Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende avapritinib til behandling af avanceret systemisk mastocytose

Monoterapi til voksne patienter med aggressiv systemisk mastocytose (ASM), systemisk mastocytose med associeret hæmatologisk neoplasma (SM-AHN) eller mastcelleleukæmi (MCL) efter mindst én systemisk behandling

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. avapritinib til AdvSM
2. Forhandlingsnotat fra Amgros vedr. avapritinib til AdvSM
3. Ansøgers endelige ansøgning vedr. avapritinib til AdvSM
4. Supplerende information fra ansøger

April 26th 2024

Blueprint Medicines response to Medicinrådets Udkast anbefaling vedr. avapritinib til behandling af avanceret systemisk mastocytose

Blueprint Medicines would like to thank and acknowledge the substantial work Medicinrådet has done to assess the new drug Avapritinib for the treatment of adult patients with advanced systemic mastocytosis (AdvSM). We would like to clarify and address the following points made in the assessment report.

Point 1: Burden of disease and unmet medical need

Blueprint Medicines confirms Medicinrådet's summary in this rare disease of advanced systemic mastocytosis (3 new patients approximately every year in Denmark). AdvSM patients have a decreased life expectancy (1-4 years after diagnosis). Currently, in addition to avapritinib, a targeted inhibitor for the driver of the disease (KITD816V), the only approved drug in AdvSM is the multi-kinase inhibitor midostaurin. Thus, the burden of disease and the unmet medical need is high.

Point 2: Use of a composite comparator

Currently, there is no established treatment pathway nor any Danish clinical treatment guidelines available for patients with AdvSM. In the assessment report (page 3/73), the DMC mentioned avapritinib is approved by EMA for patients with AdvSM that have received at least one prior systemic treatment, which most likely will be midostaurin in Danish clinical practice, since there are no therapies other than midostaurin licensed for the treatment of AdvSM in Denmark. Therefore, patients with AdvSM are likely to receive a mix of treatments (other than midostaurin in first line), as supported by clinical expert feedback. Consequently, the comparator treatments in the BAT basket include treatments such as cladribine (considered for second line treatment), interferon-alpha, TKIs, and AML-like treatments. It is noteworthy that these treatments are "off-label" with unproven clinical benefit, which also was recognized by the DMC.

While we submitted a composite comparator (BAT) in our base case analysis, we acknowledge the lack of any functionality for each disease sub-type or individual treatment to be assessed separately, however this is due to the lack of clinical evidence. The BAT arm is based on data from the BLU-285-2405 (RWE study) provided in the submission. We acknowledge DMC's point, that first and foremost the patients in BLU-285-2405 have received midostaurin in second line, and since midostaurin is used in first line for the treatment of AdvSM in Denmark there is a misalignment in BLU-285-2405 and the Danish clinical practice which means that the cost-effectiveness results in the BAT arm do not reflect Danish clinical practice, where cladribine will be prescribed in second line.

However, we think that BLU-285-2405 should be considered as adequate and "best available" for capturing the complexity of the current Danish clinical practice. Furthermore, DMC mentioned in section 3.2 of the assessment report, that based on the few studies within AdvSM it has been assessed that midostaurin is better than cladribine with a better documented effect compared to cladribine as well. However, the use of cladribine is based on one simple retrospective study (BLU-285-2405) and DMC assumes that the HR for avapritinib vs cladribine would most likely be lower compared to the submitted HR for avapritinib vs BAT of 0.47. However, it was not possible to estimate the real difference between this comparison which probably would have been beneficial for avapritinib's case.

As mentioned in section 2.7 of the assessment report, DMC highlighted that some patients would experience severe gastrointestinal side effects from the treatment with midostaurin and would most likely benefit from switching from midostaurin to avapritinib, and the DMC reported that data indicates that avapritinib is at least as effective as midostaurin, however, with a lower incidence of gastrointestinal side effects such as nausea and vomiting. Based on this reflection, DMC conducted their own scenario analysis to demonstrate the cost aspects of a potential shift from midostaurin to avapritinib, assuming that the treatment duration wouldn't differ between midostaurin and avapritinib.

Point 3: Stem cell transplantation in CEM, therapeutic option

We acknowledge the rationale behind the choice of excluding HSCT in the model as subsequent treatment. Allo-HSCT was not considered as a comparator in the model, since clinical experts noted that avapritinib would not displace allo-HSCT but be used alongside it as bridge to transplant in a proportion of patients who have shown a good SM response to treatment, are sufficiently fit to receive the transplant and have an available donor.

While consensus groups advocate for allogeneic hematopoietic cell transplantation (allo-HCT) in drug-resistant and high-risk AdvSM cases, guidance on patient selection and integrating KIT inhibitors into transplant protocols remains limited. That said, there is a lack of information on the optimal timing, how KIT Inhibitors may fit into the transplant algorithm and currently, there is no clinical experience with avapritinib in the pretransplant setting; however, because many patients undergo transplantation without being in CR, they are at a high risk of relapse, and KIT inhibitors should therefore be considered, with particular focus on therapies that can induce the best possible remission of SM (ideally as per the mIWG CR/CRh/PR criteria) and/or AHN. (McLornan DP et al., 2024)

Given the fact that we do not have any Danish clinical expert statement or opinion on this matter, we acknowledge the scarcity or/and unknown use of allo-HSCT in Danish clinical practice and in alignment with DMC's decision to exclude allo-HSCT in the model is understood.

Conclusions

The avapritinib clinical development program remains the most comprehensive evidence base for advanced systemic mastocytosis patients to date and is a treatment option for this population with high unmet medical need in this rare disease. The evidence base will have limitations due to the nature of this rare indication and the lack of clinical experience with targeted therapies. As a company, we have provided the best available evidence. We hope Medicinrådet will consider all the above-mentioned points in its decision.

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25.04.2024
BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	22.05.2024
Leverandør	Blueprint Medicines
Lægemiddel	Ayvakyt (avapritinib)
Ansøgt indikation	Monoterapi til behandling af voksne patienter med aggressiv systemisk mastocytose (ASM), systemisk mastocytose med associeret hæmatologisk neoplasma (SM-AHN) eller mastcelleleukæmi (MCL) efter mindst én systemisk behandling.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Ayvakyt (avapritinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Ayvakyt	100 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	200 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	300 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	50 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	25 mg	30 stk.	211.200	[redacted]	[redacted]

Prisen er **betinget** af Medicinrådets anbefaling af Ayvakyt til behandling af **både** aggressiv systemisk mastocytose (ASM) og til behandling af gastrointestinal stromal tumor (GIST).

Hvis Medicinrådet ikke anbefaler Ayvakyt til begge indikationer, indkøbes lægemidlet til følgende forhandlede pris.

Tabel 2: Ubetinget pristilbud

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP, (DKK)	Rabatprocent ift. AIP
Ayvakyt	100 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	200 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	300 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	50 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	25 mg	30 stk.	211.200	[redacted]	[redacted]

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, som gælder fra den 23.05.2024. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Tabel 3 viser lægemiddeludgiften for Ayvakyt i relation til Rydapt (midostaurin), der bliver brugt til behandling af patienter med ASM i 1. linje.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Ayvakyt (avapritinib)	200 mg	30 stk.	200 mg én gang dagligt	[redacted] Betinget pris	[redacted]
Ayvakyt (avapritinib)	200 mg	30 stk.	200 mg én gang dagligt	[redacted] Ubetinget pris	[redacted]
Rydapt (midostaurin)	25 mg	112 stk.	100 mg én gang dagligt	[redacted]	[redacted]
Rydapt (midostaurin)	25 mg	112 stk.	200 mg én gang dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	Bestillerforum har bestilt en vurdering i oktober 2021. Firmaet har ikke sendt en ansøgning endnu.	Link til vurdering
Sverige	Ikke ansøgt		
England	Under vurdering		Link til vurdering

Application for the assessment of avapritinib (Ayvakyt®) as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis, systemic mastocytosis with an associated haematological neoplasm or mast cell leukaemia, after at least one systemic therapy

Contact information

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Abbreviations

Abbreviation	Meaning
2L	Second Line
AdvSM	Advanced Systematic Mastocytosis
AdvSM-SAF	Advanced Systematic Mastocytosis Symptom Assessment Form
AE(s)	Adverse Event(s)
AHN	Associated Haematologic Neoplasm
AIC	Akaike Information Criterion
AIM	American Initiative in Mast Cell Diseases
AIP	Pharmacy Purchasing Prices
Allo-HSCT	See HSCT
AML	Acute Myeloid Leukaemia
ANC	Absolute Neutrophil Count
ASM	Aggressive Systemic Mastocytosis
ATP	Adenosine Triphosphate
BAT	Best Available Treatment
B-findings	Burden of Disease Findings
BIC	Bayesian Information Criterion
CD	Cluster of Differentiation
CEM	Cost-effectiveness model
C-findings	Cytoreduction-Requiring Findings
CHMP	Committee for Medicinal Products for Human Use
CI	Clinical Improvement/Confidence Interval
CR	Complete Remission
CRh	Complete Remission with Partial Recovery of Peripheral Blood Counts
CT	Computerised Tomography

CTC	Common Terminology Criteria
DC	Discrete Choice
DCO	Data Cut-Off
DKK	Danish Krone
DMC	Danish Medicines Council
DRG	Danish diagnosis related groups
ECG	Electrocardiogram
ECNM	European Competence Network on Mastocytosis
ECOG	Eastern Cooperative Oncology Group
ED	Emergency Department
EMA	European Medicines Agency
EOT	End of Treatment
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
FACT-G	Functional Assessment of Cancer Therapy General
GIST	Gastrointestinal Stromal Tumours
GP	General Practitioner
HCRU	Healthcare Resource Utilisation
HCT/HSCT/allo-HSCT	Haematopoietic Stem Cell Transplant
HLA	Human Leukocyte Antigen
Hgb	Haemoglobin
HR(s)	Hazard Ratio(s)
HRQoL	Health-Related Quality of Life
HSUV	Health State Utility Value
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IM	Intramuscular
IPD	Individual Patient Data
ISM	Indolent Systematic Mastocytosis
ITC	Indirect Treatment Comparison
IV	Intravenous/intravenously
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis
KIT	v-kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog
KM	Kaplan-Meier
LOR	Loss of Response
LOT	Lines of therapy
LY	Life-Years
MAC	Myeloablative Conditioning Regime

MAE(s)	Mean Absolute Error
MAIC	Matched Adjusted Indirect Comparison
MC	Mast Cell
MCL	Mast Cell Leukaemia
MinR	Minor Response
mIWG-MRT-ECNM	Modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
PartSA	Partitioned Survival
PCR	Pure Clinical Response
PD	Progressed Disease
PDGFRA	Platelet-Derived Growth Factor Receptor Alpha
PF	Progression-Free
PFS	Progression-Free Survival
PH	Proportional Hazard
PR	Partial Remission
PRO	Patient Reported Outcome
QALY(s)	Quality-Adjusted Life-Year(s)
QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
QoL	Quality of Life
RAC-RE	Response Assessment Committee Response-Evaluable population
RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
SD	Stable Disease
SM	Systematic Mastocytosis
SM-AHN	Systemic Mastocytosis with an Associated Haematological Neoplasm
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SSM	Smouldering Systematic Mastocytosis
TA	Technology appraisal
TKI	Tyrosine Kinase Inhibitors
TLR	Targeted Literature Review
ToT	Time on Treatment
TTO	Time-Trade-Off

US	Ultrasound
WHO	World Health Organisation

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Ayvakyt®
Generic name	Avapritinib
Therapeutic indication as defined by EMA	Avapritinib is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy (1).
Marketing authorization holder in Denmark	Blueprint Medicines (Netherlands) B.V.
ATC code	L01EX18
Combination therapy and/or co-medication	Given as monotherapy.
(Expected) Date of EC approval	Avapritinib received market authorisation from the EMA on the 24th of March 2022 for the treatment of patients with Advanced Systemic Mastocytosis (AdvSM) (1).
Has the pharmaceutical received a conditional marketing authorization?	No, only for GIST indication.
Accelerated assessment in the European Medicines Agency (EMA)	No.
Orphan drug designation (include date)	Granted orphan designation by the European Medicines Agency (EMA) for the treatment of AdvSM on the 26th of October 2018 (EU/3/18/2074). The orphan drug designation was confirmed at the beginning of 2022 (2).
Other therapeutic indications approved by EMA	Avapritinib is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the PDGFRA D842V mutation (1).
Other indications that have been evaluated by the DMC (yes/no)	No.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Ayvakyt® (avapritinib) 25 mg; 30 x 25 mg film coated tablets (Not available in Denmark, but EMA approved (1)) Ayvakyt® (avapritinib) 50 mg; 30 x 50 mg film coated tablets (Not available in Denmark, but EMA approved (1)) Ayvakyt® (avapritinib) 100 mg; 30 x 100 mg film coated tablets

Overview of the pharmaceutical	
	Ayvakyt® (avapritinib) 200 mg; 30 x 200 mg film coated tablets Ayvakyt® (avapritinib) 300 mg; 30 x 300 mg film coated tablets (Not used in AdvSM, only GIST)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Avapritinib is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy (1).
Dosage regiment and administration:	200 mg orally once daily on an empty stomach. Treatment should be continued until disease progression or unacceptable toxicity occurs (1).
Choice of comparator	Best available treatment (BAT) which includes current standard of care (SoC).
Prognosis with current treatment (comparator)	Median overall survival of patients with ASM = 41 months; SM-AHN = 24 - 35 months, MCL = 2 – 23 months. The estimated median OS for avapritinib-treated patients was 49.0 months versus 26.8 months for BAT-treated patients (3).
Type of evidence for the clinical evaluation	Indirect comparison (inverse probability weighting).
Most important efficacy endpoints (Difference/gain compared to comparator)	ORR: EXPLORER 72.7% (avapritinib); PATHFINDER 59.6% (avapritinib) HR: 0.47 (avapritinib vs BAT; RAC-RE)
Most important serious adverse events for the intervention and comparator	Avapritinib: anaemia and subdural haematoma = 3.4%
Impact on health-related quality of life	Clinical documentation: PATHFINDER (April 2021 DCO) (4, 5): QLQ-C30 scores mapped to EQ-5D-3L and to EQ-5D-5L to inform the PF HSUV. Result: 0.654 (CI: NA) (RAC-RE). TLR findings to use PFS and PD ratio for calculation of PD HSUV. Result: 0.645 (CI: NA) (RAC-RE). Grulke et al.: QLQ-C30 scores mapped to EQ-5D to inform post-HSCT HSUVs (first month, to month 6, 6-12 months, and 12+ months). Results: 0.620, 0.760, 0.796, and 0.796, respectively (no CI available).
Type of economic analysis that is submitted	Cost-utility analysis. Partitioned survival model combined with a semi-Markov model.
Data sources used to model the clinical effects	Avapritinib: IPD data from PATHFINDER (April 2021 DC) (6), BAT: ITC data from BLU-285-2405 (3).
Data sources used to model the health-related quality of life	PATHFINDER (April 2021 DC), Stein et al., Joshi et al., Leunis et al., Mamolo et al., and Grulke et al., (7-11)

Summary	
Life years gained	Avapritinib: XXXXXXXX, BAT: XXXXXXXX
QALYs gained	Avapritinib: XXXXXXXX, BAT: XXXXXXXX
Incremental costs	XXXXXXXX DKK
ICER (DKK/QALY)	XXXXXXXX DKK /QALY
Uncertainty associated with the ICER estimate	The OS HR avapritinib versus BAT parameter is the most influential parameter followed by the response OR avapritinib versus midostaurin, and distribution of BAT (midostaurin) parameters.
Number of eligible patients in Denmark	Incidence: an annual incidence of 3 new patients. Among the incidence population, it is expected that 2 new AdvSM patient would be eligible for 2nd line treatment every year, as one third of the incidence patients would not qualify for this treatment (2 out of 3). For the patients on treatment, on average, the duration is approximately 23 months (1-2 drop offs ever year), both based on clinical experience from other EU countries (12). This will result in 1 new eligible patient every second year. Prevalence: 14 eligible patients in Year 1. Eligible patients in Year 5: 16 patients.
Budget impact (in year 5)	XXXXXXXX

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Description of the disease

Advanced Systemic Mastocytosis (AdvSM) is a debilitating and life-threatening disease that imparts a heavy burden on patients due to the numerous symptoms that can affect multiple different organs (13-18). AdvSM encompasses the most severe forms of systematic mastocytosis (SM), which is a rare, heterogenous disease characterised by an accumulation of neoplastic mast cells in the bone marrow in addition to other organs and tissues (19). SM is now classified by the World Health Organisation (WHO) as a myeloid neoplasm. AdvSM makes up only 5% - 10% of SM cases (6), but it represents the most aggressive and life-threatening forms and is divided into aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL).

3.1.1.1 Pathophysiology

Mast cells belong to the first line of defence against external invaders in the skin, digestive tract, and respiratory tract. Mast cells contain granules with a broad repertoire of ready-

to-use immune-related molecules, e.g., tryptase. In mastocytosis patients, the mast cells are monoclonal in nature. This is shown by the presence of a defined point mutation in their DNA (20). This mutation is called the D816V mutation of the KIT proto-oncogene. SM is a rare hematologic neoplasm that is associated with the KIT D816V mutation in 93% of cases. The KIT D816V mutation drives the increased proliferation and accumulation of neoplastic mast cells, leading to severe, debilitating and often unpredictable symptoms and poor quality of life (QoL) (20).

3.1.1.2 Symptoms

The symptoms of mastocytosis can arise from the release of mast cell mediators or from massive infiltration of organs and tissues by mast cells. Due to the wide variety of symptoms and the relative unfamiliarity with the disease, the diagnosis of advanced systemic mastocytosis is often made late, which can lead to unnecessary morbidity and life-threatening organ damage (C-findings - see section 3.1.1.3) - e.g., bone marrow dysfunction with cytopenia's, hepatomegaly with impairment of liver function, hypersplenism, malabsorption with hypoalbuminemia, weight loss, skeletal lesions, and ascites.

3.1.1.3 Diagnosis

SM is divided into five subtypes in accordance with the 2022 updated WHO criteria (Table 1): two non-advanced subtypes (indolent systemic mastocytosis [ISM] and smoldering systemic mastocytosis [SSM]) and three advanced subtypes (ASM, SM-AHN and MCL) (21, 22). This dossier has focused on ASM, SM-AHN and MCL.

The diagnosis of SM is made when one major and one minor criterion are both met, or when three or more minor criteria are met. The major criterion involves the identification of dense aggregates of masts cells in biopsies of the bone marrow and other organs beyond the skin, while the minor criteria include atypical morphology of mast cells, the presence of an activating KIT mutation, expression of cell-surface markers usually not present on mast cells, and elevated serum levels (21-23).

Table 1 Criteria for diagnosis of SM

Major criterion
Multifocal dense infiltrates of tryptase- and/or CD117-positive MCs (≥15 MCs in aggregates) in sections of BM and/or other extracutaneous organ(s).
Minor criterion
In biopsy sections of BM or other extracutaneous organs, >25% of all MCs in the infiltrate are spindle-shaped or have atypical morphology; or, of all MCs in BM aspirate smear, >25% are immature or atypical.
KIT point mutations at codon 816 or in other critical regions of KIT in BM, blood, or another extracutaneous organ.
MCs in BM, blood, or other extracutaneous organ express CD25, CD2, and/or CD30 in addition to normal MC markers.
Baseline serum tryptase concentration >20 ng/mL (in case of SM-AHN, this is not valid as an SM minor criterion).
B-Findings
These findings indicate a higher disease burden due to mast cell infiltrates and expansion of the neoplastic process to multiple hematopoietic cell lines. However, this is not accompanied by limitations of organ functions.
Infiltration of mast cells into the bone marrow is >30% and serum tryptase is > 200 µg/L

Hypercellular bone marrow with fat cell loss, discrete signs of dysplasia or myeloproliferation but without substantial cytopenia or the WHO criterion for MDS or MPN.
Organomegaly: palpable hepatomegaly, palpable splenomegaly, or palpable lymphadenopathy. When seen with CT/ultrasound, these organs are enlarged >2 cm. There are no signs of restriction of organ functions.
C-Findings
Indicators of organ damage from mast cell infiltration.
Bone marrow dysfunction characterized by 1 or more cytopenia's: absolute neutrophil granulocyte count <1,0*109/L or Hb <6 mmol/L or platelet count <100*109/L, but no evidence of associated non-mast cell haematological malignancy.
Hepatomegaly with or without ascites and with impairment of liver function
Palpable splenomegaly accompanied by hypersplenism
Malabsorption with hypoalbuminemia and weight loss
Skeletal lesions: large osteolytic foci with pathological fractures
Life-threatening organ damage from mast cell infiltration into an affected organ.

Abbreviations: BM = bone marrow; CD = cluster of differentiation; KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MC = mast cell; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated haematologic neoplasm. Source: Valent et al., 2021 (24); Khoury et al., 2022 (21); Arber et al., 2022 (22).

3.1.1.3.1 AdvSM

If the criteria for the diagnosis of SM are met, separate criteria exist to differentiate all three forms of AdvSM. The criteria are based on the proportion of mast cells in bone marrow aspirate, meeting WHO criteria for an associated haematological neoplasm, or the presence of various C-findings (25, 26).

ASM

Diagnosis of ASM is dependent on identification of one or more clinical findings known as C-findings, which indicate organ damage from the infiltration of mast cells (24-27).

SM-AHN

Diagnosis of SM-AHN depends on the diagnosis of SM, in addition to also meeting the WHO criteria for an AHN (26). A number of associated neoplasms have been identified in patients with SM-AHN, including neoplasms of myeloid origin, lymphoma, myeloma, and chronic lymphocytic leukaemia (14, 28). Patients with SM-AHN can also present C-findings.

MCL

MCL is differentiated from SM by further increased levels of mast cell infiltrations in the bone marrow. Specifically, the diagnosis of MCL is made when the proportion of mast cells in bone marrow aspirate is demonstrated to be 20% or greater. Patients with MCL can also present C - findings. Although the clinical presentation and prognosis of systemic mastocytosis is characterized by its heterogeneity, the underlying pathogenesis is largely shared and D816V mutations in KIT, regardless of subtype, are found in 93% of all cases of systemic mastocytosis.

3.1.1.4 Mortality

ASM, SM-AHN and MCL are serious and life-threatening conditions (14). The conditions are accompanied by severe and unpredictable symptoms due to mast cell infiltration into various organs. These disabling symptoms are associated with organ damage (up to organ failure) and limited survival, partly due to a long process of diagnosis of mostly many years. The life expectancy of patients with SM depends on the specific subtype. Patients with MCL have a poor prognosis with overall survival in common practice being only between 2 and 23 months (28). The prognosis of patients with SM-AHN is related to the coexistence

of the haematological disease. The average survival is between 24 and 35 months, depending on the aggressiveness of the SM and associated hemopathy (28). The median survival of patients with ASM is 41 months (26). In this subtype, complications may occur leading to potentially fatal anaphylactic shock or progression to MCL. The progression of the disease can be slow or rapid. In the case of rapid progression, serum tryptase levels increase rapidly, causing, or exacerbating damage to various organs in a short period of time, and often accelerating progression to MCL (26). Among the approved treatments for AdvSM, results from a Phase II 10-year follow up of AdvSM patients (ASM, SM-AHN and MCL) who received midostaurin, the median overall survival for the entire cohort and MCL was 40 months and 18.5 months respectively (29).

3.2 Patient population

The incidence of AdvSM in Denmark is estimated to be 0.06/100 000 people, which corresponds to approximately 3 new cases per year in Denmark based on a Danish epidemiological study done on AdvSM patients by Cohen et al., 2014 (30). Based on market research done by the applicant, there the current prevalence of AdvSM in Denmark is estimated to be 20 patients (31).

To account for the number of eligible AdvSM patients who have received prior systematic therapy, Dutch clinical experts and the applicants market research state that 70% of the prevalence population would be eligible for 2nd line targeted treatment (14 patients in Year 1) (31, 32). Among the incidence population, it is expected that 2 new AdvSM patient would be eligible for 2nd line treatment every year, as one third of the incidence patients would not qualify for this treatment (2 out of 3). For the patients on treatment, on average, the duration is approximately 23 months (1-2 drop offs ever year), both based on clinical experience from other EU countries (12). This will result in 1 new eligible patient every second year as shown in Table 3 below.

Table 2 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	3	3	3	3	3
Prevalence in Denmark	18	18	19	19	20
Global prevalence*	MCL: extremely rare (<1% of SM cases) (33). ASM global prevalence is estimated to be between 1/250,000-400,000 (34). SM-AHN prevalence in Europe estimated to be between 1/7,700-10,400 (35).				

Table 3 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	14	15	15	16	16

3.3 Current treatment options

3.3.1 Current treatment options

The Danish Medicines Council (DMC) and Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) have not developed treatment guidelines for AdvSM patients in Denmark. Based on communications with the DMC, the current first line treatment choice for AdvSM patients in Denmark is midostaurin, in accordance with the EMA label (36). However, it is expected some patients may not be eligible for treatment with midostaurin and will

receive other cytoreductive therapies. Treatment options beyond first line includes a mix of off-label cytoreductive therapies such as cladribine; tyrosine kinase inhibitors (TKIs; imatinib, nilotinib, and dasatinib), interferons (interferon-alpha-2a and peg-interferon-alpha), & acute myeloid leukaemia (AML) like treatments (azacytidine and cytarabine based treatments) as well as symptomatic treatments, which would be considered BAT in Denmark.

The international treatment guidelines by the National Comprehensive Cancer Network (NCCN) and the joint effort from the European Competence Network on Mastocytosis (ECNM) and the American Initiative in Mast Cell Diseases (AIM) (37, 38) provide the most comprehensive disease management pathways for AdvSM, including detailed treatment pathways for ASM, SM-AHN and MCL, in addition to stepwise prophylactic approaches for the treatment of common symptoms of SM. The approaches to symptom treatment and use of cytoreductive treatments aligns with published clinical expert recommendations (26).

3.3.1.1 Treatment of symptoms

The treatment of symptoms in patients with SM should be considered in all patients (26, 37). NCCN and ECNM-AIM guidelines provide recommendations for the prevention and treatment of anaphylaxis, which is a severe and common side effect of SM (37, 38). This includes the use of antihistamines and epinephrine, complemented by IV fluids, oxygen, corticosteroids, and bradykinin inhibitors.

3.3.1.2 Treatment guidelines for AdvSM

To effectively treat AdvSM, treatments that target clonally expanded mast cells can be used (26, 37, 39). Treatment pathways provided in the NCCN guidelines for ASM, MCL and SM-AHN focus on diagnosis, patient counselling (including specialist referral, symptom counselling, avoidance of mast cell activation, and management of anaphylaxis with epinephrine), cytoreductive treatments, and monitoring and reassessment based on response to treatment (37).

3.3.1.2.1 HSCT

HSCT can be a curative therapy for patients with AdvSM. According to clinicians, advanced age is a significant deterrer when determining whether to refer patients for HSCT. In 2016, an expert consensus on HSCT in AdvSM was published, stating that HSCT should only be considered in patients under the age of 60 who have a complete HLA-matched sibling donor or an unrelated donor with no comorbidities (40). Therefore, HSCT is only suitable for a limited subset of patients with AdvSM (40). Eligibility for and subsequent efficacy of HSCT is enhanced in patients that demonstrate remission in their condition after receiving therapy. Two patients from the EXPLORER trial who demonstrated CR from avapritinib treatment received HSCT. Importantly, both patients are still in complete remission after the transplant (41). This demonstrates the efficacy of avapritinib, and suggests that when combined with HSCT, a curative option might be available for patients with AdvSM.

3.3.1.2.2 Cytoreductive therapies

A number of therapies that target mast cells are considered when treating AdvSM (17, 28, 39). This includes therapies with EMA approval, namely avapritinib and midostaurin, and other medications that are used off-label (37).

Therapies indicated for treatment of AdvSM

Avapritinib and midostaurin are the only therapies specifically indicated for use in patients with: ASM, SM-AHN, and MCL (1, 36). Midostaurin is used line agnostic while avapritinib

is approved after prior systemic therapy. Midostaurin is an inhibitor of multiple tyrosine kinases (36), but its specific activity against KIT D816V is less than that of avapritinib (42). In a phase 2 open label study of midostaurin in patients with AdvSM, ORR was 60%; however, this assessment used the Valent criteria (43), which do not require full resolution of C-findings, in addition to presenting other drawbacks in assessing treatment response (44). Post hoc analyses using the IWG-MRT-ECNM criteria demonstrated a 28% ORR, with CR in less than 1% of patients (36).

Off-label therapies

Off-label therapies considered for use in patients with AdvSM include imatinib, dasatinib, nilotinib, cladribine, and interferon alpha. Due to lesser efficacy or issues with safety, there are included in the NCCN guidelines as "other recommended regimens" (37). Imatinib lacks efficacy against KIT D816V (17, 28, 39), which is present in approximately 93% of AdvSM cases (17, 42, 45-48). For this reason, the off-label use of imatinib is only considered in patients who do not contain the specific KIT D816V variant (17, 37). Similar to imatinib, dasatinib and nilotinib have shown low response rates when tested in patients with AdvSM (17). Both are considered to possibly be effective in patients with AdvSM that are negative for KIT D816V (17). Cladribine and interferon alpha are used to target mast cells and have shown some efficacy against AdvSM. Given the toxicity profile, treatment with cladribine is particularly indicated for patients where rapid debulking of disease is desired. Cladribine is associated with adverse events (AEs) including neutropenia and lymphopenia, resulting in immunosuppression and opportunistic infection (17, 28, 39). Interferon alpha (with or without additional prednisolone) has shown activity, although responses are delayed and relapse is common after treatment cessation, highlighting that interferon alpha may not kill mast cells (28). Additionally, interferon alpha is associated with numerous AEs, including flu-like symptoms, bone pain, fever, cytopenia's, depression, and hypothyroidism (28, 39).

3.3.1.3 Unmet need in treatment of AdvSM

AdvSM is a debilitating and life-threatening disease (13, 14). In addition to shortened survival, the burden of disease is very high from the patient perspective (28), and severe, disabling and unpredictable symptoms due to mast cell infiltration and damage in various organs (15-18). AdvSM severely impacts patients' Health-Related Quality of Life (HRQoL), demonstrated by patient reported outcome measures that suggest comparability to depression and lung cancer (48). While midostaurin has demonstrated activity against KIT D816V in vitro, this activity has been shown to be approximately 10 times lower compared to avapritinib (42). Additionally, when using more effective novel tools to assess the efficacy of midostaurin in patients with AdvSM, response to therapy and complete remission are decreased in comparison to avapritinib. This has been demonstrated in an indirect treatment comparison (ITC), which demonstrated superior results for avapritinib when considering OS, ORR, and CR in patients with AdvSM. Of note, regarding midostaurin, the ECNM stated (49): However, only a few patients enter complete remissions and the number of patients with advanced SM who relapse under treatment with midostaurin is relatively high. Therefore, there is need for a therapy for AdvSM that has proven efficacy supported by the most data-driven measures of response to treatment and can specifically target mast cells expressing the KIT D816V variant, which is the main underlying driver of AdvSM. There is a need to provide rescue to patients who have had

disease progress while receiving prior systemic therapies while providing an adequate safety profile with established dosing and patient populations that allow for safe usage.

3.4 The intervention

Table 4 Key descriptive information of avapritinib

Overview of intervention	
Therapeutic indication relevant for the assessment	Avapritinib is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy (1).
Method of administration	Oral tablets.
Dosing	200 mg orally once daily on an empty stomach.
Dosing in the health economic model (including relative dose intensity)	200 mg orally once daily.
Should the pharmaceutical be administered with other medicines?	No, given as monotherapy.
Treatment duration / criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity occurs (1).
Necessary monitoring, both during administration and during the treatment period	Avapritinib has been associated with an increased incidence of haemorrhagic adverse reactions, including serious and severe adverse reactions, like gastrointestinal haemorrhage and intracranial haemorrhage in patients with AdvSM. Routine surveillance of haemorrhagic adverse reactions must include physical examination. Complete blood counts, including platelets, and coagulation parameters must be monitored, particularly in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding. Adverse reactions of intracranial haemorrhage occurred in patients who received avapritinib. Before initiating avapritinib the risk for intracranial haemorrhage should be carefully considered in patients with potential increased risk including those with thrombocytopenia, vascular aneurysm or a history of intracranial haemorrhage or cerebrovascular accident within the prior year. Patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, and/or focal weakness) during treatment with avapritinib must interrupt dosing of avapritinib and inform their healthcare professional immediately. Brain imaging by magnetic resonance imaging (MRI) or computed tomography (CT) may be performed at the discretion of the physician based on severity and the clinical presentation. For patients with observed intracranial haemorrhage during treatment with avapritinib, regardless of severity grade, avapritinib must be permanently discontinued. See Table 5. Serious adverse reactions of intracranial haemorrhage were reported in patients with AdvSM receiving avapritinib. The exact mechanism is unknown. The incidence of intracranial haemorrhage was higher in patients with platelet counts <50 x 109/L and in patients with a starting dose of ≥300 mg. Considering the above, a platelet count must be

Overview of intervention	
	performed prior to initiating therapy. Avapritinib is not recommended in patients with platelet counts <50 x 109/L. Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks of treatment, monitor platelet counts every 2 weeks (or more frequently as clinically indicated) if values are less than 75 x 109/L, every 4 weeks if values are between 75 and 100 x 109/L, and as clinically indicated if values are greater than 100 x 109/L. Manage platelet counts of <50 x 109/L by temporarily interrupting avapritinib. Platelet support may be necessary, and the recommended dose modification in Table 5 must be followed. Thrombocytopenia was generally reversible by reducing or interrupting avapritinib in clinical studies. The maximum dose for patients with AdvSM must not exceed 200 mg once daily. Cognitive effects, such as memory impairment, cognitive disorder, confusional state, and encephalopathy, can occur in patients receiving avapritinib. The mechanism of the cognitive effects is not known. It is recommended that patients are clinically monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, and/or difficulty with cognitive functioning. Patients must notify their healthcare professional immediately if they experience new or worsening cognitive symptoms. For patients with observed cognitive effects related to treatment with avapritinib, the recommended dose modification in Table 5 must be followed. In clinical studies, dose reductions or interruptions improved Grade ≥2 cognitive effects compared to no action. In patients with AdvSM, localised (facial, periorbital, peripheral, pulmonary oedema, pericardial and/or pleural effusion) or generalised oedema, and ascites have been observed with a frequency category of at least common. Other localised oedemas (laryngeal oedema) have been reported uncommonly. Therefore, it is recommended that patients be evaluated for these adverse reactions including regular assessment of weight and respiratory symptoms. An unexpected rapid weight gain or respiratory symptoms indicating fluid retention must be carefully investigated and appropriate supportive care and therapeutic measures, such as diuretics, should be undertaken. For patients presenting with ascites, it is recommended to evaluate the aetiology of ascites. Prolongation of QT interval has been observed in patients AdvSM treated with avapritinib in clinical studies. QT interval prolongation may induce an increased risk of ventricular arrhythmias, including Torsade de pointes. Avapritinib should be used with caution in patients with known QT interval prolongation or at risk of QT interval prolongation (e.g. due to concomitant medicinal products, pre-existing cardiac disease and/or electrolyte disturbances). Concomitant administration with strong or moderate CYP3A4 inhibitors should be avoided due to the increased risk of adverse reactions, including QT prolongation and related arrhythmias. If concomitant use of moderate CYP3A4 inhibitors cannot be avoided. Interval assessments of QT by electrocardiogram (ECG) should be considered if avapritinib is taken concurrently with medicinal products that can prolong QT interval. Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions in patients with AdvSM. Patients who present with diarrhoea, nausea and vomiting should be evaluated to exclude disease-related aetiologies. Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrheal, or antacid

Overview of intervention	
	properties. The hydration status of patients experiencing gastrointestinal adverse reactions must be closely monitored and treated as per standard clinical practice. Treatment with avapritinib in patients with AdvSM is associated with anaemia, neutropenia and/or thrombocytopenia. Complete blood counts must be performed on a regular basis during the treatment with avapritinib. Treatment with avapritinib is associated in patients with AdvSM with elevations in bilirubin and liver transaminases. Liver function (transaminases and bilirubin) should be monitored regularly in patients receiving avapritinib. Co-administration with strong or moderate CYP3A inhibitors should be avoided because it may increase the plasma concentration of avapritinib. Co-administration with strong or moderate CYP3A inducers should be avoided because it may decrease the plasma concentrations of avapritinib. Exposure to direct sunlight must be avoided or minimised due to the risk of phototoxicity associated with avapritinib. Patients must be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).
Need for diagnostics or other tests (e.g. companion diagnostics).	N/A
Package size(s)	Ayvakyt® (avapritinib) 25 mg; 30 x 25 mg film coated tablets (Not available in Denmark, but EMA approved (1)) Ayvakyt® (avapritinib) 50 mg; 30 x 50 mg film coated tablets (Not available in Denmark, but EMA approved (1)) Ayvakyt® (avapritinib) 100 mg; 30 x 100 mg film coated tablets Ayvakyt® (avapritinib) 200 mg; 30 x 200 mg film coated tablets Ayvakyt® (avapritinib) 300 mg; 30 x 300 mg film coated tablets (Not used in AdvSM, only GIST)

Table 5 Recommended dose modifications for avapritinib for adverse reactions in AdvSM patients

Adverse reaction	Severity*	Dose modification (1)
Intracranial haemorrhage	All grades	Permanently discontinue avapritinib
Cognitive effects**	Grade 1	Continue at the same dose, reduce dose or interrupt until improvement to baseline or resolution. Resume at the same dose or at a reduced dose.
	Grade 2 or Grade 3	Interrupt therapy until improved to baseline, Grade 1, or resolution. Resume at the same dose or at a reduced dose.
	Grade 4	Permanently discontinue avapritinib
Thrombocytopenia	Less than 50 x 109/L	Interrupt dosing until platelet count is ≥ 50 x 109/L, then resume at reduced dose (see Table 6). If platelet count does not recover above 50 x 109/L, consider platelet support.
Other	Grade 3 or Grade 4	Interrupt therapy until less than or equal to Grade 2. Resume at the same dose or at a reduced dose, if warranted.

Table 6 Recommended dose reductions for avapritinib for adverse events in AdvSM patients

Dose reduction	AdvSM (starting dose 200 mg) (1)
First	100 mg once daily
Second	50 mg once daily
Third	25 mg once daily

3.4.1 Treatment with avapritinib

Avapritinib (AYVAKYT®) is EMA-approved therapy for use in AdvSM patients who have received at least one prior systematic therapy, and is, besides Midostaurin, the only targeted therapy designed for potent and selective inhibition of KIT D816V (1).

3.4.1.1 Mechanism of action

Avapritinib is a Type 1 kinase inhibitor that has demonstrated in vitro activity against the KIT D816V variant protein, which is associated with AdvSM (1). With sub-nanomolar potency, avapritinib binds and inhibits the KIT protein while in its active conformation, stopping constitutive receptor activation and therefore halting further downstream signalling pathways that promote mast cell activation (1, 42). Avapritinib specifically targets the ATP-binding site on KIT, preventing the activation of downstream-signalling pathways and uncontrolled mast cell activation and proliferation mediated by KIT D816V variant protein-mediated receptor dimerization (50). Avapritinib thus has both a much greater potency and a much more specific action than midostaurin.

3.4.2 The intervention in relation to Danish clinical practice

As mentioned in section 3.3.1, since midostaurin is expected by the DMC to be used mainly as first line treatment of AdvSM patients, avapritinib is expected to be used as monotherapy in second line for AdvSM patients who have previously received midostaurin or other cytoreductive treatments. The introduction of avapritinib monotherapy is expected to replace the current second line treatment pathway for AdvSM patients who have received midostaurin or other cytoreductive therapies in Denmark (BAT).

3.5 Choice of comparator(s)

As mentioned above, no official Danish treatment guidelines are available for the rare disease AdvSM. Current treatment options for AdvSM after first line would be BAT, which include symptomatic management, supportive care, and cytoreductive therapy. Hence, the comparator considered relevant for this submission is comprised of a mix of off-label treatments including cladribine, TKIs (imatinib, nilotinib, and dasatinib), interferons (interferon-alpha-2a and peg-interferon-alpha), and AML like treatments (azacytidine and cytarabine based treatments). As shown in Table 52, the assumed proportion of comparators used in clinical practice is based on a previous midostaurin NICE assessment (51). The majority of patients (>50%) are expected to receive cladribine, with the rest of the treatments to a lesser extent. Therefore, a summary of cladribine will be presented below.

Table 7 Key descriptive information of cladribine

Overview of comparator	
Generic name	Cladribine
ATC code	L01BB04

Overview of comparator	
Mechanism of action	The mechanism of action of cladribine is attributed to the incorporation of 2-chlorodeoxyadenosine-5'-triphosphate (CdATP) into DNA strands: the synthesis of new DNA in dividing cells is blocked and the DNA repair mechanism is inhibited, resulting in an accumulation of DNA strand breaks and a decrease of NAD (nicotinamide adenine dinucleotide) and ATP concentration, even in resting cells. Furthermore, CdATP inhibits ribonucleotide reductase, the enzyme responsible for the conversion of ribonucleotides into deoxyribonucleotides. Cell death occurs from energy depletion and apoptosis.
Method of administration	Solution for injection and oral tablets.
Dosing	The recommended dose for cladribine is 0.14mg/kg body weight daily for 5 consecutive days.
Dosing in the health economic model (including relative dose intensity)	0.14mg/kg body weight daily for 5 consecutive days for 9 cycles.
Should the pharmaceutical be administered with other medicines?	No, given as monotherapy.
Treatment duration/ criteria for end of treatment	Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	Cladribine 2mg/mL; 1x5mL or 5x5mL vials of solution for injection. Cladribine 10mg; 1x10mg, 4 x10mg or 6x10mg oral tablets.

Sources: medicinpriser.dk; SmPC for cladribine (52, 53)

3.6 Cost-effectiveness of the comparator(s)

The comparators within BAT have not been previously assessed by the DMC for AdvSM patients. According to the DMC methods guideline, if a comparator has not previously been assessed by the DMC, a comparison against placebo should be made, including cost-effectiveness (54). The comparison of avapritinib against placebo in an orphan setting is not possible as there is no published clinical evidence of placebo's efficacy in AdvSM patients.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 8 Efficacy outcome measures relevant for the application

Outcome measure	Time point	Definition (6)	How was the measure investigated
Overall response rate (ORR)	April 2021 DCO	Overall response rate was defined as the proportion of patients with a confirmed best response of CR, CRh, PR, or CI by mIWG-MRT-ECNM criteria. The ORR was tested against the null hypothesis of 28% generated using midostaurin ORR (CR+PR+CI) of 28.3% by IWG-MRT-ECNM criteria. In addition, the CR+CRh+PR rate was tested against the null hypothesis of 17% generated using	mIWG-MRT-ECNM criteria

Outcome measure	Time point	Definition (6)	How was the measure investigated
		midostaurin CR+PR rate of 17% by IWG-MRT-ECNM criteria.	
Overall survival (OS)	April 2021 DCO	Overall survival is defined as the time in months from the start of treatment to the date of death. Patients who die before or on the data cutoff date were considered to have had an overall survival event. All patients who did not have a death record prior to or on the cutoff date were censored at the last date known alive.	
Progression-free survival (PFS)	April 2021 DCO	Progression-free survival was defined as the time in months from the start of treatment to the date of first documented PD or death due to any cause, whichever occurs first. If a patient had not had an event, progression-free survival was censored at the date of last valid assessment that was loss of response or better	

Validity of outcomes

Disease response to treatment was assessed using mIWG-MRT-ECNM criteria, radiographic, laboratory, and clinical assessments. Radiographic, laboratory, and clinical tests and evaluations are standard and appropriate for the evaluation of patients with AdvSM. The mIWG-MRT-ENCM criteria were developed in consultation with AdvSM experts, regulatory authorities, and authors of the published original IWG-MRT-ECNM consensus response criteria for AdvSM and are considered a reliable measure of response to treatment (6). OS and PFS are standard efficacy outcomes often used in oncology studies and has been used in previous DMC submissions.

4. Health economic analysis

A cost-utility analysis was conducted based on a Danish adaptation of an Excel-based global cost-effectiveness model (CEM). The objective of the CEM is to assess the cost-effectiveness of avapritinib versus standard of care (SoC) in AdvSM. The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained.

4.1 Model structure

A cohort partitioned survival (PartSA) model, combined with a semi-Markov simulation, is used to perform the cost-utility analysis, and estimate long-term costs and health benefits of avapritinib compared with best available treatment (BAT) in AdvSM. The PartSA model simulates the time in state of the cohort receiving ongoing therapy with avapritinib and the comparators, alongside a state-transition model that simulates transitions of the cohort receiving allo-HSCT. This is because the PartSA model cannot accommodate additional health states that cannot be modelled using mutually exclusive survival curves. The model structure is depicted in Figure 1.

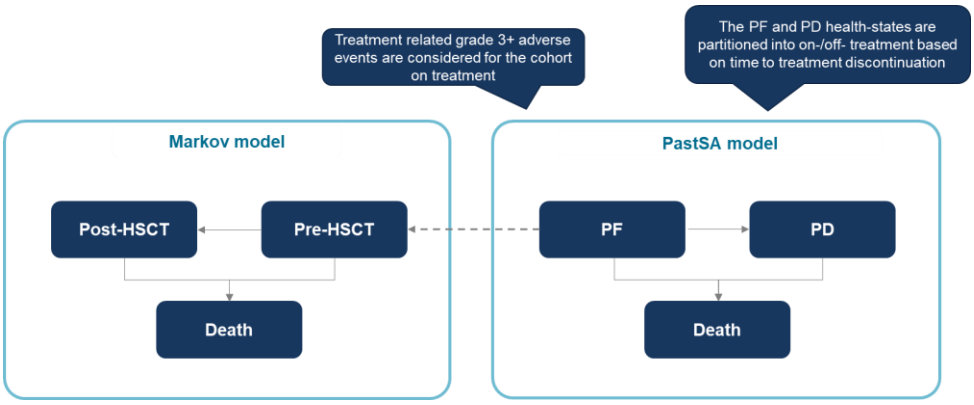

Figure 1 Model structure

Abbreviations: HSCT: haematopoietic stem cell transplant, PF: progression-free, PD: progressed disease, PartSA: partitioned survival analysis

The model includes five mutually exclusive health states; progression-free (PF), progressed disease (PD), pre-HSCT, post-HSCT, and death. PF can be defined as stable disease, whereas progression implies a worsening of the disease. The PartSA method employs a collection of survival curves that are not mutually exclusive to determine state membership. The cohort is initially placed in the PF health state, and any subsequent transitions to the PD or death health states in the sequence are determined by the PFS and OS curves, respectively. Time-on-Treatment (ToT) curve is used to define the proportion of the cohort on treatment over time in avapritinib and the BAT arm. For costing purposes, the PF and PD health states is subdivided into 'on treatment' and 'off treatment'. See Table 9 for description of the health states and the sub-states included in the PartSA model.

Table 9 Health states and sub-states in the PartSA model

Health state	Sub-state	Definition	Membership
PF		**Progression-free (alive and stable disease)**	**PFS**
	On primary tx	Progression-free - exposed to primary tx	Minimum data point (ToT / PFS, whichever occurs first)
	Off primary tx	Progression-free – switched to post-discontinuation	PFS – PF on primary treatment (tx)
PD		Progressed / post-progression (alive and worsening of disease)	OS - PFS
	On primary tx	Progressed disease – continue primary tx	ToT – PF on primary tx
	Off primary tx	Progressed disease – post-progression treatment	PD – PD on primary tx
Death		Dead	Total cohort - OS

Abbreviations: PF: progression-free, PD: progressed disease, PFS: progression-free survival, tx: treatment, ToT: time on treatment, OS: overall survival, PartSA: partitioned survival analysis.

Following the initial selection of patients based on response status (CR and ORR), selection for allo-HSCT in each arm also relies on the proportions of patients defined as 'fit' for transplant and of the availability of donors (parameters obtained from the literature, see section 8.4 for further details). The proportion of the cohort selected to receive allo-HSCT is subtracted to the total cohort in PF at the beginning of the simulation and starts the

simulation in the pre-HSCT health-state. The pre-HSCT health-state is introduced since it is expected that patients will not receive allo-HSCT immediately after treatment start and therefore will still be receiving cytoreductive therapy for a number of cycles from model start to when they undergo allo-HSCT. The cohort reside in the pre-HSCT for 12 cycles unless it transitions to the death health-state. Thus, at 1 year, the cohort is then assumed to receive allo-HSCT and transitions to the post-HSCT health-state. The model assumes no progression to PD health-state from post-HSCT, since in the only long-term study on allo-HSCT in AdvSM identified in the literature the PFS and OS curves overlaps, suggesting that all failures after allo-HSCT resulted in death.

4.2 Model features

Table 10 describes the model features.

Table 10 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with AdvSM after at least 1 prior systemic therapy. Base case 200mg Response Assessment Committee Response-Evaluable (RAC-RE) population from PATHFINDER.	Label is line with EMA approval (1). Patient population in this analysis matches the population considered by the EMA during its assessment.
Perspective	Limited societal perspective	According to DMC guidelines (55)
Time horizon	Lifetime (23 years)	To capture all health benefits and costs in line with DMC guidelines. Given the mean age of 66 and 65 years in the avapritinib cohort and the BAT cohort, respectively, a time horizon of 23 years was considered a fair approximation of a lifetime time horizon (3).
Cycle length	1 month	The frequency of administration for different drugs in AdvSM varies. Avapritinib is taken daily (oral). Cladribine and "AML-like treatments" are administered as one-off treatments, whereas interferons and tyrosine kinase inhibitors are administered weekly and daily respectively (see section 3.3). As in the midostaurin model submitted to NICE for treatment of AdvSM (TA728, Committee papers, section B.3.2.2 Model structure), a cycle length of one month was considered appropriate (assuming 365.2425 days/12 = 30.44 days per month)(51).
Half-cycle correction	Yes	
Discount rate	3.5%	According to DMC guidelines (55)
Intervention	Avapritinib	
Comparator(s)	BAT	Currently, no Danish treatment guidelines in AdvSM is available. The current clinical management consists of symptom control coupled with cytoreductive therapy, including:

Model features	Description	Justification
		cladribine, interferon alpha, imatinib and more (51, 56), refer to Section 3.5 and Section 11.1.
Outcomes	OS, PFS (from ToT)	

Abbreviations: AdvSM: advanced systemic mastocytosis, EMA: European Medicines Agency, RAC-RE: response assessment committee response-evaluable population, DMC: Danish Medicines Council, NICE: National Institute for Health and Care Excellence, BAT: best available treatment, OS: overall survival, PFS: progression-free survival, ToT: time on treatment.

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical SLR was conducted on 22 June 2023, the full details of which is provided in Appendix H. The SLR search aimed to address the following:

- To evaluate and summarise evidence pertaining to the efficacy, safety and tolerability of treatment options used in patients with AdvSM.

In summary, 72 publications were identified, which included 30 unique studies. From these, 3 studies are considered most relevant to include for this submission to inform the comparative analysis of avapritinib vs BAT. 2 studies (the EXPLORER (57) and PATHFINDER (20)) were most appropriate to describe the efficacy of avapritinib for AdvSM patients. For the BAT comparator, BLU-285-2405 was the most appropriate as it was designed as an external control, observational, retrospective study comparing the effect of avapritinib in patients treated in studies EXPLORER and PATHFINDER and real-world patients treated with BAT (3).

Table 11 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Reiter A, Schwaab J, DeAngelo DJ, Gotlib J, Deininger MW, Pettit KM, Alvarez-Twose I, Vannucchi AM, Panse J, Platzbecker U, Hermine O, Dybedal I, Lin HM, Rylova SN, Ehlert K, Dimitrijevic S, Radia DH. Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis. Blood Adv. 2022 Nov 8;6(21):5750-5762. doi: 10.1182/bloodadvances.2022007539 (3) DeAngelo DJ, Radia DH, George TI, Robinson WA, Quiery AT, Drummond MW, Bose P, Hexner EO, Winton EF, Horny HP, Tugnait M, Schmidt-Kittler O, Evans EK, Lin HM, Mar BG, Verstovsek S, Deininger MW, Gotlib J. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. Nat Med. 2021 Dec;27(12):2183-2191. doi: 10.1038/s41591-021-01538-9. Epub 2021 Dec 6. (57) (4) (6)	EXPLORER	NCT02561988	Start: 10/03/2016 Completion: 19/01/2023	Avapritinib for AdvSM
Gotlib J, Reiter A, Radia DH, Deininger MW, George TI, Panse J, Vannucchi AM, Platzbecker U, Alvarez-Twose I, Mital A, Hermine O, Dybedal I, Hexner EO, Hicks LK, Span L, Mesa R, Bose P, Pettit KM, Heaney ML, Oh ST, Sen J, Lin HM, Mar BG, DeAngelo DJ. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med. 2021 Dec;27(12):2192-2199. doi: 10.1038/s41591-021-01539-8. Epub 2021 Dec 6. (20) (4) (6)	PATHFINDER	NCT03580655	Start: 21/11/2018 Completion: Ongoing	Avapritinib for AdvSM

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Reiter A, Gotlib J, Álvarez-Twose I, Radia DH, Lübke J, Bobbili PJ, Wang A, Norregaard C, Dimitrijevic S, Sullivan E, Louie-Gao M, Schwaab J, Galinsky IA, Perkins C, Sperr WR, Sriskandarajah P, Chin A, Sendhil SR, Duh MS, Valent P, DeAngelo DJ. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. Leukemia. 2022 Aug;36(8):2108-2120. doi: 10.1038/s41375-022-01615-z. Epub 2022 Jul 5. PMID: 35790816; PMCID: PMC9343245. (3)	BLU-285-2405	-	Start: 26/03/2021 Completion: 04/10/2021	BAT for AdvSM

Abbreviations: AdvSM= advanced systemic mastocytosis, HSCT= hematopoietic stem cell transplantation, BAT= best available treatment

5.2 Literature used for the assessment of health-related quality of life

A utility SLR was conducted on 26 June 2023, the full details of which is provided in Appendix I. The SLR search aimed to address the following:

- To identify utility values associated with AdvSM.

In summary, 0 publications were identified from the utility SLR. However, as mentioned in Appendix H, the HRQoL from PATHFINDER was identified as part of the clinical SLR and is used in this submission for avapritinib to inform PF HSUV. In order to inform PD HSUVs as well as post-HSCT HSUVs, a TLR can be found in Appendix I.4 and I.6, respectively.

- Progressed disease: AML was considered the most appropriate proxy to inform the model, since it presents OS and clinical symptoms similar to AdvSM. As result, the papers from Stein, Joshi, Leunis and Mamolo et al. (11) (8) (9) (10). were defined as preferred studies and used to calculate the ratio between progression free and progressive disease utility values. Two papers were based on Time Trade-Off (TTO) and Discrete Choice (DC) experiments conducted on the general population. The two other papers were based on utility scores measured directly on real patients.
- Post-HSCT: Grulke et al. (7) is considered appropriate option to source the QoL during and after HSCT.

Table 12 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Mamolo CM, Cappelleri JC, Hoang CJ, et al. A real-world, cross-sectional, community survey of symptoms and health-related quality of life of adults with acute myeloid leukemia. Futur Oncol. 2019;15(16):1895-1909. doi:10.2217/fon-2018-0842 (10)	PD calculation. Freferred study and used to calculate the ratio between progression free and progressive disease utility values	Section 10, 10.2 and Appendix I

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Stein EM, Yang M, Guerin A, et al. Assessing utility values for treatment-related health states of acute myeloid leukemia in the United States. Health Qual Life Outcomes. 2018;16(1). doi:10.1186/s12955-018-1013-9 (11)	PD calculation. Freferred study and used to calculate the ratio between progression free and progressive disease utility values	Section 10, 10.2 and Appendix I
Joshi N, Hensen M, Patel S, Xu W, Lasch K, Stolk E. Health State Utilities for Acute Myeloid Leukaemia: A Time Trade-off Study. Pharmacoeconomics. 2019;37(1):85-92. doi:10.1007/s40273-018-0704-8 (8)	PD calculation. Freferred study and used to calculate the ratio between progression free and progressive disease utility values	Section 10, 10.2 and Appendix I
Leunis A, Redekop WK, Uyl-de Groot CA, Löwenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: A single-center study. Eur J Haematol. 2014;93(3):198-206. doi:10.1111/ejh.12324 (9)	PD calculation. Freferred study and used to calculate the ratio between progression free and progressive disease utility values	Section 10, 10.2 and Appendix I
Grulke N, Albani C, Bailer H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. Bone Marrow Transplant. 2012;47:473-482. doi:10.1038/bmt.2011.107 (7)	Post-HSCT HSUV. The data reported by Grulke et al. (7) were used as input in the mapping algorithm from Young et al. (58) to obtain the corresponding EQ-5D values.	Section 10, 10.2 and Appendix I

Abbreviations: PD= progressed disease, HSCT= hemapoietic stem cell transplantation, HSUV= health state utility value, EQ-5D=EuroQol-5 Dimension.

5.3 Literature used for inputs for the health economic model

At the time of writing this submission dossier, a SLR on health economic models was not conducted in time to accommodate the new DMC submission template. Previous assumptions that have been used in past submission dossiers were still deemed relevant for this dossier and are listed in the table below. Furthermore, a TLR was conducted to define HSCT efficacy in AdvSM patients. The paper of Ustun et al. was identified as the main source of information about the outcomes of HSCT in AdvSM patients. See Table 13 below.

Table 13 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
NICE Single Technology Appraisal. Midostaurin for treating advanced systemic mastocytosis [ID1573]. Novartis Pharmaceuticals UK Ltd. March 2020 (51) Wiernik PH, Banks PLC, Case DC, Arlin ZA, Periman P 0, Todd MB, et al. Cytarabine Plus Idarubicin or Daunorubicin as Induction and Consolidation Therapy for Previously Untreated Adult Patients With Acute	Administration costs	Selected based on previous HTA submissions	Section 11.3

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Myeloid Leukemia [Internet]. Vol. 79, Blood. 1992. Available from: http://ashpublications.org/blood/article-pdf/79/2/313/606083/313.pdf (59) Meloni G, Concetta Petti Istituto Regina Elena -Istituti Fisioterapici Ospitalieri M. Mitoxantrone, etoposide, and intermediate-dose cytarabine: An effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. Artic J Clin Oncol. Published online 1991. Doi:10.1200/JCO.1991.9.7.1210 (60) Röllig C, Kramer M, Gabrecht M, et al. Intermediate-dose cytarabine plus mitoxantrone versus standard-dose cytarabine plus daunorubicin for acute myeloid leukemia in elderly patients. Ann Oncol. 2018;29(4):973-978. Doi:10.1093/annonc/mdy030 (61)			
NICE Single Technology Appraisal. Midostaurin for treating advanced systemic mastocytosis [ID1573]. Novartis Pharmaceuticals UK Ltd. March 2020 (51)	Distribution of BAT	Selected based on previous HTA submissions	Section 11.1
NICE Single Technology Appraisal. Midostaurin for treating advanced systemic mastocytosis [ID1573]. Novartis Pharmaceuticals UK Ltd. March 2020 (51) Wiernik PH, Banks PLC, Case DC, Arlin ZA, Periman P 0, Todd MB, et al. Cytarabine Plus Idarubicin or Daunorubicin as Induction and Consolidation Therapy for Previously Untreated Adult Patients With Acute Myeloid Leukemia [Internet]. Vol. 79, Blood. 1992. Available from: http://ashpublications.org/blood/article-pdf/79/2/313/606083/313.pdf (59) Meloni G, Concetta Petti Istituto Regina Elena -Istituti Fisioterapici Ospitalieri M. Mitoxantrone, etoposide, and intermediate-dose cytarabine: An effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. Artic J Clin Oncol [Internet]. 1991 [cited 2021 Jun 3]; Available from: https://www.researchgate.net/publication/21109875 (60) Röllig C, Kramer M, Gabrecht M, Hänel M, Herbst R, Kaiser U, et al. Intermediate-dose cytarabine plus mitoxantrone versus standard-dose cytarabine plus daunorubicin for acute myeloid leukemia in elderly patients. Ann Oncol [Internet]. 2018 Apr 1 [cited 2021 Jun 3];29(4):973–8. Available from: https://pubmed.ncbi.nlm.nih.gov/29390048/ (61) Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood [Internet]. 2015 Jul 16 [cited 2021 Jun 3];126(3):291–9. Available from: http://ashpublications.org/blood/article-pdf/126/3/291/1390433/291.pdf (62)	Dosing regimen for BAT treatments	Selected based on previous HTA submissions	Section 11.1

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Verstovsek S et al. Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. Clinical Cancer Research : an Official Journal of the American Association for Cancer Research. 2008 Jun;14(12):3906-3915. DOI: 10.1158/1078-0432.ccr-08-0366. (63) Hochhaus A et al. Nilotinib in patients with systemic mastocytosis: analysis of the phase 2, open-label, single-arm nilotinib registration study. J Cancer Res Clin Oncol. 2015 Nov;141(11):2047-60. Doi: 10.1007/s00432-015-1988-0. Epub 2015 May 23. PMID: 26002753; PMCID: PMC4768228. (64) Barete S, Lortholary O, Damaj G, Hirsch I, Chandesris MO, Elie C, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood. 2015 Aug 20;126(8):1009–16. (65)			
National Institute for Health and Care Excellence. Midostaurin for untreated acute myeloid leukaemia [TA523]. https://www.nice.org.uk/guidance/ta523/documents/committee-papers-2National Institute for Health and Care Excellence. Midostaurin for untreated acute myeloid leukaemia [TA523]. https://www.nice.org.uk/guidance/ta523/documents/committee-papers-2 (66)	HSCT costs (medical oncologist follow-up costs)	Selected based on previous HTA submissions	Section 11.6
Ustun C, Reiter A, Scott BL, et al. Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. J Clin Oncol. Published online 2014. doi:10.1200/JCO.2014.55.2018 (58)	HSCT efficacy in AdvSM patients	TLR	Section 8.1

Abbreviations: HTA= health technology assessment, BAT= best available treatment, HSCT= hemapoietic stem cell transplantation

6. Efficacy

6.1 Efficacy of avapritinib compared to BAT for ASM, SM-AHN or MCL, after at least one systemic therapy

6.1.1 Relevant studies

The EXPLORER (BLU-285-2101, NCT02561988) and PATHFINDER (BLU-285-2202, NCT03580655) studies describe the efficacy of avapritinib in AdvSM patients and are described in Table 15.

Table 14 Relevant studies included

Reference	Trial name	NCT identifier	Dates of study	Used in comparison of
Reiter A, Schwaab J, DeAngelo DJ, Gotlib J, Deininger MW, Pettit KM, Alvarez-Twose I, Vannucchi AM, Panse J, Platzbecker U, Hermine O, Dybedal I, Lin HM, Rylova SN, Ehlert K, Dimitrijevic S, Radia DH. Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis. Blood Adv. 2022 Nov 8;6(21):5750-5762. Doi: 10.1182/bloodadvances.2022007539 DeAngelo DJ, Radia DH, George TI, Robinson WA, 32eutr AT, Drummond MW, Bose P, Hexner EO, Winton EF, Horny HP, Tugnait M, Schmidt-Kittler O, Evans EK, Lin HM, Mar BG, Verstovsek S, Deininger MW, Gotlib J. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. Nat Med. 2021 Dec;27(12):2183-2191. Doi: 10.1038/s41591-021-01538-9. Epub 2021 Dec 6.	EXPLORER	NCT02561988	Start: 10/03/2016 Completion: 19/01/2023	Avapritinib for AdvSM
Gotlib J, Reiter A, Radia DH, Deininger MW, George TI, Panse J, Vannucchi AM, Platzbecker U, Alvarez-Twose I, Mital A, Hermine O, Dybedal I, Hexner EO, Hicks LK, Span L, Mesa R, Bose P, Pettit KM, Heaney ML, Oh ST, Sen J, Lin HM, Mar BG, DeAngelo DJ. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med. 2021 Dec;27(12):2192-2199. Doi: 10.1038/s41591-021-01539-8. Epub 2021 Dec 6.	PATHFINDER	NCT03580655	Start: 21/11/2018 Completion: Ongoing	Avapritinib for AdvSM
Reiter A, Gotlib J, Álvarez-Twose I, Radia DH, Lübke J, Bobbili PJ, Wang A, Norregaard C, Dimitrijevic S, Sullivan E, Louie-Gao M, Schwaab J, Galinsky IA, Perkins C, Sperr WR, Sriskandarajah P, Chin A, Sendhil SR, Duh MS, Valent P, DeAngelo DJ. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. Leukemia. 2022 Aug;36(8):2108-2120. Doi: 10.1038/s41375-022-01615-z. Epub 2022 Jul 5. PMID: 35790816; PMCID: PMC9343245.	BLU-285-2405	-	Start: 26/03/2021 Completion: 04/10/2021	BAT for AdvSM

Table 15 Overview of study design for studies included in the comparison

Trial name, NCT-number	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
EXPLORER NCT02561988 (57)	EXPLORER was a Phase 1, open-label, single-arm, multicentre, dose escalation and dose expansion clinical study.	7 years	AdvSM patients diagnosed with either ASM, SM-AHN or MCL	In Part 1, patients received oral avapritinib of 30, 60, 100, 130, 200, 300, and 400 mg QD. Part 2 was initiated at the RP2D of 300 mg QD, however the dose was reduced to 200 mg QD. Avapritinib was dosed daily for 28-day cycles.	N/A	Primary outcome measures: 1. Maximum tolerated dose (MTD) of avapritinib 2. Number of patients with adverse and serious adverse events and changes in physical findings, vital signs, clinical laboratory results and ECG findings 3. Recommended Phase 2 dose (RP2D) of avapritinib Secondary outcome measures: 1. Maximum plasma concentration of avapritinib. Blood samples may be taken at pre-dose, and 0.5, 1, 2, 4, 8 and 24 hrs post dose (plus 10 and 48 hrs post dose in Part 2) on Cycle 1 Day 1 and Cycle 1 Day 15, Pre-dose of Cycle 2 to 4, Day 1 2. Time to maximum plasma concentration of avapritinib. Blood samples may be taken at pre-dose, and 0.5, 1, 2, 4, 8 and 24 hrs post dose (plus 10 and 48 hrs post dose in Part 2) on Cycle 1 Day 1 and Cycle 1 Day 15, Pre-dose of Cycle 2 to 4, Day 1 3. Overall Response Rate. Including complete remission (CR), CR with partial recovery of peripheral blood (CRh), partial remission (PR) and clinical improvement (CI) using modified International Working Group Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European competence network on mastocytosis (ECNM) criteria; and duration of response (DOR) 4. Morphologic response. Including morphologic complete remission (mCR), morphologic CR with partial recovery of peripheral blood (mCRh), and morphologic partial remission (mPR) based on Pure Pathologic Response 5. Changes in levels of serum tryptase and levels of V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) D816V allele burden in blood 6. Changes in patient reported symptoms and quality of life using the Patient Global Impression of Symptom Severity (PGIS) scale 7. Changes in patient reported quality of life using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C-30) 8. Changes in patient reported outcomes using the advanced SM symptom assessment form (AdvSM-SAF) 9. Change in liver volume by imaging 10. Change in spleen volume by imaging

Trial name, NCT-number	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
PATHFINDER NCT03580655 (20)	PATHFINDER is an open-label, Phase 2, single-arm, multicentre clinical study.	Ongoing	AdvSM patients diagnosed with either ASM, SM-AHN or MCL	Avapritinib was administered orally, in either 200 mg or 300 mg daily at 28-day cycles	N/A	Primary outcome measures: 1. Objective response rate (ORR) based on modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) response criteria Secondary outcome measures: 1. Mean Change from Baseline in Advanced Systemic Mastocytosis-Symptom Assessment Form (AdvSM-SAF) Total Symptom Score. 0 – 80 points (higher value represents worse symptom outcomes) 2. Objective response rate. Including morphologic complete remission (mCR), morphologic CR with partial recovery of peripheral blood (mCRh), and morphologic partial remission (mPR) based on Pure Pathologic Response 3. Time-to-response (TTR) 4. Duration of Response (DOR) [Tim 5. Progression-free Survival (PFS) 6. Overall Survival (OS) 7. Changes in bone marrow mast cells 8. Change in serum tryptase 9. Change in V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog aspartate 816 valine (KIT D816V) mutation burden 10. Change in liver volume by imaging 11. Change in spleen volume by imaging 12. Clinical benefit based on modified IWG-MRT-ECNM consensus criteria 13. Change in PGIS 14. Change in EORTC QLQ-C30 15. Safety of Avapritinib as assessed by incidence of adverse events 16. Area Under Curve (0 to Tau) for Avapritinib

6.1.2 Comparability of studies

6.1.2.1 Comparability of patients across studies

Table 16 presents the baseline characteristics (both unweighted and weighted) with key confounding factors between the avapritinib and BAT arms. Baseline characteristics were compared using the standard differences (3). Refer to section 7 for further details.

Table 16 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

Baseline characteristicsa	Unweighted sample			IPTW-Weighted sampleb		
	Avapritinib[c]	BAT[c]	Standardized Difference[d]	Avapritinib[c]	BAT[c]	Standardized Difference[d]
Number of unique patients	**N = 176**	**N = 141**		**Effective (N = 172)**	**Effective (N = 134)**	
Number of lines of therapy	**N = 176**	**N = 222**		**Effective (N = 172)**	**Effective (N = 210)**	
Demographic characteristics						
Age (years)[e]			6.5%			9.2%
Mean (SD)	66.3 (10.7)	65.5 (11.8)		66.4 (10.5)	65.3 (12.4)	
Median (min, max)	68.0 (31.0, 88.0)	67.8 (20.9, 87.5)		68.0 (31.0, 88.0)	67.9 (20.9, 87.5)	
Sex, n (%)			15.0%*			5.3%
Female	73 (41.5%)	76 (34.2%)		40.0%	37.4%	
Male	103 (58.5%)	146 (65.8%)		60.0%	62.6%	
Region, n (%)			98.7%*			12.3%*
North America	102 (58.0%)	34 (15.3%)		34.4%	28.6%	
Europe	74 (42.0%)	188 (84.7%)		65.6%	71.4%	

Medical history						
Performance status						
ECOG[f]						
n (%)	176 (100.0%)	222 (100.0%)		100.0%	100.0%	
Mean (SD)	1.2 (0.8)	1.0 (0.7)		1.2 (0.8)	1.1 (0.7)	
Median (min, max)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)		1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	
ECOG category, n (%)						
0	36 (20.5%)	50 (22.5%)	5.0%	16.3%	19.2%	7.4%
1	92 (52.3%)	129 (58.1%)	11.8%*	59.0%	56.2%	5.8%
≥2	48 (27.3%)	43 (19.4%)	18.8%*	24.6%	24.7%	0.1%
Anemia,[g] n (%)	104 (59.1%)	125 (56.3%)	5.6%	55.4%	57.8%	5.0%
Thrombocytopenia,[h] n (%)	67 (38.1%)	120 (54.1%)	32.5%*	38.9%	43.9%	10.2%*
Disease characteristics						
AdvSM subtype diagnosis,[i] n (%)						
SM-AHN	119 (67.6%)	121 (54.5%)	27.1%*	58.4%	58.2%	0.5%
ASM	29 (16.5%)	68 (30.6%)	33.8%*	26.5%	25.2%	3.0%
MCL	28 (15.9%)	33 (14.9%)	2.9%	15.1%	16.6%	4.3%
Skin involvement						
Any skin involvement, n (%)	58 (33.0%)	71 (32.0%)	2.1%	30.3%	32.5%	4.8%
Leukocyte count						

≥16 × 10^9/L, n (%)	33 (18.8%)	54 (24.3%)	13.6%*	18.5%	19.8%	3.3%
Serum tryptase[j] (ng/mL)						
≥125 ng/mL, n (%)	132 (75.0%)	144 (64.9%)	22.2%*	72.5%	71.0%	3.2%
***SRSF2/ASXL1/RUNX1* (S/A/R) mutation panel**						
Number that were tested for at least one mutation, n (%)	176 (100.0%)	169 (76.1%)		100.0%	70.8%	
Number of mutated genes within S/A/R panel, n (%)						
0	92 (52.3%)	66 (29.7%)		55.3%	26.7%	
1	54 (30.7%)	68 (30.6%)	0.1%	28.7%	30.1%	3.1%
≥2	30 (17.0%)	35 (15.8%)	3.5%	16.0%	13.9%	5.8%
Prior therapy						
Prior systemic therapy						
Patients with prior systemic therapy, n (%)	110 (62.5%)	104 (46.8%)		52.8%	49.6%	
Number of prior lines of systemic therapy received, n (%)						
Mean (SD)	1.0 (1.1)	0.1 (0.3)		0.8 (1.0)	0.1 (0.3)	
Median (min, max)	1.0 (0.0, 6.0)	0.0 (0.0, 2.0)		1.0 (0.0, 6.0)	0.0 (0.0, 2.0)	
0	66 (37.5%)	118 (53.2%)	31.8%*	47.2%	50.4%	6.4%
1	68 (38.6%)	69 (31.1%)	15.9%*	33.1%	32.4%	1.5%
2	28 (15.9%)	24 (10.8%)	15.0%*	14.6%	12.6%	5.6%

≥3	14 (8.0%)	11 (5.0%)	12.2%*	5.1%	4.6%	2.7%
Prior treatments received, n (%)						
TKI therapy	92 (52.3%)	50 (22.5%)	64.6%*	37.1%	29.9%	15.2%*
Cytoreductive therapy	33 (18.8%)	61 (27.5%)	20.8%*	20.1%	22.1%	4.8%
Biologic or other systemic therapy[k]	23 (13.1%)	30 (13.5%)	1.3%	14.9%	15.2%	0.7%
Agent-level information available[l]	**N = 176**	**N = 196**		**Effective (N = 172)**	**Effective (N = 193)**	
TKI						
Midostaurin	81 (46.0%)	32 (16.3%)		33.7%	21.9%	
Dasatinib	6 (3.4%)	7 (3.6%)		1.9%	3.6%	
Ibrutinib	2 (1.1%)	0 (0.0%)		0.5%	0.0%	
Imatinib	10 (5.7%)	10 (5.1%)		3.2%	7.2%	
Nilotinib	2 (1.1%)	0 (0.0%)		0.8%	0.0%	
Ripretinib	5 (2.8%)	1 (0.5%)		1.6%	0.4%	
Ruxolitinib	2 (1.1%)	0 (0.0%)		0.6%	0.0%	
Cytoreductive therapy						
Cladribine	22 (12.5%)	34 (17.3%)		15.6%	13.6%	
Azacitidine	5 (2.8%)	2 (1.0%)		1.9%	0.9%	
Decitabine	2 (1.1%)	2 (1.0%)		0.7%	1.7%	
Chlorambucil	1 (0.6%)	0 (0.0%)		0.3%	0.0%	
Hydroxyurea	9 (5.1%)	17 (8.7%)		3.7%	7.0%	

Biologic				
Brentuximab vedotin	3 (1.7%)	2 (1.0%)	1.2%	3.1%
Obinituzumab	1 (0.6%)	0 (0.0%)	0.3%	0.0%
Rituximab	1 (0.6%)	0 (0.0%)	0.3%	0.0%
Interferon-alfa	14 (8.0%)	20 (10.2%)	11.1%	9.1%
Pegylated interferon	3 (1.7%)	8 (4.1%)	2.7%	4.3%

Abbreviations: AdvSM: advanced systemic mastocytosis; ASM: aggressive systemic mastocytosis; BAT: best available therapy; ECOG: Eastern Cooperative Oncology Group; IPTW: inverse probability of treatment weighting; max: maximum; MCL: mast cell leukaemia; min: minimum; S/A/R: SRSF2/ASXL1/RUNX1; SD: standard deviation; SM-AHN: systemic mastocytosis with an associated hematologic neoplasm; TKI: tyrosine kinase inhibitor. Notes:*Standardized difference greater than 10%.

a The baseline period was defined as 8 weeks leading up to the index date for the avapritinib cohort and the 12 weeks leading up to the index date for the BAT cohort.

b Stabilized IPTW weights accounted for age, sex, region, ECOG score, anemia (hemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100 x 109/L), AdvSM subtype, skin involvement, leukocyte count of 16 × 109 per L or higher, serum tryptase level of 125 ng/mL or higher, number of mutated genes within the SRSF2/ASXL1/RUNX1 gene panel, number of prior lines of therapy, and types of prior therapy. To reduce variability, stabilized weights were capped at the 1st and 99th percentiles.

c The trial and real-world samples were restricted to patients with available ECOG score during any time before to 3 months after the index date.

d For continuous variables, the standardized difference was calculated by dividing the absolute difference in means of avapritinib cohort vs. BAT cohort by the pooled standard deviation of both cohorts. The pooled standard deviation was the square root of the average of the squared standard deviations. For categorical variables with 2 levels, the standardized difference was calculated using the following equation where P1 was the respective proportion of avapritinib cohort, and P2 was the respective proportion of BAT cohort: $|P1-P2|/\sqrt{p(1-p)}$, where $p = (P1+P2)/2$. For each variable, a standardized difference greater than 10% was indicative of meaningful imbalance between the two cohorts, per Austin and Stuart (2015),33 and were denoted with "*".

e Only the year of birth was collected for the BAT cohort. Patients' age was calculated using the mid-point of the birth year as approximate dates of birth.

f For the BAT cohort, ECOG and Karnofsky scores assessed during 12 months before to 3 months after the index date were considered. For the lines of therapy for which patients had no ECOG score on record during this period (N = 9 lines of therapy), the Karnofsky score closest to the index date in the same period was converted to an ECOG score. The conversion was performed according to Oken et al.36

g For both the avapritinib cohort and the BAT cohort, anemia included reported anemia and hemoglobin less than 10 g/dL.

h For both the avapritinib cohort and the BAT cohort, thrombocytopenia included reported thrombocytopenia and platelet count less than 100 x 109/L.

i The AdvSM subtype was assessed at the last diagnosis evaluation prior to or on the index date.

j Observations with missing serum tryptase level were imputed as not having serum tryptase level greater than or equal to 125 ng/mL.

k Other systemic therapy included steroids and thalidomide or derivatives.

l Agent-level information for prior treatments was reported among patients from all study sites except Medical University of Vienna (Austria) (N=26 lines of therapy), where only treatment class information was collected per local regulations.

Source: Reiter et al., 2022 (3)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Due to the orphan nature of the disease, very little is known about the patient characteristics in Danish clinical practice. We have assumed the Danish patients are similar to those seen in the EXPLORER and PATHFINDER studies.

Table 17 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	66.32	66.32
Males	70%	70%

6.1.4 Efficacy – EXPLORER (BLU-285-2101, NCT02561988)

Evidence for the key outcomes from the EXPLORER study in AdvSM patients are presented in the sections below. The Response Adjudication Committee Response-Evaluable (RAC-RE) population was the primary efficacy population for efficacy analyses which included the enrolled safety population by central diagnosis and were evaluable by the mIWG-MRT-ECNM criteria (6). The RAC-RE population presented below are patients who received 200 mg daily of avapritinib with prior systematic therapy, as per the Market Authorisation Application to the EMA.

The primary data source for the EXPLORER study that are presented in this submission are:

- The clinical study report (CSR), with the most recent efficacy and safety data cut off (DCO) from April 2021 (median follow-up of 26.0 months for the RAC-RE population who received 200 mg of avapritinib with prior systematic therapy) (6).

6.1.4.1 Overall response rate

ORR was the secondary efficacy endpoint for the EXPLORER study (6). The ORR efficacy results are based on the April 2021 DCO. Table 18 presents the response rates from the EXPLORER study. The ORR (CR + CRh + PR + CI) of 72.7% is significantly higher than the prespecified null hypothesis of 28% ($p < 0.0001$, Wald test). Responses occurred in all subtypes of AdvSM.

Table 18 Summary of centrally adjudicated overall response rates of AdvSM patients; EXPLORER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Parameters	ASM N = 1	SM-AHN N = 6	MCL N = 4	All AdvSM N = 11
ORR (CR + CRh + PR + CI), n (%, 95% CI)	1 (100, 2.5-100)	4 (66.7, 22.3-95.7)	3 (75.0, 19.4-99.4)	8 (72.7, 39.0-94.0)
CR + CRh + PR, n (%, 95% CI)	1 (100, 2.5-100)	4 (66.7, 22.3-95.7)	3 (75.0, 19.4-99.4)	8 (72.7, 39.0-94.0)
CR + CRh, n (%, 95% CI)	1 (100, 2.5-100)	2 (33.3, 4.3-77.7)	0	3 (27.3, 6.0-61.0)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; MCL = mast cell leukaemia; ORR = overall response rate; PR = partial remission; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: EXPLORER CSR; Table 9 (6)

6.1.4.2 Duration of response

The latest DOR results are based on the April 2021 DCO. The median DOR was not reached for the RAC-RE AdvSM population who received 200 mg of avapritinib with prior

systematic therapy (6). Table 19 provides an overview of the results from the EXPLORER study.

Table 19 Summary of centrally adjudicated duration of response of AdvSM patients; EXPLORER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Parameters	ASM N = 1	SM-AHN N = 6	MCL N = 4	All AdvSM N = 11
DOR, median months (95% CI)	N = 1 NE (NE, NE)	N = 4 NE (11.2, NE)	N = 3 NE (NE, NE)	N = 8 NE (NE, NE)
Censored, n (%)	1 (100)	3 (75)	4 (100)	7 (87.5)
Kaplan-Meier estimates				
• 12 months (%)	-	75.0	100.0	83.3
• 24 months (%)	-	-	100	83.3
Duration of CR + CRh + PR, median months (95% CI)	N = 1 NE (NE, NE)	N = NR NE (11.2, NE)	N = 3 NE (21.6, NE)	N = 8 NE (NE, NE)
Kaplan-Meier estimates				
• 12 months (%)	-	75.0	100.0	83.3
• 24 months (%)	-	-	100.0	83.3

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; DOR = duration of response; MCL = mast cell leukaemia; NE = not evaluable; NR = not reported PR = partial remission; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: EXPLORER CSR; Table 9 (6)

6.1.4.3 Time to response

The time to response results is based on the April 2021 DCO. Table 20 provides an overview of the results from the EXPLORER study. Figure 2 presents the Kaplan Meier curve for time to response.

Table 20 Summary of centrally adjudicated time to response of AdvSM patients; EXPLORER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Parameters	ASM N = 1	SM-AHN N = 6	MCL N = 4	All AdvSM N = 11
Time to response (CR + CRh + PR + CI), median months (range)	N = 1 9.30 (9.3-9.3)	N = 4 2.32 (0.3-26.7)	N = 3 9.46 (1.6-9.5)	N = 8 6.05 (0.3-26.7)
Time to CR + CRh + PR, median months (range)	N = 1 9.30 (9.3, 9.3)	N = 4 4.19 (1.8, 26.7)	N = 3 9.46 (1.6, 9.5)	N = 8 7.44 (1.6, 26.7)
Time to CR + CRh, median months (range)	N = 1 9.30 (9.3, 9.3)	N = 2 20.73 (9.2, 32.2)	-	N = 3 9.30 (9.2, 32.2)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; MCL = mast cell leukaemia; PR = partial remission; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: EXPLORER CSR; Table 9 (6)

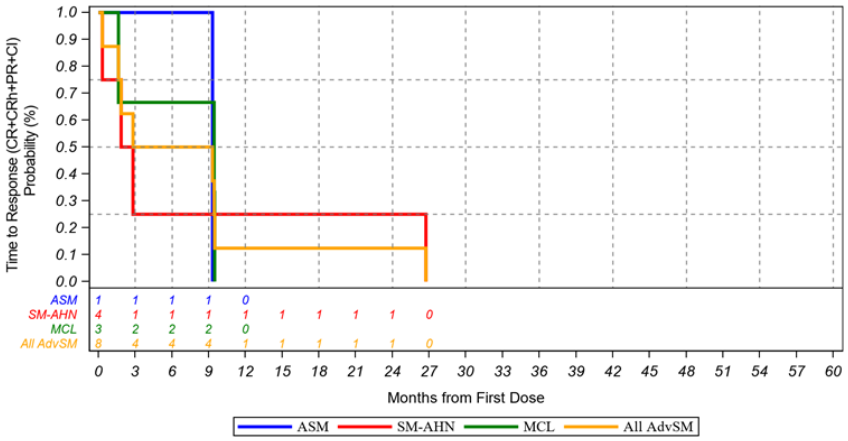

Figure 2 Time to response KM curve of centrally adjudicated time to response of AdvSM patients; EXPLORER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; MCL = mast cell leukaemia; PR = partial remission; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: EXPLORER CSR; Figure 35.2.2.6 (6)

6.1.4.4 Overall survival

OS was an explorative endpoint for the EXPLORER study (6). The OS efficacy results are based on the April 2021 DCO. The median OS was not reached for the RAC-RE AdvSM population who received 200 mg of avapritinib with prior systematic therapy (6). Table 21 provides an overview of the results from the EXPLORER study.

Table 21 Summary of centrally adjudicated overall survival of AdvSM patients; EXPLORER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Kaplan-Meier estimates	ASM N = 1	SM-AHN N = 6	MCL N = 4	All AdvSM N = 11
OS median, months (95% CI)	NE (NE, NE)	NE (8.0, NE)	NE (NE, NE)	NE (13.0, NE)
Kaplan-Meier estimates				
• 12 months (%)	100	66.7	100	81.8
• 24 months (%)	-	50.0	100	71.6

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; MCL = mast cell leukaemia; OS = overall survival; NE = not evaluable; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: EXPLORER CSR; Table 9 (6)

6.1.4.5 Progression-free survival

PFS was an explorative endpoint for the EXPLORER study (6). The PFS efficacy results are based on the April 2021 DCO. The median PFS was not reached for the RAC-RE AdvSM population who received 200 mg of avapritinib with prior systematic therapy (6). Table 22 provides an overview of the results from the EXPLORER study.

Table 22 Summary of centrally adjudicated progression-free survival of AdvSM patients; EXPLORER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Kaplan-Meier estimates	ASM N = 1	SM-AHN N = 6	MCL N = 4	All AdvSM N = 11
PFS median, months (95% CI)	NE (NE, NE)	NE (8.0, NE)	NE (NE, NE)	NE (13.0, NE)
Kaplan-Meier estimates				
• 12 months (%)	100	66.7	100	81.8

• 24 months (%)	-	50.0	100	71.6

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; MCL = mast cell leukaemia; NE = not evaluable; PFS = progression-free survival; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: EXPLORER CSR; Table 9 (6)

6.1.5 Efficacy – PATHFINDER (BLU-285-2202, NCT03580655)

Evidence for the key outcomes from the PATHFINDER study in AdvSM patients are presented in the sections below. The RAC-RE population was the primary efficacy population for efficacy analyses which included the enrolled safety population by central diagnosis and were evaluable by the mIWG-MRT-ECNM criteria (6). The RAC-RE population presented below are patients who received 200 mg daily of avapritinib with prior systematic therapy, as per the Market Authorisation Application to the EMA.

The primary data source for the PATHFINDER study that are presented in this submission are:

- The CSR, with the most recent efficacy and safety DCO from April 2021 (median follow-up of 14.6 months for the RAC-RE population who received 200 mg of avapritinib with prior systematic therapy) (6).

6.1.5.1 Overall response rate

ORR was the primary efficacy endpoint for the PATHFINDER study (6). The ORR efficacy results are based on the April 2021 DCO. Table 23 presents the response rates from the PATHFINDER study. Responses occurred in all subtypes of AdvSM, with an ORR (CR + CRh + PR + CI) across subtypes of 59.6%, significantly higher than the pre-specified null hypothesis of 28% ($p < 0.0001$, Wald test). The CR + CRh + PR rate was 51.1% and also statistically significant compared to the pre-specified null hypothesis of 17% ($p < 0.0001$, Wald test). Based on the deepening of responses in the BLU-285-2101 more CRs or CRhs are expected to develop with longer duration of therapy.

Table 23 Summary of centrally adjudicated overall response rates of AdvSM patients; PATHFINDER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Parameters	ASM N = 8	SM-AHN N = 29	MCL N = 10	All AdvSM N = 47
ORR (CR + CRh + PR + CI), n (%)	5 (62.5)	19 (65.5)	4 (40.0)	28 (59.6)
95% CI	(24.5, 91.5)	(45.7, 82.1)	(12.2, 73.8)	(44.3, 73.6)
CR + CRh + PR, n (%)	5 (62.5)	16 (55.2)	3 (30.0)	24 (51.1)
95% CI	(24.5, 91.5)	(35.7, 73.6)	(6.7, 65.2)	(34.4, 63.7)
CR + CRh, n (%)	2 (25.0)	3 (10.3)	0	5 (10.6)
95% CI	(3.2, 65.1)	(2.2, 27.4)	-	(3.5, 23.1)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; MCL = mast cell leukemia; NE = not evaluable; ORR = overall response rate; PR = partial remission; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: PATHFINDER CSR; Table 19 (6)

6.1.5.2 Duration of response

The latest DOR results are based on the April 2021 DCO. The median DOR was not reached for the RAC-RE AdvSM population who received 200 mg of avapritinib with prior systematic therapy (6). Table 24 provides an overview of the results from the PATHFINDER study

Table 24 Summary of centrally adjudicated duration of response of AdvSM patients; PATHFINDER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Parameters	ASM N = 5	SM-AHN N = 19	MCL N = 4	All AdvSM N = 28
DOR, median months (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Censored, n (%)	5 (100)	17 (89.5)	4 (100)	26 (92.9)
Kaplan-Meier estimates				
• 12 months, % (95% CI)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
• 24 months, % (95% CI)	NA	83.3 (62.2, 100.0)	NA	85.6 (66.9, 100.0)
Duration of CR + CRh + PR, median months (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimates				
• 12 months, % (95% CI)	100.0 (100.0, 100.0)	90.0 (71.4, 100.0)	100.0 (100.0, 100.0)	92.3 (77.8, 100.0
• 24 months, % (95% CI)	NA	90.0 (71.4, 100.0)	NA	92.3 (77.8, 100.0

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; DOR = duration of response; MCL = mast cell leukaemia; NE = not evaluable; PR = partial remission; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: PATHFINDER CSR; Table 21 (6)

6.1.5.3 Time to response

The time to response results is based on the April 2021 DCO. Table 25 provides an overview of the results from the PATHFINDER study. Figure 3 presents the Kaplan Meier curve for time to response.

Table 25 Summary of centrally adjudicated time to response of AdvSM patients; PATHFINDER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

	ASM N = 5	SM-AHN N = 19	MCL N = 4	All AdvSM N = 28
Time to response (CR + CRh + PR + CI), median months (range)	2.30 (1.8, 5.5)	1.94 (0.5, 5.5)	3.60 (1.7, 12.2)	1.94 (0.5, 12.2)
Time to CR + CRh + PR, median months (range)	2.30 (1.8, 5.5)	3.19 (1.7, 14.8)	5.59 (1.7, 12.2)	3.19 (1.7, 14.8)
Time to CR + CRh, median months (range)	2.76 (1.8, 3.7)	5.59 (1.8, 14.8)	-	3.71 (1.8, 14.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; MCL = mast cell leukaemia; PR = partial remission; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: PATHFINDER CSR; Table 21 (6)

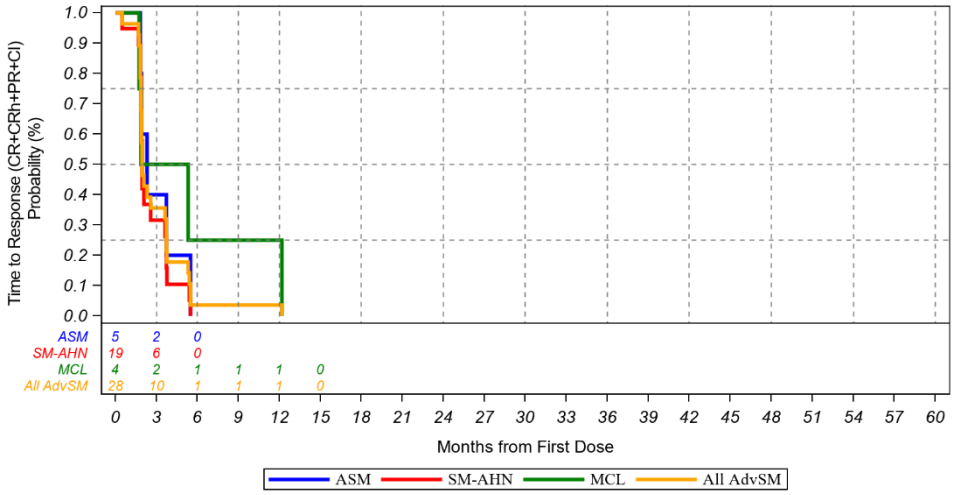

Figure 3 Time to response KM curve of centrally adjudicated time to response of AdvSM patients; PATHFINDER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; MCL = mast cell leukaemia; PR = partial remission; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: PATHFINDER CSR; Figure 35.2.2.6 (6)

6.1.5.4 Overall survival

OS was a secondary endpoint for the PATHFINDER study (6). The OS efficacy results are based on the April 2021 DCO. The median OS was not reached for the RAC-RE AdvSM population who received 200 mg of avapritinib with prior systematic therapy (6). Table 26 provides an overview of the results from the PATHFINDER study.

Table 26 Summary of centrally adjudicated overall survival of AdvSM patients; PATHFINDER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Kaplan-Meier estimates	ASM N = 8	SM-AHN N = 29	MCL N = 10	All AdvSM N = 47
Events	0	8 (27.6)	3 (30.0)	11 (23.4)
Censors	8 (100.0)	21 (72.4)	7 (70.0)	36 (76.6)
Median follow-up, months (95% CI)	8.6 (7.3, 16.9)	17.8 (13.2, 20.7)	14.6 (11.1, 17.0)	14.6 (11.2, 17.8)
OS median, months (95% CI)	NE (NE, NE)	NE (17.5, NE)	NE (13.5, NE)	NE (17.5, NE)
Kaplan-Meier estimates				
• 12 months,% (95% CI)	100.0 (100.0, 100.0)	79.0 (64.0, 94.0)	80.0 (55.2, 100.0)	82.7 (71.8, 93.6)
• 24 months,% (95% CI)	-	65.8 (45.0, 86.6)	66.7 (35.1, 98.2)	67.8 (49.8, 85.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; MCL = mast cell leukaemia; OS = overall survival; NE = not evaluable; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: PATHFINDER CSR; Table 22 (6)

6.1.5.5 Progression-free survival

PFS was a secondary endpoint for the PATHFINDER study (6). The PFS efficacy results are based on the April 2021 DCO. The median PFS was not reached for the RAC-RE AdvSM population who received 200 mg of avapritinib with prior systematic therapy (6). Table 27 provides an overview of the results from the PATHFINDER study.

Table 27 Summary of centrally adjudicated progression-free survival of AdvSM patients; EXPLORER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Kaplan-Meier estimates	ASM N = 8	SM-AHN N = 29	MCL N = 10	All AdvSM N = 47
Events	0	9 (31.0)	3 (30.0)	12 (25.5)
Censors	8 (100)	20 (69.0)	7 (70.0)	35 (74.5)
Median, months (95% CI)	NE (NE, NE)	NE (17.4, NE)	NE (10.5, NE)	NE (17.5, NE)
Kaplan-Meier estimates				
• 12 months,% (95% CI)	100.0 (100.0, 100.0)	75.2 (59.3, 91.2)	68.6 (38.9, 98.3)	77.5 (65.0, 89.9)
• 24 months,% (95% CI)	-	61.6 (40.0, 83.1)	68.6 (38.9, 98.3)	65.5 (47.1, 84.0)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; MCL = mast cell leukaemia; NE = not evaluable; PFS = progression-free survival; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm. Source: PATHFINDER CSR; Table 23 (6)

7. Comparative analyses of efficacy

To inform the comparative analyses between avapritinib and BAT for AdvSM patients, an indirect comparison using inverse probability weighting (IPW) was done between the pooled AdvSM populations from the EXPLORER and PATHFINDER studies and BLU-285-2405 (3). Patients in BLU-285-2405 received BAT, which primarily consisted cytoreductive, biologic therapies and TKI therapies (3). The indirect comparison included the safety population who received all doses of avapritinib (N = 176) from the EXPLORER and PATHFINDER studies (3). The outcome described are OS based on the April 2021 DCO as described above. The efficacy outcome is also used in the health economic model.

7.1.1 Differences in definitions of outcomes between studies

The primary endpoint was OS, defined for the BAT cohort as the time interval between initiation of each line of therapy and death due to any cause, and for the avapritinib cohort as the time interval between the first dose of avapritinib and death due to any cause. If alive at study end, patients were censored at the date of last contact (BAT cohort), or at the last known date alive (avapritinib cohort) (3).

7.1.2 Method of synthesis

A full description of the methods used for this analysis are presented in Appendix C. The IPTW approach used weights to create a “pseudo-population” (effective sample after IPTW-weighting) in which the distribution of baseline covariates is approximately the same in each patient cohort under comparison. In this way, confounding by measured baseline characteristics was mitigated (3).

Imbalances in baseline characteristics between the avapritinib and BAT cohorts were first assessed using standardized differences and is presented above in Table 16 (3). The standardized difference for continuous variables was calculated by dividing the absolute difference in means of avapritinib cohort vs. BAT cohort by the pooled standard deviation of both cohorts (67). The pooled standard deviation was the square root of the average of the squared standard deviations. For categorical variables, the standardized difference was calculated using the following equation where $Pavapritinib$ was the respective

proportion of the avapritinib cohort, and $PBAT$ was the respective proportion of the BAT cohort:

$$\frac{|\hat{P}_{avapritinib}-\hat{P}_{BAT}|}{\sqrt{\frac{1}{2}\times[\hat{P}_{avapritinib}\times(1-\hat{P}_{avapritinib})+\hat{P}_{BAT}\times(1-\hat{P}_{BAT})]}}.$$

For each variable, a standardized difference greater than 10% was considered indicative of meaningful imbalance between the two cohorts (67).

To implement the IPTW approach, weights were created through propensity score (PS) modelling, where the PS was defined as the probability of receiving treatment (i.e., receiving treatment with avapritinib), conditional on an observed set of baseline covariates. All a priori specified key covariates, regardless of the magnitude of the standardized difference, were included in the PS model based on published literature (68, 69). This included: age, sex, region (North America or Europe), performance status as assessed by the ECOG score, presence of anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100×10^9/L), AdvSM subtype (SM-AHN, ASM, or MCL), presence of skin involvement (including reported mastocytosis in the skin or urticaria), leukocyte count of 16×10^9/L or higher, serum tryptase concentration of 125 ng/mL or higher, testing and number of mutations within the SRSF2/ASXL1/RUNX1 (S/A/R) panel, number of prior LOTs received, and types of prior therapy (TKI therapy, cytotoxic therapy, or biologic or other systemic therapy) received (3). Based on the PS, for each LOT included in the analysis, IPTW weights were calculated as the inverse of the conditional probability of being in the respective treatment group (i.e., avapritinib or BAT), conditional on the pre-specified key covariates included in the model. The PS, and thus weights, were estimated from a logistic regression model. To enhance precision in the effect estimates, the weight for each included LOT was stabilized by the marginal probability of being in the respective treatment group. Stabilized IPTW weights were calculated as $wi=P(Ti=1)Ti/pi+P(Ti=0)1-Ti/1-pi$, where pi and Ti are the estimated PS and the treatments (0 or 1), respectively, and $P(Ti=1)$ is the marginal probability the LOT was received as part of the treatment (avapritinib) cohort and $P(Ti=0)$ is the marginal probability that the LOT was received as part of the external control (BAT) cohort, for LOT i, respectively. To reduce variability, stabilized weights were truncated at the 1st and 99th percentiles (3). Summary statistic of the IPT weights are shown below.

Table 28 Summary of statistics of truncated stabilised weights for inverse probability of treatment weighting analysis of overall survival

Study sample	N	Mean (SD)	Min	Max
Overall[a]	389	0.98 (0.84)	0.47	5.81
Avapritinib cohort	176	0.96 (0.80)	0.47	5.81
Best available therapy cohort	213	0.99 (0.87)	0.56	5.81

Abbreviations: Max: maximum; min: minimum; SD: standard deviation.
Note: [1] Stabilized weights were truncated at the 1st and 99th percentiles
Source: Reiter et al., 2022 (3)

7.1.3 Results from the comparative analysis

Table 29 presents IPW-adjusted Kaplan-Meier survival estimates and HR for OS of avapritinib vs BAT. Further details are presented in the next sections.

Table 29 Results from the comparative analysis of avapritinib vs. BAT for AdvSM patients

Outcome measure			Unweighted sample[a]		Weighted sample[b]			
Overall: Avapritinib vs BAT	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**
Number of unique patients	N=176	N=141	-	-	ESS N=172	ESS N=136	-	-
Number of Lines of therapy	N=176	N = 222	-	-	ESS N = 172	ESS N = 210	-	-
Deaths of unique patients, n (%)	34 (19.3)	84 (59.6)	-	-	36 (20.9)	76 (55.6)	-	-
Unique patients censored due to avapritinib initiation, n (%)	-	21 (14.9)	-	-	-	25 (18.4%)	-	-
Unique patients censored due to new primary malignancy after index date, n (%)	-	6 (4.3)	-	-	-	8 (5.9)	-	-
Mean follow-up (months)	17.9	25.7	-	-	17.9	25.7	-	-
Median OS, months (95% CI)	NR (46.9, NE)	23.4 (19.5, 32.6)	-	-	49.0 (46.9, NE)	26.8 (18.2, 39.7)	-	-
HR (95% CI)[c]			0.39 (0.26, 0.58)	<0.001			0.48 (0.29, 0.79)	0.004
Kaplan-meier survival estimates				Log-rank p				Log-rank p
12 months	87.3%	72.0%	-	<0.001	86.4%	73.8%	–	0.013
24 months	77.5%	49.2%	-	<0.001	74.5%	50.9%	–	<0.001
36 months	70.7%	40.1%	-	<0.001	67.9%	42.7%	–	<0.001

Outcome measure			Unweighted sample[a]				Weighted sample[b]	
Overall: Avapritinib vs BAT	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**
48 months	58.7%	26.6%	-	<0.001	61.9%	30.0%	–	<0.001
60 months	50.3%	20.2%	-	<0.001	36.8%	23.4%	–	0.001
Outcome measure	**Unweighted sample**				**Weighted samplef**			
Avapritinib PATHFINDER (RAC-RE population, 200 mg) vs BAT 2L+	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**
Number of unique patients	N = 47	N = 73	-	-	ESS N=41	ESS N=67	-	-
Lines of therapy	N = 47	N = 104	-	-	ESS N = 41	ESS N = 99	-	-
Median OS, months (95% CI)	NR (NE,NE)	20.3 (14.9, 33.9)	-	-	NR (17.5, NE)	17.2 (14.6, 33.9)	-	-
HR (95% CI)[d]			0.52 (0.26, 1.03)	0.060			0.47 (0.21,1.09)[e]	0.080

Abbreviations: BAT = best available treatment; HR = hazard ratio; NE = not evaluable; NR = not reached; OS = overall survival

a Patients from the BAT cohort could contribute multiple lines of therapy. A total of 222 lines of therapy were contributed by 141 real-world patients in the unweighted BAT cohort.

b Stabilized weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anaemia (haemoglobin <10 g/dl), thrombocytopenia (platelet count <100 × 109/l), AdvSM subtype, skin involvement, leukocyte count of 16 × 109/l or higher, serum tryptase level of 125 ng/ml or higher, number of mutated genes within the SRSF2/ASXL1/RUNX1 gene panel, number of prior lines of therapy, and prior use of tyrosine kinase inhibitor, cytoreductive, biologic or other systemic therapy.

b Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference of greater than 10% after weighting, which included region, presence of thrombocytopenia at baseline, and prior use of tyrosine kinase inhibitor therapy, using a doubly robust approach.

c Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference of greater than 10% after weighting, using a doubly robust approach. HR and the corresponding 95% CI and p value were presented. Two-sided p value <0.05 was considered statistically significant without multiplicity adjustment.

d Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference of greater than 10% after weighting, using a doubly robust approach. HR and the corresponding 95% CI and p value were presented. Two-sided p value <0.05 was considered statistically significant without multiplicity adjustment.
e IPTW-weighted multivariable Cox proportional hazards model further adjusted for sex, region, presence of anaemia at baseline, presence of thrombocytopenia at baseline, AdvSM subtype, prior use of tyrosine kinase inhibitor therapy, and prior use of cytoreductive therapy.
f Stabilized weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anaemia (haemoglobin <10 g/dl), thrombocytopenia (platelet count <100 × 109/l), AdvSM subtype, skin involvement, leukocyte count of 16 × 109/l or higher, serum tryptase level of 125 ng/ml or higher, number of mutated genes within the SRSF2/ASXL1/RUNX1 gene panel
Source: Reiter et al., 2022 (3)

7.1.4 Efficacy – Overall survival

In the overall population, which includes the safety population for both EXPLORER and PATHFINDER, the IPTW weighted analysis had shown OS was significantly improved in the avapritinib cohort vs the BAT cohort ([HR] [95% CI] = 0.48 [0.29, 0.79]; P=0.004), after adjustment for key covariates. Figure 4 presents the IPW-unadjusted Kaplan–Meier survival functions for OS for avapritinib vs BAT. In the PATHFINDER RAC-RE population who had received 200 mg daily of avapritinib with prior systematic therapy, a similar positive trend can be seen of avapritinib demonstrating improved OS efficacy vs BAT ([HR] [95% CI] = 0.47 [0.21, 1.09]; P=0.080) after adjusting for key covariates. Figure 5 presents the IPW-unadjusted Kaplan–Meier survival functions for OS for avapritinib vs BAT within this population.

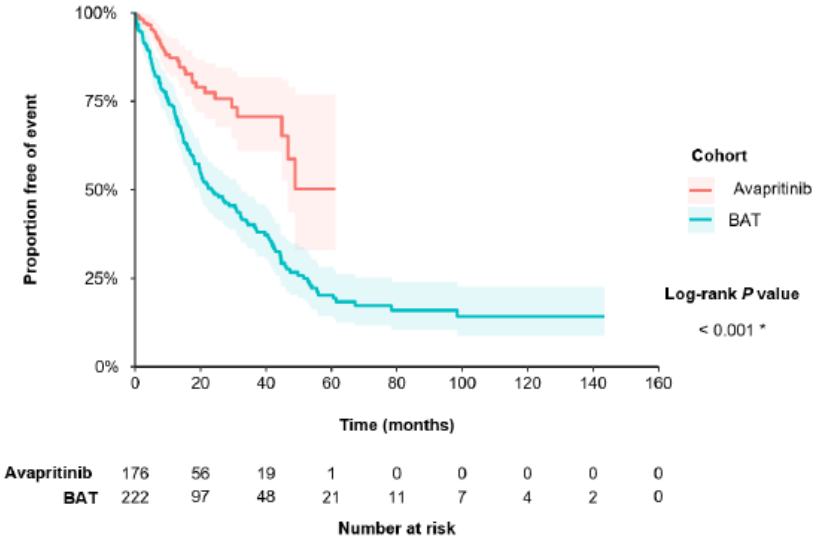

Figure 4 Unweighted overall survival comparison of avapritinib vs BAT; pooled EXPLORER and PATHFINDER; safety population; April 2021 DCO

Abbreviations: BAT = best available therapy; OS = overall survival.

Note: Data for avapritinib are presented from the EXPLORER and PATHFINDER trials up until the 20 April 2021 data cut. Source: Blueprint Medicines. Data on file (53); Reiter et al., 2022 (3)

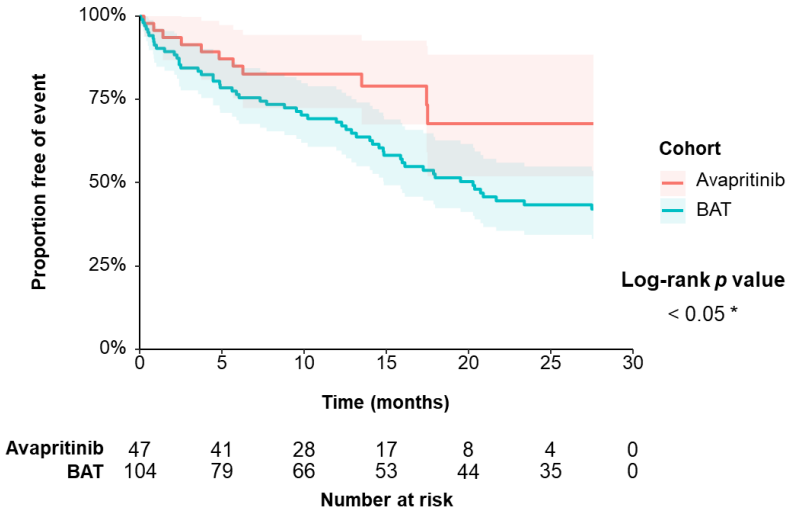

Figure 5 Unweighted overall survival comparison of avapritinib vs BAT; PATHFINDER; RAC-RE; 200 mg; prior systematic therapy; April 2021 DCO

Abbreviations: 2L+: second or later line of therapy; AdvSM: advanced systemic mastocytosis; BAT: best available therapy; RAC-RE: response assessment committee adjudicated response-evaluable.
Note:[a] A total of 47 lines of therapy were contributed by 47 trial patients in the unweighted avapritinib cohort. A total of 104 lines of therapy were contributed by 73 real-world patients in the unweighted BAT cohort. The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort. Source: Reiter et al., 2022 (3)

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Avapritinib time-to-event data from PATHFINDER (Base case 200mg RAC-RE population = 47 patients, data cut-off (DCO): April 2021, refer to Section 6.1.5.4) have been used to calculate the OS, PFS and ToT Kaplan-Meier (KM) curves, which allows the model to determine health-state (and sub-states) membership.

BLU-285-2405 is an ITC between patients treated with avapritinib in the EXPLORER and PATHFINDER trials and real-world patients treated with BAT, for the primary endpoint of OS and ToT. The resulting OS hazard ratios (HRs) for avapritinib vs BAT were used to adjust the hazard observed with avapritinib at each cycle of the analysis, assuming the proportional hazards (PH) assumption is met. The OS HR applied in the model was HR: 0.47 [0.21; 1.09] based on the subgroup in the 2L+ treatment line (3).

This ITC could not provide an estimate of the relative PFS for BAT due to the inconsistency of the progression criteria used in the PATHFINDER/EXPLORER and in the BLU-285-2405. Since many of the BAT treatments are assumed until progression, hence the ToT curve was used as proxy for the PFS curve in the base case. In a scenario analysis, the OS HR was assumed to be held also for the PFS, calculating the BAT PFS by applying the OS HR to the avapritinib PFS curve.

The ToT HR provided by the ITC was calculated by comparing the prior-treated patients in both EXPLORER and PATHFINDER trials with the prior-treated patients in the external comparator arm. This population does not match completely with the base case cohort, which is based on PATHFINDER only. Therefore, the assumption was made that the HR calculated on the pooled trials held also for the PATHFINDER population. The ToT HR applied in the model was HR: 0.36 [0.22; 0.57] (3).

HSCT related mortality

Given the fact that HSCT is a relative novel intervention for the AdvSM patients, there are few data available regarding its outcomes. A TLR was conducted to define the OS and the PFS of AdvSM patients treated with HSCT. The paper of Ustun et al. (70) reported the PFS and OS of AdvSM patients treated with HSCT over a 3-year time-horizon. The KM curves were digitized and, subsequently, the algorithm published by Guyot et al. (71) were used to generate pseudo individual patient data (pseudo-IPD). The data were then used to fit different parametric distributions, allowing to extrapolate the OS over the model time horizon.

8.1.1 Extrapolation of efficacy data

Parametric fitting of KM curves was performed to extrapolate beyond the observation period using the following distribution: Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma. The base case analysis uses a full parametric approach, whereby

to avoid having jumps in the hazard observed with KM curves the parametric curves are applied from time zero.

Age- and sex-specific all-cause mortality rates for the general Danish population were also calculated for each cycle and all-cause mortality hazard rate based on Danish statistics, provided by the DMC (72).

The selection of base case parametric functions for OS and PFS for avapritinib and BAT were informed by: Goodness-of-fit statistics (i.e., Akaike information criterion (AIC) and Bayesian information criterion (BIC)) and visual inspection to assess the concordance between predicted and observed curves. Finally clinical plausibility of long-term extrapolations was evaluated based on smoothed hazard plots and clinical plausibility.

8.1.1.1 Extrapolation of overall survival (OS)

Table 30 summarises assumptions and extrapolation methods of OS.

Table 30 Summary of assumptions associated with extrapolation of overall survival (OS)

Method/approach	Description/assumption
Data input	Avapritinib: IPD data from PATHFINDER (April 2021 DCO). BAT: ITC data from BLU-285-2405 (retrospectively collected up to October 4, 2021).
Model	For OS, the following standard parametric models: Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma were fitted to each treatment arm.
Assumption of proportional hazards between intervention and comparator	Yes.
Function with best AIC fit	Avapritinib: Exponential, BAT: NA
Function with best BIC fit	Avapritinib: Exponential, BAT: NA
Function with best visual fit	Avapritinib: Exponential, BAT:NA
Function with the best fit according to external evidence	Not applicable.
Function with best fit according to evaluation of smoothed hazard assumptions	Avapritinib: Exponential according to AIC/BIC, BAT: NA
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No
Selected parametric function in base case analysis	Avapritinib: Exponential, BAT: NA
Validation of selected extrapolated curves	The exponential model assumed that the hazard remains constant over time, and this appears to be in line with the observation that most deaths occurred at the time of progression, (i.e. there were not many patients' post-progression and alive which would drive a much higher hazard of death from the time of progression onwards). This seems to be also in line with long-term survival of

Method/approach	Description/assumption
	AdvSM patients, which at 20 years from diagnosis shows at best no more than 10% of cohort alive.

Abbreviations: IPD: individual patient data, DCO: data cut-off, BAT: best available treatment, ITC: indirect treatment comparison, OS: overall survival, HR: hazard ratio, PH: proportional hazard, NA: not applicable, AIC: Akaike54 information criteria, BIC: Bayesian54 information criteria, AdvSM: advanced systemic mastocytosis.

Figure 6 presents the extrapolation models (Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma) for OS in the avapritinib arm. The figure shows the extrapolation over the lifetime horizon.

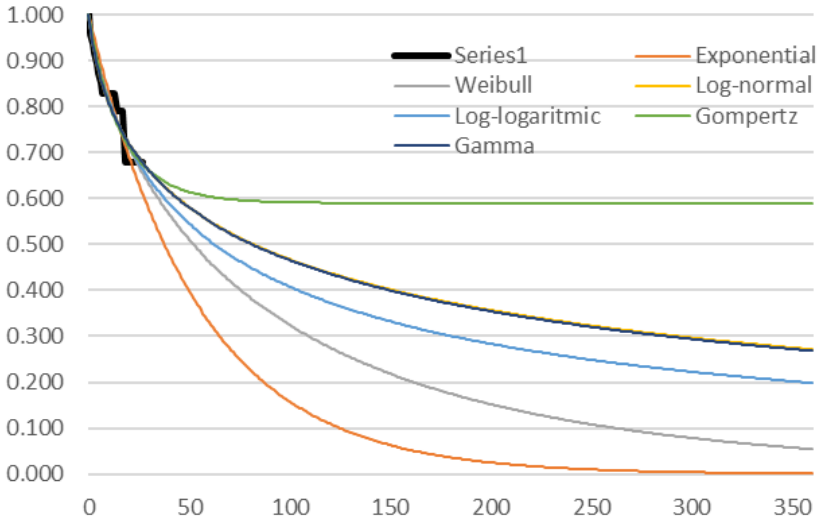

Figure 6 Extrapolation model for OS, avapritinib, data from PATHFINDER (Base case 200mg RAC-RE population) – lifetime horizon

Note: Months on the x-axis and survival probability on y-axis.

8.1.1.1.1 Extrapolation of overall survival (OS) for post-HSCT

Among the several KM curves presented by Ustun et al. (70), three were selected to be included in the model:

1. the one related to the entire population, (all patients)
2. its upper confidence limit and, (upper c limit)
3. the one related to the patients who was given a myeloablative conditioning regime (MAC)

In the base case, the selected population is the MAC patients. This is because only the responders who are fit enough for HSCT are eligible for it. These patients are assumed to undergo a full myeloablative conditioning, since the reduced intensity conditioning is reserved for more fragile patients, who, in the model, where not eligible for HSCT at all.

To explore the uncertainty of the selected patient population for allo-HSCT, scenarios with all patients and the upper confidence limit patient populations will be explored in sensitivity analyses.

Table 31 Summary of assumptions associated with extrapolation of overall survival (OS) for post-HSCT

Method/approach	Description/assumption
Data input	AdvSM patients treated with HSCT: Pseudo-IPD data from Ustun et al (70).
Model	For OS and PFS, six standard parametric models: Exponential, Log-normal, Log-logistic, Weibull, Gompertz and Gamma were fitted to each treatment arm.

Method/approach	Description/assumption
Assumption of proportional hazards between intervention and comparator	Not applicable.
Function with best AIC fit	MAC patients: Gamma
Function with best BIC fit	MAC patients: Gamma
Function with best visual fit	MAC patients: Gamma
Function with the best fit according to external evidence	Not applicable.
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable.
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No.
Assumptions of waning effect	No.
Assumptions of cure point	Yes. The proportion of the HSCT cohort surviving 1 year reached a cure-point after which either the average hazard between 1 and year 4 of the extrapolated curves or the mortality of the overall population is applied.
Selected parametric function in base case analysis	MAC patients: Gamma
Validation of selected extrapolated curves	Not applicable.

Abbreviations: AdvSM: advanced systemic mastocytosis, HSCT: haematopoietic stem cell transplantation, IPD: individual patient data, OS: overall survival, PFS: progression-free survival, MAC: myeloablative conditioning regime.

Figure 7 present the extrapolation models (Exponential, Weibull, Log-normal, Log-logistic, Gompertz, and Gamma) for OS (post-HSCT). The figure shows the extrapolation over 10 years.

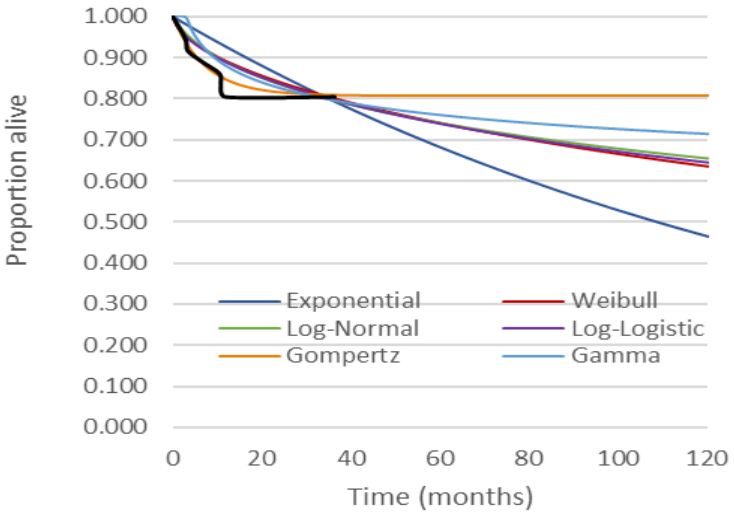

Figure 7 Extrapolation model for OS (post-HSCT), data Ustun et al., MAC patients (10 years)

8.1.1.2 Extrapolation of progression-free survival (PFS)

Table 32 summarises assumptions and extrapolation methods of PFS.

Table 32 Summary of assumptions associated with extrapolation of progression-free survival (PFS)

Method/approach	Description/assumption
Data input	Avapritinib: IPD data from PATHFINDER (April 2021 DCO). BAT: ITC data from BLU-285-2405 (retrospectively collected up to October 4, 2021) (ToT used).
Model	In the base case the BAT PFS was assumed to be the same as the BAT ToT. For BAT ToT, the following standard parametric models: Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma were fitted to each treatment arm.
Assumption of proportional hazards between intervention and comparator	In an alternative scenario the assumption was made that the OS HR held also for the PFS and that the PH assumption was met, hence the BAT PFS was calculated by applying the OS HR to the avapritinib PFS curve.
Function with best AIC fit	Avapritinib: Log-normal, BAT: NA
Function with best BIC fit	Avapritinib: Exponential, BAT: NA
Function with best visual fit	Avapritinib: Exponential, BAT: NA
Function with the best fit according to external evidence	Not applicable.
Function with best fit according to evaluation of smoothed hazard assumptions	Avapritinib: Log-normal according to AIC/BIC, BAT: NA
Adjustment of background mortality with data from Statistics Denmark	Yes.
Adjustment for treatment switching/cross-over	No.
Assumptions of waning effect	No.
Assumptions of cure point	No.
Selected parametric function in base case analysis	Avapritinib: Exponential, BAT: NA
Validation of selected extrapolated curves	Not applicable. However, visual inspection indicates that various scenarios can be created that are clinically implausible because PFS and OS curves cross. As Figure 26 in Appendix D.27 illustrates, only the Exponential model does not cross with OS.

Abbreviations: IPD: individual patient data, DCO: data cut-off, BAT: best available treatment, ITC: indirect treatment comparison, ToT: time on treatment, OS: overall survival, PFS: progression-free survival, HR: hazard ratio, NA: not applicable, AIC: Akaike information criteria, BIC: Bayesian information criteria.

Figure 8 presents the extrapolation models (Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma) for PFS in the avapritinib arm. The figure shows the extrapolation over the lifetime horizon.

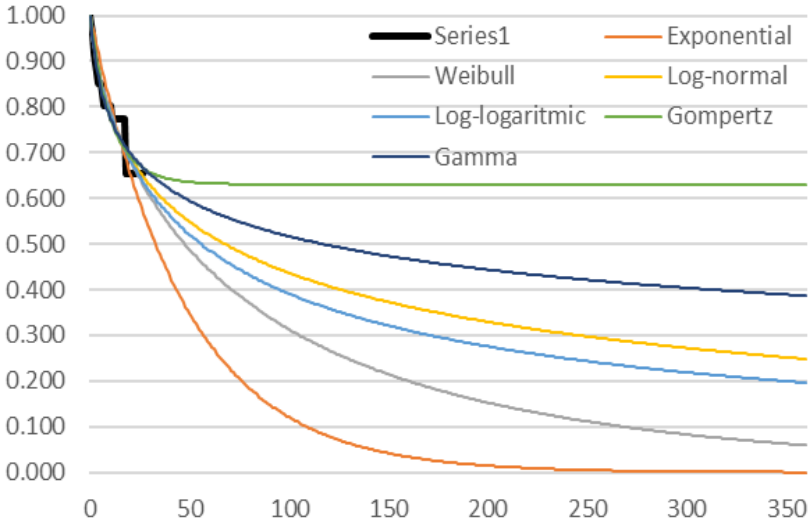

Figure 8 Extrapolation model for PFS, avapritinib, data from PATHFINDER (Base case 200mg RAC-RE population) – lifetime horizon

Note: Months on the x-axis and survival probability on y-axis.

8.1.1.3 Extrapolation of time-on-treatment (ToT)

Table 33 summarises assumptions and extrapolation methods of ToT.

Table 33 Summary of assumptions associated with extrapolation of time-on-treatment (ToT)

Method/approach	Description/assumption
Data input	Avapritinib: IPD data from PATHFINDER (April 2021 DCO). BAT: ITC data from BLU-285-2405 (retrospectively collected up to October 4, 2021).
Model	For ToT, the following standard parametric models: Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma were fitted to each treatment arm.
Assumption of proportional hazards between intervention and comparator	Yes.
Function with best AIC fit	Avapritinib: Log-normal, BAT: NA
Function with best BIC fit	Avapritinib: Log-normal, BAT: NA
Function with best visual fit	Avapritinib: Exponential, BAT: NA
Function with the best fit according to external evidence	Not applicable.
Function with best fit according to evaluation of smoothed hazard assumptions	Avapritinib: Gompertz according to AIC/BIC, BAT: NA
Adjustment of background mortality with data from Statistics Denmark	Yes.
Adjustment for treatment switching/cross-over	No.
Assumptions of waning effect	No.
Assumptions of cure point	No.
Selected parametric function in base case analysis	Avapritinib: Exponential, BAT: NA

Method/approach	Description/assumption
Validation of selected extrapolated curves	Some patients may come off treatment hence not displaying disease activity. The Log-normal or Log-logistic parametric distribution seems clinical plausible.

Abbreviations: IPD: individual patient data, DCO: data cut-off, BAT: best available treatment, ITC: indirect treatment comparison, ToT: time on treatment, HR: hazard ratio, RAC-RE: response assessment committee response-evaluable population, NA: not applicable, AIC: Akaike information criteria, BIC: Bayesian information criteria.

Figure 9 presents the extrapolation models (Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma) for ToT in the avapritinib arm. The figure shows the extrapolation over the lifetime horizon.

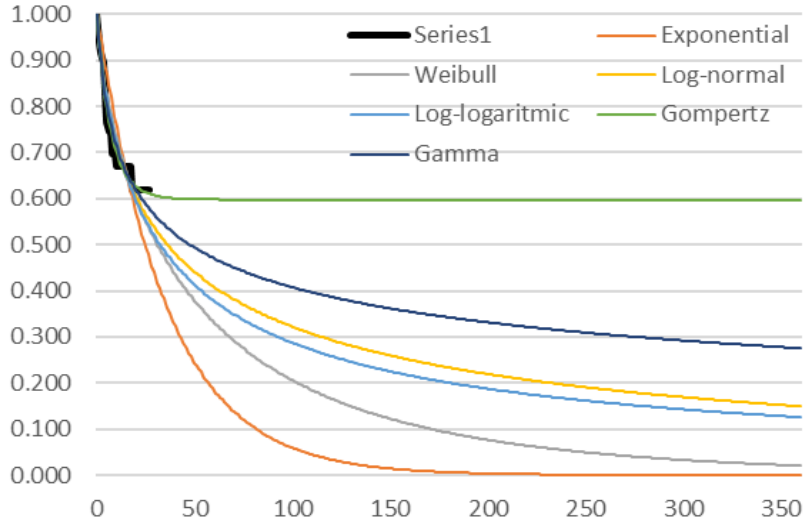

Figure 9 Extrapolation model for ToT, avapritinib, data from PATHFINDER (Base case 200mg RAC-RE population) – lifetime horizon

Note: Months on the x-axis and survival probability on y-axis.

8.1.2 Calculation of transition probabilities

The cohort enters the model in the PF health state and any transition to PD and death health states along the sequence is defined by the PFS and OS curves. The proportion of the cohort selected to receive allo-HSCT is subtracted to the total cohort in PF at the beginning of the simulation and starts the simulation in the pre-HSCT health-state. Following the initial selection of patients based on response status (CR and ORR), selection for allo-HSCT in each arm also relies on the proportions of patients defined as 'fit' for transplant and of the availability of donors (parameters that were obtained from the literature). This results on the final proportion of the cohort which enters the model in the pre-HSCT health-state in each arm. Based on clinical support, the cohort reside in the pre-HSCT for 12 cycles unless it transitions to the death health-state. At 1 year, the cohort is then assumed to receive allo-HSCT and transitions to the post-HSCT health-state.

The probability of death in the post-HSCT health-state is estimated based on observed OS curve in patients receiving allo-HSCT reported in the literature and extrapolated over time. The model assumes no progression to PD health-state from post-HSCT, since in the only long-term study on allo-HSCT in AdvSM identified in the literature (70) the PFS and OS curves overlaps, suggesting that all failures after allo-HSCT resulted in death. Thus, transitions from post-HSCT to death health-state should already be adequately capturing transplant failures. Table 34 and Table 35 provides the transition probabilities applied in the model for each the avapritinib arm and BAT arm, respectively.

Table 34 Transitions in the health economic model, avapritinib arm

Health state (from)	Health state (to)	Description of method	Reference
PF	PF	1-(sum of exit transitions)	(6)
	Pre-HSCT	Response status (CR and ORR) and selection criteria	(3, 6)
	Post-HSCT	NA	-
	PD	Dynamic PFS data PATHFINDER, RAC-RE population	(6)
	Death	NA	-
Pre-HSCT	Pre-HSCT	First 12 months: 1 – Dynamic OS data PATHFINDER, RAC-RE population	(6)
		After 12 months: 0	
	Post-HSCT	First 12 months: 0	
		After 12 months: 1 – Dynamic OS data PATHFINDER, RAC-RE population	(6)
	Death	Dynamic OS data PATHFINDER, RAC-RE population	(6)
Post-HSCT	Post-HSCT	1-(sum of exit transitions)	(6)
	Death	First 12 months post-HSCT: 1 – Dynamic Ustun et al. OS data.	(70)
		After 12 months post-HSCT: 1 – Average of probability of death from year 1 to year 4 post-transplant	(70)
Death	Death	100% of full cohort	(6)

Abbreviations: PF= progression-free, HSCT= hematopoietic stem cell transplantation, CR= complete response, ORR= overall response rate, PD=progressed disease, PFS= progression-free survival, NA= not applicable, OS= overall survival.

Table 35 Transitions in the health economic model, BAT arm

Health state (from)	Health state (to)	Description of method	Reference
PF	PF	1-(sum of exit transitions)	(6)
	Pre-HSCT	Response status (CR and ORR) and selection criteria	(3, 6)
	Post-HSCT	NA	-
	PD	Dynamic PFS data PATHFINDER, RAC-RE population	(6)
	Death	NA	-
Pre-HSCT	Pre-HSCT	First 12 months: 1 – Dynamic OS data PATHFINDER, RAC-RE population applied with a HR of 2.04	(6)
		After 12 months: 0	
	Post-HSCT	First 12 months: 0	
		After 12 months: 1 – Dynamic OS data PATHFINDER, RAC-RE population applied with a HR of 2.04	(6)
	Death	Dynamic OS data PATHFINDER, RAC-RE population applied with a HR of 2.04	(6)
Post-HSCT	Post-HSCT	1-(sum of exit transitions)	(6)
	Death	First 12 months post-HSCT: 1 – Dynamic Ustun et al. OS data.	(70)
		After 12 months post-HSCT: 1 – Average of probability of death from year 1 to year 4 post-transplant	(70)
Death	Death	100% of full cohort	(6)

Abbreviations: PF= progression-free, HSCT= hematopoietic stem cell transplantation, CR= complete response, ORR= overall response rate, PD=progressed disease, PFS= progression-free survival, NA= not applicable, OS= overall survival.

Figure 10 and Figure 11 illustrates the proportion of patients in each health state receiving avapritinib or BAT, respectively.

Figure 10: Proportion of patients in each health state receiving avapritinib (lifetime horizon)
Abbreviations: BAT=best available treatment, PF= progression-free, PD= progressed disease

Figure 11: Proportion of patients in each health state receiving BAT (lifetime horizon)
Abbreviations: BAT=best available treatment, PF= progression-free, PD= progressed disease

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Avapritinib parametric models

Data from PATHFINDER show that in the first 6 months the ToT and PFS curves cross, with on average 1.1% of the cohort being in the ToT and not in PFS curve (73). In the base case this was adjusted so that the ToT does not cross the PFS curve, see Figure 12.

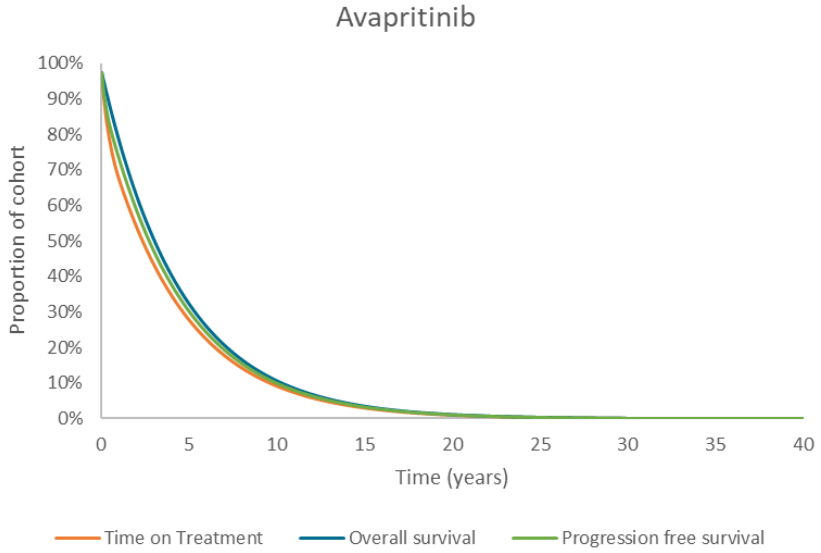

Figure 12 Avapritinib survival curves defining health state membership

In the economic model, crossing curves can also produce implausible patient numbers and was therefore resolved in the model by means of a mathematical adjustment. Essentially, the mathematical adjustment is applied to avoid negative proportion of the cohort in a health-state induced by the crossing of two curves.

Comparator extrapolation – HR ratios

The ITC could not provide an estimate of the relative PFS because the progression criteria used in the retrospective study were not consistent with those used in EXPLORER and PATHFINDER. In the model it was assumed that only the proportion of the cohort treated with midostaurin could achieve a response rate high enough to be eligible for HSCT (for the cohort treated with the off-label BAT treatments was assumed a 0% response in any of the disease sub-type). The source of evidence used to inform the relative ORR and CR of midostaurin vs avapritinib was a matched adjusted indirect comparison (MAIC). The main evidence base for midostaurin were the D2201 and A2213 studies (74). The estimated ORR and the CR were corrected by the percentage of the BAT cohort allocated to midostaurin and were applied to the BAT arm. The resulting OS HRs for avapritinib vs BAT were used to adjust the hazard observed with avapritinib at each cycle of the analysis, assuming the PH assumption is met, refer to Appendix D.

The ToT HR provided by the ITC was calculated by comparing the prior-treated patients in both EXPLORER and PATHFINDER trials with the prior-treated patients in the external comparator arm. This population does not match completely with the base case cohort, which is based on PATHFINDER only. Table 36 shows an overview of the key modelling assumptions made regarding OS and ToT HRs when used in the base case analysis (ToT as proxy for PFS in BAT arm).

Table 36 Hazard ratios used in the model for the OS and the ToT

	Analysis	Characteristics of the population on which the alternative HR was calculated	HR Mean (CI)	Assumption needed to use the alternative HR
Base case: PATHFINDER, all disease subtypes, 200 mg, prior treated, RAC-RE population	OS	/	0.47 (0.21,1.09) (3).	/
	ToT	Pooled, all disease subtypes, 200 mg, prior treated, safety population	0.36 (0.22, 0.57) (3).	The HR observed in the pooled safety population holds also for the base case 200mg RAC-RE population

Abbreviations: RAC-RE: response assessment committee response-evaluable population, OS: overall survival, ToT: time on treatment, HR: hazard ratio, CI: confidence interval.

As Figure 13 illustrates, patients enter the model in the PF health state. In the base case the PFS is assumed to be the same as the ToT (BAT treatment is assumed to be interrupted at progression). However, as explained above, the model allows to test an alternative scenario where the BAT PFS is derived by applying the OS HR to the avapritinib PFS curve. In this scenario the ToT curve may cross the PFS curve. In this case the BAT treatment is assumed to continue after progression until the treatment discontinuation as defined by ToT occurs.

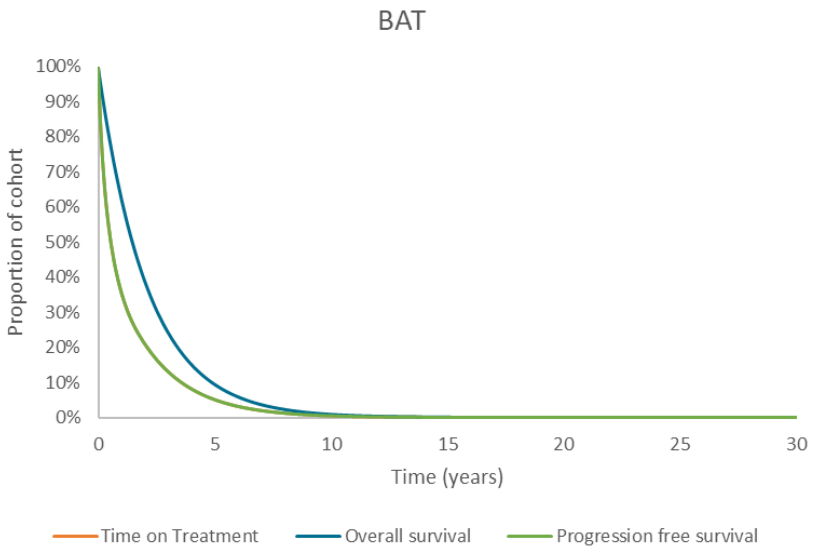

Figure 13 BAT survival curves defining health state membership.

Abbreviations: BAT = best available treatment

HSCT related mortality

As previously mentioned, a TLR was conducted to define the OS and the PFS of AdvSM patients treated with HSCT. Ustun et al (70). Informs the outcomes of HSCT in AdvSM patients. Based on Ustun et al., it was noticed that the PFS and the OS overlapped in many of the sub-analyses presented in the paper, suggesting that most of the progression events were due to the patient's death. Therefore, no progression health state was included after the HSCT and only the OS was used. It was observed that 1 year after HSCT most of the KM curves flattened, indicating a dramatic reduction in mortality. Consequently, the assumption was made in the model, that the proportion of the HSCT cohort surviving 1 year reached a cure-point after which either the average hazard between 1 and year 4 of the extrapolated curve or the mortality of the overall population is applied, whichever is

greater. This allows to adjust for the rise of the hazard in the long-term due to ageing of the cohort.

HSCT related eligibility

Following the opinion of clinical experts, to maximize outcomes post-transplant, a good response in SM should be considered as first criteria to define eligibility for allo-HSCT. Although, complete remission in SM is the most optimal situation, a patient with partial remission could be considered eligible if young, has a good matching donor and the clinical situation suggests that without the transplant the patient could start worsening.

To ensure the analysis reflects the expected clinical practice on allo-HSCT in AdvSM, the model estimate the proportion of the cohort eligible for allo-HSCT (i.e. transitioning to pre-HSCT health-state at the beginning of the simulation), starting from the proportion of patients achieving complete response (CR) by disease sub-type and by treatment and further filtering for 1) presence of haematological neoplasm, 2) fit for transplant and 3) having an available donor (related or unrelated). Since, based on clinical opinion, partial response/stable disease patients may be considered for allo-HSCT, the model allows to option to define the proportion of allo-HSCT eligible cohort starting from the proportion of patients achieving ORR, instead of CR (base case). This is explored in a scenario analysis. For each of the included scenarios, data on avapritinib ORR and CR by disease subtype were obtained from the correspondent population, considering best achieved response by means of IWG criteria. The IWG rather than m-IWG criteria was chosen to allow comparison with midostaurin in the MAIC. Table 37 reports the response rates used in the base-case analysis.

Table 37 Avapritinib overall response and complete response (IWG) from PATHFINDER, MAIC prior ATN, PATHFINDER 200mg

	Overall response	Complete response
ASM	50.0%	0.0%
SM-AHN	50.0%	7.1%
MCL	40.0%	0.0%

Abbreviations: ASM: aggressive systemic mastocytosis, SM-AHN: systemic mastocytosis with associated haematological neoplasm , MCL: mast cell leukaemia

Midostaurin ORR and CR proportions were estimated using the odds ratio (OR) obtained from the MAIC of avapritinib vs midostaurin, to adjust the proportions in avapritinib arm (Table 38). The MAIC OR were estimated in all patients (rather than by disease sub-type) and were applied assuming that the relative effect observed in the overall population would hold in the disease subtype of interest.

Table 38 Results of MAIC on overall response and complete response (all characteristics except C-findings) for avapritinib vs midostaurin, base case 200mg RAC-RE population

	Overall response	Complete response
Mean OR avapritinib vs midostaurin	1.78	2.94
95% CI lower	0.87	0.13
95% CI upper	3.69	66.51

Abbreviations: OR: odds ratio, CI: confidence interval.

The estimated ORR and the CR were corrected by the percentage of the BAT cohort allocated to midostaurin and were applied to the BAT arm (0% in the base case, 20% and 50% in scenario analyses).

Additional criteria for allo-HSCT eligibility included in the model is as follows:

- Presence of AHN as criteria for transplant: The base case analysis assumes that the presence of haematological neoplasm is a required criteria for allo-HSCT eligibility. Thus, 0% of ASM patients would be considered eligible. However, the model allows this criterion to conclude ASM responders.
- Proportion fit for transplant: The model assumes that 50% of the initially selected patients based on response would be considered sufficiently fit to undergo allo-HSCT.
- Sibling donor availability: Based on the findings of Lafarge et al. (75) and of Tomblyn et al. (76), the sibling donor availability has been set at 26%. These publications were obtained through a TLR.
- Non-related donor availability: Based on the findings of Milone et al. (77), the non-related donor availability rate has been set at 67%. Milone et al was also found through a TLR.

8.5 Overview of modelled average treatment length and time in model health state

Table 39 and Table 40 presents the estimates in the model for the modelled average PFS and OS, respectively. The estimates are undiscounted, without half-cycle correction and adjusted for background mortality of the Danish population, as requested by the DMC.

Table 39 PFS estimates in the model

	Modelled average [PFS] (reference in Excel)	Modelled median [PFS] (reference in Excel)	Observed median [PFS] from relevant study
Avapritinib	[redacted]	[redacted]	[redacted]
BAT	[redacted]	[redacted]	[redacted]

Abbreviations: BAT: best available treatment, PFS: progression-free survival.
Note: The median duration of treatment / ToT was 43.3 months in the avapritinib cohort (200mg 2L+), and 5.2 months in the BAT cohort. Source: Reiter et al., 2022 (3)

Table 40 OS estimates in the model

	Modelled average [OS] (reference in Excel)	Modelled median [OS] (reference in Excel)	Observed median [OS] from relevant study
Avapritinib	[redacted]	[redacted]	[redacted]
BAT	[redacted]	[redacted]	[redacted]

Abbreviations: BAT: best available treatment, OS: overall survival, NA: not applicable.
Source: Reiter et al., 2022 (3)

Table 41 presents the modelled average treatment length and time in the model health states.

Table 41 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (months)

Treatment	Treatment length [months]	PF	PD	Pre-transplant	Post-transplant
Avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT: best available treatment, PF: progression-free, tx: treatment, PD: progressed disease. Tx: treatment (primary treatment).

9. Safety

9.1 Safety data from the clinical documentation

The best available data on the safety of avapritinib for AdvSM patients is available from the pooled safety data of both EXPLORER and PATHFINDER studies based on the latest DCO (April 2021) (4).

The safety population consists of all patients both EXPLORER and PATHFINDER studies who received at least one dose of avapritinib (4). The safety population included 193 patients from both parts 1 and 2 of the EXPLORER and PATHFINDER studies, of which, 126 patients received avapritinib 200 mg daily, which will be reported below. Across both studies, the safety population who were treated with 200 mg of avapritinib were treated for a median duration of 41.00 week (4).

Table 42 Overview of safety events for avapritinib. EXPLORER and PATHFINDER; safety population analysis set; 200mg; April 2021 DCO

	Avapritinib (N=126)
Number of adverse events, n	126
Number and proportion of patients with ≥1 adverse events, n (%)	126 (100)
Number of serious adverse events, n	48
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	48 (38.1)
Number of CTCAE grade ≥ 3 events, n	95
Number and proportion of patients with ≥ 1 CTCAE grade 3 events, n (%)	95 (75.4)
Number of adverse reactions, n	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NR
Number and proportion of patients who had a dose reduction, n (%)	91 (72.2)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	38 (30.2)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	23 (18.3)

Abbreviations: NR = Not reported.

Note: Adverse Events are coded using MedDRA 18.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall.

Source: Safety CSR; Table 25 (4)

Serious adverse events with a frequency of ≥2% for the safety population is provided in Table 43 below. Full details of serious adverse events and adverse events of special interest from the NAVIGATOR study are provided in Appendix E.

Table 43 Serious adverse events with a frequency of ≥2% for avapritinib. EXPLORER and PATHFINDER; safety population analysis set; 200mg; April 2021 DCO

Adverse events	Avapritinib (N=126)
Serious adverse event, n (%)	48 (38.1)
Anaemia	4 (3.2)
Subdural haematoma	4 (3.2)
Ascites	3 (2.4)

Note: Adverse Events are coded using MedDRA 18.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall.
Source: Safety CSR; Table 41 (4)

The incidences of AEs associated with avapritinib in the model were based on data from the PATHFINDER trial (4). The analysis included only grade 3 and above AEs observed in at least 5% of the patients treated with an avapritinib dose of 200 mg, as reported in Table 31 of the clinical study report (April 2021 DCO) (4). The incidence of AEs for BAT was based on cladribine informed by the SmPC for Litak® and by Barete et al, refer to Section 9.2 below. Table 44 shows the AEs used in the model.

Table 44 Adverse events used in the health economic model

Adverse events	Avapritinib	SoC	Source	Justification
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**		
Adverse event, n (%)	126	68 / 62	(4, 52, 65)	Grade ≥3 Aes with ≥ 5% incidence
Thrombocytopenia	23	31	(4, 52)	–
Anaemia	27	34	(4, 52, 65)	–
Other haematological disorders[a]	39	88	(4, 65)	–
Sepsis	NA	7	(65)	–
Fever of unknown origin	NA	4	(65)	–

Abbreviations: NA: not applicable, SoC: standard of care
Note: only reported AE (5% > grade 3 or above) is listed in the table.
a: For avapritinib, “other haematological disorders” cover: 66neutropenia (n=21 (16.7%)), neutrophil count decreased (n=10 (7.9%)), and platelet count decreased (n=8 (6.3%)), for SoC, “other haematological disorders” cover: 66neutropenia (n=32) and absolute lymphocyte decreased (n=56).

9.2 Safety data from external literature applied in the health economic model

As mentioned, the incidence of AEs for BAT was based on cladribine informed by the SmPC for Litak® and by Barete et al (using cladribine as a proxy for the incidence of AE in all other BAT treatments), refer to Section 9.2 below. The reason for this, is that cladribine constitutes the largest of the BAT basket (54% (refer to Table 52), followed by interferon-alpha (24%). However, no robust safety data associated with interferon-alpha in AdvSM were found (A study by Casassus et al. (78), reported AEs from Interferon-α treatment for AdvSM; cytopenia’s in six patients, severe depression in three patients, and both cytopenia’s and depression in two patients. However, none grade specifications). Therefore, the incidence rates of AEs from interferon-alpha were set equal to zero. This is considered a conservative approach, since Casassus et al. reported significant withdrawal rates due to AEs, including cytopenia and systemic symptoms.

In scenario analyses, 10 % and 50% patients are assumed to receive midostaurin in 2L (refer to 11.1 for further description), the incidence of AEs for BAT was calculated by taking the weighted average of the AEs in midostaurin and the AEs in the other treatments included within the BAT basket. The AE incidences were then included in the model after adjusting for the monthly cycle length. The incidence of AEs in midostaurin was based on the data reported in the summary of product characteristics (36).

Table 45 Grade 3 and above adverse events that appear in more than 5% of patients

Adverse events	Avapritinib (N=126) (4)			SoC (N=68 from (a) Barete et al (65) / N=62 from (b) from Litak SmPC (52)			Difference, % (95% CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	126	89	NA	(a)68 (b)62	164	NA	NA	NA
Thrombocytopenia	NA	23	0.00694	NA	(b) 31	0.0143	NA	NA
Anaemia	NA	27	0.00830	NA	(b) 34	0.0164	NA	NA
Other haematological disorders[a]	NA	39	0.00163	NA	(a) 88	0.0106	NA	NA
Fever of unknown origin	NA	NA	NA	NA	(a) 4.0	0.0005	NA	NA
Sepsis	NA	NA	NA	NA	(a) 7.0	0.0010	NA	NA

Note: a: For avapritinib, “other haematological disorders” cover: neutropenia (n=21 (16.7%)), neutrophil count decreased (n=10 (7.9%)), and platelet count decreased (n=8 (6.3%)), for SoC, “other haematological disorders” cover: neutropenia (n=32) and absolute lymphocyte decreased (n=56).
Abbreviations: NA: not applicable, SoC: standard of care, CI: confidence interval.

10. Documentation of health-related quality of life (HRQoL)

Health state utility values (HSUV) are applied per health state in the model. Only the HSUV of the PF health state is derived from the same clinical study informing efficacy. QoL in EXPLORER and PATHFINDER were measured by means of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30 Questionnaire). A mapping algorithm identified via a targeted literature review (TLR) was used to map QLQ-C30 scores into EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) at the patient level, (more details in Appendix I). In the base case, EQ-5D-3L tariffs were then applied to derive utility value in PF. In a scenario analysis, the QLQ-C30 data were mapped to EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) and weighted with Danish tariffs. Since most patients in EXPLORER and PATHFINDER died shortly after progression, there were only two observations for which QoL measurement was recorder post-progression. Thus, it was impractical to derive utility in PD based on observations post-progression in EXPLORER and PATHFINDER. For this reason, another TLR was conducted to identify a relative difference in utility post-progression vs pre-progression in conditions like AdvSM and was applied to PF utility to derive the utility in PD health-state. More details on this are also reported in Appendix I. Data on fit to transplant/donor availability, survival and QoL of allo-HSCT were not collected in EXPLORER and PATHFINDER and therefore were also retrieved in the literature through a third TLR, also described in Appendix I.

Table 46 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
QLQ-C30	EXPLORER and PATHFINDER	Mapped to EQ-5D-3L and to EQ-5D-5L to inform the PF HSUV (4, 5).

Abbreviations: EQ-5D-5L: EuroQol 5-dimension 5-level, EQ-5D-3L: EuroQol 5-dimension 5-level, QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, PF: progression-free, HSUV: health state utility value.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

HSUV for PF was derived from the results of the EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 questionnaire is a commonly used instrument for the measurement of QoL. It assesses a patient's perception of disease symptoms at a point in time. The EORTC QLQ-C30 has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial. The EORT QLQ-C30 was used in the manner it was validated for, as reported in Appendix F Health-related quality of life. The study design did not bring a risk of bias of the utility analyses. The global health status, functional scales, and symptom scales were analysed in the RAC-RE (n=47) patients at April 2021 population, see Appendix F for further details on the EORTC QLQ C-30; All domains for avapritinib base case 200mg RAC-RE population (April 2021 DCO). The EORTC QLQ-C30 global health score was expected to increase over time, indicating that patients' QoL improved during treatment with avapritinib.

10.1.2 Data collection

QoL assessments of the trial were correlated with advanced systemic mastocytosis symptom assessment form (AdvSM-SAF) scores and with other measures of efficacy and/or safety. The EORTC QLQ-C30 questionnaire was completed at each study visit through Cycle 17 and at end of treatment (EOT) if EOT is before Cycle 17 (Appendix F). No imputation was made for completely missing date unless otherwise specified. The general imputation rules mentioned below applied to partially missing or impossible dates:

- If the stop date was not missing, and the imputed start date is after the stop date, the start date was imputed by the stop date.
- If the start date was not missing, and the imputed stop date was before the start date, then the imputed stop date was equal to the start date.
- Any imputed needed to be logical. For example, last dose date should not be later than death date.

The pattern of missing data and completion from the PAHTFINDER study is reported in Table 47.

Table 47 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	47	6 (12.77%)	NA	NA
Cycle 1, D8	47	45 (95.74%)	-	-
Cycle 1, D15	47	10 (21.28%)	-	-
Cycle 1, D22	47	44 (93.62%)	-	-
Cycle 2, D2	47	8 (17.02%)	-	-
Cycle 2, D15	47	46 (97.87%)	-	-
Cycle 3, D1	47	15 (31.91%)	-	-
Cycle 4, D1	47	45 (95.74%)	-	-
Cycle 5, D1	47	18 (38.30%)	-	-
Cycle 6, D1	47	45 (95.74%)	-	-
Cycle 7, D1	47	21 (44.68%)	-	-
Cycle 8, D1	47	43 (91.49%)	-	-
Cycle 9, D1	47	25 (53.19%)	-	-
Cycle 10, D1	47	45 (95.74%)	-	-
Cycle 11, D1	47	32 (68.09%)	-	-
Cycle 12, D1	47	46 (97.87%)	-	-
Cycle 14, D1	47	34 (72.34%)	-	-

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 15, D1	47	45 (95.74%)	-	-
Cycle 17, D1	47	37 (78.72%)	-	-
Cycle 18, D1	47	46 (97.87%)	-	-

Note: Only observation related to quality-of-life (QoL) prior to the progression data (i.e., only PFS records) were used to calculate the mean, standard deviation, median, minimum and maximum estimates at each timepoint, and change from baseline.
Abbreviations: D: refers to "day", NA: not applicable.

10.1.3 HRQoL results

EQ-5D data for the avapritinib base case 200mg RAC-RE population from baseline and up to cycle 18, D1 is presented in Table 48. The EQ-5D data is UK weighted and the EQ-5D utility value used in the model is the mean PFS utility value (for the PF health state). Figure 14 display the mean change in EQ-5D utility values (including error bars showing the standard deviations) from baseline up until Cycle 18, D1 for avapritinib.

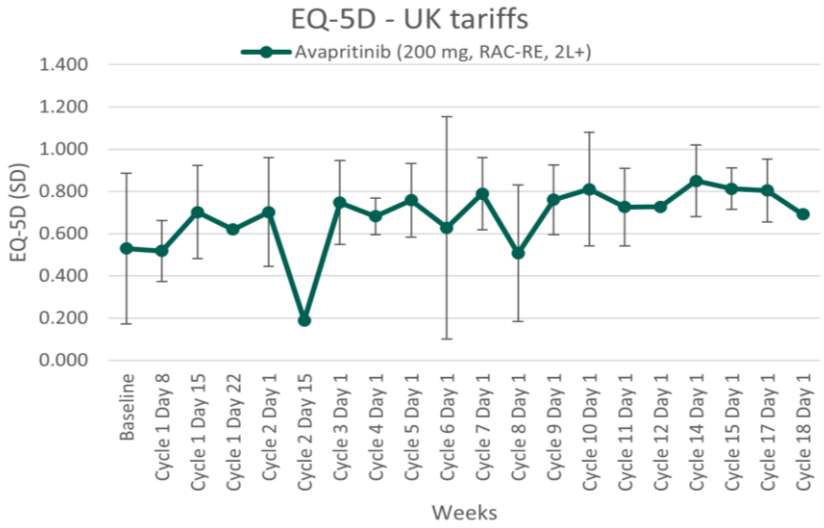

Figure 14 EQ-5D (UK weighted) mean change from baseline for avapritinib (base case 200mg RAC-RE population)

Abbreviations: SD: standard deviation, RAC-RE: response assessment committee response-evaluable population, 2L: second line +, EQ-5D: EuroQol 5-Dimensions.

The mean change in EQ-5D utility values with Danish weights is provided in Appendix F (Figure 39).

Table 48 HRQoL EQ-5D summary statistics

	Avapritinib		BAT		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	41	0.530 (0.055)	NA	NA	NA
Cycle 1, D8	2	0.518 (0.109)	NA	NA	NA
Cycle 1, D15	37	0.702 (0.036)	NA	NA	NA
Cycle 1, D22	3	0.620 (NA)	NA	NA	NA

	Avapritinib		BAT		Intervention vs. comparator
Cycle 2, D2	39	0.702 (0.041)	NA	NA	NA
Cycle 2, D15	1	0.189 (NA)	NA	NA	NA
Cycle 3, D1	32	0.747 (0.035)	NA	NA	NA
Cycle 4, D1	2	0.682 (0.061)	NA	NA	NA
Cycle 5, D1	29	0.758 (0.032)	NA	NA	NA
Cycle 6, D1	2	0.628 (0.373)	NA	NA	NA
Cycle 7, D1	26	0.789 (0.034)	NA	NA	NA
Cycle 8, D1	4	0.507 (0.162)	NA	NA	NA
Cycle 9, D1	22	0.761 (0.035)	NA	NA	NA
Cycle 10, D1	2	0.810 (0.190)	NA	NA	NA
Cycle 11, D1	15	0.726 (0.047)	NA	NA	NA
Cycle 12, D1	1	0.727 (NA)	NA	NA	NA
Cycle 14, D1	13	0.850 (0.047)	NA	NA	NA
Cycle 15, D1	2	0.813 (0.070)	NA	NA	NA
Cycle 17, D1	10	0.805 (0.047)	NA	NA	NA
Cycle 18, D1	1	0.691 (NA)	NA	NA	NA

Abbreviations: D: refer to day, SE: standard error, CI: confidence interval, NA: not applicable.

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

As described in section 10.1, the HSUV for the PF health state was derived from the QLQ – C30 questionnaire used in the PATHFINDER study, April 2021 DCO (4, 5). The base case analysis of the economic model uses the HSUV mapped to EQ-5D-3L and using UK tariffs as mentioned in Appendix F. A scenario analysis then explores the impact of mapping to EQ-5D-5L and using Danish tariffs using the methodology provided by Jensen et al (2021) (79). Danish tariffs are not applied in the base case for consistency across all HSUV of the model, due to the methodology used to derive the PD HSUV, which is obtained by applying a ratio to the PF HSUV as described in section 0 (so no Danish tariffs can be applied to the PD HSUV). In the base and in all scenario analyses, HSUV are age-adjusted according to the methods described in the Appendiks: Aldersjustering for sundhedsrelateret livskvalitet of the DMC guidelines (80). The description of the mapping for both the base case and scenario analysis is described in Appendix F. HSUVs calculated with the mapping algorithm on the data from PATHFINDER is for the 200mg RAC-RE (base case) population and the Pooled PATHFINDER/EXPLORER – all doses, RAC-RE population (scenario analysis). This scenario analysis aligns the HSUVs with the population included in the ITC and therefore aligns relative efficacy evidence with QoL evidence. The results are presented in Table 49.

10.2.2 Disutility calculation

Disutilities are included in the model as scenario analysis but as they are derived from the literature, they are presented in section 10.3.4.

10.2.3 HSUV results

Table 49 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff used	Comments / applicable population
HSUV for pre-progressed				
Pre-progression RAC-RE population (base case)	0.654 [NA-NA]	EQ-5D-3L	UK	Derived from Pathfinder 2L+, 200mg, RAC-RE, applied as base case for 2L+, 200mg, RAC-RE (4, 5).
Pre-progression (scenario RAC-RE population DK tariffs)	0.732 [0.66-0.802]	EQ-5D-5L	DK	Scenario analysis applied to the 200mg RAC-RE population (4, 5).
Pre-progression (scenario Pooled – RAC-RE population)	0.6538 [NA-NA]	EQ-5D-3L	UK	Scenario analysis. Derived from PATHFINDER, Pooled PATHFINDER and EXPLORER – All doses – RAC-RE (4, 5).

Abbreviations: HSUV: health state utility value, NA: not applicable, EQ-5D-3L: EuroQol 5-Dimensions 3-Levels, RAC-RE: response assessment committee response-evaluable population , 2L: second line, CI: confidence interval.
Note: HSUV calculated with the mapping algorithm on the data from PATHFINDER is for the 200mg RAC-RE (base case) population and the Pooled PATHFINDER/EXPLORER – all doses, RAC-RE population (scenario analysis).

10.3 Presentation of the health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.3.1 Study design

Details on study design are not available for the HSUV derived from the literature.

10.3.2 Data collection

Details on data collection are not available for the HSUV derived from the literature.

10.3.3 HRQoL Results

Details on HRQoL results are not available for the HSUV derived from the literature.

10.3.4 HSUV and disutility results

While the approach detailed in section 10.2.1 provided reliable results for the utility value associated with the progression free health state, it proved impractical to define the utility value after progression, since in the datasets there was only one QoL observation for patients with a progressive disease, even when pooling observations from EXPLORER and PATHFINDER to increase the sample size. Therefore, a TLR was conducted to inform the model, which is reported in detail in Appendix I (Note, the TLR findings are based on analogue diseases, but were not specific for AdvSM and hence was not reported in the SLR). Based on the findings of the TLR, four papers were used to calculate a ratio between PF and PD utility values. Two papers were based on Time Trade-Off (TTO) and Discrete Choice (DC) experiments conducted on the general population (11) (8). The two other papers were based on utility scores measured directly on real patients (9) (10). For the base case analysis, the paper presenting the PF HSUV which was the closest to the Pathfinder PF HSUV was selected to generate the ratio to be applied to obtain the PD HSUV. The study which reported the closest PF HSUV to the Pathfinder PF HSUV was

Mamolo et al. 2019 (10) which reported a PF HSUV of 0.74. Additionally, two scenario analyses were explored which used an aggregate ratio based on both a plane average and a weighted average of the ratios derived from the four papers reported in Table 51, with the number of patients in each paper defining the weights. Finally, the QoL of the group undergoing HSCT were taken from Grulke et al. (7). This is in line with previous submissions (66). A TLR was conducted to exclude the presence of other relevant papers addressing the QoL after HSCT. Before undergoing the transplant, the HSCT cohort is assumed to spend 1 year in a pre-HSCT state and to experience the same utility value as in the PF state. Grulke et al. (7) estimated HSUV based on UK tariffs. For the purpose of our analysis, we also explored a scenario analysis with HSUV based on Danish tariffs, based on the methods described by Jensen et al, 2021 (79). Additionally, in a scenario analysis, the impact of including disutilities as reported in Table 51 is explored. Table 50 reports all the HSUVs used in the model for the base case 200mg RAC-RE population. Table 51 reports all the HSUV derived from the literature and served as inputs to estimate the HSUV used in the model for the base case 200mg RAC-RE population.

Table 50 Overview of health state utility values [and disutilities]

	Results	Instrument	Tariff used	Comments
HSUVs for progressed disease (PD)				
Progressed RAC-RE population (Base-case)	0.645	EQ-5D-3L	Ratio: US Pathfinder: UK	Ratio derived from Mamolo et al, applied to Pre-progression RAC-RE population utility (0.654) (10)
Progressed RAC-RE population (scenario with average ratio)	0.47	Ratio: mixed methods Pathfinder: EQ-5D-3L	Ratio: mixed Pathfinder: UK	Average ratio, applied to Pre-progression RAC-RE population utility (0.654)
Progressed RAC-RE population (scenario with weighted average ratio)	0.47	Ratio: mixed methods Pathfinder: EQ-5D-3L	Ratio: mixed Pathfinder: UK	Weighted average ratio, applied to Pre-progression RAC-RE population utility (0.654)
Progressed RAC-RE population **(Scenario with DK tariffs)**	0.72	Ratio: EQ-5D-3L Pathfinder: EQ-5D-5L	Ratio: US Pathfinder: DK	Ratio derived from Mamolo et al, applied to Pre-progression RAC-RE population DK weights utility (0.732) (10)
Progressed RAC-RE population (scenario with average ratio and DK tariffs)	0.53	Ratio: mixed Pathfinder: EQ-5D-5L	Ratio: mixed Pathfinder: DK	Average ratio, applied to Pre-progression RAC-RE population DK weights utility (0.732)
Progressed RAC-RE population (scenario with weighted average ratio and DK tariffs)	0.52	Ratio: mixed Pathfinder: EQ-5D-5L	Ratio: mixed Pathfinder: DK	Weighted average ratio, applied to Pre-progression RAC-RE population DK weights utility (0.732)
Progressed Pooled RAC-RE population (Scenario)	0.645	EQ-5D-3L	Ratio: US Pathfinder: UK	Ratio derived from Mamolo et al, applied to Pre-progression Pooled

	Results	Instrument	Tariff used	Comments
				RAC-RE population utility (0.6538) (10)
Progressed Pooled RAC-RE population (scenario with average ratio)	0.47	Ratio: mixed methods Pathfinder: EQ-5D-3L	Ratio: mixed Pathfinder: UK	Average ratio, applied to Pooled Pre-progression RAC-RE population utility (0.6538)
Progressed Pooled RAC-RE population (scenario with weighted average ratio)	0.47	Ratio: mixed methods Pathfinder: EQ-5D-3L	Ratio: mixed Pathfinder: UK	Weighted average ratio, applied to Pre-progression Pooled RAC-RE population utility (0.6538)
HSUV following HSCT				
Allo-HSCT, first month	0.620	QLQ-C30	UK	Grulke et al 2012(7)
Allo-HSCT, to month 6	0.760	QLQ-C30	UK	Grulke et al 2012(7)
Allo-HSCT, to month 12	0.796	QLQ-C30	UK	Grulke et al 2012(7)
Allo-HSCT, from month 12	0.796	QLQ-C30	UK	Grulke et al 2012(7)
Allo-HSCT, first month (scenario with DK tariffs)	0,806	EQ-5D-5L	DK	Grulke et al 2012 (Danish tariffs Jensen et al, 2021) (7) (79)
Allo-HSCT, to month 6 (scenario with DK tariffs)	0,919	EQ-5D-5L	DK	Grulke et al 2012 (Danish tariffs Jensen et al, 2021) (7) (79)
Allo-HSCT, to month 12 (scenario with DK tariffs)	0,952	EQ-5D-5L	DK	Grulke et al 2012 (Danish tariffs Jensen et al, 2021) (7) (79)
Allo-HSCT, from month 12 (scenario with DK tariffs)	0,952	EQ-5D-5L	DK	Grulke et al 2012 (Danish tariffs Jensen et al, 2021) (7) (79)

Abbreviations: HSUV: health state utility value, EQ-5D-3L: EuroQol 5-Dimensions 3-Levels, RAC-RE: response assessment committee response-evaluable population, 2L: second line, CI: confidence interval.

Table 51 Overview of literature-based health state utility values

	Results	Instrument	Tariff used	Comments
HSUV for progressed disease (PD)				
Stein 2018 (11)	CR: 0.87 [NA; NA] relapse: 0.355 [NA; NA]	Discrete Choice experiment	US	Used in scenario for calculation of ratio to obtain PF HSUV
Joshi 2019 (8)	Long term follow-up: 0.89 relapsed: 0.51 [NA; NA]	Composite time trade-off	UK	Used in scenario for calculation of ratio to obtain PF HSUV

	Results	Instrument	Tariff used	Comments
Leunis 2014 (9)	CR after 1L: 0.83 [NA; NA] relapsed: 0.78 [NA; NA]	EQ-5D and QLQ-C30	NL	Used in scenario for calculation of ratio to obtain PF HSUV
Mamolo 2019 (10)	PF: 0.74 PD: 0.73	EQ-5D-3L	US	Used in scenario for calculation of ratio to obtain PF HSUV
HSUV following HSCT				
Allo-HSCT, first month	0.620	QLQ-C30	UK	Reference: Grulke et al 2012(7)
Allo-HSCT, to month 6	0.760	QLQ-C30	UK	Reference: Grulke et al 2012(7)
Allo-HSCT, to month 12	0.796	QLQ-C30	UK	Reference: Grulke et al 2012(7)
Allo-HSCT, from month 12	0.796	QLQ-C30	UK	Reference: Grulke et al 2012(7)
Disutilities				
Thrombocytopenia	0.108	QLQ-C30 and EQ-5D-3L	UK	TA627 (81)
Anaemia	0.119	QLQ-C30 and EQ-5D-3L	UK	TA627 (81)
Other haematological disorders	0.087815	QLQ-C30 and EQ-5D-3L EQ-5D	UK UK	TA627 (Febrile Neutropenia, Neutropenia, Hypokalemia) (81) Sullivan 2011 (Other Hematologic Conditions)(82)
Acute myeloid leukaemia	0.175	standard gamble (SG) or TTO	NA	Shabaruddin 2013 (83)
Gastrointestinal bleed	0.0512	EQ-5D	UK	Sullivan 2011 (Other Gastrointestinal Disorders) (82)
Cardiac arrest	0.0626	EQ-5D	UK	Sullivan 2011 (Acute Myocardial Infarct) (82)
Non-malignant gastro-intestinal tract disorders	0.049686	QLQ-C30 and EQ-5D-3L	UK	TA604 (Colitis) (84) TA627 (Nausea, Diarrhoea) Sullivan 2011 (Other Gastrointestinal Disorders) (82)
Non-malignant hepatobiliary or pancreatic disorder	0.041733	EQ-5D	UK	Sullivan 2011 (Other Liver Diseases) (82) Sullivan 2011 (Cholelithiasis) (82)

	Results	Instrument	Tariff used	Comments
Haemorrhagic cerebrovascular disorders	0.1171	EQ-5D	UK	Sullivan 2011 (Cva) (82)
Cerebrovascular accident, nervous system infections, or encephalopathy	0.0856	EQ-5D	UK	Sullivan 2011 (Other Brain Conditions) (82)
Pneumonia	0.2	QLQ-C30 and EQ-5D-3L	UK	TA627 (81)
Pleural effusion	0.0776	EQ-5D	UK	Sullivan 2011 (Other Lung Diseases) (82)
Low back pain	0.1442	EQ-5D	UK	Sullivan 2011 (Intervertebral Disc Dis) (82)
Hypertension	0.0375	EQ-5D	UK	Sullivan 2011 (Essential Hypertension) (82)
Unspecified oedema	0.06	SG and TTO	NA	Shabaruddin 2013 (83)
Fever of unknown origin	0.11	EQ-5D	UK	TA604 (84)
Breast disorders	0.0033	EQ-5D	UK	Sullivan 2011 (Other Breast Disorders) (82)
Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head Injury	0.094	QLQ-C30 and EQ-5D-3L	UK	TA627 (Fatigue) (81) TA604 (Asthenia) (84)
Sleep disorders	0.066	NA	NA	Lubetkin 2018 (85)
Other respiratory disorders	0.041467	EQ-5D	UK	TA604 (Dyspnoea) (84) Sullivan 2011 (Oth Resp System Diseases) (82)
Sepsis	0.267	QLQ-C30 and EQ-5D-3L	UK	TA627 (81)
Hearth failure or shock	0.0626	EQ-5D	UK	Sullivan 2011 (Acute Myocardial Infarct) (82)
Headache, migraine or cerebrospinal fluid leak	0.02295	EQ-5D	UK	Sullivan 2011 (Migraine) (82) Sullivan 2011 (Chronic Sinusitis) (82)
Peripheral vascular disorders	0.057	QLQ-C30 and EQ-5D-3L	UK	TA627 (Hypotension) (81)
Kidney or urinary tract infections	0.0054	EQ-5D	UK	Sullivan 2011 (Oth Urinary Tract Disor) (82)
Skin disorders	0.195	QLQ-C30 and EQ-5D-3L	UK	TA627 (81)

	Results	Instrument	Tariff used	Comments
Non-malignant, ear, nose, mouth, throat or neck disorders	0.0103	EQ-5D	UK	Sullivan 2011 (Other Ear And Sense Organ Disorders) (82)

Abbreviations: CR: complete response; PF: progression-free ; PD : progressed, HSUV: health state utility value, EQ-5D-3L: EuroQol 5-Dimensions 3-Levels, RAC-RE: response assessment committee response-evaluable population, 2L: second line, CI: confidence interval.

11. Resource use and associated costs

Costs and resource use vary dependent on the administered treatment and health states. The model includes direct medical costs, as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective as described in the DMC guidelines (55). All costs were valued in 2024 Danish Krone (DKK), except costs sourced from DMC's unit cost catalogue (2023).

The following section regarding cost and resource use is presented per health state, containing information regarding drug acquisition costs, administration costs, disease management costs, follow-up costs, AE costs and costs associated with allo-HSCT and post-progression. Drug costs are sourced from Medicinpriser.dk and applied as pharmacy purchasing prices (apotekernes indkøbspris, AIP) (53). Disease management, administration costs, allo-HSCT costs, and AE costs are based on Danish diagnosis related groups (DRG) tariffs from 2024 and DMC catalogue for unit costs (2023) (86, 87). Patient and transportation costs are based on the DMC catalogue for unit costs and are presented in a separate section covering all patient- and transportation costs for all health states (86).

11.1 Pharmaceutical costs (intervention and comparator)

Avapritinib

Avapritinib is an oral therapy provided as tablets containing 300 (not for AdvSM), 200, 100, 50, or 25 mg, all with the same list price of XXXXXXXX DKK per pack of 30 tablets, informed by Blueprint Medicine (12). The dosing regimen of avapritinib is 200 mg once daily and is aligned with the recommended starting dose of avapritinib and the PATHFINDER trial (73). The acquisition cost of avapritinib is presented in Table 53.

Best available treatment (BAT)

BAT comprises of a mix of off-label treatments including cladribine, TKIs (imatinib, nilotinib, and dasatinib), interferons (interferon-alpha-2a and peg-interferon-alpha), and AML like treatments (azacytidine and cytarabine based treatments). In the base case, the distribution of the cohort allocated to each off-label treatment in the BAT basket was based on the NICE TA728 allocation share, refer to Table 52, (TA728, Committee papers, Table 40) (51).

Table 52 Distribution of the cohort among the different treatment modalities in the BAT arm

Pharmaceutical	% proportion of patients receiving
Cladribine	53.65%
Interferon alpha-2a	2.05%

Pharmaceutical	% proportion of patients receiving
Imatinib	4.51%
Peg-interferon alpha 2a	24.23%
AML-like treatment[a]	15.56%
Midostaurin	0% (scenarios: 50% and 20%)

Note: AML-like treatments include: azacitidine, AML-like (C+D), (C+I), (C+M+E), and (C+M)
Abbreviations: AML-like: acute myeloid leukemia-like, C: cytarabine, D: daunorubicin, E: etoposide, I: idarubicine, M: mitoxantrone

In the base case, the proportion of patients receiving midostaurin is 0%. This is considered conservative since Swedish clinical experts (88) have reported midostaurin use post first-line treatment (20%). Therefore, in a scenario analysis, patients are assumed to receive 20% midostaurin. Furthermore, in another scenario analysis, the observed midostaurin usage observed in BLU-285-2405 (second line (2L+) of approximately 50%) (3) will be explored.

The acquisition cost of BAT is presented in Table 53. The proportion of patients receiving each therapy was taken from GID-TA10503/TA728 (TA728, Committee papers, Table 40) (51) and BLU-285-2405 (3). The dosing regimen of BAT is based on the literature (51, 62) (63, 64) (65), and reported in (63, 64) (65), and reported in Table 54. To reflect the different posology, the drug costs were modelled in different ways: avapritinib, (midostaurin for scenario), TKIs and interferons were costed per cycle, while cladribine and AML-like treatments were associated with a One-Off cost.

Table 53 Pharmaceutical costs used in the model

Pharmaceutical	Strength (mg)	Package size	Pharmacy purchase price [DKK] (53)
Avapritinib	300	30	XXXXXXXX
	200	30	XXXXXXXX
	100	30	XXXXXXXX
	50	30	XXXXXXXX
	25	30	XXXXXXXX
Cladribine	10	1	2,700.00
Interferon alpha-2a	180	4	4,996.28
Imatinib	400	30	6,674.63
Nilotinib	50	120	21,807.34
Dasatinib	140	30	22,400.00
Peg-interferon alpha 2a	180	4	4,996.28
Azacitidine	100	1	498.00
Cytarabine	100	10	100.00
Daunorobicine	20	1	726.59
Idarubicine	100	5	1,350.00
Mitoxantrone	5	1	15,042.00
Etoposide	100	5	90.00

Pharmaceutical	Strength (mg)	Package size	Pharmacy purchase price [DKK] (53)
Midostaurin	20	2x28	44,517.51

Note: avapritinib 300mg is not used for treatment of AdvSM. Furthermore, the packages with 50mg and 25mg are not available at medicinpriser.dk. AML-like treatment includes: AML-like treatment C+D (cytarabine and daunurobicine), AML-like treatment C+I (cytarabine and idarubicine), AML-like treatment C+M+E (cytarabine, mitoxantrone, and etoposide), and AML-like treatment C+M (cytarabine and mitoxantrone). Furthermore, Interferon alpha-2a is not available in Denmark. Set equal to peg-interferon alpha-2a. Abbreviations: DKK: Danish Krone.

Table 54: Dosing regimen related to the drugs included in comparator arm

Regimen	Dose	Frequency	Source
Cladribine	0.14 mg/kg	Given day 1-5, maximum number of 9 cycle	NICE TA728 (51) and Barete et al. (65)
Interferon-alpha	180 mcg/week	Median admin per cycle = 4	NICE TA728 (51)
Imatinib	400mg/day	Once daily	NICE TA728 (51)
Peg-interferon alpha 2a	Assumed equal to interferon-alpha (peg-interferon alpha is not available in Denmark)		
AML-like treatment	Azacitidine based: 2 packs per administration were used, for a total of 7 administrations per cycle for 6 cycles. Cytarabine based: several drugs and schedules, depending on what is reported in the literature		Dombret et al. (62), Wiernik et al. (59), Meloni et al. (60), and Röllig et al (61).
Midostaurin	200 mg/day	Daily	NICE TA728 (51)

11.2 Pharmaceutical costs – co-administration

Not applicable.

11.3 Administration costs

Avapritinib, TKIs (imatinib, nilotinib, dasatinib), and midostaurin are all administered orally; hence no administration costs are applied. Table 55 summarizes the unit costs of the treatment administration. The unit costs for the mode of administration were obtained from DRG tariffs 2023 or from the DMC's unit cost catalogue and are applied to the administration cost in the model (86, 87).

Table 55 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral	NA	0.00	NA	Assumption
IV	See Table 56	1,989.00	17MA98	DRG 2024 (87)
Subcutaneous	See Table 56	441.00	NA	DMC catalogue (86)
IV with hospitalisation (per day)	See Table 56	2,926.23	17MA04	DRG 2024 (87)

Note: DRG code 17MA04 for IV administration with hospitalisation beyond the trim point (trim point = 14), corresponding to 2,926.64 DK (trim point: value for the maximum number of bed days covered by the individual DRG rate)
Abbreviations: IV: intravenously, NA: not applicable, DMC: Danish Medicines Council, DRG: diagnosis related groups.

Interferons are administered subcutaneous, and it has been assumed that 15% of patients will require nursing assistance for administration, informed by GID-TA10503/TA728 (TA728, Committee papers, Section B.3.5.1, "Intervention and comparator costs and

resource use) (51). 65% of patients were assumed to receive Cladribine in an outpatient setting during the first cycle, while 35% were assumed to be hospitalized for 9 days. In the remaining cycles only 5% of the administrations were assumed to occur in an inpatient setting, In line with TA728, (TA728, Committee papers, Section B.3.5.1, "Intervention and comparator costs and resource use) (51). AML-like treatment is assumed to be administered intravenously (IV). All assumptions regarding the administration settings are provided in Table 56.

Table 56 Administration settings for included comparators.

Treatment and administration	% of patients		Days, n		Reference
	1st cycle	Subsequent cycles	1st cycle	Subsequent cycles	
Cladribine					
IV with hospitalisation	35%	5%	9	9	**TA728, (TA728, Committee papers, Section B.3.5.1, "Intervention and comparator costs and resource use)** (51)
IV (outpatient)	65%	95%	5	5	
C + M + E					
IV with hospitalisation	35%	5%	6	6	Amadori et al. (60)
IV (outpatient)	65%	95%	6	6	Amadori et al. (60)
C + M					
IV with hospitalisation	35%	5%	6	6	Röllig et al. (61)
IV (outpatient)	65%	95%	4	4	Röllig et al. (61)
Interferons					
Subcutaneous (nurse)	15%	15%	12	12	TA728 (TA728, Committee papers, Section B.3.5.1, "Intervention and comparator costs and resource use) (51).
Azacitidine					
IV (outpatient)	100%	100%	7	7	Dombret et al. (62)
C + D / C + I					
IV with hospitalisation	100%	100%	7	7	Wiernik et al. (59)

Abbreviations: C: cytarabine, D: daunorubicin, E: etoposide, I: idarubicine, M: mitoxantrone (AML-like treatments), IV: intravenously.

11.4 Disease management costs

The costs of disease management are assumed to vary between PF and PD. Within the PF health state, a distinction has been done between the first six cycles, the cycles between the 6th and 12th cycle and the cycles after the 12th cycle. This approach is in line with the one used in previous HTA submission for midostaurin for treating AdvSM (TA728, Committee papers, Section B.3.5.2, "Health-state unit costs and resource use") (51). To inform the quantity of resourced used, clinical expert were interviewed. Resource use in the model is reported in Table 57 (51).

Table 57 Disease management costs used in the model

Activity	Frequency				Unit cost [DKK]	Reference
	0-6 m	6-12 m	12 + m	Any cycle		
GP-visit surgery	Every 4 weeks	Every 54 weeks	Every 54 weeks	Every 54 weeks	1,049.00	DMC catalogue (86)
District nurse visit	Every 4 weeks	Every 54 weeks	Every 54 weeks	Every 54 weeks	441.00	DMC catalogue (86)
Cancer nurse visit	Every 4 weeks	Every 54 weeks	Every 54 weeks	Every 54 weeks	577.00	DMC catalogue (86)
Pain/symptom management	Every 4 weeks	Every 54 weeks	Every 54 weeks	Every 54 weeks	147.85	DMC catalogue (86)
Depression management	Every 4 weeks	Every 54 weeks	Every 54 weeks	Every 54 weeks	2,089.00	Psykiatritakster 2024(89)
Outpatient visit (oncology)	Every 4 weeks	Every 54 weeks	Every 54 weeks	Every 54 weeks	1,049.00	DMC catalogue (86)
ED use	NA	NA	NA	Every 4 weeks	40,973.00	DRG 2024, 17MA04 (87)
Hospitalisation days	NA	NA	NA	Every 4 weeks	2,926.64	DRG 2024, 17MA04 (87)
ICU	NA	NA	NA	Every 4 weeks	40,973.00	DRG 2024, 17MA04 (87)
Bone marrow biopsy	Every 4 weeks	Every 87 weeks	Every 54 weeks	Every 54 weeks	14,190.00	DRG 2024, DD470C (87)
ECG	Every 4 weeks	Every 87 weeks	Every 54 weeks	Every 54 weeks	1,989.00	DRG 2024 17MA98 (87)
CT scan	NA	NA	NA	Every 54 weeks	2,585.00	DRG 2024, 30PR06 (87)
Chest X Ray	NA	NA	NA	Every 54 weeks	1,697.00	DRG 2024, 30PR18 (87)
US scan	NA	NA	NA	Every 54 weeks	2,086.00	DRG 2024, 30PR10 (87)
MRI scan	NA	NA	NA	Every 54 weeks	2,511.00	DRG 2024, 30PR02 (87)
Blood test	Every 4 weeks	Every 87 weeks	Every 54 weeks	Every 54 weeks	103.00	Region Hovedstaden (90)
Bone densitometry	NA	NA	NA	Every 54 weeks	2,021.00	DRG 2024, 30PR02 (87)

Abbreviations: DKK: Danish Krone, DMC: Danish Medicines Council, DRG: diagnosis-related groups, GP: general practitioner, ED: emergency department, ICU: intensive care unit, ECG: electrocardiogram, CT: computed tomography, US: ultrasound, MRI: magnetic resonance imaging, NA: not applicable.

11.5 Costs associated with management of adverse events

The model captures the costs associated with the management of treatment-related AEs with Common Terminology Criteria (CTC) grade of 3, 4 or 5. The incidence on included AEs were obtained from the PATHFINDER trial and from external literature (65) (36) (52).

The costs of each AE related treatment have been corrected in the model for the per-cycle incidence of the correspondent AE. By default, all AEs with an incidence of more than 5% in any of the arms of the trials were considered. The costs of each AE related treatment have been corrected in the model for the per-cycle incidence of the correspondent AEs. Estimated unit costs per AE are shown in Table 58Table 58.

Table 58 Cost associated with management of adverse events

	DRG code	Unit cost (DKK)/DRG tariff(87)
Thrombocytopenia	DRG 2024, 16MA03, (DD696), >12	37,129.00
Anaemia	DRG 2024, 16MA10, (DD649), >12	27,121.00
Other haematological disorders	DRG 2024, 16MA03. (DD709), >12	37,129.00
Gastrointestinal bleed	DRG 2024, 17MA01, (DC928), >12	48,340.00
Acute myeloid leukaemia	DRG 2024, 16MA05, (DD594), >12	41,154.00
Sepsis	DRG 2024, 18MA01, (DA419), >12	50,299.00
Hearth failure or shock	DRG 2024, 05MA07, (DI469), >12	19,623.00
Cardiac arrest	DRG 2024, 05MA07, (DI469), >12	19,623.00
Cerebrovascular accident, nervous system infections, or encephalopathy	DRG 2024, 01MA03, (DG048), >12	72,892.00
Haemorrhagic cerebrovascular disorders	DRG 2024, 01MA05, (DI619), >12	44.492.00
Non-malignant gastro-intestinal tract disorders	DRG 2024, 06MA11, (DR119), >12	7,818.00
Non-malignant hepatobiliary or pancreatic disorder	DRG 2024, 07MA05, (DK768), >12	36,225.00
Pneumonia	DRG 2024, 04MA14, (DJ189), >12	35,426.00
Pleural effusion	DRG 2024, 04MA09, (DJ919), >12	39,036.00
Low back pain	DRG 2024, 08MA14, (DM549), >12	23,522.00
Hypertension	DRG 2024, 05MA08, (DR030), >12	2,167.00
Syncope or collapse	DRG 2024, 05MA98, (DR559), >12	1,183.00
Unspecified oedema	DRG 2024, 23MA03, (DR609), >12	5,103.00
Tendency to fall, senility or other condition affective cognitive functions	DRG 2024, 01MA17, (DR296), >12	28,723.00
Fever of unknown origin	DRG 2024, 18MA04, (DR509), >12	21,529.00
Breast disorders	DRG 2024, 05MA03, (DR074), >12	4,007.00
Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head Injury	DRG 2024, 01MA10, (DG408), >12	23,734.00
Sleep disorders	DRG 2024, 19MA09, (DF5100), >12	15,159.00
Other respiratory disorders	DRG 2024, 04MA24, (DJ984), >12	31,294.00
Headache, migraine or cerebrospinal fluid leak	DRG 2024, 23MA03, (DR519), >12	5,103.00

	DRG code	Unit cost (DKK)/DRG tariff(87)
Peripheral vascular disorders	DRG 2024, 05MA08, (DI999), >12	2,167.00
Kidney or urinary tract infections	DRG 2024, 11MA07, (DN390), >12	30,859.00
Skin disorders	DRG 2024, 09MA03, (DL989), >12	20,231.00
Non-malignant, ear, nose, mouth, throat or neck disorders	DRG 2024, 03MA09, (DH938), >12	1,331.00

Abbreviations: DKK: Danish Krone, DRG: diagnosis-related groups.

11.6 Subsequent treatment costs

Costs related to allo-HSCT were applied to the proportion of patients estimated to undergo a HSCT procedure. It should be mentioned that allo-HSCT was considered as a subsequent line of therapy, and it is assumed that patients eligible for allo-HSCT will spend 1 year in the pre-HSCT state, to which the resource use and costs is assumed to be equivalent to average of the per-cycle cost across the PF states (0-6 and 6-12 months). The cost of allo-HSCT is applied as one-off, assumed to include pre-HSCT costs, hospitalisation costs, oncologist follow- up costs. Starting from the 12th month after HSCT a cured state was assumed, which has been associated with zero costs per cycle. The unit cost of allo-HSCT is based on the 2024 DRG tariff 26MP22 corresponding to 904,674.00 DKK. The cost of 1,066.00 DKK is applied for the first year after HSCT, reflecting the oncologist follow-up costs (DMC unit cost catalogue). This is in line with the assumptions made in TA523 (TA523, Committee papers, Table 41) (66). Table 59 summarizes the costs associated with allo–HSCT.

Table 59 Cost associated with allo-HSCT

	Cost (DKK)
Per-cycle pre-HSTC cost	16,129
Allo-HSCT initial one-off cost	904,674
Per-cycle follow-up cost after HSTC, up to 12m	1,794
Per-cycle follow-up cost after HSTC, 12m +	0.00

Abbreviations: HSCT: haematopoetic stem cell transplantation, DKK: Danish Krone.

Costs after treatment discontinuation and after progression

In the pivotal trials of avapritinib, some patients are reported to interrupt the treatment before progression. To reflect this in the model, the cost of BAT (excluding midostaurin only in scenario analysis where proportion of patients receiving midostaurin is 20% and 50%. Excluding the midostaurin cost was deemed as appropriate since it is unrealistic that non progressed patients who interrupt avapritinib receive midostaurin instead) is assigned to a part of the avapritinib treatment arm in a PF state. In the base case, the PFS curve of the BAT arm is assumed to be the same as the ToT curve. Therefore, no part of the cohort is off treatment before progression.

11.7 Patient costs

Patient costs for transportation and time have been included based on the requirements from the DMC (55). Frequency of healthcare visits related to disease management are presented in Section 11.4 and are used for cost estimation of patient time and

transportation costs. It was assumed that each outpatient visit would take an average of 0.5 hours patient time and each inpatient visit would take an average of 16 hours patient time. The value of patients' time was DKK 203 per hour, and travel expenses were assumed to be DKK 140 per roundtrip, as per DMC's unit cost catalogue (2023) (86).

It has been assumed that certain tests and visits can be combined during a single outpatient appointment, see Table 60. Since it is assumed that patients spend 0.5 hour per outpatient visit, this is corresponding to a cost of 241.50 DKK per outpatient visit. For inpatient visit, the assumed time of 16 hours, is corresponding to a cost of 3,338.00 DKK per inpatient visit.

Table 60 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Outpatient visit (oncology) + bone marrow biopsy + ECG + BT (PD: + BD)	Setting assumption: outpatient Patient time required assumption: 30 minutes
CT + X-ray + US	Setting assumption: outpatient Patient time required assumption: 60 minutes (this is the only outpatient item where the hours per visit is assumed to be doubled)
Palliative care: pain management and cancer nurse	Setting assumption: outpatient Patient time required assumption: 30 minutes
GP - visit surgery	Setting assumption: outpatient Patient time required assumption: 30 minutes
District nurse visit	Setting assumption: outpatient Patient time required assumption: 30 minutes
Depression management	Setting assumption: outpatient Patient time required assumption: 30 minutes
MRI scan	Setting assumption: outpatient Patient time required assumption: 30 minutes
ED use	Setting assumption: inpatient Patient time required assumption: 16 hours
Hospitalisation days	Setting assumption: inpatient Patient time required assumption: 16 hours
ICU	Setting assumption: inpatient Patient time required assumption: 16 hours

Abbreviations: ECG: electrocardiogram, BT: Blood tests, PD: progressed disease, BD: bone densitometry, CT: computed tomography, US: ultrasound, GP: general practitioner, MRI: magnetic resonance imaging, ED: emergency department, ICU: intensive care unit.

Based on the weighted frequency of resource use reported in Table 57, the total costs per month for PF and PD is 1,400.70 DKK and 967.68 DKK, respectively.

11.8 Other costs (e.g., costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

The key aspects of the base case cost-effectiveness model are presented in Table 61.

Table 61 Base case overview

Feature	Description
Comparator	BAT
Type of model	Partitioned survival model (PartSA) with a semi-markov model.
Time horizon	Lifetime (23 years)
Treatment line	2L+ line. Subsequent treatment with allo-HSCT is possible.
Measurement and valuation of health effects	HRQoL measured with QLQ-C30 in PATHFINDER (April 2021 DCO) for PF patients (4, 5). QLQ-C30 was mapped into EQ-5D-3L scores using a mapping algorithm by Young et al (58). A TLR was used to identify a PFS-PD utility ratio, which was then applied to the PF utility value. The QoL of the patients undergoing allo-HSCT were taken from Grulke et al (7). UK population weights has been used to estimate health-state utility values (91).
Costs included	Pharmaceutical costs Administration costs of BAT Disease management costs Costs of adverse events Cost of allo-HSCT Patient time and transportation costs
Dosage of pharmaceutical	Fixed dosage of avapritinib
Average time on treatment	Avapritinib: XXXXXXXX , BAT: XXXXXXXX
Parametric function for PFS	Avapritinib: Exponential, BAT: Using the ToT HR derived from the ITC
Parametric function for OS	Avapritinib: Exponential, BAT: Using the OS HR derived from the ITC
Inclusion of waste	No
Average time in model health state	
PF	Avapritinib: XXXXXXXX / BAT: XXXXXXXX
PD	Avapritinib: XXXXXXXX / BAT: XXXXXXXX
Pre-transplant*	Avapritinib: XXXXXXXX / BAT: XXXXXXXX
Post-transplant*	Avapritinib: XXXXXXXX / BAT: XXXXXXXX

Note: * pre-transplant and post-transplant

Abbreviations: BAT: best available treatment, PartSA: partitioned survival, allo-HSCT: haematopoetic stem cell transplantation, HRQoL: health-related quality of life, QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 , DCO: data cut-off, EQ-5D-3L: EuroQol 5-Dimensions 3-levels, TLR: PF: progression free, PD: progressed disease, QoL: quality of life, OS: overall survival, HR: hazard ratio, ITC: indirect treatment comparison.

12.1.1 Base case results

In the model base case where avapritinib is compared against BAT, discounted results are presented in Table 62. Using a lifetime horizon, the incremental expected total life-year gain amounts to XXXXXXXX (discounted). The discounted incremental costs of XXXXXXXX DKK and incremental QALYs of XXXXXXXX resulted in an incremental cost-effectiveness ratio (ICER) of XXXXXXXX DKK / QALY versus BAT.

Table 62 Base case results, discounted estimates

	Avapritinib	BAT	Difference
Pharmaceutical costs	XXXXXXX	XXXXXXX	XXXXXXX
Pharmaceutical costs – co-administration	NA	NA	NA
Administration	XXXXXXX	XXXXXXX	XXXXXXX
Disease management costs	XXXXXXX	XXXXXXX	XXXXXXX
Costs associated with management of adverse events	XXXXXXX	XXXXXXX	XXXXXXX
Subsequent treatment costs (allo-HSCT)	XXXXXXX	XXXXXXX	XXXXXXX
Patient costs	XXXXXXX	XXXXXXX	XXXXXXX
Palliative care costs	NA	NA	NA
Total costs	XXXXXXXX	XXXXXXXX	XXXXXXXX
Life years gained, PF	XXXXXXX	XXXXXXX	XXXXXXX
Life years gained, PD	XXXXXXX	XXXXXXX	XXXXXXX
Life years gained, pre-HSCT	XXXXXXX	XXXXXXX	XXXXXXX
Life years gained, post-HSCT	XXXXXXX	XXXXXXX	XXXXXXX
Total life years	XXXXXXXX	XXXXXXXX	XXXXXXXX
QALYs, PF	XXXXXXX	XXXXXXX	XXXXXXX
QALYs, PD	XXXXXXX	XXXXXXX	XXXXXXX
QALYs, Pre-HSCT	XXXXXXX	XXXXXXX	XXXXXXX
QALYs, Post-HSCT	XXXXXXX	XXXXXXX	XXXXXXX
QALYs (adverse reactions)	NA	NA	NA
Total QALYs	XXXXXXXX	XXXXXXXX	XXXXXXXX
Incremental costs per life year gained	XXXXXXXX		
Incremental cost per QALY gained (ICER)	XXXXXXXX		

Abbreviations: BAT: best available treatment, DKK: Danish Krone, NA: not applicable, PF: progression-free, PD: progressed disease, HSCT: haematopoietic stem cell transplantation, QALY: quality-adjusted life-years, ICER: incremental cost-effectiveness ratio.

12.2 Sensitivity analyses

Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications, including details of how they varied in the model can be found in Appendix G

12.2.1 Deterministic sensitivity analyses

Univariate parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by ±10% or by a specific standard errors or predefined upper and lower limits. The 10 most influential model parameters with regards to impact on range of impact on the base case ICER are presented in Table 63 (for both the lower and upper parameter value), and as a tornado diagram in Figure 15. The OS HR avapritinib versus BAT parameter is the most influential parameter followed by the HRQoL in PF health state, and the discount rate for outcomes.

Table 63 One-way sensitivity analyses results

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	0.0	NA	[redacted]	[redacted]	[redacted]
OS HR avapritinib vs comparators, BAT – lower value	[redacted]	Range of impact on the base case ICER	[redacted]	[redacted]	[redacted]
OS HR avapritinib vs comparators, BAT – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
HRQoL in health states, Progression free – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
HRQoL in health states, Progression free – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Discount rate outcomes – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Discount rate outcomes – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
ToT HR avapritinib vs comparators, BAT – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
ToT HR avapritinib vs comparators, BAT – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Discount rate costs – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Discount rate costs – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
HRQoL in health states, Progressed disease – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
HRQoL in health states, Progressed disease – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Disease management cost, per-cycle progressed – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Disease management cost, per-cycle progressed – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Initial age (years) – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Initial age (years) – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Proportion with SM-AHN – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Proportion with SM-AHN – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
% fit for transplant – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
% fit for transplant – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]

Abbreviations: DKK: Danish Krone, QALY: quality-adjusted life-years, ICER: incremental cost-effectiveness ration, NA: not applicable, OS: overall survival, HR: hazard ratio, BAT: best available treatment, ToT: time on treatment.

Figure 15 Tornado diagram

Abbreviations: OS: overall survival, HR: hazard ratio, BAT: best available treatment, SoC: standard of care, ToT: time on treatment, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life-years

A number of scenarios were considered in the deterministic sensitivity analyses exploring variations from the base model settings (Table 61). Important factors for estimating the ICER of treatment of AdvSM with avapritinib include the chosen time horizon, the method of calculating the PFS – PD utility ratio, the choice between CR and ORR for eligibility for allo-HSCT, the analysis population, and the extrapolation method for BAT PFS. Stein et al, Joshi et al, Leunis et al and Mamolo et al were used to calculate the ratio between PF and PD utility values (11) (8) (9) (10). Variations in utility values significantly influenced the ICER. The Mamolo et al was selected for the base case, as they closely matched the PF utility result from the PATHFINDER trial. Two scenario analyses, using weighted and plain averages, reduced the ICER by more than 6%. If OR is used as the threshold for qualification for allo-HSCT, this will impact the ICER significantly. The Pooled EXPLORER and PATHFINDER, 200mg population was considered in the scenario analysis to align with the ITC population. Lastly, in the absence of PFS data for the BAT arm, in this scenario, the BAT OS HR was assumed to hold also for the PFS. In this scenario the ToT curve may cross the PFS curve. In this case the BAT treatment is assumed to continue after progression until the treatment discontinuation as defined by ToT occurs.

Table 64 Scenario analyses

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	0%	NA	[redacted]	[redacted]	[redacted]
Time horizon – 5 years	[redacted]		[redacted]	[redacted]	[redacted]
BAT PFS – use the same HR as for OS	[redacted]	ITC could not provide an estimate of the relative PFS. Refer to section 8.1 for more details.	[redacted]	[redacted]	[redacted]
Utility decrements applied	[redacted]	DMC preference	[redacted]	[redacted]	[redacted]
Population for OS post-HSCT – All patients	[redacted]	To explore the KM curves from Ustun et al. (70)	[redacted]	[redacted]	[redacted]
Population for OS post-HSCT – upper c limit patients	[redacted]	To explore the KM curves from Ustun et al. (70)	[redacted]	[redacted]	[redacted]
PF utility value – DK weighted	[redacted]	DMC method guide, DK tariffs	[redacted]	[redacted]	[redacted]
PD utility value – UK weighted, weighted average	[redacted]	Deviation in utility values found in the TLR studies	[redacted]	[redacted]	[redacted]
PD utility value – UK weighted, plain average	[redacted]	DMC method guide, DK tariffs	[redacted]	[redacted]	[redacted]
PD utility value, DK weighted – Mamolo et al.	[redacted]	DMC method guide, DK tariffs	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
PD utility value – DK weighted, weighted average	XXXXXXX	DMC method guide, DK tariffs	XXXXXXX	XXXXXXX	XXXXXXX
PD utility value – DK weighted, plain average	XXXXXXX	DMC method guide, DK tariffs	XXXXXXX	XXXXXXX	XXXXXXX
Utility value (all HSUV) with DK weights	XXXXXXX	DMC method guide, DK tariffs	XXXXXXX	XXXXXXX	XXXXXXX
PD utility value, Pooled population – UK weighted, Mamolo et al.	Captured in the scenario "Analysis population – Pooled EXPLORER and PATHFINDER - ≤ 200- AdvSM – Safety" – base case for the ratio calculation remains to be Mamolo et al.				
PD utility value, Pooled population – UK weighted, weighted average	XXXXXXX	Deviation in utility values found in the TLR studies	XXXXXXX	XXXXXXX	XXXXXXX
PD utility value, Pooled population – UK weighted, plain average	XXXXXXX	Deviation in utility values found in the TLR studies	XXXXXXX	XXXXXXX	XXXXXXX
Analysis population – Pooled EXPLORER and PATHFINDER - ≤ 200- AdvSM - Safety	XXXXXXX	To be aligned with the ITC population	XXXXXXX	XXXXXXX	XXXXXXX
Response based on overall response	XXXXXXX	The choice between CR and ORR as a threshold for qualification is uncertain.	XXXXXXX	XXXXXXX	XXXXXXX
Midostaurin % - 50%	XXXXXXX	In line with the 2L+ cohort (BLU-RWE study, 49.2%). Furthermore, Despite the EMA label of midostaurin "monotherapy for treatment of AdvSM", midostaurin has often been the preferred choice in clinical practice due to reported better response and survival rates.	XXXXXXX	XXXXXXX	XXXXXXX
Midostaurin % - 20%	XXXXXXX	Refer to above. Perceptions from clinical experts indicates that midostaurin can be used across all lines (88).	XXXXXXX	XXXXXXX	XXXXXXX

Note: Scenario analysis with PD value calculated with Danish weights can only be conducted if the PF value also is run with Danish weights, since the PD is calculated using a ratio applied to the PF value. Furthermore, the application of Danish weighted utility values for allo-HSCT (all states) can be ran when the PF and PD are also calculated on Danish tariffs. Hence the scenario with Danish utility values is conducted for all health states at once. Note: that the PFS-PD ratio will automatically be Danish weighted since the PF state is DK weighted in this scenario.
Abbreviations: DKK: Danish Krone, QALY: quality-adjusted life-years, ICER: incremental cost-effectiveness ratio, BAT: best available treatment, PF: progression-free, OS: overall survival, HR: hazard ratio, DMC: Danish Medicines Council, KM: Kaplan-Meier, HSCT: haematopoietic stem cell transplantation, PD: progressed disease, HSUV: health state utility value: AdvSM: advanced systemic mastocytosis, CR: complete response, ORR: overall response.

12.2.2 Probabilistic sensitivity analyses

A scatter plot of 1,000 simulations, including a 95% confidence cloud, is presented in Figure 16, with a cost-effectiveness acceptability curve presented in Figure 17. The full set of parameters included in the model, including details of distributional forms, are presented in Appendix G.

Figure 16 Scatter plot of 1,000 simulations
Abbreviations: QALY: quality-adjusted life-years, CE: cost-effectiveness.

Figure 17 Cost-effectiveness acceptability curve
Abbreviations: QALY: quality-adjusted life-years, WTP: willingness to pay

13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending avapritinib for treatment of AdvSM in Denmark. The budget impact

analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the cost per patient model. The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the DMC (55).

The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where avapritinib is recommended as a standard treatment and the scenario where avapritinib is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios.

13.1 Number of patients (including assumptions of market share)

For the purpose of estimating the budget impact of the introduction of avapritinib, a starting prevalence population of 14 eligible patients at Year 1 is assumed (discussed in Section 3.2). The annual incidence of 3 new patients is supported by a Danish publication by Cohen et al., 2014, who reported an estimated incidence of 0.06 (30). To account for the number of eligible AdvSM patients who have received prior systematic therapy, Dutch clinical experts and the applicants market research state that 70% of the prevalence population would be eligible for 2nd line targeted treatment (31, 32). Among the incidence population, it is expected that 2 new AdvSM patient would be eligible for 2nd line treatment every year, as one third of the incidence patients would not qualify for this treatment (2 out of 3). For the patients being on treatment on average the duration is about 23 months (1-2 drop offs ever year), both based on clinical experience from other EU countries (12). This will result in 1 new eligible patient every second year as shown in Section 3.2. The estimated numbers of patients who would be treated with avapritinib under the scenarios where avapritinib is and is not introduced (Table 65) assume that 35% would be treated with avapritinib. This market share is supported by Dutch clinical experts and Danish market research, who expect that 35% of eligible patients would receive targeted treatment (31, 32).

Table 65 Number of new patients expected to be treated over the next five-year period if avapritinib is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Avapritinib	5	5	5	6	6
BAT	9	10	10	10	10
			Non-recommendation		
Avapritinib	0	0	0	0	0
BAT	14	15	15	16	16

Abbreviations: BAT: best available treatment

13.2 Budget impact

The budget impact is informed by comparing the costs for the Danish healthcare system per year over five years in the scenario where avapritinib is recommended as standard treatment and the scenario where avapritinib is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios.

The budget impact estimated in Table 66 is based on non-discounted cost outputs (2024 DKK) from the cost-effectiveness model for five years, and the assumed eligible patients described above, as well as the assumed uptake of avapritinib for the treatment of eligible Danish AdvSM patients described above.

Table 66 Expected budget impact of recommending avapritinib for treatment of AdvSM (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Avapritinib is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Avapritinib is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK: Danish Krone

14. List of experts

Doctor Span Groningen | Internist-haematologist at the Dept. of Haematology | University Medical Centre Groningen (The Netherlands) |, was consulted during the development of this application.

Doctor Mattias Mattsson| Consultant Haematologist at the Dept of Haematology | Uppsala University Hospital (Sweden) |, was consulted during the development of this application.

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Appendix A. Main characteristics of studies included

Table 67 Main characteristic of studies included

Trial name: EXPLORER (BLU-285-2101)	NCT number: NCT02561988
Objective	This is a Phase 1, open-label, dose-escalation study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and antineoplastic activity of avapritinib (also known as BLU-285), administered orally (PO), in adult patients with advanced systemic mastocytosis and other relapsed or refractory myeloid malignancies. The study consists of 2 parts: dose-escalation (Part 1) and expansion (Part 2).
Publications – title, author, journal, year	Reiter A, Schwaab J, DeAngelo DJ, Gotlib J, Deininger MW, Pettit KM, Alvarez-Twose I, Vannucchi AM, Panse J, Platzbecker U, Hermine O, Dybedal I, Lin HM, Rylova SN, Ehlert K, Dimitrijevic S, Radia DH. Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis. Blood Adv. 2022 Nov 8;6(21):5750-5762. doi: 10.1182/bloodadvances.2022007539. DeAngelo DJ, Radia DH, George TI, Robinson WA, Quiery AT, Drummond MW, Bose P, Hexner EO, Winton EF, Horny HP, Tugnait M, Schmidt-Kittler O, Evans EK, Lin HM, Mar BG, Verstovsek S, Deininger MW, Gotlib J. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. Nat Med. 2021 Dec;27(12):2183-2191. doi: 10.1038/s41591-021-01538-9. Epub 2021 Dec 6.
Study type and design	EXPLORER was a Phase 1, open-label, single-arm, multicentre, dose escalation and dose expansion clinical study.
Sample size (n)	86
Main inclusion criteria	For Part 1: Patients must have one of the following diagnoses based on World Health Organization (WHO) diagnostic criteria: • Aggressive systemic mastocytosis (ASM). • Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and at least 1 C-finding attributable to systemic mastocytosis (SM). The AHN must be myeloid, with the following exceptions that are excluded: Acute myeloid leukaemia (AML), Myelodysplastic syndrome (MDS) that is very high- or high-risk as defined by the International prognostic scoring system for myelodysplastic syndromes (IPSS-R) and Philadelphia chromosome positive malignancies. • Mast cell leukaemia (MCL). • Histologically- or cytologically- confirmed myeloid malignancy that is relapsed or refractory to standard treatments. AML, MDS that is very high- or high-risk as defined by the IPSS-R, and Philadelphia chromosome positive malignancies are excluded. • Upon discussion with the sponsor, other relapsed or refractory, potentially avapritinib-responsive hematologic neoplasms (e.g., evidence of aberrant KIT or platelet derived

Trial name: EXPLORER (BLU-285-2101)	NCT number: NCT02561988

growth factor receptor (PDGFR) signalling) may be considered for enrolment.

For Part 2, patients must have one of the following diagnoses, based on WHO diagnostic criteria:

- ASM.
- SM-AHN. The AHN must be myeloid, with the following exceptions that are excluded: AML, MDS that is very high- or high-risk as defined by the IPSS-R, and Philadelphia chromosome positive malignancies.
- MCL.

For Part 2, Cohort 2, patients must have at least 1 measurable C-finding per modified IWG-MRT-ECNM criteria at Baseline, attributed to SM unless diagnosis is MCL, which does not require a C-finding.

- Cytopenia's: ANC < 1.0×10^9/L or haemoglobin < 10 g/dL or platelet count < 75×10^9/L.
- Symptomatic ascites or pleural effusion requiring medical intervention such as: use of diuretics (Grade 2) or ≥ 2 therapeutic paracenteses or thoracenteses (Grade 3) at least 28 days apart over the 12 weeks before study entry and 1 of the procedures is performed during the 6 weeks before study start (C1D1).
- ≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × upper limit of normal [ULN]), aspartate aminotransferase (AST; > 3.0 × ULN), alanine aminotransferase (ALT; > 3.0 × ULN), or alkaline phosphatase (> 2.5 × ULN) with 1 of the following present: ascites or clinically relevant portal hypertension or liver mast cell infiltration that is biopsy-proven or no other identified cause of abnormal liver function.
- ≥ Grade 2 hypoalbuminemia (< 3.0 g/dL).
- A spleen that is palpable ≥ 5 cm below the left costal margin.
- Transfusion-dependent anaemia defined as: transfusion of ≥ 6 units packed red blood cells (PRBCs) in the 12 weeks before start of treatment (C1D1) and most recent transfusion occurring during the preceding 4 weeks and transfusion administered for haemoglobin ≤ 8.5 g/dL and reason for transfusion is not bleeding, haemolysis, or therapy-related.

Eastern Cooperative Oncology Group (ECOG) performance status of 0-3

Main exclusion criteria	• QT interval corrected using Fridericia's formula (QTcF) >480 milliseconds • Platelet count <50,000/µL (within 4 weeks of the first dose of study drug) or receiving platelet transfusion(s) • Absolute neutrophil count <500/µL • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >3 x the upper limit of normal (ULN); >5 × ULN if associated with clinically suspected liver infiltration by mastocytosis or another disease for which the patient enrolled into the study • Total bilirubin >1.5 × ULN; >3 × ULN if associated with liver infiltration by the disease being treated or in the presence of Gilbert's Disease (In the case of Gilbert's disease, a direct bilirubin > 2.0 ULN would be an exclusion.)

Trial name: EXPLORER (BLU-285-2101)	NCT number: NCT02561988
	• Estimated (Cockroft-Gault formula) or measured creatinine clearance <40 mL/min • Brain malignancy or metastases to the brain • History of a seizure disorder or requirement for anti-seizure medication • Known risk of intracranial bleeding, such as a brain aneurysm or history of subdural or subarachnoid bleeding • Eosinophilia and known positivity for the FIP1L1-PGDFRA fusion, unless the patient has demonstrated relapse or progressive disease on prior imatinib therapy
Intervention	In Part 1, patients received single oral avapritinib doses of 30, 60, 100, 130, 200, 300, and 400 mg QD. The dose administered to a patient was dependent on which dose cohort was open for enrolment when the patient qualified for the study. Part 2 was initiated at the RP2D of 300 mg QD, however based on emerging data, the dose was reduced to 200 mg QD. Avapritinib was dosed daily for 28-day cycles.
Comparator(s)	N/A
Follow-up time	Median follow-up of 26.0 months for the RAC-RE population who received 200 mg of avapritinib with prior systematic therapy
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary outcome measures: 1. Maximum tolerated dose (MTD) of avapritinib 2. Number of patients with adverse and serious adverse events and changes in physical findings, vital signs, clinical laboratory results and ECG findings 3. Recommended Phase 2 dose (RP2D) of avapritinib Secondary outcome measures: 1. Maximum plasma concentration of avapritinib Blood samples may be taken at pre-dose, and 0.5, 1, 2, 4, 8 and 24 hrs post dose (plus 10 and 48 hrs post dose in Part 2) on Cycle 1 Day 1 and Cycle 1 Day 15, Pre-dose of Cycle 2 to 4, Day 1 2. Time to maximum plasma concentration of avapritinib Blood samples may be taken at pre-dose, and 0.5, 1, 2, 4, 8 and 24 hrs post dose (plus 10 and 48 hrs post dose in Part 2) on Cycle 1 Day 1 and Cycle 1 Day 15, Pre-dose of Cycle 2 to 4, Day 1 3. Overall Response Rate Including complete remission (CR), CR with partial recovery of peripheral blood (CRh), partial remission (PR) and clinical improvement (CI) using modified International Working Group Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European competence network on mastocytosis (ECNM) criteria; and duration of response (DOR) 4. Morphologic response Including morphologic complete remission (mCR), morphologic CR with partial recovery of peripheral blood (mCRh), and morphologic partial remission (mPR) based on Pure Pathologic Response

Trial name: EXPLORER (BLU-285-2101)	NCT number: NCT02561988

5. Changes in levels of serum tryptase and levels of V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) D816V allele burden in blood
6. Changes in patient reported symptoms and quality of life using the Patient Global Impression of Symptom Severity (PGIS) scale

Defined as change from Baseline

7. Changes in patient reported quality of life using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C-30)

Defined as change from Baseline

8. Changes in patient reported outcomes using the advanced SM symptom assessment form (AdvSM-SAF)

Defined as change from Baseline

9. Change in liver volume by imaging

mL

10. Change in spleen volume by imaging

mL

Method of analysis

ORR

Defined as the proportion of patients with a confirmed best response of CR, CRh, PR, or CI by mIWG-MRT-ECNM criteria

Defined as the proportion of patients with a confirmed best response of CR, CRh or PR by mIWG-MRT-ECNM criteria

Defined as the proportion of patients with a confirmed best response of CR or CRh by mIWG-MRT-ECNM criteria

DOR

DOR is defined as the time from first documented response (CR/CRh/PR/CI) to the date of first documented PD/LoR or death due to any cause, whichever occurs first. Responses are determined by mIWG criteria.

DOR will be analysed using KM methods and will include number of events and censors, the estimated median with two-sided 95% confidence intervals, and 25th and 75th percentiles. DOR/mDOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formulaDOR is defined as the time from first documented response (CR/CRh/PR) to the date of first documented PD/LoR or death due to any cause, whichever occurs first. Responses are determined by mIWG criteria.

DOR will be analysed using KM methods and will include number of events and censors, the estimated median with two-sided 95% confidence intervals, and 25th and 75th percentiles. DOR/mDOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula

Time to response

Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh/PR/CI) by mIWG is first met. Patients without confirmed response will be excluded from this analysis

Trial name: EXPLORER (BLU-285-2101)	NCT number: NCT02561988
	Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh/PR) by mIWG is first met. Patients without confirmed response will be excluded from this analysis Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh) by mIWG is first met. Patients without confirmed response will be excluded from this analysis **OS** OS is defined as the time from the start of treatment to the date of death. Patients who die before or on the data cutoff date will considered to have had an OS event. All Patients who do not have a death record prior to or on the cutoff date will be censored at the last date known alive. Last date known alive is defined as the last non-imputed date of any patient record prior to or on the data cutoff date in the clinical database. It can be the last visit date or last contact date that the patient is known to be alive. The survival distribution of OS will be estimated using the KM method. The median OS along with its two-sided 95% confidence intervals and 25th and 75th percentiles will be estimated. In addition, the survival rate at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula **PFS** PFS is defined as the time from the start of treatment to the date of first documented PD or death due to any cause, whichever occurs first. If a patient has not had an event, PFS is censored at the date of last valid assessment that is LoR or better. As specified in the IWG, development of AML will be treated as disease progression. The KM method will be used to estimate the PFS distribution function. The median PFS along with its two-sided 95% confidence intervals and 25th and 75th percentiles will be estimated. In addition, the event rates (or event-free) at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24-month, etc.) will be computed, along with the standard errors using Greenwood's formula
Subgroup analyses	Overall response rate analysis by RAC-RE population was presented for the following subgroups: • Age (<65 or ≥65 years) • Gender (male, female) • Region (US, Europe) • Baseline S/A/R genotype (with, without mutation) • Prior treatment with midostaurin (yes, no) • Prior antineoplastic therapy (yes, no) • Subgroup analyses for adjudicated DOR by mIWG-MRT-ECNM criteria by prior antineoplastic therapy status and prior midostaurin treatment status. • Subgroup analyses for OS by prior antineoplastic therapy status and prior midostaurin treatment status.
Other relevant information	N/A

Trial name: PATHFINDER (BLU-285-2202)	NCT number: NCT03580655
Objective	This is an open-label, single arm, Phase 2 study evaluating the efficacy and safety of avapritinib (BLU-285) in patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN), and mast cell leukaemia (MCL).
Publications – title, author, journal, year	Gotlib J, Reiter A, Radia DH, Deininger MW, George TI, Panse J, Vannucchi AM, Platzbecker U, Alvarez-Twose I, Mital A, Hermine O, Dybedal I, Hexner EO, Hicks LK, Span L, Mesa R, Bose P, Pettit KM, Heaney ML, Oh ST, Sen J, Lin HM, Mar BG, DeAngelo DJ. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med. 2021 Dec;27(12):2192-2199. doi: 10.1038/s41591-021-01539-8. Epub 2021 Dec 6.
Study type and design	PATHFINDER is an open-label, Phase 2, single-arm, multicentre clinical study.
Sample size (n)	103
Main inclusion criteria	• Patient must have a diagnosis of aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) or mast cell leukaemia (MCL) based on World Health Organization diagnostic criteria. Before enrolment, the Study Steering Committee must confirm the diagnosis of AdvSM (based on Central Pathology Laboratory assessment of bone marrow). • Patient must have a serum tryptase ≥ 20 ng/mL. • Patient must have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 3.
Main exclusion criteria	• Patient has received prior treatment with avapritinib. • Patient has received any cytoreductive therapy (including midostaurin and other TKIs, hydroxyurea, azacitidine) or an investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy (e.g., brentuximab vedotin) less than 28 days before obtaining screening BM biopsy for this study. • Patient has eosinophilia and known positivity for the FIP1L1 PGDFRA fusion unless the patient has demonstrated relapse or PD on prior imatinib therapy. Patients with eosinophilia (> 1.5 × 10^9/L), who do not have a detectable KIT D816 mutation, must be tested for a PDGFRA fusion mutation by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR). • Patient has history of another primary malignancy that has been diagnosed or required therapy within 3 years before the first dose of study drug. The following are exempt from the 3-year limit: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ of any site. • Patient has a QT interval corrected using Fridericia's formula (QTcF) > 480 msec.

Trial name: PATHFINDER (BLU-285-2202)	NCT number: NCT03580655
	• Patient has a known risk or recent history (12 months before the first dose of study drug) of intracranial bleeding (e.g., brain aneurysm, concomitant vitamin K antagonist use). • Platelet count < 50,000/µL (within 4 weeks of the first dose of study drug) or receiving platelet transfusion(s). • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x the upper limit of normal (ULN); no restriction if due to suspected liver infiltration by mast cells. • Bilirubin >1.5 × ULN; no restriction if due to suspected liver infiltration by mast cells or Gilbert's disease. (In the case of Gilbert's disease, a direct bilirubin >2 × ULN would be an exclusion.) • Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2 or creatinine > 1.5 × ULN. • Patient has a primary brain malignancy or metastases to the brain. • Patient has a history of a seizure disorder (e.g., epilepsy) or requirement for antiseizure medication.
Intervention	Avapritinib was administered as an immediate release tablet, orally, in either 200 mg or 300 mg daily at 28-day cycles
Comparator(s)	N/A
Follow-up time	Median follow-up of 14.6 months for the RAC-RE population who received 200 mg of avapritinib with prior systematic therapy
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary outcome measures: 2. Objective response rate (ORR) based on modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) response criteria Secondary outcome measures: 17. Mean Change from Baseline in Advanced Systemic Mastocytosis-Symptom Assessment Form (AdvSM-SAF) Total Symptom Score 0 - 80 points (higher value represents worse symptom outcomes) 18. Objective response rate Including morphologic complete remission (mCR), morphologic CR with partial recovery of peripheral blood (mCRh), and morphologic partial remission (mPR) based on Pure Pathologic Response 19. Time-to-response (TTR) Months 20. Duration of Response (DOR) [Tim Months 21. Progression-free Survival (PFS) Months 22. Overall Survival (OS)

Trial name: PATHFINDER (BLU-285-2202)	NCT number: NCT03580655
	Months 23. Changes in bone marrow mast cells percentage 24. Change in serum tryptase ng/mL 25. Change in V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog aspartate 816 valine (KIT D816V) mutation burden percentage 26. Change in liver volume by imaging mL 27. Change in spleen volume by imaging mL 28. Clinical benefit based on modified IWG-MRT-ECNM consensus criteria 29. Change in PGIS 0 - 10 points (higher value represents worse symptom outcomes) 30. Change in EORTC QLQ-C30 0 - 100 points (lower value represents worse quality of life) 31. Safety of Avapritinib as assessed by incidence of adverse events CTCAE version 4.0 32. Area Under Curve (0 to Tau) for Avapritinib h•ng/mL
Method of analysis	ORR Defined as the proportion of patients with a confirmed best response of CR, CRh, PR, or CI by mIWG-MRT-ECNM criteria Defined as the proportion of patients with a confirmed best response of CR, CRh or PR by mIWG-MRT-ECNM criteria Defined as the proportion of patients with a confirmed best response of CR or CRh by mIWG-MRT-ECNM criteria DOR DOR is defined as the time from first documented response (CR/CRh/PR/CI) to the date of first documented PD/LoR or death due to any cause, whichever occurs first. Responses are determined by mIWG criteria. DOR will be analysed using KM methods and will include number of events and censors, the estimated median with two-sided 95% confidence intervals, and 25th and 75th percentiles. DOR/mDOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formulaDOR is defined as the time from first documented response (CR/CRh/PR) to the date of first documented PD/LoR or death due to any cause, whichever occurs first. Responses are determined by mIWG criteria. DOR will be analysed using KM methods and will include number of events and censors, the estimated median with two-sided 95% confidence intervals, and 25th and 75th percentiles. DOR/mDOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula

Trial name: PATHFINDER (BLU-285-2202)	NCT number: NCT03580655
	Time to response Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh/PR/CI) by mIWG is first met. Patients without confirmed response will be excluded from this analysis Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh/PR) by mIWG is first met. Patients without confirmed response will be excluded from this analysis Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh) by mIWG is first met. Patients without confirmed response will be excluded from this analysis OS OS is defined as the time from the start of treatment to the date of death. Patients who die before or on the data cutoff date will considered to have had an OS event. All Patients who do not have a death record prior to or on the cutoff date will be censored at the last date known alive. Last date known alive is defined as the last non-imputed date of any patient record prior to or on the data cutoff date in the clinical database. It can be the last visit date or last contact date that the patient is known to be alive. The survival distribution of OS will be estimated using the KM method. The median OS along with its two-sided 95% confidence intervals and 25th and 75th percentiles will be estimated. In addition, the survival rate at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula PFS PFS is defined as the time from the start of treatment to the date of first documented PD or death due to any cause, whichever occurs first. If a patient has not had an event, PFS is censored at the date of last valid assessment that is LoR or better. As specified in the IWG, development of AML will be treated as disease progression. The KM method will be used to estimate the PFS distribution function. The median PFS along with its two-sided 95% confidence intervals and 25th and 75th percentiles will be estimated. In addition, the event rates (or event-free) at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24-month, etc.) will be computed, along with the standard errors using Greenwood's formula
Subgroup analyses	Analyses of ORR were performed for the subgroups of age (< 65 years, ≥ 65 years), sex (male, female), region (North America, Europe), baseline S/A/R genotype (patients with mutation [positive], patients without mutation [negative]), prior treatment with midostaurin (yes, no), and prior antineoplastic therapy (yes, no) in RE population. Analyses of DOR and PFS were performed for the subgroups of baseline S/A/R genotype, prior treatment with midostaurin, and prior antineoplastic therapy in RE population. Analysis of OS was performed in the safety population and for the same subgroups listed for DOR and PFS.
Other relevant information	N/A

Appendix B. Efficacy results per study

Results of EXPLORER and PATHFINDER are presented in Table 68 and Results per study - PATHFINDER

Table 69 below. All results are based on the latest efficacy data cut from April 2021.

Results per study - EXPLORER

Table 68 Results per study for AdvSM patients; EXPLORER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORR All AdvSM	Avapritinib	11	72.7% (39.0-94.0)	N/A	N/A	N/A	N/A	N/A	N/A	Defined as the proportion of patients with a confirmed best response of CR, CRh, PR, or CI by mIWG-MRT-ECNM criteria	
	N/A	N/A	N/A								
ORR ASM	Avapritinib	1	100% (2.5-100)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
ORR SM-AHN	Avapritinib	6	66.7% (22.3-95.7)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
ORR MCL	Avapritinib	4	75.0% (19.4-99.4)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh + PR	Avapritinib	11	72.7% (39.0-94.0)	N/A	N/A	N/A	N/A	N/A	N/A	Defined as the proportion of patients with a confirmed best	

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
All AdvSM	N/A	N/A	N/A							response of CR, CRh or PR by mIWG-MRT-ECNM criteria	
CR + CRh + PR ASM	Avapritinib	1	100% (2.5-100)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh + PR SM-SHN	Avapritinib	6	66.7% (22.3-95.7)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh + PR MCL	Avapritinib	4	75.0% (19.4-99.4)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh All AdvSM	Avapritinib	11	27.3% (6.0-61.0)	N/A	N/A	N/A	N/A	N/A	N/A	Defined as the proportion of patients with a confirmed best response of CR or CRh by mIWG-MRT-ECNM criteria	
	N/A	N/A	N/A								
CR + CRh ASM	Avapritinib	1	100% (2.5-100)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh SM-AHN	Avapritinib	6	33.3% (4.3-77.7	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh MCL	Avapritinib	4	0%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
	Avapritinib	11	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median DOR All AdvSM	N/A	N/A	N/A							DOR is defined as the time from first documented response (CR/CRh/PR/CI) to the date of first documented PD/LoR or death due to any cause, whichever occurs first. Responses are determined by mIWG criteria. DOR will be analysed using KM methods and will include number of events and censors, the estimated median with two-sided 95% confidence intervals, and 25th and 75th percentiles. DOR/mDOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula	
Median DOR ASM	Avapritinib	1	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median DOR SM-AHN	Avapritinib	6	NE (11.2, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median DOR MCL	Avapritinib	4	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month DOR All Adv SM	Avapritinib	11	88.3%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month DOR ASM	Avapritinib	1	-	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month DOR SM-AHN	Avapritinib	6	75.0%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
12-month DOR MCL	Avapritinib	3	100.0%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month DOR All AdvSM	Avapritinib	11	83.3%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month DOR ASM	Avapritinib	1	-	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month DOR SM-AHN	Avapritinib	6	-	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month DOR MCL	Avapritinib	4	100.0%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median duration CR + CRh + PR All AdvSM	Avapritinib	11	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A	DOR is defined as the time from first documented response (CR/CRh/PR) to the date of first documented PD/LoR or death due to any cause, whichever occurs first. Responses are determined by mIWG criteria.	
	N/A	N/A	N/A								
Median duration	Avapritinib	1	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
CR + CRh + PR ASM										DOR will be analysed using KM methods and will include number of events and censors, the estimated median with two-sided 95% confidence intervals, and 25th and 75th percentiles. DOR/mDOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula	
Median duration CR + CRh + PR SM-AHN	Avapritinib	6	NE (11.2, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median duration CR + CRh + PR MCL	Avapritinib	4	NE (21.6, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month CR + CRh + PR All AdvSM	Avapritinib	11	83.3%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month CR + CRh + PR ASM	Avapritinib	1	-	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
	Avapritinib	6	75.0%	N/A	N/A	N/A	N/A	N/A	N/A		

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
12-month CR + CRh + PR SM-AHN	N/A	N/A	N/A								
12-month CR + CRh + PR MCL	Avapritinib	4	100.0%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month CR + CRh + PR All AdvSM	Avapritinib	11	83.3%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month CR + CRh + PR ASM	Avapritinib	1	-	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month CR + CRh + PR SM-AHN	Avapritinib	6	-	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month CR + CRh + PR	Avapritinib	4	100.0%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
MCL											
Time to response (CR + CRh + PR + CI) median	Avapritinib	11	6.05 (0.3-26.7)	N/A	N/A	N/A	N/A	N/A	N/A	Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh/PR/CI) by mIWG is first met. Patients without confirmed response will be excluded from this analysis	
	N/A	N/A	N/A								
All AdvSM											
Time to response (CR + CRh + PR + CI) median	Avapritinib	1	9.30 (9.3-9.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
ASM											
Time to response (CR + CRh + PR + CI) median	Avapritinib	6	2.32 (0.3-26.7)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
SM-AHN											
Time to response (CR + CRh + PR + CI) median	Avapritinib	4	9.46 (1.6-9.5)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
MCL											
Time to response (CR + CRh + PR) median All AdvSM	Avapritinib	11	7.44 (1.6, 26.7)	N/A	N/A	N/A	N/A	N/A	N/A	Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh/PR) by mIWG is first met. Patients without confirmed response will be excluded from this analysis	
	N/A	N/A	N/A								
Time to response (CR + CRh + PR) median ASM	Avapritinib	1	9.30 (9.3, 9.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Time to response (CR + CRh + PR) median SM-AHN	Avapritinib	6	4.19 (1.8, 26.7)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Time to response (CR + CRh + PR) median MCL	Avapritinib	4	9.46 (1.6, 9.5)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Time to response (CR + CRh) median All AdvSM	Avapritinib	11	9.30 (9.2, 32.2)	N/A	N/A	N/A	N/A	N/A	N/A	Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh) by mIWG is first met. Patients without confirmed response will be excluded from this analysis	
	N/A	N/A	N/A								
Time to response (CR + CRh) median ASM	Avapritinib	1	9.30 (9.3, 9.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Time to response (CR + CRh) median SM-AHN	Avapritinib	6	20.73 (9.2, 32.2)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Time to response (CR + CRh) median MCL	Avapritinib	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median OS All AdvSM	Avapritinib	11	NE (13.0, NE)	N/A	N/A	N/A	N/A	N/A	N/A	OS is defined as the time from the start of treatment to the date of death. Patients who die before or on the data cutoff	
	N/A	N/A	N/A								
Median OS	Avapritinib	1	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ASM	N/A	N/A	N/A							date will considered to have had an OS event. All Patients who do not have a death record prior to or on the cutoff date will be censored at the last date known alive.	
Median OS SM-AHN	Avapritinib	6	NE (8.0, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median OS MCL	Avapritinib	4	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A							Last date known alive is defined as the last non-imputed date of any patient record prior to or on the data cutoff date in the clinical database. It can be the last visit date or last contact date that the patient is known to be alive.	
12-month OS All Adv SM	Avapritinib	11	81.8%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month OS ASM	Avapritinib	1	100%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month OS SM-AHN	Avapritinib	6	66.7%	N/A	N/A	N/A	N/A	N/A	N/A	The survival distribution of OS will be estimated using the KM method. The median OS along with its two-sided 95% confidence intervals and 25th and 75th percentiles will be estimated. In addition, the survival rate at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the	
	N/A	N/A	N/A								
12-month OS MCL	Avapritinib	4	100%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month OS All AdvSM	Avapritinib	11	71.6%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
24-month OS ASM	Avapritinib	1	-	N/A	N/A	N/A	N/A	N/A	N/A	standard errors using Greenwood's formula	
	N/A	N/A	N/A								
24-month OS SM-AHN	Avapritinib	6	50.0%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month OS MCL	Avapritinib	4	100%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median PFS All AdvSM	Avapritinib	11	NE (13.0, NE)	N/A	N/A	N/A	N/A	N/A	N/A	PFS is defined as the time from the start of treatment to the date of first documented PD or death due to any cause, whichever occurs first. If a patient has not had an event, PFS is censored at the date of last valid assessment that is LoR or better. As specified in the IWG, development of AML will be treated as disease progression. The KM method will be used to estimate the PFS distribution	
	N/A	N/A	N/A								
Median PFS ASM	Avapritinib	1	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median PFS SM-AHN	Avapritinib	6	NE (8.0, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median PFS MCL	Avapritinib	4	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
12-month PFS All Adv SM	Avapritinib	11	81.8%	N/A	N/A	N/A	N/A	N/A	N/A	function. The median PFS along with its two-sided 95% confidence intervals and 25th and 75th percentiles will be estimated. In addition, the event rates (or event-free) at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula	
	N/A	N/A	N/A								
12-month PFS ASM	Avapritinib	1	100%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month PFS SM-AHN	Avapritinib	6	66.7%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month PFS MCL	Avapritinib	4	100%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month PFS All AdvSM	Avapritinib	11	71.6%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month PFS ASM	Avapritinib	1	-	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month PFS SM-AHN	Avapritinib	6	50%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of EXPLORER (BLU-285-2101, NCT02561988)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
24-month PFS MCL	Avapritinib	4	100%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results per study - PATHFINDER

Table 69 Results per study for AdvSM patients; PATHFINDER; RAC-RE population; 200 mg; prior systematic therapy; April 2021 DCO

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORR All AdvSM	Avapritinib	47	59.6% (44.3, 73.6)	N/A	N/A	N/A	N/A	N/A	N/A	Defined as the proportion of patients with a confirmed best response of CR, CRh, PR, or CI by mIWG-MRT-ECNM criteria	
	N/A	N/A	N/A								
ORR ASM	Avapritinib	8	62.5% (24.5, 91.5)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
ORR	Avapritinib	29	65.5% (45.7, 82.1)	N/A	N/A	N/A	N/A	N/A	N/A		

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
SM-AHN	N/A	N/A	N/A								
ORR MCL	Avapritinib	10	40.0% (12.2, 73.8)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh + PR All AdvSM	Avapritinib	47	51.1% (34.4, 63.7)	N/A	N/A	N/A	N/A	N/A	N/A	Defined as the proportion of patients with a confirmed best response of CR, CRh or PR by mIWG-MRT-ECNM criteria	
	N/A	N/A	N/A								
CR + CRh + PR ASM	Avapritinib	8	62.5% (24.5, 91.5)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh + PR SM-SHN	Avapritinib	29	55.2% (35.7, 73.6)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh + PR MCL	Avapritinib	10	30.0% (6.7, 65.2)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh All AdvSM	Avapritinib	47	10.6% (3.5, 23.1)	N/A	N/A	N/A	N/A	N/A	N/A	Defined as the proportion of patients with a confirmed best response of CR or CRh by mIWG-MRT-ECNM criteria	
	N/A	N/A	N/A								
CR + CRh	Avapritinib	8	25.0% (3.2, 65.1)	N/A	N/A	N/A	N/A	N/A	N/A		

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ASM	N/A	N/A	N/A								
CR + CRh SM-AHN	Avapritinib	29	10.3% (2.2, 27.4)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
CR + CRh MCL	Avapritinib	10	0%	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median DOR All AdvSM	Avapritinib	28	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A	DOR is defined as the time from first documented response (CR/CRh/PR/CI) to the date of first documented PD/LoR or death due to any cause, whichever occurs first. Responses are determined by mIWG criteria. DOR will be analysed using KM methods and will include number of events and censors, the estimated median with two-sided 95% confidence intervals, and 25th and 75th percentiles. DOR/mDOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with	
	N/A	N/A	N/A								
Median DOR ASM	Avapritinib	5	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median DOR SM-AHN	Avapritinib	19	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median DOR MCL	Avapritinib	4	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month DOR All Adv SM	Avapritinib	28	100.0% (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
12-month DOR ASM	Avapritinib	5	100.0% (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A	the standard errors using Greenwood's formula	
	N/A	N/A	N/A								
12-month DOR SM-AHN	Avapritinib	19	100.0% (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month DOR MCL	Avapritinib	4	100.0% (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month DOR All AdvSM	Avapritinib	28	85.6% (66.9, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month DOR ASM	Avapritinib	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month DOR SM-AHN	Avapritinib	19	83.3% (62.2, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
	Avapritinib	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A		

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
24-month DOR MCL	N/A	N/A	N/A								
Median duration CR + CRh + PR All AdvSM	Avapritinib	28	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A	DOR is defined as the time from first documented response (CR/CRh/PR) to the date of first documented PD/LoR or death due to any cause, whichever occurs first. Responses are determined by mIWG criteria. DOR will be analysed using KM methods and will include number of events and censors, the estimated median with two-sided 95% confidence intervals, and 25th and 75th percentiles. DOR/mDOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula	
	N/A	N/A	N/A								
Median duration CR + CRh + PR ASM	Avapritinib	5	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median duration CR + CRh + PR SM-AHN	Avapritinib	19	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median duration CR + CRh + PR MCL	Avapritinib	4	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
12-month CR + CRh + PR All AdvSM	Avapritinib	28	92.3% (77.8, 100.0	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month CR + CRh + PR ASM	Avapritinib	5	100.0% (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month CR + CRh + PR SM-AHN	Avapritinib	19	90.0% (71.4, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month CR + CRh + PR MCL	Avapritinib	4	100.0% (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month CR + CRh + PR All AdvSM	Avapritinib	28	92.3% (77.8, 100.0	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
	Avapritinib	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A		

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
24-month CR + CRh + PR ASM	N/A	N/A	N/A								
24-month CR + CRh + PR SM-AHN	Avapritinib	19	90.0% (71.4, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month CR + CRh + PR MCL	Avapritinib	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Time to response (CR + CRh + PR + CI) median All AdvSM	Avapritinib	28	1.94 (0.5, 12.2)	N/A	N/A	N/A	N/A	N/A	N/A	Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh/PR/CI) by mIWG is first met. Patients without confirmed response will be excluded from this analysis	
	N/A	N/A	N/A								
Time to response (CR + CRh + PR + CI) median	Avapritinib	5	2.30 (1.8, 5.5)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ASM											
Time to response (CR + CRh + PR + CI) median	Avapritinib	19	1.94 (0.5, 5.5)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
SM-AHN											
Time to response (CR + CRh + PR + CI) median	Avapritinib	4	3.60 (1.7, 12.2)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
MCL											
Time to response (CR + CRh + PR) median	Avapritinib	28	3.19 (1.7, 14.8)	N/A	N/A	N/A	N/A	N/A	N/A	Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh/PR) by mIWG is first met. Patients without confirmed response will be excluded from this analysis	
	N/A	N/A	N/A								
All AdvSM											
Time to response (CR + CRh + PR) median	Avapritinib	5	2.30 (1.8, 5.5)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ASM											
Time to response (CR + CRh + PR) median	Avapritinib	19	3.19 (1.7, 14.8)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
SM-AHN											
Time to response (CR + CRh + PR) median	Avapritinib	4	5.59 (1.7, 12.2)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
MCL											
Time to response (CR + CRh) median	Avapritinib	28	3.71 (1.8, 14.8)	N/A	N/A	N/A	N/A	N/A	N/A	Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh) by mIWG is first met. Patients without confirmed response will be excluded from this analysis	
	N/A	N/A	N/A								
All AdvSM											
Time to response (CR + CRh) median	Avapritinib	5	2.76 (1.8, 3.7)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
ASM											

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Time to response (CR + CRh) median SM-AHN	Avapritinib	19	5.59 (1.8, 14.8)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Time to response (CR + CRh) median MCL	Avapritinib	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median OS All AdvSM	Avapritinib	47	NE (17.5, NE)	N/A	N/A	N/A	N/A	N/A	N/A	OS is defined as the time from the start of treatment to the date of death. Patients who die before or on the data cutoff date will considered to have had an OS event. All Patients who do not have a death record prior to or on the cutoff date will be censored at the last date known alive. Last date known alive is defined as the last non-imputed date of any patient record prior to or on the data	
	N/A	N/A	N/A								
Median OS ASM	Avapritinib	8	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median OS SM-AHN	Avapritinib	29	NE (17.5, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median OS MCL	Avapritinib	10	NE (13.5, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month OS	Avapritinib	47	82.7% (71.8, 93.6)	N/A	N/A	N/A	N/A	N/A	N/A		

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
All Adv SM	N/A	N/A	N/A							cutoff date in the clinical database. It can be the last visit date or last contact date that the patient is known to be alive. The survival distribution of OS will be estimated using the KM method. The median OS along with its two-sided 95% confidence intervals and 25th and 75th percentiles will be estimated. In addition, the survival rate at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula	
12-month OS ASM	Avapritinib	8	100.0% (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month OS SM-AHN	Avapritinib	29	79.0% (64.0, 94.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month OS MCL	Avapritinib	10	80.0% (55.2, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month OS All AdvSM	Avapritinib	47	67.8% (49.8, 85.8)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month OS ASM	Avapritinib	8	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month OS SM-AHN	Avapritinib	29	65.8% (45.0, 86.6)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
24-month OS MCL	Avapritinib	10	66.7% (35.1, 98.2)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median PFS All AdvSM	Avapritinib	47	NE (17.5, NE)	N/A	N/A	N/A	N/A	N/A	N/A	OS is defined as the time from the start of treatment to the date of death. Patients who die before or on the data cutoff date will considered to have had an OS event. All Patients who do not have a death record prior to or on the cutoff date will be censored at the last date known alive. Last date known alive is defined as the last non-imputed date of any patient record prior to or on the data cutoff date in the clinical database. It can be the last visit date or last contact date that the patient is known to be alive.	
	N/A	N/A	N/A								
Median PFS ASM	Avapritinib	8	NE (NE, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median PFS SM-AHN	Avapritinib	29	NE (17.4, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median PFS MCL	Avapritinib	10	NE (10.5, NE)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month PFS All Adv SM	Avapritinib	47	77.5% (65.0, 89.9)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month PFS	Avapritinib	8	100.0% (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A	The survival distribution of OS will be estimated using the KM	

Results of PATHFINDER (BLU-285-2202, NCT03580655)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References (6)
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ASM	N/A	N/A	N/A							method. The median OS along with its two-sided 95% confidence intervals and 25th and 75th percentiles will be estimated. In addition, the survival rate at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24- month, etc.) will be computed, along with the standard errors using Greenwood's formula	
12-month PFS	Avapritinib	29	75.2% (59.3, 91.2)	N/A	N/A	N/A	N/A	N/A	N/A		
SM-AHN	N/A	N/A	N/A								
12-month PFS	Avapritinib	10	68.6% (38.9, 98.3)	N/A	N/A	N/A	N/A	N/A	N/A		
MCL	N/A	N/A	N/A								
24-month PFS	Avapritinib	47	65.5% (47.1, 84.0)	N/A	N/A	N/A	N/A	N/A	N/A		
All AdvSM	N/A	N/A	N/A								
24-month PFS	Avapritinib	8	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
ASM	N/A	N/A	N/A								
24-month PFS	Avapritinib	29	61.6% (40.0, 83.1)	N/A	N/A	N/A	N/A	N/A	N/A		
SM-AHN	N/A	N/A	N/A								
24-month PFS	Avapritinib	10	68.6 (38.9, 98.3)	N/A	N/A	N/A	N/A	N/A	N/A		
MCL	N/A	N/A	N/A								

Appendix C. Comparative analysis of efficacy

The main results of the indirect treatment comparison are presented in Section 7.

C.1 Summary of trials used for the indirect comparison

As described in Appendix H, 30 unique studies were identified in the Clinical SLR that included AdvSM patients.

Most of the identified studies contained limited information on patient characteristics and had unclear inclusion and exclusion criteria for treatments. While 2 studies were identified for midostaurin, is it often not used on its own and is used in combination with cytoreductive therapies and biological treatments, which encompasses the BAT treatment arm used in clinical practice.

In order to best inform on the comparison of avapritinib vs BAT, the BLU-285-2405 study was most appropriate as the study consisted included AdvSM patients who were receiving BAT and was used as an external control arm against avapritinib.

Individual patient data as of the April 20, 2021, data cut-off from the Phase I EXPLORER and Phase II PATHFINDER trials were used in this analysis. In EXPLORER, the starting dose of avapritinib was escalated from 30 to 400 mg daily while in PATHFINDER, all but two patients received 200 mg daily (3).

To generate real-world data on BAT, a multi-centre, observational, retrospective chart review study was conducted. Longitudinal, individual-level data were collected using medical chart abstraction among eligible patients with AdvSM who received systemic treatment at participating study sites in Europe and the US. De-identified patient data were abstracted from medical records into a standardized eCRF from March 26, 2021, to October 4, 2021 (3).

External control patients may have initiated treatment with different lines of treatments at the study sites. For example, some patients may have initiated treatment with first-line therapy at a study site while other patients may have received second or later lines (2L+) of therapy ("2L+ cohort") at a study site, having received 1L therapy elsewhere. Patients were not required to initiate 1L therapy at a study site to be eligible for this study. Where data on multiple lines therapy were available for a single eligible patient, information for all lines was collected, and all LOTs were included in this analysis. The index date was defined as the date of initiation of each line of systemic therapy at a participating site (3).

C.1.1 Patient selection

Patients receiving treatment with BAT for AdvSM were identified based on inclusion and exclusion criteria similar to those from EXPLORER and PATHFINDER. Adults (aged ≥ 18 years) with a diagnosis of AdvSM and documented subtype in their chart (ASM, SM-AHN, or MCL), and who had received ≥1 line of systemic therapy (not necessarily as first line (1L)) for AdvSM at a participating site on or after January 1, 2009, were included. If a patient received multiple lines of therapy at a participating site, data on all available therapies were collected and analysed (i.e., the patient could contribute more than one line of therapy to the analysis). The date of initiation of each line of therapy at the participating site was defined as the index date (3).

Patients in the BAT cohort were excluded if they had a history of another primary malignancy that was diagnosed or required therapy within 3 years before the index date, except for completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ at any site, or if they received avapritinib as the first therapy for AdvSM (3).

A number of prognostic factors for survival and clinical outcomes in patients with AdvSM, as well as confounders for the treatment effect on survival were considered based on published literature (3). These a priori defined key adjustment covariates included age, sex, region (North America or

Europe), performance status as assessed by the ECOG score, presence of anaemia (haemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100 × 10^9/L), AdvSM subtype (SM-AHN, ASM, or MCL), presence of skin involvement (including reported mastocytosis in the skin or urticaria), leukocyte count of 16 × 10^9/L or higher, serum tryptase concentration of 125 ng/mL or higher, testing and number of mutations within the SRSF2/ASXL1/RUNX1 (S/A/R) panel, number of prior LOTs received, and types of prior therapy (TKI therapy, cytotoxic therapy, or biologic or other systemic therapy) received (3).

C.1.2 Methods and outcomes

The primary endpoint of BLU-285-2405 was OS, defined for the BAT cohort as the interval of time between initiation of each eligible line of systemic treatment and death due to any cause. Patients who did not die during the observation period were considered censored at the date of last contact with the participating study site. For the avapritinib cohort, OS was defined as the interval of time between the first dose of avapritinib and death due to any cause. Patients who did not die during the observation period were censored at the last known alive date. A subgroup analysis of OS was included for RAC-RE patients from the PATHFINDER study as well.

Analysis of primary endpoint

Unadjusted OS was analysed using the Kaplan-Meier method. The median time to death, corresponding 95% confidence interval, and log-rank test P value were reported. Unadjusted Cox proportional hazards models were used to obtain hazard ratios, corresponding 95% CIs and P values, with robust variance estimation to account for the within-subject correlation of BAT cohort patients who contributed multiple LOTs. Unadjusted survival rates at 3, 6, 9, 12, 18, 24, 30, 36, 48, and 60 months were obtained using the Nelson-Aalen Estimator. Unadjusted OS estimates up to each of these timepoints were obtained using the KM method with a log-rank test.

Comparative analyses, adjusting for key baseline covariates, employed a two-step process to obtain an effect estimate that was doubly robust against confounding: (1) prior to reviewing or analysing outcome data, stabilised IPTW weights were created and applied to balance the differences in key covariates between the avapritinib and BAT cohorts, and (2) an IPTW-weighted multivariable Cox proportional hazards model, with further adjustment for remaining imbalances in the distribution of key covariates in the weighted cohorts, was used to compare survival between the avapritinib and BAT cohorts.

Stabilised inverse probability of treatment weights

The IPTW approach used weights to create a “pseudo-population” (effective sample after IPTW-weighting) in which the distribution of baseline covariates is approximately the same in each patient cohort under comparison. In this way, confounding by measured baseline characteristics was mitigated.

Imbalances in baseline characteristics between the avapritinib and BAT cohorts were first assessed using standardized differences. The standardized difference for continuous variables was calculated by dividing the absolute difference in means of avapritinib cohort vs. BAT cohort by the pooled standard deviation of both cohorts. The pooled standard deviation was the square root of the average of the squared standard deviations. For categorical variables, the standardized difference was calculated using the following equation where $Pavapritinib$ was the respective proportion of the avapritinib cohort, and $PBAT$ was the respective proportion of the BAT cohort:

$$\frac{|\hat{P}_{avapritinib} - \hat{P}_{BAT}|}{\sqrt{\frac{1}{2} \times [\hat{P}_{avapritinib} \times (1 - \hat{P}_{avapritinib}) + \hat{P}_{BAT} \times (1 - \hat{P}_{BAT})]}}.$$

For each variable, a standardized difference greater than 10% was considered indicative of meaningful imbalance between the two cohorts.

To implement the IPTW approach, weights were created through propensity score modelling, where the PS was defined as the probability of receiving treatment (i.e., receiving treatment with

avapritinib), conditional on an observed set of baseline covariates. All a priori specified key covariates, regardless of the magnitude of the standardized difference, were included in the PS model. Based on the PS, for each LOT included in the analysis, IPTW weights were calculated as the inverse of the conditional probability of being in the respective treatment group (i.e., avapritinib or BAT), conditional on the pre-specified key covariates included in the model. The PS, and thus weights, were estimated from a logistic regression model. To enhance precision in the effect estimates, the weight for each included LOT was stabilized by the marginal probability of being in the respective treatment group. Stabilized IPTW weights were calculated as $wi = P(Ti = 1)Ti/pi + P(Ti=0)1-Ti/1-pi$, where pi and Ti are the estimated PS and the treatments (0 or 1), respectively, and $P(Ti=1)$ is the marginal probability the LOT was received as part of the treatment (avapritinib) cohort and $P(Ti=0)$ is the marginal probability that the LOT was received as part of the external control (BAT) cohort, for LOT i, respectively. To reduce variability, stabilized weights were truncated at the 1st and 99th percentiles.

Weighted Cox proportional hazards model

Adjusted analysis was conducted using weighted Cox regression models, which included a single variable for treatment (i.e., avapritinib vs. BAT), and any key covariates that remained unbalanced (i.e., covariates with standardized differences greater than 10%) after weighting by stabilized IPTW weights.

Robust variance estimation was used in Cox models to account for the within-subject correlation of BAT cohort patients contributing multiple LOTs as well as the application of weights. The proportional hazards assumption was evaluated using the Kolmogorov-type supremum tests, in which a P value less than 0.05 suggests violation of the proportionality assumption. An adjusted Cox proportional hazards model provided the HR with 95% CI and P value.

Adjusted survival rates at 3, 6, 9, 12, 18, 24, 30, 36, 48, and 60 months were obtained using the Nelson-Aalen Estimator, weighted by stabilized IPTW weights. Adjusted OS estimates up to each of these timepoints were obtained using the KM method with log-rank test, weighted by stabilized IPTW weights.

A two-sided P value less than 0.05 was considered statistically significant without multiplicity adjustment. All data cleaning and analyses were conducted using SAS® Enterprise Guide® version 7.1 and R version 3.6.3.

C.1.3 Results

Key baseline covariates before and after weighting for OS

Key covariates, assessed prior to or at the start of each eligible LOT, before and after IPTW weighting are presented in Table 70. The OS analyses included 176 unique patients in the avapritinib cohort contributing 176 LOTs, and 141 unique patients in the BAT cohort contributing 222 LOTs. Before weighting, meaningful imbalance between the avapritinib and the BAT cohorts, as indicated by a standardized difference greater than 10%, was observed for sex, region, ECOG score, presence of thrombocytopenia, AdvSM subtype diagnosis, having a leukocyte count of 16 × 10^9/L or higher, having serum tryptase concentration of 125 ng/mL or higher, number of prior LOTs, having received prior TKI therapy, and having received prior cytotoxic therapy. Region had the largest standardized difference (98.7%) as more patients in the avapritinib cohort were from North America than in the BAT cohort (58.0% vs. 15.3%).

Mean age was similar in both cohorts (66.3 years in the avapritinib cohort vs. 65.5 years in the BAT cohort). Relative to the BAT cohort, a higher proportion of patients in the avapritinib cohort were female (41.5% vs. 34.2%), from North America, had an ECOG score of 1 or higher (79.6% vs. 77.5%), had an AdvSM subtype diagnosis of SM-AHN (67.6% vs. 54.5%), had a serum tryptase concentration of 125 ng/mL or higher (75.0% vs. 64.9%), had received 1 (38.6% vs. 31.1%), 2 (15.9% vs. 10.8%), or more than 2 (8.0% vs. 5.0%) prior lines of systemic therapy, and had received prior TKI therapy (52.3% vs. 22.5%). However, lower proportions of the avapritinib cohort vs. the BAT cohort had thrombocytopenia (38.1% vs. 54.1%), an AdvSM subtype diagnosis of ASM (16.5% vs. 30.6%), a

leukocyte count of 16 × 109/L or higher (18.8% vs. 24.3%) and received prior cytotoxic therapy (18.8% vs. 27.5%).

The truncated stabilized IPTW weights, calculated based on all the key baseline covariates, had a mean of 0.96 (SD: 0.71), with range 0.46 to 4.45 (Table 71). Since large weights can contribute to large variability of the estimator, the absence of very large and very small weights suggests that our IPTW model was appropriate and stable.

After weighting by truncated stabilized IPTW weights, standardized differences decreased to below 10% for most of the imbalanced key covariates, indicating that the two cohorts were then well balanced with regards to these characteristics. Some characteristics still remained imbalanced based on the 10% threshold including region (weighted proportion from North America in avapritinib vs. BAT: 34.4% vs. 28.6%; standardized difference: 12.3%), presence of thrombocytopenia (weighted proportion in avapritinib vs. BAT: 38.9% vs. 43.9%; standardized difference: 10.2%), and treatment with prior TKI therapy (weighted proportion in avapritinib vs. BAT: 37.1% vs. 29.9%; standardized difference: 15.2%)

Unweighted sample

In the unweighted sample, there were 34 (19.3%) deaths in 176 unique avapritinib patients and 84 (59.6%) deaths in 141 unique BAT patients (Table 72). In the BAT cohort, 21 (14.9%) unique patients were censored due to avapritinib initiation, and 6 (4.3%) unique patients were censored due to development of a new primary malignancy after the index date. The mean follow-up durations were 17.9 months for the avapritinib cohort and 25.7 months for the BAT cohort. Median OS was not reached (NR) (95% CI: 46.9, not estimable [NE]) for the avapritinib cohort and was 23.4 months (95% CI: 19.5, 32.6) for the BAT cohort. Unweighted KM analysis suggested that OS was significantly improved in the avapritinib cohort compared to the BAT cohort; log-rank P<0.001). Similarly, unweighted Cox regression with a robust sandwich variance estimator revealed consistently improved OS for the avapritinib cohort compared to the BAT cohort (HR [95% CI]: 0.39 [0.26, 0.58]; P<0.001).

Survival rates were higher for the avapritinib cohort relative to the BAT cohort across all time points in the unweighted sample (e.g., avapritinib vs. BAT at 6 months: 94.7% vs. 83.0%; at 12 months: 87.3% vs. 72.0%; at 24 months: 77.5% vs. 49.2%; at 36 months: 70.7% vs. 40.1%). Comparing survival rates between the cohorts suggested that survival was significantly improved for the avapritinib cohort compared to the BAT cohort at all time points tested with log rank P=0.017 at 3 months, and P≤0.001 for all subsequent time points.

IPTW-weighted sample

After weighting, there were 36 (20.9%) deaths in an effective sample size (original sample size weighted by truncated stabilized IPTW weights) of 172 patients for the avapritinib cohort and 76 (55.9%) deaths in an effective sample size of 136 patients treated with BAT (Table 72). In the BAT cohort, 18.4% and 5.9% of the effective sample size were censored due to avapritinib initiation or development of a new primary malignancy after the index date, respectively.

The weighted median OS was 49.0 months (95% CI: 46.9, NE) for the avapritinib cohort and 26.8 months (95% CI: 18.2, 39.7) for the BAT cohort. In adjusted analyses, OS was significantly improved in the avapritinib cohort compared with the BAT cohort (HR [95% CI]: 0.48 [0.29, 0.79]; P=0.004), even with further adjustment for region, presence of thrombocytopenia at baseline, and prior use of TKI therapy (i.e., variables that had a standardized difference of greater than 10% after weighting).

IPTW-weighted survival rates were higher for the avapritinib cohort relative to the BAT cohort across all time points (e.g., avapritinib vs. BAT at 6 months: 96.4% vs. 84.8%; at 12 months: 86.4% vs. 73.8%; at 24 months: 74.6% vs. 50.9%; at 36 months: 68.0% vs. 42.7%). Survival was significantly improved for the avapritinib cohort at all time points tested, except at 3 months (P=0.087), with P<0.05 at 6, 9, and 12 months, and P≤0.001 for all other time points.

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Table 70 Summary of baseline characteristics before and after inverse probability of treatment weighting

Baseline characteristics[a]	Unweighted sample			IPTW-Weighted sample[b]		
	Avapritinib[c]	BAT[c]	Standardized Difference[d]	Avapritinib[c]	BAT[c]	Standardized Difference[d]
Number of unique patients	**N = 176**	**N = 141**		**Effective N = 172**	**Effective N = 134**	
Number of lines of therapy	**N = 176**	**N = 222**		**Effective N = 172**	**Effective N = 210**	
Demographic characteristics						
Age (years)[e]			6.5%			9.2%
Mean (SD)	66.3 (10.7)	65.5 (11.8)		66.4 (10.5)	65.3 (12.4)	
Median (min, max)	68.0 (31.0, 88.0)	67.8 (20.9, 87.5)		68.0 (31.0, 88.0)	67.9 (20.9, 87.5)	
Sex, n (%)			15.0%*			5.3%
Female	73 (41.5%)	76 (34.2%)		40.0%	37.4%	
Male	103 (58.5%)	146 (65.8%)		60.0%	62.6%	
Region, n (%)			98.7%*			12.3%*
North America	102 (58.0%)	34 (15.3%)		34.4%	28.6%	
Europe	74 (42.0%)	188 (84.7%)		65.6%	71.4%	
Medical history						
Performance status						
ECOG[f]						

n (%)	176 (100.0%)	222 (100.0%)		100.0%	100.0%	
Mean (SD)	1.2 (0.8)	1.0 (0.7)		1.2 (0.8)	1.1 (0.7)	
Median (min, max)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)		1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	
ECOG category, n (%)						
0	36 (20.5%)	50 (22.5%)	5.0%	16.3%	19.2%	7.4%
1	92 (52.3%)	129 (58.1%)	11.8%*	59.0%	56.2%	5.8%
≥2	48 (27.3%)	43 (19.4%)	18.8%*	24.6%	24.7%	0.1%
Anemia,[g] n (%)	104 (59.1%)	125 (56.3%)	5.6%	55.4%	57.8%	5.0%
Thrombocytopenia,[h] n (%)	67 (38.1%)	120 (54.1%)	32.5%*	38.9%	43.9%	10.2%*
Disease characteristics						
AdvSM subtype diagnosis,[i] n (%)						
SM-AHN	119 (67.6%)	121 (54.5%)	27.1%*	58.4%	58.2%	0.5%
ASM	29 (16.5%)	68 (30.6%)	33.8%*	26.5%	25.2%	3.0%
MCL	28 (15.9%)	33 (14.9%)	2.9%	15.1%	16.6%	4.3%
Skin involvement						
Any skin involvement, n (%)	58 (33.0%)	71 (32.0%)	2.1%	30.3%	32.5%	4.8%
Leukocyte count						
≥16 × 10^9/L, n (%)	33 (18.8%)	54 (24.3%)	13.6%*	18.5%	19.8%	3.3%
Serum tryptase[j] (ng/mL)						
≥125 ng/mL, n (%)	132 (75.0%)	144 (64.9%)	22.2%*	72.5%	71.0%	3.2%
***SRSF2/ASXL1/RUNX1* (S/A/R) mutation panel**						

Number that were tested for at least one mutation, n (%)	176 (100.0%)	169 (76.1%)		100.0%	70.8%	
Number of mutated genes within S/A/R panel, n (%)						
0	92 (52.3%)	66 (29.7%)		55.3%	26.7%	
1	54 (30.7%)	68 (30.6%)	0.1%	28.7%	30.1%	3.1%
≥2	30 (17.0%)	35 (15.8%)	3.5%	16.0%	13.9%	5.8%
Prior therapy						
Prior systemic therapy						
Patients with prior systemic therapy, n (%)	110 (62.5%)	104 (46.8%)		52.8%	49.6%	
Number of prior lines of systemic therapy received, n (%)						
Mean (SD)	1.0 (1.1)	0.1 (0.3)		0.8 (1.0)	0.1 (0.3)	
Median (min, max)	1.0 (0.0, 6.0)	0.0 (0.0, 2.0)		1.0 (0.0, 6.0)	0.0 (0.0, 2.0)	
0	66 (37.5%)	118 (53.2%)	31.8%*	47.2%	50.4%	6.4%
1	68 (38.6%)	69 (31.1%)	15.9%*	33.1%	32.4%	1.5%
2	28 (15.9%)	24 (10.8%)	15.0%*	14.6%	12.6%	5.6%
≥3	14 (8.0%)	11 (5.0%)	12.2%*	5.1%	4.6%	2.7%
Prior treatments received, n (%)						
TKI therapy	92 (52.3%)	50 (22.5%)	64.6%*	37.1%	29.9%	15.2%*
Cytoreductive therapy	33 (18.8%)	61 (27.5%)	20.8%*	20.1%	22.1%	4.8%
Biologic or other systemic therapy[k]	23 (13.1%)	30 (13.5%)	1.3%	14.9%	15.2%	0.7%

Agent-level information available[l]	N = 176	N = 196	Effective N = 172	Effective N = 193
TKI				
Midostaurin	81 (46.0%)	32 (16.3%)	33.7%	21.9%
Dasatinib	6 (3.4%)	7 (3.6%)	1.9%	3.6%
Ibrutinib	2 (1.1%)	0 (0.0%)	0.5%	0.0%
Imatinib	10 (5.7%)	10 (5.1%)	3.2%	7.2%
Nilotinib	2 (1.1%)	0 (0.0%)	0.8%	0.0%
Ripretinib	5 (2.8%)	1 (0.5%)	1.6%	0.4%
Ruxolitinib	2 (1.1%)	0 (0.0%)	0.6%	0.0%
Cytoreductive therapy				
Cladribine	22 (12.5%)	34 (17.3%)	15.6%	13.6%
Azacitidine	5 (2.8%)	2 (1.0%)	1.9%	0.9%
Decitabine	2 (1.1%)	2 (1.0%)	0.7%	1.7%
Chlorambucil	1 (0.6%)	0 (0.0%)	0.3%	0.0%
Hydroxyurea	9 (5.1%)	17 (8.7%)	3.7%	7.0%
Biologic				
Brentuximab vedotin	3 (1.7%)	2 (1.0%)	1.2%	3.1%
Obinituzumab	1 (0.6%)	0 (0.0%)	0.3%	0.0%
Rituximab	1 (0.6%)	0 (0.0%)	0.3%	0.0%
Interferon-alfa	14 (8.0%)	20 (10.2%)	11.1%	9.1%

Pegylated interferon	3 (1.7%)	8 (4.1%)	2.7%	4.3%

Abbreviations:
AdvSM: advanced systemic mastocytosis; ASM: aggressive systemic mastocytosis; BAT: best available therapy; ECOG: Eastern Cooperative Oncology Group; IPTW: inverse probability of treatment weighting; max: maximum; MCL: mast cell leukaemia; min: minimum; S/A/R: SRSF2/ASXL1/RUNX1; SD: standard deviation; SM-AHN: systemic mastocytosis with an associated hematologic neoplasm; TKI: tyrosine kinase inhibitor.
Notes:
*Standardized difference greater than 10%.
a The baseline period was defined as 8 weeks leading up to the index date for the avapritinib cohort and the 12 weeks leading up to the index date for the BAT cohort.
b Stabilized IPTW weights accounted for age, sex, region, ECOG score, anemia (hemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100 x 109/L), AdvSM subtype, skin involvement, leukocyte count of 16 × 109 per L or higher, serum tryptase level of 125 ng/mL or higher, number of mutated genes within the SRSF2/ASXL1/RUNX1 gene panel, number of prior lines of therapy, and types of prior therapy. To reduce variability, stabilized weights were capped at the 1st and 99th percentiles.
c The trial and real-world samples were restricted to patients with available ECOG score during any time before to 3 months after the index date.
d For continuous variables, the standardized difference was calculated by dividing the absolute difference in means of avapritinib cohort vs. BAT cohort by the pooled standard deviation of both cohorts. The pooled standard deviation was the square root of the average of the squared standard deviations. For categorical variables with 2 levels, the standardized difference was calculated using the following equation where P1 was the respective proportion of avapritinib cohort, and P2 was the respective proportion of BAT cohort: $|P1-P2|/\sqrt{p(1-p)}$, where $p = (P1+P2)/2$. For each variable, a standardized difference greater than 10% was indicative of meaningful imbalance between the two cohorts, per Austin and Stuart (2015),33 and were denoted with "*".
e Only the year of birth was collected for the BAT cohort. Patients' age was calculated using the mid-point of the birth year as approximate dates of birth.
f For the BAT cohort, ECOG and Karnofsky scores assessed during 12 months before to 3 months after the index date were considered. For the lines of therapy for which patients had no ECOG score on record during this period (N = 9 lines of therapy), the Karnofsky score closest to the index date in the same period was converted to an ECOG score. The conversion was performed according to Oken et al.36
g For both the avapritinib cohort and the BAT cohort, anemia included reported anemia and hemoglobin less than 10 g/dL.
h For both the avapritinib cohort and the BAT cohort, thrombocytopenia included reported thrombocytopenia and platelet count less than 100 x 109/L.
i The AdvSM subtype was assessed at the last diagnosis evaluation prior to or on the index date.
j Observations with missing serum tryptase level were imputed as not having serum tryptase level greater than or equal to 125 ng/mL.
k Other systemic therapy included steroids and thalidomide or derivatives.
l Agent-level information for prior treatments was reported among patients from all study sites except Medical University of Vienna (Austria) (N=26 lines of therapy), where only treatment class information was collected per local regulations.
Source: Reiter et al., 2022 (3)

Table 71 Summary of statistics of truncated stabilised weights for inverse probability of treatment weighting analysis of overall survival

Study sample	N	Mean (SD)	Min	Max
Overall[a]	389	0.98 (0.84)	0.47	5.81
Avapritinib cohort	176	0.96 (0.80)	0.47	5.81
Best available therapy cohort	213	0.99 (0.87)	0.56	5.81

Abbreviations: Max: maximum; min: minimum; SD: standard deviation.
Note:
[1] Stabilized weights were truncated at the 1st and 99th percentiles

Source: Reiter et al., 2022 (3)

Table 72 Summary of overall survival in safety population and PATHFINDER RAC-RE population; 200 mg; April 2021 DCO

Outcome measure	Unweighted sample[a]				Weighted sample[b]			
Overall: Avapritinib vs BAT	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**
Number of unique patients	N=176	N=141	-	-	ESS N=172	ESS N=136	-	-
Number of Lines of therapy	N=176	N = 222	-	-	ESS N = 172	ESS N = 210	-	-
Deaths of unique patients, n (%)	34 (19.3)	84 (59.6)	-	-	36 (20.9)	76 (55.6)	-	-
Unique patients censored due to avapritinib initiation, n (%)	-	21 (14.9)	-	-	-	25 (18.4%)	-	-
Unique patients censored due to new primary malignancy after index date, n (%)	-	6 (4.3)	-	-	-	8 (5.9)	-	-
Mean follow-up (months)	17.9	25.7	-	-	17.9	25.7	-	-
Median OS, months (95% CI)	NR (46.9, NE)	23.4 (19.5, 32.6)	-	-	49.0 (46.9, NE)	26.8 (18.2, 39.7)	-	-
HR (95% CI)[c]			0.39 (0.26, 0.58)	<0.001			0.48 (0.29, 0.79)	0.004
Kaplan-meier survival estimates				Log-rank p				Log-rank p
12 months	87.3%	72.0%	-	<0.001	86.4%	73.8%	–	0.013

Outcome measure	Unweighted sample[a]				Weighted sample[b]			
Overall: Avapritinib vs BAT	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**
24 months	77.5%	49.2%	-	<0.001	74.5%	50.9%	–	<0.001
36 months	70.7%	40.1%	-	<0.001	67.9%	42.7%	–	<0.001
48 months	58.7%	26.6%	-	<0.001	61.9%	30.0%	–	<0.001
60 months	50.3%	20.2%	-	<0.001	36.8%	23.4%	–	0.001
	Unweighted sample				**Weighted sample[f]**			
Avapritinib PATHFINDER (RAC-RE population, 200 mg) vs BAT 2L+	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**	**Avapritinib**	**BAT**	**Estimate (95% CI)**	**p-value**
Number of unique patients	N = 47	N = 73			ESS N=41	ESS N=67		
Lines of therapy	N = 47	N = 104			ESS N = 41	ESS N = 99		
Median OS, months (95% CI)	NR (NE,NE)	20.3 (14.9, 33.9)			NR (17.5, NE)	17.2 (14.6, 33.9)		
HR (95% CI)[d]			0.52 (0.26, 1.03)	0.060			0.47 (0.21,1.09)[e]	0.080

Abbreviations: BAT = best available treatment; HR = hazard ratio; NE = not evaluable; NR = not reached; OS = overall survival

a Patients from the BAT cohort could contribute multiple lines of therapy. A total of 222 lines of therapy were contributed by 141 real-world patients in the unweighted BAT cohort.

b Stabilized weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anaemia (haemoglobin <10 g/dl), thrombocytopenia (platelet count <100 × 109/l), AdvSM subtype, skin involvement, leukocyte count of 16 × 109/l or higher, serum tryptase level of 125 ng/ml or higher, number of mutated genes within the SRSF2/ASXL1/RUNX1 gene panel, number of prior lines of therapy, and prior use of tyrosine kinase inhibitor, cytoreductive, biologic or other systemic therapy.

b Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference of greater than 10% after weighting, which included region, presence of thrombocytopenia at baseline, and prior use of tyrosine kinase inhibitor therapy, using a doubly robust approach.
c Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference of greater than 10% after weighting, using a doubly robust approach. HR and the corresponding 95% CI and p value were presented. Two-sided p value <0.05 was considered statistically significant without multiplicity adjustment.
D Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference of greater than 10% after weighting, using a doubly robust approach. HR and the corresponding 95% CI and p value were presented. Two-sided p value <0.05 was considered statistically significant without multiplicity adjustment.
e IPTW-weighted multivariable Cox proportional hazards model further adjusted for sex, region, presence of anaemia at baseline, presence of thrombocytopenia at baseline, AdvSM subtype, prior use of tyrosine kinase inhibitor therapy, and prior use of cytoreductive therapy.
f Stabilized weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anaemia (haemoglobin <10 g/dl), thrombocytopenia (platelet count <100 × 109/l), AdvSM subtype, skin involvement, leukocyte count of 16 × 109/l or higher, serum tryptase level of 125 ng/ml or higher, number of mutated genes within the SRSF2/ASXL1/RUNX1 gene panel
Source: Reiter et al., 2022 (3)

Appendix D. Extrapolation

This appendix specifies the extrapolation of the endpoints: OS, PFS, and ToT for both the avapritinib and BAT treatment arm. OS, PFS and ToT use the datasets from PATHFINDER IPD data for avapritinib and RWE BLU-285-2405 for BAT.

Extrapolation of overall survival (OS)

D.1 Data input

OS in the avapritinib arm was captured and extrapolated based on the information available from the PATHFINDER (April 2021 DCO). For the BAT arm, the OS was captured and extrapolated based on the ITC analysis of the RWE BLU-285-2405. The KM data from PATHFINDER and RWE BLU-285-2405 is shown in Figure 18.

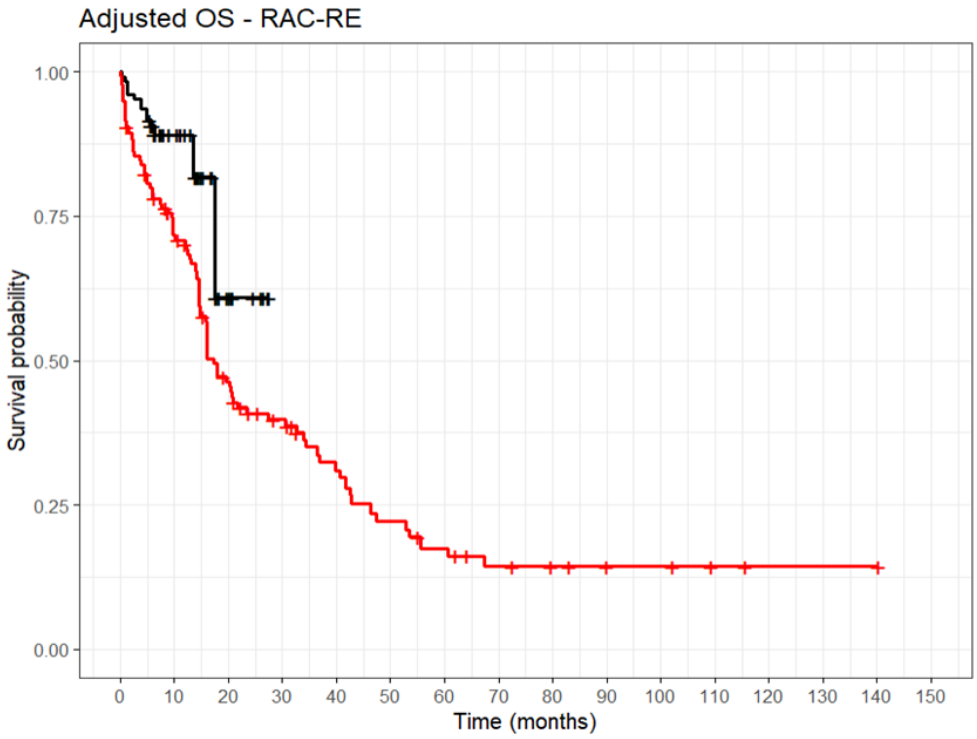

Figure 18 OS KM data for avapritinib and BAT. Adjusted analysis - Base case 200mg RAC-RE population. (BAT= red, avapritinib= black)

Abbreviations: OS: overall survival, RAC-RE: response assessment committee response-evaluable population

D.2 Model

Extrapolation of OS was generated by fitting parametric models to the KM curves from the IPD data from the PATHFINDER study (April 2021 DCO). Six parametric distributions were fitted to the data, including: Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma.

Based on the OS data derived from the PATHFINDER study and RWE BLU-285-2405, separate individual parametric models were chosen for the avapritinib arm and BAT arm. The exponential parametric model was selected to model the OS in the avapritinib arm.

Avapritinib

Given the low number of events in the Kaplan–Meier data, it is difficult to evaluate the fit of the parametric models. Figure 19 shows the extrapolation model of OS for avapritinib over the time horizon (40 years).

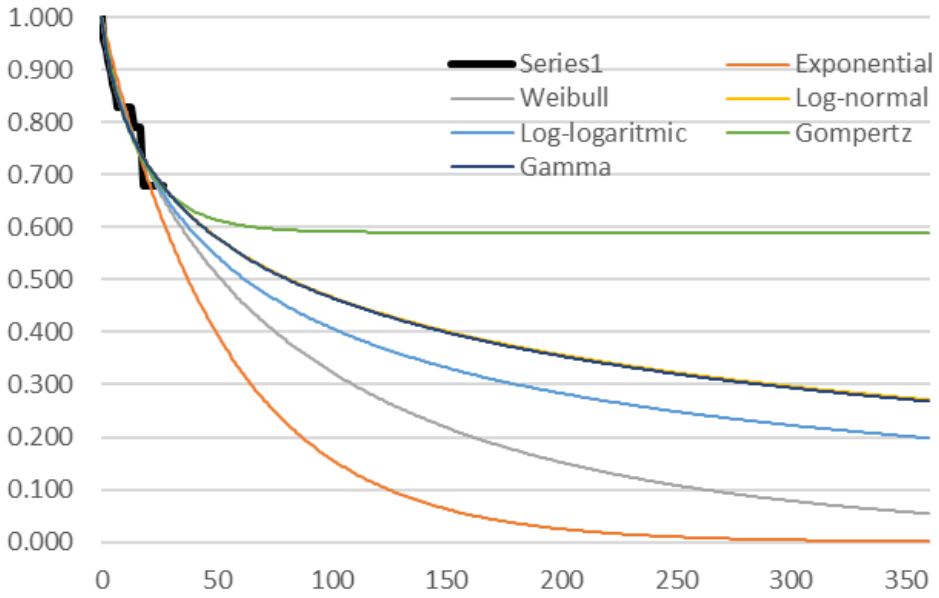

Figure 19 Extrapolation model for OS, avapritinib, data from PATHFINDER (Base case 200mg RAC-RE population) – lifetime horizon

Note: Months on x-axis, survival probability on y-axis

BAT

To estimate the OS for BAT, HR was taken from ITC analysis, assuming PH holds. In the case of OS, the HR applied in the model was HR: 0.47 [0.21; 0.49] was applied.

Table 73 presents the OS survival rates over time for avapritinib and BAT.

Table 73 OS survival rates at set time points – avapritinib (Base case 200mg RAC-RE population) vs BAT

Time point	Avapritinib Survival rate	BAT Survival rate
3 months	95.3%	85.4%
6 months	90.8%	79.1%
9 months	89.1%	75.6%
12 months	89.1%	70.1%
18 months	60.9%	47.2%
24 months	60.9%	40.9%
30 months	60.9%	39.8%
36 months	60.9%	35.1%
42 months	60.9%	27.9%
48 months	60.9%	22.2%

Abbreviations: BAT: best available treatment.

D.3 Proportional hazards

The validity of the proportional hazard (PH) assumption was assessed using log-cumulative hazards and Schoenfeld residuals plots. The Schoenfeld plot for avapritinib vs BAT is shown in Figure 20. The log-cumulative hazard plot for avapritinib vs BAT is shown in Figure 21.

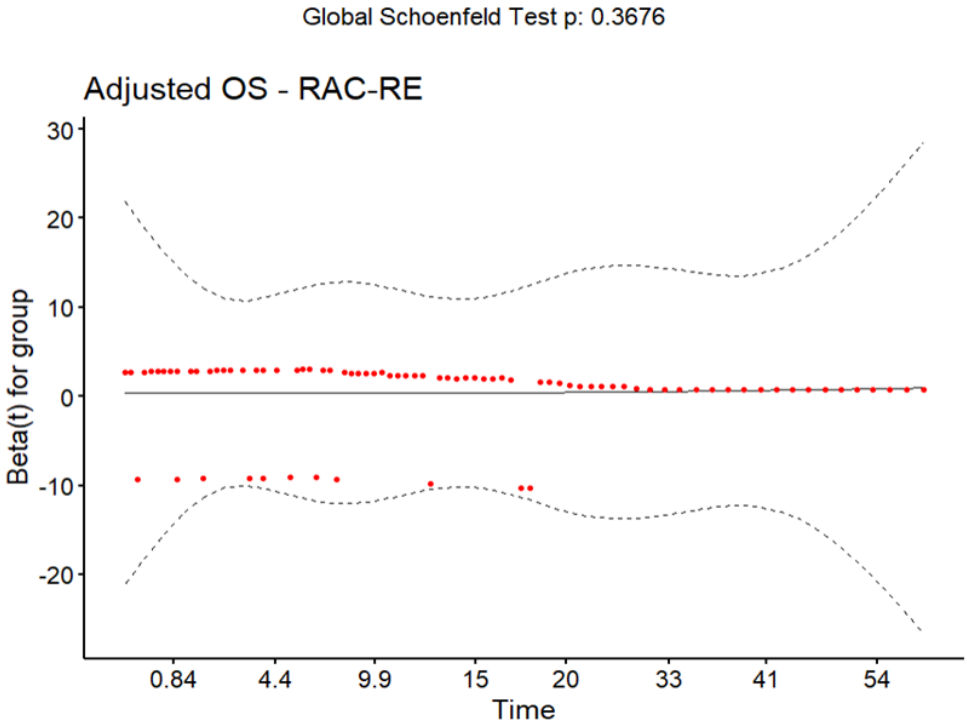

Figure 20 Shoenfeld plot for OS avapritinib vs BAT - adjusted analysis, Base case 200mg RAC-RE population

Abbreviations: OS: overall survival, RAC: response assessment committee response-evaluable population.

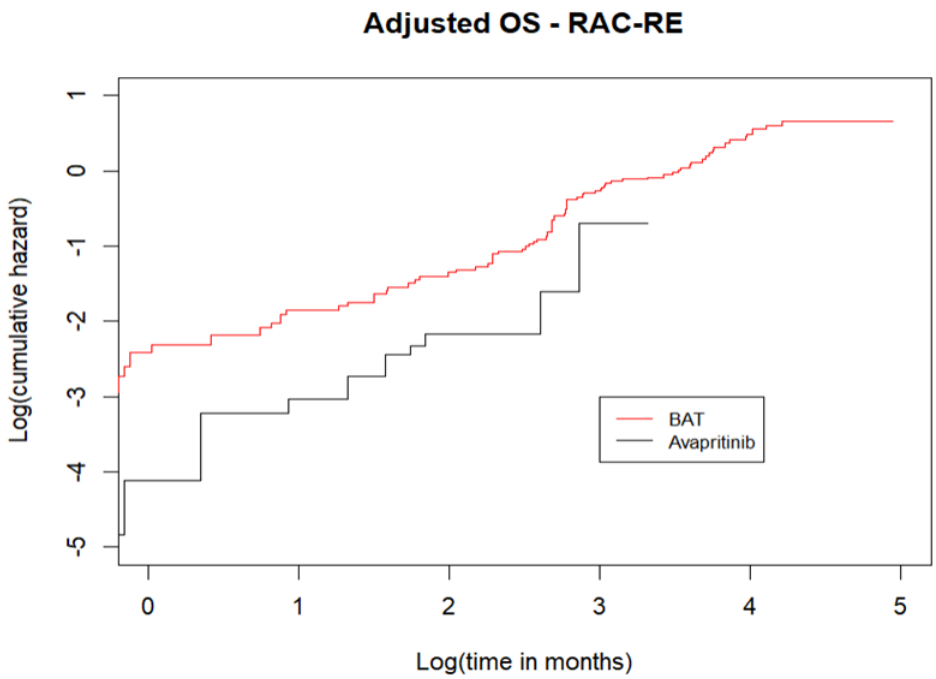

Figure 21 Log-cumulative hazard plot for OS avapritinib vs BAT - adjusted analysis, Base case 200mg RAC-RE population

Abbreviations: OS: overall survival, RAC: response assessment committee response-evaluable population.

The plots showed that avapritinib and BAT are relatively parallel and does not cross at any time. Furthermore, the p-value from the Schoenfeld test is 0.36, indicating that the test did not detect a significant violation of the PH assumption. Therefore, the PH assumption is not violated, and thus is assumed.

D.4 Evaluation of statistical fit (AIC and BIC)

Fit statistics in form of AIC and BIC are presented for all curves for OS in Table 74. AIC and BIC provide a summary of how well curves fit within the observed period. Given the relative immaturity of the data, and that all values are relatively close to one another, AIC and BIC should not be used as the main reason for curve selection. Instead, this should be done based on clinical plausibility of the long-term extrapolation and the underlying assumed hazard profile based on the curve chosen.

Table 74 OS statistical fit, AIC and BIC (Base case 200mg RAC-RE population, PATHFINDER April 2021 DCO)

Model	Avapritinib	
	AIC	BIC
Exponential	112.5952	114.5655
Weibull	113.6103	117.5509
Log-normal	113.4722	117.41278
Log-logistic	113.589	117.5296
Gompertz	113.8941	117.8347

Gamma	115.4584	121.3693

Abbreviations: AIC: akaike information criterion, BIC: bayesian information criterion.

The Exponential model has the best statistical fit according to both the AIC + BIC statistics.

D.5 Evaluation of visual fit

Most of the curves (refer to Figure 19) demonstrate a visually good fit and yield similar long-term extrapolations. There are no sharp hazard changes, and in each instance, the curves appear to indicate that most patients have reached death by the end of the time horizon. However, in the case of the Gompertz model, the survival curve demonstrates a slow gradual decline and presents an unrealistic clinical picture.

D.6 Evaluation of hazard functions

Smoothed hazard plot for OS for avapritinib is shown in Figure 22. When looking at smoothed hazards plot in Figure 22, the exponential model assumed that the hazard remains constant over time, and this appears to be in line with the observation that most deaths occurred at the time of progression, (i.e. there were not many patients post-progression and alive which would drive a much higher hazard of death from the time of progression onwards). This seems to be also in line with long-term survival of AdvSM patients, which at 20 years from diagnosis shows at best no more than 10% of cohort alive. From the smoothed hazard plot and from what is clinically expected, the exponential distribution was chosen for the base case.

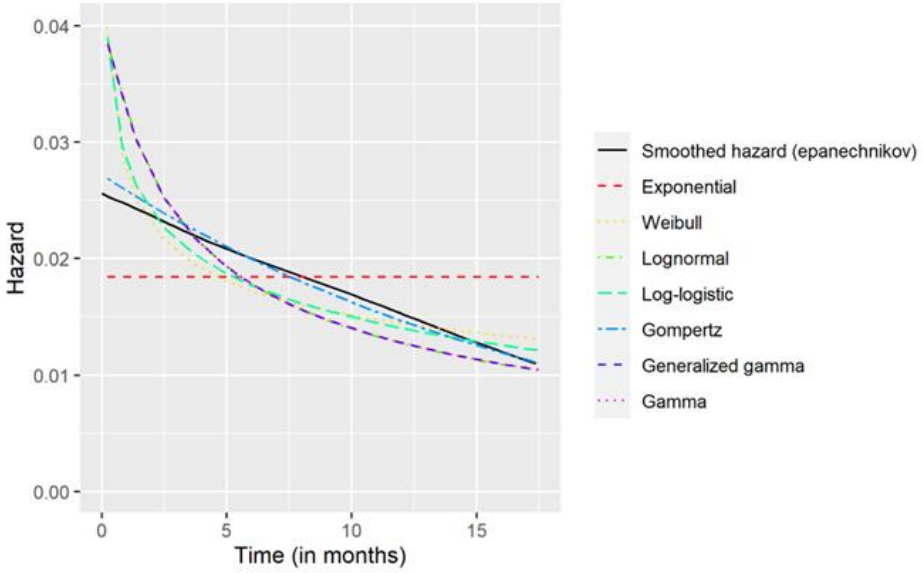

Figure 22 Smoothed hazard plot for OS - avapritinib, PATHFINDER (April 2021 DCO) - Base case 200mg RAC-RE population

Furthermore, a study of the hazard (rates of events) was conducted, for both within the trial period and best-fitting parametric beyond the trial. Turning points could not be identified and single full parametric approach was deemed appropriate.

The best AIC + BIC statistics for the smoothed hazard plot for avapritinib OS was Exponential.

D.7 Adjustment of background mortality

OS estimates are corrected for background mortality under the assumption that the age- and gender-adjusted risk of death from AdvSM of patients can never be lower than the age- and gender-adjusted mortality risk of the general population. In any period and for any treatment where modelled OS suggested lower mortality than the general population, all-cause mortality hazard rate based on the Statistics Denmark (72, 92).

D.8 Adjustment for treatment switching/cross-over

Not applicable.

D.9 Waning effect

Not applicable.

D.10 Cure-point

Not applicable.

D.11 Validation and discussion of extrapolated curves

The extrapolated survival curves have been discussed and validated with different European clinical experts.

Extrapolation of overall survival (OS) for post-HSCT

Following the opinion of clinical experts, to maximize outcomes post-transplant, a good response in SM should be considered as first criteria to define eligibility for allo-HSCT. Although, complete remission in SM is the most optimal situation, a patient with partial remission could be considered eligible if young, has a good matching donor and the clinical situation suggests that without the transplant the patient could start worsening. Priority selection by sub-type would be:

1. ASM: SM remission, young, no comorbidities (fit for transplant) and good matching donor.
2. AHN and MCL: SM remission, change in clinical situation suggesting associated haematological neoplasm may be/is worsening, no comorbidities (fit for transplant) and good matching donor. Nevertheless, if a good matching donor exist and the patient is young, they may be offered transplant even with stable is associated haematological neoplasm.

Ustun et al. (70) was identified as the main source of information about the outcomes of HSCT in AdvSM patients. A retrospective observational study was conducted and the PFS and the OS of AdvSM patients treated with SCT over a 3-year time-horizon were reported. First, it was noticed that the PFS and the OS overlapped in many of the sub-analyses presented in the paper, suggesting that most of the progression events were due to the patient's death. Therefore, no progression health state was included after the HSCT and only the overall survival was used.

Moreover, it was observed that 1 year after HSCT most of the KM curves flattened, indicating a reduction in mortality. Consequently, the assumption was made in the model, that the proportion of the HSCT cohort surviving 1 year reached a cure-point after which either the average hazard between 1 and year 4 of the extrapolated curve or the mortality of the overall population is applied, whichever is greater. This allows to adjust for the rise of the hazard in the long-term due to ageing of the cohort.

Among the several KM curves presented by Ustun et al., three were selected to be included in the model:

I. the one related to the entire population,

II. its upper confidence limit and;

III. the one related to the patients who was given a myeloablative conditioning regime (MAC).

In the base case, the selected population is the MAC patients. This is because only the responders who are fit enough for HSCT are eligible for it. These patients are assumed to undergo a full myeloablative conditioning, since the reduced intensity conditioning is reserved for more fragile patients, who, in the model, where not eligible for HSCT at all.

D.12 Data input

The KM curves were digitized from the publication by Ustun et al. (70) and, subsequently, the algorithm published by Guyot et al. were used to generate pseudo individual patient data (pseudo-IPD).

Figure 23 shows the pseudo-IPD data generated from the Ustun et al (70).

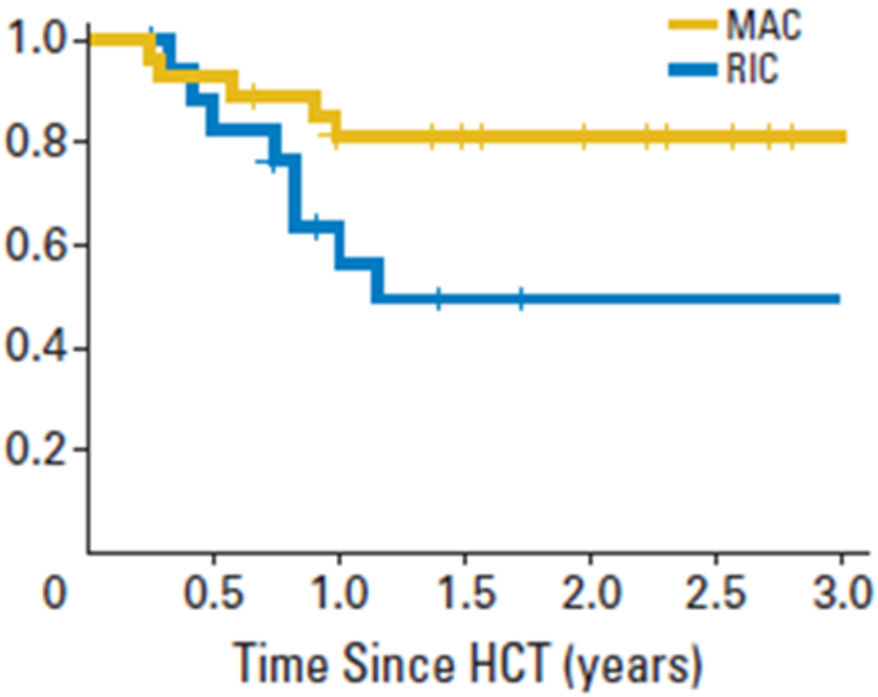

Figure 23 KM data generated from Ustun et al - MAC patients

Abbreviations: HCT: haematipoietic stem cell transplantation, MAC: myeloablative conditioning, RIC: reduced intensity conditioning.

D.13 Model

The data generated from Ustun et al. were used to fit different parametric distributions (Exponential, Weibull, Log-normal, Log-logistic, Gompertz, and Gamma), allowing to extrapolate the overall survival over the model time horizon. The best fitting was selected based on AIC/BIC values, visual inspection, and internal/external validity.

Figure 24 shows the extrapolation model of OS (post-HSCT) for MAC patients.

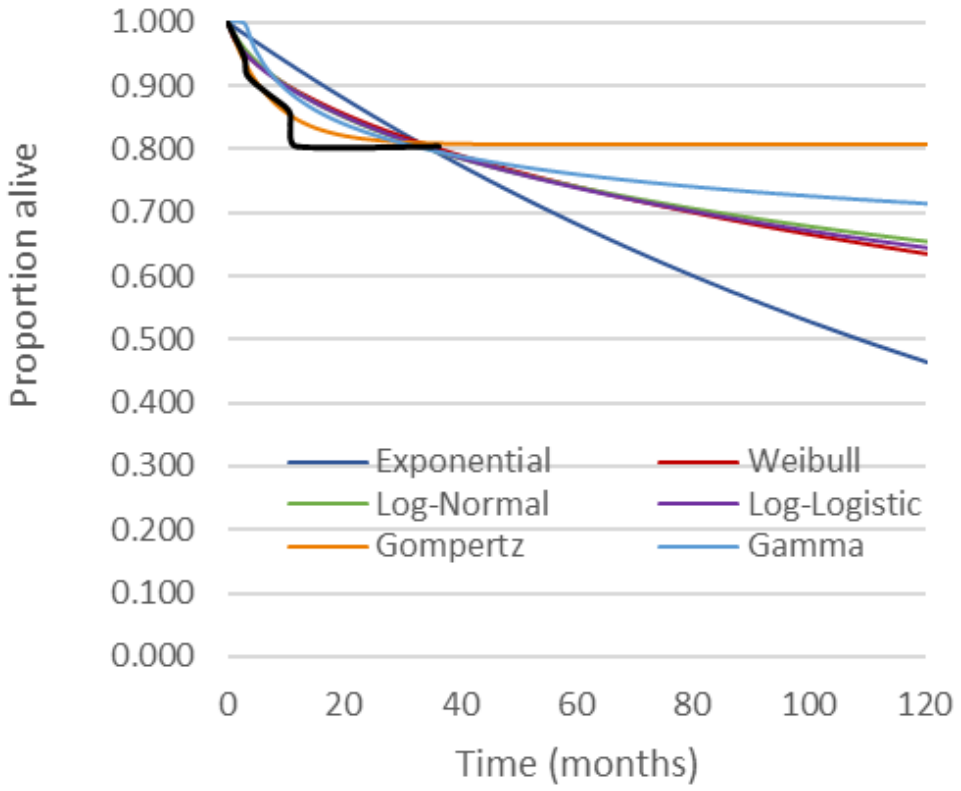

Figure 24 Extrapolation model on the pseudo-KM data from Ustun et al, MAC patients, (120 months)

D.14 Proportional hazards

Not applicable.

D.15 Evaluation of statistical fit (AIC and BIC)

Table 75 presents the statistical fit of OS (post-HSCT) parametric model for MAC patients.

Table 75 OS (post-HSCT) statistical fit, AIC and BIC

Model	MAC patients	
	AIC	BIC
Exponential	148.7422	150.7852
Weibull	148.9014	152.9875
Log-normal	147.2421	151.3282
Log-logistic	148.4534	152.5395
Gompertz	150.2376	154.3237
Gamma	144.6298	150.7589

Abbreviations: MAC: myeloablative conditioning, AIC: akaike information criterion, BIC: bayesian information criterion.

The gamma model produces the best statistical fit according to both the AIC and BIC statistics.

D.16 Evaluation of visual fit

The visual observation of the parametric OS curve for post-HSCT shows that the Gamma distribution closely matches the tails of the KM curve.

D.17 Evaluation of hazard functions

Not applicable.

D.18 Adjustment of background mortality

To keep the mortality risk of eligible patients, equivalent to or greater than the general population in all model cycles, all outcomes were capped by general mortality using Danish life tables provided by the DMC (72).

D.19 Adjustment for treatment switching/cross-over

Not applicable.

D.20 Waning effect

Not applicable.

D.21 Cure-point

The proportion of the HSCT cohort surviving 1 year reached a cure-point after which either the average hazard between 1 and year 4 of the extrapolated curves or the mortality of the overall population is applied. This allows to adjust for the rise of the hazard in the long-term due to ageing of the cohort.

D.22 Validation and discussion of extrapolated curves

Not applicable.

Extrapolation of progression-free survival (PFS)

D.23 Data input

Avapritinib

The PFS KM curve was generated considering that the progression and the date of progression corresponded the one reported by central-adjudicated response, by means of the modified IWG criteria, hence the model includes the PFS curve estimated on the RAC-RE analysis set. Figure 25 show avapritinib KM data.

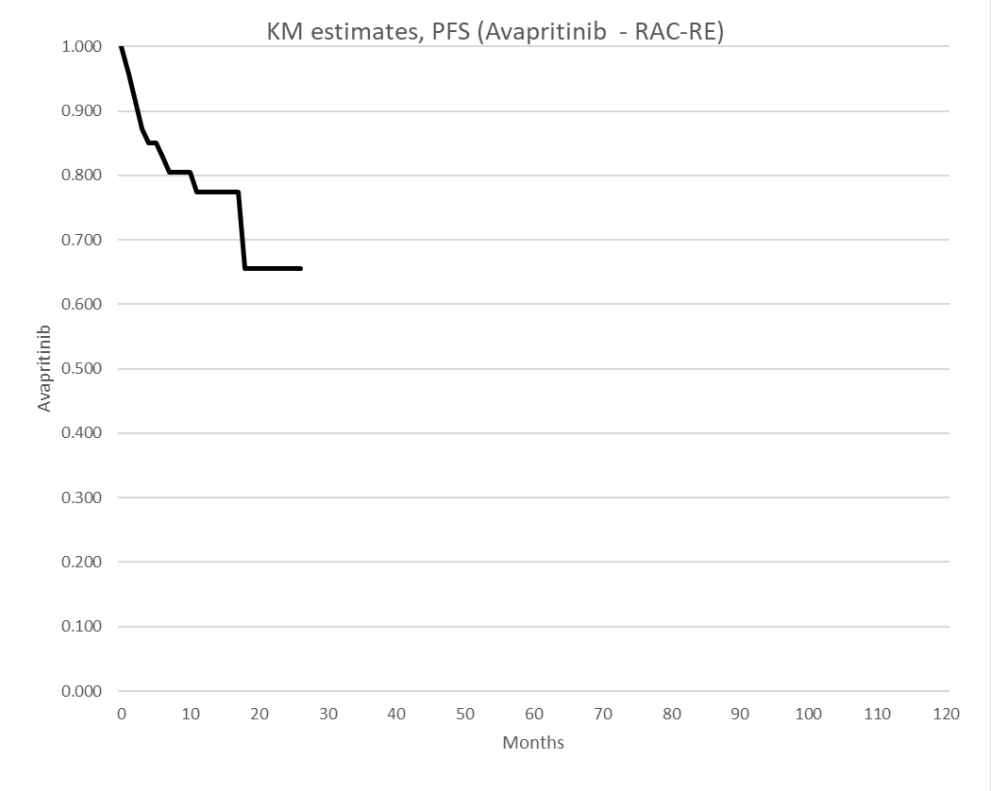

Figure 25 PFS KM data for avapritinib. Base case 200mg RAC-RE population.

Abbreviations: KM: Kaplan-Meier, PFS: progression-free survival, RAC-RE: response assessment committee response-evaluable population

BAT

The indirect comparison could not provide an estimate of the relative PFS because the progression criteria used in the retrospective study were not consistent with those used in EXPLORER and PATHFINDER.

For the PFS two different scenarios were implemented in the model:

1. Many of the BAT treatments are assumed until progression. This justifies the use of the ToT curve as proxy for the PFS curve. The base case is therefore: BAT PFS was assumed to be the same as the BAT ToT.
2. In an alternative scenario the assumption was made that the OS HR held also for the PFS and that the PH assumption was met. Therefore, the BAT PFS was calculated by applying the OS HR to the Avapritinib PFS curve.

D.24 Model

Extrapolation of PFS was generated by fitting parametric models to the KM curves from the RAC-RE analysis set from the PATHFINDER study (April 2021 DCO). Six parametric distributions were fitted to the data, including: Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma.

Avapritinib

Figure 26 shows the extrapolation model of PFS for avapritinib over the lifetime horizon.

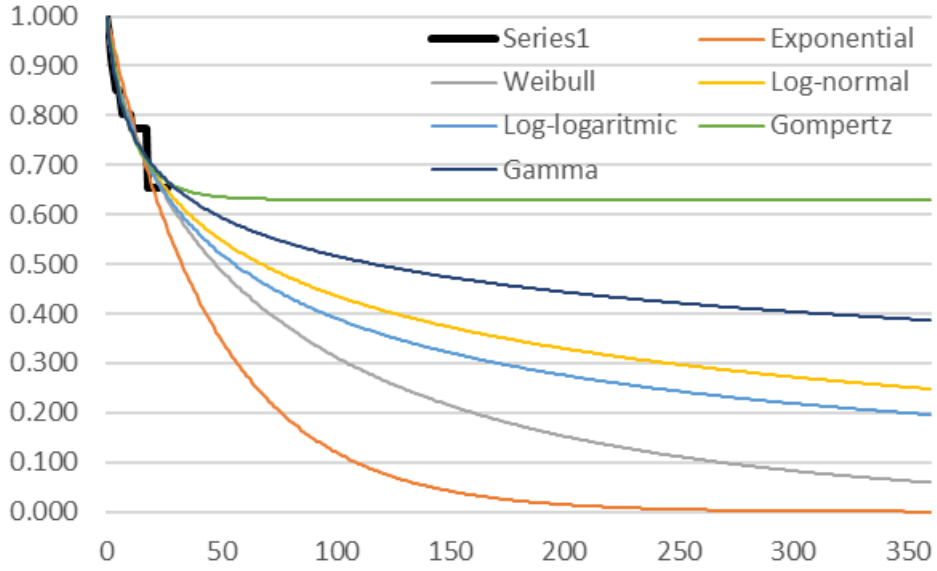

Figure 26 Extrapolation model for PFS, avapritinib, data from PATHFINDER (Base case 200mg RAC-RE population) - lifetime horizon

Note: Months on x-axis, survival probability on y-axis.

BAT

In the base case the BAT PFS was assumed to be the same as the BAT ToT.

D.25 Proportional hazards

As mentioned previously, an alternative scenario applied the assumption was made that the OS HR held also for the PFS and that the PH assumption was met, refer to Section D.3 for testing of the PH assumption for OS.

D.26 Evaluation of statistical fit (AIC and BIC)

Table 76 presents the statistical fit of each OS parametric model for avapritinib.

Table 76 PFS statistical fit, AIC and BIC (Base case 200mg RAC-RE population, PATHFINDER April 2021 DCO)

Model	Avapritinib	
	AIC	BIC
Exponential	118.533	120.3831
Weibull	118.3217	122.022
Log-normal	117.46143	121.16172
Log-logistic	118.1002	121.8005
Gompertz	118.3042	122.0045

Gamma	119.1833	124.7338

Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion

The Log-normal model has the best statistical fit according to the AIC + BIC statistics.

D.27 Evaluation of visual fit

Most of the curves (refer to Figure 26) demonstrate a visually good fit and yield similar long-term extrapolations. Again, in the case of the Gompertz model, the survival curve demonstrates a slow gradual decline and presents an unrealistic clinical picture. Considering that in the model there are six parametric extrapolations that can be selected by the user, various scenarios can be created that are clinically implausible because PFS and OS curves cross. As Figure 27 illustrates, only the Exponential model does not cross with OS.

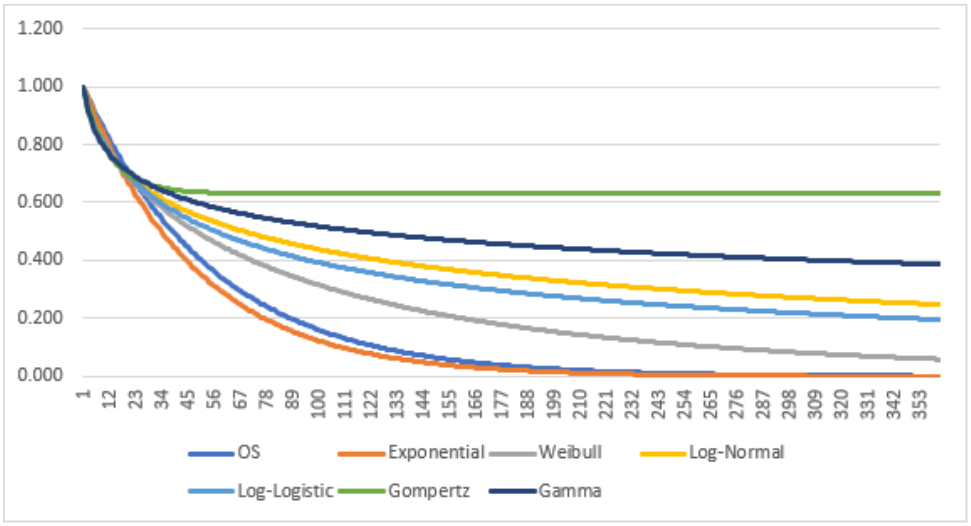

Figure 27 Comparison of OS and PFS extrapolation models, avapritinib (Base case 200mg RAC-RE population)

Note: Months on a-axis, survival probability on y-axis.

D.28 Evaluation of hazard functions

Smoothed hazard plot for avapritinib PFS is shown in Figure 28. The best AIC + BIC statistics for the smoothed hazard plot for avapritinib PFS was Log-normal.

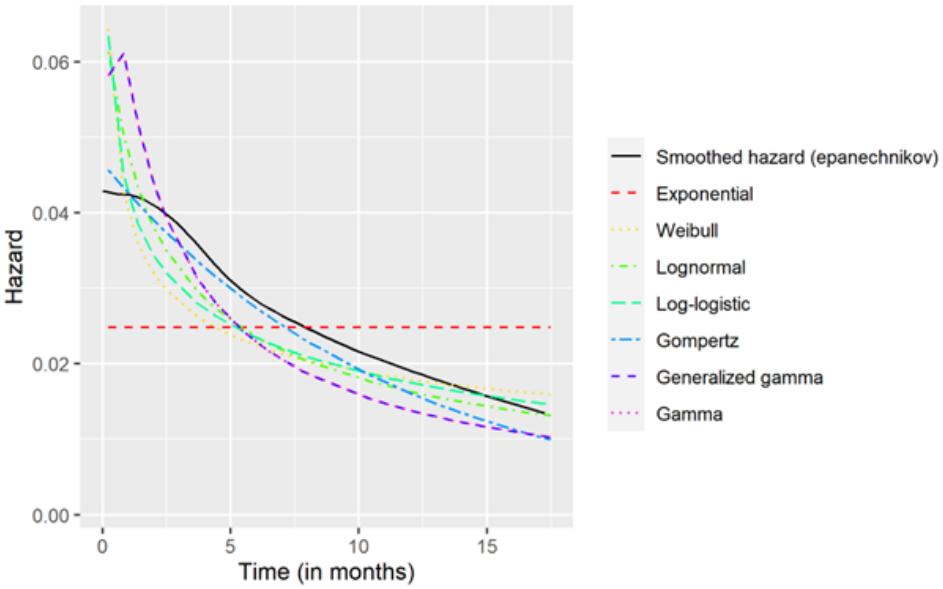

Figure 28 Smoothed hazard plot for PFS - avapritinib, PATHFINDER (April 2021 DCO) - Base case 200mg RAC-RE population

However, it can again be mentioned that the Exponential models assume that the hazard remains constant over time, and this appears to be in line with the observation that most deaths occurred at the time of progression, (i.e. there were not many patients post-progression and alive which would drive a much higher hazard of death from the time of progression onwards). This seems to be also in line with long-term survival of AdvSM patients, which at 20 years from diagnosis shows at best no more than 10% of cohort alive.

D.29 Adjustment of background mortality

Not applicable.

D.30 Adjustment for treatment switching/cross-over

Not applicable.

D.31 Waning effect

Not applicable.

D.32 Cure-point

Not applicable.

D.33 Validation and discussion of extrapolated curves

Not applicable.

Extrapolation of time-on-treatment (ToT)

D.34 Data input

ToT in the avapritinib arm was captured and extrapolated based on the information available from the PATHFINDER (April 2021 DCO). For the BAT arm, the ToT was captured and extrapolated based on the ITC analysis of the RWE BLU-285-2405. The KM data from PATHFINDER and RWE BLU-285-2405 is shown in Figure 29.

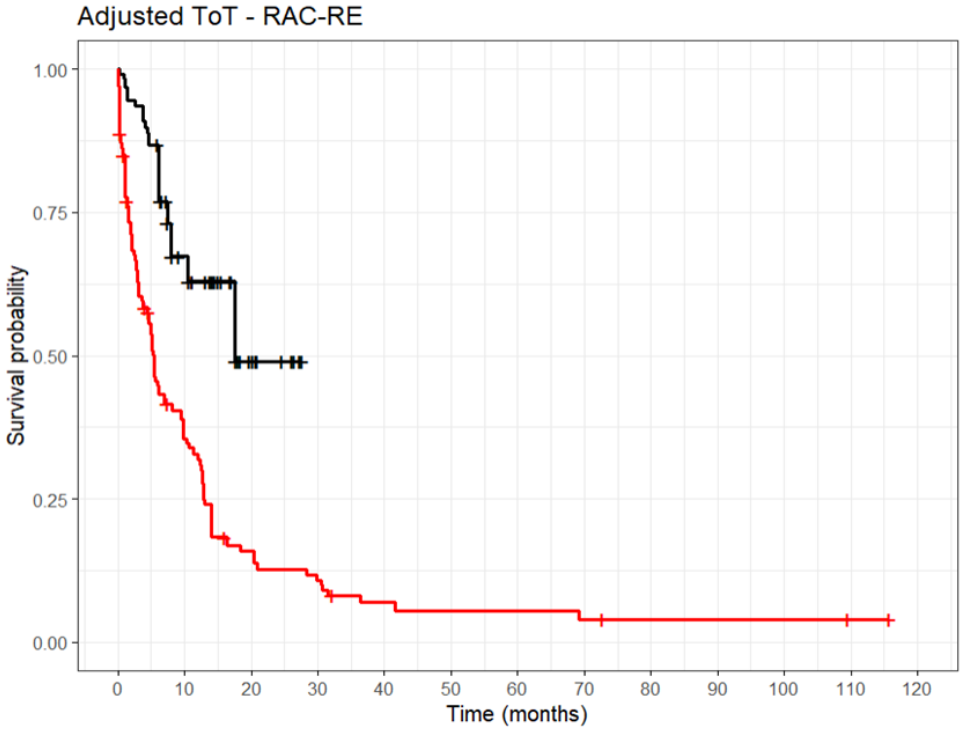

Figure 29 ToT KM data for avapritinib vs BAT - adjusted analysis, Base case 200mg RAC-RE population. (BAT= red, avapritinib= black)

Abbreviations: ToT: time on treatment, RAC-RE: response assessment committee response-evaluable population

D.35 Model

Extrapolation of ToT was generated by fitting parametric models to the KM curves from the IPD data from the PATHFINDER study (April 2021 DCO). Six parametric distributions were fitted to the data, including: Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Gamma.

Avapritinib

Figure 30 shows the extrapolation model of ToT for avapritinib over the lifetime horizon.

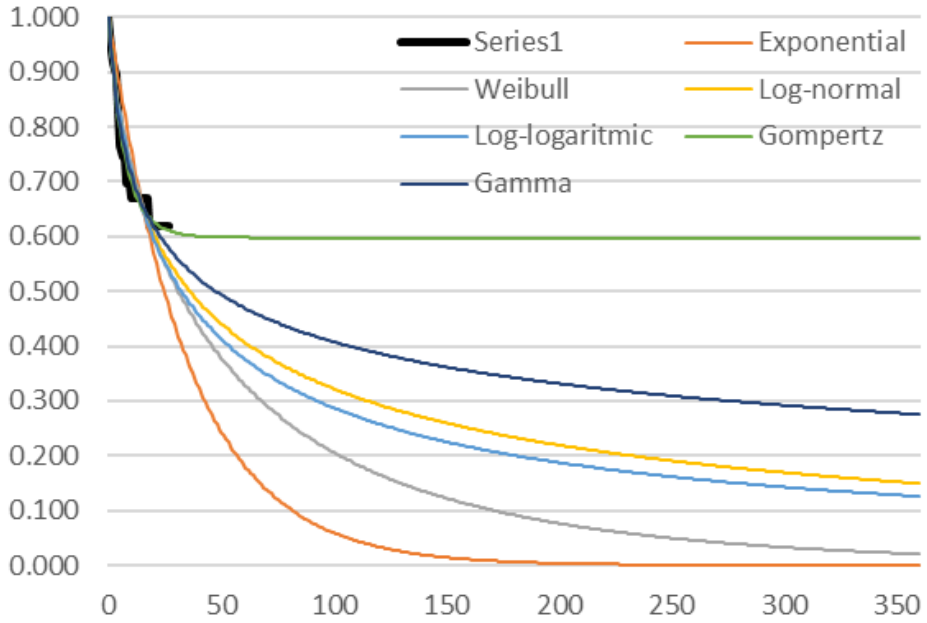

Figure 30 Extrapolation model for ToT, avapritinib, data from PATHFINDER (Base case 200mg RAC-RE population) - lifetime horizon

Note: Months on a-axis, survival probability on y-axis.

BAT

To estimate the ToT for BAT, HR was taken from ITC analysis, assuming PH holds. In the case of OS, the HR applied in the model was HR: 0.36 [0.22; 0.57] was applied (3).

Table 77 presents the ToT survival rates over time for avapritinib and BAT.

Table 77 ToT survival rates at set time points – avapritinib (Base case 200mg RAC-RE population) vs BAT

Time point	Avapritinib Survival rate	BAT Survival rate
3 months	93.7%	62.8%
6 months	86.9%	44.7%
9 months	67.3%	40.3%
12 months	63.0%	32.8%
18 months	49.0%	16.8%
24 months	49.0%	12.7%
36 months	NA	8.1%

Abbreviations: BAT: best available treatment, NA: not applicable

D.36 Proportional hazards

The validity of the PH assumption was assessed using log-cumulative hazards and Schoenfeld residuals plots. The Schoenfeld plot for avapritinib vs BAT is shown in Figure 31. The log-cumulative hazard plot for avapritinib vs BAT is shown in Figure 32.

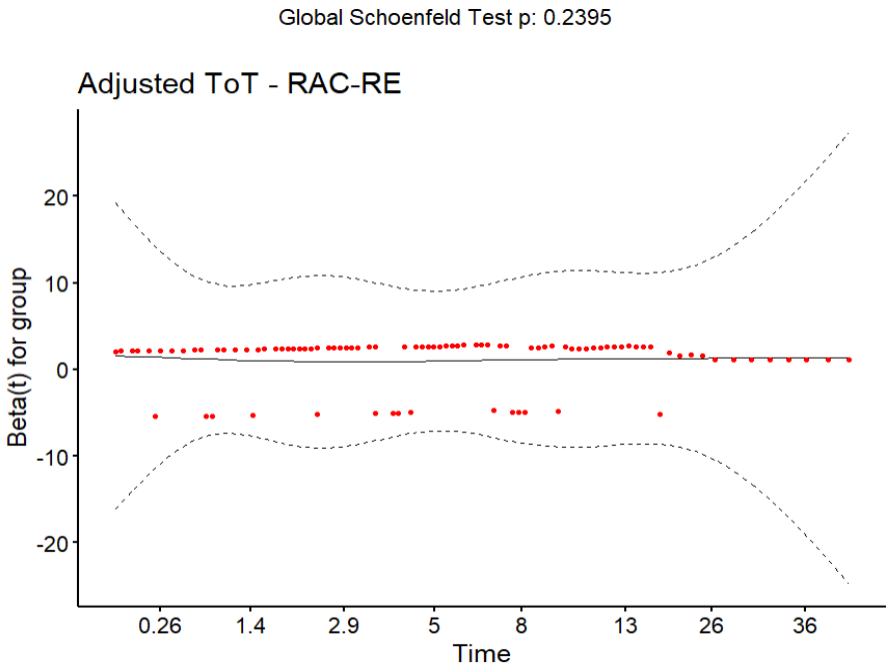

Figure 31 Shoenfeld plot for ToT avapritinib vs BAT - adjusted analysis, Base case 200mg RAC-RE population

Abbreviations: ToT: time on treatment, RAC-RE: response assessment committee response-evaluable population

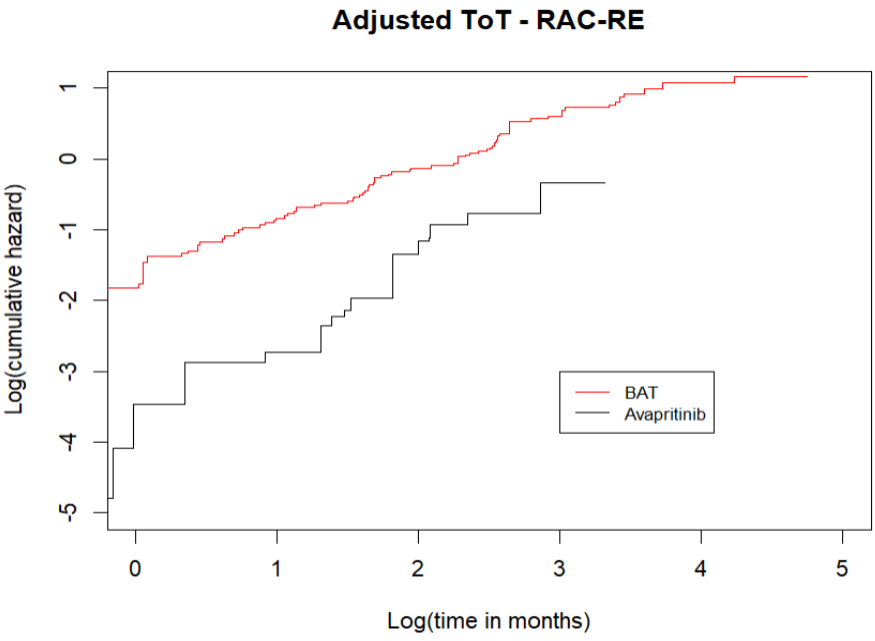

Figure 32 Log-cumulative hazard plot for ToT avapritinib vs BAT - adjusted analysis, Base case 200mg RAC-RE population

Abbreviations: ToT: time on treatment, RAC-RE: response assessment committee response-evaluable population, BAT: best available treatment.

The plots showed that avapritinib and BAT are relatively parallel and does not cross at any time. Furthermore, the p-value from the Schoenfeld test is 0.24, indicating that the test

did not detect a significant violation of the PH assumption. Therefore, the PH assumption is not violated, and thus is assumed.

D.37 Evaluation of statistical fit (AIC and BIC)

Table 78 presents the statistical fit of each ToT parametric model for avapritinib.

Table 78 ToT statistical fit, AIC and BIC (Base case 200mg RAC-RE population, PATHFINDER April 2021 DCO)

Model	Avapritinib	
	AIC	BIC
Exponential	149.1796	151.1499
Weibull	148.5359	152.4765
Log-normal	147.08104	151.02162
Log-logistic	147.947	151.8876
Gompertz	147.1316	151.0721
Gamma	148.7135	154.6243

Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion

The Log-normal model has the best statistical fit according to the AIC + BIC statistics.

D.38 Evaluation of visual fit

Most of the curves (refer to Figure 30) demonstrate a visually good fit and yield similar long-term extrapolations. Again, in the case of the Gompertz model, the survival curve demonstrates a slow gradual decline and presents an unrealistic clinical picture.

Considering that in the model there are six parametric extrapolations that can be selected by the user, various scenarios can be created that are clinically implausible because PFS and OS curves cross. As Figure 33 illustrates, only the Exponential model does not cross with OS.

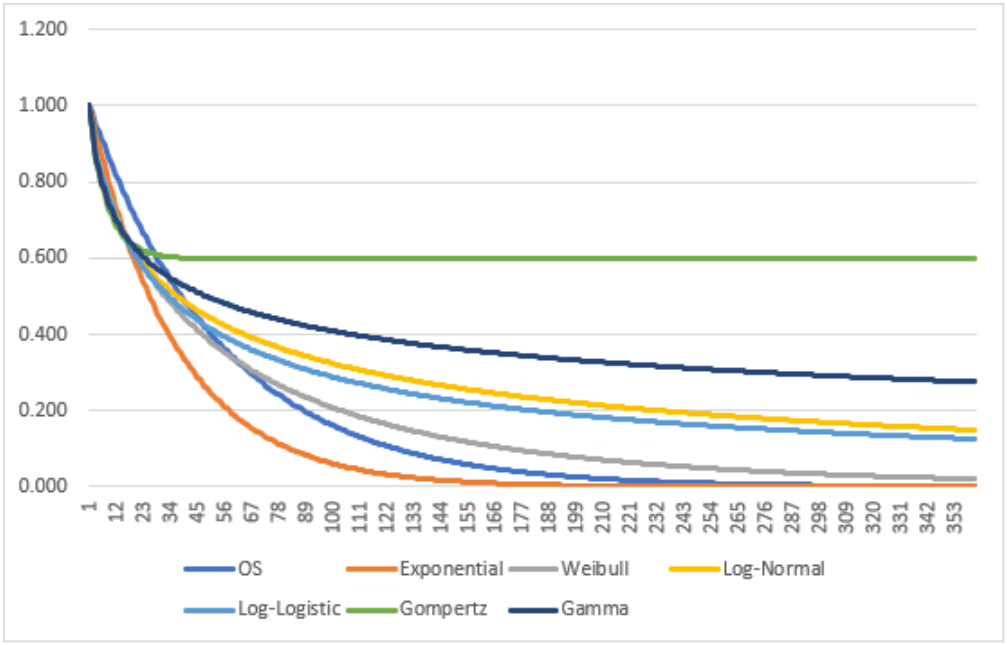

Figure 33 Comparison of OS and ToT extrapolation models, avapritinib (Base case 200mg RAC-RE population)

D.39 Evaluation of hazard functions

Smoothed hazard plot for avapritinib ToT is shown in Figure 34. The best AIC + BIC statistics for the smoothed hazard plot for avapritinib ToT was Gompertz.

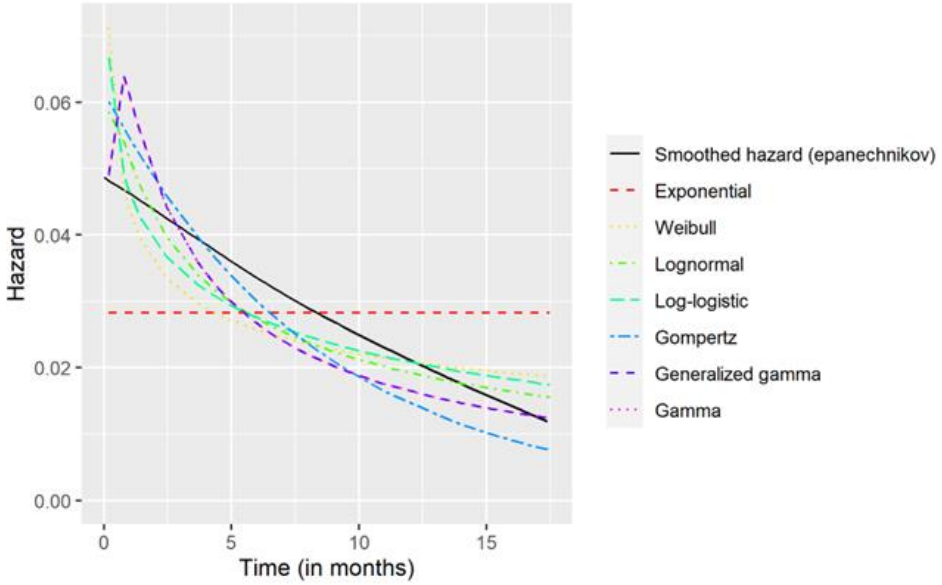

Figure 34 Smoothed hazard plot for OS - avapritinib, PATHFINDER (April 2021 DCO) - Base case 200mg RAC-RE population

Despite that Gompertz showed the best fits according to the AIC + BIC statistics, the Gompertz model showed clinically unrealistic picture. The same argument that has been used for OS and PFS is also applicable to ToT. That said, the Exponential models assume a constant hazard over time, which appears to be more clinically realistic.

D.40 Adjustment of background mortality

Not applicable.

D.41 Adjustment for treatment switching/cross-over

Not applicable.

D.42 Waning effect

Not applicable.

D.43 Cure-point

Not applicable.

D.44 Validation and discussion of extrapolated curves

Not applicable.

Appendix E. Serious adverse events

Table 79 details the serious adverse events with a frequency of >1% for the safety population in the EXPLORER and PATHFINDER studies. Table 80 details the adverse events of special interest in the EXPLORER and PATHFINDER studies.

As shown in the table below, a total of 8 deaths occurred in this population group who received 200 mg of avapritinib across both studies (4). No specific adverse event leading to death was reported in more than 1 patient (4).

Table 79 Serious adverse events with a frequency of >1% for avapritinib. EXPLORER and PATHFINDER; safety population analysis set; 200mg; April 2021 DCO

Adverse events, n (%)	Avapritinib (N=126)
Patients with ≥1 SAE	48 (38.1)
Anaemia	4 (3.2)
Subdural haematoma	4 (3.2)
Ascites	3 (2.4)
Pleural effusion	2 (1.6)
Acute kidney damage	2 (1.6)
Gastrointestinal haemorrhage	2 (1.6)
Diverticulitis	2 (1.6)
Haemorrhage	2 (1.6)
Intra-abdominal haemorrhage	2 (1.6)
Osteomyelitis	2 (1.6)
Pneumothorax	2 (1.6)
Patients with any adverse event leading to death	8 (6.3)

Note: Adverse Events are coded using MedDRA 18.1. AEs refer to TEAEs which is defined as an AE that occurs during or after administration of the first dose of study drug through 30 days after the last dose of study drug, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens intensity or is subsequently considered study drug-related by the Investigator. All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
Source: Safety CSR; Table 25 (4)

Table 80 Adverse events of special interest. EXPLORER and PATHFINDER; safety population analysis set; 200mg; April 2021 DCO

Adverse events, n (%)	Avapritinib (N=126)
Cognitive effects	24 (19.0)
• Cognitive disorder	15 (11.9)
• Somnolence	1 (<1)
• Delirium	1 (<1)
• Dementia	1 (<1)
• Disorientation	1 (<1)
• Mental status change	1 (<1)
• Memory impairment	7 (5.6)
• Confusional state	3 (2.4)
Intracranial bleeding	4 (3.2)
• Subdural haematoma	4 (3.2)

Note: Adverse Events are coded using MedDRA 18.1. AEs refer to TEAEs which is defined as an AE that occurs during or after administration of the first dose of study drug through 30 days after the last dose of study drug, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens intensity or is subsequently considered study drug-related by the Investigator. All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
Source: Safety CSR; Table 57 & 62 (4)

Appendix F. Health-related quality of life

The EORTC QLQ-C30 (version 3.0) is a 30-item questionnaire used to evaluate QoL, and includes five functional domains (physical (PF), cognitive (CF), role (RF), emotional (EF), and social (SF)), three symptom scales (fatigue (FA), nausea and vomiting (NV), and pain (PA)), a global health status / QoL scale (QL), and six single items (dyspnea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), and financial difficulties (FI)). Patients will complete the EORTC QLQ-C30 at each visit through Cycle 17 and at EOT, if EOT is before or at Cycle 17.

All of the scales and single-item measures range in score from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. Scoring method is outlined in Table 81 and the following paragraphs.

Table 81. Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range	Version 3.0 Item numbers	Function scales
Global health Status /QoL	QL	2	6	29, 30	
Functional Scales					
Physical functioning	PF	5	3	1 to 5	F
Role functioning	RF	2	3	6,7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social function	SF	2	3	26, 27	F
Symptom scales/items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14,15	
Pain	PA	2	3	9, 19	
Dyspnea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

Raw score (RS) is calculated as the average item score when at least half of the items are not missing. After RS is calculated, a linear transformation to 0-100 will be applied to get the score (S) use ranges provided in Table 81. For functional scales S = (1- (RS-1)/range) x 100. For symptom scales / items and global health status S= ((RS-1)/range) x 100.

Summary statistics and change from Baseline to D1 of each cycle will be presented for all calculated scores. Box plots of change from Baseline to D1 of each cycle will be presented, including all patients in the RAC-RE Population with Baseline score. As a sensitivity analysis, cumulative density function (CDF) plots of QoL were produced at D1 of each cycle from C2 to C17. Similar CDF plots were produced for all 6 functional scales at D1 of C3, C7, C11 and C17.

Figure 35, Figure 36, Figure 37 and Figure 38 shows four of the domains (independent of being PFS or PD) that were used to calculate the mean, standard deviation, median, minimum and maximum estimates at each timepoint. The domains: Global health status, Physical functioning, Role functioning, and Emotional functioning (4, 5).

Global Health Status							
Visit	Subgroup	n	Mean	StdDev	Median	Min	Max
Baseline	ASM	6	51.39	17.01	50	33.33	75
Baseline	MCL	9	34.26	14.1	33.33	16.67	58.33
Baseline	SM-AHN	26	33.97	28.37	33.33	0	100
Baseline	Total	41	36.59	24.85	33.33	0	100
Cycle 1 Day 8	SM-AHN	2	25	11.79	25	16.67	33.33
Cycle 1 Day 8	Total	2	25	11.79	25	16.67	33.33
Cycle 1 Day 15	ASM	6	47.22	13.61	45.83	33.33	66.67
Cycle 1 Day 15	MCL	8	47.92	22.16	45.83	25	75
Cycle 1 Day 15	SM-AHN	23	55.07	23.4	58.33	16.67	100
Cycle 1 Day 15	Total	37	52.25	21.66	50	16.67	100
Cycle 1 Day 22	ASM	1	50		50	50	50
Cycle 1 Day 22	MCL	1	25		25	25	25
Cycle 1 Day 22	SM-AHN	1	16.67		16.67	16.67	16.67
Cycle 1 Day 22	Total	3	30.56	17.35	25	16.67	50
Cycle 2 Day 1	ASM	5	46.67	13.94	50	33.33	66.67
Cycle 2 Day 1	MCL	9	46.3	25.72	50	0	75
Cycle 2 Day 1	SM-AHN	25	55	22.18	58.33	16.67	91.67
Cycle 2 Day 1	Total	39	51.92	22.09	50	0	91.67
Cycle 2 Day 15	SM-AHN	1	16.67		16.67	16.67	16.67
Cycle 2 Day 15	Total	1	16.67		16.67	16.67	16.67
Cycle 3 Day 1	ASM	5	51.67	12.36	50	33.33	66.67
Cycle 3 Day 1	MCL	6	40.28	12.27	37.5	25	58.33
Cycle 3 Day 1	SM-AHN	22	62.12	15.59	66.67	33.33	83.33
Cycle 3 Day 1	Total	33	56.57	16.64	58.33	25	83.33
Cycle 4 Day 1	MCL	1	33.33		33.33	33.33	33.33
Cycle 4 Day 1	SM-AHN	1	58.33		58.33	58.33	58.33
Cycle 4 Day 1	Total	2	45.83	17.68	45.83	33.33	58.33
Cycle 5 Day 1	ASM	7	48.81	15.54	50	25	66.67
Cycle 5 Day 1	MCL	7	46.43	19.75	50	8.33	66.67
Cycle 5 Day 1	SM-AHN	16	52.08	21.62	54.17	0	83.33
Cycle 5 Day 1	Total	30	50	19.45	50	0	83.33
Cycle 6 Day 1	MCL	1	50		50	50	50
Cycle 6 Day 1	SM-AHN	1	83.33		83.33	83.33	83.33
Cycle 6 Day 1	Total	2	66.67	23.57	66.67	50	83.33
Cycle 7 Day 1	ASM	5	51.67	20.75	58.33	16.67	66.67
Cycle 7 Day 1	MCL	4	58.33	11.79	62.5	41.67	66.67
Cycle 7 Day 1	SM-AHN	17	62.75	17.71	66.67	25	83.33
Cycle 7 Day 1	Total	26	59.94	17.48	66.67	16.67	83.33
Cycle 8 Day 1	ASM	2	33.33	35.36	33.33	8.33	58.33
Cycle 8 Day 1	SM-AHN	2	62.5	29.46	62.5	41.67	83.33
Cycle 8 Day 1	Total	4	47.92	31.46	50	8.33	83.33
Cycle 9 Day 1	ASM	3	63.89	19.25	75	41.67	75
Cycle 9 Day 1	MCL	6	52.78	18	54.17	25	75
Cycle 9 Day 1	SM-AHN	13	51.28	23.53	58.33	0	83.33
Cycle 9 Day 1	Total	22	53.41	21.15	58.33	0	83.33
Cycle 10 Day 1	ASM	1	50		50	50	50
Cycle 10 Day 1	SM-AHN	1	83.33		83.33	83.33	83.33
Cycle 10 Day 1	Total	2	66.67	23.57	66.67	50	83.33
Cycle 11 Day 1	ASM	2	25	11.79	25	16.67	33.33
Cycle 11 Day 1	MCL	5	50	15.59	50	25	66.67
Cycle 11 Day 1	SM-AHN	8	64.58	13.91	66.67	41.67	83.33
Cycle 11 Day 1	Total	15	54.44	19.12	58.33	16.67	83.33
Cycle 12 Day 1	ASM	1	33.33		33.33	33.33	33.33
Cycle 12 Day 1	Total	1	33.33		33.33	33.33	33.33
Cycle 14 Day 1	ASM	1	50		50	50	50
Cycle 14 Day 1	MCL	2	79.17	5.89	79.17	75	83.33
Cycle 14 Day 1	SM-AHN	10	74.17	12.08	79.17	50	83.33
Cycle 14 Day 1	Total	13	73.08	12.8	75	50	83.33
Cycle 15 Day 1	ASM	1	16.67		16.67	16.67	16.67
Cycle 15 Day 1	SM-AHN	1	83.33		83.33	83.33	83.33
Cycle 15 Day 1	Total	2	50	47.14	50	16.67	83.33
Cycle 17 Day 1	ASM	1	50		50	50	50
Cycle 17 Day 1	MCL	1	66.67		66.67	66.67	66.67
Cycle 17 Day 1	SM-AHN	8	66.67	7.72	66.67	50	75
Cycle 17 Day 1	Total	10	65	8.61	66.67	50	75
Cycle 18 Day 1	ASM	1	33.33		33.33	33.33	33.33
Cycle 18 Day 1	Total	1	33.33		33.33	33.33	33.33

Figure 35 EORTC QLQ C-30 - Global health status, avapritinib 200mg RAC-RE population

Physical functioning							
Visit	**Subgroup**	**n**	**Mean**	**StdDev**	**Median**	**Min**	**Max**
Baseline	ASM	6	67.78	27.46	70	20	100
Baseline	MCL	9	53.33	30.73	60	0	100
Baseline	SM-AHN	26	48.97	29.75	46.67	0	100
Baseline	Total	41	52.68	29.66	46.67	0	100
Cycle 1 Day 8	SM-AHN	2	43.33	4.71	43.33	40	46.67
Cycle 1 Day 8	Total	2	43.33	4.71	43.33	40	46.67
Cycle 1 Day 15	ASM	6	71.11	26.22	76.67	26.67	100
Cycle 1 Day 15	MCL	8	69.17	29.59	76.67	13.33	100
Cycle 1 Day 15	SM-AHN	23	61.16	24.67	53.33	0	100
Cycle 1 Day 15	Total	37	64.5	25.63	73.33	0	100
Cycle 1 Day 22	ASM	1	60		60	60	60
Cycle 1 Day 22	MCL	1	46.67		46.67	46.67	46.67
Cycle 1 Day 22	SM-AHN	1	33.33		33.33	33.33	33.33
Cycle 1 Day 22	Total	3	46.67	13.33	46.67	33.33	60
Cycle 2 Day 1	ASM	5	78.67	18.5	86.67	53.33	100
Cycle 2 Day 1	MCL	9	64.44	26.67	73.33	6.67	93.33
Cycle 2 Day 1	SM-AHN	25	58.67	29.75	66.67	0	100
Cycle 2 Day 1	Total	39	62.56	28.1	66.67	0	100
Cycle 2 Day 15	SM-AHN	1	0		0	0	0
Cycle 2 Day 15	Total	1	0		0	0	0
Cycle 3 Day 1	ASM	5	66.67	33.33	73.33	13.33	100
Cycle 3 Day 1	MCL	6	65.56	18.58	63.33	46.67	100
Cycle 3 Day 1	SM-AHN	22	69.09	21.53	70	26.67	100
Cycle 3 Day 1	Total	33	68.08	22.35	66.67	13.33	100
Cycle 4 Day 1	MCL	1	53.33		53.33	53.33	53.33
Cycle 4 Day 1	SM-AHN	1	60		60	60	60
Cycle 4 Day 1	Total	2	56.67	4.71	56.67	53.33	60
Cycle 5 Day 1	ASM	7	65.71	27.6	53.33	26.67	100
Cycle 5 Day 1	MCL	7	64.76	19.89	66.67	40	93.33
Cycle 5 Day 1	SM-AHN	16	74.17	20.64	80	26.67	100
Cycle 5 Day 1	Total	30	70	21.92	76.67	26.67	100
Cycle 6 Day 1	MCL	1	93.33		93.33	93.33	93.33
Cycle 6 Day 1	SM-AHN	1	73.33		73.33	73.33	73.33
Cycle 6 Day 1	Total	2	83.33	14.14	83.33	73.33	93.33
Cycle 7 Day 1	ASM	5	73.33	28.67	86.67	33.33	100
Cycle 7 Day 1	MCL	4	61.67	6.38	63.33	53.33	66.67
Cycle 7 Day 1	SM-AHN	17	72.94	18.63	73.33	26.67	100
Cycle 7 Day 1	Total	26	71.28	19.39	73.33	26.67	100
Cycle 8 Day 1	ASM	2	43.33	4.71	43.33	40	46.67
Cycle 8 Day 1	SM-AHN	2	60	0	60	60	60
Cycle 8 Day 1	Total	4	51.67	10	53.33	40	60
Cycle 9 Day 1	ASM	3	80	20	80	60	100
Cycle 9 Day 1	MCL	6	57.78	14.4	56.67	40	80
Cycle 9 Day 1	SM-AHN	13	72.82	20.99	80	26.67	100
Cycle 9 Day 1	Total	22	69.7	20.02	73.33	26.67	100
Cycle 10 Day 1	ASM	1	60		60	60	60
Cycle 10 Day 1	SM-AHN	1	86.67		86.67	86.67	86.67
Cycle 10 Day 1	Total	2	73.33	18.86	73.33	60	86.67
Cycle 11 Day 1	ASM	2	33.33	18.86	33.33	20	46.67
Cycle 11 Day 1	MCL	5	64	21.4	53.33	40	86.67
Cycle 11 Day 1	SM-AHN	8	79.17	13.54	76.67	60	100
Cycle 11 Day 1	Total	15	68	22.28	73.33	20	100
Cycle 12 Day 1	ASM	1	80		80	80	80
Cycle 12 Day 1	Total	1	80		80	80	80
Cycle 14 Day 1	ASM	1	60		60	60	60
Cycle 14 Day 1	MCL	2	83.33	4.71	83.33	80	86.67
Cycle 14 Day 1	SM-AHN	10	79.33	18.97	83.33	33.33	100
Cycle 14 Day 1	Total	13	78.46	17.46	80	33.33	100
Cycle 15 Day 1	ASM	1	86.67		86.67	86.67	86.67
Cycle 15 Day 1	SM-AHN	1	60		60	60	60
Cycle 15 Day 1	Total	2	73.33	18.86	73.33	60	86.67
Cycle 17 Day 1	ASM	1	60		60	60	60
Cycle 17 Day 1	MCL	1	80		80	80	80
Cycle 17 Day 1	SM-AHN	8	81.67	18.43	86.67	40	100
Cycle 17 Day 1	Total	10	79.33	17.62	86.67	40	100
Cycle 18 Day 1	ASM	1	66.67		66.67	66.67	66.67
Cycle 18 Day 1	Total	1	66.67		66.67	66.67	66.67

Figure 36 EORTC QLQ C-30 – Physical functioning, avapritinib 200mg RAC-RE population

Role functioning							
Visit	**Subgroup**	**n**	**Mean**	**StdDev**	**Median**	**Min**	**Max**
Baseline	ASM	6	50	33.33	50	0	83.33
Baseline	MCL	9	24.07	26.5	16.67	0	66.67
Baseline	SM-AHN	26	40.38	35.95	41.67	0	100
Baseline	Total	41	38.21	34	33.33	0	100
Cycle 1 Day 8	SM-AHN	2	0	0	0	0	0
Cycle 1 Day 8	Total	2	0	0	0	0	0
Cycle 1 Day 15	ASM	6	58.33	36.13	66.67	0	100
Cycle 1 Day 15	MCL	8	43.75	26.63	50	0	66.67
Cycle 1 Day 15	SM-AHN	23	49.28	33.14	50	0	100
Cycle 1 Day 15	Total	37	49.55	31.79	50	0	100
Cycle 1 Day 22	ASM	1	50		50	50	50
Cycle 1 Day 22	MCL	1	16.67		16.67	16.67	16.67
Cycle 1 Day 22	SM-AHN	1	50		50	50	50
Cycle 1 Day 22	Total	3	38.89	19.25	50	16.67	50
Cycle 2 Day 1	ASM	5	70	24.72	66.67	33.33	100
Cycle 2 Day 1	MCL	9	40.74	26.5	50	0	66.67
Cycle 2 Day 1	SM-AHN	25	53.33	31.18	50	0	100
Cycle 2 Day 1	Total	39	52.56	29.99	50	0	100
Cycle 2 Day 15	SM-AHN	1	0		0	0	0
Cycle 2 Day 15	Total	1	0		0	0	0
Cycle 3 Day 1	ASM	5	56.67	36.51	66.67	0	100
Cycle 3 Day 1	MCL	6	38.89	38.97	33.33	0	100
Cycle 3 Day 1	SM-AHN	22	62.88	26.69	66.67	16.67	100
Cycle 3 Day 1	Total	33	57.58	30.93	66.67	0	100
Cycle 4 Day 1	MCL	1	33.33		33.33	33.33	33.33
Cycle 4 Day 1	SM-AHN	1	66.67		66.67	66.67	66.67
Cycle 4 Day 1	Total	2	50	23.57	50	33.33	66.67
Cycle 5 Day 1	ASM	7	50	44.1	33.33	0	100
Cycle 5 Day 1	MCL	7	30.95	24.4	33.33	0	66.67
Cycle 5 Day 1	SM-AHN	16	59.38	25.8	66.67	0	100
Cycle 5 Day 1	Total	30	50.56	31.71	50	0	100
Cycle 6 Day 1	MCL	1	83.33		83.33	83.33	83.33
Cycle 6 Day 1	SM-AHN	1	100		100	100	100
Cycle 6 Day 1	Total	2	91.67	11.79	91.67	83.33	100
Cycle 7 Day 1	ASM	5	66.67	40.82	66.67	0	100
Cycle 7 Day 1	MCL	4	41.67	16.67	33.33	33.33	66.67
Cycle 7 Day 1	SM-AHN	17	60.78	22	66.67	33.33	100
Cycle 7 Day 1	Total	26	58.97	25.92	66.67	0	100
Cycle 8 Day 1	ASM	2	33.33	47.14	33.33	0	66.67
Cycle 8 Day 1	SM-AHN	2	58.33	11.79	58.33	50	66.67
Cycle 8 Day 1	Total	4	45.83	31.55	58.33	0	66.67
Cycle 9 Day 1	ASM	3	83.33	28.87	100	50	100
Cycle 9 Day 1	MCL	6	33.33	27.89	25	0	66.67
Cycle 9 Day 1	SM-AHN	13	55.13	27.54	66.67	16.67	100
Cycle 9 Day 1	Total	22	53.03	30.7	58.33	0	100
Cycle 10 Day 1	ASM	1	50		50	50	50
Cycle 10 Day 1	SM-AHN	1	66.67		66.67	66.67	66.67
Cycle 10 Day 1	Total	2	58.33	11.79	58.33	50	66.67
Cycle 11 Day 1	ASM	2	33.33	47.14	33.33	0	66.67
Cycle 11 Day 1	MCL	5	40	43.46	33.33	0	100
Cycle 11 Day 1	SM-AHN	8	77.08	15.27	66.67	66.67	100
Cycle 11 Day 1	Total	15	58.89	35	66.67	0	100
Cycle 12 Day 1	ASM	1	83.33		83.33	83.33	83.33
Cycle 12 Day 1	Total	1	83.33		83.33	83.33	83.33
Cycle 14 Day 1	ASM	1	33.33		33.33	33.33	33.33
Cycle 14 Day 1	MCL	2	66.67	0	66.67	66.67	66.67
Cycle 14 Day 1	SM-AHN	10	73.33	17.92	66.67	50	100
Cycle 14 Day 1	Total	13	69.23	19.06	66.67	33.33	100
Cycle 15 Day 1	ASM	1	100		100	100	100
Cycle 15 Day 1	SM-AHN	1	33.33		33.33	33.33	33.33
Cycle 15 Day 1	Total	2	66.67	47.14	66.67	33.33	100
Cycle 17 Day 1	ASM	1	50		50	50	50
Cycle 17 Day 1	MCL	1	50		50	50	50
Cycle 17 Day 1	SM-AHN	8	77.08	26.63	83.33	33.33	100
Cycle 17 Day 1	Total	10	71.67	26.12	66.67	33.33	100
Cycle 18 Day 1	ASM	1	66.67		66.67	66.67	66.67
Cycle 18 Day 1	Total	1	66.67		66.67	66.67	66.67

Figure 37 EORTC QLQ C-30 – Role functioning, avapritinib 200mg RAC-RE population

Emotional functioning							
Visit	**Subgroup**	**n**	**Mean**	**StdDev**	**Median**	**Min**	**Max**
Baseline	ASM	6	56.94	28.59	45.83	33.33	91.67
Baseline	MCL	9	59.26	27.46	58.33	8.33	100
Baseline	SM-AHN	26	59.94	29.06	62.5	0	100
Baseline	Total	41	59.35	27.96	58.33	0	100
Cycle 1 Day 8	SM-AHN	2	62.5	5.89	62.5	58.33	66.67
Cycle 1 Day 8	Total	2	62.5	5.89	62.5	58.33	66.67
Cycle 1 Day 15	ASM	6	62.5	23.42	66.67	33.33	83.33
Cycle 1 Day 15	MCL	8	58.33	25.97	54.17	25	100
Cycle 1 Day 15	SM-AHN	23	74.28	22.32	75	25	100
Cycle 1 Day 15	Total	37	68.92	23.7	66.67	25	100
Cycle 1 Day 22	ASM	1	58.33		58.33	58.33	58.33
Cycle 1 Day 22	MCL	1	41.67		41.67	41.67	41.67
Cycle 1 Day 22	SM-AHN	1	41.67		41.67	41.67	41.67
Cycle 1 Day 22	Total	3	47.22	9.62	41.67	41.67	58.33
Cycle 2 Day 1	ASM	5	71.67	26.74	75	33.33	100
Cycle 2 Day 1	MCL	9	62.96	26.39	66.67	25	100
Cycle 2 Day 1	SM-AHN	25	73.67	23.65	75	25	100
Cycle 2 Day 1	Total	39	70.94	24.4	75	25	100
Cycle 2 Day 15	SM-AHN	1	25		25	25	25
Cycle 2 Day 15	Total	1	25		25	25	25
Cycle 3 Day 1	ASM	5	61.67	22.52	58.33	33.33	91.67
Cycle 3 Day 1	MCL	6	59.72	28.1	66.67	16.67	100
Cycle 3 Day 1	SM-AHN	22	78.79	18.5	83.33	41.67	100
Cycle 3 Day 1	Total	33	72.73	22.07	75	16.67	100
Cycle 4 Day 1	MCL	1	66.67		66.67	66.67	66.67
Cycle 4 Day 1	SM-AHN	1	75		75	75	75
Cycle 4 Day 1	Total	2	70.83	5.89	70.83	66.67	75
Cycle 5 Day 1	ASM	7	57.14	25.2	50	16.67	100
Cycle 5 Day 1	MCL	7	57.14	30.59	58.33	8.33	100
Cycle 5 Day 1	SM-AHN	16	81.25	24.81	91.67	25	100
Cycle 5 Day 1	Total	30	70	28.16	75	8.33	100
Cycle 6 Day 1	MCL	1	8.33		8.33	8.33	8.33
Cycle 6 Day 1	SM-AHN	1	91.67		91.67	91.67	91.67
Cycle 6 Day 1	Total	2	50	58.93	50	8.33	91.67
Cycle 7 Day 1	ASM	5	63.33	22.52	58.33	41.67	100
Cycle 7 Day 1	MCL	4	64.58	34.94	70.83	16.67	100
Cycle 7 Day 1	SM-AHN	17	76.96	20.31	83.33	33.33	100
Cycle 7 Day 1	Total	26	72.44	23.07	75	16.67	100
Cycle 8 Day 1	ASM	2	29.17	41.25	29.17	0	58.33
Cycle 8 Day 1	SM-AHN	2	87.5	5.89	87.5	83.33	91.67
Cycle 8 Day 1	Total	4	58.33	41.39	70.83	0	91.67
Cycle 9 Day 1	ASM	3	69.44	19.25	58.33	58.33	91.67
Cycle 9 Day 1	MCL	6	69.44	29.19	70.83	16.67	100
Cycle 9 Day 1	SM-AHN	13	71.79	29.17	83.33	16.67	100
Cycle 9 Day 1		22	70.83	26.94	75	16.67	100
Cycle 10 Day 1	ASM	1	66.67		66.67	66.67	66.67
Cycle 10 Day 1	SM-AHN	1	91.67		91.67	91.67	91.67
Cycle 10 Day 1	Total	2	79.17	17.68	79.17	66.67	91.67
Cycle 11 Day 1	ASM	2	41.67	0	41.67	41.67	41.67
Cycle 11 Day 1	MCL	5	63.33	26.74	66.67	25	100
Cycle 11 Day 1	SM-AHN	8	84.38	16.33	87.5	50	100
Cycle 11 Day 1	Total	15	71.67	24.15	75	25	100
Cycle 12 Day 1	ASM	1	83.33		83.33	83.33	83.33
Cycle 12 Day 1	Total	1	83.33		83.33	83.33	83.33
Cycle 14 Day 1	ASM	1	50		50	50	50
Cycle 14 Day 1	MCL	2	87.5	17.68	87.5	75	100
Cycle 14 Day 1	SM-AHN	10	90	15.61	95.83	50	100
Cycle 14 Day 1	Total	13	86.54	18.17	91.67	50	100
Cycle 15 Day 1	ASM	1	100		100	100	100
Cycle 15 Day 1	SM-AHN	1	66.67		66.67	66.67	66.67
Cycle 15 Day 1	Total	2	83.33	23.57	83.33	66.67	100
Cycle 17 Day 1	ASM	1	50		50	50	50
Cycle 17 Day 1	MCL	1	58.33		58.33	58.33	58.33
Cycle 17 Day 1	SM-AHN	8	75	17.82	70.83	50	100
Cycle 17 Day 1	Total	10	70.83	18.11	66.67	50	100
Cycle 18 Day 1	ASM	1	100		100	100	100
Cycle 18 Day 1	Total	1	100		100	100	100

Figure 38 EORTC QLQ C-30 – Emotional functioning, avapritinib 200mg RAC-RE population

F.1.1 Mapping

Base case

As briefly mentioned in section 10.1, a TLR was conducted which aimed at identifying a suitable mapping algorithm to transform the QLQ-C30 scores in health utility values identified a total of 6 papers reporting an algorithm suitable to the present analysis. To select a final algorithm among the ones retrieved, several key-aspects of the included populations were compared with the ones of the AdvSM patients. Such key-aspects range from baseline characteristics, like age and geographical area, to other factors, like type of disease and prognosis. A full description of the TLR methodology and results is reported in Appendix I. The algorithm described by Young et al. (58) appeared to be the best candidate to be used for mapping EORTC QLQ-C30 to EQ-5D in patients with AdvSM (58). The estimation population showed a EORTC QLQ-C30 Average Global Health Score very close to that of the PATHFINDER population and a mean age similar to that of AdvSM patients. The average OS of the included population in the algorithm derivation dataset is higher by approx. 2 years than the average OS in AdvSM patients. However, this appeared to be the case when comparing OS vs any of the other identified studies due to the severity of the disease in AdvSM and related very short survival (approx. 24 months). Finally, although the algorithm is not externally validated, the associated Shrinkage coefficient demonstrates its solid external validity. The Young et al. (58) paper aimed at investigating a range of potential models to develop mapping functions from 2 widely used cancer-specific measures (Functional Assessment of Cancer Therapy General (FACT-G) and EORTC-QLQ-C30) and to identify the best model (58). Four data sets were used in this analysis: One contained the FACT-G and EQ-5D, and the remaining three contained the QLQ-C30 and EQ-5D and were combined to produce a reliable mapping function. The FACT-G data set consisted of 530 US respondents with 13 different types of stage III and IV cancers who completed the EQ-5D and FACT-G.23 Fifty-two percent of respondents are male, and the average age of the sample is 59 years. The 3 data sets combined for the QLQ-C30 mapping analysis are a randomized controlled trial of 572 patients with multiple myeloma (VISTA study; ClinicalTrials.gov number NCT00111319),24 and 100 patients with breast cancer and 99 patients with lung cancer having consultations at a Canadian cancer clinic (Vancouver Cancer Clinic data). This gave a total of 771 cases for the mapping study; 44% of responders are male, and the mean age of patients is 68 years. Although the inclusion criteria of this mapping study were broader than the PATHFINDER study, all were oncological patients, so the QoL status reported by patients is not expected to vary significantly between patients. Models were fitted using backward regression, and variables are removed from the model if nonsignificant at p\0.1. When variables are highly correlated (correlation. 0.7), the variable that is most significant and judged most likely to map to the EQ-5D based on prior expectations was selected. Standard errors of regression coefficients were calculated from bootstrap estimates with 5000 bootstrap samples for each model. Model goodness of fit was measured using AIC, BIC, and MAE, in which smaller values indicate better model fit. Model performance was also assessed visually by plotting observed and predicted EQ-5D values. Standard model tests were also examined, including R2 and adjusted R2 for OLS and pseudo R2 for the other models; the Ramsey Regression Equation Specification Error Test (RESET) was used in OLS to test whether nonlinear combinations of variables in the model help explain the variability, where a significant result indicated that a nonlinear model was more appropriate. Sigma was

reported for tobit and truncated regression models and was the equivalent to RMSE in linear regression models. The link test was used to check model specification. The Hosmer–Lemeshow test was used to assess goodness of fit for logistic regression models (first part of 2-part models), which assessed whether predicted probabilities agree with observed probabilities and should be nonsignificant for a model that accurately predicts observed values. Seven models' specifications (models 2 to 8; model 1 was excluded because the QLQ-C30 did not have an overall total score) were fitted for the QLQ-C30. The item-level models gave the best model predictions for OLS and tobit models (model 8, including items and sociodemographic characteristics). These models were best at predicting the overall mean EQ-5D value. Item-level models with sociodemographic characteristics gave the best model performance for 2-part models. The 2-part model resulted in a more accurate prediction of the median than predictions for OLS, tobit, splining, and response mapping. The splining model had the least deviation from the shrinkage coefficient of 1 (model 3). The best-performing response-mapping model included all domains with age and gender for some of the dimensions, and this model had the lowest MAEs on average (MAE=0.134). None of the models predicted the full range of observed EQ-5D values, with no predictions at the best or worst EQ-5D values. The mean ranking indicated that the response mapping was the best-performing model (mean rank = 2.4), with OLS and tobit also performing well (mean = 2.6, mean = 2.8, respectively) and splining giving the poorest overall performance (mean = 3.7). A mapping algorithm to transform QLQ-C30 scores into EQ-5D-3L scores published by Young et al was used (58). Country-specific EQ-5D tariffs were used to estimate the PF utility. UK EQ-5D-3L tariff published by Dolan et al. was used (91). QLQ scores mapped to EQ-5D utilities the utility were stratified by progression status: First, the progression date of each patient was identified. In addition, all the QoL observations prior to that date were used to calculate the average PFS utility value of each patient. Finally, all the average patient values were aggregated in a single score. Three HSUV based were calculated with this mapping algorithm on data from the following populations:

- PATHFINDER - 200 mg - RAC-RE (April 2021 DCO) (base case) (4, 5).
- Pooled PATHFINDER and EXPLORER - All doses - RAC-RE (April 2021 DCO) (scenario analysis). This scenario analysis aligns the HSUVs with the population included in the ITC and therefore aligns relative efficacy evidence with QoL evidence.

Scenario analysis with Danish tariffs

In a scenario analysis, the results of the EORTC QLQ-C30 questionnaire were mapped to EQ-5D-5L with Danish tariffs based on the methodology of Jensen et al. 2021 (79), as required in the DMC guidelines (55). A mapping algorithm to transform QLQ-C30 scores into EuroQol 5-dimension 5-level EQ-5D-5L scores published by Hagiwara et al was used (93). The aim of the study conducted by Hagiwara et al. was to develop direct and indirect (response) mapping algorithms from the EORTC QLQ-C30 and the FACT-G onto the EQ-5D-5L index (93). The authors of the Hagiwara et al. (93) study conducted the QOL-MAC study, a multicenter, cross-sectional study to develop mapping algorithms for EORTC QLQ-C30 and FACT-G onto the EQ-5D-5L index. This study was conducted in 14 hospitals in Japan from November 2018 to March 2019. The target sample size (1200 patients) was not formally based on statistical considerations. This study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by each participating

hospital. The authors enrolled patients with locally advanced, metastatic, or recurrent cancer with the following eligibility criteria: aged 20 or above; with lung, stomach, colorectal, or breast cancer, or any other solid tumour; under drug therapy; and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3. Patients were excluded who received treatment for multiple primary tumours or who are not able to respond to the questionnaires. Both outpatients and inpatients were included to collect a variety of data on health status that patients with cancer could experience. As for the mapping applied in the base case, although the inclusion criteria of this mapping study were broader than the PATHFINDER study, all were oncological patients, so the QoL status reported by patients is not expected to vary significantly between patients. They defined the analysis population for EORTC QLQC30 as eligible patients having both EQ-5D-5L index and all 15 subscale scores and for FACT-G as eligible patients having both EQ-5D-5L index and all 4 subscale scores. They summarized the patient characteristics and responses to EQ-5D-5L, EORTC QLQ-C30, and FACT-G in each analysis population. As a preliminary assessment of the conceptual overlap of the two source measures to EQ-5D-5L, we calculated Spearman's rank correlation coefficient between the subscale scores of the two source measures and the responses to the five items in EQ-5D-5L. The authors described the statistical analyses they conducted in the following way:

"We developed the mapping algorithms for each source measure using 7 regression methods. Based on qualitative and quantitative assessments of the conceptual overlap between the source and target measures, all 5 functioning subscales, global health status, and two symptom subscales (fatigue and pain) were selected as initial candidate variables for direct mapping of EORTC QLQ-C30, and all 4 well-being subscales were selected as initial candidate variables for direct mapping of FACTG. For indirect mapping, we selected subscales that had an absolute rank correlation of≥0.4 (EORTC QLQ-C30) and≥0.3 (FACT-G) for each EQ-5D-5L item as initial candidate variables. Furthermore, we included age and sex into the initial candidate variables in all regression methods. We selected explanatory variables using the backward selection method, which sequentially omitted variables with the largest P value>0.15. This P value criterion approximately corresponds to the backward selection based on the Akaike information criterion. No higher-order terms or interaction terms were considered. The seven regression methods were linear regression, beta regression, tweedie regression, tobit regression, two-part linear regression, two-part beta regression, and ordinal logistic regression. All the regression methods except ordinal logistic regression were directly applied to the EQ-5D-5L index, whereas ordinal logistic regression was applied to each EQ-5D-5L item and used to develop the indirect mapping algorithms. In beta regression, we transformed the EQ-5D-5L index to (observed index−(−0.025))/(1−(−0.025)) (−0.025 is the lowest index in the Japanese value set). In tweedie regression, we transformed the EQ-5D-5L index into disutility from full health (i.e., 1−observed index). In tobit regression, we set the lower and upper bounds of−0.025 and 1, respectively. In two-part regression methods, we predicted full health using logistic regression. In two-part beta regression, we transformed the EQ-5D-5L index to (observed index−(−0.025))/(0.895−(−0.025)) (0.895 is the second largest index in the Japanese value set). In beta and two-part beta regressions, we added 0.005 and subtracted 0.005 at the lower and upper bounds, respectively. We calculated the predicted EQ-5D-5L index as an expected value provided by the fitted models. For ordinal logistic regression, the predicted

EQ-5D-5L index was calculated as 1 minus the sum of disutilities of the 5 levels weighted by the predicted probabilities over the 5 items.

We first evaluated the performance of our mapping algorithms based on root mean squared error (RMSE), mean absolute error (MAE), and Pearson's correlation coefficient between the observed and predicted EQ5D-5L indexes. These measures were calculated for the whole sample and ninefold cross validation. In the cross validation, we randomly divided the whole sample into 9 subsamples (approximately 100 patients in each subsample); repeatedly conducted variable selection in 8 subsamples and calculated the performance measures for the remaining subsample; and averaged them in subsamples to compute overfitting-corrected performance measures. After selecting the mapping algorithms with a good predictive performance in terms of the above three measures, we checked the selected mapping algorithms in terms of face validity. We eliminated any explanatory variables that had regression coefficients with a sign that was the opposite of what was anticipated and P>0.05 and estimated the regression models to obtain the final mapping algorithms. We simulated the EQ-5D-5L index from the selected final mapping algorithms and compared the mean observed and simulated EQ-5D-5L indexes in various subgroups. Furthermore, we plotted the cumulative distribution functions of observed and simulated EQ5D-5L indexes." (93). For EORTC QLQ-C30, two-part beta regression provided the best model in all three measures for the whole sample with RMSE = 0.099 and MAE=0.075, whereas linear regression provided the best model in all three measures for cross-validation. The difference in the predictive performance was marginal between linear regression and two-part beta regression in the whole sample and cross-validation. Ordinal logistic regression had a performance that was comparable to these models for the whole sample and cross-validation. The three mapping algorithms (linear, two-part beta, and ordinal logistic regression) for EORTC QLQ-C30 were well calibrated except for the subgroup with the highest global health status score. The mapping algorithms based on two-part beta regression predicted more EQ-5D-5L index below 0.6 and less EQ5D-5L index between 0.6 to 0.9 than the observed EQ5D-5L data. The mapping algorithms based on ordinal logistic regression provided a smaller proportion of full health than the observed EQ-5D-5L data. These features were applicable to both EORTC QLQ-C30 and FACTG. For EORTC QLQ-C30, the mapping algorithm based on linear regression provided a larger proportion of full health than the true EQ-5D-5L data. Based on the above evaluations, the authors recommended two-part beta regression for direct mapping algorithms and ordinal logistic regression for indirect mapping algorithms for both EORTC QLQ-C30 and FACT-G. HSUV were calculated with this mapping algorithm based on data of two populations:

- PATHFINDER - 200 mg - RAC-RE (April 2021 DCO) (4, 5).
- PATHFINDER - 200 mg - SM-AHN + MCL - RAC-RE (April 2021 DCO) (4, 5).

Figure 39 display the mean change in EQ-5D utility values (DK weighted) (including error bars showing the standard deviations) from baseline up until Cycle 18, D1 for avapritinib.

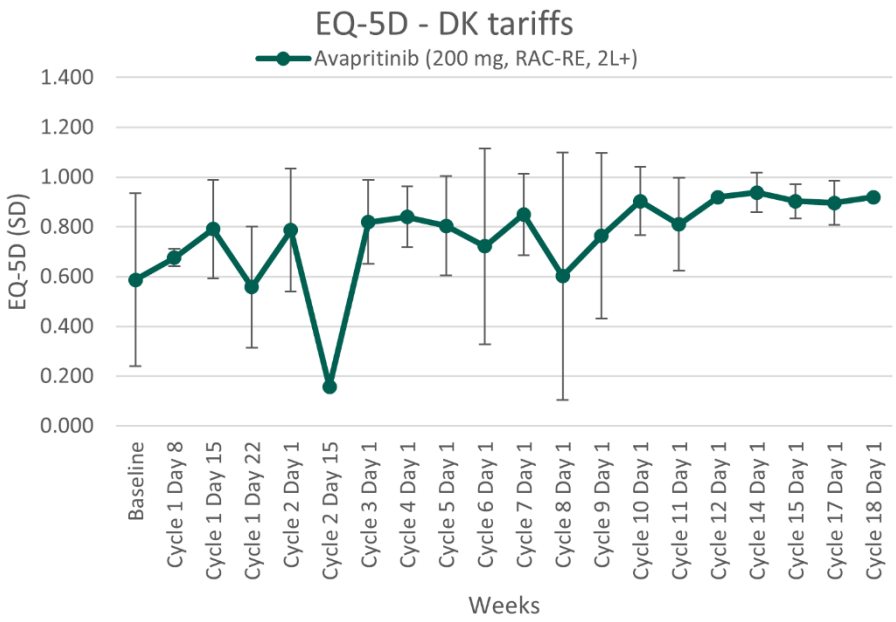

Figure 39 EQ-5D (DK weighted) mean change from baseline for avapritinib (base case 200mg RAC-RE population)

Post-HSCT QoL

The data reported by Grulke et al. (7) were used as input in the mapping algorithm from Young et al. (58) to obtain the corresponding EQ-5D values based on QLQ-C30 scores (previously described in this section).

Data:

Patients in the samples were either awaiting HSCT or had survived up to 24 years post-transplantation. Most patients were examined before the start of HSCT treatment. The age of patients at the time of HSCT ranged from 14 to 70 years, with an average age of about 40–45 years. Diagnoses included acute leukemia, chronic myeloid leukemia, other hematological diseases (mostly lymphoma), and solid tumors (mostly breast cancer). Data from 38 samples (2800 patients) across 33 papers were analysed, presenting mean and standard deviation scores.

Analysis/results:

In 33 papers 38 different samples of patients receiving HSCT who filled in the QLQ-C30. In total, our review covers data from about 2800 patients. Grulke et al. focused on comparing unweighted means and medians for the QLQ-C30 scales at 7 different time points related to HSCT. The researchers performed arithmetic comparisons to assess the differences between unweighted means and medians, as well as between weighted and unweighted means and medians. The analysis favored unweighted arithmetic means, which were used for further evaluations.

Table I Average values (rounded to integers) for means and s.d.s, minimum and maximum (in parentheses) for the QLQ-C30 scales as reported in the reviewed studies by time in relation to HSCT

QLQ-C30 scale		*Before HSCT*	*During hospitalization*	*At discharge*	*Up to 6 months after HSCT*	*7–12 months after HSCT*	*More than 1 up to 3 years after HSCT*	*More than 3 years after HSCT*
GH	Mean (range)	63 (39–76)	38 (32–43)	53 (40–64)	60 (51–73)	67 (59–73)	72 (67–76)	74 (66–82)
	s.d. (range)	20 (12–25)	18 (13–23)	19 (15–22)	21 (16–30)	22 (19–24)	21 (20–22)	21 (14–28)
PF	Mean (range)	80 (66–89)	54 (53–54)	64 (53–75)	72 (61–87)	81 (73–89)	81 (73–91)	86 (78–92)
	s.d. (range)	17 (9–24)	29 (28–29)	21 (17–24)	21 (8–27)	21 (19–22)	20 (15–23)	18 (12–33)
EF	Mean (range)	68 (54–86)	66 (58–74)	65 (54–79)	75 (56–93)	74 (54–84)	74 (64–82)	74 (57–86)
	s.d. (range)	23 (17–31)	27 (24–29)	23 (20–25)	23 (9–31)	22 (19–26)	22 (20–25)	25 (19–32)
CF	Mean (range)	81 (70–89)	68 (63–73)	69 (62–79)	79 (64–89)	82 (73–89)	79 (71–93)	77 (69–87)
	s.d. (range)	21 (13–27)	28 (26–30)	24 (20–27)	24 (14–33)	25 (15–34)	21 (19–23)	26 (17–31)
RF	Mean (range)	62 (38–80)	34 (34–37)	41 (29–52)	54 (32–77)	75 (63–88)	72 (58–81)	78 (60–91)
	s.d. (range)	30 (17–36)	37 (34–40)	36 (28–43)	33 (24–43)	28 (21–33)	30 (29–31)	28 (21–34)
SF	Mean (range)	63 (48–83)	52 (46–57)	52 (42–72)	63 (53–81)	76 (65–87)	73 (64–87)	77 (61–88)
	s.d. (range)	29 (21–36)	32 (31–33)	31 (23–41)	30 (19–36)	24 (20–32)	25 (20–28)	28 (20–35)
FA	Mean (range)	38 (20–54)	70(69–71)	58 (47–71)	49 (30–61)	33 (24–46)	32 (26–41)	30 (21–40)
	s.d. (range)	25 (19–30)	30 (29–31)	24 (20–26)	27 (18–37)	22 (13–29)	25 (23–28)	25 (19–30)
NV	Mean (range)	13 (5–22)	63 (56–69)	31 (15–47)	14 (4–27)	8 (3–15)	7 (3–14)	4 (1–10)
	s.d. (range)	23 (14–33)	32 (27–36)	30 (17–38)	21 (8–31)	18 (9–27)	13 (12–15)	11 (3–19)
PA	Mean (range)	18 (2–36)	47 26–67)	34 (24–46)	21 (4–29)	21 (15–28)	22 (14–28)	16 (11–28)
	s.d. (range)	24 (8–31)	38 (37–38)	29 (20–38)	25 (10–38)	24 (16–27)	26 (26–27)	23 (17–32)
AP	Mean (range)	18 (11–24)	76 (64–87)	53 (39–78)	33 (4–54)	11 (1–17)	10 (6–13)	8 (0–14)
	s.d. (range)	28 (17–35)	34 (28–40)	34 (32–35)	32 (12–41)	16 (7–21)	18 (13–23)	16 (0–27)
CO	Mean (range)	8 (2–22)	19 (18–19)	11 (4–18)	6 (0–24)	7 (2–12)	9 (7–11)	8 (3–16)
	s.d. (range)	16 (8–27)	30 (28–31)	23 (11–32)	15 (0–37)	16 (11–23)	18 (15–20)	19 (9–29)
DI	Mean (range)	15 (8–21)	49 (47–51)	38 (20–57)	16 (9–33)	12 (1–19)	12 (4–16)	10 (4–23)
	s.d. (range)	26 (18–34)	39 (33–44)	33 (27–39)	24 (18–36)	19 (7–29)	20 (11–25)	18 (11–29)
DY	Mean (range)	24 (14–33)	24 (22–26)	29 (24–35)	27 (16–44)	26 (16–35)	19 (6–33)	20 (13–34)
	s.d. (range)	30 (20–38)	35 (33–37)	32 (25–39)	29 (17–43)	32 (27–38)	19 (13–23)	24 (3–36)
SL	Mean (range)	28 (11–42)	50 (49–50)	44 (22–73)	25 (13–33)	23 (14–31)	26 (9–37)	26 (13–40)
	s.d. (range)	31 (22–38)	38 (35–40)	31 (26–36)	29 (17–36)	30 (23–34)	28 (27–30)	30 (23–36)
FI	Mean (range)	28 (15–46)	35 (29–40)	31 (22–40)	36 (21–50)	23 (19–37)	25 (7–31)	23 (11–42)
	s.d. (range)	33 (28–42)	39 (37–40)	33 (31–36)	34 (29–40)	31 (29–32)	28 (18–34)	32 (18–41)
Data were based	Mean n_p	758–1090	49	93–127	134–225	551–753	692–734	674–878
on n_p patients	Mean n_s	13–18	2	4–6	6–11	5–7	5–6	13–16
from n_s samples	s.d. n_p	355–719	49	93–127	134–225	44–661[a]	355	566–735
	s.d. n_s	10–15	2	4–6	6–11	2–5	3	10–13

Abbreviations: AP = appetite loss; CF = cognitive functioning; CO = constipation; DI = diarrhoea; DY = dyspnoea; EF = emotional functioning; FA = fatigue; FI = financial difficulties; GH = global health; HSCT = haematopoietic stem cell transplantation; NV = nausea and vomiting; PA = pain; PF = physical functioning; RF = role functioning; SF = social functioning; SL = insomnia.
[a]Extreme outlier (scale FI); ignoring the outlier the range would be 459–661.

Figure 40 Grulke et al QLQ-C30 scores

Figure 40 shows distinct trends in the central tendency and range of scores for the QLQ-C30 at different measure points throughout the HSCT trajectory. Notably, there is a discernible decrease in functioning and an increase in symptomatology from the pre-HSCT testing time to the during-hospitalization period, with scores during hospitalization and at discharge consistently registering as the lowest for functioning scales and the highest for symptom scales (Results indicate that QoL is lowest during inpatient time, improving about 1 year after HSCT).

Mapping:

A mapping algorithm from Young et al. (58) was used to obtain the corresponding EQ-5D values based on QLQ-C30 scores. These were subsequently transformed in health utility values using the UK Tariff (base case). Figure 40

Appendix G. Probabilistic sensitivity analyses

Table 82 shows the distributional assumptions of model parameters.

Table 82. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Population characteristics				
Initial age	66.32	53.32	79.32	Gamma
Proportion of males	70.2%	7.0%	82.8%	Beta
Body surface area	1.84	0.18	2.20	Gamma
Weight (kg)	71.20	57.24	85.15	Gamma
Proportion with ASM	17.0%	13.7%	20.4%	Dirichlet
Proportion with SM-AHN	61.7%	49.6%	73.8%	Dirichlet
Proportion with MCL	21.3%	17.1%	25.4%	Dirichlet
Clinical				
Avapritinib PFS, exponential - intercept	-3.855	NA	NA	Cholesky
Avapritinib PFS, exponential - scale	0.00	NA	NA	Cholesky
Avapritinib PFS, exponential - shape	0.00	NA	NA	Cholesky
Avapritinib PFS HR vs comparator, BAT	0.47	0.42	0.52	Log-normal
Avapritinib OS, exponential - intercept	-3.9926	NA	NA	Cholesky
Avapritinib OS, exponential - scale	0.00	NA	NA	Cholesky

Avapritinib OS, exponential - shape	0.00	NA	NA	Cholesky
Avapritinib OS HR vs comparator, BAT	0.47	0.21	1.09	Log-normal
Avapritinib ToT, exponential - intercept	-3.5654	NA	NA	Cholesky
Avapritinib ToT, exponential - scale	0.00	NA	NA	Cholesky
Avapritinib ToT, exponential - shape	0.00	NA	NA	Cholesky
Avapritinib ToT HR vs comparator, BAT	0.36	0.22	0.57	Log-normal
Clinical, allo-HSCT				
Response OR vs avapritinib – comparators, midostaurin	2.94	0.13	66.51	Log-normal
Response rates (best response), ASM, AVA	0%	0%	0%	Beta
Response rates (best response), SM-AHN, AVA	4%	3.54%	3.54%	Beta
Response rates (best response), MCL, AVA	0%	0%	0%	Beta
% fit for transplant	0.50	0.40	0.60	Beta
Siblings' donor availability	0.26	0.21	0.31	Beta
Non-related donor availability	0.67	0.54	0.80	Beta
HSCT OS, gamma - intercept	1.0898	NA	NA	Cholesky
HSCT OS, gamma - scale	0.2995	NA	NA	Cholesky

HSCT OS, gamma - shape	-37.3436	NA	NA	Cholesky
Prob of death from 1 year post-transplant	0.0033	0.0026	0.0039	Beta
Adverse events				
Thrombocytopenia (AVA)	0.00694	0.0056	0.0083	Beta
Thrombocytopenia (SOC)	0.0143	0.0115	0.0171	Beta
Anaemia (AVA)	0.00830	0.0067	0.0099	Beta
Anaemia (SOC)	0.0164	0.0132	0.0196	Beta
Other haematological disorders (AVA)	0.00163	0.0013	0.0019	Beta
Other haematological disorders (SOC)	0.0106	0.0085	0.0127	Beta
Sepsis (SOC)	0.0010	0.0008	0.0012	Beta
Fever of unknown origin (SOC)	0.0005	0.0004	0.0007	Beta
HSUV				
Progression free	0.654	0.526	0.783	Normal
Progressed	0.645	0.519	0.772	Normal
Allo-HSCT, first month	0.620	0.498	0.742	Normal
Allo-HSCT, to month 6	0.760	0.611	0.909	Normal
Allo-HSCT, to month 12	0.796	0.640	0.952	Normal
Allo-HSCT, from month 12	0.796	0.640	0.952	Normal
Duration of AE (days)	14.0	11.3	16.7	Gamma

Costs				
Distribution of BAT treatment, Cladribine	53.65	43.1	64.2	Dirichlet
Distribution of BAT treatment, Interferon alpha	2.05	1.6	2.5	Dirichlet
Distribution of BAT treatment, Imatinib	4.51	3.6	5.4	Dirichlet
Distribution of BAT treatment, Peg-interferon alpha	24.23	19.5	29.0	Dirichlet
Distribution of BAT treatment, AML-like treatments	15.56	12.5	18.6	Dirichlet
Distribution of BAT treatment, Midostaurin	0	0	0	Dirichlet
Administration costs, Cladribine administration – one-off	146,520	117,802.3	175,238.2	Gamma
Administration costs, Axacitidine administration – one-off	83,538	67,164.6	99,911.4	Gamma
Administration costs, other AML like administration – one-off	142,690	114,723	170,657.6	Gamma
Administration costs, SC	66.15	53.2	79.1	Gamma
Disease management costs, per-cycle PF, cycles 0-6	23,537	18,923.7	28,150.3	Gamma
Disease management costs, per-cycle PF, cycles 6-12	8,721.4	7,012	10,430.8	Gamma

Disease management costs, per-cycle PF, cycles 12plus	1,886.5	1,516.8	2,256.3	Gamma
Disease management costs, per-cycle PD	87,721.8	70,528.3	104,915.2	Gamma
% receiving post-progression treatment	0.50	0.40	0.60	Beta
Allo-HSCT cost, per-cycle pre-HSCT cost	16,129.2	12,967.9	19,290.5	Gamma
Allo-HSCT cost, initial one-off cost	904,674	727,357.9	1,081,990.1	Gamma
Allo-HSCT cost, per-cycle follow-up cost after STC, up to 12m	1,794.4	1,442.7	2,146.1	Gamma
AE cost - Thrombocytopenia	37,129.0	29,851.7	44,406.3	Gamma
AE cost - Anaemia	27,121.0	21,805.3	32,436.7	Gamma
AE cost - Other haematological disorders	37,129.0	29,851.7	44,406.3	Gamma
AE cost - Gastrointestinal bleed	48,340.0	38,865.4	57,814.6	Gamma
AE cost - Acute myeloid leukaemia	41,154.0	33,087.8	49,220.2	Gamma
AE cost - Sepsis	50,299.0	40,440.4	60,157.6	Gamma
AE cost - Heart failure or shock	19,623.0	15,776.9	23,469.1	Gamma
AE cost - Cardiac arrest	19,623.0	15,776.9	23,469.1	Gamma
AE cost - Cerebrovascular accident, nervous	72,892.0	58,605.2	87,178.8	Gamma

system infections, or encephalopathy				
AE cost - Hemorrhagic cerebrovascular disorders	44,492.0	35,771.6	53,212.4	Gamma
AE cost - Non-malignant gastrointestinal tract disorders	7,818.0	6,285.7	9,350.3	Gamma
AE cost - Non-malignant hepatobiliary or pancreatic disorder	36,225.0	29,124.9	43,325.1	Gamma
AE cost - Pneumonia	35,426.0	28,482.5	42,369.5	Gamma
AE cost - Pleural effusion	39,036.0	31,384.9	46,687.1	Gamma
AE cost - Low back pain	23,522.0	18,911.7	28,132.3	Gamma
AE cost - Hypertension	2,167.0	1,742.3	2,591.7	Gamma
AE cost - Syncope or collapse	1,183.0	951.1	1,414.9	Gamma
AE cost - Unspecified edema	5,103.0	4,102.8	6,103.2	Gamma
AE cost - Tendency to fall, senility, or other condition affecting cognitive functions	28,723.0	23,093.3	34,352.7	Gamma
AE cost - Fever of unknown origin	21,529.0	17,309.3	25,748.7	Gamma
AE cost - Breast disorders	4,007.0	3,221.6	4,792.4	Gamma
AE cost - Muscular, balance, cranial, or peripheral nerve disorders, epilepsy, or head Injury	23,734.0	19,082.1	28,385.9	Gamma

AE cost - Sleep disorders	15,159.0	12,187.8	18,130.2	Gamma
AE cost - Other respiratory disorders	31,294.0	25,160.4	37,427.6	Gamma
AE cost - Headache, migraine, or cerebrospinal fluid leak	5,103.0	4,102.8	6,103.2	Gamma
AE cost - Peripheral vascular disorders	2,167.0	1,742.3	2,591.7	Gamma
AE cost - Kidney or urinary tract infections	30,859.0	24,810.6	36,907.4	Gamma
AE cost - Skin disorders	20,231.0	16,265.7	24,196.3	Gamma
AE cost - Non-malignant ear, nose, mouth, throat, or neck disorders	1,331.0	1,070.1	1,591.9	Gamma
Patient time/transportation costs, PF	1,400.7	1,126.2	1,675.2	Gamma
Patient time/transportation costs, PD	967.7	778.0	1,157.3	Gamma

Appendix H. Literature searches for the clinical assessment

Literature searches for the clinical assessment

A global SLR was conducted which aimed to address the following research question:

- To evaluate and summarise evidence pertaining to the efficacy, safety and tolerability of treatment options used in patients AdvSM.

In order to adapt the global SLR into the context of this submission dossier for the DMC, it will be necessary to narrow down the inclusion and exclusion criteria of the original PICO-T described in Table 90, specifically the interventions of interest, as the interventions searched in the global SLR is much wider in scope compared to treatments offered in Denmark. As mentioned in section 3.3, BAT (which consists of a mix of off-label cytoreductive therapies such as cladribine; TKIs [imatinib, nilotinib, and dasatinib], interferons [interferon-alpha-2a and peg-interferon-alpha], & AML like treatments [azacytidine and cytarabine based treatments] as well as symptomatic treatments) are considered the most appropriate comparator in Denmark for the AdvSM patient population. All other criterions are to remain unchanged as they still remain relevant for this application.

The inclusion and exclusion criteria in Table 90 has been adapted to show a separate Danish specific inclusion and exclusion criteria for this submission, from which, the study selection for this assessment will be based on. The global inclusion and exclusion criteria can still be seen in Table 90 for full transparency on how the search strings were developed and how the adaption was done.

As detailed in Table 83, Table 84 and Table 85 the clinical SLR search was conducted on 22 June 2023.

The searches were performed in the following indexed databases via OVID:

- Embase® (via Ovid.com)
- MEDLINE® and Epub Ahead of Print, In-Process, In-Data-review & Other Non-Indexed Citations, Daily and Versions (via Ovid.com)
- Cochrane Central Register of Controlled Trials (CCTR) (via Ovid.com)
- Cochrane Database of Systematic Reviews (CDSR) (via Ovid.com)
- Database of Abstracts of Review of Effects (DARE) (via Ovid.com)
- Health Technology Assessment (HTA) Database (via Ovid.com)

Electronic searching in the literature databases was not limited according to timeframe because clinical outcomes is generally advised not to limit electronic searching by time frame. The searches were not limited to English language.

Bibliographies of systematic reviews were screened to ensure that initial searches captured all the relevant utility studies.

In addition to the databases, proceedings of 4 conferences were searched for the last 2 years (2021–2023) to identify any studies of interest. These included:

- American Society of Clinical Oncology (ASCO) Annual meeting
- European Society for Medical Oncology (ESMO) Congress
- American Society of Haematology (ASH) Annual meeting
- European Haematology Association (EHA) Congress

The data identified through electronic and manual searches were supplemented by the data available on HTA websites. The following international HTA websites were searched to identify any relevant HTAs:

- National Institute for Health and Care Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- All Wales Medicines Strategy Group (AWMSG)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Gemeinsamer Bundesausschuss (GBA)
- Haute Autorite de Sante (HAS)
- Zorginstituutnederland (ZIN)
- National Centre for Pharmacoeconomics (NCPE)
- Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS)

Table 83 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Medline and Medline In-Process	Ovid	1946 – 20 June 2023	22 June 2023
Embase	Ovid	1974 – 20 June 2023	22 June 2023
CCTR	Ovid	1 January 1995 – May 2023	22 June 2023
CDSR	Ovid	1 January 2005 – 20 June 2023	22 June 2023
DARE	Ovid	Inception - 1st Quarter 2016	22 June 2023
HTA	Ovid	Inception - 4th Quarter 2016	22 June 2023

Abbreviations: CCTR = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; HTA = Health Technology Assessment

Table 84 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	"mastocytosis	22 June 2023

Source name	Location/source	Search strategy	Date of search
		mast cell"	
SMC	https://www.scottishmedicines.org.uk/home	"mastocytosis mast cell"	22 June 2023
AWMSG	https://awttc.nhs.wales/	"mastocytosis mast cell"	22 June 2023
CADTH	https://www.cadth.ca/search	"mastocytosis mast cell"	22 June 2023
GBA	https://www.g-ba.de/english/	"mastocytosis mast cell"	22 June 2023
HAS	https://www.has-sante.fr/jcms/p_3291681/en/hta-the-has-a-lead-player-in-the-european-cooperation-for-health-technology-assessment	"mastocytosis mast cell"	22 June 2023
ZIN	https://english.zorginstituutnederland.nl/	"mastocytosis mast cell"	22 June 2023
NCPE	https://www.ncpe.ie/submission-process/hta-guidelines/	"mastocytosis mast cell"	22 June 2023
AEMPS	https://www.aemps.gob.es/informa-en/the-spanish-agency-of-medicines-and-medical-devices-aemps-recommends-using-voluntary-harmonisation-procedure-before-the-official-submission-of-a-multi-state-ct-application/?lang=en	"mastocytosis mast cell"	22 June 2023

Abbreviations: NICE = National Institute for Health and Care Excellence; CADTH = Canadian Agency for Drugs and Technologies in Health; SMC = Scottish Medicines Consortium; AWMSG = All Wales Medicines Strategy Group; GBA = Gemeinsamer Bundesausschuss; HAS = Haute Autorite de Sante; ZIN = Zorginstituutnederland; NCPE = National Centre for Pharmacoeconomics; AEMPS = Agencia Espanola de Medicamentos y Productos Sanitarios

Table 85 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO General meeting	https://meetings.asco.org/abstracts-presentations/search?query=*&q=*&sortBy=AbstractBrowse&filters=%7B%22presentationType%22:%5B%7B%22key%22:%22Abstract%20Presentation%22%7D,%7B%22key%22:%22Poster%22%7D,%7B%22key%22:%22Abstract%22%7D%5D,%22meetingTypeName%22:%5B%7B%22key%22:%22ASCO%20Annual%20Meeting%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222021%22%7D%5D%7D&size=50	Electronic search	"mastocytosis mast cell"	22 June 2023
ESMO	https://oncologypro.esmo.org/meeting-resources/esmo-congress	Electronic search	"mastocytosis mast cell"	22 June 2023
EHA	https://library.ehaweb.org/eha/#!*menu=6*browseby=3*sortby=2*ce_id=2035	Electronic search	"mastocytosis mast cell"	22 June 2023
ASH	https://ashpublications.org/blood	Electronic search	"mastocytosis mast cell"	22 June 2023

Abbreviations: ASH = American Society of Haematology; ASCO = American Society of Clinical Oncology; EHA = European Haematology Association; ESMO = European Society of Medical Oncology.

H.1 Search strategies

The search strategies were based on the PICOS-T developed for this clinical SLR (Table 90). Relevant MeSH and Emtree terms were used in the relevant databases as well as free text terms.

Table 86 to Table 89 present the search hits in Medline, Embase, Cochrane databases and EBM.

Table 86 Search strategy for Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations

No.	Query	Results
#1	exp Mastocytosis/ or exp Mastocytosis, Systemic/	6,920
#2	exp Leukemia, Mast-Cell/	237
#3	("acute basophilic leukaemia" or "acute basophilic leukemia" or "basophilic leucemia" or "basophilic leukaemia" or "basophilic leukemia").tw.	1,745
#4	(mastocytosis or "systemic mastocytosis" or "mast cell leukemia" or "mast cell leukaemia").tw.	4,328

#5	1 or 2 or 3 or 4	9,807
#6	(avapritinib or "blu 285" or "blu-285" or blu285 or "70c366" or ayvakit or ayvakyt* or "blu 112317" or "blu112317" or "c 366" or "c366" or "cs 3007" or "cs3007" or "x 720776" or "x720776").tw.	182
#7	(midostaurin or rydapt or midostaurine or "pkc 412" or pkc412 or "cgp 41251" or cgp41251).tw.	766
#8	exp Imatinib Mesylate/	11,498
#9	(imatinib or gleevac or gleevec or glivec or glivic or ruvise or "cgp 57148" or "cgp-57148*" or cgp57148* or "signal transduction inhibitor 571" or "st 1571" or st1571 or "sti 571" or "sti-571" or sti571 or "st-1571" or "220127-57-1" or "8a1o1m485b" or "bkj8m8g5hi" or "aer 901" or "aer901" or "av 101" or "av101" or egitinib or glipox or imagerolan or imakrebin or imanivec or imaniver or imarem or imatek or imatenil or imatilek or impentri or itivas or latib or leutipol or leuzek or meaxin or nibix or plivatinib or "qti 571" or "qti571" or vianib or "vr 325" or "vr325" or "yd 312" or "yd312").tw.	16,183
#10	exp Interferon-alpha/	29,956
#11	("alpha interferon" or "interferon alpha" or "interferon-alpha" or "interferon alfa" or alfaferone or alferon or "alpha ferone" or cilferon or ginterferon or "interferon, leucocyte" or "interferon, leukocyte" or introma or kemron or "leucocyte interferon" or leukinferon or leukinferron or "leukocyte interferon" or refecon a or sumiferon or sumipheron or veldona).tw.	29,815
#12	(peginterferon or "pegylated interferon" or "pegylated interferon alpha" or "peginterferon alpha" or "alfa peginterferon" or "alpha peginterferon" or "peginterferon alfa").tw.	8,570
#13	exp Cladribine/	1,743
#14	(cladribine or biodribin or intocel or leustat or leustatin or leustatine or litak or litax or mavenclad or movectro or mylinax or "rwj 26251" or rwj26251).tw.	1,715
#15	(nilotinib or tasigna or "amn-107" or "amn 107" or amn107).tw.	2,493
#16	exp Dasatinib/	2,594
#17	(dasatinib or sprycel or uxil or "bms 354825*" or "bms-354825*" or "bms 354825 03" or "bms 354825-03" or "bms 35482503" or bms354825 or "bms354825 03" or "bms354825-03" or bms35482503).tw.	4,072
#18	exp Everolimus/	5,643
#19	(everolimus or affinitor or afinitor or certican or votubia or zortress or "nvp rad 001" or "nvp rad001" or "rad 001*" or "rad-001*" or "rad 001a" or rad001 or rad001a or "sdz rad" or rad666).tw.	7,967
#20	(masitinib or alsitek or kinaction or masatinib or masican or masipro or masivet or masiviera or "ab 1010" or "ab-1010" or ab1010).tw.	180
#21	(ripretinib or ginlock or dcc2618 or "dcc 2618").tw.	104
#22	(elenestinib or "blu 263" or blu263).tw.	2
#23	exp Azacitidine/	8,029
#24	(azacitidine or "5 azacyd" or "5 azacytidin" or "5 azacytidine" or azacitidin or azacytidine or gerodaza or ladakamycin or laziros or mylosar or onureg or vidaculem or vidaza or zassida or "cc 486" or cc486 or "nex 18" or "nex 18a" or nex18 or nex18a or "ns 17" or ns17 or "nsc 102816" or nsc102816	5,669

	or "ts 020" or ts020 or "u 18496" or u18496 or "wr 183027" or wr183027).tw.	
#25	exp Brentuximab Vedotin/	828
#26	(brentuximab or adcetris or "cac10-vcmmae" or "sgn 35" or sgn35).tw.	1,321
#27	(ibrutinib or imbruvica or "cra 032765" or cra032765 or "jnj 54179060" or jnj54179060 or "pci 32765" or "pci 32765 00" or "pci 32765-00" or pci32765 or "pci32765 00" or "pci32765-00").tw.	3,239
#28	(tagraxofusp or "tagraxofusp erzs" or "tagraxofusp-erzs" or elzonris or "dt 388 il 3" or "dt il 3" or dt388il3 or dtil3 or "sl 401" or sl401).tw.	94
#29	(bezuclastinib or "cgt 9486" or cgt9486 or "plx 9486" or plx9486).tw.	4
#30	exp Thalidomide/	9,771
#31	(thalidomide or contergan or distaval or isomin or kedavon or kevadon or neurosedin or neurosedyne or sedalis or "shin naito" or softenon or synovir or talimol or talizer or telagan or telargan or thado or thaled or thalidomid or thalimodide or thalix or thalomid or "cc 2001" or cc2001 or "fpf 300" or fpf300 or "k 17" or "nsc 66847" or "vp 02" or vp02).tw.	8,828
#32	exp Cytarabine/	15,510
#33	(cytarabine or alcysten or alexan or "ara C" or "ara-cell" or arabinocytosil or arabinofuranosyl or arabinoside or arabinosine or arabinosyl or arabitin or aracytidine or aracytin or aracytine or citabion or citaloxan or citarabina or cytarabine or cyclocide or cylocide or "cystosine arabinoside" or cytarabide or cytarabine or cytarabinoside or cytarbine or cytarine or "cytidine arabinoside" or cytoarabine or "cytosa u" or cytosar or "cytosar 4" or "cytosar u" or "cytosin arabinoside" or "cytosine arabinose" or "cytosine arabinofuranoside" or "cytosine arabinonucleoside" or "cytosine arabinose" or "cytosine arabinoside" or "cytosine arabinosine" or "cytosine beta arabinofuranoside" or "cytosine beta arabinoside" or "cytosine beta d arabinofuranoside" or cytovis or depocyt or depocyte or "dtc 101" or dtc101 or iretin or laracit or novumtrax or "nsc 63878" or nsc63878 or tarabine or "tarabine pfs" or "u 19920 a" or "u 19920a" or u19920a or udicil or "udicil cs").tw.	17,493
#34	exp Daunorubicin/	72,621
#35	(daunorubicin or cerubidin or cerubidine or dannomycin or daunamycin or daunarubicin or "dauno rubidomycin" or daunobin or daunoblastin or daunoblastina or daunoblastine or daunoextra or daunomycin or daunomycine or daunorrubicina or daunorubicine or daunorubidomycin or daunorubimycin or daunoxome or daurorubicin or daunomycin or daunorubicin or "fi 6339" or fi6339 or maxidauno or "ndc 0082 4155" or "ndc 00824155" or "ndc0082 4155" or ndc00824155 or "nsc 82 151" or "nsc 82151" or nsc82151 or "rp 13057" or rp13057 or rubidiomycin or rubidomycin or rubidomycine or rubilem or "rubomycin c" or "rubomycine c" or trixilem or "trixilem ru").tw.	7,738
#36	(fludarabine or "2 fluoro 9 beta d arabinofuranosyladenine" or "2 fluoroadenine 9 arabinoside" or "2 fluoroadenine 9beta d arabinofuranoside" or "2 fluoroadenine arabinofuranoside" or "2 fluoroadenine arabinoside" or "2 fluoroara a" or "2 fluorovidarabine" or "9 arabinofuranosyl 2 fluoroadenine" or "9 beta arabinofuranosyl 2 fluoroadenine" or "9 beta d arabinofuranosyl 2 fluoroadenine" or "9 beta dextro arabinofuranosyl 2 fluoroadenine" or "9beta arabinofuranosyl 2 fluoroadenine" or "9beta d arabinofuranosyl 2 fluoroadenine" or "9beta dextro arabinofuranosyl 2 fluoroadenine" or "adenine,9beta dextro	6,022

	arabinofuranosyl 2 fluoro" or "arabinofuranosyl 2 fluoroadenine" or "arabinosyl 2 fluoroadenine" or "f ara A" or "vidarabine,2 fluoro").tw.	
#37	("AML-like" or "AML like" or HiDAC or "FLAG IDA" or "FLAG-IDA").mp.	304
#38	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	201,252
#39	5 and 38	612
#40	("Case Reports" or Comment or Editorial or Letter).pt.	4,281,356
#41	exp Animals/ not (exp Animals/ and exp Humans/)	5,133,522
#42	40 or 41	9,304,231
#43	**39 not 42**	**339**

Table 87 Search strategy for Embase

No.	Query	Results
#1	exp systemic mastocytosis/ or exp mastocytosis/	8,209
#2	exp mast cell leukemia/	1,770
#3	("acute basophilic leukaemia" or "acute basophilic leukemia" or "basophilic leucemia" or "basophilic leukaemia" or "basophilic leukemia").tw.	1,884
#4	(mastocytosis or "systemic mastocytosis" or "mast cell leukemia" or "mast cell leukaemia").tw.	6,607
#5	1 or 2 or 3 or 4	11,078
#6	exp avapritinib/	461
#7	(avapritinib or "blu 285" or "blu-285" or blu285 or "70c366" or ayvakit or ayvakyt* or "blu 112317" or "blu112317" or "c 366" or "c366" or "cs 3007" or "cs3007" or "x 720776" or "x720776").tw.	396
#8	exp midostaurin/	3,518
#9	(midostaurin or rydapt or midostaurine or "pkc 412" or pkc412 or "cgp 41251" or cgp41251).tw.	2,504
#10	exp imatinib/	48,735
#11	(imatinib or gleevac or gleevec or glivec or glivic or ruvise or "cgp 57148" or "cgp-57148*" or cgp57148* or "signal transduction inhibitor 571" or "st 1571" or st1571 or "sti 571" or "sti-571" or sti571 or "st-1571" or "220127-57-1" or "8a1o1m485b" or "bkj8m8g5hi" or "aer 901" or "aer901" or "av 101" or "av101" or egitinib or glipox or imagerolan or imakrebin or imanivec or imaniver or imarem or imatek or imatenil or imatilek or impentri or itivas or latib or leutipol or leuzek or meaxin or nibix or plivatinib or "qti 571" or "qti571" or vianib or "vr 325" or "vr325" or "yd 312" or "yd312").tw.	33,870
#12	exp alpha interferon/	91,474
#13	("alpha interferon" or "interferon alpha" or "interferon-alpha" or "interferon alfa" or alfaferone or alferon or "alpha ferone" or cilferon or ginterferon or "interferon, leucocyte" or "interferon, leukocyte" or introma or kemron or "leucocyte interferon" or leukinferon or leukinferron or "leukocyte interferon" or refecon a or sumiferon or sumipheron or veldona).tw.	38,115
#14	exp peginterferon/	27,599

#15	(peginterferon or "pegylated interferon" or "pegylated interferon alpha" or "peginterferon alpha" or "alfa peginterferon" or "alpha peginterferon" or "peginterferon alfa").tw.	15,963
#16	exp cladribine/	8,985
#17	(cladribine or biodribin or intocel or leustat or leustatin or leustatine or litak or litax or mavenclad or movectro or mylinax or "rwj 26251" or rwj26251).tw.	3,783
#18	exp nilotinib/	11,204
#19	(nilotinib or tasigna or "amn-107" or "amn 107" or amn107).tw.	6,993
#20	exp dasatinib/	17,643
#21	(dasatinib or sprycel or uxil or "bms 354825*" or "bms-354825*" or "bms 354825 03" or "bms 354825-03" or "bms 35482503" or bms354825 or "bms354825 03" or "bms354825-03" or bms35482503).tw.	10,267
#22	exp everolimus/	36,043
#23	(everolimus or affinitor or afinitor or certican or votubia or zortress or "nvp rad 001" or "nvp rad001" or "rad 001*" or "rad-001*" or "rad 001a" or rad001 or rad001a or "sdz rad" or rad666).tw.	20,639
#24	exp masitinib/	758
#25	(masitinib or alsitek or kinaction or masatinib or masican or masipro or masivet or masiviera or "ab 1010" or "ab-1010" or ab1010).tw.	366
#26	exp ripretinib/	289
#27	(ripretinib or ginlock or dcc2618 or "dcc 2618").tw.	212
#28	(elenestinib or "blu 263" or blu263).tw.	7
#29	exp azacitidine/	18,547
#30	(azacitidine or "5 azacyd" or "5 azacytidin" or "5 azacytidine" or azacitidin or azacytidine or gerodaza or ladakamycin or laziros or mylosar or onureg or vidaculem or vidaza or zassida or "cc 486" or cc486 or "nex 18" or "nex 18a" or nex18 or nex18a or "ns 17" or ns17 or "nsc 102816" or nsc102816 or "ts 020" or ts020 or "u 18496" or u18496 or "wr 183027" or wr183027).tw.	12,090
#31	exp brentuximab vedotin/	5,471
#32	(brentuximab or adcetris or "cac10-vcmmae" or "sgn 35" or sgn35).tw.	3,949
#33	exp ibrutinib/	11,701
#34	(ibrutinib or imbruvica or "cra 032765" or cra032765 or "jnj 54179060" or jnj54179060 or "pci 32765" or "pci 32765 00" or "pci 32765-00" or pci32765 or "pci32765 00" or "pci32765-00").tw.	8,604
#35	exp tagraxofusp/	298
#36	(tagraxofusp or "tagraxofusp erzs" or "tagraxofusp-erzs" or elzonris or "dt 388 il 3" or "dt il 3" or dt388il3 or dtil3 or "sl 401" or sl401).tw.	317
#37	exp bezuclastinib/	12
#38	(bezuclastinib or "cgt 9486" or cgt9486 or "plx 9486" or plx9486).tw.	23
#39	exp thalidomide/	31,167
#40	(thalidomide or contergan or distaval or isomin or kedavon or kevadon or neurosedin or neurosedyne or sedalis or "shin naito" or softenon or synovir or talimol or talizer or telagan or telargan or thado or thaled or	14,974

	thalidomid or thalimodide or thalix or thalomid or "cc 2001" or cc2001 or "fpf 300" or fpf300 or "k 17" or "nsc 66847" or "vp 02" or vp02).tw.	
#41	exp cytarabine/	69,126
#42	(cytarabine or alcysten or alexan or "ara C" or "ara-cell" or arabinocytosil or arabinofuranosyl or arabinoside or arabinosine or arabinosyl or arabitin or aracytidine or aracytin or aracytine or citabion or citaloxan or citarabina or cytarabine or cyclocide or cylocide or "cystosine arabinoside" or cytarabide or cytarabine or cytarabinoside or cytarbine or cytarine or "cytidine arabinoside" or cytoarabine or "cytosa u" or cytosar or "cytosar 4" or "cytosar u" or "cytosin arabinoside" or "cytosine arabinose" or "cytosine arabinofuranoside" or "cytosine arabinonucleoside" or "cytosine arabinose" or "cytosine arabinoside" or "cytosine arabinosine" or "cytosine beta arabinofuranoside" or "cytosine beta arabinoside" or "cytosine beta d arabinofuranoside" or cytovis or depocyt or depocyte or "dtc 101" or dtc101 or iretin or laracit or novumtrax or "nsc 63878" or nsc63878 or tarabine or "tarabine pfs" or "u 19920 a" or "u 19920a" or u19920a or udicil or "udicil cs").tw.	30,153
#43	exp daunorubicin/	30,940
#44	(daunorubicin or cerubidin or cerubidine or dannomycin or daunamycin or daunarubicin or "dauno rubidomycin" or daunobin or daunoblastin or daunoblastina or daunoblastine or daunoextra or daunomycin or daunomycine or daunorrubicina or daunorubicine or daunorubidomycin or daunorubimycin or daunoxome or daurorubicin or daunomycin or daunorubicin or "fi 6339" or fi6339 or maxidauno or "ndc 0082 4155" or "ndc 00824155" or "ndc0082 4155" or ndc00824155 or "nsc 82 151" or "nsc 82151" or nsc82151 or "rp 13057" or rp13057 or rubidiomycin or rubidomycin or rubidomycine or rubilem or "rubomycin c" or "rubomycine c" or trixilem or "trixilem ru").tw.	11,495
#45	exp fludarabine/	34,094
#46	(fludarabine or "2 fluoro 9 beta d arabinofuranosyladenine" or "2 fluoroadenine 9 arabinoside" or "2 fluoroadenine 9beta d arabinofuranoside" or "2 fluoroadenine arabinofuranoside" or "2 fluoroadenine arabinoside" or "2 fluoroara a" or "2 fluorovidarabine" or "9 arabinofuranosyl 2 fluoroadenine" or "9 beta arabinofuranosyl 2 fluoroadenine" or "9 beta d arabinofuranosyl 2 fluoroadenine" or "9 beta dextro arabinofuranosyl 2 fluoroadenine" or "9beta arabinofuranosyl 2 fluoroadenine" or "9beta d arabinofuranosyl 2 fluoroadenine" or "9beta dextro arabinofuranosyl 2 fluoroadenine" or "adenine,9beta dextro arabinofuranosyl 2 fluoro" or "arabinofuranosyl 2 fluoroadenine" or "arabinosyl 2 fluoroadenine" or "f ara A" or "vidarabine,2 fluoro").tw.	16,234
#47	("AML-like" or "AML like" or HiDAC or "FLAG IDA" or "FLAG-IDA").mp.	1,186
#48	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47	373,831
#49	5 and 48	1,719
#50	(Editorial or Letter or Note).pt.	3,035,011
#51	"case report*".ti.	404,176
#52	exp animal/ not (exp animal/ and exp human/)	5,193,222
#53	50 or 51 or 52	8,546,946
#54	**49 not 53**	**1,473**

Table 88 Search strategy for CCTR and CDSR

No.	Query	Results
#1	exp mastocytosis/ or exp mastocytosis, systemic/	50
#2	exp leukemia, mast-cell/	1
#3	("acute basophilic leukaemia" or "acute basophilic leukemia" or "basophilic leucemia" or "basophilic leukaemia" or "basophilic leukemia").tw.	3
#4	(mastocytosis or "systemic mastocytosis" or "mast cell leukemia" or "mast cell leukaemia").tw.	105
#5	1 or 2 or 3 or 4	120
#6	(avapritinib or "blu 285" or "blu-285" or blu285 or "70c366" or ayvakit or ayvakyt* or "blu 112317" or "blu112317" or "c 366" or "c366" or "cs 3007" or "cs3007" or "x 720776" or "x720776").tw.	39
#7	(midostaurin or rydapt or midostaurine or "pkc 412" or pkc412 or "cgp 41251" or cgp41251).tw.	126
#8	exp Imatinib Mesylate/	521
#9	(imatinib or gleevac or gleevec or glivec or glivic or ruvise or "cgp 57148" or "cgp-57148*" or cgp57148* or "signal transduction inhibitor 571" or "st 1571" or st1571 or "sti 571" or "sti-571" or sti571 or "st-1571" or "220127-57-1" or "8a1o1m485b" or "bkj8m8g5hi" or "aer 901" or "aer901" or "av 101" or "av101" or egitinib or glipox or imagerolan or imakrebin or imanivec or imaniver or imarem or imatek or imatenil or imatilek or impentri or itivas or latib or leutipol or leuzek or meaxin or nibix or plivatinib or "qti 571" or "qti571" or vianib or "vr 325" or "vr325" or "yd 312" or "yd312").tw.	1,625
#10	exp Interferon-alpha/	3,539
#11	("alpha interferon" or "interferon alpha" or "interferon-alpha" or "interferon alfa" or alfaferone or alferon or "alpha ferone" or cilferon or ginterferon or "interferon, leucocyte" or "interferon, leukocyte" or introma or kemron or "leucocyte interferon" or leukinferon or leukinferron or "leukocyte interferon" or refecon a or sumiferon or sumipheron or veldona).tw.	4,930
#12	(peginterferon or "pegylated interferon" or "pegylated interferon alpha" or "peginterferon alpha" or "alfa peginterferon" or "alpha peginterferon" or "peginterferon alfa").tw.	3,465
#13	exp Cladribine/	124
#14	(cladribine or biodribin or intocel or leustat or leustatin or leustatine or litak or litax or mavenclad or movectro or mylinax or "rwj 26251" or rwj26251).tw.	435
#15	(nilotinib or tasigna or "amn-107" or "amn 107" or amn107).tw.	460
#16	exp Dasatinib/	144
#17	(dasatinib or sprycel or uxil or "bms 354825*" or "bms-354825*" or "bms 354825 03" or "bms 354825-03" or "bms 35482503" or bms354825 or "bms354825 03" or "bms354825-03" or bms35482503).tw.	502
#18	exp Everolimus/	1,761
#19	(everolimus or affinitor or afinitor or certican or votubia or zortress or "nvp rad 001" or "nvp rad001" or "rad 001*" or "rad-001*" or "rad 001a" or rad001 or rad001a or "sdz rad" or rad666).tw.	3,940

#20	(masitinib or alsitek or kinaction or masatinib or masican or masipro or masivet or masiviera or "ab 1010" or "ab-1010" or ab1010).tw.	115
#21	(ripretinib or ginlock or dcc2618 or "dcc 2618").tw.	41
#22	(elenestinib or "blu 263" or blu263).tw.	6
#23	exp Azacitidine/	459
#24	(azacitidine or "5 azacyd" or "5 azacytidin" or "5 azacytidine" or azacitidin or azacytidine or gerodaza or ladakamycin or laziros or mylosar or onureg or vidaculem or vidaza or zassida or "cc 486" or cc486 or "nex 18" or "nex 18a" or nex18 or nex18a or "ns 17" or ns17 or "nsc 102816" or nsc102816 or "ts 020" or ts020 or "u 18496" or u18496 or "wr 183027" or wr183027).tw.	1,008
#25	exp Brentuximab Vedotin/	40
#26	(brentuximab or adcetris or "cac10-vcmmae" or "sgn 35" or sgn35).tw.	371
#27	(ibrutinib or imbruvica or "cra 032765" or cra032765 or "jnj 54179060" or jnj54179060 or "pci 32765" or "pci 32765 00" or "pci 32765-00" or pci32765 or "pci32765 00" or "pci32765-00").tw.	758
#28	(tagraxofusp or "tagraxofusp erzs" or "tagraxofusp-erzs" or elzonris or "dt 388 il 3" or "dt il 3" or dt388il3 or dtil3 or "sl 401" or sl401).tw.	8
#29	(bezuclastinib or "cgt 9486" or cgt9486 or "plx 9486" or plx9486).tw.	5
#30	exp Thalidomide/	1,010
#31	(thalidomide or contergan or distaval or isomin or kedavon or kevadon or neurosedin or neurosedyne or sedalis or "shin naito" or softenon or synovir or talimol or talizer or telagan or telargan or thado or thaled or thalidomid or thalimodide or thalix or thalomid or "cc 2001" or cc2001 or "fpf 300" or fpf300 or "k 17" or "nsc 66847" or "vp 02" or vp02).tw.	1,565
#32	exp Cytarabine/	1,520
#33	(cytarabine or alcysten or alexan or "ara C" or "ara-cell" or arabinocytosil or arabinofuranosyl or arabinoside or arabinosine or arabinosyl or arabitin or aracytidine or aracytin or aracytine or citabion or citaloxan or citarabina or cytarabine or cyclocide or cylocide or "cystosine arabinoside" or cytarabide or cytarabine or cytarabinoside or cytarbine or cytarine or "cytidine arabinoside" or cytoarabine or "cytosa u" or cytosar or "cytosar 4" or "cytosar u" or "cytosin arabinoside" or "cytosine arabinose" or "cytosine arabinofuranoside" or "cytosine arabinonucleoside" or "cytosine arabinose" or "cytosine arabinoside" or "cytosine arabinosine" or "cytosine beta arabinofuranoside" or "cytosine beta arabinoside" or "cytosine beta d arabinofuranoside" or cytovis or depocyt or depocyte or "dtc 101" or dtc101 or iretin or laracit or novumtrax or "nsc 63878" or nsc63878 or tarabine or "tarabine pfs" or "u 19920 a" or "u 19920a" or u19920a or udicil or "udicil cs").tw.	3,274
#34	exp Daunorubicin/	6,231
#35	(daunorubicin or cerubidin or cerubidine or dannomycin or daunamycin or daunarubicin or "dauno rubidomycin" or daunobin or daunoblastin or daunoblastina or daunoblastine or daunoextra or daunomycin or daunomycine or daunorrubicina or daunorubicine or daunorubidomycin or daunorubimycin or daunoxome or daurorubicin or daunomycin or daunorubicin or "fi 6339" or fi6339 or maxidauno or "ndc 0082 4155" or "ndc 00824155" or "ndc0082 4155" or ndc00824155 or "nsc 82 151" or "nsc 82151" or nsc82151 or "rp 13057" or rp13057 or rubidiomycin or rubidomycin or rubidomycine or rubilem or "rubomycin c" or "rubomycine c" or trixilem or "trixilem ru").tw.	1,140

#36	(fludarabine or "2 fluoro 9 beta d arabinofuranosyladenine" or "2 fluoroadenine 9 arabinoside" or "2 fluoroadenine 9beta d arabinofuranoside" or "2 fluoroadenine arabinofuranoside" or "2 fluoroadenine arabinoside" or "2 fluoroara a" or "2 fluorovidarabine" or "9 arabinofuranosyl 2 fluoroadenine" or "9 beta arabinofuranosyl 2 fluoroadenine" or "9 beta d arabinofuranosyl 2 fluoroadenine" or "9 beta dextro arabinofuranosyl 2 fluoroadenine" or "9beta arabinofuranosyl 2 fluoroadenine" or "9beta d arabinofuranosyl 2 fluoroadenine" or "9beta dextro arabinofuranosyl 2 fluoroadenine" or "adenine,9beta dextro arabinofuranosyl 2 fluoro" or "arabinofuranosyl 2 fluoroadenine" or "arabinosyl 2 fluoroadenine" or "f ara A" or "vidarabine,2 fluoro").tw.	1,514
#37	("AML-like" or "AML like" or HiDAC or "FLAG IDA" or "FLAG-IDA").mp.	160
#38	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	29,079
#39	**5 and 38**	**48**
#40	**CDSR**	**0**
#41	**CCTR**	**48**

Table 89 Search strategy for DARE and HTA

No.	Query	Results
#1	exp mastocytosis/ or exp mastocytosis, systemic/	1
#2	exp leukemia, mast-cell/	0
#3	("acute basophilic leukaemia" or "acute basophilic leukemia" or "basophilic leucemia" or "basophilic leukaemia" or "basophilic leukemia").tw.	0
#4	(mastocytosis or "systemic mastocytosis" or "mast cell leukemia" or "mast cell leukaemia").tw.	2
#5	1 or 2 or 3 or 4	2
#6	**DARE**	**0**
#7	**HTA**	**2**

H.2 Systematic selection of studies

All SLR search algorithms were generated using population, interventions/comparators, outcomes, study design, and time period (PICOS-T)-related elements outlined in Table 90 below. These were generated from the research question pertinent to each section.

Bibliographies of additional, published, relevant systematic review articles were examined to obtain references. Bibliographies of accepted studies were reviewed to obtain further relevant references.

In the first pass, each abstract was reviewed by two independent investigators as to its suitability for inclusion in the study according to the above-defined selection criteria. Discrepancies were resolved by a third investigator. For abstracts that were deemed relevant during the first-level review, full-text articles were retrieved and reviewed.

In the second pass, the full-text version of each publication accepted in the first pass was reviewed by one investigator. All publications rejected at this stage were reviewed by a second investigator to confirm the rejection decision. For each excluded study, a specific

reason for exclusion was provided and by a second investigator. A third investigator was consulted to resolve disagreements where necessary.
Data extraction was performed in the following steps:

1. Information from the full-text articles was extracted independently into data extraction forms by one investigator.
2. Data extraction was independently validated by a second investigator; a third investigator was consulted to resolve disagreements as necessary.

Publications reporting duplicate results were not extracted into the data extraction table.

Table 90 Inclusion and exclusion criteria for clinical SLR

	Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
PICOS-T	**Global SLR**		**Danish adaption**	
Population	Adult (age ≥18 years) patients with AdvSM which includes: • ASM • SM-AHN • MCL	• Patients with cutaneous mastocytosis, indolent or smoldering SM • Patients with disease other than AdvSM • Paediatric population • Healthy volunteers	Unchanged	
Intervention	All approved or investigational pharmacological interventions used for the treatments of AdvSM: • Avapritinib • Midostaurin • Imatinib • Interferon alpha • Pegylated interferon alpha • Cladribine • Nilotinib • Dasatinib	Non-pharmacological interventions	All approved or investigational pharmacological interventions used for the treatments of AdvSM in Denmark: • Avapritinib • Midostaurin • Imatinib • Interferon alpha • Pegylated interferon alpha • Cladribine • Nilotinib	Non-pharmacological interventions • Everolimus • Masitinib • Ripretinib • Elenestinib • Brentuximab vedotin • Ibrutinib • Tagraxofusp • Bezuclastinib • Thalidomide

	Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
PICOS-T	**Global SLR**		**Danish adaption**	
	• Everolimus • Masitinib • Ripretinib • Elenestinib • Azacitidine • Brentuximab vedotin • Ibrutinib • Tagraxofusp • Bezuclastinib • Thalidomide		• Dasatinib • Azacitidine	
Comparators	• Placebo • Best supportive care (author defined) • Any other pharmacological/non-pharmacological intervention • No comparator limit for single-arm trials	None		Unchanged
Outcomes	• Overall response rate (including complete and partial remission) • Survival (including overall survival, progression-free survival,	Not reporting any of the outcomes included in the list		Unchanged

	Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
PICOS-T	**Global SLR**		**Danish adaption**	

	and event-free survival)
	• Duration of response
	• Treatment effect on HRQL (including patient-reported outcomes)
	• Mastocytosis Symptom Assessment Form score
	• Incidence of adverse events
	• Study/treatment discontinuation (including proportion of patients and time to discontinuation)
	• Pure pathologic response
	• Subgroup extracted:
	  ○ Disease sub-types of AdvSM
	  ○ Line of therapy			

Study design	• Randomised controlled trials (RCTs) • Non-randomised	• Letters, comments, and editorials • Case series or case reports	Unchanged	

	Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
PICOS-T	**Global SLR**		**Danish adaption**	
	controlled trials (nRCTs) • Single-arm trials • Retrospective and prospective cohort studies • Real-world evidence studies • Systematic reviews*			
Language	No limits	None	Unchanged	
Countries	No limits	None	Unchanged	
Time limit	No limits	None	Unchanged	

Abbreviation: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; HRQL = health-related quality of life; HSCT = haematopoietic stem-cell transplantation; MCL = mast cell leukemia; RCT = randomised controlled trial; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm; SC = standard care.
Note: * Systematic reviews will be included and flagged for bibliography searches. ^List is not exhaustive. A detailed extraction grid will be prepared before the data extraction stage and will be finalised after alignment as per the requirements

The PRISMA flow diagram of the clinical SLR is presented in Figure 41 below. Among the 1862 publications initially identified and screened from multiple databases, 1737 were excluded, leaving 125 publications for further evaluation of eligibility. 1 study could not be retrieved and 60 were excluded during full-text screening. In addition, 8 relevant publications were included in the review. As some studies were associated with multiple publications, secondary publications were combined. Hence, the evidence comprised of 30 non-RCT/observational studies from 72 publications, but no RCTs were identified.

From these studies, 3 were considered most appropriate to inform the Danish submission dossier. The remaining studies either had a comparator that is not used in Denmark or did not have the outcomes of interest.

Details of the included studies from the clinical SLR are provided in Table 91 below.

To best inform on the clinical efficacy of avapritinib, the EXPLORER (57) and PATHFINDER (20) studies are most relevant to for this patient population group. In order to inform the comparative effectiveness of avapritinib vs BAT, BLU-285-2405 (3) provides the most

complete data set that is currently available for this patient population and will form the basis for the indirect treatment comparison.

HRQoL was also part of the scope for the clinical SLR within this population group, based on the results of the SLR, the PATHFINDER (20) is the most relevant source for the HRQoL for avapritinib within this patient population.

H.2.1 PRISMA

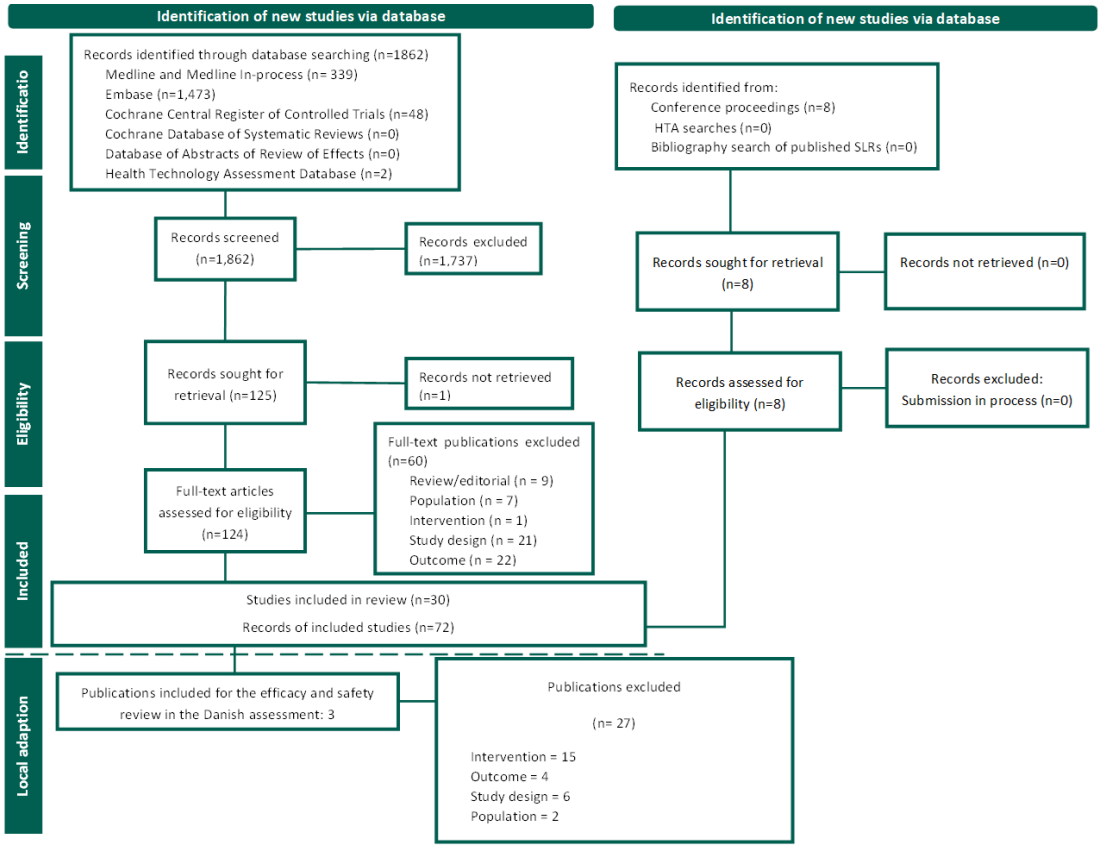

Figure 41 Clinical PRISMA flow diagram

H.2.2 Included studies

Table 91 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator	Primary outcome and follow-up period	Secondary outcome and follow-up period
Non-randomised controlled trials and observational studies						
Gotlib et al., 2021 (PATHFINDER) NCT03580655	To present the results of a prespecified interim analysis from the PATHFINDER trial of avapritinib 200 mg QD in adult patients with a centrally confirmed diagnosis of advanced systemic mastocytosis (AdvSM).	Phase 2, single arm, open-label multicentre study	Patients with AdvSM confirmed by central review (n = 62)	Avapritinib 200 mg or 100 mg once daily	Overall response rate (ORR)	Mean baseline change in AdvSM–Symptom Assessment Form Total Symptom Score and quality of life, time to response, duration of response, progression-free survival, overall survival, changes in measures of disease burden and safety.
Reiter et al., 2022 (BLU-285-2405) NCT04695431	To compare the efficacy of avapritinib to a real-world cohort of similar patients receiving best available therapy (BAT) for advanced systemic mastocytosis (AdvSM).	Retrospective, multicentre study	Adult patients with a diagnosis of AdvSM and documented subtype in their chart (ASM, SM-AHN, or MCL), and who had received ≥1 line of systemic therapy	Avapritinib The starting dose of avapritinib escalated from 30 to 400 mg daily (in EXPLORER,) and ≤200 mg daily (in PATHFINDER) BAT (Midostaurin/ Ripretinib/ Ibrutinib/	Overall survival	duration of therapy, change in serum tryptase levels from baseline to 2 months, maximum reduction in serum tryptase levels from baseline, adverse events that resulted in treatment modification or

Study/ID	Aim	Study design	Patient population	Intervention and comparator	Primary outcome and follow-up period	Secondary outcome and follow-up period
				Dasatinib/ Imatinib/ Cladribine/ Hydroxyurea/ Azacitidine/ Interferon-alfa/ Pegylated interferon/ Brentuximab vedotin/ Gemtuzumab ozogamicin)		discontinuation, hospitalization, or death.
DeAngelo et al., 2021 (EXPLORER) NCT02561988	To evaluate safety, efficacy and patient-reported outcomes of avapritinib in adult patients with advanced systemic mastocytosis (AdvSM)	Phase 1, single arm, open-label, multicentre study	Patients with AdvSM (n = 22)	Avapritinib 200 mg QD to 300 mg QD (dose expansion)	Safety	overall response rate, duration of response, changes in measures of mast cell burden (percentage of BM mast cells, serum tryptase concentration, KIT D816V VAF by ddPCR, and spleen and liver volumes), clinical improvement, patient-reported outcomes, time to response, overall survival and progression free survival

H.2.3 Excluded studies

Table 92 provides an overview of the publications excluded with reasons.

Table 92 Overview of publications excluded at full-text screening from the clinical SLR

Reference	Reason for exclusion
Johannes Lübke, Nicole Naumann, Timo Brand, Hans-Peter Horny, Martina Rudelius, Karl Sotlar, Georgia Metzgeroth, Alice Fabarius, Wolf-Karsten Hofmann, Juliana Schwaab, Andreas Reiter; Predicting the Clinical Course of Treatment with Midostaurin in Patients with Advanced Systemic Mastocytosis. Blood 2023; 142 (Supplement 1): 1834. doi: https://doi.org/10.1182/blood-2023-182322	Wrong intervention
Cristina Papayannidis, Francesco Mannelli, Lara Crosera, Roberta Parente, Alessandra Romano, Michela Rondoni, Chiara Elena, Marianna Criscuolo, Nicola Di Renzo, Fiorina Giona, Fabrizio Pane, Daniela Cilloni, Elena Maria Elli, Maurizio Miglino, Patrizio Mazza, Alessandra Malato, Lara Pochintesta, Roberta Bini, Diletta Valsecchi, Federica Irene Grifoni; Real-World Management of Advanced Systemic Mastocytosis Treated with Midostaurin: Analysis of Patients Who Completed 12 Months of Follow-up from an Italian Observational Study (OVIDIO). Blood 2022; 140 (Supplement 1): 9685–9687. doi: https://doi.org/10.1182/blood-2022-156371	Wrong intervention
Christopher J. Saunders, Chandan Saha, Priya Sriskandarajah, Helen Cashman, Andrew J Wilson, Jonathan Lambert, Matthew Lawes, David Tucker, Simone Green, Manish Jain, Victoria Stables, Juanah Addada, Theingi Yin, Huw Roddie, Bethan Psaila, Deepti H. Radia; The Use of Avapritinib in Advanced Systemic Mastocytosis: Report of an Open-Label Compassionate Use Program in the United Kingdom. Blood 2022; 140 (Supplement 1): 3976–3977. doi: https://doi.org/10.1182/blood-2022-166073	Wrong intervention
Marie-Olivia Chandesris, Gandhi Damaj, Danielle Canioni, Chantal Brouzes, Laure Cabaret, Katia Hanssens, Isabelle Durieu, Stéphane Durupt, Sophie Besnard, Odile Beyne-Rauzy, David Launay, Aurélie Schiffmann, Mathilde Niault, Dana Ranta, Philippe Agape, Cyrill Faure, Sylvain P Chantepie, Nicolas Daguindau, Philippe Bourget, Patrice Dubreuil, Olivier Lortholary, Olivier Hermine; Treatment of Advanced Systemic Mastocytosis with PKC412: The French Compassionate Use Programme Experience and Historical Comparison. Blood 2014; 124 (21): 3193. doi: https://doi.org/10.1182/blood.V124.21.3193.3193	Wrong intervention
Casassus P, Caillat-Vigneron N, Martin A, Simon J, Gallais V, Beaudry P, Eclache V, Laroche L, Lortholary P, Raphaël M, Guillevin L, Lortholary O. Treatment of adult systemic mastocytosis with interferon-alpha: results of a multicentre phase II trial on 20 patients. Br J Haematol. 2002 Dec;119(4):1090-7. doi: 10.1046/j.1365-2141.2002.03944.x. PMID: 12472593.	Wrong outcome
Rossignol J, Nizard S, Blanc A-S, et al. Therapeutic management and outcome of patients with advanced systemic mastocytosis treated with midostaurin: a comprehensive real-life study in the French national healthcare database. Hematol Oncol. 2022; 40(5): 1030-1040. https://doi.org/10.1002/hon.3062	Wrong intervention

Helbig G, Koclęga A, Gaweł WB, Włodarczyk M, Rodzaj M, Łabędź A, Hus I, Raźny M. The Efficacy of Cladribine (2-CdA) in Advanced Systemic Mastocytosis. Indian J Hematol Blood Transfus. 2020 Oct;36(4):661-666. doi: 10.1007/s12288-020-01279-8. Epub 2020 Apr 15. PMID: 33093752; PMCID: PMC7572963.	Wrong study design
Mohamad Jawhar, Juliana Schwaab, Manja Meggendorfer, Nicole Naumann, Hans-Peter Horny, Karl Sotlar, Torsten Haferlach, Karla Schmitt, Alice Fabarius, Peter Valent, Wolf-Karsten Hofmann, Nicholas C.P. Cross, Georgia Metzgeroth, Andreas Reiter. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. Haematologica 2017;102(6):1035-1043; https://doi.org/10.3324/haematol.2017.163964.	Wrong study design
Lübke J, Schwaab J, Naumann N, Horny HP, Weiß C, Metzgeroth G, Kreil S, Cross NCP, Sotlar K, Fabarius A, Hofmann WK, Valent P, Gotlib J, Jawhar M, Reiter A. Superior Efficacy of Midostaurin Over Cladribine in Advanced Systemic Mastocytosis: A Registry-Based Analysis. J Clin Oncol. 2022 Jun 1;40(16):1783-1794. doi: 10.1200/JCO.21.01849. Epub 2022 Mar 2. PMID: 35235417.	Wrong study design
Elena et al., 2017. Selection and Efficacy of Cytoreductive Agents in Patients with Mastocytosis Included in the Registry of the European Competence Network on Mastocytosis (ECNM). https://doi.org/10.1182/blood.V130.Suppl_1.1650.1650	Wrong study design
Reiter, A.1,*; Gotlib, J.2; Álvarez-Twose, I.3; Radia, D. H.4; Luebke, J.1; Bobbili, P. J.5; Wang, A.5; Norregaard, C.6; Dimitrijević, S.7; Sullivan, E.6; Louie-Gao, M.6; Schwaab, J.1; Galinsky, I. A.8; Perkins, C.2; Sperr, W. R.9; Sriskandarajah, P.4; Chin, A.5; Sendhil, S. R.5; Duh, M. S.5; Valent, P.9; DeAngelo, D. J.8. P1014: OVERALL SURVIVAL IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS RECEIVING AVAPRITINIB VERSUS MIDOSTAURIN OR CLADRIBINE. HemaSphere 6():p 904-905, June 2022. | DOI: 10.1097/01.HS9.0000846924.89785.04	Wrong intervention
Lübke, J., Naumann, N., Metzgeroth, G. et al. Response and resistance to cladribine in patients with advanced systemic mastocytosis: a registry-based analysis. Ann Hematol 102, 2077–2085 (2023). https://doi.org/10.1007/s00277-023-05180-y	Wrong population
Mohamad Jawhar, Juliana Schwaab, Nicole Naumann, Hans-Peter Horny, Karl Sotlar, Torsten Haferlach, Georgia Metzgeroth, Alice Fabarius, Peter Valent, Wolf-Karsten Hofmann, Nicholas C. P. Cross, Manja Meggendorfer, Andreas Reiter; Response and progression on midostaurin in advanced systemic mastocytosis: KIT D816V and other molecular markers. Blood 2017; 130 (2): 137–145. doi: https://doi.org/10.1182/blood-2017-01-764423	Wrong intervention
Szudy-Szczyrek A, Bachanek-Mitura O, Gromek T, Chromik K, Mital A, Szczyrek M, Krupski W, Szumiło J, Kanduła Z, Helbig G, et al. Real-World Efficacy of Midostaurin in Aggressive Systemic Mastocytosis. Journal of Clinical Medicine. 2021; 10(5):1109. https://doi.org/10.3390/jcm10051109	Wrong intervention
Reiter et al., 2017. POOLED SURVIVAL ANALYSIS OF MIDOSTAURIN CLINICAL STUDY DATA (D2201 + A2213) IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS (ADVSM) COMPARED WITH HISTORICAL CONTROLS. EHA Library. Reiter A. 06/25/17; 182075; S788	Wrong intervention

Cristina Papayannidis et al., PKC412 (midostaurin) is safe and highly effective in systemic mastocytosis: Follow up of a single-center Italian compassionate use.. JCO 32, 7113-7113(2014). DOI:10.1200/jco.2014.32.15_suppl.7113	Wrong intervention
Hochhaus, A., Baccarani, M., Giles, F.J. et al. Nilotinib in patients with systemic mastocytosis: analysis of the phase 2, open-label, single-arm nilotinib registration study. J Cancer Res Clin Oncol 141, 2047–2060 (2015). https://doi.org/10.1007/s00432-015-1988-0	Wrong intervention
Singh A, Al-Kali A, Begna KH, Litzow MR, Larsen JT, Sher T, Abdelmagid MG, Farrukh F, Reichard KK, Gangat N, Pardanani A, Tefferi A. Midostaurin therapy for advanced systemic mastocytosis: Mayo Clinic experience in 33 consecutive cases. Am J Hematol. 2022 May;97(5):630-637. doi: 10.1002/ajh.26498. Epub 2022 Feb 22. PMID: 35156231.	Wrong intervention
Kennedy VE, Perkins C, Reiter A, Jawhar M, Lübke J, Kluin-Nelemans HC, Shomali W, Langford C, Abuel J, Hermine O, Niedoszytko M, Gorska A, Mital A, Bonadonna P, Zanotti R, Tanasi I, Mattsson M, Hagglund H, Triggiani M, Yavuz AS, Panse J, Christen D, Heizmann M, Shoumariyeh K, Müller S, Elena C, Malcovati L, Fiorelli N, Wortmann F, Vucinic V, Brockow K, Fokoloros C, Papageorgiou SG, Breynaert C, Bullens D, Doubek M, Ilerhaus A, Angelova-Fischer I, Solomianyi O, Várkonyi J, Sabato V, Rüfer A, Schug TD, Hermans MAW, Fortina AB, Caroppo F, Bumbea H, Gulen T, Hartmann K, Elberink HO, Schwaab J, Arock M, Valent P, Sperr WR, Gotlib J. Mast cell leukemia: clinical and molecular features and survival outcomes of patients in the ECNM Registry. Blood Adv. 2023 May 9;7(9):1713-1724. doi: 10.1182/bloodadvances.2022008292. PMID: 36094848; PMCID: PMC10182174.	Wrong study design
Olivier Hermine, Isabelle Hirsh, Gandhi Damaj, Catherine Granpeix, Stéphane Barète, Felipe Suarez, Olivia Chansderis, David Ghez, Richard Delarue, Fanny Lanternier, Benedicte Deau, Helene Coignard, Sylvie Fraitag, Danielle Canioni, Philippe Casassus, Patrice Dubreuil, Olivier Lortholary; Long Term Efficacy and Safety of Cladribine In Adult Systemic mastocytosis: a French Multicenter Study of 44 Patients. Blood 2010; 116 (21): 1982. doi: https://doi.org/10.1182/blood.V116.21.1982.1982	Wrong outcome
Angelo DJ, George TI, Linder A, Langford C, Perkins C, Ma J, Westervelt P, Merker JD, Berube C, Coutre S, Liedtke M, Medeiros B, Sternberg D, Dutreix C, Ruffie PA, Corless C, Graubert TJ, Gotlib J. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. Leukemia. 2018 Feb;32(2):470-478. doi: 10.1038/leu.2017.234. Epub 2017 Jul 24. PMID: 28744009.	Wrong intervention
Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, Awan FT, Hexner E, Mauro MJ, Sternberg DW, Villeneuve M, Huntsman Labed A, Stanek EJ, Hartmann K, Horny HP, Valent P, Reiter A. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016 Jun 30;374(26):2530-41. doi: 10.1056/NEJMoa1513098. PMID: 27355533.	Wrong intervention
Lim KH, Pardanani A, Butterfield JH, Li CY, Tefferi A. Cytoreductive therapy in 108 adults with systemic mastocytosis: Outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. Am J Hematol. 2009 Dec;84(12):790-4. doi: 10.1002/ajh.21561. PMID: 19890907.	Wrong outcome

Tefferi A, Kittur J, Farrukh F, Begna KH, Patnaik MM, Al-Kali A, Elliott MA, Reichard KK, Gangat N, Pardanani A. Cladribine therapy for advanced and indolent systemic mastocytosis: Mayo Clinic experience in 42 consecutive cases. Br J Haematol. 2022 Feb;196(4):975-983. doi: 10.1111/bjh.17932. Epub 2021 Nov 3. PMID: 34729775.	Wrong population
Stéphane Barete, Olivier Lortholary, Gandhi Damaj, Isabelle Hirsch, Marie Olivia Chandesris, Caroline Elie, Mohamed Hamidou, Isabelle Durieu, Felipe Suarez, Bernard Grosbois, Nicolas Limal, Emmanuel Gyan, Claire Larroche, Gérard Guillet, Jean Emmanuel Kahn, Philippe Casassus, Karima Amazzough, Hélène Coignard-Biehler, Sophie Georgin-Lavialle, Ludovic Lhermitte, Sylvie Fraitag, Danielle Canioni, Patrice Dubreuil, Olivier Hermine; Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood 2015; 126 (8): 1009–1016. doi: https://doi.org/10.1182/blood-2014-12-614743	Wrong study design
Pagano L, Valentini CG, Caira M, Rondoni M, Van Lint MT, Candoni A, Allione B, Cattaneo C, Marbello L, Caramatti C, Pogliani EM, Iannitto E, Giona F, Ferrara F, Invernizzi R, Fanci R, Lunghi M, Fianchi L, Sanpaolo G, Stefani PM, Pulsoni A, Martinelli G, Leone G, Musto P. Advanced mast cell disease: an Italian Hematological Multicenter experience. Int J Hematol. 2008 Dec;88(5):483-488. doi: 10.1007/s12185-008-0166-4. Epub 2008 Nov 26. PMID: 19034614.	Wrong outcome
Jason Gotlib, John H. Baird, Tracy I. George, Cheryl Langford, Isabel Reyes, Justin Abuel, Cecelia Perkins, Kurt Schroeder, Prithviraj Bose, Srdan Verstovsek; A phase 2 study of brentuximab vedotin in patients with CD30-positive advanced systemic mastocytosis. Blood Adv 2019; 3 (15): 2264–2271. doi: https://doi.org/10.1182/bloodadvances.2019000152	Wrong intervention
Patnaik, M.M., Rangit Vallapureddy, Lasho, T.L. et al. A comparison of clinical and molecular characteristics of patients with systemic mastocytosis with chronic myelomonocytic leukemia to CMML alone. Leukemia 32, 1850–1856 (2018). https://doi.org/10.1038/s41375-018-0121-1	Review/Editorial
Budnik J., Milano M.T. A registry-based analysis of survival outcomes in mast cell leukemia. Leukemia Research. 78 (pp 24-28), 2019. https://dx.doi.org/10.1016/j.leukres.2019.01.005	Wrong intervention
Pieri L., Bonadonna P., Elena C., Papayannidis C., Grifoni F.I et al. A survey on clinical and biological characteristic and therapy management of an italian series of 455 adult patients with systemic mastocytosis on behalf of italian registry of mastocytosis. Blood. Conference: 56th Annual Meeting of the American Society of Hematology, ASH 2014. San Francisco, CA United States. Conference Publication: (var.pagings). 124(21) (no pagination), 2014.	Wrong outcome
Valent P., Akin C., Sperr W.R., Escribano L., Arock M. et al. Aggressive systemic mastocytosis and related mast cell disorders: Current treatment options and proposed response criteria. Leukemia Research. 27(7) (pp 635-641), 2003. https://dx.doi.org/10.1016/S0145-2126%2802%2900168-6	Review/Editorial
Jain P., Wang S., Kantarjian H.M., Sarwari N., Patel K.P et al. Aleukemic mast cell leukemia (aMCL)-clinical characteristics and outcomes. Blood. Conference: 58th Annual Meeting of the American Society of Hematology, ASH 2016. San Diego, CA United States. 128(22) (no pagination), 2016.	Wrong outcome

Sriskandarajah P., Oni C., Woodley C., Asirvatham S., Ciesielska M. Application of Prognostic Scoring in Systemic Mastocytosis Patients within a UK Centre of Excellence: Guys and St Thomas' NHS Foundation Trust'. Blood. Conference: 63rd American Society of Hematology Annual Meeting and Exposition, ASH 2021. Atlanta, GA United States. 138(SUPPL 1) (pp 3625), 2021. https://dx.doi.org/10.1182/blood-2021-152234	Wrong outcome
Dybedal I., Skipper Madsen S., Fykse Halstensen R., Stenberg V., Farkas L et al. Ascites a manifestation of aggressive systemic mastocytosis can successfully be treated with midostaurin (PKC412). Haematologica. Conference: 21st Congress of the European Hematology Association. Copenhagen Denmark. 101(Supplement 1) (pp 810), 2016.	Wrong outcome
Kluin-Nelemans H.C., Oldhoff J.M., Van Doormaal J.J., Van't Wout J.W., Verhoef G et al. Cladribine therapy for systemic mastocytosis. Blood. 102(13) (pp 4270-4276), 2003. https://dx.doi.org/10.1182/blood-2003-05-1699	Wrong study design
Liang E., Perkins C., Lu R., Shi H., Dimitrijevic S et al. CLINICOPATHOLOGIC AND MOLECULAR CORRELATES OF ORGAN DAMAGE ACROSS THE SPECTRUM OF ADVANCED SYSTEMIC MASTOCYTOSIS. HemaSphere. Conference: Congress of the European Hematology Association, EHA 2022. Virtual. 6(Supplement 3) (pp 1784-1785), 2022. https://dx.doi.org/10.1097/01.HS9.0000852292.38263.b8	Wrong outcome
Ediriwickrema A., DeAngelo D.J., George T.I., Rosenberg-Hasson Y, Perkins C et al. Comprehensive cytokine profiling of patients with advanced systemic mastocytosis treated with midostaurin. Blood. Conference: 60th Annual Meeting of the American Society of Hematology, ASH 2018. San Diego, CA United States. 132(Suppl. 1) (no pagination), 2018. https://dx.doi.org/10.1182/blood-2018-99-117689	Wrong outcome
Anonymous. Corrigendum to 'MPN-395: Efficacy and Safety of <=200 mg Avapritinib in Patients with Advanced Systemic Mastocytosis: Pooled Results from the Phase 1 EXPLORER and Interim Phase 2 PATHFINDER Studies. Clinical Lymphoma, Myeloma and Leukemia. 22(4) (pp 276), 2022. https://dx.doi.org/10.1016/j.clml.2021.12.002	Wrong study design
Moura D.S., Sultan S., Georgin-Lavialle S., Pillet N., Montestruc F et al. Depression in patients with mastocytosis: Prevalence, features and effects of masitinib therapy. PLoS ONE. 6(10) (no pagination), 2011. Article Number: e26375. https://dx.doi.org/10.1371/journal.pone.0026375	Wrong population
Reiter A., Gotlib J., Alvarez-Twose I., Radia D.H., Luebke J et al. DURATION OF TREATMENT AND REDUCTION IN SERUM TRYPTASE LEVELS IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS TREATED WITH AVAPRITINIB VERSUS BEST AVAILABLE THERAPY. HemaSphere. Conference: Congress of the European Hematology Association, EHA 2022. Virtual. 6(Supplement 3) (pp 1742-1743), 2022. https://dx.doi.org/10.1097/01.HS9.0000852292.38263.b8	Wrong outcome
Deininger M.W., DeAngelo D.J., Radia D.H., George T.I., Yang G et al. Effective control of advance systemic mastocytosis with avapritinib: Mutational analysis from the explorer clinical study. Blood. Conference: 63rd American Society of Hematology Annual Meeting and Exposition, ASH	Wrong outcome

2021. Atlanta, GA United States. 138(SUPPL 1) (pp 318), 2021. https://dx.doi.org/10.1182/blood-2021-150872	
Radia D., Drummond M.W., Deininger M.W., George T.I., Dimitrijevic S et al. Efficacy and safety of avapritinib as first-line treatment of patients with advanced systemic mastocytosis: Results of EXPLORER and PATHFINDER clinical study. British Journal of Haematology. Conference: 62nd Annual Scientific Meeting of the British Society for Haematology. Virtual. 197(SUPPL 1) (pp 25-27), 2022. https://dx.doi.org/10.1111/bjh.18132	Wrong study design
Vannucchi A.M., Radia D., DeAngelo D., Deininger M., Reiter A et al. EFFICACY AND SAFETY OF AVAPRITINIB IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS: POOLED RESULTS FROM THE PHASE 1 EXPLORER AND INTERIM PHASE 2 PATHFINDER STUDIES. Haematologica. Conference: 17th Congress of the Italian Society of Experimental Hematology. Roma Italy. 107(SUPPL 1) (pp 25-26), 2022.	Wrong outcome
Reiter A., Schwaab J., DeAngelo D.J., Gotlib J., Deininger M.W et al. Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis. Blood Advances. 6(21) (pp 5750-5762), 2022. https://dx.doi.org/10.1182/bloodadvances.2022007539	Wrong outcome
George T.I., Karner K.H., Moser K.A., Rets A., Fredericks M et al. Efficacy of avapritinib in patients with advanced systemic mastocytosis: Hematologic and bone marrow responses from the phase 2 open-label, single-arm, pathfinder study. Blood. Conference: 63rd American Society of Hematology Annual Meeting and Exposition, ASH 2021. Atlanta, GA United States. 138(SUPPL 1) (pp 2565), 2021. https://dx.doi.org/10.1182/blood-2021-146873	Wrong outcome
Tzogani K., Yu Y., Meulendijks D., Herberts C., Hennik P et al. European Medicines Agency review of midostaurin (Rydapt) for the treatment of adult patients with acute myeloid leukaemia and systemic mastocytosis. ESMO Open. 4(6) (no pagination), 2019. Article Number: e000606. https://dx.doi.org/10.1136/esmoopen-2019-000606	Review/Editorial
Parikh S.A., Kantarjian H.M., Richie M.A., Cortes J.E., Verstovsek S et al. Experience with everolimus (RAD001), an oral mammalian target of rapamycin inhibitor, in patients with systemic mastocytosis. Leukemia and Lymphoma. 51(2) (pp 269-274), 2010. https://dx.doi.org/10.3109/10428190903486220	Wrong study design
Bahcecioglu AB, Etgul S, Aslan T, Aydin MS, Malkan UY et al. Experience with pegylated interferon &agr;-2a in 30 patients diagnosed with hematologic neoplasms. Blood. Vol.128(22): 2016-12-03 to 2016-12-06. 58th Annual Meeting of the American Society of Hematology, ASH 2016. San Diego, CA. United States. Netherlands American Society of Hematology.	Wrong population
Jungmayr P. Hematologic neoplasia: Midostaurin in advanced systemic mastocytosis. [German]. Arzneimitteltherapie. 36(12) (pp 457-458), 2018.	Review/Editorial
Alvarez-Twose I., Matito A., Morgado J.M., Sanchez-Munoz L., Jara-Acevedo M et al. Imatinib in systemic mastocytosis: a phase IV clinical trial in patients lacking exon 17 KIT mutations and review of the literature. Oncotarget. 8(40) (pp 68950-68963), 2017. https://dx.doi.org/10.18632/oncotarget.10711	Wrong study design

Droogendijk H.J., Kluin-Nelemans H.J.C., Van Doormaal J.J., Oranje A.P., Van De Loosdrecht A.A et al. Imatinib mesylate in the treatment of systemic mastocytosis: A phase II trial. Cancer. 107(2) (pp 345-351), 2006. https://dx.doi.org/10.1002/cncr.21996	Wrong study design
Dalal B.I., Horsman D.E., Bruyere H., Forrest D.L. Imatinib mesylate responsiveness in aggressive systemic mastocytosis: Novel association with a platelet derived growth factor receptor beta mutation. American Journal of Hematology. 82(1) (pp 77-79), 2007. https://dx.doi.org/10.1002/ajh.20833	Wrong study design
Pilkington H., Smith S., Roskell N., Iannazzo S. Indirect treatment comparisons of avapritinib versus midostaurin for patients with advanced systemic mastocytosis. Future Oncology. 18(13) (pp 1583-1594), 2022. https://dx.doi.org/10.2217/fon-2021-1509	Review/Editorial
Laroche M., Livideanu C., Paul C., Cantagrel A. Interferon alpha and pamidronate in osteoporosis with fracture secondary to mastocytosis. American Journal of Medicine. 124(8) (pp 776-778), 2011. https://dx.doi.org/10.1016/j.amjmed.2011.02.038	Wrong population
Czarnetzki BM, Algermissen B, Jeep S, Haas N, Nurnberg W et al. Interferon treatment of patients with chronic urticaria and mastocytosis. Journal of the American Academy of Dermatology. 30(3):500-1, 1994 Mar.	Wrong population
Jawhar M., Schwaab J., Alvarez-Twose I., Shoumariyeh K., Naumann N. Mars. Mutation-adjusted risk score for advanced systemic mastocytosis. Journal of Clinical Oncology. 37(31) (pp 2846-2856), 2019. https://dx.doi.org/10.1200/JCO.19.00640	Wrong study design
Paul C., Sans B., Suarez F., Casassus P., Barete S et al. Masitinib for the treatment of systemic and cutaneous mastocytosis with handicap: A phase 2a study. American Journal of Hematology. 85(12) (pp 921-925), 2010. https://dx.doi.org/10.1002/ajh.21894	Wrong population
Wharin S., Myers B. Mast cell disorders-experience of a tertiary referral centre. British Journal of Haematology. Conference: 58th Annual Scientific Meeting of the British Society for Haematology. Liverpool United Kingdom. 181(Supplement 1) (pp 57), 2018. https://dx.doi.org/10.1111/bjh.15226	Wrong population
Jain P., Wang S., Patel K.P., Sarwari N., Cortes J et al. Mast cell leukemia (MCL): Clinico-pathologic and molecular features and survival outcome. Leukemia Research. 59 (pp 105-109), 2017. https://dx.doi.org/10.1016/j.leukres.2017.05.018	Wrong outcome
Jawhar M., Schwaab J., Meggendorfer M., Naumann N., Kluger S et al. Mast cell leukemia: Clinical heterogeneity, molecular aberrations and prognostic factors. Oncology Research and Treatment. Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Medizinische Onkologie 2016. Leipzig Germany. 39(Supplement 3) (pp 24), 2016. https://dx.doi.org/10.1159/000449050	Wrong outcome
Jawhar M., Schwaab J., Meggendorfer M., Naumann N., Horny H.-P et al. Mast cell leukemia: Clinical heterogeneity, molecular aberrations, treatment responses, survival, and prognostic factors. Blood. Conference:	Wrong outcome

58th Annual Meeting of the American Society of Hematology, ASH 2016. San Diego, CA United States. 128(22) (no pagination), 2016.	
Anonymous. Midostaurin (Rydapt) for AML and advanced systemic mastocytosis. Medical Letter on Drugs & Therapeutics. 59(1527):e140, 2017 08 14.	Wrong study design
Knapper S., Cullis J., Drummond M.W., Evely R., Everington T et al. Midostaurin a multi-targeted oral kinase inhibitor in systemic mastocytosis: Report of an open-label compassionate use program in the United Kingdom. Blood. Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011. San Diego, CA United States. Conference Publication: (var.pagings). 118(21) (no pagination), 2011.	Wrong outcome
Chandesris MO, Damaj G, Canioni D, Brouzes C, Lhermitte L et al. Midostaurin in Advanced Systemic Mastocytosis. New England journal of medicine. Vol.374(26):2605-2607p, 2016. https://doi.org/10.1056/NEJMc1515403	Review/Editorial
Abuhelwa Z., Beran A., Kahlon N., Sayeh W., Khokher W et al. Midostaurin in advanced systemic mastocytosis: A systematic review and meta-analysis. Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO 2022. Online. 40(16 Supplement 1) (no pagination), 2022. https://dx.doi.org/10.1200/JCO.2022.40.16_suppl.e19084	Review/Editorial
Abuhelwa Z., Beran A., Kahlon N., Sayeh W., Khokher W et al. Midostaurin in Advanced Systemic Mastocytosis: A Systematic Review and Meta-analysis. American journal of therapeutics. (no pagination), 2022. https://dx.doi.org/10.1097/MJT.0000000000001508	Review/Editorial
Radia D., DeAngelo D., Deininger M.W., Reiter A., Sen J et al. MPN-395: Efficacy and Safety of <=200 mg Avapritinib in Patients with Advanced Systemic Mastocytosis: Pooled Results from the Phase 1 EXPLORER and Interim Phase 2 PATHFINDER Studies. Clinical Lymphoma, Myeloma and Leukemia. Conference: Society of Hematologic Oncology 2021 Annual Meeting. Hilton Americas, Houston United States. 21(Supplement 1) (pp S367-S368), 2021. https://dx.doi.org/10.1016/S2152-2650%2821%2901843-7	Wrong outcome
Vega-Ruiz A., Cortes J.E., Sever M., Manshouri T., Quintas-Cardama A et al. Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis. Leukemia Research. 33(11) (pp 1481-1484), 2009. https://dx.doi.org/10.1016/j.leukres.2008.12.020	Wrong outcome
Heinrich M.C., Joensuu H., Demetri G.D., Corless C.L., Apperley J et al. Phase II, open-label study evaluating the activity of imatinib in treating life-threatening malignancies known to be associated with imatinib-sensitivetyrosine kinases. Clinical Cancer Research. 14(9) (pp 2717-2725), 2008. https://dx.doi.org/10.1158/1078-0432.CCR-07-4575	Wrong study design
Pilkington H., Smith S., Roskell N., Iannazzo S. POSA33 Matching-Adjusted Indirect Comparisons of Avapritinib Versus Midostaurin Among Patients with Advanced Systemic Mastocytosis. Value in Health. Conference: ISPOR Europe 2021. Virtual, Online. 25(1 Supplement) (pp S24), 2022. https://dx.doi.org/10.1016/j.jval.2021.11.106	Review/Editorial

Taylor F., Shields A., Li S., Yip C., Padilla B et al. PRO143 PSYCHOMETRIC EVALUATION OF THE ADVANCED SYSTEMIC MASTOCYTOSIS SYMPTOM ASSESSMENT FORM (ADVSM-SAF) IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS. Value in Health. Conference: ISPOR Europe 2019. Copenhagen Denmark. 22(Supplement 3) (pp S868), 2019. https://dx.doi.org/10.1016/j.jval.2019.09.2472	Wrong study design
Anonymous. Rapid Responses to Avapritinib (BLU-285) in Mastocytosis. Cancer discovery. 8(2) (pp 133), 2018. https://dx.doi.org/10.1158/2159-8290.CD-NB2017-177	Wrong study design
Butterfield J.H. Response of severe systemic mastocytosis to interferon alpha. British Journal of Dermatology. 138(3) (pp 489-495), 1998. https://dx.doi.org/10.1046/j.1365-2133.1998.02131.x	Wrong study design
Rondoni M., Paolini S., Colarossi S., Fabbri A., Pregno P et al. Response to Dasatinib in patients with systemic mastocytosis with D816V KIT mutation: 9 Italian cases. Haematologica. Conference: 42 Congress of the Italian Society of Hematology. Milano Italy. Conference Publication: (var.pagings). 94(SUPPL. 4) (pp 54), 2009.	Wrong outcome
Hauswirth A.W., Simonitsch-Klupp I., Uffmann M., Koller E., Sperr W.R et al. Response to therapy with interferon alpha-2b and prednisolone in aggressive systemic mastocytosis: Report of five cases and review of the literature. Leukemia Research. 28(3) (pp 249-257), 2004. https://dx.doi.org/10.1016/S0145-2126%2803%2900259-5	Wrong study design
George T., Karner K.H., Moser K.A., Rets A., Reiter A et al. RESPONSES TO AVAPRITINIB IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS: HISTOPATHOLOGIC ANALYSES FROM EXPLORER AND PATHFINDER CLINICAL STUDIES. HemaSphere. Conference: Congress of the European Hematology Association, EHA 2022. Virtual. 6(Supplement 3) (pp 1764-1765), 2022. https://dx.doi.org/10.1097/01.HS9.0000852292.38263.b8	Wrong outcome
Wimazal F., Geissler P., Shnawa P., Sperr W.R., Valent P. Severe life-threatening or disabling anaphylaxis in patients with systemic mastocytosis: A single-center experience. International Archives of Allergy and Immunology. 157(4) (pp 399-405), 2012. https://dx.doi.org/10.1159/000329218	Wrong study design
Lee P., George T.I., Shi H., Evans E.K., Singh T. Systemic mastocytosis patient experience from mast cell connect, the first patient-reported registry for mastocytosis. Blood. Conference: 58th Annual Meeting of the American Society of Hematology, ASH 2016. San Diego, CA United States. 128(22) (no pagination), 2016.	Wrong outcome
Kudlaty E., Perez M., Stein B.L., Bochner B.S., Kuang F.L. Systemic mastocytosis with an associated hematologic neoplasm complicated by recurrent anaphylaxis: prompt resolution of anaphylaxis with the addition of avapritinib. The journal of allergy and clinical immunology. In practice. (no pagination), 2021. https://dx.doi.org/10.1016/j.jaip.2021.02.040 (11)	Wrong study design
Damaj G., Bernit E., Ghez D., Claisse J.-F., Schleinitz N et al. Thalidomide in advanced mastocytosis. British Journal of Haematology. 141(2) (pp 249-253), 2008. https://dx.doi.org/10.1111/j.1365-2141.2008.07038.x	Wrong study design

Gruson B., Lortholary O., Canioni D., Chandesris M.-O., Lanternier F et al. Thalidomide in advanced mastocytosis. results from an open-label, multicentric, phase II study. Blood. Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011. San Diego, CA United States. Conference Publication: (var.pagings). 118(21) (no pagination), 2011.	Wrong outcome
Gruson B., Lortholary O., Canioni D., Chandesris O., Lanternier F et al. Thalidomide in systemic mastocytosis: Results from an open-label, multicentre, phase II study. British Journal of Haematology. 161(3) (pp 434-442), 2013. https://dx.doi.org/10.1111/bjh.12265	Population
Borate U., Mehta A., Reddy V., Tsai M., Josephson N et al. Treatment of CD30-positive systemic mastocytosis with brentuximab vedotin. Leukemia Research. 44 (pp 25-31), 2016. https://dx.doi.org/10.1016/j.leukres.2016.02.010	Wrong study design
Pardanani A., Hoffbrand A.V., Butterfield J.H., Tefferi A. Treatment of systemic mast cell disease with 2-chlorodeoxyadenosine. Leukemia Research. 28(2) (pp 127-131), 2004. https://dx.doi.org/10.1016/S0145-2126%2803%2900185-1	Wrong study design
Worobec A.S., Kirshenbaum A.S., Schwartz L.B., Metcalfe D.D. Treatment of three patients with systemic mastocytosis with interferon alpha-2b. Leukemia and Lymphoma. 22(5-6) (pp 501-508), 1996. http://dx.doi.org/10.3109/10428199609054789	Wrong study design
Reiter A., Radia D.H., Drummond M.W., Deininger M.W., George T.I et al. Oncology Research and Treatment. Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Medizinische Onkologie. Wien Austria. 45(Supplement 2) (pp 23-24), 2022. https://dx.doi.org/10.1159/000526456	Wrong study design
Hermine O., Radia D., Deangelo D.J., Deininger M.W., Reiter A et al. Efficacite et securite d'emploi de <= 200 mg d'avapritinib chez des patients atteints de mastocytose systemique avancee : resultats pooles de l'etude de phase 1 EXPLORER et de l'analyse intermediaire de l'etude de phase 2 PATHFINDER. Hematologie. Conference: 48. Congres de la Societe Francaise d'Hematologie, SFH 2022. Paris France. 28(Supplement 1) (pp 82-83), 2022. https://dx.doi.org/10.1684/hma.2022.1737	Wrong outcome

H.3 Quality assessment

The quality assessment for non-randomised controlled trials and observational studies was evaluated using the Downs and Black checklist (94). Each item in this checklist is checked as 'yes', 'no', or 'unable to determine'. The results of the quality assessment are presented below.

Table 93 Quality assessment of studies

Question no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Study name																										
Gotlib et al., 2021 (PATHFINDER) NCT03580655	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	U	N	N	N	N	Y	Y	Y	Y	Y	Y	N	N	N	Y
Reiter et al., 2022 NCT04695431	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	U	N	N	N	N	Y	Y	Y	Y	Y	U	N	N	N	U
DeAngelo et al., 2021 (EXPLORER) NCT02561988	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	U	N	N	N	N	Y	Y	Y	Y	Y	Y	N	N	N	U

For non-RCTs and observational studies (Downs and Black checklist) (94)

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the introduction or methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the interventions of interest clearly described?
5. Are the distributions of principal confounders in each group of patients to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristics of patients lost to follow-up been described?

10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?

14. Was an attempt made to blind study subjects to the intervention they have received?

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

16. If any of the results of the study were based on 'data dredging', was this made clear?

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?

18. Were the statistical tests used to assess the main outcomes appropriate?

19. Was compliance with the intervention(s) reliable?

20. Were the main outcome measures used accurate (valid and reliable)?

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?

23. Were study subjects randomized to intervention groups?

24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

26. Were losses of patients to follow-up considered?

Abbreviations: N = no; Y = yes; U = unable to determine

H.4 Unpublished data

No unpublished literature is used to inform the clinical section of the dossier.

Appendix I. Literature searches for health-related quality of life

Health-related quality-of-life search

As reported in section 10, the following TLRs were conducted to inform the HSUV included in the model.

I. To identify the mapping algorithm that best matches with the characteristics of the AdvSM population, to transform the QLQ-C30 scores collected during the trials in EQ-5D values.

II. To identify a relative difference in utility post-progression vs pre-progression in conditions similar to AdvSM.

III. To define the QoL utility values during and after HSCT.

Full TLR reports can be found in Appendix I.4 and I.6. Note that the TLR contains findings from studies on similar disease and not specifically for AdvSM.

I.1 Search strategies

The SLR search aimed to address the following research questions:

- To identify utility values associated with AdvSM

As detailed in Table 94, Table 95 and Table 96, the HRQoL SLR search was conducted on 26 June 2023.

The searches were performed in the following indexed databases via OVID:

- MEDLINE® and MEDLINE® In-Process (via Ovid.com)
- Embase® (via Ovid.com)
- Cochrane databases (via Ovid.com), including the following:
  - Cochrane Central Register of Controlled Trials (CCTR)
  - Cochrane Database of Systematic Reviews (CDSR)
- Evidence-based Medicine (EBM) Reviews (via Ovid.com), including the following:
  - Database of Abstracts of Reviews of Effects (DARE)
  - Health Technology Assessment (HTA)
  - National Health Service Economic Evaluation Database (NHSEED)
- Econlit (via Ovid.com)
- ScHARRHUD (via www.scharrhud.org)

Electronic searching in the literature databases was not limited according to timeframe because utility data are considered clinical outcomes for which it is generally advised not

to limit electronic searching by time frame. The searches were not limited to English language.

Bibliographies of systematic reviews were screened to ensure that initial searches captured all the relevant utility studies.

In addition to the databases, proceedings of 4 conferences were searched for the last 2 years (2021–2023) to identify any studies of interest. These included:

- American Society of Clinical Oncology (ASCO) Annual meeting
- American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium
- European Society for Medical Oncology (ESMO) Congress
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

The data identified through electronic and manual searches were supplemented by the data available on HTA websites. The following international HTA websites were searched to identify any relevant HTAs:

- National Institute for Health and Care Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- All Wales Medicines Strategy Group (AWMSG)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Gemeinsamer Bundesausschuss (GBA)
- Haute Autorite de Sante (HAS)
- Zorginstituutnederland (ZIN)
- National Centre for Pharmacoeconomics (NCPE)
- Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS)

Table 94 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Medline and Medline In-Process	Ovid	1946 – 22 June 2023	26 June 2023
Embase	Ovid	1974 – 23 June 2023	26 June 2023
CCTR	Ovid	From May 2023	26 June 2023
CDSR	Ovid	2005 – 20 June 2023	26 June 2023
DARE	Ovid	1st Quarter 2016	26 June 2023
HTA	Ovid	4th Quarter 2016	26 June 2023
NHSEED	Ovid	1st Quarter 2016	26 June 2023
Econlit	Ovid	1886 – June 15 2023	26 June 2023
ScHARRHUD	ScHARRUD webpage	Unlimited	26 June 2023

Abbreviations: CCTR = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; HTA = Health Technology Assessment; NHSEED = National Health Service Economic Evaluation Database.

Table 95 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	mastocytosis mast cell	dd.mm.yyyy
SMC	https://www.scottishmedicines.org.uk/home	mastocytosis mast cell	26 June 2023
AWMSG	https://awttc.nhs.wales/	mastocytosis mast cell	26 June 2023
CADTH	https://www.cadth.ca/search	mastocytosis mast cell	26 June 2023
GBA	https://www.g-ba.de/english/	mastocytosis mast cell	26 June 2023
HAS	https://www.has-sante.fr/jcms/p_3291681/en/hta-the-has-a-lead-player-in-the-european-cooperation-for-health-technology-assessment	mastocytosis mast cell	26 June 2023
ZIN	https://english.zorginstituutnederland.nl/	mastocytosis mast cell	26 June 2023
NCPE	https://www.ncpe.ie/submission-process/hta-guidelines/	mastocytosis mast cell	26 June 2023
AEMPS	https://www.aemps.gob.es/informa-en/the-spanish-agency-of-medicines-and-medical-devices-aemps-recommends-using-voluntary-harmonisation-procedure-before-the-official-submission-of-a-multi-state-ct-application/?lang=en	mastocytosis mast cell	26 June 2023

Abbreviations: NICE = National Institute for Health and Care Excellence; CADTH = Canadian Agency for Drugs and Technologies in Health; SMC = Scottish Medicines Consortium; AWMSG = All Wales Medicines Strategy Group; GBA = Gemeinsamer Bundesausschuss; HAS = Haute Autorite de Sante; ZIN = Zorginstituutnederland; NCPE = National Centre for Pharmacoeconomics; AEMPS = Agencia Espanola de Medicamentos y Productos Sanitarios

Table 96 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO Gastrointestina	https://meetings.asco.org/abstracts-presentations/search?q	Electronic search	mastocytosis mast cell	26 June 2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
l Cancers Symposium	uery=*&q=*&sortBy=AbstractBrowse&filters=%7B%22presentationType%22:%5B%7B%22key%22:%22Abstract%20Presentation%22%7D,%7B%22key%22:%22Poster%22%7D,%7B%22key%22:%22Abstract%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222021%22%7D%5D,%22meetingTypeName%22:%5B%7B%22key%22:%22Gastrointestinal%20Cancers%20Symposium%22%7D%5D%7D&size=50			
ESMO	https://oncologypro.esmo.org/meeting-resources/esmo-congress	Electronic search	mastocytosis mast cell	26 June 2023
ISPOR	https://www.ispor.org/heor-resources/presentations-database/search	Electronic search	mastocytosis mast cell	26 June 2023
ASCO Gastrointestinal Cancers Symposium	https://meetings.asco.org/abstracts-presentations/search?query=*&q=*&sortBy=AbstractBrowse&filters=%7B%22presentationType%22:%5B%7B%22key%22:%22Abstract%20Presentation%22%7D,%7B%22key%22:%22Poster%22%7D,%7B%22key%22:%22Abstract%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222021%22%7D%5D,%22meetingTypeName%22:%5B%7B%22key%22:%22Gastrointestinal%20Cancers%20Symposium%22%7D%5D%7D&size=50	Electronic search	mastocytosis mast cell	26 June 2023

Abbreviations: ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research

All SLR search algorithms were generated using population, interventions/comparators, outcomes, study design, and time period (PICOS-T)-related elements outlined in Table 97 below. These were generated from the research question pertinent to each section.

Bibliographies of additional, published, relevant systematic review articles were examined to obtain references. Bibliographies of accepted studies were reviewed to obtain further relevant references.

In the first pass, each abstract was reviewed by two independent investigators as to its suitability for inclusion in the study according to the above-defined selection criteria. Discrepancies were resolved by a third investigator. For abstracts that were deemed relevant during the first-level review, full-text articles were retrieved and reviewed.

In the second pass, the full-text version of each publication accepted in the first pass was reviewed by one investigator. All publications rejected at this stage were reviewed by a second investigator to confirm the rejection decision. For each excluded study, a specific reason for exclusion was provided and validated by a second investigator. A third investigator was consulted to resolve disagreements where necessary.

Data extraction was performed in the following steps:

3. Information from the full-text articles was extracted independently into data extraction forms by one investigator.
4. Data extraction was independently validated by a second investigator; a third investigator was consulted to resolve disagreements as necessary.

Publications reporting duplicate results were not extracted into the data extraction table.

Table 97 Inclusion and exclusion criteria for utilities SLR

PICOS-T	Inclusion criteria	Exclusion criteria
Population	Adult (age ≥18 years) patients with AdvSM which includes: • ASM • SM-AHN • MCL	• Patients with cutaneous mastocytosis, indolent or smoldering SM • Patients with disease other than AdvSM • Paediatric population • Healthy volunteers
Intervention	No limits	None
Comparators	No limits	None
Outcomes	All types of utilities data including health state utility data, disutilities, mapping from QoL (i.e., SF-36), etc.	Studies not reporting utility values
Study design	• Studies reporting utility data • Economic evaluations reporting patients' utility values • Systematic reviews*	• Letters, comments, and editorials • Case series or case reports

Language	No limits	None
Countries	No limits	None
Time limit	No limits	None

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; QoL = quality of life; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm
Note: * Bibliographies of systematic review articles were screened to ensure that all relevant studies are identified in the SLR.

Table 98 to Table 99 present the search hits in Medline, Embase, Cochrane databases, EBM, Econlit and ScHARRHUD.

Table 98 Search strategy for Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations

No.	Query	Results
#1	exp Mastocytosis/ or exp Mastocytosis, Systemic/	6,920
#2	exp Leukemia, Mast-Cell/	238
#3	("acute basophilic leukaemia" or "acute basophilic leukemia" or "basophilic leucemia" or "basophilic leukaemia" or "basophilic leukemia").tw.	1,744
#4	(mastocytosis or "systemic mastocytosis" or "mast cell leukemia" or "mast cell leukaemia").tw.	4,328
#5	1 or 2 or 3 or 4	9,806
#6	exp "Quality of Life"/	268,005
#7	exp "Value of Life"/	5,806
#8	exp Quality-Adjusted Life Years/	15.686
#9	exp "Surveys and Questionnaires"/	1,210,551
#10	exp Health Surveys/	623,621
#11	exp Health Status/	439,168
#12	exp Health Status Indicators/	342,186
#13	exp Self Report/	43,101
#14	exp Disability Evaluation/	56,363
#15	exp Models, Economic/	16,215
#16	exp Visual Analog Scale/	4,109
#17	(qol or (quality adj2 life) or (value adj2 (money or monetary)) or "life quality" or "life qualities" or utility or utilities or disutility or disutilities or "well being" or wellbeing or "quality adjusted" or "adjusted life" or "life year" or "life years" or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* or "short form*" or shortform* or shorform or shortfrom or sf* or euroqol* or "euro qol*" or eq5d or "eq 5d" or "eq5-d" or euroqual* or "euro qual*" or "eq-sdq" or eqsdq or hql or hrql or hqol or "h qol" or hrqol or "hr qol" or "health* year* equivalent*" or hye or hyes or (health adj3 (status or index)) or hui or hui1 or hui2 or "hui-2" or hui3 or "hui-3" or HSUV or HSUVs or rosser or (quality adj2 (wellbeing or "well being")) or qwb or (willingness adj2 pay) or wtp or (patient adj1 report*) or "standard gamble*" or (standard adj1 gamble*) or "time	1,207,151

No.	Query	Results
	trade off" or "time tradeoff" or timetradeoff or tto or "visual analog* scale" or vas or vas10 or "vas 10").mp.	
#18	(preference* adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).mp.	27,444
#19	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	2,316,991
#20	5 and 19	330
#21	("Case Reports" or Comment or Editorial or Letter).pt.	4,282,652
#22	exp Animals/ not (exp Animals/ and exp Humans/)	5,133,436
#23	21 or 22	9,305,441
#24	20 not 23	225

Table 99 Search strategy for Embase

No.	Query	Results
#1	exp systemic mastocytosis/ or exp mastocytosis/	8,221
#2	exp mast cell leukemia/	1,773
#3	("acute basophilic leukaemia" or "acute basophilic leukemia" or "basophilic leucemia" or "basophilic leukaemia" or "basophilic leukemia").tw.	1,886
#4	(mastocytosis or "systemic mastocytosis" or "mast cell leukemia" or "mast cell leukaemia").tw.	6,616
#5	1 or 2 or 3 or 4	11,092
#6	exp "quality of life"/	651,888
#7	exp socioeconomics/	1,320,780
#8	exp quality adjusted life year/	35,610
#9	exp questionnaire/	923,857
#10	exp health survey/	268,491
#11	exp health status/	311,063
#12	exp health status indicator/	41,260
#13	exp self report/	153,638
#14	exp Nottingham Health Profile/	651
#15	exp Sickness Impact Profile/	2,375
#16	exp disability assessment/	45,757
#17	exp economic model/	3,775
#18	exp visual analog scale/	123,630
#19	(qol or (quality adj2 life) or (value adj2 (money or monetary)) or "life quality" or "life qualities" or utility or utilities or disutility or disutilities or	1,885,464

No.	Query	Results
	"well being" or wellbeing or "quality adjusted" or "adjusted life" or "life year" or "life years" or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* or "short form*" or shortform* or shorform or shortfrom or sf* or euroqol* or "euro qol*" or eq5d or "eq 5d" or "eq5-d" or euroqual* or "euro qual*" or "eq-sdq" or eqsdq or hql or hrql or hqol or "h qol" or hrqol or "hr qol" or "health* year* equivalent*" or hye or hyes or (health adj3 (status or index)) or hui or hui1 or hui2 or "hui-2" or hui3 or "hui-3" or HSUV or HSUVs or rosser or (quality adj2 (wellbeing or "well being")) or qwb or (willingness adj2 pay) or wtp or (patient adj1 report*) or "standard gamble*" or (standard adj1 gamble*) or "time trade off" or "time tradeoff" or timetradeoff or tto or "visual analog* scale" or vas or vas10 or "vas 10").mp.	
#20	(preference* adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).mp.	36,867
#21	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	4,015,454
#22	5 and 21	754
#23	(Editorial or Letter or Note).pt.	3,036,644
#24	"case report*".ti.	404,619
#25	exp animal/ not (exp animal/ and exp human/)	5,196,261
#26	23 or 24 or 25	8,551,968
#27	22 not 26	658

Table 100 Search strategy for CCTR and CDSR

No.	Query	Results
#1	exp mastocytosis/ or exp mastocytosis, systemic/	50
#2	exp leukemia, mast-cell/	1
#3	("acute basophilic leukaemia" or "acute basophilic leukemia" or "basophilic leucemia" or "basophilic leukaemia" or "basophilic leukemia").tw.	3
#4	(mastocytosis or "systemic mastocytosis" or "mast cell leukemia" or "mast cell leukaemia").tw.	105
#5	1 or 2 or 3 or 4	120
#6	exp "Quality of Life"/	42,474
#7	exp "Value of Life"/	46
#8	exp Quality-Adjusted Life Years/	1,932
#9	exp "Surveys and Questionnaires"/	70,003
#10	exp Health Surveys/	36,756
#11	exp Health Status/	50,934
#12	exp Health Status Indicators/	26,864

No.	Query	Results
#13	exp Self Report/	3,982
#14	exp Disability Evaluation/	4,306
#15	exp Models, Economic/	571
#16	exp Visual Analog Scale/	5,167
#17	(qol or (quality adj2 life) or (value adj2 (money or monetary)) or "life quality" or "life qualities" or utility or utilities or disutility or disutilities or "well being" or wellbeing or "quality adjusted" or "adjusted life" or "life year" or "life years" or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* or "short form*" or shortform* or shorform or shortfrom or sf* or euroqol* or "euro qol*" or eq5d or "eq 5d" or "eq5-d" or euroqual* or "euro qual*" or "eq-sdq" or eqsdq or hql or hrql or hqol or "h qol" or hrqol or "hr qol" or "health* year* equivalent*" or hye or hyes or (health adj3 (status or index)) or hui or hui1 or hui2 or "hui-2" or hui3 or "hui-3" or HSUV or HSUVs or rosser or (quality adj2 (wellbeing or "well being")) or qwb or (willingness adj2 pay) or wtp or (patient adj1 report*) or "standard gamble*" or (standard adj1 gamble*) or "time trade off" or "time tradeoff" or timetradeoff or tto or "visual analog* scale" or vas or vas10 or "vas 10").mp.	282,745
#18	(preference* adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).mp.	4,571
#19	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	340,487
#20	5 and 19	39
#21	CDSR	3
#22	CCTR	36

Table 101 Search strategy for DARE, HTA and NHSEED

No.	Query	Results
#1	exp mastocytosis/ or exp mastocytosis, systemic/	1
#2	exp leukemia, mast-cell/	0
#3	("acute basophilic leukaemia" or "acute basophilic leukemia" or "basophilic leucemia" or "basophilic leukaemia" or "basophilic leukemia").tw.	0
#4	(mastocytosis or "systemic mastocytosis" or "mast cell leukemia" or "mast cell leukaemia").tw.	2
#5	1 or 2 or 3 or 4	2
#6	DARE	0
#7	HTA	2
#8	NHSEED	0

Table 102 Search strategy for Econlit

No.	Query	Results
#1	(mastocytosis or "systemic mastocytosis" or "mast cell leukemia" or "mast cell leukaemia").mp.	0
#2	("acute basophilic leukaemia" or "acute basophilic leukemia" or "basophilic leucemia" or "basophilic leukaemia" or "basophilic leukemia").mp.	0
#3	1 or 2	0

Table 103 Search strategy for ScHARRHUD

No.	Query	Results
#1	mastocytosis or mast cell	0

The PRISMA flow diagram of the HRQoL SLR is presented in Figure 42 below. Among the 924 publications initially identified and screened from multiple databases, 899 were excluded, leaving 25 publications for further evaluation of eligibility. However, upon assessment, all the studies were deemed ineligible for inclusion, resulting in none being included in the final SLR.

Table 104 provides an overview of the publications excluded with reasons.

Table 104 Overview of publications excluded at full-text screening from the health-related quality of life SLR

No.	Publication	Exclusion reason
#1	Maurer M, Siebenhaar F, Hartmann K, Reiter A, Radia D, Deininger MW et al. Avapritinib improves overall symptoms, skin lesions and quality of life in patients with advanced systemic mastocytosis in the pathfinder study..Oncol Res Treat. 2021 Sep;44(Suppl. 2). doi: 10.1111/all.15094	Wrong outcome (QoL data only)
#2	Maurer M, Siebenhaar F, Hartmann K, Reiter A, Radia D, Deininger MW et al. Avapritinib improves overall symptoms, skin lesions and quality of life in patients with advanced systemic mastocytosis in the PATHFINDER study. Allergy. 2021 Nov;76(Suppl. 110):22. doi: 10.1159/000518417	Wrong outcome (QoL data only)
#3	Taylor F, Kreil S, Reiter A, Horny H, Evans E, Mazar I et al. Cognitive debriefing of the advanced systemic mastocytosis symptom assessment form (ADVSM-SAF). Value Health. 2017;20(5):A335-336	Wrong study design
#4	Schmidt T J, Sellin J, Molderings G J, Conrad R, Mucke M. Correction: Health-related quality of life and health literacy in patients with systemic mastocytosis and mast cell activation syndrome. Orphanet J. Rare Dis. 2023; 18(1) doi: 10.1186/s13023-023-02645-1	Wrong study design
#5	Corrigendum to 'MPN-395: Efficacy and Safety of <=200 mg Avapritinib in Patients with Advanced Systemic	Wrong study design

	Mastocytosis: Pooled Results from the Phase 1 EXPLORER and Interim Phase 2 PATHFINDER Studies'. Clin Lymphoma Myeloma Leuk. 2022;22(4):276. doi: 10.1016/j.clml.2021.12.002	
#6	Moura DS, Sultan S, Georgin-Lavialle S, Pillet N, Montestruc F, Gineste P et al. Depression in patients with mastocytosis: prevalence, features and effects of masitinib therapy. PLoS One. 2011;6(10):e26375. doi: 10.1371/journal.pone.0026375	Wrong population
#7	Mazar I, Evans E. Taylor F. Patki A. Ojo O, Lamoureux R E et al. Development and content validity of the advanced systemic mastocytosis symptom assessment form (ADVSM-SAF). Value Health. 2016;19(7):A386.	Wrong study design
#8	Gotlib J, Kluin-Nelemans H C, George T I, Akin C, Sotlar K, Hermine O et al. Durable responses and improved quality of life with midostaurin (PKC412) in advanced Systemic Mastocytosis (SM): Updated stage 1 results of the global D2201 trial. Blood. 2013;122(21)	Wrong outcome (QoL data only)
#9	Gotlib J, Reiter A, Radia DH, Deininger MW, George TI, Panse J et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med. 2021;27(12):2192-2199. doi: 10.1038/s41591-021-01539-8	Wrong outcome (QoL data only)
#10	Schuster B, Ziehfreund S, Albrecht H, Spinner CD, Biedermann T, Peifer C et al. Happiness in dermatology: a holistic evaluation of the mental burden of skin diseases. J Eur Acad Dermatol Venereol. 2020;34(6):1331-1339. doi: 10.1111/jdv.16146	Wrong population
#11	Schmidt TJ, Sellin J, Molderings GJ, Conrad R, Mucke M. Health-related quality of life and health literacy in patients with systemic mastocytosis and mast cell activation syndrome. Orphanet J. Rare Dis.2022;17(1):295. doi: 10.1186/s13023-022-02439-x	Wrong population
#12	Oztop N, Demir S, Beyaz S, Unal D, Colakoglu B, Buyukozturk S et al. Impact of mental health on disease activity in mastocytosis during COVID-19 pandemic. Allergol Int. 2022;71(1):109-116. doi: 10.1016/j.alit.2021.08.002	Wrong study design
#13	Cariou C, Tremblay G, Dolph M, Brandt PS, Forsythe A. INCREMENTAL QUALITY-ADJUSTED SURVIVAL ANALYSIS WHEN NO HEAD TO HEAD DATA ARE AVAILABLE: A CASE STUDY OF MIDOSTAURIN (MIDO) VERSUS STANDARD OF CARE (SOC) IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS (ASM). Value Health. 2018;21(Supp 3):S473. doi: 10.1016/j.jval.2018.09.2791	Wrong outcome
#14	Pyatilova P, Siebenhaar F. Measuring Symptom Severity and Quality of Life in Mastocytosis. Immunol Allergy Clin North Am. 2023. doi: 10.1016/j.iac.2023.04.003	Review/Editorial
#15	Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K. Hermine O et al. Midostaurin (PKC412) demonstrates a high rate of durable responses in patients with advanced systemic mastocytosis: Results from the fully	Wrong outcome (QoL data only)

	accrued global phase 2 CPKC412D2201 Trial. Blood. 2014;124(21)	
#16	Hartmann K, Gotlib J, Akin C, Hermine O, Awan FT, Hexner E et al. Midostaurin improves quality of life and mediator-related symptoms in advanced systemic mastocytosis. J Allergy Clin Immunol. 2020;146(2):356-366.e4. doi: 10.1016/j.jaci.2020.03.044	Wrong outcome (QoL data only)
#17	Mesa RA, Sullivan EM, Dubinski D, Carroll B, Slee VM, Jennings SV et al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient Survey. Cancer. 2022;128(20):3691-3699. doi: 10.1002/cncr.34420	Wrong outcome
#18	Nowak A, Gibbs BF, Amon U. Pre-inpatient evaluation on quality and impact of care in systemic mastocytosis and the influence of hospital stay periods from the perspective of patients: a pilot study. J Dtsch Dermatol Ges. 2011;9(7):525-32. doi: 10.1111/j.1610-0387.2011.07638.x	Wrong population
#19	Taylor F, Shields A, Li S, Yip C, Padilla B, Green T et al. PRO143 PSYCHOMETRIC EVALUATION OF THE ADVANCED SYSTEMIC MASTOCYTOSIS SYMPTOM ASSESSMENT FORM (ADVSM-SAF) IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS. Value Health. 2019;22(Supp 3):S868. doi: 10.1016/j.jval.2019.09.2472	Wrong study design
#20	Vermeiren MR, Kranenburg LW, van Daele PLA, Gerth van Wijk R, Hermans MAW. Psychological functioning and quality of life in patients with mastocytosis: A cross-sectional study. Ann Allergy Asthma Immunol. 2020;124(4):373-378.e2. doi: 10.1016/j.anai.2019.12.020	Wrong outcome
#21	Siebenhaar F, Fortsch A, Krause K, Weller K, Metz M, Magerl M et al. Rupatadine improves quality of life in mastocytosis: a randomized, double-blind, placebo-controlled trial. Allergy. 2013;68(7):949-52. doi: 10.1111/all.12159	Wrong population
#22	Lee P, George TI, Shi H, Evans EK, Singh T, Boral AL et al. Systemic mastocytosis patient experience from mast cell connect, the first patient-reported registry for mastocytosis. Blood. 2016;128(22)	Wrong outcome (QoL data only)
#23	Gruson B, Lortholary O, Canioni D, Chandesris M-O, Lanternier F, Grosbois B et al. Thalidomide in advanced mastocytosis. results from an open-label, multicentric, phase II study. Blood. 2011;118(21)	Wrong outcome
#24	Gruson B, Lortholary O, Canioni D, Chandesris O, Lanternier F, Bruneau J et al. Thalidomide in systemic mastocytosis: results from an open-label, multicentre, phase II study. Br J Haematol. 2013;161(3):434-42. doi: 10.1111/bjh.12265	Wrong outcome
#25	Spolak-Bobryk N, Niedoszytko M, Jassem E, Chelminska M, Lange M, Majkowicz M et al. The role of the clinical and psychological symptoms of mastocytosis in the	Wrong population

patient's quality of life. Postepy Dermatol Alergol. 2022;39(4):688-696. doi: 10.5114/ada.2021.108433

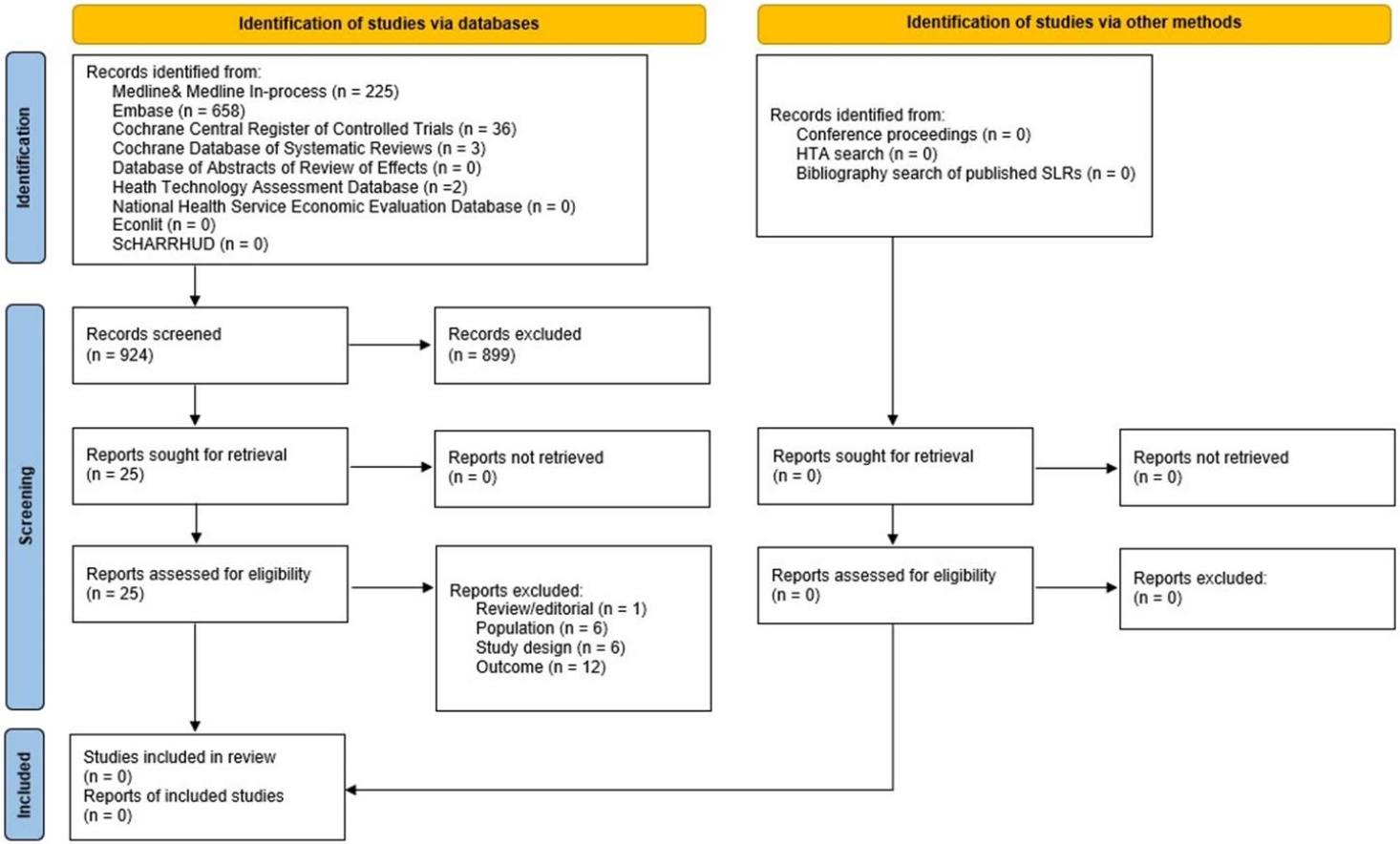

Figure 42 HRQoL PRISMA flow diagram

I.2 Quality assessment and generalizability of estimates

Not applicable as no studies were identified.

I.3 Unpublished data

N/A

I.4 TLR report – Mapping algorithm from QLQ-C30 to EQ-5D

I.4.1 Methods

The target literature research was conducted on PubMed and Embase using the strings "qlq c30" "eortc qlq c30", "eq 5d ", "systemic mastocytosis", "quality of life" "mapping" combined as reported in Table 33. The queries were conducted including all possible searching fields.

Table 105 - Strings for the target literature search

	Query	PubMed	Embase
#1	qlq c30	4,276	8,724
#2	eortc qlq c30	3,588	7,593
#3	qlq c30 OR eortc qlq c30	4,276	8,724
#4	eq 5d	8,714	16,509
#5	systemic mastocytosis	2,419	4,070
#6	quality of life	415,897	717,625
#7	mapping	432,522	312,100
#8	(qlq c30 OR eortc qlq c30) AND eq 5d	185	531
#9	(qlq c30 OR eortc qlq c30) AND systemic mastocytosis	0	2
#10	systemic mastocytosis AND quality of life	44	114
#11	(qlq c30 OR eortc qlq c30) AND mapping	54	90
#12	(qlq c30 OR eortc qlq c30) AND mapping AND systemic mastocytosis	0	0

As a first step we considered the results obtained with the string number 11 for title and abstract screening. The results obtained by the other combination of strings were screened only if the first selection didn't provide satisfactory results.

The studies retrieved via the search were screened against the inclusion and exclusion criteria reported in Table 111. Diseases that are like AdvSM in terms of main symptoms were identified through a preliminary research and used to define the inclusion criteria. The diseases that most commonly enter in differential diagnosis with AdvSM are: carcinoid syndrome, Zollinger-Ellison syndrome, lymphomas, other types of mast cell activation syndromes (95) (96). Furthermore, other diseases listed under the same ICD-11 group of AdvSM ("Neoplasms of hematopoietic or lymphoid tissues") and under the ICD-11 group "Chronic myeloproliferative disorders, malignant" were taken into consideration (97).

Table 106 - Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients 18 years and older	Patients younger than 18 years
Applied mapping methods/tools to convert EORTC QLQ-C30 into EQ-5D values	Any study not reporting any applied mapping tools/methods which allows to convert EORTC QLQ-C30 into EQ-5D values
Patients suffering from one of the following diseases: • neoplasms of hematopoietic or lymphoid tissues • Chronic myeloproliferative disorders, malignant • carcinoid syndrome • Zollinger-Ellison syndrome other mast-cell activation syndromes	Patients suffering from diseases not listed in the inclusion criteria
Language: English	Any study not published in the English language

Titles and abstracts were screened first and only if they appeared to meet inclusion criteria, the full text was reviewed. Identified studies meeting the inclusion criteria were reported in tabulated format with the following details:

- Authors, title, journal and year of publication
- Population characteristics (age, percentage of male patients and geographic area)
- Clinical condition
- Prognosis of patients
- Type of mapping method
- EQ-5D tariffs used

Studies not meeting the inclusion criteria were excluded and reported in a separate table listing the article authors and year of publication and the reason for exclusion.

Among all identified and included EORTC QLQ-C30 to EQ-5D mapping methods, two preferred tools were selected based on similarities with AdvSM in terms of population characteristics, clinical symptoms and prognosis of patients. The overall survival (OS) of AdvSM patients depends on the disease sub-group and is 28 months on average (14) (26). Diseases with a similar OS, like, for example, relapsed non-Hodgkin lymphomas (NHL), could represent an appropriate comparison in terms of survival time. All such aspects are

known factors to influence the QoL of patients and the way patients responds to QoL-questionnaires.

I.4.2 Results

After having excluded duplicates, a total of 98 publications were identified through string number 11 and selected for screening.

A first per-title selection excluded 68 publications:

- 47 were related to diseases not in scope;
- 18 were related to a topic different from developing a mapping algorithm;
- 3 mapped a scale different from either EORTC QLQ-C30 or EQ-5D.

A second per-abstract selection excluded 17 publications:

- 6 were related to diseases not in scope
- 1 was related to a topic different from developing a mapping algorithm
- 10 didn't report the algorithm's details needed to replicate the results

Finally, 7 further publications were excluded after full-text reading because the described algorithms were estimated on a dataset that didn't encompass any of the diseases in scope. The included publications are reported in Table 112.

Table 107 – Included populations

Author	Year	Population characteristics and clinical condition	Prognosis	Type of mapping	EQ-5D Tarif
I Proskorovsky et al. (98)	2014	N=154 patients Mean age: 66.4 % male: 0.63 Geographic area: UK and DE Disease: Multiple Myeloma (MM)	4-5 years	Multivariate linear regression	UK Tariff
R Huan Xu et al. (99)	2020	N=2,222 patients Mean age: 40.97 % male: 0.50 Geographic area: China Disease: Lymphoma with at least two lines of therapy	2 years	Multivariate linear regression	CN Tariff
MM Versteegh et al. (100)	2012	N=723 MM patients and 789 NHL patients Mean age in MM set: 54	4-5 years	Multivariate linear regression	NL Tariff

		Mean age in NHL set: 72 % male: n/a Geographic area: BE, NL Disease: MM and NHL			
R Crott et al. (101)	2013	N=172 MM patients and 132 NHL patients Mean age in MM set: 48 Mean age in NHL set: 72 Geographic area: NL % male: n/a Disease: MM and NHL	4-5 years	Multivariate linear regression	UK Tariff
T Young et al. (58)	2015	Considering only the MM dataset: N= 572 patients Mean age:71.79 % male: 0.5 Geographical area: US, CA Disease: MM	4-5 years	Multinomial logit model	No country specific tariff is applied (the model predicts the 3 levels of each item of EQ-5D-3L)
S Kharroubi et al. (102)	2015	N= 1839 patients Mean age: 64.75 % male: 0.59 Geographic area: UK, NZ, ZA Disease: MM	4-5 years	Different type of models	Not reported

Proskorovsky et al. (98) estimated and validated a multivariate linear regression model that predicts EQ-5D-3L associated utility values. They used a data-set of 154 patients suffering from Multiple Myeloma (MM) coming from UK and DE (103). More than half of the patients (57%) had no prior treatment. Data were gathered alongside a cohort study. UK Tariffs were used to derive the utility values. The authors used as independent variables the scores of EORTC QLQ-C30 questionnaire together with one item of the questionnaire extension specific for myeloma patients (EORTC QLQ-MY20 module). A 10-folds cross-validation (CV) was used to test the goodness of performance of the algorithm showing a root mean square error (RMSE) of 0.163 and an adjusted R2 of 0.7028.

Huan Xu et al. (99) estimated and validated 72 different algorithms based on data from an online cross-sectional study. The data-set included 2222 Chinese patients, suffering from

lymphoma and treated with at least two previous lines of therapy. The models were validated through a 10-folds CV. The best performing model identified by the authors is a linear regression model predicting the EQ-5D-5L associated utility values. To calculate the utility values, the authors used the CN Tariff, ranging from 0.932 to 0.968 for urban male and 0.912 to 0.971 for urban female residents (104). For the best performing model, a RMSE of 0.1282, a R2 of 0.6046 and a mean absolute error (MAE) of 0.088 were reported.

Versteegh et al. (100) estimated 4 linear regression models based on data from the HOVON study (105-107). The HOVON 24 (107) and HOVON 25 (105) studies are randomized clinical trials that measure the effectiveness of different treatments in MM patients with previously untreated MM and previously untreated NHL, respectively. The authors used a dataset of 723 patients suffering from MM to estimate the algorithms and a dataset of 789 patients suffering from NHL to externally validate them. The population included adult patients in Belgium and the Netherlands. Among all reported algorithms, the best performing was a linear regression model, which uses the individual scores of the EORTC QLQ-C30 items as independent dummy variables. The algorithm predicts the EQ-5D-3L associated utility values using the NL Tariff. The corresponding average R2 was 0.765 and the average adjusted RMSE and MAE were 0.1275 and 0.08625, respectively.

Moreover, the authors investigated the discriminatory ability of the predicted utilities between different disease severity levels. This was done by confronting the correlation between the observed EQ-5D scores and ECOG score with the correlation between the predicted EQ-5D score and ECOG score. The two correlation coefficients were identical (-0.19), thus confirming good discriminative power of the algorithm.

Crott et al. (101) used a data-set of patients suffering from breast-cancer to estimate a linear regression model to predict the EQ-5D-3L associated disutilities. Dutch tariffs were used. Data were obtained from the HOVON study (105) (106) . Despite the algorithm was initially developed in a breast-cancer dataset (108), the authors then externally validated the same algorithm on a data-set consisting of 172 patients suffering from MM and 132 patients suffering from NHL. For the MM dataset, the authors reported an adjusted R2 of 0.61, a RMSE of 0.16 and a MAE of 0.122. For the NHL dataset, the authors reported an adjusted R2 of 0.62, a RMSE of 0.19 and a MAE of 0.137.

Young et al. (58) estimated new algorithms based on data from the VISTA study(ClinicalTrials.gov number NCT00111319), a randomized clinical trial aimed at determining the efficacy of bortezomib in patients with previously untreated MM. The dataset includes 572 patients suffering from MM, 100 patients suffering from breast cancer and 99 patients suffering from lung cancer. The algorithms were validated through bootstrapping resampling and ANOVA was used to investigate the discriminatory ability between different levels of disease severity. The disease severity was defined based on the score of the item QLQ_29 of the EORTC QLQ-C30 questionnaire. The item 29 of the EORTC QLQ-C30, together with the item 30, measures the general QoL of the responder. It is scored on a scale from 1 (very poor) to 7 (excellent).

The best performing algorithm identified by the authors was a multinomial logit model, which predicted the probability of each observation to have a specific score within each item of the EQ-5D-3L. Thus, the algorithm allows to predict the level of each item of the EQ-5D-3L, which can then be used to estimate utility values using country specific EQ-5D tariffs of choice. For this algorithm, the authors reported a MAE of 0.134 and a Shrinkage coefficient of 1.179. A shrinkage coefficient of less than 1 (the typical value expected for a shrinkage coefficient) reflects an ‘‘overfitting’’ of the data.

Kharroubi et al. (102) estimated 4 different algorithms on a data-set of 1,839 patients suffering from MM and originating from the UK, New Zeeland (NZ) and South Africa (ZA). The data were obtained from the MIELOMA-IX trial (109), a multicenter, randomized phase III trial aimed at comparing the efficacy of two different chemotherapy regimens in newly diagnosed MM patients Two of the four algorithms were linear regression models that predicted EQ-5D-3L utilities including only complete observations. The other two algorithms considered also incomplete observations by computing missing values using a Bayesian imputation. Among the independent variables considered, two were items of the EORTC QLQ-MY20 extension module (module specific for MM).

In the complete-case analysis, the authors used 75% of the complete-case dataset (1658 patients) as estimation set and 25% as validation set. In the incomplete-case analysis, the full dataset was used for the estimation and the 25% of the complete-case set was used for the validation.

The authors didn’t identify a model performing better than the others, since the four models demonstrate very similar measures of performance.
Table 108 reports the performance measures reported for each of the mapping models meeting the inclusion criteria.

Table 108 - Performance measures of algorithms meetings inclusion criteria

Author		R2	R2_adjusted	RMSE	MAE	Shrinkage coefficient
I Proskorovsky et al. (98)			0.7028	0.163		
R Huan Xu et al. (99)		0.6046		0.1282	0.088	
MM Versteegh et al. (100)	Baseline	0.75		0.16	0.12	
	2nd treatment cycle	0.79		0.13	0.1	
	4th treatment cycle	0.79		0.12	0.08	
	6th treatment cycle	0.75		0.15	0.1	
	3-month follow-up	0.82		0.1	0.07	
	6-month follow-up	0.74		0.11	0.07	

	10-month follow-up	0.68		0.16	0.09	
	18-month follow-up	0.8		0.09	0.06	
	Average	0.765		0.1275	0.08625	
R Crott et al. (101)	MM set		0.61	0.16	0.122	
	NHL set		0.62	0.19	0.137	
T Young et al. (58)					0.134	1.179
S Kharroubi et al. (102)	OLS (Unequal Variances)	0.7003	0.6979	0.1861		
	OLS (Equal Variances)	0.7002	0.6979	0.1876		
	Bayesian Multiple Imputation	0.7028	0.7004	0.1861		
	Frequentist Multiple Imputation	0.7014	0.6992	0.1876		

I.4.3 Discussion

The goal of this target literature research was to identify the best suited algorithm to map EORTC QLQ-C30 scores into EQ-5D scores in patients suffering from AdvSM. Among all identified studies meeting inclusion criteria, several aspects were considered to judge the suitability of the mapping algorithm and select the preferred one. Firstly, the publications must report all the necessary data to replicate the results. All identified publications meeting the inclusion criteria described the algorithms in detail and reported all coefficients necessary to replicate the mapping. However, the algorithms presented by Proskorovsky et al. (98) and Kharroubi et al. (102) included some items of the EORTC QLQ-MY20 extension module, which is specific to MM. This is expected to limit the applicability of these algorithms on datasets that only include items of the EORTC QLQ-C30 core-questionnaire, as it is the case for AdvSM EORTC QLQ-C30 questionnaire.

Secondly, we compared the population used to estimate (or validate) the algorithms with AdvSM population in terms of key-aspect, ranging from the baseline characteristics, like the age and the geographic area, to other factors, like the disease type and the prognosis. Regarding the age, the mean age of the patients considered by Kharroubi et al. (102), by Young et al. (58) and by Proskorovsky et al. (98) is 64.75, 71.79 and 66.4 years, respectively. This is in line with the mean age of AdvSM patients, namely 65 years.

Crott et al. (101) and Versteegh et al. (100) both used data from the HOVON data-set (105-107). This included a group of MM patients and a group of NHL patients. While the latter had a mean age of 72 years, in line with the age of the AdvSM population, the former had a mean age of 54 years (Versteegh et al. (100)) and 48 years (Crott et al. (101)). This means that at least a part of the population considered by the two authors were younger than the AdvSM patients.

Finally, Huan Xu et al. (99) report a mean age of the included population of 40.97 years, considerably lower than the age of AdvSM patients.

Regarding the sex, the percentage of male patients ranges from 50% in Young et al. (58) and Huan Xu et al. (99) to 63% in Proskorovsky et al. (98). This is slightly higher than the

percentage of male patients affected on average by AdvSM, namely 45%. All studies meeting the inclusion criteria were estimated and validated on datasets including patients suffering from either lymphoma or MM. The only exception is the publication from Crott et al. (101) that externally validates an algorithm originally estimated on a data-set of patients suffering from breast cancer (108). Their publication is included in this review because the external validation is based on a dataset of patients suffering from either NHL or MM. Their algorithm showed an adjusted R2 below the average, but a RMSE and a MAE which do not differ substantially from those of the other algorithms originally developed in NHL or MM. Nevertheless, the authors stressed that coefficients of the algorithms changed substantially following re-estimation on the new external validation dataset versus the original dataset. Thus, this may suggest that the mapping algorithm developed by Crott et al. (101), 66 is more disease-specific than expected and should be used with great caution with external data-sets on diseases which are importantly different than those used to develop the algorithm (MM vs breast cancer). Finally, in terms of disease prognosis, the majority of the publications (58, 98, 100-102) included patients with a newly diagnosed MM/NHL, whose 4-5 year OS is higher than the 28 months average OS for AdvSM.

The only publication including patients whose prognosis is in line with the AdvSM is Huan Xu et al. (99). They included lymphoma patients with already two previous lines of therapy, whose OS is around 2 years and therefore like the AdvSM OS.

The third, but not least important, element considered was the QoL of patients in the datasets of the studies meeting the inclusion criteria and how this compared with QoL of patients with AdvSM included in the Pathfinder trial. All the included studies (Table 114) reported the EORTC QLQ-C30 scores of the patients in the respective estimation and/or validation datasets. reports the mean EORTC QLQ-C30 Global Health Score observed in the Pathfinder trial at baseline and the values reported for the population in each included study. As it can be observed, patients in the data-sets used by Young et al. (58) and Kharroubi et al. (102) seem to have most similar QoL to patients in the Pathfinder trial in terms of Average Global Health Score.

Table 109 - Reported EORTC QLQ-C30 Global Health Score

Publication	EORTC QLQ-C30 Average Global Health Score	Time point
Pathfinder	50.15	Average
I Proskorovsky et al. (98)	60.1	Cross-sectional
R Huan Xu et al. (99)	59.88	Cross-sectional
MM Versteegh et al. (100)	68.7	Pooled from multiple time-points
R Crott et al. (101)	68.7	Pooled from multiple time-points
T Young et al. (58)	48.48	Not reported
S Kharroubi et al. (102)	51.53	Pooled from multiple time-points

Fourthly, we took in consideration the geography of the Tariffs used to estimate the EQ-5D associated utilities. Proskorovsky et al. (98), Crott et al. (101) and Young et al. (58) all

used the UK Tariff, while Versteegh et al. (100) used the NL Tariff and Huan Xu et al. (99) the CN Tariff.

Finally, but not least, the performance measures of the included algorithm were taken into account to define best suitability for our objective. Mapping and model-fitting literature does not suggest a single criterion for use in selecting the best-fitting model, and the most appropriate measure may depend on the purpose of the mapping function. Among different validation techniques, an external validation should be preferred, since models with so many independent variables could potentially overfit and have a poor performance when used on an external dataset. Although showing good performance measures, the algorithms described by Proskorovsky et al. (98) was internally validated through CV. Also the algorithm described by Young et al. (58) is internally validated through bootstrapping resampling, but the Shrinkage coefficient associated with it demonstrates its good external validity. The algorithm described by Versteegh et al. (100) not only shows the best goodness of performance measures among all the algorithms in scope but is also validated on an external data-set.

I.4.4 Conclusions

Considering the elements described above, the algorithm described by Young et al. (58) would appear to be the best candidate to be used for mapping EORTC QLQ-C30 to EQ-5D in patients with AdvSM. The estimation population shows a EORTC QLQ-C30 Average Global Health Score very close to that of the Pathfinder population and a mean age similar to that of AdvSM patients. The average OS of the included population in the algorithm derivation dataset is higher by approx. 2 years than the average OS in AdvSM patients. However, this appears to be the case when comparing OS vs any of the other identified studies due to the severity of the disease in AdvSM and related very short survival (approx. 24 months). An important advantage of the mapping proposed by Young et al. (58) is that any country specific EQ-5D-3L tariff can be applied to the model. This makes it applicable to any geographic area. Finally, although the algorithm is not externally validated, the associated Shrinkage coefficient demonstrates its solid external validity.

Alternatively, in case the model should be adopted in the context of the Dutch market, the algorithm developed by Versteegh et al. (100) represents the best option. Indeed, this algorithm uses the NL Tariff to calculate the EQ-5D associated utilities and demonstrates the best performance measures among all identified.

The two other algorithms using the UK Tariffs are the ones described by Proskorovsky et al. (98) and Crott et al. (101). Unfortunately, the first one included an item of EORTC QLQ-MY20, which is specific for MM as independent variables. Thus, its use is limited to datasets of patients with MM and likely not to be applicable in AdvSM datasets. The second one should be considered with great caution, since it was originally estimated on a dataset of patient suffering from a disease not in scope and, according to the authors themselves, its external validity could be weak.

I.5 TLR report – HSUV after AdvSM progression

I.5.1 Methods

Six different research-strings were defined and used to conduct the search on PubMed (Table 110). The haematological neoplasms typically associated with AdvSM were considered as comparable conditions and therefore included in the search strings. A filter was adopted to search only papers published between 2011 to 2021.

Table 110 - TLR on QoL after AdvSM progression - Literature research strings

Query	Results
advanced systemic mastocytosis AND quality of life	7
myelodysplastic syndrome AND quality of life	288
chronic myelomonocytic leukaemia AND quality of life	21
myeloproliferative neoplasms AND quality of life	401
myeloproliferative neoplasms AND relapse AND quality of life	22
acute myeloid leukaemia AND quality of life	369

The table above reports the inclusion criteria. Only papers were included that reported both a pre-progression and a post-progression utility score. The ratio between the two scores were then calculated and applied to the PFS utility that was based on AdvSM data and obtained by the QoL analysis. Compared to applying an absolute utility value retrieved in the literature, this approach still considers the original AdvSM population and simply uses the identified ratio to correct the utility value parameter. This minimizes the bias related to the fact that proxy conditions were used instead of AdvSM.

Table 111 - TLR on QoL after AdvSM progression - inclusion criteria

Item	Definition
Type of studies	Studies reporting QoL measures estimated using QLQ-C30, EQ-5D questionnaire and reporting usable scores
Time Horizon	2011-2021
Geography	Western Europe and US
Conditions	Advanced systemic mastocytosis Myelodysplastic syndrome chronic myelomonocytic leukaemia myeloproliferative neoplasms Acute myeloid leukaemia
Progression status	Studies reporting both the pre-progression and the post-progression utility value
Study design	Primary research (review of other studies and cost-effectiveness analysis were not included)

Language	Language: English

The retrieved publications were filtered by means of their title, abstract and full text. A further selection was then applied based on the similarity between the described conditions and AdvSM. To this scope, the following characteristics were considered:

- overall survival;
- mean age at diagnosis;
- clinical symptoms;
- criteria used to define the progression state.

I.5.2 Results

The TLR identified 904 unique papers. Moreover, an additional paper was reviewed that, despite not being retrieved by the adopted search keys, was deemed as relevant (110). Thus, the total number of reviewed papers amounts to 905.
A first per-title selection excluded 801 publications:

- 445 addressed topics not in scope;
- 244 were not related to QoL measurements;
- 63 were classified as secondary research;
- 49 included a population not in scope.

A second per-abstract selection excluded 75 publications:

- 49 used a scale of measure not in scope;
- 19 didn't report the QoL of a progressive health state;
- 3 didn't report the data relevant for the present analysis;
- 2 were classified as secondary research;
- 1 addressed topics not in scope;
- 1 were not related to QoL measurements.

A final per-full-text selection excluded 17 publications:

- 8 didn't report the data relevant for the present analysis;
- 7 didn't report the QoL of a progressive health state;
- 6 didn't allow to compare between pre- and post-progression QoL;
- 1 was classified as secondary research;
- 1 addressed topics not in scope;

After the screening process, 6 papers were included in the results (Table 112).

Table 112 - Results of the TLR on QoL after AdvSM progression

Author	Country	Study design	Pathology	n. Patients	PF QoL	PD QoL	Tariff
Stein 2018 (11)	US	Cross-sectional	AML	300	Utility in CR: 0.87	Utility at relapse: 0.355	Discrete choice experiment in US

Joshi 2019 (8)	UK	Cross-sectional	AML	210	Utility in long term follow-up: 0.89	Utility in R/R patients: 0.51	TTO UK population
Leunis 2014 (9)	NL	Cross-sectional	AML	92	CR after 1L, non-relapsed: 0.83	Utility in R/R patients: 0.78	Not reported
Mamolo 2019 (10)	US	Cross-sectional	AML	439	0.74	0.73	US Tariff
Guest 2014	UK	Cross-sectional	CML	235	0.97 (TTO) 0.87 (SG)	0.9 (TTO) 0.72 (SG)	/
Szabo 2010 (110)	International	Cross-sectional	CML	357	0.89-0.68	0.79-0.22	US and UK Tariff

In line with the adopted inclusion criteria, all papers reported about haematological neoplasms that are potentially associated with AdvSM. Based on the conditions for similarity described at the end of section I.5.1, AML was considered the most appropriate proxy to inform the model, since it presents OS and clinical symptoms similar to AdvSM. As result, the papers from Stein (11), Joshi (8), Leunis (9) and Mamolo(10) were defined as preferred studies and used to calculate the ratio between progression free and progressive disease utility values. Two papers were based on Time Trade-Off (TTO) and Discrete Choice (DC) experiments conducted on the general (11) (8). The two other papers were based on utility scores measured directly on real patients (9) (10). To create an aggregate ratio both a plane average and a weighted average were used, with the number of patients in each paper defining the weights.

The resulting ratio between utility value in progression free and in progressed state is 0.728 when using the plane average and 0.721 when using the weighted average. These ratios lead to a utility value in the AdSM progression health state of 0.490 and 0.486, respectively.

I.6 TLR report - HSUV after post-HSCT

I.6.1 Methods

One research string was defined and used to conduct the search on PubMed (Table 113). A filter was adopted to search only papers published between 2011 to 2021.

Since the autologous HSCT is not considered a treatment option for AdvSM patients[4], only papers referring to or including allogeneic HSCT patients were taken into consideration. Moreover, only papers that reported observations at multiple timepoints were included,

since a single QoL value was considered inappropriate to inform the model. Papers using QLQ-C30 as scale of measure were included only if they reported both functioning and symptom items, since both are needed to map the QLQ-C30 to the EQ-5D.
The inclusion criteria are reported in Table 114. The retrieved publications were filtered by means of their title, abstract and full text.

Table 113 - TLR on QoL after HSCT - Literature research string

Query	Results
(hematopoietic stem cell transplantation[MeSH Terms]) AND (quality of life[MeSH Terms])	598

Table 114 - TLR on QoL after HSCT - inclusion criteria

Item	Definition
Type of studies	- Studies reporting QoL measures during and after allogeneic HSCT - QoL must be reported either as utility value, EQ-5D score or QLQ-C30 score - multiple timepoint observations
Time Horizon	2011-2021
Population	HSCT adults (>18 years old)
Geography	Western Europe and US
Conditions	Haematological diseases
Language	Language: English

I.6.2 Results

The TLR identified 598 unique publications.
A first per-title selection excluded 503 publications:

- 358 addressed a topic not in scope;
- 77 were not related to QoL measurements;
- 61 included a population not in scope;
- 5 were referred to autologous HSCT;
- 1 used a scale of measure not in scope;
- 1 addressed a condition not in scope.

A second per-abstract selection excluded 66 publications:

- 29 used a scale of measure not in scope;
- 21 included a population not in scope;
- 8 addressed a topic not in scope;
- 2 were not related to QoL measurements;

- 3 was referred to autologous HSCT;
- 1 addressed a condition not in scope;
- 1 didn't report the data relevant for the present analysis;
- 1 was a cross-sectional study.

A third per-full-text selection excluded 25 publications:

- 8 used a scale of measure not in scope;
- 3 were referred to autologous HSCT;
- 2 were cross-sectional studies;
- 9 didn't report the data relevant for the present analysis;
- 2 included a population not in scope;
- 1 was referred to a topic not in scope.

After the screening process, 4 papers were included in the results (Table 115).

Table 115 - Results of the TLR on QoL during and after HSCT

Author	Country	Study design	Pathology	n. Patients	Time horizon	Measurement scale
Frödin 2015	SE	Observational prospective	Haematological malignancies	94	12 timepoints from prior to the conditioning to 3 years after HSCT	EORTC-QLQC30
Andersson 2011	SE	Observational prospective	Several neoplasms	202	6 timepoints from before HSCT to 1 year after HSCT	EORTC-QLQC30
Grulke 2012 (7)	/	Review	Several neoplasms	2800	7 timepoints from before HSCT to more than 3 years after HSCT	EORTC-QLQC30

Abasaeed 2018	US	Observational prospective	Haematological malignancies	23	3 timepoints from before HSCT to 80 days after HSCT	EORTC-QLQC30

The publication from Grulke et al. (7) was selected to inform the model due to two reasons:

- the paper is structured as a systematic review and synthesizes data from 33 publications, which results in a sample size considerably larger than the other publications;
- the paper informed the model used in the NICE submission of Midostaurin in Acute Myeloid Leukemia (66). Since this was not criticized by the ERG, it is safe to assume that it represents the best option to source the QoL during and after HSCT.

The data reported by Grulke et al. were used as input in the mapping algorithm from Young et al. (58) to obtain the corresponding EQ-5D values. These were subsequently transformed in health utility values using the UK Tariff. Table 116 summarizes the utility values attributed to the cohort's portion treated with HSCT.

Table 116 – Health utility values attributed to the cohort's portion treated with HSCT

Health state	Associated utility value
Pre-HSCT	0.689
Hospitalization	0.620
Discharge	0.620
From 0 to 6 months after HSCT	0.760
From 7 after HSCT onwards	0.796

Appendix J. Literature searches for input to the health economic model

N/A

At the time of writing this submission dossier, a SLR on health economic models was not conducted in time to accommodate the new DMC submission template.

J.1 TLR report - HSCT efficacy in AdvSM patients

J.1.1 Methods

One research string was defined and used to conduct a search on PubMed (**Error! Reference source not found.**). A filter was adopted to include only papers published between 2011 and 2021.

A list of the adopted inclusion criteria is reported in Error! Reference source not found.. Only primary research addressing the OS and the PFS following HSCT in AdvSM patients were considered.

The retrieved articles were screened against the defined inclusion criteria by means of a three-phase procedure. First, the titles were screened, then the abstracts and lastly the full-texts.

Table 117 - TLR on HSCT efficacy in AdvSM patients – Literature research string

Query	Results
((advanced systemic mastocytosis) AND (hematopoietic stem cell transplantation[MeSH Terms]))	6

Table 118 - TLR on HSCT efficacy in AdvSM patients - inclusion criteria

Item	Definition
Type of studies	- Studies reporting OS after HSCT - Studies reporting PFS after HSCT
Time horizon	2011 - 2021
Population	HSCT adults (>18 years old)
Conditions	AdvSM
Study design	Primary research (review of other studies and cost-effectiveness analysis were not included)
Language	Language: English

J.1.2 Results

The research string identified 6 papers. The only primary research is represented by the retrospective study from Ustun et al. (70), which retrieved data from 57 AdvSM patients who were treated with HSCT. They found that the average OS at 1 and 3 years after HSCT is 62% and 57%, respectively. Among the MCL patients, these values decrease to 25% and 17%, whereas among the SM-AHN patients they increase to 78% and 74%. A similar pattern is shown by the PFS, which, among the AdvSM population, is 55% and 51% at 1 and 3 years after HSCT, respectively. Among the MCL patients these values decrease to 17% both at 1 and 3 years after HSCT, whereas, among the SM-AHN patient, they increase to 43%.

The other 5 selected papers were narrative reviews describing the different treatment options for AdvSM and were therefore excluded. However, all of them mentioned the HSCT as a potentially curative option and referred to the study of Ustun et al. (70) as the main supportive evidence for the use of HSCT in AdvSM.

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DMC: At the moment we do have a few questions that we hope you can help to address (hopefully in a week):

1. **Regarding the populations in EXPLORE and PATHFINDER that have received midostaurin or other treatments before study enrolment:**
    - **Were there any inclusion/excluding criteria stating whether the patients should be well treated or eg. have failed their existing therapy?**
        - *BPM: The inclusion and exclusion in both studies were designed to include AdvSM patients who were either treatment experienced or treatment naïve. Therefore, patients were not required to have failed existing therapy.*

          The first patient was enrolled in Part 1 of the phase 1 study, EXPLORER in March 2016 when cladribine and interferon alfa were considered the clinical standard of care and before the approval of midostaurin in 2017. For this reason, patients were enrolled irrespective of prior therapy and the majority of the patients enrolled were midostaurin-naïve.

          In PATHFINDER, patients receiving cytoreductive therapy within the preceding 12 weeks must have discontinued therapy due to disease progression, refractory disease, lack of efficacy, or intolerance. Cytoreductive was defined as: including midostaurin and other TKIs, hydroxyurea, azacitidine. For cladribine, interferon alpha, pegylated interferon and any antibody therapy (eg, brentuximab vedotin) less than 28 days before obtaining screening BM biopsy for this study were excluded from the study.
          For Germany only, patients must have been previously treated with midostaurin, unless use of midostaurin is medically contraindicated according to the summary of product characteristics. Midostaurin must have been discontinued due to disease progression, refractory disease, lack of efficacy, or intolerance.

    - **If not Do you have any information about the reasons why these patients have been taken off their existing therapy (lack of response, disease progression, toxicity etc.)**
        - *BPM: Please see the attached CSR which contains all data on prior therapies received from patients in EXPLORER and PATHFINDER (page 10 contains the pooled data).*

          Of the AdvSM RAC-RE patients who received 200mg of avapritinib who received prior therapy (n=58 [EXPLORER, n = 11; PATHFINDER, n = 47, population used in the submission), 46 patients (52.3%) previously received midostaurin and 10 patients (11.4%) previously received cladribine, along with various other cytoreductive therapies as detailed in the CSR.

          Of the patients who previously received midostaurin, 17 patients (37.0%) discontinued treatment due to PD/relapse and 13 patients (28.3%) discontinued due to toxicity.

          Of note, none of the patients who received midostaurin or any other prior antineoplastic therapy achieved complete response.

          As mentioned in the submission, not all patients will receive midostaurin in the 1L setting as can be seen from our data, hence why we have included additional scenario analyses in the CEM where midostaurin is used in 20% & 50% of patients in 2L.

2. **Tabel 44: adverse events use in the model**
   - **Avapritinib: We believe the table only reflect Grade ≥ 3 events. Therefore, the number of patients should be only 95 (not 126) patients?**
     - *BPM: We acknowledge that proportion of patients experiencing any grade > 3 event(s) should be changed to 95 and not 126 (see attached). This should be changed.*

Table 25: Summary of Adverse Events (Updated Safety Population)

Patients with any:	AdvSM		
	200 mg N=126 n (%)	≥ 300 mg N=50 n (%)	All N=193 n (%)
AE	126 (100.0)	50 (100.0)	193 (100.0)
SAE	48 (38.1)	37 (74.0)	97 (50.3)
Grade ≥ 3 AE	95 (75.4)	47 (94.0)	158 (81.9)
Related AE	120 (95.2)	50 (100.0)	186 (96.4)
Related SAE	15 (11.9)	16 (32.0)	34 (17.6)
Grade ≥ 3 related AE	75 (59.5)	37 (74.0)	123 (63.7)
AE leading to discontinuation from study drug	23 (18.3)	13 (26.0)	40 (20.7)
Related AE leading to discontinuation from study drug	9 (7.1)	8 (16.0)	19 (9.8)
AE leading to dose interruption	84 (66.7)	41 (82.0)	137 (71.0)
AE leading to dose reduction	91 (72.2)	46 (92.0)	141 (73.1)
AESI of intracranial bleeding	4 (3.2)	8 (16.0)	12 (6.2)
Related AESI of intracranial bleeding	3 (2.4)	6 (12.0)	9 (4.7)
Serious AESI of intracranial bleeding	4 (3.2)	6 (12.0)	10 (5.2)
AESI of intracranial bleeding leading to discontinuation from study drug	3 (2.4)	3 (6.0)	6 (3.1)
AESI of cognitive effects	24 (19.0)	28 (56.0)	59 (30.6)
Related AESI of cognitive effects	23 (18.3)	22 (44.0)	51 (26.4)
Serious AESI of cognitive effects	1 (< 1)	4 (8.0)	5 (2.6)
AESI of cognitive effects leading to discontinuation from study drug	2 (1.6)	2 (4.0)	5 (2.6)
AE leading to death	8 (6.3)	6 (12.0)	15 (7.8)

   - **Cladribine: Please explain were the numbers of 62 patients and the exact reference and section/page number for the number of patients with ≥ grade 3 AE, anaemia (34) and other hematological disorders (as we can find this information in the stated references)**
     - *BPM: In the Litak SmPC from EMA in section 4.8 "Undesirable effects" on page 6 (see attached). The AE data was taken from the summary of AE reported in the EMA submission in hairy cell leukaemia (**HCL**) which corresponds to the 62 patients. Regarding the hematological disorder question: For SoC cladribine, it is said in the Litak SmPC: "*severe thrombocytopenia (21% (58/279), HCL 50% (**31**/62)) and severe anaemia (14% (21/150), HCL 55% (**34**/62))" (see same attached screenshot from the SmPC)

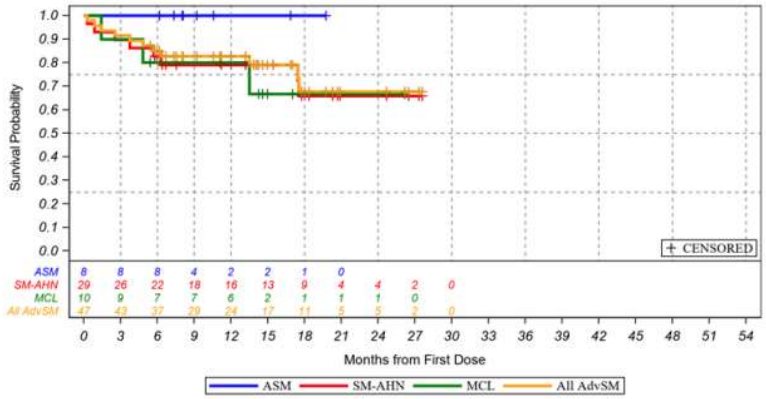
4.8 Undesirable effects

Summary of the safety profile

Very common adverse reactions observed during the three most relevant clinical trials with cladribine in 279 patients treated for various indications and in 62 patients with hairy cell leukaemia (HCL) were myelosuppression, especially severe neutropenia (41% (113/279), HCL 98% (61/62)), severe thrombocytopenia (21% (58/279), HCL 50% (31/62)) and severe anaemia (14% (21/150), HCL 55% (34/62)), as well as severe immunosuppression/lymphopenia (63% (176/279), HCL 95% (59/62)), infections (39% (110/279), HCL 58% (36/62)) and fever (up to 64%).

3. **The reason for no information on OS-rate for ASM at 24 months in PATHFINDER?**
   - *BPM: There were no ASM patients by 24 months, hence no results for the 24-month OS rate. Please refer to the KM plot below with the number at risk.*

Figure 4: Overall Survival in Patients with Prior Systemic Therapy (20 April 2021, BLU-285-2202, RE Population, 200 mg)



Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; MCL = mast cell leukemia; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm.

4. **We just wonder why the HR 95 % CI for PFS (0,42; 0,52) in the excel-model (see below) are different from the 95 % CI for OS (0,21; 1,09). Last part aligns with the information in the application.**
   - *BPM: As mentioned in the submission dossier, for the PFS two different scenarios were implemented in the model:*
     1. *The use of the ToT curve as proxy for the PFS curve.*
     2. *An alternative scenario: an assumption was made that the OS HR held also for the PFS and that the PH assumption was met. Therefore, the BAT PFS was calculated by applying the OS HR to the Avapritinib PFS curve.*

     Therefore, after having an additional look at this question, we acknowledge that if arguing that in for the scenario analysis where the BAT PFS is derived by applying the OS HR to the Avapritinib PFS, this should also include the confidence intervals. This should be changed.

5. **The ToT HR applied in the model was HR: 0.36 [0.22; 0.57] (p. 52 ref Reiter 2022). But the 95%CI in Reiter 2022. Is 0,36 (0,26; 0,51).**
   - *BPM: We acknowledge that the ToT HR value should match with the publication by Reiter et al 2022 (0.36 (CI: 0.26; 0.51). this change should be made in the sheet "Clinical data".*

Fra: Marcel Herold <MHerold@blueprintmedicines.com>
Sendt: Wednesday, March 6, 2024 2:16:58 PM
Til: Dorte Glintborg <DGL@medicinraadet.dk>
Cc: Olivier Ponet <OPonet@blueprintmedicines.com>; Hedwig Silies <HSilies@blueprintmedicines.com>
Emne: RE: Avapritinib: An urgent question regarding SM-AHN

Dear Dorte Glintborg,

Thank you very much for your E-Mail and sorry for my slight delay in responding.

In regards to your questions please find below the inclusion and exclusion criteria of the Pathfinder study. As you indicated we included SM-AHN patients in the study; please refer to the inclusion/exclusion criteria below for more insights.

In regard to the respective treatment for this subtype the exclusion criteria made clear that patients **should have stopped any cytoreductive therapy** (including TKIs, hydroxyurea, azacitidine), cladribine, interferon alpha, pegylated interferon and any antibody therapy before obtaining BM biopsy for the study. Furthermore the exclusion criteria states that **cytoredutive therapy may not be restarted during screening or while on study**.

In summary, patients in pathfinder **didn't receive treatment for their AHN in combination with Avapritinib** which is also reflected in the label: "AYVAKYT is indicated as **monotherapy** for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy."

If you have any other questions please let me know.

Thanks,
Marcel

5.2 Inclusion Criteria

Patients meeting the following criteria will be eligible for participation in the study:

1. Patients who are ≥ 18 years of age.
2. Patients must have 1 of the following diagnoses as confirmed by WHO diagnostic criteria (Appendix 4, Appendix 5, and Appendix 6). Before enrollment, the SSC must confirm the diagnosis of AdvSM (based on Central Pathology Laboratory assessment of BM).
    - ASM.
    - SM-AHN.
        - The AHN must be myeloid, with the following exceptions that are excluded:
            - AML.
            - Myelodysplastic syndrome that is very high- or high-risk, as defined by the International Prognostic Scoring System for Myelodysplastic Syndromes (Greenberg et al, 2012).
            - A myeloid AHN with ≥ 10% BM or PB blasts.
            - Philadelphia chromosome-positive malignancies.
        - Incidental indolent, low-grade lymphoid AHNs (eg, chronic lymphocytic leukemia) not requiring treatment are eligible.
    - MCL, including diagnoses with an AHN component.

5.3 Exclusion Criteria

Patients meeting any of the following criteria will not be eligible for participation in the study:

1. Patient has received prior treatment with avapritinib.
2. Patient has received any cytoreductive therapy (including midostaurin and other TKIs, hydroxyurea, azacitidine) or an investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy (eg, brentuximab vedotin) less than 28 days before obtaining screening BM biopsy for this study. If the patient has progressive disease and it is in the patient's best interest to enroll in the study rapidly, cytoreductive therapy may be discontinued 1 day before the screening BM biopsy with approval from the Medical Monitor. Cytoreductive therapy may not be restarted during Screening or while on study.

From: Dorte Glintborg <DGL@medicinraadet.dk>
Sent: Montag, 4. März 2024 08:14
To: Marcel Herold <MHerold@blueprintmedicines.com>
Subject: VS: Avapritinib: An urgent question regarding SM-AHN

[EXTERNAL SENDER]

Dear Marcel Herold

I received an autoreply from Hedwig Siles and therefore forward this request to you (please see the email below).

Best regards!

Dorte Glintborg

Fra: Dorte Glintborg
Sendt: 4. marts 2024 08:10
Til: Hedwig Silies <HSilies@blueprintmedicines.com>
Emne: Avapritinib: An urgent question regarding SM-AHN

Dear Hedwig

I have recieved a question from our expert committee that I hope you might be able to answer before we have our meeting in the expert committee.

Did the patients with SM-AHN either receive or require treatment for their SM or AHN alongside their treatment with avapritib?
(for example treatment for their CMML)

Will you be able to answer this question before Wednesday morning this week?

Best regards!

Dorte Glintborg

Questions from Medicinraadet regarding HTA for Avapritinib in advSM (March 7th 2024) and Blueprint Medicines's answers (March 13th 2024)

More specific characterization of SM AHN patients

Did the SM-AHN group only include patients where the mastocytosis-component are aggressive?
The inclusion criteria for PATHFINDER enrollment requested patients with criteria for advSM which includes aggressive SM (ASM), mast cell leukemia (MCL) or SM patients with associated haematologic neoplasm (SM-AHN). (s. chapter 5.2 SMPC below).

5.2 Inclusion Criteria

Patients meeting the following criteria will be eligible for participation in the study:

1. Patients who are ≥ 18 years of age.
2. Patients must have 1 of the following diagnoses as confirmed by WHO diagnostic criteria (Appendix 4, Appendix 5, and Appendix 6). Before enrollment, the SSC must confirm the diagnosis of AdvSM (based on Central Pathology Laboratory assessment of BM).
   - ASM.
   - SM-AHN.
     - The AHN must be myeloid, with the following exceptions that are excluded:
       - AML.
       - Myelodysplastic syndrome that is very high- or high-risk, as defined by the International Prognostic Scoring System for Myelodysplastic Syndromes (Greenberg et al, 2012).
       - A myeloid AHN with ≥ 10% BM or PB blasts.
       - Philadelphia chromosome-positive malignancies.
     - Incidental indolent, low-grade lymphoid AHNs (eg, chronic lymphocytic leukemia) not requiring treatment are eligible.
   - MCL, including diagnoses with an AHN component.

Nevertheless, for response evaluation in the PATHFINDER patients with advSM required to have at least one evaluable C-finding, therefore by WHO criteria all patients did not have non-advanced SM as SM component (exclusion of SM subtypes as BMM, ISM or SSM) but (adv)SM.
According to WHO classification SM-AHN diagnosis is classified as an advSM disease regardless of type of SM present and require TKI/cytoreductive treatment.

In other words: Did the SM-AHN group also include patients with bone marrow mastocytosis, indolent SM or smoldering SM (non-aggressive SM-part)?
No, the SM-AHN patient group did not include patients with BMM, ISM or SSM (non-advanced SM patients).

If no to the last question: How did the studie-enrollement ensure that the patient with non-aggressive SM-part was not included in the study?
As mentioned above, for response evaluation in the PATHFINDER patients with advSM required to have at least one evaluable C-finding, therefore by WHO criteria all patients did not have non-advanced SM as SM component (exclusion of SM subtypes as BMM, ISM or SSM) but (adv)SM.

In addition, the AdvSM diagnosis of patients enrolled in the Pathfinder study was confirmed by the study steering committee, based on central pathology laboratory assessment, see criteria 2 below.

More specific information about the EMA patient population and the RAC-RE population

The expert committee also had important questions regarding the difference between the 79 patients that we believe fulfills the EMA-indication (200 mg, 2L+) and the 47 patients RAC-RE-population. What did exactly happen for the 32 patients?

The 79 patients are based on a pooled analysis of PATHFINDER and EXPLORER. **EMA-label population** included **67 patients** of the 107 patients enrolled in the PATHFINDER study that had at least one prior systemic therapy and were treated at a starting dose of 200 mg orally once daily (see SMPC).
RAC-RE population: As stated in SmPC, the response-evaluable population according to modified IWG-MRT-ECNM criteria as adjudicated by a central committee (the **R**esponse **a**ssessment **c**ommittee) includes **47 patients** with a diagnosis of AdvSM,

- who had received at least 1 dose of avapritinib,
- had at least 2 post-baseline bone marrow assessments and
- had been on study for at least 24 weeks or had an end of study visit.

The objective responses in the Pathfinder trial were evaluated using the mIWG-MRT-ECNM criteria. According to these criteria patients need to have an evaluable, e.g. quantifiable C-finding, attributed to SM, meeting the defined criteria, to be able to be evaluated for objective response. Steering committee, consisting of key experts in SM field, were evaluating each patient eligibility. At the data cut 47 patients (RAC-RE) fulfilled above criteria for response evaluation and had enough follow up to confirm the response, as requirement of mIWG criteria. Compared to previous criteria modified IWG criteria had more strict definition of C-finding to enable more objective response evaluation. Therefore, some C-findings e.g weight loss and large osteolytic lesions were defined as non -measurable by mIWG criteria.

What are the reasons that this very big share of the patient population was not adjudicated response-evaluable by the 'response assessment committee'?

The non-evaluable cohort of **20 patients** included patients without evaluable C-finding at baseline, mainly due to evaluable C-finding that resolved with prior cytoreductive treatment or C-finding which was non evaluable by modified criteria.

How many of the 32 patients discontinued the treatment with avapritinib and what was the reason for that?

All non-evaluable patients were included in the analysis of OS as part of safety population. The median OS was not reached in in RAC-RE population, as well as in the overall safety population (n=67), including all 20 non-evaluable patients.

What was the distribution of ASM, SM-AHN and MCL in the 32 patients? How many had earlier received midostaurin or cladribin?

There is no analysis currently available to answer these questions. Please be aware that midostaurin was not available during the start of the EXPLORER study. BPM can ask Biostats to analyze the distribution of the 20 non-evaluable patients in ASM, SM-AHN and MCL but this will take at least two weeks. Please let us know whether this is useful within the current timeframe with DMC HTA assessment.

Table 99.1.1.2.2
Disease Diagnosis
RE Population
Study: BLU-285-2101

	<200 mg (N=8)	200 mg (N=16)	300 mg (N=27)	200+300 mg (N=43)	All Doses (N=56)
ASM	0	1 (6.3)	3 (11.1)	4 (9.3)	4 (7.1)
SM-AHN	7 (87.5)	9 (56.3)	19 (70.4)	28 (65.1)	39 (69.6)
CEL	0	0	0	0	0
CMML	4 (50.0)	4 (25.0)	11 (40.7)	15 (34.9)	20 (35.7)
MPN	0	0	0	0	0
MDS	1 (12.5)	1 (6.3)	2 (7.4)	3 (7.0)	5 (8.9)
MDS/MPN-U	2 (25.0)	3 (18.8)	6 (22.2)	9 (20.9)	13 (23.2)
OTHER	0	1 (6.3)	0	1 (2.3)	1 (1.8)
MCL	1 (12.5)	6 (37.5)	5 (18.5)	11 (25.6)	13 (23.2)
CEL	0	0	0	0	0
CMML	0	0	0	0	0
MPN	0	0	0	0	0
MDS	0	0	0	0	0
MDS/MPN-U	0	0	0	0	0
OTHER	0	0	0	0	0

Notes: Based on RAC/SSC disease diagnosis assessment
Notes: Abbreviations: ASM= Aggressive Systemic Mastocytosis, SM-AHN= Systemic Mastocytosis with an Associated Hematologic Neoplasm of non-mast-cell Lineage, MCL= Mast Cell Leukemia, CEL= Chronic Eosinophilic Leukemia, CMML= Chronic Myelomonocytic Leukemia, MPN= Myeloproliferative Neoplasms, MPN-U= Myeloproliferative Neoplasms Unclassifiable, MDS= Myelodysplastic Syndrome

Table 99.1.1.2.2
Disease Diagnosis
RE Population
Study: BLU-285-2202

	200 mg (N=72)	All Doses (N=74)
ASM	12 (16.7)	12 (16.2)
SM-AHN	48 (66.7)	50 (67.6)
CEL	5 (6.9)	5 (6.8)
CMML	25 (34.7)	25 (33.8)
MPN	1 (1.4)	1 (1.4)
MDS	5 (6.9)	5 (6.8)
MDS/MPN-U	9 (12.5)	11 (14.9)
OTHER	3 (4.2)	3 (4.1)
MCL	12 (16.7)	12 (16.2)
CEL	0	0
CMML	1 (1.4)	1 (1.4)
MPN	2 (2.8)	2 (2.7)
MDS	0	0
MDS/MPN-U	1 (1.4)	1 (1.4)
OTHER	0	0

Notes: Based on RAC/SSC disease diagnosis assessment
Notes: Abbreviations: ASM= Aggressive Systemic Mastocytosis, SM-AHN= Systemic Mastocytosis with an Associated Hematologic Neoplasm of non-mast-cell Lineage, MCL= Mast Cell Leukemia, CEL= Chronic Eosinophilic Leukemia, CMML= Chronic Myelomonocytic Leukemia, MPN= Myeloproliferative Neoplasms, MPN-U= Myeloproliferative Neoplasms Unclassifiable, MDS= Myelodysplastic Syndrome

Table 99.1.1.2.2
Disease Diagnosis
RE Population
Study: BLU-285-2101 and BLU-285-2202

	<200 mg (N=10)	200 mg (N=88)	300 mg (N=27)	200+300 mg (N=115)	All Doses (N=130)
ASM	0	13 (14.8)	3 (11.1)	16 (13.9)	16 (12.3)
SM-AHN	9 (90.0)	57 (64.8)	19 (70.4)	76 (66.1)	89 (68.5)
CEL	0	5 (5.7)	0	5 (4.3)	5 (3.8)
CMML	4 (40.0)	29 (33.0)	11 (40.7)	40 (34.8)	45 (34.6)
MPN	0	1 (1.1)	0	1 (0.9)	1 (0.8)
MDS	1 (10.0)	6 (6.8)	2 (7.4)	8 (7.0)	10 (7.7)
MDS/MPN-U	4 (40.0)	12 (13.6)	6 (22.2)	18 (15.7)	24 (18.5)
OTHER	0	4 (4.5)	0	4 (3.5)	4 (3.1)
MCL	1 (10.0)	18 (20.5)	5 (18.5)	23 (20.0)	25 (19.2)
CEL	0	0	0	0	0
CMML	0	1 (1.1)	0	1 (0.9)	1 (0.8)
MPN	0	2 (2.3)	0	2 (1.7)	2 (1.5)
MDS	0	0	0	0	0
MDS/MPN-U	0	1 (1.1)	0	1 (0.9)	1 (0.8)
OTHER	0	0	0	0	0

Notes: Based on RAC/SSC disease diagnosis assessment
Notes: Abbreviations: ASM= Aggressive Systemic Mastocytosis, SM-AHN= Systemic Mastocytosis with an Associated Hematologic Neoplasm of non-mast-cell Lineage, MCL= Mast Cell Leukemia, CEL= Chronic Eosinophilic Leukemia, CMML= Chronic Myelomonocytic Leukemia, MPN= Myeloproliferative Neoplasms, MPN-U= Myeloproliferative Neoplasms Unclassifiable, MDS= Myelodysplastic Syndrome

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Study 2101

	Starting Dose (QD)				
	<200 mg (N=8) n (%)	200 mg (N=16) n (%)	300 mg (N=27) n (%)	<=200 mg (N=24) n (%)	All Doses (N=56) n (%)
Prior Antineoplastic Therapy (n (%))					
No	5 (62.5)	5 (31.3)	11 (40.7)	10 (41.7)	22 (39.3)
Yes	3 (37.5)	11 (68.8)	16 (59.3)	14 (58.3)	34 (60.7)
Midostaurin	1 (12.5)	9 (56.3)	9 (33.3)	10 (41.7)	19 (33.9)
Cladribine	0	2 (12.5)	4 (14.8)	2 (8.3)	8 (14.3)
Imatinib	0	2 (12.5)	2 (7.4)	2 (8.3)	4 (7.1)
Hydroxycarbamide	0	0	3 (11.1)	0	3 (5.4)
Interferon	0	2 (12.5)	1 (3.7)	2 (8.3)	3 (5.4)
Azacitidine	0	0	0	0	2 (3.6)
Brentuximab Vedotin	0	0	2 (7.4)	0	2 (3.6)
Ibrutinib	1 (12.5)	0	0	1 (4.2)	2 (3.6)
Investigational Antineoplastic Drugs	0	1 (6.3)	1 (3.7)	1 (4.2)	2 (3.6)
Ruxolitinib	0	0	1 (3.7)	0	2 (3.6)
Chlorambucil	0	0	1 (3.7)	0	1 (1.8)
Dasatinib	0	1 (6.3)	0	1 (4.2)	1 (1.8)
Decitabine	0	0	1 (3.7)	0	1 (1.8)
Nilotinib	0	1 (6.3)	0	1 (4.2)	1 (1.8)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Study 2101

	Starting Dose (QD)				
	<200 mg (N=8) n (%)	200 mg (N=16) n (%)	300 mg (N=27) n (%)	<=200 mg (N=24) n (%)	All Doses (N=56) n (%)
Prior Antineoplastic Therapy (n (%)) (Cnt..)					
Obinutuzumab	0	0	1 (3.7)	0	1 (1.8)
Peginterferon Alfa-2a	1 (12.5)	0	0	1 (4.2)	1 (1.8)
Rituximab	0	0	1 (3.7)	0	1 (1.8)
Best Response to Any Prior Antineoplastic Therapy					
CR	0	0	0	0	0
PR	0	1 (6.3)	1 (3.7)	1 (4.2)	2 (3.6)
CI	1 (12.5)	1 (6.3)	1 (3.7)	2 (8.3)	4 (7.1)
SI	0	0	2 (7.4)	0	2 (3.6)
SD	1 (12.5)	5 (31.3)	9 (33.3)	6 (25.0)	16 (28.6)
PD	0	1 (6.3)	2 (7.4)	1 (4.2)	4 (7.1)
NA	0	0	1 (3.7)	0	2 (3.6)
NE	1 (12.5)	3 (18.8)	0	4 (16.7)	4 (7.1)
Prior Tyrosine Kinase (TKI) Therapy (n (%))					
Yes	3 (37.5)	11 (68.8)	14 (51.9)	14 (58.3)	32 (57.1)
No	5 (62.5)	5 (31.3)	13 (48.1)	10 (41.7)	24 (42.9)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Study 2101

	Starting Dose (QD)				
	<200 mg (N=8) n (%)	200 mg (N=16) n (%)	300 mg (N=27) n (%)	<=200 mg (N=24) n (%)	All Doses (N=56) n (%)
Prior Radiation Therapy (n (%))					
Yes	0	0	0	0	0
No	8 (100)	16 (100)	27 (100)	24 (100)	56 (100)
Prior Cancer Related Surgery-Procedures (n (%))					
Yes	8 (100)	13 (81.3)	26 (96.3)	21 (87.5)	51 (91.1)
No	0	3 (18.8)	1 (3.7)	3 (12.5)	5 (8.9)
Prior Midostaurin (n (%))					
Yes	1 (12.5)	9 (56.3)	9 (33.3)	10 (41.7)	19 (33.9)
No	7 (87.5)	7 (43.8)	18 (66.7)	14 (58.3)	37 (66.1)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Study 2101

	Starting Dose (QD)				
	<200 mg (N=8) n (%)	200 mg (N=16) n (%)	300 mg (N=27) n (%)	<=200 mg (N=24) n (%)	All Doses (N=56) n (%)
Best Response to Prior Midostaurin [1] (n (%))					
CR	0	0	0	0	0
PR	0	1 (11.1)	1 (11.1)	1 (10.0)	2 (10.5)
CI	1 (100)	0	1 (11.1)	1 (10.0)	2 (10.5)
SI	0	0	2 (22.2)	0	2 (10.5)
SD	0	4 (44.4)	2 (22.2)	4 (40.0)	6 (31.6)
PD	0	2 (22.2)	1 (11.1)	2 (20.0)	3 (15.8)
NA	0	0	2 (22.2)	0	2 (10.5)
NE	0	2 (22.2)	0	2 (20.0)	2 (10.5)
Reason for Discontinuation of Prior Midostaurin [1] (n (%))					
Completed Scheduled Cycles	0	0	0	0	0
PD/Relapse	1 (100)	2 (22.2)	5 (55.6)	3 (30.0)	8 (42.1)
Refractory	0	0	0	0	0
Toxicity	0	4 (44.4)	2 (22.2)	4 (40.0)	6 (31.6)
Other	0	2 (22.2)	2 (22.2)	2 (20.0)	4 (21.1)
Unknown	0	1 (11.1)	0	1 (10.0)	1 (5.3)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Study 2101

	Starting Dose (QD)				
	<200 mg (N=8) n (%)	200 mg (N=16) n (%)	300 mg (N=27) n (%)	<=200 mg (N=24) n (%)	All Doses (N=56) n (%)
Duration of Treatment on Midostaurin (months)					
n	1	9	9	10	19
Mean (StdDev)	10.2 (-)	8.2 (4.98)	14.6 (17.23)	8.4 (4.73)	11.4 (12.38)
Median	10.2	8.0	6.2	8.4	8.0
Min, Max	10, 10	2, 17	5, 58	2, 17	2, 58

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Study 2202

	Starting Dose (QD) 200 mg (N=72) n (%)	All Doses (N=74) n (%)
Prior Antineoplastic Therapy (n (%))		
No	25 (34.7)	25 (33.8)
Yes	47 (65.3)	49 (66.2)
Midostaurin	37 (51.4)	39 (52.7)
Cladribine	8 (11.1)	10 (13.5)
Interferon Alfa	7 (9.7)	7 (9.5)
Hydroxycarbamide	5 (6.9)	6 (8.1)
Imatinib	5 (6.9)	5 (6.8)
Dasatinib	4 (5.6)	4 (5.4)
Azacitidine	3 (4.2)	3 (4.1)
Investigational Antineoplastic Drugs	2 (2.8)	2 (2.7)
Decitabine	1 (1.4)	1 (1.4)
Nilotinib	1 (1.4)	1 (1.4)
Peginterferon Alfa-2a	1 (1.4)	1 (1.4)
Protein Kinase Inhibitors	1 (1.4)	1 (1.4)
Purine Analogues	1 (1.4)	1 (1.4)
Stem Cells Nos	1 (1.4)	1 (1.4)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Study 2202

	Starting Dose (QD) 200 mg (N=72) n (%)	All Doses (N=74) n (%)
Prior Antineoplastic Therapy (n (%)) (Cnt..)		
Thalidomide	1 (1.4)	1 (1.4)
Best Response to Any Prior Antineoplastic Therapy		
CR	0	0
PR	8 (11.1)	10 (13.5)
CI	10 (13.9)	10 (13.5)
SD	15 (20.8)	15 (20.3)
PD	7 (9.7)	7 (9.5)
Other	6 (8.3)	6 (8.1)
Missing	1 (1.4)	1 (1.4)
Prior Tyrosine Kinase (TKI) Therapy (n (%))		
Yes	44 (61.1)	46 (62.2)
No	28 (38.9)	28 (37.8)
Prior Radiation Therapy (n (%))		
Yes	0	0
No	72 (100)	74 (100)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Study 2202

	Starting Dose (QD) 200 mg (N=72) n (%)	All Doses (N=74) n (%)
Prior Midostaurin (n (%))		
Yes	37 (51.4)	39 (52.7)
No	35 (48.6)	35 (47.3)
Best Response to Prior Midostaurin [1] (n (%))		
CR	0	0
PR	5 (13.5)	6 (15.4)
CI	8 (21.6)	8 (20.5)
SD	10 (27.0)	10 (25.6)
PD	5 (13.5)	6 (15.4)
Other	8 (21.6)	8 (20.5)
Missing	1 (2.7)	1 (2.6)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Study 2202

	Starting Dose (QD) 200 mg (N=72) n (%)	All Doses (N=74) n (%)
Reason for Discontinuation of Prior Midostaurin [1] (n (%))		
Completed Scheduled Cycles	0	0
PD/Relapse	15 (40.5)	17 (43.6)
Refractory	2 (5.4)	2 (5.1)
Other	11 (29.7)	11 (28.2)
Toxicity	9 (24.3)	9 (23.1)
Unknown	2 (5.4)	2 (5.1)
Duration of Treatment on Midostaurin (months)		
n	43	45
Mean (StdDev)	16.8 (22.41)	18.9 (27.18)
Median	9.0	9.0
Min, Max	0, 122	0, 124

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Studies 2101 and 2202

	Starting Dose (QD)				
	<200 mg (N=10) n (%)	200 mg (N=88) n (%)	300 mg (N=27) n (%)	<=200 mg (N=98) n (%)	All Doses (N=130) n (%)
Prior Antineoplastic Therapy (n (%))					
No	5 (50.0)	30 (34.1)	11 (40.7)	35 (35.7)	47 (36.2)
Yes	5 (50.0)	58 (65.9)	16 (59.3)	63 (64.3)	83 (63.8)
Midostaurin	3 (30.0)	46 (52.3)	9 (33.3)	49 (50.0)	58 (44.6)
Cladribine	2 (20.0)	10 (11.4)	4 (14.8)	12 (12.2)	18 (13.8)
Hydroxycarbamide	1 (10.0)	5 (5.7)	3 (11.1)	6 (6.1)	9 (6.9)
Imatinib	0	7 (8.0)	2 (7.4)	7 (7.1)	9 (6.9)
Interferon Alfa	0	7 (8.0)	0	7 (7.1)	7 (5.4)
Azacitidine	0	3 (3.4)	0	3 (3.1)	5 (3.8)
Dasatinib	0	5 (5.7)	0	5 (5.1)	5 (3.8)
Investigational Antineoplastic Drugs	0	3 (3.4)	1 (3.7)	3 (3.1)	4 (3.1)
Interferon	0	2 (2.3)	1 (3.7)	2 (2.0)	3 (2.3)
Brentuximab Vedotin	0	0	2 (7.4)	0	2 (1.5)
Decitabine	0	1 (1.1)	1 (3.7)	1 (1.0)	2 (1.5)
Ibrutinib	1 (10.0)	0	0	1 (1.0)	2 (1.5)
Nilotinib	0	2 (2.3)	0	2 (2.0)	2 (1.5)
Peginterferon Alfa-2a	1 (10.0)	1 (1.1)	0	2 (2.0)	2 (1.5)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Studies 2101 and 2202

	Starting Dose (QD)				
	<200 mg (N=10) n (%)	200 mg (N=88) n (%)	300 mg (N=27) n (%)	<=200 mg (N=98) n (%)	All Doses (N=130) n (%)
Prior Antineoplastic Therapy (n (%)) (Cnt..)					
Ruxolitinib	0	0	1 (3.7)	0	2 (1.5)
Chlorambucil	0	0	1 (3.7)	0	1 (<1)
Obinutuzumab	0	0	1 (3.7)	0	1 (<1)
Protein Kinase Inhibitors	0	1 (1.1)	0	1 (1.0)	1 (<1)
Purine Analogues	0	1 (1.1)	0	1 (1.0)	1 (<1)
Rituximab	0	0	1 (3.7)	0	1 (<1)
Stem Cells Nos	0	1 (1.1)	0	1 (1.0)	1 (<1)
Thalidomide	0	1 (1.1)	0	1 (1.0)	1 (<1)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Studies 2101 and 2202

	Starting Dose (QD)				
	<200 mg (N=10) n (%)	200 mg (N=88) n (%)	300 mg (N=27) n (%)	<=200 mg (N=98) n (%)	All Doses (N=130) n (%)
Best Response to Any Prior Antineoplastic Therapy					
CR	0	0	0	0	0
PR	2 (20.0)	9 (10.2)	1 (3.7)	11 (11.2)	12 (9.2)
CI	1 (10.0)	11 (12.5)	1 (3.7)	12 (12.2)	14 (10.8)
SI	0	0	2 (7.4)	0	2 (1.5)
SD	1 (10.0)	20 (22.7)	9 (33.3)	21 (21.4)	31 (23.8)
PD	0	8 (9.1)	2 (7.4)	8 (8.2)	11 (8.5)
NA	0	0	1 (3.7)	0	2 (1.5)
NE	1 (10.0)	3 (3.4)	0	4 (4.1)	4 (3.1)
Other	0	6 (6.8)	0	6 (6.1)	6 (4.6)
Missing	0	1 (1.1)	0	1 (1.0)	1 (<1)
Prior Tyrosine Kinase (TKI) Therapy (n (%))					
Yes	5 (50.0)	55 (62.5)	14 (51.9)	60 (61.2)	78 (60.0)
No	5 (50.0)	33 (37.5)	13 (48.1)	38 (38.8)	52 (40.0)
Prior Radiation Therapy (n (%))					
Yes	0	0	0	0	0
No	10 (100)	88 (100)	27 (100)	98 (100)	130 (100)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Studies 2101 and 2202

	Starting Dose (QD)				
	<200 mg (N=10) n (%)	200 mg (N=88) n (%)	300 mg (N=27) n (%)	<=200 mg (N=98) n (%)	All Doses (N=130) n (%)
Prior Cancer Related Surgery-Procedures (n (%))					
Yes	8 (80.0)	13 (14.8)	26 (96.3)	21 (21.4)	51 (39.2)
No	0	3 (3.4)	1 (3.7)	3 (3.1)	5 (3.8)
Prior Midostaurin (n (%))					
Yes	3 (30.0)	46 (52.3)	9 (33.3)	49 (50.0)	58 (44.6)
No	7 (70.0)	42 (47.7)	18 (66.7)	49 (50.0)	72 (55.4)
Best Response to Prior Midostaurin [1] (n (%))					
CR	0	0	0	0	0
PR	1 (33.3)	6 (13.0)	1 (11.1)	7 (14.3)	8 (13.8)
CI	1 (33.3)	8 (17.4)	1 (11.1)	9 (18.4)	10 (17.2)
SI	0	0	2 (22.2)	0	2 (3.4)
SD	0	14 (30.4)	2 (22.2)	14 (28.6)	16 (27.6)
PD	1 (33.3)	7 (15.2)	1 (11.1)	8 (16.3)	9 (15.5)
NA	0	0	2 (22.2)	0	2 (3.4)
NE	0	2 (4.3)	0	2 (4.1)	2 (3.4)
Other	0	8 (17.4)	0	8 (16.3)	8 (13.8)
Missing	0	1 (2.2)	0	1 (2.0)	1 (1.7)

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.

Table 35.1.10.1.4 Prior Therapies
RAC-RE Population
Studies 2101 and 2202

	Starting Dose (QD)				
	<200 mg (N=10) n (%)	200 mg (N=88) n (%)	300 mg (N=27) n (%)	<=200 mg (N=98) n (%)	All Doses (N=130) n (%)
Reason for Discontinuation of Prior Midostaurin [1] (n (%))					
Completed Scheduled Cycles	0	0	0	0	0
PD/Relapse	3 (100)	17 (37.0)	5 (55.6)	20 (40.8)	25 (43.1)
Refractory	0	2 (4.3)	0	2 (4.1)	2 (3.4)
Toxicity	0	13 (28.3)	2 (22.2)	13 (26.5)	15 (25.9)
Other	0	13 (28.3)	2 (22.2)	13 (26.5)	15 (25.9)
Unknown	0	3 (6.5)	0	3 (6.1)	3 (5.2)
Duration of Treatment on Midostaurin (months)					
n	3	52	9	55	64
Mean (StdDev)	45.4 (67.84)	15.3 (20.69)	14.6 (17.23)	17.0 (24.94)	16.6 (23.91)
Median	10.2	8.6	6.2	8.7	8.3
Min, Max	2, 124	0, 122	5, 58	0, 124	0, 124

Source: Listings 16.2.4.4, 16.2.4.5, 16.2.4.6
Notes: Prior therapies are coded using WHO DD B2 enhanced, version March 2017. Prior therapy is defined as all treatment that started once in the respective patient count.
[1] Percentages based on total number of patients with Prior Midostaurin.