Medicinrådet

Bilag til Medicinrådets anbefaling vedr. erdafitinib til behandling af inoperabel eller metastatisk urotelialkræft med specifikke FGFR3-genændringer efter forudgående behandling med mindst én behandlingslinje med PD-1/-L1-hæmmer

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. erdafitinib
2. Forhandlingsnotat fra Amgros vedr. erdafitinib
3. Ansøgers endelige ansøgning vedr. erdafitinib

Johnson&Johnson

Response letter
March 24th, 2025

Dear Medicines Council

Johnson & Johnson appreciates the opportunity to review the assessment report concerning erdafitinib (Balversa) for adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor. We acknowledge the effort put into the report but wish to point out specific choices made in the DMC assessment which have a substantial impact on the results and which we do not agree with. Particularly we would like to highlight the following aspects:

- Choice of ITT population for the comparator instead of vinflunin subgroup
- Choice of conservative survival extrapolation

Choice of Comparator Population

We note that DMC has chosen to use the intention-to-treat (ITT) population from the clinical trial as the primary comparator. In our submission, we focused on the vinflunin subgroup based on prior guidance received during our dialogue meeting with the DMC secretariat as well as previous submissions done in the disease area. This subgroup analysis is aligned with the treatment landscape for bladder cancer and provides a more relevant context for evaluating the clinical effectiveness of erdafitinib.

We note that the DMC has made a sensitivity analysis using the vinflunin subgroup moving the QALY gain from 0,28 to 0,37 and we hope that the council will take this into their consideration as we believe it better reflects clinical practice in Denmark.

Choice of OS Extrapolation

The DMC base case adopts the Weibull OS extrapolation, which we believe does not reflect the most clinically plausible scenario for long-term benefits of erdafitinib (Balversa). The choice of OS extrapolation made by DMC appears to diverge from choices in other countries including Norway (assessment report not published yet but it will be before DMC decision) and UK (NICE) where the log-logistic OS extrapolation has been applied. NICE states in their draft guidance page 16 that “The committee thought that when compared to the most optimistic and pessimistic models the log-logistic curve provided an acceptable fit to the observed data and plausible estimates of long-term survival. The committee concluded that although associated with uncertainty the log-logistic distribution would be appropriate to extrapolate OS for erdafitinib…”[i]

Again, we note that DMC has made a sensitivity analysis using the log-logistic distribution to extrapolate the OS for erdafitinib (Balversa). This almost doubles the ICER gain from 0,28 to 0,52 which has a major impact on the ICER. We sincerely hope that the council will take this into their consideration.

Conclusion

Thank you for your consideration of these important points. We sincerely hope that the DMC will take our perspectives into consideration when discussing the case.

We sincerely hope that the DMC will make erdafitinib (Balversa) available for patients given the low ICER, very small budget impact, the mature data package and the high severity of the disease.

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[i] https://www.nice.org.uk/guidance/indevelopment/gid-ta10252, page 16

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24.03.2025

KLE/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.04.2025
Leverandør	Johnson & Johnson
Lægemiddel	Balversa (erdafitinib)
Ansøgt indikation	Erdafitinib til behandling af inoperabel eller metastatisk urotelialkræft med specifikke FGFR3-genændringer efter forudgående behandling med mindst én behandlingslinje med PD-1/-L1-hæmmer
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende priser på Balversa (erdafitinib):

*Tabel 1: Forhandlede priser som er gældende hvis Medicinrådet **anbefaler** Balversa.*

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Balversa	3 mg (84 stk. filmovertrukne tabl.)	87.060,24	[redacted]	[redacted]
Balversa	4 mg (56 stk. filmovertrukne tabl.)	87.060,24	[redacted]	[redacted]
Balversa	5 mg (28 stk. filmovertrukne tabl.)	87.060,24	[redacted]	[redacted]

Priserne er betinget af Medicinrådets anbefaling.

Hvis Medicinrådet *ikke* anbefaler Balversa, indkøbes det til AIP.

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted] Medicinrådet anbefalede i oktober 2024 Opdivo (nivolumab) i kombination med cisplatin og gemcitabin og i december 2024 Padcev (enfortumab vedotin) i kombination med Keytruda (pembrolizumab) til behandling af patienter med inoperabel eller metastatisk urotelialt carcinom i **første linje.**

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Balversa	4 mg (56 stk. filmovertrukne tabl.)	8 mg dagligt*	[redacted]	[redacted]
Javlor (vinflunin)	25 mg/ml, 10 ml, 1 stk. (konc. til inf.væske)	509,6 mg hver 3. uge**	[redacted]	[redacted]

Jf. vurderingsrapport **s. 43*

Jf. vurderingsrapport **S. 43: 280 mg/ m² gennemsnitligt kropsoverfladeareal (BSA) = 1,82 m²

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	Ingen kommentarer	Link til status
England	Under vurdering	Ingen kommentarer	Link til status
Sverige	Ikke ansøgt	Ingen kommentarer	Link til database

Opsummering

[redacted]

Application for the assessment of erdafitinib (Balversa®) for adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

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Abbreviations

Abbreviation	Meaning
1L	First Line
ADC	Antibody Drug Conjugate
AE	Adverse Event
AFT	Accelerated Failure Time
AIC	Akaike Information Criterion
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area-Under-The-Curve
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
CADTH	Canadian Agency for Drugs and Technologies in Health
CENTRAL	Cochrane Central Register of Controlled Trials
CHEMO	Chemotherapy
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Oral Clearance
CMA	Cost-Minimisation Analysis
CNS	Central Nervous System
CPI	Checkpoint Inhibitor
CPS	Combined Positive Score
CR	Complete Response
CrCl	Creatinine Clearance
CrI	Credible Interval
CSR	Central Serous Retinopathy
CT	Computerized Tomography
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
CUA	Cost-Utility Analysis
DCR	Disease Control Rate
DMC	Danish Medicines Council
Doc	Docetaxel
DOR	Duration of Response
DRG	Diagnosis Related Groups
DSA	Deterministic Sensitivity Analysis
DSU	Decision Support Unit
ECCO	European Cancer Organization

Abbreviation	Meaning
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ C30	European Organization for The Research and Treatment Of Cancer
EQ-5D-5L	EuroQOL 5-dimensions
ERDA	Erdafitinib
ESMO	European Society for Medical Oncology
ESS	Effective Sample Size
EU	European Union
EV	Enfortumab Vedotin
FACT-BI	Functional Assessment of Cancer Therapy-Bladder
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
GFR	Glomerular Filtration Rate
HAS	European Society for Medical Oncology
HCRU	Healthcare Resource Use
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSUVs	Health State Utility Values
HTA	Health Technology Assessment
HUI	Health Utility Index
IC50	Half Maximal Inhibitory Concentration
ICER	Incremental Cost-Effectiveness Ratio
IEC	Independent Ethics Committee
IPD	Individual Patient Data
IQR	Interquartile Range
IQWiG	The Institute for Quality and Efficiency in Healthcare
IRB	Institutional Review Board
ITC	Indirect Treatment Comparison
ITT	Intention-To-Treat
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier
LA	Locally Advanced
M	Metastasis
MAIC	Matching-Adjusted Indirect Comparison
max	Maximum
MCMC	Monte Carlo Markov Chain
MEQ	Morphine-Equivalent Dose

Abbreviation	Meaning
mg	Milligram
MIBC	Muscle-Invasive Bladder Cancer
min	Minimum
mL	Mililiter
MMAE	Monomethyl Auristatin E
MMRM	Mixed-Effects Model with Repeated Measures
MRI	Magnetic Resonance Imaging
MUC	Metastatic Urothelial Carcinoma
mUC	Metastatic Urothelial Carcinoma
N	Node
N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NE	Not Evaluable
NGS	Next Generation Sequencing
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NR	Not Reported
NTRK	Neurotrophic Tyrosine Receptor Kinase
NYHAC	New York Heart Association Classification
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
OWSA	One-Way Sensitivity Analysis
Pac	Paclitaxel
PAIC	Population-Adjusted Indirect Comparison
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressive Disease
PD-(L)1	Programmed Death-(Ligand) 1
PFS	Progression-Free Survival
PGIS	Patient-Global Impression of Severity
PH	Proportional Hazards
PICO	Patient, Intervention, Comparator, Outcome
PR	Partial Response
PRO	Patient-Reported Outcome
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
QLQ	Quality of Life Questionnaire
QoL	Quality Of Life
RCT	Randomized Controlled Trial
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumours

Abbreviation	Meaning
RR	Risk Ratio
SD	Stable Disease
SE	Standard Error
SLR	Systematic Literature Review
SMC	Scottish Medicine Consortium
SMD	Standardised Mean Difference
Subs	Subsequent
T	Tumour
TEAE	Treatment-Emergent Adverse Event
TNM	Tumour Node Metastasis
TSD	Technical Support Document
TTD	Time to Treatment Discontinuation
TURBT	Transurethral Resection of the Bladder Tumour
UC	Urothelial Carcinoma
ULN	Upper Limit Of Normal
US	United States
VAS	Visual Analogue Scale
Vin	Vinflunine
Vs.	Versus

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Balversa®
Generic name	Erdafitinib
Therapeutic indication as defined by EMA	Erdafitinib as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting (1).
Marketing authorization holder in Denmark	Johnson & Johnson
ATC code	L01EN01
Combination therapy and/or co-medication	Given as Monotherapy
(Expected) Date of EC approval	22nd of August 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? **No** Is the product suitable for a joint Nordic assessment? **No** If no, why not? **Different treatment practices across Nordic countries.**

Overview of the medicine	
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Erdafitinib 3 mg film-coated tablets; 84 film-coated tablets (1) Erdafitinib 4 mg film-coated tablets; 56 film-coated tablets (1) Erdafitinib 5 mg film-coated tablets; 28 film-coated tablets (1)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Erdafitinib as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting (1).
Dosage regiment and administration	The recommended starting dose of erdafitinib is 8 mg orally once daily (1). This dose should be maintained, and serum phosphate level should be assessed between 14 and 21 days after initiating treatment. Up-titrate the dose to 9 mg once daily if the serum phosphate level is <9.0 mg/dL, and there is no drug-related toxicity.
Choice of comparator	Vinflunine 320 mg per m^2 given as an intravenous infusion every three weeks (2). Enfortumab vedotin (EV) 1.25 mg/kg given as a 30-minute infusion (3).
Prognosis with current treatment (comparator)	2L treatment with vinflunine has demonstrated a median overall survival of 6.9 months when compared to best supportive care which had demonstrated a median overall survival of 4.6 months (4). EV is a 3L treatment option, and has demonstrated a median OS of 12.9 months in clinical trials (5).
Type of evidence for the clinical evaluation	The main efficacy and safety evidence for erdafitinib are derived from the THOR C1 trial. The THOR trials consisted of 2 cohorts and only cohort 1 is reported for this application. A matching-adjusted indirect comparison (MAIC) was conducted with data from THOR C1 for erdafitinib and from EV-301 for EV to inform comparative effectiveness.
Most important efficacy endpoints (Difference/gain compared to comparator)	**Trial median overall survival**: 12.06 months v[redacted]onths (erdafitinib vs. vinflunine); **MAIC hazard ratio (HR)** = 0.92 (Erdafitinib vs. EV).

Summary	
	Trial median progression-free survival: 5.55 months vs. 3.58 months (erdafitinib vs. vinflunine); **MAIC HR** = 0.92 (erdafitinib vs. EV). **Trial overall response rate**: RR = 3.13 (erdafitinib vs EV); **MAIC OR** = 1.45 (erdafitinib vs. EV).
Most important serious adverse events for the intervention and comparator	Serious TEAEs (≥3%) in any treatment arm (erdafitinib and chemotherapy) by preferred term were febrile neutropenia (0% and 6.3%), urinary tract infection (4.4% and 1.8%), haematuria (3.7% and 0.9%), and febrile bone marrow aplasia (0% and 3.6%). For EV, 51.4% of patients experienced grade ≥3 adverse events: (EV vs chemotherapy) maculopapular rash 7.4% vs 0% and decreased neutrophil count 6.1% vs 13.4% (6).
Impact on health-related quality of life	Clinical documentation: The impact on HRQoL was measured in THOR C1 with EQ-5D-5L. Health economic model: Progression-based health-state utility values are used to estimate different impact on health-related quality-of-life of the treatment arms. Erdafitinib compared against EV was assumed to have equal effect.
Type of economic analysis that is submitted	A cost-utility analysis will be provided against vinflunine in the form of a three-health state partitioned survival model. Overall survival and progression-free survival will be included in the model as the relevant endpoints. A cost-minimisation analysis against EV will be provided.
Data sources used to model the clinical effects	Head-to-head data from THOR C1 and clinical data from the MAIC of erdafitinib vs. EV.
Data sources used to model the health-related quality of life	EQ-5D-5L collected during the THOR clinical trial.
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	The health state utility value for the progressed disease state was associated with the highest uncertainty, followed by the proportion of FGFR3 patients who test positive for alterations.
Number of eligible patients in Denmark	[redacted]

Summary	
Budget impact (in year 5)	[redacted]

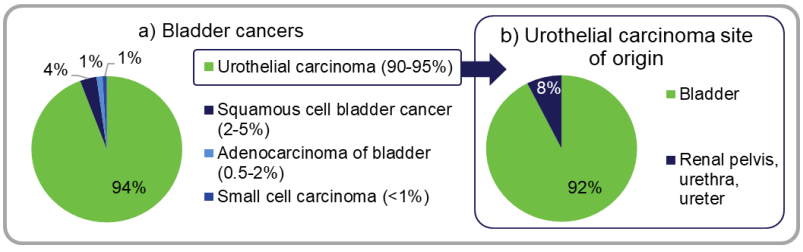
3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology

Urothelial carcinoma (UC) occurs due to malignant transformation and growth of urothelial cells. UC refers to any cancer that forms from the urothelial lining of the urinary system (the renal pelvis, ureters, prostate, bladder, or urethra). Patients with UC often have multiple carcinomas of the bladder and upper urinary tract (7). Bladder cancer is the most common UC due to its comparatively large surface area of urothelium Figure 1 (8). More than 90% of cases of bladder cancer are UCs (8, 9).

Figure 1. Distribution and type of cancers in the urothelial tract



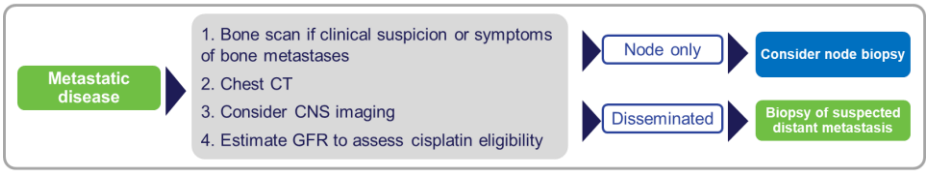
Source: Martin et al., 2016 (8).

Urothelial carcinoma can become locally advanced (LA) (spreading to surrounding organs), or metastatic (spreading to other areas of the body). In Europe in 2020, 5-15% of new bladder cancer cases were metastatic (10, 11). Of the 25-30% of patients with muscle-invasive bladder cancer (MIBC) at diagnosis, 25% have undetected metastatic disease in regional lymph nodes (12). Nearly 50% of patients with MIBC who undergo curative-intent treatment eventually relapse and develop metastatic UC (mUC) (10, 13). Local recurrences account for approximately 10% – 30% of relapses, whereas distant metastases are more common (14).

3.1.2 Clinical presentation and diagnosis

Patients with mUC present with symptoms including being unable to urinate, bone or lower back pain, feeling tired or weak, loss of appetite and weight loss, and swelling in the feet (15). If UC is suspected, a cystoscopy is carried out, followed by transurethral resection of the bladder tumour (TURBT) if abnormalities are detected. Laboratory studies, such as a complete blood cell count and chemistry profile including alkaline phosphatase, must be performed and the patients assessed for the presence of regional or distant metastases. This evaluation should include chest imaging and a bone scan in patients with symptoms or clinical suspicion of bone metastasis (e.g., elevated alkaline phosphatase, focal bone pain). An abdominal/pelvic Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) scan is used to assess the local and regional extent of disease (14, 16). If the evidence of spread is limited to nodes, nodal biopsy should be considered, and patients should be managed for positive nodal disease. The steps for metastatic disease classification as per the National Comprehensive Cancer Network (NCCN) guidelines are described in Figure 2.

Figure 2. NCCN Bladder cancer diagnostic guidelines for metastatic disease



Source: NCCN 2023 (14).
Abbreviations: CNS, central nervous system; CT, computerized tomography; GFR, glomerular filtration rate; NCCN, National Comprehensive Cancer Network.

Accurate staging of the tumour is critical to establish the prognosis (17). The tumour, node, metastasis (TNM) system is used to grade tumours, according to the size and location (T), whether it has reached the regional lymph nodes (N) and whether it has metastasized (M) (18) (Table 1).

Table 1. TNM staging and disease map

Description	Stage	Tumour	Node	Metastasis
Non-muscle-invasive	I	T1	N0	M0
Muscle invasive	II	T2a – T2b	N0	M0
	III	T3a – T3b, T4a	N0	M0
Locally advanced	IV	T4b	N0	M0
	IV	Any T	N1-N3	M0
Metastatic	IV	Any T	Any N	M1

Source: Bellmunt et al., 2014 (19).
Abbreviations: M, metastasis; N, node; T, tumour.

3.1.2.1 FGFR alterations

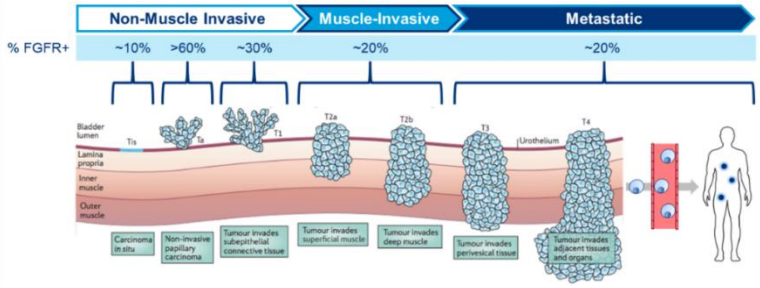
The fibroblast growth factor receptors (FGFR) family of transmembrane receptor kinases are important for cell functions such as proliferation, survival, migration, and

differentiation. Overexpression and abnormal regulation of FGFR activity has been implicated in UC (20, 21) and is associated with carcinogenesis (22). Tumours that harbour FGFR alterations are sensitive to FGFR inhibition (22).

The frequency of FGFR alterations varies by bladder tumour stage and grade (Figure 3) (23). The prevalence of FGFR mutations and gene fusions in mUC patients is 15-20%, with FGFR3 mutations identified in up to 42% of all UCs, up to 20% of metastatic disease cases, and up to 15% of muscle-invasive bladder tumours (10, 24-27).

Evidence regarding the prognostic impact of susceptible FGFR alterations in mUC remains inconclusive; a real-world study concluded that FGFR3 alterations are neither predictive nor prognostic in patients with mUC receiving first-line platinum-based CT or second-line immunotherapy (28).

Figure 3. FGFR alteration frequency by bladder tumour stage



Source: Knowles and Hurst 2015 (23).
Abbreviations: FGFR, fibroblast growth factor receptor.

3.1.3 Patient prognosis

Many patients experience disease progression after treatment with an anti-PD-(L)1 agent. At the same time, data from clinical trials have shown limited overall survival (OS) and progression-free survival (PFS) benefit for patients who have progressed after ≥1 line of therapy.

A Danish study looking into patterns of survival in each line, for 1,278 patients with locally advanced or mUC, observed a median survival of 13.5 months from diagnosis. Median survival from start of 1st, 2nd and 3rd line was 12.1, 9.8 and 8.6 months respectively (29).

2nd line treatment with vinflunine has demonstrated a median OS of 6.9 months when compared to best supportive care which had demonstrated a median OS of 4.6 months (4). 2nd line pembrolizumab has demonstrated a median OS of 10.3 months (30). For patients that have received chemotherapy and a PD-(L)1 inhibitor, EV is a 3L treatment option, demonstrating a median OS of 12.9 months in a clinical trial (5).

3.1.4 Impact on health-related quality of life

Across all stages of UC there are symptoms that negatively impact health-related quality of life (HRQoL), and patients with LA/mUC experience additional symptom burden.

LA/mUC is associated with symptoms such as urinary problems, pain, fatigue, loss of appetite and weight loss, and swelling in the feet which are burdensome to patients (15). LA/mUC patients treated with chemotherapy followed by a checkpoint inhibitor (N=24) were interviewed about their symptoms. Ongoing symptoms were fatigue (92%), haematuria (88%), pain (75%), and urinary symptoms (71%) (31).

A recent survey of 53 mUC patients and 26 patients with MIBC receiving treatment in a real-world clinical setting in Denmark, showed a poorer global QoL for mUC patients compared to MIBC patients (54, ± standard deviation [SD] 24 versus 73, ±SD 19) on the European Organization for the Research and Treatment of Cancer Quality Of Life (EORTC QLQ) C30. Patients with mUC also had more severe pain (38 versus 19), fatigue (48 versus 25), and urinary scores (25 versus 38) compared to MIBC patients. The 5 most prevalent Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2 symptoms were frequent urination (37%), fatigue (35%), pain (31%), dry mouth (23%), and swelling of the arms or legs (23%). For patients experiencing hospitalization during treatment, the mean global QoL was lower throughout treatment (mean global QoL 60, ±SD 21) compared to the patients who were not hospitalized (mean global QoL 70, ±SD 20) (32).

3.2 Patient population

The available evidence on mUC contains little to no epidemiological information. As most bladder cancer cases are urothelial carcinomas (see section 3.1) data on bladder cancer is used as proxy.

In Denmark, from 2015 to 2021 (the latest available year), the yearly incidence has been approximately 2,200 cases and total prevalence has been around 22,000 cases (33). It is assumed 90% of these cases are urothelial carcinomas, a further 5% are metastatic at diagnosis whilst 25% are muscle invasive. Of the MIBC cases, about 50% will develop metastatic disease. This results in an estimated 370 patients annually with mUC in Denmark.

Table 2. Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022*	2023*
Bladder cancer					
Incidence in Denmark	2,330	2,339	2,410	2,410	2,410
Prevalence in Denmark	21,873	22,255	22,746	22,746	22,746
mUC incidence in Denmark	365	366	370	370	370
mUC prevalence in Denmark	3,446	3,506	3,582	3,582	3,582

*As incidence and prevalence data not available, assumed constant from 2021 onwards
Abbreviations: mUC, metastatic urothelial carcinoma.

The patient population relevant for this assessment constitutes patients who received at least one line of a PD-(L)1 inhibitor and have an FGFR alteration. Earlier, DMC estimated a yearly incidence of 150 patients who receive treatment for newly diagnosed mUC (34). DMC deemed a yearly incidence of 48 patients with UC progressing after receiving at least one PD-(L)1 and platinum-based chemotherapy acceptable (35). Assuming 18% of these patients have an FGFR3 alteration, Johnson & Johnson estimates the number of patients eligible for treatment with erdafitinib to be 9 patients every year.

A Danish clinical expert was consulted for this submission (36), and in addition to the above patient estimates, the clinician estimated that 10% of the patients with mUC are cisplatin ineligible and PD-(L)1 positive (15 patients). This subgroup will receive immunotherapy in 1L and would therefore become eligible for erdafitinib after progression per the EMA indication. Incorporating the 18% of FGFR3 alteration incidence rate, this would result in an estimated 2 additional patients on a yearly basis.

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	11	11	11	11	11

3.3 Current treatment options

The DMC has not developed a treatment guideline for mUC patients in Denmark. However, clinical guidelines from the Danish Bladder Cancer Group (2024 update) are considered most relevant for the Danish treatment algorithm (Figure 4) and the choice of local comparators for this submission (37). Cisplatin-based chemotherapy is considered standard of care in first line (1L) since the late 1980's in mUC (16). However, with advances in immuno-oncology, new treatments have become available such as antibodies targeting PD-(L)1 receptors (38).

In Denmark, the treatment algorithm begins with assessing eligibility for platinum-based chemotherapies and PD-(L)1 expression (37). Patients eligible for cisplatin therapy in 1L will receive it in combination with gemcitabine for 4-6 cycles. Patients who are cisplatin ineligible and are PD-(L)1 negative or cannot tolerate immunotherapy will receive carboplatin combined with gemcitabine for 4-6 cycles or gemcitabine monotherapy. Patients that received platin-based chemotherapy in 1L and have not progressed can be treated with maintenance treatment with avelumab for up to 2 years (37).

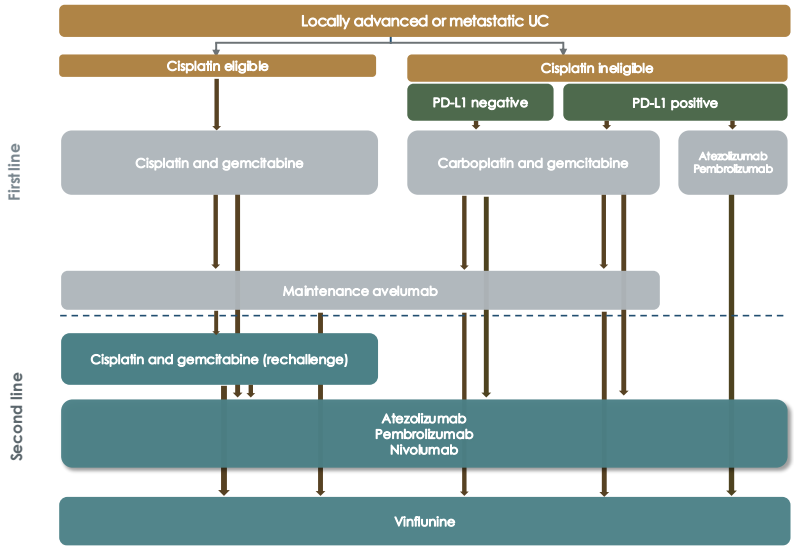
Patients who are cisplatin ineligible and PD-(L)1 positive can receive atezolizumab or pembrolizumab. Upon progression, patients who received cisplatin in combination with gemcitabine can be reinduced with the same combination, if still eligible. Patients without

prior treatment with immunotherapy can receive immunotherapy and patients that have received immunotherapy can receive vinflunine (37).

The updated 2024 ESMO guidelines include erdafitinib, with strengthened evidence, for FGFR-driven tumours, upon disease progression (39). The ESMO guidelines present a slightly different treatment algorithm than the guidelines from the Danish Bladder Cancer Group, due to differences in availability of treatments. EV in combination with-pembrolizumab and sacituzumab govitecan are not recommended in Denmark.

Of note, EV was recently approved by the DMC in August 2024 for mUC patients after treatment with platinum-based chemotherapy and a PD-1/-L1 inhibitor (35).

Figure 4. Current treatment algorithm



Source: Adapted from the Danish Bladder Cancer Group guideline (37)
Abbreviations: mUC, metastatic urothelial carcinoma; PD-L1, Programmed Death-(Ligand) 1; UC, urothelial carcinoma.

3.4 The intervention

Erdafitinib is a highly selective and potent oral pan-FGFR tyrosine kinase inhibitor with high affinity and inhibitory activity at low nanomolar levels for all FGFR family members (FGFR 1, 2, 3 and 4) (40). In FGFR pathway activated cancer cell lines, the concentration required for 50% tumour growth inhibition (IC50) is in the low nanomolar range 0.1 to 129.2 nanomolar (41). Binding of erdafitinib to the FGFRs results in prolonged inhibition of FGFR signalling, thereby inhibiting tumour growth (40).

CHMP positive opinion was granted on the 28th of July 2024 and European market authorisation was granted on the 22nd of August 2024. These are based on the results from Cohort 1 (C1) of the phase III trial, THOR (THOR C1) (42).

Table 4. Key descriptive information of erdafitinib

Overview of intervention	
Therapeutic indication relevant for the assessment	Erdafitinib as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma, harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting (1).
ATMP	N/A
Method of administration	The tablets should be swallowed whole with or without food at about the same time each day. If vomiting occurs any time after taking erdafitinib, the next dose should be taken the next day (1).
Dosing	The recommended starting dose of erdafitinib is 8mg orally once daily, with the possibility of up-titration to 9 mg (1).
Dosing in the health economic model (including relative dose intensity)	The model includes an estimation of the average costs of treating with erdafitinib over 28 days by averaging the proportions of doses received in THOR with the costs of the combination of tablets needed to achieve that dose. See section 11.1 for more details.
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treatment should continue until disease progression or unacceptable toxicity occurs (1).
Necessary monitoring, both during administration and during the treatment period	Patients on treatment with erdafitinib require monthly ophthalmological examinations during the first 4 months of treatment and every 3 months afterwards (1).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	FGFR testing, mostly by next generation sequencing (NGS). In the cost effectiveness model, the cost of NGS testing is included for the proportion of patients who have an FGFR genetic alteration, accounting for the costs of the tests that are negative. Currently this test is not done on patients in Denmark, but it can be included in the gene testing panel.
Package size(s)	3 mg film-coated tablets; 84 film-coated tablets (1), 4 mg film-coated tablets; 56 film-coated tablets (1), 5 mg film-coated tablets; 28 film-coated tablets (1)

3.4.1 The intervention in relation to Danish clinical practice

Based on the results of the THOR C1 study, the EMA indication, and the updated ESMO guidelines, erdafitinib is expected to be offered to patients harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a

PD-(L)1 and have progressed. Thus, in Denmark, replacing vinflunine and EV for this subgroup (42, 43). The placement of erdafitinib in the Danish clinical practice was also confirmed by the Danish clinical expert (36).

3.5 Choice of comparator(s)

In accordance with the treatment guidelines by the Danish Bladder Cancer Group, the relevant comparators for this assessment are vinflunine and EV (37).

Table 5. Key descriptive information of vinflunine

Overview of comparator	
Generic name	Vinflunine
ATC code	L01CA05
Mechanism of action	Vinflunine binds to tubulin at or near to the vinca binding sites inhibiting its polymerisation into microtubules, which results in treadmilling suppression, disruption of microtubule dynamic, mitotic arrest and apoptosis. In vivo, vinflunine displays significant antitumor activity against a broad spectrum of human xenografts in mice both in terms of survival prolongation and tumour growth inhibition. (2).
Method of administration	Intravenous infusion (2)
Dosing	The recommended dose is 320 mg/m² vinflunine as 20-minute intravenous infusion every 3 weeks (2).
Dosing in the health economic model (including relative dose intensity)	• 320 mg/m² every 3 weeks • RDI: 99.8% (42)
Should the medicine be administered with other medicines?	In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 after each vinflunine administration (2).
Treatment duration/ criteria for end of treatment	Until disease progression, withdrawal or unacceptable toxicity (2).
Need for diagnostics or other tests (i.e. companion diagnostics)	Not applicable (2).
Package size(s)	Concentrate for solution for infusion, 25 mg/mL 1 x 2 millilitres; 25 mg/mL 1 x 10 millilitres

Abbreviations: kg, kilogram; mg, miligram; mL, mililiter.

Table 6. Key descriptive information of enfortumab vedotin

Overview of comparator	
Generic name	Enfortumab vedotin
ATC code	L01FX13
Mechanism of action	EV is an antibody drug conjugate (ADC) targeting Nectin-4, an adhesion protein located on the surface of the urothelial cancer cells. It is comprised of a fully human IgG1-kappa antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalisation of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death. MMAE released from EV targeted cells can diffuse into nearby Nectin-4 low-expressing cells resulting in cytotoxic cell death (3).
Method of administration	Intravenous infusion (3)
Dosing	Given as an intravenous infusion (at a dose of 1.25 mg per kilogram of body weight with a maximum of 125 mg per dose) over 30 minutes on days 1, 8, and 15 of a 28-day cycle (3).
Dosing in the health economic model (including relative dose intensity)	• 1.25 mg/kg on days 1, 8, 15 of a 28-day cycle • RDI: 79.4% (6)
Should the medicine be administered with other medicines?	No (3).
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity (3).
Need for diagnostics or other tests (i.e. companion diagnostics)	Not applicable (3).
Package size(s)	EV (Padcev®): 20 mg. Powder for concentrate for solution for infusion. Intravenous use vial (glass) 1 vial; 30 mg. Powder for concentrate for solution for infusion. Intravenous use vial (glass) 1 vial.

Abbreviations: kg, kilogram; mg, miligram; mL, mililiter.

3.6 Cost-effectiveness of the comparator(s)

EV has been assessed by DMC in September 2022 for third line treatment of patients with mUC and received a negative recommendation, and was then reassessed in August 2024, after which a positive recommendation followed. EV was assessed as being cost-effective compared to vinflunine, despite having higher treatment costs (35). The cost-effectiveness of vinflunine has not been previously assessed by the DMC.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

OS, PFS and ORR are the most relevant outcomes for this assessment.

Table 7. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS)	15.9 months	OS is defined as the time from randomization to the date of death due to any causes. The OS (in months) is calculated as: (date of death − date of randomization + 1)/30.4375.	If the subject is alive or the vital status is unknown (for example, lost to follow-up or withdrew consent etc.), the OS will be censored at the date the subject was last known to be alive. Subjects lacking data beyond randomization will have their OS censored at the date of randomization.
Progression-free survival (PFS)	15.9 months	PFS is defined as duration (in days) from the date of randomization to the date of disease progression (or relapse from CR) assessed per RECIST v1.1 by the investigator or death, whichever is reported first.	PFS will be censored at the date of the last adequate disease assessment for subjects who do not have disease progression and are alive, as well as for subjects with unknown disease progression or unknown survival status as of the clinical cutoff date. Also, if there is no post-baseline tumour assessment for a subject, PFS will be censored on the date of randomization.
Overall response rate (ORR)	15.9 months	The ORR is defined as the proportion of subjects who achieve complete response (CR) or partial response (PR), as assessed per RECIST v1.1 by the investigator	Subjects will be considered as non-responders if they do not have CR or PR while on study, or do not have a baseline or post-baseline tumour assessment, or do not have

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		among intention-to-treat (ITT) Analysis set of a treatment group.	adequate baseline tumour evaluation, or die, or have progressive disease, or drop out for any reason or take subsequent therapy prior to reaching a CR or PR.

* Time point for data collection used in analysis (follow up time for time-to-event measures).

Validity of outcomes

OS, PFS and ORR are standard clinical study endpoints, which are considered to be reliable and relevant for this submission and have previously been used by the DMC for multiple oncology submission dossiers.

4. Health economic analysis

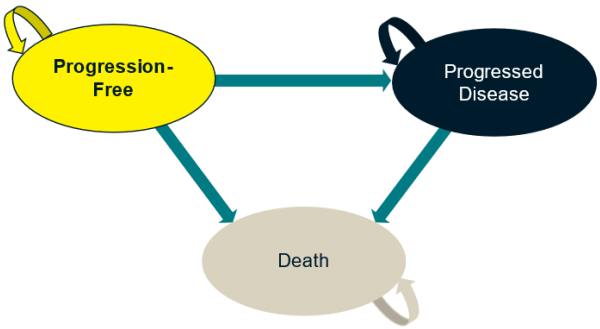
The health economic analysis that was conducted is a cost-utility analysis (CUA) against vinflunine, as both incremental gains and incremental costs are generated by the new treatment strategy, compared to the current standard-of-care for adult patients with unresectable or metastatic UC, harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor. A cost-minimisation analysis (CMA) was also conducted against EV, where the effect was considered to be equal for the intervention and the comparator.

4.1 Model structure

The model structure in the CUA is a three-state partitioned survival model, which is most commonly used in oncology modelling and is an established method with straightforward implementation and explanation (44). This model structure is consistent with the clinical outcomes typically employed in oncology trials and those reported in THOR. A partitioned survival model does not require the definition of explicit transitions between health states and automatically incorporates time dependencies in the event rates. Partitioned survival models allow the proportion of patients in each health state to be defined by the individual survival curves extrapolated from the trial data. A partitioned survival model structure has also been used in this indication in previous National Institute for Health Care and Excellence (NICE) submissions (45, 46), and a previous DMC submission (47).

Within the same model, EV is also included as a comparator, but in a cost-minimization analysis. The MAIC against EV showed higher effect for erdafitinib against EV, without being statistically significant. Thus, it was assumed that the effect of erdafitinib and EV is equal.

Figure 5. Model structure of the three-state partitioned survival model



4.2 Model features

Table 8 contains an overview of key model features in the health economic analysis and their justifications. No deviations from the DMC methods guide were made, and the model features were aligned with the clinical guidelines.

Table 8. Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with unresectable or metastatic UC, harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor	This patient population is the best reflection of the clinical evidence and has a clear place in the treatment pathway, as it will align directly with the placement of vinflunine and EV.
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	10 years	In line with what the DMC has previously accepted in mUC model of EV(35).
Cycle length	7 days (1 week)	This cycle length is considered sufficiently short to accurately capture key clinical outcomes and dosing regimens of erdafitinib with its comparators.
Half-cycle correction	Yes	Half-cycle correction is applied to time spent in each health state in the base case by averaging the state membership at the start and end of each cycle.

Model features	Description	Justification
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Erdafitinib doses received as per THOR C1 trial.	Aligned with THOR trial, as no real-world evidence is available on usage of erdafitinib.
Comparator(s)	Vinflunine (320 mg/m2) EV (1.25 mg/kg)	Aligns with the head-to-head comparator in the THOR trial and is recommended treatment for patients in this indication. EV was recently recommended by the DMC in this indication (35).
Outcomes	Costs are captured from a limited societal perspective. The health outcomes are modelled through OS and PFS. State-dependent utilities are estimated from the THOR trial to capture the benefits of erdafitinib.	

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical assessment of erdafitinib is based on the head-to-head THOR study of erdafitinib vs. vinflunine. A systematic literature review (SLR) was conducted to identify literature relevant for this application (see Appendix H), including the clinical assessment of EV. In Table 9, the trials identified in the SLR are described. In addition, the publication for the MAIC of erdafitinib vs. EV in included in the below table and is described in Section 7. The MAIC is available as a publication (48) and a technical report (data on file) (49).

Table 9. Relevant literature included in the assessment of efficacy and safety

Reference*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Loriot, Y., Matsubara, N., Park, S. H., Huddart, R. A., Burgess, E. F., Houede, N., Banek, S., Guadalupi, V., Ku, J. H., Valderrama, B. P., Tran, B., Triantos, S., Kean, Y., Akapame, S., Deprince, K., Mukhopadhyay, S., Stone, N. L., & Siefker-Radtke, A. O. (2023). Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. N Engl J Med, 389(21), 1961-1971. https://doi.org/10.1056/NEJMoa2308849 (42)	THOR C1	NCT03390504	Start (actual): 23/03/2018 Primary completion (estimated): 11/09/2024 Study completion (estimated): 01/11/2026	Erdafitinib vs. chemotherapy (docetaxel & vinflunine) for adult patients with previously treated, metastatic or surgically unresectable urothelial cancer harbouring selected fibroblast growth factor receptor (FGFR) aberrations.
Rosenberg, J. E., Powles, T., Sonpavde, G. P., Loriot, Y., Duran, I., Lee, J.-L., Matsubara, N., Vulsteke, C., Castellano, D. E., Mamtani, R., Wu, C., Matsangou, M., Campbell, M. S., & Petrylak, D. P. (2022). Long-term outcomes in EV-301: 24-month findings from the phase 3 trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. Journal of Clinical Oncology, 40(16_suppl), 4516-4516. https://doi.org/10.1200/JCO.2022.40.16_suppl.4516 (5)	EV-301	NCT03474107	Start (actual): 15/07/2018 Primary completion (actual): 15/07/2020 Study completion (estimated): 28/02/2025	EV vs. vinflunine, docetaxel or paclitaxel for adult patients with previously treated locally advanced or metastatic urothelial cancer *
Van Sanden S, Youssef A, Baculea S, Stubbs K, Triantos S, Yuan Z, Daly C. Matching-Adjusted Indirect Comparison of the Efficacy and Safety of	N/A	N/A	N/A	Erdafitinib vs. EV

Reference*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Erdafitinib vs Enfortumab Vedotin in Patients with Locally Advanced Metastatic Urothelial Carcinoma. J Health Econ Outcomes Res. 2024 Aug 20;11(2):49-57. doi: 10.36469/001c.120954 (48, 49)				

* In this submission, data from EV-301 is utilised in the indirect comparison of EV and erdafitinib (section 7).

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

The assessment of HRQoL in relation to health states is based on the head-to-head THOR C1 study of erdafitinib vs. vinflunine, therefore no SLR was deemed necessary. Disutility values in relation to adverse events were sourced from standard publications.

Table 10. 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
Loriot, Y., Matsubara, N., Park, S. H., Huddart, R. A., Burgess, E. F., Houede, N., Banek, S., Guadalupi, V., Ku, J. H., Valderrama, B. P., Tran, B., Triantos, S., Kean, Y., Akapame, S., Deprince, K., Mukhopadhyay, S., Stone, N. L., & Siefker-Radtke, A. O. (2023). Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. N Engl J Med, 389(21), 1961-1971. https://doi.org/10.1056/NEJMoa2308849	Progression-free disease	10.2.1
	Progressed disease	10.2.1
Beusterien, K. M., Davies, J., Leach, M., Meiklejohn, D., Grinspan, J. L., O'Toole, A., & Bramham-Jones, S. (2010). Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes*, *8*, 50. https://doi.org/10.1186/1477-7525-8-50	Anaemia	10.2.3
Lloyd, A., Nafees, B., Narewska, J., Dewilde, S., & Watkins, J. (2006). Health state utilities for metastatic breast cancer. *Br J Cancer*, *95*(6), 683-690. https://doi.org/10.1038/sj.bjc.6603326	Hyponatraemia (assumed equivalent to fatigue)	10.2.3

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
	Hyperphosphatemia (assumed equivalent to fatigue)	10.2.3
Nafees, B., Lloyd, A. J., Dewilde, S., Rajan, N., & Lorenzo, M. (2017). Health state utilities in non-small cell lung cancer: An international study. *Asia Pac J Clin Oncol*, *13*(5), e195-e203. https://doi.org/10.1111/ajco.12477	Onycholysis (assumed equivalent to rash)	10.2.3
	Neutropenia	10.2.3
	Febrile neutropenia	10.2.3
	Fatigue	10.2.3
	Maculopapular rash (assumed equivalent to rash)	10.2.3
	Leukopenia (assumed equal to neutropenia)	10.2.3
	Decreased neutrophil count (assumed equal to neutropenia)	10.2.3
NICE. (2022). *Nivolumab with ipilimumab for untreated advanced renal cell carcinoma* https://www.nice.org.uk/guidance/ta780/resources/nivolumab-with-ipilimumab-for-untreated-advanced-renal-cell-carcinoma-pdf-82611550117573	Palmar-plantar erythrodysesthesia syndrome (assumed equal to stomatitis)	10.2.3
NICE. (2018). *Lenvatinib with everolimus for previously treated advanced renal cell carcinoma* https://www.nice.org.uk/guidance/ta498/resources/lenvatinib-with-everolimus-for-previously-treated-advanced-renal-cell-carcinoma-pdf-82605093673669	Stomatitis	10.2.3

5.3 Literature used for inputs for the health economic model

Model inputs/estimates were sourced from the THOR C1 (erdafitinib and vinflunine) and EV-301 (EV) trials identified in the clinical SLR above, so a health economic input SLR was not needed for this submission.

Table 11. 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
Loriot, Y., Matsubara, N., Park, S. H., Huddart, R. A., Burgess, E. F., Houede, N., Banek, S., Guadalupi, V., Ku, J. H., Valderrama, B. P., Tran, B., Triantos, S., Kean, Y., Akapame, S., Deprince, K., Mukhopadhyay, S., Stone, N. L., & Siefker-Radtke, A. O. (2023). Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. N Engl J Med, 389(21), 1961-1971. https://doi.org/10.1056/NEJMoa2308849 (42)	Erdafitinib administration	SLR	11.3
	Erdafitinib OS	SLR	8.1.1.1
	Erdafitinib PFS	SLR	8.1.1.2
	Erdafitinib TTD	SLR	8.1.1.3
	Erdafitinib AE rates	SLR	9.1
	Vinflunine administration	SLR	11.3
	Vinflunine OS	SLR	8.1.1.1
	Vinflunine PFS	SLR	8.1.1.2
	Vinflunine TTD	SLR	8.1.1.3
	Vinflunine AE rates	SLR	9.1
	HCRU	SLR	11.4
Rosenberg, J. E., Powles, T., Sonpavde, G. P., Loriot, Y., Duran, I., Lee, J.-L., Matsubara, N., Vulsteke, C., Castellano, D. E., Mamtani, R., Wu, C., Matsangou, M., Campbell, M. S., & Petrylak, D. P. (2022). Long-term outcomes in EV-301: 24-month findings from the phase 3 trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced	EV administration	SLR	7
	EV OS *	SLR	0
	EV PFS *	SLR	7.1.5
	EV TTD *	SLR	7.1.5

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
urothelial carcinoma. Journal of Clinical Oncology, 40(16_suppl), 4516-4516. https://doi.org/10.1200/JCO.2022.40.16_suppl.4516 (5)	EV AE rates *	SLR	7
	HCRU	SLR	N/A

* Input value is based on the Bucher anchored MAIC (THOR and EV-301) described in section 7.

6. Efficacy

6.1 Efficacy of erdafitinib compared to vinflunine for adult patients with FGFR altered mUC, who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor

6.1.1 Relevant studies

The THOR C1 trial (NCT03390504) describes the efficacy of erdafitinib vs. chemotherapy (docetaxel or vinflunine) in patients with FGFR altered mUC who have previously received at least one line of therapy containing a PD-1/PD-L1 inhibitor. A post-hoc analysis was conducted to specifically investigate the treatment effects of the vinflunine subgroup in the THOR C1 chemotherapy arm (42, 50), as this best reflects Danish clinical practice. To better support the consistency of the effect of erdafitinib, the chemotherapy arm of THOR C1 (i.e., ITT population) will also be supported alongside the vinflunine subgroup results to provide better context for the DMC and to interpret the results of the MAIC sufficiently.

EV is an additional comparator relevant to Danish clinical practice based on feedback from DMC given at a dialogue meeting between the DMC secretariat and Johnson & Johnson held on July 3rd, 2024. The EV-301 trial (NCT03474107) describes the efficacy of EV vs. chemotherapy (docetaxel, paclitaxel or vinflunine) in patients with mUC who had received a prior platinum-containing chemotherapy and had disease progression during or after PD-1/PD-L1 inhibitor treatment (5). The vinflunine subgroup of the EV-301 study is not publicly available, therefore the chemotherapy comparator arm will be presented in this submission.

In order to compare erdafitinib to EV based on the current literature available, a MAIC was deemed appropriate to compare the efficacy between the two interventions since a common comparator arm is available from both the THOR C1 and EV-301 trials (chemotherapy) (49). Ideally, a MAIC would have been done to against the vinflunine subgroups of both trials, however the publicly available results for the EV-301 vinflunine subgroup were not sufficiently detailed to facilitate such a comparison.

Table 12. Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
THOR C1 (NCT03390504) (42, 50)	Randomized, phase III study of erdafitinib compared with vinflunine or docetaxel in subjects with mUC and selected FGFR gene aberrations	2018-2024 (to be completed)	Patients with FGFR positive mUC who have progressed after 1 or 2 prior treatments, at least 1 of which includes a PD-[L]1 inhibitor	Oral erdafitinib tablets at a starting dose of 8 mg daily, up-titrated to 9 mg daily if the serum phosphate level is <9.0 mg/dL, and there is no drug-related toxicity.	**Vinflunine:** 20-minute IV infusion of vinflunine 320/m^2 **Docetaxel:** 1-hour infusion of 75 mg/m^2 docetaxel	**Primary:** • OS: up to 3 years **Secondary:** • PFS: up to 3 years • ORR: up to 3 years • Change from Baseline in Participant-Reported Health Status and Physical Functioning Scales of the Functional Assessment of Cancer Therapy-Bladder (FACT-BI): up to 3 years • Time Until Symptom Deterioration (Subset of FACT-BI Items): up to 3 years • Change from Baseline in Patient-Global Impression of Severity (PGIS) Score: up to 3 years • Change from Baseline in the Visual Analogue Scale (VAS) of the EQ-5D-5L: up to 3 years • Change from Baseline in the Utility Scale of the EuroQOL 5-dimensions (EQ-5D-5L): up to 3 years • Duration of Response (DOR): up to 3 years

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						• Number of Participants with Adverse Events as a Measure of Safety: up to 3 years • Oral Clearance (CL/F) of Erdafitinib: Day 14 (Cycle 1), Day 1 (Cycle 2) • Area Under the Plasma Concentration-Time Curve from Time Zero to Time 't' (AUC[0-t]) of Erdafitinib: Day 14 (Cycle 1), Day 1 (Cycle 2)
EV-301 (NCT03474107) (5)	Randomized, phase III, open-label study of enfortumab vedotin or investigator-chosen standard chemotherapy (docetaxel, paclitaxel, or vinflunine)	2018 – 2024 (to be completed)	Patients with locally advanced or metastatic UC who had received prior platinum-containing chemotherapy and had disease progression during or after PD-1/L1 inhibitor treatment	Intravenous infusion of enfortumab vedotin 1.25 mg/kg	**Vinflunine:** 20-minute IV infusion of vinflunine 320/m^2 **Docetaxel:** 1-hour infusion of 75 mg/m^2 docetaxel **Paclitaxel:** 1-hour infusion of 175 mg/m^2 paclitaxel on day 1 of every 21-day cycle	**Primary:** • OS: up to 3 years **Secondary:** • PFS: up to 2 years • ORR: up to 2 years • DCR: up to 2 years • DOR: up to 2 years • Safety assessed by Adverse Events: up to 2 years • Number of participants with laboratory value abnormalities and/or adverse events: up to 2 years

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						• Number of participants with vital signs abnormalities and/or adverse events: up to 2 years • Safety assessed by 12- lead electrocardiogram (ECG): up to 2 years • Safety assessed by Eastern Cooperative Oncology Group Performance Status (ECOG PS): up to 2 years • Patient reported outcome assessed by quality of life: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30): up to 2 years • Patient reported outcome assessed by quality of life: EQ-5D-5L questionnaire: up to 2 years

6.1.2 Comparability of studies

6.1.2.1 Comparability of patients across studies

Baseline patient characteristics in each arm of THOR and EV-301 are listed in Table 13.

The proportions of patients who were ≥75 years old, non-smokers, with primary disease originating in the urinary tract, and visceral metastasis were generally comparable between the two trials.

There were some notable differences in sex and geographic distribution between the two trials. There was a slightly lower percentages of males in THOR (70.6% [erdafitinib]) than in EV-301 (79.1% [EV]; standardised mean difference [SMD]: 0.16) (49). THOR had a significantly lower percentage of patients from the United States (US) than EV-301 (5.9% [erdafitinib]; vs. 14.3% [EV], respectively; SMD: 0.25) which may be attributed to the availability of alternative therapies and competing clinical studies that admit "all comers" without the need for biomarker testing, as well as the commercial availability of EV in that region (21).

Regarding disease characteristics, fewer patients in THOR had a history of diabetes or hyperglycaemia compared with EV-301 (8.1% [erdafitinib] vs. 18.6% [EV]; SMD: 0.27). A larger proportion of patients in THOR had lower Bellmunt risk scores (0 to 1) compared with EV-301 patients (75.7% [erdafitinib] vs. 66.8% [EV]; SMD: 0.16). A smaller proportion of patients in THOR had liver metastasis compared with EV-301 (22.8% [erdafitinib] vs. 30.9% [EV], respectively; SMD: 0.15). Due to eligibility criteria, 9.4% of patients in THOR had an ECOG PS score of 2 vs. 0% in EV-301, and 87.6% of patients in THOR received platinum therapy vs. all patients in EV-301. Additionally, 12.5% of patients in EV-301 received more than 3 prior lines of therapy.

Table 13. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	THOR C1			EV-301	
	Erdafitinib (N = 136)	Chemotherapy (N = 130)	Vinflunine subgroup (N = 48)	EV (N = 301)	Chemotherapy (N = 307)
Age in years					
Median (min, max)	66.0 (32,	69.0 (35, 86)	[redacted]	68.0	68.0 (30.0, 88.0)
≥75, n (%)	26 (19.1)	30 (23.1)	[redacted]	52	68 (22.1)
Sex, n (%)					
Male	96 (70.6)	94 (72.3)	[redacted]	238	232 (75.6)
Geographic region n (%)					
Western Europe	82 (60.3)	80 (61.5)	[redacted]	126	129 (42.0)
United States	8 (5.9)	5 (3.8)	[redacted]	43	44 (14.3)
Rest of the world	46 (33.8)	45 (34.6)	[redacted]	132	134 (43.6)
Race, n (%)					

White	81 (59.6)	63 (48.5)		-	-
Asian	37 (27.2)	40 (30.8)		-	-
Black or African	0	1 (0.8)		-	-
Multiple	0	1 (0.8)		-	-
Not reported	18 (13.2)	25 (19.2)		-	-
Tobacco use, n (%)					
Former user	-	-	-	167	164 (53.4)
Current user	-	-		29 (9.6)	31 (10.1)
Never used	44 (32.4)	47 (36.2)		91	102 (33.2)
Not reported or	-	-		14 (4.7)	10 (3.3)
History of diabetes or hyperglycemia, n (%)					
Yes	11 (8.1)	22 (16.9)		56	58 (18.9)
ECOG PS score, n (%)					
0	63 (46.3)	51 (39.2)		120	124 (40.4)
1	61 (44.9)	66 (50.8)		181	183 (59.6)
2	12 (8.8)	13 (10.0)		-	-
Bellmunt risk score, n (%)					
0–1	103 (75.7)	95 (73.1)		201	208 (67.8)
≥2	33 (24.3)	35 (26.9)		90	96 (31.3)
Not reported	-	-		10 (3.3)	3 (1.0)
Origin site of primary disease, n (%)					
Upper urinary tract	41 (30.1)	48 (36.9)		98	107 (34.9)
Bladder or other site	95 (69.9)	82 (63.1)		203	200 (65.1)
Sites of metastasis, n/total (%)					
Lymph node only	-	-		34/301	28/306 (9.2)
Visceral site	101 (74.3)	97 (74.6)		234/301	250/306 (81.7)
Liver	31 (22.8)	38 (29.2)		93/301	95/307 (30.9)

PD-L1 status					
Low expression (CPS	89 (92.7)	68 (86.1)	[redacted]	-	-
FGFRa/t, n/total (%)					
Mutations	108/135	107/129 (82.3)	-	-	-
Fusions	25/135	19/129 (14.6)	-	-	-
Mutations and	2/135	3/129 (2.3)	-	-	-
Histologic type at initial diagnosis, n/total (%)					
Urothelial or	-	-	-	229/301	230/305 (75.4)
Urothelial carcinoma,	-	-	-	45/301	42/305 (13.8)
Other§	-	-	-	27/301	33/305 (10.8)
Histologic type at baseline, n (%)					
Transitional cell	128 (94.1)	124 (95.4)	[redacted]		
Transitional cell	8 (5.9)	6 (4.6)	[redacted]		
Previous systemic therapies, n (%)					
1–2	135 (99.3)	130 (100)	[redacted]	262	270 (87.9)
≥3	1 (0.7)	-	[redacted]	39	37 (12.1)
Prior platinum-based chemotherapy, n (%)					
None	14 (10.3)	19 (14.6)	-	0	0
Best response among patients who previously received checkpoint inhibitor treatment, n (%)¶					
Response	-	-	-	61	50 (16.3)
No response	-	-	-	207	215 (70.0)
Time since diagnosis of metastatic or locally advanced disease in months					
Median (min, max)	-	-	-	14.8	13.2 (0.3, 118.4)
Time from diagnosis of surgically unresectable or metastatic disease to randomization in months					
Median (min, max)	12.9 (0.6,	11.7 (1.8, 63.5)	[redacted]	-	-

Source: Van Staden S (48), THOR C1 CSR for vinflunine subgroup; Tables TSIDEM11A & TSIDC11A (50).

* Percentages may not total 100 because of rounding.

§ Other histologic types include adenocarcinoma, squamous-cell carcinoma, and pseudosarcomatic differentiation.

¶ The best response among patients who had a response was defined as a confirmed complete or partial response; among patients who did not have a response, the best response was defined as stable disease or progressive disease.

Abbreviations: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; min, minimum; max, maximum; PD-L1, Programmed Death-(Ligand) 1.

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

The characteristics of the patients included in the THOR C1 trial seem to reflect the Danish population well. The proportion of male/female in bladder and urinary cancer was sourced from NORDCAN (51), the other characteristics were previously accepted by the DMC in the assessment of EV in an equivalent indication (35).

Table 14. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population ((35))	Value used in health economic model (THOR C1 ITT)
Age	68 years	66.3 years
Gender	74% male, 26% female (51)	71.4% male, 28.6% female
Patient weight	73.9 kg	72.9 kg
Body surface area (BSA) (m^2)	1.9 m^2	1.82 m^2

6.1.4 Efficacy – results per THOR C1

The outcomes from the THOR C1 trial are presented in the section below. As mentioned at the beginning of the section, to better support the consistency of the effect of erdafitinib, the chemotherapy arm (i.e., ITT population) will be reported alongside the vinflunine subgroup arm to provide better context to the DMC and to interpret the results of the MAIC sufficiently. It is worth noting that the THOR trial was not designed and therefore not powered to assess treatment effect within subgroups, and the number of patients in some subgroups was small.

The source of the primary data for THOR C1 presented in this submission is based on the publication from Loriot et al., 2023 (42) and the respective clinical study report (50).

6.1.4.1 OS

The OS for erdafitinib vs. the vinflunine subgroup of patients in THOR C1 was a post-hoc analysis (50). The latest OS efficacy results are based on a median follow-up of 15.9 months (clinical cutoff: 15 January 2023) (50).

Patients treated with erdafitinib had a longer median OS and a significantly lower hazard of OS events (HR = 0.64; 95% CI: 0.47, 0.88; p-value=0.0050) than patients who received chemotherapy (ITT population) (50). A longer OS was also observed for patients treated with erdafitinib vs. vinflunine (HR = 0.54; 95% CI: 0.36, 0.81; Table 15) (50) and was consistent (based on HR) with the primary analysis of erdafitinib vs. chemotherapy. This represents a 46% reduction in risk of death for patients in the erdafitinib treatment arm vs. the vinflunine treatment arm.

The Kaplan-Meier (KM) curves are shown [redacted]d Figure 7.

Table 15. OS for erdafitinib vs. vinflunine vs. chemotherapy; unstratified analysis; cohort 1 ITT analysis set

	Erdafitinib N = 136	Vinflunine N = 48	Chemotherapy N = 130
OS median, months (95% CI)	12.06 (10.28, 16.36)	[redacted]	7.79 (6.54, 11.07)
6-month survival rate (95% CI)	0.85 (0.77, 0.90)	[redacted]	0.66 (0.56, 0.74)
12-month survival rate (95% CI)	0.51 (0.41, 0.60)	[redacted]	0.38 (0.28, 0.47)
24-month survival rate (95% CI)	0.26 (0.17, 0.36)	[redacted]	0.20 (0.11, 0.31)
HR (95% CI)*		0.54 (0.36, 0.81)	0.64 (0.47, 0.88)

Source: THOR C1 clinical study report; TEFOS20A (50).

Note: OS in months is calculated as (date of death – date of randomization+1)/30.4375. If the subject is alive or the vital status is unknown (for example, lost to follow-up or withdrew consent etc.), OS is censored at the date the subject was last known to be alive. Subjects lacking data beyond randomization have their OS censored at the date of randomization.

*Hazard ratio and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the only explanatory variable. A hazard ratio less than 1 indicates longer survival time in the erdafitinib arm as compared to the docetaxel and vinflunine arms, respectively.

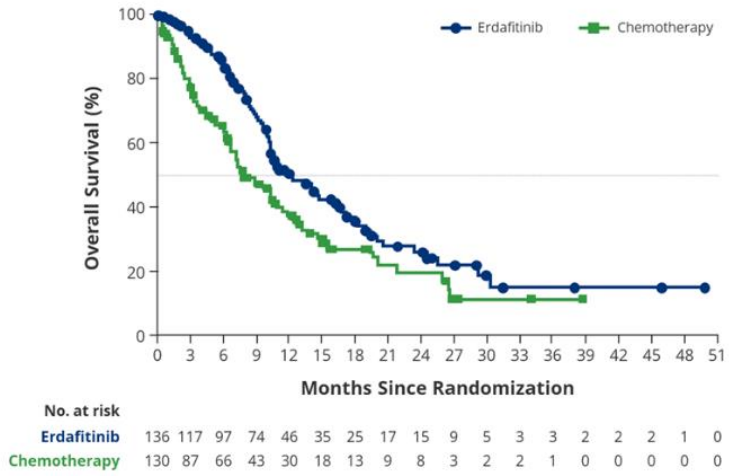
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

[redacted]

Source: IPD data analyses (data on file) (52).

Abbreviation: ITT, intention-to-treat.

Figure 7. Kaplan-Meier OS curves for erdafitinib vs. chemotherapy; cohort 1 ITT analysis set



Source: THOR C1 clinical study report (50)

Abbreviation: ITT, intention-to-treat.

6.1.4.2 PFS

The PFS for erdafitinib vs. the vinflunine subgroup of patients in THOR C1 was a post-hoc analysis (50). The latest PFS efficacy results are based on a median follow-up of 15.9 months (clinical cutoff: 15 January 2023) (50).

Patients treated with erdafitinib had a longer median PFS and a significantly lower hazard of PFS events (HR = 0.58; 95% CI: 0.44, 0.77; P-value= 0.0002) than patients who received chemotherapy (ITT population) (50). As with OS, a numerically longer PFS was observed for patients treated with erdafitinib vs. vinflunine (HR = 0.64; 95% CI: 0.44, 0.93; Table 16) (50) and was consistent (based on HR) with the primary analysis of erdafitinib vs. chemotherapy. This represents a 36% reduction in risk of disease progression for patients in the erdafitinib treatment arm vs. the vinflunine treatment arm. The KM curves are shown i[redacted] Figure 9.

Table 16. PFS for erdafitinib vs. vinflunine vs. chemotherapy; unstratified analysis; cohort 1 ITT analysis set

	Erdafitinib N = 136	Vinflunine N = 48	Chemotherapy N = 130
PFS median, months (95% CI)	5.55 (4.40, 5.65)	[redacted]	2.73 (1.81, 3.68)
6-month survival rate (95% CI)	0.37 (0.28, 0.46)	[redacted]	0.27 (0.19, 0.37)
12-month survival rate (95% CI)	0.17 (0.10, 0.25)	[redacted]	0.08 (0.03, 0.15)
24-month survival rate (95% CI)	0.05 (0.01, 0.12)	[redacted]	0.04 (0.00, 0.13)
HR (95% CI)*		0.64 (0.44, 0.93)	0.58 (0.44, 0.78)

Source: THOR C1 clinical study report; TEFPFS14A (50).

Note: PFS in months is defined as time from the date of randomization to the date of disease progression (assessed per RECIST v1.1 by the investigator) or relapse from complete response or death, whichever is reported first divided by 30.4375. PFS is censored at the date of the last adequate disease assessment for subjects who do not have disease progression and are alive, as well as for subjects with unknown disease progression or unknown survival status as of the clinical cutoff date. Also, if there is no post baseline tumor assessment for a subject, PFS is censored on the date of randomization. Subjects who die or have disease progression after starting subsequent anti-cancer therapy will be censored at the last tumor assessment date.

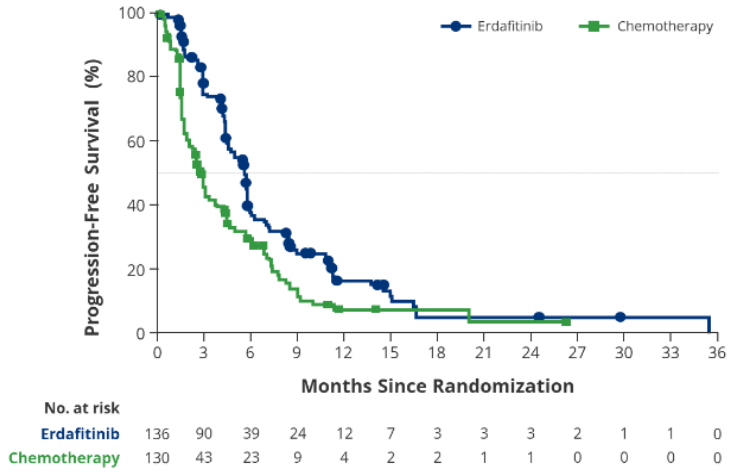
*Hazard ratio and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the explanatory variable. A hazard ratio less than 1 indicates longer survival time in the erdafitinib arm as compared to the docetaxel and vinflunine arms, respectively.

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

[redacted]

Abbreviations: ITT, intention-to-treat.

Figure 9. Kaplan-Meier PFS curves for erdafitinib vs. chemotherapy; cohort 1 ITT analysis set



Source: THOR C1 clinical study report (50)

Abbreviations: ITT, intention-to-treat

6.1.4.3 ORR

The ORR for erdafitinib vs. the vinflunine subgroup of patients in THOR C1 was a post-hoc analysis (50). The latest ORR efficacy results are based on a median follow-up of 15.9 months (clinical cutoff: 15 January 2023) (50).

The ORR (CR + PR) by investigator assessment and per RECIST 1.1 was 45.6% for the erdafitinib treatment group and 11.5% for the chemotherapy treatment group (ITT population) (50). The difference in ORR between treatment groups was statistically significant (RR = 3.94; 95% CI: 2.37, 6.57; 2-sided p<0.001), based on a 2-sided and multiplicity-adjusted significance level of 0.019 (50). The ORR for patients treated with erdafitinib was 45.6%, compared to 14.6% for patients treated with vinflunine (RR = 3.13; 95% CI: 1.54, 6.35; Table 17) (50) and was consistent (based on RR) with the primary analysis of erdafitinib vs. chemotherapy. This represents more than [redacted] f achieving an objective response for patients in the erdafitinib treatment arm vs. the vinflunine treatment arm.

Table 17. Summary of best overall response for erdafitinib vs. vinflunine; unstratified analysis; cohort 1 ITT analysis set

	Erdafitinib N = 136	Vinflunine N = 48	Chemotherapy N = 130
Best overall response, n (%)			
Complete response (CR)	9 (6.6%)	[redacted]	1 (0.8%)
Partial response (PR)	53 (39.0%)	[redacted]	14 (10.8%)
Stable disease (SD)	50 (36.8%)	[redacted]	41 (31.5%)
Progressive disease (PD)	14 (10.3%)	[redacted]	31 (23.8%)
Not evaluable (NE)	10 (7.4%)	[redacted]	43 (33.1%)
Objective response rate (CR + PR), n (%)	62 (45.6%)	[redacted]	15 (11.5%)
Relative risk (95% CI)		[redacted]	3.94 (2.37, 6.57)
Disease control rate (CR + PR + SD), n (%)	112 (82.4%)	[redacted]	56 (43.1%)
Relative risk (95% CI)		[redacted]	1.91 (1.55, 2.35)

Source: THOR C1 clinical study report; TEFBORU07A (50).

Note: Minimum duration requirement for SD is 6 weeks from the date of randomization. Stable disease includes subjects with no measurable disease at baseline and their best response was Non-CR/Non-PD.

ORR: Relative risk greater than 1 indicates that the probability of achieving an objective response (PR or CR) is higher on the Erdafitinib arm compared to the docetaxel and vinflunine arms, respectively.

DCR: Relative risk greater than 1 indicates that the probability of achieving a response of SD or better is higher on the Erdafitinib arm compared to the docetaxel and vinflunine arms, respectively.

Abbreviations: CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

6.1.5 Efficacy – results per EV-301

The outcomes from the EV-301 trial are presented in the section below. The source of the primary data for EV-301 presented in this submission is based on the publication from Rosenberg et al., 2023 (5).

6.1.5.1 OS

The OS for EV vs. chemotherapy in EV-301 was the primary endpoint for the ITT population (5). The latest OS efficacy results are based on a median follow-up of 23.75 months (data cutoff: 30 July 2021) (5).

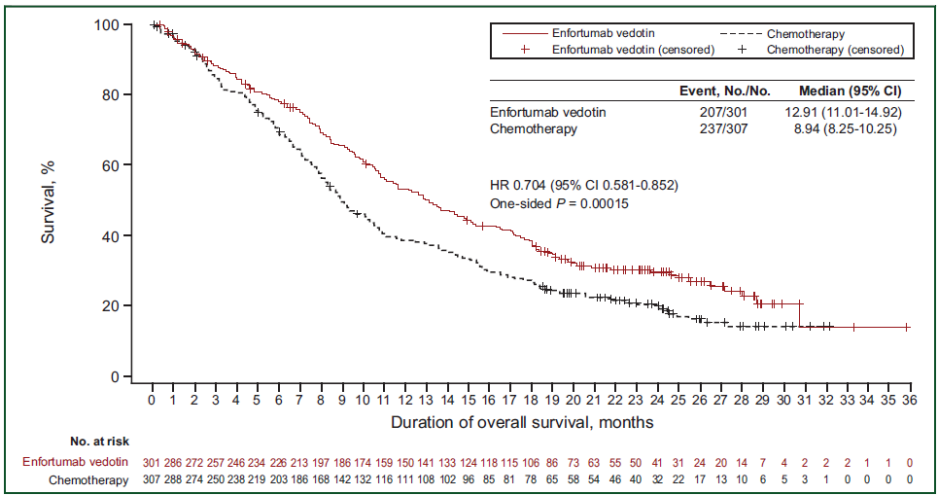
A statistically significant improvement in OS was observed for patients treated with EV vs. chemotherapy (HR = 0.70; 95% CI: 0.58, 0.85; Table 18) (5). This represents a 30% reduction in risk of death for patients in the EV treatment arm vs. the chemotherapy treatment arm. The KM curves are shown in Figure 10.

Table 18. OS for EV vs. chemotherapy; ITT analysis set

	EV N = 301	Chemotherapy N = 307
OS median, months (95% CI)	12.91 (11.01, 14.92)	8.94 (8.25, 10.25)
HR (95% CI)		0.70 (0.58, 0.85)
1-sided P value		0.00015

Source: Rosenberg et al., 2023 (5)
Abbreviations: CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.

Figure 10. Kaplan-Meier OS curves for EV vs. chemotherapy; ITT analysis set



Source: Rosenberg et al., 2023 (5)
Abbreviations: CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.

6.1.5.2 PFS

The PFS for EV vs. chemotherapy in EV-301 was the secondary endpoint for the ITT population (5). The latest PFS efficacy results are based on a median follow-up of 23.75 months (data cutoff: 30 July 2021) (5).

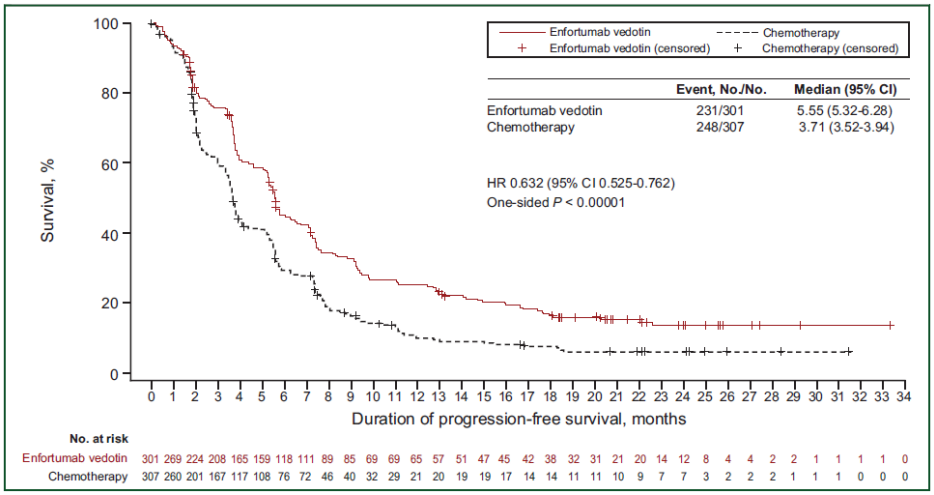
A statistically significant improvement in PFS was observed for patients treated with EV vs. chemotherapy (HR = 0.63; 95% CI: 0.53, 0.76; Table 22) (5). This represents a 37% reduction in risk of disease progression for patients in the EV treatment arm vs. the chemotherapy treatment arm. The KM curves are shown in Abbreviations: CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.
Figure 11.

Table 19. PFS for EV vs. chemotherapy; ITT analysis set

	EV N = 301	Chemotherapy N = 307
PFS median, months (95% CI)	5.55 (5.32, 6.28)	3.71 (3.52, 3.94)
HR (95% CI)		0.63 (0.53, 0.76)
1-sided P value		0.00001

Source: Rosenberg et al., 2023 (5).
Abbreviations: CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Figure 11. Kaplan-Meier PFS curves for EV vs. chemotherapy; ITT analysis set



Source: Rosenberg et al., 2023 (5).
Abbreviations: CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

6.1.5.3 ORR

The ORR for EV vs. chemotherapy in EV-301 was the secondary endpoint for the ITT population (5). The latest ORR efficacy results are based on a median follow-up of 23.75 months (data cutoff: 30 July 2021) (5).

The ORR for patients treated with EV was 41.32%, compared to 18.58% for patients treated with chemotherapy (5).

Table 20. Summary of Investigator-Assessed Response (Response Evaluable Population[a]); ITT analysis set

	EV N = 288	Chemotherapy N = 296
Best overall response[b], n (%)		
Complete response (CR)	20 (6.9%)	10 (3.4%)
Partial response (PR)	99 (34.4%)	45 (15.2%)
Stable disease (SD)	88 (30.6%)	103 (34.8%)
Progressive disease (PD)	44 (15.3%)	84 (28.4%)
Not evaluable (NE)	37 (12.8%)	54 (18.2%)
Objective response rate (CR + PR), n (%)	119 (41.32%)	55 (18.58%)
95% CI	35.57 - 47.25	14.32 - 23.49
Stratified 1-sided P value	< 0.001	
Disease control rate[c] (CR + PR + SD), n (%)	207 (71.88%)	158 (53.38%)
95% CI	66.30 - 76.99	47.52 - 59.17
Stratified 1-sided P value	< 0.001	

Source: Rosenberg et al., 2023 (5).

Note: [a]All randomized patients with measurable disease at baseline.

[b]Per Response Evaluation Criteria In Solid Tumours version 1.1. CR or PR was confirmed by 2 scans ≥ 4 wk apart. Minimum duration for SD was 7 wk.

[c]Proportion of patients with BOR of confirmed CR, confirmed PR, or SD (≥ 7 wk).

Abbreviations: CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

7. Comparative analyses of efficacy

Vinflunine is included in the THOR C1 trial as a part of the chemotherapy comparator arm. As the head-to-head data are available, this section is irrelevant for this comparator. However, in the absence of a head-to-head trial comparing erdafitinib and EV, an indirect treatment comparison (ITC) was required to estimate the relative efficacy and safety of these treatments. In this section, the ITC of erdafitinib and EV is described. The ITC finds no statistically significant difference in the efficacy of erdafitinib vs. EV. For this reason, the efficacy of erdafitinib vs. EV is assumed equal in the health economic analysis.

7.1.1 Differences in definitions of outcomes between studies

The OS, PFS, ORR, and CR were deemed comparable between the two trials. A summary of the definition of each endpoint considered for the ITCs is presented in detail in Appendix C.

7.1.2 Method of synthesis

A MAIC was undertaken for the comparative analysis of erdafitinib and EV, utilizing individual patient data (IPD) from the THOR C1 trial and aggregate data from the EV-301 trial (data cutoff: 30 July 2021; 23.75 months median follow-up). A brief description of the methodology of the MAIC is provided here, while a detailed description is provided in in Appendix C.

7.1.2.1 Feasibility of indirect treatment comparisons

A comparability assessment of the THOR and EV-301 trials was undertaken to ensure that there are no systematic differences between the studies, apart from the interventions being compared. The comparability assessment included a comparison of study characteristics (design, trial phase, sample size etc.), study population (inclusion and exclusion criteria and baseline characteristics), interventions and common comparators as well as study outcomes. Based on the comparability assessment, the studies were deemed sufficiently comparable (49).

Both THOR C1 and EV-301 randomized patients to physician's choice of chemotherapy, which was determined prior to trial enrolment. "Physician's choice of chemotherapy" in both trials is considered sufficiently comparable to be considered a common comparator (49).

7.1.2.2 Methods

An anchored MAIC, via the common comparator "physician's choice of chemotherapy" was conducted according to guidance from the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 (53).

The MAIC was adjusted for Bellmunt risk score, ECOG PS, presence of liver metastases and visceral metastases, origin of primary disease, smoking status, history of diabetes or hypoglycaemia, geographic region, age and gender. All analyses were conducted in SAS 9.4, except for the estimation of probabilistic summaries, which was conducted in WinBUGS (49).

Harmonization of eligibility criteria

To address the differences in the inclusion and exclusion criteria between the THOR C1 and EV-301 trials, an additional set of restriction criteria were applied to patients in THOR C1 to better align the trial population with that of EV-301. Patients in THOR C1 who met the following criteria were excluded from the analysis (49):

- ECOG PS 2
- No prior platinum-based chemotherapy
- More than one prior chemotherapy

Matching the baseline characteristics

After harmonizing the eligibility criteria of THOR C1 to EV-301, balancing weights were first derived. These weights were estimated using a propensity score-type logistic regression

equation that predicted whether a given type of patient originates from THOR C1 or EV-301 as a function of baseline characteristics. The weights (w_i) were estimated using the method of moments rather than by maximum likelihood (as might otherwise be the case), because only aggregate data (averages and percentages) for the selected covariates were available for EV-301's population (54). These weights were then used to calculate the effective sample size (ESS) achieved after weighting patients. The ESS was calculated by $(\sum w_i)^2/(\sum w_i^2)$ (49). After the individual patient weights were computed, the distribution of weights was assessed to identify any overly influential observation[redacted]

[redacted]

Source: Balversa MAIC report (data on file) (49)

The individual patient weights were employed to compute adjusted relative effects for patients in THOR C1, reflecting the estimated impact of erdafitinib vs. physician's choice of chemotherapy within the patient population of EV-301 trial. Binary outcomes in THOR C1 were quantified as odds ratios (OR) through weighted logistic regression, while time-to-event outcomes were quantified as hazard ratios (HR) through weighted Cox proportional hazards (PH) models, with the treatment included as a covariate. The standard error (SE) of the relative effects were computed using a robust sandwich estimator (55). Subsequently, these adjusted relative effects were compared with the observed relative effects of EV vs. chemotherapy in EV-301 to estimate the comparative effectiveness of erdafitinib vs. EV through a Bayesian network meta-analysis (NMA) (49).

Fixed-effects NMA models were fitted in Bayesian framework using Monte Carlo Markov Chain (MCMC) simulation methods implemented in WinBUGS. The weighted relative effects of erdafitinib vs. physician's choice of chemotherapy and observed relative effects of EV vs. physician's choice of chemotherapy were synthesized in the NMA model (e.g., log-HRs for PFS and OS, log-ORs for ORR, CR, and safety outcomes), where a normal likelihood and identity link were used following the methods described in NICE DSU TSD 2 (56). Non-informative normal (0, 100^2) priors were assigned to the basic relative effect parameters. All models were run using three chains with a burn-in period of 50,000 iterations. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic and

history plots (57, 58). A further simulation sample of 50,000 iterations for each chain was used to inform the results (49).

For all outcomes, the relative effects and their 95% credible intervals (CrI) of erdafitinib vs. EV were estimated. In addition, to aid the interpretation of binary outcomes, risk ratios (RRs) were also derived from the logistic regression models and included in the report. For time-to-event outcomes, the KM curves for the adjusted THOR C1 population were displayed for visual comparison, alongside the original KM curves from both THOR C1 and EV-301.

Response evaluable population

The analyses for response outcomes (ORR and CR) were restricted to the response-evaluable populations from both trials. Criteria validated by clinical experts were used to select response-evaluable patients in THOR C1. Patients who were not evaluable at baseline (defined in THOR C1 as patients without target lesions at baseline) or at follow-up were excluded from these analyses. The underlying assumption of the MAIC analyses for these outcomes is that the distributions of baseline characteristics in EV-301's ITT population are similar to those in the response evaluable population.

Assessment of proportional hazards

The MAIC of erdafitinib vs. EV for time-to-event outcomes assumes PH holds for the erdafitinib vs. chemotherapy comparison within the matched THOR C1 data, as well as the EV vs. chemotherapy comparison within the observed EV-301 data. To assess this assumption, the log-cumulative hazards for each treatment group were visually compared within these trial datasets (see Appendix C.3). Schoenfeld residuals plots were also visually inspected, and the Grambsch and Therneau test was conducted to quantitatively assess if there was evidence suggesting violation of the PH assumption (59).

Sensitivity analyses

Lastly, the following sensitivity analyses were conducted to assess the robustness of the results:

1. Impact of covariates included in adjustment
2. Impact of population differences in terms of prior lines of therapy

The sensitivity analyses are detailed in Appendix C.

7.1.3 Results from the comparative analysis

Baseline summaries of the covariates considered for adjustment are presented in Table 8 for patients in the THOR and EV-301 trials. Baseline characteristics for THOR were summarized across three distinct datasets:

1. Observed dataset: This refers to the initial, unmodified dataset.
2. Exclusion criteria applied dataset: This dataset was derived after aligning THOR's eligibility criteria with EV-301. A total of 69 patients were excluded from THOR because they had an ECOG PS of 2 (n = 25), no prior platinum-based

chemotherapy (n = 33), or more than one prior chemotherapy (n = 11), the distribution of baseline characteristics slightly changed, most notably for ECOG PS, which was to be expected.

3. Matched dataset: This dataset involves an additional level of refinement, where patients in the 'Exclusion criteria applied dataset' were weighted to adjust for differences in baseline covariates between THOR and EV-301.

After applying the individual patient weights to the remaining THOR patients, the average baseline characteristics matched those observed in EV-301. The ESS decreased from 197 to 126, marking a 36% reduction, yet this was deemed adequate for a plausible comparison. Table 21 presented the baseline characteristics of EV-301 and THOR C1 before and after matching patients.

Table 21. Baseline characteristics for EV-301 and THOR C1 before and after matching patients

	EV-301 Observed (N = 608)	THOR Observed (N = 266)	THOR Exclusion criteria applied (n = 197)	THOR Matched (ESS = 126/n=197)
Bellmunt risk score (%)				
0-1	68	74	78	68
2	32	26	22	32
ECOG PS (%)				
0	40	43	48	40
1	60	48	52	60
Presence of liver metastasis (%)				
Yes	25	26	26	25
Presence of visceral metastasis (%)				
Yes	66	74	76	66
Origin of primary disease (%)				
Upper urinary tract	34	33	35	34
Bladder or other site	66	67	65	66
Smoking status (%)				
Never smoked	33	34	31	33
History of diabetes or hyperglycemia (%)				
Yes	19	12	12	19
Region (%)				
Western Europe	42	61	60	42
US	14	5	5	14
Other	44	34	36	44
Age in years				
median	68	67	67	68
≥75 (%)	20	21	20	20
Sex				
Male (%)	77	71	71	77

Source: Balversa MAIC report (data on file) (49)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance score; ESS = effective sample size

Results from the MAIC for OS, PFS and ORR are reported in Table 22 below.

Table 22. Results from the comparative analysis of erdafitinib vs. EV (MAIC analyses)

Outcome measure	Erdafitinib vs. chemotherapy	EV vs. chemotherapy	Result (Erdafitinib vs. EV)
OS	HR (observed): 0.64 (95% CI: 0.47; 0.88, p < 0.01)	HR (observed): 0.70 (95% CI: 0.56; 0.89, p = N/A)	HR: 0.92 (95% CI 0.55; 1.54, p = 0.74)
PFS	HR (observed): 0.58 (0.44; 0.78, p < 0.01)	HR (observed): 0.63 (0.53; 0.76, p = N/A)	HR: 0.92 (95% CI 0.55; 1.53, p = 0.74)
ORR	N/A	N/A	OR: 1.45 (95% CI 0.45; 4.64, p = 0.54)

Source: Balversa MAIC report (data on file) (49)

Abbreviations: CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; N/A, not applicable; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

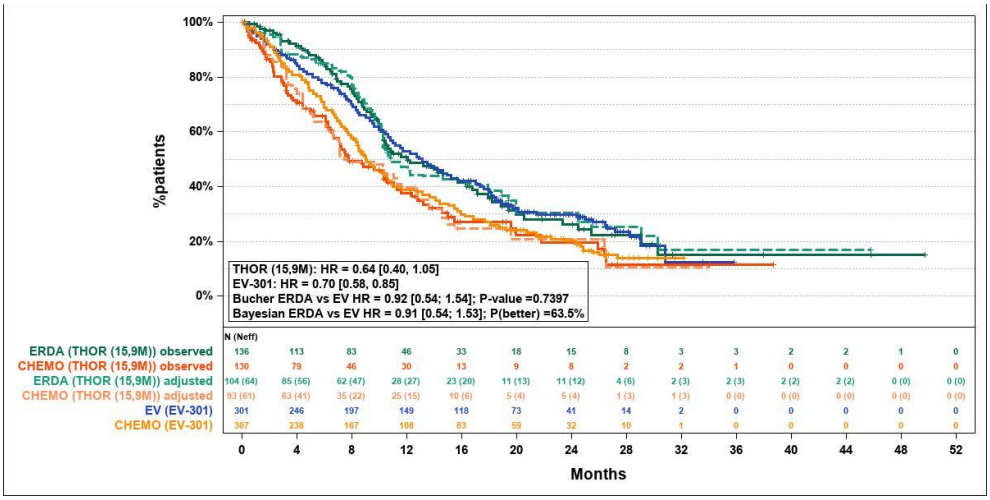
7.1.4 Efficacy – results per OS

In terms of OS, the matching adjustment had limited impact on the relative effectiveness, as the HRs of erdafitinib vs. EV were consistent before and after matching (Figure 13, Table 23).

The Bucher HR was not statistically significant at the conventional significance level of p < 0.05, nor at a more lenient threshold of p < 0.1. Additionally, the CI for the HR includes 1, indicating that the true effect could potentially be null (no effect difference). This further supports the conclusion that the HR is not statistically significant.

The width of the corresponding confidence intervals increased after matching THOR C1 patients, which was in line with the decrease in ESS.

Figure 13. Overall survival – Kaplan-Meier curves



Source: Balversa MAIC report (data on file) (49)

Abbreviations: CHEMO, chemotherapy; ERDA, erdafitinib; EV, enfortumab vedotin; HR, hazard ratio.

Table 23. Within-trial and between-trial comparative analysis of OS (Bucher method)

	EV vs. chemotherapy (EV-301)	Erdafitinib vs. chemotherapy (THOR C1)	Erdafitinib vs. EV (Anchored MAIC)
Observed	HR: 0.70 (95% CI 0.58; 0.85, p = N/A)	HR: 0.64 (95% CI 0.47; 0.88, p < 0.01)	HR: 0.91 (95% CI 0.63; 1.31, p = 0.61)
Exclusion criteria applied	-	HR: 0.65 (95% CI 0.44; 0.94, p = 0.02)	HR: 0.92 (95% CI 0.60; 1.40, p = 0.69)
Matched	-	HR: 0.65 (95% CI 0.40; 1.05, p = 0.07)	HR: 0.92 (95% CI 0.55; 1.54, p = 0.74)

Source: Balversa MAIC report (data on file) (49)

Abbreviations: CI, confidence interval; EV, enfortumab vedotin; MAIC, matching-adjusted indirect comparison; N/A, not applicable; OS, overall survival.

In the sensitivity analyses where each covariate was cumulatively adjusted for one by one, the MAIC estimates for the HR of erdafitinib vs. EV were consistent across all covariates.

Similar results were observed when comparing OS of the matched THOR C1 patients with the ITT patients and patients in the subgroup who received 1-2 prior lines in EV-301.

The longer-term OS results in EV-301 were similar to the interim results, thus having negligible impact on the HR of erdafitinib vs. EV estimated by the MAIC.

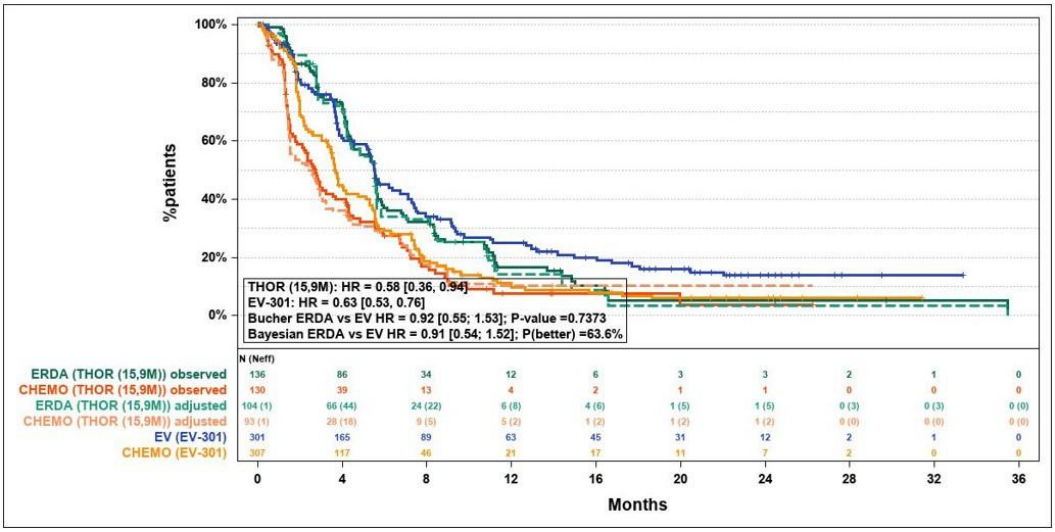
7.1.5 Efficacy – results per PFS

In terms of PFS, the HRs of erdafitinib vs. EV were consistent before and after matching the THOR C1 patients to EV-301's population (Figure 14, Table 24).

The Bucher HR was not statistically significant at the conventional significance level of $p < 0.05$, nor at a more lenient threshold of $p < 0.1$. Additionally, the CI for the HR includes 1, indicating that the true effect could potentially be null (no effect difference). This further supports the conclusion that the HR is not statistically significant.

The confidence intervals widened after matching THOR C1 patients, which was in line with the decrease in ESS.

Figure 14. Progression-free survival – Kaplan-Meier curves



Source: Balversa MAIC report (data on file) (49)

Abbreviations: CHEMO, chemotherapy; ERDA, erdafitinib; EV, enfortumab vedotin; HR, hazard ratio.

Table 24. Within-trial and between-trial comparative analysis of PFS (Bucher method)

	EV vs. chemotherapy (EV-301)	Erdafitinib vs. chemotherapy (THOR C1)	Erdafitinib vs. EV (Anchored MAIC)
Observed	HR: 0.63 (95% CI 0.53; 0.76, p = N/A)	HR: 0.58 (95% CI 0.44; 0.78, p < 0.01)	HR: 0.92 (95% CI 0.65; 1.30, p = 0.64)
Exclusion criteria applied	-	HR: 0.54 (95% CI 0.38; 0.75, p < 0.01)	HR: 0.85 (95% CI 0.58; 1.25, p = 0.41)
Matched	-	HR: 0.58 (95% CI 0.36; 0.94, p = 0.03)	HR: 0.92 (95% CI 0.55; 1.53, p = 0.74)

Source: Balversa MAIC report (data on file) (49)

Abbreviations: CI, confidence interval; EV, enfortumab vedotin; MAIC, matching-adjusted indirect comparison; N/A, not applicable; PFS, progression-free survival.

In the sensitivity analyses where each covariate was cumulatively adjusted for one by one, the MAIC estimates for the HR of erdafitinib vs. EV were consistent across all covariates.

Similar results were observed when comparing PFS of the matched THOR C1 patients to the PFS outcomes of the ITT patients and patients in the subgroup who received 1-2 prior lines in EV-301.

The longer-term PFS results in EV-301 were similar to the interim results, thus having negligible impact on the HR of erdafitinib vs. EV estimated by the MAIC.

7.1.6 Efficacy – results per ORR

In terms of ORR, the relative effects of erdafitinib vs. EV increased after matching the THOR C1 patients to EV-301's population (Table 25).

Table 25. Between-trial comparative analysis of ORR (Bucher method)

	Erdafitinib vs. EV (Anchored MAIC)
Observed	OR: 1.28 (95% CI 0.56; 2.94, p = 0.56)
Exclusion criteria applied	OR: 1.59 (95% CI 0.63; 4.07, p = 0.33)
Matched	OR: 1.45 (95% CI 0.45; 4.64, p = 0.54)

Source: Balversa MAIC report (data on file) (49)

Abbreviations: CI, confidence interval; EV, enfortumab vedotin; OR, odds ratio; ORR, overall response rate; RR, risk ratio.

In the sensitivity analyses where each covariate was cumulatively adjusted for one by one, the MAIC estimates of erdafitinib vs. EV were consistent across all covariates.

The longer-term ORR results in EV-301 were close to the interim findings, thus having minimal influence on the estimated relative effect of erdafitinib vs. EV estimated by the MAIC.

8. Modelling of efficacy in the health economic analysis

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

8.1.1 Extrapolation of efficacy data

In order to model costs and effects of erdafitinib and vinflunine in mUC, efficacy data from the THOR C1 trial was extrapolated to the model horizon. The three extrapolated efficacy measures were overall survival, progression-free survival, and time to treatment discontinuation.

A real-world study in Nordic centres studied post-pembrolizumab survival in mUC (60). This study will be leveraged to validate the survival of the vinflunine arm in overall and progression-free survival. For erdafitinib, the phase II, single arm trial (BLC2001) had a substantially longer follow-up than the THOR C1 trial and can be used to validate the erdafitinib survival (61).

8.1.1.1 Extrapolation of overall survival

Overall survival of erdafitinib and vinflunine was modelled using patient level data from THOR C1. Analysis of OS shows strong evidence of improvement for patients treated with erdafitinib versus vinflunine, with a HR of 0.54 (95% CI: 0.36–0.81), representing a 46% reduction in the rate of all-cause death for patients receiving erdafitinib versus vinflunine.

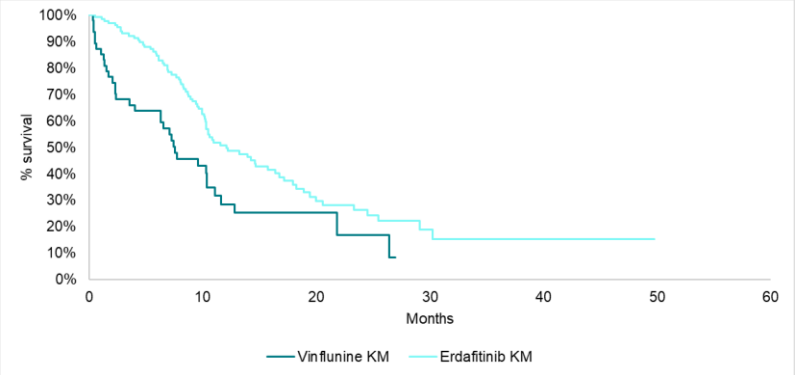
Table 26. Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	Time-to-event data for OS was collected directly from THOR C1.
Model	Full parametrization was applied in extrapolating the efficacy. Seven functional forms were used to fit OS curves.
Assumption of proportional hazards between intervention and comparator	The proportional hazard assumption is not valid for the comparison of erdafitinib to vinflunine, as seen in log-cumulative hazard plots of OS, PFS, and TTD for erdafitinib versus each trial comparator (Figure 33).
Function with best AIC fit	Erdafitinib: Log-logistic model Vinflunine: Exponential model
Function with best BIC fit	Erdafitinib: Log-logistic model Vinflunine: Exponential model
Function with best visual fit	Erdafitinib: The visual fit of the models is reasonable; however, the exponential and Gompertz initially underestimate survival and then overestimate it beyond 10 months. Vinflunine: All seven curves provide a good visual fit to the KM curve, but the log-logistic and log-normal curves provide more optimistic long-term projections than the remaining models.
Function with best fit according to evaluation of smoothed hazard assumptions	Erdafitinib: Log-logistic, log-normal and generalized gamma distribution followed the smoothed hazard for the erdafitinib arm closely. Vinflunine: Out of the seven curves, only the exponential distribution shows a similar trend with the other models assuming a declining hazard beyond 3 months.
Validation of selected extrapolated curves (external evidence)	Erdafitinib: Phase II, single arm with median follow-up of 49 months. Vinflunine: Real-world study of post-pembrolizumab mUC survival
Function with the best fit according to external evidence	Erdafitinib: The median OS of the log-logistic model (13.1 months) aligns acceptably with the reported median OS (11.3 months) in the long-term follow-up of phase II study of erdafitinib (61). Vinflunine: The median OS of the exponential model (7.6 months) aligns very well with the reported median OS

Method/approach	Description/assumption
	reported in the vinflunine group in the real-world study of 7.7 months (60).
Selected parametric function in base case analysis	Erdafitinib: Log-logistic model Vinflunine: Exponential model
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

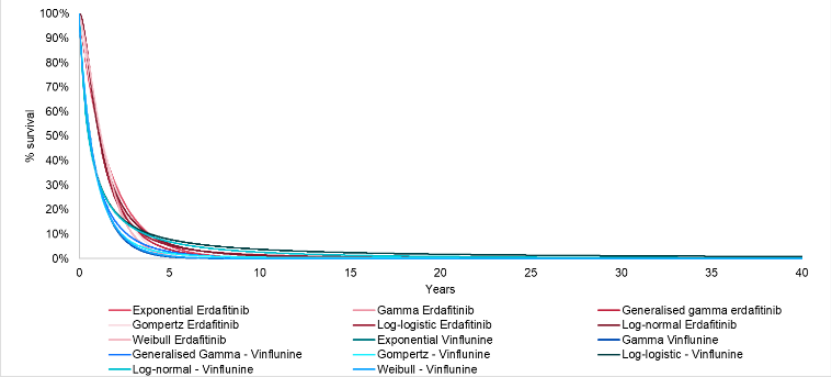
Abbreviations: EV, enfortumab vedotin; KM, Kaplan-Meier; OS, Overall survival.

Figure 15. Kaplan-Meier curves of overall survival of erdafitinib and vinflunine



Abbreviations: KM, Kaplan-Meier.

Figure 16. Investigated extrapolations of overall survival for both treatments over modelled time horizon



8.1.1.2 Extrapolation of progression-free survival

PFS was also modelled using patient level data from THOR C1. Analysis of PFS shows strong evidence of improvement for patients treated with erdafitinib versus vinflunine with a hazard ratio of 0.64 (95% CI: 0.44–0.93), representing a 36% reduction in the rate of disease progression or death for patients receiving erdafitinib versus vinflunine.

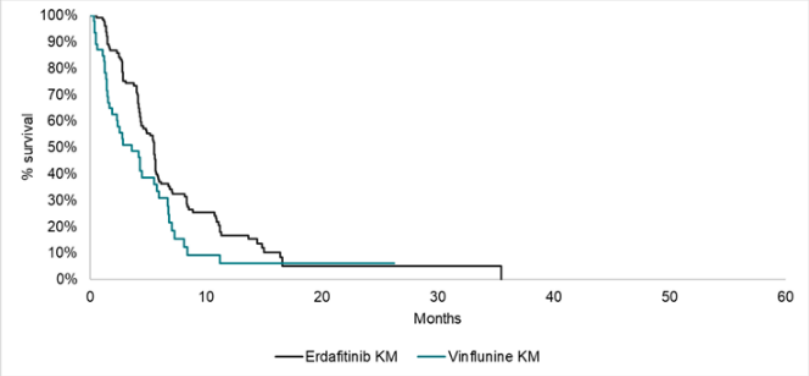
Table 27. Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	Time-to-event data for PFS was collected directly from THOR C1.
Model	Full parametrization was applied in extrapolating the efficacy. Seven functional forms were used to fit PFS curves.
Assumption of proportional hazards between intervention and comparator	The proportional hazard assumption is not valid for the comparison of erdafitinib to vinflunine, as seen in log-cumulative hazard plots of OS, PFS, and TTD for erdafitinib versus each trial comparator (Figure 33).
Function with best AIC fit	Erdafitinib: Log-normal model Vinflunine: Log-normal model
Function with best BIC fit	Erdafitinib: Log-normal model Vinflunine: Log-normal model
Function with best visual fit	Erdafitinib: The log-normal, log-logistic, and generalized gamma curves all fit the KM curve closely. Vinflunine: The visual fit to the KM curve is close with all models
Function with best fit according to evaluation of smoothed hazard assumptions	Erdafitinib: Log-logistic, log-normal and gen. gamma Vinflunine: None of the distributions stand out.
Validation of selected extrapolated curves (external evidence)	Erdafitinib: Phase II, single arm with median follow-up of 49 months. Vinflunine: Real-world study of post-pembrolizumab mUC survival
Function with the best fit according to external evidence	Erdafitinib: The median PFS of the log-logistic model (5.3 months) aligns very well with the reported median PFS (5.5 months) in the long-term follow-up of phase II study of erdafitinib (61). Vinflunine: The median PFS of the log-logistic model (3.6 months) aligns very well with the reported median PFS

Method/approach	Description/assumption
	reported in the vinflunine group in the real-world study of 3.4 months (60).
Selected parametric function in base case analysis	Erdafitinib: Log-logistic model Vinflunine: Log-normal model
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

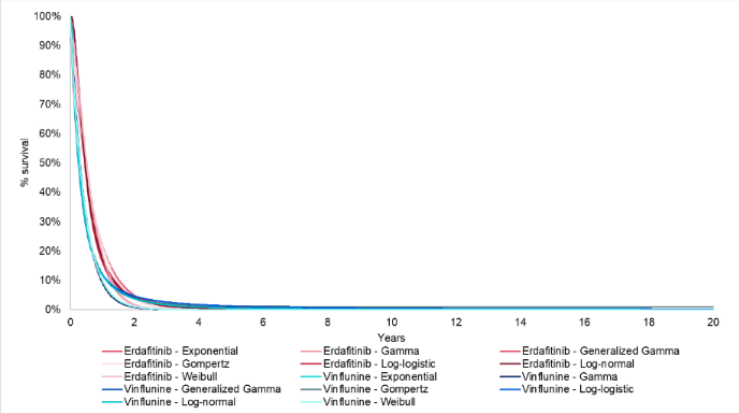
Abbreviations: EV, enfortumab vedotin; KM, Kaplan-Meier; N/A, not applicable; PFS, Progression-free survival.

Figure 17. Kaplan-Meier curves of progression-free survival of erdafitinib and vinflunine



Abbreviations: KM, Kaplan-Meier

Figure 18. Investigated extrapolations of progression-free survival for all treatments over model time horizon



8.1.1.3 Extrapolation of time to treatment discontinuation

The safety population from THOR C1 was used to derive TTD data, and seven parametric models were fitted and evaluated using the same approach that was taken for OS and PFS.

For patients on erdafitinib, the THOR C1 protocol allowed for treatment upon progression, However, based on clinical practice, the SmPC of erdafitinib and the previous assessment of EV (47), treatment should be stopped if the patient progresses. Thus, the model assumed the TTD is capped by the PFS. Not capping of TTD by PFS is investigated in a scenario analysis.

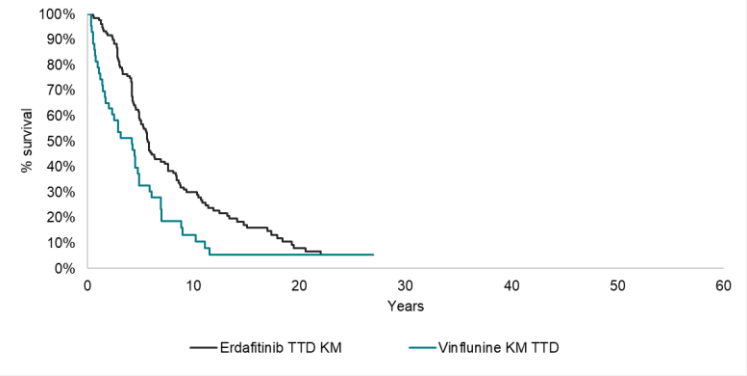
Table 28. Summary of assumptions associated with extrapolation of TTD

Method/approach	Description/assumption
Data input	The safety population from THOR C1 was used to derive TTD data
Model	Full parametrization was applied in extrapolating the efficacy. Seven functional forms were used to fit TTD curves.
Assumption of proportional hazards between intervention and comparator	The proportional hazard assumption is not valid for the comparison of erdafitinib to vinflunine, as seen in log-cumulative hazard plots of OS, PFS, and TTD for erdafitinib versus each trial comparator (Figure 33).
Function with best AIC fit	Erdafitinib: Log-logistic model Vinflunine: Log-normal model
Function with best BIC fit	Erdafitinib: Log-logistic model Vinflunine: Exponential model
Function with best visual fit	Erdafitinib: Log-logistic model has a good visual fit Vinflunine: All parametric models provide reasonable visual fit to the KM curve

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	Erdafitinib: Generalized gamma, log-logistic Vinflunine: None of the distributions stand out as a good fit
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Erdafitinib: Log-logistic model Vinflunine: Log-normal model
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

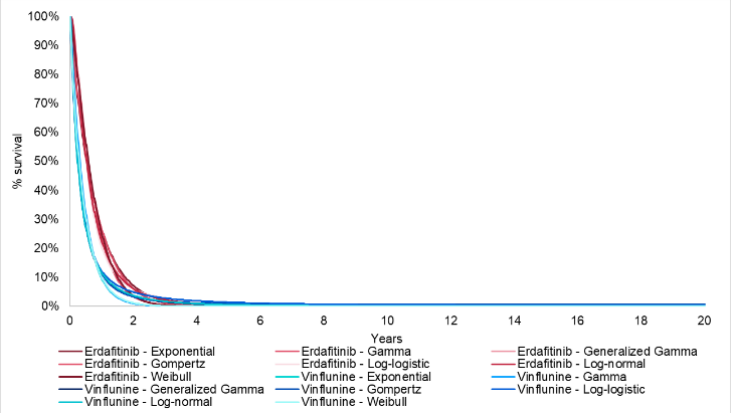
Abbreviations: KM, Kaplan-Meier; PFS, Progression-free survival; TTD, Time to treatment discontinuation.

Figure 19. Kaplan-Meier curves of time to treatment discontinuation of erdafitinib and vinflunine



Abbreviations: KM, Kaplan-Meier; TTD, Time to treatment discontinuation.

Figure 20. Investigated extrapolations of time to treatment discontinuation for all treatments over modelled time horizon



8.1.2 Calculation of transition probabilities

Not applicable in this three-state partitioned survival model.

Table 29. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

Subsequent treatment does not affect the disease progression in this model, it only incurs costs. The distribution and duration of subsequent treatments are described in Section 0.

8.4 Other assumptions regarding efficacy in the model

Erdafitinib is being considered as a last line of therapy. As such, it was deemed unnecessary to include a stopping rule or consider long-term waning of treatment effect. Because more than 90% of patients discontinue treatment within 2 years and more than 95% die within 5 years, inclusion of these elements would have a negligible impact on model outcomes.

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

Overall survival was the primary endpoint in the THOR C1 trial. The observed median from THOR C1 and the modelled estimates of overall survival are presented in Table 30 below.

The average overall survival was estimated as area-under-the-curve (AUC) of the chosen overall survival extrapolation.

Table 30. Estimates of primary endpoint in the model

	Modelled average overall survival	Modelled median overall survival	Observed median from THOR C1
Erdafinitib	1.78 years	1.11 years	1.00 years
Vinflunine	0.91 years	0.63 years	0.63 years

The average treatment duration and progression-free survival were estimated as area-under-the-curve of the chosen overall survival extrapolation. The time spent in progressed disease is the delta (difference) between the AUC of the modelled average overall survival and the modelled averaged progression-free survival. The modelled treatment duration and time spent in the two model health states is presented in Table 31.

Table 31. Overview of modelled average treatment length and time in model health states, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length	Progression-free	Progressed disease
Erdafitinib	0.66 years (capped by PFS)	0.69 years	1.09 years
Vinflunine	0.47 years (capped by PFS)	0.50 years	0.39 years

9. Safety

9.1 Safety data from the clinical documentation

In the THOR C1 study, the safety data was analysed using the safety analysis set, which included 247 patients (erdafitinib treatment arm = 135; chemotherapy treatment arm = 112) who received at least 1 dose of study drug (50). The latest safety data are based on a median follow-up of 15.9 months (clinical cutoff: 15 January 2023) (50). The median extent of exposure was 146.0 days (range: 5 to 1162 days) in the erdafitinib group and 43.0 days (range: 1 to 820 days) in the chemotherapy group (50).

In the EV-301 study, the safety data was analysed using the safety analysis set, which included patients who received any amount of trial drug (6).

The latest safety data from EV-301 based on the 23.75 median follow-up (data cutoff 30 July 2021) only describes treatment-related adverse events and would not be comparable to the safety data from THOR C1 (6). Therefore, the previous data cutoff (15 July 2020) of EV-301 will be described below, as more comprehensive adverse event data is publicly available and is based off a median follow-up of 11.1 months (6).

Table 32. Overview of safety events

		THOR C1		EV-301	
	Erdafitinib (N=135)	Chemo-therapy (N=112)	Vinflunine subgroup (N=43)	EV (N=296)	Chemo-therapy (N=291)
Number of adverse events, n	Not available	Not available	Not available	Not reported	Not reported
Number and proportion of patients with ≥1 adverse events, n (%)	133 (98.5%)	109 (97.3%)	[redacted]	290 (98.0%)	288 (99.0%)
Number of serious adverse events*, n	Not available	Not available	Not available	Not reported	Not reported
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	56 (41.5%)	47 (42.0%)	Not available	138 (46.6%)	128 (44.0%)
Number of CTCAE grade ≥ 3 events, n	Not available	Not available	Not available	Not reported	Not reported
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	85 (63.0%)	72 (64.3%[redacted]		210 (70.9%)	193 (66.3%)
Number of adverse reactions, n	Not available	Not available	Not available	Not reported	Not reported
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	Not available	Not available	Not available	Not reported	Not reported
Number and proportion of patients who had a dose reduction, n (%)	93 (68.9%)	27 (24.1%)	Not available	101 (34.1%)	81 (27.8%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	106 (78.5%)	102 (91.1%)	Not available	Not reported	Not reported
Number and proportion of patients who discontinue treatment	19 (14.1%)	20 (17.9%)	Not available	51 (17.2)	51 (17.5)

	THOR C1			EV-301	
	Erdafitinib (N=135)	Chemo-therapy (N=112)	Vinflunine subgroup (N=43)	EV (N=296)	Chemo-therapy (N=291)
due to adverse events, n (%)					

Source: THOR C1 clinical study report (50); Powles et al., 2021 (6).

*A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EV, enfortumab vedotin.

Serious adverse event data is not available for EV-301, therefore only THOR C1 will be presented in the table below. In Table 33, the serious adverse events in THOR C1 with an incidence of 5% or higher are presented.

Table 33. Serious adverse events with a frequency of ≥ 5%; THOR C1; safety analysis

Adverse events	Erdafitinib (N=135)	Chemotherapy (N=112)
	Number of patients with adverse events	**Number of patients with adverse events**
Febrile neutropenia	0	7 (6.3%)

Source: THOR C1 clinical study report (50).

*A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

AEs applied in the health economic model are presented in Table 34. Most AEs are assumed to occur early in the treatment; therefore, their consequences in costs and QALYs are incurred once at model start.

Table 34. Adverse events used in the health economic model

Adverse events	Erdafitinib	Vinflunine	EV		
	Frequency used in economic model			**Source**	**Justification**
Palmar-plantar erythrodysesthesia syndrome	9.63%	0.00%	0.00%	THOR CSR section 5.2.2.1.2 (erdafitinib) and IPD analysis (vinflunine);	The model includes all grade ≥ 3 treatment-emergent AEs experienced by at least 5% of

Adverse events	Erdafitinib	Vinflunine	EV		
Stomatitis	8.15%	4.65%	0.00%	Powles et al. 2021 (6) (EV)	patients in the safety population in either treatment arm in THOR C1. It was assumed that minor AEs that affected less than 5% of patients would have negligible impact on QALYs and costs.
Anaemia	7.41%	13.95%	2.70%		
Hyponatraemia	7.41%	4.65%	0.00%		
Onycholysis	5.93%	0.00%	0.00%		
Hyperphosphatemia	5.19%	0.00%	0.00%		
Neutropenia	0.00%	16.28%	4.73%		
Leukopenia	0.00%	4.65%	0.00%		
Febrile neutropenia	0.00%	4.65%	0.68%		
Fatigue	0.00%	2.33%	6.42%		
Maculopapular rash	0.00%	0.00%	7.43%		
Decreased neutrophil count	0.00%	0.00%	6.08%		

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

N/A, the health economic model does not use safety data from external literature.

Table 35. Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			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	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

In the THOR C1 phase 3 trial, scores for the FACT-BI, PGI-S, and EQ-5D-5L were obtained for patients receiving erdafitinib and chemotherapy (among which vinflunine). The EQ-5D-5L is the only instrument informing health state utilities, thus the only one described in this chapter.

Table 36. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	THOR C1 clinical trial	The EQ-5D-5L outcomes are used to directly estimate Danish values

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The instrument EQ-5D-5L was considered to be the most transferable and informative for the decision problem, as this is a widely accepted measure of HRQoL and allows for direct estimation of Danish utility values in line with the DMC guidelines (62).

The population contributing to the HRQoL differs from the population contributing to the clinical data, as the HRQoL data was pooled from the three comparator subgroups in the THOR C1 trial.

The VAS and utility scale of the EQ-5D-5L were captured. The VAS asks a patient to mark on a scale from 0 to 100 (0 being worst health imaginable, and 100 best health imaginable), how their overall health is that day. The EQ-5D-5L asks if a patient has any problems on a 5-point scale across 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). These health states were then converted into a Health Utility Index (HUI), where 1 represents full health and 0 represents dead.

To evaluate changes in scores from baseline, descriptive statistics (number of observations, mean, standard deviation, minimum, maximum) were produced for the EQ-5D-5L by visit. For the EQ-5D-5L, descriptive summaries for follow-up are also presented. A mixed-effects model with repeated measures (MMRM) analysis was conducted estimating change from baseline at each scheduled visit between the 2 treatment arms for EQ-5D-5L scores. Changes from baseline were fitted to a mixed-effects model including patients as a random effect, and baseline value, treatment group, time in month, treatment-by-time interaction, and stratification factors as fixed effects.

10.1.2 Data collection

In Table 37, all relevant time points are reported (i.e., time points where the number of expected forms received changed). Missing data and completion were calculated by combining the observations of the erdafitinib and the comparator arms, as health state utility values were estimated independently of treatment.

EQ-5D questionnaires were completed prior to any other study procedure on Day 1 and day 14 in cycle 1 and thereafter on day 1 in the subsequent 21-day study cycles until end of treatment. No imputation was performed in cases of missing questionnaires (i.e., questionnaires expected but not completed by patients remaining at risk at a scheduled assessment time). All available EQ-5D-5L questionnaires in THOR C1 that were used in the estimation of utility values were completed in full (i.e., there were no missing responses in any of the five domains).

Table 37. 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)
Erdafitinib				
Cycle 1 (day 1)	136	10 (7.4%)	136	126 (92.6%)
Cycle 1 (day 14)	136	21 (16.0%)	131	110 (84.0%)
Cycle 2 (day 1)	136	11 (8.6%)	128	117 (91.4%)
Cycle 3 (day 1)	136	20 (16.1%)	124	104 (83.9%)
Cycle 4 (day 1)	136	19 (16.2%)	117	98 (83.8%)
Cycle 5 (day 1)	136	20 (18.9%)	106	86 (81.1%)
Cycle 6 (day 1)	136	19 (19.8%)	96	77 (80.2%)
Cycle 7 (day 1)	136	14 (15.9%)	88	74 (84.1%)
Cycle 8 (day 1)	136	17 (22.4%)	76	59 (77.6%)
Cycle 9 (day 1)	136	10 (15.4%)	65	55 (84.6%)
Cycle 10 (day 1)	136	13 (24.1%)	54	41 (75.9%)
Cycle 11 (day 1)	136	5 (10.9%)	46	41 (89.1%)
Cycle 12 (day 1)	136	6 (13.6%)	44	38 (86.4%)
Cycle 13 (day 1)	136	7 (17.5%)	40	33 (82.5%)
Cycle 14 (day 1)	136	8 (22.2%)	36	28 (77.8%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 15 (day 1)	136	2 (6.5%)	31	29 (93.5%)
Cycle 16 (day 1)	136	3 (10.3%)	29	26 (89.7%)
Cycle 17 (day 1)	136	4 (15.4%)	26	22 (84.6%)
Cycle 18 (day 1)	136	3 (13.0%)	23	20 (87.0%)
Cycle 19 (day 1)	136	3 (14.3%)	21	18 (85.7%)
Cycle 20 (day 1)	136	1 (5.3%)	19	18 (94.7%)
Cycle 21 (day 1)	136	2 (11.1%)	18	16 (88.9%)
Cycle 22 (day 1)	136	4 (25.0%)	16	12 (75.0%)
Cycle 23 (day 1)	136	2 (15.4%)	13	11 (84.6%)
Cycle 24 (day 1)	136	0 (0.0%)	13	13 (100.0%)
Cycle 25 (day 1)	136	2 (15.4%)	13	11 (84.6%)
Cycle 26 (day 1)	136	2 (16.7%)	12	10 (83.3%)
Cycle 27 (day 1)	136	2 (18.2%)	11	9 (81.8%)
Cycle 28 (day 1)	136	1 (12.5%)	8	7 (87.5%)
Cycle 29 (day 1)	136	2 (28.6%)	7	5 (71.4%)
Cycle 30 (day 1)	136	0 (0.0%)	5	5 (100.0%)
Cycle 31 (day 1)	136	1 (20.0%)	5	4 (80.0%)
Cycle 32 (day 1)	136	0 (0.0%)	4	4 (100.0%)
Cycle 33 (day 1)	136	0 (0.0%)	4	4 (100.0%)
Cycle 34 (day 1)	136	0 (0.0%)	4	4 (100.0%)
Cycle 35 (day 1)	136	1 (25.0%)	4	3 (75.0%)
Cycle 36 (day 1)	136	0 (0.0%)	3	3 (100.0%)
Cycle 37 (day 1)	136	0 (0.0%)	3	3 (100.0%)
Cycle 38 (day 1)	136	0 (0.0%)	3	3 (100.0%)
Cycle 39 (day 1)	136	0 (0.0%)	3	3 (100.0%)
Cycle 40 (day 1)	136	1 (33.3%)	3	2 (66.7%)
Cycle 41 (day 1)	136	0 (0.0%)	2	2 (100.0%)
Cycle 42 (day 1)	136	0 (0.0%)	2	2 (100.0%)
Cycle 43 (day 1)	136	0 (0.0%)	2	2 (100.0%)
Cycle 44 (day 1)	136	0 (0.0%)	2	2 (100.0%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 45 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 46 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 47 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 48 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 49 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 50 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 51 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 52 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 53 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 54 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 55 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 56 (day 1)	136	0 (0.0%)	1	1 (100.0%)
Cycle 57 (day 1)	136	1 (100.0%)	1	0 (0.0%)
Cycle 58 (day 1)	136	0 (0.0%)	0	0 (0.0%)
Cycle 59 (day 1)	136	0 (0.0%)	0	0 (0.0%)
Cycle 60 (day 1)	136	0 (0.0%)	0	0 (0.0%)
End of treatment	136	0 (0.0%)	54	54 (100.0%)
Chemotherapy				
Cycle 1 (day 1)	130	24 (18.5%)	130	106 (81.5%)
Cycle 1 (day 14)	130	23 (24.7%)	93	70 (75.3%)
Cycle 2 (day 1)	130	7 (8.5%)	82	75 (91.5%)
Cycle 3 (day 1)	130	13 (20.0%)	65	52 (80.0%)
Cycle 4 (day 1)	130	8 (15.4%)	52	44 (84.6%)
Cycle 5 (day 1)	130	10 (23.3%)	43	33 (76.7%)
Cycle 6 (day 1)	130	6 (15.8%)	38	32 (84.2%)
Cycle 7 (day 1)	130	4 (12.5%)	32	28 (87.5%)
Cycle 8 (day 1)	130	4 (16.0%)	25	21 (84.0%)
Cycle 9 (day 1)	130	5 (23.8%)	21	16 (76.2%)
Cycle 10 (day 1)	130	6 (35.3%)	17	11 (64.7%)
Cycle 11 (day 1)	130	2 (16.7%)	12	10 (83.3%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 12 (day 1)	130	4 (36.4%)	11	7 (63.6%)
Cycle 13 (day 1)	130	4 (40.0%)	10	6 (60.0%)
Cycle 14 (day 1)	130	2 (28.6%)	7	5 (71.4%)
Cycle 15 (day 1)	130	3 (42.9%)	7	4 (57.1%)
Cycle 16 (day 1)	130	2 (33.3%)	6	4 (66.7%)
Cycle 17 (day 1)	130	1 (20.0%)	5	4 (80.0%)
Cycle 18 (day 1)	130	1 (25.0%)	4	3 (75.0%)
Cycle 19 (day 1)	130	1 (25.0%)	4	3 (75.0%)
Cycle 20 (day 1)	130	2 (66.7%)	3	1 (33.3%)
Cycle 21 (day 1)	130	1 (33.3%)	3	2 (66.7%)
Cycle 22 (day 1)	130	2 (66.7%)	3	1 (33.3%)
Cycle 23 (day 1)	130	1 (33.3%)	3	2 (66.7%)
Cycle 24 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 25 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 26 (day 1)	130	2 (100.0%)	2	0 (0.0%)
Cycle 27 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 28 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 29 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 30 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 31 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 32 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 33 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 34 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 35 (day 1)	130	1 (50.0%)	2	1 (50.0%)
Cycle 36 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 37 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 38 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 39 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 40 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 41 (day 1)	130	1 (100.0%)	1	0 (0.0%)

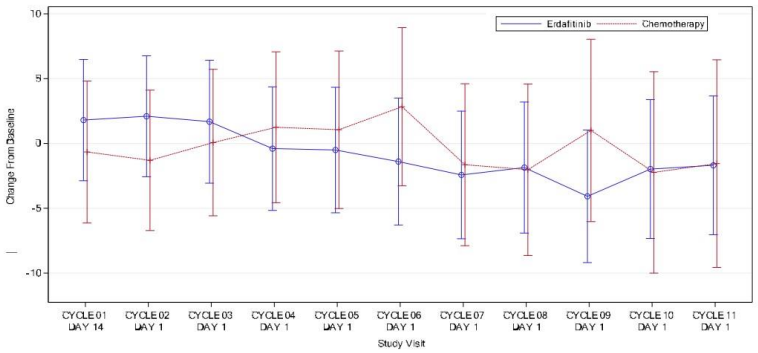
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 42 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 43 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 44 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 45 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 46 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 47 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 48 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 49 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 50 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 51 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 52 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 53 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 54 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 55 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 56 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 57 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 58 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 59 (day 1)	130	1 (100.0%)	1	0 (0.0%)
Cycle 60 (day 1)	130	1 (100.0%)	1	0 (0.0%)
End of treatment	130	0 (0.0%)	58	58 (100.0%)

Abbreviations: HRQoL, health-related quality of life.

10.1.3 HRQoL results

Baseline results for EQ-5D-5L VAS were comparable between erdafitinib and comparator treatments arms as shown in Table 38. Statistical analysis was not performed for these data, however, EQ-5D-5L scores on the VAS and HUI were maintained (Figure 21 and Figure 22), suggesting there was no worsening of general HRQoL. The graphs are displaying change in utility scores from baseline; hence it is not possible to include cycle 1 day 1 in these graphs. Due to these limited number of observations, the analysis only included the first 11 cycles.

Figure 21. EQ-5D-5L VAS scores of erdafitinib and comparator arm in THOR

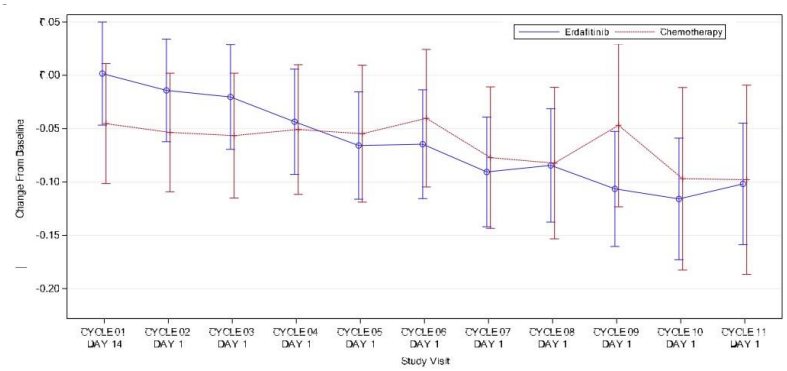


No. of patients:											
	Erdafitinib	131	128	124	117	106	96	88	76	65	54	46
	Chemotherapy	93	82	65	52	43	38	32	25	21	17	12

Source: THOR C1 CSR: GPROEQ07A.

Abbreviations: EQ-5D-5L, EuroQOL 5-dimensions; VAS, visual analogue scale.

Figure 22. EQ-5D-5L Health Utility Index scores for erdafitinib and comparator arm in THOR

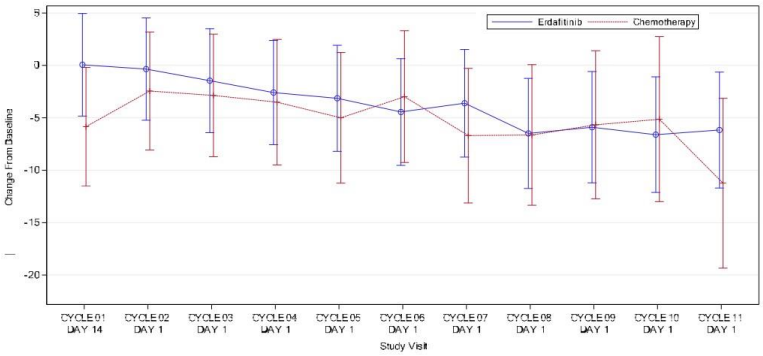


No. of patients:											
	Erdafitinib	131	128	124	117	106	96	88	76	65	54	46
	Chemotherapy	93	82	65	52	43	38	32	25	21	17	12

Source: THOR C1 CSR: GPROEQ07A.

Abbreviations: EQ-5D-5L, EuroQOL 5-dimensions.

Figure 23. FACT-BI scores for erdafitinib and comparator arm in THOR



No. of patients:											
	Erdafitinib	131	128	124	117	106	96	88	76	65	54	46
	Chemotherapy	93	82	65	52	43	38	32	25	21	17	12

Table 38. HRQoL EQ-5D-5L summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (SE); 95% CI [p-value]
Baseline	136	67.09 (19.553)	130	64.42 (20.306)	Not reported
Cycle 1 (day 1)	126 (93%)	1.97 (1.974)	107 (82%)	-3.17(-2.286)	5.14 (1.729) ; 1.74, 8.54 [0.0031]
Cycle 1 (day 14)	112 (85%)	2.19 (1.969)	73 (78%)	-1.34 (2.272)	3.53 (1.707) ; 0.18, 6.89 [0.0391]
Cycle 2 (day 1)	118 (92%)	0.72 (2.003)	76 (93%)	-1.94 (2.362)	2.65 (1.849) ; -0.98, 6.29 [0.1518]
Cycle 3 (day 1)	107 (863%)	-0.11 (2.008)	53 (82%)	-2.10 (2.418)	1.99 (1.919) ; -1.78, 5.76 [0.3003]
Cycle 4 (day 1)	99 (85%)	-0.72 (2.042)	46 (88%)	-3.08 (2.520)	2.36 (2.074) ; -1.71, 6.43 [0.2554]
Cycle 5 (day 1)	86 (81%)	-1.70 (2.055)	34 (79%)	-1.18 (2.540)	-0.52 (2.119) ; -4.68, 3.64 [0.8053]
Cycle 6 (day 1)	79 (82%)	-0.67 (2.074)	32 (84%)	-4.28 (2.596)	3.61 (2.202) ; -0.71, 7.93 [0.1014]
Cycle 7 (day 1)	74 (84%)	-3.00 (2.120)	28 (88%)	-4.92 (2.714)	1.92 (2.386) ; 2.76, 6.60 [0.4218]
Cycle 8 (day 1)	60 (79%)	-2.57 (2.146)	22 (8800%)	-3.41 (2.863)	0.84 (2.579) ; -4.22, 5.90 [0.7452]
Cycle 9 (day 1)	55 (85%)	-3.36 (2.230)	17 (85%)	-3.59 (3.190)	0.23 (3.00) ; -5.67, 6.13 [0.9360]
Cycle 10 (day 1)	42 (78%)	-2.57 (2.238)	11 (69%)	-8.87 (3.286)	6.30 (3.109) ; 0.20, 12.40 [0.0429]
Cycle 11 (day 1)	41 (89%)	-0.89 (1.879)	10 (83%)	-3.44 (2.181)	2.55 (1.457) ; -0.32, 5.42 [0.0815]

Abbreviations: EQ-5D-5L, EuroQOL 5-dimensions; HRQoL, health-related quality of life; HUI, health utility index; SE, standard error; VAS visual analogue scale.

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

10.2.1 HSUV calculation

Utilities were estimated with MMRMs using pooled data from both treatment arms. The progression-free health state utility was based on the area under the curve of mean utility estimates for each treatment cycle among patients remaining progression-free. Progressed disease state utility was estimated from questionnaires of patients who were known to have progressed (i.e., excluding questionnaires after censoring for PFS) using a single MMRR that accounted for correlations between EQ-5D measurements from the same patient. Compound symmetry covariance structure was selected as it resulted in the lowest AIC. These analyses were conducted in SAS.

Age-related utility decrements are included in the model base case to account for the natural decline in quality of life associated with age, according to the DMC's methods guide (62).

10.2.1.1 Mapping

No mapping of utility values was needed as Danish values were estimated directly from THOR C1 EQ-5D-5L observations using the Danish EQ-5D-5L value set (63).

10.2.2 Disutility calculation

N/A, as disutilities incurred by AEs are estimated from literature. The durations of AEs were sourced from THOR C1.

10.2.3 HSUV results

As a scenario analysis, the multivariable regression for estimation HSUVs was investigated.

Table 39. Overview of health state utility values, duration of adverse events and related disutilities

	Results Mean (SE)	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression-free	0.788 (0.001)	EQ-5D-5L	DK	Estimate is based on mean of both THOR C1 trial arms.
Progressed disease	0.717 (0.024)	EQ-5D-5L	DK	Estimate is based on mean of both THOR C1 trial arms.

Abbreviations: DK, Denmark; HSUV, health state utility values; SE, standard error.

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

10.3.1 Study design

N/A, only used for disutilities due to AEs.

10.3.2 Data collection

N/A, only used for disutilities due to AEs.

10.3.3 HRQoL Results

N/A, only used for disutilities due to AEs.

10.3.4 HSUV and disutility results

As described in section 9.1, the model includes all grade ≥ 3 treatment-emergent AEs experienced by at least 5% of patients in the safety population in either treatment arm in THOR C1 or in the EV arm of EV-301. It was assumed that minor AEs that affected less than 5% of patients would have a negligible impact on QALYs and costs, and that all relevant adverse events are captured.

AE-related utility decrements were informed by literature (Table 39.). The QALY losses associated with AEs were calculated by multiplying the utility decrement by the duration of the AE. They were then multiplied by the proportion of patients experiencing the AE with each treatment to obtain treatment-specific AE-related QALY losses.

Duration of AEs was informed by the THOR C1 trial and is also summarised in Table 39. For each patient experiencing a particular grade ≥ 3 AE, the total cumulative time spent with that AE was calculated by summing the durations of distinct occurrences of the same event type; for occurrences with missing end dates, duration was assumed equal to the mean of complete observations. The mean time for each AE was then obtained by averaging the times across all patients who experienced that AE.

Table 40. Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

Table 41. Overview of literature-based health state utility values

Adverse event	Duration in days (SE)	Source duration	Utility (SE)	Source utility
Palmar-plantar erythrodysesthesia syndrome	31.2 (6.9)	THOR C1	−0.040 (NA)	Assumed equal to stomatitis (following TA780(64))

Adverse event	Duration in days (SE)	Source duration	Utility (SE)	Source utility
Stomatitis	16.6 (5.2)	THOR C1	−0.040 (NA)	TA498 (64)
Anaemia	26.1 (5.3)	THOR C1	−0.090 (0.020)	Beusterien et al. (2010) (65)
Hyponatraemia	12.9 (2.6)	THOR C1	−0.115 (NA)	Lloyd et al. (2006) (66); assumed equivalent to fatigue
Onycholysis	80.1 (53.4)	THOR C1	−0.032 (0.012)	Nafees et al. (2009) (67); assumed equivalent to skin reactions
Hyperphosphataemia	9.4 (1.3)	THOR C1	−0.115 (NA)	Nafees et al. (2009) (67); assumed equivalent to fatigue
Neutropenia	16.4 (4.4)	THOR C1	−0.090 (0.015)	Nafees et al. (2009) (67)
Leukopenia	14.0 (4.1)	THOR C1	−0.090 (0.016)	Assumed equal to neutropenia
Febrile	5.3 (0.8)	THOR C1	−0.090 (0.016)	Nafees et al. (2009) (67)
Fatigue	129.5 (35.7)	THOR C1	−0.073 (0.018)	Nafees et al. (2009) (67)
Maculopapular rash	80.1 (53.4)	THOR C1	−0.032 (0.012)	Nafees et al. (2009) (67); assumed equal to immune mediated rash
Decreased neutrophil count	16.4 (4.4)	THOR C1	-0.090 (0.015)	Assumed equal to neutropenia

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

Erdafitinib is available as 3 mg (84 tablets), 4 mg (56 tablets) and 5 mg (28 tablets) film-coated tablets at a price [redacted] The model includes an estimation of the average costs of treating with erdafitinib over 28 days by averaging the proportions of doses received in THOR C1 with the costs of the combination of tablets needed to achieve that dose. This is a straightforward approach of capturing dose modifications of erdafitinib.

Dose (mg)	Combination of tablets needed to receive that dose	Proportion of doses in THOR C1

3	1 x 3 mg	0.01%
4	1 x 4 mg	12.99%
5	1 x 5 mg	9.15%
6	2 x 3 mg	19.73%
7	3 mg + 4 mg	1.17%
8	2 x 4 mg	30.38%
9	3 x 3 mg	26.56%
12	4 x 3 mg or 3 x 4 mg	0.00%

Source: THOR C1 CSR.

However, missed doses would still affect the amount of erdafitinib used, and consequently the acquisition cost. Therefore, an estimate of the proportion of erdafitinib doses missed in THOR C1 (17.1%) was included in the model and its inverse was applied to the erdafitinib acquisition cost. This proportion was calculated by dividing the number of erdafitinib doses administered by the total number of days on treatment in the erdafitinib trial arm.

Vinflunine is available in 2 mL and 10 mL vials, with a strength of 25 mg/mL at a pharmacy purchasing price of respectively DKK 8,746[1] and DKK 1,749[2]. Relative dosing intensity (RDI) is applied to drug acquisition costs of vinflunine (based on data from THOR C1), since not all patients who are receiving treatment necessarily receive the full course of therapy because of missed doses or dose reductions.

EV is available in cartons of one 20 mg and 30 mg single-dose vials at a pharmacy purchasing price of respectively DKK 4,643[3] and DKK 6,964[4]. RDI is applied to drug acquisition costs of EV (based on data from EV-301), since not all patients who are receiving treatment necessarily receive the full course of therapy because of missed doses or dose reductions.

Where dosing is dependent on weight or BSA, drug wastage can occur if vial sharing is not allowed or possible. The model allows taking this into account by assuming that only discrete combinations of available vial sizes can be used. With this approach, the proportion of patients requiring each discrete combination of vials is calculated based on the expected distribution of weight or BSA in the population. This distribution is modelled using mean and standard deviation of weight or BSA in THOR C1 and assuming that the logarithm of weight or BSA is approximately normally distributed. This intermediate calculation can be found in the model in the 'Drug Wastage Calculation' sheet. No wastage is assumed in the use of erdafitinib, as different combinations of tablets are matched to the received dose.

[1] 487068. Medicinpriser.dk; [2] 166840. Medicinpriser.dk; [3] 166450. Medicinpriser.dk; [4] 188470. Medicinpriser.dk

Table 42. Medicine costs used in the model

Medicine	Dose	Relative dose intensity (RDI)	Frequency	Vial sharing
Erdafitinib	Doses received as per THOR C1 trial (ranging from 3 to 9 mg per day) , orally.	82.9%	Once daily for 21 days on a 21-day cycle until progression, withdrawal, or intolerable toxicity	No, oral drug
Vinflunine	320 mg/m^2 as a 20-minute intravenous infusion	99.8%	Once every 3 weeks until progression, withdrawal, or intolerable toxicity	No vial sharing assumed.
EV	1.25 mg/kg as a 30-minute infusion	79.4%	Days 1, 8, and 15 of a 28-day cycle	No vial sharing assumed.

Notes: RDI of erdafitinib and vinflunine are sourced from THOR C1 CSR, and RDI of EV is sourced from EV-301. Average patient BSA and weight are sourced from THOR C1 ITT population and is described in Table 13.

Abbreviations: EV, enfortumab vedotin; RDI, relative dose intensity.

11.2 Medicine costs – co-administration

N/A

11.3 Administration costs

The cost of an IV infusion is sourced from the DRG tariff of 2024. The frequency of IV administration is dependent on the treatment regimen of vinflunine and EV. Erdafitinib is administered orally. No further administration costs were assumed.

Table 43. Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	Once every three weeks for vinflunine. Once day 1, 8, and 15 of a 28-day cycle for EV.	1,989	MDC17 1-dagsgruppe, pat. mindst 7 år (DRG 1 day visit)	DRG 2024

11.4 Disease management costs

Erdafitinib is associated with potential ophthalmological complications. It was identified that erdafitinib causes a slightly elevated risk of eye conditions such as central serous retinopathy and retinal pigment epithelial detachment, which can cause a visual field defect. To ensure that this is detected as soon as possible, and that subsequent regimen adjustments can be made, frequent testing is recommended. A single ophthalmological consultation was costed as DKK 280.34 in line with the Takstkort 2024 of the ophthalmologist. Patients are assumed to require monthly ophthalmological examinations during the first 4 months of treatment and every 3 months afterwards. As this is considered 'monitoring' of patients on erdafitinib, these ophthalmological consultations are captured within disease management costs.

Medical resource use in the model is defined by health state separately for each intervention, but in the base case it was assumed that there would be no differences in resource use between treatments (except for tests described in Section 11.8). To estimate healthcare resource use cost, a micro-costing approach is undertaken whereby the frequencies of individual resources are combined with information about their unit costs.

Table 44. Disease management costs used in the model

Activity	Frequency (every X months)	Unit cost [DKK]	DRG code	Reference
Opthalmology consultation unit costs	Monthly during first four months of treatment and every three months afterwards	280.34	1 konsultation Øjenlægehjælp. Takstkort 14B 2024	1 konsultation Øjenlægehjælp. Takstkort 14B 2024

Health-state	PFS	PS			
GP consultation	3.85	1.39	160.72	Honorartabel, dagtid, Konsultation	TA788 (GP home consultation) (46)
District nurse	3.70	1.04	453	Nurse salary Table 1. Sygeplejersker.	TA788 (46)
Health home visit	3.85	1.39	1,541.57	House health check. Honorartabel April-Oct 24. Sundhedstjek til borgere på botilbud + tidsforbrugstillæg og evt. kørselsgodtgørelse	TA788 (GP home consultation) (46)
Dietician	16.67	6.25	1,374	Diætvejledning. 49PR04	TA788 (46)

Activity	Frequency (every X months)		Unit cost [DKK]	DRG code	Reference
Oncologist consultation	1.14	1.08	504.72	1 konsultation Kirurgi, Takstkort 22. April 2024	TA788 (46)
Urologist	14.29	25.00	504.72	1 konsultation Kirurgi, Takstkort 22. April 2024	TA788 (46)

Abbreviations: DRG, diagnosis related groups; GP, general practitioner.

11.5 Costs associated with management of adverse events

The base case analysis included grade ≥ 3 treatment-emergent AEs with an incidence of at least 5%. AE unit costs are presented in Table 45. Most AEs are assumed to occur early in the treatment; therefore, their consequences (cost, QALY loss) are incurred once at model start. All adverse events excluding febrile neutropenia are assumed handled as ambulatory visits. For febrile neutropenia hospitalisation can be needed and the DRG tariff used covers up to 10 days of hospitalisation.

Table 45. Cost associated with management of adverse events

	DRG code	Unit cost/DKK DRG tariff
Palmar-plantar erythrodysesthesia syndrome	DRG 2024, 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år, diagnosis: DL271 Lokaliseret dermatitis forårsaget af indtaget lægemiddel	DKK 1,625
Stomatitis	DRG 2024, 03MA98: MDC03 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DK121B: Stomatitis UNS	DKK 2,107
Anaemia	DRG 2024, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD649: Anæmi UNS	DKK 2,111
Hyponatraemia	DRG 2024, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE871A: Hyponatriæmi	DKK 1,847
Onycholysis	Assumed same as palmar-plantar erythrodysaesthesia syndrome	DKK 1,625
Hyperphosphataemia	DRG 2024, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE871A: Hyponatriæmi	DKK 1,847
Neutropenia	DRG 2024, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS	DKK 2,111
Leukopenia	DRG 2024, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728H: Leukopeni	DKK 2,111
Febrile neutropenia	DRG 2024, 16MA03: Granulo- og trombocytopeni, Diagnosis: DD709A: Neutropeni og agranulocytose	DKK 37,129

	DRG code	Unit cost/DKK DRG tariff
Fatigue	DRG 2024, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse	DKK 5,103
Maculopapular rash	DRG 2024, 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR219: Hududslæt UNS	DKK 1,625
Decreased neutrophil count	Assumed same as neutropenia	DKK 2,111

Abbreviations: DRG, diagnosis related groups.

11.6 Subsequent treatment costs

No subsequent treatments were considered in this health economic analysis. The distribution of subsequent treatments was similar between erdafitinib and the chemotherapy comparator arm (ITT), which has a larger sample size than the vinflunine subgroup only. Based on comparability on the subsequent treatments, it is assumed that costs associated with subsequent treatment will be comparable between erdafitinib and vinflunine or EV. This is in line with what was previously accepted by the DMC in the recent submission of EV in regard to modelling subsequent treatments (35).

Table 46. Distribution of subsequent treatments in THOR

	Cohort 1 Erdafitinib (n = 106) Number (%) received	 Chemo PC (n = 102) Number (%) received
Carboplatin	8 (7.5)	9 (8.8)
Gemcitabine	6 (5.7)	10 (9.8)
Paclitaxel	8 (7.5)	6 (5.9)
Docetaxel	4 (3.8)	2 (2.0)
Vinflunine	4 (3.8)	0 (0.0)
Pembrolizumab	4 (3.8)	4 (3.9)
Derazantinib	3 (2.8)	3 (2.9)
EV	19 (17.9)	13 (12.7)
Sacituzumab	3 (2.8)	0 (0.0)
No active treatment	62 (58.5)	55 (53.9)

Source: THOR C1 CSR, Table 17

Abbreviations: Chemo PC, Chemotherapy of Physician's Choice.

Table 47. Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
N/A	N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

Table 48. Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Transport to hospital	Unless otherwise explained, the Medicines Council assumes that the distance to a hospital was 20 km in driving distance in 2016 with an average of 3.79 kr. per kilometre, corresponding to a transport cost to and from the treatment at the hospital of 151.60 kr.
Patient time costs for drug administration	The Medicines Council assumes 188 kr. per hour as the cost for patient time. Erdafitinib: None, as oral treatment. Vinflunine: 20 minutes (THOR) EV: 30 minutes (EV-301)
Patient costs for disease management	A patient time cost or transportation cost of 188 kr. per hour is included as part of disease management activities. The total cost is calculated based on the assumed number of hours. GP consultation: 1 hour of patient time; 1 hour of travel District nurse: 1 hour of patient time; 1 hour of travel Health home visit: 1 hour of patient time Dietician: 1 hour of patient time; 1 hour of travel Oncologist consultation: 2 hours of patient time; 1 hour of travel Urologist: 1 hour of patient time; 1 hour of travel Ophthalmological consultation: 2 hours of patient time; 1 hour of travel
Patient costs for AE management	A patient time cost or transportation cost of 188 kr. per hour is included as part of AE management activities. The total cost is calculated based on the assumed number of hours. Palmar-plantar erythrodysaesthesia syndrome: 2 hours of patient time; 1 hour of travel Stomatitis: 2 hours of patient time; 1 hour of travel Anaemia: 6 hours of patient time; 1 hour of travel Hyponatraemia: 4 hours of patient time; 1 hour of travel Onycholysis: 4 hours of patient time; 1 hour of travel

Activity	Time spent [minutes, hours, days]
	Hyperphosphataemia: 4 hours of patient time; 1 hour of travel Neutropenia: 4 hours of patient time; 1 hour of travel Leukopenia: 4 hours of patient time; 1 hour of travel Febrile neutropenia: 4 hours of patient time; 1 hour of travel Fatigue: 4 hours of patient time; 1 hour of travel Maculopapular rash: 1 hour of patient time; 1 hour of travel Decreased neutrophil count: 4 hours of patient time; 1 hour of travel

11.8 Other costs

The model assumes 100% of erdafitinib patients are tested for FGFR in clinical practice. It applies the cost of testing as a one-off cost in the first cycle. NGS panels are regarded as the best method for genetic testing using sequencing panels to detect abnormalities across a wide range of different genes simultaneously (including FGFR) (68). The unit cost of DKK 5,000 was used in the model. This unit cost for an NGS test has previously been used in fully processed assessments from the Medicines Council, including entrectinib and larotrectinib for the treatment of neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours (69). This cost was divided by the expected prevalence of FGFR alterations to obtain the average cost per one identified positive case. The FGFR alteration rate of 16.6% observed in THOR C1 was used.

The end-of-life cost was conservatively excluded from the analysis as it would be applied to all arms in the same manner and produce a small effect. This is in line with previous DMC decisions where not enough justification was offered for end-of-life cost (69).

Table 49. Other cost used in the model

Activity	Unit costs (DKK)	Source
FGFR test	5,000	DMC decision on pemigatinib (69)

12. Results

12.1 Base case overview

An overview of the model settings in this health economic analysis are given in Table 50.

Table 50. Base case overview

Feature	Description
Comparator	Vinflunine (320 mg/m2) and EV (1.25 mg/kg)
Type of model	Partitioned survival model
Time horizon	10 years
Treatment line	After at least one line of PD-1 or PD-L1 inhibitor
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in THOR C1 trial (70). Danish population
Costs included	Drug acquisition (including subsequent treatments) costs, healthcare resource use costs, AE costs, patient- and time costs, testing costs
Dosage of medicine	Erdafinitib has a standardized dose. Vinflunine is based on body surface area. EV is weight-based.
Average time on treatment	Erdafitinib: 0.66 years Vinflunine: 0.47 years
Parametric function for PFS	Erdafitinib: Log-logistic Vinflunine: Log-normal
Parametric function for OS	Erdafitinib: Log-logistic Vinflunine: Exponential
Inclusion of waste	Drug wastage included by not assuming vial sharing
Average time in model health state Progression-free	Erdafitinib: 0.69 years Vinflunine: 0.50 years
Average time in model health state Progressed disease	Erdafitinib: 1.09 years Vinflunine: 0.39 years

12.1.1 Base case results

The outcomes of the base case deterministic model are presented in Table 51, split out over costs categories and health outcomes.

Table 51. Base case results, discounted estimates

	Erdafitinib	Vinflunine	EV	Vs. vinflunine	Vs. EV
Medicine costs	569,295	184,803	470,970	384,492	98,325
Administration	0	17,326	52,916	-17,326	-52,916
Disease management costs	40,928	20,850	40,928	20,078	0
FGFR and ophthalmology testing costs	33,199	0	0	33,199	33,199
Costs associated with management of	813	2,766	984	-1,952	-171
Patient costs	3,367	2,382	6,766	985	-3,399
Total costs	**647,602**	**228,128**	**572,564**	**419,474**	**75,038**
Life years gained (progression-free)	0.661	0.480	0.661	0.180	-
Life years gained (progressed)	0.937	0.404	0.937	0.533	-
Total life years	**1.597**	**0.885**	**1.597**	**0.713**	**-**
QALYs (Progression-free)	0.520	0.378	0.520	0.143	-
QALYs (Progressed disease)	0.671	0.290	0.671	0.381	-
QALYs (adverse reactions)	-0.002	-0.003	-0.003	0.001	-
Total QALYs	**1.190**	**0.666**	**1.189**	**0.524**	**-**
Incremental costs per life year gained				**588,324**	**-**
Incremental cost per QALY gained (ICER)				**800,681**	**-**

12.2 Sensitivity analyses

Sensitivity analysis was undertaken through a pairwise analysis between erdafitinib and vinflunine. Deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and scenario analyses will be presented here for the pairwise comparison of erdafitinib and vinflunine.

For the pairwise comparison of erdafitinib and EV, which follows a cost-minimizing approach, it is not informative to perform these sensitivity analyses. As a CMA assumes there is no difference between modelled outcomes and survival. As the disease progression is equivalent in these treatment arm, the costs incurred by HCRU are also equal, and these estimates do not influence the pairwise comparison. The main driver of the difference in costs between erdafitinib and EV are the costs incurred by the treatment, its administration, and the FGFR testing costs, which are all sourced according to the corresponding sources recommended in the Danish costing manual (71) and therefore assumed to be minimally affected by uncertainty.

12.2.1 Deterministic sensitivity analyses

Deterministic sensitivity analysis was undertaken through completion of one-way sensitivity analysis (OWSA). OWSA was implemented by replacing each numeric base-case input with its lower and upper bound, one-by-one, while all other inputs remained unchanged at their base case value. The value bounds were set to the bounds of 95% confidence intervals if those were reported in the input source. In other cases, bounds of central 95% probability intervals of the distributions selected for PSA were used, under the assumption that they approximated 95% confidence intervals. Inputs that are not associated with parameter uncertainty were excluded from the OWSA.

Table 52 contains the 10 most influential parameters, measured by impact on the ICER, from the OWSA that was performed.

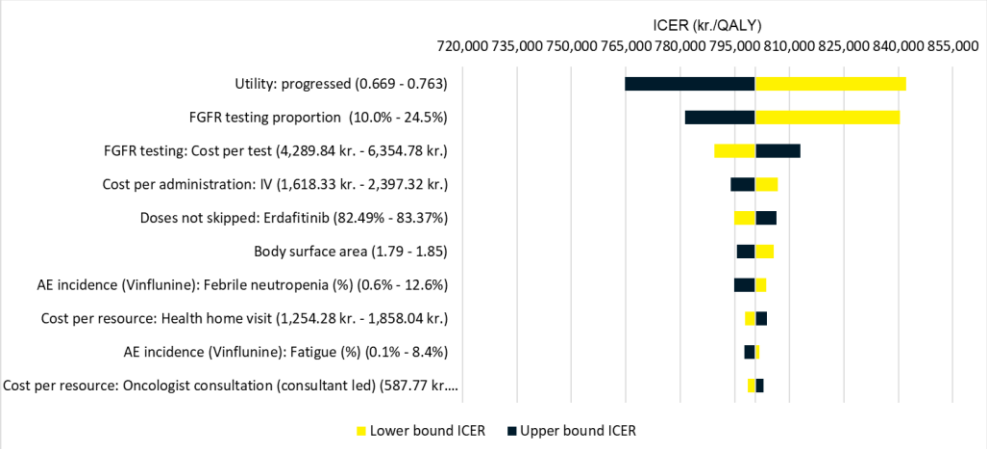
Table 52. One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case					**800,681**
Utility: progressed	Upper: 0.76		419,474	0.548	764,843
	Lower: 0.67		419,474	0.498	842,180
FGFR testing proportion	Upper: 24%		409,291	0.524	781,244
	Lower: 10%		440,337	0.524	840,505
FGFR testing: cost per test	Upper:6,355		425,987	0.524	813,113
	Lower:4,290		413,562	0.524	789,396
	Upper:2,397		415,917	0.524	793,892

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Cost per IV	Lower:1,618		422,703	0.524	806,844
Doses not skipped: erdafitinib	Upper: 83%		422,488	0.524	806,435
	Lower: 82%		416,429	0.524	794,870
Body surface area (m^2)	Upper: 1.85		416,779	0.524	795,537
	Lower: 1.79		422,139	0.524	805,769
AE incidence (vinflunine): febrile neutropenia (%)	Upper: 13%		416,461	0.524	794,775
	Lower: 1%		421,023	0.524	803,719
Cost per resource: health home visit	Upper:1,858		421,108	0.524	803,800
	Lower:1,254		417,991	0.524	797,850
AE incidence (vinflunine): fatigue	Upper: 8.4%		419,106	0.525	797,568
	Lower: 0.1%		419,611	0.523	801,846
Cost per resource: Oncologist consultation	Upper: 870		420,638	0.524	802,902
	Lower: 588		418,418	0.524	798,665

Figure 24 presents a tornado diagram showing the 10 parameters with the greatest impact on the ICER of erdafitinib versus vinflunine.

Figure 24. Tornado diagram of 10 most influential parameters in the OWSA



Abbreviations: AE, adverse events; FGFR; fibroblast growth factor receptor; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life years; Subs, subsequent.

The scenario analysis results are presented in Table 53 where the 10 most impactful model settings are presented. The resulting ICERs and their differences against the base case are presented.

These scenarios tested regarded assumptions on dosing of the treatments, drug wastage, approach and estimation of HSUVs, as well as choice of parametric distribution for the extrapolations. For the parametric distributions of the extrapolation, the best three statistical fits, besides the base case, are tested as scenarios.

The scenario with the biggest impact is the use of the lognormal distribution for OS of vinflunine. This was tested as all next best three statistical fits were tested systematically. Not only is this clearly not the best fit, but this scenario is clinically highly implausible. The lognormal implies a long-term OS rate for vinflunine, that does not align with clinical reality.

Table 53. Results of scenario analyses

Scenario name	ICER	Difference to base case ICER
Base case		**800,681**
20-year time horizon	761,721	-38,960
Exclude dose skipping	1,024,376	223,694
Exclude ophthalmology costs	797,870	-2,811
Exclude FGFR testing costs	740,124	-60,557
Exclude AE management costs	804,408	3,727
All discount rates to 0%	756,460	-44,222
All discount rates to 5%	818,966	18,285
Use time to death health state utility values	791,932	-8,749
Lognormal distribution for OS of erdafitinib (#2	749,265	-51,417
Gen. gamma distribution for OS of erdafitinib (#3	871,515	70,834
Gamma distribution for OS of erdafitinib (#4 best	1,013,230	212,549
Weibull AFT distribution for OS of vinflunine (#2	854,346	53,664
Gamma distribution for OS of vinflunine (#3 best	834,461	33,780
Lognormal distribution for OS of vinflunine (#4	1,666,454	865,773
Lognormal distribution for PFS of erdafitinib (#1	774,640	-26,041
Gen. gamma distribution for PFS of erdafitinib (#3	793,736	-6,945
Gamma distribution for PFS of erdafitinib (#4 best	733,137	-67,544
Lognormal distribution for PFS of vinflunine (#1	800,681	0
Exponential distribution for PFS of vinflunine (#3	846,570	45,889
Gen. gamma distribution for PFS of vinflunine (#4	800,391	-291
Log-normal distribution for TTD of erdafitinib (#2	800,681	0
Gen. gamma distribution for TTD of erdafitinib (#3	785,727	-14,955
Gamma distribution for TTD of erdafitinib (#4 best	724,647	-76,034
Log-normal distribution for TTD of vinflunine (#2	796,491	-4,190
Exponential distribution for TTD of vinflunine (#3	849,404	48,723

Gompertz distribution for TTD of vinflunine (#4	805,783	5,102

Abbreviations: AE, adverse events; FGFR; fibroblast growth factor receptor; gen., generalised; ICER, incremental cost-effectiveness ratio, OS, overall survival; PFS; progression-free survival; TTD, time to treatment discontinuation.

12.2.2 Probabilistic sensitivity analyses

PSA was performed within the cost-effectiveness analysis and conducted for 5,000 iterations. This analysis randomly samples parameters from the chosen probability distributions that represent uncertainty around their values. The results include both expected outcomes that account for joint parameter uncertainty and the impact of parameter uncertainty on model results. The convergence plots in both Figure 25 and Figure 26 show that a high number of iterations decreases the difference between results of current and previous iterations, indicating that additional iterations would have a negligible impact on the results.

Figure 25. Convergence plot of incremental QALYs for simulations in the PSA

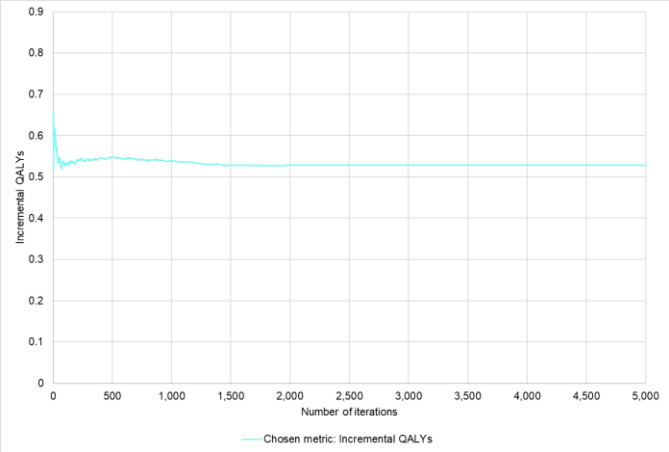
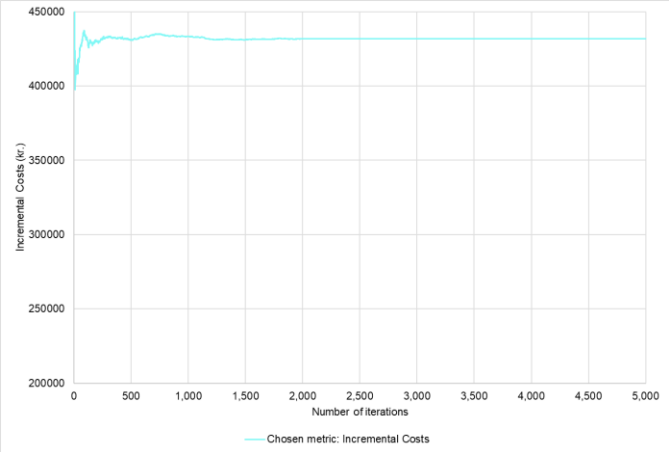


Figure 26. Convergence plot of incremental costs for simulations in the PSA



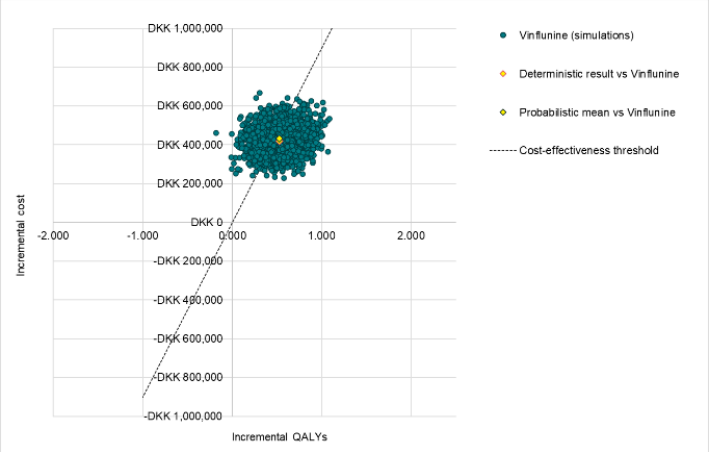
The average PSA outcomes for the comparison of erdafitinib and vinflunine are displayed in Table 54.

Table 54. Mean results of probabilistic sensitivity analysis

	Incremental LYs	Incremental QALYs	Incremental costs	ICER (DKK/QALY)
Probabilistic analysis (Versus vinflunine)	0.716	0.526	431,588	820,044

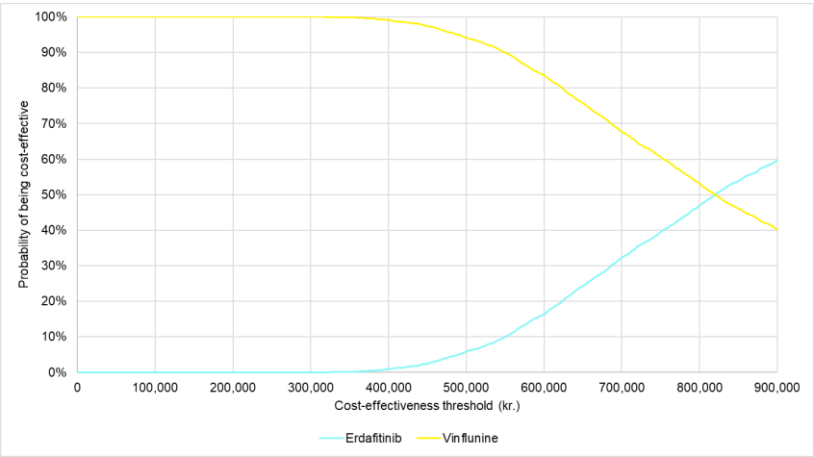
In Figure 27, the cost-effectiveness plane is plotted, which displays the incremental costs and incremental QALYs per iteration from the PSA. This displays the spread of resulting ICERs from the 5,000 iterations. These iterations also inform the cost-effectiveness acceptability curve which is presented in Figure 28. The cost-effective plane shows that almost all iterations are in the North-East quadrant meaning that almost all simulations would results in higher costs and higher benefits of erdafitinib against vinflunine.

Figure 27. Cost-effectiveness plane with the probabilistic results plotted on incremental costs and QALYs



The cost-effectiveness acceptability curve presents the probability of the treatments being cost-effective over multiple WTP-thresholds. At a WTP of approximately DKK 820,800, erdafitinib has a 50% probability of being cost-effective.

Figure 28. Cost-effectiveness acceptability curve



13. Budget impact analysis

The market shares in this indication, in case of non-recommendation, assume treatment by vinflunine and EV, taking market shares of 20% and 80%, respectively, across all years. The rationale of this estimate is that not all patients will receive EV, leaving 20% of the patients to receive vinflunine.

The market shares in this indication, in case of recommendation, assume erdafitinib to take up 50% in year 1, 60% in year 2, and then going up to 77% for the remaining years. The remaining market share is taken by EV.

Number of patients (including assumptions of market share)

Table 55. Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Erdafitinib	6	7	8	8	8
Vinflunine	0	0	0	0	0
EV	6	4	3	3	3
			Non-recommendation		
Erdafitinib	-	-	-	-	-
Vinflunine	2	2	2	2	2
EV	9	9	9	9	9

Budget impact

In Table 56, the results of the budget impact analysis are described.

Per patient annual costs were calculated based on average time spent on treatment, in progression-free state and in progressed disease state in each year after treatment initiation estimated in the cost-effectiveness model.

Table 56. Expected budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]				
The medicine under consideration is NOT recommended	[redacted]				

	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 57. Main characteristic of studies included; THOR C1

Trial name: THOR C1	NCT number: 03390504
Objective	The purpose of this study is to evaluate efficacy of erdafitinib versus chemotherapy in participants with advanced urothelial cancer harbouring selected fibroblast growth factor receptor (FGFR) aberrations who have progressed after 1 or 2 prior treatments, at least 1 of which includes an anti-programmed death ligand 1(PD-[L]1) agent (cohort 1).
Publications – title, author, journal, year	Loriot, Y., Matsubara, N., Park, S. H., Huddart, R. A., Burgess, E. F., Houede, N., Banek, S., Guadalupi, V., Ku, J. H., Valderrama, B. P., Tran, B., Triantos, S., Kean, Y., Akapame, S., Deprince, K., Mukhopadhyay, S., Stone, N. L., & Siefker-Radtke, A. O. (2023). Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. N Engl J Med, 389(21), 1961-1971. https://doi.org/10.1056/NEJMoa2308849 (42).
Study type and design	Randomized, phase III study of erdafitinib compared with vinflunine or docetaxel in subjects with mUC and selected FGFR gene aberrations.
Sample size (n)	ITT: n = 266 (Erdafitinib: n = 136; Chemotherapy: n = 130 [docetaxel: n = 82; vinflunine: n = 48])
Main inclusion criteria	• Histologic demonstration of transitional cell carcinoma of the urothelium. Minor components (less than [<] 50 percent [%] overall) of variant histology such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable • Metastatic or surgically unresectable urothelial cancer • Documented progression of disease, defined as any progression that requires a change in treatment, prior to randomization • Cohort 1: Prior treatment with an anti-PD-(L) 1 agent as monotherapy or as combination therapy; no more than 2 prior lines of systemic treatment. • A woman of childbearing potential who is sexually active must have a negative pregnancy test (beta human chorionic gonadotropin [beta hCG]) at Screening (urine or serum) • Participants must meet appropriate molecular eligibility criteria • Eastern Cooperative Oncology Group (ECOG) performance status Grade 0, 1, or 2

Trial name: THOR C1		NCT number: 03390504
	• Adequate bone marrow, liver, and renal function	
Main exclusion criteria	• Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to randomization • Active malignancies (that is, requiring treatment change in the last 24 months). The only allowed exceptions are: urothelial cancer, skin cancer treated within the last 24 months that is considered completely cured, localized prostate cancer with a gleason score of 6 (treated within the last 24 months or untreated and under surveillance) and localized prostate cancer with a gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence. • Symptomatic central nervous system metastases • Received prior fibroblast growth factor receptor (FGFR) inhibitor treatment • Known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients • Current central serous retinopathy (CSR) or retinal pigment epithelial detachment of any grade. • History of uncontrolled cardiovascular disease • Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions	
Intervention	Erdafitinib: oral tablets at a starting dose of 8 mg daily. n = 136	
Comparator(s)	Vinflunine: 20-minute IV infusion at 320/m^2 n = 48 Docetaxel: 1-hour IV infusion at 75 mg/m^2 n = 82	
Follow-up time	Median follow-up: 15.9 months	
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** *Primary:*	

Trial name: THOR C1	NCT number: 03390504

- OS: up to 3 years

Secondary:

- PFS: up to 3 years
- ORR: up to 3 years

Other endpoints:

Secondary:

- Change from Baseline in Participant-Reported Health Status and Physical Functioning Scales of the Functional Assessment of Cancer Therapy (FACT-BI): up to 3 years
- Time Until Symptom Deterioration (Subset of FACT-BI Items): up to 3 years
- Change from Baseline in Patient-Global Impression of Severity (PGIS) Score: up to 3 years
- Change from Baseline in the Visual Analog Scale (VAS) of the EQ-5D-5L: up to 3 years
- Change from Baseline in the Utility Scale of the EQ-5D-5L: up to 3 years
- Duration of Response (DOR): up to 3 years
- Number of Participants with Adverse Events (AEs) as a Measure of Safety: up to 3 years
- Oral Clearance (CL/F) of Erdafitinib: Day 14 (Cycle 1), Day 1 (Cycle 2)
- Area Under the Plasma Concentration-Time Curve from Time Zero to Time 't' (AUC[0-t]) of Erdafitinib: Day 14 (Cycle 1), Day 1 (Cycle 2)

Method of analysis	The primary and secondary efficacy analysis will be based on the ITT Analysis set that includes all randomized subjects. The survival curves will be described using KM methods together with estimated median (in months), etc., with 95% CI for each treatment group. A stratified log-rank test will be used to compare the treatment groups (within each cohort) at an overall alpha level of 0.05 for the primary analyses. The stratification factors to be used in the analysis are as follows: ECOG performance status (0 or 1 vs. 2), disease distribution (presence vs. absence of visceral [lung, liver, or bone] metastases) and region (North America vs. EU vs. ROW). For objective response rates: A stratified Cochran-Mantel-Haenszel (CMH) test will be used to test treatment difference at a significance level of 0.05 and to estimate the relative risk and p-values between the treatment groups. The 95% confidence limits (CLs) for the relative risks will also be calculated based on the Wald statistics. The stratification factors to be used in the analysis are as follows: region (North America

Trial name: THOR C1	NCT number: 03390504
	vs. EU vs. ROW), ECOG performance status (0 or 1 vs. 2), and disease distribution (presence vs. absence of visceral metastases in lung, liver, or bone).
Subgroup analyses	Post hoc analyses were added after the database lock which included: • subgroup analysis of median OS, PFS and ORR for subjects who received vinflunine and docetaxel
Other relevant information	N/A

Table 58. Main characteristic of studies included; EV-301

Trial name: EV-301	NCT number: 03474107
Objective	The purpose of this study was to evaluate efficacy of enfortumab vedotin (EV) versus chemotherapy in patients with locally advanced or metastatic urothelial cancer.
Publications – title, author, journal, year	Rosenberg, J. E., Powles, T., Sonpavde, G. P., Loriot, Y., Duran, I., Lee, J.-L., Matsubara, N., Vulsteke, C., Castellano, D. E., Mamtani, R., Wu, C., Matsangou, M., Campbell, M. S., & Petrylak, D. P. (2022). Long-term outcomes in EV-301: 24-month findings from the phase 3 trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. Journal of Clinical Oncology, 40(16_suppl), 4516-4516. https://doi.org/10.1200/JCO.2022.40.16_suppl.4516 (48)
Study type and design	Randomized, phase III, open-label study of enfortumab vedotin or investigator-chosen standard chemotherapy (docetaxel, paclitaxel, or vinflunine)
Sample size (n)	ITT: n = 608 (EV: n = 301; Chemotherapy: n = 307)
Main inclusion criteria	• Subject is legally an adult according to local regulation at the time of signing informed consent. • Subject has histologically or cytologically confirmed urothelial carcinoma (i.e., cancer of the bladder, renal pelvis, ureter, or urethra). Subjects with urothelial carcinoma (transitional cell) with squamous differentiation or mixed cell types are eligible. • Subject must have experienced radiographic progression or relapse during or after a checkpoint inhibitor (CPI) (anti-programmed cell death protein 1 (PD1) or anti-programmed death-ligand 1 (PD-L1)) for locally advanced or metastatic disease. Subjects who discontinued CPI treatment due to toxicity are eligible provided that the subjects have evidence

of disease progression following discontinuation. The CPI need not be the most recent therapy. Subjects for whom the most recent therapy has been a non-CPI based regimen are eligible if the subjects have progressed/relapsed during or after the subjects most recent therapy. Locally advanced disease must not be amenable to resection with curative intent per the treating physician.

- Subject must have received a platinum containing regimen (cisplatin or carboplatin) in the metastatic/locally advanced, neoadjuvant or adjuvant setting. If platinum was administered in the adjuvant/neoadjuvant setting subject must have progressed within 12 months of completion.
- Subject has radiologically documented metastatic or locally advanced disease at baseline.
- An archival tumor tissue sample should be available for submission to central laboratory prior to study treatment. If an archival tumor tissue sample is not available, a fresh tissue sample should be provided. If a fresh tissue sample cannot be provided due to safety concerns, enrollment into the study must be discussed with the medical monitor.
- Subject has ECOG PS of 0 or 1
    - The subject has the following baseline laboratory data:
    - absolute neutrophil count (ANC) ≥ 1500/mm3
    - platelet count ≥ 100 × 10^9/L
    - hemoglobin ≥ 9 g/dL
    - serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease
    - creatinine clearance (CrCl) ≥ 30 mL/min as estimated per institutional standards or as measured by 24-hour urine collection (glomerular filtration rate [GFR] can also be used instead of CrCl)
    - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN or ≤ 3 x ULN for subjects with liver metastases
- Female subject must either:
- Be of nonchildbearing potential: Postmenopausal (defined as at least 1 year without any menses for which there is no other obvious pathological or physiological cause) prior to screening, or documented surgically sterile (e.g.,

hysterectomy, bilateral salpingectomy, bilateral oophorectomy).

- Or, if of childbearing potential: Agree not to try to become pregnant during the study and for at least 6 months after the final study drug administration, and have a negative urine or serum pregnancy test within 7 days prior to Day 1 (Females with false positive results and documented verification of negative pregnancy status are eligible for participation), and if heterosexually active, agree to consistently use a condom plus 1 form of highly effective birth control per locally accepted standards starting at screening and throughout the study period and for at least 6 months after the final study drug administration.
- Female subject must agree not to breastfeed or donate ova starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.
- A sexually active male subject with female partner(s) who is of childbearing potential is eligible if:
- Agrees to use a male condom starting at screening and continue throughout the study treatment and for at least 6 months after final study drug administration. If the male subject has not had a vasectomy or is not sterile as defined below the subjects female partner(s) is utilizing 1 form of highly effective birth control per locally accepted standards starting at screening and continue throughout study treatment and for at least 6 months after the male subject receives final study drug administration.
- Male subject must not donate sperm starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.
- Male subject with a pregnant or breastfeeding partner(s) must agree to abstinence or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for at least 6 months after the final study drug administration.
- Subject agrees not to participate in another interventional study while on treatment in present study.

Inclusion Criteria for COE:

- Subject is eligible for the COE if they continue to meet all inclusion criteria from the main protocol in addition to the following when the patient is evaluated for eligibility to participate in the COE portion of the study:
- Institutional review board (IRB)/ independent ethics committee (IEC) approved written COE informed consent and privacy language as per national regulations (e.g., health

Trial name: EV-301		NCT number: 03474107
	insurance portability and accountability act [HIPAA] Authorization for US sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable). • Subject was randomized to Arm B and is either currently on study treatment or has discontinued study treatment due to intolerance, AE or progression of disease and has not started a new systemic anticancer treatment.	
Main exclusion criteria	• Subject has preexisting sensory or motor neuropathy Grade ≥ 2. • Subject has active central nervous system (CNS) metastases. Subjects with treated CNS metastases are permitted on study if all the following are true: o CNS metastases have been clinically stable for at least 6 weeks prior to screening o If requiring steroid treatment for CNS metastases, the subject is on a stable dose ≤ 20 mg/day of prednisone or equivalent for at least 2 weeks o Baseline scans show no evidence of new or enlarged brain metastasis o Subject does not have leptomeningeal disease • Subject has ongoing clinically significant toxicity (Grade 2 or higher with the exception of alopecia) associated with prior treatment (including systemic therapy, radiotherapy or surgery). Subject with ≤ Grade 2 immunotherapy-related hypothyroidism or panhypopituitarism may be enrolled when well-maintained/controlled on a stable dose of hormone replacement therapy (if indicated). Subjects with ongoing ≥ Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism are excluded. Subjects with ongoing immunotherapy related colitis, uveitis, or pneumonitis or subjects with other immunotherapy related AEs requiring high doses of steroids (> 20 mg/day of prednisone or equivalent) are excluded. • Subject has prior treatment with EV or other monomethyl auristatin E (MMAE)-based Antibody drug conjugates (ADCs). • Subject has received prior chemotherapy for urothelial cancer with all available study therapies in the control arm (i.e., both prior paclitaxel and docetaxel in regions where vinflunine is not an approved therapy, or prior paclitaxel, docetaxel and vinflunine in regions where vinflunine is an approved therapy). • Subject has received more than 1 prior chemotherapy regimen for locally advanced or metastatic urothelial cancer,	

including chemotherapy for adjuvant or neo-adjuvant disease if recurrence occurred within 12 months of completing therapy. The substitution of carboplatin for cisplatin does not constitute a new regimen provided no new chemotherapeutic agents were added to the regimen.

- Subject has history of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with nonmelanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.
- Subject is currently receiving systemic antimicrobial treatment for viral, bacterial, or fungal infection at the time of first dose of EV. Routine antimicrobial prophylaxis is permitted.
- Subject has known active Hepatitis B (e.g., hepatitis B surface antigen (HBsAg) reactive) or active hepatitis C (e.g., hepatitis C virus (HCV) Ribonucleic Acid (RNA) [qualitative] is detected).
- Subject has known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2).
- Subject has documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III-IV within 6 months prior to the first dose of study drug.
- Subject has radiotherapy or major surgery within 4 weeks prior to first dose of study drug.
- Subject has had chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug.
- Subject has known hypersensitivity to EV or to any excipient contained in the drug formulation of EV; OR subject has known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells.
- Subject has known hypersensitivity to the following: docetaxel or to any of the other excipients listed in product label, including polysorbate 80, paclitaxel or to any of the other excipients listed in product label, such as macrogolglycerol ricinoleate 35 (Ph.Eur.); and vinflunine or to any of the other excipients listed in product label such as

Trial name: EV-301	NCT number: 03474107
	other vinca alkaloids (vinblastine,vincristine, vindesine, vinorelbine). • Subject has known active keratitis or corneal ulcerations. • Subject has other underlying medical condition that would impair the ability of the subject to receive or tolerate the planned treatment and follow-up. • History of uncontrolled diabetes mellitus within 3 months of the first dose of study drug. Uncontrolled diabetes is defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c between 7 and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained. Exclusion Criteria for COE • Subject will be excluded from participation in the COE if they meet any of the exclusion criteria listed in the main protocol or if any of the following apply when the patient is evaluated for eligibility to participate in the COE portion of the study: • Subject has been diagnosed with a new malignancy while on Arm B in the EV-301 study. Subjects with nonmelanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed. • Subject has already started commercial EV or arrangements have been made for subject to start commercial EV which is reimbursed in their country. Additionally, if EV is commercially available with reimbursement in the potential subject's country, the subject can consider transitioning to the commercial product unless otherwise discussed with sponsor.
Intervention	Enfortumab vedotin: Intravenous infusion at 1.25 mg/kg
Comparator(s)	Vinflunine: 20-minute IV infusion at 320/m^2 Docetaxel: 1-hour infusion at 75 mg/m^2 Paclitaxel: 1-hour infusion at 175 mg/m^2 on day 1 of every 21-day cycle
Follow-up time	Median follow-up = 23.75 months (latest)
Is the study used in the health economic model?	Yes

Trial name: EV-301	NCT number: 03474107
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** *Primary:* • OS: up to 3 years *Secondary:* • PFS: up to 2 years • ORR: up to 2 years **Other endpoints:** • DCR: up to 2 years • DOR: up to 2 years • Safety assessed by Adverse Events (AEs): up to 2 years • Number of participants with laboratory value abnormalities and/or adverse events: up to 2 years • Number of participants with vital signs abnormalities and/or adverse events: up to 2 years • Safety assessed by 12- lead electrocardiogram (ECG): up to 2 years • Safety assessed by Eastern Cooperative Oncology Group Performance Status (ECOG PS): up to 2 years • Patient reported outcome assessed by quality of life: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30): up to 2 years • Patient reported outcome assessed by quality of life: EuroQOL 5-dimensions (EQ-5D -5L) questionnaire: up to 2 years
Method of analysis	OS and PFS were analysed using stratified log-rank tests and stratified Cox proportional hazard models; median OS and PFS rates were estimated using the Kaplan-Meier method. Median follow-up was determined based on reverse Kaplan-Meier estimates. Comparisons between response rates were analysed using stratified Cochrane Mantele Haenszel tests; differences [with corresponding 95% confidence interval (CIs)] in response rates were estimated. Subgroup analysis for OS was prespecified. Safety outcomes were analysed with summary statistics.
Subgroup analyses	N/A
Other relevant information	N/A

Appendix B. Efficacy results per study

Results per study

Table 59. Results per study; THOR C1; vinflunine subgroup

Results of THOR C1; NCT03390504											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS; months (95% CI)	Erdafitinib	136	12.06 (10.28, 16.36)	[redacted]	N/A	N/A	N/A	N/A	N/A	Hazard ratio and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the only explanatory variable. A hazard ratio less than 1 indicates longer survival time in the erdafitinib arm as compared to the docetaxel and vinflunine arms, respectively.	(50)
	Vinflunine	48	[redacted]								
6-month survival rate (95% CI)	Erdafitinib	136	0.85% (0.77, 0.90)	[redacted]	N/A	N/A	N/A	N/A	N/A		
	Vinflunine	48	[redacted]								
12-month survival rate (95% CI)	Erdafitinib	136	0.51% (0.41, 0.60)	[redacted]	N/A	N/A	N/A	N/A	N/A		
	Vinflunine	48	[redacted]								

Results of THOR C1; NCT03390504											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
24-month survival rate (95% CI)	Erdafitinib	136	0.26% (0.17, 0.36)	[redacted]	N/A	N/A	N/A	N/A	N/A		
	Vinflunine	48	[redacted]								
OS Hazard ratio (95% CI)	Erdafitinib	136	N/A	N/A	N/A	N/A	0.54	0.36, 0.81	N/A		
	Vinflunine	48	N/A								
Median PFS; months (95% CI)	Erdafitinib	136	5.55 (4.40, 5.65[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	Hazard ratio and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the explanatory variable. A hazard ratio less than 1 indicates longer survival time in the erdafitinib arm as compared to the docetaxel and vinflunine arms, respectively.	
	Vinflunine	48	[redacted]								
6-month survival rate (95% CI)	Erdafitinib	136	0.37% (0.28, 0.46)	[redacted]	N/A	N/A	N/A	N/A	N/A		
	Vinflunine	48	[redacted]								
	Erdafitinib	136	0.17% (0.10, 0.25)	[redacted]	N/A	N/A	N/A	N/A	N/A		

Results of THOR C1; NCT03390504											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
12-month survival rate (95% CI)	Vinflunine	48	[redacted]								
24-month survival rate (95% CI)	Erdafitinib	136	0.05% (0.01, 0.12)	[redacted]	N/A	N/A	N/A	N/A	N/A		
	Vinflunine	48	[redacted]								
PFS Hazard ratio (95% CI)	Erdafitinib	136	N/A	N/A	N/A	N/A	0.64	0.44, 0.93	N/A		
	Vinflunine	48	N/A								
CR, n (%)	Erdafitinib	136	9 (6.6%)	[redacted]	N/A	N/A	N/A	N/A	N/A	Minimum duration requirement for SD is 6 weeks from the date of randomization. Stable disease includes subjects with no measurable disease at baseline and their best response was Non-CR/Non-PD.	
	Vinflunine	48	[redacted]								
PR, n (%)	Erdafitinib	136	53 (39.0%)	[redacted]	N/A	N/A	N/A	N/A	N/A		
	Vinflunine	48	[redacted]								
SD, n (%)	Erdafitinib	136	50 (36.8%)	[redacted]	N/A	N/A	N/A	N/A	N/A		

Results of THOR C1; NCT03390504											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Vinflunine	48	[redacted]							ORR: Relative risk greater than 1 indicates that the probability of achieving an objective response (PR or CR) is higher on the Erdafitinib arm compared to the docetaxel and vinflunine arms, respectively. DCR: Relative risk greater than 1 indicates that the probability of achieving a response of SD or better is higher on the Erdafitinib arm compared to the docetaxel and vinflunine arms, respectively.	
PD, n (%)	Erdafitinib	136	14 (10.3%)	[redacted]	N/A	N/A	N/A	N/A	N/A		
	Vinflunine	48	[redacted]								
NE, n (%)	Erdafitinib	136	10 (7.4%)	[redacted]	N/A	N/A	N/A	N/A	N/A		
	Vinflunine	48	[redacted]								
ORR, n (%)	Erdafitinib	136	62 (45.6%)	[redacted]	N/A	N/A	3.13	1.54, 6.35	N/A		
	Vinflunine	48	[redacted]								
DCR, n (%)	Erdafitinib	136	112 (82.4%)	[redacted]	N/A	N/A	[redacted]	[redacted]	N/A		
	Vinflunine	48	[redacted]								

Table 60. Results per study; THOR C1; chemotherapy arm

Results of THOR C1; NCT03390504											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS; months (95% CI)	Erdafitinib	136	12.06 (10.28, 16.36)	4.27	N/A	N/A	N/A	N/A	N/A	Hazard ratio and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the only explanatory variable. A hazard ratio less than 1 indicates longer survival time in the erdafitinib arm as compared to the docetaxel and vinflunine arms, respectively.	(50) and (42)
	Chemotherapy	130	7.79 (6.54, 11.07)								
6-month survival rate (95% CI)	Erdafitinib	136	0.85% (0.77, 0.90)	0.19	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	130	0.66% (0.56, 0.74)								
12-month survival rate (95% CI)	Erdafitinib	136	0.51% (0.41, 0.60)	0.13	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	130	0.38% (0.28, 0.47)								
	Erdafitinib	136	0.26% (0.17, 0.36)	0.06	N/A	N/A	N/A	N/A	N/A		

Results of THOR C1; NCT03390504											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
24-month survival rate (95% CI)	Chemotherapy	130	0.20% (0.11, 0.31)								
OS Hazard ratio (95% CI)	Erdafitinib	136	N/A	N/A	N/A	N/A	0.64	0.47, 0.88	N/A		
	Chemotherapy	130	N/A								
Median PFS; months (95% CI)	Erdafitinib	136	5.55 (4.40, 5.65)	2.82	N/A	N/A	N/A	N/A	N/A	Hazard ratio and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the explanatory variable. A hazard ratio less than 1 indicates longer survival time in the erdafitinib arm as compared to the docetaxel and vinflunine arms, respectively.	
	Chemotherapy	130	2.73 (1.81, 3. 68)								
6-month survival rate (95% CI)	Erdafitinib	136	0.37% (0.28, 0.46)	0.10	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	130	0.27% (0.19, 0.37)								
	Erdafitinib	136	0.17% (0.10, 0.25)	0.09	N/A	N/A	N/A	N/A	N/A		

Results of THOR C1; NCT03390504											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
12-month survival rate (95% CI)	Chemotherapy	130	0.08% (0.03, 0.15)								
24-month survival rate (95% CI)	Erdafitinib	136	0.05% (0.01, 0.12)	0.01	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	130	0.04% (0.00, 0.13)								
PFS Hazard ratio (95% CI)	Erdafitinib	136	N/A	N/A	N/A	N/A	0.58	0.44, 0.13	N/A		
	Chemotherapy	130	N/A								
CR, n (%)	Erdafitinib	136	9 (6.6%)	5.8	N/A	N/A	N/A	N/A	N/A	Minimum duration requirement for SD is 6 weeks from the date of randomization. Stable disease includes subjects with no measurable disease at baseline and their best response was Non-CR/Non-PD.	
	Chemotherapy	130	1 (0.8%)								
PR, n (%)	Erdafitinib	136	53 (39.0%)	28.2	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	130	14 (10.8%)								

Results of THOR C1; NCT03390504											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
SD, n (%)	Erdafitinib	136	50 (36.8%)	5.3	N/A	N/A	N/A	N/A	N/A	ORR: Relative risk greater than 1 indicates that the probability of achieving an objective response (PR or CR) is higher on the Erdafitinib arm compared to the docetaxel and vinflunine arms, respectively. DCR: Relative risk greater than 1 indicates that the probability of achieving a response of SD or better is higher on the Erdafitinib arm compared to the docetaxel and vinflunine arms, respectively.	
	Chemotherapy	130	41 (31.5%)								
PD, n (%)	Erdafitinib	136	14 (10.3%)	-13.5	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	130	31 (23.8%)								
NE, n (%)	Erdafitinib	136	10 (7.4%)	-25.7	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	130	43 (33.1%)								
ORR, n (%)	Erdafitinib	136	62 (45.6%)	34.1	N/A	N/A	3.94	2.37, 6.57	N/A		
	Chemotherapy	130	15 (11.5%)								
DCR, n (%)	Erdafitinib	136	112 (82.4%)	39.3	N/A	N/A	1.91	1.55, 2.35	N/A		

Results of THOR C1; NCT03390504											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Chemotherapy	130	56 (43.1%)								

Table 61. Results per study; EV-301

Results of EV-301; NCT03474107											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS; months (95% CI)	EV	301	12.91 (11.01, 14.92)	3.97	N/A	N/A	N/A	N/A	N/A	OS and PFS were analysed using stratified log-rank tests and stratified Cox proportional hazard models; median OS and PFS rates were estimated using the Kaplan-Meier method. Median follow-up was determined based on	(5)
	Chemotherapy	307	8.94 (8.25, 10.25)								
OS Hazard ratio (95% CI)	EV	301	N/A	N/A	N/A	N/A	0.70	0.58, 0.85	0.00015		
	Chemotherapy	307	N/A								
	EV	301	5.55 (5.32, 6.28)	1.84	N/A	N/A	N/A	N/A	N/A		

Results of EV-301; NCT03474107											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS; months (95% CI)	Chemotherapy	307	3.71 (3.52, 3.94)							reverse Kaplan-Meier estimates.	
PFS Hazard ratio (95% CI)	EV	301	N/A	N/A	N/A	N/A	0.63	0.53, 0.76	0.00001		
	Chemotherapy	307	N/A								
CR, n (%)	EV	288	20 (6.9%)	3.5	N/A	N/A	N/A	N/A	N/A	Comparisons between response rates were analysed using stratified Cochrane Mantele Haenszel tests; differences [with corresponding 95% confidence interval (CIs)] in response rates were estimated. Subgroup analysis for OS was prespecified. Safety outcomes were analysed with summary statistics.	
	Chemotherapy	296	10 (3.4%)								
PR, n (%)	EV	288	99 (34.4%)	19.2	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	296	45 (15.2%)								
SD, n (%)	EV	288	88 (30.6%)	-4.2	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	296	103 (34.8%)								
PD, n (%)	EV	288	44 (15.3%)	-13.1	N/A	N/A	N/A	N/A	N/A		

Results of EV-301; NCT03474107											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Chemotherapy	296	84 (28.4%)								
NE, n (%)	EV	288	37 (12.8%)	-5.4	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	296	54 (18.2%)								
ORR, n (%)	EV	288	119 (41.32%)	22.74	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	296	55 (18.58%)								
DCR, n (%)	EV	288	207 (71.88%)	18.50	N/A	N/A	N/A	N/A	N/A		
	Chemotherapy	296	158 (53.38%)								

Appendix C. Comparative analysis of efficacy

C.1 Comparability assessment

As described in section 7.1.1, a comparability assessment of study characteristics, study population, interventions and common comparators as well as study outcomes was undertaken. The comparability assessment is detailed in the following. Based on the comparability assessment, the studies were deemed sufficiently comparable.

C.1.1 Study characteristics

The study characteristics for the THOR C1 and EV-301 trials are summarized in section 7.

THOR C1 and EV-301 are both open-label, international, phase 3, randomized controlled trials (RCT) which stratified patients by geographic region, Eastern Cooperative Oncology Group performance status (ECOG PS) score, and the presence of metastasis (THOR: visceral metastasis, EV-301: liver metastasis) at the time of randomization.

Patients enrolled in THOR C1 were followed up for a median of 15.9 months; in EV-301, patients had a median follow-up of 11.1 months at interim analysis and 23.75 months at final analysis. Neither trial allowed for treatment crossover during the analysis periods of interest for the base-case ITCs (randomization up to interim analysis for both studies). No other differences were observed regarding the study design of the two trials. Despite variations in study characteristics, the trials are deemed sufficiently comparable to support ITC analysis.

Table 62. Study characteristics of THOR C1 and EV-301

	THOR	EV-301
Study design	RCT	RCT
Trial phase	Phase 3	Phase 3
Blinding	Open label	Open label
Concealment of randomization	Adequate	Adequate
Strata during randomization	Geographic region (North America vs. EU vs rest of the world) ECOG PS ((0 or 1) vs. 2) Presence of visceral metastasis: lung, liver, or bone (yes vs. no)	Geographic region (Western Europe vs. US vs. rest of the world) ECOG PS (0 vs. 1) Presence of liver metastasis (yes vs. no)
Number of patients (ITT population)	Cohort 1^: Erdafitinib: 136	EV: 301 Chemo: 307

	Chemo: 130	
Location	International	International
Median follow-up (months)	Cohort 1: Interim/final*: 15.9	Interim analysis: 11.1 Final analysis: 23.75
Cross-over	Crossover allowed after interim analysis$	Allowed if positive results observed in interim analysis$

^Cohort 2 investigates erdafitinib vs pembrolizumab among subjects who had not received prior anti-PD (L)1 agent, and thus is not relevant for this ITC.

* Cohort 1 was stopped at interim analysis due to superiority of erdafitinib over chemotherapy; interim analysis is considered final analysis.

$ In both trials, there is no cross-over within the interim analysis data-cut, which served as the basis for the MAIC. However, it remains uncertain whether the final analysis for EV-301 include any instances of cross-over, and if so, whether the analysis has been appropriately adjusted to account for it.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; EV, Enfortumab Vedotin; ITT, Intention-to-treat; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; US, United States

C.1.2 Population

Trial inclusion/exclusion criteria

An overview of the eligibility criteria of THOR C1 and EV-301 is presented in Table 63. THOR C1 enrolled adults with metastatic or surgically unresectable UC who had at least one FGFR alteration; EV-301 enrolled adults with LA/mUC (EV-301) regardless of genetic alteration status.

All patients in both trials were previously treated. In THOR, patients had up to two prior systemic therapies and had received an anti-PD-(L)1 therapy in any setting, including neo-adjuvant, adjuvant, or metastatic treatment, without a specific requirement for platinum-based therapy. Additionally, the majority of subjects (94%) had previously undergone systemic therapy for metastatic urothelial cancer.

Patients enrolled in EV-301 were eligible to have received multiple prior lines of systemic therapy, which must include an anti-PD-L1 agent, with the condition of no more than one prior chemotherapy regimen in the locally advanced or metastatic disease setting and a platinum-based therapy in any setting. Patients in THOR C1 had an ECOG PS score of 0 to 2 while patients in EV-301 had ECOG PS scores from 0 to 1.

No other differences were observed in the key eligibility criteria.

Table 63. Key inclusion/exclusion criteria of THOR C1 and EV-301 trial

	THOR (NCT03390504)	EV-301 (NCT03474107)
Inclusion criteria		
Age	≥ 18 years	≥ 18 years
Disease status	Histologic demonstration of transitional cell carcinoma of the urothelium Metastatic or surgically unresectable urothelial cancer	Histologically or cytologically confirmed urothelial carcinoma Has radiologically documented metastatic or locally advanced disease at baseline
Progression and prior treatment	Documented progression of disease, defined as any progression that requires a change in treatment, prior to randomization Prior treatment with an anti-PD-(L) 1 agent as monotherapy or as combination therapy, given as neo-adjuvant, adjuvant, or in metastatic line of treatment as frontline or maintenance therapy ≤ 2 prior lines of systemic treatment	Have experienced radiographic progression or relapse during, or after CPI (anti-PD-1 or anti-PD-L1) for locally advanced or metastatic disease Have received a platinum containing regimen in the metastatic/locally advanced, neoadjuvant or adjuvant setting. If platinum was administered in the adjuvant/neoadjuvant setting subject must have progressed within 12 months of completion.
ECOG PS	0-2	0-1
Baseline laboratory data	ANC ≥ 1500/mm3 platelet count >75,000/mm3 (≥100,000/mm3 for Cohort 1 subjects at sites choosing vinflunine chemotherapy) hemoglobin >8.0 g/dL total bilirubin ≤1.5 x ULN OR direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5xULN [≤1xULN for Cohort 1 subjects at sites choosing docetaxel chemotherapy] CrCl >30 mL/min either directly measured via 24-hour urine collection or calculated using the Cockcroft-Gault formula ALT and AST ≤2.5x institutional ULN or ≤5x institutional ULN for subjects with liver metastases (For subjects in Cohort 1 at sites choosing docetaxel chemotherapy, both the ALT and AST values must be ≤1.5×ULN concomitant with alkaline phosphatase of ≤2.5×ULN)	ANC ≥ 1500/mm3 platelet count ≥ 100 x 109/L hemoglobin ≥ 9 g/dL serum total bilirubin ≤ 1.5 x ULN or ≤ 3 x ULN for subjects with Gilbert's disease CrCl ≥ 30 mL/min as estimated per institutional standards or as measured by 24hour urine collection (GFR can also be used instead of CrCl) ALT and AST ≤ 2.5 × ULN or ≤ 3 x ULN for subjects with liver metastases

	Phosphate: <ULN within 14 days of treatment and prior to Cycle 1 Day 1 (medical management allowed)	
Molecular	Tumors must have ≥1 of the following translocations: FGFR2-BICC1, FGFR2-CASP7, FGFR3- TACC3, FGFR3-BAIAP2L1; or 1 of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C	
Exclusion criteria		
Disease status	Active malignancies (requiring treatment change in the last 24 months) with the exception of urothelial cancer Skin cancer treated within the last 24 months that is considered completely cured localized prostate cancer with a Gleason score of 6 (treated within the last 24 months or untreated and under surveillance) localized prostate cancer with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence Symptomatic CNS metastases Current CSR or retinal pigment epithelial detachment of any grade	Has preexisting sensory or motor neuropathy Grade ≥ 2 Has active CNS metastases
Prior treatment	Received prior FGFR inhibitor treatment Not recovered from reversible toxicity of prior anticancer therapy Major surgery within 4 weeks before randomization	Prior treatment with EV or other MMAE-based ADCs Received prior chemotherapy for UC with all available study therapies in the control arm Received >1 prior chemotherapy regimen for locally advanced or metastatic urothelial cancer Ongoing clinically significant toxicity (≥ Grade 2 with the exception of alopecia) associated with prior treatment Radiotherapy or major surgery within 4 weeks prior to first dose of study drug
Medical history	History of uncontrolled cardiovascular disease Known active AIDS (human immunodeficiency virus (HIV) infection) Known active hepatitis B or C infection	History of another malignancy within 3 years History of a cerebral vascular, unstable angina, myocardial infarction, or cardiac symptoms (NYHAC III-IV) within 6 months prior trial

Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions	Known history of HIV infection Known active hepatitis B or C Known active keratitis or corneal ulcerations History of uncontrolled diabetes mellitus within 3 months prior study

Abbreviations: ADC, antibody drug conjugate; AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CNS, central nervous system; CPI, checkpoint inhibitor; CrCl, Creatinine Clearance; CSR, central serous retinopathy; EV, Enfortumab Vedotin; FGFR, fibroblast growth factor receptor; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; NYHAC, New York Heart Association (NYHA) Classification; MMAE, monomethyl auristatin E; PD-(L)1, programmed death-(ligand) 1; ULN, upper limit of normal.

Baseline characteristics

Baseline patient characteristics in each arm of THOR C1 and EV-301 are listed in Table 64.

The proportions of patients who were ≥75 years old, non-smokers, with primary disease originating in the urinary tract, and visceral metastasis were generally comparable between the two trials.

There were some notable differences in sex and geographic distribution between the two trials. There was a slightly lower percentages of males in THOR (70.6% [erdafitinib]) than in EV-301 (79.1% [EV]; standardized mean difference [SMD]: 0.16). THOR C1 had a significantly lower percentage of patients from the US than EV-301 (5.9% [erdafitinib]; vs 14.3% [EV], respectively; SMD: 0.25) which may be attributed to the availability of alternative therapies and competing clinical studies that admit "all comers" without the need for biomarker testing, as well as the commercial availability of EV in that region.

Regarding disease characteristics, fewer patients in THOR C1 had a history of diabetes or hyperglycemia compared with EV-301 (8.1% [erdafitinib] vs 18.6% [EV]; SMD: 0.27). A larger proportion of patients in THOR had lower Bellmunt risk scores (0 to 1) compared with EV-301 patients (75.7% [erdafitinib] vs 66.8% [EV]; SMD: 0.16). A smaller proportion of patients in THOR C1 had liver metastasis compared with EV-301 (22.8% [erdafitinib] vs 30.9% [EV], respectively; SMD: 0.15).

Due to eligibility criteria, 9.4% of patients in THOR C1 had an ECOG PS score of 2 vs 0% in EV-301, and 87.6% of patients in THOR C1 received platinum therapy vs all patients in EV-301. Additionally, 12.5% of patients in EV-301 received more than 3 prior lines of therapy.

Table 64. Patient baseline characteristics

	THOR C1 NCT03390504	EV-301 NCT03474107

	Erdafitinib (N = 136)	Chemotherapy (N = 130)	Enfortumab Vedotin (N = 301)	Chemotherapy (N = 307)
Age in years				
Median (min, max)	66.0 (32, 85)	69.0 (35, 86)	68.0 (34.0, 85.0)	68.0 (30.0, 88.0)
≥75, n (%)	26 (19.1)	30 (23.1)	52 (17.3)	68 (22.1)
Sex, n (%)				
Male	96 (70.6)	94 (72.3)	238 (79.1)	232 (75.6)
Geographic region n (%)				
Western Europe	82 (60.3)	80 (61.5)	126 (41.9)	129 (42.0)
United States	8 (5.9)	5 (3.8)	43 (14.3)	44 (14.3)
Rest of the world	46 (33.8)	45 (34.6)	132 (43.9)	134 (43.6)
Race, n (%)				
White	81 (59.6)	63 (48.5)	-	-
Asian	37 (27.2)	40 (30.8)	-	-
Black or African American	0	1 (0.8)	-	-
Multiple	0	1 (0.8)	-	-
Not reported	18 (13.2)	25 (19.2)	-	-
Tobacco use, n (%)				
Former user	-	-	167 (55.5)	164 (53.4)
Current user	-	-	29 (9.6)	31 (10.1)
Never used	44 (32.4)	47 (36.2)	91 (30.2)	102 (33.2)
Not reported or unknown	-	-	14 (4.7)	10 (3.3)
History of diabetes or hyperglycemia, n (%)				

Yes	11 (8.1)	22 (16.9)	56 (18.6)	58 (18.9)
ECOG PS score, n (%)				
0	63 (46.3)	51 (39.2)	120 (39.9)	124 (40.4)
1	61 (44.9)	66 (50.8)	181 (60.1)	183 (59.6)
2	12 (8.8)	13 (10.0)	-	-
Bellmunt risk score, n (%)				
0–1	103 (75.7)	95 (73.1)	201 (66.8)	208 (67.8)
≥2	33 (24.3)	35 (26.9)	90 (29.9)	96 (31.3)
Not reported	-	-	10 (3.3)	3 (1.0)
Origin site of primary disease, n (%)				
Upper urinary tract	41 (30.1)	48 (36.9)	98 (32.6)	107 (34.9)
Bladder or other site	95 (69.9)	82 (63.1)	203 (67.4)	200 (65.1)
Sites of metastasis, n/total (%)				
Lymph node only	-	-	34/301 (11.3)	28/306 (9.2)
Visceral site	101 (74.3)	97 (74.6)	234/301 (77.7)	250/306 (81.7)
Liver	31 (22.8)	38 (29.2)	93/301 (30.9)	95/307 (30.9)
PD-L1 status				
Low expression (CPS <10), n (%)	89 (92.7)	68 (86.1)	-	-
FGFRa/t, n/total (%)				
Mutations	108/135 (79.4)	107/129 (82.3)	-	-
Fusions	25/135 (18.4)	19/129 (14.6)	-	-
Mutations and fusions	2/135 (1.5)	3/129 (2.3)	-	-
Histologic type at initial diagnosis, n/total (%)				

Urothelial or transitional-cell carcinoma	-	-	229/301 (76.1)	230/305 (75.4)
Urothelial carcinoma, mixed types	-	-	45/301 (15.0)	42/305 (13.8)
Other§	-	-	27/301 (9.0)	33/305 (10.8)
Histologic type at baseline, n (%)				
Transitional cell carcinoma	128 (94.1)	124 (95.4)		
Transitional cell carcinoma with minor components (<50% overall) of variant histology	8 (5.9)	6 (4.6)		
Previous systemic therapies, n (%)				
1–2	135 (99.3)	130 (100)	262 (87.0)	270 (87.9)
≥3	1 (0.7)	-	39 (13.0)	37 (12.1)
Prior platinum-based chemotherapy, n (%)				
None	14 (10.3)	19 (14.6)	0	0
Best response among patients who previously received checkpoint inhibitor treatment, n (%)¶				
Response	-	-	61 (20.3)	50 (16.3)
No response	-	-	207 (68.8)	215 (70.0)
Time since diagnosis of metastatic or locally advanced disease in months				
Median (min, max)	-	-	14.8 (0.2, 114.1)	13.2 (0.3, 118.4)
Time from diagnosis of surgically unresectable or metastatic disease to randomization in months				
Median (min, max)	12.9 (0.6, 74.6)	11.7 (1.8, 63.5)	-	-

* Percentages may not total 100 because of rounding.

§ Other histologic types include adenocarcinoma, squamous-cell carcinoma, and pseudosarcomatic differentiation

¶ The best response among patients who had a response was defined as a confirmed complete or partial response; among patients who did not have a response, the best response was defined as stable disease or progressive disease.

Abbreviations: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; min, minimum; max, maximum

C.1.3 Intervention and common comparator

The choice of appropriate ITC method depends in part on the existence of a valid common comparator. Both THOR C1 and EV-301 randomized patients to physician's choice of chemotherapy, which was determined prior to trial enrolment. Vinflunine or docetaxel were used in both trials, and paclitaxel was an option in EV-301. Dosage information for each treatment investigated in both trials is listed in Table 65.

While some patients in the chemotherapy arm of EV-301 trial received paclitaxel, docetaxel and paclitaxel are assumed to be equivalent in terms of efficacy, as per individual clinician consultation. Therefore, "physician's choice of chemotherapy" in both trials is considered sufficiently comparable to be considered a common comparator.

Table 65. Treatment characteristics of THOR C1 and EV-301

	THOR		EV-301	
Intervention	Erdafitinib	Chemotherapy (Vin, Doc)	Enfortumab Vedotin	Chemotherapy (Vin, Doc, Pac)
Dose	8 mg with a pharmacodynamically guided increase in the dose to 9 mg on day 14	Vin: 320 mg/m2 Doc: 75 mg/m2	1.25 mg/kg	Vin: 320 mg/m2 Doc: 75 mg/m2 Pac: 175 mg/m2
Frequency and cycle length	Once daily for 21 days in a 21-day cycle	Vin/Doc: once every 3 weeks	Days 1, 8, and 15 of a 28-day cycle.	Vin/Doc/Pac: Day 1 of a 21-day cycle.
Route of administration	Oral	Vin/Doc: IV	IV	Vin/Doc/Pac: IV
Treatment duration	until the occurrence of disease progression or unacceptable toxic effects.		Until radiological disease progression as determined per investigator assessment or other discontinuation criteria were met or upon study termination, or study completion, whichever occurred first.	

Abbreviations: Doc, docetaxel; IV, Intravenous; NR, not reported; Pac, paclitaxel; Vin, vinflunine

C.1.4 Outcomes

The availability of outcomes and statistics reported by each trial influence whether an ITC is possible, while the comparability of outcome measurements influence the validity of ITCs. Within RCTs, interventions are compared using the exact same criteria for each outcome of interest. However, these criteria may vary between trials, potentially leading to bias in ITCs. The criteria used to define an event, the person(s) who assessed the criteria for an event, and observation period may influence the observed effects.

A summary of the definition of each endpoint considered for the ITCs is presented in Table 66. Overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and complete response (CR) were deemed comparable between the two trials.

While both trials relied on RECIST 1.1 criteria to determine disease progression, there is a difference in the timing of progression assessment. EV-301 conducted PFS and response assessments every 8 weeks (± 7 days) throughout the study, whereas THOR C1 did so every 6 weeks (± 7 days) for the first year, and the assessments were performed as clinically indicated after the first year. This discrepancy is expected to introduce some bias in the ITC, but the impact should be minimal.

Adverse events (AE) in THOR C1 were reported by patients, while AEs were investigator assessed in EV-301. However, the process remains fundamentally the same: patients report their symptoms or other health-related issues to the investigator, who then records them in the clinical database as AEs and reports them to the sponsor. While there may be slight variations in how individuals describe this process, the core procedure remains consistent.

Table 66. Summary of outcome measurements in THOR C1 and EV-301

	THOR C1	EV-301
OS		
Outcome definition	the time from the date of randomization until the documented date of death	the time from the date of randomization until the documented date of death from any cause
Time frame (median, month)	15.9	11.1*
PFS		
Criteria	RECIST v1.1	RECIST v1.1
Assessor (BICR, investigator, other)	Investigator	Investigator

Outcome definition	time from the date of randomization to the date of disease progression or relapse from complete response or death, whichever is reported first divided	time from date of randomization until date of documented radiological disease progression or until death due to any cause, whichever occurred first
Timing of assessment	every 6 weeks (± 7 days)^	every 8 weeks (± 7 days)
Time frame (median, month)	15.9	11.1*
ORR		
Criteria	RECIST v1.1	RECIST v1.1
Assessor (BICR, investigator, other)	Investigator	Investigator
Outcome definition	the proportion of participants who achieve CR or PR	the proportion of participants with CR or PR
Timing of assessment	every 6 weeks (± 7 days)^	every 8 weeks (± 7 days)
Time frame (median, month)	15.9	11.1
CR		
Criteria	RECIST v1.1	RECIST v1.1
Assessor (BICR, investigator, other)	Investigator	Investigator
Outcome definition	NR	disappearance of all target and nontarget lesions
Timing of assessment	every 6 weeks (± 7 days)^	every 8 weeks (± 7 days)
Time frame (median, month)	15.9	11.1
Adverse events		
Criteria	CTCAE v 4.03	CTCAE v 4.03
Assessor (BICR, investigator, other)	Subject	Investigator

Time frame	From date of signed informed consent up to 30 days after last dose,	From date of signed informed consent up to 30 days after last dose,

*A longer follow-up time of month 23.75 is available for OS, PFS, and TRAEs.
^Every 6 weeks (± 7 days) for the first year, and then as per clinically indicated.
Abbreviations: BICR, Blinded Independent Central Review; CR, complete response; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; PR, partial response; ORR, objective or overall response rate.

C.1.5 Identification of treatment effect modifiers

The appropriateness and validity of an ITC method depends on whether there are differences in the distribution of treatment effect modifiers (TEM) across trials. When differences exist, population-adjusted indirect comparison (PAIC) methods such as the matching-adjusted indirect comparison (MAIC) may be used to adjust for these differences, provided there is enough overlap between the populations of the two trials (i.e., THOR C1 and EV-301) (53).

Potential effect modifiers for metastatic UC were selected based on literature and expert clinician consultations. These include risk factors, ECOG score, liver metastases, haemoglobin level, visceral disease, primary site (bladder or urethra), smoking status, time since prior therapy, previous treatments, age, gender, and transitional cell type.

This list of variables was limited to those available for comparison between the THOR C1 and EV-301 trial populations. EV-301 also reported additional variables, but these were not considered when comparing populations for reasons outlined in Table 67.

Variables were ranked by importance for the indication, as determined by clinicians. The MAIC results were reported for scenarios ranging from including only the most important variable to including all variables.

Table 67. Variables available for trial population comparison, prioritized by clinical relevance

Rank*	Variable
1	Belmunt risk score (0-1, ≥2)
2	ECOG PS (0, 1)
3	Presence of liver metastases (yes, no)
4	Presence of visceral metastases (yes, no)

5	Origin of primary disease (upper urinary tract, bladder or other site)
6	Smoking status (never smoked**, other)
7	History of diabetes or hypoglycaemia (yes, no)
8	Geographic region (Western Europe, US, rest of the world)
9	Age (median; ≥75 years, < 75 years)
10	Male (yes, no)

* Ranked from (1) being the most likely to (10) being the least likely to be a treatment effect modifier.
** "Other" includes "former user", "current user", "not reported or unknown"
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; US, United States

Table 68. Variables reported in EV-301 that could not be appropriately matched

Variable	Reason for exclusion
Histologic type at initial diagnosis (urothelial or transitional-cell carcinoma, urothelial carcinoma mixed types, other)	Categories not comparable to those recorded in THOR
Presence of lymph node only metastases (yes, no)	Presence of lymph node metastases was recorded in THOR, but data does not indicate if it was the only type of metastases
Prior systemic therapies (≥3)	THOR C1 limited to 1-2 prior therapies
Best response among patients who previously received CPI (response, no response)	Not recorded in THOR
Median time since diagnosis of metastatic or locally advanced disease	THOR C1 only recorded time since diagnosis (not time since metastatic diagnosis)

Abbreviations: CPI, checkpoint inhibitor; ITC, indirect treatment comparison

C.1.6 Summary of feasibility concerns

The characteristics of the trials' designs, common comparators, and outcome measurements between the two trials are considered sufficiently comparable to facilitate an ITC.

As discussed in Section 7, the chemotherapy arm in both trials was considered sufficiently similar to serve as a common comparator. Therefore, it is possible to anchor the ITCs between drug erdafitinib and EV using chemotherapy.

As such, the validity of ITCs depends on the balance of TEMs across trials. Since there are differences in potential TEMs, network meta-analysis (NMA), which relies on all TEMs being balanced across trials (56), is not appropriate for comparing erdafitinib and EV. To adjust for these population definitions, PAIC methods such as MAIC are recommended. Nevertheless, the validity and reliability of a PAIC is contingent on the ability to adjust for all imbalances in TEMs, as well as a sufficient sample size after population adjustment (72).

There were differences in population characteristics that could not be adjusted for via PAICs. For example, THOR C1 patients harbor FGFR gene alterations, while EV-301 patients represent an all-comer population. In addition, all but one patient in THOR C1 received no more than two prior lines of systemic therapy, while a small proportion of patients in EV-301 (13%) received at least three prior systemic therapies, meaning it was not possible to match THOR patients to EV-301 patients with ≥3 prior therapies. However, it is not clear if THOR C1 and EV-301 had similar definitions for prior systemic therapies.

C.2 Methods used for ITC

MAICs between erdafitinib and EV were conducted using IPD from THOR C1, and aggregate data from EV-301. Patients were first excluded from THOR C1 based on EV-301's eligibility criteria, and subsequently, their baseline characteristics were matched to those of EV-301, as described in Section 0. All analyses were conducted in SAS 9.4, except for the estimation of probabilistic summaries, which was conducted in WinBUGS.

C.2.1 Harmonization of eligibility criteria

To address the differences in the inclusion and exclusion criteria between the THOR and EV-301 trials, an additional set of restriction criteria were applied to patients in THOR to better align the trial population with that of EV-301. Patients in THOR who met the following criteria were excluded from the analysis:

- ECOG PS 2
- No prior platinum-based chemotherapy
- More than one prior chemotherapy

C.2.2 Matching the baseline characteristics

An anchored MAIC, via the common comparator "physician's choice of chemotherapy" was conducted according to guidance from the National Institute for Health Care and Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 18 (53). Covariates were adjusted for in the MAIC.

After harmonizing the eligibility criteria of THOR C1 to EV-301, balancing weights were first derived so that the average baseline characteristics after re-weighting patients in THOR C1 matched the published aggregate characteristics of EV-301 patients. These weights were estimated using a propensity score-type logistic regression equation that predicted whether a given type of patient originates from THOR C1 or EV-301 as a function of baseline characteristics. The weights (w_i) were estimated using the method of moments rather than by maximum likelihood (as might otherwise be the case), because only aggregate data (averages and percentages) for the selected covariates were available for EV-301's population (54). These weights were then used to calculate the effective sample size (ESS) achieved after weighting patients. The ESS was calculated by $(\sum w_i)^2/(\sum w_i^2)$. After the individual patient weights were computed, the distribution of weights was assessed to identify any overly influential observations (see .

The individual patient weights were employed to compute adjusted relative effects for patients in THOR, reflecting the estimated impact of erdafitinib vs. physician's choice of chemotherapy within the patient population of EV-301 trial. Binary outcomes in THOR C1 were quantified as odds ratios (OR) through weighted logistic regression, while time-to-event outcomes were quantified as hazard ratios (HR) through weighted Cox proportional hazards (PH) models, with the treatment included as a covariate. The standard error (SE) of the relative effects were computed using a robust sandwich estimator (55). Subsequently, these adjusted relative effects were compared with the observed relative effects of EV vs. chemotherapy in EV-301 to estimate the comparative effectiveness of erdafitinib vs. EV through a Bayesian NMA.

Fixed-effects NMA models were fitted in Bayesian framework using Monte Carlo Markov Chain (MCMC) simulation methods implemented in WinBUGS. The weighted relative effects of erdafitinib vs. physician's choice of chemotherapy and observed relative effects of EV vs. physician's choice of chemotherapy were synthesized in the NMA model (e.g., log-HRs for PFS and OS, log-ORs for ORR, CR, and safety outcomes), where a normal likelihood and identity link were used following the methods described in NICE DSU TSD 2 (56). Non-informative normal(0, 100^2) priors were assigned to the basic relative effect parameters. All models were run using three chains with a burn-in period of 50,000 iterations. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic and history plots (57, 58). A further simulation sample of 50,000 iterations for each chain was used to inform the results.

For all outcomes, the relative effects and their 95% credible intervals (CrI) of erdafitinib vs. EV were estimated. In addition, to aid the interpretation of binary outcomes, risk ratios (RRs) were also derived from the logistic regression models and included in the report. For time-to-event outcomes, the Kaplan-Meier (KM) curves for the adjusted THOR population were displayed for visual comparison, alongside the original KM curves from both THOR C1 and EV-301.

C.2.3 Response evaluable population

The analyses for response outcomes (ORR and CR) were restricted to the response-evaluable populations from both trials. Criteria validated by clinical experts were used to select response-evaluable patients in THOR. Patients who were not evaluable at baseline (defined in THOR C1 as patients without target lesions at baseline) or at follow-up were excluded

from these analyses. The underlying assumption of the MAIC analyses for these outcomes is that the distributions of baseline characteristics in EV-301's intention-to-treat (ITT) population are similar to those in the response evaluable population.

C.2.4 Assessment of proportional hazards

The MAIC of erdafitinib vs. EV for time-to-event outcomes assumes PH holds for the erdafitinib vs. chemotherapy comparison within the matched THOR C1 data, as well as the EV vs. chemotherapy comparison within the observed EV-301 data. To assess this assumption, the log-cumulative hazards for each treatment group were visually compared within these trial datasets. Schoenfeld residuals plots were also visually inspected, and the Grambsch and Therneau test was conducted to quantitatively assess if there was evidence suggesting violation of the PH assumption (59).

C.2.5 Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of the results:

1. Impact of covariates included in adjustment: To assess the impact of adjusting for each covariate on the results, several sensitivity analyses were conducted, where each covariate was cumulatively adjusted for one-by-one in order of their clinical relevance as ranked.
2. Impact of population differences in terms of prior lines of therapy: It was not possible to match the patients who had received three or more lines of therapy in EV-301's ITT population as all but one patient in THOR C1 had received no more than two therapies. Therefore, a sensitivity analysis was carried out using data from the subgroup in EV-301 who had received only 1-2 prior lines of treatment. However, one limitation of this sensitivity analysis was that the baseline characteristics of the 1-2 prior lines subgroup were not available; patients could only be matched based on the distribution of baseline characteristics in EV-301's ITT population. This MAIC is only valid if the distribution of the baseline characteristics was similar between the 1-2 prior lines subgroup and ITT populations with respect to any treatment effect modifiers. As such, this sensitivity analysis should be interpreted with caution. These subgroup data were only publicly available for PFS, OS, and ORR among the ITT population (not among the response evaluable population). The sensitivity analyses were thus limited to PFS and OS.

C.3 Results from the comparative analysis

C.3.1 Baseline characteristics

Baseline summaries of the covariates considered for adjustment are presented in Table 8 for patients in the THOR C1 and EV-301 trials. Baseline characteristics for THOR C1 were summarized across three distinct datasets:

1. Observed dataset: This refers to the initial, unmodified dataset.
2. Exclusion criteria applied dataset: This dataset was derived after aligning THOR's eligibility criteria with EV-301. A total of 69 patients were excluded from THOR C1 because they had an ECOG PS of 2 (n = 25), no prior platinum-based chemotherapy (n = 33), or more than one prior chemotherapy (n = 11), the distribution of baseline characteristics slightly changed, most notably for ECOG PS, which was to be expected.
3. Matched dataset: This dataset involves an additional level of refinement, where patients in the 'Exclusion criteria applied dataset' were weighted to adjust for differences in baseline covariates between THOR C1 and EV-301.

After applying the individual patient weights to the remaining THOR C1 patients, the average baseline characteristics matched those observed in EV-301. The ESS decreased from 197 to 126, marking a 36% reduction, yet this was deemed adequate for a plausible comparison. Table 21 presented the baseline characteristics of EV-301 and THOR C1 before and after matching patients.

Table 69. Baseline characteristics for EV-301 and THOR C1 before and after matching patients

	EV-301 Observed (N = 608)	THOR C1 Observed (N = 266)	THOR C1 Exclusion criteria applied (n = 197)	THOR C1 Matched (ESS = 126/n=197)
Bellmunt risk score (%)				
0-1	68	74	78	68
2	32	26	22	32
ECOG PS (%)				
0	40	43	48	40
1	60	48	52	60
Presence of liver metastasis (%)				
Yes	25	26	26	25
Presence of visceral metastasis (%)				
Yes	66	74	76	66

Origin of primary disease (%)				
Upper urinary tract	34	33	35	34
Bladder or other site	66	67	65	66
Smoking status (%)				
Never smoked	33	34	31	33
History of diabetes or hyperglycemia (%)				
Yes	19	12	12	19
Region (%)				
Western Europe	42	61	60	42
US	14	5	5	14
Other	44	34	36	44
Age in years				
median	68	67	67	68
≥75 (%)	20	21	20	20
Sex				
Male (%)	77	71	71	77

Source: Balversa MAIC report (data on file) (49)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance score; ESS = effective sample size

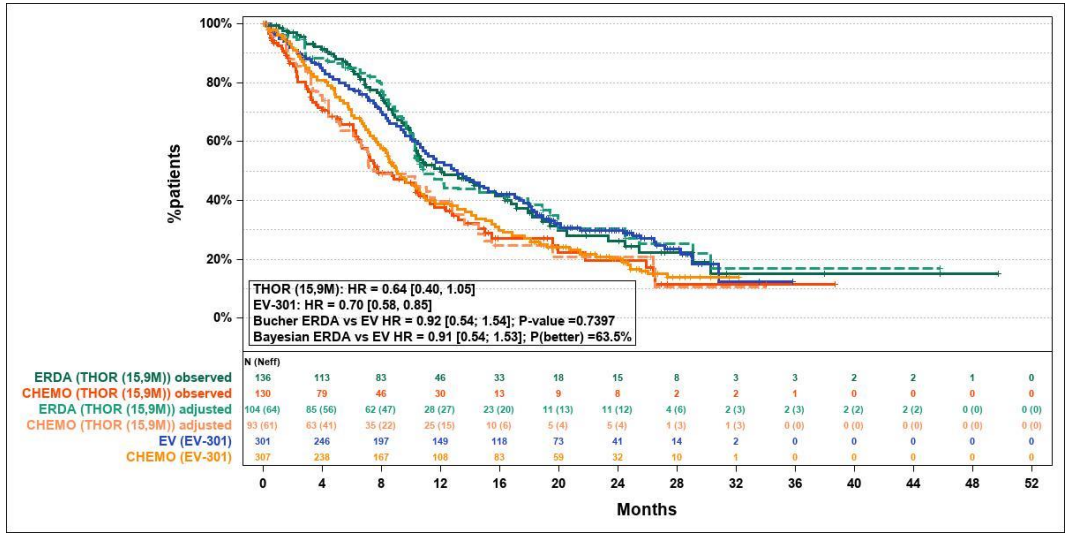
C.3.2 Efficacy – results per OS

In terms of OS, the matching adjustment had limited impact on the relative effectiveness, as the HRs of erdafitinib vs. EV were consistent before and after matching (Figure 13, Table 23).

The Bucher hazard ratio (HR) was not statistically significant at the conventional significance level of $p < 0.05$, nor at a more lenient threshold of $p < 0.1$. Additionally, the confidence interval (CI) for the HR includes 1, indicating that the true effect could potentially be null (no effect difference). This further supports the conclusion that the HR is not statistically significant.

The width of the corresponding confidence intervals increased after matching THOR C1 patients, which was in line with the decrease in ESS.

Figure 29. Overall survival – Kaplan-Meier curves



Source: Balversa MAIC report (data on file) (49)

Abbreviations: CHEMO, chemotherapy; ERDA, erdafitinib; EV, enfortumab vedotin; HR, hazard ratio.

Table 70. Within-trial and between-trial comparative analysis of OS (Bucher method)

	EV vs. chemotherapy (EV-301)	Erdafitinib vs. chemotherapy (THOR C1)	Erdafitinib vs. EV (Anchored MAIC)
Observed	HR: 0.70 (95% CI 0.58; 0.85, p = N/A)	HR: 0.64 (95% CI 0.47; 0.88, p < 0.01)	HR: 0.91 (95% CI 0.63; 1.31, p = 0.61)
Exclusion criteria applied	-	HR: 0.65 (95% CI 0.44; 0.94, p = 0.02)	HR: 0.92 (95% CI 0.60; 1.40, p = 0.69)
Matched	-	HR: 0.65 (95% CI 0.40; 1.05, p = 0.07)	HR: 0.92 (95% CI 0.55; 1.54, p = 0.74)

Source: Balversa MAIC report (data on file) (49)

Abbreviations: CI, confidence interval; EV, enfortumab vedotin; OS, overall survival.

In the sensitivity analyses where each covariate was cumulatively adjusted for one by one, the MAIC estimates for the HR of erdafitinib vs. EV were consistent across all covariates.

Similar results were observed when comparing OS of the matched THOR C1 patients with the ITT patients and patients in the subgroup who received 1-2 prior lines in EV-301.

The longer-term OS results in EV-301 were similar to the interim results, thus having negligible impact on the HR of erdafitinib vs. EV estimated by the MAIC.

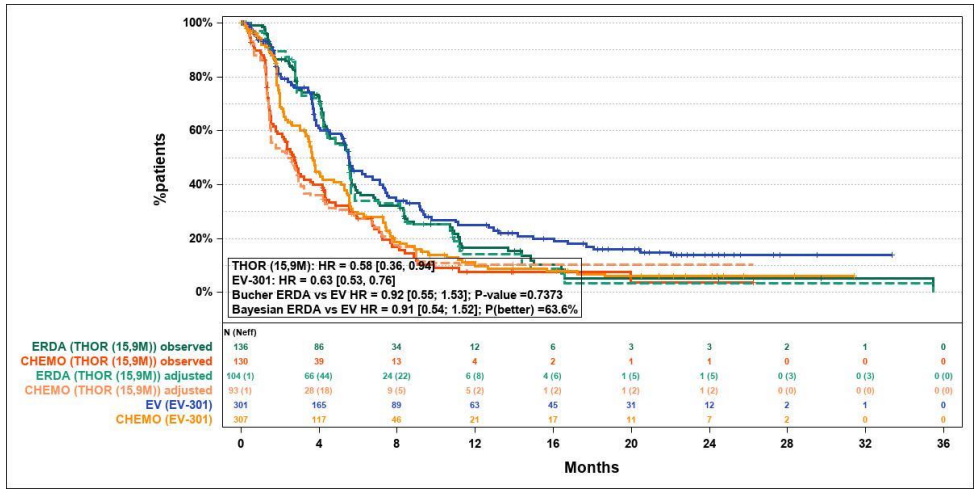
C.3.3 Efficacy – results per PFS

In terms of PFS, the HRs of erdafitinib vs. EV were consistent before and after matching the THOR C1 patients to EV-301's population (Figure 14, Table 24).

The Bucher hazard ratio (HR) was not statistically significant at the conventional significance level of $p < 0.05$, nor at a more lenient threshold of $p < 0.1$. Additionally, the confidence interval (CI) for the HR includes 1, indicating that the true effect could potentially be null (no effect difference). This further supports the conclusion that the HR is not statistically significant.

The confidence intervals widened after matching THOR C1 patients, which was in line with the decrease in ESS.

Figure 30. Progression-free survival – Kaplan-Meier curves



Source: Balversa MAIC report (data on file) (49)

Abbreviations: CHEMO, chemotherapy; ERDA, erdafitinib; EV, enfortumab vedotin; HR, hazard ratio.

Table 71. Within-trial and between-trial comparative analysis of PFS (Bucher method)

	EV vs. chemotherapy (EV-301)	Erdafitinib vs. chemotherapy (THOR C1)	Erdafitinib vs. EV (Anchored MAIC)
Observed	HR: 0.63 (95% CI 0.53; 0.76, p = N/A)	HR: 0.58 (95% CI 0.44; 0.78, p < 0.01)	HR: 0.92 (95% CI 0.65; 1.30, p = 0.64)
Exclusion criteria applied	-	HR: 0.54 (95% CI 0.38; 0.75, p < 0.01)	HR: 0.85 (95% CI 0.58; 1.25, p = 0.41)
Matched	-	HR: 0.58 (95% CI 0.36; 0.94, p = 0.03)	HR: 0.92 (95% CI 0.55; 1.53, p = 0.74)

Source: Balversa MAIC report (data on file) (49)

Abbreviations: CI, confidence interval; EV, enfortumab vedotin; PFS, progression-free survival.

In the sensitivity analyses where each covariate was cumulatively adjusted for one by one, the MAIC estimates for the HR of erdafitinib vs. EV were consistent across all covariates

Similar results were observed when comparing PFS of the matched THOR C1 patients to the PFS outcomes of the ITT patients and patients in the subgroup who received 1-2 prior lines in EV-301.

The longer-term PFS results in EV-301 were similar to the interim results, thus having negligible impact on the HR of erdafitinib vs. EV estimated by the MAIC.

C.3.4 Efficacy – results per ORR

In terms of ORR, the relative effects of erdafitinib vs. EV increased after matching the THOR C1 patients to EV-301's population (Table 25).

Table 72. Between-trial comparative analysis of ORR (Bucher method)

	Erdafitinib vs. EV (Anchored MAIC)
Observed	OR: 1.28 (95% CI 0.56; 2.94, p = 0.56)
Exclusion criteria applied	OR: 1.59 (95% CI 0.63; 4.07, p = 0.33)
Matched	OR: 1.45 (95% CI 0.45; 4.64, p = 0.54)

Source: Balversa MAIC report (data on file) (49)

Abbreviations: CI, confidence interval; EV, enfortumab vedotin; OR, odds ratio; ORR, objective or overall response rate; RR, risk ratio.

In the sensitivity analyses where each covariate was cumulatively adjusted for one by one, the MAIC estimates of erdafitinib vs. EV were consistent across all covariates.

The longer-term ORR results in EV-301 were close to the interim findings, thus having minimal influence on the estimated relative effect of erdafitinib vs. EV estimated by the MAIC.

C.4 Limitations

A systematic identification of treatment effect modifiers in UC was not carried out for this MAIC. Instead, an approach was taken so that all possible covariates were adjusted for, based on what was mutually recorded and reported in THOR and EV-301. Cumulative adjustment for each covariate on a one-by-one basis produced consistent results with sufficient ESS; therefore, any risk of over-adjustment was considered negligible. Nevertheless, the MAIC results could be biased due to unmeasured or unknown treatment effect modifiers, which is an inherent limitation of any MAIC.

Known covariates that could not be adjusted for included presence of lymph node only metastasis, best response to checkpoint inhibitors, and median time since diagnosis of metastatic or locally advanced disease, since these covariates were not recorded similarly in THOR.

In addition, it was not possible to adjust for differences in the distribution of patients with FGFR alterations. This issue arose as THOR C1 exclusively recruited patients with FGFR alterations, whereas EV-301 did not assess FGFR during enrolment and thus included patients from an all-comer population. It is not clear how this factor may impact the results of the MAICs, as the effect of EV in an FGFR-positive vs. FGFR-negative population was not investigated. Lastly, THOR C1 only recruited patients with ≤2 prior systemic therapies, while a small but notable proportion of EV-301 patients had ≥3 prior systemic therapies, making it impossible to completely adjust for differences in this covariate. Nevertheless, sensitivity analyses were conducted for OS and PFS based on reported subgroup data for EV-301 patients with ≤2 prior systemic therapies; there was minimal difference in the base-case MAIC results and these sensitivity MAIC results.

Results for PFS are considered conservative for erdafitinib, as progression in THOR C1 trial may be detected earlier due to more frequent radiographic assessments. Specifically, assessments in THOR C1 trial were conducted every 6 weeks (± 7 days), compared to every 8 weeks (± 7 days) in EV-301 trial. As for the impact on response evaluation, namely ORR and CR, the direction of potential bias is less clear. But given the relatively small different in the evaluation frequency, any bias is expected to be minimal and not significant.

Furthermore, the comparison of erdafitinib vs. EV in terms of ORR and CR were conducted based on the response-evaluable populations. This approach was chosen because the response data in EV-301 trial were measured in this manner, and the same method was applied to the THOR C1 to ensure a fair comparison. Given that the ITT population were well-balanced after matching, it was anticipated that the subgroups of similarly selected patients in both trials were alike, thereby minimizing any impact on the comparison results.

Another limitation arising regarding the follow-up time for AE analyses. The follow-up period of THOR C1 (15.9 months) is longer than EV's short-term data (11.1 months) but shorter compared to their long-term data (23.75 months). The analyses assumed that the relative treatment effects between trials are consistent over time. This means any increase in AEs due to extended follow-up was expected to be proportionate across treatment arms. The observed consistency in AE outcomes between THOR C1 and both short-term and long-term data of EV-301 appears to support this assumption in the end.

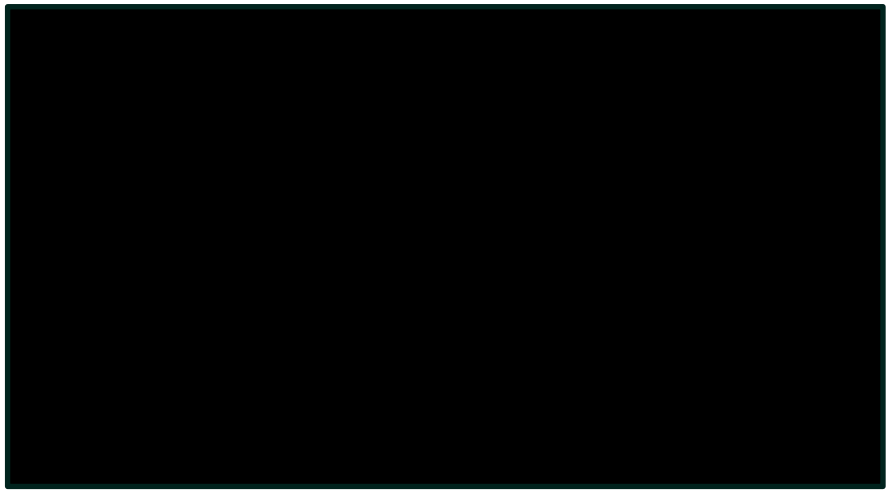
The was minor deviation from the PH assumption for the comparison of erdafitinib vs. chemotherapy in terms of OS and PFS, both before and after matching. Thus, the HR of erdafitinib vs. chemotherapy represents a summary of the HRs that might slightly variate over time. Consequently, the relative effectiveness of erdafitinib vs. EV could also display a bit of variation across different time periods – this variation is expected to be very limited.

Finally, as the MAIC is a post-hoc analysis of trials, it may not be statistically powered to detect a difference in treatment effect with high certainty. Its ESS is limited by the original size of the trials and can be further reduced by harmonization and matching in trial populations, making it challenging in determining the degree of certainty in cases where there is a meaningful difference in efficacy between the treatments being compared.

C.5 Proportional hazard assumptions

C.5.1 OS PH assumption test

[redacted]



C.5.2 PFS PH assumption test

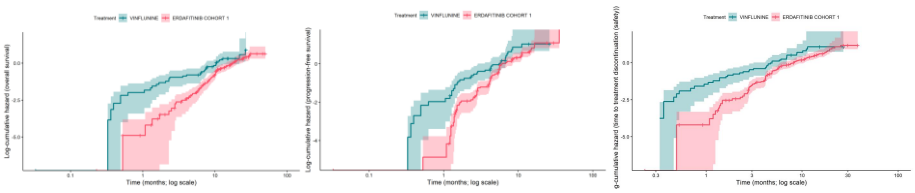
[redacted]

Appendix D. Extrapolation

Parametric survival curves were fitted to time-to-event individual patient data (IPD) from THOR, to inform OS, PFS, and TTD over a lifetime time horizon in the erdafitinib and vinflunine arms. Time-to-event data for PFS and OS were collected directly in THOR. Time-to-event data for the TTD endpoint were derived using the timepoints of treatment discontinuation events from subject disposition data and deaths from the OS time-to-event data. Patients were then censored from the TTD curves where no treatment discontinuation event was observed before the date the patient was last known alive, as per the censoring rule applied to the OS analysis.

Both separately fitted and jointly fitted survival curves were considered for inclusion in the economic model. Jointly fitted models, which assume either proportional hazards (PH) or accelerated failure time (AFT) between the treatments, were excluded from the model because exploratory statistical analyses indicated that the PH assumption is not valid for the comparison of erdafitinib to vinflunine, as seen in log-cumulative hazard plots of OS, PFS, and TTD for erdafitinib versus each trial comparator (Figure 33). The HR of erdafitinib vs. vinflunine of OS, PFS, and TTD seem to vary slightly over time.

Figure 33. Log-cumulative hazard plots of erdafitinib versus vinflunine



(Left: OS, middle: PFS, right: TTD)

Seven functional forms (exponential, Weibull, log-normal, log-logistic, Gompertz, gamma and generalized gamma) were used to fit survival curves for each endpoint and treatment. The survival curves were evaluated based on the following criteria:

- *Visual fit* – comparing the extrapolated curves to the KM curves and smoothed hazard plots to observed hazards
- *Statistical criteria* – comparing Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics among curve fits; lower AIC and/or BIC indicate better agreement with the data
- *Face validity and clinical plausibility*
    - Evaluating clinical plausibility by comparing survival projections at key timepoints (landmarks)
    - Checking that selected PFS and TTD curves for a given treatment do not cross the selected OS curve

The most representative model fit for each treatment and endpoint was selected for the base case analysis.

In model calculations, the risk of OS, PFS and TTD events at each model cycle was constrained to be no lower than the age- and sex-specific general population mortality in Denmark (73). This assumption was applied because a patient with mUC should not have

a lower risk of mortality than a healthy individual of the same age and sex, and PFS and TTD events include deaths.

D.1 Extrapolation of overall survival

D.1.1 Data input

Time-to-event patient-level data for OS was collected directly from THOR C1 for erdafitinib and vinflunine treatment arms.

D.1.2 Model

In model calculations, the risk of OS, PFS and TTD events at each model cycle was constrained to be no lower than the age- and sex-specific general population mortality for Denmark. This assumption was applied because a patient with LA/mUC should not have a lower risk of mortality than a healthy individual of the same age and sex, and PFS and TTD events include deaths.

Median OS in the erdafitinib arm of THOR C1 was 12.1 (95% CI: 10.3 to 16.4) months. The OS KM estimates for the erdafitinib arm and the seven fitted parametric models are shown in Figure 34. The models were fitted and evaluated for use in the base case analysis using the methods detailed above.

Figure 34. Overall survival parametric and Kaplan-Meier curves of erdafitinib

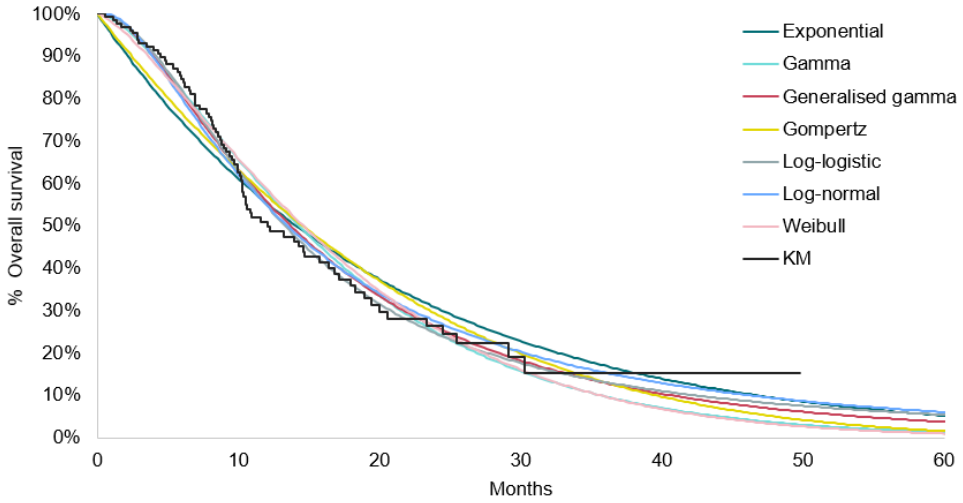
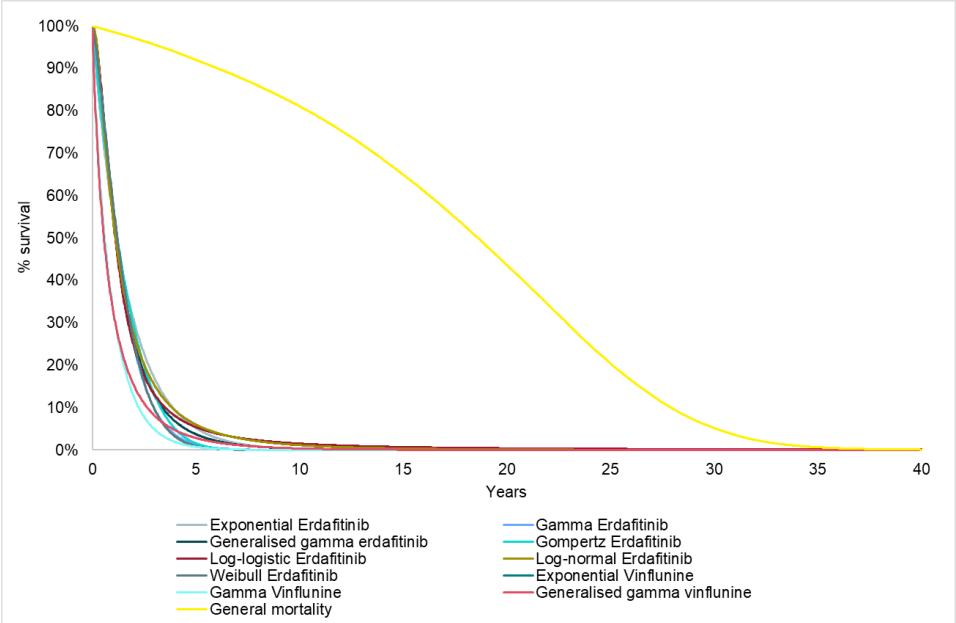


Figure 35. Overall survival parametric extrapolations of erdafitinib and general mortality over 40 years



Median OS in the vinflunine arm of THOR C1 was 7.6 (95% CI: 4.0 to 10.35) months. The OS KM estimates for the vinflunine arm and the seven fitted parametric models are shown in Figure 36. The models were fitted and evaluated for use in the base case analysis using the methods detailed above.

Figure 36. Overall survival parametric and Kaplan-Meier curves of vinflunine

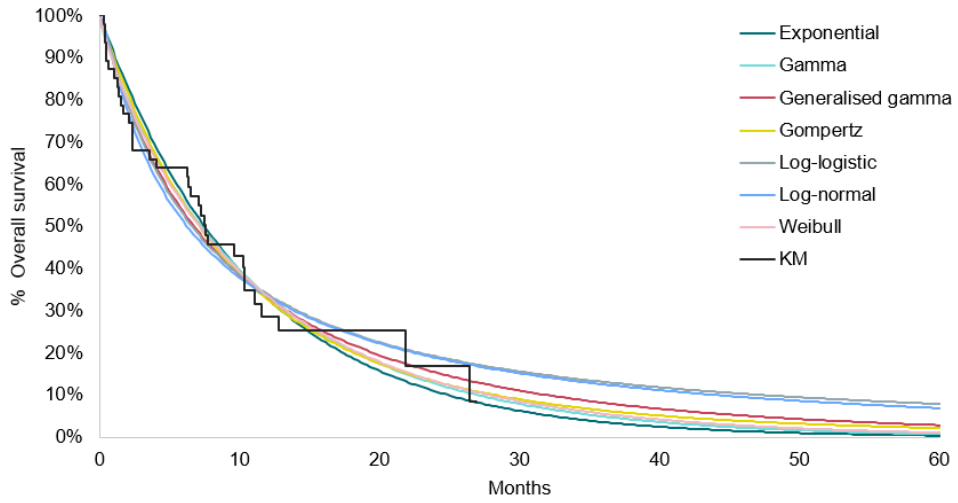
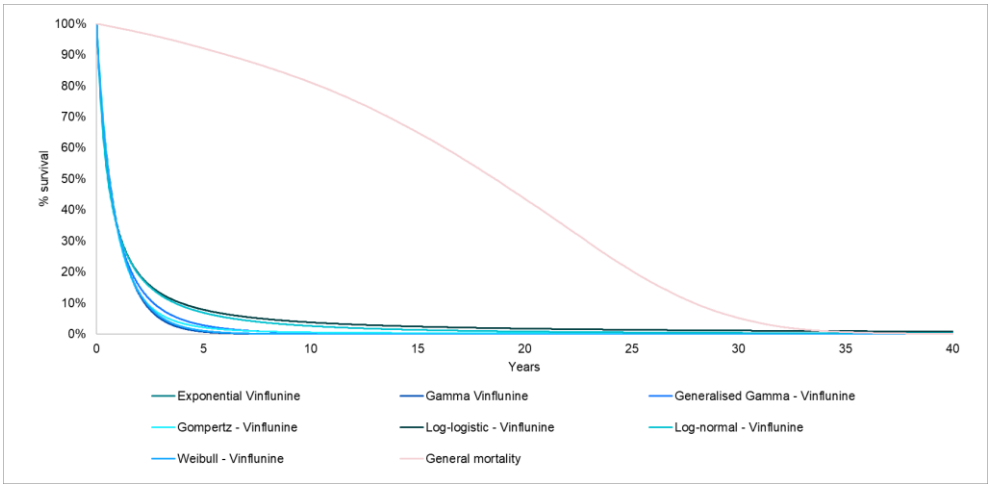


Figure 37. Overall survival parametric and general mortality curves of vinflunine over 40 years



D.1.3 Proportional hazards

The log-cumulative hazard curves are relatively straight, but they do not appear parallel. Rather, they converge (Figure 39). This suggests that the PH assumption may be violated. The Schoenfeld individual test (Figure 40) also indicated a violation of the PH assumption ($p < 0.05$). The quantile pairs lie approximately on a straight line (Figure 40), but do not pass through the origin. This suggests that the AFT assumption is potentially violated. Ultimately, the PH assumption is likely violated. As per NICE TSD 14 guidance (74), standard parametric curves fitted individually to each treatment arm are recommended. Potentially, a piecewise modelling approach may most closely fit the OS data, but standard parametric curves are likely to provide an adequate fit.

Figure 38. Log-cumulative hazard plot

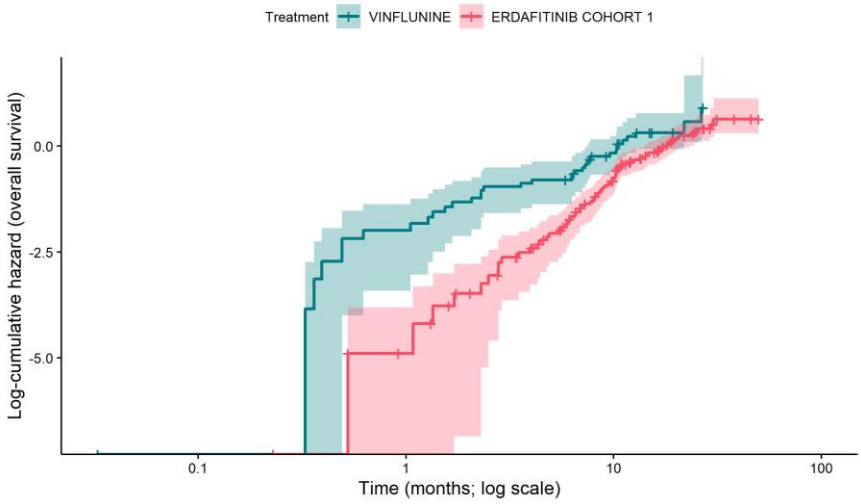


Figure 39. Schoenfeld residual plot of overall survival log-hazard ratios in THOR C1 (erdafitinib vs. vinflunine)

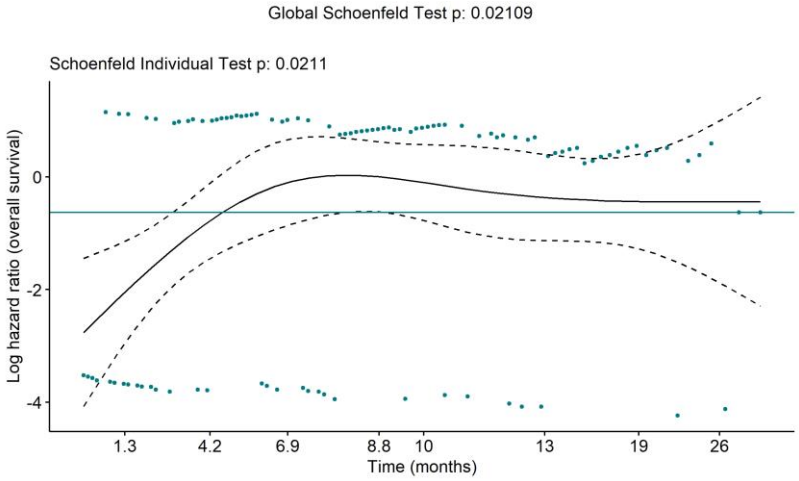
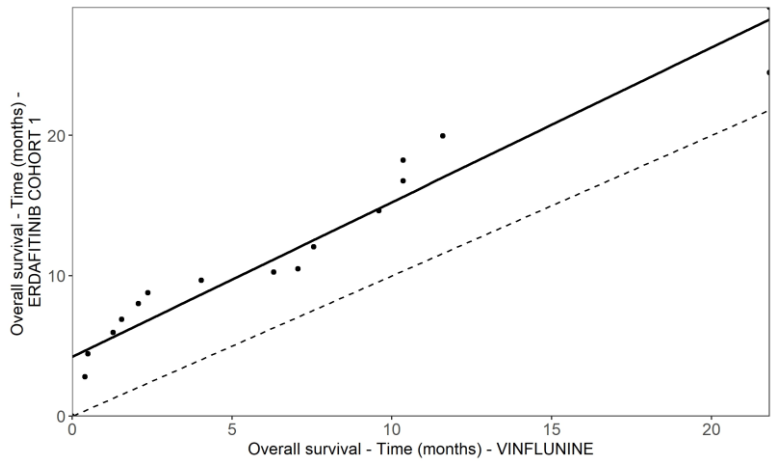


Figure 40. QQ plot of overall survival in erdafitinib and vinflunine arms



D.1.4 Evaluation of statistical fit (AIC and BIC)

AIC and BIC statistics for each model are presented in Table 73. The log-logistic model provides the lowest AIC and BIC values for erdafitinib; however, log-normal and generalized gamma provided similarly good statistical fit. For vinflunine, the exponential model provides the lowest AIC and BIC values, though the other six models seem provide a similar fit.

Table 73. AIC and BIC statistics of overall survival distributions

Distribution	Erdafinitib		Vinflunine	
	AIC	BIC	AIC	BIC
Exponential	619.4	622.3	**231.8**	**233.6**
Gamma	608.6	614.4	233.1	236.8
Generalized gamma	607.7	616.5	234.8	240.4
Gompertz	620.0	625.8	233.5	237.2
Log-logistic	**602.9**	**608.7**	234.5	238.3
Log-normal	606.8	612.7	233.4	237.1
Weibull	611.6	617.4	233.0	236.7

Note: Best statistical fit is highlighted in **bold**.

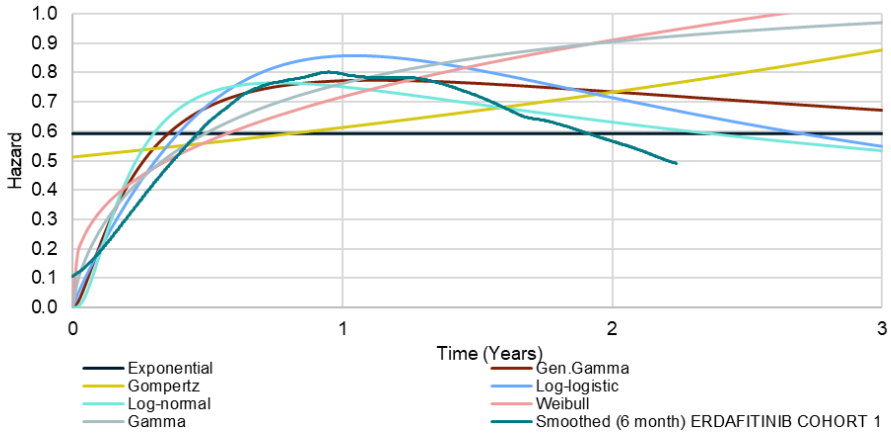
D.1.5 Evaluation of visual fit

For erdafitinib, the visual fit of the models is reasonable; however, the exponential and Gompertz initially underestimate survival and then overestimate it beyond 10 months. For vinflunine, all seven curves provide a good visual fit to the KM curve, but the log-logistic and log-normal curves provide more optimistic long-term projections than the remaining models.

D.1.6 Evaluation of hazard functions

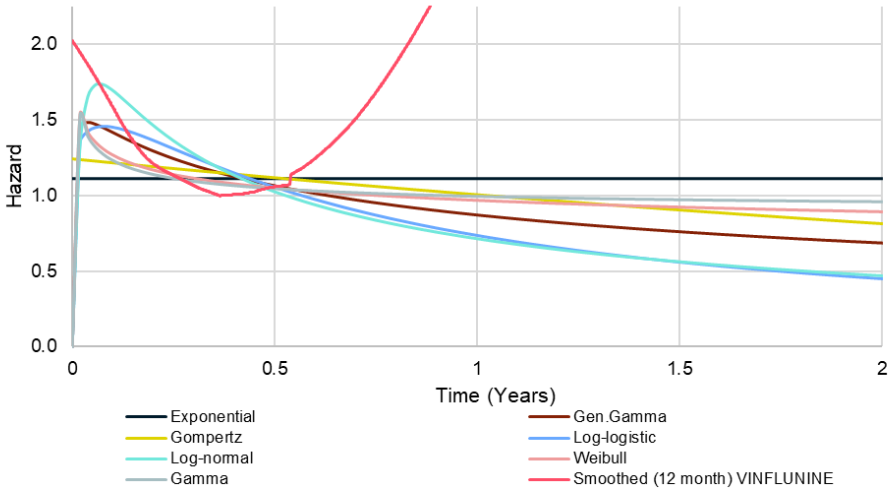
Figure 41 presents the smoothed hazard for the erdafitinib arm against the hazard function of each parametric model. The smoothed hazard initially increases and then begins to decrease from around 1 year. A similar shape is observed with the log-logistic, log-normal and generalised gamma distributions; however, the remaining curves either assume constant (exponential) or monotonically increasing hazard (gamma, Gompertz, Weibull).

Figure 41. Overall survival erdafitinib hazard plot



For vinflunine (Figure 42) none of the distributions stand out in terms of matching the smoothed hazard estimates.

Figure 42. Overall survival vinflunine hazard plot



D.1.7 Validation and discussion of extrapolated curves

Table 74. Landmark analysis overall survival

Modelled landmarks (years)	Distribution	Erdafitinib	Vinflunine
1	Exponential	0.548	0.323
	Gamma	0.573	0.330
	Generalized gamma	0.550	0.326
	Gompertz	0.565	0.321
	Log-logistic	**0.540**	0.335
	Log-normal	0.541	0.330
	Weibull	0.580	0.329
5	Exponential	0.052	0.004
	Gamma	0.013	0.007
	Generalized gamma	0.037	0.028
	Gompertz	0.016	0.022
	Log-logistic	**0.054**	0.079
	Log-normal	0.060	0.069
	Weibull	0.010	0.011
10	Exponential	0.003	0.000
	Gamma	0.000	0.000
	Generalized gamma	0.003	0.004
	Gompertz	0.000	0.006
	Log-logistic	**0.015**	0.038
	Log-normal	0.012	0.026
	Weibull	0.000	0.000

The maturity of the data of erdafitinib meant all models tended to fit the observed data reasonably well. As such, it was most relevant to consider the behaviour of the observed hazard function for base case curve selection. Given the log-logistic model had the lowest AIC/BIC values and a hazard function that closely resembled the observed smoothed hazard, it was selected for erdafitinib OS in the base case. A full breakdown of the projected survival rates for erdafitinib at different landmark timepoints is provided in Table 74.

For vinflunine, the log-normal and log-logistic results are clear outliers, predicting survival in the vinflunine arm that is over double the prediction of any other curves at 5 years. When compared with external studies (45, 60) assessing OS of chemotherapy in LA/mUC, a predicted survival rate of 7% at 5 years also appears implausible (e.g, TA692 (45) reports 5-year OS of 2–3%). Furthermore, the log-logistic and log-normal curves predict higher

survival than erdafitinib at 5, 10, and 20 years, which is considered clinically improbable. Based on an assessment of the observed hazard, and long-term clinical plausibility, the log-normal and log-logistic curves were therefore ruled out from the base case selection.

Turning to the other functional forms, the exponential curve is associated with the lowest AIC and BIC statistics and provides a close fit to the KM data. Additionally, the exponential curve predicts 2-year survival to be around 15.5%, which is similar to an external study in the LA/mUC indication (KEYNOTE-045) which reported 2-year OS of 14.3% in the chemotherapy arm (75). Therefore, the exponential curve was identified as the most plausible curve to represent vinflunine.

D.1.8 Adjustment of background mortality

In model calculations, the risk of OS, PFS and TTD events at each model cycle was constrained to be no lower than the age- and sex-specific general population mortality in Denmark (73).

D.1.9 Adjustment for treatment switching/cross-over

No adjustments have been made for treatment switching and/or crossing-over.

D.1.10 Waning effect

Erdafitinib is being considered as a late line of therapy. As such, it was deemed unnecessary to include a stopping rule or consider long-term waning of treatment effect. Because more than 90% of patients discontinue treatment within 2 years and more than 95% die within 5 years, inclusion of these elements would have a negligible impact on model outcomes.

D.1.11 Cure-point

See section D.1.10

D.2 Extrapolation of progression-free survival

D.2.1 Data input

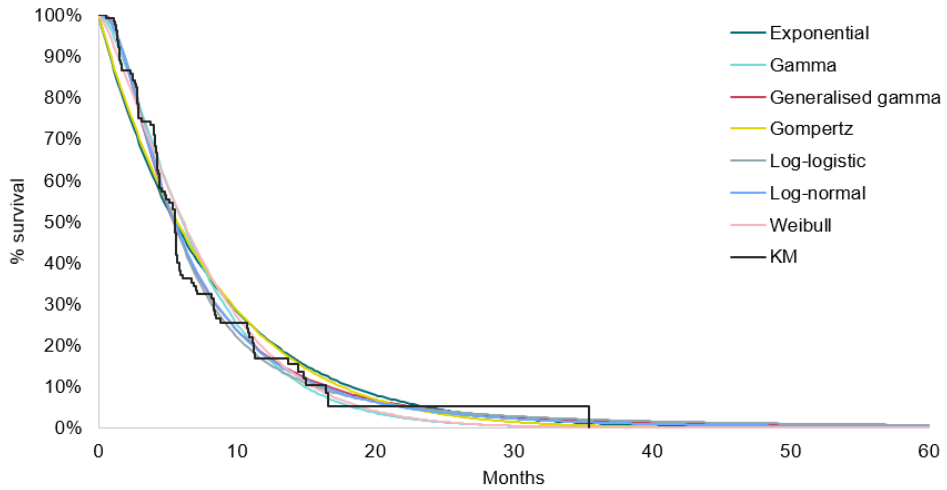
Time-to-event patient-level data for PFS was collected directly from THOR C1 for erdafitinib and vinflunine treatment arms.

D.2.2 Model

Analysis of PFS shows strong evidence of improvement for patients treated with erdafitinib versus vinflunine with a hazard ratio of 0.64 (95% CI: 0.44–0.93), representing a 36% reduction in the rate of disease progression or death for patients receiving erdafitinib versus vinflunine.

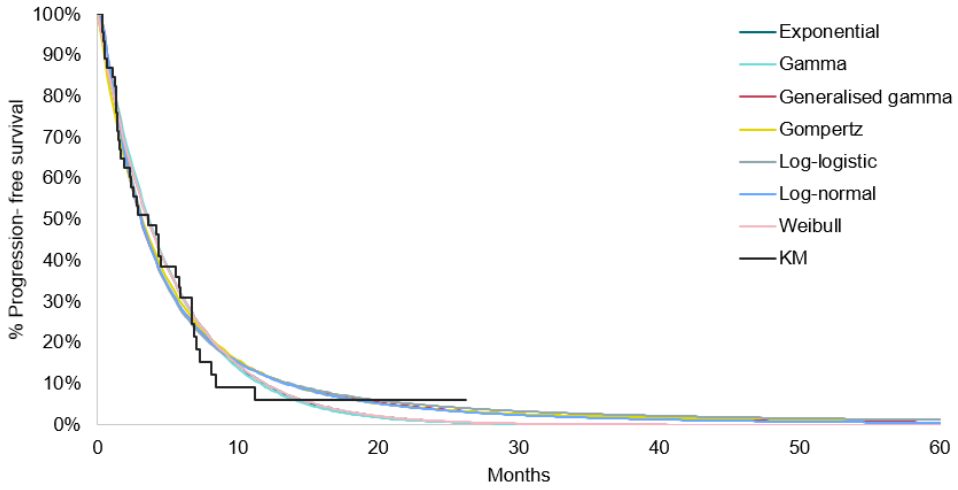
Median PFS in the erdafitinib arm of THOR C1 was 5.55 (95% CI: 4.40–5.65) months. The PFS KM estimates for the erdafitinib arm and the seven fitted parametric models are shown in Figure 43. The models were fitted and evaluated for use in the base case analysis using the methods detailed above.

Figure 43. Progression-free survival parametric and Kaplan-Meier curves of erdafitinib



Median PFS in the vinflunine arm of THOR C1 was 3.6 months (95% CI: 1.6 to 5.8). The PFS KM estimates for the vinflunine arm and the seven fitted parametric models are shown in Figure 44. The models were fitted and evaluated for use in the base case analysis using the methods detailed above.

Figure 44. Progression-free survival parametric and Kaplan-Meier curves of vinflunine



D.2.3 Proportional hazards

The log-cumulative hazard curves are relatively straight, but they do not appear parallel. Rather, they converge (Figure 45). This suggests that the PH assumption may be violated. The Schoenfeld individual test also indicated a violation of the PH assumption ($p < 0.05$). The quantile pairs lie approximately on a straight line, but do not pass through the origin.

This suggests that the AFT assumption is potentially violated. Ultimately, the PH assumption is likely violated. As per NICE TSD 14 guidance, standard parametric curves fitted individually to each treatment arm are recommended. Potentially, a piecewise modelling approach may most closely fit the PFS data, but standard parametric curves are likely to provide an adequate fit.

Figure 45. Log-cumulative hazard plot

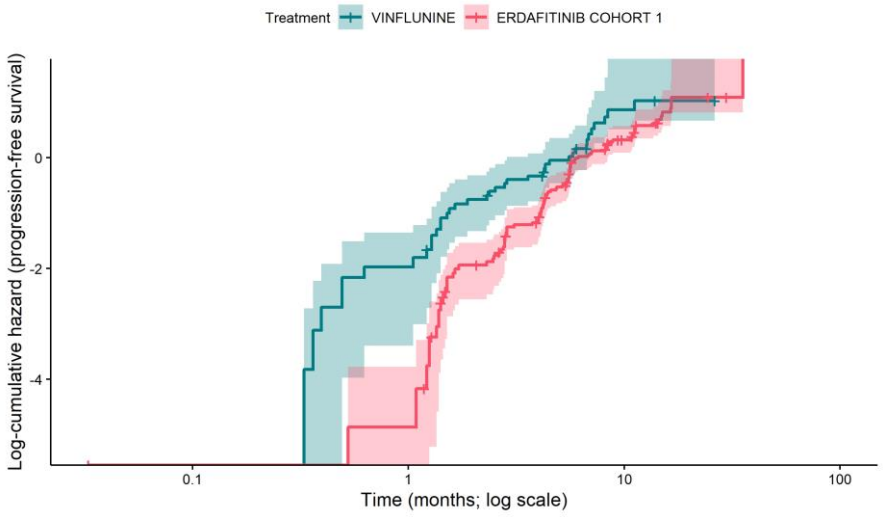


Figure 46. Schoenfeld residual plot of log hazard ratios of progression-free survival in THOR C1 (Erdafitinib vs. vinflunine)

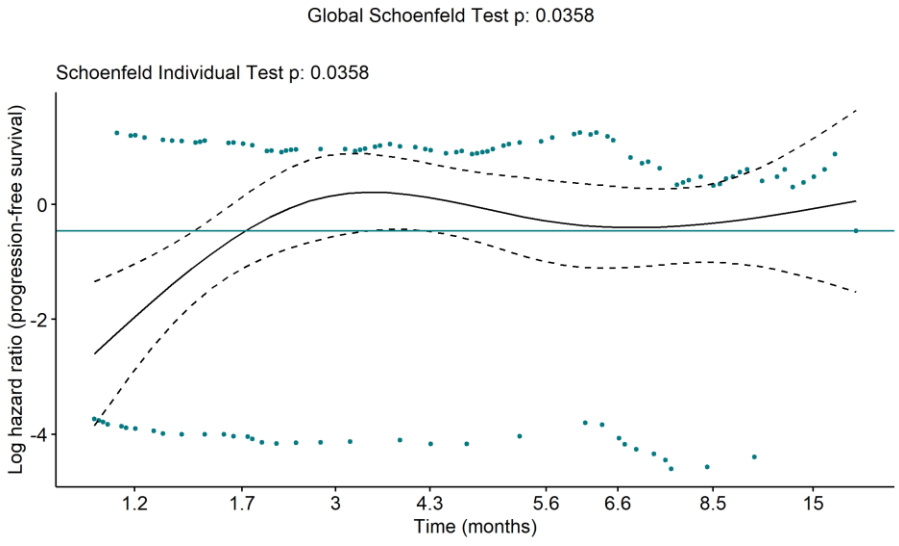
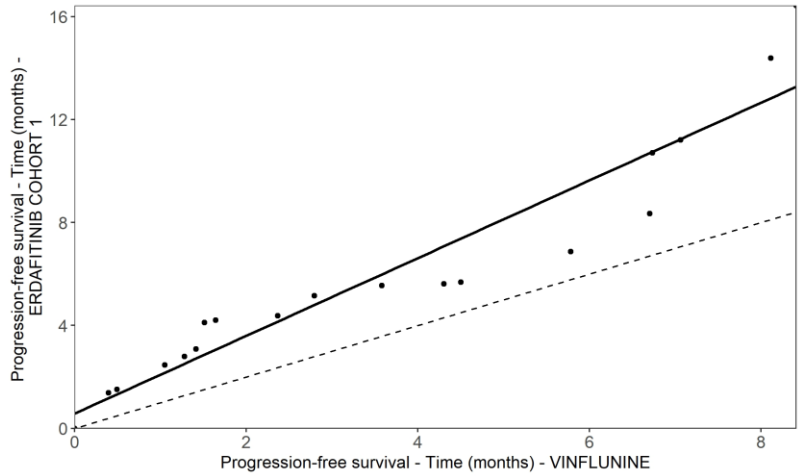


Figure 47. QQ plot of progression-free survival of erdafitinib and vinflunine



D.2.4 Evaluation of statistical fit (AIC and BIC)

Table 75. AIC and BIC statistics of progression-free survival distributions

Distribution	Erdafinitib		Vinflunine	
	AIC	BIC	AIC	BIC
Exponential	621.8	624.8	202.8	204.7
Gamma	606.8	612.7	204.7	208.4
Generalized gamma	597.6	606.3	202.3	208.0
Gompertz	623.3	629.1	203.1	206.8
Log-logistic	596.2	602.0	201.2	205.0
Log-normal	**595.8**	**601.6**	**200.3**	**204.1**
Weibull	613.1	618.9	204.8	208.6

Erdafitinib: AIC and BIC measures indicate the log-normal, log-logistic and generalized gamma curves provide the best statistical fit to the data.

Vinflunine: The log-normal has the lowest statistical fit, but the distributions all seem to have a good statistical fit to the data in the vinflunine arm.

D.2.5 Evaluation of visual fit

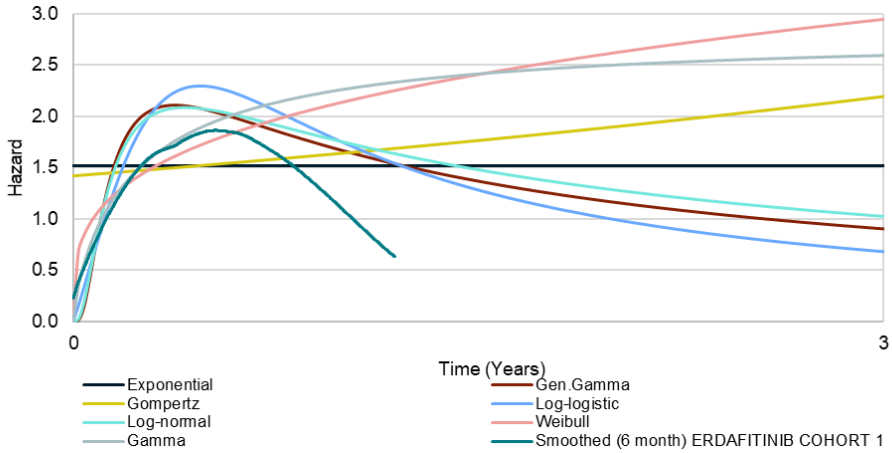
Erdafitinib: Visual inspection indicates that the exponential and Gompertz curves initially underestimate survival and then overestimate it beyond 7 months, while the log-normal, log-logistic, and generalized gamma curves all fit the KM curve more closely.

Vinflunine: The visual fit to the KM curve is close with all models, and the AIC and BIC values suggest that all curves have similarly good statistical fit to the data.

D.2.6 Evaluation of hazard functions

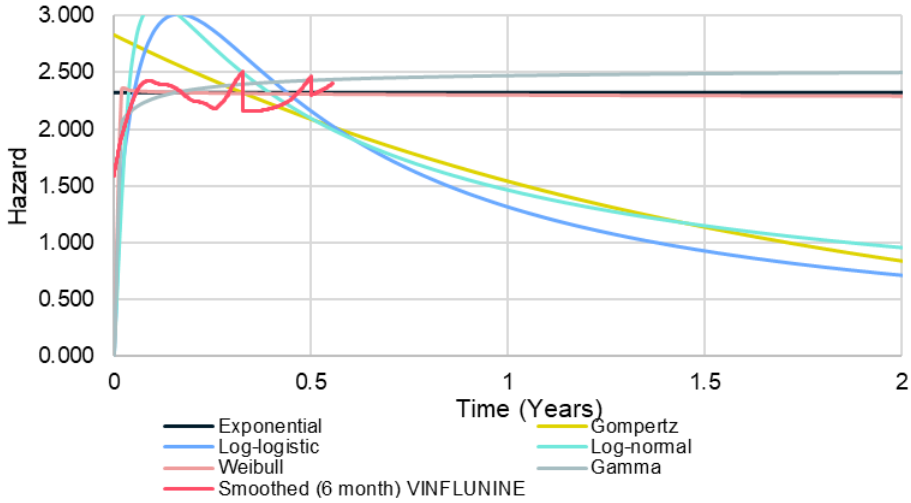
For erdafitinib (Figure 48), the log-normal, log-logistic, and generalized gamma curves all fir the smoothed hazard estimate, where it rises first and then diminishes.

Figure 48. Progression-free survival erdafitinib hazard plot



For vinflunine (Figure 49), none of the distributions stand out in terms of matching the smoothed hazard estimates.

Figure 49. Progression-free survival vinflunine hazard plot



D.2.7 Validation and discussion of extrapolated curves

Table 76. Landmark analysis progression-free survival

Modelled landmarks (years)	Distribution	Erdafitinib	Vinflunine
1	Exponential	0.214	0.095
	Gamma	0.168	0.088

	Generalized gamma	0.173	0.118
	Gompertz	0.212	0.117
	Log-logistic	0.157	0.117
	Log-normal	0.171	0.116
	Weibull	0.184	0.095
5	Exponential	0.001	0.000
	Gamma	0.000	0.000
	Generalized gamma	0.004	0.006
	Gompertz	0.000	0.012
	Log-logistic	0.007	0.012
	Log-normal	0.002	0.005
	Weibull	0.000	0.000
10	Exponential	0.000	0.000
	Gamma	0.000	0.000
	Generalized gamma	0.000	0.001
	Gompertz	0.000	0.010
	Log-logistic	0.002	0.004
	Log-normal	0.000	0.001
	Weibull	0.000	0.000

Erdafitinib: The log-logistic curve has acceptable visual fit, and similar statistical fit to log-normal and generalized gamma. The median PFS of the log-logistic model (3.6 months) aligns very well with the reported median PFS reported in the vinflunine group in the real-world study of 3.4 months (60). Therefore, the base case assumes log-logistic model for PFS extrapolation of erdafitinib arm.

Vinflunine: The long-term projections in Table 76 more optimistic with the log-normal and log-logistic curves (5–10% remaining progression-free at 20 months) than with other distributions (< 5% remaining progression-free at 20 months). The log-normal distribution was selected for the base case as having the lowest AIC and BIC values, which is consistent with selections for other interventions.

D.2.8 Adjustment of background mortality

See section D.1.8

D.2.9 Adjustment for treatment switching/cross-over

See section D.1.9

D.2.10 Waning effect

See section D.1.10

D.2.11 Cure-point

See section D.1.10

D.3 Extrapolation of time to treatment discontinuation

D.3.1 Data input

By the data cutoff for this analysis, 106 patients (78.5%) discontinued treatment or died in the erdafitinib arm of THOR, and the median TTD was 5.7 (95% CI: 5.0 to 7.6) months.

By the data cutoff for this analysis, 40 patients (93.0%) in the subgroup treated with vinflunine in THOR C1 discontinued treatment or died, and the median TTD was 4.2 (95% CI: 2.0 to 5.9) months.

D.3.2 Model

Figure 50. Time to treatment discontinuation parametric and Kaplan-Meier curves of erdafitinib

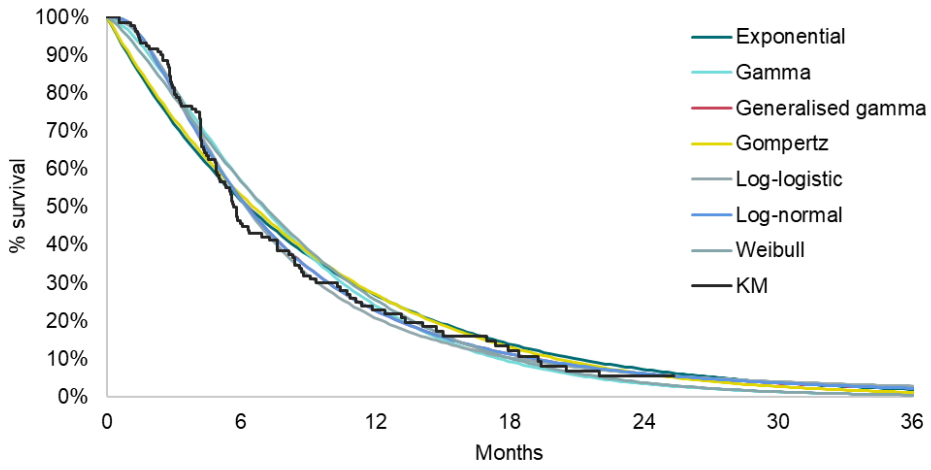
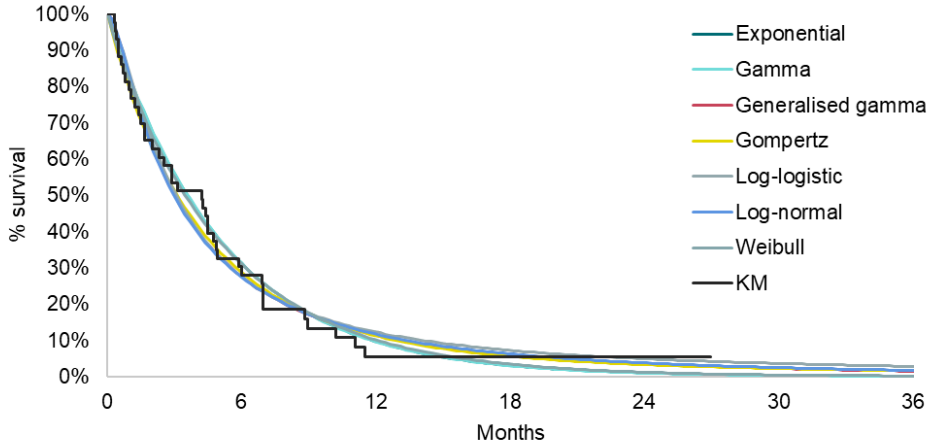


Figure 51. Time to treatment discontinuation parametric and Kaplan-Meier curves of vinflunine



D.3.3 Proportional hazards

The log-cumulative curves are relatively straight, but they do not appear parallel; rather, they converge towards the end. This suggests that the PH assumption may be violated. The Schoenfeld individual test also suggests that the PH assumption is violated ($p < 0.05$). The quantile pairs approximately lie on a straight line through the origin, suggesting the AFT assumption is valid.

NICE TSD 14 recommends that standard parametric curves be fit individually to each treatment arm where PH does not hold but log-cumulative hazard curves are straight. There is also potential that a piecewise modelling approach may most closely fit the TTD data, but standard parametric curves will likely provide an adequate fit

Figure 52. Log-cumulative hazard plot

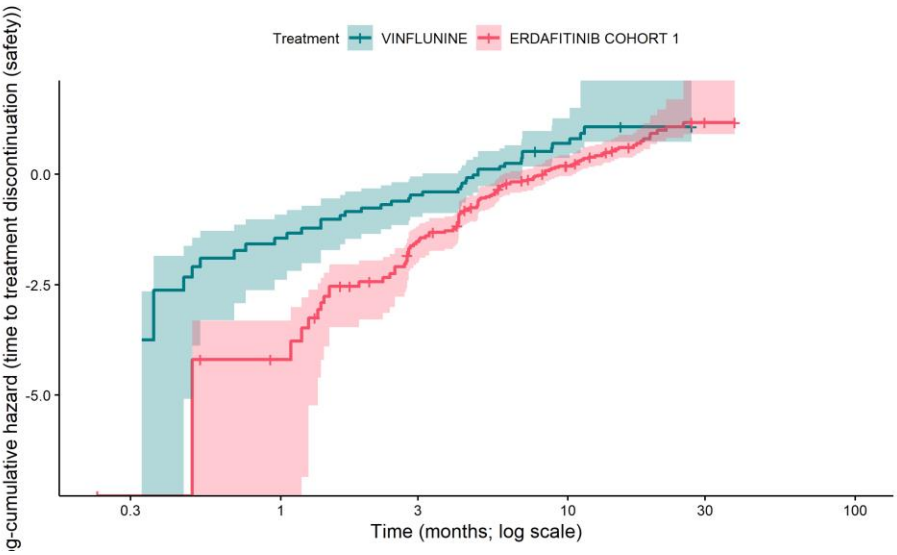


Figure 53. Schoenfeld residuals plot

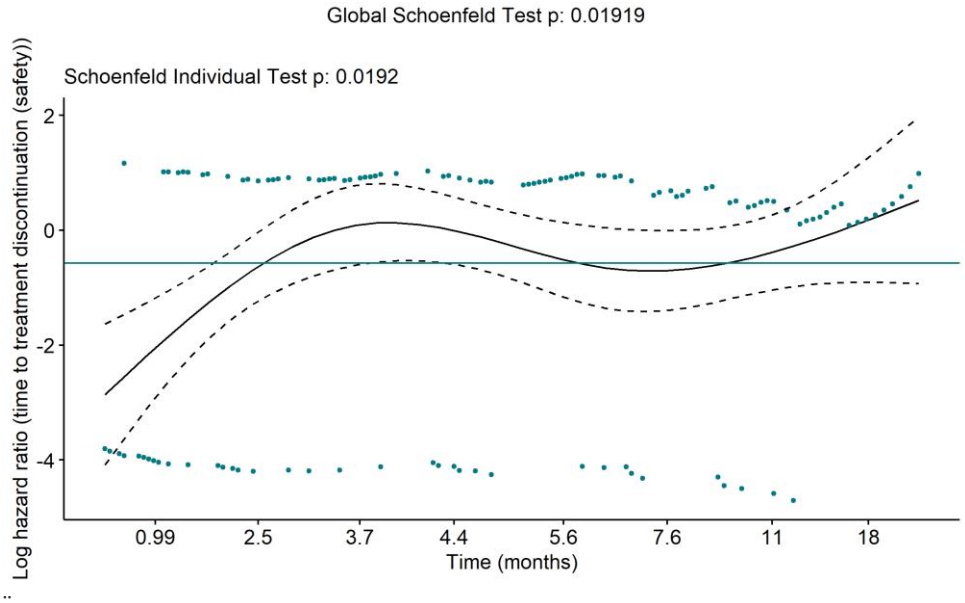
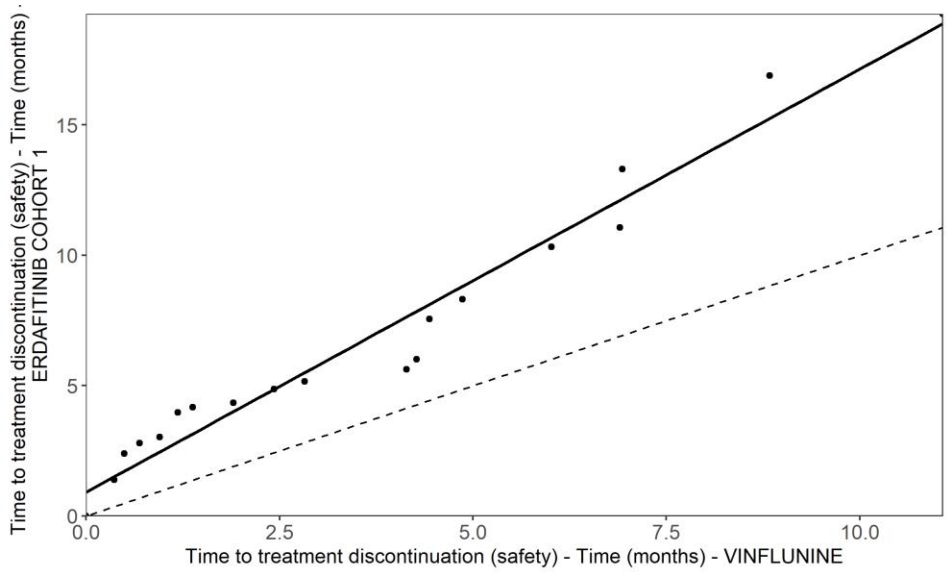


Figure 54. Quantile-Quantile plot



D.3.4 Evaluation of statistical fit (AIC and BIC)

Distribution	Erdafinitib		Vinflunine	
	AIC	BIC	AIC	BIC
Exponential	682.1	685.0	213.0	**214.8**
Gamma	668.7	674.5	215.0	218.5

Generalized gamma	660.8	669.5	213.5	218.8
Gompertz	683.5	689.3	213.2	216.7
Log-logistic	**658.0**	**663.8**	212.9	216.4
Log-normal	658.8	664.6	**211.5**	215.0
Weibull	674.2	680.0	214.9	218.4

Erdafitinib: AIC and BIC statistics are lowest for the log-logistic curve, with log-normal and generalised gamma models also providing equally good fits to the data.

Vinflunine: AIC and BIC do not differ substantially between the models, with log-normal having the lowest AIC and exponential having the lowest BIC.

D.3.5 Evaluation of visual fit

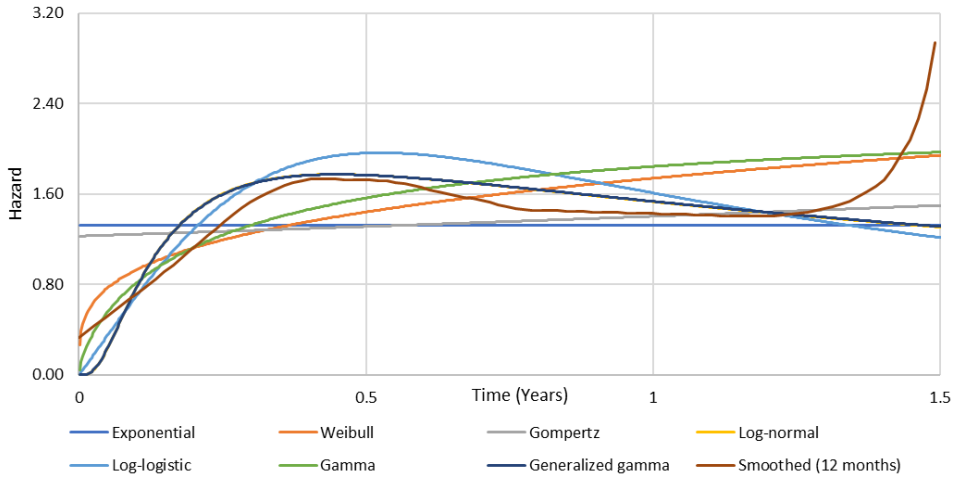
Erdafitinib: Figure 51 presents the seven parametric models that were fitted to the erdafitinib time to treatment discontinuation or death data and evaluated for inclusion in the base case analysis. The Gompertz and exponential model estimates are lower than the KM estimates up to around 4 months but match the KM estimates well thereafter.

Vinflunine: Figure 51 presents the seven parametric models for vinflunine TTD. All parametric models provide reasonable visual fit to the KM curve.

D.3.6 Evaluation of hazard functions

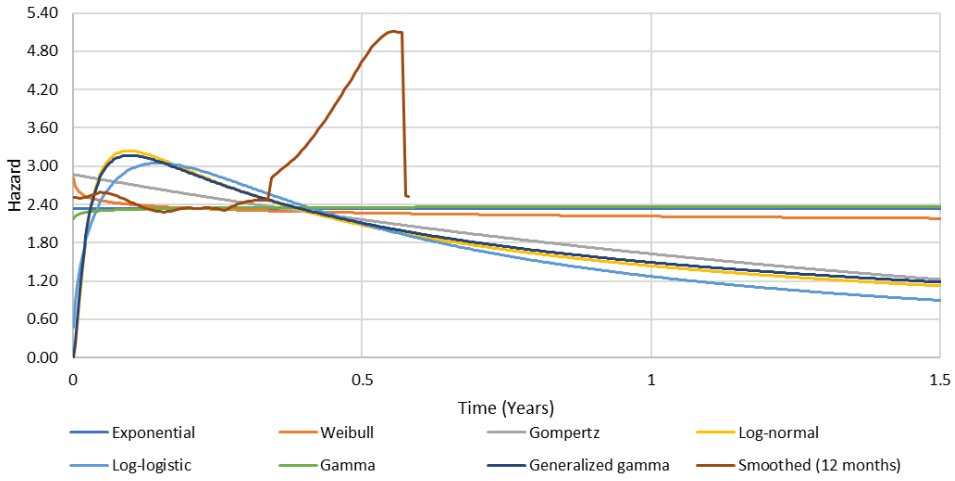
The smoothed hazard estimate of erdafitinib seems to follow the generalized gamma and the log-logistic curve for the most part of the plot, but then increases (Figure 55).

Figure 55. Time to treatment discontinuation erdafitinib hazard plot



None of the distributions stand out as a good match with the smoothed hazard estimate of vinflunine (Figure 56).

Figure 56. Time to treatment discontinuation vinflunine hazard plot



D.3.7 Validation and discussion of extrapolated curves

Table 77. Landmark analysis time to treatment discontinuation

Modelled landmarks (years)	Distribution	Erdafitinib	Vinflunine
1	Exponential	0.267	0.097
	Gamma	0.240	0.096
	Generalized gamma	0.227	0.114
	Gompertz	0.269	0.112
	Log-logistic	0.208	0.122
	Log-normal	0.227	0.117
	Weibull	0.255	0.101
5	Exponential	0.001	0.000
	Gamma	0.000	0.000
	Generalized gamma	0.005	0.004
	Gompertz	0.000	0.009
	Log-logistic	0.010	0.013
	Log-normal	0.005	0.005
	Weibull	0.000	0.000
10	Exponential	0.000	0.000
	Gamma	0.000	0.000
	Generalized gamma	0.000	0.001
	Gompertz	0.000	0.007
	Log-logistic	0.002	0.005

Log-normal	0.000	0.001
Weibull	0.000	0.000

Erdafitinib: Based on these assessments, the log-logistic curve was selected for the base case analysis, which estimates that 20.8% and 1% of patients would remain on treatment at 1 year and 5 years, respectively.

Vinflunine: The log-normal distribution predicts almost identical TTD to the generalised gamma distribution, and the exponential curve is almost identical to the gamma curve. The log-logistic distribution predicts the highest long-term TTD. The log-normal distribution was selected for the base case based on the lowest AIC and more conservative long-term TTD than the second-best log-logistic distribution, predicting 11.7%, 1.7% and 0.5% of patients on treatment at 1, 3 and 5 years, respectively.

D.3.8 Adjustment of background mortality

See section D.1.8

D.3.9 Adjustment for treatment switching/cross-over

See section D.1.9

D.3.10 Waning effect

See section D.1.10

D.3.11 Cure-point

See section D.1.10

Appendix E. Serious adverse events

Table 78. Serious TEAE's with a frequency of ≥ 2% in any treatment group by System Organ Class and Preferred Term; THOR C1; safety analysis set

Adverse events	Erdafitinib (N=135)	Chemotherapy (N=112)
Subjects with 1 or more serious TEAEs	56 (41.5%)	47 (42.0%)
System organ class		
Preferred item		
Infections and infestations	21 (15.6%)	16 (14.3%)

Adverse events	Erdafitinib (N=135)	Chemotherapy (N=112)
Urinary tract infection	6 (4.4%)	2 (1.8%)
Blood and lymphatic system disorders	2 (1.5%)	16 (14.3%)
Febrile neutropenia	0	7 (6.3%)
Febrile bone marrow aplasia	0	4 (3.6%)
Neutropenia	0	3 (2.7%)
General disorders and administration site conditions	7 (5.2%)	8 (7.1%)
Pyrexia	2 (1.5%)	3 (2.7%)
General physical health deterioration	1 (0.7%)	3 (2.7%)
Renal and urinary disorders	10 (7.4%)	4 (3.6%)
Haematuria	5 (3.7%)	1 (0.9%)
Acute kidney injury	3 (2.2%)	0
Metabolism and nutrition disorders	7 (5.2%)	2 (1.8%)
Hyponatraemia	3 (2.2%)	1 (0.9%)

Table 79. Summary of deaths; cohort 1 ITT analysis set

	Erdafitinib N = 136	Chemotherapy N = 130	Vinflunine N = 48
Deaths during study	77 (56.6%)	78 (60.0%)	NA
Progressive Disease	63 (46.3%)	63 (48.5%)	NA
Adverse Event	8 (5.9%)	10 (7.7%)	NA
Related to study agent	1 (0.7%)	6 (4.6%)	4 (8.3%)
Not Related to study agent	5 (3.7%)	4 (3.1%)	NA

	Erdafitinib N = 136	Chemotherapy N = 130	Vinflunine N = 48
Relationship unknown	2 (1.5%)	0 (0.0%)	NA
COVID-19 related	0 (0.0%)	1 (0.8%)	NA
Other	5 (3.7%)	4 (3.1%)	NA
Cause Unknown	1 (0.7%)	1 (0.8%)	NA

Source: THOR C1 clinical study report; TSFDTH01A; Table 12 (50)

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

Table 80. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Patient characteristics				
Age at model start	66.30	65.13	67.50	Log-Normal
Proportion male	71.43%	0.66	0.77	Beta
Weight	72.88	70.91	74.90	Log-Normal
Body surface area	1.82	1.79	1.85	Log-Normal
Hazard ratios OS				
OS HR Chemo PC: applied to erdafitinib	1.5625	1.14	2.13	Log-Normal
OS HR vinflunine: applied to erdafitinib	1.851	1.23	2.78	Log-Normal
OS HR EV: applied to erdafitinib	1	0.65	1.83	Log-Normal
Hazard ratios PFS				
PFS HR Chemo PC: applied to erdafitinib	1.724	1.28	2.27	Log-Normal
PFS HR vinflunine: applied to erdafitinib	1.5625	1.08	2.27	Log-Normal
PFS HR EV: applied to erdafitinib	1	0.65	1.83	Log-Normal
Relative dose intensity				
Doses not skipped: Erdafitinib	82.93%	0.82	0.83	Beta
RDI: Docetaxel	98.14%	0.94	1.00	Beta
RDI: Vinflunine	99.77%	0.99	1.00	Beta

RDI: Enfortumab vedotin	79.35%	0.77	0.81	Beta
Drug administration costs				
Cost per administration: Oral	0	0.00	0.00	Gamma
Cost per administration: IV	1,989	1618	2397	Gamma
Adverse event costs				
Cost per AE: Palmar-plantar erythrodysaesthesia syndrome	1,625.00	1322	1959	Gamma
Cost per AE: Stomatitis	2,107.00	1714	2540	Gamma
Cost per AE: Anaemia	2,111.00	1718	2544	Gamma
Cost per AE: Hyponatraemia	1,847.00	1503	2226	Gamma
Cost per AE: Onycholysis	1,625.00	1322	1959	Gamma
Cost per AE: Hyperphosphataemia	1,847.00	1503	2226	Gamma
Cost per AE: Neutropenia	2,111.00	1718	2544	Gamma
Cost per AE: Leukopenia	2,111.00	1718	2544	Gamma
Cost per AE: Febrile neutropenia	37,129.00	30210	44751	Gamma
Cost per AE: Fatigue	5,103.00	4152	6151	Gamma
Cost per AE: Maculopapular rash	1,625.00	1322	1959	Gamma
Cost per AE: Decreased neutrophil count	2,111.00	1718	2544	Gamma
Health care resource use (testing costs)				
FGFR testing proportion	0.17	0.10	0.24	Beta
FGFR testing: Cost per test	5,000	4,068.20	6,026.45	Gamma
Ophthalmological consultation unit costs	280	228.10	337.89	Gamma

Health care resource use (treatment dependent)				
Cost per resource: GP consultation	160.72	130.77	193.71	Gamma
Cost per resource: District nurse	453.00	368.58	546.00	Gamma
Cost per resource: Health home visit	1,541.57	1,254.28	1,858.04	Gamma
Cost per resource: Dietician	1,374.00	1,117.94	1,656.07	Gamma
Cost per resource: Oncologist consultation (consultant led)	504.72	410.66	608.33	Gamma
Cost per resource: Urologist	504.72	410.66	608.33	Gamma
Cost per resource: Blood sample	0.00	0.00	0.00	Gamma
Cost per resource: CT scan	0.00	0.00	0.00	Gamma
Cost per resource: MRI	0.00	0.00	0.00	Gamma
Cost per resource: PET-CT scan	0.00	0.00	0.00	Gamma
Cost per resource: A&E visit	0.00	0.00	0.00	Gamma
Cost per resource: Inpatient hospitalisation	0.00	0.00	0.00	Gamma
Other costs				
Cost per resource: Driving cost per km	3.79	3.08	4.57	Gamma
Resource use: Average distance from hospital (km)	20.00	16.27	24.11	Gamma
Cost per resource: patients admin cost per minute	188.00	152.96	226.59	Gamma
Patient admin time				
Patient admin time: Erdafitinib	0.00	0.00	0.00	Gamma
Patient admin time: Docetaxel	1.00	0.81	1.21	Gamma
Patient admin time: Vinflunine	0.33	0.27	0.40	Gamma

Patient admin time: Enfortumab vedotin	0.50	0.41	0.60	Gamma
Utility values				
Utility: progression-free	0.788	0.786	0.789	Beta
Utility: progressed	0.717	0.669	0.763	Beta

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

H.1.1.1 Objective

Two SLRs were conducted to support this submission for erdafitinib; one primary SLR with searches conducted in March 2023, and an SLR update, with searches conducted from March 2023 to April 2024. The objective of the SLRs were to:

Identify and summarize efficacy and safety outcomes from clinical trials of potential competitors to erdafitinib, in patients with locally advanced, metastatic, or surgically unresectable urothelial carcinoma with progressive disease after receiving at least one prior systemic therapy, one of which must be an ICI therapy.

H.1.1.2 Methods

The following established international guidelines for conducting systematic reviews were followed throughout this project:

- The Cochrane Handbook for Systematic Reviews of Interventions, version 6.3 (76).
- The PRISMA (formerly QUORUM) good reporting guidelines for systematic reviews (77).

H.1.1.3 Information sources

H.1.1.3.1 Bibliographic databases

The bibliographic databases presented in Table 81 were used to conduct the primary SLR. Ovid Embase, PubMed and the Cochrane Library (Cochrane Reviews and CENTRAL) were searched on March 10, 2023, from database inception to ensure that all relevant data are captured.

Table 81. Bibliographic databases included in the literature search (primary search)

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	From 1974 to March 9th, 2023	10.03.2023
Medline	Ovid	From 1946 to March 9th, 2023	10.03.2023
Cochrane Library (CENTRAL and Cochrane Reviews)	Cochrane Library	NR	10.03.2023

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; NR, Not reported.

The bibliographic databases presented in Table 82 were used to conduct the updated SLR searches. Date limits were applied to capture all new publications released after the primary search.

Table 82. Bibliographic databases included in the literature search (updated search)

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	From March 10th, 2023, to April 2024	01.05.2024
Medline	Embase.com	From March 10th, 2023, to April 2024	01.05.2024
Cochrane Library (CENTRAL and Cochrane Reviews)	Cochrane Library	NR	01.05.2024

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; NR, Not reported.

H.1.1.3.2 Conference proceedings and other sources

An approach of citation searching and key author searching in addition to key conference searches was used. The described approach is a combination of Cochrane guidelines (76) and the Canadian Agency for Drugs and Technology in Health practical search tool (78). The searches included:

- Searches of the following key conferences for the last two years (2021-2023): ASCO and ESMO (detailed in Table 83)
- Checking the reference lists of published relevant systematic reviews.
- Citation searches on key authors and included studies.

Table 83. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	https://www.asco.org/	NR	Urothelial carcinoma or bladder cancer	10.03.2023
ESMO	https://www.esmo.org/	NR	Urothelial carcinoma or bladder cancer	10.03.2023

Abbreviations: ASCO; American society of clinical oncology; ESMO; European society for medical oncology

H.1.2 Search strategies

The strategy included subject indexing terms and free-text search terms to ensure it captured a high proportion of the relevant articles. The population and intervention search terms were developed through literature searching and evidence gathering. A draft Embase (Ovid) strategy was validated by cross-checking the results with known, relevant studies that had been identified during a previous SLR in urothelial cancer. The Embase (Ovid) search string strategy was translated appropriately for the additional databases.

No language limits were applied to the search, however English language abstracts only will be included at the title/ abstract screening stage.

H.1.2.1 Primary search

H.1.2.1.1 Embase

Table 84. Search strategy table for Ovid Embase (March 10th, 2023)

No.	Query	Results
1	exp bladder tumor/	104022
2	(bladder adj3 (cancer or cancers or carcinoma or carcinomas or adenoma or adenomas or adenocarcinoma or adenocarcinomas or squamous or neoplasm or neoplasms or neoplastic or neoplasia or tumor or tumors or tumour or tumours or malignancy or malignancies)).tw.	86120
3	((urothelium or urothelial) adj3 (cancer or cancers or carcinoma or carcinomas or adenoma or adenomas or adenocarcinoma or adenocarcinomas or squamous or neoplasm or neoplasms or neoplastic or neoplasia or tumor or tumors or tumour or tumours or malignancy or malignancies)).tw.	29584
4	(transitional cell adj3 (cancer or cancers or carcinoma or carcinomas or adenoma or adenomas or adenocarcinoma or adenocarcinomas or squamous or neoplasm or neoplasms or neoplastic or neoplasia or tumor or tumors or tumour or tumours or malignancy or malignancies)).tw.	13055
5	transitional cell carcinoma/	35056
6	(tcc or transitional cell).tw.	18240
7	exp ureter tumor/	4435
8	exp urethra tumor/	2402
9	((urethra or urethras or ureter or ureters or urinary or renal pelvis) adj3 (cancer or cancers or carcinoma or carcinomas or adenoma or adenomas or adenocarcinoma or adenocarcinomas or squamous or neoplasm or neoplasms or neoplastic or neoplasia or tumor or tumors or tumour or tumours or malignancy or malignancies)).tw.	20319
10	or/1-9	150337
11	cisplatin/	214222
12	(cisplatin or cisplatinum or platamin or neoplatin or cismaplat or cis-Diamminedichloroplatinum or Platinum Diamminodichloride or Diamminodichloride, Platinum or cis-Platinum or cis Platinum or Dichlorodiammineplatinum or cis-Dichlorodiammineplatinum or NSC-119875 or Platino or Platinol or Biocisplatinum or Platidiam).ab,du,kw,ti,tn,dq.	224560
13	(MVAC or CMV or GC or PGC or CGP or GemCarbo or GemCis or platinum combination$ or platinum chemotherapy).ab,du,kw,ti,tn,dq.	235189
14	(regimen$ adj2 platinum).ab,du,kw,ti,tn,dq.	2762
15	doxecitine/	140
16	exp antineoplastic antimetabolite/	609948
17	(methotrexate or MTX or amethopterin or Mexate or Methotrexate Sodium or Sodium, Methotrexate or Methotrexate, Sodium Salt or Methotrexate, Disodium Salt or Methotrexate Hydrate or Hydrate, Methotrexate or Methotrexate, Dicesium Salt or Dicesium Salt Methotrexate).ab,du,kw,ti,tn,dq.	214708
18	(vinblastine or Vincaleukoblastine or Lemblastine or Velban or Vinblastina Lilly or Velbe or Vinblastine Sulfate or Sulfate, Vinblastine or Vinblastinsulfat-Gry or Cellblastin or Vinblastin Hexal).ab,du,kw,ti,tn,dq.	40303
19	(doxorubicin or Farmiblastina or Ribodoxo or Rubex or Adriamycin or Adriblastin or Adriblastine or Adriblastina or Adriablastine or Adriablastin or Adrimedac or	225080

	DOXO-cell or DOXO cell or Urokit Doxo-cell or Urokit Doxo cell or Doxolem or Doxorubicin Hexal or Doxorubicin Hydrochloride or Hydrochloride, Doxorubicin or Doxorubicin NC or Doxorubicina Ferrer Farm or Doxorubicina Funk or Doxorubicina Tedec or Doxorubicine Baxter or Doxotec or Myocet or Onkodox).ab,du,kw,ti,tn,dq.	
20	methotrexate/	204992
21	vinblastine/	37814
22	doxorubicin/	216813
23	gemcitabine/	70276
24	(gemc?tabin$ or Gemzar$ or difluorodeoxycytidine or difluorocytidine or DFDC or difluoro or deoxycytidine or gemcitabine hydrochloride or monophosphate).ab,du,kw,ti,tn,dq.	138133
25	paclitaxel/	129918
26	(paclitaxel or Anzatax or NSC-125973 or NSC 125973 or NSC125973 or Taxol or Taxol A or Bris Taxol or Taxol, Bris or Paxene or Praxel or 7-epi-Taxol or 7 epi Taxol or Onxol).ab,du,kw,ti,tn,dq.	136447
27	carboplatin/	83947
28	(carboplatin or CBDCA or Blastocarb or Carbosin or Carbotec or Ercar or Neocarbo or Paraplatin or Paraplatine or Platinwas or Ribocarbo or Carboplat or Nealorin).ab,du,kw,ti,tn,dq.	86945
29	(Ifosfamide or mitoxana).ab,du,kw,ti,tn,dq.	35009
30	docetaxel/	71128
31	(docetaxel or docetaxel hydrate or docetaxel trihydrate or docetaxol or docetaxel anhydrous or N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol or Taxoltere metro or Taxotere or NSC 628503 or RP 56976 or RP-56976).ab,du,kw,ti,tn,dq.	73578
32	(vinflunine or Javlor).ab,du,kw,ti,tn,dq.	1144
33	vinflunine/	1091
34	(epirubicin or Epidoxorubicin or Epiadriamycin or EPI cell or EPIcell or Epilem or Farmorubicina or NSC 256942 or NSC256942 or Ellence or Pharmorubicin or Farmorubicine or Farmorubicin or Epirubicin Hydrochloride or Hydrochloride, Epirubicin).ab,du,kw,ti,tn,dq.	33056
35	epirubicin/	32253
36	anthracycline$.ab,du,kw,ti,tn,dq.	44942
37	(taxane$ or taxoid$).ab,du,kw,ti,tn,dq.	32970
38	(immunotherap$ or anti pdl1 or pdl1).ab,du,kw,ti,tn,dq.	214868
39	pembrolizumab/	33603
40	(pembrolizumab or Keytruda or MK-3475).ab,du,kw,ti,tn,dq.	35234
41	atezolizumab/	13402
42	(atezolizumab or MDPL3280 or Tecentriq or RG7446 or RG-7446).ab,du,kw,ti,tn,dq.	14066
43	nivolumab/	34958
44	(Nivolumab or Opdivo).ab,du,kw,ti,tn,dq.	36335
45	ipilimumab/	23027

46	(ipilimumab or Anti CTLA 4 MAb Ipilimumab or Yervoy or "MDX 010" or MDX010 or MDX CTLA 4).ab,du,kw,ti,tn,dq.	23888
47	avelumab/	5644
48	(Avelumab or bavencio).ab,du,kw,ti,tn,dq.	5845
49	durvalumab/	9132
50	(durvalumab or infinzi).ab,du,kw,ti,tn,dq.	9436
51	erdafitinib/	730
52	(erdafitinib or balversa).ab,du,kw,ti,tn,dq.	786
53	(dovitinib or TKI 258 or TKI258 or CHIR 258 or CHIR258).ab,du,kw,ti,tn,dq.	1260
54	BGJ398.ab,du,kw,ti,tn,dq.	341
55	(5 fluorouracil or 5FU or Fluoruracil or Lederle or Medac or Hexal or Adrucil or Carac or Efudix or Efudex or Fluoroplex or Flurodex or Fluorouracil Mononitrate or Fluorouracil Monopotassium Salt or Fluorouracil Monosodium Salt or Fluorouracil Potassium Salt or FluorouracilGRY or Fluorouracil GRY or Fluorouracile Dakota or Dakota, Fluorouracile or Fluorouracilo Ferrer Far or Fluracedyl or Haemato FU or Neofluor or Onkofluor or Ribofluor).ab,du,kw,ti,tn,dq.	52791
56	fluorouracil/	155842
57	pemetrexed/	18356
58	(Pemetrexed or Pemetrexed Disodium or Disodium, Pemetrexed or LY 231514 or LY231514 or Alimta).ab,du,kw,ti,tn,dq.	19012
59	ramucirumab/	4436
60	(ramucirumab or Cyramza or IMC1121B or IMC 1121B).ab,du,kw,ti,tn,dq.	4732
61	bevacizumab/	71843
62	(bevacizumab or avastin or nsc 704865 or nsc704865).ab,du,kw,ti,tn,dq.	74169
63	enfortumab vedotin/	507
64	(enfortumab vedotin or padcev).ab,du,kw,ti,tn,dq.	538
65	sacituzumab govitecan/	744
66	(sacituzumab govitecan or trodelvy).ab,du,kw,ti,tn,dq.	801
67	disitamab vedotin/	57
68	disitamab vedotin.ab,du,kw,ti,tn,dq.	61
69	or/11-68	1550843
70	10 and 69	30774
71	Randomized controlled trial/	773998
72	Controlled clinical trial/	468721
73	random$.ti,ab.	1938642
74	randomization/	98414
75	intermethod comparison/	294886
76	placebo.ti,ab.	362110
77	(compare or compared or comparison).ti.	597768

78	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	2722504
79	(open adj label).ti,ab.	107181
80	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	271663
81	double blind procedure/	208105
82	parallel group$1.ti,ab.	31773
83	(crossover or cross over).ti,ab.	123135
84	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	409358
85	(assigned or allocated).ti,ab.	482196
86	(controlled adj7 (study or design or trial)).ti,ab.	444153
87	(volunteer or volunteers).ti,ab.	279942
88	human experiment/	640547
89	trial.ti.	396171
90	or/71-89	6223756
91	(random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	9373
92	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	339860
93	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.	21284
94	(Systematic review not (trial or study)).ti.	252523
95	(nonrandom$ not random$).ti,ab.	18745
96	"random fields$".ti,ab.	1074
97	(random cluster adj3 sampl$).ti,ab.	1525
98	(review.ab. and review.pt.) not trial.ti.	1095367
99	"we searched".ab. and (review.ti. or review.pt.)	48583
100	"update review".ab.	137
101	(databases adj4 searched).ab.	60454
102	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1216211
103	Animal experiment/ not (human experiment/ or human/)	2554132
104	or/91-103	4270578
105	90 not 104	5498225
106	70 and 105	6284
107	limit 106 to yr="2006 -Current"	5117

H.1.2.1.2 Medline

Table 85. Search strategy table for Ovid Medline (March 10th, 2023)

No.	Query	Results
1	Urinary Bladder Neoplasms/	61,680
2	(bladder adj3 (cancer or cancers or carcinoma or carcinomas or adenoma or adenomas or adenocarcinoma or adenocarcinomas or squamous or neoplasm or neoplasms or neoplastic or neoplasia or tumor or tumors or tumour or tumours or malignancy or malignancies)).tw.	61,683
3	((urothelium or urothelial) adj3 (cancer or cancers or carcinoma or carcinomas or adenoma or adenomas or adenocarcinoma or adenocarcinomas or squamous or neoplasm or neoplasms or neoplastic or neoplasia or tumor or tumors or tumour or tumours or malignancy or malignancies)).tw.	17,569
4	(transitional cell adj3 (cancer or cancers or carcinoma or carcinomas or adenoma or adenomas or adenocarcinoma or adenocarcinomas or squamous or neoplasm or neoplasms or neoplastic or neoplasia or tumor or tumors or tumour or tumours or malignancy or malignancies)).tw.	10,603
5	Carcinoma, Transitional Cell/	20,958
6	(tcc or transitional cell).tw.	14,098
7	Ureteral Neoplasms/	5,045
8	exp Urethral Neoplasms/	2,647
9	((urethra or urethras or ureter or ureters or urinary or renal pelvis) adj3 (cancer or cancers or carcinoma or carcinomas or adenoma or adenomas or adenocarcinoma or adenocarcinomas or squamous or neoplasm or neoplasms or neoplastic or neoplasia or tumor or tumors or tumour or tumours or malignancy or malignancies)).tw.	15,854
10	or/1-9	100,440
11	cisplatin/	57,864
12	(cisplatin or cisplatinum or platamin or neoplatin or cismaplat or cis-Diamminedichloroplatinum or Platinum Diamminodichloride or Diamminodichloride, Platinum or cis-Platinum or cis Platinum or Dichlorodiammineplatinum or cis-Dichlorodiammineplatinum or NSC-119875 or Platino or Platinol or Biocisplatinum or Platidiam).ti,ab,kw.	75,609
13	(MVAC or CMV or GC or PGC or CGP or GemCarbo or GemCis or platinum combination$ or platinum chemotherapy).ti,ab,kw.	164,866
14	(regimen$ adj2 platinum).ti,ab,kw.	1,381
15	(doxecitin$ or deoxycytidin$ or "cytosine deoxyriboside" or "deoxyribose cytidine").ti,ab,kw.	7,954
16	exp antimetabolites, antineoplastic/	166,547
17	(methotrexate or MTX or amethopterin or Mexate or Methotrexate Sodium or Sodium, Methotrexate or Methotrexate, Sodium Salt or Methotrexate, Disodium Salt or Methotrexate Hydrate or Hydrate, Methotrexate or Methotrexate, Dicesium Salt or Dicesium Salt Methotrexate).ti,ab,kw.	49,282
18	(vinblastine or Vincaleukoblastine or Lemblastine or Velban or Vinblastina Lilly or Velbe or Vinblastine Sulfate or Sulfate, Vinblastine or Vinblastinsulfat-Gry or Cellblastin or Vinblastin Hexal).ti,ab,kw.	9,803
19	(doxorubicin or Farmiblastina or Ribodoxo or Rubex or Adriamycin or Adriblastin or Adriblastine or Adriblastina or Adriablastine or Adriablastin or Adrimedac or DOXO-cell or DOXO cell or Urokit Doxo-cell or Urokit Doxo cell or	67,469

	Doxolem or Doxorubicin Hexal or Doxorubicin Hydrochloride or Hydrochloride, Doxorubicin or Doxorubicin NC or Doxorubicina Ferrer Farm or Doxorubicina Funk or Doxorubicina Tedec or Doxorubicine Baxter or Doxotec or Myocet or Onkodox).ti,ab,kw.	
20	methotrexate/	41,003
21	vinblastine/	12,867
22	doxorubicin/	59,612
23	gemcitabine/	12,409
24	(gemc?tabin$ or Gemzar$ or difluorodeoxycytidine or difluorocytidine or DFDC or difluoro or deoxycytidine or gemcitabine hydrochloride or monophosphate).ti,ab,kw.	73,571
25	paclitaxel/	30,335
26	(paclitaxel or Anzatax or NSC-125973 or NSC 125973 or NSC125973 or Taxol or Taxol A or Bris Taxol or Taxol, Bris or Paxene or Praxel or 7-epi-Taxol or 7 epi Taxol or Onxol).ti,ab,kw.	40,558
27	carboplatin/	12,904
28	(carboplatin or CBDCA or Blastocarb or Carbosin or Carbotec or Ercar or Neocarbo or Paraplatin or Paraplatine or Platinwas or Ribocarbo or Carboplat or Nealorin).ti,ab,kw.	17,214
29	Ifosfamide/	5,029
30	(Ifosfamide or mitoxana).ti,ab,kw.	6,401
31	docetaxel/	12,111
32	(docetaxel or docetaxel hydrate or docetaxel trihydrate or docetaxol or docetaxel anhydrous or N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol or Taxoltere metro or Taxotere or NSC 628503 or RP 56976 or RP-56976).ti,ab,kw.	18,086
33	(vinflunine$ or Javlor).ti,ab,kw.	302
34	epirubicin/	5,474
35	(epirubicin or Epidoxorubicin or Epiadriamycin or EPI cell or EPIcell or Epilem or Farmorubicina or NSC 256942 or NSC256942 or Ellence or Pharmorubicin or Farmorubicine or Farmorubicin or Epirubicin Hydrochloride or Hydrochloride, Epirubicin).ti,ab,kw.	6,519
36	anthracycline$.ti,ab,kw.	16,476
37	(taxane$ or taxoid$).ti,ab,kw.	10,677
38	(immunotherap$ or anti pdl1 or pdl1).ti,ab,kw.	133,751
39	(pembrolizumab$ or Keytruda or MK-3475).ti,ab,kw.	7,698
40	(atezolizumab or MDPL3280 or Tecentriq or RG7446 or RG-7446).ti,ab,kw.	2,517
41	nivolumab/	4,924
42	(Nivolumab or Opdivo).ti,ab,kw.	8,352
43	ipilimumab/	2,817
44	(ipilimumab or Anti CTLA 4 MAb Ipilimumab or Yervoy or "MDX 010" or MDX010 or MDX CTLA 4).ti,ab,kw.	4,689
45	(Avelumab or bavencio).ti,ab,kw.	816
46	(durvalumab or infinzi).ti,ab,kw.	1,272

47	(erdafitinib or balversa).ti,ab,kw.	176
48	(dovitinib or TKI 258 or TKI258 or CHIR 258 or CHIR258).ti,ab,kw.	207
49	BGJ398.ti,ab,kw.	136
50	fluorouracil/	44,743
51	(5 fluorouracil or 5FU or Fluoruracil or Lederle or Medac or Hexal or Adrucil or Carac or Efudix or Efudex or Fluoroplex or Flurodex or Fluorouracil Mononitrate or Fluorouracil Monopotassium Salt or Fluorouracil Monosodium Salt or Fluorouracil Potassium Salt or FluorouracilGRY or Fluorouracil GRY or Fluorouracile Dakota or Dakota, Fluorouracile or Fluorouracilo Ferrer Far or Fluracedyl or Haemato FU or Neofluor or Onkofluor or Ribofluor).ti,ab,kw.	36,323
52	pemetrexed/	2,447
53	(Pemetrexed or Pemetrexed Disodium or Disodium, Pemetrexed or LY 231514 or LY231514 or Alimta).ti,ab,kw.	3,969
54	(ramucirumab or Cyramza or IMC1121B or IMC 1121B).ti,ab,kw.	1,176
55	bevacizumab/	13,963
56	(bevacizumab or avastin or nsc 704865 or nsc704865).ti,ab,kw.	20,024
57	(enfortumab vedotin or padcev).ti,ab,kw.	175
58	(sacituzumab govitecan or trodelvy).ti,ab,kw.	210
59	disitamab vedotin.ti,ab,kw.	15
60	or/11-59	770,930
61	10 and 60	12,251
62	randomized controlled trial.pt.	588,393
63	controlled clinical trial.pt.	95,211
64	randomized.ab.	595,375
65	placebo.ab.	236,395
66	drug therapy.fs.	2,570,962
67	randomly.ab.	403,641
68	trial.ab.	638,896
69	groups.ab.	2,487,002
70	or/62-69	5,600,341
71	exp animals/ not humans.sh.	5,100,930
72	70 not 71	4,884,155
73	(news or comment or editorial or letter or case reports).pt.	4,434,060
74	case report.ti.	300,199
75	73 or 74	4,478,760
76	61 and 72	7,000
77	76 not 75	5,921
78	limit 77 to yr="2006 -Current"	3,611

H.1.2.1.3 Cochrane Library

Table 86. Search strategy table for Cochrane Library (March 10th, 2023)

No.	Query	Results
#1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees	1954
#2	bladder NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)	5184
#3	(urothelium OR urothelial) NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)	1400
#4	transitional cell NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)	1553
#5	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees	732
#6	tcc OR transitional cell	2224
#7	MeSH descriptor: [Ureteral Neoplasms] explode all trees	33
#8	MeSH descriptor: [Urethral Neoplasms] explode all trees	19
#9	(urethra OR urethras OR ureter OR ureters OR urinary OR renal pelvis) NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)	7338
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	11270
#11	MeSH descriptor: [Cisplatin] explode all trees	5907
#12	cisplatin OR cisplatinum OR platamin OR neoplatin OR cismaplat OR cis-Diamminedichloroplatinum OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR cis-Platinum OR cis Platinum OR Dichlorodiammineplatinum OR cis-Dichlorodiammineplatinum OR NSC-119875 OR Platino OR Platinol OR Biocisplatinum OR Platidiam	16544
#13	MVAC OR CMV OR GC OR PGC OR CGP OR GemCarbo OR GemCis OR platinum combination* OR platinum chemotherapy	18603
#14	regimen* NEAR/2 platinum	661
#15	doxecitin* OR deoxycytidin* OR "cytosine deoxyriboside" OR "deoxyribose cytidine"	2071
#16	MeSH descriptor: [Antimetabolites, Antineoplastic] explode all trees	1283
#17	methotrexate OR MTX OR amethopterin OR Mexate OR Methotrexate Sodium OR Sodium, Methotrexate OR Methotrexate, Sodium Salt OR Methotrexate, Disodium Salt OR Methotrexate Hydrate OR Hydrate, Methotrexate OR Methotrexate, Dicesium Salt OR Dicesium Salt Methotrexate	14025
#18	vinblastine OR Vincaleukoblastine OR Lemblastine OR Velban OR Vinblastina Lilly OR Velbe OR Vinblastine Sulfate OR Sulfate, Vinblastine OR Vinblastinsulfat-Gry OR Cellblastin OR Vinblastin Hexal	1942

#19	doxorubicin OR Farmiblastina OR Ribodoxo OR Rubex OR Adriamycin OR Adriblastin OR Adriblastine OR Adriblastina OR Adriablastine OR Adriablastin OR Adrimedac OR DOXO-cell OR DOXO cell OR Urokit Doxo-cell OR Urokit Doxo cell OR Doxolem OR Doxorubicin Hexal OR Doxorubicin Hydrochloride OR Hydrochloride, Doxorubicin OR Doxorubicin NC OR Doxorubicina Ferrer Farm OR Doxorubicina Funk OR Doxorubicina Tedec OR Doxorubicine Baxter OR Doxotec OR Myocet OR Onkodox	9558
#20	MeSH descriptor: [Methotrexate] explode all trees	4749
#21	MeSH descriptor: [Vinblastine] explode all trees	1270
#22	MeSH descriptor: [Doxorubicin] explode all trees	5457
#23	MeSH descriptor: [Gemcitabine] explode all trees	2287
#24	gemc?tabin* OR Gemzar* OR difluorodeoxycytidine OR difluorocytidine OR DFDC OR difluoro OR deoxycytidine OR gemcitabine hydrochloride OR monophosphate	9108
#25	MeSH descriptor: [Paclitaxel] explode all trees	4465
#26	paclitaxel OR Anzatax OR "NSC-125973" OR NSC 125973 OR NSC125973 OR Taxol OR Taxol A OR Bris Taxol OR Taxol,Bris OR Paxene OR Praxel OR "7-epi-Taxol" OR 7 epi Taxol OR Onxol	12280
#27	MeSH descriptor: [Carboplatin] explode all trees	2930
#28	carboplatin OR CBDCA OR Blastocarb OR Carbosin OR Carbotec OR Ercar OR Neocarbo OR Paraplatin OR Paraplatine OR Platinwas OR Ribocarbo OR Carboplat OR Nealorin	8451
#29	MeSH descriptor: [Ifosfamide] explode all trees	615
#30	Ifosfamide OR mitoxana	1561
#31	MeSH descriptor: [Docetaxel] explode all trees	2616
#32	docetaxel OR docetaxel hydrate OR docetaxel trihydrate OR docetaxol OR docetaxel anhydrous OR "N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol" OR Taxoltere metro OR Taxotere OR NSC 628503 OR "RP-56976" OR RP 56976	8305
#33	vinflunine* OR Javlor	149
#34	MeSH descriptor: [Epirubicin] explode all trees	1346
#35	epirubicin OR Epidoxorubicin OR Epiadriamycin OR EPI cell OR EPIcell OR Epilem OR Farmorubicina OR NSC 256942 OR NSC256942 OR Ellence OR Pharmorubicin OR Farmorubicine OR Farmorubicin OR Epirubicin Hydrochloride OR Hydrochloride, Epirubicin	3909
#36	anthracycline*	3588
#37	taxane* OR taxoid*	4514
#38	immunotherap* OR anti pdl1 OR pdl1	16501
#39	pembrolizumab* OR Keytruda OR MK-3475	2736
#40	atezolizumab OR MDPL3280 OR Tecentriq OR RG7446 OR RG-7446	1271
#41	MeSH descriptor: [Nivolumab] explode all trees	740
#42	Nivolumab OR Opdivo	2736
#43	MeSH descriptor: [Ipilimumab] explode all trees	367
#44	ipilimumab OR Anti CTLA 4 MAb Ipilimumab OR Yervoy OR "MDX 010" OR MDX010 OR MDX CTLA 4	1748
#45	Avelumab OR bavencio	360

#46	durvalumab OR infinzi	1000
#47	erdafitinib OR balversa	33
#48	dovitinib OR TKI 258 OR TKI258 OR CHIR 258 OR CHIR258	66
#49	BGJ398	16
#50	MeSH descriptor: [Fluorouracil] explode all trees	7252
#51	5 fluorouracil OR 5FU OR Fluoruracil OR Lederle OR Medac OR Hexal OR Adrucil OR Carac OR Efudix OR Efudex OR Fluoroplex OR Flurodex OR Fluorouracil Mononitrate OR Fluorouracil Monopotassium Salt OR Fluorouracil Monosodium Salt OR Fluorouracil Potassium Salt OR FluorouracilGRY OR Fluorouracil GRY OR Fluorouracile Dakota OR Dakota, Fluorouracile OR Fluorouracilo Ferrer Far OR Fluracedyl OR Haemato FU OR Neofluor OR Onkofluor OR Ribofluor	10657
#52	MeSH descriptor: [Pemetrexed] explode all trees	793
#53	Pemetrexed OR Pemetrexed Disodium OR Disodium, Pemetrexed OR LY 231514 OR LY231514 OR Alimta	2470
#54	ramucirumab OR Cyramza OR IMC1121B OR IMC 1121B	632
#55	MeSH descriptor: [Bevacizumab] explode all trees	2615
#56	bevacizumab OR avastin OR nsc 704865 OR nsc704865	7490
#57	enfortumab vedotin OR padcev	50
#58	sacituzumab govitecan OR trodelvy	94
#59	disitamab vedotin	0
#60	(Loriot, #9253-`#59)	99654
#61	#10 AND #60 with Publication Year from 2006 to 2023, with Cochrane Library publication date Between Jan 2006 and Apr 2023, in Trials	2842

H.1.2.2 Updated search

H.1.2.2.1 Embase and Medline

In the updated search, Embase and Medline were searched simultaneously using the same search string (Table 87).

Table 87. Search strategy table for Embase.com Embase and Medline (May 1st, 2024)

No.	Query	Results
1	'bladder tumor'/exp	117076
2	(bladder NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)):ti,ab,tn	93307
3	((urothelium OR urothelial) NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)):ti,ab,tn	32014

4	transitional:ti,ab,tn AND ((cell NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)):ti,ab,tn)	14476
5	'transitional cell carcinoma'	42333
6	tcc:ti,ab,tn OR 'transitional cell':ti,ab,tn	18933
7	'ureter tumor'/exp	5694
8	'urethra tumor'/exp	3079
9	((urethra OR urethras OR ureter OR ureters OR urinary OR 'renal pelvis') NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)):ti,ab,tn	22473
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	168897
11	cisplatin	237187
12	cisplatin OR cisplatinum OR platamin OR neoplatin OR cismaplat OR 'cis-diamminedichloroplatinum' OR 'platinum diamminodichloride' OR 'diamminodichloride, platinum' OR 'cis-platinum' OR 'cis platinum' OR dichlorodiammineplatinum OR 'cis-dichlorodiammineplatinum' OR 'nsc-119875' OR platino OR platinol OR biocisplatinum OR platidiam	237987
13	gemcarbo OR gemcis	173
14	gemcitabine	79012
15	gemc*tabin* OR gemzar* OR difluorodeoxycytidine OR difluorocytidine OR dfdc OR difluoro OR deoxycytidine OR 'gemcitabine hydrochloride' OR monophosphate	158073
16	paclitaxel	146047
17	paclitaxel OR anzatax OR 'nsc-125973' OR 'nsc 125973' OR nsc125973 OR taxol OR 'taxol a' OR 'bris taxol' OR 'taxol, bris' OR paxene OR praxel OR '7-epi-taxol' OR '7 epi taxol' OR onxol	147476
18	carboplatin	93543
19	carboplatin OR cbdca OR blastocarb OR carbosin OR carbotec OR ercar OR neocarbo OR paraplatin OR paraplatine OR platinwas OR ribocarbo OR carboplat OR nealorin	93668
20	docetaxel	78706
21	docetaxel OR 'docetaxel hydrate' OR 'docetaxel trihydrate' OR docetaxol OR 'docetaxel anhydrous' OR 'n-debenzoyl-n-tert-butoxycarbonyl-10-deacetyltaxol' OR 'taxoltere metro' OR taxotere OR 'nsc 628503' OR 'rp 56976' OR 'rp-56976'	78804
22	pembrolizumab	43194
23	pembrolizumab OR keytruda OR 'mk-3475'	43241
24	atezolizumab	18356
25	atezolizumab OR mdpl3280 OR tecentriq OR rg7446 OR 'rg 7446'	18364
26	#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	542090
27	#10 AND #26	21450

28	'randomized controlled trial'	1108570
29	'controlled clinical trial'	474332
30	random*:ti,ab	2056274
31	randomization	143718
32	'intermethod comparison'	307752
33	placebo:ti,ab	376172
34	compare:ti OR compared:ti OR comparison:ti	645428
35	(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)	2902743
36	(open NEXT/1 label):ti,ab	114548
37	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab	283192
38	'double blind procedure'	218583
39	'parallel group*':ti,ab	33413
40	crossover:ti,ab OR 'cross over':ti,ab	128075
41	((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR 'group*' OR 'intervention*' OR 'patient*' OR 'subject*' OR 'participant*')):ti,ab	432050
42	assigned:ti,ab OR allocated:ti,ab	509046
43	(controlled NEAR/7 (study OR design OR trial)):ti,ab	470991
44	volunteer:ti,ab OR volunteers:ti,ab	290085
45	'human experiment'	661736
46	trial:ti	427443
47	#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	6703319
48	(('random*' NEAR/1 'sampl*' NEAR/7 ('cross section*' OR 'questionnaire*' OR 'survey*' OR 'database*')):ti,ab) NOT ('comparative study' OR 'controlled study' OR 'randomi*ed controlled':ti,ab OR 'randomly assigned':ti,ab)	10205
49	'cross-sectional study' NOT ('randomized controlled trial' OR 'controlled clinical study' OR 'controlled study' OR 'randomi*ed controlled':ti,ab OR 'control group*':ti,ab)	409431
50	((case NEAR/1 control*):ti,ab) AND random*:ti,ab NOT 'randomi*ed controlled':ti,ab	22349
51	'systematic review':ti NOT (trial:ti OR study:ti)	281682
52	'nonrandom*':ti,ab NOT 'random*':ti,ab	19411
53	'random fields*':ti,ab	1101
54	('random cluster' NEAR/3 'sampl*'):ti,ab	1638
55	review:ab AND review:it NOT trial:ti	1176817
56	'we searched':ab AND (review:ti OR review:it)	52338
57	'update review':ab	141
58	(databases NEAR/4 searched):ab	67279

59	(rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset*:ti) AND 'animal experiment'	1253454
60	'animal experiment' NOT ('human experiment' OR 'human')	2333775
61	#48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60	4359462
62	#47 NOT #61	5915096
63	#27 AND #62	4787
64	#63 AND [10-03-2023]/sd	574

H.1.2.2.2 Cochrane Library

Table 88. Search strategy table for Cochrane Library (May 1st, 2024)

No.	Search terms	Hits
#1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees	2354
#2	bladder NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)	5707
#3	(urothelium OR urothelial) NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)	1595
#4	transitional cell NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)	1736
#5	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees	856
#6	tcc OR transitional cell	2319
#7	MeSH descriptor: [Ureteral Neoplasms] explode all trees	40
#8	MeSH descriptor: [Urethral Neoplasms] explode all trees	22
#9	(urethra OR urethras OR ureter OR ureters OR urinary OR renal pelvis) NEAR/3 (cancer OR cancers OR carcinoma OR carcinomas OR adenoma OR adenomas OR adenocarcinoma OR adenocarcinomas OR squamous OR neoplasm OR neoplasms OR neoplastic OR neoplasia OR tumor OR tumors OR tumour OR tumours OR malignancy OR malignancies)	8148
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	12175
#11	MeSH descriptor: [Cisplatin] explode all trees	6403
#12	cisplatin OR cisplatinum OR platamin OR neoplatin OR cismaplat OR cis-Diamminedichloroplatinum OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR cis-Platinum OR cis Platinum OR Dichlorodiammineplatinum OR cis-Dichlorodiammineplatinum OR NSC-119875 OR Platino OR Platinol OR Biocisplatinum OR Platidiam	17267
#13	GemCarbo OR GemCis OR platinum combination* OR platinum chemotherapy	8147
#14	regimen* NEAR/2 platinum	696

#15	MeSH descriptor: [Gemcitabine] explode all trees	2577
#16	gemc?tabin* OR Gemzar* OR difluorodeoxycytidine OR difluorocytidine OR DFDC OR difluoro OR deoxycytidine OR gemcitabine hydrochloride OR monophosphate	9711
#17	MeSH descriptor: [Paclitaxel] explode all trees	5098
#18	paclitaxel OR Anzatax OR "NSC-125973" OR NSC 125973 OR NSC125973 OR Taxol OR Taxol A OR Bris Taxol OR Taxol,Bris OR Paxene OR Praxel OR "7-epi-Taxol" OR 7 epi Taxol OR Onxol	13115
#19	MeSH descriptor: [Carboplatin] explode all trees	3306
#20	carboplatin OR CBDCA OR Blastocarb OR Carbosin OR Carbotec OR Ercar OR Neocarbo OR Paraplatin OR Paraplatine OR Platinwas OR Ribocarbo OR Carboplat OR Nealorin	8961
#21	MeSH descriptor: [Docetaxel] explode all trees	2936
#22	docetaxel OR docetaxel hydrate OR docetaxel trihydrate OR docetaxol OR docetaxel anhydrous OR "N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol" OR Taxoltere metro OR Taxotere OR NSC 628503 OR "RP-56976" OR RP 56976	8782
#23	taxane* OR taxoid*	4905
#24	immunotherap* OR anti pdl1 OR pdl1	18696
#25	pembrolizumab* OR Keytruda OR MK-3475	3283
#26	atezolizumab OR MDPL3280 OR Tecentriq OR RG7446 OR RG-7446	1524
#27	#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	61880
#28	#10 AND #27 with Publication Year from 2023 to 2024, with Cochrane Library publication date Between Mar 2023 and Apr 2024, in Trials	278

H.1.3 Systematic selection of studies

H.1.3.1 Eligibility criteria

This systematic literature review used participants, intervention, comparator, and outcome (PICO) elements to select relevant studies (Table 89).

Table 89 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients (≥18 years) with locally advanced (T3b and T4a), surgically unresectable or metastatic urothelial cancer (stage IV disease) who have received at least one line of prior systemic therapy, one of which was an ICI therapy (e.g., PD-(L)1). Trials where stage of advanced disease is not specified will be included.	Pediatric population is not eligible.	
Intervention	Any pharmacological treatment for the specified patient population such as: • Platinum-based chemotherapy regimens (including cisplatin, carboplatin)	All other interventions.	Only intervention relevant to this submission, i.e. erdafitinib, is included.

	• Immunotherapy as monotherapy or combination therapy (pembrolizumab, atezolizumab, nivolumab, ipilimumab, avelumab, durvalumab, erdafitinib, dovitinib, bevacizumab, ramucirumab) • Antibody-drug conjugates (EV, sacitizumab govitecan, disitamab vedotin) • Other chemotherapy regimens or single agent chemotherapy (fluorouracil, pemetrexed, doxecitine, methotrexate, doxorubicin, gemcitabine, paclitaxel, docetaxel, vinflunine, epirubicin, anthracycline)		
Comparators	Any intervention	No restrictions.	Only comparators relevant to this submission, i.e. vinflunine and EV, is included.
Outcomes	Efficacy and safety outcomes as relevant to THOR, e.g. • OS • PFS • ORR • DOR • AEs • PROs (FACT-Bl, PGI-S, EORTC QLQ C30, and the EQ-5D-5L/ EQ-5D-3L)	Outcomes not relevant to the THOR trial.	
Study design/ publication type	All Phase II, III, or IV RCTs in the patient population of interest.	All other study designs.	
Language restrictions	Articles and abstracts in English only. English language abstracts of these will be included if they contain relevant information.	Publications in other languages than English.	
Geography	Any geographic location.	No restrictions.	

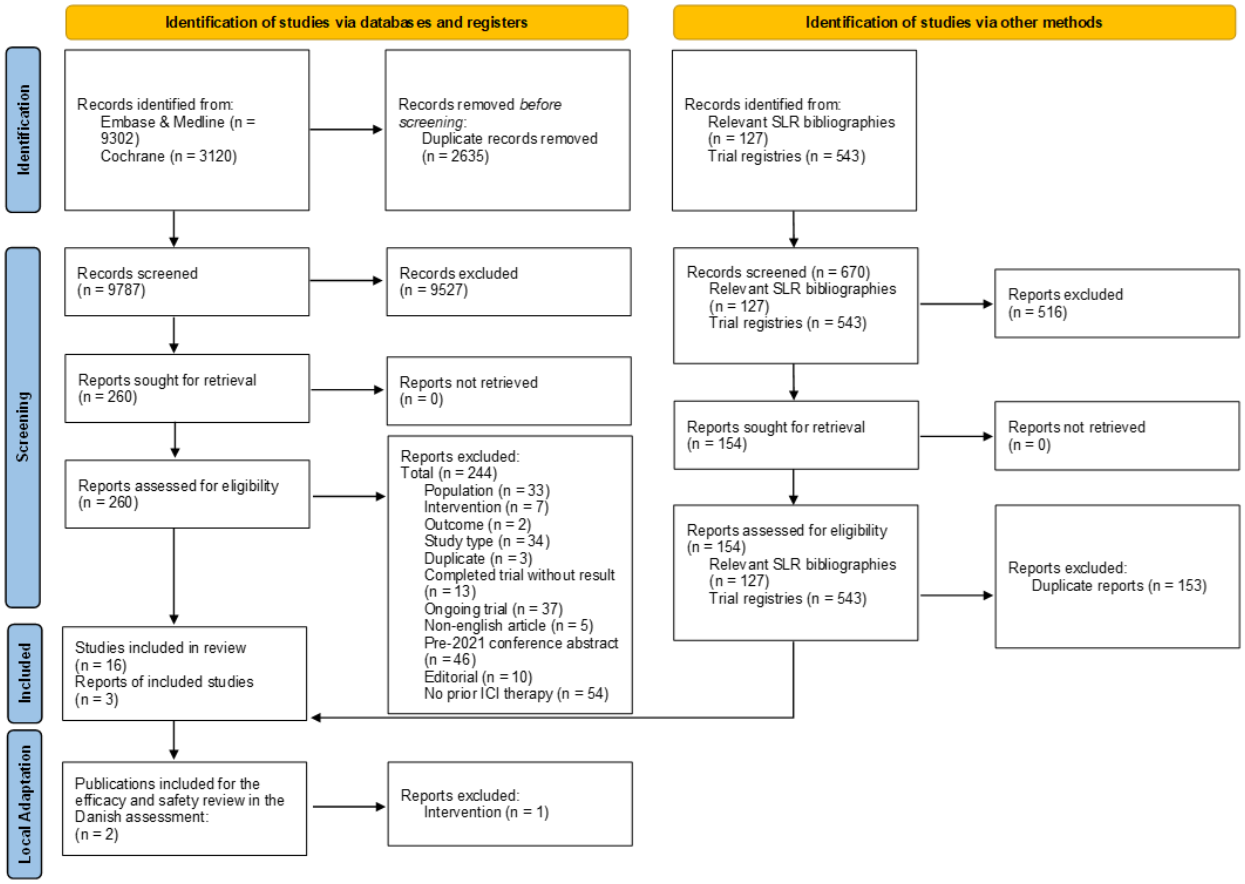
Abbreviations: Abbreviations: AE, adverse events; DOR, duration of response; EORTC QLQ C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EV, Enfortumab vedotin; FACT-BI, functional assessment of cancer therapy-bladder; ORR, overall response rates; OS, overall survival; PFS, progression-free survival; PGI-S, patient global impression of severity scale; PROs, patient reported outcomes; RCTs, randomized control trial.

H.1.3.2 Study selection process

Search results were imported into EndNote and duplicates were removed using an established method (79). The titles and abstracts were screened for inclusion guided by the PICO criteria (Table 89) by two blinded reviewers using PICO portal (80). Any discrepancies between reviewers were resolved by a third reviewer.

Full texts of studies identified via title/ abstract screening and grey literature searches were retrieved and assessed for eligibility. Where full text manuscripts were not available, abstracts were included. Full text screening was conducted by two blinded reviewers using PICO portal (80). Any discrepancies between reviewers were resolved by a third reviewer. Reasons for exclusion were noted in an Excel spreadsheet. The results were a list of studies meeting all PICO criteria and are therefore eligible for inclusion. The screening process and resulting identification of papers of the primary search is represented in a PRISMA flow diagram shown in Figure 57.

Figure 57 PRISMA flow diagram



H.1.3.2.1 Global SLR

In the SLR, database searches were conducted on March 10, 2023 and May 1 2024. In total, database searches identified 12,422 records of which, 9,302 were identified in Ovid Embase and Medline, and 3,120 in Cochrane library. Database records were combined into a single EndNote library and de-duplicated using an established method (79). Following deduplication, title and abstract of 9,787 records were screened for relevance. This led to the exclusion of 9,527 records. The full texts of the remaining 260 records were assessed for relevance and 244 records were excluded.

Additionally, citation checking of previously published SLRs, as well as a manual search of relevant trial registries was conducted. This yielded an additional 670 references which were screened and assessed for eligibility, with 669 excluded in total.

In the SLR, 3 studies (EV-301 (6), THOR C1 (42) and RANGE (81); reported in 16 publications) were identified.

H.1.3.2.2 Local adaptation

To inform this submission for erdafitinib in Denmark, the global SLR has been adapted to exclude all studies not relevant in a Danish setting. For this reason, only two studies identified in the clinical SLRs (EV-301 and THOR C1) have been included as RANGE did not include a comparator of interest (docetaxel + ramucirumab).

H.1.3.3 Summary of included studies

A summary of the included studies in the local adaptation is presented in Table 90.

Table 90 Overview of study design for studies included in the analyses (local adaptation)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
EV-301 **NCT03474107**	To confirm the clinical benefit of enfortumab vedotin over standard chemotherapy in patients with previously treated advanced UC.	Global, open-label phase III study.	Adult patients with previously treated locally advanced or metastatic urothelial cancer.	EV (n = 301) Chemotherapy (n = 307)	OS (from randomization until the analysis cut-off date of 15-Jul-2020 (median OS follow-up was 11.10 months).	PFS, clinical response (from randomization until the analysis cut-off date of 15-Jul-2020 (median OS follow-up was 11.10 months) and safety (From first dose up to 30 days after last dose).
THOR C1 **NCT03390504**	To assess erdafitinib versus chemotherapy in patients with previously treated advanced UC.	Randomized, Phase III, open label, multicenter trial.	Adult patients with metastatic or surgically unresectable urothelial cancer harbouring selected fibroblast growth factor receptor (FGFR) aberrations.	Erdafitinib (n = 136) Vinflunine or docetaxel (n = 130)	OS (from date of first randomization to the date of participant's death (approximately up to 3 years)).	PFS, ORR and safety (from date of first randomization to approximately up to 3 years).

H.1.4 Excluded full text references

A list of excluded publications in the SLR, including reason for exclusion, is provided in Table 91.

Table 91 List of excluded publications (primary search)

Author (year)	DOI/URL	Reason for exclusion
Petrylak (2017)	10.1016/S0140-6736(17)32365-6	Comparator
Euctr, N. L.(2015)	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2014-003655-66-NL	Completed trial without result
JapicCti(2014)	https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-JapicCTI-142739	Completed trial without result
Per(2015)	https://trialsearch.who.int/Trial2.aspx?TrialID=PER-074-14	Completed trial without result
Euctr, S. E.(2017)	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-001319-36-SE	Completed trial without result
Umin(2009)	https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000002450	Completed trial without result
Nct(2014)	https://clinicaltrials.gov/show/NCT02109328	Completed trial without result
Euctr, A. T.(2015)	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2014-005396-82-AT	Completed trial without result
Euctr, F. R.(2017)	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2016-005068-33-FR	Completed trial without result
Nct(2007)	https://clinicaltrials.gov/show/NCT00578526	Completed trial without result
Nct(2013)	https://clinicaltrials.gov/show/NCT01828736	Completed trial without result
Nct(2014)	https://clinicaltrials.gov/show/NCT02240017	Completed trial without result
Nct(2018)	https://clinicaltrials.gov/show/NCT03389438	Completed trial without result
Nct(2019)	https://clinicaltrials.gov/show/NCT03980041	Completed trial without result
Ooi, W. L.(2011)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01016350/full	Editorial
du Toit, J.(2012)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=364420058	Editorial
Riaz, I. B.(2021)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02194634/full	Editorial
Horiguchi, M.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01455603/full	Editorial
Anonymous(2018)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed19&AN=2001193548	Editorial

Burki, T. K.(2019)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med16&AN=31378458	Editorial
Matsubara, N.(2023)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexb&AN=2018864168	Excluded as Duplicate
Sternberg, C. N.(2023)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02487426/full	Excluded as Duplicate
Nct(2011)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02046483/full	Excluded as Duplicate
Matsumoto, R.(2021)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02305468/full	Intervention
Noguchi, M.(2016)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01133894/full	Intervention
Tissot, G.(2023)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexb&AN=2022493560	Intervention
Obara, W.(2017)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed18&AN=616106104	Intervention
Ochi, T.(2006)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed9&AN=44622577	Non-English article
Rexer, H.(2011)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00882136/full	Non-English article
Rexer, H.(2015)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01097569/full	Non-English article
Xia, H.(2019)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed20&AN=2004379566	Non-English article
Grulllich, C.(2020)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med17&AN=32103289	Non-English article
Vulsteke, C.(2022)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02389677/full	Ongoing trial
Euctr, N. L.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02068370/full	Ongoing trial
Grivas, P.(2021)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02260869/full	Ongoing trial
Muro, K.(2021)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02283884/full	Ongoing trial
Sadeghi, S.(2022)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02454576/full	Ongoing trial
Euctr, E. S.(2019)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02068588/full	Ongoing trial
Subbiah, V.(2021)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed22&AN=636985450	Ongoing trial
Euctr, A. T.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01909651/full	Ongoing trial
Euctr, H. U.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01908177/full	Ongoing trial
Umin(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01910419/full	Ongoing trial

Umin(2015)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01880809/full	Ongoing trial
jRcts(2021)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02330175/full	Ongoing trial
Nct(2021)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02289586/full	Ongoing trial
Nct(2021)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02289773/full	Ongoing trial
Euctr, N. L.(2022)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02513004/full	Ongoing trial
Galsky, M.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexa&AN=639738066	Ongoing trial
Joshi, M.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed23&AN=638833909	Ongoing trial
Nct(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01578546/full	Ongoing trial
Euctr, E. S.(2019)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02067790/full	Ongoing trial
Nct(2019)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01965340/full	Ongoing trial
Nct(2020)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02181843/full	Ongoing trial
Nct(2020)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02205769/full	Ongoing trial
Nct(2010)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01576342/full	Ongoing trial
Nct(2013)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02024161/full	Ongoing trial
Umin(2013)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01800590/full	Ongoing trial
Nct(2015)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01492717/full	Ongoing trial
Nct(2021)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02332255/full	Ongoing trial
Reck, M.(2021)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed22&AN=2014622130	Ongoing trial
Gravis, G.(2022)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02454721/full	Ongoing trial
Koshkin, V. S.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed23&AN=2020168351	Ongoing trial
Muro, K.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed23&AN=2018943264	Ongoing trial
Powles, T.(2022)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02389666/full	Ongoing trial
Spigel, D.(2023)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexb&AN=2022447887	Ongoing trial

Euctr, E. S.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01910430/full	Ongoing trial
Nct(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01599422/full	Ongoing trial
Nct(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01589198/full	Ongoing trial
Nct(2019)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01965342/full	Ongoing trial
Champiat, S.(2022)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02469261/full	Outcome
van der Heijden, M. S.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed23&AN=2015558552	Outcome
Euctr, G. B.(2007)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01882461/full	Population
Nct(2007)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01591802/full	Population
Siefker-Radtke, A. O.(2009)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed11&AN=70241480	Population
Euctr, S. E.(2013)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01873551/full	Population
Sumiyoshi, T.(2013)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med10&AN=23412116	Population
Pal, S. K.(2021)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed22&AN=635867220	Population
Joshi, M.(2022)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02389694/full	Population
Vignani, F.(2023)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02471097/full	Population
Ctri(2019)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02065960/full	Population
Ctri(2020)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02167063/full	Population
Roberts, J. T.(2006)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00626942/full	Population
Kwak, H.(2007)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed10&AN=351068330	Population
Higano, C. S.(2008)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med7&AN=18404692	Population
Nct(2008)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02031571/full	Population
Nct(2009)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01524904/full	Population
Montie, J. E.(2010)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01738269/full	Population

Nct(2011)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01533389/full	Population
Nct(2011)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01534332/full	Population
Li, C.(2012)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=365392376	Population
Bamias, A.(2013)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00878318/full	Population
Hussain, M.(2014)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed15&AN=373800882	Population
Nct(2015)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01553660/full	Population
Isrctn(2016)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01810219/full	Population
Nct(2016)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01592230/full	Population
Hussain, S. A.(2022)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02394788/full	Population
Johnson, M.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexa&AN=2018800805	Population
Taarnhoj, G. A.(2022)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02463927/full	Population
Nct(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01566353/full	Population
Naya, Y.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01649897/full	Population
Nct(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01795605/full	Population
Galsky, M. D.(2020)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexb&AN=631477618	Population
Nct(2020)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02206247/full	Population
Petrylak, D. P.(2015)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01136291/full	Pre 2021 Conference abstract
Bellmunt, J.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01397680/full	Pre 2021 Conference abstract
De Wit, R.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01438265/full	Pre 2021 Conference abstract
Petrylak, D. P.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01438285/full	Pre 2021 Conference abstract
Quinn, D.(2017)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed18&AN=617436596	Pre 2021 Conference abstract

Necchi, A.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01756616/full	Pre 2021 Conference abstract
Culine, S.(2010)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed11&AN=70146229	Pre 2021 Conference abstract
Kim, Y. S.(2013)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed14&AN=71101187	Pre 2021 Conference abstract
Bajorin, D. F.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01750276/full	Pre 2021 Conference abstract
Petrylak, D.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01438344/full	Pre 2021 Conference abstract
Bellmunt, J.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01789154/full	Pre 2021 Conference abstract
Bellmunt, J.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01709443/full	Pre 2021 Conference abstract
Drakaki, A.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01772148/full	Pre 2021 Conference abstract
Fradet, Y.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01789123/full	Pre 2021 Conference abstract
Matsubara, N.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01789212/full	Pre 2021 Conference abstract
Powles, T.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01715061/full	Pre 2021 Conference abstract
Von Amsberg, G.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01936140/full	Pre 2021 Conference abstract
Wong, Y.(2011)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed12&AN=70700847	Pre 2021 Conference abstract
Grivas, P.(2012)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=71003907	Pre 2021 Conference abstract
Ikeda, M.(2012)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=70863616	Pre 2021 Conference abstract
Kudou, S.(2013)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed14&AN=71031463	Pre 2021 Conference abstract

Loriot, Y.(2016)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01296226/full	Pre 2021 Conference abstract
Choueiri, T. K.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01407329/full	Pre 2021 Conference abstract
Culine, S.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01407347/full	Pre 2021 Conference abstract
De Wit, R.(2017)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed18&AN=617436053	Pre 2021 Conference abstract
Zhang, T.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01438260/full	Pre 2021 Conference abstract
Powles, T.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01792251/full	Pre 2021 Conference abstract
Sridhar, S. S.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01787726/full	Pre 2021 Conference abstract
Sternberg, C. N.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01961551/full	Pre 2021 Conference abstract
De Wit, R.(2019)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01937801/full	Pre 2021 Conference abstract
Van Der Heijden, M. S.(2019)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02073581/full	Pre 2021 Conference abstract
Yu, E. Y.(2019)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01989826/full	Pre 2021 Conference abstract
Motzer, R. J.(2014)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01055890/full	Pre 2021 Conference abstract
Bellmunt, J.(2015)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01130028/full	Pre 2021 Conference abstract
De Wit, M.(2015)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed16&AN=72068128	Pre 2021 Conference abstract
Font, A.(2016)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01765289/full	Pre 2021 Conference abstract
Powderly, J.(2016)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01295352/full	Pre 2021 Conference abstract

SiefkerRadtke, A. O.(2016)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01294444/full	Pre 2021 Conference abstract
Ackerman, C.(2017)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed18&AN=618007061	Pre 2021 Conference abstract
Balar, A. V.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01792263/full	Pre 2021 Conference abstract
Loriot, Y.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01709449/full	Pre 2021 Conference abstract
Zhang, T.(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01787709/full	Pre 2021 Conference abstract
De Santis, M.(2020)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02146728/full	Pre 2021 Conference abstract
Drakaki, A.(2020)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02097577/full	Pre 2021 Conference abstract
Moreno, V.(2020)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed21&AN=631170064	Pre 2021 Conference abstract
Siefker-Radtke, A. O.(2020)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed21&AN=2007890071	Pre 2021 Conference abstract
Tagawa, S. T.(2021)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed23&AN=2017283684	Study Type
Ogawa, M.(2020)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med17&AN=32132064	Study Type
Sweeney, C. J.(2006)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed9&AN=46638903	Study Type
Grimm, M. O.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed23&AN=637625263	Study Type
Grivas, P.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed23&AN=637625015	Study Type
Siefker-Radtke, A. O.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexa&AN=2016678428	Study Type
Euctr, E. S.(2017)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01904071/full	Study Type
Necchi, A.(2017)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed18&AN=620758654	Study Type
Loriot, Y.(2019)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01954712/full	Study Type
Takahashi, T.(2006)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med6&AN=16418182	Study Type

Anonymous(2008)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed10&AN=352300441	Study Type
Bellmunt, J.(2011)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed12&AN=361186289	Study Type
Cao, M.(2011)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00860766/full	Study Type
Niegisch, G.(2011)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00806576/full	Study Type
Harshman, L. C.(2013)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00962497/full	Study Type
Chi, C. O.(2014)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01879115/full	Study Type
Nct(2015)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02047979/full	Study Type
Umin(2016)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01844397/full	Study Type
Alva, A. S.(2021)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02260866/full	Study Type
Chen, H.(2021)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed22&AN=2014621310	Study Type
Gutierrez, M.(2021)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med19&AN=33148673	Study Type
Plimack, E. R.(2021)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed22&AN=635904062	Study Type
Siefker-Radtke, A. O.(2021)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed22&AN=634496815	Study Type
Sonpavde, G.(2021)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed22&AN=634496849	Study Type
Castellano, D. E.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed23&AN=637624720	Study Type
Champiat, S.(2022)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed23&AN=2020175810	Study Type
Umin(2018)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01901783/full	Study Type
Degboe, A.(2019)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed20&AN=626726763	Study Type
Kapetanakis, V.(2019)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed20&AN=2003471644	Study Type
O'Donnell, P. H.(2020)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med17&AN=31581306	Study Type
Pal, S. K.(2020)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med18&AN=32208524	Study Type
Sonpavde, G.(2020)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med18&AN=32552295	Study Type
Taylor, M. H.(2020)	https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed21&AN=2005703328	Study Type

Huang G. (2024)	10.1007/s00432-023-05584-3	Review/Editorial
O'Dwyer R.T. (2024)		Review/Editorial
Parikh M. (2024)	10.1038/s41568-024-00705-7	Line of therapy
Catto J.W.F. (2023)	10.1016/j.annonc.2023.10.108	Disease
Kawahara T. (2023)	10.3390/cancers15174227	Study design
Santoni M. (2023)	10.1007/s00262-022-03349-4	Review/Editorial
Rizzo A. (2023)	10.1007/s00262-023-03366-x	Review/Editorial
Milowsky M. (2023)	10.1097/JU.0000000000003361.08	Line of therapy
Matsubara N. (2023)	10.1002/cam4.5165	Intervention
Sternberg C.N. (2023)	10.1200/JCO.21.02303	Intervention
TaarnhÃ¸j, GA (2023)	10.1186/s41687-023-00640-5	Intervention

H.1.5 Quality assessment

Randomized controlled studies were quality assessed according to the risk of bias assessment suggested in the NICE STA guidance (82) and is provided in Table 92 below for the included studies.

Table 92: Risk of bias in RCTs

Author (year), study name, NCT	Randomization methods	Allocation concealment	Groups similar at outset	Blinding method	Group imbalances/ dropouts	Outcomes reported	ITT and missing data
Powles et al. 2021 **EV-301** **NCT03474107**	Low risk Patients were randomized using interactive response technology	Low risk Allocation of treatment groups was concealed	Low risk Patient characteristics were balanced between groups	High risk This was an open-label study	High risk There were more dropouts in the control group than the treatment group	Low risk All outcomes are presented in the key reference and subsequent publications	Low risk An ITT analysis was conducted, and missing data was accounted for in the methods
Loriot Y et al. **THOR C1** **NCT03390504**	Low risk Patients were randomized 1:1 to receive oral erdafitinib (8 mg per day with pharmacodynamically guided up titration to 9 mg on day 14) or investigators choice of chemotherapy (vinflunine, 320 mg/m² every 3 weeks; docetaxel, 1-hour infusion of 75 mg/m²)	High risk Allocation concealment was not discussed.	Low risk Key prognostic factors were the same at baseline in each arm.	High risk Blinding not discussed.	High risk There were more dropouts in the control group than the treatment group.	Low risk All outcomes presented in study methods were discussed in the results section.	Low risk All analyses were performed on an ITT basis.

Abbreviations: ITT, intention to treat

H.1.6 Unpublished data

N/A

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

N/A

Appendix J. Literature searches for input to the health economic model

N/A

Appendix K. Overview of previous treatments for THOR C1

Table 93 provides a summary of prior anti-cancer therapy from the THOR C1 trial. Table 94 provides a summary of prior anti-PDL1 therapy by line of therapy. Table 95 provides a summary of prior anti-cancer therapy by line of therapy.

Table 93. Summary of prior anti-cancer therapy, cohort 1 ITT analysis set

	Erdafitinib N = 136	Chemotherapy N = 130	Vinflunine N = 48
Radiation therapy	39 (28.7%)	44 (33.8%)	[redacted]
Prior urinary surgery	122 (89.7%)	116 (89.2%)	[redacted]
Chemotherapy	123 (90.4%)	114 (87.7%)	[redacted]
Any Platinum-based therapy	122 (89.7%)	111 (85.4%)	[redacted]
Cisplatin	76 (55.9%)	59 (45.4%)	[redacted]
Gem-cisplatin	69 (50.7%)	55 (42.3%)	[redacted]
No Gem-Cisplatin or MVAC	0 (0.0%)	0 (0.0%)	[redacted]
MVAC	7 (5.1%)	4 (3.1%)	[redacted]
Carboplatin	37 (27.2%)	41 (31.5%)	[redacted]
Gem-carboplatin	36 (26.5%)	40 (30.8%)	[redacted]
Other carboplatin	1 (0.7%)	1 (0.8%)	[redacted]
Multiple platinum-based therapy	8 (5.9%)	10 (7.7%)	[redacted]
No platinum-based therapy	1 (0.7%)	3 (2.3%)	[redacted]
Antibody drug conjugate	0 (0.0%	2 (1.5%)	[redacted]
Enfortumab Vedotin	0 (0.0%)	2 (1.5%)	[redacted]
Anti-PD-(L)1 therapy	135 (99.3%)	128 (98.5%)	[redacted]

Pembrolizumab	47 (34.6%)	47 (36.2%)	[redacted]
Avelumab	31 (22.8%)	28 (21.5%)	[redacted]
Atezolizumab	26 (19.1%)	26 (20.0%)	[redacted]
Nivolumab	11 (8.1%)	13 (10.0%)	[redacted]
Durvalumab	13 (9.6%)	4 (3.1%)	[redacted]
Tislelizumab	5 (3.7%)	3 (2.3%)	[redacted]
Toripalimab	2 (1.5%)	2 (1.5%)	[redacted]
Not Specified	1 (0.7%)	2 (1.5%)	[redacted]
Cemiplimab	0 (0.0%)	1 (0.8%)	[redacted]
Sintilimab	0 (0.0%)	1 (0.8%)	[redacted]
Tocilizumab	0 (0.0%)	1 (0.8%)	[redacted]

Source: THOR C1 clinical study report; TSIPAT01A; Table 12 (50).

Abbreviations: MVAC = methotrexate/vinblastine/doxorubicin/cisplatin or methotrexate/vinblastine/epirubicin/cisplatin; Gem = Gemcitabine.

Percentages are based on the number of subjects in analysis set of the corresponding treatment group.

Table 94. Summary of prior anti-PDL1 therapy by line of therapy, cohort 1 ITT analysis set

	Erdafitinib N = 136	Chemotherapy N = 130	Vinflunine N = 48
One line of prior systemic therapy	45 (33.1%)	33 (25.4%)	[redacted]
Anti-PD-(L)1 therapy	44 (32.4%)	31 (23.8%)	[redacted]
Avelumab	14 (10.3%)	8 (6.2%)	[redacted]
Durvalumab	11 (8.1%)	3 (2.3%)	[redacted]
Nivolumab	7 (5.1%)	6 (4.6%)	[redacted]
Atezolizumab	5 (3.7%)	4 (3.1%)	[redacted]
Pembrolizumab	4 (2.9%)	5 (3.8%)	[redacted]

Tislelizumab	1 (0.7%)	2 (1.5%)	[redacted]
Toripalimab	2 (1.5%)	1 (0.8%)	[redacted]
Tocilizumab	0 (0.0%)	1 (0.8%)	[redacted]
Not Specified	0 (0.0%)	1 (0.8%)	[redacted]
Two lines of prior systemic therapy	90 (66.2%)	97 (74.6%)	[redacted]
Anti-PD-(L)1 therapy	90 (66.2%)	97 (74.6%)	[redacted]
Avelumab	17 (12.5%)	20 (15.4%)	[redacted]
Durvalumab	2 (1.5%)	1 (0.8%)	[redacted]
Nivolumab	4 (2.9%)	7 (5.4%)	[redacted]
Atezolizumab	20 (14.7%)	22 (16.9%)	[redacted]
Pembrolizumab	43 (31.6%)	42 (32.3%)	[redacted]
Tislelizumab	4 (2.9%)	1 (0.8%)	[redacted]
Toripalimab	0 (0.0%)	1 (0.8%)	[redacted]
Tocilizumab	0 (0.0%)	0 (0.0%)	[redacted]
Not Specified	1 (0.7%)	1 (0.8%)	[redacted]

Source: THOR C1 clinical study report; TSIPAT09A (50).

Percentages are based on the number of subjects in analysis set of the corresponding treatment group.

Note: One subject with 3 prior lines of prior systemic therapy is not included in this table.

Table 95. Summary of prior anti-cancer therapy by line of therapy; cohort 1 ITT analysis set

Patients receiving prior therapy, n (%)	Erdafitinib N = 136	Chemotherapy N = 130	Vinflunine N = 48
One line of prior systemic therapy	45 (33.1%)	33 (25.4%)	[redacted]
Chemotherapy + anti-PD-(L)1 therapy	33 (24.3%)	15 (11.5%)	[redacted]
Anti-PD-(L)1 therapy	11 (8.0%)	16 (12.3%)	[redacted]

Chemotherapy	1 (0.7%)	2 (1.5%)	[redacted]
Other	0 (0.0%)	2 (1.5%)	[redacted]
Two lines of prior systemic therapy	90 (66.2%)	97 (74.6%)	[redacted]
Anti-PD-(L)1 therapy	76 (55.9%)	76 (58.5%)	[redacted]
Chemotherapy	10 (7.4%)	14 (10.8%)	[redacted]
ADC	0	2 (1.5%)	[redacted]
Other	4 (2.9%)	7 (5.4%)	[redacted]

Source: THOR C1 clinical study report; TSIPAT05A (50).

Percentages are based on the number of subjects in analysis set of the corresponding treatment group.

Note: One subject with 3 prior lines of prior systemic therapy is not included in this table.

Abbreviations: ADC = adjuvant-drug conjugate; NA = not applicable PD-(L)1 = programmed death-(ligand) 1.

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