Medicinrådet

Bilag til Medicinrådets vurdering af osimertinib i kombination med kemoterapi til førstelinjebehandling af patienter med fremskreden EGFR-muteret ikke-småcellet lungekræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. osimertinib i kombination med kemoterapi
2. Forhandlingsnotat fra Amgros vedr. osimertinib i kombination med kemoterapi
3. Ansøgers endelige ansøgning vedr. osimertinib i kombination med kemoterapi

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

23.01.2026

Note on DMC draft assessment report regarding Tagrisso (osimertinib) in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

AstraZeneca would like to thank the DMC secretariat for the evaluation of Tagrisso and appreciate the opportunity to comment on the draft assessment report.

Overall, the Secretariat and the Expert committee acknowledge the positive results from the FLAURA2 trial, a head-to-head trial comparing efficacy and safety between Tagrisso in combination with pemetrexed and platinum-based chemotherapy (CTx) and Tagrisso monotherapy. Mature data are available on progression-free-survival (PFS) and overall survival (OS), and the trial demonstrated significant benefit of treating patients with Tagrisso in combination with CTx for high-risk patients and patients with CNS metastases vs. current standard of care.

In response to the DMC assessment report, there are some concerns to be highlighted that may bias the decision. Since 2019, the standard of care for patients with EGFR-mutated advanced NSCLC has been Tagrisso monotherapy until progression or unacceptable toxicity. As noted in the assessment report, Tagrisso monotherapy remains an efficacious and well tolerated treatment.

FLAURA2 introduces a clinically meaningful option for treatment intensification by adding a platinum-based chemotherapy doublet to the current standard. In FLAURA2, the combination achieved a 9.9-month incremental increase in median OS versus Tagrisso monotherapy (47.5 months vs 37.6 months), representing a substantial survival benefit for the intent to treat (ITT) population. The trial enrolled a high proportion of patients with CNS involvement (222 patients; 39.9% of the ITT population at baseline). In this subgroup, the combination improved CNS PFS, supporting its role as a beneficial intensification strategy for patients with CNS metastases, who typically have higher disease burden, poorer prognosis, and greater deterioration in quality of life compared with those without CNS involvement.

AstraZeneca considers two core assumptions in the DMC health economic analysis to be clinically implausible.

- **Treatment beyond progression is overestimated for patients on Tagrisso + CTx**
- **OS extrapolation underestimates the survival gain observed with Tagrisso + CTx in FLAURA2**

With respect to treatment duration extrapolation, the DMCs main analysis assumes that nearly all patients in the combination arm who are alive at the 8-year landmark have progressed and remain on Tagrisso thereby overpredicting treatment duration beyond progression. The analysis predicts that patients in the Tagrisso plus-CTx arm receive, on average, 9 months of treatment beyond progression, versus 6 months in the monotherapy arm. The assessment report notes that model results are highly sensitive to assumptions about treatment duration and acknowledges that the base case overpredicts treatment duration in the combination arm by 2–3 months. In the clinical trial, only a proportion of patients were treated beyond progression, and the observed duration beyond progression was similar across arms. AstraZeneca acknowledges that the original model did not include extrapolation options to reflect a 2–3month reduction in the combination arm's treatment duration.

Since the initial submission, a new data cutoff with substantially longer follow up on treatment duration in the clinical trial has become available, which can reduce uncertainty around these extrapolations. Following dialogue with the Secretariat, an updated model and accompanying technical documentation have been provided using the new data cutoff ahead of the decision.

AstraZeneca would like to encourage the DMC to consider analyses conducted with the updated model, as this offers a stronger decision basis by reducing uncertainty inherent to shorter follow-up.

Regarding OS extrapolation, we believe the health economic results presented by DMC do not reflect the survival benefit observed in FLAURA2. The trial demonstrated a 9.9-month median OS gain with the addition of CTx and sustained separation of the OS curves through the final OS cutoff.

The current extrapolation underestimates the long-term efficacy of Tagrisso in EGFR-mutated patients and the added benefit of the platinum-based doublet. The extrapolation implies that long-term survival for patients treated with either the combination or monotherapy would be worse than that observed for the overall stage IV population in the Danish Lung Cancer registry at the 10-year landmark(Registry report 2024, 10-year survival in all stage IVA/IVB adenocarcinoma patients: **3-6%**, DMC base case, estimated 10-year survival: **4%** in osimertinib + CTx, **0%** in osimertinib monotherapy)[1]. The registry includes data from patients who do not have targeted therapies as well as patients who have lung cancer types with worse prognoses than EGFR-mutated NSCLC. AstraZeneca considers the optimistic scenario for OS extrapolation to be clinically plausible and more consistent with the observed survival benefit in FLAURA2.

To conclude, AstraZeneca would like to point out that the Medicinrådet's assumptions in their health economic base case analysis are overly pessimistic with regards to survival, and the chosen extrapolations do not show the positive results that the Medicinrådet acknowledge from the FLAURA2 trial. Furthermore, the Medicinrådet extrapolates the duration of treatment based on clinically implausible assumptions.

Medicinrådet should note that the FLAURA2 model is driven by impact of adding chemotherapy to the current standard of care, Tagrisso monotherapy. The ICER reported by Medicinrådet is highly sensitive to assumptions about treatment duration and the implied OS benefit from survival extrapolations for patients on Tagrisso + chemotherapy, which naturally increases drug costs in the combination arm as survival extends. In short, the incremental cost is driven by longer progression-free survival (prolonging Tagrisso treatment) and the addition of chemotherapy, rather than by Tagrisso costs alone.

AstraZeneca would like to point out that FLAURA2 has been reimbursed in both Sweden and Finland and is currently in process in Norway with a decision by Beslutningsforum expected in Q1, 2026. FLAURA2 is recommended as first choice in the clinical guidelines in Norway.

Kind regards,

Cecilie Astrup
Market Access Manager
AstraZeneca A/S

Martin Phuc Tran
HTA manager
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[1] https://www.sundk.dk/media/cadgkmwq/dlcr-aarsrapport-2024-offentliggjort-version-07-08-2025.pdf

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03.02.2026

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.02.2026
Leverandør	AstraZeneca
Lægemiddel	Tagrisso (osimertinib)
Ansøgt indikation	Osimertinib i kombination med pemetrexed og platinbaseret kemoterapi til førstelinjebehandling af voksne patienter med fremskreden NSCLC, hvis tumorer har EGFR exon 19-deletioner eller exon 21 (L858R)-substitutionsmutationer
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Tagrisso (osimertinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Tagrisso	40 mg (30 stk.)	36.981,73	[redacted]	[redacted]
Tagrisso	80 mg (30 stk.)	36.981,73	[redacted]	[redacted]

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Tagrisso (osimertinib) monoterapi er i dag førstevalg til patientpopulationen.

[redacted]

Tabel 2 viser de samlede lægemiddeludgifter til et behandlingsforløb for hhv. Tagrisso monoterapi, Tagrisso i kombination med pemetrexed + kemoterapi og Rybrevant i kombination med Lazcluze. Bemærk at behandlingslængderne er forskellige mellem de tre behandlingsalternativer. Behandling med både Tagrisso og Lazcluze kan fortsætte efter regression, en del af behandlingen vil derfor foregå som monoterapi, dvs. uden hhv. pemetrexed + kemoterapi og Rybrevant, jf. Medicinrådets vurdering af hhv. *osimertinib i kombination med pemetrexed og platin-baseret kemoterapi til førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungekræft* og *amivantamab i kombination med lazertinib til førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungekræft*.

Behandlingsvarighederne er oplyst af Medicinrådet og forbundet med usikkerhed.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient for et behandlingsforløb

Behandling	Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsforløb (SAIP, DKK)
Tagrisso monoterapi	Tagrisso	80 mg (30 stk.)	80 mg dagligt, oral Behandlingsvarighed: [redacted]	[redacted]	[redacted]
Tagrisso kombinationsbehandling	Tagrisso	80 mg (30 stk.)	80 mg dagligt, oral Behandlingsvarighed: [redacted]	[redacted]	[redacted]
	Pemetrexed "Ever Pharma"	25 mg (20 ml)	500 mg/m^2* hver 3. uge, i.v. Behandlingsvarighed: [redacted]	[redacted]	[redacted]
	Carboplatin "Fresenius Kabi"	10 mg (45 ml)	400 mg/m^2*, hver 3. uge i 4 serier, i.v. Behandlingsvarighed: [redacted]	[redacted]	[redacted]
	Tagrisso i kombination med pemetrexed og carboplatin				[redacted]
Rybrevant + Lazcluze	Lazcluze	240 mg (28 stk.)	240 mg dagligt, oral Behandlingsvarighed: [redacted]	[redacted]	[redacted]
	Rybrevant	350 mg (1 stk.)**	*Under 80 kg:* Uge 1-4: 1.050 mg ugentlig, i.v. Derefter: 1.050 mg hver 2. uge, i.v. *80 kg eller over:* Uge 1-4: 1.400 mg ugentlig, i.v. Derefter: 1.400 mg hver 2. uge, i.v. Behandlingsvarighed: [redacted]	[redacted]	[redacted]
	Rybrevant i kombination med Lazcluze *Under 80 kg:* *80 kg eller over:*				[redacted]

*BSA =1,84, jf. Medicinrådets vurdering af osimertinib i kombination med pemetrexed og platin-baseret kemoterapi til førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungekræft

**Der er en lille prisforskel mellem i.v. og s.c. formulering på Rybrevant, men det ligger i samme prisleje.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til status
England	Anbefalet		Link til vurdering
Sverige	Ikke vurderet	Vurderes ikke nationalt	Link til oversigt

Opsummering

[redacted]

Application for the assessment of Tagrisso (osimertinib) in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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Table of contents

Tables and Figures

Table of tables

Table of figures

Abbreviations

Abbreviation	Definition	Abbreviation	Definition
1L	First line	**IV**	Intravenous
2L	Second line	**KM**	Kaplan-Meier
AE	Adverse event	**LS**	Least squares
AUC	Area under the curve	**MedDRA**	Medical Dictionary for Regulatory Activities
BICR	Blinded independent central review	**MMRM**	Mixed models for repeated measures
cFAS	CNS full analysis set	**NC**	Not calculable
CI	Confidence interval	**NSCLC**	Non-small cell lung cancer
CNS	Central nervous system	**OR**	Overall response
CTCAE	Common terminology criteria for adverse events	**ORR**	Objective response rate
cEFR	CNS evaluable for response	**OS**	Overall Survival
CTx	Chemotherapy	**PD-L1**	Programmed death-ligand
DCO	Data cut-off	**PFS**	Progression-free survival
DCR	Disease control rate	**PGIS**	Patient global impression of severity
DMC	Danish Medicine Council	**PH**	Proportional hazard
EGFR	Epidermal growth factor receptor	**PRO**	Patient reported outcome
EMA	European Medicines Agency	**PS**	Performance status
EORTC QLC	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire	**PSM**	Partitioned survival model
EQ-5D	EuroQoL 5-dimension	**Q3W**	Once every 3 weeks
Ex19del	Exon 19 deletion	**QALY**	Quality adjusted life year
FAS	Full analysis set	**QD**	Once daily
FDA	Food and Drug Administration	**RCT**	Randomised controlled trial
GHS	Global Health Status	**RDI**	Relative dose intensity
HR	Hazard ratio	**RECIST**	Response Evaluation Criteria in Solid Tumours
HRQoL	Health related quality of life	**SAE**	Serious adverse event

HSUV	Health state utility values	**SAP**	Statistical analysis plan
ICER	Incremental cost-effectiveness ratio	**SAS**	Safety analysis set
IDMC	Independent Data Monitoring Committee	**SD**	Standard deviation
ILD	Interstitial lung disease	**SLR**	Systematic literature review
IO	Immune-oncology	**SmPC**	Summary of Product Characteristics
IQR	Interquartile range	**SoC**	Standard of care
IRC	Independent review committee	**TTD**	Time to treatment discontinuation
ITT	Intention-to-treat		

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Tagrisso
Generic name	Osimertinib
Therapeutic indication as defined by EMA	TAGRISSO is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sweden
ATC code	L01EB04
Combination therapy and/or co-medication	Yes
(Expected) Date of EC approval	Approved July 4th 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	**TAGRISSO as monotherapy is indicated for:** • the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (see section 5.1). (ADAURA) • the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. (FLAURA) • the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. (AURA3) • the treatment of adult patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution

Overview of the medicine	
	mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy (LAURA)
Other indications that have been evaluated by the DMC (yes/no)	• Tagrisso monotherapy as first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. (FLAURA) **Outcome**: Recommended • Tagrisso monotherapy as adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. (ADAURA). **Outcome**: Partially recommended • Tagrisso monotherapy as treatment of patients will locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemotherapy (LAURA) **Outcome**: Ongoing case at the DMC.
Joint Nordic assessment (JNHB)	**Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)?** Yes, but Denmark is the only country with restricted recommendation for the ADAURA indication. **Is the product suitable for a joint Nordic assessment?** No **If no, why not**? Different processes/systems. FLAURA2 is already reimbursed in Finland and Sweden
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	40 mg, 30 film-coated tablets 80 mg, 30 film-coated tablets

2. Summary table

Summary	
Indication relevant for the assessment	The application is according to the approved label, i.e. no deviations from the EMA indication.
Dosage regiment and administration	Osimertinib (80 mg once daily) and intravenous pemetrexed (500 mg/m^2 every 3rd week) plus either cisplatin (75 mg/m^2) or carboplatin (AUC of 5 mg/ml/min), administered intravenously on day 1 of 21-day cycles for four cycles. This treatment was followed by osimertinib (80 mg once daily) plus pemetrexed maintenance therapy (500 mg per square meter) every 3 weeks.

Summary	
Choice of comparator	Osimertinib monotherapy (80 mg once daily). A 40 mg strength is available for dose reductions. Osimertinib is an established standard treatment and has been clinical practice for 1st line advanced EGFRm NSCLC in Denmark since DMC approval in April 2019
Prognosis with current treatment (comparator)	Current Danish clinical practice for 1st line treatment of EGFRm patients is osimertinib monotherapy. Osimertinib monotherapy was investigated in the FLAURA trial (approved by DMC in April 2017), where the median OS was 38.6 months (95% CI, 34.5 to 41.8) in the osimertinib group and 31.8 months (95% CI, 26.6 to 36.0) in the comparator group (2nd gen TKIs) (HR= 0.80; 95.05% CI, 0.64 to 1.00; P=0.046). The osimertinib monotherapy comparator arm in FLAURA2 showed at the final OS DCO a comparable median OS of 37.6 months. The patients in both trials do resemble the Danish EGFRm population.
Type of evidence for the clinical evaluation	Head-to-head study: FLAURA2 trial, NCT04035486: Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. N Engl J Med. 2023;389(21):1935-1948. doi:10.1056/NEJMoa2306434(1)
Most important efficacy endpoints (Difference/gain compared to comparator)	The primary endpoint was investigator-assessed progression-free survival, which was defined as the time from randomization until objective disease progression or death from any cause in the absence of progression (according to RECIST, version 1.1). Secondary end points included overall survival, objective response, duration of response, disease control, depth of response, second progression–free survival and safety.
Most important serious adverse events for the intervention and comparator	**Osimertinib + CTx vs. osimertinib** SAEs were reported in 45.7% (n=126) of patients in the osimertinib + CTx arm and 27.3% (n=75) of patients in the osimertinib monotherapy arm. The most frequently reported SAEs (≥2% of patients) in the osimertinib + CTx arm were anaemia, pneumonia, COVID-19, pulmonary embolism, febrile neutropenia, and platelet count decreased; in the osimertinib monotherapy arm, pneumonia was the most frequently reported SAE. In the osimertinib + CTx arm, the events predominantly reflect the known safety profile of the individual CTx agents. While pneumonia is a commonly reported comorbidity in patients with advanced NSCLC, the frequency of SAEs of COVID-19 and COVID-19 pneumonia was likely influenced by the timing of the study in relation to the COVID-19 pandemic. In addition, a larger number of patients in the osimertinib + CTx arm were reported to experience a causally related SAE

Summary	
	compared with the osimertinib monotherapy arm (20.3%/56 patients and 6.5%/18 patients, respectively), which was mainly due to AEs reported as causally related to pemetrexed (17.4%/48 patients).
Impact on health-related quality of life	In this application, HRQoL outcomes have been presented from the PROs instruments, EORTC QLQ-C30, EQ-VAS and EQ-5D-5L. Across the instruments, a non-clinically meaningful benefit was observed in both study arms, indicating the clinically significant efficacy benefit observed with the addition of CTx to osimertinib treatment was achieved with no clinically meaningful deterioration in HRQoL. **EORTC-QLQ-C30**, GHS/QoL estimate difference between groups: -4.06 (-6.42, -1.69). **Health economic model**: Equal HSUV was applied for both treatment arms.
Type of economic analysis that is submitted	**Type of analysis**: Cost-utility analysis **Type of model**: Partitioned survival model
Data sources used to model the clinical effects	Cost-utility analysis, partitioned survival model based on TTD, PFS and OS curves from the FLAURA2 trial
Data sources used to model the health-related quality of life	EQ-5D-5L data from FLAURA2 – mapped to Danish tariffs.
Life years gained	0.98 years
QALYs gained	0.87 QALY
Incremental costs	284,312 DKK
ICER (DKK/QALY)	326,380 DKK/QALY
Uncertainty associated with the ICER estimate	Health state utilities values for progression-free health state and progressed disease health state, followed by discount rates on outcomes and costs.
Number of eligible patients in Denmark	Incidence: approx. 75-80 patients annually
Budget impact (in year 5)	16.8m DKK

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

3.1 The medical condition

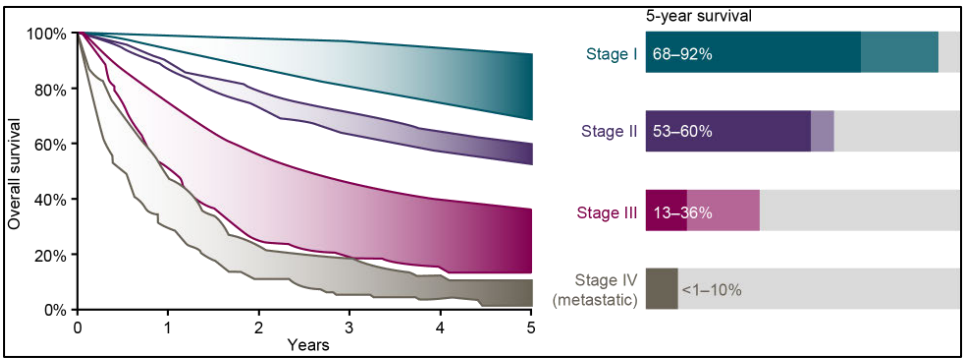
Lung cancer is defined as the uncontrolled growth of abnormal cells in the lungs and is the most commonly diagnosed cancer and the leading cause of cancer mortality worldwide. (2) The two predominant forms of lung cancer are NSCLC that accounts for 85% of patients and small-cell-lung cancer (SCLC), accounting for 15% of patients. NSCLC comprises a group of cancers, which exhibit similar behavior and response to treatment. They can be categorized according to the tissue of origin: adenocarcinoma, squamous cell carcinoma and large cell lung cancer; several variants and clinical sub-types exist within each category.

Adenocarcinomas are the most common type of NSCLC, accounting for approximately 40% of lung cancers (3, 4). Recurrent driver mutations commonly found in NSCLC have a key role in the development of the disease and are targets for therapeutic agents. The most recent Danish Lung Cancer Registry report shows that 5256 patients were diagnosed with lung cancer in Denmark in 2023.

Lung cancer prognosis varies with clinical stage at diagnosis, and progressively worsens as disease advances.(5, 6) For patients with locally advanced or metastatic NSCLC, prognosis is extremely poor; the overall five-year survival rate for NSCLC varies by stage at diagnosis from 68–92% for Stage I NSCLC to <1%–10% for Stage IV NSCLC(Figure 1) (6).

Recurrent driver mutations commonly found in NSCLC have a key role in the development of disease and are targets for therapeutic agents. Epidermal growth factor receptor mutation (EGFRm) NSCLC is a common driver mutation, which is tested for in all NSCLC patients in Denmark, as it is a target for therapeutic agents and as well associated with a higher risk of various metastasis sites. Specifically, rates of brain, bone and liver metastasis are observed to be higher for *EGFR*m NSCLC patients than for those with wild type *EGFR*.(7-9) Brain metastases in particular occur at a high rate in the *EGFR*m NSCLC population; CNS metastases are detected in approximately 37% of patients with *EGFR*m advanced NSCLC at the time of diagnosis. CNS metastases are associated with decreased QoL and poor prognosis, and are a significant cause of cancer-related mortality.(10, 11)

Figure 1. Five-year NSCLC survival rates by clinical stage (AJCC 8th edition) at diagnosis (33).



Denmark specific data has been investigated in a Landscape study(12). It is an observational study conducted in three Nordic countries (January, 2011-December, 2022). In Denmark and Norway, NSCLC cohorts were established by linking nationwide, population-based healthcare registries(12). The study population included patients with NSCLC during the study period. Demographic data were summarized at NSCLC diagnosis (index date). Annual 1-, 3-, 5-year survival estimates were reported by country and metastatic status at diagnosis (M0, no metastases; M1, metastases). Age-standardized survival analyses were conducted to determine median OS by metastatic status. Analysis cohorts comprised 45,298 (Denmark), 6,986 (Finland), and 25,480 (Norway) patients. As can be seen from figure 2, Denmark is in the lower range with regards to 5 years OS per stage (55%/45%/25%/8%) compared to the rates show in figure 1.

Figure 2. 1-, 3-, and 5-year NSCLC survival rates by clinical stage

Source: Landscape study data on file(12)

3.2 Patient population

Table 1. Incidence and prevalence in the past 5 years in lung cancer (13)

Year	2019	2020	2021	2022	2023
Incidence in Denmark	4938	5096	5192	5182	5256
Incidence NSCLC	4195	4330	4415	4405	4468
Prevalence in Denmark	13730	14505	15501	16052	16901
Global prevalence *	NA	NA	NA	NA	NA

* For small patient groups, also describe the worldwide prevalence.

The recent DMC overview of patient numbers with metastatic NSCLC estimated around 220 patients with EGFR mutation. The incidence of EGFR mutations in NSCLC (Western Europe/Denmark) has been reported differently in the literature and with a span of 6 to 15 %. In the DMC treatment guideline for NSCLC, it is estimated that 95% of these patients should be offered osimertinib monotherapy. The patient population included in the FLAURA2 study are similar to patients relevant for osimertinib monotherapy in the Danish setting and the combination can potentially be available for all 220 patients with EGFRm. Based on input from experts, the combination of osimertinib plus chemotherapy will in clinical practice most likely only be offered to a minority of the potential 220 EGFRm patients. Patient selection for combination therapy will likely depend on the treating physician's assessment of a range of clinical and non-clinical factors. This may include factors such as extent of the disease or presence of other high-risk features, presence and sites of metastases (CNS etc), total tumor burden, age, eligibility for chemotherapy, performance status and a patient's individual preferences.

Figure 3. DMC split of locally advanced/metastatic NSCLC patients based on mutation/PD-L1 status

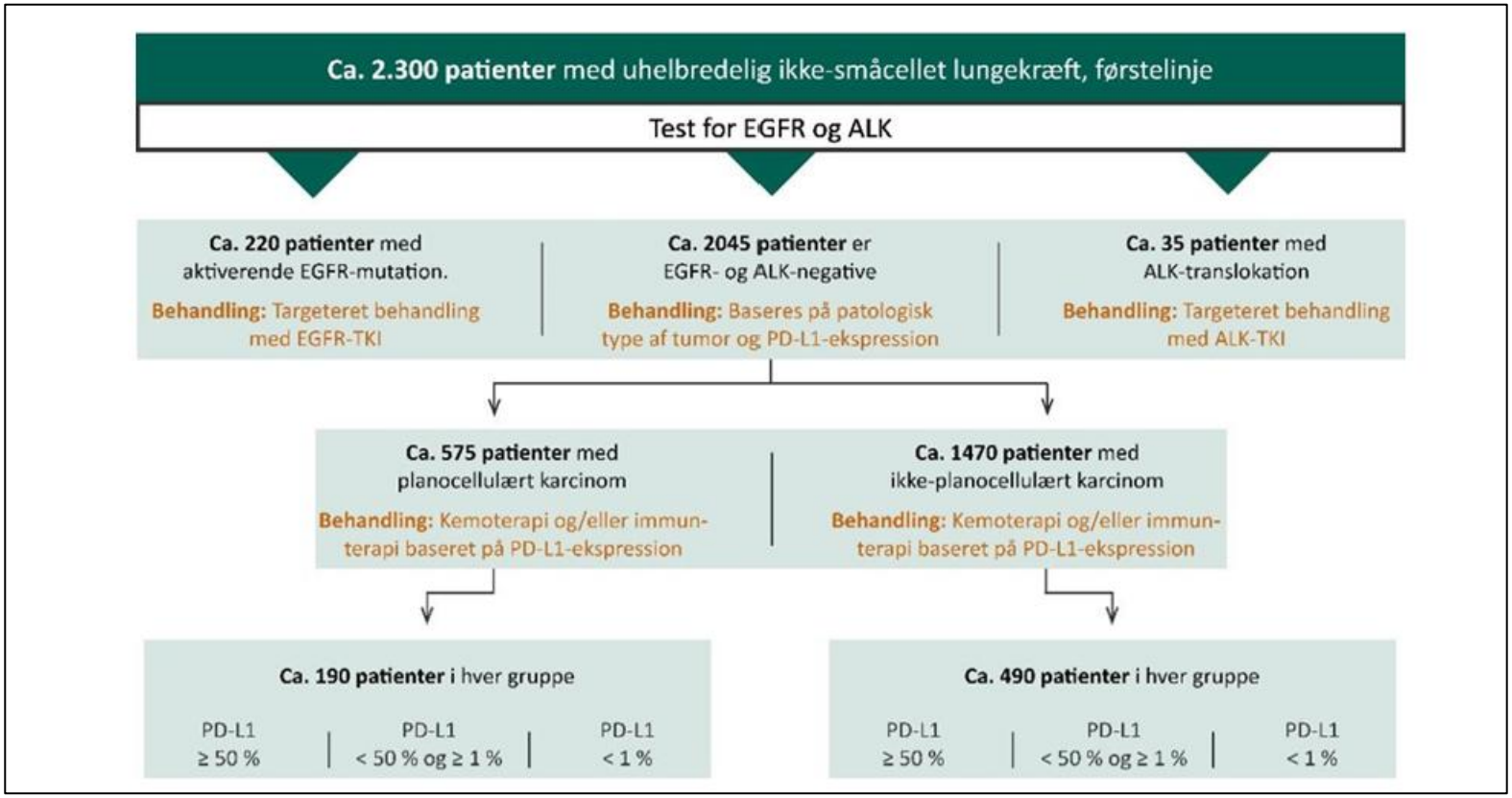


Table 2. Estimated number of EGFRm patients eligible for treatment

Year	2026	2027	2028	2029	2030
Number of patients in Denmark who are eligible for EGFRm specific treatment in the coming years	220	225	228	230	230
Number of patients in Denmark who are relevant for combination treatment in the coming years(expert validated)(14)	75	77	80	80	80

3.3 Current treatment options

1st line therapy

Based on the presence of actionable *EGFR* mutations, 1L SoC in patients with locally advanced or metastatic EGFRm NSCLC consists of treatment with EGFR TKIs. The NCCN, ESMO, DOLG and DMC guidelines all recommend osimertinib monotherapy as the preferred 1L treatment for patients with locally advanced or metastatic *EGFR*m NSCLC with Ex19del or L858R mutations, based on clinical data from the FLAURA trial (approved by DMC in April 2019(15)). In this study, Osimertinib monotherapy was compared to 2nd generation TKIs gefitinib or erlotinib. The primary endpoint was PFS, and in the trial, the observed median PFS in the osimertinib monotherapy arm was 18.9 months (15.2, 21.4) vs 10.2 months (9.6, 11.1) in the comparator arm (2nd gen TKIs) (HR 0.46 (95% CI 0.37, 0.57) p<0.0001). The observed median OS was 38.6 months (95% CI, 34.5 to 41.8) in the osimertinib arm and 31.8 months (95% CI, 26.6 to 36.0) in the comparator arm (2nd gen TKIs) (HR= 0.80; 95.05% CI, 0.64 to 1.00; P=0.046). There was also a safety benefit for osimertinib in the trial. The patients in the FLAURA trial resembled the Danish EGFRm patient characteristics and the median OS is a prediction of the current prognosis in Danish clinical practice.

Subsequent therapy following 1L therapy

Following disease progression, treatment recommendations involve local therapy (stereotactic ablative radiotherapy, stereotactic radiosurgery or surgery), or systemic therapy. In terms of systemic therapy(16);

- For patients who progressed on osimertinib, this would consist of either continuation of osimertinib treatment or alternative systemic therapy (platinum-based CTx with or without immunotherapy) depending on the site(s), mutation expression and extent of progression(16);

- For patients who progress on first- or second-generation EGFR TKI treatment, guidelines recommend evaluation of T790M mutation status and patients with a T790M-positive tumour are recommended to receive osimertinib, if not previously received in the 1L setting(16). Patients without T790M are recommended to receive platinum-based doublet CTx.

According to DOLG guidelines docetaxel or another taxane would be introduced in 2nd line after FLAURA2, due to the usage of platinum-based chemotherapy in 1st line(16).

In the FLAURA arm (osimertinib monotherapy), 2nd line would be carbo- or cisplatin + pemetrexed(16).

3.4 The intervention

Table 3. Overview of intervention, osimertinib in combination with platinum-based chemotherapy

Overview of intervention	
Indication relevant for the assessment	The application is according to the approved label, i.e. no deviations from the expected EMA indication.
ATMP	N/A
Method of administration	Osimertinib: Oral. One 80 mg tablet daily. 40 mg is available for dose reductions Cisplatin, carboplatin & pemetrexed: IV
Dosing	Osimertinib (80 mg once daily) and intravenous pemetrexed (500 mg/m² every 3rd week) plus either cisplatin (75 mg/m²) or carboplatin (AUC of 5 mg/ml/min), administered intravenously on day 1 of 21-day cycles for four cycles. This treatment was followed by osimertinib (80 mg once daily) plus pemetrexed maintenance therapy (500 mg per square meter) every 3 weeks.
Dosing in the health economic model (including relative dose intensity)	Osimertinib: 80 mg once daily, RDI: 94.6% (combo) Cisplatin (75 mg/m²) or carboplatin (AUC of 5 mg/ml/min), RDI: 100% for both Pemetrexed (500 mg/m² every 3rd week), RDI: 90%
Should the medicine be administered with other medicines?	Yes
Treatment duration / criteria for end of treatment	Treatment until disease progression or unacceptable toxicity

Overview of intervention	
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	A positive EGFR test is required. EGFR testing has been standard procedure in Denmark for more than 10 years.
Package size(s)	40 mg, 30 film-coated tablets 80 mg, 30 film-coated tablets The packaging of pemetrexed, cisplatin and carboplatin varies but all are for IV usage(vials)

3.4.1 Description of ATMP

N/A.

3.4.2 The intervention in relation to Danish clinical practice

As per the DOLG and DMC guidelines, osimertinib monotherapy is considered the preferred 1L SoC for patients with locally advanced or metastatic *EGFR*m NSCLC. Despite the observed efficacy of osimertinib monotherapy in the 1L setting, the majority of patients are expected to develop resistance to EGFR TKI therapies over time, with most patients progressing within 8–18 months of initiating EGFR TKI treatment(17-20). Tumours typically consist of heterogenous environments made up of different cell populations, and this assists the development of resistance(21). Therefore, it is conceivable that the addition of chemotherapy to osimertinib monotherapy may induce a synergistic effect and facilitate the destruction of different cancer cell populations, thereby controlling several routes of resistance and restricting the development of drug tolerance.

Evidence demonstrates that EGFR TKIs in combination with chemotherapy offer improved efficacy and manageable safety profiles compared with EGFR TKI monotherapy(22). For example, gefitinib in combination with carboplatin plus pemetrexed demonstrated improved median PFS compared with gefitinib monotherapy (20.9 months; 95% CI: 17.9, 24.4 vs 11.2 months; 95% CI: 9.0, 13.4) in a randomised, open-label, Phase III study of patients with metastatic *EGFR*m NSCLC(23). Based on this there is a strong rationale for combining osimertinib with CTx.

3.5 Choice of comparator(s)

Osimertinib monotherapy has been standard therapy for EGFRm patients since the DMC recommendation in 2019(24). EGFR testing is also well established, and reflex testing for EGFRm is part of standard clinical practice(25).

FLAURA2 is a head-to-head study vs current Danish standard of care.

Table 4. Overview of comparator, osimertinib monotherapy

Overview of comparator	
Generic name	Osimertinib
ATC code	L01EB04
Mechanism of action	Osimertinib is a Tyrosine Kinase Inhibitor (TKI). It is an irreversible inhibitor of EGFRs harbouring sensitising-mutations (EGFRm) and TKI-resistance mutation T790M
Method of administration	Oral tablet
Dosing	Osimertinib (80 mg once daily)
Dosing in the health economic model (including relative dose intensity)	80 mg daily, 97.7% (mono)
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Treatment until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	A positive EGFRm test is required. EGFR testing is standard procedure in Denmark for more than 10 years(25).
Package size(s)	80 mg, 30 tablets 40 mg, 30 tablets

3.6 Cost-effectiveness of the comparator(s)

The FLAURA regimen has been assessed and has been recommended by the DMC since 2019(15, 26), therefore no supplementary cost-effectiveness analysis is provided for osimertinib.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 5. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Primary endpoint: **Progression Free Survival**	Median follow-up in censored patients was 22.2 and 23.7 months in the osimertinib + CTx and osimertinib monotherapy arms	**PFS** (time from the date of randomisation until the date of disease progression [RECIST 1.1] or death [by any cause in the absence of progression]; any patient not known to have progressed or died at the time of analysis will be censored at the time of the latest date of assessment)	Investigator-assessed
Secondary endpoint: **Overall survival (OS)**	Median follow-up in all patients was 42.6 and 35.7 months in the osimertinib + CTx and osimertinib monotherapy arms	**OS** (time from the date of randomization until the date of death due to any cause)	Investigator-assessed
Exploratory: CNS PFS by CNS BICR assessment, cEFR analysis set	Median follow-up in censored patients was 22.0 and 14.0 months in the osimertinib + CTx and osimertinib monotherapy arms	1)Effect of osimertinib + CTx or osimertinib monotherapy on CNS metastases in patients with CNS metastases at baseline 2) Effect of osimertinib + CTx compared with osimertinib monotherapy on the prevention of CNS metastases	1) Investigator-assessed CNS PFS and best percentage change in CNS tumour size (target lesion) 2) Investigator-assessed

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

Validity of outcomes

OS, PFS and CNS-PFS are well established endpoints within oncology and NSCLC. The endpoints have been assessed by the DMC for the 1L NSCLC guideline and well as in prior assessments of TKIs within NSCLC across metastatic and non-metastatic settings(26-29).

4. Health economic analysis

4.1 Model structure

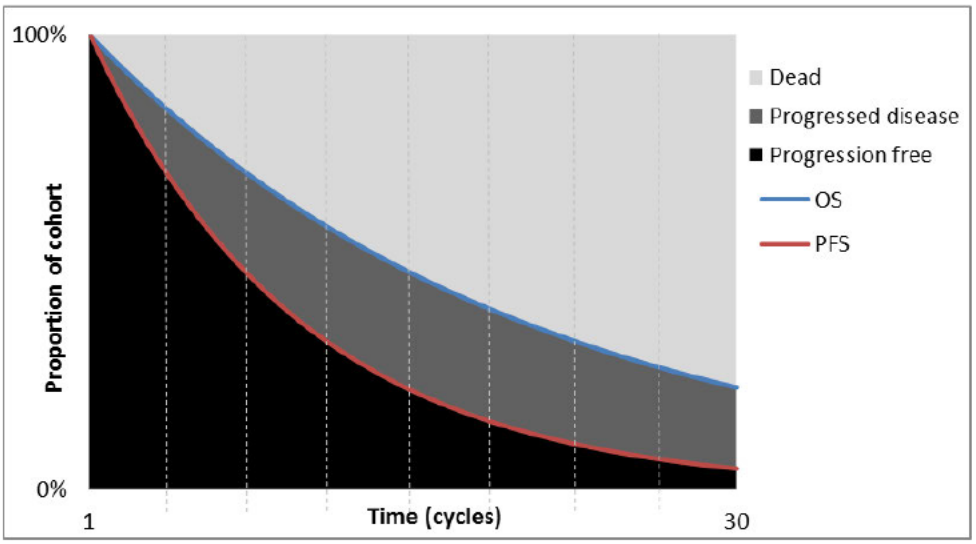
For the health economic analysis, a partitioned survival model (PSM) was chosen. The model consists of three mutually exclusive health states, illustrated in Figure 4:

- Progression-free (PF): Defined as the period before the patient has experienced disease progression
- Progressed disease (PD): Defined as the period where the patient remains alive following disease progression, and they may receive treatment with subsequent anticancer therapy and supportive care
- Dead: An absorbing state into which patients transition upon their death from any cause

The health state membership over time in the PSM is informed by the PFS and OS curves. The proportion of patients alive over time is estimated directly from the OS curve. OS is then partitioned into the PF and PD states using the PFS curve. The proportion of patients occupying the PF state is derived directly from the PFS cumulative survival probability over time, whilst the proportion occupying the PD state over time is calculated from OS minus PFS. The proportion occupying the death state over time is estimated from one minus OS.

As the FLAURA2 trial data did not extend to the modelled time horizon, extrapolation of the OS and PFS Kaplan-Meier (KM) data was necessary to inform health state memberships for the duration of the modelled time horizon.

Figure 4. PSM structure (illustrative)



4.2 Model features

Table 6. Features of the economic model

Model features	Description	Justification
Patient population	Patients with EGFRm NSCLC	Trial population relevant for clinical practice
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	30 years	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at enrolment in the FLAURA2 trial. 99.95% of patients have based after 30 years.
Cycle length	30 days	Consistent with length of treatment cycle
Half-cycle correction	Yes	Implemented for all outcomes and costs, except one-off costs and the cost of osimertinib. Costs of osimertinib were modelled on proportion of patients on treatment at the start of the model cycle to capture cost of unused tablets, if treatment discontinuation occurs before the end of each model cycle

Model features	Description	Justification
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Osimertinib + CTx	Intervention in scope for application
Comparator(s)	Osimertinib	According to national treatment guideline. Validated by Danish clinical expert(14, 26)
Outcomes	PFS, OS & TTD QALY and costs	

5. Overview of literature

No SLR is included in this application. FLAURA2 is a H2H study vs. current standard of care in EGFRm NSCLC. The comparator arm has also been evaluated and recommended by DMC in 2019(24, 26).

5.1 Literature used for the clinical assessment

Table 7. Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC. *N Engl J Med*. 2023;389(21):1935-1948. doi:10.1056/NEJMoa2306434(1) Planchard D, Jänne PA, Kobayashi K, et al. PL02.04 : First-Line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC : FLAURA2 Final Overall Survival. Conference abstract, WCLC 2025, Barcelone – 6-9th September 2025.(30)	FLAURA2	NCT04035486	Ongoing Study start date: 2nd July 2019 Primary DCO: 3rd April 2023 Updated OS DCO: 8th January 2024 Final OS DCO: 12th June 2025 Expected 5-year analysis: Q4, 2026	Osimertinib + CTx vs. osimertinib

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
FLAURA2, primary PFS DCO clinical study report(31)				
FLAURA2 OS update DCO clinical study report (32)				
FLAURA2 Final OS DCO clinical study report(33)				

* If there are several publications connected to a trial, include all publications used.

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

The head-to-head study, FLAURA2, is the sole base for the assessment of health-related quality of life between osimertinib + CTx and osimertinib, and the health state utility values used in the health economic model.

Table 8. 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
FLAURA2, primary PFS DCO clinical study report (31)	EORTC QLQ-C30 EQ-5D-5L + EQ VAS: HSUV for pre-progression and post-progression health state	Section 10

5.3 Literature used for inputs for the health economic model

Table 9. 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
NA	NA	NA	NA

6. Efficacy

6.1 Efficacy of osimertinib in combination with pemetrexed and platinum-based chemotherapy compared to osimertinib for 1st treatment of patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations

6.1.1 Relevant studies

A head-to-head comparison on efficacy and safety between osimertinib + CTx and osimertinib monotherapy as 1L treatment in patients with advanced EGFR mutated NSCLC was conducted in the FLAURA2 trial. The data from the FLAURA2-study will form the basis for an evaluation between osimertinib + CTx compared to the current standard of care, osimertinib monotherapy. A description of the clinical trial will follow in section below.

Table 10. 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 time
FLAURA2 NCT04035486 Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC. *N Engl J Med*. 2023;389(21):1935-1948. doi:10.1056/NEJMoa2306434(1) Planchard D, Jänne PA, Kobayashi K, et al. PL02.04 : First-Line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC : FLAURA2 Final Overall Survival. Conference abstract, WCLC 2025, Barcelone – 6-9th September 2025.(30)	Phase 3, randomised, open-label trial Osimertinib ± platinum + pemetrexed CTx	Ongoing **Study start date:** 2nd July 2019 **Estimated primary completion date:** 3rd April 2023 **Estimated study completion date:** 3rd June 2026	Patients with *EGFR*m locally advanced or metastatic NSCLC Full analysis set (FAS) comprise of all 557 patients randomised for treatment (osi + CTx: n=279; osi mono: n=278) Safety analysis set (SAS) comprise of all patients whom have received at least one dose of study treatment, 551 patients (osi + CTx: n=276; osi mono: n=275)	80 mg Osimertinib and intravenous pemetrexed (500 mg/m² every 3rd week) plus either cisplatin (75 mg/m²) or carboplatin (AUC of 5 mg/ml/min), administered intravenously on day 1 of 21-day cycles for four cycles. This treatment was followed by osimertinib (80 mg once daily) plus pemetrexed maintenance therapy (500 mg per square meter) every 3 weeks.	Osimertinib 80 mg (can be reduced to 40 mg) QD	**Primary:** PFS **Secondary:** OS, Landmark OS, ORR, DoR, DCR, PFS2, PFS by investigator by plasma *EGFR* mutation status

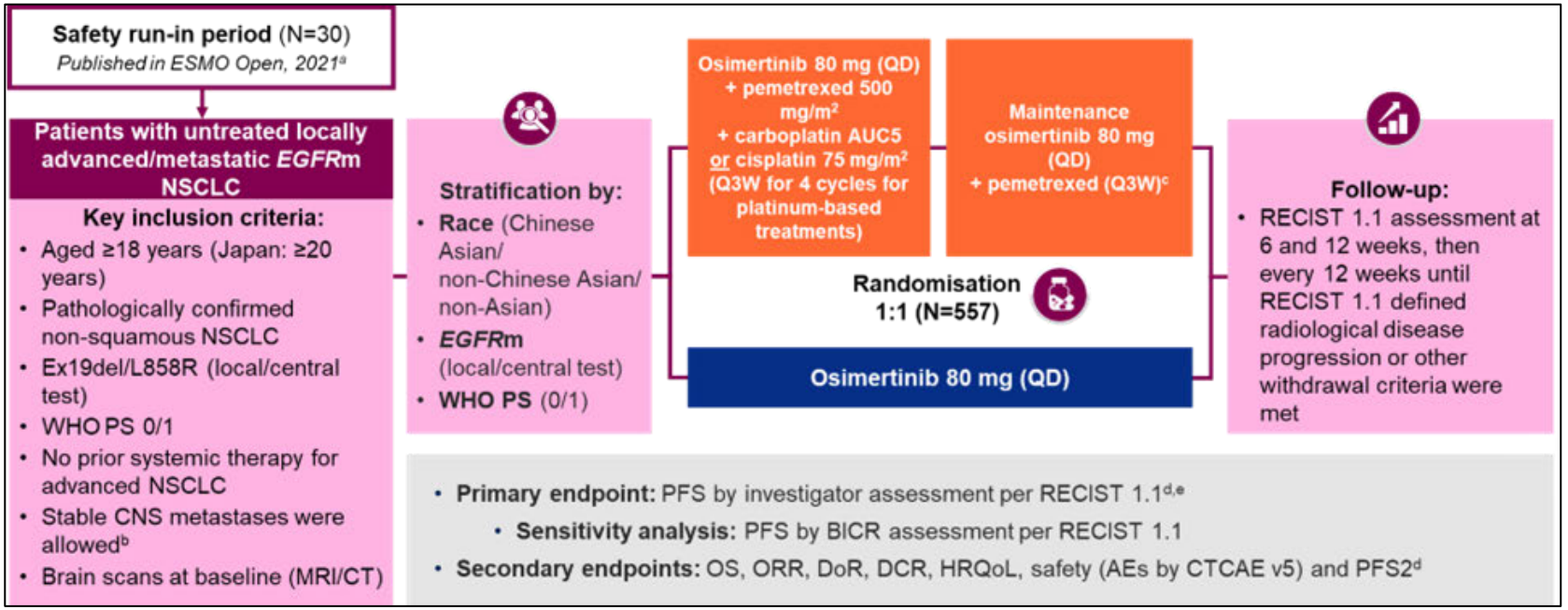
6.1.2 Comparability of studies

The application is based on a H2H study vs. standard of care in Denmark.

6.1.2.1 Comparability of patients across studies FLAURA2

FLAURA2 is a Phase III, open-label, randomised, multi-centre study examining the efficacy and safety of osimertinib + CTx vs osimertinib monotherapy, in the 1L treatment of patients with *EGFR*m locally advanced or metastatic NSCLC (according to the AJCC 8th edition)(31). The study is being conducted and sponsored by AstraZeneca(34). An overview of the trial design is shown in Figure 5. The FLAURA2 study was conducted in two separate phases: the safety run-in and the open-label Phase III randomised period. This application only describes the design and results from the randomised period. Cross-over between study arms was not allowed in FLAURA2.

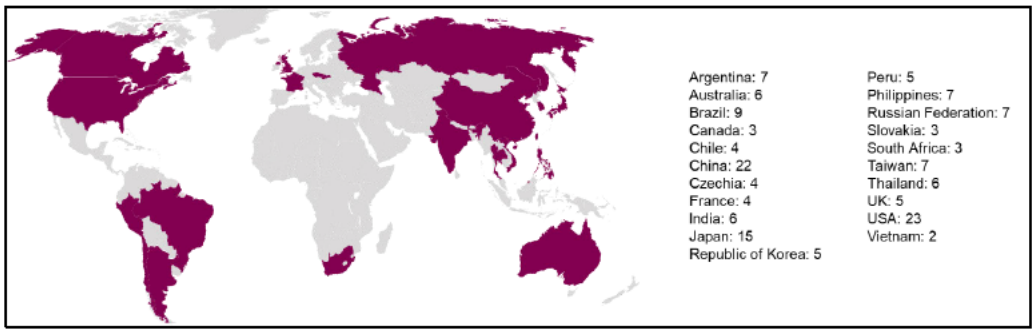
Figure 5. FLAURA2 trial design. The FLAURA2 study was conducted in two separate phases: the safety run-in and the open-label Phase III randomised period.



Footnotes: [a]Published by Planchard et al. ESMO Open (2021)(35). [b]Not requiring steroids for at least two weeks. [c]Pemetrexed maintenance continued until a discontinuation criterion was met. [d]Efficacy analyses in the FAS, defined as all patients randomised to study treatment regardless of the treatment actually received, and safety analyses in the SAS, defined as all randomised patients who received ≥1 dose of study treatment. One patient who was randomised to osimertinib + CTx received only osimertinib and was therefore included in the osimertinib monotherapy SAS. [e]The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level.

Trial enrolment was carried out at 153 trial centres across 21 countries across Europe, Asia-Pacific, North America, South America, and Africa (Figure 6).

Figure 6. Numbers of study centers in participating countries



Footnotes: The number of study centres (n=153) is as reported on ClinicalTrials.gov.
Source: *ClinicalTrials.gov (FLAURA2)*

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

Characteristic	Osimertinib + CTx (n=279)	Osimertinib monotherapy (n=278)
Median age, years (range)[a]	61.0 (26, 83)	61.5 (30, 85)
Sex, n (%)		
Male	106 (38.0)	109 (39.2)
Female	173 (62.0)	169 (60.8)
Race, n (%)		
Asian	179 (64.2)	176 (63.3)
White	74 (26.5)	83 (29.9)
American Indian or Alaska Native	11 (3.9)	6 (2.2)
Black or African	2 (0.7)	3 (1.1)
Other	13 (4.7)	10 (3.6)
Smoking status, n (%)		
Never	188 (67.4)	181 (65.1)
Smoker	91 (32.6)	97 (34.9)
Current	4 (1.4)	4 (1.4)
Former	87 (31.2)	93 (33.5)
WHO PS, n (%)[b]		
0 (Normal activity)	104 (37.3)	102 (36.7)
1 (Restricted activity)	174 (62.4)	176 (63.3)

2 (In bed less than or equal to 50% of the time)[c]	1 (0.4)	0
AJCC stage (8th edition) at initial diagnosis, n (%)		
Stage IIIB	9 (3.2)	4 (1.4)
Stage IIIC	4 (1.4)	3 (1.1)
Stage IVA	98 (35.1)	104 (37.4)
Stage IVB	168 (60.2)	167 (60.1)
Overall extent of disease at study entry, n (%)		
Metastatic[d]	265 (95.0)	271 (97.5)
Locally advanced[e]	14 (5.0)	7 (2.5)
Histology type, n (%)		
Adenocarcinoma[f]	275 (98.6)	275 (98.9)
Adenosquamous carcinoma	2 (0.7)	0
Other	2 (0.7)	3 (1.1)
***EGFR* mutation at randomisation, n (%)[g]**		
Ex19del	169 (61)	168 (60)
L858R mutation	106 (38)	107 (38)
Both Ex19del and L858R mutation	3 (1)	1 (<1)
Unknown	1 (<1)	2 (1)
Number of patients with metastases (by location), n (%)[h]		
CNS	116 (41.6)	110 (39.6)
Liver	43 (15.4)	66 (23.7)
Lung/Pleura	196 (70.3)	216 (77.7)
Lymph nodes	160 (57.3)	170 (61.2)
Bone and locomotive	132 (47.3)	142 (51.1)
Extra-thoracic	147 (52.7)	149 (53.6)
Other	64 (22.9)	58 (20.9)
Baseline tumour size (range), mm[i]		
Median	57 (10, 284)	57 (11, 221)
Time from initial diagnosis to the first dose, months		
N	277	274
Median (range)	1.1 (0, 125)	1.1 (0, 213)
***EGFR* testing method, mutation type**		
Central test	123 (44.1)	117 (42.1)

Ex19del	75 (26.9)	67 (24.1)
Exon 21 L858R	47 (16.8)	49 (17.6)
*EGFR*m unknown/not detected	1 (0.4)	1 (0.4)

Footnotes: [a]Age at study entry. [b]WHO PS is based on CRF data. [c]Patient E2805038 had a WHO PS of 1 at the time of randomisation but prior to study drug administration on C1D1 had a record of WHO PS 2. [d]Patient has any metastatic site of disease. [e]Patient has only locally advanced sites of disease. [f]Represents a combination of the following adenocarcinoma categories: NOS, acinar, papillary, bronchiolo-alevolar, and solid mucous formation. [g]The presence of EGFR mutations were based on central or local testing. [h]This is a programmatically derived composite endpoint with a list of contributing data sources. [i]The baseline tumour size was defined as the sum of the longest diameters of the target lesions.

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

The FLAURA2 trial population is similar to Danish patients with EGFRm NSCLC, with both groups showing a predominance of female patients. While the full Danish EGFRm NSCLC population may be slightly older than those in FLAURA2, the use of FLAURA2 in practice would likely require that patients are younger and/or fitter to be candidates for the combination treatment. As a result, the subset of Danish patients who would receive osimertinib + CTx would closely resemble those enrolled in the trial in terms of age. Clinical expert opinion supports that this alignment makes the FLAURA2 results relevant and transferable, despite minor differences in age within the broader Danish population(14).

Patients in clinical practice were expected to be taller than the patients in FLAURA2, however, given the high proportion of Asian patients in the FLAURA2, this is to be expected.

Despite the differences in patient characteristics, the clinical expert expected the results from FLAURA2 to be transferable to Danish clinical practice(14). As so, the values used in the health economic model has been based on the FLAURA2 trial. A scenario analysis has been conducted to understand the impact of altering these to what would be expected in Danish clinical practice.

Table 12. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)(14, 36)	Value in FLAURA2(31)	Value used in health economic model (31)
Mean age	65-70	60.8	60.8
%-age female	67%	61.4%	61.4%
Patient weight (average)	NA	64.8 kg	64.8 kg
Patient height	174 cm	162.60 cm	162.60 cm

6.1.4 Efficacy – results per FLAURA2

6.1.4.1 Progression-free survival

At the primary PFS analysis (DCO: 3rd April 2023), 286 PFS events (investigator assessed, per RECIST 1.1) had occurred in the full analysis set (FAS) (51.3% overall data maturity), with 120 PFS events (43.0%) reported in the osimertinib + CTx arm, and 166 PFS events (59.7%) reported in the osimertinib monotherapy arm(37).

A statistically significant and clinically meaningful improvement in PFS was demonstrated in the osimertinib + CTx arm compared with the osimertinib monotherapy arm (HR: 0.62; 95% CI: 0.49, 0.79; p<0.0001); this represented a 38% risk reduction in disease progression or death with osimertinib + CTx when compared to osimertinib monotherapy (Table 13) (37).

After a median PFS follow-up in censored patients of 22.2 and 23.7 months in the osimertinib + CTx and osimertinib monotherapy arms, respectively, the median PFS was 25.5 months in the osimertinib + CTx arm, approximately 8.8 months longer than the median PFS in the osimertinib monotherapy arm (16.7 months). As such, the median PFS in the osimertinib + CTx arm was approximately 50% greater than in the osimertinib monotherapy arm(37).

Table 13. Summary of PFS by investigator assessment (FAS; primary PFS analysis) (37)

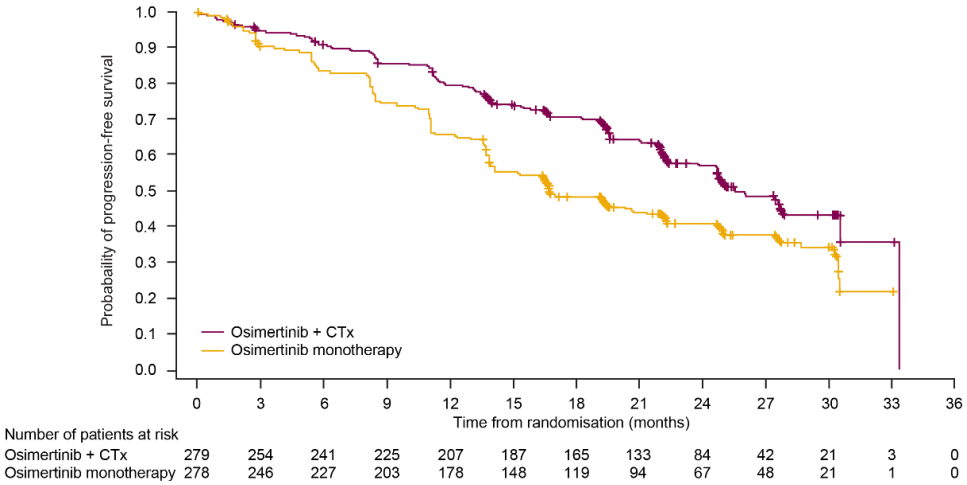
	Osimertinib + CTx (n=279)	Osimertinib monotherapy (n=278)
PFS HR (95% CI; 2-sided p-value)	0.62 (0.49, 0.79; p<0.001)	
Median PFS		
Median PFS, months (95% CI)[a]	25.5 (24.7, NC)	16.7 (14.1, 21.3)
PFS rate at 6 months, % (95% CI)[g]	90.7 (86.6, 93.6)	83.5 (78.6, 87.4)
PFS rate at 12 months, % (95% CI)[g]	79.7 (74.3, 84.1)	65.5 (59.5, 70.8)
PFS rate at 18 months, % (95% CI)[g]	70.6 (64.7, 75.7)	48.5 (42.4, 54.3)
PFS rate at 24 months, % (95% CI)[g]	57.2 (50.4, 63.3)	40.8 (34.7, 46.9)
Median (range) follow-up for PFS in censored patients, months[b]	22.2 (0, 33.1)	23.7 (0, 33.1)

[a]Calculated using the KM method. [b]Calculated as the median, minimum, and maximum time from randomisation to date of progression or date of censoring in all patients.

The Kaplan-Meier (KM) curves were similar until approximately 3 months after randomisation (Figure 3), after which there was clear and sustained separation of the curves that favoured the osimertinib + CTx arm. The delay in the separation of the PFS KM curves is not unexpected, and it corresponded with the planned timing of the second RECIST 1.1 scan at 3 months post randomisation. The clear and sustained separation in PFS was also reflected in the PFS rates at 6 months (90.7% vs 83.5% for the osimertinib + CTx and osimertinib monotherapy arms, respectively), 12 months (79.7% vs 65.5%), 18 months (70.6% vs 48.5%) and 24 months (57.2% vs 40.8%). (1, 31)

Of note, the median PFS observed for the osimertinib monotherapy arm (median PFS 16.7m [95% CI: 14.1, 21.3]) is consistent with the observed median PFS in the original pivotal trial for osimertinib monotherapy, FLAURA, where median PFS was 18.9 months (95% CI: 15.2, 21.4) (31, 38). This consistency indicates that the comparator arm in FLAURA2 serves as a reliable and robust comparator for evaluating the efficacy of osimertinib + CTx.

Figure 7. KM plot of PFS by investigator assessment (FAS; primary PFS analysis)



Footnotes: DCO: 3rd April 2023. **Source:** Planchard et al. 2023. (1)

Given the open-label design of the study, a sensitivity analysis for ascertainment bias was conducted to evaluate PFS by BICR assessment; these data were highly concordant with the investigator-based analysis (HR: 0.62; 95% CI: 0.48, 0.80; nominal p-value=0.0002), and confirmed the robustness of the evaluation(39). Based on BICR assessment, an approximate 9.5-month improvement in median PFS was observed in the osimertinib + CTx arm (29.4 months) compared with the osimertinib monotherapy arm (19.9 months)(1, 39).

6.1.4.2 Overall survival (secondary endpoint)

At the time of the final OS analysis (DCO: 12th June 2025), 315 OS events had occurred in the FAS (overall data maturity 56.6%), with 144 (51.6%) patients having died in the osimertinib + CTx arm, and 171 (61.5%) patients having died in the osimertinib monotherapy arm (Table 14)(30, 33).

The final OS analysis estimated an HR of 0.77 (95% CI: 0.61, 0.96; p=0.0202); Table 14) (30, 33). An improvement of 9.9 months median OS was observed in favour of osimertinib + CTx compared to the osimertinib monotherapy arm(30, 33). Median OS reached 47.5 months (95% CI: 41.0, NC) in the osimertinib + CTx treatment arm and 37.6 months (95% CI: 33.2, 43.2) in the osimertinib monotherapy arm(30, 33).

The increased OS benefit was maintained over time, with the KM curves maintaining separation at all landmarks beyond the crossing point, at approx. month 16.

Data from the final OS analysis demonstrated a statistically significant and a clinically meaningful improvement in OS with osimertinib + CTx compared with osimertinib monotherapy. These data confirm the clear added benefits of treating with osimertinib + CTx compared to current standard of care, osimertinib monotherapy(30, 33).

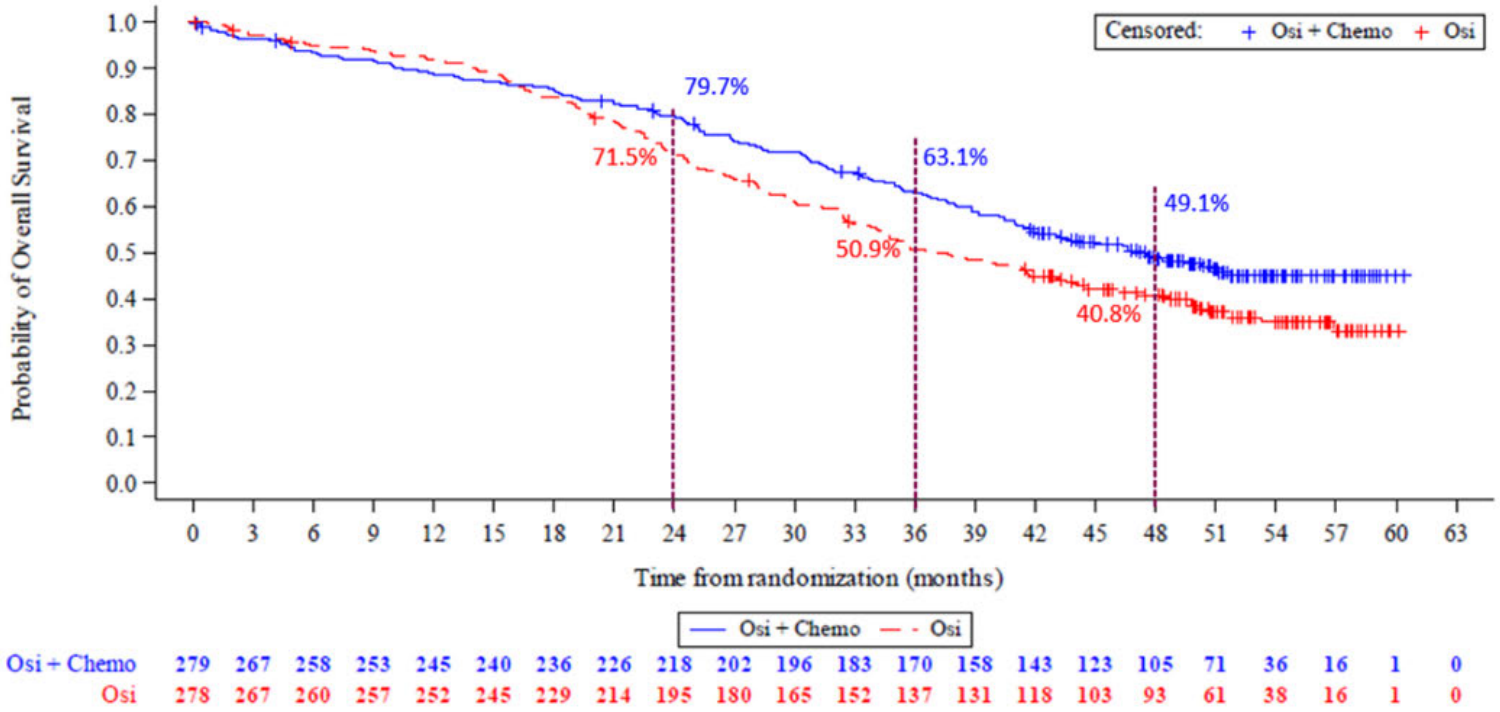
Similar to PFS, the OS of osimertinib monotherapy was investigated in the pivotal trial FLAURA. The OS outcomes observed in FLAURA2 are consistent with those OS outcomes observed in the FLAURA trial. In the FLAURA trial, the OS rate with osimertinib monotherapy was 74% (95% CI: 69%-79%) at 24 months, and 54% (95% CI: 48%-60%) at 36 months. In comparison, in FLAURA2 the OS rate, 71.5% (95% CI: 65.8%-76.5%) at 24 months, and 50.9% (95% CI: 44.8%-56.6%) at 36 months. (30, 33, 38).

Table 14. Summary of OS (FAS; Final OS analysis)

	Osimertinib + CTx (n=279)	Osimertinib monotherapy (n=278)
Total number of deaths, n (%)	144 (51.6)	171 (61.5)
Median OS (months) (95% CI)[a]	47.5 (41.0, NC)	37.6 (33.2, 43.2)
OS at 24 months (%) (95% CI)[a]	79.7 (74.5, 84.0)	71.5 (65.8, 76.5)
OS at 36 months (%) (95% CI)[a]	63.1 (57.1, 68.5)	50.9 (44.8, 56.6)
OS at 48 months (%) (95% CI)[a]	49.1 (43.0, 55.0)	40.8 (34.9, 46.6)
HR (95% CI; p-value)	0.77 (0.61, 0.96); p=0.0202)	
Median (range) follow-up for OS in all patients (months)	42.6 (0.1, 60.4)	35.7 (0.1, 60.1)

Footnotes: DCO: 12th June 2025. [a]Calculated using the KM method. **Source:** (30, 33).

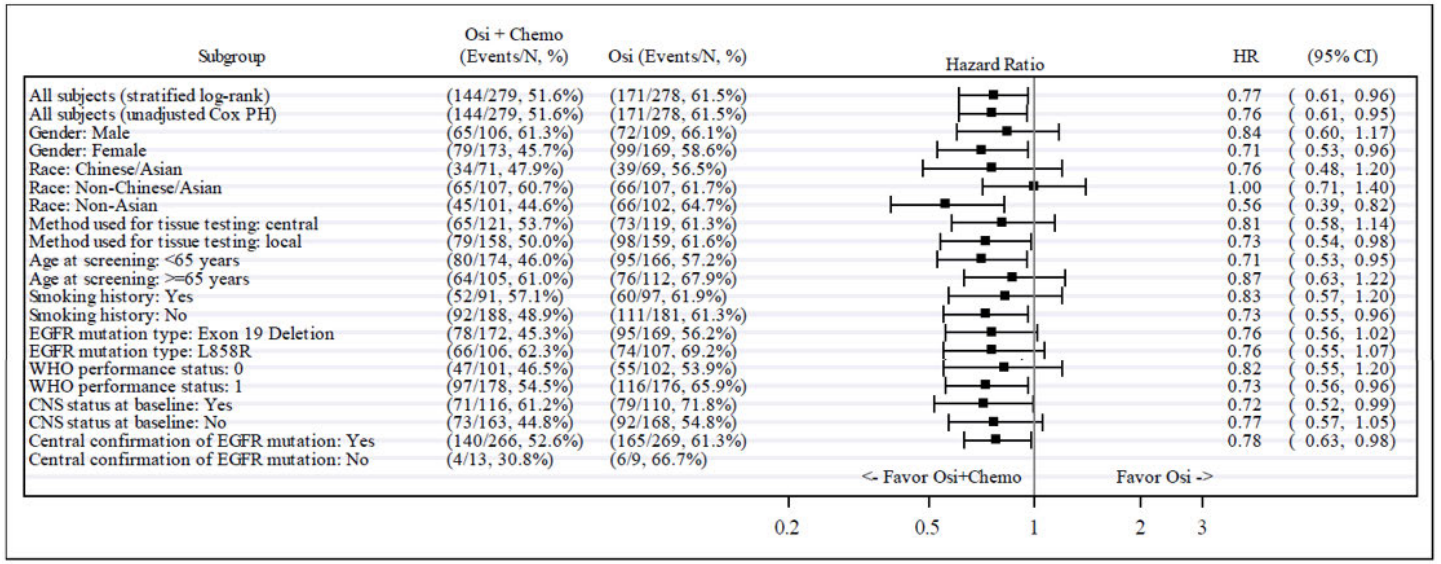
Figure 8. KM plot of OS (FAS; Final OS analysis)



Footnotes: DCO: 12th June 2025. **Source:** (30, 33).

Exploratory subgroup analyses were also performed to evaluate the consistency of treatment effect across stratification factors and subgroups prespecified for the primary PFS analysis. At the final OS analysis, the OS benefit of osimertinib + CTx vs osimertinib monotherapy was consistent across all subgroups pre-defined for the primary PFS analysis, with most point estimates below 1.0 with the expectance of the non-Chinese Asian group (HR: 1.0), although the Non-Asian group seems to benefit the most (HR: 0.56)(Figure 9) (30, 33). With OS being a secondary endpoint in the FLAURA2 trial, the study was not powered for any of the individual subgroup evaluations and no adjustments were made for multiple testing subgroup analyses. As expected in a subgroup analysis, a degree of variability was observed across all subgroups, particularly in the subgroups with a smaller number of patients and fewer OS events observed.

Figure 9. Subgroup analyses of OS (FAS; Final OS analysis)



DCO: 12th June 2025. **Source:** AstraZeneca data-on-file(33).

FLAURA2 demonstrated statistically significant and clinically meaningful improvement in the key secondary endpoint of OS with consistent benefit across most pre-defined subgroups in favour of osimertinib + CTx compared to the SoC, osimertinib monotherapy. This analysis confirms that the osimertinib + CTx regimen is a compelling 1L treatment option for patients with advanced EGFRm NSCLC.

6.1.4.3 CNS PFS by CNS BICR assessment, cEFR analysis set

At baseline, all patients received a brain scan which underwent CNS BICR assessment in order to evaluate the exploratory CNS endpoints. Results from the baseline scans revealed that 222 (39.9%) patients had CNS lesions at study initiation(31). A post-hoc analysis set (CNS evaluable for response set [cEFR]) was also created as a subset of the cFAS. This analysis set included only patients with at least one CNS measurable lesion at baseline.

Patients with measurable (cEFR) CNS lesions at baseline, when treated with osimertinib + CTx, had a 60% reduction in the risk of a CNS PFS event compared to those treated with osimertinib monotherapy (HR: 0.40; 95% CI: 0.19, 0.84; nominal p-value=0.0157), based on a data maturity of 37.2% (Table 15)(31). In the cEFR analysis set at the time of the primary PFS analysis (DCO: 3rd April 2023), median CNS PFS was not reached (95% CI: 23.0, NC) in the osimertinib + CTx arm and was 17.3 months (95% CI: 13.9, NC) in the osimertinib monotherapy arm (Table 15)(31).

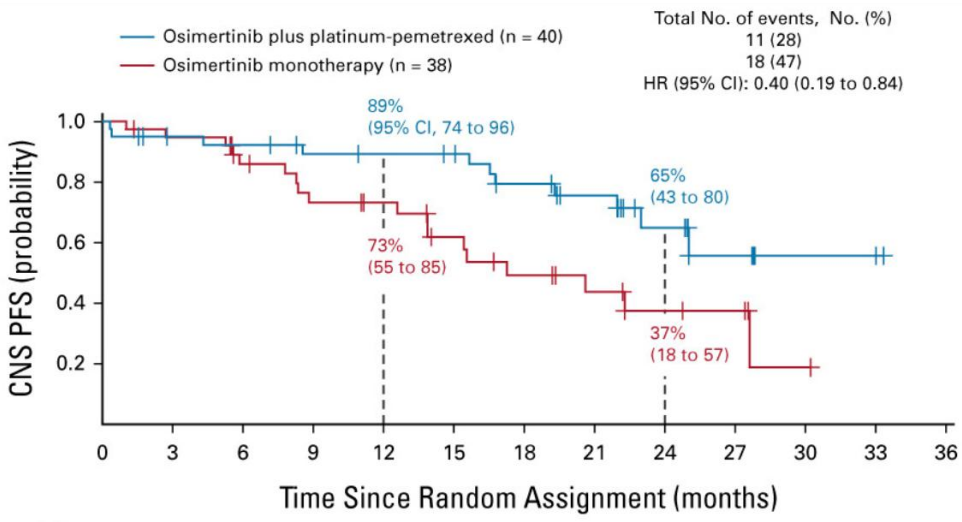
Table 15. CNS PFS by CNS BICR Assessment (cEFR analysis set; primary PFS analysis)

	Osimertinib + CTx (n=40)	Osimertinib monotherapy (n=38)
CNS progression total	11 (27.5)	18 (47.4)
CNS RECIST progression[a]	5 (12.5)	13 (34.2)
CNS target lesions[b]	2 (5.0)	7 (18.4)
CNS non-target lesions[b]	0	3 (7.9)
CNS new lesions	3 (7.5)	6 (15.8)
Death[c]	6 (15.0)	5 (13.2)
No CNS progression total	29 (72.5)	20 (52.6)
Censored death due to missing visits[d]	8 (20.0)	4 (10.5)
CNS progression free at time of analysis[e]	20 (50.0)	14 (36.8)
Withdrawn consent[e]	1 (2.5)	2 (5.3)
Comparison between groups		
Hazard ratio (95% CI; 2-sided p-value)	0.40 (0.19, 0.84; 0.0157)	
Median CNS PFS		

Median CNS PFS (months) (95% CI)[f]	NC (23.0, NC)	17.3 (13.9, NC)
CNS progression-free at 6 months (%) (95% CI)[f]	92.2 (77.7, 97.4)	85.9 (69.3, 93.9)
CNS progression-free at 12 months (%) (95% CI)[f]	89.2 (73.7, 95.8)	73.2 (54.6, 85.1)
CNS progression-free at 18 months (%) (95% CI)[f]	79.3 (61.2, 89.7)	49.1 (29.5, 66.1)
CNS progression-free at 24 months (%) (95% CI)[f]	64.9 (42.5, 80.3)	37.4 (18.2, 56.7)
Median (range) follow-up for CNS PFS in all patients (months)[g]	19.4 (0.4, 33.3)	13.2 (1.1, 30.2)
Median (range) follow-up for CNS PFS in censored patients (months)[h]	22.0 (1.6, 33.3)	14.0 (1.4, 30.2)

Footnotes: DCO: 3rd April 2023. [a]Only includes CNS progression events that occur within two consecutive scheduled visits (plus visit window) of the last evaluable CNS assessment (or randomisation). [b]CNS target lesions, CNS non-target lesions, and CNS new lesions are not necessarily mutually exclusive categories. [c]Death in the absence of CNS progression, within two visits of baseline or last evaluable CNS RECIST assessment. [d]RECIST CNS progression or death occurred more than two consecutive scheduled visits (plus visit window) after previous CNS RECIST assessment or after baseline if no CNS post-baseline assessment. Patients are censored at previous evaluable CNS RECIST assessment or randomisation date. [e]Patients known to be alive and censored at last evaluable CNS RECIST assessment. [f]Calculated using the KM method. [g]Calculated as the median, minimum, and maximum time from randomisation to date of CNS progression or date of censoring in all patients. [h]Calculated as the median, minimum, and maximum time from randomisation to date of censoring (date last known to have not progressed) in censored (not CNS progressed) patients only.

Table 16. KM plot of CNS PFS by CNS BICR Assessment (cEFR analysis set; primary PFS analysis)



6.1.5 Efficacy – results per [study name 2]

NA

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

NA

7.1.2 Method of synthesis

NA

7.1.3 Results from the comparative analysis

Table 17. Results from the comparative analysis of osimertinib + CTx vs. osimertinib

Outcome measure	Osimertinib+ CTx (N=279)	Osimertinib (N=278)	Result
PFS events, (DCO April 3rd 2023)	120 (43.0%)	166 (59.7%)	
Median PFS (DCO April 3rd 2023)	25.5 (24.7, NC)	16.7 (14.1, 21.3)	HR= 0.62 (0.49, 0.79) p<0.001
OS events (DCO Jun 12h 2025)	144 (51.6%)	171 (61.5%)	
Median OS (DCO Jun 12th 2025)	47.5 (41.0, NC)	37.6 (33.2, 43.2)	HR=0.77 (0.61, 0.96) p=0.0202
CNS PFS events, cEFR subset (DCO April 3rd, 2023)*	11 (27.5)	18 (47.4)	
Median CNS PFS, cEFR subset (DCO April 3rd 2023)*	NC (23.0, NC)	17.3m (13.9, NC)	HR= 0.40 (0.19, 0.84) p= 0.0157

*at least one CNS measurable lesion at baseline

7.1.4 Efficacy – results per [outcome measure]

NA

8. Modelling of efficacy in the health economic analysis

If a cost-minimization analysis is performed, there may be parts of this section that are not relevant to complete. Please write 'Not applicable' in this case.

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

In order to model long-term survival for PFS, OS and TTD, individual patient time-to-event data from FLAURA2 were used to generate KM plots for each outcome. The level of maturity of the data meant that extrapolation of the KM to the model time horizon was necessary. The general principles underlining the survival analysis of PFS, OS and TTD followed the approach outlined in the Technical Support Document 14 for survival analysis published by NICE DSU(40).

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of progression-free survival (PFS)

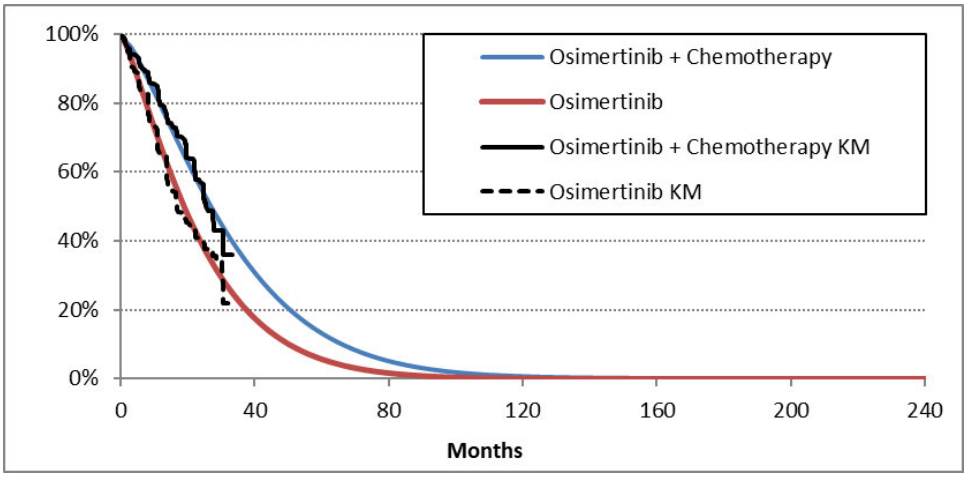
A summary of the assumptions associated with the extrapolation of PFS is provided in Table 18 for both arms in the health economic analysis. The base case extrapolation of PFS is visualized in Figure 10. Please refer to Appendix D.1 for further information on the extrapolation of PFS.

Table 18. Summary of assumptions associated with extrapolation of progression-free survival (PFS)

Method/approach	Description/assumption
Data input	FLAURA2(31)
Model	- Exponential - Weibull - Gompertz - Log-logistic - Log-normal - Gen Gamma - Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Osimertinib + CTx: Gompertz Osimertinib mono: Log-logistic
Function with best BIC fit	Osimertinib + CTx: Gompertz Osimertinib mono: Log-logistic

Function with best visual fit	Osimertinib + CTx: Weibull Osimertinib mono: Weibull or gamma
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	Osimertinib + CTx: N/A Osimertinib mono: Weibull, Gamma, Gompertz
Selected parametric function in base case analysis	Osimertinib + CTx: Weibull Osimertinib mono: Weibull
Adjustment of background mortality with data from Statistics Denmark	No, PFS capped by OS data, which is adjusted to background mortality
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 10. Base case extrapolations of PFS with observed data from FLAURA2 across entire time horizon



8.1.1.2 Extrapolation of overall survival (OS)

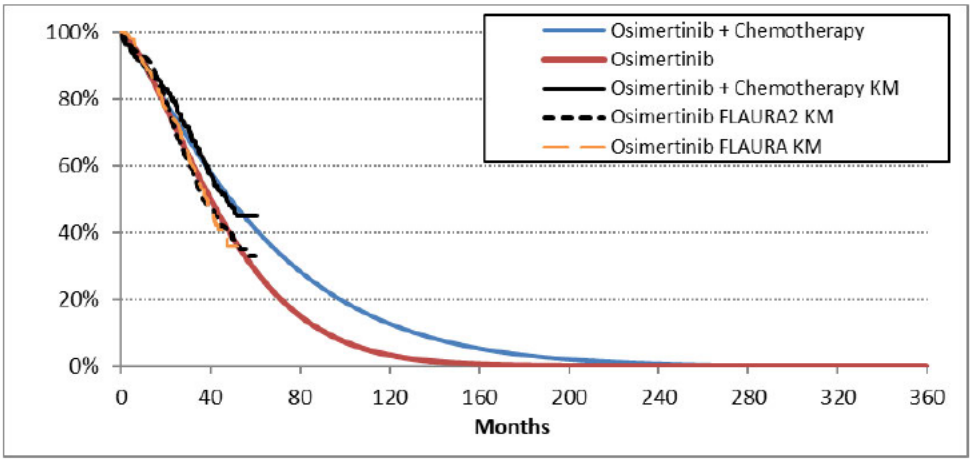
A summary of the assumptions associated with the extrapolation of OS is provided in Table 19 for both arms in the health economic analysis. The base case extrapolation of

OS is visualized in Figure 11. Please refer to Appendix D.2 for further information on the extrapolation of OS.

Table 19. Summary of assumptions associated with extrapolation of overall survival (OS)

Method/approach	Description/assumption
Data input	FLAURA2(31)
Model	- Standard parametric functions
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Osimertinib + CTx: Gompertz Osimertinib mono: Log-logistic
Function with best BIC fit	Osimertinib + CTx: Gompertz Osimertinib mono: Log-logistic
Function with best visual fit	Osimertinib + CTx: Weibull Osimertinib mono: Weibull
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	FLAURA trial on osimertinib mono arm Annual report from Danish lung cancer registry
Function with the best fit according to external evidence	Osimertinib + CTx: N/A Osimertinib mono: Weibull or gamma
Selected parametric function in base case analysis	Osimertinib + CTx: Weibull Osimertinib mono: Weibull
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

Figure 11. Base case extrapolations of OS with observed data from FLAURA2 across entire time horizon



8.1.1.3 Extrapolation of time to treatment discontinuation

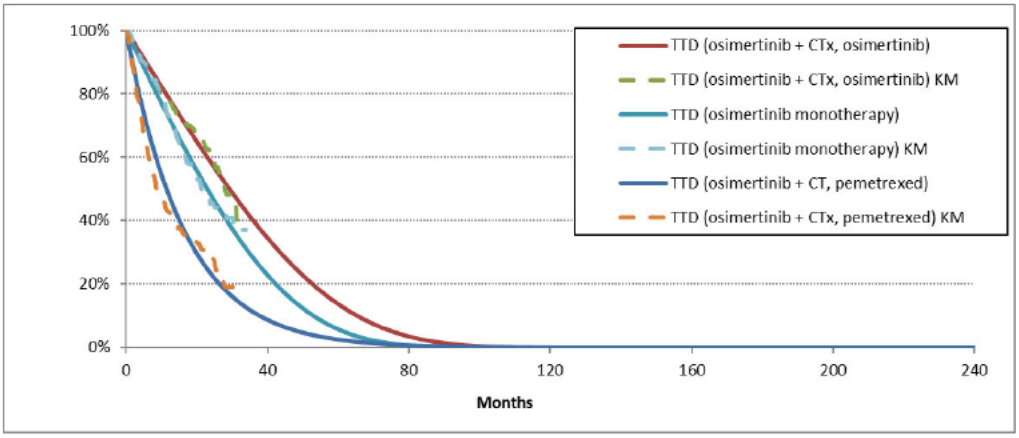
A summary of the assumptions associated with the extrapolation of TTD is provided in Table 20 for both osimertinib arms and the pemetrexed arm in the health economic analysis. The base case extrapolation of TTD is visualized in Figure 12Figure 10. Please refer to Appendix D.3 for further information on the extrapolation of TTD.

Table 20. Summary of assumptions associated with extrapolation of time to treatment discontinuation

Method/approach	Description/assumption
Data input	FLAURA2(31)
Model	- Standard parametric functions
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Osimertinib + CTx (osimertinib): Gompertz Osimertinib + CTx (pemetrexed): Log-normal Osimertinib mono: Log-logistic
Function with best BIC fit	Osimertinib + CTx (osimertinib): Exponential Osimertinib + CTx (pemetrexed): Log-normal Osimertinib mono: Log-logistic
Function with best visual fit	Osimertinib + CTx (osimertinib): Gompertz Osimertinib + CTx (pemetrexed): Exponential Osimertinib mono: Gompertz
Function with best fit according to evaluation of smoothed hazard assumptions	N/A

Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	FLAURA trial on osimertinib mono arm
Function with the best fit according to external evidence	Osimertinib + CTx: NA Osimertinib mono: Gompertz
Selected parametric function in base case analysis	Osimertinib + CTx: Gompertz Osimertinib mono: Gompertz
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

Figure 12. Base case extrapolations of TTD with observed data from FLAURA2 across entire time horizon (unbounded by PFS and OS)



8.1.2 Calculation of transition probabilities

Not applicable for chosen model approach.

Table 21. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable, no external efficacy data applied beyond FLAURA2 trial data.

8.3 Modelling effects of subsequent treatments

Not applicable, no external efficacy data applied beyond FLAURA2 trial data.

8.4 Other assumptions regarding efficacy in the model

Not applicable, no external efficacy data applied beyond FLAURA2 trial data.

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

An overview of modelled average treatment length and time in model health states is shown in Table 22. Estimates that are undiscounted and not adjusted for half cycle correction are shown in Table 23.

Table 22. Estimates in the model (undiscounted, no half-cycle correction, OS adjusted for background mortality)

	Modelled average	Modelled median	Observed median from relevant study
PFS			
Osimertinib + CTx	32.52 months ='Surv_calcs (PSM + TTD)'!BX10	25.63 months ='Surv_calcs (PSM + TTD)'!BX9	25.5 months FLAURA2 DCO April 3rd 2023
Osimertinib	23.93 months ='Surv_calcs (PSM + TTD)'!CE10	17.74 months ='Surv_calcs (PSM + TTD)'!CE9	16.7 months FLAURA2 DCO April 3rd 2023
OS			
Osimertinib + CTx	61.78 months ='Surv_calcs (PSM + TTD)'!BZ10	47.31 months ='Surv_calcs (PSM + TTD)'!BZ9	47.5 months FLAURA2 DCO June 12th 2025
Osimertinib	46.63 months ='Surv_calcs (PSM + TTD)'!CG10	39.43 months ='Surv_calcs (PSM + TTD)'!CG9	37.6 months FLAURA2 DCO June 12th 2025

Table 23. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length	Progression-free	Post-progression
Osimertinib + CTx	Osimertinib: 33.38 months Pemetrexed: 16.95 months	33.00 months	29.68 months
Osimertinib	Osimertinib: 26.76 months	24.28 months	23.03 months

9. Safety

Safety outcomes from the FLAURA2 comparing Osimertinib + CTx with osimertinib monotherapy will be presented in the following sections.

9.1 Safety data from the clinical documentation

Overall, the AEs observed in both treatment arms were consistent with the known safety profiles of the individual study treatments (Table 16). In summary, at the time of the final OS analysis (DCO: 12th June 2025):(31, 39)

- The proportion of patients with any AE causally related to the administered treatment was higher in the osimertinib + CTx arm (97.5%) compared with the osimertinib monotherapy arm (88.0%).(33)
- The overall proportion of patients with CTCAE ≥Grade 3 AEs, AEs leading to dose modifications, SAEs, and AEs leading to discontinuation of any study drug were higher in the osimertinib + CTx arm compared to the osimertinib monotherapy arm. These were primarily driven by expected chemotherapy-related toxicities such as haematologic toxic effects, gastrointestinal AEs and nausea.
- In both treatment arms, the proportion of patients who had an AE which ultimately led to death were low (8.0% in the osimertinib + CTx arm and 3.6% in the osimertinib monotherapy arm).

AE onset, frequency and severity were highest during the induction period, and gradually reduced over time. In the osimertinib + CTx arm, the onset of Grade ≥3 AEs reduced by approximately 50% between 0–3 months (n=135; 49%) and 3–9 months (n=62; 24%).(31, 39)

Table 24. Overview of safety events. (Safety analysis set) DCO: 12th June 2025(33)

	Osimerinib + CTx (N=276) (FLAURA2)	Osimertinib (N=275) (FLAURA2)	Difference, % (95 % CI)
Number of adverse events, n	6,702	3,153	NC

	Osimerinib + CTx (N=276) (FLAURA2)	Osimertinib (N=275) (FLAURA2)	Difference, % (95 % CI)
Number and proportion of patients with ≥1 adverse events, n (%)	276/276 (100.0%)	269/275 (97.8%)	2.2% (0.5%;3.9%)
Number of serious adverse events*, n	221	116	NC
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	126/276 (45.7%)	75/275 (27.3%)	18.4% (10.5%;26.3%)
Number of CTCAE grade ≥ 3 events, n	573	167	NC
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	193/276 (69.9%)	94/275 (34.2%)	35.7% (28.0%;43.5%)
Number of adverse reactions, n	NA	NA	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NA	NA	NA
Number and proportion of patients with ≥ 1 adverse event causally related to treatment, n (%)	269/276 (97.5%)	242/275 (88.0%)	9.5% (5.2%;13.7%)
Number and proportion of patients who had a dose reduction, n (%)	95/276 (34.4%)	11/275 (4.0%)	30.4% (24.4%;36.5%)
- Leading to osimertinib dose reduction	28/276 (10.1%)	11/275 (4.0%)	6.1% (1.9%;10.4%)
- Leading to chemotherapy dose reduction	78/276 (28.3%)	NA	NC
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	200/276 (72.5%)	226/275 (82.2%)	-9.7% (-16.7%;-2.8%)

	Osimerinib + CTx (N=276) (FLAURA2)	Osimertinib (N=275) (FLAURA2)	Difference, % (95 % CI)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	150/276 (54.3%)	20/275 (7.3%)	47.1% (40.4%;53.7%)
- Leading to osimertinib discontinuation	34/276 (12.3%)	20/275 (7.3%)	5.0% (0.1%;10.0%)
- Leading to any chemotherapy discontinuation#	143/276 (51.8%)	NA	NC
- **Leading to carbo- or cisplatin discontinuation**	46/276 (16.7%)	NA	NC
- **Leading to pemetrexed discontinuation**	137/276 (49.6%)	NA	NC

* 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).
Abbreviations: NA, not available; NC, not calculatable
§ CTCAE v. 5.0 must be used if available.

No SAEs occurred with a frequency of ≥5% in either treatment arm during the follow-up period. A list of all SAEs observed in the full safety analysis set in the FLAURA2 trial is available in Appendix E.

Table 25. Serious adverse events ≥5% in FLAURA2, DCO: 12th June 2025. (33)

Adverse events	Osimerinib + CTx (N=276) (FLAURA2)		Osimertinib (N=275) (FLAURA2)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	NA	NA	NA	NA

For the health economic model, AEs were included in the model to account for the potential cost and HRQoL burden of experiencing AEs whilst on treatment. The incidence rates are reported in Table 26. The inclusion criterion applied was all AEs of CTCAE grade ≥3 occurring in ≥2% of patients in any treatment arm. Only grade ≥3 events were included in the model.

Table 26. Adverse events used in the health economic model. Grade ≥3 by preferred term (≥2% patients in either treatment arm; safety analysis set; primary PFS analysis. DCO: 12 Jun 2025. (33)

Adverse events	Osimertinib plus CTx (N = 276)	Osimertinib monotherapy (N = 275)		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				
Anaemia	56 (20.3%)	4 (1.5%)	FLAURA2 clinical trial report at DCO 12 June 2025(33)	Grade ≥3 by preferred term (≥2% patients in either treatment arm)
Neutropenia	37 (13.4%)	4 (0.7%)		
Neutrophil count decreased	32 (11.6%)	2 (0.7%)		
Platelet count decreased	21 (7.6%)	0		
Thrombocytopenia	19 (6.9%)	3 (1.1%)		
Febrile neutropenia	12 (4.3%)	0		
Ejection fraction decreased	10 (3.6%)	6 (2.2%)		
White blood cell count decreased	9 (3.3%)	1 (0.4%)		
Decreased appetite	9 (3.3%)	3 (1.1%)		
Diarrhoea	9 (3.3%)	1 (0.4%)		
Fatigue	8 (2.9%)	1 (0.4%)		
Leukopenia	8 (2.9%)	0		
Pneumonia	8 (2.9%)	11 (4.0%)		
Pulmonary embolism	7 (2.5%)	3 (1.1%)		

Footnote: 12 June 2025 DCO. *COVID-19 related pneumonia was excluded from the model, despite meeting this criteria, as the study took place during the COVID-19 pandemic (first patient was randomised 15th March 2020), during the period in which pre/post exposure prophylaxis was not widely available and therapeutic options were limited. The incidence of COVID-19 AEs was therefore assumed to be an artefact of the timing of the study and therefore not relevant for inclusion in the model, which aims to reflect anticipated clinical practice.

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

N/A.

Table 27. 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	NA	NA	NA	NA	NA	NA	NA	NA

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

An assessment of EORTC QLQ-C30 and EQ-VAS data from FLAURA2 is conducted to analyze the HRQoL impact of the addition of CTx to the well-tolerated safety profile of osimertinib monotherapy. EQ-5D-5L data from FLAURA2 has been mapped to HSUVs with the Danish tariff set for the health economic model.

Table 28. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	FLAURA2	Comparison of clinical efficacy and safety
EQ-5D-5L + EQ-VAS	FLAURA2	Comparison of clinical efficacy and safety Health state utilities in HE model

10.1 Presentation of the health-related quality of life EORTC QLQ-C30

10.1.1 Study design and measuring instrument

In FLAURA2, patient reported outcomes were assessed as secondary endpoints using the EORTC QLQ-C30 questionnaire. PRO data was collected from randomization until second progression. Collection of PRO data conducted using a PRO handheld device, and the baseline ePRO should have been completed by the patients prior to dosing, whereafter ePROs would be completed by the patients at home. Data was collected on day 1, day 22 and day 43 (+/- 1 days), whereafter day 64, collection happened every 6 weeks (+/- 3 days).

Changes in score compared to baseline were evaluated. A clinically meaningful change was defined as change ≥10 points from baseline. Patients with no baseline data or no post-baseline PRO assessment will be excluded from the change from baseline analysis.

10.1.2 Data collection

The overall compliance rates for completion of the EORTC QLQ-C30 questionnaire was high in both treatment arms at baseline (>91%) and remained high (≥80%) to Week 82.

Table 29. Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	Osi + Chemo, N=279	21 (7.5%)	279	258 (92.5%)
	Osi, N=278	22 (7.9%)	278	256 (92.1%)
Week 4	Osi + Chemo, N=279	38 (13.6%)	279	241 (86.4%)
	Osi, N=278	26 (9.4%)	277	252 (91.0%)
Week 7	Osi + Chemo, N=279	49 (17.6%)	271	230 (84.9%)
	Osi, N=278	30 (10.8%)	273	248 (90.8%)
Week 10	Osi + Chemo, N=279	40 (14.3%)	268	239 (89.2%)
	Osi, N=278	30 (10.8%)	265	248 (93.6%)
Week 16	Osi + Chemo, N=279	53 (19.0%)	262	226 (86.3%)
	Osi, N=278	51 (18.3%)	252	227 (90.1%)
Week 22	Osi + Chemo, N=279	53 (19.0%)	260	226 (86.9%)
	Osi, N=278	62 (22.3%)	246	216 (87.8%)
Week 28	Osi + Chemo, N=279	71 (25.4%)	253	208 (82.2%)
	Osi, N=278	79 (28.4%)	235	199 (84.7%)
Week 34	Osi + Chemo, N=279	74 (26.5%)	247	205 (83.0%)
	Osi, N=278	85 (30.6%)	228	193 (84.6%)

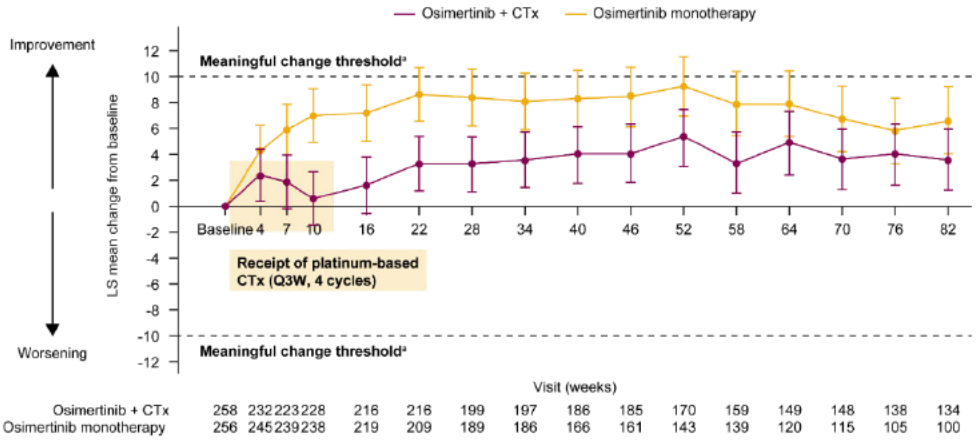
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 40	Osi + Chemo, N=279	84 (30.1%)	242	195 (80.6%)
	Osi, N=278	102 (36.7%)	213	176 (82.6%)
Week 46	Osi + Chemo, N=279	85 (30.5%)	235	194 (82.6%)
	Osi, N=278	109 (39.2%)	202	169 (83.7%)
Week 52	Osi + Chemo, N=279	99 (35.5%)	230	180 (78.3%)
	Osi, N=278	128 (46.0%)	192	150 (78.1%)
Week 58	Osi + Chemo, N=279	111 (39.8%)	217	168 (77.4%)
	Osi, N=278	134 (48.2%)	178	144 (80.9%)
Week 64	Osi + Chemo, N=279	123 (44.1%)	204	156 (76.5%)
	Osi, N=278	153 (55.0%)	162	125 (77.2%)
Week 70	Osi + Chemo, N=279	122 (43.7%)	199	157 (78.9%)
	Osi, N=278	158 (56.8%)	151	120 (79.5%)
Week 76	Osi + Chemo, N=279	135 (48.4%)	185	144 (77.8%)
	Osi, N=278	167 (60.1%)	140	111 (79.3%)
Week 82	Osi + Chemo, N=279	139 (49.8%)	175	140 (80.0%)
	Osi, N=278	172 (61.9%)	127	106 (83.5%)
Week 88	Osi + Chemo, N=279	156 (55.9%)	162	123 (75.9%)
	Osi, N=278	189 (68.0%)	116	89 (76.7%)
Week 94	Osi + Chemo, N=279	165 (59.1%)	149	114 (76.5%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Osi, N=278	194 (69.8%)	107	84 (78.5%)
Week 100	Osi + Chemo, N=279	188 (67.4%)	128	91 (71.1%)
	Osi, N=278	213 (76.6%)	94	65 (69.1%)
Week 106	Osi + Chemo, N=279	201 (72.0%)	112	78 (69.6%)
	Osi, N=278	218 (78.4%)	80	60 (75.0%)
Week 112	Osi + Chemo, N=279	223 (79.9%)	81	56 (69.1%)
	Osi, N=278	228 (82.0%)	65	50 (76.9%)
Week 118	Osi + Chemo, N=279	234 (83.9%)	59	45 (76.3%)
	Osi, N=278	235 (84.5%)	55	43 (78.2%)
Week 124	Osi + Chemo, N=279	258 (92.5%)	42	21 (50.0%)
	Osi, N=278	246 (88.5%)	49	32 (65.3%)
Week 130	Osi + Chemo, N=279	265 (95.0%)	27	14 (51.9%)
	Osi, N=278	258 (92.8%)	31	20 (64.5%)
Week 136	Osi + Chemo, N=279	267 (95.7%)	20	12 (60.0%)
	Osi, N=278	266 (95.7%)	18	12 (66.7%)
Week 142	Osi + Chemo, N=279	273 (97.8%)	13	6 (46.2%)
	Osi, N=278	275 (98.9%)	7	3 (42.9%)
Week 148	Osi + Chemo, N=279	278 (99.6%)	3	1 (33.3%)
	Osi, N=278	278 (100.0%)	2	0 (0.0%)

10.1.3 HRQoL results

Overall, a non-clinically meaningful improvement in GHS/QoL was observed in both treatment arms, indicating that the clinically significant efficacy benefit observed with the addition of CTx to osimertinib treatment was achieved with no clinically meaningful deterioration in GHS/QoL.

Figure 13. Change from baseline of EORTC QLQ-C30, primary subscale scores for Global health status/QoL (MMRM model), DCO 3rd April 2023.



Note: Figure presents change from baseline the LS means ±95% CI. The values at the base of the figure indicate number of subjects included in the analysis at each visit. A clinically meaningful change was defined as a change of ≥10 points from baseline. The overall improvement in both arms was not clinically significant. [a]Based on the FLAURA2 Clinical Trial Protocol.

Table 30. Summary of Change From Baseline in Primary PRO Domains and Symptoms, MMRM (Randomised Period – FAS) DCO 3rd April 2023(31).

Primary PRO scales	Treatment arm	N	Average LS mean [a] (95% CI)	Average difference in change from baseline in LS means (95% CI)
Scale (EORTC QLQ-C30 questionnaire)				
Global health status / QoL	Osi + Chemo	253	3.32 (1.67, 4.98)	-4.06 (-6.42, -1.69)
	Osimertinib	253	7.38 (5.70, 9.07)	
Physical function	Osi + Chemo	253	2.37 (0.70, 4.04)	-4.37 (-6.75, -1.99)
	Osimertinib	253	6.74 (5.04, 8.43)	
Fatigue	Osi + Chemo	253	-0.03 (-1.91, 1.84)	6.28 (3.60, 8.96)
	Osimertinib	253	-6.31 (-8.22, -4.40)	
Appetite loss	Osi + Chemo	253	2.87 (0.82, 4.92)	7.45 (4.52, 10.38)
	Osimertinib	253	-4.58 (-6.67, -2.48)	

10.2 Presentation of the health-related quality of life EQ-5D-5L & VAS

10.2.1 Study design and measuring instrument

The EuroQoL 5 Dimensions 5 levels (EQ-5D-5L) and EuroQoL visual analogue scale (EQ-VAS) measurements were also collected in FLAURA2 at the same time points as EORTC QLQ-C30.

10.2.2 Data collection

The overall compliance rate for EQ-5D-5L was high and consistent between treatment arms. As anticipated, the number of expected and received questionnaires decreased over time, but compliance in both arms remained ≥ 80% up to 46 weeks, and ≥ 75% up to 94 weeks. Post-disease progression, compliance was lower but broadly consistent between the treatment arms up to 40 weeks post-progression.

Table 31. Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	Osi + Chemo, N=279	28 (10.0%)	279	251 (90.0%)
	Osi, N=278	26 (9.4%)	278	252 (90.6%)
Week 4	Osi + Chemo, N=279	46 (16.5%)	279	233 (83.5%)
	Osi, N=278	30 (10.8%)	277	248 (89.5%)
Week 7	Osi + Chemo, N=279	50 (17.9%)	271	229 (84.5%)
	Osi, N=278	32 (11.5%)	273	246 (90.1%)
Week 10	Osi + Chemo, N=279	41 (14.7%)	268	238 (88.8%)
	Osi, N=278	32 (11.5%)	265	246 (92.8%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 16	Osi + Chemo, N=279	54 (19.4%)	262	225 (85.9%)
	Osi, N=278	51 (18.3%)	252	227 (90.1%)
Week 22	Osi + Chemo, N=279	53 (19.0%)	260	226 (86.9%)
	Osi, N=278	62 (22.3%)	246	216 (87.8%)
Week 28	Osi + Chemo, N=279	72 (25.8%)	253	207 (81.8%)
	Osi, N=278	81 (29.1%)	235	197 (83.8%)
Week 34	Osi + Chemo, N=279	74 (26.5%)	247	205 (83.0%)
	Osi, N=278	85 (30.6%)	228	193 (84.6%)
Week 40	Osi + Chemo, N=279	85 (30.5%)	242	194 (80.2%)
	Osi, N=278	102 (36.7%)	213	176 (82.6%)
Week 46	Osi + Chemo, N=279	85 (30.5%)	235	194 (82.6%)
	Osi, N=278	109 (39.2%)	202	169 (83.7%)
Week 52	Osi + Chemo, N=279	99 (35.5%)	230	180 (78.3%)
	Osi, N=278	128 (46.0%)	192	150 (78.1%)
Week 58	Osi + Chemo, N=279	112 (40.1%)	217	167 (77.0%)
	Osi, N=278	134 (48.2%)	178	144 (80.9%)
Week 64	Osi + Chemo, N=279	123 (44.1%)	204	156 (76.5%)
	Osi, N=278	153 (55.0%)	162	125 (77.2%)
Week 70	Osi + Chemo, N=279	123 (44.1%)	199	156 (78.4%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Osi, N=278	158 (56.8%)	151	120 (79.5%)
Week 76	Osi + Chemo, N=279	135 (48.4%)	185	144 (77.8%)
	Osi, N=278	167 (60.1%)	140	111 (79.3%)
Week 82	Osi + Chemo, N=279	140 (50.2%)	175	139 (79.4%)
	Osi, N=278	172 (61.9%)	127	106 (83.5%)
Week 88	Osi + Chemo, N=279	157 (56.3%)	162	122 (75.3%)
	Osi, N=278	189 (68.0%)	116	89 (76.7%)
Week 94	Osi + Chemo, N=279	165 (59.1%)	149	114 (76.5%)
	Osi, N=278	194 (69.8%)	107	84 (78.5%)
Week 100	Osi + Chemo, N=279	189 (67.7%)	128	90 (70.3%)
	Osi, N=278	213 (76.6%)	94	65 (69.1%)
Week 106	Osi + Chemo, N=279	201 (72.0%)	112	78 (69.6%)
	Osi, N=278	218 (78.4%)	80	60 (75.0%)
Week 112	Osi + Chemo, N=279	223 (79.9%)	81	56 (69.1%)
	Osi, N=278	228 (82.0%)	65	50 (76.9%)
Week 118	Osi + Chemo, N=279	234 (83.9%)	59	45 (76.3%)
	Osi, N=278	235 (84.5%)	55	43 (78.2%)
Week 124	Osi + Chemo, N=279	258 (92.5%)	42	21 (50.0%)
	Osi, N=278	246 (88.5%)	49	32 (65.3%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 130	Osi + Chemo, N=279	265 (95.0%)	27	14 (51.9%)
	Osi, N=278	258 (92.8%)	31	20 (64.5%)
Week 136	Osi + Chemo, N=279	267 (95.7%)	20	12 (60.0%)
	Osi, N=278	267 (96.0%)	18	11 (61.1%)
Week 142	Osi + Chemo, N=279	273 (97.8%)	13	6 (46.2%)
	Osi, N=278	275 (98.9%)	7	3 (42.9%)
Week 148	Osi + Chemo, N=279	278 (99.6%)	3	1 (33.3%)
	Osi, N=278	278 (100.0%)	2	0 (0.0%)

10.2.3 HRQoL results

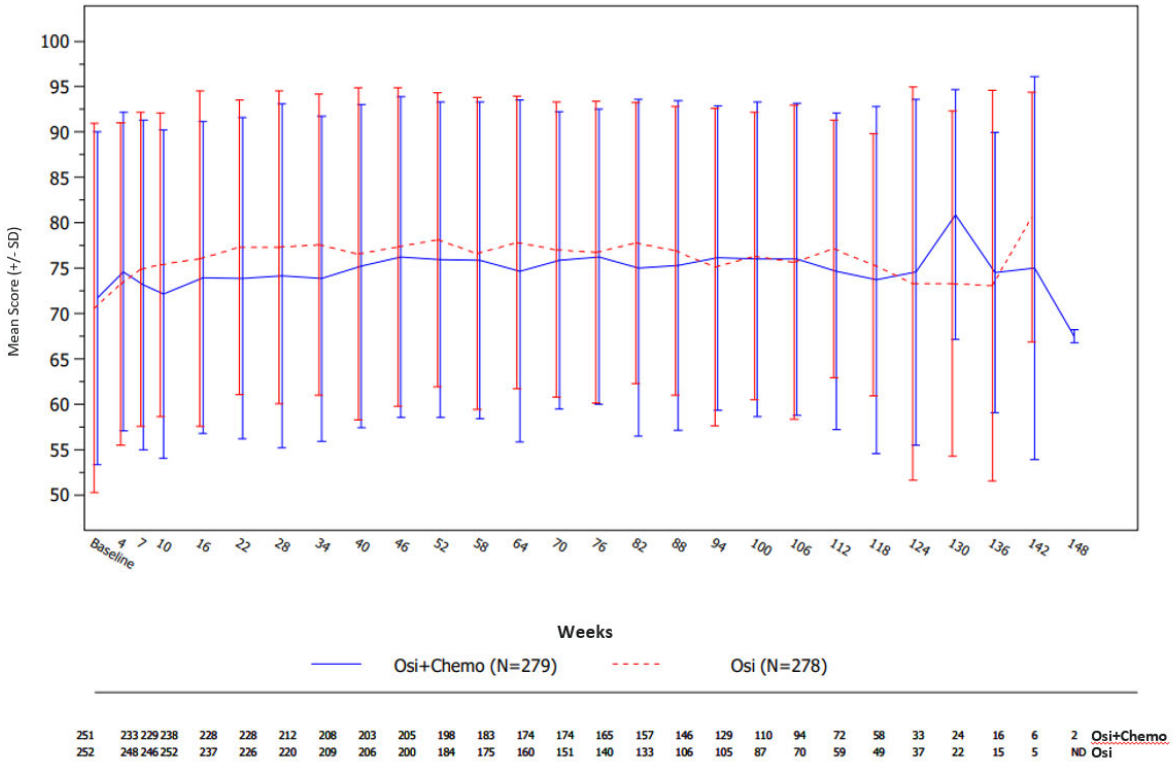
Both treatment arms were well balanced in terms of mean EQ-VAS score at baseline (71.7 in the osimertinib + CTx arm and 70.6 in the osimertinib arm). Post-baseline, mean EQ-VAS scores progressively increased (i.e, improved) in both treatment arms, with no clinically relevant differences between arms. Although a numerical difference favors osimertinib slightly, however, this could be expected with the addition of maintenance pemetrexed in the intervention arm.

Table 32. HRQoL EQ-VAS summary statistics (until 50% drop-off in either arm)

	Osimertinib + CTx		Osimertinib mono		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	251	71.70 (1.160)	252	70.60 (1.284)	1.10 (-2.29, 4.49) p=0.525
Week 4	233	74.60 (1.152)	248	73.20 (1.127)	1.40 (-1.76, 4.56) p=0.385
Week 7	229	73.20 (1.202)	246	74.90 (1.105)	-1.70 (-4.90, 1.50) p=0.298

	Osimertinib + CTx		Osimertinib mono		Intervention vs. comparator
Week 10	238	72.10 (1.173)	246	75.60 (1.065)	-3.50 (-6.61, -0.39) p=0.028
Week 16	225	74.20 (1.142)	227	77.00 (1.178)	-2.80 (-6.02, 0.42) p=0.089
Week 22	226	74.20 (1.161)	216	77.70 (1.093)	-3.50 (-6.62, -0.38) p=0.029
Week 28	207	74.40 (1.327)	197	78.90 (1.141)	-4.50 (-7.93, -1.07) p=0.010
Week 34	205	73.90 (1.257)	193	78.20 (1.180)	-4.30 (-7.68, -0.92) p=0.013
Week 40	194	75.10 (1.297)	176	77.30 (1.361)	-2.20 (-5.88, 1.48) p=0.243
Week 46	194	76.20 (1.287)	169	78.10 (1.325)	-1.90 (-5.52, 1.72) p=0.304
Week 52	180	76.30 (1.264)	150	79.30 (1.250)	-3.00 (-6.48, 0.48) p=0.092
Week 58	167	75.90 (1.336)	144	78.40 (1.333)	-2.50 (-6.20, 1.20) p=0.186
Week 64	156	75.90 (1.423)	125	79.30 (1.358)	-3.40 (-7.25, 0.45) p=0.085
Week 70	156	76.30 (1.295)	120	77.40 (1.503)	-1.10 (-4.99, 2.79) p=0.580

Figure 14. Change from baseline of EQ-VAS, DCO 3rd April 2023



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

10.3.1 HSUV calculation

10.3.1.1 Mapping

The statistical relationship between EQ-5D-5L health state utilities and treatment, and between utilities and health status was assessed using regression analysis. The mixed model for repeated measures (MMRM) analysis was conducted on a dataset excluding any observations recorded after the time of censoring for progression. The restricted maximum likelihood method (REML) was used to perform the MMRM, and the marginal ('least square') mean was estimated to provide the mean utility score by status (treatment and/or progression status) that is averaged over observations and with adjustment for repeated measures. The values from the EQ-5D-5L profiles in FLAURA2 were subsequently mapped using the Danish preference weight set(41). Please refer to Appendix F for further information on the analysis.

The model with progression status was judged to have the best fit as it had the lowest associated AIC and BIC values and has therefore been chosen for the base case. Details on statistical fit are given in Table 33. Please refer to Appendix F for a summary of the remaining models.

Table 33: Summary of HSUV models fitted to FLAURA2 EQ-5D-5L data

Terms included	Converged?	AIC	BIC
Treatment	Yes	-14369.9	-14361.3
Progression status	**Yes**	**-14401.0**	**-14392.5**
Treatment + progression status	Yes	-14392.9	-14384.4
Treatment * progression status	Yes	-14386.9	-14378.4

Footnote: The selected model is indicated using **bold** text
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; HSUV: health state utility value.

10.3.2 Disutility calculation

Disutilities associated with adverse events has been assumed to be captured within the EQ-5D-5L instrument, and inclusions of additional disutilities could lead to potential double counting of the impact of adverse events on the patients HRQoL. Therefore, disutilities associated with adverse events has been excluded.

10.3.3 HSUV results

The base case HSUVs are presented below in Table 34., along with HSUVs applied in alternative scenario analyses.

Table 34. Overview of health state utility values applied in the model

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs base case				
Pre-progression (base case)	0.898 [0.888-0.908]	EQ-5D-5L	DK	MMRM analysis with progression-status as covariate. 6,812 observation on 535 subjects.
Post-progression (base case)	0.871 [0.845-0.896]	EQ-5D-5L	DK	MMRM analysis with progression-status as covariate 612 observations on 194 subjects.
HSUVs for scenario analysis				
Pre-progression FLAURA Mapped to DK EQ-5D-5L	*0.845*	*EQ-5D-5L*	*DK*	*FLAURA(42) UK EQ-5D-3L HSUV mapped to DK EQ-5D-5L HSUV using linear model proposed by Torkilseng et al. 2025(43)*
Post-progression FLAURA Mapped to DK EQ-5D-5L	*0.775*	*EQ-5D-5L*	*DK*	*FLAURA(42) UK EQ-5D-3L HSUV mapped to DK EQ-5D-5L HSUV using linear model proposed by Torkilseng et al. 2025(43)*
Post-progression Labbe et al.(44) (scenario analysis)	*0.640*	*EQ-5D-3L*	*Canadian weights*	*Scenario analysis, alternative HSUV for metastatic health state*

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

10.4.1 Study design

Not applicable. Only used for disutilities.

10.4.2 Data collection

Not applicable. Only used for disutilities.

10.4.3 HRQoL Results

Not applicable. Only used for disutilities.

10.4.4 HSUV and disutility results

No HSUV has been sourced from literature for the health economic analysis.

Table 35. Overview of health state utility values [and disutilities]

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

Table 36 Overview of literature-based health state utility values

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

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

The medicine cost for intervention and comparator is outlined in Table 37, and they were based on prices from medicinpriser.dk (AIP).

The price of osimertinib is the same regardless of dosing, dose reductions will therefore not impact the costs of the medication. Relative dose intensity (RDI) for osimertinib and pemetrexed has been based on intended dosage and the actual administered dosage observed in FLAURA2. Hence RDI accounts for any dose reductions in the calculation of intended dosage. RDI was not calculated for cisplatin or carboplatin in FLAURA2, for the model 100% RDI has been assumed for cisplatin and carboplatin.

Wastage is included for IV treatment, as the remaining of the vial is likely spoiled as the dosing is either weight- or BSA-based. For tablet treatments, wastage is not included, as it is assumed that skipped tablets, due to interruptions, can be administered at a later point in time. The assumption on wastage is in line with prior assessments on TKIs within metastatic NSCLC, where no wastage was included for tablet treatment(45, 46).

Drug acquisition costs are applied in line with the dosing schedules, as detailed in Table 38.

In the osimertinib + CTx arm, CTx treatment consists of an initial induction phase during which patients either receive cisplatin or carboplatin (25%/75% split) in combination with pemetrexed, with both treatments administered via IV infusion once every three weeks. This is followed by maintenance treatment with pemetrexed alongside daily osimertinib. The administration of either cisplatin or carboplatin was based on the investigator's choice in the FLAURA2 trial, and the exact distribution is not presented in the clinical data. A 25%/75% split has been assumed based on clinician input.

Table 37. Unit cost of all medicines used in the model. Updated 14/08/2025

Medicine	ATC code	Strength	Packaging size	Price DKK (AIP)	Type of administration
Osimertinib	L01EB04	40/80 mg	30 stk. (blister)	37,775.00	PO
Cisplatin	L01XA01	100 mg	1 vial	493.75	IV
Carboplatin	L01XA02	450 mg	1 vial	226.39	IV
Pemetrexed	L01BA04	500 mg	1 vial	552.49	IV
Docetaxel	L01CD02	160 mg	1 vial	309.00	IV

Table 38. Dosing of medicines used in the model for primary therapy

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Osimertinib	80 mg	94.6% (combo) 97.7% (mono)	Once daily	No wastage assumed
Chemotherapy, only in Osimertinib + CTx arm				
Cisplatin (25% of patients)	75 mg/m2	100%	Every 3rd week for 4 cycles	No
Carboplatin (75% of patients)	575 mg (AUC5)	100%	Every 3rd week for 4 cycles	No
Pemetrexed	500 mg/m2	90%	Every 3rd week	No

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Osimertinib is a once daily oral therapy, no administration cost has therefore been applied for osimertinib. The platinum-based CTx and pemetrexed are administered intravenously (IV). Platinum-based CTx is administered for 4 cycles, while pemetrexed is administered from initiation of treatment and until progression or until the occurrence of unacceptable or clinically significant toxic effects alongside osimertinib. The IV administration of platinum-based CTx and pemetrexed are assumed to be administered during the same outpatient clinic visit as per the clinical study protocol of FLAURA2, hence only one occurrence of the DRG tariff has been applied for the IV infusion of platinum-based CTx and pemetrexed.

Table 39. Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	Every 3rd week for platinum-based CTx and pemetrexed*	1,900 DKK	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC349, Kræft i lunge UNS - Treatment code: BWAA6, Medicingivning intravenøst	

*Administration of platinum-based CTx and pemetrexed occurs during the same clinic visit, hence cost of IV infusion is only applied once every 3rd week.

11.4 Disease management costs

Costs related to disease management were modelled using a health-state approach. Health care resource use frequency was identified through interview with Danish clinicians(14). Unit costs of the disease management was sourced from the Danish DRG list for 2025(47).

Table 40. Disease management costs in pre-progression health state used in the model

Activity	Frequency	Unit cost [DKK]	DRG code Reference
Outpatient visit at oncology department (incl. blood test)	Every 21 days	1,330	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC349, Kræft i lunge UNS
CT scan	Every 120 days	2,701	2025 DRG code: 30PR06, CT-scanning, kompliceret - Diagnosis code: DC349, Kræft i lunge UNS - Treatment code: UXCC00, CT-skanning af thorax

Table 41. Disease management costs in post-progression health state used in the model

Activity	Frequency	Unit cost [DKK]	DRG code Reference
Outpatient visit at oncology department (incl. blood test)	Every 21 days	1,330	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC349, Kræft i lunge UNS
CT scan	Every 120 days	2,701	2025 DRG code: 30PR06, CT-scanning, kompliceret - Diagnosis code: DC349, Kræft i lunge UNS - Treatment code: UXCC00, CT-skanning af thorax
Inpatient treatment	Every 2nd year	45,920	2025 DRG code: 04MA07: Svulster i luftveje, behandling uden komplikationer, pat. Mindst 18 år - Diagnosis code: DC349, Kræft i lunge UNS

11.5 Costs associated with management of adverse events

AEs were entered in the model as one-off events. This means that the incidence data used are for the whole treatment period and the unit costs are per event and assumes that patients only experience the consequences of AEs once, regardless of the length of time they are on treatment. The AE management costs were sourced from the Danish DRG list for 2025. Most AEs can be handled in outpatient care and would only require an additional medical visit, while some of the AEs would require inpatient care (pneumonia)

Only grade 3+ AE events were considered in the model. The costs of each AE included in the model are presented in the following table.

Table 42. Cost associated with management of adverse events

	DRG code	Unit cost
Diarrhoea	2025 DRG code: 06MA11, Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. - Diagnosis code: DK529B, Ikke-infektiøs diarré UNS	DKK 4,977
Anemia	2025 DRG code: 16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DD649, Anæmi UNS	DKK 1,330
Pneumonia	50%/50% inpatient/outpatient. 2025 DRG code: 04MA13, Lungebetændelse og pleuritis, pat. mindst 60 år - Diagnosis code: DJ189, Pneumoni UNS - 2024 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DJ189, Pneumoni UNS	DKK 22,972
Neutropenia	2025 DRG code: 16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DD709, Neutropeni UNS	DKK 2,208
Neutrophil count decreased	2025 DRG code: 16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DD709, Neutropeni UNS	
Platelet count decreased	2025 DRG code: 16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DD696, Trombocytopeni UNS	
Thrombocytopenia	2025 DRG code: 16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DD696, Trombocytopeni UNS	
Febrile neutropenia	2025 DRG code: 16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DD709, Neutropeni UNS	
Leukopenia	2025 DRG code: 16MA98, MDC16 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DD728H, Leukopeni	
White blood cell count decreased	2025 DRG code: 19MA98, MDC19 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DD728, Anden forstyrrelse i hvide blodlegemer	DKK 2,571
Ejection fraction decreased	2025 DRG code: 05MA98, MDC05 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DI501, Venstresidig hjerteinsufficiens	DKK 1,268
Pulmonary embolism	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DI26, Blodprop i lunge	DKK 1,330

11.6 Subsequent treatment costs

To reflect clinical practice, the analysis accounts for the cost (drug cost, administration cost, patient and transportation costs) of subsequent treatments following progression from 1L treatment, where patients may initiate alternative treatments following progression on either osimertinib + CTx or osimertinib monotherapy. The modelling of the clinical benefit of subsequent treatment is implicitly accounted for in the extrapolated OS data from FLAURA2. The total cost of subsequent treatments is applied as a one-off cost to patients entering the PD state.

The assumptions of the distribution of the subsequent treatment is based on input from a Danish clinician(14). For platinum-based CTx, as in the primary therapy, a 75%-carboplatin and 25%-cisplatin split has been assumed for subsequent therapy as well. Please see Table 43 for expected subsequent distributions for subsequent therapy.

Table 43. Expected subsequent treatment in Danish clinical practice 2L(14)

Subsequent treatments	Osimertinib + CTx arm	Osimertinib arm
Platinum-based CTx + pemetrexed maintenance	0%	50%
Docetaxel	60%	30%
Best supportive care (no treatment)	40%	10%

Table 44 Modelled subsequent treatment in Danish clinical practice 2L(14)

Subsequent treatments	Osimertinib + CTx arm	Osimertinib arm
Cisplatin + pemetrexed maintenance	0%	12.5%
Carboplatin + pemetrexed maintenance	0%	37.5%
Docetaxel	60%	30%
Best supportive care (no treatment)	40%	10%

Table 45. Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Cisplatin	75 mg/m2	100%	Every 3rd week	No

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Carboplatin	575 mg	100%	Every 3rd week	No
Pemetrexed	500 mg	100%	Every 3rd week	No
Docetaxel	75 mg/m2	100%	Every 3rd week	No

Table 46 Subsequent treatment duration

Treatments	Duration of treatment (number of 30-day cycle)	Duration of treatment source
Cisplatin	2.23	Socinski et al., 2018 {Socinski, 2018 #71}
Carboplatin	2.23	Socinski et al., 2018 {Socinski, 2018 #71}
Pemetrexed	4.26	Mok et al. 2017 {Mok, 2017 #72}
Docetaxel	3.04	Kim et al., 2008(48)

11.7 Patient costs

Patient costs were included in the health economic analysis for disease management and for treatment administration for primary and subsequent therapies. For each visit, disease management or treatment administration and the cost of transport have been added as well. The frequencies of the patient costs are based on the frequencies presented in Table 47 for disease management and Table 48 for treatment administration.

The unit costs have been sourced from the unit cost list by the DMC(50), see Table 49.

Table 47. Patient time spent for disease management used in the model

Activity	Time spent
Outpatient visit at oncology department (incl. blood test)	1 hour
Outpatient visit at lung medicine department (monitoring)	1 hour
CT scan	1 hour
PET-CT scan	1 hour
Inpatient treatment	24 hours

Table 48 Patient time spent for per administration of medicines used in the model, based on SmPC of treatments

Treatment	Time spent
Osimertinib	0 hours assumed, oral treatment. Treatment is assumed to be dispensed during oncologist visit.
Docetaxel	1 h for infusion
Pemetrexed	10 min for infusion
Cisplatin	2 h for infusion – administered along with pemetrexed, transport not included to avoid double counting
Carboplatin (AUC5)	Mean of 37.5 min assumed (midpoint between 15 and 60) for infusion – administered along with pemetrexed, transport not included to avoid double counting

Table 49. Unit costs used in the model for patient cost (50)

Activity	Cost [DKK]
Cost per patient hour	DKK 188.00
Cost per transport	DKK 140.00

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

N/A.

12. Results

12.1 Base case overview

Table 50. Base case overview

Feature	Description
Intervention	Osimertinib + CTx
Comparator	Osimertinib monotherapy
Type of model	Partitioned survival model
Time horizon	30 years
Treatment line	1st line modelled by TTD extrapolation and subsequent treatment modelled as one-off cost at progression
Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L in FLAURA2 study(31). Danish population weights were used to estimate health-state utility values.
Costs included	Medicine costs Administration costs Disease management costs Costs of adverse events Subsequent treatment costs Patient costs
Dosage of medicine	Osimertinb + CTx: Fixed dose, osimertinib 80 mg PO daily in combination with cisplatin: 75 mg/m2 every 3rd week or carboplatin: 575 mg (AUC5) for 4 cycle and pemetrexed: 500 mg/m2 every 3rd week Osimertinib monotherapy: Fixed dose, osimertinib 80 mg PO daily
Parametric function for PFS	Osimertinib + CTx: Weibull Osimertinib mono: Weibull
Parametric function for OS	Osimertinib + CTx: Weibull Osimertinib mono: Weibull
Parametric function for TTD	Osimertinib + CTx (osimertinib): Gompertz Osimertinib + CTx (pemetrexed): Exponential Osimertinib mono: Gompertz

Feature	Description
Inclusion of waste	Vial wastage is included for IV treatment. Tablet wastage is not included for tablet treatments.
Average time on treatment	Osimertinib + CTx (osimertinib): 32.88 months Osimertinib + CTx (pemetrexed): 16.46 months Osimertinib mono: 26.27 months
Average time in model health state - Pre-progression	Osimertinib + CTx: 32.51 months Osimertinib mono: 23.78 months
Average time in model health state - Post-progression	Osimertinib + CTx: 62.19 months Osimertinib mono: 62.19 months

12.1.1 Base case results

The base case results are presented in Table 51. Over the lifetime time horizon, the total discounted cost associated with osimertinib + CTx was 1,469,654 DKK, while the total discounted LYs and QALYs accrued were 4.59 and 4.07, respectively.

The total discounted cost of osimertinib monotherapy was 1,187,760 DKK, while placebo had accumulated a discounted 3.61 LYs and a discounted 3.20 QALYs.

The main driver for the incremental cost is the additional acquisition cost of osimertinib for the prolonged time on treatment. The incremental cost per QALY gained for osimertinib + CTx vs. osimertinib monotherapy was 326,380 DKK.

Table 51. Base case results, discounted estimates

	Osimertinib + CTx [DKK]	Osimertinib [DKK]	Difference
Drug acquisition costs	1,194,311	981,731	212,581
Drug administration costs	27,177	0	27,177
Adverse event costs	2,294	1,080	1,213
Disease management costs	201,121	160,856	40,266
Subsequent treatment cost	4,732	13,333	-8,601
Patient costs	40,019	30,761	9,259
Total costs	**1,469,654**	**1,187,760**	**281,894**

	Osimertinib + CTx [DKK]	Osimertinib [DKK]	Difference
Life years gained (Pre-progression)	2.57	1.91	0.66
Life years gained (Post-progression)	2.02	1.70	0.32
Total life years	**4.59**	**3.61**	**0.98**
QALYs (progression-free)	2.31	1.71	0.59
QALYs (post-progression)	1.76	1.48	0.28
Total QALYs	**4.07**	**3.20**	**0.87**
Incremental costs per life year gained			**DKK 290,897**
Incremental cost per QALY gained (ICER)			**DKK 326,380**

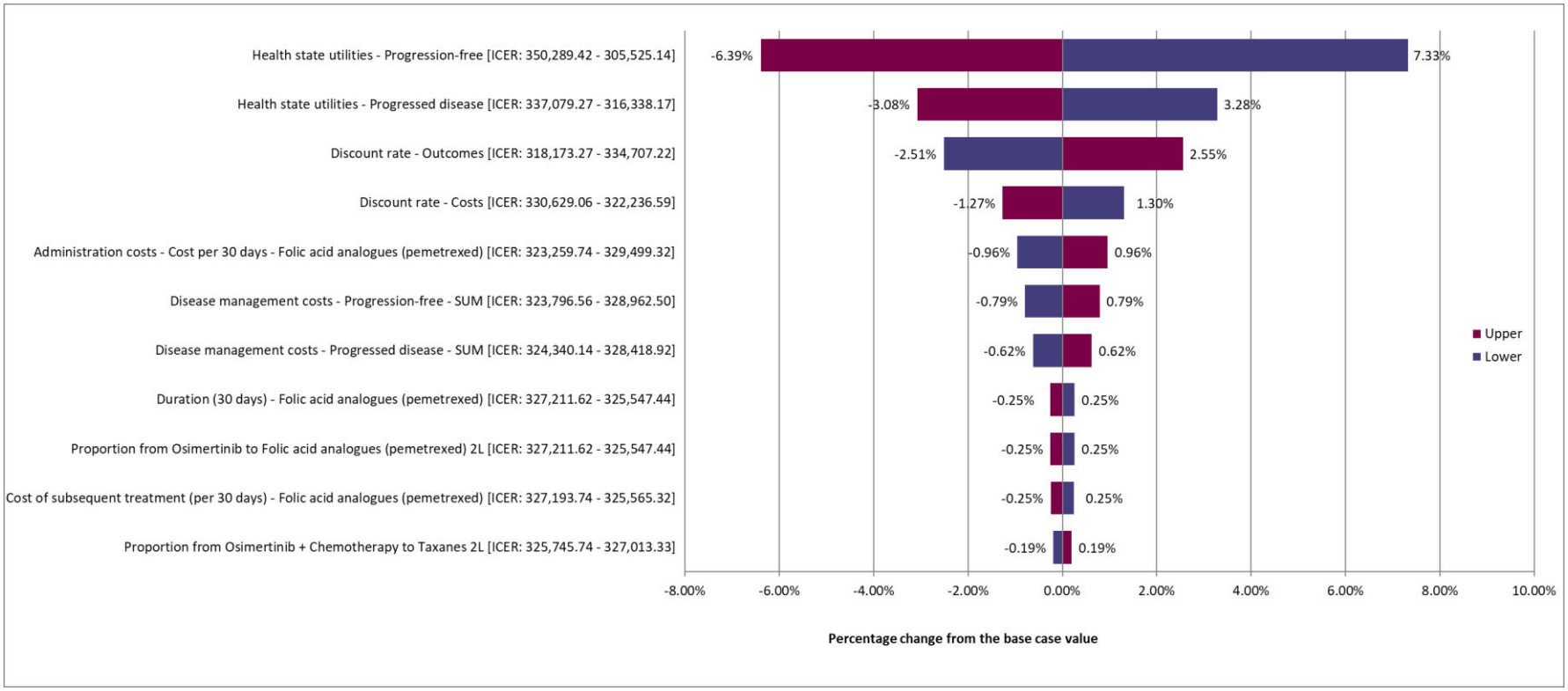
12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The DSA produces tornado plots for osimertinib plus CTx compared with osimertinib monotherapy, showing the inputs that the total costs in each arm, total QALYs in each arm, ICER, incremental QALYs and incremental costs are most sensitive to. The user can select the percentage variation from baseline for each variable; 10% is used as the default variation in the base case. The ICER tornado plot is shown in Figure 15.

The ICER tornado plot shows that the ICER is most sensitive to health state utility values for the progression-free health state (between -6.39% and 7.33%). The health state utility values for the progressed disease health state have the second highest impact on ICER (between -3.08% and 3.28%). Varying other input values leads to no more than a 2.55% change in ICER compared with the base case, suggesting that the ICER is less sensitive to these inputs.

Figure 15. ICER Tornado plot for DSA



Abbreviations: DSA: deterministic sensitivity analysis; ICER: incremental cost-utility ratio.

12.2.2 Scenario analysis

Results for the scenario analyses are presented in Table 52. In the majority of the scenario analyses, the ICER for osimertinib plus CTx versus osimertinib monotherapy varied by less than 10% except one scenario, indicating the model is robust to changes in the assumptions made.

The scenarios with the largest impact on the ICER was observed using the Weibull curve for the TTD of osimertinib monotherapy (-22.66%), using the Labbe et al. post-progression HSUV (9.19 %) and using FLAURA UK HSUV mapped to DK EQ-5D-5L (9.19%).

Table 52. Scenario analyses explored in the model

Category	Scenario	ICER (DKK per QALY)	Diff-%
Base case	Base case	326,380 DKK	-
Efficacy scenarios	Use the Gamma extrapolation for the PFS curves of both treatment arms	320,393 DKK	-1.83%
	Use the Gamma extrapolation for the OS curves of both treatment arms	309,921 DKK	-5.04%
	Use the Weibull curve for the TTD of osimertinib monotherapy	252,426 DKK	-22.66%
Utility scenarios	Use HSUVs sourced from FLAURA UK HSUV mapped to DK EQ-5D-5L	352,989 DKK	8.15%
	Use data from Labbe et al.(44) for post-progression HSUV	356,382 DKK	9.19%
Patient characteristics	Average age 70, mean height 174 cm, proportion of females 67%	327,160 DKK	0.24%

12.2.3 Probabilistic sensitivity analyses

The mean results of the probabilistic sensitivity analysis are presented in Table 53 for osimertinib + CTx and osimertinib monotherapy using 1000 Monte Carlo simulations. Over the lifetime time horizon, the total discounted costs and QALYs associated with osimertinib + CTx were 1,506,000 DKK and 4.09 QALY, respectively. For placebo, total costs were 1,203,236 DKK and total QALYs were 3.22. Consistent with the deterministic base case, osimertinib + CTx had higher total costs and QALYs than osimertinib monotherapy.

Table 53. Discounted results of the probabilistic analysis

Regimen	Mean Total Costs (DKK)	Mean Total QALYs	ΔCosts (DKK)	ΔQALYs	Incremental cost per QALY (DKK per QALY)
Osimertinib + CTx	1,506,108 DKK	4.09	-	-	-
Osimertinib monotherapy	1,203,466DKK	3.22	302,642	0.87	347,408 DKK per QALY

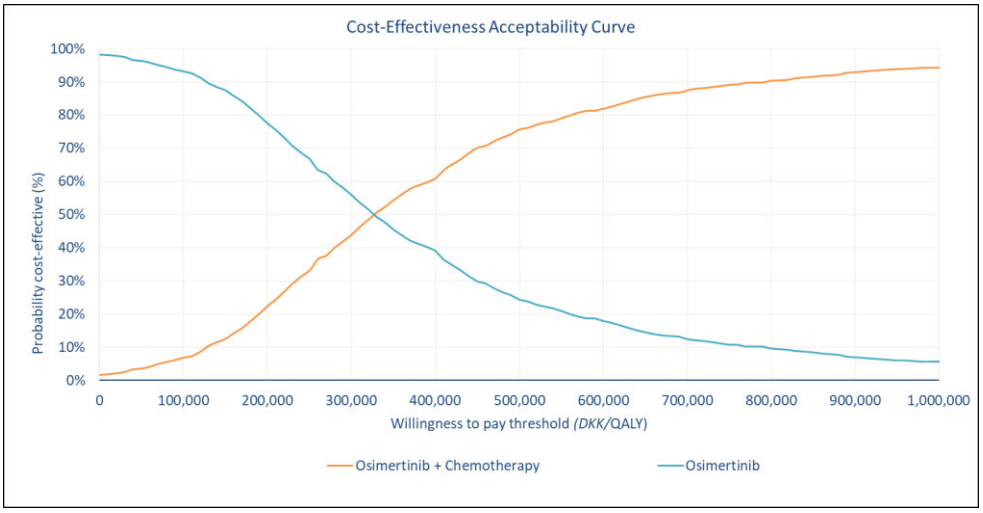
Abbreviations: QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio.

The cost-effectiveness plane for osimertinib + CTx and osimertinib monotherapy is shown in Figure 16. It shows the distribution of all the simulations from the PSA as well as the willingness-to-pay (WTP) threshold of 500,000 DKK per QALY. Osimertinib + CTx is more costly but more effective (QALYs) in 98.1% of simulations.

Figure 16. The cost-effectiveness plane

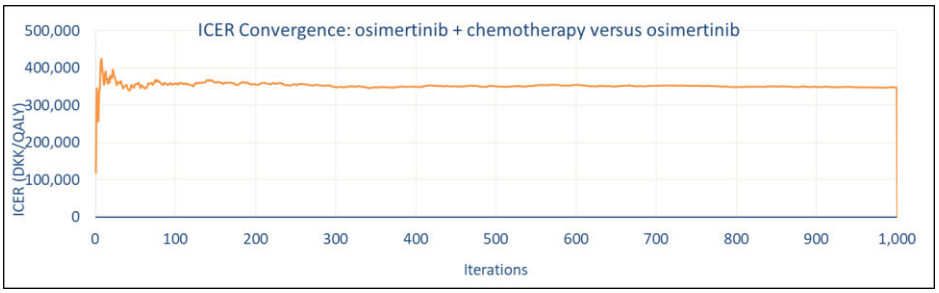
The cost-effectiveness acceptability curve for osimertinib + CTx vs. osimertinib monotherapy is shown in Figure 17. The CEAC shows the probability that the treatment is acceptable based on various acceptability thresholds. Osimertinib + CTx had a higher probability of being cost-effective vs osimertinib at willingness to pay thresholds greater than 330,000 DKK per QALY.

Figure 17. The cost-effectiveness acceptability curve



Convergence plots show the variation in the ICERs generated by the probabilistic simulations against the number of iterations or samples. The plot, Figure 18, demonstrate that probabilistic results were stable by approx. 300 iterations, suggesting that 1000 iterations is a sufficient number to reach a stable result.

Figure 18. ICER Convergence plot.



13. Budget impact analysis

Number of patients (including assumptions of market share)

As stated in section 3.2, the DMC estimates around 220 patients with EGFR mutation annually in Denmark. Currently all patients receiving osimertinib monotherapy. With the introduction of osimertinib + CTx, it is expected that a minor proportion of the total cohort would be relevant for treatment with the combination therapy. The selection would be based on multiple factors, including patient preference and at the physician's discretion. Based on the input from a Danish clinician, osimertinib + CTx would possibly be offer to approx. 1/3 of the total cohort(14). This is reflected in the number presented in the Table 54.

Table 54. Number of new patients expected to be treated over the next five-year period if the osimertinib in combination with chemotherapy is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Osimertinib + CTx	75	77	80	80	80
Osimertinib monotherapy	145	148	148	150	150
			Non-recommendation		
Osimertinib + CTx	0	0	0	0	0
Osimertinib monotherapy	220	225	228	230	230

Budget impact

The budget impact is obtained by multiplying the patient numbers in Table 54 with the cost per patient. The budget impact increase from around DKK 2.1m in year 1 to a budget impact of DKK 16.8m in year 5 (Table 55).

Table 55. Expected budget impact of recommending the osimertinib in combination with chemotherapy for patients with EGFRm advanced NSCLC, [million] DKK (undiscounted)

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	102.6m	173.3m	222.5m	253.7m	271.7m
The medicine under consideration is NOT recommended	100.5m	168.2m	213.5m	240.6m	254.8m
Budget impact of the recommendation	**2.1m**	**5.1m**	**9.0m**	**13.2m**	**16.8m**

14. List of experts

Jon Lykkegaard Andersen, chief physician, dept. of oncology at Herlev and Gentofte Hospital

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Appendix A. Main characteristics of studies included

Table 56. Main characteristic of studies included

Trial name: FLAURA2	NCT number: NCT04035486
Objective	Evaluate efficacy and safety of first-line osimertinib with platinum-pemetrexed chemotherapy versus osimertinib monotherapy in EGFRm advanced/metastatic NSCLC.
Publications – title, author, journal, year	Planchard D, Feng PH, Karaseva N, et al. Osimertinib plus platinum-pemetrexed in newly diagnosed epidermal growth factor receptor mutation-positive advanced/metastatic non-small-cell lung cancer: safety run-in results from the FLAURA2 study. *ESMO Open*. 2021;6(5):100271. doi:10.1016/j.esmoop.2021.100271(51) Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC. *N Engl J Med*. 2023;389(21):1935-1948. doi:10.1056/NEJMoa2306434(37) Jänne PA, Planchard D, Kobayashi K, et al. CNS Efficacy of Osimertinib With or Without Chemotherapy in Epidermal Growth Factor Receptor-Mutated Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2024;42(7):808-820. doi:10.1200/JCO.23.02219(51)
Study type and design	Phase 3, randomised, open-label trial. The study is conducted and sponsored by AstraZeneca. The FLAURA2 study was conducted in two separate phases: the safety run-in and the open-label Phase III randomised period. Crossover between treatment arms was not permitted within the study.
Sample size (n)	A total of 557 patients were randomly assigned to the osimertinib–chemotherapy group (279 patients) or the osimertinib group (278 patients).
Main inclusion criteria	1. Male or female, at least 18 years of age; patients from Japan at least 20 years of age. 2. Pathologically confirmed non-squamous Non-Small Cell Lung Cancer (NSCLC). NSCLC of mixed histology is allowed. 3. Newly diagnosed locally advanced (clinical stage IIIB, IIIC) or metastatic Non-Small Cell Lung Cancer (NSCLC) (clinical stage IVA or IVB) or recurrent Non-Small Cell Lung Cancer (NSCLC) not amenable to curative surgery or radiotherapy. 4. The tumor harbors 1 of the 2 common epidermal growth factor receptor (EGFR) mutations known to be associated with Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) sensitivity (Ex19del or L858R), either alone or in combination with other epidermal growth factor receptor (EGFR) mutations, which may include T790M.

Trial name: FLAURA2	NCT number: NCT04035486
	5. Patients must have untreated advanced Non-Small Cell Lung Cancer (NSCLC) not amenable to curative surgery or radiotherapy. 6. WHO PS of 0 to 1 at screening with no clinically significant deterioration in the previous 2 weeks. 7. Life expectancy >12 weeks at Day 1. 8. Willing to use contraception as appropriate during the study and for a period of time after discontinuing study treatment.
Main exclusion criteria	1. Spinal cord compression; and unstable brain metastases, with stable brain metastases who have completed definitive therapy, are not on steroids, and have a stable neurological status for at least 2 weeks after completion of the definitive therapy and steroids can be enrolled. Patients with asymptomatic brain metastases can be eligible for inclusion if in the opinion of the Investigator immediate definitive treatment is not indicated 2. Past medical history of Interstitial Lung Disease (ILD), drug-induced Interstitial Lung Disease, radiation pneumonitis that required steroid treatment, or any evidence of clinically active Interstitial Lung Disease. 3. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol, or active infection including Hep. B, Hep. C and HIV. Screening for chronic conditions is not required. Active infection will include any patients receiving treatment for infection. 4. QT prolongation or any clinically important abnormalities in rhythm. 5. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: o Absolute neutrophil count below the lower limit of normal (<LLN) o Platelet count below the LLN o Hemoglobin <90 g/L. The use of granulocyte colony stimulating factor support, platelet transfusion and blood transfusions to meet these criteria is not permitted. o ALT >2.5 x the upper limit of normal (ULN) if no demonstrable liver metastases or >5 x ULN in the presence of liver metastases

- AST >2.5 x ULN if no demonstrable liver metastases or >5 x ULN in the presence of liver metastases
- Total bilirubin >1.5 x ULN if no liver metastases or >3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases
- Creatinine clearance <60 mL/min calculated by Cockcroft and Gault equation or 24 hour urine collection (refer to Appendix I for appropriate calculation)

6. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of osimertinib.
7. Prior treatment with any systemic anti-cancer therapy for advanced Non-Small Cell Lung Cancer (NSCLC) not amenable to curative surgery or radiation including chemotherapy, biologic therapy, immunotherapy, or any investigational drug. Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic therapies, investigational agents are permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease.
8. Prior treatment with an Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI).
9. Major surgery within 4 weeks of the first dose of investigational product (IP). Procedures such as placement of vascular access, biopsy via mediastinoscopy or biopsy via video assisted thoracoscopic surgery are permitted.
10. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of investigational product (IP).
11. History of hypersensitivity to active or inactive excipients of investigational product (IP) or drugs with a similar chemical structure or class to investigational product (IP).

Intervention	Osimertinib (80 mg once daily) and intravenous pemetrexed (500 mg/m^2 every 3rd week) plus either cisplatin (75 mg/m^2) or carboplatin (AUC of 5 mg/ml/min), administered intravenously on day 1 of 21-day cycles for four cycles. This treatment was followed by osimertinib (80 mg once daily) plus pemetrexed maintenance therapy (500 mg per square meter) every 3 weeks. N = 279

Trial name: FLAURA2	NCT number: NCT04035486
Comparator(s)	Osimertinib monotherapy (80 mg once daily). A 40 mg strength is available for dose reductions. N = 278
Follow-up time	OS: Osi + CTx: 42.6m; Osi mono: 35.7m
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary:** PFS **Secondary:** OS, LOS, ORR, DoR, DCR, PFS2, PFS by investigator by plasma *EGFR* mutation status **Exploratory:** PRO-CTCAE symptoms, PGIS, EQ-5D-5L, Investigator-assessed CNS PFS, CNS ORR, CNS DoR, CNS DCR and best percentage change in CNS tumour size (target lesion)
Method of analysis	The primary analysis of PFS (based on investigator assessment, according to RECIST 1.1), was planned to occur when approximately 278 PFS events and at least 16 months of follow-up (after last patient entered the trial) had occurred in the 556 randomised patients (approximately 50% data maturity). In order to provide strong control of the type 1 error rate at the 2-sided 0.5% alpha level, the primary endpoint PFS and the key secondary efficacy endpoint OS were tested in sequential order in the FAS. If PFS was statistically significant at the time of the primary PFS analysis, then subsequent hypothesis testing for OS would be performed at overall α = 0.05 significance level (2-sided) using O'Brien Fleming spending function. If the PFS analysis was not statistically significant at the time of the primary PFS analysis, then the hypothesis testing of OS was not to be performed. If the previous analysis in the sequence was not statistically significant, the alpha would not be transferred to subsequent analyses(31). Two analyses of OS were planned as part of the hierarchical testing procedure: the first was to be conducted at the time of the primary analysis of PFS, with a final analysis to be performed at approximately 60% data maturity, when approximately 334 death events (across both arms) have occurred.(1) Additionally, an unplanned second interim OS analysis was performed in response to a regulatory authority (FDA) request. Initially, OS was the only endpoint to be updated, and the efficacy boundary was p=0.000001 (nominal 10^{-6} alpha spend). However, subsequent treatment data were also updated in response to a further request from the FDA; no other data were reported at this second interim analysis of OS.

Trial name: FLAURA2	NCT number: NCT04035486
	Data from the primary PFS analysis (DCO: 3rd April 2023) and the final OS analysis (DCO: 12th June 2025) are reported in this application.
Subgroup analyses	[For each analysis, provide the following information: - characteristics of included population - method of analysis - was it pre-specified or post hoc? - assessment of validity, including statistical power for pre-specified analyses.]
Other relevant information	**Planned analysis FLAURA2** There was one interim analysis planned prior to the primary analysis of PFS for futility, in order to assess whether there was any potential lack of efficacy in the osimertinib + CTx arm compared to the osimertinib monotherapy arm. This futility analysis was planned for when approximately 83 PFS events had occurred after the start of randomization and was performed by the Independent Data Monitoring Committee (IDMC). The futility boundary was based on the conditional probability of showing statistical significance for the primary endpoint of PFS, which was based on 278 events in approximately 556 patients. The exact figure used for the futility boundary was to be calculated by the AstraZeneca statistician (or delegate) and sent to the IDMC at the time of the interim analysis, based on the number of events which had occurred at that time(31).

Appendix B. Efficacy results per study

Results per study

Table 57. Results per study

Results of FLAURA2 (NCT04035486)											
				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		
PFS investigator	Osimertinib + CTx	279	25.5 (24.7, NC)	8.8 m	NC	NC	HR=0.62	0.49, 0.79;	p<0.001	Tumour assessments (computerised tomography or magnetic resonance imaging scans of the chest/abdomen plus any other sites where disease is suspected or known at baseline, and brain imaging) for the primary endpoint of PFS and response-based secondary endpoints were assessed according to the RECIST 1.1 and were based on investigator assessment. DCO: 3rd April 2023	Planchard et al. November 8, 2023. N Engl J Med 2023; 389:1935-1948
	Osimertinib mono	278	16.7 (14.1, 21.3)								
CNS-PFS With CNS metastases	Osimertinib + CTx	40	NC (23.0, NC)	NC	NC	NC	HR: 0.40;	0.19, 0.84	p=0.0157	Tumour assessments (computerised tomography or magnetic resonance imaging scans of the chest/abdomen plus any other sites where disease is	Planchard et al. November 8, 2023. N Engl J Med 2023; 389:1935-1948

Results of FLAURA2 (NCT04035486)											
				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		
Investigator assessed	Osimertinib mono	38	17.3 (13.9, NC)							suspected or known at baseline, and brain imaging) for the primary endpoint of PFS and response-based secondary endpoints were assessed according to the RECIST 1.1 and were based on investigator assessment. .DCO: 3rd April 2023	
mOS (DCO: 3rd Apr 2023)	Osimertinib + CTx	279	NR(31.9, NA)	NC	NC	NC	HR=0.90	0.65, 1.24	p=0.5238	OS data at the first interim OS analysis were only 26.8% mature, with 71 patients (25.4%) having died in the osimertinib + CTx arm, and 78 patients (28.1%) having died in the osimertinib monotherapy arm. The absolute difference in effect is estimated using a two-sided t-test. **(DCO: 3rd April 2023)**	Planchard et al. November 8, 2023. N Engl J Med 2023; 389:1935-1948
	Osimertinib mono	278	NR(NR; NR)								
mOS (DCO: 8th Jan 2024)	Osimertinib + CTx	279	NR (38.0, NC)	NC	NC	NC	HR=0.75	0.57, 0.97	p=0.0280	At the time of this second interim OS analysis (DCO: 8th January 2024), 226 OS events had occurred in the FAS (overall data maturity 40.6%), with 100 (35.8%) patients having died in the osimertinib +	Valdiviezo N, FLAURA2 post-progression outcomes. Presented at the European
	Osimertinib mono	278	36.7 (33.2, NC)								

Results of FLAURA2 (NCT04035486)											
				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		
										NCCTx arm, and 126 (45.3%) patNCients having died in the osimertinib monotherapy arm (**DCO 8 Jan 2024**)	Lung Cancer Congress 2024
mOS (DCO: 12th Jun 2025)	Osimertinib + CTx	279	47.5 (41.0, NC)	NC	NC	NC	HR=0.77	0.61, 0.96	p=0.0202	At the time of the final OS analysis, 315 OS events had occurred in the FAS (overall data maturity 56.6%), with 144 (51.6%) patients having died in the osimertinib + CTx arm, and 171 (61.5%) patients having died in the osimertinib monotherapy arm. (**DCO 12 June 2025**)	Clinical study report, Final OS analysis DCO 12th June 2025 (33) WCLC 2025 poster: (30)
	Osimertinib mono	278	37.6 (33.2, 43.2)								

Appendix C. Comparative analysis of efficacy

NA. The application is based on a H2H vs. current standard treatment.

Table 58. Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Appendix D. Extrapolation

D.1 Extrapolation of PFS

D.1.1 Data input

Data input for extrapolation of PFS was sourced from the FLAURA2 trial.

D.1.2 Model

The following standard parametric models were fitted to the available data: exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma, and gamma distributions.

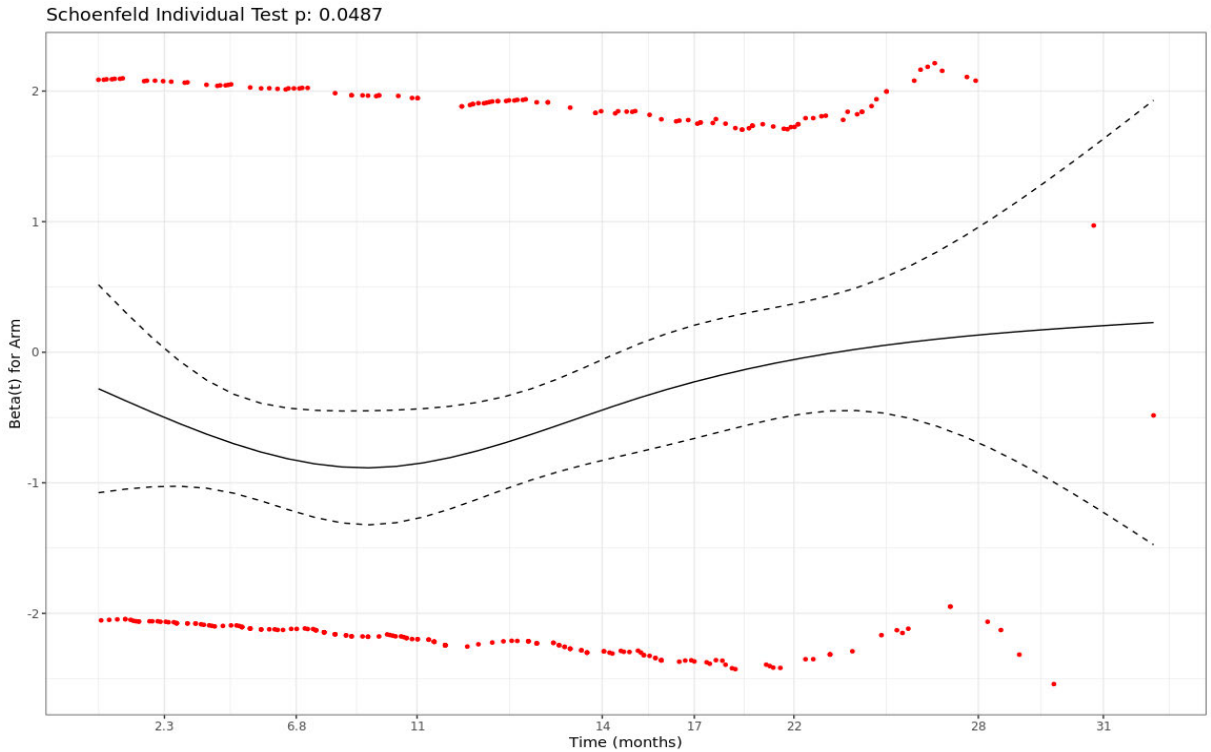
D.1.3 Proportional hazards

The first step in selecting the choice of parametric survival model for PFS was to assess whether the PHA was upheld for the FLAURA2 data.

Figure 19 shows that the plot of the Schoenfeld residuals against time does not show a pattern of changing residuals; the p-value for Schoenfeld residuals test is bordering significance (p=0.0487). However, the log cumulative hazard curves (

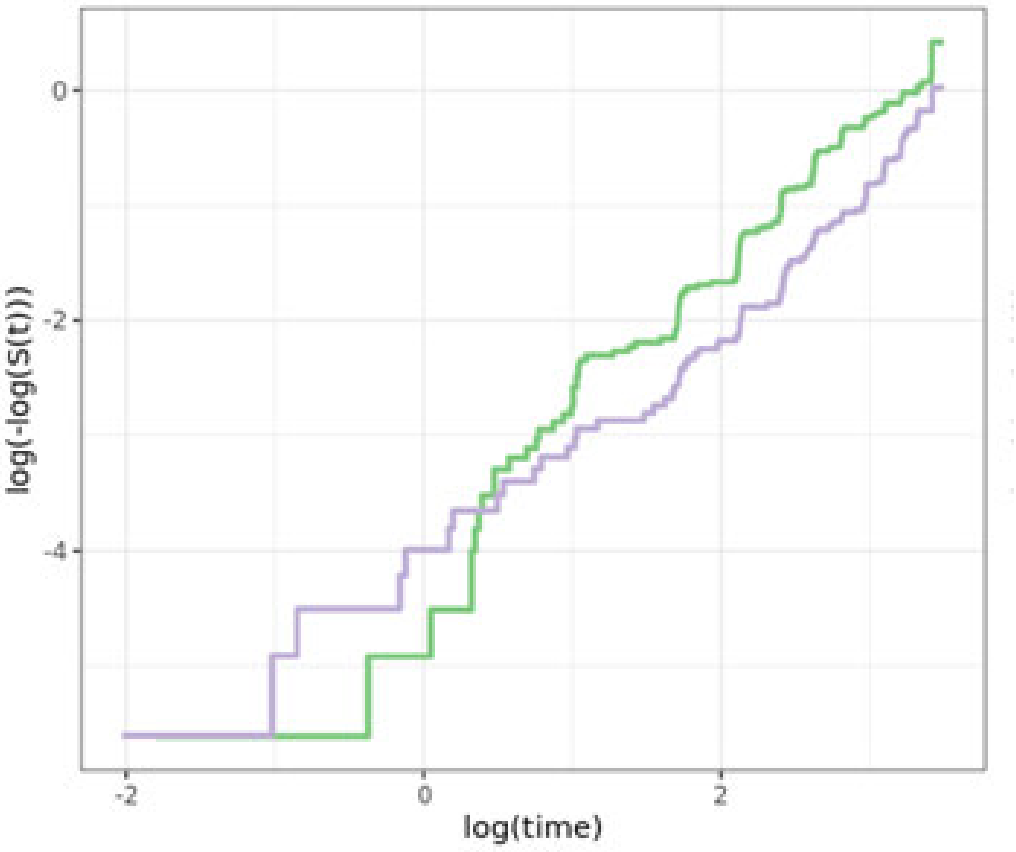
Figure 20) were not parallel over time, indicating that the treatment effect varied over the trial period. On this basis it was considered that there was a violation of the PHA.

Figure 19. Schoenfeld residual plot for PFS from FLAURA2



Abbreviations: PFS: progression-free survival.

Figure 20 Log-cumulative hazard plot for PFS from FLAURA2



Abbreviations: PFS: progression-free survival.

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

For the osimertinib plus CTx arm, the AIC and BIC rankings indicated that the Gompertz, generalised gamma and Weibull distributions were the best fitting

For the osimertinib monotherapy arm, the log-normal and exponential models were excluded based on statistical fit. The AIC and BIC rankings indicated that the log-logistic, gamma and Weibull distributions were the best fitting.

Table 59. Goodness of fit statistics – FLAURA2 PFS

Distribution	Osimertinib plus CTx		Osimertinib monotherapy	
	AIC (Rank)	BIC (Rank)	AIC (Rank)	BIC (Rank)
Exponential	1,139.5 (6)	1,143.1 (5)	1,143.1 (7)	1,430.7 (4)
Weibull	**1,130.3 (3)**	**1,137.6 (2)**	**1,137.6 (3)**	**1,428.3 (3)**
Gompertz	1,123.4 (1)	1,130.7 (1)	1,130.7 (6)	1,433.1 (7)
Log-logistic	1,137.6 (5)	1,144.9 (6)	1,144.9 (1)	1,426.5 (1)
Lognormal	1,154.9 (7)	1,162.2 (7)	1,162.2 (5)	1,432.6 (6)
Generalised gamma	1,126.7 (2)	1,137.6 (2)	1,137.6 (4)	1,432.3 (5)
Gamma	1,132.7 (4)	1,140.0 (4)	1,140.0 (2)	1,427.4 (2)

Footnote: Base case extrapolation is shown in **bold**; best fit distributions are shown in green highlight.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CTx: chemotherapy.

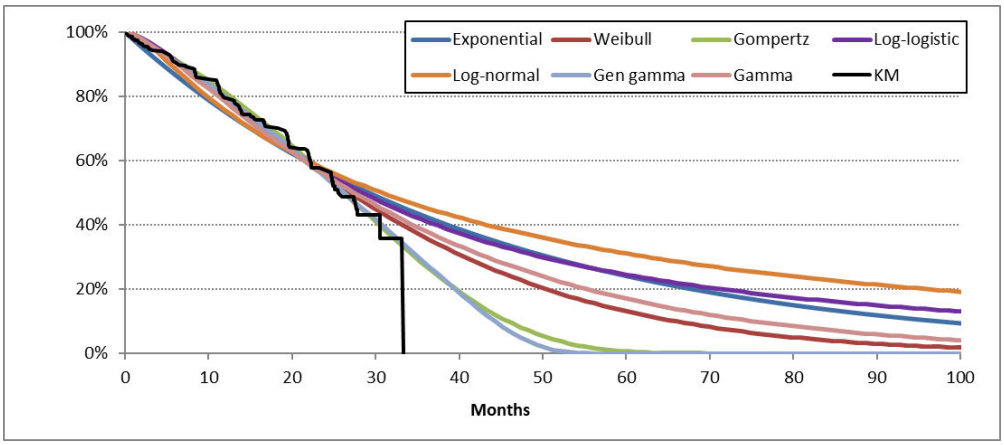
D.1.5 Evaluation of visual fit

Standard parametric models were fitted separately to the PFS data from the FLAURA2 trial for osimertinib plus CTx and osimertinib monotherapy arms. These are presented in Figure 21 and Figure 22.

For the osimertinib plus CTx arm, the exponential, log-logistic and log-normal models were excluded based on poor visual. Of the remaining distributions, the AIC and BIC rankings indicated that the Gompertz, generalised gamma and Weibull distributions were the best fitting. The Gompertz and the generalised gamma, however, might be overfitted to the tail of the observed data providing an overly pessimistic extrapolated curve that is not observed or replicated in the osimertinib monotherapy arm. Weibull appears to be a fair fitting model on the observed data from FLAURA2.

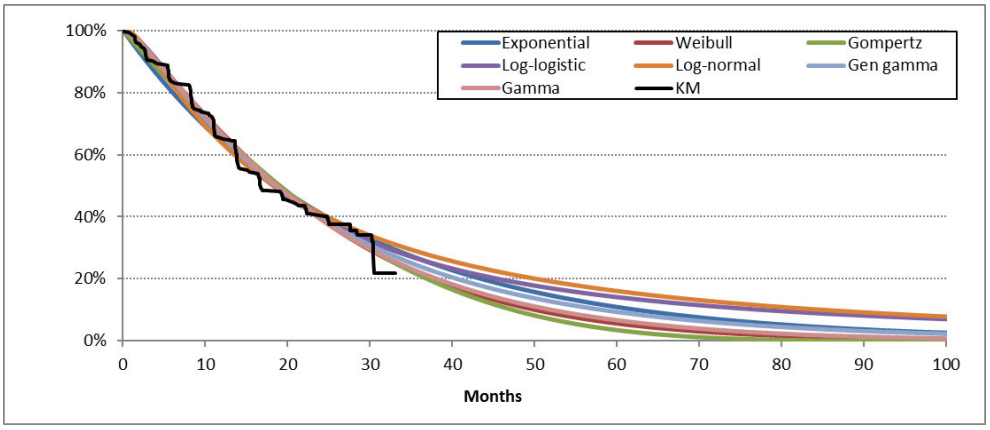
For the osimertinib monotherapy arm, all curves appear to fit fairly well on the observed data. The log-normal and log-logistic appears to generate long and clinically implausible tails for the extrapolations of PFS. Weibull and gamma fit the observed data well and provides a reasonable extrapolation beyond the observed data.

Figure 21. Parametric models fitted to osimertinib plus CTx FLAURA2 PFS data



Footnote: Curves on the figure are not bounded by OS.
Abbreviations: KM: Kaplan-Meier.

Figure 22. Parametric models fitted to osimertinib monotherapy FLAURA2 PFS data

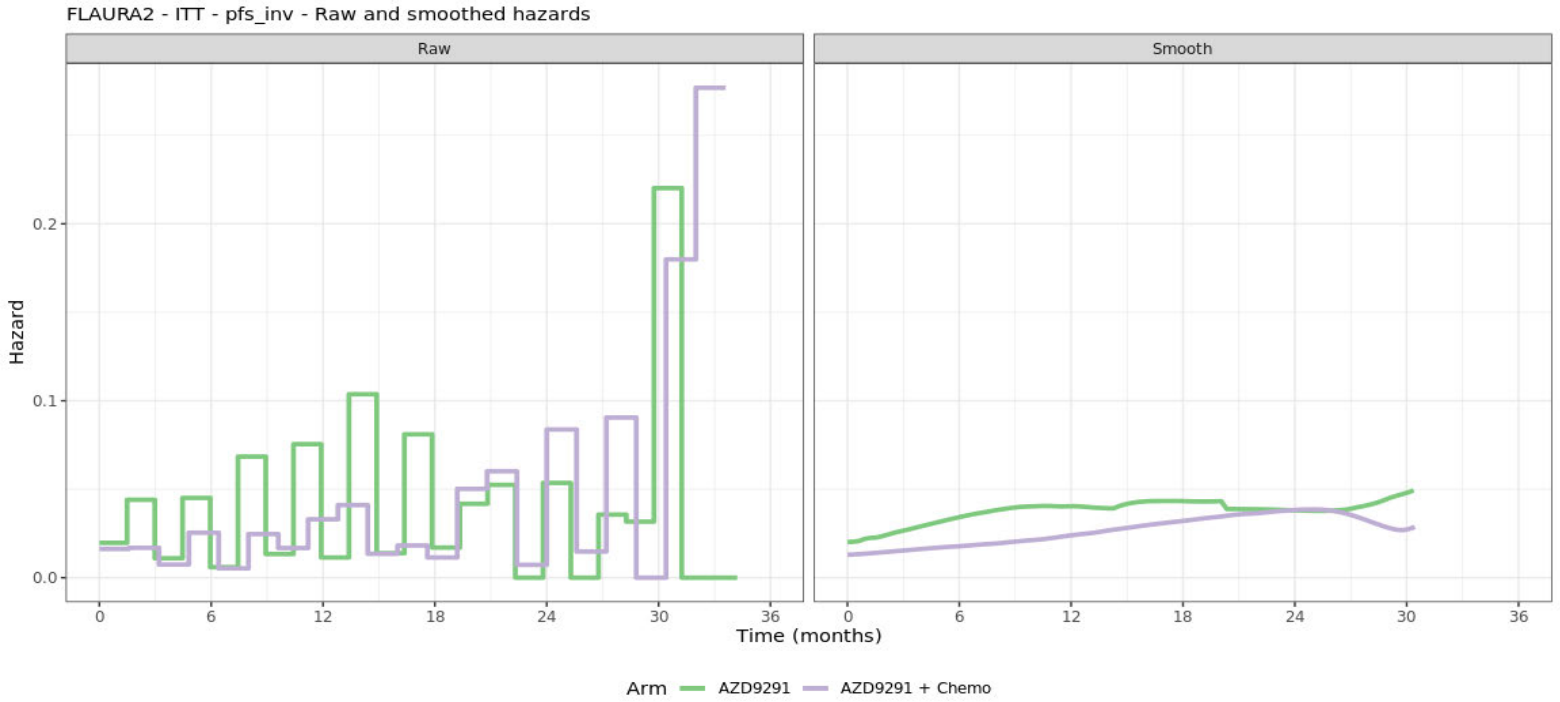


Footnote: Curves on the figure are not bounded by OS.
Abbreviations: KM: Kaplan-Meier.

D.1.6 Evaluation of hazard functions

To explore whether standard parametric models were appropriate, plots of the raw and smoothed hazards were considered (Figure 23). The raw hazard plot shows that the hazards are relatively constant over the duration of the trial, although there is a change at the end of the trial in both arms, driven by low patient numbers. For both trial arms, the smoothed hazards appear relatively stable over the duration of trial period, with an increasing trend. For this reason, standard parametric models were considered appropriate for PFS.

Figure 23. Raw and smoothed hazards for PFS from FLAURA2



D.1.7 Validation and discussion of extrapolated curves

As a number of possible curves remained in both arms after consideration of both statistical and visual fit, curve selection for the base case was primarily informed by clinical plausibility when considering both treatment arms. In addition, the same curve was considered for both treatment arms in order to align with NICE TSD 14, which recommends fitting parametric models of the same type to both treatment arms in the absence of substantial justification that this would not be appropriate. Given that osimertinib is administered in both the intervention and comparator arms, it was deemed reasonable to assume that the hazards would follow the same parametric distribution.

The curves remaining in both arms (i.e. had not yet been excluded on the basis of statistical or visual fit in either arm) were the Weibull, gamma, Gompertz and generalised gamma curves. None of the remaining curves crossed the projected OS curve, and therefore could not be excluded on this basis. When either the Gompertz or generalised gamma curves were used in both arms, the PFS curves crossed each other, resulting in a greater long-term proportion of progression-free patients in the osimertinib monotherapy arm compared with the osimertinib plus CTx arm. This was considered clinically implausible, therefore Gompertz and generalised gamma curves were excluded from consideration for both the osimertinib plus CTx arm and the osimertinib monotherapy arm.

The remaining curves (i.e. Weibull and gamma) were both considered plausible in terms of crossing of PFS and could not be excluded on the basis of statistical or visual fit. Furthermore, based on the predicted and observed survival at key landmarks for osimertinib plus CTx and osimertinib monotherapy presented in Table 61 and

Table 62, the Weibull and gamma curves were both considered to generate plausible estimates of long-term survival.

The Weibull curve was selected as the base case extrapolation for both the osimertinib plus CTx arm and the osimertinib monotherapy comparator arm as it had slightly better statistical fits overall compared to the gamma curve. The Weibull was the third- and second-best ranked curve by AIC and BIC, respectively, in the osimertinib plus CTx arm and the third best ranked curve in the osimertinib monotherapy arm for both AIC and BIC. In contrast, for both AIC and BIC, gamma was the fourth best ranked curve in the osimertinib plus CTx arm and the second-best ranked curve in the osimertinib monotherapy arm. The gamma curve was therefore explored as a scenario analysis.

A summary of the curve selections is given in Table 60.

Table 60. Plausible PFS parametric models used in the base case

	Osimertinib plus CTx	Osimertinib monotherapy
Base case	**Weibull**	**Weibull**
Scenario	Gamma	Gamma

Abbreviations: CTx: chemotherapy; PFS: progression-free survival.

Table 61: Osimertinib plus CTx predicted and observed mean, median and landmark rates (PFS)

	Mean	Median	1 year	2 years	3 years	5 years	10 years	15 years
FLAURA2	–	25.46	79.71%	57.15%	NR	NR	NR	NR
Exponential	41.50	28.58	74.62%	56.34%	42.53%	24.24%	5.81%	1.39%
Weibull	**32.49**	**25.63**	**78.47%**	**54.98%**	**36.01%**	**13.37%**	**0.59%**	**0.01%**
Gompertz	26.48	25.63	80.61%	55.00%	27.35%	0.74%	0.00%	0.00%
Log-logistic	43.29	27.60	77.94%	56.18%	41.28%	24.71%	6.82%	1.81%
Log-normal	45.47	29.57	75.10%	57.14%	45.42%	31.25%	6.82%	1.81%
Generalised gamma	25.89	25.63	79.25%	54.63%	28.01%	0.00%	0.00%	0.00%
Gamma	35.42	26.61	77.66%	55.35%	38.16%	17.25%	2.02%	0.22%

Abbreviations: CTx: chemotherapy; PFS: progression-free survival.

Table 62. Osimertinib monotherapy predicted and observed mean, median and landmark rates (PFS)

	Mean	Median	1 year	2 years	3 years	5 years	10 years	15 years

FLAURA2	–	16.66	65.49%	40.84%	NR	NR	NR	NR
Exponential	26.88	17.74	63.27%	40.77%	26.27%	10.91%	1.17%	0.12%
Weibull	**23.78**	**17.74**	**66.22%**	**39.08%**	**21.65%**	**5.84%**	**0.13%**	**0.00%**
Gompertz	22.70	17.74	65.73%	39.73%	21.24%	3.70%	0.00%	0.00%
Log-logistic	31.26	17.74	64.43%	39.55%	26.35%	14.28%	4.44%	1.08%
Log-normal	32.32	17.74	62.89%	40.77%	28.55%	16.13%	4.44%	1.08%
Generalised gamma	26.14	17.74	65.01%	39.34%	23.97%	9.31%	1.06%	0.15%
Gamma	24.40	17.74	65.90%	39.04%	22.28%	6.88%	0.30%	0.01%

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of OS

D.2.1 Data input

Data input for extrapolation of OS was sourced from the FLAURA2 trial (31).

D.2.2 Model

The following standard parametric models were fitted to the available data: exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma, and gamma distributions.

Based on the previous analysis plan based on the earlier DCOs on OS data, additional spline models were also fitted. As standard parametric model appears to fit and extrapolate the OS data well, the spline models are only included for completeness to allow for alternative models to estimate patients' survival. Further information on the spline models has been included in Appendix L.

D.2.3 Proportional hazards

Figure 24 shows the plot of the Schoenfeld residuals against time. This does not show a pattern of changing residuals over time, and the p-value for Schoenfeld residuals test is non-significant (p=0.8142), indicating that the PHA could not be rejected on these grounds. However, the log cumulative hazard, log odds and log normal curves (

Figure 25) were not parallel and all cross over time, indicating that the treatment effect varied over the trial period. On this basis it was considered that there was a violation of the PHA.

Figure 24. Schoenfeld residual plot for OS from FLAURA2

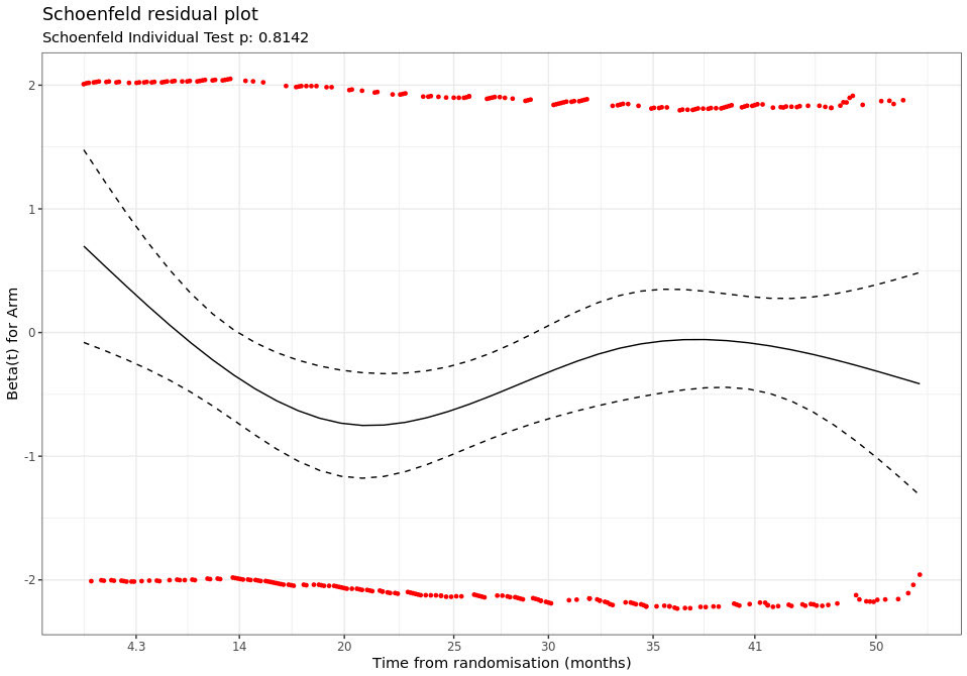
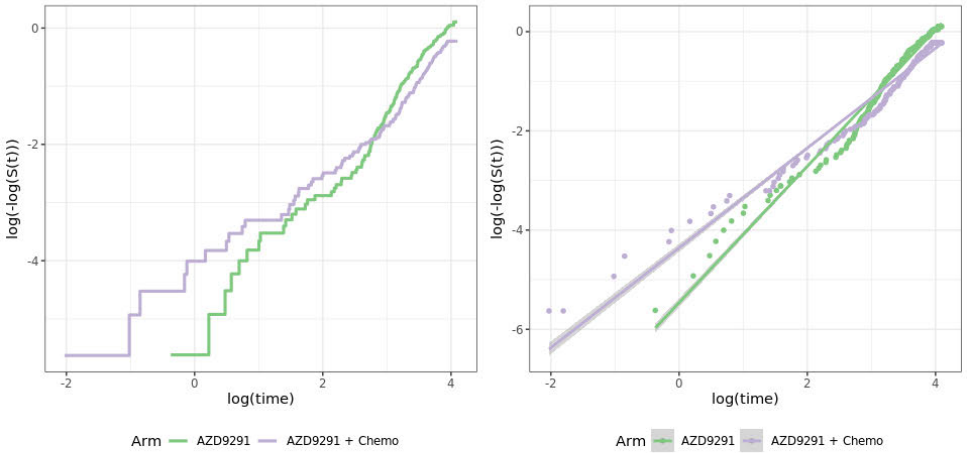
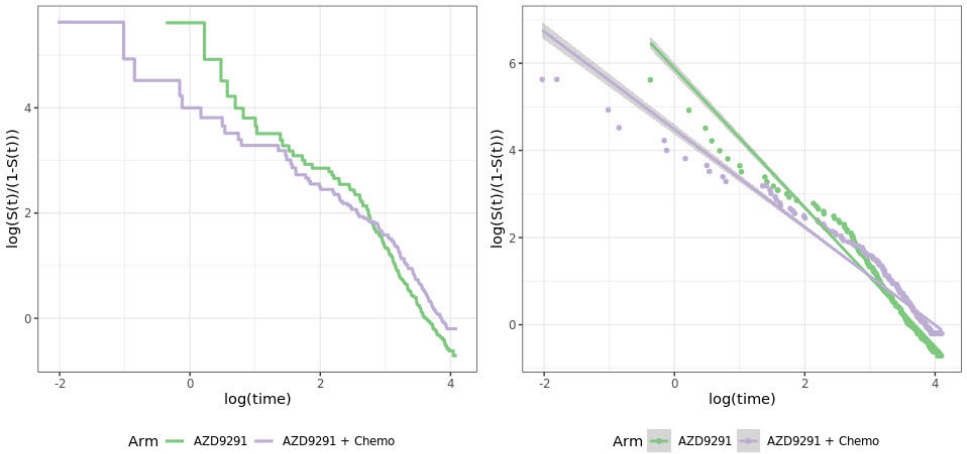

Schoenfeld residual plot
Schoenfeld Individual Test p: 0.8142
Beta(t) for Arm
2
1
0
-1
-2
4.3
14
20
25
30
35
41
50
Time from randomisation (months)

Figure 25. Log-cumulative hazard, log-odds and log-normal plots for OS from FLAURA2

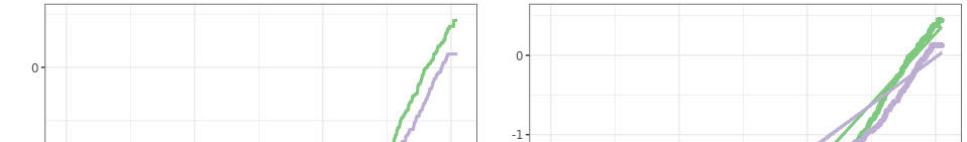
Log cumulative hazards vs. log time



Log odds vs. log time



Log normal vs. log time



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

The AIC and BIC statistics, indicating the within-trial goodness-of-fit of each model for osimertinib plus CTx and osimertinib monotherapy, are provided Table 63.

For the osimertinib plus CTx arm, the Gompertz, Weibull and generalized gamma distributions provided the best fits based on the AIC and BIC statistics amongst standard parametric models. The log-normal and log-logistic were excluded based on poor statistical fit. The AIC/BIC values for all remaining distributions had a relatively narrow range and there were multiple models that provided reasonable fits based on the best fit statistics alone.

For the osimertinib monotherapy arm, the log-logistic, Weibull and Gamma distributions provided the best fits based on AIC and BIC statistics. However, similarly to the osimertinib plus CTx arm, the majority of models provided reasonable fits according to these statistics, with the exception of exponential and log-normal.

Overall, the standard parametric models fit the observed data fairly well, with the exception of log-normal and log-logistic for the osimertinib plus CTx arm and generalized exponential and log-normal for the osimertinib arm.

Table 63. Goodness of fit statistics – FLAURA2 OS (ranking amongst standard parametric models)

Distribution	Osimertinib plus CTx		Osimertinib monotherapy	
	AIC (Rank)	BIC (Rank)	AIC (Rank)	BIC (Rank)
Exponential	1524.1 (5)	1527.7 (3)	1727.5 (7)	1731.1 (7)
Weibull	**1520.2 (3)**	**1527.5 (2)**	**1702.9 (2)**	**1710.2 (2)**
Gompertz	1515.7 (1)	1523.0 (1)	1710.9 (5)	1718.2 (5)
Log-logistic	1528.1 (6)	1535.3 (6)	1702.8 (1)	1710.1 (1)
Lognormal	1550.8 (7)	1558.1 (7)	1720.7 (6)	1727.9 (6)
Generalised gamma	1518.5 (2)	1529.4 (5)	1704.8 (4)	1715.7 (4)
Gamma	1521.9 (4)	1529.2 (4)	1703.3 (3)	1710.5 (3)

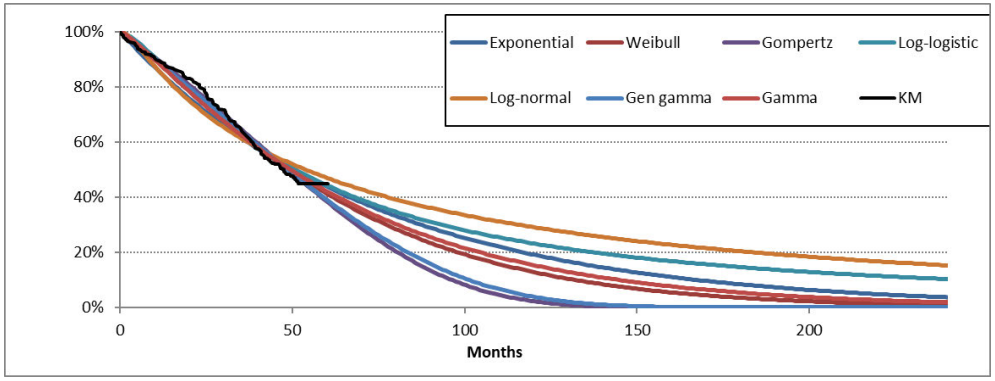
Footnote: Base case extrapolation is shown in **bold**; best fit distributions are shown in green highlight.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CTx: chemotherapy.

D.2.5 Evaluation of visual fit

The standard parametric and spline extrapolations fitted to the osimertinib plus CTx KM data from FLAURA2 are presented in Figure 26 and Figure 39, respectively. Similarly, the standard parametric and spline extrapolations fitted to the osimertinib monotherapy KM data from FLAURA2 are presented in Figure 27 and Figure 40, respectively.

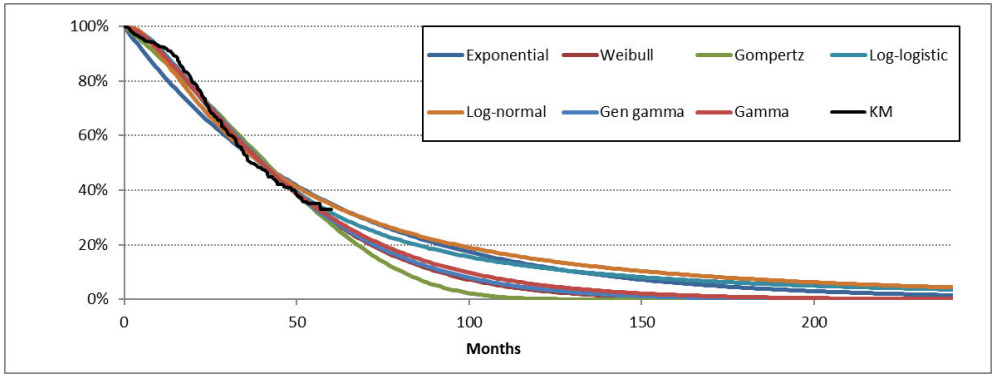
The standard parametric curves appear to provide a fairly good visual fit to the KM data from FLAURA2. For both arms, the standard parametric curves generally appeared to slightly underestimate survival up to month 35 compared to the KM and then appears to provide a wide range of tails, spanning from overly optimistic long-term extrapolations to pessimistic long-term extrapolations.

Figure 26. Standard parametric models fitted to osimertinib plus CTx FLAURA2 OS data



Footnote: Curves on the figure are not bounded by GPM.

Figure 27. Standard parametric models fitted to osimertinib monotherapy FLAURA2 OS data



Footnote: Curves on the figure are not bounded by GPM.

D.2.6 Evaluation of hazard functions

To explore whether standard parametric models were appropriate, plots of the raw and smoothed hazards were considered (Figure 28. and Figure 29.). As specified in NICE DSU TSD 21, complex hazard functions cannot be represented well by standard parametric models, and flexible models (such as spline-based models) that allow hazard functions with complex shapes should also be considered. The raw hazard plot shows that the hazard changes over the course of the trial, and that there is a drop in the hazard in both arms towards the end of the trial period, although this is driven by low patient numbers at risk close to the end of follow-up. For the osimertinib plus CTx arm, the smoothed hazard appears to increase from the start of the trial to ~39 months, before consistently decreasing until the end of the trial follow-up. However, the low number at risk towards the end of the follow-up should be kept in mind when evaluating the hazard towards the end of the curve.

For the osimertinib monotherapy arm, the hazard increases from the time of randomisation to ~28 months, before decreasing until the end of the trial follow-up.

Figure 28. Raw hazard plot for OS from FLAURA2

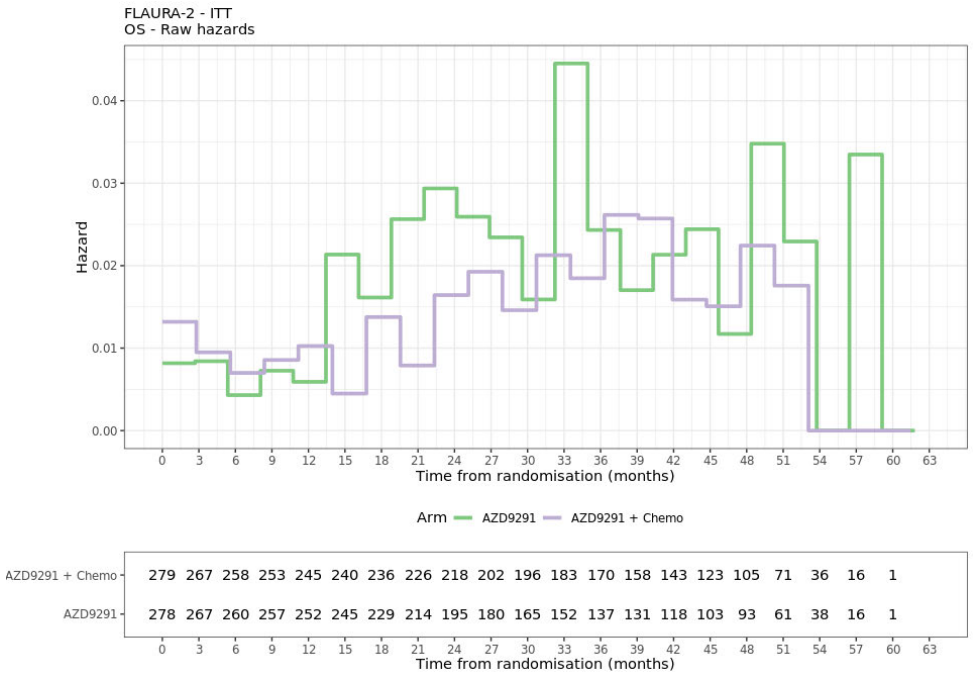
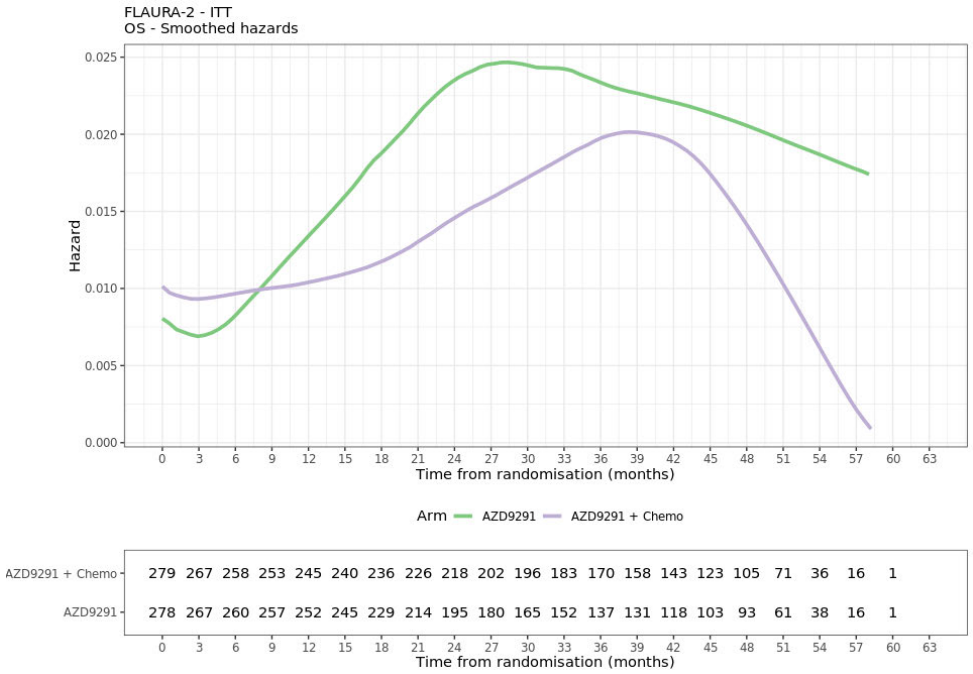


Figure 29. Smoothed hazard plot for OS from FLAURA2



Abbreviations: ITT, intention-to-treat; OS, overall survival.

D.2.7 Validation and discussion of extrapolated curves

The clinical plausibility of the long-term extrapolation of curves was informed by data from previous studies in this indication; these published data indicate typical survival estimates to be around 15–25% at 5 years for patients treated with first generation EGFR TKIs, dropping to around 5–7% at 7–9 years. It was

therefore assumed that approximately 5% of patients alive at 10 years would also represent a clinically plausible, yet conservative, estimate for survival in the model, given the survival benefit associated with osimertinib.

In addition, survival data reported by Winfree *et al.* (2022) were also used to inform model selection (52). This was a retrospective observational study conducted in 244 patients with EGFRm advanced NSCLC where 73% received 1L EGFR TKI, of which 46% received a 3rd generation EGFR TKI. The results indicated that approximately 25% of patients were alive at 5 years. Given a large proportion of patients received a 3rd generation EGFR TKI, defined as osimertinib in the study, it was considered reasonable to expect that at least 25% of patients would also be alive in the osimertinib monotherapy arm at 5 years. In the Danish Lung Cancer Registry report, a more heterogenic population comprising all NSCLC patients with stage IV adenocarcinoma is presented. In this data set, approx. 3% of patients appears to be alive at the 10-year landmark (53). It could be suspected that patients would survive for longer in a more homogenous EGFR-mutated patient population, if treated with a 3rd gen EGFR-TKI. Hence the 3% could be considered a pessimistic floor at the 10-year landmark for patients treated with either osimertinib monotherapy and osimertinib plus CTx.

Selection of curve fits

Osimertinib plus CTx

Osimertinib plus CTx, of the standard parametric curves presented in Table 65, the Gompertz and Gen Gamma curve underpredict long-term survival of patients, where long-term survival at 10- and 15-years are below the survival observed with osimertinib monotherapy in clinical practice, hence the Gompertz and Gen Gamma has been excluded for extrapolation of OS. Log-normal and log-logistic are excluded for extrapolation of OS, as the curves appears to overpredict long-term survival of patients much beyond what could be expected in clinical practice, estimating between 14.6% and 20.4% of patients to be alive after 15-years.

The remaining curves, Exponential, Weibull and Gamma functions, all appear to provide clinically plausible extrapolations of long-term survivals of patients. The exponential curve assumes a constant hazard throughout the time horizon, which does not align with the observed hazards in FLAURA2, where hazards change over time. The exponential curve has therefore been excluded for extrapolation. The Weibull and Gamma curves predicts clinically plausible long-term survival with 3.5% and 5.4% of patients alive at 15-year landmark. For the base-case, the more conservative extrapolation of the two curves has been chosen. Hence, the Weibull curve is used for the base case extrapolation of OS.

Osimertinib monotherapy

For the osimertinib monotherapy arm, the Gompertz function underestimates long-term survival, predicting nearly all patients to be dead beyond 10-years, which does not reflect the survival in clinical practice. The log-normal, log-logistic and exponential functions appears to overpredict long-term survival when compared to data form the Danish Lung Cancer registry (53). Remaining are the Weibull, gamma and gen-gamma functions, which all appear to provide reasonable and clinically plausible long-term extrapolations in line with what is observed in the Danish Lung Cancer registry in a more heterogeneous population (53).

As none of the remaining curves could be excluded on the basis of clinical plausibility, the Weibull curve was selected for the base case in order to align with the base-case curve chosen for OS for osimertinib plus CTx. As previously discussed, this approach is in line with NICE TSD 14, which recommends fitting parametric models of the same type to both treatment arms in the absence of substantial justification that this would not be appropriate (40).

Scenario analysis

The Gamma curve fits the data well and predicts clinically plausible long-term extrapolations of survival based as described above. The Gamma curve provides a clinically plausible alternative to Weibull for the extrapolation of OS. Scenario analysis was therefore conducted using the Gamma curve for both the osimertinib plus CTx and osimertinib monotherapy arm. A summary of the curve selections is given Table 64.

Figure 30. Comparison between Weibull and gamma normal curves alongside observational data from FLAURA2. Parametric models used in the base case and scenario analyses

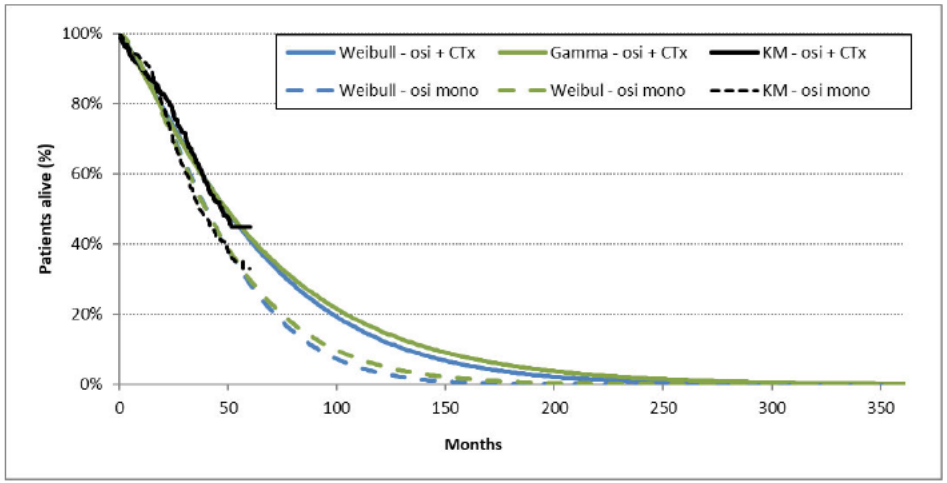


Table 64. Plausible OS parametric models used in the base case and scenario analyses

	Osimertinib plus CTx	Osimertinib monotherapy
Base case	Weibull	Weibull
Scenario	Gamma	Gamma

Abbreviations: CTx: chemotherapy; OS: overall survival.

Table 65. Osimertinib plus CTx predicted and observed mean, median and landmark rates (OS)

	Mean (mth)	Median(mth)	2 years	3 years	4 years	5 years	10 years	15 years

FLAURA2	–	47.51	79.71%	63.14%	49.15%	45.02%	-	-
Exponential	72.09	49.28	71.70%	60.92%	51.76%	43.98%	19.21%	8.39%
Weibull	**62.19**	**48.30**	**74.54%**	**62.10%**	**51.04%**	**41.51%**	**12.90%**	**3.49%**
Gompertz	51.68	47.31	76.47%	63.83%	51.04%	38.70%	2.31%	0.00%
Log-logistic	87.97	50.27	73.94%	61.91%	52.21%	44.51%	23.24%	14.63%
Log-normal	101.23	52.24	70.78%	60.80%	53.17%	47.13%	29.14%	20.38%
Generalised gamma	52.87	47.31	75.44%	63.03%	50.90%	39.41%	3.95%	0.02%
Gamma	66.06	48.30	73.83%	61.76%	51.28%	42.37%	15.40%	5.40%

Note: Landmarks capped to general population mortality. Base case extrapolation is shown in **bold**;
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CTx: chemotherapy.

Abbreviations: CTx: chemotherapy; mth: months; OS: overall survival.

Table 66. Osimertinib monotherapy predicted and observed mean, median and landmark rates (OS)

	Mean (mth)	Median(mth)	2 years	3 years	4 years	5 years	10 years	15 years
FLAURA2	-	37.62	71.51%	50.86%	40.82%	32.96%	-	-
Exponential	57.03	38.44	65.53%	53.27%	43.31%	35.21%	12.29%	4.29%
Weibull	**46.82**	**39.43**	**71.95%**	**55.48%**	**40.97%**	**29.16%**	**3.30%**	**0.21%**
Gompertz	43.46	40.41	71.88%	56.67%	41.63%	27.92%	0.23%	0.00%
Log-logistic	61.02	38.44	70.80%	54.07%	41.30%	32.03%	11.76%	5.99%
Log-normal	65.22	38.44	68.04%	53.63%	42.93%	34.91%	14.72%	7.58%
Generalised gamma	47.42	39.43	71.75%	55.28%	40.98%	29.46%	3.91%	0.35%
Gamma	49.09	38.44	71.16%	54.85%	41.14%	30.28%	5.45%	0.86%

Note: Landmarks capped to general population mortality. Base case extrapolation is shown in **bold**;
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CTx: chemotherapy.

D.2.8 Adjustment of background mortality

OS has been adjusted to the Danish background mortality.

D.2.9 Adjustment for treatment switching/cross-over

N/A

D.2.10 Waning effect

N/A

D.2.11 Cure-point

N/A

D.3 Extrapolation of TTD

D.3.1 Data input

Data input for extrapolation of PFS was sourced from the FLAURA2 trial.

Individual patient TTD data from the FLAURA2 trial, in the form of time-to-event data, were available to inform the time on treatment for both treatment arms in the model. In the intervention arm, TTD data were available for osimertinib and pemetrexed separately, whilst the comparator arm only necessitated TTD for osimertinib monotherapy.

D.3.2 Model

The following standard parametric models were fitted to the available data: exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma, and gamma distributions.

D.3.3 Proportional hazards (osimertinib dataset)

Figure 31 shows the plot of the Schoenfeld residuals against time for osimertinib TTD. This does not show a pattern of changing residuals over time, and the p-value for Schoenfeld residuals test is non-significant (p=0.801), indicating that the PHA could be considered reasonable. However, the log cumulative hazard curves (

Figure 32) were not parallel over time, indicating that the treatment effect varied over the trial period. On this basis it was considered that there was a violation of the PHA for osimertinib TTD.

Figure 31. Schoenfeld residual plot for osimertinib TTD from FLAURA2

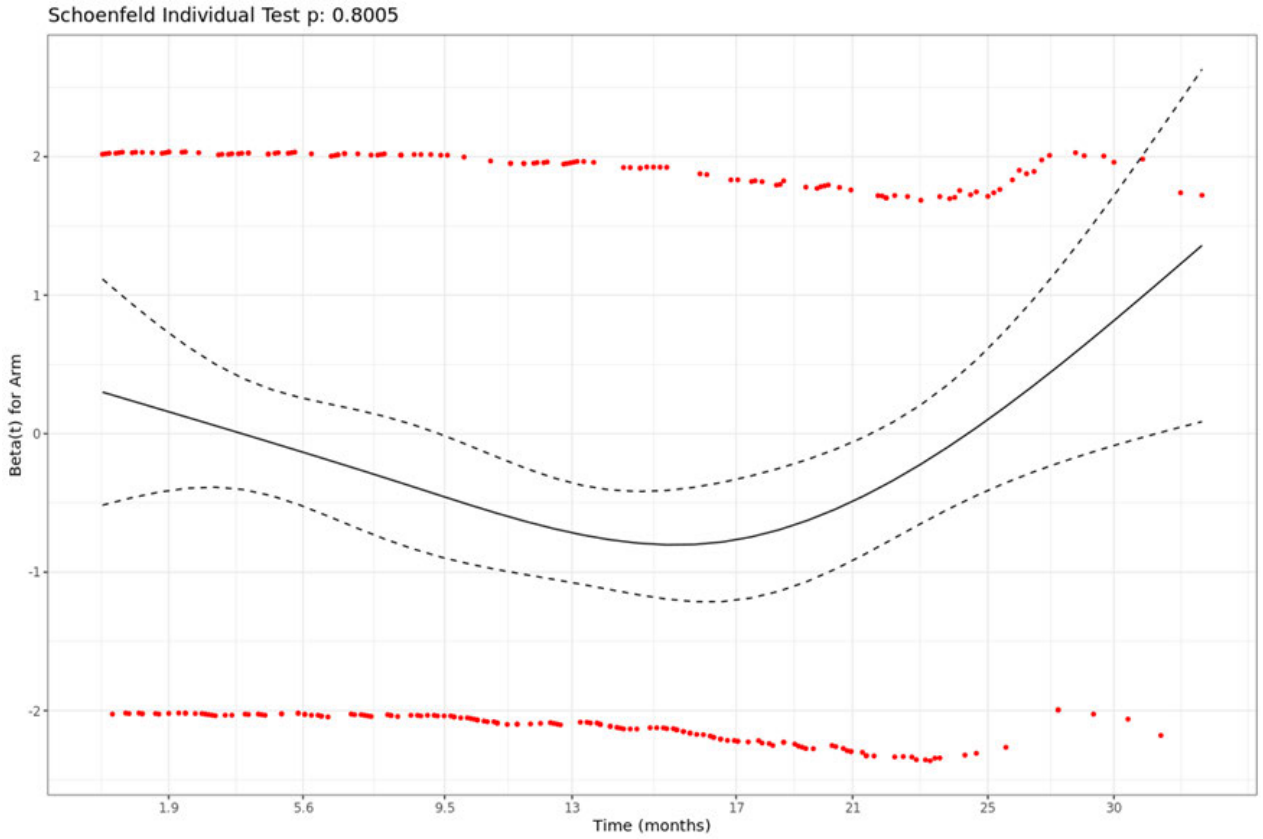
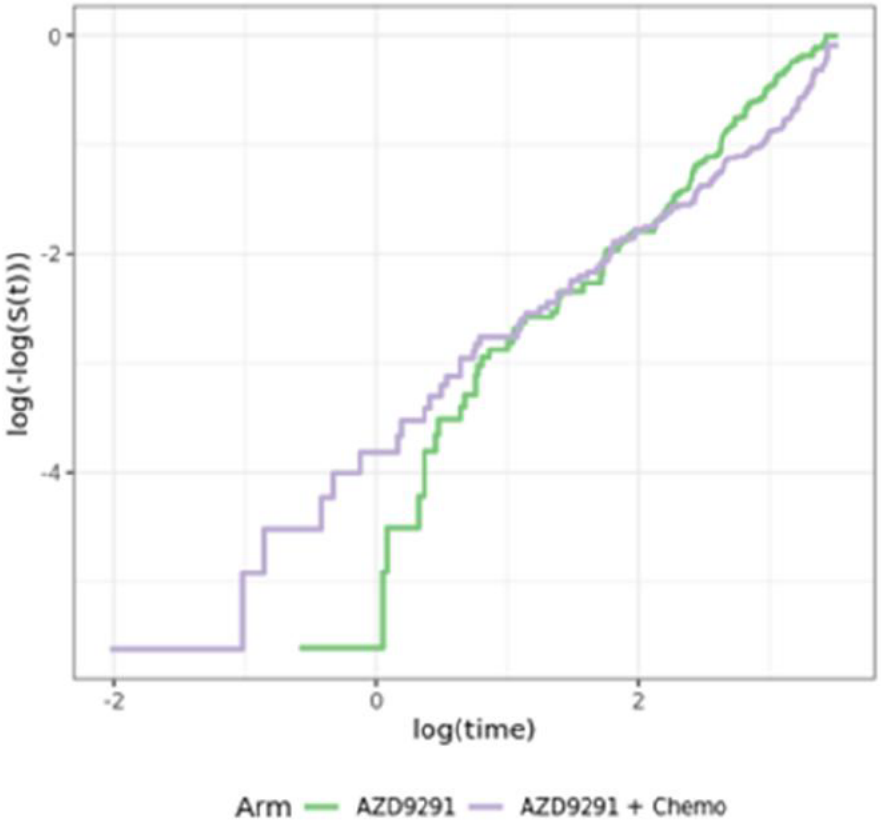


Figure 32. Log-cumulative hazard plot for osimertinib TTD from FLAURA2



Abbreviations: TTD: time to treatment discontinuation.

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

D.3.4.1 Osimertinib (as part of osimertinib plus CTx)

Of the distributions, the AIC and BIC rankings suggest that the Gompertz distribution was the best statistically fitting extrapolation for the osimertinib TTD data but all extrapolations generally had good fit to the observed data and therefore no extrapolations were excluded based on visual and statistical fit alone.

Table 67. Goodness of fit statistics – osimertinib (as part of osimertinib plus CTx)

Distribution	Osimertinib (as part of osimertinib plus CTx)	
	AIC (Rank)	BIC (Rank)
Exponential	1181.30 (3)	1184.90 (1)
Weibull	1182.80 (5)	1190.10 (3)
Gompertz	**1180.50 (1)**	**1187.80 (2)**
Log-logistic	1187.70 (6)	1194.90 (6)
Lognormal	1194.50 (7)	1201.80 (7)
Generalised gamma	1181.00 (2)	1191.90 (5)

Gamma	1183.00 (4)	1190.30 (4)

Footnote: Base case extrapolation is shown in **bold**; best fit distributions are shown in green highlight
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CTx: chemotherapy; TTD: time to treatment discontinuation.

D.3.4.2 Pemetrexed (as part of osimertinib plus CTx)

Of the distributions, the AIC and BIC rankings suggest that the Gompertz distribution was the best statistically fitting extrapolation for the osimertinib TTD data but all extrapolations generally had good fit to the observed data and therefore no extrapolations were excluded based on visual and statistical fit alone.

Table 68. Goodness of fit statistics – pemetrexed (as part of osimertinib plus CTx)

Distribution	Pemetrexed (as part of osimertinib plus CTx)	
	AIC (Rank)	BIC (Rank)
Exponential	**1590.70 (6)**	**1594.30 (5)**
Weibull	1589.80 (5)	1597.10 (6)
Gompertz	1582.50 (4)	1589.70 (4)
Log-logistic	1575.90 (3)	1583.20 (2)
Lognormal	1571.30 (1)	1578.50 (1)
Generalised gamma	1573.10 (2)	1584.00 (3)
Gamma	1591.60 (7)	1598.80 (7)

Footnote: Base case extrapolation is shown in **bold**; best fit distributions are shown in green highlight

D.3.4.3 Osimertinib monotherapy

The AIC and BIC scores showed that all parametric distributions were a good fit to the observed data and therefore no extrapolations were excluded based on visual and statistical fit alone.

Table 69. Goodness of fit statistics – osimertinib monotherapy

Distribution	Osimertinib monotherapy	
	AIC (Rank)	BIC (Rank)
Exponential	1361.50 (7)	1365.20 (5)
Weibull	1355.00 (3)	1362.30 (3)
Gompertz	**1359.20 (6)**	**1366.50 (6)**
Log-logistic	1354.30 (1)	1361.50 (1)
Lognormal	1357.90 (5)	1365.10 (4)
Generalised gamma	1356.00 (4)	1366.90 (7)
Gamma	1354.40 (2)	1361.60 (2)

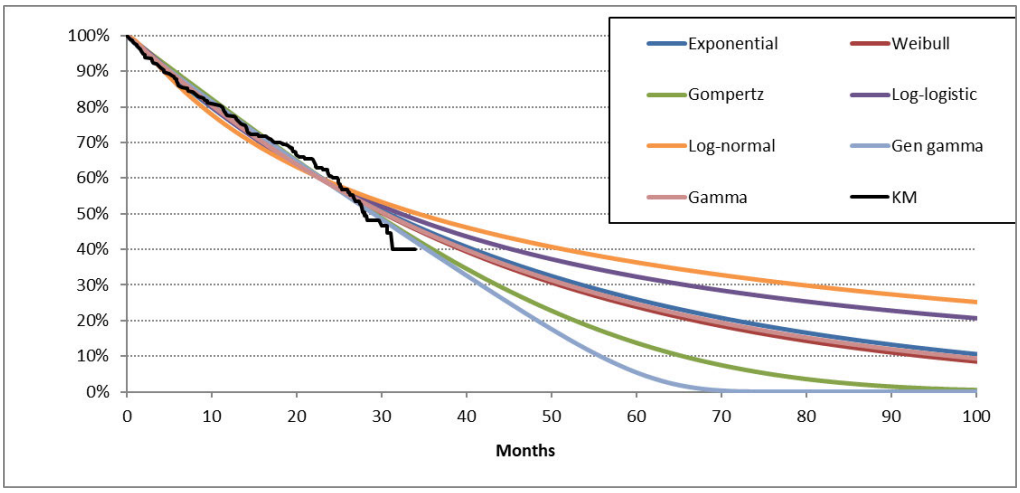
Footnote: Base case extrapolation is shown in **bold**; best fit distributions are shown in green highlight

D.3.5 Evaluation of visual fit

D.3.5.1 Osimertinib (as part of osimertinib plus CTx)

Extrapolated curves fitted to the TTD data of osimertinib (as part of the osimertinib plus CTx arm) are presented in Figure 33.

Figure 33. Parametric models fitted to osimertinib (as part of the osimertinib plus CTx) TTD data

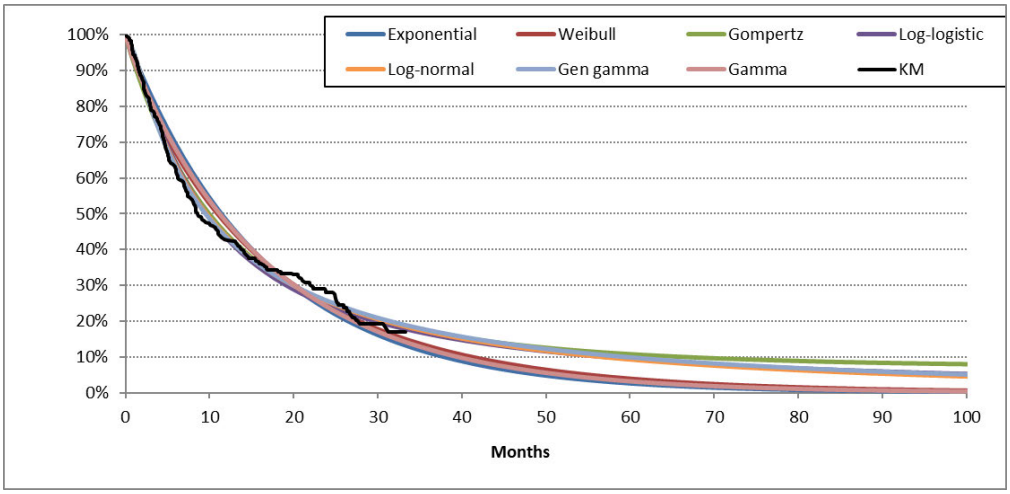


Footnote: Curves on the figure are not bounded by OS

D.3.5.2 Pemetrexed (as part of osimertinib plus CTx)

Parametric curves fitted to the TTD data of pemetrexed (as part of osimertinib plus CTx) are presented in Figure 34.

Figure 34. Parametric models fitted to pemetrexed (as part of osimertinib plus CTx) TTD data

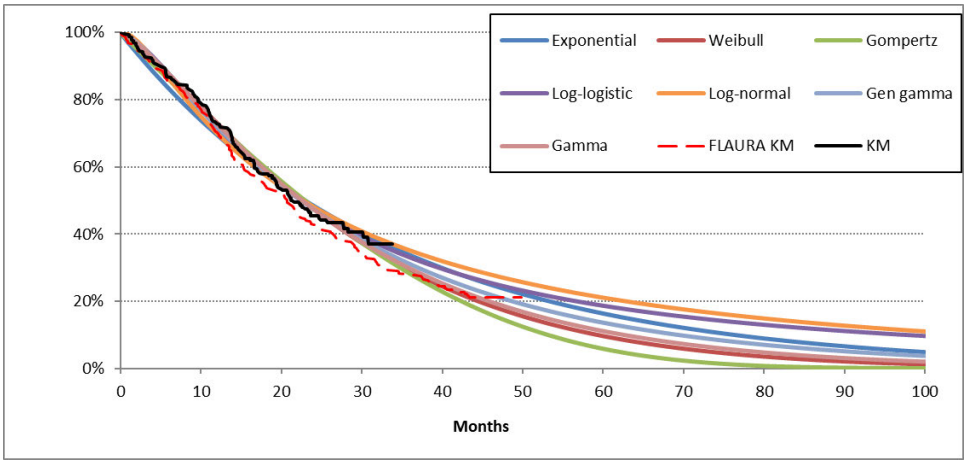


Footnote: Curves on the figure are not bounded by OS

D.3.5.3 Osimertinib monotherapy

Parametric curves fitted to the TTD data of osimertinib monotherapy are presented in Figure 35.

Figure 35. Parametric models fitted to osimertinib monotherapy TTD data



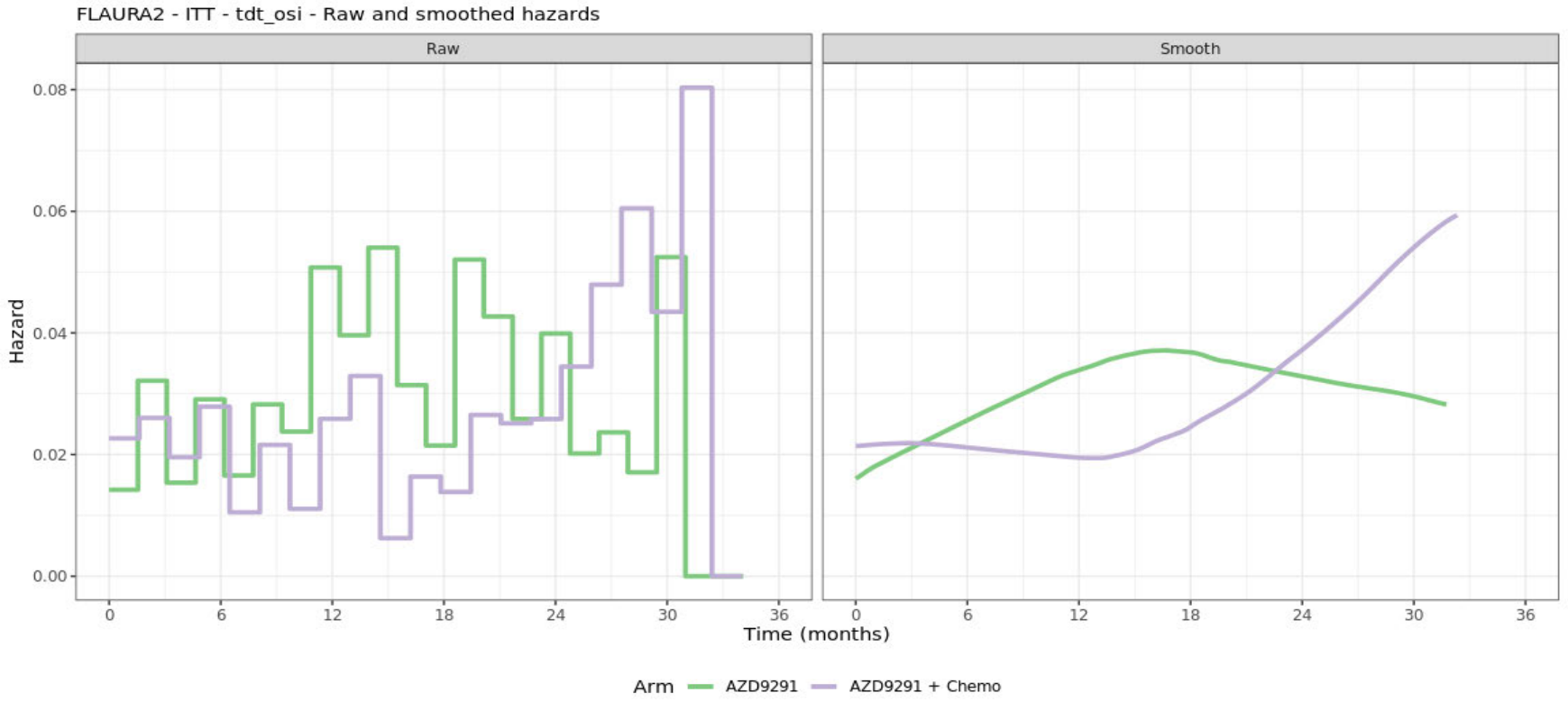
Footnote: Curves on the figure are not bounded by OS

D.3.6 Evaluation of hazard functions

To explore whether standard parametric models were appropriate, plots of the raw and smoothed hazards were considered (

Figure 36). The raw hazard plot shows that the hazards are relatively constant over the duration of the trial, although there is a change at the end of the trial in both arms, driven by low patient numbers. For both trial arms, the smoothed hazards appear relatively stable over the duration of trial period, with an increasing trend. For this reason, standard parametric models were deemed appropriate for TTD.

Figure 36. Raw and smoothed hazards for osimertinib TTD from FLAURA2



D.3.7 Validation and discussion of extrapolated curves

A summary of the preferred curve selections for TTD is given in Table 70.

Table 70. Summary of TTD parametric models used in the base case and scenario analyses

	Osimertinib plus CTx (osimertinib)	Osimertinib plus CTx (pemetrexed)	Osimertinib monotherapy
Base case	Gompertz	Exponential	Gompertz
Scenarios	N/A	N/A	Weibull

D.3.7.1 Osimertinib (as part of osimertinib plus CTx)

When considering clinical plausibility, log-logistic and log-normal curves of osimertinib TTD sharply crossed the projected base case OS curve between months 50 and 60 and therefore were considered logically implausible and excluded from consideration. The generalized gamma curve of osimertinib TTD was also excluded from consideration as this curve crossed sharply underneath the projected base case PFS curve at approximately month 45 (see Figure 37). This was considered clinically implausible because, in clinical practice, patients frequently continue treatment with osimertinib beyond the time of progression.

The remaining extrapolations either did not cross the projected base case OS or PFS curves (Weibull and gamma) or only marginally crossed (i.e. were more aligned with) the projected base case PFS (Gompertz) or OS curves (exponential) and therefore could not be excluded on the basis of clinical plausibility or statistical and/or visual fit. Thus, the Gompertz curve was adopted in the base case analysis as it had the best statistical fit of the remaining plausible curves.

Figure 37. Gompertz extrapolation for osimertinib TTD in osimertinib plus CTx arm and base case curves for PFS and OS

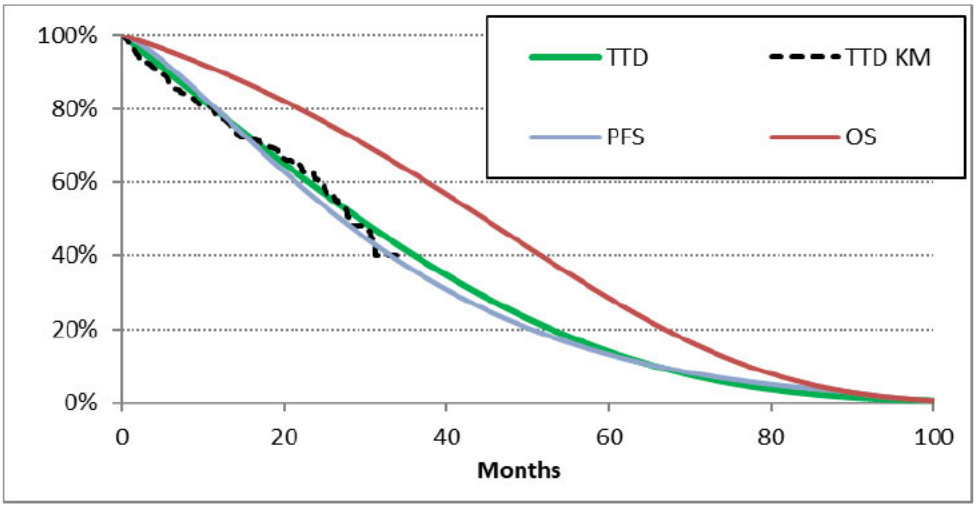


Table 71. Osimertinib (as part of osimertinib plus CTx) predicted and observed mean, median and landmark TTD data

	Mean	Median	1 year	2 years	3 years	5 years	10 years	15 years
FLAURA2	–	27.96	77.60%	60.70%	40.10%	NR	NR	NR
Exponential	40.95	29.57	75.80%	58.10%	44.50%	26.10%	3.20%	0.20%
Weibull	40.11	29.57	76.60%	58.00%	43.50%	24.00%	3.20%	0.20%
Gompertz	32.88	28.58	78.20%	58.10%	40.00%	14.00%	0.00%	0.00%
Log-logistic	42.71	31.54	75.80%	58.50%	46.70%	32.30%	3.20%	0.20%
Log-normal	43.18	33.51	73.80%	58.60%	48.80%	32.50%	3.20%	0.20%
Generalised gamma	29.91	27.6	77.50%	57.90%	39.00%	5.80%	0.00%	0.00%
Gamma	40.51	29.57	76.30%	58.00%	43.90%	24.90%	3.20%	0.20%

D.3.7.2 Pemetrexed (as part of osimertinib plus CTx)

Extrapolations of pemetrexed TTD that crossed the projected base case OS curve were considered logically implausible and TTD curves that crossed the projected base case PFS curve were considered clinically implausible as patients would not be expected to continue pemetrexed post-progression, even if continuing treatment with osimertinib. The Gompertz, log-logistic, log-normal and generalized gamma extrapolations all crossed the projected PFS curve and were, therefore, excluded from consideration. The remaining plausible extrapolations (exponential, Weibull, gamma) were fairly similar in terms of visual and statistical fit, and therefore were considered for clinical plausibility of the long-term survival estimates.

The key landmarks over time of pemetrexed (as part of the osimertinib plus CTx) are presented in Table 72. Typically, it is not expected that patients would continue pemetrexed treatment beyond five years. As a result, the exponential distribution was selected to model pemetrexed TTD as it projected the lowest proportion of patients on treatment at five years of the remaining curves (Table 72).

Table 72. Pemetrexed (as part of osimertinib plus CTx) predicted and observed mean, median and landmark TTD data

	Mean	Median	1 year	2 years	3 years	5 years	10 years	15 years
FLAURA2	–	8.51	42.96%	28.01%	17.06%	NR	NR	NR
Exponential	16.46	10.84	47.32%	23.06%	11.24%	2.67%	0.07%	0.00%
Weibull	17.21	9.86	46.30%	24.21%	13.04%	3.99%	0.23%	0.02%
Gompertz	25.28	8.87	43.79%	25.31%	17.28%	11.02%	6.82%	1.81%
Log-logistic	23.03	8.87	42.53%	24.44%	16.53%	9.62%	4.32%	1.81%
Log-normal	22.35	8.87	43.01%	25.32%	17.02%	9.34%	3.40%	1.70%

Generalised gamma	23.19	8.87	42.80%	25.60%	17.55%	10.03%	3.98%	1.81%
Gamma	16.79	9.86	46.90%	23.79%	12.20%	3.25%	0.12%	0.00%

D.3.7.3 Osimertinib monotherapy

When considering clinical plausibility, the log-logistic and log-normal curves of osimertinib TTD crossed the projected OS curve at approximately month 70 and 75, respectively, and were therefore considered logically implausible for predicting the TTD of osimertinib monotherapy.

The key landmarks over time of osimertinib monotherapy are summarised in Table 73.

Of the remaining plausible extrapolations (exponential, Weibull, gompertz, generalised gamma and gamma), the exponential and generalised gamma curves diverged further from the projected PFS curve over time, and both end up crossing the gompertz TTD curve of the osimertinib plus CTx arm at approximately month 53 and 61, which conflicts with the logical expectation of the osimertinib mono arm being treated shorter time than the combination arm, and therefore have been been excluded for extrapolation of TTD for the comparator arm.

Weibull, gompertz and gamma curves all converge towards the projected PFS curve, however, the Weibull and gamma curves both cross the TTD curve of osimertinib plus CTx arm at a month 81 and 72, respectively, hence potentially overestimating the osimertinib cost acquisition cost in the comparator arm. Although the gompertz curve does cross the projected PFS curve, it does not cross the TTD curve of the osimertinib plus CTx arm. Hence, this should be seen as the more conservative curve choice for projecting TTD, potentially underestimating the osimertinib acquisition cost in the osimertinib arm. Thus, the gompertz curve was used to model osimertinib TTD in the comparator arm. This approach is also in line with NICE TSD 14, which recommends fitting parametric models of the same type to both treatment arms in the absence of substantial justification that this would not be appropriate(40). A scenario analysis of the Weibull TTD curve was conducted.

Table 73. Osimertinib monotherapy predicted and observed mean, median and landmark TTD data

	Mean	Median	1 year	2 years	3 years	5 years	10 years	15 years
FLAURA2	–	21.19	73.00%	45.40%	37.00%	NR	NR	NR
Exponential	32.12	21.68	69.00%	48.30%	33.80%	16.60%	1.30%	0.10%
Weibull	28.31	21.68	72.40%	47.30%	29.10%	9.80%	0.40%	0.00%
Gompertz	**26.27**	**21.68**	**71.90%**	**47.80%**	**28.20%**	**6.00%**	**0.00%**	**0.00%**
Log-logistic	33.02	21.68	71.10%	47.30%	33.00%	18.80%	1.30%	0.10%
Log-normal	33.7	21.68	69.30%	47.90%	35.10%	21.20%	1.30%	0.10%
Generalised gamma	31.02	21.68	71.40%	47.20%	31.10%	13.80%	1.30%	0.10%

Gamma	29.32	21.68	72.10%	47.20%	29.80%	11.30%	0.80%	0.10%

D.3.8 Adjustment of background mortality

N/A

D.3.9 Adjustment for treatment switching/cross-over

N/A

D.3.10 Waning effect

N/A

D.3.11 Cure-point

N/A

Appendix E. Serious adverse events

Table 74. Summary of serious adverse events by system organ class and preferred term - Randomization Period (Safety analysis set), Final OS analysis. 12 June 2025 DCO

	Number (%) of subjects		
System organ class/ MedDRA preferred term	Osi + Chemo (N=276)	Osi (N=275)	Total (N=551)
Subjects with any serious adverse event	**126 (45.7)**	**75 (27.3)**	**201 (36.5)**
Infections and infestations	38 (13.8)	32 (11.6)	70 (12.7)
Pneumonia	9 (3.3)	12 (4.4)	21 (3.8)
COVID-19	8 (2.9)	2 (0.7)	10 (1.8)
COVID-19 pneumonia	4 (1.4)	5 (1.8)	9 (1.6)
Sepsis	3 (1.1)	2 (0.7)	5 (0.9)
Urinary tract infection	3 (1.1)	1 (0.4)	4 (0.7)
Dengue fever	2 (0.7)	0 (0.0)	2 (0.4)
Appendicitis	1 (0.4)	1 (0.4)	2 (0.4)
Pneumonia aspiration	1 (0.4)	1 (0.4)	2 (0.4)
Skin infection	1 (0.4)	1 (0.4)	2 (0.4)
Cellulitis	1 (0.4)	0 (0.0)	1 (0.2)
Herpes zoster	1 (0.4)	0 (0.0)	1 (0.2)
Lower respiratory tract infection	1 (0.4)	0 (0.0)	1 (0.2)
Pneumonia mycoplasmal	1 (0.4)	0 (0.0)	1 (0.2)
Pneumonia streptococcal	1 (0.4)	0 (0.0)	1 (0.2)
Postoperative wound infection	1 (0.4)	0 (0.0)	1 (0.2)
Pyelonephritis acute	1 (0.4)	0 (0.0)	1 (0.2)
Septic shock	1 (0.4)	0 (0.0)	1 (0.2)
Wound infection	1 (0.4)	0 (0.0)	1 (0.2)
Gastroenteritis	0 (0.0)	2 (0.7)	2 (0.4)
Appendiceal abscess	0 (0.0)	1 (0.4)	1 (0.2)
Ear infection	0 (0.0)	1 (0.4)	1 (0.2)
Gastroenteritis viral	0 (0.0)	1 (0.4)	1 (0.2)
Gastrointestinal infection	0 (0.0)	1 (0.4)	1 (0.2)
Lower respiratory tract infection bacterial	0 (0.0)	1 (0.4)	1 (0.2)
Lymphangitis	0 (0.0)	1 (0.4)	1 (0.2)
Respiratory tract infection	0 (0.0)	1 (0.4)	1 (0.2)

Scrub typhus	0 (0.0)	1 (0.4)	1 (0.2)
Blood and lymphatic system disorders	**19 (6.9)**	**2 (0.7)**	**21 (3.8)**
Anaemia	9 (3.3)	2 (0.7)	11 (2.0)
Febrile neutropenia	6 (2.2)	0 (0.0)	6 (1.1)
Granulocytopenia	1 (0.4)	0 (0.0)	1 (0.2)
Leukopenia	1 (0.4)	0 (0.0)	1 (0.2)
Myelosuppression	1 (0.4)	0 (0.0)	1 (0.2)
Neutropenia	1 (0.4)	0 (0.0)	1 (0.2)
Thrombocytopenia	1 (0.4)	0 (0.0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**18 (6.5)**	**20 (7.3)**	**38 (6.9)**
Pulmonary embolism	7 (2.5)	2 (0.7)	9 (1.6)
Interstitial lung disease	2 (0.7)	5 (1.8)	7 (1.3)
Dyspnoea	2 (0.7)	2 (0.7)	4 (0.7)
Acute respiratory failure	2 (0.7)	0 (0.0)	2 (0.4)
Pneumothorax	1 (0.4)	4 (1.5)	5 (0.9)
Hypoxia	1 (0.4)	1 (0.4)	2 (0.4)
Epistaxis	1 (0.4)	0 (0.0)	1 (0.2)
Pleuritic pain	1 (0.4)	0 (0.0)	1 (0.2)
Pneumonitis	1 (0.4)	0 (0.0)	1 (0.2)
Pneumothorax spontaneous	1 (0.4)	0 (0.0)	1 (0.2)
Pulmonary oedema	1 (0.4)	0 (0.0)	1 (0.2)
Respiratory failure	1 (0.4)	0 (0.0)	1 (0.2)
Pleural effusion	0 (0.0)	2 (0.7)	2 (0.4)
Asthma	0 (0.0)	1 (0.4)	1 (0.2)
Bronchial obstruction	0 (0.0)	1 (0.4)	1 (0.2)
Haemoptysis	0 (0.0)	1 (0.4)	1 (0.2)
Organising pneumonia	0 (0.0)	1 (0.4)	1 (0.2)
Pulmonary artery thrombosis	0 (0.0)	1 (0.4)	1 (0.2)
Pulmonary congestion	0 (0.0)	1 (0.4)	1 (0.2)
Gastrointestinal disorders	**14 (5.1)**	**6 (2.2)**	**20 (3.6)**
Diarrhoea	5 (1.8)	1 (0.4)	6 (1.1)
Vomiting	3 (1.1)	1 (0.4)	4 (0.7)
Nausea	3 (1.1)	0 (0.0)	3 (0.5)
Colitis	1 (0.4)	0 (0.0)	1 (0.2)
Diverticular perforation	1 (0.4)	0 (0.0)	1 (0.2)

Food poisoning	1 (0.4)	0 (0.0)	1 (0.2)
Gastritis	1 (0.4)	0 (0.0)	1 (0.2)
Gastrointestinal haemorrhage	1 (0.4)	0 (0.0)	1 (0.2)
Gastrooesophageal reflux disease	1 (0.4)	0 (0.0)	1 (0.2)
Inguinal hernia	1 (0.4)	0 (0.0)	1 (0.2)
Upper gastrointestinal haemorrhage	1 (0.4)	0 (0.0)	1 (0.2)
Upper gastrointestinal perforation	1 (0.4)	0 (0.0)	1 (0.2)
Abdominal pain	0 (0.0)	1 (0.4)	1 (0.2)
Ascites	0 (0.0)	1 (0.4)	1 (0.2)
Intestinal obstruction	0 (0.0)	1 (0.4)	1 (0.2)
Large intestinal obstruction	0 (0.0)	1 (0.4)	1 (0.2)
Stomatitis	0 (0.0)	1 (0.4)	1 (0.2)
Cardiac disorders	**12 (4.3)**	**5 (1.8)**	**17 (3.1)**
Cardiac failure	3 (1.1)	1 (0.4)	4 (0.7)
Coronary artery stenosis	2 (0.7)	0 (0.0)	2 (0.4)
Acute myocardial infarction	1 (0.4)	1 (0.4)	2 (0.4)
Endocarditis noninfective	1 (0.4)	1 (0.4)	2 (0.4)
Cardiac arrest	1 (0.4)	0 (0.0)	1 (0.2)
Coronary artery disease	1 (0.4)	0 (0.0)	1 (0.2)
Heart failure with preserved ejection fraction	1 (0.4)	0 (0.0)	1 (0.2)
Left ventricular dysfunction	1 (0.4)	0 (0.0)	1 (0.2)
Myocardial infarction	1 (0.4)	0 (0.0)	1 (0.2)
Myocarditis	1 (0.4)	0 (0.0)	1 (0.2)
Tachycardia	1 (0.4)	0 (0.0)	1 (0.2)
Atrial fibrillation	0 (0.0)	1 (0.4)	1 (0.2)
Mitral valve disease	0 (0.0)	1 (0.4)	1 (0.2)
Pericardial effusion	0 (0.0)	1 (0.4)	1 (0.2)
Injury, poisoning and procedural complications	**11 (4.0)**	**3 (1.1)**	**14 (2.5)**
Hip fracture	3 (1.1)	0 (0.0)	3 (0.5)
Spinal compression fracture	2 (0.7)	0 (0.0)	2 (0.4)
Femur fracture	1 (0.4)	0 (0.0)	1 (0.2)
Fibula fracture	1 (0.4)	0 (0.0)	1 (0.2)
Humerus fracture	1 (0.4)	0 (0.0)	1 (0.2)
Lower limb fracture	1 (0.4)	0 (0.0)	1 (0.2)
Patella fracture	1 (0.4)	0 (0.0)	1 (0.2)

Radiation pneumonitis	1 (0.4)	0 (0.0)	1 (0.2)
Road traffic accident	1 (0.4)	0 (0.0)	1 (0.2)
Brain herniation	0 (0.0)	1 (0.4)	1 (0.2)
Femoral neck fracture	0 (0.0)	1 (0.4)	1 (0.2)
Lumbar vertebral fracture	0 (0.0)	1 (0.4)	1 (0.2)
Investigations	**11 (4.0)**	**1 (0.4)**	**12 (2.2)**
Platelet count decreased	6 (2.2)	0 (0.0)	6 (1.1)
Neutrophil count decreased	2 (0.7)	0 (0.0)	2 (0.4)
Blood creatinine increased	1 (0.4)	0 (0.0)	1 (0.2)
Hepatic enzyme increased	1 (0.4)	0 (0.0)	1 (0.2)
International normalised ratio increased	1 (0.4)	0 (0.0)	1 (0.2)
Transaminases increased	1 (0.4)	0 (0.0)	1 (0.2)
White blood cell count decreased	1 (0.4)	0 (0.0)	1 (0.2)
Lymphocyte count decreased	0 (0.0)	1 (0.4)	1 (0.2)
Nervous system disorders	10 (3.6)	11 (4.0)	21 (3.8)
Ischaemic stroke	2 (0.7)	0 (0.0)	2 (0.4)
Cerebral ischaemia	1 (0.4)	1 (0.4)	2 (0.4)
Intracranial pressure increased	1 (0.4)	1 (0.4)	2 (0.4)
Cerebral venous sinus thrombosis	1 (0.4)	0 (0.0)	1 (0.2)
Haemorrhage intracranial	1 (0.4)	0 (0.0)	1 (0.2)
Lacunar infarction	1 (0.4)	0 (0.0)	1 (0.2)
Paraesthesia	1 (0.4)	0 (0.0)	1 (0.2)
Transient ischaemic attack	1 (0.4)	0 (0.0)	1 (0.2)
Vagus nerve disorder	1 (0.4)	0 (0.0)	1 (0.2)
Seizure	0 (0.0)	2 (0.7)	2 (0.4)
Cerebral haemorrhage	0 (0.0)	1 (0.4)	1 (0.2)
Cerebrovascular accident	0 (0.0)	1 (0.4)	1 (0.2)
Encephalopathy	0 (0.0)	1 (0.4)	1 (0.2)
Headache	0 (0.0)	1 (0.4)	1 (0.2)
Presyncope	0 (0.0)	1 (0.4)	1 (0.2)
Somnolence	0 (0.0)	1 (0.4)	1 (0.2)
Subarachnoid haemorrhage	0 (0.0)	1 (0.4)	1 (0.2)
Syncope	0 (0.0)	1 (0.4)	1 (0.2)
Metabolism and nutrition disorders	9 (3.3)	4 (1.5)	13 (2.4)
Hyponatraemia	4 (1.4)	2 (0.7)	6 (1.1)

Decreased appetite	4 (1.4)	1 (0.4)	5 (0.9)
Cachexia	1 (0.4)	0 (0.0)	1 (0.2)
Hyperkalaemia	1 (0.4)	0 (0.0)	1 (0.2)
Hypokalaemia	0 (0.0)	1 (0.4)	1 (0.2)
Vascular disorders	7 (2.5)	2 (0.7)	9 (1.6)
Embolism	2 (0.7)	1 (0.4)	3 (0.5)
Deep vein thrombosis	2 (0.7)	0 (0.0)	2 (0.4)
Venous thrombosis limb	2 (0.7)	0 (0.0)	2 (0.4)
Hypovolaemic shock	1 (0.4)	0 (0.0)	1 (0.2)
Haematoma	0 (0.0)	1 (0.4)	1 (0.2)
Hepatobiliary disorders	7 (2.5)	1 (0.4)	8 (1.5)
Drug-induced liver injury	2 (0.7)	0 (0.0)	2 (0.4)
Hepatic function abnormal	2 (0.7)	0 (0.0)	2 (0.4)
Cholecystitis acute	1 (0.4)	1 (0.4)	2 (0.4)
Bile duct stone	1 (0.4)	0 (0.0)	1 (0.2)
Cholecystitis	1 (0.4)	0 (0.0)	1 (0.2)
Cholelithiasis	1 (0.4)	0 (0.0)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (2.2)	5 (1.8)	11 (2.0)
Colon cancer	1 (0.4)	1 (0.4)	2 (0.4)
Dermatofibrosarcoma protuberans	1 (0.4)	0 (0.0)	1 (0.2)
Follicular lymphoma	1 (0.4)	0 (0.0)	1 (0.2)
Prostate cancer	1 (0.4)	0 (0.0)	1 (0.2)
Rectosigmoid cancer	1 (0.4)	0 (0.0)	1 (0.2)
Uterine leiomyoma	1 (0.4)	0 (0.0)	1 (0.2)
Basal cell carcinoma	0 (0.0)	2 (0.7)	2 (0.4)
Breast cancer	0 (0.0)	1 (0.4)	1 (0.2)
Renal cancer	0 (0.0)	1 (0.4)	1 (0.2)
Renal and urinary disorders	6 (2.2)	1 (0.4)	7 (1.3)
Nephrolithiasis	2 (0.7)	0 (0.0)	2 (0.4)
Renal failure	2 (0.7)	0 (0.0)	2 (0.4)
Acute kidney injury	1 (0.4)	1 (0.4)	2 (0.4)
Ureterolithiasis	1 (0.4)	0 (0.0)	1 (0.2)

General disorders and administration site conditions	5 (1.8)	4 (1.5)	9 (1.6)
Pyrexia	2 (0.7)	1 (0.4)	3 (0.5)
Asthenia	1 (0.4)	0 (0.0)	1 (0.2)
General physical health deterioration	1 (0.4)	0 (0.0)	1 (0.2)
Sudden death	1 (0.4)	0 (0.0)	1 (0.2)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Fatigue	0 (0.0)	1 (0.4)	1 (0.2)
Non-cardiac chest pain	0 (0.0)	1 (0.4)	1 (0.2)
Musculoskeletal and connective tissue disorders	4 (1.4)	2 (0.7)	6 (1.1)
Arthralgia	1 (0.4)	0 (0.0)	1 (0.2)
Joint swelling	1 (0.4)	0 (0.0)	1 (0.2)
Muscular weakness	1 (0.4)	0 (0.0)	1 (0.2)
Osteonecrosis of jaw	1 (0.4)	0 (0.0)	1 (0.2)
Back pain	0 (0.0)	1 (0.4)	1 (0.2)
Rotator cuff syndrome	0 (0.0)	1 (0.4)	1 (0.2)
Ear and labyrinth disorders	3 (1.1)	2 (0.7)	5 (0.9)
Otolithiasis	1 (0.4)	0 (0.0)	1 (0.2)
Vertigo positional	1 (0.4)	0 (0.0)	1 (0.2)
Vestibular disorder	1 (0.4)	0 (0.0)	1 (0.2)
Vertigo	0 (0.0)	2 (0.7)	2 (0.4)
Endocrine disorders	1 (0.4)	1 (0.4)	2 (0.4)
Inappropriate antidiuretic hormone secretion	1 (0.4)	0 (0.0)	1 (0.2)
Secondary adrenocortical insufficiency	0 (0.0)	1 (0.4)	1 (0.2)
Eye disorders	1 (0.4)	1 (0.4)	2 (0.4)
Cataract	1 (0.4)	1 (0.4)	2 (0.4)
Immune system disorders	1 (0.4)	0 (0.0)	1 (0.2)
Anaphylactic reaction	1 (0.4)	0 (0.0)	1 (0.2)
Psychiatric disorders	1 (0.4)	0 (0.0)	1 (0.2)
Completed suicide	1 (0.4)	0 (0.0)	1 (0.2)

Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.4)	1 (0.2)
Rash maculo-papular	0 (0.0)	1 (0.4)	1 (0.2)

Appendix F. Health-related quality of life

F.1 Introduction

This report details the analysis of Danish utility values derived from the EQ-5D-5L profiles in FLAURA2 using the 5L Danish value set by Jensen CE, 2021[1] .

The analysis was based on ITT data from DCO 1.

This report summarises the background, methods and results of the descriptive summary and regression analysis of EQ-5D-5L health state utility data in the FLAURA2 study.

F.2 Background

Quality of life was assessed within FLAURA2 using the EQ5D. The assessment schedule for EQ-5D-5L in FLAURA2 is available from the clinical study protocol.

The EQ-5D is a standardised measure of self-reported health, developed by the EuroQol Group. There are 5 dimensions or domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. In the 5-level ('5L') version of the questionnaire, there are 5 possible levels of response that a subject can give for each dimension: no, mild, moderate, severe, and severe / unable to.

An EQ-5D profile consists of a 5-digit value, with each digit representing a subject's response for each domain. The EQ-5D profiles can be converted to a health state utilities using country-specific value sets that are reflective of the country of interest. The maximum health state utility value is 1, which represents 'full health'. A value of 0 corresponds to a quality of life equivalent to being dead, and negative values are possible which represent a quality of life worse than death.

The results of the utility analysis are intended to provide input data for cost-effectiveness models, which are required in developing cost-utility analysis. Utilities are present in the calculation of quality-adjusted life years (QALYs), which are subsequently used to generate the Incremental Cost Effectiveness Ratio (ICER). These are both used to support health technology assessment and reimbursement submissions.

F.3 Methods

A descriptive summary of the EQ-5D health state utilities by arm and study visit, and by arm and progression status is provided in the results section. The summary analysis includes estimates of mean, standard deviations, median, and interquartile range (IQR) of utility scores in the ITT analysis set of FLAURA2, consisting of all completed EQ-5D-5L measures (excluding EQ-5D-5L with any missing domain responses).

The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis. To account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method[2] was used to model EQ-5D-5L health state utilities. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, must be omitted from the analysis.

The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomised) Treatment
- Progression status (pre-progression, post-progression)
- Treatment + Progression status
- Treatment + Progression status + Treatment * Progression status (Both terms and their interaction included)

The correlation of repeated utility measurements within subjects over time was captured via the specification of covariance structures for the MMRM. This report presents the results from the models using the first covariance structure in the sequence that successfully converged for all models (i.e., for each of the 4 covariate options). If for a particular set of covariates none of the models converged, then no results are presented for that model, and the remaining model results are based on the most flexible covariance structure for which the models converged.

The hierarchy of covariance structures tested, in order of most to least flexible, is shown below:

Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.

Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.

Autoregressive, order 1 (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.

Toeplitz – as above for number 2, but each visit shares the same variance.

Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

For each model, parameter estimates, and marginal ('least square') means are presented including 95% confidence intervals.

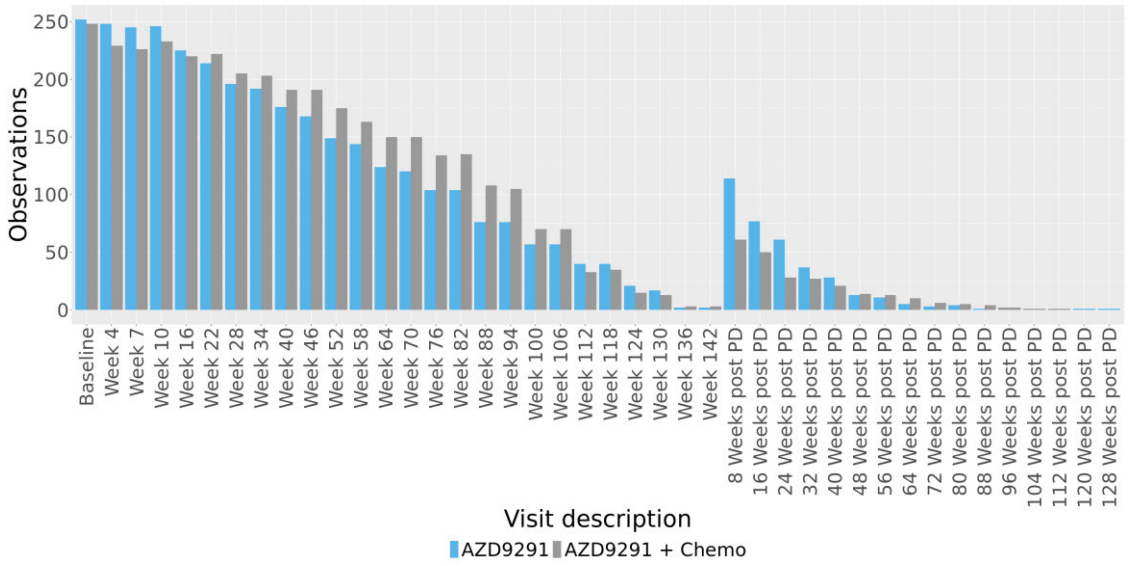
The marginal ('least square') mean provides a model-based estimate of the mean utility score by status (treatment and/or Progression status) that is averaged over observations and with adjustment for repeated measures. The estimated marginal mean and its associated standard error or confidence interval can be used as utility inputs to the global cost-effectiveness model.

All regression output is saved as a spreadsheet file including covariance matrices for the parameters. Confidence intervals are based on robust standard error estimates.

Analysis was performed in R 4.1.0 using the mmrm package 0.3.14 for model fitting.

F.4 Results - Descriptive analysis

In total, 7685 EQ-5D-5L observations were available from 539 patients. Of these, 6812 observations were recorded pre progression and 612 were recorded post progression. 261 were recorded after censoring for progression, and was not included in the analysis.



Utility summary statistics

Treatment	Scenario	Subjects	Observations	Mean (SD)	Median (IQR)	Min	Max
AZD9291	At baseline visit	252	252	0.81 (0.25)	0.89 (0.77, 0.96)	-0.23	1.00
AZD9291 + Chemo	At baseline visit	248	248	0.86 (0.17)	0.92 (0.81, 0.98)	-0.14	1.00
AZD9291	All visits	268	3,651	0.89 (0.16)	0.95 (0.86, 1.00)	-0.76	1.00
AZD9291 + Chemo	All visits	267	3,773	0.88 (0.16)	0.93 (0.84, 1.00)	-0.76	1.00
Pooled treatments	Pre progression	535	6,812	0.89 (0.15)	0.95 (0.85, 1.00)	-0.76	1.00
Pooled treatments	Post progression	194	612	0.83 (0.24)	0.88 (0.81, 1.00)	-0.76	1.00
AZD9291	Pre progression	268	3,286	0.90 (0.15)	0.95 (0.87, 1.00)	-0.76	1.00
AZD9291	Post progression	124	365	0.83 (0.24)	0.88 (0.81, 0.95)	-0.76	1.00
AZD9291 + Chemo	Pre progression	267	3,526	0.89 (0.15)	0.93 (0.85, 1.00)	-0.38	1.00
AZD9291 + Chemo	Post progression	70	247	0.84 (0.23)	0.89 (0.81, 1.00)	-0.76	1.00
AZD9291	Unknown status	65	88	0.88 (0.19)	0.93 (0.87, 1.00)	-0.07	1.00
AZD9291 + Chemo	Unknown status	97	173	0.88 (0.14)	0.91 (0.84, 0.97)	0.08	1.00

F.5 Results - Regression analysis

The results presented in this section were generated from MMRMs with the following covariance structure: Autoregressive - order 1 with Heterogeneity.

Goodness of fit

Description	converges	AIC	BIC
Treatment	TRUE	-11377.3	-11193.1
Progression status	TRUE	**-11378.6**	-11194.4
Treatment + Progression status	TRUE	-11374.4	-11190.3
Treatment * Progression status	TRUE	-11372.2	-11188.1

The best fitting model in terms of AIC was the model including a term for Progression status.

F.6 Results - Summary of Statistical fits

The following tables contain summaries of the point estimates and marginal means produced from each model. Complete tables for each model with degrees of freedom and standard errors are in the appendix.

F.6.1 Point Estimates

Summary of point estimates

Parameter	Treatment	Progression status	Treatment + Progression status	Treatment * Progression status
(Intercept)	0.903 [SE = 0.006] (p = <0.001)	0.898 [SE = 0.005] (p = <0.001)	0.905 [SE = 0.007] (p = <0.001)	0.907 [SE = 0.006] (p = <0.001)
AZD9291 + Chemo	-0.013 [SE = 0.010] (p = 0.191)		-0.014 [SE = 0.010] (p = 0.156)	-0.017 [SE = 0.010] (p = 0.081)
Post progression		-0.027 [SE = 0.013] (p = 0.036)	-0.030 [SE = 0.013] (p = 0.023)	-0.046 [SE = 0.018] (p = 0.011)
AZD9291 + Chemo: Post progression				0.045 [SE = 0.025] (p = 0.076)
AIC score	-11377.3	-11378.6	-11374.4	-11372.2

F.6.2 Marginal Means

Summary of marginal means

Parameter	Treatment	Progression status	Treatment + Progression status	Treatment * Progression status
AZD9291	0.903 (0.891, 0.916)			
AZD9291 + Chemo	0.890 (0.876, 0.905)			
Pre progression		0.898 (0.888, 0.908)		
Post progression		0.871 (0.845, 0.896)		
AZD9291:Pre progression			0.905 (0.893, 0.918)	0.907 (0.894, 0.920)
AZD9291 + Chemo:Pre progression			0.891 (0.877, 0.906)	0.890 (0.875, 0.905)
AZD9291:Post progression			0.876 (0.848, 0.903)	0.861 (0.824, 0.897)
AZD9291 + Chemo:Post progression			0.862 (0.834, 0.889)	0.888 (0.854, 0.922)
AIC score	-11377.3	-11378.6	-11374.4	-11372.2

F.7 Appendix

Observations per visit

Visit description	AZD9291	AZD9291 + Chemo
Baseline	252	248
Week 4	248	229
Week 7	245	226
Week 10	246	233
Week 16	225	220
Week 22	214	222
Week 28	196	205
Week 34	192	203
Week 40	176	191
Week 46	168	191
Week 52	149	175
Week 58	144	163
Week 64	124	150
Week 70	120	150
Week 76	104	134
Week 82	104	135
Week 88	76	108
Week 94	76	105
Week 100	57	70
Week 106	57	70
Week 112	40	33
Week 118	40	35
Week 124	21	15
Week 130	17	13
Week 136	2	3
Week 142	2	3
8 Weeks post PD	114	61

Visit description	AZD9291	AZD9291 + Chemo
16 Weeks post PD	77	50
24 Weeks post PD	61	28
32 Weeks post PD	37	27
40 Weeks post PD	28	21
48 Weeks post PD	13	14
56 Weeks post PD	11	13
64 Weeks post PD	5	10
72 Weeks post PD	3	6
80 Weeks post PD	4	5
88 Weeks post PD	1	4
96 Weeks post PD		2
104 Weeks post PD		1
112 Weeks post PD		1
120 Weeks post PD	1	
128 Weeks post PD	1	

F.8 Model fits:

F.8.1 Model terms: Treatment

Parameter Estimates

Parameter	Estimate	SE	DF	t.value	p_value	95% LCL	95% UCL
(Intercept)	0.903	0.006	7422.0	139.004	<0.001	0.891	0.916
AZD9291 + Chemo	-0.013	0.010	7422.0	-1.307	0.191	-0.032	0.006

Marginal means

TRT01P	Estimate	SE	DF	95% LCL	95% UCL
AZD9291	0.903	0.006	7422.0	0.891	0.916
AZD9291 + Chemo	0.890	0.007	7422.0	0.876	0.905

F.8.2 Model terms: Progression status

Parameter Estimates

Parameter	Estimate	SE	DF	t.value	p_value	95% LCL	95% UCL
(Intercept)	0.898	0.005	7422.0	178.271	<0.001	0.888	0.908
Post progression	-0.027	0.013	7422.0	-2.102	0.036	-0.053	-0.002

Marginal means

PFFL	Estimate	SE	DF	95% LCL	95% UCL
Pre progression	0.898	0.005	7422.0	0.888	0.908
Post progression	0.871	0.013	7422.0	0.845	0.896

F.8.3 Model terms: Treatment + Progression status

Parameter Estimates

Parameter	Estimate	SE	DF	t.value	p_value	95% LCL	95% UCL
(Intercept)	0.905	0.007	7421.0	139.255	<0.001	0.893	0.918
AZD9291 + Chemo	-0.014	0.010	7421.0	-1.418	0.156	-0.033	0.005
Post progression	-0.030	0.013	7421.0	-2.280	0.023	-0.055	-0.004

Marginal means

TRT01P	PFFL	Estimate	SE	DF	95% LCL	95% UCL
AZD9291	Pre progression	0.905	0.007	7421.0	0.893	0.918
AZD9291 + Chemo	Pre progression	0.891	0.007	7421.0	0.877	0.906
AZD9291	Post progression	0.876	0.014	7421.0	0.848	0.903
AZD9291 + Chemo	Post progression	0.862	0.014	7421.0	0.834	0.889

F.8.4 Model terms: Treatment * Progression status

Parameter Estimates

Parameter	Estimate	SE	DF	t.value	p_value	95% LCL	95% UCL
(Intercept)	0.907	0.006	7420.0	139.713	<0.001	0.894	0.920
AZD9291 + Chemo	-0.017	0.010	7420.0	-1.746	0.081	-0.037	0.002
Post progression	-0.046	0.018	7420.0	-2.542	0.011	-0.082	-0.011

Parameter	Estimate	SE	DF	t.value	p_value	95% LCL	95% UCL
AZD9291 + Chemo: Post progression	0.045	0.025	7420.0	1.774	0.076	-0.005	0.095

Marginal means

TRT01P	PFFL	Estimate	SE	DF	95% LCL	95% UCL
AZD9291	Pre progression	0.907	0.006	7420.0	0.894	0.920
AZD9291 + Chemo	Pre progression	0.890	0.008	7420.0	0.875	0.905
AZD9291	Post progression	0.861	0.019	7420.0	0.824	0.897
AZD9291 + Chemo	Post progression	0.888	0.017	7420.0	0.854	0.922

Appendix G. Probabilistic sensitivity analyses

A summary of the parameter distributions used in the probabilistic analysis and examples of type of inputs they are used for is given in Table 75.

Table 75. Parameter distributions used in the probabilistic analysis

Distribution	Type of input used for	Justification
Multivariate (covariance modelled using Cholesky decomposition)	Parameters for parametric models	Captures correlation between different parameters for the same fitted curve
Lognormal	Baseline characteristics (age, weight and height)	Values are > 0 and have a multiplicative distributions
Beta	Percentages, such as AE incidence rates HSUVs	Values are between 0 and 1
Gamma	AE disutilities (always negative) AE durations Resource use frequency	Values are > 0
Dirichlet	Subsequent treatment distributions	Multiple (>2) linked percentage values which must sum to 100%

Abbreviations: AE: adverse event; HSUV: health state utility value.

Appendix H. Literature searches for the clinical assessment

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

[Follow section 3 of the methods guide. Describe how the literature search was performed. Explain the selection of the search criteria and terms used, search filters, and the inclusion and exclusion criteria. Sufficient details should be provided so that the results may be reproduced.
Literature searches that are more than one year old are generally not accepted. If this is the case, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

If an existing/global systematic literature review (SLR) is (re)used the appendix must be filled out with data/information from such SLR and it must be clear how the SLR has been adapted to the current application. The inclusion and exclusion criteria, PRISMA flowchart, and list of excluded full text references should reflect the purpose of the application. Thus, unedited technical reports or SLRs will not be accepted in/as the appendix. Please find an editable PRISMA flowchart at the end of this document. This diagram is to be used when existing SLRs are (re)used, so it is clear how it has been locally adapted, i.e. how many references are included and excluded from the original SLR. As mentioned above, if the literature search is more than a year old, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

Objective of the literature search: What questions is the literature search expected to answer?

Databases/other sources: Fill in the databases and other sources, e.g. conference material used in the literature search.]

Table 76. Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Table 77 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
e.g. EMA website			dd.mm.yyyy

Abbreviations:

Table 78. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

H.1.1 Search strategies

[Describe the development of the search strategy and search string. Specify the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.).]

[The search must be documented with exact search strings line by line as run, incl. results, for each database.]

Table 79. of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348

No.	Query	Results
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

H.1.2 Systematic selection of studies

[Describe the selection process, incl. number of reviewers and how conflicts were resolved. Provide a table with criteria for inclusion or exclusion. If the table relates to an existing SLR broader in scope, please indicate which criteria are relevant for the current application.]

Table 80. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population			
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

[Insert the PRISMA flow diagram(s) here (see example here) or use the editable diagram at the end of this document. If an existing SLR is used, the editable diagram is to be used, so it is clear how many references have been included and excluded from the original SLR.]

Table 81. Overview of study design for studies included in the analyses

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
Study 1						
Study 2						

H.1.3 Excluded fulltext references

[Please provide in a list or table the references that were excluded during fulltext screening along with a short reason. If using an existing, locally adapted SLR, please fill in the references originally included in the SLR but excluded in the current application.]

H.1.4 Quality assessment

[Describe strengths and weaknesses of the literature search performed.]

H.1.5 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted].

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

Not applicable, no SLR conducted for HRQoL.

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

J.1 External literature for input to the health economic model

N/A.

J.1.1 Example: Systematic search for [...]

N/A.

Table 51. Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

N/A

J.1.2 Example: Targeted literature search for [estimates]

N/A.

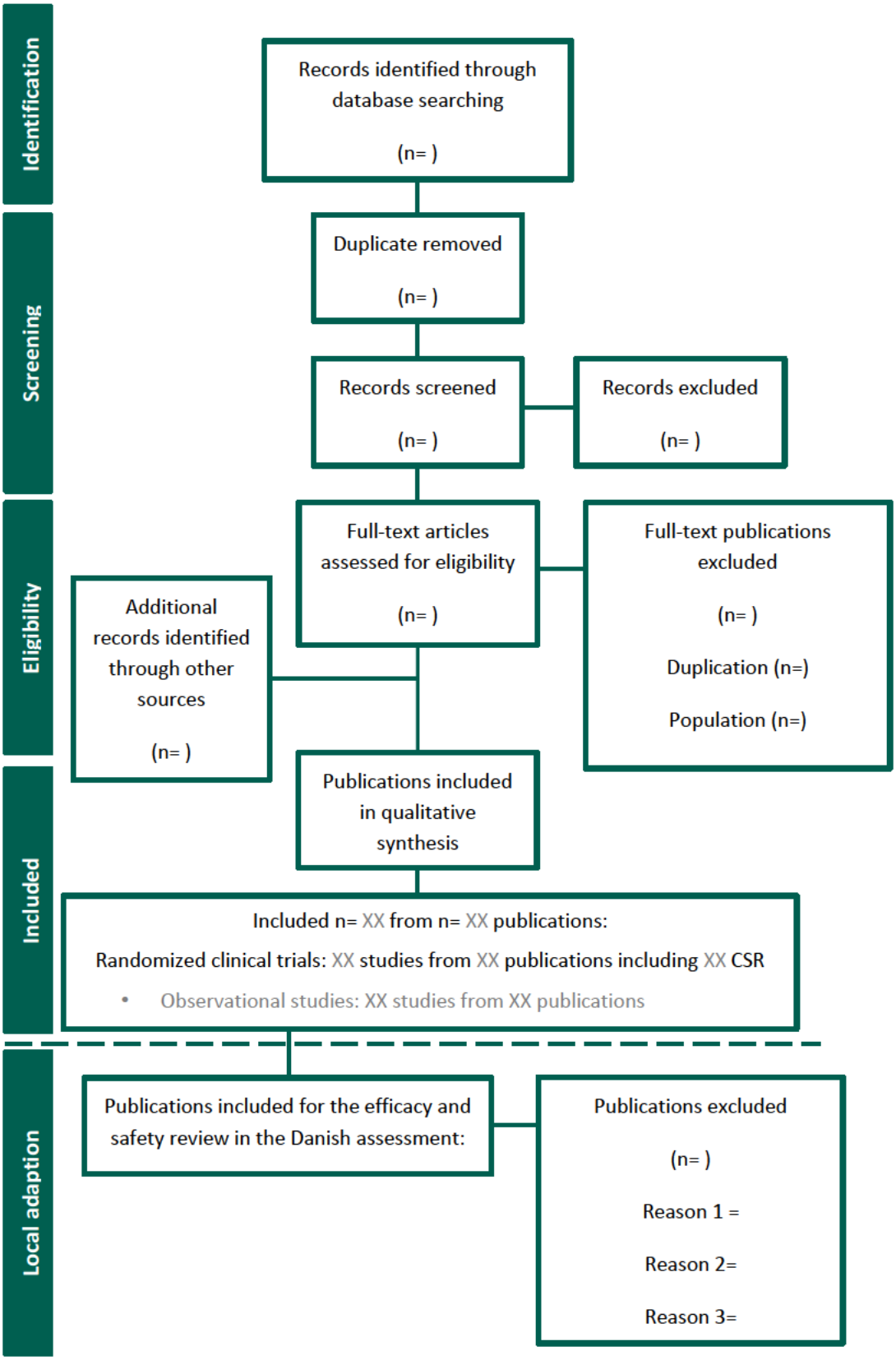
Table 52. Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Abbreviations:

N/A.

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



Appendix K. Subsequent treatments observed in FLAURA2

Table 82. Post-study treatment – Subsequent anticancer therapy (Randomised Period – FAS)

Subsequent anti-cancer therapy[b]	Number (%) of patients [a]	
	Osi + Chemo (N = 279)	Osimertinib (N = 278)
Any post-treatment anti-cancer therapy	121 (43.4)	170 (61.2)
Types of post-treatment anticancer therapy received		
Platinum chemotherapy	50 (17.9)	133 (47.8)
Folic acid analogues (pemetrexed)	24 (8.6)	100 (36.0)
Taxanes chemotherapy	48 (17.2)	71 (25.5)
First or second-generation EGFR-TKI	34 (12.2)	40 (14.4)
Third generation EGFR-TKI	41 (14.7)	55 (19.8)
VEGF Inhibitor – Monoclonal antibody	28 (10.0)	62 (22.3)
PD-1/PD-L1 inhibitor - Immunotherapy	22 (7.9)	47 (16.9)

[a] The number of patients is shown with percentages (%) calculated as the proportion of patients in the FAS

[b] Please note that the data in the table above are preliminary as additional medical review of subsequent lines of therapy is ongoing, including grouping of therapies by treatment line and type of anticancer therapy.

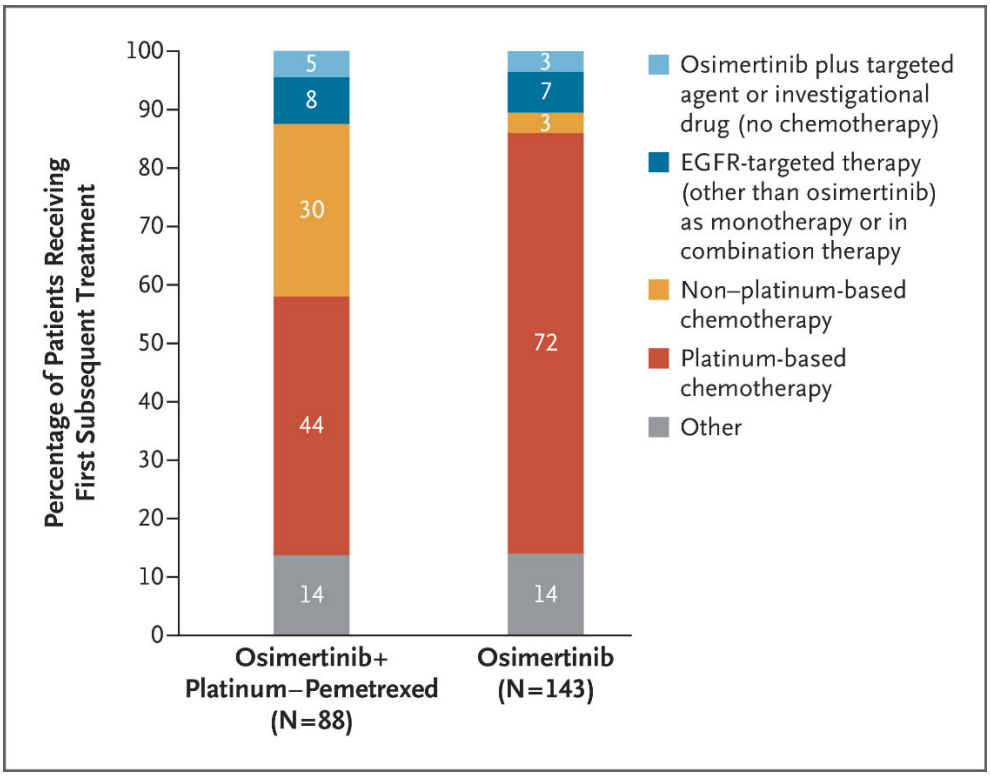
A patient may be counted in multiple rows if they receive more than one post treatment anticancer therapy. Includes anticancer therapies with a start date after the last dose date of study treatment.

Note: Treatment beyond progression is not counted as a subsequent anticancer therapy.

WHO Drug Dictionary version September 2022 format B3.

DCO: 12 June 2025 (data-on-file) (33)

Figure 38. Summary of First Subsequent Treatments Received in FLAURA2 at DCO: 12 Jun 2025(54).



Appendix L. OS splines models

Figure 39. Spline models fitted to osimertinib plus CTx FLAURA2 OS data

Footnote: Curves on the figure are not bounded by GPM.

Figure 40. Spline models fitted to osimertinib monotherapy FLAURA2 OS data

Footnote: Curves on the figure are not bounded by GPM.

Standard parametric models and spline models

Table 83. Goodness of fit statistics – FLAURA2 OS (ranking amongst standard parametric models and spline models)

Distribution	Osimertinib plus CTx		Osimertinib monotherapy	
	AIC (Rank)	BIC (Rank)	AIC (Rank)	BIC (Rank)
Exponential	1524.1 (13)	1527.7 (4)	1727.5 (15)	1731.1 (15)
Weibull	1520.2 (11)	1527.5 (3)	1702.9 (9)	1710.2 (2)
Gompertz	1515.7 (4)	1523.0 (1)	1710.9 (13)	1718.2 (11)
Log-logistic	1528.1 (14)	1535.3 (14)	1702.8 (8)	1710.1 (1)
Lognormal	1550.8 (15)	1558.1 (15)	1720.7 (14)	1727.9 (14)
Generalised gamma	1518.5 (9)	1529.4 (7)	1704.8 (11)	1715.7 (8)
Gamma	1521.9 (12)	1529.2 (6)	1703.3 (10)	1710.5 (3)
Spline models				

1 spline-hazard	[redacted]	[redacted]	[redacted]	[redacted]
2 spline-hazard	[redacted]	[redacted]	[redacted]	[redacted]
3 spline-hazard	[redacted]	[redacted]	[redacted]	[redacted]
1 spline-odds	[redacted]	[redacted]	[redacted]	[redacted]
2 spline-odds	[redacted]	[redacted]	[redacted]	[redacted]
3 spline-odds	[redacted]	[redacted]	[redacted]	[redacted]
1 spline-normal*	[redacted]	[redacted]	[redacted]	[redacted]
2 spline-normal	[redacted]	[redacted]	[redacted]	[redacted]
3 spline-normal	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: Base case extrapolation is shown in **bold**; best fit distributions are shown in green highlight. *Results were not available as the model did not converge..

Table 84. Osimertinib plus CTx predicted and observed mean, median and landmark rates for spline models (OS)

	Mean	Median	2 years	3 years	4 years	5 years	10 years	15 years
FLAURA2	–	47.51	79.71%	63.14%	49.15%	-	-	-
Splines								
1 spline-hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 spline-hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 spline-hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 spline-odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 spline-odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 spline-odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 spline-normal*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 spline-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 spline-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Landmarks capped to general population mortality. *Results were not available as the model did not converge

Abbreviations: CTx: chemotherapy; OS: overall survival.

Table 85. Osimertinib monotherapy predicted and observed mean, median and landmark rates for spline models (OS)

	Mean	Median	2 years	3 years	4 years	5 years	10 years	15 years
FLAURA2	-	37.62	71.51%	50.86%	40.82%	-	-	-
Splines								
1 spline-hazard	[redacted]							
2 spline-hazard	[redacted]							
3 spline-hazard	[redacted]							
1 spline-odds	[redacted]							
2 spline-odds	[redacted]							
3 spline-odds	[redacted]							
1 spline-normal*	-	-	-	-	-	-	-	-
2 spline-normal	[redacted]							
3 spline-normal	[redacted]							

Note: Landmarks capped to general population mortality. *Results were not available as the model did not converge

Abbreviations: OS: overall survival.

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