

Bilag til Medicinrådets vurdering af osimertinib til NSCLC med EGFRm efter kemoradioterapi

Vers. 1.0



Bilagsoversigt

1. Ansøgers notat til Rådet vedr. osimertinib
2. Amgros' forhandlingsnotat vedr. osimertinib
3. Ansøgning vedr. osimertinib

Draft assessment report regarding Tagrisso (osimertinib) for the treatment of adult patients with locally advanced, unresectable NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy

AstraZeneca would like to thank you for the assessment of Tagrisso (osimertinib) and appreciate the opportunity to comment on the draft assessment report.

Overall, AstraZeneca finds the DMC report to be balanced and thorough. In Danish clinical practice, between 6-10 patients are currently diagnosed with unresectable NSCLC harbouring an EGFR mutation following platinum-based chemoradiation. Currently, these patients lack targeted treatment options and receive only active monitoring following the chemoradiation, unless the disease has progressed to a metastatic stage. In contrast, patients whose tumours do not carry an EGFR mutation are eligible for immunotherapy following chemoradiation.

This discrepancy in available treatments highlights a significant unmet need for patients with EGFR-mutated unresectable NSCLC. As illustrated in the LAURA trial, patients face a high risk of progression to metastatic disease following platinum-based chemoradiation if not treated with active therapy. In the placebo arm, the observed median progression-free survival (PFS) was only 5.6 months. Diagnosis of the patients in LAURA was determined by the investigators per local clinical practice, which lead to PET scan staging not being conducted for all patients, and this is a limitation for the study. However, in a stratified analysis, a consistent PFS benefits with osimertinib versus placebo was observed in patients who did and did not receive pre-CRT PET scans in LAURA¹, indicating it that the difference PET scans did not result in an underestimated PFS in LAURA.

Progression to metastatic NSCLC is linked to both increased mortality as well as a high disease burden and poorer quality of life. EGFRm NSCLC is characterised by a high occurrence of central nervous system (CNS) metastases, with upwards of 70% occurring in the CNS². These CNS metastases are associated with a higher disease burden and lead to faster deterioration of the quality of life for the patients.

Currently, Tagrisso is only introduced after patients progress to metastatic disease, which results in increased disease burden and poorer survival prognosis. By providing access to Tagrisso at an earlier stage, the LAURA regimen may reduce the risks associated with disease progression and offer improved outcomes for these patients, where the disease has been identified at an earlier stage.

As Tagrisso currently only is administered after disease progression for patients diagnosed with unresectable stage III EGFRm NSCLC, addressing this unmet need in Danish practice would likely not result in significant additional costs. Introducing Tagrisso in this setting, as part of the LAURA regimen, would most likely shift treatment initiation of Tagrisso to a stage where the disease is more limited. Thus, providing patients with earlier and better disease control and to some extent prevention of CNS metastasis. Given the small eligible patient group—estimated at only 6 to 10 individuals—the budget impact of implementing LAURA remains modest. At list price, the estimated budget impact at year 5 is 2.8m DKK.

In conclusion, the addition of LAURA to the treatment algorithm can address the gap in the current disease management of EGFRm NSCLC at a low budget impact. Providing a treatment option to the few patients, improving the prognosis for these patients, as well as prolonging the period where patients are not impacted by the higher disease burden and poorer quality of life associated with metastatic disease.

Kind regards,

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¹ [https://www.annalsofoncology.org/article/S0923-7534\(24\)03823-7/fulltext](https://www.annalsofoncology.org/article/S0923-7534(24)03823-7/fulltext)

² <https://onlinelibrary.wiley.com/doi/10.1002/cam4.3306>

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Forhandlingsnotat

03.10.2025

DBS/MBA/LSC

Dato for behandling i Medicinrådet	29.10.2025
Leverandør	AstraZeneca
Lægemiddel	Tagrisso (osimertinib)
Ansøgt indikation	Monoterapi til behandling af voksne patienter med lokalt avanceret, inoperabel ikke-småcellet lungekræft (NSCLC), hvis tumorer har EGFR-exon 19-deletioner eller exon 21 (L858R) substitutionsmutationer, og hvis sygdom ikke er progredieret under eller efter platinbaseret kemoradioterapi.
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.	37.775,00		
Tagrisso	80 mg, 30 stk.	37.775,00		

Aftaleforhold

Konkurrencesituationen

Der er på nuværende tidspunkt ikke konkurrence på denne indikation. En ny indikationsudvidelse af Tagrisso i kombination med kemoterapi som førstelinje behandling af patienter med NSCLC er under vurdering i Medicinrådet. Derudover er Lazcluze (lazertinib) i kombination med Rybrevant (amivantamab) som førstelinje behandling til patienter med NSCLC med EGFR-exon 19-deletioner eller exon 21 (L858R) substitutionsmutationer også under vurdering i Medicinrådet.

Tabel 2 viser den årlige lægemiddeludgift for Tagrisso.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Tagrisso	80 mg, 30 stk.	80 mg (oral) dagligt		

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Under vurdering	Link til status
Sverige	Ikke ansøgt	

Opsummering



Application for the assessment of Tagrisso for the treatment of adult patients with locally advanced, unresectable NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy

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



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Abbreviations

Abbreviation	Definiton
DMC	Danish Medicine Council
1L	First-line
2L	Second-line
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
BICR	Blinded independent central review
BIM	Budget impact model
cCRT	Concurrent chemoradiotherapy
CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus-19
CRT	Chemoradiotherapy
CT	Computerised tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumour deoxyribonucleic acid
CTx	Chemotherapy
DCO	Data cut-off
ECG	Electrocardiogram
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
<i>EGFRm</i>	Epidermal growth factor receptor-mutant
<i>EGFRwt</i>	Epidermal growth factor receptor-wildtype
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQoL 5-dimension



Abbreviation	Definiton
EQ-5D-5L	EuroQoL 5-dimension 5-level
Ex19del	Exon 19 deletion
FAS	Full Analysis Set
HR	Hazard ratio
HRQoL	Health related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ILD	Interstitial lung disease
ITT	Intention-to-treat
KM	Kaplan-Meier
LY	Life year
M	Metastasis
MEK	Mitogen-activated protein kinase
Min	Minimum
MMRM	Mixed models for repeated measures
MRI	Magnetic resonance imaging
N	Node
NA	Not applicable
NC	Not calculable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NSCLC	Non-small cell lung cancer
OR	Odds ratio
OS	Overall Survival
PD	Progressive disease
PD-L1	Programmed cell death-ligand 1
PF	Progression-free



Abbreviation	Definiton
PFS	Progression-free survival
PFS2	Time to second progression on a subsequent treatment
PRO	Patient reported outcome
PS	Performance status
QALY	Quality-adjusted life year
QLQ-C30	Quality of Life Questionnaire Core-30
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy
RWE	Real-world evidence
SAE	Serious adverse event
SCLC	Small cell lung cancer
sCRT	Sequential chemoradiotherapy
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
Std	Standard deviation
TKI	Tyrosine kinase inhibitor
TNM	Tumour-node-metastasis
TDT	Time to treatment discontinuation
WBRT	Whole brain radiotherapy



1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Tagrisso
Generic name	Osimertinib
Therapeutic indication as defined by EMA	Tagrisso as monotherapy for the treatment of adult patients with 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 chemoradiation therapy.
Marketing authorization holder in Denmark	AstraZeneca
ATC code	L01EB04
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	23/12/2024
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) TAGRISSO is indicated in combination with: • pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours



Overview of the medicine	
	have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. (FLAURA2)
Other indications that have been evaluated by the DMC (yes/no)	Yes (FLAURA and ADAURA)
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 a prior indication (ADAURA) Is the product suitable for a joint Nordic assessment? No If no, why not? Different processes/systems.
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 expected label, i.e. no deviations from the expected EMA indication.
Dosage regimen and administration	Oral osimertinib at a dose of 80 mg once daily
Choice of comparator	Placebo
Prognosis with current treatment (comparator)	In Denmark, the current standard of care is watchful monitoring for patients with locally advanced unresectable NSCLC following definitive platinum-based chemoradiation therapy, as outlined in the DLCC guidelines(1). In the LAURA trial, the placebo arm aligns with the current Danish clinical practice for patients with locally advanced unresectable NSCLC following platinum-based chemoradiation therapy(2). A median progression-free survival (PFS) of 5.6 months was observed in patients receiving a placebo in the trial(2).
Type of evidence for the clinical evaluation	Head-to-head study, LAURA(2-4)



Summary	
Most important efficacy endpoints (Difference/gain compared to comparator)	- PFS - OS - CNS-PFS
Most important serious adverse events for the intervention and comparator	The most frequently observed SAE in the LAURA trial are: - Radiation pneumonitis - Pneumonia - Gastroenteritis - Pneumonitis
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, the clinically significant efficacy benefit observed with osimertinib treatment occurred without clinically meaningful deterioration in HRQoL compared to current clinical practice. EORTC-QLQ-C30, GHS/QoL estimate difference between groups: -1.9 (-5.89, 2.00). 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: State-transition model
Data sources used to model the clinical effects	Data from LAURA has been used to model the clinical effects observed in the osimertinib and placebo arm.
Data sources used to model the health-related quality of life	EQ-5D-5L dataset from LAURA trial on DK tariff set(5)
Life years gained	1.80 years
QALYs gained	1.76 QALYs
Incremental costs	1,047,522 DKK
ICER (DKK/QALY)	593,662 DKK/QALY
Uncertainty associated with the ICER estimate	The parameters with the highest impact on the ICER are HSUV in progression-free health state, the HSUV in the post-progression health state and the discount rate on accrued QALYs.
Number of eligible patients in Denmark	Incidence: 6-10 patients eligible annually Prevalence: NA
Budget impact (in year 5)	2.9m



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 both the most commonly diagnosed cancer and the leading cause of cancer mortality worldwide (6). There are two main forms of lung cancer: NSCLC (accounting for 85% of patients) and small-cell-lung cancer (SCLC, accounting for 15% of patients) (7). NSCLC comprises a group of cancers which exhibit similar behavior and response to treatment, and can be categorized according to the tissue of origin, including adenocarcinoma, squamous cell carcinoma and large cell lung cancer; several variants and clinical subtypes exist within each category (8). Adenocarcinoma is the most common form of NSCLC, accounting for approximately 40% of lung cancers (9, 10).

Lung cancer is the second most common form of cancer in Denmark, and is the form of cancer causing most deaths each year(11). The prognosis of lung cancer has been historically poor, however, with the influx of new advanced therapies, the prognosis for lung cancer patients has improved year on year.

Early-stage NSCLC is often asymptomatic, and patients are therefore at risk of delayed diagnosis, which impacts the cure rates and survival (12). Patients may live for several years before showing symptoms, during which time metastases may develop if not diagnosed early. In addition to the largely asymptomatic nature of early disease, when patients do begin to show symptoms they are often non-specific, such as a cough(13) leading to approximately 70% of NSCLC patients being diagnosed first with unresectable, advanced NSCLC (12, 14-17).

Approximately 25% of patients with NSCLC are diagnosed with stage III disease(11). This patient population is diverse, with a minority having resectable tumors, while the majority (~80%) are classified as having unresectable disease(18-20). Patients with unresectable disease have a worse prognosis than patients for whom surgery is an option. (11). Standard of care in patients with unresectable, locally advanced NSCLC consists of definitive platinum-based chemoradiotherapy (CRT). The 5-year survival for stage IIIB lung cancer has improved from 5% between 2004-07 to 17% between 2016-19(11). Currently, consolidation durvalumab, a programmed cell death ligand-1 (PD-L1) immune checkpoint inhibitor, is a treatment option for patients without an ALK- or EGFR-mutation (EGFRm) following CRT. This leaves patients with unresectable Stage III *EGFRm* NSCLC without a treatment option following CRT, while patients with locally advanced (stage IIIB and IIIC) *EGFRm* NSCLC can be treated with osimertinib according to the FLAURA label(21).



3.2 Patient population

In 2023, 5086 patients were diagnosed with lung cancer in Denmark, of which 4162 were diagnosed with NSCLC.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Lung cancer incidence in Denmark (11)	5009	4914	5120	5102	5086
NSCLC incidence in Denmark (%-rate) (11)	4084 (81.9%)	3912 (82.1%)	4075 (81.9%)	4103 (81.3%)	4162 (81.7%)
Stage III lung incidence in Denmark n (%-rate) (11)	IIIA: 472 (9.4%) IIIB: 346 (6.9%) IIIC: 165 (3.3%)	IIIA: 443 (9.0%) IIIB: 320 (6.5%) IIIC: 143 (2.9%)	IIIA: 422 (8.2%) IIIB: 347 (6.8%) IIIC: 131 (2.6%)	IIIA: 443 (8.7%) IIIB: 312 (6.1%) IIIC: 178 (3.5%)	IIIA: 455 (8.9%) IIIB: 330 (6.5%) IIIC: 143 (2.8%)
EGFR positive rate in Denmark (11)	17.1%	15.2%	11.6%	13.7%	15.1%

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

In Denmark, the majority of stage III patients are either deemed resectable or locally advanced (stage IIIB/IIIC) and are therefore either eligible resection followed by osimertinib or candidates for osimertinib as per the recommendation DMC recommendation for FLAURA(22, 23).

The patients relevant for this application are patients diagnosed with unresectable stage III EGFRm NSCLC, who is deemed eligible for chemoradiation and who have not progressed during or following curative chemoradiation.

In Denmark, the estimated number of eligible patients with unresectable stage III EGFRm NSCLC who is deemed eligible for chemoradiation and who have not progressed during or following curative chemoradiation is approx. 6-10 patients annually(24).



Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	6-10	6-10	6-10	6-10	6-10

3.3 Current treatment options

The Danish clinical guidelines recommend reflex testing in genetic characterization of mutations, including EGFRm, in patients with non-squamous NSCLC(25).

As discussed above, the population relevant for this assessment are patients with EGFR-mutated unresectable stage III NSCLC that have received chemoradiation with curative intent and have not progressed during or following this therapy.

For patients with early-stage disease, surgery is the preferred option. However, some patients with stage III NSCLC are considered unresectable and eligible for chemoradiation. In the Danish treatment guidelines, concomitant chemoradiotherapy (cCRT) is recommended as the first treatment for patients with unresectable stage III NSCLC. Radiotherapy consisting of 2 Gy x 33 fractions is recommended in Danish clinical practice. The chemotherapy given should be platinum based, but according to the Danish clinical guidelines there is no strong consensus on which regimen is most effective(1). The commonly used regimen is carboplatin AUC on the first day and 80 mg/m² vinorelbine on day 1, 8 and 15 of the 21-day cycle. Patients will receive 3 cycles of chemotherapy in total concomitantly with radiotherapy.

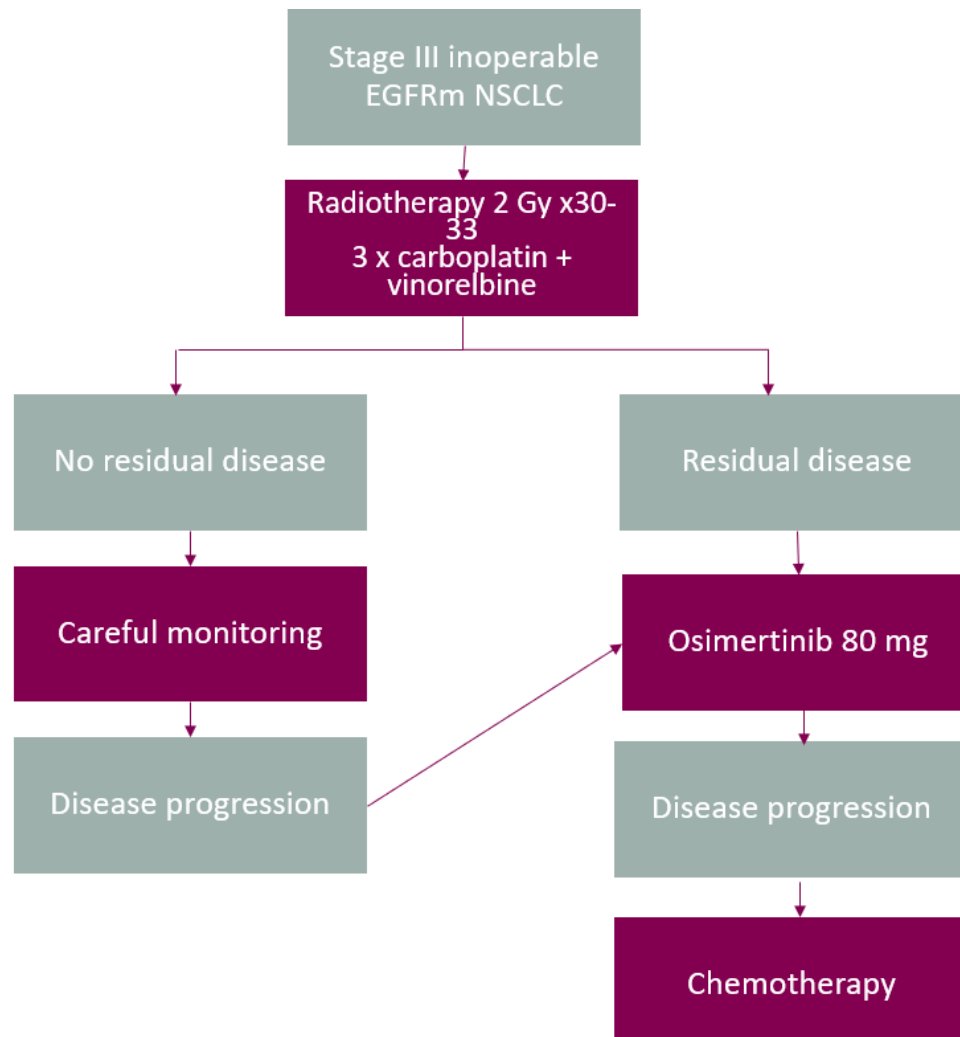
Upon completion of CRT, patients with PD-L1 positive tumors with no EGFR mutations or ALK-alterations can receive durvalumab, a PD-L1 checkpoint inhibitor, for up to 12 months(1). Patients with EGFR-mutations will, according to the Danish guidelines, not receive any active treatment after CRT unless they have residual disease(1). The current standard of care is watchful monitoring for these patients, since they are not eligible for treatment with durvalumab.

According to the guidelines, patients will be monitored for 5 years for disease progression(26). Patients without residual disease after 5 years will be followed up for potential disease activity by a general practitioner in the primary section(26).

Should the patient progress after treatment with curative intent or have persistent disease after completed chemoradiation, they will be treated as for stage IV disease. For stage IV EGFR-mutated NSCLC, first line treatment is osimertinib 80 mg daily until disease progression or unacceptable disease toxicity(23). Upon disease progression on osimertinib, patients can be treated with chemotherapy(27). Immunotherapy is not recommended in patients with EGFR-mutated NSCLC(23).



Figure 1. Treatment algorithm for stage III EGFR-mutated NSCLC who are ineligible for surgery.
Adapted from (1, 27).



Note: vino, vinorelbine.

Patients with unresectable Stage III *EGFR*m NSCLC are at high risk of progression to the metastatic stage, a transition that profoundly impacts patient outcomes, if not treated. An alarming 70% of patients with unresectable Stage III *EGFR*m disease will experience disease recurrence or metastasis within 2 years following CRT, with over half developing distant metastasis upon progression(28-30). Studies highlight that *EGFR* mutations confer a worse median PFS versus *EGFR* wildtype (*EGFR*wt) tumours (hazard ratio [HR] = 1.68-3.23, $p < 0.05$), (31-33) and a higher incidence of distant metastases.(34-36) Progression from Stage III NSCLC to metastatic Stage IV disease is associated with a steep decline in the 5-year survival rate dropping from 34.8% to a mere 8.2%.(37) Progression to metastatic disease is not only linked to increased mortality but also to the emergence of additional symptoms and increased psychological burden, significantly diminishing quality of life (QoL).(38-43) The CNS is a common site of distant metastases in this population, accounting for approximately 70% of such cases.(29) Moreover, patients with *EGFR*m NSCLC face nearly double the risk of developing CNS metastases (38% vs. 70%) compared to those with *EGFR*wt NSCLC, leading to a rapid deterioration in QoL.(35)



As emphasized by the data above, there is currently a high unmet need for a targeted treatment option for patients with unresectable Stage III *EGFR* NSCLC post-CRT, which could effectively delay disease progression, and the severe clinical and humanistic burdens associated with advancing to metastatic disease.

3.4 The intervention

Osimertinib selectively and irreversibly inhibits mutated *EGFR* proteins, such as those with an Ex19del, the L858R point mutation in exon 21, and the TKI-resistance mutation T790M, without inhibiting wild-type *EGFR* (44); it is thought that the irreversible inhibition of mutant *EGFR* will prevent the acquired resistance to treatment that is seen with reversible *EGFR* inhibitors (44, 45). This mechanism of action makes osimertinib pharmacologically distinct from first-(erlotinib, gefitinib) and second-generation (afatinib, dacomitinib) *EGFR* TKIs (44).

Osimertinib is a tablet taken once daily. The recommended dose is 80 mg, which can be reduced to 40 mg if required due to adverse events (21). Osimertinib is currently recommended by the DMC for patients with locally advanced and metastatic (stage IIIB–IV) *EGFR*-mutated NSCLC(23), as well as adjuvant therapy for patients who have undergone complete tumor resection for stage IIIA *EGFR*-mutated NSCLC(46).

Table 3. Overview of osimertinib

Overview of intervention	
Indication relevant for the assessment	The application is according to the EMA label, i.e. no deviations from the expected EMA indication.
ATMP	N/A
Method of administration	Oral
Dosing	80 mg PO daily
Dosing in the health economic model (including relative dose intensity)	80 mg PO daily
Should the medicine be administered with other medicines?	No concomitant medication.
Treatment duration / criteria for end of treatment	Treatment with osimertinib should continue until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	No additional monitoring required.



Overview of intervention

Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Reflex testing is already in place for EGFR mutation in Denmark for all patients with non-squamous NSCLC regardless of staging. Patients are assumed to have been tested at diagnosis of NSCLC, and the cost of testing has therefore not been included in the base case,
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Package size(s)	40 mg, 30 film-coated tablets 80 mg, 30 film-coated tablets
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3.4.1 Description of ATMP

N/A.

3.4.2 The intervention in relation to Danish clinical practice

As discussed in section 3.3, patients who have completed CRT currently do not receive active treatment today but are monitored closely until progression. Once the patients experience disease progression, they would be treated with osimertinib per the treatment guidelines(47).

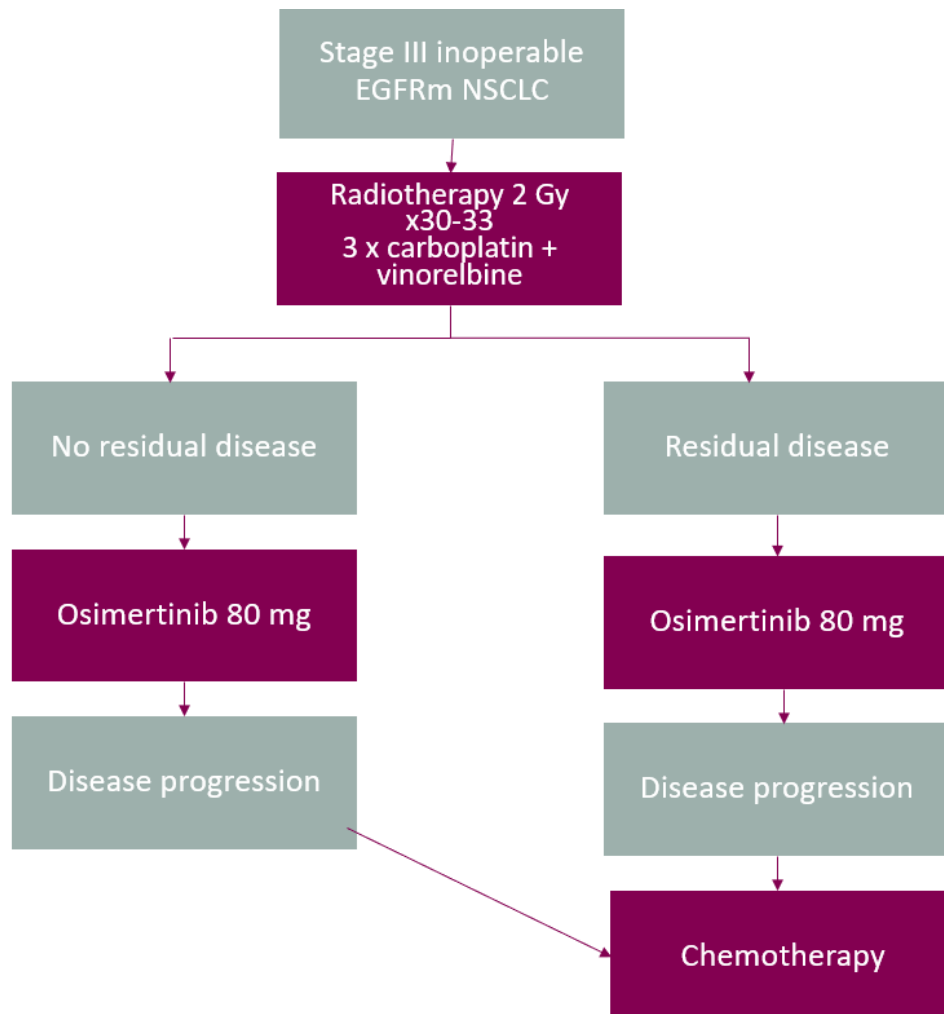
If reimbursed, osimertinib will be administered following the completion of CRT for patients with unresectable stage III EGFR-mutated NSCLC who do not have residual disease after CRT. The treatment should continue until disease progression or unacceptable toxicity as defined in EMA label(48). Considering the current median PFS of just 5 months for this population(49), introducing osimertinib earlier could reduce the risk of progression and enhance treatment tolerance, potentially extending the progression-free state in exchange for a slightly lengthened treatment duration with osimertinib.

Since current standard of care after CRT for this patient population is monitoring only, placebo is a relevant comparator in this setting. This is in line with the comparator arm in the LAURA trial(49).

A summary of the updated treatment algorithm is described in Figure 2 below.



Figure 2. Proposed updated treatment algorithm should the new treatment be introduced



3.5 Choice of comparator(s)

In the LAURA trial, the comparator is placebo, and no active treatment was therefore administered in the trial.

In Denmark, the current standard of care for patients with EGFRm stage III unresectable NSCLC following definitive platinum-based CRT is active monitoring. This has been outlined in the DLGG guidelines(1). As described in detail in 3.1, the substantial risk of progression to metastatic Stage IV after CRT alone, underscores a critical need for consolidating targeted treatment options. The risk of CNS progression, a drastic decline in survival rates and the associated impact on quality of life highlight the urgent necessity for interventions that can delay progression and alleviate these severe impacts.

As the comparator arm in the LAURA is reflective of the Danish clinical practice, data from the placebo arm will be used as the comparator for this analysis.



Table 4. Overview of comparator

Overview of comparator	
Generic name	N/A
ATC code	N/A
Mechanism of action	N/A
Method of administration	N/A
Dosing	N/A
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	N/A
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	N/A

3.6 Cost-effectiveness of the comparator(s)

Comparator is placebo, hence no cost-effectiveness analysis has been included for the comparator in this application.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Progression-free survival (PFS), overall survival (OS) and CNS progression-free survival (CNS PFS) are relevant outcomes for this application. The efficacy outcomes are summarized in Table 5.



Table 5. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival (PFS) LAURA	5 th January 2024 DCO: <i>Median FU:</i> <i>Osimertinib: 22.0 months</i> <i>Placebo: 5.6 months</i>	Time from the date of randomization until the date of disease progression or death regardless of whether the patient withdrew from randomized therapy or received another anti-cancer therapy prior to progression	PFS using BICR assessment according to RECIST v1.1
Overall survival (OS) LAURA	5 th January 2024 DCO: <i>Median FU:</i> <i>Osimertinib: 29.5 months</i> <i>Placebo: 28.1 months</i> 29 th November 2024 DCO: <i>Median FU:</i> <i>Osimertinib: 42.6 months</i> <i>Placebo: 37.5 months</i>	OS is defined as the time from randomization to death from any cause.	Patients are followed up for survival status every 12 weeks until death, withdrawal of consent or end of the study i.e., at the final OS analysis, whichever occurs first.
CNS progression-free survival (CNS PFS) LAURA	5 th January 2024 DCO: <i>Median FU:</i> <i>Osimertinib: 24.6 months</i> <i>Placebo: 5.7 months</i>	CNS PFS is defined as the time from the date of randomization until the date of CNS progression or death.	Time to CNS PFS (time to the earliest of CNS progression or death) using BICR assessments according to RECIST v1.1 by independent neuroradiologist review.
Second progression-free survival (PFS2) LAURA	5 th January 2024 DCO	Second progression-free survival is defined as the time from the date of randomisation to the earliest of the progression events following first objective disease progression, subsequent to the first subsequent therapy, or death.	Time to second progression event following first progression according to RECIST v1.1.
Time to progression (TTP)	5 th January 2024 DCO	Time to progression is a reanalysis of PFS data from the trial, where death has been censored.	Reanalysis of PFS data, censored for death.



Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Post-progression survival (PPS)	5 th January 2024 DCO	Post-progression survival is defined as the time from tumour progression according to RECIST until the date of death. (i.e. date of death or censoring – date of tumour progression + 1). Only patients who have progressed are included in this analysis population	Reanalysis of PFS and OS data. Only patients who have progressed are included in this analysis.

* 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(22, 47, 50, 51).

4. Health economic analysis

4.1 Model structure

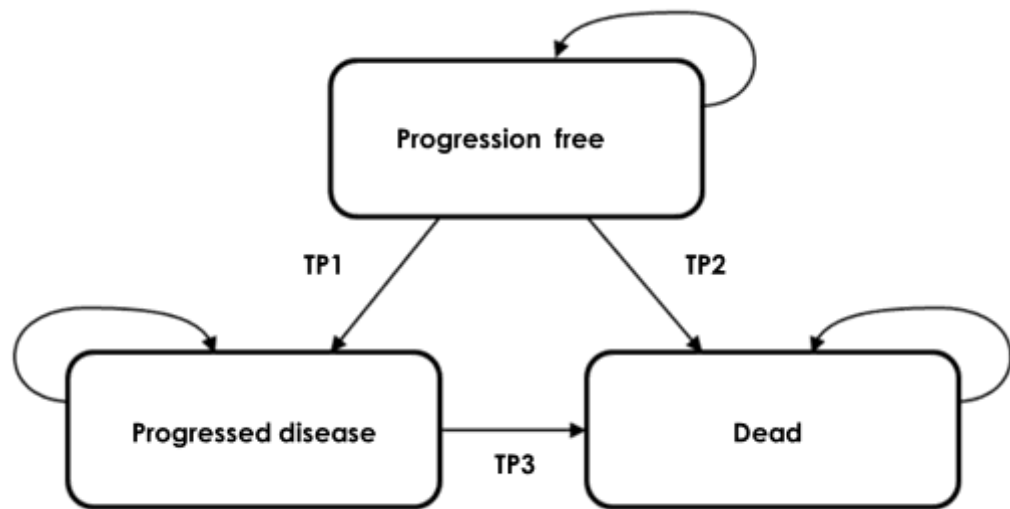
A three-health state semi-Markov model was developed for the STM as the base case. The transition probabilities between different health states were based on the time-spent in each health state. Progression-free (PF) and progressed disease (PD) were modelled using tunnel states that track the time spent in the respective health state over time. The methodology follows the guidance from the international society for pharmacoeconomic and outcomes research (ISPOR)(52).

The health states of interest were selected to represent the main events that patients may experience over the course of their treatment for NSCLC and were aligned with the primary and secondary endpoints of LAURA trial, and included:

- Progression-free (PF) state
- Progressed disease (PD) state
- Dead

The model structure for the base case is presented in Figure 3. Patients enter the model in the PF state, and then transition to the PD or to dead, which is an absorbing state. Patients in the PD state can transition to dead.

Figure 3. State transition model structure



Abbreviations: TP: transition probability

The transition probabilities (TPs) were estimated by utilising PFS as well as time-to-progression (TTP), and post-progression survival (PPS)(53). TP1 is based on TTP, TP2 is based on the difference between PFS and TTP, and TP3 is based on PPS (see section 8.1.2 for further information on the transition probabilities).

4.1.1 Justification for choice of modelling approach (STM vs. PSM)

The limitations of a partitioned survival model (PSM) are that PFS and OS are modelled independently, which may result in analysis results that are implausible, such as crossing OS and PFS curves. In a PSM, the proportions of patients are directly estimated at each time point using time-to-event endpoints from the trials, and therefore rely on independent extrapolations for OS and PFS.(54) Contrasting with a PSM, the state transition model (STM) approach allows a logical relationship between PFS and OS curves due to the survival extrapolations being explicitly linked: the probability of death is modelled as a function of the patient health state (i.e. progression free and post-progression in the simplest model structure). This addresses the curve crossing limitation of the PSM and is also a particularly attractive approach when OS data is immature and may not allow for a reliable extrapolation, while the long-term STM OS estimates are based on all available progression of disease data available.

Considering that LAURA presented immature OS estimates at the time of the primary analyses (~20%), using a state transition structure was considered to be more appropriate than using a partitioned survival model. The limitations associated with OS data maturity can be partly countered by using a STM in which the OS is estimated based on PFS and post-progression survival (PPS). A dependency between the estimation of all endpoints ensures survival functions are explicitly linked.

The main efficacy inputs required for the STM are illustrated in Figure 3.

Table 6. STM efficacy estimation



Efficacy	Estimate approach
Time to progression (TTP)	Estimated using parametric curves fitted to the LAURA trial data
Post progression survival (PPS)	Estimated using parametric curves fitted to the LAURA trial data
Pre progression survival	Estimated as the difference in probability between TPP and PFS, which were estimated using parametric curves fitted to the LAURA trial data
Overall survival (OS)	OS = Patients in PF + Patients in PD
Death	Death=1-OS

Abbreviations: PFS: progression free survival; TTP: time to progression; PPS: post-progression survival; OS: overall survival

4.2 Model features

The main features of the economic model are described in Table 7.

Table 7. Features of the economic model

Model features	Description	Justification
Patient population	Unresectable EGFRm stage III NSCLC following CRT	Trial population relevant for clinical practice
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	38.6 years (lifetime)	Lifetime time horizon to capture all health benefits and costs in line with DMC guidelines.
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.
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years



Model features	Description	Justification
Intervention	Osimertinib	Intervention in scope for application
Comparator(s)	Placebo	According to national treatment guideline.
Outcomes	Time to progression (TTP) Progression-free survival (PFS) Post progression survival (PPS) Overall survival (OS)	Trial data outcomes to populate state transition model.



5. Overview of literature

5.1 Literature used for the clinical assessment

This application is based on the head-to-head study LAURA (NCT03521154) comparing osimertinib to placebo in patients with unresectable EGFRm stage NSCLC whose disease has not progressed following definitive platinum-based CRT. The intervention in LAURA is the first one in this clinical setting and the trial comparator is relevant also for Danish clinical practice. No systematic literature review has therefore been conducted.



Table 8. Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Lu S, Kato T, Dong X, et al. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. <i>N Engl J Med.</i> 2024;391(7):585-597. doi:10.1056/NEJMoa2402614 (2) Lu S, Ahn MJ, Reungwetwattana T, et al. Osimertinib after definitive chemoradiotherapy in unresectable stage III epidermal growth factor receptor-mutated non-small-cell lung cancer: analyses of central nervous system efficacy and distant progression from the phase III LAURA study. <i>Ann Oncol.</i> 2024;35(12):1116-1125. doi:10.1016/j.annonc.2024.08.2243(57) Data on file: LAURA Clinical Study Report, January 2024 (58) Data on file: LAURA update OS analysis, November 2024	LAURA	NCT03521154	Start: 19/07/2018(55) Completion: 29/06/26(55) 1st DCO: 5h January 2024 DCO, OS upon request from regulatory body of Japan: 29th November 2024. Presented at ELCC 2025(56). Final OS analysis estimated: H1 2027, approx. 120 events in total	Osimertinib vs. placebo for patients with unresectable EGFRm stage III NSCLC whose disease has not progressed following definitive platinum-based CRT



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*
Data on file: LAURA OS update, DCO: 29 th November 2024 (presented at ELCC 2025)				
Ramalingam, S.S. et al. LBA4: Osimertinib (osi) after definitive chemoradiotherapy (CRT) in patients (pts) with unresectable (UR) stage III EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC): Updated overall survival (OS) analysis from the LAURA study. Journal of Thoracic Oncology, Volume 20, Issue 3, S123 - S124(56)				

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

Table 9. 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
Data on file: LAURA Clinical Study Report, January 2024 (58)	EORTC QLQ-C30	Section 0, 0 and 10.3
	EQ-5D-5L VAS	



Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
	EQ-5D-5L based HSUV for pre-progressed and post-progressed health state derived from mixed-effect model based on clinical trial data.	
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. <i>Health Qual Life Outcomes</i> . 2008;6:84. Published 2008 Oct 21. doi:10.1186/1477-7525-6-84(59)		
Monahan M, Ensor J, Moore D, Fitzmaurice D, Jowett S. Economic evaluation of strategies for restarting anticoagulation therapy after a first event of unprovoked venous thromboembolism. <i>J Thromb Haemost</i> . 2017;15(8):1591-1600. doi:10.1111/jth.13739(60)		
Goeree R, Villeneuve J, Goeree J, Penrod JR, Orsini L, Tahami Monfared AA. Economic evaluation of nivolumab for the treatment of second-line advanced squamous NSCLC in Canada: a comparison of modeling approaches to estimate and extrapolate survival outcomes. <i>J Med Econ</i> . 2016;19(6):630-644. doi:10.3111/13696998.2016.1151432(61)	Disutility decrement adverse events, please see Section 10.4.4	Section 10.4.4
Crossan C, Tsochatzis EA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. <i>Health Technol Assess</i> . 2015;19(9):1-vi. doi:10.3310/hta19090(62)		
NICE Technology appraisal guidance: Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer, TA654(63)		



5.3 Literature used for inputs for the health economic model

All clinical input used to inform the health economic model expect utility decrements for adverse events has been sourced from the LAURA trial.

Table 10. 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
Data on file: LAURA Clinical Study Report, DCO: 5 th January 2024 (58)	TPP, PFS, OS, TDT, Adverse events	Clinical trial of interest for comparison	Section 8 Section 9 Section 10
Data on file: LAURA OS update, DCO: 29 th November 2024 (to be published at ELCC 2025)			



6. Efficacy

6.1 Efficacy of osimertinib compared to placebo for patients with unresectable stage III EGFRm NSCLC, who has not progressed during or following curative chemoradiation

6.1.1 Relevant studies

The LAURA trial is a phase 3, double-blind, placebo-controlled, randomized trial(2). The study aimed to evaluate the efficacy and safety of osimertinib, a third-generation EGFR tyrosine kinase inhibitor, in patients with unresectable stage III EGFR-mutated non-small-cell lung cancer (NSCLC) who did not show disease progression during or after chemoradiotherapy.

Patients were randomly assigned in a 2:1 ratio to receive either osimertinib or a placebo. Patients were stratified at randomization based on prior chemoradiation strategy (concomitant vs sequential CRT), tumor stage prior to chemoradiation (IIIA vs IIIB/IIIC) and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs. enrolled at non-Chinese site or patient declaring themselves of non-Chinese ethnicity).

Patients in the intervention group received osimertinib at a dose of 80 mg orally once daily, while patients in the comparator group received a matching placebo. Open-label osimertinib was offered to patients at progression if, in the opinion of the treating physician, they were continuing to derive clinical benefit (for patients assigned to the osimertinib group), or if treatment was in accordance with local clinical practice and the judgement of their treating physician (for patients assigned to the placebo group).



Table 11. 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
LAURA, NCT03521154	Phase III, double-blind, randomized, placebo-controlled, multicenter trial.	Study Start 2018-07-19 Primary Completion 2024-01-05 Study Completion (expected): 2027 H1	Patients with EGFRm stage III NSCLC whose disease has not progressed during or following platinum-based chemoradiation therapy	Osimertinib (80 mg, oral, once daily)	Placebo (oral, once daily)	Primary endpoint: PFS assessed by BICR using RECIST v1.1. Secondary endpoints: OS, CNS-PFS, time to first subsequent treatment, time to second progression (PFS2) & PROs. Median follow-up (Jan 2024 DCO): 29.5 months for osimertinib patients, 28.1 months for placebo patients Median follow-up (Nov 2024 DCO): 39.4 months for osimertinib patients, 35.2 for placebo patients



6.1.2 Comparability of studies

Not relevant, head-to-head trial used for comparative analysis.

6.1.2.1 Comparability of patients across studies

The baseline characteristics of patients included in the LAURA trial are presented in Table 12.

Table 12. Baseline characteristics of patients in LAURA study used for the comparative analysis of efficacy and safety (ITT population)(2)

Characteristic	Osimertinib (n=143)	Placebo (n=73)
Age, median (range)	62 (36, 84)	64 (37, 83)
Sex, n (%)		
Male	53 (37)	31 (42)
Female	90 (63)	42 (58)
Race, n (%)		
Asian	116 (81)	62 (85)
Non-Asian	27 (19)	11 (15)
Smoking status, n (%)		
Never	102 (71)	49 (67)
Smoker – Current	4 (3)	1 (1)
Smoker – Former	37 (26)	23 (32)
WHO PS, n (%)		
0	80 (56)	31 (42)
1	63 (44)	42 (58)
AJCC-UICC disease stage, n (%)		
Stage IIIA	52 (36)	24 (33)
Stage IIIB	67 (47)	38 (52)
Stage IIIC	24 (17)	11 (15)
Pre-CRT PET scan, n (%)		
Yes	79 (55)	33 (45)
No	64 (45)	40 (55)
Histology type, n (%)		
Adenocarcinoma	139 (97)	69 (95)
Squamous cell carcinoma	3 (2)	2 (3)
Other ^e	1 (1)	2 (3)



Tissue <i>EGFR</i> mutation type at screening, n (%)		
Ex19del	74 (52)	43 (59)
L858R mutation	68 (48)	30 (41)
Type of CRT, n (%)		
cCRT	131 (92)	62 (85)
sCRT	12 (8)	11 (15)
Response to prior CRT, n (%)		
CR	4 (3)	3 (4)
PR	67 (47)	27 (37)
SD	61 (43)	37 (51)
PD	0	0
Non-evaluable	11 (8)	6 (8)
CNS metastases at baseline, n (%)		
CNS metastases per neuroradiologist BICR	14 (10)	5 (7)

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

In the LAURA trial, patients were slightly younger than observed in clinical practice(24, 64), but this is commonly seen in clinical trials. In the clinical trial, similar proportion of females was enrolled compared to Danish clinical practice(64). Based on the subgroup analysis from the LAURA trial (see section 6.1.4.1.1), the efficacy seems to be strong regardless of age and gender.

The clinical trial primarily enrolled patients from Asia, while the patient population in Denmark is expected to be predominantly white. This issue was thoroughly addressed during the EMA procedure, which concluded that there were no grounds to anticipate different responses in white patients compared to Asian patients. The rationale was based on the absence of relative differences in efficacy between different populations, as well as no differences in the exposure of osimertinib in different ethnic groups(65). Furthermore upon discussion with a Danish clinician, the LAURA trial outcomes are expected to be transferable to Danish clinical practice despite the high proportion of enrolled Asian patients(24).

Therefore, it was deemed that the result from LAURA would be generalizable to a Danish population.

The patient characteristics had a minor impact on the outcomes of the health economics, therefore, characteristics from the LAURA trial has been applied in the health economic model. Scenario analysis with patient characteristics from Table 13 on the Danish population has conducted to demonstrate the minor impact of patient characteristics on the model outcomes.



Table 13. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population	Value used in health economic model (2)
Age (mean)	65-70 years(24) (64)	61.4 years
Gender (%-female)	60%(64)	61 %
Patient weight (average)	76 kg(24)	62.3 kg
Height (average)	174 cm(24)	160.8 cm

6.1.4 Efficacy results in the LAURA clinical trial

6.1.4.1 Progression-free survival

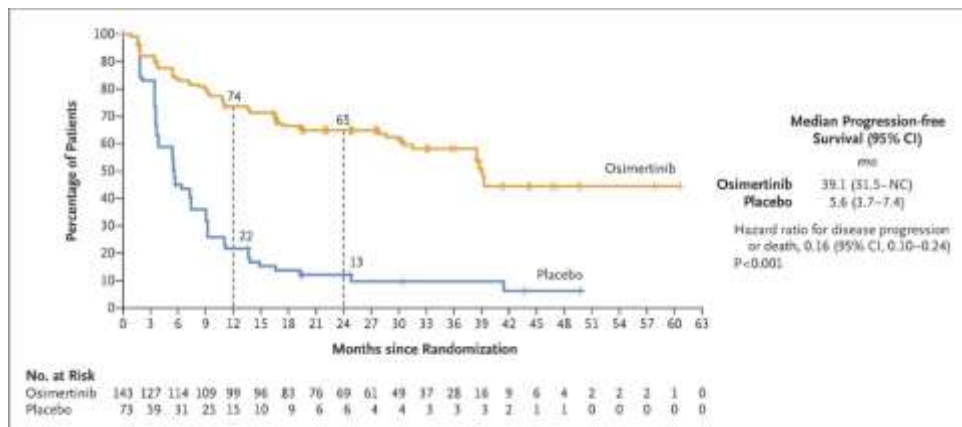
At the primary data cut-off (DCO: 5th January 2024), the median progression free survival, as assessed by a blinded independent central review (BICR), was 39.1 months (31.5 months – NC) for the osimertinib arm compared to 5.6 months (3.7- 7.4 months) for patients who received placebo (Figure 4). The percentages of the patients who were alive and progression-free at 12 months and 24 months, respectively, were 74% (95% CI, 65% to 80%) and 65% (95% CI, 56% to 73%) with osimertinib and 22% (95% CI, 13% to 32%) and 13% (95% CI, 6% to 22%) with placebo. The data for the placebo arm clearly highlights the poor prognosis of the current standard of care and underlining the unmet need for a treatment alternative that can extend survival and enhance quality of life for patients with unresectable EGFRm stage III NSCLC in Denmark.

The hazard ratio for disease progression or death was 0.16 (95 % CI, 0.10 – 0.24) in favor of osimertinib, with a p-value of less than 0.001. Investigator-assessed progression-free survival results were consistent with the findings of the blinded independent central review. The results were also consistent for progression in the CNS, a particular challenge in patients with EGFR-mutated NSCLC, where the hazard ratio for CNS-progression was 0.17 (95% CI, 0.09 – 0.32) (presented in section 6.1.4.3) (49).

The median duration of follow-up for progression-free survival in all patients was 22.0 months (range, <0.1 to 60.6 months) in the osimertinib group and 5.6 months (range, <0.1 to 49.7 months) in the placebo group; the median duration of follow-up for progression-free survival in patients whose data were censored was 27.7 months (range, <0.1 to 60.6 months) in the osimertinib group and 19.5 months (range, <0.1 to 49.7 months) in the placebo group.



Figure 4. Progression-free survival according to blinded independent central review, DCO: 5th January 2024(2)



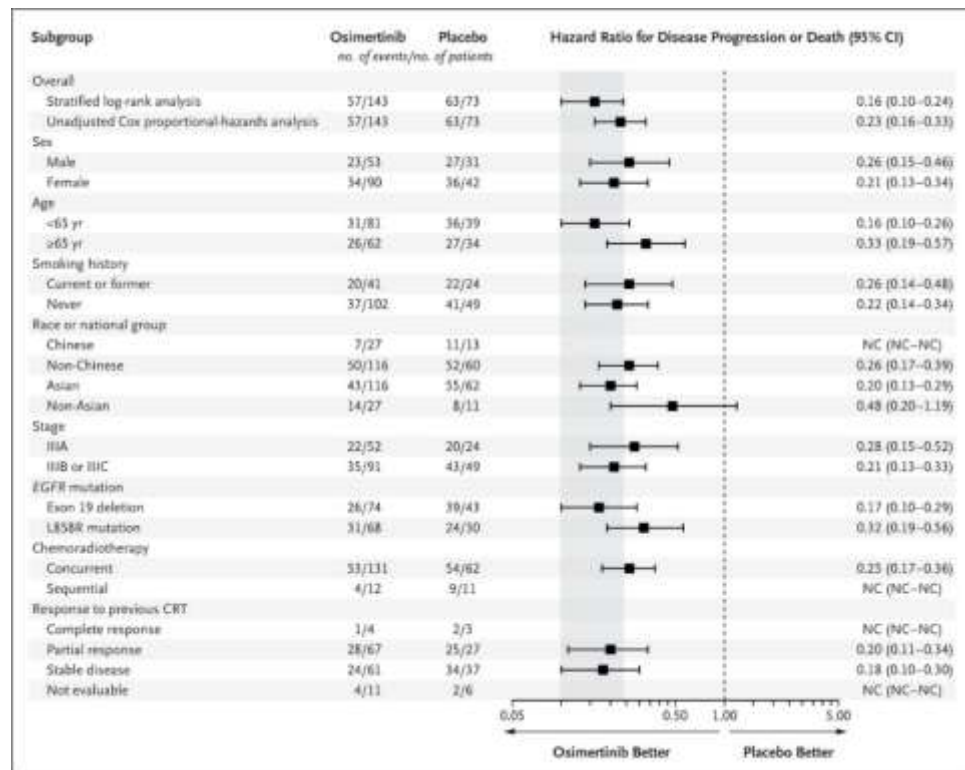
Tick marks indicate censored data, and vertical dashed lines indicate the times of landmark analyses of progression-free survival. CI denotes confidence interval, and NC not calculable.(2)

6.1.4.1.1 Subgroup analysis

The progression-free survival benefit favoring osimertinib was observed in all prespecified subgroups with sufficient events for analysis, with hazard ratios ranging from 0.16 to 0.48. The forest plot of different subgroups is shown in Figure 5.



Figure 5. Subgroup analysis of progression-free survival according to blinded independent central review. (2)



6.1.4.2 Overall survival

6.1.4.2.1 Primary data cut (5th January 2024)

At the time of the initial data-cut (DCO: 5th January 2024), 43 of the patients in the study had died (data maturity, 20%); the 36-month overall survival was 84% (95% CI, 75 to 89) with osimertinib and 74% (95% CI, 57 to 85) with placebo. The hazard ratio for overall survival was 0.81 (95% CI, 0.42 to 1.56; $P=0.53$), which was not significant at this interim analysis.

Median OS in the osimertinib arm was 54.0 months (95% CI: 46.5, NC) and was not reached (95% CI: 42.1, NC) in the placebo arm (Table 14). Of note, the median OS for osimertinib is estimated based on a single event with few patients at risk and therefore, should be interpreted with caution due to limited data available at this timepoint.

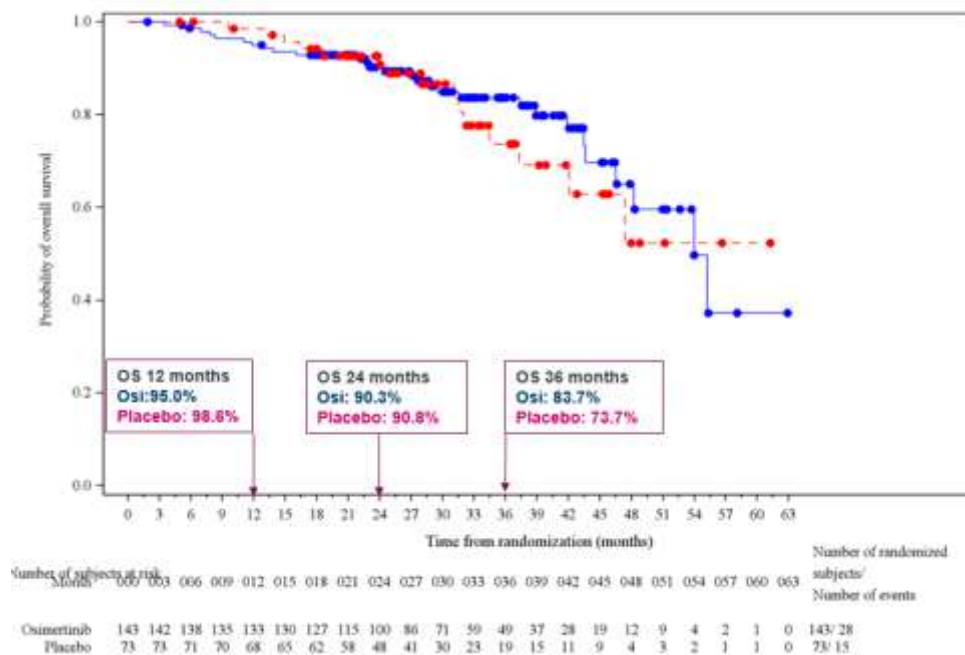
Patients who had progressed in the placebo arm could receive osimertinib upon progression. In the LAURA-trial, 81% of the patients who had disease progression received open-label osimertinib. This, together with the low number of deaths, resulted in the non-significant difference. EMA noted that the overall survival curves appear to start separating after 33 months (65), and further data-cuts will give more information on the overall survival benefit.



Table 14. Median OS estimates on Jan 2024 DCO.(66)

	% (# events)	Median OS, months (95% CI)	HR (95% CI)	2-sided p-value
Osimertinib (N=143)	19.6% (28)	53.95 (46.49, NC)	0.81 (0.42, 1.56)	0.530
Placebo (n=73)	20.5% (15)	NC (42.05, NC)		

Figure 6. Overall survival, Jan 2024 DCO.(66)



6.1.4.2.2 Updated OS data-cut (November 2024)

A second, ad-hoc analysis was conducted on a data-cut November 29th 2024 upon a request from the Japanese regulatory body and presented at ELCC 2025 between the 26-29 March 2025(56). Only OS was analysed for this ad-hoc analysis. At this data cut, 66 of the patients had died (data maturity 31%), the 36-month overall survival was 81.8 % (95% CI, 74% - 87%) with osimertinib and 72.5 % (95% CI, 59% – 82%) with placebo (Figure 7)(56). The hazard ratio for overall survival was 0.67 (95% CI, 0.40 to 1.14; P=0.140), which was not significant at this interim analysis(56).

As observed in the DCO from 5th January 2024, a large proportion of patients who had progressed in the placebo arm go on to receive osimertinib upon progression. In the LAURA-trial, 78% (n=54) of the patients who had disease progression received open-label osimertinib. This, together with the low number of deaths, resulted in the non-significant difference. Comparing to the first DCO on OS, the separation of the curves is even more prominent in this updated analysis, beyond the separation point at month 33. Additionally, the hazard ratio has reduced from the first data cut despite the minor



increase in events from the first data cut (11% increase in maturity to 31% from 1st data cut).

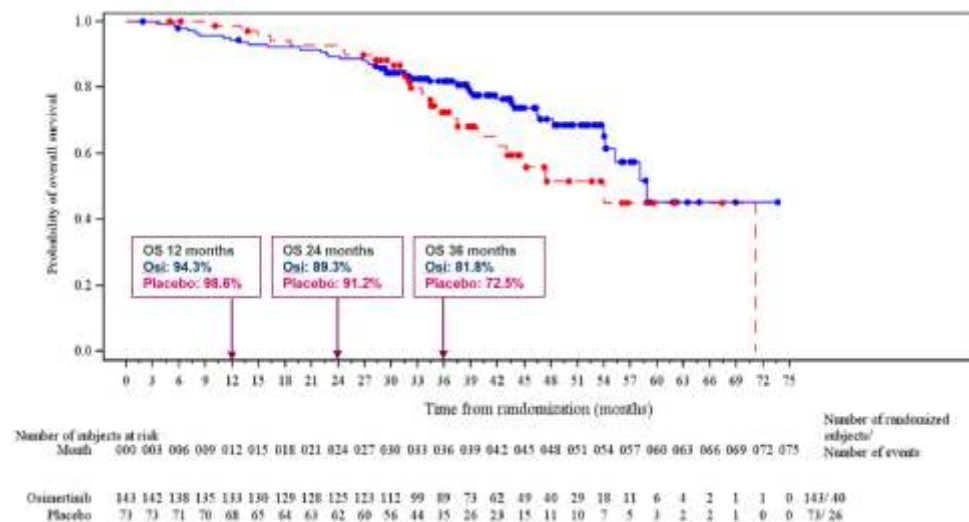
The updated OS analysis suggests a favorable trend in OS benefits when treating patients with unresectable EGFRm stage III NSCLC using osimertinib, compared with current clinical practices in Denmark. The LAURA trial highlights osimertinib's potential to address a significant unmet need in current clinical practice, as EGFR-mutated patients currently lack active treatment options post-chemoradiation. In contrast, patients without EGFR mutations have durvalumab available following chemoradiation.

The LAURA trial remains ongoing, with a final OS data cut planned at 60% maturity(49). This will occur when approximately 120 death events have been recorded across both arms, anticipated in the first half of 2027.

Table 15. Median OS estimates: DCO 29th November 2024(56).

	% (# events)	Median OS, months (95% CI)	HR (95% CI)	2-sided p-value
Osimertinib (N=143)	28.0% (40)	58.81 (54.08, NC)	0.67 (0.40, 1.14)	0.140
Placebo (n=73)	35.6% (26)	53.98 (42.05, NC)		

Figure 7. Updated analysis of overall survival.(56)



6.1.4.3 CNS-PFS

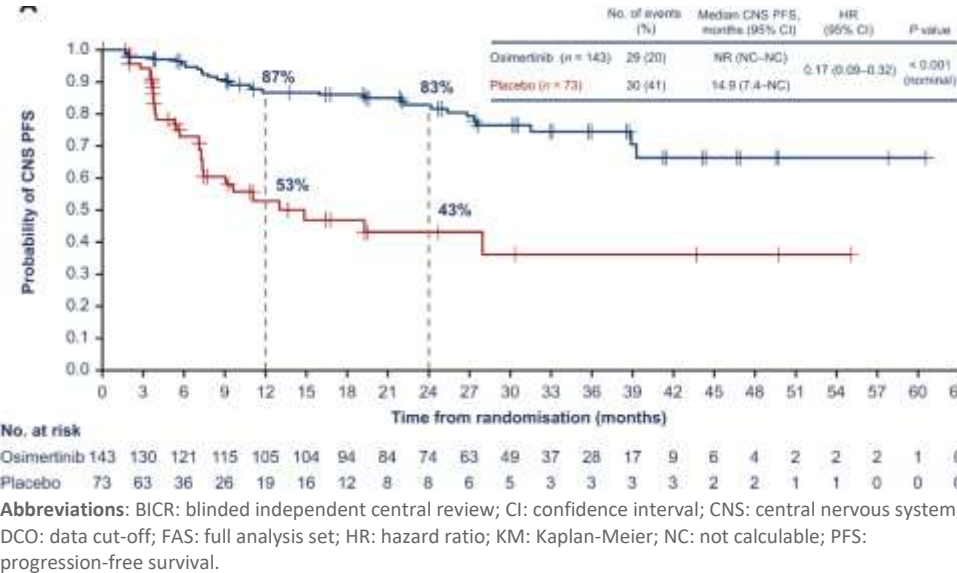
Treatment with osimertinib demonstrated a nominally statistically significant and clinically meaningful improvement in CNS PFS (based on neuroradiologist BICR assessment according to RECIST v1.1) compared to placebo (HR = 0.17 [95% CI: 0.09, 0.32], nominal p-value < 0.001), based on a data maturity of 27%.(67) Of note, the



statistical significance of CNS PFS could not be formally tested at the current DCO date per the multiple testing procedure, as OS did not reach a statistical significance at its interim analysis. (58, 67)

There was a clear separation of the KM curves in favor of osimertinib starting at the first post-baseline scan at Week 8, with the separation of the curves sustained throughout the follow-up period (Figure 8). The KM estimate of median CNS PFS was not reached (95% CI: NC, NC) for patients in the osimertinib arm compared to 14.9 months (95% CI: 7.4, NC) for patients the placebo arm, with KM estimates demonstrating that a greater proportion of patients in the osimertinib arm were alive and CNS progression-free at all assessed timepoints compared to those in the placebo arm (Figure 8).(49)

Figure 8. KM plot of CNS PFS by neuroradiologist BICR assessment (FAS) DCO: 5th January 2024(49).



6.1.4.4 PFS2

A consistently significant improvement in second progression-free survival on a subsequent treatment (PFS2) was observed following treatment with osimertinib.

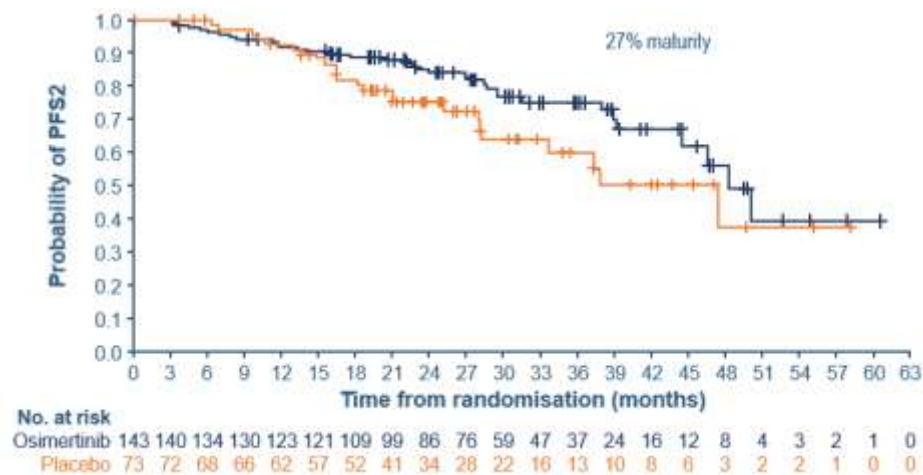
The HR for PFS2 was 0.62 (95% CI: 0.35 – 1.08, p=0.088), a clinically meaningful improvement in PFS2 for patients in the osimertinib arm compared with patients in the placebo arm. Overall, 34 patients (24%) in the osimertinib arm and 24 patients (33%) in the placebo arm had a PFS2 event, with an overall data maturity of 27%.

A separation between treatment arms of the KM curves from approximately 12 months post-randomisation was observed in favour of the osimertinib arm, demonstrating continued clinical benefit beyond initial progression (Figure 9).



Median time to PFS2 was similar between the treatment arms (48.20 months [95% CI: 44.42, NC] in the osimertinib arm and 47.38 months [95% CI: 28.22, NC] in the placebo arm). However, these medians were estimated based on a single event and should be interpreted with caution considering the limited number of patients (less than 10% of initial cohort) who remained at risk at the tail of the KM curve (Figure 9).

Figure 9: Kaplan-Meier plot of second progression-free survival (FAS) DCO: 5th January 2024(49).

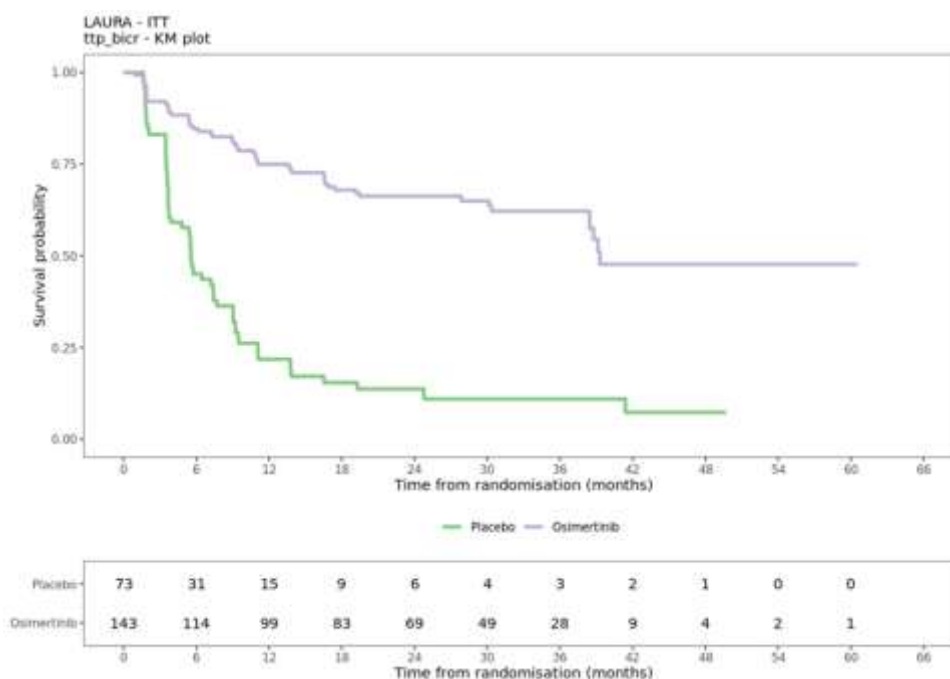


6.1.5 Time to progression

Of 143 patients at risk in the osimertinib arm, 53 patients had a BICR confirmed disease progression event (37.1% maturity)(58). The median time-to-progression was 39.3 months (95% CI: 38.4–NC), which was consistent with the median progression-free survival (39.1 months [95% CI: 31.5–NC])(58). Of the 73 patients at risk in the placebo arm, 62 patients had a BICR confirmed disease progression event (84.9% maturity)(58). The median time-to-progression was 5.6 months (95% CI: 3.7–7.4), which was consistent with the median progression-free survival (5.6 months [95% CI: 3.7–7.4])(58).



Figure 10. TTP Kaplan-Meier curve of osimertinib and placebo from the LAURA trial. DCO: 5th January 2024(58).



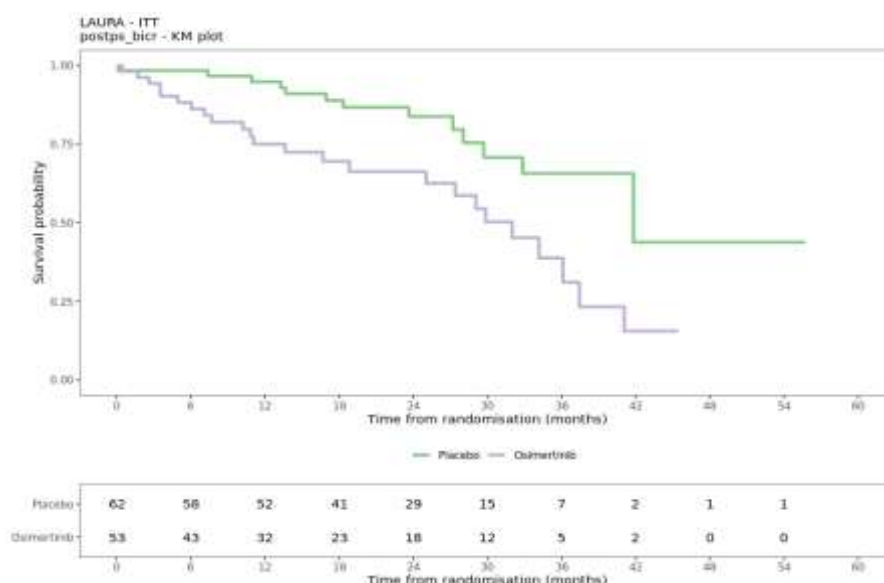
6.1.6 Post-progression survival

Due to the immaturity in the osimertinib TTP survival curve, the osimertinib PPS curve starts with only 53 patients at risk (of the 143 subjects randomised in the trial). Twenty-four patients of the 53 at risk had a death event (45.3% maturity) at the time of the analysis (data cut-off: 5th January 2024)(58). The median PPS for osimertinib is 32.0 months (95% CI: 18.8–NC)(58). Of note, there is a steeper decrease in the KM plot observed from approximately 24 months. However, only 18 patients remain at risk at this timepoint, and hence small event numbers can lead to large visual changes in the KM.

Sixty-two patients in the placebo arm (of the originally randomised 73 subjects) are at risk in the PPS curve and 13 patients had a death event (21.0% maturity) at the time of DCO1. The median PPS for placebo is 41.8 months (95% CI: 32.69, NC) (58).



Figure 11. Post-progression Kaplan-Meier curve of osimertinib and placebo from the LAURA trial.
DCO: 5th January 2024(58).



7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

Not relevant, head-to-head trial used for comparative analysis.

7.1.2 Method of synthesis

Not relevant, head-to-head trial used for comparative analysis.

7.1.3 Results from the comparative analysis

Comparative results for the comparison between osimertinib and placebo for patients with unresectable EGFRm stage NSCLC whose disease has not progressed following definitive platinum-based CRT are presented below(68, 69).

Table 16. Results from the comparative analysis of osimertinib vs. placebo for patients with unresectable EGFRm stage III NSCLC whose disease has not progressed following definitive platinum-based CRT(68, 69).

Outcome measure	Osimertinib (N=143)	Placebo (N=73)	Difference
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Progression-free survival, DCO: 5th January 2024.



Outcome measure	Osimertinib (N=143)	Placebo (N=73)	Difference
Median PFS*	39.1 months (95% CI: 31.5 – NC)	5.6 months (95% CI: 3.7 – 7.4)	33.5 months
PFS HR	-	-	HR: 0.16 (95% CI: 0.10 – 0.24)
1 year PFS-rate*	74% (95% CI: 65% - 80%)	22% (95% CI: 13% - 32%)	52 %-points
2 year PFS-rate*	65% (95% CI: 56% - 73%)	13% (95% CI: 6% - 22%)	52 %-points
Overall survival, DCO: 5th January 2024.			
Median OS [§]	54.0 months (95% CI: 46.5 – NC)	NC (95% CI: 42.1 - NC)	NC
OS HR [§]	-	-	HR: 0.81 (95% CI: 0.42 – 1.56)
2 year OS-rate [§]	90.3% (95% CI: 83.8% - 94.2%)	90.8% (95% CI: 80.5% - 95.8%)	0.5%-points
3 year OS-rate [§]	83.7% (95% CI: 75.3% - 89.4%)	73.7% (95% CI: 56.7% - 84.9%)	10%-points
Overall survival, DCO: 29th November 2024.			
Median OS [§]	58.8 months (95% CI: 54.1 – NC)	54.0 months (95% CI: 42.1 – NC)	4.8 months
OS HR [§]	-	-	HR: 0.67 (95% CI: 0.40 – 1.14)
2 year OS-rate [§]	89.3% (95% CI: 83% - 95%)	91.2% (95% CI: 82% - 96%)	1.9%-points
3 year OS-rate [§]	81.8% (95% CI: 74% - 87%)	72.5% (95% CI: 59% - 82%)	9.3%-points
CNS-PFS, DCO: 5th January 2024.			
Median CNS-PFS*	NC (95% CI: NC – NC)	14.9 months (95% CI: 7.4 – NC)	NC
CNS-PFS HR	-	-	HR: 0.17 (95% CI: 0.09 – 0.32)



Outcome measure	Osimertinib (N=143)	Placebo (N=73)	Difference
1 year CNS-PFS-rate [§]	87% (95% CI: 79.4% - 91.5%)	53% (95% CI: 38.3% - 65.6%)	34%-points
2 year CNS-PFS-rate [§]	83% (95% CI: 74.7% - 88.5%)	43% (95% CI: 28.0% - 57.7%)	40%-points
PFS2, DCO: 5th January 2024			
Median PFS2*	48.2 months (95% CI: 44.42 – NC)	47.38 months (95% CI: 28.22 - NC)	0.8 months
PFS2 HR*	-	-	HR: 0.62 (95% CI: 0.35 – 1.08) p=0.088
TTP, DCO: 5th January 2024			
Median TPP*	39.3 months (95% CI: 38.4 – NC)	5.6 months (95% CI: 3.7 – 7.4)	33.7 months
PPS, DCO: 5th January 2024			
Median PPS*	32.0 months (95% CI: 18.8 – NC)	41.8 months (95% CI: 32.69 – NC)	9.8 months

Note: PFS and CNS-PFS is assessed by BICR

Legend: *: DCO 5th January 2024, §: DCO: 29th November 2024

7.1.4 Efficacy – results per [outcome measure]

Not applicable, comparative analysis between osimertinib and placebo provided in section 6.

8. Modelling of efficacy in the health economic analysis

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

Data from the LAURA trial (DCO: 5th January 2024) was used to inform efficacy estimations for osimertinib and placebo(58). Data from an ad-hoc OS analysis (DCO: 29th November 2024) is used for validation of aggregated OS curves in the STM model see section 8.5.1.



The STM used time to progression (TTP), PPS, PFS and general population mortality to model transitions between the PF, PD and dead health states. Parametric survival modelling was used to extrapolate these results after the trial follow-up period and over the lifetime horizon. A summary of the trial data used to model the transition between health states is provided in Table 17; each transition probability (TP) is described in further detail below.

8.1.1 Extrapolation of efficacy data

Parametric survival modelling was needed to estimate efficacy endpoints for osimertinib and placebo after the trial follow up period. The data from the trial that were used for this modelling are outlined in Table 17.

Table 17. LAURA trial clinical endpoints

Modelled efficacy endpoint	Description
Progression-free survival (PFS)	PFS was a primary endpoint of the LAURA trial and is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdrew from randomized therapy or received another anti-cancer therapy prior to progression.
Time to progression (TTP)	To calculate TTP, a reanalysis of PFS data from the trial was conducted to censor for deaths.
Pre-progression survival (PFS – TTP)	PFS – TTP was used to calculate pre-progression survival
Post-progression survival (PPS)	PPS analysis was conducted to determine time to death following the first BICR confirmed PFS event. PPS is defined as the time from tumour progression according to RECIST until the date of death. (i.e. date of death or censoring – date of tumour progression + 1). Only patients who have progressed are included in this analysis population.
Treatment duration (TDT)	Time to discontinuation of treatment (TDT) was a secondary end point of the trial and defined as the time from randomization to the earlier of the date of study treatment discontinuation (regardless of the reason for study treatment discontinuation) or death. TDT is not bounded by PFS in this model to align with clinical practice.

Abbreviations: PFS: progression-free survival; TDT: time-to-treatment discontinuation; TTP: time to progression

A variety of standard parametric curves were considered for survival modelling (i.e. exponential, Weibull, lognormal, generalized gamma, loglogistic, Gompertz, gamma). The most appropriate curves were selected according to the NICE Decision Support Unit (DSU) guidance(70). Additionally, as a final step after assessing individual transitions, the fit of the aggregated PFS and OS curves was visually inspected to assess fit of the modelled data to the observed LAURA trial PFS and OS KM curves.



8.1.1.1 Extrapolation of time to progression (TTP)

Summary of extrapolation of time to progression (TTP) is presented in Table 18. Please refer to Appendix D for full description of extrapolation choice.

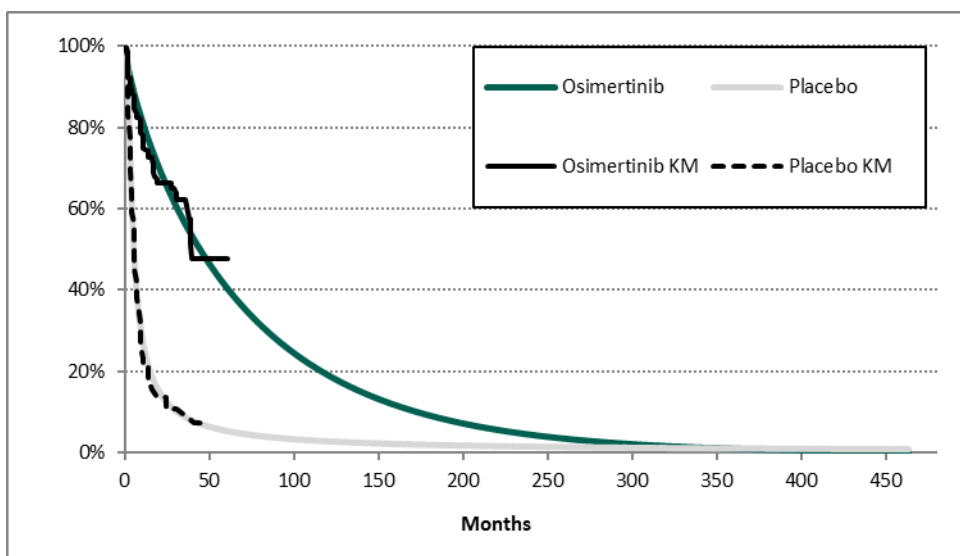
Table 18. Summary of assumptions associated with extrapolation of time to progression

Method/approach	Description/assumption
Data input	LAURA trial(58)
Survival models	- 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: Gen-gamma Placebo: Gen-gamma
Function with best BIC fit	Osimertinib: Log-normal Placebo: Gen-gamma
Function with best visual fit	Osimertinib: Log-normal Placebo: Gen-gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Osimertinib: Log-logistic or Gen-gamma Placebo: Gen-gamma
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	Osimertinib: Gamma Placebo: Gen-gamma
Adjustment of background mortality with data from Statistics Denmark	NA
Adjustment for treatment switching/cross-over	NA
Assumptions of waning effect	No



Method/approach	Description/assumption
Assumptions of cure point	No

Figure 12. Base-case extrapolations of TPP overlayed with observed data for TPP in clinical trial.



8.1.1.2 Extrapolation of post-progression survival (PPS)

Summary of extrapolation of post-progression survival (PPS) is presented in Table 19. Please refer to Appendix D for full description of extrapolation choice.

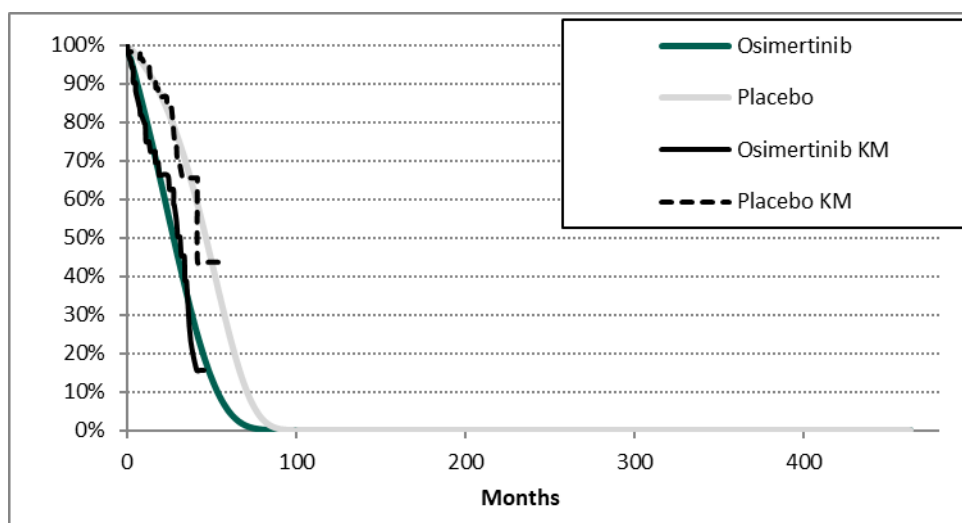
Table 19. Summary of assumptions associated with extrapolation of post-progression survival (PPS)

Method/approach	Description/assumption
Data input	LAURA trial(58)
Models	- 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: Gompertz Placebo: Gompertz
Function with best BIC fit	Osimertinib: Exponential Placebo: Exponential



Method/approach	Description/assumption
Function with best visual fit	Osimertinib: Exponential or Gompertz Placebo: Gompertz
Function with best fit according to evaluation of smoothed hazard assumptions	Osimertinib: Gompertz Placebo: Gompertz
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	Osimertinib: Gompertz Placebo: Gompertz
Adjustment of background mortality with data from Statistics Denmark	Yes, age- and gender-matched background mortality is used to cap OS of patients in all treatment arms in model.
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 13. Base-case extrapolations of PPS overlaid with observed data for PPS in clinical trial.





8.1.1.3 Extrapolation of treatment duration (TDT)

Summary of extrapolation of treatment duration (TDT) is presented in Table 20. Please refer to Appendix D for full description of extrapolation choice.

In clinical practice and in the LAURA study protocol, osimertinib treatment can go beyond progression, if deemed relevant for patients(24, 71). Therefore, to allow for treatment beyond progression, the TDT has not been capped by TDT in the health economic model.

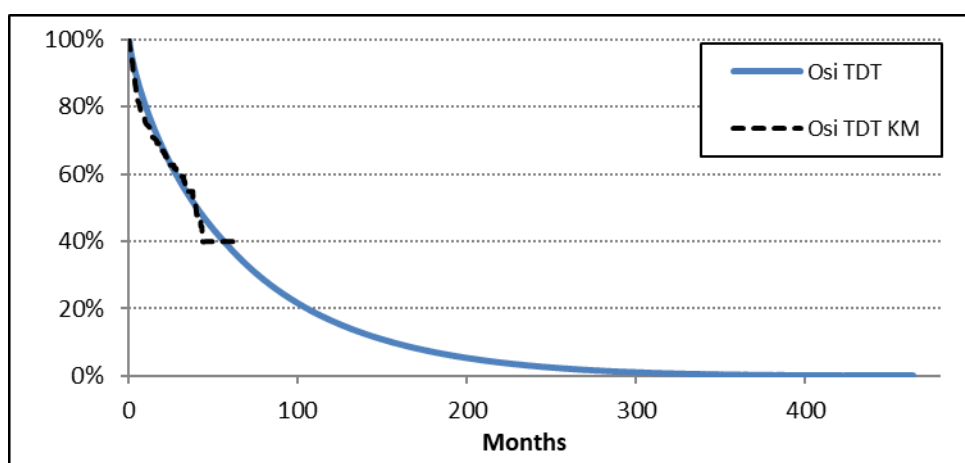
Table 20. Summary of assumptions associated with extrapolation of treatment duration (TDT)

Method/approach	Description/assumption
Data input	LAURA trial
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: Log-normal Placebo: NA
Function with best BIC fit	Osimertinib: Log-normal Placebo: NA
Function with best visual fit	Osimertinib: Gamma Placebo: NA
Function with best fit according to evaluation of smoothed hazard assumptions	NA
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	Osimertinib: Gamma Placebo: NA
Adjustment of background mortality with data from Statistics Denmark	NA



Method/approach	Description/assumption
Adjustment for treatment switching/cross-over	NA
Assumptions of waning effect	NA
Assumptions of cure point	NA

Figure 14. Base-case extrapolations of TDT overlayed with observed data for PPS in clinical trial.



8.1.1.4 Extrapolation of progression-free survival (PFS)

Summary of extrapolation of PFS is presented in The PFS parametric survival distribution selected matches the survival distribution chosen for TTP in an attempt to avoid to the logical inconsistency of the TTP and PFS curves crossing as far as possible. Hence, for extrapolation of PFS, the gamma curve have been applied for the osimertinib and and the gen-gamma curve for the placebo arm, in line with the extrapolation of TTP.

Table 21. Please refer to Appendix D for full description of extrapolation choice.

The PFS parametric survival distribution selected matches the survival distribution chosen for TTP in an attempt to avoid to the logical inconsistency of the TTP and PFS curves crossing as far as possible. Hence, for extrapolation of PFS, the gamma curve have been applied for the osimertinib and and the gen-gamma curve for the placebo arm, in line with the extrapolation of TTP.

Table 21. Summary of assumptions associated with extrapolation of treatment duration (TDT)

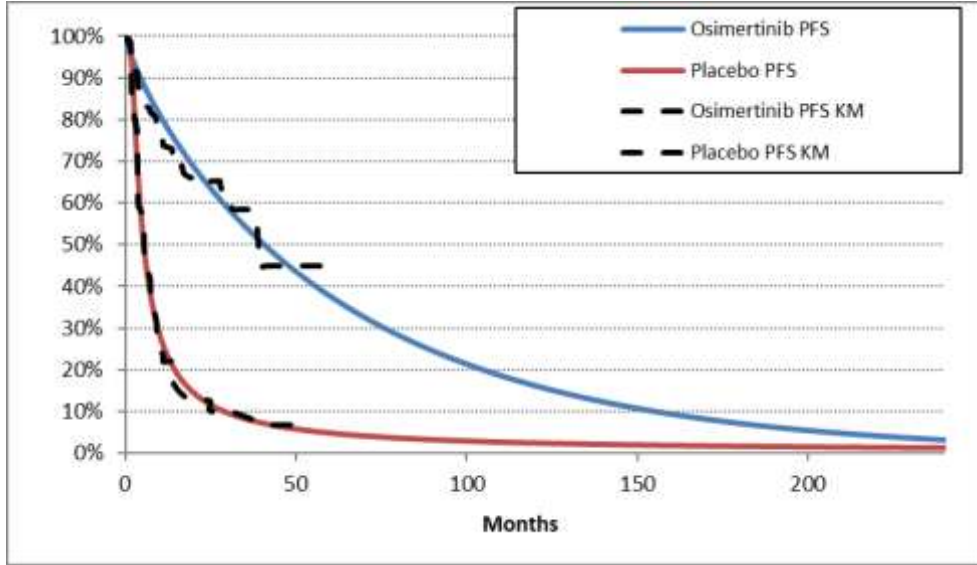
Method/approach	Description/assumption
Data input	LAURA trial
Model	- Exponential - Weibull - Gompertz - Log-logistic



Method/approach	Description/assumption
	- Log-normal - Gen-gamma - Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Osimertinib: Gen-gamma Placebo: Gen-gamma
Function with best BIC fit	Osimertinib: Log-normal Placebo: Gen-gamma
Function with best visual fit	Osimertinib: Gamma or Weibull Placebo: Gen-gamma or gompertz
Function with best fit according to evaluation of smoothed hazard assumptions	Osimertinib: No conclusive best fit Placebo: Gen-gamma
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	Osimertinib: Gamma Placebo: Gen-gamma
Adjustment of background mortality with data from Statistics Denmark	NA
Adjustment for treatment switching/cross-over	NA
Assumptions of waning effect	NA
Assumptions of cure point	NA



Figure 15. Base-case extrapolations of PFS (gamma for osimertinib and gen gamma for placebo) in clinical trial.



8.1.2 Calculation of transition probabilities

Three transitions were estimated in the model: PF to PD (TP1), PF to dead (TP2) and PD to dead (TP3). The calculation of these TPs is detailed below

- **TP1 (TTP):** To estimate this transition probability, TTP data was derived from the clinical trial. TTP is defined as the time from randomization to tumour progression explicitly (i.e. deaths without progression are censored observations rather than counted as events). Parametric curves were fitted to the TTP data and extrapolated over a lifetime horizon in order to calculate TP1.

$$TP_1(t, t - u) = 1 - \frac{S^{TTP}(t)}{S^{TTP}(t - u)}$$

where *TP*, transition **probability**; *S*, **predicted survival at time t**; *t*, **time**; *u*, **cycle length**

- **TP2:** The PFS curve reflects both PD and death. As such, the transition from PF to dead is based on differences between the PFS and TTP curves. The changing slopes of the PFS and TTP curves over time reflect the changing hazards, indicating that TP1 and TP2 are dependent of the time spent in the PFS health state.

$$TP_2 = 1 - TP_1 - \frac{S^{PFS}(t)}{S^{PFS}(t - u)}$$

where *TP*, transition **probability**; *S*, **predicted survival at time t**; *t*, **time**; *u*, **cycle length**

- **TP3 (PPS):** Transitions from PD to dead were estimated from the PPS curve. PPS was extrapolated by fitting a parametric curve to PPS Kaplan-Meier data from the clinical trial. This curve was then used to calculate TP3. Changes in the hazard of the PPS curve over time meant that TP3 was a function of the time spent in the PD health state but was not dependent on time spent in the PF state.



$$TP3 = 1 - \frac{S^{PPS}(t)}{S^{PPS}(t-u)}$$

where TP, transition probability; S, predicted survival at time t; t, time; u, cycle len

Table 22. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
PF	PD	Derived from TTP curve	TSD19(72)
	Death	Difference between PFS and TTP	TSD19(72)
PD	Death	Derived from PPS curve	TSD19(72)

Abbreviations: PD: Progressive disease, PF: Progression free, PFS: Progression-free survival, PPS: Post-progression survival, TTP: Time to progression

Health state occupancy in the health economic model is presented in Figure 16 and Figure 17 for the osimertinib and placebo arm respectively.

Figure 16. Health state occupancy – osimertinib arm

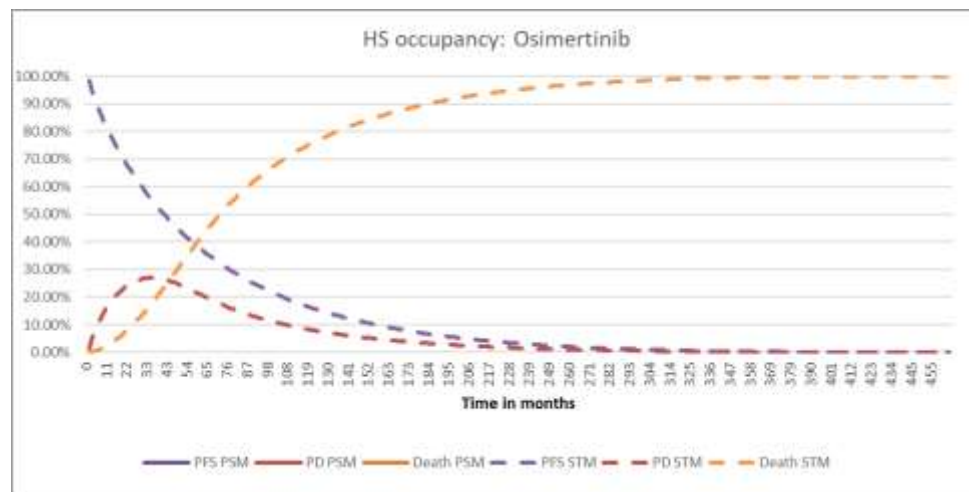
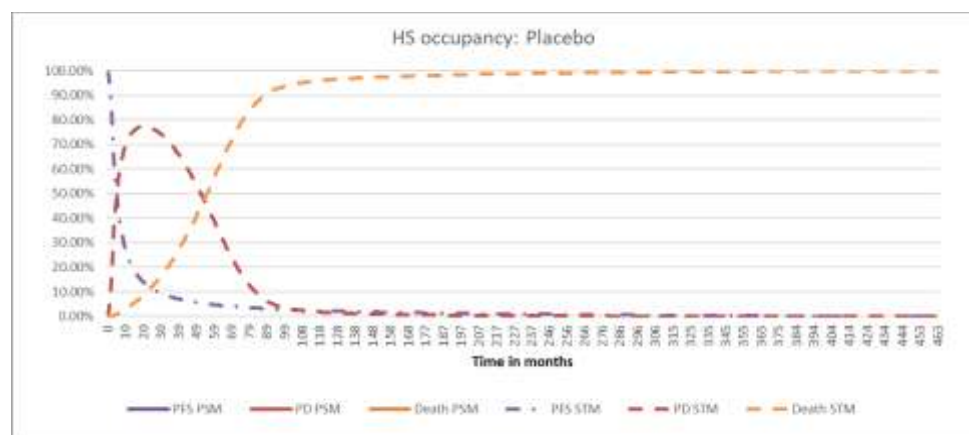


Figure 17. Health state occupancy – placebo arm





8.2 Presentation of efficacy data from [additional documentation]

N/A, no external efficacy data has been applied in the health economic analysis beyond the observed trial data from LAURA.

8.3 Modelling effects of subsequent treatments

N/A, effects of subsequent treatment has not been modelled beyond the observed trial data from LAURA.

8.4 Other assumptions regarding efficacy in the model

N/A.

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 23. Estimates that are undiscounted and not adjusted for half cycle correction are shown in Table 24.



Table 23. Estimates in the model

	Modelled average (reference in Excel)	Modelled median (reference in Excel)	Observed median from relevant study
Progression-free survival			
Osimertinib	63.02 months (='Deterministic Results'!F66)	39.43 months (='Deterministic Results'!L66)	31.1 months (95% CI: 31.5 – NC months)
Placebo	15.39 months (='Deterministic Results'!F67)	4.93 months (='Deterministic Results'!L67)	5.6 months (95% CI: 3.7 – 7.4 months)
Overall survival			
Osimertinib	89.53 months (='Deterministic Results'!H66)	69.98 months (='Deterministic Results'!N66)	58.81 months* (95% CI: 54.08, NC)
Placebo	59.73 months (='Deterministic Results'!H67)	55.20 months (='Deterministic Results'!N67)	53.98 months* (95% CI: 42.05, NC)

Note: Modelled OS outcomes have been adjusted for background mortality as per DMC guidance.
*, OS based on DCO 29th November 2024.

Table 24. 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	Progressed disease
Osimertinib	62.98 months	63.51 months	26.51 months
Placebo	NA	15.88 months	44.34 months

8.5.1 Assessment of aggregated PFS and OS curves

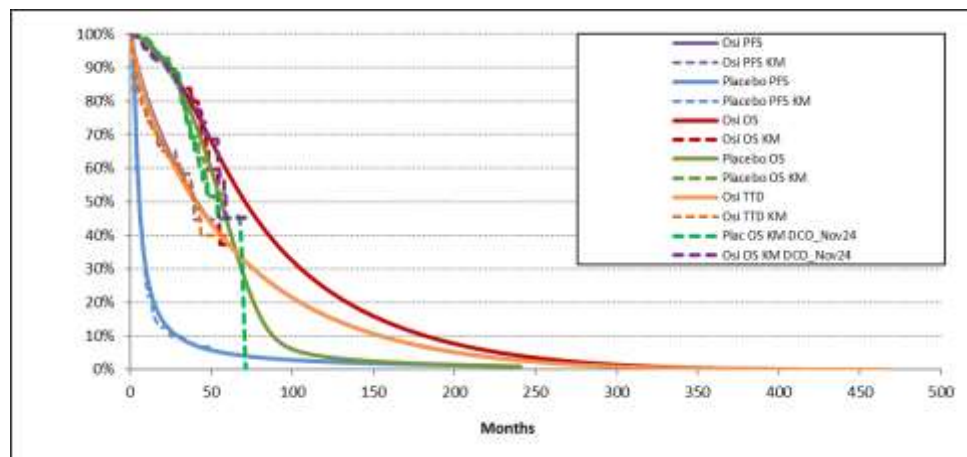
In the STM, the OS is determined by a combination of survival models (pre-progression death as well as post-progression death). The PFS parametric survival distribution selected matches the survival distribution chosen for TTP in an attempt to avoid to the logical inconsistency of the TTP and PFS curves crossing as far as possible. Both PFS and OS are shown in Figure 18.



The LAURA trial has demonstrated an overwhelming PFS benefit for osimertinib and a favorable OS trend, with a HR of 0.81 (95% CI: 0.42–1.56, $p=0.530$), which should be interpreted in the context of low maturity at the time of the analysis (20%). Placebo patients appear to experience more optimistic survival outcomes in the PPS setting (Figure 13 above), which should be interpreted in the context of substantial degree of crossover (around 80%) to osimertinib following BICR-confirmed disease progression in the placebo arm. The PFS benefit of osimertinib (i.e. the delayed transition of patients from the PF health state to the PD health state) results in a long-term OS benefit from the STM (i.e. when OS is a function of all three transition probabilities in the model).

The modelled OS curve (aggregated curve of TTP curve [*Gamma*] and PPS curve [*Gompertz*]) for the osimertinib arm has a good fit to the KM data from the latest DCO (Nov 2024) for as long as there are reliable data, i.e. up to 51-54 months. After that point, there is too much censoring in the osimertinib arm to make any reliable comparisons between the modelled OS and the KM OS data.

Figure 18. Base case survival curves in STM



Abbreviations: KM: Kaplan-Meier; OS: overall survival; Osi: osimertinib; PFS: progression-free survival; STM: state transition model

A similar STM approach was previously used for predicting long-term benefits of durvalumab in unresectable stage III NSCLC whose disease had not progressed after platinum-based CRT(73). Later data cut-offs with increasing OS maturity confirmed the validity of the original modelling for long-term predictions(73, 74). A difference in the modelling for durvalumab in unresectable stage III NSCLC after platinum-based CRT compared with the one used here was that the PPS modelling was based on pooled PPS data from both arms, while the model used here is based on independent modelling of the osimertinib arm and the control arm.



9. Safety

9.1 Safety data from the clinical documentation

Overall, the majority of AEs were non-serious, mild or moderate in severity, and did not lead to permanent osimertinib discontinuation, indicating that osimertinib was well-tolerated. The majority of patients in both treatment arms experienced at least one AE (osimertinib arm: 140 patients [98%]; placebo arm: 64 patients [88%]).

Table 25 includes adverse events with an onset date on or after the date of the first dose and up to and including the earlier of 28 days following the date of the last dose of study medication, hence all figures are on treatment-emergent adverse events.

Table 25 Overview of safety events, DCO: 5th January 2024.

	Osimertinib (N=143) Median exposure: 24.0 months(71)	Placebo (N=73) Median exposure: 8.3 months(71)	Difference, % (95 % CI)
Number of adverse events, n	NR	NR	NC
Number and proportion of patients with ≥1 adverse events, n (%)	140/143 (97.9%)	64/73 (87.7%)	10.2% (2.3%;18.1%)
Number of serious adverse events*, n	NR	NR	NC
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	55/143 (38.5%)	11/73 (15.1%)	23.4% (12.0%;34.8%)
Number of CTCAE grade ≥ 3 events, n	NR	NR	NC
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events [§] , n (%)	50/143 (35.0%)	9/73 (12.3%)	22.6% (11.8%;33.5%)
Number of adverse reactions, n	NR	NR	NC
Number and proportion of patients with ≥ 1	NR	NR	NC



	Osimertinib (N=143) Median exposure: 24.0 months(71)	Placebo (N=73) Median exposure: 8.3 months(71)	Difference, % (95 % CI)
adverse reactions, n (%)			
Number and proportion of patients with ≥ 1 adverse event possibly related to treatment, n (%)	115/143 (80.4%)	30/73 (41.1%)	39.3% (26.3%;52.4%)
Number and proportion of patients who had a AE-related dose reduction, n (%)	12/143 (8.4%)	1/73 (1.4%)	7.0% (1.8%;12.3%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	63/143 (44.1%)	66/73 (90.4%)	-46.4% (-56.9%,- 35.8%)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	18/143 (12.6%)	4/73 (5.5%)	7.1% (-0.4%;14.6%)

Abbreviations: NC, not calculatable; NR, not reported

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

§ CTCAE v. 5.0 must be used if available.

Note: Total exposure was calculated using the dates of the first and last doses of study treatment (excluding cross-over) in months

As of the DCO (5th January 2024), serious adverse events (SAE) had been reported by 38% (n=55) of patients in the osimertinib group and 15% (n=11) of patients in the placebo group. However, it's important to consider that the exposure time for osimertinib was nearly three times longer than that of the placebo group. This difference in exposure time may contribute significantly to the disparity in reported SAEs between the two groups.



Table 26 Serious adverse events (Reported in (Reported in ≥ 2 Patients in Either Treatment Arm) (Safety Analysis Set), DCO: 5th January 2024.

Adverse events	Osimertinib (N=143) Median exposure: 24.0 months(71)		Placebo (N=73) Median exposure: 8.3 months(71)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Radiation pneumonitis	15 (10.5)	NA	2 (2.7)	NA
Pneumonia	7 (4.9)	NA	3 (4.1)	NA
Gastroenteritis	2 (1.4)	NA	0	NA
Pneumonitis	2 (1.4)	NA	0	NA

* 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](#)).

For the health economic model, all CTCAE grade 3 or higher AEs observed in more than 2 patients in the LAURA trial assessed by investigator as possibly related to osimertinib were included for the osimertinib and placebo arms. See Table 27.

Table 27 Adverse events possibly related to treatment, >3 CTCAE grade 3 used in the health economic model.

Adverse events	Intervention	Comparator	Source	Justification
	Frequency used in economic model for intervention	Frequency used in economic model for comparator		
Pneumonitis	1.40%	0.00%	(71)	CTCAE grade 3 or higher AEs observed in more than 2 patients in the LAURA trial assessed by investigator as possibly related to osimertinib were included for the osimertinib and placebo arms
Diarrhoea	1.40%	0.00%		
Radiation pneumonitis	1.40%	0.00%		



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

N/A, no safety data was sourced from external literature has been applied in health economic model.

Table 28 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

For the documentation of health-related quality of life (HRQoL), data on EORTC QLQ-C30 and EuroQol EQ-5D-5L and EQ-5D VAS have been presented in the following sections.

Table 29 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	LAURA trial(66)	<i>Comparative analysis between osimertinib and placebo</i>
EQ-5D-5L & EQ-VAS	LAURA trial(66)	<i>VAS: Comparative analysis between osimertinib and placebo</i> <i>EQ-5D-5L: Comparative analysis between osimertinib and placebo and health state utilities in HE model</i>



Data collection of HRQoL PROs

Data collection of HRQoL were conducted using ePROs, which was assigned to patients on the day of randomization.

EORTC QLQ-C30 and EQ-5D-5L data were then collected at randomization, weekly up to week 8, thereafter every 4 weeks (± 3 days) relative to randomization during the treatment period. Additionally, data were to be collected at treatment discontinuation visit following BICR-confirmed disease progression and at week 8 (± 3 days), week 16 (± 3 days) and week 32 (± 3 days) post-progression during survival follow-up.

For patients who discontinue study treatment prior to BICR-confirmed progression, PROs should be collected at the study treatment discontinuation visit and continue to be collected at the same frequency as the treatment period during progression follow-up until BICR-confirmed disease progression, then at disease progression and at week 8 (± 3 days) , week 16 (± 3 days) and week 32 (± 3 days) post-progression.

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

10.1.1 Study design and measuring instrument

EORTC QLQ-C30 data were collected in the LAURA trial. Change from baseline in these measures was included as a secondary endpoint.

The EORTC QLQ-C30 data were summarised descriptively with respect to change from baseline and clinically relevant changes (≥ 10 points from baseline). Mixed models for repeated measures (MMRM) were used to estimate changes from baseline in each patient reported outcome (PRO) symptom score.

10.1.2 Data collection

The overall compliance rates for completion of the EORTC QLQ-C30 questionnaires were high at baseline ($>90\%$) and remained $>70\%$ until Week 32, with rates comparable between treatment arms. See Table 30.

Table 30 Pattern of missing data and completion(66)

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)



Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 4	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 8	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 16	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 24	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 32	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 40	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 48	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 56	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 64	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 72	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 80	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 88	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 96	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 104	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 112	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX



Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 120	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 128	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 136	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 144	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 152	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 160	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX
Week 168	Osimertinib: n=143 Placebo: n=73	XXXX	XXXX	XXXX

10.1.3 HRQoL results

Patient-reported outcomes were assessed as secondary endpoints using the EORTC QLQ-C30 questionnaires. A clinically meaningful change was defined as change ≥ 10 points from baseline(75).

Overall, a non-clinically meaningful worsening in GHS/QoL and physical functioning was observed in both treatment arms. This indicates that the clinically significant efficacy benefit observed with osimertinib treatment occurred without clinically meaningful deterioration in GHS/QoL or physical functioning. In general, only minimal changes from baseline were observed for fatigue and appetite loss in both treatment arms; no clinically meaningful changes from baseline were observed for such symptoms based on analysis of the EORTC QLQ-C30.

Table 31. HRQoL EORTC QLQ-C30 summary statistics (66).

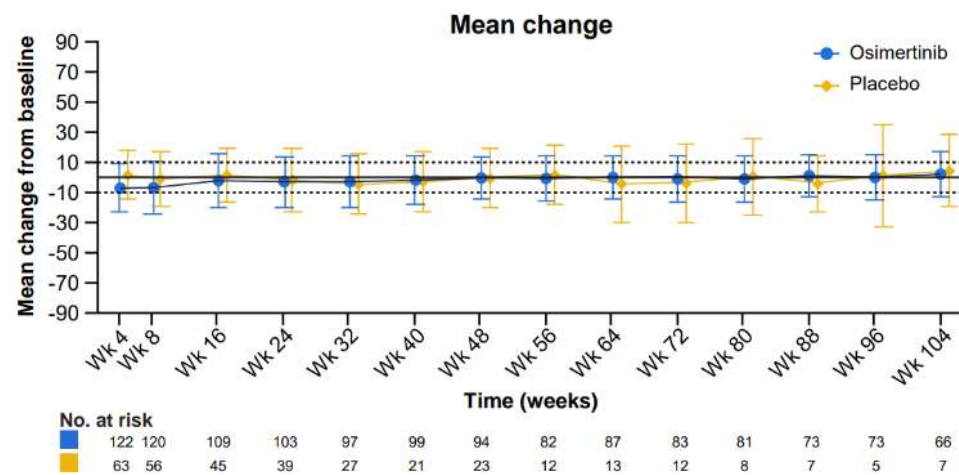
Primary PRO scales/items	Treatment arm	N	Estimate for treatment arm (95% CI)	Estimate for difference between groups (95% CI)
EORTC QLQ-C30 questionnaire: functional/symptom scales				
GHS/QoL [§]	Osimertinib	128	-3.9 (-5.98, -1.82)	-1.9 (-5.89, 2.00)
	Placebo	67	-2.0 (-5.30, 1.40)	



Physical function [§]	Osimertinib	128	-4.0 (-6.06, -1.90)	-0.6 (-4.42, 3.26)
	Placebo	67	-3.4 (-6.63, -0.18)	
Fatigue*	Osimertinib	128	5.1 (2.49, 7.68)	1.6 (-3.18, 6.46)
	Placebo	67	3.4 (-0.62, 7.50)	
Appetite loss*	Osimertinib	128	3.3 (0.50, 6.13)	8.1 (2.77, 13.37)
	Placebo	67	-4.8 (-9.25, -0.26)	

Note: Positive values indicate improvement for functioning parameters[§] (physical functioning and GHS/QoL from base line), and worsening (increase of symptoms) for symptom parameters* (fatigue and appetite loss).

Figure 19. Change in GHS/QoL scale over time: mean change from baseline(66).



Note: Mean change shows visits with at least 5 patients in each arm. Wk, week.

10.2 Presentation of the health-related quality of life EQ-5D-5L + EQ-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 LAURA at the same time points as EORTC QLQ-C30.

10.2.2 Data collection

The overall compliance rates for completion of the EQ-5D-5L and EQ-5D VAS questionnaires were high at baseline (>90%) and remained high in the osimertinib throughout the trial, while the compliance rate varied in the placebo arm beyond week 32. See Table 30.



Table 32 Pattern of missing data and completion(66)

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	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=13 (9.1%) Placebo: n=5 (6.8%)	Osimertinib: n=141 Placebo: n=73	Osimertinib: n=130 (92.2%) Placebo: n=68 (93.2%)
Week 4	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=15 (10.5%) Placebo: n=9 (12.3%)	Osimertinib: n=140 Placebo: n=73	Osimertinib: n=128 (91.4%) Placebo: n=64 (87.7%)
Week 8	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=17 (11.9%) Placebo: n=16 (21.9%)	Osimertinib: n=138 Placebo: n=72	Osimertinib: n=126 (91.3%) Placebo: n=57 (79.2%)
Week 16	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=28 (19.6%) Placebo: n=27 (37.0%)	Osimertinib: n=132 Placebo: n=66	Osimertinib: n=115 (87.1%) Placebo: n=46 (69.7%)
Week 24	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=33 (23.1%) Placebo: n=30 (41.1%)	Osimertinib: n=127 Placebo: n=54	Osimertinib: n=110 (86.6%) Placebo: n=43 (79.6%)
Week 32	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=39 (27.3%) Placebo: n=43 (58.9%)	Osimertinib: n=122 Placebo: n=41	Osimertinib: n=104 (85.2%) Placebo: n=30 (73.2%)
Week 40	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=36 (25.2%) Placebo: n=51 (69.9%)	Osimertinib: n=120 Placebo: n=34	Osimertinib: n=107 (89.2%) Placebo: n=22 (64.7%)
Week 48	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=43 (30.1%) Placebo: n=48 (65.8%)	Osimertinib: n=113 Placebo: n=31	Osimertinib: n=100 (88.5%) Placebo: n=25 (80.6%)
Week 56	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=56 (39.2%) Placebo: n=60 (82.2%)	Osimertinib: n=111 Placebo: n=25	Osimertinib: n=87 (78.4%) Placebo: n=13 (52.0%)
Week 64	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=51 (35.7%) Placebo: n=58 (79.5%)	Osimertinib: n=109 Placebo: n=22	Osimertinib: n=92 (84.4%) Placebo: n=15 (68.2%)
Week 72	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=55 (38.5%) Placebo: n=61 (83.6%)	Osimertinib: n=108 Placebo: n=20	Osimertinib: n=88 (81.5%) Placebo: n=12 (60.0%)



Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 80	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=60 (42.0%) Placebo: n=64 (87.7%)	Osimertinib: n=104 Placebo: n=13	Osimertinib: n=83 (79.8%) Placebo: n=9 (69.2%)
Week 88	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=69 (48.3%) Placebo: n=66 (90.4%)	Osimertinib: n=95 Placebo: n=12	Osimertinib: n=74 (77.9%) Placebo: n=7 (58.3%)
Week 96	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=69 (48.3%) Placebo: n=67 (91.8%)	Osimertinib: n=87 Placebo: n=10	Osimertinib: n=74 (85.1%) Placebo: n=6 (60.0%)
Week 104	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=74 (51.7%) Placebo: n=66 (90.4%)	Osimertinib: n=80 Placebo: n=9	Osimertinib: n=69 (86.3%) Placebo: n=7 (77.8%)
Week 112	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=85 (59.4%) Placebo: n=69 (94.5%)	Osimertinib: n=73 Placebo: n=7	Osimertinib: n=58 (79.5%) Placebo: n=4 (57.1%)
Week 120	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=87 (60.8%) Placebo: n=70 (95.9%)	Osimertinib: n=67 Placebo: n=6	Osimertinib: n=56 (83.6%) Placebo: n=3 (50.0%)
Week 128	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=91 (63.6%) Placebo: n=71 (97.3%)	Osimertinib: n=56 Placebo: n=6	Osimertinib: n=52 (92.9%) Placebo: n=2 (33.3%)
Week 136	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=104 (72.7%) Placebo: n=70 (95.9%)	Osimertinib: n=52 Placebo: n=5	Osimertinib: n=39 (75.0%) Placebo: n=3 (60.0%)
Week 144	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=105 (73.4%) Placebo: n=70 (95.9%)	Osimertinib: n=43 Placebo: n=4	Osimertinib: n=38 (88.4%) Placebo: n=3 (75.0%)
Week 152	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=110 (76.9%) Placebo: n=71 (97.3%)	Osimertinib: n=39 Placebo: n=4	Osimertinib: n=33 (84.6%) Placebo: n=2 (50.0%)
Week 160	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=116 (81.1%) Placebo: n=71 (97.3%)	Osimertinib: n=34 Placebo: n=4	Osimertinib: n=27 (79.4%) Placebo: n=2 (50.0%)
Week 168	Osimertinib: n=143 Placebo: n=73	Osimertinib: n=124 (86.7%) Placebo: n=70 (95.9%)	Osimertinib: n=28 Placebo: n=3	Osimertinib: n=19 (67.9%) Placebo: n=3 (100.0%)



10.2.3 HRQoL results

The two treatment arms are fairly comparable throughout the study. Beyond week 40, the sample size decrease to below 30 in the placebo arms and data should be interpreted with caution beyond this timepoint.

Table 33 HRQoL EQ VAS summary statistics(66)

Timepoint	Osimertinib (N=143)		Placebo (N=73)	
	n	Mean (95% CI)	n	Mean (95% CI)
Baseline	130	76.8 (74.1-79.5)	68	79.8 (76.4-83.2)
Week 4	129	73.7 (70.9-76.5)	65	77.3 (73.2-81.4)
Week 8	127	71 (68.3-73.7)	58	76.4 (72.2-80.6)
Week 16	116	74.6 (71.7-77.5)	46	76.6 (72.5-80.7)
Week 24	110	74.4 (71.5-77.3)	43	74.7 (70-79.4)
Week 32	104	74.6 (71.8-77.4)	30	73.5 (66.5-80.5)
Week 40	107	74.9 (72-77.8)	22	71.7 (62.7-80.7)
Week 48	100	77.5 (74.8-80.2)	25	74.8 (68.7-80.9)
Week 56	87	76.7 (73.9-79.5)	13	80.8 (73.6-88)
Week 64	92	78 (75.2-80.8)	15	74.2 (63.2-85.2)
Week 72	89	76.9 (73.9-79.9)	13	71.2 (57.9-84.5)
Week 80	88	77 (74.2-79.8)	9	72 (57.9-86.1)
Week 88	79	77.7 (74.7-80.7)	8	69.8 (57.2-82.4)
Week 96	79	77.4 (74.1-80.7)	6	66.8 (46.6-87)
Week 104	71	77.2 (74.2-80.2)	8	79.5 (70.4-88.6)
Week 112	62	77.5 (74.3-80.7)	4	71.3 (50-92.6)
Week 120	61	77.1 (73.7-80.5)	3	76 (56.4-95.6)
Week 128	52	76.8 (73.2-80.4)	2	71 (33.8-108.2)
Week 136	44	75.4 (71-79.8)	3	80 (68.7-91.3)
Week 144	39	73.3 (68.1-78.5)	3	73.3 (40.1-106.5)
Week 152	35	75.9 (70.5-81.3)	2	90.5 (79.7-101.3)
Week 160	30	75.2 (70.8-79.6)	2	87.5 (72.8-102.2)



Week 168	22	78.2 (71.1-85.3)	3	81.3 (68.9-93.7)
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Note: VAS ranges from 0 (worst imaginable health) to 100 (best imaginable health).
Baseline is defined as the latest evaluable assessment on or prior to the day of first dose.
The post-baseline assessment closest to the scheduled visit date (calculated from day of randomization) is summarized.
Timepoints are reported by visit for each treatment group provided there are at least ≥ 20 subjects with data across both treatment groups.
Data are summarized up to 32 weeks (+/- 3 days) following BICR-confirmed disease progression.

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

10.3.1 HSUV calculation

Utility values in the model were obtained from the LAURA trial using the health-state based utility approach. HRQoL data were collected in the LAURA trial using the EQ-5D-5L questionnaires. EQ-5D-5L data was initially collected through patient reported outcomes at randomization(66). It was then collected throughout the treatment period at week 4, week 8 and every 8 weeks thereafter (relative to randomization). EQ-5D-5L data was also collected at treatment discontinuation, and at progression and survival follow-up(66). The number of observations collected is presented in Table 34.

Table 34. The number of subjects and observations for EQ-5D-5L data collected in the LAURA trial(2)

Treatment	Scenario	Subjects	Observations
Pooled treatments	Pre progression	213	2,189
Pooled treatments	Post progression	102	435

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 LAURA were subsequently mapped using the Danish preference weight set(5). Please refer to Appendix F for further information on the analysis.

The results of the utility showed that there was no significant difference of utility between different treatments and only health states had a significant impact on the utility. Therefore, the HSUV estimated based on progression status has been applied for the base case analysis.

**Table 35 Overview of marginal means, derived from the EQ-5D-5L analysis**

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs base case				
Pre-progression	0.917 [0.901-0.932]	EQ-5D-5L	DK	MMRM analysis with progression-status as covariate
Post-progression	0.845 [0.802-0.888]	EQ-5D-5L	DK	MMRM analysis with progression-status as covariate
HSUVs (treatment specific) not excluded in analysis				
Pre-progression (osimertinib)	0.919 [0.901-0.936]	EQ-5D-5L	DK	MMRM analysis with progression-status as covariate
Post-progression (osimertinib)	0.812 [0.736-0.889]	EQ-5D-5L	DK	MMRM analysis with progression-status as covariate
Pre-progression (80mg placebo)	0.912 [0.880-0.944]	EQ-5D-5L	DK	MMRM analysis with progression-status as covariate
Post-progression (80mg placebo)	0.872 [0.828-0.915]	EQ-5D-5L	DK	MMRM analysis with progression-status as covariate

10.3.2 Disutility calculation

Utility decrements due to AEs were applied in the model as a one-off decrements in the first model cycle for grade 3+ AEs. The disutilities and durations of AEs has been sourced from publications and previous HTA submissions, see Table 38.

10.3.3 HSUV results

The base case HSUVs are presented below in Table 36, along with HSUVs applied in alternative scenario analyses.

Table 36 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs base case				
Pre-progression (base case)	0.917	EQ-5D-5L	DK	MMRM analysis with progression-status as covariate



	Results [95% CI]	Instrument	Tariff (value set) used	Comments
	[0.901- 0.932]			
Post-progression (base case)	0.845 [0.802- 0.888]	EQ-5D-5L	DK	MMRM analysis with progression- status as covariate
HSUVs for scenario analysis				
<i>Post-progression Labbe et al.(76)</i> (scenario analysis)	0.640	EQ-5D-3L	Canadian weights	Scenario analysis, alternative HSUV for metastatic health state
<i>Post-progression FLAURA(63)</i> (scenario analysis)	0.794	EORTC QLQ-C30 mapped into EQ-5D- 3L UK	UK	Scenario analysis, Alternative HSUV for metastatic health state
<i>Post-progression FLAURA(63)</i> Mapped to DK EQ-5D-5L (scenario analysis)	0.845	EQ-5D-5L	DK	FLAURA(77) UK EQ-5D-3L HSUV mapped to DK EQ-5D-5L HSUV using linear model proposed by Torkilseng et al. 2025(78)
HSUVs (treatment specific) not excluded in analysis				
Pre-progression (osimertinib)	0.919 [0.901- 0.936]	EQ-5D-5L	DK	MMRM analysis with progression- status as covariate
Post-progression (osimertinib)	0.812 [0.736- 0.889]	EQ-5D-5L	DK	MMRM analysis with progression- status as covariate
Pre-progression (80mg placebo)	0.912 [0.880- 0.944]	EQ-5D-5L	DK	MMRM analysis with progression- status as covariate
Post-progression (80mg placebo)	0.872 [0.828- 0.915]	EQ-5D-5L	DK	MMRM analysis with progression- status as covariate



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

Table 37 Overview of health state utility values [and disutilities]

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

Table 38 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments	Duration of AE [Days]	Comment
AE Disutilities						
Pneumonia	-0.01	NA	NA	Goeree et al. (2016)(61)	14.66(63)	Assumption based on assumption TA654(63).
Diarrhoea	-0.05	EQ-5D VAS	N/A	Nafees et al. (2008)(59)	5.53(63)	Assumption based on assumption TA654(63).
Radiation pneumonia	-0.01	EQ-5D VAS	N/A	Nafees et al. (2008)(59).	14.66(63)	Assumption based on assumption TA654(63).



11. Resource use and associated costs

The costs associated with the management of patients with EGFRm Stage III NSCLC following CRT are described below. Included costs are reported in 2025 Danish kroner (DKK). The model includes the following costs, which are discussed in detail below:

- Drug costs
- Administration costs
- Disease management costs
- Adverse events related costs
- Subsequent treatments costs
- Patient costs
- Other costs

11.1 Medicines - intervention and comparator

The medicine cost for intervention is outlined in Table 39, and they were based on prices from medicinpriser.dk (AIP). The model also allows specification of simple percentages discounts for all included medicines, including subsequent treatments.

The price of osimertinib is the same regardless of dosing, reducing the impact of dose reductions on the costs, and no wastage is assumed in this case. Drug acquisition costs are applied in line with the dosing schedules, as detailed in Table 40. No treatment stop was applied for osimertinib as per EMA label and study protocol (65, 71).

A scenario analysis has been conducted to analyze the impact of the wastage associated with dose reductions. It is assumed that this wastage is equivalent to a half blister package. The cost associated with wastage has been included in the first model cycle for the 8.4% of osimertinib patients, who experienced a dose reduction in the LAURA trial(71). The results of the analysis is presented in Table 56.

Table 39 Unit cost of all medicines used in the model

Medicine	ATC code	Strength	Packaging size	Price (AIP) [DKK]	Type of administration
Osimertinib	L01EB04	40/80 mg	30 stk. (blister)	38,585.29	PO



Table 40 Dosing of medicines used in the model for primary therapy

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Tagrisso (osimertinib)	80.00	100%	Daily	No

11.2 Medicines – co-administration

No concomitant medicine is required to be administered with osimertinib.

11.3 Administration costs

No administration cost of osimertinib was assumed, due to the per oral administration. No active treatment is administered in the placebo arm, hence no administration cost is applied for this arm either.

Some of the subsequent treatments are administered via IV infusion. The cost of an IV infusion has been sourced from the Danish DRG list for 2025(79).

Table 41 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
PO administration	Daily	0	No administration cost assumed for PO treatment	
IV infusion	Depending on subsequent treatment	1,330.00	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC349, Kræft i lunge UNS - Treatment code: BWAA6, Medicingivning intravenøst	

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(24). Unit costs of the disease management was sourced from the Danish DRG list for 2025(79).



Table 42 Pre-progression disease management costs used in the model

Activity	Frequency per year	Unit cost [DKK]	DRG code	Reference
Outpatient oncologist visit (year 1-2)	4	DKK 1,330.00	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC349, Kræft i lunge UNS	
Outpatient oncologist visit (year 3+)	2	DKK 1,330.00	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC349, Kræft i lunge UNS	
Chest X-ray:	2	DKK 1,731.00	2025 DRG code: 30PR18, Røntgenundersøgelse (alm), ukompliceret - Diagnosis code: DC349, Kræft i lunge UNS - Treatment code: UXRC00, Røntgenundersøgelse af thorax	
CT scan (chest) (year 1-2)	4	DKK 2,701.00	2025 DRG code: 30PR06, CT-scanning, kompliceret - Diagnosis code: DC349, Kræft i lunge UNS - Treatment code: UXCC00, CT-skanning af thorax	
CT scan (chest) (year 3+)	2	DKK 2,701.00	2025 DRG code: 30PR06, CT-scanning, kompliceret - Diagnosis code: DC349, Kræft i lunge UNS - Treatment code: UXCC00, CT-skanning af thorax	

Table 43 Post-progression disease management costs used in the model

Activity	Frequency per year	Unit cost [DKK]	DRG code	Reference
Outpatient oncologist visit	4	DKK 1,330.00	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC349, Kræft i lunge UNS	
Chest X-ray	1	DKK 1,731.00	2025 DRG code: 30PR18, Røntgenundersøgelse (alm), ukompliceret - Diagnosis code: DC349, Kræft i lunge UNS - Treatment code: UXRC00, Røntgenundersøgelse af thorax	
CT scan (chest)	4	DKK 2,701.00	2025 DRG code: 30PR06, CT-scanning, kompliceret - Diagnosis code: DC349, Kræft i lunge UNS - Treatment code: UXCC00, CT-skanning af thorax	
CT scan (other)	1	DKK 2,401.00	2025 DRG code: 30PR07, CT-scanning, ukompliceret, el. osteodensitometri - Diagnosis code: DC349, Kræft i lunge UNS -	



Activity	Frequency per year	Unit cost [DKK]	DRG code	Reference
				Treatment code: UXCA05, CT-skanning af kranie

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, febrile neutropenia and pulmonary embolism). Only grade 3+ AE events observed in more than 2 patients were considered in the model. The costs of each AE included in the model are presented in the following table.

Table 44 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Pneumonitis	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DJ189, Pneumoni UNS	DKK 1,330.00
Diarrhoea	2025 DRG code: 06MA11, Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. - Diagnosis code: DK529B, Ikke-infektøs diarré UNS	DKK 1,330.00
Radiation pneumonitis	2025 DRG code: 04MA98, MDC04 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DJ189, Pneumoni UNS	DKK 1,330.00

11.6 Subsequent treatment costs

Upon discontinuation of the primary treatment, a proportion of patients can switch to a subsequent active treatment, modelled as a single basket of treatments for a mean treatment duration upon entry to the PD health state. These treatments were assumed to affect costs only, as the survival impact was expected to be captured within the OS and PPS curve of index maintenance therapy treatments.



The composition of the subsequent treatment basket and the proportion of patients receiving each subsequent treatment was informed from a Danish clinician to capture the expected Danish clinical practice following either osimertinib or placebo in unresectable stage III EGFR mutated NSCLC(24). Please see Table 45 for the expected subsequent treatment in clinical practice. The subsequent treatment distribution applied in the model are presented in Table 46.

Table 45 Expected subsequent treatment in Danish clinical practice based on HCP input following osimertinib or placebo(24)

Subsequent treatments	Osimertinib arm	Placebo arm
First line metastatic treatment		
Osimertinib	10%	100%
Platinum doublet	90%	0%
<i>Total, first line subsequent treatment</i>	100%	100%
Second line metastatic treatment		
Osimertinib	0%	10%
Platinum doublet	0%	90%
Docetaxel	80%	0%
BSC/Study protocol therapy (not costed)	20%	0%
<i>Total, second line subsequent treatment</i>	100%	100%

Table 46 Subsequent treatment distribution applied in the economic model(24)

	Osimertinib	Placebo	Source
First line subsequent treatment			
Osimertinib	10%	100%	Clinical expert input
Pemetrexed	90%	0%	Clinical expert input – part of platinum doublet
Carboplatin (AUC5)	90%	0%	Clinical expert input – part of platinum doublet



Second line subsequent treatment

Osimertinib	0%	10%	Clinical expert input
Pemetrexed	0%	90%	Clinical expert input – part of platinum doublet
Carboplatin (AUC5)	0%	90%	Clinical expert input – part of platinum doublet
Docetaxel	80%	0%	Clinical expert input
BSC/study protocol (not costed in model)	20%	0%	Clinical expert input

11.6.1 Duration of subsequent treatments

The subsequent treatment durations included in the model were retrieved from the relevant literature including FLAURA2 for the osimertinib monotherapy, with appropriate sources according to the treatment. See Table 47 for the durations of each treatment and the sources.

During interview with a Danish clinician, the practice of rechallenging with osimertinib was discussed. In Danish clinical practice, rechallenging with osimertinib is considered relevant for cases where patients discontinued the treatment due to toxicity or reasons other than progression(24). For these osimertinib-experienced patients, a complete resistance mechanism to osimertinib has likely not yet developed. However, they might develop resistance more quickly than treatment-naïve patients, potentially reducing the progression-free survival (PFS) and, consequently, the duration of osimertinib treatment when rechallenging the tumour(24).

In the model, the treatment duration of osimertinib as a subsequent therapy depends on whether patients were naïve to osimertinib or had been previously exposed. For osimertinib-naïve (placebo) patients, the modeled mean duration of osimertinib monotherapy for progression-free patients from the FLAURA2 trial is used. If patients had been exposed to osimertinib previously and are rechallenged, the treatment duration is assumed to resemble the mean of 8.6 months observed in the AURA3 trial (80). This rationale is based on patients in the AURA3 trial, who had progressed on first- or second-generation EGFR-TKIs, having built some resistance mechanisms that osimertinib could overcome. These patients are assumed to serve as a suitable proxy for those who had previously been on osimertinib but were discontinued for reasons other than progression.

For the chemotherapies used as subsequent treatment., treatment durations has been sourced in literature in comparable trials. Please refer to Table 47 for further information.

Table 47 Subsequent treatment duration

Treatments	Duration of treatment	Duration of treatment comment/source
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	(number of 30-day cycle)	
Docetaxel	3.04*	Mean treatment duration of docetaxel. Kim et al., 2008(81)
Pemetrexed	4.26*	Mean duration of platinum+pemetrexed-based chemo. Mok et al. 2017(80)
Carboplatin (AUC5)	2.23*	Median duration of treatment, assumed to be applicable for carboplatin duration. Socinski et al. 2018(82)
Osimertinib (naïve patients)	29.34	FLAURA2 (modelled mean treatment duration for osi mono arm)
Osimertinib (osi experience patients)	8.73*	Calculated mean based on mean treatment duration. AURA3(80)

*Duration of treatment converted from months to 30-day model cycles. Where one month is assumed to be equivalent to 1.0146 cycles.

Table 48 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Docetaxel	75 mg/m ²	1.00	Every 3 weeks (IV)	Yes
Pemetrexed	500 mg/m ²	1.00	Every 3 weeks (IV)	Yes
Carboplatin (AUC5)	575 mg	1.00	Every 3 weeks (IV)	Yes
Osimertinib	80 mg	1.00	PO daily	Yes

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, it be disease management or treatment administration, a cost for transport have been added as well. The frequencies of the patient costs are based on the frequencies presented in Table 42 and Table 43 for disease management and Table 40 and Table 48 for treatment administration.

The unit costs have been sourced from the unit cost list by the DMC(83), see Table 51.

No patient costs have been included for the management of adverse events, as the impact of these is deemed neglectable due to the low frequencies adverse events observed. This is also evident in the impact of adverse events on the incremental cost in the health economic analysis.



Table 49 Patient time spent for disease management used in the model

Activity	Time spent
Outpatient oncologist visit	1 hour + 1 hour for transport
Chest X-ray	1 hour + 1 hour for transport
CT scan (chest)	1 hour + 1 hour for transport
CT scan (other)	1 hour + 1 hour for transport
ECG	Assumed to be included in the oncologist visit

Table 50 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 + 1 h for transport
Pemetrexed	3 h for infusion + 1 h for transport
Carboplatin (AUC5)	Mean of 37.5 min assumed (midpoint between 15 and 60) for infusion + 1h for transport

Table 51 Unit costs used in the model for patient cost (83)

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

11.8 Other costs

N/A.



12. Results

12.1 Base case overview

Table 52 Base case overview

Feature	Description
Comparator	Placebo
Type of model	State-transition model
Time horizon	38.6 years (life time)
Treatment line	Stage III EGFRm NSCLC, whose disease has not progressed during or following platinum-based chemoradiotherapy
Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L in LAURA study(66). 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	Fixed dose, osimertinib 80 mg PO daily
Average time on treatment	Osimertinib: 4.48 years Placebo: N/A
Parametric function for time-to-progression	Osimertinib: Gamma Placebo: Gen gamma
Parametric function for post-progression survival	Osimertinib: Gompertz Placebo: Gompertz
Inclusion of waste	Yes
Average time in model health state	Osimertinib: 4.49 years
- Pre-progression	Placebo: 1.14 years
Average time in model health state	Osimertinib: 1.82 years
- Post-progression	Placebo: 3.37 years



12.1.1 Base case results

The base case results are presented in Table 53. Over the lifetime time horizon, the total discounted cost associated with osimertinib was 2,319,175 DKK, while the total discounted LYs and QALYs accrued were 6.31 and 5.66, respectively.

The total discounted cost of placebo was 1,271,654 DKK, while placebo had accumulated a discounted 4.51 LYs and a discounted 3.90 QALYs. The incremental cost per QALY gained for osimertinib vs. placebo was 593,662 DKK.

The key cost drivers for osimertinib arm were drug acquisition costs for the primary therapy, which accounted for 92% of total costs, whereas the key drivers for placebo arm were subsequent treatment costs which accounted for 91% of total costs. The high cost of acquiring primary therapy drugs in the osimertinib arm was partially offset by the lower cost of subsequent treatments, while the placebo arm experienced higher costs for subsequent treatments. Osimertinib was also associated with lower HCRU costs because patients spent more time in the progression-free health state.

To conclude, the LAURA regimen presents a promising solution to address the existing treatment gap for patients with EGFRm unresectable stage III NSCLC following chemoradiation, where no current treatment options are available. In the present Danish clinical practice, these patients typically experience disease progression to a metastatic state within approximately 6 months(58),. At that point, they begin 1L metastatic treatment with osimertinib.

Implementing the LAURA regimen would effectively bridge this 6-month treatment-free gap between chemoradiation and the initiation of osimertinib treatment. By doing so, it offers significant potential benefits, such as reducing the risk of future CNS metastasis and lowering the eventual tumour burden by earlier intervention with osimertinib. This approach not only aims to suppress tumour growth more promptly but also potentially improves long-term survival outcomes compared to the current clinical practice as demonstrated in the LAURA trial(56, 58).

Table 53 Base case results, discounted estimates

	Osimertinib [DKK]	Placebo [DKK]	Difference [DKK]
Drug acquisition costs	2,138,220	0	2,138,220
Drug administration costs	0	0	0
Adverse event costs	107	0	107
Disease management costs	101,533	90,644	10,889
Subsequent treatment costs	48,431	1,154,556	-1,106,125



	Osimertinib [DKK]	Placebo [DKK]	Difference [DKK]
Other costs	0	0	0
Patient costs	30,884	26,453	4,431
Total costs	2,319,175	1,271,654	1,047,552
Life years gained (Pre-progression)	4.49	1.14	3.35
Life years gained (Post-progression)	1.82	3.37	-1.55
Total life years	6.31	4.51	1.80
QALYs (progression-free)	4.12	1.05	3.07
QALYs (post-progression)	1.54	2.85	-1.31
QALYs (adverse reactions)	-0.0001	0.0000	-0.0001
Total QALYs	5.66	3.90	1.76
Incremental costs per life year gained			<u>DKK 583,014</u>
Incremental cost per QALY gained (ICER)			<u>DKK 593,662</u>



12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Results of the deterministic sensitivity analysis is presented in Figure 20 and Table 54. The top three parameters which had the greatest impact on the ICER were HSUV in progression-free health state, the HSUV in the post-progression health state and the discount rate on accrued QALYs. If discount rate were ignored in the deterministic sensitivity analysis, the next uncertain parameter is found to be the treatment duration of the osimertinib in the subsequent therapy for the placebo arm.

Figure 20. Tornado diagram of ICER

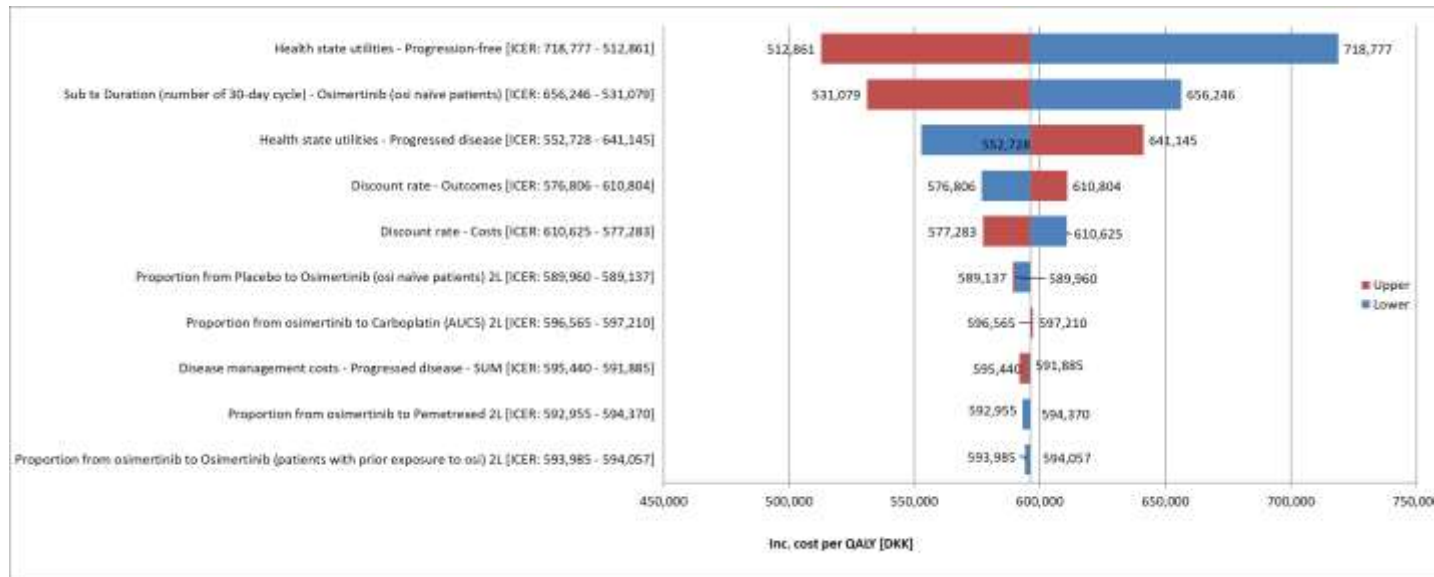




Table 54 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			1,047,522	1.76	593,662
Health state utilities - Progression-free	+/- 10%	Assumption	1,047,522	1.46	718,777
			1,047,522	2.04	512,861
Sub Tx Duration (number of 30-day cycle) - Osimertinib (Placebo arm patients)	+/- 10%	Assumption	1,157,950	1.76	656,246
			937,093	1.76	531,079
Health state utilities - Progressed disease	+/- 10%	Assumption	1,047,522	1.90	552,728
			1,047,522	1.63	641,145
Discount rate - Costs	+/- 10%	DMC guidance	1,047,522	1.82	576,806
			1,047,522	1.71	610,804
Discount rate - Outcomes	+/- 10%	DMC guidance	1,077,452	1.76	610,625
			1,018,620	1.76	577,283



12.2.2 Probabilistic sensitivity analyses

The mean results of the probabilistic sensitivity analysis are presented in Table 55 for osimertinib and placebo using 1000 Monte Carlo simulations. Over the lifetime time horizon, the total discounted costs and QALYs associated with osimertinib were 2,084,710 DKK and 5.28, respectively. For placebo, total costs were 1,310,752 DKK and total QALYs were 3.65. Consistent with the deterministic base case, osimertinib had higher total costs and QALYs than placebo.

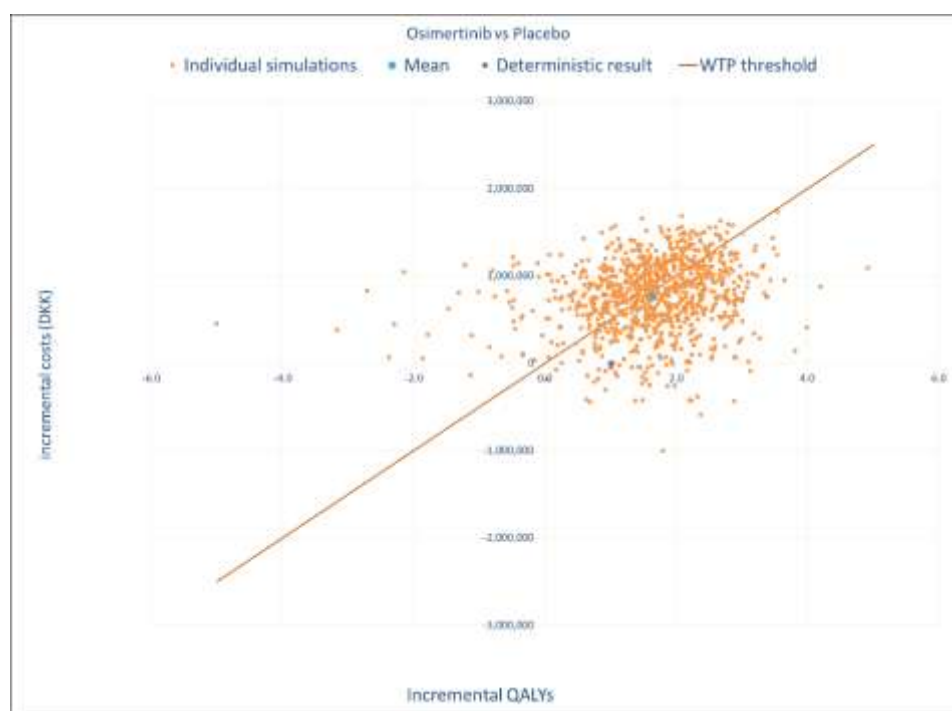
Table 55. Discounted results of the probabilistic analysis

Regimen	Mean Total Costs	Mean Total QALYs	ΔCosts	ΔQALYs	Incremental cost per QALY (vs. placebo)
Osimertinib	2,084,710 DKK	5.28	-	-	-
Placebo	1,310,419 DKK	3.65	773,291 DKK	1.63	475,130 DKK per QALY

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

The cost-effectiveness plane for osimertinib and placebo is shown in Figure 21. 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 is more costly but more effective (QALYs) in 93% of simulations.

Figure 21. The cost-effectiveness plane

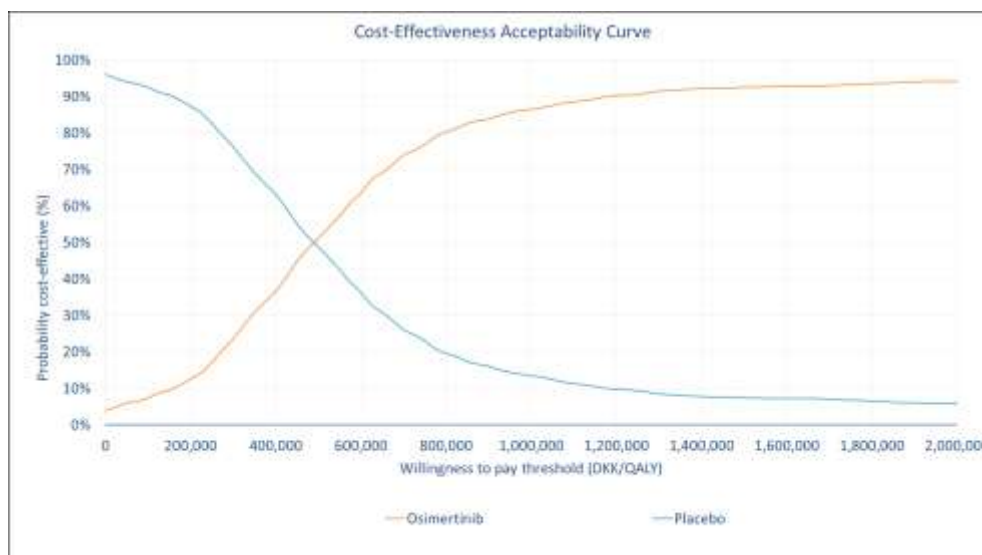


The cost-effectiveness acceptability curve for osimertinib vs. placebo is shown in Figure 22. The CEAC shows the probability that the treatment is acceptable based on various



acceptability thresholds. At a typical willingness to pay threshold of 500,000 DKK per QALY, osimertinib only had a 51.30% probability of being cost effective. Osimertinib had a higher probability of being cost-effective vs placebo at willingness to pay thresholds greater than 500,000 DKK per QALY.

Figure 22. 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 23, demonstrate that probabilistic results were stable by approx. 700 iterations, suggesting that 1000 iterations is a sufficient number to reach a stable result.

Figure 23. ICER convergence plot



12.2.3 Scenario analysis

The results of other scenario analyses are presented below Table 56.

Table 56. Results of scenario analyses

	Osimertinib	Placebo	Incremental (vs. Placebo)
Base case			
Total cost	DKK 2,386,729	DKK 1,037,504	DKK 1,047,522



Total QALYs	5.66	3.90	1.76
ICER	-	-	DKK 593,662
Subsequent treatment - Mean modelled treatment duration from FLAURA2 for osimertinib experienced patients			
Total cost	DKK 2,386,729	DKK 1,349,225	DKK 1,037,504
Total QALYs	5.66	3.90	1.76
ICER	-	-	DKK 587,985
Log-normal for osimertinib TDT			
Total cost	DKK 2,303,204	DKK 1,271,654	DKK 1,031,550
Total QALYs	5.66	3.90	1.76
ICER	-	-	DKK 584,611
Exponential for osimertinib TDT			
Total cost	DKK 2,080,437	DKK 1,271,654	DKK 808,784
Total QALYs	5.66	3.90	1.76
ICER	-	-	DKK 458,362
Gen gamma for osimertinib TDT			
Total cost	DKK 2,299,112	DKK 1,271,654	DKK 1,027,458
Total QALYs	5.66	3.90	1.76
ICER	-	-	DKK 582,292
PD utility (0.64) from Labbe et al			
Total cost	DKK 2,319,175	DKK 1,271,654	DKK 1,047,522
Total QALYs	5.29	3.21	2.08
ICER	-	-	DKK 503,244
PD utility (0.794) from FLAURA			
Total cost	DKK 2,319,175	DKK 1,271,654	DKK 1,047,522
Total QALYs	5.57	3.72	1.84
ICER	-	-	DKK 568,262
PD utility (0.845) from FLAURA mapped to EQ-5D-5L DK			
Total cost	DKK 2,319,175	DKK 1,271,654	DKK 1,047,522
Total QALYs	5.66	3.90	1.76
ICER	-	-	DKK 593,539
Exclude AE disutilities			
Total cost	DKK 2,319,175	DKK 1,271,654	DKK 1,047,522
Total QALYs	5.66	3.90	1.76
ICER	-	-	DKK 593,626
Danish patient population characteristics§			
Total cost	DKK 2,224,382	DKK 1,271,931	DKK 952,451
Total QALYs	5.40	3.83	1.57
ICER	-	-	DKK 606,818
Inclusion of wastage related to dose reductions			
Total cost	DKK 2,320,794	DKK 1,271,654	DKK 1,049,140
Total QALYs	5.66	3.90	1.76



ICER	-	-	DKK 594,580
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*Note: only apply to osimertinib group

§: Age 70 years, 60% female, 76 kg body weight, 174 cm height.

Abbreviations: TTP: time to progression; PD: progressed disease; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

13. Budget impact analysis

Number of patients (including assumptions of market share)

As mentioned in section 3.2, the patient population relevant for osimertinib is patients diagnosed with unresectable stage III EGFRm NSCLC, who is deemed eligible for chemoradiation and who have not progressed during or following curative chemoradiation. Approx. 6-10 patients is expected to be eligible for treatment with osimertinib in Denmark in this setting(24). For the budget impact analysis, the midpoint in the patient estimate (8 patients annually) has been assumed for the budget impact analysis.

For the budget impact analysis, 100% of the patients are assumed to be treated with osimertinib in the scenario, where osimertinib is recommended by the DMC for this setting. In the scenario where osimertinib is not recommended, all patients are assumed to receive no treatment, and thereby be allocated to active monitoring. Please see Table 57 for expected treatment number of patients in both scenarios in the budget impact analysis.

Table 57 Number of new patients expected to be treated over the next five-year period if osimertinib is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
Osimertinib	8	8	8	8	8
Active monitoring	0	0	0	0	0
Non-recommendation					
Osimertinib	0	0	0	0	0
Active monitoring	8	8	8	8	8

Budget impact

The budget impact is obtained by multiplying the patient numbers in Table 57 with the cost per patient. The budget impact increase from around DKK -3.8m in year 1 to a budget impact of DKK 2.9m in year 5 (Table 58).

The estimated budget impact contains a degree of uncertainty due to the methodology used in the health economic modelling for this application. In the model, costs for subsequent treatments are modelled as a one-time expense at the point of disease progression based on the PFS data.



In the LAURA trial, most patients in the placebo arm experience disease progression within the first two years, leading to a significant portion of their treatment costs occurring early in the budget impact analysis. Conversely, in the osimertinib arm, these costs are incurred later in the model timeline. This distribution results in an estimated budget savings in years 1 to 3, followed by a budget increase in years 4 and 5 in the budget impact analysis.

However, in real-world clinical practice, the costs of subsequent treatments are spread out over time rather than concentrated at a single point. As a result, the model's projected budget savings or increases might be overstated. Therefore, it is important to interpret the estimated budget impact with caution, keeping in mind the limitations of the modelling approach.

Table 58 Expected budget impact of recommending the osimertinib for the unresectable EGFRm stage III NSCLC, [million] DKK (undiscounted)

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	3.8	6.6	9.0	10.9	12.6
The medicine under consideration is NOT recommended	7.6	8.7	9.2	9.5	9.7
Budget impact of the recommendation	-3.8	-2.1	-0.2	1.4	2.9



14. List of experts

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15. References

1. Dansk Lunge Cancer Gruppe DOLG. Kurativ behandling af lokal avanceret ikke-småcellet lungekræft. 2024.
2. Lu S, Kato T, Dong X, Ahn M-J, Quang L-V, Soparattanapaisarn N, et al. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. *N Engl J Med*. 2024;391(7):585-97.
3. AstraZeneca Data on File. A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre, International Study of Osimertinib as Maintenance Therapy in Patients with Locally Advanced, Unresectable EGFR Mutation-Positive Non-Small Cell Lung Cancer (Stage III) Whose Disease Has Not Progressed Following Definitive Platinum-Based Chemoradiation Therapy (LAURA) Clinical Study report. 2024 2024.
4. AstraZeneca Data on file. LAURA, OS update DCO 29 Nov 2024. 2024.
5. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Appl Health Econ Health Policy*. 2021;19(4):579-91.
6. Lung cancer - NHS [Internet]. 2021 [Available from: <https://www.nhs.uk/conditions/lung-cancer/>].
7. Wu YL, Herbst RS, Mann H, Rukazenzov Y, Marotti M, Tsuboi M. ADAURA: Phase III, Double-blind, Randomized Study of Osimertinib Versus Placebo in EGFR Mutation-positive Early-stage NSCLC After Complete Surgical Resection. *Clin Lung Cancer*. 2018;19(4):e533-e6.
8. National Institute for Health Care Excellence. SINGLE TECHNOLOGY APPRAISAL Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small-cell lung cancer [ID925]. 2018.
9. National Institute for Health Care Excellence. Pemetrexed & Carboplatin for NSCLC or mesothelioma. 2018.
10. NHS. Docetaxel single agent for locally advanced or metastatic NSCLC. 2018.
11. Dansk Lunge Cancer Gruppe/Register. Dansk Lunge Cancer Register, Årsrapport 2023. 2024.
12. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2017;28(suppl_4):iv1-iv21.
13. Birring SS, Peake MD. Symptoms and the early diagnosis of lung cancer. *Thorax*. 2005;60(4):268-9.
14. Le Chevalier T. Adjuvant chemotherapy for resectable non-small-cell lung cancer: where is it going? *Annals of oncology : official journal of the European Society for Medical Oncology*. 2010;21 Suppl 7:vii196-8.
15. Datta D, Lahiri B. Preoperative evaluation of patients undergoing lung resection surgery. *Chest*. 2003;123(6):2096-103.
16. Cagle PT, Allen TC, Olsen RJ. Lung cancer biomarkers: present status and future developments. *Archives of pathology & laboratory medicine*. 2013;137(9):1191-8.
17. Norwegian Cancer Registry. Årsrapport - Nasjonalt kvalitetsregister for lungekreft 2024.
18. Seung SJ, Hurry M, Hassan S, Walton RN, Evans WK. Cost-of-illness study for non-small-cell lung cancer using real-world data. *Curr Oncol*. 2019;26(2):102-7.
19. Morgensztern D, Ng SH, Gao F, Govindan R. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. *J Thorac Oncol*. 2010;5(1):29-33.
20. EpiCast. EpiCast Report: Non-Small Cell Lung Cancer (NSCLC) – Epidemiology Forecast to 2025. 2016.



21. European Medicines Agency (EMA). Summary of Product Characteristics - Osimertinib 2025 [Available from: https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf.
22. Medicinrådet. Medicinrådets anbefaling vedr. osimertinib til adjuverende behandling af EGFR-muteret ikke-småcellet lungekræft. 2024.
23. Medicinrådet. Medicinrådets lægemiddelrekommandation vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet 2024.
24. AstraZeneca. Clinical Expert Statement - Jon Lykkegaard Andersen on stage III unresectable NSCLC. 2025.
25. Dansk Lunge Cancer Gruppe DOLG. Lungecancer - Patologi. 2023.
26. Sundhedsstyrelsen. Pakkeforløb for lungekræft. 2018.
27. Dansk Lunge Cancer Gruppe DOLG. Pallierende onkologisk behandling af onkogen-dreven ikke-småcellet lungekræft 2024.
28. Li J, Xu J, Yang M, Zhou Q. Therapeutic revolution for inoperable stage III non-small cell lung cancer in the immune era. *Cancer Biol Med*. 2022;19(5):569-72.
29. Horinouchi H, Atagi S, Oizumi S, Ohashi K, Kato T, Kozuki T, et al. Real-world outcomes of chemoradiotherapy for unresectable Stage III non-small cell lung cancer: The SOLUTION study. *Cancer Med*. 2020;9(18):6597-608.
30. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16(2):187-99.
31. Tanaka K, Hida T, Oya Y, Oguri T, Yoshida T, Shimizu J, et al. EGFR Mutation Impact on Definitive Concurrent Chemoradiation Therapy for Inoperable Stage III Adenocarcinoma. *Journal of Thoracic Oncology*. 2015;10(12):1720-5.
32. Ishihara M, Igawa S, Sasaki J, Otani S, Fukui T, Ryuge S, et al. Evaluation of concurrent chemoradiotherapy for locally advanced NSCLC according to EGFR mutation status. *Oncol Lett*. 2017;14(1):885-90.
33. Park SE, Noh JM, Kim YJ, Lee HS, Cho JH, Lim SW, et al. EGFR Mutation Is Associated with Short Progression-Free Survival in Patients with Stage III Non-squamous Cell Lung Cancer Treated with Concurrent Chemoradiotherapy. *Cancer Res Treat*. 2019;51(2):493-501.
34. Brouns AJWM, van Veelen A, Veerman GDM, Steendam C, Dursun S, van der Leest C, et al. Incidence of Bone Metastases and Skeletal-Related Events in Patients With EGFR-Mutated NSCLC Treated With Osimertinib. *JTO Clinical and Research Reports*. 2023;4(5):100513.
35. Kelly WJ, Shah NJ, Subramaniam DS. Management of Brain Metastases in Epidermal Growth Factor Receptor Mutant Non-Small-Cell Lung Cancer. *Frontiers in Oncology*. 2018;8:208.
36. Kato T, Casarini I, Cobo M, Faivre-Finn C, Hegi-Johnson F, Lu S, et al. Targeted treatment for unresectable EGFR mutation-positive stage III non-small cell lung cancer: Emerging evidence and future perspectives. *Lung Cancer*. 2024;187:107414.
37. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2023 April 19. [cited 2023 November 8]. Available from: <https://seer.cancer.gov/statistics-network/explorer/>. Data source(s): SEER Incidence Data, November 2023 Submission (1975-2020), SEER 22 registries.
38. Hendriks LEL, Hermans BCM, van den Beuken-van Everdingen MHJ, Hochstenbag MMH, Dingemans A-MC. Effect of Bisphosphonates, Denosumab, and Radioisotopes on Bone Pain and Quality of Life in Patients with Non-Small Cell Lung Cancer and Bone Metastases: A Systematic Review. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*. 2016;11(2):155-73.



39. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. *Onco Targets Ther.* 2016;9:1023-8.
40. Eggen AC, Reyners AKL, Shen G, Bosma I, Jalving M, Leighl NB, et al. Death anxiety in patients with metastatic non-small cell lung cancer with and without brain metastases. *Journal of pain and symptom management.* 2020;60(2):422-9.
41. An E, Lo C, Hales S, Zimmermann C, Rodin G. Demoralization and death anxiety in advanced cancer. *Psychooncology.* 2018;27(11):2566-72.
42. Shin D-Y, Na II, Kim CH, Park S, Baek H, Yang SH. EGFR Mutation and Brain Metastasis in Pulmonary Adenocarcinomas. *Journal of Thoracic Oncology.* 2014;9(2):195-9.
43. Bovi JA. Prevention of Brain Metastases. *Front Neurol.* 2018;9:758.
44. European Medicines Agency (EMA). Osimertinib Summary of Product Characteristics. . 2020.
45. Santarpia M, Liguori A, Karachaliou N, Gonzalez-Cao M, Daffinà MG, D'Aveni A, et al. Osimertinib in the treatment of non-small-cell lung cancer: design, development and place in therapy. *Lung Cancer.* 2017;8:109-25.
46. Medicinrådet. Medicinrådets anbefaling vedr. osimertinib til adjuverende behandling af EGFR-muteret ikke-småcellet lungekræft Post-operative patienter med stadium IB, II el. IIIA-sygdom og exon 19-deletion eller exon 21 (L858R)-mutation i EGFR. 2024.
47. Medicinrådet. Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til førstelinjebehandling af uheldelig ikke-småcellet lungekræft. 2020.
48. European Medicines A. Osimertinib Summary of Product Characteristics.
49. Lu S, Ahn MJ, Reungwetwattana T, Özgüroğlu M, Kato T, Yang JCH, et al. Osimertinib after definitive chemoradiotherapy in unresectable stage III epidermal growth factor receptor-mutated non-small-cell lung cancer: analyses of central nervous system efficacy and distant progression from the phase III LAURA study☆. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2024;35(12):1116-25.
50. Medicinrådet. Medicinrådets anbefaling vedr. alectinib til adjuverende behandling af ALK-positiv ikke-småcellet lungekræft. 2024.
51. Medicinrådet. Medicinrådets vurdering vedrørende lorlatinib til behandling af uheldelig ALK-positiv ikke-småcellet lungekræft. 2021.
52. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, Kuntz KM. State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. *Value in Health.* 2012;15(6):812-20.
53. Lu S, Casarini I, Kato T, Cobo M, Özgüroğlu M, Hodge R, et al. Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non-small-cell Lung Cancer: LAURA Trial in Progress. *Clinical Lung Cancer.* 2021;22(4):371-5.
54. Patel S, Zhao S, Wei L, Li M, Bertino E, Presley C, et al. P21.02 Incidence and Outcomes of Brain Metastases in Unresectable Stage III Patients with NSCLC Treated with Durvalumab after Chemoradiation. *Journal of Thoracic Oncology.* 2021;16(3):S363-S4.
55. Clinicaltrials.gov. A global study to assess the effects of osimertinib following chemoradiation in patients with stage III unresectable non-small cell lung cancer (LAURA). Available at: <https://clinicaltrials.gov/ct2/show/NCT03521154>. Last accessed: June 2023. 2020.
56. Ramalingam SS, Ozguroglu M, Ahn MJ, Dong X, Yang JCH, Oizumi S, et al. LBA4: Osimertinib (osi) after definitive chemoradiotherapy (CRT) in patients (pts) with unresectable (UR) stage III EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC):



- Updated overall survival (OS) analysis from the LAURA study. *Journal of Thoracic Oncology*; Elsevier; 2025. p. S123-S4.
57. Lu S, Ahn MJ, Baisamut TR, Ozguroglu M, Kato T, Yang JCH, et al. 1241MO Osimertinib (osi) after definitive chemoradiotherapy (CRT) in unresectable (UR) stg III EGFRm NSCLC: Analyses of CNS and distant progression from the phase III LAURA study. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2024;35:S794-S5.
58. AstraZeneca Data on F. A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre, International Study of Osimertinib as Maintenance Therapy in Patients with Locally Advanced, Unresectable EGFR Mutation-Positive Non-Small Cell Lung Cancer (Stage III) Whose Disease Has Not Progressed Following Definitive Platinum-Based Chemoradiation Therapy (LAURA) Clinical Study report. 2024 2024.
59. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. 2008;6(1):84.
60. Monahan M, Ensor J, Moore D, Fitzmaurice D, Jowett S. Economic evaluation of strategies for restarting anticoagulation therapy after a first event of unprovoked venous thromboembolism. *Journal of Thrombosis and Haemostasis*. 2017;15(8):1591-600.
61. Goeree R, Villeneuve J, Goeree J, Penrod JR, Orsini L, Tahami Monfared AA. Economic evaluation of nivolumab for the treatment of second-line advanced squamous NSCLC in Canada: a comparison of modeling approaches to estimate and extrapolate survival outcomes. *Journal of Medical Economics*. 2016;19(6):630-44.
62. Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, Rodríguez-Perálvarez M, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. *Health Technology Assessment*. 2015;19(9):1-410.
63. National Institute for H, Care E. Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer. 2020.
64. AstraZeneca. Data on file - Danish registry data on EGFRm stage IIIB/C pateints from 2017-2022. 2025.
65. European Medicines Agency (EMA). Assessment report - Tagrisso, Procedure No. EMEA/H/C/004124/II/0056. 2025.
66. AstraZeneca Data on F. LAURA Clinical Study Report – Osimertinib (AZD9291)-D5160C00048. 28 March 2024.
67. Lu S, Ahn MJ, Reungwetwattana T, Özgüroğlu M, Kato T, Yang JCH, et al. Osimertinib after definitive chemoradiotherapy in unresectable stage III epidermal growth factor receptor-mutated non-small-cell lung cancer: analyses of central nervous system efficacy and distant progression from the phase III LAURA study ☆. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2024;0(0).
68. AstraZeneca. Data on File. FLAURA2 Clinical Study Report (DCO 03 Apr 2023). 2023.
69. AstraZeneca. Data on File. FLAURA2 Second Interim Analysis of OS (DCO 08 Jan 2024). 2024.
70. Latimer NR. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. 2013;33(6):743-54.
71. Lu S, Kato T, Dong X, Ahn M-J, Quang L-V, Soparattanapaisarn N, et al. Final LAURA Clinical Study Protocol (edition 5.0) in Supplementary Appendix of Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. *N Engl J Med*. 2024;391(7):585-97.
72. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. 2017.



73. Dunlop W, van Keep M, Elroy P, Perez ID, Ouwens MJNM, Sarbajna T, et al. Cost Effectiveness of Durvalumab in Unresectable Stage III NSCLC: 4-Year Survival Update and Model Validation from a UK Healthcare Perspective. *Pharmacoeconomics Open*. 2022;6(2):241-52.
74. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2022;40(12):1301-11.
75. Musoro JZ, Coens C, Sprangers MAG, Brandberg Y, Groenvold M, Flechtner HH, et al. Minimally important differences for interpreting EORTC QLQ-C30 change scores over time: A synthesis across 21 clinical trials involving nine different cancer types. *Eur J Cancer*. 2023;188:171-82.
76. Labbé C, Leung Y, Silva Lemes JG, Stewart E, Brown C, Cosio AP, et al. Real-World EQ5D Health Utility Scores for Patients With Metastatic Lung Cancer by Molecular Alteration and Response to Therapy. *Clinical Lung Cancer*. 2017;18(4):388-95.e4.
77. National Institute for Health and Care Excellence (NICE). Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer (TA654). 2020.
78. Torkilseng EB, Clarke N, Sopina L, Oddershede L, Wolf RT, Lawrance R, et al. Predicting Danish EQ-5D-5L Utilities Based on United Kingdom EQ-5D-3L Utilities for Use in Health Economic Models. *Pharmacoecon Open*. 2025.
79. Sundhedsdatastyrelsen. DRG-takster 2025. 2025.
80. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or Platinum–Pemetrexed in EGFR T790M–Positive Lung Cancer. *New England Journal of Medicine*. 2017;376(7):629-40.
81. Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu Y-L, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *The Lancet*. 2008;372(9652):1809-18.
82. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *New England Journal of Medicine*. 2018;378(24):2288-301.
83. Medicinrådet. Værdisætning af enhedsomkostninger, v1.8. 2024.



Appendix A. Main characteristics of studies included

Table 59 Main characteristic of studies included

Trial name:		NCT number: NCT03521154
Objective	A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer	
Publications – title, author, journal, year	Trial in progress publication: Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non-small-cell Lung Cancer: LAURA Trial in Progress, Lu S, Casarini I, Kato T, et al., <i>Clin Lung Cancer</i>. 2021 Primary publication: Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC, Lu S, Kato T, Dong X, et al., <i>N Engl J Med</i>. 2024 Secondary publication: Osimertinib after definitive chemoradiotherapy in unresectable stage III epidermal growth factor receptor-mutated non-small-cell lung cancer: analyses of central nervous system efficacy and distant progression from the phase III LAURA study, Lu S, Ahn MJ, Reungwetwattana T, et al., <i>Ann Oncol</i>. 2024	
Study type and design	Double-blind, randomized, placebo-controlled, phase III study. Patients were randomly assigned in a 2:1 ratio (osimertinib to placebo) using a stratified randomization approach. This was conducted via an interactive voice/web response system (IVRS/IWRS). Stratification was done based on prior chemoradiation strategy (concurrent vs sequential), tumor stage prior to chemoradiation (IIIA vs IIIB/IIIC), and China cohort (enrolled at a Chinese site and patient declaring themselves of Chinese ethnicity vs non-Chinese). Study is ongoing with expected final read-out in 2027.	
Sample size (n)	n = 216; 143 patients in osimertinib arm, 73 patients in placebo arm	
Main inclusion criteria	1. Male or female aged at least 18 years. 2. Patients with histologically documented NSCLC of predominantly non-squamous Pathology who present with locally advanced, unresectable (Stage III) disease (according to Version 8 of the International Association for the Study of Lung Cancer [IASLC] Staging Manual in Thoracic Oncology). 3. The tumor harbours one of the two common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations, assessed by cobas® EGFR Mutation Test v2 (Roche Diagnostics) or FoundationOne® test in a CLIA certified (USA sites) or an accredited local laboratory (sites outside of the USA) or by central testing (cobas® v2 only).	



Trial name:	NCT number: NCT03521154
	- Patients must have received either concurrent chemoradiation or sequential chemoradiation including at least 2 cycles of platinum based chemotherapy and a total dose of radiation of 60 Gy $\pm$10% (54 to 66 Gy). - Chemoradiation must be completed $\leq$6 weeks prior to randomization. - Patients must not have had disease progression during or following definitive platinum-based, chemoradiation therapy. - World Health Organization (WHO) performance status of 0 or 1. - Life expectancy >12 weeks at Day 1. - Female patients who are not abstinent (in line with the preferred and usual lifestyle choice) must be using adequate contraceptive measures, must not be breast feeding, and must have a negative pregnancy test prior to first dose of study drug; or female patients must have an evidence of non-childbearing potential.
Main exclusion criteria	- Mixed small cell and non-small cell lung cancer histology - History of interstitial lung disease (ILD) prior to chemoradiation - Symptomatic pneumonitis following chemoradiation - Any unresolved toxicity Common Terminology Criteria for Adverse Events (CTCAE) > Grade 2 from the prior chemoradiation therapy - Any of the following cardiac criteria: - Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG - Patient with any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes - Inadequate bone marrow reserve or organ function - History of other malignancies, except: adequately treated non-melanoma skin cancer or lentigo maligna, curatively treated in-situ cancer, or other solid tumors curatively treated with no evidence of disease for > 5 years following the end of treatment and which, in the opinion of the treating physician,



Trial name:		NCT number: NCT03521154	
		do not have a substantial risk of recurrence of the prior malignancy.	
		8. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses; or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV).	
		9. 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	
		10. Prior treatment with any prior chemotherapy, radiation therapy, immunotherapy or investigational agents for NSCLC outside of that received in the definitive setting for Stage III disease (chemotherapy and radiotherapy in SCRT and CCRT regimens is allowed for treatment of Stage III disease).	
		11. Prior treatment with EGFR-TKI therapy	
		12. Major surgery as defined by the investigator within 4 weeks of the first dose of study drug.	
		13. Patients currently receiving (unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be strong inducers of CYP3A4 (at least 3 weeks prior to receiving the first dose of study drug).	
		14. Contraindication to MRI, including but not limited to, claustrophobia, pace makers, metal implants, intracranial surgical clips and metal foreign bodies	
Intervention		Osimertinib 80 mg, per oral. Treatment can continue until disease progression, unacceptable toxicity or other discontinuation criteria are met.	
Comparator(s)		Placebo	
Follow-up time		DCO 5 Jan 2024: The median follow-up for OS in censored patients was 30.9 months (range: 1.9 to 62.9 months) for osimertinib arm and 28.1 months (range: 4.49 to 61.2 months for the placebo arm. DCO 29 Nov 2024: Median follow-up for OS in censored patients was 42.61 months for the osimertinib arm and 36.52 months for the placebo arm.	
Is the study used in the health economic model?		Yes	
Primary, secondary and exploratory endpoints		Primary Endpoint • Progression-Free Survival (PFS) measured by: ○ Blinded Independent Central Review (BICR) assessment according to RECIST v1.1	



Trial name:

NCT number: NCT03521154

- Sensitivity analysis of PFS using Investigator assessment according to RECIST v1.1

Secondary Endpoints

- **Efficacy of osimertinib treatment compared with placebo** by assessment of PFS in patients with:
 - EGFR Ex19del or L858R mutation
 - EGFRm+ Ex19del or L858R detectable in plasma-derived ctDNA
- **CNS Progression-Free Survival (CNS PFS)** measured by:
 - Time to CNS PFS (time to the earliest of CNS progression or death) using BICR assessments according to RECIST v1.1
 - Cumulative incidence rate of CNS PFS by BICR at 12 and 24 months
- **Overall Survival (OS)**
- **Objective Response Rate (ORR), Duration of Response (DoR), Disease Control Rate (DCR), and tumor shrinkage**, using BICR assessments according to RECIST v1.1
- **Time to treatment discontinuation (TTD)**
- **Post-progression Assessments:**
 - Second progression-free survival on a subsequent treatment (PFS2)
 - Time to first subsequent therapy (TFST)
 - Time to second subsequent therapy (TSST)
- **Disease-related symptoms and health-related Quality of Life (QoL)** using:
 - Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30)
 - Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13)
- **Safety and tolerability profile of osimertinib compared with placebo**, assessed by:
 - Adverse Events (graded by CTCAE v5)
 - Clinical chemistry, hematology, and urinalysis
 - Vital signs, physical examination, and weight
 - ECG parameters
 - Left ventricular ejection fraction
 - WHO Performance Status
- **Pharmacokinetics (PK) of osimertinib**, measured by:
 - Trough plasma concentrations of osimertinib and its metabolite AZ5104
 - Population PK analysis parameters if conducted

Exploratory Objectives

- Adverse effects using PRO-CTCAE
- Patients' overall impression of the severity of cancer symptoms using PGIS
- Health state utility comparison using EQ-5D-5L
- Health resource use associated with osimertinib treatment versus placebo



Trial name:		NCT number: NCT03521154	
		• Relationship between osimertinib PK and selected endpoints • Baseline tumor EGFR mutation status comparison with evaluable results from baseline plasma samples • Comparison of local EGFR mutation test results with retrospective central cobas® EGFR Mutation Test v2 results • DNA collection for future exploratory research on genetic influences on PK, response, and cancer susceptibility • Relationship between PK and blood-borne biomarkers • Association between exploratory biomarkers and key efficacy endpoints using archival tumor samples • Longitudinal analysis of ctDNA for mutations and expression changes • Assessment of innate and acquired resistance mechanisms to study treatment	
Method of analysis		All efficacy analyses were conducted on an intention-to-treat (ITT) basis. The analyses used the following methods: • Kaplan–Meier Method: This was used to estimate rates of progression-free survival (PFS) and overall survival (OS). • Stratified Log-Rank Test: Employed for treatment comparisons, stratified by factors such as chemoradiation strategy (concurrent vs sequential), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC), and China cohort. • Cox Proportional Hazards Regression: Hazard ratios adjusted for stratification factors such as chemoradiation strategy and disease stage were estimated with this regression method.	
Subgroup analyses		N/A	
Other relevant information		N/A	



Appendix B. Efficacy results per study

Results per study

Table 60 Results per study

Results of LAURA NCT03521154										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	References
Median PFS (DCO: 5th Jan 2024)	Osimertinib	143	39.1 months (95% CI: 31.5 – NC)	33.5 months	NA	NA	HR: 0.16	0.10 - 0.24	<0.0001	Median derived using Kaplan Meier estimator. HR and 95% CI calculated with a Cox proportional hazards model.
	Placebo	73	5.6 months (95% CI: 3.7 – 7.4)							
PFS rate 1-year (DCO: 5th Jan 2024)	Osimertinib	143	74% (95% CI: 65% - 80%)	52%-point	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator
	Placebo	73	22% (95% CI: 13% - 32%)							



PFS rate 2-year (DCO: 5th Jan 2024)	Osimertinib	143	65% (95% CI: 56% - 73%)	52%-point	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator	LAURA CSR(58)
	Placebo	73	13% (95% CI: 6% - 22%)								
Median OS (Jan 2024 DCO)	Osimertinib	143	54.0 months (95% CI: 46.5 – NC)	NC	NC	NC	HR: 0.81	0.42 - 1.56	0.530	Median derived using Kaplan Meier estimator. HR and 95% CI calculated with a Cox proportional hazards model.	LAURA CSR(58)
	Placebo	73	NR (95% CI: 42.1 – NC)								
OS rate 2-year (Jan 2024 DCO)	Osimertinib	143	90.3% (95% CI: 83.8% - 94.2%)	0.5%-points	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator	LAURA CSR(58)
	Placebo	73	90.8% (95% CI: 80.5% - 95.8%)								
OS rate 3-year (Jan 2024 DCO)	Osimertinib	143	83.7% (95% CI: 75.3% - 89.4%)	10%-points	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator	LAURA CSR(58)
	Placebo	73	73.7% (95% CI: 56.7% - 84.9%)								



Median OS (Nov 2024 DCO)	Osimertinib	143	58.8 months (95% CI: 54.1 – NC)	4.8 months	NA	NA	HR: 0.67	0.40 - 1.14	0.140	Median derived using Kaplan Meier estimator. HR and 95% CI calculated with a Cox proportional hazards model.	LAURA CSR(58)
	Placebo	73	54.0 months (95% CI: 42.1 – NC)								
OS rate 2- year (Nov 2024 DCO)	Osimertinib	143	89.3% (95% CI: 83% - 95%)	1.9%-points	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator	LAURA CSR(58)
	Placebo	73	91.2% (95% CI: 82% - 96%)								
OS rate 3- year (Nov 2024 DCO)	Osimertinib	143	81.8% (95% CI: 74% - 87%)	9.3%-points	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator	LAURA CSR(58)
	Placebo	73	72.5% (95% CI: 59% - 82%)								
Median CNS- PFS (DCO: 5th Jan 2024)	Osimertinib	143	NR (95% CI: NC – NC)	NC	NC	NC	HR: 0.17	0.09 - 0.32	<0.0001	Median derived using Kaplan Meier estimator. HR and 95% CI calculated with a Cox proportional hazards model.	LAURA CSR(58)
	Placebo	73	14.9 (95% CI: 7.4 – NC)								



CNS-PFS rate 1-year (DCO: 5th Jan 2024)	Osimertinib	143	87% (95% CI: 79.4% - 91.5%)	34%-points	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator	LAURA CSR(58)
	Placebo	73	53% (95% CI: 38.3% - 65.6%)								
CNS-PFS rate 2-year (DCO: 5th Jan 2024)	Osimertinib	143	83% (95% CI: 74.7% - 88.5%)	40%-points	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator	LAURA CSR(58)
	Placebo	73	43% (95% CI: 28.0% - 57.7%)								
Median PFS2 (DCO: 5th Jan 2024)	Osimertinib	143	48.2 months (95% CI: 44.42 – NC)	0.8 months	NA	NA	HR: 0.62	0.38 – 1.08	P=0.088	Median derived using Kaplan Meier estimator. HR and 95% CI calculated with a Cox proportional hazards model	LAURA CSR(58)
	Placebo	73	47.38 months (95% CI: 28.22 - NC)								
Median TTP (DCO: 5th Jan 2024)	Osimertinib	143	39.3 months (95% CI: 38.4 – NC)	33.7 months	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator	LAURA CSR(58)
	Placebo	73	5.6 months (95% CI: 3.7 – 7.4)								



Median PPS (DCO: 5th Jan 2024)	Osimertinib	143	32.0 months (95% CI: 18.8 – NC)	9.8 months	NA	NA	NA	NA	NA	Rates derived using Kaplan Meier estimator	LAURA CSR(58)
	Placebo	73	41.8 months (95% CI: 32.69 – NC)								



Appendix C. Comparative analysis of efficacy

Not applicable.



Appendix D. Extrapolation

D.1 Extrapolation of time to progression (TTP)

D.1.1 Data input

Data from the LAURA trial is used to inform the extrapolation of TPP beyond the follow-up in the clinical trial.

D.1.2 Model

Standard parametric models were used to extrapolate TTP from LAURA data, the following distributions were used:

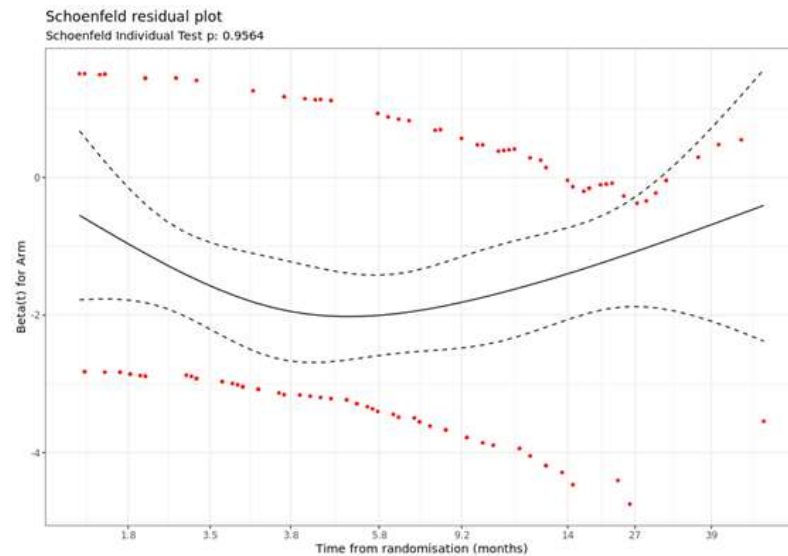
- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.1.3 Proportional hazards

The Schoenfeld and log-cumulative hazards plots for TTP are shown in Figure 24 and Figure 25, respectively. The unadjusted Grambsch-Therneau (G-T) test result was $p=0.9564$, which fails to reject the hypothesis that the proportional hazard assumption holds. The log-hazard ratio in the Schoenfeld plot showed some evidence of non-proportional hazards, (i.e., a non-horizontal line), however there was no clear pattern or trend in the treatment effect over time. The log-cumulative hazards plot showed minor departures from proportional hazards with the trend lines diverging into non-parallel lines. These results suggest that the treatment effect for osimertinib may vary over time, and hence, methods for non-proportional hazards analysis were explored and independent models were selected for the parametric models.



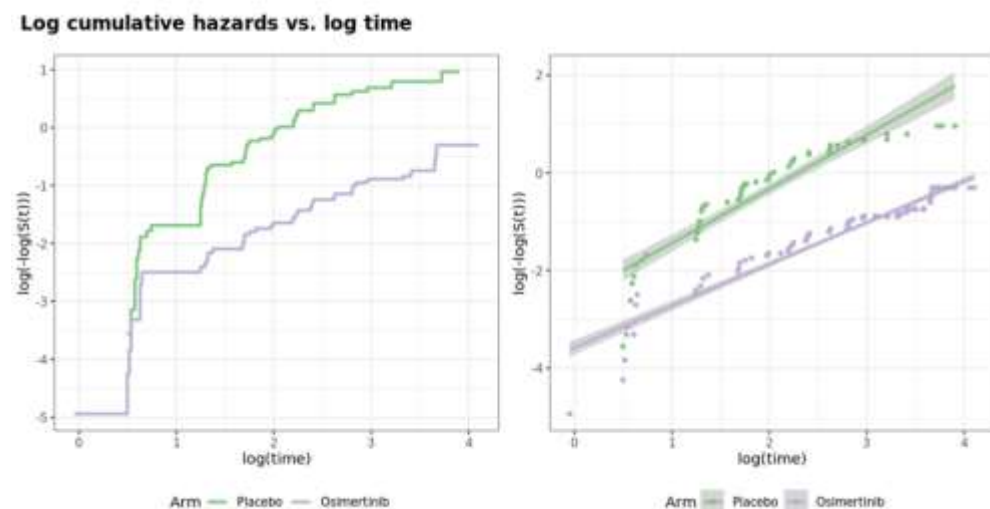
Figure 24. Schoenfeld residual plot of TTP



Abbreviations: TTP: time to progression

Source: LAURA CSR addendum (date 27 Mar 2024)(58)

Figure 25. Log curves of TTP



Abbreviations: TTP: time to progression

Source: LAURA CSR addendum (date 27 Mar 2024)(58)

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

Parametric distributions were fit independently to the osimertinib and placebo arm. Table 61 and Table 62 present the AIC and BIC statistics for each of the parametric models for osimertinib and placebo, respectively.

The log-normal and generalised gamma curves provide the best within-trial fit for the osimertinib arm, as they have the lowest AIC and BIC scores (Table 61). However, it should be noted that all AIC and BIC scores are relatively consistent. The log-normal and



generalised gamma curves both overestimate the median TTP, but the landmark survival results are relatively well aligned at 3 years (log-normal: 56.92%; general gamma: 58.69%; KM: 62.16%).

The generalised gamma, log-normal and log-logistic curves provide the best within-trial fit for the placebo arm with very similar AIC and BIC scores (Table 62). At 3 years the landmark survival results (log-normal: 3.77%; log-logistic: 3.90%; general gamma: 8.73%; KM: 10.97%) show underestimation of the log-normal and log-logistic curves and alignment with the generalized gamma curve, which more closely follows the plateau at the end of the curve. However, the plausibility of the long-term plateau for patients on placebo is an important point of consideration.

Table 61. Observed and estimated TTP rates and AIC/BIC of survival models for osimertinib

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma
AIC	541.5	540.5	538.2	538.6	535	533.6	541.2
AIC rank	7	5	3	4	2	1	6
BIC	544.5	546.4	544.1	544.6	541	542.5	547.1
BIC rank	4	6	3	5	1	2	7

Note: Bold, chosen curve fit

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

Table 62. Observed and estimated TTP rates and AIC/BIC of survival models for placebo

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma
AIC	416.3	418.3	412.6	397	397.2	387.8	417
AIC rank	5	7	4	2	3	1	6
BIC	418.6	422.9	417.2	401.6	401.8	394.6	421.6
BIC rank	5	7	4	2	3	1	6

Note: Bold, chosen curve fit

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

D.1.5 Evaluation of visual fit

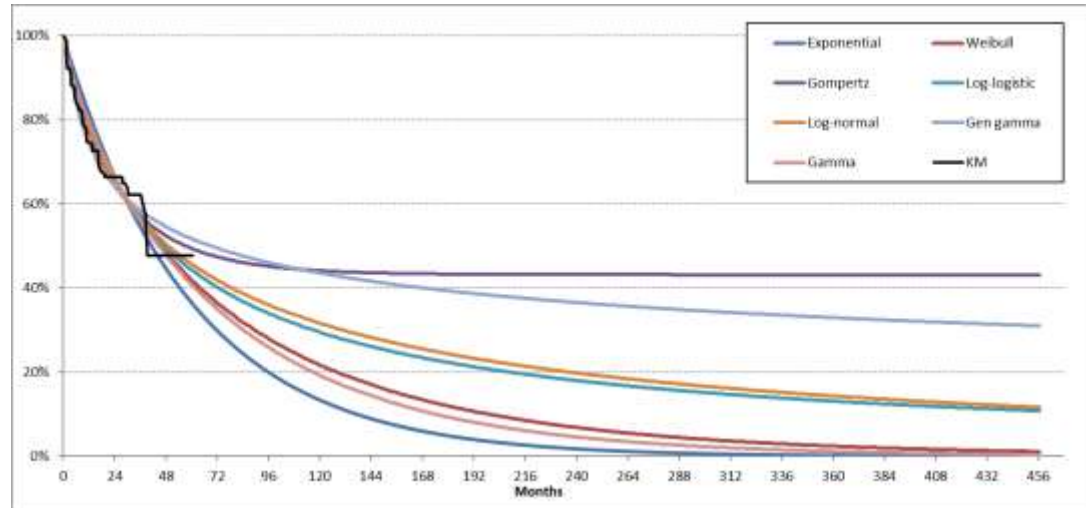
The extrapolated TTP curves were plotted together with the KM data for osimertinib and placebo from the LAURA trial using standard parametric functions (Figure 26 and Figure 27). There is a wide variation in the long-term estimates of TTP for the osimertinib arm (Figure 26), which is considered to be driven by the relatively low maturity of the data (37.1%) and uncertainty in the tail of the KM curve. The generalised gamma curve, which was one of the best fitted models based on statistical fit, provides a relatively optimistic estimate of long-term TTP. The log-normal curve, which was also a good statistical fit, provides a more conservative estimate of long-term TTP.

There is little variation in the long-term estimates of TTP for the placebo arm due to the relatively high maturity of the data; 84.9% maturity and only 13.71% patients without a progression event at 24 months (Figure 27). The generalised gamma curve estimates a



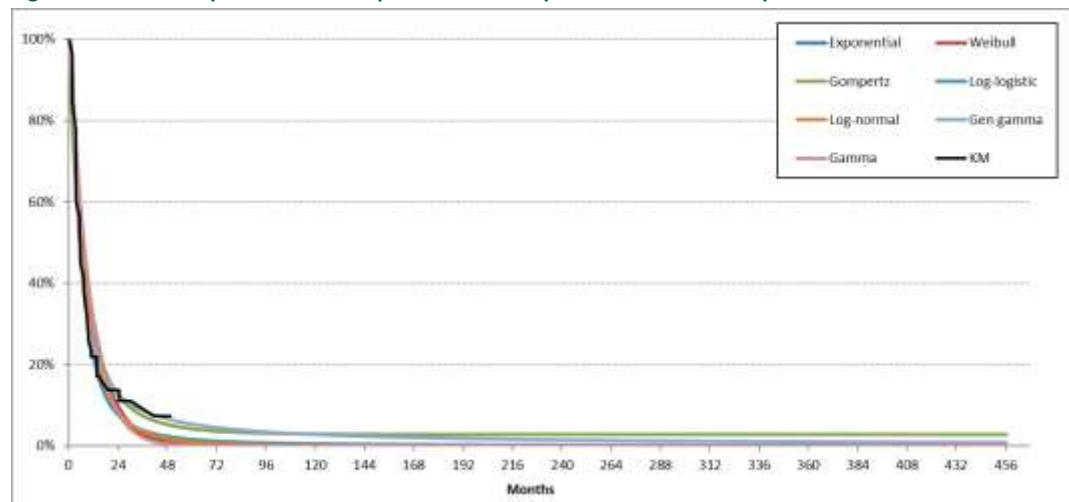
small proportion of patients will achieve long-term progression-free survival, while the log-normal curve estimates all (>99.9%) patients will have had a disease progression event by 77 months.

Figure 26. Standard parametric extrapolations and Kaplan-Meier of TTP for osimertinib



Abbreviations: KM: Kaplan-Meier; TTP: time to progression

Figure 27. Standard parametric extrapolations and Kaplan-Meier of TTP for placebo



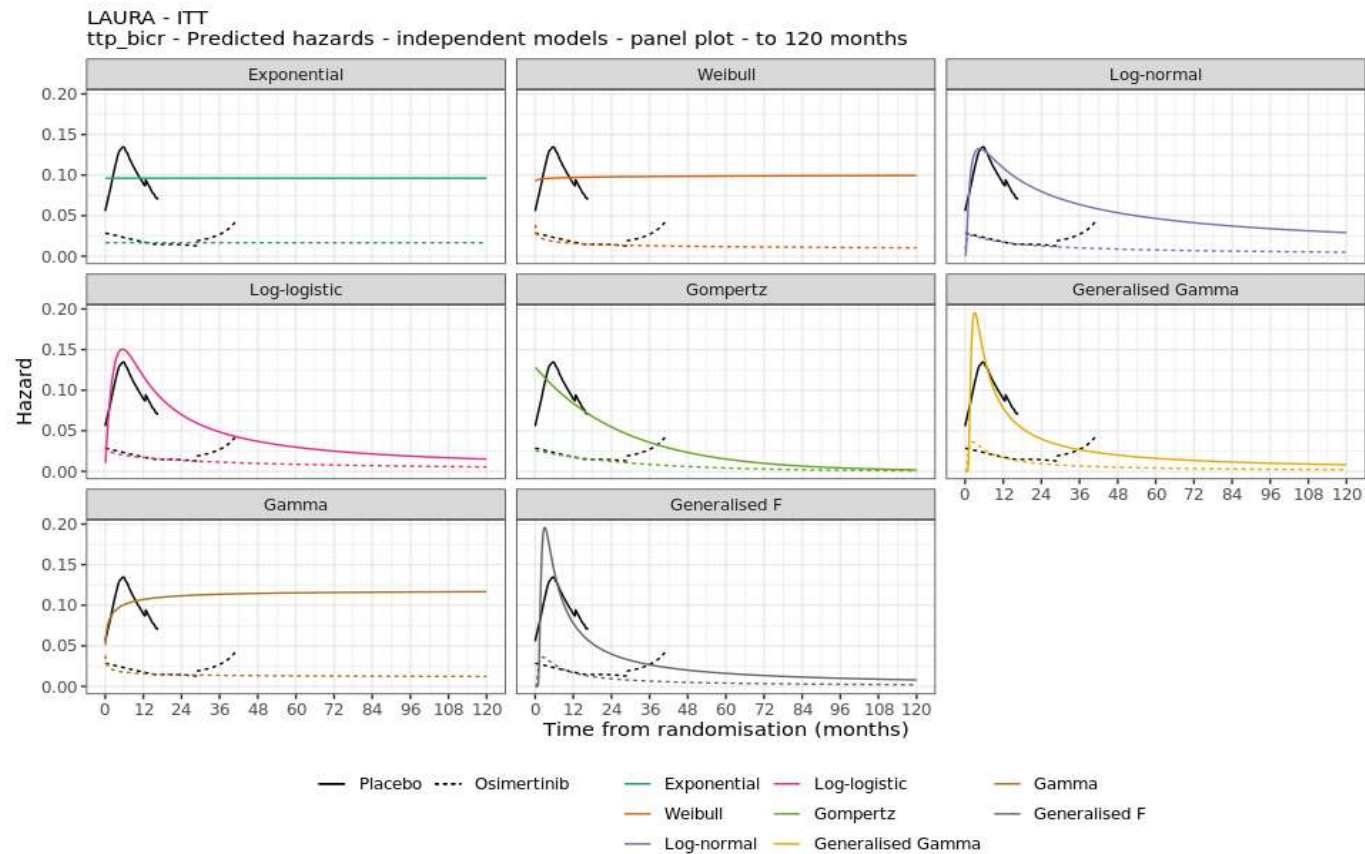
Abbreviations: KM: Kaplan-Meier; TTP: time to progression

D.1.6 Evaluation of hazard functions

Error! Reference source not found. presents the combined smoothed hazard plots for all extrapolations of the osimertinib and placebo arms. Both the log-normal and generalised gamma curves reflect the reasonably flat hazards in the osimertinib arm, which is also reflected in most of the distributions. The generalised gamma distribution overpredicts the increase in hazards in the placebo arm, while the log-normal distribution better reflects the increase in hazards up to 6 months and decrease following the 6-month turning point. The log-logistic curve also provides a reasonable visual fit to the within trial hazards.



Figure 28. Smoothed hazard plots of TPP for placebo and osimertinib





D.1.7 Validation and discussion of extrapolated curves

For the osimertinib arm, the log-normal and generalised gamma distributions provide a good statistical fit based on AIC/BIC scores, but appear overly optimistic, especially for the generalised gamma model. Similarly, the Gompertz distribution is a relatively good statistical fit but projects an optimistic long-term outcome that may not be clinically justifiable at this stage of disease. Of the remaining curves, the exponential curve predicts the median TTP consistently with the KM but projects the most conservative long-term outcomes. The remaining log-logistic, gamma and Weibull curves all have a similar statistical fit and are all within 5 points of each other on AIC and BIC. The gamma curve has a median TTP most consistent with the observed data with a more conservative long-term projection compared with the log-logistic and Weibull curves. All provide a relatively good fit on the hazard plot. The gamma curve was selected for the base case as it provided a reasonable statistical fit, was visually a reasonable fit for the KM data while providing a more clinically plausible long-term outcome and also provided a good visual fit on the hazard plot.

For the placebo arm, the generalised gamma and log-normal distributions also had the best statistical fit based on AIC and BIC statistics. In terms of visual fit to the KM data, all options except the Gompertz and generalised gamma underestimated the observed data at the tail end of the KM. The generalised gamma and log-logistic distributions provided the best visual fit to the hazard plots. Ultimately, the generalised gamma was selected for the base case as it was deemed a good fit across all three assessments.

Table 63. Observed and estimated TTP rates and AIC/BIC of survival models for osimertinib

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma	KM curve
AIC	541.5	540.5	538.2	538.6	535	533.6	541.2	
AIC rank	7	5	3	4	2	1	6	
BIC	544.5	546.4	544.1	544.6	541	542.5	547.1	
BIC rank	4	6	3	5	1	2	7	
Median (mths)	41.40	45.34	57.17	46.32	48.30	68.01	44.35	39.13
Mean (mths)	60.20	78.96	215.13	117.94	124.56	189.43	71.7	
1 year	82.04%	79.33%	77.59%	78.32%	77.72%	74.79%	79.84%	74.95%
2 years	67.30%	66.55%	65.00%	65.46%	65.23%	64.46%	66.88%	66.26%
3 years	55.21%	56.75%	57.44%	56.51%	56.92%	58.69%	56.67%	62.16%
5 years	37.15%	42.37%	49.60%	44.68%	46.04%	51.90%	41.37%	47.71%
10 years	13.58%	21.86%	44.12%	29.59%	31.73%	43.61%	19.42%	
15 years	4.96%	12.00%	43.30%	22.32%	24.39%	39.33%	9.37%	



Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

Table 64. Observed and estimated TTP rates and AIC/BIC of survival models for placebo

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma	KM curve
AIC	416.3	418.3	412.6	397	397.2	387.8	417	
AIC rank	5	7	4	2	3	1	6	
BIC	418.6	422.9	417.2	401.6	401.8	394.6	421.6	
BIC rank	5	7	4	2	3	1	6	
Median (mths)	6.90	6.90	5.91	5.91	5.91	4.93	6.90	5.52
Mean (mths)	10.90	10.88	23.08	10.91	10.74	18.76	10.7	
1 year	32.06%	32.11%	28.96%	22.93%	26.52%	24.96%	31.94%	21.81%
2 years	10.28%	10.14%	12.84%	7.80%	8.80%	12.95%	8.73%	13.71%
3 years	3.29%	3.18%	7.53%	3.90%	3.77%	8.78%	2.30%	10.97%
5 years	0.34%	0.31%	4.21%	1.58%	1.04%	5.37%	0.15%	-
10 years	0.00%	0.00%	2.86%	0.45%	0.12%	2.73%	0.00%	
15 years	0.00%	0.00%	2.73%	0.21%	0.03%	1.84%	0.00%	

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

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 post-progression survival (PPS)

D.2.1 Data input



Data from the LAURA trial is used to inform the extrapolation of TTP beyond the follow-up in the clinical trial.

D.2.2 Model

Standard parametric models were used to extrapolate TTP from LAURA data, the following distributions were used:

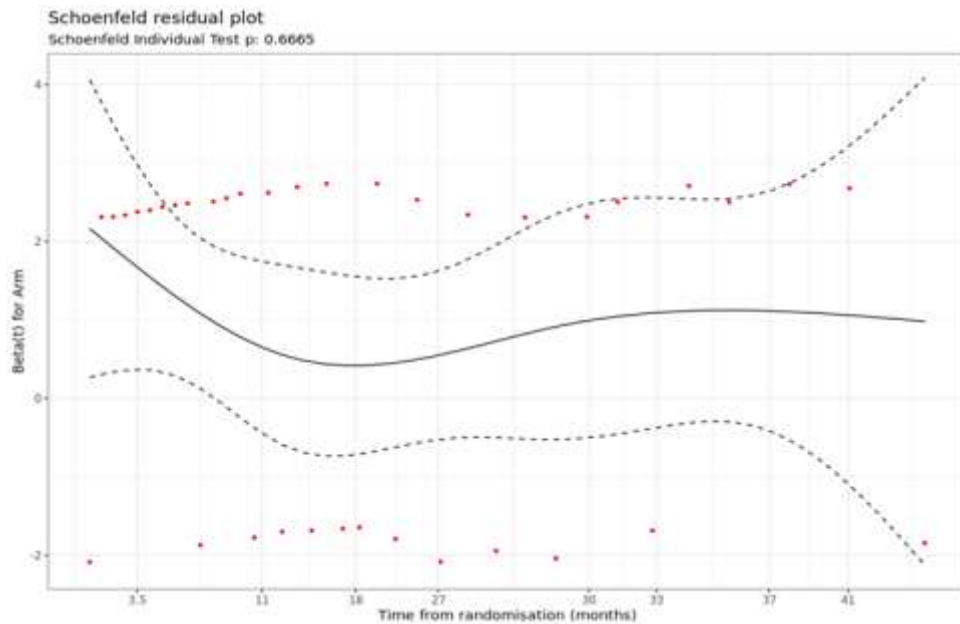
- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.2.3 Proportional hazards

The Schoenfeld and log-cumulative hazards plots for TTP are shown in Figure 24 and Figure 25, respectively. The unadjusted G-T test result was $p=0.6665$, which fails to reject the hypothesis that the proportional hazard assumption holds. The log-hazard ratio in the Schoenfeld plot showed some evidence of non-proportional hazards, (i.e., a non-horizontal line), however there was no clear pattern or trend in the treatment effect over time. The log-cumulative hazards plot showed minor departures from PH with a decreasing separation at the tail. These results suggest that the treatment effect for osimertinib may vary over time, and hence independent models were selected for the parametric models.

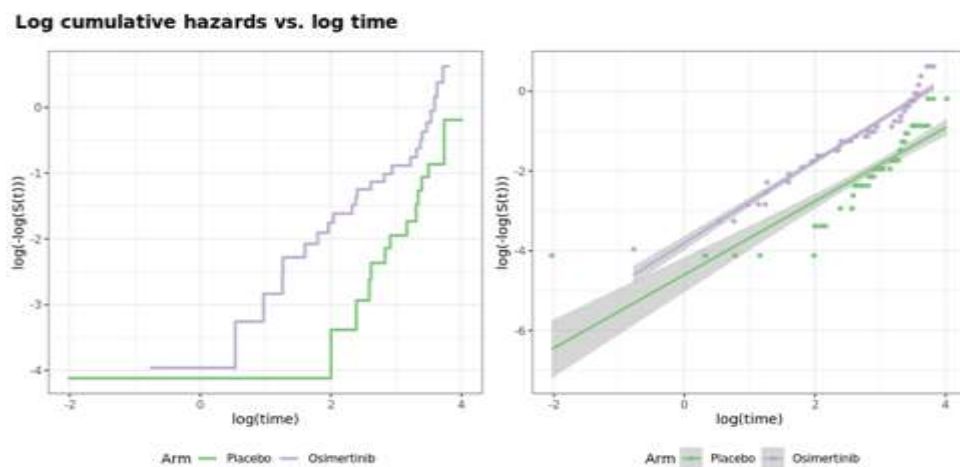


Figure 29. Schoenfeld residual plot of TTP



Source: LAURA CSR addendum (date 27 Mar 2024)(58)

Figure 30. Log curves of TTP



Source: LAURA CSR addendum (date 27 Mar 2024)(58)

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

Parametric distributions were fit independently to the osimertinib and placebo arms. The AIC and BIC statistics for each of the parametric models are presented in Table 61 and Table 62 for osimertinib and placebo, respectively.

The exponential and Gompertz distributions provide the best within-trial fit for the osimertinib arm based on BIC and the Gompertz and generalised-gamma distributions based on AIC, as they have the lowest scores, although the difference in AIC scores between the generalised-gamma and exponential models is only 0.1 (Table 61). However, all AIC and BIC scores are relatively consistent. All curves estimate a relatively



consistent median PPS (26.61–27.6 months), but underpredict compared to the observed data (31.18 months). However, the long-term estimates vary, with projections between 0.00–14.4% at 10 years.

The exponential and Gompertz distributions provide the best within-trial fit for the placebo arm, as they have the lowest AIC and BIC scores (Table 62). Conversely, all the distributions overestimate the median PPS for the placebo arm and the range of estimates for the median and long-term PPS outcomes vary more widely, with projections between 0.00–14.90% at 10 years.

Table 65. Observed and PPS TTP rates and AIC/BIC of survival models for osimertinib

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma
AIC	226.7	227.4	225.4	230.2	232	226.6	227.8
AIC rank	3	4	1	6	7	2	5
BIC	228.6	231.4	229.3	234.2	235.9	232.5	231.8
BIC rank	1	3	2	6	7	5	4

Note: Bold, chosen curve fit

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

Table 66. Observed and estimated PPS rates and AIC/BIC of survival models for placebo

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma
AIC	149.8	150.5	148.1	151.4	156.9	151.7	151
AIC rank	2	3	1	5	7	6	4
BIC	152	154.7	152.3	155.6	161.2	158.1	155.2
BIC rank	1	3	2	5	7	6	4

Note: Bold, chosen curve fit

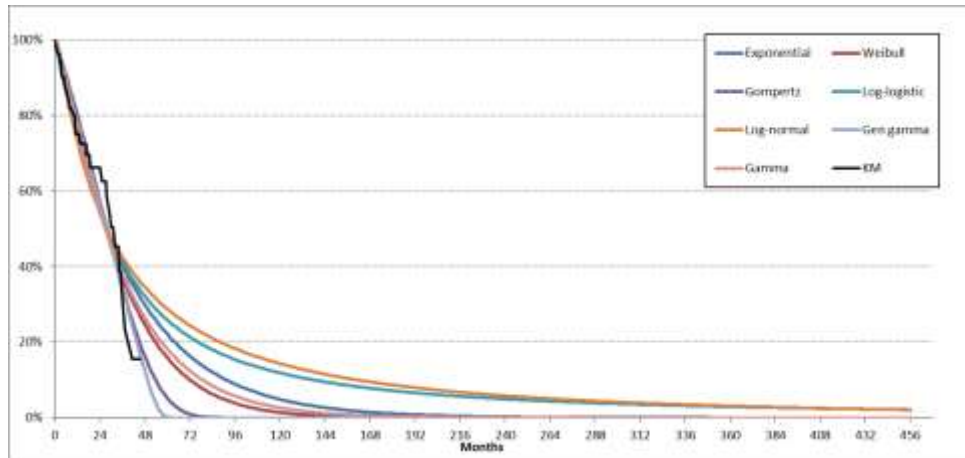
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

D.2.5 Evaluation of visual fit

The extrapolated PPS curves were plotted together with the KM data for osimertinib and placebo from the LAURA trial using standard parametric functions. There is some variation in long-term PPS outcomes for the osimertinib arm (Figure 26). The Gompertz distribution provides a more conservative estimate while the exponential distribution is more optimistic. There is also a wide variation in long-term PPS estimates in the placebo arm, with the distributions diverging from approximately 30 months (Figure 27). The Gompertz curve is the most conservative but fits the KM data more closely than any other curve option.

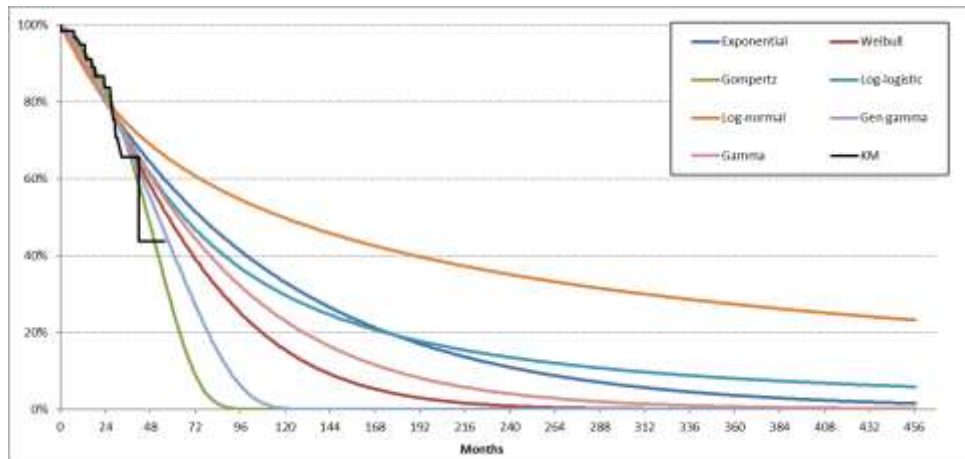


Figure 31. Standard parametric extrapolations and Kaplan-Meier of PPS for osimertinib



Abbreviations: KM: Kaplan-Meier; TTP: time to progression

Figure 32. Standard parametric extrapolations and Kaplan-Meier of PPS for placebo



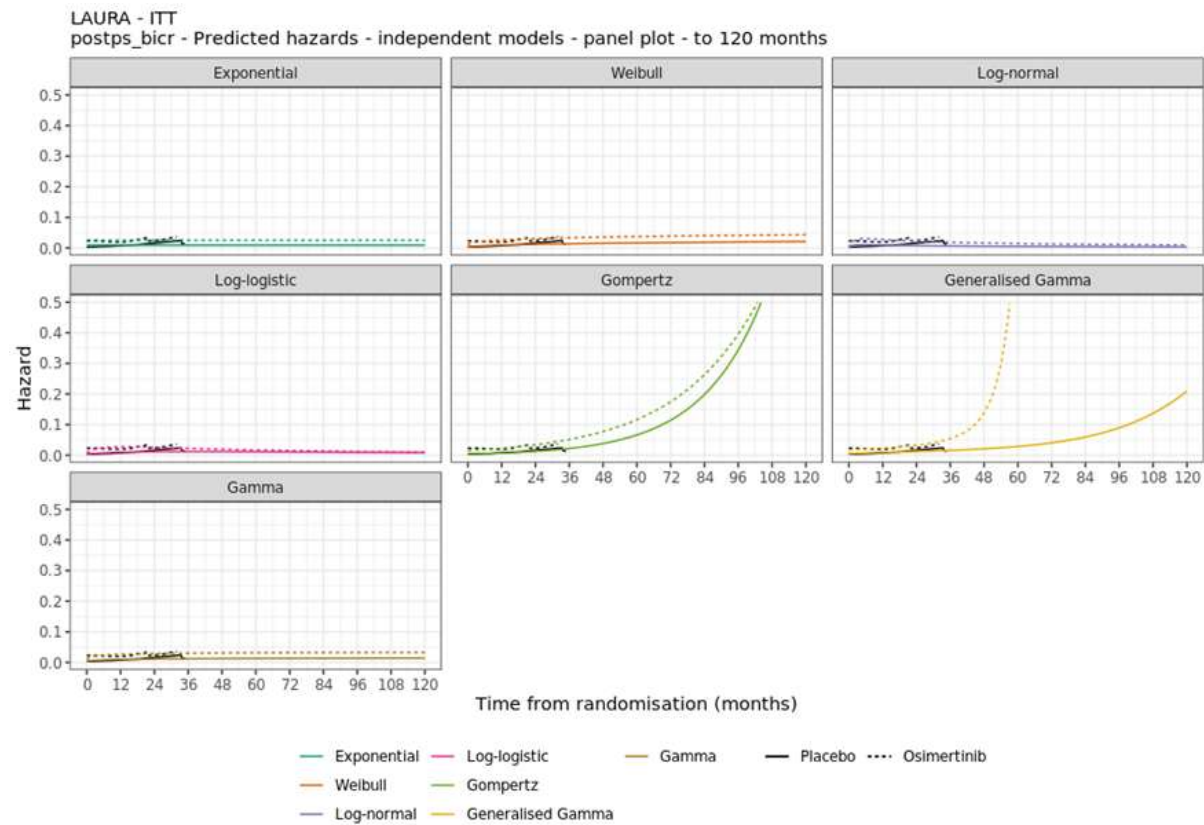
Abbreviations: KM: Kaplan-Meier; TTP: time to progression

D.2.6 Evaluation of hazard functions

Error! Reference source not found. presents the smoothed hazard plots for all extrapolations of the osimertinib and placebo arms. The generalised gamma and Gompertz curves are the only selections which reflect the observed increase in hazards, other parametric models have a much flatter hazard profile. However, the Gompertz distribution more closely aligns with the smoothed hazard profile of both osimertinib and placebo.



Figure 33. Smoothed hazard plots of PPS for placebo and osimertinib





D.2.7 Validation and discussion of extrapolated curves

The Gompertz distribution was selected as the base case for both the osimertinib and the placebo arms. The selection was made based on the good statistical fit to the observed data and good visual fit to the KM data, particularly for the placebo arm. Additionally, it is the only option that appropriately reflects the increasing hazards in both arms hence being the only clinically reasonable option for extrapolating the TTP, in a disease stage where the risk of progression is prominent.

Based on the similar trends in PPS KM curves and smoothed hazards for the osimertinib and placebo arms, it was considered most appropriate to select the same distribution for both arms.

Table 67. Observed and estimated TTP rates and AIC/BIC of survival models for osimertinib

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma	KM curve
AIC	226.7	227.4	225.4	230.2	232	226.6	227.8	
AIC rank	3	4	1	6	7	2	5	
BIC	228.6	231.4	229.3	234.2	235.9	232.5	231.8	
BIC rank	1	3	2	6	7	5	4	
Median (mths)	26.61	26.61	27.60	27.60	27.60	26.61	26.61	31.18
Mean (mths)	40.16	34.49	29.58	56.60	61.09	27.99	36.50	
1 year	74.22%	77.42%	80.31%	76.41%	73.34%	78.61%	76.54%	75.01%
2 years	55.08%	55.18%	57.85%	55.55%	54.68%	56.86%	54.98%	66.22%
3 years	40.88%	37.77%	35.41%	41.72%	42.93%	34.97%	38.70%	38.77%
5 years	22.52%	16.33%	5.67%	26.19%	29.09%	0.32%	18.61%	-
10 years	4.95%	1.42%	0.00%	11.92%	14.40%	0.00%	2.68%	
15 years	1.09%	0.09%	0.00%	7.17%	8.69%	0.00%	0.37%	

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

Table 68. Observed and estimated TTP rates and AIC/BIC of survival models for placebo

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma	KM curve
AIC	149.8	150.5	148.1	151.4	156.9	151.7	151	
AIC rank	2	3	1	5	7	6	4	
BIC	152	154.7	152.3	155.6	161.2	158.1	155.2	
BIC rank	1	3	2	5	7	6	4	



Median (mths)	74.91	57.17	46.32	66.04	118.28	52.24	62.09	41.79
Mean (mths)	106.15	69.81	45.94	107.10	163.52	53.00	83.14	
1 year	89.67%	92.18%	93.61%	92.24%	89.50%	92.12%	91.56%	94.84%
2 years	80.40%	81.24%	83.57%	81.42%	80.97%	81.32%	81.02%	83.81%
3 years	72.09%	69.80%	68.73%	70.97%	74.42%	69.06%	70.70%	65.67%
5 years	57.96%	48.81%	27.53%	53.97%	64.76%	42.01%	52.62%	-
10 years	33.29%	15.69%	0.00%	29.94%	49.90%	0.25%	23.24%	
15 years	19.12%	4.01%	0.00%	19.19%	41.12%	0.00%	9.81%	

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

D.2.8 Adjustment of background mortality

The occupancy of the health states was adjusted to background mortality in the model, as so hazard of overall survival did not become lower than the hazard of mortality observed in the Danish background population.

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 treatment duration (TDT)

D.3.1 Data input

Data from the LAURA trial is used to inform the extrapolation of TDT beyond the follow-up in the clinical trial.

D.3.2 Model

Standard parametric models were used to extrapolate TDT from LAURA data, the following distributions were used:

- Exponential
- Weibull



- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.3.3 Proportional hazards

N/A – extrapolation of TDT only necessary for osimertinib arm.

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

Parametric distributions were fit independently to the osimertinib arm. The AIC and BIC statistics for each of the parametric models are presented in Table 61 for.

The log-normal and gen-gamma distributions provide the best within-trial fit for the osimertinib arm based on AIC and the Log-normal and log-logistic distributions based on BIC, as they have the lowest scores (Table 61). However, all AIC and BIC scores are relatively consistent across the parametric distributions.

Table 69. Observed and PPS TTP rates and AIC/BIC of survival models for osimertinib

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma
AIC	630.3	627.2	627.7	626.3	623.7	625.5	627.8
AIC rank	7	4	5	3	1	2	6
BIC	633.2	633.1	633.7	632.2	629.7	634.3	633.7
BIC rank	4	3	5	2	1	7	5

Note: Bold, chosen curve fit

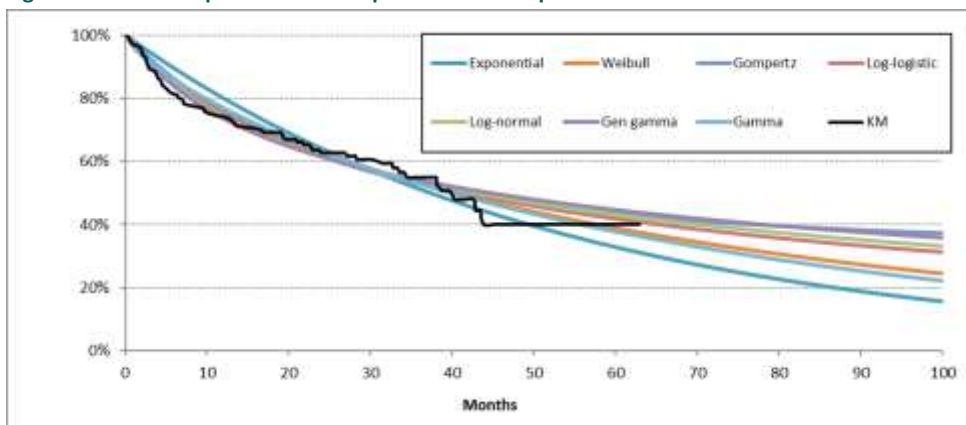
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

D.3.5 Evaluation of visual fit

The extrapolated TDT curves were plotted together with the KM data for osimertinib from the LAURA trial using standard parametric functions. There is some variation in extrapolation of the TDT tail for the osimertinib arm (Figure 26). In the model TDT will be capped by PFS, as patients are treated until progression in the clinical trial.



Figure 34. Standard parametric extrapolations and Kaplan-Meier of TDT for osimertinib



Abbreviations: KM: Kaplan-Meier.

D.3.6 Evaluation of hazard functions

N/A, not available for TDT.

D.3.7 Validation and discussion of extrapolated curves

As patients are treated until progression, the TDT curve is modelled consistently with the TTP curve and PFS curve (i.e. the same distribution is selected). The modelled TDT and PFS curves are presented in Figure 35. For the base case, the Gamma curve has been selected to align with the selected TPP and PFS curves. Scenario analyses has been conducted with the exponential, log-normal and gen-gamma functions for extrapolation of TDT in the osimertinib arm.

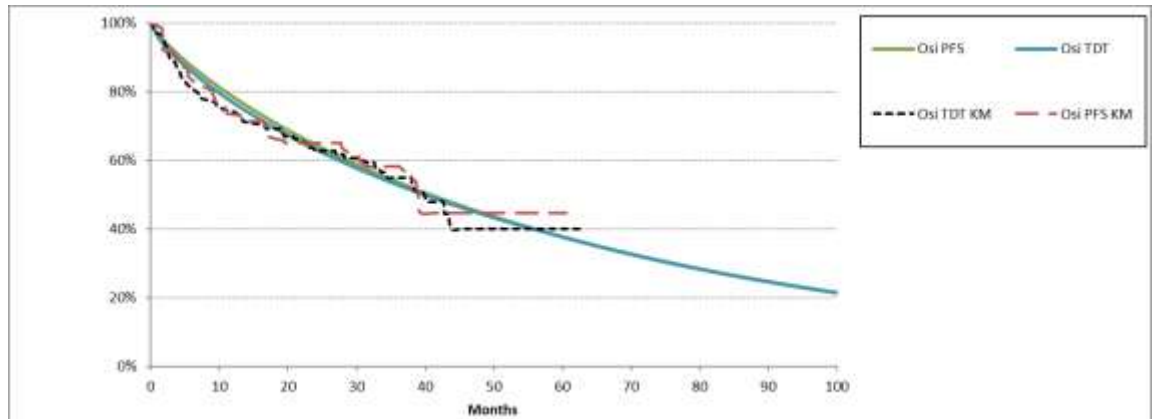
Table 70. Observed and estimated TDT rates and AIC/BIC of survival models for osimertinib

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma	KM curve
AIC	630.3	627.2	627.7	626.3	623.7	625.5	627.8	
AIC rank	7	4	5	3	1	2	6	
BIC	633.2	633.1	633.7	632.2	629.7	634.3	633.7	
BIC rank	4	3	5	2	1	7	5	
Median (mths)	36.47	39.43	40.41	40.41	40.41	40.41	39.43	39.69
Mean (mths)	54.06	62.91	62.75	62.69	62.56	62.46	62.98	

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TDT: treatment duration.



Figure 35. The modelled TDT curve



Abbreviations: Osi: osimertinib; PFS: progression-free survival; TDT: time to treatment discontinuation

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

D.4 Extrapolation of progression-free survival (PFS)

D.4.1 Data input

Data from the LAURA trial is used to inform the extrapolation of PFS beyond the follow-up in the clinical trial.

D.4.2 Model

Standard parametric models were used to extrapolate PFS from LAURA data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal

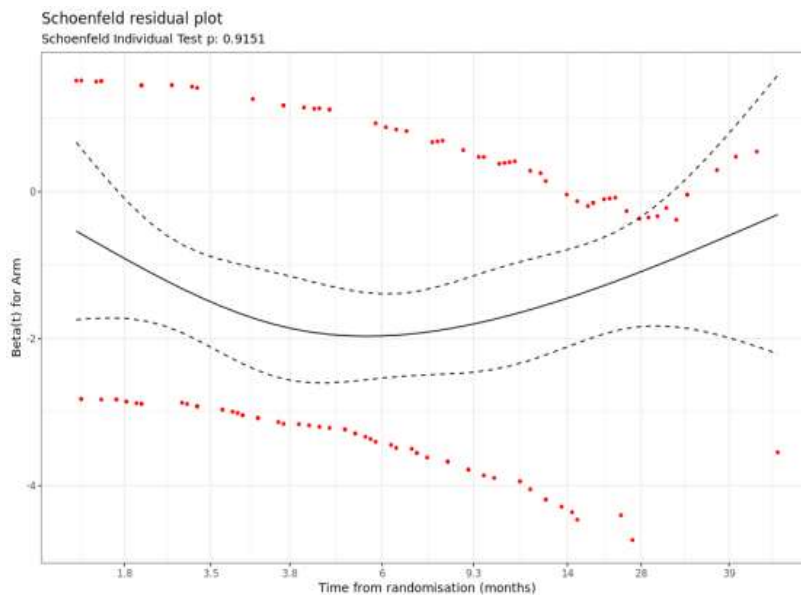


- Log-logistic
- Generalised gamma

D.4.3 Proportional hazards

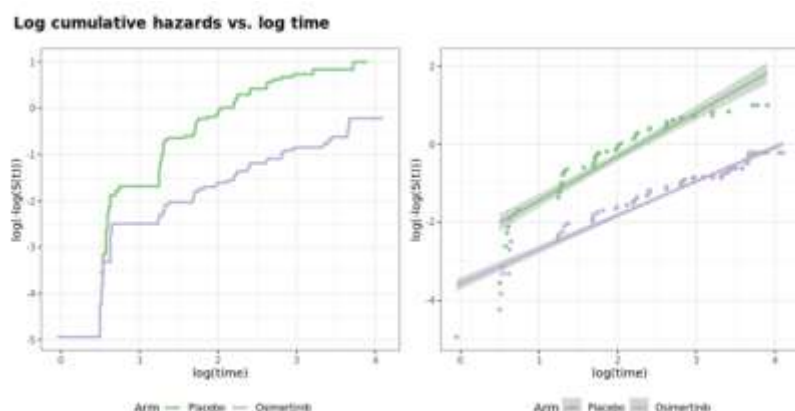
The Schoenfeld and log-cumulative hazards plots for TTP are shown in Figure 36 and Figure 37, respectively. The unadjusted G-T test result was $p=0.09151$, which fails to reject the hypothesis that the proportional hazard assumption holds. The log-hazard ratio in the Schoenfeld plot showed some evidence of non-proportional hazards, (i.e., a non-horizontal line), however there was no clear pattern or trend in the treatment effect over time. The log-cumulative hazards plot showed minor departures from PH with slight increasing separation at the tail. These results suggest that the treatment effect for osimertinib may vary over time, and hence independent models were selected for the parametric models.

Figure 36. Schoenfeld residual plot of PFS



Source: LAURA CSR addendum (date 27 Mar 2024)(58)

Figure 37. Log curves of PFS



Source: LAURA CSR addendum (date 27 Mar 2024)(58)

D.4.4 Evaluation of statistical fit (AIC and BIC)

Parametric distributions were fit independently to the osimertinib arm. The AIC and BIC statistics for each of the parametric models are presented in Table 71 and Table 72.

For both osimertinib and placebo arms, the Generalized Gamma (Gen gamma) distribution provides the best statistical fit for PFS extrapolation based on the lowest AIC and BIC values. In the osimertinib group, Gen gamma and Log-normal models are close contenders, while Gen gamma stands out as the clear best fit in the placebo group.

Table 71. AIC/BIC of PFS extrapolation for osimertinib

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gen gamma	Gamma
AIC	573.9	573.4	571.5	571.5	567.9	567	574
Rank	6	5	3	3	2	1	7
BIC	576.9	579.3	577.5	577.4	573.8	575.9	575.9
Rank	4	7	6	5	1	2	2

Note: Bold, chosen curve fit

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

Table 72. AIC/BIC of PFS extrapolation for placebo

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal	Gen-gamma	Gamma
AIC	421	423	417.8	401.6	401.8	393.2	421.4
AIC rank	6	8	5	3	4	1	7
BIC	423.3	427.5	422.3	406.1	406.4	400.1	426
BIC rank	6	8	5	3	4	1	7

Note: Bold, chosen curve fit

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; TTP: time to progression.

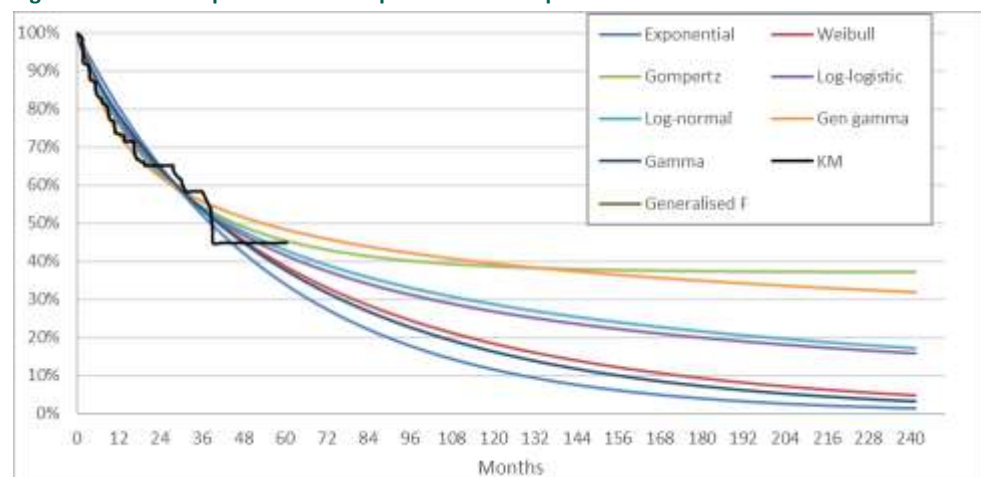
D.4.5 Evaluation of visual fit



The extrapolated PFS curves were plotted together with the KM data for osimertinib and placebo from the LAURA trial using standard parametric functions. There is some variation in long-term PFS outcomes for the osimertinib arm (Figure 38). Where, gen-gamma and Gompertz provides overly optimistic fits, while Gamma, Weibull and the exponential function provide a bit more reasonable fits.

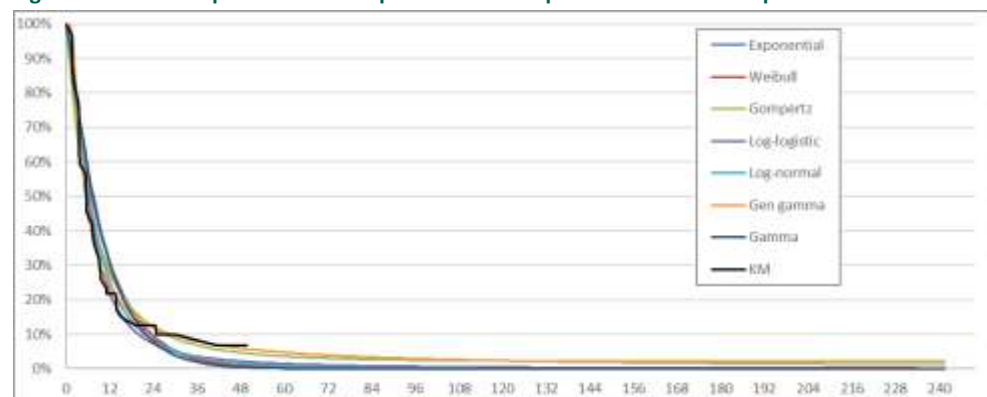
There is also slight variation in long-term PFS estimates in the placebo arm, with the distributions diverging from approximately 24 months (Figure 39). The Gen gamma and gompertz curves appears to fit the data best, and provide reasonable long-terms extrapolations than the remaining curve options.

Figure 38. Standard parametric extrapolations and Kaplan-Meier of PFS for osimertinib



Abbreviations: KM: Kaplan-Meier.

Figure 39. Standard parametric extrapolations and Kaplan-Meier of PFS for placebo



Abbreviations: KM: Kaplan-Meier.

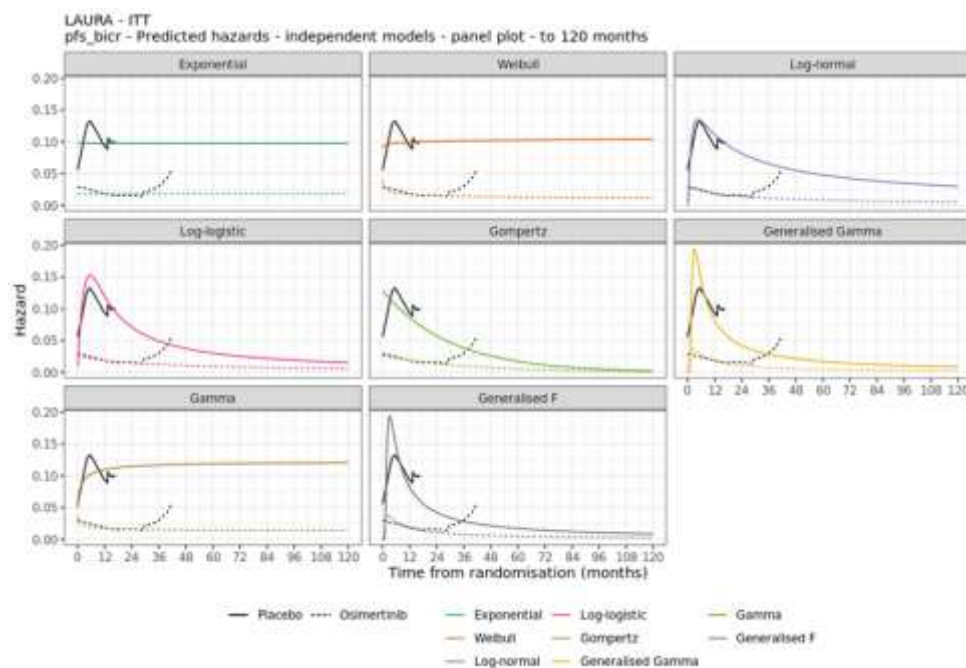
D.4.6 Evaluation of hazard functions



Figure 40 presents the combined smoothed hazard plots for all extrapolations of the osimertinib and placebo arms. For the osimertinib arm, most curves appear to predict the hazard within reason until the 30 months point, where the observed hazard increases, however, this sharp change could be attested to the low number of events at this point.

For the placebo arm, the generalized gamma function, appears to best reflect the observed hazard in the LAURA trial, with a. increasing hazard until approx. 6 months, after which the hazard gradually decreases over time.

Figure 40 Smoothed hazard plots of PFS for placebo and osimertinib



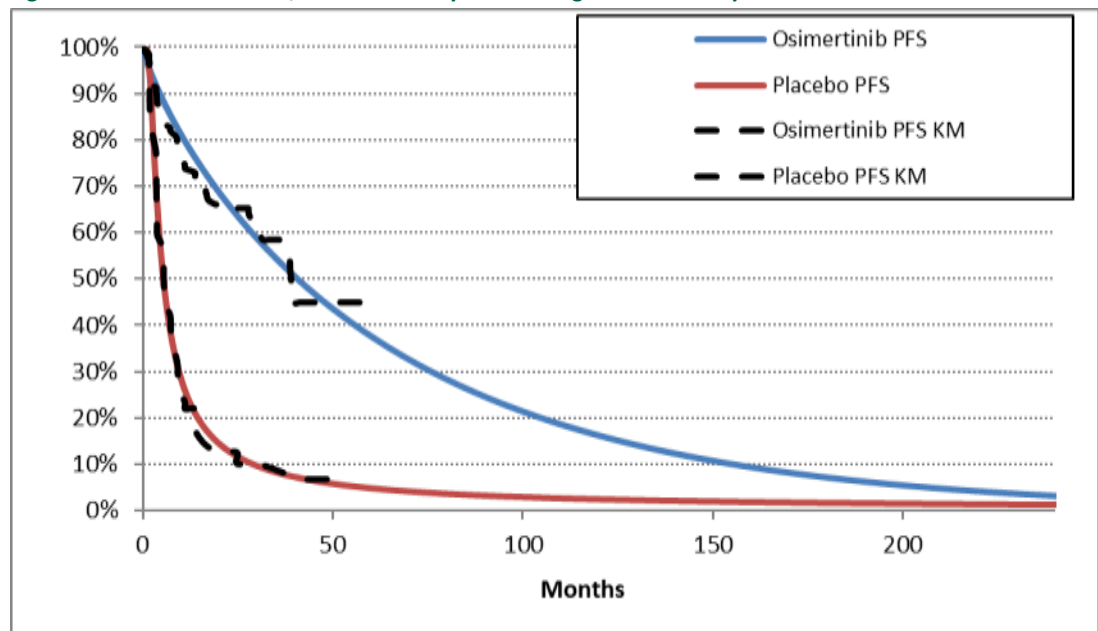
D.4.7 Validation and discussion of extrapolated curves

In the model, PFS was fitted and extrapolated using a consistent distribution with TTP (i.e. Gamma – osi; Gen gamma - placebo). For each cycle, the percentage of patients who do not progress from the previous cycle is calculated using TTP. Subtracted from this calculation is the percentage of patients who do not progress or die from the previous cycle, which is calculated using PFS. The difference between these two calculations then gives the probability of transitioning from PF to dead for each respective cycle. General population mortality is then adjusted for by setting a cap whereby if general population mortality in that cycle is greater than the calculated transition probability of pre-progression death, the model uses general population mortality to inform the transition.

The PFS parametric survival distribution selected matches the survival distribution chosen for TTP in an attempt to avoid to the logical inconsistency of the TTP and PFS curves crossing as far as possible. Hence, for extrapolation of PFS, the gamma curve have been applied for the osimertinib arm and and the gen-gamma curve for the placebo arm, in line with the extrapolation of TTP.



Figure 41. The modelled PFS, not bounded by OS or background mortality.



D.4.8 Adjustment of background mortality

N/A

D.4.9 Adjustment for treatment switching/cross-over

N/A

D.4.10 Waning effect

N/A

D.4.11 Cure-point

N/A



Appendix E. Serious adverse events

Table 73. All serious adverse events observed in LAURA (58)

System organ class / Preferred term	Osimertinib (N=143)	Placebo (N=73)
Subjects with any SAE	55 (38.5)	11 (15.1)
INFECTIONS AND INFESTATIONS	17 (11.9)	4 (5.5)
Bacterial pyelonephritis	1 (0.7)	0
Biliary tract infection	1 (0.7)	0
Bronchitis	1 (0.7)	0
COVID-19	1 (0.7)	0
Chronic hepatitis B	1 (0.7)	0
Dengue fever	1 (0.7)	0
Gastroenteritis	2 (1.4)	0
Pneumocystis jirovecii pneumonia	1 (0.7)	0
Pneumonia	7 (4.9)	3 (4.1)
Pneumonia aspiration	0	1 (1.4)
Pneumonia viral	1 (0.7)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4 (2.8)	1 (1.4)
Benign ovarian tumour	1 (0.7)	0
Bowen's disease	1 (0.7)	0
Colon cancer	0	1 (1.4)
Prostate cancer	1 (0.7)	0
Small intestine carcinoma	1 (0.7)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (1.4)	0
Anaemia	1 (0.7)	0
Thrombocytopenia	1 (0.7)	0
CARDIAC DISORDERS	3 (2.1)	1 (1.4)
Acute myocardial infarction	1 (0.7)	0
Aortic valve disease	1 (0.7)	0
Myocardial infarction	0	1 (1.4)
Myocardial ischaemia	1 (0.7)	0
VASCULAR DISORDERS	2 (1.4)	1 (1.4)
Aortic aneurysm rupture	0	1 (1.4)
Deep vein thrombosis	1 (0.7)	0



Venous thrombosis limb	1 (0.7)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (4.2)	2 (2.7)
Haemoptysis	1 (0.7)	0
Interstitial lung disease	1 (0.7)	0
Pleural effusion	1 (0.7)	1 (1.4)
Pneumonitis	2 (1.4)	0
Pneumothorax	0	1 (1.4)
Pneumothorax spontaneous	1 (0.7)	0
Pulmonary embolism	1 (0.7)	1 (1.4)
GASTROINTESTINAL DISORDERS	2 (1.4)	1 (1.4)
Large intestine polyp	1 (0.7)	0
Nausea	0	1 (1.4)
Oesophageal stenosis	1 (0.7)	0
HEPATOBIILIARY DISORDERS	1 (0.7)	0
Hepatic failure	1 (0.7)	0
RENAL AND URINARY DISORDERS	2 (1.4)	0
Prerenal failure	1 (0.7)	0
Ureterolithiasis	1 (0.7)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.7)	0
Uterine prolapse	1 (0.7)	0
NERVOUS SYSTEM DISORDERS	0	1 (1.4)
Cerebrovascular accident	0	1 (1.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (1.4)
Malaise	0	1 (1.4)
INVESTIGATIONS	1 (0.7)	0
Alanine aminotransferase increased	1 (0.7)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	19 (13.3)	2 (2.7)
Femur fracture	1 (0.7)	0
Meniscus injury	1 (0.7)	0
Radiation pneumonitis	15 (10.5)	2 (2.7)
Road traffic accident	1 (0.7)	0
Upper limb fracture	1 (0.7)	0



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 LAURA using the 5L Danish value set by Jensen CE, 2021(5).

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 LAURA study.

F.2 Background

Quality of life was assessed within LAURA using the EQ5D. The assessment schedule for EQ-5D-5L in LAURA 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 LAURA, 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 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:

1. Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.
2. Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.
3. 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.
4. Toeplitz – as above for number 2, but each visit shares the same variance.
5. 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



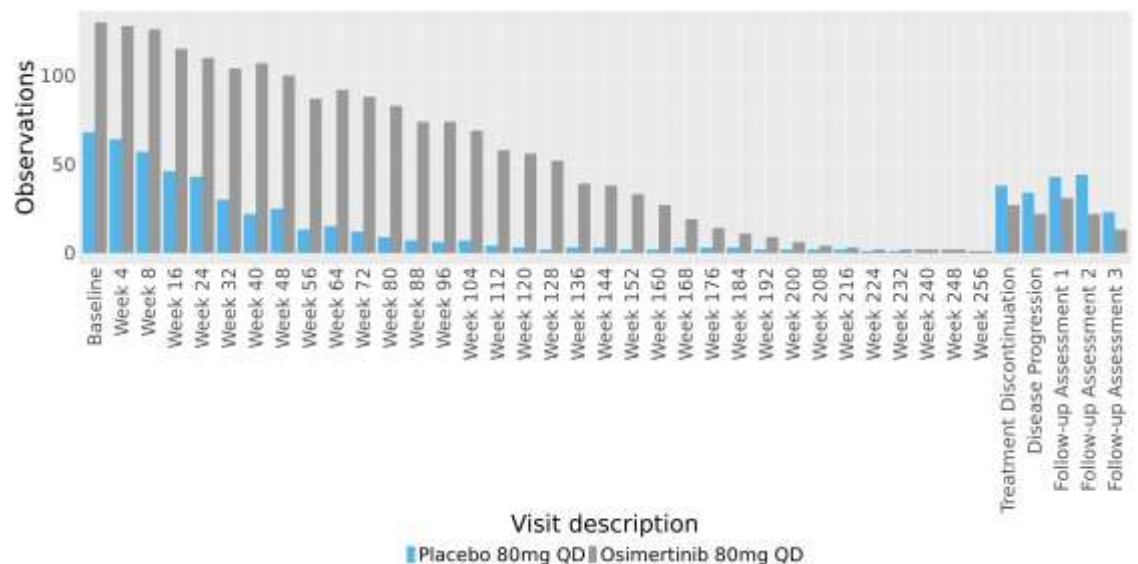
associated standard error or confidence interval can be used as utility inputs to the global cost-effectiveness model.

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 0.3.11 for model fitting.

F.4 Results - Descriptive analysis

In total, 2688 EQ-5D-5L observations from 213 patients was used in the EQ-5D-5L analysis. Of these 2688, 2253 observations were recorded pre progression and 435 were recorded Post progression. Additionally, 64 observations were recorded after censoring for progression, these observations were excluded for the analysis.





Utility summary statistics

Treatment	Scenario	Subjects	Observations	Mean (SD)	Median (IQR)	Min	Max
Placebo 80mg QD	At baseline visit	████	████	████	████	████	████
Osimertinib 80mg QD	At baseline visit	████	████	████	████	████	████
Placebo 80mg QD	All visits	████	████	████	████	████	████
Osimertinib 80mg QD	All visits	████	████	████	████	████	████
Pooled treatments	Pre progression	████	████	████	████	████	████
Pooled treatments	Post progression	████	████	████	████	████	████
Placebo 80mg QD	Pre progression	████	████	████	████	████	████
Placebo 80mg QD	Post progression	████	████	████	████	████	████
Osimertinib 80mg QD	Pre progression	████	████	████	████	████	████
Osimertinib 80mg QD	Post progression	████	████	████	████	████	████
Placebo 80mg QD	Unknown status	████	████	████	████	████	████
Osimertinib 80mg QD	Unknown status	████	████	████	████	████	████

F.5 Results - Regression analysis

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



Goodness of fit

Description	converges	AIC	BIC
Treatment	TRUE	-3531.1	-3524.4
Progression status	TRUE	-3576.9	-3570.2
Treatment + Progression status	TRUE	-3570.9	-3564.1
Treatment * Progression status	TRUE	-3574.7	-3568.0

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)	████	0.917 [SE = 0.008] (p = <0.001)	████	████
Osimertinib 80mg QD	████		████	████
Post progression		-0.072 [SE = 0.022] (p = 0.001)	████	████
Osimertinib 80mg QD: Post progression				████
AIC score	████	-3576.9	████	████

F.6.2 Marginal Means



Summary of marginal means

Parameter	Treatment	Progression status	Treatment + Progression status	Treatment * Progression status
Placebo 80mg QD	████			
Osimertinib 80mg QD	████			
Pre progression		0.917 (0.901, 0.932)		
Post progression		0.845 (0.802, 0.888)		
Placebo 80mg QD:Pre progression			████	████
Osimertinib 80mg QD:Pre progression			████	████
Placebo 80mg QD:Post progression			████	████
Osimertinib 80mg QD:Post progression			████	████
AIC score	████	-3576.9	████	████

F.7 Appendix

F.7.1 Observations per visit



Visit description	Placebo 80mg QD	Osimertinib 80mg QD
Baseline	████	████
Week 4	████	████
Week 8	████	████
Week 16	████	████
Week 24	████	████
Week 32	████	████
Week 40	████	████
Week 48	████	████
Week 56	████	████
Week 64	████	████
Week 72	████	████
Week 80	████	████
Week 88	████	████
Week 96	████	████
Week 104	████	████
Week 112	████	████
Week 120	████	████
Week 128	████	████
Week 136	████	████
Week 144	████	████
Week 152	████	████
Week 160	████	████
Week 168	████	████
Week 176	████	████
Week 184	████	████
Week 192	████	████
Week 200	████	████
Week 208	████	████
Week 216	████	████
Week 224	████	████



Week 232		
Week 240		
Week 248		
Week 256		
Treatment Discontinuation		
Disease Progression		
Follow-up Assessment 1		
Follow-up Assessment 2		
Follow-up Assessment 3		

F.8 Model fits:

F.8.1 Model terms: Treatment

Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
(Intercept)						
Osimertinib 80mg QD						

Marginal means

TRT01P	Estimate	SE	DF	95% LCL	95% UCL
Pre progression					
Post progression					

F.8.2 Model terms: Progression status

Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
(Intercept)	0.917	0.008	375.5	<0.001	0.901	0.932
Post progression	-0.072	0.022	1749.7	0.001	-0.115	-0.029



Marginal means

pffl	Estimate	SE	DF	95% LCL	95% UCL
Pre progression	0.917	0.008	375.5	0.901	0.932
Post progression	0.845	0.022	1043.2	0.802	0.888

F.8.3 Model terms: Treatment + Progression status

Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
(Intercept)	████	████	████	████	████	████
Osimertinib 80mg QD	████	████	████	████	████	████
Post progression	████	████	████	████	████	████

Marginal means

TRT01P	pffl	Estimate	SE	DF	95% LCL	95% UCL
Placebo 80mg QD	Pre progression	████	████	████	████	████
Osimertinib 80mg QD	Pre progression	████	████	████	████	████
Placebo 80mg QD	Post progression	████	████	████	████	████
Osimertinib 80mg QD	Post progression	████	████	████	████	████

F.8.4 Model terms: Treatment * Progression status



Parameter Estimates

Parameter	pffl	Estimate	SE	DF	95 % LCL	95 % UCL	pffl	Esti mate
(Intercept)	Pre progression							
Osimertinib 80mg QD	Pre progression							
Post progression	Post progression							
Osimertinib 80mg QD: Post progression	Post progression							

Marginal means

TRT01P	pffl	Estimate	SE	DF	95% LCL	95% UCL
Placebo 80mg QD	Pre progression					
Osimertinib 80mg QD	Pre progression					
Placebo 80mg QD	Post progression					
Osimertinib 80mg QD	Post progression					



Appendix G. Probabilistic sensitivity analyses

Table 74. Overview of parameters in the PSA

Input name	Mean	SE	Dist.	Alpha	Beta
Body weight (kg)	62.30	13.15	Lognormal	4.11	0.21
Height (cm)	160.80	8.27	Lognormal	5.08	0.05
Survival function [Osimertinib] TDT - Shape	0.75		Multivariate	-0.29	-0.29
Survival function [Osimertinib] TDT - Scale	0.01		Multivariate	-4.48	-4.48
Survival function [Osimertinib] TDT - Coef. 3	0.00		Multivariate	0.00	0.00
Survival function [Osimertinib] TDT - Coef. 4	0.00		Multivariate	0.00	0.00
Survival function [Osimertinib] TDT - Coef. 5	0.00		Multivariate	0.00	0.00
Survival function [Osimertinib] TDT - Treatment	0.00		Multivariate	0.00	0.00
Survival function [Placebo] TDT - Shape	0.08		Multivariate	-2.57	-2.57
Survival function [Placebo] TDT - Scale	0.00		Multivariate	0.00	0.00
Survival function [Placebo] TDT - Coef. 3	0.00		Multivariate	0.00	0.00
Survival function [Placebo] TDT - Coef. 4	0.00		Multivariate	0.00	0.00
Survival function [Placebo] TDT - Coef. 5	0.00		Multivariate	0.00	0.00
Survival function [Placebo] TDT - Treatment	0.00		Multivariate	0.00	0.00
Survival function [Osimertinib] PFS - Shape	0.82		Multivariate	-0.20	-0.20
Survival function [Osimertinib] PFS - Scale	0.01		Multivariate	-4.36	-4.36
Survival function [Osimertinib] PFS - Coef. 3	0.00		Multivariate	0.00	0.00
Survival function [Osimertinib] PFS - Coef. 4	0.00		Multivariate	0.00	0.00
Survival function [Osimertinib] PFS - Coef. 5	0.00		Multivariate	0.00	0.00
Survival function [Osimertinib] PFS - Treatment	0.00		Multivariate	0.00	0.00
Survival function [Placebo] PFS - Shape	1.31		Multivariate	1.31	1.31
Survival function [Placebo] PFS - Scale	0.74		Multivariate	-0.30	-0.30
Survival function [Placebo] PFS - Coef. 3	-1.32		Multivariate	-1.32	-1.32
Survival function [Placebo] PFS - Coef. 4	0.00		Multivariate	0.00	0.00
Survival function [Placebo] PFS - Coef. 5	0.00		Multivariate	0.00	0.00
Survival function [Placebo] PFS - Treatment	0.00		Multivariate	0.00	0.00



Survival function [Osimertinib] PF->PD - Coef. 1	0.80	Multivariate	- 0.23	- 0.23
Survival function [Osimertinib] PF->PD - Coef. 2	0.01	Multivariate	- 4.50	- 4.50
Survival function [Osimertinib] PF->PD - Coef. 3	0.00	Multivariate	0.00	0.00
Survival function [Osimertinib] PF->PD - Coef. 4	0.00	Multivariate	0.00	0.00
Survival function [Osimertinib] PF->PD - Coef. 5	0.00	Multivariate	0.00	0.00
Survival function [Osimertinib] PF->PD - Coef. Treatment	0.00	Multivariate	0.00	0.00
Survival function [Placebo] PF->PD - Coef. 1	1.28	Multivariate	1.28	1.28
Survival function [Placebo] PF->PD - Coef. 2	0.73	Multivariate	- 0.31	- 0.31
Survival function [Placebo] PF->PD - Coef. 3	-1.42	Multivariate	- 1.42	- 1.42
Survival function [Placebo] PF->PD - Coef. 4	0.00	Multivariate	0.00	0.00
Survival function [Placebo] PF->PD - Coef. 5	0.00	Multivariate	0.00	0.00
Survival function [Placebo] PF->PD - Coef. Treatment	0.00	Multivariate	0.00	0.00
Survival function [Osimertinib] PD->Death - Coef. 1	0.03	Multivariate	0.03	0.03
Survival function [Osimertinib] PD->Death - Coef. 2	0.02	Multivariate	- 4.20	- 4.20
Survival function [Osimertinib] PD->Death - Coef. 3	0.00	Multivariate	0.00	0.00
Survival function [Placebo] PD->Death - Coef. 1	0.05	Multivariate	0.05	0.05
Survival function [Placebo] PD->Death - Coef. 2	0.00	Multivariate	- 5.47	- 5.47
Survival function [Placebo] PD->Death - Coef. 3	0.00	Multivariate	0.00	0.00
Survival function [Placebo] PF->Death - Coef. 4	0.00	Multivariate	0.00	0.00
Survival function [Placebo] PF->Death - Coef. 5	0.00	Multivariate	0.00	0.00
Survival function [Placebo] PF->Death - Coef. Treatment	0.00	Multivariate	0.00	0.00
Neutropenia - Osimertinib	0.00	Beta	0.00	0.00
Neutropenia - Placebo	0.00	Beta	0.00	0.00
Thrombocytopenia - Osimertinib	0.00	Beta	0.00	0.00
Thrombocytopenia - Placebo	0.00	Beta	0.00	0.00
Decreased appetite - Osimertinib	0.00	Beta	0.00	0.00
Decreased appetite - Placebo	0.00	Beta	0.00	0.00
Acute myocardial infarction - Osimertinib	0.00	Beta	0.00	0.00
Acute myocardial infarction - Placebo	0.00	Beta	0.00	0.00
Left ventricular dysfunction - Osimertinib	0.00	Beta	0.00	0.00
Left ventricular dysfunction - Placebo	0.00	Beta	0.00	0.00



Myocarditis - Osimertinib	0.00	Beta	0.00	0.00
Myocarditis - Placebo	0.00	Beta	0.00	0.00
Deep vein thrombosis - Osimertinib	0.00	Beta	0.00	0.00
Deep vein thrombosis - Placebo	0.00	Beta	0.00	0.00
Interstitial lung disease - Osimertinib	0.00	Beta	0.00	0.00
Interstitial lung disease - Placebo	0.00	Beta	0.00	0.00
pleural effusion - Osimertinib	0.00	Beta	0.00	0.00
pleural effusion - Placebo	0.00	Beta	0.00	0.00
Pneumonitis - Osimertinib	0.01	Beta	98.5 9	695 0.41
Pneumonitis - Placebo	0.00	Beta	0.00	0.00
Pulmonary embolism - Osimertinib	0.00	Beta	0.00	0.00
Pulmonary embolism - Placebo	0.00	Beta	0.00	0.00
Diarrhoea - Osimertinib	0.01	Beta	98.5 9	695 0.41
Diarrhoea - Placebo	0.00	Beta	0.00	0.00
Hepatic failure - Osimertinib	0.00	Beta	0.00	0.00
Hepatic failure - Placebo	0.00	Beta	0.00	0.00
Dry skin - Osimertinib	0.00	Beta	0.00	0.00
Dry skin - Placebo	0.00	Beta	0.00	0.00
Rash maculo-papular - Osimertinib	0.00	Beta	0.00	0.00
Rash maculo-papular - Placebo	0.00	Beta	0.00	0.00
Asthenia - Osimertinib	0.00	Beta	0.00	0.00
Asthenia - Placebo	0.00	Beta	0.00	0.00
Alanine aminotransferase increased - Osimertinib	0.00	Beta	0.00	0.00
Alanine aminotransferase increased - Placebo	0.00	Beta	0.00	0.00
Blood creatine phosphokinase increased - Osimertinib	0.00	Beta	0.00	0.00
Blood creatine phosphokinase increased - Placebo	0.00	Beta	0.00	0.00
Electrocardiogram QT prolonged - Osimertinib	0.00	Beta	0.00	0.00
Electrocardiogram QT prolonged - Placebo	0.00	Beta	0.00	0.00
Gamma-glutamyltransferase increased - Osimertinib	0.00	Beta	0.00	0.00
Gamma-glutamyltransferase increased - Placebo	0.00	Beta	0.00	0.00
Radiation pneumonitis - Osimertinib	0.01	Beta	98.5 9	695 0.41
Radiation pneumonitis - Placebo	0.00	Beta	0.00	0.00
Anemia - Osimertinib	0.00	Beta	0.00	0.00



Anemia - Placebo	0.00		Beta	0.00	0.00
Pneumonia - Osimertinib	0.00		Beta	0.00	0.00
Pneumonia - Placebo	0.00		Beta	0.00	0.00
AE 24 - Osimertinib	0.00		Beta	0.00	0.00
AE 24 - Placebo	0.00		Beta	0.00	0.00
AE 25 - Osimertinib	0.00		Beta	0.00	0.00
AE 25 - Placebo	0.00		Beta	0.00	0.00
Cost of adverse event - Neutropenia	2208.0 0	0.00	Gamma	100. 00	22.0 8
Cost of adverse event - Thrombocytopenia	2208.0 0	0.00	Gamma	100. 00	22.0 8
Cost of adverse event - Decreased appetite	0.00	0.00	Gamma	0.00	0.00
Cost of adverse event - Acute myocardial infarction	1268.0 0	0.00	Gamma	100. 00	12.6 8
Cost of adverse event - Left ventricular dysfunction	1268.0 0	0.00	Gamma	100. 00	12.6 8
Cost of adverse event - Myocarditis	1268.0 0	0.00	Gamma	100. 00	12.6 8
Cost of adverse event - Deep vein thrombosis	1268.0 0	0.00	Gamma	100. 00	12.6 8
Cost of adverse event - Interstitial lung disease	1330.0 0	0.00	Gamma	100. 00	13.3 0
Cost of adverse event - pleural effusion	1330.0 0	0.00	Gamma	100. 00	13.3 0
Cost of adverse event - Pneumonitis	1330.0 0	0.00	Gamma	100. 00	13.3 0
Cost of adverse event - Pulmonary embolism	1330.0 0	0.00	Gamma	100. 00	13.3 0
Cost of adverse event - Diarrhoea	4977.0 0	0.00	Gamma	100. 00	49.7 7
Cost of adverse event - Hepatic failure	2072.0 0	0.00	Gamma	100. 00	20.7 2
Cost of adverse event - Radiation pneumonitis	1330.0 0	0.00	Gamma	100. 00	13.3 0
Cost of adverse event - Anemia	1330.0 0	0.00	Gamma	100. 00	13.3 0
Cost of adverse event - Pneumonia	22972. 00	0.00	Gamma	100. 00	229. 72
Disutility from adverse event - Neutropenia	0.00	0.02	Gamma	- 12.4 5	- 0.97
Disutility from adverse event - Thrombocytopenia	0.00	0.00	Gamma	- 9.74	0.00



Disutility from adverse event - Decreased appetite	0.00	0.01	Gamma	- 12.2 2	- 0.34
Disutility from adverse event - Acute myocardial infarction	0.00	0.01	Gamma	- 14.3 8	- 0.99
Disutility from adverse event - Left ventricular dysfunction	0.00	0.01	Gamma	- 14.3 8	- 0.99
Disutility from adverse event - Myocarditis	0.00	0.01	Gamma	- 14.3 8	- 0.99
Disutility from adverse event - Deep vein thrombosis	0.00	0.01	Gamma	- 15.6 2	- 1.84
Disutility from adverse event - Interstitial lung disease	0.00	0.01	Gamma	- 16.6 6	- 3.08
Disutility from adverse event - pleural effusion	0.00	0.01	Gamma	- 16.6 6	- 3.08
Disutility from adverse event - Pneumonitis	0.00	0.01	Gamma	- 16.6 6	- 3.08
Disutility from adverse event - Pulmonary embolism	0.00	0.01	Gamma	- 15.6 2	- 1.84
Disutility from adverse event - Diarrhoea	0.00	0.00	Gamma	- 6.66	0.00
Disutility from adverse event - Hepatic failure	0.00	0.00	Gamma	- 6.92	0.00
Disutility from adverse event - Dry skin	0.00	0.00	Gamma	- 9.33	0.00
Disutility from adverse event - Rash maculo-papular	0.00	0.00	Gamma	- 9.33	0.00
Disutility from adverse event - Asthenia	0.00	0.00	Gamma	- 8.52	0.00
Disutility from adverse event - Alanine aminotransferase increased	0.00	0.00	Gamma	- 8.88	0.00
Disutility from adverse event - Blood creatine phosphokinase increased	0.00	0.00	Gamma	- 8.88	0.00
Disutility from adverse event - Electrocardiogram QT prolonged	0.00	0.00	Gamma	- 8.88	0.00
Disutility from adverse event - Gamma-glutamyltransferase increased	0.00	0.00	Gamma	- 8.88	0.00
Disutility from adverse event - Radiation pneumonitis	0.00	0.00	Gamma	- 10.7 3	0.00



Disutility from adverse event - Anemia	0.00	0.02	Gamma	- 8.52	0.00
Disutility from adverse event - Pneumonia	0.00	0.02	Gamma	- 8.52	0.00
Duration of adverse event - Neutropenia	14.66	0.00	Gamma	2.68	0.15
Duration of adverse event - Thrombocytopenia	14.66	0.00	Gamma	2.68	0.15
Duration of adverse event - Decreased appetite	14.66	0.00	Gamma	2.68	0.15
Duration of adverse event - Acute myocardial infarction	14.00	0.00	Gamma	2.63	0.14
Duration of adverse event - Left ventricular dysfunction	14.00	0.00	Gamma	2.63	0.14
Duration of adverse event - Myocarditis	14.00	0.00	Gamma	2.63	0.14
Duration of adverse event - Deep vein thrombosis	30.00	0.00	Gamma	3.40	0.30
Duration of adverse event - Interstitial lung disease	14.66	0.00	Gamma	2.68	0.15
Duration of adverse event - pleural effusion	14.66	0.00	Gamma	2.68	0.15
Duration of adverse event - Pneumonitis	14.66	0.00	Gamma	2.68	0.15
Duration of adverse event - Pulmonary embolism	30.00	0.00	Gamma	3.40	0.30
Duration of adverse event - Diarrhoea	5.53	0.00	Gamma	1.71	0.06
Duration of adverse event - Hepatic failure	14.66	0.00	Gamma	2.68	0.15
Duration of adverse event - Dry skin	14.66	0.00	Lognormal	2.68	0.15
Duration of adverse event - Rash maculo-papular	14.66	0.00	Lognormal	2.68	0.15
Duration of adverse event - Asthenia	23.78	0.00	Lognormal	3.16	0.24
Duration of adverse event - Alanine aminotransferase increased	14.66	0.00	Lognormal	2.68	0.15
Duration of adverse event - Blood creatine phosphokinase increased	14.66	0.00	Lognormal	2.68	0.15
Duration of adverse event - Electrocardiogram QT prolonged	14.66	0.00	Lognormal	2.68	0.15
Duration of adverse event - Gamma-glutamyltransferase increased	14.66	0.00	Lognormal	2.68	0.15
Duration of adverse event - Radiation pneumonitis	14.66	0.00	Lognormal	2.68	0.15
Duration of adverse event - Anemia	7.00	0.00	Lognormal	1.94	0.07
Duration of adverse event - Pneumonia	7.00	0.00	Lognormal	1.94	0.07
Health state utilities - Progression-free	0.92	0.01	Beta	108 9.61	98.6 2
Health state utilities - Progressed disease	0.85	0.02	Beta	227. 82	41.7 9
Progression-free - Resource usage per cycle - Outpatient oncologist visit: year 1	0.33	0.00	Gamma	100. 00	0.00



Progression-free - Resource usage per cycle - Outpatient oncologist visit: year 2	0.33	0.00	Gamma	100. 00	0.00
Progression-free - Resource usage per cycle - Outpatient oncologist visit: year 3+	0.16	0.00	Gamma	100. 00	0.00
Progression-free - Resource usage per cycle - Chest X-ray: year 1	0.16	0.00	Gamma	100. 00	0.00
Progression-free - Resource usage per cycle - Chest X-ray: year 2	0.16	0.00	Gamma	100. 00	0.00
Progression-free - Resource usage per cycle - Chest X-ray: year 3+	0.16	0.00	Gamma	100. 00	0.00
Progression-free - Resource usage per cycle - CT scan (chest): year 1	0.33	0.00	Gamma	100. 00	0.00
Progression-free - Resource usage per cycle - CT scan (chest): year 2	0.33	0.00	Gamma	100. 00	0.00
Progression-free - Resource usage per cycle - CT scan (chest): year 3+	0.16	0.00	Gamma	100. 00	0.00
Progression-free - Unit cost (DKK) - Outpatient oncologist visit: year 1	1330.0 0	0.00	Gamma	100. 00	13.3 0
Progression-free - Unit cost (DKK) - Outpatient oncologist visit: year 2	1330.0 0	0.00	Gamma	100. 00	13.3 0
Progression-free - Unit cost (DKK) - Outpatient oncologist visit: year 3+	1330.0 0	0.00	Gamma	100. 00	13.3 0
Progression-free - Unit cost (DKK) - Chest X-ray: year 1	1731.0 0	0.00	Gamma	100. 00	17.3 1
Progression-free - Unit cost (DKK) - Chest X-ray: year 2	1731.0 0	0.00	Gamma	100. 00	17.3 1
Progression-free - Unit cost (DKK) - Chest X-ray: year 3+	1731.0 0	0.00	Gamma	100. 00	17.3 1
Progression-free - Unit cost (DKK) - CT scan (chest): year 1	2701.0 0	0.00	Gamma	100. 00	27.0 1
Progression-free - Unit cost (DKK) - CT scan (chest): year 2	2701.0 0	0.00	Gamma	100. 00	27.0 1
Progression-free - Unit cost (DKK) - CT scan (chest): year 3+	2701.0 0	0.00	Gamma	100. 00	27.0 1
Progression-free - Unit cost (DKK) - CT scan (other)	2701.0 0	0.00	Gamma	100. 00	27.0 1
Progression-free - Average length of a visit - Outpatient oncologist visit: year 1	2.00	0.00	Gamma	100. 00	0.02
Progression-free - Average length of a visit - Outpatient oncologist visit: year 2	2.00	0.00	Gamma	100. 00	0.02
Progression-free - Average length of a visit - Outpatient oncologist visit: year 3+	2.00	0.00	Gamma	100. 00	0.02
Progression-free - Average length of a visit - Chest X-ray: year 1	2.00	0.00	Gamma	100. 00	0.02
Progression-free - Average length of a visit - Chest X-ray: year 2	2.00	0.00	Gamma	100. 00	0.02



Progression-free - Average length of a visit - Chest X-ray: year 3+	2.00	0.00	Gamma	100.00	0.02
Progression-free - Average length of a visit - CT scan (chest): year 1	2.00	0.00	Gamma	100.00	0.02
Progression-free - Average length of a visit - CT scan (chest): year 2	2.00	0.00	Gamma	100.00	0.02
Progression-free - Average length of a visit - CT scan (chest): year 3+	2.00	0.00	Gamma	100.00	0.02
Progression-free - Average length of a visit - CT scan (other)	2.00	0.00	Gamma	100.00	0.02
Progressed disease - Resource usage per year - Outpatient oncologist visit	0.33	0.00	Gamma	100.00	0.00
Progressed disease - Resource usage per year - Chest X-ray	0.08	0.00	Gamma	100.00	0.00
Progressed disease - Resource usage per year - CT scan (chest)	0.33	0.00	Gamma	100.00	0.00
Progressed disease - Resource usage per year - CT scan (other)	0.08	0.00	Gamma	100.00	0.00
Progressed disease - Unit cost (DKK) - Outpatient oncologist visit	1330.00	0.00	Gamma	100.00	13.30
Progressed disease - Unit cost (DKK) - Chest X-ray	1731.00	0.00	Gamma	100.00	17.31
Progressed disease - Unit cost (DKK) - CT scan (chest)	2701.00	0.00	Gamma	100.00	27.01
Progressed disease - Unit cost (DKK) - CT scan (other)	2401.00	0.00	Gamma	100.00	24.01
Progressed disease - Average length of a visit - Outpatient oncologist visit	2.00	0.00	Gamma	100.00	0.02
Progressed disease - Average length of a visit - Chest X-ray	2.00	0.00	Gamma	100.00	0.02
Progressed disease - Average length of a visit - CT scan (chest)	2.00	0.00	Gamma	100.00	0.02
Progressed disease - Average length of a visit - CT scan (other)	2.00	0.00	Gamma	100.00	0.02
Progressed disease - Average length of a visit - ECG	0.00	0.00	Gamma	0.00	0.00
Progressed disease - Average length of a visit - Community nurse visit	0.00	0.00	Gamma	0.00	0.00
Progressed disease - Average length of a visit - Clinical nurse specialist	0.00	0.00	Gamma	0.00	0.00
Progressed disease - Average length of a visit - GP visit	0.00	0.00	Gamma	0.00	0.00
Administration costs - Osimertinib	0.00	0.00	Gamma	0.00	0.00
Administration costs - Placebo	0.00		Gamma	0.00	0.00
Administration costs - Societal cost per 30 days (DKK) , Osimertinib	0.00		Gamma	0.00	0.00



Administration costs - Societal cost per 30 days (DKK) , Placebo	0.00		Gamma	0.00	0.00
Administration costs - Societal cost per 30 days (DKK) , Docetaxel	737.14		Gamma	100.00	7.37
Administration costs - Societal cost per 30 days (DKK) , Etoposide	670.00		Gamma	100.00	6.70
Administration costs - Societal cost per 30 days (DKK) , Gemcitabine	452.14		Gamma	100.00	4.52
Administration costs - Societal cost per 30 days (DKK) , Paclitaxel	1274.29		Gamma	100.00	12.74
Administration costs - Societal cost per 30 days (DKK) , Pemetrexed	513.33		Gamma	100.00	5.13
Administration costs - Societal cost per 30 days (DKK) , Vinorelbine	0.00		Gamma	0.00	0.00
Administration costs - Societal cost per 30 days (DKK) , Cisplatin	1005.71		Gamma	100.00	10.06
Administration costs - Societal cost per 30 days (DKK) , Carboplatin (AUC5)	636.43		Gamma	100.00	6.36
Administration costs - Societal cost per 30 days (DKK) , Osimertinib	0.00		Gamma	0.00	0.00
Administration costs - Societal cost per 30 days (DKK) , Radiotherapy	2960.00		Gamma	100.00	29.60
Administration costs - Societal cost per 30 days (DKK) , Atezolizumab	602.86		Gamma	100.00	6.03
Administration costs - Societal cost per 30 days (DKK) , Nivolumab	904.29		Gamma	100.00	9.04
Administration costs - Societal cost per 30 days (DKK) , Bevacizumab	602.86		Gamma	100.00	6.03
Administration costs - Societal cost per 30 days (DKK) , Afatinib	0.00		Gamma	0.00	0.00
Administration costs - Societal cost per 30 days (DKK) , Erlotinib	0.00		Gamma	0.00	0.00
Administration costs - Societal cost per 30 days (DKK) , Gefitinib	0.00		Gamma	0.00	0.00
Sub tx Duration (number of 30-day cycle) - Docetaxel	3.04	0.00	Lognormal	1.11	0.03
Sub tx Duration (number of 30-day cycle) - Etoposide	0.70	0.00	Lognormal	-0.36	0.01
Sub tx Duration (number of 30-day cycle) - Gemcitabine	0.70	0.00	Lognormal	-0.36	0.01
Sub tx Duration (number of 30-day cycle) - Paclitaxel	3.04	0.00	Lognormal	1.11	0.03
Sub tx Duration (number of 30-day cycle) - Pemetrexed	4.26	0.00	Lognormal	1.44	0.04
Sub tx Duration (number of 30-day cycle) - Vinorelbine	0.70	0.00	Lognormal	-0.36	0.01



Sub tx Duration (number of 30-day cycle) - Cisplatin	2.23	0.00	Lognormal	0.80	0.02
Sub tx Duration (number of 30-day cycle) - Carboplatin (AUC5)	2.23	0.00	Lognormal	0.80	0.02
Sub tx Duration (number of 30-day cycle) - Osimertinib (osi naïve patients)	29.34	0.00	Lognormal	3.37	0.29
Sub tx Duration (number of 30-day cycle) - Radiotherapy	1.00	0.00	Lognormal	0.00	0.01
Sub tx Duration (number of 30-day cycle) - Atezolizumab	8.32	0.00	Lognormal	2.11	0.08
Sub tx Duration (number of 30-day cycle) - Nivolumab	8.32	0.00	Lognormal	2.11	0.08
Sub tx Duration (number of 30-day cycle) - Bevacizumab	8.32	0.00	Lognormal	2.11	0.08
Sub tx Duration (number of 30-day cycle) - Afatinib	6.80	0.00	Lognormal	1.91	0.07
Sub tx Duration (number of 30-day cycle) - Erlotinib	13.90	0.00	Lognormal	2.63	0.14
Sub tx Duration (number of 30-day cycle) - Gefitinib	11.67	0.00	Lognormal	2.45	0.12
Sub tx Duration (number of 30-day cycle) - Sub_tx_17	0.00	0.00	Lognormal	0.00	0.00
Sub tx Duration (number of 30-day cycle) - Sub_tx_18	0.00	0.00	Lognormal	0.00	0.00
Sub tx Duration (number of 30-day cycle) - Osimertinib (patients with prior exposure to osi)	8.73	0.00	Lognormal	2.16	0.09
Cost of subsequent treatment (per 30 days) - Docetaxel	2250.00	0.00	Gamma	100.00	22.50
Cost of subsequent treatment (per 30 days) - Etoposide	2613.70	0.00	Gamma	100.00	26.14
Cost of subsequent treatment (per 30 days) - Gemcitabine	1837.50	0.00	Gamma	100.00	18.38
Cost of subsequent treatment (per 30 days) - Paclitaxel	2187.86	0.00	Gamma	100.00	21.88
Cost of subsequent treatment (per 30 days) - Pemetrexed	3320.71	0.00	Gamma	100.00	33.21
Cost of subsequent treatment (per 30 days) - Vinorelbine	5303.57	0.00	Gamma	100.00	53.04
Cost of subsequent treatment (per 30 days) - Cisplatin	2328.57	0.00	Gamma	100.00	23.29
Cost of subsequent treatment (per 30 days) - Carboplatin (AUC5)	2545.71	0.00	Gamma	100.00	25.46
Cost of subsequent treatment (per 30 days) - Osimertinib	38585.29	0.00	Gamma	100.00	385.85
Cost of subsequent treatment (per 30 days) - Radiotherapy	31521.00	0.00	Gamma	100.00	315.21



Cost of subsequent treatment (per 30 days) - Atezolizumab	43260.91	Gamma	100.00	432.61
Cost of subsequent treatment (per 30 days) - Nivolumab	46686.71	Gamma	100.00	466.87
Cost of subsequent treatment (per 30 days) - Bevacizumab	15437.64	Gamma	100.00	154.38
Cost of subsequent treatment (per 30 days) - Afatinib	0.00	Gamma	0.00	0.00
Cost of subsequent treatment (per 30 days) - Erlotinib	10007.14	Gamma	100.00	100.07
Cost of subsequent treatment (per 30 days) - Gefitinib	5587.50	Gamma	100.00	55.88
Proportion of receiving subsequent treatment Osimertinib 2L	1.00	Beta	-1.00	0.00
Proportion of receiving subsequent treatment Placebo 2L	1.00	Beta	-1.00	0.00
Proportion of receiving subsequent treatment Osimertinib 3L	1.00	Beta	-1.00	0.00
Proportion of receiving subsequent treatment Placebo 3L	1.00	Beta	-1.00	0.00
Proportion from osimertinib to Pemetrexed 2L	0.90	Dirichlet	0.83	100.00
Proportion from osimertinib to Carboplatin (AUC5) 2L	0.90	Dirichlet	0.82	100.00
Proportion from osimertinib to Osimertinib (patients with prior exposure to osi) 2L	0.10	Dirichlet	0.10	100.00
Proportion from Placebo to Osimertinib (osi naïve patients) 2L	1.00	Dirichlet	0.91	100.00
Proportion from osimertinib to Pemetrexed 3L	0.00	Dirichlet	0.00	0.00
Proportion from osimertinib to Cisplatin 3L	0.00	Dirichlet	0.00	0.00
Proportion from osimertinib to Carboplatin (AUC5) 3L	0.00	Dirichlet	0.00	0.00
Proportion from osimertinib to Osimertinib (patients with prior exposure to osi) 3L	0.00	Dirichlet	0.00	0.00
Proportion from Placebo to Pemetrexed 3L	0.90	Dirichlet	0.89	100.00
Proportion from Placebo to Cisplatin 3L	0.00	Dirichlet	0.00	0.00
Proportion from Placebo to Carboplatin (AUC5) 3L	0.90	Dirichlet	0.94	100.00
Proportion from Placebo to Osimertinib (patients with prior exposure to osi) 3L	0.10	Dirichlet	0.09	100.00



Appendix H. Literature searches for the clinical assessment

Not applicable.



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

I.1 Health-related quality-of-life search

N/A, no literature search 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, no literature search conducted for input to HE model.



Appendix K. Proportional hazards plots for PFS and OS.

K.1 PFS

The Schoenfeld residual plot, log cumulative hazards, log odds and log normal versus log time plots for PFS are shown below.

Figure 42. Schoenfeld residual plot for PFS BICR(68)

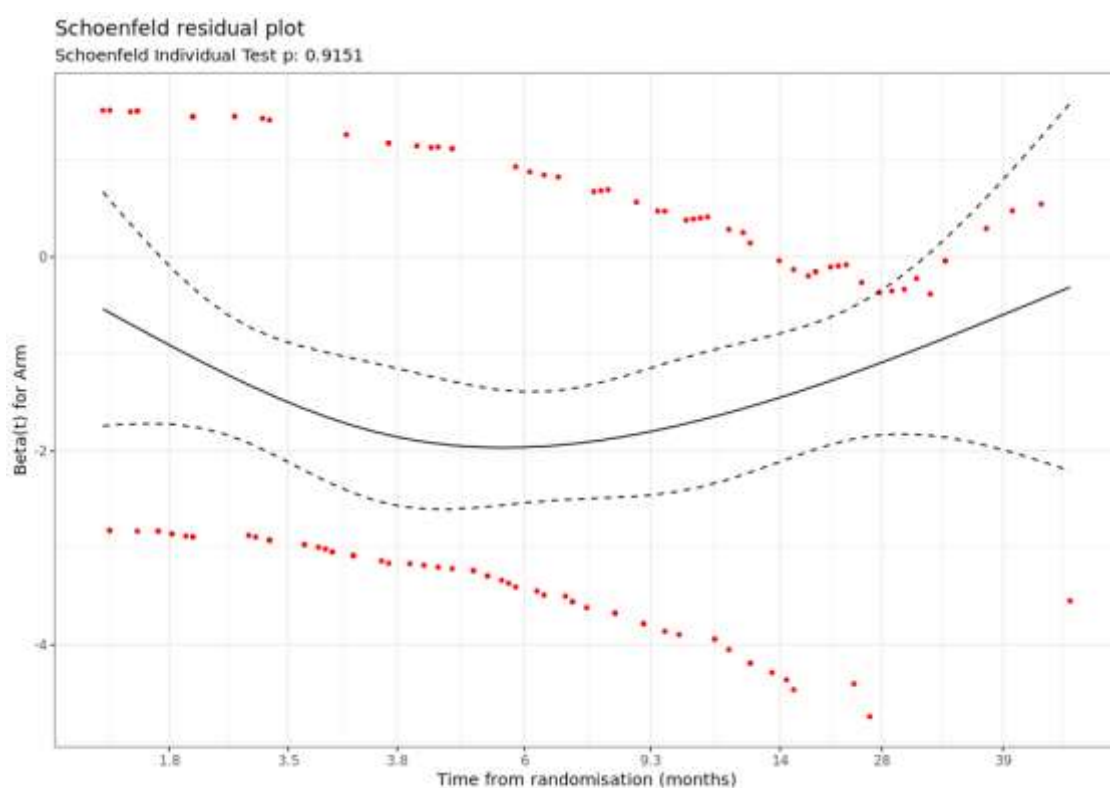
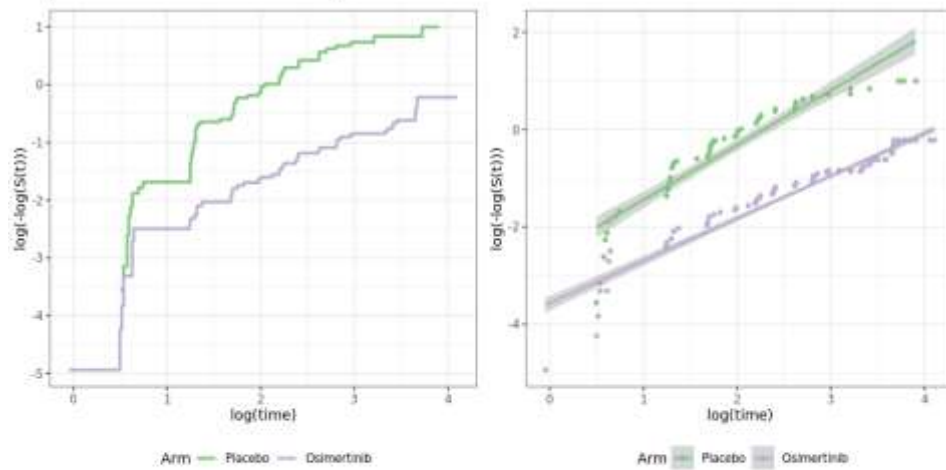


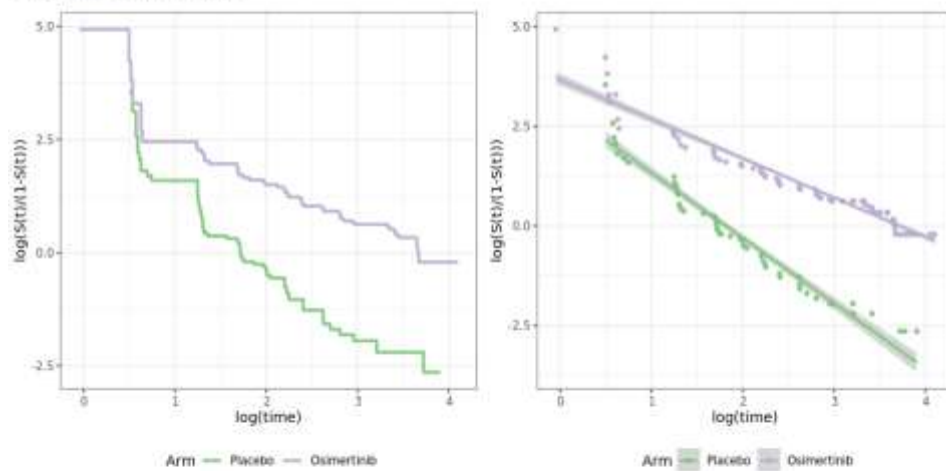


Figure 43. Log cumulative, Log odds and log normal plots for PFS(68)

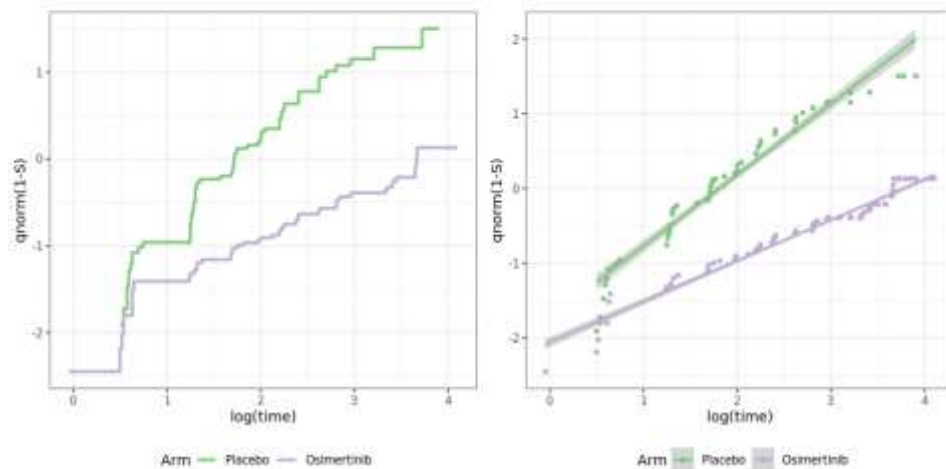
Log cumulative hazards vs. log time



Log odds vs. log time



Log normal vs. log time





K.2 OS

The Schoenfeld residual plot, log cumulative hazards, log odds and log normal versus log time plots for OS are shown below.

Figure 44. Schoenfeld residual plot for OS(68)

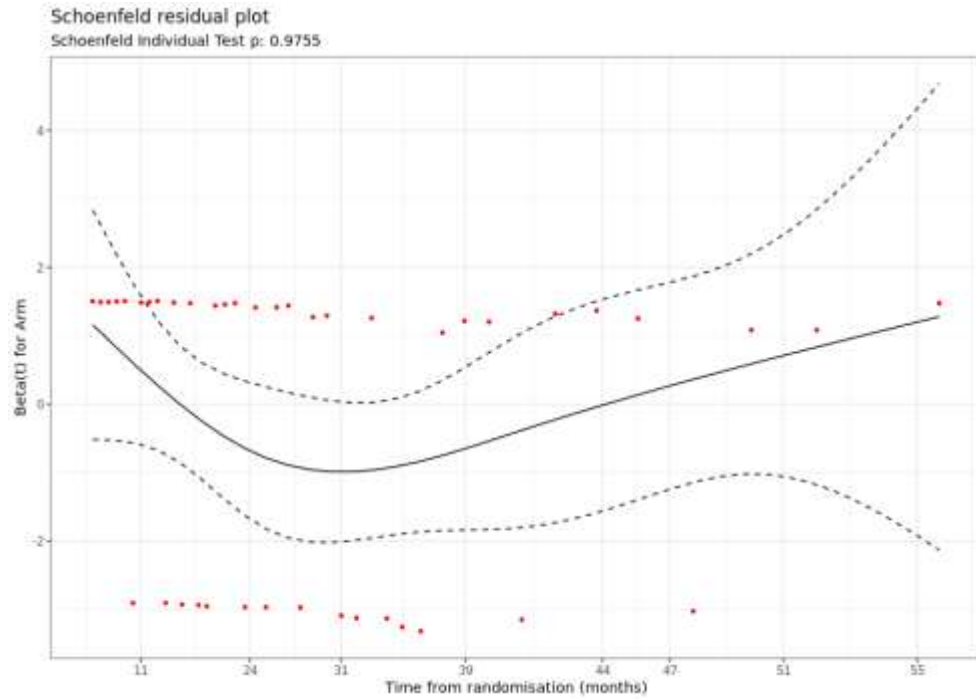
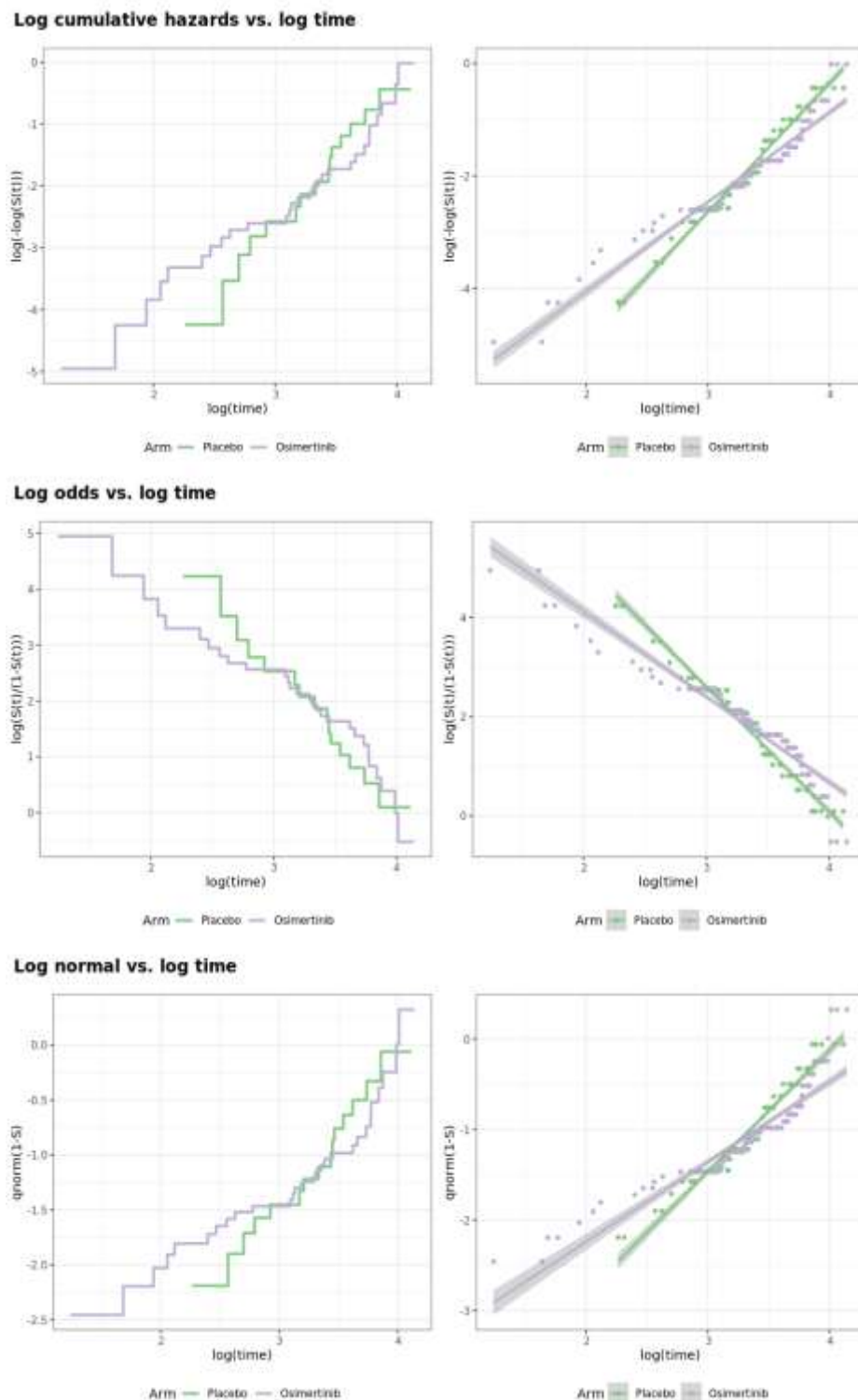




Figure 45. Log cumulative, Log odds and log normal plots for OS(68)



K.3 CNS-PFS



The log cumulative hazards, log odds and log normal versus log time plots are shown below.

Figure 46. Schoenfeld residual plot for CNS-PFS(68)

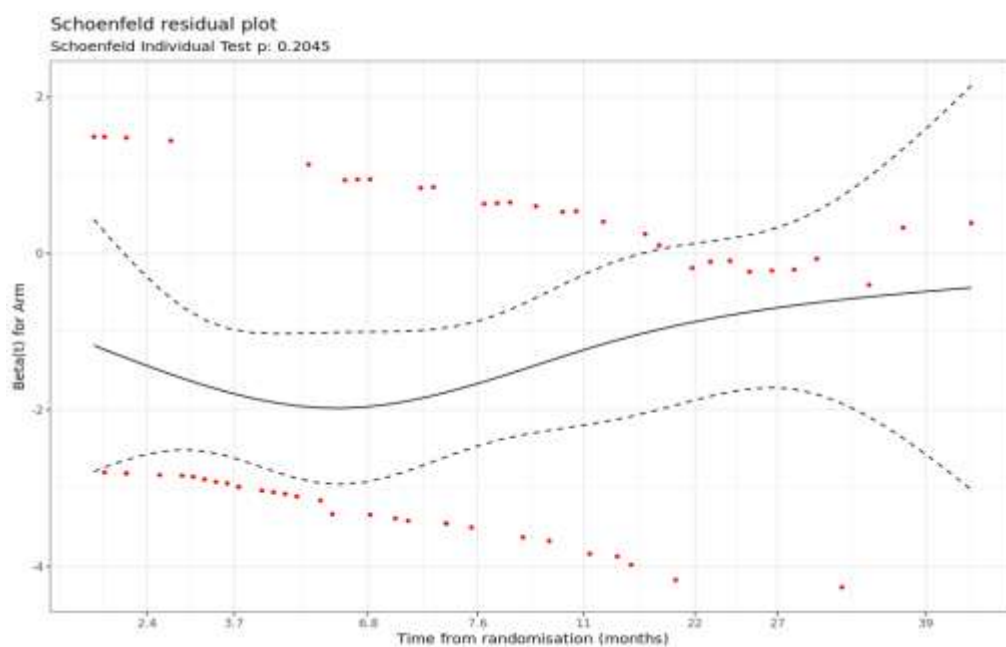
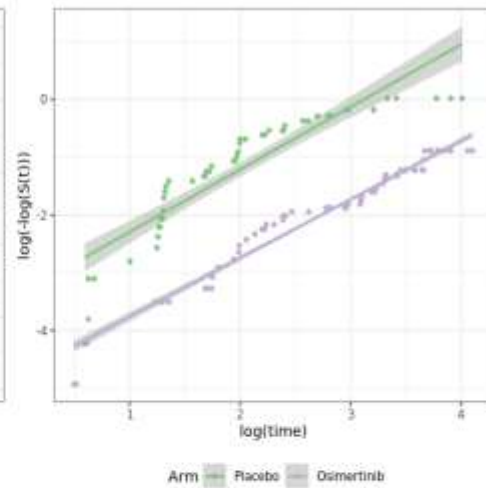
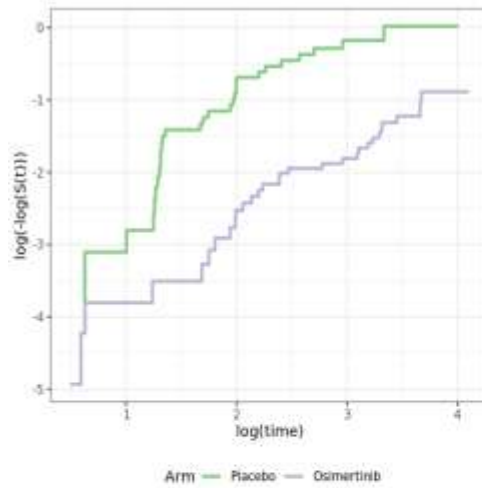


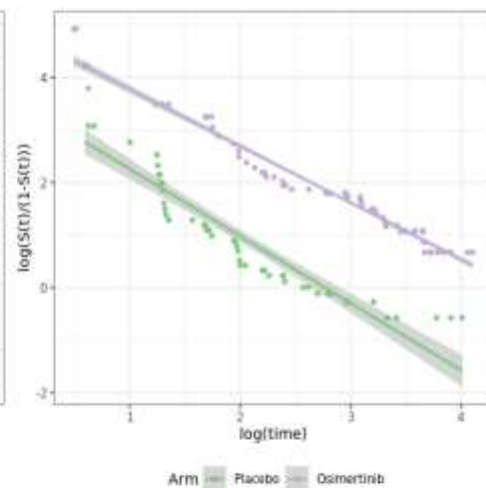
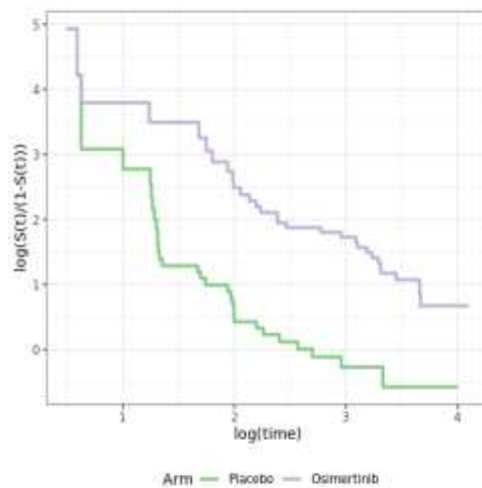


Figure 47 Log cumulative, Log odds and log normal plots for CNS-PFS(68)

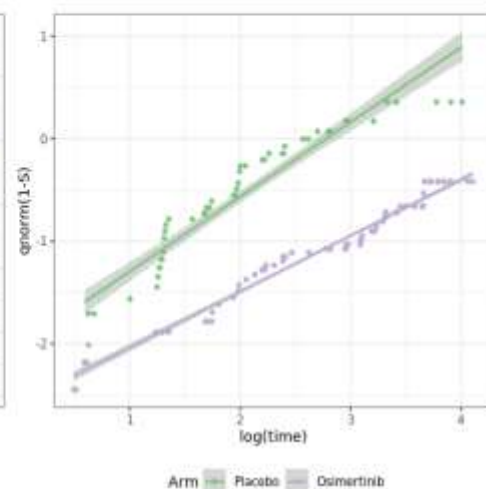
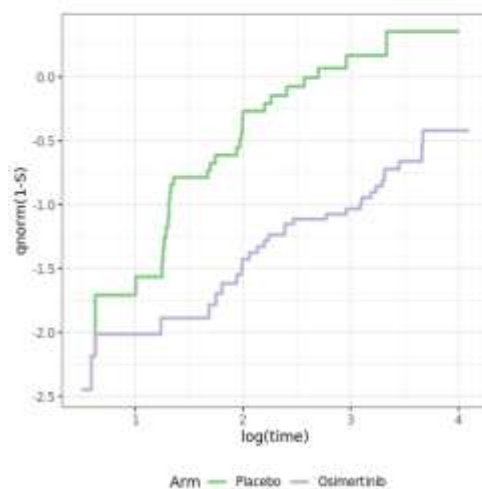
Log cumulative hazards vs. log time



Log odds vs. log time



Log normal vs. log time





Appendix L. Subsequent treatment distribution in LAURA

Table 75. Subsequent anti-cancer therapies observed in the LAURA trial for DCO 05 Jan 2024 and DCO 29 Nov 2024.

	DCO 05 January 2024		DCO 29 November 2024	
	Number (%) of patients ^a			
	Osimertinib	Placebo	Osimertinib	Placebo
	(N = 143)	(N = 73)	(N = 143)	(N = 73)
Discontinued randomized study treatment	63 (44.1)	66 (90.4)	74 (51.7)	69 (94.5)
Any post-treatment anti-cancer therapy	42 (29.4)	57 (78.1)	54 (37.8)	60 (82.2)
No post-treatment anti-cancer therapy	21 (14.7)	9 (12.3)	20 (14.0)	9 (12.3)
Ongoing randomized study treatment	80 (55.9)	7 (9.6)	69 (48.3)	4 (5.5)
Types of post-treatment anticancer therapy received (in any line)				
EGFR-TKI	28 (19.6) [44.4]	57 (78.1) [86.4]	37 (25.9) [50.0]	60 (82.2) [87.0]
First or second-generation EGFR-TKI	12 (8.4) [19.0]	7 (9.6) [10.6]	13 (9.1) [17.6]	8 (11.0) [11.6]
Third generation EGFR-TKI	16 (11.2) [25.4]	52 (71.2) [78.8]	24 (16.8) [32.4]	55 (75.3) [79.7]
Osimertinib ^a	15 (10.5) [23.8]	51 (69.9) [77.3]	22 (15.4) [29.7]	54 (74.0) [78.3]
EGFR and MET inhibitor – Monoclonal antibody	0	0	1 (0.7) [1.4]	0
Cytotoxic chemotherapy	21 (14.7) [33.3]	11 (15.1) [16.7]	28 (19.6) [37.8]	15 (20.5) [21.7]
Platinum compounds ^b	19 (13.3) [30.2]	7 (9.6) [10.6]	25 (17.5) [33.8]	11 (15.1) [15.9]
VEGF Inhibitor – Monoclonal antibody	8 (5.6) [12.7]	5 (6.8) [7.6]	10 (7.0) [13.5]	7 (9.6) [10.1]
PD-1/PD-L1 inhibitor - Immunotherapy	5 (3.5) [7.9]	1 (1.4) [1.5]	6 (4.2) [8.1]	1 (1.4) [1.4]
Other	2 (1.4) [3.2]	2 (2.7) [3.0]	2 (1.4) [2.7]	2 (2.7) [2.9]
Radiotherapy	21 (14.7) [33.3]	5 (6.8) [7.6]	28 (19.6) [37.8]	7 (9.6) [10.1]

The number of subjects is shown with percentages (%) calculated as the proportion of subjects in the FAS and [%] as the proportion of subjects who discontinued randomised study treatment



Subjects may be counted in multiple rows if they received more than one ant-cancer therapy or a combination therapy which contains drug substances from multiple classifications

Legend: a Note other 3rd generation EGFR-TKIs were also reported, full list in source IEMT; b Note other chemotherapy agents were also reported, full list in source IEMT

Table 76. First and Second Post-treatment Disease-related Anticancer Therapy (FAS). DCO 05 January 2024.

	Number (%) of patients ^a	
	Osimertinib	Placebo
	(N = 143)	(N = 73)
Discontinued randomised study treatment	63 (44.1)	66 (90.4)
<i>Received first post-treatment anticancer therapy</i>		
Yes	42 (29.4)	57 (78.1)
No	21 (14.7)	9 (12.3)
<i>Types of first post-treatment disease-related anticancer therapy received</i>		
EGFR-TKI	22 (15.4) [34.9]	56 (76.7) [84.8]
First or second-generation EGFR-TKI	7 (4.9) [11.1]	5 (6.8) [7.6]
Third generation EGFR-TKI	15 (10.5) [23.8]	51 (69.9) [77.3]
Osimertinib	14 (9.8) [22.2]	50 (68.5) [75.8]
Aumolertinib	1 (0.7) [1.6]	1 (1.4) [1.5]
Radiotherapy	17 (11.9) [27.0]	5 (6.8) [7.6]
Cytotoxic chemotherapy	16 (11.2) [25.4]	3 (4.1) [4.5]
Platinum compounds	14 (9.8) [22.2]	2 (2.7) [3.0]
Folic acid analogues (pemetrexed)	9 (6.3) [14.3]	2 (2.7) [3.0]
Taxanes	5 (3.5) [7.9]	2 (2.7) [3.0]
Other ^b	3 (2.1) [4.8]	0
VEGF Inhibitor – Monoclonal antibody	5 (3.5) [7.9]	1 (1.4) [1.5]
PD-1/PD-L1 inhibitor - Immunotherapy	4 (2.8) [6.3]	0
Other	2 (1.4) [3.2]	0
<i>Received second post-treatment disease-related anticancer therapy</i>		
Yes	14 (9.8)	14 (19.2)



No (received only one post-treatment anticancer therapy)	28 (19.6)	43 (58.9)
--	-----------	-----------

Types of second post-treatment anticancer therapy received

Cytotoxic chemotherapy	8 (5.6) [12.7]	8 (11.0) [12.1]
Platinum compounds	5 (3.5) [7.9]	5 (6.8) [7.6]
Folic acid analogues (pemetrexed)	4 (2.8) [6.3]	3 (4.1) [4.5]
Taxanes	4 (2.8) [6.3]	3 (4.1) [4.5]
Other ^c	0	2 (2.7) [3.0]
EGFR-TKI	3 (2.1) [4.8]	5 (6.8) [7.6]
First or second-generation EGFR-TKI	2 (1.4) [3.2]	2 (2.7) [3.0]
Third generation EGFR-TKI	1 (0.7) [1.6]	3 (4.1) [4.5]
Osimertinib	1 (0.7) [1.6]	2 (2.7) [3.0]
Furmonertinib	0	1 (1.4) [1.5]
VEGF Inhibitor	3 (2.1) [4.8]	3 (4.1) [4.5]
PD-1/PD-L1 inhibitor - Immunotherapy	2 (1.4) [3.2]	0
Radiotherapy	4 (2.8) [6.3]	0
Other	0	2 (2.7) [3.0]

^a The number of patients is shown with percentages (%) calculated as the proportion of patients in the FAS and secondly [%] as the proportion of patients who discontinued randomised study treatment.

^b Includes pyrimidine analogues and vinca alkaloids and analogues.

^c Includes podophyllotoxin derivatives and pyrimidine analogues.

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. The second post-treatment anticancer therapy is the second treatment started on or after the last dose date of randomised study treatment.

Note: Per protocol, open-label osimertinib treatment was not to be a second line post-treatment therapy; however, it is included in the count of therapies when determining the second line post-treatment therapy. WHO Drug Dictionary version September 2022 format B3. A subsequent medical review has taken place to assign treatment classifications.



DCO: 05 January 2024

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