Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende 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

Vers. 2.0

Bilagsoversigt

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

Medicinrådet
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Re: Assessment report for osimertinib (Tagrisso) for adjuvant treatment of adult patients with early-stage (IB, II, IIIA) EGFR mutated (EGFRm) non-small cell lung cancer (NSCLC) after tumour resection with curative intent

Firstly, we would like to thank you for reassessing the recommendation of osimertinib in adjuvant NSCLC as standard of care in Denmark. In the first assessment which was submitted in August 2021, Medicinrådet did not recommend osimertinib as standard of care in this setting mainly due to immature data. In this resubmission AstraZeneca have provided the latest data cuts which include final disease-free survival (DFS) update and 5-year significant overall survival (OS) data. The last data cuts were consistent with the substantial efficacy that was observed in the primary analysis (DCO January 2020) **which also led to positive recommendations and access in all the Nordic countries (except Denmark) and most European Countries. With this reassessment we hope that patients in Denmark also will have access to the same treatment in this setting.**

Survival data (OS)
In the assessment report it is mentioned that Medicinrådet is not unequivocally convinced that survival is significantly better in the osimertinib arm despite the median DFS being 65.8 months (95% CI 61.7; NC) in osimertinib arm compared to 28.1 months (95% CI 22.1; 35.0) in placebo arm with a HR of 0.27 (95% CI 0.21; 0.34)[1]. The main arguments from Medicinrådet are that the 5-year OS is not yet mature, due to relatively few events/lack of median OS. Further that not all the patients in the placebo arm are treated optimally compared to Danish clinical practice, as not all eligible patients progressing to more advanced disease received osimertinib.

- Regarding the maturity of OS data in the ADAURA trial, it is firstly important to bear in mind that to reach median OS in this setting the expected follow up would need to be more than 10 years. Given the consistent and strong results seen at every data read-out in ADAURA, we do not find it appropriate or considerate for Danish patients to wait more than 10 years for access to the best treatment in the curative setting. Treating these patients in the curative intent setting will keep them disease free as long as possible, which is in line with treatment intent also in Danish clinical practice.
- The reason why patients in the placebo arm were not offered osimertinib upon progression was because it was not yet the established standard of care in the first-line advanced setting at the beginning of the trial. Medicinrådet suggests that the placebo arm is underperforming as not all eligible patients were treated with osimertinib upon progression, thereby indirectly making the osimertinib arm overperform compared to the effect expected to be seen in Danish clinical practice once osimertinib is introduced as standard of care. However, we do not agree with this line of reasoning. Data in the latest report from the Danish lung cancer registry, which were cited in the AZ reimbursement submission, estimate the 5-year survival rate for disease stages IB, IIA, IIB and IIIC to be 59, 59, 55 and 53 % respectively,[2] while in ADAURA the 5-year survival rates in the placebo arm for stages IB, II and IIIC are 88, 78 and 67 % respectively.[3] This clearly indicates that the placebo arm did not underperform when comparing to the latest Danish data.

[1] Herbst et al. J Clin Oncol;41(10):1830-1840.
[2] Dansk Lunge Cancer Register Årsrapport 2022 (Table 8.2.1.4). https://www.lungecancer.dk/wp-content/uploads/2023/06/Årsrapport-2022-DLCR-offentlig.pdf
[3] Tsuboi et al. N Engl J Med. 2023;389(2):137-14

- Secondly, we do not find it realistic for Medicinrådet to assume that the increase in DFS with osimertinib will not lead to more patients being cured and that once patients in the osimertinib arm have disease recurrence they will all progress quicker than in the comparator arm. It should be clearly stated in the assessment report what kind of evidence/source this assumption is based on, especially when choosing a very pessimistic scenario for extrapolation as a base case/main analysis given that the trial data points towards a completely different scenario being more likely.

The sensitivity analysis that Medicinrådet have also included in their assessment report acknowledges a cure and survival benefit from keeping more patient's disease free for longer. This analysis is also more in-line with prior assessments from other countries, for instance the assessment made by the HTA body in Norway, which found ADAURA to be much more cost-effective than in Medicinrådets assessment report (ICER of 179 000 – 581 000 NOK/QALY in different scenarios based on public list price)[4] which also led to a recommendation in 2022.

To summarise, the main issue with the health economic evaluation is that it is very cautious and conservative in its assumptions. We think that Medicinrådets extrapolation of disease-free survival is clinically implausible since it implies that there is very little long-term benefit of osimertinib beyond what has already been observed in the trial. We think this is clinically implausible as the overall survival advantage for osimertinib is statistically significant (OS HR 0.49; 95% CI 0.34 to 0.70; 2-sided p<0.001)[3] with the current maturity of the data and with a separation between the OS curves that is increasing over time.In the ADAURA trial, the safety and tolerability profile of osimertinib is consistent with what have been observed previously. Most adverse events were nonserious, and there was no evidence of late-emergent adverse events with continued treatment during the three-year period.[5] It is therefore surprising to see Medicinrådet highlighting that some patients are expected to be "affected by adverse events without having any clinical benefit". With this statement we assume that Medicinrådet is referring to the 30% of Danish patients that do not have a recurrence after resection. However, today there is no ideal way to predict which patients will be among the 30%, and osimertinib has demonstrated benefits in all stages (IB-IIIA NSCLC).[1,3]
We hope that with this reassessment with more mature data confirming the overwhelming efficacy observed in the data cut in the first assessment done by Medicinrådet in 2021-22 **osimertinib will now also be available to the estimated 24 Danish patients like it is in 24 other European Countries:**

1. Norway
2. Sweden
3. Finland
4. Iceland
5. UK
6. Germany
7. Poland
8. Lithuania
9. Estonia
10. Czech Republic
11. Netherlands
12. France
13. Spain
14. Portugal
15. Switzerland
16. Italy
17. Austria
18. Croatia
19. Slovenia
20. Hungary
21. Romania
22. Greece
23. Bulgaria
24. Ireland

Kind regards,
Mattias Ekman, Health Economic Scientific Lead
Anni Thomsen, Medical Advisor
Bianca Kennedy Hall, Market Access Manager

[4] https://www.dmp.no/globalassets/documents/Offentlig-finansiering-og-pris/Metodevurderinger/T/Tagrisso_monoterapi--NSCLC--subgruppe_2022.pdf
[5] John et al. J Thorac Oncol.;18(9):1209-1221.

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24.04.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	22.05.2024
Leverandør	AstraZeneca
Lægemiddel	Tagrisso (osimertinib)
Ansøgt indikation	Til adjuverende behandling af EGFR-muteret ikke-småcellet lungekræft
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Tagrisso (osimertinib):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP, (DKK)	SAIP (DKK) pr. 01.05.2024	Betinget pristilbud	Rabatprocent ift. AIP
Tagrisso	40 mg	30 stk.	38.585,29	[redacted]	[redacted]	[redacted]	[redacted]
Tagrisso	80 mg	30 stk.	38.585,29	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

Tagrisso indgår i udbuddet på lægemidler indenfor EGFR-muteret ikke-småcellet lungekræft. Den nye aftale starter den 01.05.2024.

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på adjuverende behandling af EGFR-muteret ikke-småcellet lungekræft. Tagrisso er førstevalg i lægemiddelrekommandationen til behandling af patienter med aktiverende EGFR-mutation. [redacted]

Tabel 1: Lægemiddeludgift pr. patient for et års behandling

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Tagrisso	80 mg	30 stk.	80 mg dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Medicinrådet

Application for the assessment of Tagrisso (osimertinib) for adjuvant treatment of adult patients with early-stage (IB, II, IIIA) EGFRmutated (EGFRm) non-small cell lung cancer (NSCLC) after tumour resection with curative intent.

Submitted by AstraZeneca August 30th 2021.
1st validation received from DMC February 4th 2022

Revised by AstraZeneca 17th March 2022
Revised by AstraZeneca 2nd May 2022

Resubmission accepted by DMC 14th June 2023
New application submitted 30th August 2023

1st validation questions received 11th Oct 2023
Revised and resubmitted by AstraZeneca 26th Oct 2023

2nd validation questions received 8th Nov 2023
Revised and resubmitted by AstraZeneca 24th Nov 2023

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Tagrisso
Generic name	Osimertinib

Overview of the pharmaceutical	
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sverige
ATC code	L01EB04
Pharmacotherapeutic group	EGFR-TKI
Active substance(s)	Osimertinib
Pharmaceutical form(s)	Tablets. 40 or 80 mg in packs of 30 tablets
Mechanism of action	Osimertinib is a third-generation, active EGFR-TKI that selectively inhibits both EGFR-TKI sensitizing and EGFR T790M-resistance mutations.
Dosage regimen	80 mg once daily. Can be reduced to 40 mg. Treatment is until progression in 1st and 2nd line. In the adjuvant setting treatment until progression or maximum 3 years
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	TAGRISSO as monotherapy is indicated for: • the adjuvant treatment of adult patients with early-stage (IB, II, IIIA) EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) after tumour resection with curative intent.
Other approved therapeutic indications	TAGRISSO as monotherapy is indicated for: • the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations. • the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.
Will dispensing be restricted to hospitals?	Yes, labelled BEGR
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Packs of 30 tablets. Strengths 40 and 80 mg
Orphan drug designation	No

2. Abbrevations

Abbreviation	Explanation
AE	Adverse Event
ALT	Alanine amino transferase

Abbreviation	Explanation
aNSCLC	Advanced Non-Small Cell Lung Cancer
AURA2	AURA phase II single arm clinical trial
AURA3	AURA phase III randomised controlled trial
AZ9291	Osimertinib
BBB	Blood-Brain Barrier
BICR	Blinded Independent Central Review
CI	Confidence Interval
CNS	Central Nervous system
CR	Complete Response
CT	Computerised Tomography
ctDNA	Circulating tumour DNA
DCR	Disease Control Rate
DCO	Data Cut-Off
DoR	Duration of Response
EGFR	Epidermal Growth Factor Receptor
EGFRm	Epidermal Growth Factor Receptor mutation
EGFR-TKI	Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor
EORTC QLQ-C30/LC13	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
Ex19del	Exon 19 deletion
Ex20	Exon 20
FAS	Full Analysis Set
FLAURA	FLAURA phase III randomised controlled trial
FLAURA DCO1	FLAURA Data Cut-Off 1 (12th June 2017)
FLAURA DCO2	FLAURA Data Cut-Off 2 September 2019
HER	Human Epidermal growth factor Receptor
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IRC	Independent Review Committee
ITC	Indirect comparison
ITT	Intend to Treat

Abbreviation	Explanation
IQR	Interquartile range
KM	Kaplan-Meier
L858R	A common EGFR point mutation
mPFS	Median PFS
NSCLC	Non-Small Cell Lung Cancer
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDC	Platinum Doublet Chemotherapy
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PFS2	Second Progression-Free Survival
PR	Partial Response
PRO(s)	Patient-Reported Outcome(s)
PSA	Probabilistic Sensitivity Analysis
QoL	Quality of Life
RECIST	Response evaluation Criteria in Solid Tumours
SAE(s)	Serious Adverse Event(s)
SD	Standard Deviation
SoC	Standard of Care
TDT	Time to Discontinuation of Treatment
TFST	Time to First Subsequent Therapy or death
TSST	Time to Second Subsequent Therapy or death
TKI	Tyrosine Kinase Inhibitor

Text, tables and figures marked yellow should be treated confidential

3. Tables and Figures

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4. Summary

4.1 Application and data update

In Aug 2021, AstraZeneca submitted the first application (QALY) for adjuvant treatment of early EGFR-positive NSCLC based on 3 year DFS and immature OS data. The OS data was immature since the ADAURA study was unblinded two years early, following a recommendation from an Independent Data Monitoring Committee (IDMC) that determined that the overwhelming efficacy demonstrated that osimertinib has a positive benefit-risk profile for the treatment of patients with stage IB–IIIA EGFRm NSCLC who have undergone complete tumour resection (with or without adjuvant chemotherapy) at the primary and subsequent updated DFS analyses. Our original application containing this data reached Day 0 on May 2nd 2022 and on 26th October 2022 the Danish Medicines Council (DMC) did not recommend osimertinib in this setting mainly due to immature OS data.

At ASCO 2023 updated (5 years) and significant OS data was presented and simultaneously published in the New England Journal of Medicine. Based on these more mature OS data plus the final DFS update, AstraZeneca submitted a request for a reevaluation to the DMC. The request was accepted on June 14th 2023 and we now present to you this updated data, including an updated cost per QALY analysis. For consistency, we have used the "old" template for this application, as agreed with the DMC, since we have submitted before the deadline of August 31st 2023.

In the current application, we have updated both the medical and health economic part of the application with the new data released in May 23, and include new data from three additional publications. Consistent with the overwhelming efficacy observed at the primary analysis (DCO 17th January 2020), in the updated DFS analysis (DCO 11th April 2022), ADAURA demonstrated a clinically significant 77% reduction in the risk of disease recurrence or death for patients with stage II–IIIA disease treated with osimertinib, compared with patients randomised to placebo (HR 0.23; 95% CI 0.18, 0.30; 2-sided p<0.0001). Similarly, in the overall population, a clinically significant 73% reduction in the risk of disease recurrence or death was observed for patients in the overall population randomised to osimertinib compared with patients randomised to placebo (HR 0.27; 95% CI 0.21, 0.34; 2-sided p<0.0001). The increased data

maturity at the updated DFS analysis and the magnitude of treatment benefit for patients in the osimertinib arm in both the stage II–IIIA and overall populations, in combination with continuing narrow CIs of the HR, provides further confidence that these results are a reliable estimate of treatment benefit. A clinically meaningful DFS benefit of osimertinib was also consistently observed in all pre-specified subgroups with sufficient events for analysis.

OS is a secondary outcome in ADAURA and immature OS data was the key issue raised by DMC in the 2022 rejection. Updated OS data was presented and published in May this year. Among patients with stage II to IIIA disease, the 5-year OS showed a significant and mature result (overall HR for death, 0.49; 95.03% CI 0.33, 0.73; p<0.001). In the overall population (stage IB-IIIA), the 5-year OS result was HR= 0.49; 95.03% CI, 0.34, 0.70; p<0.001.

HRQoL was maintained in both study arms, with more than 75% of stage II–IIIA patients not experiencing a clinically meaningful deterioration in the physical and mental components of the SF-36 or death. This is of particular importance considering the negative impact of alternative treatment options on patients' HRQoL. Furthermore, at the updated DFS analysis, an exploratory analysis of CNS recurrences demonstrated a clinically meaningful 76% and 64% reduction in the risk of CNS disease recurrence or death in the osimertinib arm compared to placebo for both stage II–IIIA patients (HR 0.24; 95% CI 0.14, 0.42; p<0.0001) and the overall population (HR 0.36; 95% CI 0.23, 0.57; p<0.0001), respectively; as CNS recurrence is known to have a detrimental impact on patients' quality of life, these data support the further positive benefit of osimertinib in this treatment setting beyond DFS alone.

There were no clinically significant changes in safety observed from the primary analysis (DCO 17th January 2020) to the updated DFS analysis (DCO 11th April 2022). Osimertinib was shown to be generally well-tolerated, with the majority of AEs non-serious, mild or moderate in severity, and not resulting in treatment discontinuation. From ADAURA, it can be concluded that osimertinib has an acceptable safety and tolerability profile for treating patients with EGFRm NSCLC in the adjuvant setting, consistent with previous clinical studies and post-marketing experience in the advanced and metastatic settings. (1-3)

Overall, the benefit-risk balance for the long-term use (36-month treatment duration) of osimertinib in patients in the curative setting is positive, and it is anticipated that osimertinib will provide a substantial advancement in the clinical management of stage IB–IIIA EGFRm NSCLC.

AstraZeneca believe that the updated and mature data will answer the questions and uncertainty that was raised by DMC based on the primary analysis in the 2021 Application.

4.2 Indication and intervention

Osimertinib is a third-generation tyrosine kinase inhibitor (TKI), which acts as an irreversible inhibitor of EGFR sensitising mutations.(4). Osimertinib selectively and irreversibly inhibits *EGFR* mutations including Ex19del, the L858R point mutation in exon 21, and T790M, which makes osimertinib structurally and pharmacologically distinct from first- and second-generation TKIs.(5) Inhibition of EGFR signalling by osimertinib prevents downstream oncogenic consequences such as cell proliferation, angiogenesis and cell survival. Compared with first- and second-generation EGFR TKIs, emerging data indicates that osimertinib is able to cross both the intact and compromised blood brain barrier.(4, 6) This is further supported by clinical trial data from FLAURA, a Phase III RCT comparing osimertinib with gefitinib or erlotinib EGFR-TKIs, which reported that CNS progression was observed in 17 patients (6%) in the osimertinib group and 42 (15%) in the standard EGFR-TKI group, therefore illustrating the CNS efficacy of osimertinib.(7)

The EMA approved indications:

- First-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations.
- Treatment of adult patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC
- Adjuvant treatment of adult patients with early-stage (IB, II and IIIA) epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) after complete tumour resection with curative intent. Osimertinib is indicated for EGFRm patients whose tumours have exon 19 deletions or exon 21 (L858R) mutations.

The adjuvant indication was granted on May 28th 2021 and is the background for this updated application to DMC.

4.3 Summary of clinical outcome in the ADAURA study

The ADAURA study, is a Phase III, double-blind, randomised, placebo-controlled, multicentre trial, which enrolled 682 patients. ADAURA examines the efficacy and safety of osimertinib vs placebo, in patients with EGFRm stage IB–IIIA NSCLC (according to the AJCC 7th edition), following complete tumour resection with or without adjuvant chemotherapy.(8) The first subject was enrolled on 21st October 2015. The updated DFS analyses provided are based on a data cut-off date of 11th April 2022 and database lock date of 24th June 2020. The OS analyses presented here are based on a data cut-off date of 27th January 2023, updated since our previous application in Aug 2021. The study is still ongoing, at the time of DCO. In ADAURA, treatment is until progression or maximum 3 years.

At data cut-off of 11th April 2022, in stage II-IIIA disease, median follow-up was 44.2 months with osimertinib and 19.6 months with placebo. The primary endpoint of ADAURA, DFS in patients with stage II–IIIA disease, showed a statistically significant and clinically meaningful 77% reduction in the risk of disease recurrence or death for patients randomised to osimertinib, compared with patients randomised to placebo. HR 0.23 (95 % CI 0.18; 0.30) ; p<0.001).(2, 5). Furthermore, in the overall population (stage IB–IIIA patients), a statistically significant and clinically meaningful 73% reduction in the risk of disease recurrence or death was observed for patients treated with osimertinib vs. placebo HR=0.27 (95% CI 0.21; 0.34; p<0.0001). 4-year DFS rate was 73% with osimertinib and 38% with placebo.(4, 5) Fewer patients treated with osimertinib had local/regional and distant recurrence versus placebo. Distant metastasis was the most frequent site in the overall population of both osimertinib and placebo. In the osimertinib arm 13.3% of patients experienced a distant metastasis compared to 32.2% in the placebo arm of overall population. Additionally, the CNS DFS HR in stage II-IIIA was 0.24 (95% CI 0.14; 0.42).(2).
Osimertinib is the first targeted agent to provide a significant DFS benefit by keeping patients in the curative intent setting for longer.

OS was the secondary endpoint of the ADAURA trial, which had immature data at previous DCOs. At the 5 years DCO 18.2 % maturity was reached for the overall population and 21.3% for stage II-IIIA with a follow-up period of 59.9 months for the osimertinib arm and 56.2 months for the placebo group. Median OS was not reached for osimertinib or the placebo arm. In the stage II and IIIA patient-population there was a statistical significant difference between the two patient-groups with a HR of 0.49 (95.03% CI 0.33, 0.73; p<0.001). In the overall population there was a significant difference in survival with a HR of 0.49 (95.03% CI 0.34, 0.70; p<0.001) favoring osimertinib to the placebo arm. All patients had completed study treatment at the time of previous DCO in Apr 2022.(9)

These data underscore that ADAURA is the first global phase III study to demonstrate statistically significant DFS that translates to unprecedented OS benefit in patients with EGFR-mutated stage IB-IIIA NSCLC.

At the final analysis of DFS data, all patients had completed or discontinued study treatment. Among the 680 patients included in the safety analysis set (337 in the osimertinib group; 343 in the placebo group), adverse events (AEs any grade) were reported in 330 patients (98%) in the osimertinib group and 309 patients (90%) in the placebo group. Grade 3 or higher was reported in 79 patients (23%) and 48 patients (14%), respectively. Serious adverse events (SAEs) were reported in 68 patients (20%) in the osimertinib group and 47 patients (14%) in the placebo group. Fatal adverse events were reported in 1 patient in the osimertinib group and 2 patients in the placebo group, but were not considered by the investigator to be causally related to the study drug. (2, 9)

The updated safety report was published by John et al in the Journal of Thoracic Oncology (JTHO) in May 2023 and concluded that no new safety signals were reported and HRQoL was maintained with 3 years of adjuvant osimertinib treatment.(3)

4.4 Comparator

The comparator in ADAURA is placebo with or without chemotherapy. The choice to use or not use chemotherapy in the ADAURA study was based on investigator and patient choice. Around 60 % of patients in the ADAURA trial had received adjuvant chemotherapy before randomization, lower in stage IB and higher in stage II and III.

The median number of adjuvant chemotherapy cycles received was 4 in stage IB and stage II-IIIA patient populations in both treatment arms, which is in line with the maximum allowed number of treatment cycles per protocol.

In the period between the rejection from DMC and this resubmission no new treatment in this clinical setting has been recommended by DMC or included in Danish guidelines and placebo +/- chemotherapy is still the most relevant comparator. Following the introduction of adjuvant chemotherapy 17 years ago, there have been no new adjuvant treatment options for patients with early stage, resectable NSCLC.(10) Danish guidelines state that adjuvant therapy should be considered for all patients with stage II–IIIA NSCLC with negative surgical margins (no residual traces of tumour [R0]).(11) Patients with stage IB can be eligible for adjuvant treatment if the size of the tumor is >4 cm.(12) In Denmark, the adjuvant treatment should consist of four series of platinum based doublet treatment and should be initiated within 6-8 weeks after surgery. The Danish national guidelines list cisplatin and vinorelbine as the adjuvant chemotherapeutics.(11) Current guidelines do not include targeted treatments. Due to the availability of a direct comparative study, we have not performed a systematic literature search(SLR).

4.5 Summary of health economic analysis

For the health economic analysis of osimertinib, a cost-utility analysis was performed, comparing osimertinib with active monitoring. The outcomes of the analysis were incremental costs per quality adjusted life year (QALY), and life year (LY) gained. Both the quality of life and life span are of interest as EGFR-mutated NSCLC in stage IB-IIIA in the adjuvant setting is associated with relatively short survival. Hence, additional lifetime spent with the best possible health-related quality of life (HRQoL) was considered as relevant.
The base-case analysis includes both direct treatment and healthcare utilization costs as well as indirect costs associated with treatment in accordance with the extended health service perspective.

A previously developed semi-Markov model was adapted to the Danish setting and used to perform the cost-effectiveness analysis. Key model inputs: the efficacy of the comparators, total drug use, adverse events, and utilities were sourced from ADAURA, FLAURA, CancerLinQ, background mortality, and validated by Danish clinical experts. (4, 5) Costs and healthcare resource use were estimated from public sources and published literature. (55-57, 67) Incremental cost-effectiveness ratios (ICERs) were assessed for life-years (LY) gained and quality-adjusted life years

(QALYs) gained. The ICER for adjuvant use of osimertinib was 375 810 DKK per QALY gained. In comparison to active monitoring, osimertinib was found to be cost effective in Denmark, with incremental cost of 338 900 DKK and incremental QALY of 0.90 QALYs as well as 1.10 life years gained. In addition, both deterministic and probabilistic sensitivity analyses were conducted. The tornado diagram from the one way deterministic sensitivity analysis (OWSA) showed the acquisition cost of osimertinib in the disease-free health state had the largest impact on the ICER followed by the utility value for patients treated with osimertinib in the same health state. The cost effectiveness acceptability curve from the probabilistic sensitivity analysis showed that osimertinib had a 64% probability of being cost-effective at a willingness-to-pay of 700 000 DKK per QALY gained. The budget impact in year 5 after introduction of osimertinib in the adjuvant NSCLC setting was estimated to be DKK 16 million.

4.6 Overall conclusion

ADAURA is a randomised, double-blinded, global, placebo-controlled phase III trial in the adjuvant treatment of 682 patients with Stage IB, II, IIIA EGFRm NSCLC with complete tumour resection and optional, standard post-operative adjuvant chemotherapy. In the experimental arm, patients were treated with Tagrisso 80mg once-daily oral tablets for three years or until disease recurrence. The trial enrolled patients in more than 200 centres across more than 20 countries, including the US, Europe, South America, Asia and the Middle East. The primary endpoint is DFS and data readout was originally anticipated in 2022. However, in 2020, the overwhelming efficacy observed in ADAURA led to a recommendation from an Independent Data Monitoring Committee (IDMC) to unblind ADAURA, two years earlier than planned. AstraZeneca submitted an application to the DMC in 2021 with the results from the primary analysis. OS is a secondary outcome in ADAURA and immature OS data was the key issue raised by DMC in the 2022 rejection.

Since then, additional data have been released and three new major publications has been published, which we present here. We include 4 years DFS data that confirm findings from the primary analysis and more mature OS data that show significant benefit of osimertinib vs. placebo. Long-term adjuvant treatment of TKIs are different from the long-standing short duration adjuvant chemotherapy treatment and the longer duration of treatment needs to be balanced against tolerability and maintained HRQoL(SF-36). Long-term tolerability was published in 2023, which we present here as well, and no new safety concerns were identified after 3 years exposure to osimertinib indicating that this treatment duration had minimal effect on the overall safety and tolerability profile of osimertinib.

Osimertinib is a well-established treatment option in metastatic EGFR+ NSCLC disease and the side-effect profile is well known to any oncologist in Denmark treating NSCLC with targeted therapies. We hope that the DMC will find their original concerns over the data presented in 2021 to be sufficiently address by the mature follow up data that we present in this updated application, to conclude that the overwhelming DFS benefit from the primary analysis has translated to an OS benefit for EGFRm NSCLC patients with a tolerable safety profile that didn´t result in a decline of HRQoL compared to placebo.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

Lung cancer

Lung cancer is defined as the uncontrolled growth of abnormal cells in the lungs, and is the most commonly diagnosed cancer and the leading cause of cancer mortality worldwide.(13) The two predominant forms of lung cancer are non-small cell lung cancer (NSCLC) that accounts for 85% of patients and small-cell-lung cancer (SCLC), accounting for 15% of patients.(14) NSCLC comprises a group of cancers, which exhibit similar behavior and response to treatment. They can be categorized according to the tissue of origin: adenocarcinoma, squamous cell carcinoma and large cell lung cancer; several variants and clinical sub-types exist within each category.(15) Adenocarcinomas are the most common type of NSCLC, accounting for approximately 40% of lung cancers.(16, 17) Recurrent driver mutations commonly found in NSCLC have a key role in the development of disease and are targets for therapeutic agents. Evidence has shown that the overall pooled prevalence for endothelial growth factor receptor mutation positive (*EGFRm+*) NSCLC, across all stages, is 32.3% and this ranges globally from 14.1% in Europe to 38.4% in China. (18) Additionally, data suggest that young patients with stage I–IV NSCLC harbour more driver mutations compared with older patients, with the rate of EGFRm documented in the young, white population being 20%–30%.(19) The most recent Danish Lung Cancer Registry report shows that 4893 patients were diagnosed with lung cancer in Denmark in 2021.(20) (21)

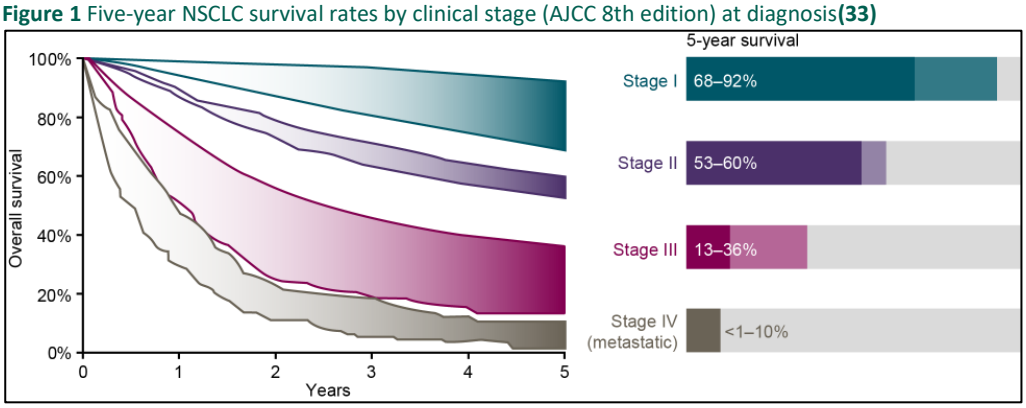
Lung cancer symptoms

Early stage NSCLC is often asymptomatic and patients are therefore at risk of delayed diagnosis, which impacts cure rates and survival.(22-25) Patients may live for several years before showing symptoms, increasing the risk of distant metastases and more advanced disease at diagnosis. In addition to the largely asymptomatic nature of early disease, the initial symptoms are often non-specific, such as a cough.(24) As a consequence, approximately 70% of NSCLC patients will be diagnosed with unresectable, advanced NSCLC.(26-28)

Prognosis and recurrence rates

NSCLC is associated with a notably poor prognosis in comparison with other tumour types, such as colon, rectal and breast cancer.(29-31) The overall five-year survival rate for NSCLC (all stages) is 22.3% in Denmark.(20, 21) This varies by stage at diagnosis from 68%–92% for stage I NSCLC to <1%–10% for stage IV NSCLC (Figure 1).(32, 33)

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

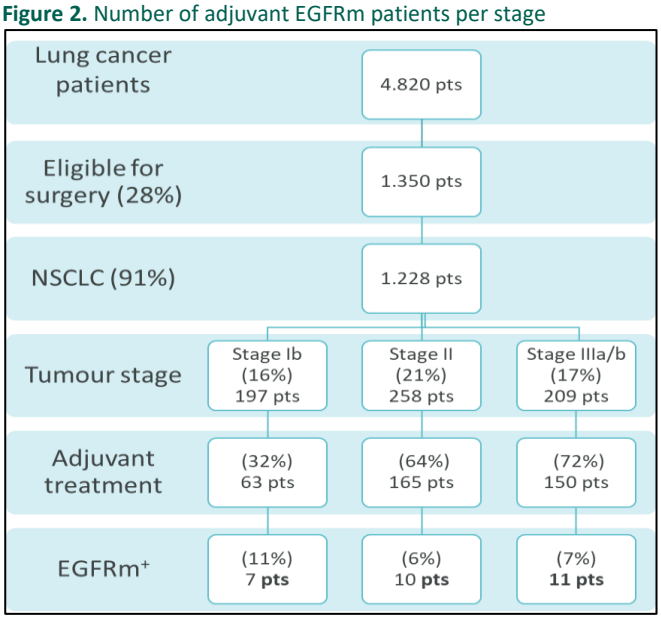


Despite the curative intent of treatment in early stages, recurrence in patients with stage IB–III NSCLC remains common, regardless of post-operative chemotherapy use.(34) For patients with stage IB–IIIA NSCLC, adjuvant

chemotherapy improves overall survival (OS) by ~5% and disease free survival (DFS) by ~6% after five years.(34-36) The five-year NSCLC recurrence rates vary by disease stage, with recurrence seen in approximately 45% of patients with stage IB, which increases to approximately 62% and 76% in patients with stage II and stage III respectively (Figure 1).(34)

Common sites of distant recurrence for NSCLC includes the brain, lung, bone and liver.(37) Approximately 41% of NSCLC patients develop brain metastases during the course of their disease, making the brain the most common site of distant recurrence in NSCLC.(37) Brain metastases are likely to contribute to the poor survival seen in patients with NSCLC and comprises a substantial symptom burden.(38, 39)
The expected patient numbers for adjuvant osimertinib treatment in Denmark are less than 30 and the patient funnel is shown in Figure 2.

Figure 2. Number of adjuvant EGFRm patients per stage



The percentages supplied for resected patients, NSCLC, and tumour stages are found in the Danish Lung Cancer Registry with data from 2018.(20). The incidence number in figure 2 is a bit lower that stated in table 3 but is due to different sources. The numbers are still relevant. The percentages on adjuvant treatment is based on expected percentages based on patients currently receiving curative intended chemotherapy. The NSCLC epidermal growth factor receptor mutation (EGFRm) rates are from the ELCC 2021 abstract EGFR mutation (EGFRm) prevalence and mortality in patients with stage IB–IIIA NSCLC: a cohort study in Denmark (Jakobsen, 2021 ELCC, 65P).(40)

Danish patient characteristics

In the ADAURA trial the patient characteristics for EGFRm patients was predominantly female (68-72%), Asian (64%), with a median age of 62-64 years. The characteristics of Danish patients that are diagnosed with early stage resectable NSCLC are listed in **Table 1**. It should be noted that several Danish hospitals have not routinely performed EGFR testing on resectable patients until May 2021 since there was no adjuvant targeted therapy approved. This is illustrated by the high percentage of not tested patients listed in **Table 1**. However, hospitals like Aarhus University hospital have done reflex next generation sequencing testing of all resectable NSCLC patients since 2018. From data on file there is indication that Danish EGFRm patients are diagnosed in earlier stages (IB-IIA).

Table 1 Patient characteristics of early stage NSCLC patients from Denmark compared to stage

Characteristics all pts	Data on file(41)				Data on file(42)
	IB	IIA	IIIB	IIIA	
N	302	154	378	511	
Age (median)	72	73	70	70	
Sex (% female)	138(46)	67(44)	154(41)	236(46)	
Weight(average, kg)					
Male					73 (n=178)
Female					70 (n=101)
EGFR (%)					
Not tested	185(61)	99(64)	238(63)	259(51)	
WT	94(31)	47(31)	132(35)	237(46)	
EGFRm+	23(7.6)	8(5.2)	8(2.1)	15(2.9)	
Adenocarcinoma (%)	182(60)	79(51)	192(51)	287(56)	
Chemotherapy(yes)	27(9)	21(14)	161(43)	300(59)	
Recurrence rates all pts	IB	II	III		
CNS metastasis (%)	6(2.0)	22(4,1)	40(13.2)		
Local (%)	21 (7)	33(6.2)	59(9.7)		
Regional (%)	27 (8.9)	44(8.3)	94(15.5)		
Distant (%)	16 (5.3)	56(10.5)	91(15.0)		
Unknown relapse site (%)	12 (4.0)	28(5.3)	60(9.9)		
% of patients with relapse	25.2%	30.3%	50.1%		
Characteristics pts with EGFR test					
	IB	IIA	IIIB	IIIA	
EGFRm+ (%)	23(20)	8(14.5)	8(5.7)	15(6)	

***Source**: Data on file(1) is data from resectable st.Ib-IIIa NSCLC patients treated at Aarhus University hospital from 2010-2018.(41) Data on file (2) is data from stage III NSCLC patients at Aarhus University hospital.(42)*

5.1.1 Patient populations relevant for this application

The characteristics of early stage resectable Danish EGFRm patients from data on file sources are summarized in Table 2. The patient characteristics for resectable EGFRm patients are supplemented with a larger Danish cohort from RWE data from the Danish lung cancer registry (2013-2018). This work was presented at the European Lung Cancer conference in 2020 and was later published in Cancer medicine and included 195 EGFRm patients.(40, 42). There was an overall prevalence of 8% EGFRm in the stage IB-IIIA NSCLC cohort.(40, 42) The demographic and characteristics of the larger cohort showed that 71% of Danish patients with EGFRm were women compared to 56% in the EGFR wild type group of the early stage patients.(40, 42) Additionally, Danish EGFRm patients had a median smoking pack years of 10 (Q1=0, Q3=30) compared to 40 (Q1=25,Q3=50) in the negative group. Age and disease stage at diagnosis was not different between the EGFRm and negative group. Of note, the CNS metastasis occurrence for Danish early stage NSCLC patients in(41) was between 8-14% and for the EGFRm patients it was 8%. In the ADAURA trial the occurrences of CNS metastasis in the overall population was 15% (n=50/343) in the placebo arm compared to 7% (n=25/339) in the

osimertinib arm. The HR for CNS DFS HR was 0.36 (95% CI, 0.23 to 0.57). In the stage II/IIIA population receiving osimertinib 15/18 metastases occurred following completion of treatment.

Table 2. Patient characteristics of Danish EGFRm patients

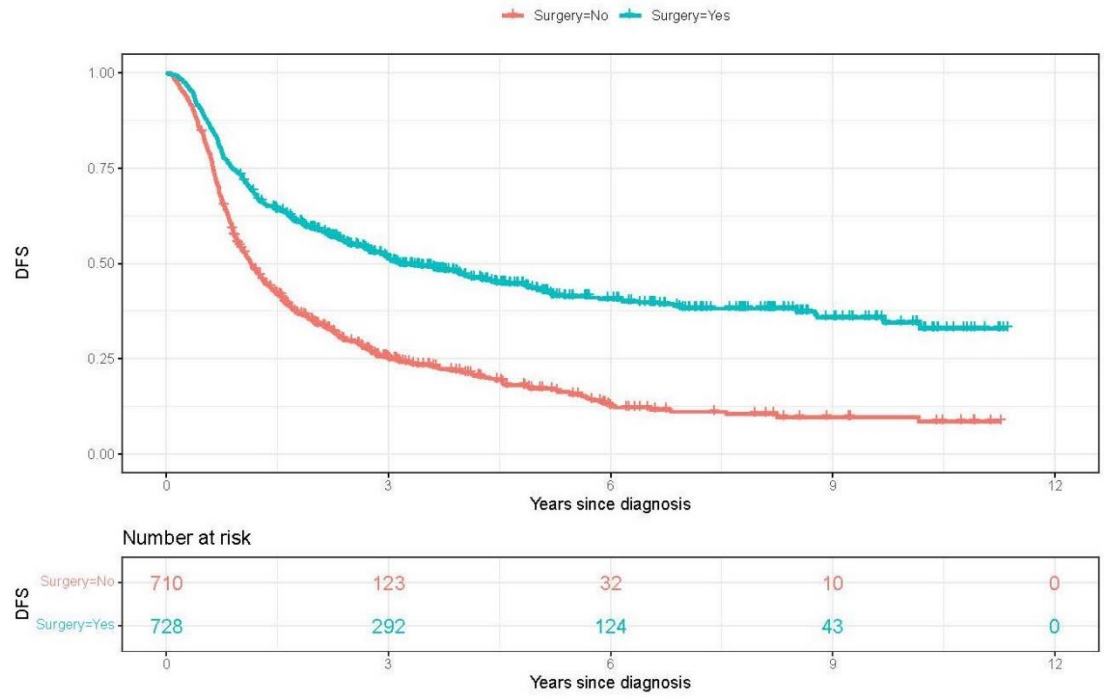
Characteristics of Danish st. Ib-IIIa NSCLC patients with EGFRm				
EGFR mutation prevalence and mortality in patients with stage IB-IIIA NSCLC: a cohort study in Denmark **E. Jakobsen, A. Taylor, V. Ehrenstein, 2021, JTO, DOI:https://doi.org/10.1016/S1556-0864(21)01907-9(40)**				**Data on file(41)**
		EGFRm (n=195)	EGFR wild type (n=2,273)	EGFRm(54)
Sex	Female	138 (71)	1264 (56)	32(59)
Age, years	<60 60-69 70-79 >80	28(14) 56(29) 77(39) 34(17)	348(15) 188(8) 591(26) 821(36)	Median(IQR) 72
Disease stage at diagnosis	Ib IIa IIb IIIa	81 (42) 9 (5) 43(22) 62(32)	673(30) 188(8) 591(26) 821(36)	
Histology	Adenocarcinoma	174(89)	1,878(83)	53 (98)
Smoking	Pack-years, median (Q1-Q3)	10 (0-30)	40 (25-50)	
CNS metastasis(yes)				2(8)
Chemotherapy(no)				14(26)

Source: *Data on file(1) is data from resectable st.Ib-IIIa NSCLC patients treated at Aarhus University hospital from 2010-2018.*(35)

DFS for Danish EGFRm+ patients

The median DFS of Danish early stage resectable NSCLC patients with stage IB-III was estimated from 728 patients (EGFRm or EGFR wt) to be 37.8 months calculated from the first visit until disease progression.(41) In ADAURA, the median DFS was 65.8 months for the osimertinib arm (95% CI 61.7, NC) and 28.1 (95% CI 22.1, 35.0) months in the placebo group, which gave a Hazard ratio for disease recurrence or death of 0.27 (95% CI 0.21, 0.34), p<0.0o01.

Figure 3. DFS KM curve for st. IB-III patients **in** Central Denmark Region from 2010 to 2018 treated at Aarhus University Hospital.



Median disease free survival in months stratified by surgery

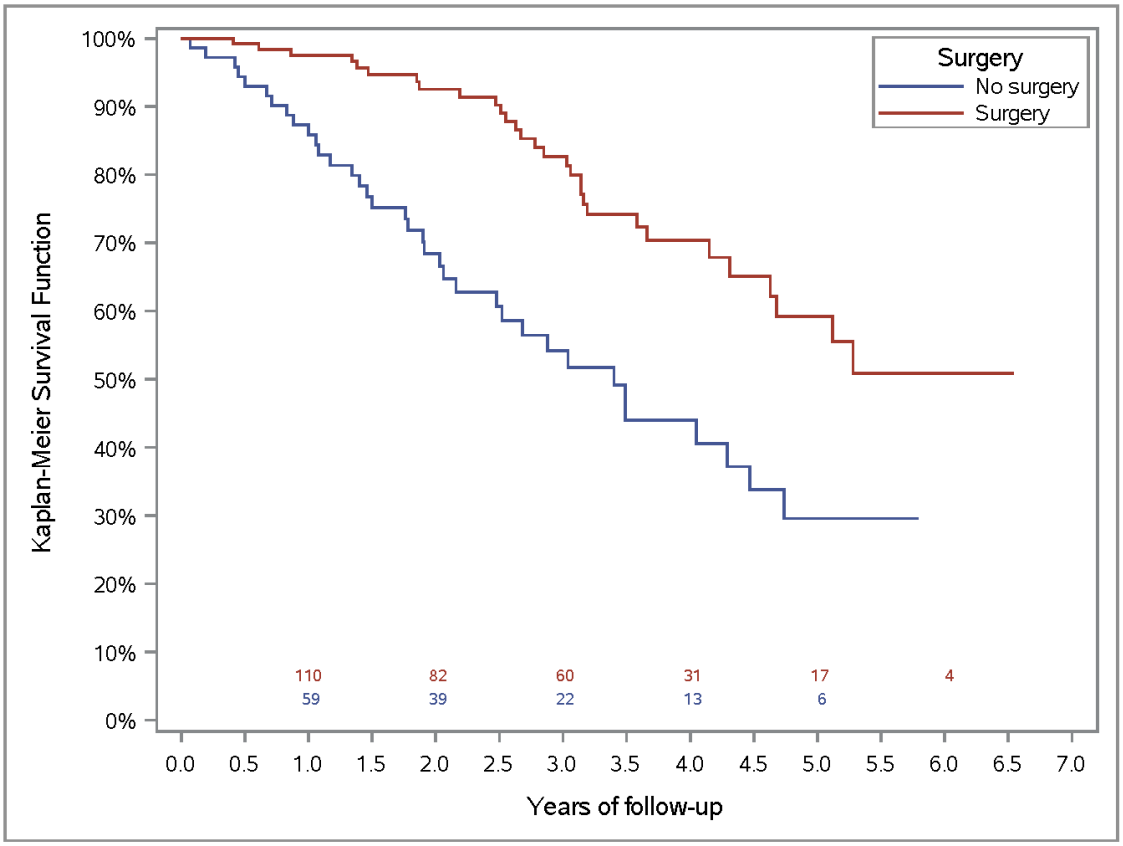
	median	lower	upper
Surgery=No	13,7	12,2	15.5
Surgery=Yes	37,8	32,6	51,1

Source: Data from resectable st.Ib-IIIa NSCLC patients treated at Aarhus University hospital from 2010-2020.(41)

Survival of EGFRm patients in Denmark from 2013-2018

The survival of 110 early stage resectable EGFRm patients are shown in Figure 4 and includes surgery vs no surgery for stage Ib-IIIa. The median survival is 5.2 years for patients receiving surgery. This is comparable to other data from Denmark in a national cohort within same time span. (40) The OS in Denmark for EGFRm patients that receive surgery is worse than both treatment arms in ADAURA. At the 5 years follow-up the median survival was not reached for osimertinib (87.6% still alive) or placebo (77.7% still alive).

Figure 4. Survival data from Danish EGFRm+ patients from 2013-2018 (40)



Source: *Data from resectable st.Ib-IIIa NSCLC patients treated at Aarhus University hospital from 2010-2018(41)*

Representation of the Danish target population in ADAURA

This application has included the estimated annual number of Danish patients that are expected to be eligible for adjuvant osimertinib treatment. The eligible patient characteristics are shown in Figure 2, from early stage resected NSCLC patients with EGFRm and the DFS and OS. The expected annual number of Danish patients is 28, which is only 2% of the annual resected NSCLC patients diagnosed with stage Ib-IIIa(Table 3 and Table 4). This illustrates the low prevalence of potential Danish patients, which make large cohort patient descriptions a challenging task. However, in this application we have made the effort to provide relevant Danish data by using several RWE datasets. In the ADAURA trial, the average resectable EGFRm patient was a 63 year old Asian female. Of note, a subgroup DFS analysis between Asians and non-Asians showed no difference in risk for cancer relapse or death Figure 10. The average early stage resectable Danish patient is a 70-73 year old male (Table 1). However, the patient characteristics of Danish EGFRm patients look similar to the ADAURA study with 71% of pts being female and generally of younger age with 43% younger than 70 years in the EGFRm group compared to 23% in the EGFR wild type pts Table 2. It is worth noting in Table 1 that the majority of patients was not tested for their EGFR status. We included retrospective data from AUH (35) to be included in Table 1 and Table 2 and the DFS in Figure 3. These data help evaluate the medical gaps created by the unplanned early data cutoff that the independent monitoring committee recommended based on the early superiority control for ADAURA. The 37.8 months DFS from first visit in the early stage NSCLC Danish patients(728 pts) are not directly comparable to the 21.9 months DFS from randomization (343 pts) of the placebo population in EGFRm

ADAURA patients. Finally, the Kaplan Meier OS in figure 4 shows that median OS for the Danish target population is about 5 years (110 pts), which is worse than both treatment arms in ADAURA (343 pts). The OS and DFS data illustrates the medical need for additional treatment in this patient group to prevent relapse and offer additional treatment to a curable group of patients. The 3.2 year median DFS of Danish patients indicate that these patients do maintain the known recurrence pattern of NSCLC, but they have longer survival potential with optimal treatment.

Table 3. Incidence and prevalence in the past 5 years(18, 43)

Year	2017	2018	2019	2020	2021
Incidence in Denmark (Lung Cancer)	4881	4922	4938	5096	5192
Incidence in Denmark (NSCLC)	4150	4185	4195	4330	4415
Prevalance Denmark	12031	12974	13730	14505	15501

Source: https://www.cancer.dk/dyn/resources/File/file/8/10128/1675423238/kraefttilfaelde-2021.pdf

Table 4. Estimated number of patients eligible for EGFRm adjuvant treatment*

Year	2024	2025	2026	2027	2028
Number of patients in Denmark eligible to use Osimertinib based on indication	28	29	29	29	30

**The numbers are based on the same numbers as the first application, but adjusted to 2024-2028 numbers.*
Source: see figure 2 for patient journey and table 3. The percentages supplied for resected patients, NSCLC, and tumour stages are found in the Danish Lung Cancer Registry with data from 2018.(15). The incidence number in figure 2 is a bit lower that stated in table 3 but is due to different sources. The numbers are still relevant. The percentages on adjuvant treatment is based on expected percentages based on patients currently receiving curative intended chemotherapy. The NSCLC epidermal growth factor receptor mutation (EGFRm) rates are from the ELCC 2021 abstract EGFR mutation (EGFRm) prevalence and mortality in patients with stage IB–IIIA NSCLC: a cohort study in Denmark (Jakobsen, 2021 ELCC, 65P).(34)

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Resectable, stage IB-IIIA, EGFRm NSCLC

Early stage NSCLC is defined by American Joint Committee on Cancer (AJCC) (7^{th}/8^{th} edition) as stage I–IIIA disease, and is typically considered resectable and therefore potentially curable.(22) Despite this, there is still a risk of circulating tumour cells and micro metastases, which have been shown to be associated with an increased risk of recurrence.(44, 45) The ultimate treatment goal in patients with early NSCLC is to improve the chance of cure after surgery. However, the 5-year OS has only improved by 3–5% for early disease patients in recent years with the current standard of care.(34, 46-48) Adjuvant treatment with osimertinib in the early setting has shown to clearly improve survival, which is in line with what was observed in the metastatic disease setting.(49)
The cornerstone of treatment for patients with resectable NSCLC is surgical removal of the tumour, which aims to achieve complete resection.(12, 22, 50) Patients in Denmark with stage I-II are recommended for surgical resection if they do not have any medical contraindications.(12) For patients with more advanced disease up to st. IIIb, adjuvant treatment could be considered for surgical resection depending on placement, and minimal lymph node involvement.(12) In Denmark, 28.6% of all lung cancers are treated with curative intended surgery.(20)

Following surgical resection, adjuvant chemotherapy is recommended to reduce the risk of recurrence and spread of disease. Danish guidelines state that adjuvant therapy should be considered for all patients with stage II–IIIA NSCLC with negative surgical margins (no residual traces of tumour [R0]).(11)

Patients with stage Ib can be eligible for adjuvant treatment if the tumor is >4 cm.(12) In Denmark, the adjuvant treatment should consist of four series of platinum based doublet treatment and should be initiated within 6-8 weeks after surgery. The Danish national guidelines list cisplatin and vinorelbine as the adjuvant chemotherapeutics.(11) Despite being indicated in metastatic disease, there are currently no targeted treatments available in the adjuvant setting for patients with EGFRm NSCLC, following complete resection.

Osimertinib and expected Danish patient numbers

Osimertinib is a third-generation tyrosine kinase inhibitor (TKI), which acts as an irreversible inhibitor of EGFR sensitising mutations.(4) As opposed to first- and second-generation EGFR TKIs, preclinical data indicate that osimertinib is able to cross both the intact and compromised blood brain barrier.(5) This is further supported by clinical trial data from FLAURA, a Phase III RCT comparing osimertinib with gefitinib or erlotinib EGFR-TKIs.(7) Osimertinib is already indicated for the treatment of patients with locally advanced or metastatic NSCLC with activating EGFR mutations.(4, 51) In the adjuvant setting it is licensed for daily treatment (80 mg) after complete tumour resection, in adult patients with NSCLC whose tumours have EGFR Exon 19 deletion (Ex19del) or exon 21 (L858R) substitution mutations. As shown in table 4 the estimated patient number for the adjuvant indication will be just below 30 a year.

5.2.2 Choice of comparator(s)

Osimertinib was compared to placebo in the ADAURA trial. There is no active treatment as standard of care for targeted therapies in adjuvant early stage NSCLC. Additionally, investigators in ADAURA had the option to treat with or without adjuvant chemotherapy. The proportion of patients receiving adjuvant platinum-based chemotherapy was well-balanced between treatment arms at ~60% in each arm, and for all disease stages. In line with international standard of care treatment recommendations, a limited number of patients with stage IB disease at the time of diagnosis received adjuvant chemotherapy treatment (26.4%), compared with approximately three quarters of all patients with stage II–IIIA disease (75.5% [stage IIA: 71.0%; stage IIB: 72.7%; stage IIIA: 79.6%]).(4, 5) The increased use of chemotherapy in later stages is also reflected in data from Denmark.(41)

5.2.3 Description of the comparator(s)

The comparator for this is placebo.

5.3 The intervention

Osimertinib

The induction of osimertinib would make it the first targeted therapy in the adjuvant setting for early stage NSCLC patients. The patients can be treated with or without concomitant chemotherapy. Besides the change in the treatment paradigm for this group of patients, it would also require that patient samples are tested for EGFRm with an appropriate testing method prior to initiation of osimertinib treatment. Treatment is until progression or a maximum of 3 years.

Hepatic impairment

Osimertinib is mainly eliminated by the liver. Data have shown that patients with mild hepatic impairment or moderate hepatic impairment had no increase in exposure compared to patients with normal hepatic function, after a single 80 mg dose of osimertinib. There are no data available on patients with severe hepatic impairment.(4)
Based on clinical studies, no dose adjustments are necessary in patients with mild or moderate hepatic impairment. The safety and efficacy of osimertinib has not been established in patients with severe hepatic impairment, and is therefore not recommended for use in this population until additional data become available. (4)

Renal impairment

Clinical data have shown that patients with mild, moderate or severe renal impairment had similar exposure to osimertinib, compared to patients with normal renal function.(4)
No dose adjustments are necessary in patients with mild, moderate or severe renal impairment. The safety and efficacy of osimertinib in patients with end-stage renal disease or on dialysis has not been established, therefore caution should be exercised when treating this patient group.(4)

EGFR test

In ADAURA, patients were also required to have confirmation by the central laboratory (using the cobas® EGFR Mutation Test on tissue samples), that the tumour harboured one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations including T790M. As a consequence, when considering the use of osimertinib as adjuvant treatment in patients with NSCLC, the EGFR mutation positive status (exon 19 deletions (Ex19del) or exon 21 L858R substitution mutations (L858R)) indicates treatment eligibility. EGFR testing is a standard method in Denmark generated from use of 1st generation TKIs and later also osimertinib for these patients. The most common method for Danish centers that perform surgery has since 2018 been next-generation sequencing of patient samples. A validated test should be performed in a clinical laboratory using tumour tissue DNA from biopsy or surgical specimen.

Patients with a poor performance status (i.e. WHO >1) were not allowed to enter the study, however, considering the early stage of the disease this may be representative of the intended target population.
The choice of placebo as comparator is considered acceptable, since no other treatment option is currently approved or recommended by DMC in Denmark for this patient population.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A literature search would not be relevant for osimertinib in the adjuvant setting since there is no clinical practice for targeted therapies against EGFRm following surgery. Also a direct comparative study of osimertinib vs current standard(placebo) is available(ADAURA). AstraZeneca have performed a SLR to identify published clinical efficacy and safety data of osimertinib and relevant comparators for the adjuvant treatment of stage IB–IIIA NSCLC, including

patients with EGFRm stage IB–IIIA NSCLC. Searches of electronic databases were performed on 23rd July 2020 along with handsearching of conference proceedings, clinical trial registries, regulatory sources (FDA and EMA) and reference lists. The electronic database searches identified 9,807 articles.

Overall, a total of 26 publications, including the ADAURA clinical study report (CSR), reporting on 13 unique studies, were deemed relevant for extraction. Only one trial was identified in the SLR that provides clinical evidence that is directly relevant and that was the ADAURA trial. The number of publications from the ADAURA trial has increased since our last application(see table 5).

6.2 List of relevant studies

Table 5. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Osimertinib in resected EGFR-mutated Non-Small-Cell Lung Cancer, Wu et. al., NEJM, 2020 https://www.nejm.org/doi/full/10.1056/NEJMoa2027071	ADAURA	NCT02511106	Randomisation: 21 Oct 2015 to February 2019 Completion date: 25th Jan 2023	Osimertinib monotherapy vs. placebo for Patients with stage IB–IIIA EGFRm NSCLC, who have had complete tumour resection, with or without post-operative adjuvant chemotherapy
Three-Year Safety, Tolerability, and Health-Related Quality of Life Outcomes of Adjuvant Osimertinib in Patients With Resected Stage IB to IIIA EGFR-Mutated NSCLC: Updated Analysis From the Phase 3 ADAURA Trial. Thomas John, M.B.B.S., PhD et al. J Thorac Oncol. 2023 https://pubmed.ncbi.nlm.nih.gov/37236398/	ADAURA	NCT02511106	See above	See above
Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non–small-cell lung cancer: updated results from the phase III randomized ADAURA trial. Herbst RS, Wu Y-L,	ADAURA	NCT02511106	See above	See above

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
John T, et al J Clin Oncol 2023; 41: 1830-40. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10082285/ Erratum published April 26th 2023 https://ascopubs.org/doi/10.1200/JCO.23.00658?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed				
Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. Tsuboi et al. NEJM June 4, 389:137-147 2023 https://www.nejm.org/doi/full/10.1056/NEJMoa2304594	ADAURA	NCT02511106	See above	See above

For detailed information about included studies, refer to appendix B.

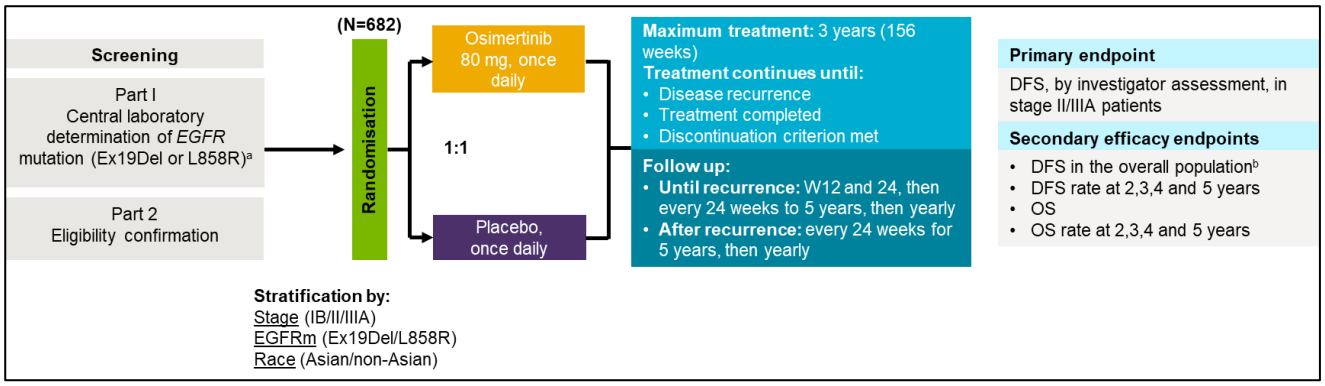
7. Efficacy and safety

7.1 Efficacy and safety of Osimertinib compared to placebo for resected stage Ib-IIIa NSCLC patients (ADAURA)

7.1.1 Relevant studies

ADAURA (NCT02511106) is a Phase III, double-blinded, randomised, placebo-controlled, multi-centre trial examining the clinical benefit of osimertinib treatment in patients with EGFRm stage IB–IIIA NSCLC (according to the AJCC 7th edition), following complete tumour resection with or without adjuvant chemotherapy, shown in Figure 5.(5, 52)

Figure 5. Design of the ADAURA trial



Footnotes: *[a]Centrally confirmed in tissue; [b]Stage IB/II/IIIA.*

Included patients were randomised 1:1 to receive either:

- **Osimertinib:** 80 mg (reduced dose 40 mg) tablet, OD
- **Placebo:** placebo tablet, OD

Stratification:

- Disease stage:
    - Stage IB
    - Stage II
    - Stage IIIA
- Mutation type, as confirmed by a central laboratory using a tissue-based test, either alone or in combination with other *EGFR* mutations as confirmed by a central test:
    - Ex19del
    - L858R

  In the rare event that a patient had both of these sensitising mutations, they were stratified to Ex19del.
- Race:
    - Asian
    - Non-Asian

Assessment schedule

Following randomisation, baseline radiological assessments (CT scans) were performed within the 28 days prior to study drug initiation. Following randomisation, subsequent assessments for the primary study endpoint DFS were planned to be performed at Week 12, Week 24, then every 24 weeks until 5 years (264 weeks), and then yearly thereafter, until disease recurrence was recorded. The same assessment schedule was followed if a patient discontinued study treatment prior to disease recurrence, or received another anti-cancer treatment.(53)
Following disease recurrence, patients were planned to undergo radiological assessment for subsequent progression in accordance with local clinical practice and assessments for OS were planned to be performed every 24 weeks for 5 years (264 weeks) and then yearly thereafter, until the study closure.(53)

Recurrence was categorized as local/regional or distant, and when recurrence was first documented at any site, complete restaging according to the AJCC 7th edition classification was required to identify all sites of recurrence.(52, 53)

Patient disposition

Patient disposition in the ADAURA study is summarised in
Figure 6. In total, 682 patients were randomised, 339 to the osimertinib arm, and 343 to the placebo arm. 99.4% of patients in the osimertinib arm and 100% of patients in the placebo arm were treated during the trial. (5)
At the time of the updated DFS analysis (DCO 11th April 2022), of the 680 patients who received study treatment, no patients in either arm remained on study treatment. (5)

- A higher proportion of patients in the osimertinib arm (222/337, 65.9%) had completed the 3 years of study treatment than patients in the placebo arm (139/343, 40.5%)

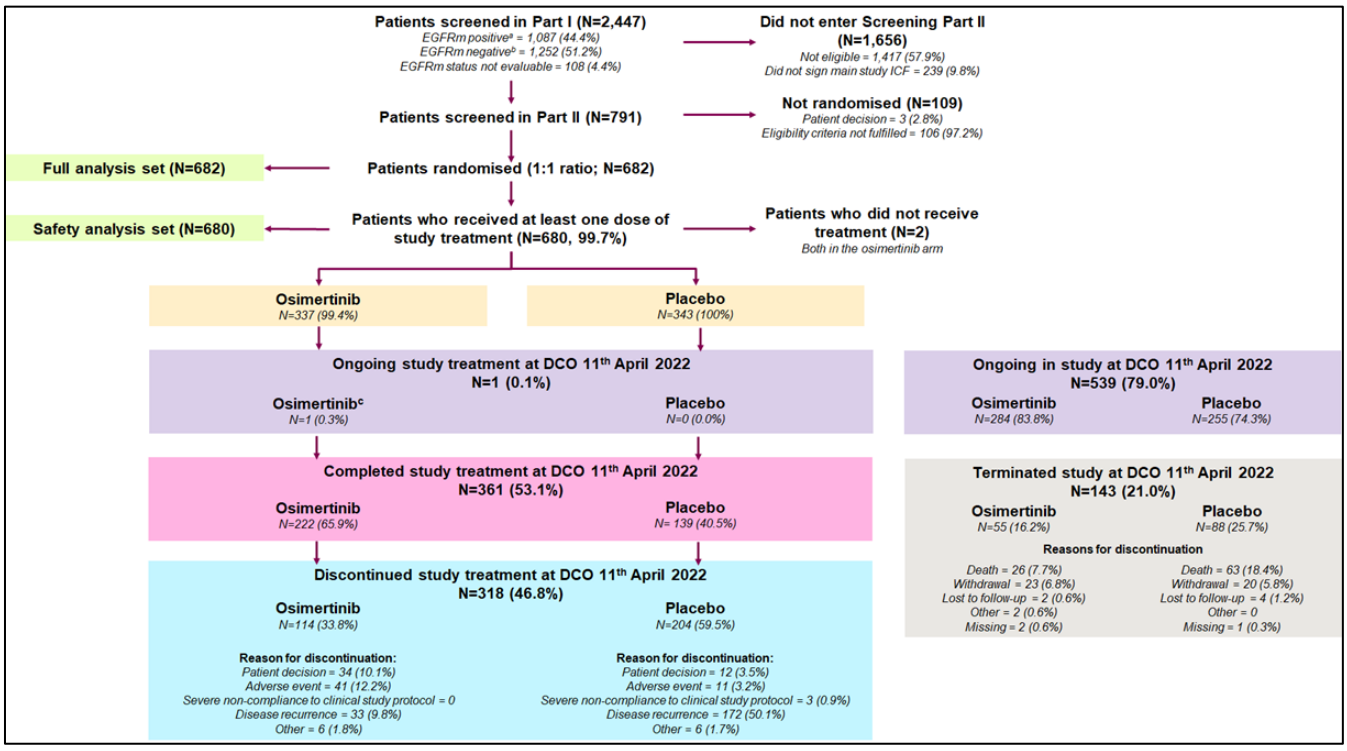
- A total of 114/337 (33.8%) patients in the osimertinib arm discontinued osimertinib, and 204/343 (59.5%) patients in the placebo arm discontinued placebo
    - In the osimertinib arm, the most common reason for discontinuation of study treatment was AEs (41/337; 12.2%), whereas in the placebo arm disease recurrence was the most common reason for discontinuation (172/343; 50.1%)

Population characteristics

A summary of the patient characteristics for the overall population is shown in Appendix C. The majority of patients randomised in the study were female, and Asian, with a median age of 63.0 years (range 30 to 86 years). Overall, demographics and patient characteristics were consistent between treatment arms, with no notable discrepancies evident in any characteristic.(5, 54)

Approximately one third of patients randomised in the study had AJCC (7th Edition) stage IB disease, approximately one third had stage II disease, and approximately one third had stage IIIA disease at the time of diagnosis. As a stratification factor, disease stage was well-balanced across treatment arms.
In terms of prior treatments for their NSCLC, all patients had undergone a type of resection surgery that was aligned with the study protocol; for most patients this was lobectomy, with a small number of patients having undergone sleeve resection, bilobectomy or pneumonectomy. The disposition of patients in ADAURA can be seen in
Figure 6. The proportion of patients receiving adjuvant platinum-based chemotherapy was well-balanced between treatment arms at ~60% in each arm, and for all disease stages. In line with international standard of care treatment recommendations, a limited number of patients with stage IB disease at the time of diagnosis received adjuvant chemotherapy treatment (26.4%), compared with approximately three quarters of all patients with stage II–IIIA disease (75.5% [stage IIA: 71.0%; stage IIB: 72.7%; stage IIIA: 79.6%])(5)

Figure 6. Patient disposition ADAURA



Footnotes: *[a]Includes any EGFR mutation detected by the cobas® test, not limited to Exon 19 deletions and L858R mutations; [b]No EGFR mutation detected in targeted EGFR regions by the cobas® test; [c]One patient in the osimertinib arm (E1337014) did not have an exact date of death recorded and had discontinuation status marked as "not answered". This patient's reason for terminating the study is classed as missing and the death is not included in this figure.* ***Source:*** *AstraZeneca Data on File (ADAURA CSR).(5)*

For detailed study characteristics refer to Appendix B. For baseline characteristics of patients included in each study refer to Appendix C.

Rationale for 3 years adjuvant treatment

In ADAURA, osimertinib and placebo were continued until recurrence of disease, a treatment discontinuation criterion was met, or until treatment was completed. The maximum treatment duration period was 3 years (156 weeks). The three years of osimertinib treatment in ADAURA was chosen based on several factors. In other adjuvant EGFR-TKI studies, the duration of therapy was 2 years. In these studies, recurrence occurred within 1 year of TKI discontinuation or DFS benefit reduced after 2 years of TKI. Given that the highest rate of recurrence is seen within the first 2-3 years after complete tumor resection, it was reasonable to aim for at least 2-3 years of treatment duration in this setting. Based on the above considerations, in the ADAURA study, the maximum treatment duration period is 3 years. AstraZeneca continues to evaluate other treatment durations that can be alternatives for the current duration of adjuvant osimertinib therapy.

7.1.2 Efficacy and safety – ADAURA

DFS in patients with stage II–IIIA NSCLC (Primary endpoint. Updated with DCO April 2022)

The overwhelming efficacy observed in ADAURA led to a recommendation from an IDMC to unblind ADAURA two years earlier than planned. The most recent DCO for the primary analysis ADAURA reached 51% DFS maturity in the stage II–IIIA population (247 DFS events, 75/233 [32%] in the osimertinib arm and 167/237 [70%] in the placebo arm). Median follow-up for DFS in stage II–IIIA patients was 44.2 months in the osimertinib arm vs 19.6 months in the placebo arm.(2, 5). The median DFS was longer for osimertinib with 65.8 months (95% CI 54.4 to NC) compared to placebo with 21.9 months (95% CI, 16.6 to 27.5). HR was 0.23 (95% CI, 0.18 to 0.30) and demonstrated a statistically significant and clinically meaningful improvement in DFS for patients with stage II–IIIA NSCLC compared with placebo (Figure 7, Table 6). Based on KM estimates, the percentage of patients who remained disease-free in the osimertinib arm was 97.8% at 12 months, 90.0% at 24 months, 83.5% at 36 months, 69.5% at 48 months, 54.0% at 60 months compared with 61.4%, 46.1%, 33.8%, and 28.5% and 24.9% of patients in the placebo arm, respectively.(2, 5)

Figure 7. DFS in stage II-IIIA patients (FAS)(8)

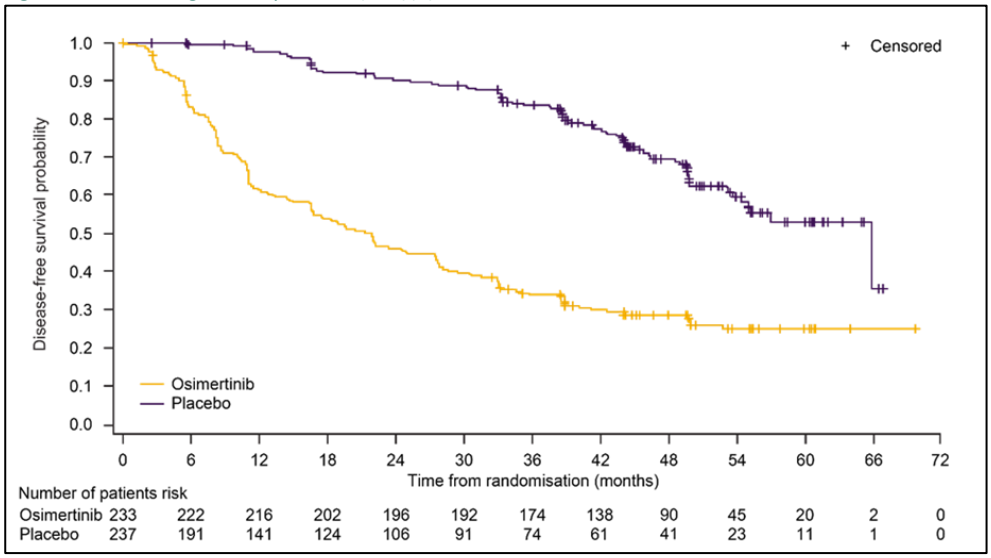


Table 6. mDFS stage II–IIIA patients (FAS)(5, 54)

	Osimertinib (N=233)	Placebo (N=237)
Events, n (%), 51,5% maturity[a]	75 (32.2)	167 (70.5)
Median DFS, months (95% CI)	65.8 (54.4, NC)	21.9 (16.6, 27.5)
HR[b] (99.06% CI;[c] p-value)	0.23 (0.18, 0.30; p<0.0001)	

Footnotes: DCO: 11th April 2022. [a]:DFS events are NSCLC recorded as local/regional or distant, or death. DFS events that do not occur within two scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events. [b]:Patients who had evidence of disease at study entry have been censored at day one. [c]The analysis was calculated using a log rank test stratified by stage (II vs IIIA), race (Asian vs Non-Asian) and mutation type (Ex19del vs L858R). Stratification factors are as recorded in IVRS. A HR <1 favours osimertinib. The HR and CI are obtained directly from the U and V statistics (Berry, et al. [1991]; Selke & Siegmund [1983).

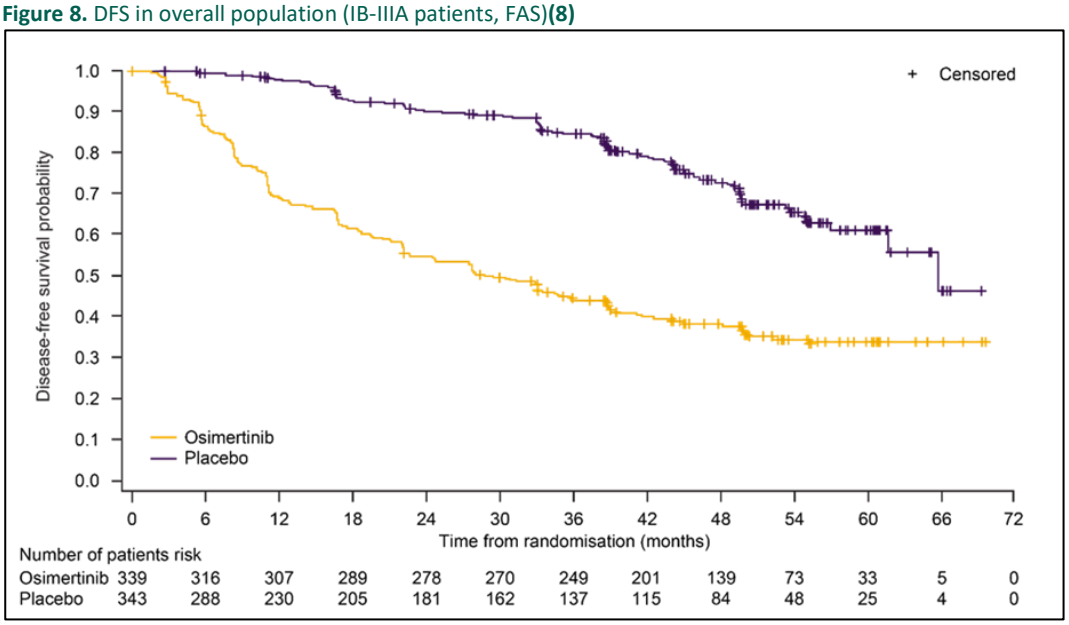
DFS in the overall population (stage IB–IIIA patients). Updated with DCO April 2022

At the updated DFS analysis (DCO 11th April 2022), in the overall study population, 94 (27.7%) patients in the osimertinib arm and 211 (61.5%) patients in the placebo arm had experienced a DFS event. Median follow-up for DFS in all patients was 44.2 months in the osimertinib arm vs 27.7 months in the placebo arm; all patients had had the opportunity for at least 3 years of follow-up, with 75.1% and 27.7% having had the opportunity for at least 4 and 5 years of follow-up, respectively. (Figure 8, Table 7) Consistent with the results observed at the primary analysis (DCO 17th January 2020: osimertinib vs placebo (HR=0.20; 99.12% CI 0.145, 0.273; 2-sided p<0.0001), at the updated DFS analysis, osimertinib demonstrated a clinically significant improvement in DFS for the overall population (stage IB–IIIA patients) vs placebo:

- A 73% reduction in risk of disease recurrence or death was observed for patients in the osimertinib arm vs the placebo arm (median DFS: osimertinib 65.8 months, placebo 28.1 months; HR 0.27; 95% CI 0.21, 0.34; 2-sided p<0.0001)(5, 54)

- Based on KM estimates, the percentage of patients who remained disease-free in the osimertinib arm was 97.8% at 12 months, 90.1% at 24 months, 84.5% at 36 months, 72.7% at 48 months and 60.9% at 60 months, compared with 68.9%, 54.5%, 44.4%, 37.8% and 33.6% of patients in the placebo arm, respectively(5)

Figure 8. DFS in overall population (IB-IIIA patients, FAS)**(8)**



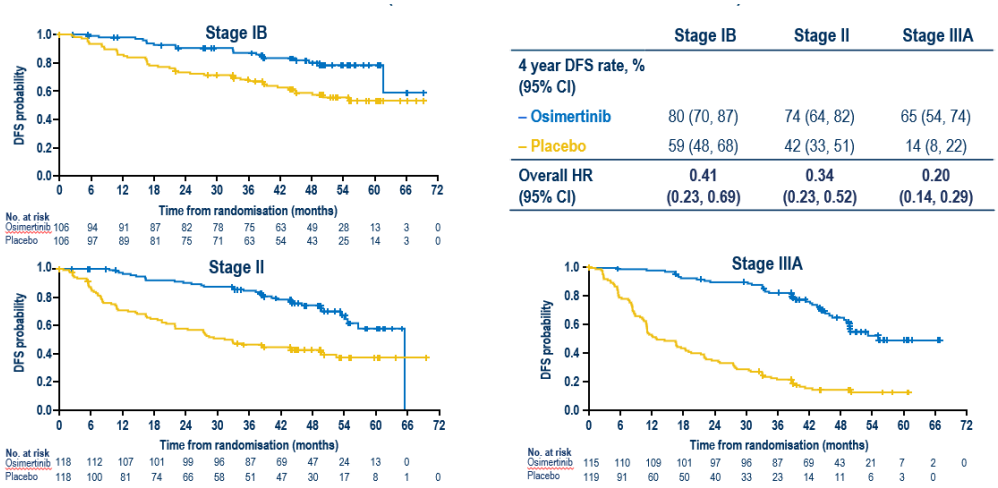
Footnotes: *DCO: 11th April 2022. The DFS rate at 60 months should be interpreted with caution due to the impact of censoring and the low number of patients at risk at this timepoint (33 patients in the osimertinib arm, 25 patients in the placebo arm).*

Table 7. DFS in overall population (stage IB–IIIA patients,FAS)***(5, 54)***

	Osimertinib (N=339)	Placebo (N=343)
Events, n (%), 44.7% maturity[a]	94 (27.7)	211 (61.5)
Median DFS, months (95% CI)	65.8 (61.7, NC)	28.1 (22.1, 35.0)
HR[b] (95% CI; 2-sided p-value)	0.27 (0.21, 0.34; p<0.0001)	

Footnotes*: DCO: 11th April 2022. DFS events are NSCLC recorded as local/regional or distant, or death. DFS events that do not occur within two scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events. bPatients who had evidence of disease at study entry have been censored at day one. The analysis was performed using a log rank test stratified by stage (IB vs II vs IIIA), race (Asian vs Non-Asian) and mutation type (Exon 19 deletion vs L858R). Stratification factors are as recorded in IVRS. A HR <1 favours osimertinib. The HR and CI are obtained from the U and V statistics (Berry, et al. [1991]; Selke & Siegmund [1983]).*

Figure 9. DFS by stage



Source: AstraZeneca data on file: Osimertinib as adjuvant therapy in patients with resected EGFRm stage IB–IIIA NSCLC: updated results from ADAURA ESMO-2022

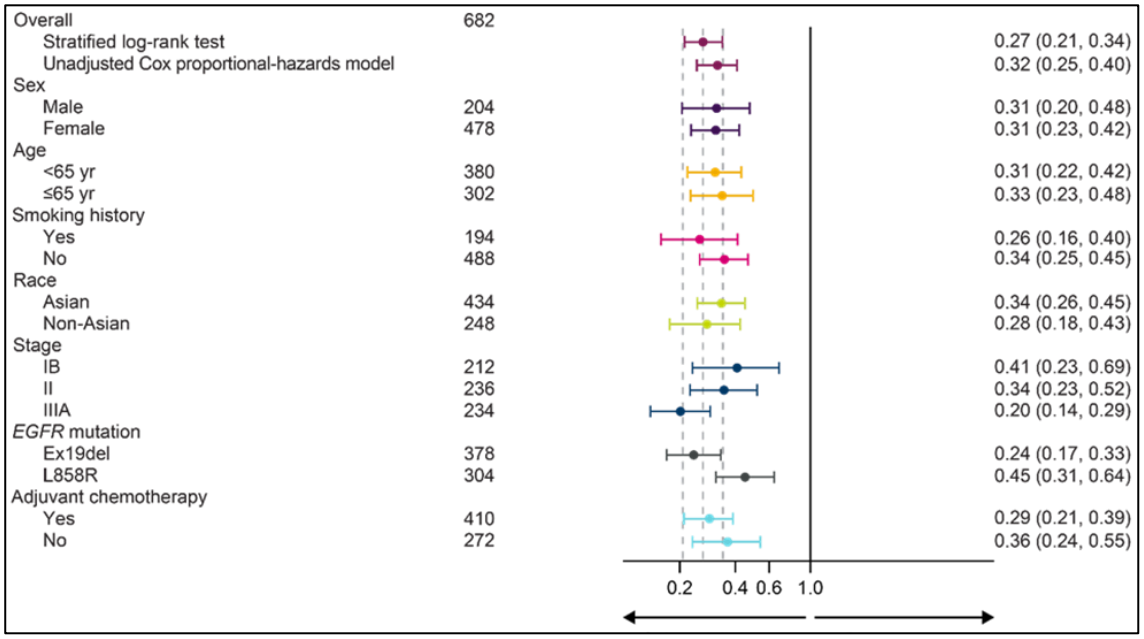
Subgroup analyses of DFS. Updated with DCO April 2022

At the updated DFS analysis (DCO 11th April 2022), in analyses of DFS in pre-specified exploratory subgroups by clinical characteristics, clinically meaningful reductions in the risk of disease recurrence or death (ranging from 80% to 55%) were observed for osimertinib vs placebo across all subgroups in the overall population Figure 10.(5, 54) Considering the subgroup analysis by disease stage, there were fewer events in the placebo arm in the stage IB subgroup than in stage II or IIIA, which is consistent with the better prognosis of patients with stage IB disease. The HR for a DFS event in patients with stage IB disease was 0.41 (95% CI 0.23, 0.69) indicating the high efficacy of osimertinib in these patients, despite their relatively good prognosis.(5)

At the updated DFS analysis, data from subgroup analyses were largely consistent with those seen at the primary analysis (DCO 17th January 2020). However, the HR for a DFS event in the stage II patient subgroup was 0.34 (95% CI0.23, 0.52) at the updated DFS analysis, compared with a HR of 0.17 (95% CI 0.08, 0.31) for these patients at the primary analysis. This may be accounted for by the relative immaturity of these data (only 11 events had occurred in

the osimertinib arm) and the low number of patients who had completed 36 months of treatment (10.7%) at the primary analysis. (5)

Figure 10. Subgroup analysis of DFS (FAS)(8)



Footnotes: *DCO: 11th April 2022.The subgroup analysis was performed with the use of a Cox proportional-hazards model that included trial regimen, subgroup, and the treatment-by-subgroup interaction term. Subgroup categories with less than 20 events were excluded from the analysis. Race was reported by the patients. The middle vertical dashed line indicates the median and the outer dashed lines indicate the 95% confidence interval for the overall hazard ratio (all patients). A hazard ratio of less than 1 implies a lower risk of disease recurrence or death with osimertinib than with placebo.*

Sensitivity analyses of DFS

The following sensitivity analyses for DFS (in both stage II–IIIA patients, and the overall population) were conducted at the primary analysis (DCO 17th January 2020):

- Evaluation time bias
- Attrition bias
- Quantitative interactions

There was no evidence of evaluation time bias or attrition bias, and a global interaction test suggested that the direction of treatment benefit was consistent across all subgroups. Please refer to the primary analysis CSR for further details.(5)

Secondary endpoints. Updated with DCO January 2023

OS in stage II–IIIA patients (interim analysis)

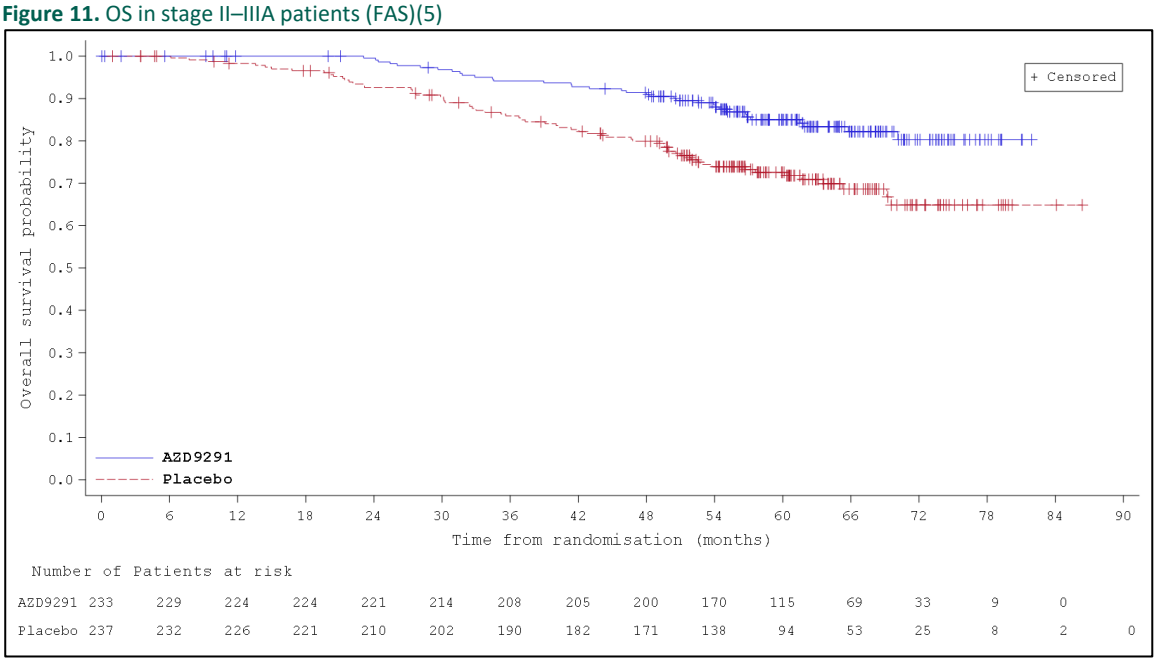
At the time of the DCO, OS data in the stage II–IIIA population had reached 21,3% maturity, with 100 deaths occurring overall. Median follow-up for OS in stage II–IIIA patients was 59.9 months in the osimertinib arm vs 56.2 months in the placebo arm.(5)
Osimertinib demonstrated unprecedented OS benefit which was highly statistically significant in patients with EGFR-mutated stage IB–IIIA NSCLC after complete resection (Figure 11, Table 8)

- The HR for an OS event in patients with stage II–IIIA NSCLC was 0.49 (95% CI 0.33, 0.73; p=0,0004), indicating a 60% reduction in risk of death for patients treated with osimertinib vs placebo, although this did not reach statistical significance(5)

- Based on KM estimates, the percentage of patients who remained alive in the osimertinib arm was 99.5% at 24 months, 94.1% at 36 months, 91% at 48 months, and 85% at 60 months compared with 92.6%, 85.9%, 79.9%, and 72.6% of patients in the placebo arm, respectively(5)

- Median OS not reached in either arm, for either population

Figure 11. OS in stage II–IIIA patients (FAS)(5)



***Footnotes**: alpha spending at 0,0497*

Source: AstraZeneca Data on File. ADAURA Clinical Study Report Addendum: Updated DFS Analysis DCO 11th April 2022.

Table 8. OS in stage II-IIIA patients (FAS)(5, 54) (FAS)(5)

	Osimertinib (N=233)	Placebo (N=237)
Events, n (%), 21.3% maturity[a]	35 (15.0)	65 (27.4)
Median OS, months (95% CI)	NR (NC, NC)	NR (NC, NC)
HR (95% CI; 99.98% CI;[b] p-value)	0.49 (0.33, 0.73; p=0.0004)	

***Footnotes:** [a]OS events that do not occur within two scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events. The analysis was performed using a log rank test stratified by stage (II vs IIIA), race (Asian vs Non-Asian) and mutation type (Ex19del vs L858R). The HR and CI are obtained directly from the U and V statistics[b]The adjusted CI is computed at the 2-sided 99.98% level, considering a 2-sided significance level of 0.0002 for the interim analysis, based on the Haybittle-Peto spending function.*

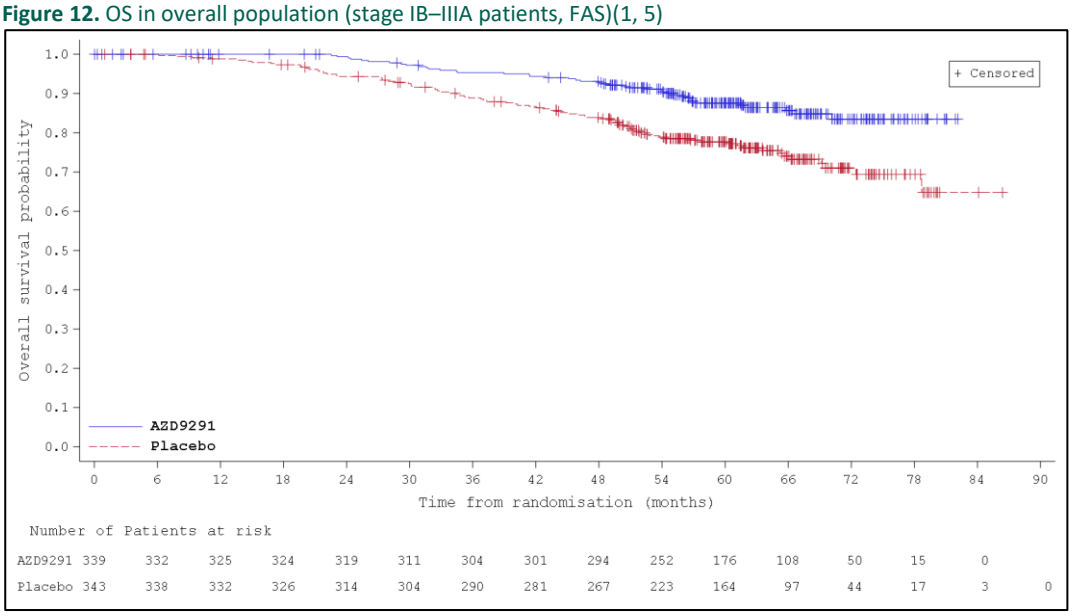
OS in the overall population (stage IB–IIIA patients). Updated with DCO January 2023

At the time of the DCO, OS data in the overall population had reached 18.3% maturity, with 124 events reported.(5) Median follow-up for OS in all patients was 59.9 months in the osimertinib arm vs 56.2 months in the placebo arm.(5)

Initial data suggest that, in all patients, osimertinib treatment provides a clinically meaningful improvement in OS, compared with placebo Figure 12, Table 9):

- The HR for OS in the overall population (stage IB–IIIA patients) was 0.48 (95% CI 0.23, 1.02; p=0.0553), indicating a 52% reduction in risk of death for patients treated with osimertinib vs placebo(5)
- Based on KM estimates, the percentage of patients who remained alive in the osimertinib arm was 99.6% at 24 months, and 93.9% at 36 months, compared with 94.7% and 91.8% of patients in the placebo arm, respectively(5)

Figure 12. OS in overall population (stage IB–IIIA patients, FAS)(1, 5)



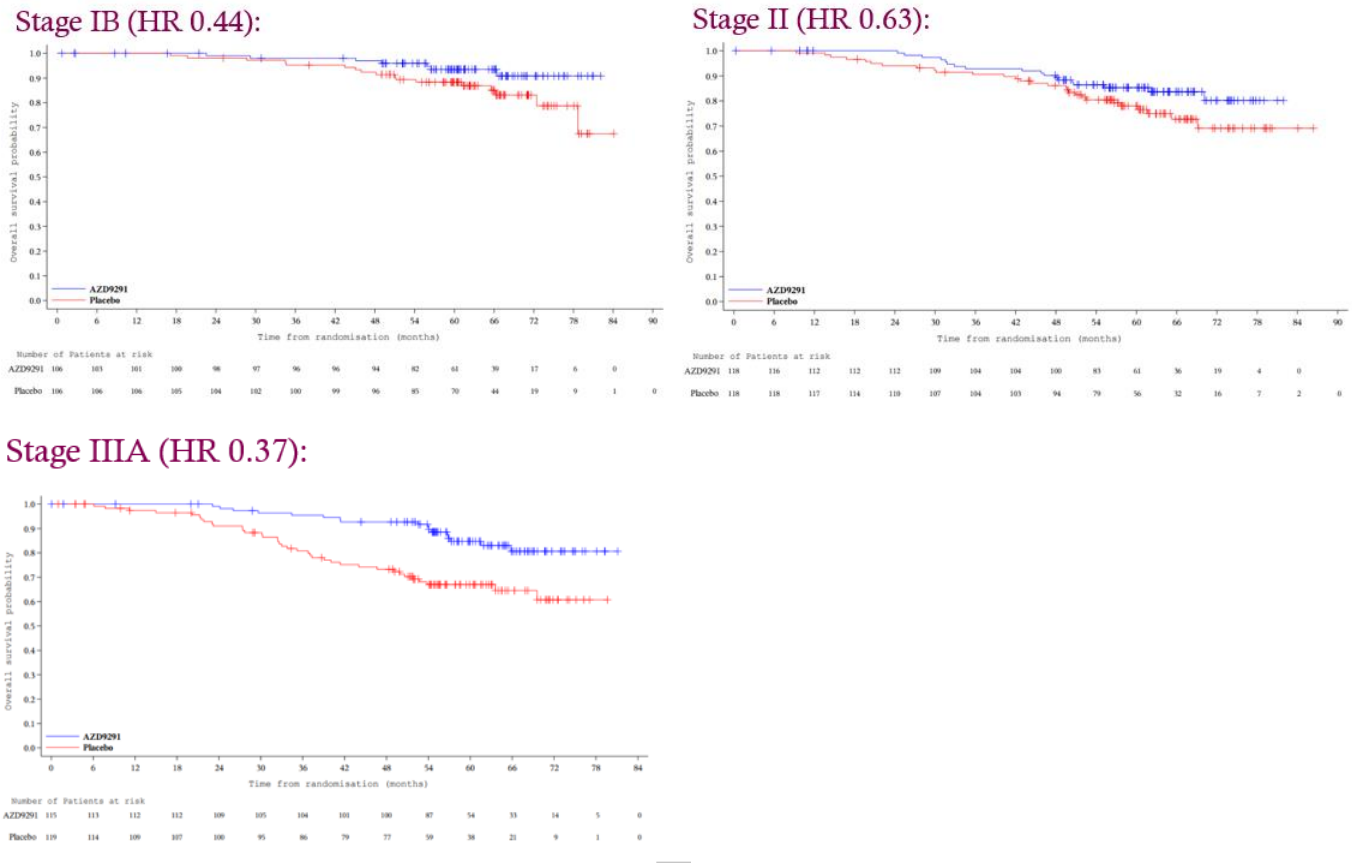
Source: AstraZeneca Data on File. ADAURA Clinical Study Report Addendum: Updated DFS Analysis DCO 11th April 2022.

Table 9. OS in overall population (stage IB–IIIA patients (FAS)(5, 54) FAS)(5)

	Osimertinib (N=339)	Placebo (N=343)
Events, n (%), 18.2% maturity[a]	42 (12.4)	82 (23.9)
Median OS, months (95% CI)	NR (NC, NC)	NC (NC, NC)
HR (95% CI; 99.98% CI;[b] p-value)	0.49 (0.34, 0.70; p<0.0001)	

Footnotes: *[a]OS events that do not occur within two scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events. The analysis was performed using an unstratified log rank test due to low event counts in the strata combinations. The HR and CI are obtained directly from the U and V statistics. [b]The adjusted CI is computed at the 2-sided 99.98% level, considering a 2-sided significance level of 0.0002 for the interim analysis, based on the Haybittle-Peto spending function.*

Figure 13.



Source: AstraZeneca Data on File ADAURA OS analysis Jan 2023.

Exploratory efficacy variables

A number of additional exploratory efficacy variables were investigated in ADAURA, with key endpoints presented in the following sub-sections. It should be noted, however, that the immaturity of DFS at the DCO limits the clinical significance of the reported results.

Site(s) of disease recurrence

A summary of disease recurrence status is shown in Table 9.
In stage II–IIIA patients, 32.2% of patients treated with osimertinib and 70.5% of patients treated with placebo experienced a disease recurrence event or death by the time of the updated DFS analysis (DCO 11th April 2022).(5, 54)
In both the osimertinib and the placebo arms, distant recurrence occurred most frequently (osimertinib: 16.3%;

placebo: 37.1%). The minority of patients experiencing a disease recurrence event had both local/regional and distant recurrence (osimertinib: 1.3%; placebo: 6.3%).(5, 54)

Similar results were observed in the overall study population, where 27.7% of osimertinib-treated patients, and 61.5% of placebo-treated patients, experienced a disease recurrence event or death by the time of the updated DFS analysis.(5, 54) As for the stage II–IIIA population, distant recurrence occurred most frequently in both the osimertinib (16.3%) and the placebo arms (37.1%). This finding differs from that reported for the primary analysis (DCO 17th January 2020), which showed that the majority of recurrence events in the osimertinib arm were local/regional only. Notably, in the osimertinib arm, the proportions of patients that experienced local/regional vs distant recurrences only were more balanced (stage II–IIIA population: 14.2% vs 16.3%, respectively; overall population: 12.4% vs 13.3%) than at the primary analysis (7.3% vs 3.4% and 6.8% vs 2.9%, respectively). (5, 54) This change in pattern of disease recurrence between analyses may be explained by the immaturity of these data at the primary analysis; given the increased maturity of data at the updated DFS analysis, the observations at this DCO are considered to be more representative of the true clinical pattern of recurrences in patients receiving adjuvant osimertinib therapy. (5, 54)

Nevertheless, given the percentage of patients with any distant disease recurrence remained lower in the osimertinib arm vs the placebo arm, the observed data continue to indicate that osimertinib may be active in providing effective systemic disease control, albeit by a smaller magnitude to that observed at the primary analysis. (5, 54).

Table 9. Disease recurrence status at time of DCO (FAS)**(5, 54)**

	Osimertinib	Placebo
Stage II–IIIA patients	**N=233**	**N=237**
Total disease recurrence or death	75 (32.2)	167 (70.5)
Disease recurrence	74 (31.8)	164 (69.2)
Local/regional only	33 (14.2)	61 (25.7)
Distant only	38 (16.3)	88 (37.1)
Local/regional and distant	3 (1.3)	15 (6.3)
Death[a]	1 (0.4)	3 (1.3)
Overall population (stage IB–IIIA patients)	**N=339**	**N=343**
Total disease recurrence or death	94 (27.7)	211 (61.5)
Disease recurrence	93 (27.4)	205 (59.8)
Local/regional only	42 (12.4)	78 (22.7)
Distant only	45 (13.3)	107 (31.2)
Local/regional and distant	6 (1.8)	20 (5.8)
Death[a]	1 (0.3)	6 (1.7)

Footnotes: *DCO: 11th April 2022. [a]Death in the absence of disease recurrence, or death occurring within 2 visits of baseline where the patient has no evaluable assessments or no baseline data*

Time to first and second subsequent anti-cancer therapies. Updated with DCO April 2022.

At the time of the updated DFS analysis (DCO 11th April 2022), time to first subsequent therapy (TFST) had reached 38.1% maturity. Median TFST was not calculable in the osimertinib arm, and 38.4 months in the placebo arm; the HR point estimate favoured osimertinib (Table 10).(5)

The time to second subsequent therapy (TSST) endpoint had reached 22.0% maturity at the updated DFS analysis. Median TSST was not calculable in both the osimertinib arm and the placebo arm; the HR point estimate favoured osimertinib (Table 10).(5)

A summary of the different classes of anti-cancer therapies received is shown in Table 11. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors were the most frequently received subsequent anti-cancer therapies.

Table 10. Time to first and second subsequent anti-cancer therapies (overall population, FAS)(5)

	Osimertinib (N=339)	Placebo (n=343)
TFST		
Events, n (%), 24.2% maturity	71 (20.9)	189 (55.1)
Death	8 (11.3)	18 (9.5)
First subsequent cancer therapy	63 (88.7)	171 (90.5)
Median TFST, months (95% CI)	NC (NC, NC)	38.4 (30.1, 46.2)
HR (95% CI; p-value)	0.26 (0.20, 0.33; p<0,0001)	
TSST		
Events, n (%), 10.4% maturity	44 (13.0)	106 (30.9)
Death	21 (47.7)	36 (34.0)
Second subsequent cancer therapy	23 (52.3)	70 (66.0)
Median TSST, months (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI; p-value)	0.37 (0.26, 0.50); p<0.0001	

Table 11. Summary of all subsequent anticancer therapies(overall population, FAS)(5)

	Osimertinib (N=339)	Placebo (n=343)
	n = 76 (22)	**n = 184 (54)**
EGFR-TKIs	58 (76)	162 (88)
Osimertinib	31 (41)	79 (43)
Gefitinib	13 (17)	55 (30)
Afatinib	7 (9)	30 (16)
Erlotinib	6 (8)	24 (13)
Icotinib	2 (3)	15 (8)
Aumolertinib Mesilate	1 (1)	1 (1)
Aumolertinib	0	1 (1)
Dacomitinib	0	1 (1)
Other EGFR-TKI	0	1 (1)
Epitinib	0	1 (1)
Furmonertinib	0	1 (1)
Chemotherapy		
Platinum compounds	20 (26)	43 (23)
Pemetrexed	13 (17)	27 (15)
Taxanes	8 (11)	20 (11)
Pyrimidine analogues	4 (5)	9 (5)
Vinca alkaloids and analogues	1 (1)	6 (3)
Etoposide	0	2 (1)
Anthracyclines and related substances	1 (1)	1 (1)
Irinotecan	1 (1)	1 (1)
Cyclophosphamide	0	1 (1)
Radiotherapy	30 (39)	53 (29)

Other anticancer treatments		
VEGF / VEGF receptor inhibitors	5 (7)	18 (10)
PD-1 / PD-L1 inhibitors	4 (5)	6 (3)
Unspecified herbal / traditional medicine	2 (3)	3 (2)
Other protein kinase inhibitors	1 (1)	4 (2)
Denosumab	1 (1)	3 (2)
VEGF receptor-TKIs	0	2 (1)
Other antineoplastic agents	1 (1)	0
Crizotinib	0	1 (1)
Amivantamab	0	1 (1)

Source: *Tsuboi et. al 2023, supplementary appendices*

PFS. Updated with DCO January 2023.

At the updated PFS analysis (DCO January 2023), PFS in the overall population had reached 20.4% maturity. Median PFS was not calculable in the osimertinib arm, and was 66.2 months in the placebo arm; the HR point estimate favoured osimertinib (Table 12).(5)

Table 12. Analysis of progression-free survival (Full analysis set: overall population). DCO Jan 2023

	Osimertinib (N=339)	Placebo (n=343)
Events, n (%), 8.7% maturity	40 (11.8)	99 (28.9)
Median PFS, months (95% CI)	C (NC, NC)	66.2 (66.2, NC)
HR (95% CI; p-value)	0.32 (0.23, 0.45; p<0.0001)	

Footnotes: *DCO 11th April 2022. The analysis was performed using a log rank test stratified by stage (IB vs II vs IIIA), race (Asian vs Non-Asian) and mutation type (Ex19del vs L858R). Stratification factors are as recorded in IVRS. A hazard ratio <1 favours AZD9291. The HR and CI are obtained directly from the U and V statistics (Berry, et al. [1991]; Selke & Siegmund [1983]). [a]PFS events are type of disease progression after disease recurrence or death. Patients will be censored at the latest progression assessment date or disease recurrence assessment date if the patient has not had a recurrence, progression or death.*

Analysis of CNS recurrence. Updated DCO April 2022

As osimertinib has previously shown CNS efficacy in patients treated in the advanced/metastatic setting, an exploratory analysis of CNS recurrence was performed.(5)

In the overall population 75 patients were reported to have experienced disease recurrence in the CNS or death, with the majority of these events occurring in patients with stage II–IIIA disease (36 patients).(54) by the time of the updated DFS analysis (DCO 11th April 2022), with the majority of these events occurring in patients with stage II–IIIA disease (63 patients). A clinically meaningful improvement in investigator-assessed CNS DFS for patients on osimertinib compared to patients on placebo was observed (Table 13).

Patients with stage II–IIIA NSCLC:

- HR of 0.24 (95% CI 0.14, 0.42; 2-sided p<0.0001), indicating a 76% reduction in risk of CNS recurrence or death (5)
- Based on KM estimates, the percentage of patients who remained CNS recurrence-free at 60 months was 78.6% in the osimertinib arm vs 69.3% in the placebo arm (5)

Overall population (stage IB–IIIA patients):

- HR of 0.36 (95% CI 0.23, 0.57; 2-sided p<0.0001), indicating an 64% reduction in risk of CNS recurrence or death (5, 54)
- Based on KM estimates, the percentage of patients who remained CNS recurrence-free at 60 months was 84.8% in the osimertinib arm vs 77.2% in the placebo (5)

Whilst the number of events within this analysis are small, the low number of events in the osimertinib arm and the clinically meaningful difference between treatment arms support previous findings of osimertinib CNS activity.(5)

Table 13. Summary of disease recurrence in the CNS(5, 54)

	Osimertinib	Placebo
	N=233	**N=237**
Events, n (%)[a]	22 (9.4)	41 (17.3)
CNS recurrence	18 (7.7)	32 (13.5)
Death[b]	4 (1.7)	9 (3.8)
HR (95% CI; p-value)[c]	0.24 (0.14, 0.42; p<0.0001)	
	N=339	**N=343**
Events, n (%)[a]	25 (7.4)	50 (14.6)
CNS recurrence[d]	20 (5.9)	38 (11.1)
Death[b]	5 (1.5)	12 (3.5)
HR (95% CI; p-value)[c]	0.36 (0.23, 0.57; p<0.0001)	

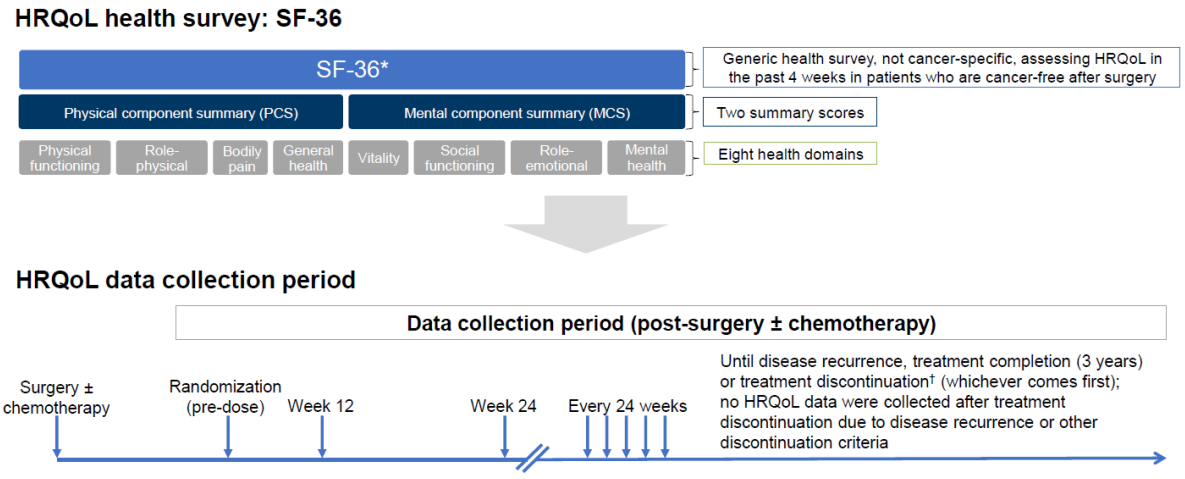
***Footnotes**: DCO 11th April 2022. [a]DFS events are defined as disease recurrences in the CNS, or death. DFS events that do not occur within two scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events; [b]Death in the absence of CNS disease recurrence, or death occurring within two visits of baseline where the patient has no evaluable assessments or no baseline data; [c]The analysis was performed using an unstratified log rank test due to low event counts in the strata combinations. The HR and CI are obtained directly from the U and V statistics (Berry G, et al. A comparison of two simple hazard ratio estimators based on the logrank test. Stat Med. 1991;10(5): 749-755; Sellke T, Siegmund D. Sequential Analysis of the Proportional Hazards Model. Biometrika 1983; 70(2):315-326); [d]Patients E5708002 (osimertinib arm) and E4314002 (placebo arm) were included as having CNS recurrence; however, those patients had CNS metastases.*

Health-related quality of life(DCO January 2020)

A generic HRQoL questionnaire (SF-36) was selected as the patient reported outcome endpoint in ADAURA. The rationale for this was that adjuvant-stage patients with no evidence of disease, such as those enrolled in ADAURA, are predominantly asymptomatic and, compared with a lung cancer-specific questionnaire, a generic HRQoL measure was considered to better capture the different aspects of physical and mental health of these patients.(5)
In the overall population, compliance rates for SF-36 were high (>90%) in both study arms, from baseline through to Week 144, with a minor reduction to 87.2% and 84.8% at Week 156 in the osimertinib and placebo arms, respectively.(5)

SF-36 was collected at randomization (pre-dose) and then at 12 weeks, 24 weeks and then every 24 weeks relative to randomization until recurrence, treatment discontinuation or treatment completion (55) (Figure 14).

Figure 14. SF-36 domains and data collection period

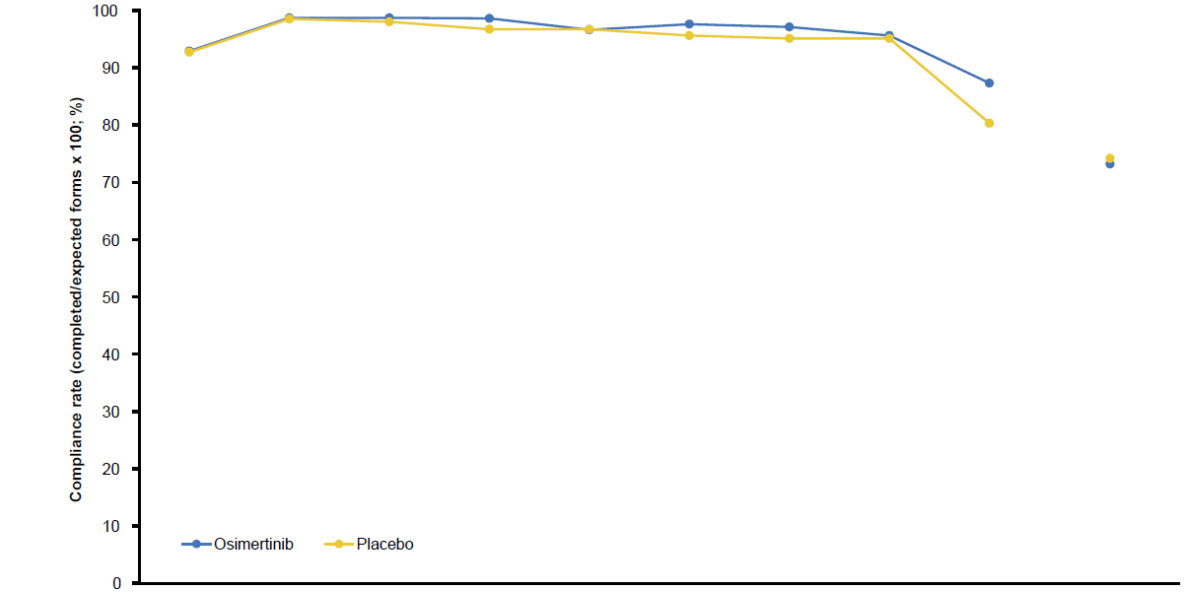


Source: John et al. (55), Supplementary Fig. 2.

Baseline SF-36 scores, including both individual health domains and component scores, were comparable between study arms. Mean baseline Physical Component Summary (PCS) scores and Mental Component Summary (MCS) scores indicated that patients enrolled in ADAURA were highly functioning in terms of the physical and mental subcomponents of HRQoL, with a relatively small degree of impairment in comparison to the general population; the greatest impairment was observed in the following SF-36 health domains: Role Limitations–Physical, Social Functioning and Role Limitations–Emotional.(5)

All randomized patients were included in HRQoL analyses, and compliance rates were high across time points in both groups (baseline: 93% [n = 314 of 338] and 93% [n = 316 of 341]; week 156: 87% [n = 193 of 221] and 80% [n = 110 of 137]; discontinuation: 73% [n = 82 of 112] and 74% [n = 147 of 198] in the osimertinib and placebo groups, respectively (Figure 15).

Figure 15 HRQoL compliance rates over time

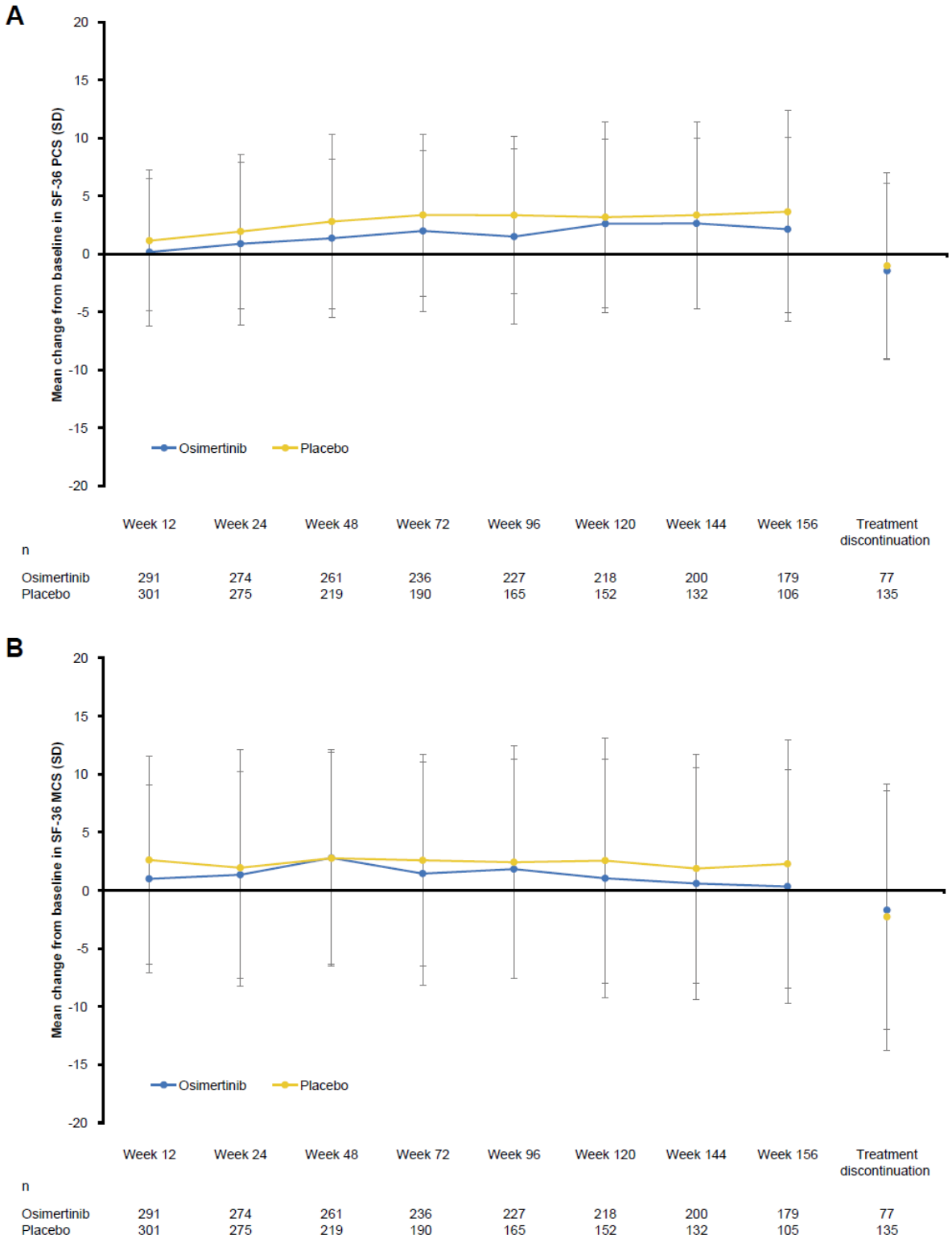


Expected forms (N)										
Osimertinib	338	316	298	284	262	249	238	225	221	112
Placebo	341	329	301	241	209	182	164	144	137	198

Source: John et al. (55)Supplementary Fig. 4.

Differences in SF-36 PCS between osimertinib and placebo were minimal at all time points, including at the treatment discontinuation visit (<1.5 points). Differences of less than 3 points were observed across time points for SF-36 MCS. Most patients in both groups remained stable or had improvements in SF-36 PCS and MCS T-scores up to week 156, compared with baseline. On the basis of definitions from the SF-36 third edition scoring manual, there were no clinically meaningful changes from baseline in mean SF-36 PCS or MCS T-scores in either group (Fig. 5 A and B).

Figure 16. Change in (A) SF-36 PCS and (B) MCS T-scores from baseline to week 156 and at treatment discontinuation in the overall population



MCS: Mental component summary; PCS: Physical component summary; SF-36, Short-Form-36 health survey.

Source: John et al. (55)Figure 4A and B.

The absolute values and change from baseline was be calculated for each domain and summary scale at each scheduled post-baseline assessment. The visit response to the SF-36v2 at each assessment was categorized as improved, worsened and stable based on the changes from baseline using the criteria for a minimum clinically important difference (MCID) as shown in Table 14 .

Table 14. Visit response categories based on the changes from baseline

	Visit response		
Score	**Improved**	**Worsened**	**Stable**
PCS	≥ + 3.1	≤ - 3.1	Otherwise
MCS	≥ + 3.8	≤ - 3.8	Otherwise
PF	≥ + 3.5	≤ - 3.5	Otherwise
RP	≥ + 3.2	≤ - 3.2	Otherwise
BP	≥ + 4.5	≤ - 4.5	Otherwise
GH	≥ + 5.7	≤ - 5.7	Otherwise
VT	≥ + 5.5	≤ - 5.5	Otherwise
SF	≥ + 5.0	≤ - 5.0	Otherwise
RE	≥ + 3.8	≤ - 3.8	Otherwise
MH	≥ + 5.5	≤ - 5.5	Otherwise

Source: EMA (2021) (ADAURA EPAR, Table 32); Tsuboi (9) ADAURA protocol

For missing data, imputation rules were implemented per user's manual for SF-36V2 Health Survey, third edition. Subscale raw scores were imputed if at least half of the subscale items were available using the mean value of the available items of the respective subscale.

HRQoL, as measured by SF-36 health domains and component summary scores, was maintained overall in both treatment arms. The proportion of patients reporting clinically relevant improvements from baseline in PCS over time increased in both osimertinib and placebo arms from Week 12 (29.9% vs 33.2%) to Week 48 (41.0% vs 50.2%), declined transiently at Week 72 (38.7% vs 50.0%), and again increased at Week 96 (43.0% vs 53.2%). In both the osimertinib and placebo arms, the proportion of patients reporting a clinically meaningful improvement in MCS from baseline increased from Week 12 (34.4% vs 41.5%) to Week 48 (46.4% vs 49.3%), followed by a decrease to Week 96 (37.0% vs 44.4%).(5)

Time to deterioration in PCS and MCS (stage II–IIIA patients)

Time to deterioration (TTD) of HRQoL was defined as time from date of randomisation to:(5)

- The date of first clinically important worsening confirmed at the subsequent assessment, or
- Death (by any cause) in the absence of a clinically important worsening, provided death occurred within two assessment visits of the last assessment where HRQoL could be evaluated and regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to symptom deterioration

Over 75% of patients with stage II–IIIA disease did not experience a clinically meaningful deterioration in PCS or death (osimertinib: 75.1%; placebo: 83.5%), or a clinically meaningful deterioration in MCS or death (osimertinib: 77.7%; placebo: 78.1%;Table 15):

Confirmed deterioration in PCS or death was seen in 58 patients (24.9%) in the osimertinib arm and in 39 patients (16.5%) in the placebo arm(5):

- A trend of shorter TTD of PCS or death was observed in the osimertinib arm (HR 1.43, 97.5% CI 0.90, 2.25; p=0.0817)
- The median TTD was not reached in either treatment arm

Confirmed deterioration in MCS or death was seen in 52 patients (22.3%) in the osimertinib arm and in 52 (21.9%) patients in the placebo arm(5)

- No difference in TTD of MCS or death was observed between the osimertinib and placebo arms (HR 0.90, 97.5% CI 0.58, 1.40; p=0.5949)
- Median TTD was 39.0 months (95% CI NC, NC) in the osimertinib arm and was not reached for the placebo arm at the time of analysis

Table 15. Summary of SF-36 TTD (FAS, stage II–IIIA patients)(5)

	Osimertinib (N=233)	Placebo (N=237)
Total number of patients with confirmed deterioration or death	58 (24.9)	39 (16.5)
Deterioration	57 (24.5)	37 (15.6)
Death	1 (0.4)	2 (0.8)
Median deterioration-free survival (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI; p-value)	1.43 (0.96, 2.13; p=0.0817)	
Total number of patients with confirmed deterioration or death	52 (22.3)	52 (21.9)
Deterioration	51 (21.9)	49 (20.7)
Death	1 (0.4)	3 (1.3)
Median deterioration-free survival (95% CI)	39.0 (NC, NC)	NC (NC, NC)
HR (95% CI; p-value)	0.90 (0.61, 1.33; p=0.5949)	

Treatment exposure(DCO April 2022)

At the updated DFS analysis (DCO 11th April 2022), the median duration of follow-up was 44.2 months in the osimertinib arm, and 19.6 months in the placebo arm(3).
The duration of treatment exposure is summarised in table 16. The median duration of exposure to osimertinib was longer than the exposure to placebo (35.8 vs 25.1 months). In both arms, the median total treatment duration was similar to the median actual (excluding dose interruptions) treatment duration, showing that most patients were able to receive the assigned treatment and that the duration of any treatment interruptions was short (3).

Table 16 Duration of exposure in ADAURA (SAS; updated DFS analysis)

Duration of osimertinib or placebo exposure	**Osimertinib**	**Placebo**
Median treatment duration, months (range)[a]	35.8 (0, 38)	25.1 (0, 39)
Median actual treatment duration, months (range)[b]	35.4 (0, 38)	25.1 (0, 39)

Footnotes: *DCO: 11th April 2022. [a]Total exposure time = ((last dose date where dose >0 mg – first dose date) + 1)/30.4375; [b]Actual exposure time = ((last dose date where dose >0 mg – first dose date) + 1) – total duration of dose interruption (i.e. number of days with dose = 0 mg))/30.4375.*
Source: John el al 2023 (3)

Overview of AEs in ADAURA(updated with DCO April 2022)

At the updated DFS analysis (DCO 11th April 2022), the majority of patients in both study arms reported an AE (osimertinib: 97.9%; placebo: 90.1%)(56) AEs of any cause, including Grade ≥3 AEs, occurred in a greater proportion of patients in the osimertinib arm, compared with the placebo arm (
Tabel 17); however, the majority of AEs in the osimertinib arm were non-serious, mild or moderate in severity, and did not lead to treatment discontinuation. Similar results were observed when considering only the AEs that were causally related to study treatment; notably, the analysis of these AEs indicates that a large proportion of Grade ≥3 AEs were not due to study treatment. In total, there was one fatal AE in the osimertinib arm and two fatal AEs in the placebo arm; these were not causally related to treatment. (1)
A review of categorical AE data split by disease stage (analysed separately for patients staged with II–IIIA, and IB disease) did not reveal any notable differences in terms of the incidences of patients with any AE, SAEs, Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 AEs, AEs leading to permanent discontinuation of randomised treatment, and AEs leading to dose modifications, to that observed in the overall SAS.

Dose interruptions due to AEs occurred in a higher proportion of patients in the osimertinib arm (27.0%) compared with the placebo arm (12.5%). In both arms, the median total treatment duration was similar to the median actual (excluding dose interruptions) treatment duration, showing that most patients were able to receive the assigned treatment and that the duration of any treatment interruptions was short.(56, 57)

Dose reductions and treatment discontinuations followed a similar trend. In the osimertinib arm:

- Stomatitis (five patients, 1.5%) and paronychia (four patients, 1.2%) were the most common AEs leading to dose reductions, followed by hypertension, diarrhoea, nausea and prolonged QT interval (two patients each, 0.6%)
- Interruptions due to AEs were mostly driven by diarrhoea and stomatitis
- The most common AE leading to treatment discontinuation was ILD, occurring in 2.4% of patients, followed by diarrhoea, decreased appetite and pruritus (all 0.9%)

With the exception of hypertension and nausea, these AEs are well-characterised osimertinib adverse drug reactions (ADRs) and are consistent with the known safety profile of osimertinib; these findings are therefore not unexpected.

Tabel 17. Summary of AEs

AEs	Osimertinib (N=337)	Placebo (N=343)	RR (95% CI)
AEs due to any cause			
All grade AEs, n (%)	330 (97.9)	309 (90.1)	1.09 (1.05; 1.13)
Grade ⩾3 AEs, n (%)	79 (23.4)	48 (14.0)	1.68 (1.21; 1.32)
SAEs, n (%)[a]	68 (20.2)	47 (13.7)	1.47 (1.05; 2.07)
Deaths, n (%)	1 (0.3)	2 (0.6)	0.51 (0.05; 5.59)
Dose interruptions due to AEs, n (%)	91 (27.0)	43 (12.5)	2.15 (1.55; 3.00)
Dose reductions due to AEs, n (%)	42 (12.5)	3 (0.9)	14.25 (4.46; 45.53)
Discontinuations due to AEs, n (%)	43 (12.8)	9 (2.6)	4.86 (2.41; 9.82)
AEs causally related to study treatment[b]			
All grade AEs, n (%)	308 (91.4)	199 (58.0)	1.58 (1.43; 1.73)
Grade ⩾3 AEs, n (%)	36 (10.7)	7 (2.0)	5.23 (2.36; 11.60)
SAEs, n (%)[a]	10 (3.0)	2 (0.6)	5.09 (1.12; 23.05)
Deaths, n (%)	0	0	NC
Discontinuations due to AEs, n (%)	35 (10.4)	5 (1.5)	7.12 (2.83; 17.97)

Footnotes: *DCO: 11th April 2022. [a]Includes events with an outcome of death. [b]AEs assessed by investigator. NC: Not calculable.*
Source*: AstraZeneca Data on File. ADAURA Clinical Study Report Addendum: Updated DFS Analysis DCO 11th April 2022 (1)*

Common AEs(updated with DCO April 2022)

A summary of AEs reported for ≥10% of patients in the either treatment arm is presented in Table 18. The most frequently reported AEs in the osimertinib arm were diarrhoea, paronychia, dry skin, pruritus, cough, and stomatitis. The most frequently reported AEs in the placebo arm were diarrhoea and cough(table 18).
Between treatment arms, the incidence of the AEs of diarrhoea, paronychia, dry skin, pruritus, stomatitis, and decreased appetite were reported with an incidence of at least 10 percentage points higher in the osimertinib arm;

these AEs (with the exception of decreased appetite) have previously been identified as osimertinib ADRs based on a full evaluation of data across the entire clinical programme, and are therefore not unexpected.

Table 18 AEs reported in ≥10% of patients in the either treatment arm (SAS; updated DFS analysis)

MedDRA preferred term, n (%)	Osimertinib (N=337)	Placebo (N=343)
Diarrhoea	159 (47.2)	70 (20.4)
Paronychia	92 (27.3)	5 (1.5)
Dry skin	84 (24.9)	23 (6.7)
Pruritus	70 (20.8)	30 (8.7)
Cough	66 (19.6)	61 (17.8)
Stomatitis	59 (17.5)	15 (4.4)
Upper respiratory tract infection	53 (15.7)	37 (10.8)
Nasopharyngitis	50 (14.8)	36 (10.5)
Decreased appetite	48 (14.2)	13 (3.8)
Dermatitis acneiform	41 (12.2)	16 (4.7)
Mouth ulceration	39 (11.6)	10 (2.9)
Weight decreased	35 (10.4)	9 (2.6)
Nausea	34 (10.1)	20 (5.8)
Arthralgia	23 (6.8)	37 (10.8)

Footnotes: *DCO: 11th April 2022. Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy; MedDRA version 24.1.* ***Source****: AstraZeneca Data on File. ADAURA Clinical Study Report Addendum: Updated DFS Analysis DCO 11th April 2022 and John et al (1, 3)*

Grade ≥3 AEs (updated DCO April 2022)

Overall, the proportion of patients who had a Grade ≥3 AE was low in both treatment arms (osimertinib: 23.4%; placebo: 14.0%), indicating that the majority of AEs reported in the study were mild or moderate in severity. A summary of Grade ≥3 AEs reported in more than two patients in either treatment arm is presented in

Table 19. The most common AEs of Grade ≥3 were diarrhoea, stomatitis, pneumonia and electrocardiogram QT prolonged in the osimertinib arm, and pneumonia and hypertension in the placebo arm.
A total of 36 patients (10.7%) had Grade ≥3 AEs considered by the investigator to be causally related to osimertinib treatment, with paronychia, stomatitis, diarrhoea, ECG QT prolonged, ejection fraction decreased and decreased appetite being reported as causally related in ≥2 patients. These AEs (with the exception of decreased appetite) are well characterised osimertinib adverse drug reactions and are consistent with the known osimertinib safety profile.

Table 19. Summary of Grade ≥3 AEs reported in ≥2 patients in either treatment arm (SAS; updated DFS analysis)

MedDRA preferred term, n (%)	Osimertinib (N=337)	Placebo (N=343)
Patient with any Grade ≥3 AE	68 (20.2)	47 (13.4)
Diarrhoea	9 (2.7)	1 (0.3)
Stomatitis	6 (1.8)	0
Pneumonia	4 (1.2)	4 (1.2)
Electrocardiogram QT prolonged	4 (1.2)	1 (0.3)
Paronychia	3 (0.9)	0
Hypertension	3 (0.9)	4 (1.2)
Gastroenteritis	2 (0.6)	0
Upper respiratory tract infection	2 (0.6)	0
Viral upper respiratory tract infection	2 (0.6)	0
Decreased appetite	2 (0.6)	0
Cataract	2 (0.6)	0
Femur fracture	2 (0.6)	1 (0.3)
Osteoarthritis	0	2 (0.6)
Hyperuricaemia	2 (0.6)	1 (0.3)
Hyponatraemia	2 (0.6)	1 (0.3)
Large intestine polyp	2 (0.6)	0
Ureterolithiasis	2 (0.6)	0
Asthenia	1 (0.3)	2 (0.6)
Ejection fraction decreased	2 (0.6)	1 (0.3)
Neutrophil count decreased	2 (0.6)	0
Weight decreased	2 (0.6)	0

Footnotes: *DCO: 11th April 2022. Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy; MedDRA version 24.1; CTCAE version 4.03.* ***Source****: AstraZeneca Data on File. ADAURA Clinical Study Report Addendum: Updated DFS Analysis DCO 11th April 2022 (1).*

Serious AEs(updated DCO April 2022)

SAEs were reported in 20.2% of osimertinib-treated patients and 13.7% of placebo-treated patients, with pneumonia being the most commonly reported SAE in both treatment arms (Table 20).

Table 20. SAEs reported in ≥2 patients in either treatment arm (SAS; updated DFS analysis)

MedDRA preferred term, n (%)	Osimertinib (N=337)	Placebo (N=343)
Patient with any SAE		
Pneumonia	5 (1.5)	4 (1.2)
Cataract	2 (0.6)	0
Diarrhoea	2 (0.6)	0
Acute kidney injury	2 (0.6)	0
Ureterolithiasis	2 (0.6)	0
Femur fracture	2 (0.6)	1 (0.3)
Influenza	2 (0.6)	0
Hyperuricaemia	2 (0.6)	1 (0.3)
Large intestine polyp	2 (0.6)	0

Footnotes: *DCO: 11th April 2022. Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy; MedDRA version 24.1.* ***Source****: AstraZeneca Data on File. ADAURA Clinical Study Report Addendum: Updated DFS Analysis DCO 11th April 2022 (1)*

AEs of special interest (updated DCO April 2022)

AEs of special interest for osimertinib, which are AEs considered to be potential risks associated with osimertinib treatment, are summarised in Table 21. At the updated DFS analysis (DCO 11th April 2022), with the exception of the ejection fraction decreased AE, all events for AEs of special interest for osimertinib occurred in the osimertinib arm; a decreased ejection fraction was observed in 4.5% of patients treated with osimertinib and 2.6% of patients treated with placebo.

Table 21. AEs of special interest for osimertinib (updated DFS analysis)

AEs, n (%)	Osimertinib (N=337)	Placebo (N=343)
Interstitial lung disease[a]		
Interstitial lung disease	8 (2.4)	0
Pneumonitis	3 (0.9)	0
Ejection fraction decreased	15 (4.5)	9 (2.6)
Cardiac failure	1 (0.3)	0
Pulmonary oedema	1 (0.3)	0
Cardiac myopathy	2 (0.6)	0

Footnotes: *DCO: 11th April 2022. [a]Interstitial lung disease comprising the following MedDRA preferred terms: interstitial lung disease, pneumonitis, acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, lung disorder, pulmonary toxicity, and pulmonary fibrosis****. Source****: AstraZeneca Data on File. ADAURA Clinical Study Report Addendum: Updated DFS Analysis DCO 11th April 2022 (1).*

Deaths (updated with DCO April 2022)

Overall, by the time of the updated DFS analysis (DCO 11th April 2022), 28 (8.3%) patients treated with osimertinib and 65 (19.0%) patients treated with placebo died (Table 22); the majority of these occurred post-disease recurrence. The majority of deaths were due to NSCLC, and not reported as AEs. There were two fatal AEs in the placebo arm, which was also related to the underlying disease, and one fatal AE in the osimertinib arm.

Table 22. All deaths in ADAURA (FAS; updated DFS analysis)

	Osimertinib (N=339)	Placebo (N=343)
Total number of deaths, n (%)	28 (8.3)	65 (19.0)
Death due to NSCLC only	24 (7.1)	51 (14.9)
AE with outcome of death only	1 (0.3)	1 (0.3)
AE with outcome of death only with start date falling after 28-day follow-up period	0	0
Death related to NSCLC and AE with an outcome of death	0	1 (0.3)
Other deaths[a]	1 (0.3)	8 (2.3)

Footnotes: *DCO: 11th April 2022. Death related to NSCLC is determined by the investigator; rows are mutually exclusive, patients are only reported in one category. [a]Patients who died and are not captured in the earlier categories.* ***Source****: AstraZeneca Data on File. ADAURA Clinical Study Report Addendum: Updated DFS Analysis DCO 11th April 2022 (1)*

Conclusions data and safety(DCO April 2022)

Following recommendation from an independent data monitoring committee after determination of overwhelming efficacy, the ADAURA study was unblinded early, and demonstrated that osimertinib has a positive benefit-risk profile for the treatment of patients with stage IB–IIIA EGFRm NSCLC who have undergone complete tumour resection (with or without adjuvant chemotherapy) at the primary and subsequent updated DFS analyses.
Consistent with the overwhelming efficacy observed at the primary analysis (DCO 17th January 2020), in the updated DFS analysis (DCO 11th April 2022), ADAURA demonstrated a clinically significant 77% reduction in the risk of disease recurrence or death for patients with stage II–IIIA disease treated with osimertinib, compared with patients randomised to placebo (HR 0.23; 95% CI 0.18, 0.30; 2-sided p<0.0001). Similarly, in the overall population, a clinically significant 73% reduction in the risk of disease recurrence or death was observed for patients in the overall population randomised to osimertinib compared with patients randomised to placebo (HR 0.27; 95% CI 0.21, 0.34; 2-sided p<0.0001). The increased data maturity at the updated DFS analysis and the magnitude of treatment benefit for patients in the osimertinib arm in both the stage II–IIIA and overall populations, in combination with continuing narrow CIs of the HR, provides further confidence that these results are a reliable estimate of treatment benefit. A clinically meaningful DFS benefit of osimertinib was also consistently observed in all pre-specified subgroups with sufficient events for analysis.
OS is a secondary outcome in ADAURA and immature OS data was the key issue raised by DMC in the 2022 rejection. Updated data was presented and published in May this year. Among patients with stage II to IIIA disease, the 5-year OS showed a significant and mature result (overall HR for death, 0.49; 95.03% CI 0.33, 0.73; p<0.001). In the overall population, the 5-year OS result was HR= 0.49; 95.03% CI 0.34, 0.70; p<0.001.

HRQoL was maintained in both study arms, with more than 75% of stage II–IIIA patients not experiencing a clinically meaningful deterioration in the physical and mental components of the SF-36 or death. This is of particular importance considering the negative impact of alternative treatment options on patients' HRQoL. Furthermore, at the updated DFS analysis, an exploratory analysis of CNS recurrences demonstrated a clinically meaningful 76% and 64% reduction in the risk of CNS disease recurrence or death in the osimertinib arm compared to placebo for both stage II–IIIA patients (HR 0.24; 95% CI 0.14; 0.42; p<0.0001) and the overall population (HR 0.36 (95% CI 0.23; 0.57; p<0.0001), respectively; as CNS recurrence is known to have a detrimental impact on patients' quality of life, these data support the further positive benefit of osimertinib in this treatment setting beyond DFS alone.
Osimertinib was shown to be generally well-tolerated, with the majority of AEs non-serious, mild or moderate in severity, and not resulting in treatment discontinuation. There were no clinically significant changes in safety observed from the primary analysis (DCO 17th January 2020) to the updated DFS analysis (DCO 11th April 2022). From ADAURA, it can be concluded that osimertinib has an acceptable safety and tolerability profile for treating patients with EGFRm NSCLC in the adjuvant setting, consistent with previous clinical studies and post-marketing experience in the advanced and metastatic settings(1, 3)

Overall, the benefit-risk balance for the long-term use (36-month treatment duration) of osimertinib in patients in the curative setting is positive, and it is anticipated that osimertinib will provide a substantial advancement in the clinical management of stage IB–IIIA EGFRm NSCLC. AstraZeneca believe that the updated and mature data will answer the questions and uncertainty that was raised by DMC based on the primary analysis.

For detailed efficacy and safety results, refer to Appendices D and E.

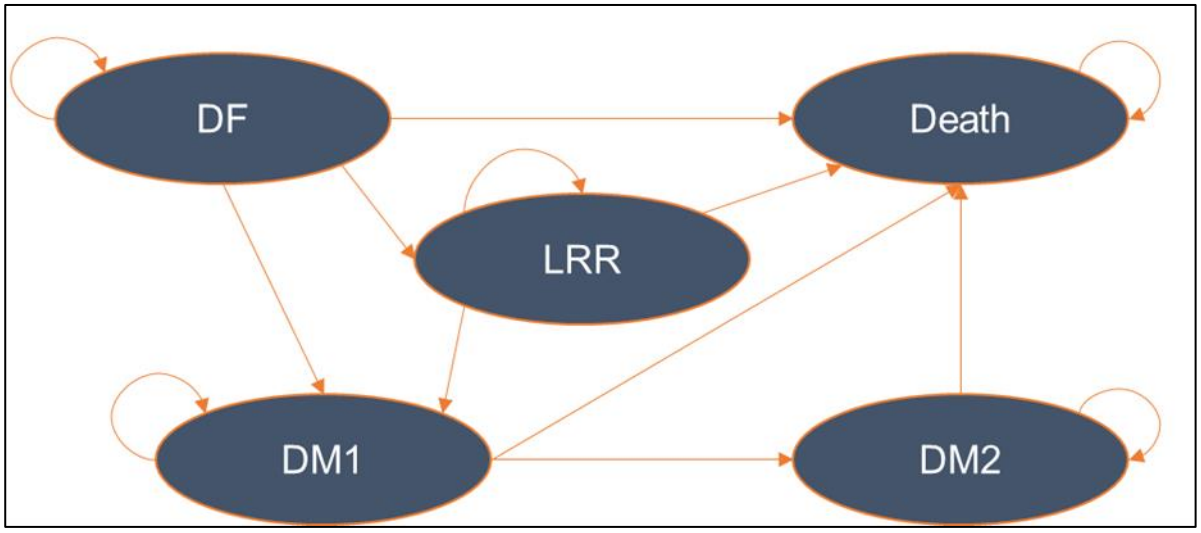
8. Health economic analysis

The purpose of the health economic analysis is to examine the cost effectiveness of osimertinib as adjuvant treatment in comparison to active monitoring in Stage IB-IIIA NSCLC patients with EGFR-mutation who are completely tumour-resected. A cost-utility analysis was performed, comparing osimertinib with active monitoring and the outcomes of the analysis were incremental costs per quality-adjusted life year (QALY), and life year (LY) gained.
Both the quality of life and life span are of interest as the patient population is associated with relatively short survival. Hence, additional lifetime spent with the best possible health-related quality of life (HRQoL) was considered as relevant. The base-case analysis includes both direct treatment and healthcare utilization costs as well as indirect costs associated with the treatment in accordance with limited societal perspective.

8.1 Model

A *semi*-Markov model was developed in Microsoft Excel, comprising five health states that represent the disease course and survival of patients over time: EGFR-mutated NSCLC patients enter the model in the health state of disease free 'DF', which is defined as the time of progression free survival, post resection, in early stages. For each cycle patients were set to stay in DF until the occurrence of 'Death', locoregional recurrence 'LRR' or distant metastases with 1st line treatment 'DM1'. Patients progressed to DM1 from either DF or LRR can further progress to 2nd line treatment for distant metastases 'DM2', or 'Death' as the absorbing state (Figure 17).
The starting age (63 years, i.e., mean age from ADAURA) and gender distribution (70.1% female based on the overall population of ADAURA) at model entry reflected the baseline characteristics of patients in the ADAURA trial. (58)

Figure 17. Cost-effectiveness Model Structure



The model used a cycle length of 4.35 weeks (30.44 days) to align with recurrent costs and timing of patients' treatment and was sufficiently granular to capture events occurring as a patient's disease progresses. A half cycle correction was applied to adjust for the timing of state transitions throughout each cycle.
Treatment costs included costs of drug acquisition, administration, and monitoring. Costs associated with adverse events (AEs) were estimated per episode and were applied once at the beginning of the simulation, based on the proportion of patients in each treatment arm who experience each AE. In accordance with the Medicinrådet guidelines for the submission, a 3.5 % discount rate was applied in the base case for both costs and benefits (QALYs) in the first 35 years. Beyond 35 years, 2.5% discount rate was applied for the last 2 years of the 37-year time horizon used in the base case. For a treatment that affects mortality, a life-long perspective needs to be used to capture the whole difference in costs and health effects. Hence, the model uses a lifetime horizon.

To ensure that it reflects Danish clinical practice, two clinical experts were consulted to ensure that the clinical pathway and disease complexity as well as important differences in costs and outcomes between treatments were accurately captured by the model (59, 60).

The model design was based on the approaches that have been accepted in past NICE appraisals for the adjuvant treatment of cancer. The approach is consistent with previous NICE technology appraisals in early-stage cancer (TA107, TA424, TA569 and TA632), and the model structure was discussed and validated at an independent UK clinical advisory board in November 2020. The adopted method provides numerous advantages over alternative modelling approaches, such as the partitioned survival model, that are more frequently used for cost-effectiveness studies in metastatic cancer.

Firstly, the partitioned survival model relies heavily on the direct extrapolation of overall survival data, which is highly uncertain in situations of low OS data maturity (18% for stage IB-IIIA in ADAURA). With state transition models, the overall survival curve is estimated indirectly through the transition of patients between states, whose risk profile can

be informed by data from more mature intermediary endpoints (e.g. DFS) and information from external sources. The use of a partitioned survival model would therefore yield highly uncertain estimates of cost-effectiveness at this stage.

Secondly, the partitioned survival method relies on the independent extrapolation of nested endpoints, such as DFS (alive and free of distant and locoregional recurrence) and OS (alive), to predict the numbers occupying each state over time. To ensure consistent predictions with partitioned survival modelling, the cumulative survival probabilities for DFS must always be less OS. The introduction of further states (e.g., states for distant and locoregional recurrence) requires the addition of further endpoints, such as DDFS (distant disease-free survival), which also must be constrained to values less than OS (and to be greater than DFS). As the curves are modelled independently, a series of ad hoc decision rules must be introduced to address scenarios where the curves cross during extrapolation. This introduces further avoidable uncertainty into the modelling approach. These rules are not required for state transition methods given that OS is modelled as the product of DFS transition risks and the risks of death after recurrence.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

The input data used for the base case was mainly derived from the pivotal trial ADAURA (58), clinical trial FLAURA (58), database CancerLinQ (61), clinical expertise (59, 60), and literature. Where needed, data was extrapolated based on goodness-fit statistics and clinical plausibility. A summary of included clinical inputs is presented in Table 23.

Table 23. Estimates applied in the health economic model

Variable	Value	Source
Patient characteristics		
Mean starting age	63 years	ADAURA (58)
Mean body surface area	1.70 m^2	Danish clinical experts (59, 60)
Mean body weight	65 kg	Danish clinical experts (59, 60)
Survival analysis		
DF to LR	Generalized Gamma	ADAURA (58), FLAURA (62), CancerLinQ (61), best fits
DF to DM1	Generalized Gamma	
LR to DM1	Lognormal	
DM1 to DM2	Weibull	
DM1 to Death	Exponential	
DM2 to Death	Weibull	
Cure point		
Osimertinib	48 - 96 months (8 years)	International and Danish clinical experts (59, 60)
Active monitoring	48 - 60 months (5 years)	
Cure percentage		
Osimertinib	0% in year 4, increasing to 95% in year 8	

Active monitoring	0% in year 4, increasing to 95% in year 5	International and Danish clinical experts (59, 60)
Adverse events – osimertinib		
Paronychia	0.9%	ADAURA (58)
Decreased Appetite	0.6%	
Diarrhoea	1.8%	
Stomatitis	1.5%	
ECG QT prolonged	0.9%	
Adverse events – Active monitoring		
Paronychia	0.0%	ADAURA (58)
Decreased Appetite	0.0%	
Diarrhoea	0.3%	
Stomatitis	0.0%	
ECG QT prolonged	0.3%	
Quality of life (EQ-5D-5L)		
DFS	0.825	ADAURA (58)
LR	0.825	ADAURA assumption
DM1	0.794	FLAURA (62)
DM2	0.640	FLAURA (62)

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

Lung cancer is one of the most common cancers in Denmark. (13) The two predominant forms of lung cancer are NSCLC (accounting for 85% of patients) and small-cell-lung cancer (SCLC, accounting for 15% of patients).(14) (16, 17) Recurrent driver mutations commonly found in NSCLC have a key role in the development of disease and are targets for therapeutic agents. Evidence has shown that the overall pooled prevalence for EGFR positive NSCLC, across all stages, is 32.3% globally.(18) According to a larger Danish cohort from RWE data from the Danish lung cancer registry, 195 NSCLC patients are EGFR positive.
Early stage NSCLC is considered resectable and potentially curable. However as early stages are asymptomatic patients are therefore at risk of delayed diagnosis, which impacts cure rates and survival.(22-25)

In regards to early stages, patients with resectable NSCLC are potentially curable. The goal is therefore to increase the survival rate by surgically removing the tumour and achieve complete resection. Following surgical resection, adjuvant chemotherapy is recommended to reduce the risk of recurrence and spread of disease. Danish guidelines state that adjuvant therapy should be considered for all patients with stage II–IIIA NSCLC with negative surgical margins (no residual).(11)

However, despite the curative intent of treatment, recurrence in patients with stage IB–III remains relatively common regardless of post-operative chemotherapy. (34) (See section 5.1 for more detailed patient characteristics).
As there is currently no targeted treatments available in the adjuvant setting for patients with EGFRm NSCLC following complete resection, this patient population is considered eligible for the current health economic analysis.

Clinical documentation submitted (in relation to clinical practice)

The pivotal trial assessing osimertinib (ADAURA) included stage IB-IIIA NSCLC patients with histologically or cytologically confirmed *EGFR*-mutated, following complete tumour resection with or without adjuvant chemotherapy. Any of the *EGFR* mutation types with or without any other concomitant mutations were accepted. Median age at treatment initiation was 63 years. Mean body weight was 63 kg and mean body surface (BSA) was 1.67 m^2. According to clinical expert opinion the patient population in ADAURA is representative of the Danish population eligible for treatment with osimertinib in Denmark. However, average weight and BSA were different based on clinical expert opinion and were adjusted accordingly.(59, 60) The characteristics from the trial, which were also confirmed by one of the clinical experts were tested in a scenario analysis. See Table 24 for details.
There may be some differences in the patient population in the study compared with clinical practice. Regarding age, general early stage lung cancer patients in Denmark are slightly younger than in the ADAURA trial, 60 vs 63 years of age, according to the clinical expert.(59, 60) An earlier DMC's assessment of osimertinib as 2nd line treatment for distant metastatic NSCLC, the mean age was set to be 65. When considering 1st line treatment for distant metastatic NSCLC patients can be expected to be a year younger on average.(63) Based on this, it is reasonable to assume that patients receiveing adjuvant treatment after complete recention will be younger with 63 years being a good estimate. The generaliziability of age from ADAURA is therefore assumed to be valid for Denmark.

Table 24. Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (60)	Used in the model	Danish clinical practice (59)
Age at treatment start	63	63	60
Body weight (kg)	63	65	65
Body surface (m2)	1.67 m^2	1.70 m^2	1.70 m^2

8.2.2.2 Intervention

In the Danish lung cancer treatment guidelines osimertinib is not used in adjuvant setting for NSCLC patients, but it has been adopted for the treatment of adult patients with locally advanced or metastatic EGFR-mutation positive NSCLC.(63) Osimertinib as monotherapy is indicated as the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have active epidermal growth factor receptor (*EGFR*).

Inputs used in the cost-effectiveness analysis are primarily informed by the clinical trials ADAURA, FLAURA and clinical literature in combination with clinical expertise.(14, 59, 60, 62) In the model treatments were administered according

to treatment cycles. Osimertinib (80 mg) was administered orally daily for up to three years. A summary of intervention characteristics is found in Table 25. Posology of the intervention and available dosing recommendations for osimertinib are based on ADAURA.(58)

Intervention in the clinical documentation submitted:

The key clinical documentation in this health economic assessment is the pivotal trial ADAURA.(58) See sections 6 and 7 for details of results of ADAURA and on patient population above.

Intervention as in the health economic analysis submitted:

Inputs used in the cost-effectiveness analysis are primarily informed by the clinical trial ADAURA and clinical literature in combination with clinical expertise.(14, 59, 60, 62).To estimate the treatment duration of osimertinib as well as associated drug acquisition and administration costs the extended mean of the treatment exposure from ADAURA was used.

Table 25. Intervention

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice (59, 60)
Posology	Drug: Osimertinib 80 mg orally once daily	Drug: Osimertinib 80 mg orally once daily	Drug: Osimertinib 80 mg orally once daily
Length of treatment	Up to 3 years	Up to 3 years	Up to 3 years
The pharmaceutical's position in the Danish clinical practice	1st line EGFR-directed treatment	1st line EGFR-directed treatment	1st line EGFR-directed treatment

8.2.2.3 Comparators

In Denmark, the recommended first-line treatment for patients with EGFR-mutated NSCLC is active monitoring. As there are no licensed comparator treatments in this treatment setting, the appropriate comparator is active monitoring (i.e. routine clinical management without osimertinib). This has been validated by Danish clinical experts.(59, 60)
The most relevant comparator for the osimertinib in Denmark is active monitoring which is in line with Danish treatment guidelines.(64)

8.2.2.4 Relative efficacy outcomes

Relative efficacy outcomes used to compare osimertinib with active monitoring were DFS and OS, as well as CNS DF. All relative efficacy outcomes were based on data from the trials ADAURA and FLAURA, as well as from the CancerLinQ database (Table 26) (58, 61, 62).

The Danish treatment guidelines for lung cancer describe the goal of adjuvant treatment of stage I-II lung cancer as curative.(64) Both DFS and OS as well as safety and quality of life were main endpoints in the ADAURA (58) and are applied in the health economic analysis for Osimertinib in Table 27. Hence, it is believed that the clinical data derived from the pivotal trial for osimertinib reflect Danish clinical practice.

A semi-Markov model was used to analyse the cost-effectiveness of osimertinib in Denmark. The model was directly based on key outcomes of the ADAURA pivotal trial, FLAURA trial as well as CancerLinQ database, which represent treatment goals for Denmark: disease-free survival, quality of life, and overall survival.

Table 26. Summary of text regarding value

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint: **Disease-free survival (DFS)**	Osimertinib: 65.8 months Active monitoring: 28.1 months	Osimertinib: 73 months (the discrepancy is mainly a censoring effect, as the KM median was reached close to the end of follow-up) Active monitoring: 28 months
Secondary endpoint: **Overall-survival (OS)**	Median not reached. Landmark 5-year OS 88% for osimertinib and 78% for active monitoring for patients with stage IB to IIIA disease	Median not reached . ADAURA OS not used explicitly in the modelling but used for validation. Modelled 5-year OS 86.7% for osimertinib and 78.5% for active monitoring for patients with stage IB to IIIA disease

Table 27. Summary of text regarding relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study: **Disease-free survival (DFS)**	DFS was defined as the time from randomisation to disease recurrence or death from any cause	DFS represents a relevant outcome measure with regards to treatments for EGFR-mutate, NSCLC. Based on DFS, treatments may be prioritized over others.	Relevant.
Secondary endpoints: **Overall survival**	Defined as time from randomization to death from any cause.	OS represents a relevant outcome measure with regards to treatments for EGFR-mutated NSCLC. Based on OS, treatments may be prioritized over others.	Relevant.

8.2.2.5 Adverse reaction outcomes

Safety was one of the secondary outcomes in the ADAURA trial.(58) Adverse events included amongst others diarrhea, stomatitis, and paronychia. The frequency differed across patients and between the treatment options.

In the assessment, grade 3+ treatment-emergent adverse events occurring in at least 2 patients in both treatment arms were included for both osimertinib and active monitoring (Table 28). The incidence of adverse events was derived from the ADAURA trial.(58) Hence, both the values used in the model and the clinical documentation are the same.

Table 28. Adverse reaction outcomes

Adverse reaction outcome	Osimertinib	Active monitoring
Paronychia	0.9%	0.0%
Decreased Appetite	0.6%	0.0%
Diarrhoea	1.8%	0.3%
Stomatitis	1.5%	0.0%
ECG QT prolonged	0.9%	0.3%
Source:	ADAURA (58)	ADAURA (58)

8.3 Extrapolation of relative efficacy

The relative efficacy used to inform the *semi*-Markov model (Table 26) was sourced from ADAURA where possible. Additional sources used for the relative efficacy was the phase 3 clinical trial FLAURA, Danish life tables, a Danish clinical expert and data from the US real-world evidence database CancerLinQ, with data for over 1.4 million patients with a primary lung cancer diagnosis. Efficacy data was extrapolated over the time horizon of the model. The methods for extrapolations are summarized below with details given in section in Table 29.

8.3.1 Time to event data – summarized

Table 29. The main settings for the extrapolation in the base case is presented

Transition probability	Setting	Data source
TP1: DF -> LRR	Generalized gamma	ADAURA (58)
TP2: DF -> 1L DM	Generalized gamma	ADAURA (58)
TP3: DF -> Death	Background mortality	ADAURA (58) / Danish life tables (Statistic Denmark: https://www.statbank.dk/HISB8)(65)
TP4: LRR -> 1L DM	Lognormal	CancerLinQ

Transition probability	Setting	Data source
TP5: LRR -> Death	Background mortality	CancerLinQ / Danish life tables (65)
TP:6 1L DM -> 2L DM	Weibull	FLAURA (62)
TP7: 1L DM -> Death	Exponential / Background mortality	FLAURA (62)/ Danish life tables (65)
TP8: 2L DM -> Death	Weibull	FLAURA (62)/ Danish life tables (65)
Cure	95% from year 5 onwards for active monitoring and 95% for year 8 and onwards for osimertinib	International and Danish clinical experts (59, 60)
Retreatment	50% of the osimertinib patients can be retreated	Danish clinical experts (59, 60)
Treatment waning	No	

The inputs regarding effectiveness (DFS/OS) for osimertinib were sourced from ADAURA. The two main inputs regarding effectiveness used in the model and economic analysis were DFS and OS. The intention to treat (ITT) population from the ADAURA trial was used to conduct the survival analyses for DFS and OS.
Due to the available follow-up time of the current data-cut off ADAURA and the event-rate for patients treated with osimertinib, limited post-recurrence data were available from ADAURA. To inform the probability of transition from LRR to DM1 data was used from CancerLinQ instead, a US real-world evidence database comprising over 1.4 million patients with a primary lung cancer diagnosis.(61) From the CancerLinQ database, patients with EGFRm-positive NSCLC in stage IB–IIIA following tumour resection who had experienced local/regional recurrence were selected ('ADAURA-like' population).
The transition probabilities for the distant metastases health states were primarily estimated using the FLAURA phase 3 trial, which evaluates osimertinib versus erlotinib or gefitinib as first-line treatment in patients with *EGFR*-mutated (*EGFR*m) advanced NSCLC.(62)

The survival analyses informing the base case of the economic analysis used the following algorithm:

- Graphical and formal testing to assess the proportional hazard (PH) assumption.
- Survival distributions fitted to the Kaplan-Meier (KM) data (exponential, log-logistic, Weibull, Gompertz, lognormal, generalized gamma).
- Assessment of goodness-of-fit statistics (AIC and BIC).

- Graphical assessment of the extrapolation of the different survival models.
- The final selection of the survival model was based on a combination of goodness-of-fit and clinical plausibility as assessed by six UK clinical experts.

The generalized gamma distribution was selected for transitions from DF to LRR and for DF to first-line metastatic (DM1), as this survival model provided the best balance between goodness-of-fit with observed data and plausible long-term extrapolations in each treatment arm. The mortality rate for patients that were disease free in ADAURA was low, with no events in the osimertinib arm and two in the placebo arm. Thus, it is assumed that patient's risk of death in the DF health state is the same as the general population.
Due to limited post-recurrence follow-up data available from the ADAURA trial at the data cut-off, the transitions from local/regional recurrence (LRR) to 1st line treatment of distant metastases (DM1) for both treatment arms were modelled using the real-world database CancerLinQ, from patients matched with the population in ADAURA. For the transitions between the health states representing distant metastasis data from the phase 3 trial FLAURA was used.

8.3.2 Long-term disease-free survival

As cure or long-term DFS is an important and possible outcome of the patient population considered in the cost effectiveness analysis, a cure assumption was included to fully capture the expected functional cure of these patients beyond the currently available follow up DFS data from ADAURA. The rationale supporting this important component within the model is outlined below.

8.3.2.1 Feedback from KEEs and clinical practice

Two interviews were conducted in 2021 with specialist physician Edyta M. Urbanska MD, PhD. from Rigshospitalet and Chief Physician Peter Meldgaard MD, PhD. from Aarhus University Hospital. The interview conducted with the Danish clinicians confirmed that in Danish clinical practice, patients with completely resected early-stage NSCLC are typically discharged from care after 5 years if they have not experienced disease recurrence. Patients are at greatest risk of recurrence 18–24 months post-surgery and therefore if patients remain disease free at 5 years, they can be considered functionally cured or long-term disease-free. Clinicians generally consider the risk of recurrence to be very low after 5 years, with the risk of recurrence reducing as time since surgery increases.(59, 60)

8.3.2.2 Clinical data and context

Complete surgical resection represents a potentially curative pathway for early-stage NSCLC, and it is expected that adjuvant treatment with osimertinib will increase the proportion of patients achieving long-term DFS. Adjuvant osimertinib has been demonstrated to statistically significantly reduce the risk of post-surgical disease recurrence vs active monitoring, which is predicted to result in a reduced risk of disease progression and death.(4)
When considering the reduction in disease recurrence observed with osimertinib in ADAURA it is notable that, when recurrence did occur, this was more frequently at local/regional sites in the osimertinib group, and by contrast, more frequently distant metastases in the active monitoring group.(58) Thus, if a patient does experience recurrence when treated with osimertinib, the patient is more likely to experience local/regional recurrence (compared with patients treated with SoC), and treatment options at this stage of the pathway include an additional opportunity for curative treatment (chemoradiation). The risk of CNS recurrence or death was also significantly reduced by 82% with osimertinib in the overall population (HR: 0.18; p<0.0001).(58) Hence, the reduction in distant metastases is an important clinical benefit of osimertinib, that suggests improved survival and a potential for an extended disease-free period.

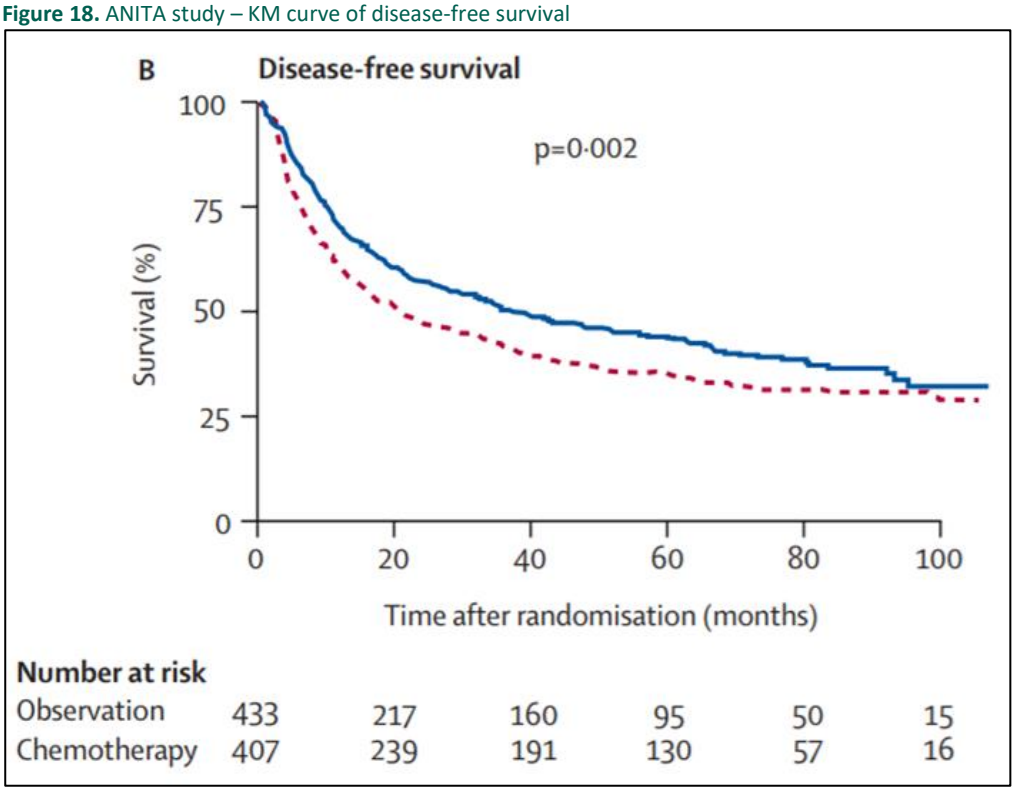
8.3.2.3 Published literature

To further support the assumption of functional cure in the economic analysis, a literature search was conducted to identify published studies evaluating long term DFS rates (> 3 – 4 years) in patients with early stage (stage I-III) NSCLC following complete surgical resection. Although published data on longer-term survival outcomes in this setting are limited – particularly in stage IB–IIIA *EGFR*m-positive NSCLC – several studies were identified in patients with completely resected stage IB–IIIA NSCLC.(66, 67) These studies indicate that the underlying risk of disease recurrence in the earlier follow-up period (noted as less than 36–48 months) is not representative of the risk of recurrence at later time periods. Generally, patients who are disease-free following complete tumour resection appear to be exposed to a far higher risk of recurrence early in the follow-up period, with the risk of recurrence decreasing over time. It is important to note that the extrapolation of DFS data from the ADAURA trial to derive the transition probabilities applied in the cost effectiveness model are based on a period (up to 48 months) that appears to correspond with an increased risk of recurrence rate. As a result, the extrapolated DFS curves from ADAURA are likely to overestimate the long-term rate of disease recurrence.

One trial identified that provided long-term DFS outcomes in early stage resected NSCLC was the ANITA study, a phase II, open-label, multicentre RCT which compared adjuvant vinorelbine plus cisplatin vs observation in patients with completely resected stage IB–IIIA NSCLC (66) . In total, 840 patients were enrolled and randomly assigned to observation or 30 mg/m^2 vinorelbine plus 100 mg/m^2 cisplatin. Disease stage and WHO performance status at baseline were comparable with the population enrolled in ADAURA, although there were differences between the two studies in proportion of females, type of surgery and tumour histology.

After a median follow-up of 76 months in the chemotherapy arm and 77 months in the observation arm, median OS was 65.7 months (95% CI: 47.9, 88.5) and 43.7 months (95% CI: 35.7, 52.3), respectively.(66) Median DFS was 36.3 months (95% CI: 28.0, 52.1) in the chemotherapy group and 20.7 months (95% CI: 16.1, 28.6) in the observation group .(66) However, regardless of treatment arm, there appeared to be a plateau in the DFS curve from approximately 48–60 months' follow-up (Figure 18), suggesting that after this timepoint, the majority of patients are no longer at risk of disease recurrence, and thus providing further support for a functional cure in this patient population.

Figure 18. ANITA study – KM curve of disease-free survival

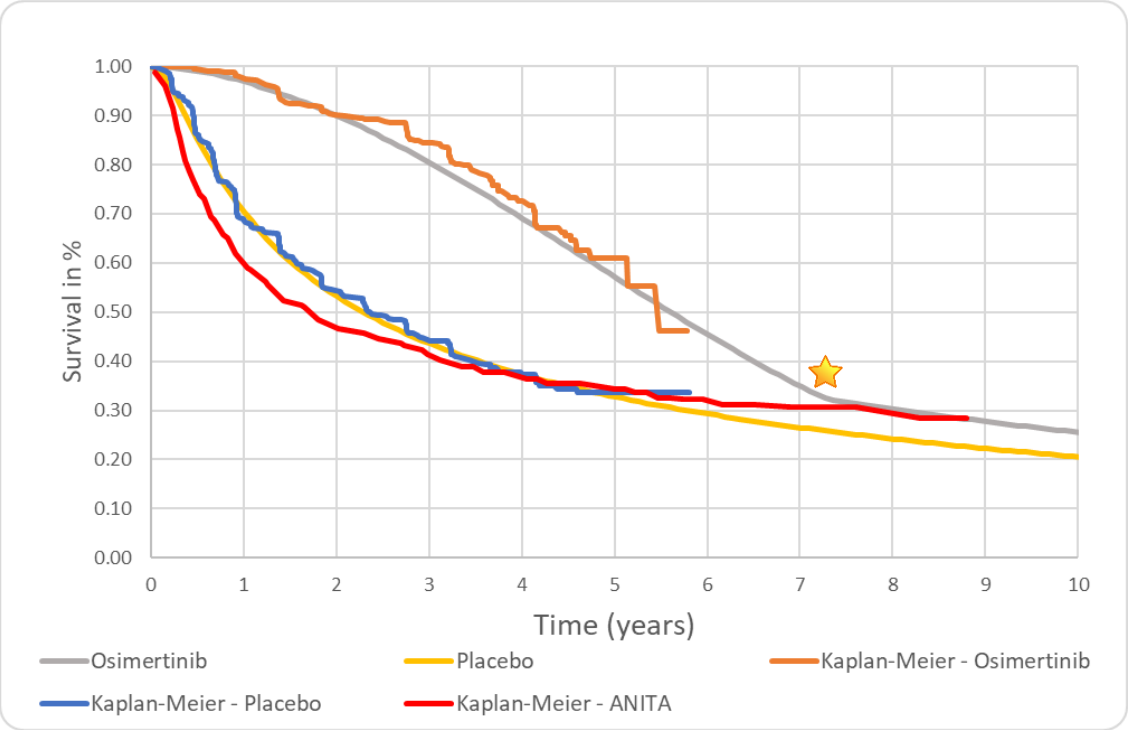


The data in the figure is extrapolated from(29)

To explore this further, pseudo-patient level data were derived from the KM DFS curve of the observation arm of the ANITA study using the algorithm developed by Guyot et al, 2012.(67) This dataset was extrapolated and compared alongside the best fitting combined extrapolated DFS curves from the ADAURA placebo arm (TP1 [DFS to LR]: generalised gamma; TP2 [DFS to DM1]: generalised gamma), since both patient groups received similar treatment regimens in their respective trials and is therefore a more relevant comparison than data from the chemotherapy arm of ANITA (Figure 19 below).

Applying a 0% cure proportion in the ADAURA active monitoring arm suggests that the risk of disease recurrence beyond 60 months may be overestimated in the ADAURA active monitoring arm when compared with the observed long-term DFS data from the ANITA study cohort. Therefore, it is reasonable to assume that the extrapolated disease recurrence in osimertinib-treated patients is also overestimated.

Figure 19. Unadjusted ADAURA DFS extrapolations versus ANITA DFS (0% cure proportion)

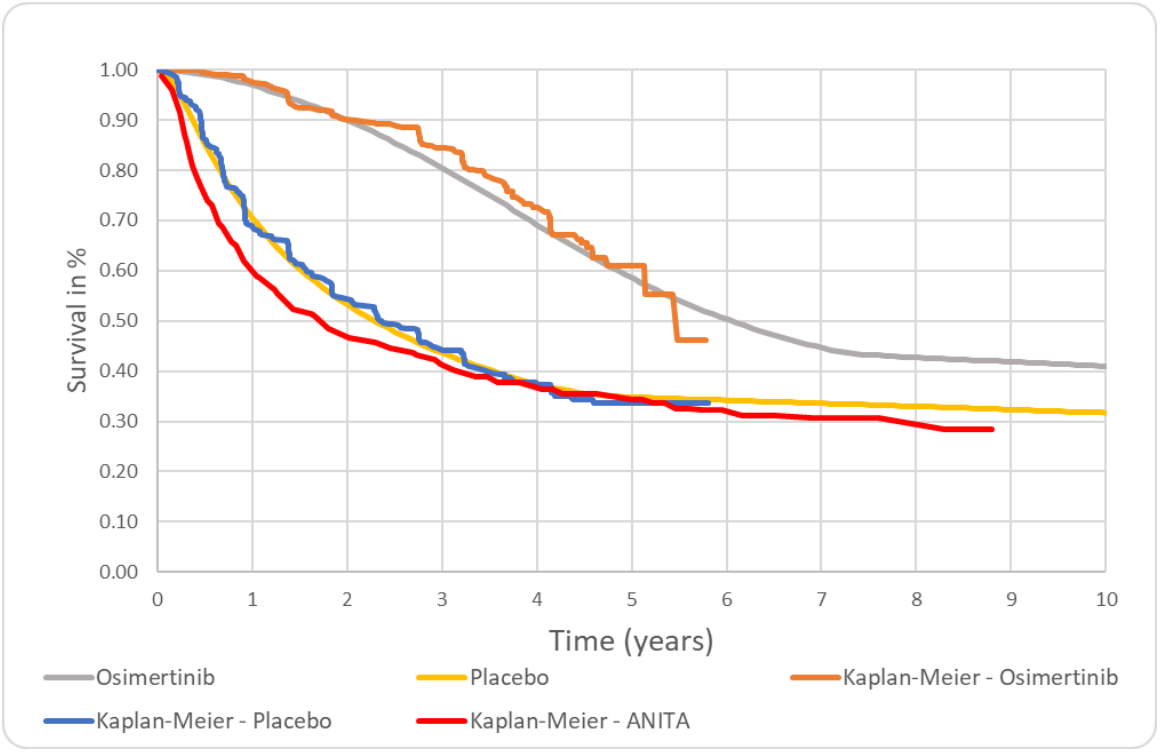


The data in the figure is extrapolated from(29)

⭐ *The breaking point at year 7.20 is due to the assumption that if Osimertinib TP1/2<placebo, Osimertinib = placebo. The choice of this condition is further explained later in this section.*

Conversely, when a cure rate starting from year 4 with 0% to the start of year 8 with 95% was applied to the osimertinib arm, and a cure rate starting from year 4 with 0% to the start of year 5 with 95% was applied to the placebo arm, the predicted DFS rates from the ADAURA active monitoring arm were more consistent with the longer-term DFS KM curve from ANITA (Figure 20).

Figure 20. Adjusted ADAURA DFS extrapolations versus ANITA DFS (95% cure proportion)



The data in the figure is extrapolated from (Table 30) and the flexsurvcure package in R was used to run parametric mixture cure models that is shown here.

Further statistical analyses were also performed to estimate a plausible rate of cure in patients with stage IB–IIIA surgically-resected NSCLC. A series of parametric mixture cure models (MCM) were fitted to the pseudo-patient level DFS data from the active monitoring arm of the ANITA trial. The MCM analysis was performed using the flexsurvcure package in R.(68) Overall, the MCM analysis estimated cure fraction rates ranging from 23–31% and predicted DFS rates at 5 years of 33–34% for the ANITA trial and predicted DF rates at seven years of around 31% (Table 30).
The results of the analysis were consistent with opinion from Danish and UK clinical experts given based on the 17 January 2020 data cut-off, providing further support for the curative potential in this setting. Using the landmark method in the CEM at five years, the estimated rate of cure for the active monitoring arm of ADAURA was comparable to the range estimated in this analysis (Table 30). This supports the validity of the model extrapolations, and the use of the landmark method to predict cure.

Table 30. Estimated cure fraction rates and DFS 5- and 7-year rates

Model	AIC	Cure fraction (%)	DFS at 5 years (%)	DFS at 7 years (%)
Generalised Gamma	2675.93	30.5 (25.8, 45.1)	33.3	31.3
Lognormal	2635.82	27.9 (22.7, 33.8)	33.9	31.3
Loglogistic	2646.56	27.3 (22.1, 33.2)	33.8	31.5
Gompertz	2667.83	22.9 (9.5, 45.9)	33.9	31.1
Exponential	2673.97	30.6 (26.0, 35.5)	33.3	31.3
Gamma	2673.97	30.6 (26.0, 35.8)	33.3	31.3
Weibull	2675.93	30.5 (25.8, 35.5)	33.3	31.3

Due to the immaturity of DFS data in the ADAURA trial, uncertainty around the cure/long-term DFS assumption was tested in scenario analyses. Scenarios tested included applying different cure timepoints, varying the percentage of patients cured and applying an increasing percentage of cured patients over time.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

HRQoL was assessed in the ADAURA trial using the SF-36 questionnaire (version 2, standard) for the DF and LRR health states.(58) Assessments were made at the following time points: baseline, day 1 (pre-dose), at 12 weeks, 24 weeks, and then every 24 weeks relative to randomisation (±7 days) until either treatment completion (3 years) or discontinuation. The FLAURA trial (62), assessing osimertinib as first-line treatment for patients with previously untreated, EGFR mutation–positive advanced NSCLC, provided HRQoL data for the health states 1L and 2L DM.

Given that HRQoL was available from key clinical trial data (ADAURA and FLAURA), the trial HRQoL data was utilised within the model. As health state utility values in this form were not directly available from patients in the FLAURA (EORTC QLQ-LC13) and ADAURA (SF-36) trials, mapping onto the EQ-5D-3L index was required. FLAURA (62) data were previously mapped to EQ-5D-3L and for the purpose of this cost-effectiveness model HRQoL data from ADAURA were mapped from SF-36 to EQ-5D-3L using the algorithm by Rowen et al.(69) There is no quality of life for caregivers included in the model. As described in Rowen et al. (2009), coefficients of the GLS model (model 3) with interaction terms were applied (SF-36 domains abbreviated) and with the EQ-5D utility score is the dependent variable. To obtain utility scores, UK-specific preference weights were used to calculate utility values. Observations with missing data were excluded from the analyses, however compliance rates for the SF-36 questionnaire were high (>90%) in the overall ADAURA study population through to Week 144 (ADAURA Clinical Study Report). Three covariates were considered in this analysis: AE; baseline utility; and treatment effect. Adverse events were analysed to capture any disutility due to any grade 3 or higher AE and derived such that utilities were accounted for from first onset of the adverse event until death/end of study. Baseline utilities were included to ensure that treatment effect could be measured correctly. Regression analyses using repeated measures mixed effect (RMME) models were conducted. This method uses both fixed and random effects, so that the effects of the covariates can be determined while simultaneously correcting for individual patient

effects. Note that cycle (24 weeks as time of measurement) is included as random effect in the base case, however cycle is explored as a scenario analysis as fixed effect. Further details regarding the mapping are included in Appendix I.

The utilities used within the model are presented in Table 31.

Table 31. Utilities values used in the global model (presented in Appendix H)

Health state	Utility value	SE	Source
DF			
Disease-free survival	0.825	0.018	ADAURA (58)
Disease-free survival: Osimertinib	0.825	0.018	ADAURA (58)
Disease-free survival: SoC	0.825	0.018	ADAURA (58)
LRR			
Local regional	0.825	0.018	Assumption

Local regional: Osimertinib	0.825	0.018	Assumption
Local regional: SoC	0.825	0.018	Assumption
DM			
1st line distant metastasis	0.794	0.0069	FLAURA (62)
1st line distant metastasis: Osimertinib	0.794	0.0069	FLAURA (62)

1st line distant metastasis: SoC	0.794	0.0069	FLAURA (62)
2nd+ line distant metastasis	0.640	0.030	FLAURA (62)
Primary treatment beyond 2nd+ line distant metastasis	0.640	0.030	FLAURA (62)

Key: DF, disease-free survival; DM, distant metastasis; LRR, local/regional Recurrence; SE, standard error; SoC, standard of care

Disutilities associated with adverse events were included within the model. Utility values were sourced from the paper by Nafees et al (2017) (70), and Nafeess et al. (2008).(71) The study by Nafees et al (2017), considered HRQoL, as measured by the EQ-5D, in patients with metastatic NSCLC; utilities in Nafees et al (2008) were sourced from standard gamble interviews to derive health state utility scores. The frequency of AEs experienced in each of the treatment arms – based on ADAURA trial data – was used to calculate a one-off AE disutility for osimertinib (−0.002185) and placebo (active monitoring) (−0.000140).(58) Disutilities occurring as a result of AEs were applied in the first model cycle only, as it is reasonable to assume that treatment-related AEs are most likely to occur shortly after initiating a new therapy. The AE disutilities and associated frequencies used to estimate treatment-related disutilities used in the model are presented in Table 32.

Table 32. Summary of AE related disutility values applied in cost-effectiveness analysis

AE	Disutility	Frequency	
		Osimertinib	Placebo (active monitoring)
Paronychia	−0.0325	0.9%	0%
Decreased Appetite	−0.05	0.6%	0%
Diarrhoea	−0.0468	1.8%	0.3%
Stomatitis *	−0.05	1.5%	0%
ECG QT prolonged **	0	0.9%	0.3%

* Assumed similar to decreased appetite; ** Assumption

8.4.2 Health state utility values used in the health economic model

In the base case analysis, the EQ-5D values, mapped from SF-36, from the pivotal clinical trial ADAURA (58), as well as FLAURA (62) trial were used. These values represent the best quality of life (QoL) estimates for the relevant patient group. The QoL values from ADAURA and FLAURA also capture the QoL estimates for the most relevant comparator in Denmark, active monitoring. According to the Danish guidelines, EQ-5D-5L with Danish weights should be used. As the data was mapped using algorithms only available for the UK value set, Danish values for EQ-5D-5L were not possible to use. Nonetheless, the health state utility values are still considered relevant for the Danish population. More details of the mapping is found in Appendix I.

The model includes an adjustment for the impact of aging on the HSU value of the population. This is to avoid HSU values in the model exceeding those of the general population, and to incorporate the effects of increasing comorbidities with age on HRQOL. This is modelled using either the general population HSU norm equation from Ara and Brazier et al. (2010) or Danish data provided by Medicinrådet. The age adjustment recommended by Medicinrådet is used in the base case.[1]

8.5 Resource use and costs

Costs for resource use in hospitals and drug costs were included in the health economic model. Table 33 and Table 36 present drug acquisition costs of the Osimertinib, and post-progression treatments, respectively. The relative dose intensity of all treatments are shown in Table 34 whereas dose description of post progression treatments are detailed in Table 35. For the analysis, the pharmacy purchasing price (wholesale price) was used and was sourced from medicinpriser.dk. Table 37 details the treatment duration in each health state in parallel with disease progression. Table 38 presents the costs of oral administration and chemotherapy delivery.

Additionally, the frequencies of healthcare utilization for routine care as well as monitoring are shown in Table 39 – Table 41. The associated costs for the varying healthcare utilization are presented in Table 42– Table 45.

[1] Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509–18; Medicinrådet Guidelines. Appendiks: Aldersjustering for sundhedsrelateret livskvalitet.

Table 46 shows the costs linked to adverse events management. Additionally, end-of-life costs were included to reflect increased resource use towards the end of life (see Table 47).

According to the restricted societal perspective of the health economic analysis indirect costs were included. These include travel costs and time spent due to treatment for patients and are presented in details in section 8.5.1. Indirect costs were calculate and applied according to the guidelines (72) For details see Table 48 – Table 49.

Table 33. Osimertinib unit cost in Denmark

Drug	Strength (mg)	Pack size	Pack price (DKK) - PPP	Source
Osimertinib	40	30	39 453.26	AstraZeneca/ medicinpriser.dk
	80	30	39 453.26	AstraZeneca/ medicinpriser.dk

PPP: Pharmacy purchasing price, PSP: Pharmacy selling price

For the estimation of osimertinib costs in DF (initial use), the proportion of patients remaining on osimertinib treatment was based on the observed KM curve for time to treatment discontinuation in the ADAURA study. As per the study protocol, patients randomised to osimertinib received treatment until recurrence of disease, a treatment discontinuation criterion was met, or the 3-year treatment period was completed. Based on this maximum duration, there was sufficient follow-up data from the ADAURA trial to directly observe time on adjuvant treatment, without the need for additional extrapolation.

For the base case analysis, vial-sharing for intravenous chemotherapy was not assumed to occur, therefore wastage costs were included.

Furthermore, the actual dose delivered may differ from the planned dose per treatment cycle as a result of missing or delayed doses and toxicity-related dose reductions. Therefore, to capture the ratio of actual dose delivered to scheduled dose, the relative dose intensity (RDI) adjustments were applied to the planned dose per cycle. As patients are more likely to miss, postpone or receive smaller doses than to receive additional doses per cycle the assumption was made, in the model, that the RDI is bounded between 0% and 100%. Where RDIs were not reported from the relevant clinical trials, assumptions were made as noted in the table below.

Table 34. Relative dose intensity

Drug	Relative dose intensity	Source
Osimertinib	98.9%	ADAURA and FLAURA trial (62)
Pemetrexed	100%	Assumption
Cisplatin	100%	Assumption
Docetaxel	100%	Assumption

Table 35. Systemic treatments post-progression

Treatment/Drug	Dose (mg)	Total dose (mg)	Doses per cycle	Treatment duration (model cycles)
Pemetrexed	500 mg/m2	1	21	2.8
Cisplatin	75 mg/m2	1	21	2.8
Docetaxel	75 mg/m2	1	21	2.8

Table 36. Cost of systemic treatments

Drug	Vial size/ tablet dose	Pack size	Cost per pack (AIP, DKK)	Source
Pemetrexed	100 mg	1	110.50 kr	medicinpriser.dk
Cisplatin	50 mg	1	100.00 kr	medicinpriser.dk
Docetaxel	80 mg	1	150.00 kr	medicinpriser.dk

Patients in LRR are being treated with Chemoradiotherapy (radiotherapy + PDC), based upon inputs from clinical experts in the Denmark. Patients receiving placebo in DF are treated with osimertinib in DM1, as this is the SoC in the Denmark.

The impact of introducing osimertinib in resected stage IB-IIIA EGFRm NSCLC on subsequent treatments (i.e. the rest of the treatment pathway) is not established as the use of osimertinib in the adjuvant setting represents a step change in clinical practice. Clinicians have noted that retreatment with osimertinib in the metastatic setting is possible provided successful treatment was achieved in the adjuvant setting and argued that this could be done after 60 months for 50% of the patients, whereas the other 50% receives PDC. Patients who received osimertinib in DF and progressed before 60 months receive PDC in DM1. Patients who are treated with PDC in DM1 receive Docetaxel in DM2, the other patients are treated with PDC in DM2, once again based on Danish expert input.

Table 37. Drug use per health state

Health state	Treatment arm	
DF	Osimertinib (capped at 36 months [i.e. 36 model cycles])	Active monitoring
LRR	PDC + radiotherapy (2.8 model cycles or until progression)	PDC + radiotherapy (2.8 model cycles or until progression)
DM1	Enter DM1 <60 months after initiating adjuvant Osimertinib: • PDC: 100% (3.4 model cycles or until progression)	Osimertinib (until progression)

	Enter DM1 ≥60 months after initiating adjuvant Osimertinib: • Osimertinib retreatment: 50% (until progression) • PDC: 50% (3.4 model cycles or until progression)	
DM2	If retreated with osimertinib in DM1: PDC (3.4 model cycles or until death) If not retreated with osimertinib in DM1 (i.e. received PDC): Docetaxel (2.8 model cycles or until death)	PDC (3.4 model cycles or until progression)

DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; LRR, local/regional recurrence; PDC, pemetrexed plus cisplatin. The duration of each subsequent therapy in each health state is given in parentheses.

Table 38. Cost of administration

Resource	Unit cost (DKK)	Comment	Source
Simple chemotherapy delivery	2321	DRG 2023 (01MA98). MDC01 1-dagsgruppe, pat. Mindst 7 år.	(73)
Complex chemotherapy delivery	2321	DRG 2023 (01MA98). MDC01 1-dagsgruppe, pat. mindst 7 år.	(73)

Simple chemotherapy delivery

The cost of an intravenous administration was assumed to be DKK 2321, based on a DRG cost (DRG 2023: 01MA98. MDC01 1-dagsgruppe, pat. Mindst 7 år.)

Complex chemotherapy delivery

The cost of an intravenous administration was assumed to be DKK 2321, based on a DRG cost (DRG 2023: 01MA98. MDC01 1-dagsgruppe, pat. Mindst 7 år.)

Table 39 – Table 41 show the frequencies of resource use in healthcare, which were collected from two Danish clinicians as expert opinions.

Table 39. Monthly healthcare utilization frequencies for routine care

Resource Item	DF	LRR	DM 1	DM 2	Source
Hospitalisation	0.00	0.00	0.00	0.04	Danish clinicians (59) (60)
Oncologist visits (subsequent)	0.00	0.33	0.33	0.50	Danish clinicians (59) (60)
Surgeon visits	0.00	0.13	0.00	0.00	Danish clinicians (59) (60)

Resource Item	DF	LRR	DM 1	DM 2	Source
Pulmonologist/ respiratory physician (subsequent)	0.33	0.00	0.00	0.00	Danish clinicians (59) (60)
Emergency room	0.00	0.00	1.00	2.00	Danish clinicians (59) (60)
CT scans	0.33	0.33	0.33	0.50	Danish clinicians (59) (60)
PET-CT scans	0.00	0.13	0.08	0.00	Danish clinicians (59) (60)

Table 40. Healthcare resource items and utilization for CNS metastasis

	Frequency per cycle	Source
Consultant/Oncologist outpatient visit	0.33	Danish clinicians (59) (60)
Cancer nurse visit	0.33	Danish clinicians (59) (60)
Full blood test	0.33	Danish clinicians (59) (60)
Biochemistry	0.33	Danish clinicians (59) (60)

Table 41. Monthly healthcare utilization frequencies radiation therapy

	Item	Locoregional recurrence	CNS metastasis
Radiation	Stereotactic radiation*	0	6
	Whole brain radiation*	0	1
	Radiotherapy fractions	20	0

*It was assumed that 50% of the patients receive stereotactic radiation and 50% whole brain radiation.

Table 42. Health care utilization unit costs for routine care

Resource Use	Cost (DKK)	Comment	Source
Hospitalisation	41 919.00	04MA07 Svulster i luftveje, behandling uden komplikationer, pat. mindst 18 år	DRG 2023

Resource Use	Cost (DKK)	Comment	Source
Oncologist visits (subsequent)	516.00	Overlæger (30 min)	https://medicinraadet.dk/media/gpjgcotu/v%C3%A6rdis%C3%A6tning-af-enhedsomkostninger-vers-1-7.pdf
Surgeon visits	524.61	Konsultation hos speciallæge i kirurgi, inflated to 2023*	https://laeger.dk/media/y14fgmnq/takstkort-22-kirurgi.pdf (72)
Pulmonologist/ respiratory physician (subsequent)	516.00	Overlæger (30 min)	https://medicinraadet.dk/media/gpjgcotu/v%C3%A6rdis%C3%A6tning-af-enhedsomkostninger-vers-1-7.pdf
Emergency room	2 231.00	01MA98. MDC01 1-dagsgruppe, pat. mindst 7 år	DRG 2023 (73)
CT scans	2 023.00	30PR07 CT-scanning, ukompliceret, el. Osteodensitometri	DRG 2023 (73)
PET-CT scans	2 103.00	Assumed same as MRI	DRG 2023 (73)

* inflated to 2023 (Inflation rate: 1.088 (74))

Hospitalization

Less than one hospitalization event per cycle was included in the DM2 health state based on clinical expert opinion (59) (60). The cost per event reflects a DRG costs for lung cancer. The unit cost was estimated to be DKK 41 919.(73)

Oncologist visit

Oncologist visits were included based on the assumption that the relevant patient population attends follow-up visits within specialized services. Less than 1 visit per cycle was included LRR, DM1, and DM2 health states based on clinical expert opinion. (59) (60) The cost applied in the model represents the cost per one oncologist visit (30 min) and was derived from the unit cost document published by the DMC (DKK 516).(75)

Surgeon visits

Less than one surgeon visit per cycle was included in the LRR health state based on clinical expert opinion.(59, 60) The cost per visit reflects the cost of a specialist care visit for surgery. The unit cost was derived from the unit cost documents recommended by DMC (DKK 482.16, inflated to 2023– Inflation rate: 1.088. (75)

Pulmonologist/respiratory physician visit

Less than one pulmonologist/respiratory physician visit was included per cycle in the DF health state based on the assumption that the relevant patient population attends follow-up visits within specialized services.(59, 60) The cost applied in the model represents the cost per one medical visit (30 min) and was derived from the unit cost document published by the DMC (DKK 516). (75)

Emergency room

One emergency room hospitalization per cycle was included in the DM1 health state and two hospitalizations in the DM2 health state based on clinical expert opinion.(59, 60) The unit cost was sourced from the DRG 2023 price list and was estimated to be DKK 2 321 (01MA98. MDC01 1-dagsgruppe, pat. mindst 7 år)(73).

CT scan

Less than one CT scan per cycle was included for all patients based on clinical expert opinion. (60) The cost per scan was derived from the DRG 2023 price list. The unit cost was estimated to be DKK 2 023.

PET-CT scans

Less than one PET-CT scan per year was included per year in the L33 and DM1 health states based on clinical expert opinion.(59, 60) The cost per scan was derived from the DRG 2023 price list. The unit cost was estimated to be DKK 2,103.

When considering the healthcare utilization for routine care of CNS metastasis, the associated unit costs are shown in Table 43. Each resource use is explained in detail below.

These costs as well as the brain radiation costs in Table 44 below were applied to 10.8% in the osimertinib arm and 21.0% in the placebo arm (5).

Table 43. Health care utilization unit costs for CNS metastasis

Resource use	Cost (DKK)	Comment	Source
Consultant/Oncologist outpatient visit	516.00	Overlæger, 30 min	DMC unit cost guidance(75)
Cancer nurse visit	226.50	Sygeplejersker, 30 min	DMC unit cost guidance (75)
Full blood test	21.63	Takstkort 29A, Laboratorieundersøgelser, Blod	(76)
Biochemistry	187.44	Takstkort 29A, Laboratorieundersøgelser (P-kreatinin + P-glucose + C-reaktivt protein (CRP) + B-hæmoglobin)	(76)

Consultant/Oncologist outpatient visit

Oncologist visits were included based on the assumption that the relevant patient population attends follow-up visits within specialized services. The cost applied in the model represents the cost per one oncologist visit (30 min) and was derived from the unit cost document published by the DMC (DKK 516).(75)

Cancer nurse visit

Specialist nurse visits were included based on the assumption that the relevant patient population attends follow-up visits within specialized care. The cost applied in the model represents the cost per one nurse visit (30 min) and was derived from the unit cost document published by the DMC (DKK 226.50). (75)

Full blood test

For patients with CNS metastasis, less than one full blood test per cycle was included based on clinical expert opinion .(59, 60) The unit cost for blood tests was estimated to be DKK 21.63 according to a lab medicine price list.(72, 77)

Biochemistry

For patients with CNS metastasis, less than one biochemistry test was taken per month was included based on clinical expert opinion. (59, 60) The unit cost for biochemistry test was estimated to be DKK 187.44 according to a lab medicine price list. (72, 77)

Table 44. Health care utilization inputs for monitoring care

Resource item	Comment	Unit cost (DKK)	Reference
Whole brain irradiation	Treated with stereotactic radiotherapy, 50% of patients considered to incur a one-off cost	28 371	27MP02 Strålebehandling, kompleks, 3-4 fraktioner. DRG 2023 (78)
Stereotactic brain radiation	Treated with whole brain radiotherapy, 50% of patients considered to incur a one-off cost	8 247	27MP10 Stereotaksi. DRG 2023 (78)

Whole brain irradiation

For patients who progressed due to brain metastases, radiation therapy was applied. It was assumed that 50% of these patients would receive whole brain irradiation. The cost was applied once a year. The unit cost was estimated to be DKK 28 371 based on the Danish DRG list of 2023 (DRG code: 27MP02 Strålebehandling, kompleks, 3-4 fraktioner).(79)

Stereotactic brain radiation

For patients who progressed due to brain metastases, radiation therapy was applied. It was assumed that 50% of these patients would receive stereotactic brain radiation. The cost was applied as a one-off cost and reflecting the cost for a stereotactic brain radiation in an outpatient setting. The unit cost was estimated to be DKK 8 247 based on the Danish DRG list of 2023 (DRG code: 27MP10 Stereotaksi).(79)

As part of other direct medical costs, the cost for the EGFR mutation test was included. It was assumed that the test is only conducted for in the first cycle for patients in the osimertinib arm, and for patients in the active monitoring arm when they are treated with Osimertinib in either of the distant metastasis health states. Cost is presented in Table 45.

Table 45. Cost of EGFR mutation test

Resource item	**Unit cost (DKK)**	**Reference**
EGFR mutation test	3 234	DRG 2023. 31PR03 Genetisk risikovurdering og rådgivning (78)

The management of adverse events was included in the model for grade 3+ treatment-emergent adverse events occurring in at least 2 patients for both arms.

Table 46 shows the included adverse events as well as the assumed unit costs for each event.

Table 46. Health care utilization inputs for the management of adverse events

Input	Cost (DKK)	Comment/assumption	Reference
Paronychia	19 941	09MA03 Lettere eller moderat hudsygdom, u. kompl. bidiag.	DRG 2023 (78)
Decreased Appetite	7 530	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år,u. kompl. bidiag.	DRG 2023 (78)
Diarrhea	29 719	06MA10 Betændelse i spiserør, mave og tarm m.v., pat. mindst 18 år, m. kompl. bidiag.	DRG 2023 (78)
Stomatitis	1 324	03MA09 Andre sygdomme i øre, næse, mund og hals	DRG 2023 (78)
ECG QT prolonged	17 735	05MA07 Hjertearytmi og synkope	DRG 2023 (78)

Paronychia

The cost of management of paronychia was applied as a one-off cost. The management of paronychia was assumed to be contained under the DRG for moderate or mild skin disease. A cost of DKK 19 941 was applied.

Decreased appetite

The cost of management of decreased appetite was applied as a one-off cost. The management of decreased appetite was assumed to be contained under the DRG for malabsorption and inflammation of the esophagus, stomach and intestines, without complications, when the patient is at least 18 years old. A cost of DKK 7 530 was applied.

Diarrhoea

The cost of management of diarrhoea was applied as a one-off cost. The management of diarrhea was assumed to be contained under the DRG for inflammation of the esophagus, stomach and intestines, with complications, when the patient is at least 18 years old. A cost of DKK 29 719 was applied.

Stomatitis

The cost of management of stomatitis was applied for every time the event occurs. The management of stomatitis was assumed to be contained under the DRG for other diseases of the ear, nose, mouth, or throat. A cost of DKK 1 324 was applied.

ECG QT prolonged

The cost of management of ECG QT prolonged was applied as a one-off cost. The management of ECG QT prolonged was assumed to be contained under the DRG for cardiac arrhythmia and syncope. A cost of DKK 17 735 was applied.

A one-off cost is applied at the transition to the death health state to represent the cost of palliative care. No other costs are associated with the death health state. The end of life cost or 'Terminal care cost' is presented in Table 47. The cost was derived from a previous decision document published by Amgros and inflated to 2023. (77)

Table 47. End of life costs

Unit cost (DKK)	Source
79 581.95*	As proposed for Kadcyla (HER2+) by Amgros (80)

* inflated to 2023 (Inflation rate: 1.159 (74))

8.5.1 Patient Time and Transportation Costs

For the analysis, a restricted societal perspective was applied to consider patient costs based on the Danish Medicine Council's guidelines of unit cost evaluation. (64) The patient costs are calculated based on the number of hospital or clinic visits required to receive each treatment, as well as the transportation time that a patient would take to visit a hospital or clinic and back home. Transport time is assumed to be one hour per visit (30 minutes each way), and the cost were set to DKK 140 (equivalent to 20 km travel distance) per visit. Table 49 details the frequency and value for transport time per model cycle.

The monetary value for each health care visit include the effective patient time per visit, including waiting time, and was set to be DKK 203 per hour according to the DMC costing guidelines. (72)

Table 48. Overview of applied indirect costs for routine care

Resource item	Assumed time use	Cost per visit (DKK)	Reference
Oncologist	2 h	406	DMC costing guidelines (75)
Specialist nurse	2 h	406	DMC costing guidelines (75)
Nurse	2 h	406	DMC costing guidelines (75)
GP	2 h	406	DMC costing guidelines (75)
Transportation costs per visit	-	140	DMC costing guidelines (75)

Table 49. Frequency and value for time of transport per month

Population	Proportion of time spent due to treatment			
	Disease free	**Locoregional recurrence**	**1st line of distant metastasis**	**2nd line of distant metastasis**
Frequency per month	0.7	0.9	1.8	3
Value per month	1.3	1.8	3.5	6.1

8.6 Results

8.6.1 Base case overview

An overview of the base case is presented in Table 50.

Table 50. Base case overview

Setting	Value/choice
Comparator	Active monitoring
Type of model	Semi-Markov model
Time horizon	37 years (life time)
Treatment line	Adjuvant setting
Measurement and valuation of health effects	Health-related quality of life data from ADAURA (58) and FLAURA .(62)
Included costs	Pharmaceutical costs Healthcare utilization costs Costs of adverse events Indirect costs (patient time and transport costs)
Dosage of pharmaceutical	Oral administration of 80 mg daily
Parametric function DF to LR	Generalized Gamma
Parametric function DF to DM1	Generalized Gamma
Parametric function LR to DM 1	Lognormal
Parametric function DM1 to DM2	Weibull
Parametric function DM 1 to Death	Exponential
Parametric function DM2 to Death	Weibull

8.6.2 Base case results

Table 51 presents total costs, life-years gained, QALYs, and incremental costs per QALY for osimertinib versus active monitoring. Compared with active monitoring, osimertinib generated 0.90 incremental QALYs and 1.10incremental life-years gained, and osimertinib-treated cohort had higher total lifetime costs. The ICER was DKK 375 810 QALY gained.

Table 52 shows the time spent in years per patients in each health state for osimertinib versus active monitoring.

Table 51. Base case results (Discounted)

	Osimertinib (DKK)	Active monitoring (DKK)	Incremental (DKK)	ICER (DKK)
Total cost	1 431 523	1 093 068	338 900	
LYs	11.01	9.90	1.10	307 383
QALYs	8.71	7.80	0.90	375 810

LYs: Life years, QALYs: Quality-adjusted life years

Table 52. Time per health state (Life years per patient, discounted)

Health state	Osimertinib (LY)	Active monitoring (LY)	Incremental LYs
Disease-free	8.75	6.20	2.54
Logoregional recurrence	0.85	1.25	-0.40
1st line distant metastasis	0.41	1.51	-1.10
2nd line distant metastasis	1.00	0.94	0.06
Total	11.01	9.90	1.10

Table 53 presents a breakdown of costs by category. The incremental cost of DKK 338 900 for osimertinib versus active monitoring was predominantly due to additional drug acquisition costs.

Table 53. Summary of Costs (Discounted)

Cost category	Estimated costs (DKK)	
	Osimertinib	**Active monitoring**
Treatment administration costs	3 487	2 141
Treatment acquisition costs, first line	1 094 542	0
Treatment acquisition costs, subsequent lines	96 140	806 994
Disease management costs	116 365	159 048
AE costs	939	142
Terminal care costs	49 297	52 345
EGFR testing costs	3 233	1 698
Patient and carer costs	50 537	52 571
Travel costs	17 427	18 128
Total costs	**1 431 967**	**1 093 068**

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

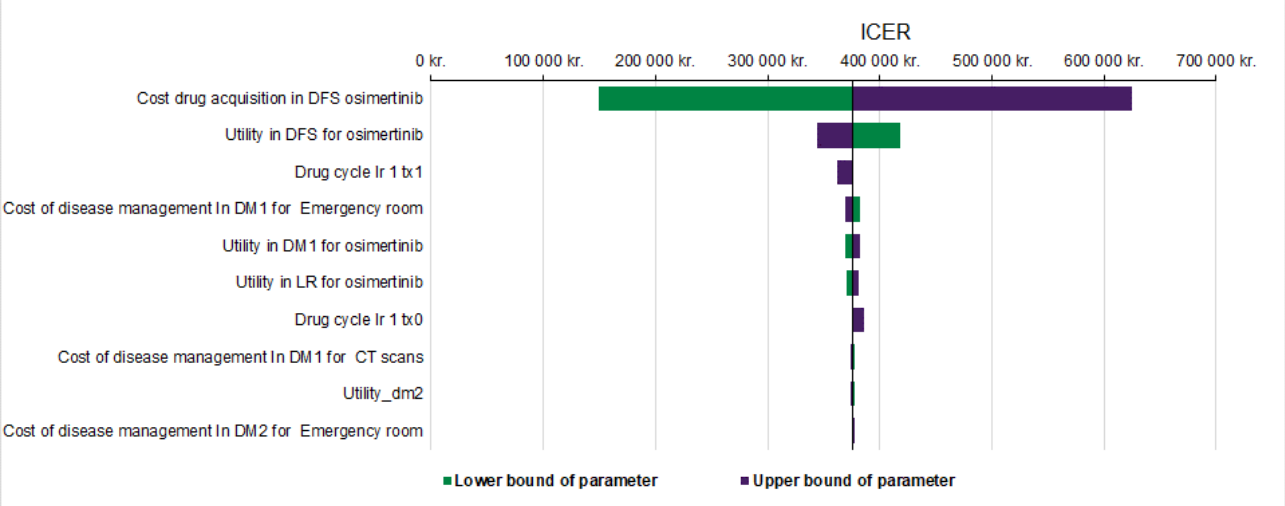
A one-way deterministic sensitivity analysis (OWSA) was conducted on osimertinib versus active monitoring. Where upper and lower 95% confidence intervals were not available, input values were varied by 10% for both lower and upper bound. (An assumed standard error of 10% was used to estimate the confidence interval for model parameters with unknown uncertainty. The choice is somewhat arbitrary but the purpose of the analysis is to highlight parameters that are driving the results.).

Table 54 shows the results of the OWSA including the 25 values which had the largest impact on the ICER when being varied. The tornado diagram in Figure 21 shows the ten most sensitive values. The acquisition cost of osimertinib in the disease-free health state had the largest impact on the ICER followed by the utility value for patients in the disease-free health state in the osimertinib arm.

Table 54. Results of OWSA

Top 25 parameters identified from OWSA			
Parameter	**Lower bound (DKK)**	**Upper bound (DKK)**	**Absolute difference (DKK)**
Cost drug acquisition in DFS osimertinib	149 615	624 981	475 365
Utility in DFS for osimertinib	418 312	343 547	74 766
Drug cycle LR 1 tx1	375 810	361 984	13 826
Cost of disease management In DM1 for Emergency room	382 156	368 820	13 336
Utility in DM1 for osimertinib	369 631	382 046	12 415
Utility in LR for osimertinib	369 949	381 395	11 447
Drug cycle LR 1 tx0	375 810	385 583	9 773
Cost of disease management In DM1 for CT scans	377 654	373 779	3 874
Utility DM2	377 228	374 452	2 776
Cost of disease management In DM2 for Emergency room	375 126	376 564	1 439

Figure 21. Tornado diagram



In Table 55 below the results of the scenario analyses are presented.

Table 55. Scenario analyses

Scenario	Base case	Base case ICER (DKK)	ICER (Scenario) (DKK)
Payer perspective	Restricted societal	375 810	378 843
Weight: 63 kg **Age: 63 years** **BSA: 1.67 m²**	Weight: 65 kg Age: 63 years BSA: 1.70 m²		375 810
Population II-IIIA	IB-IIIA		245 247
Starting age 60 years	63 years		340 015
Time horizon 5 years	37 years		2 961 174
Time horizon 10 years	37 years		826 228
Time horizon 15 years	37 years		532 421
Time horizon 20 years	37 years		437 090
Time horizon 30 years	37 years		381 625
Discount rate – Effect: 0%	3.5%		243 126
Discount rate – Effect: 5%			442 540
Discount rate – Costs: 0%	3.5%		316 363
Discount rate – Costs: 5%			396 255
EGFR test costs not included	Included		374 108
CNS costs not included	Included		380 545
Standardized mortality rate of 2 applied for normal mortality	Not applied		496 132

Scenario	Base case	Base case ICER (DKK)	ICER (Scenario) (DKK)
Correction DM1 to DM2	Applied		339 931
TP1 – Lognormal	Generalized gamma		342 452
TP1 – Weibull			323 933
TP2 – Lognormal	Generalized gamma		256 294
TP4 - Loglogistic	Lognormal		374 276
Both arms: Cure at 60 months for 95% with no warm-up	Tagrisso: Cure starting at 48 months with 48 month warm-up. Placebo: Cure starting at 48 months 12 month warm-up. 95% cure percentage		156 991
Tagrisso: Cure starting at 48 months with 12-month warm-up, eventually reaching 95% cure	As above		144 038
Placebo: Cure starting at 48 month with 48-month warm-up, eventually reaching 95% cure	As above		256 187
Tagrisso: Cure starting at 60 months with 48-month warm-up. Placebo: Cure staring at 60 months 12-month warm-up. 95% cure percentage	As above		478 372
Tagrisso: Cure starting at 72 months with 48-month warm-up. Placebo: Cure staring at 72 months 12-month warm-up. 95% cure percentage	As above		578 969
Tagrisso: Cure starting at 48 months with 60-month warmup. Placebo: Cure starting at 48 months with 24-month warmup	As above		405 505
Tagrisso: Cure starting at 48 months with 12-month warmup. Placebo: Cure starting at 48 months with 12-month warmup. Cure percentage increasing from 50% to 95%	As above		137 149
Tagrisso: Cure starting at 48 months. Placebo: Cure starting at 48 months. No warm-up in either arm.	As above		546 138
Both arms: 80% end cure percentage	As above		487 022

Scenario	Base case	Base case ICER (DKK)	ICER (Scenario) (DKK)
Both arms: 90% end cure percentage	As above		382 982
Both arms: 100% end cure percentage	As above		368 763

8.7.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analyses (PSA) were conducted to establish the impact of parameter uncertainty of the cost effectiveness of osimertinib versus active monitoring. A total of 1000 iterations were run. An overview of all assumptions regarding the PSA is presented in Appendix J (section 21).

Figure 22 presents the cost-effectiveness plane, which showed that majority (77.5%) of all 1000 iterations were in the North-East quadrant indicating osimeritinib is more effective and more costly in comparison to active monitoring in all iterations.

Figure 22. Cost-effectiveness plane

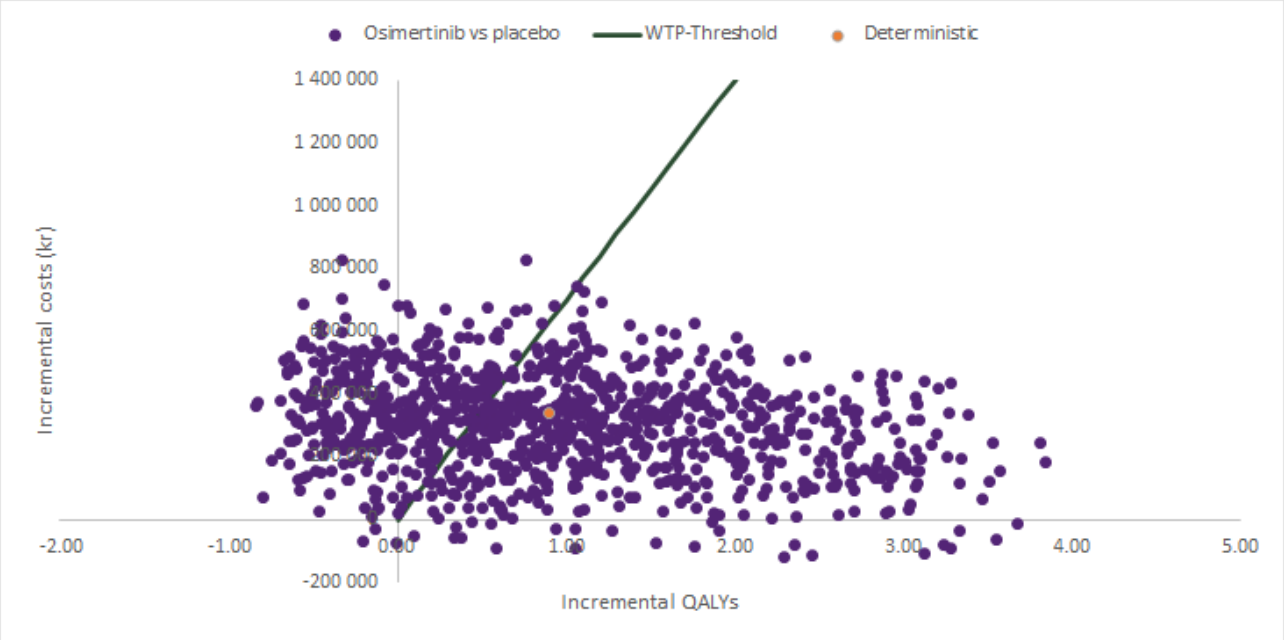
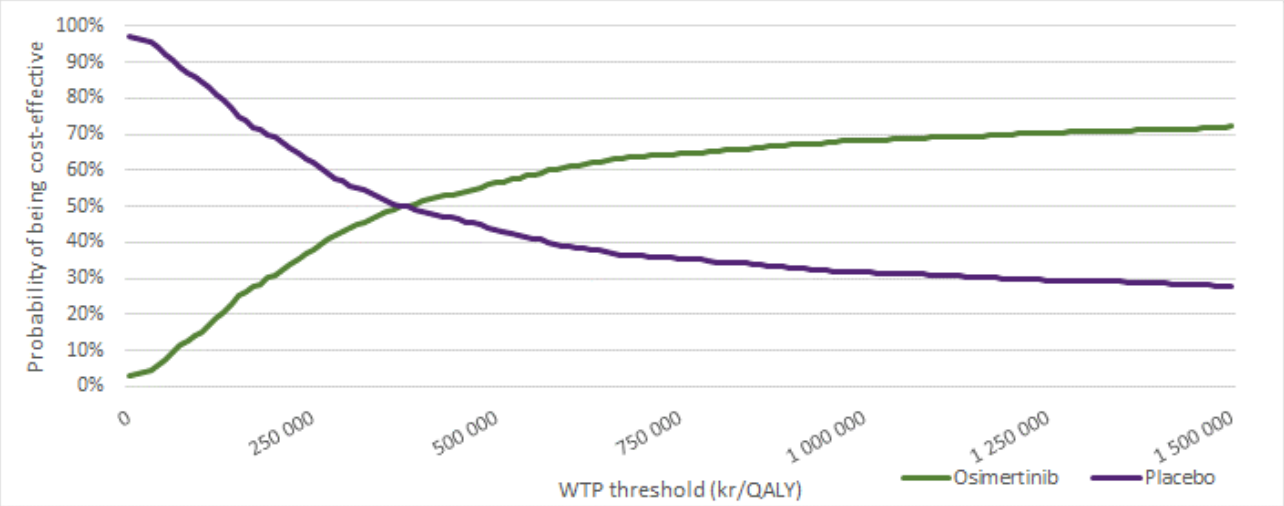


Figure 23 presents the cost-effectiveness acceptability curve (CEAC). The CEAC showed that osimertinib had a 64% probability of being cost-effective at a willingness-to-pay of DKK 700 000.

Figure 23. Cost-effectiveness acceptability curve



9. Budget impact analysis

The introduction of osimertinib is not believed to incur any substantial costs to the Danish health services beyond the cost of drug. The budget impact of osimertinib is presented below. For the BIM, the main driver of costs is the treatment acquisition costs, while costs other than drug costs are low in comparison to the differences in drug costs between osimertinib and active monitoring.

9.1 Number of patients

See (Figure 2, section 5.1) for the estimate of Danish patient numbers. The uptake of Osimertinib in Denmark is estimated to start at 30% and to increase to 55% in the second year, after which it increases to 60% in the third year, 75% in the fourth year, and 85% in the fifth year. The market share are based on internal assumptions and experiences from previous indications. The uptake will most likely be gradual even with a positive recommendation but the given good clinical data the market share will eventually reach 85% at peak year sales. The resulting number of patients if osimertinib is recommended is shown in Table 56. Table 57 shows the forecasted number patients for active monitoring, if osimertinib is not recommended. The analysis assumes that no new *EGFR*m targeted therapy enters the Danish market in adjuvant setting during the time period.

Table 56. Number of new patients per year expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Osimertinib	8	16	17	22	25
Active monitoring	20	13	12	7	5

Table 57. Number of new patients per year expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Osimertinib	0	0	0	0	0
Active monitoring	28	29	29	29	30

9.2 Expenditure per patient

The expenditure per patient for osimertinib showed an decreasing trend over the course of three years. This is due to the TTD data used for the calculation. Since osimertinib is only administered up to three years, no first-line treatment costs are incurred in 4th and 5th year as shown in Table 58.

For active monitoring, the cost trend is increasing for the first three years, as more a more patients are affected by relapses, but as the rate of new relapses decreases over time, the cost per patient starts to decrease again beyond 3 years, as shown in Table 59.

Table 58. Costs per patient per year - osimertinib

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
Treatment administration costs	6	145	493	878	1 151
Treatment acquisition costs	429 618	379 331	347 994	14 649	5 401
Disease management costs	1 151	2 288	5 391	10 039	14 337
AE costs	939	0	0	0	0
Other direct costs	3 233	0	0	0	0
Terminal care	595	862	1 664	2 925	4 303
Total cost	435 542	382 626	355 541	28 491	25 191

Table 59. Costs per patient per year – active monitoring

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
Treatment administration costs	22	171	313	371	368

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
Treatment acquisition costs	52 167	125 377	143 263	139 133	123 270
Disease management costs	6 453	14 899	19 715	22 071	21 992
AE costs	142	0	0	0	0
Other direct costs	590	490	300	208	124
Terminal care	771	2 115	3 706	4 839	5 423
Total cost	60 145	143 051	167 298	166 621	151 177

9.3 Budget impact

Table 60, Table **61**, and Table 62 shows the expected budget impact if osimertinib is recommended. The results are budget impact over 5 years, showing the total number of patients times the drug cost starting every year and follow the treatment regimen. For Osimertinib patients receive treatment over three years. The budget impact shows an increasing trend associated with the increasing market uptake.

Table 60. Costs per year - if the pharmaceutical ***is*** recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Osimertinib					
Treatment administration costs	48	1 317	6 552	17 845	25 774
Treatment acquisition costs	3 634 882	9 973 324	16 405 960	21 717 890	25 618 022
Disease management costs	9 737	37 475	101 691	235 143	331 907
AE costs	7 945	14 785	16 371	20 770	23 893
Other direct costs	27 353	50 900	56 360	71 506	82 256
Terminal care	5 036	16 665	38 024	79 132	109 263
Osimertinib - Total	**3 685 002**	**10 094 465**	**16 624 957**	**22 142 288**	**26 191 115**
Active monitoring					
Treatment administration costs	425	3 653	8 642	13 502	9 787

	Year 1	Year 2	Year 3	Year 4	Year 5
Treatment acquisition costs	1 029 860	1 882 091	5 049 567	6 433 876	4 642 417
Disease management costs	127 399	227 653	656 124	910 403	655 540
AE costs	2 810	2 241	1 655	1 050	712
Other direct costs	11 648	13 437	19 103	18 015	12 730
Terminal care	15 216	30 029	109 368	173 535	124 854
Active monitoring - Total	**1 187 360**	**2 159 105**	**5 844 458**	**7 550 381**	**5 446 040**
Total both	**4 872 362**	**12 253 571**	**22 469 415**	**29 692 669**	**31 637 155**

Table 61. Costs per patient per year - if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Osimertinib	0	0	0	0	0
Active monitoring					
Treatment administration costs	607	5 439	14 362	25 032	25 418
Treatment acquisition costs	1 471 229	5 029 223	9 145 024	13 206 075	13 430 774
Disease management costs	181 999	604 903	1 169 990	1 809 991	1 840 433
AE costs	4 015	4 075	4 136	4 198	4 334
Other direct costs	16 641	30 714	39 648	46 098	47 090
Terminal care	21 737	81 711	187 459	326 745	332 039
Active monitoring - Total	**1 696 229**	**5 756 066**	**10 560 621**	**15 418 139**	**15 680 088**

Table 62 shows the expected budget impact if osimertinib is recommended. The results are budget impact over 5 years, showing the total number of patients times the drug cost starting every year and follow the treatment regimen. For osimertinib patients receive treatment over three years. The budget impact shows an increasing trend associated with the increasing market uptake.

Table 62. Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is introduced	4 872 362	12 253 571	22 469 415	29 692 669	31 637 155
Minus: **The pharmaceutical under consideration is NOT introduced**	1 696 229	5 756 066	10 560 621	15 418 139	15 680 088
Budget impact of the recommendation	3 176 133	6 497 504	11 908 794	14 274 530	15 957 067

10. Discussion on the submitted documentation

Patients with NSCLC have a poor prognosis with high morbidity and mortality. For patients diagnosed in early stages who can be surgically treated the prognosis is improved but the risk of relapse remains high. In Denmark, after successful surgical treatment, patients are offered adjuvant chemotherapy but currently no targeted adjuvant treatment is recommended or commonly used.
Osimertinib, as studied in the Phase 3 ADAURA-trial, have demonstrated important clinical benefits as an adjuvant treatment for patients with EGFR-positive tumors. In the trial the treatment was given until disease progression or intolerable toxicity for up to 3 years. The trial demonstrated an 80% reduction in risk of disease recurrence or death for patients in the osimertinib arm vs the placebo arm (median DFS: osimertinib KM estimate 65.8 months, placebo 28.1 months; HR 0.27; 95% CI 0.21, 0.34; p<0.0001.
A previously developed semi-Markov model was adapted to the Danish setting and used to perform the cost-effectiveness analysis. Key model inputs: the efficacy of the comparators, total drug use, adverse events, and utilities were sourced from ADAURA, FLAURA, CancerLinQ, background mortality, and validated by Danish clinical experts. Costs and healthcare resource use were estimated from public sources and published literature. Incremental cost-effectiveness ratios (ICERs) were assessed for life-years (LY) gained and quality-adjusted life years (QALYs) gained. The adjuvant use of osimertinib was found to be cost effective versus current standard of care in Denmark, being more costly (338 900 DKK) and more effective (+0.90 QALYs). The budget impact in year 5 after introduction of osimertinib in the adjuvant NSCLC setting was estimated to be DKK 16 million.

10.1 Strengths and limitations

The model structure attempts to address the complex treatment pathway in EGFR-mutated NSCLC as patients experience disease recurrence by capturing LRR, DM1 and DM2. By using a mix of real-world evidence (CancerLinQ in LRR) and clinical trials (ADAURA in DF, FLAURA in DM1, DM2) the issues with the immature OS in ADAURA were also overcome with the modelling approach and structure.
Given the approach and relative data immaturity, several model assumptions were required, e.g., around long-term risk of recurrence and retreatment. Although these assumptions have been validated with clinical experts, the model has been set up to be very flexible around the assumptions and can easily be adjusted by the user. The model robustness was tested with multiple scenario analyses, which showed that the results were robust as the variation was low between the scenarios.

From ADAURA there is only limited data available to inform the transition from LRR to DM1. However, this is addressed by identifying a like-for-like patient cohort from CancerLinQ, a US registry, which allowed fitting parametric distributions from LRR to DM1 and LRR to death.

There is a lack of HSUVs available in published literature, including the LRR health state. This required assumptions, such as setting the HSUV in the LRR health state equal to the DF health state. These assumptions were tested in both the DSA and scenario analysis and the model results are robust to changes to HSUVs.
Another limitation of the analysis was the need to extrapolate outcomes beyond follow-up to model a lifetime horizon. Methodological best practices were followed for extrapolation and for choosing the most clinically valid distributions. DSA indicated the model was robust. The price of osimertinib in the DF state yielded the largest deviation from the base case.

10.2 Conclusions

Osimertinib is a highly efficacious, well tolerated, and innovative treatment offering a potentially curative benefit and represents a paradigm shift as a targeted adjuvant treatment options to selected patients and healthcare providers, in

a disease area with significant unmet need. Further to the important clinical benefits of osimertinib to patients, it is also a highly cost-effective treatment when compared against established clinical management dominating active monitoring. We hope that the DMC will find their original concerns over the data presented in 2021 to be sufficiently addressed by the mature follow up data that we present in this updated application, to conclude that the overwhelming DFS benefit from the primary analysis has translated to an OS benefit for EGFRm NSCLC patients with a tolerable safety profile that didn´t result in a decline of HRQoL compared to placebo.

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12. Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

ADAURA is a direct comparative study and the compactor in the study reflect Danish treatment recommendations. For the EGFRm specific population in adjuvant treatment we evaluate that a SLR will not generate further data/publications that will support the application. In preparation for a global document AstraZeneca performed a SLR to identify published clinical efficacy and safety data of osimertinib and relevant comparators for the adjuvant treatment of stage IB–IIIA NSCLC, including patients with EGFRm stage IB–IIIA NSCLC. Searches of electronic databases were performed on 23rd July 2020 along with handsearching of conference proceedings, clinical trial registries, regulatory sources (FDA and EMA) and reference lists. The electronic database searches identified 9,807 articles.

Overall, a total of 26 publications, including the ADAURA clinical study report (CSR), reporting on 13 unique studies, were deemed relevant for extraction. Only one trial was identified in the SLR that provides clinical evidence that is directly relevant and that was the ADAURA trial.

Data on file from Aarhus University hospital was included from an ongoing observation study of treatment patterns, clinical outcomes, and diagnostic work up for stage I-IIIa NSCLC in a real life setting (TILLEUL).

12.1 Search strategy

Systematic selection of studies

No SLR was performed as a relevant study comparing with relevant standard of care is available.

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
ADAURA	Assess the efficacy and safety of osimerinib vs. Placebo, in patients with EGFRm Positive stage IB-IIIA NSCLC, following complete tumour resection with or without adjuvant chemotherapy	Interventional	Stage IB to IIIA(overall population) Median follow-up for DFS in all patients was 22.1 months in the osimertinib arm vs 16.6 months in the placebo arm	Osimertinib (339) vs Placebo (343)	The primary end point was DFS according to investigator assessment among patients with stage II to IIIA disease.	The secondary end points included DFS in the overall population of patients with stage IB to IIIA disease, overall survival, and safety. Median follow-up for DFS in stage II–IIIA patients was 22.1 months in the osimertinib arm vs 14.9

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						months in the placebo arm
TILLEUL (data on file 1)	Describe treatment reality	Observational	St. I-IIIa NSCLC pts from Aarhus University Hospital	Sample size, n=1345	2010-2020	

12.2 Quality assessment

12.3 Unpublished data

The data from TILLEUL, an observational study to evaluate treatment patterns, clinical outcomes, and diagnostic work up for stage I-IIIa NSCLC pts in a real world setting is expected to be published in Q3 2022 and be presented in Q2 2022 as an abstract in a major lung cancer focused conference. The objective of the study is to describe the diagnostic work-up in relation to biomarkers (EGFRm), describe the frequency and type of EGFRm, describe treatment patterns in relation to adjuvant chemotherapy or other modalities, and describe real world DFS and OS for stage I-IIIa NSCLC patients. The study includes 1345 patients treated at Aarhus University Hospital from 2010-2020.

13. Appendix B Main characteristics of included studies

Trial name: ADAURA	NCT number: NCT02511106
Objective	Examining the clinical benefit of osimertinib treatment in patients with EGFRm stage IB–IIIA NSCLC (according to the AJCC 7th edition),(52) following complete tumour resection with or without adjuvant chemotherapy.(5)
Publications – title, author, journal, year	Osimertinib in resected EGFR-mutated non-small-cell lung cancer, Wu et. Al., NEJM, 2020
Study type and design	ADAURA (NCT02511106) is a Phase III, double-blinded, randomized randomly in a 1:1 ratio, placebo-controlled, multi-centre trial. The trial is active not recruiting. The efficacy observed in ADAURA led to a recommendation from an Independent Data Monitoring Committee (IDMC) to unblind ADAURA two years earlier than planned; patients and investigators remain blinded to individual treatment allocations, therefore future results will still come from a sufficiently blinded clinical trial.(5)
Sample size (n)	682 (339 osimertinib and 343 placebo).

Main inclusion and exclusion criteria	**Inclusion criteria:** • Male or female • ≥18 years of age • Histologically confirmed diagnosis of primary NSCLC on predominantly non-squamous histology • MRI or CT scan of the brain must be done prior to surgery as it is considered SoC[a] • Patients must be classified post-operatively as stage IB, II or IIIA on the basis of pathologic criteria; staging was conducted in accordance with the TNM staging system for lung cancer (7th edition) • Confirmation by the central laboratory that the tumour harbours one of the 2 common *EGFR* mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other *EGFR* mutations including T790M • Complete surgical resection of the primary NSCLC was mandatory. All gross disease must have been removed at the end of surgery. All surgical margins of resection must be negative for tumour[b] • Complete recovery from surgery and standard post-operative therapy (if applicable) at the time of randomisation[c] • WHO Performance Status of 0 to 1. • Male patients should have been willing to use barrier contraception. Female patients should be using adequate contraceptive measures, should 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-child-bearing potential[d] • Provision of informed consent prior to any study specific procedures, sampling and analyses **Exclusion criteria:** • Previous randomisation and treatment in ADAURA • Treatment with any of the following: ✓ Pre-operative, post-operative or planned radiation therapy for the current lung cancer ✓ Pre-operative (neo-adjuvant) platinum-based or other chemotherapy ✓ Any prior anticancer therapy, including investigational therapy, for treatment of NSCLC other than standard platinum-based doublet post-operative adjuvant chemotherapy ✓ Prior treatment with neoadjuvant or adjuvant EGFR-TKI ✓ -Major surgery (including primary tumour surgery, excluding placement of vascular access) within 4 weeks of the first dose of study drug ✓ Patients currently receiving medications or herbal supplements known to be potent inducers of CYP3A4 (at least 3 week prior) ✓ Treatment with an investigational drug within five half-lives of the compound or any of its related material • Patients who had only segmentectomies or wedge resections • History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ cancer, or other solid tumours curatively treated with no evidence of disease for >5 years following the end of treatment

Trial name: ADAURA	NCT number: NCT02511106
	• Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy. • Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses; or active infection including hepatitis B, hepatitis C and HIV • 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 • Any of the following cardiac criteria: ✓ Mean resting QTc interval >470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTcF value ✓ Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG ✓ Any factors that increase the risk of QTc prolongation or risk of arrhythmic events, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QTc • Past medical history of ILD, drug induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD • Inadequate bone marrow reserve or organ function • Women who were breastfeeding. • History of hypersensitivity to active or inactive excipients of osimertinib, or drugs with a similar chemical structure or class to osimertinib. • Judgment by the Investigator that the patient should not participate in the study if the patient was unlikely to comply with study procedures, restrictions, and requirements Involvement in the planning and/or conduct of the study
Intervention	Osimertinib (80 mg [reduced dose 40 mg] orally, QD) vs placebo (QD) until recurrence of disease, treatment discontinuation or treatment completion. The treatment duration period was 3 years. 339 pts received the intervention
Comparator	Placebo with or without adjuvant chemotherapy

Trial name: ADAURA	NCT number: NCT02511106
Follow-up time	The efficacy observed in ADAURA led to a recommendation from an IDMC to unblind ADAURA two years earlier than planned. As such, at the DCO (17th January 2020) for the primary analysis, ADAURA had reached 33.2% DFS maturity in the stage II–IIIA population (156 DFS events, 26/233 [11.2%] in the osimertinib arm and 130/237 [54.9%] in the placebo arm). Median follow-up for DFS in stage II–IIIA patients was 22.1 months in the osimertinib arm vs 14.9 months in the placebo arm; the majority of patients (98.7%) had had at least 1-year of follow-up, with 61.1% having had at least 2 years of follow-up, and 18.3% having had at least 3-years of follow-up.(5) Median follow-up for DFS in all patients was 22.1 months in the osimertinib arm vs 16.6 months in the placebo arm
Is the study used in the health economic model?	Yes

	Priority	Type	Endpoint Description	Assessment
Primary, secondary and exploratory endpoints	Primary (stage II-III)	Efficacy	**DFS** (time from the date of randomisation until the date of disease recurrence or death [by any cause in the absence of recurrence])	Investigator-assessed
	Secondary	Efficacy	**DFS rate at 2, 3, 4 and 5 years** (proportion of patients alive and disease-free at 2, 3, 4 and 5 years, respectively, estimated from KM plots of the primary endpoint of DFS at the time of primary analysis). Full population	Investigator-assessed
		Efficacy	**OS** (time from the date of randomization until date of death due to any cause; any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive)	Investigator-assessed
		Efficacy	**OS rate at 2, 3, 4 and 5 years** (the proportion of patients alive at 2, 3, 4, and 5 years respectively, estimated from a KM plot of OS at the time of the primary analysis	Investigator-assessed
		HRQoL	Effect of osimertinib on HRQoL compared with placebo	SF-36
		Safety	Safety and tolerability of osimertinib compared with placebo	AEs (graded by CTCAE v4.03), clinical chemistry, haematology, urinalysis, vital signs, physical examination, weight, digital ECG, LVEF, WHO performance status and ophthalmologic assessment
		Pharmacokinetics (PK)	Characterise the PK of osimertinib and its metabolites (AZ5104 and AZ7550)	Blood sampling results

Trial name: ADAURA				NCT number: NCT02511106
	Exploratory	Health resource use	To compare health resource use associated with osimertinib treatment vs placebo	Health resource use module
		Efficacy	To compare the effects of osimertinib or placebo on post-recurrence outcomes	Time to next treatment(s); type of recurrence(s) (local/regional or distant); site(s) of relapse; type of next treatment(s) (including procedures, radiotherapy, and anticancer agents); PFS, as determined by investigator assessment
		Efficacy	To assess the benefit of osimertinib on CNS recurrence patients	CNS recurrence
Method of analysis	Disease-free survival was analyzed with the use of a log-rank test stratified according to disease stage, mutational status, and race. The Breslow approach was used to handle tied events. For the planned primary analysis, we determined that approximately 247 disease recurrence events or deaths in 490 patients with stage II to IIIA disease (50%) would provide 80% power to detect a hazard ratio of 0.70 at a two-sided alpha level of 5%. To control type I error at the 5% two-sided level, a prespecified hierarchical testing procedure was used; if significance was shown for disease-free survival among patients with stage II to IIIA disease, then disease-free survival would be tested for the overall population (patients with stage IB to IIIA disease). If this result was significant, overall survival would then be tested. The trial was not powered for overall survival. The independent data monitoring committee met regularly to review safety. After a planned meeting in 2019 to assess futility, but not superiority, when at least 83 disease recurrence events or deaths had occurred in patients with stage II to IIIA disease, the committee requested assessment of efficacy data at the next scheduled meeting for safety (April 2020). On the basis of review of these data, the committee recommended that the trial be unblinded at a trial level early to complete primary reporting. Given these unplanned reviews of efficacy for superiority, the alpha allocation had to be revised to control the overall type I error. Reviews of disease-free survival among patients with stage II to IIIA disease were conducted when 85 events and 156 events had been observed. The planned data cutoff date for the primary event-based analysis was February 2022. The data cutoff date for this unplanned interim analysis was January 17, 2020.			

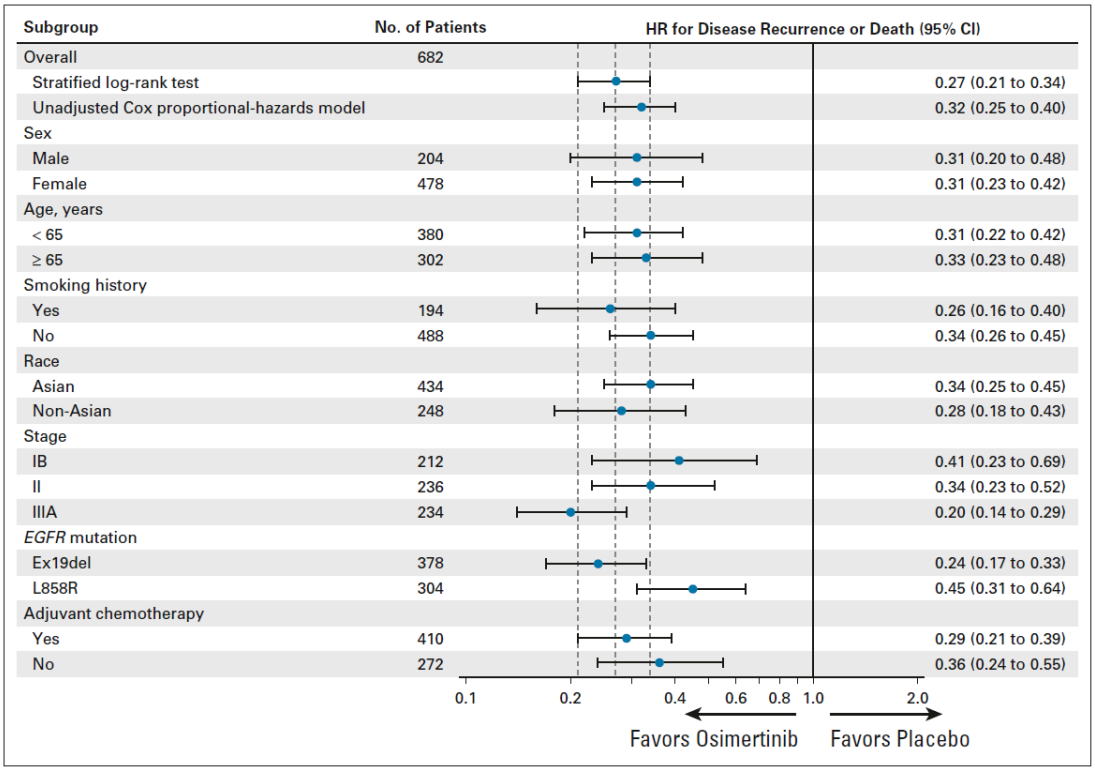
Trial name: ADAURA	NCT number: NCT02511106

Subgroup analyses

Subgroup analyses of DFS

In analyses of DFS in pre-specified, exploratory subgroups by clinical characteristics, clinically meaningful reductions in the risk of disease recurrence or death (ranging from 88% to 61%) were observed for osimertinib vs placebo across all subgroups

Subgroup analyses of DFS (FAS)



Source: Herbst et al. (2)

The subgroup analysis was performed with the use of a Cox proportional-hazards model that included trial regimen, subgroup, and the treatment-by-subgroup interaction term. Subgroup categories with less than 20 events were excluded from the analysis. Race was reported by the patients. The middle vertical dashed line indicates the median and the outer dashed lines indicate the 95% confidence interval for the overall hazard ratio (all patients). A hazard ratio of less than 1 implies a lower risk of disease recurrence or death with osimertinib than with placebo.

Other relevant information

14. Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 63. Patient's baseline characteristics from CancerLinQ data (61)

Baseline demographics	ADAURA-like cohort (n=97)
Age	
Mean, years (SD)	66.1 (9.9)
Median, years (Q1, Q3)	68.0 (60.0, 73.0)
Male gender, n (%)	28 (28.9)
Race, n (%)	
White	64 (67.4)
Black or African American	13 (13.7)
Asian	8 (8.4)
Native Hawaiian or Other Pacific Islander	1 (1.1)
Other Race	7 (7.4)
Unknown	2 (2.1)
Missing	2
Histology	
Adenocarcinoma	93 (95.9%)
Other carcinoma	4 (4.1%)
Disease stage	
Stage IB	36 (37.1%)
Stage II	36 (37.1%)
Stage IIIA	25 (25.8%)
Surgical procedure	
Bilobectomy of lung	5 (5.2%)
Lobectomy of lung	43 (44.3%)
Pneumonectomy	3 (3.1%)
Thoracoscopic lobectomy of lung	46 (47.4%)
***EGFR* mutation type**	

Baseline demographics	ADAURA-like cohort (n=97)
Exon 19 Deletion	26 (26.8%)
G719X	13 (13.4%)
L858R	11 (11.3%)
Unknown type	47 (48.5%)
Disease progression	
Recurrent tumour	13 (13.4%)
Tumour progression (finding)	84 (86.6%)
Survival status	
Survived	71 (73.2%)
Died	26 (26.8%)
***EGFR* tested before metastases**	
Missing	2
***EGFR* after met**	8 (8.4%)
***EGFR* b4 met**	87 (91.6%)
Site of metastases	
Missing	55
Bone	9 (21.4%)
Brain	8 (19.0%)
Liver	2 (4.8%)
Lung	8 (19.0%)
lymph node	5 (11.9%)
Other	8 (19.0%)
Pleura	2 (4.8%)
Months from surgery to metastases	
Missing	55
Mean (SD)	29.6 (19.0)
Median (Q1, Q3)	27.9 (14.7, 38.4)
Follow up duration in months	
Mean (SD)	45.8 (26.4)
Median (Q1, Q3)	44.4 (24.1, 68.7)
Performance status	
Missing	71
grade 0	10 (38.5%)
grade 1	13 (50.0%)

Baseline demographics	ADAURA-like cohort (n=97)
grade 2	2 (7.7%)
grade 3	1 (3.8%)
Medication received	
No treatment received	29 (29.9%)
Treatment received	68 (70.1%)
Chemotherapy	
No	50 (51.5%)
Yes	47 (48.5%)
***EGFR*-TKIs**	
No	59 (60.8%)
Yes	38 (39.2%)
Immunotherapy	
No	88 (90.7%)
Yes	9 (9.3%)

Table 64. Patient demographics and baseline characteristics of CancerLinQ stage II-IIIA subgroup (61)

Baseline demographics	ADAURA-like cohort (n=62)
Age	
Mean, years (SD)	66.7 (9.6)
Median, years (Q1, Q3)	68.0 (60.0, 73.0)
Male gender, n (%)	23 (37.1)
Race, n (%)	
White	40 (66.7)
Black or African American	9 (15.0)
Asian	6 (10.0)
Other Race	3 (5.0)
Unknown	2 (3.3)
Missing	2
Histology	
Adenocarcinoma	58 (93.5%)
Other carcinoma	3 (4.8%)
Squamous cell carcinoma	1 (1.6%)
Disease stage	
Stage II	37 (59.7%)
Stage IIIA	25 (40.3%)
Surgical procedure	

Baseline demographics	ADAURA-like cohort (n=62)
Bilobectomy of lung	4 (6.5%)
Lobectomy of lung	29 (46.8%)
Pneumonectomy	3 (4.8%)
Thoracoscopic lobectomy of lung	26 (41.9%)
***EGFR* mutation type**	
Exon 19 Deletion	16 (25.8%)
G719X	8 (12.9%)
L858R	7 (11.3%)
Unknown type	31 (50.0%)
Disease progression	
Recurrent tumour	10 (16.1%)
Tumour progression (finding)	52 (83.9%)
Survival status	
Survived	43 (69.4%)
Died	19 (30.6%)
Site of metastases	
Missing	34
Bone	6 (21.4%)
Brain	6 (21.4%)
Liver	1 (3.6%)
Lung	5 (17.9%)
Lymph node	4 (14.3%)
Other	5 (17.9%)
Pleura	1 (3.6%)
Months from surgery to metastases	
Missing	34
Mean (SD)	28.7 (18.4)
Median (Q1, Q3)	27.9 (14.2, 38.3)
Follow up duration in months	
Mean (SD)	43.4 (26.0)
Median (Q1, Q3)	39.6 (23.2, 65.5)
Performance status	
Missing	44
grade 0	6 (33.3%)

Baseline demographics	ADAURA-like cohort (n=62)
grade 1	10 (55.6%)
grade 2	2 (11.1%)
Medication received	
No treatment received	15 (24.2%)
Treatment received	47 (75.8%)
Chemotherapy	
No	25 (40.3%)
Yes	37 (59.7%)
***EGFR*-TKIs**	
No	39 (62.9%)
Yes	23 (37.1%)
Immunotherapy	
No	55 (88.7%)
Yes	7 (11.3%)

Table 65. Patient baseline characteristics of ADAURA trial (3)

Characteristic, %	Osimertinib (n=339)	Placebo (n=343)
Sex: male / female	32 / 68	28 / 72
Age, median (range), years	64 (30–86)	62 (31–82)
Smoking status: smoker* / non-smoker	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO performance status: 0 / 1	64 / 36	64 / 36
AJCC staging at diagnosis (7th edition): IB / II / IIIA	31 / 35 / 34	31 / 34 / 35
Histology: adenocarcinoma / other†	95 / 5	96 / 4
EGFR mutation at randomization‡: Ex19del / L858R	55 / 45	56 / 44
Adjuvant chemotherapy: yes / no	55 / 45	56 / 44

Patient Characteristics	Osimertinib (N=339)	Placebo (N=343)
Age, median, years (range)	64.0 (30, 86)	62.0 (31, 82)
Male, n (%)	109 (32.2)	95 (27.7)
Race, n (%)		
White	122 (36.0)	122 (35.6)
Asian	216 (63.7)	218 (63.6)
Other	1 (0.3)	2 (0.6)
Missing	0	1 (0.3)
WHO performance status, n (%)		
0 (Normal activity)	216 (63.7)	218 (63.6)
1 (Restricted activity)	123 (36.3)	125 (36.4)
AJCC staging at diagnosis, n (%)[a]		
IB	107 (31.6)	109 (31.8)
IIA	86 (25.4)	90 (26.2)
IIB	29 (8.6)	26 (7.6)
IIIA	117 (34.5)	118 (34.4)
EGFR mutations by cobas® central test, n (%)[b]		
Exon 19 deletion	185 (54.6)	188 (54.8)
L858R	153 (45.1)[c]	155 (45.2)
Histology type, n (%)[c]		
Adenocarcinoma: acinar	85 (25.1)	82 (23.9)
Adenocarcinoma: papillary, malignant	43 (12.7)	44 (12.8)
Adenocarcinoma: malignant	183 (54.0)	188 (54.8)
Adenocarcinoma: bronchiolo-alveolar	11 (3.2)	13 (3.8)
Adenocarcinoma: solid with mucous formation	4 (1.2)	5 (1.5)
Bronchial gland carcinoma (not otherwise specified)	1 (0.3)	2 (0.6)
Carcinoma, adenosquamous, malignant	4 (1.2)	5 (1.5)
Other	8 (2.4)	4 (1.2)
Lung cancer resection type, n (%)		
Lobectomy	328 (96.8)	322 (93.9)
Sleeve resection	1 (0.3)	3 (0.9)
Bilobectomy	7 (2.1)	8 (2.3)
Pneumonectomy	3 (0.9)	10 (2.9)

Table 66. Patient baseline characteristics of FLAURA trial (62)

Characteristic (FAS)	Osimertinib N=279	SoC TKI N=277
Median age, years (range)	64.0 (26–85)	64.0 (35–93)
Male gender, n %	101 (36)	105 (38)
Race, n (%)		
Asian	174 (62)	173 (62)
White	101 (36)	100 (36)
Other	4 (1)	4 (1)
Smoking status, n (%)		
Never	182 (65)	175 (63)
Current	8 (3)	9 (3)
Former	89 (32)	93 (34)
WHO performance status, n (%)		
0 (normal activity)	112 (40)	116 (42)
1 (restricted activity)	167 (60)	160 (58)
Missing data	0	1 (0.4)
Overall disease classification, n (%)		
Metastatic[†]	264 (95)	262 (95)
Locally advanced[‡]	14 (5)	15 (5)
Missing	1 (0.4)	0
CNS metastases[§]	53 (19)	63 (23)
Visceral metastases	94 (34)	103 (37)
Liver metastases	41 (15)	37 (13)
***EGFR* mutations by central test**		
Exon 19 deletion	158 (57)	155 (56)
L858R	97 (35)	90 (32)
***EGFR*m not detected, invalid test, or inadequate sample**	24 (9)	32 (12)
***EGFR* mutations at randomisation**		
Exon 19 deletion	175 (63)	174 (63)
L858R	104 (37)	103 (37)

Table 67. Patient's baseline characteristics of ANITA trial (21)

Characteristic	Chemotherapy (n=407)	Observation (n=433)
Age (years)		
Median (range)	59 (32–75)	59 (18–75)
<55 years	134 (33%)	152 (35%)
≥55 years	273 (67%)	281 (65%)
Sex		
Male	346 (85%)	375 (87%)
Female	59 (14%)	56 (13%)
Missing	2 (<1%)	2 (<1%)
Time from surgery to randomisation (days)		
Median (range)	34 (6–54)	33 (7–52)
Type of surgery		
Pneumonectomy	155 (38%)	155 (36%)
Lobectomy	233 (57%)	253 (58%)
Other	16 (4%)	23 (5%)
Missing	3 (1%)	2 (<1%)
Postoperative stage		
I	146 (36%)	155 (36%)
II	89 (22%)	114 (26%)
IIIA	166 (41%)	159 (37%)
IIIB–IV	2 (<1%)	2 (<1%)
Missing	4 (1%)	3 (1%)
Lymph nodal status		
N0	179 (44%)	188 (43%)
N1	107 (26%)	136 (31%)
N2	118 (29%)	106 (24%)
Missing	3 (1%)	3 (1%)
Histology		
Squamous-cell carcinoma	240 (59%)	253 (58%)
Non squamous-cell carcinoma	163 (40%)	175 (41%)
Mixed squamous and non-squamous	1 (<1%)	3 (1%)
Missing	3 (1%)	2 (<1%)
WHO performance status		

Characteristic	Chemotherapy (n=407)	Observation (n=433)
0	196 (48%)	225 (52%)
1	192 (47%)	189 (44%)
2	14 (3%)	14 (3%)
Missing	5 (1%)	5 (1%)

14.1 Comparability of patients across studies

Comparability of the study populations with Danish patients eligible for treatment

We have provided data on Danish patients that are eligible in the section Patient populations relevant for this application. The patient population in ADAURA is predominantly female and Asian with a median age of 63 years. In comparison the Danish target population is also predominantly female and the median age is predominantly below 70. This is comparable to the ADAURA population. We have provided PFS and OS curves of Danish patients in Figure 3 and Figure 4, which indicate that the Danish group has comparable trends to that of the placebo group in the ADAURA trial.

15. Appendix D Efficacy and safety results per study

15.1 Definition, validity and clinical relevance of included outcome measures

Table 68 .Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
DFS (primary) **DFS(secondary)**	DFS primary endpoint: Assess the Efficacy of osimertinib Compared to Placebo as Measured by Disease Free Survival (DFS). Defined as the time from the date of randomization until the date of disease recurrence or death (by any cause in the absence of recurrence) DFS Secondary endpoint: DFS Rate at 2, 3 and 5 Years: • From date of randomization until date of disease recurrence or death (by any cause in the absence of recurrence), up to approximately 4 years. Assessed at 2 years and 3 years. • Defined as the percentage of patients alive and disease free at 2, 3 and 5 years, respectively, estimated from Kaplan Meier plots of the primary endpoint of DFS at the time of the primary analysis	DFS is measured based on investigator assessment and will be assessed in both the overall population and the subset of patients with stage II-IIIA cancer. The primary analysis of DFS will occur when approximately 247 disease recurrence events have been observed in approximately 490 patients who are in Stage IIA-IIIA (i.e. non-IB). If the true DFS hazard ratio (HR) for the comparison of AZD9291 versus placebo in this patient population is 0.70, 247 disease recurrence events will provide 80% power to demonstrate a statistically significant difference in DFS at a 5% 2-sided significance level.	DFS primary endpoint: Important/critical DFS represents a direct measure of the study drug's efficacy as it is not confounded by the efficacy of subsequent therapies used after disease relapse. Moreover, data has shown that the DFS benefit seen with the use of chemotherapy in the adjuvant setting was consistent with an improvement in the OS outcome. DFS secondary endpoint: less Important

Outcome measure	Definition	Validity	Clinical relevance
AE and SAE	Includes AEs and SAE with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy; MedDRA version 22.1. CTCAE version 4.03.	The AEs and SAEs are being reported at both AEs/SAEs overall but also related to treatment(assessed by the investigator)	Critical
OS	OS: • From date of randomization until date of death due to any cause, up to approximately 4 years. • Defined as the time from the date of randomization until date of death due to any cause.	For the analysis, any survival calls were made strictly after the date of the Data Cut Off (DCO) for the analysis. If patients are confirmed to be alive or if the death date is post the DCO date these patients were censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients were obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, death dates may be found by checking publicly available death registries where it is possible to do so under applicable local laws. If a patient was known to have died where only a partial death date was available, then the date of death were imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided: a. For Missing day only – using the 1st of the month	Important Due to the early stage of the disease the number of events are low and the OS maturity low

Outcome measure	Definition	Validity	Clinical relevance
		b. For Missing day and Month – using the 1st of January. If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e. censored at the last known alive date.	
HRQoL	Symptoms (HRQoL) by SF-36v2 Health Survey. [Time Frame: Measured by SF-36 Questionnaire at baseline, 12 week, 24 week and then every 24 weeks until study complete, disease recurrence or other discontinuation criteria met, up to approximately 3 years.] Change from baseline will be calculated for each domain and summary scale at each scheduled post-baseline assessment. The SF-36 includes eight domains: Physical Functioning (PF); Role Limitations-Physical (RP), Vitality (VT), General Health Perceptions (GH), Bodily Pain (BP), Social Function (SF), Role Limitations-Emotional (RE), and Mental Health (MH) and two summary scores: The Physical Component Summary (PCS) and Mental Component Summary (MCS). Final scores for each scale range from 0-100 with higher scores indicating better health. The included Items use Likert scales with 3-6 points. Raw scores for the scales are computed across items in the same domain and are then transformed via a weighting system to a 0-100 domain with higher scores indicating better health.	To minimize bias and enhance compliance appropriate procedures were used to be followed throughout the study. All study personnel were trained to instruct the patient in a standardized way and further be responsible for providing all relevant instructions and training to the patients. All the significance and the relevance of the data were explained carefully to the patients to ensure motivation to comply with data collection. Following were applied: · The patient must complete it in private, taking his or her own time. · The patient must complete it before any investigations or discussions about their disease with the clinic staff. · It must be completed prior to any other study-related procedures. · The patient should be given sufficient time to complete at their own speed, and the patient should be reassured that there are no right or wrong answers and that the answers are strictly confidential. · Help should not be given from relatives or clinical, with the exception that the patient can receive help from a study nurse in understanding the instructions. However under no circumstances should help in interpreting the questions or in selecting responses be	Important/critical HRQoL is an important tool especially in as the we are measuring an active compound vs. placebo

Outcome measure	Definition	Validity	Clinical relevance
		provided. · A form will be completed by the clinic staff to indicate if a questionnaire has been completed at each visit, and if not, the reason will be recorded. · On completion of the questionnaire it should be handed back to the person responsible for questionnaires who should check for completeness. · Only one answer should be recorded for each question.	
(TFST) Time to first subsequent therapy			Important/Low importance At the time of the DCO, TFST had reached 24.2%. Median TFST was not calculable in the osimertinib arm, and 39.8 months in the placebo arm
(TSST)The time to second subsequent therapy			Important/Low importance The time to second subsequent therapy (TSST) endpoint had reached 10.4% maturity at the DCO. Median TSST was not calculable in the osimertinib arm, and 48.2 months in the placebo arm; the HR point estimate favoured osimertinib .

Table 69. Results per endpoint updated with efficacy and safety numbers from DCO April 2022 and January 2023 (HQoL is primary analysis).

Table A3a ADAURA (NCT02511106)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Ref.
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
mDFS (II-IIIA)	Osimertinib	233	NR (38.8, NC) 11.2%	NR	NA	NA	HR=0.17	99.06% CI (0.11, 0.26)	p<0.001	DFS events are NSCLC recorded as local/regional or distant, or death. DFS events that do not occur within two scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events. [b]Patients who had evidence of disease at study entry have been censored at day one. The analysis was performed using a log rank test stratified by stage (II vs IIIA), race (Asian vs Non-Asian) and mutation type (Exon 19 deletion vs L858R). Stratification factors are as recorded in the interactive voice response system. The HR and CI are obtained directly from the U and V statistics.The adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis. Primary analysis	Osimertinib in resected EGFR-mutated Non-Small-Cell Lung Cancer, Wu et. al., NEJM, 2020
	Placebo	237	19.6 (16.6, 24.5) 54.9 %								

Table A3a ADAURA (NCT02511106)											
DFS(IB–IIIA). Overall population	Osimertinib	339	NR (NC, NC)	NR	NA	NA	HR=0.20	(0.15, 0.27)	p<0.0001	See above	See above
	Placebo	343	27.5 (22.0, 35.0)								
mDFS (II-IIIA)	Osimertinib	233	65.8 (54.4, NC]	43,9 m	NA	NA	HR= 0.23 (95%	(0.18, 0.30)		Median duration of follow-up for DFS was 44.2 months (range, 0-67 months) among the 233 patients on osimertinib and 19.6 months (range, 0-70 months) among the 237 patients on placebo.Update from DCO April 11 2022	Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non–small-cell lung cancer: updated results from the phase III randomized ADAURA trial. Herbst RS, Wu Y-L, John T, et al J Clin Oncol 2023; 41: 1830-40.
	Placebo	237	21.9 (16.6, 27.5)								
DFS(IB–IIIA). Overall populations	Osimertinib	339	65.8 (61.7 to NC)	37.7 m	NA	NA	HR=0.27	0.21 to 0.34)		Osimeritnib group 28% maturity and placebo 62% maturity; overall maturity 45%.Update from DCO April 11 2022	See above
	Placebo	343	28.1 (22.1 to 35.0)								
OS (II–IIIA)	Osimertinib	233	NR (NC, NC) 8 (3.4%)	3.8 %	NA	NA	HR=0.40	(0.18, 0.89)	p=0.0244	OS events that do not occur within two scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in	Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA

Table A3a ADAURA (NCT02511106)											
	Placebo	237	NR (NC, NC) 17 (7.2 %)							the number of events. The analysis was performed using a log rank test stratified by stage (II vs IIIA), race (Asian vs Non-Asian) and mutation type (Ex19del vs L858R). The HR and CI are obtained directly from the U and V statistics. Primary analysis	non–small-cell lung cancer: updated results from the phase III randomized ADAURA trial. Herbst RS, Wu Y-L, John T, et al J Clin Oncol 2023; 41: 1830-40.
OS (IB–IIIA)	Osimertinib	339	NR (NC, NC) 9 (2.7 %)	3.1 %	NA	NA	HR=0.48	(0.23, 1.02)	p=0.0553	See above	See above
	Placebo	343	48.2 (48.2, NC) 20 (5.8 %)								
OS (II–IIIA). Overall population	Osimertinib	233	85% (79; 89)	12 %	NA	NA	HR=0.49	95.03% CI, (0.33, 0.73)	0.001	Follow-up was 59.9 months (range, 0 to 82) in the osimertinib group and 56.2 months (range, 1 to 86) in the placebo group. DCO January 27, 2023	Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. Tsuboi et al. NEJM June 4, 389:137-147 2023
	Placebo	237	73 % (66; 78)								
OS (IB–IIIA)	Osimertinib	339	88% (83, 91)	10 %	NA	NA	HR=0.49	95.03% CI, (0.34, 0.70)	<0.001	Follow-up: 60.4 months (range, 0 to 82) in the osimertinib group and 59.4 months (range, 1 to 86) in the placebo group. January 27, 2023	See above
	Placebo	343	78% (73; 82)								

Table A3a ADAURA (NCT02511106)											
Any AE	Osimertinib	339	330 (97.9%)	7.8 %	NA	NA	RR=1.08	(1.08, 1.12)		AEs of any cause, including Grade ≥3 AEs, occurred in a greater proportion of patients in the osimertinib arm, compared with the placebo arm. DCO April 2022	
	Placebo	343	309 (90.1%)								
SAE(due to any cause)	Osimertinib	339	68 (20.2 %)	6.5 %	NA	NA	RR = 1.43	(1.15, 1.78)	NA	Includes events with an outcome of death. DCO Primary analysis. DCO April 2022 RR calculated by AZ	Osimertinib for resected EGFR-mutated stage IB-IIIA non–small-cell lung cancer: updated results from the phase III randomized ADAURA trial. Herbst RS, Wu Y-L, John T, et al J Clin Oncol 2023; 41: 1830-40.
	Placebo	343	47 (13.7 %)								
SAE (causally related to study treatment)	Osimertinib	339	10 (3.0)	2.4 %	NA	NA	RR = 5.06	(1.12, 22.92)	NA	Includes events with an outcome of death. AEs assessed by investigator. DCO April 2022 RR calculated by AZ	See above
	Placebo	343	2 (0.6)								
Grade ≥3 AEs (AEs due to any cause)	Osimertinib	339	79 (23.4)	9.4 %	NA	NA	RR = 1.67	(1.20, 2.31)	NA	At the primary DCO, the median duration of follow-up was 22.1 months in the osimertinib arm, and 14.9 months in the placebo arm. DCO April 2022 RR calculated by AZ	See above
	Placebo	343	48 (14.0)								

Table A3a ADAURA (NCT02511106)											
Grade ≥3 AEs (causally related to study treatment)	Osimertinib	339	36 (10.7%)	8.7 %	NA	NA	RR = 5.04	(2.35, 11.53)	NA	AEs assessed by investigator. DCO Arpil 2022. RR calculated by AZ	See above
	Placebo	343	7 (2.0%)								
Discontinuations due to AEs(causally related to study treatment)	Osimertinib	339	35 (10.4%)	8.9 %	NA	NA	RR= 7.08	(2.81, 17.86)	NA	DCO Arpil 2022. RR calculated by AZ	
	Placebo	343	5 (1.5 %)								
SF-36 component MSC	Osimertinib	339	1.34 (0.60, 2.08)	-1.34	(-2.40, -0.28)	NA	NA	NA	NA	A generic HRQoL questionnaire (SF-36) was selected as the patient reported outcome endpoint in ADAURA. The rationale for this was that adjuvant-stage patients with no evidence of disease, such as those enrolled in ADAURA, are predominantly asymptomatic and, compared with a lung cancer-specific questionnaire. Change from baseline was examined until Week 96, to ensure balanced comparison between arms, given the earlier discontinuation in completing the SF-36 health survey in the placebo arm, due to earlier events of disease recurrence; Based on the 3rd edition of the SF-36 scoring manual.	See above
	Placebo	343	2.68 (1.92, 3.44)								

Table A3a ADAURA (NCT02511106)											
										A difference of +/- 3 is regarded as a clinical meaningful difference. Primary Analysis	
SF-36 component PCS	Osimertinib	339	1.13 (0.54, 1.72)	-1.18	(-2.02, -0.34)	NA	NA	NA	NA	See above. A difference of +/- 2 is regarded as a clinical meaningful difference. Primary Analysis	See above
	Placebo	343	2.31 (1.70, 2.91)								
PFS Overall IB-IIIA	Osimertinib	339	70.1 (66.4, NC)	3.9 m	NA	NA	HR=0.32	(0.23, 0.44)	<0.0001	DCO Jan 27 2023	
	Placebo	343	66.2 (57.6, 72.4)								
Investigator-assessed CNS DFS. Overall populations. Number of events	Osimertinib	339	25 (7.4 %)	7.2 %	NA	NA	HR=0.36	(0.23, 0.57)	<0.0001	DFS events are defined as disease recurrences in the CNS, or death. DFS events that do not occur within two scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events; Death in the absence of CNS disease recurrence, or death occurring within two visits of baseline where the patient has no evaluable assessments or no baseline data	Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non–small-cell lung cancer: updated results from the phase III randomized ADAURA trial. Herbst RS, Wu Y-L, John T, et al J Clin Oncol 2023; 41: 1830-40
	Placebo	343	50 (14.6 %)								
	Osimertinib	233	22 (9.4%)	7.9 %	NA	NA	HR=0.24	(0.14, 0.42	<0.0001	See above	See above

Table A3a ADAURA (NCT02511106)											
Investigator-assessed DFS CNS recurrence free (II–IIIA). Number of events.	Placebo	237	41 (17.3%)								
Median TFST	Osimertinib	339	NC (NC , NC) 26 %	31.7%	NA	NA	HR=0.28	(0.22, 0.36)	<0.0001	First subsequent anti-cancer therapy or death (Full analysis set: overall population). DCO Jan 2023	AstraZeneca data on file
	Placebo	343	35.4 (29.0, 45.1) 57,7%								
Median TSST	Osimertinib	339	44 (13.0)	59(17.9%)	NA	NA	HR=0.37	(0.26, 0.50);	p<0.0001	Second subsequent anti-cancer therapies (including radiotherapy). DCO April 2022	Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non–small-cell lung cancer: updated results from the phase III randomized ADAURA trial. Herbst RS, Wu Y-L, John T, et al J Clin Oncol 2023; 41: 1830-40

16. Appendix E Safety data for intervention and comparator(s)

16.1 Overview of AEs in ADAURA

Safety profile of osimertinib and comparator are described in Efficacy and safety – ADAURA section 7.2.1.

Safety and tolerability were assessed in the ADAURA study in terms of AEs (including SAEs), deaths, laboratory data, vital signs, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), WHO performance status, ophthalmologic assessment and treatment exposure. All safety data are summarised by treatment arm, including patients who had dose reductions, and no formal statistical analyses were performed. Overall, the safety profile of osimertinib was consistent with previous trials of osimertinib.
The majority of patients in both study arms reported an AE (osimertinib: 97.9%; placebo: 90.1%). AEs of any cause, including Grade ≥3 AEs, occurred in a greater proportion of patients in the osimertinib arm, compared with the placebo arm; however, the majority of AEs in the osimertinib arm were non-serious, mild or moderate in severity, and did not lead to treatment discontinuation. Similar results were observed when considering only the AEs that were causally related to study treatment; notably, the analysis of these AEs indicates that a large proportion of Grade ≥3 AEs were not due to study treatment. Osimertinib is well established as it has been recommended and used several years in Denmark for 1st (EGFRm) and 2nd line(T790m). Side effects are manageable and the two different strengths(80 and 40 mg) allows for dose-reductions.

17. Appendix F Comparative analysis of efficacy and safety

DFS and OS updates from latest DCO has been captured in Table 3A/Table 69. As the application is based on a direct comparative study Table A4 would include same values af table A3/Table 69 and we see no need to include table A4 and it has been omitted from this updated application.

18. Appendix G – Extrapolation

18.1 Survival analysis

The inputs regarding effectiveness for osimertinib were sourced from the pivotal trial ADAURA, evaluating the efficacy and safety of osimertinib compared to active monitoring for the treatment of individuals with *EGFR*-mutated NSCLC. The two main inputs regarding effectiveness used in the model and economic analysis were DFS and OS. The intention to treat (ITT) population from the ADAURA trial was used to conduct the survival analyses for DFS and OS.
As limited post-recurrence follow-up data were available from ADAURA at the data cut-off time-point (January 2020), parametric survival modelling was used to estimate the probability of transition from LRR to DM1 using data from CancerLinQ, a US real-world evidence database comprising over 1.4 million patients with a primary lung cancer diagnosis.(61) The transition probabilities for the distant metastases health states are primarily estimated from survival modelling using the FLAURA phase 3 trial, which evaluates osimertinib versus erlotinib or gefitinib as first-line treatment in patients with E*GFR*-mutated (E*GFRm*) advanced NSCLC. (62)

18.2 Transition probabilities

The base case was set by using the parametric distributions with the best statistical fit and clinical plausibility for each transition, where for every possible combination of the parametric distribution in TP1 (DF to LR) and TP2 (DF to DM1) the mean square error (MSE) was calculated. Here the distributions for the other transition probabilities from TP3 to TP8 are kept the same. Based on the ADAURA Kaplan-Meier data for both DFS and OS, the MSE is then calculated. See Table 73 for the ranking of all 36 combinations based upon TP1 and TP2 for both DFS and OS. The generalised gamma distribution was selected for TP1 and also for TP2, as this distribution appears to provide the best balance between goodness of fit with observed data and plausible long-term extrapolations in each treatment arm. Among all 36 possible combinations, this combination was ranked 1st in DFS and 2nd in OS in terms of MSE. This combination of distributions results in the aggregated DFS and OS shown in Figure 24. Aggregated DFS without cure compared to ADAURA DFFigure 24 and Figure 25, respectively.
The base case parametric distributions applied for each transition are shown in Table 70. In addition, scenario analyses were also performed to test different curve selections.

Table 70. Main settings for the base case

Transition	Setting	Data source
TP1: DF -> LRR	Generalized gamma	ADAURA
TP2: DF -> 1L DM	Generalized gamma	ADAURA
TP3: DF -> Death	Background mortality	ADAURA / Danish life tables* (65)
TP4: LRR -> 1L DM	Lognormal	CancerLinQ (61)
TP5: LRR -> Death	Background mortality	CancerLinQ (61) / Danish life tables*(65)
TP:6 1L DM -> 2L DM	Weibull	FLAURA (62)
TP7: 1L DM -> Death	Exponential / Background mortality	FLAURA (62) / Danish life tables* (65)

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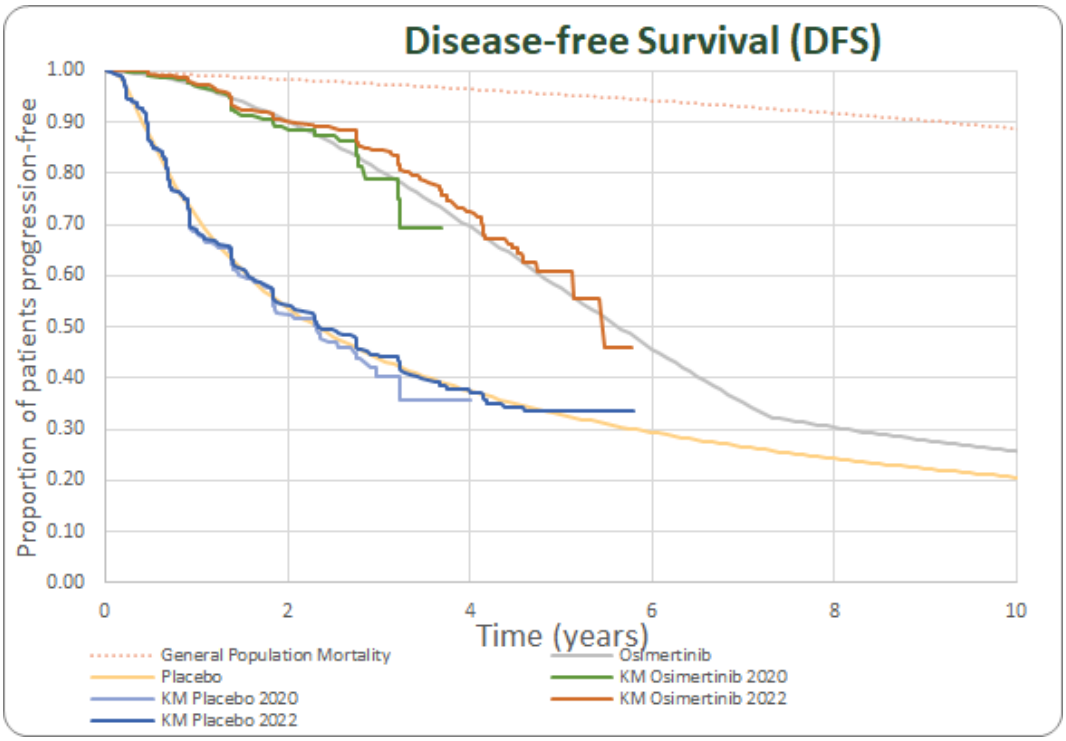
Transition	Setting	Data source
TP8: 2L DM -> Death	Weibull	FLAURA (62) / Danish life tables* (65)
Cure	48 - 96 months (8 years) for osimertinib 48 - 60 months (5 years) for active monitoring	Clinical experts
Cure percentage	95%	Clinical experts
Retreatment	50% of the osimertinib patients can be retreated	Clinical experts
Treatment waning	No	
Calibration HR in TP4-TP8	0.7263	Calibrated using ADAURA

*Statistic Denmark, Life Tables 2021-2022: https://www.statbank.dk/HISB8

Key: DF, Disease-free health state; 1L DM, 1st line distant metastasis; 2L DM, 2nd line distant metastasis, LRR, local/regional, TP: Transition probability

Figure 24. Aggregated DFS without cure compared to ADAURA DF



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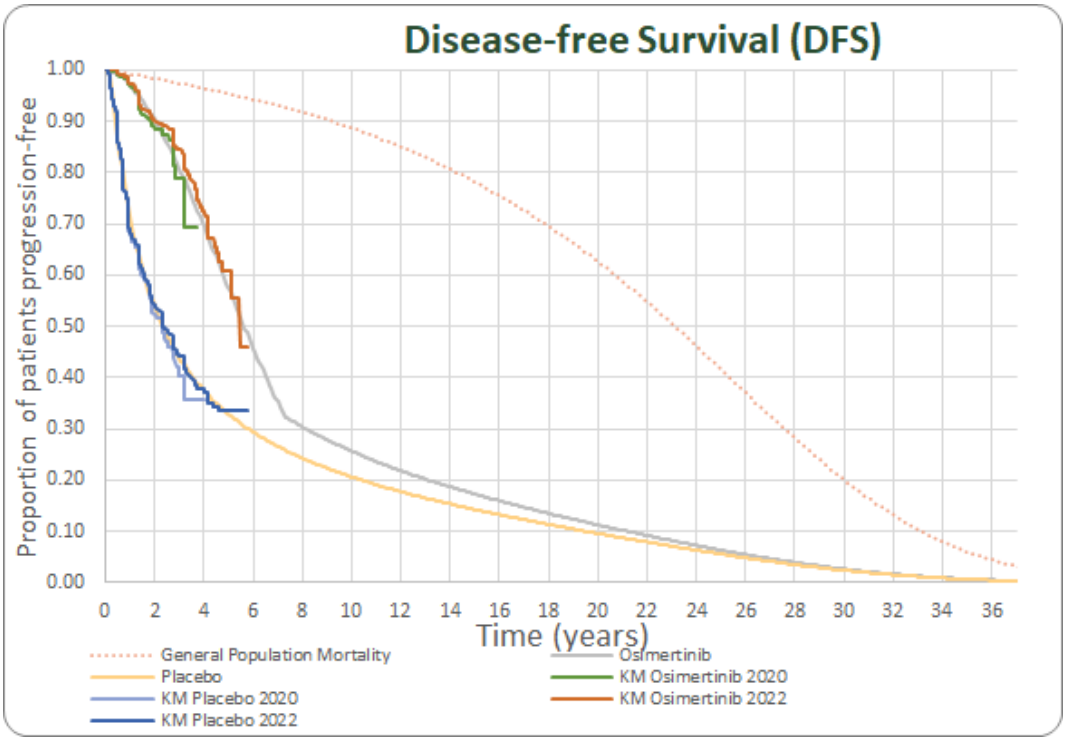
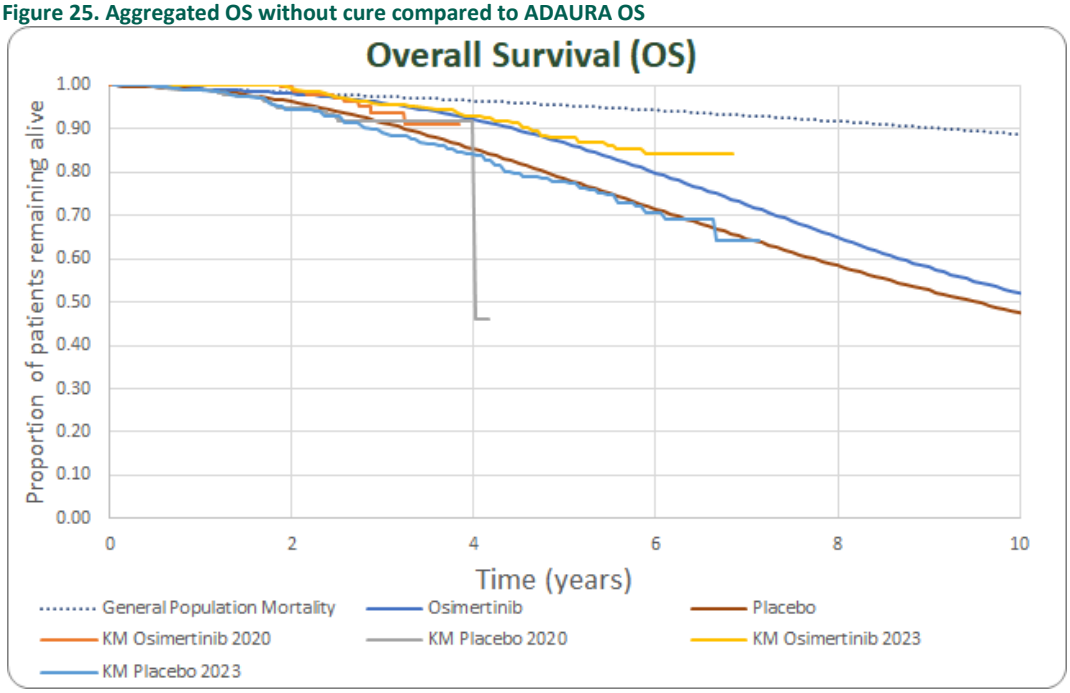


Figure 25. Aggregated OS without cure compared to ADAURA OS



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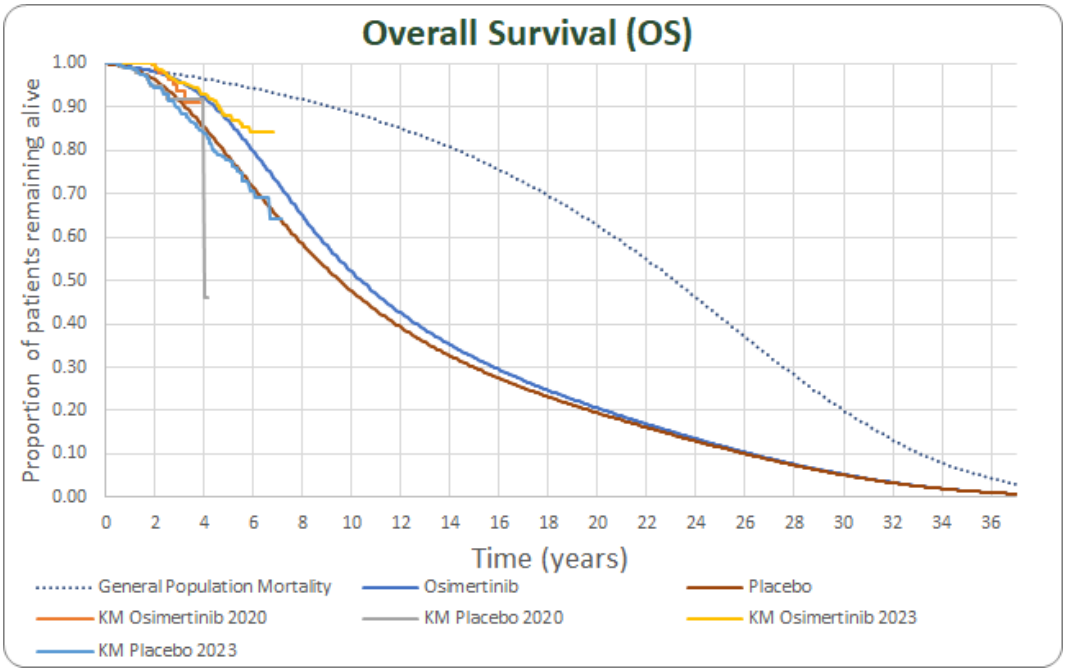

The fit compared to the ADAURA KM is good for both DFS and OS, although for osimertinib the OS data fits well until 60 months, after which the Kaplan-Meier becomes non-informative due to censoring and the low number of patients at risk. In an independent UK advisory board held in November 2020, clinical experts argued that both DFS and OS extrapolations may be too pessimistic, and that cure or long-term disease free survival is expected, i.e. within a certain timeframe or landmark, a patient that has not experienced disease recurrence or death would be assumed effectively cured. Their risk of dying would thus be similar to that observed for the general population, and thus application of general population background mortality to these patients would be a more clinically valid approach. This was confirmed with Danish clinical experts (59, 60).

In further interviews conducted with three Canadian and one UK clinician it was confirmed that patients in their respective countries with completely resected early-stage NSCLC are typically discharged from care after five years of being treatment free if they have not experienced disease recurrence. Patients are at greatest risk of recurrence 18 to 24 months post surgery, and therefore if patients remain treatment- and disease free for five years, they can be considered functionally cured. Clinicians generally consider the risk of recurrence to be very low after five years, with the risk of recurrence reducing as time since surgery increases. In addition, interviewed clinicians advised that, in patients who are treatment free after five years and have been discharged from care, it is reasonable to assume that survival is similar to that of the general population (given that these patients may now be considered functionally cured).

The clinicians also agreed that a gradually increasing percentage of patients could be assumed to be functionally cured before the five-year treatment-free mark is reached.

Based on this feedback, it was assumed that there is a gradual transition to cure in both arms. This gradual transition was assumed to take place over 1 year for the active surveillance arm (0% at year 4, 95% at year 5) and 4 years for the Osimertinib arm (0% cure at 4 years, 95% at year 8). The assumption that 95% of patients would be cured if remained DF is consistent with the preferred approach described in NICE technology appraisals in adjuvant, early-stage NSCLC (TA569, TA642). In both appraisals, the ERG and the appraisal committee agreed that the maximum proportion of patients to be 'cured' at the final timepoint (i.e., no

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longer at risk of disease recurrence) should be set to 95% and that it was clinically implausible to assume 100% of patients could be 'cured'.
With the assumption of cure the fit of the DFS and OS curves compared to the ADAURA KM remains good, and now shows more positive survival rates beyond 5 years in both treatment arms, consistent with curative intent following complete tumour resection (see Figure 26 and Figure 27). A landmark comparison for the final base case is presented in Table 71 and Table 72.

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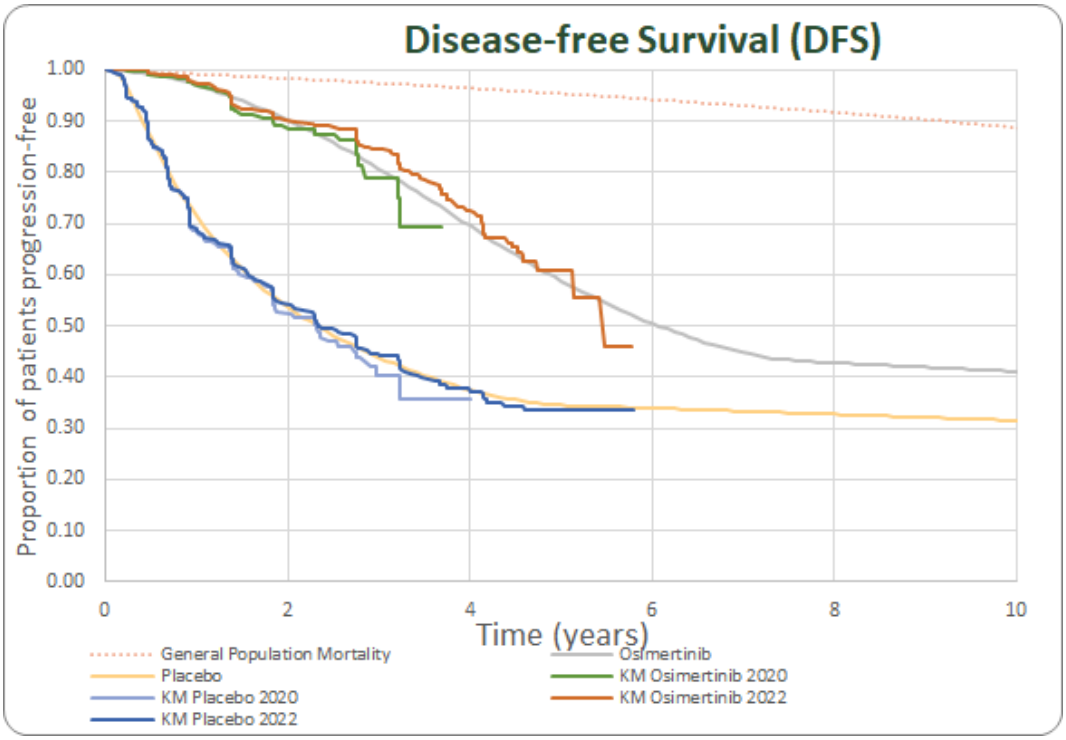
Figure 26. Aggregated DFS curve with cure and the Kaplan-Meier from ADAURA



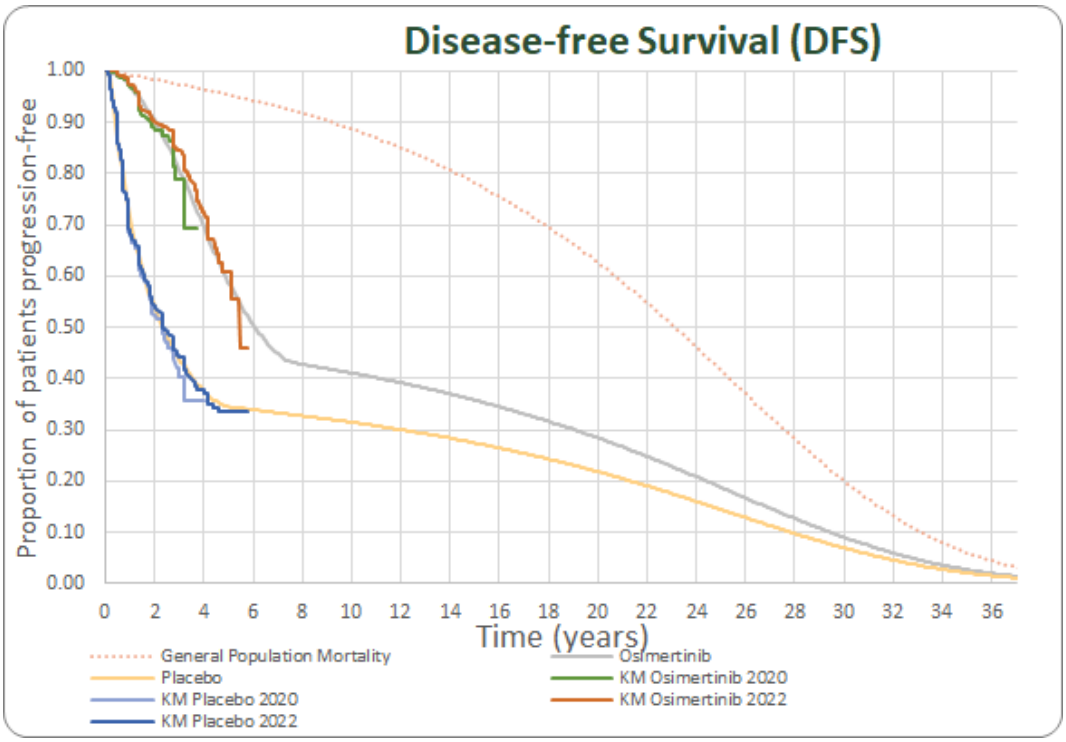


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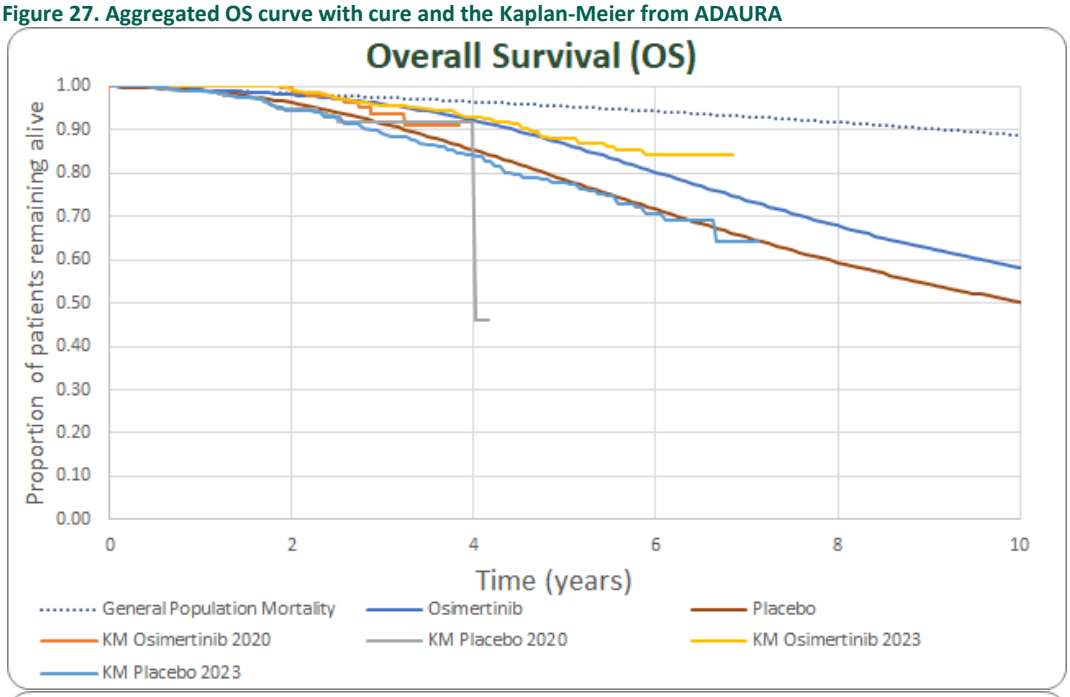
Figure 27. Aggregated OS curve with cure and the Kaplan-Meier from ADAURA



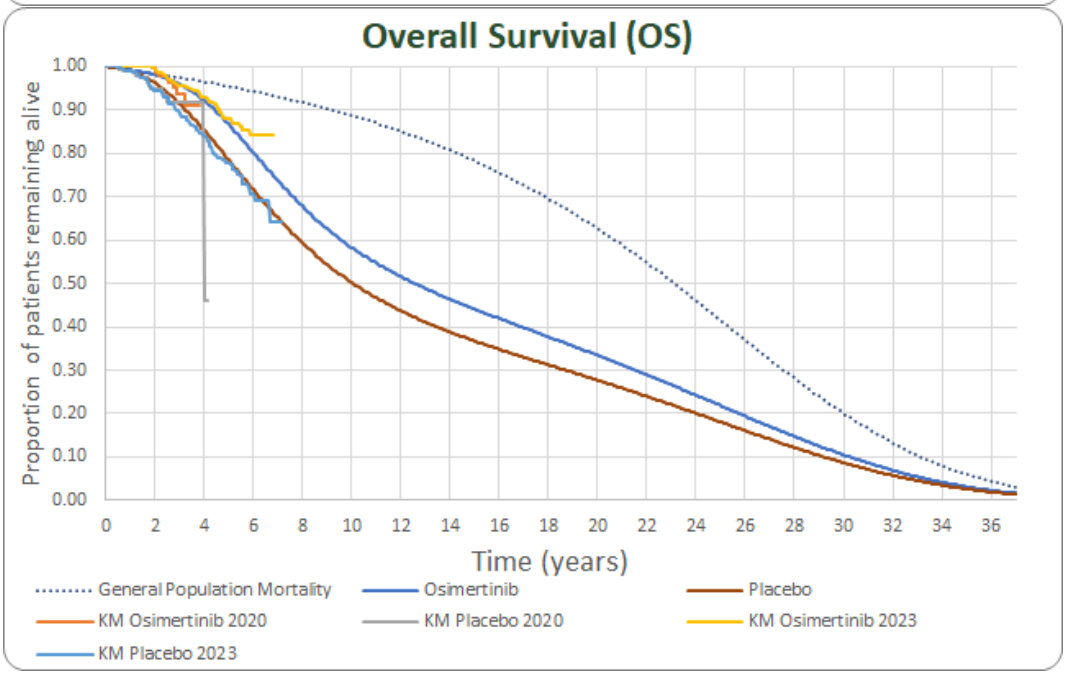


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Table 71. Landmark comparison of aggregated DFS and ADAURA DFS with cure

	Osimertinib (modelled)	ADAURA osimertinib	Placebo (modelled)	ADAURA placebo
Median (months)	72.0	-	18.0	27.9
% at 1 year	96.9	97.4	70.3	68.5
% at 2 years	89.9	89.1	53.2	52.8
% at 3 years	80.4	78.9	43.6	40.3
% at 4 years	69.1	-	37.4	35.8
% at 5 years	58.5	-	34.8	-
% at 10 years	41.1	-	31.8	-

Key: NR, not reported

Table 72. Landmark comparison of aggregated OS and ADAURA OS with cure assumption

	Osimertinib (modelled)	ADAURA osimertinib	Placebo (modelled)	ADAURA placebo
Median (months)	150.0	-	112.0	-
% at 1 year	99.2	100.0	98.9	98.8
% at 2 years	98.0	99.6	96.1	94.7
% at 3 years	95.8	93.9	91.3	91.8
% at 4 years	92.0	-	85.1	91.8
% at 5 years	86.7	-	78.2	-
% at 10 years	58.5	-	50.3	-

Key: NR, not reported

Table 73 presents the ranking of all 36 combinations based upon TP1 and TP2 for both DFS and OS. As noted above the generalised gamma distribution was selected for both TP1 and TP2 and these curves appear to provide the best balance between goodness of fit with observed data and plausible long-term extrapolations in each treatment arm. Among all 36 possible combinations, this combination was ranked 1st for DFS and 2nd for OS in terms of MSE (and best MSE ranking overall).

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Table 73. Overview of the different combinations of fit for TP1 and TP2 and the resulting MSE

Combination	TP1	TP2	MSE DF	MSE OS	MSE total
1	Generalised Gamma	Generalised Gamma	0.0479	0.2889	0.3369
2	Lognormal	Generalised Gamma	0.0550	0.2888	0.3438
3	Exponential	Generalised Gamma	0.0499	0.2945	0.3443
3	Exponential	Generalised Gamma	0.0499	0.2945	0.3443
4	Loglogistic	Generalised Gamma	0.0635	0.2896	0.3531
5	Gompertz	Generalised Gamma	0.0617	0.2918	0.3535
6	Weibull	Generalised Gamma	0.0657	0.2891	0.3547
7	Generalised Gamma	Lognormal	0.0716	0.2956	0.3673
8	Exponential	Lognormal	0.0739	0.3016	0.3755
9	Generalised Gamma	Gompertz	0.0622	0.3177	0.3799
10	Lognormal	Lognormal	0.0874	0.2954	0.3829
11	Generalised Gamma	Exponential	0.0803	0.3084	0.3887
12	Generalised Gamma	Weibull	0.0868	0.3028	0.3896
13	Lognormal	Gompertz	0.0732	0.3174	0.3906
14	Generalised Gamma	Loglogistic	0.0868	0.3076	0.3944
15	Gompertz	Lognormal	0.0997	0.2987	0.3984
16	Loglogistic	Lognormal	0.1022	0.2962	0.3984
17	Exponential	Gompertz	0.0778	0.3239	0.4017
18	Weibull	Lognormal	0.1065	0.2958	0.4023
19	Exponential	Weibull	0.0945	0.3092	0.4036
20	Lognormal	Exponential	0.0971	0.3081	0.4052

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Combination	TP1	TP2	MSE DF	MSE OS	MSE total
21	Loglogistic	Gompertz	0.0884	0.3181	0.4065
22	Exponential	Loglogistic	0.0933	0.3140	0.4072
23	Lognormal	Weibull	0.1067	0.3025	0.4092
24	Weibull	Gompertz	0.0920	0.3176	0.4096
25	Lognormal	Loglogistic	0.1055	0.3074	0.4129
26	Gompertz	Gompertz	0.0960	0.3207	0.4167
27	Loglogistic	Exponential	0.1101	0.3088	0.4189
28	Gompertz	Exponential	0.1106	0.3117	0.4223
29	Exponential	Exponential	0.1072	0.3153	0.4225
30	Weibull	Exponential	0.1148	0.3083	0.4231
31	Loglogistic	Weibull	0.1256	0.3032	0.4287
32	Loglogistic	Loglogistic	0.1232	0.3081	0.4313
33	Gompertz	Weibull	0.1260	0.3060	0.4320
34	Gompertz	Loglogistic	0.1228	0.3109	0.4337
35	Weibull	Weibull	0.1314	0.3027	0.4341
36	Generalised Gamma	Generalised Gamma	0.0479	0.2889	0.3369

Key: TP1, transition probability one; TP2, transition probability two; MSE, mean squared error; DF, disease-free; OS, overall survival.

18.2.1 Selection of survival models

18.2.1.1 TP1: disease-free (DF) to local/regional recurrence (LRR)

KM data

For the model's DF to LRR transition, KM data for the time to local/regional recurrence from the ADAURA trial was used. Parametric curves were fitted to the data presented in Figure 28 applying the methods described below.

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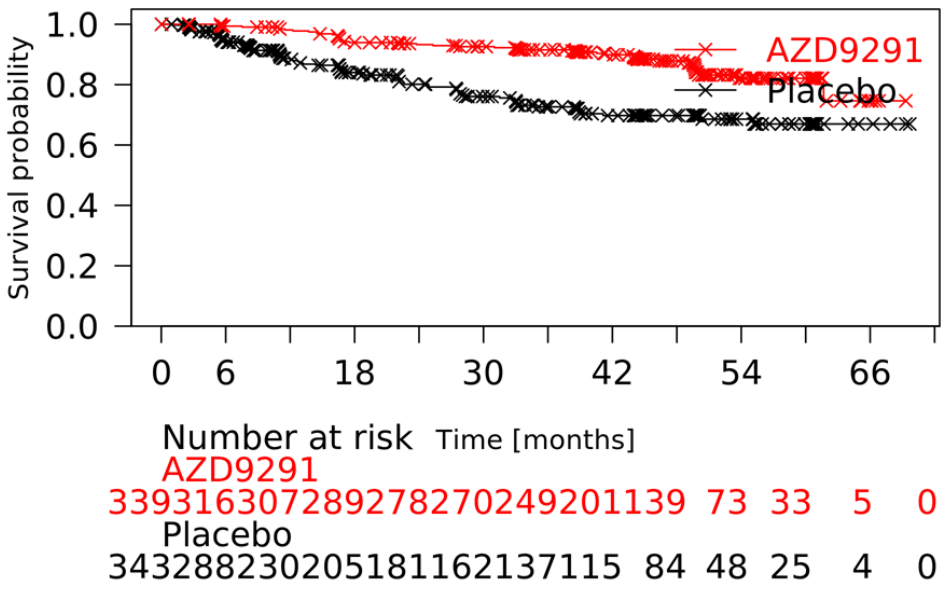
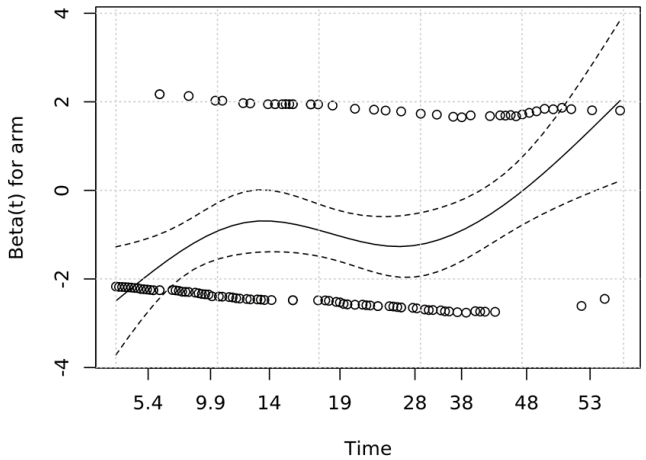
Figure 28. KM curves for time to local/regional recurrence in the osimertinib and active monitoring arms of ADAURA.



Assessment of the proportional hazard assumption

In Figure 29 the cumulative hazards plot and the Schoenfeld residuals plot can be found for the transition DF to LRR with the statistical test results. The Schoenfeld residuals plot and the Schoenfeld residuals test (p=0.003) indicate that the proportional hazards assumption is violated. This means that the combined fits option is not good and the individual fits were applied in the model.

Figure 29. Schoenfeld residuals and cumulative hazard plot for the transition DF to LRR (TP1)



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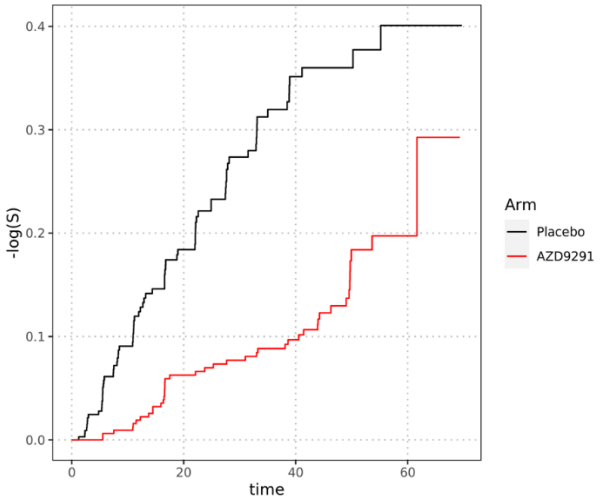

Goodness of fit for parametric distributions

The independent models of the parametric distributions were assessed for their goodness of fit based upon visual inspection and whether the extrapolation was clinically realistic. Figure 30 shows the fits and extrapolations for the transition from DF to LRR (TP1), with the AIC and BIC values presented in Table 74. Figure 31 shows all curve in the same figure. In the first data-cut, six UK clinical experts predicted that functional cure was expected both in the osimertinib and active monitoring arm. In addition, the UK clinical experts agreed that survival for patients treated with osimertinib could never be lower than for those who were treated with placebo. Thus, the following condition was implemented in TP1 and TP2 formulas in order curves not to cross:

$$IF(osimertinib\ TP1 < placebo\ TP1, osimertinb\ TP1 = placebo\ TP1)$$

Together with the updated distributions, the UK clinical experts' opinion was taken into account, which led exponential, Weibull and log-logistic distributions being excluded as they produced pessimistic long-term survival estimates incompatible with the underlying functional cure assumption. From the remaining distributions, the log-normal curve results in the lowest AIC and BIC in osimertinib arm; however, visually, the extrapolation beyond the trial period in the placebo arm is clinically considered too pessimistic in the long term. Based on the visual inspection, generalised gamma distribution which gives the lowest AIC in the placebo arm was selected for both the osimertinib and placebo arm. Weibull and log-normal distributions were tested in scenario analyses.

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Figure 30. Extrapolations for DF to LRR (TP1).

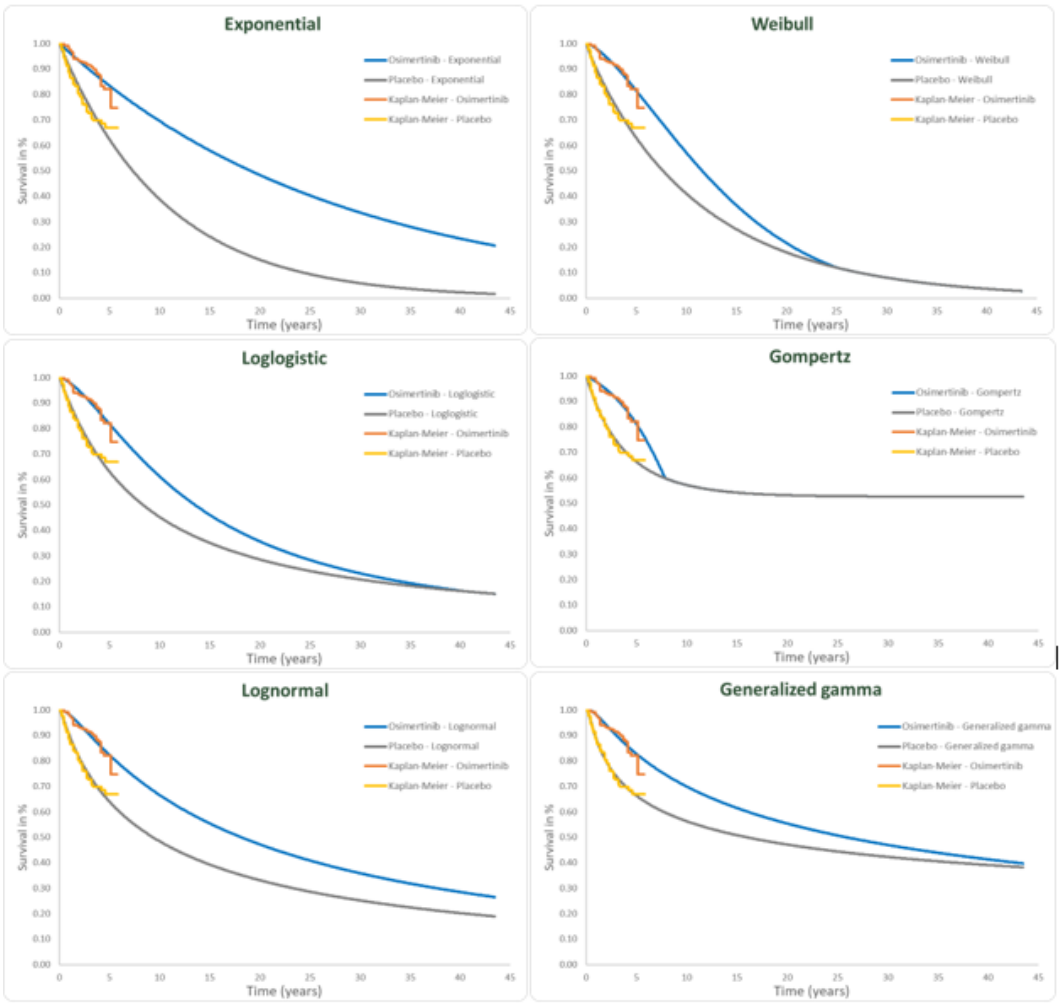

Figure 31. Extrapolation of DF to LRR (TP1) for all parametric curves

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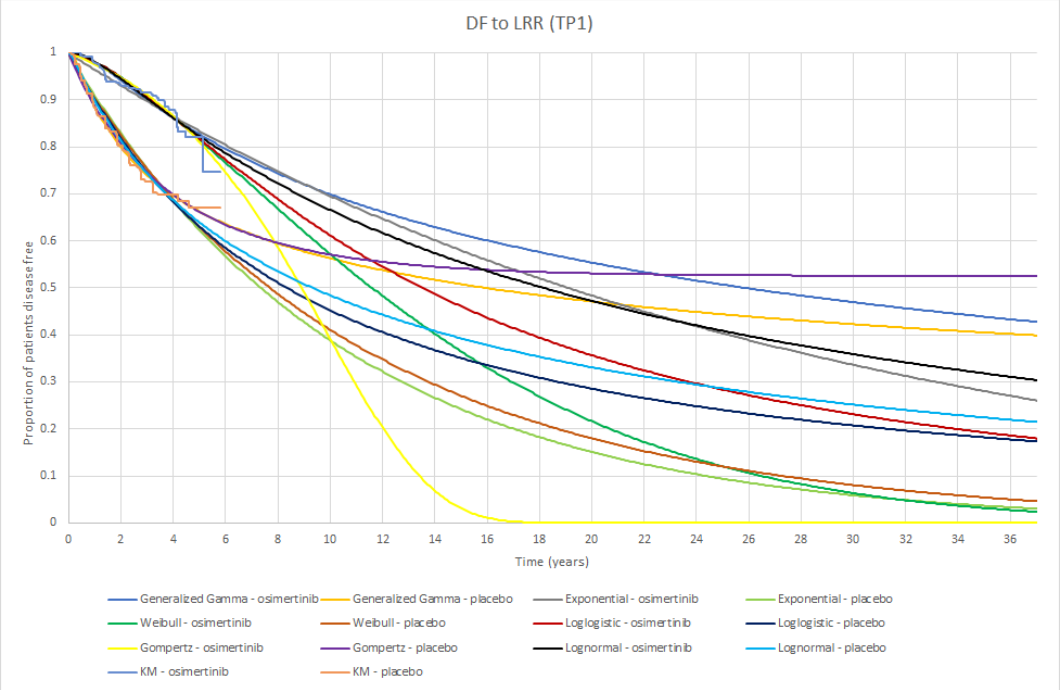

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Table 74. AIC and BIC values for the fitted distributions to the transition DF to LRR

	Individual fits				Combined fits	
	Osimertinib		Placebo (Active monitoring)			
Model	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	572.92	576.75	913.12	916.96	1486.04	1495.09
Weibull	568.98	576.63	914.82	922.49	1487.47	1501.05
Log-logistic	569.00	576.66	911.67	919.34	1482.95	1496.52
Gompertz	570.55	578.20	910.29	917.96	1487.79	1501.37
Log-normal	567.86	575.51	905.73	913.40	1473.62	1487.20
Generalized gamma	569.63	581.11	903.18	914.69	1469.16	1487.26

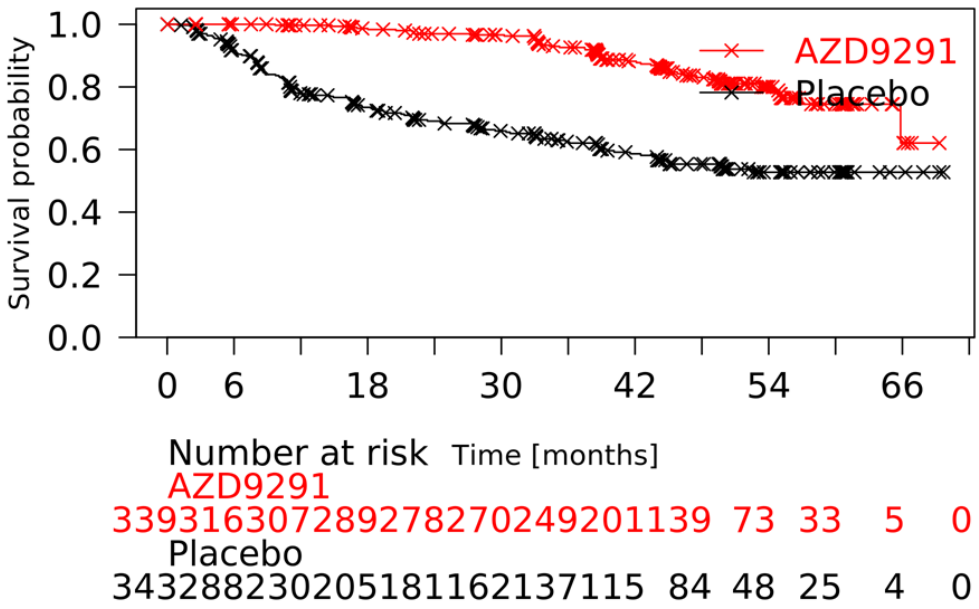
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Bold values: preferred distribution

18.2.1.2 TP2: disease-free (DF) to 1st line treatment of distant metastases (DM1)

KM data

For the transition from the DF to DM1 state, KM data for the time to distant metastases from the ADAURA trial was used. Parametric curves were fitted to the data presented in Figure 32 applying the methods described below.

Figure 32. KM curves for time to distant metastases survival in the osimertinib and active monitoring arms of ADAURA.



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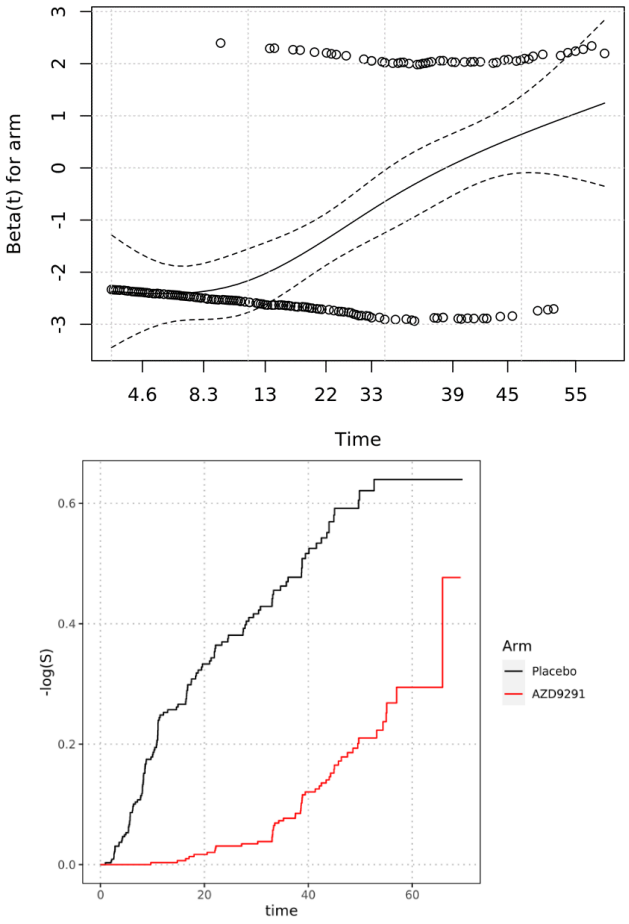
Assessment of the proportional hazards assumption

The Schoenfeld residuals plot and the cumulative hazard plot for the transition from DF to DM1 is shown in Figure 33. Since the Schoenfeld residuals and cumulative hazards plots plot do not show a linear trend with a gradient of zero, the proportional hazards assumption does not hold (p<0.001) meaning single dependent models are not a viable option and individual fitted models must be used. Therefore, individual fits using the same distribution were applied to align with NICE DSU TSD 14, which recommends using the same parametric function for both treatment arms where feasible.

Figure 33. Schoenfeld residuals and cumulative hazard plot for the transition DF to DM1 (TP2).



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Goodness of fit for parametric distributions

Parametric distributions were assessed for their goodness of fit based upon visual inspection and whether the extrapolation is clinically realistic.

Figure 34 shows the fits and extrapolations for the transition from DF to DM1 (TP2), with the AIC and BIC values presented in Table 75. Figure 35 shows all curve in the same figure. In the first data-cut, six UK clinical experts predicted that functional cure was expected both in the osimertinib and active monitoring arm. In addition, the UK clinical experts agreed that survival for patients treated with osimertinib could never be lower than for those who were treated with placebo. Thus, the following condition was implemented in TP1 and TP2 formulas in order curves not to cross:

$$IF(osimertinib\ TP2 < placebo\ TP2, osimertinb\ TP2 = placebo\ TP2)$$

Based on visual inspection of the extrapolations and the expectation of six UK clinical experts that cure was expected both in the osimertinib and active monitoring arms, the exponential, Weibull and Gompertz distributions can be excluded. From the rest distributions, the generalised gamma distribution provides a clinically plausible estimate and also the best statistical fit (i.e., the lowest AIC and BIC values as shown in Table 71) in the active monitoring arm. For the osimertinib KM data, the log-logistic distribution provides the best statistical fit (Table 75); however, generalised gamma also looks very similar to log-logistic predictions. To maintain the consistency, the generalised gamma distribution was selected for this specific transition for both

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arms, whereas the log-logistic distribution was explored as a scenario..

Figure 34. Extrapolations for DF to 1L DM (TP2).

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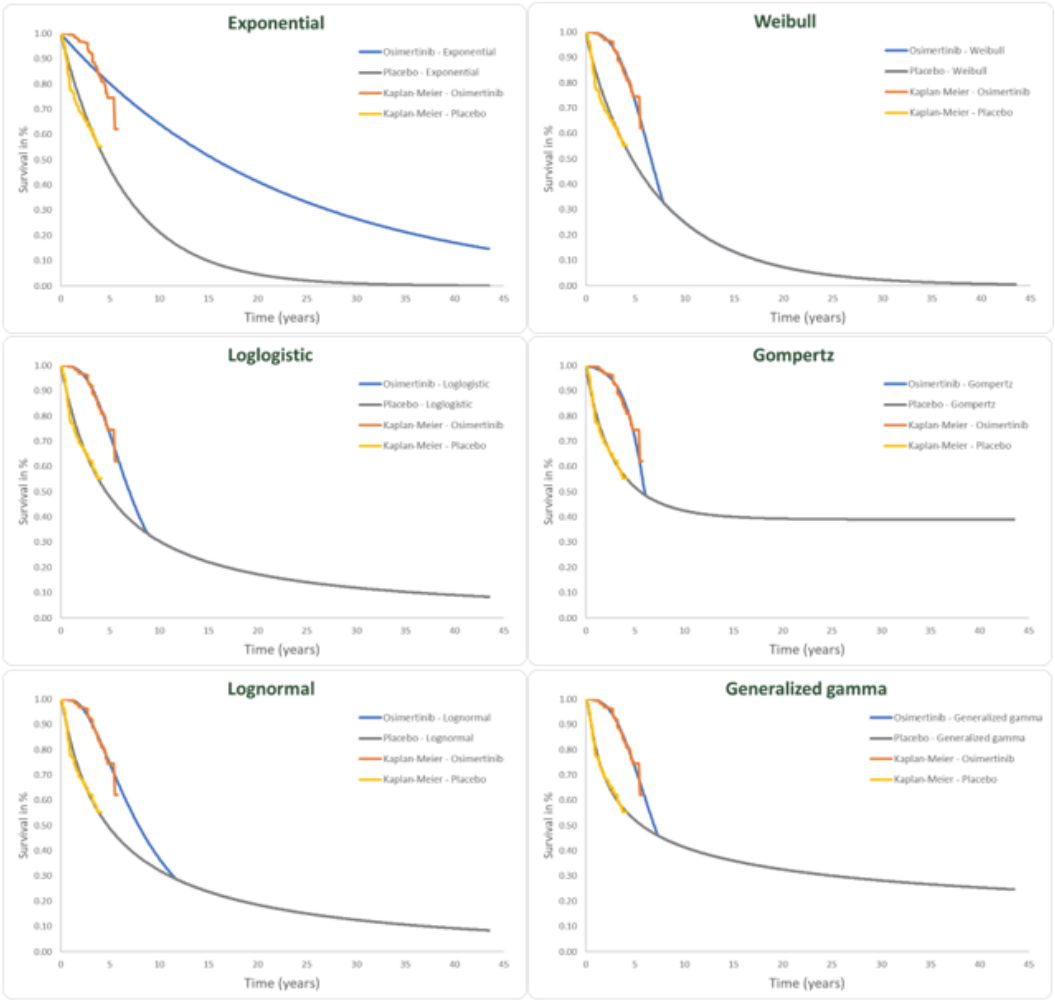

Figure 35. Extrapolation of DF to 1L DM (TP2) for all parametric curves

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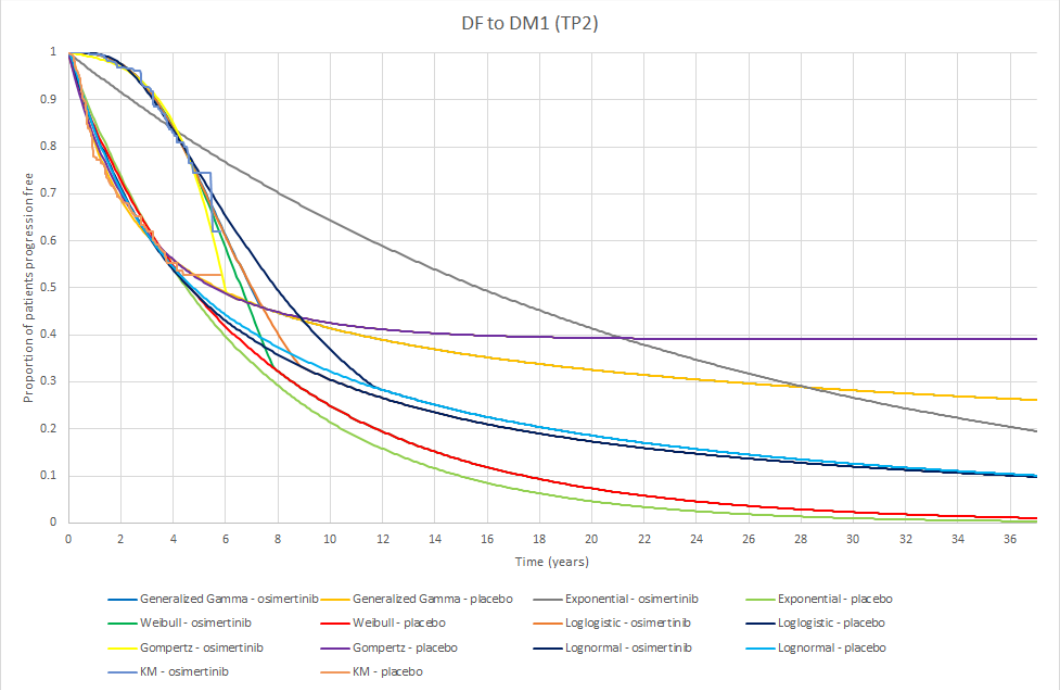

Table 75. AIC and BIC values for the fitted distributions to the transition of DF to 1L DM.

	Individual fits				Combined fits	
	Osimertinib		Placebo (Active monitoring)			
Model	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	675.46	679.29	1361.67	1365.51	2037.13	2046.18
Weibull	630.62	638.27	1362.21	1369.88	2036.89	2050.46
Log-logistic	630.35	638.01	1354.22	1361.90	2022.81	2036.38
Gompertz	636.02	643.67	1353.02	1360.76	2038.53	2052.10
Log-normal	631.33	638.98	1344.13	1351.80	2005.24	2018.81
Generalized gamma	**632.37**	**643.84**	**1335.81**	**1347.32**	**1984.91**	**2003.01**

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Bold values: preferred distribution

Implications for DFS and OS

Modelled DFS and OS curves based on all possible combinations of extrapolations for DF —> LR and DF —> DM1 are included in Figure 36 and Figure 37. As there are 6 different distributions for each transition DF —> LR and DF —> DM1, there 6 x 6 = 36 combinations for each arm and 36 x 2 = 72 different extrapolated curves in total for DFS and OS respectively.

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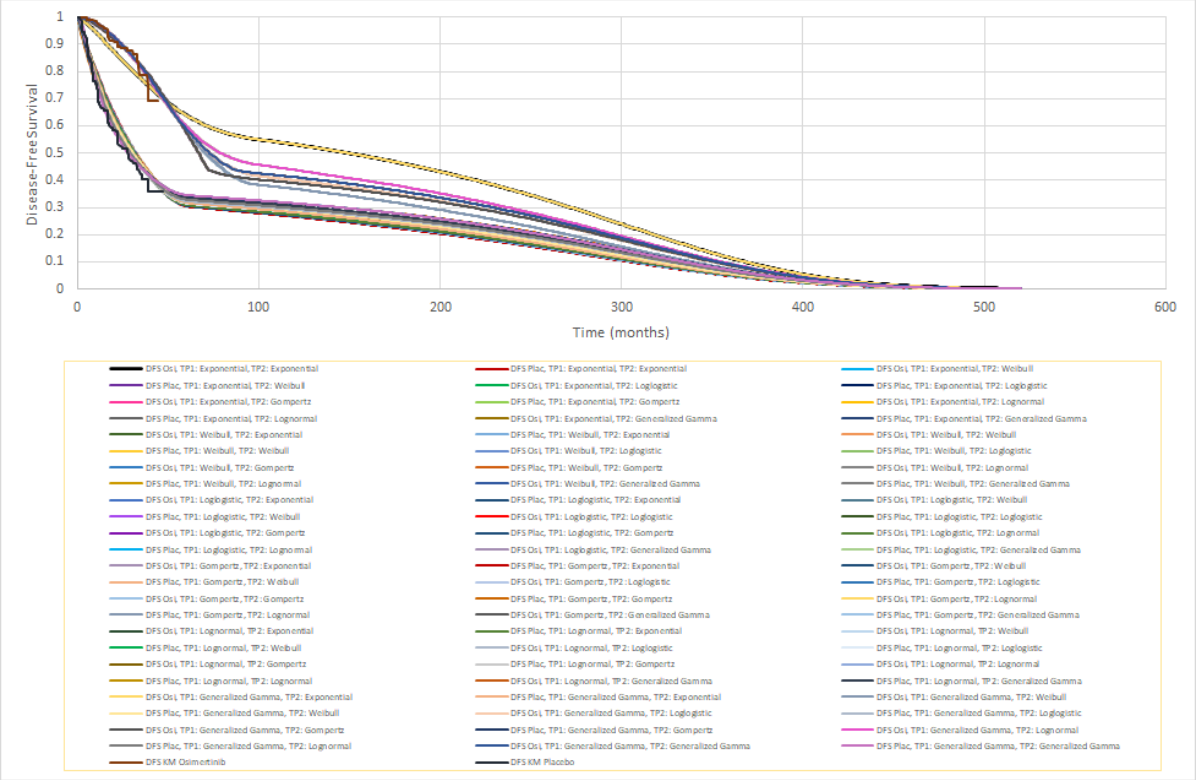
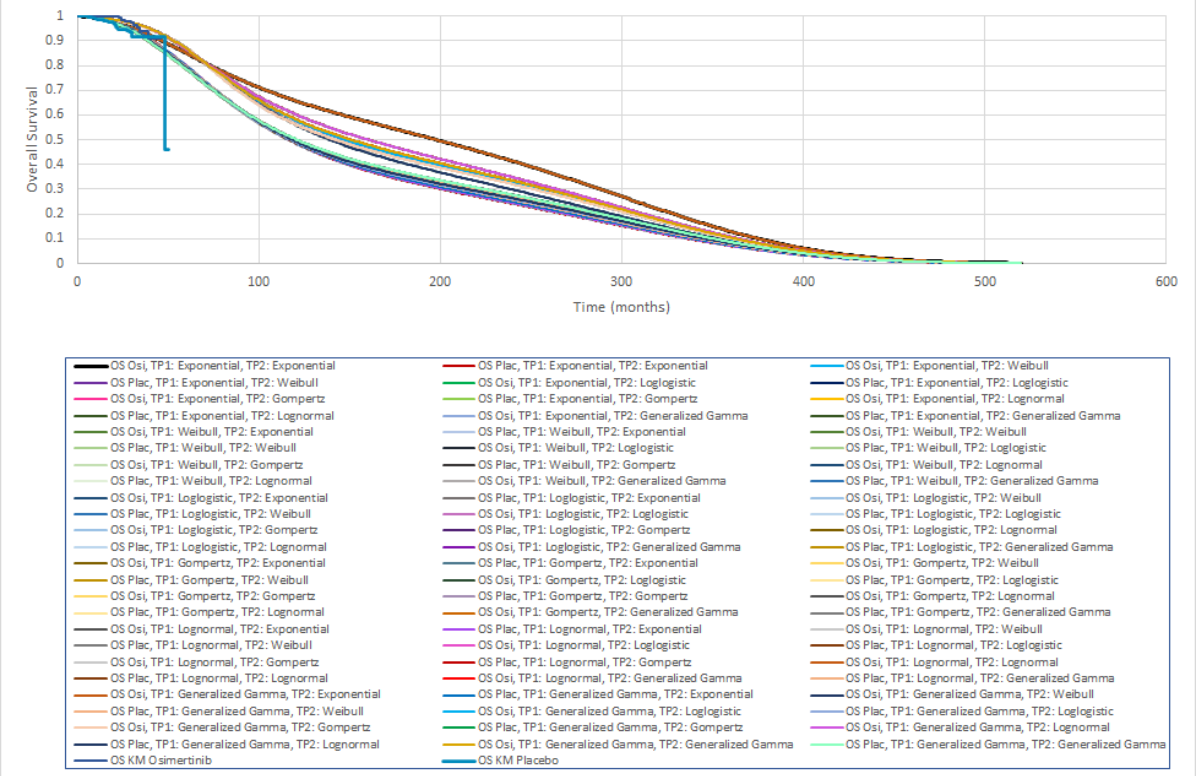
DFS curves based on all possible combinations of extrapolations for DF —> LR and DF —> DM1



OS curves based on all possible combinations of extrapolations for DF —> LR and DF —> DM1



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18.2.1.3 TP3: disease-free (DF) to death

At the ADAURA April 2022 data cut-off, very few deaths had occurred among stage IB to IIIA patients who remained DF (one in the osimertinib arm and six in the placebo arm). As a result, no parametric models could be reliably fitted to the data to estimate the transition from DF state to death.(8) This transition was therefore modelled using the background mortality in the age-adjusted Danish population.

18.2.1.4 Post-DFS calibration

The 2023 data cut with longer follow-up on OS showed that the original model underestimated the OS, but that the DFS was predicted relatively well. This means that the underestimation was caused by predictions in post-DFS survival. A possible explanation for this is that patients in ADAURA were post-surgery patients instead of newly diagnosed stage IIIB/IV (as is the case in FLAURA).
To investigate this, an SLR was conducted which focused on studies in EGFRm NSCLC and reported outcomes (median PFS/OS or HR PFS/OS) for both post-surgery recurrence and newly diagnosed stage IIIB/IV patients. This SLR search resulted in 1 049 hits, of which nine remained after the full-text screening. Four studies reported median PFS for both groups, one study reported median OS, one study showed a PFS HR between post-surgery vs newly diagnosed stage IIIB/IV and one study included OS HR. All identified studies were with Japanese patients only.
The aggregated result per outcome is shown in Figure 38. Patients with post-surgery recurrence consistently report better survival compared with those with newly diagnosed stage IIIB/IV NSCLC. There was close to no difference between median PFS/OS and PFS/OS HR, meaning that the efficacy improvement happens in PFS and continues after metastatic progression.

Figure 38. Aggregated efficacy outcomes for post-DFS calibration SLR

	Efficacy improvement	Total n
Median PFS	0.603	377
Median OS	0.669	172
PFS HR	0.448	202
OS HR	0.472	213
Weighted average	**0.554**	

Given the SLR results, applying a calibration factor to the efficacy modelled in the LRR, DM1 and DM2 health states is a valid approach to correcting the underestimated prediction since the efficacy in these health states was based upon newly diagnosed patients instead of those with post-surgery recurrence.
To calculate the calibration factor, the absolute difference between the predicted OS and ADAURA's OS KM was taken for both arms. A value of 0.7263 was found to minimise this absolute difference and is used in the

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final model, applied as a HR to the efficacy of the survival curves for both arms in the LRR, DM1 and DM2 health states. Before the calibration factor was applied, the modelled subsequent therapies were brought in line with the subsequent therapies as found in the ADAURA trial. This ensured that the calibration factor impacts the efficacy as measured in the ADAURA trial.
The approach and resulting calibration factor were also discussed with three clinicians from Canada and one from the UK. They agreed with the approach and the magnitude of the calibration factor.

18.2.1.5 Modelling of local/regional recurrence (TP4 and TP5)

Due to limited post-recurrence follow-up data available from the ADAURA trial at the latest data cut-off (11 April 2022), the transitions from local/regional recurrence (LRR) to 1st line treatment of distant metastases (DM1) for both treatment arms were modelled using CancerLinQ data (see Appendix C) (61). This is a real-world database, collecting electronic health record (EHR) data from 1.4 million US cancer patients. A retrospective analysis of data from CancerLinQ was conducted and data from 1 January 2014 to 31 December 2018 were used. From this database, patients with *EGFR*m-positive NSCLC in stage IB–IIIA following tumour resection ('ADAURA-like' population) who had experienced local/regional recurrence were selected (n=97). For each patient, the time to distant metastases is determined, defined as time to metastatic disease when a metastases diagnosis was found or the date of first systemic treatment in the absence of metastatic identification. In the absence of available data from ADAURA at data cut-off, the transition probability from LRR to DM1 was assumed to be equivalent between the osimertinib and active monitoring arms.
The use of the CancerLinQ data for the model was supported by UK clinical experts, who considered the patient population comparable with the ADAURA patient population. Baseline characteristics of patients from CancerLinQ is presented in Appendix C.

A calibrated HR was applied to the CancerLinQ TPs to align with the ADAURA 2023 OS data cut. The ADAURA 2023 OS data cut informed the post-DFS survival of ADAURA, where the model underestimates the OS for both arms. Given that DFS fits well, was likely caused by the transition from LRR, DM1, and DM2, populated using CancerLinQ and FLAURA. Clinical experts agreed that this was likely due to ADAURA patients being post surgery instead of newly diagnosed with metastatic disease. Here, post-surgery patients are already being monitored, allowing a quicker diagnosis and thus a quicker treatment, resolving in a better survival for post-surgery patients, as also showed in Mitsudomi et al (2010). To account for this, a calibration HR was applied to all post-DFS transitions (transition probability TP4 to TP8) for both arms, keeping the HR the same for all TPs. An HR of 0.726 was calibrated to fit with the ADAURA OS Kaplan-Meier (KM) curve.
Also, a statistical cure was assumed after five years following the critique of the evidence review group on the original NICE submission.

18.2.1.6 TP4: local/regional (LR) to 1st line treatment of distant metastases (DM1)

KM data
For the transition from LRR to DM1, KM data for the time to distant metastases from the CancerLinQ database was used to both treatment arms.(61) Parametric curves were fitted to the data presented in Figure 39 applying the methods described below.

Figure 39. KM curve for time to distant metastases from CancerLinQ (61)**.**

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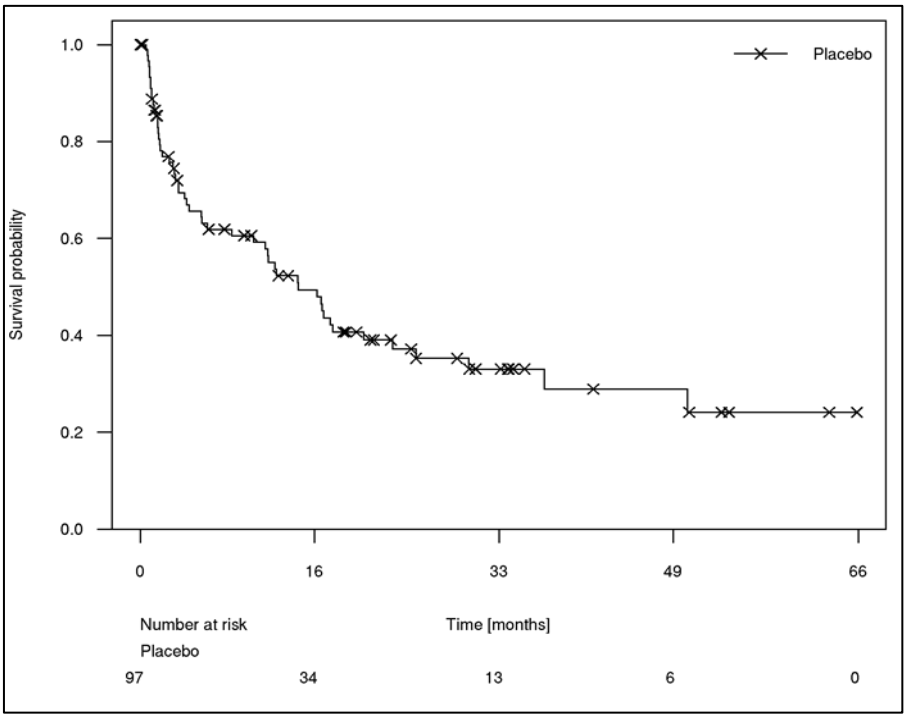

Assessment of the proportional hazard assumption

Since the data were analysed as one group, testing the proportional hazards assumption was not feasible.

Goodness of fit for parametric distributions

Parametric distributions were assessed for their goodness of fit based upon visual inspection and whether the extrapolation is clinically realistic. Figure 11 shows the fits and extrapolations for the transition from LRR to 1L DM (TP4). All parametric curves for the CancerLinq are shown in Figure 40. Based on visual inspection of the extrapolations and clinical plausibility, the exponential and Weibull curves were excluded because of their pessimistic long-term survival estimates (providing a poor fit compared to the tail of the KM curve), external clinical data and UK expert opinion, while the Gompertz distribution was excluded because it provided a clinically implausible long tail and the generalised gamma distribution was excluded because of a poor fit to the tail of the KM curve. The lognormal and loglogistic distributions appear similar based upon visual inspection, however AIC and BIC values indicate the lognormal distribution is preferred based on best statistical fit (Table 76). The loglogistic distribution was explored as a scenario analysis.

Figure 40. Extrapolation of LRR to 1L DM (TP4)

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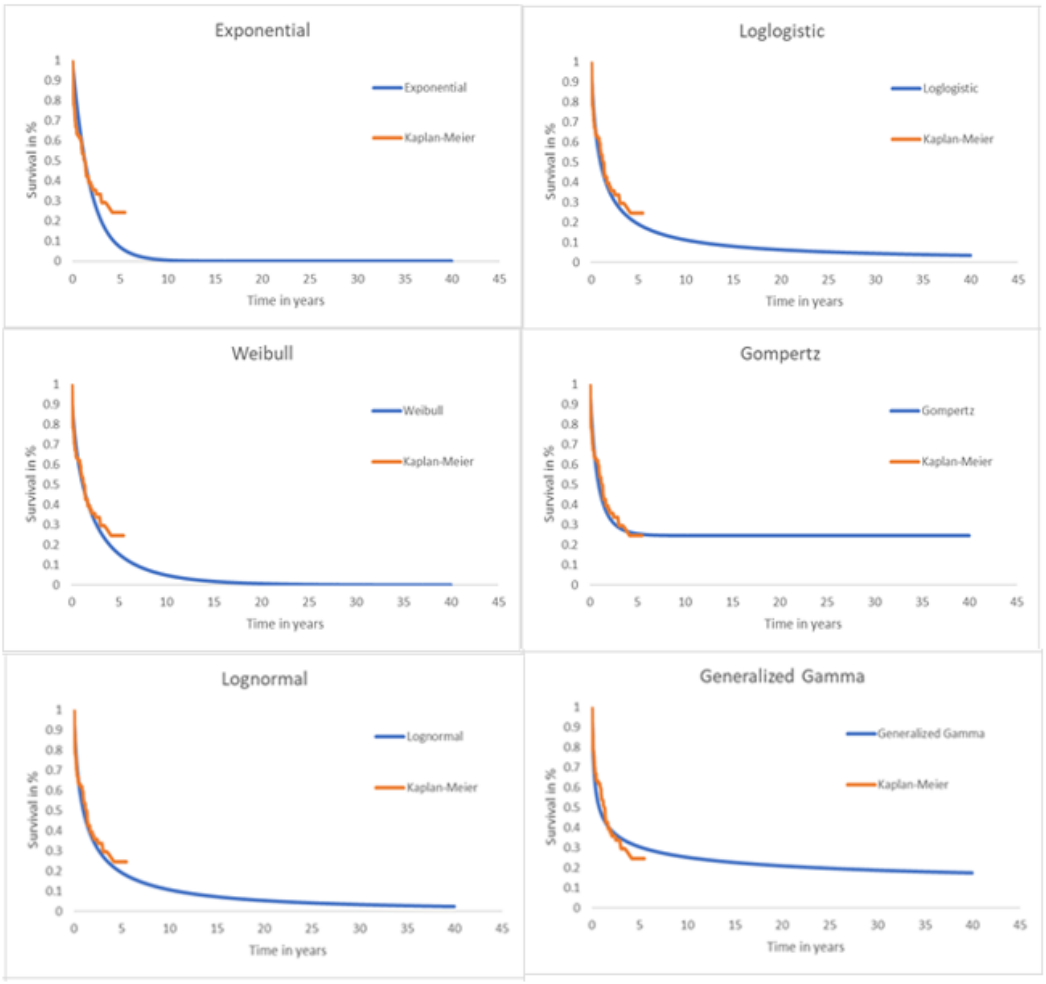

Figure 41. Extrapolation of LRR to 1L DM (TP4) for all parametric curves.

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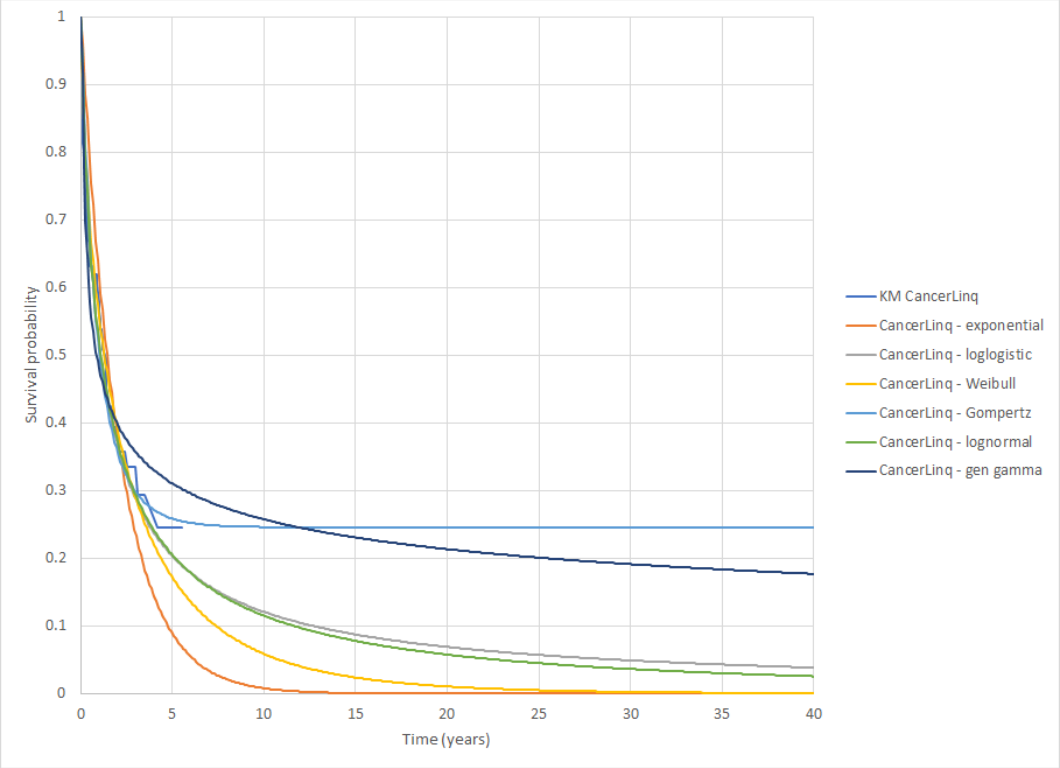

Table 76. AIC and BIC values for the fitted distributions to the transition LRR to 1L DM.

Model	AIC	BIC
Generalized Gamma	422.30	430.03
Lognormal	**427.52**	**432.67**
Loglogistic	431.48	436.63
Gompertz	432.72	437.87
Weibull	436.34	441.49
Exponential	447.83	450.40

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Bold values: preferred distribution

18.2.1.7 TP5: local/regional (LR) to death

In the CancerLinQ dataset only two death events were recorded, and thus it was not feasible to fit parametric models for extrapolation in the model(61). Therefore, this transition is modelled using background mortality in the age-adjusted Danish population. It should be noted that patients in the LRR state are still at higher risk of death than patients in the DF state because of the higher likelihood of developing distant recurrence and the higher associated mortality risk associated with distant metastases. In a scenario analysis the sensitivity of the ICER to all transitions to death was explored by applying a standardised mortality rate, where the general

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population hazard is multiplied by a factor of 2, implying the risk of dying is twice as high as for the general population.

18.2.1.8 Modelling of distant metastases (TP6 to TP8)

For both treatment arms, the transition probabilities from DM1 and DM2 were calculated based on the distribution of first-line and second-line treatments for advanced *EGFR*m NSCLC. The primary data source used to model the survival of patients with metastatic *EGFR*m-positive NSCLC was the FLAURA trial.(62) FLAURA is a phase 3, double-blind, randomised, controlled trial and assesses the efficacy and safety of osimertinib versus gefitinib or erlotinib as first-line treatment in patients with locally advanced or metastatic *EGFR*m-positive NSCLC (stage IIIB or IV) that is not amenable to curative surgery or radiotherapy (patient baseline characteristics are provided in Appendix C. These data were considered clinically relevant in terms of modelling distant metastases in the current model by six UK clinical experts. Since the FLAURA study used PFS, time to treatment discontinuation (or death) and OS as endpoints, the datasets required for the extrapolation of each separate transition probability could not be derived directly. Therefore, the competing risks methodology described by Williams et al, 2017, was used to determine each dataset for use in the model.(81) In addition, instead of RECIST-based PFS, time to discontinuation of treatment was applied due to maturity of the data from the latest data cut-off from FLAURA (DCO2; June 2019), and also to be consistent with measurement of treatment costs in the DF state (based on time to treatment discontinuation) of the model.

18.2.1.9 Osimertinib arm

Following input from six UK clinical experts, in the base case analysis it is assumed that retreatment with osimertinib in the DM1 state would be possible. This was confirmed by the Danish clinical experts interviewed.(59, 60) However, the proportion of patients who would receive retreatment with osimertinib is unknown as this is a step change in clinical practice and there have been no clinical studies in the use of osimertinib in patients who have received prior osimertinib treatment for resected stage IB-IIIA *EGFR*m NSCLC. Therefore, it may be implausible to assume that *all* patients would receive retreatment with osimertinib on progression to DM1. In addition, UK clinical experts advised that retreatment with other TKIs (including first and second-generation *EGFR*-TKIs) would not be considered as these are generally considered to be less efficacious versus osimertinib. Whilst the proportion of patients is uncertain, six UK clinicians advised that retreatment with osimertinib would at least be considered in practice if (i) patients did not discontinue their adjuvant therapy within 36 months of starting treatment and (ii) did not experience disease recurrence (LRR or distant metastases) within 48 months.

In the base case analysis, retreatment with osimertinib is assumed to occur at 5 years. This time point was selected as feedback from interviews with clinicians also suggested patients in current clinical practice are most at risk of recurrence within 18–24 months post-surgery. Therefore, the model applies this conservative assumption by adding the 18 to 24-month risk period to the end of the three-year treatment duration (i.e. 5 years from treatment initiation). Scenario analyses are also provided exploring the impact of retreatment at 4 and 6 years in the model. Also, as noted above given the uncertainty in the proportion of patients retreated with osimertinib, the economic model assumes that 80% of patients would be retreated at the 5–year time point, and alternative proportions are also explored in scenario analyses.

Patients who progressed before the 5-year time point are assumed to be treated with platinum doublet chemotherapy. For the 50% of patients which are not retreated with osimertinib after the 5-year time point, it was assumed they could be treated with a SoC TKI (erlotinib/gefitinib) or second-generation *EGFR*-TKI (afatinib/dacomitinib) as per the comparator arm of the FLAURA trial or platinum doublet chemotherapy.(62)

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As the standard of care in FLAURA is SoC TKI (erlotinib/gefitinib) the efficacy of chemotherapy might be overestimated in the model by applying transition probabilities reflective of a more efficacious therapy than chemotherapy in the DM state. The IPASS study compared gefitinib versus carboplatin/paclitaxel in Asian patients with *EGFR* mutation-positive advanced NSCLC and showed that although the OS with gefitinib and carboplatin/paclitaxel is similar, gefitinib outperforms carboplatin/paclitaxel in terms of the PFS endpoint.(82) A network meta-analysis (NMA) by Holleman et al based on this study and other studies of SoC TKIs estimated a PFS HR of 0.43 comparing chemotherapy to gefitinib.(83) An exploratory scenario analysis was thus conducted to test the impact of adjusting the efficacy of SoC TKIs versus chemotherapy by applying a HR of 0.43 to the transition from DM1 to DM2 (TP6). This was explored in a scenario analysis.
In a second scenario the findings from the NMA by Holleman et al are tested. This publication shows no statistical significant difference in OS between platinum-based chemotherapy and gefitinib.(83) When the PFS HR (DM1 to DM2, TP6) is applied in the multi-state model, the OS HR differs between chemotherapy and gefitinib. Therefore, a second HR needs to be applied to PPS (DM2 to death, TP8). A HR of 2.0 is set up in such way that the resulting OS is equal (in the FLAURA setting, (62)) for chemotherapy and the SoC TKI. Applying this HR significantly prolongs the time spent in DM2, which could arguably be due to those chemotherapy patients crossing over to an *EGFR* TKI post-progression but might not be considered clinically plausible for the SoC TKI treatment arm.

18.2.1.10 Active monitoring arm

It was assumed that all patients who received active monitoring in the DF health state will get treated with osimertinib at DM1. As osimertinib is the most efficacious TKI compared to SoC TKIs also noted by clinicians, it is assumed that it would be a preferred treatment over other treatments for these patients. TP6: 1st line treatment of distant metastases (DM1) to 2nd+ line treatment of distant metastases (DM2)

KM data

For the model's DM1 to DM2 transition, KM data for the time to discontinuation of treatment (TTD) (censoring deaths) from the FLAURA trial were used instead of PFS data as RECIST PFS data were only collected until DCO1 (June 2017) in the FLAURA trial.(62) Conversely TTD and OS data were collected until DCO2 (June 2019) when 60% OS event maturity was reached. Parametric curves were fitted to the data presented in applying the methods described below.

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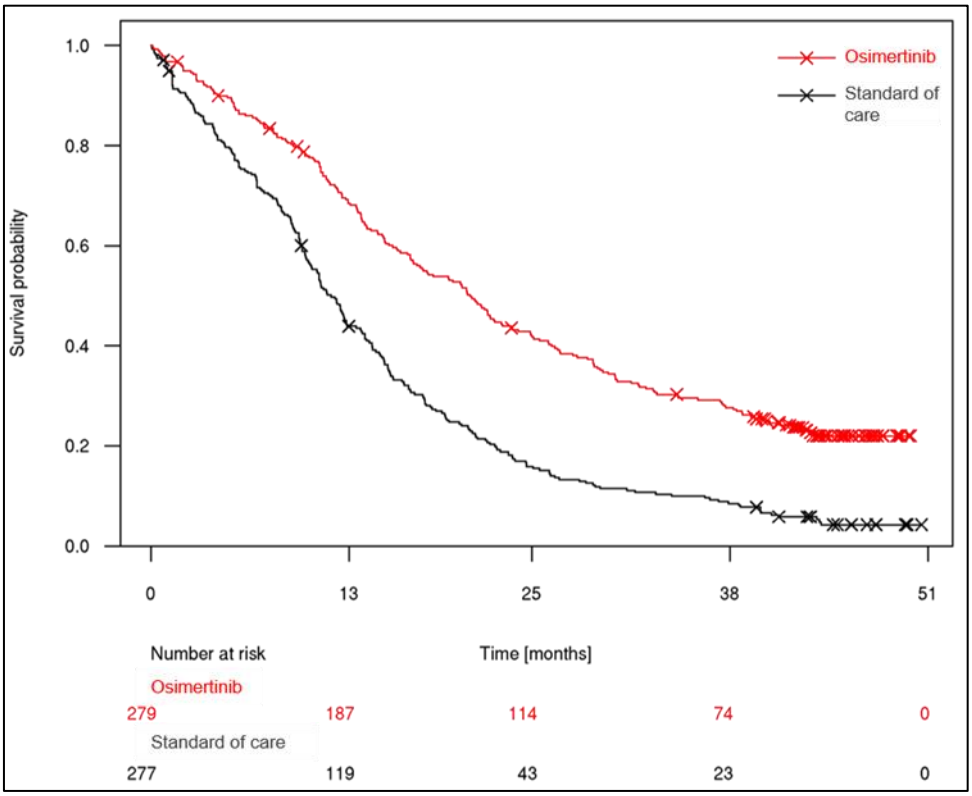
Figure 42. KM curves for the time to discontinuation of treatment (censoring deaths) in the osimertinib and active monitoring arms of FLAURA.(62)



Assessment of the proportional hazards assumption

The Schoenfeld residuals and cumulative hazard plot for the transition DM1 to DM2 is shown in Figure 43. Since the cumulative hazard plot show a linear trend and the Schoenfeld residuals plot do not show time dependence, the PH assumption was assumed to hold (p=0.777). Therefore, both combined fits (where the same distribution is fitted to both arms, with a treatment effect on the active arm), and individual fits (where each arm is fitted to a separate distribution). For consistency with the parametric modelling based on the ADAURA DCO1 DFS data, individual fitted models were applied for the base case analysis.

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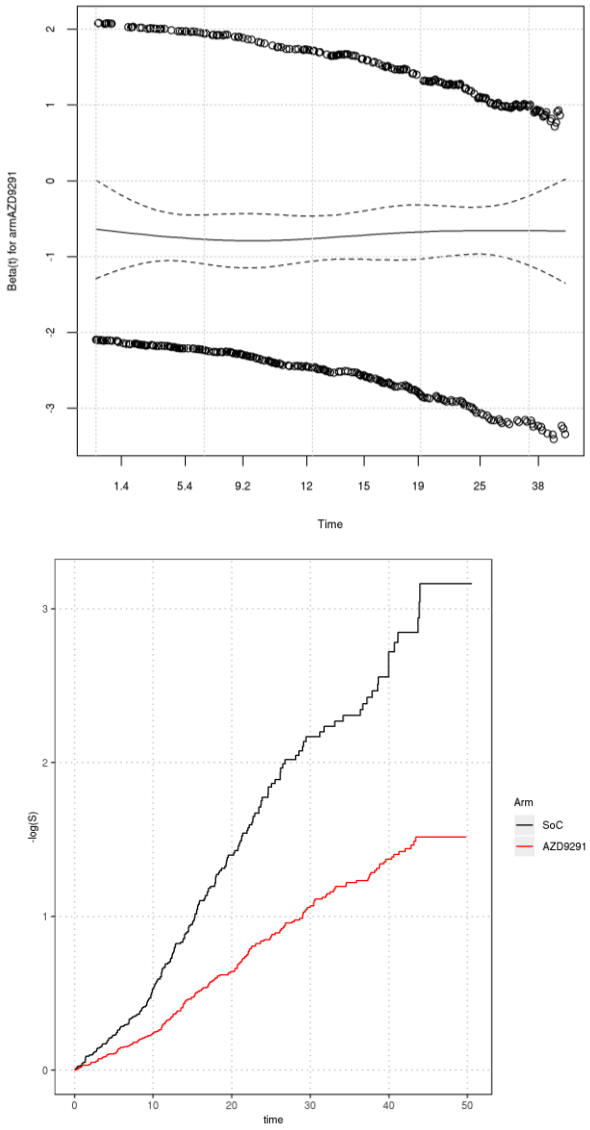
Figure 43. Schoenfeld residuals and cumulative hazard plot for the transition 1L DM to 2L DM (TP6).



Goodness of fit for parametric distributions

Individual parametric models were assessed for their goodness of fit based upon visual inspection and whether the extrapolation is clinically realistic.

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Figure 44 shows the fits and extrapolations for the transition from DM1 to DM2 (TP6), with the AIC and BIC values presented in Table 77. All parametric curves for the placebo arm are shown in Figure 45 and all curves for the osimertinib arm are shown in Figure 46. Clinical experts in the UK argued that the log-logistic and log-normal parametric distributions were deemed to overfit the tail of the standard of care (SoC) EGFR-TKI arm from the FLAURA trial and were thus considered as clinically implausible and excluded.(62) Of the four remaining clinically plausible distributions resulting in very similar shape of the curves and estimates, the Weibull distribution was selected for the base case analysis as it shows the best statistical fit based on the AIC and BIC values in both arms.

Figure 44. Extrapolation of DM1 to DM2 (TP6).

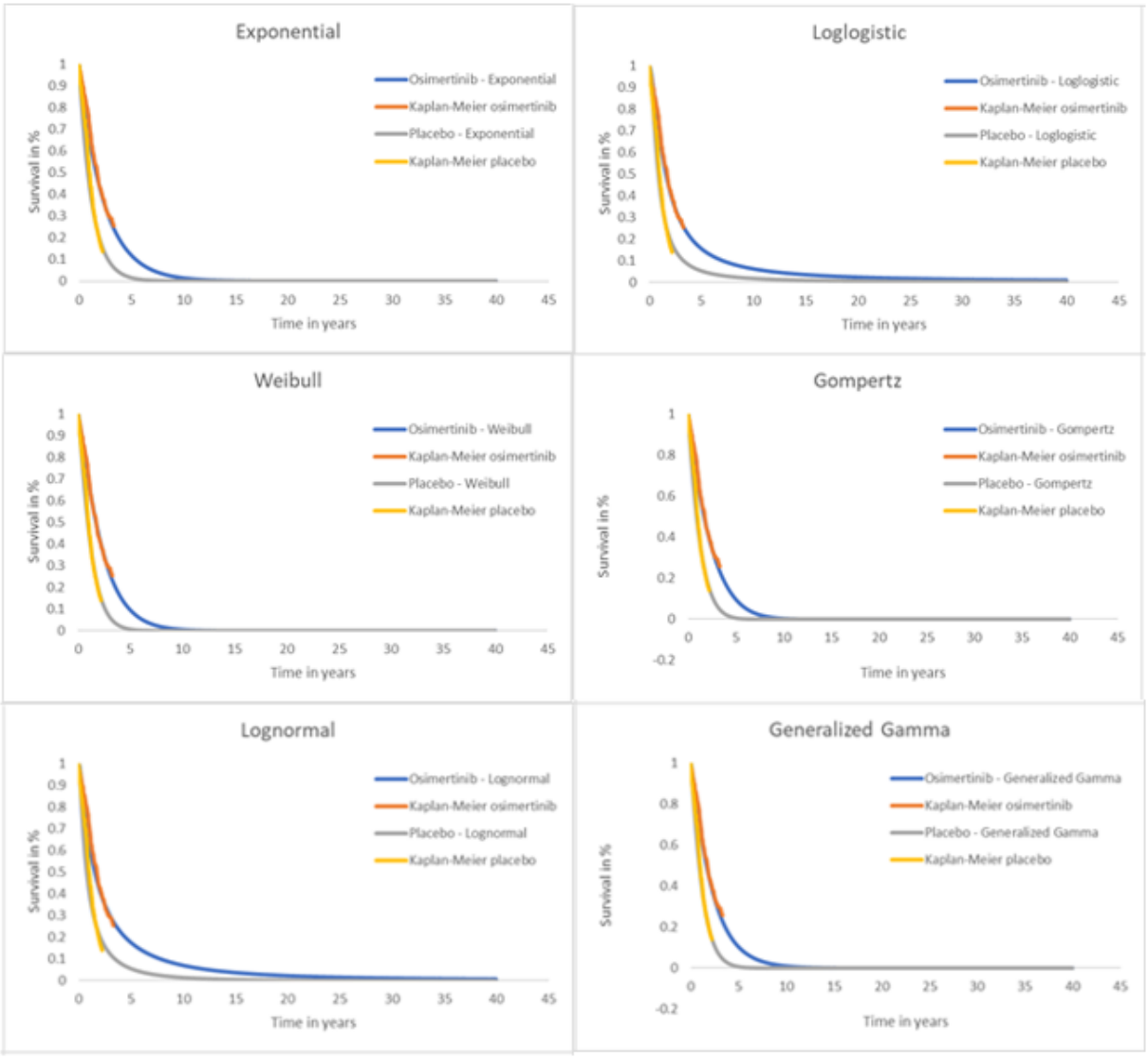

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Figure 45. Extrapolation of DM1 to DM2 (TP6) for the placebo arm – all in one.

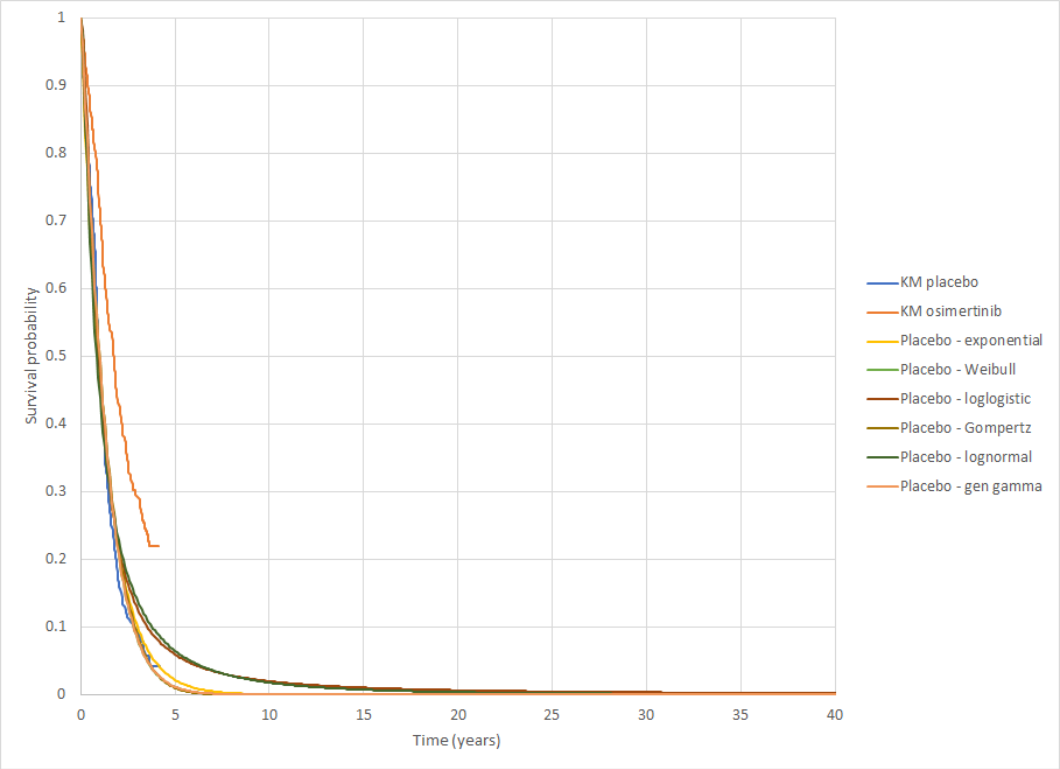

Figure 46. Extrapolation of DM1 to DM2 (TP6) for the osimertinib arm – all in one.

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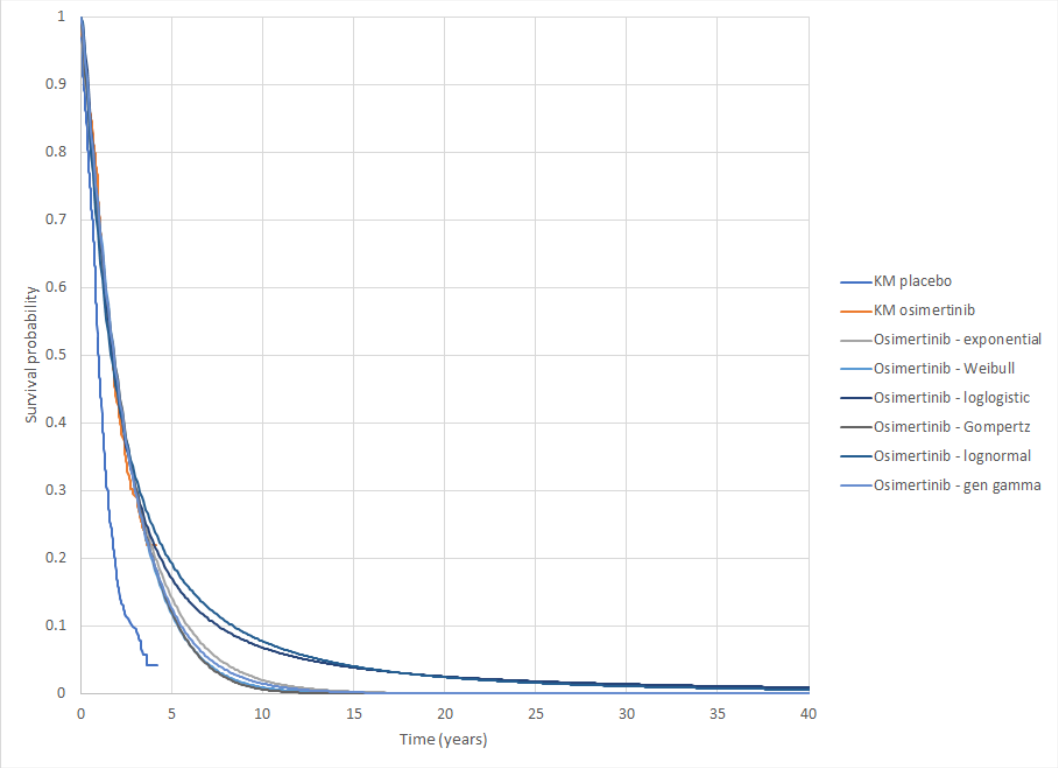

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Table 77. Goodness of fit for 1L DM to 2L DM

	Combined fits				Individual fits	
	Osimertinib		SoC			
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Weibull	**1865.18**	**1872.45**	**1945.91**	**1953.15**	3809.14	3822.10
Generalized Gamma	1866.59	1877.48	1947.90	1958.77	3810.93	3828.22
Gompertz	1868.25	1875.51	1950.20	1957.45	3816.76	3829.72
Exponential	1867.24	1870.87	1951.26	1954.89	3818.51	3827.15
Loglogistic	1865.74	1873.00	1966.60	1973.85	3831.81	3844.77
Lognormal	1886.11	1893.37	1999.94	2007.19	3884.91	3897.87

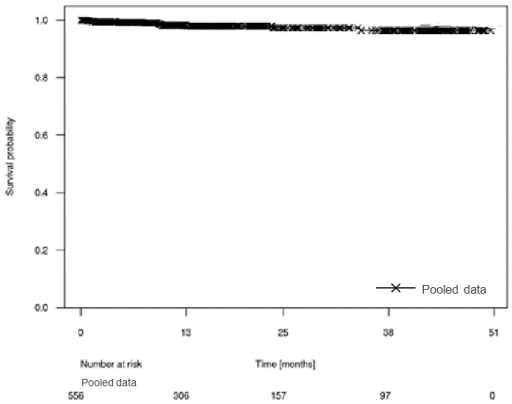
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; SoC, standard of care; Bold values: preferred distribution

18.2.1.11 TP7: 1st line treatment of distant metastases (1L DM) to death

KM data

For the model's DM1 to death transition, combined KM data (based on pooled analysis of data from both treatment arms) for the time to death (censoring discontinuation of treatment) from the FLAURA trial was used given the low number of death events observed across treatment arms (n=11).(62) As additional justification, the stratified analysis showed no difference between treatment groups. Parametric curves were fitted to the combined KM data presented in Figure 47 applying the methods described below.

Figure 47. KM curves for the time to death (censoring discontinuation of treatment) using pooled data of both treatment arms of FLAURA (62).



Goodness of fit for parametric distributions

Parametric distributions were assessed for their goodness of fit based on visual inspection and whether the extrapolation is clinically realistic. Although the distributions as shown in Figure 48 fit the KM data from FLAURA well, overall, the extrapolations are not clinically plausible as they generally provide higher survival estimates than the application of background mortality rates, see Figure 49.(62) However, the exponential distribution has the most clinically plausible extrapolation for patients in a metastatic setting and best statistical fit based

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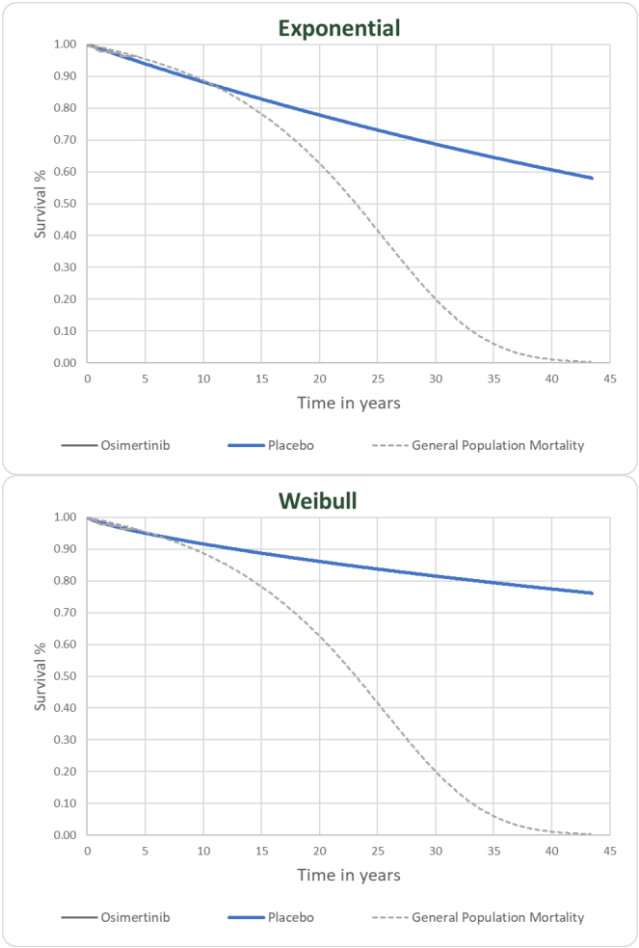
on AIC and BIC values (Table 78); therefore, this distribution was applied until it was exceeded by the hazard of the background mortality. Thereafter, background mortality based on the age-adjusted Danish population was applied.

Figure 48. Extrapolation of 1L DM to death (TP7)



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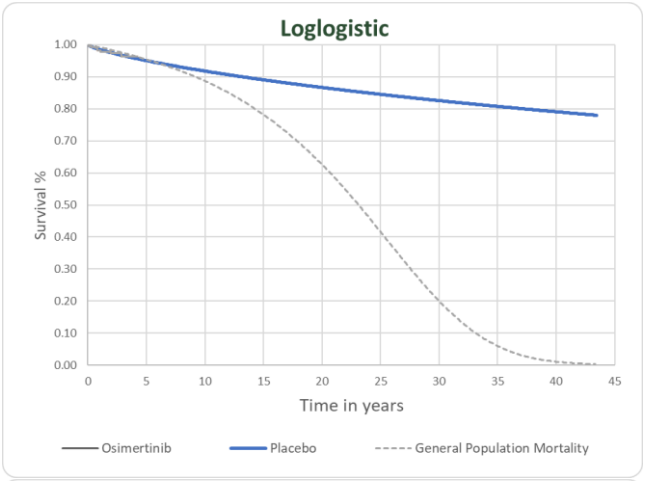

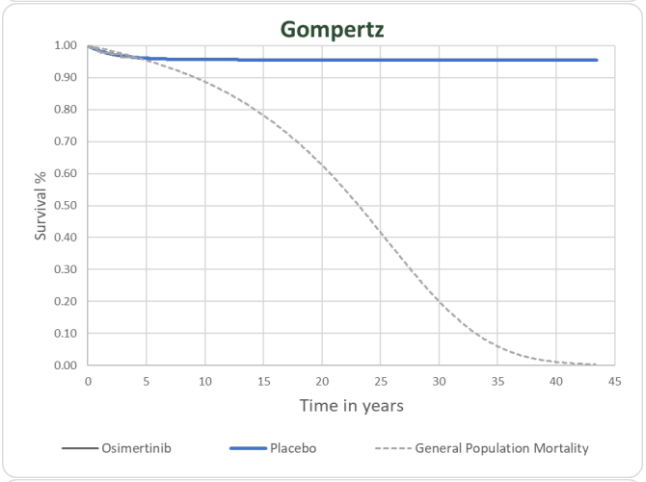

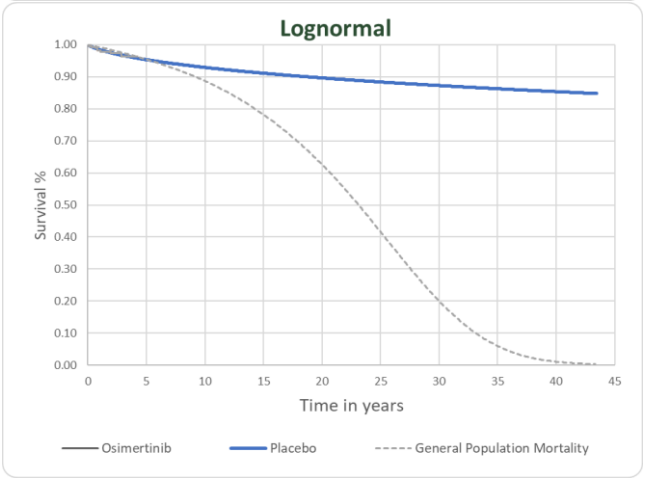

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Figure 49. Extrapolation of 1L DM to death (TP7) with all parametric curves.

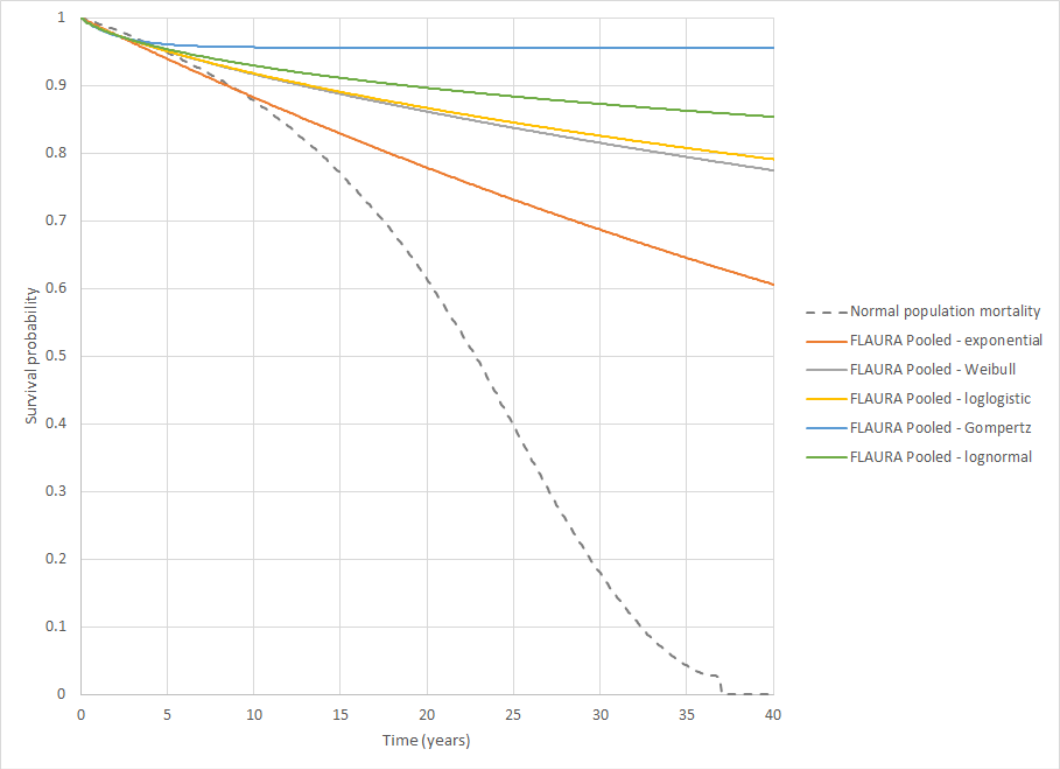

Table 78. Goodness of fit for DM1 to death.

	Osimertinib		SoC	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	**174.97**	**179.29**	**174.97**	**179.29**
Weibull	175.94	184.58	175.94	184.58
Log logistic	175.91	184.55	175.91	184.55
Gompertz	175.40	184.05	175.4	184.05
Lognormal	175.38	184.03	175.38	184.03
Gen. gamma	176.92	189.88	176.92	189.88

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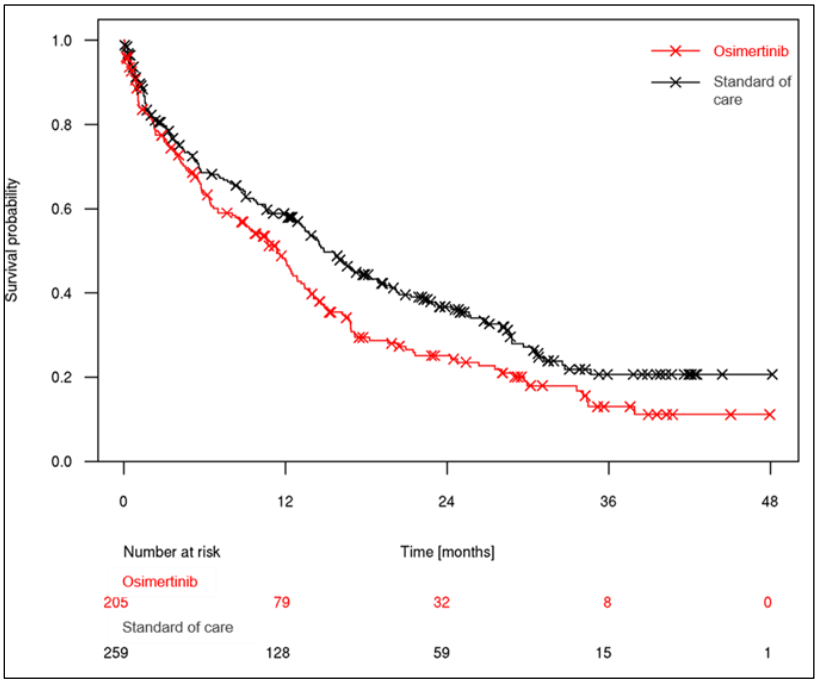
18.2.1.12 TP8: 2nd+ line treatment of distant metastases (2L DM) to death

KM data

For the model's DM2 to death transition, KM data for the time from treatment discontinuation to death data from the FLAURA trial was used.(62) Note that osimertinib arm of FLAURA is received by the patients receiving active monitoring in DF and vice versa. Parametric curves were fitted to the separate treatment arms as presented in Figure 50 applying the methods described below.

Figure 50. KM curves for post time to discontinuation of treatment in the osimertinib and SoC arms of FLAURA (62).



Assessment of the proportional hazards assumption

The Schoenfeld residuals and cumulative hazard plot for the transition of 2L DM to death are shown in Figure 51. Since the cumulative hazard plot show a linear trend and the Schoenfeld residuals are stable with time, it can be assumed that the proportional hazards assumption does hold (p-value of 0.812). Since the proportional hazard assumption does hold, combined fits where the same distribution is fitted on both arms with a treatment effect on the active arm, as well as individual fits where each arm is fitted individually, can be used. Again, for consistency with the parametric modelling based on the ADAURA DCO1 DFS data, individual fitted models were applied for the base case analysis.

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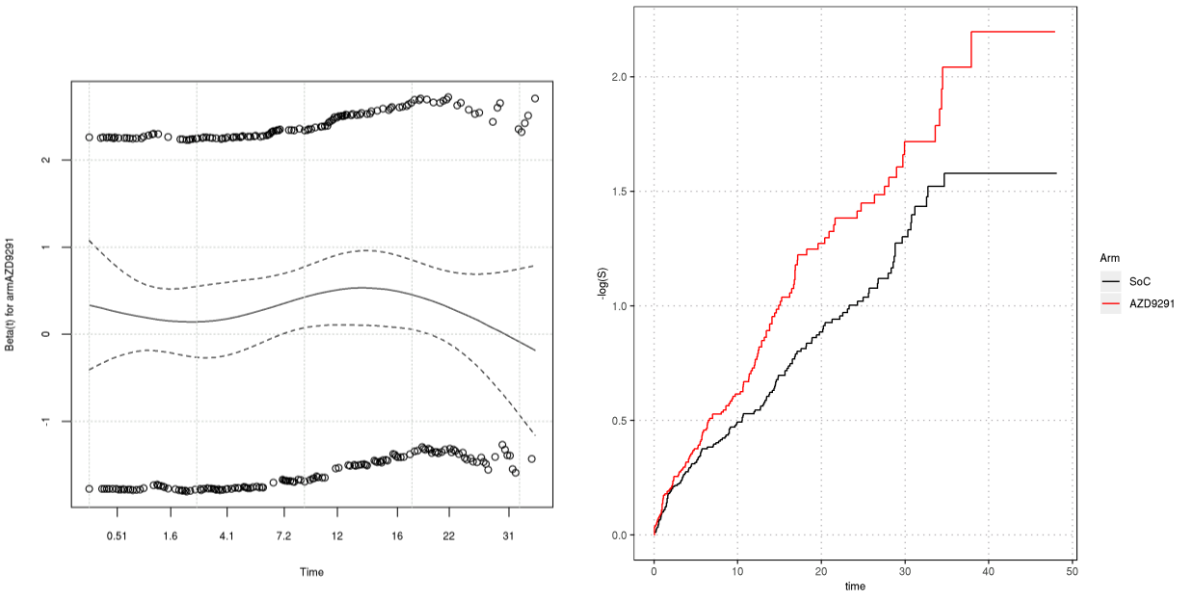
Figure 51. Schoenfeld residuals and cumulative hazard plot for the transition 2L DM to death (TP8).



Goodness of fit for parametric distributions

Independent parametric distributions were assessed for their goodness of fit based on visual inspection and whether the extrapolation is clinically realistic. Figure 52 shows the fits and extrapolations for the transition from DM2 to death (TP8), with the AIC and BIC values provided in the Table 79. All parametric curves for the placebo arm are shown in Figure 53 and all curves for the osimertinib arm are shown in Figure 54. As data for this endpoint were relatively mature, all possible extrapolations provided reasonably consistent survival extrapolations; however the Gompertz provided implausibly long tails in the survival curves whilst the log-logistic and lognormal provided poor fits to the tail of the osimertinib arm from FLAURA.(62) Based on statistical fit, the Weibull distribution provides the best fit; therefore, this distribution was selected for the base case analysis.

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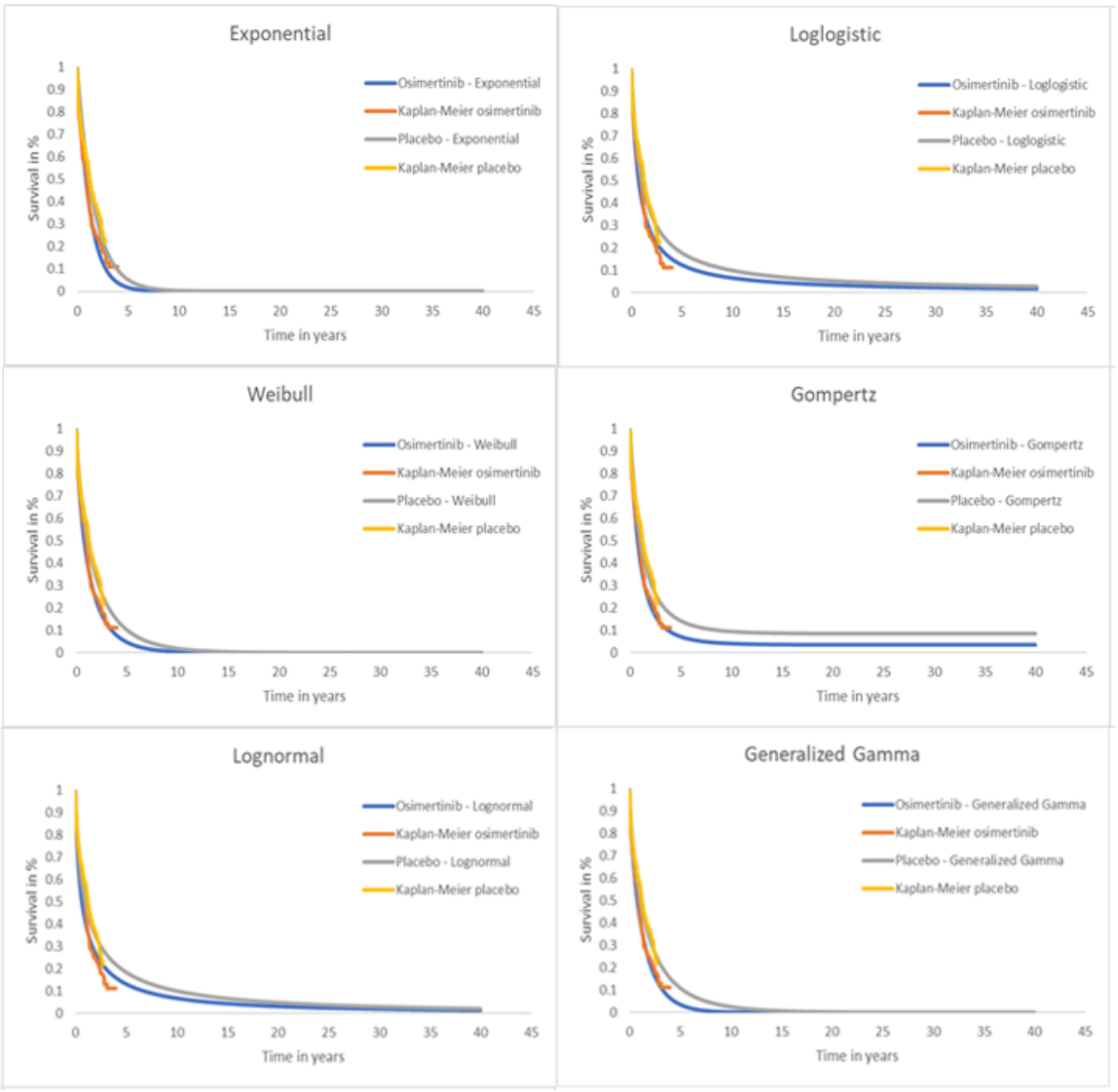
Figure 52. Extrapolation of 2L DM to death (TP8).[2]



[2] Note that osimertinib arm of FLAURA is received by the patients receiving active monitoring in DF state and vice versa.

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Figure 53. Extrapolation of 2L DM to death (TP8) for the placebo arm – all in one.

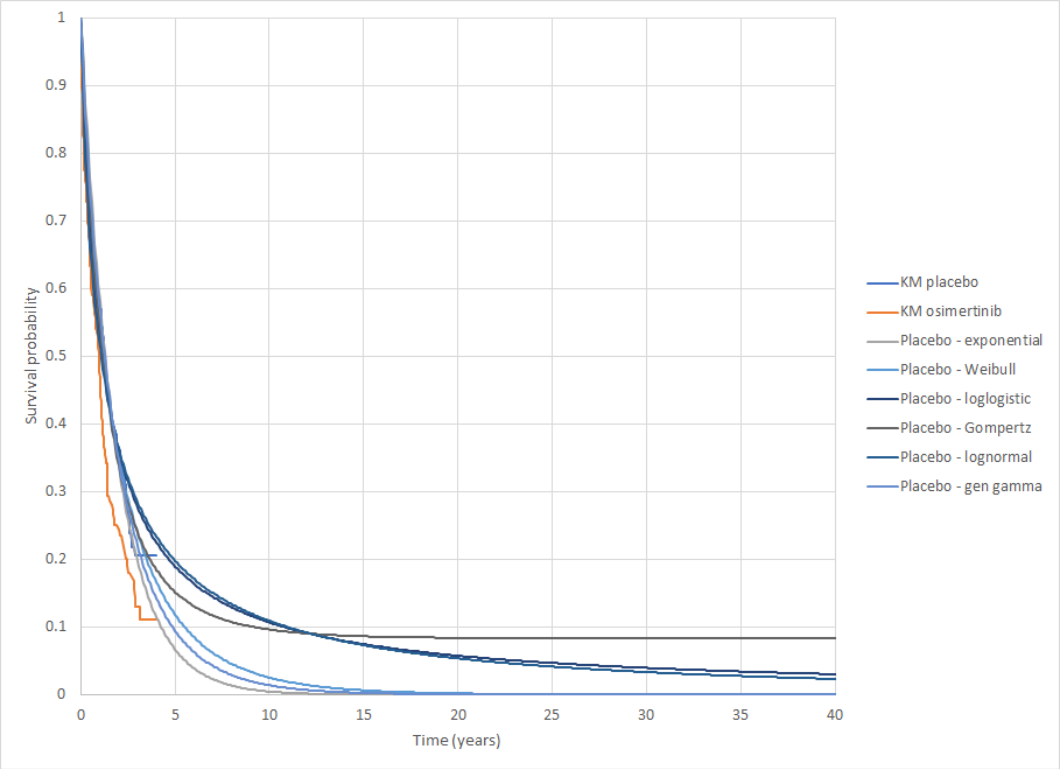

Figure 54. Extrapolation of 2L DM to death (TP8) for the osimertinib arm – all in one.

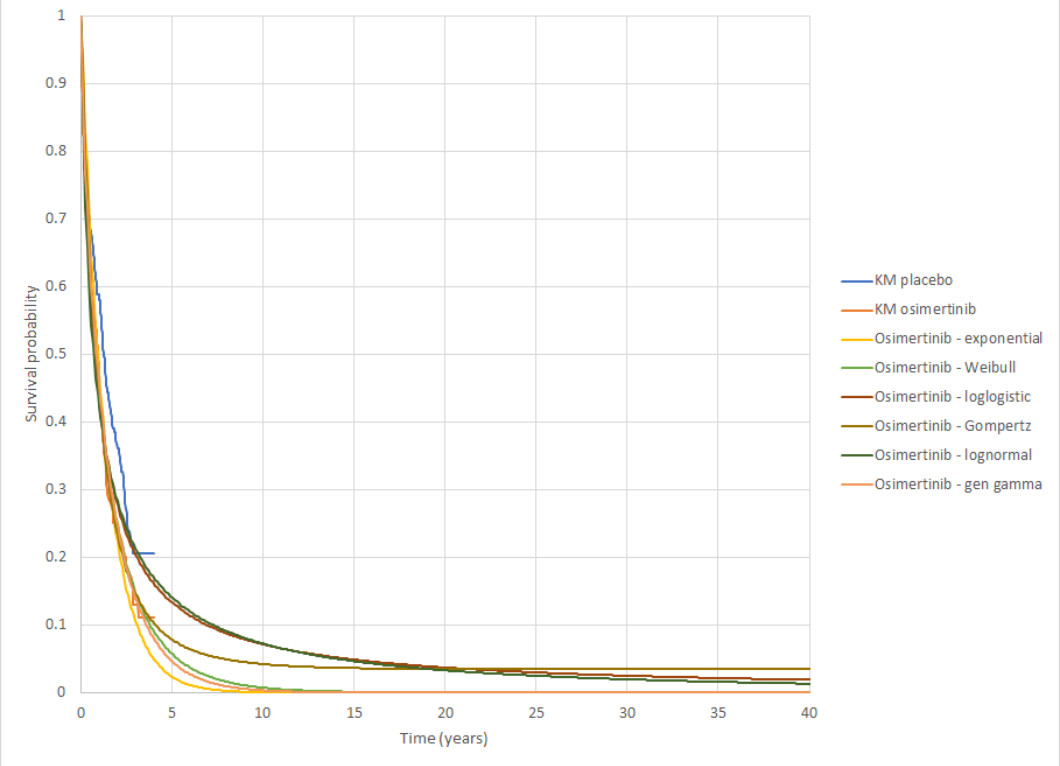

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Table 79. Goodness of fit for DM2 to death.

	Combined fits				Individual fits	
	Osimertinib		SoC			
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Weibull	**1106.90**	**1113.55**	**1316.81**	**1323.93**	2421.72	2434.14
Generalized Gamma	1108.51	1118.48	1318.73	1329.40	2423.61	2440.16
Loglogistic	1117.82	1124.47	1322.66	1329.78	2438.59	2451.01
Gompertz	1114.31	1120.96	1323.71	1330.83	2436.03	2448.45
Lognormal	1125.08	1131.72	1324.37	1331.48	2447.45	2459.87
Exponential	1118.40	1121.73	1329.18	1332.73	2447.58	2455.86

Key: AIC, Akaike information criterion; BIC, Bayesian information criterionAppendix H – Literature search for HRQoL data

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19. Appendix H – Literature search to support the estimation of the calibration hazard

The 2023 data cut with longer follow-up on OS showed that the original model underestimated the OS, but that the DFS was predicted relatively well. This means that the underestimation was caused by predictions in post-DFS survival. A possible explanation for this is that patients in ADAURA were post-surgery patients instead of newly diagnosed stage IIIB/IV (as is the case in FLAURA).

To investigate this, an SLR was conducted which focused on studies in EGFRm NSCLC and reported outcomes (median PFS/OS or HR PFS/OS) for both post-surgery recurrence and newly diagnosed stage IIIB/IV patients.

Literature Searches	
Databases	Embase
Search date(s)	July 5th, 2023

PICO:

Domain	**Inclusion Criteria**	**Exclusion Criteria**
Population	Adult patients with advanced NSCLC (Stage IIIb/IV or with metastatic disease) harbouring EGFR mutations.	Patients with NSCLC without advanced disease and/or not harbouring EGFR mutations
Intervention	EGFR inhibitors (e.g., afatinib, erlotinib, gefitinib, osimertinib etc.)	Non-EGFR inhibitors
Comparison(s)	Any or none	NA
Outcomes	Clinical efficacy outcomes (e.g., OS, PFS etc.) reported in patients with advanced disease who were treatment naïve or had recurrent disease following prior surgery	Any outcomes not listed in the inclusion critieria
Study Design	- RCTs - Single-arm trials - Open label extensions - Non-randomized trials	- Observational studies such as cohort or case control studies, case reports, case series - Animal and purely genetic or pharmacokinetic studies - Reviews - Conference abstracts
Additional Limits		
Time period	2009-July 2023	Studies published prior to 2009
Language	English language studies	Non-English language studies

Search Strategy

#	Search terms	Hits [July 5th, 2023]
1	NSCLC.ti,ab.	110362
2	('non-small-cell lung' or 'non small cell lung').ti,ab.	132030
3	1 or 2	152676
4	(EGFR or 'epidermal growth factor receptor').ti,ab.	179604

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#	Search terms	Hits [July 5th, 2023]
5	(afatinib or dacomitinib or erlotinib or gefitinib or osimertinib or amivantamab or mobocertinib).ti,ab.	27116
6	3 and 4	31354
7	5 and 6	12464
8	exp Randomized Controlled Trial/ or exp Random Allocation/ or exp randomization/	866875
9	exp placebo/	405169
10	exp double blind procedure/ or exp single blind procedure/ or exp crossover procedure/	310066
11	exp clinical trial/ or exp phase 2 clinical trial/ or exp phase 3 clinical trial/ or exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/	2276423
12	exp multicenter Study/	381957
13	randomized controlled trial.pt.	0
14	controlled clinical trial.pt.	0
15	random$.ti,ab,kw.	1990323
16	blind$.ti,ab,kw.	509139
17	(placebo$ or assign* or allocat* or volunteer*).ti,ab,kw.	1272738
18	(parallel$ or factorial$ or crossover* or cross over*).ti,ab,kw.	598759
19	trial.ti.	406750
20	('phase 3' or 'phase 2' or 'phase 1' or 'phase III' or 'phase II' or 'phase I').af.	437409
21	((single or double or triple) adj3 (blind* or mask* or dummy)).af.	368317
22	('double-blind' or 'double-blinded').af.	301325
23	(open label or open-label).af.	110157
24	("single arm" or "single-arm" or "single group" or "single-group").ti,ab.	34373
25	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	4774003
26	7 and 25	5210
27	exp Animals/ not exp humans/	5199695
28	conference abstract.pt.	4807133
29	review.pt.	3117610
30	(letter or editorial).pt.	2093105
31	27 or 28 or 29 or 30	14632092
32	26 not 31	1781
33	limit 32 to (human and english language)	1690
34	(untreated or metastatic or advanced).ti,ab,mp.	1497289
35	33 and 34	1197

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#	Search terms	Hits [July 5th, 2023]
36	limit 35 to yr="2009 - Current"	1049

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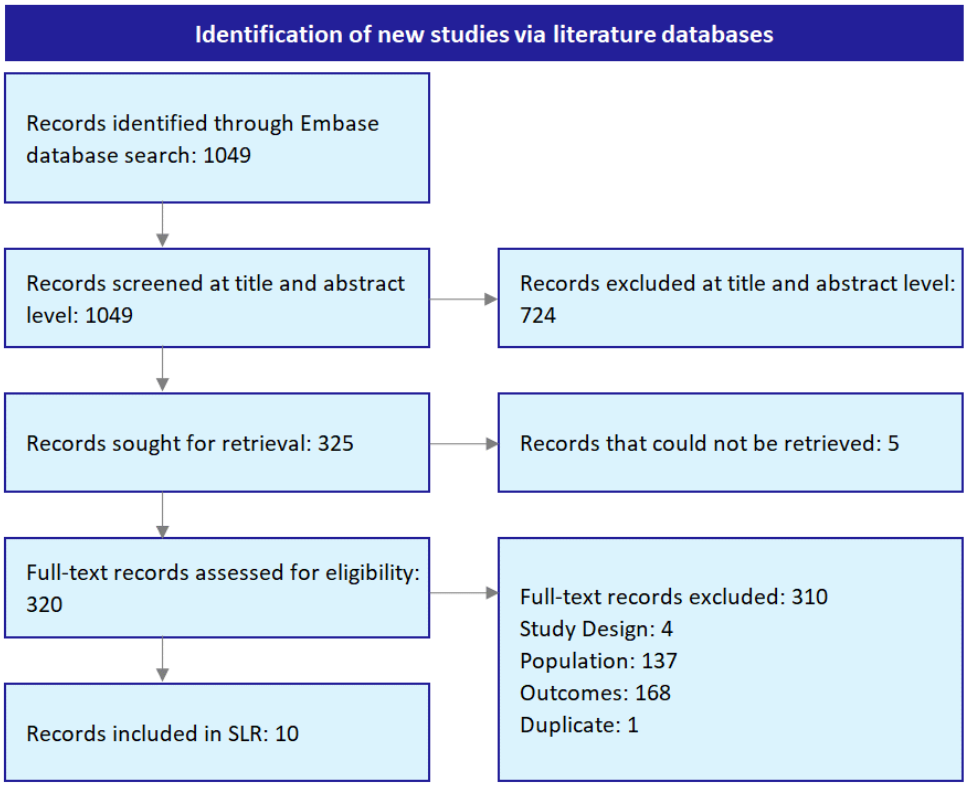
PRISMA Flow Diagram



The SLR search resulted in 1 049 hits, of which ten remained after the full-text screening. Four studies reported median PFS for both groups, one study reported median OS, one study showed a PFS HR between post-surgery vs newly diagnosed stage IIIB/IV and one study included OS HR. All identified studies were with Japanese patients only.

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List of Included Studies

RefID	Authors	Title	Journal	Issue
12	Takata S, Morikawa K, Tanaka H, et al.	Prospective exosome-focused translational research for afatinib (EXTRA) study of patients with nonsmall cell lung cancer harboring EGFR mutation: an observational clinical study.	Therapeutic Advances in Medical Oncology	2023; 15
99	Kenmotsu H, Wakuda K, Mori K, et al.	Randomized Phase 2 Study of Osimertinib Plus Bevacizumab Versus Osimertinib for Untreated Patients With Nonsquamous NSCLC Harboring EGFR Mutations: WJOG9717L Study.	Journal of Thoracic Oncology	2022; 17: 1098-1108
104*	Haratake N, Shimokawa M, Seto T, et al.	Survival benefit of using pemetrexed for EGFR mutation-positive advanced non-small-cell lung cancer in a randomized phase III study comparing gefitinib to cisplatin plus docetaxel (WJTOG3405).	International Journal of Clinical Oncology	2022; 27: 1404-1412
161	Ninomiya T, Nogami N, Kozuki T, et al.	Survival of chemo-naive patients with EGFR mutation-positive advanced non-small cell lung cancer after treatment with afatinib and bevacizumab: updates from the Okayama Lung Cancer Study Group Trial 1404.	Japanese journal of clinical oncology	2021
251	Yamamoto N, Seto T, Nishio M, et al.	Erlotinib plus bevacizumab vs erlotinib monotherapy as first-line treatment for advanced EGFR mutation-positive non-squamous non-small-cell lung cancer: Survival follow-up results of the randomized JO25567 study.	Lung Cancer	2021; 151: 20-24
269	Nishio M, Seto T, Reck M, et al.	Ramucirumab or placebo plus erlotinib in EGFR-mutated, metastatic non-small-cell lung cancer: East Asian subset of RELAY.	Cancer Science	2020; 111: 4510-4525
394*	Saito H, Fukuhara T, Furuya N, et al.	Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial.	The Lancet. Oncology	2019
409	Yoshioka H, Shimokawa M, Seto T, et al.	Final overall survival results of WJTOG3405, a randomized phase III trial comparing gefitinib versus cisplatin with docetaxel as the first-line treatment for patients with stage IIIB/IV or postoperative recurrent EGFR mutation-positive non-small-cell lung cancer.	Annals of Oncology	2019; 30: 1978-1984
872	Goto K, Nishio M, Yamamoto N, et al.	A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal	Lung Cancer	2013; 82: 109-114

		growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC).		
1011	Mitsudomi T, Morita S, Yatabe Y, et al.	Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial.	The Lancet Oncology	2010; 11: 121-128

*RefID #104 and #269 were later excluded, as enough detail was not reported or it was the wrong population (not post-operative patients).

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Outcomes

Study Characteristics:

RefID	Author	Year	Trial Name	Location	Study type	EGFR+?	Intervention(s)	Line of therapy
12	Takata S.Morikawa K.Tan	2023	EXTRA	Japan	Single-arm, observational	Yes	afatinib	1L
99	Kenmotsu H.Wakuda K.N	2022	WJOG9717L	Japan	Open-label, Ph II	Yes	osimertinib v osimertinib + bevacizumab	1L
161	Ninomiya T.Nogami N.Ko	2021	Okayama Lung Cancer Study Group Trial 1404	Japan	Ph I	Yes	afatinib + bevacizumab	
251	Yamamoto N.Seto T.Nish	2021	JO25567 study	Japan	Open-label, Ph II	Yes	erlotinib + bevacizumab v erlotinib mono	1L
394	Saito H.Fukuhara T.Furuy	2019	NEJ026	Japan	Ph III	Yes	erlotinib + bevacizumab v erlotinib mono	
409	Yoshioka H.Shimokawa N	2019	WJTOG3405		Ph III	Yes	getfitinib	1L
							cisplatin + docetaxel	1L
							getfitinib v cisplatin + docetaxel	1L
							[univariate analysis]	1L
							[multivariate analysis]	1L
872	Goto K.Nishio M.Yamam	2013	JO22903	Japan	Ph II	Yes	erlotinib	1L
1011	Mitsudomi T.Morita S.Ya	2010	WJTOG3405	Japan	Ph III	Yes	getfitinib	1L
							cisplatin + docetaxel	1L
							getfitinib v cisplatin + docetaxel	1L
							[univariate analysis]	1L
							[multivariate analysis]	1L

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Stage IIIB/IV Outcomes

		Stage IIIB/IV											
RefID	Author	n	Median PFS	LCL	UCL	PFS HR	LCL	UCL	Median OS	LCL	UCL	OS HR	LCL	UCL
12	Takata S.Morikawa K.Tan	75	15.4	12.2	20.2	--	--	--	--	--	--	--	--	--
99	Kenmotsu H.Wakuda K.M	97	--	--	--	0.84	0.497	1.419	--	--	--	--	--	--
161	Ninomiya T.Nogami N.Ko	9	24	--	--	--	--	--	--	--	--	--	--	--
251	Yamamoto N.Seto T.Nish	123	--	--	--	--	--	--	--	--	--	1.01	0.64	1.58
394	Saito H.Fukuhara T.Furuy	182	--	--	--	: 0.26; Stag:	0.05; Stag:	1.29; Stag	--	--	--	--	--	--
409	Yoshioka H.Shimokawa M	51	--	--	--	--	--	--	27.5	--	--	--	--	--
		50	--	--	--	--	--	--	32.8	--	--	--	--	--
		101	--	--	--	--	--	--	--	--	--	1.22	0.68	2.2
		101	--	--	--	--	--	--	--	--	--	--	--	--
		101	--	--	--	--	--	--	--	--	--	--	--	--
872	Goto K.Nishio M.Yamam	77	10.9	9.7	12.5	--	--	--	--	--	--	--	--	--
1011	Mitsudomi T.Morita S.Ya	51	8.4	--	--	--	--	--	--	--	--	--	--	--
		50	5.3	--	--	--	--	--	--	--	--	--	--	--
		101	--	--	--	0.333	0.203	0.544	--	--	--	--	--	--
		101	--	--	--	--	--	--	--	--	--	--	--	--
		101	--	--	--	--	--	--	--	--	--	--	--	--

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Post-Operative Recurrence Outcomes

			Post-operative recurrence											
RefID	Author	n	Median PFS	LCL	UCL	PFS HR	LCL	UCL	Median OS	LCL	UCL	OS HR	LCL	UCL
12	Takata S.Morikawa K.Tan	28	27.7	18.8	NC	--	--	--	--	--	--	--	--	--
99	Kenmotsu H.Wakuda K.M	25	--	--	--	0.913	0.264	3.159	--	--	--	--	--	--
161	Ninomiya T.Nogami N.Ko	10	NR	--	--	--	--	--	--	--	--	--	--	--
251	Yamamoto N.Seto T.Nish	29	--	--	--	--	--	--	--	--	--	0.28	0.08	0.92
394	Saito H.Fukuhara T.Furuy	42	--	--	--	0.4	0.14	1.18	--	--	--	--	--	--
409	Yoshioka H.Shimokawa M	35	--	--	--	--	--	--	44.5	--	--	--	--	--
		36	--	--	--	--	--	--	45.5	--	--	--	--	--
		71	--	--	--	--	--	--	--	--	--	1.26	0.82	1.96
		71	--	--	--	--	--	--	--	--	--	--	--	--
		71	--	--	--	--	--	--	--	--	--	--	--	--
872	Goto K.Nishio M.Yamam	25	18.2	9.7	NR	--	--	--	--	--	--	--	--	--
1011	Mitsudomi T.Morita S.Ya	35	13.7	--	--	--	--	--	--	--	--	--	--	--
		36	8.1	--	--	--	--	--	--	--	--	--	--	--
		71	--	--	--	0.574	0.313	1.052	--	--	--	--	--	--
		71	--	--	--	--	--	--	--	--	--	--	--	--
		71	--	--	--	--	--	--	--	--	--	--	--	--

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IIB/IV vs Post-Operative Recurrence

		IIB/IV vs Post-op recurrence							
RefID	Author	n	PFS HR	LCL	UCL	OS HR	LCL	UCL	Comments
12	Takata S.Morikawa K.Tan	28	--	--	--	--	--	--	--
99	Kenmotsu H.Wakuda K.M	25	--	--	--	--	--	--	Favours osi + bevacizumab (both subgroups)
161	Ninomiya T.Nogami N.Ko	10	--	--	--	--	--	--	From figure S2
251	Yamamoto N.Seto T.Nish	29	--	--	--	--	--	--	Supplement 1; Post op in favour of erlo + bev
394	Saito H.Fukuhara T.Furuy	42	--	--	--	--	--	--	Favours erlo + bev
409	Yoshioka H.Shimokawa M	35	--	--	--	0.432	0.254	0.734	--
		36	--	--	--	0.531	0.307	0.921	--
		71	--	--	--	--	--	--	favours cisplatin + docetaxel; supplement 2
		71	--	--	--	0.476	0.325	0.697	post op v stage III/IV; supplement 1
		71	--	--	--	0.459	0.312	0.673	post op v stage III/IV; supplement 1
872	Goto K.Nishio M.Yamam	25	--	--	--	--	--	--	--
1011	Mitsudomi T.Morita S.Ya	35	--	--	--	--	--	--	--
		36	--	--	--	--	--	--	--
		71	--	--	--	--	--	--	favours gefitinib
		71	0.463	0.22	0.976	--	--	--	post op v stage III/IV
		71	0.433	0.29	0.649	--	--	--	post op v stage III/IV

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Summary of the SLR outcomes

The aggregated result per outcome is shown in the table below. Patients with post-surgery recurrence consistently report better survival compared with those with newly diagnosed stage IIIB/IV NSCLC. There was close to no difference between median PFS/OS and PFS/OS HR, meaning that the efficacy improvement happens in PFS and continues after metastatic progression.

	Efficacy improvement	Total n
Median PFS	0.603	377
Median OS	0.669	172
PFS HR	0.448	202
OS HR	0.472	213
Weighted average	**0.554**	

Given the SLR results, applying a calibration factor to the efficacy modelled in the LRR, DM1 and DM2 health states is a valid approach to correcting the underestimated prediction since the efficacy in these health states was based upon newly diagnosed patients instead of those with post-surgery recurrence.

To calculate the calibration factor, the absolute difference between the predicted OS and ADAURA's OS KM was taken for both arms. A value of 0.7263 was found to minimise this absolute difference and is used in the final model, applied as a HR to the efficacy of the survival curves for both arms in the LRR, DM1 and DM2 health states. Before the calibration factor was applied, the modelled subsequent therapies were brought in line with the subsequent therapies as found in the ADAURA trial. This ensured that the calibration factor impacts the efficacy as measured in the ADAURA trial. The approach and resulting calibration factor were also discussed with three clinicians from Canada and one from the UK. They agreed with the approach and the magnitude of the calibration factor.

20. Appendix I Mapping of HRQoL data

SF-36 data from the osimertinib treatment arm of the ADAURA trial were the primary source of health state utility values (HSUVs). The EQ-5D-3L is the instrument preferred by NICE and other European health technology assessment agencies for the assessment of HRQoL. As HSUVs in this form were not directly available from patients in the ADAURA trial, mapping from SF-36 onto the EQ-5D-3L index was required.

20.1 Mapping methodology

SF-36 in ADAURA

The SF-36 questionnaire was 'translated' to EQ-5D utility scores using the approach of Rowen et al, 2009, which adheres to the guidance set out in NICE TSD 10.(84, 85) Linear regression models were used to estimate the utilities using the generalised least squares (GLS) technique. As described in Rowen et al, 2009, coefficients of the GLS model (model 3) with interaction terms were applied (SF-36 domains abbreviated).(85) A list of the interaction terms are available in the full utility mapping report (86)S; the EQ-5D utility score is the dependent variable. To obtain utility scores, UK-specific preference weights were used to calculate utility values(87). Observations with missing data were excluded from the analyses, however compliance rates for the SF-36 questionnaire were high (>90%) in the overall ADAURA study population through to Week 144(88).

Exploratory descriptive analyses were carried out using the data, which were additionally used for validation purposes. Baseline utilities were calculated and compared between the osimertinib and placebo (active monitoring) treatment arms. The mean utility per reported cycle was also calculated so that any change in utility over time could be observed, as well as end of treatment and follow-up utilities.

Three covariates were considered in this analysis: AE; baseline utility; and treatment effect. Adverse events were analysed to capture any disutility due to any grade 3 or higher AE and derived such that utilities were accounted for from first onset of the adverse event until death/end of study. Baseline utilities were included to ensure that treatment effect could be measured correctly, as recommended in NICE DSU TSD 12.(89) Regression analyses using repeated measures mixed effect (RMME) models were conducted. This method uses both fixed and random effects, so that the effects of the covariates can be determined while simultaneously correcting for individual patient effects. Note that cycle (24 weeks as time of measurement) is included as random effect in the base case, however cycle is explored as a scenario analysis as fixed effect.

Univariate analyses were also performed to explore the impact of different covariates. Starting with the full model, including all covariates and their interaction terms with treatment, a backwards stepwise approach was used to remove non-significant predictors at each step until a final model containing only the significant terms were left. A p-value of 0.05 was used to determine statistical significance for each of the predictors. To determine the best fitting model, the appropriateness was assessed by the AIC and BIC scores. The following outlines the equation used in the base case analysis in R:

*lmer (utility ~ AE + baseline + tx + AE*tx + baseline*tx + (1| SUBJID), [dataset])*

Abbreviations: SUBJID: subject identification number, AE: adverse events, tx: treatment effect
Note: lmer is a function in the lme4 package of R that allows the estimates of the parameters in linear mixed-effects models to be determined.

Prior to data analysis, validation checks were performed. In the ADAURA trial, there were 682 patients (339 receiving osimertinib; 343 receiving placebo), with 40 grade 3+ AEs (related to treatment) reported (32 in osimertinib; 8 in placebo). These numbers were also found in the data required for analysis and thus passed the validation checks.
Three scenarios were explored to test the impact of specific variables on utility values: the effect of stage of NSCLC at baseline, defined as stage IB or non-stage IB; the sex of the patient; and the age of the patient. The latter variable was tested using both a linear term, and using an age squared term. For each scenario the descriptive statistics were generated, and a univariate analysis was performed. The main findings of these analyses concluded that the disease stage at baseline did not show a statistically significant effect on utility, however, both sex and age did. However, adding sex and age into the base model selected would not alter the utilities, as in the cost-effectiveness analysis, the mean age and sex (in percentage) from ADAURA are used and thus would recreate the model without age and sex covariates. Further details regarding the scenario analysis is described in the full utility mapping report(86).
To calculate the mean utility per cycle, the baseline utility, screening and end of treatment (EOT) observations were excluded.

EORTC QLQ-C30 in FLAURA

In FLAURA, EORTC QLQ-C30 (-LC13) were collected:

- Every 6 weeks until disease progression
- Upon discontinuation of treatment
- Every 6 weeks following disease progression

To use these data in the model, an algorithm was required to map EORTC QLQ-C30 or QLQ-LC13 to EQ-5D to produce HSU values.

Algorithm search strategy

A search was conducted for mapping algorithms of EORTC QLQ-C30 or QLQ-LC13 to the EQ-5D (either EQ-5D-3L or EQ-5D-5L). The inclusion criteria required that lung cancer patients must be included in the study. From each study identified, the authors' preferred algorithm was then extracted, along with the measures used to determine goodness of fit.

- The following three sources were searched:
    - The University of Oxford Health Economics Research Centre database Oxford mapping database (only studies including lung cancer were included)
    - PubMed
    - A study by Doble et al. (2016), reporting the validation of existing mapping algorithms between the EORTC-QLQ-C30 and the EQ-5D in a large dataset

A summary of the identified algorithms is presented in Table 80.

Table 80. Summary of identified mapping algorithms

Study	PRO-mapped	N	Country of EQ-5D value set	Type of cancer	Type of model	Fit statistics used
Jang et al. (2010)[1]	QLQ-C30 to EQ-5D	172	US	Lung	Linear	Adjusted R^2 MSE
Kim et al. (2012)[2]	QLQ-C30 to EQ-5D	893	Korea	All	OLS	R^2 MAE RMSE
Crott et al. (2013)[3]	QLQ-C30 to EQ-5D	172	UK	Breast	OLS	Adjusted R^2 MAE RMSE
Young et al. (2015)[4]	QLQ-C30 to EQ-5D	771	NA	All	Response mapping	MAE
Khan et al. (2016)[5]	QLQ-C30 to EQ-5D-3L and EQ-5D-5L	98	UK	Lung	Beta-binomial	R^2 MAE RMSE
Khan and Morris (2014)[6]	QLQ-C30 to EQ-5D-3L	670	UK	Lung	Beta-binomial	R^2 MAE RMSE

MAE: mean absolute error; MSE: mean square error; N: number of patients; NA: not applicable; OLS: ordinary least squares; PRO: patient-reported outcome; QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; RMSE: root mean square error.

1. Jang et al. J Thorac Oncol, 2010; 5: 1953-7. 2. Kim et al. Health Qual Life Outcomes, 2012; 10: 151. 3. Crott et al. Qual Life Res, 2013; 22: 1045-54. 4. Young et al. Med Decis Making, 2015; 35: 912-26. 5. Khan et al. Health Qual Life Outcomes, 2016; 14: 60. 6. Khan and Morris. Health Qual Life Outcomes, 2014; 12: 163.

Studies in which the UK EQ-5D value set were not used or whose mapping could not be applied to the UK (Kim et al. 2012; Jang et al. 2010) were excluded from final consideration. Crott et al. (2013) was excluded from final consideration due to the mapping being developed in breast cancer patients (although the paper attempted to validate it in lung cancer patients). Therefore, the mapping algorithms that were validated using the AURA2 and AURA3 trials were Young et al. (2015), Khan and Morris (2014) and Khan et al. (2016). Since none of the mapping algorithms utilised the QLQ-LC13 questionnaire, this was not considered in the validation of the algorithms.

Algorithm validation/selection

Data from AURA2 and AURA3 was combined for validation of the existing algorithms. Observed EQ-5D-3L utility values were derived using the cross-walk (van Hout et al. 2012) algorithm from the EQ-5D-5L observed responses in the AURA trials. The three selected mapping algorithms were applied to the QLQ-C30 data separately to obtain predicted EQ-5D-3L utility values (UK tariff).

The methods utilised to validate the algorithms were as follows:

- Comparison of the populations; to identify the level of overlap in demographic and base line disease characteristics between AURA2/3 and the populations from the mapping algorithms
- Graphical summaries and statistical analyses; to assess the ability of the algorithms to predict the observed EQ-5D through the use of:

- scatterplots of predicted versus observed values
- calculation of mean absolute error (MAE) and root mean squared error (RMSE) (lower values suggest better performing algorithms)
- scatterplots of the errors

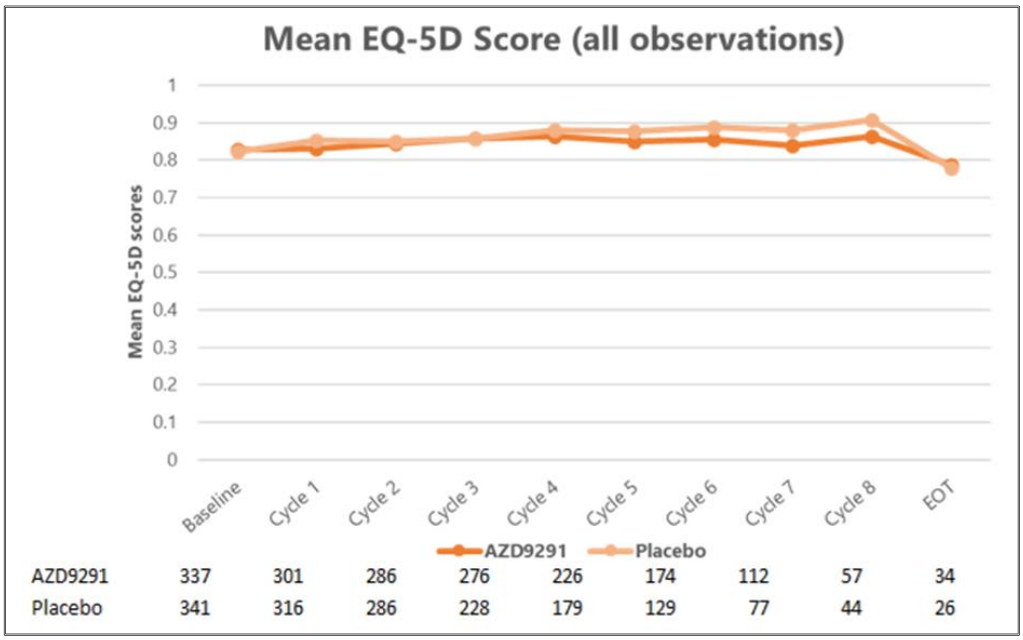
- Subgroup analyses; to ensure the algorithms fitted equally across all groups

Considering all the methods used to conduct this validation, the mapping by Young et al. (2015) fitted the observed data well and was utilised to map FLAURA EORTC values to EQ-5D. The algorithms by Khan and Morris (2014) and Khan et al. (2016), however, did not provide a good fit to the observed data overall and were not be considered further for application to the FLAURA dataset.

20.2 Results of mapping analysis

As shown in Figure 55 and Table 81, the difference between the two treatment populations is minimal. Over time, the mean utility increases for both treatment arms (with comparable patient numbers in each arm), with a decrease seen at the EOT, likely explained by the fact that there are fewer patients within each arm (111 and 65 for placebo (active monitoring) and osimertinib, respectively).

Figure 55. Mean EQ-5D scores from ADAURA (all observations)



Abbreviations: EOT, end of treatment; AZD9291, osimertinib

Table 81. Mean EQ-5D scores, from ADAURA

	Tx	*n*	Mean utility	SD	95% CI
Baseline	Placebo	341	0.823	0.144	(0.541-1.105)
	Osimertinib	337	0.829	0.137	(0.560-1.098)
Day 1	Placebo	316	0.854	0.132	(0.595-1.113)
	Osimertinib	301	0.831	0.154	(0.529-1.133)
12 weeks	Placebo	286	0.850	0.153	(0.550-1.150)
	Osimertinib	286	0.845	0.156	(0.539-1.151)
24 weeks	Placebo	228	0.859	0.150	(0.565-1.153)
	Osimertinib	276	0.858	0.138	(0.588-1.128)
48 weeks	Placebo	179	0.881	0.141	(0.605-1.157)
	Osimertinib	226	0.864	0.138	(0.594-1.134)
72 weeks	Placebo	129	0.878	0.144	(0.596-1.160)
	Osimertinib	174	0.849	0.158	(0.539-1.159)
96 weeks	Placebo	77	0.887	0.125	(0.642-1.132)
	Osimertinib	112	0.857	0.149	(0.565-1.149)
120 weeks	Placebo	44	0.880	0.148	(0.590-1.170)
	Osimertinib	57	0.840	0.180	(0.487-1.193)
144 weeks	Placebo	26	0.908	0.128	(0.657-1.159)
	Osimertinib	34	0.863	0.149	(0.571-1.155)
156 weeks (EOT)	Placebo	111	0.780	0.163	(0.461-1.099)
	Osimertinib	65	0.788	0.195	(0.406-1.170)

Abbreviations: EOT, end of treatment; SD, standard deviation; Tx, treatment

Mean utility for observations with or without a grade 3+ AE were also calculated for each treatment arm, the results of which can be seen in Table 82. The utilities are measured from the point of first AE until death or end of follow-up (whichever occurs first). As expected, when an AE was not experienced, mean utility for both treatment arms was higher.

Table 82. Mean utility for observations with or without AE (by treatment arm)

	Treatment	*n*	Mean	SD	Q1	Median	Q3
With CTCAE Grade 3+	Placebo	28	0.776	0.159	0.672	0.811	0.877
	Osimertinib	95	0.792	0.197	0.663	0.836	0.963
Without CTCAE Grade 3+	Placebo	1669	0.853	0.146	0.778	0.888	0.968
	Osimertinib	1733	0.846	0.147	0.760	0.886	0.958

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Note: n here refers to the number of observations, not the number of patients

The results from the RMME univariate analyses for included covariates along with their parameter estimates are shown in Table 83. The impact of grade 3+ AE and baseline utility covariates are significant (p-value <0.05). Both values are negative, implying that utility will decrease as a result. In this case for example, if a patient has a utility of 0.7, an AE will cause the

utility to drop to 0.673. Treatment effect was found not to be statistically significant (p-value >0.05), thus indicating that there is neither a positive nor negative effect of treatment.

Table 83. RMME univariate analyses results

Model	Intercept	Estimate	SD	t value	p-value
Covariate 1 (AE)	0.839	−0.271	0.014	−1.974	0.048
Covariate 2 (Baseline)	0.843	−0.021	0.004	−5.336	0.000
Covariate 3 (Treatment effect)	0.834	0.008	0.010	0.828	0.408

Abbreviations: AE, adverse event; RMME, repeated measures mixed effects; SD, standard deviation.

The base case was derived using backwards selection (using steps and AIC/BIC statistics), starting with the full model (model 0) containing the three covariates and the interaction terms with treatment (Table 84). Treatment effect is highly non-significant; however, this cannot be removed before the interaction terms; the non-significant interaction term between adverse events and treatment effect is removed first (model 1). Treatment effect is still non-significant, however as the interaction term between baseline and treatment effect is non-significant as well, this is removed next (model 2). Treatment effect remains non-significant and is then removed. This gives us a final model containing only significant covariates (model 3). Table 84 and Table 85 outlines the parameter estimates obtained using model 3.

Table 84. Backwards selection of RMME model; AIC/BIC statistics

Model	AIC	BIC
0 (Full model with 3 covariates and interaction terms with treatment)	−5,611.1	−5,561.7
1 (Interaction term between AE and treatment removed)	−5,617.1	−5,573.9
2 (Interaction term between AE and treatment, and baseline and treatment, removed)	−5,623.3	−5,586.3
3 (Treatment effect, interaction term between AE and treatment, and baseline and treatment, removed)	−5,632.1	−5,601.3

Abbreviations: AE, adverse event; AIC, Akaike information criterion; BIC, Bayesian information criterion; RMME, repeated measures mixed effect.

Table 85. Parametric estimates for Model 3

	Estimate	SD
Intercept	0.844	0.005
Covariate 1 (AE)	−0.039	0.014
Covariate 2 (Baseline)	−0.023	0.004

Abbreviations: AE, adverse event; SD, standard deviation.

To calculate the final health state utilities before and after an adverse event, the following equations were used:

$$\textit{Intercept} + (\textit{baseline coefficient} \times \textit{average baseline})$$

$$\textit{Intercept} + (\textit{baseline coefficient} \times \textit{average baseline}) + \textit{adverse event coefficient}$$

The final health state utility values for the DF health state are shown in Table 86.

Table 86. Final estimated health state utilities for DF health state

	Mean
DF state	0.825
DF state including Grade 3+ CTCAE	0.802

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events; DF, disease-free.

A diagnostic analysis of predicted EQ-5D utility values against the observed utility values demonstrated predicted values to match the observed values well, confirming the model validity. The model became less robust at more severe EQ-5D utility values (<0.50), similar to the findings of Rowen et al. (85) who attributed this phenomenon to floor effects associated with the SF-36. Nevertheless, the model still provides a good estimation of health state utility values as the impact of this floor effect would be minimal considering the relatively high SF-36 scores recorded in ADAURA and associated mapped utility values.

21. Appendix J Probabilistic sensitivity analyses

Table 87. Parameters included in the probabilistic sensitivity analysis

Category	Parameter	PSA distribution	Motivation for distribution
Patient characteristics	BSA	Normal	Central limit theorem (CLT) – mean BSA
Survival extrapolations	Survival model coefficients	Normal - Cholesky decomposition	Parameters are assumed to be jointly normally distributed based on the CLT
HRQoL	Utilities	Beta	Assumption/Non-negative 0-1
	AE disutilities	Beta	Assumption/Non-negative 0-1
	Age-adjustment regression coefficients	Beta	Assumption/Non-negative 0-1
AEs	Frequency of AEs	Beta	Binominal data – the beta distribution ensures values between 0-1
Costs	Acquisition costs	Gamma	Costs are assumed to be right-skewed and non-negative values not possible.
	Administration costs	Gamma	
	Disease management costs	Gamma	
	Terminal care costs	Gamma	
	AE costs	Gamma	
	EGFR testing costs	Gamma	
	CNS metastasis costs	Gamma	

Parameters excluded from the PSA are total costs and discount rates. Individual cost items are varied in the PSA, thus totals are excluded. Discount rates are given and are without uncertainty.

Table 88. Summary of base case variables applied in the economic model

Value	Current	Distribution
BSA	1.67	Normal
utility_dfs_osimertinib	0.825195488	Beta
utility_dfs_placebo	0.825195488	Beta
utility_lr_osimertinib	0.825195488	Beta
utility_lr_placebo	0.825195488	Beta
utility_dm1_osimertinib	0.794	Beta
utility_dm1_placebo	0.794	Beta
utility_dm2	0.64	Beta
utitility_ae_Paronychia	-0.0325	Beta
utitility_ae_DecreasedAppetite	-0.05	Beta
utitility_ae_Diarrhoea	-0.0468	Beta
utitility_ae_Stomatitis	-0.05	Beta
utitility_ae_ECGQTprolonged	0	Beta
cost_drug_admin_dfs_osimertinib_first_cycle	0	Gamma
cost_drug_admin_lr_PDC_first_cycle	25445.75	Gamma
cost_drug_admin_lr_Cisplatin_first_cycle	25445.75	Gamma
cost_drug_admin_dm1_osimertinib_first_cycle	0	Gamma
cost_drug_admin_dm1_Erlotinib_first_cycle	0	Gamma
cost_drug_admin_dm1_Gefitinib_first_cycle	0	Gamma
cost_drug_admin_dm1_Afatinib_first_cycle	0	Gamma
cost_drug_admin_dm1_PDC1_first_cycle	25445.75	Gamma
cost_drug_admin_dm1_PDC2_first_cycle	25445.75	Gamma
cost_drug_admin_dm1_PDC3_first_cycle	25445.75	Gamma
cost_drug_admin_dm1_PDC4_first_cycle	25445.75	Gamma
cost_drug_admin_dm2_osimertinib_first_cycle	0	Gamma
cost_drug_admin_dm2_PDC_first_cycle	25445.75	Gamma
cost_drug_admin_dm2_Pemetrexed_first_cycle	25445.75	Gamma
cost_drug_admin_dm2_Docetaxel_first_cycle	25445.75	Gamma
cost_drug_admin_dm2_Cisplatin_first_cycle	25445.75	Gamma
cost_drug_admin_dfs_osimertinib_subsequent_cycles	0	Gamma
cost_drug_admin_lr_PDC_subsequent_cycles	25445.75	Gamma
cost_drug_admin_lr_Cisplatin_subsequent_cycles	25445.75	Gamma
cost_drug_admin_dm1_osimertinib_subsequent_cycles	0	Gamma
cost_drug_admin_dm1_Erlotinib_subsequent_cycles	0	Gamma
cost_drug_admin_dm1_Gefitinib_subsequent_cycles	0	Gamma
cost_drug_admin_dm1_Afatinib_subsequent_cycles	0	Gamma
cost_drug_admin_dm1_PDC1_subsequent_cycles	25445.75	Gamma

cost_drug_admin_dm1_PDC2_subsequent_cycles	25445.75	Gamma
cost_drug_admin_dm1_PDC3_subsequent_cycles	25445.75	Gamma
cost_drug_admin_dm1_PDC4_subsequent_cycles	25445.75	Gamma
cost_drug_admin_dm2_osimertinib_subsequent_cycles	0	Gamma
cost_drug_admin_dm2_PDC_subsequent_cycles	25445.75	Gamma
cost_drug_admin_dm2_Pemetrexed_subsequent_cycles	25445.75	Gamma
cost_drug_admin_dm2_Docetaxel_subsequent_cycles	25445.75	Gamma
cost_drug_admin_dm2_Cisplatin_subsequent_cycles	25445.75	Gamma
cost_drug_acquisition_dfs_tx0	42712.31196	Gamma
cost_drug_acquisition_dfs_tx1	0	Gamma
cost_drug_acquisition_lr_tx1	14111.44954	Gamma
cost_drug_acquisition_dm1_tx1	42712.31196	Gamma
cost_drug_acquisition_dm2_tx1	7175.867216	Gamma
cost_disease_management_dfs_hospitalization	148.6817248	Gamma
cost_disease_management_dfs_Oncologist_visits_subsequent	113.1690439	Gamma
cost_disease_management_dfs_Surgeon_visits	68.24372728	Gamma
cost_disease_management_dfs_Pulmonologist_respiratory_physician_subsequent	201.4961026	Gamma
cost_disease_management_dfs_Other_specialist_visit	192.6153929	Gamma
cost_disease_management_dfs_Emergency_room	2319.246743	Gamma
cost_disease_management_dfs_CT_scans	145.7860743	Gamma
cost_disease_management_dfs_MRI	101.8160911	Gamma
cost_disease_management_dfs_PET_scans	106.6644764	Gamma
cost_disease_management_dfs_PET_CT_scans	150.299944	Gamma
cost_disease_management_dfs_Ultrasound	76.30718686	Gamma
cost_disease_management_dfs_Nuclear_medicine_studies	125.7778607	Gamma
cost_disease_management_lr_hospitalization	257.7149897	Gamma
cost_disease_management_lr_Oncologist_visits_subsequent	838.0029693	Gamma
cost_disease_management_lr_Surgeon_visits	83.40900001	Gamma
cost_disease_management_lr_Pulmonologistrespiratory_physician_subsequent	315.7692348	Gamma
cost_disease_management_lr_Other_specialist_visit	303.6242642	Gamma
cost_disease_management_lr_Emergency_room	4279.384312	Gamma
cost_disease_management_lr_CT_scans	371.3708419	Gamma
cost_disease_management_lr_MRI	213.3289528	Gamma
cost_disease_management_lr_PET_scans	213.3289528	Gamma
cost_disease_management_lr_PET_CT_scans	101.7429158	Gamma
cost_disease_management_lr_Ultrasound	553.4225873	Gamma
cost_disease_management_lr_Nuclear_medicine_studies	213.3289528	Gamma
cost_disease_management_dm1_hospitalization	446.0451745	Gamma

cost_disease_management_dm1_Oncologist_visits_subsequent	804.6043003	Gamma
cost_disease_management_dm1_Surgeon_visits	67.76981251	Gamma
cost_disease_management_dm1_Pulmonologistrespiratory_physician_subsequent	151.8121321	Gamma
cost_disease_management_dm1_Other_specialist_visit	197.3557718	Gamma
cost_disease_management_dm1_Emergency_room	5760.709651	Gamma
cost_disease_management_dm1_CT_scans	485.3141684	Gamma
cost_disease_management_dm1_MRI	319.9934292	Gamma
cost_disease_management_dm1_PET_scans	533.3223819	Gamma
cost_disease_management_dm1_PET_CT_scans	266.661191	Gamma
cost_disease_management_dm1_Ultrasound	165.3322382	Gamma
cost_disease_management_dm1_Nuclear_medicine_studies	691.7782341	Gamma
cost_disease_management_dm2_hospitalization	446.0451745	Gamma
cost_disease_management_dm2_Oncologist_visits_subsequent	804.6043003	Gamma
cost_disease_management_dm2_Surgeon_visits	67.76981251	Gamma
cost_disease_management_dm2_Pulmonologistrespiratory_physician_subsequent	151.8121321	Gamma
cost_disease_management_dm2_Other_specialist_visit	197.3557718	Gamma
cost_disease_management_dm2_Emergency_room	5760.709651	Gamma
cost_disease_management_dm2_CT_scans	485.3141684	Gamma
cost_disease_management_dm2_MRI	319.9934292	Gamma
cost_disease_management_dm2_PET_scans	533.3223819	Gamma
cost_disease_management_dm2_PET_CT_scans	266.661191	Gamma
cost_disease_management_dm2_Ultrasound	165.3322382	Gamma
cost_disease_management_dm2_Nuclear_medicine_studies	691.7782341	Gamma
cost_end_of_life_Hospital	68888.61304	Gamma
cost_ae_Paronychia	11157	Gamma
cost_ae_Decreased_Appetite	5130	Gamma
cost_ae_Diarrhoea	22115	Gamma
cost_ae_Stomatitis	1186	Gamma
cost_ae_ECG_QT_prolonged	15488	Gamma
frequency_ae_Paronychia_osimertinib	0.009	Beta
frequency_ae_Decreased_Appetite_osimertinib	0.006	Beta
frequency_ae_Diarrhoea_osimertinib	0.018	Beta
frequency_ae_Stomatitis_osimertinib	0.015	Beta
frequency_ae_ECG_QT_prolonged_osimertinib	0.009	Beta
frequency_ae_Paronychia_placebo	0	Beta
frequency_ae_Decreased_Appetite_placebo	0	Beta
frequency_ae_Diarrhoea_placebo	0.003	Beta
frequency_ae_Stomatitis_placebo	0	Beta

frequency_ae_ECG_QT_prolonged_placebo	0.003	Beta
cost_other_direct_placeholder1	0	Gamma
cost_other_direct_EGFRmutationtest	3443.130435	Gamma
cost_cns_one_off	28229	Gamma
cost_cns_cycle	5335.768325	Gamma
drug_cycle_df_tx0	36	Gamma
drug_cycle_lr_1_tx0	2.759753593	Gamma
drug_cycle_lr_2_tx0	3.449691992	Gamma
drug_cycle_dm1_no_retreatment_1_tx0	3.449691992	Gamma
drug_cycle_dm1_no_retreatment_2_tx0	3.449691992	Gamma
drug_cycle_dm1_no_retreatment_3_tx0	3.449691992	Gamma
drug_cycle_dm1_no_retreatment_4_tx0	3.449691992	Gamma
drug_cycle_dm1_retreatment_1_tx0	444	Gamma
drug_cycle_dm1_retreatment_2_tx0	444	Gamma
drug_cycle_dm1_retreatment_3_tx0	444	Gamma
drug_cycle_dm1_retreatment_4_tx0	444	Gamma
drug_cycle_dm1_retreatment_5_tx0	3.449691992	Gamma
drug_cycle_dm1_retreatment_6_tx0	3.449691992	Gamma
drug_cycle_dm1_retreatment_7_tx0	3.449691992	Gamma
drug_cycle_dm1_retreatment_8_tx0	3.449691992	Gamma
drug_cycle_dm2_no_retreatment_1_tx0	3.449691992	Gamma
drug_cycle_dm2_no_retreatment_2_tx0	2.759753593	Gamma
drug_cycle_dm2_no_retreatment_3_tx0	2.759753593	Gamma
drug_cycle_dm2_no_retreatment_4_tx0	2.759753593	Gamma
drug_cycle_dm2_retreatment_1_tx0	444	Gamma
drug_cycle_dm2_retreatment_2_tx0	3.449691992	Gamma
drug_cycle_dm2_retreatment_3_tx0	2.759753593	Gamma
drug_cycle_dm2_retreatment_4_tx0	2.759753593	Gamma
drug_cycle_lr_1_tx1	2.759753593	Gamma
drug_cycle_lr_2_tx1	3.449691992	Gamma
drug_cycle_dm1_1_tx1	444	Gamma
drug_cycle_dm1_2_tx1	444	Gamma
drug_cycle_dm1_3_tx1	444	Gamma
drug_cycle_dm1_4_tx1	444	Gamma
drug_cycle_dm1_5_tx1	3.449691992	Gamma
drug_cycle_dm1_6_tx1	3.449691992	Gamma
drug_cycle_dm1_7_tx1	3.449691992	Gamma
drug_cycle_dm1_8_tx1	3.449691992	Gamma

drug_cycle_dm2_1_tx1	444	Gamma
drug_cycle_dm2_2_tx1	3.449691992	Gamma
drug_cycle_dm2_3_tx1	2.759753593	Gamma
drug_cycle_dm2_4_tx1	2.759753593	Gamma
drug_share_lr_1_tx0	1	Beta
drug_share_lr_2_tx0	0	Beta
drug_share_dm1_no_retreatment_1_tx0	0	Beta
drug_share_dm1_no_retreatment_2_tx0	0	Beta
drug_share_dm1_no_retreatment_3_tx0	0	Beta
drug_share_dm1_no_retreatment_4_tx0	1	Beta
drug_share_dm1_retreatment_1_tx0	1	Beta
drug_share_dm1_retreatment_2_tx0	0	Beta
drug_share_dm1_retreatment_3_tx0	0	Beta
drug_share_dm1_retreatment_4_tx0	0	Beta
drug_share_dm1_retreatment_5_tx0	0	Beta
drug_share_dm1_retreatment_6_tx0	0	Beta
drug_share_dm1_retreatment_7_tx0	0	Beta
drug_share_dm1_retreatment_8_tx0	0	Beta
drug_share_dm2_no_retreatment_1_tx0	0	Beta
drug_share_dm2_no_retreatment_2_tx0	0	Beta
drug_share_dm2_no_retreatment_3_tx0	1	Beta
drug_share_dm2_no_retreatment_4_tx0	0	Beta
drug_share_dm2_retreatment_1_tx0	0	Beta
drug_share_dm2_retreatment_2_tx0	1	Beta
drug_share_dm2_retreatment_3_tx0	0	Beta
drug_share_dm2_retreatment_4_tx0	0	Beta
drug_share_lr_1_tx1	1	Beta
drug_share_lr_2_tx1	0	Beta
drug_share_dm1_1_tx1	1	Beta
drug_share_dm1_2_tx1	0	Beta
drug_share_dm1_3_tx1	0	Beta
drug_share_dm1_4_tx1	0	Beta
drug_share_dm1_5_tx1	0	Beta
drug_share_dm1_6_tx1	0	Beta
drug_share_dm1_7_tx1	0	Beta
drug_share_dm1_8_tx1	0	Beta
drug_share_dm2_1_tx1	0	Beta
drug_share_dm2_2_tx1	1	Beta

drug_share_dm2_3_tx1	0	Beta
drug_share_dm2_4_tx1	0	Beta
drug_cost_lr_1_tx0	67749.62969	Gamma
drug_cost_lr_2_tx0	25950.97047	Gamma
drug_cost_dm1_no_retreatment_1_tx0	703.4595424	Gamma
drug_cost_dm1_no_retreatment_2_tx0	1527.944382	Gamma
drug_cost_dm1_no_retreatment_3_tx0	4598.96131	Gamma
drug_cost_dm1_no_retreatment_4_tx0	25950.97047	Gamma
drug_cost_dm1_retreatment_1_tx0	42712.31196	Gamma
drug_cost_dm1_retreatment_2_tx0	10479.57951	Gamma
drug_cost_dm1_retreatment_3_tx0	6170.89875	Gamma
drug_cost_dm1_retreatment_4_tx0	16529.60898	Gamma
drug_cost_dm1_retreatment_5_tx0	703.4595424	Gamma
drug_cost_dm1_retreatment_6_tx0	1527.944382	Gamma
drug_cost_dm1_retreatment_7_tx0	4598.96131	Gamma
drug_cost_dm1_retreatment_8_tx0	25950.97047	Gamma
drug_cost_dm2_retreatment_1_tx0	42712.31196	Gamma
drug_cost_dm2_retreatment_2_tx0	25950.97047	Gamma
drug_cost_dm2_retreatment_3_tx0	25587.89457	Gamma
drug_cost_dm2_retreatment_4_tx0	340.3836496	Gamma
drug_cost_df_tx1	0	Gamma
drug_cost_lr_1_tx1	67749.62969	Gamma
drug_cost_lr_2_tx1	25950.97047	Gamma
drug_cost_dm1_1_tx1	42712.31196	Gamma
drug_cost_dm1_2_tx1	10479.57951	Gamma
drug_cost_dm1_3_tx1	6170.89875	Gamma
drug_cost_dm1_4_tx1	16529.60898	Gamma
drug_cost_dm1_5_tx1	703.4595424	Gamma
drug_cost_dm1_6_tx1	1527.944382	Gamma
drug_cost_dm1_7_tx1	4598.96131	Gamma
drug_cost_dm1_8_tx1	25950.97047	Gamma
drug_cost_dm2_1_tx1	42712.31196	Gamma
drug_cost_dm2_2_tx1	25950.97047	Gamma
drug_cost_dm2_3_tx1	25587.89457	Gamma
drug_cost_dm2_4_tx1	340.3836496	Gamma
drug_cost_dm2_acbp_1_tx0	46294.06057	Gamma
drug_cost_dm2_acbp_2_tx0	26393.05631	Gamma
drug_cost_dm2_acbp_3_tx0	339.3443056	Gamma

drug_cost_dm2_acbp_4_tx0	325.1546329	Gamma
drug_cycle_dm2_acbp_1_tx0	444	Gamma
drug_cycle_dm2_acbp_2_tx0	444	Gamma
drug_cycle_dm2_acbp_3_tx0	2.759753593	Gamma
drug_cycle_dm2_acbp_4_tx0	2.759753593	Gamma
drug_cost_dm2_acbp_1_tx1	46294.06057	Gamma
drug_cost_dm2_acbp_2_tx1	26393.05631	Gamma
drug_cost_dm2_acbp_3_tx1	339.3443056	Gamma
drug_cost_dm2_acbp_4_tx1	325.1546329	Gamma
drug_cycle_dm2_acbp_1_tx1	444	Gamma
drug_cycle_dm2_acbp_2_tx1	444	Gamma
drug_cycle_dm2_acbp_3_tx1	2.759753593	Gamma
drug_cycle_dm2_acbp_4_tx1	2.759753593	Gamma
drug_admin_dm2_acbp_1	25445.75	Gamma
drug_admin_dm2_acbp_2	0	Gamma
weight_live	63	Gamma
drug_cost_dm2_retreatment_5_tx0	363.0758929	Gamma
drug_share_dm2_retreatment_5_tx0	0	Beta
drug_cycle_dm2_retreatment_5_tx0	2.759753593	Gamma
drug_cost_dm2_5_tx1	363.0758929	Gamma
drug_share_dm2_5_tx1	0	Beta
drug_cycle_dm2_5_tx1	2.759753593	Gamma
drug_cycle_lr_3_tx0	1	Gamma
drug_cycle_lr_3_tx1	1	Gamma
drug_share_lr_3_tx0	0	Beta
drug_share_lr_3_tx1	0	Beta
drug_cost_lr_3_tx0	115354	Gamma
drug_cost_lr_3_tx1	115354	Gamma
cost_drug_admin_dm1_Dacomitinib_first_cycle	0	Gamma
cost_drug_admin_dm1_Dacomitinib_subsequent_cycles	0	Gamma
drug_cycle_dm1_retreatment_9_tx0	444	Gamma
drug_cycle_dm1_9_tx1	444	Gamma
drug_share_dm1_retreatment_9_tx0	0	Gamma
drug_share_dm1_9_tx1	0	Gamma
drug_cost_dm1_retreatment_9_tx0	18770.88864	Gamma
drug_cost_dm1_9_tx1	18770.88864	Gamma
df_indirect_costs	2259.263864	Gamma
lr_indirect_costs	3278.940452	Gamma

dm1_indirect_costs	3840.328542	Gamma
dm2_indirect_costs	3840.328542	Gamma

	Expected value	Standard error	Reason / Rationale / Source	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Probabilities							
Efficacy Outcome A	0.72	0.06		Beta	α: 165	β: 78	Prob_dists!C43
HSUV							
State A	0.79	0.01		Beta	α: 1112	β: 301	Prob_dists!C133
Costs							
Hospitalization	20000			Gamma	α: 4	β: 5613	Prob_dists!C248