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. 1.0

Bilagsoversigt

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

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Til Medicinrådet

29. september 2022

Notat vedrørende udkast til anbefaling af osimertinib til adjuverende behandling af tidlig EGFR+ NSCLC

AstraZeneca (AZ) takker for udkastet til vurdering af Tagrisso(osimertinib) som adjuverende behandling efter operation af NSCLC i stadie IB-IIIA sygdom og exon 19-deletion/exon 21 (L858)-mutation i EGFR.

Vi har forståelse for, at det kan at være udfordrende at vurdere en adjuverende behandling efter operation af tidlig stadie NSCLC-patienter(kurativ intenderet operation) da det kan have en lang tidshorisont at få robuste overlevelsesdata(OS). Dette afspejles også i de meget umodne OS der var tilgængelige ved tidspunktet hvor Medicinrådet modtog vores ansøgning. I en netop publiceret opdateret 4 års analyse fra ESMO 2022 er der stadig få events i OS analysen mens data for DFS og CNS beskyttelse bekræftes i opdateringen.

Vi sætter pris på den grundige vurdering Medicinrådet har givet ved at præsentere hovedanalyser, hvor den ene viser at behandling med osimertinib er cost-effektiv med en QALY gevinst på 2,72.

Der er punkter vi beder Medicinrådet vurdere/inkludere:

På trods af de umodne OS-data så vil et behandlingstilbud med osimertinib utvivlsomt være klinisk relevant for de ca. 28 patienter(om året) vi forventer vil være kandidater til at modtage den adjuverende behandling i Danmark. ADAURA studiet viser, at der i osimertinib-armen er nedsat risiko for at få kræft igen og reduktion af udbredelsen af kræften. At være kræftfri så længe som muligt har en værdi og sygdomsfri overlevelse (DFS) er et direkte mål for effekten af et lægemiddel. ADAURA viser både signifikant og klinisk relevant effekt af osimertinib sammenlignet med standardbehandlingen og samtidig forblev livskvaliteten for patienterne uændret. Størrelsesordenen af forskellen på DFS mellem osimertinib og placebo-gruppen med aktiv opfølgning er hidtil uset. Dette var også grunden til at studiet blev anbefalet at stoppe 2 år før tid af en uafhængig Data Monitoreringskomite, grundet overvældende effekt af osimertinib vs. komparator.

Det er derfor uforstående, at Medicinrådet vælger at lave en konservativ model, hvor der **ingen** effekt er indberegnet af osimertinib-behandlingen. Osimertinib er allerede godkendt og anbefalet i Danmark som targeteret behandling, da der via FLAURA studiet er vist forbedret OS for patienter med avanceret NSCLC. Derfor virker den konservative tilgang i forbindelse med ADAURA, hvor det både konkluderes at osimertinib er dyrere og har mindre effekt end aktiv follow-up, ikke funderet i et sandsynligt klinisk billede af patientpopulationen der er behandles med osimertinib i et ADAURA set-up. Dette kan alene baseres på størrelsesordenen af DFS effekt.

Udkommet af den konservative model, er at der ikke er konkrete rekommandationer tilstede i rapporten hvilket medfører, at det er vanskeligt for beslutningstagerne i Medicinrådet at foretage en endelige vurdering, da det er svært at drage nogen konklusion ud fra udkastet. Assessment-rapporten fra en tilsvarende AZ ansøgning i Norge udregnede(maj 2022) ligeledes en konservativ model hvor de estimerede en trinvis cost-effektiv ratio på 580 000 NOK for hvert QALY. QALY fordelen til osimetinib blev i deres konservative model vurderet til 1,27 til en trinvis pris på 738 000 NOK (Statens legemiddelverk, 2022). ADAURA indikatonen blev efterfølgende anbefalet i Norge. Selvom der kan være forskelle landene imellem (pris, resourcer mm), viser eksemplet en markant forskel på hvordan data vurderes i de konservative modeller mellem to ellers sammenlignelige lande.

Vi vil påpege, at Medicinrådets beslutningen om ikke at udarbejde en budget-impact analyse ikke giver mening for AZ da behandlingstiden med osimertinib er fastsat til 3 år. Derfor bør der ikke opstå usikkerhed omkring omkostningerne ved behandlingen. Derudover har AZ også, i arbejdet med ansøgningen, lavet et grundigt arbejde for at give Medicinrådet et korrekt antal af relevante danske ADAURA patienter, hvormed dette burde kunne estimeres.

Det er ikke korrekt, at der på trods af en vis usikkerhed om varighed af respons i umodne data, ikke som minimum kan udregnes hvad reduktionen af underliggende og efterfølgende behandlinger vil være ved at reducere antallet af tilbagefald i så betydelig grad som der er vist i ADAURA studiet.
Det er værd at påpege, at de DFS data fra ADAURA, der er anvendt i ansøgningen er fra 2 års data cut-off. Der er som nævnt i mellemtiden offentliggjort 4 års DFS data efter at alle patienter i studiet havde haft mulighed for at modtage 3 års behandling med osimetinib. Derudover fremgår det også af datasættet, at beskyttelsen overfor progression i CNS, som tidligere er dokumenteret i FLAURA studiet, også viste klar positiv tendens i ADAURA ved begge data cut-off's.

Selvom der findes tidligere EGFR-targeterede studier(ikke osimetinib) i adjuverende behandling der ikke viser en øget (signifikant) OS på trods af positive DFS data, understreger vi at størrelsesorden for DFS-effekten i disse studier slet ikke er sammenlignelig med ADAURA (Kelly 2015, Pennel 2019, Wu 2020, Yue 2018, Zhong 2018). En meta-analyse der inddrog individuelle patientdata baseret på 17 adjuverende kemoterapi-studier i tidlig stadie NSCLC demonstrerede en korrelation mellem effekten af DFS med signifikant forbedret OS. Dette omfattende studie understøtter DFS som surrogat endepunkt for OS ved adjuverende behandling af patienter der modtager kurativ intenderet behandling (Mauguen 2013). Medicinrådet henviser til en metaanalyse artikel fra Chen et. al fra 2021 der ikke er baseret på individuel patient data. Artiklen konkluderer delvist, at der ikke var sammenhæng mellem DFS og OS for EGFR-targeteret behandling, men artiklen har ikke inkluderet ADAURA OS data. Derudover bør det bemærkes, at resultaterne er delvist drevet af et studie fra 2013 med ialt kun 15 EGFRm patienter(Goss 2013).

Medicinrådet konkluderer på side 46 i rapporten, at det er usikkert hvilken behandling der skal tilbydes ADAURA-patienterne hvis de oplever tilbagefald efter adjuverende EGFR-behandling og at de ikke nødvendigvis kan indgå i FLAURA indikationen(genbehandling med osimetinib). Efter rådføring med danske onkologer er vi usikre på hvad der henvises til af dokumentation, da sammenligning af tidlig-stadie patienter der har modtaget kurativt intenderet behandling med patienter med avanceret sygdom er en udfordring. Vi vil gerne tilføje til Medicinrådets muligheder for genbehandling af disse patienter, at dansk onkologisk behandling af NSCLC-patienter med targeterbare onkogene drivere inkluderer afdækning af resistensmekanismer efter progression med osimertinib. Den specifikke resistensmekanisme vil derefter styre muligheden for genbehandling.

Vi har derudover følgende mindre bemærkningerne:

- Vi gør opmærksom på at DFS sammenligningen i ADAURA-studiet og de danske tal fra Aarhus ikke kan sammenlignes 1:1 da der er forskel på inklusionstidspunktet, hvormed forskellen vil være mindre.

- Til at vurdere hvordan placebo-armen i ADAURA klarede sig anvender Medicinrådet kilder som vi mener kan være problematiske at bruge som sammenligning:

    - Medicinrådet citerer ANITA studiet. Mens det er korrekt, at det er tale om adjuverende behandling af tidlig stadie patienter kan det ikke bruges som sammenligning, da histologisammensætningen i ANITA består af ca. 60% planocellulært karcinom , hvilket har en mere positiv prognose end adenokarcinom som er den dominerende type i ADAURA (>96%). (Kawase 2012)

    - Saw (2021, reference 10 i rapporten) bruges også som sammenligning med ADAURA kontrol gruppen. Vi gør opmærksom på, at data er fra Singapore med 89% kinesiske patienter og 82% aldrig rygere, hvilket er højere end i ADAURA (64% og 75% respektivt).

- På side 30 omkring Medicinrådets vurdering af SF-36 bliver det beskrevet at milde grad 1-2 bivirkninger som diarré og de sjældne tilfælde af pneumonitis ikke er afspejlet i de tilgængelige livkvalitetsmålinger. Vi mener denne formulering er uklar. Vi vil gerne specificere, at hvis bivirkninger påvirker livskvaliteten for patienterne så ville det været afspejlet i resultaterne for livskvalitet, hvor der ikke var forskel mellem osimertinib og placebo i ADAURA.

Vi håber, at Medicinrådet vil inkludere ovenstående i deres endelige vurdering.

Med venlig hilsen

AstraZeneca A/S

Søren Clausen
Market Access Head

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26. september 2022
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.10.2022
Leverandør	AstraZeneca
Lægemiddel	Tagrisso (osimertinib)
Ansøgt indikation	Tagrisso (osimertinib) som monoterapi er indiceret til adjuverende behandling efter komplet tumorresektion hos voksne patienter med stadie IB-IIIA ikke-småcellet lungecancer (NSCLC), hvis tumorer har epidermal vækstfaktorreceptor (EGFR) exon 19-deletioner eller exon 21 (L858R)-substitutionsmutationer.

Forhandlingsresultat

Amgros har følgende pris på Tagrisso (osimertinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP	Nuværende SAIP	Rabatprocent ift. AIP
Tagrisso (osimertinib)	80 mg/tabletter	30 stk.	41.502,45	[redacted]	[redacted]
Tagrisso (osimertinib)	80 mg/tabletter	30 stk.	41.502,45	[redacted]	[redacted]

Tagrisso (osimertinib) er en del af et udbud på lungekræft, og aftalerne løber indtil 31.03.2023 med

mulighed for 2 x 6 måneders forlængelse.
[redacted]

Informationer fra forhandlingen

Der kommer opfølgende data på PFS (ESMO 22) og leverandøren forventer, at der kommer opfølgende data på OS i staren af 2023.
[redacted]

Konkurrencesituationen

Der er ikke konkurrence på adjuverende behandling af EGFR-positiv ikke-småcellet lungekræft. Tagrisso (osimertinib) er førstevalg i lægemiddelrekommandationen til behandling af patienter med aktiverende EGFR-mutation, hvor der heller ikke er konkurrence.
[redacted].

Tabel 2: Årlige lægemiddelpriser

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Tagrisso (osimertinib)	80 mg dagligt	80 mg (30 stk.)	[redacted]	12,2	[redacted]

Status fra andre lande

Norge: Godkendt til standardbehandling d. 29.08.2022[1].
Sverige: behandles ikke af NT-rådet, da der er tale om en tabletbehandling[2].
England: Godkendt i Cancer Drugs Fund. Behandlingen stoppes efter maksimalt 3 år eller ved progression[3].

Konklusion

[redacted]

[1] Osimertinib (Tagrisso) - Indikasjon III (nyemetoder.no)
[2] Tagrisso (osimertinib) - Janusinfo.se
[3] 1 Recommendations | Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection | Guidance | NICE

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

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Tagrisso
Generic name	Osimertinib
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sverige
ATC code	L01EB04
Pharmacotherapeutic group	TKI
Active substance(s)	Osimertinib
Pharmaceutical form(s)	Tablets. 40 or 80 mg in packs of 30
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

Overview of the pharmaceutical	
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
aNSCLC	Advanced Non-Small Cell Lung Cancer
AURA2	AURA phase II single arm clinical trial
AURA3	AURA phase III randomised controlled trial
AURAexp	AURAexpansion trial; phase I dose expansion trial
AURAexp DCO3	AURAexpansion Data Cut-Off 3
AZ9291	Osimertinib
BBB	Blood-Brain Barrier
BICR	Blinded Independent Central Review
CI	Confidence Interval
CNS	Central Nervous system

Abbreviation	Explanation
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
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

Abbreviation	Explanation
PDC	Platinum Doublet Chemotherapy
PET	Positron Emission Tomography
PFS	Progression-Free Survival as determined by investigator assessment following subsequent line therapy
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	Stable Disease
StD	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

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4. Summary

4.1 Indication and intervention

Osimertinib is a third-generation tyrosine kinase inhibitor (TKI), which acts as an irreversible inhibitor of EGFR sensitising mutations.(1) Osimertinib selectively and irreversibly inhibits *EGFR* mutations, such as those with the Ex19del, the L858R point mutation in exon 21, and T790M, which makes osimertinib structurally and pharmacologically distinct from first- and second-generation TKIs.(2) 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 preclinical data has indicated that osimertinib is able to cross both the intact and compromised blood brain barrier.(1) 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.(3)

The approved indications in the locally advanced and metastatic setting are:

- 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

On May 28th 2021 Tagrisso was approved for:

- The 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. *Tagrisso* is indicated for EGFRm patients whose tumours have exon 19 deletions or exon 21 (L858R) mutations.

The adjuvant indication is the background for this application to Medicine Council.

4.2 ADAURA

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.(4) The first subject was enrolled on 21 October 2015. The analyses provided are based on a data cut-off date of 17 January 2020 and database lock date of 24 June 2020. The study is still ongoing, at the time of DCO, enrolment was complete and all patients had been followed for at least one year. In ADAURA, treatment is until progression or maximum 3 years.

The primary endpoint of ADAURA, DFS in patients with stage II–IIIA disease, showed a statistically significant and clinically meaningful 83% reduction in the risk of disease recurrence or death for patients randomised to osimertinib, compared with patients randomised to placebo (hazard ratio [HR] 0.17; 99.06 % confidence interval (CI): (0.11, 0.26); p<0.001).(2) This result was consistent across prespecified exploratory subgroups. Furthermore, in the overall population (stage IB–IIIA patients), a statistically significant and clinically meaningful 80% reduction in the risk of disease recurrence or death was observed for patients treated with osimertinib vs placebo (HR 0.20; 95% CI 0.15, 0.27; p<0.0001).(1, 2)

OS was the secondary endpoint of the ADAURA trial, and OS results were immature at the time of the initial analysis (5.3% maturity reached in the stage II–IIIA population).(2) However, OS data so far suggest that in patients with stage II–IIIA NSCLC, osimertinib treatment may provide an improvement in OS, compared with placebo (25 deaths in total in the stage II–IIIA population; 8 in the osimertinib arm and 17 in the placebo arm).

The safety profile of osimertinib was consistent with previous trials and post-marketing experience of osimertinib.(1, 2) All-grade adverse events (AEs) of any cause (97.6% vs 89.2%), including Grade ≥3 AEs (20.2% vs 13.4%) and serious AEs (SAEs; 16.0% vs 12.2%). HRQoL was maintained (no clinically meaningful increase or decrease during study period) 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 short form survey-36 (SF-36), or death.

4.3 Comparator

The comparator in ADAURA is placebo with or without chemotherapy. The choice to use or not use chemotherapy was based on PI 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 4.0 in both the 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.

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]).(5)
Patients with stage IB can be eligible for adjuvant treatment if the size of the tumor is >4 cm.(6) 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.(5) Following the introduction of adjuvant chemotherapy 15 years ago, there have been no new adjuvant treatment options for patients with early stage, resectable NSCLC.(7) Current guidelines do not include targeted treatments as these(before the approval of osimertinib) have not been available/licensed in the adjuvant setting for patients with EGFRm NSCLC, following complete resection. Due to this we find the comparator arm of the ADAURA study a relevant comparator for osimertinib to evaluate it according to Danish treatment habits and guidelines. Due to the availability of a direct comparative study, we have not performed a Systematic Literature Search.

4.4 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 a Danish clinical expert. (1, 2) 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 130 093 per QALY gained. In comparison to active monitoring, osimertinib was found to be cost effective in Denmark, with incremental cost on 353 244 DKK and incremental QALY on 2.72 QALYs as well as 3.33 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 100% probability of being cost-effective at a willingness-to-pay of 600,000 DKK.

Overall Conclusion

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; patients and investigators remain blinded to individual treatment allocations, therefore future results will still come from a sufficiently blinded clinical trial.
The primary endpoint of ADAURA, DFS in patients with stage II–IIIA disease, showed a statistically significant and clinically meaningful 83% reduction in the risk of disease recurrence or death for patients randomised to osimertinib, compared with patients randomised to placebo (hazard ratio [HR] 0.17; 99.06% confidence interval [CI] 0.11, 0.26; p<0.001). This result was consistent across prespecified exploratory subgroups. Furthermore, in the overall population (stage IB–IIIA patients), a statistically significant and clinically meaningful 80% reduction in the risk of disease recurrence or death was observed for patients treated with osimertinib vs placebo (HR 0.20; 95% CI 0.15, 0.27; p<0.0001).
Additionally, an exploratory analysis of CNS recurrences demonstrated a clinically meaningful 86% (stage II–IIIA patients) and 82% (overall population) reduction in the risk of CNS disease recurrence or death in the osimertinib arm compared to placebo.
HRQoL was maintained (no clinically meaningful increase or decrease during study period) 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 short form survey-36 (SF-36), or death.

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.

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.(8) 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).(9) 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.(10) Adenocarcinoma is the most common form of NSCLC, accounting for approximately 40% of lung cancers.(11, 12) 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. (13) 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%.(14) Annually, 4820 patients are diagnosed with lung cancer in Denmark according to the most recent numbers from the Danish Lung Cancer Registry.(15)

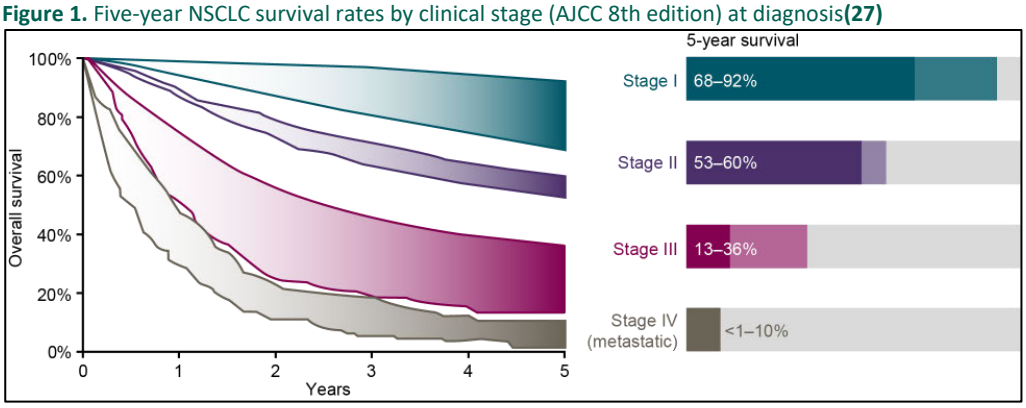
Lung cancer symptoms

Early stage NSCLC is often asymptomatic and patients are therefore at risk of delayed diagnosis, which impacts cure rates and survival.(16-19) 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.(18) As a consequence approximately 70% of NSCLC patients will be diagnosed with unresectable, advanced NSCLC.(20-22)

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.(23-25) The overall five-year survival rate for NSCLC (all stages) is 16% in Denmark.(15) This varies by stage at diagnosis from 68%–92% for stage I NSCLC to <1%–10% for stage IV NSCLC (figure 1).(26, 27)

Figure 1. Five-year NSCLC survival rates by clinical stage (AJCC 8th edition) at diagnosis**(27)**

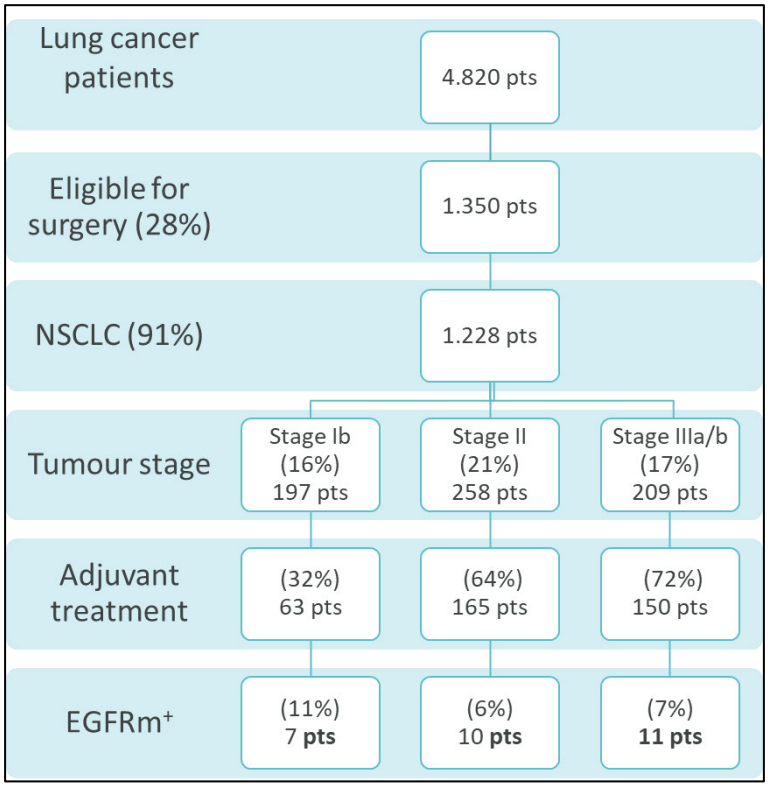


Despite the curative intent of treatment in early stages, recurrence in patients with stage IB–III NSCLC remains relatively common, regardless of post-operative chemotherapy use.(28) For patients with stage IB–IIIA NSCLC, adjuvant chemotherapy improves overall survival (OS) by ~5% and disease free survival (DFS) by ~6% after five years.(28-30) 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).(28)

Common sites of distant recurrence for NSCLC include the brain, lung, bone and liver.(31) 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.(31) Brain metastases are likely to contribute to the poor survival seen in patients with NSCLC and comprises a substantial symptom burden.(32, 33)
The Expected patient numbers for adjuvant Osimertinib treatment in Denmark are 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 from 2018.(15) 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)

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 since there until May 2021 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).

Characteristics all pts					
	IB	IIA	IIIB	IIIA	
N(%)	302	154	378	511	
Age (median IQR)	72	73	70	70	
Sex (%) female	138(46)	67(44)	154(41)	236(46)	
Weight(average, kg) Male Female					
EGFR (%) Not tested WT EGFRm+	 185(61) 94(31) 23(7.6)	 99(64) 47(31) 8(5.2)	 238(63) 132(35) 8(2.1)	 259(51) 237(46) 15(2.9)	
Adenocarcinoma	182(60)	79(51)	192(51)	287(56)	
Chemotherapy(yes)	27(9)	21(14)	161(43)	300(59)	
Characteristics pts with EGFR test					
	IB	IIA	IIIB	IIIA	
EGFRm+ (%)	23(20)	8(14.5)	8(5.7)	15(6)	

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 included 195 EGFRm patients.(34, 36). There was an overall prevalence of 8% EGFRm in the stage IB-IIIA NSCLC cohort.(34, 36) 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.(34, 36) 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(35) was between 8-14% and for the EGFRm patients it was 8%. In the ADAURA trial the occurrences of CNS metastasis in the placebo arm was 9.6% (n=39/343) compared to 1.8% (n=6/339) in the osimertinib arm.

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(34)				[redacted]
	N (%)	**EGFRm (n=195)**	**Negative (n=2,273)**	**EGFRm(54)**
Sex	Female	138 (71)	1264 (56)	[redacted]
Age, years	<60 60-69 70-79 >80	28(14) 56(29) 77(39) 34(17)	348(15) 188(8) 591(26) 821(36)	[redacted]
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)	[redacted]
Smoking	Pack-years, median (Q1-Q3)	10 (0-30)	40 (25-50)	
CNS metastasis(yes)				[redacted]
Chemotherapy(no)				[redacted]

[redacted]

Disease-free survival for danish EGFRm+ patients

[redacted] In ADAURA, the median DFS was not calculable for the Osimertinib arm (95% CI, NR-NR) and 27,5 (95% CI, 22,0-35,0 months) months in the placebo group, which gave a Hazard ratio for disease recurrence or death by 0,2 (99,12% CI, 0,14-0,30) P<0,001.

[redacted]

[redacted]

[redacted]) DFS was calculated as time from first visit until disease detection following surgery or disease progression in cohort that was not offered surgery.

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. At the time of the unplanned data cutoff time point a median OS was not reached for the Osimertinib group and the placebo group had a median OS of 48,2 months (around 4 years).

[redacted]

[redacted]

Representation of the Danish target population in ADAURA

This application has included the expected annual number of danish patients that are expected to be eligible for adjuvant Osimertinib treatment in figure 2, the characteristics early stage resected NSCLC patients with EGFRm and the PFS and OS of the danish target population. 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 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 female 63 year old Asian. Of note, A subgroup DFS analysis between Asians and non-asians showed no difference in risk for cancer relapse or death (Figure9). 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. To our knowledge Aarhus University Hospital (AUH) is the only danish hospital that routinely has tested resectable NSCLC patients since 2018. Hence, we included retrospective data from AUH (35) to be included in table 1+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. As a consequence, the DFS, PFS and OS data from ADAURA are immature. In figure 3 the median DFS of danish patients is estimated from resected NSCLC treated at AUH.(35) The

37,8 months DFS from first visit in the early stage NSCLC danish patients(728 pts) are not directly comparable to the 27,5 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 better than the 4 years observed in the placebo group in ADAURA(343 pts). The OS and DFS data illustrates the medical need for additional treatment in this patient group. 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(13, 37)

Year	2016	2017	2018	2019	2020
Incidence in Denmark	4750	4864	4916	4889	NA
Incidence in Denmark NSCLC	4040	4135	4180	4160	NA
Prevalence in Denmark	11223	12031	12974	13730	NA
Global prevalence *	NA*	NA	NA	NA	NA

*Due to difference I prevalence of EGFR it is not possible calculated exact global numbers. Zhang *et al.* performed a systematic literature review (SLR) and meta-analysis, and identified that the prevalence of *EGFR* mutations varied globally; with higher prevalence reported in Asia (38.4% [95% CI 36.5%, 40.3%]), followed by North and South America (24.4% [22.1, 26.8]) and Europe (14.1% [12.7%, 15.5%]).

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

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	28	28	28	29	29

Source: see figure 2 for patient journey

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) stage I–IIIA disease, and is typically considered resectable and therefore potentially curable.(16) 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.(38, 39) 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.(28, 40-42) Targeted therapies in the early setting may improve survival as they have in metastatic disease.(43) The cornerstone of treatment for patients with resectable NSCLC is surgical removal of the tumour, which aims to achieve complete resection.(6, 16, 44) Patients in Denmark with stage I-II are recommended for surgical resection if they do not have any medical contraindications.(6) 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.(6) In Denmark, 28% of all lung cancers are treated with curative intended surgery.(15)

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]).(5)
Patients with stage Ib can be eligible for adjuvant treatment if the tumor is >4 cm.(6) 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.(5)
Following the introduction of adjuvant chemotherapy 15 years ago, there have been no new treatment options for patients with early stage, resectable NSCLC.(7) 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.(1) 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.(2) This is further supported by clinical trial data from FLAURA, a Phase III RCT comparing osimertinib with gefitinib or erlotinib EGFR-TKIs.(3) Osimertinib is already indicated for the treatment of patients with locally advanced or metastatic NSCLC with activating *EGFR* mutations.(1, 45) 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%]).(1, 2) The increased use of chemotherapy in later stages is also reflected in data from Denmark.(35)

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. Beside 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 dose 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.(1)
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.(1)

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.(1)
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.(1)

EGFR test

In the ADAURA patient 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 Tagrisso 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 osimeritnib in and 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 treatment options are currently

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 comparing study of osimertinib vs current standard(placebo) is available(ADAURA). 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.

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	ADAURA	NCT02511106	Start: 21 Oct 2015 Est. 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

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

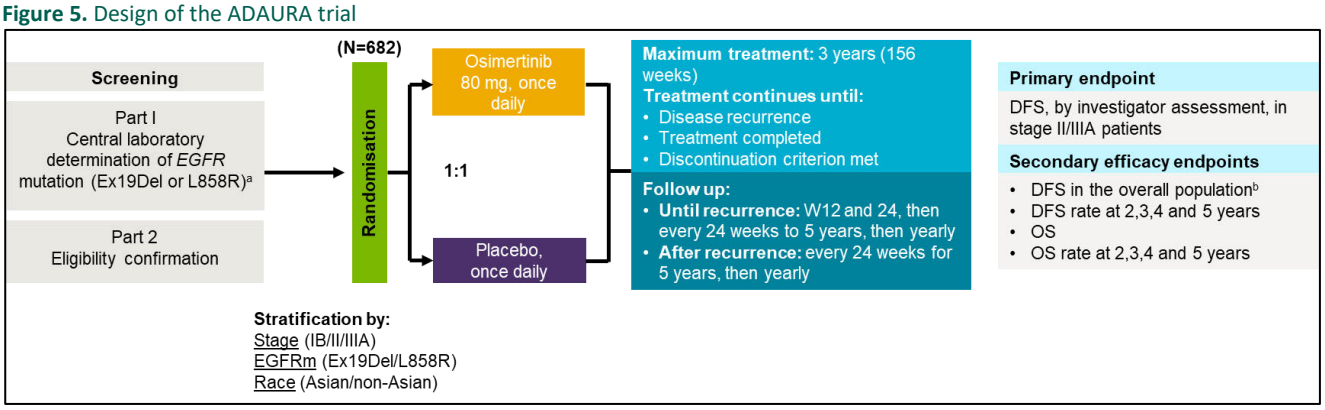
7. Efficacy and safety

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.(2, 46)

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) osimertinib tablet, OD
- **Placebo:** placebo tablet, OD

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 highest rate of recurrence in NSCLC is seen within the first 2–3 years after complete tumour resection, therefore it was deemed reasonable to aim for at least 2–3 years of treatment duration in this setting.(2) (47)
Randomisation of patients to each study arm was stratified by the following demographics:

- 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.(47)
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.(47)
Recurrence was categorised 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.(46, 47)

Patient disposition

Patient disposition in the ADAURA study is summarised in figure 6 **Error! Reference source not found.**. 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.(2)
At the DCO (17th January 2020), of the 680 patients who received study treatment, 205/337 (60.8%) patients in the osimertinib arm and 136/343 (39.7%) patients in the placebo arm remained on treatment.(2)

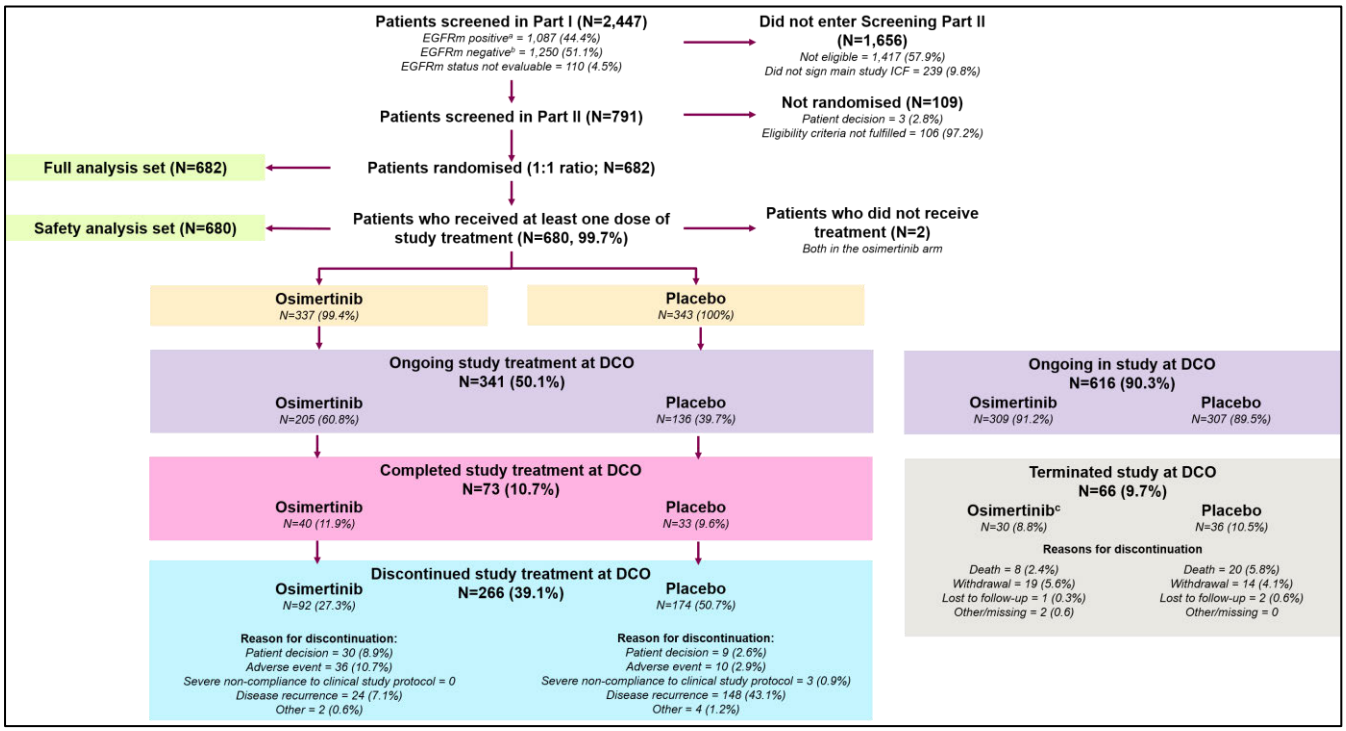
- A higher proportion of patients in the osimertinib arm (40/337, 11.9%) had completed the 3 years of study treatment than patients in the placebo arm (33/343, 9.6%)

- A total of 92/337 (27.3%) patients in the osimertinib arm discontinued osimertinib, and 174/343 (50.7%) patients in the placebo arm discontinued placebo
    - In the osimertinib arm, the most common reason for discontinuation of study treatment was AEs (36/337; 10.7%), whereas in the placebo arm disease recurrence was the most common reason for discontinuation (148/343; 43.1%)

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.(2, 48)
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.
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%]).(2)

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).(2)

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

7.1.2 Efficacy and safety – ADAURA

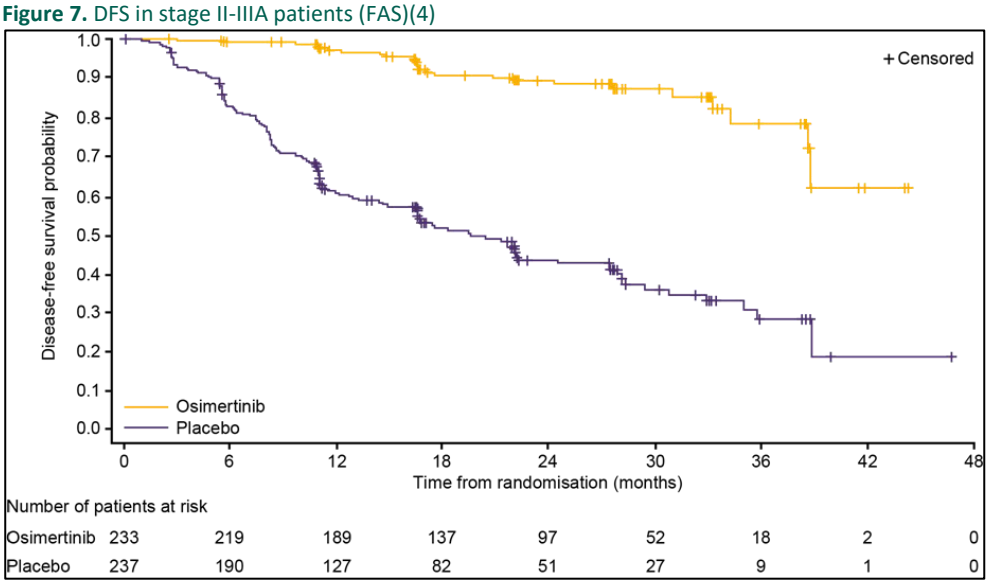
DFS in patients with stage II–IIIA NSCLC(Primary endpoint)

The overwhelming efficacy observed in ADAURA led to a recommendation from an IDMC to unblind ADAURA two years earlier than planned. As such, at the DCO 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.(2)
Even at this level of data immaturity and relatively short follow-up, osimertinib already demonstrated a statistically significant and clinically meaningful improvement in DFS for patients with stage II–IIIA NSCLC compared with placebo (figure 7, table 6).

- An 83% reduction in risk of disease recurrence or death was observed for patients in the osimertinib arm compared with the placebo arm (median DFS: osimertinib KM estimate not reached, placebo 19.6 months; HR 0.17; 99.06% CI 0.11, 0.26; p<0.001).(2, 48)

- Based on KM estimates, the percentage of patients who remained disease-free in the osimertinib arm was 97.2% at 12 months, 89.5% at 24 months, and 78.3% at 36 months, compared with 60.8%, 43.6% and 27.9% of patients in the placebo arm, respectively.(2)

Figure 7. DFS in stage II-IIIA patients (FAS)(4)



Footnotes: *The DFS rate at 36 months should be interpreted with caution due to the impact of censoring and the low number of patients at risk at this timepoint (18 patients in the osimertinib arm, 9 patients in the placebo arm).*

Table 6. mDFS stage II–IIIA patients (FAS)(2, 48)

		Osimertinib (N=233)	Placebo (N=237)
Events, n (%), 33.2% maturity[a]		26 (11.2)	130 (54.9)
Median DFS, months (95% CI)		NR (38.8, NC)	19.6 (16.6, 24.5)
HR[b] (99.06% CI;[c] p-value)		0.17 (0.11, 0.26; p<0.001)	

Footnotes: *[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. 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.{SELLKE, 1983 #91} 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, based on the O'Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis.*

DFS in the overall population (stage IB–IIIA patients)

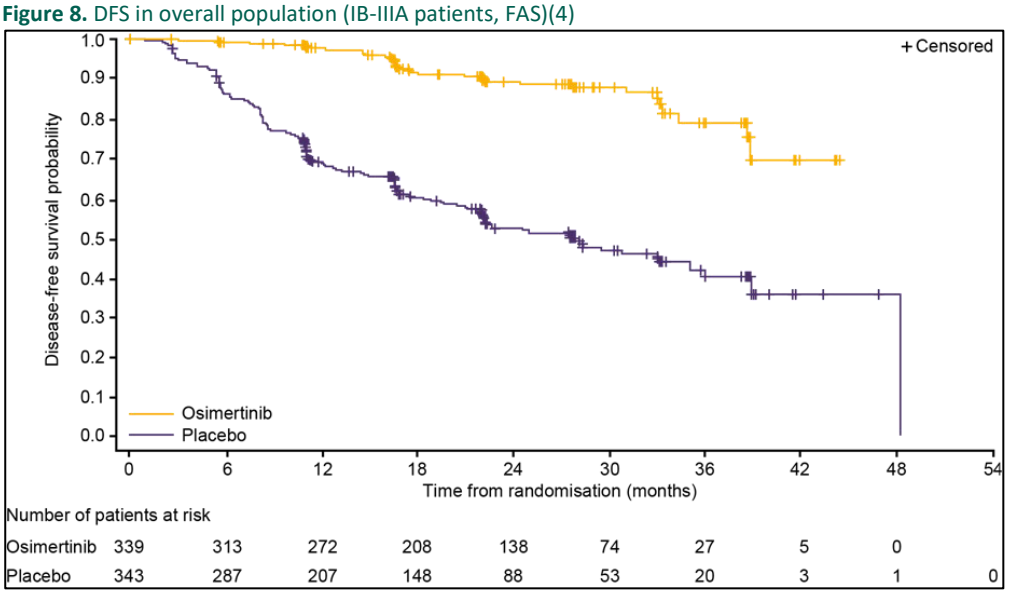
In the overall study population, 37 (10.9%) patients in the osimertinib arm and 159 (46.6%) patients in the placebo arm had experienced a DFS event at the DCO of the primary analysis. Median follow-up for DFS in all patients was 22.1 months in the osimertinib arm vs 16.6 months in the placebo arm; the majority of patients (99.1%) in the overall study population experienced at least 1 year of follow-up, with 65.1% having at least 2 years of follow-up, and 19.5% having at least 3 years of follow-up.(2)

Osimertinib demonstrated a statistically significant and clinically meaningful improvement in DFS for the overall FAS population (stage IB–IIIA patients) treated with osimertinib compared with placebo (figure 8, table 7)

- An 80% reduction in risk of disease recurrence or death was observed for patients in the osimertinib arm vs the placebo arm (median DFS: osimertinib KM estimate not reached, placebo 27.5 months; HR 0.20; 95% CI 0.15, 0.27; p<0.0001)(2, 48)

- Based on KM estimates, the percentage of patients who remained disease-free in the osimertinib arm was 97.4% at 12 months, 89.1% at 24 months, and 78.9% at 36 months, compared with 68.5%, 52.4% and 40.0% of patients in the placebo arm, respectively(2)

Figure 8. DFS in overall population (IB-IIIA patients, FAS)(4)



Footnotes: *The DFS rate at 36 months should be interpreted with caution due to the impact of censoring and the low number of patients at risk at this timepoint (27 patients in the osimertinib arm, 20 patients in the placebo arm).*

Table 7. DFS in overall population (stage IB–IIIA patients,FAS)(2, 48).

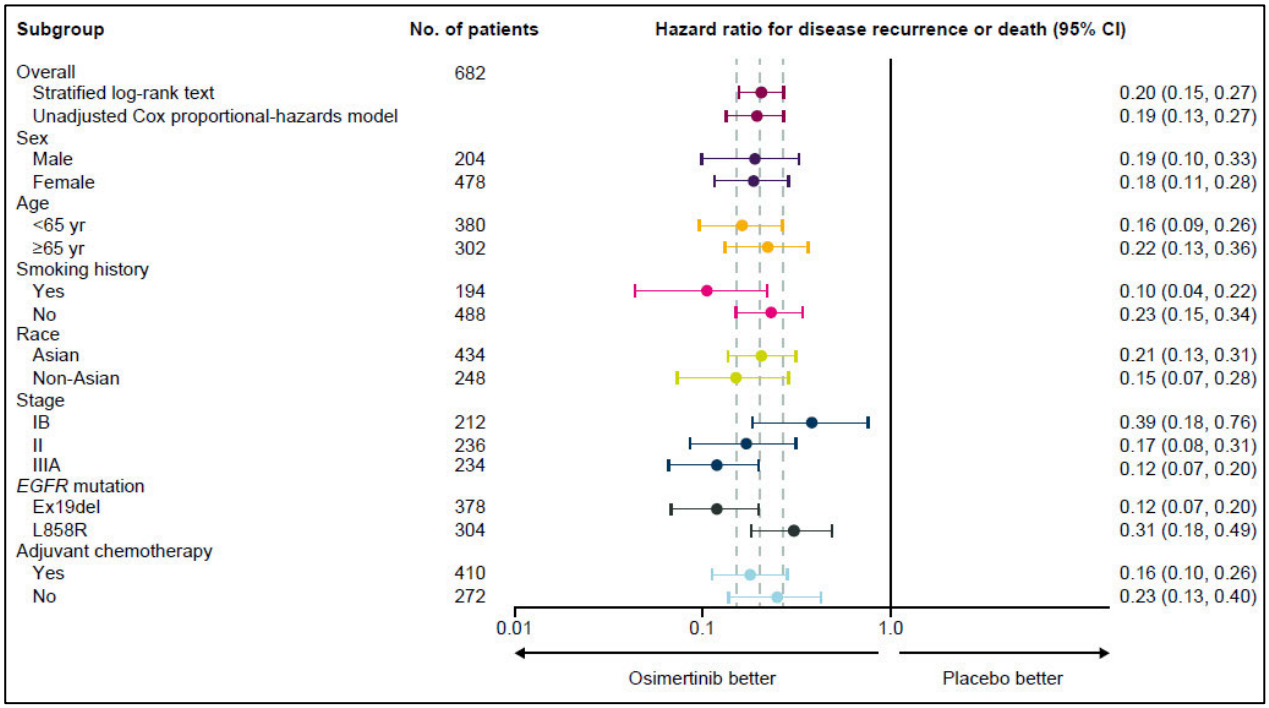
	Osimertinib (N=339)	Placebo (N=343)
Events, n (%), 28.7% maturity[a]	37 (10.9)	159 (46.4)
Median DFS, months (95% CI)	NR (NC, NC)	27.5 (22.0, 35.0)
HR (95% CI; 99.12% CI;[b] p-value)	0.20 (0.15, 0.27; 0.14, 0.30; p<0.0001)	

Footnotes: *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. 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 (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. The HR and CI are obtained from the U and V statistics (Berry, et al., 1991; Selke & Siegnumd, 1983).* [b]*The adjusted CI is computed at the 2-sided 99.12% level, considering a 2-sided significance level of 0.0088 for the interim analysis, based on the O'Brien and Fleming spending function, assuming 317 DFS events for the final analysis.*

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 (figure 9).(2, 48) Considering the subgroup analysis by 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 0.39 (95% CI 0.18, 0.76) indicating the high efficacy of osimertinib in these patients, despite their relatively good prognosis.(2)

Figure 9. Subgroup analysis of DFS (FAS)(4)



Footnotes: *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) are available in the CSR:

- 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 CSR for further details.(2)

Secondary endpoints

Overall survival in stage II–IIIA patients (interim analysis)

At the time of the DCO, OS data in the stage II–IIIA population had reached 5.3% maturity, with only 25 deaths occurring overall. Median follow-up for OS in stage II–IIIA patients was 26.1 months in the osimertinib arm vs 24.6 months in the placebo arm.(2)

Initial immature data suggest that, in patients with stage II–IIIA NSCLC, osimertinib treatment provides an improvement in OS, compared with placebo (figure 10, table 8)

- The HR for an OS event in patients with stage II–IIIA NSCLC was 0.40 (95% CI 0.18, 0.89; p=0.0244), indicating a 60% reduction in risk of death for patients treated with osimertinib vs placebo, although this did not reach statistical significance(2)

- Based on KM estimates, the percentage of patients who remained alive in the osimertinib arm was 100.0% at 24 months, and 91.7% at 36 months, compared with 92.6% and 89.0% of patients in the placebo arm, respectively(2)

Figure 10. OS in stage II–IIIA patients (FAS)(2)

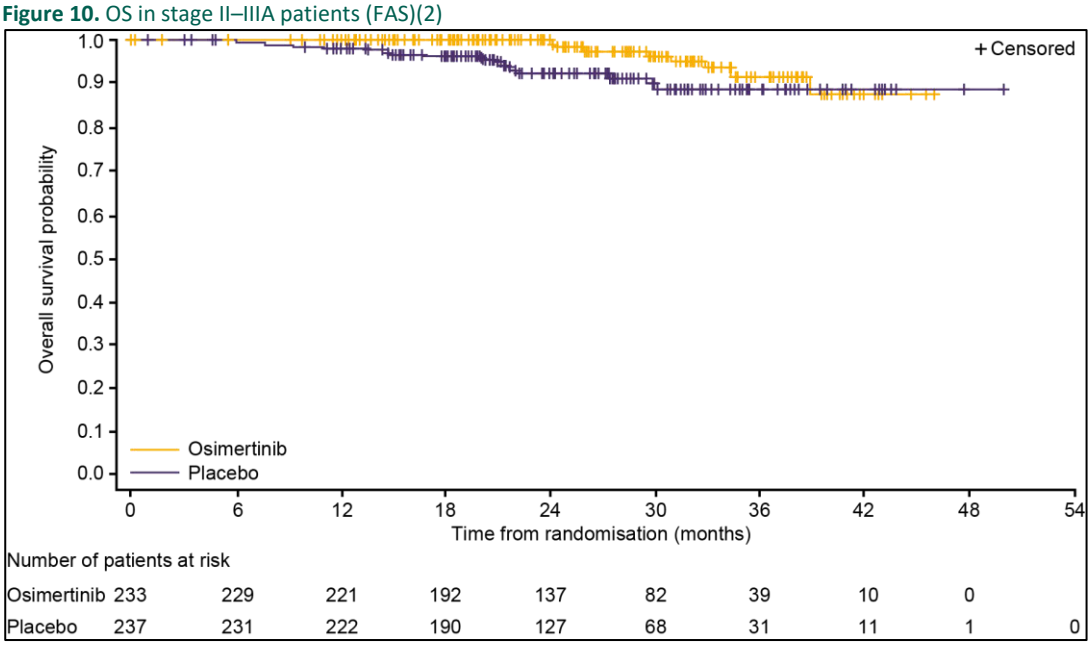


Table 8. OS in stage II-IIIA patients (FAS)(2, 48)

	Osimertinib (N=233)	Placebo (N=237)
Events, n (%), 5.3% maturity[a]	8 (3.4)	17 (7.2)
Median OS, months (95% CI)	NR (NC, NC)	NR (NC, NC)
HR (95% CI; 99.98% CI;[b] p-value)	0.40 (0.18, 0.89; 0.09, 1.83; p=0.0244)	

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.{SELLKE, 1983 #91}[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)

As OS did not reach statistical significance in the primary population (stage II–IIIA NSCLC), the OS analysis in the overall population is regarded as exploratory. At the time of the DCO, OS data in the overall population had reached 4.3% maturity, with only 29 events reported, and the majority of patients were still in survival follow up (616 patients) [90.3%] overall: 309 patients [91.2%] in the osimertinib arm, and 307 patients [89.5%] in the placebo arm).(2)
Median follow-up for OS in all patients was 26.1 months in the osimertinib arm vs 25.9 months in the placebo arm.(2)
Initial data suggest that, in all patients, osimertinib treatment provides a clinically meaningful improvement in OS, compared with placebo (figure 11, 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(2)
- 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(2)

Figure 11. OS in overall population (stage IB–IIIA patients, FAS)**(**2)

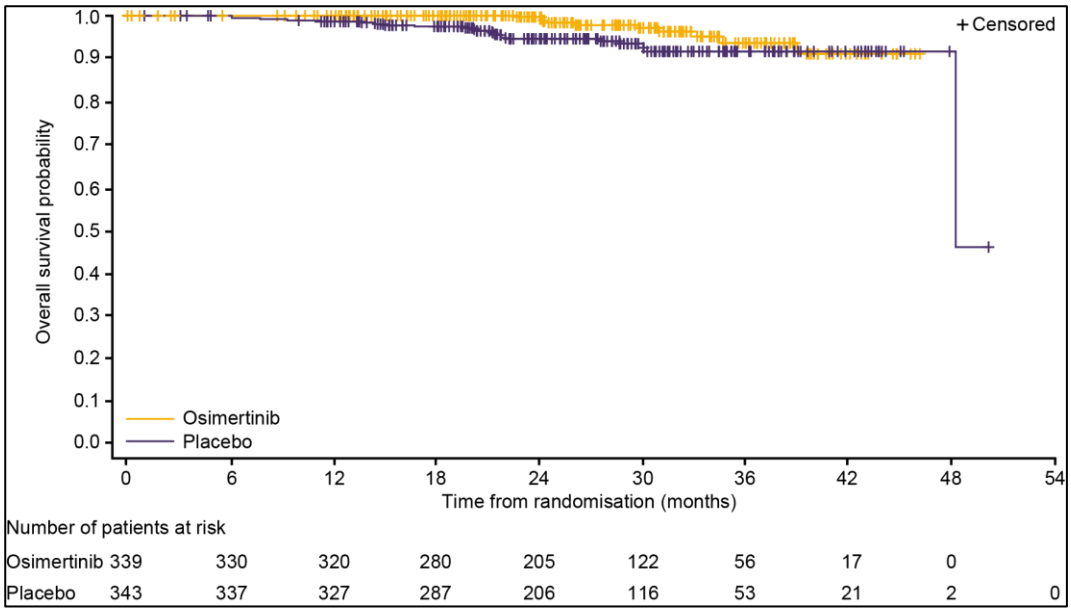


Table 9. OS in overall population (stage IB–IIIA patients (FAS)(2, 48)

	Osimertinib (N=339)	Placebo (N=343)
Events, n (%), 4.3% maturity[a]	9 (2.7)	20 (5.8)
Median OS, months (95% CI)	NR (NC, NC)	48.2 (48.2, NC)
HR (95% CI; 99.98% CI;[b] p-value)	0.48 (0.23, 1.02; 0.12, 1.98; p=0.0553)	

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.*

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 10.

In stage II–IIIA patients, 11.2% of patients treated with osimertinib and 54.9% of patients treated with placebo experienced a disease recurrence event or death by the DCO.(2, 48) In the osimertinib arm, the most frequent site of disease recurrence was local/regional only (7.3%), whereas in the placebo arm, distant recurrence occurred most frequently (28.3%). The minority of patients experiencing a disease recurrence event had both local/regional and distant recurrence (osimertinib: 0.4%; placebo: 5.9%).(2, 48)

Similar results were observed in the overall study population, where 10.9% of osimertinib-treated patients, and 46.4% of placebo-treated patients, experienced a disease recurrence event or death by the DCO.(2, 48) As for the stage II–IIIA population, in the osimertinib arm, the most frequent site of disease recurrence was local/regional only (6.8%), whereas in the placebo arm, distant recurrence only occurred most frequently (22.7%).

Table 10. Disease recurrence status at time of DCO (FAS)(2, 48)

	Osimertinib	Placebo
Stage II–IIIA patients	**N=233**	**N=237**
Total disease recurrence or death	26 (11.2)	130 (54.9)
Disease recurrence	26 (11.2)	129 (54.4)
Local/regional only	17 (7.3)	48 (20.3)
Distant only	8 (3.4)	67 (28.3)
Local/regional and distant	1 (0.4)	14 (5.9)
Death[a]	0	1 (0.4)
Overall population (stage IB–IIIA patients)	**N=339**	**N=343**
Total disease recurrence or death	37 (10.9)	159 (46.4)
Disease recurrence	37 (10.9)	157 (45.8)
Local/regional only	23 (6.8)	61 (17.8)
Distant only	10 (2.9)	78 (22.7)
Local/regional and distant	4 (1.2)	18 (5.2)
Death[a]	0	2 (0.6)

Footnotes: *[a]Death in the absence of disease recurrence.*

Time to first and second subsequent anti-cancer therapies

At the time of the DCO, time to first subsequent therapy (TFST) had reached 24.2% maturity. Median TFST was not calculable in the osimertinib arm, and 39.8 months in the placebo arm; the HR point estimate favoured osimertinib (table 11).(2)

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 11).(2)

A summary of the different classes of anti-cancer therapies received is shown in table 12. Protein kinase inhibitors were the most frequently received subsequent anti-cancer therapies.

Table 11. Time to first and second subsequent anti-cancer therapies (overall population, FAS)(2)

	Osimertinib (N=339)	Placebo (n=343)
TFST		
Events, n (%), 24.2% maturity	31 (9.1)	134 (39.1)
Death	1 (3.2)	9 (6.7)
First subsequent cancer therapy	30 (96.8)	125 (93.3)
Median TFST, months (95% CI)	NC (NC, NC)	39.8 (30.8, NC)
HR (95% CI; p-value)	0.20 (0.14, 0.27; p<0.0001)	
TSST		
Events, n (%), 10.4% maturity	15 (4.4)	56 (16.3)
Death	6 (40.0)	14 (25.0)
Second subsequent cancer therapy	9 (60.0)	42 (75.0)
Median TSST, months (95% CI)	NC (43.2, NC)	48.2 (48.2, NC)
HR (95% CI; p-value)	0.25 (0.16, 0.41; p<0.0001	

Table 12. Summary of first and second subsequent anti-cancer therapies (overall population, FAS)(2)

	Osimertinib (N=339)	Placebo (n=343)
First subsequent anti-cancer therapy		
Patients with first subsequent anti-cancer therapy, n (%)	39 (9.1)	125 (36.4)
All other therapeutic products	0	1 (0.3)
Bisphosphonates	0	1 (0.3)
Detoxifying agents for anti-neoplastic treatment	1 (0.3)	0
Folic acid analogues	5 (1.5)	4 (1.2)
Monoclonal antibodies	3 (0.9)	5 (1.5)
Other plant alkaloids and natural products	1 (0.3)	0
Platinum compounds	9 (2.7)	8 (2.3)
Protein kinase inhibitors	17 (5.0)	94 (27.4)
Pyrimidine analogues	3 (0.9)	1 (0.3)
Taxanes	1 (0.3)	5 (1.5)
Unspecified herbal and traditional medicine	0	2 (0.6)
Vinca alkaloids and analogues	0	1 (0.3)
Second subsequent anti-cancer therapy		
Patients with second subsequent anti-cancer therapy, n (%)	9 (2.7)	42 (12.2)
Folic acid analogues	1 (0.3)	5 (1.5)
Monoclonal antibodies	3 (0.9)	2 (0.6)
Other drugs affecting bone structure and mineralisation	0	1 (0.3)
Platinum compounds	1 (0.3)	9 (2.6)
Podophyllotoxin derivatives	0	1 (0.3)
Protein kinase inhibitors	3 (0.9)	22 (6.4)
Pyrimidine analogues	0	1 (0.3)
Taxanes	1 (0.3)	0
Vinca alkaloids and analogues	1 (0.3)	0

At the DCO, PFS in the overall population had reached 8.7% maturity. Median PFS was not calculable in the osimertinib arm, and was 48.2 months in the placebo arm; the HR point estimate favoured osimertinib (table 13).(2)

Table 13. PFS (overall population, FAS)(2)

	Osimertinib (N=339)	Placebo (n=343)
Events, n (%), 8.7% maturity	13 (3.8)	46 (13.4)
Median PFS, months (95% CI)	NC (NC, NC)	48.2 (NC, NC)
HR (95% CI; p-value)	0.24 (0.14, 0.41; p<0.0001)	

Analysis of CNS recurrence

As osimertinib has previously shown CNS efficacy in patients treated in the advanced/metastatic setting, an exploratory analysis of CNS recurrence was performed.(2)
In the overall population, 45 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).(48) A clinically meaningful improvement in investigator-assessed CNS DFS for patients on osimertinib compared to patients on placebo based was observed (table 14):

Patients with stage II–IIIA NSCLC:

- HR of 0.14 (95% CI 0.07, 0.27; p<0.0001), indicating an 86% reduction in risk of CNS recurrence or death(2)
- Based on KM estimates, the percentage of patients who remained CNS recurrence-free at 24 months was 98.8% in the osimertinib arm vs 79.7% in the placebo arm(2)

Overall population (stage IB–IIIA patients):

- HR of 0.18 (95% CI 0.10, 0.33; p<0.0001), indicating an 82% reduction in risk of CNS recurrence or death(2, 48)
- Based on KM estimates, the percentage of patients who remained CNS recurrence-free at 24 months was 98.0% in the osimertinib arm vs 85.0% in the placebo arm(2)

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.(2)

Table 14. Summary of disease recurrence in the CNS(2, 48)

	Osimertinib	Placebo
Stage II–IIIA	**N=233**	**N=237**
Events, n (%)[a]	4 (1.7)	32 (13.5)
CNS recurrence	3 (1.3)	27 (11.4)
Death[b]	1 (0.4)	5 (2.1)
HR (95% CI; p-value)[c]	0.14 (0.07, 0.27; p<0.0001)	
Overall population (stage IB–IIIA patients)	**N=339**	**N=343**
Events, n (%)[a]	6 (1.8)	39 (11.4)
CNS recurrence[d]	4 (1.2)	33 (9.6)
Death[b]	2 (0.6)	6 (1.7)
HR (95% CI; p-value)[c]	0.18 (0.10, 0.33; p<0.0001)	

***Footnotes**: [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.{SELLKE, 1983 #91}[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

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.(2)

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.(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.(2)

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%).(2)

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:(2)

- 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(2):

- 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(2)

- 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)(2)

	Osimertinib (N=233)	Placebo (N=237)
PCS		
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)	
MCS		
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

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.(2). The duration of treatment exposure is summarised in table 16. The median duration of exposure to osimertinib was longer than the exposure to placebo (22.5 vs 18.7 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.(2)

Table 16. Duration of exposure in ADAURA (SAS)(2)

	Osimertinib (N=337)	Placebo (N=343)
Duration of osimertinib or placebo exposure		
Median treatment duration, months (range)[a]	22.5 (0, 38)	18.7 (0, 36)
Median actual treatment duration, months (range)[b]	22.2 (0, 38)	18.3 (0, 36)

Footnotes: *[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.*

Overview of AEs in ADAURA

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 (table 16) 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.(2)
The majority of patients in both study arms reported an AE (osimertinib: 97.6%; placebo: 89.2%).(2, 48) AEs of any cause, including Grade ≥3 AEs, occurred in a greater proportion of patients in the osimertinib arm, compared with the placebo arm (table 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 placebo arm; this was not causally related to treatment.(2)

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.(2)
Dose interruptions due to AEs occurred in a higher proportion of patients in the osimertinib arm (23.7%) compared with the placebo arm (10.8%). 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.(2)
Dose reductions and treatment discontinuations followed a similar trend. In the osimertinib arm:(2)

- 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 and decreased appetite (both 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

Table 17. Summary of AEs (SAS)(2, 48)

AEs	Osimertinib (N=337)	Placebo (N=343)
AEs due to any cause		
All grade AEs, n (%)	329 (97.6)	306 (89.2)
Grade ≥3 AEs, n (%)	68 (20.2)	46 (13.4)
SAEs, n (%)[a]	54 (16.0)	42 (12.2)
Deaths, n (%)	0	1 (0.3)
Dose interruptions due to AEs, n (%)	80 (23.7)	37 (10.8)
Dose reductions due to AEs, n (%)	29 (8.6)	3 (0.9)
Discontinuations due to AEs, n (%)	37 (11.0)	10 (2.9)
AEs causally related to study treatment[b]		
All grade AEs, n (%)	305 (90.5)	192 (56.0)
Grade ≥3 AEs, n (%)	32 (9.5)	8 (2.3)
SAEs, n (%)[a]	8 (2.4)	2 (0.6)
Deaths, n (%)	0	0
Discontinuations due to AEs, n (%)	31 (9.2)	5 (1.5)

Footnotes: *[a]Includes events with an outcome of death. [b]AEs assessed by investigator.*

Common AEs

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.(2)
Between treatment arms, the incidence of the AEs of diarrhoea, paronychia, dry skin, pruritus, and stomatitis were reported with an incidence of at least 10 percentage points higher in the osimertinib arm; these AEs have previously been identified as osimertinib ADRs based on a full evaluation of data across the entire clinical programme, and are therefore not unexpected.(2)

Table 18. Summary of AEs reported in ≥10% of patients in either treatment arm (SAS)(2)

MedDRA preferred term, n (%)	Osimertinib (N=337)	Placebo (N=343)
Diarrhoea	156 (46.3)	68 (19.8)
Paronychia	85 (25.2)	5 (1.5)
Dry skin	79 (23.4)	22 (6.4)
Pruritus	65 (19.3)	30 (8.7)
Cough	62 (18.4)	57 (16.6)
Stomatitis	59 (17.5)	14 (4.1)
Nasopharyngitis	47 (13.9)	35 (10.2)
Upper respiratory tract infection	45 (13.4)	35 (10.2)
Decreased appetite	44 (13.1)	13 (3.8)
Mouth ulceration	39 (11.6)	8 (2.3)
Dermatitis acneiform	37 (11.0)	16 (4.7)

Footnotes: *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 22.1.*

Grade ≥3 AEs

Overall, the proportion of patients who had a Grade ≥3 AE was low in both treatment arms (osimertinib: 20.2%; placebo: 13.4%), 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 and pneumonia in the osimertinib arm, and pneumonia and hypertension in the placebo arm.(2)

A total of 32 patients (9.5%) had Grade ≥3 AEs considered by the investigator to be causally related to osimertinib treatment, with paronychia, stomatitis, diarrhoea, ECG QT prolonged and decreased appetite being reported as causally related in ≥2 patients. These AEs (with the exception of decreased appetite) are well characterised osimertinib ADRs and are consistent with the known osimertinib safety profile, and were therefore not unexpected.(2)

Table 19. Summary of Grade ≥3 AEs reported in ≥2 patients in either treatment arm (SAS)(2, 48)

MedDRA preferred term, n (%)	Osimertinib (N=337)	Placebo (N=343)
Patient with any Grade ≥3 AE	68 (20.2)	46 (13.4)
Diarrhoea	8 (2.4)	1 (0.3)
Stomatitis	6 (1.8)	0
Pneumonia	4 (1.2)	4 (1.2)
Paronychia	3 (0.9)	0
Hypertension	3 (0.9)	4 (1.2)
Electrocardiogram QT prolonged	3 (0.9)	1 (0.3)
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)

Footnotes: *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 22.1; CTCAE version 4.03.*

Serious AEs

SAEs were reported in 16.0% of osimertinib-treated patients and 12.2% of placebo-treated patients (table 20), with pneumonia being the most commonly reported SAE in both treatment arms.(2)

Table 20. SAEs reported in ≥2 patients in either treatment arm (SAS)(2)

MedDRA preferred term, n (%)	Osimertinib (N=337)	Placebo (N=343)
Patient with any SAE	54 (16.0)	42 (12.2)
Pneumonia	5 (1.5)	4 (1.2)
Cataract	3 (0.9)	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)

Footnotes: *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 22.1.*

AEs of special interest

AEs of special interest for osimertinib, which are AEs considered to be potential risks associated with osimertinib treatment, are summarised in table 21. 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 3.6% of patients treated with osimertinib and 2.9% of patients treated with placebo.(2)

Table 21. AEs of special interest for osimertinib(2)

AEs, n (%)	Osimertinib (N=337)	Placebo (N=343)
Interstitial lung disease[a]	10 (3.0)	0
Interstitial lung disease	8 (2.4)	0
Pneumonitis	2 (0.1)	0
Cardiac failure	16 (4.7)	10 (2.9)
Ejection fraction decreased	12 (3.6)	10 (2.9)
Cardiac failure	1 (0.3)	0
Pulmonary oedema	1 (0.3)	0
Cardiac myopathy	2 (0.6)	0

Footnotes: *[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 CSR).(2)*

Deaths

Overall, 9 (2.7%) patients treated with osimertinib and 20 (5.8%) patients treated with placebo died at DCO (table 22); the majority of these occurred post-disease recurrence. The majority of deaths were due to NSCLC, and not reported as AEs. There was one fatal AE, in the placebo arm, which was also related to the underlying disease.(2)

Table 22. All deaths in ADAURA (FAS)**(2, 48)**

	Osimertinib (N=339)	Placebo (N=343)
Total number of deaths, n (%)	9 (2.7)	20 (5.8)
Death due to NSCLC only	9 (2.7)	18 (5.2)
AE with outcome of death only	0	0
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]	0	1 (0.3)

Footnotes: *Death related to NSCLC is determined by the investigator; [a]Patients who died and are not captured in the earlier categories.*

Conclusions

Following recommendation from an IDMC 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). ADAURA is the first global trial of a targeted therapy to show statistically significant and clinically meaningful benefit in the adjuvant treatment of early stage NSCLC.
In the primary analysis, ADAURA demonstrated a highly statistically significant and clinically meaningful 83% 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 0.17; 95% CI 0.12, 0.23; p<0.0001); similarly, in the overall population, a highly statistically significant and clinically meaningful 80% 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 0.20; 95% CI 0.15, 0.27; p<0.0001). 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 although the OS data were only 4.3% mature at the time of this current analysis, they already suggest an improvement in OS in patients treated with osimertinib compared to placebo. Further analyses of OS will be completed at later timepoints when the data are suitably mature to draw conclusions.
In addition to achieving unprecedented DFS efficacy in this setting, 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, an exploratory analysis of CNS recurrences demonstrated a clinically meaningful 86% and 82% reduction in the risk of CNS disease recurrence or death in the osimertinib arm compared to placebo for both stage II–IIIA patients (HR 0.14; 95% CI 0.07, 0.27; p<0.0001) and the overall population (HR 0.18; 95% CI 0.10, 0.33; 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. 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.
The ADAURA study was a robust, double-blinded, randomised, placebo-controlled trial that was prospectively designed to reduce the risk of bias and conducted to a high standard, investigating the addition of osimertinib to the current standard of care. Conducting the primary analysis two years ahead of schedule introduces limitations related to the maturity of data and the fact that the minority (19.5% in the overall population) of patients had had the opportunity to receive the planned study treatments for three years, potentially impacting the complete characterisation of benefit for the planned three-year treatment duration. However, the results of the current analysis provide robust data to support a benefit-risk assessment of long-term treatment with osimertinib in the adjuvant setting, as more than half of the overall study population had had the opportunity for at least 2 years of follow up (65% of patients), and 61% of patients in osimertinib arm were continuing on study treatment at the time of the primary DCO.

In ADAURA, patient demographics and baseline characteristics were well balanced between the study arms, and the intended population of patients with stage IB–IIIA, EGFRm NSCLC who had undergone complete tumour resection was enrolled. Patient characteristics for the overall study population were consistent with the expected demographic and patient characteristics of an EGFRm NSCLC adjuvant population; for example, the proportion of patients who had

received platinum-based adjuvant chemotherapy before randomisation was aligned with the expected use based on treatment guidelines.
Overall, the benefit-risk balance for the long-term use 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.

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

7.1.3 Comparative analyses of efficacy and safety

Results from the comparative analysis

This application is based on one direct comparative study and no information is provided in this section.

7.2 Efficacy and safety of Osimertinib monotherapy as 1L treatment compared to standard of care (gefitinib or erlotinib) for patients with EGFRm locally advanced or metastatic NSCLC

7.2.1 Relevant studies

Clinical trial data from FLAURA, a Phase III RCT comparing osimertinib with gefitinib or erlotinib EGFR-TKIs, supports that Osimertinib is able to cross both the intact and compromised blood brain barrier.

7.2.2 Efficacy and safety – results per study

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.(3) The findings were consistent regardless of whether patients had known or treated CNS metastases at trial entry.(3)

7.2.3 Comparative analyses

8. Health economic analysis

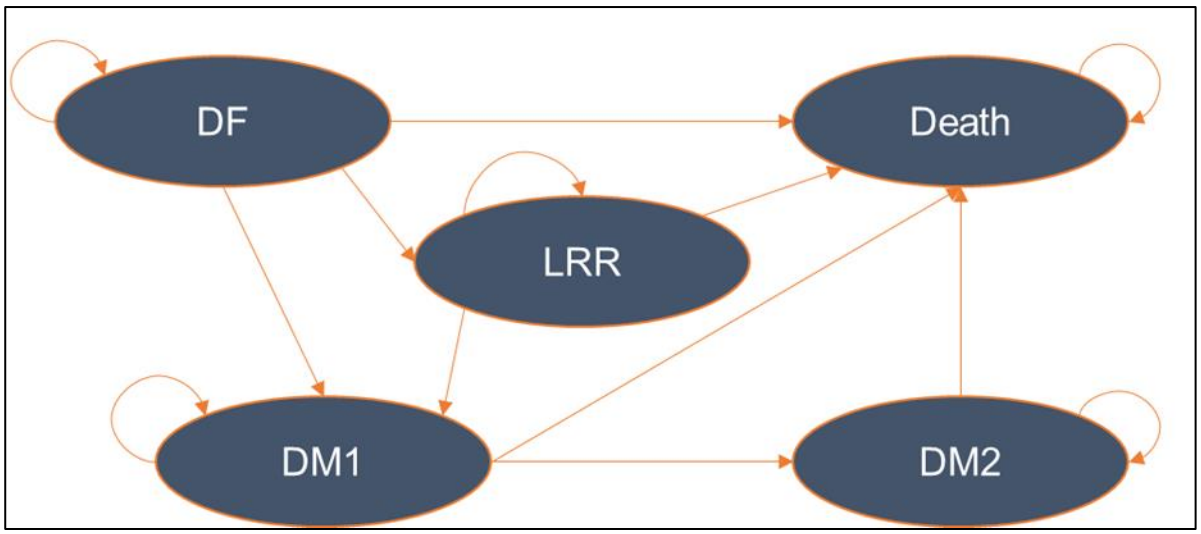
The purpose of the health economic analysis is examine the cost effectiveness of osimertinib as adjuvant treatment in comparison to active monitoring in NSCLC patients with EGFR-mutation Stage IB-IIIA who are completely tumour-resected. A cost-utility analysis was performed, comparing osimertinib with 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 populations 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 defines 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 12).
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. (49)

Figure 12. 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 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 AEs.In accordance with the Medicinraadet 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. Afterwards 2.5% discount rate was applied for the last 2 years.

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 it reflects Danish clinical practice, two clinical experts was 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 (50, 51).

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 (4% 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 (49), clinical trial FLAURA (49), database CancerLinQ (52), clinical expertise (50, 51), 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 (49)
Mean body surface area	1.70 m^2	Danish clinical expert (50, 51)
Mean body weight	65 kg	Danish clinical expert (50, 51)
Survival analysis		
DF to LR	Lognormal	ADAURA (49), FLAURA (53), CancerLinQ (52), 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	60 months	KOL (50, 51)
Active monitoring	60 months	
Cure percentage		
Osimertinib	95%	Danish clinical expert (50, 51)
Active monitoring	95%	
Adverse events – osimertinib		
Paronychia	0.9%	ADAURA (49)
Decreased Appetite	0.6%	
Diarrhoea	1.8%	
Stomatitis	1.5%	
ECG QT prolonged	0.9%	
Adverse events – Active monitoring		
Paronychia	0.0%	ADAURA (49)
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 (49)
LR	0.825	ADAURA assumption
DM1	0.794	FLAURA (53)
DM2	0.640	FLAURA (53)

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. (8) 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).(9) (11, 12) 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.(13) According to a larger danish cohort from RWE data from 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.(16-19)

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).(5)
However, despite the curative intent of treatment, recurrence in patients with stage IB–III remains relatively common regardless of post-operative chemotherapy. (28) (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, these 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 patients with histologically or cytologically confirmed *EGFR*-mutated stage IB-IIIA NSCLC, 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.(50, 51) 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 lung cancer patients in Denmark are slightly younger than in the ADAURA trial, 60 vs 63 years of age, according to the clinical expert.(50, 51) 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.(54) 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. (51)	Used in the model	Danish clinical practice (50)
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.(54) 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.(9, 50, 51, 53) 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.(49)

Intervention in the clinical documentation submitted:

The key clinical documentation in this health economic assessment is the pivotal trial ADAURA.(49) See 6 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.(9, 50, 51, 53) In the model treatments were administered according to treatment cycles of 21 days. Osimertinib (80 mg) was administered orally once daily. Posology of the intervention are based on ADAURA .
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 (50, 51)
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 a Danish clinical expert.(50, 51)
The most relevant comparator for the osimertinib in Denmark is active monitoring which is in line with Danish treatment guidelines.(55)

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) (49, 52, 53).
The Danish treatment guidelines for lung cancer describe the goal of adjuvant treatment of stage I-II lung cancer as curative.(55) Both DFS and OS as well as safety and quality of life were main endpoints in the ADAURA (49) 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: median not reached Active monitoring: 27.5 months	Osimertinib: 159 months Active monitoring: 24 months
Secondary endpoint: **Overall-survival (OS)**	Median not reached	Median not reached

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.(49) 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.(49) 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 (49)	ADAURA (49)

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

	Setting	Data source
TP1: DF -> LRR	Lognormal	ADAURA (49)
TP2: DF -> 1L DM	Generalized gamma	ADAURA (49)
TP3: DF -> Death	Background mortality	ADAURA (49) / Danish life tables(56)
TP4: LRR -> 1L DM	Lognormal	CancerLinQ
TP5: LRR -> Death	Background mortality	CancerLinQ / Danish life tables (56)
TP:6 1L DM -> 2L DM	Weibull	FLAURA (53)
TP7: 1L DM -> Death	Exponential / Background mortality	FLAURA (53)/ Danish life tables (56)
TP8: 2L DM -> Death	Weibull	FLAURA (53)/ Danish life tables (56)
Cure	100% from year 5 onwards	Danish clinical expert (50, 51)
Retreatment	80% of the osimertinib patients can be retreated	Danish clinical expert (50, 51)
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.(52) 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.(53)

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 lognormal distribution was selected for transitions from DF to LRR and the generalised gamma for DF to first-line metastatic (DM1), these survival models 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 KOLss and clinical practice

Two interviews were conducted 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.(50, 51)

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.(49) 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).(49) 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.

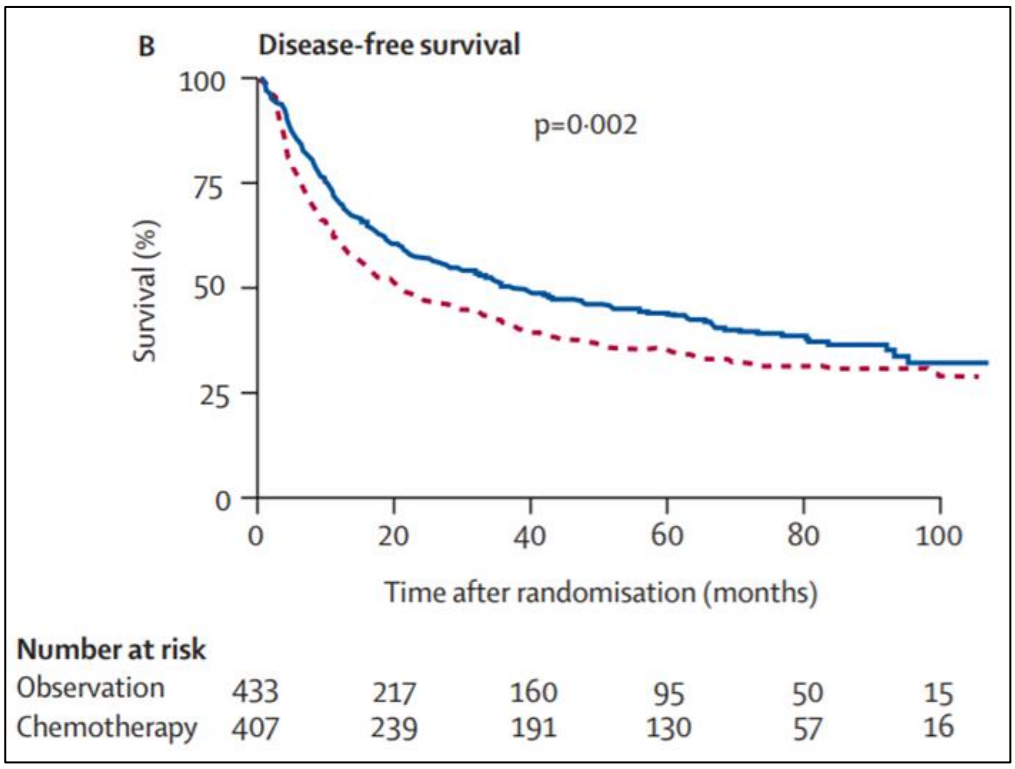
8.3.2.3 Published literature

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.(57, 58) 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 (57) . 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.(57) 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 .(57) However, regardless of treatment arm, there appeared to be a plateau in the DFS curve from approximately 48–60 months' follow-up (figure 13), 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 13. ANITA study – KM curve of disease-free survival

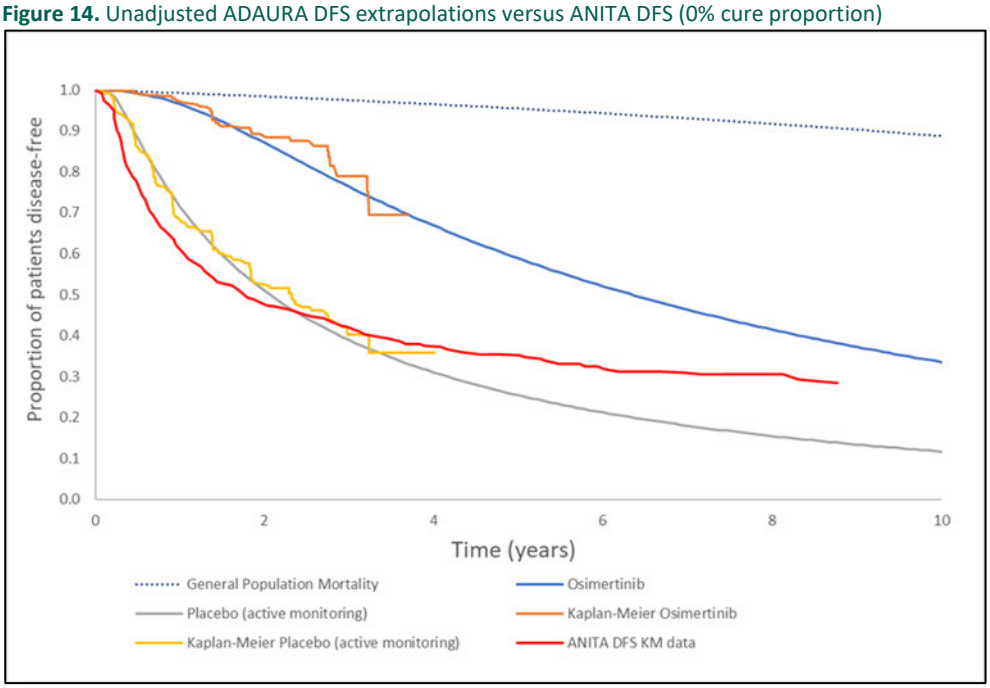


The data in the figure is extrapolated from(29)

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.(58) This dataset was extrapolated and compared alongside the best fitting combined extrapolated DFS curves from the ADAURA placebo arm (TP1 [DFS to LR]: lognormal; 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 14 below).

Applying a 0% cure proportion in the ADAURA active monitoring arm suggests that the risk of disease recurrence beyond 48 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.

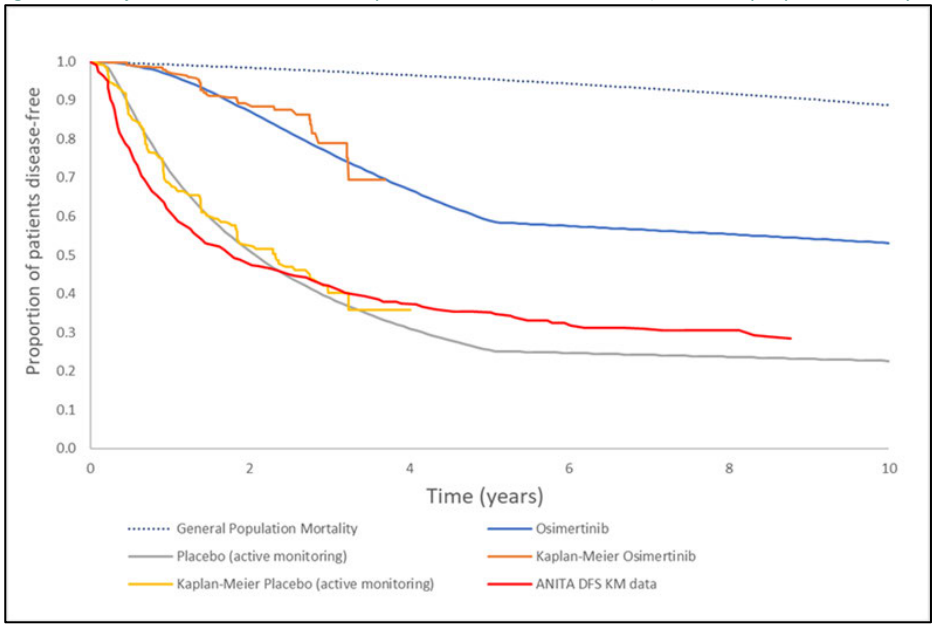
Figure 14. Unadjusted ADAURA DFS extrapolations versus ANITA DFS (0% cure proportion)



The data in the figure is extrapolated from(29)

Conversely, when the assumption of a cure rate of 95% at 5 years was applied to both arms in the model, the predicted DFS rates from the ADAURA active monitoring arm were more consistent with the longer-term DFS KM curve from ANITA (figure 15).

Figure 15. Adjusted ADAURA DFS extrapolations versus ANITA DFS (95% cure proportion at 5 years)



The data in the figure is extrapolated from(table 29) 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.(59) Overall, the MCM analysis estimated cure fraction rates ranging from 16–31% and predicted DFS rates at 5 years of 33–35% for the ANITA trial (table 30).
The results of the analysis were consistent with opinion from UK clinical experts, providing further support for the curative potential in this setting. Using the landmark method in the cost effectiveness model at 5 years, the estimated rate of cure for the active monitoring arm of ADAURA (combined DFS at 5 years: 25.6%; 95% assumed to be cured at 5 years: 24.3%) is 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

Model	AIC	Cure fraction (%)	DFS at 5 years (%)
Generalised Gamma	2628.17	15.6 (4.0, 45.1)	34.6
Lognormal	2635.82	27.9 (22.7, 33.8)	33.9
Loglogistic	2646.56	27.3 (22.1, 33.2)	33.8
Gompertz	2667.83	22.9 (9.5, 45.9)	33.9
Exponential	2673.97	30.6 (26.0, 35.5)	33.3
Gamma	2675.12	30.8 (26.3, 35.8)	33.2
Weibull	2675.93	30.5 (25.8, 35.5)	33.3

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.(49) 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 (53), 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 (53) 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.(60) 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 (49)
Disease-free survival: Osimertinib	0.825	0.018	ADAURA (49)
Disease-free survival: SoC	0.825	0.018	ADAURA (49)
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 (53)
1st line distant metastasis: Osimertinib	0.794	0.0069	FLAURA (53)
1st line distant metastasis: SoC	0.794	0.0069	FLAURA (53)

2nd+ line distant metastasis	0.640	0.030	FLAURA (53)
Primary treatment beyond 2nd+ line distant metastasis	0.640	0.030	FLAURA (53)

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 (61), and NICE TA653.(62) The study by Nafees et al, considered HRQoL, as measured by the EQ-5D, in patients with metastatic NSCLC; disutilities used in NICE TA653 were sourced from a clinical trial of patients with EGFR T790M mutation positive advanced NSCLC. 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).(49) 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 (49), as well as FLAURA (53) 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.[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.
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 (63) 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	42,566	AstraZeneca
	80	30	42,566	AstraZeneca

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 assumed to occur, therefore wastage costs were excluded.

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.

[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 34. Relative dose intensity

Drug	Relative dose intensity	Source
Osimertinib	98.9%	FLAURA trial (53)
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	1,163 kr	Danish Medicines Agency
Cisplatin	50 mg	1	100 kr	Danish Medicines Agency
Docetaxel	80 mg	1	150 kr	Danish Medicines Agency

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) Enter DM1 ≥60 months after initiating adjuvant Osimertinib: • Osimertinib retreatment: 50% (until progression) • PDC: 50% (3.4 model cycles or until progression)	Osimertinib (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	752*	Assumed to be the cost based on the use of time for a physician and nurse per IV administration following the first administration.	(63, 64)
Complex chemotherapy delivery	1,505*	Assumed to be the cost based on the use of time for a physician and nurse per IV administration following the first administration.	(63, 64)

IV: Intravenous,* inflated to 2021 (Inflation rate: 1.003 (65))

Simple chemotherapy delivery

The cost of an intravenous administration was assumed to be DKK 752 (DKK 658 + DKK 92) per administration. The cost was based on the use of time for a physician and nurse per IV administration following the first administration. For the administration and following observation time, it was assumed that a physician is involved for 30 minutes and a nurse is involved for 10 minutes.(64) For a physician an hourly cost of DKK 1,316 (Overlæger) was assumed, for a nurse (Sygeplejeske) DKK 554.(63) The cost was then inflated to 2021.(65)

Complex chemotherapy delivery

The cost of an intravenous administration was assumed to be DKK 1,419 (DKK 1,316 + DKK 185) per administration. The cost was based on the use of time for a physician and nurse per IV administration following the first administration. For the administration and following observation time, it was assumed that a physician is involved for 60 minutes and a nurse is involved for 20 minutes.(64)

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

	DF	LRR	DM 1	DM 2	Source
Hospitalisation	0.00	0.00	0.00	0.04	Danish clinician (50) (51)
Oncologist visits (subsequent)	0.00	0.33	0.33	0.50	Danish clinician (50) (51)
Surgeon visits	0.00	0.13	0.00	0.00	Danish clinician (50) (51)
Pulmonologist/ respiratory physician (subsequent)	0.33	0.00	0.00	0.00	Danish clinician (50) (51)
Emergency room	0.00	0.00	1.00	2.00	Danish clinician (50) (51)
CT scans	0.33	0.33	0.33	0.50	Danish clinician (50) (51)
PET-CT scans	0.00	0.13	0.08	0.00	Danish clinician (50) (51)

Table 40. Healthcare resource items and utilization for CNS metastasis

	Frequency per cycle	Source
Consultant/Oncologist outpatient visit	0.33	Danish clinician (50) (51)
Cancer nurse visit	0.33	Danish clinician (50) (51)
Full blood test	0.33	Danish clinician (50) (51)
Biochemistry	0.33	Danish clinician (50) (51)

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	35,784	udgiften pr. Indlæggelse	Table 3.1 ("Udgift pr. borger opdelt på dækningsgrad, intensitet og tyngde") in SUNDHEDS- OG ÆLDREØKONOMISK ANALYSE from 2018 (https://sum.dk/Media/0/4/Sundheds-og-aeldreoekonomisk-analyse-okt-2018.pdf), inflated to 2020 using the health index from https://fred.stlouisfed.org/series/CP0600DKM086NEST
Oncologist visits (subsequent)	1,320	Overlæger, inflated to 2021*	
Surgeon visits	453	Konsultation hos speciallæge i kirurgi, inflated to 2021*	(63)
Pulmonologist/ respiratory physician (subsequent)	1,320	Overlæger, inflated to 2021*	(63)
Emergency room	3,353	MDC01 1-dagsgruppe, pat. mindst 7 år	(66)
CT scans	1,835	30PR07 CT-scanning, ukompliceret, el. Osteodensitometri	(66)
PET-CT scans	2,319	Assumed same as MRI	(66)

* inflated to 2021 (Inflation rate: 1.003 (65))

Hospitalization

Less than one hospitalization event per cycle was included in the DM2 health state based on clinical expert opinion (50) (51). The cost per event reflects the cost of an ICU bed per day. The unit cost was estimated to be DKK 35,784.

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. (50) (51) The cost applied in the model represents the cost per one oncologist visit and was derived from the unit cost document published by the DMC (DKK 1,320.22, inflated to 2021 – Inflation rate: 1.003.(63, 67)

Surgeon visits

Less than one surgeon visit per cycle was included in the LRR health state based on clinical expert opinion.(50, 51) The cost per visit reflects the cost of a specialist care visit with an additional cost for an oncologist visit. The unit cost was derived from the unit cost document published by the DMC (DKK 453.35, inflated to 2021 – Inflation rate: 1.003.(63, 67)

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.(50, 51) The cost applied in the model represents the cost per one pulmonologist/respiratory physician visit and was derived from the unit cost document published by the DMC (DKK 1,320.22, inflated to 2021 – Inflation rate: 1.003.(63, 68)

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.(50, 51) The unit cost was sourced from the DRG price list and was estimated to be DKK 3,353.

CT scan

Less than one CT scan per cycle was included for all patients based on clinical expert opinion. (51) The cost per scan was derived from the DRG price list. The unit cost was estimated to be DKK 1,835.

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.(50, 51) The cost per scan was derived from the DRG price list. The unit cost was estimated to be DKK 2,319.

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.

Table 43. Health care utilization unit costs for CNS metastasis

Resource use	Cost	Comment	Source
Consultant/Oncologist outpatient visit	1,320	Overlæger	(63)
Cancer nurse visit	555	Sygeplejersker	(63)
Full blood test	49	Blodtagning fra blodåre pr. forsendelse	(63)
Biochemistry	49	Bioanalytikere	(63)

* inflated to 2021 (Inflation rate: 1.003 (65))

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 and was derived from the unit cost document published by the DMC (DKK 1.320.22, inflated to 2021 – Inflation rate: 1.003.(63, 68)

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 per visit reflects the cost of one nurse visit (one hour). The unit cost was estimated (Sygeplejersker) to be DKK 555 based on the unit cost document published by the DMC (DKK 555, inflated to 2021 – Inflation rate: 1.003.(63, 67)

Full blood test

For patients with CNS metastasis, less than one full blood test per cycle was included based on clinical expert opinion .(50, 51) The cost for full blood test reflects sampling for laboratory examination at the doctor's office or submission to medical laboratory and the hematological analysis with cell counter. The unit cost was estimated to be DKK 49.31 according to the unit cost document published by the DMC (inflated to 2021 – Inflation rate: 1.003.(63, 68)

Biochemistry

For patients with CNS metastasis, less than one biochemistry test was taken per month was included based on clinical expert opinion. (50, 51) The unit cost was estimated to be DKK 49.31 according to the unit cost document published by the DMC (inflated to 2021 – Inflation rate: 1.003. (63, 68)

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	24,160	(66)
Stereotactic brain radiation	Treated with whole brain radiotherapy, 50% of patients considered to incur a one-off cost	5,383	(66)

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 24,160 based on the Danish DRG list or 2021 (DRG code: 27MP02 Strålebehandling, kompleks, 3-4 fraktioner).(69)

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 5,383 based on the Danish DRG list or 2021 (DRG code: 27MP10 Stereotaksi).(69)
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 osimeritinib 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	3,443	(66)

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	11,157	09MA03 Lettere eller moderat hudsygdom, u. kompl. bidiag.	(66)
Decreased Appetite	5,130	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år,u. kompl. bidiag.	(66)
Diarrhea	22,115	06MA10 Betændelse i spiserør, mave og tarm m.v., pat. mindst 18 år, m. kompl. bidiag.	(66)
Stomatitis	1,186	03MA09 Andre sygdomme i øre, næse, mund og hals	(66)
ECG QT prolonged	15,488	05MA07 Hjertearytmi og synkope	(66)

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 11,157 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 5,130 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 22,115 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 1,186 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 15,488 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 2021. (68)

Table 47. End of life costs

Unit cost (DKK)	Source
68,888*	As proposed for Kadcyla (HER2+) by Amgros (67)

* inflated to 2021 (Inflation rate: 1.003 (65))

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 100 (equivalent to 14 km) 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 180 per hour according to the guidelines. (63)

Table

Table 48. Overview of applied indirect costs for routine care

Resource item	Assumed time use	Cost per visit (DKK)	Reference
Oncologist	4 h	721*	(63)
Specialist nurse	4 h	721*	(63)
Nurse	4 h	721*	(63)
GP	4 h	721*	(63)
Transportation costs per visit	-	101*	(63)

* inflated to 2021 (Inflation rate: 1.003 (65))

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	2.7	3.7	7	12.2

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 (49) and FLAURA .(53)
Included costs	Pharmaceutical costs Healthcare utilization costs Costs of adverse events Indirect costs
Dosage of pharmaceutical	Oral administration of 80 mg daily
Parametric function DF to LR	Lognormal
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 2.59 incremental QALYs and 3.33 incremental life-years gained, and osimertinib-treated cohort had higher total lifetime costs. The ICER was DKK 136 490 per 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	1,558,793	1,205,549	353,244	
LYs	11.57	8.24	3.33	106,085
QALYs	9.22	6.51	2.72	130,093

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

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

Health state	Osimertinib (DKK)	Active monitoring (DKK)	Incremental (DKK)
Disease-free	10.05	5.16	4.89
Logoregional recurrence	0.52	0.85	-0.33
1st line distant metastasis	0.43	1.42	-0.99
2nd line distant metastasis	0.58	0.82	-0.24
Total	11.57	8.24	3.33

Table 53 presents a breakdown of costs by category. The incremental cost of DKK 353,244 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	5,964	6,948
Intervention costs	1,180,915	0
Subsequent treatment costs	84,629	806,672
Disease monitoring costs	136,242	204,300
Hospitalization costs	10,299	14,666
AE costs	686	113
Terminal care costs	41,453	49,360
EGFR testing costs	3,442	2,178
Patient and carer costs	83,557	106,518
Travel costs	11,605	14,794
Total costs	**1,558,793**	**1,205,549**

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

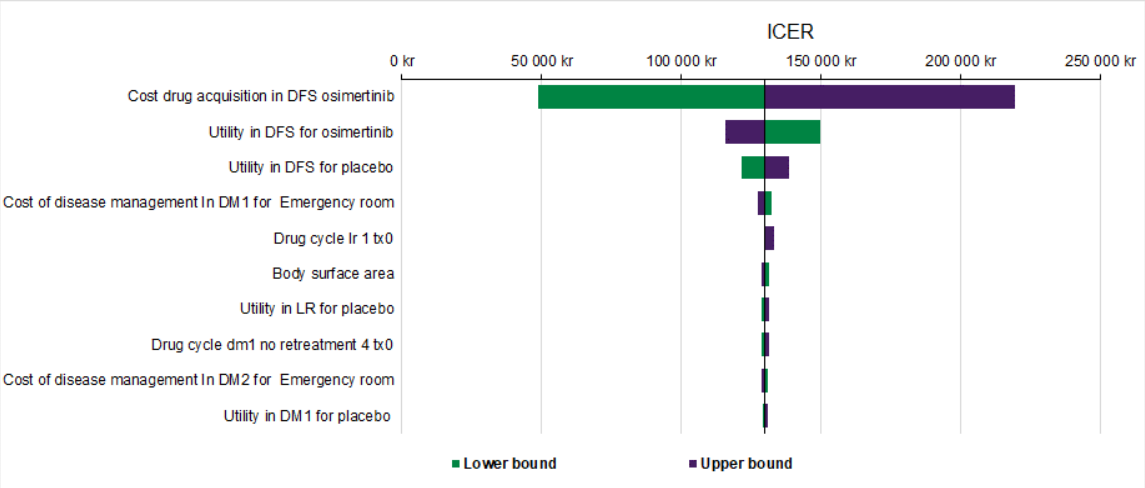
A one-way deterministic sensitivity analysis (OWSA) was conducted on osimertinib versus active monitoring. Where upper and lower 95% confidence intervals were not available, input values were varied by 10% for both lower and upper bound. (An assumed standard error of 10% was used to estimate the confidence 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 16 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**	**Upper bound**	**Absolute difference**
Cost drug acquisition in DFS osimertinib	51,455.05	230,162.58	178,707.52
Utility in DFS for osimertinib	15,7631.35	12,1436.15	36,195.20
Utility in DFS for placebo	12,7632.29	14,5845.84	18,213.55
Cost of disease management in DM1 for Emergency room	13,9059.50	13,3659.77	5,399.74
Drug cycle LR 1 tx0	13,6490.13	13,9813.11	3,322.99
Body surface area	13,8018.47	13,4961.79	3,056.68
Utility in LR for placebo	13,4938.87	13,7956.02	3,017.15

Drug cycle DM1 no retreatment4 tx0	13,5014.73	13,7875.91	2,861.18
Cost of disease management in DM2 for Emergency room	13,7755.49	13,5096.23	2,659.26
Utility in DM1 for placebo	13,5501.96	13,7468.87	1,966.91

Figure 16. 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	130,093	139,723
Weight: 63 kg **Age: 63 years** **BSA: 1.67 m²**	Weight: 65 kg Age: 63 years BSA: 1.70 m²		130,224
Population II-IIIA	IB-IIIA		55,666
Starting age 60 years	63 years		115,149
Time horizon 5 years	37 years		1,303,135
Time horizon 10 years	37 years		322,022
Time horizon 15 years	37 years		191,963
Time horizon 20 years	37 years		152,690
Time horizon 30 years	37 years		131,676
Discount rate – Effect: 0%	3.5%		80,558
Discount rate – Effect: 5%			156,201
Discount rate – Costs: 0%	3.5%		110,823
Discount rate – Costs: 5%			137,101
Standardized mortality rate applied	Not applied		184,700
Hazard ratio DM1 to DM2	Not applied		131,924
Hazard ratio DM2 to death	Not applied		141,155
TP1 – Loglogistic	Lognormal		133,747
TP1 – Weibull			125,140
TP2 – Lognormal	Generalized gamma		120,817
TP4 - Loglogistic	Lognormal		130,682

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 1,000 iterations were run. An overview of all assumptions regarding the PSA is presented in Appendix J (section 20).

Figure 17 presents the cost-effectiveness plane, which showed that majority of all 1,000 iterations were in the North-East quadrant indicating osimeritinib is more effective and more costly in comparison to active monitoring in all iterations.

Figure 17. Cost-effectiveness plane

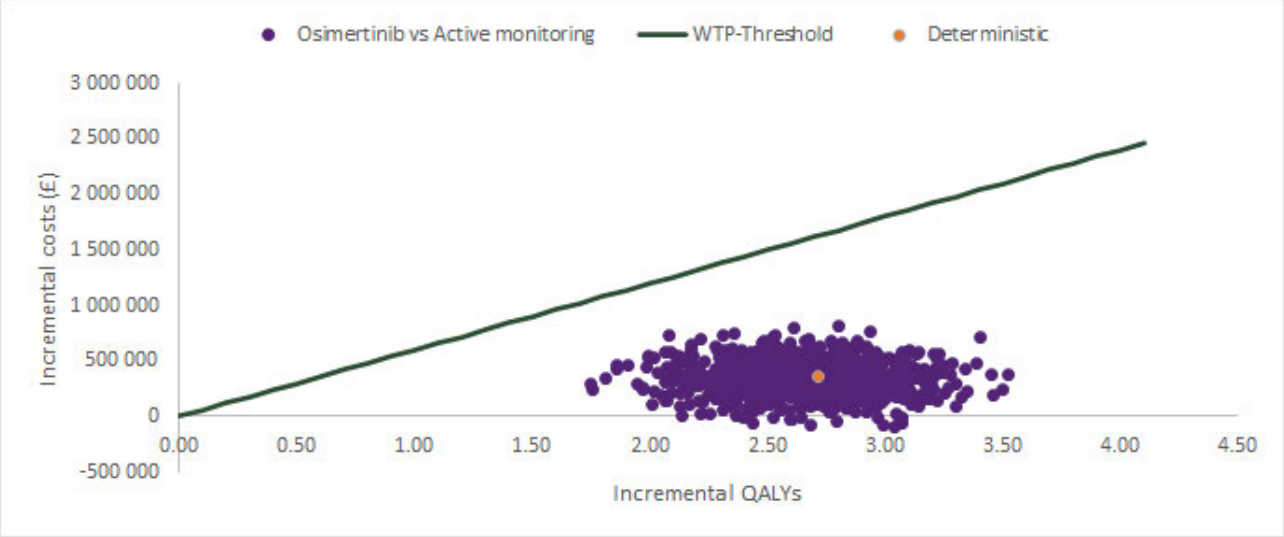
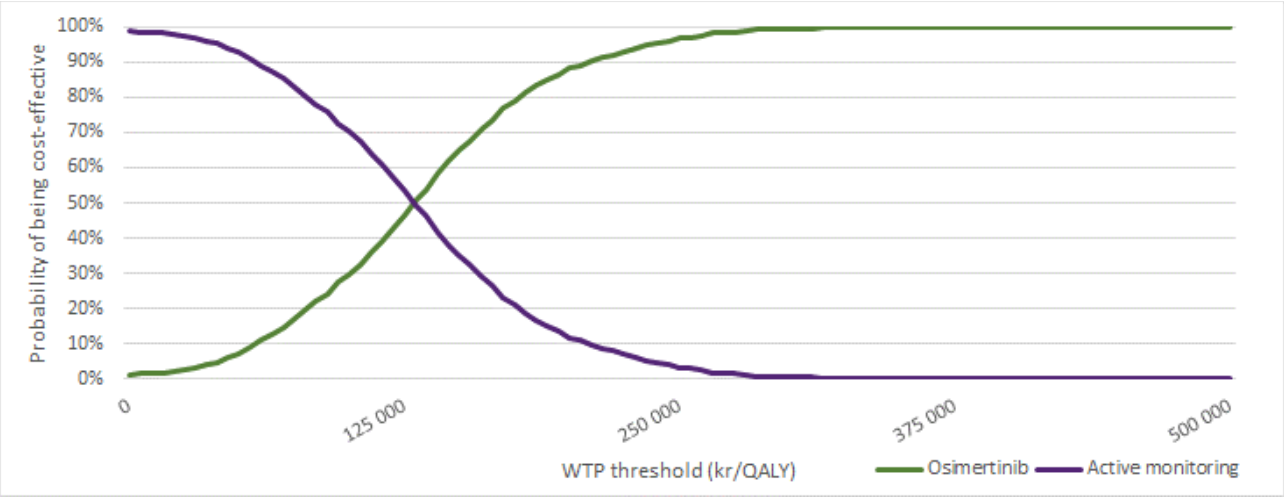


Figure 18 presents the cost-effectiveness acceptability curve (CEAC). The CEAC showed that osimertinib had a 100% probability of being cost-effective at a willingness-to-pay of DKK 600,000.

Figure 18. 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, costs other than drug costs are considered to be neglible in comparison to the differences in drug costs between osimertinib and active monitoring. Thus costs including the specialist health services and the health and care services were excluded as these are believed to be similar for the two treatment options in the time horizon of the budget impact.

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 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 patients 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	24	41	55	64
Active monitoring	19	32	44	51	55

Table 57. Number of patients 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	28	29	29	29

9.2 Expenditure per patient

In the scenario where Osimertinib is introduced, the expenditure per patient 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 costs are incurred in 4th and 5th year as shown in Table 58.
In the scenario where Osimertinib is not introduced, no costs are calculated to be incurred, since active monitoring is considered to have no drug costs, as shown in Table 59.

Table 58. Costs per patient per year - if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Osimertinib	4,012,108	11,027,768	18,232,665	24,419,999	29,289,279
Active monitoring	1,450,185	4,196,369	6,622,736	8,322,224	6,126,252

Table 59. 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	2,071,693	6,745,802	12,058,855	17,220,845	21,917,301

9.3 Budget impact

Table 60 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. 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	5,462,294	15,224,137	24,855,401	32,742,223	35,415,531
Minus: The pharmaceutical under consideration is NOT introduced	2,071,693	6,745,802	12,058,855	17,220,845	21,917,301
Budget impact of the recommendation	3,390,600	8,478,335	12,796,546	15,521,377	13,498,230

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 not reached, placebo 27.5 months; HR 0.20; 95% CI 0.15, 0.27; 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 a Danish clinical expert. 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 (353,244 DKK) and more effective (+2.59 QALYs).

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 very 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.

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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 case 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,	Interventional	Stage IB to IIIA(overall population) Median follow-up for DFS in all patients was 22.1 months in	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

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
	following complete tumour resection with or without adjuvant chemotherapy		the osimertinib arm vs 16.6 months in the placebo arm			survival, and safety. 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
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),(46) following complete tumour resection with or without adjuvant chemotherapy.(2)
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.(2)
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(s)	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.(2) 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

Primary, secondary and exploratory endpoints	Priority	Type	Endpoint Description	Assessment
	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.			

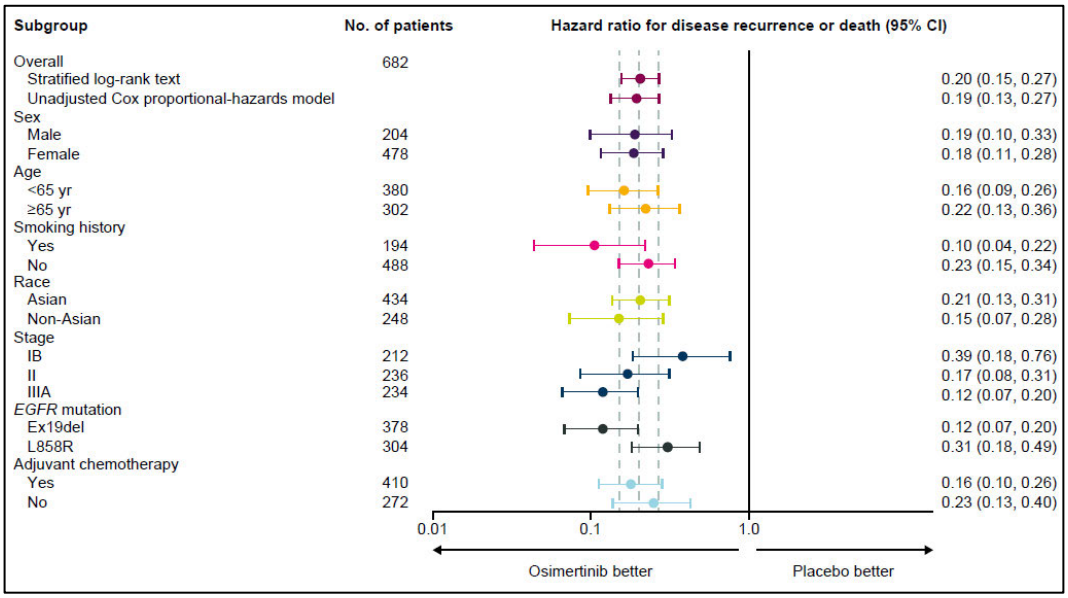
Trial name: ADAURA	NCT number: NCT02511106

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)



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 61. Patient's baseline characteristics from CancerLinQ data (52)

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**	
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%)
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 12. Patient demographics and baseline characteristics of CancerLinQ stage II-IIIA subgroup (52)

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	
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%)
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 63. 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 64. Patient baseline characteristics of FLAURA trial (53)

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

	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		
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 Table 1 and 2. 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 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

Outcome measure	Definition	Validity	Clinical relevance
DFS (primary)	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 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
DFS(secondary)	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		

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 .

15.2 Results per study

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	
	Placebo	237	19.6 (16.6, 24.5) 54.9 %								
DFS(IB–IIIA)	Osimertinib	339	NR (NC, NC)	NR	NA	NA	HR=0.20	(0.15, 0.27)	p<0.0001	See above	
	Placebo	343	27.5 (22.0, 35.0)								

Table A3a ADAURA (NCT02511106)]											
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 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	
	Placebo	237	NR (NC, NC) 17 (7.2 %)								
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	
	Placebo	343	48.2 (48.2, NC) 20 (5.8 %)								
SAE(due to any cause)	Osimertinib	339	54 (16.0 %)	3.8 %	NA	NA	RR = 1.30	(0.90, 1.89)	NA	Includes events with an outcome of death RR calculated by AZ	
	Placebo	343	42 (12.2 %)								
SAE (causally related to study treatment)	Osimertinib	339	8 (2.4 %)	1.8 %	NA	NA	RR = 4.05	(0.87, 18.9)	NA	Includes events with an outcome of death. AEs assessed by investigator RR calculated by AZ	
	Placebo	343	2 (0.6 %)								
Grade ≥3 AEs (AEs due to any cause)	Osimertinib	339	68 (20.2%)	6.8%	NA	NA	RR = 1.50	(1.06, 2.11)	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. RR calculated by AZ	
	Placebo	343	46 (13.4%)								

Table A3a ADAURA (NCT02511106)]											
Grade ≥3 AEs (causally related to study treatment)	Osimertinib	339	32 (9.5 %)	7.2%	NA	NA	RR = 4.05	(1.89, 8.65)	NA	AEs assessed by investigator AEs assessed by investigator RR calculated by AZ	
	Placebo	343	8 (2.3 %)								
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. A difference of +/- 3 is regarded as a clinical meaningful difference	
	Placebo	343	2.68 (1.92, 3.44)								
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	
	Placebo	343	2.31 (1.70, 2.91)								
PFS	Osimertinib	339	NC (NC, NC) 13 (3.8 %)	9.6 %	NA	NA	HR = 0.24	(0.14, 0.41)	p<0.0001	At the DCO, PFS in the overall population had reached 8.7% maturity	
	Placebo	343	48.2 (NC, NC) 46 (13.4%)								

Table A3a ADAURA (NCT02511106)]											
Median TFST	Osimertinib	339	NR (NC, NC) 31 (9.1 %)	20 %	NA	NA	HR=0.20	(0.14, 0.27)	p<0.0001	At the time of the DCO, time to first subsequent therapy (TFST) had reached 24.2% maturity	
	Placebo	343	39.8 (30.8, NC) 134 (39.1%)								
Median TSST	Osimertinib	339	NC (43.2, NC) 15 (4.4%)	11.9%	NA	NA	HR= 0.25	(0.16, 0.41)	p<0.0001	The time to second subsequent therapy (TSST) endpoint had reached 10.4% maturity at the DCO	
	Placebo	343	48.2 (48.2, NC) 56 (16.3%)								

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 section 7.2.1 and table 17 to 22.

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: 97.6%; placebo: 89.2%). 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. In total, there was one fatal AE in the placebo arm; this was not causally related to treatment.

17. Appendix F Comparative analysis of efficacy and safety

Table A4 ADAURA									
Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	*P* value	Difference	CI	*P* value		
mDFS (II-IIIA)	ADAURA	NR	NA	NA	HR=0.17	(0.11, 0.26) CI: 99.06 %	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	Yes
mDFS(IB–IIIA)	ADAURA	NR	NA	NA	HR=0.20	(0.15, 0.27)	p<0.0001	See above	Yes
OS (II–IIIA)	ADAURA	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 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	Yes
OS (IB–IIIA)	ADAURA	3.1 %	NA	NA	HR=0.48	(0.23, 1.02)	p=0.0553	See above	Yes

Table A4 ADAURA									
SAE(due to any cause)	ADAURA	3.8 %	NA	NA	RR = 1.30	(1.06, 2.11)	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. RR calculated by AZ	Yes
SAE (causally related to study treatment)	ADAURA	1.8 %	NA	NA	RR = 4.05	(0.87, 18.9)	NA	Includes events with an outcome of death. AEs assessed by investigator RR calculated by AZ	Yes
Grade ≥3 AEs (AEs due to any cause)	ADAURA	6.8 %	NA	NA	RR = 1.50	(1.06, 2.11)	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. RR calculated by AZ	Yes
Grade ≥3 AEs (causally related to study treatment)	ADAURA	7.2 %	NA	NA	RR = 4.05	(1.89, 8.65)	NA	AEs assessed by investigator AEs assessed by investigator RR calculated by AZ	Yes
SF-36 component PCS	ADAURA	-1.18	(-2.02, -0.34)	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. A difference of +/- 3 is regarded as a clinical meaningful difference	Yes

Table A4 ADAURA									
SF-36 component MSC	ADAURA	-1.18	(-2.02, -0.34)	NA	NA	NA	NA	. A difference of +/- 2 is regarded as a clinical meaningful difference	Yes
PFS	ADAURA	9.6 %	NA	NA	HR = 0.24	(0.14, 0.41)	p<0.0001	At the DCO, PFS in the overall population had reached 8.7% maturity	Yes
Median TFST	ADAURA	20 %	NA	NA	HR = 0.20	(0.14, 0.27)	p<0.0001	At the time of the DCO, time to first subsequent therapy (TFST) had reached 24.2 % maturity	Yes
Median TSST	ADAURA	11.9 %	NA	NA	HR= 0.25	(0.16, 0.41)	p<0.0001	At the time of the DCO, time to first subsequent therapy (TSST) had reached 10.4 % maturity	Yes

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.(52) 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 *EGFR*-mutated (*EGFR*m) advanced NSCLC. (53)

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 **Error! Reference source not found.** for the ranking of all 36 combinations based upon TP1 and TP2 for both DFS and OS. The lognormal distribution was selected for TP1 and generalised gamma for 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 2nd in both DFS and OS in terms of MSE. This combination of distributions results in the aggregated DFS and OS shown in figure 19 and figure 20, respectively.
The base case parametric distributions applied for each transition are shown in table 66. In addition, scenario analyses were also performed to test different curve selections.

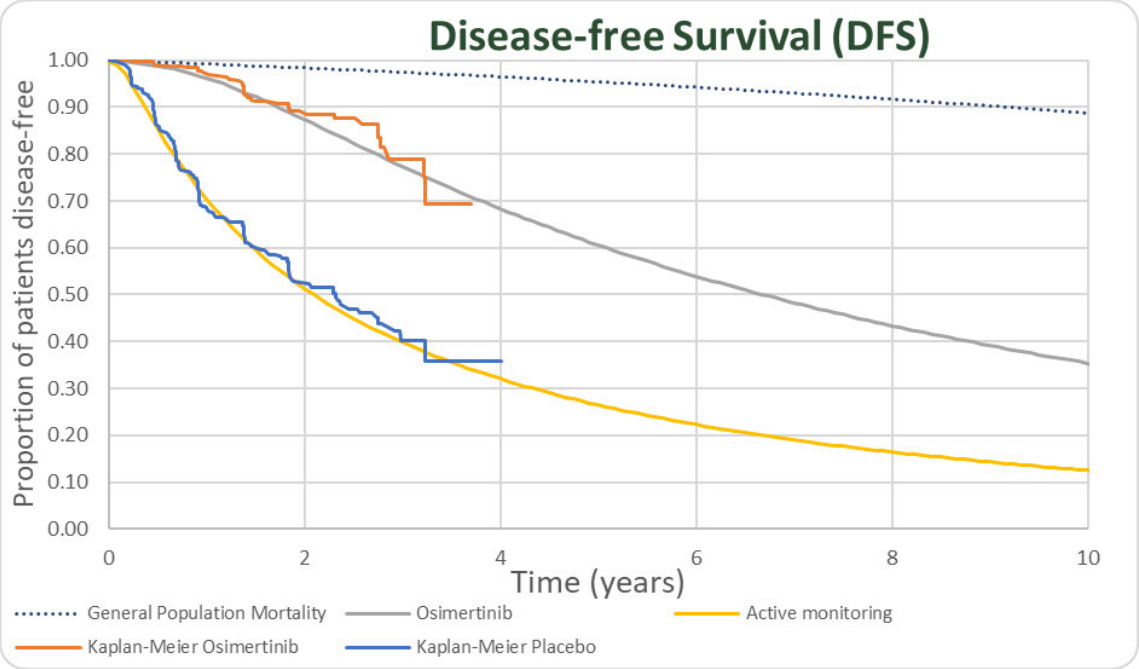
Table 66. Main settings for the base case

	Setting	Data source
TP1: DF -> LRR	Lognormal	ADAURA
TP2: DF -> 1L DM	Generalized gamma	ADAURA
TP3: DF -> Death	Background mortality	ADAURA / Danish life tables (56)
TP4: LRR -> 1L DM	Lognormal	CancerLinQ (52)
TP5: LRR -> Death	Background mortality	CancerLinQ (52) / Danish life tables (56)
TP:6 1L DM -> 2L DM	Weibull	FLAURA (53)
TP7: 1L DM -> Death	Exponential / Background mortality	FLAURA (53) / Danish life tables (56)
TP8: 2L DM -> Death	Weibull	FLAURA (53) / Danish life tables (56)

Cure	100% from year 5 onwards	Clinical expert
Retreatment	80% of the osimertinib patients can be retreated	Clinical expert
Treatment waning	No	

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 19. Aggregated DFS without cure compared to ADAURA DF



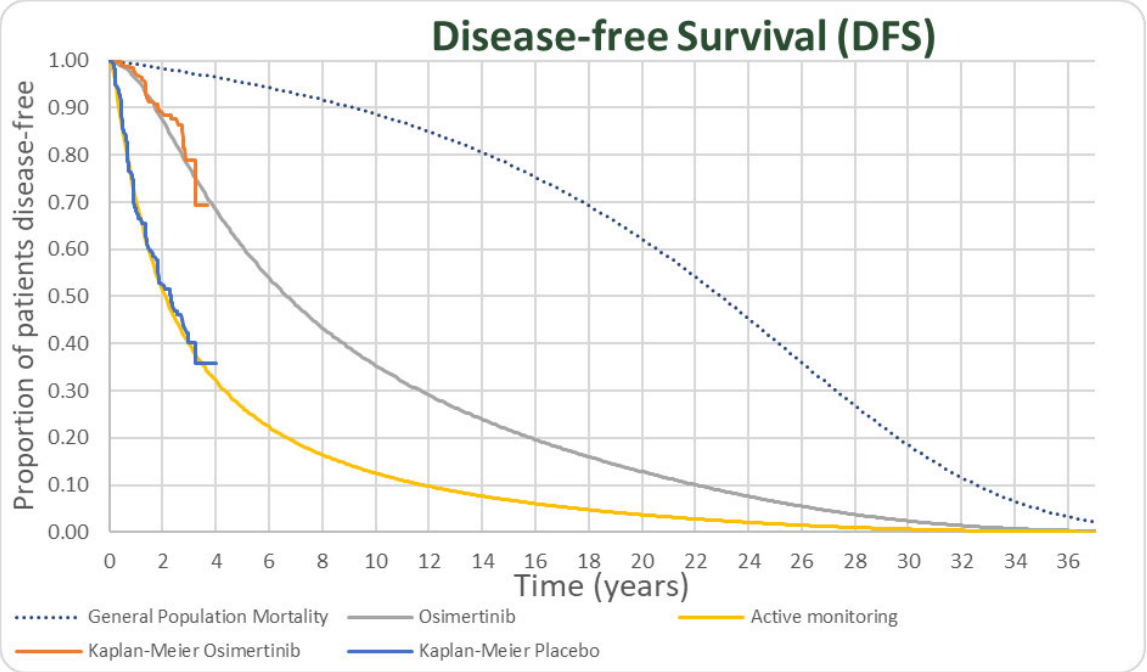
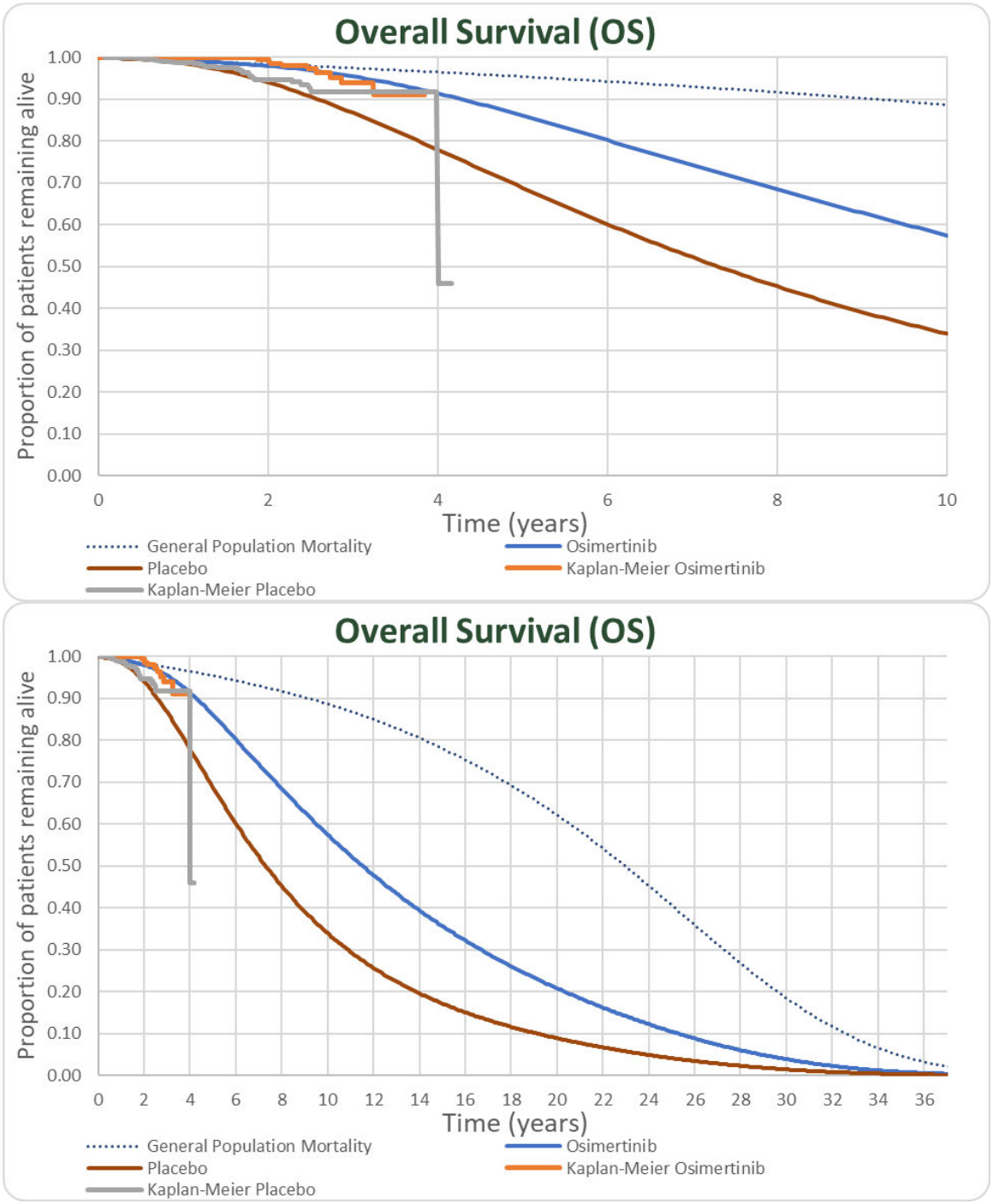


Figure 20. Aggregated OS without cure compared to ADAURA OS



The fit compared to the ADAURA KM is good for both DFS and OS, although for active monitoring the OS data fits well until 36 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 (50, 51).

Based on this feedback, the base case applies a cure assumption whereby 100% of patients who remain disease-free at Year 5 are assumed to be cured for the remainder of the time horizon. 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 **Error! Reference source not found.** and **Error! Reference source not found.**). A landmark comparison for the final base case is presented in **Error! Reference source not found.** and **Error! Reference source not found.**.

Figure 2. Aggregated DFS curve with cure and the Kaplan-Meier from ADAURA

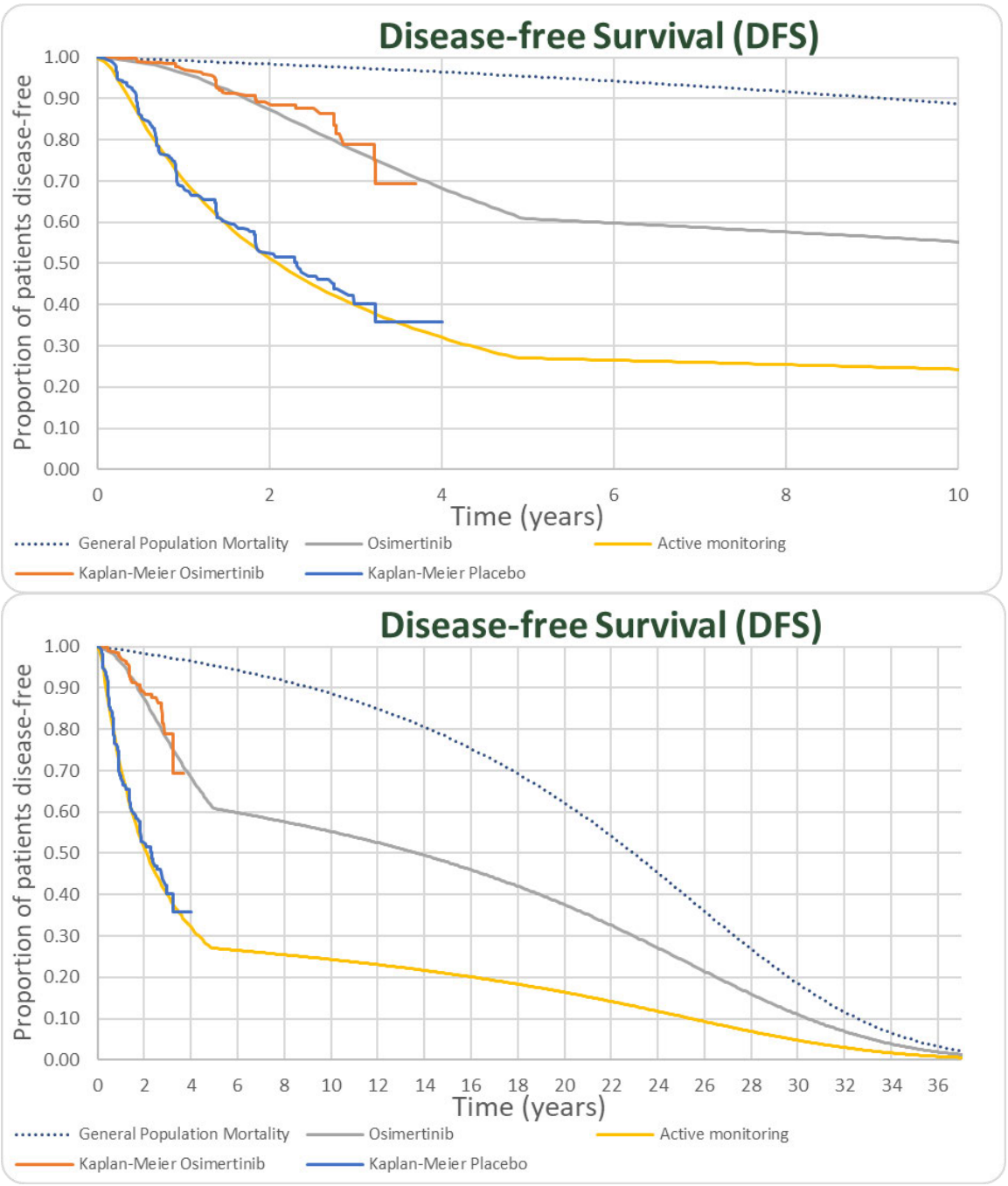
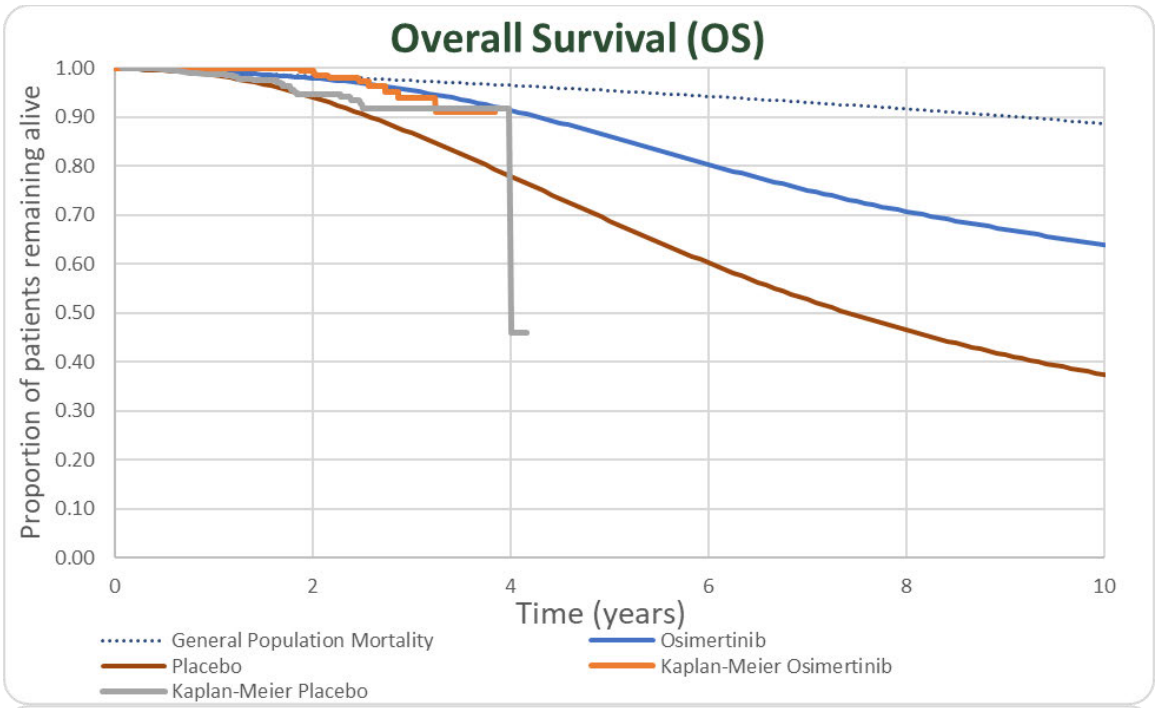


Figure 3. Aggregated OS curve with cure and the Kaplan-Meier from ADAURA



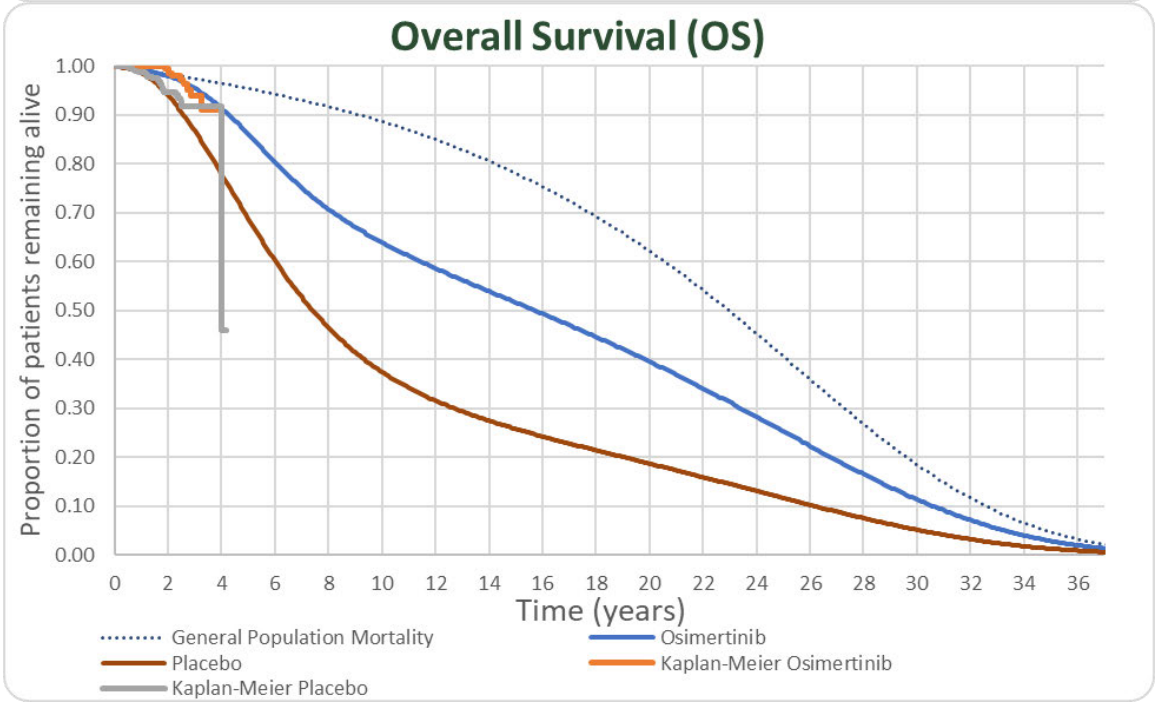


Table 67. Landmark comparison of aggregated DFS and ADAURA DFS with cure

	Osimertinib	ADAURA osimertinib	Placebo	ADAURA placebo
Mean (months)	183.0	--	91.4	--
Median (months)	35.1	NR	24.9	27.9
% at 1 year	96.8%	97.4%	74.9%	68.5%
% at 2 years	88.2%	89.1%	53.8%	52.8%
% at 3 years	78.2%	78.9%	41.4%	40.3%
% at 4 years	69.1%	--	33.2%	35.8%
% at 5 years	61.2%	--	27.3%	--
% at 10 years	55.4%	--	24.1%	--

Key: NR, not reported

Table 68. Landmark comparison of aggregated OS and ADAURA OS with cure assumption

	Osimertinib	ADAURA osimertinib	Placebo	ADAURA placebo
Mean (months)	199.2	--	131.8	--
Median (months)	187.6	NR	89.3	NR
% at 1 year	99.2%	100.0%	99.0%	98.8%
% at 2 years	98.1%	99.6%	94.9%	94.7%
% at 3 years	95.7%	93.9%	87.9%	91.8%
% at 4 years	91.8%	--	79.1%	45.9%
% at 5 years	86.6%	--	69.9%	--
% at 10 years	63.8%	--	37.6%	--

Key: NR, not reported

Table 69 presents the ranking of all 36 combinations based upon TP1 and TP2 for both DFS and OS. As noted above the lognormal distribution was selected for TP1 and generalised gamma for 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 2nd in both DFS and OS in terms of MSE.

Table 69. 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	0.047928	0.288935	0.336862
2	Lognormal	Generalised Gamma	0.054964	0.288829	0.343793
3	Exponential	Generalised Gamma	0.049886	0.294461	0.344347
3	Exponential	Generalised Gamma	0.049886	0.294461	0.344347
4	Loglogistic	Generalised Gamma	0.063546	0.289551	0.353097
5	Gompertz	Generalised Gamma	0.061678	0.291792	0.35347
6	Weibull	Generalised Gamma	0.065665	0.289078	0.354743
7	Generalised Gamma	Lognormal	0.071649	0.295622	0.36727
8	Exponential	Lognormal	0.073898	0.301647	0.375545
9	Generalised Gamma	Gompertz	0.062162	0.317695	0.379858
10	Lognormal	Lognormal	0.08743	0.295446	0.382876
11	Generalised Gamma	Exponential	0.080278	0.308421	0.388699
12	Generalised Gamma	Weibull	0.086796	0.302793	0.389589
13	Lognormal	Gompertz	0.073196	0.317432	0.390628
14	Generalised Gamma	Loglogistic	0.086795	0.307629	0.394423
15	Gompertz	Lognormal	0.099655	0.298748	0.398403
16	Loglogistic	Lognormal	0.102242	0.296193	0.398435
17	Exponential	Gompertz	0.077789	0.323895	0.401685
18	Weibull	Lognormal	0.106527	0.295756	0.402283
19	Exponential	Weibull	0.094454	0.309159	0.403613
20	Lognormal	Exponential	0.09711	0.308086	0.405196
21	Loglogistic	Gompertz	0.08839	0.318137	0.406528
22	Exponential	Loglogistic	0.093258	0.313979	0.407236
23	Lognormal	Weibull	0.106746	0.302472	0.409218
24	Weibull	Gompertz	0.092021	0.3176	0.409621
25	Lognormal	Loglogistic	0.105467	0.307393	0.412859

26	Gompertz	Gompertz	0.095998	0.320747	0.416745
27	Loglogistic	Exponential	0.110149	0.308777	0.418927
28	Gompertz	Exponential	0.110589	0.311706	0.422295
29	Exponential	Exponential	0.107174	0.315348	0.422522
30	Weibull	Exponential	0.114828	0.308292	0.42312
31	Loglogistic	Weibull	0.125563	0.303171	0.428734
32	Loglogistic	Loglogistic	0.1232	0.308146	0.431346
33	Gompertz	Weibull	0.126039	0.305956	0.431995
34	Gompertz	Loglogistic	0.122826	0.310889	0.433715
35	Weibull	Weibull	0.131408	0.302708	0.434117
36	Weibull	Loglogistic	0.128195	0.3077	0.435894

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

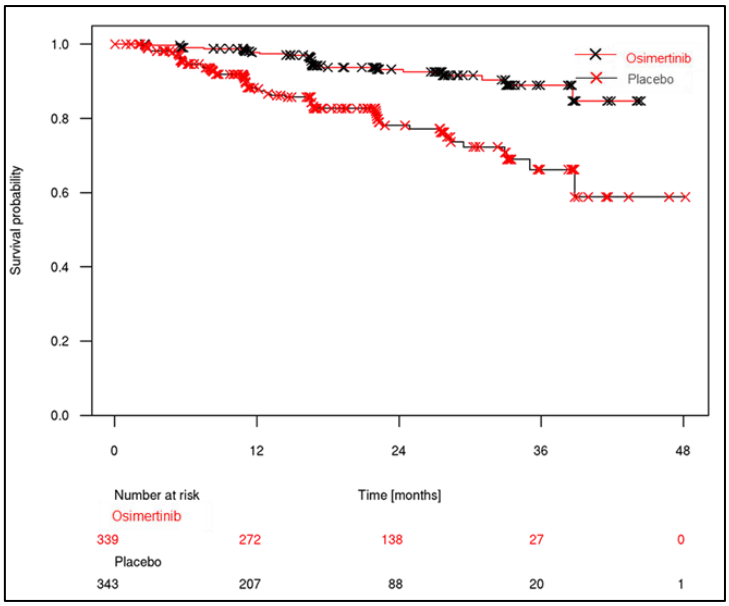
18.2.1 Selection of survival models

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 4 applying the methods described below.

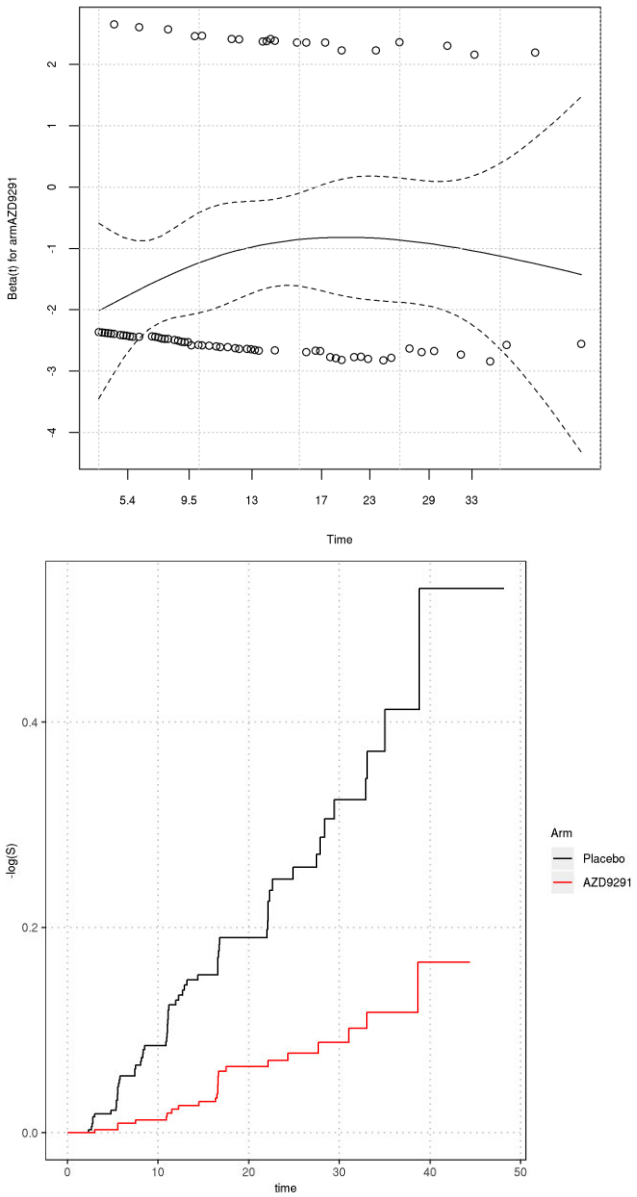
Figure 4. KM curves for time to local/regional recurrence in the osimertinib and active monitoring arms of ADAURA.



Assessment of the proportional hazard assumption

In Figure 5 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=0.286) indicate that the proportional hazards assumption holds, whereas this conclusion based on visual inspection of the log cumulative hazards plot is less certain. As such both individual fits and combined fits (single dependent model with a treatment coefficient for osimertinib) can be used; however due to the uncertainty around the PH assumption the individual fits were applied in the model.

Figure 5. Schoenfeld residuals and cumulative hazard plot for the transition DF to LRR (TP1).



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 6 shows the fits and extrapolations for the transition from DF to LRR (TP1), with the AIC and BIC values presented in Table 70. All parametric curves for the placebo arm are shown in Figure 6b

and all curves for the osimertinib arm are shown in Figure 6c. Based on visual inspection of the extrapolations and the expectation of six UK clinical experts that functional cure is expected both in the osimertinib and active monitoring arm, the exponential, Weibull, Gompertz and loglogistic distributions were excluded as they produce pessimistic long-term survival estimates incompatible with the underlying functional cure assumption. From the remaining distributions, the lognormal distribution fits the KM data best, both visually (i.e. maintaining the expected treatment effect between the arms) and statistically. Based on the functional cure expectations by clinicians, both of these distributions present a more clinically plausible scenario than other distributions. As presented in table 70 the lognormal curve results in the lowest AIC and BIC in both arms. Therefore, this distribution was selected for the base case analysis, whereas the Weibull and loglogistic distributions are tested in a scenario analysis.

Figure 6. Extrapolations for DF to LRR (TP1).

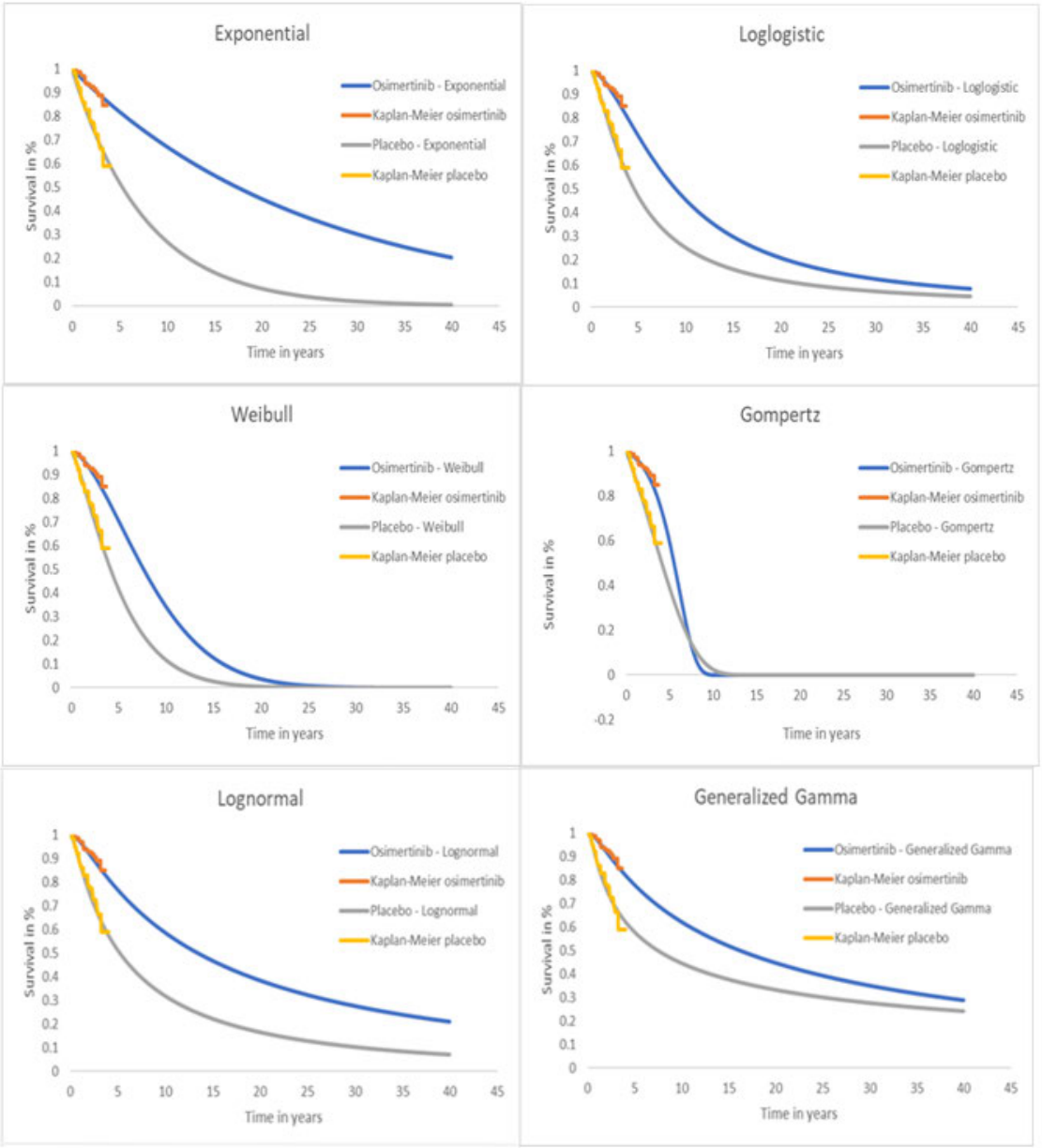


Figure 6b. Extrapolations for DF to LRR (TP1) for the placebo arm – all in one.

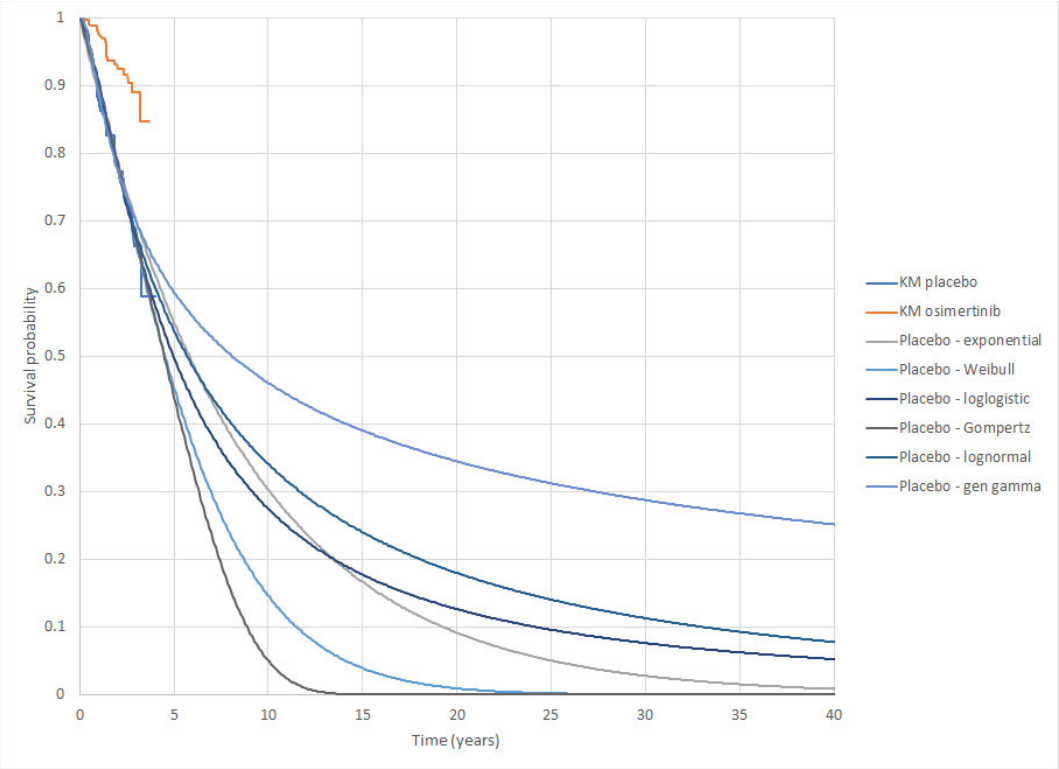


Figure 6c. Extrapolations for DF to LRR (TP1) for the osimertinib arm – all in one.

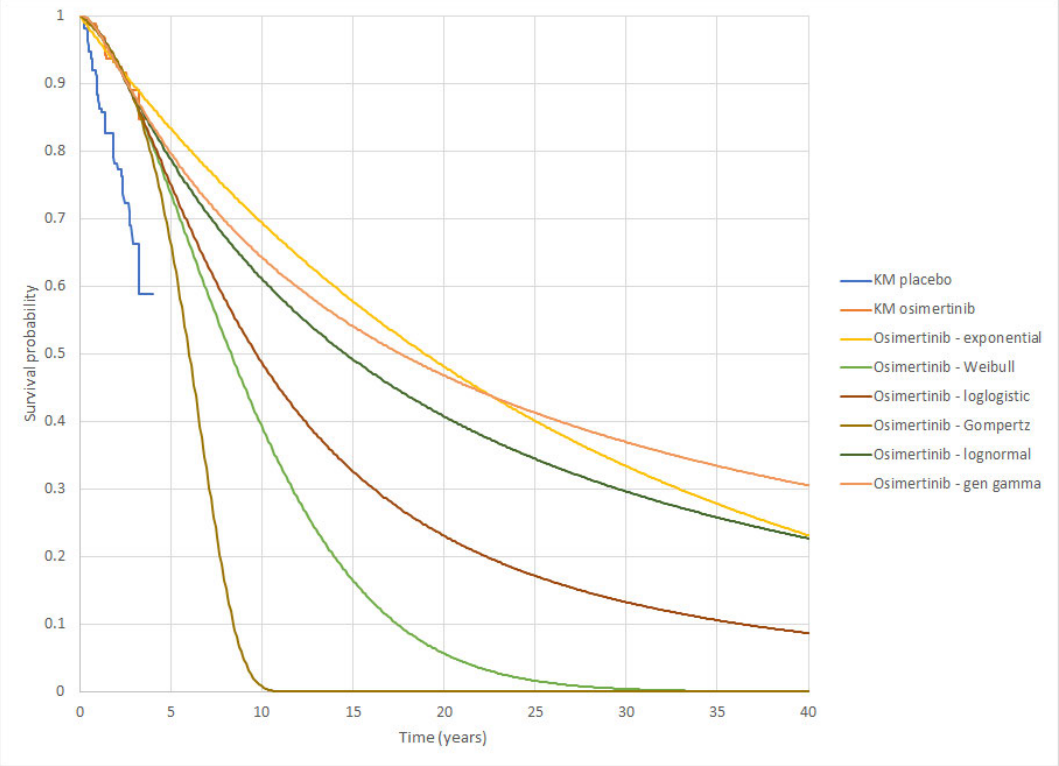


Table 70. AIC and BIC values for the fitted distributions to the transition DF to LRR

	Individual fits				Combined fits	
	Osimertinib		Placebo (Active monitoring)			
Model	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	309.89	317.54	678.46	686.13	986.36	999.93
Loglogistic	310.55	318.2	681.99	689.67	991.24	1004.82
Weibull	310.66	318.32	683.06	690.73	992.83	1006.41
Generalised Gamma	311.86	323.33	679.09	690.6	987.4	1005.5
Gompertz	312.82	320.47	686.36	694.03	998.08	1011.65
Exponential	314.32	318.15	685.82	689.66	1000.14	1009.19

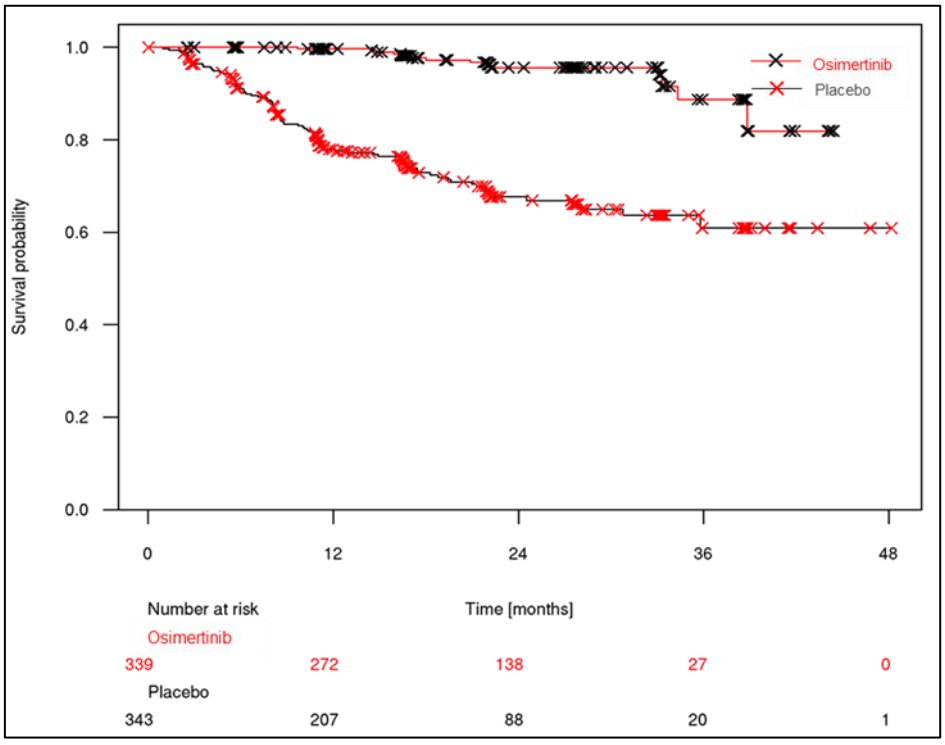
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Bold values: preferred distribution

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 7 applying the methods described below.

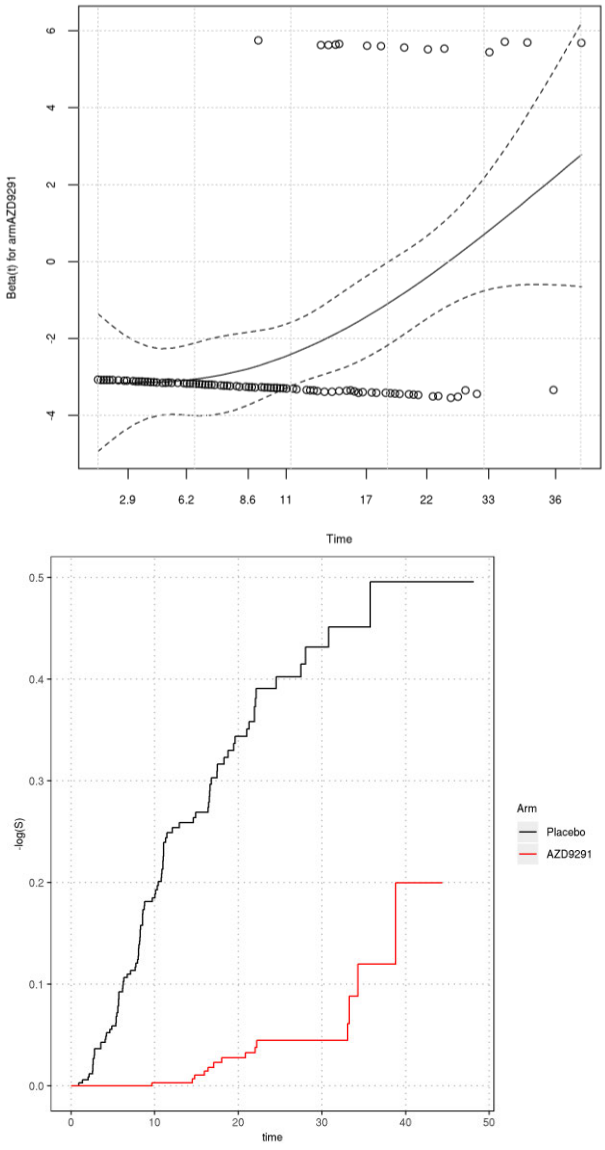
Figure 7. KM curves for time to distant metastases survival in the osimertinib and active monitoring arms of ADAURA.



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



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 9 shows the fits and extrapolations for the transition from DF to DM1 (TP2), with the AIC and BIC values presented in table 71 . All parametric curves for the placebo arm are shown in Figure 9b and all curves for the osimertinib arm are shown in Figure 9c. Based on visual inspection of the extrapolations and the expectation of six UK clinical experts that cure is expected both in the osimertinib and active monitoring arm, the exponential, Weibull, Gompertz and loglogistic distributions can be excluded. From the lognormal and generalised gamma distribution, the generalised gamma distribution provides a clinically more 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 lognormal distribution provides the best statistical fit, however, the curves cross each other, which is not considered clinically plausible by clinical experts. The generalised gamma curves were therefore considered more clinically plausible, and this distribution was selected for this specific transition for both arms, whereas the lognormal distribution is explored as scenario.

Figure 9. Extrapolations for DF to 1L DM (TP2).

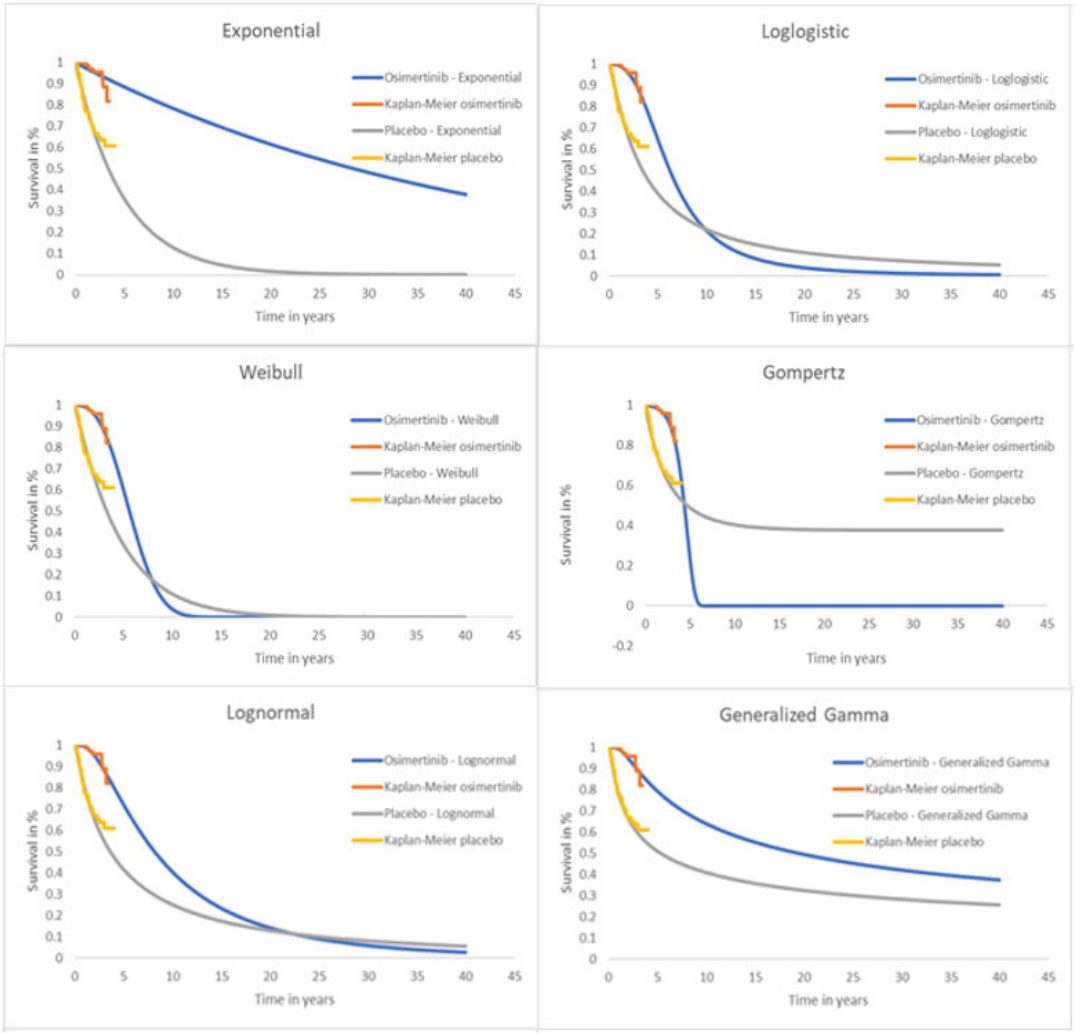


Figure 9b. Extrapolations for DF to 1L DM (TP2) for the placebo arm – all in one.

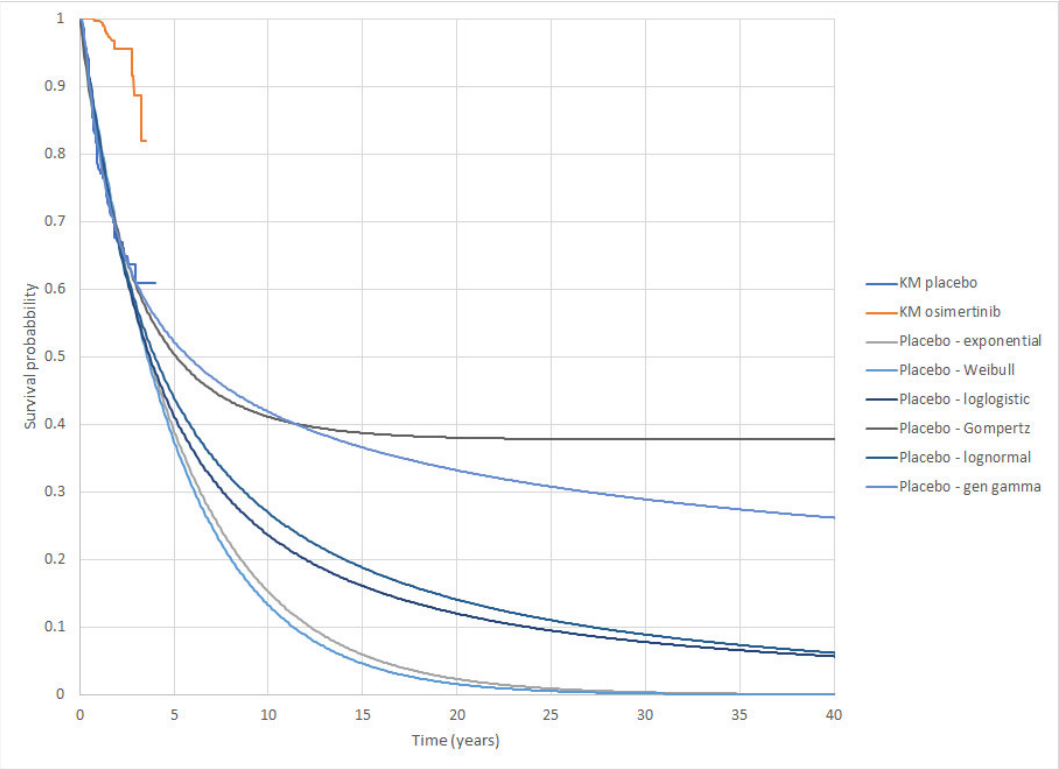


Figure 9c. Extrapolations for DF to 1L DM (TP2) for the osimertinib arm – all in one.

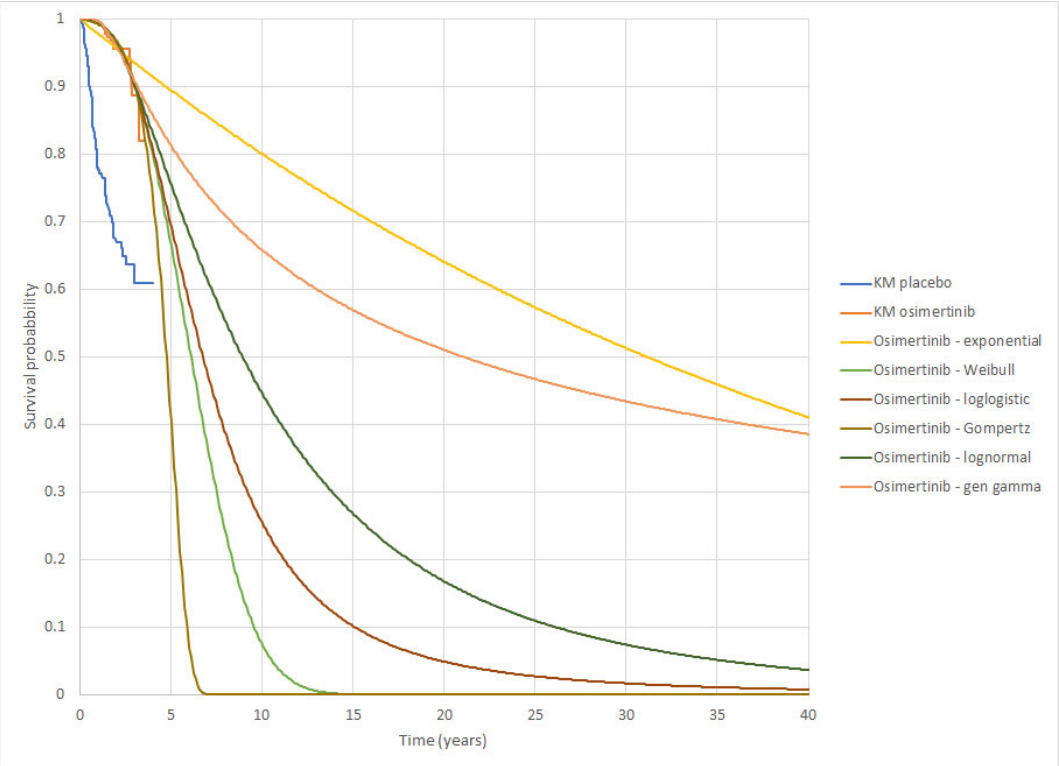


Table 71. AIC and BIC values for the fitted distributions to the transition of DF to 1L DM.

	Individual fits		Combined fits	
	Osimertinib	Placebo		

			(Active monitoring)			
Model	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	195.16	206.64	974.42	985.93	1166.57	1184.67
Lognormal	193.49	201.14	979.52	987.20	1176.61	1190.18
Loglogistic	194.17	201.82	987.45	995.12	1189.44	1203.02
Gompertz	196.52	204.18	990.13	997.81	1197.09	1210.67
Exponential	206.01	209.84	991.11	994.95	1197.12	1206.17
Weibull	194.19	201.84	992.91	1000.58	1197.09	1210.67

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

18.2.1.3 TP3: disease-free (DF) to death

At the ADAURA data cut-off (January 2020), very few deaths had occurred among stage IB–IIIA patients who remained DF (0 in the osimertinib arm and 2 in the placebo arm) As a result of this, no parametric models could be reliably fitted to the data to estimate the transition from DF state to death.(4) This transition was therefore modelled using the background mortality in the age-adjusted Danish population.

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

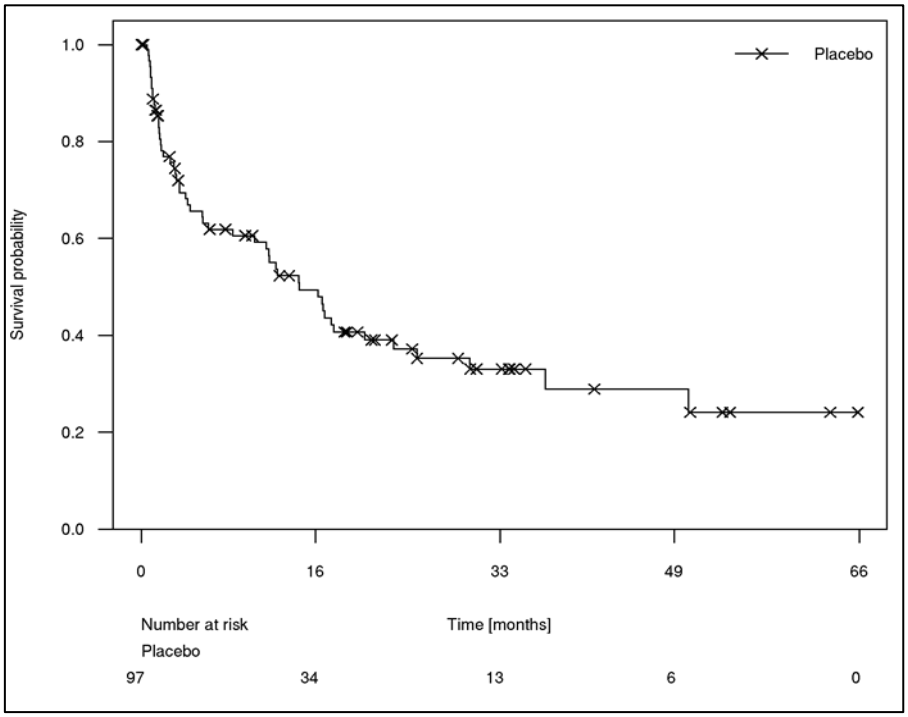
Due to limited post-recurrence follow-up data available from the ADAURA trial at the data cut-off (January 2020), the transitions from local/regional recurrence (LRR) to 1st line treatment of distant metastases (DM1) for both treatment arms were modelled using CancerLinQ data (seeAppendix C) (52). This 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.

18.2.1.5 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.(52) Parametric curves were fitted to the data presented in Figure 10 applying the methods described below.

Figure 10. KM curve for time to distant metastases from CancerLinQ (52).



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 11b.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 72). The loglogistic distribution was explored as a scenario analysis.

Figure 11. Extrapolation of LRR to 1L DM (TP4)

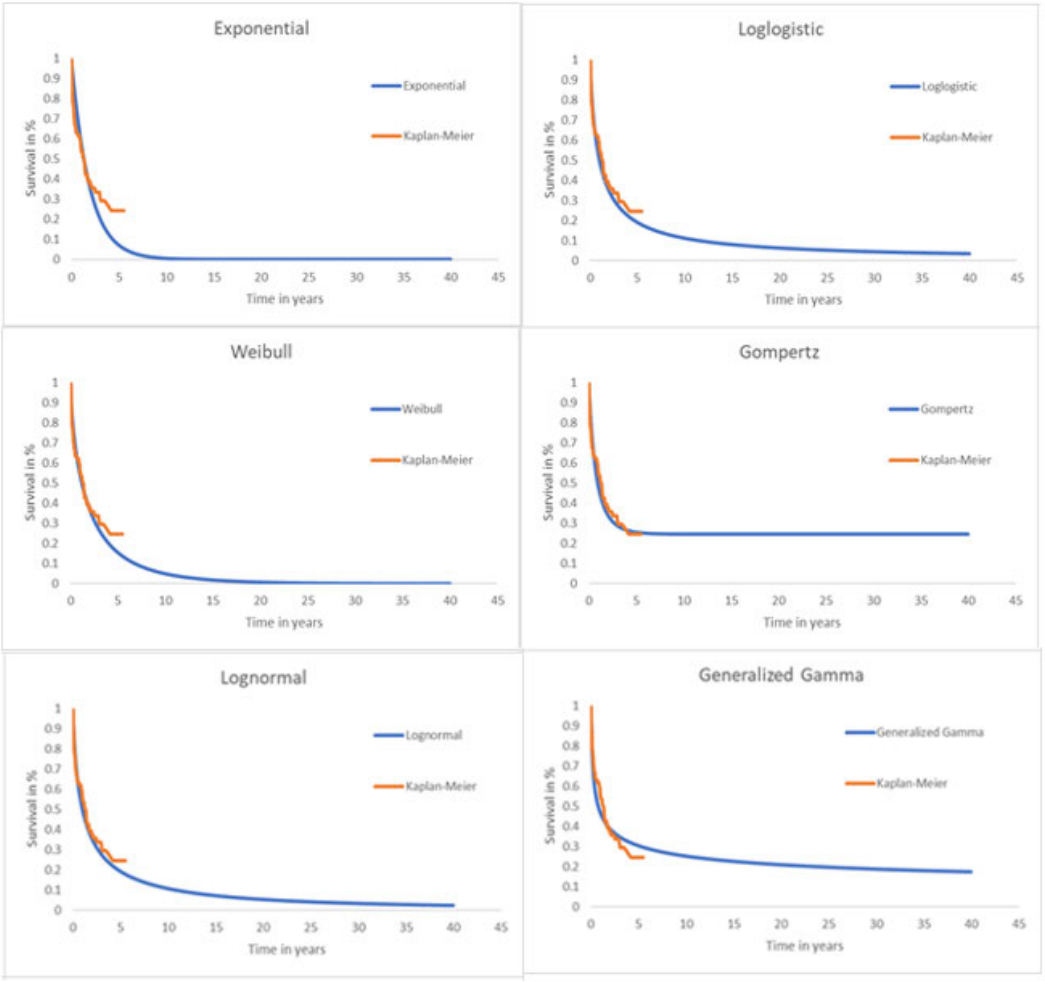


Figure 11b. Extrapolation of LRR to 1L DM (TP4) for all parametric curves.

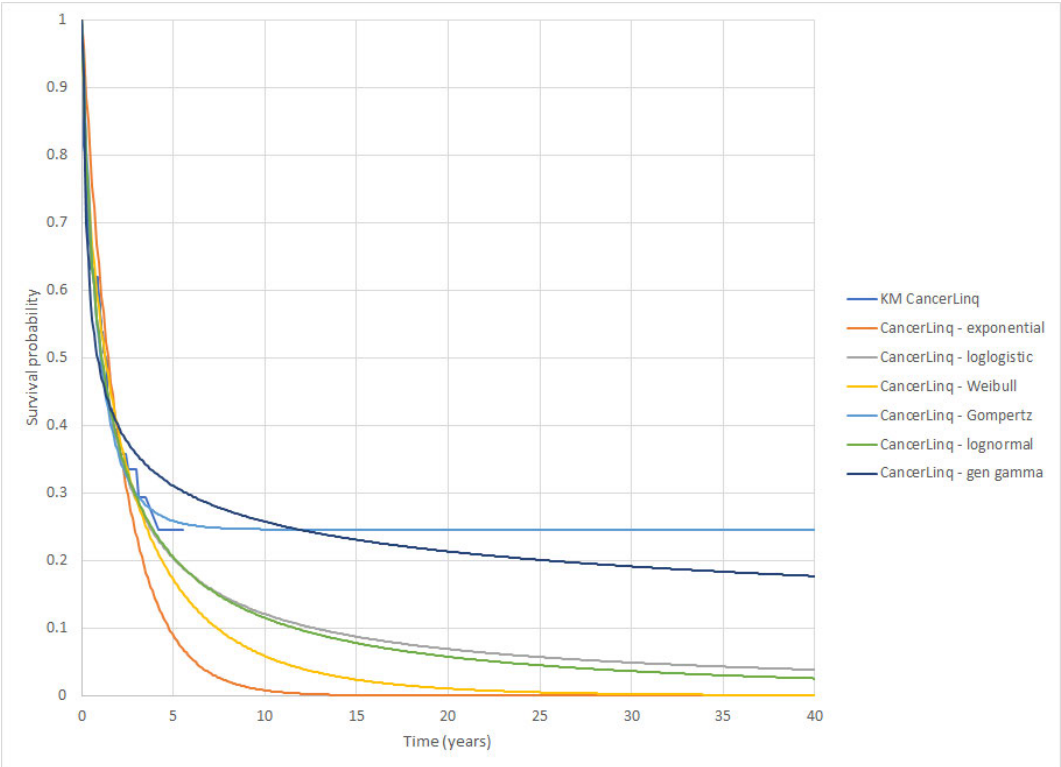


Table 12. AIC and BIC values for the fitted distributions to the transition LRR to 1L DM.

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

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

18.2.1.7 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.(53) 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 inAppendix 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.(70) 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.

18.2.1.8 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.(50, 51) 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 20% 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.(53) 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.(71) 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.(72) 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.(72) 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, (53)) 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.

18.2.1.9 Active monitoring arm

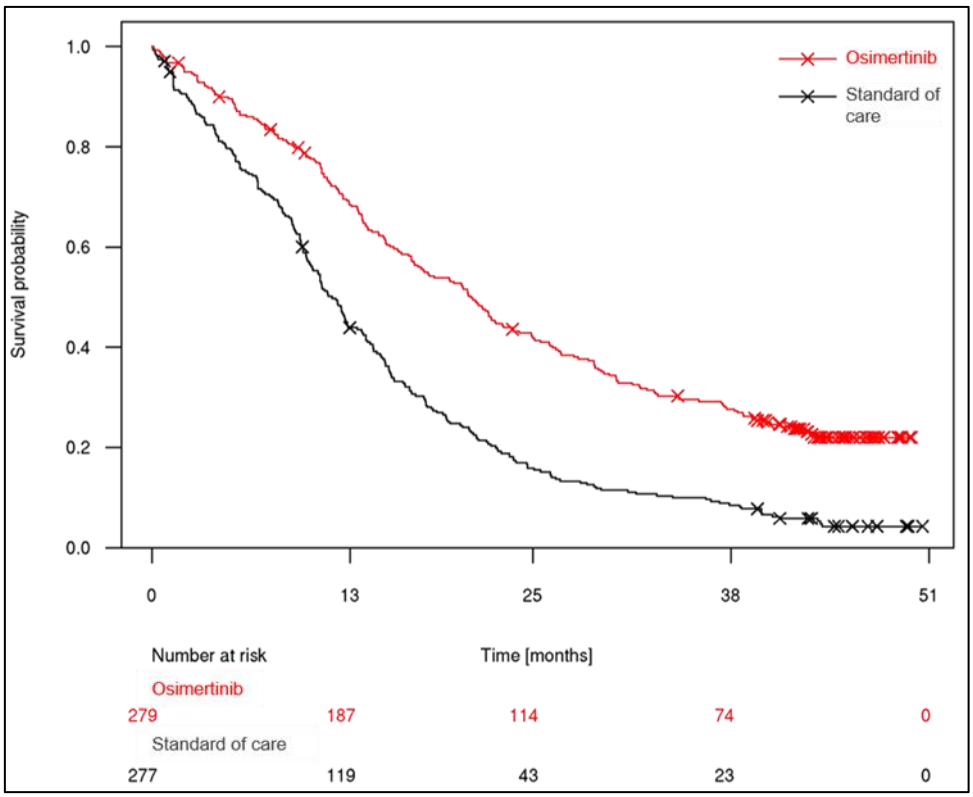
It was assumed that all patients who received active monitoring in the DF health state will get treated with osimertinib at DM1. As osimertinib is the most efficacious TKI compared to SoC TKIs also noted by clinicians, it is assumed that it would be a preferred treatment over other treatments

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.(53) 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 Figure 12 applying the methods described below.

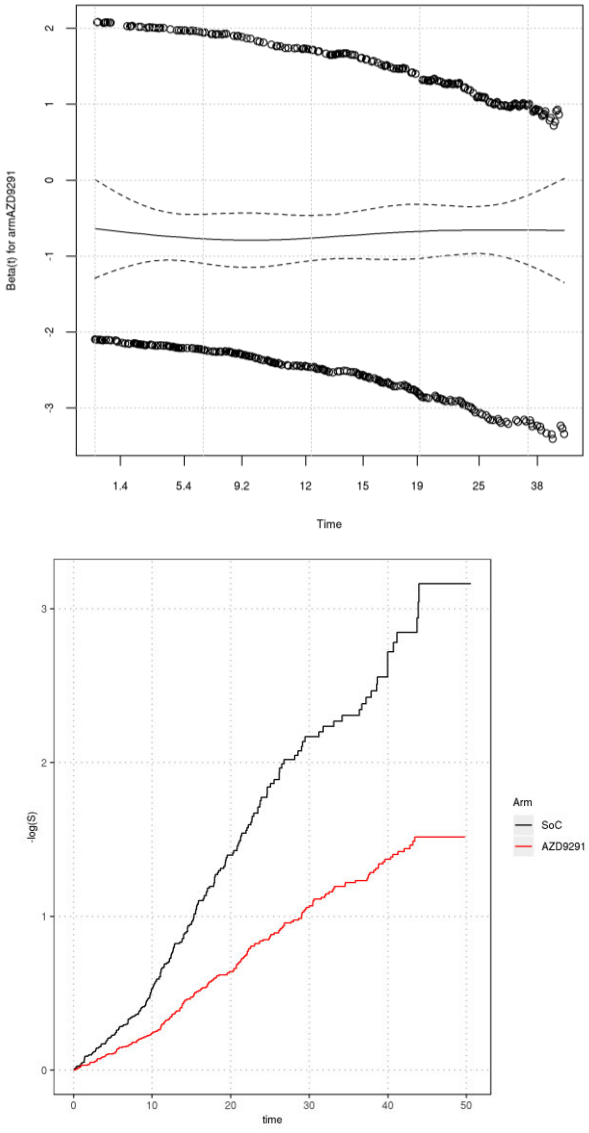
Figure 12. KM curves for the time to discontinuation of treatment (censoring deaths) in the osimertinib and active monitoring arms of FLAURA.(53)



Assessment of the proportional hazards assumption

The Schoenfeld residuals and cumulative hazard plot for the transition DM1 to DM2 is shown in Figure 13. 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.

Figure 13. 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.

Figure 14 shows the fits and extrapolations for the transition from DM1 to DM2 (TP6), with the AIC and BIC values presented in table 73. All parametric curves for the placebo arm are shown in Figure 14b and all curves for the osimertinib arm are shown in Figure 14c. 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.(53) 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 14. Extrapolation of DM1 to DM2 (TP6).

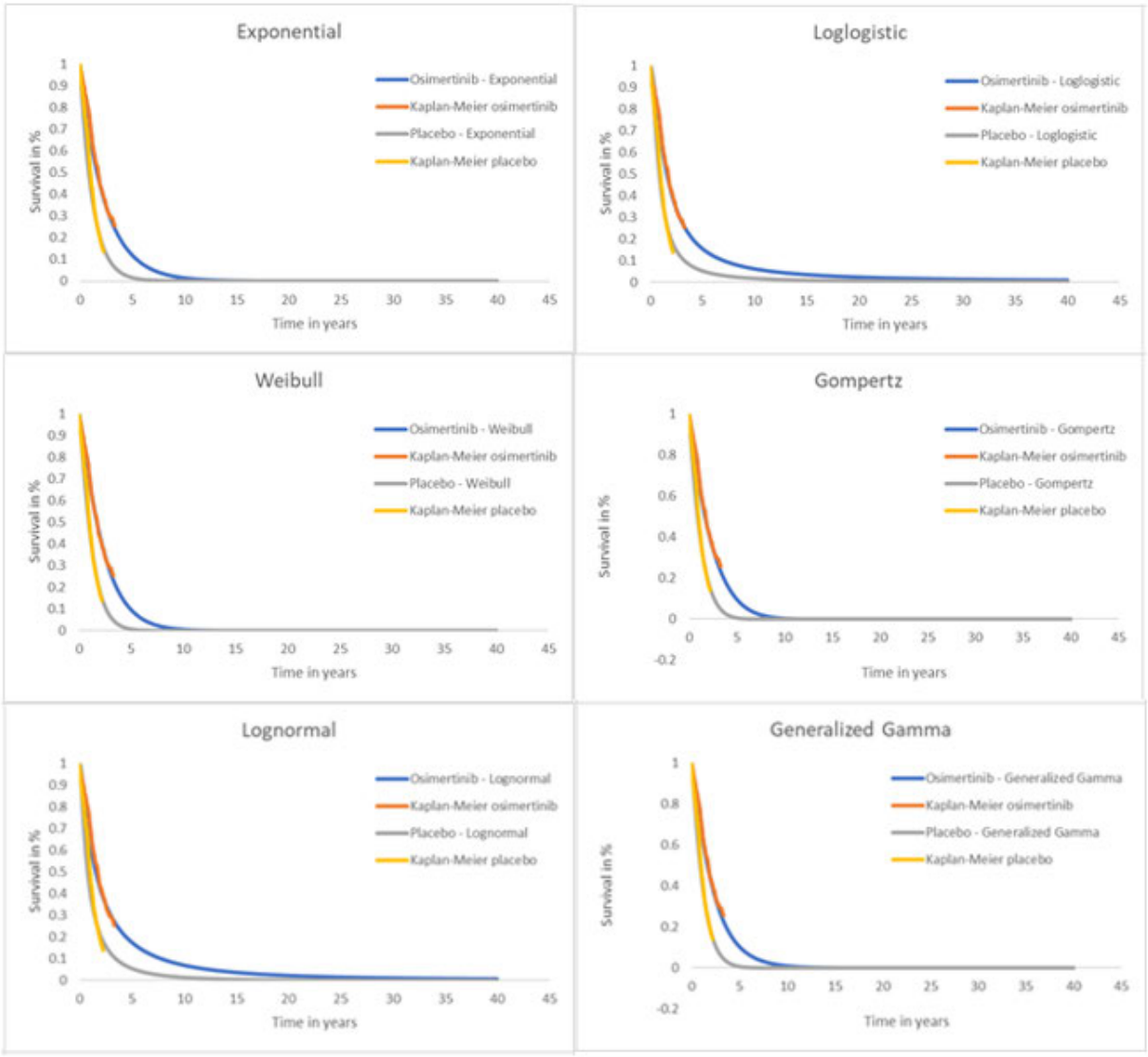


Figure 14b. Extrapolation of DM1 to DM2 (TP6) for the placebo arm – all in one.

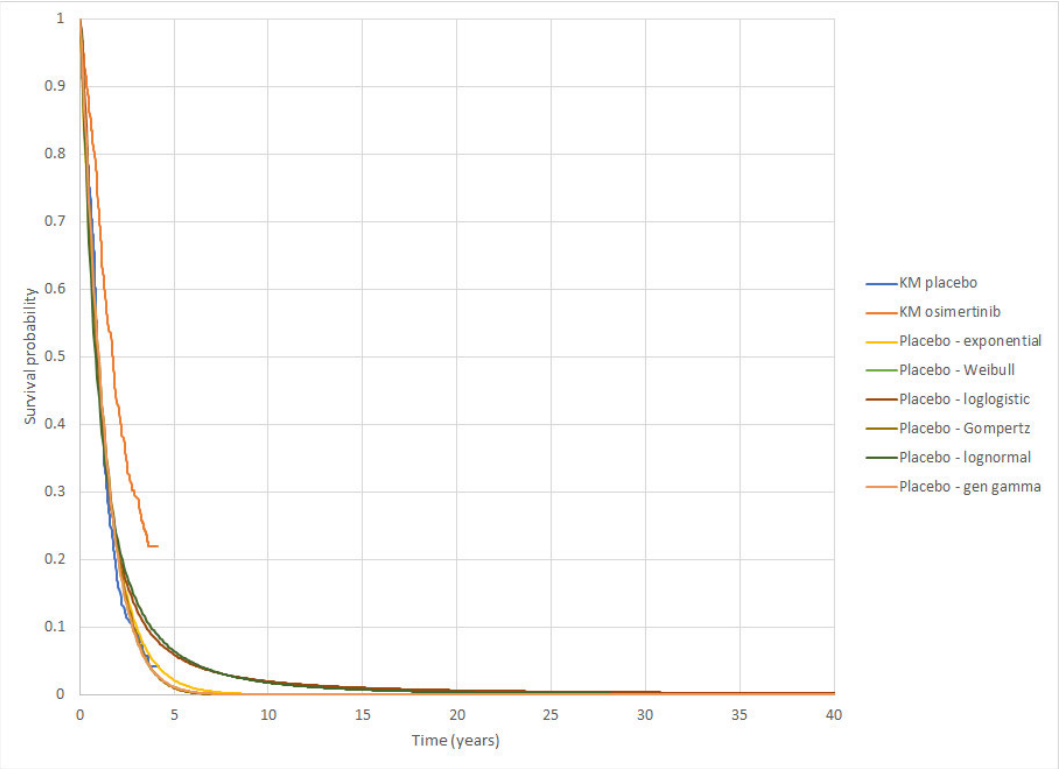


Figure 14c. Extrapolation of DM1 to DM2 (TP6) for the osimertinib arm – all in one.

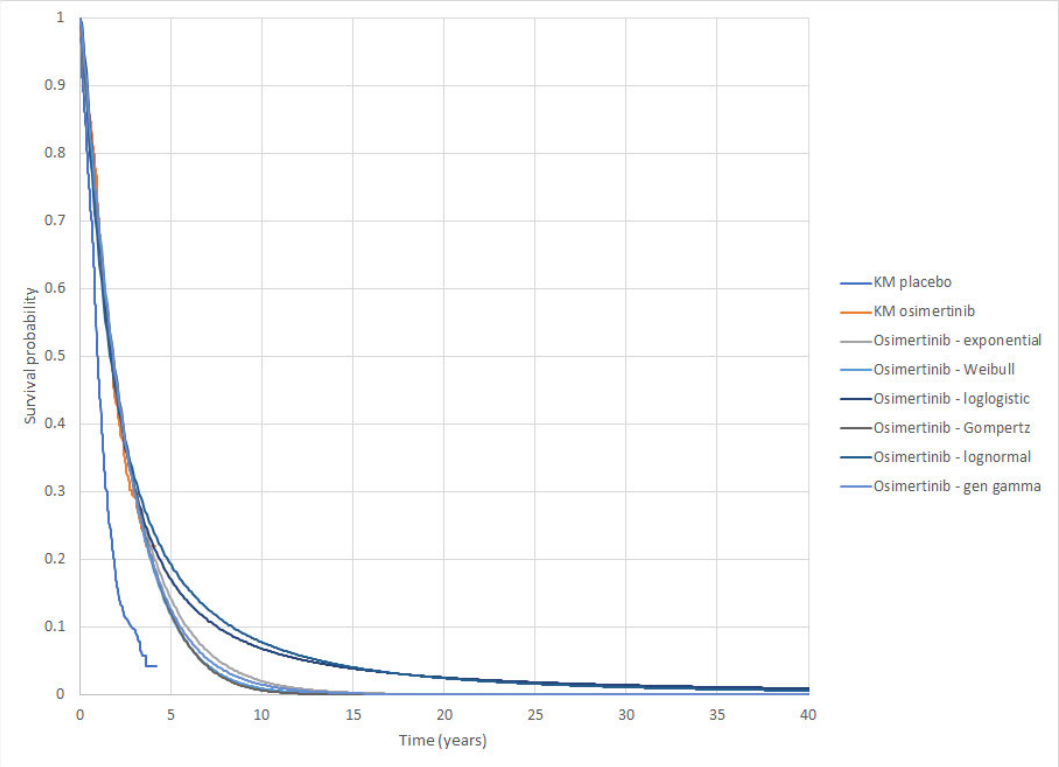


Table 73. Goodness of fit for 1L DM to 2L DM

	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

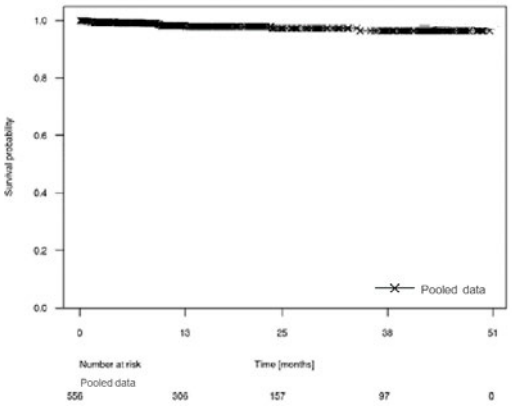
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; SoC, standard of care; Bold values: preferred distribution

18.2.1.10 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).(53) As additional justification, the stratified analysis showed no difference between treatment groups. Parametric curves were fitted to the combined KM data presented in Figure 15 applying the methods described below.

Figure 15. KM curves for the time to death (censoring discontinuation of treatment) using pooled data of both treatment arms of FLAURA (53).

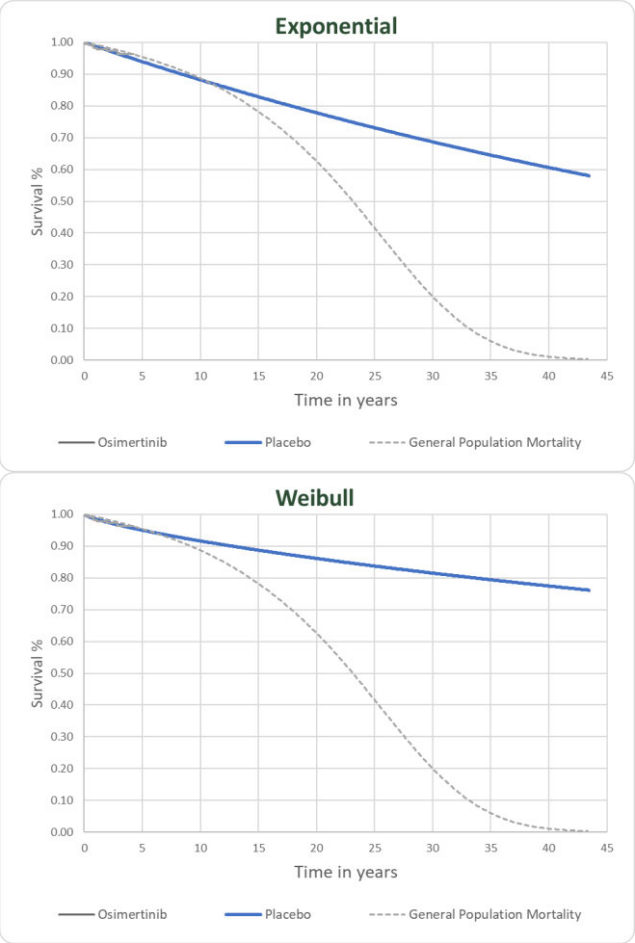


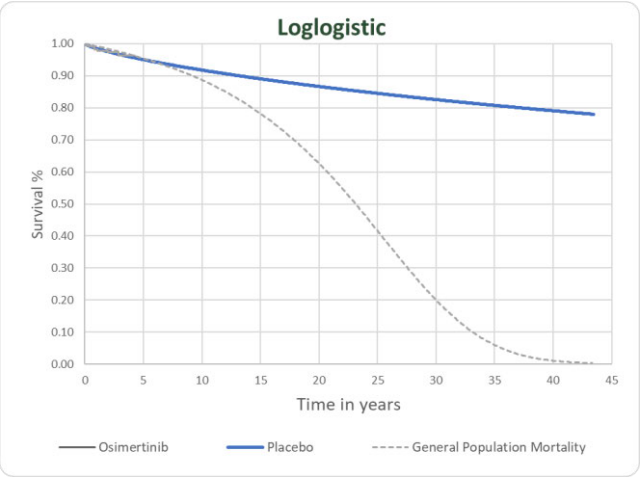
Goodness of fit for parametric distributions

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 16 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 16.(53) However, the exponential distribution has the most clinically plausible extrapolation for patients in a metastatic setting and best statistical fit based on AIC and BIC values (table 74); 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 16. Extrapolation of 1L DM to death (TP7)




Loglogistic
Survival %
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
5
10
15
20
25
30
35
40
45
Time in years
Osimertinib
Placebo
General Population Mortality


Gompertz
Survival %
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
5
10
15
20
25
30
35
40
45
Time in years
Osimertinib
Placebo
General Population Mortality

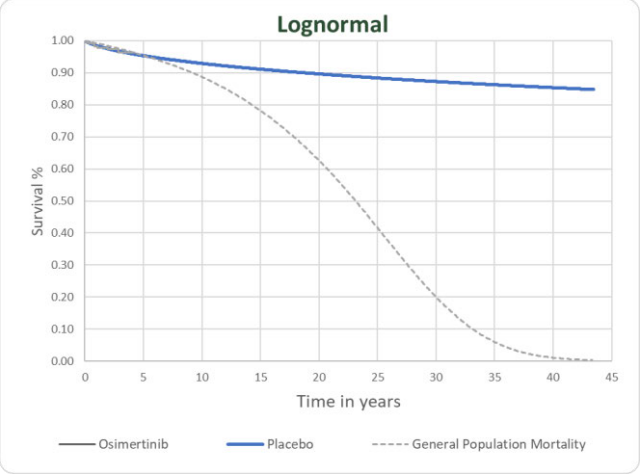

Lognormal
Survival %
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
5
10
15
20
25
30
35
40
45
Time in years
Osimertinib
Placebo
General Population Mortality

Figure 16b. Extrapolation of 1L DM to death (TP7) with all parametric curves.

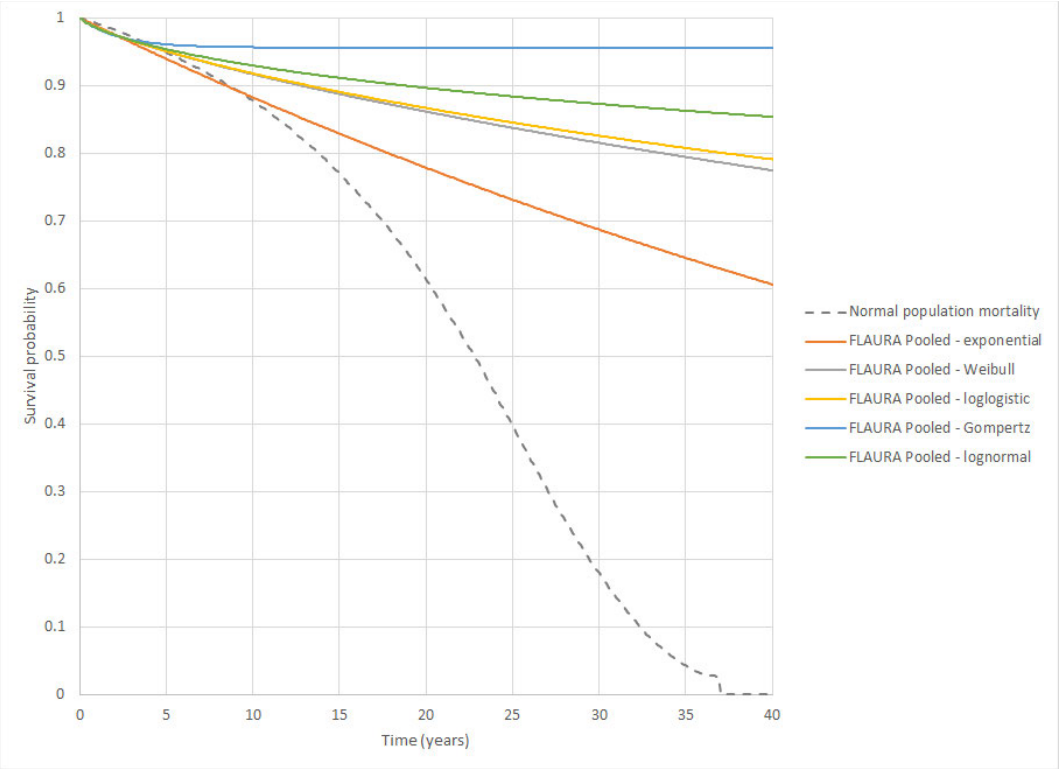


Table 74. Goodness of fit for DM1 to death.

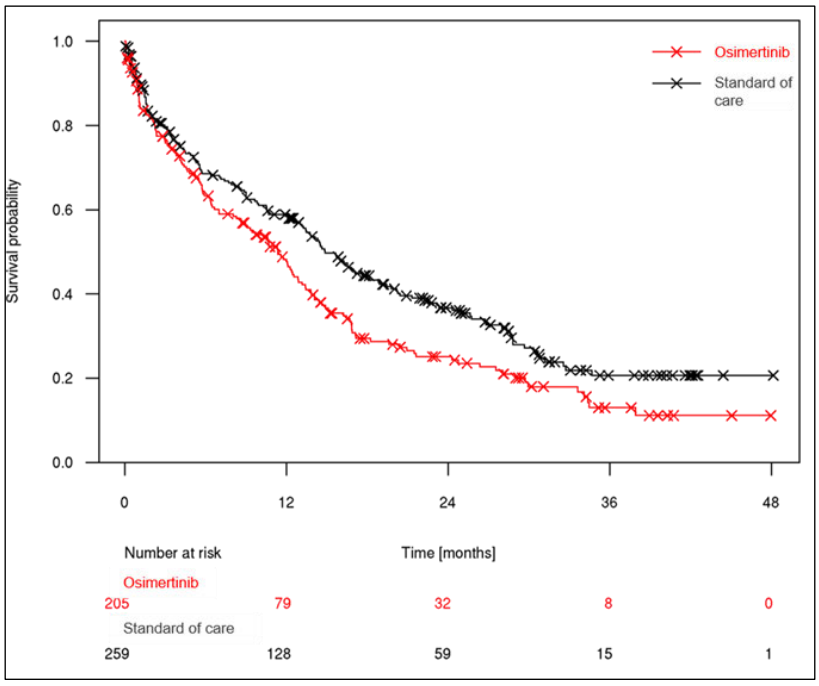
	Osimertinib		SoC	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	**174.97**	**179.29**	**174.97**	**179.29**
Weibull	175.94	184.58	175.94	184.58
Log logistic	175.91	184.55	175.91	184.55
Gompertz	175.40	184.05	175.4	184.05
Lognormal	175.38	184.03	175.38	184.03
Gen. gamma	176.92	189.88	176.92	189.88

18.2.1.11 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.(53) 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 17 applying the methods described below.

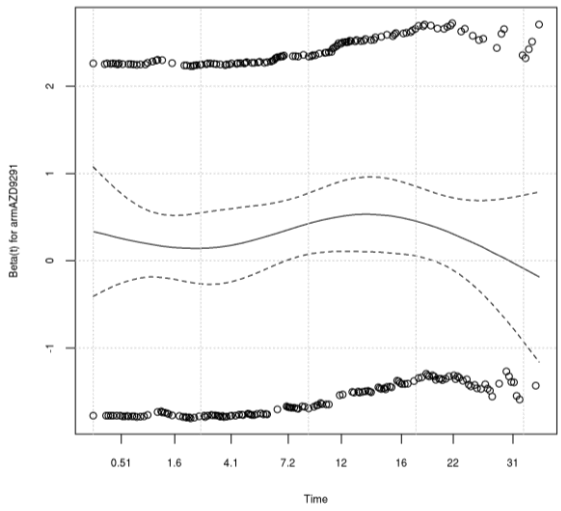
Figure 17. KM curves for post time to discontinuation of treatment in the osimertinib and SoC arms of FLAURA (53).

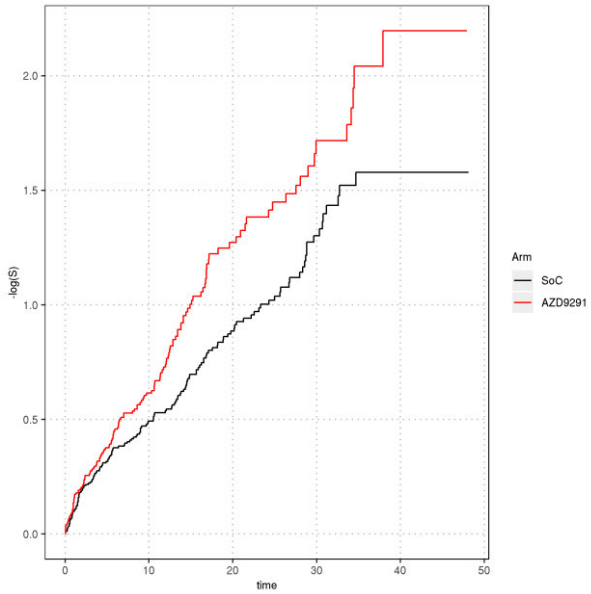


Assessment of the proportional hazards assumption

The Schoenfeld residuals and cumulative hazard plot for the transition of 2L DM to death are shown in Figure 18. 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.

Figure 18. Schoenfeld residuals and cumulative hazard plot for the transition 2L DM to death (TP8).

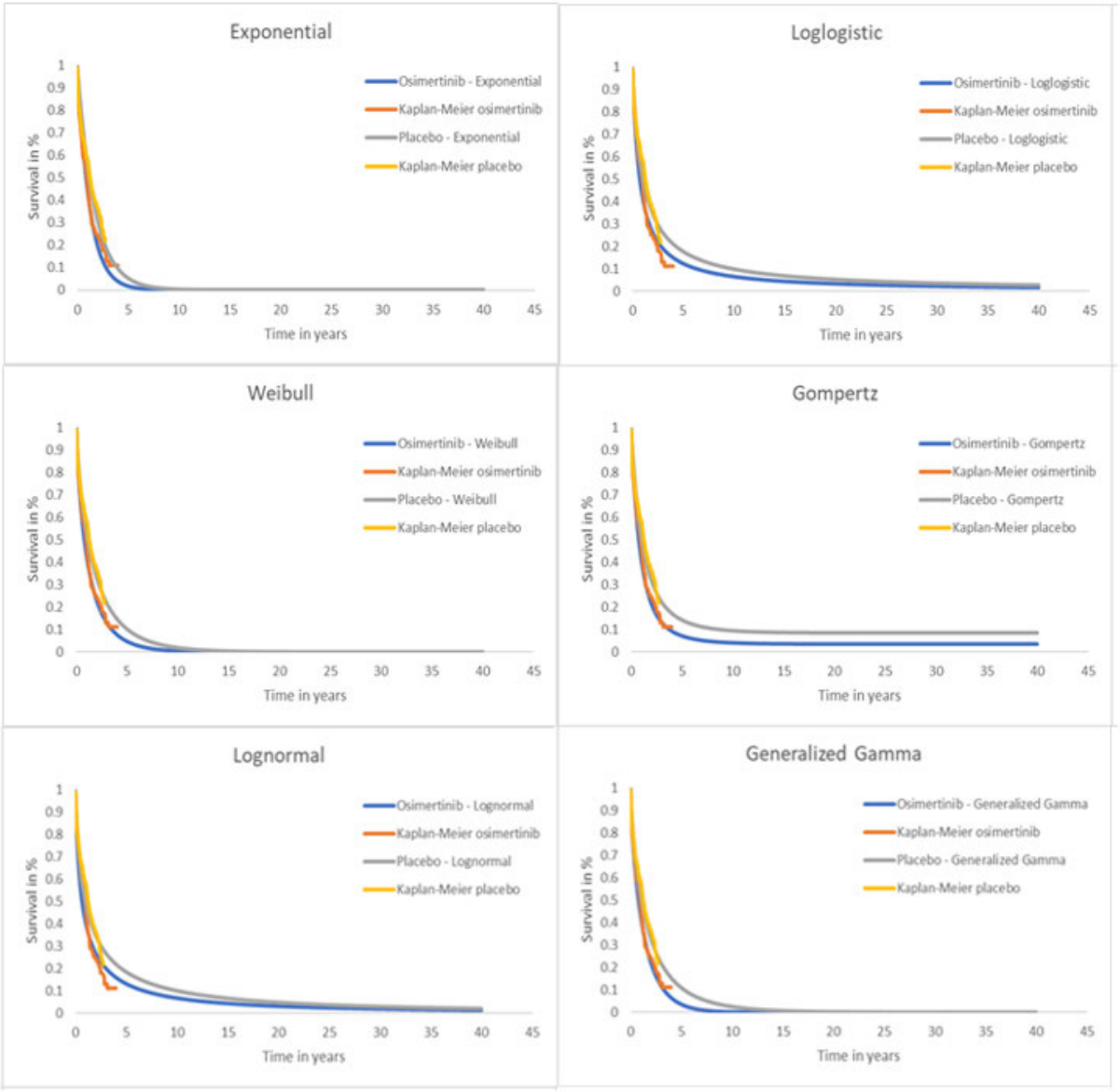




Goodness of fit for parametric distributions

Independent parametric distributions were assessed for their goodness of fit based on visual inspection and whether the extrapolation is clinically realistic. Figure 19 shows the fits and extrapolations for the transition from DM2 to death (TP8), with the AIC and BIC values provided in the table 75. All parametric curves for the placebo arm are shown in Figure 19b and all curves for the osimertinib arm are shown in Figure 19c. 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.(53) Based on statistical fit, the Weibull distribution provides the best fit; therefore, this distribution was selected for the base case analysis.

Figure 19. 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.

Figure 19b. Extrapolation of 2L DM to death (TP8) for the placebo arm – all in one.

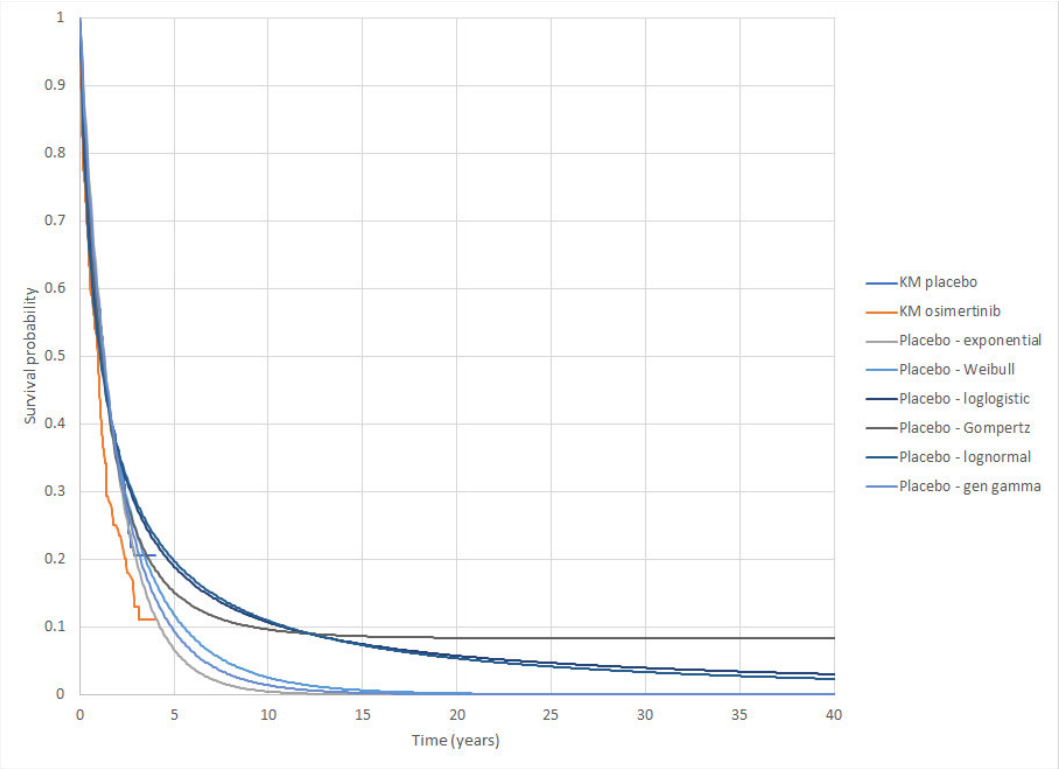


Figure 19c. Extrapolation of 2L DM to death (TP8) for the osimertinib arm – all in one.

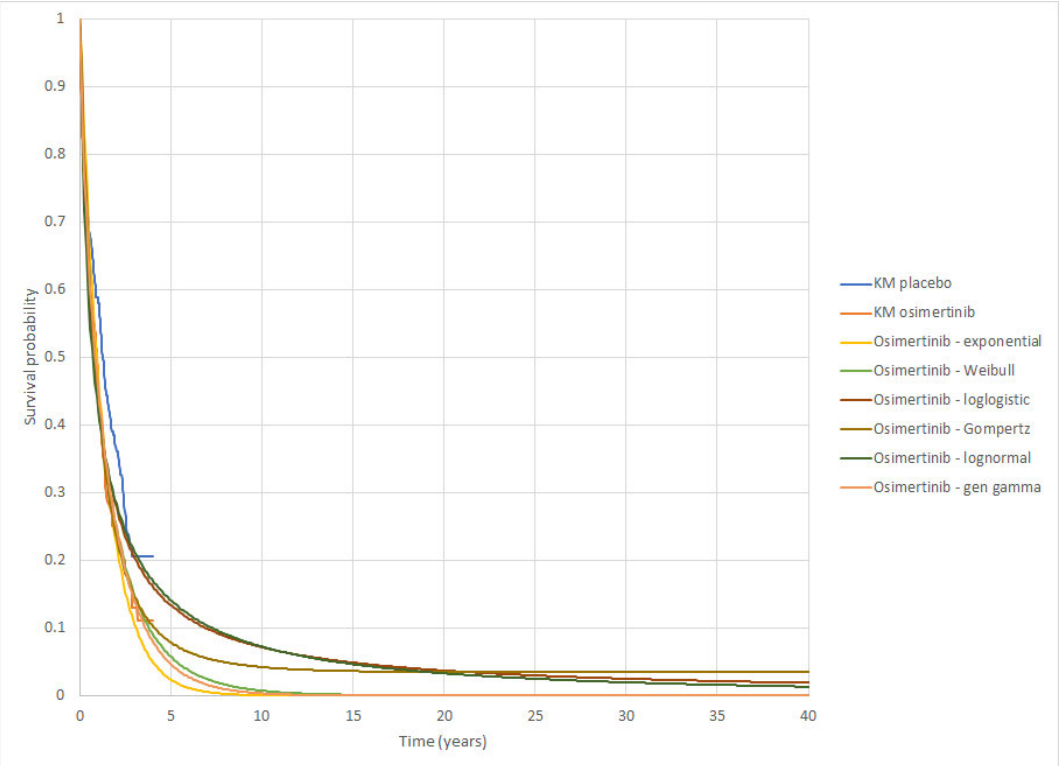


Table 75. Goodness of fit for DM2 to death.

	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

19. Appendix H – Literature search for HRQoL data

The search syntaxes that were used to find information on HRQoL linked to early stage NSCLC for each electronic database are available in table 76. PICOS criteria for HRQoL are presented in table 79.

Table 76. Pubmed search strategy for HRQoL

Category	No.	Search Algorithm	Search Yield results 24th September 2020
Disease terms	**#1**	("lung neoplasms"[MeSH] OR "carcinoma, non small cell lung"[MeSH] OR lung carcinom*[tiab] OR lung neoplasm*[tiab] OR lung cancer[tiab] OR "NSCLC"[tiab] OR non small cell lung cancer [tiab])	292,239
Disease specification terms	**#2**	(epidermal growth factor receptor[tiab] OR *EGFR*[tiab] OR tyrosine kinase inhibit*[tiab] OR TKI[tiab] OR monoclonal antibod*[tiab])	238,212
Setting terms	**#3**	(early-stage[tiab] OR early-stage[tiab] OR early[tiab] OR adjuvant[tiab] OR neoadjuvant OR stage ib[tiab] OR stage 1[tiab] OR stage one[tiab] OR stage ii[tiab] OR stage 2 [tiab] OR stage two[tiab] OR stage iiia[tiab] OR stage 3a[tiab] OR stage three[tiab] OR stage 3[tiab])	1,738,345

HRQoL	**#4**	(Patient reported outcomes[tiab] OR quality of life[tiab] OR Utilities [tiab] OR Disutility [tiab] OR Utility [tiab] "EuroQol"[tiab] OR "EQ-5D"[tiab] OR "SF-36"[tiab] OR Health utility index[tiab] OR time trade off [tiab] OR Standard gamble [tiab] OR Mapping [tiab] OR Economic model[tiab] OR cost-effectiveness[tiab] OR cost-utility[tiab]) OR 'Value of Life'[mh] OR 'HR-PRO'[tiab] OR 'HR PRO'[tiab] OR 'HRQL'[tiab] OR 'HRQoL'[tiab] OR 'QL'[tiab] OR 'QoL'[tiab] OR 'quality of life'[tw] OR 'life quality'[tw] OR quality of life[tiab] OR 'Quality-Adjusted Life Years'[mh] OR 'quality adjusted life'[tiab] OR qaly*[tiab] OR health index*[tiab] OR health indices'[tiab] OR 'health utility index'[tiab] OR 'health profile*[tiab] OR 'health status'[tw] OR patient reported outcome*[tiab] OR utility[tiab] OR disutility[tiab] OR utilities[tiab] OR disutilities[tiab] OR 'EuroQoL'[tiab] OR 'EQ-5D'[tiab] OR 'euro qol'[tiab] OR 'eq5d'[tiab] OR 'eq 5d'[tiab] OR 'SF-36'[tiab] OR 'sf36'[tiab] OR 'sf 36'[tiab] OR 'short form 36'[tiab] OR 'shortform 36'[tiab] OR 'short form36'[tiab] OR 'shortform36'[tiab] OR 'time trade off'[tiab] OR 'time tradeoff'[tiab] OR visual analog* scale*[tiab] OR 'VAS'[tiab] OR 'standard gamble'[tiab] OR mapping[tiab] OR 'economic model'[tiab] OR 'cost-effectiveness'[tiab] OR 'cost utility'[tiab] OR 'functional status questionnaire'[tiab] OR 'discrete choice experiment*[tiab] OR 'Personal trade-off'[tiab] OR "hui"[tiab] OR 'hui1'[tiab] OR 'hui2'[tiab] OR 'hui3'[tiab] OR 'health utility index'[tiab] OR (utilit*[tiab] AND (valu*[tiab] OR measur*[tiab] OR health[tiab] OR life[tiab] OR estimat*[tiab] OR elicit*[tiab] OR disease[tiab] OR score*[tiab] OR weight[tiab])) OR (preference*[tiab] AND (valu*[tiab] OR measur*[tiab] OR health[tiab] OR life[tiab] OR estimat*[tiab] OR elicit*[tiab] OR	1,037,935

		disease[tiab] OR score*[tiab] OR instrument[tiab] OR instruments[tiab]))	
Language	**#5**	English[lang]	26,887,262
Limitation	**#6**	("Letter" [ptyp] OR "Editorial" [ptyp] OR "Historical Article" [ptyp] OR "Case Reports" [ptyp] OR (animals[mh] NOT humans [mh]))	8,587,762
	#7	(#1 AND #2 AND #3 AND #4 AND #5) NOT #6	**101**

Table 77. Embase search strategy for HRQoL

Category	No.	Search Algorithm	Search Yield results 16th October 2020
Disease terms	**#1**	'lung tumor'/exp OR (lung AND tumor*:ab,ti) OR 'non small cell lung cancer'/exp OR (non AND small AND cell AND lung AND cancer:ab,ti) OR (lung AND carcinom*:ab,ti) OR (lung AND cancer:ab,ti) OR 'nsclc':ab,ti	604,073
Disease specification terms	**#2**	'epidermal growth factor receptor':ab,ti OR *EGFR*:ab,ti OR 'tyrosine kinase inhibit*':ab,ti OR tki:ab,ti OR 'monoclonal antibod*':ab,ti	390,201
Setting terms	**#3**	early stage':ab,ti OR early:ab,ti OR adjuvant:ab,ti OR neoadjuvant:ab,ti OR 'stage ib':ab,ti OR 'stage 1':ab,ti OR 'stage one':ab,ti OR 'stage ii':ab,ti OR 'stage 2':ab,ti OR 'stage two':ab,ti OR 'stage iiia':ab,ti OR 'stage 3a':ab,ti OR 'stage three':ab,ti OR 'stage 3':ab,ti	2.393,416
HRQoL terms	**#4**	'Value of Life'/exp OR 'hr-pro':ab,ti OR 'hr pro':ab,ti OR 'hrql':ab,ti OR 'hrqol':ab,ti OR 'ql':ab,ti OR 'qol':ab,ti OR 'quality of life'/exp OR 'quality of life':ab,ti OR 'life quality':ab,ti OR 'Quality-Adjusted Life Years'/exp OR 'quality adjusted life':ab,ti OR qaly*:ab,ti OR health index*:ab,ti OR 'health indices':ab,ti OR 'health utility index':ab,ti OR 'health	1,013,562

		profile':ab,ti OR 'health status':ab,ti OR patient reported outcome*:ab,ti OR 'utility':ab,ti OR 'disutility':ab,ti OR 'utilities':ab,ti OR 'euroqol':ab,ti OR 'euro qol':ab,ti OR 'eq5d':ab,ti OR 'eq 5d':ab,ti OR 'euroqual':ab,ti OR 'euro qual':ab,ti OR 'euroqol':ab,ti OR 'eq-5d':ab,ti OR 'sf36':ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'short form36':ab,ti OR 'shortform36':ab,ti OR 'sf thirtysix':ab,ti OR 'sfthirtysix':ab,ti OR 'sfthirty six':ab,ti OR 'sf thirty six':ab,ti OR 'shortform thirtysix':ab,ti OR 'shortform thirty six':ab,ti OR 'short form thirtysix':ab,ti OR 'short form thirty six':ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR 'visual analog scale':ab,ti OR 'VAS':ab,ti OR 'standard gamble':ab,ti OR 'mapping':ab,ti OR 'economic model':ab,ti OR 'cost-effectiveness':ab,ti OR 'cost utility':ab,ti OR 'functional status questionnaire':ab,ti OR 'discrete choice experiment':ab,ti OR 'Personal trade-off':ab,ti OR 'hui':ab,ti OR 'hui1':ab,ti OR 'hui2':ab,ti OR 'hui3':ab,ti OR 'health utility index':ab,ti OR (utility*:ab,ti AND (valu*:ab,ti OR measur*:ab,ti OR health:ab,ti OR life:ab,ti OR estimate*:ab,ti OR elicit*:ab,ti OR disease:ab,ti OR score*:ab,ti OR weight:ab,ti)) OR (preference*:ab,ti AND (valu*:ab,ti OR measur*:ab,ti OR health:ab,ti OR life:ab,ti OR estimate*:ab,ti OR elicit*:ab,ti OR disease:ab,ti OR score*:ab,ti OR instrument:ab,ti OR instruments:ab,ti))	
Language	**#5**	[English]/lim	31,987,914
Limitations	**#6**	letter:it OR editorial:it OR (review:it OR 'review literature as topic'/exp OR 'literature review':ti NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)) OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)) OR 'case report*':ab,ti OR 'case series':ab,ti	10,377,247

#7	(#1 AND #2 AND #3 AND #4 AND #5) NOT #6	**359**

Table 78. Cochrane search strategy for HRQoL

Date the search was conducted	16th October 2020
Search terms	Number of hits
NSCLC AND utility	**264**

Table 79. PICOS criteria for HRQoL

	Inclusion Criteria	Exclusion Criteria
Population	• Patients with histologically or cytologically confirmed 1b-3a NSCLC with *EGFR* mutations; • Any treatment line	• Patients with wild-type mutation or any other mutation; • Any other indication (relapsed or refractory disease, etc); Patients with stage IA, IIIB-IV NSCLC
Intervention and comparators	Any intervention	NA
Outcomes	Any HRQoL values related to the indication and/ or the intervention that are given in EQ-5D, SF-6D and other questionnaires.	Studies that do not contain any relevant outcomes
Study design	• Randomized controlled trials (RCTs); • Economic Evaluations; • SLRs	Any other study design
Language restrictions	English	Any other language
Date	• Databases: NA; • Conferences: After January 2017	• Databases: NA; • Conferences: Before January 2017
Country	Any country	NA

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.

19.1 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.(73, 74) 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).(74) A list of the interaction terms are available in the full utility mapping report (75)S; the EQ-5D utility score is the dependent variable. To obtain utility scores, UK-specific preference weights were used to calculate utility values(76). 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(77).

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.(78) 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(75).
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

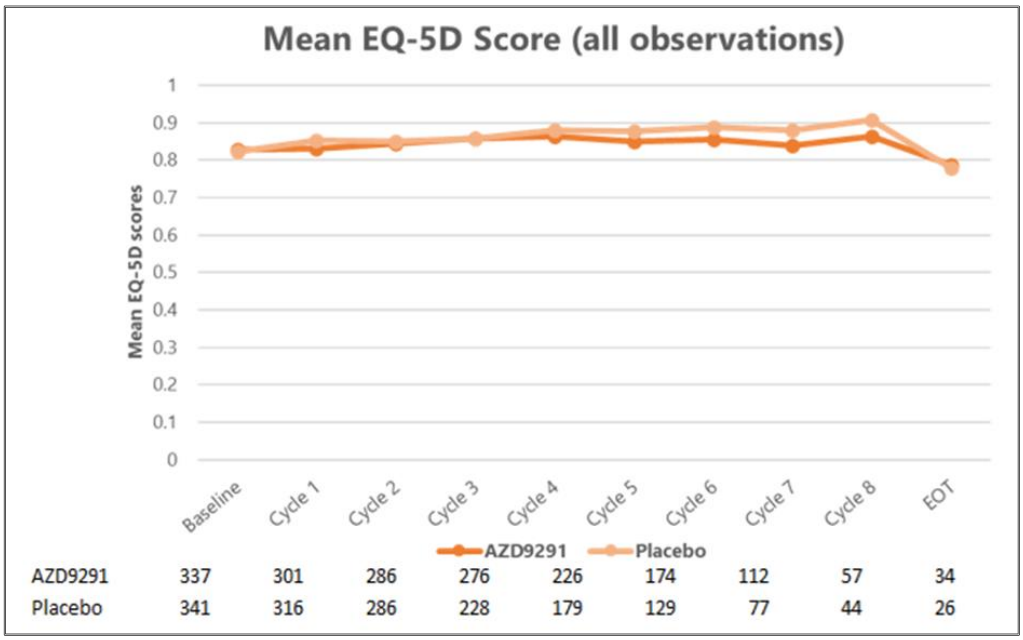
- Subgroup analyses; to ensure the algorithms fitted equally across all groups

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.

19.2 Results of mapping analysis

As shown in Figure 20 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 20. 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. 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 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:

Intercept + (baseline coefficient × average baseline)

Intercept + (baseline coefficient × average baseline) + 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. (74) 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.

20. 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