

Amivantamab plus Lazertinib vs Osimertinib plus Chemotherapy for the First-line Treatment of Advanced Non-Small Cell Lung Cancer



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List of abbreviations

AE.....adverse event	cFAS.....CNS full analysis set
AEsadverse events	CI.....confidence interval
AIHTAAustrian Institute for Health Technology Assessment	CNS.....central nervous system
AMV+LAZ...amivantamab plus lazertinib	CoI.....conflict of interest
AUCarea under the curve	CSPclinical study protocol
BIAbudget impact analysis	CTcomputed tomography
BICRblinded independent central review	DCR.....disease control rate
CDA-AMC....Canada's Drug Agency	DOR.....duration of response
CEA.....cost-effectiveness analysis	ECOG.....Eastern Cooperative Oncology Group
cEFRCNS evaluable for response	EGFR.....epidermal growth factor receptor
	EMA.....European Medicines Agency

EOT.....end of treatment	NICE.....National Institute for Health and Care Excellence
EPAREuropean Public Assessment Report	NIHONational Institute for Value and Technologies in Healthcare
EUnetHTA ...European Network for Health Technology Assessment	NMAnetwork meta-analysis
Ex19delexon 19 deletion	NR.....not reported
HER2human epidermal growth factor receptor 2	NR.....not reached
HR.....hazard ratio	NRCs.....non-randomised controlled studies
HRQoLhealth-related quality of life	NRG1neuregulin 1
HTAhealth technology assessment	NSCLCnon-small cell lung cancer
HTDhealth technology developer	ORRobjective response rate
ICERincremental cost-effectiveness ratio	OS.....overall survival
IQWiG.....Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	OSM+CHEM osimertinib plus chemotherapy
IPDindividual patient data	PAS.....patient access scheme
IRR.....infusion-related reaction	PD-L1programmed death-ligand 1
ITCindirect treatment comparison	PFS.....progression-free survival
ITTintention-to-treat	PFS2.....progression-free survival after first subsequent therapy
IV.....intravenous	PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analyses
IVRS.....interactive voice response system	PRO.....patient-reported outcome
IWRS.....interactive web response system	PSperformance status
KRASKirsten rat sarcoma viral proto-oncogene	QALYquality-adjusted life-year
L858R.....leucine-to-arginine substitution at codon 858	QoLquality of life
LCC.....large cell carcinoma	RCT.....randomised controlled trial
LKF.....leistungsorientierte Kranken- anstaltenfinanzierung (<i>performance- oriented hospital financing</i>)	RECISTResponse Evaluation Criteria in Solid Tumours
LMWH.....low-molecular-weight heparin	RETrearranged during transfection
LOGiKLung Oncology Group in Kyushu	RoB.....risk of bias
MAICmatching-adjusted indirect comparison	ROS1ROS proto-oncogene 1
MRImagnetic resonance imaging	SAEs.....serious adverse events
mTASQmodified Treatment Satisfaction Questionnaire	SAP.....statistical analysis plan
N.....number of patients	SATs.....single-arm trials
n.....number of events	SC.....subcutaneous
NAnot applicable	SCCsquamous cell carcinoma
NCnot calculable	SmPCsummary of product characteristics
NCCNNational Comprehensive Cancer Network	TEAEs.....treatment-emergent adverse events
NEnot estimable	TKI.....tyrosine kinase inhibitor
NEJSG.....North-East Japan Study Group	TMBtumour mutational burden
NGS.....next-generation sequencing	TTDtime to treatment discontinuation
	TTSP.....time to symptomatic progression
	TTST.....time to subsequent therapy
	VTE.....venous thromboembolism
	WHO.....World Health Organization

Zusammenfassung

Hintergrund

Lungenkrebs ist weltweit die häufigste krebsbedingte Todesursache und mit 5.533 Neuerkrankungen im Jahr 2024 die dritthäufigste Krebserkrankung in Österreich. Das nicht-kleinzellige Lungenkarzinom (NSCLC) macht rund 85 % aller Lungenkarzinome aus und ist mit einer ungünstigen Prognose verbunden. Fast die Hälfte der Patient:innen wird erst im metastasierten Stadium diagnostiziert. Die 5-Jahres-Überlebensrate bei metastasiertem NSCLC liegt bei lediglich rund 4 %. Obwohl Tabakkonsum der wichtigste Risikofaktor bleibt, tritt etwa ein Viertel aller Erkrankungen bei Nichtraucher:innen auf.

Das NSCLC wird zunehmend anhand seines molekularen Profils klassifiziert, das therapeutisch relevante Treibermutationen umfasst. Veränderungen des epidermalen Wachstumsfaktor-Rezeptors (EGFR) gehören zu den wichtigsten molekularen Alterationen. Sie treten überwiegend bei Adenokarzinomen sowie häufiger bei Nichtraucher:innen, Frauen und asiatischen Patient:innen auf. Weltweit weisen rund 32 % der NSCLC-Patient:innen eine EGFR-Mutation auf, in Europa beträgt die Prävalenz etwa 14 %. Österreichische Registerdaten zeigen eine EGFR-Mutationsrate von 11 %, davon entfallen etwa 60 % auf häufige Mutationen, insbesondere Exon-19-Deletionen und Exon-21-L858R-Substitutionen.

Für die Erstlinienbehandlung des fortgeschrittenen NSCLC mit diesen häufigen EGFR-Mutationen stehen unter anderem Amivantamab plus Lazertinib sowie Osimertinib plus platinbasierte Chemotherapie zur Verfügung, beide werden auch in internationalen Leitlinien als Therapieoptionen angeführt. Amivantamab plus Lazertinib kombiniert einen intravenös oder subkutan verabreichten bispezifischen Antikörper mit einer oralen zielgerichteten Therapie, während die zielgerichtete Therapie mit Osimertinib oral in Kombination mit intravenös verabreichter Pemetrexed- und platinbasierter Chemotherapie eingesetzt wird.

Beide Therapien sind zugelassen und in Österreich bereits verfügbar. Für die Entscheidung über ihren Einsatz sind neben der klinischen Wirksamkeit und Sicherheit insbesondere die unterschiedlichen Behandlungskosten sowie die Anforderungen an Verabreichung, Supportivtherapie und Monitoring in den Krankenanstalten relevant. Der vorliegende HTA-Bericht bewertet daher die klinischen, gesundheitsökonomischen und organisatorischen Aspekte beider Therapieoptionen aus der Perspektive des österreichischen Gesundheitssystems und berücksichtigt zusätzlich die Verfügbarkeit der subkutanen Formulierung von Amivantamab.

Klinische Evidenz

Für den direkten Vergleich von Amivantamab plus Lazertinib mit Osimertinib plus Chemotherapie liegt derzeit keine randomisierte Vergleichsstudie vor. Zwar wurden mehrere indirekte Vergleiche identifiziert, deren Aussagekraft jedoch aufgrund methodischer Limitationen und teilweise eingeschränkter Transparenz begrenzt ist. Für die Bewertung wurden daher zusätzlich die Ergebnisse der beiden pivotalen randomisierten Phase-III-Studien MARIPOSA (Amivantamab plus Lazertinib) und FLAURA2 (Osimertinib plus Chemotherapie), die jeweils Osimertinib-Monotherapie als Vergleichstherapie untersuchten, deskriptiv gegenübergestellt. Die einarmige Phase-II-Studie OPAL zu Osimertinib plus Chemotherapie wurde als ergänzende Evidenz berücksichtigt.

Beide Kombinationstherapien zeigten gegenüber der Osimertinib-Monotherapie einen signifikanten Vorteil hinsichtlich des Gesamtüberlebens und des progressionsfreien Überlebens. Das mediane progressionsfreie Überleben betrug unter Amivantamab plus Lazertinib 23,7 Monate und unter Osimertinib plus Chemotherapie 25,5 Monate gegenüber jeweils rund 17 Monaten unter Osimertinib-Monotherapie. Beide Kombinationstherapien verlängerten zudem die Ansprechdauer und zeigten mit 83-86 % vergleichbar hohe objektive Ansprechraten. Das mediane Gesamtüberleben war unter Amivantamab plus Lazertinib zum Zeitpunkt der letzten Auswertung noch nicht erreicht (36,7 Monate unter Osimertinib-Monotherapie), unter Osimertinib plus Chemotherapie betrug das mediane Gesamtüberleben 47,5 Monate gegenüber 37,6 Monaten unter Osimertinib-Monotherapie. Aufgrund des unterschiedlichen Reifegrads der Daten ist ein Vergleich des Gesamtüberlebens zwischen den beiden Kombinationstherapien derzeit jedoch

nicht abschließend möglich. Beim intrakraniellen progressionsfreien Überleben zeigte sich numerisch ein Vorteil für Osimertinib plus Chemotherapie. Aufgrund unterschiedlicher Analysepopulationen und methodischer Unterschiede zwischen den Studien lässt sich daraus jedoch kein gesicherter Vorteil gegenüber Amivantamab plus Lazertinib ableiten. Insgesamt konnte kein klinisch relevanter Vorteil einer der beiden Kombinationstherapien gegenüber der jeweils anderen mit ausreichender Evidenzsicherheit nachgewiesen werden.

Die indirekten Vergleiche kamen zu unterschiedlichen Ergebnissen hinsichtlich der vergleichenden Wirksamkeit, wobei diese Unterschiede wesentlich auf die jeweils angewandte Methodik zurückzuführen sind. Sowohl das National Institute for Health and Care Excellence (NICE) als auch die Canada's Drug Agency (CDA-AMC) kamen zu dem Schluss, dass die vorgelegten indirekten Vergleiche keine hinreichende Evidenz zur Beurteilung der vergleichenden Wirksamkeit lieferten und die bestehende Unsicherheit daher nicht ausreichend reduziert werden konnte. Die Canada's Drug Agency ging in ihrer gesundheitsökonomischen Bewertung daher von einer gleichwertigen Wirksamkeit beider Therapien aus.

Hinsichtlich der Sicherheit unterscheiden sich die beiden Therapien weniger hinsichtlich der Gesamthäufigkeit unerwünschter Ereignisse als vielmehr hinsichtlich ihres Nebenwirkungsprofils. Schwere unerwünschte Ereignisse (Grad ≥ 3) traten unter beiden Kombinationstherapien häufig auf (rund 80 % unter Amivantamab plus Lazertinib bzw. 70 % unter Osimertinib plus Chemotherapie). Unter Amivantamab plus Lazertinib standen vor allem infusionsbedingte Reaktionen, Hauttoxizitäten und venöse Thromboembolien (rund 40 %) im Vordergrund, während unter Osimertinib plus Chemotherapie überwiegend hämatologische Nebenwirkungen wie Neutropenie und Anämie beobachtet wurden. Daten zur gesundheitsbezogenen Lebensqualität fehlen für beide Therapien. Angesichts der unterschiedlichen Nebenwirkungsprofile und Verabreichungsformen wären entsprechende Daten für die Bewertung der patient:innenrelevanten Unterschiede zwischen den Therapien von besonderer Bedeutung.

Für den Vergleich der subkutanen mit der intravenösen Formulierung von Amivantamab wurde mit PALOMA-3 eine randomisierte Phase-III-Studie identifiziert. Primäres Ziel der Studie war der Vergleich der Pharmakokinetik der beiden Darreichungsformen. Die subkutane Formulierung zeigte hinsichtlich der objektiven Ansprechrates eine Nichtunterlegenheit gegenüber der intravenösen Formulierung. Darüber hinaus zeigte sich ein numerisch längeres Gesamtüberleben unter der subkutanen Formulierung. Da die Analyse des Gesamtüberlebens nicht präspezifiziert war, ist dieser Befund jedoch vorsichtig zu interpretieren und erlaubt keinen belastbaren Schluss auf einen Überlebensvorteil. Die subkutane Anwendung war zudem mit einer deutlich kürzeren Applikationsdauer und einem geringeren Zeitaufwand für Patient:innen und Gesundheitspersonal verbunden. Gleichzeitig traten infusionsbedingte Reaktionen und venöse Thromboembolien seltener auf als unter der intravenösen Formulierung. 77 % der Patient:innen bevorzugten die subkutane gegenüber der bisherigen intravenösen Verabreichung. Da PALOMA-3 ausschließlich vorbehandelte Patient:innen einschloss, ist die Übertragbarkeit der Ergebnisse auf die Anwendung in der Erstlinientherapie jedoch eingeschränkt.

Insgesamt bestehen wesentliche Evidenzlücken. Neben dem Fehlen einer direkten Vergleichsstudie sind die Daten zum Gesamtüberleben für Amivantamab plus Lazertinib noch nicht vollständig ausgereift. Weitere Analysen der MARIPOSA-Studie werden bis 2027 erwartet. Darüber hinaus fehlen für beide Kombinationstherapien vergleichende Daten zur gesundheitsbezogenen Lebensqualität sowie österreichische Real-World-Daten zur Wirksamkeit und Sicherheit unter Alltagsbedingungen.

Gesundheitsökonomische Aspekte

Für die gesundheitsökonomische Bewertung wurden zwei Kosten-Effektivitätsanalysen aus den Health Technology Assessments des NICE und der CDA-AMC herangezogen. Aufgrund der Unsicherheit hinsichtlich der vergleichenden klinischen Wirksamkeit wurden die Ergebnisse beider Analysen wesentlich durch die jeweiligen Wirksamkeits- und Preisannahmen bestimmt.

Trotz unterschiedlicher Modellierungsansätze und Gesundheitssysteme gelangten beide HTA-Institutionen zu ähnlichen Schlussfolgerungen. Auf Basis öffentlich verfügbarer Preise war Amivantamab plus Lazertinib im Vergleich mit Osimertinib plus Chemotherapie mit sehr ungünstigen Kosten-Effektivitätsverhältnissen oder hohen Zusatzkosten ohne entsprechenden klinischen Mehrwert für Patient:innen ver-

bunden. Im Bericht des NICE beruhte die Kosteneffektivität maßgeblich auf vertraulichen Preisnachlässen. Die CDA-AMC ging aufgrund der Unsicherheit hinsichtlich der vergleichenden Wirksamkeit von einer vergleichbaren Wirksamkeit der beiden Therapien aus und leitete daraus keinen klinisch begründeten Preisaufschlag für Amivantamab plus Lazertinib ab.

Da für Österreich bislang keine Budget-Impact-Analyse verfügbar war, wurde im Rahmen dieses HTA eine eigene Analyse aus Sicht des österreichischen Gesundheitssystems durchgeführt. Unter Berücksichtigung der Arzneimittelkosten, der Verabreichungskosten sowie der routinemäßigen bildgebenden Verlaufskontrollen ergaben sich jährliche direkte medizinische Kosten von rund 207.000 Euro pro Patient:in für Amivantamab plus Lazertinib gegenüber rund 129.000 Euro pro Patient:in für Osimertinib plus Chemotherapie. Die daraus resultierenden Mehrkosten von rund 78.000 Euro pro Patient:in und Jahr sind überwiegend auf die höheren Arzneimittelkosten von Amivantamab plus Lazertinib zurückzuführen.

Bei einer geschätzten Zielpopulation von rund 140 neu behandelten Patient:innen pro Jahr würde eine vollständige Behandlung mit Amivantamab plus Lazertinib gegenüber Osimertinib plus Chemotherapie zu zusätzlichen Ausgaben von rund 11 Millionen Euro pro Jahr bzw. 33 Millionen Euro über drei Jahre führen. Da beide Therapien bereits in der österreichischen Versorgung eingesetzt werden, stellt dieses Szenario keine Prognose der tatsächlichen Ausgabenentwicklung dar, sondern zeigt die Kostendifferenz bei vollständiger Behandlung der Zielpopulation mit der jeweils einen oder anderen Therapie.

Für Krankenanstalten ist zusätzlich die unterschiedliche Finanzierungsverantwortung relevant. Während die Kosten oral verabreichter Arzneimittel im niedergelassenen Bereich grundsätzlich über die gesetzliche Krankenversicherung finanziert werden, sind die Kosten für im Krankenhaus verabreichte Arzneimittel und deren Verabreichung im stationären Bereich Teil der Krankenanstaltenfinanzierung. Aus Sicht der Krankenanstalten ergeben sich für Amivantamab jährliche direkte medizinische Kosten von rund 145.000 Euro pro Patient:in, verglichen mit rund 67.000 Euro für Pemetrexed plus Platin.

Die Ergebnisse der Budget-Impact-Analyse sind mit Unsicherheit behaftet. Die Analyse basiert auf einem hypothetischen Szenario, in dem die gesamte Zielpopulation jeweils mit einer der beiden Therapieoptionen behandelt wird, sowie auf öffentlich verfügbaren Preisen und der Annahme einer einjährigen Behandlungsdauer. Die tatsächlichen finanziellen Auswirkungen hängen hingegen von der Verteilung der Patient:innen auf die beiden Therapieoptionen, der tatsächlichen Behandlungsdauer, möglichen Preisvereinbarungen sowie den Finanzierungsstrukturen zwischen den Versorgungssektoren ab.

Organisatorische Aspekte

Voraussetzung für den Einsatz beider Kombinationstherapien ist der Nachweis einer häufigen EGFR-Mutation. In Österreich ist die hierfür erforderliche molekulare Diagnostik etabliert und wird bei Vorliegen einer adenokarzinomatösen Komponente routinemäßig bereits zum Zeitpunkt der Diagnose und unabhängig vom Tumorstadium eingeleitet. Damit bestehen grundsätzlich die diagnostischen Voraussetzungen für den Einsatz beider Therapien.

Die organisatorischen Anforderungen der beiden Therapien unterscheiden sich jedoch deutlich. Osimertinib plus Chemotherapie verbindet eine orale Therapie mit etablierten Abläufen der platinbasierten Chemotherapie, einschließlich Prämedikation, Hydrierung und hämatologischen Monitoring. Amivantamab plus Lazertinib erfordert insbesondere bei intravenöser Anwendung zusätzliche Prämedikation und eine entsprechende Infusionskapazität, da einzelne Infusionen bis zu fünf Stunden dauern können. Eine wesentliche zusätzliche Anforderung stellt das Management venöser Thromboembolien dar. In der österreichischen Versorgung wird eine Thromboseprophylaxe über mindestens sechs Monate sowie eine fortlaufende Beurteilung des Blutungsrisikos empfohlen, zusätzlich ist ein strukturiertes Management dermatologischer Nebenwirkungen erforderlich.

Die subkutane Formulierung von Amivantamab reduziert die Applikationsdauer sowie den Zeitaufwand für Patient:innen und Gesundheitspersonal und geht mit weniger infusionsbedingten Reaktionen einher. Die wesentlichen Anforderungen an Thromboseprophylaxe, Monitoring und dermatologische Supportivtherapie bleiben jedoch bestehen. Der organisatorische Gesamtaufwand von Amivantamab plus Lazertinib wird durch die subkutane Formulierung daher nur teilweise reduziert.

Die sichere Durchführung von Amivantamab plus Lazertinib erfordert Erfahrung im Management des spezifischen Nebenwirkungsprofils sowie eine strukturierte interdisziplinäre Zusammenarbeit. Dies kann insbesondere kleinere Zentren vor größere organisatorische Herausforderungen stellen als spezialisierte Einrichtungen mit hohen Fallzahlen. Nach Einschätzung österreichischer klinischer Expert:innen ist die Anwendung von Amivantamab plus Lazertinib derzeit gering, während Osimertinib plus Chemotherapie die Erstlinienversorgung dominiert.

Die Übertragbarkeit der Studienergebnisse auf die österreichische Routineversorgung ist eingeschränkt, da die pivotalen Studien ein selektiertes Patient:innenkollektiv mit gutem Allgemeinzustand einschlossen. Österreichische Registerdaten (LALUCA Register) könnten künftig dazu beitragen, die Evidenz zur Anwendung beider Therapien unter Routinebedingungen zu ergänzen.

Schlussfolgerungen

Die derzeit verfügbare Evidenz spricht für eine vergleichbare klinische Wirksamkeit von Amivantamab plus Lazertinib und Osimertinib plus Chemotherapie in der Erstlinienbehandlung des fortgeschrittenen NSCLC mit häufigen EGFR-Mutationen. Aufgrund der fehlenden direkten Vergleichsstudie kann ein möglicher Unterschied zwischen den beiden Therapien nicht abschließend beurteilt werden. Die Therapien unterscheiden sich vor allem hinsichtlich ihres Nebenwirkungsprofils, nicht jedoch hinsichtlich der Gesamtbelastung durch unerwünschte Ereignisse.

Für Österreich ist Amivantamab plus Lazertinib mit deutlich höheren Behandlungskosten und einem größeren organisatorischen Aufwand verbunden als Osimertinib plus Chemotherapie. Die subkutane Formulierung reduziert zwar den Aufwand der Arzneimittelverabreichung, verringert die zusätzlichen Anforderungen an Supportivtherapie und Monitoring jedoch nur teilweise.

Die vorliegenden Ergebnisse sind vor dem Hintergrund der bestehenden Evidenzunsicherheiten zu interpretieren. Derzeit liegen weder direkte Vergleichsstudien noch Real-World-Daten vor. Zudem war das mediane Gesamtüberleben für Amivantamab plus Lazertinib zum Zeitpunkt der letzten Auswertung noch nicht erreicht. Für beide Therapien liegen außerdem keine Daten zur gesundheitsbezogenen Lebensqualität vor. Österreichische Registerdaten könnten künftig dazu beitragen, die bestehenden Evidenzlücken zu reduzieren und die Evidenzbasis zur vergleichenden Wirksamkeit und Sicherheit zu erweitern.

Insgesamt lässt sich auf Basis der derzeit verfügbaren Evidenz kein eindeutiger klinischer Vorteil einer der beiden Kombinationstherapien ableiten. Die Entscheidung über den Einsatz von Amivantamab plus Lazertinib sollte daher neben patient:innenbezogenen Faktoren auch die verfügbaren personellen und organisatorischen Ressourcen sowie die mit der Therapie verbundenen finanziellen Auswirkungen berücksichtigen.

Summary

Disease background and treatment

Lung cancer is the leading cause of cancer-related mortality worldwide and the third most common malignancy in Austria, where 5,533 new cases were recorded in 2024. Non-small cell lung cancer (NSCLC) accounts for around 85% of all lung cancers and carries a poor prognosis, in part because almost half of patients present with stage IV disease at diagnosis. The 5-year survival rate for metastatic NSCLC is only about 4%. While tobacco smoking remains the leading risk factor, roughly a quarter of cases occur in never-smokers.

NSCLC is defined by its molecular profile, including oncogenic driver mutations. Alterations in the epidermal growth factor receptor (EGFR) are the most clinically relevant, occurring almost exclusively in adenocarcinoma and mostly in never-smokers, women, and Asians. The global prevalence of EGFR mutations is around 14% in the European population. Based on Austrian data, EGFR mutations represent 11% of NSCLC cases, of which about 60% are common mutations (exon 19 deletions or exon 21 L858R substitutions).

Overview of the assessed technologies

The NCCN and Onkopedia guidelines list both amivantamab plus lazertinib and osimertinib plus platinum-based chemotherapy among the treatment options for advanced NSCLC with common EGFR mutations.

Amivantamab (RYBREVENT[®]) is a fully human EGFR-MET bispecific antibody that simultaneously targets EGFR and MET on tumour cells and stimulates an immune response against them. Because it binds the extracellular domain of EGFR, it retains activity irrespective of intracellular resistance mutations that limit tyrosine-kinase inhibitors (TKIs), and its anti-MET activity addresses a frequent TKI-resistance mechanism. It is given in combination with lazertinib, an oral third-generation, CNS-penetrant EGFR TKI, with which it acts synergistically. The intravenous (IV) formulation was authorised in the EU in March 2025 in combination with lazertinib for first-line advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitutions. The subcutaneous (SC) formulation was additionally authorised in June 2025.

Osimertinib (TAGRISSO[®]), a third-generation, CNS-active, oral EGFR TKI first authorised in the EU in 2016, is approved in combination with pemetrexed and platinum-based chemotherapy for the same indication. This combination received EU approval in July 2024.

Clinical effectiveness and safety

No head-to-head trial compares amivantamab plus lazertinib with osimertinib plus chemotherapy. The evidence base therefore rests on two pivotal phase 3 RCTs assessed against a common osimertinib-monotherapy arm, MARIPOSA (amivantamab plus lazertinib) and FLAURA2 (osimertinib plus chemotherapy), supported by the single-arm OPAL study and by indirect treatment comparisons (ITCs).

Each combination showed a clear benefit over osimertinib monotherapy in its own trial. In MARIPOSA, median overall survival (OS) was not yet reached with amivantamab plus lazertinib versus 36.7 months for osimertinib (HR 0.75; $p=0.005$), and median progression-free survival (PFS) was significantly longer (23.7 vs 16.6 months; HR 0.70; $p<0.001$). In FLAURA2, osimertinib plus chemotherapy achieved a median OS of 47.5 versus 37.6 months (HR 0.77; $p=0.02$) and a median PFS of 25.5 versus 16.7 months (HR 0.62; $p<0.001$). Both combinations also prolonged duration of response and showed comparably high objective response rates (83-86%). Direct OS comparison remains uncertain because MARIPOSA's median OS had not yet been reached, whereas FLAURA2 reported a mature median. Notably, the lower bounds of the 95% CIs were similar (42.9 vs 41.0 months). Intracranial PFS was numerically longer with osimertinib plus chemotherapy (30.2 vs 25.4 months), but neither regimen showed statistically significant im-

provement over osimertinib monotherapy in prespecified analyses. This comparison is uncertain due to differences in CNS assessment methods, imaging schedules, eligibility criteria, and data cut-offs between trials.

ITCs were limited by methodological differences between trials. An independent reconstructed-patient-data ITC found a statistically significant PFS advantage for osimertinib plus chemotherapy (HR 0.79, $p=0.044$), but no OS difference (HR 1.06, $p=0.637$). Such comparisons are complicated by differences in assessment methods (blinded central review in MARIPOSA versus open-label investigator assessment in FLAURA2), data cut-offs, and follow-up durations, all of which affect time-dependent outcomes. Both NICE and CDA-AMC concluded that the submitted ITC approaches did not adequately resolve comparative efficacy uncertainty. CDA-AMC therefore assumed equivalent efficacy in its base case.

The two regimens differed qualitatively in safety rather than in overall burden. Grade ≥ 3 adverse events were common with both (80% with amivantamab plus lazertinib; 70% with osimertinib plus chemotherapy). Amivantamab plus lazertinib was characterised by skin toxicity (rash, paronychia, acneiform dermatitis) and venous thromboembolism (VTE), whereas osimertinib plus chemotherapy was dominated by myelosuppression (anaemia, neutropenia, thrombocytopenia). Given their markedly different toxicity profiles and administration routes, health-related quality-of-life data would be particularly important in distinguishing between regimens with otherwise broadly comparable efficacy. However, such data were absent from both trials.

For the comparison of the SC and IV formulations of amivantamab, one randomised phase III trial, PALOMA-3, was identified. The primary objective of the study was to compare the pharmacokinetics of the two formulations. The SC formulation demonstrated non-inferiority to the IV formulation in terms of objective response rate. In addition, numerically longer overall survival was observed with the SC formulation. However, as the analysis of OS was not prespecified, this finding should be interpreted with caution and does not allow for a robust conclusion regarding a survival benefit. Patient-reported outcomes and administration time strongly favoured SC administration, and 77% of patients preferred the SC injection over prior IV infusion.

Economic aspects

Two published cost-utility analyses within the NICE and CDA-AMC HTA reports both concluded that amivantamab plus lazertinib is not cost-effective compared with osimertinib plus chemotherapy at publicly available prices. Favourable results depended entirely on confidential pricing arrangements rather than on demonstrated incremental clinical benefit. In the NICE analysis, the regimen dominated its comparators at confidential patient-access-scheme prices but produced an ICER of about £1.13 million per QALY at list prices, while CDA-AMC, assuming equal efficacy, found an incremental cost of about CA\$81,300 per patient with no additional benefit, and recommended reimbursement only if the price does not exceed the least costly relevant comparator.

In the absence of an Austrian budget impact analysis, one was conducted from the healthcare-payer perspective using ex-factory prices, considering drug acquisition, administration, and monitoring costs. The estimated total annual direct medical cost per patient was €207,250 for amivantamab plus lazertinib (IV or SC) versus €128,998 for osimertinib plus chemotherapy, a difference of €78,252, driven mainly by higher drug acquisition costs. Applied to an estimated eligible population of approximately 140 newly treated patients per year, full substitution of osimertinib plus chemotherapy by amivantamab plus lazertinib would increase expenditure by roughly €10.96 million annually, or a cumulative €32.87 million over three years. Because both regimens are already in routine use, the estimate assumes full substitution and public prices and should be read as an upper bound. Also, in case of negotiated pricing, this could alter the budget impact in Austria.

Organisational aspects

Both regimens depend on next-generation sequencing-based detection of a common EGFR mutation, an infrastructure well established in Austria. They diverge substantially in delivery. Osimertinib plus chemotherapy combines an oral agent with familiar platinum-based chemotherapy requiring pre-hydration, antiemetics and haematological monitoring. Amivantamab plus lazertinib combines intravenous amivantamab with daily oral lazertinib. Premedication (corticosteroids, antihistamines, antipyretics) and prolonged infusions of up to five hours requiring dedicated infusion capacity are driven by the amivantamab component. Its greatest organisational demand is venous thromboembolism management, which is attributable to the combination rather than to amivantamab alone, with Austrian clinicians recommending at least six months of thromboprophylaxis alongside continuous bleeding-risk assessment, plus prophylactic antibiotics and topical dermatologic care for skin toxicities.

The subcutaneous formulation of amivantamab eases administration, with fewer infusion-related reactions, a lower VTE rate, and shorter chair and staff time, but does not reduce the underlying prophylaxis and monitoring burden. Both regimens require delivery in specialised, high-volume centres, but amivantamab plus lazertinib carries a distinct learning curve in toxicity management, which, in a country where roughly 90% of lung cancer patients are cared for by pulmonologists rather than oncologists, may concentrate competent delivery in fewer institutions and widen regional disparities. Real-world uptake in Austria appears low, with osimertinib plus chemotherapy dominating first-line practice. A gap between the ECOG PS 0-1 trial populations and routine care further limits transferability. Austrian registry data via LALUCA could help fill this evidence gap, including quality-of-life outcomes that were absent from the pivotal trials.

Conclusion

The available evidence suggests broadly comparable clinical efficacy between amivantamab plus lazertinib and osimertinib plus chemotherapy in the first-line treatment of advanced NSCLC with common EGFR mutations, but the absence of direct comparative evidence leaves any true difference uncertain. Their safety profiles differ qualitatively rather than in overall burden. In the Austrian setting, amivantamab plus lazertinib is associated with substantially higher treatment costs and greater organisational burden than osimertinib plus chemotherapy. This burden is only partially diminished by the subcutaneous formulation. These conclusions remain preliminary as no real-world evidence or comparative studies are available. Median OS for amivantamab plus lazertinib was not yet reached at the final analysis, with updated data expected through 2027, and quality-of-life outcomes are absent for both regimens, a gap that Austrian registry data could help address. Overall, the current evidence does not support a clear clinical advantage of either regimen over the other, so hospitals and treating clinicians will need to determine whether implementation of amivantamab plus lazertinib is feasible and justified within their local organisational context, while considering patient preferences, toxicity profiles and the additional costs associated with the treatment.

1 Introduction

1.1 Non-Small Cell Lung Cancer

1.1.1 Disease characteristics and epidemiology

Lung cancer is the leading cause of cancer-related mortality worldwide [1]. In Austria, 5,533 new cases were recorded in 2024, making it the third most common malignancy for both sexes [2]. Despite novel treatments, 5-year overall survival remains around 20%, comparable to the European level. Lung cancer comprises 19% of all cancer deaths in Austria. [3]. Tobacco smoking is the most common risk factor for lung cancer worldwide, increasing the risk of lung cancer 10-30 times compared to never-smokers. Although the smoking prevalence has decreased in the last 20 years, the global incidence of lung cancer in non-smokers is on the rise. In never-smokers, other factors drive lung cancer development, including air pollution, occupational exposure (asbestos, arsenic), radon, obstructive lung diseases, pulmonary fibrosis, pulmonary infections (tuberculosis), pathogenic germline variants, and hereditary predisposition [1].

Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases overall and has a high mortality rate, with metastatic NSCLC showing a 5-year net survival rate of just 4% [4]. A contributing factor to high mortality is also late diagnosis, with almost half of NSCLC patients presenting at stage IV at initial diagnosis [5]. While smoking is responsible for a majority of NSCLC cases, 25% occur in lifelong never-smokers, a population composed mostly of women across all age groups, races and ethnicities [1].

NSCLC develops from the lung's epithelial cells and is classified into three main histological subtypes: adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma (LCC). The most prevalent is adenocarcinoma, accounting for 50% of NSCLC cases [1]. Lung adenocarcinomas arise in the peripheral bronchioloalveolar epithelium and exhibit a distinct molecular profile. SCC constitutes 20-30% of NSCLC cases and originates from the central bronchial epithelium; it is more strongly associated with tobacco smoking than adenocarcinoma [5, 6]. Its genomic landscape is characterised by complexity with very few druggable oncogene alterations. LCC is defined as a heterogeneous group of undifferentiated epithelium-derived tumours [1] with aggressive behaviour and rapidly growing tumours often located in the peripheral lung tissue, accounting for 10-15% of NSCLC cases [5]. In general, tobacco-associated lung cancers are typically characterised by high genomic complexity, where multiple co-occurring alterations drive tumour growth [1].

Lungenkrebs:
häufige Krebserkrankung
mit hoher Mortalität

NSCLC:
schlechte Prognose
durch späte Diagnose

NSCLC-Subtypen
mit unterschiedlichem
molekularem Profil

1.1.2 Symptoms and Diagnostics

The typical symptoms of NSCLC include persistent cough, haemoptysis, weight loss and dyspnoea, although none are specific to the disease [1]. Diagnosis of lung cancer in young and never-smoking patients, often thought to be at low risk of cancer, can be challenging and contributes to delayed diagnosis [7]. The diagnostic workup requires a complete medical history, laboratory tests, and imaging with a contrast-enhanced computed tomography (CT) of

Lungenkrebsdiagnostik:
Staging und Histologie

the chest and upper abdomen. Fluorodeoxyglucose positron emission tomography should be performed in all patients eligible for curative-intent therapy to detect occult metastases, and brain magnetic resonance imaging (MRI) is recommended in most patients, given the high incidence of brain involvement. Tissue diagnosis is essential for pathological confirmation, histological subtyping, and biomarker evaluation, while it is important to obtain sufficient tissue for complete diagnosis [1]. To determine the stage of lung cancer, an assessment of the primary tumour, regional lymph nodes, and organs where metastases may be present is required. Upon diagnosis of NSCLC, the proportion of patients in stages I-II, III, and IV is approximately 25%, 35%, and 40%, respectively [8].

In Austria, lung cancer diagnosis is not confined to specialised cancer centres but takes place across larger hospitals equipped with departments of thoracic surgery, pulmonology, and oncology. Pathological diagnosis, however, is expected to be available at all types of pathological institutes, regardless of their size or setting. The recommended diagnostic workup algorithm aligns with international standards and is intended to be applied consistently across all institutions [9].

Beyond the diagnostic pathway for symptomatic patients, the early detection of asymptomatic disease is currently under discussion in Austria. Two large randomised trials of low-dose CT (LDCT) screening showed that annual LDCT reduces lung cancer mortality by 20 to 33% [10, 11]. The European Society of Radiology and the European Respiratory Society therefore recommend LDCT screening for high-risk individuals aged 50 to 74 years with a significant smoking history [12]. Germany and Poland have already launched national screening programs. Health-economic modelling by the Austrian Institute for Health Technology Assessment indicates that a risk-adapted LDCT program based on the NELSON criteria would be cost-effective in Austria, though quality assurance, centre accreditation, eligibility assessment and equitable access remain open questions [3].

Non-squamous NSCLC, particularly adenocarcinoma, is characterised by a range of key oncogenic driver alterations, including EGFR, ALK, ROS1, BRAF V600, MET, RET, NTRK, neuregulin 1 (NRG1), KRAS, and HER2, each representing a distinct and potentially targetable molecular subtype of the disease. Characterising these driver alterations has become integral to NSCLC management, informing not only prognosis but also the selection of targeted therapies matched to individual tumour biology. Additionally, biomarkers such as PD-L1 expression and tumour mutational burden (TMB) have been investigated as predictive tools to guide immunotherapy selection, although their reliability varies [13].

In this context, molecular testing represents an essential component of the diagnostic workup and is crucial for guiding subsequent treatment selection as part of precision and personalised cancer medicine. DNA and RNA derived from tumour tissue remain the standard source for genomic analysis, though plasma-derived circulating tumour DNA serves as a complementary source, particularly for resistance testing [1, 9]. Next-generation sequencing (NGS) panels are preferred as they allow simultaneous multi-gene analysis, reducing the risk of tissue exhaustion through sequential single-gene testing. Accordingly, automatic molecular testing for mutations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), B-Raf proto-oncogene V600 (BRAF V600), neurotrophic tropomyosin receptor kinase (NTRK), human epidermal growth factor receptor 2 (HER2),

Österreich:
standardisierte Diagnostik
nach internationalen
Leitlinien

Niedrigdosis-CT-Screening
in Österreich noch nicht
etabliert

molekulare Alterationen
(EGFR, ALK, ROS1,
BRAF V600, MET, RET,
NTRK, NRG1, KRAS und
HER2) bestimmen
Therapieauswahl

molekulare Testung
mittels Next Generation
Sequencing als
diagnostischer Standard

rearranged during transfection (RET), mesenchymal-epithelial transition factor exon 14 (MET exon 14), Kirsten rat sarcoma viral proto-oncogene (KRAS), and programmed death-ligand 1 (PD-L1) is routinely performed at the time of diagnosis [9]. Genomic analysis may also serve to distinguish multiple primary lung tumours from intrapulmonary metastases, or to differentiate a pulmonary lesion as a primary lung tumour from one originating as a metastasis from another primary cancer [1].

The Austrian guidelines specifically recommend testing regardless of disease stage, ensuring a complete molecular profile is available at diagnosis and at recurrence so that targeted therapy can be selected accordingly. Pathological institutes are preferred over commercial laboratories, as morphological context is essential for accurate interpretation and tumour board communication [9]. These practices mirror major international guidelines: both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend EGFR mutation testing for all patients with advanced or metastatic non-squamous NSCLC [5].

Österreich:
molekulare Testung
unabhängig vom
Krankheitsstadium

1.1.3 Molecular landscape and EGFR mutations

Among the oncogenic drivers in NSCLC, EGFR mutations represent one of the most clinically relevant molecular alterations in NSCLC. These almost exclusively occur in lung adenocarcinoma and most commonly in patients with no smoking history, females, and patients of Asian ethnicity [7]. While the overall pooled prevalence of EGFR mutations in NSCLC is 32%, the prevalence in the European population is 14% [14]. It is hypothesised that air pollution might be the cause of the growth of lung epithelial cells harbouring EGFR mutations [1].

EGFR is a transmembrane protein localised at the cellular surface and a member of a family of tyrosine kinase receptors, expressed by epithelial cells in skin, lung, or gastrointestinal mucosa. Physiologically, activation of the EGFR protein triggers intracellular pathways implicated in the survival, growth, and proliferation of the cell, which results in tissue regeneration and wound healing. However, mutations occurring in the kinase domain of EGFR, particularly in exons 18 through 21, can lead to constitutive, ligand-independent activation of the receptor. Unlike normal EGFR signalling, which is tightly regulated, this constitutive activation results in continuous and uncontrolled downstream signalling, which drives unrestrained cell proliferation and survival. As a consequence, EGFR-mutant cells become dependent on, or “addicted to”, this aberrant signalling for their survival, which both underlies their oncogenic behaviour and makes them particularly sensitive to EGFR-targeted therapies. Not all EGFR mutations, however, carry the same clinical significance or confer the same sensitivity to targeted treatment [7].

Pathophysiologie
der EGFR-Mutation

The most common EGFR mutations are exon 19 deletions (ex19del), typically involving loss of amino acids E746-A750, and exon 21 L858R point mutations [7]. They account for 80-85%, while the uncommon mutations – comprising all other kinase domain mutations outside of L858R and ex19del – are less frequent (15-20%). Common mutations are predictive of favourable clinical response to EGFR tyrosine kinase inhibitors (TKIs). In Austria, based on the data from two centres in Vienna collected between November 2020 and February 2025, EGFR mutations represented 11% of NSCLC cases, of which 60% comprised the common EGFR mutations [15].

häufige EGFR-Mutationen:
Exon-19-Deletion und
Exon-21-L858R

1.2 Lung cancer registries

In Austria, several registries exist that record and evaluate cancer in the Austrian population. The first, established in 1983, was the Austrian National Cancer Registry, collecting epidemiological data on incidence, prevalence, mortality, and survival across all cancer types nationwide. It was followed by regional registries in Carinthia, Salzburg, Tyrol, and Vorarlberg. More recently, hospital-based clinical quality registers have emerged in Lower and Upper Austria, pooling data from 24 and 11 hospitals, respectively, combining web-based software with dedicated quality management teams to provide detailed data [16]. However, real-world data on the diagnostic and therapeutic management of lung cancer patients in Austria remain scarce, and no existing registry has focused specifically on comprehensive molecular biomarker and NGS data in an unselected lung cancer population. Notably, Vienna, despite having the highest lung cancer incidence of all Austrian federal states, lacked a dedicated clinical lung cancer registry prior to 2020.

The Landsteiner Lung Cancer Research Platform (LALUCA) was established to fill precisely this gap. A prospective, multicentre clinical registry (NCT-04733430), LALUCA, was launched in November 2020 by the Karl Landsteiner Institute for Lung Research and Pulmonary Oncology and collects comprehensive clinical, diagnostic, molecular, and treatment data from lung cancer patients at two high-volume centres in Vienna: Klinik Floridsdorf and Klinik Ottakring. Beyond basic patient characteristics, the registry captures 180 variables across 17 categories, including biomarkers and treatment modalities, while a particular emphasis is placed on NGS molecular biomarker data. As of 2023, 1,200 patients were enrolled, with an ongoing recruitment rate of approximately 400 per year. Of these, 46% were female, and 70% were aged 61-80, predominantly current or former smokers. Nearly half (49%) were diagnosed at stage IVA/B, and approximately 85% had NSCLC, with adenocarcinoma as the most common subtype (54%). Patients are actively followed up every 6 months, with data quality maintained. Expansion to additional Austrian sites is planned, with the broader aim of informing clinical guidelines and healthcare policy decisions [16].

Lungenkrebsregister in Österreich mit begrenzten Real-World-Daten

klinisches Lungenkrebsregister LALUCA in Wien

1.3 Treatment of NSCLC with common EGFR mutations

Dependence of tumour survival on a specific mutated gene, termed oncogene addiction in NSCLC, has supported the development of targeted therapies. The predominant class is tyrosine kinase inhibitors (TKIs), small molecules that bind to the adenosine triphosphate (ATP)-binding pocket of the active kinase domain. Antibody-based approaches include bispecific antibodies such as amivantamab, which simultaneously targets EGFR and MET, and antibody-drug conjugates, which deliver a cytotoxic payload after binding a tumour surface antigen [1].

zielgerichtete Therapien auf Basis von Treibermutationen

Given the central role of constitutive EGFR signalling in driving tumour growth, EGFR-targeted TKIs have become a cornerstone of treatment in this setting. In 2004, two pivotal studies demonstrated a relationship between EGFR kinase domain mutations and response to EGFR-targeted TKIs in NSCLC, paving the way for the use of these mutations to guide patient selection for targeted therapy. Osimertinib, a third-generation irreversible EGFR TKI, became the established standard of care for the first-line treatment of advanced NSCLC harbouring common EGFR mutations, owing to its potent and selective inhibition of both sensitising EGFR mutations and the T790M resistance mutation, its central nervous system (CNS) penetrance, and its favourable tolerability profile compared with earlier-generation TKIs [7]. Lazertinib is another oral third-generation EGFR-TKI, selective for mutant EGFR over the wild-type receptor, with pronounced CNS penetrance and activity against both sensitising mutations and T790M. Lazertinib is administered in combination with the EGFR-MET bispecific antibody amivantamab, a regimen that has become a further first-line option in EGFR-mutated advanced NSCLC [17].

Despite the high efficacy of EGFR TKIs, resistance can develop, such as resistance to first- and second-generation EGFR-targeting TKIs due to acquisition of the EGFR^{T790M} mutation. Tumours treated with third-generation EGFR TKIs, which also target EGFR^{T790M}, can develop other resistance mutations such as EGFR^{C797S}. Additionally, co-mutations in TP53 reduce the effectiveness of TKIs in tumours with EGFR mutations or with oncogenic fusions. As resistance to EGFR TKI monotherapy invariably develops, combination strategies have been investigated with the aim of proactively addressing resistance mechanisms, either by simultaneously targeting multiple pathways or by eliminating tumour clones that are refractory to EGFR inhibition alone [1].

Based on NCCN Clinical Practice Guidelines in Oncology [18] and Onkopedia [19], the preferred first-line treatments for advanced NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations are osimertinib monotherapy, osimertinib and pemetrexed plus chemotherapy or amivantamab plus lazertinib. Other drugs such as afatinib, dacomitinib, erlotinib, erlotinib plus bevacizumab, and erlotinib plus ramucirumab can be used as well. While the three first-line treatment options are now available, there are currently no validated biomarkers or evidence-based tools to guide the choice between them. Clinical factors, patient characteristics, comorbidities, and shared decision-making between the treating clinician and the patient, therefore, play a central role in treatment selection [20].

Osimertinib in combination with platinum-based chemotherapy and pemetrexed

Osimertinib is a third-generation, irreversible, CNS-active, oral EGFR TKI that potently and selectively inhibits both EGFR-TKI-sensitising and EGFR^{T790M} resistance mutations. It was first authorised in the EU as Tagrisso® in February 2016. Its indication was expanded in July 2024 to include the combination treatment with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations [21]. Notably, osimertinib combination with platinum-based chemotherapy and pemetrexed (hereafter “osimertinib plus chemotherapy”) has shown significantly longer progression-free survival (PFS) and overall survival (OS) in comparison to osimertinib monotherapy [22, 23]. The exact mechanisms underlying the observed clinical benefit of the combination over monotherapy

Osimertinib als etablierte Erstlinientherapie bei EGFR-mutiertem NSCLC

neue Kombinationstherapien erweitern die Erstlinienoptionen

Resistenzmechanismen fördern Kombinationstherapien

Leitlinien bevorzugen 3 Erstlinienoptionen bei EGFR Ex19del/L858R:
1. Osimertinib Monotherapie,
2. Osimertinib plus Chemotherapie,
3. Amivantamab plus Lazertinib

Osimertinib: Monotherapie (2016) und Kombination mit Chemotherapie (2024) zugelassen

verbesserte Wirksamkeit durch die Kombination

are currently not fully understood. Osimertinib is a highly potent and selective EGFR-TKI, whereas therapy with pemetrexed and a platinum-based agent has a nonselective antitumour effect. It is speculated that the combination overcomes intratumour heterogeneity by eliciting an additive effect by means of the killing of different cell populations to improve clinical outcomes [22].

Amivantamab in combination with lazertinib

Amivantamab is a novel, fully human EGFR-MET bispecific antibody that simultaneously targets EGFR and MET, two proteins expressed on the surface of cancer cells. Its antigen-binding fragment is composed of two distinct domains, one recognising EGFR and the other recognising the MET proto-oncogene, enabling dual receptor targeting. Beyond pathway inhibition, amivantamab also stimulates an immunological response against tumour cells harbouring EGFR-activating mutations. Because amivantamab binds to the extracellular domain of EGFR, it retains activity independently of resistance mutations that may arise in the intracellular kinase domain during disease progression. This is a key advantage over TKIs, which bind intracellularly and are therefore vulnerable to such mutations. Furthermore, its activity against MET pathway hyperactivation addresses one of the most frequent and clinically significant mechanisms of resistance to EGFR TKIs [20].

Lazertinib is a third-generation, CNS-penetrant EGFR TKI with demonstrated efficacy against activating EGFR mutations and T790M mutations. Amivantamab and lazertinib act synergistically against EGFR pathological activity, producing therapeutic effects in patients whose tumours harbour EGFR-activating mutations [20]. The intravenous (IV) formulation of amivantamab as Rybrevant® was initially authorised in the EU as a monotherapy in December 2021 for the treatment of patients with EGFR exon 20 insertion mutations. This indication was extended in March 2025 to include the combination with lazertinib for the first-line treatment of adult patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations. In June 2025, the subcutaneous (SC) formulation of amivantamab was additionally authorised, offering a more convenient route of administration with a reduced risk of infusion-related reactions [24].

The combination of amivantamab plus lazertinib has demonstrated statistically significant improvement in PFS and OS in a phase 3 trial in patients with previously untreated EGFR-mutated (exon 19 deletion or L858R substitution), locally advanced or metastatic NSCLC in comparison to osimertinib [17, 25].

Both osimertinib plus chemotherapy and amivantamab plus lazertinib are authorised in the EU and recommended by current guidelines as first-line options for advanced NSCLC with common EGFR mutations [18, 19]. However, each has been compared only with osimertinib monotherapy. No head-to-head trials directly comparing the two combinations are available, and no validated biomarker has been established to identify which patients are most likely to benefit from either regimen. Consequently, the comparative evidence regarding efficacy and safety remains uncertain. In addition, the implications of the two treatment options for clinical implementation, including organisational requirements and economic consequences, remain unclear, limiting the ability to determine which regimen may be more appropriate in routine clinical practice.

Amivantamab:
zielgerichtete
Antikörpertherapie

Lazertinib:
EGFR-Tyrosinkinase-
Inhibitor

Amivantamab
plus Lazertinib:
verbesserte Wirksamkeit
der Kombination

kein direkter Vergleich der
beiden Erstlinientherapien

This health technology assessment therefore evaluates the clinical effectiveness, safety, organisational aspects and economic consequences of the respective treatment options, in order to support evidence-based and patient-centred healthcare decision-making in Austria.

Ziel der Bewertung

2 Research scope

2.1 Research questions

This HTA addresses the following research questions concerning the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with EGFR exon 19 deletions or exon 21 L858R substitution mutations:

Forschungsfragen

- **RQ1:** What is the comparative effectiveness and safety of amivantamab (IV/SC) plus lazertinib versus osimertinib plus chemotherapy?
- **RQ2:** What is the comparative effectiveness and safety of amivantamab (IV) plus lazertinib versus amivantamab (SC) plus lazertinib and what are the organisational and economic aspects of these two administration routes?
- **RQ3:** What are the economic aspects of the treatment with amivantamab (IV/SC) plus lazertinib compared to osimertinib plus chemotherapy?
- **RQ4:** What are the organisational aspects of the treatment with amivantamab (IV/SC) plus lazertinib compared to osimertinib plus chemotherapy?

2.2 Inclusion criteria

Inclusion criteria for relevant clinical studies are summarised in Table 2-1. Clinical experts were consulted to confirm the clinical relevance of the outcomes selected for the PICO (Population, Intervention, Comparator, Outcome) framework.

Einschlusskriterien

For the non-clinical domains, relevant economic literature reporting health economic evaluations of amivantamab and osimertinib was considered, together with publications addressing organisational aspects of these treatments.

Table 2-1: Inclusion criteria for the clinical studies

Population	Adult patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer with common mutations (exon 19 deletion or exon 21 L858R mutation)
Intervention	RQ 1, 3, 4: Amivantamab (intravenous/subcutaneous) plus Lazertinib RQ 2: Amivantamab (intravenous) plus Lazertinib
Comparison	RQ 1, 3, 4: Osimertinib plus pemetrexed and platinum-based chemotherapy RQ 2: Amivantamab (subcutaneous) plus Lazertinib
Outcomes	RQ 1, 2: ■ Efficacy: OS, PFS, DOR, Objective response rate (ORR), Median time to symptomatic progression, Median time to treatment discontinuation, Median time to subsequent therapy, Median PFS after first subsequent therapy, Intracranial PFS, Intracranial objective response, Median duration of intracranial objective response, Second PFS after first subsequent therapy, Disease control ■ Quality of life ■ Safety: AEs in total, Serious AEs, Severe AEs, Death, Treatment discontinuation, Treatment interruption RQ 3: cost-effectiveness (ICER) RQ 4: organisational aspects

Study design	■ Systematic reviews, HTAs ■ RCTs ■ NRCs ■ ITCs ■ SATs ■ CEA (for RQ 3) Excluded: <i>in vitro</i> , animal, case studies, conference abstracts, letters to the editors and authors' responses
Languages	■ English, German

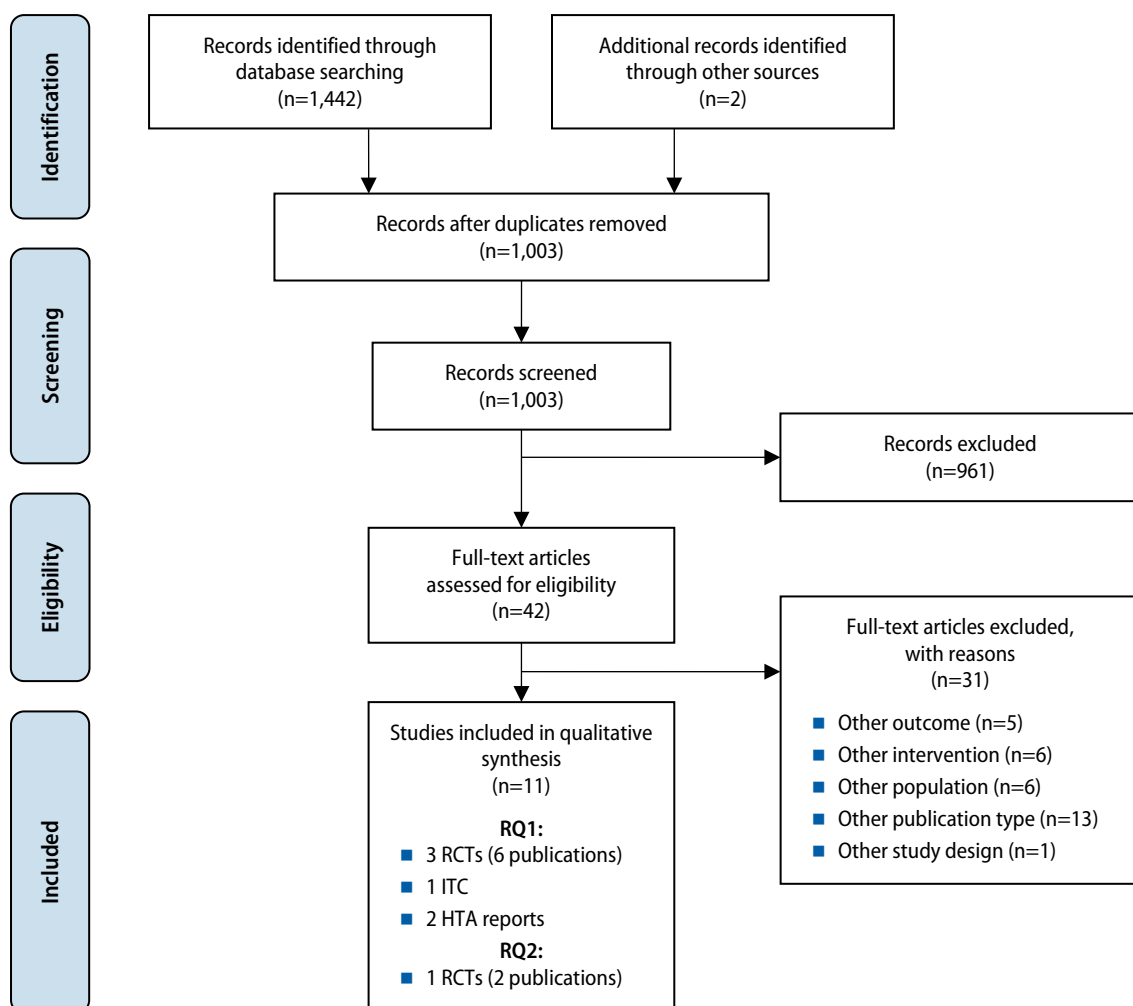
Abbreviations: AEs ... adverse events, CEA ... cost-effectiveness analysis, DOR ... duration of response, EGFR ... epidermal growth factor receptor, ICER ... incremental cost-effectiveness ratio, ITC ... indirect treatment comparison, NRCs ... non-randomised controlled studies, NSCLC ... non-small cell lung cancer, OS ... overall survival, PFS ... progression-free survival, RCTs ... randomised controlled trials, SATs ... single-arm trials.

3 Methods

This HTA employed a multi-domain assessment approach, following the European Network for Health Technology Assessment (EUnetHTA) methodology [26]. The implemented methods were tailored to address the research questions.

**Bewertung basierend auf
EUnetHTA Core Model®**

3.1 Systematic literature search and study selection



Abbreviations: HTA ... health technology assessment, ITC ... indirect treatment comparison, PRISMA ... Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT ... randomised controlled trial.

Figure 3-1: PRISMA Flow Diagram

The systematic literature search was conducted between 4 and 6 March 2026 across four databases: Medline via Ovid, Embase, The Cochrane Library, and INAHTA. The detailed search strategies are in the Appendix. The search was limited to English and German, excluding *in vitro*, animal and case studies, conference abstracts, letters to the editors and authors' responses. After deduplication, 1,001 records were identified through the database search. In addition, two records were identified through hand searching, resulting in 1,003 records that were screened for relevance to the clinical, economic and organisational research questions addressed in this report. The selected references were screened by two independent researchers (EM, JE), and a third researcher was involved in case of disagreement to resolve the differences.

**systematische
Literatursuche in
4 Datenbanken**

1.001 Treffer

The study selection process for the clinical effectiveness and safety assessment is presented in the PRISMA flow diagram in Figure 3-1. Publications informing the economic and organisational assessments were identified through the same systematic search and supplemented by hand search, but only the selection process for studies relevant for clinical effectiveness and safety is displayed in the PRISMA flow diagram.

Literaturauswahl

3.2 Data analysis and evidence synthesis

3.2.1 Clinical effectiveness and safety

Data extraction from the selected publications was systematically performed by one researcher (EM) and cross-checked by a second one (JE).

Datenextraktion

Risk of bias of the included studies was assessed using the Cochrane Risk of Bias (RoB) tool v.2 for randomised controlled studies [27], in duplicate by two reviewers (EM and JE) and differences were settled by a third assessor (SGG). It was assessed per outcome.

**RoB-Bewertung der RCTs
mittels Cochrane RoB v.2**

For indirect treatment comparisons (ITC), no formal appraisal tool was applied. Instead, their methodological characteristics and limitations, including study design, comparability of study populations, handling of effect modifiers and confounding, and other potential sources of uncertainty, were described narratively alongside the results. Clinical evidence from health technology assessments (HTAs), ITCs and individual studies was synthesised narratively. The strength of the evidence and its uncertainties were described qualitatively.

**indirekte
Therapievergleiche:
narrative Bewertung
der Limitationen**

3.2.2 Economic evaluation

Included health economic evaluations were synthesised narratively.

**gesök. Evaluationen:
narrative Synthese**

A three-year budget impact analysis was performed comparing the cost of amivantamab plus lazertinib and osimertinib plus chemotherapy treatment. Only direct medical costs were considered. For this purpose, the prices of amivantamab, lazertinib, osimertinib and chemotherapy were extracted from the Austrian Apotheker-Verlag online catalogue [28]. For the cost of intravenous administration, hospital cost data from the Austrian procedure- and diagnosis-related groups (Leistungsorientierte Krankenanstaltenfinanzierung, LKF) catalogue were used. The cost of the subcutaneous administration was deemed to be equal to the intravenous one in the Austrian hospital setting.

**Budget-Impact-Analyse
(BIA) für Österreich**

The eligible population was defined as patients with NSCLC with common EGFR mutations in stage IV. The patient number for this population was approximated based on incidence data from Statistik Austria [2], reported prevalence of NSCLC among all lung cancer cases worldwide [14], and the LALUCA registry from two clinical centres in Vienna [15].

**Schätzung der
Zielpopulation für BIA**

3.2.3 Organisational evaluation

Relevant publications on organisational aspects were summarised narratively. The findings from the literature were complemented by input obtained through consultation with clinical experts.

**narrative Synthese
organisatorischer Aspekte**

4 Results: Clinical effectiveness and safety of amivantamab plus lazertinib versus osimertinib plus chemotherapy

4.1 Evidence base

This chapter evaluates the clinical effectiveness and safety of amivantamab in combination with lazertinib versus osimertinib plus chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with EGFR exon 19 deletions or exon 21 L858R substitution mutations. No primary study directly comparing amivantamab plus lazertinib with osimertinib plus chemotherapy was identified. Consequently, the evidence base comprised three clinical studies relevant to the assessment of the two treatment strategies, namely MARIPOSA [17, 25], FLAURA2 [22, 23, 29] and OPAL [30], reported in six publications, together with evidence from two HTA reports and one published indirect treatment comparison. The following sections present the characteristics and findings of these evidence sources.

Evidenzbasis

4.2 Outcomes

4.2.1 Outcomes for effectiveness

Following GRADE principles for outcome prioritisation, overall survival (OS), progression-free survival (PFS), duration of response (DOR), and objective response rate (ORR) were considered critical for addressing Research Questions 1 and 2. All other outcomes were considered important. No formal GRADE assessment was conducted.

**relevante
Wirksamkeitsendpunkte**

Overall survival

Overall survival is regarded as the final patient-centred outcome in oncology. Improvement in OS clearly demonstrates a clinical benefit which is meaningful to the patients [31]. In both the MARIPOSA and FLAURA2 trials, OS was a key secondary endpoint, defined as the time from randomisation until death from any cause and assessed in the full analysis population. In each trial, the population-level summary measures were the Kaplan-Meier median OS and landmark survival rates at defined time points, with the treatment effect expressed as a hazard ratio for death [23, 25].

Gesamtüberleben (OS)

Progression-free survival

Progression-free survival is defined as the time from randomisation until the first evidence of disease progression or death from any cause, with patients who are alive and progression-free at the time of evaluation, or who are lost to follow-up, being censored [31]. In both the MARIPOSA and FLAURA2 trials, PFS was the primary endpoint, assessed in the full analysis population, with the median estimated by the Kaplan-Meier method and the treatment effect expressed as a hazard ratio for disease progression or death. Disease progres-

**progressionsfreies
Überleben (PFS)**

sion was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in both trials. However, the assessment differed in that PFS was determined by blinded independent central review in MARIPOSA and by investigator assessment in FLAURA2 [17, 22].

PFS after first subsequent therapy

Progression-free survival after first subsequent therapy (referred to as second PFS after first subsequent therapy in Cho et al. (2024), and median PFS after first subsequent therapy in Janne et al. (2026)) was defined as the time from randomisation to second objective disease progression, occurring after subsequent treatment following the initial PFS event, or death, whichever came first. Patients without a second progression or death at the time of analysis were censored at the last time known to be alive and progression-free. The studies differed in their method of progression assessment: in Cho et al. (2024), second progression was explicitly based on investigator assessment and analysed using the same method as the primary PFS analysis, whereas Janne et al. (2026) did not specify the assessment method [17, 23].

**progressionsfreies
Überleben nach erster
Folgetherapie (PFS2)**

Duration of response

Duration of response is defined as the time from the date of first documented response (complete response [CR] or partial response [PR]) until the date of documented progression or death, whichever comes first. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint [17].

Ansprechdauer (DOR)

Objective response rate

Objective response rate (ORR) is a measure of antitumour activity and is defined as the proportion of patients who have a partial or complete response to therapy according to a predefined set of response criteria [31]. In the MARIPOSA and FLAURA2 trials, tumour response was assessed according to RECIST version 1.1. In MARIPOSA, response was determined by blinded independent central review, whereas in FLAURA2 it was based on investigator assessment [17, 22].

**objektive Ansprechrate
(ORR)**

Time to symptomatic progression

Time to symptomatic progression (TTSP) is defined as the time from randomisation to any of the following (whichever occurs earlier): onset of new symptoms or symptom worsening that is considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms. The TTSP for a participant who does not experience any of these events was censored on the date on which the participant was last known to be event-free [17].

**Zeit bis zur
symptomatischen
Progression (TTSP)**

Time to subsequent therapy

Time to subsequent therapy (TTST) was defined as the time from randomisation to the start of the first subsequent anticancer therapy following study treatment discontinuation, or death, whichever occurred first. Patients who had not received subsequent therapy and had not died at the time of analysis were censored at the date last known to be alive without subsequent therapy [17, 23].

**Zeit bis zur Folgetherapie
(TTST)**

Time to treatment discontinuation

Time to treatment discontinuation (TTD) is a measure of treatment durability, defined as the time from randomisation to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. TTD captures clinical benefit for participants continuing treatment beyond RECIST v1.1-defined disease progression.

**Zeit bis zum
Therapieabbruch (TTD)**

In MARIPOSA, TTD was reported as a formal time-to-event secondary endpoint. In FLAURA2, while the protocol defined specific discontinuation criteria (RECIST-defined progression, patient/investigator decision, adverse events, non-compliance, and pregnancy), discontinuation outcomes were reported descriptively as proportions and reasons for discontinuation rather than as a formal time-to-event analysis [17, 22].

Disease control rate

Disease control rate (DCR) was defined as the percentage of patients achieving the best overall response of complete response, partial response, or stable disease per RECIST v1.1. Assessment was performed by blinded independent central review (BICR) in Cho et al. (2024) and by the investigator in Janne et al. (2026), the latter additionally requiring stable disease to be confirmed at least 6 weeks after randomisation [17, 23].

**Krankheitskontrollrate
(DCR)**

Intracranial objective response

Intracranial objective response rate (also referred to as CNS ORR in Janne et al. (2026)) was defined as the proportion of patients with a history of brain metastases at screening who achieved an intracranial complete or partial response, as assessed by BICR. Data obtained up until intracranial disease progression or the last evaluable intracranial assessment in the absence of progression were included. Responses occurring after the initiation of subsequent anticancer therapy were not counted [25, 29].

**intrakranielle objektive
Ansprechrate**

Duration of intracranial objective response

Median duration of intracranial objective response (intracranial DOR in Cho et al. (2024), CNS DOR in Janne et al. (2026)) was defined as the time from first documented intracranial CR or PR until intracranial progression or death, whichever came first, with censoring at the last evaluable brain scan in the absence of either event. Unlike Janne et al. (2026), which continued follow-up irrespective of subsequent therapy, Cho et al. (2024) censored patients at the last intracranial assessment prior to initiation of subsequent anticancer therapy [25, 29].

**Dauer des intrakraniellen
objektiven Ansprechens**

Intracranial PFS

Intracranial PFS is defined as the time from randomisation until the date of objective intracranial disease progression or death, whichever comes first, based on BICR using RECIST v1.1. Participants who have not progressed intracranially or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment [25].

**intrakranielles
progressionsfreies
Überleben**

Quality of life

Health-related quality of life (HRQoL) was assessed using patient-reported outcome (PRO) instruments in both studies. Both used the EORTC QLQ-C30 and EQ-5D-5L. Janne et al. (2026) additionally included the EORTC QLQ-LC13 (a lung-cancer-specific 13-item module) and PRO-CTCAE, while Cho et al. (2024) additionally included the NSCLC-SAQ (a 7-item questionnaire assessing cough, pain, dyspnoea, fatigue, and poor appetite) and PGIS/PGIC (single-item global impression questionnaires). The analytic approach also differed: Cho et al. (2024) analysed time to worsening on the EORTC QLQ-C30 using Kaplan-Meier and a stratified Cox proportional-hazard model, while Janne et al. (2026) evaluated change from baseline and time to deterioration, defining a minimum clinically relevant change as a score change of ≥ 10 points [17, 23].

**gesundheitsbezogene
Lebensqualität**

4.2.2 Outcomes for safety

Adverse events

Adverse events (AEs) were defined as any untoward medical occurrence in a patient administered a medicinal product, regardless of causal relationship, graded per NCI CTCAE version 5.0. Death was captured as CTCAE grade 5 (death related to AE) [17, 23, 31].

**sicherheitsbezogene
Endpunkte:
unerwünschte Ereignisse,**

Serious AEs

Serious AEs (SAEs) were defined as any AE resulting in death, being life-threatening, requiring hospitalisation, resulting in persistent disability or incapacity, or constituting an important medical event jeopardising the patient [17, 23].

**schwerwiegende und
schwere unerwünschte
Ereignisse,**

Severe AEs

Severe AEs were defined per NCI CTCAE grade ≥ 3 , with grade 3 indicating severe but not immediately life-threatening events and grade 4 indicating life-threatening consequences [17, 23].

Treatment-emergent AEs

Treatment-emergent AEs were assessed using different observation windows. In MARIPOSA, the observation window was defined as from first dose through last dose plus 30 days (or start of subsequent therapy, whichever was earlier), whereas FLAURA2 used a 28-day window after discontinuation [17, 23].

**behandlungsbedingte
unerwünschte Ereignisse,**

Treatment discontinuation and treatment interruption

Treatment discontinuation is the permanent cessation of a trial agent, after which the patient does not resume that treatment. Treatment interruption is a temporary hold of a trial agent, after which treatment is resumed. In the safety setting, both are typically reported as the proportion of patients experiencing an event (most often an adverse event) that led to discontinuation or interruption of any trial agent, and reflect the tolerability of each regimen.

**Therapieabbruch und
Therapieunterbrechung**

4.3 Included clinical studies

As no direct comparative evidence addressing the PICO (scope of assessment) was available, evidence from the pivotal trials was presented separately. Efficacy and safety outcomes were compared descriptively across studies using a naïve cross-trial comparison. Therefore, any observed differences should be interpreted with caution. The evidence comprised three clinical studies (reported in six publications): MARIPOSA [17, 25], FLAURA2 [22, 23, 29] and OPAL [30].

Characteristics of the studies

Two of the three included pivotal studies were phase 3 randomised controlled trials (MARIPOSA and FLAURA2), whereas OPAL was a phase 2 non-randomised study. MARIPOSA was a three-arm trial comparing amivantamab plus lazertinib with osimertinib and lazertinib monotherapy, while FLAURA2 was a two-arm trial comparing osimertinib plus platinum-based chemotherapy and pemetrexed with osimertinib monotherapy. OPAL evaluated two platinum-based chemotherapy regimens combined with osimertinib without a control arm. For this assessment, both OPAL treatment arms were considered together because they represented relevant comparator regimens within the assessment scope.

MARIPOSA and FLAURA2 were international multicentre studies conducted across 28 and 21 countries, respectively, whereas OPAL was conducted in Japan. The eligibility criteria were broadly comparable across studies. Eligible patients were previously untreated adults with EGFR-mutated (exon 19 deletion or L858R) locally advanced or metastatic NSCLC and ECOG performance status of 0-1. FLAURA2 additionally restricted enrolment to patients with non-squamous NSCLC and explicitly permitted patients with neurologically stable central nervous system (CNS) metastases. OPAL additionally restricted enrolment to patients aged 20 to 75 years. The median time from diagnosis to randomisation in MARIPOSA was approximately 1.4-1.5 months, whereas this was not reported in FLAURA2.

The studies also differed with respect to outcome assessment. PFS was assessed in all three studies; however, it was the primary endpoint in both phase 3 trials, assessed by blinded independent central review according to RECIST v1.1 in MARIPOSA and by investigator assessment in FLAURA2, whereas in OPAL PFS was a secondary endpoint. OS was a secondary endpoint in MARIPOSA and FLAURA2 but an exploratory endpoint in OPAL. ORR was a secondary endpoint in the two phase 3 trials but, together with safety, constituted the primary endpoint of OPAL. Disease control rate was evaluated in FLAURA2 and OPAL but not specified as a secondary endpoint in MARIPOSA. Intracranial efficacy outcomes also differed between studies: intracranial PFS was a secondary endpoint in MARIPOSA, whereas CNS-specific outcomes were exploratory endpoints in FLAURA2 and were not reported in OPAL.

Both MARIPOSA and FLAURA2 reported results from pre-specified primary and updated analyses with median follow-up of 22.0 months in both arms of MARIPOSA, and 16.5 to 19.5 months across the arms of FLAURA2. OPAL reported an initial analysis of response and safety followed by an updated analysis of PFS and OS. The median follow-up was 33.4 months in OPAL [17, 22, 23, 25, 29, 30].

An overview of the included pivotal studies is presented in Table 4-1.

**3 klinische Studien:
MARIPOSA,
FLAURA2,
OPAL**

**2 Phase-3 RCTs und
1 Phase-2 nicht-
randomisierte Studie**

**vergleichbare
Einschlusskriterien**

**unterschiedliche Erhebung
und Bewertung der
Endpunkte PFS, OS, ORR,
Krankheitskontrollrate**

**unterschiedliche
Nachbeobachtungszeiten**

Table 4-1: Characteristics of the included studies investigating amivantamab plus lazertinib and osimertinib plus chemotherapy in NSCLC

Study (Author, year)	MARIPOSA (NCT04487080) Cho et al. (2024), Yang et al. (2025) [17, 25]	FLAURA2 (NCT04035486) Planchard et al. (2023), Janne et al. (2024), Janne et al. (2026) [22, 23, 29]	OPAL (jRCTs031180226) ¹ Saito et al. (2023) [30]
Study design	Phase 3, international, randomised controlled trial; Amivantamab + lazertinib (open-label), osimertinib (blinded), lazertinib (blinded), randomised in a 2:2:1 ratio	Phase 3, international, open-label, randomised controlled trial Osimertinib + chemotherapy vs. osimertinib monotherapy, randomised in a 1:1 ratio	Phase 2, multicentre, open-label, non-randomised trial Osimertinib + cisplatin + pemetrexed (Arm A) and osimertinib + carboplatin + pemetrexed (Arm B)
Data cut-off date	Primary analysis: August 11, 2023 Final analysis: December 4, 2024	Primary analysis: April 3, 2023 Final analysis: June 12, 2025	Response and safety data: February 28, 2022 Updated cut-off for PFS and OS: August 31, 2022
Completion status	Estimated: 06/2027	Estimated: 12/2026	Completed: 02/2023
Intervention	Amivantamab + lazertinib (Study arm 1) ■ Cycle 1: amivantamab IV, 1050 mg weekly (or 1400 mg for body weight ≥ 80 kg) first 4 weeks, first infusion split over 2 days (350 mg day 1, remainder day 2). ■ Cycle 2 onwards: the same amivantamab dose administered every 2 weeks. ■ Lazertinib (240 mg) orally daily.	Osimertinib + platinum + pemetrexed (Study arm 1) ■ Osimertinib 80 mg orally once daily ■ Pemetrexed 500 mg/m² IV + cisplatin 75 mg/m² or carboplatin (AUC 5 mg/mL/min) IV on day 1 of 21-day cycles for 4 cycles ■ Followed by osimertinib 80 mg once daily + pemetrexed 500 mg/m² maintenance every 3 weeks	Osimertinib + platinum + pemetrexed (Arms A and B) ■ Osimertinib 80 mg orally once daily ■ Pemetrexed 500 mg/m² IV + cisplatin 75 mg/m² IV (Arm A) or carboplatin (AUC 5 mg/mL/min) IV (Arm B) on day 1 of 21-day cycles for 4 cycles ■ Followed by osimertinib 80 mg once daily + pemetrexed 500 mg/m² maintenance every 3 weeks
Comparator	Osimertinib 80 mg daily orally (Study arm 2) Lazertinib 240 mg daily orally (Study arm 3)	Osimertinib 80 mg orally once daily (Study arm 2)	Osimertinib + pemetrexed with either: ■ cisplatin (Arm A) ■ carboplatin (Arm B)
Country	International (267 sites across 28 countries) ■ North America: USA 20, Mexico 8, Canada 4, Puerto Rico 1 ■ South America: Brazil 15, Argentina 5 ■ Europe: Russia 15, Spain 17, France 13, Italy 13, Germany 11, Turkey 10, Hungary 6, Poland 6, UK 8, Ukraine 5, Belgium 5, Portugal 4, Netherlands 4 ■ Asia: China 33, Japan 20, South Korea 9, Taiwan 8, Israel 6, Malaysia 6, India 5, Thailand 4 ■ Oceania: Australia 8	International (153 sites across 21 countries) ■ North America: USA 23, Canada 3 ■ South America: Brazil 9, Argentina 7, Chile 4, Peru 5 ■ Europe: Russia 7, France 4, UK 5, Slovakia 3, Czechia 4, ■ South Africa 3 ■ Asia: China 22, Japan 15, Taiwan 7, Thailand 6, Philippines 7, South Korea 5, India 6, Vietnam 2 ■ Oceania: Australia: 6	Japan (multicentre)
Funding/Conflict of interest (Col)	Funded by Janssen Research and Development. Col not disclosed.	Funded by AstraZeneca. Col not disclosed.	Funded by North-East Japan Study Group (NEJSG) and Lung Oncology Group in Kyushu (LOGiK); grant supported by AstraZeneca. Several Col of authors were disclosed with various pharmaceutical companies.
Inclusion criteria	Patients (≥ 18 years) with previously untreated EGFR-mutated (exon 19 deletion or L858R), locally advanced or metastatic NSCLC with at least 1 measurable lesion. ECOG score 0 or 1.	Patients ≥ 18 years (≥ 20 years in Japan) with previously untreated locally advanced or metastatic non-squamous NSCLC with EGFR exon 19 deletion or L858R mutation (alone or in combination with other EGFR mutations); WHO performance status 0 or 1; neurologically stable CNS metastases permitted.	Patients (20-75 years) with treatment-naïve EGFR-mutated (exon 19 deletion or L858R) advanced non-squamous NSCLC; clinical stage IIIB, IIIC, IVA, IVb or relapsed; ECOG PS 0-1; measurable disease per RECIST v1.1; adequate organ function.

Study (Author, year)	MARIPOSA (NCT04487080) Cho et al. (2024), Yang et al. (2025) [17, 25]	FLAURA2 (NCT04035486) Planchard et al. (2023), Janne et al. (2024), Janne et al. (2026) [22, 23, 29]	OPAL (jRCTs031180226) ¹ Saito et al. (2023) [30]
Number of patients	Amivantamab–Lazertinib (N=429) Osimertinib (N=429) Lazertinib (N=216)	Osimertinib+Platinum+Pemetrexed (N=279) Osimertinib (N=278)	Cisplatin arm A (N=34); Carboplatin arm B (N=33) Total (N=67)
Primary endpoint	Progression-free survival (PFS) determined on the basis of blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1	PFS (investigator-assessed)	Safety and objective response rate
Secondary endpoints	Overall survival (OS), objective response, duration of response (DOR), PFS after the first subsequent therapy, time to symptomatic progression, intracranial PFS	OS, objective response, DOR, disease control, depth of response, second PFS	Complete response rate, disease control rate, PFS
Exploratory endpoints	None	CNS PFS, CNS objective response rate, CNS duration of response, CNS disease control rate, CNS tumour shrinkage in patients with baseline CNS metastases.	OS

Abbreviations: AUC ... area under the curve, CNS ... central nervous system, CoI ... conflict of interest, DOR ... duration of response, ECOG ... Eastern Cooperative Oncology Group, EGFR ... epidermal growth factor receptor, IV ... intravenous, L858R ... leucine-to-arginine substitution at codon 858, LOGiK ... Lung Oncology Group in Kyushu, N ... number of patients, NCT ... National Clinical Trial, NEJSG ... North-East Japan Study Group, NSCLC ... non-small cell lung cancer, OS ... overall survival, PFS ... progression-free survival, PS ... performance status, RECIST ... Response Evaluation Criteria in Solid Tumours, TKI ... tyrosine kinase inhibitor, WHO ... World Health Organization.

Note: ¹Despite the RCT design, the study was treated as a single-arm study for this assessment because both study arms were relevant comparators within the assessment scope. Therefore, only pooled study results were extracted.

Characteristics of the patient population

The baseline characteristics of patients enrolled in the included studies were broadly comparable, although some differences were observed (see Table 4-2). In MARIPOSA and FLAURA2, the median age was nearly identical (63-64 years in MARIPOSA versus 61-62 years in FLAURA2), with a similar age distribution: approximately 55-62% of patients were under 65 years, around 29-33% were aged 65 to 74, and 8-12% were 75 or older. In OPAL, the median age was 67 years. The proportion of female patients was comparable (59-64% in MARIPOSA versus 61-62% in FLAURA2 and 64% in OPAL). Never-smokers accounted for approximately 67-70% in the three trials. EGFR mutation distribution was nearly identical in MARIPOSA and FLAURA2, with exon 19 deletions around 60% and L858R in 40% of patients. In OPAL, it was 52% for L858R and 46% for exon 19 deletion. Adenocarcinoma was the dominant histology in all three trials (97-99%). Regarding disease extent, MARIPOSA and FLAURA2 trials enrolled predominantly stage IVa-IVb patients, with metastatic disease in the vast majority. Bone metastases were frequent in both (42-51%), and liver metastases occurred in 15-24%. In OPAL, disease stage IVa and IVb accounted for 40% and 48% of patients, respectively.

A few notable differences were noted in the patient population, especially in racial composition. MARIPOSA comprised 58-59% Asian patients and 38% white patients, while in FLAURA2 the figures were 63-64% and 27-30%, respectively. The OPAL trial enrolled an exclusively Japanese population. In ECOG performance status, MARIPOSA had a slightly higher proportion of patients with a score of 1 (65-67%) than FLAURA2 (62-63%). In OPAL, the majority of patients had an ECOG performance status of 0 (69%). While FLAURA2 permitted patients with neurologically stable CNS metastases and reported CNS metastasis rates of 40-42%, MARIPOSA reported brain metastases

ähnliche demografische und klinische Patientencharakteristika:
Alter,
Geschlecht,
Raucherstatus,
EGFR-Mutation,
Tumorstadium

relevante Unterschiede der Studienpopulationen:
Ethnizität,
ECOG-Performanzstatus,
CNS-Metastasen,
Histologie

ses in approximately 40-41% but did not separately report CNS metastasis status in the same way. In OPAL CNS metastases were present in 33% of patients at baseline. Additionally, FLAURA2 enrolled only non-squamous NSCLC, whereas MARIPOSA included a small proportion of squamous-cell and other histologies (approximately 1-2%). Prior surgical history was reported differently across the two trials. In MARIPOSA, prior cancer-related surgery was explicitly recorded in 11-12% of patients, whereas in FLAURA2 surgery prior to study entry was reported without cancer-specific qualification, and at a substantially higher rate (39-43%) [17, 22, 23, 25].

Table 4-2: Patients' characteristics of the included studies investigating amivantamab plus lazertinib and osimertinib plus chemotherapy in NSCLC

Study	MARIPOSA1 [17]		FLAURA2 [22]		OPAL [30]
	Amivantamab + lazertinib (N=429)	Osimertinib (N=429)	Osimertinib + platinum-pemetrexed (N=279)	Osimertinib (N=278)	Cisplatin + carboplatin (N=67)
Age, median (range) – yr	64 (25-88)	63 (28-88)	61 (26-83)	62 (30-85)	67 (26-75)
Age, distribution – n (%)					
<65 yr	235 (55)	237 (55)	174 (62) ⁴	166 (60) ⁴	NR
65 to <75 yr	143 (33)	139 (32)	82 (29) ⁴	88 (32) ⁴	NR
≥75 yr	51 (12)	53 (12)	23 (8) ⁴	24 (9) ⁴	NR
Female sex – n (%)	275 (64)	251 (59)	173 (62)	169 (61)	43 (64)
Race or ethnic group – n (%)					
Asian	250 (58)	251 (59)	179 (64)	176 (63)	67 (100)
White	164 (38)	165 (38)	74 (27)	83 (30)	0
Black	4 (1)	3 (1)	2 (1)	3 (1)	0
Bodyweight, median (range) – kg	62 (32-118)	62 (35-109)	NR	NR	NR
ECOG/WHO performance status score – n (%)					
0	141 (33)	149 (35)	104 (37)	102 (37)	46 (69)
1	288 (67)	280 (65)	174 (62)	176 (63)	21 (31)
2	0	0	1 (<1)	0	0
History of smoking – n (%)					
No	299 (70)	295 (69)	188 (67)	181 (65)	46 (69)
Yes	130 (30)	134 (31)	91 (33)	97 (35)	21 (31)
History of brain metastases – n (%)	178 (41)	172 (40)	NR	NR	NR
CNS metastasis					
Yes	NR	NR	116 (42)	110 (40)	22 (33)
No	NR	NR	163 (58)	168 (60)	45 (67)
Stage					
Locally advanced	NR	NR	14 (5)	7 (3)	NR
Metastatic	NR	NR	265 (95)	271 (97)	NR
IVa	146 (34) ^{2,3}	150 (35) ^{2,3}	98 (35) ^{3,4}	104 (37) ⁴	27 (40)
IVb	233 (54) ^{2,3}	236 (55) ^{2,3}	168 (60) ^{3,4}	167 (60) ⁴	32 (48)
Extrathoracic metastases – n (%)	NR	NR	147 (53)	149 (54)	NR
Liver metastases – n (%)	64 (15) ²	72 (17) ²	43 (15)	66 (24)	NR
Bone and locomotor-system metastases – n (%)	206 (49) ²	180 (42) ²	132 (47)	142 (51)	NR

Study	MARIPOSA1 [17]		FLAURA2 [22]		OPAL [30]
	Amivantamab + lazertinib (N=429)	Osimertinib (N=429)	Osimertinib + platinum-pemetrexed (N=279)	Osimertinib (N=278)	Cisplatin + carboplatin (N=67)
EGFR mutation – n (%)					
Ex19del	258 (60)	257 (60)	169 (61)	168 (60)	31 (46)
L858R	172 (40)	172 (40)	106 (38)	107 (38)	35 (52)
Both	0	0	3 (1)	1 (<1)	1 (>1)
Histologic characteristics – n (%)					
Adenocarcinoma	417 (97)	415 (97)	275 (99)	275 (99)	66 (99)
Adenosquamous carcinoma			2 (1)	0	0
Squamous-cell carcinoma	6 (1)	5 (1)	2 (1)	3 (1)	0
Large-cell carcinoma	3 (1)	0	0	0	0
Other	2 (<1)	9 (2)			1 (1)
Median time from initial diagnosis to randomisation (range) – mo	1.5 (0.2-207.9)	1.4 (0.3-162.8)	NR	NR	NR
Total number of subjects with any prior therapies for lung cancer – n (%)	112 (26) ²	104 (24) ²	NR	NR	NR
Prior systemic therapy	8 (2) ¹	10 (2) ¹	NR	NR	NR
Prior radiotherapy	73 (17) ²	65 (15) ²	NR	NR	NR
Prior cancer-related surgery	53 (12) ²	49 (11) ²	107 (39) ^{4,5}	120 (43) ^{4,5}	NR
Last therapy before random assignment – n (%)					
Osimertinib	NR	NR	NR	NR	NR
Chemotherapy	NR	NR	NR	NR	NR
Follow-up, median – mo	22.0	22.0	19.5	16.5	33.4
Duration of treatment, median (range) – mo	Cut-off August 11, 2023: 18.5 Cut-off December 4, 2024: 27.0	Cut-off August 11, 2023: 18.5 Cut-off December 4: 22.4	Cut-off April 3, 2023: 22.3 Cut-off June 12, 2025: 30.5 (0.1-59.0)	Cut-off April 3, 2023: 19.3 Cut-off June 12: 21.2 (0.1-59.2)	23.4 (0.1-31.2) – 25.5 (0.7-30.7)

Abbreviations: CNS ... central nervous system, ECOG ... Eastern Cooperative Oncology Group, EGFR ... epidermal growth factor receptor, Ex19del ... exon 19 deletion, L858R ... leucine-to-arginine substitution at codon 858, mo ... months, N ... number of patients, NR ... not reported, NSCLC ... non-small cell lung cancer, WHO ... World Health Organization, yr ... years.

Notes:

¹ Lazertinib monotherapy arm is not presented as it is not relevant for the assessment

² Data from EPAR of Rybrevant,

³ Cancer stage at initial diagnosis,

⁴ Data from EPAR of Tagrisso,

⁵ Reported as surgery prior to study entry without any specification.

4.4 Results: Clinical effectiveness

The outcomes in this section are from analyses at different data cut-offs and are summarised below (Table 4-3). For MARIPOSA, PFS, ORR, and DOR are from the primary analysis (cut-off 11 Aug 2023; median follow-up 22.0 months) [17], while OS, TTSP, TTD, time to subsequent therapy, PFS after first subsequent therapy, and all intracranial outcomes are from the final OS analysis (cut-off 4 Dec 2024; median follow-up 37.8 months) [25]. For FLAURA2, PFS, ORR, DOR, and DCR are from the primary analysis (cut-off 3 Apr 2023) [22]; intracranial outcomes from the preplanned CNS analysis (same cut-off) [29]; and OS from the final OS analysis (cut-off 12 Jun 2025) [23]. For OPAL (single-arm phase 2), outcomes are from the updated analysis (median follow-up 33.4 months) [30]. As follow-up duration varies, cross-trial differences in time-dependent outcomes may partly reflect maturity rather than true treatment differences, mainly for intracranial comparisons, where MARIPOSA data derive from the later cut-off (~38 months) and FLAURA2 from the earlier one (~20 months).

**unterschiedliche
Evidenzgrundlage der
Wirksamkeitsendpunkte:
PFS, ORR und DOR aus
Primäranalysen;
OS und intrakranielle
Endpunkte aus finalen
Analysen**

4.4.1 Overall survival

Both amivantamab plus lazertinib and osimertinib plus chemotherapy demonstrated a statistically significant improvement in OS compared to osimertinib monotherapy. In MARIPOSA, the median OS had not yet been reached in the amivantamab plus lazertinib arm (versus 36.7 months with osimertinib; HR 0.75; $p=0.005$), while in FLAURA2, osimertinib plus chemotherapy achieved a median OS of 47.5 months compared to 37.6 months with osimertinib monotherapy (HR 0.77; $p=0.02$). In OPAL, which lacked a comparator arm, median OS had also not been reached at the time of the updated data cut-off, with a median follow-up of 33.4 months. The 12- and 24-month OS rates in this trial were 96.9% (95% CI: 88.3-99.2) and 92.3% (95% CI: 82.5-96.7), respectively [23, 25, 30]. See Table 4-3.

**signifikanter
OS-Vorteil beider
Kombinationstherapien
gegenüber Osimertinib;
OPAL ohne Vergleichsarm**

4.4.2 Progression-free survival

The median PFS was 23.7 months for amivantamab plus lazertinib in MARIPOSA and 25.5 months for osimertinib plus chemotherapy in FLAURA2. In MARIPOSA, amivantamab plus lazertinib significantly prolonged PFS compared to osimertinib monotherapy (23.7 months [95% CI: 19.1-27.7] versus 16.6 months [95% CI: 14.8-18.5]; HR 0.70 [95% CI: 0.58-0.85]; $p<0.001$). Similarly, in FLAURA2, osimertinib plus chemotherapy demonstrated a significant PFS benefit over osimertinib monotherapy (25.5 months [95% CI: 24.7-NC] versus 16.7 months [95% CI: 14.1-21.3]; HR 0.62 [95% CI: 0.49-0.79]; $p<0.001$). In OPAL, the median PFS was 31.0 months (95% CI: 26.8-NR) in the pooled population; however, given the single-arm design and exclusively Japanese population, this figure is not directly comparable to the other trials. See Table 4-3.

**signifikante
PFS-Verlängerung beider
Kombinationstherapien;
OPAL: medianes PFS
31 Monate**

4.4.3 Duration of response

Both experimental regimens significantly improved DOR relative to osimertinib monotherapy. In MARIPOSA, median DOR was 25.8 months (95% CI: 20.1-NE) with amivantamab plus lazertinib versus 16.8 months (95% CI: 14.8-18.5) with osimertinib. In FLAURA2, it was 24.0 months (95% CI: 20.9-27.8) with osimertinib plus chemotherapy versus 15.3 months (95% CI: 12.7-19.4) with osimertinib monotherapy [17, 22]. See Table 4-3.

längere Ansprechdauer unter beiden Kombinationstherapien gegenüber Osimertinib

4.4.4 Objective response rate

In MARIPOSA, the ORR was 86% (95% CI: 83-89) with amivantamab plus lazertinib versus 85% (95% CI: 81-88) with osimertinib. In FLAURA2, the ORR for osimertinib plus chemotherapy was 83% (95% CI: 78-87) in comparison to 76% (95% CI: 70-80) with osimertinib. In the OPAL study, the ORR was 90.9% (95% CI: 84.0-97.8) in the pooled population [17, 22, 30]. See Table 4-3.

hohe ORR in allen Studien (83-91 %); kein klarer Unterschied zwischen den Kombinationstherapien

4.4.5 Time to symptomatic progression

Median TTSP was reported only in the MARIPOSA study and was longer in the amivantamab plus lazertinib group 43.6 (95% CI: 36.0-NE) compared to the osimertinib group 29.3 (95% CI: 26.4-33.4); HR: 0.69 (95% CI: 0.57-0.83) [25]. See Table 4-3.

MARIPOSA: längere Zeit bis zur symptomatischen Progression

4.4.6 Time to subsequent therapy

Median time to subsequent therapy was reported only in the MARIPOSA study and was longer in the amivantamab plus lazertinib group [30.3 (95% CI: 26.6-34.4) months] versus the osimertinib group [24.0 (95% CI: 22.2-26.2) months]; 0.76 (95% CI: 0.64-0.90) [25]. See Table 4-3.

MARIPOSA: längere Zeit bis zur Folgetherapie

4.4.7 PFS after first subsequent therapy

Median progression-free survival after first subsequent therapy reported only in the MARIPOSA trial was longer following the treatment with amivantamab plus lazertinib [42.9 (95% CI: 37.6-NE) months] versus osimertinib [32.8 (95% CI: 29.7-37.0) months]; HR: 0.74 (95% CI: 0.61-0.90) [25]. See Table 4-3.

MARIPOSA: längeres PFS nach 1. Folgetherapie

4.4.8 Time to treatment discontinuation

Median TTD, reported only in the MARIPOSA trial, was longer with amivantamab plus lazertinib [27.0 (95% CI: 22.3-30.6) months] in comparison to osimertinib [22.6 (95% CI: 20.3-24.5) months]; HR: 0.79 (95% CI: 0.67-0.93) [25]. See Table 4-3.

MARIPOSA: längere Behandlungsdauer bis Therapieabbruch

4.4.9 Disease control rate

DCR was comparable between osimertinib plus chemotherapy [95% (95% CI: 92-98)] and osimertinib [94% (95% CI: 90-96)] in the FLAURA2 study. In the OPAL study, it reached 97.0% (95% CI: 92.8-100). No DCR data were available for MARIPOSA [22, 30]. See Table 4-3.

**FLAURA2 und OPAL:
hohe
Krankheitskontrollrate**

4.4.10 Intracranial objective response

Intracranial ORR was 78% (95% CI: 71-84) with amivantamab plus lazertinib in MARIPOSA and 73% (95% CI: 64-81) with osimertinib plus chemotherapy in FLAURA2 (cFAS population). Neither trial demonstrated a statistically significant difference in intracranial ORR between the experimental and osimertinib monotherapy arms (MARIPOSA: odds ratio 1.01 [95% CI: 0.61-1.65]; FLAURA2 cFAS: odds ratio 1.19 [95% CI: 0.67-2.14]; $p=0.5492$). No intracranial ORR data were available for OPAL [25, 29]. See Table 4-3.

**keine signifikanten
Unterschiede der
intrakraniellen ORR
gegenüber Osimertinib**

4.4.11 Duration of intracranial objective response

The median duration of intracranial objective response was 35.7 months (95% CI: 25.8-NE) with amivantamab plus lazertinib in MARIPOSA and not reached (95% CI: 23.8-NC) with osimertinib plus chemotherapy in FLAURA2 (cFAS population); cross-trial comparison is limited by differences in CNS population definitions and data cut-off dates. In both trials, the duration of intracranial response was longer in the experimental arm compared to osimertinib monotherapy (MARIPOSA: 35.7 versus 29.6 months [95% CI: 23.9-34.1]; FLAURA2 cFAS: NRe [95% CI: 23.8-NC] versus 26.2 months [95% CI: 19.4-NC]). No data were available for OPAL [25, 29]. See Table 4-3.

**längere intrakranielle
Ansprechdauer
unter beiden
Kombinationstherapien**

4.4.12 Intracranial PFS

Intracranial PFS was 25.4 months (95% CI: 20.1-29.5) with amivantamab plus lazertinib in MARIPOSA and 30.2 months (95% CI: 28.4-NC) with osimertinib plus chemotherapy in FLAURA2 (cFAS population). In neither trial did the experimental regimen demonstrate a statistically significant improvement in intracranial PFS over osimertinib monotherapy (MARIPOSA: HR 0.79 [95% CI: 0.61-1.02]; FLAURA2 cFAS: HR 0.58 [95% CI: 0.33-1.01]; $p=0.0548$), although in the FLAURA2 cEFR population, a statistically significant benefit was observed (HR 0.40 [95% CI: 0.19-0.84]; $p=0.0157$). No data were available for OPAL [25]. See Table 4-3.

**kein konsistenter Vorteil
beim intrakraniellen PFS;
signifikanter Effekt nur
in der cEFR-Population
von FLAURA2**

4.4.13 Quality of life

No health-related quality of life data were reported for either trial.

**keine Daten zur
gesundheitsbezogenen
Lebensqualität verfügbar**

Table 4-3: Efficacy results of the studies investigating amivantamab plus lazertinib and osimertinib plus chemotherapy in NSCLC

Study (Author, year) Outcomes	MARIPOSA (NCT04487080) Cho et al. (2024) [17], Yang et al. (2025) [25]		FLAURA2 (NCT04035486) Planchard et al. (2023) [22], Janne et al. (2024) [29], Janne et al. (2026) [23]		OPAL (JRCTs031180226) Saito et al. (2023) [30]
	Amivantamab + lazertinib (N=429) ¹	Osimertinib (N=429) ¹	Osimertinib+ platinum-pemetrexed (N=279)	Osimertinib (N=278)	Platinum-based chemotherapy (N=66)
Overall survival, median (95% CI) – mo	NE (42.9-NE)	36. 7 (33.4-41.0)	47.5 (41.0-NC) ²	37.6 (33.2-43.2) ²	NRe (NRe–NRe)
HR (95% CI)	0.75 (0.61-0.92); p=0.005		0.77 (0.61-0.96); p=0.02		NA
Progression-free survival, median (95% CI) – mo	23.7 (19.1-27.7)	16.6 (14.8-18.5)	25.5 (24.7-NC)	16.7 (14.1-21.3)	31.0 (26.8-NR)
HR (95% CI)	0.70 (0.58-0.85); p<0.001		0.62 (0.49-0.79); p<0.001		NA
Duration of response, median (95% CI) – mo	25.8 (20.1-NE)	16.8 (14.8-18.5)	24.0 (20.9-27.8)	15.3 (12.7-19.4)	NR
Objective response rate (95% CI) – %	86 (83-89)	85 (81-88)	83 (78-87)	76 (70-80)	90.9 (84.0-97.8)
Odds ratio (95% CI)	1.15 (0.78-1.70)		NR		NA
Time to symptomatic pro- gression, median (95% CI) – mo	43.6 (36.0-NE)	29.3 (26.4-33.4)	NR	NR	NR
HR (95% CI)	0.69 (0.57-0.83)		NR		NR
Time to treatment discontinua- tion, median (95% CI) – mo	27.0 (22.3-30.6)	22.6 (20.3-24.5)	NR	NR	NR
HR (95% CI)	0.79 (0.67-0.93)		NR		NR
Time to subsequent therapy, median (95% CI) – mo	30.3 (26.6-34.4)	24.0 (22.2-26.2)	NR	NR	NR
HR (95% CI)	0.76 (0.64-0.90)		NR		NR
PFS after first subsequent therapy, median (95% CI) – mo	42.9 (37.6-NE)	32.8 (29.7-37.0)	NR	NR	NR
HR (95% CI)	0.74 (0.61-0.90)		NR		NR
Disease control (95% CI) – %	NR	NR	95 (92-98)	94 (90-96)	97.0 (92.8-100)
Overall survival, 12-month rate, (95% CI) – %	NR	NR	NR	NR	96.9 (88.3-99.2)
Overall survival, 24-month rate, (95% CI) – %	NR	NR	NR	NR	92.3 (82.5-96.7)
Intracranial PFS/CNS PFS, median (95% CI) – mo	25.4 (20.1-29.5)	22.2 (18.4-26.9)	cFAS: 30.2 (28.4-NC) ³ cEFR: NR (23.0-NC) ⁴	cFAS: 27.6 (22.1-NC) ³ cEFR: 17.3 (13.9-NC) ⁴	NR
HR (95% CI)	0.79 (0.61-1.02)		cFAS: 0.58 (0.33-1.01); p=0.0548 cEFR: 0.40 (0.19-0.84); p=0.0157		NR
Intracranial objective response/ CNS response (95% CI) – %	78 (71-84)	77 (71-83)	cFAS: 73 (64-81) ³ cEFR: 88 (73-96) ⁴	cFAS: 69 (59-78) ³ cEFR: 87 (72-96) ⁴	NR
Odds ratio (95% CI)	1.01 (0.61-1.65)		cFAS: 1.19 (0.67-2.14); p=0.5492 cEFR: 1.06 (0.28-4.00); p=0.9308		NR
Duration of intracranial/CNS objective response, median (95% CI) – mo	35.7 (25.8-NE)	29.6 (23.9-34.1)	cFAS: NR (23.8-NC) ³ cEFR: NR (21.6-NC) ⁴	cFAS: 26.2 (19.4-NC) ³ cEFR: 20.9 (12.6-NC) ⁴	NR

Abbreviations: cEFR ... CNS evaluable for response, cFAS ... CNS full analysis set, CI ... confidence interval, CNS ... central nervous system, HR ... hazard ratio, mo ... months, N ... number of patients, NA ... not applicable, NC ... not calculable, NCT ... National Clinical Trial, NE ... not estimable, NR ... not reported, NRe ... not reached, OS ... overall survival, PFS ... progression-free survival.

Notes:

¹ Cut-off date for Overall survival, Median time to symptomatic progression, Median time to treatment discontinuation, Median time to subsequent therapy, Median PFS after first subsequent therapy, Intracranial PFS, Intracranial objective response, Duration of intracranial objective response: December 4, 2024, Cut-off date for all other outcomes: August 11, 2023;

² Cut-off date for overall survival data: June 12, 2025, Cut-off date for all other outcomes: April 3, 2023;
³ Reported from proportion of population from FLAURA2, cFAS (n=222), osimertinib plus platinum-pemetrexed (n=118), osimertinib monotherapy (n=104) comprised of patients with ≥ 1 CNS lesion at baseline, whether measurable or nonmeasurable;
⁴ Reported from proportion of population from FLAURA2, cEFR (n=78), osimertinib plus platinum-pemetrexed (n=40), osimertinib monotherapy (n=38) comprised of patients with ≥ 1 measurable target CNS lesion at baseline.

4.5 Results: Safety

4.5.1 Adverse events

Adverse events of any grade occurred in all patients across both experimental arms of amivantamab plus lazertinib and osimertinib plus chemotherapy in both MARIPOSA and FLAURA2 trials. AE rates were similarly high in the osimertinib monotherapy comparator arms (>99% in MARIPOSA and 98% in FLAURA2). The grade ≥ 3 toxicity profiles differed between the two experimental regimens. In MARIPOSA, the predominant grade ≥ 3 adverse events with amivantamab plus lazertinib were skin-related (rash 17%, paronychia 12%, dermatitis acneiform 9%), alongside hypoalbuminaemia (6%), increased alanine aminotransferase (7%), and pulmonary embolism (9%); venous thromboembolism as a grouped term occurred in 40% of patients. In FLAURA2, grade ≥ 3 events with osimertinib plus chemotherapy were predominantly myelosuppressive, including anaemia (20%), neutropenia (11%), thrombocytopenia (7%), and decreased platelet count (7%) [23, 25].

In the OPAL study, the overall any-grade adverse event rate was not reported. However, the most common any-grade adverse events in the total population were haematological, including anaemia (95%), decreased neutrophil count (76%), and thrombocytopenia (88%). Frequently reported non-haematological adverse events included nausea (61%), increased aspartate aminotransferase (84%), increased alanine aminotransferase (67%), anorexia (58%), oral mucositis (45%), diarrhoea (48%), and prolonged QTc (40%) [30]. All details are provided in Table 4-4.

4.5.2 Serious adverse events

Serious adverse events were more frequent with amivantamab plus lazertinib (55%) than with osimertinib monotherapy (41%) in MARIPOSA, and similarly more frequent with osimertinib plus chemotherapy (46%) than with osimertinib monotherapy (27%) in FLAURA2. No serious adverse event data were reported for OPAL [23, 25]. See Table 4-4.

unterschiedliche
Nebenwirkungsprofile der
Kombinationstherapien:

MARIPOSA:
Hauttoxizität,
Thromboembolien

FLAURA2/OPAL:
Hämatologische Toxizität

schwerwiegende
unerwünschte Ereignisse
(UE) unter beiden
Kombinationstherapien
häufiger als unter
Osimertinib

4.5.3 Severe adverse events (grade ≥3)

Grade ≥3 severe adverse events were higher in both experimental arms compared to their respective osimertinib monotherapy comparators. In MARIPOSA, grade ≥3 events occurred in 80% of patients receiving amivantamab plus lazertinib versus 52% with osimertinib. In FLAURA2, the corresponding rates were 70% with osimertinib plus chemotherapy versus 34% with osimertinib monotherapy. In the OPAL study, grade ≥3 treatment-emergent adverse events occurred in 90% of patients. The most common grade ≥3 events were haematological, including decreased neutrophil count (45%), thrombocytopenia (21%), and anaemia (22%). Non-haematological grade ≥3 events included prolonged QTc (12%) and anorexia (13%). No treatment-related deaths were reported [23, 25, 30]. See Table 4-4.

**schwere UE (≥ Grad 3)
unter beiden
Kombinationstherapien
häufiger;
OPAL: überwiegend
hämatologische
Toxizitäten**

4.5.4 Deaths

In the MARIPOSA trial, adverse events resulting in death occurred in 9% and 8% of patients in the amivantamab plus lazertinib and osimertinib group, respectively. In the FLAURA2 trial, these were recorded in 8% and 4% in the osimertinib plus chemotherapy and osimertinib monotherapy arms, respectively. No treatment-related deaths were reported in OPAL [23, 25]. See Table 4-4.

**Todesfälle infolge UE
überwiegend vergleichbar;
keine therapiebedingten
Todesfälle in OPAL**

4.5.5 Treatment discontinuation

Discontinuation for any reason was lower with amivantamab plus lazertinib (62%) than with osimertinib monotherapy (72%) in MARIPOSA, and similarly lower with osimertinib plus chemotherapy (72%) compared to osimertinib monotherapy (82%) in FLAURA2. Discontinuation specifically due to adverse events was higher with both experimental regimens: 23% with amivantamab plus lazertinib versus 14% with osimertinib in MARIPOSA, and 12% with osimertinib plus chemotherapy versus 7% with osimertinib monotherapy in FLAURA2. In OPAL, 52% of patients discontinued treatment overall, with 15% discontinuing due to adverse events [23, 25, 30]. See Table 4-4.

**Therapieabbrüche
aufgrund UE unter beiden
Kombinationstherapien
häufiger;
Therapieabbruch
insgesamt seltener als
unter Osimertinib**

4.5.6 Treatment interruption

In MARIPOSA, adverse events led to interruption of any trial agent in 83% of patients with amivantamab plus lazertinib versus 39% with osimertinib monotherapy. In FLAURA2, dose interruption of osimertinib occurred in 43% of patients with osimertinib plus chemotherapy versus 19% with osimertinib monotherapy [17, 22]. See Table 4-4.

**Therapieunterbrechungen
aufgrund UE unter beiden
Kombinationstherapien
häufiger**

Table 4-4: Safety results of the studies investigating amivantamab plus lazertinib and osimertinib plus chemotherapy in NSCLC

Study (Author, year)	MARIPOSA (NCT04487080) Yang et al. (2025) [25]		FLAURA2 (NCT04035486) Janne et al. (2026) [23]		OPAL (jRCTs031180226) Saito et al. (2023) [30]
	Amivantamab + lazertinib (N=421) ¹	Osimertinib (N=428) ¹	Osimertinib + Platinum-pemetrexed (N=276)	Osimertinib (N=275)	Cisplatin + carboplatin arm (N=67)
Any adverse event, n (%)	421 (100)	426 (>99)	276 (100)	269 (98)	NR
Severe adverse events grade ≥3, n (%)	337 (80)	224 (52)	193 (70)	94 (34)	NR
Treatment-emergent adverse events grade ≥3, n (%)	NR	NR	NR	NR	60 (90)
Serious adverse events, n (%)	233 (55)	177 (41)	126 (46)	75 (27)	NR
Any adverse event resulting in death, n (%)	37 (9)	34 (8)	22 (8)	10 (4)	NR
Treatment-related deaths, n (%)	NR	NR	NR	NR	0
Discontinued treatment, n (%)	260 (62) ¹	310 (72) ¹	200 (72) ^{2,3}	226 (82)	35 (52) ⁴
Disease progression	140 (33)	234 (55)	127 (46)	185 (67)	NR
Adverse event	97 (23)	62 (14)	34 (12)	20 (7)	10 (15) ⁴
Withdrawal by patient	19 (5)	13 (3)	16 (6)	7 (3)	NR
Physician's decision	2 (0.5)	1 (0.2)	0	0	NR
Non-compliance	1 (0.2)	0	0	0	NR
CSP criteria	0	0	2 (1)	1 (<1)	NR
Lack of response	0	0	1 (<1)	4 (1)	NR
Lost to follow-up	1 (0.2)	0	0	0	NR
Severe non-compliance to protocol	0	0	1 (<1)	0	NR
Other	1 (0.2)	0	19 (7)	9 (3)	NR
Event leading to interruption of any trial agent, n (%)	350 (83)	165 (39)	120 (43)	52 (19)	NR

Abbreviations: CSP ... clinical study protocol, N ... number of patients, NCT ... National Clinical Trial, NR ... not reported.

Notes:

¹ Cut-off date: December 4, 2024,

² Cut-off date: June 12, 2025,

³ numbers reported for those who discontinued osimertinib,

⁴ Calculated by pooling the Cisplatin and Carboplatin group.

4.6 HTA reports and indirect treatment comparison

In addition to the pivotal studies described above, we identified three sources reporting indirect treatment comparisons (ITCs) of the efficacy and safety of amivantamab plus lazertinib versus osimertinib plus chemotherapy: one published ITC by Torchia et al. (2025) [32] and two ITCs included in the HTA reports by NICE [33] and CDA-AMC [34]. These sources differed in both their purpose and methodology. Torchia et al. (2025) independently reconstructed individual patient data (IPD) from the published Kaplan-Meier curves of the MARIPOSA [17, 25] and FLAURA2 [22, 23] trials to perform an indirect comparison, whereas the HTA reports critically appraised the ITC submitted by the health technology developer (HTD) as part of the reimbursement dossier, including a cost-effectiveness model. The HTA bodies evaluated the methodology, assumptions, and robustness of the submitted analysis, exploring alternative approaches where needed to assess the uncertainty of the results.

3 indirekte Vergleiche:
1 unabhängiger ITC und
2 HTA-Bewertungen
des vom Hersteller
eingereichten ITC

4.6.1 ITC by Torchia et al. (2025)

Methods

Torchia et al. (2025) conducted an IPD-based indirect comparison of MARIPOSA and FLAURA2 by reconstructing individual patient data from published Kaplan–Meier curves using the iKM algorithm, based on digitised survival curves and reported numbers at risk. Eligible trials were phase 3 RCTs comparing first-line experimental treatment for advanced EGFR-mutated NSCLC against osimertinib monotherapy. MARIPOSA (amivantamab plus lazertinib vs. osimertinib; N=1,375) and FLAURA2 (osimertinib plus chemotherapy vs. osimertinib; N=557) were included, yielding 1,415 patients across four arms; the lazertinib monotherapy arm was excluded.

Efficacy outcomes (PFS, OS, intracranial PFS) were assessed in the ITT population and pre-specified subgroups (CNS/liver metastases, EGFR/TP53 mutation status), with experimental arms compared only if control arms showed no statistically significant differences. Safety analysis included grade ≥ 3 adverse events occurring in $\geq 10\%$ of patients, compared within and across trials.

Efficacy results

In the ITT population, osimertinib plus chemotherapy demonstrated a marginally statistically significant improvement in PFS compared with amivantamab plus lazertinib (HR 0.79, 95% CI: 0.63-0.99; $p=0.044$), though no significant difference in OS was observed (HR 1.06, 95% CI: 0.84-1.33; $p=0.637$). The PFS advantage of osimertinib plus chemotherapy was more pronounced in patients with CNS metastases (HR 0.63, 95% CI: 0.45-0.89; $p=0.008$), without liver metastases (HR 0.73, 95% CI: 0.57-0.95; $p=0.017$), and with the EGFR L858R mutation (HR 0.68, 95% CI: 0.48-0.95; $p=0.024$). No significant PFS difference was observed in patients without CNS metastases or with exon 19 deletions. In patients with CNS metastases, osimertinib plus chemotherapy also demonstrated a statistically significant improvement in intracranial PFS (HR 0.52, 95% CI: 0.34-0.78; $p=0.002$). Subgroup OS data were not available at the time of the analysis.

Safety results

The safety analysis was based on aggregate event counts from the primary publications, compared with Mantel–Haenszel fixed-effect odds ratios. Control arms were verified for consistency before the experimental arms were compared. Cross-trial comparison of the experimental arms, indirect and unadjusted for between-trial differences (odds ratios expressed as osimertinib plus chemotherapy versus amivantamab plus lazertinib), showed that grade ≥ 3 anaemia and neutropenia were significantly more frequent with osimertinib plus chemotherapy (OR 6.30 and 137.31, respectively), while grade ≥ 3 cutaneous rash and paronychia were significantly more frequent with amivantamab plus lazertinib (OR 0.02 and 0.06, respectively). Adverse events specific to amivantamab plus lazertinib, including infusion-related reactions (any grade in $>60\%$; grade ≥ 3 in 6%) and venous thromboembolic events (any grade in $\sim 40\%$; grade ≥ 3 in 11%), were not included in the formal safety analysis, as they did not individually reach the 10% threshold for grade ≥ 3 events.

**rekonstruierte
Patientendaten aus
MARIPOSA und FLAURA2:
Indirekter Vergleich über
Osimertinib**

**PFS-Vorteil für
Osimertinib +
Chemotherapie;
kein OS-Unterschied;
größter Nutzen bei
CNS-Metastasen und L858R**

**unterschiedliche
Toxizitätsprofile:
Hämatologische Toxizität
vs. Hauttoxizität;
Amivantamab-spezifische
Nebenwirkungen
nicht berücksichtigt**

Limitations

While this approach enables patient-level time-to-event analyses in the absence of original IPD, the reconstructed data represent an approximation of the original trial data and may introduce additional uncertainty into the estimated treatment effects. The authors also noted several potential sources of bias inherent to the indirect nature of the comparison. Differences in brain assessment schedules between studies, with systematic assessment in patients without baseline CNS metastases performed only in MARIPOSA, may have influenced PFS outcomes. A higher proportion of patients with ECOG PS 0 and a lower median age in FLAURA2 could additionally favour that regimen. The exclusion of venous thromboembolic events and infusion-related reactions from the safety analysis was noted as a clinically significant limitation. Results were therefore considered hypothesis-generating.

wesentliche Limitationen:
indirekter Vergleich,
Unterschiede im
Studiendesign und
unvollständige
Sicherheitsanalyse

4.6.2 ITC in NICE HTA report

The HTA report of NICE [33] included an assessment of the HTD's ITC of amivantamab plus lazertinib versus osimertinib plus chemotherapy.

**Bewertung des vom
Hersteller eingereichten
ITC durch NICE**

Methods

The HTD initially explored several approaches for the ITC. A conventional hazard ratio (HR)-based ITC was considered first. However, because the treatment effect in MARIPOSA violated the proportional hazards assumption for both PFS and OS, the HTD concluded that conventional HR-based and parametric ITCs were not appropriate. As an alternative, the HTD initially assumed that between-trial differences could be captured through the common osimertinib treatment arm by estimating the HR for osimertinib in MARIPOSA relative to FLAURA2 and applying this estimate to the osimertinib plus chemotherapy survival curves from FLAURA2. During the NICE appraisal, additional analyses accounting for time-varying treatment effects and differences in baseline patient characteristics were requested. Following this, the HTD adopted an unanchored matching-adjusted indirect comparison (MAIC) as its base-case analysis, arguing that fractional polynomial and parametric ITCs produced implausible long-term survival estimates and that a naïve comparison did not adequately account for between-trial differences. For safety outcomes, the HTD submitted a Bayesian network meta-analysis (NMA) informed by an anchored MAIC, which was subsequently critically appraised by NICE.

**mehrere Ansätze für
den indirekten Vergleich
geprüft**

Efficacy results

The HTD's analysis concluded that amivantamab plus lazertinib offers a sustained long-term survival benefit over osimertinib plus chemotherapy, attributed to differences in mechanism of action, quality of response, immunomodulatory effects, and resistance mechanisms rather than to a quantified statistical margin. The underlying ITC estimates for OS, PFS and TTD were redacted, so no numeric comparative result is available.

**NICE bewertete die
Herstellerevidenz kritisch:
keine belastbare Evidenz
für einen
Wirksamkeitsunterschied**

NICE rejected the HTD's initial osimertinib-anchored adjustment, noting that it did not represent a true population adjustment and relied on assumptions that were considered implausible. Specifically, the adjustment operated in opposite directions for PFS and OS, while the osimertinib Kaplan-Meier curves

crossed for PFS, OS and TTD, suggesting that the proportional hazards assumption between arms was unlikely to hold. Given the similar baseline characteristics and small differences in within-trial HRs (individual-trial HRs vs. osimertinib: MARIPOSA PFS 0.70 [95% CI: 0.58-0.85], OS 0.75 [0.61-0.92]; FLAURA2 PFS 0.62 [0.49-0.79], OS 0.75 [0.57-0.97]), NICE instead preferred a naïve comparison of the amivantamab-plus-lazertinib arm of MARIPOSA against the osimertinib-plus-chemotherapy arm of FLAURA2, while acknowledging that this approach did not account for residual population differences.

The HTD subsequently performed the anchored MAIC; however, because the trial populations were already highly similar (841 patients retained; effective sample size 693), the adjustment had little impact on the estimated treatment effects. Overall, NICE concluded that none of the ITC approaches adequately addressed the uncertainty regarding the comparative efficacy of amivantamab plus lazertinib versus osimertinib plus chemotherapy.

Safety results

For safety outcomes, the HTD performed a Bayesian NMA supported by an anchored MAIC. This analysis indicated a more favourable profile for amivantamab plus lazertinib than for osimertinib plus chemotherapy, with lower risks of grade ≥ 3 AEs and SAEs. However, these comparative results were presented only as forest plots, with no numeric odds ratios or confidence intervals.

**Sicherheitsvorteil einer
Therapie nicht begründet
Unterschiedliche
Toxizitätsprofile**

NICE did not accept this conclusion. Instead, it compared the trial arms directly and found that both grade ≥ 3 AEs and SAEs occurred more frequently in the amivantamab-plus-lazertinib arm of MARIPOSA than in the osimertinib-plus-chemotherapy arm of FLAURA2. Rather than concluding that one regimen was safer overall, NICE considered the two regimens to have distinct toxicity profiles. Amivantamab plus lazertinib was associated with higher rates of grade ≥ 3 rash, paronychia, infusion-related reactions and venous thromboembolism, whereas osimertinib plus chemotherapy was associated with higher rates of grade ≥ 3 anaemia, neutropenia and thrombocytopenia.

NICE also noted that the osimertinib monotherapy arms differed markedly between trials in grade ≥ 3 AE, SAE and discontinuation rates, suggesting the MARIPOSA population may have been more likely to have such events recorded, highlighting the uncertainty of cross-trial AE comparisons and reinforcing that any indirect comparison should be interpreted with caution.

Limitations

The report noted several limitations of the ITC, including the violation of proportional hazards, reliance on an unanchored comparison whose adjustment could not be validated, and cross-trial differences in follow-up intensity and data-cut timing that may have affected the AE comparisons.

**wesentliche Limitationen
begrenzen die Validität des
indirekten Vergleichs**

4.6.3 ITC in CDA-AMC HTA report

CDA-AMC reviewed an ITC of amivantamab plus lazertinib versus osimertinib plus chemotherapy submitted by the HTD of amivantamab.

**Bewertung des vom
Hersteller eingereichten
ITC durch CDA-AMC**

Methods

The HTD submitted five network meta-analyses (NMAs), informed by a systematic literature review (conducted in 2020, updated in 2022), to estimate the comparative efficacy and safety of amivantamab plus lazertinib versus relevant comparators. Separate fixed-effect Bayesian NMAs were conducted for each outcome (OS, PFS, ORR, all AEs, and SAEs). The evidence network comprised the MARIPOSA, FLAURA, and FLAURA2 trials. Based on clinical expert input, CDA-AMC identified osimertinib monotherapy and osimertinib plus chemotherapy to be the relevant Canadian comparators. Treatment effect modifiers identified by the HTD were ECOG performance status, cancer histology, presence of brain metastases, race or ethnicity, and common EGFR mutation type.

**indirekter Vergleich mittels
Netzwerk-Metaanalyse**

Efficacy and safety results

The specific NMA point estimates and 95% credible intervals for the comparison of amivantamab plus lazertinib with osimertinib plus chemotherapy were redacted from the public report. Based on the submitted evidence, CDA-AMC concluded that there was insufficient evidence to demonstrate a difference between the two regimens for OS, PFS, all AEs, and SAEs, although amivantamab plus lazertinib appeared to be favoured for ORR. However, because the comparative estimates and corresponding credible intervals were redacted, the magnitude of these effects could not be reported. Consequently, in its economic reanalysis, CDA-AMC assumed equivalent efficacy between amivantamab plus lazertinib and osimertinib plus chemotherapy. CDA-AMC also noted substantial uncertainty surrounding the NMA results, as reflected by the wide 95% credible intervals, which were likely driven by between-study clinical and methodological heterogeneity.

**CDA-AMC bestätigte
keinen Unterschied
zwischen den Therapien;
Gleichwertigkeit für die
ökonomische Bewertung
angenommen**

Limitations

The critical appraisal noted several sources of uncertainty, including between-study clinical and methodological heterogeneity, the use of fixed-effect models, and insufficiently justified study exclusion criteria. The systematic literature review was conducted only up to 2022; therefore, more recent publications or updated OS data may not have been captured, and 14 studies were excluded due to lacking an intervention of interest. The three trials informing the network differed in design (open-label, mixed, and double-blind), introducing a potential source of bias, and the network structure precluded evaluation of its consistency. Treatment effect modifiers were generally balanced across studies except for the prevalence of brain metastases, while smoking status and cancer stage were not reported in FLAURA2. Differences in follow-up duration and disease-assessment frequency were noted, though their potential impact on the comparative estimates was uncertain. Overall, CDA-AMC considered these limitations to increase uncertainty in the NMA results without changing its overall conclusions.

**methodische
Unsicherheiten schränken
die Aussagekraft der
Netzwerk-Metaanalyse ein**

5 Results: Clinical effectiveness and safety of intravenous versus subcutaneous amivantamab plus lazertinib

5.1 Included studies

For the comparison of clinical effectiveness and safety of intravenous versus subcutaneous amivantamab plus lazertinib, one clinical study was identified.

Evidenzbasis:
1 Phase-3-RCT

Characteristics of the study

PALOMA-3 (NCT05388669) was a phase 3, international, open-label, randomised controlled trial comparing subcutaneous amivantamab plus lazertinib versus intravenous amivantamab plus lazertinib, randomised in a 1:1 ratio. A single data cut-off was reported as of January 3, 2024. The study is detailed in two publications reporting efficacy and safety results [35] and patient-reported outcomes with resource utilisation [36].

**direkter Vergleich
der Applikationsformen:
subkutan vs. intravenöses
Amivantamab**

Subcutaneous amivantamab (coformulated with hyaluronidase) was administered at 1,600 mg (2,240 mg for patients ≥ 80 kg) by manual injection weekly for the first four weeks, then every two weeks, combined with lazertinib 240 mg orally once daily. The comparator arm received intravenous amivantamab at 1,050 mg (1,400 mg for patients ≥ 80 kg) weekly for the first four weeks, with the first infusion split over two days, then every two weeks, plus lazertinib 240 mg orally once daily. The trial was conducted across 187 sites in 20 countries. Eligible patients were aged ≥ 18 years with confirmed advanced or metastatic NSCLC harbouring an EGFR exon 19 deletion or exon 21 L858R mutation, disease progression on or after osimertinib (or another approved third-generation EGFR-TKI) and platinum-based chemotherapy (irrespective of sequence). A total of 418 patients were randomised. The PALOMA-3 trial was primarily designed as a pharmacokinetic non-inferiority study comparing subcutaneous and intravenous amivantamab. The co-primary endpoints were C_{trough} (trough serum concentration immediately before the next scheduled dose) and AUC, which are pharmacokinetic measures of drug exposure rather than patient-relevant outcomes. Although ORR and PFS were assessed as key secondary endpoints and OS as a prespecified exploratory endpoint, the study was not powered to demonstrate differences in these clinical outcomes. Therefore, these results should be interpreted with caution [35]. See details of the study in Table 5-1.

**Pharmakokinetik als
primärer Endpunkt;
Wirksamkeit sekundär**

Table 5-1: Characteristics of the PALOMA-3 study investigating intravenous and subcutaneous formulation of amivantamab in NSCLC

Study (Author, year)	PALOMA-3 (NCT05388669) [35, 36] – Alexander et al. (2025), Leighl et al. (2024)
Study design	Phase 3, international, open-label, randomised controlled trial; subcutaneous amivantamab + lazertinib vs. intravenous amivantamab + lazertinib, randomised in a 1:1 ratio
Data cut-off date	January 3, 2024
Completion status	Estimated: 06/2027
Intervention	Subcutaneous amivantamab + lazertinib (Study arm 1) ■ Subcutaneous amivantamab (coformulated with hyaluronidase), 1600 mg (2,240 mg for ≥ 80 kg weight) by manual injection weekly for first 4 weeks, then every 2 weeks. ■ Lazertinib 240 mg orally once daily.

Study (Author, year)	PALOMA-3 (NCT05388669) [35, 36] – Alexander et al. (2025), Leighl et al. (2024)
Comparator	Intravenous amivantamab + lazertinib (Study arm 2) ■ Amivantamab IV 1,050 mg (1400 mg for ≥80 kg weight) weekly for first 4 weeks (first infusion split over 2 days: 350 mg day 1, remainder day 2), then every 2 weeks. ■ Lazertinib 240 mg orally once daily.
Country	International (187 sites across 20 countries) ■ North America: USA 17, Canada 2 ■ South America: Brazil 16, Argentina 6 ■ Europe: Spain 17, Turkey 11, Italy 9, Germany 6, Poland 5, France 4, Portugal 4, United Kingdom 4 ■ Asia: Israel 5, China 32, Japan 18, South Korea 9, Taiwan 8, Malaysia 6, Thailand 3 ■ Oceania: Australia 6
Funding/Conflict of interest (CoI)	Funded by Janssen Research & Development, LLC. Multiple authors disclosed CoI with various pharmaceutical companies.
Inclusion criteria	Patients (≥18 years) with confirmed advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutation; disease progression on or after osimertinib (or another approved third-generation EGFR-TKI) and platinum-based chemotherapy (irrespective of sequence); at least 1 measurable lesion; ECOG PS 0-1; locally treated brain metastases required to be clinically stable and asymptomatic.
Number of patients	Subcutaneous amivantamab + lazertinib (N=206); Intravenous amivantamab + lazertinib (N=212); Total randomised (N=418)
Primary endpoint	Co-primary pharmacokinetic endpoint: Ctrough and AUC; either predose on cycle-2-day-1 or at steady state (cycle-4-day-1)
Secondary endpoints	Objective response rate and PFS
Exploratory endpoints	OS

Abbreviations: AUC ... area under the curve, CoI ... conflict of interest, Ctrough ... trough concentration, ECOG ... Eastern Cooperative Oncology Group, EGFR ... epidermal growth factor receptor, IV ... intravenous, L858R ... leucine-to-arginine substitution at codon 858, N ... number of patients, NCT ... National Clinical Trial, NSCLC ... non-small cell lung cancer, OS ... overall survival, PFS ... progression-free survival, PS ... performance status, TKI ... tyrosine kinase inhibitor.

Characteristics of the patient population

PALOMA-3 enrolled 418 patients, randomised to subcutaneous amivantamab plus lazertinib (n=206) or intravenous amivantamab plus lazertinib (n=212). In contrast to MARIPOSA, FLAURA2, and OPAL, which enrolled treatment-naïve patients, PALOMA-3 recruited a previously treated population. All patients had progressed on or after osimertinib (or another third-generation EGFR-TKI) and platinum-based chemotherapy. The last therapy before randomisation was osimertinib in 44-45% of patients and chemotherapy in 55-56%, with a median time from initial diagnosis to randomisation of approximately 33-35 months, reflecting the later-line setting. The two arms were well balanced at baseline. The median age was 61-62 years, with the majority of patients aged under 65 years (57-65%) and few aged 75 or older (9-10%). Most patients were female (67% in both arms) and Asian (61% in both arms), with White patients comprising 36-38%. The majority of patients were never-smokers (68% in both arms) and had an ECOG performance status of 1 (71-72%). EGFR mutations were distributed between exon 19 deletion (65-66%) and L858R (34-35%). Nearly all patients had adenocarcinomas (98-99%). Brain metastases at baseline were present in 34% of patients in both arms. Median follow-up was 7 months in both arms [35]. For details, see Table 5-2.

Studienpopulation:
Vorbehandelte
PatientInnen

Vergleichbare
Ausgangscharakteristika:
Alter,
Geschlecht,
Ethnizität,
EGFR-Mutation,
Hirnmetastasen

Table 5-2: Patients' characteristics of the included study investigating intravenous and subcutaneous formulation of amivantamab in NSCLC

Study (Author, year)	PALOMA-3 (NCT05388669) Leighl et al. (2024) [35]	
	Subcutaneous amivantamab (N=206)	Intravenous amivantamab (N=212)
Age, median (range) – yr	61 (35-82)	62 (29-81)
Age, distribution – n (%)		
<65 yr	133 (65)	120 (57)
65 to <75 yr	55 (27)	70 (33)
≥75 yr	18 (9)	22 (10)
Female sex – n (%)	138 (67)	141 (67)
Race or ethnic group – n (%)		
Asian	126 (61)	129 (61)
White	78 (38)	77 (36)
Black	1 (0.5)	3 (1)
Bodyweight, median (range) – kg	61.8 (35-130)	60.1 (33-150)
ECOG/WHO performance status score – n (%)		
0	58 (28)	61 (29)
1	148 (72)	151 (71)
2	0	0
History of smoking – n (%)		
No	141 (68)	145 (68)
Yes	65 (32)	67 (32)
History of brain metastases – n (%)	70 (34)	72 (34)
CNS metastasis		
Yes	NR	NR
No	NR	NR
Stage		
Locally advanced	NR	NR
Metastatic	NR	NR
IVa	NR	NR
IVb	NR	NR
Extrathoracic metastases – n (%)	NR	NR
Liver metastases – n (%)	NR	NR
Bone and locomotor-system metastases – n (%)	NR	NR
EGFR mutation – n (%)		
Ex19del	135 (66)	138 (65)
L858R	71 (34)	74 (35)
Both	0	0
Histologic characteristics – n (%)		
Adenocarcinoma	204 (99)	207 (98)
Adenosquamous carcinoma	0	0
Squamous-cell carcinoma	1 (<1)	3 (1)
Large-cell carcinoma	1 (<1)	1 (<1)
Other	0	1 (<1)
Median time from initial diagnosis to randomisation (range) – mo	34.5 (2.8-91.3)	33.7 (6.1-156.9)
Total number of subjects with any prior therapies for lung cancer – n (%)	NR	NR

Study (Author, year)	PALOMA-3 (NCT05388669) Leighl et al. (2024) [35]	
	Subcutaneous amivantamab (N=206)	Intravenous amivantamab (N=212)
Prior systemic therapy	NR	NR
Prior radiotherapy	NR	NR
Prior cancer-related surgery	NR	NR
Last therapy before random assignment – n (%)		
Osimertinib	91 (44)	96 (45)
Chemotherapy	115 (56)	116 (55)
Follow-up, median – months	7.0	7.0
Duration of treatment, median (range) – mo	4.7 (0.1-13.2)	4.1 (0.0-13.2)

Abbreviations: CNS ... central nervous system, ECOG ... Eastern Cooperative Oncology Group, EGFR ... epidermal growth factor receptor, Ex19del ... exon 19 deletion, L858R ... leucine-to-arginine substitution at codon 858, mo ... months, N ... number of patients, NR ... not reported, NSCLC ... non-small cell lung cancer, WHO ... World Health Organization, yr ... years.

5.2 Results

5.2.1 Overall survival

Subcutaneous amivantamab plus lazertinib was associated with a longer OS than intravenous amivantamab plus lazertinib (HR 0.62 [95% CI: 0.42-0.92]). However, OS was a prespecified exploratory endpoint, and the reported p-value (nominal p=0.021) was not derived from a prespecified confirmatory hypothesis testing. Therefore, the result should be considered exploratory and interpreted with caution [35]. See Table 5-3.

nominaler OS-Vorteil der subkutanen Formulierung

5.2.2 Progression-free survival

Subcutaneous amivantamab plus lazertinib was characterised by a numerically longer median PFS compared to intravenous amivantamab plus lazertinib (6.1 months [95% CI: 4.3-8.1] versus 4.3 months [95% CI: 4.1-5.7]; HR 0.84 [95% CI: 0.64-1.10]; p=0.20) [35]. See Table 5-3.

kein signifikanter Unterschied im PFS

5.2.3 Duration of response

The median duration of response was longer with subcutaneous amivantamab plus lazertinib compared to intravenous amivantamab plus lazertinib (11.2 months [95% CI: 6.1-NE] versus 7.1 months [95% CI: 5.3-NE]), though no formal statistical comparison was reported for this endpoint [35]. See Table 5-3.

längere Ansprechdauer unter subkutanem Amivantamab; kein statistischer Vergleich berichtet

5.2.4 Objective response rate

The ORR was 30% (95% CI: 24-37) with subcutaneous amivantamab plus lazertinib and 33% (95% CI: 26-39) with intravenous amivantamab plus lazertinib, confirming non-inferiority of the subcutaneous formulation (relative risk 0.92 [95% CI: 0.70-1.23]; p=0.001) [35]. See Table 5-3.

Nichtunterlegenheit der subkutanen Formulierung hinsichtlich der ORR bestätigt

5.2.5 Disease control rate

The DCR was 75% (95% CI: 69-81) with subcutaneous amivantamab plus lazertinib and 71% (95% CI: 64-77) with intravenous amivantamab plus lazertinib. The DCR was not protocol-specified and was calculated as the sum of complete response, partial response, and stable disease. No formal statistical comparison between arms was performed [35]. See Table 5-3.

ähnliche
Krankheitskontrollraten,
jedoch kein formaler
Vergleich

5.2.6 Patient-reported outcomes

Cancer therapy satisfaction was a prespecified secondary endpoint of PALOMA-3 and was assessed using the modified Treatment Administration Satisfaction Questionnaire (mTASQ), completed at study day 1 and study day 57, measuring the impact of treatment administration across five domains (physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction) on a scale of 0-100. Completion rates were 94% and 92% at study day 1 and 88% and 79% at study day 57 in the subcutaneous and intravenous arms, respectively, with missing data primarily due to device failures, sites failing to administer the questionnaire, and participant illness. Patient-reported outcomes consistently favoured subcutaneous administration. At study day 1, 66% of patients receiving subcutaneous amivantamab reported feeling not at all restricted by their injection versus 29% in the intravenous arm ($p<0.001$), with comparable results at study day 57 (60% versus 42%; $p=0.004$). Feeling not at all bothered by administration time was reported by 69% versus 30% at study day 1 ($p<0.001$) and 71% versus 45% at study day 57 ($p<0.001$). Regarding impact on daily activities, 36% versus 7% of patients reported gaining time for other things at study day 1 ($p<0.001$), with similar results at study day 57 (37% versus 6%; $p<0.001$). All p-values are nominal and not adjusted for multiplicity. Overall, in the subcutaneous arm, 77% of patients preferred the subcutaneous injection over their historical experience with intravenous treatments [36]. See Table 5-3.

Patientenpräferenz für
subkutanes Amivantamab

The following outcomes were not reported in the PALOMA-3 study: time to symptomatic progression, time to subsequent therapy, PFS after first subsequent therapy, time to treatment discontinuation, intracranial objective response, duration of intracranial objective response, intracranial PFS, and health-related quality of life.

keine Daten zu mehreren
patientenrelevanten
Endpunkten

Table 5-3: Efficacy results of the PALOMA-3 study investigating intravenous versus subcutaneous formulation of amivantamab plus lazertinib in NSCLC

Study (Author, year) Outcomes	PALOMA-3 (NCT05388669) Alexander et al. (2025) [36], Leighl et al. (2024) [35]	
	Subcutaneous (N=206)	Intravenous (N=212)
Overall survival, median (95% CI) – mo	12.9 (12.9-NE)	NE (10.2-NE)
HR (95% CI) ¹	0.62 (0.42-0.92); $p=0.02$	
Progression-free survival, median (95% CI) – mo	6.1 (4.3-8.1)	4.3 (4.1-5.7)
HR (95% CI)	0.84 (0.64-1.10), $p=0.20$	
Duration of response, median (95% CI) – mo	11.2 (6.1-NE)	7.1 (5.3-NE)
Objective response rate (95% CI) – %	30 (24-37)	33 (26-39)
Relative risk for non-inferiority (95% CI)	0.92 (0.70 to 1.23), $p=0.001$	
Disease control rate (95% CI) – %	75 (69-81)	71 (64-77)

Study (Author, year) Outcomes	PALOMA-3 (NCT05388669) Alexander et al. (2025) [36], Leighl et al. (2024) [35]	
	Subcutaneous (N=206)	Intravenous (N=212)
Quality of life data – questionnaire		
Answer “Not at all restricted” for question “How restricted do you feel when receiving the injection/infusion?” at Study day 1 – %	66	29
Nominal p< 0.001		
Answer “Not at all restricted” for question “How restricted do you feel when receiving the injection/infusion?” at Study day 57 – %	60	42
Nominal p=0.004		
Answer “Not at all bothered” for question “How bothered do you feel by the time it takes for the injection/infusion?” at Study day 1 – %	69	30
Nominal p< 0.001		
Answer “Not at all bothered” for question “How bothered do you feel by the time it takes for the injection/infusion?” at Study day 57 – %	71	45
Nominal p< 0.001		
Answer “Gained a lot of time” or “Gained some time” for question “Does setting up the injection/infusion mean you lose or gain time for other things?” at Study day 1 – %	36	7
Nominal p< 0.001		
Answer “Gained a lot of time” or “Gained some time” for question “Does setting up the injection/infusion mean you lose or gain time for other things?” at Study day 57 – %	37	6
Nominal p< 0.001		

Abbreviations: CI ... confidence interval, HR ... hazard ratio, mo ... months, N ... number of patients, NE ... not estimable, NR ... not reported.

Note: 195% CIs were not adjusted for multiplicity and should not be used in place of hypothesis testing; P value is nominal, nominal p-value, not adjusted for multiplicity.

5.3 Results – safety

5.3.1 Adverse events

Adverse events of any grade occurred in 99% of patients in both the subcutaneous and intravenous amivantamab plus lazertinib groups. The rate of infusion-related reactions was markedly lower with subcutaneous administration (13% vs 66%), with grade ≥3 events occurring in only 0.5% versus 4% of patients. Venous thromboembolism was also less frequent in the subcutaneous arm (9% vs 14%), with lower rates of deep-vein thrombosis (2% vs 5%), despite approximately 80% of patients in both arms receiving prophylactic anticoagulation. See Table 5-4.

vergleichbare Gesamtrate an UE; weniger Infusionsreaktionen und Thromboembolien unter subkutanem Amivantamab

5.3.2 Serious adverse events

Serious adverse events were comparable between the subcutaneous and intravenous amivantamab plus lazertinib groups, 29% and 30%, respectively. See Table 5-4.

vergleichbare Rate schwerwiegender UE

5.3.3 Severe adverse events (grade ≥3)

Grade ≥3 severe adverse events occurred at a comparable rate in the subcutaneous and intravenous amivantamab plus lazertinib arms, affecting 52% and 56% of patients, respectively. The most common grade ≥3 events in both arms were acneiform dermatitis (9% subcutaneous vs 6% intravenous) and lymphopenia (<1% vs 8%). Paronychia (4% vs 1%), rash (4% vs 4%), hypoalbuminaemia (2% vs 3%), and increased alanine aminotransferase (3% vs 3%) also occurred at grade ≥3, at similar rates across the two formulations. See Table 5-4.

vergleichbare Rate
schwerer UE (≥ Grad 3)

5.3.4 Deaths

Adverse events resulting in death were reported in 3% of patients in the subcutaneous arm and 5% in the intravenous arm. See Table 5-4.

vergleichbare Rate
tödlicher UE

5.3.5 Treatment discontinuation

Overall treatment discontinuation rates were comparable between the two arms (55% subcutaneous versus 54% intravenous). Discontinuation due to disease progression was the most common reason in both arms (41% and 40%), followed by discontinuation due to adverse events (11% and 12%). See Table 5-4.

vergleichbare
Therapieabbrüche
insgesamt und aufgrund
von UE

5.3.6 Treatment interruption

Treatment interruption data were not reported in the study.

keine Daten zu
Therapieunterbrechungen

Table 5-4: Safety results of the PALOMA-3 study investigating intravenous versus subcutaneous formulation of amivantamab plus lazertinib in NSCLC

Study (Author, year)	PALOMA-3 (NCT05388669) Leighl et al. (2024) [35]	
	Subcutaneous (N=206)	Intravenous (N=210)
Any adverse event, n (%)	204 (99)	209 (99)
Severe adverse events grade ≥3, n (%)	107 (52)	118 (56)
Treatment-emergent adverse events grade ≥3, n (%)	NR	NR
Serious adverse events, n (%)	59 (29)	64 (30)
Any adverse event resulting in death, n (%)	7 (3)	10 (5)
Treatment-related deaths, n (%)	NR	NR
Discontinued treatment, n (%)	114 (55)	114 (54)
Disease progression	85 (41)	83 (40)
Adverse event	23 (11)	25 (12)
Withdrawal by patient	4 (2)	5 (2)
Physician's decision	2 (1)	1 (0.5)
Non-compliance	0	0
CSP criteria	0	0

Study (Author, year)	PALOMA-3 (NCT05388669) Leighl et al. (2024) [35]	
	Subcutaneous (N=206)	Intravenous (N=210)
Lack of response	0	0
Lost to follow-up	0	0
Severe non-compliance to protocol	0	0
Other	0	0

Abbreviations: CSP ... clinical study protocol, N ... number of patients, NR ... not reported, n ... number of events.

6 Risk of bias

In the MARIPOSA study, the risk of bias (RoB) was considered low for the OS and PFS outcomes. For the safety outcomes, it was high, due to the open-label design, which introduced a potentially biased identification of subjective adverse events, as unblinded investigators may have been prone to expect more toxicities in the amivantamab-lazertinib arm [17, 25].

MARIPOSA:
niedriges Verzerrungsrisiko für OS/PFS, hohes für Sicherheitsendpunkte

In the FLAURA2 study, the RoB was high across all outcomes. For OS and PFS, the main concern was deviations from intended interventions, as treatment beyond progression was permitted at investigator discretion. The difference in subsequent therapies might have influenced survival. Additionally, for PFS, high risk arose from an investigator assessment instead of blinded review. Safety outcomes were similarly judged high risk due to the open-label design and the potential for different identification of toxicities [22, 23].

FLAURA2:
hohes Verzerrungsrisiko für alle Endpunkte

In the PALOMA-3 study, for PFS, ORR, and SAEs, the RoB was rated as presenting some concerns, due to absence of formal blinded review. QoL was rated high risk driven by informative missing data, response bias from participants' awareness of their treatment assignment, and selective reporting concerns. IRR was also rated high risk, as the open-label setting likely led investigators to differentially attribute symptoms to IRR based on known arm-specific profiles [35].

PALOMA-3:
moderates Verzerrungsrisiko für PFS, ORR und SUE; hohes für QoL und Infusionsreaktionen

For detailed assessment of the risk of bias, see Appendix, Table A-1.

7 Economic aspects

7.1 Published cost-effectiveness analyses

7.1.1 Cost-effectiveness of amivantamab plus lazertinib assessed by NICE

For the purposes of the HTA by NICE [33], the health technology developer (HTD) submitted a cost-utility analysis to evaluate the cost-effectiveness of amivantamab plus lazertinib for the first-line treatment of adults with untreated EGFR mutation-positive (exon 19 deletions or exon 21 L858R substitution) locally advanced or metastatic non-small-cell lung cancer. The comparators were osimertinib monotherapy and osimertinib plus platinum-based chemotherapy. Because there was no head-to-head trial against osimertinib plus chemotherapy, clinical data for this comparison were derived from an ITC linking the MARIPOSA and FLAURA2 trials (see 4.6.2). The comparative efficacy of amivantamab plus lazertinib versus osimertinib plus chemotherapy was considered highly uncertain, and the committee concluded that none of the ITC approaches presented adequately resolved this uncertainty.

In the HTD's updated base case (reflecting the September 2025 FLAURA2 data), at confidential patient access scheme (PAS) prices for amivantamab and lazertinib, this regimen dominated both comparators (more effective and less costly). The ICERs at PAS prices were -£135,124.56 per QALY versus osimertinib monotherapy and -£987,103.32 per QALY versus osimertinib plus chemotherapy. This dominance depends on the confidential discount applied to the combination rather than on a lower list price, since at official list prices the same comparison yielded an ICER of £1,125,203.27 per QALY versus osimertinib plus chemotherapy, far above NICE's usual willingness-to-pay threshold. The comparison is also asymmetric, since osimertinib is included at its list price because its own confidential discount was unavailable to the HTD. Total undiscounted life years were 5.10 for amivantamab plus lazertinib and 4.75 for osimertinib plus chemotherapy (an incremental 0.35 life years). Total costs, total QALYs, and incremental QALYs were redacted in the HTA report. Probabilistic sensitivity analysis at a £30,000 per QALY threshold indicated that, at PAS prices, amivantamab plus lazertinib retained a high probability of being cost-effective against both comparators, driven by better health outcomes combined with lower costs.

Deterministic sensitivity analysis showed that, for the comparison against osimertinib plus chemotherapy, the shape of the OS extrapolation for amivantamab plus lazertinib was the most influential parameter, and all results produced negative ICERs reflecting dominance at PAS prices. While amivantamab plus lazertinib appeared cost-effective at PAS prices, the committee's position reflected residual uncertainty in the ITC against osimertinib plus chemotherapy, which it did not consider resolved by any of the methods presented, rather than treating the base-case results as settled.

NICE: Kosten-Nutzen-Bewertung auf Basis indirekter Vergleichsdaten mit verbleibender Unsicherheit

Kosteneffektivität nur bei vertraulichen Rabatten

Kosten-Nutzen-Bewertung durch Unsicherheit der indirekten Evidenz eingeschränkt

7.1.2 Cost-effectiveness of amivantamab plus lazertinib assessed by CDA-AMC

The HTD submitted a cost-utility analysis to evaluate the cost-effectiveness of amivantamab plus lazertinib for the first-line treatment of adults with locally advanced or metastatic NSCLC harbouring EGFR exon 19 deletions or exon 21 L858R substitution mutations to CDA-AMC [34]. The analysis used a partitioned survival model, adopted the perspective of the Canadian publicly funded health care payer, and applied a lifetime horizon of 15 years, with outcomes expressed in quality-adjusted life-years (QALYs) and life-years. Among the comparators was osimertinib plus platinum-based chemotherapy (carboplatin or cisplatin plus pemetrexed). Because there was no head-to-head trial against this comparator, clinical inputs for this comparison were drawn from a network meta-analysis (NMA), see 4.6.3. At the submitted price, treatment with amivantamab plus lazertinib was estimated to cost approximately \$12,135 per 28-day cycle, based on a unit price of \$1,676.00 for amivantamab (50 mg/mL) and \$103.60 and \$310.82 for the 80 mg and 240 mg lazertinib tablets, respectively. Because the comparative efficacy of amivantamab plus lazertinib versus osimertinib plus chemotherapy was considered highly uncertain, CDA-AMC assumed equivalent clinical efficacy between the two regimens in its base case.

Because the two regimens were assumed to be equally effective, the analysis produced no incremental QALY difference, and a conventional ICER (cost per QALY gained) could not be calculated for this comparison. The comparison therefore reduced to one cost alone: in the CDA-AMC base case, amivantamab plus lazertinib was more costly than osimertinib plus chemotherapy, with an incremental cost of \$81,302, while being no more effective. On this basis, CDA-AMC concluded that there was insufficient clinical evidence to justify a price premium for amivantamab plus lazertinib over osimertinib plus chemotherapy, and the committee recommended that the drug be reimbursed only if its cost does not exceed that of the least costly relevant comparator in this setting.

CDA-AMC:
Kosten-Nutzen-Bewertung
auf Grundlage indirekter
Evidenz

CDA-AMC ging von
einer gleichwertigen
Wirksamkeit aus;
kein Preisaufschlag
gerechtfertigt

7.2 Austrian budget impact analysis

7.2.1 Eligible population

Both amivantamab plus lazertinib and osimertinib with pemetrexed and chemotherapy are indicated for first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with EGFR exon 19 deletions or exon 21 L858R substitution mutations.

For the purposes of budget impact analysis (BIA), the eligible population was estimated by sequentially applying inclusion criteria to Austrian and international lung cancer epidemiology. Annual lung cancer incidence in Austria is approximately 5,533 patients [2]. According to the real-world data from a systematic review of 456 studies, 85% of lung cancer patients are diagnosed with NSCLC [14]. Within the NSCLC population, EGFR mutations occur in 11% of cases based on the Austrian LALUCA registry, with 60% representing common mutations. Finally, 46% of these patients present with stage IV disease [15]. Overall, this translates into an eligible population of approximately 140 patients per year in Austria.

Zielpopulation der
Budget-Impact-Analyse

Schätzung der
Zielpopulation:
ca. 140 Patienten/Jahr

7.2.2 Direct medical costs of amivantamab plus lazertinib and osimertinib plus chemotherapy

For the direct medical costs, the following were considered: drug, intravenous/subcutaneous administration at an oncological department, MRI and CT scans. The pre-treatment costs (antithrombotics) were omitted from the analysis due to low cost, as well as the cost for next-generation sequencing since it is tested routinely in clinical practice. The costs for all the drugs (amivantamab, lazertinib, osimertinib, chemotherapy) were extracted from the Warenverzeichnis Online, published by the Österreichischer Apotheker-Verlag on 5 May 2026 [28]. Details of all the costs are provided in Table 7-1 and Table 7-2.

Acquisition costs

According to the RYBREVANT® (amivantamab) SmPC [37], the amivantamab plus lazertinib regimen comprises amivantamab intravenous 1050 mg weekly (1,400 mg if body weight ≥80 kg) during the first four weeks with the first infusion split over two days (350 mg on day 1 and the remainder on day 2), and every two weeks from cycle 2 onwards, together with lazertinib 240 mg orally once daily. On this basis, one cycle requires three 350-mg vials. The subcutaneous formulation is administered as a fixed dose of 1,600 mg (2,240 mg if body weight ≥80 kg) once weekly during the first four weeks and every two weeks from cycle 2 onwards, without the split first dose applied to the intravenous route [35]. For the intravenous amivantamab, a cost of €1,406 per vial was used, resulting in a cost of €4,218 per cycle; the cost of one cycle of subcutaneous amivantamab likewise amounts to €4,218. The price of one package of lazertinib was €4,745 for a 28-day treatment, corresponding to €169.45 per tablet. Over one year of treatment, this amounts to 84 vials of amivantamab (€118,104.00) and 365 lazertinib tablets (€61,849.25), resulting in a combined annual acquisition cost of €179,953.25 per patient; the subcutaneous formulation yields the same combined acquisition cost.

According to the TAGRISSO® SmPC [38] and the FLAURA2 trial [22], the osimertinib plus chemotherapy regimen comprises osimertinib 80 mg orally once daily together with pemetrexed 500 mg/m² intravenously and cisplatin 75 mg/m² (or carboplatin AUC 5) intravenously on day 1 of 21-day cycles for four cycles, followed by osimertinib 80 mg once daily plus pemetrexed 500 mg/m² maintenance every three weeks. The cost of osimertinib for a 30-tablet package was €5,083.50, corresponding to €169.45 per tablet. The cost of one vial of pemetrexed was €325. For the chemotherapy treatment, cisplatin was chosen, with a cost of €41 for a 100 mg vial and €7 for a 10 mg vial. Over one year, this yields osimertinib at €61,849.25 (365 tablets), pemetrexed at €11,700.00 across the four induction cycles and €38,025.00 across the thirteen maintenance cycles, and cisplatin at €164.00 for the 100-mg vials plus €112.00 for the 10-mg top-up vials. The total annual acquisition cost therefore amounts to €111,850.25 per patient.

Administration costs

For the intravenous/subcutaneous treatment, an administration cost of €845.71 per administration was included for both amivantamab and pemetrexed with chemotherapy. Intravenous amivantamab is administered in the oncological day-care unit and amounts to 29 administrations per year, resulting in an annual administration cost of €24,525.59. The subcutaneous formulation amounts

Einbezogene
Kostenkomponenten
(direkte Kosten)

Jährliche
Arzneimittelkosten:

Amivantamab + Lazertinib:
180.000 €

Osimertinib +
Chemotherapie:
112.000 €

mehr Applikationen und
höhere
Verabreichungskosten für
Amivantamab + Lazertinib

to 28 administrations per year owing to its slightly different dosing regimen. Since this difference is negligible, the annual administration cost of subcutaneous amivantamab is considered equal to that of the intravenous formulation. For the osimertinib plus chemotherapy regimen, pemetrexed is administered in the hospital day-care clinic across the four induction cycles and thirteen maintenance cycles, corresponding to 17 administrations per year, giving an annual administration cost of €14,377.07. Oral osimertinib and lazertinib, administered in the outpatient setting, do not incur any administration cost.

Monitoring costs

In line with the MARIPOSA trial, brain MRI (average cost €253.48; range €106.26-414.20) and CT (average cost €142.37; range €61.41-238.00) were assumed to be performed every eight weeks, equivalent to seven times per year, for both treatment arms. This results in annual monitoring costs of €1,774.36 for MRI and €996.59 for CT, totalling €2,770.95 per patient per year.

**für beide Therapien
identische
Monitoringkosten
(2.771 €/Jahr)**

Total direct medical costs

Considering all cost items, the total annual direct medical costs of amivantamab (28 infusions) plus lazertinib amount to €207,249.80 per patient, for both the intravenous and subcutaneous formulations. For the osimertinib plus platinum (4 cycles) plus pemetrexed (17 cycles) regimen, the total annual direct medical costs amount to €128,998.27 per patient. These estimates assume one year of treatment, while the median treatment duration reported in the pivotal studies was longer (27.0 months for amivantamab plus lazertinib and 30.5 months for osimertinib plus chemotherapy) [23, 25].

**höhere jährliche
Gesamtkosten für
Amivantamab + Lazertinib**

These estimates reflect the Austrian healthcare system (payer) perspective, in which both the oral drugs (lazertinib and osimertinib) and the hospital-administered drugs are included in the total direct medical cost. However, the financial burden for hospitals differs because the oral drugs are prescribed in the outpatient setting and reimbursed by the statutory health insurance. From a hospital perspective, only the costs of hospital-administered drugs (amivantamab versus pemetrexed plus platinum) and their administration are relevant. Under this perspective, the annual direct medical costs amount to €145,400.55 per patient for amivantamab and €67,149.02 per patient for pemetrexed plus platinum.

**Krankenhauskosten
unterscheiden sich von der
Kostenträgerperspektive**

Table 7-1: Amivantamab (IV/SC) plus lazertinib – Annual Treatment Costs per patient

Item	Dosing/Duration (<80 kg)	Package cost (€)	Package volume	Unit cost (€)	Costing unit	Volume per cycle	Cost per cycle (€)	Total volume (per year)	Total cost (per year, €)	Source/Notes
Acquisition costs										
Amivantamab IV ¹	1050 mg	1,406.00	1	1,406.00	350 mg/vial	3 vials	4,218.00	84 vials	118,104.00	RYBRENT® SmPC [37], cost from APOTHEKER-VERLAG – RYBRENT IKONZ DFL350MG/7ML (IV), RYBRENT INJ DFL1600MG/10ML (SC)
Lazertinib ²	240 mg	4,744.60	28	169.45	240 mg/tablet	1 tablet	169.45	365 tablets	61,849.25	LAZCLUZE® SmPC [39], cost from APOTHEKER-VERLAG – LAZCLUZE FTBL 240MG
Subtotal – Acquisition costs									179,953.25	
Administration costs										
IV infusion administration (oncology day-care unit)	1 per day	-	-	845.71	per day	1	845.71	29 days ³	24,525.59	Cost from LKF
Monitoring costs										
MRI (brain)	Every 8 weeks	-	-	-	-	-	253.48	7/year	1774.36	MARIPOSA trial, cost from payers
CT	Every 8 weeks	-	-	-	-	-	142.37	7/year	996.59	MARIPOSA trial, cost from payers
TOTAL ANNUAL COSTS									€207,249.80	

Abbreviations: AUC ... area under the curve, CT ... computed tomography, IV ... intravenous, LKF ... leistungsorientierte Krankenhausfinanzierung (performance-oriented hospital financing), MRI ... magnetic resonance imaging, pt ... patient, SC ... subcutaneous.

Note:

¹ Subcutaneous amivantamab acquisition cost is identical to IV.

² Lazertinib is an oral drug administered in the outpatient setting; it is dispensed by public pharmacies and reimbursed through social insurance, and therefore incurs no hospital administration cost.

³ Due to the slightly different dosing regimen, subcutaneous amivantamab requires 28 administration visits per year versus 29 for IV amivantamab. This difference is considered negligible; hence, the total cost of SC amivantamab is considered equal to the IV formulation.

Table 7-2: Osimertinib plus platinum and pemetrexed – Annual Treatment Costs per patient

Item	Dosing/Duration (75 kg or 1.77 m)	Unit cost (€)	Costing unit	Volume per cycle (units)	Cost per cycle (€)	Total volume (cycles per pt/year)	Total cost (€)	Source/Notes
Acquisition costs								
Osimertinib ¹	80 mg	169.45	80 mg	1 tablet	61,849.25	365 tablets/year	61,849.25	FLAURA2 study: 80 mg per day, cost from APOTHEKER-VERLAG – TAGRISSO FTBL 80MG
Pemetrexed	885 mg	325.00	885 mg	9	2,925.00	4	11,700.00	FLAURA2 study: Pemetrexed 500 mg/m ² IV day 1 of 21-day cycles for 4 cycles, cost from APOTHEKER-VERLAG PEMETREXED ACC 100MG/4ML
Pemetrexed maintenance	885 mg	325.00	885 mg	9	2,925.00	13	38,025.00	FLAURA2 study: Pemetrexed 500 mg/m ² maintenance every 3 weeks, cost from APOTHEKER-VERLAG PEMETREXED ACC 100MG/4ML
Cisplatin 100 mg	132.75 mg	41.00	100 mg	1	41.00	4	164.00	FLAURA2 study: Cisplatin ² 75 mg/m ² (or carboplatin AUC 5) IV day 1 of 21-day cycles for 4 cycles, cost from APOTHEKER-VERLAG – CISPLATIN ACC 100MG/100ML, CISPLATIN ACC 10MG/10ML
Cisplatin 10 mg		7.00	10 mg	4	28.00	4	112.00	
Subtotal – Acquisition costs							111,850.25	
Administration costs								
IV infusion administration (oncology day-care unit)	-	845.71	per day	-	-	17 days	14,377.07	Cost from LKF
Subtotal – Administration costs							14,377.07	
Monitoring costs								
MRI	Every 8 weeks	-	-	-	253.48	7/year	1774.36	MARIPOSA trial, cost from payers
CT	Every 8 weeks	-	-	-	142.37	7/year	996.59	MARIPOSA trial, cost from payers
TOTAL ANNUAL COSTS (per year)							€128,998.27	

Abbreviations: AUC ... area under the curve, CT ... computed tomography, IV ... intravenous, MRI ... magnetic resonance imaging, pt ... patient.

Notes:

¹ Osimertinib is an oral drug administered in the outpatient setting; it is dispensed by public pharmacies and reimbursed through social insurance, and therefore incurs no hospital administration cost.

² For the purposes of BIA, the cost of cisplatin was chosen instead of carboplatin, as the costs are similar.

7.2.3 Incremental cost comparison

Both amivantamab plus lazertinib and osimertinib plus pemetrexed and chemotherapy are reimbursed and used in routine clinical practice in Austria. Therefore, rather than estimating the budget impact of introducing a new product, this analysis estimates the cost consequences of treating the eligible Austrian population with one regimen versus the other, from the healthcare payer perspective. Indirect costs were not included, consistent with the healthcare payer perspective, and because Austrian data on these costs are not available.

**beide Therapien
bereits erstattet;
Kostenvergleich aus Sicht
des österreichischen
Gesundheitskostenträgers**

Total annual treatment cost per patient

The total annual cost of treating one patient amounts to €207,250 for amivantamab plus lazertinib and €128,998 for osimertinib plus pemetrexed and chemotherapy. The difference of €78,252 per patient per year is driven by the higher acquisition cost of amivantamab plus lazertinib (€179,953 vs. €111,850) and, to a lesser extent, by its higher administration cost (€24,526 vs. €14,377); monitoring costs are identical across both regimens (€2,771).

**jährliche Mehrkosten:
78.252 € je behandelter
Person**

Population-level cost comparison

Applying the estimated eligible population of approximately 140 newly treated patients per year, the total annual cost amounts to €29,014,971 if all eligible patients were treated with amivantamab plus lazertinib, compared with €18,059,758 if all were treated with osimertinib plus pemetrexed and chemotherapy. Since both regimens are already in use, the actual expenditure depends on the real-world division of patients across the two options, which is currently uncertain.

**bei 140 Patient:innen/Jahr:
Mehrkosten von
11,0 Mio. €/Jahr
gegenüber Osimertinib +
Chemotherapie**

Assuming a stable eligible population of 140 newly treated patients per year (420 patients over three years) and one full year of treatment per patient, the total direct medical cost over the three-year period amounts to €87,044,912 for amivantamab plus lazertinib and €54,179,273 for osimertinib plus pemetrexed and chemotherapy, resulting in an incremental cost of €10,955,213 per year and €32,865,639 over three years, in favour of osimertinib plus chemotherapy. The detailed results are presented in Table 7-3 and Figure 7-1.

**auch aus Krankenhaussicht
deutlich höhere
Behandlungskosten
für Amivantamab**

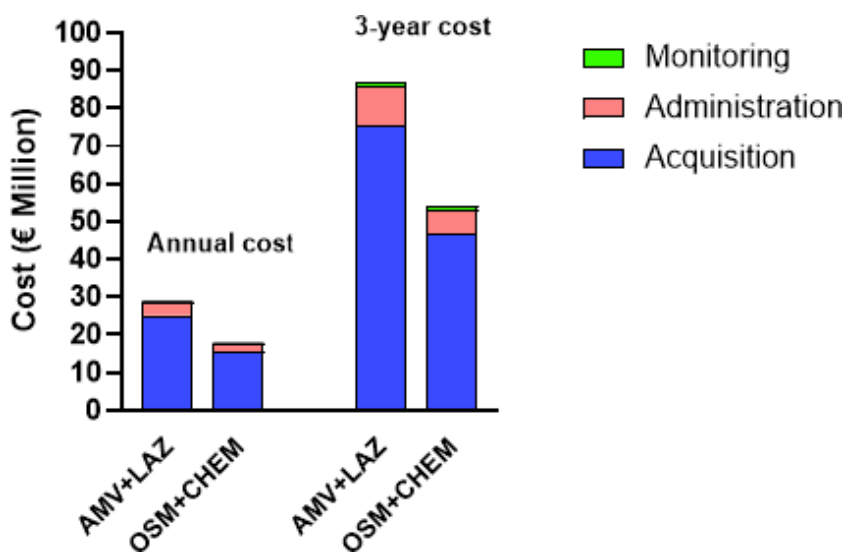
Considering only the hospital costs and assuming 140 newly treated patients per year, the hospital outpatient treatment with amivantamab would cost €20,356,077 for one year and €61,068,231 for three years. In case of treatment with pemetrexed plus platinum, this would amount to €9,400,863 and €28,202,588 per one and three years, respectively.

Table 7-3: Incremental cost comparison – amivantamab plus lazertinib vs. osimertinib plus chemotherapy

Cost category	Year 1	Year 2	Year 3	Total per 3 years
Amivantamab + lazertinib				
New pts treated per year	140	140	140	420
Acquisition costs	€25,193,455	€25,193,455	€25,193,455	€75,580,365
Administration costs	€3,433,583	€3,433,583	€3,433,583	€10,300,748
Monitoring costs	€387,933	€387,933	€387,933	€1,163,799
Total cost	€29,014,971	€29,014,971	€29,014,971	€87,044,912

Cost category	Year 1	Year 2	Year 3	Total per 3 years
Osimertinib + chemotherapy				
New pts treated per year	140	140	140	420
Acquisition costs	€15,659,035	€15,659,035	€15,659,035	€46,977,105
Administration costs	€2,012,790	€2,012,790	€2,012,790	€6,038,369
Monitoring costs	€387,933	€387,933	€387,933	€1,163,799
Total cost	€18,059,758	€18,059,758	€18,059,758	€54,179,273
Incremental cost	+€10,955,213	+€10,955,213	+€10,955,213	+€32,865,639

Abbreviations: pts ... patients.



Abbreviations: AMV+LAZ ... amivantamab + lazertinib,
OSM+CHEM ... osimertinib + pemetrexed and chemotherapy.

Figure 7-1: Annual and 3-year direct medical costs of amivantamab plus lazertinib versus osimertinib plus pemetrexed and chemotherapy for the eligible Austrian population, by cost component.

7.2.4 Limitations

Several limitations should be acknowledged for this analysis. The eligible patient population was derived by combining Austrian and international lung cancer epidemiology data and the resulting estimate may not fully reflect the true number of patients in Austria. Because both regimens are already established in clinical practice, the analysis assumes a hypothetical scenario in which the entire eligible population receives one regimen or the other. In reality, patients are distributed across both treatment options, and the actual budget impact will depend on future prescribing patterns. Drug acquisition and administration costs were calculated assuming one full year of treatment per patient, whereas in routine practice treatment is frequently discontinued for various reasons, which may lead to an overestimation of the true costs. The prices used for the hospital-administered drugs are based on the ex-factory price listed in the Warenverzeichnis, which represents only an approximate

**Populationsschätzung
und Kostenannahmen
begrenzen die
Aussagekraft**

value, as the actual price behind the corresponding LKF code is not publicly available. Prophylactic antithrombotics and next-generation sequencing (NGS) were excluded because they were expected to have a negligible impact on overall costs. In the case of NGS, it also forms part of the routine diagnostic work-up for NSCLC and is therefore incurred equally by both regimens, leaving the incremental comparison unaffected. Additionally, costs associated with adverse-event management were not modelled due to insufficient data. Finally, indirect costs were not considered since standardised Austrian data are missing.

8 Organisational aspects

This chapter addresses the organisational requirements of first-line amivantamab plus lazertinib relative to the osimertinib-based comparators in Austria. It covers the molecular diagnostic infrastructure needed to identify eligible patients, the delivery and monitoring burden of each regimen, the impact of the subcutaneous amivantamab formulation, and the organisation of care.

**Organisation
von Diagnostik,
Therapiedurchführung
und Nachsorge**

8.1 EGFR testing infrastructure in Austria

Eligibility for first-line targeted treatment of EGFR-mutated advanced NSCLC, including osimertinib plus chemotherapy or amivantamab plus lazertinib, depends on prior detection of an EGFR common mutation by next-generation sequencing (NGS) [15, 17, 22].

**molekularer
EGFR-Nachweis als
Voraussetzung für
zielgerichtete Therapie**

In Austria, the diagnosis of lung cancer is not centralised in dedicated cancer centres but is limited to large hospitals with departments of thoracic surgery, pulmonology, and oncology. The diagnosis of NSCLC automatically triggers molecular testing. The Austrian working group on lung pathology and oncology recommends that this testing is initiated at diagnosis in all cases with an adenocarcinoma component, independent of stage. NGS panels are preferred because they examine EGFR exons 18-21 together with other actionable drivers (ALK, ROS1, BRAF, NTRK, MET, RET, HER2, KRAS) from limited tissue. This testing should be available in all diagnostic institutes, with a target turnaround time of 7-10 working days and in-house testing preferred over commercial laboratories for quality control and tumour-board communication [9]. This approach is not the European norm, as automatic testing at diagnosis has been reported in only 14 of 21 European countries, and only about a third of European laboratories use single-gene EGFR testing followed by NGS [16].

**routinemäßige
molekulare Testung
bei NSCLC-Diagnose
in Österreich**

8.2 Treatment delivery and monitoring

Both regimens entail pre-treatment and monitoring requirements beyond those of oral osimertinib alone. For osimertinib plus chemotherapy, cisplatin and carboplatin require baseline renal function assessment, while the myelosuppressive toxicity accounting for most grade ≥ 3 events necessitates regular blood-count monitoring and supportive interventions. This monitoring burden is not confined to the four induction cycles, since pemetrexed maintenance continues every three weeks until progression [22, 23]. Initiation of amivantamab plus lazertinib requires assessment of thrombotic and bleeding risk factors before the first infusion together with corticosteroid, antihistamine and antipyretic premedication to mitigate infusion-related reactions [25, 40].

**Amivantamab + Lazertinib
und Osimertinib +
Chemotherapie:
erweiterte Vorbereitung
vor Therapiebeginn**

The organisational burden of amivantamab plus lazertinib is driven mainly by the intravenous amivantamab component. Amivantamab is given on a split-dose schedule in cycle 1 (350 mg on day 1 and the remainder on day 2, then weekly for the first cycle), followed by biweekly infusions from cycle 2 onward,

**intravenöse
Amivantamab-Gabe
erfordert häufige
Infusionen und Tagesklinik**

each taking up to five hours and requiring dedicated oncology infusion capacity. Lazertinib is taken orally once daily in an outpatient setting and adds monitoring for EGFR-class effects [17].

Patients on this regimen require structured monitoring across several toxicity domains. The most organisationally demanding is venous thromboembolism (VTE) management. In the absence of dedicated trial-based protocols, Austrian haematology and thoracic-oncology clinicians have issued a provisional clinical opinion adapting existing ESMO guidance on cancer-associated thrombosis to amivantamab-based therapy. This adds several scheduled steps to routine care. Before treatment, an individualised VTE- and bleeding-risk assessment is performed using a validated model such as the Khorana score or the Austrian-developed Vienna CATS model, though the Khorana score performs poorly in lung cancer. Where bleeding risk is not elevated, primary pharmacological thromboprophylaxis with a direct oral factor Xa inhibitor (apixaban or rivaroxaban) or low-molecular-weight heparin (LMWH) is given for the first six months. If VTE occurs during treatment, therapeutic-dose anticoagulation is used for at least six months. Because lung cancer patients frequently have competing bleeding risk factors such as concomitant antiplatelet therapy, haemoptysis, and brain metastases, the choice between a direct oral anti-Xa inhibitor and LMWH must be made individually with a follow-up [40]. Clinical experts confirmed that this supportive burden extends beyond anticoagulation, with prophylactic antibiotics and topical dermatologic prophylaxis administered alongside the regimen as part of routine care [41].

**erhöhter
Betreuungs-
aufwand
durch VTE-
Prophylaxe
und Supportiv-
therapie**

Osimertinib as an oral component is easily administered in an outpatient setting; however, platinum-based chemotherapy adds the complexity of intravenous cycles. Osimertinib is given orally once daily alongside intravenous pemetrexed and either cisplatin or carboplatin on day 1 of 21-day cycles for four cycles, followed by osimertinib plus pemetrexed maintenance every three weeks [22]. This requires pre-hydration, antiemetic prophylaxis, haematologic monitoring, and frequent clinic visits [22, 42].

**Chemotherapie
erfordert
regelmäßige
Infusionen
und engmaschiges
Monitoring**

8.3 Subcutaneous versus intravenous amivantamab

The phase 3 PALOMA-3 trial has shown that subcutaneous administration was associated with lower resource utilisation on every measured parameter. Participant time in the treatment chair was shorter with subcutaneous than intravenous administration at both study day 1 (median 0.4 hours [range 0-12.0] versus 6.5 hours [0-24.0]) and day 57 (0.6 hours [0-6.6] versus 3.4 hours [0.5-9.0]), noting that the 4-hour observation period was mandatory on day 1 but optional on day 57 for the subcutaneous arm. Participant time in the treatment room was likewise lower at day 1 (4.7 hours [0.1-23.7] versus 7.0 hours [1.2-24.0]) and day 57 (1.5 hours [0.1-6.6] versus 3.9 hours [0.5-8.5]). Active healthcare provider time was also reduced at day 1 (5.6 hours [0.4-11.4] versus 7.6 hours [1.6-19.2]) and day 57 (2.3 hours [0.2-8.6] versus 4.4 hours [2.5-9.5]) [36]. The study has also reported lower VTE risk with SC formulation compared to IV administration [35]. See Table 8-1.

**weniger
Behandlungs-
zeit und
Personalaufwand
unter
subkutanem
Amivantamab**

These findings are consistent with Austrian practice, where one high-volume centre reported administering amivantamab subcutaneously only due to infusion-related reactions associated with the IV formulation. Additionally, the SC injection takes approximately 5-10 minutes, compared with the longer intravenous administration of carboplatin and pemetrexed, although amivantamab is given more frequently, particularly during the first cycles, than the three-weekly chemotherapy schedule [41].

Importantly, the shorter injection time does not necessarily translate into a lower overall organisational burden since amivantamab plus lazertinib still requires ongoing prophylactic treatment and regular hospital attendance [41]. This is supported by a conference abstract that reported patient time modelled over the first year of treatment in the EU and estimated 66 hours for osimertinib plus platinum-pemetrexed, 339 hours for intravenous amivantamab plus lazertinib, and 295 hours for subcutaneous amivantamab plus lazertinib. Subcutaneous administration reduced drug-administration time from 67 to 20 hours per year, but the prophylactic burden was unchanged at 219 hours in both amivantamab arms compared with 7 hours for osimertinib plus chemotherapy. This was the single largest driver of time for the amivantamab regimens. The analysis was funded by AstraZeneca and is model-based rather than observed [43].

Ö: klinische Erfahrungen bestätigen organisatorische Vorteile der subkutanen Anwendung

Prophylaxe und Nachsorge relativieren den Zeitgewinn der subkutanen Anwendung

Table 8-1: Medical resource utilisation results of the PALOMA-3 study investigating intravenous versus subcutaneous formulation of amivantamab plus lazertinib in NSCLC

Study (Author, year) Outcomes	PALOMA-3 (NCT05388669) Alexander et al. (2025) [36]	
	Subcutaneous (N=206)	Intravenous (N=212)
Participant time in the treatment chair at Study day 1, median (range) – hours	0.4 (0-12.0)	6.5 (0-24.0)
Participant time in the treatment chair at Study day 57, median (range) – hours	0.6 (0-6.6)	3.4 (0.5-9.0)
Healthcare provider time at Study day 1, median (range) – hours	5.6 (0.4-11.4)	7.6 (1.6-19.2)
Healthcare provider time at Study day 57, median (range) – hours	2.3 (0.2-8.6) ¹	4.4 (2.5-9.5)
Participant time in treatment room at Study day 1, median (range) – hours	4.7 (0.1-23.7)	7.0 (1.2-24.0)
Participant time in treatment room at Study day 57, median (range) – hours	1.5 (0.1-6.6) ¹	3.9 (0.5-8.5)

Abbreviations: N ... number of participants, NCT ... National Clinical Trial.
Note: ¹The 4-hour observation time for subcutaneous administration was optional.

8.4 Organisation of care across Austria

Treatment of EGFR-mutated advanced NSCLC in Austria is currently concentrated at a small number of high-volume institutions [15]. The complexity of both amivantamab plus lazertinib and osimertinib plus chemotherapy administration requires delivery in specialised centres with appropriate oncological and haematological expertise. Notably, amivantamab plus lazertinib carries a particular learning curve in managing its toxicity [41].

There is no Austria-wide treatment recommendation for this indication, and payers, resources, and even drug availability differ between regions, so delivery capacity varies from hospital to hospital. The contrast between a high-volume Vienna centre, which treats a large number of EGFR-mutated patients,

Behandlung in spezialisierten Zentren erforderlich

Regionale Unterschiede in Versorgung und Behandlungskapazität

and a smaller regional centre, whose experience with the regimen is limited to a few patients, illustrates this variation. Additionally, as approximately 90% of patients with lung cancer in Austria are managed by pulmonologists rather than oncologists, close collaboration between both specialities is considered essential to ensure appropriate treatment delivery and management of treatment-related adverse events [41].

Based on expert opinion, uptake of amivantamab plus lazertinib in routine clinical practice remains limited in Austria, while osimertinib plus chemotherapy is estimated to represent the standard first-line treatment in approximately 90-95% of eligible patients. However, regional differences in treatment patterns may exist [41].

**Osimertinib +
Chemotherapie dominiert
die Versorgungspraxis**

9 Discussion

Amivantamab plus lazertinib and osimertinib plus chemotherapy are approved first-line treatments for advanced NSCLC with common EGFR mutations [18, 19]. The scope of this report was to assess, in the Austrian healthcare context, the comparative effectiveness, safety, and organisational and economic aspects of amivantamab (IV/SC) plus lazertinib against osimertinib plus chemotherapy, as well as to compare the two amivantamab administration routes with one another across the same domains. As no head-to-head trial comparing amivantamab plus lazertinib with osimertinib plus chemotherapy has been conducted, the relative benefit of one strategy over the other remains unresolved [20].

Clinical Effectiveness and Safety

The available comparative evidence consists of three ITCs comparing amivantamab plus lazertinib with osimertinib plus chemotherapy: one reported by Torchia et al. (2025) [32] and two forming part of the cost-effectiveness analyses within HTA reports (NICE and CDA-AMC) [33, 34]. All three indirectly linked the pivotal trials, MARIPOSA and FLAURA2, through their common comparator, osimertinib monotherapy. Consequently, all comparative estimates are subject to the inherent assumptions and uncertainty associated with indirect evidence.

The available ITCs reached different conclusions regarding comparative efficacy, largely reflecting methodological differences rather than fundamentally conflicting evidence. Whereas Torchia et al. reported a statistically significant PFS advantage for osimertinib plus chemotherapy, both HTA agencies concluded that the available evidence remained insufficient to establish a comparative efficacy advantage for either regimen [32]. Although the HTD argued that the mechanism of action and resistance profile of amivantamab plus lazertinib support the plausibility of improved survival, neither HTA body considered this hypothesis sufficiently supported by comparative clinical evidence.

In contrast, the available evidence was more consistent regarding safety. NICE and Torchia et al. (2025) both concluded that the two regimens have qualitatively different toxicity profiles with similar AE frequencies. While grade ≥ 3 cutaneous rash and paronychia are significantly more frequent with amivantamab plus lazertinib, grade ≥ 3 anaemia and neutropenia occur significantly more with osimertinib plus chemotherapy [32, 33].

Although the available ITCs provide the best available comparative evidence, several methodological considerations limit confidence in their findings. Importantly, the validity of an ITC depends not only on the statistical methodology employed but also on whether the treatment effects being compared estimate the same underlying clinical question. This requires sufficiently comparable trial estimands and consistent handling of intercurrent events. As the estimands of MARIPOSA and FLAURA2 were not explicitly reported, this assumption could not be verified, introducing uncertainty that cannot be resolved through statistical adjustment alone. Additional uncertainty arises from the reconstructed individual patient data methodology employed by Torchia et al. (2025) [32], while the HTA reports provided only limited insight into the underlying estimates because key results were redacted. Consequently, the

**Bewertung der
Erstlinientherapien
und Amivantamab-
Applikationsformen**

**keine direkte Evidenz
zum Vergleich der beiden
Erstlinientherapien**

**3 indirekte Vergleiche
mit unterschiedlichen
Schlussfolgerungen**

**methodische Unterschiede
erklären abweichende
Ergebnisse zur
Wirksamkeit**

**konsistente Evidenz
zur Sicherheit**

**methodische Limitationen
schränken die
Aussagekraft der
indirekten Vergleiche ein**

**narrativer Vergleich
der Zulassungsstudien
(MARIPOSA und FLAURA2)
als Grundlage der
Bewertung**

available ITCs do not provide definitive comparative evidence, and our interpretation therefore relies primarily on a narrative comparison of the pivotal MARIPOSA and FLAURA2 trials.

The MARIPOSA study investigating amivantamab plus lazertinib [17, 25], and the FLAURA2 trial evaluating osimertinib plus chemotherapy [22, 23] shared a common comparator, osimertinib monotherapy. An additional phase 2 study (OPAL), conducted exclusively in a Japanese population receiving osimertinib plus pemetrexed and either cisplatin or carboplatin, was identified and considered in the assessment [30]. However, given its phase 2 design and the limited applicability of its study population and treatment setting to the Austrian healthcare context, its findings were considered supportive rather than pivotal for the overall conclusions.

Both ongoing studies, MARIPOSA and FLAURA2, included adult patients with previously untreated EGFR-mutated (exon 19 deletion or exon 21 L858R), locally advanced or metastatic NSCLC. Although the study populations were comparable in most baseline characteristics, there were slight differences in racial composition and ECOG PS distribution. In addition, the median time from diagnosis to randomisation was very short in MARIPOSA, suggesting that a treatment-naïve population was enrolled shortly after diagnosis, whereas this was not reported in FLAURA2. The reporting of prior surgeries also differed between the trials, precluding a direct comparison of cancer-related surgeries. Thus, while these two populations appear broadly similar, they should not be regarded as directly comparable.

Both amivantamab plus lazertinib and osimertinib plus chemotherapy demonstrated a statistically significant overall survival benefit compared with osimertinib monotherapy [23, 25]. However, direct comparison of OS between the two regimens remains premature. Although MARIPOSA reported its protocol-specified final OS analysis, the median OS for amivantamab plus lazertinib had not yet been reached, whereas FLAURA2 reported a mature median, though the lower bounds of the 95% CIs were similar across the two regimens (42.9 vs. 41.0 months). Given this difference in maturity, any conclusions regarding their relative efficacy remain uncertain. Updated data are expected as both trials continue, with FLAURA2 running through 2026 and MARIPOSA through 2027 [44, 45]. Of note, in another analysis, OS curves began to separate in both MARIPOSA and FLAURA2 only after 11 and 16 months, respectively, suggesting a delayed benefit of these treatments [46]. The two regimens also appeared to provide broadly comparable improvements in PFS, DOR and ORR [17, 22]. Numerically, osimertinib plus chemotherapy appeared to provide greater intracranial benefit than amivantamab plus lazertinib. However, its intracranial PFS advantage over osimertinib monotherapy was nominally significant only in the post hoc subset of patients with measurable CNS lesions, not in the preplanned full CNS analysis set. All FLAURA2 CNS endpoints were exploratory. No significant intracranial benefit was seen with amivantamab plus lazertinib. The comparison therefore rests on numerical differences rather than formally tested outcomes, and is further limited by methodological differences between the trials, including CNS eligibility criteria, imaging schedules, progression assessment, and data cut-offs [25, 29].

For safety, overall incidence of AEs was broadly similar, but their profiles differed qualitatively, particularly regarding the nature of grade ≥ 3 events. Severe toxicities associated with amivantamab plus lazertinib were predominantly skin toxicities, hypoalbuminaemia, elevated ALT levels, and venous thromboembolism, whereas with osimertinib plus chemotherapy they were

beide Zulassungsstudien verglichen die Therapien mit Osimertinib-Monotherapie

OPAL ergänzt die Evidenzbasis

Studienpopulationen in MARIPOSA und FLAURA2 ähnlich, jedoch nicht vollständig vergleichbar

unterschiedlicher Reifegrad der OS-Daten erschwert den Vergleich

vergleichbare Verbesserungen bei PFS, DOR und ORR

Hinweise auf stärkeren intrakraniellen Nutzen von Osimertinib plus Chemotherapie

vergleichbare Häufigkeit, unterschiedliche Toxizitätsprofile

myelosuppressive, including anaemia, neutropenia, and thrombocytopenia. These qualitative differences make direct comparison difficult and suggest different clinical management challenges rather than a clear difference in overall tolerability. The higher incidence of VTE with amivantamab plus lazertinib represents an important safety consideration, given its potential impact on morbidity and the need for anticoagulant management. Overall treatment discontinuations and AE-related deaths were comparable, but discontinuations specifically due to AEs were considerably more common with amivantamab plus lazertinib [23, 25].

Inferences from these cross-trial comparisons should be made with caution. The trials differed in their primary assessment method. MARIPOSA used blinded independent central review, whereas FLAURA2 was open-label with investigator-assessed primary analyses (central review reported only as a sensitivity analysis). While OS is not affected by knowledge of treatment allocation, tumour-assessment-based outcomes (PFS, ORR, and DOR) are susceptible to bias, and AE reporting was not blinded in either trial, which may have affected the reporting of subjective, clinically apparent toxicities. Outcomes were also drawn from analyses at different cut-offs and follow-up durations. As a result, time-dependent outcomes in particular may reflect differences in maturity rather than true treatment differences.

Further limitations concern an important evidence gap, the absence of HRQoL data for either regimen. Given their markedly different toxicity profiles and administration burden, HRQoL may prove particularly important in distinguishing between treatments with otherwise broadly comparable efficacy. Both trials permitted treatment beyond progression at the investigator's discretion, and in FLAURA2 subsequent-therapy patterns differed between arms, potentially inflating the apparent benefit of osimertinib plus chemotherapy. In addition, MARIPOSA did not report rates of deviation from intended interventions, precluding assessment of a comparable source of bias. These limitations are consistent with the uncertainty highlighted by previous HTA reports.

Although in the MARIPOSA trial, amivantamab plus lazertinib was administered only as an IV infusion, an SC formulation has since been authorised. Its approval was supported by the phase 3 PALOMA-3 trial, which evaluated the SC and IV formulations of amivantamab. The trial demonstrated comparable pharmacokinetics, PFS, and DOR between the two formulations. Notably, SC amivantamab showed a numerically longer OS in comparison to the IV formulation. However, this finding reached only nominal significance, as the analysis was neither prespecified nor controlled for multiplicity; thus, the result should be interpreted with caution [35]. A potential explanation for this difference is the interaction of amivantamab with subcutaneous immune cells [47]. The overall safety profile was comparable, while lower rates of IRRs and VTE with the SC formulation may represent a clinically meaningful advantage [35]. However, the reporting of AEs may have been biased, as patients were not blinded. The applicability of PALOMA-3 to the first-line setting also remains uncertain. As the Slovak NIHO report noted, PALOMA-3 enrolled patients who had already progressed on prior therapy, limiting the direct generalisability of its findings to treatment-naïve patients receiving first-line therapy [48].

Overall, the available data suggest broadly comparable efficacy between the two regimens, with the main distinction lying in their qualitatively different safety profiles rather than in efficacy. As this was a cross-trial comparison rather than a direct randomised comparison, the certainty of the findings is in-

Unterschiede im Studiendesign und Follow-up begrenzen die Vergleichbarkeit

fehlende Lebensqualitätsdaten und weitere Evidenzlücken

subkutane Formulierung mit potenziellen organisatorischen und sicherheitsrelevanten Vorteilen

Aussagekraft durch Studiendesign und Zweitlinienpopulation eingeschränkt

Vergleichbare Wirksamkeit mit begrenzter Aussagekraft; ...

herently limited. The subcutaneous formulation of amivantamab may offer a further practical advantage for amivantamab plus lazertinib, reducing administration burden and infusion-related reactions, though its first-line role remains to be confirmed.

... potenzielle organisatorische Vorteile der subkutanen Formulierung

Economic aspects

For the economic aspects, two cost-effectiveness analyses (CEAs) were identified within two HTA reports from NICE [33] and CDA-AMC [34]. Both evaluated amivantamab plus lazertinib as first-line treatment for EGFR mutation-positive advanced NSCLC against osimertinib plus chemotherapy. These CEAs were constrained by the absence of head-to-head trial data, forcing reliance on ITCs, which both HTA bodies considered insufficiently robust to establish comparative clinical effectiveness. Consequently, economic evaluations are driven largely by assumptions regarding comparative efficacy and treatment costs.

Kosteneffektivitätsanalysen basieren auf indirekter Evidenz

Despite differences in methodology and healthcare systems, both HTA agencies reached broadly similar conclusions. Neither identified sufficient evidence to support additional expenditure for amivantamab plus lazertinib at publicly available prices. Instead, favourable economic outcomes depended primarily on confidential pricing arrangements rather than demonstrated incremental clinical benefit [33, 34].

keine Kosteneffektivität ohne vertrauliche Preisnachlässe

Additionally, a conference abstract [49] revealed in a cost-comparison analysis that first-year cost per patient for osimertinib plus chemotherapy was roughly threefold lower than for amivantamab plus lazertinib. The largest driver for cost difference was in treatment acquisition, administration, and pre-/concomitant medication. These results should, however, be interpreted with caution as methods and peer review are absent. Overall, all analyses arrived at the same conclusion despite different methods and price assumptions. The incremental clinical benefit of amivantamab plus lazertinib over osimertinib plus chemotherapy remains highly uncertain, and any favourable economic result for amivantamab plus lazertinib depends on confidential pricing rather than demonstrated superiority.

kein belegter ökonomischer Vorteil von Amivantamab + Lazertinib

As no Austria-specific budget impact analysis has been published for these treatments, we conducted a BIA from a healthcare payer perspective, considering only direct medical costs (drug acquisition, administration and monitoring). The estimated annual per-patient cost was €207,250 for amivantamab plus lazertinib (IV and SC) versus €128,998 for osimertinib plus chemotherapy, resulting in a difference of €78,252. When applied to the eligible Austrian population (approximately 140 new patients per year), full substitution of osimertinib plus chemotherapy by amivantamab plus lazertinib would increase expenditure by approximately €10.96 million annually, corresponding to a cumulative additional cost of approximately €32.87 million over the three-year horizon, representing a substantial additional cost to the payer. In addition, the budget impact is subject to uncertainty because funding responsibilities differ across healthcare sectors. Oral medicines administered in the outpatient setting are reimbursed by the health insurances, whereas inpatient treatment costs are financed by regional hospital payers and may vary across Austrian federal states. Furthermore, inpatient drug costs were estimated using ex-factory price from Warenverzeichnis, which may not fully reflect the actual costs incurred.

Budget-Impact zeigt erhebliche Mehrkosten für das österreichische Gesundheitssystem

Budget-Impact mit Unsicherheiten behaftet

Organisational aspects

From the organisational perspective, implementation of both amivantamab plus lazertinib and osimertinib plus chemotherapy depends on NGS-based detection of a common EGFR mutation, which is well established in Austria. Reflex molecular testing is initiated at diagnosis irrespective of stage, more systematic than in much of Europe, where automatic testing at diagnosis has been reported in only 14 of 21 countries [9].

The two regimens diverge substantially in administration. Osimertinib plus chemotherapy combines an oral agent with platinum-based chemotherapy requiring pre-hydration, antiemetics, haematological monitoring and regular clinic visits [22], all familiar to any lung cancer centre. Amivantamab plus lazertinib combines intravenous amivantamab with oral lazertinib taken daily. The additional organisational effort stems almost entirely from the amivantamab component: corticosteroid, antihistamine and antipyretic premedication, and biweekly infusions, each taking up to five hours and requiring dedicated infusion capacity. However, thromboembolism management, including pre-treatment bleeding-risk assessment and antithrombotic prophylaxis, is attributable to the combination rather than to amivantamab alone [17, 35].

The greatest challenge with amivantamab plus lazertinib is managing venous thromboembolism risk. Austrian clinicians have adapted ESMO cancer-associated thrombosis guidance with individualised risk scoring, recommending antithrombotic prophylaxis for at least six months alongside continuous bleeding-risk assessment [40]. Prophylactic oral antibiotics and topical dermatologic products are also needed for skin toxicities, a regimen shown in a randomised phase 2 study to significantly reduce dermatologic AEs [41, 50]. The organisational advantages of a “chemotherapy-free” amivantamab plus lazertinib are therefore partly offset by the need for prolonged thromboprophylaxis and dermatological management. Clinical experts echoed that amivantamab plus lazertinib is time- and resource-intensive despite avoiding cytotoxic chemotherapy [41].

The SC formulation eases administration but not this management burden. PALOMA-3 showed real advantages for the SC route over IV, with fewer infusion-related reactions, better tolerability, a lower VTE rate, and shorter treatment time for patients and staff [35, 36]. However, this time saving is likely overstated, as the mandatory 4-hour post-injection observation at the first cycle became optional thereafter and may have inflated the first-cycle figures. Patient-reported outcomes also favoured SC, with 77% preferring it over their prior IV treatment, though rated against historical experience rather than the trial’s IV arm [36]. However, these advantages are confined to administration. An industry-funded, non-peer-reviewed model estimated 219 hours per year on prophylaxis and safety monitoring for both SC and IV amivantamab versus just 7 hours for osimertinib plus chemotherapy, with only 47 hours saved by switching IV to SC [43]. The clinical experts likewise preferred the SC route for its fewer infusion reactions and easier administration [41].

Both regimens require delivery in specialised, high-volume centres, but amivantamab plus lazertinib carries a distinct learning curve in toxicity management that can mainly affect smaller-volume centres, concentrating competent delivery in fewer institutions and amplifying regional disparities. This is particularly relevant in Austria, where approximately 90% of patients are cared for by pulmonologists rather than oncologists, while treatment guidelines are developed predominantly by oncologists. Safe and appropriate use of amivantamab therefore requires close collaboration between pulmonologists and

**etablierte EGFR-Testung
als Voraussetzung beider
Therapien in Österreich
erfüllt**

**unterschiedliche
Anforderungen an die
Therapiedurchführung**

**Supportivmaßnahmen
erhöhen den
organisatorischen
Aufwand von
Amivantamab + Lazertinib**

**subkutane Form
erleichtert die Applikation,
nicht jedoch das
Therapiemanagement**

**Umsetzung von
Amivantamab + Lazertinib
erfordert spezialisierte
Zentren und Erfahrung**

oncologists, particularly for the management of treatment-related toxicities. This includes the management of venous thromboembolic events and thromboprophylaxis, as well as skin toxicities, which may require specialist input beyond routine pulmonology care. A structured multidisciplinary approach may therefore be important to ensure appropriate monitoring, prevention, and management of adverse events in clinical practice. According to a clinical expert consultation, real-world uptake of amivantamab plus lazertinib in Austria also appears low, with osimertinib plus chemotherapy dominating first-line cases, despite regulatory approval of the combination [41]. This suggests that the organisational and monitoring requirements for amivantamab plus lazertinib could slow down or prevent the implementation of this regimen. Given the remaining uncertainty regarding the comparative clinical benefit, together with the increased treatment complexity, safety considerations, and higher costs, the future role of amivantamab plus lazertinib in routine clinical practice in Austria remains uncertain.

The transferability issue is further underscored by a gap between trial populations and real-world practice. Both pivotal studies enrolled only ECOG PS 0-1 patients [17, 22], whereas the real-world EGFR-mutant NSCLC population includes a substantial minority with ECOG PS ≥ 2 or symptomatic brain metastases, both excluded from the trials [20]. This leaves transferability to ECOG PS ≥ 2 patients unclear, as IQWiG makes explicit [51]. Routine Austrian practice therefore includes a meaningful group of patients for whom the efficacy of the regimens is formally unestablished, yet for whom their full organisational and toxicity burden would still apply. Implementation in routine Austrian practice is also complicated by the limited representativeness of the pivotal trial populations. As with many oncology registration trials, the available evidence is derived from selected patient populations and may not fully reflect the broader spectrum of patients encountered in routine care. Consequently, clinicians may need to apply these regimens in situations where the supporting evidence is less certain, increasing reliance on specialist expertise and multidisciplinary decision-making. A concrete example is thromboprophylaxis. The six-month course recommended in Austrian practice was largely absent in MARIPOSA, which may cause the trial to overstate the VTE burden of amivantamab plus lazertinib, with real-world rates likely lower under adequate prophylaxis. This concern about applicability to routine clinical practice has also been highlighted by IQWiG [51].

Austrian real-world data on amivantamab plus lazertinib or osimertinib plus chemotherapy are not yet available. Local amivantamab experience is confined to pretreated and single-agent settings, whereas real-world evidence for osimertinib plus platinum chemotherapy is emerging and broadly consistent with FLAURA2 [20]. Austrian registry data through LALUCA could therefore fill a genuine evidence gap [15, 16], potentially capturing outcomes absent from the pivotal trials, such as effectiveness in ECOG PS ≥ 2 patients and health-related quality of life. However, the registry is currently too immature and prone to selection bias to support a routine-care comparison of the two combinations [41].

Limitationen:
Übertragbarkeit auf die
österreichische Versorgung
bleibt eingeschränkt

fehlende österreichische
Real-World-Daten

Registerdaten könnten
künftig Evidenzlücken
schließen

Conclusion

In conclusion, the available evidence suggests broadly comparable clinical efficacy between amivantamab plus lazertinib and osimertinib plus chemotherapy in the first-line treatment of advanced NSCLC with common EGFR mutations. However, the absence of direct comparative evidence leaves any true difference uncertain. Their safety profiles differ qualitatively rather than in overall burden. In the Austrian setting, amivantamab plus lazertinib is associated with substantially higher treatment costs and greater organisational burden than osimertinib plus chemotherapy. This burden is only partially diminished by the availability of the subcutaneous formulation. These conclusions remain preliminary as no real-world evidence or comparative studies are available. The median overall survival for amivantamab plus lazertinib was not yet reached at the final analysis, and updated analysis is expected as the trial continues through 2027. Quality-of-life outcomes are also absent for both regimens, a gap that Austrian registry data could help address. Overall, the current evidence does not support a clear clinical advantage of one regimen over the other. Consequently, hospitals and treating clinicians will need to determine whether implementation of amivantamab plus lazertinib is feasible and justified within their local organisational context, while considering patient preferences, toxicity profiles and the additional costs associated with the treatment.

keine Evidenz für einen eindeutigen klinischen Vorteil einer Erstlinientherapie

Amivantamab + Lazertinib mit höheren Kosten und Versorgungsaufwand

Therapiewahl unter Berücksichtigung lokaler Ressourcen und Finanzierung

10 References

- [1] Hendriks L. E. L., Remon J., Faivre-Finn C., Garassino M. C., Heymach J. V., Kerr K. M., et al. Non-small-cell lung cancer. *Nat Rev Dis Primers*. 2024;10(1):71. Epub 20240926. DOI: 10.1038/s41572-024-00551-9.
- [2] Statistik Austria. <https://www.statistik.at/>. 2026 [cited 04.05.2026]. Available from: <https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen>.
- [3] Wass R. E. and Lamprecht B. Lung cancer in Austria: epidemiology and demographic trends as a basis for early detection strategies. *Memo – Magazine of European Medical Oncology*. 2026;19(1):18-21. DOI: 10.1007/s12254-025-01092-x.
- [4] Simeone J. C., Nordstrom B. L., Patel K. and Klein A. B. Treatment patterns and overall survival in metastatic non-small-cell lung cancer in a real-world, US setting. *Future Oncol*. 2019;15(30):3491-3502. Epub 20190909. DOI: 10.2217/fon-2019-0348.
- [5] Garg P., Singhal S., Kulkarni P., Horne D., Malhotra J., Salgia R., et al. Advances in Non-Small Cell Lung Cancer: Current Insights and Future Directions. *J Clin Med*. 2024;13(14). Epub 20240718. DOI: 10.3390/jcm13144189.
- [6] Herbst R. S., Morgensztern D. and Boshoff C. The biology and management of non-small cell lung cancer. *Nature*. 2018;553(7689):446-454. DOI: 10.1038/nature25183.
- [7] Borgeaud M., Olivier T., Bar J., Saw S. P. L., Parikh K., Banna G. L., et al. Personalized care for patients with EGFR-mutant nonsmall cell lung cancer: Navigating early to advanced disease management. *CA Cancer J Clin*. 2025;75(5):387-409. Epub 20250717. DOI: 10.3322/caac.70024.
- [8] Smolarz B., Lukasiewicz H., Samulak D., Piekarska E., Kolacinski R. and Romanowicz H. Lung Cancer-Epidemiology, Pathogenesis, Treatment and Molecular Aspect (Review of Literature). *Int J Mol Sci*. 2025;26(5). Epub 20250226. DOI: 10.3390/ijms26052049.
- [9] Popper H., Gruber-Mösenbacher U., Pall G., Müllauer L., Hochmair M., Krenbek D., et al. The 2020 update of the recommendations of the Austrian working group on lung pathology and oncology for the diagnostic workup of non-small cell lung cancer with focus on predictive biomarkers. *Memo – Magazine of European Medical Oncology*. 2020;13. DOI: 10.1007/s12254-019-00565-0.
- [10] National Lung Screening Trial Research T., Aberle D. R., Adams A. M., Berg C. D., Black W. C., Clapp J. D., et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New England Journal of Medicine*. 2011;365(5):395-409. Epub 20110629. DOI: 10.1056/NEJMoa1102873.
- [11] de Koning H. J., van der Aalst C. M., de Jong P. A., Scholten E. T., Nackaerts K., Heuvelmans M. A., et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. *New England Journal of Medicine*. 2020;382(6):503-513. Epub 20200129. DOI: 10.1056/NEJMoa1911793.
- [12] Oudkerk M., Devaraj A., Vliegenthart R., Henzler T., Prosch H., Heussel C. P., et al. European position statement on lung cancer screening. *Lancet Oncology*. 2017;18(12):e754-e766. DOI: 10.1016/S1470-2045(17)30861-6.
- [13] Jeon H., Wang S., Song J., Gill H. and Cheng H. Update 2025: Management of Non-Small-Cell Lung Cancer. *Lung*. 2025;203(1):53. Epub 20250325. DOI: 10.1007/s00408-025-00801-x.
- [14] Zhang Y. L., Yuan J. Q., Wang K. F., Fu X. H., Han X. R., Threapleton D., et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7(48):78985-78993. DOI: 10.18632/oncotarget.12587.
- [15] Braschel C., Fabikan H., Rodriguez V. M., Hochmair M. J., Illini O., Ay L., et al. Clinical Impact of EGFR Mutation Subtypes on Treatment Outcomes in Advanced Non-Small Cell Lung Cancer: An Austrian Real-World Study. *Cancers*. 2026;18(2). Epub 20260116. DOI: 10.3390/cancers18020278.
- [16] Lang-Stoberl A., Fabikan H., Hochmair M., Kirchbacher K., Rodriguez V. M., Ay L., et al. The Landsteiner lung cancer research platform (LALUCA) : Objectives, methodology and implementation of a real-world clinical lung cancer registry. *Wien Klin Wochenschr*. 2025;137(7-8):197-204. Epub 20240423. DOI: 10.1007/s00508-024-02351-3.

- [17] Cho B. C., Lu S., Felip E., Spira A. I., Girard N., Lee J. S., et al. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. *New England Journal of Medicine*. 2024;391(16):1486-1498. DOI: <https://dx.doi.org/10.1056/NEJMoa2403614>.
- [18] NCCN. NSCLC Guideline. 2026 [cited 03.03.2026]. Available from: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450>.
- [19] Onkopedia. Lungenkarzinom, nicht-kleinzellig (NSCLC). 2025 [cited 03.03.2026]. Available from: <https://www.onkopedia.com/de/onkopedia/guidelines/lungenkarzinom-nicht-kleinzellig-nsclc/@guideline/html/index.html>.
- [20] Maione P., Romano F. J. and Gridelli C. Amivantamab Plus Lazertinib and Platin-Based Chemotherapy Plus Osimertinib in EGFR-Mutant NSCLC: How to Choose Among Them and When Is Monotherapy with Osimertinib Still the Best Option? *Current Oncology*. 2026;33(1):17. DOI: <https://dx.doi.org/10.3390/curroncol33010054>.
- [21] EMA. Tagrisso. [cited 02.03.2026]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/tagrisso>.
- [22] Planchard D., Janne P. A., Cheng Y., Yang J. C., Yanagitani N., Kim S. W., et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. *New England Journal of Medicine*. 2023;389(21):1935-1948. DOI: <https://dx.doi.org/10.1056/NEJMoa2306434>.
- [23] Janne P. A., Planchard D., Kobayashi K., Yang J. C., Liu Y., Valdiviezo N., et al. Survival with Osimertinib plus Chemotherapy in EGFR-Mutated Advanced NSCLC. *New England Journal of Medicine*. 2026;394(1):27-38. DOI: <https://dx.doi.org/10.1056/NEJMoa2510308>.
- [24] EMA. Rybrevant. [cited 02.03.2026]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/rybrevant>.
- [25] Yang J. C., Lu S., Hayashi H., Felip E., Spira A. I., Girard N., et al. Overall Survival with Amivantamab-Lazertinib in EGFR-Mutated Advanced NSCLC. *New England Journal of Medicine*. 2025;393(17):1681-1693. DOI: <https://dx.doi.org/10.1056/NEJMoa2503001>.
- [26] eunetha. HTA Core Model Handbook. 2018 [cited 20.05.2026]. Available from: <https://web.archive.org/web/20181213135915/http://mekat.hi.fi/htacore/ViewHandbook.aspx>.
- [27] Cochrane. Cochrane RoB 2.0 tool. 2026 [cited 21.05.2026]. Available from: <https://methods.cochrane.org/risk-bias-2>.
- [28] APOTHEKER-VERLAG. APOTHEKER-VERLAG Warenverzeichnis Online. 2026 [cited 21.05.2026]. Available from: <https://warenverzeichnis.apoverlag.at/>.
- [29] Janne P. A., Planchard D., Kobayashi K., Cheng Y., Lee C. K., Valdiviezo N., et al. CNS Efficacy of Osimertinib With or Without Chemotherapy in Epidermal Growth Factor Receptor-Mutated Advanced Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*. 2024;42(7):808-820. DOI: <https://dx.doi.org/10.1200/JCO.23.02219>.
- [30] Saito R., Sugawara S., Ko R., Azuma K., Morita R., Maemondo M., et al. Phase 2 study of osimertinib in combination with platinum and pemetrexed in patients with previously untreated EGFR-mutated advanced non-squamous non-small cell lung cancer: The OPAL Study. *European Journal of Cancer*. 2023;185:83-93. DOI: <https://dx.doi.org/10.1016/j.ejca.2023.02.023>.
- [31] HTAR. Guidance on outcomes for joint clinical assessments. 2026 [cited 21.05.2026]. Available from: https://health.ec.europa.eu/document/download/a70a62c7-325c-401e-ba42-66174b656ab8_en?filename=hta_outcomes_jca_guidance_en.pdf.
- [32] Torchia A., Sabatini A., Bengala E., Di Civita M. A., Ciurluini F., Marinelli D., et al. First-line treatment in EGFR-mutated non-small cell lung cancer: brief report of an individual patient data comparison of phase 3 clinical trials. *Lung Cancer*. 2025;210:108845. DOI: <https://dx.doi.org/10.1016/j.lungcan.2025.108845>.
- [33] NICE. Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer. NICE technology appraisal guidance 1122. National Institute for Health and Care Excellence (NICE), 2026. [cited 17.07.2026] Available from: <https://www.nice.org.uk/guidance/ta1122>.

- [34] CADTH. Lazertinib and Amivantamab. 2025 [cited 17.07.2026]. Available from: <https://www.cda-amc.ca/amivantamab>.
- [35] Leighl N. B., Akamatsu H., Lim S. M., Cheng Y., Minchom A. R., Marmarelis M. E., et al. Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor-Mutated Non-Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study. *Journal of Clinical Oncology*. 2024;42(30):3593-3605. DOI: <https://dx.doi.org/10.1200/JCO.24.01001>.
- [36] Alexander M., Cheng Y., Lee S. H., Passaro A., Spira A. I., Cho B. C., et al. Subcutaneous versus intravenous amivantamab, both in combination with lazertinib, in refractory EGFR-mutated non-small cell lung cancer: Patient satisfaction and resource utilization results from the PALOMA-3 study. *European Journal of Cancer*. 2025;227:115624. DOI: <https://dx.doi.org/10.1016/j.ejca.2025.115624>.
- [37] EMA. Rybrevant SmPC. 2026 [cited 14.07.2026]. Available from: https://www.ema.europa.eu/en/documents/product-information/rybrevant-epar-product-information_en.pdf.
- [38] EMA. Tagrisso SmPC. 2026 [cited 14.07.2026]. Available from: https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf.
- [39] EMA. Lazcluze SmPC. 2026 [cited 15.07.2026]. Available from: https://www.ema.europa.eu/en/documents/product-information/lazcluze-epar-product-information_en.pdf.
- [40] Moik F., Absenger G., Wurm R., Hochmair M. J. and Ay C. Prevention and Treatment of Venous Thromboembolism Associated with Amivantamab-Based Therapies in Patients with Lung Cancer- Provisional Clinical Opinion Based on Existing Clinical Practice Guidelines. *Cancers*. 2025;17(2). Epub 20250114. DOI: 10.3390/cancers17020259.
- [41] Clinical experts meeting. 2026.
- [42] Herrstedt J., Clark-Snow R., Ruhlmann C. H., Molassiotis A., Olver I., Rapoport B. L., et al. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. *Esmo Open*. 2024;9(2):102195. Epub 20240111. DOI: 10.1016/j.esmoop.2023.102195.
- [43] Florez N., Simmons D., Rattigan-Brown Y. and Hochmair M. J. 19P Estimated time toxicity associated with 1L use of 3rd gen EGFR TKI regimens in advanced non-small cell lung cancer in the European Union. *Esmo Open*. 2026;11. DOI: 10.1016/j.esmoop.2026.106326.
- [44] clinicaltrials.gov. A Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib in Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA). 2026 [cited 30.07.2026]. Available from: <https://clinicaltrials.gov/study/NCT04487080>.
- [45] clinicaltrials.gov. A Study of Osimertinib With or Without Chemotherapy as 1st Line Treatment in Patients With Mutated Epidermal Growth Factor Receptor Non-Small Cell Lung Cancer (FLAURA2) 2026 [cited 30.07.2026]. Available from: <https://clinicaltrials.gov/study/NCT04035486>.
- [46] Acker F., Rost M., Sebastian M. and Cortellini A. Rethinking survival metrics in EGFR-mutated NSCLC: insights from RMST analysis of FLAURA2 and MARIPOSA. *Annals of Oncology*. 2026;37(1):125-127. DOI: 10.1016/j.annonc.2025.10.1235.
- [47] Lim S. M., Kang S. S., Kim D. K., Lee S. H., Synn C. B., Baek S., et al. Exploration of Immune-Modulatory Effects of Amivantamab in Combination with Pembrolizumab in Lung and Head and Neck Squamous Cell Carcinoma. *Cancer Res Commun*. 2024;4(7):1748-1764. DOI: 10.1158/2767-9764.CRC-24-0107.
- [48] NIHO. Amivantamab (Rybrevant) + lazertinib (Lazcluze). 2026 [cited 17.07.2026]. Available from: https://niho.sk/wp-content/uploads/2025/10/NIHO_amivantamab_Rybrevantlazertinib_Lazcluze_NSCLC_hodnotenie_L187.pdf.
- [49] Freeman H., Upton E., Karia P. S., Rattigan-Brown Y., Hearmon N., Procter E., et al. EE398 Cost Comparison of Osimertinib Plus Chemotherapy Versus Amivantamab Plus Lazertinib for the First-Line Treatment of Patients With Locally Advanced or Metastatic EGFR-Mutated NSCLC. *Value in Health*. 2025;28(6):S135-S136. DOI: 10.1016/j.jval.2025.04.1997.

- [50] Cho B. C., Li W., Spira A. I., Sauder M., Feldman J., Bozorgmehr F., et al. Enhanced Versus Standard Dermatologic Management With Amivantamab-Lazertinib in EGFR-Mutated Advanced NSCLC: The COCOON Global Randomized Controlled Trial. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*. 2025;20(10):1517-1530. DOI: <https://dx.doi.org/10.1016/j.jtho.2025.07.117>.
- [51] IQWiG. Amivantamab (NSCLC, first line, combination with lazertinib) – Benefit assessment. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2025 [cited 05.05.2026]. Available from: <https://www.iqwig.de/en/projects/a25-08.html>.

Appendix

Risk of bias

Table A-1: Risk of bias of the included studies – detailed assessment

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
MARIPOSA	OS, PFS	Low Centralised randomisation with stratified random permuted blocks. Allocation concealed until assignment. Baseline characteristics well balanced across all key prognostic factors.	Low Partially open-label; no unintended deviations identified. Differences in management were protocol-defined. ITT analysis used.	Low Analyses conducted in the ITT population. No substantial missing outcome data.	Low PFS assessed by BICR using standardised RECIST criteria; OS is objective. Outcome assessors (BICR) blinded to treatment. No meaningful influence of treatment knowledge on OS or BICR-assessed PFS.	Low Endpoints pre-specified in protocol and SAP with hierarchical testing. No selective outcome or analysis reporting identified.	Low
	Safety (AEs)	Low As above.	Low Protocol-defined differences in management; no unintended deviations. Safety analysed in the safety population (received ≥ 1 dose).	Low Safety population included nearly all treated randomised participants; AEs assessed at each visit.	High Open-label design; biased ascertainment of subjective AEs likely, as unblinded investigators may probe more actively for expected toxicities. Lower risk for objective events (lab values, SAEs, fatal AEs).	Low SAP pre-specified with hierarchical testing; AE reporting followed predefined structure. No selective safety reporting identified.	High
FLAURA2	OS	Low Centralised IWRS/IVRS 1:1 randomisation with probable allocation concealment. Minor imbalance in liver metastases noted but baseline characteristics generally balanced.	High Open-label trial; protocol permitted treatment beyond progression at investigator discretion. Differential post-progression management and subsequent therapies likely influenced survival and could not be established as balanced between arms.	Low Survival data available for all randomised participants.	Low OS is binary and objective; cannot be meaningfully influenced by knowledge of treatment received.	Low OS pre-specified in protocol and SAP with hierarchical testing followed as planned. No selective reporting identified.	High
	PFS	Low As above.	High Protocol allowed treatment beyond progression at investigator discretion, likely influencing timing of progression assessment. Deviations likely affected PFS and could not be established as balanced between arms.	Low Tumour assessments at protocol-defined intervals; no substantial missing outcome data.	High Investigator-assessed PFS in an open-label trial; BICR performed as sensitivity analysis only. Subjective imaging interpretation by unblinded investigators risks differential ascertainment of progression between arms.	Low PFS pre-specified as primary endpoint; investigator-assessed and BICR results both reported as planned. No selective reporting identified.	High
	Safety (AEs)	Low As above.	High Open-label trial; chemotherapy arm required more intensive contact and monitoring. Although largely protocol-defined, the open-label setting may have allowed clinical decisions to differ directionally between arms.	Low Safety analysis set included essentially all randomised patients who received ≥ 1 dose.	High Open-label design; biased ascertainment of subjective AEs likely, as investigators may probe more actively for expected toxicities in the more intensively monitored combination arm. Lower risk for objective measurements.	Low Safety endpoints pre-specified in protocol. No selective safety reporting.	High

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
PALOMA-3	PFS	Low Centralised IWRS randomisation with probable allocation concealment. Baseline characteristics well balanced across key stratification variables and prognostic factors.	Low Open-label trial comparing SC vs IV formulations of the same drug. No systematic differential co-interventions identified. ITT analysis used.	Low Standard censoring present but not clearly imbalanced between arms; no evidence of informative censoring.	Some concerns RECIST imaging standardised across arms; no formal BICR performed. Systematic directional bias unlikely given formulation-comparison design, but subjective interpretation by unblinded investigators cannot be fully excluded.	Low PFS pre-specified in SAP with single outcome measurement and analysis.	Some concerns
	OS	Low As PFS above.	Low No evidence of systematic differential co-interventions. Full Analysis Set used.	Low Minimal loss for death endpoints.	Low OS is objective and binary; cannot be influenced by assessor awareness of treatment.	Low OS pre-specified in SAP; no selective analysis.	Low
	ORR	Low As above.	Low No evidence of systematic differential co-interventions. ITT analysis used.	Low Response data available for nearly all randomised participants.	Some concerns Assessors aware of treatment; influence on ORR possible but judged unlikely given the formulation-comparison design.	Low ORR pre-specified within the formal testing hierarchy. No selective outcome or analysis reporting identified.	Some concerns
	QoL (mTASQ)	Low As above.	Low No protocol-context deviations affecting QoL data collection. mTASQ evaluated in full analysis set.	High Different completion rates at EOT; more IV arm patients reported being too ill to complete, suggesting informative missingness. No formal imputation or sensitivity analysis performed.	High Open-label trial; participants aware of treatment assignment. mTASQ directly asks about convenience, time burden, and satisfaction, making response bias due to expectation effects very likely.	High Favourable mTASQ items emphasised in the main text. Nominal p-values reported without multiplicity adjustment; selective reporting cannot be excluded.	High
	Safety (SAEs/IRR)	Low As above.	Low No evidence of important deviations from the intended interventions. Safety analysed in the safety analysis set based on actual treatment received, standard for harms.	Low TEAEs collected from first dose until last dose + 30 days or start of next therapy. Ascertainment near-complete.	SAEs: Low IRR: High SAEs: Measurement comparable between arms; influence of treatment knowledge on objectively defined serious events judged unlikely. IRR: Large difference observed. In the open-label setting, investigators aware of the arm-specific IRR profile may differentially attribute symptoms to IRR in the IV arm.	Low Safety endpoints pre-specified in protocol with predefined AE collection and summarisation structure. No selective safety reporting.	SAEs: Some concerns IRR: High

Abbreviations: AEs ... adverse events, BICR ... blinded independent central review, EOT ... end of treatment, IRR ... infusion-related reactions, ITT ... intention-to-treat, IWRS ... interactive web response system, IVRS ... interactive voice response system, mTASQ ... modified Treatment Satisfaction Questionnaire, ORR ... objective response rate, OS ... overall survival, PFS ... progression-free survival, QoL ... quality of life, RECIST ... Response Evaluation Criteria in Solid Tumours, SAEs ... serious adverse events, SAP ... statistical analysis plan, SC ... subcutaneous, IV ... intravenous, TEAEs ... treatment-emergent adverse events.

Search strategies

The Cochrane Library

Search name: Cochrane	
Search date: 6 March 2026	
ID	Search
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
#2	((non?small OR non-small) NEAR (cancer* OR tumor* OR carcinom* OR adenom* OR adeno*c* OR neoplasm* OR malignan*)) (Word variations have been searched)
#3	(NSCLC*) (Word variations have been searched)
#4	(aNSCLC*) (Word variations have been searched)
#5	(mNSCLC*) (Word variations have been searched)
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	(amivantamab*) (Word variations have been searched)
#8	(rybrevant*) (Word variations have been searched)
#9	(cnto4424) (Word variations have been searched)
#10	("jnj 372") (Word variations have been searched)
#11	(jnj372) (Word variations have been searched)
#12	(jnj NEXT 611*) (Word variations have been searched)
#13	(jnj611*) (Word variations have been searched)
#14	("jnj 6372") (Word variations have been searched)
#15	(jnj6372) (Word variations have been searched)
#16	(osimertinib*) (Word variations have been searched)
#17	(tagrisso*) (Word variations have been searched)
#18	(mereletinib*) (Word variations have been searched)
#19	("azd 9291") (Word variations have been searched)
#20	(azd9291) (Word variations have been searched)
#21	("n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] 2 propenamide") (Word variations have been searched)
#22	("n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] 2 propenamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] acrylamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] 2 propenamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] acrylamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] prop 2 enamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidinyl] amino] phenyl] 2 propenamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidinyl] amino] phenyl] acrylamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidinyl] amino] phenyl] 2 propenamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidinyl] amino] phenyl] acrylamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methylindol 3 yl) pyrimidin 2 yl] amino] phenyl] acrylamide" OR "n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methylindol 3 yl) pyrimidin 2 yl] amino] phenyl] prop 2 enamide") (Word variations have been searched)
#23	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
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Search name: Embase		
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#34.	#33 AND 'Conference Abstract'/it	476
#33.	#27 OR #29 OR #30 OR #32	1,214
#32.	#26 AND #31	350
#31.	((double NEXT/1 blind*):de,ab,ti) OR placebo*:ab,ti OR blind*:ab,ti	950,954
#30.	#26 AND ([controlled clinical trial]/lim OR Zrandomized controlled trial]/lim)	587
#29.	#26 AND #28	460
#28.	'systematic review'/de OR 'systematic review (topic)'/de OR (('comprehensive':ti,ab,kw OR 'mapping':ti,ab,kw OR 'methodology':ti,ab,kw OR 'scoping':ti,ab,kw OR 'systematic':ti,ab,kw) AND ('search':ti,ab,kw OR 'searched':ti,ab,kw OR 'searches':ti,ab,kw OR 'studies':ti,ab,kw) AND ('cinahl':ti,ab,kw OR 'cochrane':ti,ab,kw OR 'embase':ti,ab,kw OR 'psycinfo':ti,ab,kw OR 'pubmed':ti,ab,kw OR 'medline':ti,ab,kw OR 'scopus':ti,ab,kw OR 'web of science':ti,ab,kw OR 'bibliographic review':ti,ab,kw OR 'bibliographic reviews':ti,ab,kw OR 'literature review':ti,ab,kw OR 'literature reviews':ti,ab,kw OR 'literature search':ti,ab,kw OR 'literature searches':ti,ab,kw OR 'qualitative review':ti,ab,kw OR 'qualitative reviews':ti,ab,kw OR 'quantitative review':ti,ab,kw OR 'quantitative reviews':ti,ab,kw)) OR 'comprehensive review':ti,ab,kw OR 'comprehensive reviews':ti,ab,kw OR 'comprehensive search':ti,ab,kw OR 'comprehensive searches':ti,ab,kw OR 'critical review':ti,ab,kw OR 'critical reviews':ti,ab,kw OR (('electronic database':ti,ab,kw OR 'electronic databases':ti,ab,kw OR (databases NEAR/3 searched)) AND (eligibility:ti,ab,kw OR excluded:ti,ab,kw OR exclusion:ti,ab,kw OR included:ti,ab,kw OR inclusion:ti,ab,kw)) OR 'evidence assessment':ti,ab,kw OR 'evidence review':ti,ab,kw OR 'exploratory review':ti,ab,kw OR 'framework synthesis':ti,ab,kw OR 'mapping review':ti,ab,kw OR 'meta-review':ti,ab,kw OR 'meta-synthesis':ti,ab,kw OR 'methodology review':ti,ab,kw OR 'mixed methods review':ti,ab,kw OR 'mixed methods synthesis':ti,ab,kw OR (overview NEAR/4 reviews) OR 'prisma':ab OR ('preferred':ti,ab,kw AND reporting:ti,ab,kw) OR 'prognostic review':ti,ab,kw OR 'psychometric review':ti,ab,kw OR 'rapid evidence assessment':ti,ab,kw OR 'rapid literature review':ti,ab,kw OR 'rapid literature search':ti,ab,kw OR 'rapid realist':ti,ab,kw OR 'rapid review':ti,ab,kw OR 'rapid reviews':ti,ab,kw OR 'realist review':ti,ab,kw OR 'review of reviews':ti,ab,kw OR 'scoping review':ti,ab,kw OR 'scoping reviews':ti,ab,kw OR 'scoping study':ti,ab,kw OR 'systematic evidence map':ti,ab,kw OR 'systematic evidence mapping':ti,ab,kw OR 'systematic literature':ti,ab,kw OR 'systematic medline':ti,ab,kw OR 'systematic pubmed':ti,ab,kw OR 'systematic review':ti,ab,kw OR 'systematic reviews':ti,ab,kw OR 'systematic search':ti,ab,kw OR 'systematic searches':ti,ab,kw OR 'systematical literature review':ti,ab,kw OR 'systematical review':ti,ab,kw OR 'systematical reviews':ti,ab,kw OR 'systematically identified':ti,ab,kw OR 'systematically review':ti,ab,kw OR 'systematically reviewed':ti,ab,kw OR 'umbrella review':ti,ab,kw OR 'umbrella reviews':ti,ab,kw OR '13616137':is OR 'cochrane database of systematic reviews'/jt	931,665
#27.	#26 AND ([systematic review]/lim OR [meta analysis]/lim)	399
#26.	#6 AND #25	10,485
#25.	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	12,640
#24.	'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] 2 propenamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] acrylamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidyl] amino] phenyl] 2 propenamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidyl] amino] phenyl] acrylamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidin 2 yl] amino] phenyl] prop 2 enamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidinyl] amino] phenyl] 2 propenamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidinyl] amino] phenyl] acrylamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidyl] amino] phenyl] 2 propenamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidyl] amino] phenyl] acrylamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methylindol 3 yl) pyrimidin 2 yl] amino] phenyl] acrylamide' OR 'n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methylindol 3 yl) pyrimidin 2 yl] amino] phenyl] prop 2 enamide'	3
#23.	azd9291	554
#22.	'azd 9291'	543
#21.	mereletinib*	27

#20.	tagrisso*	308
#19.	'osimertinib'/exp	11,994
#18.	jnj6372	1
#17.	'jnj 6372'	3
#16.	jnj611*	60
#15.	'jnj 611*'	104
#14.	jnj372	29
#13.	'jnj 372'	32
#12.	cnto4424	
#11.	'cnto 4424'	
#10.	rybrevant*	48
#9.	amivantanab*	3
#8.	amivantamab*	1,046
#7.	'amivantamab'/exp	1,006
#6.	#1 OR #2 OR #3 OR #4 OR #5	294,729
#5.	mnsclc*.ti,ab	1,160
#4.	ansclc*.ti,ab	1,155
#3.	nsclc	143,941
#2.	(non\$small OR 'non small') NEAR/3 (cancer* OR tumor* OR carcinom* OR adenom* OR adeno\$c* OR 'adeno-c*' OR neoplasm* OR malignan*)	232,636
#1.	'non small cell lung cancer'/exp	271,712
Total hits: 653		

Medline via Ovid

Search name: Medline	
Search date: 5 March 2026	
ID	Search
1	exp Carcinoma, Non-Small-Cell Lung/ (82237)
2	((non?small or non-small) adj3 (cancer* or tumor* or carcinom* or adenom* or adeno?c* or neoplasm* or malignan*)).mp. (120948)
3	NSCLC*.mp. (76823)
4	aNSCLC*.ti,ab. (293)
5	mNSCLC*.ti,ab. (313)
6	1 or 2 or 3 or 4 or 5 (124312)
7	amivantamab*.mp. (319)
8	amivantanab*.mp. (1)
9	rybrevant*.mp. (22)
10	cnto 4424.mp. (1)
11	cnto4424.mp. (1)
12	jnj 372.mp. (2)
13	jnj372.mp. (0)
14	jnj 611*.mp. (15)
15	jnj611*.mp. (0)
16	jnj 6372.mp. (1)
17	jnj6372.mp. (0)
18	osimertinib*.mp. (4140)
19	tagrisso*.mp. (49)
20	mereletinib*.mp. (2)

21	azd 9291.mp. (16)
22	azd9291.mp. (247)
23	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] 2 propenamide".mp. (0)
24	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidinyl] amino] phenyl] acrylamide".mp. (0)
25	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidyl] amino] phenyl] 2 propenamide".mp. (0)
26	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) 2 pyrimidyl] amino] phenyl] acrylamide".mp. (0)
27	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) pyrimidin 2 yl] amino] phenyl] acrylamide".mp. (0)
28	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 1h indol 3 yl) pyrimidin 2 yl] amino] phenyl] prop 2 enamide".mp. (0)
29	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidinyl] amino] phenyl] 2 propenamide".mp. (0)
30	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidinyl] amino] phenyl] acrylamide".mp. (0)
31	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidyl] amino] phenyl] 2 propenamide".mp. (0)
32	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methyl 3 indolyl) 2 pyrimidyl] amino] phenyl] acrylamide".mp. (0)
33	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methylindol 3 yl) pyrimidin 2 yl] amino] phenyl] acrylamide".mp. (0)
34	"n [2 [[2 (dimethylamino) ethyl] (methyl) amino] 4 methoxy 5 [[4 (1 methylindol 3 yl) pyrimidin 2 yl] amino] phenyl] prop 2 enamide".mp. (0)
35	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (4444)
36	6 and 35 (3481)
37	limit 36 to (meta analysis or "systematic review") (77)
38	((((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*)))ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (966033)
39	36 and 38 (210)
40	limit 36 to clinical trial, all (226)
41	exp randomized controlled trial/ (657198)
42	controlled clinical trial.pt. (95761)
43	randomized.ab. (735376)
44	placebo.ab. (267175)
45	clinical trials as topic.sh. (206993)
46	randomly.ab. (481619)
47	trial.ti. (360835)
48	or/41-47 (1758764)
49	exp animals/ not humans/ (5427969)
50	48 not 49 (1623598)
51	36 and 50 (357)
52	37 or 39 or 40 or 51 (583)
53	remove duplicates from 52 (582)
Total hits: 582	

INAHTA

Search name: INAHTA	
Search date: 06.03.2026	
ID #	Search query,"Hits","Searched At"
24	((azd9291) OR ("azd 9291") OR (mereletinib*) OR (tagrisso*) OR (osimertinib*) OR (jnj6372) OR ("jnj 6372") OR (jnj61186372) OR ("jnj 61186372") OR (jnj611*) OR ("jnj 611") OR (jnj372) OR ("jnj 372") OR (rybrevant*) OR (Amivantamab*)) AND ((mNSCLC*) OR (aNSCLC*) OR (NSCLC*) OR ((nonsmall OR non-small) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR neoplasm* OR malignan*)) OR ("Carcinoma Non-Small-Cell Lung"[mhe])), "29", "2026-03-06T14:35:32.000000Z"
23	((azd9291) OR ("azd 9291") OR (mereletinib*) OR (tagrisso*) OR (osimertinib*) OR (jnj6372) OR ("jnj 6372") OR (jnj61186372) OR ("jnj 61186372") OR (jnj611*) OR ("jnj 611") OR (jnj372) OR ("jnj 372") OR (rybrevant*) OR (Amivantamab*)) AND ((mNSCLC*) OR (aNSCLC*) OR (NSCLC*) OR ((nonsmall OR non-small) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR neoplasm* OR malignan*)) OR ("Carcinoma Non-Small-Cell Lung"[mhe])), "29", "2026-03-06T14:35:15.000000Z"
22	(azd9291) OR ("azd 9291") OR (mereletinib*) OR (tagrisso*) OR (osimertinib*) OR (jnj6372) OR ("jnj 6372") OR (jnj61186372) OR ("jnj 61186372") OR (jnj611*) OR ("jnj 611") OR (jnj372) OR ("jnj 372") OR (rybrevant*) OR (Amivantamab*), "29", "2026-03-06T14:34:37.000000Z"
21	azd9291, "1", "2026-03-06T14:33:41.000000Z"
20	"azd 9291", "0", "2026-03-06T14:33:28.000000Z"
19	mereletinib*, "0", "2026-03-06T14:33:11.000000Z"
18	tagrisso*, "2", "2026-03-06T14:32:45.000000Z"
17	osimertinib*, "22", "2026-03-06T14:32:30.000000Z"
16	jnj6372, "0", "2026-03-06T14:32:05.000000Z"
15	"jnj 6372", "0", "2026-03-06T14:31:56.000000Z"
14	jnj61186372, "0", "2026-03-06T14:31:26.000000Z"
13	"jnj 61186372", "0", "2026-03-06T14:31:15.000000Z"
12	jnj611*, "0", "2026-03-06T14:29:50.000000Z"
11	"jnj 611", "0", "2026-03-06T14:29:36.000000Z"
10	jnj372, "0", "2026-03-06T14:29:00.000000Z"
9	"jnj 372", "0", "2026-03-06T14:28:50.000000Z"
8	rybrevant*, "0", "2026-03-06T14:27:24.000000Z"
7	Amivantamab*, "6", "2026-03-06T14:26:51.000000Z"
6	(mNSCLC*) OR (aNSCLC*) OR (NSCLC*) OR ((nonsmall OR non-small) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR neoplasm* OR malignan*)) OR ("Carcinoma Non-Small-Cell Lung"[mhe]), "429", "2026-03-06T14:26:21.000000Z"
5	mNSCLC*, "0", "2026-03-06T14:26:01.000000Z"
4	aNSCLC*, "0", "2026-03-06T14:25:52.000000Z"
3	NSCLC*, "171", "2026-03-06T14:25:38.000000Z"
2	(nonsmall OR non-small) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR neoplasm* OR malignan*), "392", "2026-03-06T14:25:03.000000Z"
1	"Carcinoma Non-Small-Cell Lung"[mhe], "361", "2026-03-06T14:22:36.000000Z"
Total hits: 29	



HTA Austria

Austrian Institute for
Health Technology Assessment
GmbH