

Project Protocol

Amivantamab Plus Lazertinib vs Osimertinib Plus Chemotherapy in the First-line Treatment Of Advanced Non-Small Cell Lung Cancer

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Duration: Q1 2026 to Q2 2026 (2 PM)

Resources: 4 PM

Language: English (with German summary)

Background:

Lung cancer is the leading cause of cancer-related mortality worldwide. In Austria, over 5,200 new cases were recorded in 2023, making it the second most common malignancy for both sexes. Despite novel treatments, 5-year overall survival remains around 20%, comparable to the European level [1]. Worldwide, non-small cell lung cancer (NSCLC) represents 85% of lung cancer cases and has a high mortality rate. Smoking is the main cause of NSCLC, accounting for about 85% of cases [2].

NSCLC develops from the lung's epithelial cells and is categorised into three main subtypes: adenocarcinoma, squamous cell carcinoma and large cell carcinoma, of which adenocarcinoma is the most prevalent. Epidermal growth factor receptor (EGFR) mutations drive the development of NSCLC and serve as targets for personalised treatments, with 85-90% representing exon 19 deletions (Ex19del) or exon 21 L858R substitutions [2].

In the first-line treatment of patients with these mutations, both the 2026 NCCN and Onkopedia guidelines recommend osimertinib monotherapy, osimertinib plus platinum-based chemotherapy and pemetrexed or amivantamab plus lazertinib [3, 4].

Osimertinib (Tagrisso®), a third-generation, irreversible, central nervous system–active EGFR-tyrosine kinase inhibitor (TKI), was first authorised in the EU in February 2016. Its indication was expanded in July 2024 to include the combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations [5].

Amivantamab is an EGFR–MET bispecific antibody with immune cell–directing activity and a multitargeted mechanism of action. Lazertinib is a third-generation central nervous system–penetrant EGFR TKI with efficacy against activating mutations in EGFR. The intravenous formulation of amivantamab (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. Furthermore, in June 2025 the subcutaneous formulation of amivantamab was authorised [6]. Both amivantamab plus lazertinib and osimertinib plus chemotherapy are approved for the same indication, yet their comparative clinical effectiveness and safety, along with their organisational and economic implications for the healthcare system, are unclear.

Project aims:

The systematic health technology assessment will evaluate 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.

Research question:

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:

RQ 1: What is the comparative effectiveness and safety of amivantamab (i.v./s.c.) plus lazertinib versus osimertinib plus chemotherapy?

RQ 2: What is the comparative effectiveness and safety of amivantamab (i.v.) plus lazertinib versus amivantamab (s.c.) plus lazertinib?

RQ 3: What are the organisational aspects of the treatment with amivantamab (i.v./s.c.) plus lazertinib compared to osimertinib plus chemotherapy?

RQ 4: What are the economic aspects of the treatment with amivantamab (i.v./s.c.) plus lazertinib compared to osimertinib plus chemotherapy?

Methods:

A systematic literature search will be conducted in four databases together with a hand search for systematic reviews, randomised controlled trials, non-randomised controlled trials and HTA reports. Relevant references on the organisational and economic aspects will also be identified. Additionally, clinical trial registries will be searched for ongoing clinical trials. Records will be screened independently and in a blinded manner by two assessors at the abstract and full-text level. Data extraction will be systematically performed by one assessor and cross-checked by a second assessor.

The risk of bias in the included studies will be assessed using the Cochrane Risk of Bias (RoB) tool v.2 for randomised placebo-controlled studies, ROBINS-I for non-randomised studies and ROBIS for systematic reviews and HTAs. The strength of evidence will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

The extracted data will then be synthesised narratively, with a focus on summarising the efficacy and safety of the interventions. The organisational aspects will be extracted from included clinical studies and records identified by hand search, supplemented by input from clinical experts. The results will be described narratively.

For the economic aspects, available evidence, including published cost-effectiveness analyses, will be summarised narratively. In addition, a budget impact analysis of amivantamab (i.v./s.c.) plus lazertinib in comparison to osimertinib plus chemotherapy will be conducted for the Austrian context.

Inclusion criteria (PICO):

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: organisational aspects RQ 4: cost-effectiveness (ICER)
Study design	■ Systematic reviews, HTAs and ITCs ■ RCTs ■ NRCs ■ SATs ■ CEA (for RQ 4) Excluded: in vitro, 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, SAEs ... serious adverse events, SATs ... single-arm trials

Timetable:

Period	Tasks
Q1 2026	Scoping and finalising the project protocol
Q1 2026	■ Systematic literature search and manual searches ■ Selection of literature
Q1 2026	Data extraction and quality assessment
Q1-Q2 2026	Conducting budget impact analysis
Q2 2026	Writing the report
Q2 2026	Internal and external review
Q2 2026	Layout and publication

References:

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