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Tarlatamab (IMDYLLTRA®) for the treatment of extensive-stage small cell lung cancer

Health Technology Assessment

Final Report

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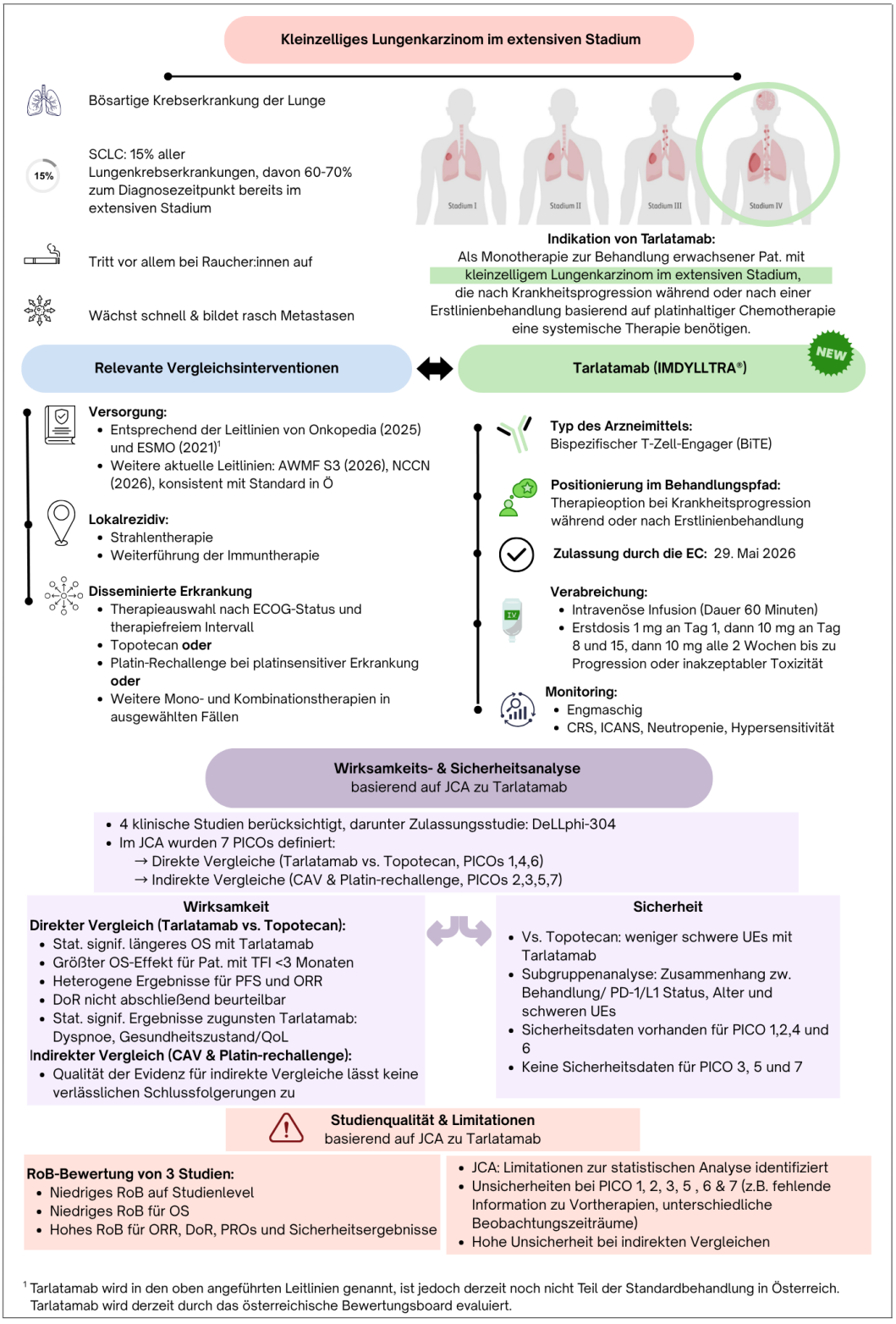
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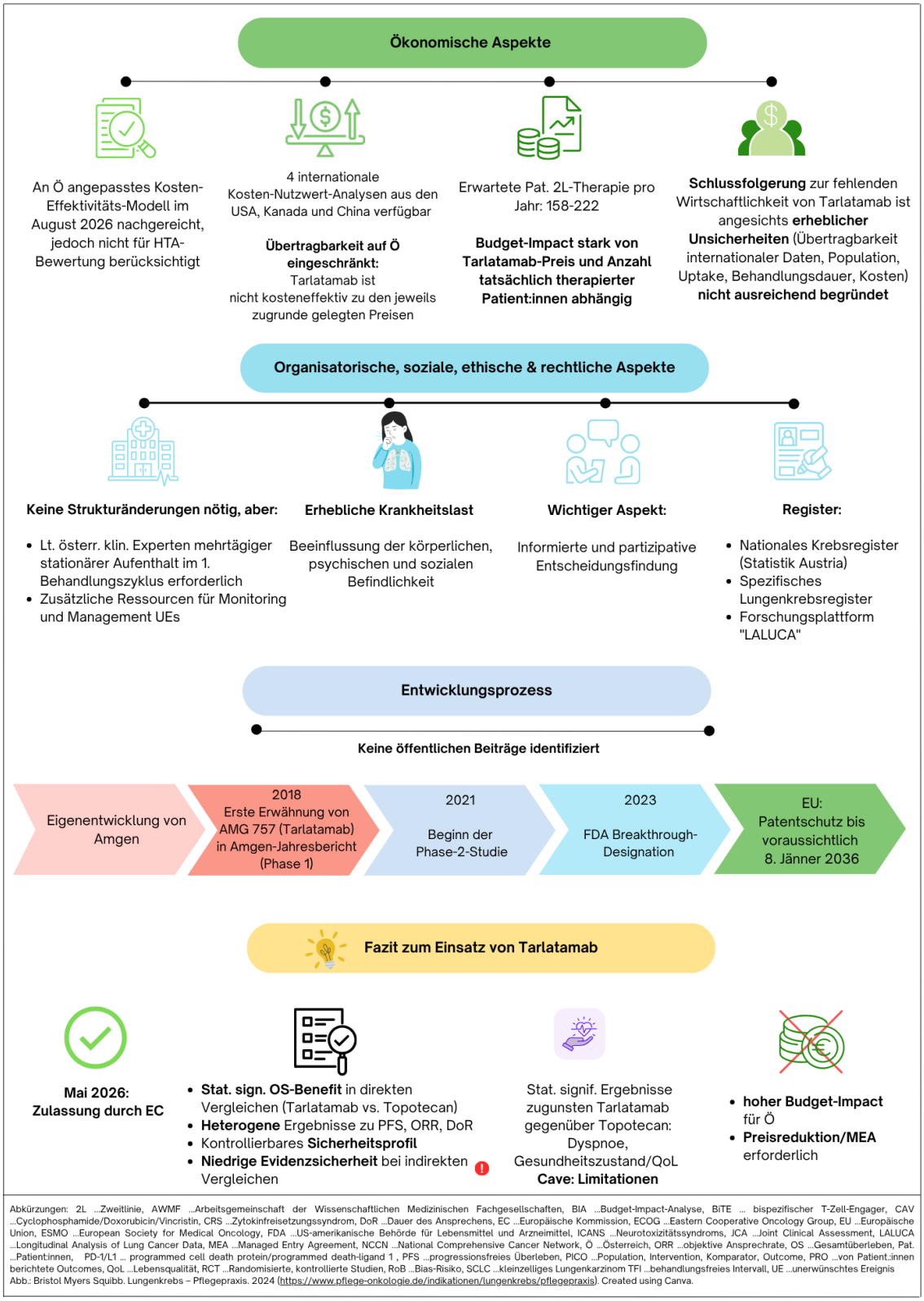
List of abbreviations

1L .....first-line
AE(s) .....adverse event(s)
AIC .....Akaike information criterion
AIHTA .....Austrian Institute for Health Technology Assessment
AJ.....adjustment
ASP.....average sales price
ASTCT.....American Society for Transplantation and Cell Therapy
ATMP.....Advanced Therapy Medicinal Product
AUC .....area under the curve
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BIA .....budget impact analysis
BO.....best overall response
BPI-SF .....Brief Pain Inventory – Short Form
BSC .....best supportive care
CAD .....Canadian dollar
CAV.....cyclophosphamide + doxorubicin + vincristine
CDA-AMC....Canada's Drug Agency
CFI .....chemotherapy-free interval
CHEC.....Consensus on Health Economic Criteria
CHEC.....Checklist for Health Economic Evaluations
CHEERS.....Consolidated Health Economic Evaluation Reporting Standards
CHMP.....Committee for Medicinal Products for Human Use
CI.....confidence interval
CrI .....Credible interval
CMS .....Centers for Medicare & Medicaid Services
CR .....complete response
CRS .....cytokine release syndrome
CTCAE .....Common Terminology Criteria for Adverse Events
DCR .....disease control rate
DLL3.....delta-like ligand 3
DoR .....duration of response
EAG.....External Assessment Group
EC.....European Commission
ECG.....electrocardiogram
ECOG PS.....Eastern Cooperative Oncology Group Performance Status
EMA.....European Medicines Agency
EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Core 30
EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer 13
EPAR .....European Public Assessment Report
EQ-5D-5L.....EuroQol questionnaire with 5 dimensions
ESMO.....European Society For Medical Oncology
ESS .....effective sample size
ES-SCLC .....extensive-stage small cell lung cancer
FACT-G.....Functional Assessment of Cancer Therapy – General
FDA .....Food and Drug Administration
FM.....final magnitude (of clinical benefit grade)
GLMM .....Generalised linear mixed model
GÖG .....Gesundheit Österreich GmbH
HR.....hazard ratio
HRQoL .....health-related quality of life
HTA .....Health Technology Assessment
HTACG.....Coordination Group on Health Technology Assessment
HTD.....health technology developer
ICANS.....Immune effector cell-associated neurotoxicity syndrome
ICD .....International Statistical Classification of Diseases and Related Health Problems
Int.....Intention
ICER .....Incremental cost-effectiveness ratio
ITC .....indirect treatment comparison
IV.....Intravenous
JCA.....Joint Clinical Assessment
LALUCA .....Longitudinal Analysis of Lung Cancer Data

LC.....lung cancer
LDH.....lactate dehydrogenase
LKF.....Austrian hospital reimbursement catalogue — Leistungsorientierte Krankenanstaltenfinanzierung
LS.....least squares
LS-SCLC.....limited-stage small cell lung cancer
MAH.....Marketing Authorisation Holder
MAIC.....matching-adjusted indirect treatment comparison
MEA.....managed entry arrangement
MG.....median gain
MMRM.....Mixed model for repeated measures
n/N.....number
NA.....not available
n.a.....not applicable
NC.....non-curative
NCCN.....National Comprehensive Cancer Network
NE.....not estimable
NHS.....National Health Service
NICE.....National Institute for Health and Care Excellence
NMA.....network meta-analysis
NR.....not reported
NRDL.....National Reimbursement Drug List (China)
NSCLC.....Non-Small Cell Lung Cancer
OR.....Odds ratio
ORR.....objective response rate
OS.....overall survival
PGIC.....Patient Global Impression of Change
PGIS.....Patient Global Impression of Severity
PD.....progressive disease
PD-(L)1.....programmed death-(ligand) 1
PFS.....progression-free survival
PICO.....Population, Intervention, Comparator, Outcome
PM.....preliminary grade
PPRI.....Pharmaceutical Pricing and Reimbursement Information
PR.....partial response
PRIME.....Priority Medicines Scheme
PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO.....patient-reported outcome
PSA.....probabilistic sensitivity analysis
PSS.....Personal Social Services
QALY.....Quality-adjusted life year
QoL.....quality of life
RCT.....randomised controlled trial
RDI.....relative dose intensity
RECIST.....Response Evaluation Criteria in Solid Tumors
RFI.....recurrence-free interval
RoB.....risk of bias
RR.....relative risk
SAE.....serious adverse event
SAP.....Statistical analysis plan
SCLC.....Small cell lung cancer
SFU.....safety follow-up
SmPC.....Summary of Product Characteristic
SoC.....Standard of care
SOC.....System Organ Class
Ss.....statistisch signifikant
ST.....standard treatment
TEAE.....treatment-emergent adverse event
TFI.....treatment-free interval
TNM.....Tumour-node-metastasis
TRAE.....treatment-related adverse event
TRT.....Tumorregister Tirol
TTE.....time-to-event
TTP.....time-to-progression
TTR.....time-to-response
US.....United States
UK CAS.....UK Cancer Analysis Service
UK.....United Kingdom
VAS.....visual analogue scale
WHO.....World Health Organization
WHO-ICTRP WHO International Clinical Trials Registry Platform
WHOQOL-100 World Health Organization Quality of Life-100
WTP.....Willingness-to-pay

Ergebnisse auf einen Blick





Abkürzungen: 2L ...Zweitlinie, AWMF ...Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, BIA ...Budget-Impact-Analyse, BiTE ... bispezifischer T-Zell-Engager, CAV ...Cyclophosphamide/Doxorubicin/Vincristin, CRS ...Zytokinfreisetzungssyndrom, DoR ...Dauer des Ansprechens, EC ...Europäische Kommission, ECOG ...Eastern Cooperative Oncology Group, EU ...Europäische Union, ESMO ...European Society for Medical Oncology, FDA ...US-amerikanische Behörde für Lebensmittel und Arzneimittel, ICANS ...Neurotoxizitätssyndroms, JCA ...Joint Clinical Assessment, LALUCA ...Longitudinal Analysis of Lung Cancer Data, MEA ...Managed Entry Agreement, NCCN ...National Comprehensive Cancer Network, Ö ...Österreich, ORR ...objektive Ansprechrate, OS ...Gesamtüberleben, Pat. ...Patient:innen, PD-1/L1 ... programmed cell death protein/programmed death-ligand 1 , PFS ...progressionsfreies Überleben, PICO ...Population, Intervention, Komparator, Outcome, PRO ...von Patient:innen berichtete Outcomes, QoL ...Lebensqualität, RCT ...Randomisierte, kontrollierte Studien, RoB ...Bias-Risiko, SCLC ...kleinzelliges Lungenkarzinom TFI ...behandlungsfreies Intervall, UE ...unerwünschtes Ereignis
Abb.: Bristol Myers Squibb. Lungenkrebs – Pflegepraxis. 2024 (https://www.pflege-onkologie.de/indikationen/lungenkrebs/pflegepraxis). Created using Canva.

Zusammenfassung

Der vorliegende Health Technology Assessment (HTA)-Bericht evaluiert Tarlatamab (IMDYLLTRA®) als Monotherapie zur Behandlung erwachsener Patient:innen mit kleinzelligem Lungenkarzinom im extensiven Stadium, die nach einer Krankheitsprogression während oder nach einer platinbasierten Erstlinien-Chemotherapie eine systemische Therapie benötigen. Tarlatamab war Gegenstand einer gemeinsamen klinischen Bewertung (Joint Clinical Assessment, JCA), die gemäß der Verordnung über die Bewertung von Gesundheitstechnologien (Verordnung [EU] 2021/2282) durchgeführt wurde. Die in diesem Bericht dargestellte klinische Evidenz basiert daher auf dem JCA.

Beschreibung der Erkrankung und Behandlungsoptionen

Das kleinzellige Lungenkarzinom (small cell lung cancer, SCLC) ist ein besonders aggressiver histologischer Subtyp des Lungenkarzinoms, der durch rasches Tumorwachstum und eine frühe Metastasierung gekennzeichnet ist. In der klinischen Praxis hat sich anstelle der üblichen Tumour-Node-Metastasis-Klassifikation (TNM-Klassifikation) ein vereinfachtes zweistufiges System etabliert: das auf einen Hemithorax begrenzte kleinzellige Lungenkarzinom (limited-stage small cell lung cancer, LS-SCLC), das mit kurativer Zielsetzung behandelt wird, und das fortgeschrittene kleinzellige Lungenkarzinom (extensive-stage small cell lung cancer, ES-SCLC), das durch eine Ausbreitung über einen Hemithorax hinaus, einschließlich Fernmetastasen, gekennzeichnet ist und nicht kurativer (palliativer) Zielsetzung behandelt wird. Zentrale Therapieziele beim ES-SCLC sind die Verlängerung des Gesamtüberlebens, die Krankheitskontrolle und der Erhalt der Lebensqualität. Der vorliegende Bericht konzentriert sich auf ES-SCLC.

Die Mehrheit der Patient:innen mit SCLC (60-70 %) befindet sich bereits zum Zeitpunkt der Diagnose im fortgeschrittenen Stadium. Tabakrauchen gilt als wichtigster Risikofaktor und liegt bei nahezu allen Betroffenen vor (etwa 98 %). Die Gesamtprognose ist ungünstig; die 5-Jahres-Überlebensrate liegt unter 10 %. In Österreich wird die Prävalenz des SCLC auf etwa 2.600 Personen geschätzt. Jährlich treten rund 617 Neuerkrankungen auf, von denen 581 dem fortgeschrittenen Stadium zuzuordnen sind. SCLC-spezifische Mortalitätsdaten sind auf nationaler Ebene nicht verfügbar.

Die österreichische klinische Praxis beim ES-SCLC orientiert sich in erster Linie an den Leitlinien der European Society for Medical Oncology (ESMO) (2021) und von Onkopedia (2025), die weitgehend mit der aktuelleren Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)-S3-Leitlinie (Version 5.01, 2026) und der National Comprehensive Cancer Network (NCCN)-Leitlinie (Version 2.2026) übereinstimmen. Therapieentscheidungen in der Zweitlinie nach oder während einer Chemoimmuntherapie richten sich nach dem Progressionsmuster: Eine lokale Progression beziehungsweise ein lokales Rezidiv wird mittels thorakaler Strahlentherapie mit anschließender Fortführung der Immuntherapie behandelt. Bei disseminierter Erkrankung erfolgt eine Einteilung nach der Bestrahlbarkeit der progredienten Läsion(en) und bei nicht bestrahlbarer Progression nach dem Eastern Cooperative Oncology Group Performance Status (ECOG PS) und dem chemotherapiefreien Intervall. Die Therapie unterscheidet sich daher in Abhängigkeit von der Platinsensitivität und dem rezidivfreien Intervall (recurrence-free interval, RFI) beziehungsweise dem therapiefreien Intervall (treatment-free interval, TFI) und umfasst folgende Behandlungsoptionen:

- Topotecan und das Cyclophosphamid/Doxorubicin/Vincristin-Regime (CAV) sind derzeitige Therapieoptionen für platinresistente Patient:innen (TFI <3 Monate);
- eine erneute platinbasierte Therapie, Topotecan und CAV sind Optionen für platinsensitive Patient:innen (TFI ≥3 Monate); Topotecan oder CAV können bei Patient:innen mit einem RFI ≤6 Monate oder bei Patient:innen eingesetzt werden, die für eine erneute platinbasierte Therapie nicht geeignet sind;
- Cisplatin oder Carboplatin in Kombination mit Etoposid können bei Patient:innen mit einem RFI >6 Monate eingesetzt werden, sofern diese für eine erneute platinbasierte Therapie geeignet sind.

Tarlatamab wird bereits in den klinischen Leitlinien für alle vier Subgruppen als Therapieoption genannt. Die Leitlinien von Onkopedia und der AWMF-S3 unterscheiden sich dabei lediglich hinsichtlich des empfohlenen Schwellenwerts für das therapiefreie Intervall (TFI). Der Einsatz von Tarlatamab in Österreich wird derzeit im Rahmen des Bewertungsverfahrens durch das österreichische Bewertungsboard evaluiert und ist Gegenstand des vorliegenden Berichts.

Überblick über das neue Arzneimittel

Tarlatamab ist ein neuartiger bispezifischer T-Zell-Engager, der gleichzeitig an Tumorzellen und T-Zellen bindet und diese dadurch in unmittelbare räumliche Nähe bringt. Dies führt zur Aktivierung der T-Zellen und in weiterer Folge zum Absterben der Tumorzellen. Die empfohlene Dosierung beträgt zunächst 1 mg an Tag 1, gefolgt von 10 mg an den Tagen 8 und 15 sowie anschließend alle zwei Wochen. Die Verabreichung erfolgt als intravenöse Infusion bis zum Fortschreiten der Erkrankung oder bis zum Auftreten einer nicht akzeptablen Toxizität.

Tarlatamab ist als Monotherapie zur Behandlung erwachsener Patient:innen mit ES-SCLC indiziert, die nach einer Krankheitsprogression während oder nach einer platinbasierten Erstlinienchemotherapie eine systemische Therapie benötigen. Am 26. März 2026 erhielt das Arzneimittel eine positive Empfehlung des Committee for Medicinal Products for Human Use (CHMP) der European Medicines Agency (EMA) und wurde am 29. Mai 2026 von der Europäischen Kommission zugelassen. Es wurde am 12. Jänner 2024 als Orphan-Arzneimittel ausgewiesen und unterliegt einer zusätzlichen Überwachung. In den Vereinigten Staaten von Amerika (USA) erteilte die Food and Drug Administration (FDA) im Jahr 2024 zunächst eine beschleunigte Zulassung, gefolgt von einer regulären Zulassung für dieselbe Indikation am 19. November 2025.

Wirksamkeit und Sicherheit

Die klinische Evidenz basiert auf der im Rahmen des Joint Clinical Assessment (JCA) bewerteten Evidenzbasis. Diese umfasst die pivotale randomisierte kontrollierte Phase-III-Studie DeLLphi-304 sowie drei ältere Studien, die für indirekte Behandlungsvergleiche (indirect treatment comparisons, ITCs) herangezogen wurden. DeLLphi-304 ist methodisch robust, die Evidenzbasis insgesamt jedoch heterogen. Die Vertrauenswürdigkeit der Evidenz aus den ITCs ist sehr niedrig.

Im JCA wurden mehrere PICO-Fragestellungen mit unterschiedlichen Populationen und Vergleichstherapien bewertet. Die drei direkt mit Topotecan verglichenen Populationen unterschieden sich insbesondere hinsichtlich des therapie- bzw. rezidivfreien Intervalls und damit der Platinsensitivität. Im Vergleich zu Topotecan zeigte Tarlatamab in allen drei Populationen einen statistisch signifikanten Vorteil im Gesamtüberleben (overall survival, OS). Der Vorteil war bei platinresistenten Patient:innen am größten (11,1 vs. 5,8 Monate; hazard ratio [HR] 0,49; 95 % KI 0,33-0,73), bei Patient:innen mit einem RFI ≤6 Monaten intermediär ausgeprägt (11,2 vs. 6,4 Monate; HR 0,58; 95 % KI 0,43-0,79) und bei platinsensitiven Patient:innen am geringsten (13,9 vs. 11,4 Monate; HR 0,63; 95 % KI 0,42-0,95). Die Ergebnisse zum progressionsfreien Überleben (progression-free survival, PFS), zur objektiven Ansprechrate (objective response rate, ORR) sowie zu von Patient:innen berichteten Endpunkten (patient-reported outcomes, PROs) und zur gesundheitsbezogenen Lebensqualität (health-related quality of life, HRQoL) in den PICO-Analysen gegenüber Topotcan waren heterogener und fielen nur in einigen Analysen zugunsten von Tarlatamab aus. Ein statistisch signifikanter Vorteil im medianen PFS wurde ausschließlich in der Population mit einem RFI ≤6 Monaten beobachtet. Zu den identifizierten Limitationen zählen das offene Studiendesign, Unterschiede in den PRO-Rücklaufquoten und die längere Behandlungsdauer unter Tarlatamab. Klinische Expert:innen stellten darüber hinaus die klinische Relevanz einer Unterteilung der Patient:innen nach Platinsensitivität infrage und wiesen darauf hin, dass der Wirkmechanismus von Tarlatamab unabhängig von der Platinsensitivität ist.

Hinsichtlich der Sicherheit war Tarlatamab im Vergleich zu Topotecan mit weniger schweren unerwünschten Ereignissen (adverse events, AEs) verbunden, wies jedoch ein charakteristisches Toxizitätsprofil auf. Hierzu zählen insbesondere das Zytokin-Freisetzungssyndrom (cytokine release syndrome, CRS; etwa 50-60 %) und das Immuneffektorzell-assoziierte Neurotoxizitätssyndrom (immune effector cell-associated

neurotoxicity syndrome, ICANS; 7,1 %). Klinische Expert:innen stuften das CRS jedoch als beherrschbar sowie überwiegend früh auftretend und niedriggradig ein.

Die Evidenz aus den ITCs zum Vergleich von Tarlatamab mit CAV, Carboplatin plus Etoposid und einer erneuten platinbasierten Therapie war schwach und weitgehend explorativ. Dies ist hauptsächlich darauf zurückzuführen, dass die historischen Vergleichsstudien vor dem routinemäßigen Einsatz von programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1)-Inhibitoren in der Erstlinientherapie durchgeführt wurden, wodurch die Vergleichbarkeit der Studienpopulationen eingeschränkt ist. In den ITCs, deren Evidenz von sehr niedriger Vertrauenswürdigkeit bis nicht verlässlich reichte, fiel das mediane OS im Vergleich mit CAV nominell zugunsten von Tarlatamab aus und war gegenüber Carboplatin plus Etoposid statistisch signifikant länger (13,9 vs. 7,5 Monate; HR 0,61; p=0,029; 95 % KI 0,39-0,95). Demgegenüber fiel das mediane PFS numerisch zugunsten der erneuten platinbasierten Therapie aus (HR 3,62; 95 % KI 1,65-7,94). Insgesamt zeigte Tarlatamab gegenüber Topotecan einen Vorteil im medianen OS bei gleichzeitig charakteristischem, aber beherrschbarem Sicherheitsprofil. Die Evidenz zu den meisten anderen Endpunkten als dem OS war jedoch mit einem hohen Verzerrungsrisiko verbunden. Die ITCs wiesen eine sehr niedrige Vertrauenswürdigkeit der Evidenz auf und erlaubten keine verlässlichen Schlussfolgerungen. Die klinischen Expert:innen bewerteten Tarlatamab insgesamt als relevante Therapieoption und hoben dessen Wirksamkeit unabhängig von der Platinsensitivität sowie dessen Wirksamkeit bei beteiligter ZNS-Erkrankungen hervor. Gleichzeitig wiesen sie darauf hin, dass Patient:innen in der klinischen Routinepraxis einen schlechteren Gesundheitszustand aufweisen können als die Studienpopulation.

Ökonomische Aspekte

Das vertriebsberechtigte Unternehmen legte für Tarlatamab kein pharmakoökonomisches Modell für Österreich im Rahmen der HTA-Berichterstellung vor. Vier identifizierte publizierte Kosten-Nutzwert-Analysen (ab der Drittlinie: Canadian Drug Agency – Agence des médicaments du Canada [CDA-AMC] [2025]; National Institute for Health and Care Excellence [NICE] [2025]; Zweitlinie: Zheng et al. [2026]; Liu et al. [2026]), die auf den Studien DeLLphi-301 oder DeLLphi-304 basierten, kamen unter den jeweiligen länderspezifischen Annahmen und Zahlungsbereitschaftsschwellen übereinstimmend zu dem Ergebnis, dass Tarlatamab nicht kosteneffektiv ist. Die berichteten inkrementellen Kosten-Nutzwert-Verhältnisse (incremental cost-effectiveness ratios, ICERs) der Basisfallanalysen variierten aufgrund unterschiedlicher Modellannahmen und zugrunde liegender Kostendaten erheblich. Sie lagen in Kanada bei etwa € 121.000 bis € 381.000 pro qualitätsadjustiertes Lebensjahr (quality-adjusted life year, QALY), im Vereinigten Königreich bei € 35.000 bis € 42.000 pro QALY unter Berücksichtigung einer vertraulichen kommerziellen Vereinbarung und eines Schweregradgewichts der Erkrankung von 1,7, in den Vereinigten Staaten bei € 638.000 bis € 1.200.000 pro QALY (Zheng et al. [2026]; Liu et al. [2026]) und in China bei etwa € 370.000 pro QALY (Liu et al. [2026]). Sämtliche ICER-Schätzungen überschritten die jeweiligen länderspezifischen Zahlungsbereitschaftsschwellen (willingness-to-pay thresholds, WTP-Schwellenwerte). Um die Kosteneffektivität zu erreichen, wären erhebliche Preisreduktionen erforderlich. Diese wurden für Kanada auf etwa 68-86 %, für die Vereinigten Staaten von Zheng et al. (2026) auf 56 % und von Liu et al. für die Vereinigten Staaten und China auf 80-95 % geschätzt. Die Übertragbarkeit dieser Ergebnisse auf Österreich ist eingeschränkt.

Darüber hinaus wurde keine Budget-Impact-Analyse (BIA) für Österreich vorgelegt. Auf Grundlage der über das österreichische Gesundheitsministerium erhobenen Fabrikabgabepreise ist Tarlatamab (IMDYLLTRA®) zu einem Preis von € [redacted] pro 1-mg-Durchstechflasche und € [redacted] pro 10-mg-Durchstechflasche verfügbar. Daraus ergeben sich geschätzte direkte medizinische Gesamtkosten von € 160.712 pro Patient:in bei einer medianen Behandlungsdauer von fünf Zyklen. Davon entfallen etwa [redacted] % auf die Arzneimittelbeschaffung und [redacted] % auf die Verabreichung. Zum Vergleich betragen die geschätzten direkten medizinischen Kosten der derzeitigen Behandlungsalternativen € 21.654 pro Patient:in für Topotecan, € 3.904 für CAV und € 14.454 für eine erneute platinbasierte Therapie. Unter der Annahme von jährlich 158-222 zu behandelnden Patienten:innen wurden drei Szenarien mit zunehmender Inanspruchnahme von Tarlatamab modelliert. Auf Grundlage der Schätzungen zu den Patient:innenzahlen des vertriebsberechtigten Unternehmens steigt die Nettobudgetauswirkung von € [redacted] im ersten Jahr auf € 1[redacted] im dritten Jahr, entsprechend einer kumulativen Budgetauswirkung von € [redacted] über

drei Jahre. Im konservativen Szenario mit einer Inanspruchnahme von [redacted]% steigt diese von € [redacted] auf € [redacted], entsprechend einer kumulativen Budgetauswirkung von € [redacted]. Im optimistischen Szenario mit einer Inanspruchnahme von [redacted]% steigt sie von € [redacted] auf € [redacted], entsprechend einer kumulativen Budgetauswirkung von € [redacted] über drei Jahre. Diese Schätzungen unterliegen einer erheblichen Unsicherheit hinsichtlich der Anzahl infrage kommender Patient:innen, der tatsächlichen Versorgungspraxis und der verfügbaren Kostendaten.

Soziale, organisatorische, ethische und rechtliche Aspekte

Für die Integration von Tarlatamab in die österreichische klinische Praxis sind keine wesentlichen strukturellen Veränderungen zu erwarten. Organisatorische Anpassungen entsprechend den spezifischen Behandlungsprotokollen werden jedoch erforderlich sein. Klinische Expert:innen empfehlen beispielsweise eine zwei- bis dreitägige stationäre Aufnahme nach der Verabreichung der ersten zwei oder drei Dosen, um unerwünschte Ereignisse frühzeitig behandeln zu können. Dies würde den Ressourcenbedarf erhöhen. Darüber hinaus wurde die Bedeutung entsprechender Schulungen für Personal im Umgang mit bispezifischen Antikörpern wie Tarlatamab hervorgehoben.

SCLC führt bei den betroffenen Patient:innen zu einer erheblichen Krankheitslast und beeinflusst deren körperliche, psychische und soziale Befindlichkeit. Die Perspektive von Patient:innen ist in diesem Bericht ausschließlich auf Grundlage der publizierten Literatur dargestellt, da es trotz intensiver Bemühungen nicht möglich war, Patient:innen für die Teilnahme an der Befragung im Rahmen der HTA-Berichterstellung zu gewinnen. Auch im JCA zu Tarlatamab wurden keine Patient:innen einbezogen. Die Darstellung der (kollektiven) Perspektive von Betreuenden wird durch die Beteiligung eines Mitglieds einer österreichischen Selbsthilfegruppe ermöglicht. Auf europäischer Ebene konnte im Rahmen des JCA zu Tarlatamab ebenfalls eine betreuende Person eingeschlossen werden.

Ein relevanter Aspekt, der im Rahmen der Erstellung dieser Bewertung identifiziert wurde, betrifft den Prozess der Therapieentscheidung. Nach Einschätzung österreichischer klinischer Expert:innen ist eine offene Kommunikation über verfügbare Therapieoptionen und deren potenzielle Auswirkungen wesentlich, um Patient:innen eine informierte Entscheidungsfindung zu ermöglichen.

Das Österreichische Nationale Krebsregister erfasst epidemiologische Daten zu Lungenkrebsfällen. Ein spezifisches klinisches Lungenkrebsregister zielt darauf ab, die Behandlungsqualität durch detaillierte Datenanalysen und die Zusammenarbeit zwischen Krankenhäusern zu verbessern. Darüber hinaus dokumentiert die österreichische Forschungsplattform LALUCA (Longitudinal Analysis of Lung Cancer Data) repräsentative Daten zu molekularen Untersuchungen, zur Abfolge systemischer Therapien und anderer Behandlungsmodalitäten sowie zum Krankheitsverlauf von Patient:innen mit Lungenkrebs.

Öffentliche Investition

Tarlatamab wurde von Amgen, einem pharmazeutischen Unternehmen mit Sitz in den USA, entwickelt. Vor der FDA-Zulassung wurden keine Übernahmen, Fusionen, Lizenzvereinbarungen oder identifizierbare öffentliche Beiträge im Zusammenhang mit der Entwicklung von Tarlatamab festgestellt. Tarlatamab und die damit verbundenen bifunktionalen Polypeptide sind durch Patente geschützt, deren Ablauf für den 8. Januar 2036 erwartet wird.

Weitere Entwicklungen (Landscape overview)

Es wurden 17 laufende klinische Studien zu Tarlatamab identifiziert. Die meisten untersuchen Tarlatamab beim SCLC in unterschiedlichen Therapielinien und in Kombination mit Chemotherapie, Immuntherapie oder Strahlentherapie. Im Vergleich dazu befinden sich derzeit lediglich drei konkurrierende Arzneimittel für die Post-Platin-Therapiesituation in Entwicklung. Entscheidungen der Europäischen Kommission über die Zulassung werden zu unterschiedlichen Zeitpunkten zwischen 2027 und 2033 erwartet.

Schlussfolgerung

Insgesamt zeigt Tarlatamab gegenüber Topotecan einen statistisch signifikanten Vorteil im medianen Gesamtüberleben bei gleichzeitig charakteristischem, aber nach Einschätzung klinischer Expert:innen grundsätzlich beherrschbarem Sicherheitsprofil. Die Evidenz zu anderen klinischen Endpunkten ist weniger eindeutig, und die indirekten Vergleiche mit weiteren relevanten Therapieoptionen weisen eine sehr niedrige Vertrauenswürdigkeit auf. Darüber hinaus ist die Übertragbarkeit der Studienpopulation auf die klinische Routinepraxis eingeschränkt.

Für Österreich wurden weder ein pharmakoökonomisches Modell noch eine Budget-Impact-Analyse im Rahmen der HTA-Berichterstellung eingereicht. Die verfügbaren internationalen gesundheitsökonomischen Bewertungen deuten übereinstimmend darauf hin, dass Tarlatamab zu den untersuchten Preisen und Annahmen nicht kosteneffektiv ist und erhebliche Preisreduktionen erforderlich wären. Gleichzeitig ist aufgrund der hohen Behandlungskosten mit einer erheblichen Budgetauswirkung zu rechnen. Der Stellenwert von Tarlatamab in der klinischen Versorgung hängt davon ab, ob der beobachtete Überlebensvorteil unter Alltagsbedingungen bestätigt werden kann und wie sich Tarlatamab im Vergleich zu verfügbaren Therapieoptionen unter den gegebenen Preisbedingungen positioniert.

Summary

This health technology assessment (HTA) evaluates tarlatamab (IMDYLLTRA®) monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. Tarlatamab was subject to a Joint Clinical Assessment (JCA), conducted in accordance with the Regulation on Health Technology Assessment (Regulation (EU) 2021/2282). The clinical evidence presented in this report is therefore based on the JCA.

Disease background

Small cell lung cancer (SCLC) is a particularly aggressive histological subtype of lung cancer, characterised by rapid tumour growth and early metastatic spread. Clinically, instead of the standard tumour-node-metastasis (TNM) classification, a simplified two-stage system has become established: limited-stage SCLC (LS-SCLC), confined to one hemithorax and treated with curative intent, and extensive-stage SCLC (ES-SCLC), characterised by spread beyond one hemithorax including distant metastases and treated with non-curative (palliative) intent. Key treatment goals in ES-SCLC are the prolongation of overall survival, disease control, and the preservation of quality of life. The present report focuses on ES-SCLC.

The majority of patients with SCLC (60-70%) are already diagnosed at the extensive stage. Tobacco smoking is considered the main risk factor, present in nearly all affected individuals (approximately 98%). The overall prognosis is poor, with a 5-year survival rate below 10%. In Austria, the prevalence of SCLC is estimated at approximately 2,600 individuals. Around 617 new cases occur annually, of which 581 are attributable to the extensive stage. SCLC-specific mortality data are not available at the national level.

Austrian clinical practice for ES-SCLC is guided primarily by the European Society for Medical Oncology (ESMO) (2021) and Onkopedia (2025) guidelines, which are largely consistent with the more recent Association of the Scientific Medical Societies in Germany (AWMF) S3 guideline (Version 5.01, 2026) and National Comprehensive Cancer Network (NCCN) guideline (Version 2.2026). Second-line treatment decisions after or during chemoimmunotherapy are guided by the pattern of progression: local progression or recurrence is managed with thoracic radiotherapy followed by continued immunotherapy, while disseminated disease is stratified according to whether the progressing lesion(s) are amenable to radiotherapy and, in the case of non-irradiable progression, according to Eastern Cooperative Oncology Group Performance Status (ECOG PS) and the chemotherapy-free interval. The available treatment options therefore differ according to platinum-sensitivity status and the recurrence-free interval (RFI) or treatment-free interval (TFI):

- topotecan and the cyclophosphamide/doxorubicin/vincristine regimen (CAV) are current options for platinum-resistant patients (TFI <3 months);
- platinum rechallenge, topotecan and CAV are options for platinum-sensitive patients (TFI ≥3 months); topotecan or CAV may be used in patients with an RFI ≤6 months or in those unsuitable for platinum rechallenge;
- cisplatin or carboplatin plus etoposide may be used in patients with an RFI >6 months suitable for platinum rechallenge.

Tarlatamab is mentioned as a treatment option across all four subgroups, with the Onkopedia and AWMF-S3 guidelines differing only in their recommended TFI threshold. The use of tarlatamab in Austria is currently being assessed as part of the Austrian Appraisal Board's assessment procedure and is the subject of this report.

Overview of the new medicinal product

Tarlatamab is a novel bispecific T-cell engager that simultaneously binds to tumour cells and T cells, bringing them into close proximity. This activates the T cells, leading to tumour cell death. The recommended dosage is an initial dose of 1 mg on day 1, followed by 10 mg on days 8 and 15 and every two weeks thereafter, administered as an intravenous infusion until disease progression or unacceptable toxicity.

Tarlatamab (IMDYLLTRA®) is indicated as monotherapy for the treatment of adult patients with ES-SCLC who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. On 26 March 2026, the medicinal product received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and was authorised by the European Commission on 29 May 2026. It was designated an orphan medicinal product on 12 January 2024 and is subject to additional monitoring. In the United States, the Food and Drug Administration (FDA) granted accelerated approval in 2024, followed by traditional approval for the same indication on 19 November 2025.

Clinical effectiveness and safety

The clinical evidence is based on the JCA of tarlatamab, which included one pivotal phase 3 randomised controlled trial (DeLLphi-304) and three older studies used for indirect treatment comparisons (ITCs). DeLLphi-304 is methodologically robust, but the overall evidence base is heterogeneous and the certainty of evidence from the ITCs is very low.

In the JCA, several PICO questions with different populations and comparators were assessed. The three populations directly compared with topotecan differed primarily in terms of the treatment-free or relapse-free interval and, consequently, platinum sensitivity. Compared with topotecan, tarlatamab showed a statistically significant overall survival (OS) benefit in all three populations. The benefit was greatest in patients with platinum-resistant disease (11.1 vs 5.8 months; hazard ratio [HR] 0.49; 95% CI 0.33-0.73), intermediate in patients with an RFI ≤6 months (11.2 vs 6.4 months; HR 0.58; 95% CI 0.43-0.79), and smallest in patients with platinum-sensitive disease (13.9 vs 11.4 months; HR 0.63; 95% CI 0.42-0.95). Results for progression-free survival (PFS), objective response rate (ORR), patient-reported outcomes (PROs), and health-related quality of life (HRQoL) in the PICO analyses against topotecan were more heterogeneous and favoured tarlatamab only in some analyses. A statistically significant benefit in median PFS was observed only in the population with an RFI ≤6 months. Identified limitations included the open-label study design, differences in PRO response rates, and the longer treatment duration with tarlatamab. Clinical experts also questioned the clinical relevance of categorising patients according to platinum sensitivity and noted that the mechanism of action of tarlatamab is independent of platinum sensitivity.

Regarding safety, tarlatamab was associated with fewer severe adverse events (AEs) than topotecan, but with distinct toxicities, particularly cytokine release syndrome (CRS; approximately 50-60%) and immune effector cell-associated neurotoxicity syndrome (ICANS; 7.1%). However, clinical experts considered CRS to be manageable and predominantly early and low-grade.

The evidence from the ITCs comparing tarlatamab with CAV, carboplatin plus etoposide and platinum rechallenge was weak and largely exploratory. This was mainly because the historical comparator studies were conducted before the routine use of PD-1/L1 inhibitors as first-line treatment, limiting the comparability of the study populations. Across the ITCs, of which the certainty of evidence ranged from very low to not reliable, median OS nominally favoured tarlatamab over CAV and was statistically significantly longer compared with carboplatin plus etoposide (13.9 vs 7.5 months; HR 0.61; 95% CI: 0.39-0.95; p=0.029), whereas PFS numerically favoured platinum rechallenge (HR 3.62; 95% CI: 1.65-7.94). Overall, tarlatamab demonstrated an OS benefit over topotecan alongside a distinct but manageable safety profile, although most outcomes other than OS were associated with a high risk of bias. The ITCs were of very low certainty and did not permit reliable conclusions. Clinical experts broadly endorsed tarlatamab as a meaningful treatment option, highlighting its efficacy irrespective of platinum-sensitivity and its activity in disease with central nervous system involvement, while cautioning that patients treated in routine clinical practice may be in poorer health than the trial population.

Economic aspects

The health technology developer (HTD) did not submit a pharmacoeconomic model for tarlatamab for Austria during preparation of the HTA report. Four identified published cost-utility analyses (third line or later: Canadian Drug Agency – Agence des médicaments du Canada [CDA-AMC] [2025]; National Institute for Health and Care Excellence [NICE] [2025]; second-line: Zheng et al. [2026]; Liu et al. [2026]), based on the DeLLphi-301 or DeLLphi-304 trials, consistently concluded that tarlatamab was not cost-effective under the respective country-specific assumptions and willingness-to-pay thresholds. The reported base-case incremental cost-effectiveness ratios (ICERs) varied substantially because of differences in model assumptions and underlying cost data. They ranged from approximately €121,000 to €381,000 per quality-adjusted life-year (QALY) in Canada; €35,000 to €42,000 per QALY in the United Kingdom, including a confidential commercial arrangement and a severity weight of 1.7; €638,000 to €1,200,000 per QALY in the United States (Zheng et al. [2026]; Liu et al. [2026]); and approximately €370,000 per QALY in China (Liu et al. [2026]). All ICER estimates exceeded the respective country-specific willingness-to-pay (WTP) thresholds. Achieving cost-effectiveness would require substantial price reductions, estimated at approximately 68-86% in Canada, 56% in the United States according to Zheng et al. (2026), and 80-95% in the United States and China according to Liu et al. The transferability of these results to Austria is limited.

In addition, no budget impact analysis (BIA) was provided by the HTD. Nevertheless, based on ex-factory prices obtained via the Austrian Ministry of Health, tarlatamab (IMDYLLTRA®) is available at € [redacted] per 1-mg vial and € [redacted] per 10-mg vial, resulting in a total direct medical cost per patient of € [redacted] for a median of five treatment cycles, of which approximately [redacted]% is attributable to drug acquisition and [redacted]% to administration. By comparison, the direct medical costs of the current standard of care are €21,654 per patient for topotecan, €3,904 for CAV and €14,454 for platinum-based rechallenge. Considering an estimated 158-222 eligible patients per year, three scenarios with increasing tarlatamab uptake were modelled. The net budget impact ranges from € [redacted] in year 1 to € [redacted] in year 3 under the HTD estimates, resulting in a cumulative three-year impact of € [redacted]; from € [redacted] to € [redacted] under a conservative [redacted]% uptake scenario, with a cumulative impact of € [redacted]; and from € [redacted] to € [redacted] under an optimistic [redacted]% uptake scenario, with a cumulative impact of € [redacted] over three years. These estimates are subject to considerable uncertainty regarding the number of eligible patients, clinical practice and available cost data.

Social, organisational, ethical and legal aspects

Substantial structural changes are not anticipated for the integration of tarlatamab into Austrian clinical practice. However, organisational adjustments in accordance with specific treatment protocols will be necessary. For example, clinical experts recommend hospitalisation for two to three days following administration of the first two or three doses to enable the prompt management of AEs, which would increase resource requirements. In addition, the importance of training of personnel in the use of bispecific antibodies like tarlatamab was emphasised.

SCLC imposes a substantial burden on patients, affecting physical, psychological, social and environmental domains. For this report, information on patients' perspectives could be obtained only from the literature. Despite intensive efforts, no eligible patients could be recruited to complete the questionnaire provided by the AIHTA. No patients were involved in the respective JCA either. The carer perspective was captured through the involvement of one member of an Austrian support group, who provided a collective perspective on patients with lung cancer. At the European level, one carer was successfully involved.

A relevant aspect identified during the preparation of this assessment concerns the treatment decision-making process. Austrian clinical experts emphasised the importance of openly discussing available treatment options and their associated effects to enable patients to make informed decisions.

The Austrian National Cancer Registry collects epidemiological data on lung cancer cases. A specific clinical lung cancer registry aims to improve treatment quality through detailed data analyses and collaboration among hospitals. In addition, the Austrian research platform LALUCA (Longitudinal Analysis of Lung

Cancer Data) documents representative data on molecular testing, sequences of systemic treatment and other treatment modalities, as well as the course of disease in patients with lung cancer.

Public investment aspect

Tarlatamab was developed by Amgen, a pharmaceutical company based in the United States. No acquisitions, mergers, licensing agreements or identifiable public contributions associated with its development before FDA approval were identified. Tarlatamab and its related bifunctional polypeptides are protected by patents that are expected to expire on 8 January 2036.

Landscape overview

Seventeen ongoing clinical trials of tarlatamab were identified. Most focus on SCLC across different treatment lines and investigate tarlatamab in combination with chemotherapy, immunotherapy or radiotherapy. In comparison, only three competing medicinal products are currently being developed for the post-platinum setting, with European Commission decisions on approval expected at different points between 2027 and 2033.

Conclusion

Overall, tarlatamab demonstrated a statistically significant median overall survival benefit compared with topotecan, alongside a distinct but, according to clinical experts, generally manageable safety profile. Evidence for other clinical outcomes was less conclusive, and the indirect comparisons with other relevant treatment options were of very low certainty. In addition, the generalisability of the trial population to routine clinical practice is limited.

No pharmacoeconomic model or budget impact analysis was submitted for Austria during preparation of the HTA report. Available international economic evaluations consistently indicate that tarlatamab is not cost-effective under the prices and assumptions assessed and that substantial price reductions would be required. At the same time, the high treatment costs are expected to result in a substantial budget impact. The role of tarlatamab in clinical practice will depend on whether the observed survival benefit can be confirmed in routine clinical practice and how tarlatamab compares with available treatment options at the given price.

1 Introduction

HTA zu Tarlatamab für erwachsene Pat. mit ES-SCLC basierend auf JCA

The objective of this report is to evaluate the clinical effectiveness and safety, as well as the economic and organisational aspects of tarlatamab (IMDYLLTRA®) monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer, who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. Tarlatamab was subject to a Joint Clinical Assessment (JCA) conducted under the Regulation on Health Technology Assessment (HTA) (Regulation (EU) 2021/2282). Therefore, the presentation of clinical evidence in this report is based on the JCA [3].

1.1 Disease background

Overview

LC: zweithäufigste Krebsdiagnose in Ö; 2 Hauptsubtypen: NSCLC und SCLC

Lung cancer (LC) is a primary malignant neoplasm originating in the lungs or bronchi and represents the second most common cancer diagnosis in Austria [4]. It is one of the leading causes of cancer-related death, characterised by a particularly poor prognosis and a high mortality-to-incidence ratio [4]. Histologically, approximately 78% of LC are classified as non-small cell lung cancer (NSCLC) and approximately 15% as small cell lung cancer (SCLC) [1].

SCLC: aggressivster Subtyp, hohe Mortalität, kaum kurative Optionen

SCLC is the most aggressive histological subtype, characterised by rapid tumour growth and early metastatic spread [3]. It accounts for a substantial proportion of LC-related mortality due to its highly aggressive clinical behaviour and limited curative treatment options [3].

Classification and stages

SCLC: ICD-11 2C25.1, Stadieneinteilung nach TNM-System

SCLC is classified as a primary malignant neoplasm of the bronchus and lung. According to the International Statistical Classification of Diseases and Related Health Problems (ICD), it is coded as 2C25.1 in ICD-11 [5]. The classification of SCLC follows the tumour-node-metastasis (TNM) staging system, as applied to other solid tumours [1].

2-Stadien-System häufig verwendet: LS-SCLC (kurativ) vs. ES-SCLC (palliativ) → Fokus des Berichts

In clinical practice, a simplified two-stage system remains widely used due to its practical relevance for the treatment choice. This system distinguishes between limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC). Within the LS, stages I and II are referred to as ‘Very Limited Disease’, while stage III corresponds to ‘Limited Disease’. The ES designation is applied from stage IV onwards. LS-SCLC refers to disease confined to one hemithorax and encompassable within a single radiation field, whereas ES-SCLC is characterised by spread beyond one hemithorax, including distant metastases. The key clinical distinction lies in the therapeutic intent: LS-SCLC is approached curatively, whereas ES-SCLC is managed with non-curative (palliative) intent [1]. Key treatment goals in ES-SCLC are the prolongation of overall survival, disease control, and the preservation of quality of life. ES-SCLC is the focus of the present report.

Clinical manifestations

ES-SCLC: respiratorische, systemische, neurologische und paraneoplastische Symptome

Patients with ES-SCLC commonly present with symptoms related to either the primary thoracic tumour or metastatic disease. Frequent respiratory manifestations include a persistent cough, dyspnoea, wheezing and haemoptysis. Tumour involvement of central airways and mediastinal structures may lead to complications such as superior vena cava syndrome, dysphagia, or vocal cord paralysis due to nerve compression. Systemic manifestations such as fatigue, anorexia, and weight loss are also common, reflecting the frequently metastatic course of the disease. Neurological and paraneoplastic syndromes may also occur, arising from ectopic hormone production or immune-mediated mechanisms [3].

Diagnosis

60-70 % der SCLC-Diagnosen im ES-Stadium; Erkrankungsalter meist 60-70 Jahre

SCLC is frequently diagnosed at an advanced stage, with 60-70% of patients presenting an ES-SCLC at the time of diagnosis, reflecting the tumour's rapid proliferation and early dissemination to distant organs [3]. The median age at diagnosis typically ranges from the mid-60s to the early 70s, with approximately 44% of patients older than 70 years [3].

LC-Diagnostik: Bildgebung, Histologie/Zytologie, Metastasenabklärung

The diagnostic work-up in suspected LC-cases follows sequential steps, as illustrated in Figure 1-1: imaging confirmation of a thoracic mass, complemented by laboratory investigations; histological or cytological verification of the diagnosis; and assessment of organ metastases [1].

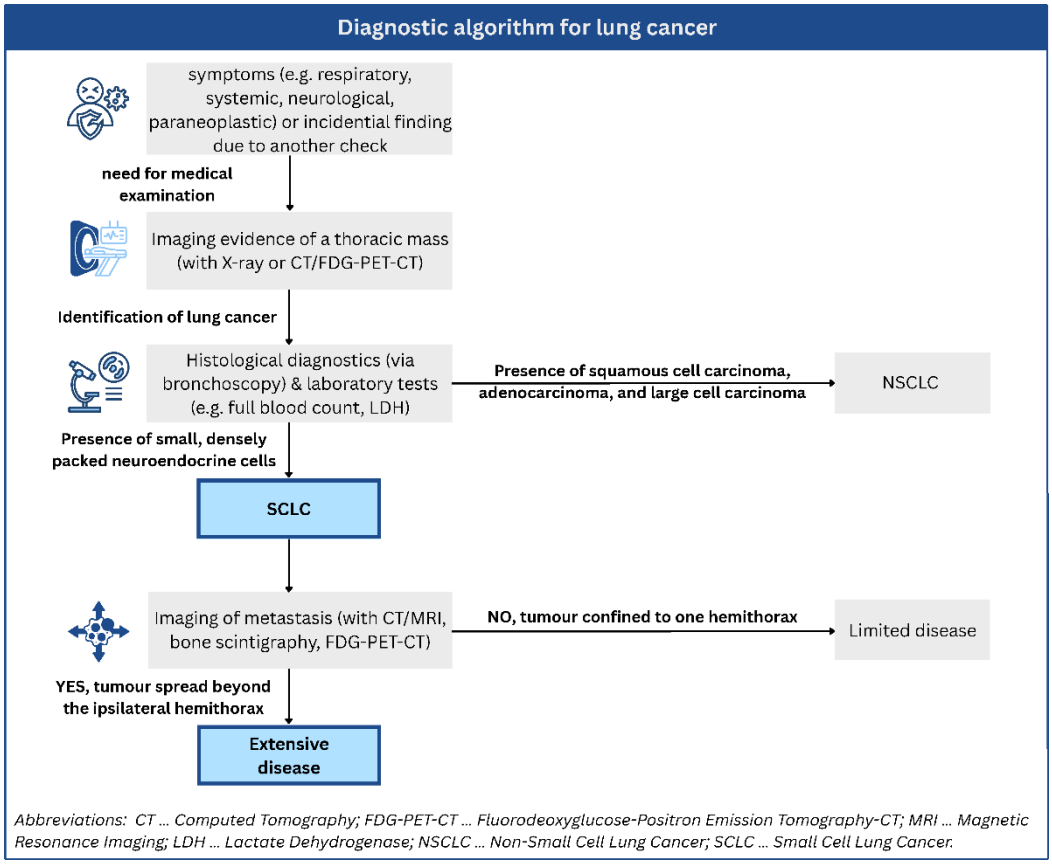


Figure 1-1: Diagnostic algorithm for lung cancer (own illustration based on [1]).

Risk factors

Tobacco exposure represents the main risk factor, with approximately 98% of patients having a history of tobacco smoking. Additional environmental and occupational risk factors include exposure to radon gas, ionising radiation, and air pollution [3].

Hauptrisikofaktor: Rauchen (98 %)

Prognosis

The prognosis of SCLC is influenced by several clinical factors. High Eastern Cooperative Oncology Group Performance Status (ECOG PS), older age, high lactate dehydrogenase (LDH) level, weight loss, and metastatic disease, particularly involving the liver and brain, are associated with poorer outcomes [3].

schlechte Prognose bei: höherem ECOG PS, hohem LDH, Metastasen (Leber, Hirn)

The overall SCLC-prognosis is poor, with a 5-year survival rate of less than 10% after diagnosis. In ES-SCLC, the chemoimmunotherapy (first-line therapy) has a median survival of 12 months (1-year survival rate: 50%), a 2-year survival rate of 20-25%, and a 3-year survival rate of 15-20% [1].

SCLC: 5-Jahres-Überlebensrate <10 %; im ES: medianes Überleben ~12 Monate mit 1L Chemoimmuntherapie

Epidemiology

In Austria, the prevalence of SCLC is estimated at approximately 2,600 individuals, based on Statistik Austria (2024) [4] data and the assumption that SCLC accounts for 15% of all LC diagnoses [1]. Prevalence is expected to be similar among men and women. Annually, the total number of patients with SCLC in Austria is estimated at 617 cases [4], of whom 581 are assumed to present with ES-SCLC [6, 7].

Prävalenz SCLC in AT (2024): 2.600 Personen

Inzidenz in AT: 617 Neuerkrankungen/Jahr, davon 581 mit ES-SCLC

Regarding mortality, LC caused an average of approximately 4,162 deaths per year in Austria between 2022 and 2024 (age-standardised rate: 43.7 per 100,000 persons) [1]. No Austria-specific epidemiological data are available to quantify the proportion of LC deaths attributable to SCLC specifically. As mentioned above, given that SCLC represents the more aggressive form of LC [3], its proportional contribution to LC mortality is expected to be high.

SCLC als aggressive Lungenkrebsform mit hohem Anteil an der Lungenkrebsmortalität

1.2 Clinical Practice in Austria

According to Austrian clinical experts [8], the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Small-Cell Lung Cancer (2021) [9] and the Onkopedia guideline (2025) [1] are used in clinical practice for the management of ES-SCLC in Austria. The Onkopedia guideline, jointly authored by German and Austrian oncology societies, adapts recommendations to the Central European context and explicitly addresses the use of tarlatamab [1]. The referred ESMO guideline is old and has not since been updated [9], which was also discussed with the clinical experts [8].

Referenzleitlinie in AT: ESMO 2021 und Onkopedia 2025

weitere aktuelle Leitlinien: AWMF S3 2026, NCCN 2026 – konsistent mit AT-Standard

The most recent international guidelines identified are: the S3 Guideline on Prevention, Diagnosis, Treatment and Follow-up of Lung Cancer (Version 5.01, April 2026[1]) from the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) [2]; and the Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer (Version 2.2026, September 2025) from the National Comprehensive Cancer Network (NCCN) [10]. Overall, the therapeutic recommendations in these international guidelines are consistent with the Austrian clinical practice described by Austrian clinical experts [8].

Lokalrezidiv: Strahlentherapie und Weiterführung der Immuntherapie

As illustrated in the treatment algorithm in Figure 1-2, second-line treatment decisions for patients with ES-SCLC progressing after or during chemoimmunotherapy are guided by the pattern of disease progression. The first decision point distinguishes between local progression/recurrence with stable metastases and disseminated disease. In the case of local progression, thoracic radiotherapy is recommended, followed by continuation of immunotherapy [1].

Therapiewahl bei disseminierter Erkrankung nach:

bestrahlbarer Progression: Radiotherapie und Fortführung der systemischen Therapie

nicht bestrahlbarer Progression: Therapieauswahl nach ECOG-PS und TFI, bzw. RFI

For disseminated disease, the algorithm differentiates between irradiable and non-irradiable progression. If a single irradiable lesion is present, such as in the brain or bone, the progressive localisation is irradiated, followed by continuation of chemotherapy and immunotherapy or maintenance immunotherapy. In cases of non-irradiable progression, treatment decisions are based on the ECOG PS and the treatment-free interval (TFI) or recurrence-free interval (RFI), dividing patients into subgroups with differing therapy options [3]:

- topotecan and the cyclophosphamide/doxorubicin/vincristine regimen (CAV) are current options for platinum-resistant patients (TFI <3 months);
- platinum rechallenge, topotecan and CAV are options for platinum-sensitive patients (TFI ≥3 months); topotecan or CAV may be used in patients with an RFI ≤6 months or in those unsuitable for platinum rechallenge;
- cisplatin or carboplatin plus etoposide may be used in patients with an RFI >6 months suitable for platinum rechallenge.

Tarlatamab ist in allen Subgruppen eine Therapieoption

Platinsensitivität ist für die Positionierung von Tarlatamab nicht ausschlaggebend

Tarlatamab is mentioned as a treatment option across all subgroups. The use of tarlatamab in Austria is currently being assessed as part of the Austrian Appraisal Board's assessment procedure and is the subject of this report. It should be noted that the Onkopedia and S3-AWMF guidelines differ in their recommended chemotherapy-free interval thresholds for treatment selection [1, 2]. The experts suggested that both guidelines can be used to guide clinical decision-making, as treatment decisions ultimately need to be individualised [8]. Platinum sensitivity status also represents a consideration when selecting treatment options in clinical practice. However, with regard to the positioning of tarlatamab, clinical experts pointed out that its mechanism of action is independent of platinum sensitivity status. Therefore, this patient stratification is not emphasised in the treatment algorithm [8].

[1] At the time of the data cut-off, Version 5.01 (April 2026) was a consultation/draft. The final version, valid from 1 July 2026 onwards, is now available via: https://www.leitlinienprogramm-onkologie.de/leitlinien/lungenkarzinom/

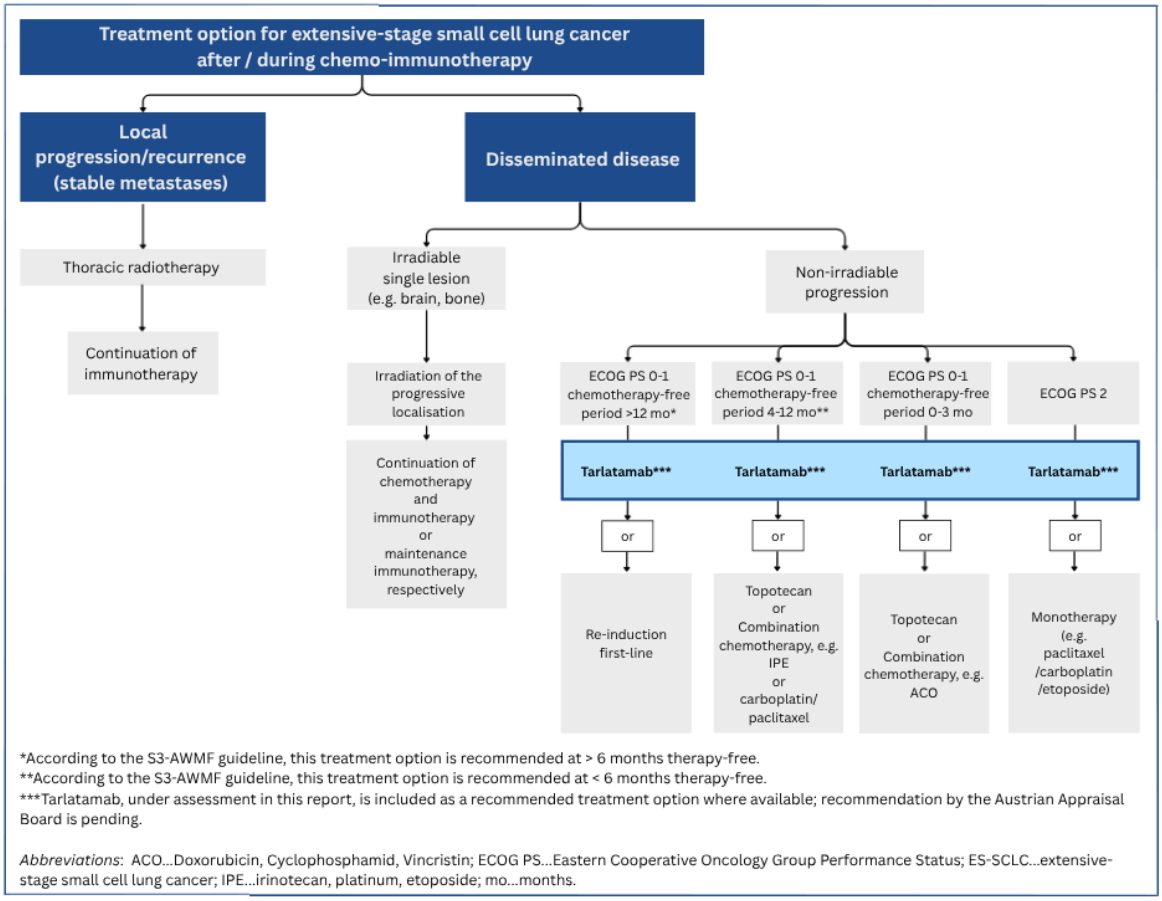


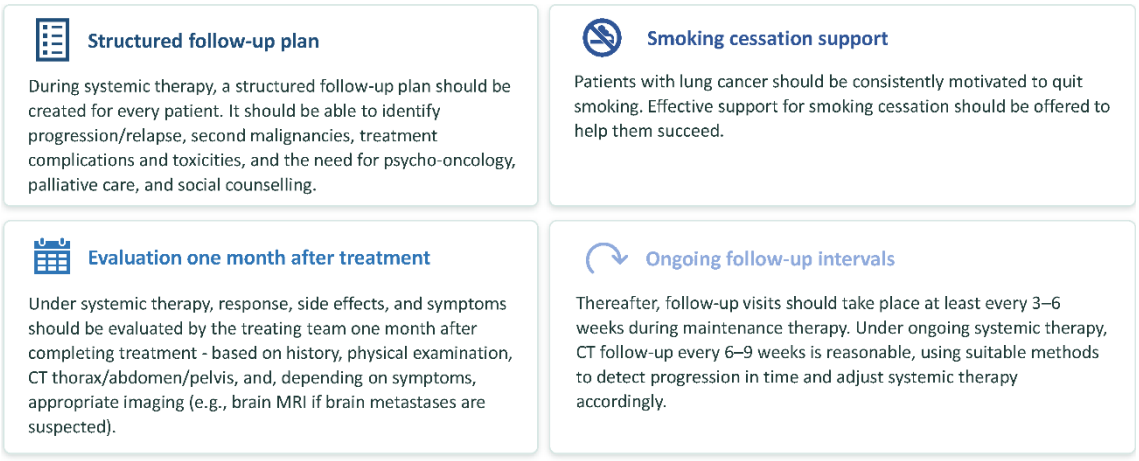
Figure 1-2: Treatment options for ES-SCLC after/during chemoimmunotherapy (own illustration based on [1-3]).

Follow-up care

Umfassendes, strukturiertes Follow-up beim ES-SCLC

Follow-up in ES-SCLC is comprehensive, encompassing structured and frequent follow-up visits alongside supportive measures such as smoking cessation support. The key recommendations from the AWMF guideline in this regard are summarised in Figure 1-3. These recommendations apply generally to patients with ES-SCLC receiving systemic therapy[2] [2].

[2] Systemic therapy refers to treatment administered via the bloodstream to act throughout the body, as opposed to local treatment approaches such as surgery or radiotherapy.



Abbreviations. CT...Computed Tomography, MRI...Magnetic Resonance Imaging.

Figure 1-3: AWMF guideline recommendations on structured follow-up, smoking cessation support, and response evaluation for patients with ES-SCLC receiving systemic therapy (own illustration based on [2]).

1.3 Medicinal product under evaluation

The medicinal product under evaluation is tarlatamab (IMDYLLTRA®), a bispecific T-cell engager, pertaining to the pharmacologic class of antineoplastic agents [11].

Tarlatamab: bispezifischer T-Zell-Engager (BiTE)

Tarlatamab binds to delta-like ligand 3 (DLL3), an oncogenic protein aberrantly expressed on SCLC tumour cells, and to CD3, expressed by T cells, thereby bringing them into close proximity. This activates T cells, leading to the production of inflammatory cytokines and the release of cytotoxic proteins, resulting in tumour cell death [12].

durch gleichzeitige Bindung an Tumorzellen und T-Zellen wird Zelltod induziert

Table 1-1 summarises the most important information about tarlatamab.

Table 1-1: Characteristics of tarlatamab (IMDYLLTRA®) [11]

INN	
Product name	IMDYLLTRA®
Active substance(s)	Tarlatamab
Anatomical Therapeutic Chemical (ATC) Code	L01FX33
Pharmacologic class	Antineoplastic agent (bispecific T-cell engager)
Manufacturer/HTD	Amgen Europe B.V.

Abbreviations: HTD … health technology developer, INN … International non-proprietary name

Regulatory status

positive CHMP-Stellungnahme im März 2026; europäische Marktzulassung seit 29. Mai 2026

On 26 March 2026, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for tarlatamab (IMDYLLTRA®), indicated as monotherapy for the treatment of adult patients with ES-SCLC, who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. The European Union-wide marketing authorisation was issued by the European Commission (EC) on 29 May 2026 [11]. The medicine is under additional monitoring[3], meaning that it is being monitored more intensively than other medicines [13].

zusätzliche Überwachung durch Behörden

Marktexklusivität für Orphan-Arzneimittel bis 2036

IMDYLLTRA® was designated as an orphan medicinal product for the treatment of SCLC on 12 January 2024 [12]. Following EC authorisation, orphan market exclusivity for "Treatment of small cell lung cancer" was granted for ten years, expiring on 1 June 2036 [14].

FDA-Zulassung für diese Indikation seit November 2025

For the United States, the US Food and Drug Administration (FDA) granted accelerated approval in 2024 and traditional approval on 19 November 2025 to tarlatamab-dlle (Imdelltra®, Amgen Inc.) for adults with ES-SCLC with disease progression on or after platinum-based chemotherapy. This application was also granted priority review and tarlatamab-dlle received breakthrough designation [15].

Table 1-2 summarises the most important regulatory information about tarlatamab.

Table 1-2: EMA regulatory information on tarlatamab (IMDYLLTRA®) [11]

Category	Status
Orphan medicinal product	Yes
Conditional marketing authorisation	No
Specific obligations of the conditional marketing authorisation	No
Additional monitoring	Yes
Accelerated approval	No
Exceptional circumstances	No
ATMP	No
PRIME	No
First approved indication	Yes
Details of ongoing early access programmes in Austria (as provided by the HTD)[a]	NA

Abbreviations: ATMP … Advanced Therapy Medicinal Product, HTD … health technology developer, NA … not available, PRIME … Priority Medicines

Note:

[a] *For further details on ongoing early access programmes, please refer to the submission dossier.*

finales JCA am 8. Juli 2026 veröffentlicht

Tarlatamab was subject to a JCA conducted under the Regulation on Health Technology Assessment (Regulation (EU) 2021/2282). Date of endorsement by the Member State Coordination Group on HTA was 22 June 2026 and the

[3] Additional monitoring is a regulatory pharmacovigilance measure routinely applied to new active substances and newly authorised biologics.

date of conclusion of the procedural review by the EC was 1 July 2026. The JCA report was finally published on 8 July 2026. For an overview of the procedural steps and their dates, see JCA report [3].

Posology and method of administration

Verabreichung als IV Infusion über 1h (an Tag 1, 8 & 15), dann alle 2 Wochen bis Progression oder inakzeptable Toxizität

Tarlatamab is available as a 1-mg and 10-mg powder for concentrate and solution for infusion [11]. The product is to be reconstituted and further diluted prior to administration by intravenous (IV) infusion, which should be conducted as a one-hour infusion in an appropriate healthcare facility under the direction and supervision of physicians experienced in the use of cancer therapy. The recommended dosage and schedule for tarlatamab are an initial dose of 1 mg on day 1, followed by 10 mg on days 8 and 15, and every two weeks thereafter until disease progression or unacceptable toxicity [14].

Requirements for pre- and post-medication and monitoring

engmaschige Überwachung während der Infusion erforderlich:

During the administration of tarlatamab, patients should be closely monitored for signs and symptoms of [14]:

CRS

- *Cytokine release syndrome (CRS):* Tarlatamab should be administered in a healthcare facility equipped to monitor and manage CRS. It should be ensured that patients are euvolemic prior to initiating the infusions. To mitigate the risk of CRS, it is important to initiate tarlatamab at the recommended starting dose.

ICANS

- *Immune effector cell-associated neurotoxicity syndrome (ICANS):* The administration of tarlatamab has been associated with ICANS, which may be serious or life-threatening and can occur up to several weeks following administration. Adverse events (AEs) that may be associated with ICANS include headache, encephalopathy, confusion, delirium, seizure, ataxia, neurotoxicity, and tremor.

Neutropenie

- *Neutropenia:* The administration of tarlatamab has been associated with neutropenia. Reported events were mainly non-serious and resolved spontaneously or with the use of granulocyte colony-stimulating factor; still, it should be monitored.

Hypersensivität

- *Hypersensitivity:* Symptoms may include, but are not limited to, rash and bronchospasm.

Begleitmedikation, um CRS-Risiko zu reduzieren:

To reduce the risk of e.g. CRS, the administration of concomitant medications is recommended [14]:

Dexamethason (vor) und

- Within one hour prior to the tarlatamab infusion, 8 mg of dexamethasone IV (or equivalent) should be administered.

Natriumchlorid (nach) der Infusion

- Immediately after completion of the tarlatamab infusion, the administration of one litre of sodium chloride 9 mg/mL (0.9%) solution for IV injection is recommended per standard of care guidelines.

Use in specific populations

Tarlatamab für bestimmte Populationen

Information on the use of tarlatamab in specific populations, derived from the EMA's European Public Assessment Report (EPAR) Product Information, is summarised in Table 1-3 [14].

Table 1-3: Use of tarlatamab in specific populations [14]

	Women of childbearing potential have to use effective contraception during and for at least 2 months after tarlatamab treatment. Tarlatamab is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown whether tarlatamab is secreted in human milk; a risk to the newborns/infants cannot be excluded. There are no clinical studies to evaluate the effect of tarlatamab on fertility.
	Tarlatamab is not recommended in patients under 18 years of age.
	No dose adjustment is required for geriatric patients.
	No dose adjustment is required in patients with mild or moderate renal impairment. Tarlatamab has not been studied in patients with severe renal impairment.
	No dose adjustment is required in patients with mild or moderate hepatic impairment. Tarlatamab has not been studied in patients with severe hepatic impairment.

2 Scope of assessment

klinische, ökonomische & organisatorische Bewertung von Tarlatamab

The objective of this report is to evaluate the clinical effectiveness and safety, as well as the economic and organisational aspects of tarlatamab (IMDYLLTRA®) monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer, who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. Tarlatamab was subject to a Joint Clinical Assessment (JCA) conducted under the Regulation on Health Technology Assessment (HTA) (Regulation (EU) 2021/2282). Therefore, the presentation of clinical evidence in this report is based on the JCA [3].

2.1 Research questions

The following research questions will be answered in the present report:

Clinical domain:

klinische Domäne: Wirksamkeit und Sicherheit

1) In patients with ES-SCLC, who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy, is tarlatamab more effective and safer compared to the current treatment options in Austria regarding patient-relevant outcomes?

Non-clinical domains:

nicht-klin. Domänen: ökonomisch, ethisch, organisatorisch, sozial, sowie öffentliche Beiträge zu Entwicklungskosten

2) What are the economic, ethical, organisational and social consequences of implementing tarlatamab into the Austrian healthcare system?

3) What were the key contributions of publicly funded research institutions and private companies in discovering and developing tarlatamab as a therapy for ES-SCLC, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to market authorisation?

2.2 PICO

relevante JCA-PICOs für Ö-Kontext

The presentation of the clinical evidence in this report is based on the JCA [3]. The PICOs (Population, Intervention, Comparator, Outcome) were defined within the JCA process, and their relevance to the Austrian healthcare context was confirmed through expert consultation [16]. The resulting seven PICOs are shown in Table 2-1.

zusätzlich Literatur für nicht klin. Bereiche berücksichtigt

Regarding the non-clinical domains, relevant economic literature was included with information about tarlatamab and standard therapy prices, other direct medical costs and health economic evaluations. In addition, relevant literature for the organisational, ethical and social domain as well as literature on public investment, such as information on public grants, funding and contributions, was considered.

Table 2-1: Assessment scope, including the patient, intervention, comparison and outcome (PICO) question for the clinical domain

PICO	Comparator	Outcomes
Population A – TFI <3 months (platinum-resistant); Intervention: Tarlatamab monotherapy		OS PFS ORR DoR Symptoms of the disease HRQoL, disease-specific Health status (EQ-5D-5L) HRQoL, generic Any AE Serious AE Severe AE (CTCAE ≥3) Death related to AE Treatment discontinuation due to AE Treatment interruption due to AE
PICO 1	Topotecan	
PICO 2	CAV	
Population B – TFI ≥3 months (platinum-sensitive); Intervention: Tarlatamab monotherapy		
PICO 3	Platinum-rechallenge (carboplatin + etoposide)	
PICO 4	Topotecan	
PICO 5	CAV	
Population C – RFI ≤6 months or not suitable for platinum-rechallenge; Intervention: Tarlatamab monotherapy		
PICO 6	Topotecan or CAV	
Population D – RFI >6 months (suitable for platinum-rechallenge); Intervention: Tarlatamab monotherapy		
PICO 7	Cisplatin or carboplatin + etoposide	

Abbreviations: *AE … adverse event, CAV … cyclophosphamide/doxorubicin/vincristine, CTCAE … Common Terminology Criteria for Adverse Events, DoR … duration of response, EQ-5D-5L … EuroQol 5-Dimension 5-Level, HRQoL … health-related quality of life, ORR … objective response rate, OS … overall survival, PFS … progression-free survival, PICO … population, intervention, comparator, outcome, RFI … recurrence-free interval, TFI … treatment-free interval*

3 Methods

This HTA employed a multi-domain assessment approach. The clinical domain is based on the Joint Clinical Assessment (JCA) of tarlatamab published on 8 July 2026 [3]. The non-clinical domain followed the European Network for Health Technology Assessment (EUnetHTA) methodology (see guiding question in Chapter 3 of the Appendix) [17] with a data cut-off of 8 May 2026.

Daten-Cut-Off: 8. Mai 2026

Systematic literature search and study selection

The scope and the clinical chapter of this assessment are based on the JCA of tarlatamab [3]. In the course of the JCA, the assessor and co-assessor reviewed the appropriateness of the sources and the search strategies of the health technology developer (HTD) with regard to the medicinal product under assessment. Search strategies were checked for appropriateness, and the results of information retrieval included in the HTD's submission dossier, submitted on 7 May 2026, were checked for completeness against searches of study registries and in MEDLINE (PubMed). Assessors did not identify additional studies. Searches were conducted in three registries (ClinicalTrials.gov, EU Clinical Trials Register, and Clinical Trials Information System) on 16 December 2025, and in MEDLINE (PubMed) on 17 December 2025. Details are provided in the JCA report in Appendix B [3].

systematische Suche durch Hersteller & Suche nach laufenden Studien durch JCA Autor:innen

The following sources were provided by the HTD in the dossier:

- List of HTD-sponsored studies on the indication (no status date reported by the HTD)
- Bibliographic search for the indication (last search on 7 October 2025)
- Search in study registries/study result databases for the indication (last search on 29 January 2026)
- Submission files to the EMA for tarlatamab (no date reported by the HTD)

verschiedene Quellen aus dem Dossier des Herstellers

For the preparation of this report, the information retrieval was supplemented at the national level by additional searches in three clinical trial registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) on 4 May 2026, which yielded 49 potentially relevant hits. In addition, the HTD submitted a national dossier on 8 May 2026, containing supplementary information to support the assessment of tarlatamab in the Austrian context.

Clinical effectiveness and safety assessment

The presentation of the clinical effectiveness and safety is based on the publicly available JCA [3]. Data extraction from the JCA report for this assessment was systematically performed by one reviewer (EM) and cross-checked by a second reviewer (MR).

Datenextraktion im 4-Augenprinzip basierend auf JCA

The risk of bias (RoB) of the included clinical evidence was assessed at outcome level using the Cochrane Risk of Bias 1.0 tool [18] by the assessor and co-assessor of the JCA. The assessment covered five predefined domains and followed the structured signalling-question approach. Domain-level judgements ("low risk", "some concerns", or "high risk of bias") were assigned and synthesised into an overall RoB judgement for each outcome and on a study level. This assessment was performed only for the direct comparison; no RoB

RoB 1.0-Tool in JCA direkte Vergleiche angewendet

tool was applied to the unanchored indirect comparisons, for which the assessors instead evaluated internal and external validity according to Member State Coordination Group on Health Technology Assessment (HTACG) methodological guidance [19].

The evidence synthesis followed a narrative approach according to the JCA. Therefore, the strength of evidence was not assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [20].

keine GRADE-Bewertung

Economic evaluation methods

To collect price information on tarlatamab, the Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) was contacted. In addition, the Pharmaceutical Pricing and Reimbursement Information (PPRI) network conducted a confidential survey to gather data on the economic aspects of tarlatamab, including pricing and managed entry agreements, across multiple European Union member states.

Preis-Infos von GÖG

Umfrage im PPRI-Netzwerk (vertraulich)

For health economic evaluations of tarlatamab, both submissions by the health technology developer (HTD) and published analyses were considered. For the latter, we screened the literature identified through manual searches via PubMed and Google Scholar.

Handsuche nach ökonomischen Analysen zu Tarlatamab

According to the implementation regulation §4(2) of the Austrian Appraisal Board, a three-year budget impact analysis, including the gross drug budget impact and additional administration-related costs, should be conducted. The following assumptions were applied:

Budgetfolgenanalyse: Abschätzung der direkten medizinischen Kosten – zahlreiche Annahmen getroffen:

- Patient population estimates and expected market shares were derived from published epidemiological data, the HTD dossier, and clinical expert estimates, and presented as scenarios to account for the uncertainty.

... Pat.-Schätzungen in verschiedenen Szenarien

- The available Austrian list price for tarlatamab was considered, provided by the Austrian Ministry of Health.

... Ö Listenpreis für Tarlatamab

- For the cost calculations, inpatient treatment cost data from the Austrian procedure- and diagnosis-related groups (Leistungsorientierte Krankenanstaltenfinanzierung, LKF) catalogue were taken.

... Kostendaten: LKF-Katalog

- Minor cost categories, such as pre-treatment and follow-up costs, were excluded from the analysis because the clinical experts considered them negligible relative to drug acquisition and administration costs.

... Kosten für Vor- & Nachbehandlungen nicht berücksichtigt

- A payer perspective from the healthcare system was adopted for the BIA, focusing solely on direct medical costs.

... Gesundheitssystem-perspektive

Organisational, ethical and social assessment

For the assessment of organisational, ethical and social aspects data was gathered from four sources:

4 Quellen: Expert:innen, Informationen aus JCAs & Literaturquellen

- Expert consultations with six leading clinicians (see Chapter 6.1 in the Appendix).
- Inclusion of relevant information from the JCA.
- Manual literature search.

- In addition, we searched for eligible patients, carers, and/or members of patient organisations in Austria to include their perspectives via structured patient questionnaires (see Chapter 6.2 in the Appendix for details). We identified one member of a support group who offered a collective perspective.

kollektive Perspektive eines Mitglieds einer Selbsthilfegruppe

Development costs and public contributions

The methodology for assessing development costs and public contributions involved several steps:

- Identifying product origins through searches for generic/non-proprietary names and trade names.
- Searching for the earliest references to identify basic research and development support and research grants.
- Exploring databases on clinical trials and research funding.
- Examining company websites for information on funding rounds, sponsors, mergers, and acquisitions.
- Searching US Securities and Exchange Commission (SEC) reports for information on acquisitions, patents and shareholders.
- Reviewing business news sources for additional information.

Entwicklungskosten und öffentliche Beiträge erhoben

Identifizierung generischer oder (nicht) geschützter Bezeichnungen

Produktherkunft & Grundlagenforschung

Finanzierungsrunden, Fusionen & Übernahmen

Landscape overview

Ongoing studies (active and recruiting) evaluating tarlatamab independent of origin found in clinicaltrials.gov are shortly summarised and reported. Additionally, we compiled a landscape overview of other therapies, which are in the development for SCLC with disease progression on or after platinum-based chemotherapy in adults, using the International Horizon Scanning Initiative (IHSI) database [21].

zusätzlicher Überblick zu laufenden Studien & SCLC-Therapien in Entwicklung

4 Clinical effectiveness and safety

Wirksamkeits- & Sicherheitsbewertung von Tarlatamab basierend auf JCA

This chapter evaluates the clinical effectiveness and safety of tarlatamab in the following indication: monotherapy for the treatment of adult patients with ES-SCLC who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. This chapter is based on the JCA report of tarlatamab, published on 8 July 2026 [3] and serves as an overview of the JCA report relevant for the Austrian healthcare context. Further details are presented in the relevant chapters and tables of the JCA report [3].

direkte Therapievergleiche (Tarlatamab vs Topotecan): PICOs 1, 4, 6

indirekte Therapievergleiche: PICOs 2, 3, 5, 7

As presented in the JCA, the HTD provided direct treatment comparisons of tarlatamab vs topotecan for PICOs 1, 4, and 6, drawing on the pivotal DeLLphi-304 study. The remaining PICOs relied on indirect treatment comparisons (ITCs): an unanchored matching-adjusted indirect comparison (MAIC) vs cyclophosphamide, doxorubicin, and vincristine (CAV) (PICO 2), a network meta-analysis (NMA) vs platinum-based retreatment or vs CAV (PICOs 3 and 5), and a Bucher ITC vs cisplatin/carboplatin plus etoposide for one outcome only (PICO 7). The ITCs used the DeLLphi-304 trial [22] on the intervention side paired with GFPC 0501 [23] (PICO 2), Baize et al. (2020) [24] (PICOs 3 and 7), and von Pawel et al. (1999) [25] (PICO 5) on the comparator side. See details in Table 4-1, where PICOs in bold represent direct comparisons.

Table 4-1: Overview of the PICOs and studies identified in the JCA for tarlatamab in ES-SCLC (based on [3])

PICO	Population	Intervention	Comparator	Evidence type	Data source
PICO 1	Population A (TFI <3 months, platinum-resistant)	Tarlatamab	Topotecan	Direct (RCT subgroup)	DeLLphi-304
PICO 2	Population A (TFI <3 months, platinum-resistant)	Tarlatamab	CAV	Indirect (unanchored MAIC)	DeLLphi-304 + GFPC 0501
PICO 3	Population B (TFI ≥3 months, platinum-sensitive)	Tarlatamab	Platinum-rechallenge	Indirect (NMA/Bucher)	DeLLphi-304 + Baize et al. (2020)
PICO 4	Population B (TFI ≥3 months, platinum-sensitive)	Tarlatamab	Topotecan	Direct (RCT subgroup)	DeLLphi-304
PICO 5	Population B (TFI ≥3 months, platinum-sensitive)	Tarlatamab	CAV	Indirect (Bayesian NMA)	DeLLphi-304 + von Pawel et al. (1999) + Baize et al. (2020)
PICO 6	Population C (RFI ≤6 months, not suitable for platinum-rechallenge)	Tarlatamab	Topotecan	Direct (RCT subgroup)	DeLLphi-304
PICO 7	Population D (RFI >6 months, suitable for platinum-rechallenge)	Tarlatamab	Platinum rechallenge (carboplatin/cisplatin + etoposide)	Indirect (Bucher ITC)	DeLLphi-304 + Baize et al. (2020)

Abbreviations: CAV … cyclophosphamide, doxorubicin, and vincristine, ITC … indirect treatment comparison, MAIC … matching-adjusted indirect comparison, NMA … network meta-analysis, RCT … randomised controlled trial, RFI … relapse-free interval, TFI … treatment-free interval

4.1 Outcomes

verschiedene Endpunkte zur Wirksamkeit und Sicherheit im JCA definiert

Outcomes for the assessment were defined using the Guidance on outcomes provided by the HTACG [19].

Efficacy outcomes assessed include overall survival (OS), progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), symptoms of the disease (assessed by the Brief Pain Inventory – Short Form [BPI-SF], dyspnoea composite score, Patient Global Impression of Severity [PGIS], and Patient Global Impression of Change [PGIC]), disease-specific health-related quality of life (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30] and Lung Cancer 13 [EORTC QLQ-LC13]), generic health-related quality of life, and health status (EuroQol 5-Dimension 5-Level [EQ-5D-5L]).

Safety outcomes assessed include the incidence of any AE, serious adverse events (SAEs), severe adverse events (defined as CTCAE grade ≥3), deaths related to an AE (defined as Common Terminology Criteria for Adverse Events [CTCAE] grade 5), treatment discontinuation due to an AE, and treatment interruption due to an AE.

More detailed definitions of the outcomes are summarised in the JCA Table 32 [3].

4.2 Characteristics of the included studies

4 klinische Studien, DeLLphi-304-Zulassungsstudie

Four clinical studies were identified and included in the JCA. The primary evidence source is DeLLphi-304 (NCT05740566) [22], the pivotal phase 3 randomised controlled trial (RCT) for the EMA marketing authorisation of tarlatamab. Three further studies informed the ITC: GFPC 0501 [23] (PICO 2), Baize et al. (2020) [24] (PICOs 3 and 7), and von Pawel et al. (1999) [25] (PICO 5). See more details on the PICOs in Table 4-1. Further characterisation of the studies is available in the JCA, Table 14 [3].

4.2.1 DeLLphi-304: PICO 1, 4 and 6

DeLLphi-304: Phase 3 Studie für PICOs 1, 4, 6

Tarlatamab vs Topotecan

The phase 3 RCT (DeLLphi-304) [22] was identified for PICOs 1, 4, and 6, comparing tarlatamab IV (step dose: 1 mg on cycle 1 day 1, then 10 mg on cycle 1 days 8 and 15, and every 2 weeks thereafter in a 28-day cycle) to topotecan IV (1.5 mg/m² [1.2 mg/m² in China] or oral 2.3 mg/m² on days 1-5 every 3 weeks) in SCLC patients who had progressed on or relapsed following platinum-based chemotherapy. Patients were randomised to:

- Tarlatamab, or
- Topotecan

Subpopulationen basierend auf dem CFI

In the DeLLphi-304 study, subpopulations were defined based on the chemotherapy-free interval (CFI):

- PICO 1: patients with CFI <90 days (tarlatamab n=85; topotecan n=81)

- PICO 4: patients with CFI ≥90 days (tarlatamab n=111; topotecan n=104)
- PICO 6: patients with CFI ≤180 days (tarlatamab n=148; topotecan n=142)

The primary analysis for all three PICOs is based on a single data cut-off on 29 January 2025, at the prespecified OS interim analysis, which met the stopping boundaries.

primäre Analyse: Daten Cut-Off 29. Jänner 2025

Study protocol amendments

The DeLLphi-304 statistical analysis plan (SAP) underwent four amendments between May 2023 and November 2024. Key revisions addressed evolving study design elements including sample size, subgroup analyses, interim analysis guidelines, and patient-reported outcome methodology. Later amendments refined AE reporting criteria, PFS censoring rules, and stratification strata in preparation for the primary analysis. For details, see Table 4-2 below.

Anpassungen des Protokolls

Table 4-2: Summary of statistical analysis plan amendments – DeLLphi-304 (based on [22])

Version	Date	Key changes
Original v1.0	10 May 2023	Original SAP
Amendment 1 (v2.0)	19 March 2024	Updated endpoints/objectives; updated study design and sample size; updated covariates/subgroups; added definitions (CFI, relative dose intensity); updated interim analysis and stopping guidelines; added sensitivity analyses; updated PRO analysis set definition
Amendment 2 (v3.0)	1 August 2024	Updated SFU period; collapsed stratification strata; added subgroups (including DLL3); updated PFS event timing; updated AE, lab, and ECG analyses; updated BOR calculation algorithm
Amendment 3 (v4.0)	24 October 2024	Added DLL3 subgroup analysis; updated subject count criteria for subgroups; updated AE section; removed disease stage subgroup; removed separate tarlatamab vs topotecan/amrubicin vs lurbinectedin subgroup analysis (moved to a separate supplementary SAP)
Amendment 4 (v5.0)	21 November 2024	Added details of AE of interest (CRS/ICANS); updated PFS sensitivity analysis censoring rules; updated imputation rules for partial/missing new anti-cancer therapy initiation date; removed non-investigational product exposure analysis

Abbreviations: AE … adverse event, BOR … best overall response, CFI … chemotherapy-free interval, CRS … cytokine release syndrome, DLL3 … delta-like ligand 3, ECG … electrocardiogram, ICANS … immune effector cell-associated neurotoxicity syndrome, PFS … progression-free survival, PRO … patient-reported outcome, SAP … statistical analysis plan, SFU … safety follow-up,

4.2.2 GFPC 0501: PICO 2

The phase 2 RCT (GFPC 0501) [23], was identified as the comparator data source for PICO 2, enrolling SCLC patients with early progression (≤3 months after first-line cisplatin-based chemotherapy). Patients were randomised to:

CFPC 0501: Phase 2-Studie für PICO 2

- CAV (cyclophosphamide 1,000 mg/m² IV, doxorubicin 45 mg/m² IV, and vincristine 1.4 mg/m² IV) on day 1 of each 28-day cycle, or
- oral lomustine 80-120 mg on day 1, cyclophosphamide 100 mg/day on days 1-6 to 1-14, and etoposide 75 mg/day on days 1-6 to 1-14 of each 28-day cycle.

Vergleichstherapie: CAV oder Lomustine

For PICO 2, an unanchored MAIC of tarlatamab vs CAV was performed using the DeLLphi-304 CFI <90 days subpopulation (tarlatamab n=109) and the full GFPC 0501 population (CAV n=66), with a data cut-off of 29 January 2025 for DeLLphi-304 (data cut-off for GFPC 0501 not reported).

ungeankerte MAIC für PICO 2-Analyse

4.2.3 Baize et al. (2020): PICOs 3 and 7

Baize et al.: Phase 3 RCT für PICOs 3 und 7

The phase 3 RCT published by Baize et al. (2020) [24] was identified as the comparator data source for PICOs 3 and 7, enrolling advanced SCLC patients who had responded to first-line platinum plus etoposide but relapsed or progressed ≥90 days after completion. Patients were randomised to:

Vergleichstherapie: Carboplatin oder Topotecan

- carboplatin area under the curve (AUC) 5 mg/mL/min IV on day 1 plus etoposide 100 mg/m² IV on days 1-3, for a maximum of six 21-day cycles, or
- topotecan 2.3 mg/m² orally on days 1-5 every 3 weeks, for a maximum of six cycles.

indirekter Therapievergleich

For PICO 3 (treatment-free interval [TFI] ≥3 months) and PICO 7 (recurrence-free interval [RFI] ≤6 months), Baize et al. (2020) informed ITC of tarlatamab vs platinum-based retreatment. The data cut-off was 16 April 2019 (final analysis 18 September 2019), used together with the DeLLphi-304 data cut-off of 29 January 2025.

4.2.4 von Pawel et al. (1999): PICO 5

von Pawel et al: ein RCT für PICO 5

One open-label multicentre RCT published by von Pawel et al. (1999) [25] was identified as the comparator data source for PICO 5, enrolling SCLC patients who had relapsed ≥60 days after first-line therapy. Patients were randomised to:

Vergleichsintervention: CAV oder Topotecan

- topotecan 1.5 mg/m²/day IV over 30 minutes on days 1-5 every 21 days (escalatable to 2.0 mg/m² in the absence of grade ≥2 toxicity), or
- CAV (cyclophosphamide 1,000 mg/m² IV [max 2,000 mg], doxorubicin 45 mg/m² IV [max 100 mg], and vincristine 2 mg IV) on day 1 of each 21-day cycle
- both until disease progression or unacceptable toxicity.

indirekter Vergleich

For PICO 5, von Pawel et al. (1999) informed an ITC of tarlatamab vs CAV in platinum-sensitive patients, used together with the DeLLphi-304 data cut-off of 29 January 2025 (data cut-off for von Pawel et al. (1999) was not reported).

Detailed characteristics are provided in Table 4-3 below and in the JCA Tables 15, 16, 18, 19, 21, 22, 24, and 25 [3].

Table 4-3: Characteristics of included studies (based on [3])

Study	DeLLphi-304 [22]	GFPC 0501 [23]	Baize et al. (2020) [24]	von Pawel et al. (1999) [25]
Reference/ID	NCT05740566	NCT00418743	NCT02738346	NCT00547651
Study type and design	Phase 3, randomised, controlled, open-label, multinational, multicentre RCT	Phase 2, randomised trial (national, multicentre)	Phase 3, randomised, open-label, multicentre trial	Study phase NR; randomised, open-label, multicentre trial
Study population	Adult patients (≥18 years) with histologically or cytologically confirmed ES-SCLC who progressed or recurred after 1L treatment with platinum-based chemotherapy; measurable disease per RECIST v1.1; ECOG PS 0 or 1; adequate organ function.	Adult patients with histologically confirmed SCLC and early disease progression (≤3 months after completing 1L cisplatin-based chemotherapy).	Patients with histologically or cytologically confirmed advanced stage IV or locally relapsed SCLC, who responded to 1L platinum plus etoposide treatment, but had disease relapse or progression at least 90 days after completion of 1L treatment.	Patients with SCLC who had relapsed at least 60 days after completion of 1L therapy.
Study arms and sample size	Arm 1: Tarlatamab (n=254) Arm 2: SoC chemotherapy (n=255): ■ Topotecan: n=185 ■ Lurbinectedin: n=47 ■ Amrubicin: n=23	Arm 1: CAV IV (n=66) Arm 2: Oral therapy (n=65) Lomustine + cyclophosphamide + etoposide	Arm 1: Carboplatin + etoposide (n=82) Arm 2: Topotecan (n=82)	Arm 1: Topotecan (n=107) Arm 2: CAV (n=104)
Study duration, data cut-off(s) and locations	Treatment period: until progression, unacceptable toxicity, withdrawal, death, or end of study Period of study: 05/2023 – ongoing (estimated completion: 03/2028) Data cut-off: 29 January 2025 (prespecified OS interim analysis; primary analysis as OS stopping boundaries fulfilled) Median follow-up: 11.2 months (OS) Locations: 166 sites in 30 countries	Treatment period: until progression or major toxicity Data cut-off: NR Median follow-up: NR Locations: France (19 centres)	Data cut-off: 16 April 2019 Final analysis: 18 September 2019 (after accrual of 142 progression events) Median follow-up: 22.7 months Locations: France (38 centres)	Treatment period: until progression or unacceptable toxicity; patients with CR/PR continued until progression, unacceptable toxicity, or 6 courses past maximal response Data cut-off: NR Median follow-up: NR Locations: NR
Study endpoints	Primary: ■ OS Key secondary (multiplicity controlled): ■ PFS ■ Change from baseline in disease-related symptoms, physical function, GHS/QoL (EORTC QLQ-C30 and QLQ-LC13) Secondary efficacy: ■ ORR (BOR of CR + PR) ■ DCR (CR + PR + SD) ■ DoR Secondary safety: ■ TEAEs ■ TRAEs Secondary PROs: Remaining subscales of EORTC QLQ-C30 and QLQ-LC13 ■ BPI-SF item #3 (pain at its worst) ■ VAS of EQ-5D-5L ■ GP5 of FACT-G ■ PRO-CTCAEs	Primary: ■ OS Secondary efficacy: ■ PFS ■ ORR ■ DCR	Primary: ■ PFS Secondary efficacy: ■ OS ■ ORR ■ DCR ■ DoR Secondary safety: ■ TRAEs	Primary: ■ ORR ■ DoR Secondary: ■ TTP ■ TTR ■ OS ■ Improvement of disease-related symptoms Secondary safety: ■ Haematological-related AEs ■ Non-haematological-related AEs

Abbreviations: 1L … first-line, AE … adverse event, BOR … best overall response, BPI-SF … Brief Pain Inventory – Short Form, CAV … cyclophosphamide/doxorubicin/vincristine, CR … complete response, DCR … disease control rate, DoR … duration of response, ECOG PS … Eastern Cooperative Oncology Group Performance Status, EORTC QLQ-C30/LC13 … European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (core/lung cancer 13), EQ-5D-5L … EuroQol 5-Dimension 5-Level, ES-SCLC … extensive-stage small cell lung cancer, ID … identification, IV … intravenous, N/n … number of randomised/included patients, NR … not reported, ORR … objective response rate, OS … overall survival, PFS … progression-free survival, PR … partial response, PRO … patient-reported outcome, PRO-CTCAE … PRO-Common Terminology Criteria for Adverse Events, QoL … quality of life, RCT … randomised controlled trial, RECIST … Response Evaluation Criteria in Solid Tumours, SCLC … small cell lung cancer, SD … stable disease, SoC … standard of care, TEAE … treatment-emergent adverse event, TRAE … treatment-related adverse event, TTP … time to progression, TTR … time to response, VAS … visual analogue scale

4.3 Results on relative effectiveness and safety

Ergebnisse werden pro Pat.-Population/PICO beschrieben

Results are presented per patient population, as defined in the JCA scope. Each population section begins with a description of the relevant study population and baseline characteristics, followed by PICO-specific results on relative effectiveness and safety. Where direct comparative data from DeLLphi-304 are available (PICOs 1, 4, 6), results are reported in full. For PICOs based on ITCs (PICOs 2, 3, 5, 7), only a limited number of outcomes could be included due to the absence of comparator data or methodological constraints.

4.3.1 PICO 1: tarlatamab vs topotecan (direct comparison)

Pat. mit ES-SCLC mit Progression innerhalb der ersten 3 Monate; Vergleich: Topotecan

PICO 1 addresses population A, comprising adult patients with ES-SCLC who progressed on or within three months of first-line platinum-based chemotherapy (TFI <3 months, platinum-resistant, n=85). The comparator is topotecan (n=81), assessed in a direct comparison using a subpopulation of DeLLphi-304.

Study population and baseline characteristics

PICO 1: Subpopulation mit CFI <90 Tage der DeLLphi-304-Studie

weniger Pat. mit Lebermetastasen und im Stadium IV in der Tarlatamab-Gruppe

Patient demographics and disease characteristics were largely balanced between treatment groups (Table 4-4). Some imbalances were noted: more patients aged 18-64 years were identified in the tarlatamab group (56.5% vs 49.4%), fewer patients in the tarlatamab group were presented with liver metastases at baseline (35.3% vs 43.2%), and fewer patients in the tarlatamab group were classified as stage IV at initial diagnosis (75.3% vs 81.5%). Approximately two-thirds of patients in both arms had received a programmed cell death 1 ligand 1 (PD-1/L1) inhibitor as part of their first-line regimen (67.1% vs 66.7%). Treatment duration was markedly longer in the tarlatamab group (median 13.5 vs 6.4 weeks), resulting in differential observation periods for patient-reported outcomes (PROs) and safety outcomes. Subsequent anticancer therapy was received by 47.6% and 45.5% of patients, respectively; information on the first subsequent line of therapy was not reported by the HTD.

Table 4-4: Baseline demographics of participants in the DeLLphi-304 patients with CFI <90 days (based on [3])

Characteristic	DeLLphi-304 (NCT05740566)	
Parameter	Tarlatamab (n=85)	Topotecan (n=81)
Age [years], mean (SD)	61.5 (10.1)	63.0 (9.6)
Age group 18-64, n (%)	48 (56.5)	40 (49.4)
Age group 65-74, n (%)	33 (38.8)	36 (44.4)
Age group 75-84, n (%)	4 (4.7)	5 (6.2)
Sex female/male, %	27.1/72.9	25.9/74.1
Weight (kg), mean (SD)	72.6 (17.5)	73.4 (16.4)
Region: Europe, n (%)	48 (56.5)	48 (59.3)
Region: Asia, n (%)	33 (38.8)	28 (34.6)
Smoking history: never, n (%)	11 (12.9)	11 (13.6)
Smoking history: current, n (%)	17 (20.0)	20 (24.7)
Smoking history: former, n (%)	57 (67.1)	50 (61.7)
ECOG PS 0, n (%)	23 (27.1)	21 (25.9)

Characteristic	DeLLphi-304 (NCT05740566)	
Parameter	Tarlatamab (n=85)	Topotecan (n=81)
ECOG PS 1, n (%)	61 (71.8)	59 (72.8)
ECOG PS 2, n (%)	1 (1.2)	1 (1.2)
Disease stage IV at initial diagnosis, n (%)	64 (75.3)	66 (81.5)
Disease stage IV at screening, n (%)	82 (96.5)	74 (91.4)
Metastatic at screening, n (%)	78 (91.8)	74 (91.4)
Brain metastases at baseline: yes, n (%)	38 (44.7)	37 (45.7)
Liver metastases at baseline: yes, n (%)	30 (35.3)	35 (43.2)
Sum of diameters of target lesions (mm), mean (SD)	93.9 (61.6)	98.5 (58.3)
CFI <90 days, n (%)	85 (100.0)	81 (100.0)
Prior lines of therapy: 1, n (%)	82 (96.5)	79 (97.5)
Time from initial diagnosis to randomisation (months), mean (SD)	7.69 (5.01)	8.00 (4.10)
Prior PD-1/L1 inhibitor therapy: yes, n (%)	57 (67.1)	54 (66.7)
Prior radiotherapy for current malignancy: yes, n (%)	45 (52.9)	43 (53.1)
Prior surgery for current malignancy: yes, n (%)	7 (8.2)	8 (9.9)
Treatment duration, median [Q1, Q3] (weeks)	13.50 [4.36, 29.14]	6.43 [0.86, 15.71]
Treatment discontinuation, n (%)	70 (82.4)	74 (91.4)
Study discontinuation, n (%)	44 (51.8)	63 (77.8)

Abbreviations: CFI … chemotherapy-free interval, ECOG PS … Eastern Cooperative Oncology Group Performance Status, N/n … number of patients, PD-1/L1 … programmed cell death protein 1/programmed death-ligand 1, Q1 … first quartile, Q3 … third quartile, SD … standard deviation

Inclusion and exclusion criteria

Ein- und Ausschlusskriterien der DeLLphi-304-Studie

Inclusion and exclusion criteria of the DeLLphi-304 study are depicted in Table 4-5. Key criteria included adults with confirmed ES-SCLC, disease progression after one prior platinum-based chemotherapy line, ECOG PS 0 or 1, and no prior therapy with tarlatamab, selective DLL3 inhibitors, or the standard-of-care (SoC) chemotherapy agents included in the trial. Radiotherapy was generally prohibited except for symptom control of bone or brain metastases, excluding the thoracic field, completed ≥7 days prior to the next tarlatamab dose.

Table 4-5: Inclusion and exclusion criteria of the DeLLphi-304 study (based on [22])

DeLLphi-304 – Eligibility criteria	
Inclusion criteria	Exclusion criteria
■ Adult patients (≥18 years) ■ Histologically or cytologically confirmed ES-SCLC ■ Disease progression or recurrence after 1L of platinum-based chemotherapy (EP/anti-PD-(L)1 therapy followed by anti-PD-(L)1 maintenance counted as one regimen) ■ Measurable disease per RECIST v1.1 ■ ECOG PS of 0 or 1 ■ Adequate organ function	■ Prior therapy with tarlatamab, any selective DLL3 inhibitor, or any of the SoC chemotherapies included in the trial ■ More than one prior systemic therapy regimen for SCLC ■ Anti-cancer therapy (chemotherapy, immunotherapy, or targeted therapy), concurrent or within 21 days prior to the first dose of study treatment ■ Major surgical procedures within 28 days prior to the first dose of study treatment ■ Live vaccines within 14 days, or other vaccines within 3 days, before the first study dose ■ Radiation therapy (may be permitted for symptom control of bone or brain metastases after consultation with the medical monitor, excluding the thoracic field, completed ≥7 days prior to next tarlatamab dose)

Abbreviations: 1L … first-line, CNS … central nervous system, DLL3 … delta-like ligand 3, ECOG PS … Eastern Cooperative Oncology Group Performance Status, EP … etoposide + platinum, ES-SCLC … extensive-stage small cell lung cancer, PD-(L)1 … programmed death-(ligand) 1, RECIST v1.1 … Response Evaluation Criteria in Solid Tumours, version 1.1, SCLC … small cell lung cancer, SoC … standard of care

Efficacy results

A concise overview of efficacy results is provided in Table 4-6 below (for details, see Tables 34-37 in the JCA report [3]).

Overall survival

OS was statistically significantly longer with tarlatamab than with topotecan (hazard ratio [HR] 0.491; 95% CI: 0.332, 0.727; p<0.001; median OS: 11.1 vs 5.8 months).

stat. sign. längeres OS mit Tarlatamab vs Topotecan

Progression-free survival

PFS did not differ statistically significantly between the treatment groups (HR 0.748; 95% CI: 0.541, 1.033; p=0.078; median PFS: 2.9 vs 2.8 months).

kein stat. sign. Unterschied in PFS

Objective response rate

The ORR was statistically significantly higher with tarlatamab than with topotecan (OR 6.698; 95% CI: 2.426, 18.496; p<0.001; ORR: 30.6% vs 6.2%).

stat. sign. höhere ORR zugunsten Tarlatamab

Duration of response

The median DoR was 4.2 months with tarlatamab vs 5.7 months with topotecan. No effect estimate could be calculated because the analysis was restricted to responders.

DoR: keine Effektgröße erhebbar

Symptoms of disease

For BPI-SF item #3 (pain at its worst)[4], no statistically significant difference was observed on either the hazard ratio scale (HR 0.754 [0.467, 1.219]; p=0.25) or in continuous mixed-model for repeated measures (MMRM) analyses. For dyspnoea (composite score), statistically significant differences in favour of tarlatamab were observed in both the time-to-first-deterioration analysis (HR 0.558; 95% CI: 0.338, 0.921; p=0.022) and the MMRM analysis at week 19 (LS mean difference: –8.73; 95% CI: –15.64, –1.83; p=0.014).

Schmerz: kein stat. sign. Unterschied

Atemnot: stat. sign. Unterschied zugunsten Tarlatamab

Health-related quality of life (HRQoL) – EORTC QLQ-C30

The MMRM analyses at week 19 also showed statistically significant differences in favour of tarlatamab for global health status/quality of life (QoL) (least squares [LS] mean difference: 9.35; 95% CI: 0.66, 18.03; p=0.035), physical functioning, role functioning, social functioning, and fatigue. No significant differences were observed for emotional functioning, cognitive functioning, nausea and vomiting, or pain. The time-to-first-deterioration analysis for global health status/QoL showed no significant difference; however, a significant difference in favour of tarlatamab was observed for physical functioning (HR 0.600; 95% CI: 0.390, 0.924; p=0.019).

stat. sign. besserer gesamter Gesundheitsstatus mit Tarlatamab, inklusive Funktionsfähigkeit

[4] BPI-SF item #3 assesses the intensity of the worst pain experienced by patients over the previous 24 hours on a 0-10 numerical rating scale and is used to evaluate changes in pain severity.

HRQoL – EORTC QLQ-LC13

For the single-item scales, coughing and pain in the chest, the time-to-first-deterioration analyses showed statistically significant differences in favour of tarlatamab (coughing: HR 0.502; 95% CI: 0.283, 0.890; p=0.017; pain in chest: HR 0.501; 95% CI: 0.271, 0.928; p=0.025).

stat. sign. längerer Zeitraum bis zur Verschlechterung mit Tarlatamab

Health status (EQ-5D-5L)

The MMRM analyses at week 19 also presented a statistically significant difference in favour of tarlatamab for the dimension 'usual activities' (LS mean difference: –0.43; 95% CI: –0.82, –0.05; p=0.027). No significant differences were observed for mobility, self-care, pain/discomfort, anxiety/depression, or the visual analogue scale (VAS). The VAS time-to-first-deterioration analysis also showed no significant difference (HR 0.662; 95% CI: 0.435, 1.008; p=0.056).

stat. sign. Unterschied lediglich für „normale Aktivitäten" zugunsten Tarlatamab

Table 4-6: Efficacy results of the DeLLphi-304 study (based on [3])

Study reference/ID Outcome Measure	DeLLphi-304		
	Tarlatamab n=85	Topotecan n=81	HR/OR [95% CI]; p-value
Efficacy outcomes			
Median PFS, months [95% CI]	2.9 [1.7, 4.2]	2.8 [1.9, 3.1]	HR 0.748 [0.541, 1.033]; p=0.078
ORR, n (%)	26 (30.6)	5 (6.2)	OR 6.698 [2.426, 18.496]; p<0.001
Median DoR, months [95% CI]	4.2 [3.0, 5.6]	5.7 [2.3, NE]	NA (biased outcome)
Symptoms of disease			
BPI-SF item #3 (pain at its worst) [95% CI]	24.1 [12.2, 34.2]	12.4 [7.8, NE]	HR 0.754 [0.467, 1.219]; p=0.25
Dyspnoea composite score [95% CI]	30.6 [20.1, 35.7]	12.5 [7.1, NE]	0.558 [0.338, 0.921]; p=0.022
HRQoL – EORTC QLQ-LC13			
Coughing [95% CI]	NE [24.6, NE]	18.5 [9.7, NE]	HR 0.502 [0.283, 0.890]; p=0.017
Pain in chest [95% CI]	42.0 [24.6, NE]	NE [15.9, NE]	HR 0.501 [0.271, 0.928]; p=0.025
Health status (EQ-5D VAS) [95% CI]	12.5 [7.8, 30.2]	6.7 [6.3, 10.0]	0.662 [0.435, 1.008]; p=0.056
Health-related quality of life (EORTC QLQ-C30)			
Global health status/QoL [95% CI]	3.1 [2.1, 5.3]	3.1 [2.3, 4.3]	0.938 [0.646, 1.363]; p=0.72
Physical functioning [95% CI]	18.5 [5.3, NE]	7.1 [3.1, 8.3]	0.600 [0.390, 0.924]; p=0.019
Health status (EQ-5D-5L) week 19			
Usual activities	-	-	–0.43 [–0.82, –0.05]; p=0.027
Mobility, self-care, pain/discomfort, anxiety/depression	-	-	No significant difference
VAS	-	-	0.73 [–7.82, 9.29]; p=0.86

Abbreviations: BPI-SF … Brief Pain Inventory – Short Form, CI … confidence interval, DoR … duration of response, EORTC QLQ-C30/LC13 … European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (core/lung cancer 13), EQ-5D-5L … EuroQol 5-Dimension 5-Level, HR … hazard ratio, HRQoL … health-related quality of life, LS … least-squares, n … number, NA … not available, NE … not estimable, OR … odds ratio, ORR … objective response rate, OS … overall survival, PFS … progression-free survival, VAS … visual analogue scale

Safety outcomes

Descriptive safety data for PICO 1 are shown in Table 4-7 below. Relative safety results with effect estimates are presented in the JCA Appendix C.3.1.1, and AEs by system organ class and preferred term in Appendix C.3.2.1. Subgroup analyses showed significant interactions between treatment and prior

Zusammenhang zw. Behandlung/PD-1/L1 Status, Alter und schweren UEs

PD-1/L1 status and age for SAEs, treatment interruption due to AEs, PFS, and EQ-5D-5L VAS (see JCA Tables 39-40 [3]).

Adverse events

Descriptive safety outcomes are presented in detail in Table 38 of the JCA. Time-to-event analyses accounting for these differences are shown in the JCA Appendix C.3.1.1 [3].

Severe adverse events (CTCAE grade ≥3)

schwere UEs bei weniger Pat. mit Tarlatamab

The proportion of patients with at least one severe AE was lower with tarlatamab than topotecan (59.5% vs 84.4%), driven by haematological toxicities with topotecan and CRS and ICANS with tarlatamab.

Serious adverse events

schwerwiegende UEs bei mehreren Pat. mit Tarlatamab

SAEs were reported in 56.0% with tarlatamab and 50.6% with topotecan, driven by serious CRS and pyrexia in the tarlatamab arm and blood and lymphatic system disorders and pneumonia in the topotecan arm. Detailed data by System Organ Class and Preferred Term are available in the JCA Appendix C.3.2.1 [3].

Deaths (adverse events of grade 5)

mehr Todesfälle bedingt durch UEs mit Topotecan

AE-related deaths occurred in 8.3% with tarlatamab and 11.7% with topotecan. The primary cause of death in both arms was progressive disease.

mehr Therapieabbrüche bedingt durch UEs mit Topotecan

Treatment discontinuation due to an AE occurred less frequently with tarlatamab than with topotecan (7.1% vs 15.6%). All discontinuations in the tarlatamab group were attributed to SAEs; in the topotecan group, discontinuations comprised both serious (10.4%) and non-serious (7.8%) causes.

Treatment interruption due to adverse event

mehr Therapie-unterbrechungen bedingt durch UEs mit Topotecan

Treatment interruption due to an AE was reported in 34.5% with tarlatamab and 46.8% with topotecan, driven by CRS and immune-mediated events with tarlatamab and cumulative haematological toxicity with topotecan.

Overall, relative safety results with effect estimates are provided in JCA Appendix C.3.1.1 [3].

Table 4-7: Safety results of the DeLLphi-304 study (based on [3])

Adverse event	Tarlatamab (n=84)	Topotecan (n=77)	Tarlatamab vs topotecan RR [95% CI]	Main drivers (tarlatamab vs topotecan)
Study reference/ID	DeLLphi-304, n (%)			
Any AEs, n (%)	83 (98.8)	77 (100.0)	0.988 [0.965, 1.012]	-
Severe AE (CTCAE grade ≥3), n (%)	50 (59.5)	65 (84.4)	0.705 [0.577, 0.862]	CRS: 59.5% vs 0%; ICANS: 7.1% vs 0%; anaemia: 33.3% vs 63.6%; neutropenia: 8.3% vs 26.0%; thrombocytopenia: 7.1% vs 26.0%; leukopenia: 11.9% vs 29.9%
SAE, n (%)	47 (56.0)	39 (50.6)	1.105 [0.826, 1.478]	Serious CRS: 25.0% vs 0%; pyrexia: 4.8% vs 0%; blood & lymphatic disorders: 2.4% vs 18.2%; pneumonia: 2.4% vs 11.7%
Death related to AE (CTCAE grade 5), n (%)	7 (8.3)	9 (11.7)	0.713 [0.279, 1.822]	Primary cause in both arms: progressive disease
Treatment discontinuation due to AE, n (%)	6 (7.1)	12 (15.6)	0.458 [0.181, 1.162]	SAEs: 7.1% vs 10.4%; non-serious AEs: 0% vs 7.8%

Adverse event	Tarlatamab (n=84)	Topotecan (n=77)	Tarlatamab vs topotecan RR [95% CI]	Main drivers (tarlatamab vs topotecan)
Study reference/ID	DeLLphi-304, n (%)			
Treatment interruption due to AE, n (%)	29 (34.5)	36 (46.8)	0.738 [0.506, 1.079]	CRS and immune-mediated events/cumulative haematological toxicity

Abbreviations: AE … adverse event, CRS … cytokine release syndrome, CTCAE … Common Terminology Criteria for Adverse Events, ICANS … immune effector cell-associated neurotoxicity syndrome, RR …relative risk, SAE … serious adverse event

4.3.2 PICO 2: tarlatamab vs CAV (ITC)

PICO 2: behandlungsfreies Intervall <3 Monaten; Vergleich: CAV

PICO 2 addresses population A, comprising adult patients with ES-SCLC who progressed on or within three months of first-line platinum-based chemotherapy (TFI <3 months, platinum-resistant, n=108). The comparator is CAV (cyclophosphamide plus doxorubicin plus vincristine) from the GFPC 0501 trial (n=66).

kein direkter Vergleich: ungeankerte MAIC

For PICO 2, the HTD submitted an unanchored MAIC, in which individual patient data from the tarlatamab arm of DeLLphi-304 were reweighted to match the aggregate baseline characteristics of the CAV population from GFPC 0501, as no direct comparative data between tarlatamab and CAV were available. A base case adjusted for age, sex, ECOG PS, and disease stage, and a scenario 2 additionally adjusting for the standard deviation of age were submitted.

Study population and baseline characteristics

Subpopulation der DeLLphi-304-Studie ähnlich mit dem CAV-Studienarm der GFPC 0501 Studie bzgl. Alter, Geschlecht, ECOG-Status, Krankheitsstadium bei Diagnose

The two populations were comparable for age, sex, ECOG PS, and disease stage at initial diagnosis (Table 4-8). However, several potentially important characteristics were not reported in GFPC 0501 and could therefore not be compared: brain metastases, liver metastases, prior anti-PD-1/L1 inhibitor exposure, time since initial diagnosis, race, and smoking history. Of these, prior PD-1/L1 inhibitor exposure is the most clinically relevant difference: approximately two-thirds of DeLLphi-304 patients had received such therapy as part of first-line treatment, whereas this drug class was not yet available during GFPC 0501 enrolment. Relevant baseline differences between the populations therefore cannot be excluded. Treatment duration in the tarlatamab arm was a median of 14.4 weeks; no treatment duration or subsequent therapy data are available for GFPC 0501.

Table 4-8: Baseline patient characteristics – PICO 2 (Population A, TFI <3 months, before and after MAIC weighting) (based on [3])

Characteristic Study reference/ID	DeLLphi-304 subpopulations			GFPC 0501
	Tarlatamab unadjusted (n=108)[a]	Tarlatamab adjusted base case (ESS=78.4)[b]	Tarlatamab adjusted scenario 2 (ESS=75.7)[c]	CAV unadjusted (n=66)
Age (years), mean (SD)	62.7 (10.4)	60.6 (10.8)	60.6 (8.7)	60.6 (8.7)
Sex female, n (%)	26 (24.1)	22.3 (24.2)	21.7 (24.3)	16 (24.2)
Sex male, n (%)	82 (75.9)	69.6 (75.8)	67.5 (75.8)	50 (75.8)
ECOG PS ≥1, n (%)	80 (74.1)	59.9 (65.2)	58.1 (65.2)	43 (65.2)
Disease stage extensive, n (%)	86 (79.6)[d]	54.3 (59.1)	52.7 (59.1)	39 (59.1)[e]
CFI <90 days, n (%)	108 (100)	91.9 (100.0)	89.2 (100.0)	66 (100)
Treatment discontinuation, n (%)	89 (81.7)	NR	NR	NR

Characteristic Study reference/ID	DeLLphi-304 subpopulations			GFPC 0501
	Tarlatamab unadjusted (n=108)[a]	Tarlatamab adjusted base case (ESS=78.4)[b]	Tarlatamab adjusted scenario 2 (ESS=75.7)[c]	CAV unadjusted (n=66)
Study discontinuation, n (%)	59 (54.1)	NR	NR	NR

Abbreviations: CAV … cyclophosphamide/doxorubicin/vincristine, CFI … chemotherapy-free interval, ECOG PS … Eastern Cooperative Oncology Group Performance Status, ESS … effective sample size, MAIC … matching-adjusted indirect comparison, n … number, NR … not reported, SD … standard deviation

Notes: Patient numbers for the DeLLphi-304 study differ across PICOs, as each PICO reflects a distinct CFI- or RFI-defined subpopulation of the same trial.

[a] *All patients from the tarlatamab arm of the DeLLphi-304 study with CFI<90 days, except 1 patient who was excluded from the analyses due to missing information on disease stage at initial diagnosis*

[b] *Adjusted for age (mean only), sex, ECOG PS, disease stage at initial diagnosis*

[c] *Same as the base case, except adjusting for both mean and standard deviation for age*

[d] *AJCC TNM stage IV at initial diagnosis in the DeLLphi-304 study was used as an approximation for the extensive stage*

[e] *GFPC 0501 reported the number of patients who did not have localised disease at diagnosis*

Inclusion and exclusion criteria

Einschlusskriterien der GFPC 0501-Studie, keine Ausschlusskriterien berichtet

Inclusion and exclusion criteria of the DeLLphi-304 study are depicted previously in Table 4-5. For GFPC 0501, eligible patients were adults with histologically confirmed SCLC who had experienced early disease progression within three months of completing first-line cisplatin-based chemotherapy (CFI <90 days). Patients were required to have fully recovered from prior treatment with no residual toxicity. Prior radiotherapy was permitted, provided it had been administered outside the measurable lesion. No formal exclusion criteria are reported in the JCA and no clinical study report was available for this study.

Efficacy results

An overview of the results is provided in Table 4-9 below (for full details see Tables 47 and 48 of the JCA report [3]).

Overall survival

stat. sign. längeres OS mit Tarlatamab vs CAV

OS was statistically significantly longer with tarlatamab than with CAV in both the adjusted base case (HR 0.48; 95% CI: 0.32, 0.70; p<0.001; median OS: 10.71 vs 5.77 months) and adjusted scenario 2 (HR 0.45; 95% CI: 0.31, 0.67; p<0.001; median OS: 10.91 vs 5.77 months).

Progression-free survival

kein stat. sign. Unterschied in PFS

PFS did not differ statistically significantly between tarlatamab and CAV for either the adjusted base case (HR 0.88; 95% CI: 0.62, 1.24; p=0.502; median PFS: 2.99 vs 3.03 months) or adjusted scenario 2 (HR 0.89; 95% CI: 0.63, 1.26; p=0.539).

Objective response rate

kein stat. sign. Unterschied in ORR

The ORR did not differ statistically significantly between tarlatamab and CAV for either the adjusted base case (Odds ratio [OR] 0.93; 95% CI: 0.45, 1.92; p=0.849; ORR: 26% vs 27%) or adjusted scenario 2 (OR 0.97; 95% CI: 0.47, 2.01; p=0.934).

No ITC was feasible for DoR, symptoms of disease, HRQoL, or health status, as these outcomes were not assessed in GFPC 0501.

kein indirekter Vergleich möglich aufgrund fehlender Vergleichsdaten

Table 4-9: Efficacy results – PICO 2 (tarlatamab vs CAV, Population A, unanchored MAIC) (based on [3])

Study reference/ID Outcome Measure	DeLLphi-304		GFPC 0501	Tarlatamab vs CAV		
	Tarlatamab Sample size[a]	Tarlatamab Median TTE	CAV Median TTE (n=66)	ESS (%[b]) (DeLLphi-304)	ITC Method	HR/OR [95% CI]; p-value
OS base case, median, months [95% CI]	91.9	10.71 [8.28, 12.81]	5.77 [4.53, 7.26]	78.4 (72.6)	MAIC base case	HR 0.48 [0.32, 0.70] p<0.001
OS scenario 2, median, months [95% CI]	89.2	10.91 [8.28, 12.81]	5.77 [4.53, 7.26]	75.7 (70.1)	MAIC scenario 2	HR 0.45 [0.31, 0.67] p<0.001
PFS base case, median, months [95% CI]	91.9	2.99 [1.74, 4.17]	3.03 [2.19, 3.88]	78.4 (72.6)	MAIC base case	HR 0.88 [0.62, 1.24] p=0.502
PFS scenario 2, median, months [95% CI]	89.2	2.99 [2.23, 4.17]	3.03 [2.19, 3.88]	75.7 (70.1)	MAIC scenario 2	HR 0.89 [0.63, 1.26] p=0.539
ORR base case, rate [95% CI]	91.9	0.26 [0.18, 0.36]	0.27 [0.18, 0.39]	78.4 (72.6)	MAIC base case	OR 0.93 [0.45, 1.92] p=0.849
ORR scenario 2, rate [95% CI]	89.2	0.27 [0.18, 0.37]	0.27 [0.18, 0.39]	75.7 (70.1)	MAIC scenario 2	OR 0.97 [0.47, 2.01] p=0.934
DoR	-	-	-	-	N/A	Not estimable (no GFPC 0501 data)

Abbreviations: CAV … cyclophosphamide/doxorubicin/vincristine, CI … confidence interval, DoR … duration of response, ESS … effective sample size after MAIC weighting, HR … hazard ratio, ITC … indirect treatment comparison, MAIC … matching-adjusted indirect comparison, n … number, N/A … not applicable, OR … odds ratio, ORR … objective response rate, OS … overall survival, PFS … progression-free survival, TTE … time-to-event

Notes: All p-values are nominal; no prespecified hypothesis testing or multiplicity adjustment was applied.

[a] *Corresponds to the sum of the weights of all individuals.*

[b] *Percentages correspond to the unweighted total sample size.*

Safety outcomes

No results for safety outcomes are available for PICO 2. An ITC was not feasible because the relevant safety outcomes were not assessed in GFPC 0501 in a form comparable to DeLLphi-304.

keine Sicherheitsergebnisse für PICO 2 verfügbar

4.3.3 PICO 3: tarlatamab vs platinum-rechallenge (ITC)

PICO 3 addresses population B, comprising adult patients with ES-SCLC who progressed at least three months after first-line platinum-based chemotherapy (TFI ≥3 months, platinum-sensitive). The comparator is retreatment with platinum-based chemotherapy (operationalised as carboplatin plus etoposide). As no direct comparative data between tarlatamab and platinum rechallenge are available, the HTD submitted an ITC using both a Bayesian NMA and a Bucher ITC. Both drew on the relevant subpopulation of DeLLphi-304 (tarlatamab [n=111] vs topotecan [n=104]) and the full population of Baize et al. (2020) (carboplatin plus etoposide [n=81] vs topotecan [n=81]) with topotecan as the common comparator. The network was then expanded to a 'population-level' network, which included all comparators within the corresponding population, by adding the von Pawel et al. (1999) study, which linked topotecan to the combination of CAV. Both methods yielded comparable point estimates.

PICO 3: Pat. mit behandlungsfreiem Intervall von ≥3 Monaten

Vergleich mit erneuter platinbasierter Chemotherapie

Study population and baseline characteristics

Subpopulation der DeLLphi-304-Studie: indirekter Vergleich mit Pat. aus Baize 2020

Unterschiede in: den Baseline-Charakteristika und der Datenverfügbarkeit und nachfolgenden Therapien

Demographic and disease characteristics were largely balanced within each study (Table 4-10). Regarding inter-study comparability, the available baseline data from Baize et al. (2020) are very limited, and several critical differences were observed between the two studies: more than 70% of DeLLphi-304 patients had received prior PD-1/L1 inhibitors, a drug class not yet available at the time of the comparator trial. Moreover, ECOG PS 2 patients were eligible (~6-8%) but practically absent from DeLLphi-304 (<1%). Liver metastases were more common in the Baize et al. (2020) (45% vs ~31%), and the proportion of patients with TFI ≥180 days was higher in the DeLLphi-304 trial (44% vs 30%). Besides, subsequent therapy data differ substantially between the two studies. Approximately 63% of Baize et al. (2020) patients received at least one subsequent therapy (mainly platinum + etoposide [21%], topotecan [17%], and CAV [14%]), compared to approximately 43% of DeLLphi-304 patients (mainly single-agent carboplatin, etoposide, and topotecan; combination chemotherapy in only 1.4%).

Table 4-10: Baseline patient characteristics – PICO 3 (Population B, TFI ≥3 months, platinum-sensitive patients, DeLLphi-304 and Baize et al. (2020)) (based on [3])

Characteristic Study reference/ID	DeLLphi-304		Baize et al. (2020)	
	Tarlatamab (n=111)	Topotecan (n=104)	Carboplatin + etoposide (n=81)	Topotecan (n=81)
Age (years), mean (SD)	63.5 (8.6)	63.9 (7.8)	NR	NR
Age (years), median (range)	NR	65 (40-80)	64 (37-84)	64 (43-81)
Age group 18-64, n (%)	56 (50.5)	49 (47.1)	NR	NR
Age group 65-74, n (%)	44 (39.6)	48 (46.2)	NR	NR
Age group 75-84, n (%)	11 (9.9)	7 (6.7)	NR	NR
Sex female/male, %	30.6/69.4	38.5/61.5	38.3/61.7	27.2/72.8
Region: Europe, n (%)	79 (71.2)	65 (62.5)	NR	NR
Region: Asia, n (%)	27 (24.3)	31 (29.8)	NR	NR
Smoking: never/current/former, n (%)	7/23/81 (6.3/20.7/73.0)	14/19/71 (13.5/18.3/68.3)	NR	NR
ECOG PS 0, n (%)	49 (44.1)	39 (37.5)	28 (34.6)	26 (32.1)
ECOG PS 1, n (%)	61 (55.0)	65 (62.5)	48 (59.3)	48 (59.3)
ECOG PS 2, n (%)	1 (0.9)	0 (0)	5 (6.2)	7 (8.6)
Extensive disease at enrolment, n (%)[a]	77 (69.4)	70 (67.3)	52 (64.2)	51 (63.0)
Brain metastases at baseline: yes, n (%)	49 (44.1)	41 (39.4)	27 (33.3)	30 (37.0)
Liver metastases at baseline: yes, n (%)	32 (28.8)	34 (32.7)	36 (44.4)	37 (45.7)
Platinum-sensitive, n (%)	111 (100)	104 (100)	81 (100)	81 (100)
CFI ≥90 days, n (%)	111 (100)	104 (100)	NR	NR
Prior lines of therapy: 1, n (%)	109 (98.2)	100 (96.2)	NR	NR
Prior PD-1/L1 inhibitor therapy: yes, n (%)	77 (69.4)	72 (69.2)	NR (not available)	NR (not available)
Prior radiotherapy: yes, n (%)	79 (71.2)	72 (69.2)	NR	NR
Treatment discontinuation, n (%)	73 (65.8)	84 (80.8)	39 (48.1)	58 (71.6)
Study discontinuation, n (%)	41 (36.9)	51 (49.0)	NR	NR

Abbreviations: CFI … chemotherapy-free interval, ECOG PS … Eastern Cooperative Oncology Group Performance Status, n … number, NR … not reported, PD-1/L1 … programmed cell death protein 1/programmed death-ligand 1, RFI … recurrence-free interval, SD … standard deviation, TFI … treatment-free interval

Notes: Patient numbers for the DeLLphi-304 study differ across PICOs, as each PICO reflects a distinct CFI- or RFI-defined subpopulation of the same trial.

[a] *AJCC TNM stage IV at initial diagnosis used as approximation for extensive stage in DeLLphi-304; comparability with the Baize 2020 definition is uncertain.*

Inclusion and exclusion criteria

Ein- und Ausschlusskriterien für PICO 3

Inclusion and exclusion criteria for DeLLphi-304 are depicted previously in Table 4-5. For Baize et al. (2020), eligible patients were adults (≥18 years) with histologically or cytologically confirmed SCLC, stage IV disease or localised relapse outside the radiation field, prior objective response to first-line platinum-based chemotherapy, measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, ECOG PS 0-2, adequate organ function, and at least 90 days between progression/relapse and the last dose of prior chemotherapy. Immunotherapy or experimental treatment as first-line therapy was an exclusion criterion. No formal exclusion criteria table is available in the JCA for Baize et al. (2020); eligibility is described narratively only.

Efficacy results

For PICO 3, results on relative effectiveness are available for OS, PFS, and ORR, derived from the ITC. An overview of results is provided in Table 4-11 below (for full details, see Tables 59 and 60 of the JCA report [3]).

Overall survival

stat. sign. längeres OS mit Tarlatamab

The OS was statistically significantly longer with tarlatamab than with carboplatin plus etoposide in both analyses. In the Bayesian NMA, the 95% credible interval excluded 1 (HR 0.61; 95% CrI: 0.39, 0.95); in the Bucher ITC, the difference was also significant (HR 0.61; 95% CI: 0.39, 0.95; p=0.029). In the individual studies used for the indirect comparison median OS was 13.9 months with tarlatamab vs 7.50 months with carboplatin plus etoposide.

Progression-free survival

kein stat. sign. Unterschied in PFS

The PFS did not differ statistically significantly between tarlatamab and carboplatin plus etoposide. In the Bayesian NMA, no significant difference was observed (HR 1.38; 95% CrI: 0.87, 2.19). Similar results were obtained with the Bucher ITC (HR 1.38; 95% CI: 0.87, 2.19; p=0.157). In the individual studies used for the indirect comparison, median PFS was 5.4 months for tarlatamab (DeLLphi-304) and 4.70 months for carboplatin plus etoposide (Baize 2020).

Objective response rate

kein stat. sign. Unterschied in ORR

The ORR did not differ statistically significantly between tarlatamab and carboplatin plus etoposide. In the Bayesian NMA, no significant difference was observed (OR 0.51; 95% CrI: 0.21, 1.25). Similar results were obtained with the Bucher ITC (OR 0.51; 95% CI: 0.21, 1.25; p=0.139). In the individual studies used for the indirect comparison, ORR was 35.1% for tarlatamab (DeLLphi-304) and 48.1% for carboplatin plus etoposide (Baize 2020).

Duration of response

kein Effektschätzer zu DoR

No comparative data were available for DoR. Therefore, the outcome is reported descriptively based on the individual study results only. Median DoR was 6.8 months for tarlatamab (DeLLphi-304) and 5.4 months for carboplatin plus etoposide (Baize et al. (2020)). No comparative effect estimate is available for this outcome.

keine Vergleichsdaten zu Symptomen und QoL

No comparative data were available for symptoms of disease, HRQoL, or health status, as these outcomes were not assessed in Baize et al. (2020).

Table 4-11: Efficacy results – PICO 3 (Tarlatamab vs carboplatin + etoposide, Population B, indirect comparison) (based on [3])

Outcome/Comparison	Study	Tarlatamab or carboplatin + etoposide/CAV Median time to event in months [95% CI]; patients with event n (%)	Topotecan Median time to event in months [95% CI]; patients with event n (%)	N (intervention/ topotecan)	Effect estimate [95% CrI/CI]; p-value
OS, months					
Tarlatamab vs topotecan	DeLLphi-304	13.9 [11.2, NE]; 41 (36.9)	11.4 [7.6, NE]; 51 (49.0)	111/104	HR 0.63 [0.41, 0.95]
Carboplatin + etoposide vs topotecan	Baize 2020	7.50 [5.40, 9.50]; 77 (95.0)	7.40 [6.00, 8.70]; 79 (98.0)	81/81	HR 1.03 [0.88, 1.20]
ITC (Bucher): tarlatamab vs carboplatin + etoposide	-	-	-	-	HR 0.61 [0.39, 0.95]; p=0.029
ITC (Bayesian NMA): tarlatamab vs carboplatin + etoposide	-	-	-	-	HR 0.61 [0.39, 0.95]
PFS, months					
Tarlatamab vs topotecan	DeLLphi-304	5.4 [4.2, 5.7]; 84 (75.7)	4.3 [3.4, 5.3]; 83 (79.8)	111/104	HR 0.79 [0.58, 1.07]
Carboplatin + etoposide vs topotecan	Baize 2020	4.70 [3.90, 5.50]; 79 (97.5)	2.70 [2.30, 3.20]; 81 (100.0)	81/81	HR 0.57 [0.40, 0.80]
ITC (Bucher): tarlatamab vs carboplatin + etoposide	-	-	-	-	HR 1.38 [0.87, 2.19]; p=0.157
ITC (Bayesian NMA): tarlatamab vs carboplatin + etoposide	-	-	-	-	HR 1.38 [0.87, 2.19]
ORR					
Tarlatamab vs topotecan	DeLLphi-304	39 (35.1)	27 (26.0)	111/104	OR 1.56 [0.86, 2.83]
Carboplatin + etoposide vs topotecan	Baize 2020	39 (48.1)	19 (23.5)	81/81	OR 3.07 [1.57, 6.10]
ITC (Bucher): tarlatamab vs carboplatin + etoposide	-	-	-	-	OR 0.51 [0.21, 1.25]; p=0.139
ITC (Bayesian NMA): tarlatamab vs carboplatin + etoposide	-	-	-	-	OR 0.51 [0.21, 1.25]
Duration of response, months – descriptive only, responders					
Tarlatamab (responders)	DeLLphi-304	6.8 [4.2, NE]	-	39 resp.	NR
Carboplatin + etoposide (responders)	Baize 2020	5.4 [2.2, 9.3]	-	39 resp.	NR

Abbreviations: CAV … cyclophosphamide + doxorubicin + vincristine, CI … confidence interval, CrI … credible interval, DoR … duration of response, HR … hazard ratio, ITC … indirect treatment comparison, N … number, NE … not estimable, NMA … network meta-analysis, NR … not reported, OR … odds ratio, ORR … objective response rate, OS … overall survival, PFS … progression-free survival, resp. … responders

Notes: All CrIs are 95% credible intervals from the Bayesian NMA; CI from the Bucher ITC. No prespecified hypothesis testing; all p-values nominal.

Safety outcomes

No results for safety outcomes are available for PICO 3. An ITC was not feasible because safety outcomes were not defined and measured consistently across the two studies: the comparator trial, Baize et al. (2020) only reported

keine Sicherheitsdaten verfügbar

treatment-related adverse events (TRAEs) and did not provide data on overall AE rates, SAEs, or the individual safety categories.

4.3.4 PICO 4 – tarlatamab vs topotecan (direct comparison)

PICO 4: Pat. mit behandlungsfreiem Intervall von ≥3 Monaten; Vergleich: Topotecan

PICO 4 addresses population B, comprising adult patients with ES-SCLC who progressed at least three months after first-line platinum-based chemotherapy (TFI ≥3 months, platinum-sensitive; n=111). The comparator is topotecan, assessed in a direct comparison using a subpopulation of DeLLphi-304 (n=104).

Study population and baseline characteristics

Subpopulation der DeLLphi-304 Studie, verglichen mit Topotecan

Demographics and disease characteristics were largely balanced (Table 4-12), with minor imbalances in sex, ECOG PS 0, and smoking status, all favouring the tarlatamab group. Treatment duration was markedly longer in the tarlatamab group (median 22.1 vs 8.1 weeks), resulting in substantially differential observation periods for PRO and safety outcomes. Approximately 70% of patients in both arms had received a prior PD-1/L1 inhibitor. Subsequent therapy was received by a similar proportion of patients in both groups (~43%), though tyrosine kinase inhibitors were more frequent in the topotecan group (32.6% vs 6.4%). Information on the first subsequent line of therapy was not reported.

Table 4-12: Baseline patient characteristics – PICO 4 (Population B, DeLLphi-304 subpopulation) (based on [3])

Characteristic Study reference/ID	DeLLphi-304	
	Tarlatamab (n=111)	Topotecan (n=104)
Age (years), mean (SD)	63.5 (8.6)	63.9 (7.8)
Age group 18-64, n (%)	56 (50.5)	49 (47.1)
Age group 65-74, n (%)	44 (39.6)	48 (46.2)
Age group 75-84, n (%)	11 (9.9)	7 (6.7)
Sex female/male, %	30.6/69.4	38.5/61.5
Region: Europe, n (%)	79 (71.2)	65 (62.5)
Region: Asia, n (%)	27 (24.3)	31 (29.8)
Smoking: never/current/former, n (%)	7/23/81 (6.3/20.7/73.0)	14/19/71 (13.5/18.3/68.3)
ECOG PS 0, n (%)	49 (44.1)	39 (37.5)
ECOG PS 1, n (%)	61 (55.0)	65 (62.5)
ECOG PS 2, n (%)	1 (0.9)	0 (0)
Extensive disease at enrolment, n (%)[a]	77 (69.4)	70 (67.3)
Disease stage IV at screening, n (%)	97 (87.4)	93 (89.4)
Brain metastases at baseline: yes, n (%)	49 (44.1)	41 (39.4)
Liver metastases at baseline: yes, n (%)	32 (28.8)	34 (32.7)
Platinum-sensitive, n (%)	111 (100)	104 (100)
CFI ≥90 days, n (%)	111 (100)	104 (100)
CFI ≥90 and <180 days, n (%)	63 (56.8)	58 (55.8)
CFI ≥180 days, n (%)	48 (43.2)	46 (44.2)
Sum of diameters of target lesions (mm), mean (SD)	85.4 (54.1)	85.9 (49.1)
Prior lines of therapy: 1, n (%)	109 (98.2)	100 (96.2)

Characteristic Study reference/ID	DeLLphi-304	
	Tarlatamab (n=111)	Topotecan (n=104)
Time from initial diagnosis to randomisation (months), mean (SD)	12.61 (6.15)	15.03 (8.69)
Prior PD-1/L1 inhibitor therapy: yes, n (%)	77 (69.4)	72 (69.2)
Prior radiotherapy: yes, n (%)	79 (71.2)	72 (69.2)
Prior surgery: yes, n (%)	9 (8.1)	6 (5.8)
Treatment duration, median [Q1, Q3] (weeks)	22.1 [4.4, 57.9]	8.1 [1.4, 15.7]
Treatment discontinuation, n (%)	73 (65.8)	84 (80.8)
Study discontinuation, n (%)	41 (36.9)	51 (49.0)

Abbreviations: CFI … chemotherapy-free interval, ECOG PS … Eastern Cooperative Oncology Group Performance Status, PD-1/L1 … programmed cell death protein 1/programmed death-ligand 1, Q1 … first quartile, Q3 … third quartile, SD … standard deviation

Notes: Patient numbers for the DeLLphi-304 study differ across PICOs, as each PICO reflects a distinct CFI- or RFI-defined subpopulation of the same trial.

[a] *AJCC TNM stage IV at initial diagnosis used as approximation for extensive stage in DeLLphi-304.*

Inclusion and exclusion criteria

Inclusion and exclusion criteria for the DeLLphi-304 study are depicted in Table 4-5 in the PICO 1 chapter.

Efficacy results

Wirksamkeitsergebnisse basierend auf einem direkten Vergleich

For PICO 4, results on relative effectiveness are available for OS, PFS, ORR, and DoR, derived from the direct comparison within DeLLphi-304. All results are based on the subpopulation of DeLLphi-304 with a CFI ≥90 days. An overview of results is provided in Table 4-13 below (full details see Tables 63-66 of the JCA report [3]).

Overall survival

stat. sign. längeres OS mit Tarlatamab

OS was statistically significantly longer with tarlatamab than with topotecan (HR 0.628; 95% CI: 0.415, 0.951; p=0.028; median OS: 13.9 vs 11.4 months).

Progression-free survival

kein stat. sign. Unterschied in PFS

PFS did not differ statistically significantly between the treatment groups (HR 0.788; 95% CI: 0.581, 1.069; p=0.13; median PFS: 5.4 vs 4.3 months).

Objective response rate

kein stat. sign. Unterschied in ORR

The ORR did not differ statistically significantly between the treatment groups (OR 1.545; 95% CI: 0.859, 2.777; p=0.15; ORR: 35.1% vs 26.0%).

Duration of response

kein Effektschätzer für DoR

The median DoR was 6.8 months with tarlatamab compared to 5.4 months with topotecan. No effect estimate could be calculated because the analysis was restricted to responders.

Symptoms of disease

For BPI-SF item #3 (pain at its worst), no statistically significant difference was observed on either the HR scale (HR 0.919; 95% CI: 0.612, 1.381; p=0.68) or in MMRM analyses at week 19 (LS mean difference: –0.24; 95% CI: –0.97, 0.50; p=0.52). For dyspnoea, statistically significant differences in favour of tarlatamab were observed in both the time-to-first-deterioration analysis (HR 0.544; 95% CI: 0.357, 0.829; p=0.004) and the MMRM analysis at week 19 (LS mean difference: –6.42; 95% CI: –11.13, –1.72; p=0.004).

kein stat. sign. Unterschied bzgl. Schmerz, jedoch hinsichtlich Atemnot

HRQoL – EORTC QLQ-C30

MMRM analyses at week 19 showed a statistically significant difference in favour of tarlatamab for global health status/QoL. Time-to-first-deterioration analyses for global health status/QoL and physical functioning did not show significant differences (details see JCA, Table 66 [3]).

stat. sign. besserer Gesundheitszustand mit Tarlatamab

HRQoL – EORTC QLQ-LC13

Dyspnoea as a composite score was analysed in two complementary ways. In the time-to-first-deterioration analysis, the difference was statistically significant in favour of tarlatamab (HR 0.544; 95% CI: 0.357, 0.829; p=0.004; median time to deterioration 38.6 vs 17.9 weeks). In the MMRM analysis of change from baseline at week 19, the difference was also statistically significant in favour of tarlatamab (LS mean difference –6.42; 95% CI: –11.13, –1.72; p=0.004). Both analyses point in the same direction (details see JCA, Tables 63-66 [3]).

stat. sign. Unterschied bzgl. Dyspnoe zugunsten Tarlatamab

Health status (EQ-5D-5L)

MMRM analyses at week 19 showed a statistically significant difference in favour of tarlatamab for the dimension ‘usual activities’ only (LS mean difference: –0.27; 95% CI: –0.53, –0.02; p=0.037). No significant differences were observed for the remaining dimensions or the VAS, including time-to-first-deterioration.

stat. sign. Unterschied zugunsten Tarlatamab bei „normalen Aktivitäten“

Table 4-13: Efficacy results – PICO 4 (Population B, DeLLphi-304 subpopulation, baseline patient characteristics) (based on [3])

Study reference/ID Outcome Measure	DeLLphi-304		Results
	Tarlatamab	Topotecan	
	Time to event [95% CI]		Effect estimate [95% CI]; p-value
Number of patients	111	104	
OS, median (months)	13.9 [11.2, NE]	11.4 [7.6, NE]	HR 0.628 [0.415, 0.951]; p=0.028
PFS, median (months)	5.4 [4.2, 5.7]	4.3 [3.4, 5.3]	HR 0.788 [0.581, 1.069]; p=0.13
ORR, n (%)	39 (35.1)	27 (26.0)	OR 1.545 [0.859, 2.777]; p=0.15
DoR, median (months)	6.8 [4.2, NE] (n=39 responders)	5.4 [3.0, 6.1] (n=27 responders)	NA (only patients with a CR or PR are considered and randomisation is no longer maintained; no effect measure can be calculated)
	Effect estimate [95% CI]; p-value		MMRM week 19 – LS mean change [95% CI]; p-value
Symptoms of disease			
BPI-SF item #3 (pain at its worst)	HR 0.919 [0.612, 1.381]; p=0.68		–0.24 [–0.97, 0.50]; p=0.52
Dyspnoea (composite score)	HR 0.544 [0.357, 0.829]; p=0.004		–6.42 [–11.13, –1.72]; p=0.004
HRQoL – EORTC QLQ-C30			
Global health status/QoL	HR 1.137 [0.827, 1.563]; p=0.44		6.37 [0.90, 11.85]; p=0.023
Physical functioning	HR 0.939 [0.641, 1.374]; p=0.74		7.47 [1.54, 13.41]; p=0.007

Study reference/ID Outcome Measure	DeLLphi-304		Results
	Tarlatamab	Topotecan	
Role functioning	NA		8.89 [1.62, 16.17]; p=0.017
Social functioning	NA		10.45 [3.28, 17.62]; p=0.005
Fatigue	NA		−10.07 [−17.05, −3.10]; p=0.005
Emotional functioning, cognitive functioning, nausea and vomiting, pain	NA		No significant difference
HRQoL – EORTC QLQ-LC13			
Dyspnoea (single-item)	NA		−5.76 [−10.82, −0.69]; p=0.026
Coughing	HR 0.681 [0.415, 1.116]; p=0.12		NA
Pain in chest	HR 0.703 [0.443, 1.117]; p=0.14		NA
Health status – EQ-5D			
VAS	0.747 [0.534, 1.044]; p=0.086		4.40 [−0.84, 9.65]; p=0.099
Health status – EQ-5D-5L			
Usual activities	NA		−0.27 [−0.53, −0.02]; p=0.037
Mobility, self-care, pain/discomfort, anxiety/depression	NA		No significant difference

Abbreviations: BPI-SF … Brief Pain Inventory – Short Form, CI … confidence interval, DoR … duration of response, EORTC QLQ-C30/LC13 … European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (core/lung cancer 13), EQ-5D-5L … EuroQol 5-Dimension 5-Level, HR … hazard ratio, HRQoL … health-related quality of life, LS … least-squares, MMRM … mixed model for repeated measures, n .,. number, NA … not available, NE … not estimable, OR … odds ratio, ORR … objective response rate, OS … overall survival, PFS … progression-free survival, QoL … quality of life, VAS … visual analogue scale

Safety outcomes

Sicherheitsergebnisse: Zusammenhang zw. Behandlung und Hirnmetastasen auf OS

Descriptive safety data for PICO 4 are shown in Table 4-14 below; relative safety results are provided in JCA Appendix C.3.1.2 and AEs by system organ class (SOC) and preferred term (PT) in Appendix C.3.2.2 [3]. Subgroup analyses showed significant interactions between treatment and brain metastasis at baseline for OS, dyspnoea, global health status/QoL, and pain in chest (JCA, Tables 68-69 [3]).

AEs of all grades – general overview

Descriptive safety outcomes are presented in detail in JCA Table 67. Time-to-event analyses are provided in JCA Appendix C.3.1.2, and detailed data by SOC and PT in JCA Appendix C.3.2.2 [3].

Severe adverse events (CTCAE grade ≥3)

weniger schwere UEs mit Tarlatamab

Severe AEs were less frequent with tarlatamab than topotecan (41.4% vs 82.8%), driven by CRS in the tarlatamab arm and haematological toxicities in the topotecan arm.

Serious adverse events

weniger schwerwiegende UEs mit Tarlatamab

SAEs were reported in 44.1% with tarlatamab and 56.6% with topotecan, driven by serious CRS in the tarlatamab arm and blood and lymphatic system disorders in the topotecan arm.

Deaths (AEs of grade 5)

AE-related deaths were comparable between groups (7.2% vs 8.1%); however, given the small numbers and open-label design, no meaningful conclusion can be drawn.

UE-bedingte Todesfälle vergleichbar

Treatment discontinuation due to adverse event

Treatment discontinuation due to an AE was less frequent with tarlatamab than topotecan.

weniger Therapieabbrüche mit Tarlatamab

Treatment interruption due to adverse event

Treatment interruption due to an AE was less frequent with tarlatamab than topotecan, driven by CRS in the tarlatamab arm and cumulative haematological toxicity in the topotecan arm.

weniger Therapieunterbrechungen mit Tarlatamab

Table 4-14: Safety results – PICO 4 (Population B, DeLLphi-304 subpopulation, baseline patient characteristics) (based on [3])

Study reference/ID	DeLLphi-304		Main drivers (tarlatamab vs topotecan)
Adverse event	Tarlatamab (n=111)	Topotecan (n=99)	
Any AE, n (%)	109 (98.2)	98 (99.0)	-
Severe AE (CTCAE grade ≥3), n (%)	46 (41.4)	82 (82.8)	CRS: 49.5% vs 0% (of which serious: 29.1% vs 0%); haematological toxicities predominant in topotecan arm
SAE, n (%)	49 (44.1)	56 (56.6)	Serious CRS: 29.1% vs 0%; blood & lymphatic disorders predominant in topotecan arm
Death related to AE (CTCAE grade 5), n (%)	8 (7.2)	8 (8.1)	Small numbers; no meaningful conclusion
Treatment discontinuation due to AE, n (%)	6 (5.4)	14 (14.1)	-
thereof serious, n (%)	4 (3.6)	11 (11.1)	-
thereof non-serious, n (%)	2 (1.8)	4 (4.0)	-
Treatment interruption due to AE, n (%)	35 (31.5)	56 (56.6)	CRS and immune-mediated events vs cumulative haematological toxicity

Abbreviations: AE … adverse event, CRS … cytokine release syndrome, CTCAE … Common Terminology Criteria for Adverse Events, n … number

Notes: Events directly related to lung cancer or disease progression were excluded.
CRS and ICANS events graded per ASTCT 2019 criteria.

4.3.5 PICO 5: tarlatamab vs CAV (ITC)

PICO 5 addresses population B (TFI ≥3 months, platinum-sensitive), with CAV as comparator. As no direct comparative data are available, the HTD submitted a Bayesian NMA based on a subpopulation of DeLLphi-304 and the complete population of von Pawel et al. (1999), with topotecan as the common comparator.

PICO 5: behandlungsfreies Intervall ≥3 Monate, verglichen mit CAV

Study population and baseline characteristics

Subpopulation der DeLLphi-304-Studie – indirekter Vergleich mit Pat. der von Pawel 1999 Studie.

limitierte Vergleichbarkeit der Baseline-Charakteristika

The PICO 5 population comprises tarlatamab patients with CFI ≥90 days from DeLLphi-304 and all patients from the CAV arm of von Pawel et al. (1999). The two populations were not comparable for several key baseline characteristics (Table 4-15). Approximately 20% of the comparator-trial patients had an ECOG PS of 2 vs <1% in DeLLphi-304, while brain metastases were considerably more frequent in DeLLphi-304 (41.8% vs 17.5%). Around a fifth of those patients also had a CFI of 60-90 days, deviating from the PICO 5 definition. Most critically, over 70% of DeLLphi-304 patients had received prior PD-1/L1 inhibitors, a drug class not yet available during that trial's enrolment period. Not all its patients had received platinum-based first-line chemotherapy either, and key variables including age and smoking history are not reported. No subsequent therapy data are available, and OS was defined differently between studies. Overall, the assessors consider the similarity assumption to be severely violated, and the certainty of all PICO 5 results is very low.

Table 4-15: Baseline patient characteristics – PICO 5 (Population B, DeLLphi-304 and von Pawel et al. (1999)) (based on [3])

Characteristic Study reference/ID	DeLLphi-304		von Pawel et al. (1999)	
	Tarlatamab (n=111)	Topotecan (n=104)	CAV (n=104)	Topotecan (n=107)
Age (years), mean (SD)	63.5 (8.6)	63.9 (7.8)	NR	NR
Sex female/male, %	30.6/69.4	38.5/61.5	31.7/68.3	43.0/57.0
Smoking history	6.3% never, 20.7% current, 73.0% former	13.5% never, 18.3% current, 68.3% former	NR	NR
ECOG PS 0-1, n (%)	110 (99.1)	104 (100)	84 (80.8)	82 (76.6)
ECOG PS 2, n (%)	1 (0.9)	0 (0)	20 (19.2)	25 (23.4)
Extensive disease at enrolment, n (%)	77 (69.4)[a]	70 (67.3)[a]	88 (84.6)	89 (83.2)
Brain metastases at baseline: yes, n (%)	49 (44.1)	41 (39.4)	25 (24.0)	12 (11.2)
Liver metastases at baseline: yes, n (%)	32 (28.8)	34 (32.7)	42 (40.4)	43 (40.2)
CFI ≥90 days, n (%)	111 (100)	104 (100)	NR	NR
CFI 60-90 days, n (%)	0 (0)	0 (0)	21 (20.2)[b]	22 (20.6)[b]
Prior 1L platinum-based chemotherapy, n (%)	111 (100)	104 (100)	82 (78.8)	82 (76.6)
Prior PD-1/L1 inhibitor therapy: yes, n (%)	77 (69.4)	72 (69.2)	NR (not available in 1999)	NR (not available in 1999)
Prior radiotherapy: yes, n (%)	79 (71.2)	72 (69.2)	58 (55.8)	66 (61.7)
Prior surgery: yes, n (%)	9 (8.1)	6 (5.8)	29 (27.9)	15 (14.0)

Abbreviations: 1L … first-line, CAV … cyclophosphamide/doxorubicin/vincristine, CFI … chemotherapy-free interval, ECOG PS … Eastern Cooperative Oncology Group Performance Status, NR … not reported, PD-1/L1 … programmed cell death protein 1/programmed death-ligand 1, SD … standard deviation, TFI … treatment-free interval

Notes: Patient numbers for the DeLLphi-304 study differ across PICOs, as each PICO reflects a distinct CFI- or RFI-defined subpopulation of the same trial.

[a] AJCC TNM stage IV at initial diagnosis used as approximation for extensive stage in DeLLphi-304.

[b] Von Pawel 1999 enrolled patients with CFI ≥60 days, meaning approximately 20% had a CFI of 60-90 days, which falls outside the PICO 5 definition of TFI ≥3 months.

Inclusion and exclusion criteria

Ein- und Ausschlusskriterien für PICO 5

Inclusion and exclusion criteria for DeLLphi-304 are depicted in Table 4-5 in the chapter PICO 1. In von Pawel et al. (1999), eligible patients were adults with histologically confirmed SCLC, disease progression at least 60 days after first-line chemotherapy, at least one measurable lesion, and ECOG PS 0-2. Notably, not all patients had received platinum-based first-line chemotherapy. No formal exclusion criteria are reported in the JCA for von Pawel et al. (1999).

Efficacy results

Wirksamkeitsergebnisse basierend auf einer Netzwerk-Metaanalyse

Results on relative effectiveness are available for OS and ORR only, derived from the Bayesian NMA. PFS could not be estimated as no PFS data were reported in von Pawel et al. (1999). An overview of the results is provided in Table 4-16 and Table 4-17 below (for full details see JCA, Tables 74 and 75 [3]).

Overall survival

kein stat. sign. Unterschied in OS

OS was not statistically significantly different between tarlatamab and CAV (HR 0.65; 95% credible interval [CrI]: 0.40, 1.08]).

Progression-free survival

kein indirekter Vergleich in PFS möglich

An ITC was not feasible as PFS data were not reported in von Pawel et al. (1999).

Objective response rate

kein stat. sign. Unterschied in ORR

There was no statistically demonstrable difference in the ORR between tarlatamab and CAV (OR 2.24; 95% CrI: 0.93, 5.55).

Duration of response

keine ITC für DoR, stattdessen medianes DoR pro Studie berichtet

An ITC was not feasible because DoR was measured only in patients who responded to treatment. Since responders are not a randomised group, the two studies' responders are no longer comparable, so no valid relative comparison can be made. For transparency, median DoR is reported per study: 6.8 months for tarlatamab (DeLLphi-304) and 14.4 weeks for CAV (von Pawel 1999).

No comparative data were available for symptoms of disease, HRQoL and health status. Median DoR is reported descriptively for each study but cannot be compared due to different units of reporting and restriction to responders.

Table 4-16: Efficacy results – PICO 5 (Population B, DeLLphi-304 and von Pawel et al. (1999)) (based on [3])

Outcome/ Study reference/ID	n	Tarlatamab/Carboplatin + Etoposide/CAV Median TTE months [95% CI]	n	Topotecan Median TTE months [95% CI]	Group difference HR [95% CrI] p-value
OS					
Tarlatamab vs topotecan DeLLphi-304	111	13.9 [11.2, NE]	104	11.4 [7.6, NE]	0.63 [0.41, 0.95][a] NR
Carboplatin + etoposide vs topotecan Baize et al. (2020)	81	7.50 [5.40, 9.50]	81	7.40 [6.00, 8.70]	1.03 [0.88, 1.20][a] NR
CAV vs topotecan von Pawel et al. (1999)	104	5.68 [NR, NR]	107	5.75 [NR, NR]	0.96 [0.73, 1.27][a] NR
Indirect comparison (Bayesian NMA[b]): tarlatamab vs CAV	-	-	-	-	0.65 [0.40, 1.08] NR
PFS					

Outcome/ Study reference/ID	n	Tarlatamab/Carboplatin + Etoposide/CAV Median TTE months [95% CI]	n	Topotecan Median TTE months [95% CI]	Group difference HR [95% CrI] p-value
Tarlatamab vs topotecan DeLLphi-304	111	5.4 [4.2, 5.7]	104	4.3 [3.4, 5.3]	0.79 [0.58, 1.07][a] NR
Carboplatin + etoposide vs topotecan Baize et al. (2020)	81	4.70 [3.90, 5.50]	81	2.70 [2.30, 3.20]	0.57 [0.40, 0.80][a] NR
CAV vs topotecan von Pawel et al. (1999)	NR	NR	NR	NR	NR
Indirect comparison (Bayesian NMA[b]): tarlatamab vs CAV	-	-	-	-	NR
DoR					
Tarlatamab vs topotecan DeLLphi-304	39	6.8 [4.2, NE]	27	5.1 [2.2, 9.3]	NR
Tarlatamab vs carboplatin + etoposide Baize et al. (2020)	39	5.4 [2.2, 9.3]	19	4.1 [1.8, 10.2]	NR
CAV vs topotecan von Pawel et al. (1999)	19	14.4 [NR, NR]	26	15.3 [NR, NR]	NR
Indirect comparison (Bayesian NMA[b]): tarlatamab vs CAV	-	-	-	-	NR

Abbreviations: CAV … cyclophosphamide/doxorubicin/vincristine, CI … confidence interval, CrI … credible interval, DoR … duration of response, HR … hazard ratio, NE … not estimable, NMA … network meta-analysis, NR … not reported, OS … overall survival, PFS … progression-free survival, TTE … time-to-event

Notes:

[a] *Effect estimates derived from the population-based Bayesian NMA.*

[b] *Population-based network considering the studies DeLLphi-304, Baize et al. (2020), and von Pawel et al. (1999).*

Table 4-17: Efficacy results (dichotomous outcomes) – PICO 5 (Population B, DeLLphi-304 and von Pawel et al. (1999)) (based on [3])

Outcome/ Study reference/ID	N	Tarlatamab/Carboplatin + Etoposide/CAV Patients with event n (%)	N	Topotecan Patients with event n (%)	OR [95% CrI] p-value
ORR					
tarlatamab vs Topotecan DeLLphi-304	111	39 (35.1)	104	27 (26.0)	1.56 [0.86, 2.83][a] NR
carboplatin + etoposide vs topotecan Baize et al. (2020)	81	39 (48.1)	81	19 (23.5)	3.07 [1.57, 6.10][a] NR
CAV vs topotecan von Pawel et al. (1999)	104	19 (18.3)	107	26 (24.3)	0.69 [0.35, 1.36][a] NR
Indirect comparison (Bayesian NMA[b]): tarlatamab vs CAV	-	-	-	-	2.24 [0.93, 5.55] NR

Abbreviations: CAV … cyclophosphamide/doxorubicin/vincristine, CrI … credible interval, N … number of patients in the analysis, NMA … network meta-analysis, NR … not reported, OR … odds ratio, ORR … objective response rate

Notes:

[a] *Effect estimates derived from the population-based Bayesian NMA.*

[b] *95% confidence interval*

Safety outcomes

No results for safety outcomes are available for PICO 5.

keine Sicherheitsergebnisse

4.3.6 PICO 6: tarlatamab vs topotecan (direct comparison)

PICO 6: rezidivfreies Intervall ≤ 6 Monate Vergleich: Topotecan

PICO 6 addresses population C (RFI ≤6 months, not suitable for retreatment with platinum-based chemotherapy), with topotecan as comparator in a direct comparison using a subpopulation of DeLLphi-304 restricted to patients with a CFI ≤180 days.

Study population and baseline characteristics

Subpopulation der DeLLphi-304 Studie, verglichen mit Topotecan

The PICO 6 population comprises tarlatamab (n=148) vs topotecan (n=142) patients from DeLLphi-304 with a CFI ≤180 days, spanning population A (CFI <90 days, 57.4%) and the short-interval segment of population B (CFI 90-180 days, 42.6%). Baseline characteristics were largely balanced (Table 4-18), with minor imbalances in ECOG PS, smoking status, and liver metastasis rates. Treatment duration was markedly longer with tarlatamab (median 16.1 vs 9.4 weeks). About two-thirds of patients in both arms had received prior PD-1/L1 inhibitors. First subsequent-line therapy was not reported. Notably, 29.9% of tarlatamab patients continued treatment beyond initial radiographic progression, vs 13.4% with topotecan.

Table 4-18: Baseline patient characteristics – PICO 6 (Population C, RFI ≤6 months, DeLLphi-304) (based on [3])

Characteristic Study reference/ID	DeLLphi-304	
	Tarlatamab (n=148)	Topotecan (n=142)
Age (years), mean (SD)	62.7 (9.7)	63.6 (8.9)
Age group 18-64, n (%)	76 (51.4)	68 (47.9)
Age group 65-74, n (%)	59 (39.9)	64 (45.1)
Age group 75-84, n (%)	13 (8.8)	10 (7.0)
Sex female/male, %	30.4/69.6	31.7/68.3
Weight (kg), mean (SD)	72.8 (15.9)	72.6 (15.6)
Region: Europe, n (%)	94 (63.5)	90 (63.4)
Region: Asia, n (%)	45 (30.4)	43 (30.3)
Smoking: never/current/former, n (%)	14/27/107 (9.5/18.2/72.3)	15/31/96 (10.6/21.8/67.6)
ECOG PS 0, n (%)	51 (34.5)	42 (29.6)
ECOG PS 1, n (%)	96 (64.9)	99 (69.7)
ECOG PS 2, n (%)	1 (0.7)	1 (0.7)
Disease stage IV at initial diagnosis, n (%)	109 (73.6)	108 (76.1)
Disease stage IV at screening, n (%)	140 (94.6)	128 (90.1)
Metastatic at screening, n (%)	135 (91.2)	131 (92.3)
Brain metastases at baseline: yes, n (%)	69 (46.6)	66 (46.5)
Liver metastases at baseline: yes, n (%)	51 (34.5)	58 (40.8)
Sum of diameters of target lesions (mm), mean (SD)	92.5 (59.0)	94.2 (55.5)
CFI <90 days, n (%)	85 (57.4)	81 (57.0)
CFI ≥90 and <180 days, n (%)	63 (42.6)	58 (40.8)
Prior lines of therapy: 1, n (%)	144 (97.3)	137 (96.5)
Time from initial diagnosis to randomisation (months), mean (SD)	8.44 (4.32)	9.06 (4.39)
Prior PD-1/L1 inhibitor therapy: yes, n (%)	101 (68.2)	96 (67.6)
Prior radiotherapy: yes, n (%)	87 (58.8)	84 (59.2)

Characteristic Study reference/ID	DeLLphi-304	
	Tarlatamab (n=148)	Topotecan (n=142)
Prior surgery: yes, n (%)	13 (8.8)	11 (7.7)
Treatment duration, median [Q1, Q3] (weeks)	16.14 [5.00, 35.14]	9.43 [3.71, 16.29]
Treatment discontinuation, n (%)	113 (76.4)	126 (88.7)
Study discontinuation, n (%)	72 (48.6)	97 (68.3)

Abbreviations: CFI … chemotherapy-free interval, ECOG PS … Eastern Cooperative Oncology Group Performance Status, PD-1/L1 … programmed cell death protein 1/programmed death-ligand 1, Q1 … first quartile, Q3 … third quartile, RFI … recurrence-free interval, SD … standard deviation

Note: Patient numbers for the DeLLphi-304 study differ across PICOs, as each PICO reflects a distinct CFI- or RFI-defined subpopulation of the same trial.

Inclusion and exclusion criteria

Inclusion and exclusion criteria of the DeLLphi-304 study are depicted in Table 4-5 in the PICO 1 chapter.

Efficacy outcomes

A concise overview of efficacy results is provided in Table 4-19 below (for details, see Tables 81-84 of the JCA report [3]).

Wirksamkeitsergebnisse

Overall survival

OS was statistically significantly longer with tarlatamab than with topotecan (HR 0.578; 95% CI: 0.426, 0.786, p<0.001, median 11.2 vs 6.4 months).

stat. sign. längeres OS mit Tarlatamab

Progression-free survival

PFS was statistically significantly longer with tarlatamab (HR 0.769; 95% CI: 0.600, 0.987, p=0.039, median 3.5 vs 3.1 months).

stat. sign. längeres PFS mit Tarlatamab

Objective response rate

ORR was statistically significantly higher with tarlatamab (OR 2.681; 95% CI: 1.504, 4.781, p<0.001, 31.8% vs 14.8%).

stat. sign. höhere ORR mit Tarlatamab

Duration of response

Median DoR was 5.6 vs 5.7 months. No effect estimate could be calculated because the analysis was restricted to responders.

kein Effektschätzer für DoR verfügbar

Symptoms of disease

No statistically significant difference was observed for BPI-SF item #3 (pain as ist worst) in either analysis. Statistically significant differences in favour of tarlatamab were observed for dyspnoea (composite score) in both time-to-first-deterioration and MMRM analyses.

stat. sign. Unterschied bzgl. Atemnot

HRQoL – EORTC QLQ-C30

MMRM analyses at week 19 showed statistically significant differences in favour of tarlatamab for global health status/QoL, physical functioning, role functioning, social functioning, and fatigue. No significant differences were observed for the remaining scales. Time-to-first-deterioration analyses for global

stat. sign. besserer Gesundheitszustand und Funktionsfähigkeit mit Tarlatamab

health status/QoL and physical functioning did not show significant differences.

HRQoL – EORTC QLQ-LC13

Statistically significant differences in favour of tarlatamab were observed in MMRM analyses for dyspnoea and in time-to-first-deterioration analyses for coughing and pain in chest.

stat. sign. Unterschied bzgl. Dyspnoe zugunsten Tarlatamab

Health status (EQ-5D-5L)

MMRM analyses at week 19 showed statistically significant differences in favour of tarlatamab for mobility and usual activities only. No significant differences were observed for the remaining dimensions or the VAS MMRM analysis. The VAS time-to-first-deterioration analysis showed a statistically significant difference in favour of tarlatamab.

stat. sign. Unterschied in Mobilität und „normalen Aktivitäten" mit Tarlatamab

Table 4-19: Efficacy results – PICO 6 (Population C, RFI ≤6 months, DeLLphi-304) (based on [3])

Study reference/ID Outcome Measure	DeLLphi-304		Results
	Tarlatamab (n=148)	Topotecan (n=142)	
	Time to event [95% CI]		Effect estimate [95% CI]; p-value
PFS, median (months)	3.5 [2.9, 4.2]	3.1 [2.8, 3.8]	HR 0.769 [0.600, 0.987]; p=0.039
ORR, n (%)	47 (31.8)	21 (14.8)	OR 2.681 [1.504, 4.781]; p<0.001
DoR, median (months)	5.6 [4.2, NE] (n=47 responders)	5.7 [3.5, 6.1] (n=21 responders)	NA (only patients with a CR or PR are considered and randomisation is no longer maintained; no effect measure can be calculated)
	Effect estimate [95% CI]; p-value		MMRM week 19 – LS mean change [95% CI]; p-value
Symptoms of disease			
BPI-SF item #3 (pain at its worst)	HR 0.823 [0.575, 1.178]; p=0.28		–0.32 [–1.02, 0.39]; p=0.37
Dyspnoea composite score	HR 0.531 [0.364, 0.774]; p<0.001		–7.92 [–12.71, –3.12]; p=0.001
HRQoL – EORTC QLQ-C30			
Global health status/QoL	HR 1.057 [0.800, 1.397]; p=0.72		7.54 [1.81, 13.28]; p=0.010
Physical functioning	HR 0.793 [0.572, 1.101]; p=0.16		11.99 [5.62, 18.35]; p<0.001
Role functioning	NA		15.18 [7.63, 22.73]; p<0.001
Social functioning	NA		12.54 [5.73, 19.34]; p<0.001
Fatigue	NA		–12.09 [–19.10, –5.07]; p<0.001
Emotional functioning, cognitive functioning, nausea and vomiting, pain	NA		No significant difference
HRQoL – EORTC QLQ-LC13			
Dyspnoea	NA		–7.52 [–12.71, –2.32]; p=0.005
Coughing	HR 0.589 [0.382, 0.909]; p=0.016		NA
Pain in chest	HR 0.644 [0.420, 0.989]; p=0.044		NA
Health status – EQ-5D			
VAS; time to first deterioration	HR 0.654 [0.482, 0.889]; p=0.007		NA
Health status			
Mobility	NA		–0.29 [–0.55, –0.03]; p=0.030
Usual activities	NA		–0.35 [–0.59, –0.10]; p=0.006
Self-care, pain/discomfort, anxiety/depression	NA		No significant difference
VAS	NA		2.62 [–2.75, 7.99]; p=0.34

Abbreviations: BPI-SF … Brief Pain Inventory – Short Form, CI … confidence interval, CR … complete response, DoR … duration of response, EORTC QLQ-C30/LC13 … European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D(-5L) … EuroQol 5-Dimension (5-Level), HR … hazard ratio, HRQoL … health-related quality of life, LS … least-squares, MMRM … mixed model for repeated measures, NA … not available, NE … not estimable, OR … odds ratio, ORR … objective response rate, OS … overall survival, PFS … progression-free survival, PR … partial response, VAS … visual analogue scale

Safety outcomes

Sicherheitsergebnisse

Descriptive safety data are summarised in Table 4-20; relative safety results are provided in JCA Appendix C.3.1.3 and AEs by system organ class and preferred term in Appendix C.3.2.3 [3]. Subgroup analyses showed significant interactions for severe and SAEs with prior PD-1/L1 status, for treatment interruption with liver metastasis at baseline, and for PFS with age (JCA, Tables 86-87 [3]).

AEs of all grades – general overview

weniger schwere UEs, Abbrüche und Unterbrechungen

Severe AEs, treatment discontinuation, and treatment interruption occurred less frequently with tarlatamab than with topotecan, while SAEs were comparable (Table 4-20).

Severe adverse events (CTCAE grade ≥3)

weniger schwere UEs mit Tarlatamab

Severe AEs were less frequent with tarlatamab than topotecan (53.1% vs 81.3%), driven by CRS in the tarlatamab arm and haematological toxicities in the topotecan arm.

Serious adverse events and Deaths (AEs of grade 5)

schwerwiegende UEs und Todesfälle vergleichbar

SAEs and deaths related to an AE were comparable between groups.

Treatment discontinuation due to adverse event

weniger Therapieabbrüche mit Tarlatamab

Treatment discontinuation due to an AE occurred in 6.1% with tarlatamab and 14.9% with topotecan.

Treatment interruption due to adverse event

weniger Therapie-unterbrechungen mit Tarlatamab

Treatment interruption due to an AE was reported in 32.7% with tarlatamab and 48.5% with topotecan.

Table 4-20: Safety results – PICO 6 (Population C, RFI ≤6 months, DeLLphi-304) (based on [3])

Study reference/ID	DeLLphi-304		Main drivers (tarlatamab vs topotecan)
Adverse event	Tarlatamab (n=147)	Topotecan (n=134)	
Any AE, n (%)	145 (98.6)	133 (99.3)	-
Severe AE (CTCAE grade ≥3), n (%)	78 (53.1)	109 (81.3)	CRS: 57.1% vs 0% (of which serious: 40.5% vs 0%); haematological toxicities predominant in topotecan arm
SAE, n (%)	80 (54.4)	74 (55.2)	Comparable between groups; detailed data by SOC and PT in JCA Appendix C.3.2.3 [3]
Death related to AE (CTCAE grade 5), n (%)	12 (8.2)	13 (9.7)	Comparable between groups
Treatment discontinuation due to AE, n (%)	9 (6.1)	20 (14.9)	-

Study reference/ID	DeLLphi-304		Main drivers (tarlatamab vs topotecan)
Adverse event	Tarlatamab (n=147)	Topotecan (n=134)	
serious, n (%)	8 (5.4)	15 (11.2)	-
non-serious, n (%)	1 (0.7)	8 (6.0)	-
Treatment interruption due to AE, n (%)	48 (32.7)	65 (48.5)	CRS and immune-mediated events vs cumulative haematological toxicity

Abbreviations: AE … adverse event, ASTCT … American Society for Transplantation and Cellular Therapy, CRS … cytokine release syndrome, CTCAE … Common Terminology Criteria for Adverse Events, ICANS … immune effector cell-associated neurotoxicity syndrome, JCA …joint clinical assessment, SAE … serious adverse event, SOC … system organ class

Notes: Events directly related to lung cancer or disease progression were excluded.
CRS and ICANS events graded per ASTCT 2019 criteria.

4.3.7 PICO 7: tarlatamab vs platinum-rechallenge (ITC)

PICO 7: rezidivfreies Intervall über 6 Monate, indirekter Vergleich mit Carboplatin plus Etoposid

PICO 7 addresses population D (RFI >6 months, suitable for platinum-re-challenge), with carboplatin plus etoposide as comparator. As no head-to-head comparative data were available, the HTD conducted an anchored Bucher ITC to estimate the relative treatment effect of tarlatamab versus carboplatin plus etoposide, using topotecan as the common comparator. The analysis was based on the CFI ≥180 days subpopulation from DeLLphi-304 (tarlatamab, n=48; topotecan, n=46) and the RFI ≥180 days subpopulation from Baize et al. (2020) (carboplatin plus etoposide, n=24; topotecan, n=25).

Study population and baseline characteristics

indirekter Vergleich mit Baize 2020 Studie: keine Baseline-Charakteristika verfügbar

The PICO 7 population is the smallest across all PICOs. No patient baseline characteristics, treatment duration, or subsequent therapy data are available for the Baize et al. (2020) PICO 7 subpopulation. Within DeLLphi-304, minor imbalances were noted in sex, brain metastasis rates, and extent of disease between arms, with approximately 70% of patients in both arms having received prior PD-1/L1 inhibitors (Table 4-21).

Table 4-21: Baseline patient characteristics – PICO 7 (Population D, RFI >6 months, DeLLphi-304 and Baize et al. (2020) overall) (based on [3])

Characteristic Study reference/ID	DeLLphi-304 (CFI ≥180 days)			Baize et al. (2020) – overall population[a]
	Tarlatamab (n=48)	Topotecan (n=46)	Carboplatin + etoposide (n=81)	Topotecan (n=81)
Age (years), mean (SD)	62.4 (8.2)	63.6 (7.7)	NR	NR
Age (years), median (range)	NR	NR	64 (37-84)	64 (43-81)
Age group 18-64, n (%)	28 (58.3)	23 (50.0)	NR	NR
Age group 65-74, n (%)	18 (37.5)	20 (43.5)	NR	NR
Age group 75-84, n (%)	2 (4.2)	3 (6.5)	NR	NR
Sex female/male, %	25.0/75.0	37.0/63.0	38.3/61.7	27.2/72.8
Smoking: never/current/former, n (%)	4/13/31 (8.3/27.1/64.6)	10/8/28 (21.7/17.4/60.9)	NR	NR
ECOG PS 0, n (%)	21 (43.8)	18 (39.1)	28 (34.5)	26 (32.1)
ECOG PS 1, n (%)	26 (54.2)	28 (60.9)	48 (59.3)	48 (59.3)
ECOG PS 2, n (%)	1 (2.1)	0 (0)	5 (6.2)	7 (8.6)

Characteristic Study reference/ID	DeLLphi-304 (CFI ≥180 days)			Baize et al. (2020) – overall population[a]
	Tarlatamab (n=48)	Topotecan (n=46)	Carboplatin + etoposide (n=81)	Topotecan (n=81)
Extensive disease at enrolment, n (%)[b]	39 (81.3)	42 (91.3)	52 (64.2)	51 (63.0)
Brain metastases at baseline: yes, n (%)	18 (37.5)	13 (28.3)	27 (33.3)	30 (37.0)
Liver metastases at baseline: yes, n (%)	11 (22.9)	11 (23.9)	36 (44.4)	37 (45.7)
Platinum-sensitive, n (%)	48 (100)	46 (100)	81 (100)	81 (100)
CFI ≥180 days, n (%)	48 (100)	46 (100)	NR	NR
Prior 1L platinum-based chemotherapy, n (%)	48 (100)	46 (100)	81 (100)	81 (100)
Prior PD-1/L1 inhibitor therapy: yes, n (%)	33 (68.8)	33 (71.7)	NR	NR
Prior radiotherapy: yes, n (%)	37 (77.1)	32 (69.6)	NR	NR
Treatment discontinuation, n (%)	30 (62.5)	35 (76.1)	39 (48.1)	58 (71.6)
Study discontinuation, n (%)	13 (27.1)	18 (39.1)	NR	NR

Abbreviations: CFI … chemotherapy-free interval, ECOG PS … Eastern Cooperative Oncology Group Performance Status, NR … not reported, PD-1/L1 … programmed cell death protein 1/programmed death-ligand 1, RFI … recurrence-free interval, SD … standard deviation

Note: Patient numbers for the DeLLphi-304 study differ across PICOs, as each PICO reflects a distinct CFI- or RFI-defined subpopulation of the same trial.

[a] *Patient characteristics for the PICO 7 subpopulation of Baize et al. (2020) (RFI ≥180 days: n=24/25) are not available. The overall population (N=81/81) is shown as an approximation only and does not represent the specific PICO 7 subgroup.*

[b] *AJCC TNM stage IV at enrolment used as approximation for extensive stage in DeLLphi-304.*

Inclusion and exclusion criteria

Inclusion and exclusion criteria for DeLLphi-304 are as described for PICO 1 (Table 4-4). For Baize et al. (2020), see section 4.3.3.

Efficacy results

PFS is the only outcome for which a comparative result could be derived.

Wirksamkeitsergebnisse

Progression-free survival

The Bucher ITC showed a statistically significant difference in favour of carboplatin plus etoposide (HR 3.62; 95% CI: 1.65, 7.94, p=0.001).

Bucher ITC: stat. sign. längeres PFS mit Carboplatin + Etoposid

No comparative data were available for OS, ORR, DoR, PROs and health status, as the relevant outcomes were not reported for the Baize et al. (2020) PICO 7 subpopulation. See details in Table 4-22.

keine Daten zu OS, ORR, DoR und PROs

Table 4-22: Efficacy results – PICO 7 (Tarlatamab vs carboplatin + etoposide, Population D, Bucher ITC) (based on [3])

Study reference/ID Outcome Measure	DeLLphi-304, n=48 Tarlatamab: Median [95% CI]; events n (%)	Baize et al. (2020), n=24 Carboplatin + etoposide: Median [95% CI]; events n (%)	Method	Indirect comparison HR [95% CI]; p-value
OS	NR (not available for subpopulation)	NR (not available for subpopulation)	N/A	Not estimable (no subpopulation data)
PFS (months)[a]	5.6 [NR]; 36 events (75.0%)[b]	NR [NR]: 23 events (95.8%)[b]	Bucher ITC	HR 3.62 [1.65, 7.94] p=0.001 (favours platinum-rechallenge)
ORR	NR (not available)	NR (not available)	N/A	Not estimable
DoR, symptoms, HRQoL, health status, safety	-	-	N/A	No data available

Abbreviations: CI … confidence interval, DoR … duration of response, HR … hazard ratio, HRQoL … health-related quality of life, ITC … indirect treatment comparison, N/A … not applicable, NR … not reported, ORR … objective response rate, OS … overall survival, PFS … progression-free survival.

Notes:

[a] *The PFS result is presented for transparency only and should not be regarded as reliable evidence on relative effectiveness. No prespecified hypothesis testing; p-value is nominal,*

[b] *Results from separate direct comparisons against topotecan (DeLLphi-304: tarlatamab vs topotecan; Baize et al. 2020: carboplatin + etoposide vs topotecan)*

Safety outcomes

No safety data are available for PICO 7.

keine Sicherheitsdaten für PICO 7 verfügbar

4.3.8 ESMO-MCBS scorecard for tarlatamab

According to the ESMO – Magnitude of Clinical Benefit Scale (ESMO-MCBS), tarlatamab was rated with a score 4, based on the OS gain and the increase in 2-year survival (see Table 4-23) [26].

ESMO-MCBS Score 4

Table 4-23: ESMO-MCBS of tarlatamab [26]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	Non-curative	2a	OS: 8.3 months	OS: 5.3 months	0.60 (95% CI, 0.47-0.77) p<0.001	HR ≤0.65 AND gain ≥2-3 months	4	-	Pending data	Pending data	4

Abbreviations: AJ … adjustment, CI … confidence interval, CR … complete response, ESMO-MCBS … European Society for Medical Oncology-Magnitude of Clinical Benefit Scale, FM … final magnitude of clinical benefit grade, HR … hazard ratio, Int … intention, MG … median gain, NA … not available, NC … non curative, OS … overall survival, PM … preliminary grade, PR … partial response, QoL … quality of life, ST … standard treatment

4.4 Certainty of the evidence

4.4.1 Risk of bias

JCA-RoB-Bewertung von 3 Studien:

niedriges RoB auf Studienlevel

niedriges RoB für OS

hohes RoB für ORR, DoR, PROs und Sicherheitsergebnisse

According to the JCA, for DeLLphi-304, Baize et al. (2020), and von Pawel et al. (1999), the overall RoB on the study level is considered low. At the level of individual outcomes, the RoB is considered low for OS. For the ORR, DoR, PROs and all safety outcomes, the RoB is high across all studies, except for the outcomes ORR and DoR in Baize et al. (2020). Here, the RoB is judged unclear, since it is not specified whether the central review of tumour assessment was blinded to the treatment. Regarding the PFS, the RoB is considered high in DeLLphi-304, while in Baize et al. (2020), the RoB is unclear. The high RoB for PFS, ORR, DoR, and all safety outcomes in DeLLphi-304 is primarily driven by the open-label design, in which investigators were not blinded to treatment allocation (see JCA Table 27 [3]). Further limitations concern missing post-baseline tumour assessments with unequal proportions between arms (affecting ORR and DoR), the post-randomisation selection inherent to DoR analyses, and the limited follow-up window for safety outcomes relative to differing treatment durations between arms.

keine RoB-Bewertung für PICO 2

For PICO 2, no RoB assessment was performed for the individual treatment arms of DeLLphi-304 and GFPC 0501 used in the unanchored ITC, as no RoB assessment tool is recommended for this type of analysis. However, the internal and external validity of the submitted ITC have been assessed according to the HTACG guidelines, and the assessors identified a number of major uncertainties in the relative effectiveness results, which are detailed in section 4.3.1.3 of the JCA [3].

4.4.2 Statistical analysis and inconsistencies

stat. Analyse der DeLLphi-304-Studie

All analyses for DeLLphi-304 are based on the data cut-off of 29 January 2025, representing the prespecified OS interim analysis, which also served as the primary analysis as the stopping boundaries were met. The statistical methods described in the SAP are assessed by the JCA as generally plausible (JCA, section 4.3.1.2.2.2 [3]).

Limitationen zur statistischen Analyse identifiziert im JCA

The JCA identifies the following limitations with regard to the statistical analysis. For time-to-event analyses, the HTD applied unstratified Cox proportional hazards models, whereas stratified analyses were prespecified in the SAP; the JCA considers the unstratified approach nonetheless adequate given the smaller PICO-specific sample sizes. Regarding censoring, administratively censored patients are combined with those censored due to incomplete follow-up in the results tables, limiting interpretability and the assessment of risk of bias. For ordinal PRO analyses, key information on how patients were distributed across response categories at baseline and at week 19 was not provided, making it impossible to judge which categories contained the majority of patients. The generalised linear mixed model (GLMM) results are therefore not presented in the JCA. Subgroup analyses of continuous PROs were likewise not presented, as statistically significant interaction tests were systematically inconsistent with the corresponding 95% CIs, rendering them implausible (JCA, sections 4.3.1.2.2.2 and 4.3.1.2.2.3 [3]). For PICO 2, no multiplicity adjustment was implemented across the MAIC analyses; all p-values are nominal. The sensitivity analyses do not adequately reduce decision uncertainty, given

the limited availability of information on confounding variables from GFPC 0501 (JCA, section 4.3.1.3.2.2 [3]).

4.4.3 Uncertainties and limitations per PICO according to the JCA

PICO 1 and 4

Unsicherheiten und potenzielle Verzerrung der Ergebnisse zu PICO 1: u. a. unterschiedliche Beobachtungszeiträume

In these direct comparisons, the OS results were affected by missing information on the first subsequent line of therapy and by the higher proportion of patients in the tarlatamab group treated beyond initial progression, which in an open-label study may have been influenced by knowledge of the assigned therapy. The PFS and ORR results were affected by unblinded assessment and the DoR results are potentially biased as only responders are included, and randomisation integrity could have not been preserved. PROs were affected by non-comparable observation periods, rapidly declining and unequal completion rates, unequal timing of assessments within treatment cycles, and a high proportion of deaths among deterioration events. Regarding safety results, AE observation periods differed substantially between groups and are not accounted for in relative risk analyses. The detailed limitations are presented in the JCA, sections 4.3.1.2.2.1 to 4.3.1.2.3 [3].

PICO 2

Unsicherheiten PICO 2: ungeankerte MAIC

In general, unanchored ITC carry an inherently greater RoB than randomised comparisons. Only 4 out of 10 identified prognostic and effect-modifying variables could be adjusted for, owing to missing data in GFPC 0501; positivity and overlap assumptions were not assessed, and all p-values are nominal, without adjustment for multiplicity. The OS results were additionally affected by missing subsequent therapy data in GFPC 0501. For PFS, censoring rules were not reported in GFPC 0501 and detection bias cannot be excluded given the solely investigator-based assessment in DeLLphi-304 vs additional central review in GFPC 0501. The ORR results were additionally affected by the exclusively investigator-based assessment in DeLLphi-304. For details, see JCA, section 4.3.1.3.3 [3].

PICO 3

Unsicherheiten PICO 3: Netzwerk-Metaanalyse

All results must be interpreted in the context of the severely violated similarity assumption between DeLLphi-304 and Baize et al. (2020), driven by substantial differences in baseline characteristics as described above, and the certainty of all effect estimates is considered very low. The NMA additionally lacks multiple closed loops, meaning consistency between direct and indirect estimates cannot be assessed, resulting in very low certainty of evidence. Inconsistencies in the Baize et al. (2020) input data and incompatible NMA code and data format further limit reproducibility. The OS results were additionally affected by the substantially different post-progression therapy patterns between DeLLphi-304 and Baize et al. (2020), which strongly confound this outcome, while PFS was affected by different assessment methods, diverging assessment intervals between studies, and limited information on censoring rules in Baize et al. (2020). ORR was affected by investigator-based assessment in DeLLphi-304 vs central review in Baize et al. (2020). For details, see JCA, sections 4.3.2.2.2.2 and 4.3.2.2.2.3 [3].

PICO 5

Unsicherheiten PICO 5: Annahme der Vergleichbarkeit zwischen den Studien stark limitiert

The similarity assumption between the considered studies is considered severely violated, resulting in very low certainty of evidence. Key differences between DeLLphi-304 and von Pawel et al. (1999) include a time gap of approximately 20 years, widespread prior PD-1/L1 inhibitor use in DeLLphi-304, substantial differences in performance status and brain metastasis rates, and missing information on age, smoking status, and subsequent therapies in von Pawel et al. (1999), the latter strongly confounding OS. ORR was affected by exclusively investigator-based assessment in DeLLphi-304 vs central blinded review in von Pawel et al. (1999), divergent response criteria (RECIST v1.1 vs World Health Organization [WHO]), and unreported assessment intervals in von Pawel et al. (1999). For details, see JCA, sections 4.3.2.4.1 and 4.3.2.4.3 [3].

PICO 6

Unsicherheiten PICO 6: u. a. fehlende Informationen zu Vortherapien

In this direct comparison, the OS results were affected by missing information on the first subsequent line of therapy and by the higher proportion of tarlatamab patients treated beyond initial radiographic progression. PFS and ORR were affected by unblinded, investigator-based assessment in an open-label study. DoR is potentially biased, as the analysis was restricted to responders and randomisation integrity is not preserved. Symptoms of disease, HRQoL (EORTC QLQ-C30 and QLQ-LC13), and health status results were affected by rapidly declining and differential PRO completion rates between arms, limiting the reliability of these outcomes. A further key limitation is the substantially longer treatment duration with tarlatamab (16.1 vs 9.4 weeks), which is not accounted for in the relative safety estimates. For details, see JCA, sections 4.3.1.2.2. [3].

PICO 7

Unsicherheiten PICO 7: Ergebnisse stark limitiert und nur aus Transparenzgründen berichtet

The PICO 7 population is the smallest across all PICOs. No patient baseline characteristics, treatment duration, or subsequent therapy data are available for the Baize et al. (2020) PICO 7 subpopulation, preventing any meaningful inter-study comparison. PFS is the only outcome for which a comparative result could be derived via a Bucher ITC; all other outcomes are unavailable. These results are highly uncertain and not reliable for assessing relative effectiveness; they are presented for transparency only. For details, see JCA section 4.3.4.2.3.2 and Table 91 [3].

However, certainty is extremely low due to very small subpopulation sizes, the complete absence of baseline characteristics for the Baize et al. (2020) subpopulation, and missing treatment duration, observation period, and subsequent therapy data.

4.5 Interpretation of results

Haupt-Evidenzbasis: DeLLphi-304-Studie

Evidenz pro PICO unterschiedlich robust

The clinical evidence for tarlatamab in adult patients with relapsed ES-SCLC following disease progression on or after first-line platinum-based chemotherapy is based on a single pivotal phase 3 RCT (DeLLphi-304) supported for the ITC by three historical comparator studies (GFPC 0501, Baize et al. (2020), von Pawel et al. (1999)). While DeLLphi-304 represents a methodologically robust

randomised controlled design, the evidence base is highly heterogeneous in strength and certainty, ranging from direct RCT-based comparisons against topotecan to indirect comparisons with severely violated similarity assumptions.

stat. sign. längere OS mit Tarlatamab in direkten Vergleichen

größter OS-Effekt für Pat. mit TFI <3 Monaten

The results in comparison to topotecan show, that tarlatamab demonstrated a statistically significant OS benefit across all three directly compared populations. The largest OS gain was observed in platinum-resistant population (PICO 1, TFI <3 months; median OS 11.1 vs 5.8 months; HR 0.491; 95% CI: 0.332, 0.727), where treatment options are most limited, and the unmet need is greatest. A more modest but still significant advantage was observed in patients with an RFI ≤6 months (11.2 vs 6.4 months; HR 0.578; 95% CI: 0.426, 0.786), and the smallest benefit in platinum-sensitive patients (TFI ≥3 months; 13.9 vs 11.4 months; HR 0.628; 95% CI: 0.415, 0.951), who carry a more favourable prognosis and for whom topotecan performs better. This gradient is consistent with the biological rationale that tarlatamab's mechanism may offer the greatest benefit where conventional chemotherapy is least effective. However, consulted clinical experts noted that tarlatamab's mechanism of action makes it effective regardless of platinum sensitivity status, which questions the clinical relevance of subdividing patients this way in practice.

heterogene Ergebnisse für PFS und ORR

DoR mit Vorsicht zu interpretieren

Against topotecan, PFS and ORR results were more heterogeneous than OS, plausibly reflecting the short PFS across arms and open-label assessment. A significant PFS benefit was seen only in patients with an RFI ≤6 months (HR 0.769; 95% CI: 0.600, 0.987, p=0.039), and ORR was significantly higher only in the platinum-resistant and RFI ≤6 months populations (p<0.001), but not in platinum-sensitive patients (p=0.15). DoR should be interpreted cautiously given post-randomisation selection bias, as only responders were included.

stat. sign. Ergebnisse zugunsten Tarlatamab: Dyspnoe, Gesundheitszustand/QoL → jedoch limitiert

PRO and HRQoL results versus topotecan were consistent across all three populations. No significant difference in pain was observed, but tarlatamab showed significant improvements in dyspnoea, global health status/QoL, physical functioning, and several EORTC QLQ-LC13 and EQ-5D-5L dimensions at week 19. However, these results should be interpreted cautiously due to declining and differential PRO completion rates, unequal assessment timing, a high proportion of deaths, and the longer treatment duration in the tarlatamab arm.

weniger UEs mit Tarlatamab

laut Expert.: CRS gut behandelbar

Regarding the safety results, tarlatamab showed fewer severe AEs than topotecan (41.4-59.5% vs 81.3-84.4%, driven by topotecan's haematological toxicity) but a distinct CRS (49.5-59.5%, 25-40% serious) and ICANS (7.1%) profile requiring specific management. Discontinuations/interruptions were less frequent with tarlatamab, though differing observation periods limit interpretability. Safety outcomes carry a high RoB, mainly due to the open-label design and longer tarlatamab exposure time, which is unaccounted for in relative-risk analyses; subgroup analyses showed significant interactions with prior PD-1/L1 exposure and liver metastasis. Clinical experts characterised CRS as manageable, largely confined to the first administrations, with about 80% of events of grade 1-2. Inpatient admission of the first treatment cycle is therefore currently standard in Austria, though outpatient management may become feasible with appropriate infrastructure.

schwache Evidenz für indirekte Vergleiche

Evidence from the ITCs is substantially weaker: in all cases the similarity assumption was unassessable or severely violated, largely because the historical comparators predate PD-1/L1 inhibitors, whereas ~70% of DeLLphi-304 patients received them first-line, an incomparability that statistical adjustment cannot resolve. Certainty is very low throughout. In comparison to CAV, OS nominally favoured tarlatamab in platinum-resistant disease (HR ~0.45-0.48), though this was confounded by missing subsequent-therapy data, while in the

other CAV comparison OS and ORR did not reach significance and PFS was inestimable. In comparison to carboplatin plus etoposide, OS was significantly longer with tarlatamab (13.9 vs 7.5 months; HR 0.61, p=0.029). In comparison to platinum-rechallenge, PFS numerically favoured rechallenge (HR 3.62 [1.65, 7.94]), but this is exploratory only, given missing baseline data and the acknowledged weakness of the rechallenge evidence itself. Experts noted that in platinum-resistant disease tarlatamab is clinically considered superior regardless of the formal data, and that the platinum-rechallenge evidence is itself limited, with outcomes inferior to those seen with tarlatamab.

Overall, the available evidence demonstrated a clinically meaningful OS benefit of tarlatamab over topotecan across all three directly compared populations, alongside a distinct but manageable safety profile characterised by CRS. In contrast, the ITCs are of very low certainty and do not provide reliable conclusions. The overall evidence base is high RoB for most outcomes other than OS. Nevertheless, the clinical experts broadly endorsed tarlatamab as a meaningful therapeutic option, highlighting its efficacy regardless of platinum-sensitivity status, activity in CNS disease, and manageable CRS, while cautioning that health status of real-world patients may differ substantially from the trial population.

hohes Verzerrungspotential außer für OS-Ergebnisse; Tarlatamab trozdem wichtige Therapieoption laut Expert:innen; Gesundheitszustand der Pat. aus der klinischen Praxis oft schlechter

5 Economic evaluation and budget impact analysis

This part includes confidential information!

In addition, the GÖG found a price for the UK: 955 GBP for 1 mg and 9.550 GBP for 10 mg.

Preisrecherche durch GÖG: Listenpreis für Tarlatamab aus UK

In the submitted dossier, the HTD reported that there is no list price for Austria, as tarlatamab is not yet commercially available. They report the list prices for the 10-mg vial of tarlatamab, applicable as of April 2026: $15,450 in the USA and £9,550 in the UK.

Angaben des Unternehmens: Listenpreise £ 9.550-$ 15.450

5.1 Pharmacoeconomic model(s)

5.1.1 Submitted pharmacoeconomic model

The HTD did not submit a pharmacoeconomic model to demonstrate the cost-effectiveness of tarlatamab in Austria.

kein Modell übermittelt

5.1.2 Economic evaluation based on pharmacoeconomic models

Characteristics of the economic evaluations and applied models

Countries and perspectives

Four published cost-utility analyses were identified evaluating the cost-effectiveness of tarlatamab in adult patients with ES-SCLC: The Canadian Drug Agency (CDA-AMC) [27] assessed tarlatamab from the perspective of a Canadian publicly funded healthcare payer. The National Institute for Health and Care Excellence (NICE) conducted an independent critical appraisal of the economic evaluation submitted by the HTD, from the UK NHS and Personal Social Services (PSS) payer perspective. Zheng et al. (2026) [28] and Liu et al. (2026) [29] adopted the US healthcare payer perspective; Liu et al. additionally conducted a parallel analysis from the Chinese healthcare payer perspective [29]. None of the identified analyses incorporated a societal perspective, and consequently, no indirect costs were considered in any of the models.

4 Kosten-Nutzwert-Analysen zu Tarlatamab (ES-SCLC):

Perspektiven: CDA-AMC (CAN), NICE (UK), Zheng (USA), Liu (USA + CHN); keine gesellschaftliche Perspektive → indirekte Kosten nicht berücksichtigt

Interventions, comparators, and target populations

All four analyses evaluated tarlatamab administered IV using a step-up dosing regimen: 1 mg on day 1, 10 mg on days 8 and 15, followed by 10 mg every two weeks in subsequent 28-day cycles until disease progression. The comparators differed across analyses, reflecting local clinical practice, including topotecan

Tarlatamab IV Step-up-Dosierung; Komparatoren regional unterschiedlich

(CAN, UK, USA, CHN), platinum agent plus etoposide (CAN, UK), CAV (CAN, UK), etoposide monotherapy (CAN), etoposide monotherapy (CAN), and lurbinectedin (USA, CHN) [27-30].

Regarding the target population, CDA-AMC (2025) and NICE (2025) evaluated tarlatamab in the third-line or later setting, specifically in adults with ES-SCLC who had progressed on or after at least two prior lines of therapy, including platinum-based chemotherapy [27, 30]. Zheng et al. (2026) and Liu et al. (2026) evaluated tarlatamab in the second-line setting, targeting adults with ES-SCLC who had progressed during or after first-line platinum-based chemotherapy [28, 29]. Efficacy data for all four analyses were sourced from the DeLLphi-301 (CDA-AMC [27], NICE [30]) or DeLLphi-304 (Zheng et al. [28], Liu et al. [29]) clinical trials.

Zielpopulation unterschiedlich:
CDA-AMC & NICE (2025) → 3L + (≥2 Vortherapien inkl. Platin)
Zheng & Liu et al. (2026) → Second-Line (nach Platin-Erstlinie)

Model structures and time horizons

All four analyses employed a partitioned survival model with three mutually exclusive health states: PFS, progressive or post-progressive disease (PD), and death, with all patients entering the model in the PFS state.

Partitioned-Survival-Modell mit 3 Gesundheitszuständen: Modelleintritt aller Pat. im PFS-Zustand;

CDA-AMC (2025) used a lifetime time horizon of 20 years with weekly cycles [27]; NICE (2025) applied a lifetime horizon consistent with the NICE reference case, though not explicitly stated in the guidance text [30]; Zheng et al. (2026) applied a 10-year time horizon using 28-day cycles [28]; and Liu et al. (2026) used a lifetime time horizon with monthly cycles [29].

Zeithorizont & Zykluslänge heterogen

While HTD preferred a log-logistic distribution for both OS arms, preferences varied across the included studies. Kaplan-Meier curves from the respective trials were digitised and fitted to multiple parametric survival distributions throughout. For OS, log-logistic was selected for the comparator (Zheng et al. (2026) [28]), Weibull and exponential for tarlatamab (CDA-AMC [27] and Zheng et al. (2026) [28], respectively), and gamma for the comparator (CDA-AMC [27]) or both arms (NICE [30]). For PFS, generalised gamma was preferred for both arms (HTD) or the comparator (NICE [30]), gamma for both arms (CDA-AMC [27]), and log-normal for tarlatamab (NICE [30], Zheng et al. (2026) [28]). Rather than selecting a single parametric distribution, Liu et al. (2026) applied an innovative AIC-weighted Bayesian model averaging approach to account for structural uncertainty in extrapolation choice [29].

Überlebenskurven (KM digitalisiert, parametrische Anpassung): präferierte Verteilungen divergent

Cost categories and utility values

All four analyses focused exclusively on direct medical costs, including drug acquisition and administration costs, routine follow-up, management of adverse events, BSC, and end-of-life or hospice care.

ausschließlich direkte medizinische Kosten: Arzneimittelkosten dominieren

Drug prices were sourced from national reimbursement sources: CDA-AMC referenced Canadian submitted prices (CAD $1,545/1-mg vial; CAD $15,450/10-mg vial) [27]; NICE referenced UK list prices (£955/1-mg vial; £9,550/10-mg vial), with a confidential commercial arrangement in place [30]; Zheng et al. (2026) sourced costs from CMS Medicare Part B average sales price (October 2025) and Drugs.com [28]; and Liu et al. (2026) used CMS Medicare Part B ASP data for the US ($1,567.49/mg) and assumed Chinese tarlatamab acquisition costs at one-third of the US list price, reflecting anticipated NRDL-driven discounts [29].

Preisquellen heterogen

CDA-AMC and NICE derived utility values from patient-level EQ-5D-5L data collected in DeLLphi-301 [28, 29]. For CDA-AMC, the HTD applied utilities of 0.834 (PFS) and 0.755 (PD), while the CDA-AMC reanalysis applied alternative values from published Canadian literature (PFS=0.720; PD=0.520) on the grounds that the HTD's values lacked face validity [27]. NICE applied MAIC-adjusted utility values reflecting the UK CAS study population as its preferred approach [30]. In the analyses by Zheng et al. (2026) and Liu et al. (2026), utility values were sourced from the published literature [28, 29]. Zheng et al. and Liu et al. both applied PFS=0.70 and PD=0.60, sourced from Vedadi et al. (2021) and related published studies [28, 29]. All analyses incorporated disutility decrements for adverse events, generally restricted to grade ≥3 events occurring above a defined incidence threshold, with CDA-AMC and NICE additionally including disutilities for grade 1/2 CRS and ICANS as tarlatamab-specific toxicities. No severity modifier was applied in the CDA-AMC, Zheng et al. (2026), or Liu et al. (2026) analyses. NICE assigned a severity weight of 1.7 because the proportional QALY shortfall exceeded 0.95, meeting the threshold for the highest severity modifier [30].

CDA-AMC & NICE aus EQ-5D-5L der DeLLphi-301-Studie

Nutzwerte: Zheng & Liu et al. (2026) aus Literatur

AE-Disutilities ab Grad ≥3, CDA-AMC & NICE zusätzlich Grad 1/2 CRS & ICANS

Schweregradmodifikator nur bei NICE

Discount rates

Discount rates were applied in accordance with national guidelines and ranged between 1.5% and 5% [27-30].

Diskontierungsraten: 1,5-5 %

Model assumptions and limitations

Across all four analyses, the key shared assumptions and limitations were as follows:

1. All analyses relied on single-arm or indirectly compared clinical efficacy data, with no direct head-to-head RCT evidence for tarlatamab versus chemotherapy available at the time of evaluation.
2. Survival extrapolations, particularly for OS in the tarlatamab arm, were identified as a major source of uncertainty in all models, with the proportion of incremental QALY benefit derived from the extrapolated period exceeding the trial follow-up data by 30% to more than 57% across analyses.
3. Regarding the utility values, in the CDA-AMC analysis, the sponsor's PFS utility (0.834) was near-equivalent to the Canadian age-matched general population norm (0.839), raising concerns about face validity in a heavily pretreated cancer population [27]. In Zheng et al. and Liu et al., utility values were sourced from external published literature rather than trial-specific data, limiting the internal consistency of health outcomes estimation [28, 29].
4. Adverse event costs were restricted to those above the defined grade and incidence thresholds, potentially underestimating real-world safety costs.

Detailed characteristics of the pharmacoeconomic evaluations are presented in Chapter 5 in the Appendix (Table 5-1).

geteilte Limitationen:

(1) keine direkten Head-to-Head-RCT-Daten

(2) OS-Extrapolation als zentrale Unsicherheitsquelle

(3) unsichere Nutzwert, z. B. externe Literaturwerte

(4) AE-Kosten nur oberhalb Grad-/Inzidenzschwellen → potenzielle Unterschätzung

Results of the economic evaluations

The four identified analyses consistently demonstrate that tarlatamab is not cost-effective at current list prices relative to the respective national WTP thresholds, across all evaluated settings and perspectives. An overview of the cost-effectiveness results is presented in Table 5-1 below. Additionally, detailed

übereinstimmendes Ergebnis aller 4 Analysen: Tarlatamab zu aktuellen Listenpreisen nicht kosteneffektiv

results of the pharmacoeconomic evaluations are presented in Chapter 5 in the Appendix (Table 5-2).

The analysis by CDA-AMC [27] reported incremental costs of CAD $189,132 in the sponsor's base case, with drug acquisition costs accounting for 91% of total tarlatamab costs. The incremental effect in the sponsor's base case was 1.06 QALYs, yielding a base-case ICER of CAD $178,286 (~ €121,000) per QALY. The CDA-AMC reanalysis, applying more conservative survival extrapolations and alternative utility values, resulted in a substantially higher ICER of CAD $559,946 (~ €381,000) per QALY. Both ICERs substantially exceed the Canadian publicly funded healthcare payer WTP threshold of CAD $50,000 per QALY. A price reduction of approximately 68% from the submitted price would be required based on the sponsor's base case, and approximately 86% based on the CDA-AMC reanalysis, to achieve cost-effectiveness at the threshold. Regarding uncertainty analyses, the single most impactful change was altering the tarlatamab OS distribution from log-logistic to Weibull, which drove the ICER to CAD $531,705 per QALY, reflecting the committee's view that the sponsor's log-logistic OS extrapolation was highly optimistic. Applying revised utility values of 0.720 (PFS) and 0.520 (PD) increased the ICER to CAD $219,962 per QALY. Notably, more than 57% of the incremental QALY benefit in the sponsor's base case was derived from the extrapolated period beyond observed trial data, a proportion that fell to 30% in the CDA-AMC reanalysis following application of more conservative OS assumptions.

CDA-AMC:
Sponsor-Base-Case

ICER ~ € 121.000 vs.
CDA-AMC-Reanalyse
mit konservativeren
Annahmen:
ICER ~ € 381.000

→ vom HDT gewählte
Überlebenskurven
sehr optimistisch

The analysis by NICE [30] was conducted under a confidential commercial arrangement between Amgen and NHS England, and specific incremental cost and QALY figures are, therefore, not fully disclosed. The HTD's post-consultation deterministic ICER was £28,449 per QALY, with a probabilistic ICER of £29,134 (~ €35,000) per QALY, inclusive of the confidential commercial arrangement and the 1.7 severity weight. In contrast, the EAG's exploratory base case, reflecting the committee's preferred assumptions, yielded a deterministic ICER of £31,437 per QALY, and a probabilistic ICER of £35,393 (~ €42,000) per QALY. Given the high degree of uncertainty, particularly arising from the unanchored MAIC, immature survival data, and potentially overestimated utility values, the committee determined that its preferred decision-making threshold was approximately £25,000 per QALY. As the committee's preferred probabilistic ICER exceeded this threshold, tarlatamab was not recommended. As in the CDA-AMC analysis, more than 57% of the incremental QALY benefit in the HDT's base case was derived from the extrapolated period beyond observed trial data. The key QALY driver was the utility value for the PF health state across both analyses.

NICE: vertrauliche
Preisvereinbarung

HTD-ICER: probabilistisch
~ € 35.000;

EAG-Base-Case:
probabilistisch ~ € 42.000

→ Empfehlung abgelehnt;
selbst 1,7-Modifikator
unzureichend

The analysis by Zheng et al. (2026) [28] reported incremental costs of $203,332, with tarlatamab identified as the primary cost driver. The incremental effect was 0.29 QALYs, yielding a base-case ICER of $701,146 (~ €638,000) per QALY. This substantially exceeds both the $150,000 and $200,000 per QALY WTP thresholds applied in the US setting. Achieving cost-effectiveness at the $200,000 per QALY threshold would require a 56% reduction from the current list price. Third-line treatment scenario analyses, including BSC alone and exclusion of subsequent treatment costs, both increased the ICER further, to $744,498 and $733,938 per QALY gained, respectively, without altering the conclusion of non-cost-effectiveness.

Zheng et al. (2026):
ICER ~ € 638.000

erforderliche
Preisreduktion ~ 56 %
($ 200.000 pro
QALY-Grenze)

The analysis by Liu et al. (2026) [29] reported incremental costs of $198,914 for the US setting and $61,879 for the Chinese setting. The incremental effect was identical across both country analyses at 0.15 QALYs. Consequently, the base-case ICER was $1,306,255 (∼ €1,200,000) per QALY in the US and $406,352 (∼ €370,000) per QALY in China. Both ICERs substantially exceed their respective WTP thresholds of $150,000 per QALY in the US and $40,247 per QALY in China, with the US ICER exceeding the threshold approximately 8.7-fold and the Chinese ICER approximately 10-fold. The deterministic sensitivity analysis identified the utility of PFS as the single most influential parameter in both country models, followed by the discount rate and the price of tarlatamab. Price-simulation analyses indicated that cost-effectiveness in the US would require tarlatamab to be priced below $349.19 per mg at a WTP of $150,000 per QALY and below $296.50 per mg at a WTP of $100,000 per QALY, representing approximately an 80% price reduction. In China, cost-effectiveness would require reductions of approximately 95% and 90% from the assumed Chinese list price. Subgroup analyses across all evaluated patient characteristics, including age, sex, region, prior anti-PD-(L)1 exposure, CFI, and presence of brain or liver metastases, consistently yielded ICERs exceeding the WTP thresholds in both countries, with the probability of cost-effectiveness equal to 0% across all subgroups.

Liu et al. (2026):
USA: ICER ~ € 1,2 Mio.
CHN: ICER ~ € 370.000

Preissimulation:
erforderliche Reduktion
~80 % (USA) bzw.
~95 % (CHN)

Subgruppenanalysen
(Alter, Geschlecht,
Region, Anti-PD-(L)1,
chemotherapiefreies
Intervall, Hirn-/
Lebermetastasen)
durchgehend nicht
kosteneffektiv
(0 % Wahrscheinlichkeit)

Overall, the health economic evidence consistently demonstrates that tarlatamab's cost-effectiveness is primarily driven by its high acquisition costs relative to the small incremental QALY gains achieved in the second- and third-line ES-SCLC settings, primarly driven by the uncertainties in the model. Key limitations acknowledged across the analyses include the following: First, survival extrapolation beyond the trial follow-up period introduces substantial uncertainty, with a large proportion of incremental QALY benefit derived from the extrapolated period in all models. Second, the absence of trial-based QoL data in the DeLLphi-304 analyses necessitated the use of utility values borrowed from external published studies, limiting the internal consistency of health outcomes estimation. Third, effectiveness data were derived from single clinical trials without a supporting systematic review, and indirect comparisons against standard-of-care chemotherapy were subject to meaningful methodological limitations, including population heterogeneity and inadequate confounding adjustment. Fourth, post-progression treatment assumptions were based on trial data and clinical guidelines and may not fully reflect heterogeneous real-world practice. Fifth, only adverse events above defined grade and incidence thresholds were modelled, potentially underestimating real-world safety costs, though sensitivity analyses consistently confirmed that this had minimal impact on the conclusions. Sixth, the costs of managing severe adverse events associated with the comparator therapies are missing due to lack of cost data. As a result, the cost assessment remains unbalanced, particularly since severe adverse events occurred more frequently with topotecan. Overall, the transferability of the study results to the Austrian context is limited, as all four analyses rely on Canadian, UK, US, or Chinese cost data and country-specific WTP thresholds, comparators that only partly reflect Austrian SoC, and evidence from single clinical trials (DeLLphi-301/304). The two HTA analyses (CDA-AMC, NICE) additionally address a 3rd-line-or-later population and apply confidential pricing, severity-weight, and utility assumptions that do not hold in Austria. In addition, survival extrapolations and externally borrowed utility values of the US and Chinese analyses remain unvalidated against European data.

Fazit: Tarlatamab-
Kosteneffektivität
primär durch hohe
Anschaffungskosten bei
kleinem QALY-Gewinn
limitiert
(2nd-/3rd-Line ES-SCLC)

Limitationen: 1 RCT,
Survivalextrapolation, etc.

Übertragbarkeit der
Ergebnisse auf Ö limitiert

Table 5-1: Main results of the included economic evaluations of tarlatamab in adult patients with extensive-stage small cell lung cancer who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy

Author, year [REF]	Country	Analysis	Incremental costs	Incremental QALYs	Base-case ICER	PSA ICER	Key assumption	Limited transferability to the Austrian context
CDA-AMC, 2025 [27]	Canada	Sponsor base case	CAD $189,132	1.06	CAD $178,286/QALY (~ €121,000)	NR	Log-logistic OS; Albertan cohort comparator; RDI 85.5%	No Austrian prices WTP thresholds or discount rates, and comparators only partly match Austrian SoC 2 HTA analyses (CDA-AMC, NICE) address a 3rd-line+ population and use confidential or country-specific pricing and severity/utility assumptions that do not apply in Austria 2 US analyses (Zheng el al., Liu et al. 2026) reflect the correct 2nd-line indication but rely on US pricing
		CDA-AMC reanalysis	CAD $222,201	0.40	CAD $559,946/QALY (~ €381,000)	NR	Weibull OS; revised utilities 0.720 (PFS)/0.520 (PD)	
NICE, 2025 [30]	UK	Company base case	Confidential	N/R	£28,449/QALY (~ €35,000)	£29,134/QALY (~ €35,000)	Unanchored MAIC vs UK CAS study; 1.7 severity weight applied	
		EAG base case	Confidential	N/R	£31,437/QALY (~ €42,000)	£35,393/QALY (~ €42,000)	EAG preferred distributions; MAIC-adjusted utility values	
Zheng et al., 2026 [28]	US	Base case	$203,332	0.29	$701,146/QALY (~ €638,000)	NR	Log-normal PFS, exponential OS; 3rd-line nivolumab/ pembrolizumab	
Liu et al., 2026 [29]	US & China	US base case	$198,914	0.15	$1,306,255/QALY (~ €1,200,000)	NR	AIC-weighted model averaging; lifetime horizon; 3% discount rate	
		China base case	$61,879	0.15	$406,352/QALY (~ €370,000)	NR	Tarlatamab price = 1/3 US list; 5% discount rate	

Abbreviations: AIC … Akaike information criterion, CAD … Canadian dollar, CDA-AMC … Canada's Drug Agency, EAG … External Assessment Group, HTA … health technology assessment, ICER … incremental cost-effectiveness ratio, MAIC … matching-adjusted indirect treatment comparison, NICE … National Institute for Health and Care Excellence, NR … not reported, OS … overall survival, PD … progressive disease, PFS … progression-free survival, PSA=probabilistic sensitivity analysis, QALY … quality-adjusted life year, RDI … relative dose intensity, UK CAS … UK Cancer Analysis Service study, WTP … willingness-to-pay

Note: Exchange rates based on approximate European Central Bank reference rates, August 2025;
PSA ICER is reported for NICE only; probabilistic results for other analyses were expressed as cost-effectiveness acceptability rather than a point estimate.

Quality assessments

Qualitätsbewertung (CHEERS & CHEC): insgesamt moderat bis gut

The quality assessment of the four included pharmacoeconomic analyses using the CHEERS 2022 checklist [31] and the CHEC quality list [32] indicates variable but generally moderate-to-good overall quality across studies, with the two academic analyses (Zheng et al. (2026) [28]; Liu et al. (2026) [29]) reporting more completely than the two HTA body assessments (CDA-AMC 2025 [27]; NICE 2025 [30]) (Tables 5-3 and 5-4 in the Appendix).

akademische Studien vollständiger berichtet als HTA-Berichte

keine Lebensqualitätsdaten von der Studie

Zheng et al. (2026) and Liu et al. (2026) achieved the highest reporting completeness, with 17 and 18 out of 28 CHEERS items fully reported and 16 and 15 out of 19 CHEC items met, respectively. Both studies document core methodological elements transparently, including study population, comparators, model structure, cost inputs, discount rates, uncertainty analyses, and conclusions [28, 29]. Liu et al. (2026) is particularly noteworthy for its dual-country perspective, its application of AIC-weighted Bayesian model averaging to ad-

dress structural uncertainty in survival extrapolation, and its comprehensive subgroup analyses across clinically relevant patient characteristics. However, both analyses share a critical methodological limitation: they lacked trial-based utility values suitable for the QALY models and therefore drew on external values from the Delphi-304, necessitating the borrowing of utility values from an external observational cohort [28, 29].

CHEC vergleichbar – Limitationen: keine Head-to-Head-Evidenz; >57 % der inkrementellen QALYs aus Extrapolation → erhebliche strukturelle Unsicherheit

The CDA-AMC (2025) and NICE (2025) assessments achieved lower CHEERS completeness scores of 15 and 14 fully reported items out of 28, respectively, with 7 and 8 items rated as only partially reported, and 6 items rated as not reported in both cases [27, 30]. Their lower scores relative to the academic publications partly reflect structural features of HTA guidance documents, in which certain methodological details, most notably the exact discount rate and time horizon in the NICE guidance, and specific utility measurement and valuation procedures, are described only partially or are not reported in the publicly available guidance text, often due to the confidential nature of the commercial arrangement between the HTD and the payer [30]. The CHEC assessments for both HTA analyses were nonetheless comparable to the academic studies, with 15 out of 19 items met, 3 items rated as unclear, and 1 item rated as not met. Both HTA reviews demonstrate particular strength in the rigour of their critical reanalyses: CDA-AMC conducted a series of seven-stepped reanalyses systematically challenging the HTD's assumptions [27], and NICE applied an independent EAG exploratory base case alongside the HTD submission [30]. However, both are constrained by the absence of direct head-to-head comparative evidence, relying instead on single-arm trial data with indirect treatment comparisons of limited robustness. In both HTA reviews, more than 57% of incremental QALY gains in the HTD's base case were derived from the extrapolated period beyond observed trial data, representing a substantial source of structural uncertainty that was not fully resolved by sensitivity analyses.

übergreifende Limitationen: eingeschränkte Übertragbarkeit und externe Validität der ICER-Schätzungen

Across all four analyses, characterisation of distributional effects and formal equity considerations were absent, and none reported the effect of patient or stakeholder engagement on study conclusions. These shared limitations reduce the overall applicability and external validity of the identified cost-effectiveness estimates and should be considered when interpreting the reported incremental cost-effectiveness ratios.

5.2 Budget impact analysis

5.2.1 Budget impact analysis submitted by the health technology developer

keine BIA vom HTD übermittelt

The HTD did not submit a BIA of tarlatamab treatment in Austria.

5.2.2 Austrian budget impact analysis

Eligible population and market share in years 1-3

Tarlatamab is recommended as monotherapy for the treatment of adults with ES-SCLC who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy [11]. As the HTD did not present a detailed derivation of the eligible Austrian population for second-line ES-SCLC treatment in the dossier, the eligible population was derived theoretically using epidemiological estimates from the literature. As previously reported, 70.8% (n=437) of the newly diagnosed patients with SCLC present with ES-SCLC [6], while an additional 80% of patients with LS-SCLC (n=144) are expected to progress to ES-SCLC within a year [7]. Considering both de novo ES-SCLC cases and those progressing from LS-SCLC, the total ES-SCLC population in Austria is estimated at 581 patients. It is further estimated that 85% of ES-SCLC patients (n=494) receive first-line induction platinum-based chemotherapy in routine clinical practice [8], while 80% to 90% can be expected to experience a relapse within a year (n=395-444) [33]. Finally, 40% to 50% of relapsing patients are assumed to be eligible to continue the treatment with second-line systemic therapy, resulting in a theoretical estimate of 158 to 222 patients per year eligible for tarlatamab treatment in Austria [33, 34].

Populationsschätzung Tarlatamab-Eligibilität Österreich basierend auf epidemiologischen Daten: 158-222 Pat./Jahr

... (ES-SCLC rezidiviert nach Platin-Chemotherapie, epidemiologisch abgeleitet)

Based on epidemiological estimates, the consulted clinical experts made different assumptions about how many patients will receive tarlatamab. In addition, there are estimates from the HTD. Thus, we present three scenarios in this BIA, each assuming an increasing uptake of tarlatamab over time:

3 Szenarien mit zunehmendem Tarlatamab-Uptake:

Scenario 1: The HTD estimated that 30, 90, and 90 patients would receive tarlatamab in 2026, 2027, and 2028, respectively [35].

1) HTD-Schätzungen für 3 Jahre

Scenario 2: Some of the consulted clinical experts estimated that approximately 25% of patients receiving second-line ES-SCLC treatment would receive tarlatamab. Applied to the projected eligible population, this results in 40, 48, and 56 patients in years 1, 2, and 3, respectively.

2) Szenario Expert.: 25 % Tarlatamab-Uptake → 40/48/56 Pat. Jahr 1-3

Scenario 3: Other consulted clinical experts assumed that nearly all patients requiring second-line ES-SCLC treatment (90%) would receive tarlatamab. Applied to the projected eligible population, this results in 142, 171, and 200 patients in years 1, 2, and 3, respectively.

3) Szenario Expert.: 90 % Tarlatamab-Uptake → 142/171/200 Pat. Jahr 1-3

According to the consulted clinical experts, the current standard of care for ES-SCLC patients who progress on or after first-line platinum-based chemotherapy in Austria comprises three treatment options: topotecan, CAV, and platinum-based retreatment. In routine clinical practice in Austria, these are estimated to be used in approximately 70%, 20%, and 10% of patients, respectively.

Standard-Therapieoptionen ES-SCLC-Rezidiv Österreich: Topotekan (70 %), CAV (20 %), Platin-Retreatment (10 %)

Direct medical costs of tarlatamab treatment per patient

Acquisition costs of tarlatamab treatment

Based on the confidential ex-factory prices submitted by HTD via the Austrian Ministry of Health, Tarlatamab (IMDYLLTRA®) is expected to be available starting in July 2026 at € [redacted] per 1-mg vial and € [redacted] per 10-mg vial. The recommended dosing regimen comprises an initial dose of 1 mg on day 1 of the first cycle, followed by 10 mg on days 8 and 15, and subsequently 10 mg on day 1 and day 15 of each 28-day cycle. Consequently, the

Tarlatamab: 1 mg (€ [redacted]) und 10 mg (€ [redacted]) € [redacted] pro Pat.

first treatment cycle requires one 1-mg vial and two 10-mg vials, while two 10-mg vials are administered per cycle from cycle 2 onwards.

This part includes confidential information!

Administration costs of tarlatamab treatment

The consulted clinical experts recommended that the first cycle doses of tarlatamab be administered in the inpatient setting, with a three-night hospitalisation per dose, to ensure adequate monitoring for adverse events, particularly CRS. The subsequent cycles can be administered in the hospital outpatient clinic. Consequently, the administration cost in the first cycle amounts to €24,030, while in the remaining four cycles, it is €6,766.

Tarlatamab-Verabreichung: Zyklus 1 stationär € 24.030; Zyklen 2-5 ambulant € 6.766

In addition, according to the Summary of Product Characteristic (SmPC) of tarlatamab, it is recommended to administer intravenously concomitant dexamethasone 8 mg and one litre of sodium chloride 9 mg/mL (0.9%) solution on days 1 and 8 [14]. However, based on clinical expert opinion, these items can be considered as cost-irrelevant.

Begleitmedikation laut Expert. kostenneutral

Additional treatment costs

According to the SmPC, CRS was the most common adverse event, reported in the pooled safety dataset for 56.7% of patients who received the tarlatamab target dose of 10 mg as monotherapy. The majority of CRS events occurred after the first two doses, with a median time to first onset of 15.9 hours [14]. During this time, the Austrian patients are expected to be monitored in the inpatient setting. For this reason, as well as due to the lack of specific cost data for CRS management, we assume these costs are included in administration costs in both inpatient and outpatient settings.

Annahme: CRS-Kosten in Verabreichungskosten enthalten

This part includes confidential information!

Standard of care costs per patient

According to the consulted clinical experts, topotecan is the most widely used systemic therapy in ES-SCLC patients who progressed on or after first-line treatment with platinum-based chemotherapy in Austria, followed by CAV and platinum-based retreatment for a few patients.

Acquisition cost of standard of care treatments

The acquisition costs of the SoC treatments are calculated based on the information from the studies used for the direct (topotecan) and indirect (CAV and platinum-based rechallenge) comparison with tarlatamab in the JCA. The dosing schedules and treatment durations are presented in Table 5-2 below. For topotecan, the average acquisition cost per patient is estimated at €4,740; for CAV, at €1,367; and for platinum-based rechallenge at €354.

Akquisitionskosten SoC: Topotecan € 4.740, CAV € 1.367, Platin-Rechallenge € 354

Table 5-2: Dosing schedules of the Austrian SoC treatments for second-line ES-SCLC management

Regimen	Dosing schedule	Median number of treatment cycles	Source [3]
A: Topotecan	Administered IV on days 1-5 in 21-day cycles: 1.5 mg/m²/day	4	DeLLphi-304 trial
B: Cyclophosphamide + doxorubicin + vincristine	All agents are administered IV on day 1 of each 28-day cycle: cyclophosphamide 1,000 mg/m², doxorubicin 45 mg/m², vincristine 1.4 mg/m²	3	GFPC 0501 study (NCT00418743) ([3] Table 18)
C: Platinum-based rechallenge (carboplatin + etoposide)	Both agents are administered IV in 21-day cycles: carboplatin AUC 5 mg/mL/min IV on day 1; etoposide 100 mg/m² IV on days 1-3	5	Baize et al. (2020) study (NCT02738346) ([3] Table 51)

Abbreviations: AUC … area under the curve, ES-SCLC … extensive-stage small cell lung cancer, IV … intravenously, SoC … standard of care

Administration costs of standard of care treatments

All three SoC treatment options are usually administered in the hospital outpatient clinic, resulting in €16,914 for a median of four treatment cycles of topotecan, €2,537 for a median of three cycles of CAV, and €3,383 for a median of five cycles of platinum-based rechallenge with carboplatin plus etoposide.

Overall, the direct medical costs of the SoC treatment options per patients were €21,654 for topotecan, €3,904 for CAV and €14,454 for platinum-based retreatment. The detailed SoC costs are illustrated in Table 5-3.

Verabreichungskosten (ambulant):
Topotekan € 16.914,
CAV € 2.537,
Platin-Rechallenge € 3.383
direkte medizinische SoC-Kosten pro Pat.

Table 5-3: Cost of the SoC second-line treatment options for ES-SCLC patients

Regimen	Topotecan	CAV	Paltinum rechallenge
Acquisition costs	Per cycle: €1,185 Per 4 cycles: €4,740	Per cycle: €445 Per 3 cycles: €1,367	Per cycle: €354 Per 5 cycles: €1,768
Administration costs	Per cycle: €4,229 Per 4 cycles: 16,914	Per cycle: €846 Per 3 cycles: €2,537	Per cycle: €3,383 Per 5 cycles: €12,686
Sum	€21,654	€3,904	€14,454

Abbreviations: CAV…cyclophosphamide + doxorubicin + vincristine, ES-SCLC…extensive-stage small cell lung cancer, SoC … standard of care

Figure 5-1 illustrates the differences in total direct medical costs between tarlatamab and the three SoC treatment options, showing that per-patient costs are significantly higher with tarlatamab.

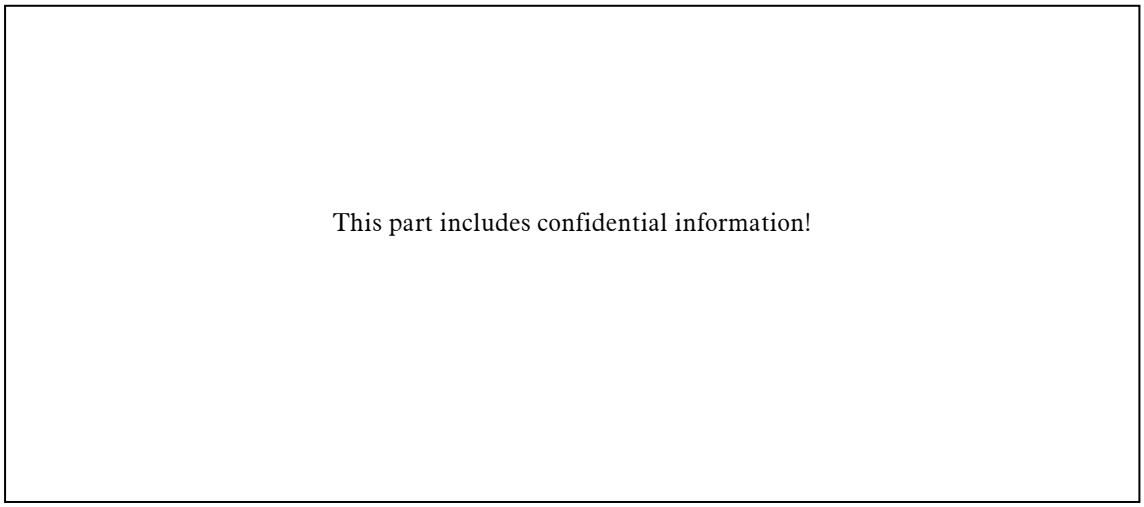


Figure 5-1: Total cost per patient and median treatment cycles – tarlatamab vs different SoC treatment options

Net budget impact in years 1-3 per scenario

This sub-chapter presents the net budget impact of introducing tarlatamab, represented by the difference in total cost between the reference scenario, in which the eligible population is treated exclusively with current SoC therapies, and three tarlatamab scenarios. The presented scenarios reflect the uncertainty surrounding the number of patients expected to receive tarlatamab in Austria (Table 5-4.

Netto-Kostenunterschied Referenzszenario (SoC) vs. drei Tarlatamab-Szenarien (variable Uptake-Raten)

Table 5-4: Cost of SoC scenario without tarlatamab (assuming median treatment durations from studies used in JCA [3])

Cost categories	Year 1	Year 2	Year 3	Total
Topotecan (70%)				
Expected patients based on expert estimations	111	133	156	-
Drug acquisition	€524,321	€630,823	€737,326	€1,892,470
Drug administration	€1,870,984	€2,251,027	€2,631,071	€6,753,082
Pre- and post-treatment	€0	€0	€0	€0
Total direct medical costs of SoC topotecan	€2,395,304	€2,881,851	€3,368,397	€8,645,552
CAV (20%)				
Expected patients based on expert estimations	32	38	44	-
Drug acquisition	€43,193	€51,967	€60,741	€155,901
Drug administration	€80,185	€96,473	€112,760	€289,418
Pre- and post-treatment	€0	€0	€0	€0
Total direct medical costs of SoC CAV	€123,378	€148,440	€173,501	€445,319
Platinum-based rechallenge (10%)				
Expected patients based on expert estimations	16	19	22	-
Drug acquisition	€27,945	€33,621	€39,297	€100,863
Drug administration	€200,463	€241,182	€281,900	€723,545
Pre- and post-treatment	€0	€0	€0	€0
Total direct medical costs of SoC platinum-based rechallenge	€228,407	€274,803	€321,198	€824,408
Total SoC costs	€2,747,090	€3,305,093	€3,863,095	€9,915,278

Abbreviations: CAV … cyclophosphamide + doxorubicin + vincristine, SoC … standard of care

Scenario 1

Scenario 1 presents the tarlatamab costs using the patient estimates submitted by the HTD. The total direct medical costs of tarlatamab, plus the costs for patients remaining on SoC, range from € [redacted] in the first year to € [redacted] in the third year, reflecting the HTD's increasing market share for tarlatamab in Austria.

Szenario 1 (HTD): Tarlatamab + SoC-Kosten € [redacted] (Jahr 1-3)

Compared to the SoC costs without tarlatamab on the market, this results in net budget impacts of € [redacted] in the first year and € [redacted] million in the third year, totalling € [redacted] over all three years. The detailed results are shown in Table 5-5.

Netto-Budget-Impact: € [redacted] (Jahr 1-3)

Table 5-5: Scenario 1 – cost of the intervention scenario, including remaining SoC costs (for median of five treatment cycles based on the DeLLphi-304 trial)

Cost categories	Year 1	Year 2	Year 3	Total
Expected patients for tarlatamab (HTD estimates)	30	90	90	-
Total tarlatamab costs	[redacted]	[redacted]	[redacted]	[redacted]
Residual SoC costs	€2,225,567	€1,740,523	€2,298,526	€6,264,616
Total costs of Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
Total SoC	€2,747,090	€3,305,093	€3,863,095	€9,915,278
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HTD…health technology developer, SoC … standard of care

Scenario 2

Scenario 2 accounts for conservative estimates from Austrian clinical experts, namely that 25% of patients who require second-line treatment for ES-SCLC will be indicated for tarlatamab. The total direct medical costs of treating the overall eligible population under this scenario range from € [redacted] to € [redacted] in years 1 and 3, respectively.

Szenario 2 (Expert. – konservativ): 25 % Tarlatamab-Indikation € [redacted] Mio. (Jahr 1-3)

Compared to the SoC scenario, this results in a net budget impact of € [redacted] in year 1, € [redacted] in year 3, totalling € [redacted] over three years (Table 5-6).

Netto-Budget-Impact: € [redacted] (Jahr 1-3)

Table 5-6: Scenario 2 – cost of the intervention scenario, including remaining SoC costs

Cost categories	Year 1	Year 2	Year 3	Total
Expected patients for tarlatamab (25%: conservative estimates by clinical experts)	40	48	56	-
Total tarlatamab costs	[redacted]	[redacted]	[redacted]	[redacted]
Residual SoC costs	€2,060,318	€2,478,820	€2,897,322	€7,436,459
Total costs of Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]
Total SoC	€2,747,090	€3,305,093	€3,863,095	€9,915,278
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: SoC … standard of care

Scenario 3

In contrast, scenario 3 accounts for optimistic estimates by Austrian clinical experts, namely that 90% of patients who require second-line treatment for ES-SCLC will be indicated for tarlatamab. The total direct medical costs of treating the overall eligible population under this scenario are substantially higher, ranging from € [redacted] to € [redacted] in years 1 and 3, respectively. Again, the assumed market share increase is based on published data of patients receiving second-line ES-SCLC treatment.

Szenario 3 (Expert. – optimistisch): 90 % Tarlatamab-Indikation · € [redacted] (Jahr 1-3)

Compared to the SoC scenario, this results in a net budget impact of € [redacted] to € [redacted] per year, totalling € [redacted] over three years (Table 5-7).

Netto-Budget-Impact: € [redacted] (Jahr 1-3)

Table 5-7: Scenario 3 – cost of the intervention scenario, including remaining SoC costs

Cost categories	Year 1	Year 2	Year 3	Total
Expected patients for tarlatamab (90%: optimistic estimates by clinical experts)	142	171	200	-
Total tarlatamab costs	[redacted]	[redacted]	[redacted]	[redacted]
Residual SoC costs	€274,709	€330,509	€386,310	€991,528
Total costs of Scenario 3	[redacted]	[redacted]	[redacted]	[redacted]
Total SoC	€2,747,090	€3,305,093	€3,863,095	€9,915,278
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC … standard of care

Comparison of scenarios 1-3

Across the three scenarios, the net budget impact escalates considerably over the three-year horizon, reflecting both the high acquisition cost of tarlatamab and the cumulative effect of patient uptake. While the SoC costs were assumed to remain stable, the introduction of tarlatamab generates a significantly higher financial burden.

Tarlatamab-Einführung verursacht deutlich höhere Kosten als SoC

Notably, scenario 3, which assumes the broadest eligibility criterion encompassing 90% of potentially eligible patients, projects the most pronounced budget impact, reaching € [redacted] in year 2 and € [redacted] in year 3.

These figures underscore the critical dependency of total expenditure on the size of the treatable population and highlight the considerable implications for the Austrian healthcare system should tarlatamab be introduced at scale.

Szenario 3 (90 % Uptake) zeigt höchste Last (€ [redacted] Jahr 3) · erhebliche Implikationen für österreichisches Gesundheitssystem

Limitations

The findings of this BIA indicate that introducing tarlatamab into the Austrian healthcare system would result in a substantial increase in pharmaceutical expenditure compared with current SoC treatments, with a cumulative net budget impact ranging from € [redacted] to € [redacted] over three years, depending on patient uptake assumptions. The analysis, however, is subject to several important limitations that should be considered when interpreting these results.

Tarlatamab-Einführung → substanzielle Steigerung der Ausgaben – mehrere Limitationen zu berücksichtigen:

First, as the HTD did not submit an Austrian-specific BIA, the eligible patient population was derived from published literature estimates (except for scenario 1 which was based on HTD assumptions), applying sequential proportions for SCLC incidence (15%), ES-disease (70%), relapse after first-line treatment (80-90%), and progression to second-line therapy (40-50%), each introducing compounding uncertainty into the baseline population of 158 to 222 eligible patients.

Population (158-222 Pat.) aus Literaturdaten abgeleitet (außer Szenario 1) → Unsicherheit

Second, the number of tarlatamab treatment cycles per patient, a key cost driver, was based on the median of five cycles observed in the DeLLphi-304 trial, which may not reflect the real-world Austrian clinical setting and could lead to either an over- or underestimation of true drug acquisition costs.

Behandlungszyklen-Annahme nicht repräsentativ für Ö

Third, the inpatient administration cost for the first treatment cycle was modelled based on nine inpatient days across three doses, an assumption derived from clinical expert consultation rather than from observed Austrian data, which introduces further uncertainty into the administration cost component.

stationäre Verabreichung Zyklus 1 → Expert.-Annahme

Fourth, costs associated with the management of CRS, observed in 56.7% of clinical trial safety pool patients, 17.3% of whom had grade ≥2 CRS [14], were set to zero in the analysis due to the absence of Austrian-specific cost data, likely underestimating the true per-patient cost burden. Similarly, ICANS monitoring and pre-treatment items were classified as cost-irrelevant, a classification supported by clinical expert opinion but that may not hold across all treatment settings.

CRS-Management-Kosten → keine Ö-Daten → Unterschätzung möglich

Fifth, the SoC treatment mix (topotecan 70%, CAV 20%, platinum rechallenge 10%) was based solely on expert estimation without empirical utilisation data, and any deviation from this distribution in practice would alter the comparator cost baseline. In addition, the platinum-based rechallenge was represented solely by the carboplatin plus etoposide combination; the cisplatin plus etoposide combination was excluded from the analysis because it was not assessed in the JCA. Therefore, current practice may not be fully represented.

SoC-Mix (Topotekan 70 %, CAV 20 %, Platin-Rechallenge 10 %) basierend auf Expert.-Schätzung ohne empirische Nutzungsdaten

Finally, standardised and widely accepted data on indirect healthcare costs are unavailable in Austria. Therefore, we followed the healthcare perspective for the analysis and did not consider indirect costs.

keine indirekten Kosten berücksichtigt

5.3 Interpretation of findings

Kosteneffektivität von Tarlatamab fraglich: unzureichende inkrementelle QALY-Gewinne zur Rechtfertigung hoher Akquisitionskosten

ICER-Spannweite € 35.000 – € 1,2 Mio. je Jurisdiktion

> 57 % QALY-Benefit aus Extrapolation jenseits Studiendaten

strukturelle Unsicherheit kritisch bei ES-SCLC (schlechte Prognose, begrenzte Evidenz Langzeitüberleben)

The economic evidence presented in this chapter is associated with considerable uncertainty regarding the economic value of tarlatamab in the Austrian healthcare context. While all four identified cost-utility analyses confirm a clinically meaningful treatment effect in second- and third-line ES-SCLC setting, the incremental QALY gains of 0.15 to 1.06, themselves subject to considerable uncertainty, are deemed to be insufficient to justify the high acquisition cost at any of the evaluated country-specific WTP thresholds. The wide range of ICERs across jurisdictions, from approximately €35,000 per QALY gained under the NICE company base case to over €1.2 million in the US analysis by Liu et al., is not merely a reflection of differing healthcare systems or price levels but rather reveals how sensitive the cost-effectiveness conclusion is to modelling choices, particularly the parametric distributions used for overall survival extrapolation. The fact that more than 57% of incremental QALY benefit in both the CDA-AMC and NICE company base cases was derived from the period beyond observed trial data is a critical methodological concern: it means that the cost-effectiveness of tarlatamab, even in its most favourable assessments, rests substantially on projected rather than observed survival benefit. When more conservative extrapolation assumptions were applied, as in the CDA-AMC reanalysis, the ICER increased more than threefold, from approximately €121,000 to €381,000 per QALY gained, illustrating the fragility of the base-case estimates. This structural uncertainty is particularly problematic in ES-SCLC, a setting characterised by poor prognosis and rapid disease progression, where long-term survival predictions carry inherently limited empirical support.

Tarlatamab € [redacted]/Pat. ([redacted] × teurer als SoC)

kumulativer Netto-Budget-Impact € [redacted] (3 Jahre); tatsächlicher Budget-Impact stark von unvorhersehbarem Verschreibungsverhalten abhängig

The Austrian BIA adds a further critical dimension by translating these per-patient cost dynamics into population-level financial consequences. At € [redacted] per patient, approximately [redacted] higher than existing SoC regimens, tarlatamab would represent a qualitative shift in expenditure for this indication, and the cumulative net budget impact of € [redacted] to € [redacted] over three years underscores that even in a small patient population, the aggregate financial risk to the Austrian healthcare system would be considerable. Crucially, the threefold difference between the lower and upper scenario bounds reflects not a marginal uncertainty but a fundamental absence of reliable Austrian utilisation data, meaning that the true budget impact is highly contingent on prescribing behaviour that cannot currently be predicted with confidence.

Erstattung zum aktuellen Listenpreis wirtschaftlich unsicher; substanzielle Preisreduktion oder MEA erforderlich

Taken together, the international cost-effectiveness evidence and the Austrian budget projections suggest that reimbursement at the current suggested list price is uncertain to justify on economic grounds. A substantial price reduction or managed entry arrangement (MEA), as pursued e.g. in the UK, would be a necessary condition for improving the economic profile of tarlatamab adoption in the Austrian setting.

6 Extended perspectives

This chapter summarises the perspectives of healthcare providers and patients and carers, along with other relevant considerations regarding tarlatamab. This combined approach provides a more multidimensional view of patient experiences, expectations, and concerns relevant to the HTA report. It outlines existing registries and describes frameworks for documenting the use of tarlatamab in Austria.

Perspektiven von Gesundheitsdienstleistern, Betroffenen und weitere relevante Aspekte

6.1 Healthcare provider perspective

Identification of eligible patients

In Austria, tarlatamab may be considered as a subsequent treatment option during routine clinical cancer management, based on treatment response and disease progression.

Tarlatamab als mögliche Behandlungsoption

Implementation considerations within the Austrian clinical practice context

Austrian clinical experts were consulted to provide specific guidance for the clinical practice context as part of the assessment (see Chapter 3). As with every new product, integrating tarlatamab into clinical practice requires careful consideration of healthcare infrastructure, training needs of all parties involved, and patient support. Although substantial structural changes are not anticipated, organisational adjustments may be required to accommodate the specific treatment protocols for tarlatamab. For example, clinical experts recommend a hospital stay of two to three days after the administration of the initial two or three doses of the product to promptly manage AEs. During later treatment, it may be possible to administer tarlatamab in a daycare clinic setting. In addition, for adequate monitoring of AEs, a more frequent use of brain imaging by computed tomography or magnetic resonance imaging might be necessary [36].

Einschätzung österr. klin. Expert:innen

keine wesentlichen strukturellen Änderungen erforderlich, aber mehrtägiger stationären Aufenthalt im 1. Behandlungszyklus erforderlich

Regarding possible, specific side effects of tarlatamab, particularly CRS and ICANS, clinical experts highlighted the importance of training medical and nursery staff to raise awareness of the symptoms. The involved staff should be able to conduct simple neurological tests to identify ICANS as early as possible [36]. For the treatment of CRS, tocilizumab, an immunosuppressant indicated for severe or life-threatening CRS [11], must be permanently available (see Figure 1-1). However, CRS primarily occurs during the first two or three administrations of tarlatamab. Later, it has a lower cumulative toxicity than chemotherapy [36].

zusätzliche Ressourcen für Monitoring und Management unerwünschter Ereignisse

Initial clinical experience with tarlatamab was described as positive, with AEs considered manageable. However, clinical experts emphasised that training should be provided, particularly in departments with no previous experience and highlighted the importance of interdisciplinary coordination [36].

erste positive Erfahrungen mit Tarlatamab in Österreich

6.2 Patient and carer perspective

6.2.1 Patient perspective

Findings from the literature

wenig Evidenz über Krankheitslast und Bedürfnisse von Pat. mit SCLC vorhanden

Given that little research has focused on the unique needs of patients with SCLC and their caregivers, the current understanding of perceived symptom burden is limited. The paucity of published qualitative research on how patients with SCLC feel and function leaves a gap in the knowledge needed to carry out patient-centred drug development in SCLC. Insights into the lives of affected patients are provided by a mixed-methods study conducted by Bebb and colleagues (2023), two qualitative interview studies by Altmann et al. (2023) and Brown et al. (2015) and a quantitative study by Santos (2025) [37-42]. To synthesise the findings, outcomes were structured using the domains of the World Health Organization Quality of Life-100 (WHOQOL-100) framework (see Figure 6-1) [43].

Krankheit betrifft alle Domänen der Lebensqualität

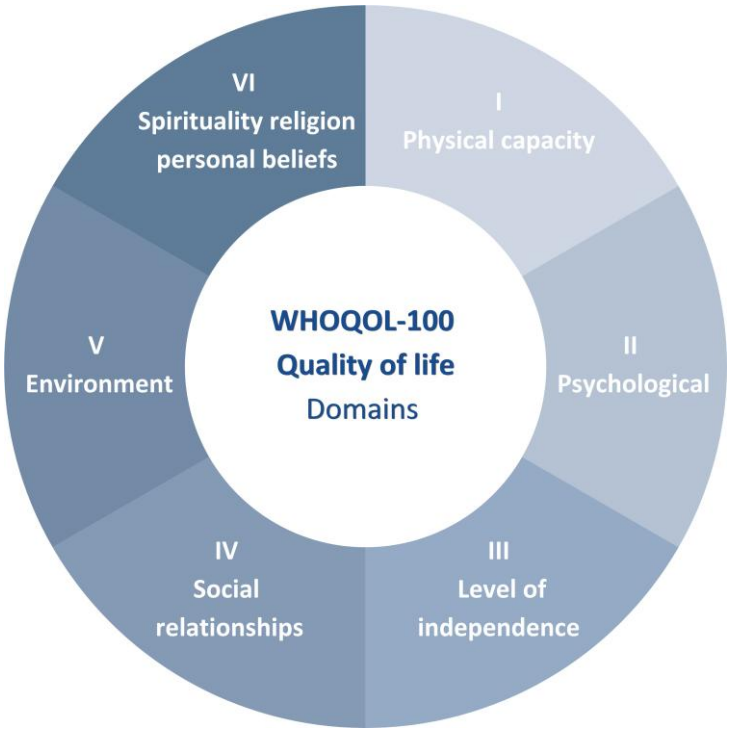


Figure 6-1: World Health Organization Quality of Life-100; schematic representation of the domains [43]

Physical capacity

Atemnot als anhaltendes Symptom, in schweren Fällen Gabe von Sauerstoff notwendig

The most common impactful symptoms in patients with ES-SCLC were shortness of breath, coughing, hoarseness, chest pain, fatigue and nausea or vomiting. Shortness of breath was a constant symptom, worsening with exertion and sometimes arising spontaneously at rest. Patients differentiated between dry coughs and those producing blood or phlegm, and some reported difficulty taking deep breaths, requiring the use of oxygen tanks [37, 38, 40].

breites Spektrum an Symptomen, verursacht durch die Erkrankung selbst oder als unerwünschte Wirkung einer Therapie

Overall, a wide range of symptoms was reported, attributed to either the disease or treatment, including hot flashes, arm/shoulder/back pain, cold extremities, hair loss, port area pain and discomfort, change in taste, dizziness, hazy or drugged feeling, difficulty or pain swallowing, voice loss/change, neuropathy pain in bones, jerking and cramping of muscles, or lack/loss of appetite. Participants also reported difficulty sleeping and stated that SCLC symptoms, particularly coughing and pain, interfered with their sleep [37, 38, 40].

Psychological

erhebliche Auswirkungen auf die mentale Gesundheit durch die unheilbare Erkrankung

Patients with ES-SCLC experienced emotional effects, particularly those who had not achieved success with treatment. Mental health was impacted substantially among patients with advanced disease. The patients were afraid of dying and reported difficulties coming to terms with this. They understood that treatments were not curative, and most just hoped to go into remission as a means of gaining more time. They also expressed sadness regarding their QoL, though treatment burden was considered worthwhile if it extended survival [38, 40].

Hoffnung auf Lebensverlängerung

Einstellung spielt wichtige Rolle: unterschiedliche Herangehensweisen einzelner Pat.

Besides, attitude played a notable role in how the respondents coped with symptoms and side effects. Most were determined to continue with life as usual despite physical challenges, finding it helpful to maintain perspective, a sense of humour, and to rationalise their difficulties [38, 40].

Level of independence

Symptome schränken alle Bereiche des täglichen Lebens ein

Patients with ES-SCLC reported impacts on leisure and hobbies, work, household chores, and daily errands outside their homes. Symptoms limited their daily activities, including cooking, cleaning, driving, taking care of personal hygiene, travelling long distances, and doing physical activity, whereas the reported strength of impact varied from "minor" (e.g., reducing vigorous exercise) to "very severe" (e.g., too tired to get out of bed) [37, 38, 40].

Aufrechterhaltung der Unabhängigkeit hat hohe Priorität

meist sind direkte Angehörige für Hilfe im Alltag verantwortlich

Patients reported reduced endurance, strength, and balance as underlying factors that limit physical functioning, including the ability to bend, squat, and walk. These limitations on work or hobbies are negatively affecting their QoL. However, maintaining independence in daily life was a high priority: patients tended to seek assistance only after exhausting their own efforts employing strategies such as rationing their energy, taking rest breaks or completing tasks more slowly. Once help was required, there was a hierarchy of preferences for support, with most preferring help from family, particularly spouses and children, over the broader social network or external agencies [37, 38, 40].

Social relationships

Familiendynamik und außerfamiliäre soziale Kontakte durch Krankheit stark beeinträchtigt

Family dynamics were substantially affected among patients with ES-SCLC, as the condition made them feel unable to participate in family activities or to be a good parent/grandparent/partner. They also felt they sometimes had to pretend to their families that they were fine. Extrafamilial social interactions were substantially affected, as patients tended to withdraw socially, due to lack of energy and willpower or embarrassment at appearing in their current state (e.g., someone who coughs all the time) [38, 40].

Betroffene ziehen sich oftmals zurück

Austausch mit anderen Betroffenen wird als hilfreich empfunden

In this regard, participants identified unique benefits of talking to other cancer patients rather than doctors, family, friends, or counsellors. Across their cancer journey, patients experienced a wide range of emotions, including shock, sadness, frustration, fear, hope, luckiness, uncertainty and isolation, and found that peer connection provided a sense of having a "fellow traveller" [38, 40].

Environment

Patients relied almost exclusively on verbal information from their doctors about diagnosis and prognosis, valuing honesty and open discussion. Many participants preferred to ask more questions or seek a second opinion from another doctor rather than turn to the internet or other sources for help [40].

offener, ehrlicher Dialog mit behandelnden Ärzt:innen wird besonders geschätzt

Although the interviewed participants were aware of available emotional support services, they expressed little interest in them, preferring to manage their emotions alone or with close family. Barriers to accessing support groups or helplines included stigma sensitivity, reluctance to open up to strangers, a wish to avoid topics such as cancer and death, fatigue, and lack of time [40].

kaum Nutzung von Selbsthilfegruppen etc.: Stigma, Dialog mit Unbekannten, Vermeidung belastender Themen

Spirituality/Religion/Personal beliefs

The facets of spirituality, including connection to a spiritual being or force, meaning in life, admiration, wholeness and integration, spiritual strength, inner peace, hope, optimism, and faith, positively contribute to the health-related QoL of LC patients, encouraging reflection on the subject through a spiritual context. This approach promotes positive coping, resilience and the development of individualised care plans for patients and their families [42].

Aspekte der Spiritualität können Lebensqualität Betroffener positiv beeinflussen, Förderung von Coping und Resilienz

Patient involvement by the AIHTA

As part of this HTA, the aim is generally to obtain additional patients' perspectives through a questionnaire, as described in the methods section (Chapter 3). Unfortunately, despite intensive efforts, no participants could be identified. This might be caused by two limiting factors: on the one hand, patients are at a very serious stage of their disease and have limited capacities. On the other hand, the timeframe for patient involvement is limited, making the timely identification of eligible patients difficult.

keine Pat. für Befragung identifiziert; mögliche Gründe: schwierige Lebenssituation, begrenztes Zeitfenster

Results from the JCA

For the JCAs, it is intended to include patients. They are selected and involved in the JCAs after the Commission has assessed their declarations of interest, in order to ensure they take part in an independent and transparent manner, free from conflict of interest [44]. An involvement is possible during the preparation of the assessment scope and in commenting on the report. However, in the JCA for tarlatamab [3], no patients were included.

JCA: Beteiligung von Pat. grundsätzlich vorgesehen; Tarlatamab: keine Pat.-Beteiligung

6.2.2 Carer perspective

Findings from the literature

In their mixed-methods study, Bebb et al. (2023) also included informal caregivers of patients with SCLC, demonstrating that the disease imposes a high personal and psychological burden on the caregivers. Caregivers of patients with ES-SCLC observed similar symptoms and impacts of the disease on the patients as those reported by the patients themselves, including shortness of breath, fatigue, and weakness. They considered fatigue one of the disease's most significant impacts. Furthermore, they reported that shortness of breath affected the patient's ability to perform simple activities such as climbing stairs, doing chores, and showering [38].

Betreuende: starke persönliche und psychische Belastung

Particularly for patients with ES-SCLC, caregiving duties were sometimes considered overwhelming. Although none of the interviewed caregivers left employment specifically to care for their patient, they wished they had more time for their careers, families, and hobbies. The caregivers further reported a reduced ability to participate in their own social lives. They also commented on their emotional impact, including anger, frustration, and the inability to do what they wanted or needed. This triggered feelings of hidden resentment and associated guilt [38]. Overall, caregivers may face many of the same challenges with work, finance, self-esteem, isolation, and negative emotions as patients [45].

Pflegeaufgaben manchmal überwältigend

eigenes Leben eingeschränkt

Involvement by the AIHTA

As described in the methods section (Chapter 3), this HTA aims to obtain additional carers' perspectives through a questionnaire, for which one member of an Austrian LC support group agreed to provide a collective response.

kollektive Perspektive von Mitglied einer Selbsthilfegruppe für Atemwegserkrankungen

The interviewed member supported what was also described in the literature that affected patients suffer from shortness of breath, they cannot manage their daily life, and their social lives are restricted. Shedding light on the situation of relatives, the person stated that fearing for the patients' lives, feeling sorry for them, and even worrying about whether they would be affected as well are essential concerns. The current healthcare situation for LC treatment in Austria was rated as "good". In general, expectations for new treatment options for LC are that surgeries will become redundant. The interviewed member did not provide any information about tarlatamab [46].

Einblick in Herausforderungen

keine Angaben zu Tarlatamab

generell hohe Erwartungen an neue Therapien

Results from the JCA

In JCAs, carer involvement is also intended [44]. With tarlatamab, one carer was included, providing written consultation during the preparation of the assessment scope and providing comments on the JCA summary report.

Kommentare einer betreuenden Person zur JCA Summary verfügbar

The person states that tarlatamab "looks positive in all QoL results, like mobility and physical functioning", but notes that it is difficult to interpret the statistics' practical implications for patients in daily life, as the explanation of these implications is lacking. The carer emphasises that even a lower-grade side effect may have a significant impact on QoL in the long run and highlights the importance of ensuring the right patient receives the treatment.

schwerwiegende Beeinträchtigung der Lebensqualität auch bereits durch niedriggradige unerwünschte Wirkungen möglich

6.3 Further considerations

Just as patients prefer an open approach to their illness [40], Austrian clinical experts also emphasise the importance of openly discussing prognosis, treatment options and their associated effects. After receiving primary chemotherapy, patients with ES-SCLC often experience a so-called "honeymoon phase", referring to a time when the patients feel better before deteriorating again and further therapy is required. The subsequent treatment line aims at an – albeit limited – prolongation of OS, but at the expense of declining QoL again. Therefore, the consulted clinical experts considered it an important ethical aspect that patients should be able to make an informed and voluntary decision about whether to receive such treatments [8].

auch österr. klin. Expert:innen betonen die Wichtigkeit eines offenen Gesprächs um den Pat. eine freie Entscheidungsfindung zu ermöglichen

6.4 Austrian registries and documentation of tarlatamab use

nationales Krebsregister von Statistik Austria, nur epidemiologische Daten

In Austria, all cancer cases are recorded within the Austrian National Cancer Registry, maintained by Statistics Austria. It includes cancer cases diagnosed or treated in hospitals [4]. Of note, it is an epidemiological registry collecting incidence and mortality data, but not information on diagnoses, disease stages or treatment.

Lungenkrebsregister vom Wiener Gesundheitsverbund und Karl Landsteiner Institut

In 2020, a specific lung cancer registry was established by the Vienna Health Network in collaboration with the Karl Landsteiner Institute for Lung Research and Pneumological Oncology. The aim of this registry is to improve treatment quality through detailed data analysis and collaboration among hospitals [47, 48].

LALUCA: Forschungsplattform mit Fokus auf diagnostische Prozesse, therapeutische Entscheidungen, und Prognose im klinischen Alltag

In addition, the Karl Landsteiner Institute for Lung Research and Pneumological Oncology funded the Austrian research platform "LALUCA" (Longitudinal Analysis of Lung Cancer Data). The purpose of this project is to document representative data on molecular testing, sequence of systemic treatment and other treatment modalities, and the course of disease in patients with lung cancer. It particularly focuses on molecular biomarker testing and next-generation sequencing of patients before the start of first-line treatment. The data are intended to assess the current state of care and develop recommendations for areas that can be improved [16].

6.5 Interpretation of findings

keine tiefgreifenden Strukturänderungen nötig, aber mehr Ressourcen für Spitalsaufenthalte und Management unerwünschter Ereignisse erforderlich

From an organisational perspective, the consulted clinical experts do not expect substantial structural changes with the implementation of tarlatamab in Austria. However, for successful treatment, organisational adjustments in line with specific treatment protocols and interdisciplinary coordination were considered essential. Attention should be paid to the early detection and management of specific AEs, i.e., CRS and ICANS, which require close monitoring and training of the involved staff. For this, and for the expected hospital stays during the first treatment cycle, more resources will be needed. The clinical experts further highlighted the importance of training personnel.

Pat.-Perspektive ausschließlich aus Literaturquellen

Patient:innen sind schwer krank

For this report, information on patients' perspectives could be obtained solely from the literature. Despite intensive efforts, no eligible patients could be recruited to answer the questionnaire provided by the AIHTA. There might be two limiting factors why those affected are so difficult to identify: on the one hand, patients are at a very serious stage of their disease and have limited capacities. On the other hand, the timeframe for patient involvement is limited, making the timely identification of eligible patients difficult.

generell hohe Erwartungen an neue LC-Produkte

Nevertheless, a member of an Austrian support group agreed to provide a collective perspective on patients with lung cancer. In describing the situation of affected patients, the statements of the person interviewed by the AIHTA align with the literature. The person did not provide any information on tarlatamab; however, expectations regarding new products in general are deemed high [46].

Beteiligung Betroffener gesetzlich vorgeschrieben und moralisch wünschenswert

Involvement of affected persons within the Austrian appraisal board process is not only a legal requirement [49] but may also be a moral obligation to offer the opportunity to participate to patients, carers and members of patient organisations. Although potential input from a single person is neither generalisable nor representative, valuable aspects (particularly regarding the Austrian context) can still be identified.

JCA: betreuende Person wünscht sich Bericht, der aussagekräftig und verständlich für Pat. ist

At a European level, it is generally intended to involve patients and carers in the JCAs [44]. In the case of tarlatamab, no patient was successfully involved, though one carer was. When commenting on the JCA summary, the person noted that interpreting data and what it means for patients' daily lives is difficult for a non-scientist. The carer states that individual experts' involvement in the JCA should help make the assessment "meaningful and understandable" for patients [3].

wesentlicher Aspekt: Möglichkeit der informierten Entscheidungsfindung

Another relevant aspect identified during the preparation of this HTA concerns the process of treatment decision-making. The evidence highlighted that patients appreciate it when their doctors discuss their condition and prognosis openly [40]. This is consistent with the approach of Austrian clinical experts, who emphasise the importance of openly discussing treatment options (shared decision-making) and their associated effects to enable patients to make informed decisions [46].

7 Development costs and public contributions

7.1 Own development costs, acquisitions and licences

Übersicht zu Entwicklungskosten

Amgen has not published the total amount of research and development (R&D) expenses attributed to IMDYLLTRA®. As this chapter relies solely on publicly accessible information, any funding amounts related to the development of tarlatamab may be incomplete. Table 7-1 provides a brief summary of the key development points of tarlatamab.

Table 7-1: IMDYLLTRA® acquisitions and public contribution overview

Originator	Developer	Information on acquisitions	Public contribution	Type of public funding
Amgen	Amgen	n.a.	n.a.	n.a.

Abbreviation: n.a.…not available

Basic research and clinical development

Entwicklungsgeschichte von Tarlatamab

Earliest mention of AMG 757 (tarlatamab) in Amgen's annual reports date back to 2018 [50]. Tarlatamab was in phase 1 early development, being already investigated for SCLC. In 2021, after successful phase 1 trials, phase 2 trial was initiated [51], where the results eventually led to a breakthrough designation by the FDA in 2023 [52].

klinische Entwicklung von Amgen finanziert und durchgeführt

Both ongoing clinical trials, as well as the pivotal international, multicentre phase 1 and 2 trials, were sponsored and investigated by Amgen as seen in Figure 7-1.

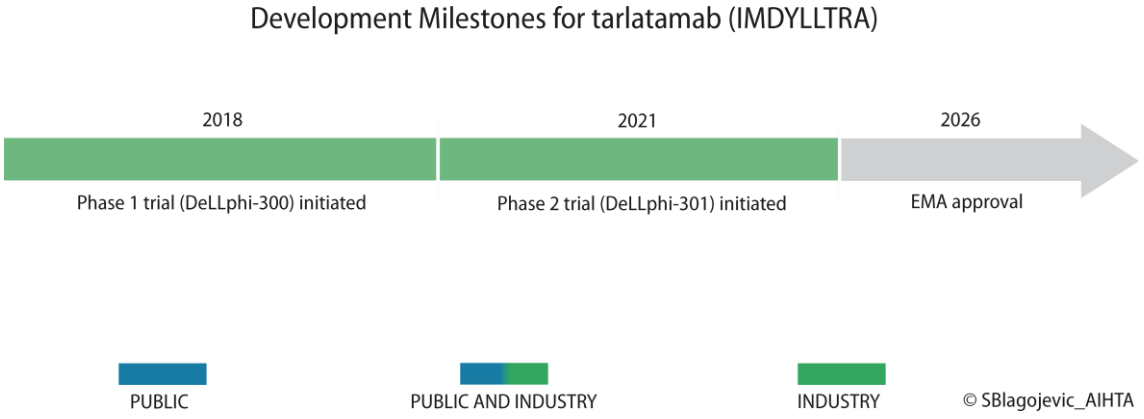


Figure 7-1: Development milestones for IMDYLLTRA®

7.2 Public contributions to drug development

We were unable to identify any public contributions to the development of tarlatamab prior to FDA approval. In 2025 and 2026 at the University of Alabama a research team was analysing a novel approach to enhance the therapeutic efficacy of tarlatamab [53].

keine öffentlichen Beiträge identifiziert vor der Zulassung durch die FDA

Patents

IMDYLLTRA® and more specifically its associated bifunctional polypeptides are under patent protection with an expected expiration on 8 January 2036 [54].

Patent geschützt in der EU bis voraussichtlich 8.1.2036

7.3 Interpretation of findings

The development of tarlatamab demonstrates a clear progression that was conducted by the developer, Amgen, themselves. No acquisitions, no mergers, no licensing agreements were identified that relate to the development of tarlatamab, leading us to conclude that tarlatamab is a industry-led pharmaceutical developement. No public contributions prior to its FDA-approval were identified either.

Tarlatamab ist das Resultat einer Eigenentwicklung von Amgen

8 Landscape overview

8.1 Ongoing studies on tarlatamab

17 laufende Studien zu Tarlatamab, davon 16 für SCLC und 1 für neuroendokrine Karzinome

Seventeen ongoing clinical studies evaluating tarlatamab were identified via ClinicalTrials.gov (see Table 8-1). Sixteen are for SCLC, and one is for neuroendocrine carcinomas of other origin. These include ten studies currently recruiting (NCT06830694, NCT07423585, NCT07061080, NCT07005128, NCT07203053, NCT07016230, NCT06814496, NCT07242547, NCT06937905, NCT07243470), six active, but not recruiting (NCT06502977, NCT05060016, NCT05740566, NCT06211036, NCT06745323, NCT06117774), and one not yet recruiting (NCT07468656).

Tarlatamab in diversen Kombinationen; teils außerhalb SCLC

Among the studies for SCLC, tarlatamab is investigated with other combinations: etoposide, carboplatin and atezolizumab (NCT06830694), durvalumab (NCT06211036, NCT07005128), durvalumab, carboplatin and etoposide (NCT07005128), radiotherapy (NCT06814496), and temozolomide (NCT07243470). The studies, not restricted to SCLC, investigate tarlatamab in advanced neuroendocrine carcinomas of the digestive system or unknown primary origin (NCT07061080), in poorly differentiated neuroendocrine carcinomas (NCT06937905, NCT07016230), and in high-grade brain tumours (NCT07243470).

Tarlatamab wird in Erstlinie ES-SCLC in 4 Studien untersucht

In the first-line setting for ES-SCLC, four trials evaluate tarlatamab. DeLLphi-305 (NCT06211036, Phase 3) combines it with durvalumab versus durvalumab alone as maintenance following platinum, etoposide and durvalumab. DeLLphi-312 (NCT07005128, Phase 3) adds tarlatamab to first-line durvalumab, carboplatin and etoposide versus that regimen alone in untreated ES-SCLC; and NCT07423585 (Phase 2) is a front-line window-of-opportunity study of tarlatamab monotherapy in ES disease. NCT06830694 (Phase 2) investigates tarlatamab with etoposide, carboplatin and atezolizumab in transformed SCLC after EGFR TKI treatment.

Tarlatamab wird in Zweitlinie/Rezidiv SCLC in 5 Studien untersucht

For the second-line/relapsed setting are five trials: DeLLphi-301 (NCT05060016, Phase 2) and DeLLphi-307 (NCT06502977, Phase 2, in Chinese subjects), both evaluating tarlatamab after two or more prior lines of treatment. DeLLphi-304 (NCT05740566, Phase 3) comparing tarlatamab with SoC after platinum-based first-line chemotherapy; and NCT07203053 (ETOP 29-25, Phase 2) in pretreated ES-SCLC patients with ECOG PS 2. DeLLphi-309 (NCT06745323, Phase 2) evaluates different tarlatamab dosing regimens.

Tarlatamab wird in limitiertem Stadium in 3 Studien untersucht

In the limited-stage setting are three trials: NCT06117774 (Phase 3) tests tarlatamab as consolidation after concurrent chemoradiation; NCT07242547 (MERLIN, Phase 2) evaluates it as maintenance after sequential chemo-radiotherapy in patients not eligible for concurrent chemo-radiotherapy; and NCT06814496 (RABBIT, Phase 1/2) combines tarlatamab with concurrent radiotherapy in DLL3-expressing tumours.

übrige Studien zu neuroendokrine Karzinome, Hirntumoren, Beobachtungen

The remaining trials are not strictly line-defined or lie outside SCLC: NCT07061080 (Phase 2), NCT06937905 (GCO-003, Phase 3) and NCT07016230 (Phase 2) in neuroendocrine carcinomas, NCT07243470 (Phase 1/2) in high-grade brain tumours, and NCT07468656 (Observational), which analyses blood samples in SCLC patients treated with tarlatamab.

8.2 Treatments in development

3 Therapien in der IHSI-Datenbank [21] identifiziert für ES-SCLC

Using the IHSI database [21], a total of three combination therapies were identified as under development for metastatic SCLC with disease progression on or after platinum-based chemotherapy in adults (see Table 8-2): Lurbinectedin, 225ac-abd147, obrixtamig. All of the identified therapies are indicated as second-line treatment, except obrixtamig, for which the treatment line is not yet defined. The identified therapies span various drug classes: lurbinectedin is a synthetic alkaloid, 225ac-abd147 is a DLL3 targeting radiopharmaceutical, and obrixtamig is a monoclonal antibody.

voraussichtliche Zulassung für Alternativprodukte August 2027, Juli 2030 und Februar 2033

For metastatic SCLC with disease progression on or after platinum-based chemotherapy in adults, the expected EC decision times are as follows: Lurbinectedin (August 2027), 225ac-abd147 (July 2030), obrixtamig (February 2033).

8.3 Interpretation of findings

weitere laufende Studien zu Tarlatamab, überwiegend SCLC über alle Therapielinien

The ongoing trial landscape for tarlatamab is broad, with seventeen studies spanning multiple disease settings. Most (sixteen of seventeen) are in SCLC. Several Phase 3 trials are underway in the first-line, second-line and limited-stage consolidation settings, suggesting the drug is being assessed for use throughout the SCLC treatment pathway. Many trials combine tarlatamab with established regimens, including platinum-etoposide chemotherapy, immunotherapy (durvalumab, atezolizumab), and radiotherapy. A smaller number of studies extend into neuroendocrine carcinomas of other origins and high-grade brain tumours, though these remain exploratory.

drei Alternativen in Entwicklung

europäische Zulassungen zwischen 2027 und 2033 erwartet

The treatments in development for ES-SCLC after progression on platinum-based chemotherapy are comparatively limited, with only three combination therapies identified. This suggests the second-line and later setting remains an area of high unmet need with few candidates advancing. The three agents represent distinct drug classes pointing to varied approaches rather than a single modality. Their expected EC decision times are staggered, from August 2027 to February 2033, implying the landscape will evolve gradually over the coming years rather than change abruptly.

Table 8-1: List of ongoing studies with tarlatamab for SCLC

Title	Trial ID	Other IDs	Phase	Status	Estimated study completion date	Additional information
Phase 2a Study Evaluating the Efficacy, Safety, Tolerability and Pharmacokinetics of Tarlatamab in Chinese Subjects With Advanced Small Cell Lung Cancer After Two or More Prior Lines of Treatment (DeLLphi-307)	NCT06502977	20230273	2	Active, not recruiting	08.01.2027	Interventional
Clinical Trial for Safety and Effectiveness Evaluation of Tarlatamab (AMG757) With Etoposide, Carboplatin and Atezolizumab in Transformed Small Cell Lung Cancer Patients From Adenocarcinoma After EGFR TKI Treatment: Phase II Multicenter Clinical Trial	NCT06830694	2025-01-014	2	Recruiting	30.06.2027	Interventional
A Phase 2 Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of Tarlatamab in Subjects With Relapsed/Refractory Small Cell Lung Cancer After Two or More Prior Lines of Treatment (DeLLphi-301).	NCT05060016	20200491 2024-511837-37 (Other Identifier) (OTHER: EU-CTR)	2	Active, not recruiting	30.12.2027	Interventional
A Front-Line Window-of-Opportunity Phase 2 Study of Tarlatamab (Bispecific T Cell Engager: DLL3-CD3) in Patients With Extensive-Stage Small-Cell Lung Cancer	NCT07423585	OSU-25028 NCI-2026-00832 (Registry Identifier) (REGISTRY: CTRP – Clinical Trial Reporting Program) OSU-25028 (Other Identifier) (OTHER: Ohio State University Comprehensive Cancer Centre)	2	Recruiting	31.12.2027	Interventional
A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy	NCT05740566	20210004	3	Active, not recruiting	26.03.2028	Interventional
A Phase 3, Open-label, Multicenter, Randomized Study of Tarlatamab in Combination With Durvalumab vs Durvalumab Alone in Subjects With Extensive-Stage Small-Cell Lung Cancer Following Platinum, Etoposide and Durvalumab (DeLLphi-305)	NCT06211036	202000412023-505989-29 (Other Identifier) (OTHER: EU CT Number)	3	Active, not recruiting	30.09.2028	Interventional
Phase II Study Of Tarlatamab Alone Or In Combination With Chemotherapy In Advanced Neuroendocrine Carcinomas Of The Digestive System Or Unknown Primary Origin	NCT07061080	GETNE T2419-2024-514327-42-00 (EU Trial (CTIS) Number)	2	Recruiting	12.2028	Interventional
Analysis of Blood Samples in Small Cell Lung Cancer Patients Treated With Tarlatamab	NCT07468656	Pro00119597	n.a.	Not yet recruiting	12.2028	Observational
A Phase 2, Open-label, Randomized, Multicenter Study of Tarlatamab Dosing Regimens in Subjects With Small Cell Lung Cancer (SCLC) (DeLLphi-309)	NCT06745323	20240092	2	Active, not recruiting	02.2029	Interventional
A Phase 3, Open Label, Multicenter, Randomized Study of First Line Tarlatamab in Combination With Durvalumab, Carboplatin and Etoposide Versus Durvalumab, Carboplatin and Etoposide in Untreated Extensive Stage Small-Cell Lung Cancer (DeLLphi-312)	NCT07005128	20240178	3	Recruiting	07.2029	Interventional

Title	Trial ID	Other IDs	Phase	Status	Estimated study completion date	Additional information
A Multicentre Phase II Trial of Tarlatamab in Patients With Pretreated Extensive-stage Small Cell Lung Cancer (ES-SCLC) and ECOG PS 2	NCT07203053	ETOP 29-25	2	Recruiting	10.2029	Interventional
Phase 2, Multicenter, Open Label, Platform Study Investigating Tarlatamab (AMG 757) in Patients With Metastatic/Locally Advanced Small-Cell Lung Cancer (SCLC) and Other Poorly Differentiated Neuroendocrine Carcinomas (NECs), With Biomarker Analysis to Characterize Response/Resistance	NCT07016230	2024-515847-47-00 2024/4014 (Other Identifier) (OTHER: CSET number (Gustave Roussy ID))	2	Recruiting	01.2030	Interventional
A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Tarlatamab Therapy in Subjects With Limited-Stage Small-Cell Lung Cancer (LS-SCLC) Who Have Not Progressed Following Concurrent Chemoradiation Therapy	NCT06117774	20230016-2023-506235-15 (Other Identifier) (OTHER: EU CT Number)	3	Active, not recruiting	04.2030	Interventional
RAdiation comBined With BIspecific T-Cell Engager in DLL3 Expressing Tumors (RABBIT) Study: A Phase I/II Study of AMG757/Tarlatamab and Concurrent Radiation Therapy in Tumors With High Prevalence of DLL3	NCT06814496	STUDY00005401 20247128 (Other Grant/Funding Number) (OTHER_GRANT: Amgen)	1 2	Recruiting	05.2030	Interventional
A Phase II Clinical Trial of Tarlatamab as Maintenance Treatment After Sequential Chemo-radiotherapy for Limited Stage SCLC Patients Not Eligible for Concurrent Chemo-radiotherapy	NCT07242547	GECP 24/01_MERLIN 2024-515201-26-00 (EU Trial (CTIS) Number)	2	Recruiting	06.2030	Interventional
A GCO Trial Exploring the Efficacy and Safety of Tarlatamab Versus Investigator-choice Chemotherapy in Pre-treated Patients With Advanced, Pulmonary or Gastroenteropancreatic Poorly Differentiated Neuroendocrine Carcinomas (NECs)	NCT06937905	GCO-003	3	Recruiting	08.2030	Interventional
A Multicenter, Open-label Phase I/II Trial Aiming to Assess the Safety and Clinical Activity of Tarlatamab in Combination With Metronomic Temozolomide in Adolescents and Adults' Patients With High Grade Brain Tumors	NCT07243470	ET23-040-2023-510568-11-00 (EU Trial (CTIS) Number)	1 2	Recruiting	10.2030	Interventional

Table 8-2: Landscape overview for metastatic small cell lung cancer with disease progression on or after platinum-based chemotherapy in adults

Indication	Active ingredient	NCT Number	Phase	Treatment line	Developer	Drug class	Estimated EC decision
Lurbinectedin							
Lurbinectedin in combination with irinotecan for second-line treatment of relapsed small cell lung cancer in adults and elderly who failed one prior platinum-containing chemotherapy, with or without anti-PD-1 or anti-PD-L1 agents	lurbinectedin	NCT05153239	3	second line	PharmaMar	synthetic alkaloid	Aug 2027

Indication	Active ingredient	NCT Number	Phase	Treatment line	Developer	Drug class	Estimated EC decision
225ac-abd147							
225ac-abd147 monotherapy for second-line treatment of locally advanced or metastatic small cell lung cancer in adults and elderly	n.a.	NCT06736418	1	second line	Abdera Therapeutics	Delta-like ligand 3 targeting radiopharmaceutical	Jul 2030
Obrixtamig							
Obrixtamig in combination with topotecan or standard of care chemotherapy for treatment of extensive-stage small cell lung cancer in adults and elderly	obrixtamig	NCT05990738	1	n.a.	Boehringer Ingelheim		Feb 2033

Abbreviation: n.a. … not applicable

9 Conclusion

This report assessed tarlatamab (IMDYLLTRA®) for the treatment of adult patients with ES-SCLC who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. Tarlatamab was subject to a JCA, conducted in accordance with the Regulation on Health Technology Assessment (Regulation (EU) 2021/2282).

klinik: sign. OS-Benefit in direkten Vergleichen (Topotecan), heterogene PFS/ORR/DoR;

beherrschbares Sicherheitsprofil (CRS, ICANS);

indirekte Vergleiche (CAV & Platin-Retherapie) sehr niedrige Evidenzsicherheit

The clinical evidence was primarily based on a single pivotal phase 3 RCT (DeLLphi-304), supported by three historical comparator studies for the ITCs. Across these sources, seven PICOs were defined: three direct comparisons with topotecan (PICOs 1, 4, 6) and four ITCs (PICOs 2, 3, 5, 7) against CAV, platinum rechallenge, or carboplatin plus etoposide. Across the three direct comparisons, tarlatamab showed a statistically significant OS benefit compared with topotecan. The numerically largest difference was observed in the platinum-resistant population, although differences between subgroups should be interpreted cautiously. Results for PFS, ORR, and DoR were less consistent. Selected PRO and HRQoL outcomes at week 19 favoured tarlatamab, but these findings were affected by methodological limitations. Tarlatamab was associated with fewer severe adverse events than topotecan, but showed a distinct toxicity profile, particularly CRS and ICANS, requiring specific monitoring and clinical expertise. Evidence from the indirect comparisons with CAV and platinum rechallenge was of very low certainty and did not permit reliable conclusions.

breite ICER-Spannweite, OS-extrapolationsabhängig; hoher Budget-Impact für Ö

Economically, four published cost-utility analyses incorporating the available clinical evidence reported incremental QALY gains ranging from 0.15 to 1.06. At the evaluated prices, tarlatamab was not cost-effective at the respective country-specific willingness-to-pay thresholds. The reported ICERs ranged from approximately €35,000 to more than €1.2 million per QALY and were highly sensitive to assumptions regarding long-term OS extrapolation. However, the four economic evaluations presented have limited transferability to Austria because of differences in healthcare settings, costs, comparator therapies, and WTP thresholds. For Austria, the estimated treatment cost was € [redacted] per patient, resulting in a projected cumulative net budget impact of € [redacted] to € [redacted] over three years. These estimates are subject to substantial uncertainty regarding the eligible population, uptake, treatment duration, and clinical practice.

Organisation: gemeinsame Entscheidungsfindung zentral

Organisationally, no major structural changes would be required for implementation, but additional resources would be needed based on feedback from Austrian clinical experts for CRS and ICANS monitoring, staff training, and multi-day hospital observation during the initial treatment period. Available patient-perspective evidence highlights the considerable burden of ES-SCLC and the importance of transparent, shared decision-making regarding potential benefits, treatment-related risks, and practical implications.

weitere laufende Studien zu Tarlatamab, überwiegend SCLC über alle Therapielinien

Tarlatamab represents an industry-led development, and no public financial contributions prior to FDA approval were identified. Its development programme is broad, with ongoing studies across multiple SCLC treatment lines, while only a limited number of competing agents are currently being developed for the post-platinum setting.

Overall, tarlatamab provides a clinically relevant OS benefit compared with topotecan in patients with ES-SCLC who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. However, uncertainty remains regarding several clinical outcomes, the results of indirect comparisons, safety, and economic value of tarlatamab. Its implementation in Austria will require appropriate patient selection and adequate management of treatment-specific toxicities, particularly cytokine release syndrome and neurologic toxicities. The conditions under which the treatment is made available, including its price, will also be relevant to its potential role in clinical practice.

OS-Nutzen für spezifische Pat. gegeben, jedoch Preisreduktionen notwendig

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