INHALE THE LATEST: NEW HORIZONS IN LUNG CANCER DRUGS

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Relevant Financial Disclosure

No one in control of the content of this activity has a relevant financial relationship with an ineligible company.

LEARNING OBJECTIVES

1. Identify newly approved agents for the treatment of lung cancer and recognize emerging indications for existing therapies
2. Describe how new therapies are incorporated into current lung cancer treatment algorithms and clinical practice

Select New Drugs in NSCLC

c-MET amplification: Telisotuzumab vedotin

Oral HER2 agents: Zongertinib, Sevabertinib

EGFR: Datopotamab deruxtecan

Subcutaneous Immunotherapy

Select New Indications in SCLC and NSCLC

SCLC

- Tarlatamab now category 1 recommendation in NCCN for 2nd line therapy in extensive stage-small cell lung cancer (ES-SCLC)
- Lurbinectedin/atezolizumab maintenance after chemo/IO in ES-SCLC (IMForte trial)
- Durvalumab consolidation after concurrent chemoradiation in limited stage (LS)-SCLC (ADRIATIC trial)

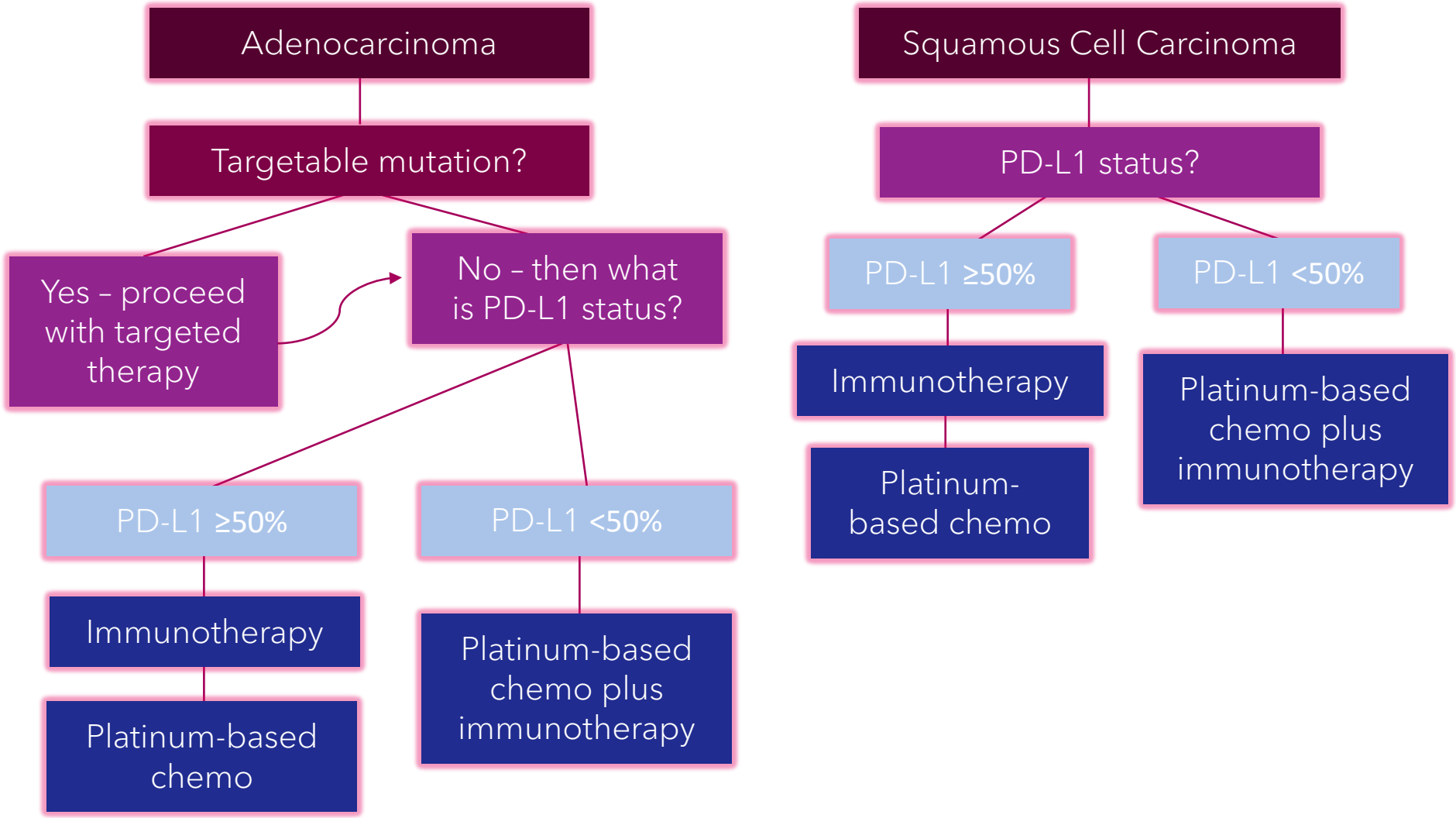
NSCLC

- Changes in EGFR: amivantamab/lazertinib 1st line, subcutaneous (SQ) amivantamab

IO = immunotherapy
EGFR = Epidermal Growth Factor Receptor
RET = Rearranged during transfection
ALK = Anaplastic Lymphoma Kinase

NEW INDICATIONS & DRUGS IN NSCLC

Advanced/Metastatic NSCLC Treatment Overview



Non-Small Cell Lung Cancer. *NCCN Clinical Practice Guidelines in Oncology*. Version 6.2026.

Biomarker/Mutation	NSCLC Incidence	Available Therapies
EGFR* (incidence) • Exon 19 deletion (45%); exon 21 L858R (40%); exon 19 insertions, S768I, L861Q, or G719X (10%) • Exon 20 insertion	10% Caucasians ~50% Asians	• Erlotinib, gefitinib, afatinib, **osimertinib‡**, dacomitinib • **Amivantamab-vmjw +/- lazertinib†‡**, sunvozertinib†‡
ERBB2 (HER2)*	3%	**Fam-trastuzumab deruxtecan-nxki**†, ado-trastuzumab emtansine, **zongertinib‡**, sevabertinib
KRAS G12C	25% (any mutation)	**Sotorasib†, adagrasib†‡**
ALK gene fusion*	5%	**Alectinib‡, brigatinib‡, lorlatinib‡, ensartinib‡,** ceritinib, crizotinib
ROS1 gene fusion	1-2%	**Repotrectinib, Crizotinib, entrectinib‡,** ceritinib, lorlatinib‡
BRAF V600E	1-2%	**Encorafenib + binimetinib**‡, dabrafenib + trametinib‡
NTRK 1/2/3 gene fusion	0.2%	Larotrectinib, entrectinib‡, repotrectinib
MET exon 14 skipping*	3-4%	**Capmatinib‡, tepotinib‡,** crizotinib
RET gene fusion	1-2%	**Selpercatinib‡, pralsetinib‡,** cabozantinib‡
NRG1 gene fusion	<1%	Zenocutuzumab-zbco†

*Associated with light or nonsmokers; †Recommended for subsequent therapy, not first-line; ‡Penetrates the blood-brain barrier; BOLD indicates NCCN preferred therapy; UNDERLINE indicates therapy commonly seen in practice

c-Met Overexpression vs MET mutation

Immunohistochemistry Report

RESULTS

c-MET: 85% of cells are positive (3+), MEETS FDA APPROVAL

INTERPRETATION

c-MET: 85% of cells are positive (3+), MEETS FDA APPROVAL

The FDA has approved telisotuzumab vedotin-tllv (Emrelis, AbbVie Inc.), a c-Met-directed antibody and microtubule inhibitor conjugate, for adults with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) with high c-Met protein overexpression [≥50% of tumor cells with strong (3+) membranous or cytoplasmic staining, who have received a prior systemic therapy.

Efficacy was evaluated in the LUMINOSITY study (NCT03539536), a multicenter, open label, multi-cohort trial. The trial included 84 patients with epidermal growth factor receptor (EGFR) wild-type, non-squamous NSCLC with high c-Met protein overexpression who had received prior systemic therapy.

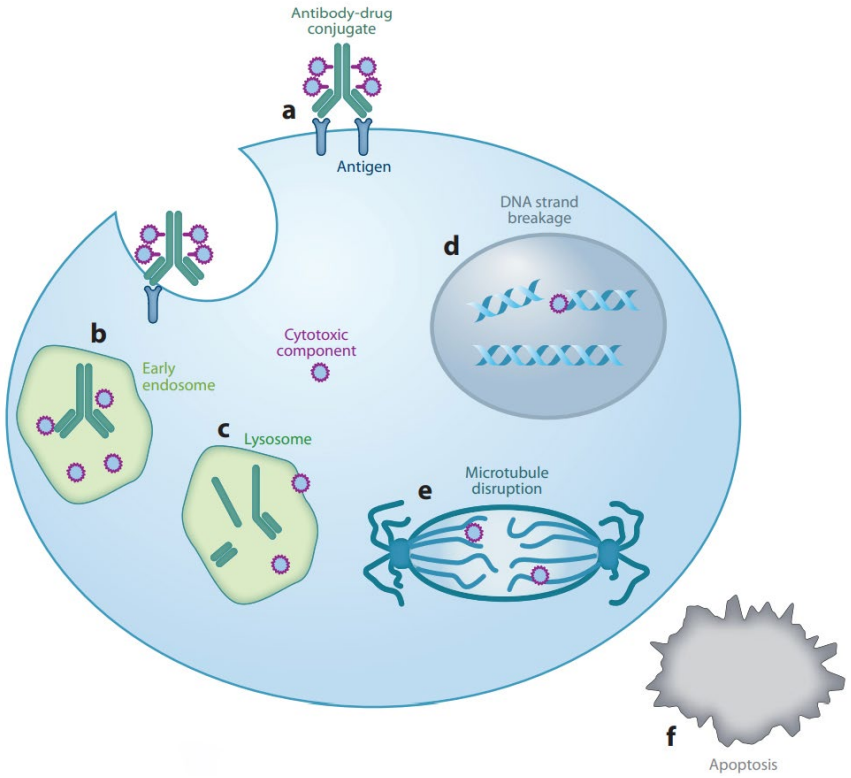
The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR), determined by blinded independent central review (BICR) according to RECIST 1.1. ORR was 35% (95% CI: 24, 46) and median DOR was 7.2 months (95% CI: 4.2, 12).

Other targeted therapies are in various phases of clinical development and may be available in an investigational context, as clinically indicated and appropriate, including antibody-drug conjugate therapies in EGFR wild-type tumors, and certain tyrosine kinase inhibitors in NSCLC with initial EGFR drivers, upon disease progression. Prognostically, increasing MET protein over-expression has been correlated with an aggressive clinical course and therapy resistance in a variety of solid tumors, including lung cancer.

Lee JB et al. *Nat Rev Clin Oncol*. 2025;22(7):640-660.
Camidge et al. *J Clin Oncol*. 2024;42:3000-3011

NGS = next generation sequencing
IHC = immunohistochemistry
TKI = tyrosine kinase inhibitor
ADC = antibody drug conjugate

Telisotuzumab vedotin (Emrelis®)



- Combines c-Met-directed antibody and microtubule inhibitor (MMAE) conjugate
- Dosing: 1.9 mg/kg IV every 14 days
- Major toxicities: peripheral neuropathy, pneumonitis/ILD, ocular, infusion-related reactions
- Drug interactions: strong CYP3A4 inhibitors may increase AUC of MMAE
- Approved for use in 2nd line advanced or metastatic NSCLC with high c-Met overexpression [≥50% of tumor cells with strong (3+) staining]

Emrelis. Package insert. AbbVie; 2025.

Telisotuzumab vedotin for high c-Met expression

LUMINOSITY trial	

Population	• Phase 2, multicenter, open-label, multi-cohort, two-stage trial, n=172
	  • Stage 1 (three cohorts): c-Met protein overexpressing nonsquamous EGFR WT, c-Met protein overexpressing nonsquamous EGFR mut, c-Met protein overexpression squamous
	  • Stage 2: only patients with c-Met protein overexpression nonsquamous EGFR WT
	• EGFR-wildtype, metastatic NSCLC with high c-Met overexpression (≥25% tumor cells with 3+ staining)
	• ≤2 previous lines of therapy (at least 1 line of chemo)

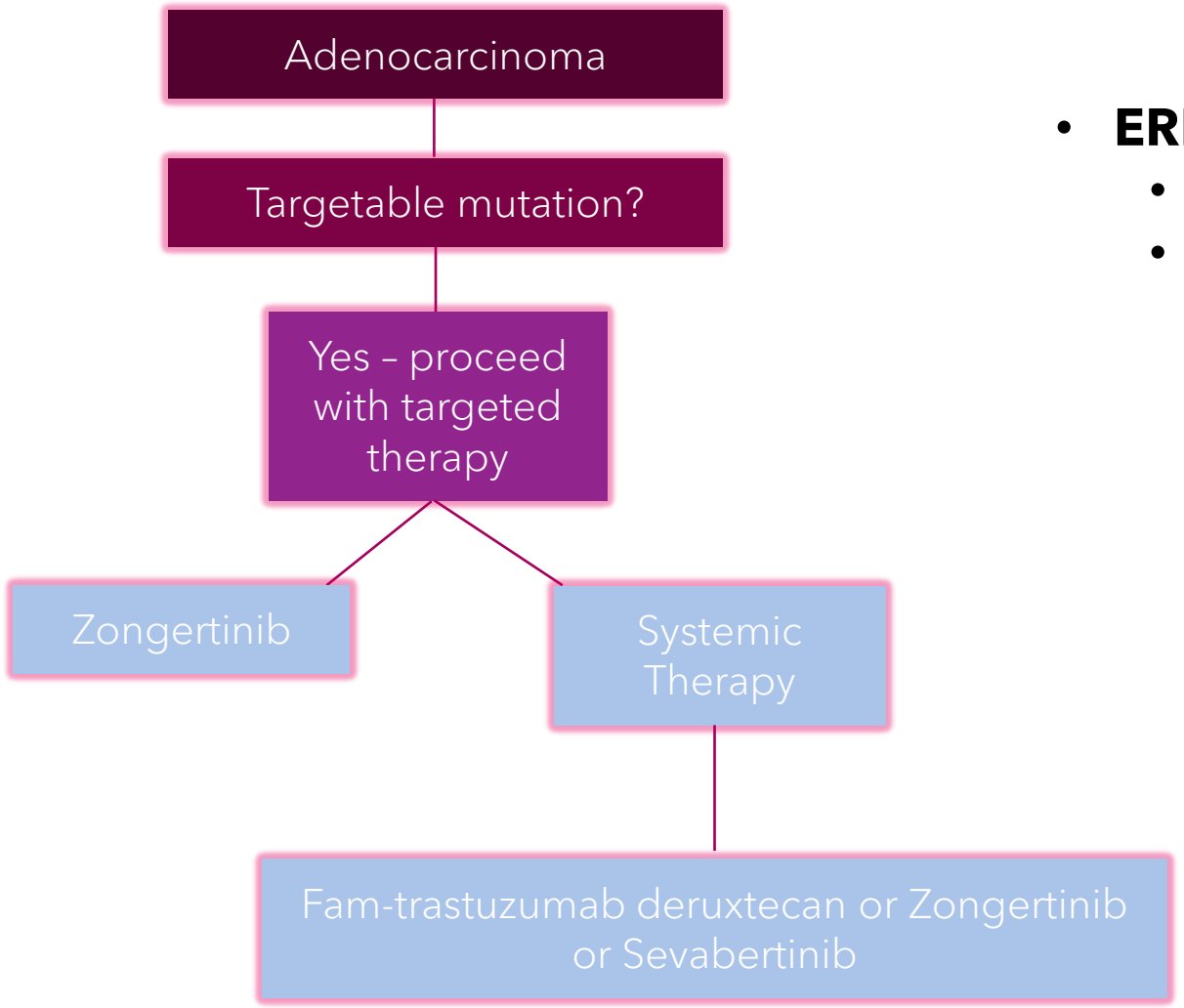
Intervention	Telisotuzumab vedotin 1.9 mg/kg every 2 weeks

Results	• At median follow-up of 20.2 months:
	  • ORR: 28.6% (95% CI, 21.7-36.2)
	  • c-Met high (≥50% 3+): 34.6%
	  • c-Met intermediate (≥25%-<50%): 22.9%
	  • Median DOR: 8.3 months (high group); 7.2 months (intermediate group)
	  • Median PFS: 5.7 months (95% CI, 4.6-6.9)
	  • Median OS: 14.5 months (95% CI, 9.9-16.6)

Adverse Events	• Most common any grade: peripheral neuropathy (30%), peripheral edema (16%), fatigue (14%) • Most common grade ≥3: peripheral neuropathy (7%), fatigue (2.3%), increased ALT (3.5%), pneumonitis (2.9%), blurry vision (1.2%), peripheral edema (1,.7%)

Camidge et al. *J Clin Oncol*. 2024;42:3000-3011.

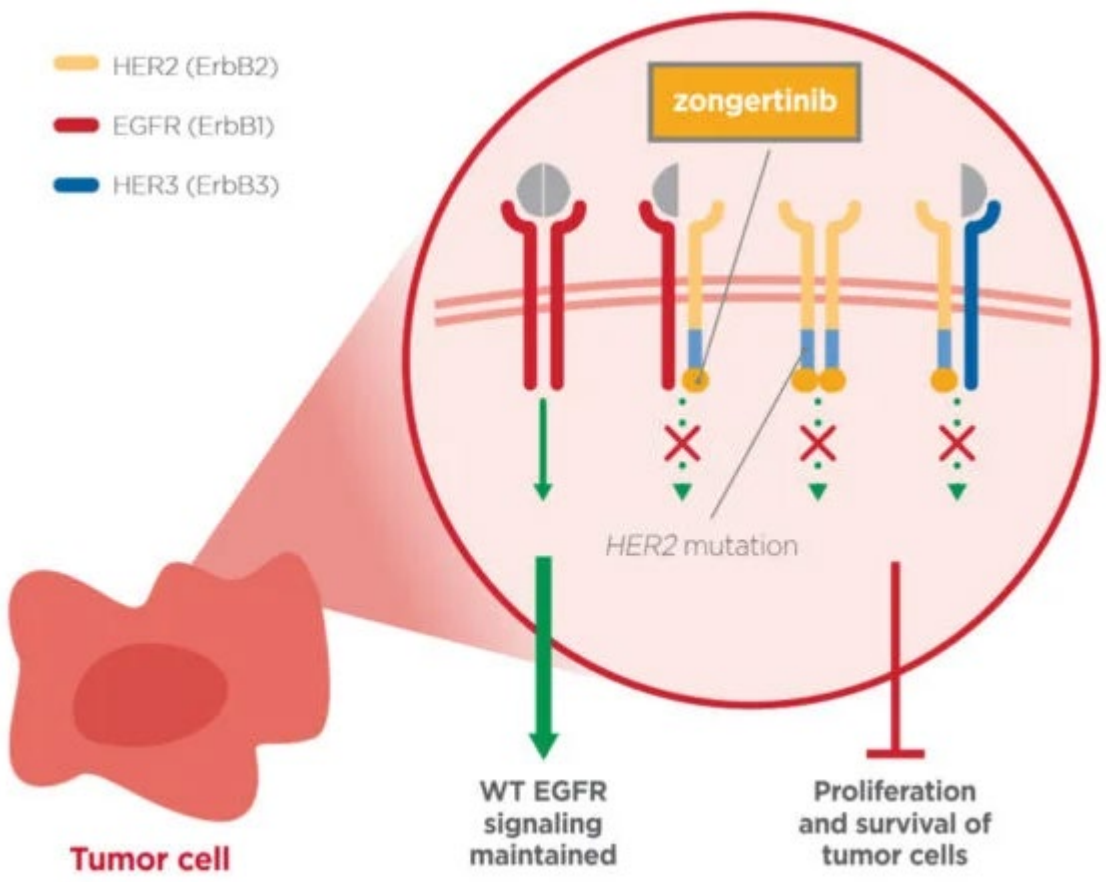
1st Line Therapy for Metastatic HER2 mut NSCLC



- **ERBB2 (HER2) Mutation**
  - Zongertinib (Hernexeos®)
  - Systemic therapy → Progression
    - Fam-trastuzumab deruxtecan (Enhertu®)
    - Zongertinib (Hernexeos®)
    - Sevabertinib (Hyrnuo®)

Non-Small Cell Lung Cancer. *NCCN Clinical Practice Guidelines in Oncology*. Version 6.2026.

Zongertinib (Hernexeos®)



- Oral kinase inhibitor targeting ERBB2 tyrosine kinase domain
- Dosing: once daily with or without food
  - <90 kg = 120 mg
  - ≥90 kg = 180 mg
- Major toxicities: hepatotoxicity, LVEF dysfunction, ILD/pneumonitis, diarrhea, rash, nausea
- Drug interactions: strong CYP3A4 inducers, BCRP substrates
- Approved for use in 2nd line advanced or metastatic NSCLC with HER2 (ERBB2) mutation (recommended as first- or second-line in NCCN)

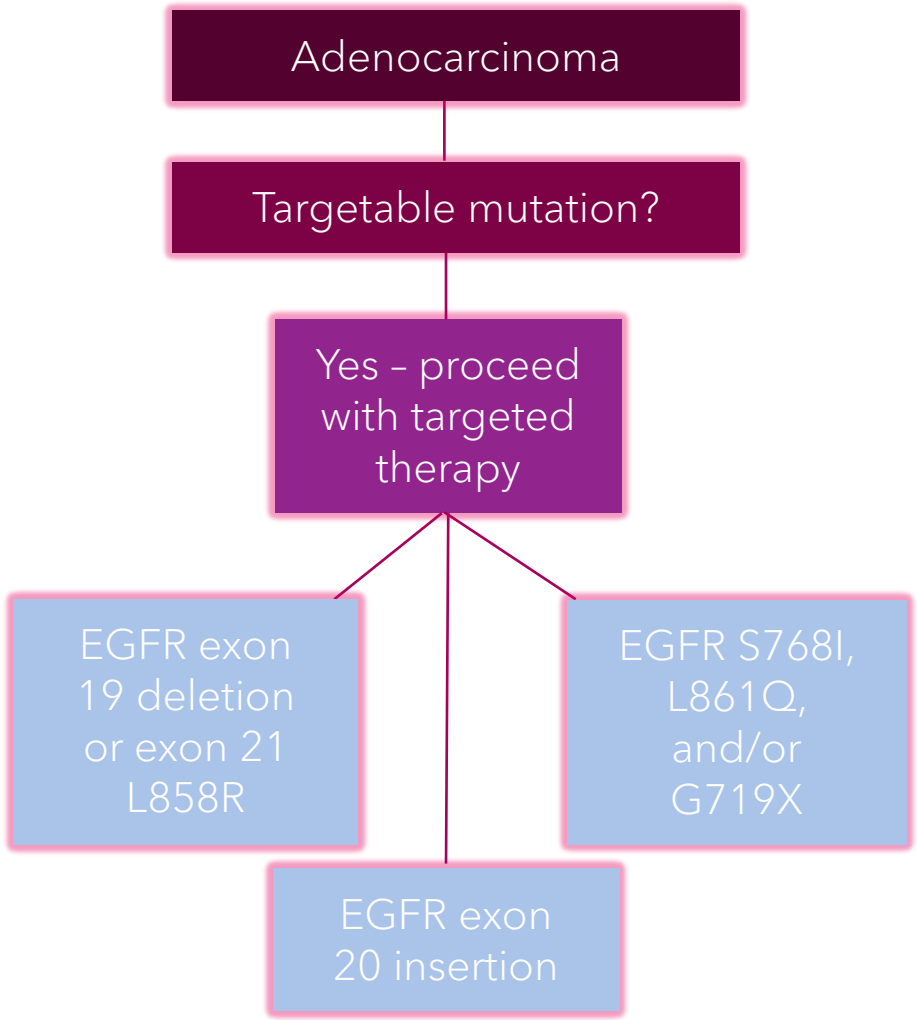
Hernexeos. Package insert. Boehringer Ingelheim Pharmaceuticals, Inc.; 2025.

Zongertinib (Hernexeos®)

Beamion LUNG-1	
Population	• Phase 1a-1b, multicohort, open-label, N=74 (cohort 2) • Metastatic nonsquamous NSCLC with HER2 mutation, treatment naïve
Intervention	Zongertinib 120 mg PO daily
Results	At median follow-up of 13.8 months (cohort 2) • ORR: 76% (95% CI, 65-84) • DOR: 15.2 months (95% CI, 9.8-NE) At median follow-up of 15.2 months (cohort 2) • Median PFS: 14.4 months (95% CI, 11.1-NE)
Adverse Events	• Any ADE grade ≥3: 45% • Most common (any grade): diarrhea (55%), rash (24%), increased ALT (18%), dysgeusia (18%) • Grade ≥3: diarrhea (3%), increased ALT (4%), increased AST (3%)

Heymach J et al. *N Engl J Med*. 2026;394:1674-1684.

1st Line Therapy for Metastatic EGFR mut NSCLC



- **EGFR Exon 19 deletion or Exon 21 L858R:**
  - Osimertinib (cat 1)
  - Osimertinib + carbo/cisplatin + pemetrexed (cat 1)
  - Amivantamab + lazertinib (cat 1)
  - Afatinib, Erlotinib, Gefitinib, Dacomitinib (cat 1)
  - Erlotinib + ramucirumab, Erlotinib + bevacizumab
  - Lazertinib
- **EGFR Exon 20 insertion:**
  - Amivantamab + carbo + pemetrexed (cat 1)
  - Systemic therapy
- **EGFR S768I, L861Q and/or G719X:**
  - Afatinib (preferred)
  - Osimertinib (preferred)
  - Erlotinib, Gefitinib, Dacomitinib

Non-Small Cell Lung Cancer. *NCCN Clinical Practice Guidelines in Oncology*. Version 6.2026.

Amivantamab (Rybrevant®) + Lazertinib (Lazcluze®)

- Approved based on MARIPOSA trial
  - Phase 3, n=1074, compared Amivantamab/Lazertinib vs Lazertinib vs Osimertinib in treatment-naïve metastatic EGFR mutated (exon 19 deletion or L858R) NSCLC
  - At median follow-up of 22 months:

Regimen	Median PFS (95% CI)	Objective Response[1] (95% CI)	Median Duration of Response (95% CI)
Amivantamab + Lazertinib	23.7 mos	86% (83-89)	25.8 mos (20.1-NE)
Osimertinib	16.6 mos	85% (81-88)	16.8 mos (14.8-18.5)

- Toxicity profile worse for combination vs osimertinib alone
  - Dose reduction required in 59% ami/laz vs 5% osimertinib
  - Treatment discontinuation in 35% ami/laz vs 14% osimertinib
- All grade ADEs in ≥15% of patients: IRR: 63% vs 0%; rash: 62% vs 31%; diarrhea: 29% vs 44%; PE: 17% vs 5%

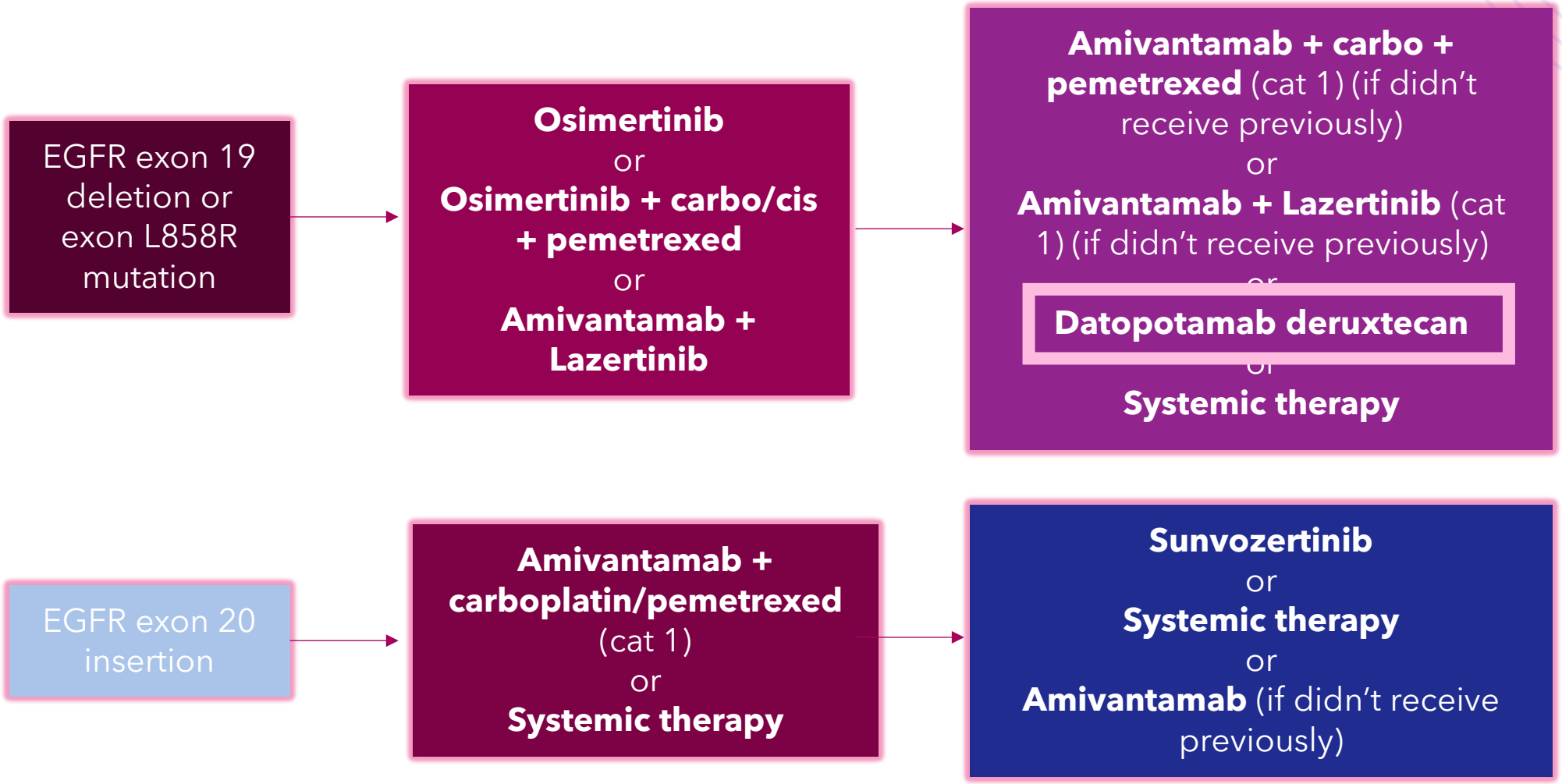
Cho BC et al. *N Engl J Med*. 2024;391:1486-98.

SQ Amivantamab (Rybrevant Faspro®)

- Approved December 2025, will likely **replace** IV Amivantamab
- Does not require IV formulation for first dose
- Requires **premedication for risk of IRR** (antihistamine, APAP, steroid)
  - Risk of IRR 13% vs 65% with IV formulation
- Carries **same risk of VTE** in combination with Lazertinib as IV formulation
- Offered in four different doses/vial sizes – potential safety risk
- **Only 28-day regimen** option for metastatic EGFR-mutated NSCLC in combination with Lazertinib

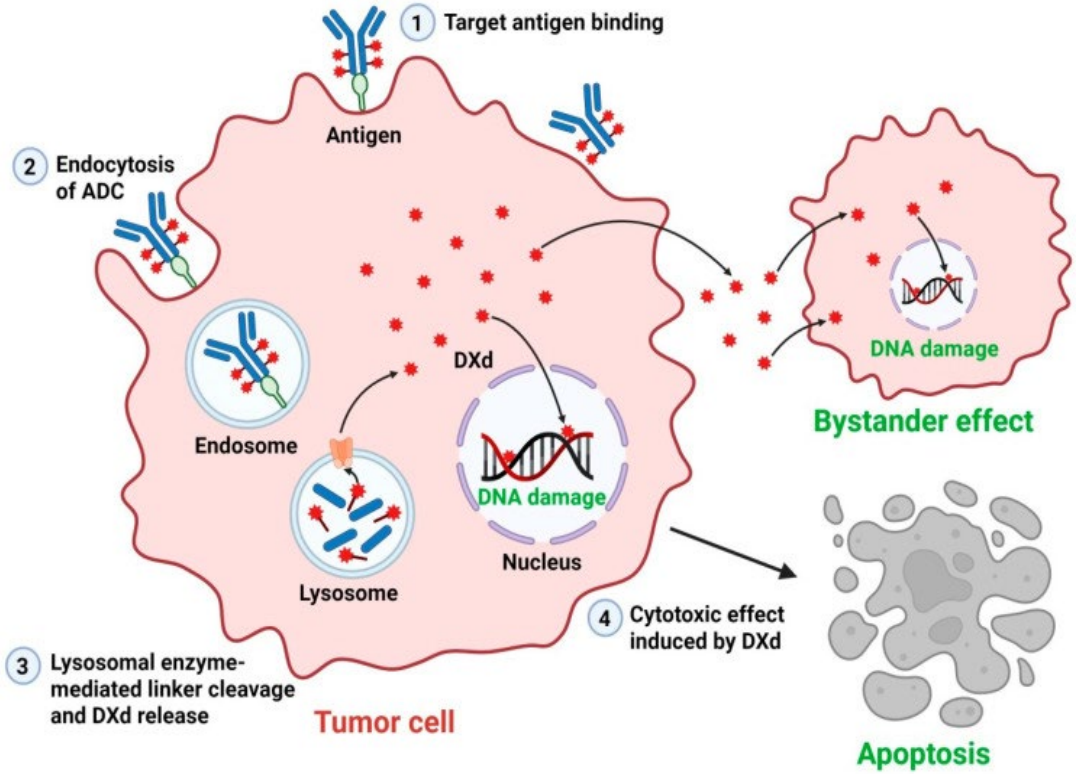
Rybrevant Faspro [package insert]. Janssen Biotech, Inc. Horsham, PA: 2025.

2nd Line Therapy for Metastatic EGFR mut NSCLC



Datopotamab deruxtecan (Datroway®)

- Combines Trop-2-directed antibody and topoisomerase inhibitor conjugate
- Dosing: 6 mg/kg IV every 21 days
- Major toxicities
  - Pneumonitis/ILD
  - Ocular: ophthalmic exam that includes visual acuity testing, slit lamp exam
  - Stomatitis/oral mucositis: recommended that patient uses dexamethasone 0.1 mg/mL mouthwash QID and PRN
  - Infusion-related reaction requires premedications (antihistamine, acetaminophen)
- Approved for use in metastatic HR+, HER2- breast cancer and metastatic EGFR+ NSCLC



Datroway. Package insert. Daiichi Sankyo; 2025.

2nd Line Dato-DXd in EGFR-mutated NSCLC

Tropion-Lung 05	
Population	• Phase 2, single arm study, n = 137 • Metastatic NSCLC with EGFR, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping, RET mutations • Progression on or after targeted therapy and platinum chemo
Intervention	Datopotamab deruxtecan 6 mg/kg IV every 21 days
Results	At median follow-up of 15.2 months (all patients) • ORR: 35.8% (95% CI, 27.8-44.4) • 43.6% EGFR; 23.5% ALK • DOR: 7 months (95% CI, 4.2-9.8) • Median PFS: 5.4 months (95% CI, 4.7-7) EGFR mutated patients at follow-up • PFS: 5.8 months (95% CI, 5.4-8.3) • Median OS: 18.3 months (95% CI, 12.4-NE)
Adverse Events	• Most common (any grade): stomatitis (56.2%), nausea (54.7%), alopecia (49.6%) • Grade ≥3: stomatitis (9.5%), amylase increase (5.1%), anemia (2.9%), nausea and decreased appetite (2.2%)

Sands J et al. *J Clin Oncol*. 2025;(43)10:1254-1265.

Subcutaneous Immunotherapy

Three products now FDA approved

- Atezolizumab and hyaluronidase-tqjs (Tecentriq Hybreza®)
  - Approved only with every 3-week dosing
- Nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®)
  - Approved for every 2, 3, and 4-week dosing
- Pembrolizumab and berahyaluronidase alfa (Keytruda Qlex®)
  - Approved for every 3 and 6-week dosing

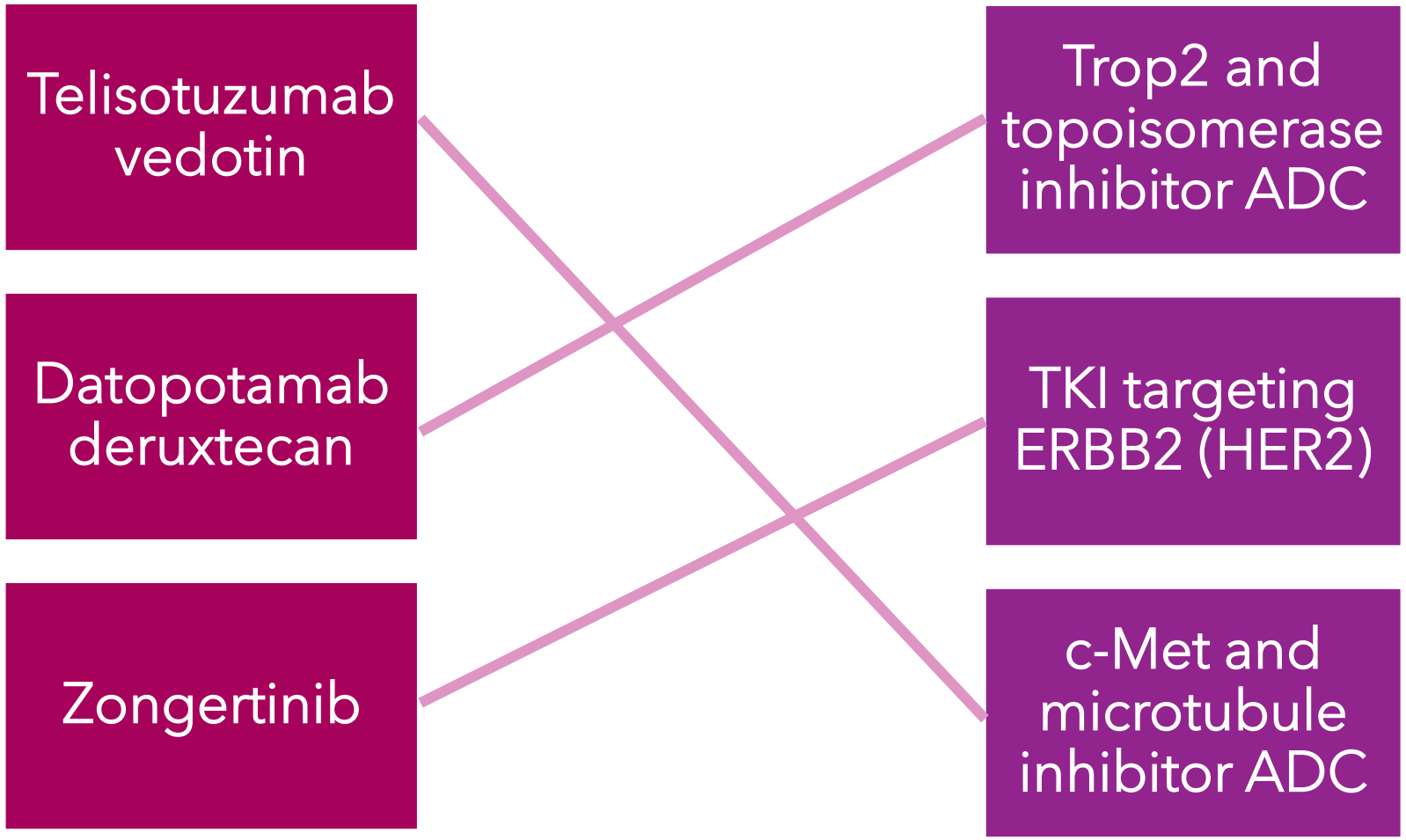
Shorten chair time and decrease compounding time

SQ doses are not equivalent to the IV formulation

- 200 mg pembrolizumab IV = 395 mg pembrolizumab and 4,800 units berahyaluronidase

Tecentriq Hybreza. Package insert. Genentech; 2024.
Opdivo Qvantig. Package insert. Bristol-Myers Squibb; 2024.
Keytruda Qlex. Package insert. Merck Sharp & Dohme; 2025.

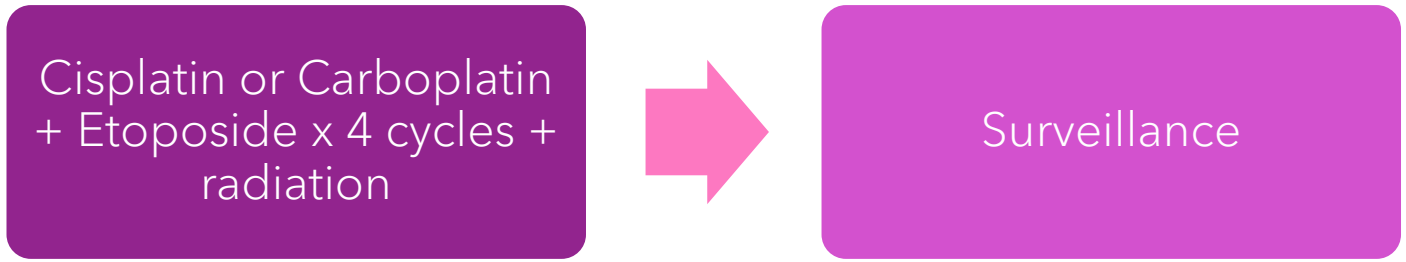
Match the Mechanism of Action to the Correct Agent



NEW INDICATIONS IN SCLC

Limited Stage SCLC

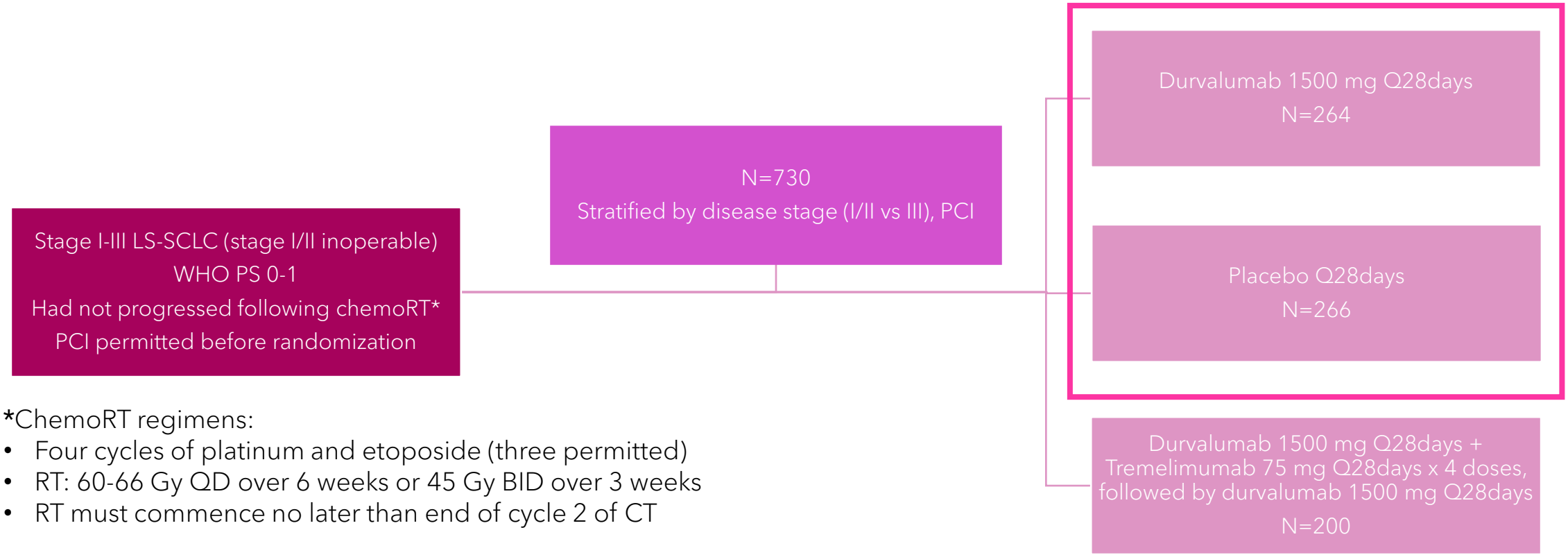
Prior to 2025-2026



Now

Small Cell Lung Cancer. NCCN Clinical Practice Guidelines in Oncology. Version 1.2027.

Adjuvant Durvalumab in LS-SCLC (ADRIATIC trial)

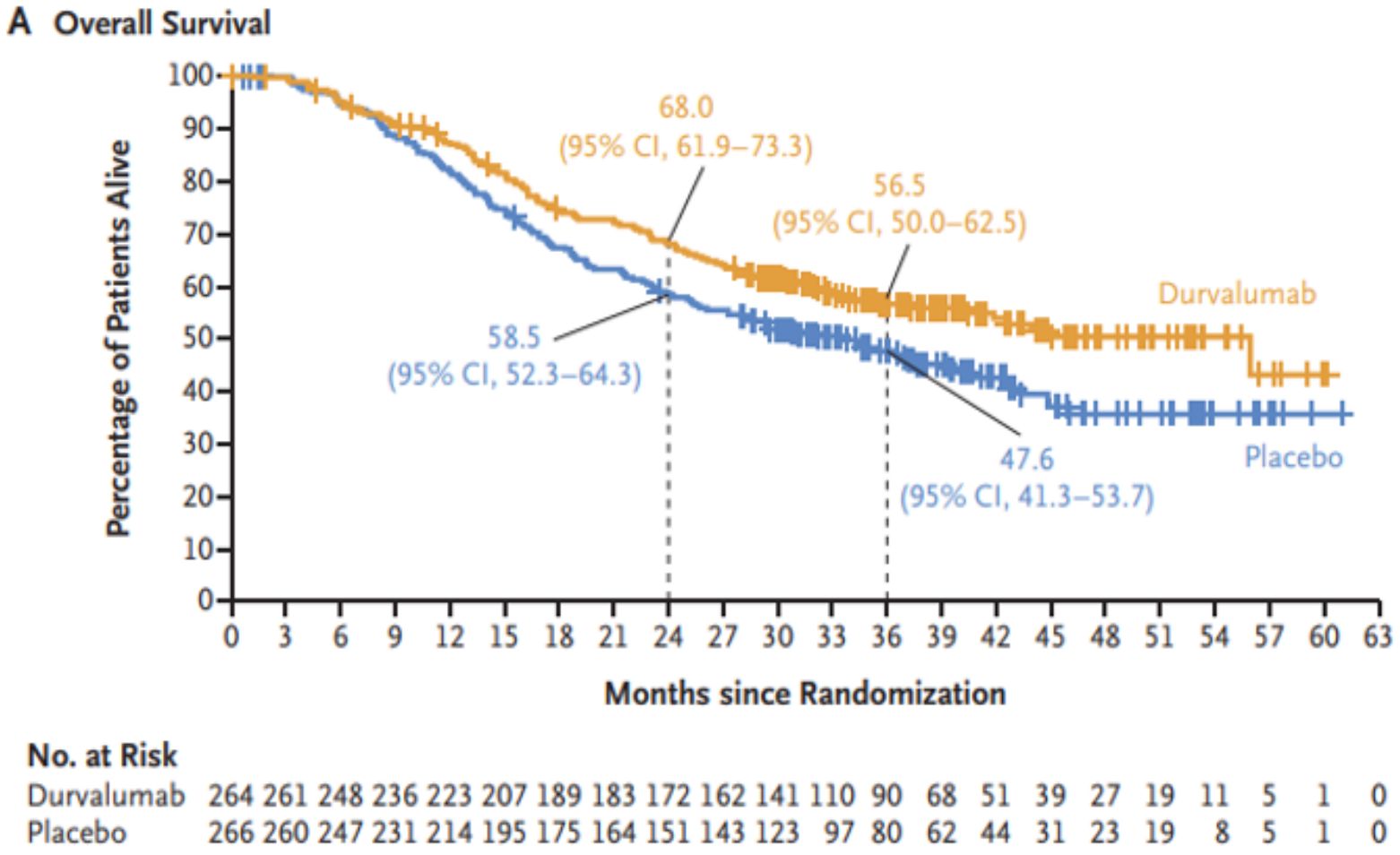


*ChemoRT regimens:

- Four cycles of platinum and etoposide (three permitted)
- RT: 60-66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks
- RT must commence no later than end of cycle 2 of CT

Cheng Y et al. *N Engl J Med*. 2024;391:1313-1327.

Adjuvant Durvalumab in LS-SCLC (ADRIATIC trial)



	No. of Deaths/ Total No. (%)	Median Overall Survival (95% CI)
		mo
Durvalumab	115/264 (43.6)	55.9 (37.3–NR)
Placebo	146/266 (54.9)	33.4 (25.5–39.9)

Stratified hazard ratio for death, 0.73 (98.321% CI, 0.54–0.98)
P=0.01

Cheng Y et al. *N Engl J Med*. 2024;391:1313-1327.

Adjuvant Durvalumab in LS-SCLC (ADRIATIC trial)

Durvalumab consolidation for up to 2 years showed significant improvement in overall survival vs placebo (median OS 55.9 vs 33.4 months; p=0.0104)

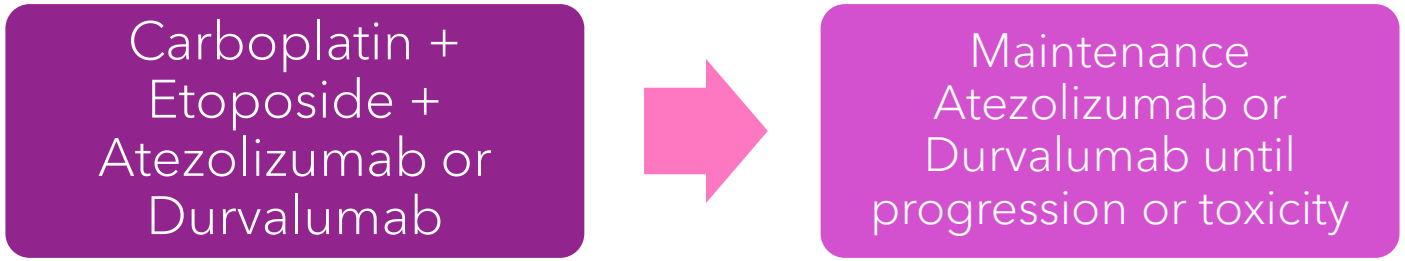
Now standard of care after completion of platinum-etoposide in limited stage SCLC

Diarrhea	5 (1.9)	0
Pneumonia	7 (2.7)	9 (3.4)
Anemia	3 (1.1)	3 (1.1)

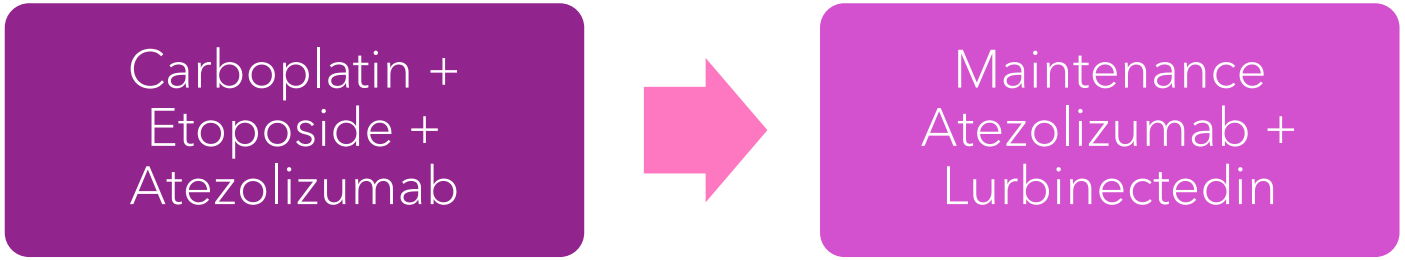
Cheng Y et al. *N Engl J Med*. 2024;391:1313-1327.

Extensive Stage SCLC

Prior to 2025-2026

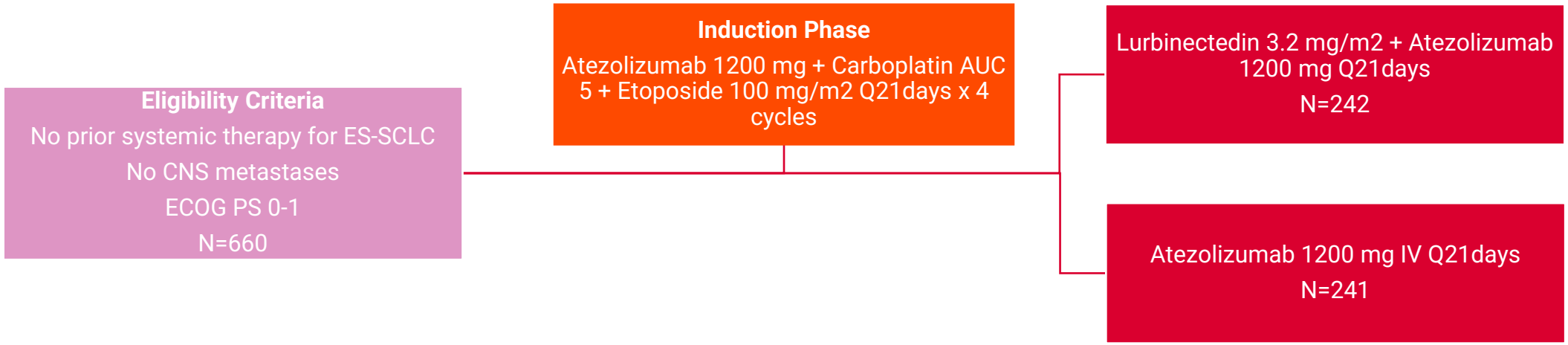


PLUS Another Option Now



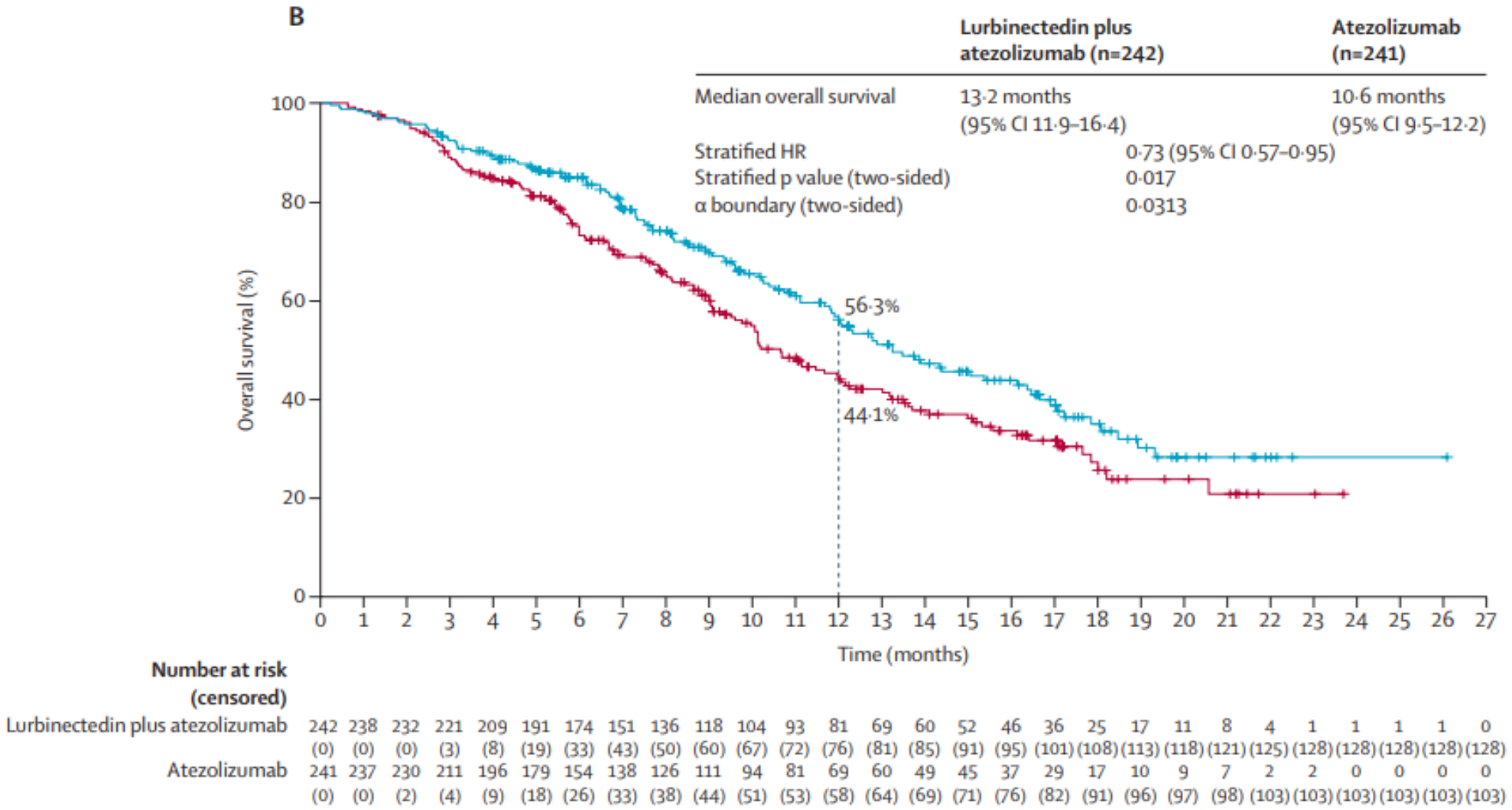
Small Cell Lung Cancer. NCCN Clinical Practice Guidelines in Oncology. Version 1.2027.

Maintenance Atezolizumab/Lurbinectedin in ES-SCLC (IMForte trial)



Paz-Ares L et al. *Lancet*. 2025;405:2129-43.

Maintenance Atezolizumab/Lurbinectedin in ES-SCLC (IMForte trial)



Paz-Ares L et al. *Lancet*. 2025;405:2129-43.

Maintenance Atezolizumab/Lurbinectedin in ES-SCLC (IMForte trial)

Pts with ≥1 AE, n (%)	Lurbinectedin + Atezolizumab (N=242)	Atezolizumab (N=240)
All-cause	235 (97.1)	194 (80.8)
Grade 3/4	92 (38)	53 (22.1)
Grade 5	12 (5)	6 (2.5)
AEs leading to discontinuation of any drug	15 (6.2)	8 (3.3)
AEs leading to dose interruption/modification of any study drug	92 (38)	33 (13.8)
Median treatment duration, months	4.1 (lurbi)/4.2 (atezo)	2.1
Median number of doses received	6.5 (lurbi)/7 (atezo)	4

Paz-Ares L et al. *Lancet*. 2025;405:2129-43.

Maintenance Atezolizumab/Lurbinectedin in ES-SCLC (IMForte trial)

First trial using maintenance therapy in ES-SCLC that meets endpoints of PFS (HR 0.54; 95% CI: 0.43, 0.67) and OS (HR 0.73; 95% CI 0.57, 0.95)

- Benefit seen across most subgroups

Higher incidence of grade 3-4 adverse events in combination arm vs atezolizumab monotherapy

- Predictable safety profile, GCSF used in lurbinectedin arm

Will likely become first line after completion of chemotherapy + immunotherapy for patients with good performance status

Paz-Ares L et al. *Lancet*. 2025;405:2129-43.

2nd Line Extensive Stage SCLC

Prior to 2025-2026

Progression → Clinical trial, Irinotecan, Lurbinectedin, Tarlatamab, Topotecan

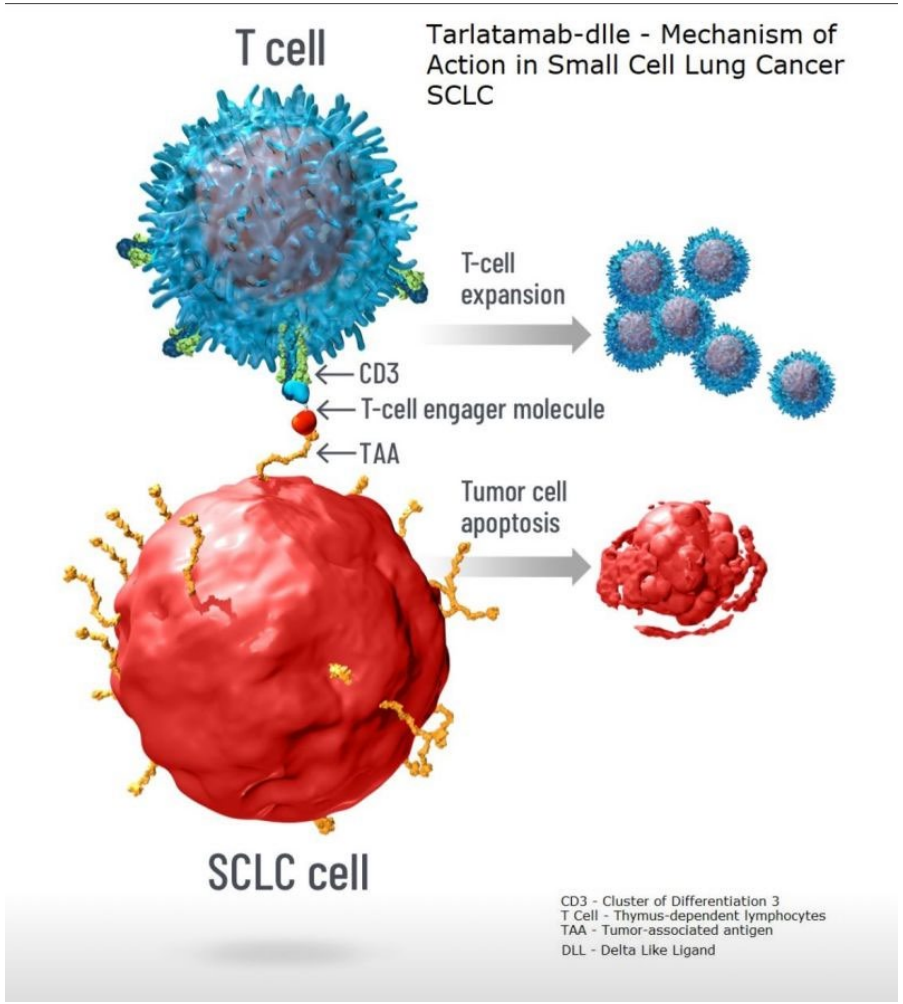
Now

Progression → Tarlatamab (cat 1), Clinical trial, Irinotecan, Lurbinectedin, Topotecan

Small Cell Lung Cancer. NCCN Clinical Practice Guidelines in Oncology. Version 1.2027.

2nd Line Tarlatamab (Imdelltra®)

- Tarlatamab granted accelerated approval in 2024 (phase 2 study, n=220)
- Phase 3 DeLLphi-304 study published in summer 2025, solidified tarlatamab's place as the standard of care for 2nd line ES-SCLC
- First bispecific T-cell engager (BiTE) approved in the lung cancer space
- Targets DLL3 on small cell lung cancer cells and CD3 on T cells leading to tumor cell lysis
  - Expressed on 85-96% of SCLC cells

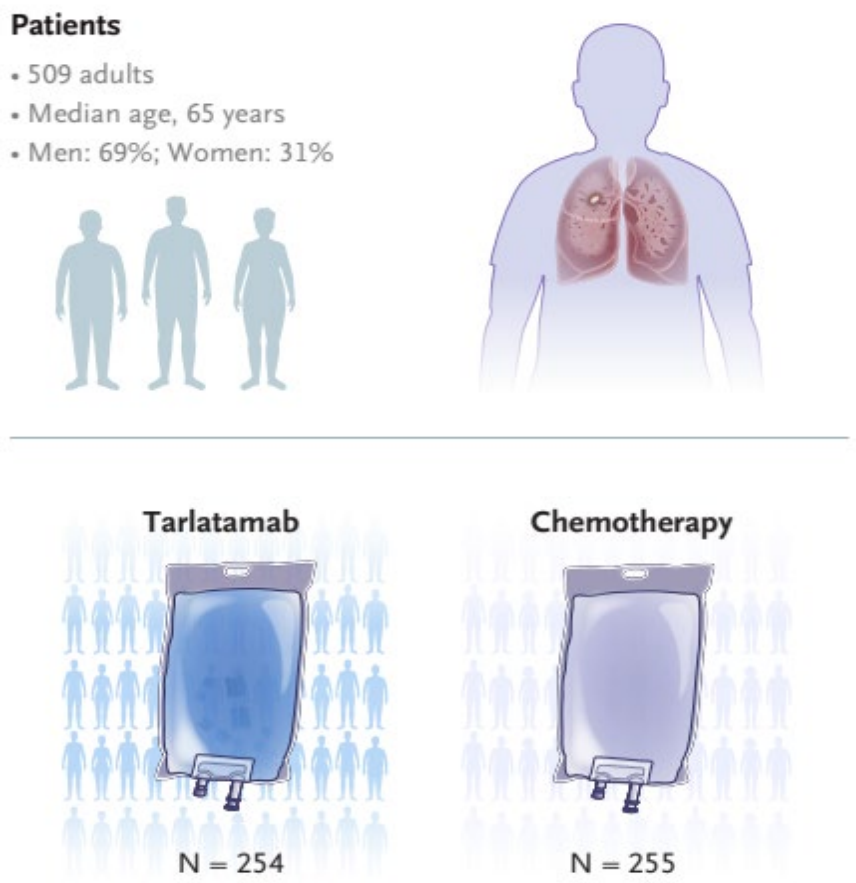


Mountzios G et al. *N Engl J Med*. 2025;393:349-361.

DLL3 = delta-like ligand 3

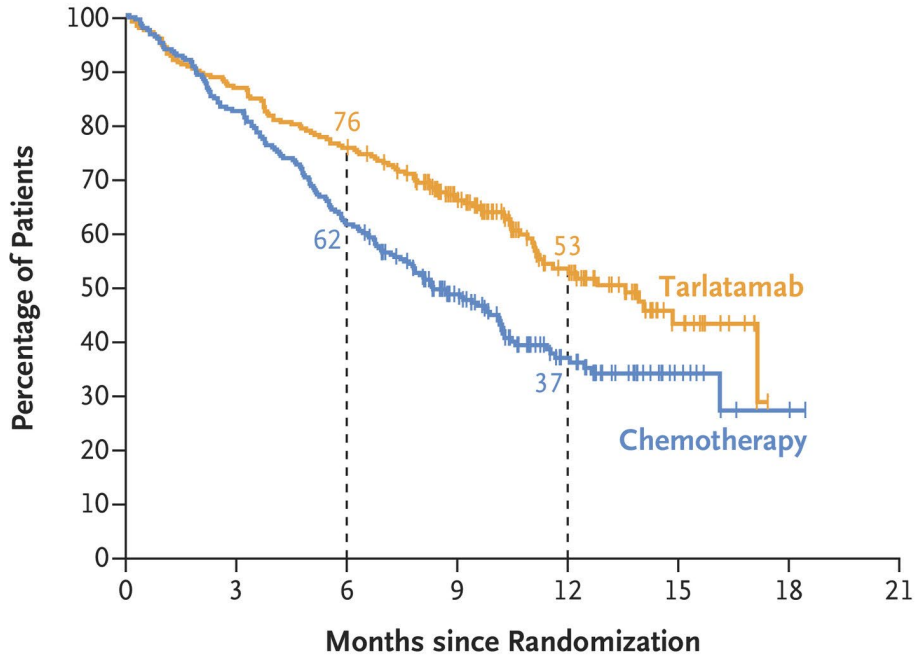
2nd Line Tarlatamab (DeLLphi 304 Trial)

- Phase 3, multinational, open-label, randomized trial
- Compared tarlatamab to chemotherapy
  - Topotecan (73%); Lurbinectedin (18%); Amrubicin (9%)
- Patients had progressed during or after platinum-based chemo
  - 71% of patients had received previous PD-1/L1 inhibitors
  - 44% of patients had platinum-resistant disease (disease progression after a chemo-free interval of <90 days)



Mountzios G et al. *N Engl J Med*. 2025;393:349-361.

2nd Line Tarlatamab (DeLLphi 304 Trial)



No. at Risk							
Tarlatamab	254	220	192	131	60	17	0
Chemotherapy	255	210	156	97	42	9	2	0

	Median Overall Survival (95% CI)
	mo
Tarlatamab (N=254)	13.6 (11.1–NR)
Chemotherapy (N=255)	8.3 (7.0–10.2)

Stratified hazard ratio for death, 0.60 (95% CI, 0.47–0.77)
P<0.001

- Tarlatamab led to **significantly longer overall survival**
- PFS favored tarlatamab
- Patient symptom scores (dyspnea, cough) favored tarlatamab

Mountzios G et al. *N Engl J Med*. 2025;393:349-361.

Tarlatamab Safety & Logistics

		CONCOMITANT MEDICATION PRE-IMDELLTRA® DOSE[1]	IMDELLTRA® ADMINISTRATION 1-HOUR IV INFUSION[1]	CONCOMITANT MEDICATION POST-IMDELLTRA® DOSE[1]	PATIENT MONITORING[1]
STEP-UP DOSE AND SCHEDULE CYCLE 1	Day 1	8 mg IV dexamethasone (or equivalent) within 1 hour prior to dose Flush IV line†	1 mg Step-up dose	1 L normal saline IV over 2–4 hours immediately following infusion	Monitor for 22–24 hours from the start of the IMDELLTRA® infusion in an appropriate healthcare setting
	Day 8		10 mg		
	Day 15		10 mg		Observe for 6–8 hours post infusion
		Following Day 1 and Day 8 of Cycle 1, recommend that patients remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of the IMDELLTRA® infusion, accompanied by a caregiver.			
CYCLE 2	Day 1		10 mg		Observe for 6–8 hours post infusion
	Day 15				
CYCLES 3–4	Day 1		10 mg		Observe for 3–4 hours post infusion
	Day 15				
CYCLES 5+	Day 1		10 mg		Observe for 2 hours post infusion
	Day 15				
		All IMDELLTRA® infusions and monitoring should take place in an appropriate healthcare setting.			

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Patient Case - LD

LD is a 48-year-old male with newly diagnosed small cell lung cancer, limited stage. He presents to clinic today for treatment discussion. ECOG 0, current smoker. CMP and CBC within normal limits.

Home medications: amlodipine 5 mg PO daily, cetirizine 10 mg PO daily PRN allergy symptoms

What therapy would you recommend?

a) Tarlatamab

b) Cisplatin + Etoposide x 4 cycles → surveillance

c) Lurbinectedin

d) Cisplatin + Etoposide x 4 cycles → durvalumab maintenance

Patient Case - LS

SL is a 62-year-old female with extensive stage small cell lung cancer that has been referred to your center for tarlatamab. She received carboplatin + etoposide + atezolizumab x 4 cycles, then atezolizumab maintenance. Treatment started 5 months ago. She has an ECOG 1 and is a former smoker.

Home medications: metformin 1000 mg PO BID, atorvastatin 40 mg PO daily, aspirin 81 mg PO daily, lisinopril 10 mg PO daily

What points would you counsel the patient on?

My Predictions of What's To Come…

NSCLC

- More trials for EGFR resistance and second-line treatment for patients that progressed on osimertinib
- New antibody-drug conjugates
- A new focus on immune resistance (STK and KEAP1 mutations)
- BiTE therapies
- CAR T cell therapy

SCLC

- Tarlatamab moving to 1st line or maintenance therapy
- New antibody-drug conjugates
- New BiTE therapies
- New DLL3 targeting therapies
- Radio-ligand therapy

INHALE THE LATEST: NEW HORIZONS IN LUNG CANCER DRUGS

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