Bispecific Antibodies in Lung Cancer: A state-of-the-art review

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Strategic Evolution of Lung Cancer Therapy

CEILING
BREAKTHROUSH

Survival / Efficacy Ceiling

Era1
Cytotoxics
Non-specific killing, high toxicity

Era 2
Precision TKI
Driver-specific, Inevitable resistance

Era 3
Checkpoint inhibitor
Durable tail, "hot" tumors only

PD-1
PD-L1

ADC: The Toxicity Ceiling

LUNG TOXICITY

Bispecific: The Biological Solution

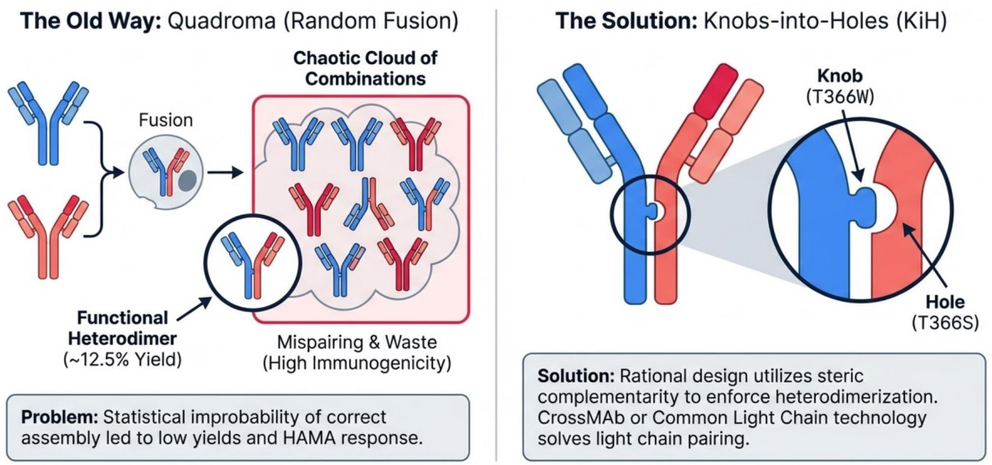
Why the Shift?

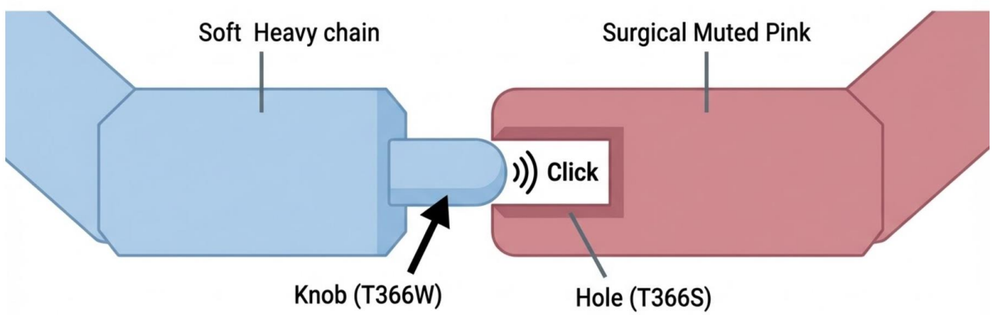
Single-agent efficacy is limited by biological redundancy.
BsAbs overcome this by:

- Bridging immune effectors to cold tumors
- Dual blockade of redundant signaling pathways
- Cooperative binding → enhanced specificity

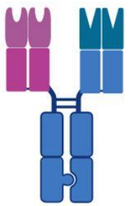
Time / Eras

Evolution of Formats: IgG-like vs. Non-IgG-like





- **Mechanism:** Knobs-into-Holes Technology
- **Principle:** Steric Complementarity enforcing correct heavy chain heterodimerization
- **Result:** >95% Correct Assembly; Plug-and-Play Manufacturing

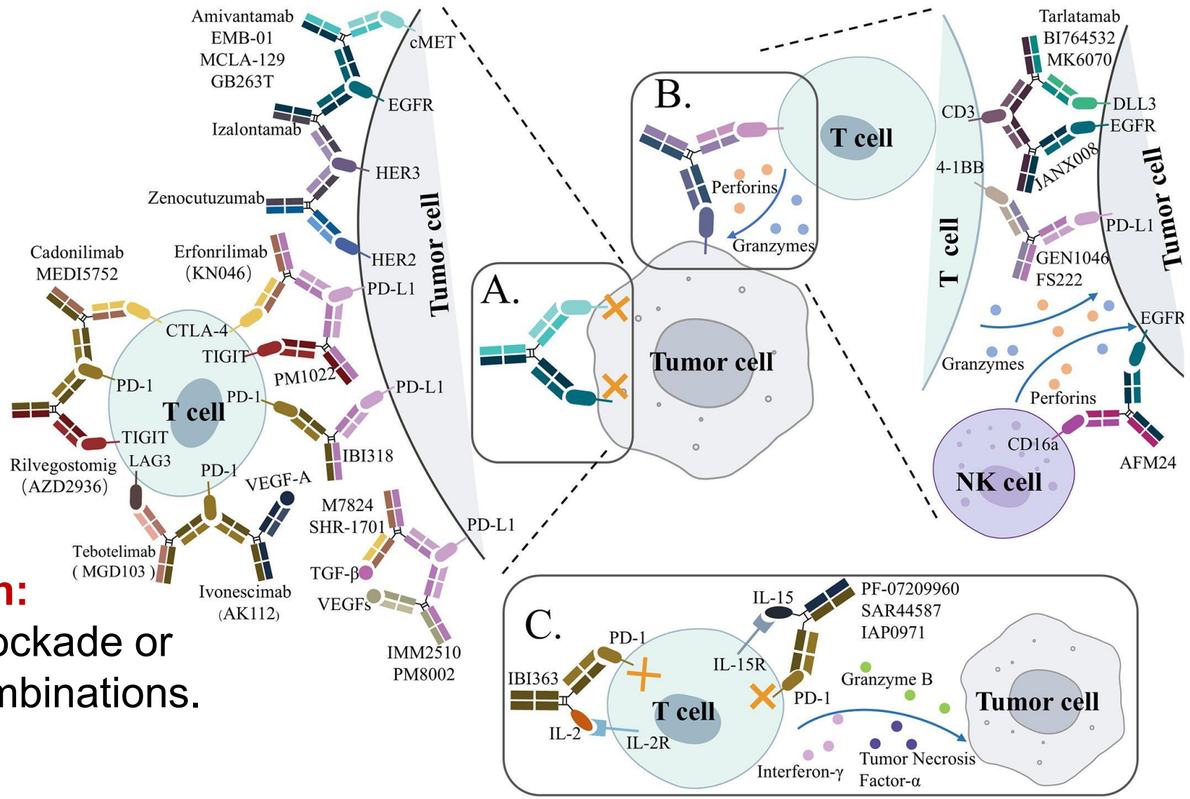
With Fc Fragment	Without Fc Fragment
	
Large (~150 kDa)	Compact (~55–60 kDa)
Long T 1/2	Short T 1/2
Fc-mediated effector function	Rapid Binding
Limited penetration	Good penetration
Potential immunogenicity	No ADCC/CDC
Systemic toxicity upon activation of effectors	Low toxicity due to selectivity of action
Well-established production	Production may be unstable
Preferred use	Preferred use
Prolonged therapy	Rapid response
Systemic action	Subcutaneous administation

Nature Protocols volume 9, pages2450–2463 (2014)
front Immunol. 2025 Nov 4;16:1679092.

The Strategic Goal

Constraining Tumor Escape in the Setting of Heterogeneity

1. Dual Inhibition:
Simultaneous blockade of two signaling pathways

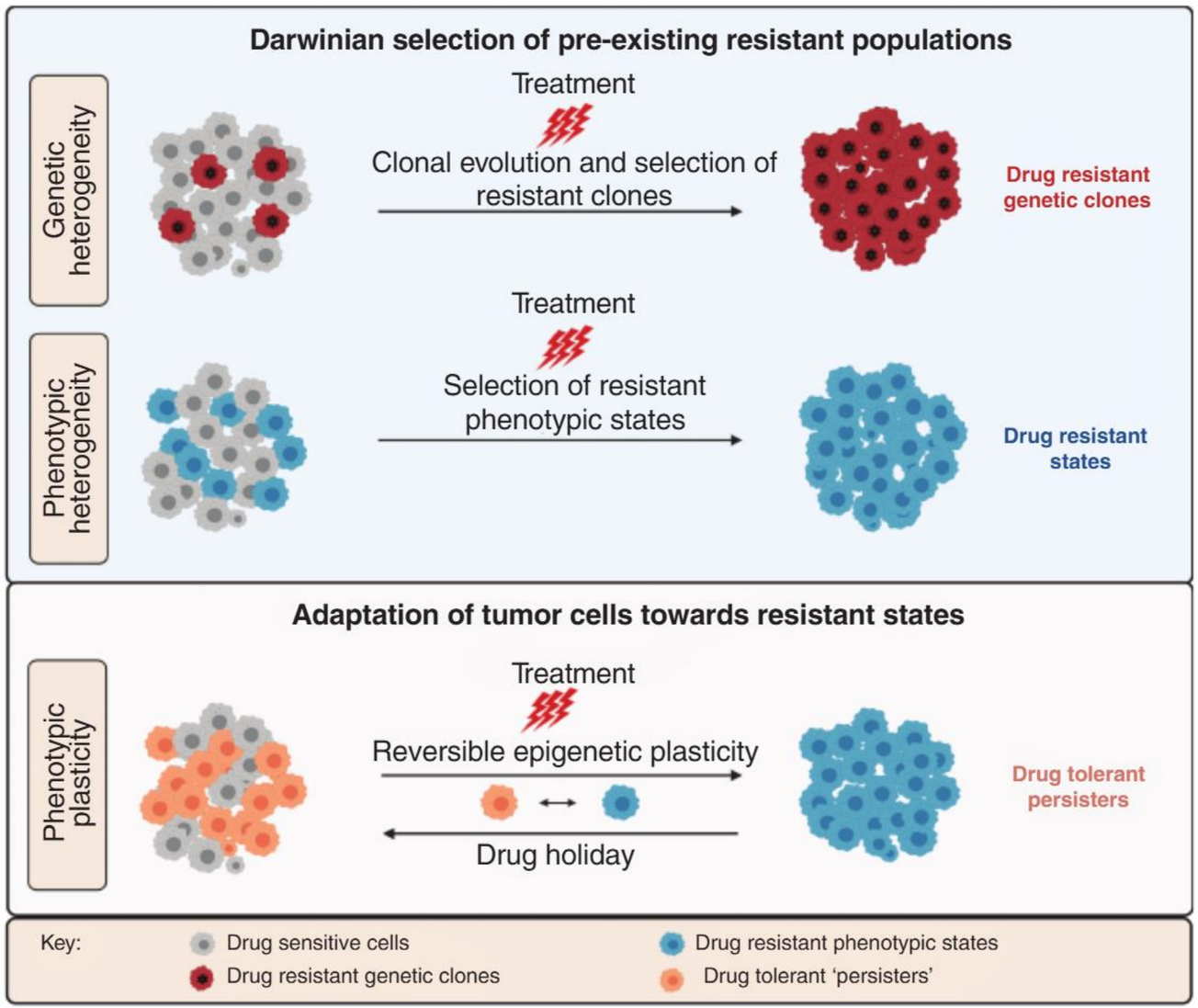


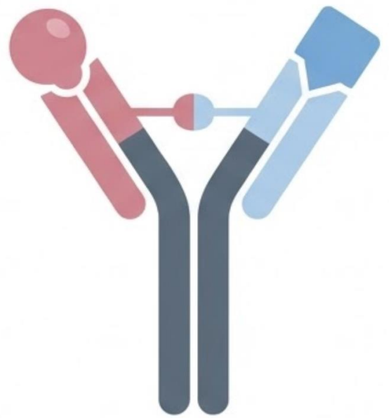
2. Immune Cell Engagers (ICEs):
Redirection of cytotoxic cells (T/NK) to tumors.

3. TME Modulation:
Dual checkpoint blockade or anti-angiogenic combinations.

4. Immunocytokines:
Antibody–cytokine fusion for targeted delivery.

The Strategic Imperative for Bispecific Antibodies in Lung Cancer
Tumor Heterogeneity + Adaptive Resistance





Bispecific Antibody

Overcoming resistance
bypass signaling

Increasing tumor specificity
reducing off-target toxicity

Turning "cold" tumors "hot"
T-cell redirection

Neuro Oncol. 2022 May 4;24(5):669-682

2024-2025 Regulatory Snapshot

Major Approvals at a Glance

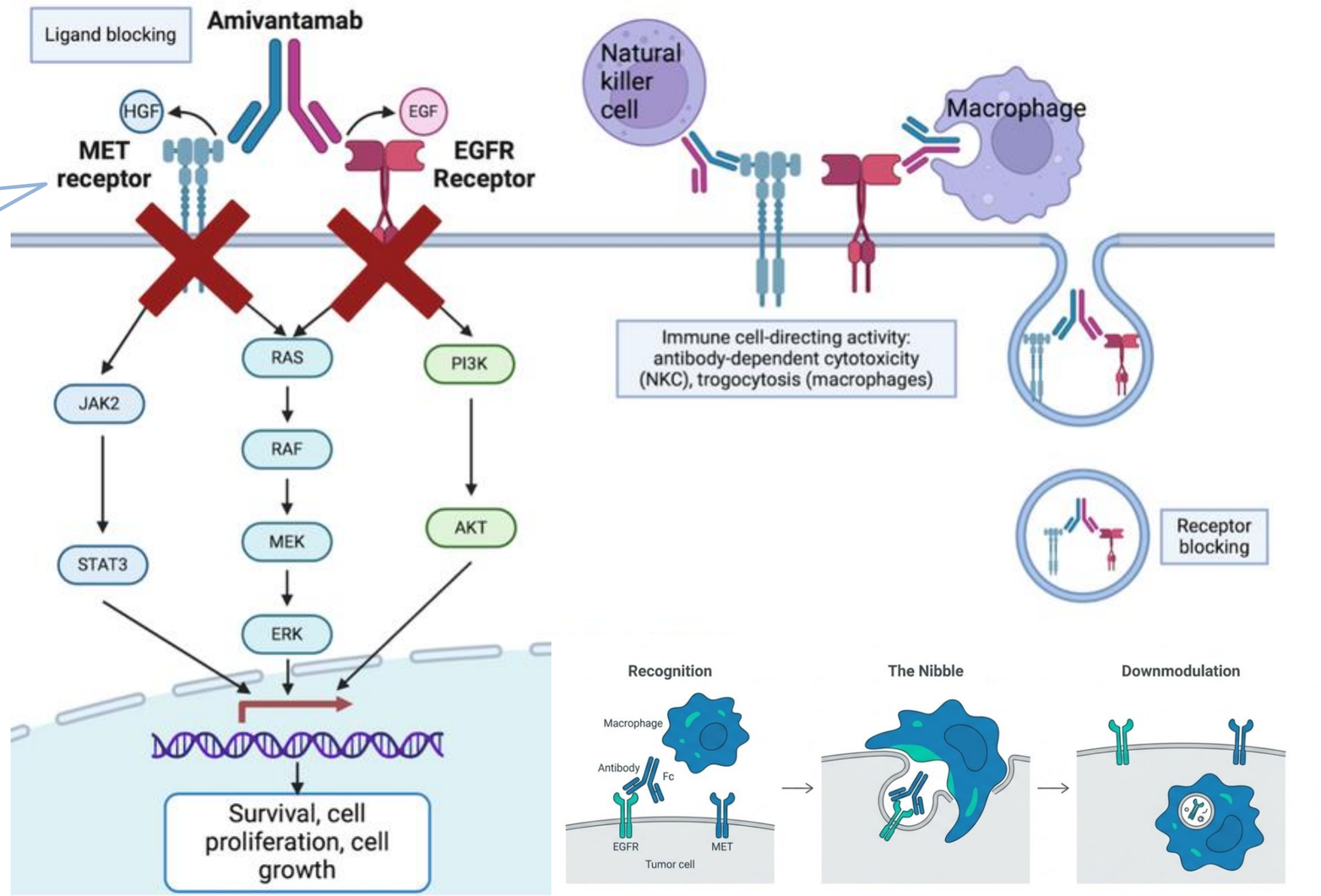
Drug	Target	Indication	FDA Approval	Key Evidence Trial	ORR/PFS/OS	Status Notes
Tarlatamab (Imdelltra)	DLL3×CD3	ES-SCLC (≥2L post-platinum)	2024.5.16 (accelerated) 2025.11.19 (full)	DeLLphi-301	ORR 40%, mPFS 4.9m, mOS 14.3m	SCLC 2L standard
Amivantamab (Rybrevant)	EGFR×MET	EGFR exon20ins NSCLC (1L w/chemo)	2024.3 (full expansion)	PAPILLON/MARIPOSA	PFS 11.4 vs 6.7m (1L)	EGFR combo backbone
Zenocutuzumab (Bizengri)	HER2×HER3	NRG1 fusion+ NSCLC (advanced)	2024.12 (accelerated)	eNRGy-1	ORR 37%	Niche NRG1 approval
Ivonescimab	PD-1×VEGF	NSCLC (PD-L1+, 1L/EGFR post-TKI)	None (PDUFA ~2026 Q4)	HARMONi-2/3	PFS 11.1 vs 5.8m (vs pembro); HR 0.51	China approved; Global BLA pending

Dual Inhibition

Amivantamab: Dual-Targeting & Immune Cell Engagement

MET affinity Optimization 40 pmol/L

Benefit
Low toxicity in normal tissue, high specificity for tumor cells



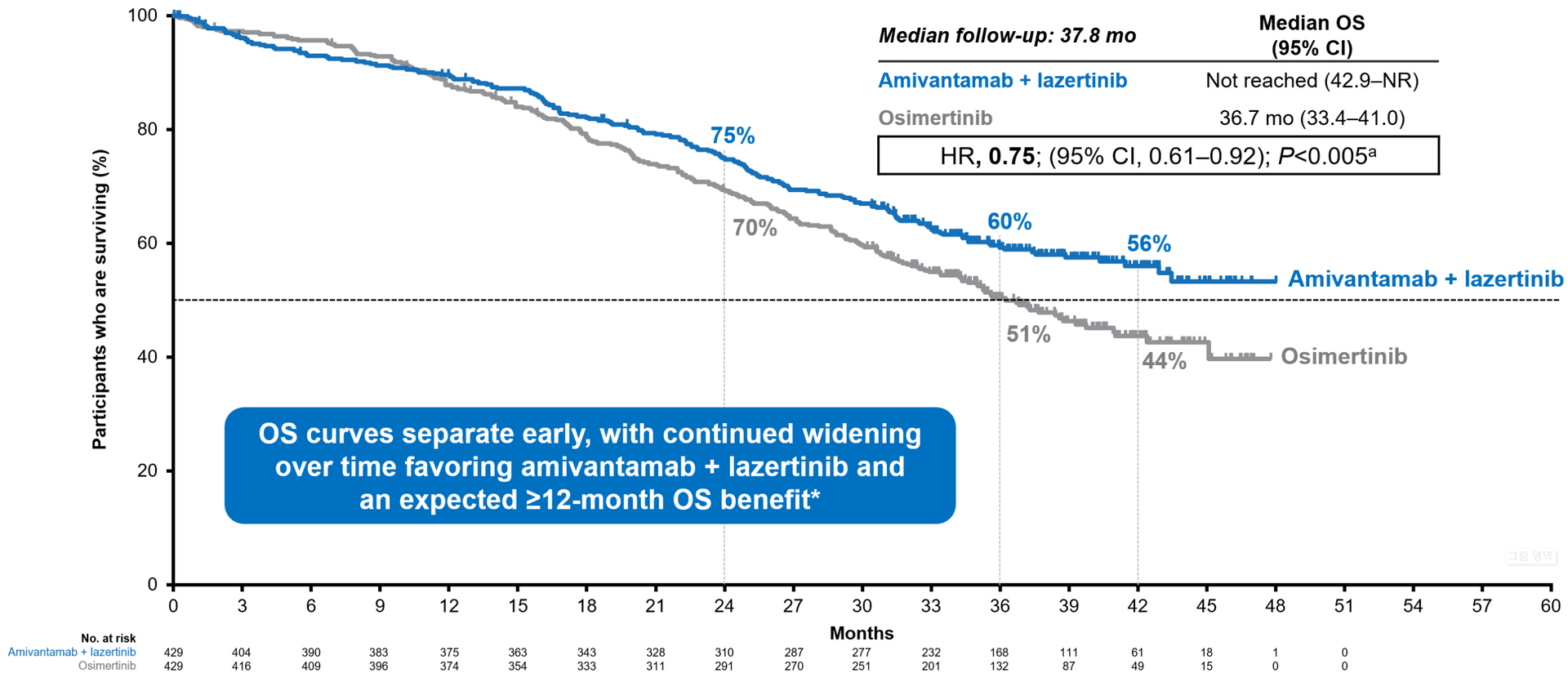
Explor Target Antitumor Ther. 2024;5(6):1297-1320

Amivantamab + Lazertinib (MARIPOSA)

Amivantamab + Lazertinib vs Osimertinib in first-line EGFR mutant advanced NSCLC

OS Update 2025

At a median follow-up of 37.8 months, amivantamab + lazertinib significantly and clinically meaningfully improved OS vs osimertinib



Based on an exponential distribution assumption of OS in both arms, the improvement in median OS is predicted to exceed 1 year.

[a]*P*-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified Cox regression model.

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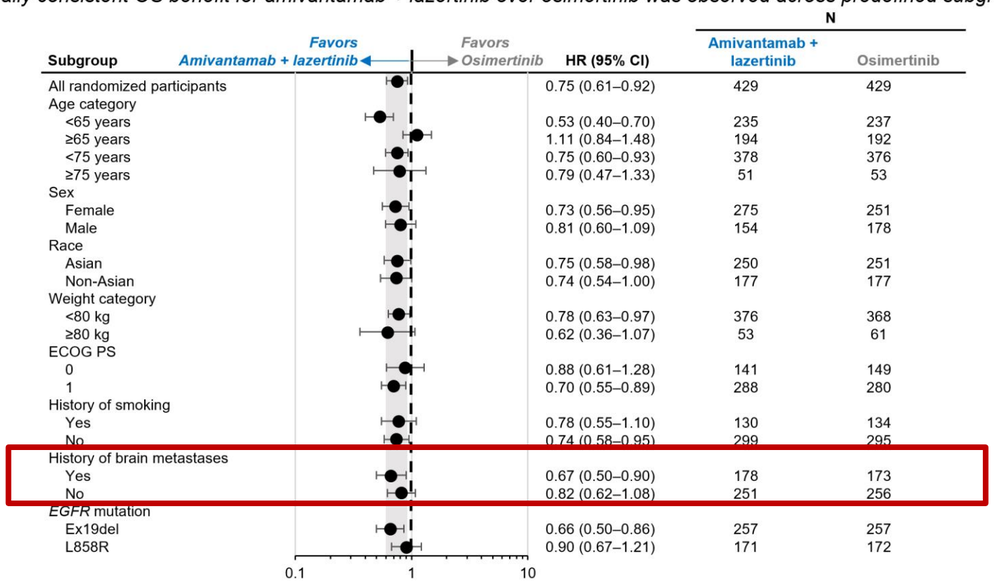
Amivantamab + Lazertinib (MARIPOSA)

OS benefit is consistent across subgroups and reinforced by durable intracranial disease control.

Overall Survival in Predefined Subgroups[a]

A generally consistent OS benefit for amivantamab + lazertinib over osimertinib was observed across predefined subgrou



Subgroup	HR (95% CI)	N: Amivantamab + lazertinib	N: Osimertinib
All randomized participants	0.75 (0.61–0.92)	429	429
Age category			
<65 years	0.53 (0.40–0.70)	235	237
≥65 years	1.11 (0.84–1.48)	194	192
<75 years	0.75 (0.60–0.93)	378	376
≥75 years	0.79 (0.47–1.33)	51	53
Sex			
Female	0.73 (0.56–0.95)	275	251
Male	0.81 (0.60–1.09)	154	178
Race			
Asian	0.75 (0.58–0.98)	250	251
Non-Asian	0.74 (0.54–1.00)	177	177
Weight category			
<80 kg	0.78 (0.63–0.97)	376	368
≥80 kg	0.62 (0.36–1.07)	53	61
ECOG PS			
0	0.88 (0.61–1.28)	141	149
1	0.70 (0.55–0.89)	288	280
History of smoking			
Yes	0.78 (0.55–1.10)	130	134
No	0.74 (0.58–0.95)	299	295
History of brain metastases			
Yes	0.67 (0.50–0.90)	178	173
No	0.82 (0.62–1.08)	251	256
EGFR mutation			
Ex19del	0.66 (0.50–0.86)	257	257
L858R	0.90 (0.67–1.21)	171	172

[a]Subgroup analyses were not part of the hypothesis testing of the trial and should not be used to infer definitive treatment effects. **Note**: Gray box indicates 95% CI of HR for all randomized participants.

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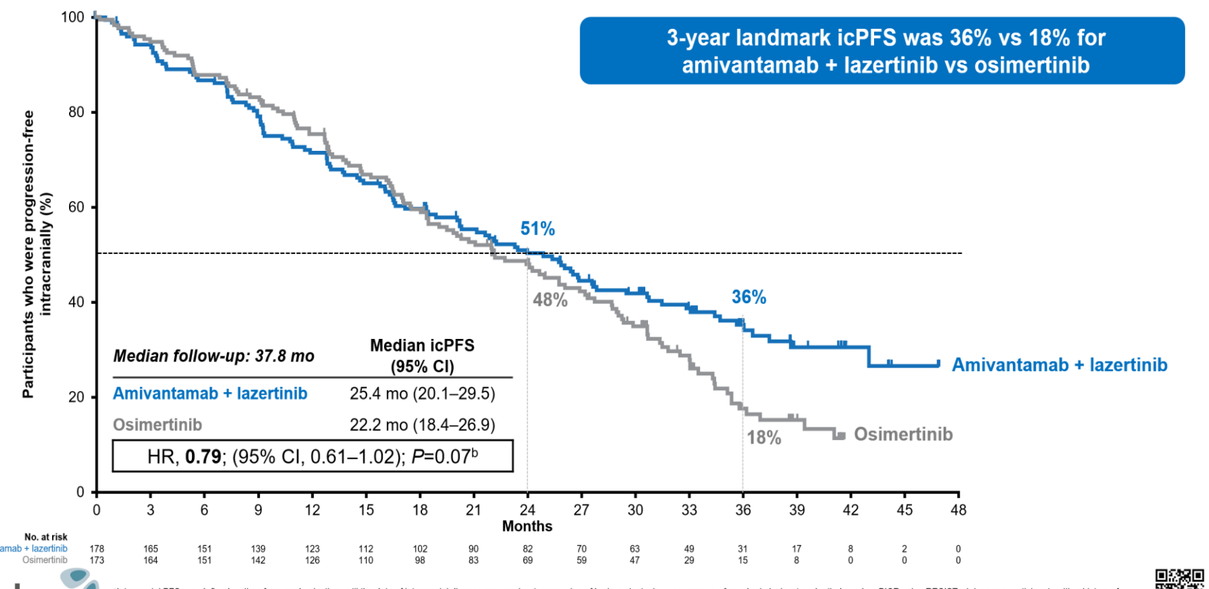
Intracranial PFS[a]

Amivantamab + lazertinib demonstrated a clinically meaningful improvement in icPFS with durable responses



[a]Intracranial PFS was defined as time from randomization until the date of intracranial disease progression (progression of brain metastasis or occurrence of new brain lesions) or death, based on BICR using RECIST v1.1 among participants with a history of brain metastases. [b]*P*-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R) and race (Asian or Non-Asian). Hazard ratio was calculated from a stratified Cox regression model.

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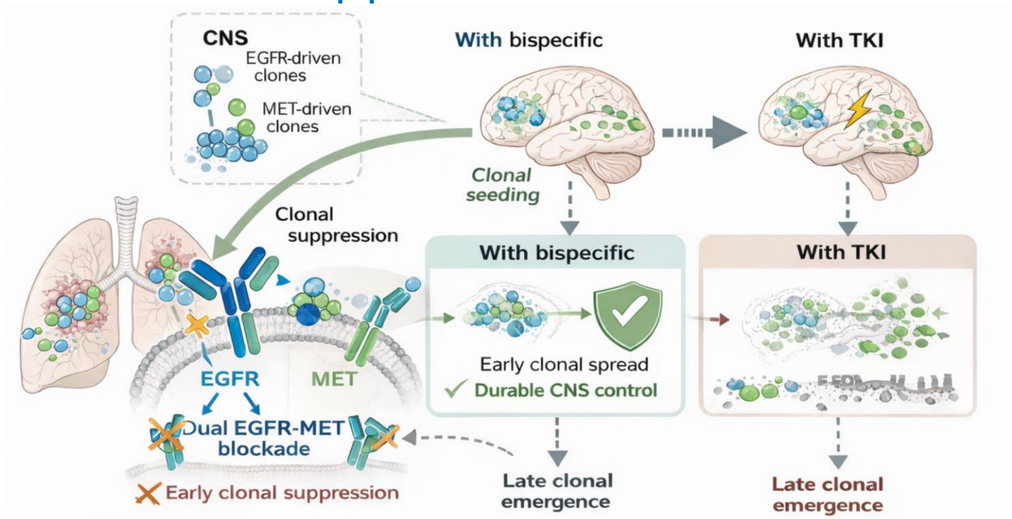
- The OS benefit of amivantamab + Lazertinib is consistent across patient subgroups and is reinfoced by dur able intracranial disease control.
- Amivantamab + lazertinib delayed the time to a participant experiencing symptoms from their lung cancer by a median of>14 months (TTSP; *P*<0.001)

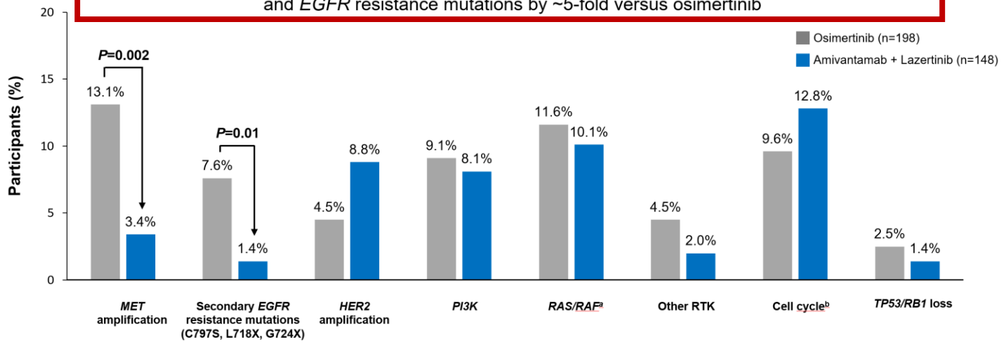
Why bispecifics make the difference in the CNS

Dual blockade suppressed resistant clones at the origin



Mechanisms of Resistance by Pathway

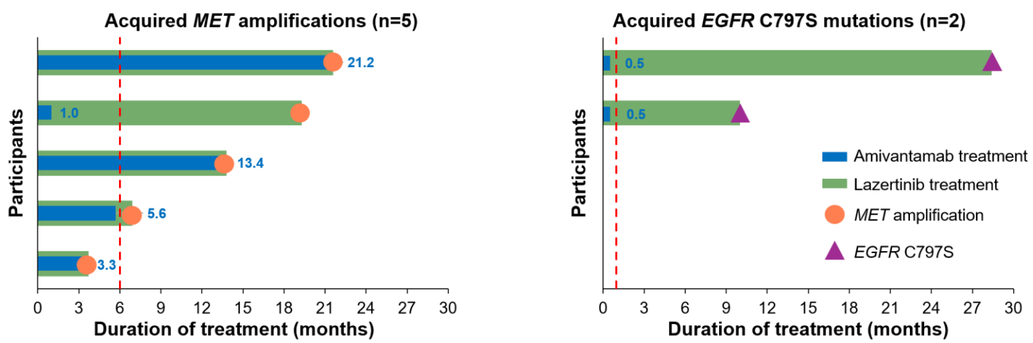
- Amivantamab + lazertinib significantly reduced the incidence of acquired *MET* amplifications by ~4-fold and *EGFR* resistance mutations by ~5-fold versus osimertinib



- No meaningful increases in other molecular escape pathways were observed with amivantamab + lazertinib

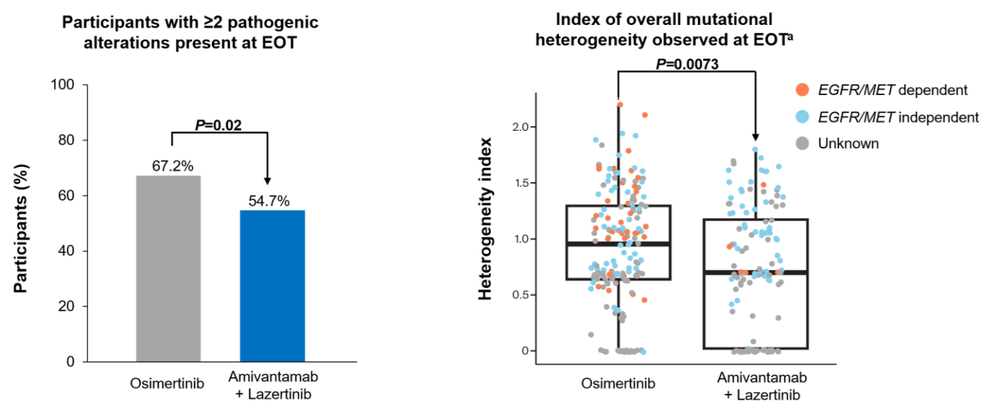
Effect of Amivantamab Treatment Duration on *MET* and *EGFR* Resistance

Longer duration of amivantamab treatment was associated with even fewer acquired MET or EGFR mutations



- 98% of participants (99/101) who received ≥6 months of amivantamab did not acquire a *MET* amplification
- No participants who received ≥1 month of amivantamab acquired a C797S *EGFR* mutation (0/101)
- SC delivery of amivantamab and previously demonstrated prophylactic management[1–3] may prolong duration of treatment, which may reduce additional opportunities for acquired resistance

Mutational Heterogeneity at End of Treatment

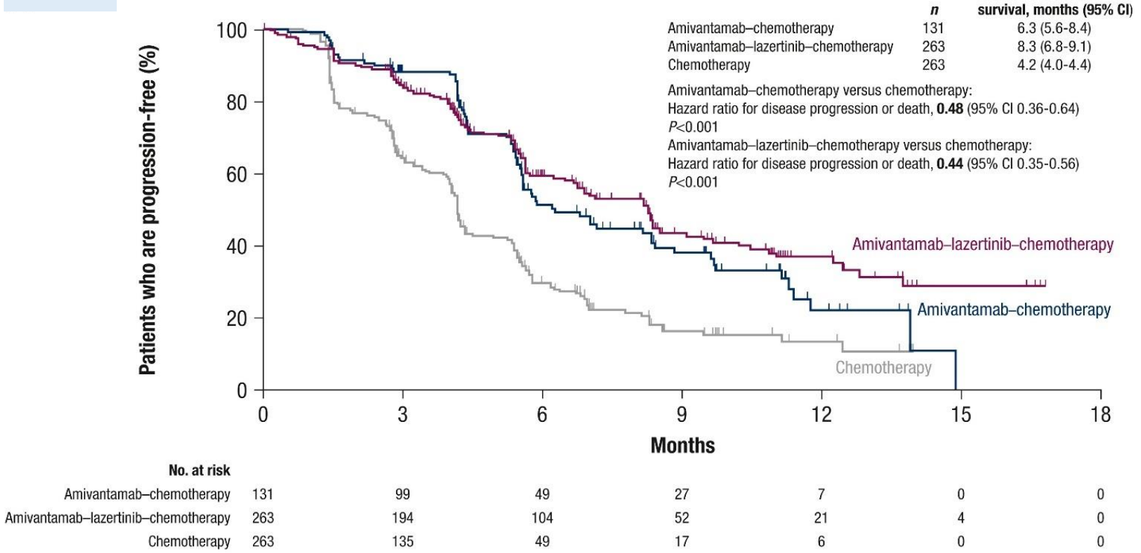


- Resistance complexity was significantly higher following osimertinib vs amivantamab + lazertinib treatment (*P*=0.02)

MARIPOSA-2: Defining the Standard After Osimertinib

randomized, open-label, PhIII study
Progressed on or after osimertinib monotherapy (as most recent line)
amivantamab(with and without lazertinib) and chemotherapy

PFS

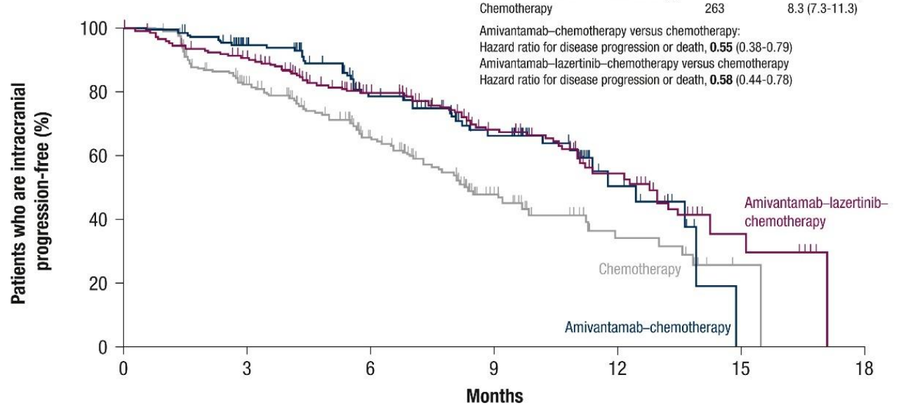


	n	Median progression-free survival, months (95% CI)
Amivantamab–chemotherapy	131	6.3 (5.6-8.4)
Amivantamab–lazertinib–chemotherapy	263	8.3 (6.8-9.1)
Chemotherapy	263	4.2 (4.0-4.4)

Amivantamab–chemotherapy versus chemotherapy:
Hazard ratio for disease progression or death, **0.48** (95% CI 0.36-0.64)
P<0.001
Amivantamab–lazertinib–chemotherapy versus chemotherapy:
Hazard ratio for disease progression or death, **0.44** (95% CI 0.35-0.56)
P<0.001

No. at risk							
Amivantamab–chemotherapy	131	99	49	27	7	0	0
Amivantamab–lazertinib–chemotherapy	263	194	104	52	21	4	0
Chemotherapy	263	135	49	17	6	0	0

Intracranial PFS



	n	Median intracranial progression-free survival, months (95% CI)
Amivantamab–chemotherapy	131	12.5 (10.8-NE)
Amivantamab–lazertinib–chemotherapy	263	12.8 (11.1-14.3)
Chemotherapy	263	8.3 (7.3-11.3)

Amivantamab–chemotherapy versus chemotherapy:
Hazard ratio for disease progression or death, **0.55** (0.38-0.79)
Amivantamab–lazertinib–chemotherapy versus chemotherapy
Hazard ratio for disease progression or death, **0.58** (0.44-0.78)

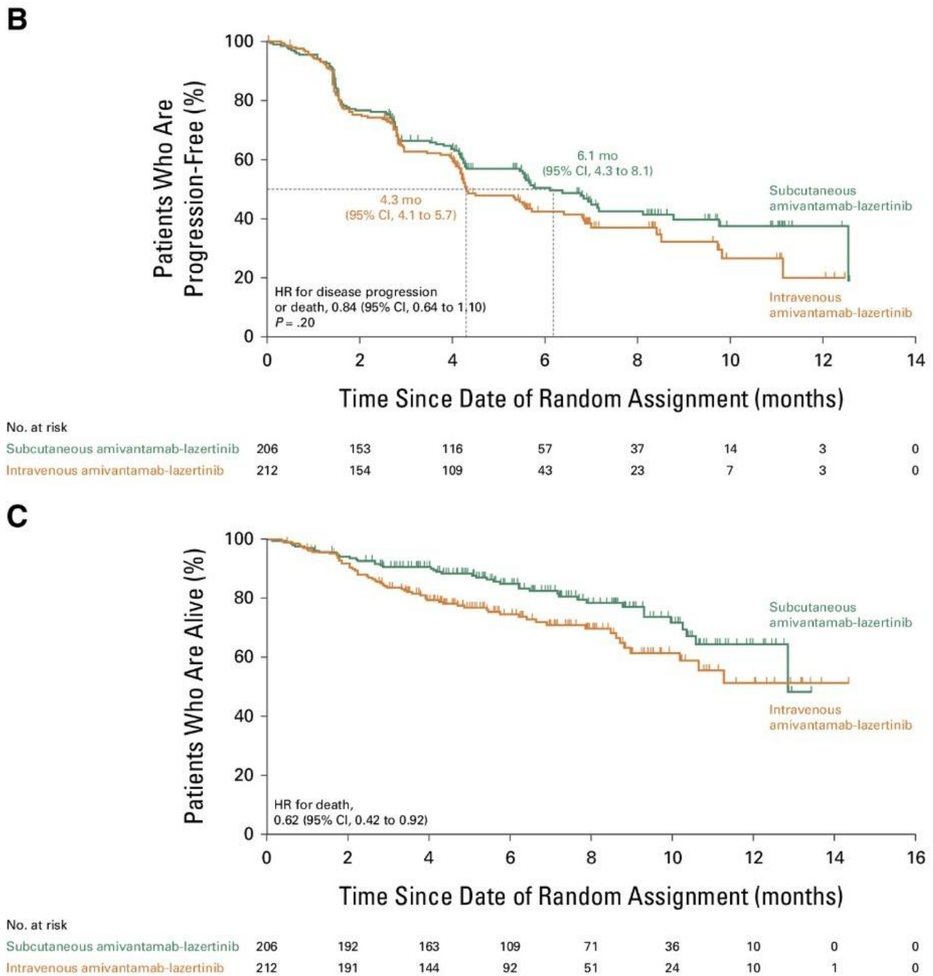
No. at risk							
Amivantamab–chemotherapy	131	103	72	40	11	0	0
Amivantamab–lazertinib–chemotherapy	263	211	135	74	32	6	0
Chemotherapy	263	167	89	37	13	1	0

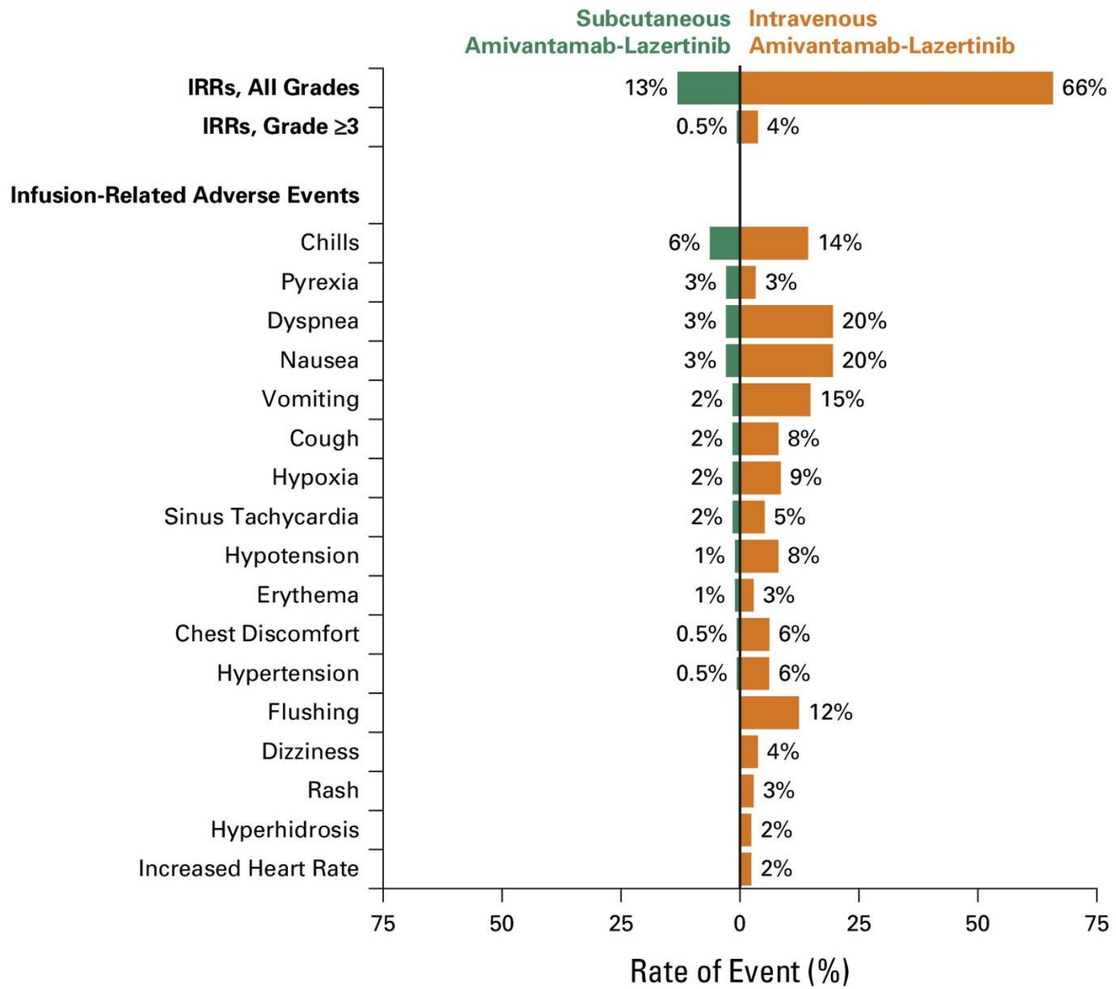
- Amivantamab + chemotherapy significantly improved PFS and intracranial PFS versus chemotherapy alone
- Amivantamab + lazertinib + chemotherapy also significantly improved PFS and intracranial PFS versus chemotherapy
- MARIPOSA-2 is the first phase III study to demonstrate superior PFS versus chemotherapy in patients progressing after osimertinib

Passaro A, et al. Ann Oncol. 2024;35(1):77-90.

Optimizing Delivery: The Shift from IV to Subcutaneous (PALOMA-3)

Non-inferiority, reduced infusion reactions, and time-saving

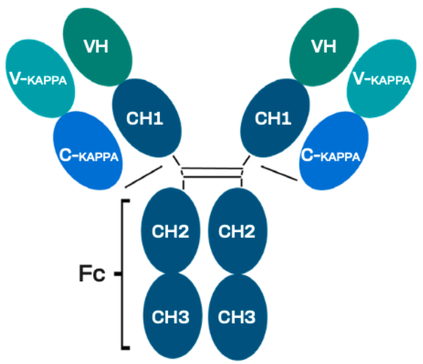




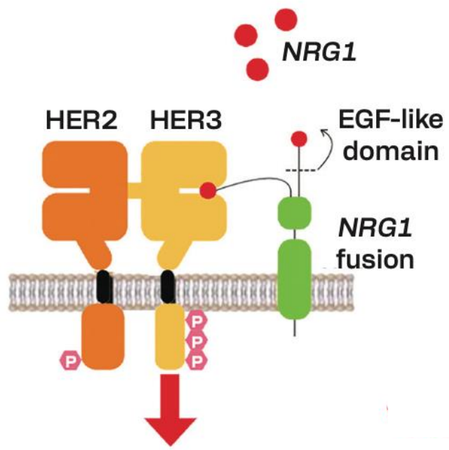
J Clin Oncol 42, 3593-3605(2024)

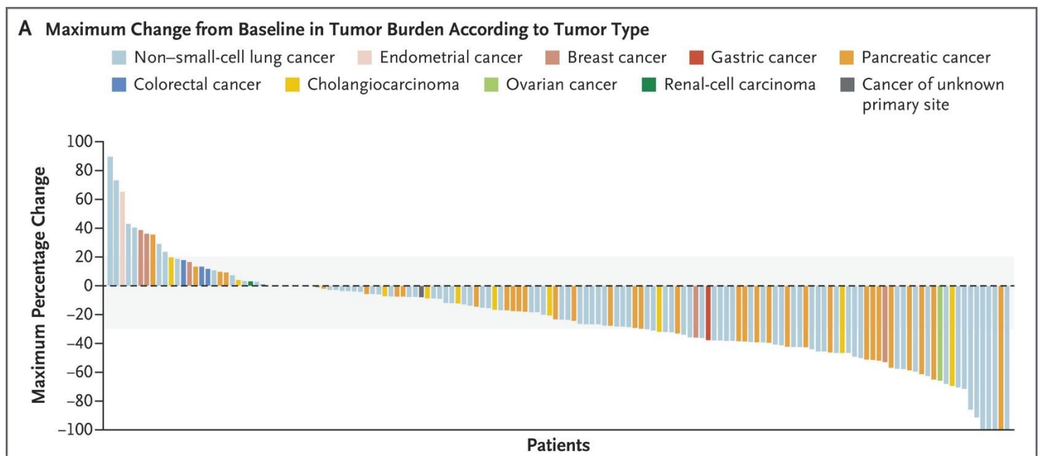
Zenocutuzumab: HER2/HER3 biAbs

The "Dock & Block" Mechanism for NRG1 Fusions



NRG1 fusion promotes HER2-HER3 dimerization, activating PI3K/AKT signaling for tumor growth.





HER2 internalization[1]

Reduction of HER2 on cell surface[1]

Induction of immune-mediated cytotoxicity (CDC, ADCC, and ADCP)[1]

TUMOR CELL DEATH

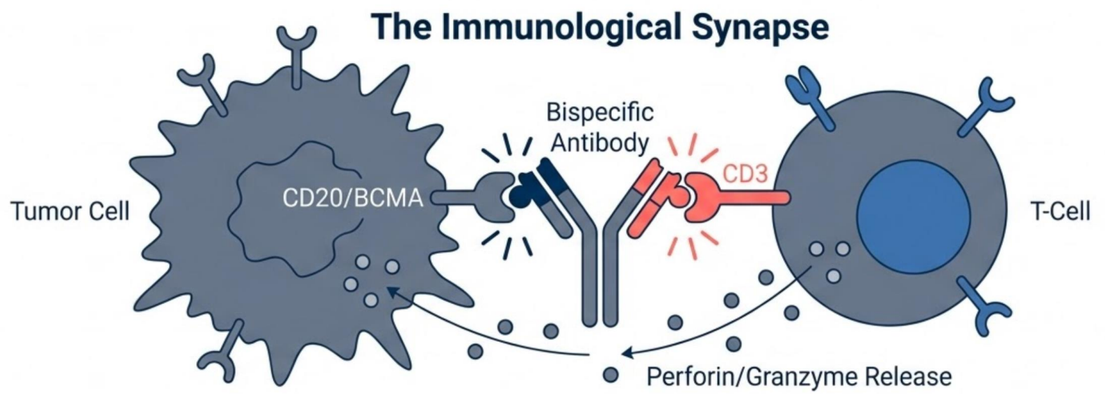
Target: NRG1 fusion-positive NSCLC.

eNRGy Study Data:

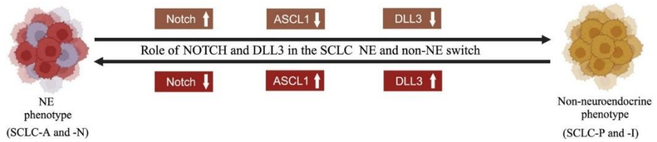
- ORR: 34%.
- Median Duration of Response: 12.9 months.
- Safety: <4% Grade ≥3 adverse events.

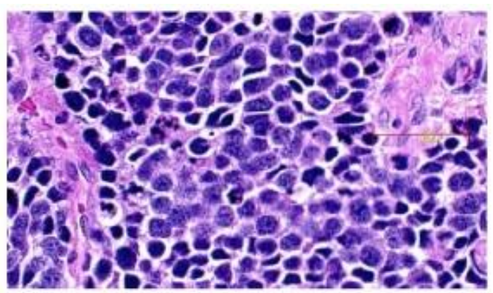
Sig Transduct Target Ther 10, 194 (2025)
N Engl J Med 2025;392:566-576

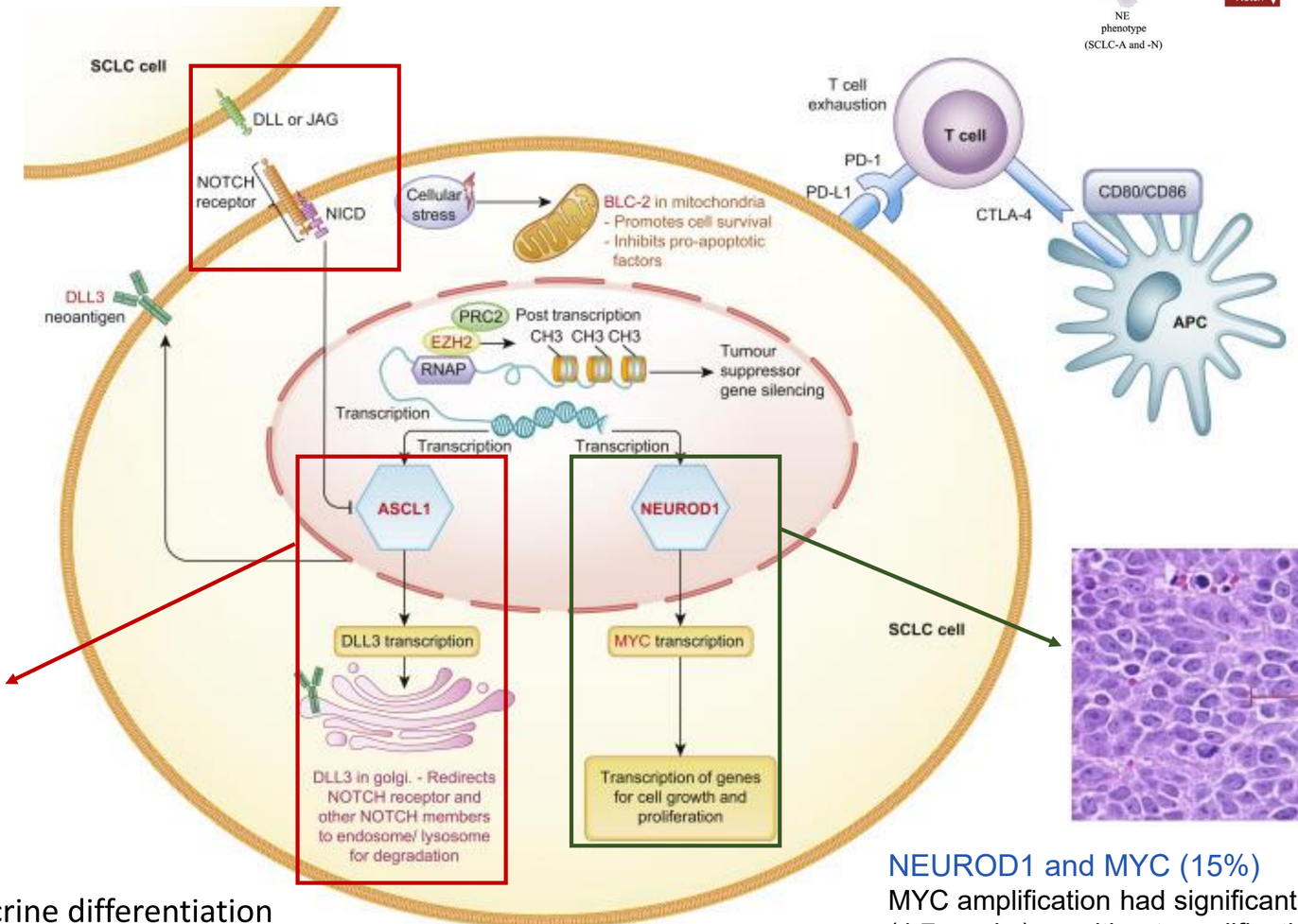
Immune Cell Engagers

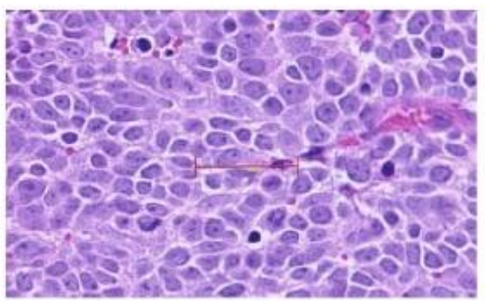


The SCLC Revolution: Why DLL3 is the Ideal Target









ASCL1 and Notch pathway (75%)

Negative regulator of neuroendocrine differentiation
— In neuroendocrine cell, acts as tumor suppressors
DLL3, a canonical ligand of NOTCH Rc
— Overexpressed in SCLC, 70-80%
— Dominant negative inhibitor of NOTCH signaling

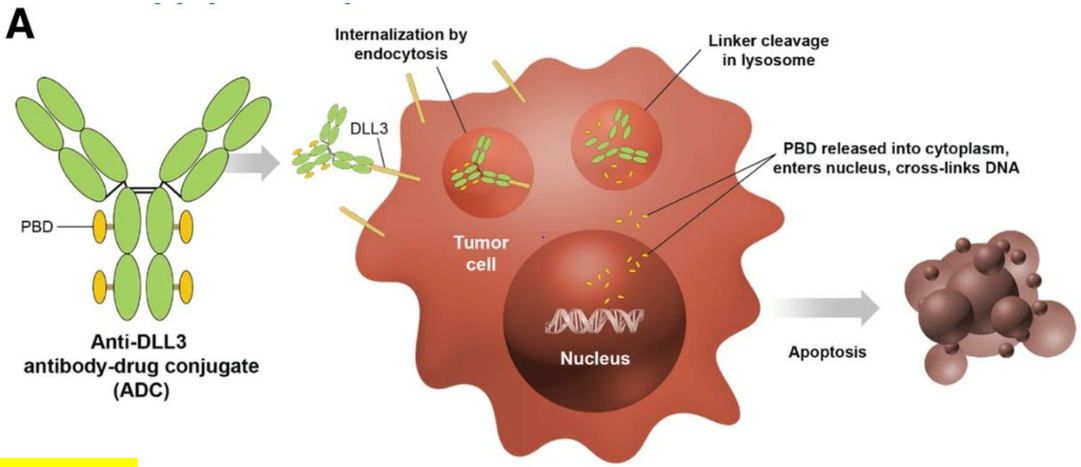
NEUROD1 and MYC (15%)

MYC amplification had significant shorter OS (4.7 weeks) vs without amplification (26.2 weeks) (Alves Rde C. et al 2014)
Related to the variant subtype

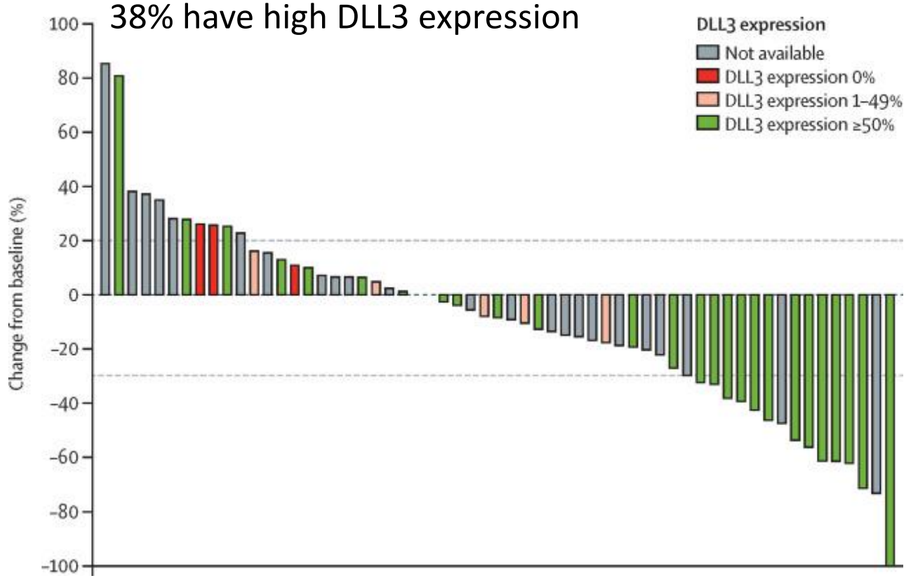
Eur J Cancer. 2019 Sep;119:132-150.

Targeting NOTCH signaling path

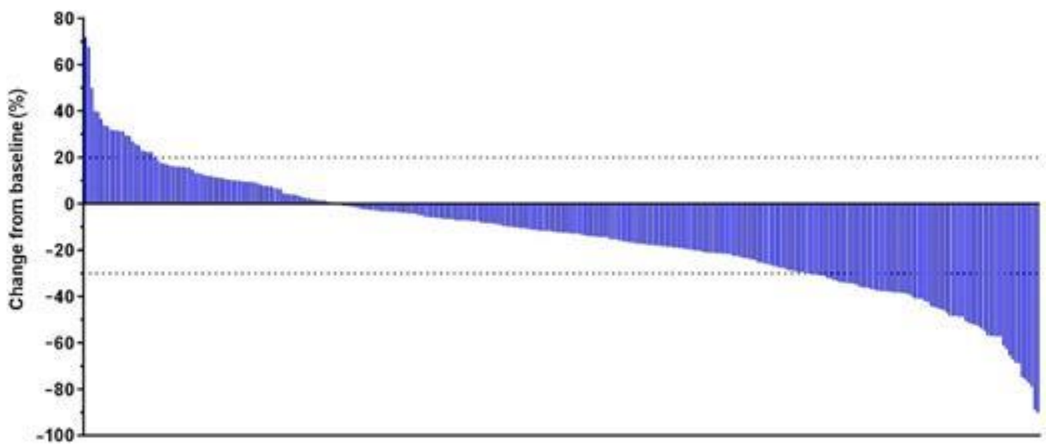
- Rovalpituzumab-tesirine (Rova-T)
- Antibody-drug conjugate, DLL3-targeting
- Anti-DLL3 moAb+ pyrrolobenzodiazepine(PBD) toxi



PhI trial. (N=74)
11/60 (18%) ORR
38% have high DLL3 expression

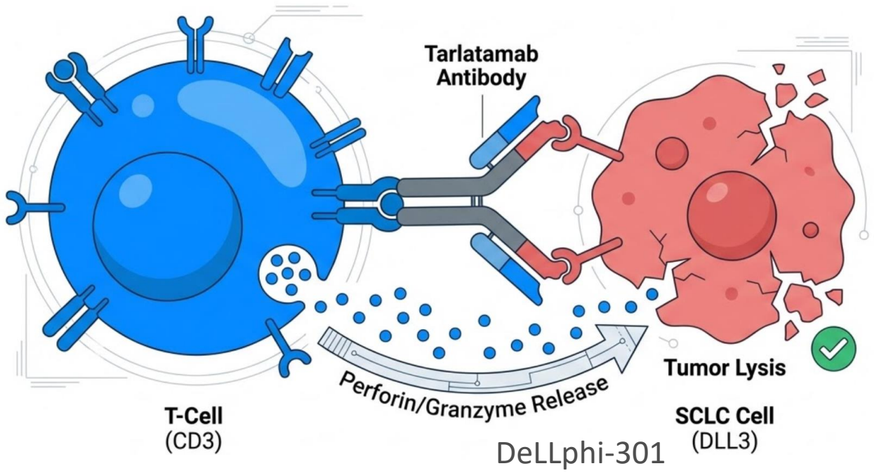


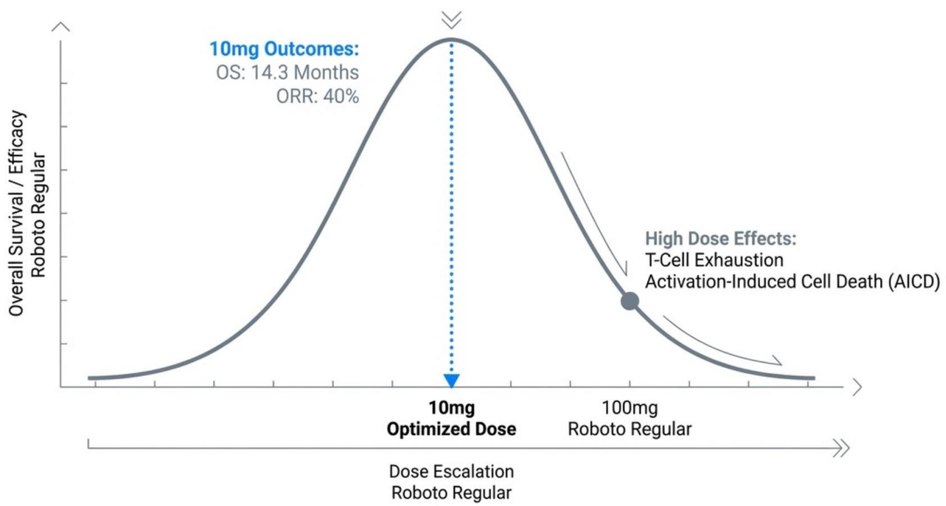
PhII TRINITY
In DLL+ patients, mostly in 3L : ORR 12%
In DLL3-high (≥ 75%) ORR 14.3%, mPFS 3.8M, mOS 5.7M
Grade 3-5 213 (63%) patients
: fatigue, photosensitivity reaction, and pleural effusion

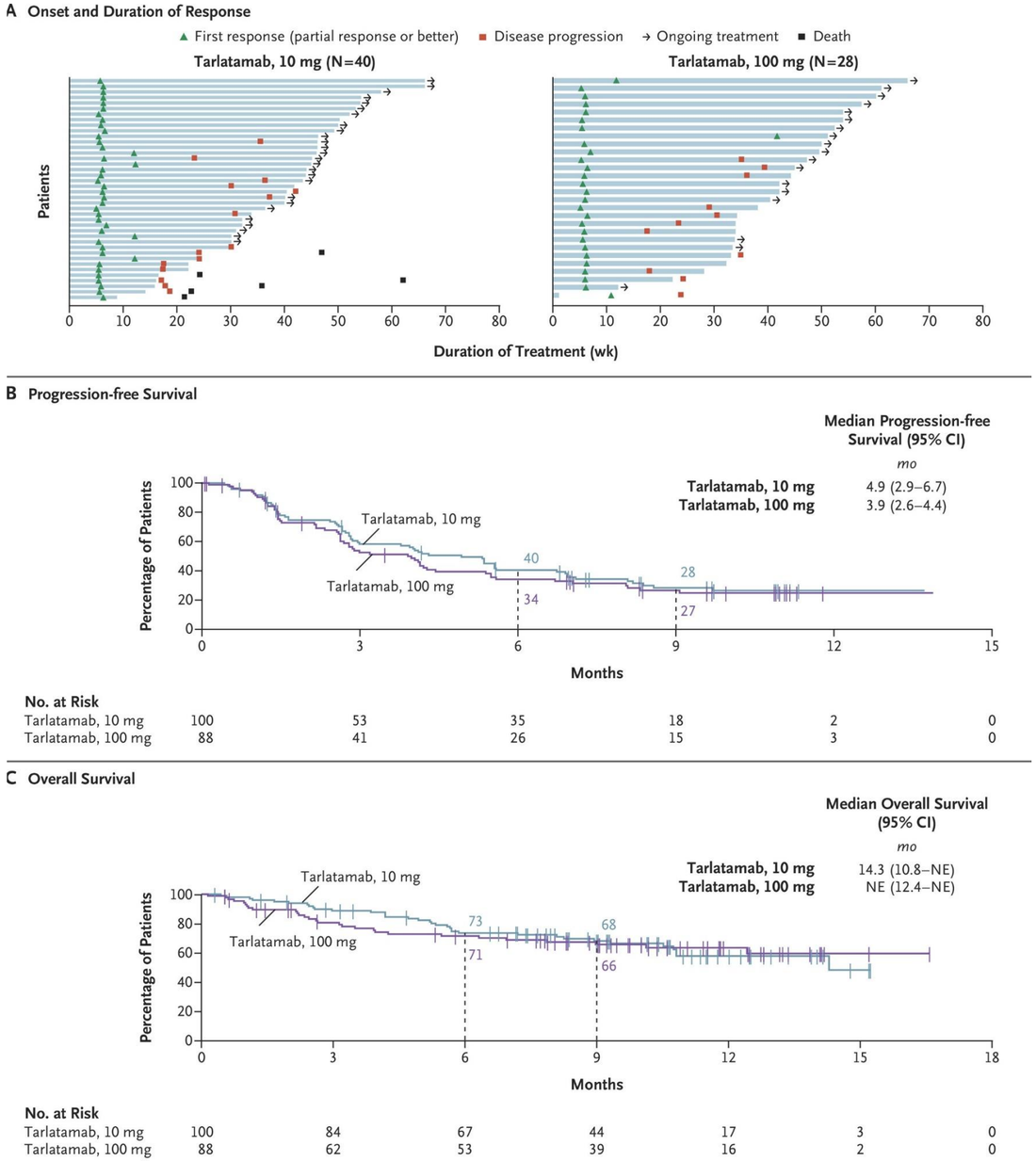


Lancet Oncol 2017; 18: 42–51, Clin Cancer Res (2019) 25 (23): 6958–6966.

Tarlatamab(DeLLphi-301)

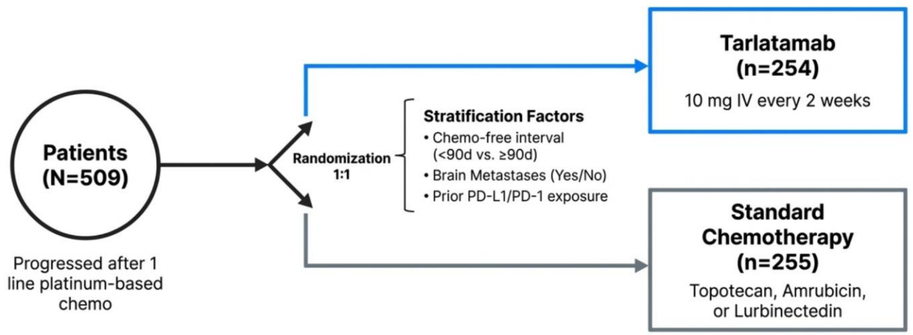




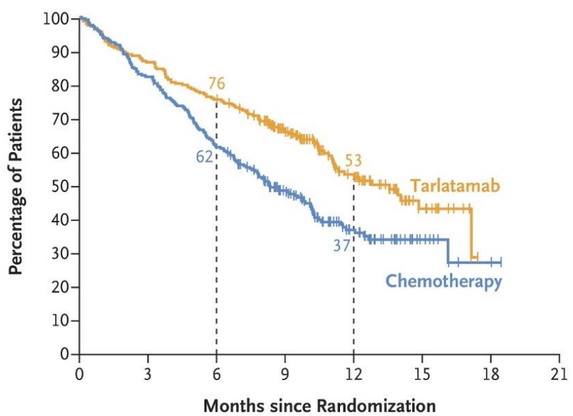


N Engl J Med 2023;389:2063-2075

DeLLphi-304: Tarlatamab vs. Standard Chemotherapy
Long-term Durability: Response Maintenance in Refractory SCLC

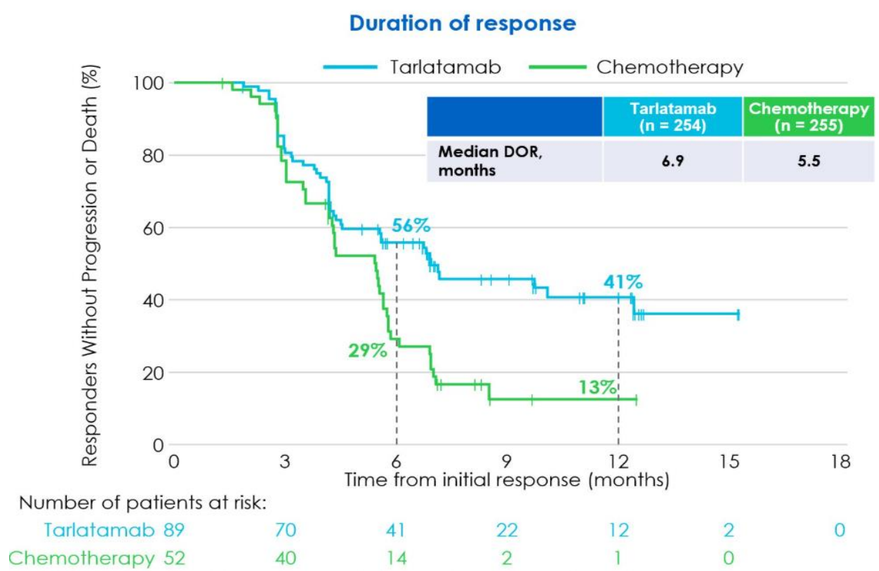


	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Best overall response[*†], n (%)		
Complete response	3 (1)	0 (0)
Partial response	86 (34)	52 (20)
Stable disease	84 (33)	112 (44)
Progressive disease	56 (22)	50 (20)
Not evaluable/no post-baseline scan	25 (10)	41 (16)
Objective response rate[‡], % (95% CI)	35 (29–41)	20 (16–26)
Median duration of response, months	6.9	5.5
Median time to objective response, months	1.5	1.4
Ongoing response at data cutoff, n[§] (%)	42 (47)	8 (15)



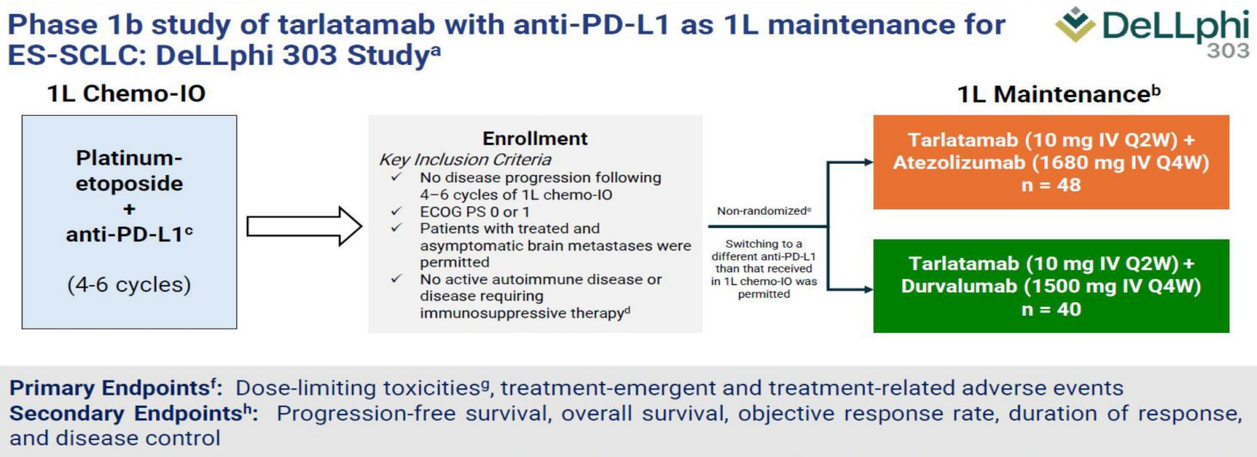
	Median Overall Survival (95% CI)
	mo
Tarlatamab (N=254)	13.6 (11.1–NR)
Chemotherapy (N=255)	8.3 (7.0–10.2)

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



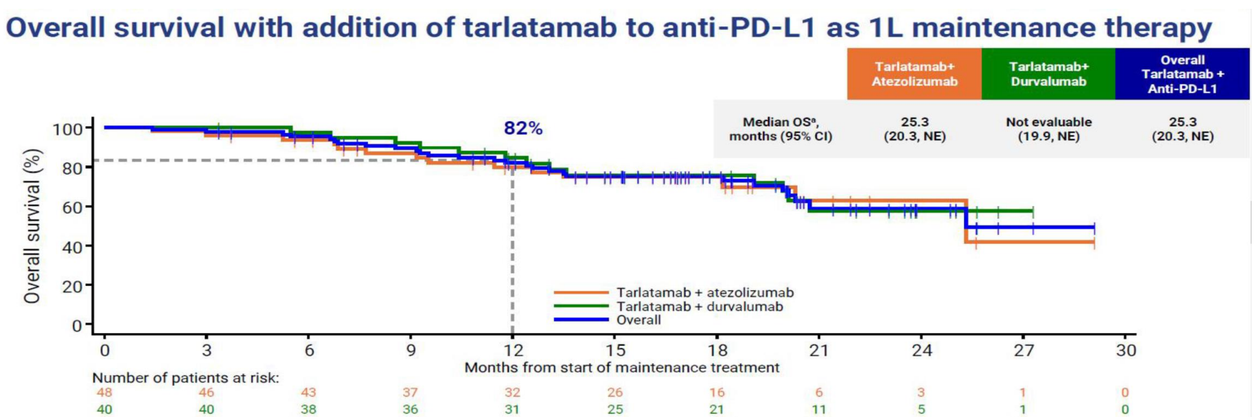
DeLLphi-303 Update (WCLC 2025)

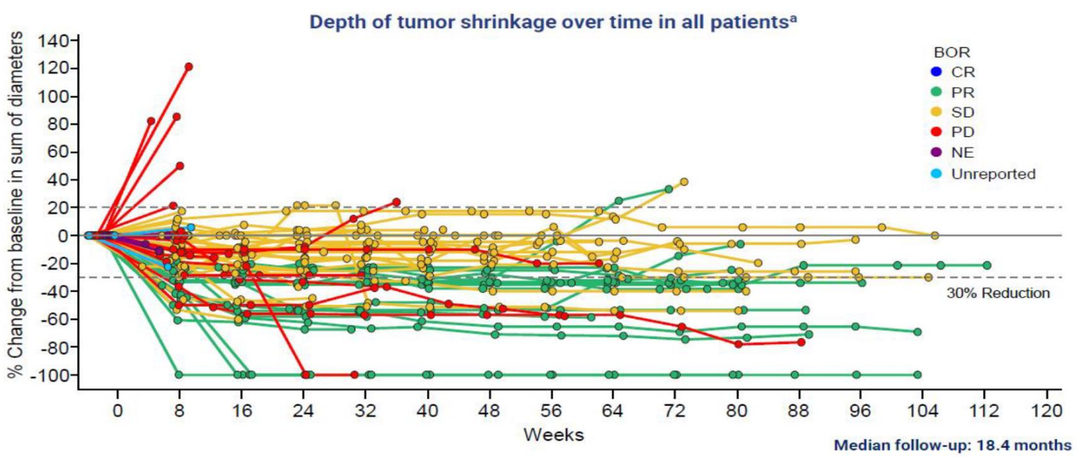
Tarlatamab + Anti-PD-L1 as 1L Maintenance: Unprecedented 25.3m OS.



- Manageable long-term safety: No DLTs or fatal AEs; CRS/ICANS predominantly grade 1–2, decreasing TEAEs over time

- Encouraging efficacy: Median OS **25.3 months**, ORR 24%, durable disease control (≥52 weeks in **36%**)



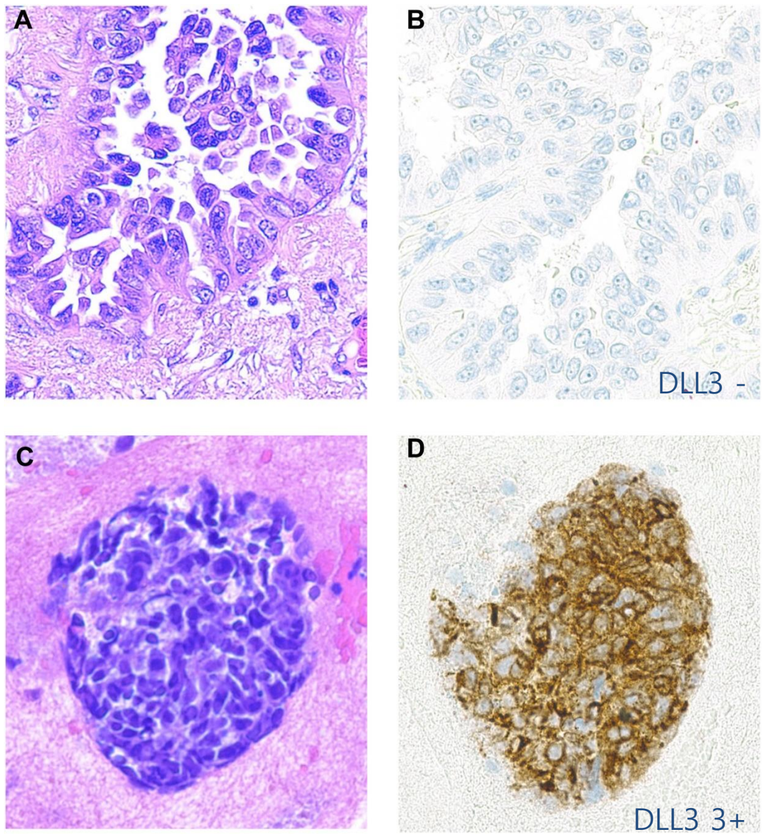


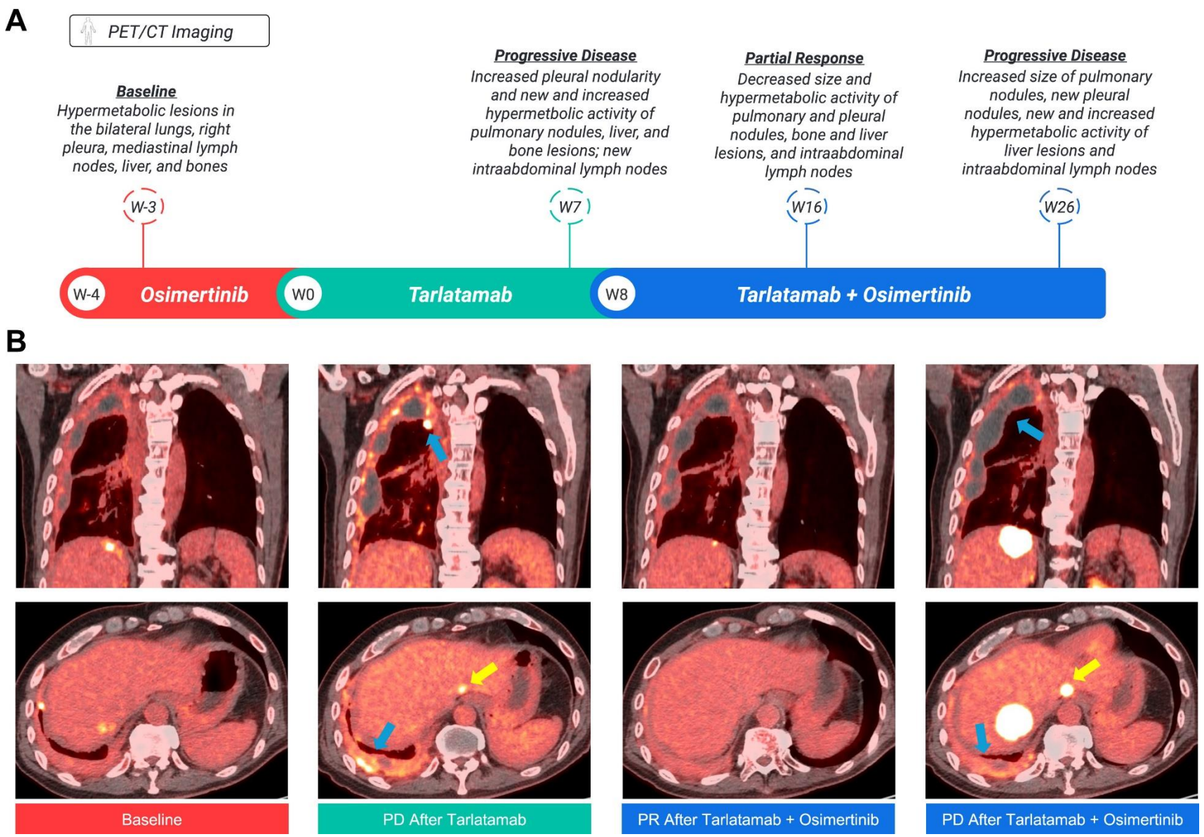
Neuroendocrine Transformation: Targeting DLL3 in EGFR-mutant NSCLC

Lung, AD

Osimertinib

Brain, SCLC



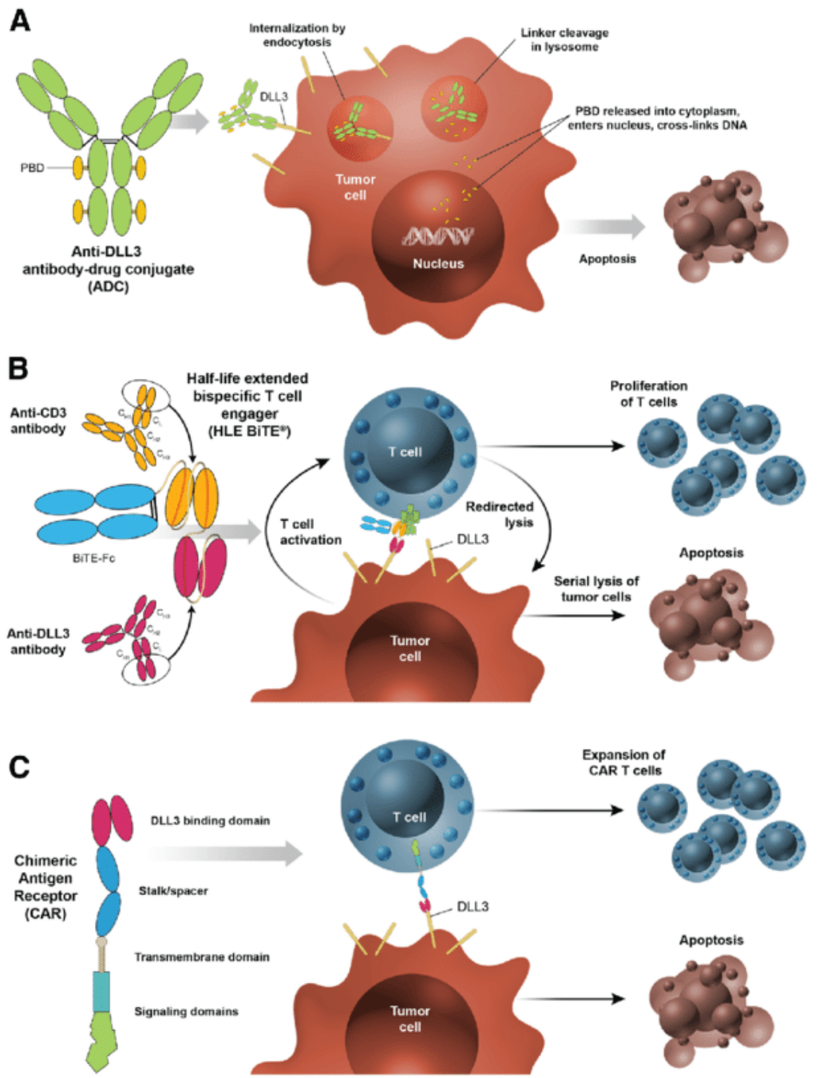


- Variable DLL3 expression observed by IHC in neuroendocrine-transformed tissue
- Strong DLL3 staining (3+) in 67% of patients (8/12)
- High DLL3 expression (≥75%) in 75% of patients (9/12)
- Supports DLL3-directed therapies as a rational strategy in this treatment-resistant population with limited options

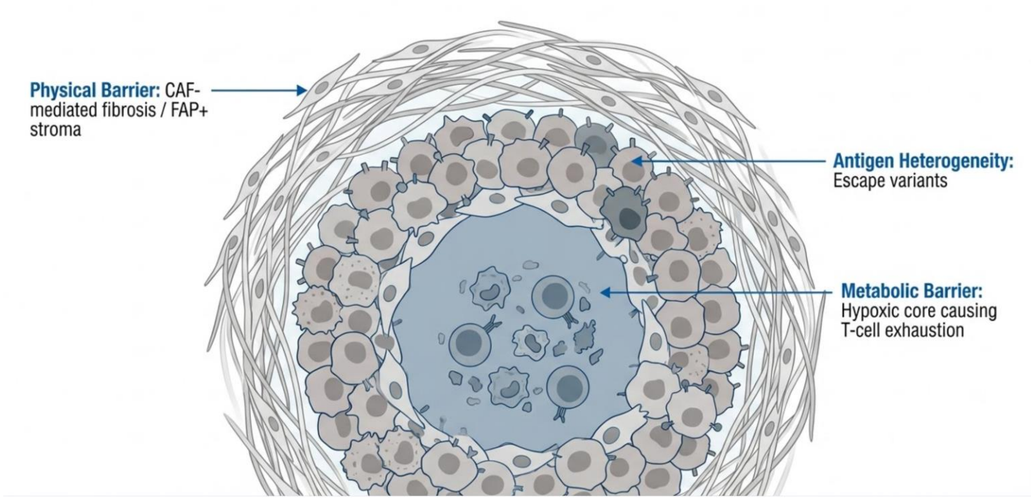
JTO Clin Res Rep. 2025 Sep 30;6(12):100913

DLL3 TCEs vs. ADCs: Comparative Analysis

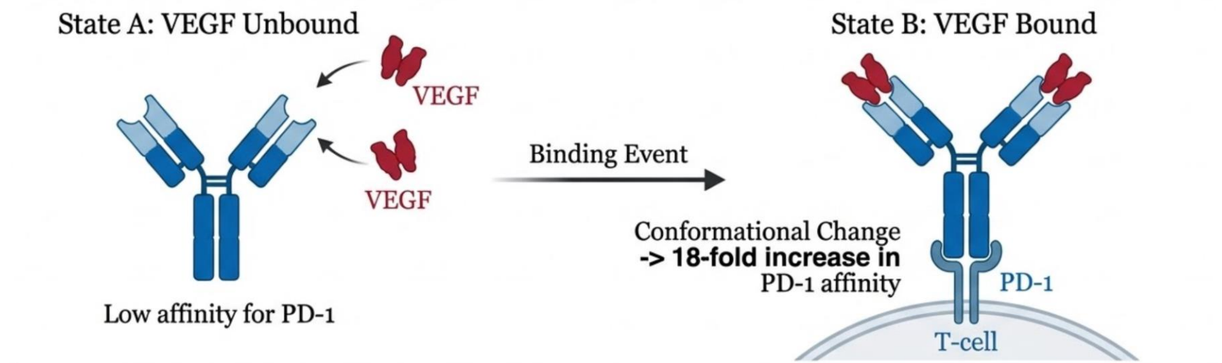
	DLL3 TCEs	DLL3 ADCs
Killing mechanism	**Active T-cell–mediated cytotoxicity**	**Payload-driven cell death**
Dependency	Functional **T-cell presence & engagement**	**DLL3 expression + internalization**
Bystander effect	Limited (immune-synapse dependent)	Possible (payload diffusion)
Tumor immune context	Requires **immune-accessible tumors**	Works in **immune-cold SCLC**
Durability potential	High (immune memory, serial killing)	Limited by payload resistance
Key toxicity	CRS, neurotoxicity	Myelosuppression, organ toxicity



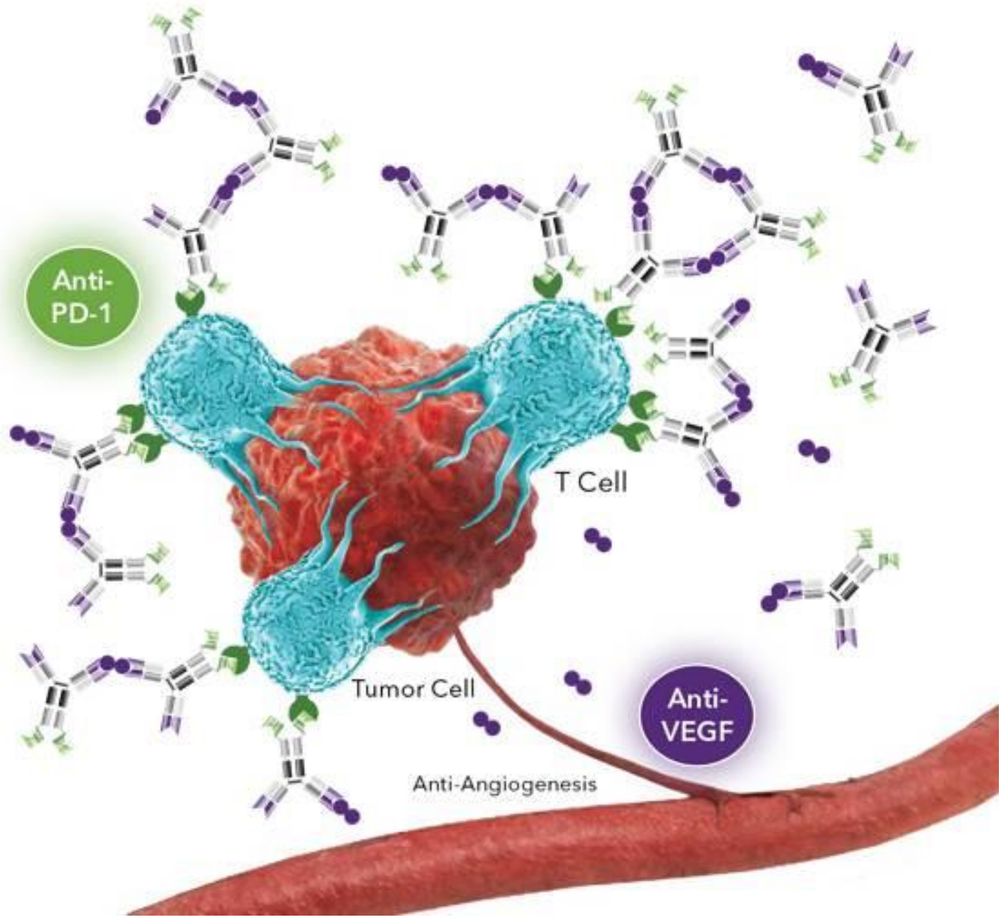
TME Modulation



Ivonescimab (AK112/SMT112)
Cooperative Binding 을 통한 Binding affinity 증가



Bio-engineered Logic Gate: In Helvetica Now Display Bold:
If VEGF is present (Tumor Microenvironment) -> Then block PD-1 strongly.
Result: Selective activation of T-cells at the tumor site, sparing healthy tissue.



News | **Articles** | January 29, 2026

FDA Accepts BLA for Ivonescimab Plus Chemotherapy in EGFR-Mutant NSCLC After TKI Progression

Ivonescimab (AK112/SMT112)

Phase 3 Study Design

HARMONi

Key Eligibility Criteria
Locally advanced or metastatic NSCLC:
- EGFR sensitizing mutation+
- Progressed on 3rd gen EGFR-TKI
- ECOG 0 or 1
- Any PD-L1 expression

Stratification factor by geographic region:
- Brain metastases (yes or no)

R 1:1

N=438

- **Ivonescimab + Chemotherapy** (N = 219)
- **Placebo + Chemotherapy** (N = 219)

Ivonescimab: 20 mg/kg Q3W
Chemotherapy:
- Carboplatin: AUC5 Q3W x 4 cycles (21 day/cycle)
- Pemetrexed: 500 mg/m² Q3W

Endpoints:

Primary
- OS, PFS by IRRC per RECIST 1.1

Secondary
- ORR by IRRC, DoR, safety and tolerability

Planned Efficacy Analyses
- PFS primary (at ~231 events) & OS interim analyses
- OS final analysis (at ~261 events)

FPI: Jan 2022 (overall)
LPI Asia: Nov 2022
LPI NA & EU (and overall): Oct 2024

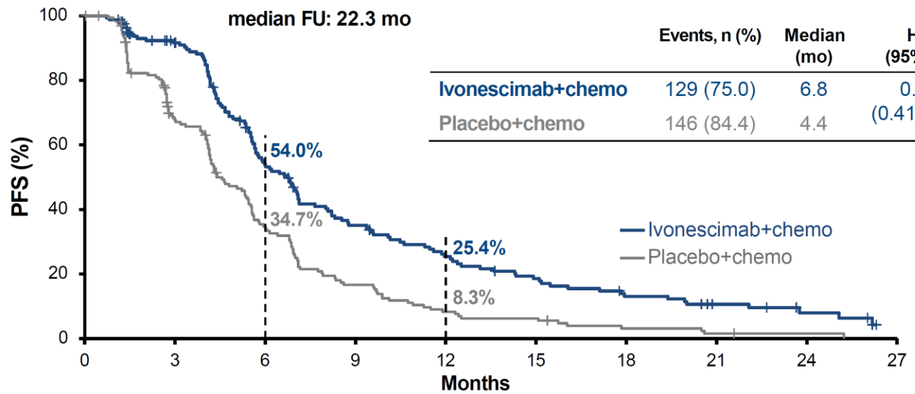
DoR=duration of response; ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; EU=Europe; FPI=first patient in; IRRC= independent radiology review committee; LPI=last patient in; mets=metastases; NA=North America; ORR=overall response rate; OS=overall survival; NSCLC=non-small cell lung cancer; TKI=tyrosine kinase inhibitor; PD-L1= programmed cell death ligand; PFS=progression-free survival; Q3W=every 3 weeks; RECIST=response evaluation criteria in solid tumors.

Note: Positive outcomes were reported from the single-region (Asia) study HARMONi-A, with PFS as the primary endpoint.

Primary Endpoint: PFS by IRRC

HARMONi

Statistically significant and clinically meaningful benefit with ivonescimab



	Events, n (%)	Median (mo)	HR (95% CI)	*P* Value
Ivonescimab+chemo	129 (75.0)	6.8	0.52 (0.41-0.66)	<0.0001
Placebo+chemo	146 (84.4)	4.4		

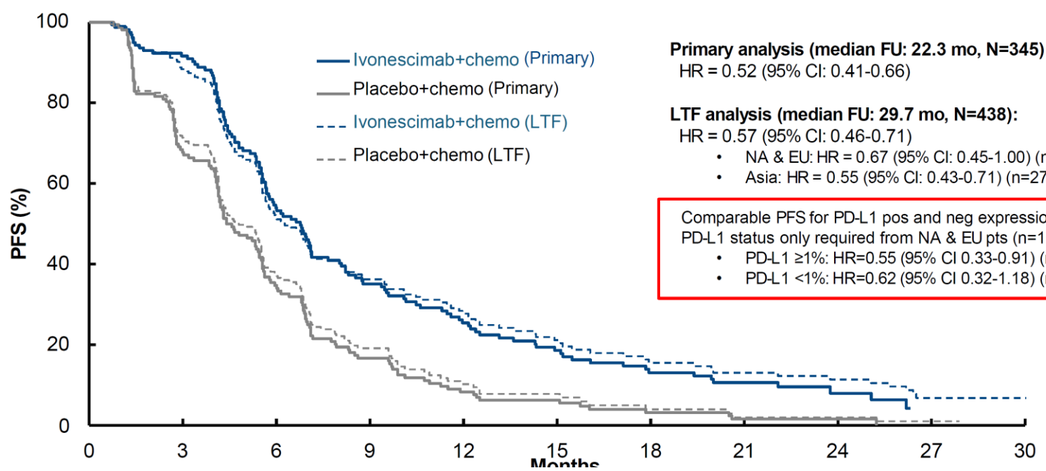
No. at risk										
Ivonescimab+chemo	172	134	76	48	34	24	16	10	5	0
Placebo+chemo	173	100	50	24	12	9	4	2	1	0

Consistent PFS benefit by investigator: HR = 0.58 (95% CI: 0.45-0.73)

PFS by IRRC: Primary Analysis vs Longer Term Follow-Up (LTF)

HARMONi

Consistent PFS between primary and LTF including all NA & EU patients



Primary analysis (median FU: 22.3 mo, N=345):
HR = 0.52 (95% CI: 0.41-0.66)

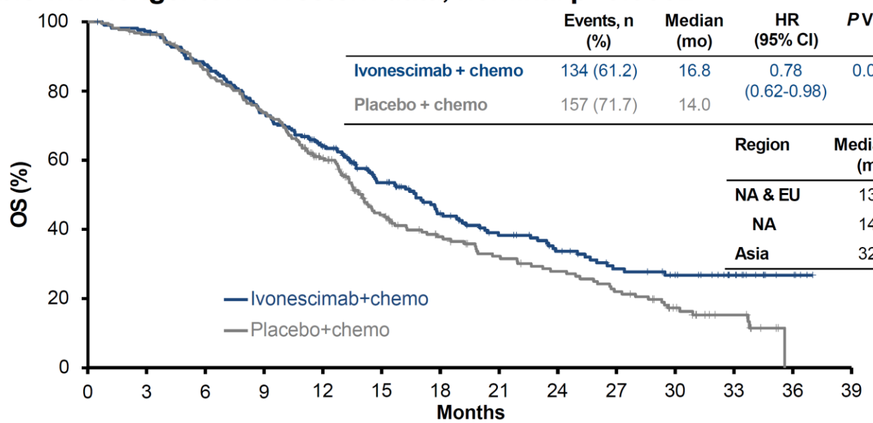
LTF analysis (median FU: 29.7 mo, N=438):
HR = 0.57 (95% CI: 0.46-0.71)
- NA & EU: HR = 0.67 (95% CI: 0.45-1.00) (n=165)
- Asia: HR = 0.55 (95% CI: 0.43-0.71) (n=273)

Comparable PFS for PD-L1 pos and neg expression.
PD-L1 status only required from NA & EU pts (n=160):
- PD-L1 ≥1%: HR=0.55 (95% CI 0.33-0.91) (n=106)
- PD-L1 <1%: HR=0.62 (95% CI 0.32-1.18) (n=54)

Overall Survival: Longer Term Western Follow-up

HARMONi

OS stable with longer term Western data, nominal p=0.0332



	Events, n (%)	Median (mo)	HR (95% CI)	*P* Value
Ivonescimab + chemo	134 (61.2)	16.8	0.78 (0.62-0.98)	0.0332
Placebo + chemo	157 (71.7)	14.0		

Region	Median FU (mo)	Median OS (mo)
NA & EU	13.7	17.0 vs. 14.0
NA	14.6	NR vs. 14.0
Asia	32.7	16.7 vs. 14.0

Data cutoff
NA&EU: Sep 2025
Asia: Apr 2025

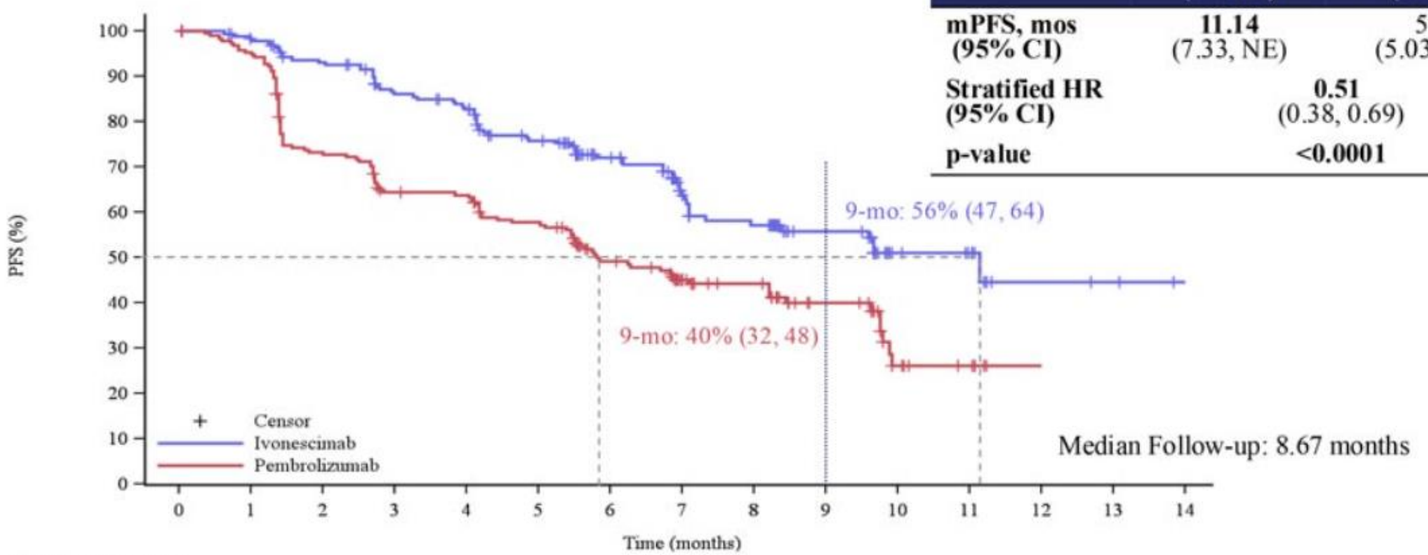
No. at risk														
Ivonescimab+chemo	219	212	190	160	127	92	68	53	43	33	26	16	5	0
Placebo+chemo	219	210	186	159	119	74	56	45	38	30	18	9	0	

Ivonescimab (AK112/SMT112)
The PD-1/VEGF Paradigm Shift (HARMONi-2)

- Randomized, double-blind, phase III study
- Ivonescimab vs Pembrolizumab: 1L PD-L1–positive (TPS ≥1%) advanced NSCLC

Primary endpoint: PFS per IRRC

	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	**11.14** (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	**0.51** (0.38, 0.69)	
p-value	**<0.0001**	



Number at risk (Events)

Ivonescimab	198(0)	189(3)	175(13)	156(26)	148(32)	128(44)	99(50)	68(60)	59(67)	38(68)	14(71)	11(71)	3(72)	2(72)	0(72)
Pembrolizumab	200(0)	187(9)	141(52)	121(69)	119(70)	103(81)	74(95)	53(101)	45(102)	25(106)	9(112)	5(112)	0(112)		

Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

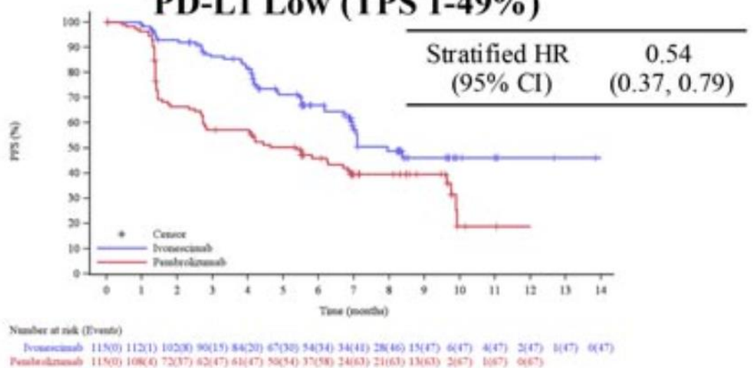
Abbreviations: mPFS, median progression-free survival; IRRC, independent radiology review committee; mo, month; NE, not estimable; HR: hazard ratio; CI, confidence interval.

Ivonescimab (AK112/SMT112)
The PD-1/VEGF Paradigm Shift (HARMONi-2)

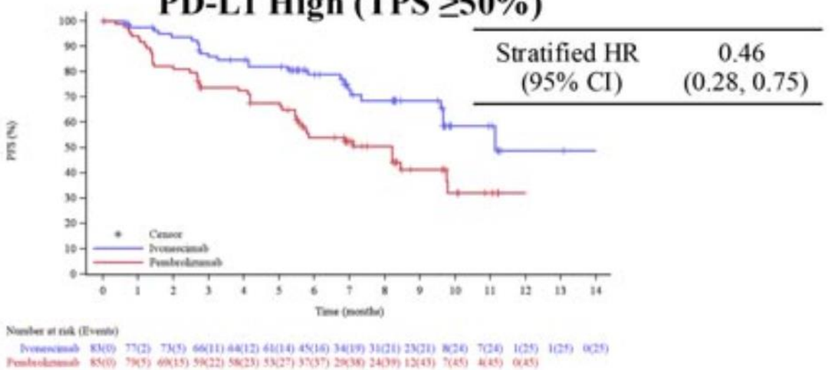
Key PFS Subgroup Analyses

PD-L1 expression

PD-L1 Low (TPS 1-49%)

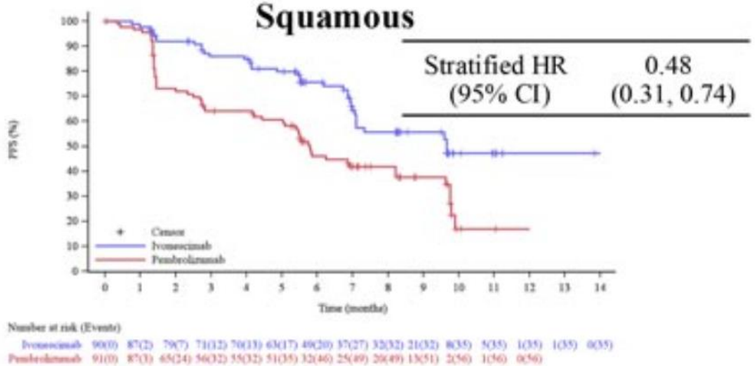


PD-L1 High (TPS ≥50%)

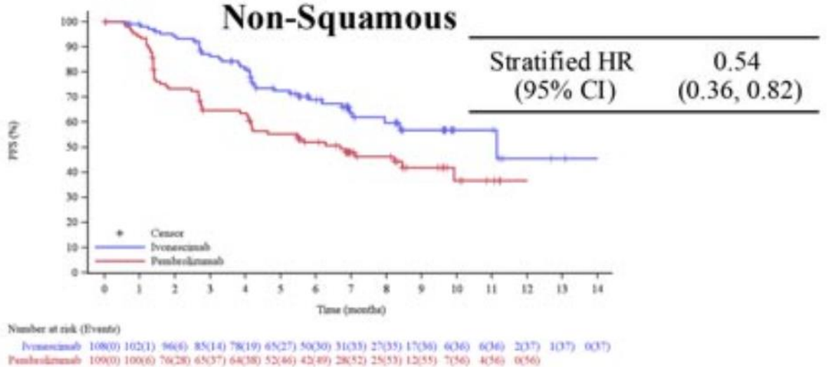


NSCLC Histology

Squamous



Non-Squamous



Ivonescimab showed meaningful improvement in PFS vs. pembrolizumab in patients with both low and high PD-L1, with squamous or non-squamous advanced NSCLC.

Abbreviations: PFS, progression-free survival; PD-L1, programmed death ligand 1; TPS, tumor proportion score; HR: hazard ratio; CI, confidence interval; NSCLC, non-small cell lung cancer.

Ivonescimab vs. Pembrolizumab (HARMONi-2 Efficacy Summary)

Outcome Metric	Ivonescimab	Pembrolizumab	Improvement / HR
Median PFS (Months)	11.14	5.82	+5.32 months (HR 0.51)
9-Month PFS Rate	56%	40%	+16%
ORR (%)	50.0%	38.5%	+11.5%
Disease Control Rate (%)	89.9%	70.5%	+19.4%
HR (Squamous Histology)	0.48	1.00 (Ref)	52% ↓
HR (PD-L1 TPS >1%)	0.46	1.00 (Ref)	54% ↓

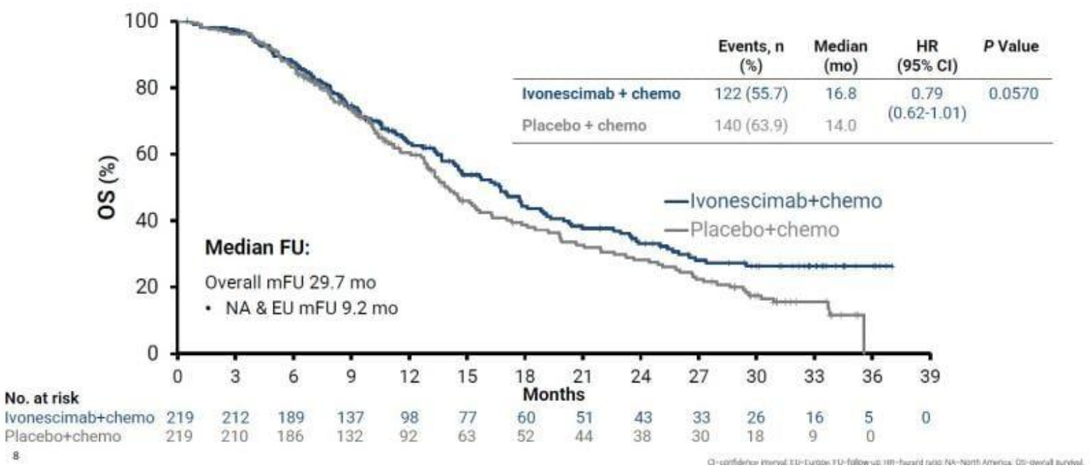
Limitations of Ivonescimab

- China-heavy phase III evidence base
- Biomarker strategy still evolving
- Long-term OS and post-progression data immature
- CRS risk remains an inherent class effect
- VEGF-related toxicity cannot be fully eliminated

Primary Endpoint: Overall Survival

HARMONi

Favorable Trend Observed; NA & EU Follow-up Not Yet Mature



	Events, n (%)	Median (mo)	HR (95% CI)	*P* Value
Ivonescimab + chemo	122 (55.7)	16.8	0.79 (0.62-1.01)	0.0570
Placebo + chemo	140 (63.9)	14.0		

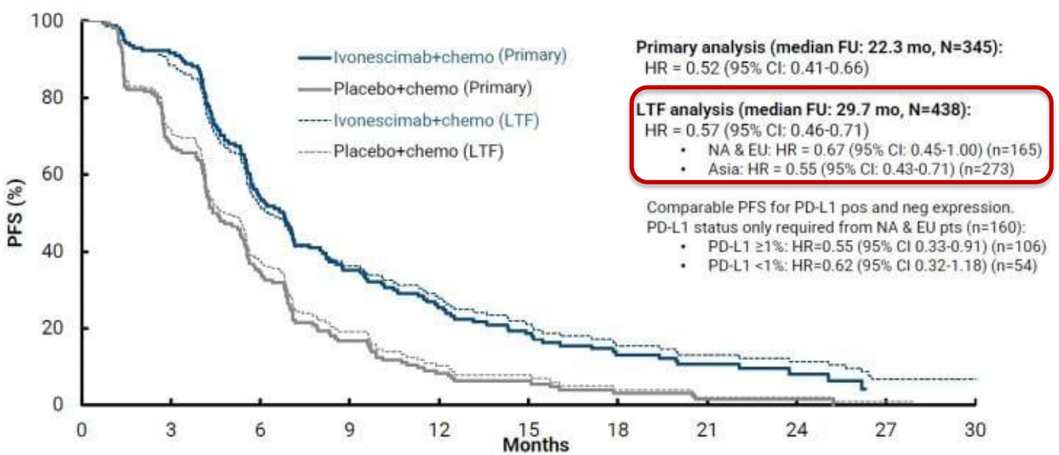
No. at risk														
Ivonescimab+chemo	219	212	189	137	98	77	60	51	43	33	26	16	5	0
Placebo+chemo	219	210	186	132	92	63	52	44	38	30	18	9	0	

8

PFS by IRRC: Primary Analysis vs Longer Term Follow-Up (LTF)

HARMONi

Consistent PFS between primary and LTF including all NA & EU patients



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Comparable PFS for PD-L1 pos and neg expression.
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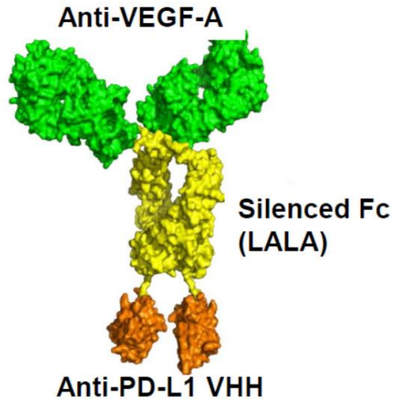
- PD-L1 <1%: HR=0.62 (95% CI 0.32-1.18) (n=54)

Global Phase III Clinical Development Program of Ivonescimab

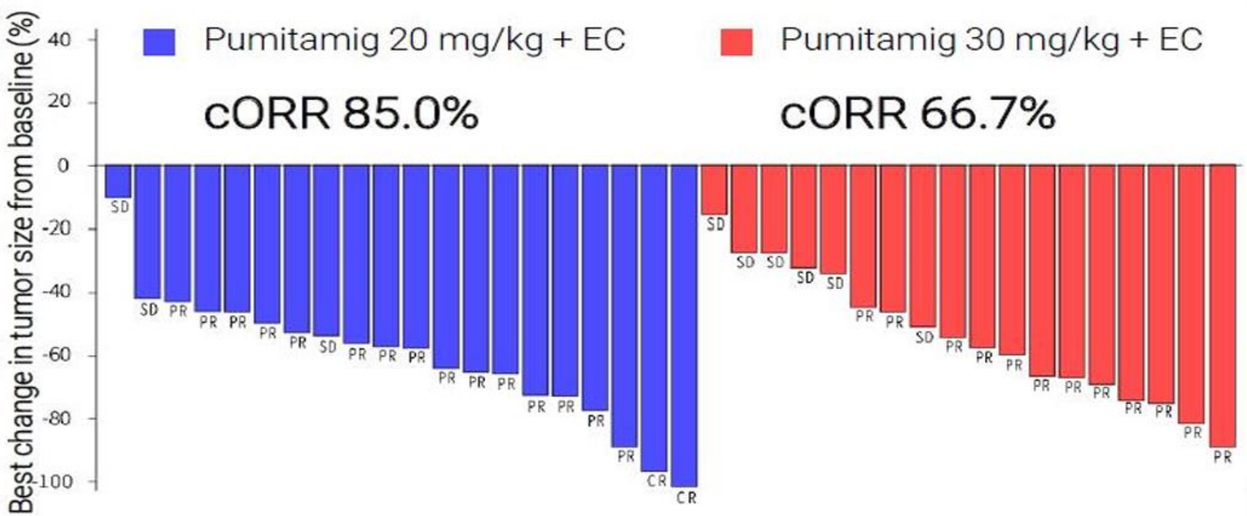
Trial	Indication	Comparator	Status
HARMONi (HARMONi-A)	EGFR-mutant advanced NSCLC(post-TKI setting)	Investigator's choice chemotherapy	**BLA accepted (US)** **Approved (China)**
HARMONi-2	First-line PD-L1–positive advanced NSCLC(all histologies)	Pembrolizumab monotherapy	**PFS superiority demonstrated** Primary endpoint met
HARMONi-3	First-line metastatic squamous and non-squamous NSCLC	Pembrolizumab + chemotherapy	**Ongoing enrollment** Global, multicenter trial
HARMONi-6	First-line advanced squamous NSCLC	Tislelizumab + chemotherapy	**PFS superiority demonstrated** **sNDA submitted (China)**

Pumitamig (BNT327/BMS-986545)
PD-L1 on tumor cells, allowing the neutralization of VEGF-A



Global PhII open-label, parallel group
pumitamig + chemotherapy untreated ES-SCLC and previously treated SCLC

Tumor response

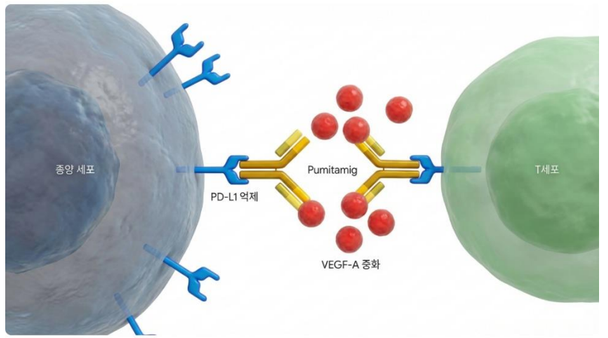


	All (N=43)	Pumitamig 20 mg/kg + EC (N=22)	Pumitamig 30 mg/kg + EC (N=21)
Evaluable patients, n	38	20	18
BOR*, n			
CR	2	2	0
PR	27	15	12
SD	9	3	6
PD	0	0	0
Primary endpoints			
uORR*, % (95% CI)	86.8 (71.9–95.6)	90.0 (68.3–98.8)	83.3 (58.6–96.4)
cORR*, % (95% CI)	76.3 (59.8–88.6)	85.0 (62.1–96.8)	66.7 (41.0–86.7)
Best % change in tumor size*, mean (std dev)	−56.7(20.5)	−60.0 (20.6)	−53.1 (20.5)
Early tumor shrinkage†, % (95% CI)	89.5 (75.2–97.1)	90.0 (68.3–98.8)	88.9 (65.3–98.6)
Secondary endpoint			
DCR*, % (95% CI)	100 (90.7–100)	100 (83.2–100)	100 (81.5–100)

Encouraging antitumor activity observed with both dose levels of pumitamig

Pumitamig (BNT327/BMS-986545)

PD-L1 on tumor cells, allowing the neutralization of VEGF-A



Clinical Endpoint	Pumitamig + Chemotherapy (Ph II)	Atezolizumab + Chemotherapy (IMpower133, Ph III)	Durvalumab + Chemotherapy (CASPIAN, Ph III)
Objective Response Rate	76.3% – 85.4%	60.2%	67.9%
Disease Control Rate	100%	–	–
Median Progression-Free Survival	6.9 months	5.2 months	5.3 months
Median Overall Survival	16.8 months *(China data, early)*	12.3 months	13.0 months

ROSETTA-Lung01(SCLC), ROSETTA-Lung02(NSCLC)

TIGIT: The "Reckoning" of 2025

TIGIT blockade amplifies anti-tumor immunity by activating $CD8^+$ T cells and NK cells while relieving Treg-driven suppression.

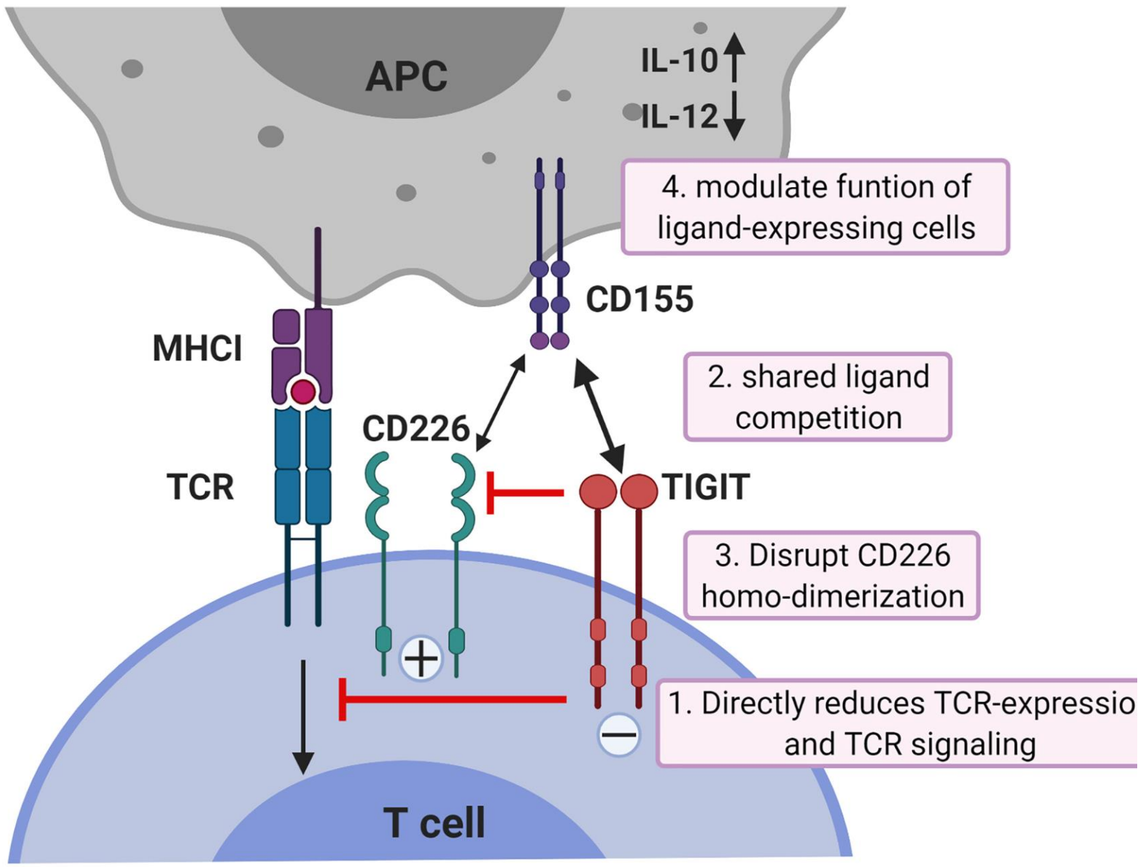
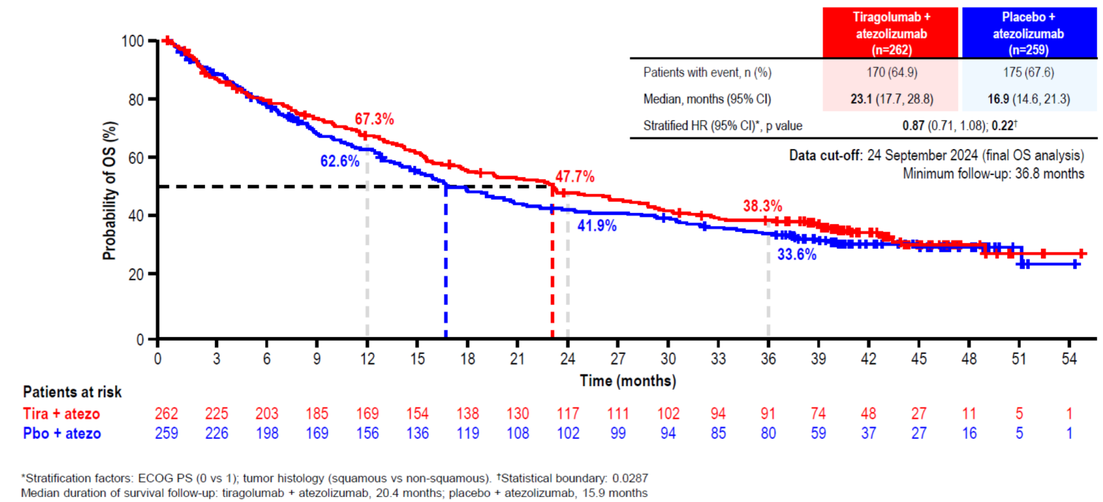


Figure adapted from Ge Z, et al. 2021.

Final OS analysis in Skyscraper-01



*Stratification factors: ECOG PS (0 vs 1); tumor histology (squamous vs non-squamous). †Statistical boundary: 0.0287
Median duration of survival follow-up: tiragolumab + atezolizumab, 20.4 months; placebo + atezolizumab, 15.9 months

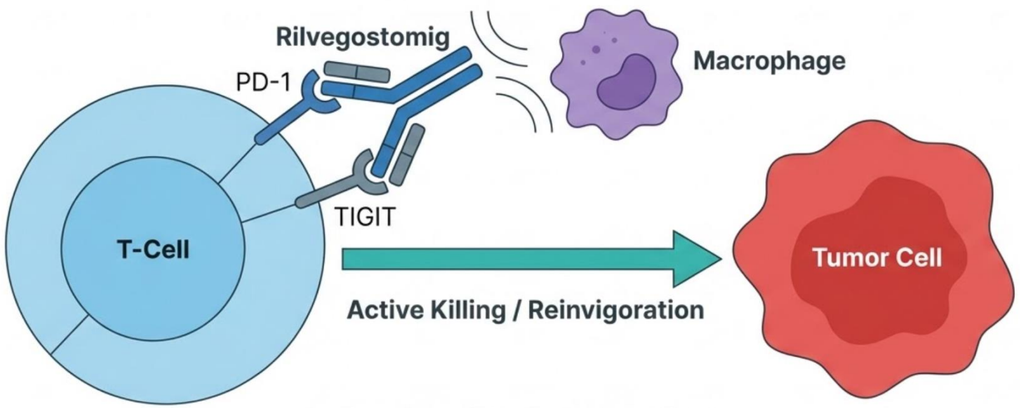
Source: Dr Solange Peters & AACR.

Roche (Tiragolumab) — STOP — SKYSCRAPER-01/02 Failed (PFS/OS)

MSD (Vibostolimab) — STOP — KeyVibe-008 Halted (Futility/Toxicity)

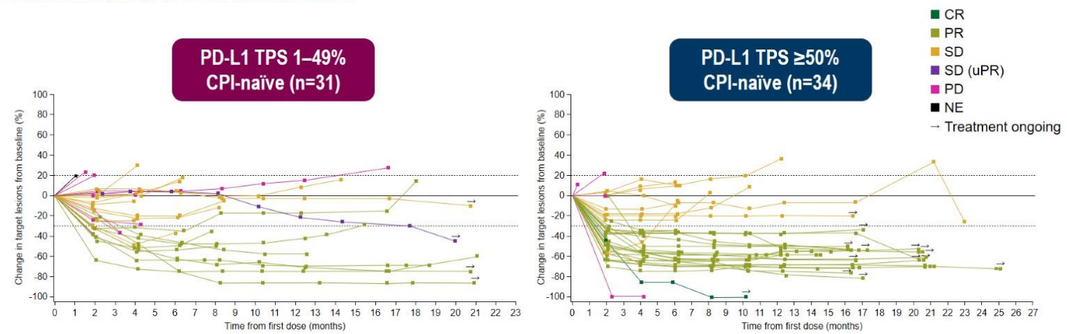
BeiGene (Ociperlimab) — STOP — AdvanTIG-302 Terminated

Rilvegostomig: Synergistic PD-1 x TIGIT Blockade



Design: Bispecific Fc-Reduced/Null
Mechanism: Pure Blockade
No ADCC: Macrophage cannot bind
Result: Preservation of Effector T-Cells

ARTEMIDE-01: ORR and DoR



	PD-L1 TPS 1–49%		PD-L1 TPS ≥50%	
	CPI-naïve (n=31)	CPI + CTx-naïve (n=18)	CPI-naïve (n=34)	CPI + CTx-naïve (n=31)
ORR, % (95% CI)	29.0 (14.2–48.0)	44.4 (21.5–69.2)	61.8 (43.6–77.8)	67.7 (48.6–83.3)
Median DoR, months (range)	9.9 (4.1–NC)	8.5 (4.1–NC)	NR (10.3–NC)	NR (10.3–NC)

ARTEMIDE-01: First-in-human study of rilvegostomig – Parts C and D (NCT04995523)

CPI-naïve, PD-L1 TPS ≥1% Stage IV NSCLC

- Up to 1 prior chemotherapy regimen for metastatic disease
- PD-L1 TPS per local test
- *EGFR/ALK* wild-type

Part A (dose escalation) and Part B (dose expansion) in CPI-resistant NSCLC not pictured

R 1:1

No stratification factors

Part C
PD-L1 TPS ≥1%
750 mg Q3W (n=34)

Part D1
PD-L1 TPS ≥50%
750 mg Q3W (n=31)

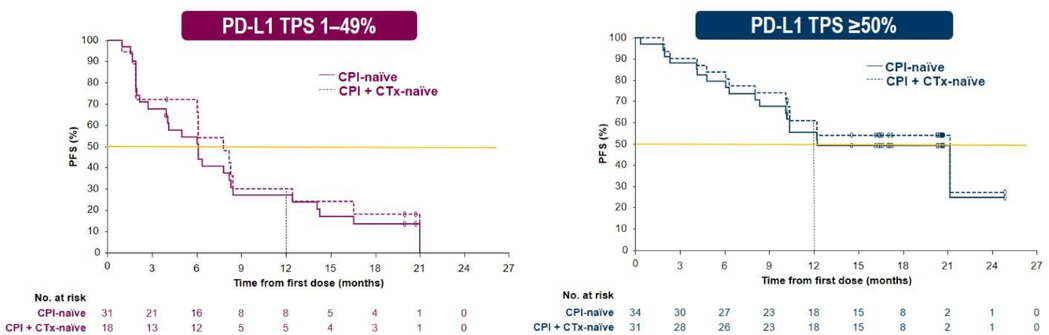
Part D2
PD-L1 TPS ≥50%
1500 mg Q3W (n=31)

Up to 35 cycles

Primary endpoints
- ORR per investigator per RECIST v1.1
- Safety

Key secondary endpoints
- DoR
- PFS

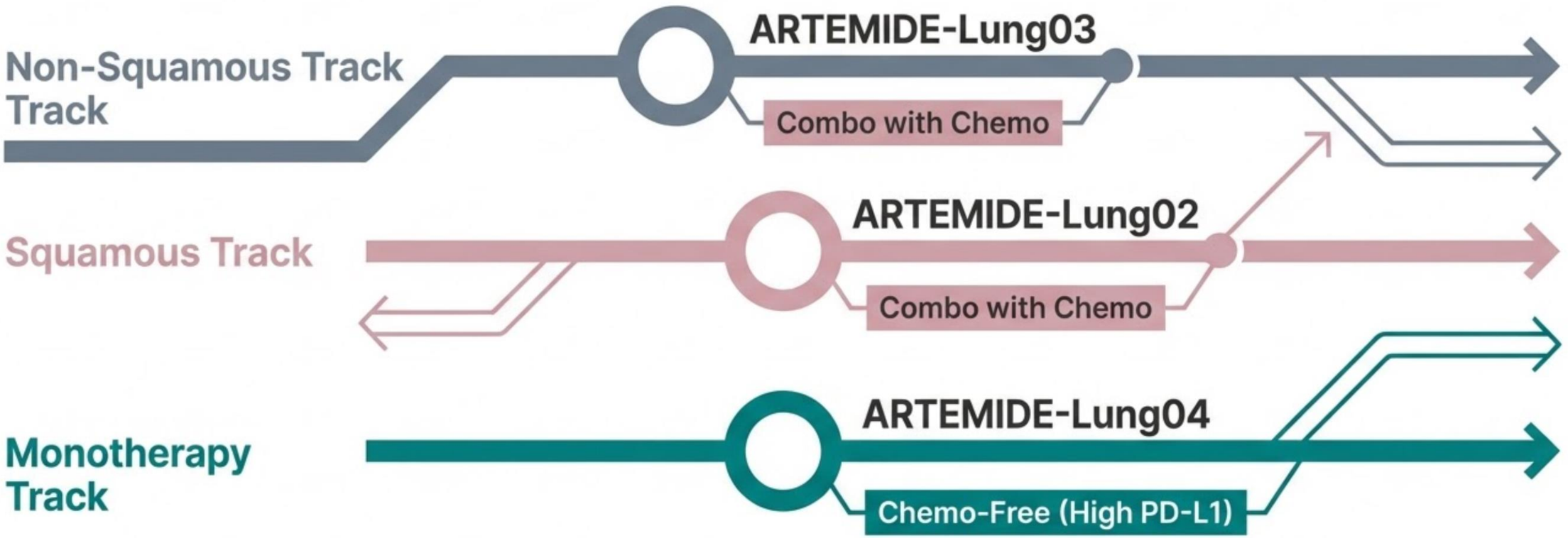
ARTEMIDE-01: PFS in CPI-naïve and CPI + CTx-naïve patients



	PD-L1 TPS 1–49%		PD-L1 TPS ≥50%	
	CPI-naïve (n=31)	CPI + CTx-naïve (n=18)	CPI-naïve (n=34)	CPI + CTx-naïve (n=31)
Median PFS, months (95% CI)	6.1 (2.7–8.3)	7.8 (1.9–12.5)	12.3 (8.4–NC)	21.2 (10.2–NC)
12-month PFS, % (95% CI)	27.2 (12.9–43.6)	30.1 (11.1–52.0)	55.5 (37.3–70.3)	60.8 (41.4–75.6)

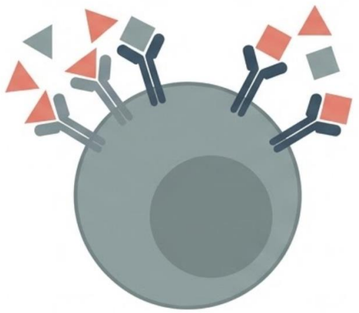
Data cutoff: 18 August 2025; interim response evaluable set – 9 weeks or one scan. CI, confidence intervals; CPI, checkpoint inhibitor; CTx, chemotherapy; NC, not calculable; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TPS, tumour proportion score

Rilvegostomig: ARTEMIDE Phase3
A multi-front offensive



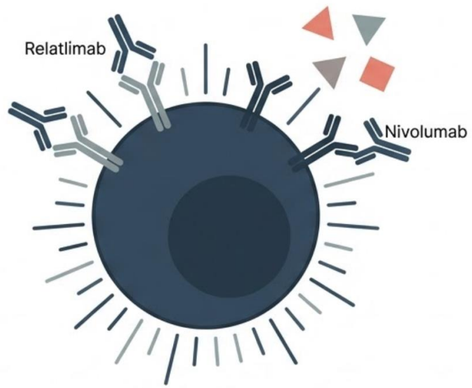
LAG-3: Lessons from RELATIVITY-104 for next-generation bispecific design

T-Cell Exhaustion
Inter Regular



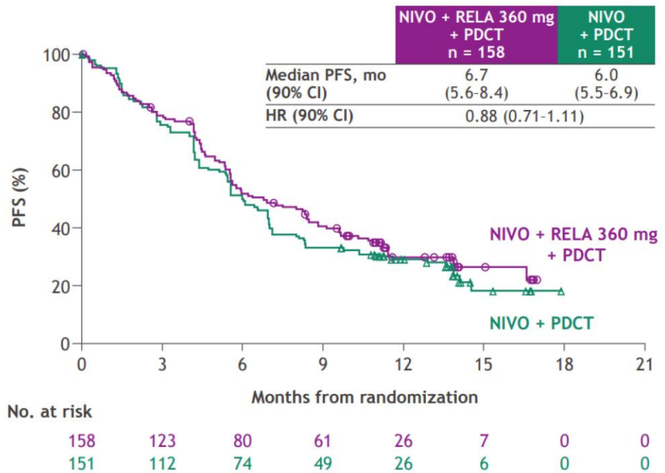
Co-expression of PD-1 & LAG-3 in
Tumor Microenvironment. Signal Blocked.

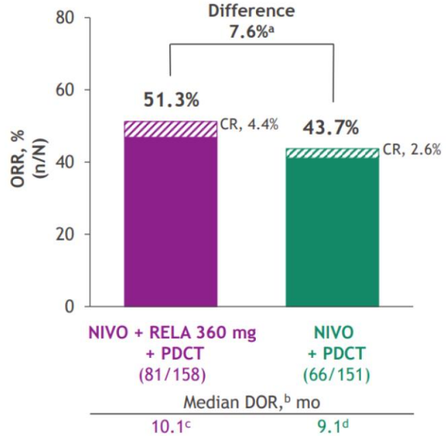
Dual Blockade Restoration
Inter Regular



Relatlimab + Nivolumab.
Enhanced proliferation & Cytokine secretion
(IL-2, IFN-gamma).

All randomized patients: PFS and ORR per BICR





Median follow-up (range) for Part 2: 10.7 (0.0-18.6) months.

RELATIVITY-104 Part 2 study design

Key eligibility criteria
- 1L stage IV/recurrent NSCLC
- No prior systemic therapy for metastatic disease
- No *EGFR*, *ALK*, *ROS-1* mutations[a]
- ECOG PS 0-1

N = 309
R 1:1

NIVO 360 mg + RELA 360 mg Q3W + PDCT[c] (4 cycles)

Prophylactic myeloid growth factor was mandatory for patients aged ≥ 60 years[d] according to guidelines[1,2]

NIVO 360 mg Q3W + PDCT[c] (4 cycles)

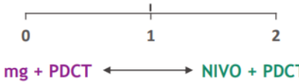
Stratified by tumor PD-L1[b] (≥ 1% vs < 1%), histology (NSQ vs SQ), and ECOG PS (0 vs 1)

Primary endpoint
- ORR (BICR)

Secondary endpoints
- PFS (BICR)
- Safety
- ORR and PFS by PD-L1
- DOR (BICR)

Stratified[a] patient subgroups: PFS and ORR per BICR

Subgroup, n[b]	mPFS, mo (90% CI) NIVO + RELA 360 mg + PDCT	mPFS, mo (90% CI) NIVO + PDCT	PFS HR (90% CI)	ORR, % (90% CI) NIVO + RELA 360 mg + PDCT	ORR, % (90% CI) NIVO + PDCT
PD-L1 ≥ 1% (n = 79, 71)	**9.8 (5.9-13.8)**	**6.1 (4.2-7.0)**	**0.63 (0.45-0.88)**	**53.2 (43.3-62.8)**	**40.8 (31.0-51.3)**
PD-L1 < 1% (n = 70, 67)	5.6 (5.3-7.0)	5.8 (5.4-7.0)	1.23 (0.89-1.70)	50.0 (39.6-60.4)	44.8 (34.4-55.5)
NSQ (n = 107, 104)	**8.3 (5.6-9.8)**	**6.0 (4.6-7.0)**	**0.86 (0.65-1.13)**	**46.7 (38.5-55.1)**	**38.5 (30.5-47.0)**
SQ (n = 51, 47)	5.6 (5.3-8.2)	5.8 (5.4-7.1)	0.97 (0.66-1.43)	60.8 (48.3-72.3)	55.3 (42.3-67.8)



From Combination to Integration: PD-1 × LAG-3 Bispecific Antibodies

Drug	Target/Format	Lung Cancer Development Stage & Features
Tebotelimab (MGD013)	PD-1 x LAG-3 DART	Phase 1 expansion cohort in solid tumors/hematologic cancers including NSCLC showed ORR and tolerability; response correlation reported in LAG-3 high expression.
RO7247669	PD-1 x LAG-3 BsAb	Phase 1 ongoing in multiple solid tumors including NSCLC; combination and radiotherapy combination studies designed.
EMB-02	PD-1 x LAG-3 BsAb (Fc engineering LALA)	FIH Phase 1 in solid tumors reported additional immune activation and tolerability from dual blockade, including NSCLC.

- Although still in early clinical development, PD-1 × LAG-3 bispecifics are being actively explored as an integrated checkpoint strategy.

Future direction

Adverse Effects of Bispecific Immunotherapy and Strategies to Overcome Them

On-target, off-tumor toxicity

Cytokine storm (Fever, Hypotension, Respiratory distress)

Neurotoxicity (Encephalopathy, Speech disorders)

Organ-specific toxicity (myocarditis, colitis)

Mitigation Strategies:

- Step-up dosing
- Subcutaneous administration
- Premedication
- CD3 affinity optimization
- In silico modeling of cross-reactivity
- Selection of antigens with restricted expression in normal tissues
- Masked antibodies

Physicochemical Barriers to Tumor Penetration

Abnormal tumor vasculature

High interstitial fluid pressure (impeding diffusion)

Dense extracellular matrix (Rich in collagen, hyaluronic acid, fibronectin)

Blood–brain barrier (<0.1% of circulating BsAbs reach CNS tumors)

Mitigation Strategies:

- Size reduction (e.g., Diabody, nanobody, scFv formats)
- ECM modulation (e.g., PEGPH20, losartan)
- Anti-VEGF therapy improves vascular access
- Protease-activated BsAbs ensure local activation

Antigenic Drift

Loss or downregulation of target antigens (Gene deletion or silencing, Alternative splicing, Post-translational modifications, HLA downregulation (for TCR-based BsAbs))

Mitigation Strategies:

- Multi-targeting
- Targeting stable or essential antigens
- Stromal targeting (e.g., FAP, PDGFRβ)
- Monitoring the antigen monitoring & therapy adaptation

Immunogenicity & Anti-Drug Antibodies

Immune response against BsAbs, ADA formation (Reduced efficacy, faster clearance, potential hypersensitivity)

Mitigation Strategies:

- Humanization of antibody regions
- Optimized linker design
- Pre-treatment immunosuppression
- Targeting B cells

Strategic Combination Partners for Bispecific Antibodies

How to unlock efficacy beyond the molecule itself

Cellular Therapy

Sequential/Bridging: Optimized for disease debulking before CAR-T infusion

Dual-targeting: Simultaneous targeting to prevent antigen-negative escape.

Durability: Enhances the persistence of the anti-tumor response.

Remission: Significantly extends the duration of patient remission.

CLINICAL RISKS

CRS, Neurotoxicity, Graft-vs-Host Disease

Checkpoint Inhibitors

Reversing Exhaustion: Prevents T-cell anergy and functional exhaustion.

Effector Enhancement: Potentiates cytotoxic activity of engaged T-cells.

Memory Formation: Supports long-term immunological memory.

Synergy: Combines immune release with directed engagement.

CLINICAL RISKS

Autoimmune complications, increased irAE severity.

Oncolytic Viruses

Microenvironment: Converts "Cold" tumors into "Hot" immunogenic sites.

T-cell Infiltration: Significantly enhances localized T-cell recruitment.

Local Production: Enables in-situ generation of BiTEs within the tumor.

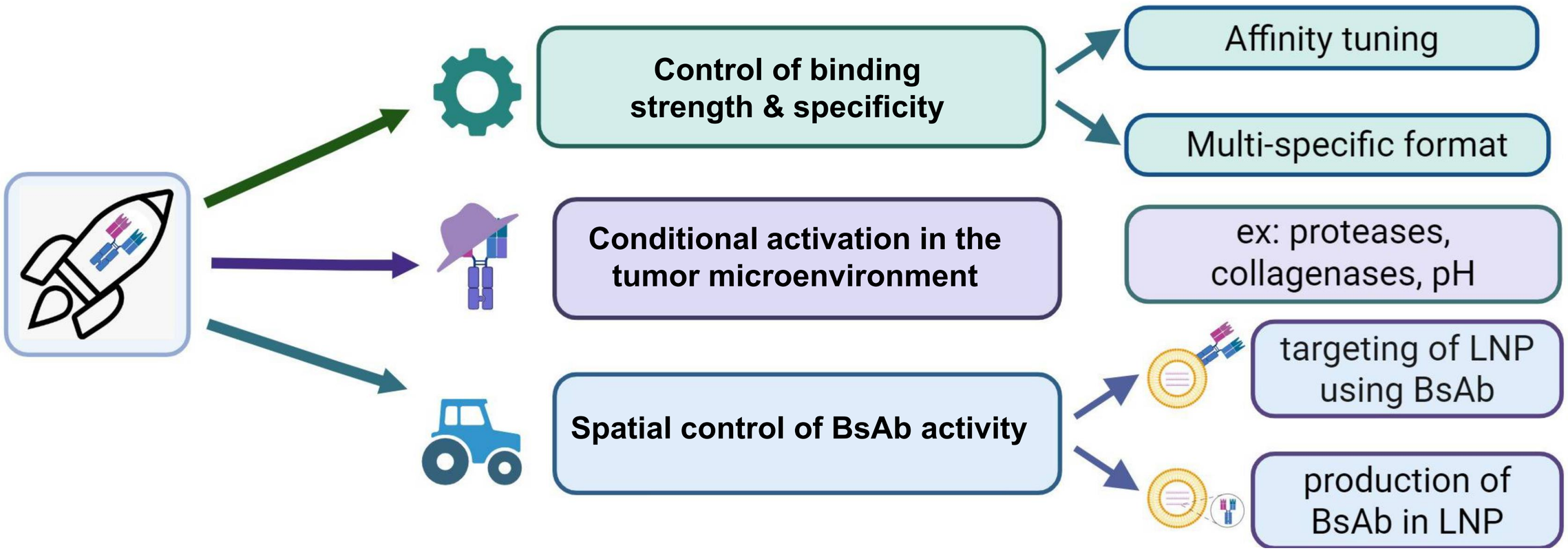
Dual Action: Direct viral lysis combined with antibody-mediated killing.

CLINICAL RISKS

Host antiviral immune response, delivery efficiency.

front Immunol. 2025 Nov 4;16:1679092.

From Target Engagement to Tumor Control: The Future of Bispecific Antibodies in Lung Cancer



Take Home Message

- BsAbs are emerging as next generation therapeutics in lung cancer, with landmark approvals and promising trial results
- Opportunities and challenges coexist: efficacy proven, but production, Immunogenicity, and cost remain hurdles
- A dynamic pipeline is underway aiming to broaden therapeutic options
- Future direction : optimize manufacturing , improve cost effectiveness, and identify new therapeutic targets to benefit more patients

Andrew Marshall

While 2025 has not been a banner year for biopharma dealmaking, antibodies that bind two or more molecular targets—so-called multispecifics—have taken center stage. The top three licensing deals and the second-largest merger of the year to date all involve bispecific assets (Table 1). And while most of the licensing and research partnership deals for bispecific therapeutics have focused on precision oncology, across industry autoimmune disease is also attracting interest.

A notable trend among these deals is the disproportionate number of assets acquired from Chinese companies. China's biotechs are gaining a reputation for antibody-engineering prowess, and "a key advantage for Chinese programs is their ability to rapidly and cheaply gain 'proof of signal' in a small human trial," said Leon Tang, founder and scientific advisor of InScienceWeTrust (ISWT) BioAdvisory. Indeed, the past year has seen bispecific antibodies take the spotlight from antibody–drug conjugate (ADC) oncology assets and technologies, which dominated the conversation in previous years.

Less for more

Over the past 12 months, biopharma dealmaking transactions fell to overall levels not seen since 2016. According to DealForma, 215 deals were announced across the industry in the first 10 months of 2025, down from 317 in 2024 and 298 in 2023. However, the top five therapy areas—oncology, neurology, infectious disease, autoimmunity, and endocrinology/metabolism (Fig. 1)—generated $12.3 billion, roughly on a par with the previous three years.

Oncology has experienced a steep drop in transactions. By October 2025, the industry had seen only 105 deals compared with 175 in 2024 and 162 in 2023 (Fig. 1). Yet each of those licenses generated on average $47.6 million—a 30% increase over the previous year ($36.6 million).

For merger and acquisition (M&A) transactions in 2024–2025 around cancer therapeutics, just 26 announcements were made in the first 10 months of this year, compared with 36 last year in its entirety. With multinational pharmaceutical companies facing a patent cliff, analysts have been predicting greater M&A activity; indeed, biopharma buyers are paying more, on average $1.1 billion per M&A deal this year compared with $475 million per deal last year. Cancer remains the dominant dealmaking category, accounting for more than a third of all 2024 biopharma transactions in both number and total value (Fig. 2).

Of the big biopharma companies, Roche, AstraZeneca, and AbbVie have been very active across the dealmaking landscape, clinching billion dollar deals in cancer. In January 2025, Roche closed its $1.5 billion acquisition of chimeric antigen receptor T-cell (CAR-T) therapy developer Poseida Therapeutics. AbbVie signed a ~$2.2 billion deal around bispecific T-cell engagers with Xilio Therapeutics in February. And in March, AstraZeneca agreed to pay up to $1 billion for the in vivo CAR-T therapy pioneer EsoBiotec.

However, other big players have also made splashes. Banner M&A deals included Eli Lilly and Company's $2.5 billion takeover of Scorpion Therapeutics in January; Merck KGaA's $3.4 billion enterprise value ($3.9 billion equity value) acquisition of SpringWorks Therapeutics, which concluded in July; and Sanofi's $9.5 billion acquisition of Blueprint Medicines, which was announced in June.

The Scorpion Therapeutics deal gives Lilly an oncology beachhead around STX-478, a once-daily, oral, mutant-selective phosphatidylinositol 3 kinase alpha (PI3Kα) inhibitor program for breast cancer and other advanced solid tumors. As part of the agreement, Scorpion spun out Antares Therapeutics, with a $177 million funding round (Lilly took a minority equity interest) and the sale of two

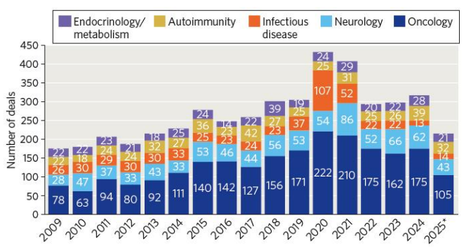


Fig.1 | Biopharma activity. Number of biopharma research and development (R&D) deals by therapeutic area. Source: DealForma. YTD, year to date.

Fig.2 | Top five merger and acquisition deal values by therapeutic area. Data are shown in $ billion, from 2024 to 2025 year-to-date. Source: DealForma.