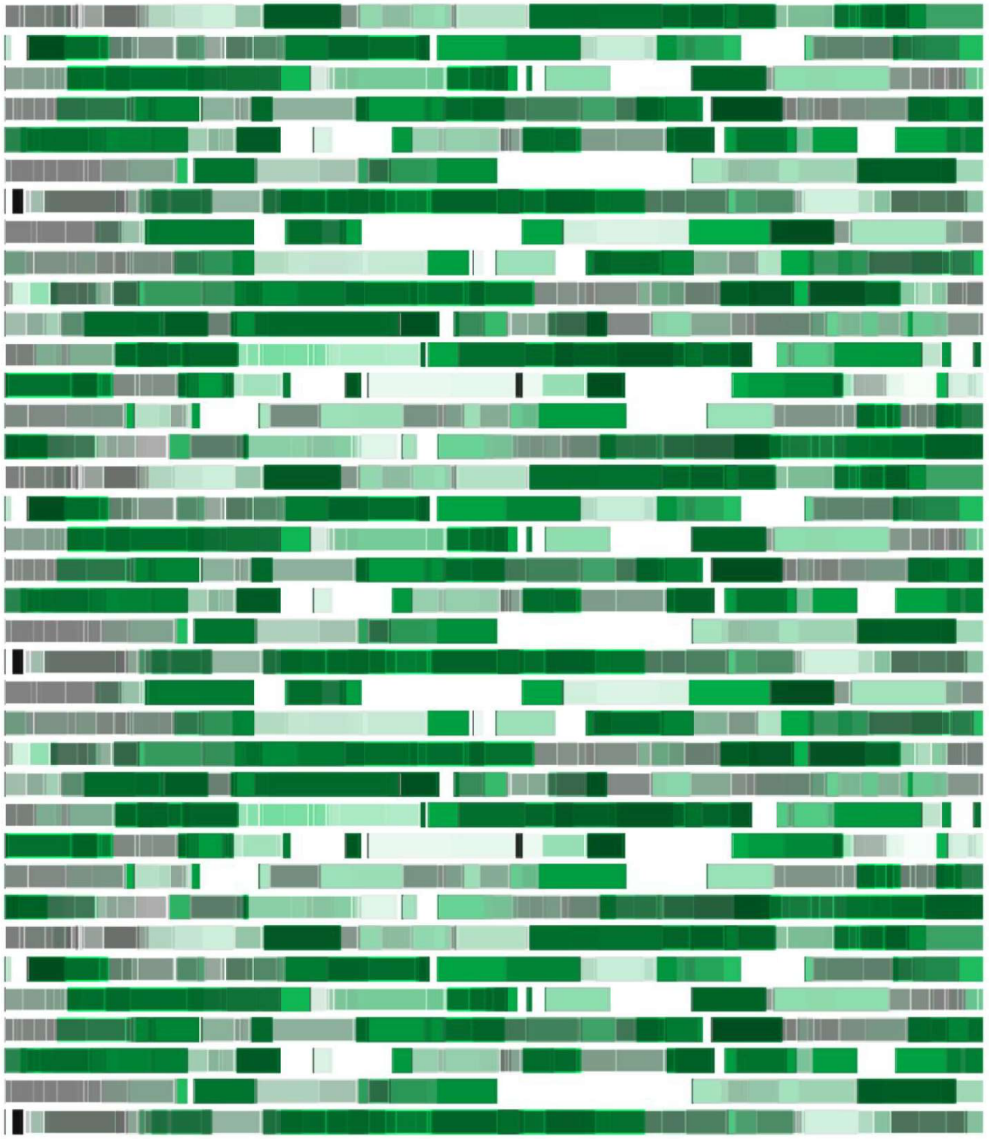
III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026

DIFERENTES ESTRATEGIAS DE INMUNOTERAPIA EN EL CÁNCER MICROCÍTICO DE PULMÓN EN ENFERMEDAD EXTENSA



Antonio Calles Blanco

Hospital General Universitario Gregorio Marañón, Madrid

Organizador por:

HENDERE HEALTHCARE

DECLARATION OF INTERESTS

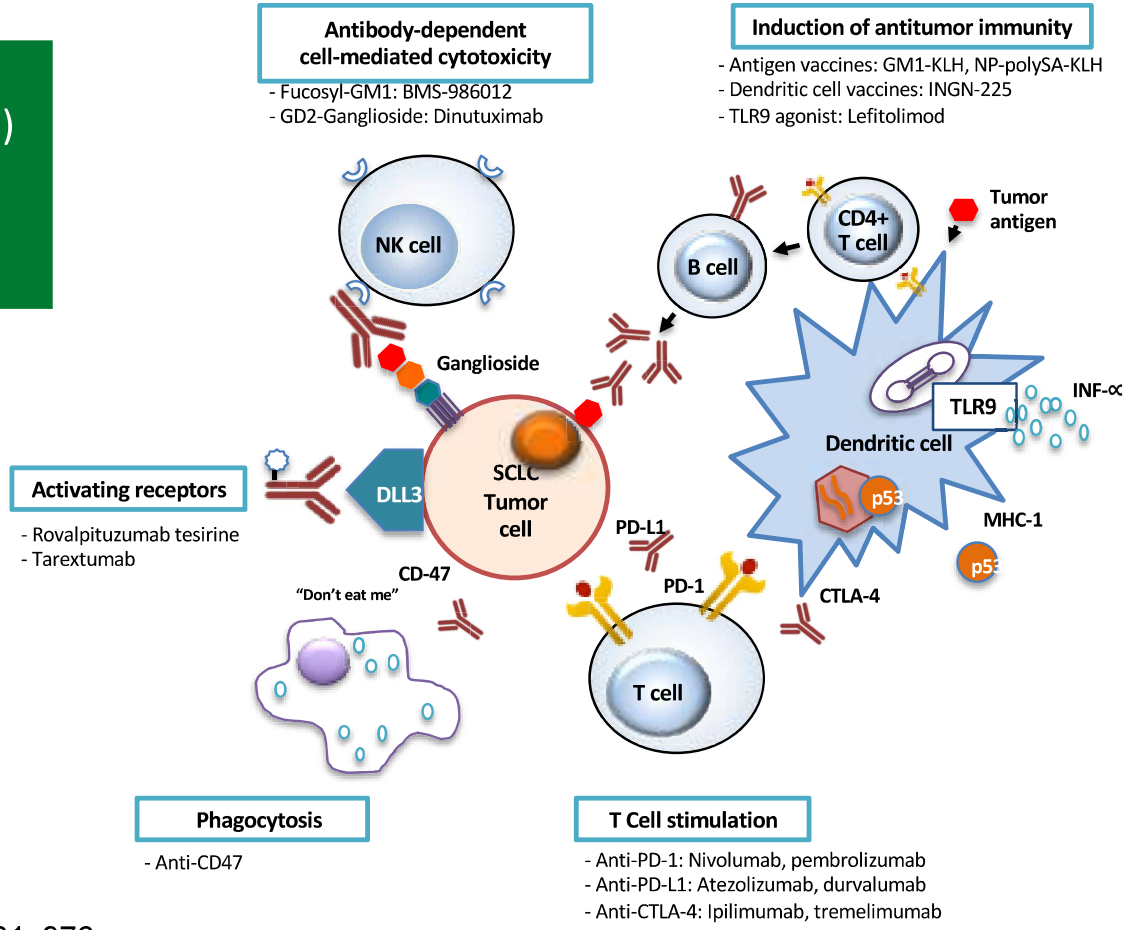
- **Honoraria:** AstraZeneca, Boehringer-Ingelheim, Amgen, Bayer, Pfizer, Roche, Novartis, Takeda, Sanofi/Regeneron, Merck KGaA, Merck Sharp & Dohme, and Bristol-Myers Squibb.
- **Consulting or advisory role:** AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche/Genentech, Eli Lilly and Company, Novartis, Takeda, Merck Sharp & Dohme, and Bristol-Myers Squibb.
- **Research grants**: Merck Sharp & Dome, Pfizer.
- **Travel financial support**: Roche, Boehringer-Ingelheim, Merck Sharp & Dohme, and Bristol-Myers Squibb.
- **Stock Ownership:** None

OUTLINE

- Immune checkpoint inhibitors
- Bi-specific antibodies
- T-cell engagers
- CAR-T cell therapies

SELECTED TYPES OF IMMUNOTHERAPY FOR SCLC

Immune landscape of SCLC:
- High TMB (smoking signature)
- Low PD-L1 expression
- HLA downregulation
- Cold TME

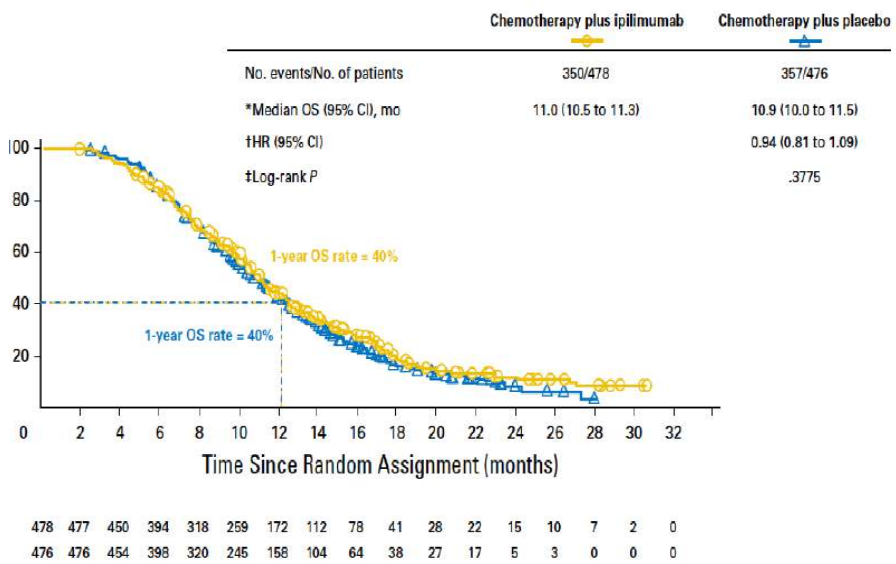


Calles A et al, *Clinical Transl Oncol.* 2019;21:961–976.

NEGATIVE PHASE 3 STUDIES OF ANTI-CTLA4 IPILIMUMAB IN ES-SCLC

CA184-516

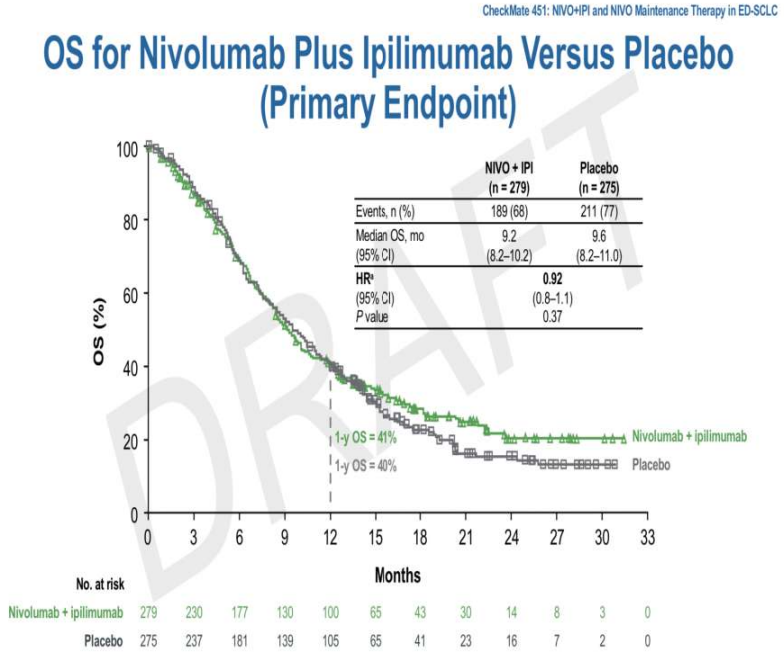
1st line, plus PE



No difference in OS (11 vs 10.9 months)
No difference in PFS (4.6 vs 4.4 months)

CheckMate 451

Maintenance, after PE

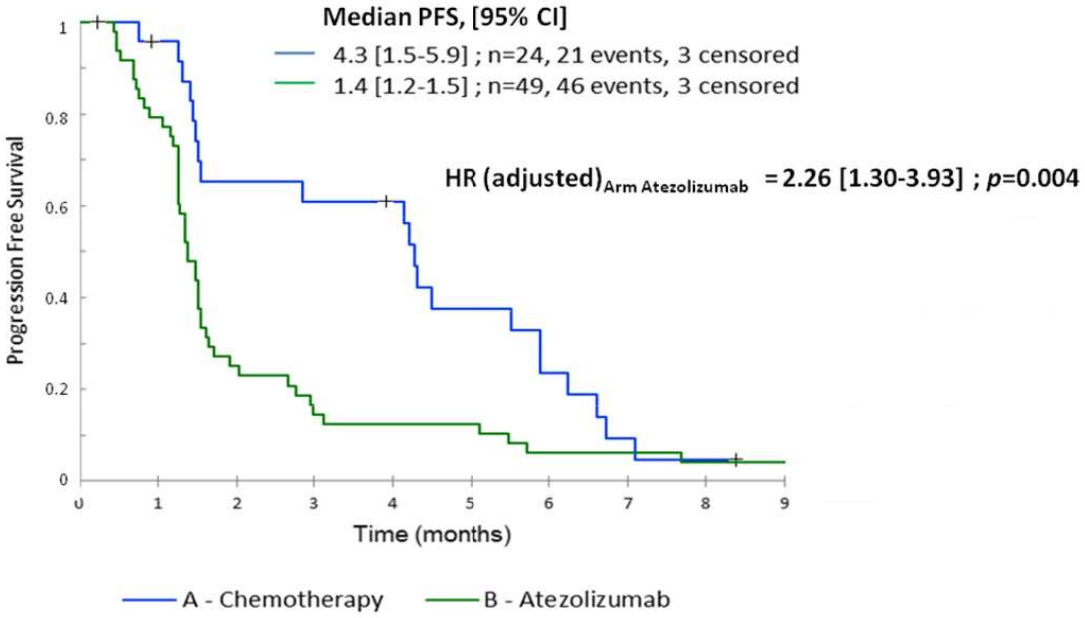


1L = first-line; CT = chemotherapy; CRT = chemoradiation therapy; CTLA-4 = cytotoxic T lymphocyte antigen-4; PD-1 = programmed-death 1; PD-L2 = PD ligand 2
PLT = platinum-based; [a]Where locally approved

Reck, JCO 2016; Owonikoko JCO 2021

NEGATIVE SINGLE AGENT PD(L)-1 ICI VS CHEMOTHERAPY IN 2L SCLC

IFCT 1603



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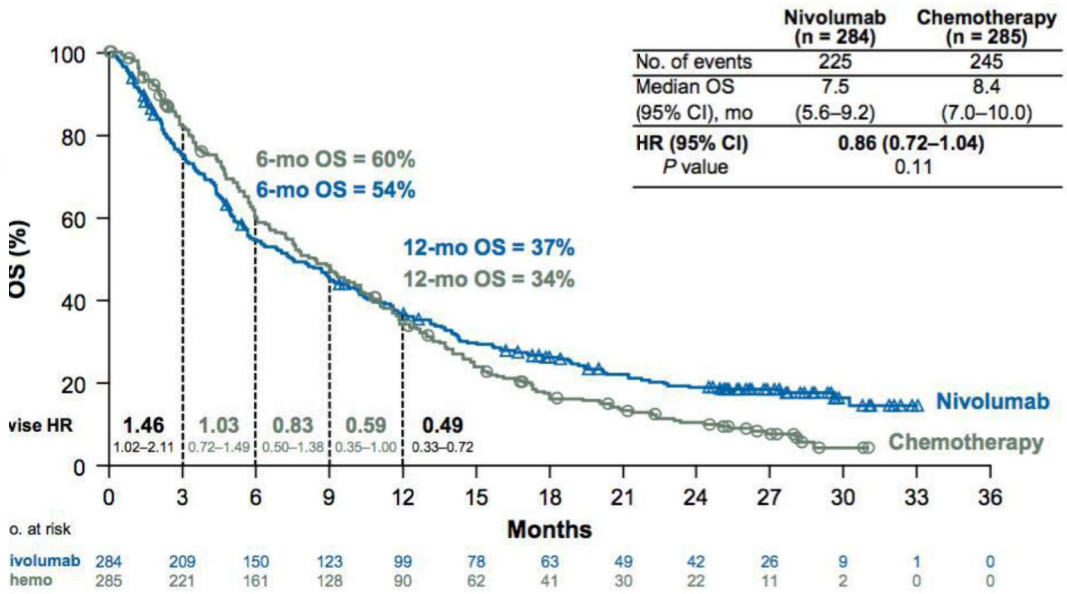


	Nivolumab (n = 284)	Chemotherapy (n = 285)
No. of events	225	245
Median OS	7.5	8.4
(95% CI), mo	(5.6–9.2)	(7.0–10.0)
HR (95% CI)	**0.86 (0.72–1.04)**	
P value	0.11	

1L = first-line; CT = chemotherapy; CRT = chemoradiation therapy; CTLA-4 = cytotoxic T lymphocyte antigen-4; PD-1 = programmed-death 1; PD-L2 = PD ligand 2
PLT = platinum-based; [a]Where locally approved

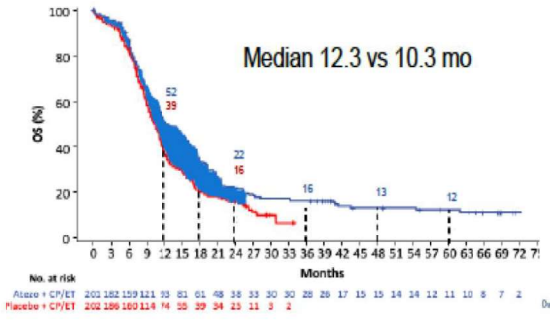
Pujol JL *et al. J Thorac Oncol* 2019;14:903–913

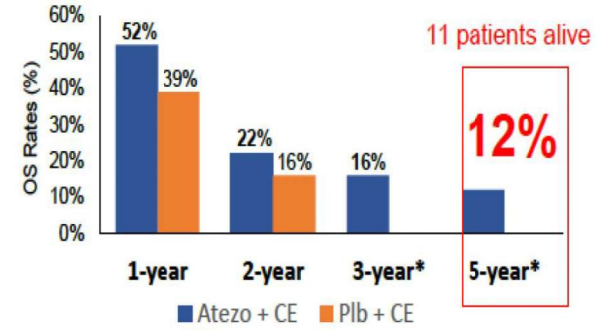
PH3 RCT ADDING ANTI-PD-L1 TO CHEMOTHERAPY IN 1L ED-SCLC

MODEST BUT CONSISTENT LONG-TERM BENEFIT

IMpower133 and IMbrella A

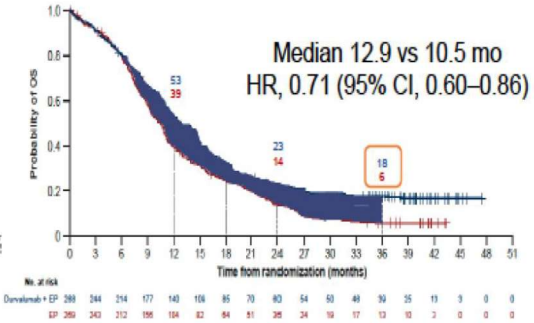
Atezolizumab + CP/ET vs CP/ET + Plb[1-2]

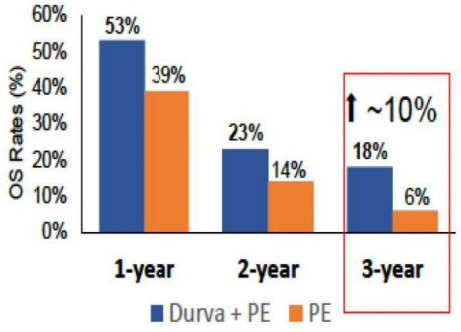




CASPIAN

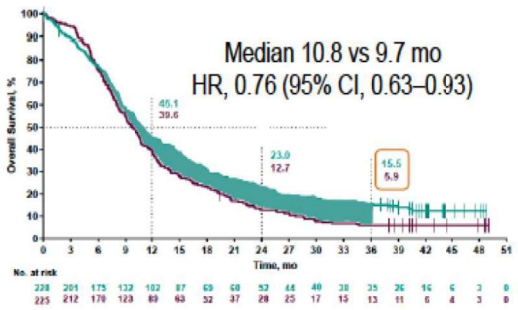
Durvalumab + P/ET vs P/ET[3-4]

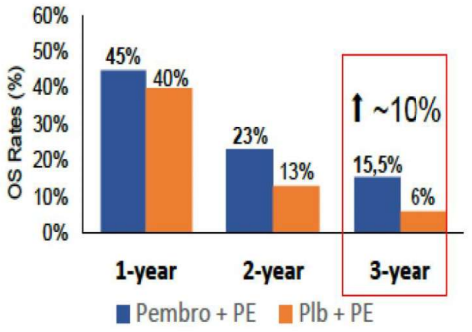




KEYNOTE-604

Pembrolizumab + P/ET vs P/ET + Plb[5-6]



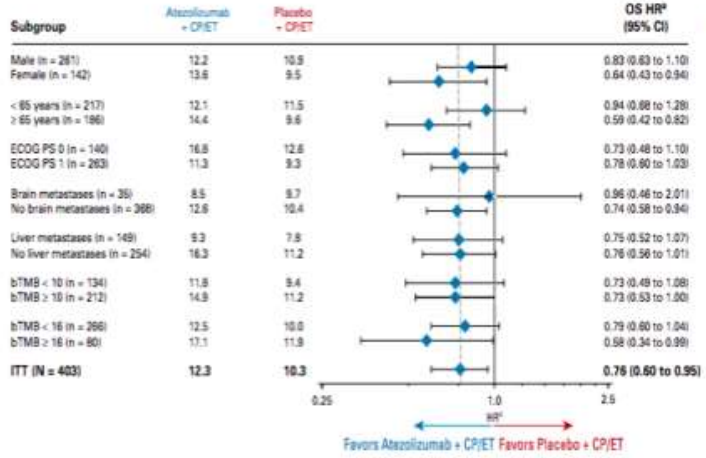


CP, carboplatin; ET, etoposide; P, platinum; Plb, placebo; NE, not estimable. * OS rates at 3-5 years were not estimable in the control arm as rollover to IMbrella A was not permitted.

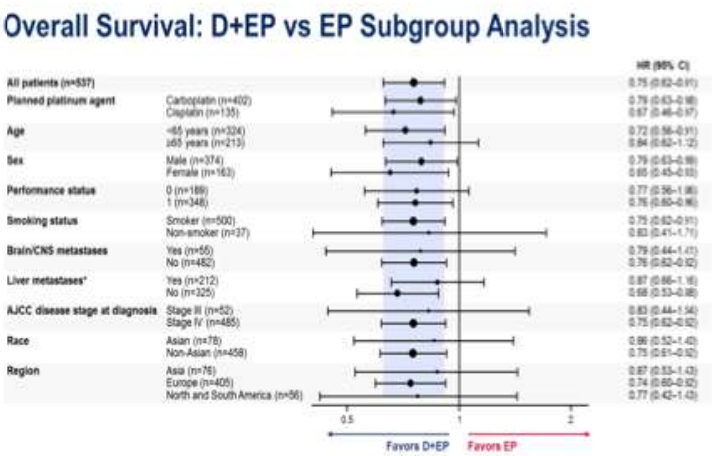
1.- Horn L, et al. N Engl J Med 2018; 2.- Liu S, et al. OA01.04, WCLC 2023; 3.- Paz-Ares L, et al. Lancet 2019; 4.- Paz-Ares L, et al. ESMO Open 2022; 5.- Rudin CM, et al. J Clin Oncol 2020; 6.- Rudin CM, et al. WCLC 2022

PH3 RCT ADDING ANTI-PD-L1 TO CHEMOTHERAPY IN 1L ED-SCLC

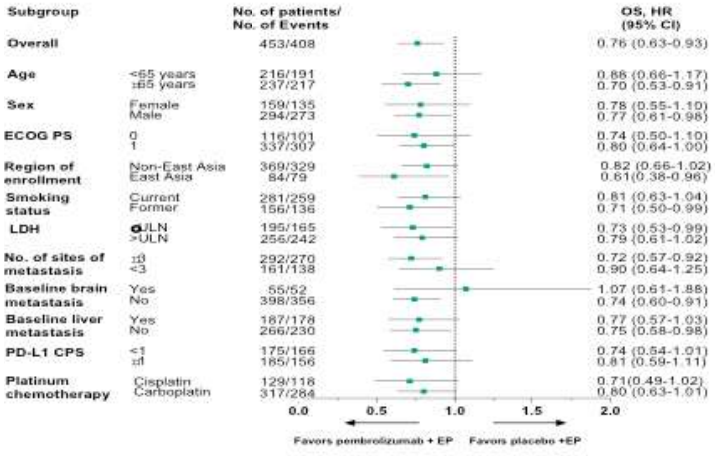
Subgroup analysis



IMpower133



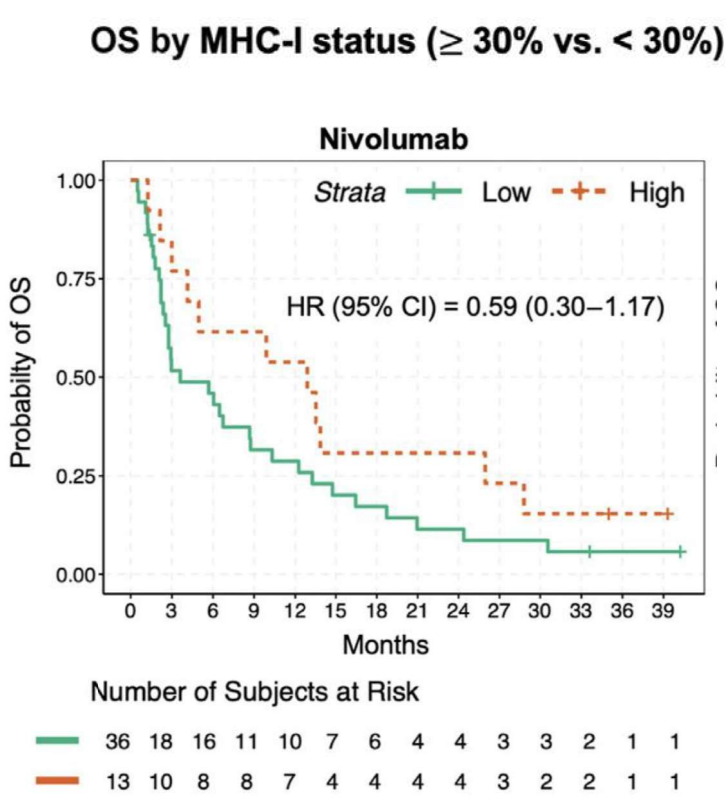
CASPIAN

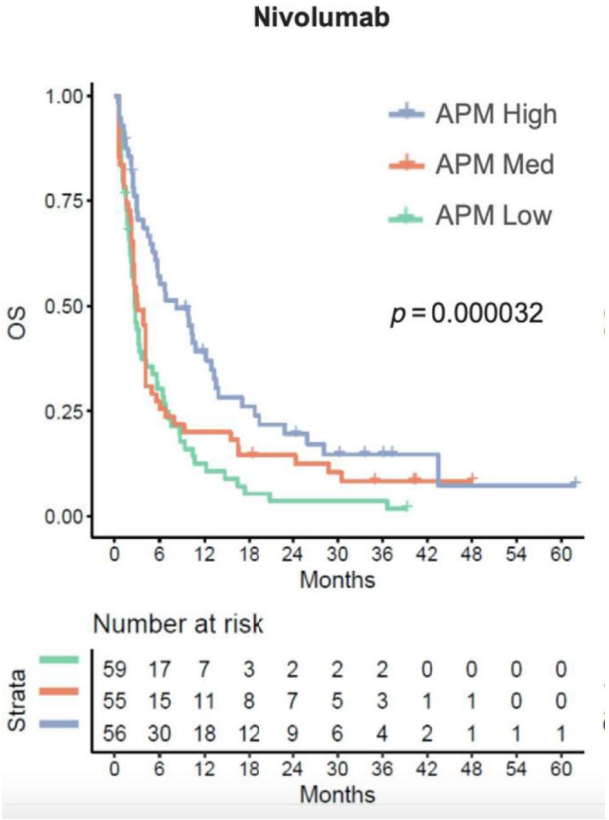


KEYNOTE-604

- ✓ No subgroup obtained a more sustained benefit from the combination
- ✓ Prolonged OS in patients w/o brain mets or liver mets (prognostic factor)

ANTIGEN PROCESSING MACHINERY AND PRESENTATION IS CRITICAL FOR DURABLE BENEFIT WITH ICI

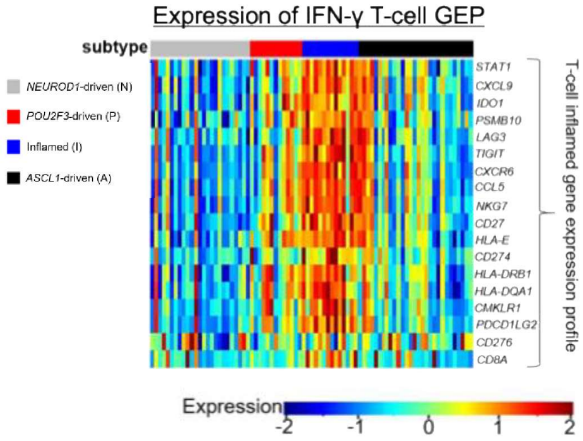


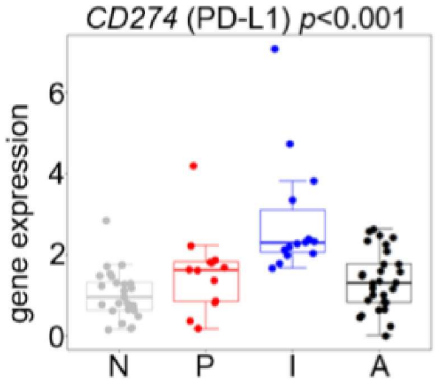


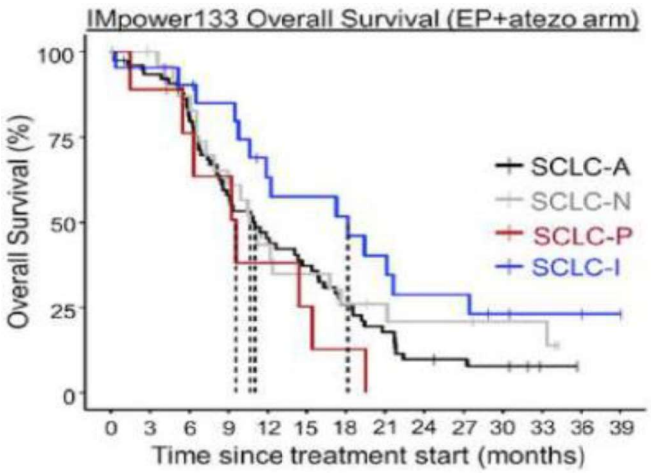
Rudin , et al. JTO 2023

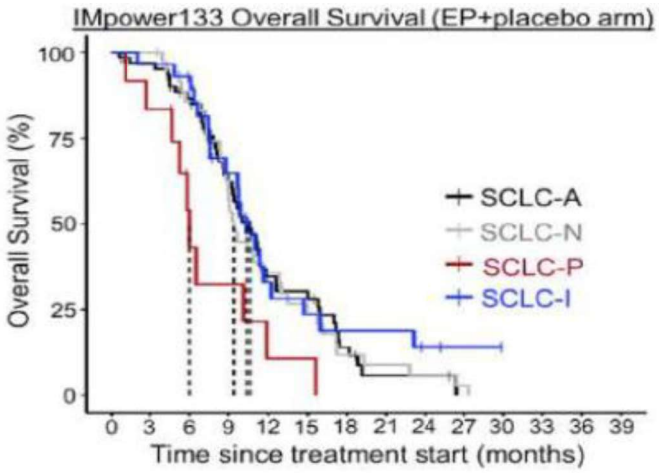
INFLAMED SCLC SUBTYPE IS PREDICTIVE OF ICI BENEFIT

- SCLC-I → Inflamed subgroup (≃14%)
- Defined by low transcriptional expression of ASCL1, NEUROD1, POU2F3
- Uniquely expressed genes (immune checkpoints, INF-g signatures and HLAs)

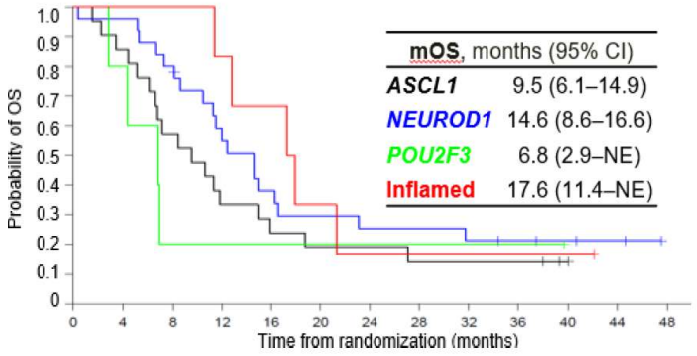






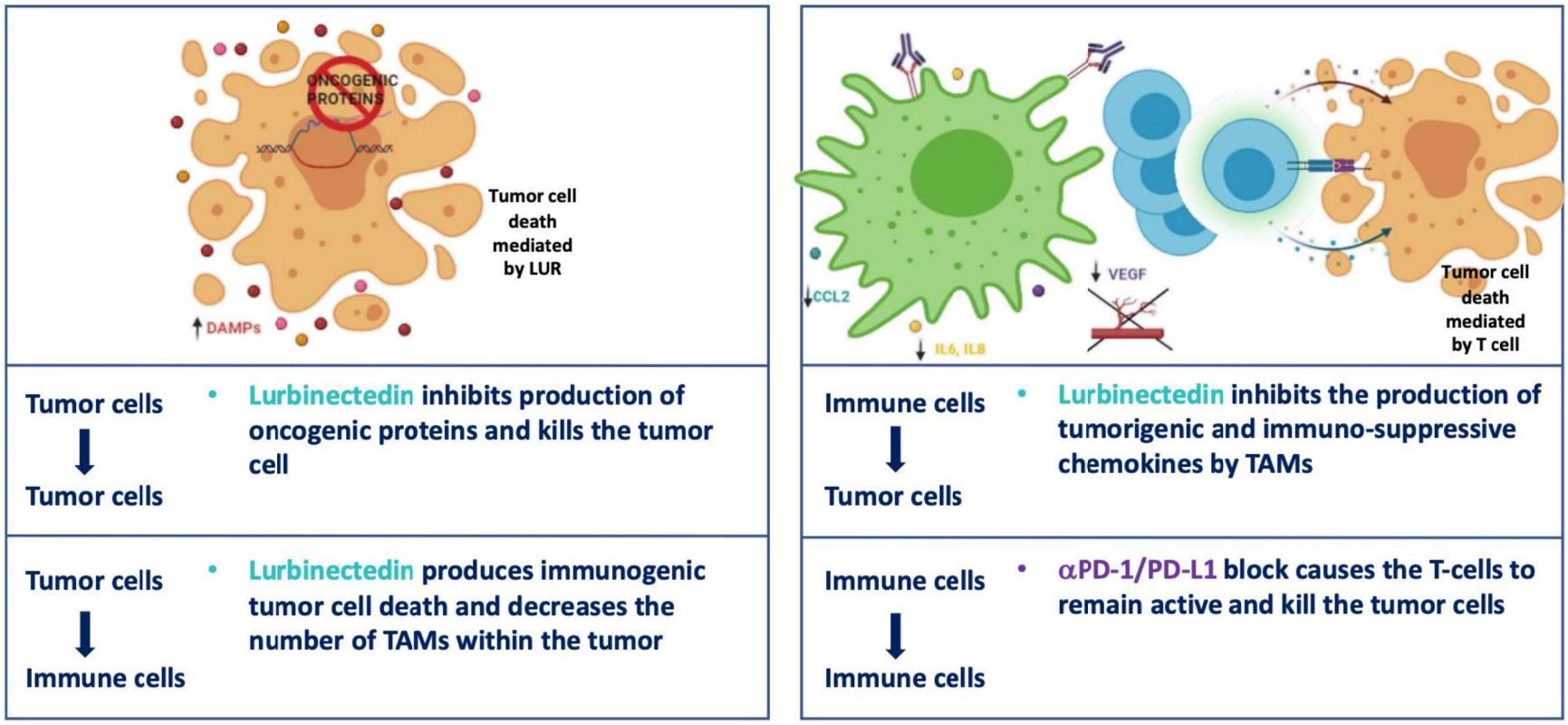


CASPIAN: durvalumab + EP arm[2]



Gay et al. Cancer Cell 2021 Xie M, et al. AACR 2022

SYNERGISTIC ACTION OF LURBINECTEDIN + APD-1/PD-L1 : RATIONALE



Tumor Cell Death and Immune Response

Calles A et al, *Mol Can Ther.* 2025;24:828–839.

2SMALL Phase I-II

Atezolizumab + Lurbinectedin

OBJECTIVES

The primary objective of Phase I part was to determine the safety profile, the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II studies of LUR in combination with ATZ in advanced SCLC patients progressing after platinum double chemotherapy.

Additional efficacy objectives included the Overall Response Rate (ORR) and the Progression Free Survival (PFS) analysis.

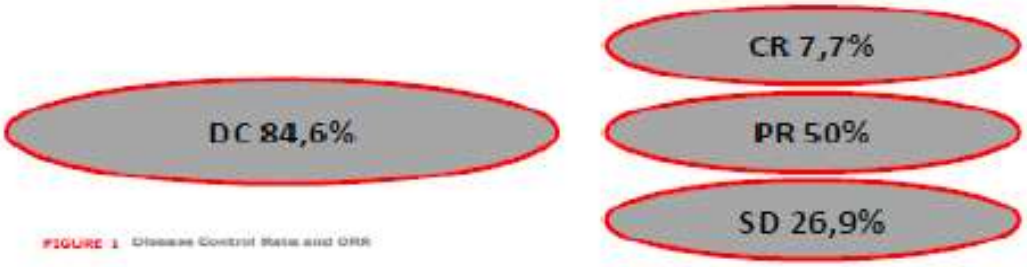


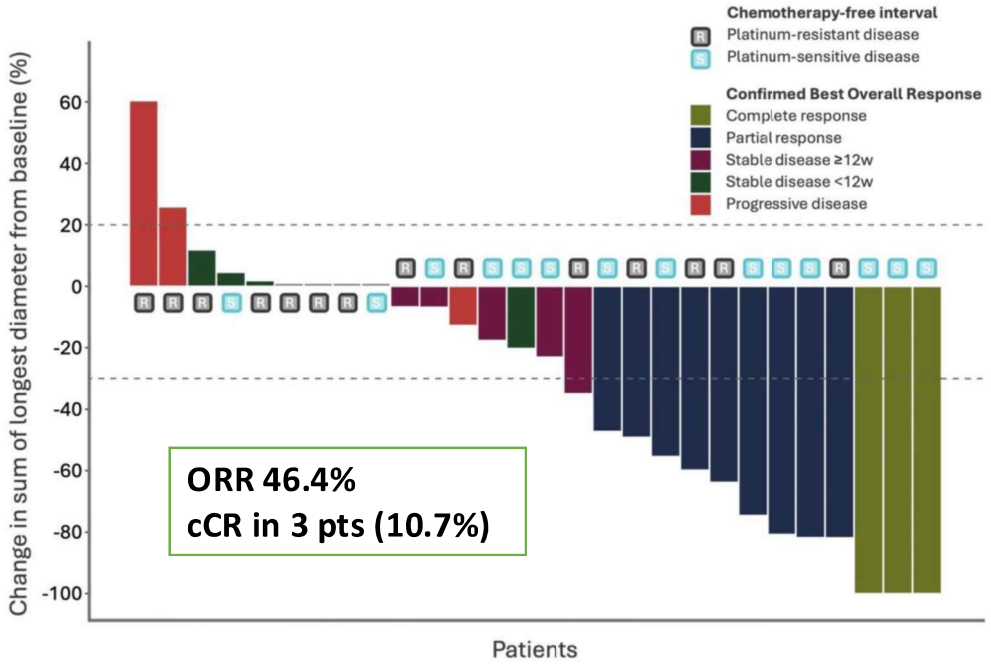
FIGURE 1 Disease Control Rate and ORR

mPFS 4.47

Ponce SITC 2021

LUPER Phase I-II

Pembrolizumab + Lurbinectedin

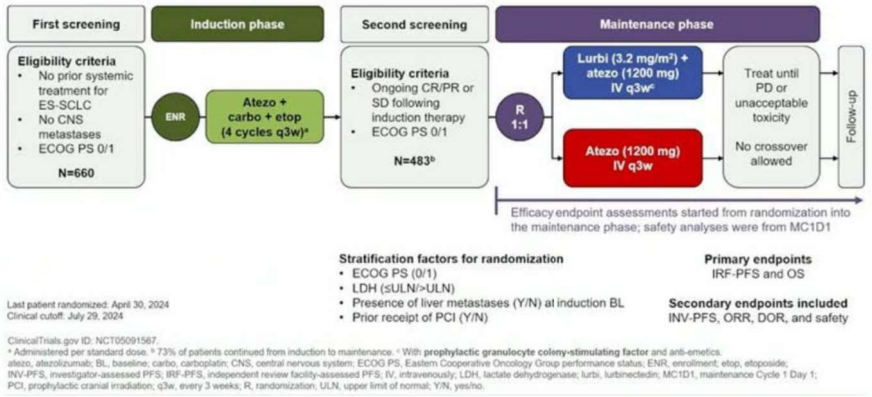


mPFS 5.3mo (10 vs 3 months in CTFI >90d vs <90d)

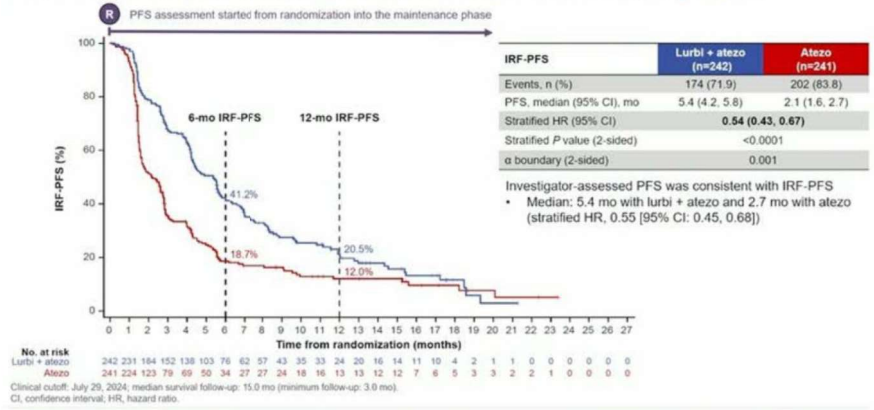
Calles J Thor Oncol 2025

IMFORTE TRIAL: MAINTENANCE LURBINECTEDIN + ATEZOLIZUMAB IMPROVES SURVIVAL

IMforte study design



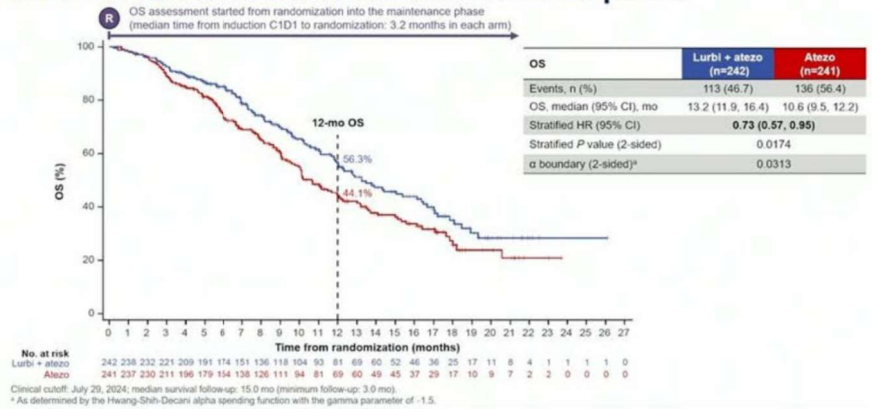
IRF-PFS from randomization into maintenance phase



IRF-PFS	Lurbi + atezo (n=242)	Atezo (n=241)
Events, n (%)	174 (71.9)	202 (83.8)
PFS, median (95% CI), mo	5.4 (4.2, 5.8)	2.1 (1.6, 2.7)
Stratified HR (95% CI)	**0.54 (0.43, 0.67)**	
Stratified *P* value (2-sided)	<0.0001	
α boundary (2-sided)	0.001	

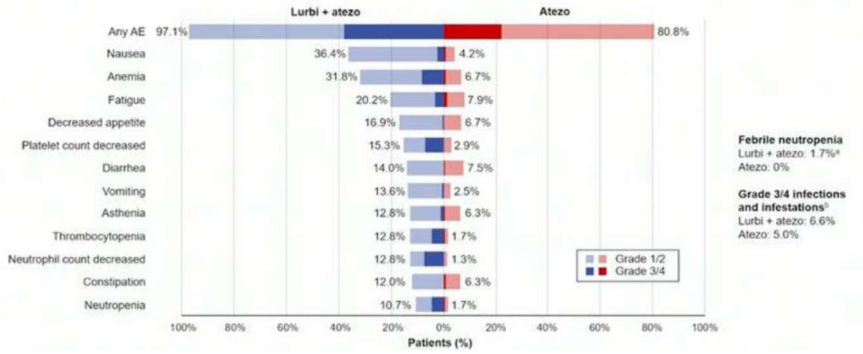
Investigator-assessed PFS was consistent with IRF-PFS
- Median: 5.4 mo with lurbi + atezo and 2.7 mo with atezo (stratified HR, 0.55 [95% CI: 0.45, 0.68])

OS from randomization into maintenance phase



OS	Lurbi + atezo (n=242)	Atezo (n=241)
Events, n (%)	113 (46.7)	136 (56.4)
OS, median (95% CI), mo	13.2 (11.9, 16.4)	10.6 (9.5, 12.2)
Stratified HR (95% CI)	**0.73 (0.57, 0.95)**	
Stratified *P* value (2-sided)	0.0174	
α boundary (2-sided)[a]	0.0313	

All-cause AEs with incidence ≥10% in either arm

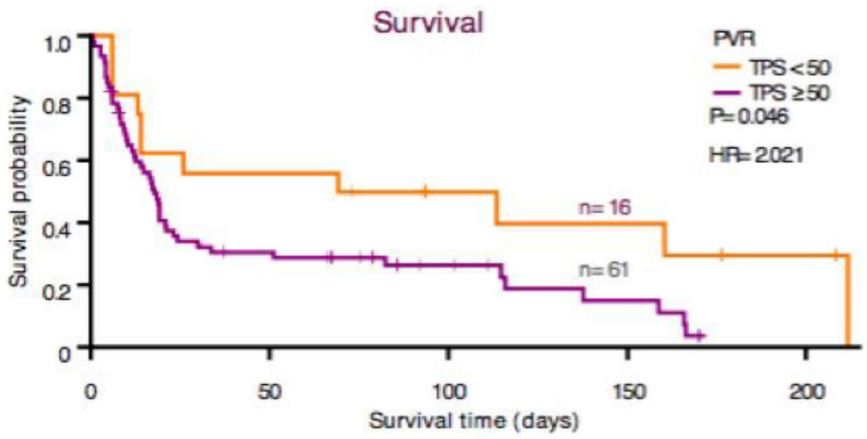


Febrile neutropenia
Lurbi + atezo: 1.7%[a]
Atezo: 0%

Grade 3/4 infections and infestations[b]
Lurbi + atezo: 6.6%
Atezo: 5.0%

Paz-Ares, L et al. ASCO 2025; Paz-Ares, L et al. *The Lancet* 2025

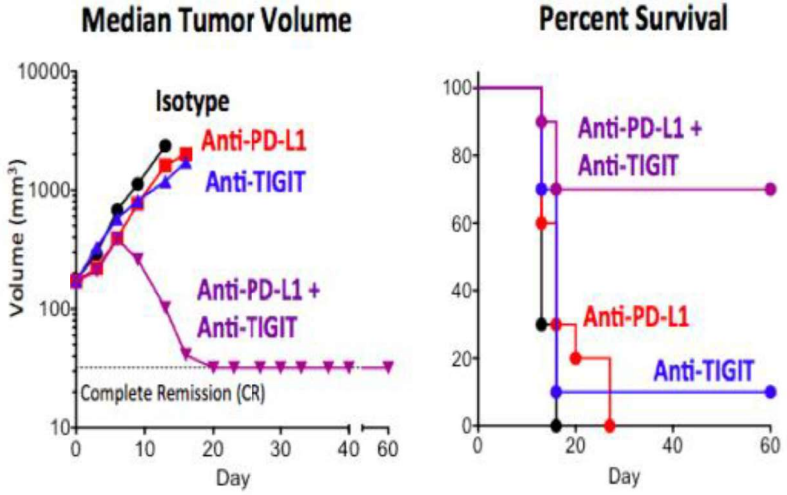
TIGIT IS AN INHIBITORY RECEPTOR EXPRESSED ON T CELLS & NK CELLS AND PVR-TIGIT IS HIGHLY EXPRESSED IN SCLC SAMPLES



- ✓ 77 tumor SCLC samples (mRNA & IHC)
- ✓ PVR broadly expressed in SCLC samples and associated with worse prognosis

In preclinical mouse models, combination treatment with anti-TIGIT and anti-PD-L1 antibodies synergistically improves tumor control and prolongs survival

CT26 Preclinical Model



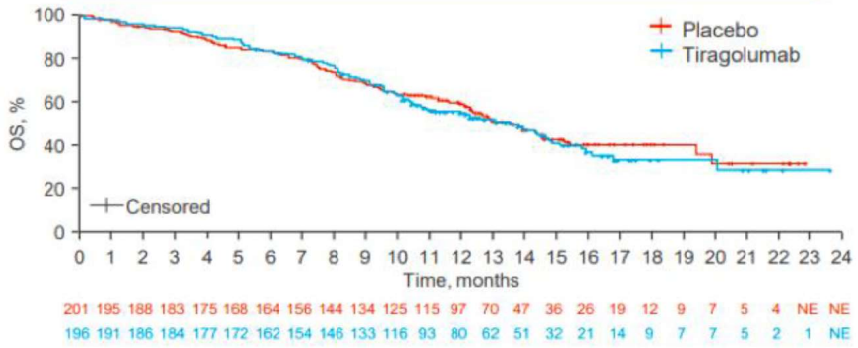
Yu AACR 2018; Johnston Cancer Cell 2014

ANTI-TIGIT ADDED TO CHEMO+IO FAILED TO IMPROVE SURVIVAL IN 1L ES-SCLC

SKYSCRAPER-02 (n=490)

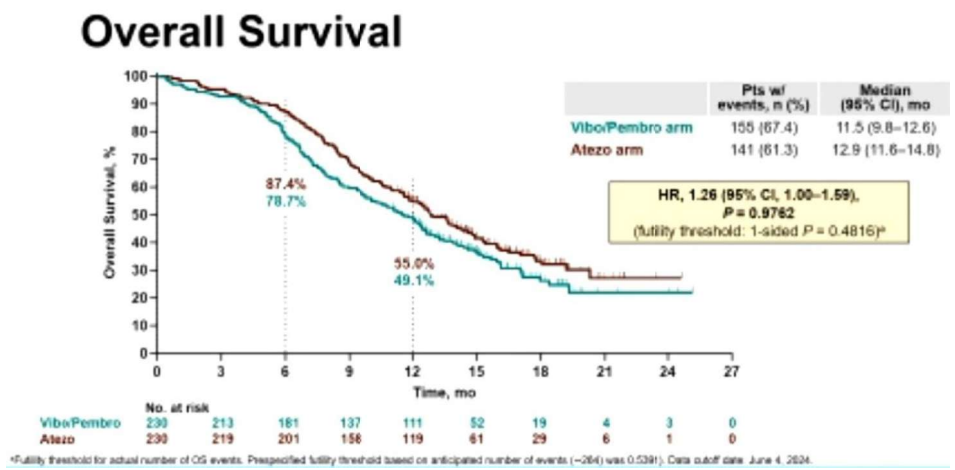
ACE + Tiragolumab/placebo

	Tiragolumab + atezolizumab + CE (n=196)	Placebo + atezolizumab + CE (n=201)
Events, n (%)	107 (54.6)	105 (52.2)
mOS, mo (95%CI)	13.6 (10.8, 14.9)	13.6 (12.3, 15.2)
HR[a] (95%CI); p-value	1.04 (0.79, 1.36); 0.7963	



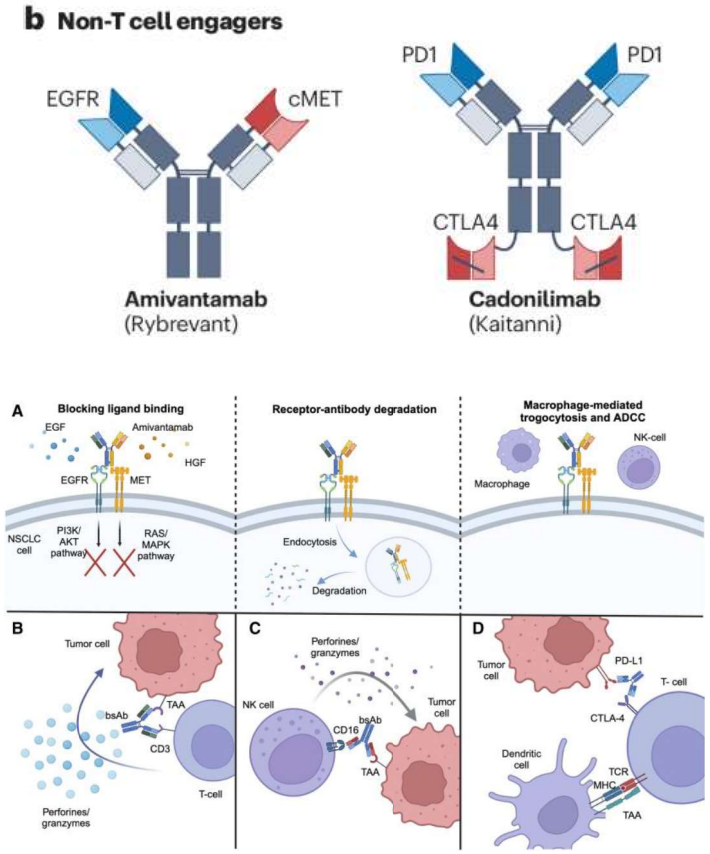
KeyVibe-008 (n=460)

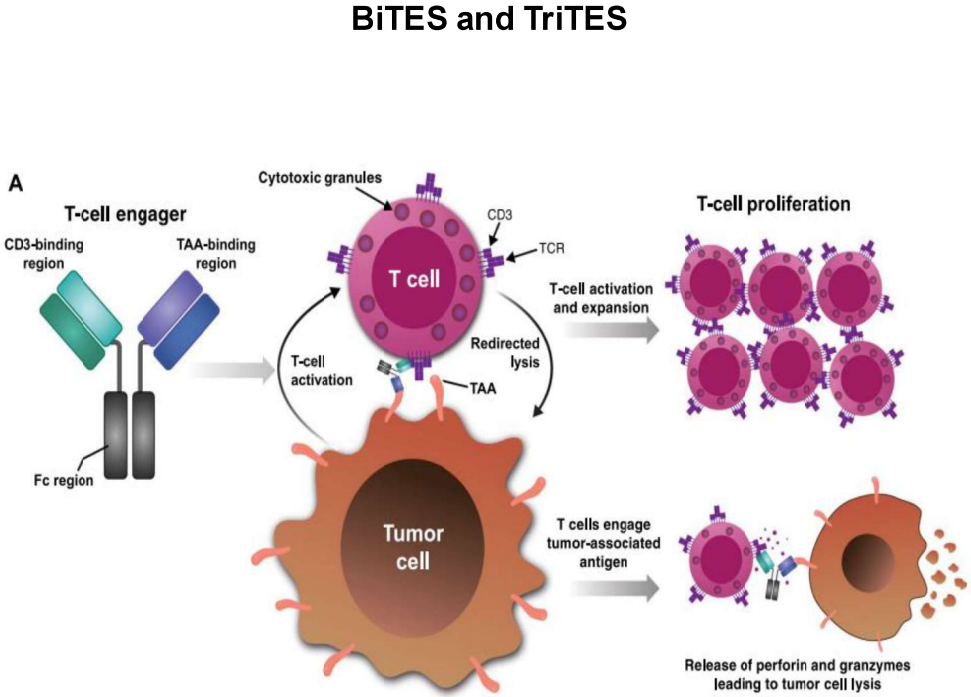
Vibostolimab + Pembro + CE vs ACE



Rudin C, et al. *J Clin Oncol* 2024; Sands J, et al. STIC 2024

BISPECIFICS AND TCE IN ES-SCLC: BACKGROUND

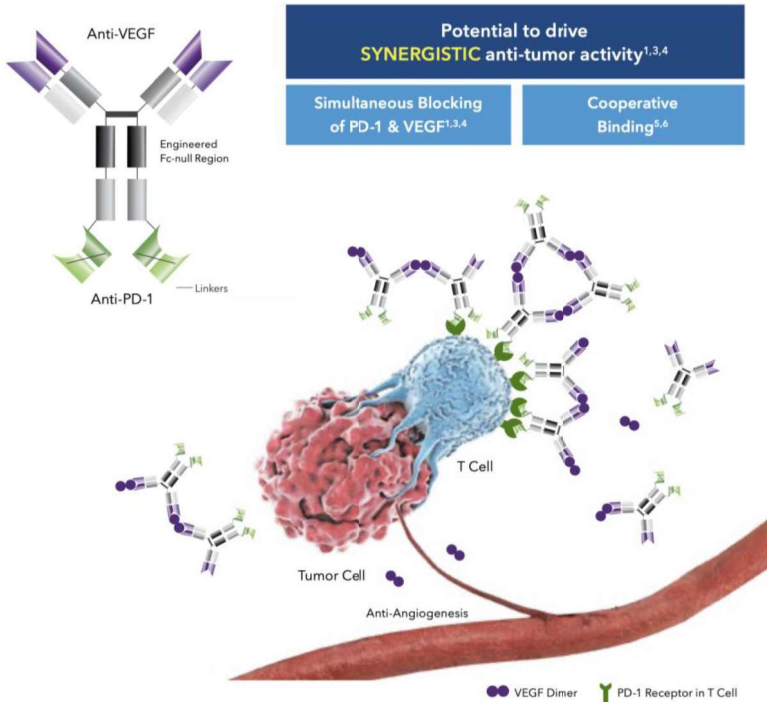




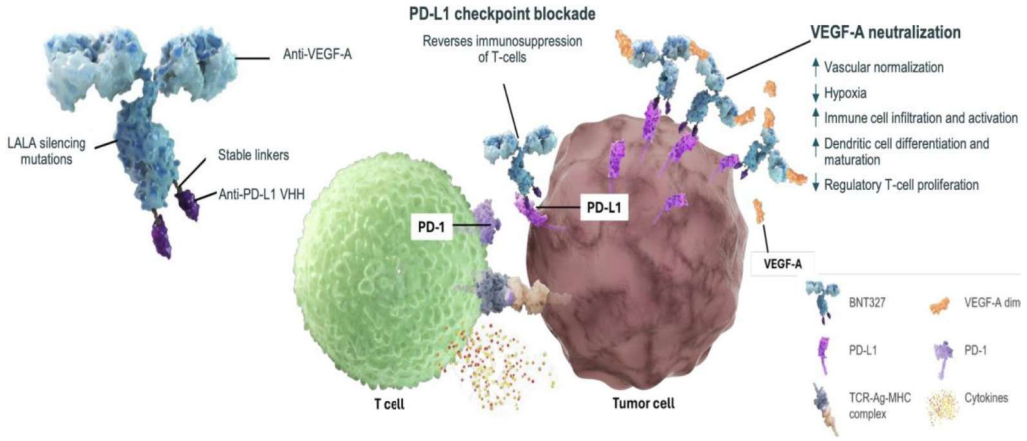
Guidi. ASCO Ed Book 2025; Fu, et al. Sig Transduct Target Ther 2022; Rudin et al. Mol Oncol 2023

PD-L1XVEGF BI-SPECIFICS IN ES-SCLC

Ivonescimab (AK112)

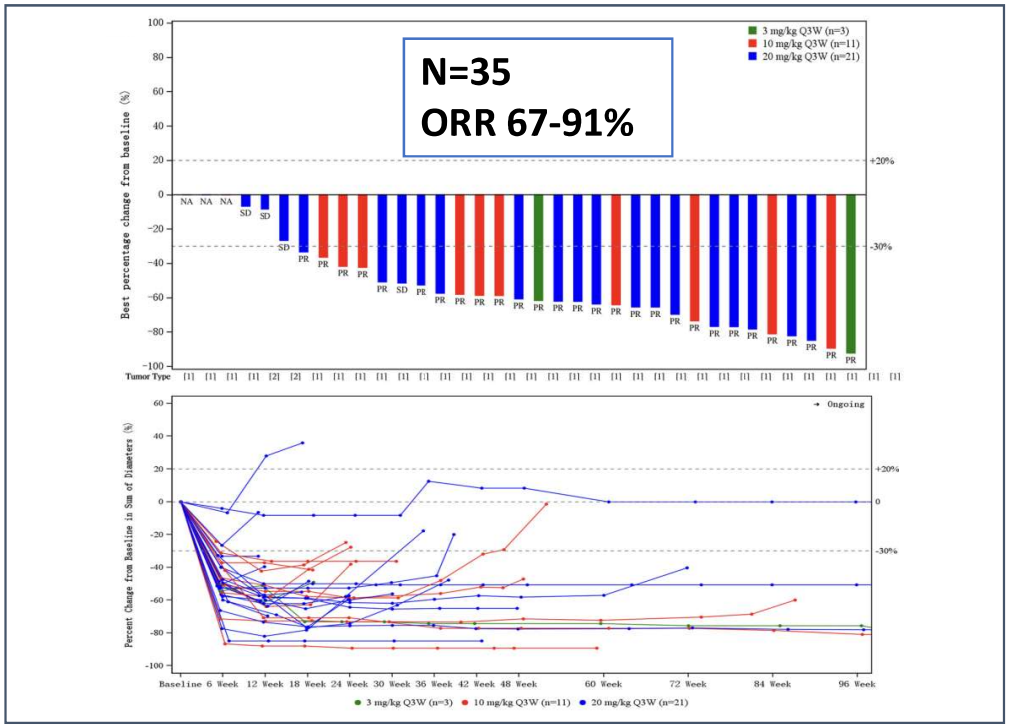


Ph2 Pumitamig (BNT 327)



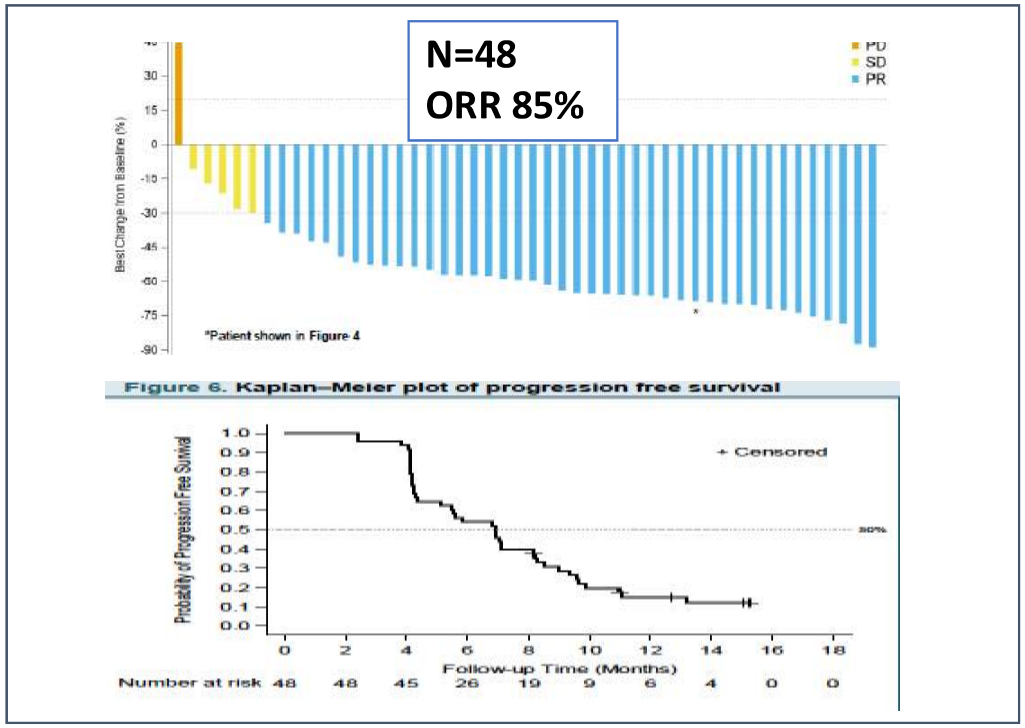
NOVEL PD-L1XVEGF BI-SPECIFICS SHOW PROMISE IN SCLC

Ph 1b Ivonescimab (AK112) + CE



Ph II with CE-cadonilimab-ivonescimab planned (NCT06620796)

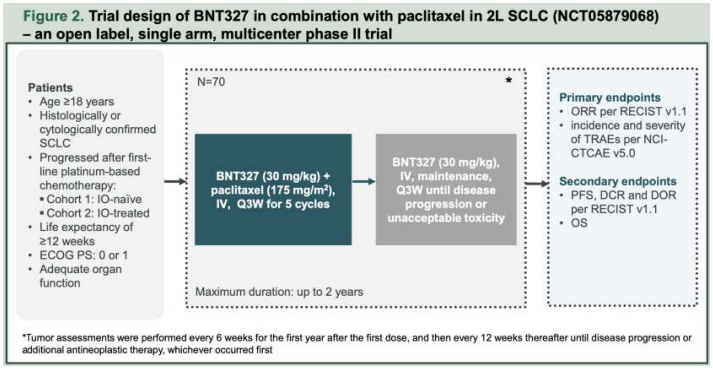
Ph2 Pumitamig (BNT 327) + CE

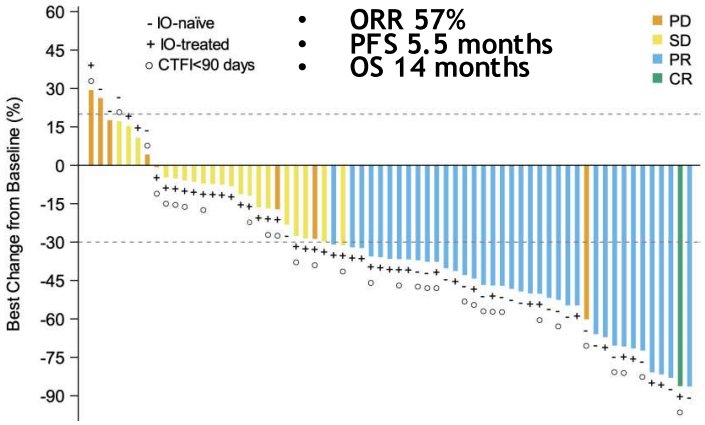


Phase III trial planned comparing BNT327 + CE vs ACE (NCT06712355)

Chen Z, et al. *J Thorac Oncol* 2025; Cheng Y, et al. ELCC 2025

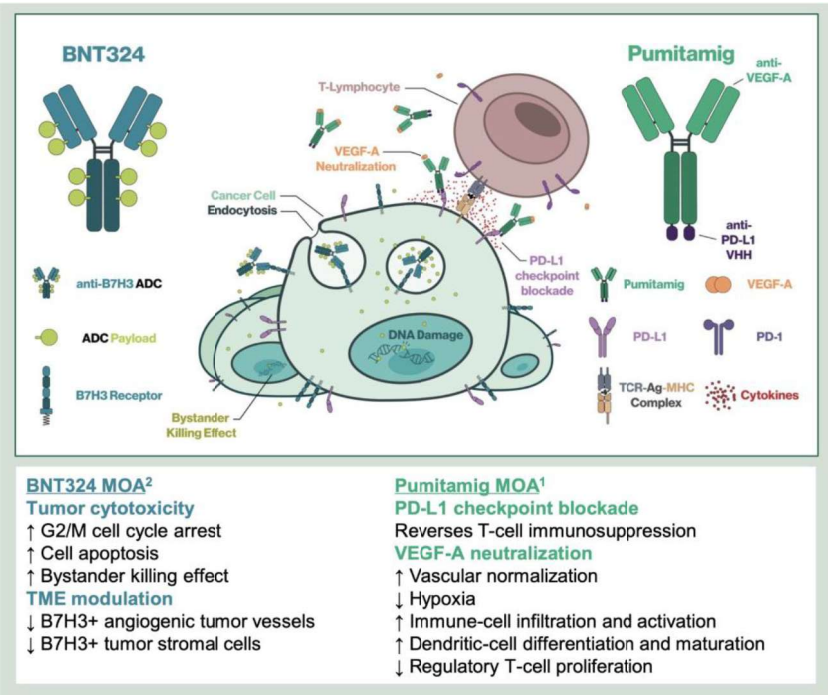
PUMITAMIG: PD-L1XVEGF COMBINATIONS IN SCLC





- ORR 57%
- PFS 5.5 months
- OS 14 months

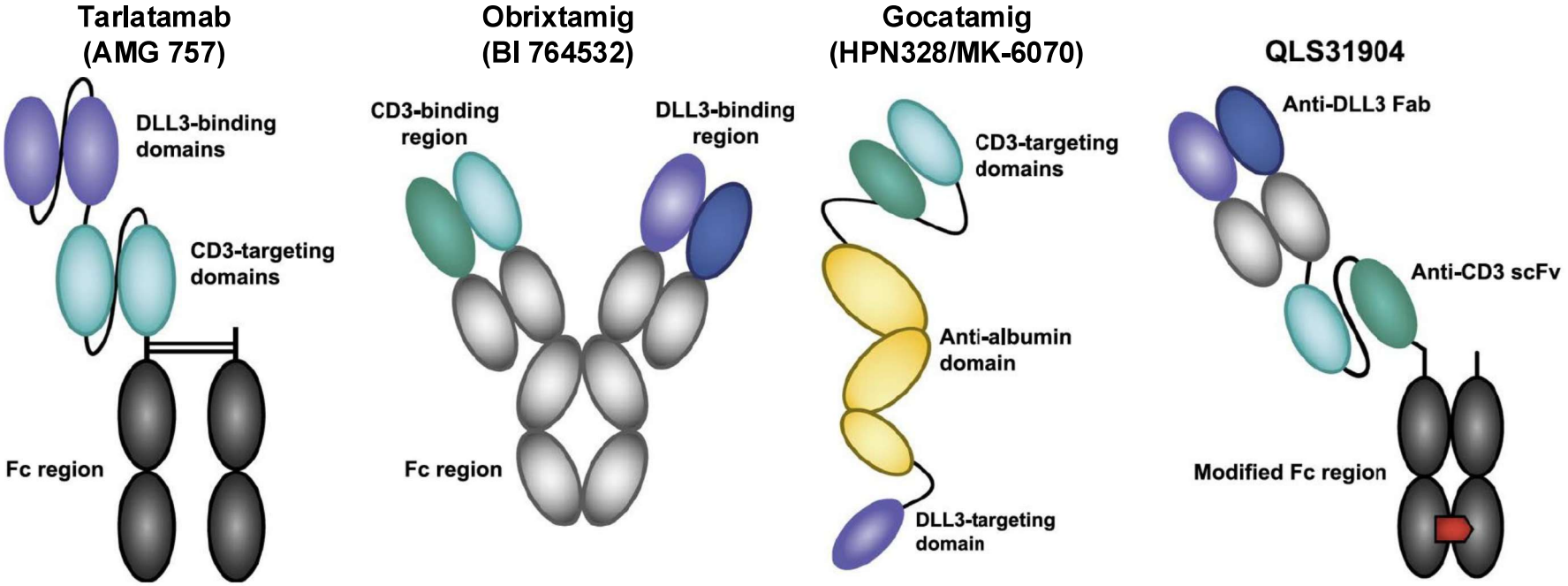
BNT324-01: A Phase 1b/2 Trial of BNT324/DB-1311 (B7H3 ADC) With BNT327 (PD-L1 x VEGF-A bsAb)



- Phase III trial of BNT327 + paclitaxel vs topotecan/paclitaxel in 2L SCLC in China (NCT06616532)

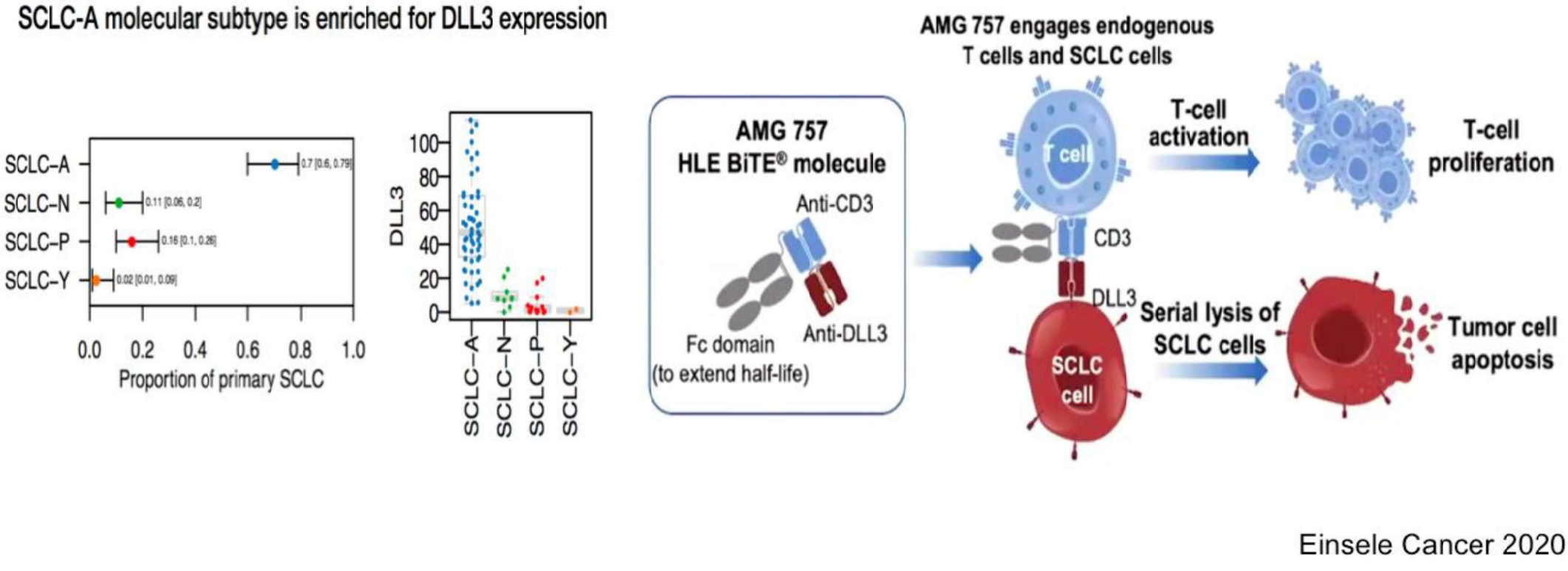
Chen Z, et al. ELCC 2025

OTHER WAYS AROUND THE FAILURE OF ANTIGEN PRESENTATION: DIRECT BINDING WITH BI- OR TRI-SPECIFIC T CELL ENGAGERS



Rudin et al., ***J Hematol Oncol*** 2023

TARLATAMAB (AMG757): A HALF-LIFE EXTENDED BISPECIFIC T-CELL ENGAGER BITE ANTI-DLL3



Einsele Cancer 2020

TARLATAMAB IMPROVES SURVIVAL IN 2L ES-SCLC

Randomized, controlled, phase 3 DeLLphi-304 study (NCT05740566)

DeLLphi 304

Key inclusion criteria
- Histologically or cytologically confirmed SCLC
- Progression after 1L platinum-based chemotherapy +/- anti-PD-(L)1
- ECOG PS 0 or 1
- Asymptomatic, treated or untreated brain metastases

Randomization stratified by
- Prior anti-PD-(L)1 exposure (yes/no)
- Chemotherapy-free interval (< 90 days vs ≥ 90 to < 180 days vs ≥ 180 days)
- Presence of (previous/current) brain metastases (yes/no)
- Intended chemotherapy (topotecan/amrubicin vs lurbinectedin)

R 1:1 (N = 509)

- Tarlatamab (n = 254)
- Chemotherapy* (n = 255)

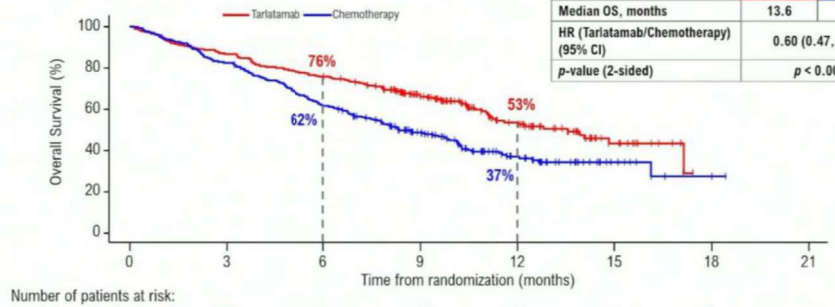
Topotecan (n = 185); Lurbinectedin (n = 47); Amrubicin (n = 23)

Primary Endpoint: Overall survival
Key Secondary Endpoints: Progression-free survival, patient-reported outcomes
Other Secondary Endpoints: Objective response, disease control, duration of response, safety

*Topotecan was used in all countries except Japan, lurbinectedin in Australia, Canada, Republic of Korea, Singapore and the United States, and amrubicin in Japan.
1L, first-line; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **PD-(L)1**, programmed death (ligand)-1; **R**, randomization; **SCLC**, small cell lung cancer.

DeLLphi-304 met its primary endpoint with tarlatamab demonstrating superior overall survival over chemotherapy

	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median OS, months	13.6	8.3
HR (Tarlatamab/Chemotherapy) (95% CI)	0.60 (0.47, 0.77)	
p-value (2-sided)	*p* < 0.001	

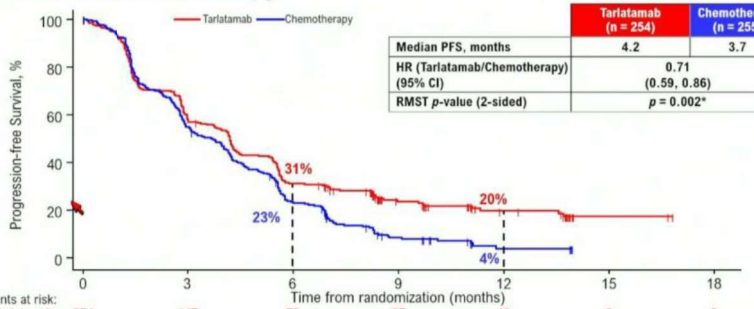


Number of patients at risk:

Tarlatamab	254	220	192	131	60	17	0
Chemotherapy	255	210	156	97	42	9	2	0

Progression-free survival was significantly longer with tarlatamab vs chemotherapy

	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median PFS, months	4.2	3.7
HR (Tarlatamab/Chemotherapy) (95% CI)	0.71 (0.59, 0.86)	
RMST *p*-value (2-sided)	*p* = 0.002*	



Number of patients at risk:

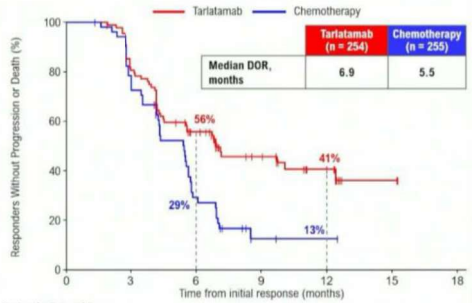
Tarlatamab	254	147	78	37	18	2	0
Chemotherapy	255	137	56	15	3	0	

Tarlatamab was associated with more frequent and more durable responses

	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)

Duration of response

	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median DOR, months	6.9	5.5



Number of patients at risk:

Tarlatamab	89	70	41	22	12	2	0
Chemotherapy	52	40	14	2	1	0	

Rudin, C et al. ASCO 2025; Mountzios, G et al. *N Engl J Med* 2025

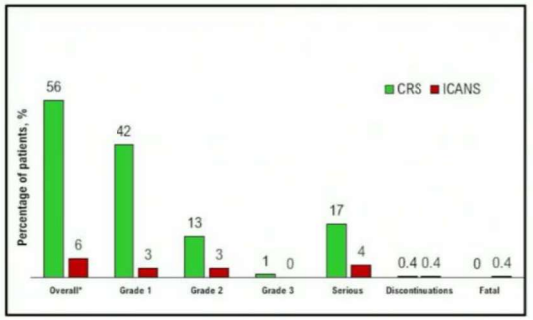
TARLATAMAB SAFETY PROFILE IN 2L ES-SCLC: DELLPHI-304 TRIAL

Tarlatamab had a more favorable safety profile

	Tarlatamab (n = 252)*	Chemotherapy (n = 244)*
Median duration of treatment, months, (range)	4.2 (< 1–17)	2.5 (< 1–15)
All grade, TEAEs, n (%)	249 (99)	243 (100)
All grade, TRAEs n (%)	235 (93)	223 (91)
Grade ≥ 3 TRAEs, n (%)	67 (27)	152 (62)
Serious TRAEs, n (%)	70 (28)	75 (31)
TRAEs leading to dose interruption and/or dose reduction, n (%)	48 (19)	134 (55)
TRAEs leading to discontinuation, n (%)	7 (3)	15 (6)
Treatment-related grade 5 events†, n (%)	1 (0.4)	4 (2)

CRS and ICANS events were consistent with tarlatamab's established safety profile

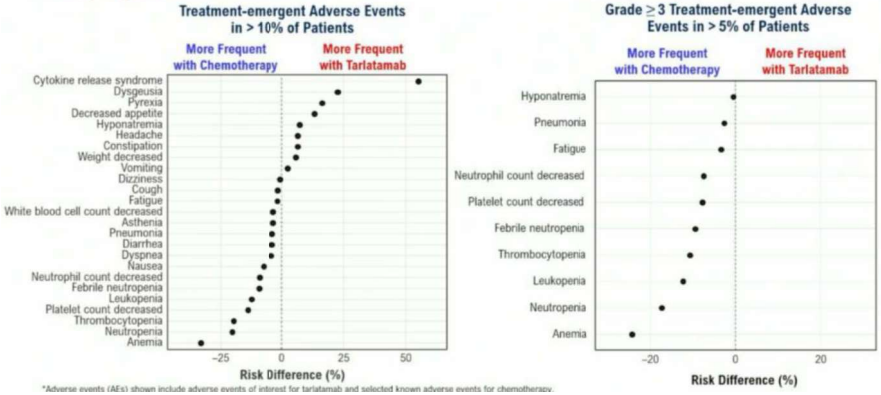
Treatment-emergent CRS and ICANS with tarlatamab



CRS with first two infusions

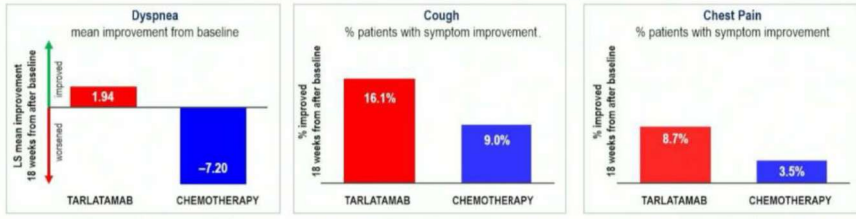
Tarlatamab (N = 252)	Minimum required monitoring duration: 6 - 8 Hours (n = 43)	48 Hours (n = 209)
Treatment emergent CRS, n (%)*	16 (37)	125 (60)
Grade 1	12 (28)	94 (45)
Grade 2	4 (9)	28 (13)
Grade 3	0 (0)	3 (1)
Serious adverse events	3 (7)	39 (19)
Leading to discontinuation of IP	0 (0)	1 (0.5)
Median time to intervention from last tarlatamab dose (hours)	17	27

Patients treated with tarlatamab experienced lower incidence of high-grade AEs



*Adverse events (AEs) shown include adverse events of interest for tarlatamab and selected known adverse events for chemotherapy.

Tarlatamab improved symptoms of dyspnea and cough after 18 weeks from baseline



LS mean difference = -9.14*
95% CI (-12.64, -5.64)
$p < 0.001$

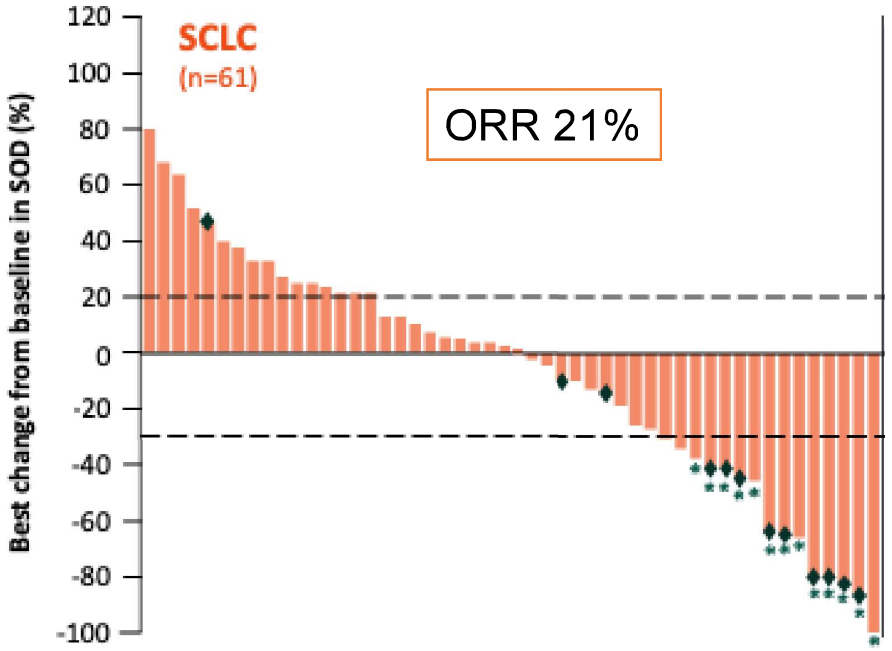
Odds ratio = 2.04*
95% CI (1.17, 3.55)
$p = 0.012$

Odds ratio = 1.84*
95% CI (0.89, 3.81)
$p = 0.1$
(Did not meet statistical significance)

Rudin, C et al. ASCO 2025; Mountzios, G et al. *N Engl J Med* 2025

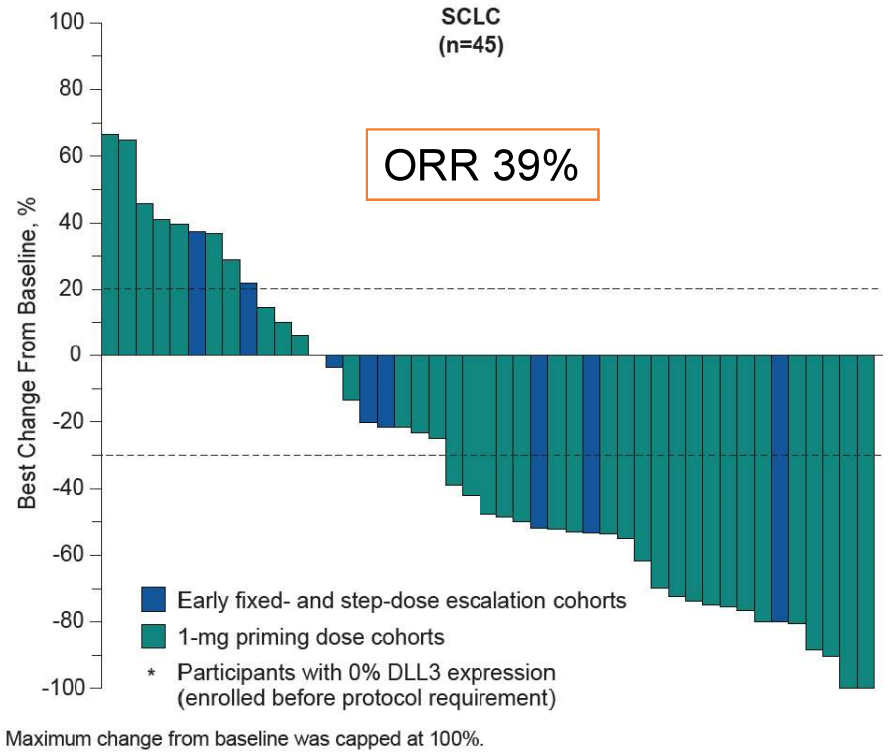
OTHER DLL3/CD3 BITES FOR SCLC

Obrixtamig (BI 764532)



CRS 57% (most G1-2)

Gocatamig (MK 6070; HPN328)

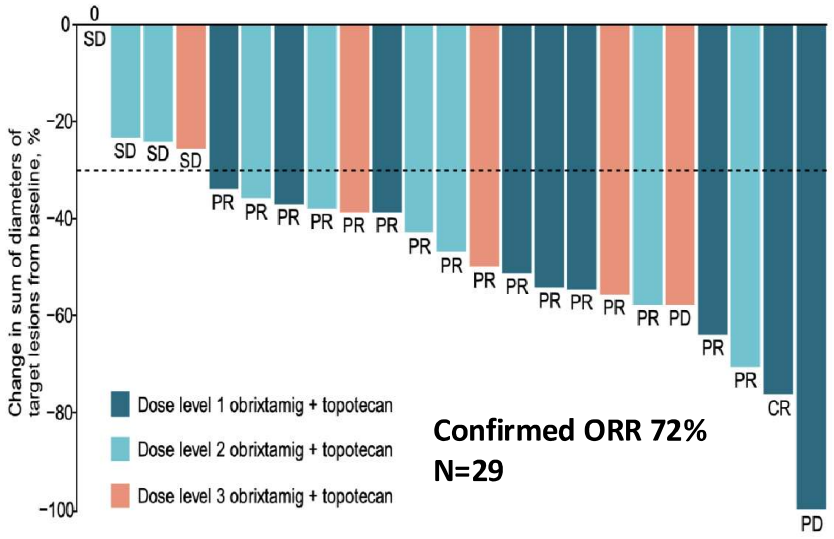


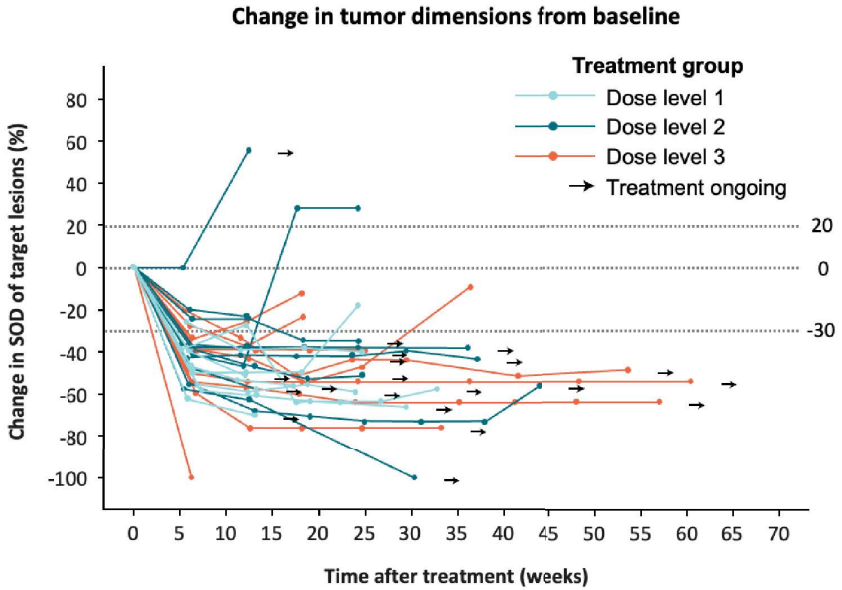
CRS 63% (97% G1-2)

Wermke *J Clin Oncol* 2025 ; Beltran ASCO 2024

DLL3 BITES IN THE RELAPSED/REFRACTORY SETTING: COMBINATIONS

- DAREON-9: Obrixtamig + topotecan *(NCT05990738)*
- MK-6070-002: Gocatamig (MK-6070) + Ifinatamab Deruxtecan (I-DXd) *(NCT06780137)*
- DeLLphi-310: Tarlatamab + YL201 (B7H3 ADC) +/- ICI *(NCT06898957)*





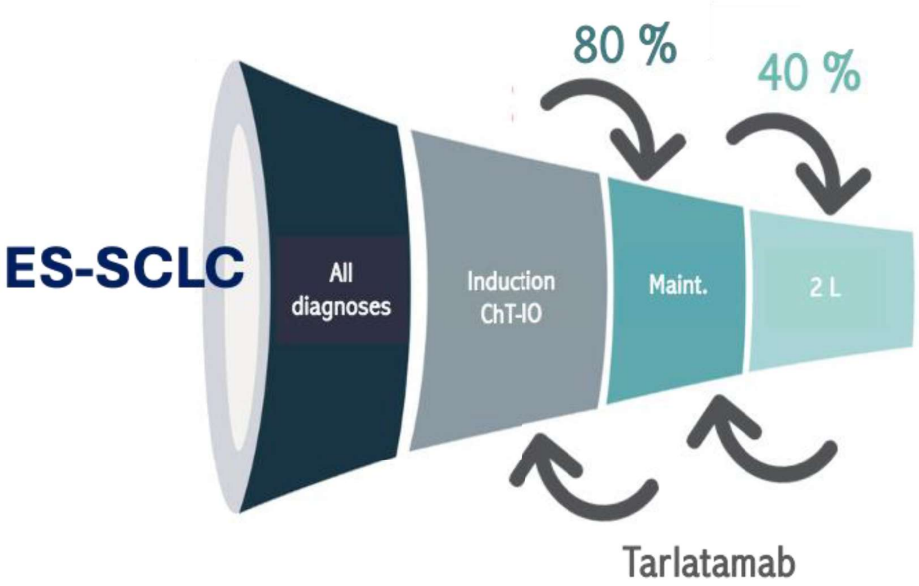
Wermke et al, ASCO 2025; ESMO 2025

Why Bringing DLL3 Targeting to the Front Line?

Biologic Plausibility

- **Primary** immune activation
- Potential **synergism** with ChT
- **Promote** local **inflammation**
  (↑ T-Cell, Cold ->Hot Microenviroment)
- Sustain **immune pressure** with CPI

High Drop-Off Rates

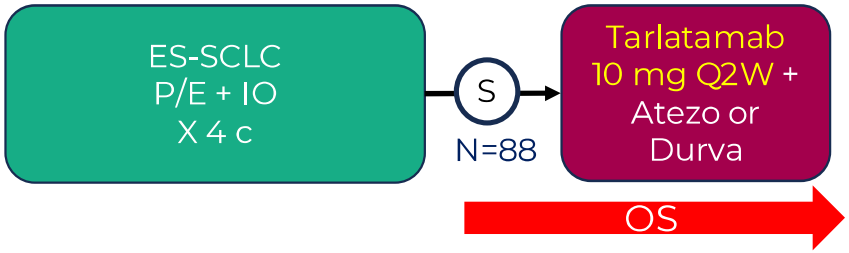


1.- Iams W, Flatiron Health RW cohort 2025-05, ISPOR 2025; 2.- Reck M, JTO 2022; 3.- Paz-Ares L, Lancet 2025; 4.- Chen X, J ImmunoTherapy Cancer 2020

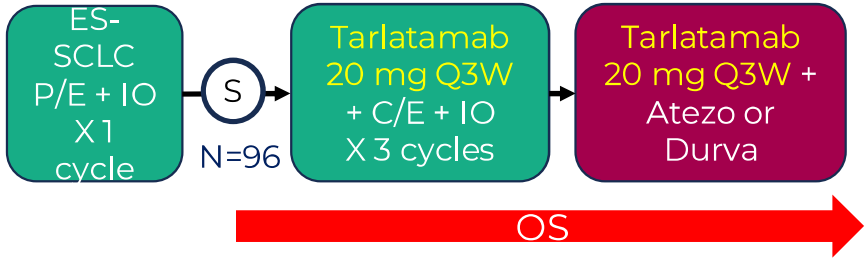
DeLLphi-303: Moving Tarlatamab Upfront in ES-SCLC

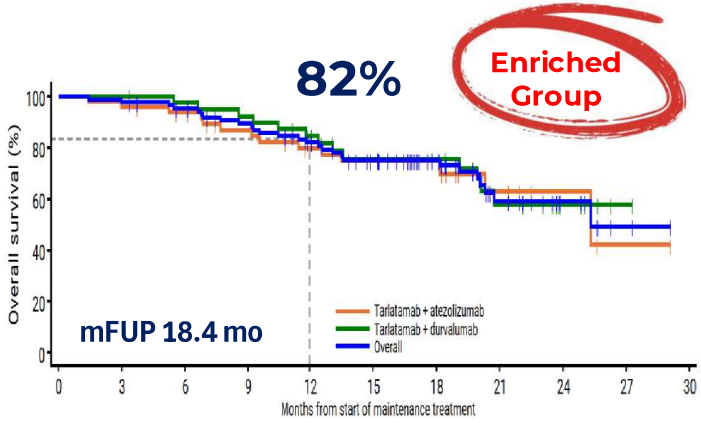
DeLLphi-303: Phase 1b (*dose expansion*)

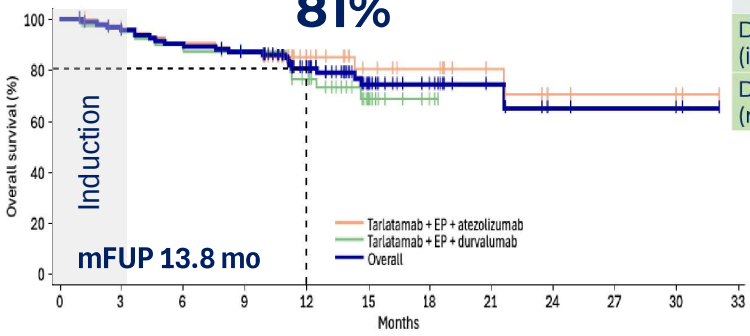
PART 5/6/8: MAINTENANCE ONLY



PART 2/4/7: CONCOMITANT ChT-IO + MAINTENANCE







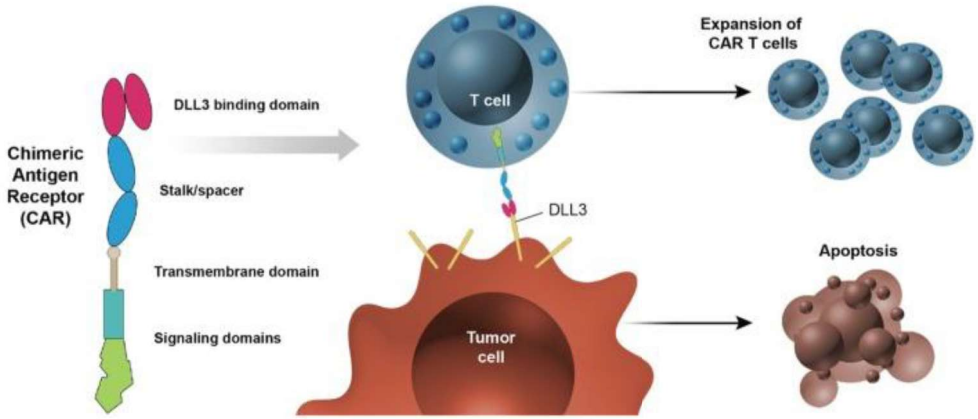
Study	mOS (mo)	12 mo OS
P/E (control arms)[1-2]	~10	~40%
IMpower133 [1]	12.3	52%
CASPIAN [2]	12.9	53%
DeLLphi-313 (induction) [3]	NE	81%
DeLLphi-313 (maintenance)[4]	25.3	82%

1.- Wermke M, ESMO 2025; 2.- Paulson KG, Lancet Oncol 2025

Pivotal confirmatory trials completed accrural DeLLphi-305 (NCT06211036) & DeLLphi-312 (NCT07005128)

CHIMERIC ANTIGEN RECEPTOR-T (CAR-T) CELL THERAPIES IN SCLC

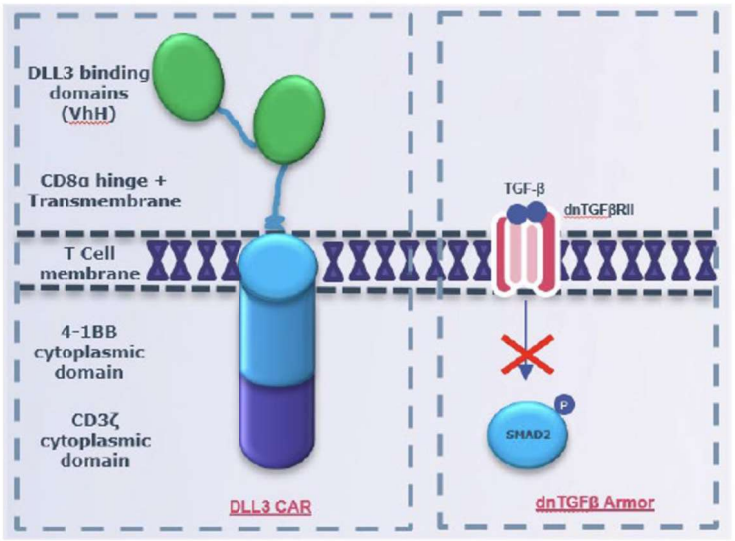
AMG 119



Zhou et al. J Clin Pharmacol 2024; Sands et al. SITC 2025

LB2102

-The dnTGF-βRII armor inhibits the TGFβ1-TGFβR pathway in LB2102 CAR-T cells.
-Armored LB2102 cells overcome TGFβ1-induced growth inhibition and maintain proliferation.



CONCLUSIONS

- SCLC exhibits heterogeneous immune landscape despite common features (high TMB, low PD-L1, HLA down, cold TME)
- Selected types of immunotherapy have demostrated individual activity but most failed to confirm benefit in larger randomized trials
    - Predictive biomarkers remain elusive
- Most sucessful immuno-based treatment strategies in ES-SCLC include:
    - Chemo-anti-PD(L)-1 ICI in 1L induction
    - Lurbi-ICI in 1L-maintenance
    - DLL3 TCE
- Optimal treatments sequence remains unclear, but early combinations in 1L will be likely necessary to overcome patient attrition due to SCLC agressive biology.

Thanks for your attention!

Hospital General Universitario Gregorio Marañón

antonio.calles@salud.madrid.org

@Tony_Calles