New Developments in SCLC

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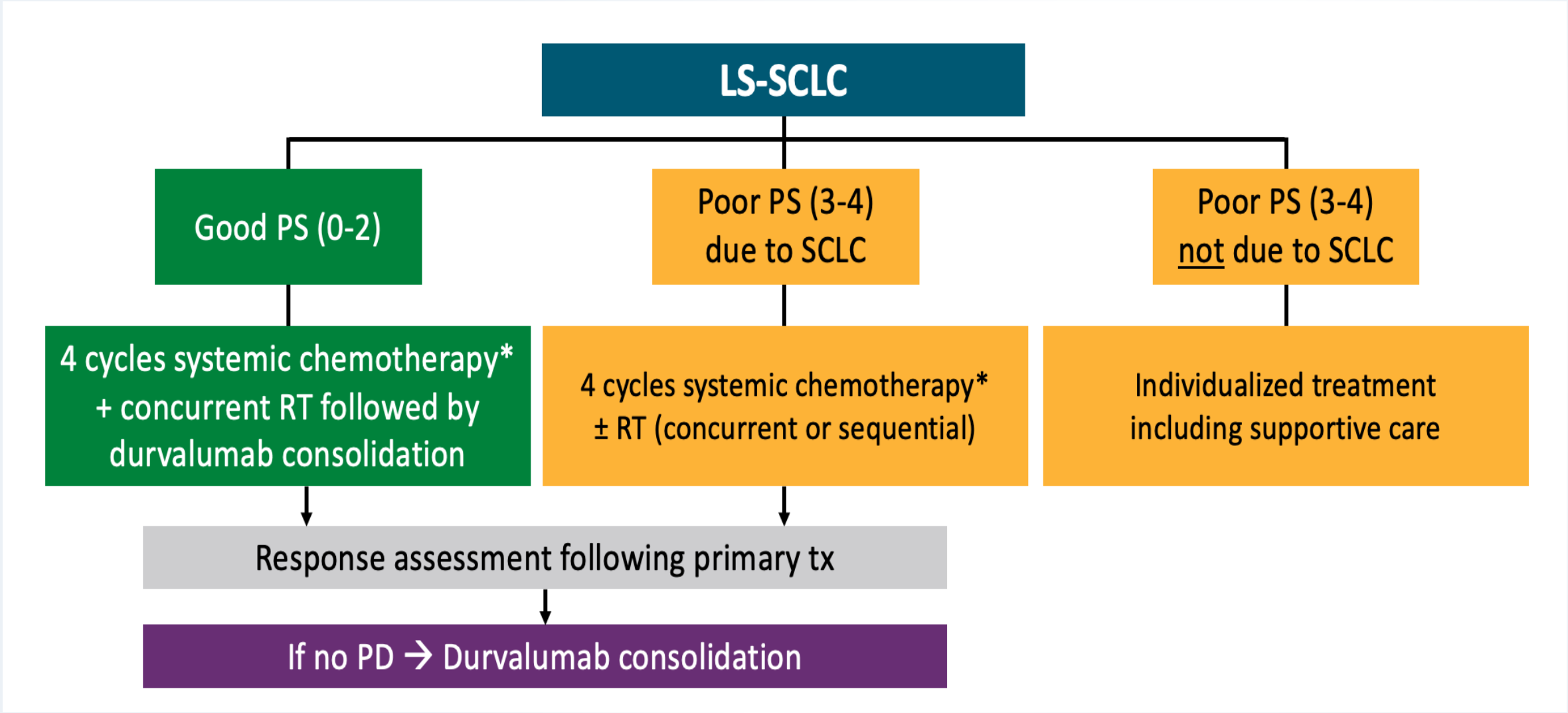
Disclosures

Consultant/Advisor/Speaker: Jazz, Genentech, BI, AstraZeneca, Novocure, Catalyst, OncoC4, J&J

Current Clinical Guidelines on Primary Treatment for LS-SCLC

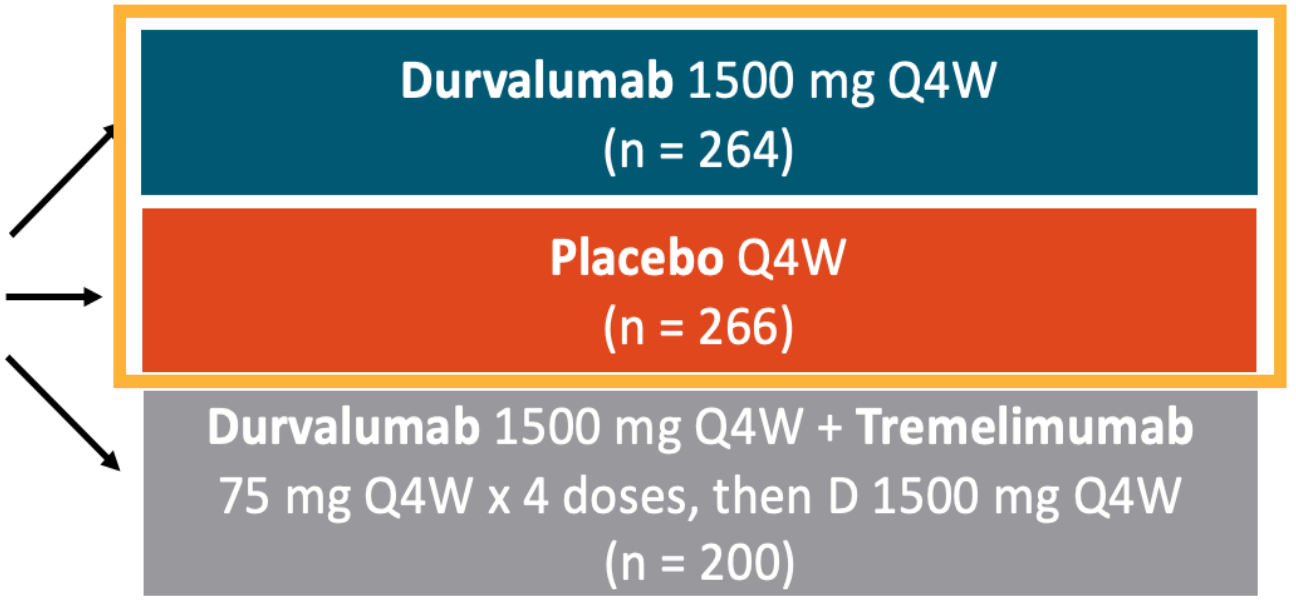


NCCN. Clinical guidelines in oncology: small cell lung cancer. v4.2025. nccn.org. Kalemkerian. JCO. 2025;43:101.

ADRIATIC: Consolidation Therapy With Durvalumab for LS-SCLC

Stage I/II inoperable or stage III LS-SCLC; no progression after cCRT*; PCI allowed prior to randomization; cCRT and PCI completed 1-42 days prior to randomization; WHO PS 0/1
(N = 730)

*3-4 cycles of platinum and etoposide; RT: 60-66 Gy QD over 6 wk or 45 Gy BID over 3 wk; RT must start no later than end of cycle 2 of CT.



Until investigator-determined PD or intolerable AE, or 24 mo of tx

- **Coprimary endpoints:** PFS by BICR per RECIST v1.1; OS for durvalumab vs placebo
- **Secondary endpoints:** PFS by BICR per RECIST v1.1; OS for durvalumab + tremelimumab vs placebo; OS/PFS landmarks; safety

1. Cheng. NEJM. 2024;391:1313. 2. NCT03703297.

ADRIATIC: Baseline Characteristics

Variable, %	Durvalumab (n = 264)	Placebo (n = 266)
Median age, yr (range)	62.0 (28-84)	62.0 (28-79)
Male sex	67.4	70.7
Race		
▪ White	49.2	51.5
▪ Asian	49.6	45.5
▪ Other	1.1	3.0
WHO PS 0/1	50.0/50.0	47.4/52.6
Smoking status		
▪ Current	23.9	20.7
▪ Former	67.4	69.5
▪ Never	8.7	9.8
AJCC disease stage at diagnosis		
▪ I	3.0	4.1
▪ II	9.5	8.6
▪ III	87.5	87.2

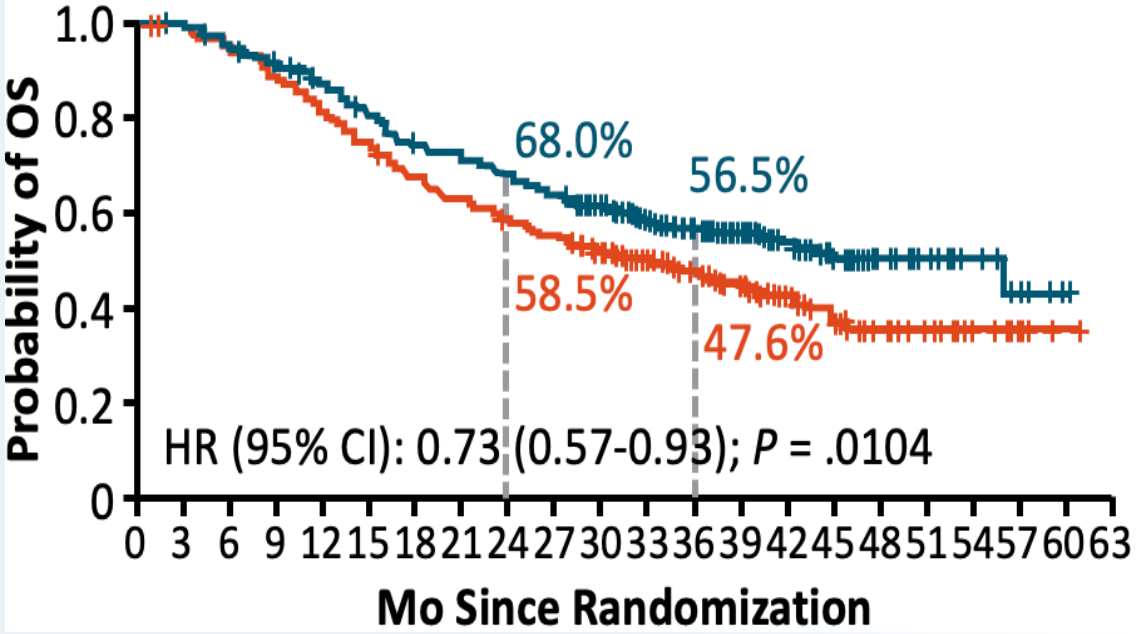
Variable, %	Durvalumab (n = 264)	Placebo (n = 266)
Prior CT regimen		
▪ Cisplatin/etoposide	65.5	66.9
▪ Carboplatin/etoposide	34.5	33.1
Prior radiation schedule		
▪ Once daily	73.9	70.3
▪ Twice daily	26.1	29.7
Best response to prior cCRT	11.7	12.8
▪ CR	72.3	75.2
▪ PR	15.9	12.0
▪ SD		
Prior PCI		
▪ Yes	53.8	53.8
▪ No	46.2	46.2

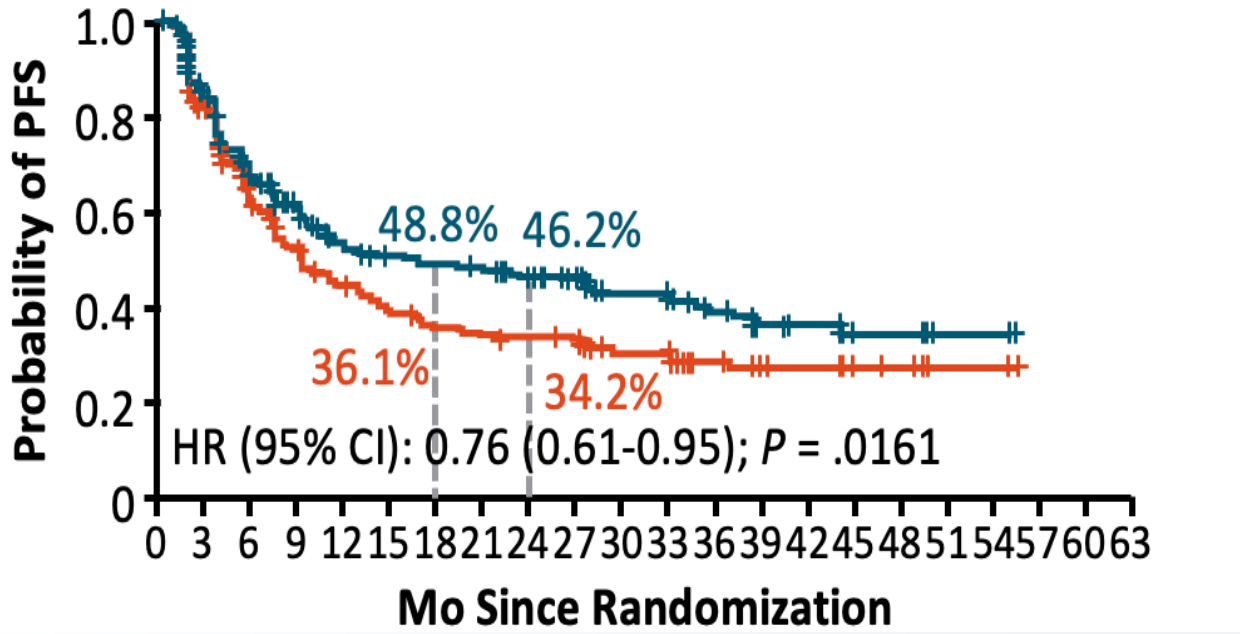
1. Cheng. NEJM. 2024;391:1313. 2. NCT03703297.

ADRIATIC: Efficacy

OS	Durvalumab (n = 264)	Placebo (n = 266)
Events, n (%)	115 (43.6)	146 (54.9)
Median OS, mo (95% CI)	55.9 (37.3-NE)	33.4 (25.5-39.9)

PFS	Durvalumab (n = 264)	Placebo (n = 266)
Events, n (%)	139 (52.7)	169 (63.5)
Median PFS, mo (95% CI)	16.6 (10.2-28.2)	9.2 (7.4-12.9)

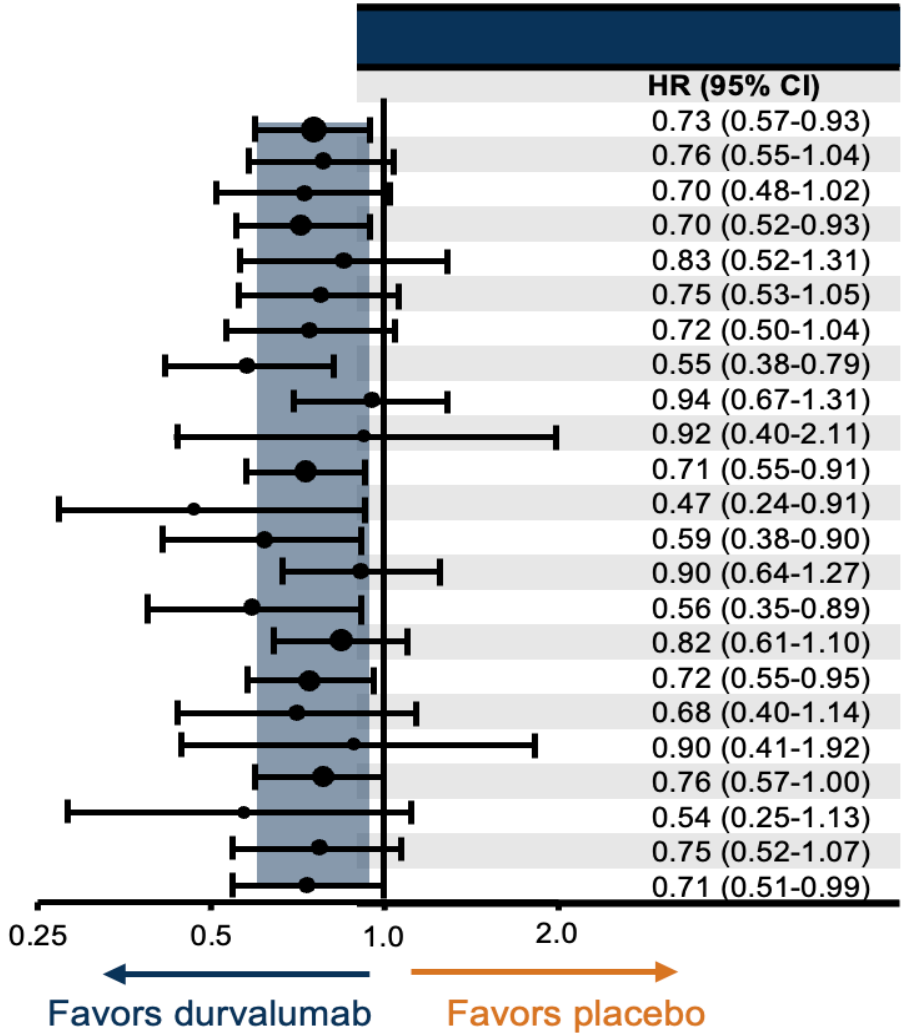




1. Cheng. NEJM. 2024;391:1313. 2. NCT03703297.

ADRIATIC: OS Subgroup Analysis

		Events/Patients, n/N	
		Durvalumab	Placebo
All patients		115/264	146/266
Age, y	<65	69/160	83/162
	≥65	46/104	63/104
Sex	Male	79/178	108/188
	Female	36/86	38/78
Race	White	60/130	77/137
	Asian	53/131	64/121
WHO performance status	0	48/133	74/131
	1	67/131	72/135
AJCC disease stage at diagnosis	I/II	11/33	12/34
	III	104/231	134/232
Time from end of cCRT[a] to randomization, d	<14	14/32	24/32
	≥14 to <28	37/79	51/80
	≥28	64/153	71/154
Prior chemotherapy regimen	Carboplatin-etoposide	31/91	46/88
	Cisplatin-etoposide	84/173	100/178
Prior radiation schedule	Once daily	92/195	107/187
	Twice daily	23/69	39/79
Best response to prior cCRT	Complete response	12/31	15/34
	Partial response	88/191	116/200
	Stable disease	15/42	15/32
Prior PCI	Yes	53/142	67/143
	No	62/122	79/123

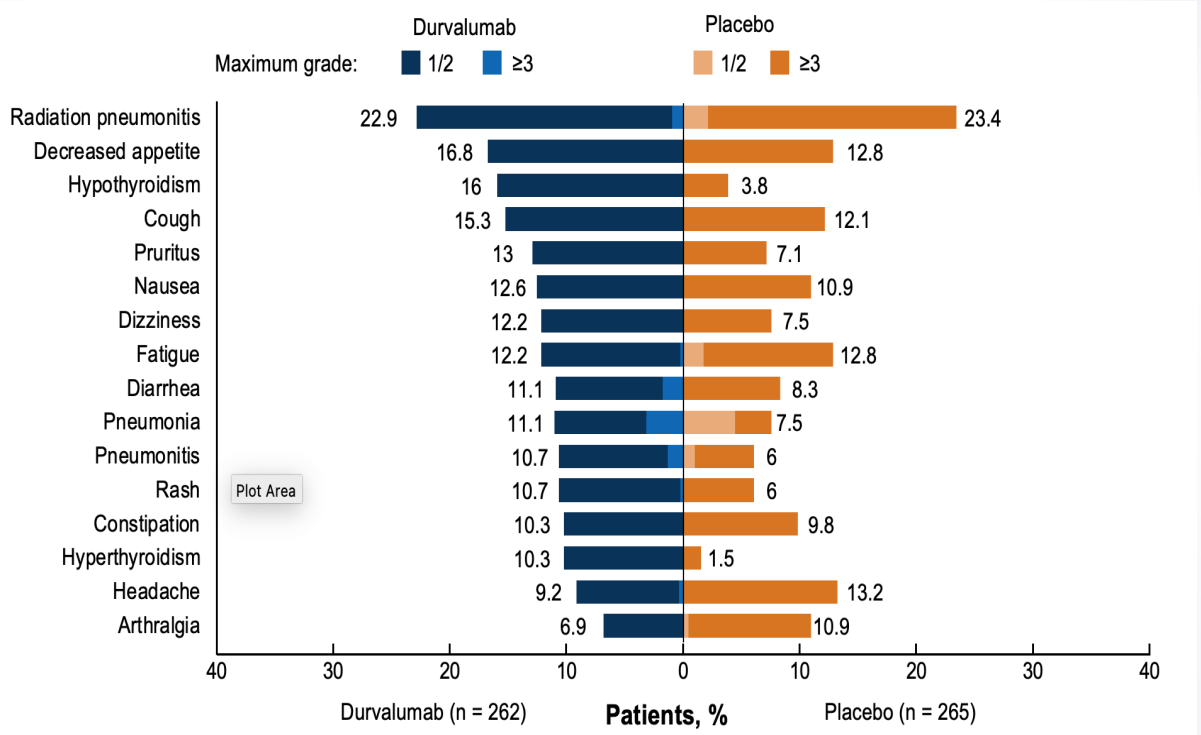


1. Cheng. NEJM. 2024;391:1313. 2. NCT03703297.

ADRIATIC: Safety

		Durvalumab (n = 262)	Placebo (n = 265)
Durvalumab or placebo doses, n	Median (range)	9 (1-26)	9 (1-26)
	Mean (standard deviation)	12.9 (9.6)	11.8 (9.2)
Any-grade all-cause AEs, n (%)		247 (94.3)	234 (88.3)
Maximum grade 3/4 AEs		64 (24.4)	64 (24.2)
Serious AEs		78 (29.8)	64 (24.2)
AEs leading to treatment discontinuation		43 (16.4)	28 (10.6)
AEs leading to death		7 (2.7)	5 (1.9)
Treatment-related[b] AEs leading to death		2 (0.8)[c]	0
Any-grade immune-mediated AEs[c]		84 (32.1)	27 (10.2)
Maximum grade 3/4 immune-mediated AEs		14 (5.3)	4 (1.5)

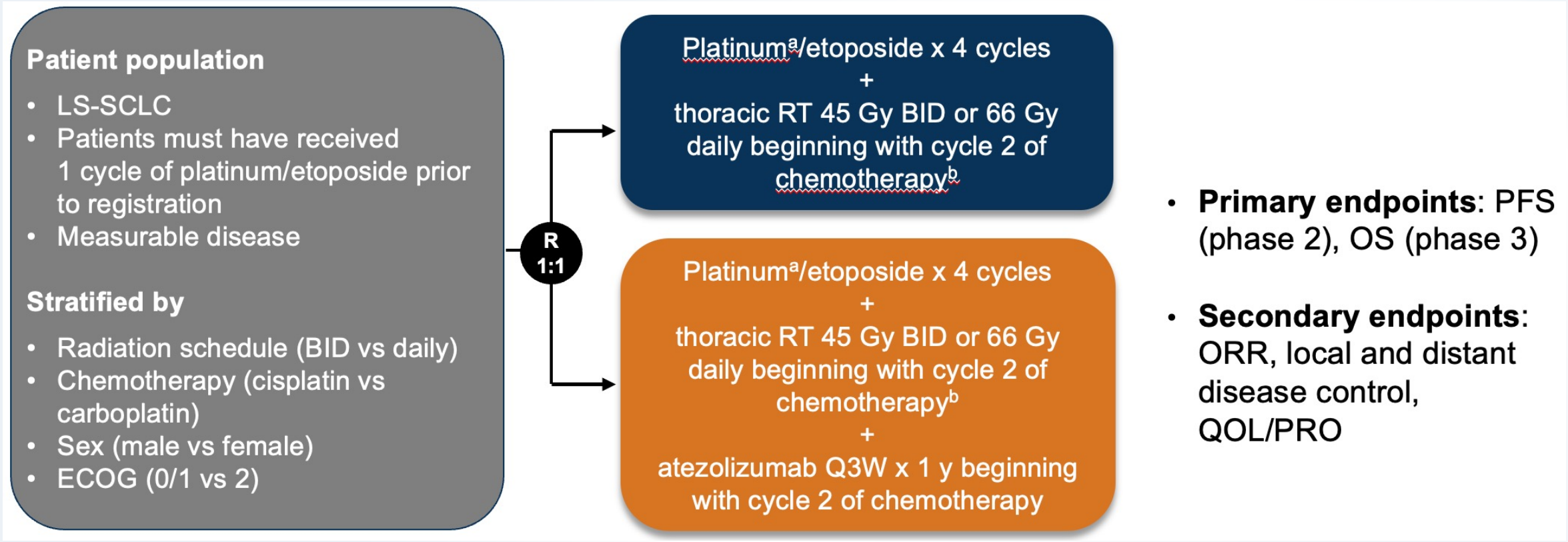
Most Frequent AEs



1. Cheng. NEJM. 2024;391:1313. 2. NCT03703297.

NRG LU005: cCRT +/- Atezolizumab in LS-SCLC

Phase 2/3, Randomized Study of cCRT ± Atezolizumab in LS-SCLC

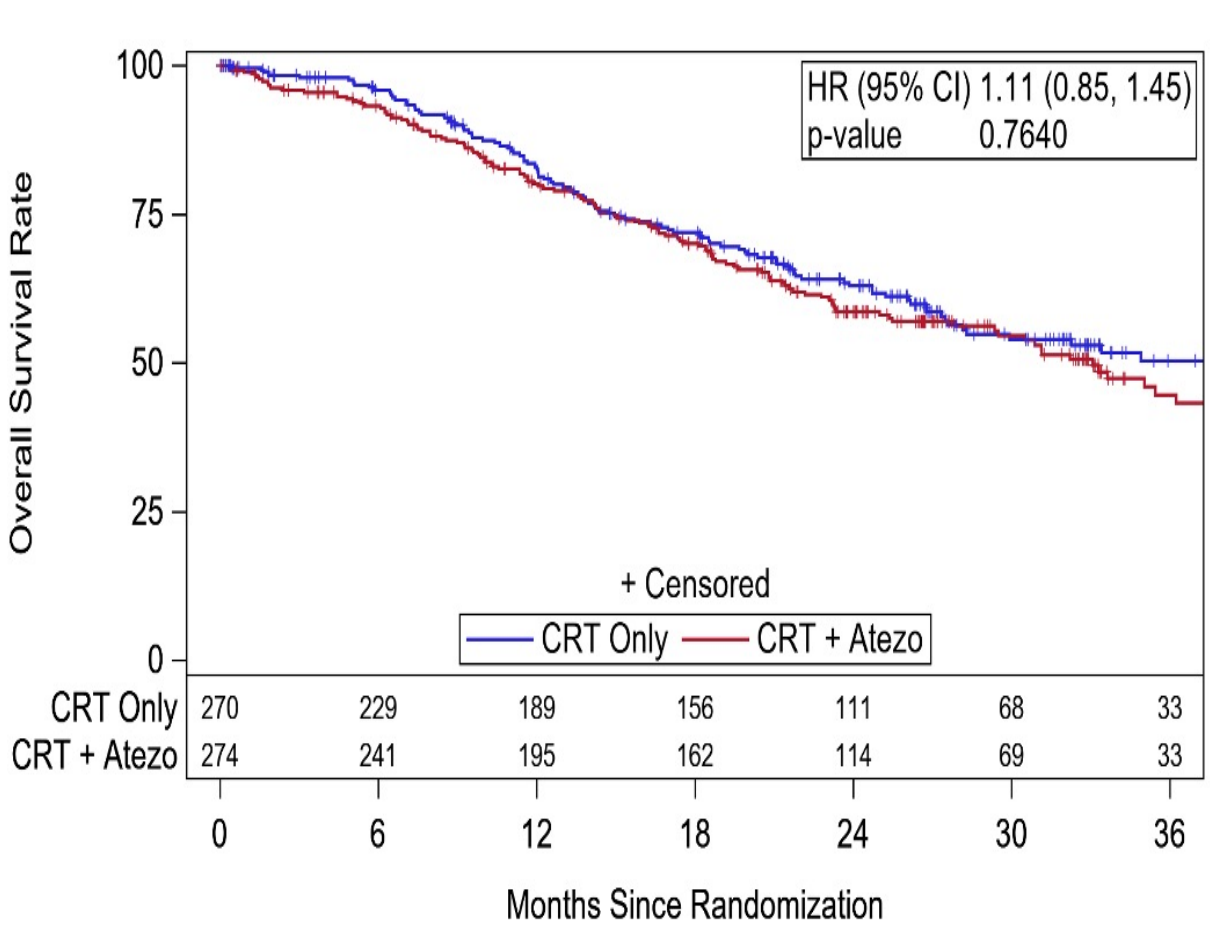


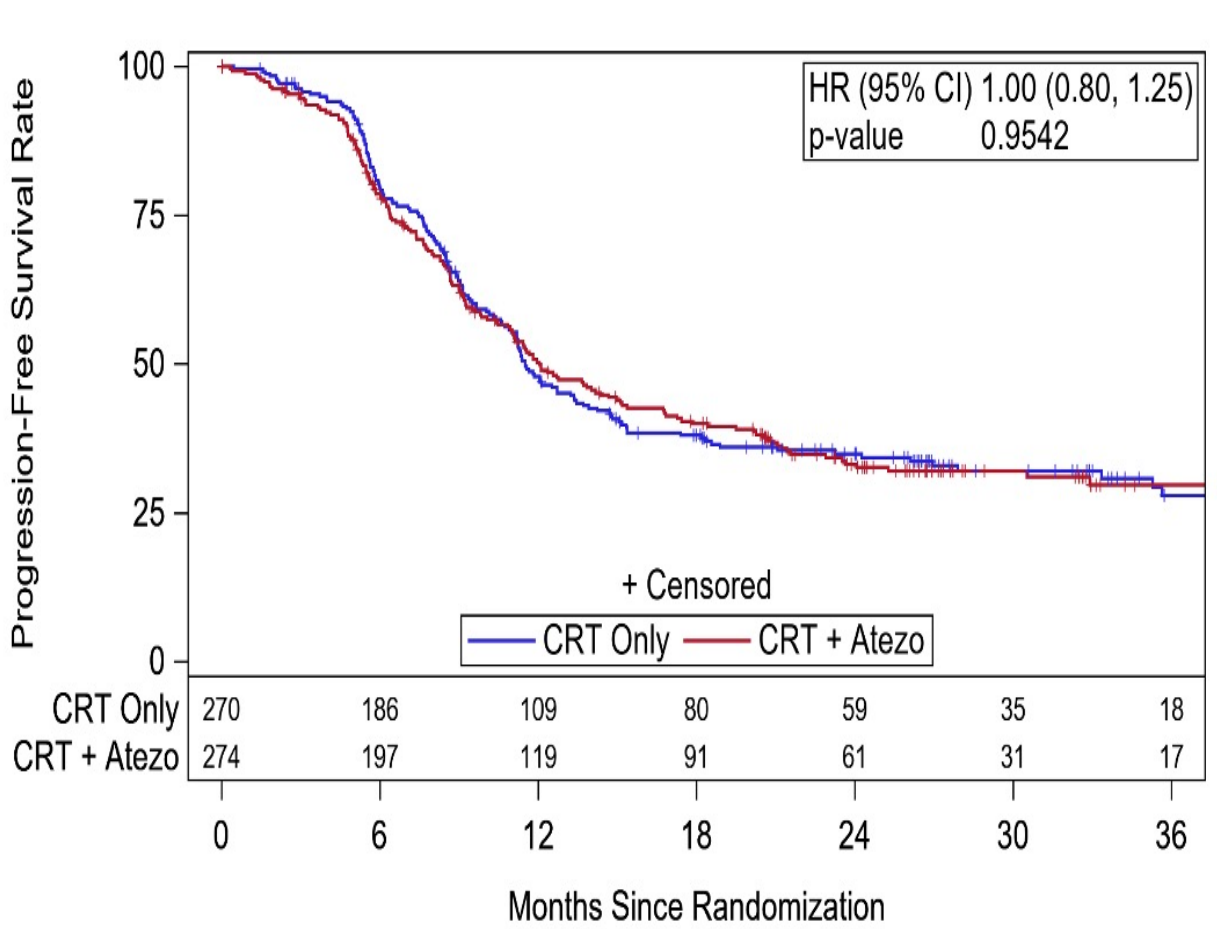
- **Primary endpoints**: PFS (phase 2), OS (phase 3)
- **Secondary endpoints**: ORR, local and distant disease control, QOL/PRO

Higgins KA et al. ASTRO 2024. Abstract LBA02.

NRG LU005: cCRT +/- Atezolizumab in LS-SCLC

- Concurrent atezolizumab did not improve survival for patients with LS-SCLC compared with standard chemoradiation





Higgins KA et al. ASTRO 2024. Abstract LBA02.

1L chemoimmunotherapy for ES-SCLC

Study	Agent	Sample Size	mPFS / HR	mOS / HR	1y OS Rate
IMpower 133 *Liu, JCO 2021*	Atezolizumab	403 pts	5.2m HR 0.77	12.3m HR 0.76	52%
CASPIAN *Paz-Ares, ESMO Open 2022*	Durvalumab	805 pts	5.1m HR 0.80	12.9m HR 0.71	53%
EA5161 (phase II) *Leal, ASCO 2020*	Nivolumab	160 pts	5.5m HR 0.68	11.3m HR 0.73	50%
KEYNOTE 604 *Rudin, WCLC 2022*	Pembrolizumab	453 pts	4.8m HR 0.70	10.8m HR 0.76	45%
ASTRUM 005 *Cheng, JAMA 2022*	Serplulimab	585 pts	5.7m HR 0.48	15.4m HR 0.63	61%
CAPSTONE-1 *Wang, Lancet Oncol 2022*	Adebrelimab	462 pts	5.8m HR 0.67	15.3m HR 0.72	63%
RATIONALE-312 *Cheng, WCLC 2023*	Tislelizumab	457 pts	4.8m HR 0.63	15.5m HR 0.75	63%

Canaslan K, Leal T. Maxing Out with Chemoimmunotherapy in ES-SCLC. Chinese Clinical Oncology, 2025.

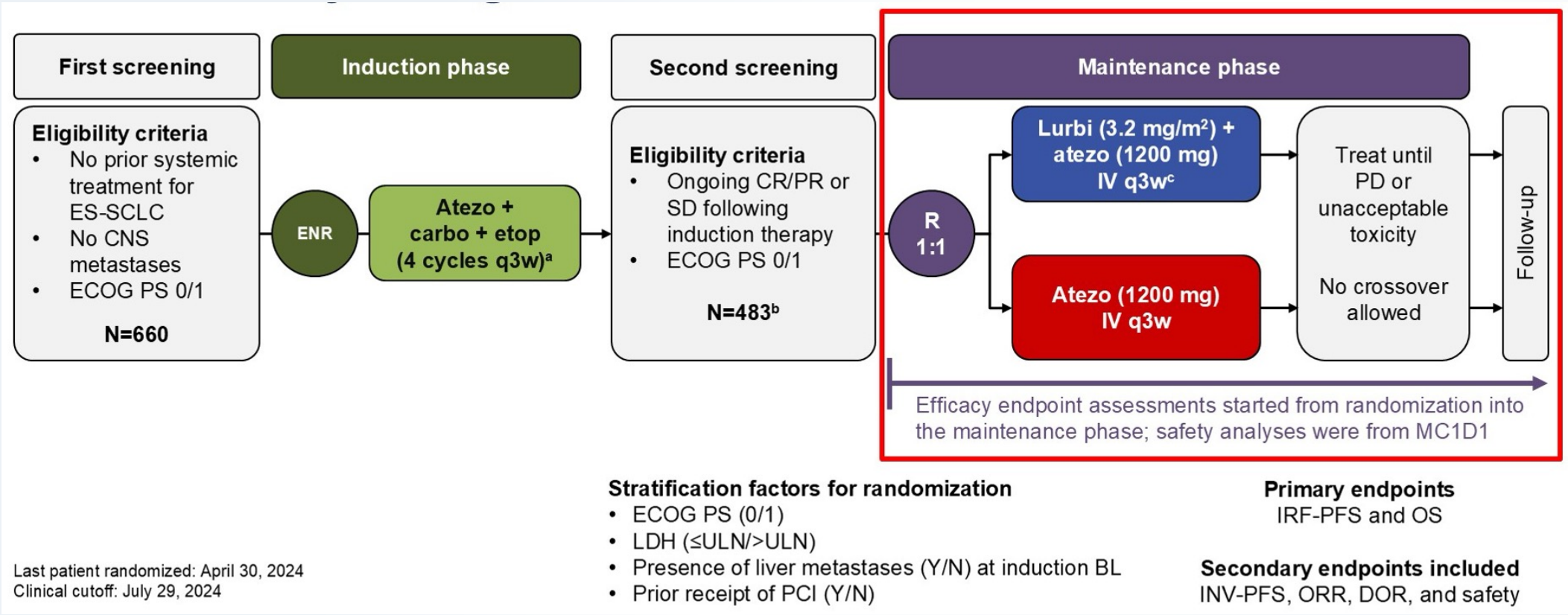
ES-SCLC: 1L Maintenance

Study (characteristics)	Start of the accrual End of the accrual	Induction therapy	Maintenance therapy	N pts	PFS (ms) (95% CI)	HR (95% CI) *p-value*	OS (ms) (95% CI)	HR (95% CI) *p-value*
Chemotherapy								
Nie K et al, 2020	January 2017	PE or PI x 4-6	S-1	45	6.35	1.057	10.82	0.860
Phase 2	November 2018	cycles +/- PCI	*vs* placebo	44	5.98	(0.656-1.707)	10.09	(0.374-1.617)
ED, not progressed						*p=0.820*		*p=0.905*
Immunotherapy								
Peters S et al, 2021	December 2015	PE x 4 cycles +	Nivolumab +	78	10.7	1.02 (0.66-1.58)	NR	0.95 (0.59-1.52)
Phase 2	April 2019	concomitant	Ipilimumab x 4 cycles → Nivolumab up to 12 ms	75	14.5	*p=0.93*	32.1	*p=0.82*
LD, not progressed		thoracic RT + PCI	*vs* observation					
Owonikoko TK et al, 2021*	October 2015	Platinum-based x	Nivolumab +	279	1.7	0.72 (0.60-0.87)	9.2	0.92 (0.75-1.12)
Phase 3	January 2018	3-4 cycles +/- PCI	Ipilimumab x 4 cycles → Nivolumab up to 24 ms	275	1.4		9.6	*p=0.37*
ED, not progressed			*vs* placebo					
			Nivolumab up to 24 ms	280	1.9	0.67 (0.56-0.81)	10.4	0.84 (0.69-1.02)
			vs placebo	275	1.4		9.6	
Gladkov O et al, 2015	May 2007	Platinum-based x		64	1.5	1.01 (0.76-1.34)	12.3	1.10 (0.84-1.44)
Phase 2	January 2011	4 cycles +/- PCI	Cyclophosphamide/ tucotuzumab	44	1.4		14.1	
ED, in CR or PR			*vs* best-supportive care					
Target therapy								
Johnson ML et al, 2021	February 2017	PE or PI x 4	Rova-T	372	3.7	0.51 (0.44-0.60)	8.8	1.1 (0.9-1.4) #
Phase 3	July 2019	cycles +/- PCI	*vs* placebo	376	1.4	#	9.9	*p=0.237*
ED, not progressed						*p<0.001*		
Ai X et al, 2021	July 2018	PE x 4 cycles +/-	Niraparib	125	1.54	0.66 (0.46-0.95)	9.92	1.03 (0.62-1.73)
Phase 3	February 2020	PCI	*vs* placebo	60	1.36		11.43	*p= 0.9052*
ED, in CR or PR						*p=0.0242*		
Sun JL et al, 2018	June 2013	PE x 4 cycles +/-	Pazopanib	48	3.7	0.44 (0.29-0.69)	10.6	1.14 (0.74-1.76)
Phase 2	July 2016	PCI	*vs* placebo	47	1.8		12.9	*p=0.54*
ED, not progressed						*p<0.0001*		
Ready NE et al, 2015	March 2007	PE x 4-6 cycles	Sunitinib	44	3.7	1.62 (1.27-2.08)	9.0	1.28 (0.79-2.10)
Phase 2	December 2011	+/- PCI	*vs* placebo	41	2.1		6.9	*p=0.16*
ED, not progressed						*p=0.02*		
Other agents								
Santo A et al, 2019	May 2012	PE x 4-6 cycles	Lanreotide up to 12 ms	39	3.6	1.51 (0.90-2.50)	9.5	1.30 (0.64-2.65)
Phase 3	April 2016	+/ thoracic RT +/- PCI	*vs* observation	32	2.3		4.7	
LD and ED, in CR or PR						*p=0.11*		*p=0.47*

- Several trial failed to show a survival benefit from maintenance therapy in SCLC.
- PFS benefit, but not OS, with immunotherapy maintenance was reported.
- Signal could have been stronger if all pts had received induction chemoimmunotherapy
- Which patients could benefit the most from IO maintenance?

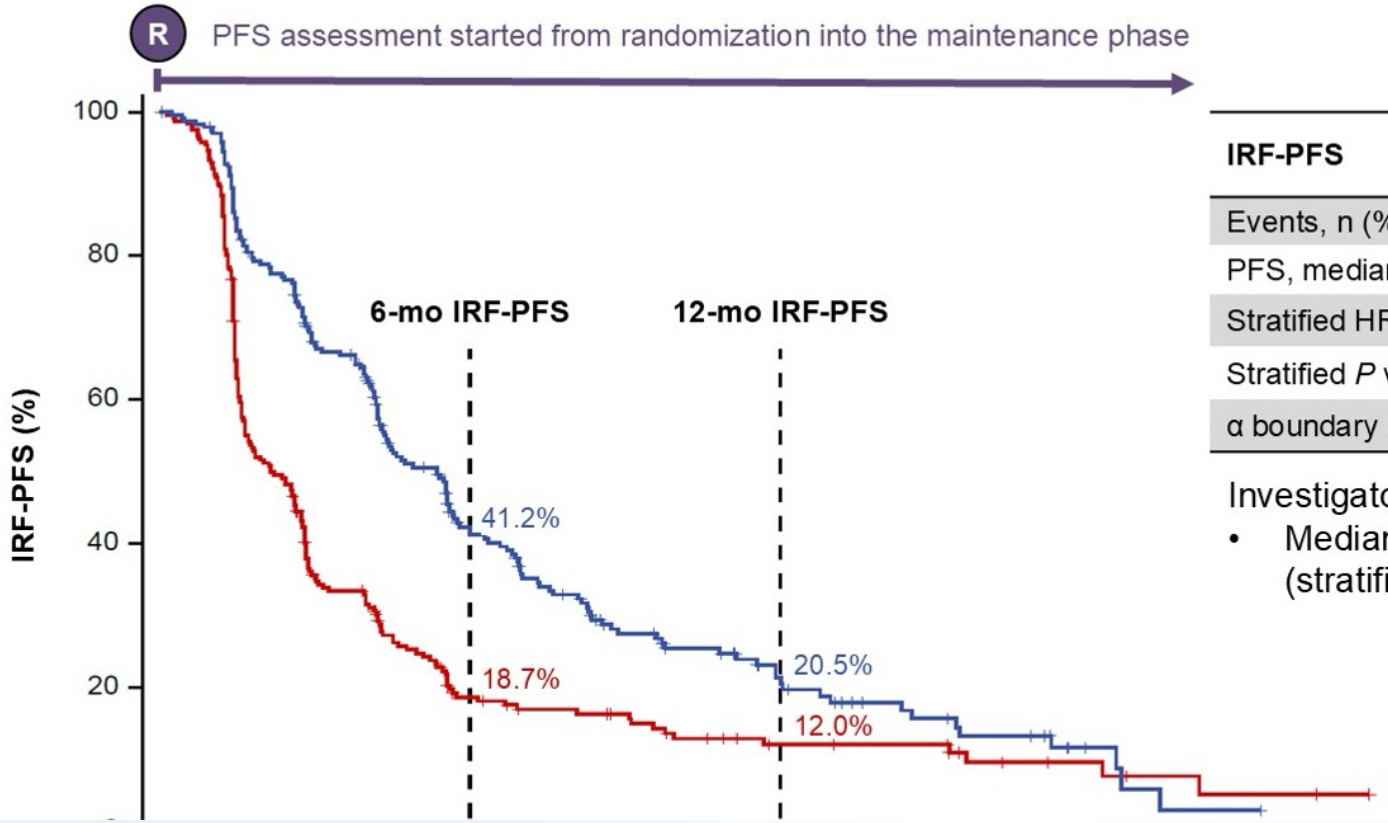
Belluomini Let al. / Seminars in Oncology 49 (2022) 389–39

IMforte: Lurbinectedin + Atezolizumab as First-line Maintenance Therapy in ES-SCLC



NCT05091567. Paz-Ares. WCLC 2022. Abstr EP14.01-015. Paz-Ares. ASCO 2025. Abstr 8006.

IMforte: IRF-PFS



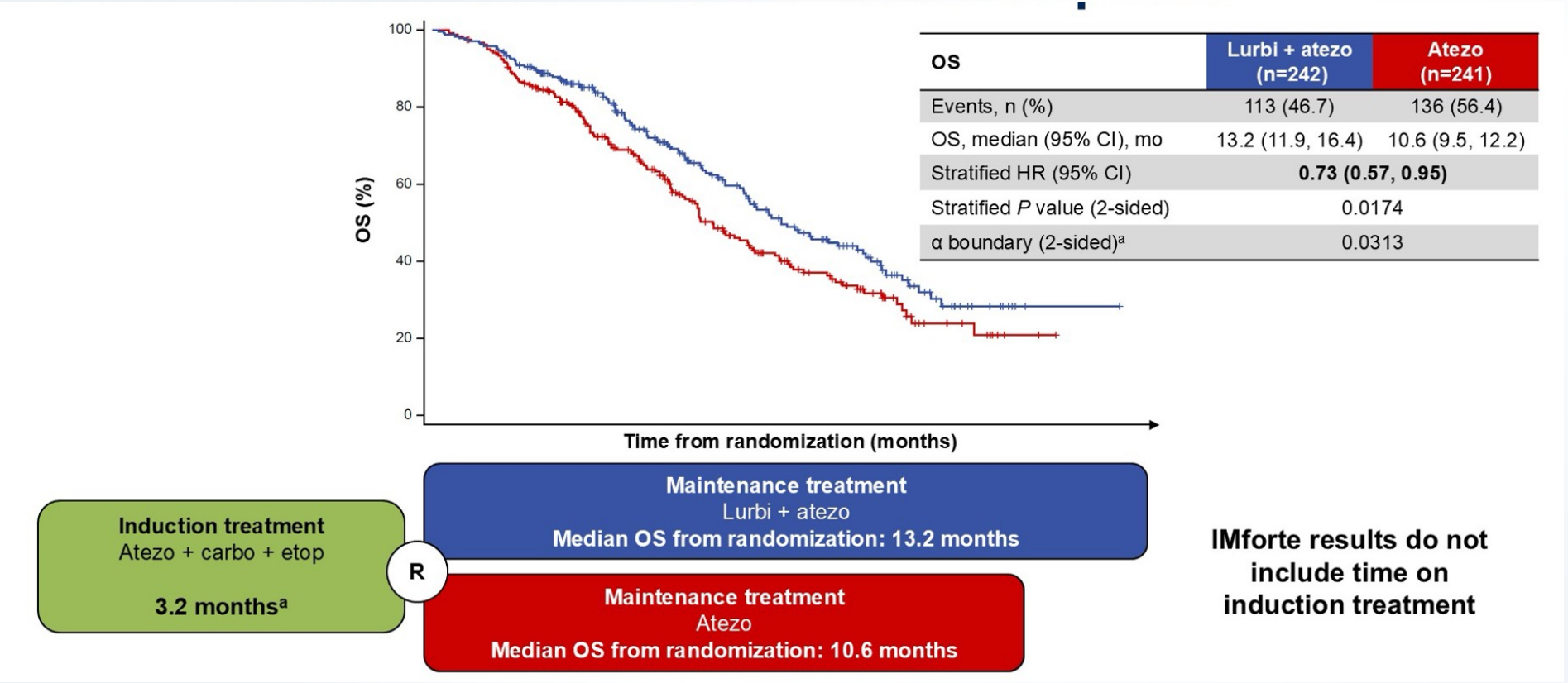
IRF-PFS	Lurbi + atezo (n=242)	Atezo (n=241)
Events, n (%)	174 (71.9)	202 (83.8)
PFS, median (95% CI), mo	5.4 (4.2, 5.8)	2.1 (1.6, 2.7)
Stratified HR (95% CI)	**0.54 (0.43, 0.67)**	
Stratified *P* value (2-sided)	<0.0001	
α boundary (2-sided)	0.001	

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])

NCT05091567. Paz-Ares. WCLC 2022. Abstr EP14.01-015. Paz-Ares. ASCO 2025. Abstr 8006.

IMforte: OS



NCT05091567. Paz-Ares. WCLC 2022. Abstr EP14.01-015. Paz-Ares. ASCO 2025. Abstr 8006.

IMforte: Safety

Patients with ≥1 AE, n (%)	Lurbi + atezo (n=242)	Atezo (n=240)
All-cause AEs	235 (97.1)	194 (80.8)
Grade 3/4 AEs	92 (38.0)	53 (22.1)
Treatment-related Grade 3/4 AEs	62 (25.6)	14.0 (5.8)
Grade 5 AEs	12 (5.0)	6 (2.5)
Treatment-related Grade 5 AEs	2 (0.8)[a]	1 (0.4)[b]
Serious AEs	75 (31.0)	41 (17.1)
AEs leading to discontinuation of any study drug	15 (6.2)	8 (3.3)
AEs leading to dose interruption/ modification of any study drug[c]	92 (38.0)	33 (13.8)

Patients with ≥1 AE, n (%)	Lurbi + atezo (n=242)	Atezo (n=240)
Lurbinectedin AESI[d]	93 (38.4)	62 (25.8)
Grade 5 AESI	7 (2.9)	4 (1.7)
Atezolizumab AESI[d]	76 (31.4)	54 (22.5)
Grade 5 AESI	0	0
Atezolizumab AESI requiring corticosteroids	40 (16.5)	18 (7.5)
Median treatment duration, mo	4.1 (lurbi)/ 4.2 (atezo)	2.1
Median number of doses received	6.5 (lurbi)/ 7.0 (atezo)	4.0

NCT05091567. Paz-Ares. WCLC 2022. Abstr EP14.01-015. Paz-Ares. ASCO 2025. Abstr 8006.

IMforte: All Cause AEs with incidence ≥ 10%

Patients with ≥1 AE, n (%)	Lurbi + atezo (n=242)	Atezo (n=240)
All-cause AEs	235 (97.1)	194 (80.8)
Grade 3/4 AEs	92 (38.0)	53 (22.1)
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NCT05091567. Paz-Ares. WCLC 2022. Abstr EP14.01-015. Paz-Ares. ASCO 2025. Abstr 8006.

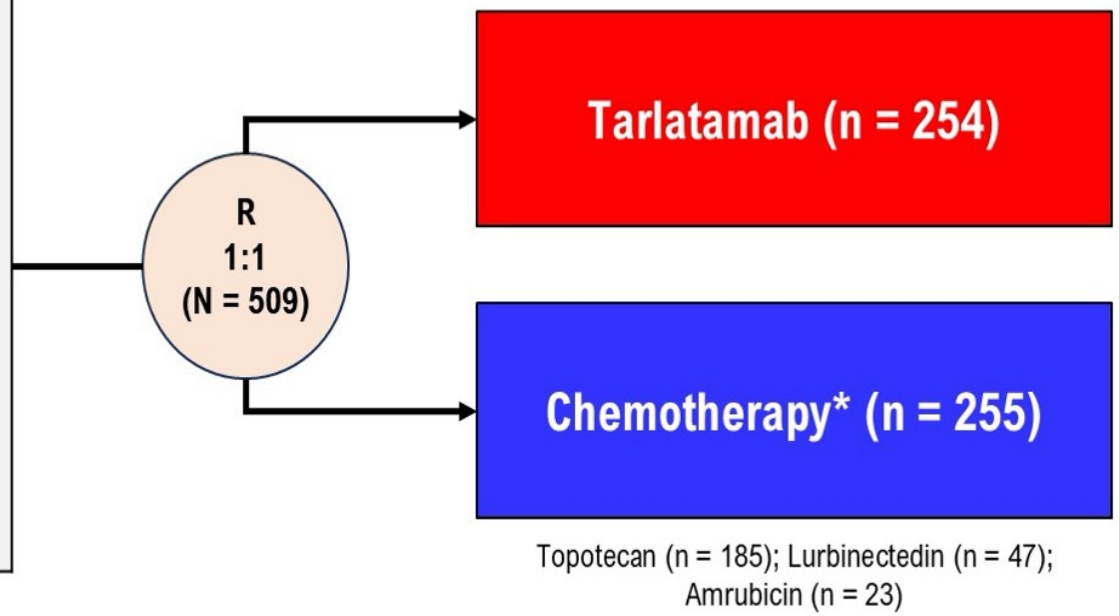
DeLLphi-304: Phase 3 of tarlatamab versus SOC

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)

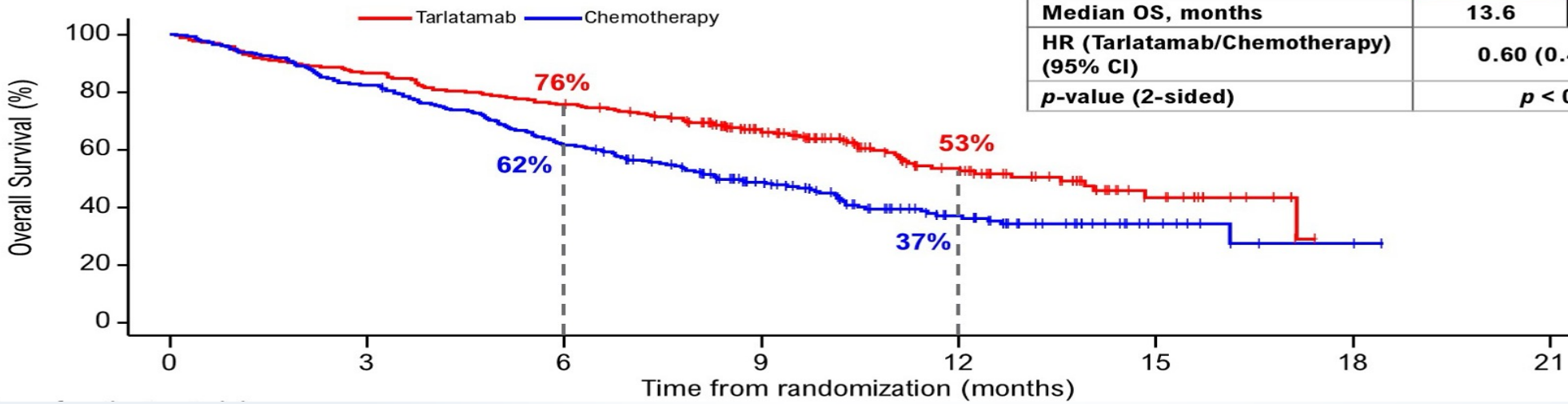


Primary Endpoint: Overall survival
Key Secondary Endpoints: Progression-free survival, patient-reported outcomes
Other Secondary Endpoints: Objective response, disease control, duration of response, safety

Rudin et al. ASCO 2025. Mountzious et al. NEJM 2025.

DeLLphi-304: Phase 3 of tarlatamab versus SOC

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

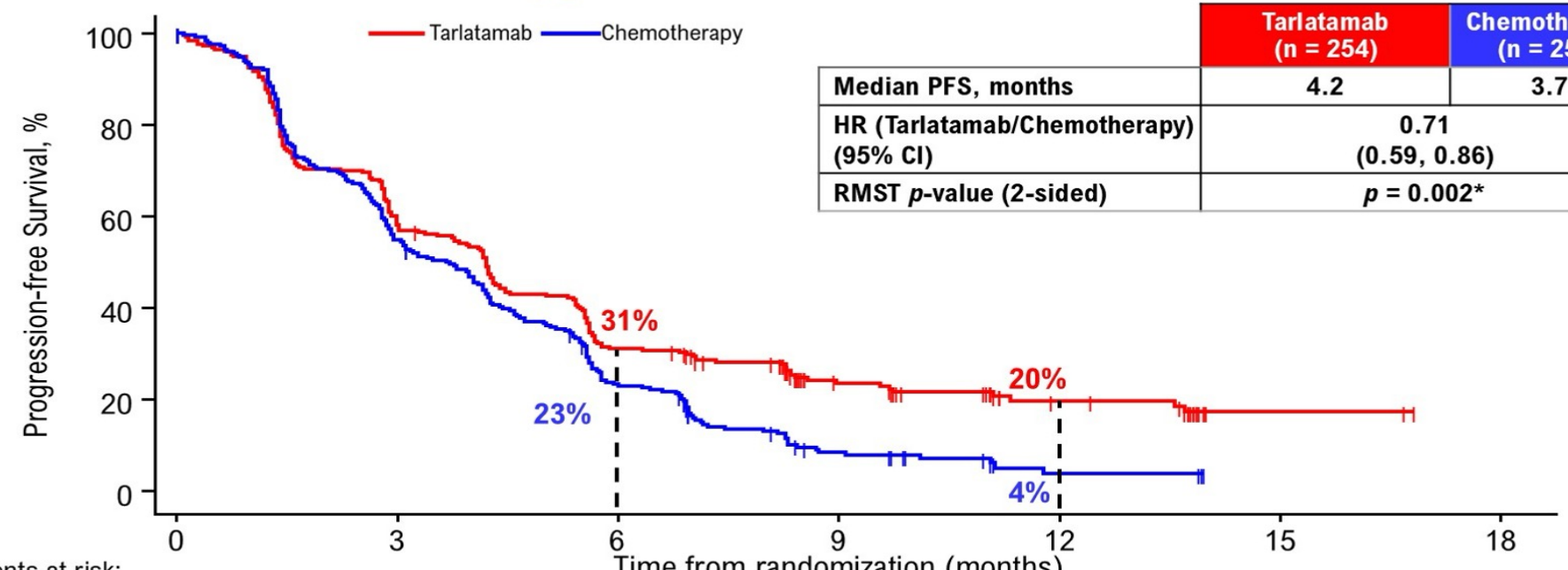


	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median OS, months	13.6	8.3
HR (Tarlatamab/Chemotherapy) (95% CI)	0.60 (0.47, 0.77)	
p-value (2-sided)	$p < 0.001$	

Rudin et al. ASCO 2025. Mountzious et al. NEJM 2025.

DeLLphi-304: Phase 3 of tarlatamab versus SOC

Progression-free survival was significantly longer with tarlatamab vs chemotherapy

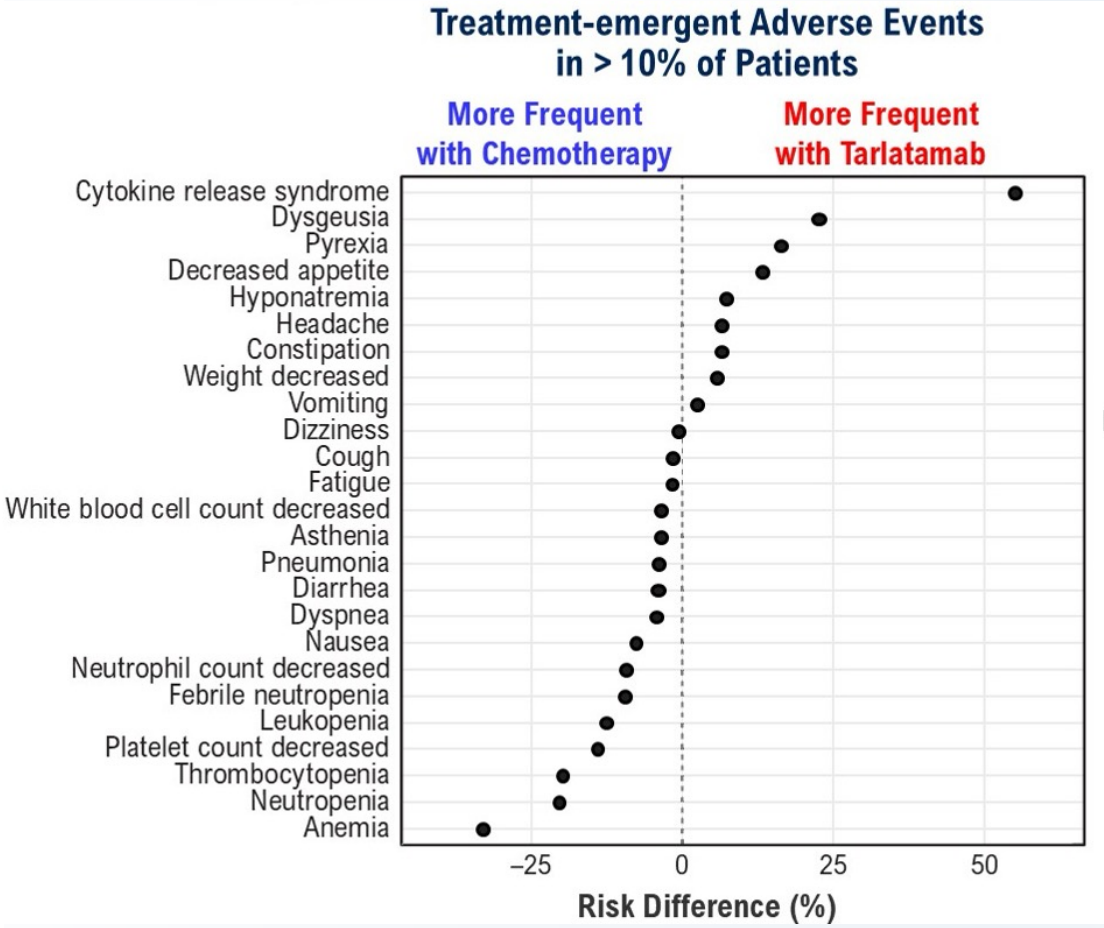


	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median PFS, months	4.2	3.7
HR (Tarlatamab/Chemotherapy) (95% CI)	0.71 (0.59, 0.86)	
RMST *p*-value (2-sided)	*p* = 0.002*	

Rudin et al. ASCO 2025. Mountzious et al. NEJM 2025.

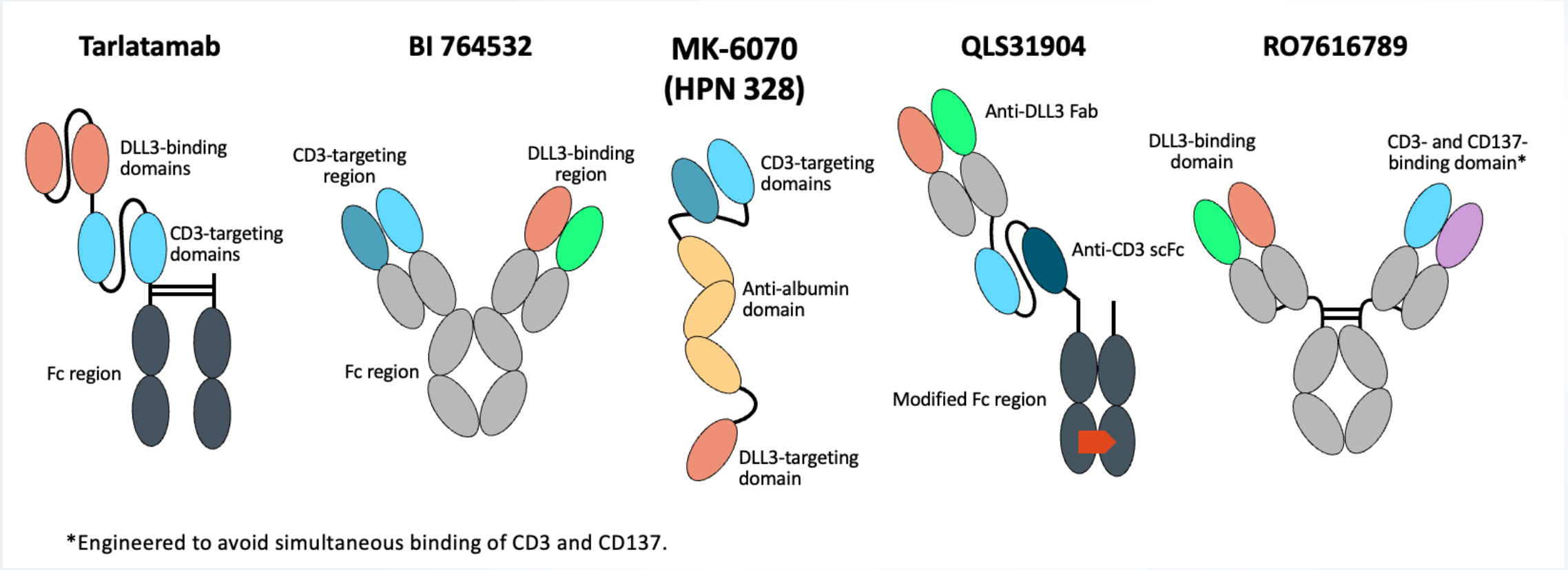
DeLLphi-304: Safety

	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)



Rudin et al. ASCO 2025. Mountzious et al. NEJM 2025.

T cell engagers in development

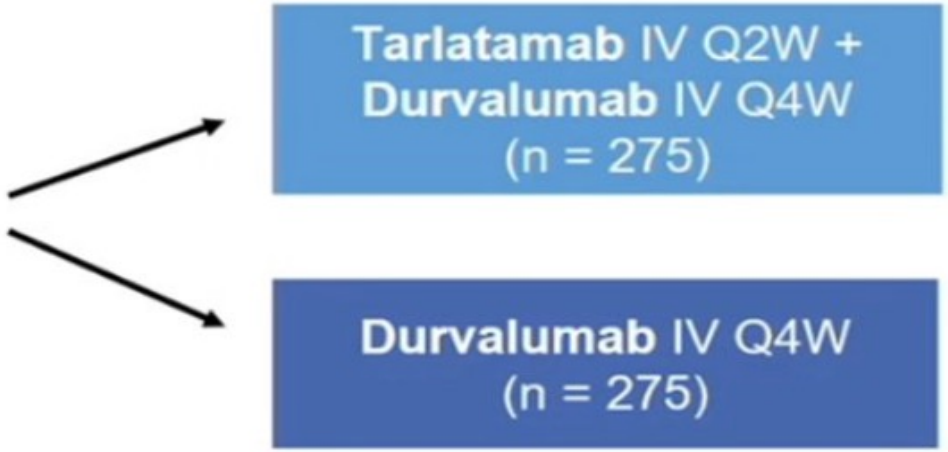


*Engineered to avoid simultaneous binding of CD3 and CD137.

DeLLphi-305: Durvalumab +/- Tarlatamab in 1L Maintenance

- International, open-label, randomized phase III study

- Adults with ES-SCLC who completed 3-4 cycles of platinum/etoposide with concurrent durvalumab as first-line tx without disease progression
- no symptomatic CNS mets
- ECOG PS 0-1



- Primary endpoint: Overall Survival
- Secondary endpoints: PFS, ORR, DCR, DoR, TTP, safety, QoL

NCT06211036

#TPS8127

DAREON™-8: A Phase I, open-label, dose escalation/expansion trial of the DLL3-targeting T-cell engager, BI 764532, combined with first-line standard of care (platinum, etoposide, and anti-PD-L1 antibody) in patients with extensive-stage small cell lung carcinoma (ES-SCLC)

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Objectives

- **Primary objectives**: MTD of BI 764532 and/or RDE/RP2D for target and step-in doses (part A: dose escalation); confirm safety and tolerability of BI 764532 at the RDE/RP2D in combination with different SoC regimens (chemotherapy + PD-L1) (part B: dose expansion)
- **Secondary objectives**: evaluate the BI 764532 dose-tolerability relationship during the on-treatment period (part A: dose escalation); assess the efficacy of BI 764532 + SoC (part B: dose expansion)

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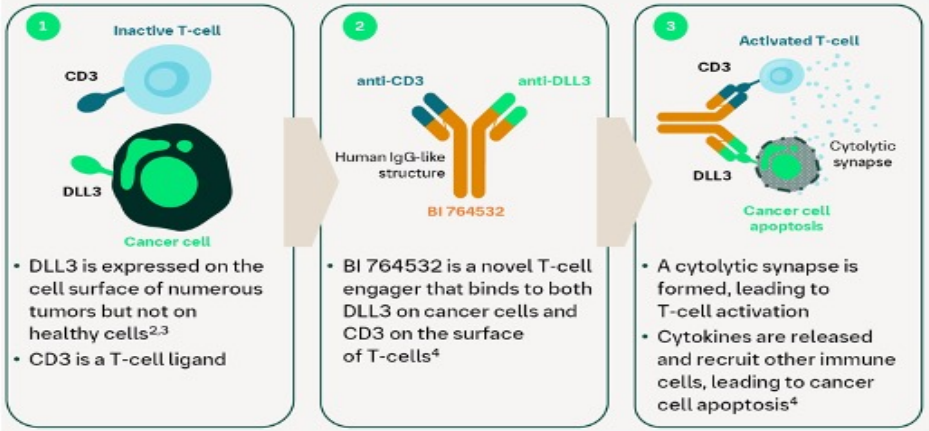
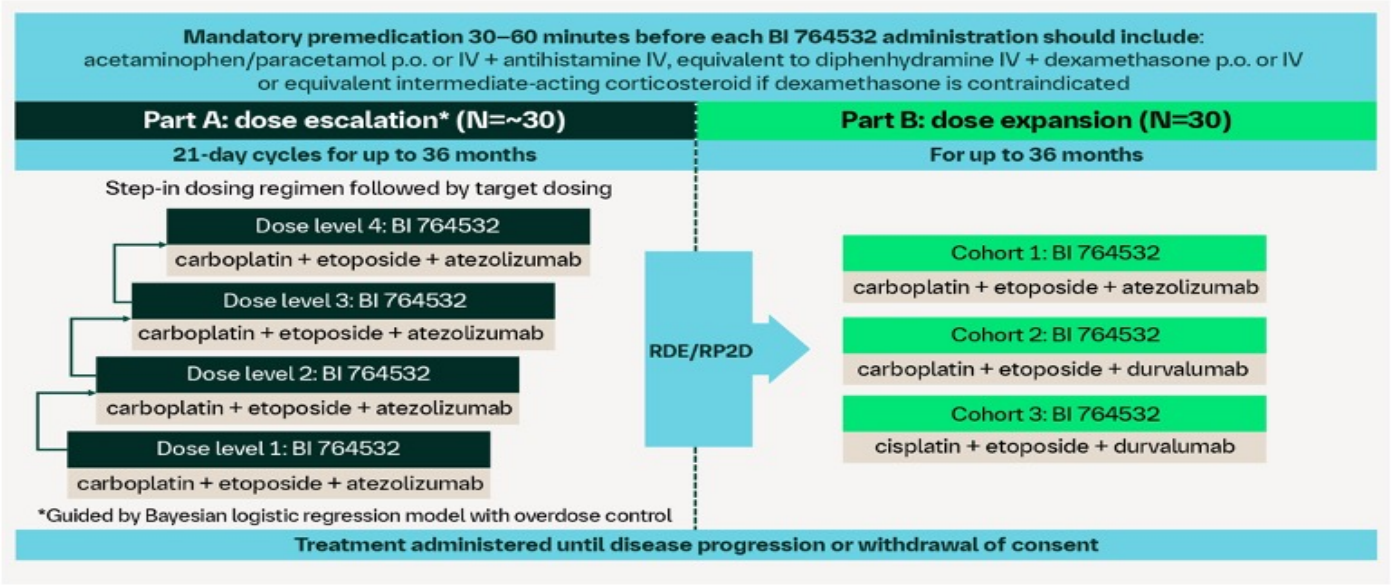
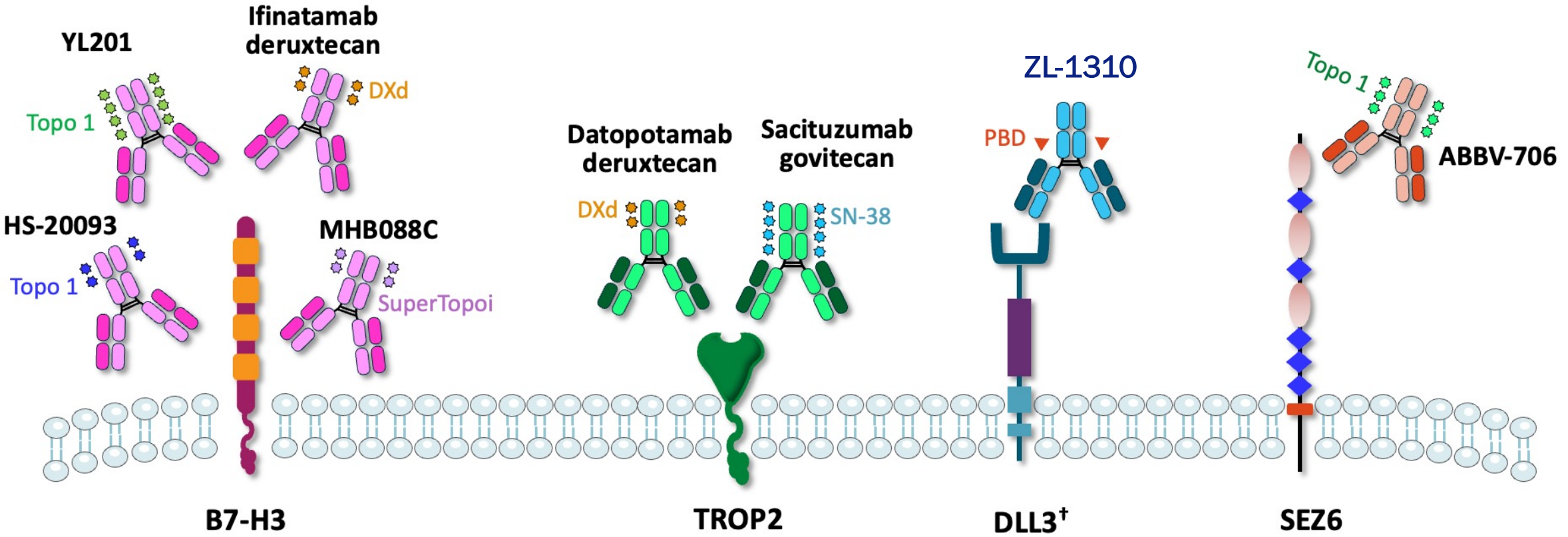


Primary Objective: MTD of BI 764532 and/or RDE/RP2D; confirm safety at the RP2D in combination with different SOC regiments

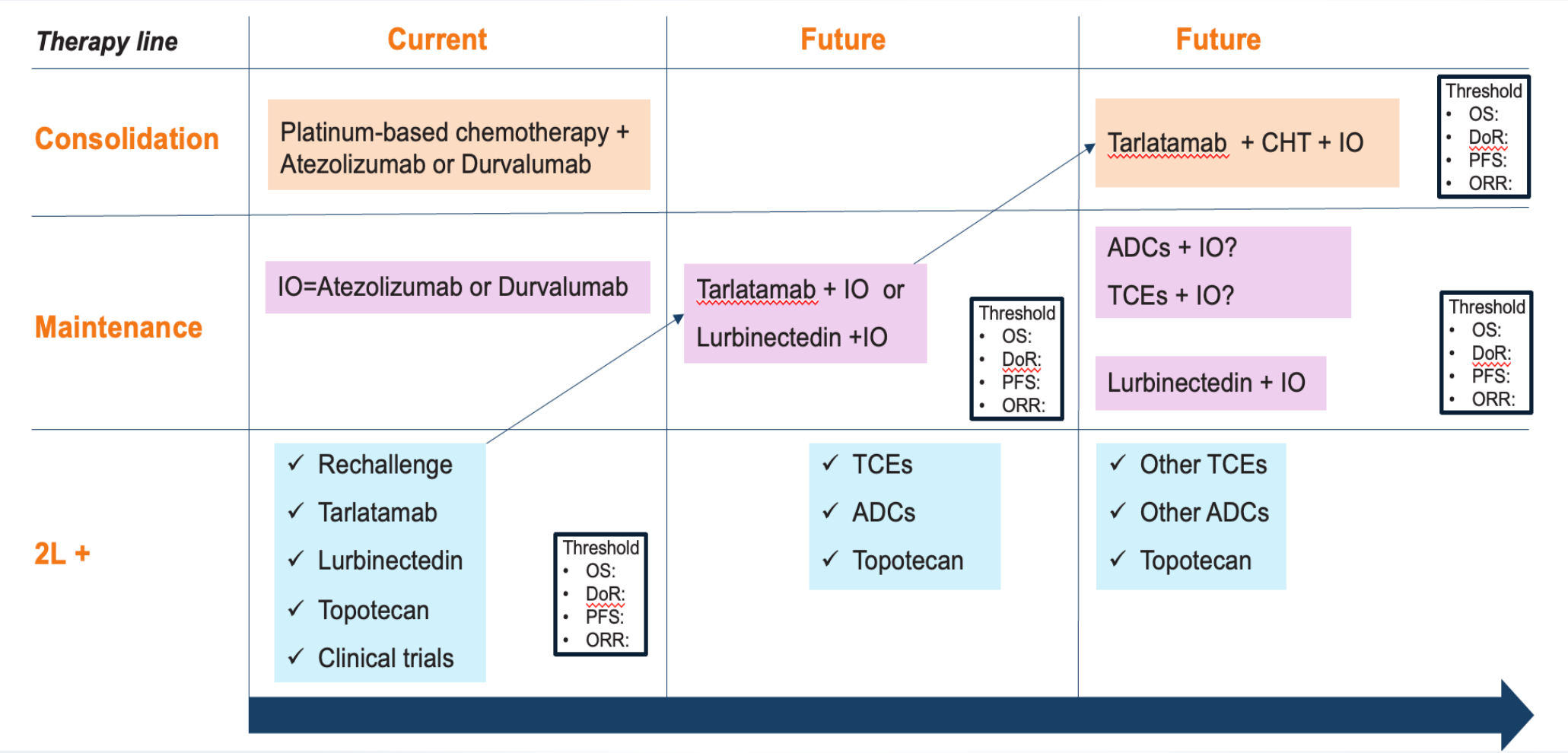
Secondary Objectives: evaluate BI 764532 dose-tolerability relationship during on-treatment period; assess efficacy in combination with SOC



Select ADC Targets Under Investigation in SCLC



What does the future look like?



Ticiana Leal, MD, Winship Cancer Institute, Emory University

Take Home Messages

- Novel strategies have to go beyond chemoimmunotherapy with immune checkpoint inhibitors in ES-SCLC.
- 1L maintenance Lurbinectedin in Combination With Atezolizumab improves PFS and OS.
- Tarlatamab led to improved OS in second-line.
- The front-line setting has the potential to shift with the addition of T cell engagers in maintenance and in 1L.
- ADCs are promising therapeutic strategies; however, it is important to understand target expression patterns to optimize ADC therapy