Limited Stage SCLC:2023

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Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

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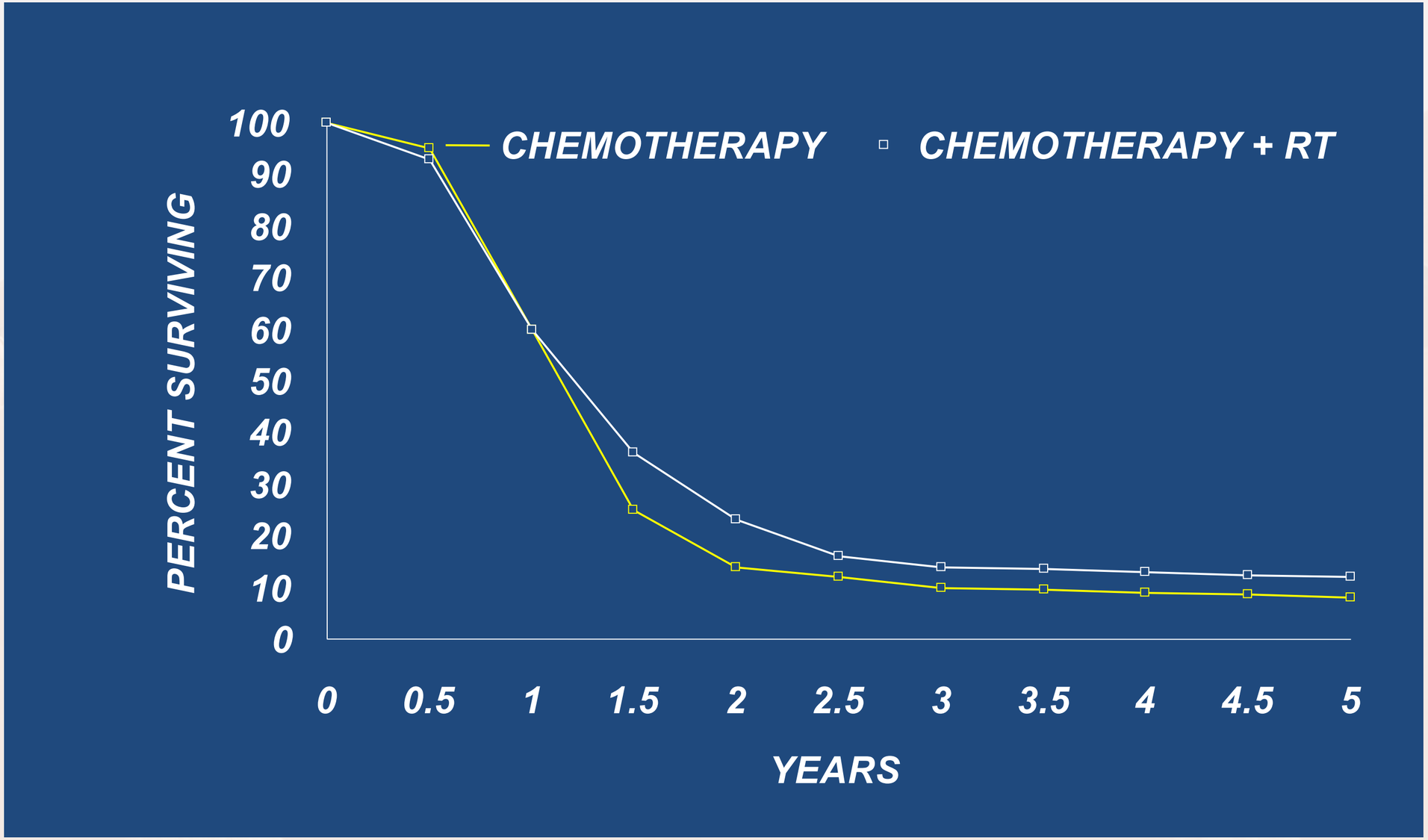
Limited Stage Small cell lung cancer

- Chemotherapy vs Chemotherapy + RT (N = 2103)



Chemotherapy with Chest Radiotherapy in LSCLC

Table 2. Therapeutic Regimens

Modality	Schedule
First-line chemotherapy	Cisplatin 60 mg/m^2 IV day 1; etoposide 120 mg/m^2/d IV days 1-3; repeat every 3 weeks
	Cisplatin 80 mg/m^2 IV day 1; etoposide 100 mg/m^2/d IV days 1-3; repeat every 3-4 weeks
	Cisplatin 80 mg/m^2 IV day 1; etoposide 80 mg/m^2/d IV days 1-3; repeat every 3 weeks
	Cisplatin 25 mg/m^2 IV days 1-3; etoposide 80 mg/m^2/d IV days 1-3; repeat every 3-4 weeks
	Cisplatin 60 mg/m^2 IV day 1; etoposide 120 mg/m^2/d IV days 1-3; repeat every 3 weeks
	Carboplatin AUC 5 IV day 1; etoposide 100 mg/m^2/d IV days 1-3; repeat every 4 weeks
	Carboplatin AUC 5 IV day 1; etoposide 80 mg/m^2/d IV days 1-3; repeat every 3-4 weeks
Thoracic radiotherapy	1.5 Gy twice daily (at least 6 hours apart) in 3 weeks for total dose of 45 Gy
	1.8 Gy daily over 6.5 weeks to total dose of at least 60 Gy
Prophylactic cranial irradiation	25 Gy in 10 daily fractions
	30 Gy in 10-15 daily fractions

LSCLC QD or BID RT

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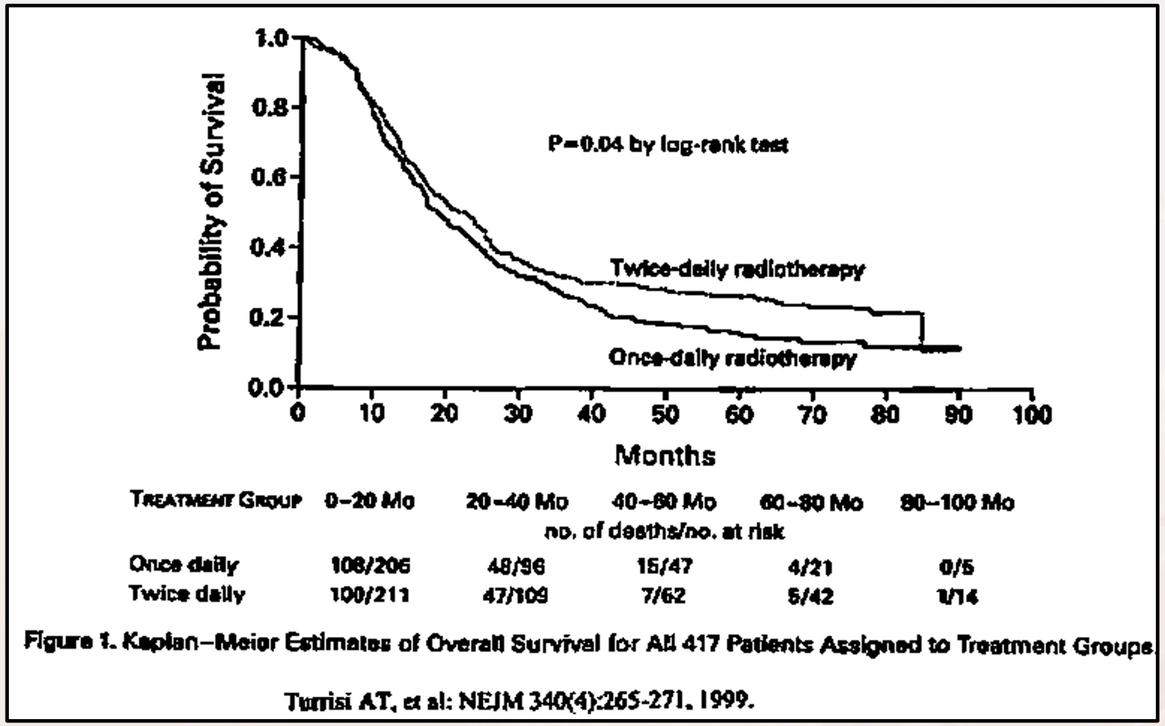
Intergroup 45 Gy QD vs BID

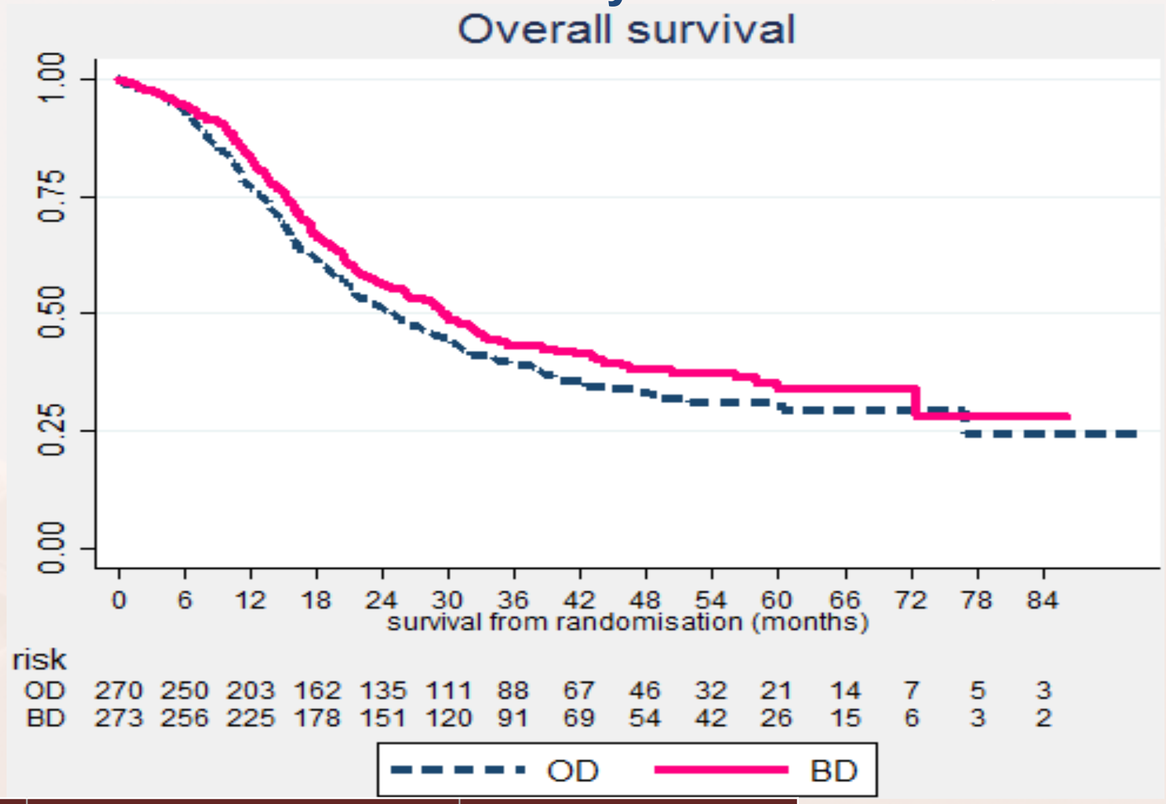


Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

Figure 1. Kaplan–Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

Turrisi AT, et al: NEJM 340(4):265-271, 1999.

CONVERT 45 Gy BID vs 60 GY QD



OS(n=543)	BD	OD	Log-rank
Median Mo.	30 (24-34)	25 (21-31)	p=0.15
1-year	83% (78-87)	76% (71-81)	
2-year	56% (50-61)	51% (45-57)	
3-year	43% (37-49)	39% (33-45)	

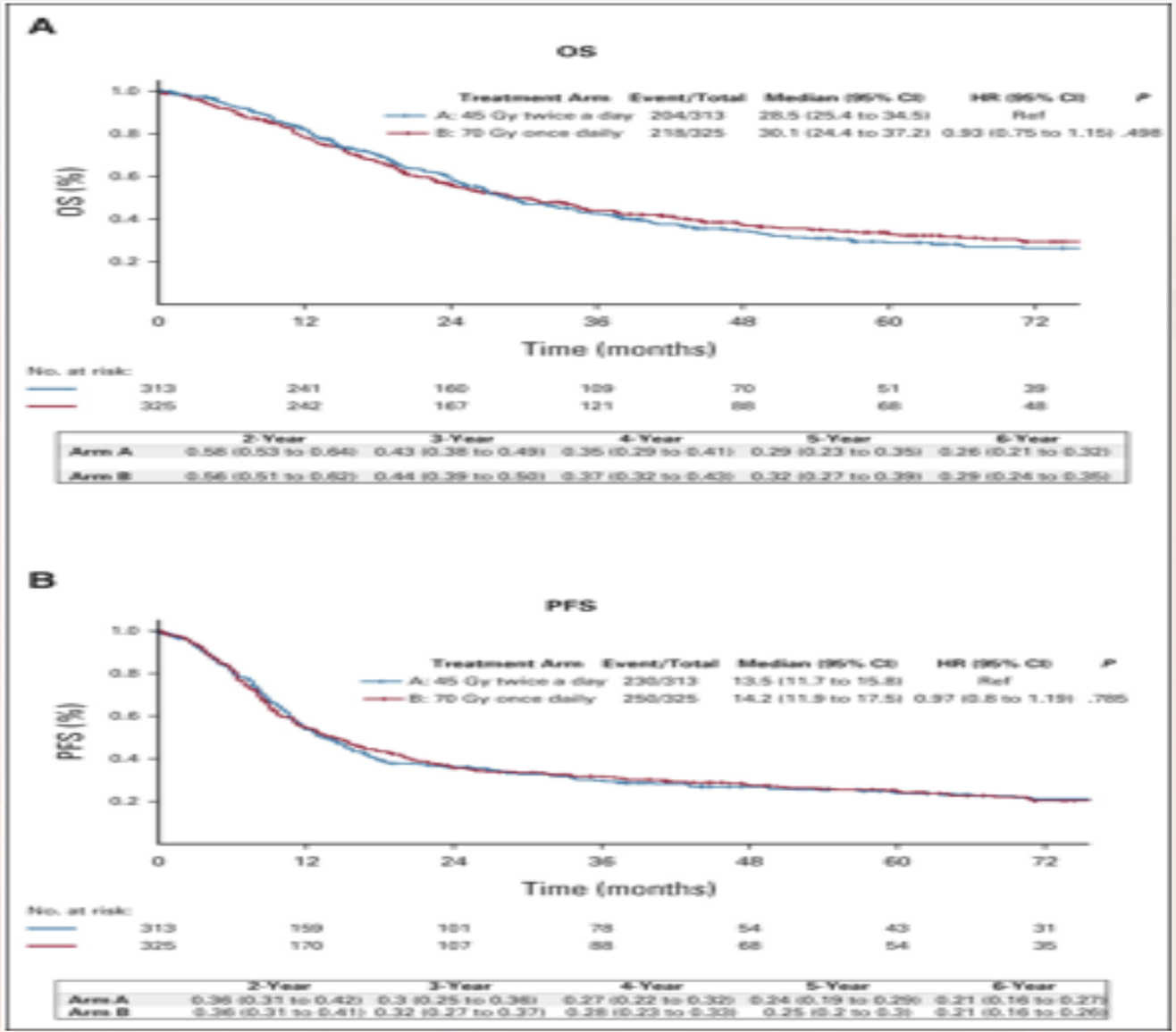
Phase III trials of once-daily thoracic radiation therapy compared towith twice daily in combination with cisplatin and etoposide

First author [reference no.]	#No. of patients	Chemotherapy	Thoracic radiation therapy	Median overall survival (months)	Hazard ratio or *p* value	5-year overall survival rate
Turrisi [22]	206	Cisplatin and etoposide, 4 cycles	45 Gy once daily starting cycle 1	19	$p = .04$	16%
	211	Cisplatin and etoposide, 4 cycles	45 Gy twice daily starting cycle 1	23		26%
Schild [23]	131	Cisplatin and etoposide, 6 cycles	50.4 Gy daily starting cycle 4	20.6	$p = .68$	21%
	130	Cisplatin and etoposide, 6 cycles	Split course: 24 Gy, a 2.5 week break, and 24 Gy starting cycle 4	20.6		22%
Faivre-Finn [24]	274	Cisplatin and etoposide, 4–6 cycles	45 Gy twice daily starting cycle 2	30	HR: 1.18, $p = .14$	34%
	273	Cisplatin and etoposide, 4–6 cycles	66 Gy once daily starting cycle 2	25		31%

Abbreviation: HR, hazard ratio.

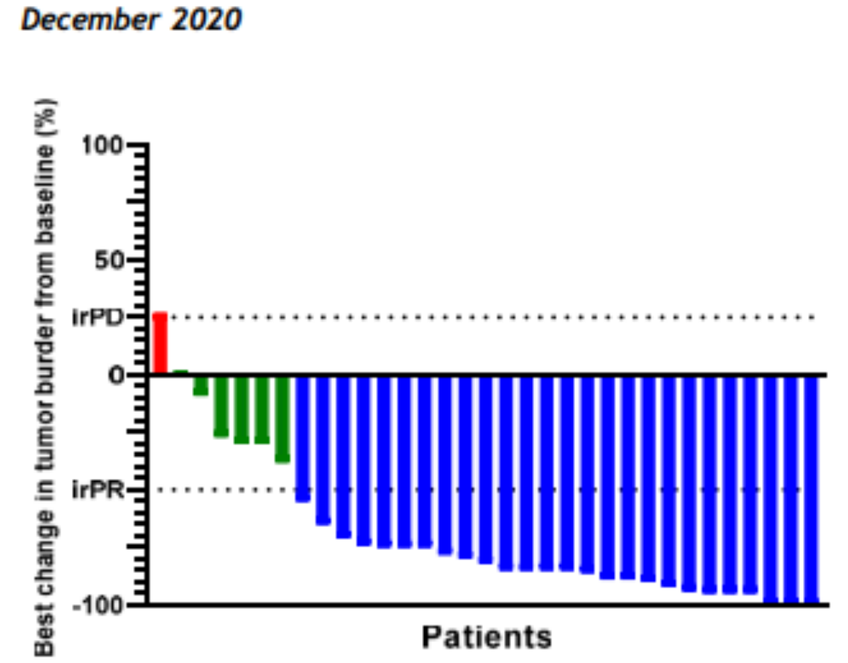
CALGB 30610(Alliance)/RTOG0538
Once daily thoracic radiotherapy in LS SCLC

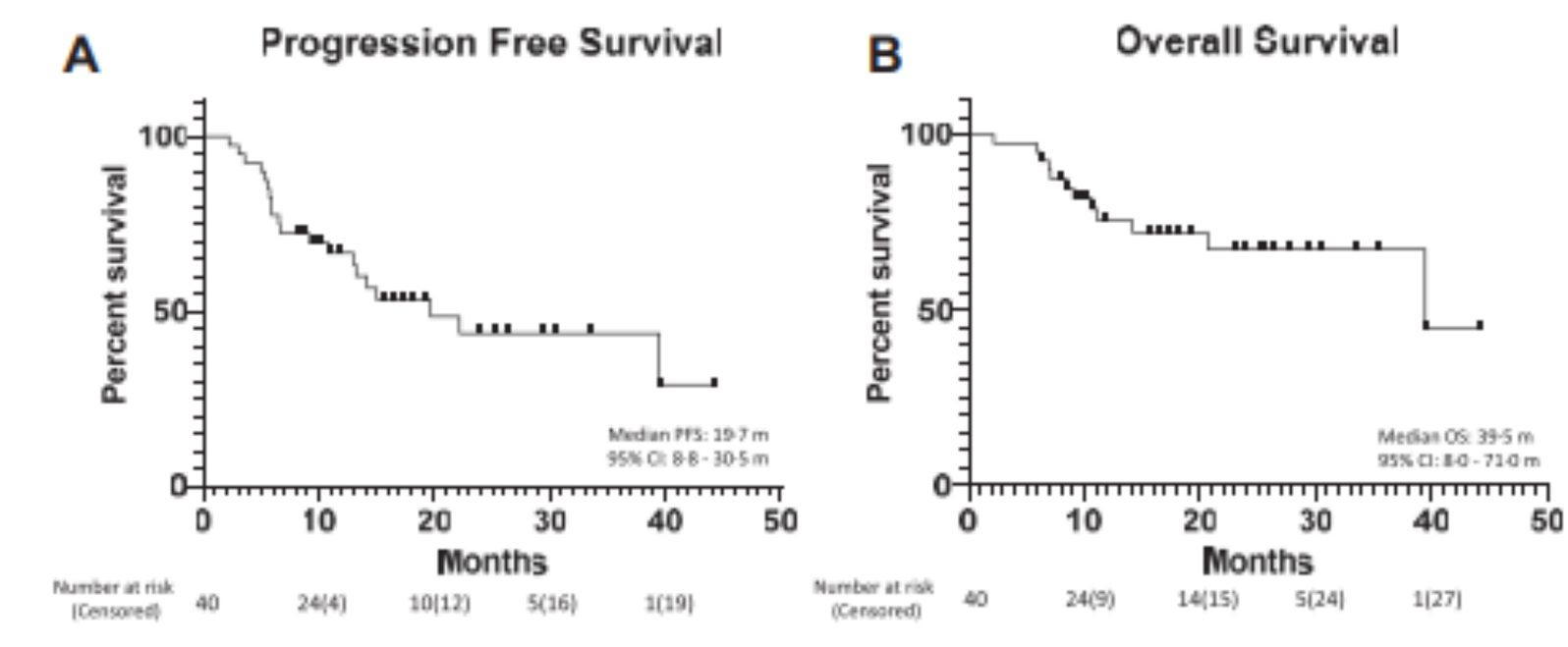
No advantage of 70 gy QD vs 45 Gy BID



Jeffrey Bogart, et al; *Journal of Clinical Oncology* 2023 412394-2402.
DOI: 10.1200/JCO.22.01359

Pembro with concurrent CT/RT in Lim SCLC

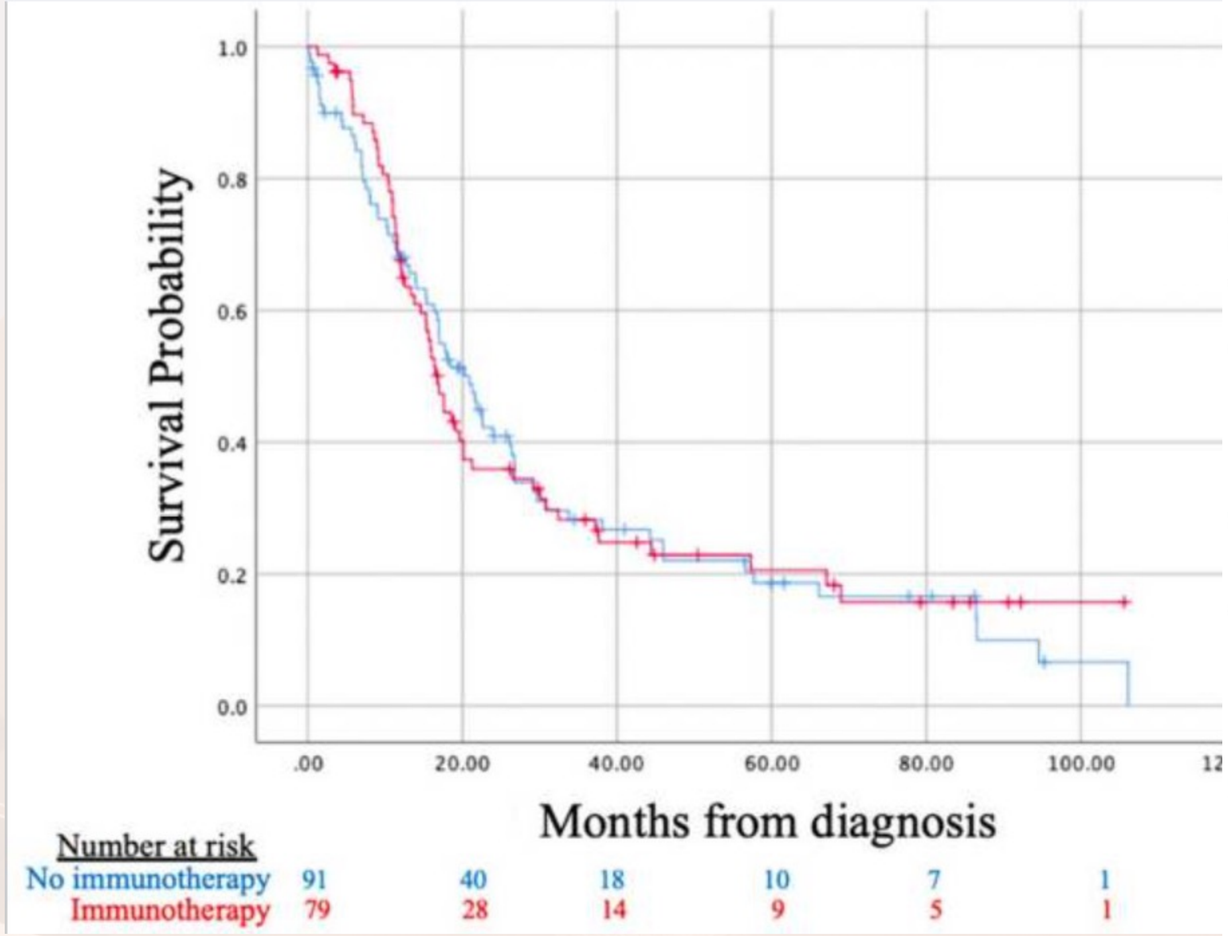




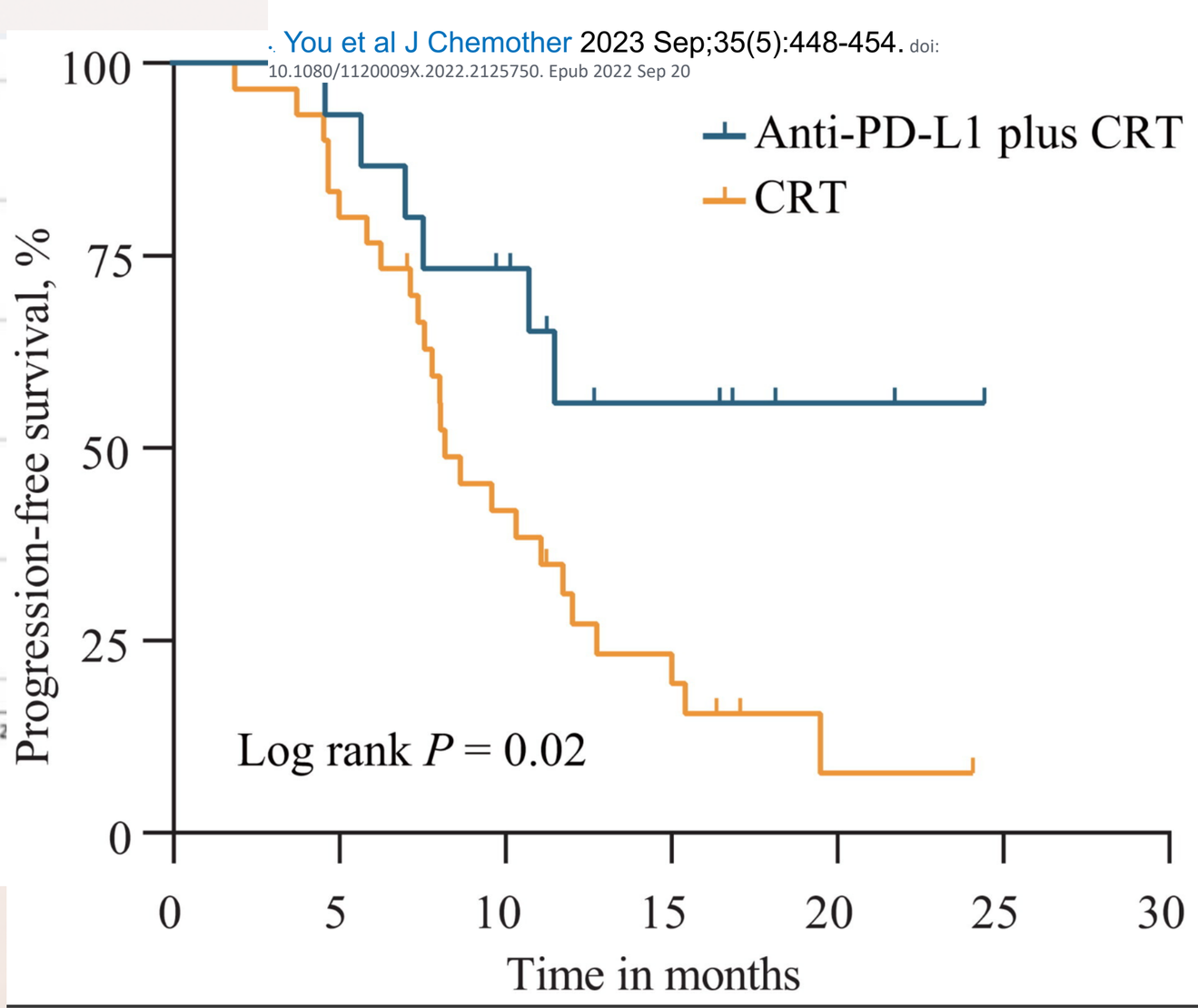
Welsh j et al JTO 15:1919-27, 2020

Randomized trial results pending

Limited “Real World data” on the addition of Immunotherapy to CT/RT in LSCLC



. You et al J Chemother 2023 Sep;35(5):448-454. doi: 10.1080/1120009X.2022.2125750. Epub 2022 Sep 20



Ongoing phase II and Phase III Trials in Lim. SCLC

Bogart et al:JCO

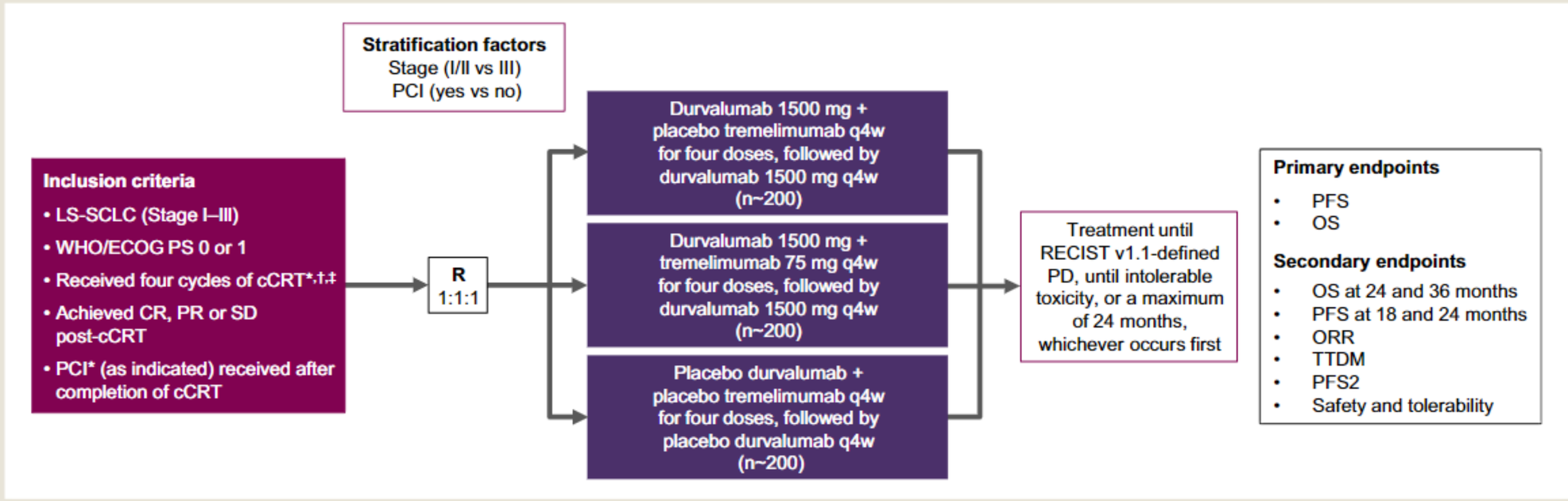
Agent	Mechanism of Action	Phase	Sample Size	Primary End Point	NCT
Concurrent with chemoradiation and as consolidation					
Durvalumab	Anti–PD-L1	2	51	PFS	NCT03585998
Durvalumab (DOLPHIN)	Anti–PD-L1	2	105	PFS	NCT04602533
Pembrolizumab concurrent followed by pembrolizumab ± olaparib (KEYLYNK-013)	Anti–PD-1 and PARP inhibitor	3	672	PFS, OS	NCT04624204
Atezolizumab (NRG LU-005)	Anti–PD-L1	2 or 3	506	PFS or OS	NCT03811002
Sintilimab induction plus platinum-etoposide, followed by chemoradiation and sintilimab consolidation	Anti–PD-1	2	140	PFS	NCT04189094
Consolidation following chemoradiation					
Toripalimab	Anti–PD-1	2	170	PFS	NCT04418648
SHR-1316	Anti–PD-1	2	60	PFS	NCT04647357
Atezolizumab (ACHILES)	Anti–PD-L1	2	212	2 year OS	NCT03540420
Ipilimumab and nivolumab (STIMULI)	Anti–CTLA-4 and anti–PD-1	2	174	OS, PFS	NCT02046733
Durvalumab plus or minus tremelimumab (ADRIATIC)	Anti–PD-L1 and anti–CTLA-4	3	724	PFS, OS	NCT03703297
Atezolizumab ± tiragolumab	Anti–PD-L1 and anti–TIGIT	2	150	PFS	NCT04308785

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte-4; ICI, immune checkpoint inhibitor; LS-SCLC, limited-stage small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

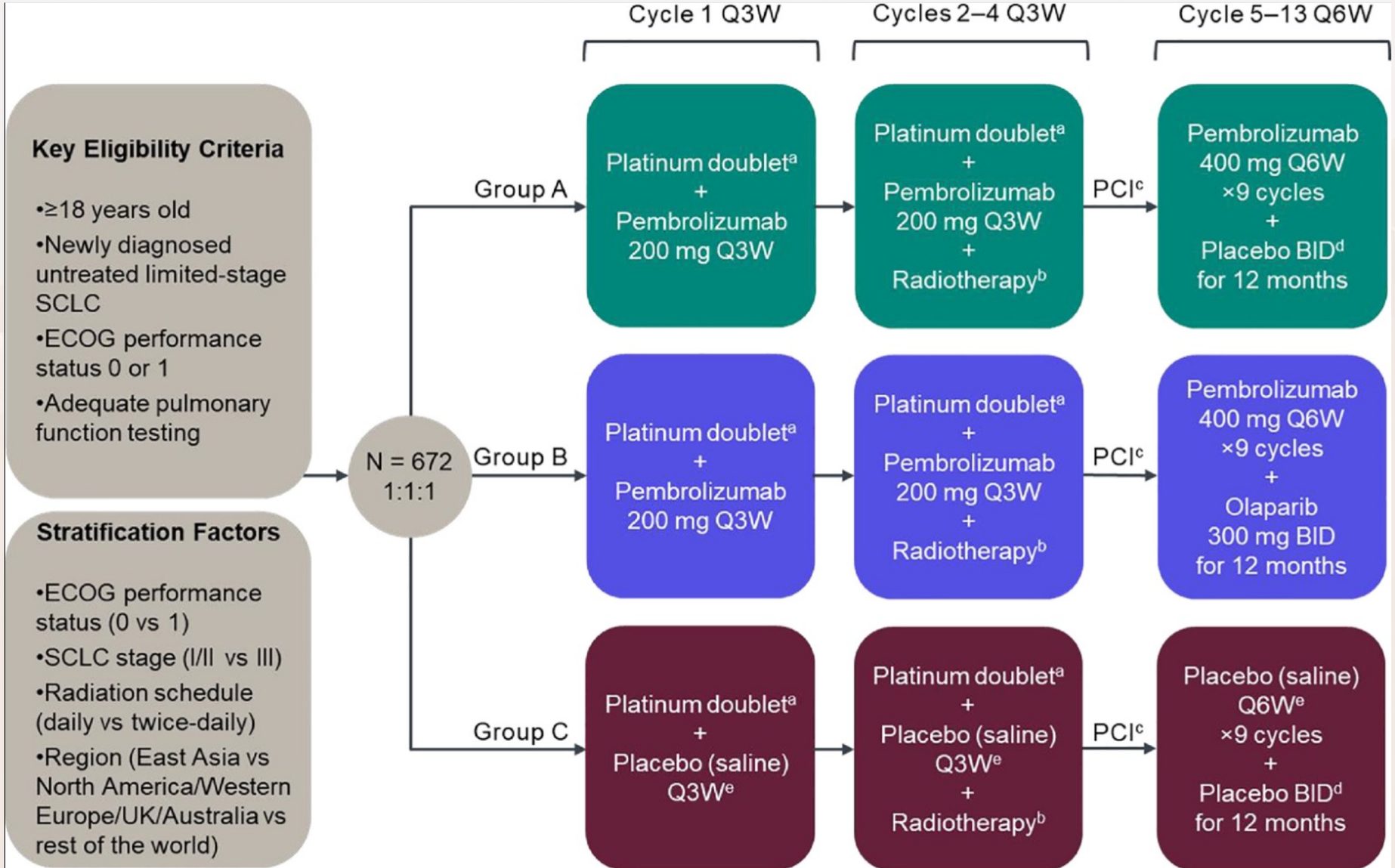
CT/RT +/- Dura or Durva Tremi

The ADRIATIC Study

Figure 1 **Study Design. *Concurrent Chemoradiotherapy (cCRT) and Prophylactic Cranial Irradiation (PCI) Must Be Completed Within 1 to 42 Days Before Randomization and Treatment Initiation. †Three Cycles of Platinum-based Chemotherapy Is Permitted if Disease Control Was Achieved and No Additional Benefit Can Be Expected From an Additional Cycle as Determined by the Investigator. ‡The Radiotherapy Component Must Have Been Initiated No Later Than the End of Cycle 2 of Chemotherapy and Consist of Either 60 to 66 Gy Over 6 weeks (Standard Once-daily Schedule) or 45 Gy Over 3 Weeks (Hyperfractionated Twice-daily Schedule)**



Keylink-013 Study Design

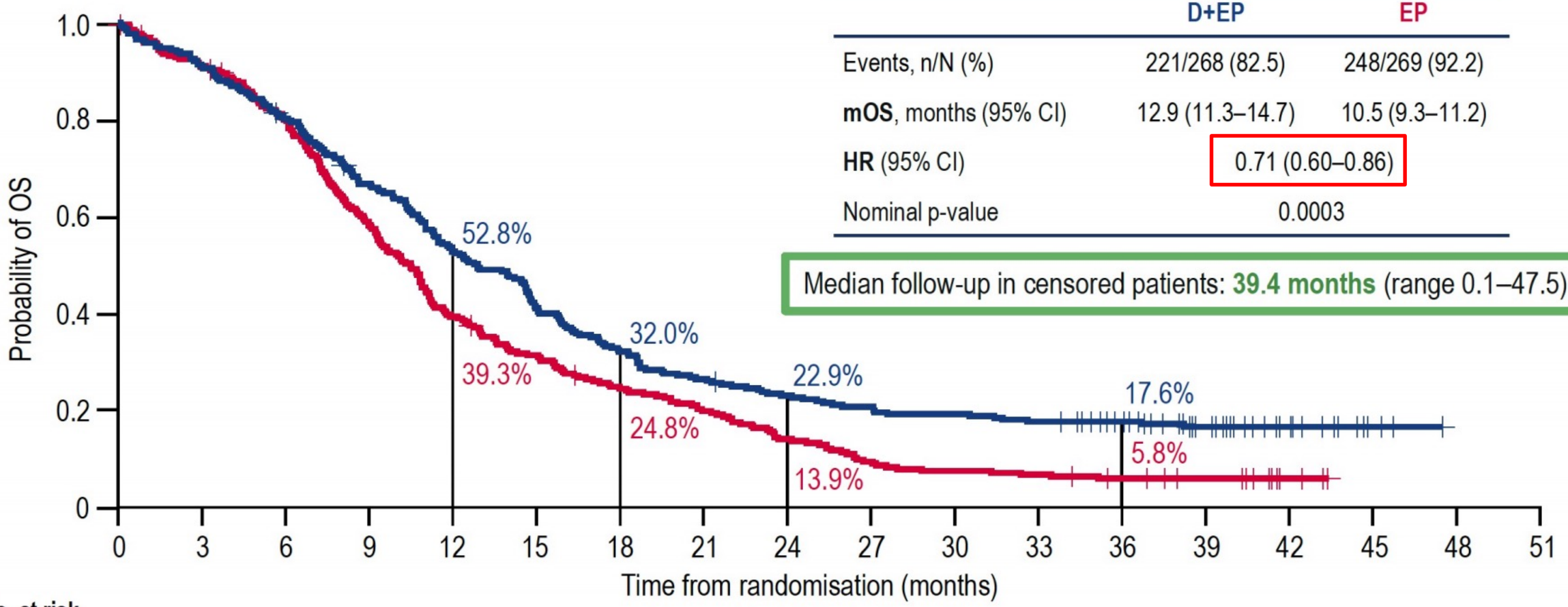


CASPIAN 3-Year OS Update: Durvalumab + EP vs EP[1]

If IO Increases LTS to 18% in ESCLC Will it Increase LTS in LSCLC as well?

	D+EP	EP
Events, n/N (%)	221/268 (82.5)	248/269 (92.2)
mOS, months (95% CI)	12.9 (11.3–14.7)	10.5 (9.3–11.2)
HR (95% CI)	0.71 (0.60–0.86)	
Nominal p-value	0.0003	

Median follow-up in censored patients: **39.4 months** (range 0.1–47.5)



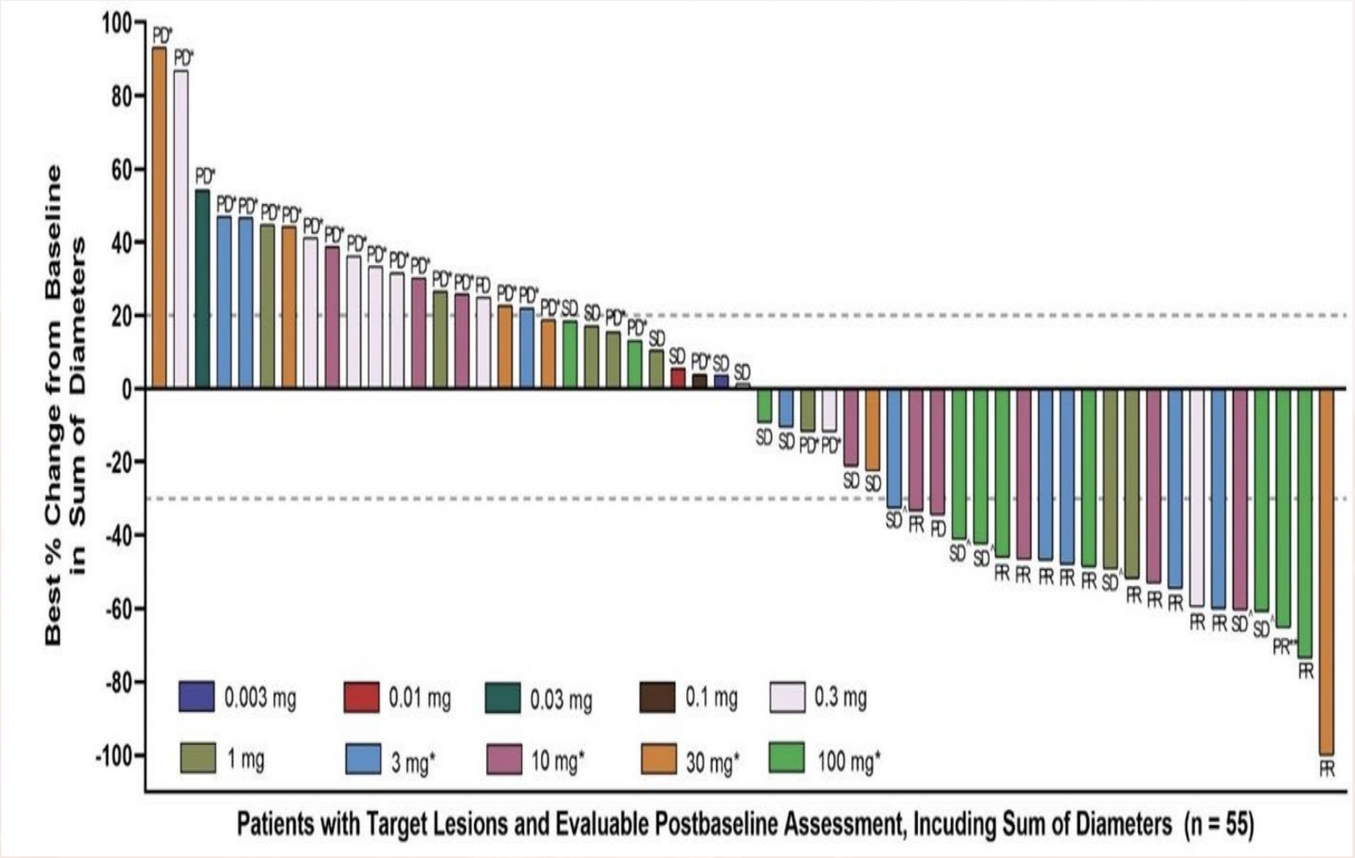
No. at risk

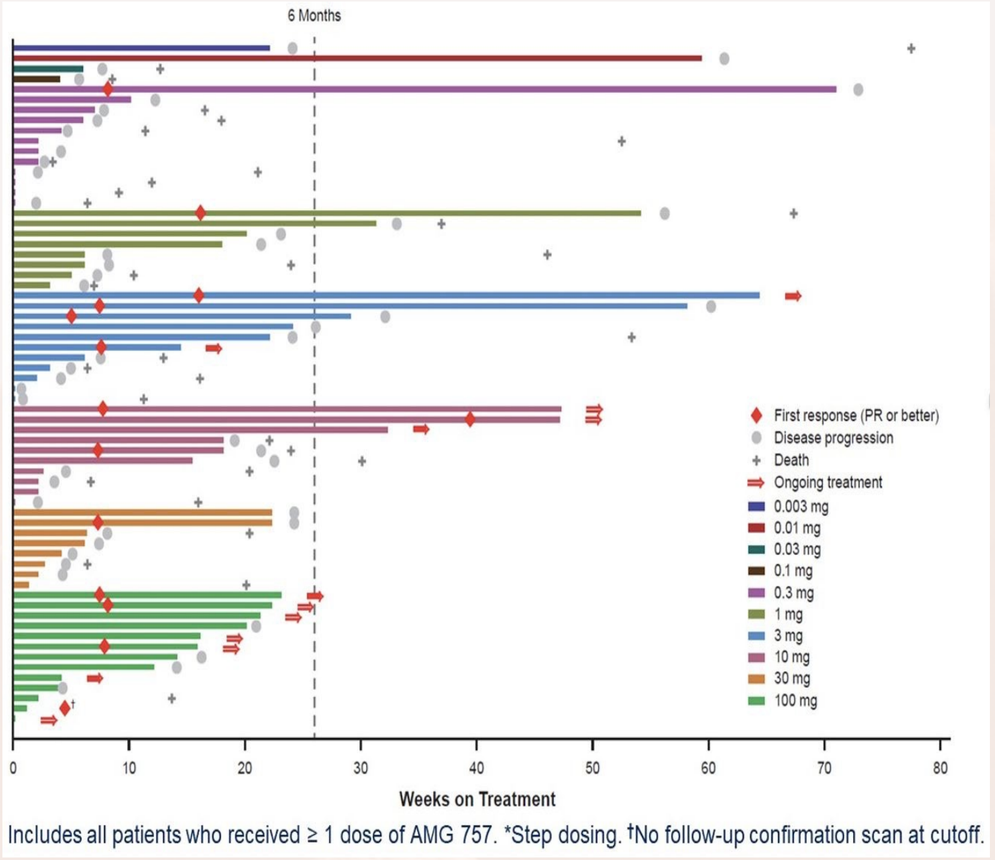
D+EP	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

Data cutoff: March 22, 2021. Size of circle is proportional to the number of events across both treatment groups.

1. Paz-Ares LG et al. ESMO 2021. Abstract LBA61.

The Future: ?Bites, Trites: AMG757 Tarlatamab





Includes all patients who received ≥ 1 dose of AMG 757. *Step dosing. †No follow-up confirmation scan at cutoff.

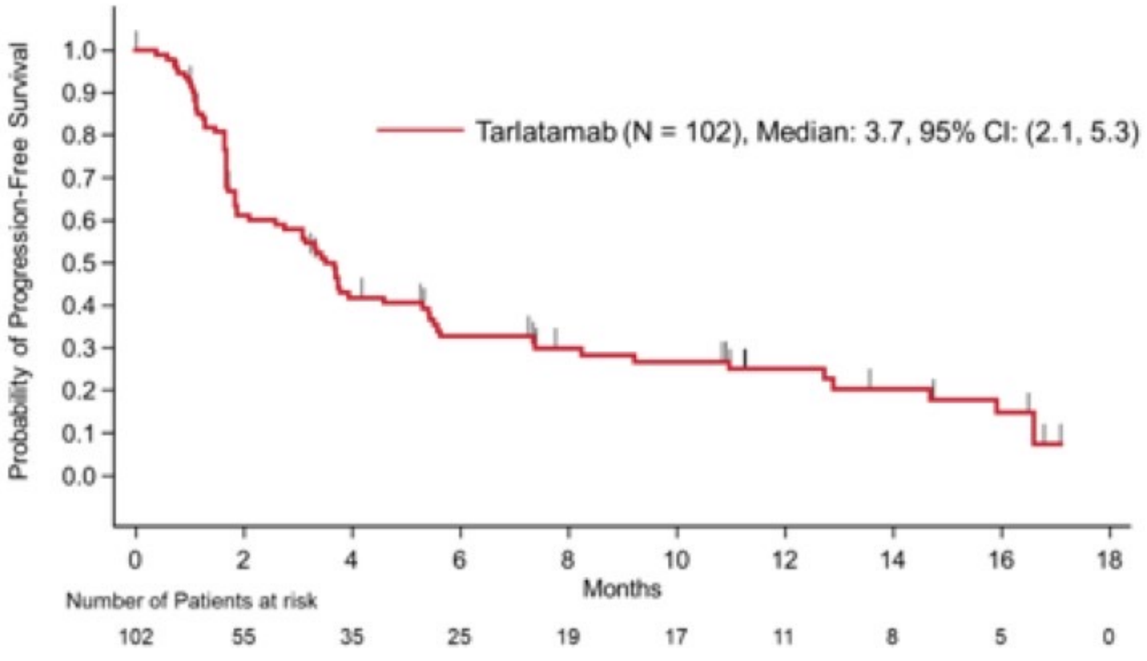
- Tox: Mostly CRS (44% all grade, 2% G3+)
- DLTs: G5 pneumonitis (1), G3 encephalopathy (1)
- ORR: 20%, but 30+% @ higher doses
- mDoR: 8.7m

Owonikoko et al. ASCO 2021

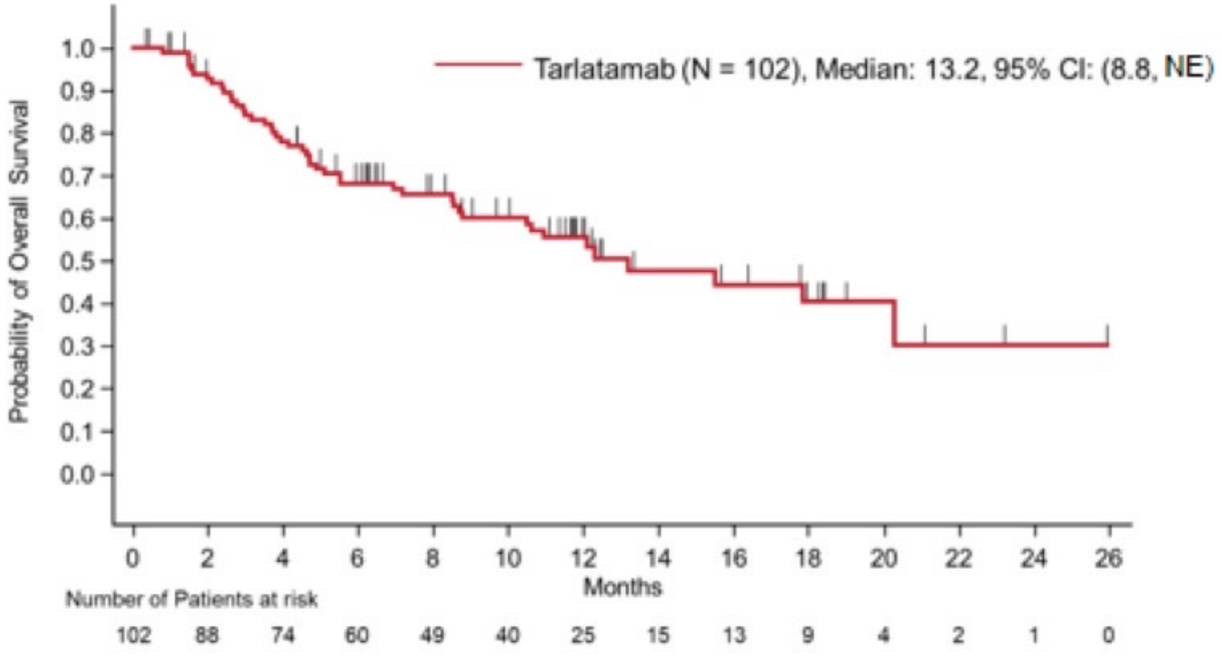
Harpoon and BI also have DLL3 Bites with similar preliminary data

Survival with Tarlatamab in Previously Treated SCLC

Progression-Free Survival



Overall Survival



Median overall survival of 13.2 months (95% CI: 8.8, NE)

CI, confidence interval; NE, not estimable; SCLC, small cell lung cancer

*Survival analysis population (N=102) included subjects who received their first dose on or prior to 16Dec2021 to allow at least 6 months of follow-up to allow sufficient data maturity before data cutoff.

Borghaei H, et al. Presented at World Conference on Lung Cancer (WCLC) 2022 Annual Meeting, August 6-9, 2022; Vienna, Austria.

The Future: ? ADCs

ADCs in SCLC: Summary

Target	Payload/MOA	Agent	Drug Ab ratio (DAR)	SCLC activity RR, DOR	Source
DLL3	Pyrrolobenzodiazepine (PBD)	Rovalpituzumab Tesirine; Rova-T	~2	--	
TROP2	SN-38; topo I inhibitor Deruxtecan; topo I inhibitor	Sacituzumab-govitecan; IMMU-132 Datopotamab deruxtecan; DS-1062a	~7-8 ~4	N=50, ORR 14%; DOR 5.7 mo	NCT01631552 Gray, et al. CCR 2017 NCT03401385
B7-H3 (CD276)	Deruxtecan; topo I inhibitor	Ifinatamab deruxtecan; DS-7300, I-DXd	~4	N=19, 58% ORR; DOR 5.5 mo	NCT04145622
SEZ6	Calicheamycin; induces DS breaks Proprietary	ABBV-011 ABBV-706	~2	--	NCT03639194 NCT05599984
CEACAM5	Maytansinoid DM4; MT inhibitor	Tusamitamab ravtansine (SAR408701)	~3.8	--	NCT02187848
B7-H3	Clezutoclax;BCL2/XL inhibitor	Mirzotamab clezutoclax; ABBV-155		--	NCT03595059