Limited and Extensive Stage SCLC:
New Standard of Care and Novel Advances

Alberto Chiappori, MD
Senior Member
Department of Thoracic Oncology
Moffitt Cancer Center

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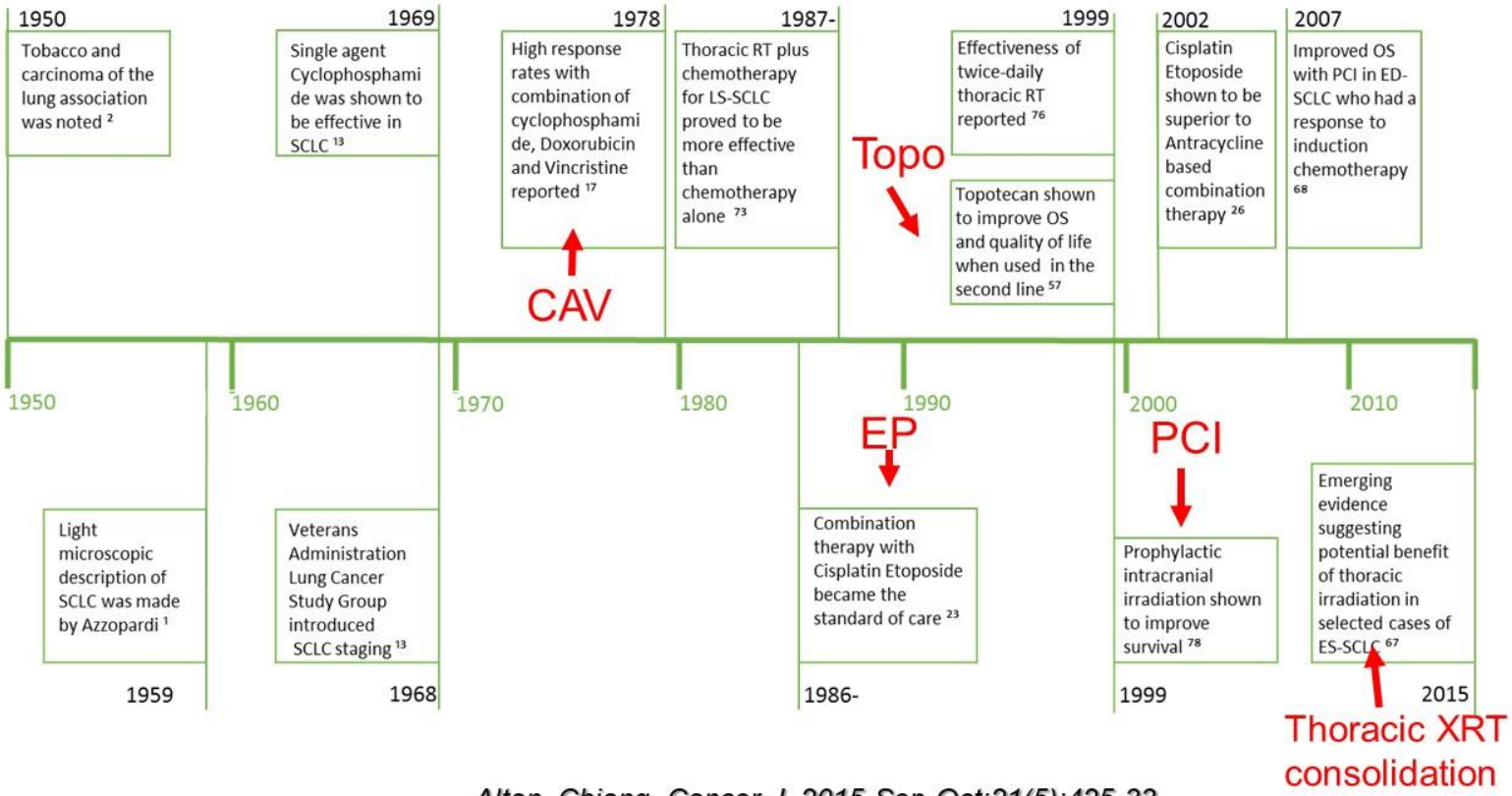
IMMUNOTHERAPY

The Past Era of Chemotherapy and Radiation

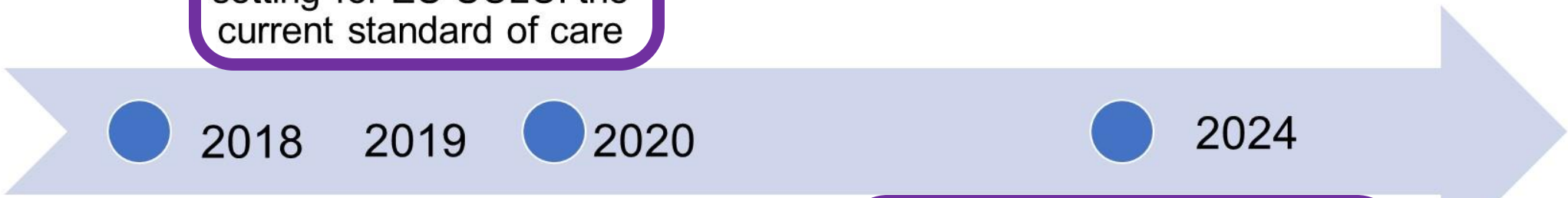


Altan, Chiang. Cancer J. 2015 Sep-Oct;21(5):425-33

The Current Era of Immunotherapy (IO)

IMpower-133 and CASPIAN:

Using IO in the frontline setting for ES-SCLC: the current standard of care



Checkmate-032 and KEYNOTE-158:
Using IO in 3L setting, subsequently withdrawn due to negative phase III trials but still in NCCN guidelines if no prior IO exposure

ADRIATIC:

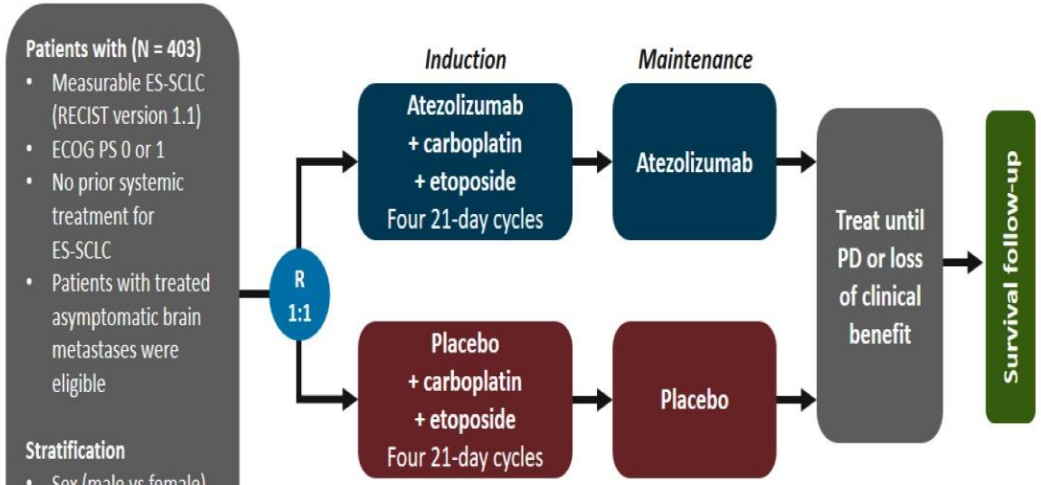
Using IO as consolidation in the limited stage setting ASCO 2024, likely to be approved by FDA

ES-SCLC Immunotherapy

New First Line Standard

First-Line Treatment: IMpower133

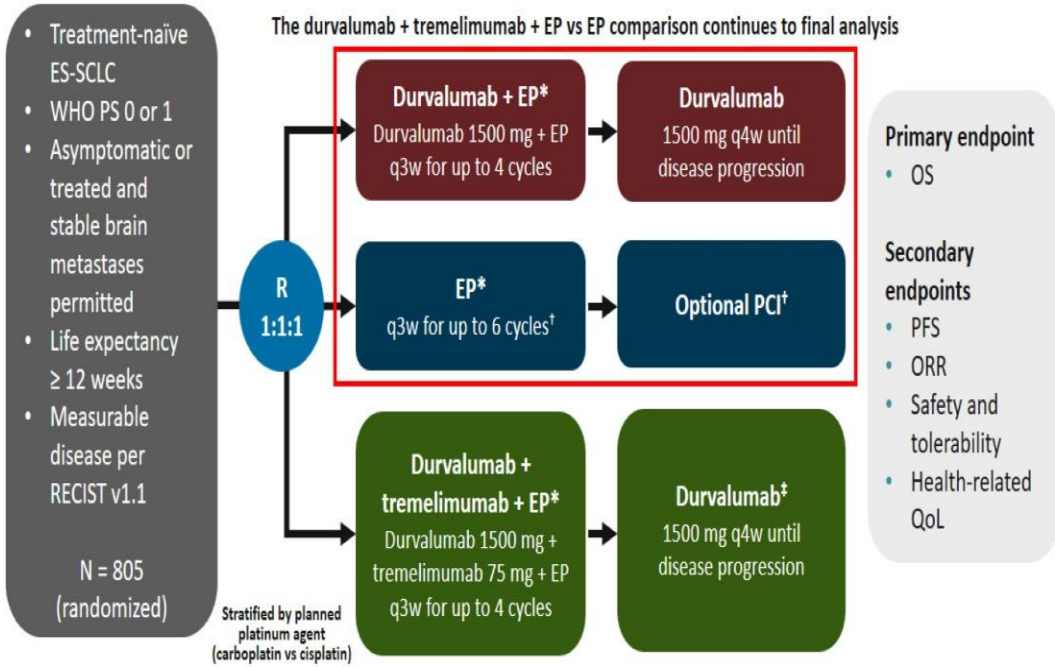
Study Design



Note: Atezolizumab, 1200 mg IV, Day 1; Carboplatin, AUC 5 mg/mL/min IV, Day 1; Etoposide, 100 mg/m 2 IV, Days 1–3.
*Only patients with treated brain metastases were eligible.
Horn L, et al. *N Engl J Med*. 2018;379:2220-2229; Reck M, et al. ESMO 2019. Presentation 1736O.

First-Line Treatment: CASPIAN

Study Design



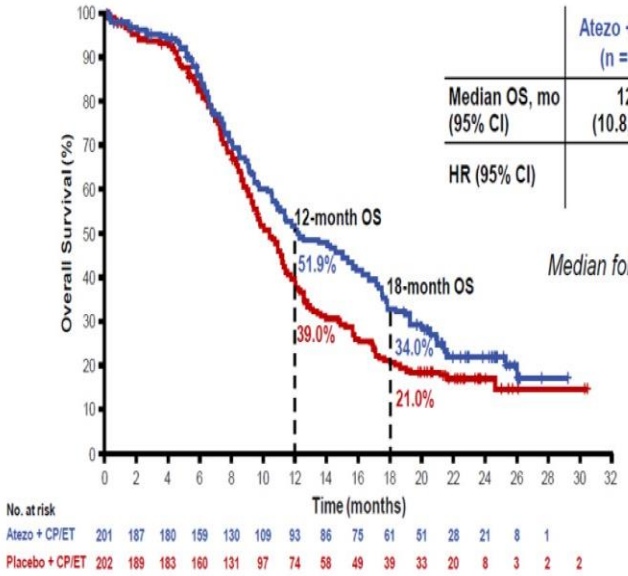
*EP consists of etoposide 80–100 mg/m^2 with either carboplatin AUC 5-6 or cisplatin 75-80 mg/m^2; †Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion; ‡Patients received an additional dose of tremelimumab post-EP.
Paz-Ares L, et al. *Lancet*. 2019;394:1929-1939; Paz-Ares L, et al. WCLC 2019. Presentation PL02.11.

ES-SCLC Chemo-Immunotherapy

New First Line Standard

First-Line Treatment: IMpower133

Updated Results



	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)
HR (95% CI)	0.76 (0.60, 0.95) p = 0.0154[a]	

Median follow-up, 22.9 months

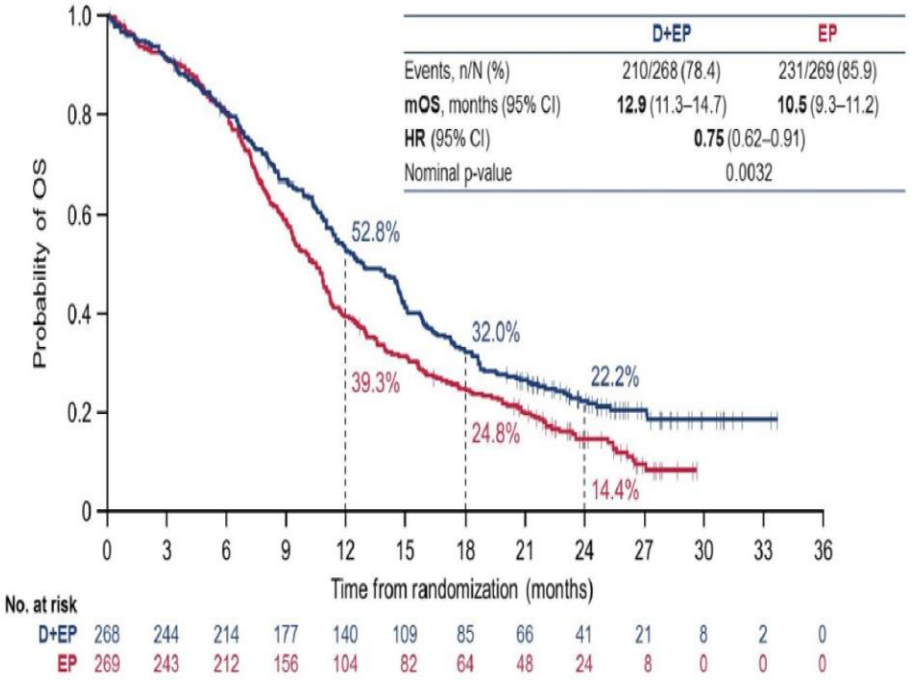
[a]p-value is provided for descriptive purpose.
CCOD 24 January 2019

Endpoint	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
ORR, %	60.2	64.4
mDOR, mo	4.2	3.9

Reck M, et al. ESMO 2019. Presentation 1736O.

First-Line Treatment: CASPIAN

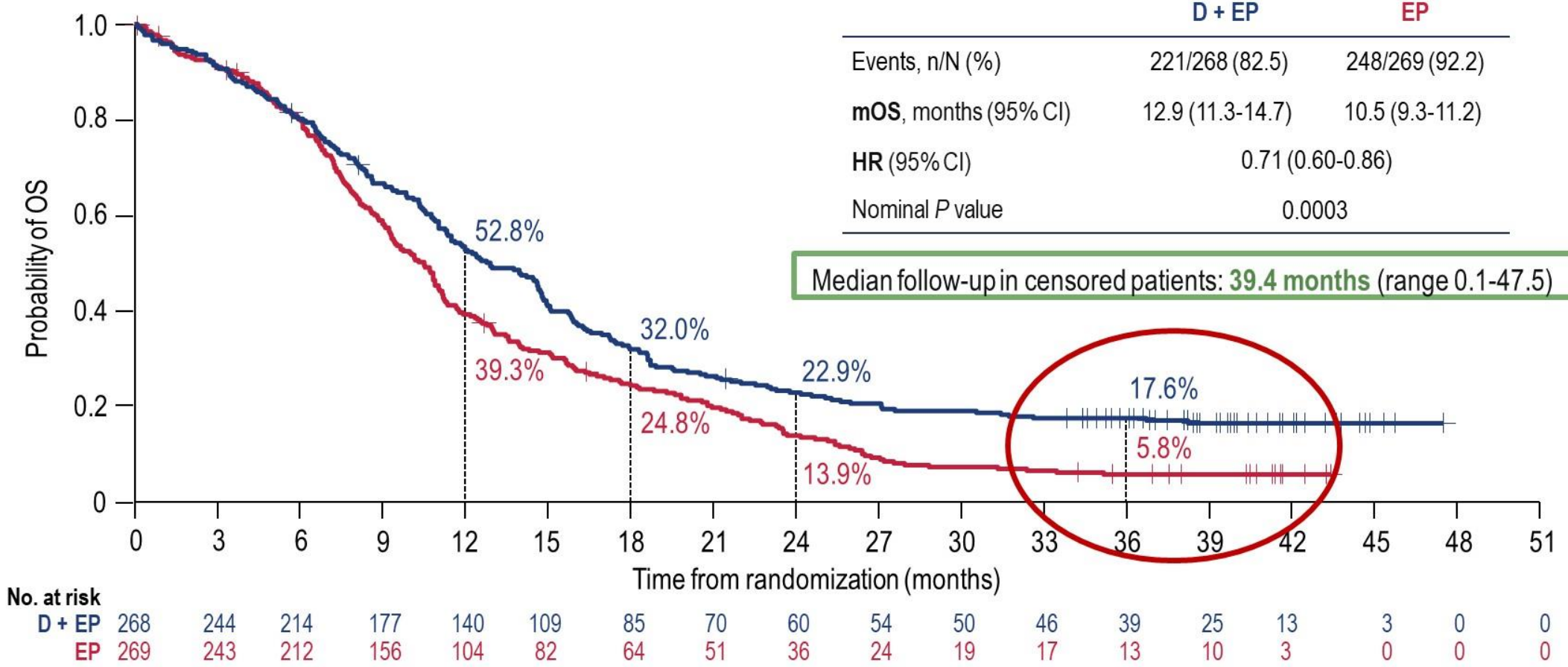
Updated OS



	D+EP	EP
Events, n/N (%)	210/268 (78.4)	231/269 (85.9)
mOS, months (95% CI)	**12.9** (11.3–14.7)	**10.5** (9.3–11.2)
HR (95% CI)	**0.75** (0.62–0.91)	
Nominal p-value	0.0032	

Paz-Ares L, et al. ASCO® 2020. Presentation 9002.

CASPIAN 3-Year OS Update: Durvalumab/EP vs EP



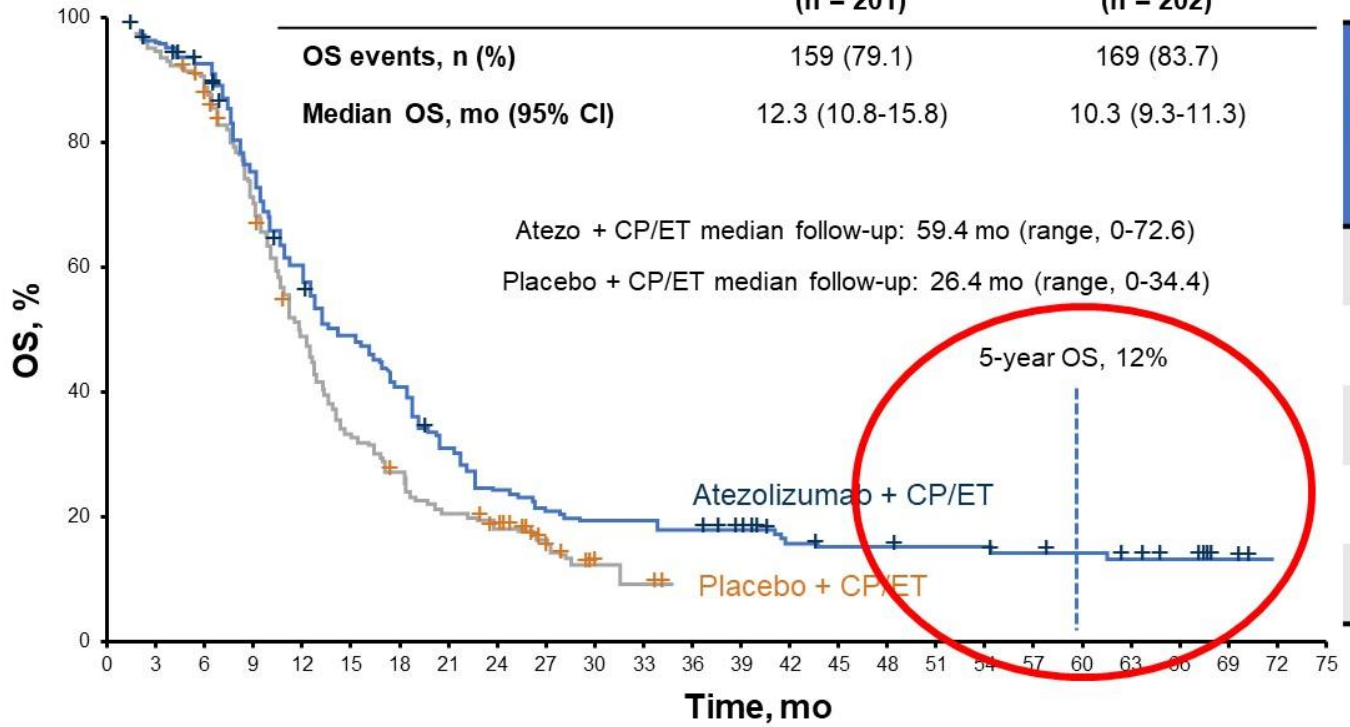
	D + EP	EP
Events, n/N (%)	221/268 (82.5)	248/269 (92.2)
mOS, months (95% CI)	12.9 (11.3-14.7)	10.5 (9.3-11.2)
HR (95% CI)	0.71 (0.60-0.86)	
Nominal *P* value	0.0003	

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

Data cutoff: March 22, 2021. Paz-Ares LG, et al. *Ann Oncol*. 2021;32(suppl 5):S1283-S1346.

IMpower133 and IMbrella A: Long-Term OS

	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
OS events, n (%)	159 (79.1)	169 (83.7)
Median OS, mo (95% CI)	12.3 (10.8-15.8)	10.3 (9.3-11.3)



No. at Risk																								
Atezo + CP/ET	201	182	159	121	93	81	61	48	38	33	30	30	28	26	17	15	15	14	14	12	11	10	8	7	2
Placebo + CP/ET	202	186	160	114	74	55	39	34	25	11	3	2													

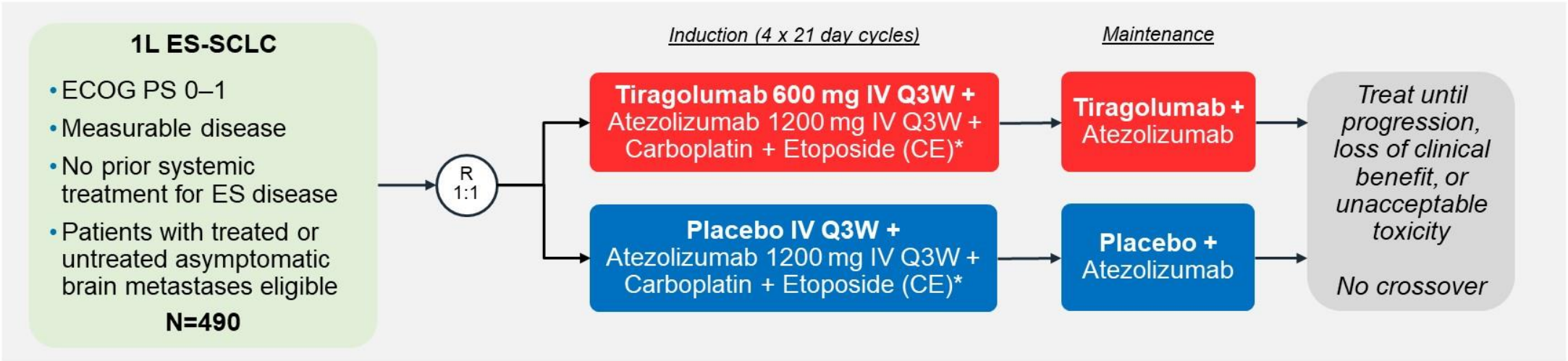
OS Rate, y	IMpower133 & IMbrella A: Atezo + CP/ET, % (95% CI) (n = 201)	IMpower133 Only: Placebo + CP/ET, % (95% CI) (n = 202)
1	52 (45-59)	39 (32-46)
2	22 (16-28)	16 (11-21)
3	16 (11-21)	NE[a]
4	13 (8-18)	NE[a]
5	12 (7-17)	NE[a]

Clinical cutoff date: 16 Mar 2023.

[a] OS rates were NE in the control arm as rollover to IMbrella A was not permitted.

1. Liu S et al. WCLC 2023. Oral presentation.

SKYSCRAPER-02: randomized, double-blind, placebo-controlled study of tiragolumab + atezolizumab + chemotherapy in patients with untreated ES-SCLC



Stratification Factors:

- **ECOG PS** (0 vs. 1)
- **Brain metastases** (Yes vs. No)
- **LDH** (≤ ULN vs. > ULN)

Co-Primary Endpoints:

- OS and investigator-assessed PFS in **Primary Analysis Set** (all randomized patients without presence or history of brain metastases at baseline)

Secondary Endpoints:

- PFS and OS in **Full Analysis Set** (all randomized patients)
- Confirmed objective response rate
- Duration of response
- Safety
- Pharmacokinetics
- PROs

Primary analysis

- Cut-off date of 6 February 2022
- Median follow-up of 14.3 months (Primary Analysis Set)

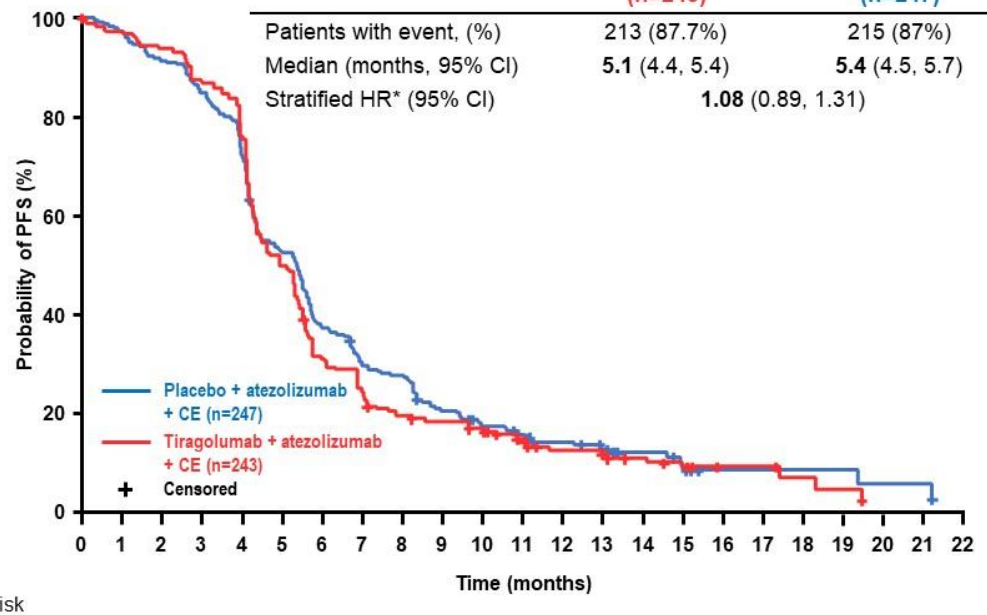
NCT04256421

*Carboplatin IV AUC 5 mg/mL per min Q3W and etoposide IV 100mg/m^2 body surface area days 1–3 Q3W

PFS and OS: Full Analysis Set

PFS in the Full Analysis Set

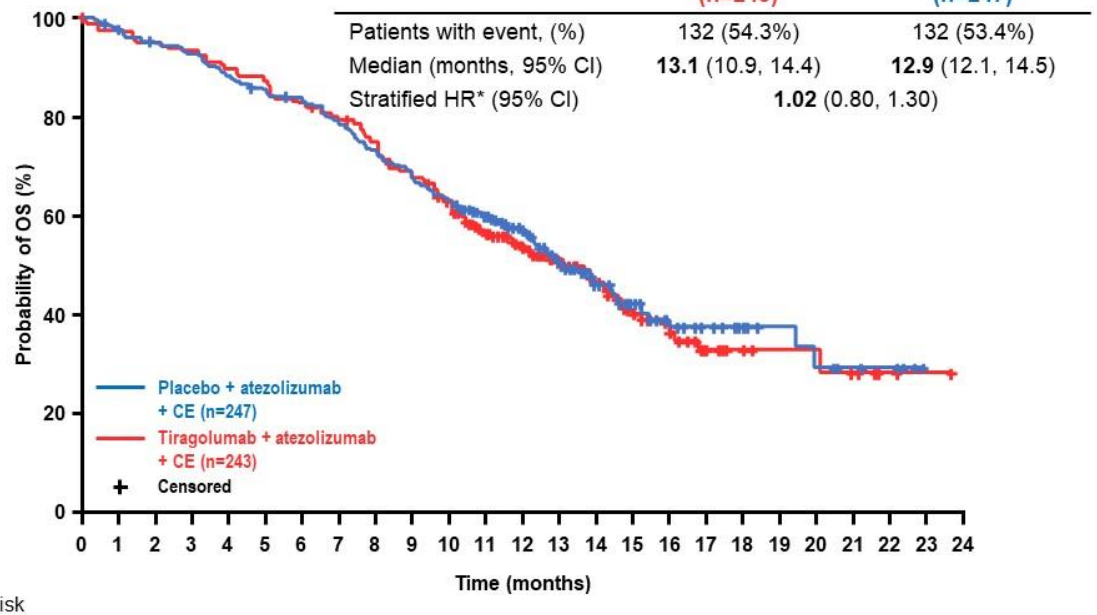
	Tiragolumab + atezolizumab + CE (n=243)	Placebo + atezolizumab + CE (n=247)
Patients with event, (%)	213 (87.7%)	215 (87%)
Median (months, 95% CI)	**5.1** (4.4, 5.4)	**5.4** (4.5, 5.7)
Stratified HR* (95% CI)	**1.08** (0.89, 1.31)	



No. at risk																						
Placebo + atezo + CE	247	237	224	207	185	128	92	73	66	49	40	34	26	20	11	8	3	3	3	3	2	2	NE
Tiragolumab + atezo + CE	243	232	224	209	188	120	74	59	45	41	35	27	18	18	12	9	5	5	3	2	NE	NE	NE

Interim OS in the Full Analysis Set

	Tiragolumab + atezolizumab + CE (n=243)	Placebo + atezolizumab + CE (n=247)
Patients with event, (%)	132 (54.3%)	132 (53.4%)
Median (months, 95% CI)	**13.1** (10.9, 14.4)	**12.9** (12.1, 14.5)
Stratified HR* (95% CI)	**1.02** (0.80, 1.30)	

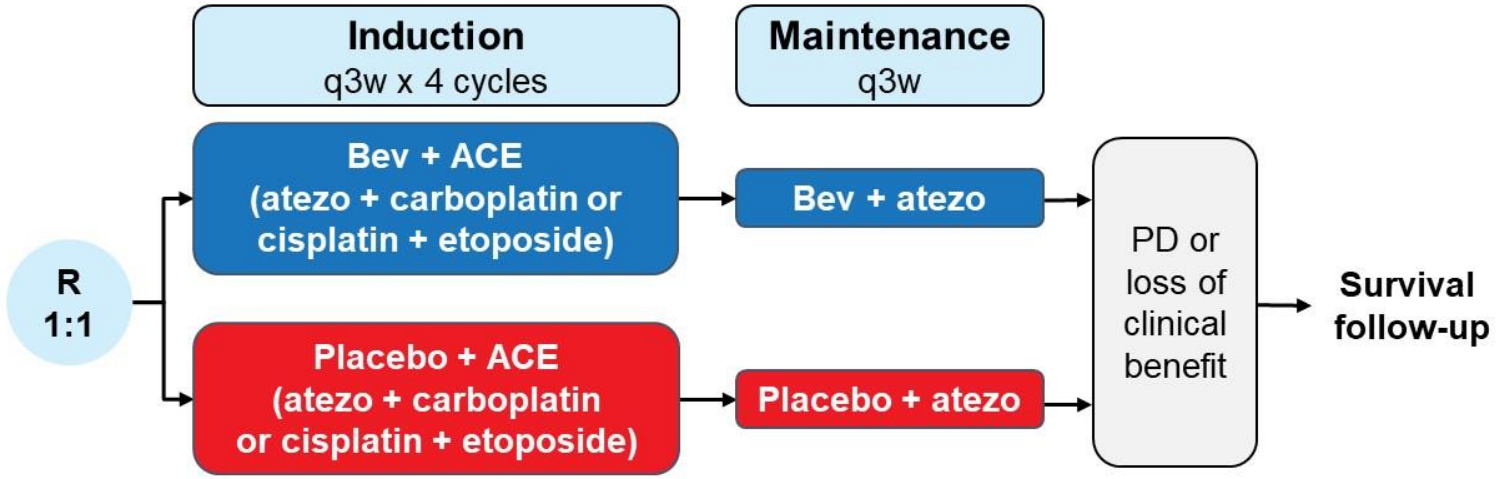


No. at risk																								
Placebo + atezo + CE	247	240	232	226	215	207	202	190	176	165	152	134	109	80	52	40	26	19	12	9	7	5	4	NE	NE
Tiragolumab + atezo + CE	243	235	228	225	216	210	199	190	176	161	141	114	90	70	56	36	24	14	9	7	7	5	2	1	NE

*Stratification factors are: ECOG, LDH
Data cut-off: 6 February 2022 (median follow-up:13.9 months)

BEAT-SC: study design[a]

Key eligibility criteria
- Measurable ES-SCLC
- ECOG PS 0-1
- Age ≥20 years (≥18 years in China)
- No prior systemic treatment for ES-SCLC
- No contraindications for bev use[b]



Stratification factors for randomization
- Sex (male vs female)
- ECOG PS (0 vs 1)
- Platinum agents (cisplatin vs carboplatin)

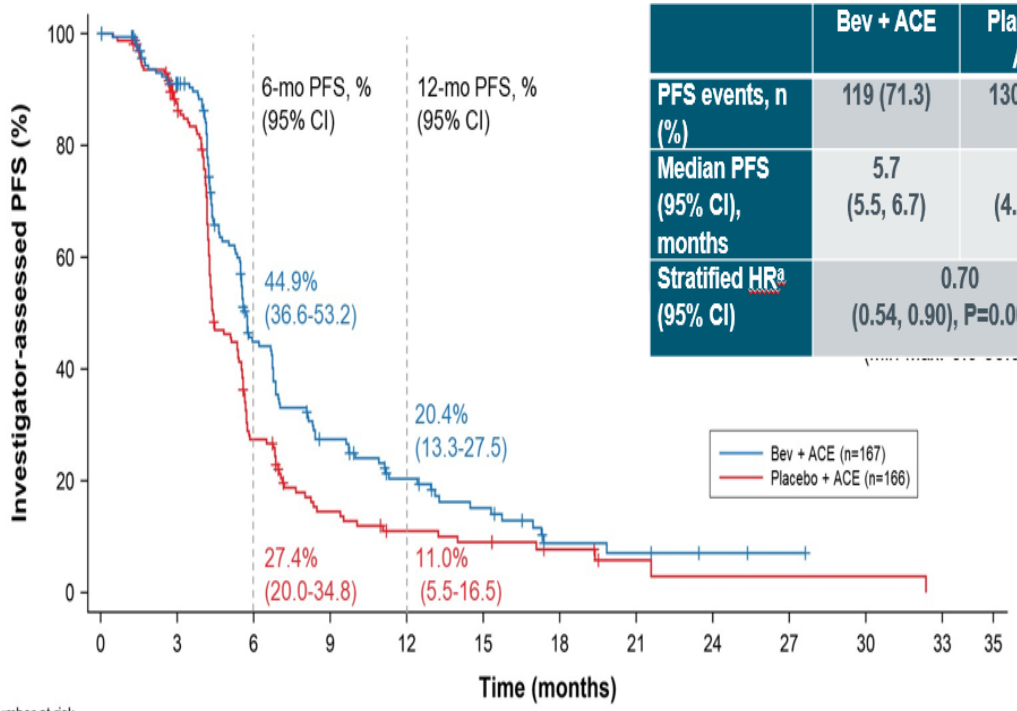
Primary endpoint
- Investigator-assessed PFS

Key secondary endpoints
- PFS per independent review, OS, investigator-assessed ORR, DOR
- Safety
- Subgroup analyses

Bevacizumab 15 mg/kg, atezolizumab 1200 mg, carboplatin AUC5 or cisplatin 80 mg/m^2 (75-80 mg/m^2 in China) and etoposide 100 mg/m^2 were administered, with etoposide given on Days 1-3. ACE, atezo + carboplatin or cisplatin + etoposide; DOR, duration of response; ORR, objective response rate. [a]Japanese registry of ClinicalTrials ID, jRCT2080224946. [b]Including history of hemoptysis, prior or current bloody sputum, tumor infiltration into thoracic great vessels, tumor extending directly into trachea/bronchus, uncontrolled hypertension, history of hypertensive crisis/encephalopathy, recent cerebrovascular accident or frequent transient ischemic attacks, significant vascular disease (e.g., aortic aneurysm), current or recent use of aspirin/dipyridamole/ticlopidine/clopidogrel/cilostazol, current use of full-dose anticoagulants or thrombolytic agents, evidence of bleeding diathesis or coagulopathy in absence of anticoagulation, history of abdominal or tracheoesophageal fistula or gastrointestinal perforation, gastrointestinal obstruction/fistula/diverticulitis, evidence of unexplained abdominal free air and serious/non-healing wound/active ulcer/untreated bone fracture.

Survival Outcomes

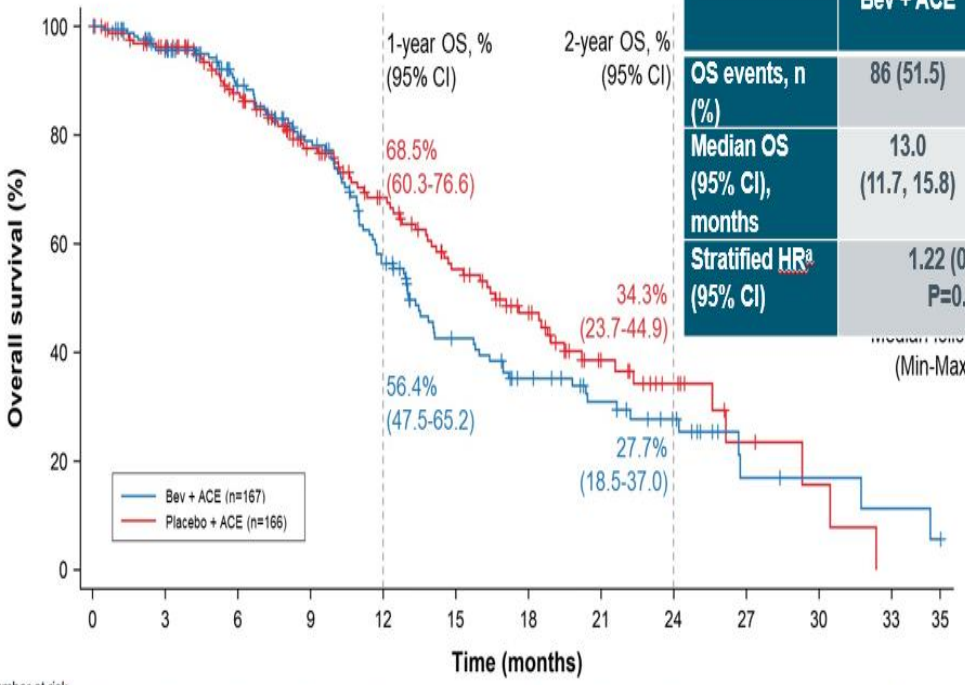
Investigator Assessed PFS (Pri. Endpoint)



	Bev + ACE	Placebo + ACE
PFS events, n (%)	119 (71.3)	130 (78.3)
Median PFS (95% CI), months	5.7 (5.5, 6.7)	4.4 (4.3, 5.4)
Stratified HR[a] (95% CI)	0.70 (0.54, 0.90), P=0.0060[a,b]	

[a]Stratified by sex and ECOG PS. [b]Stratified log-rank test; 2-sided α boundary: 0.05

First Interim OS Analysis (Sec. Endpoint)



	Bev + ACE	Placebo + ACE
OS events, n (%)	86 (51.5)	74 (44.6)
Median OS (95% CI), months	13.0 (11.7, 15.8)	16.6 (14.0, 20.2)
Stratified HR[a] (95% CI)	1.22 (0.89, 1.67) P=0.2212[a,b]	

(Min-Max: 0.0-35.0 months)

CCOD, clinical cutoff date. [a]Stratified by sex and ECOG PS. [b]Stratified log-rank test; 2-sided α boundary: 0.0079.

ADRIATIC study design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomization

N=730

R‡

Durvalumab
1500 mg Q4W
N=264

Placebo
Q4W
N=266

Durvalumab + tremelimumab
D 1500 mg Q4W + T 75 mg Q4W for 4 doses, followed by D 1500 mg Q4W
N=200

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

Stratified by:
Disease stage (I/II vs III)
PCI (yes vs no)

Treatment until investigator-determined progression or intolerable toxicity, or for a **maximum of 24 months**

Dual primary endpoints:
- Durvalumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Key secondary endpoints:
- Durvalumab + tremelimumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Other secondary endpoints:
- OS/PFS landmarks
- Safety

*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

BICR, blinded independent central review; BID, twice daily; CT, chemotherapy; D, durvalumab; PCI, prophylactic cranial irradiation; PS, performance status; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; T, tremelimumab; WHO, World Health Organization.

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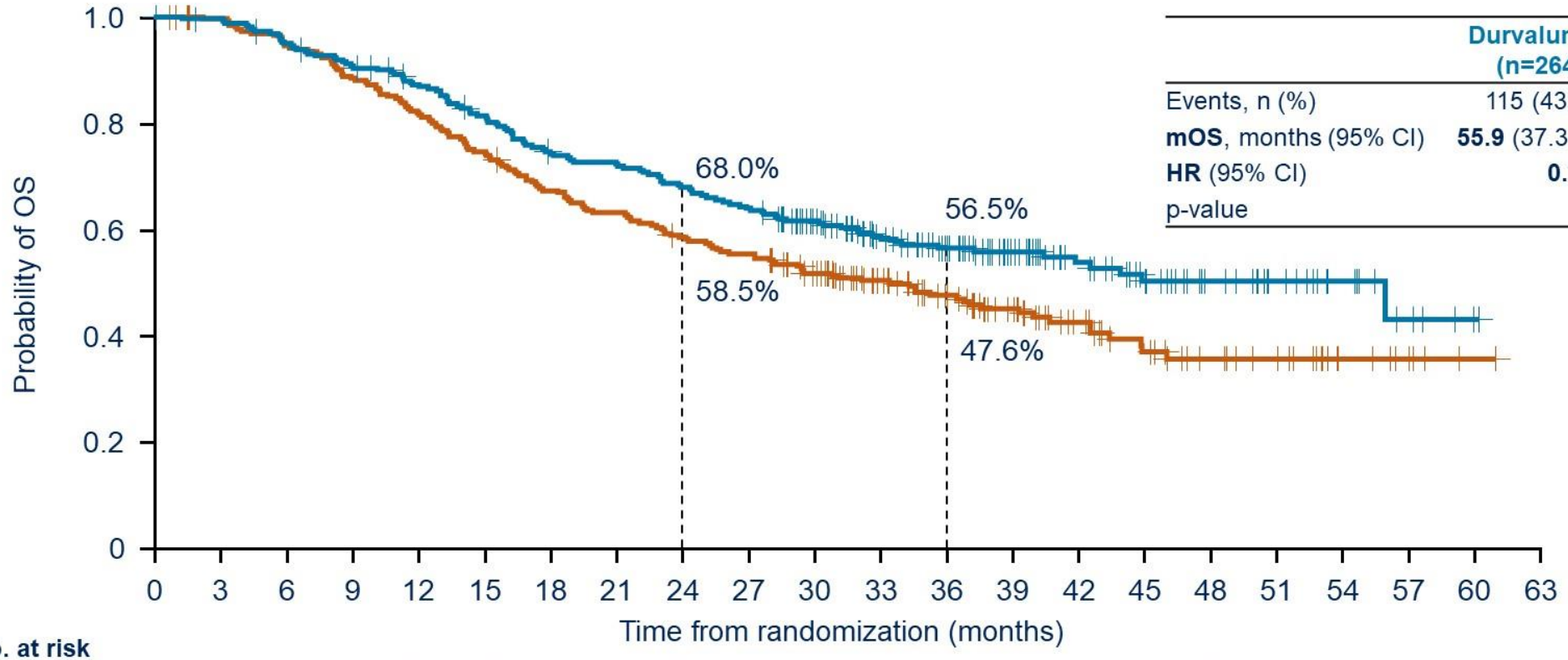
Overall survival (dual primary endpoint)

- Median duration of follow up in censored patients: 37.2 months (range 0.1–60.9)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

No. at risk																						
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints.

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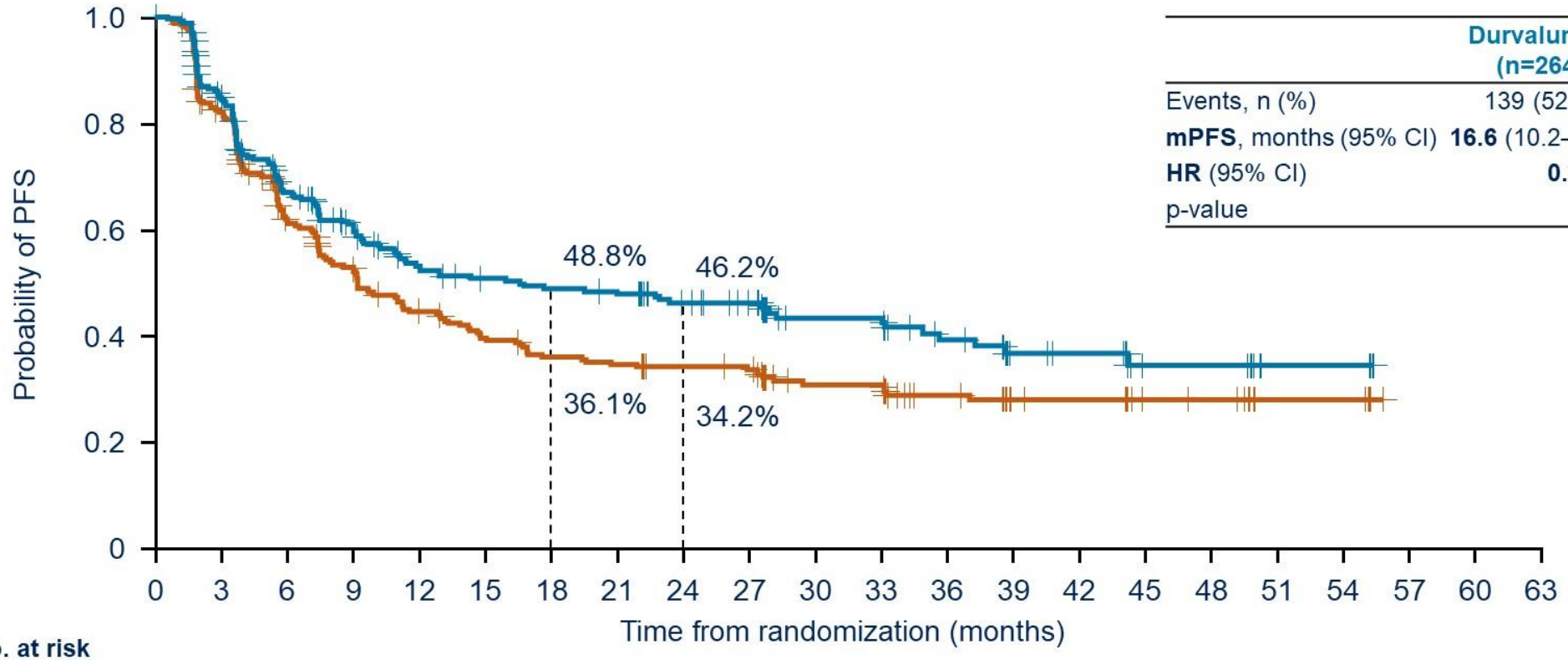
CI, confidence interval; mOS, median OS; NE, not estimable.

Progression-free survival* (dual primary endpoint)

- Median duration of follow up in censored patients: 27.6 months (range 0.0–55.8)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

No. at risk																						
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

*By BICR per RECIST v1.1.

PFS was analyzed using a stratified log-rank test adjusted for disease stage (I/II vs III) and receipt of PCI (yes vs no). The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for PFS was achieved through the recycling multiple testing procedure framework and testing at the 5% (2-sided) alpha level (adjusted for an interim and final analysis).

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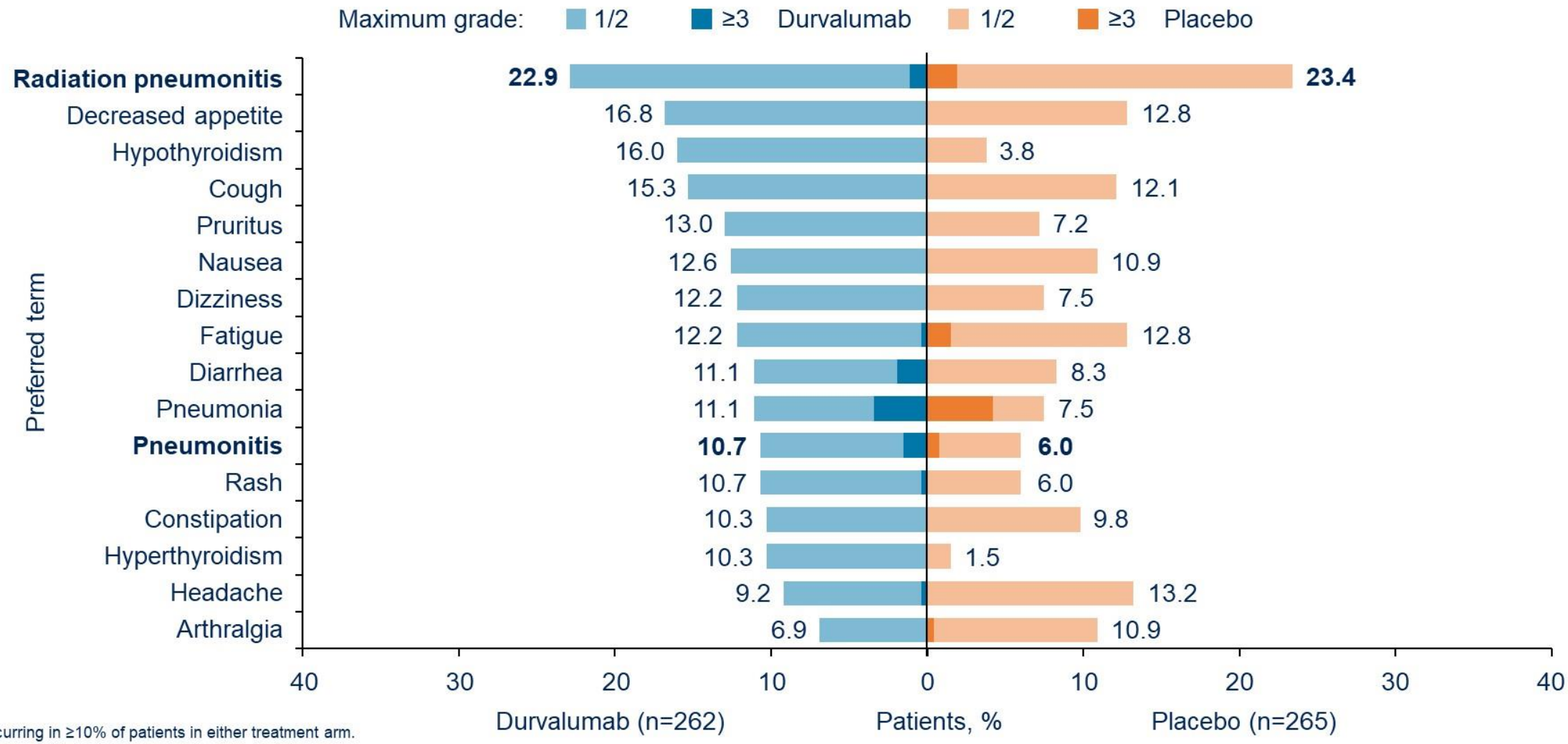
mPFS, median PFS.

Most frequent AEs*



*Occurring in ≥10% of patients in either treatment arm.

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Relapsed SCLC

Lurbinectedin (Single Arm Phase II Basket Trial)

Lurbinectedin[a,b]

- Synthetic analog of trabectedin used to treat soft-tissue sarcoma
- Selective inhibitor of oncogenic transcription
  - Covalently binds CG-rich sequences mainly located near promoters; inhibits RNA Pol II associated to DNA and leads to its specific degradation
- May also influence the TM via processes, including suppression of immune cells (eg, TAMs)

Trigo, Lancet Oncol 2020

	Overall (n=105)
ORR, % (95% CI)	35.2 (26.2-45.2)
Best response	n (%)
- PR (confirmed)	37 (35.2) #
- SD	35 (33.3)
- PD	28 (26.7)
- NE* (non- evaluable)	5 (4.8)
Disease Control Rate,% (95% CI)	68.6 (58.8-77.3)

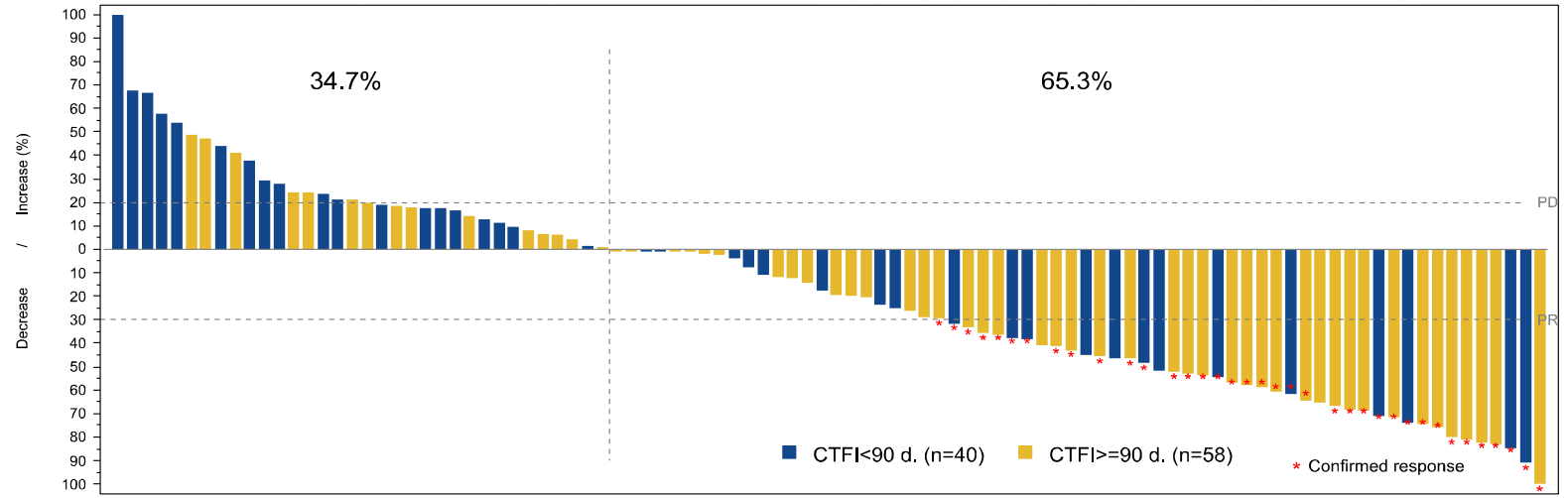
5 of 8 patients who failed prior immunotherapy had confirmed response

* Treatment discontinuation without any tumor assessment performed

	Resistant CTFI< 90 days (n=45)	Sensitive CTFI ≥ 90 days (n=60)
ORR, % (95% CI)	22.2 (11.2-37.1)	45.0 (32.1-58.4)
Best response (confirmed)	n (%)	n (%)
- PR	10 (22.2) #	27 (45.0) #
- SD	13 (28.9)	22 (36.7)
- PD	18 (40.0)	10 (16.7)
- NE* (non- evaluable)	4 (8.9)	1 (1.7)
Disease Control Rate), % (95% CI)	51.1 (35.8-66.3)	81.7 (69.6-90.5)

3 of 5 patients with resistant disease and 2 of 3 patients with sensitive disease who failed prior immunotherapy had confirmed response

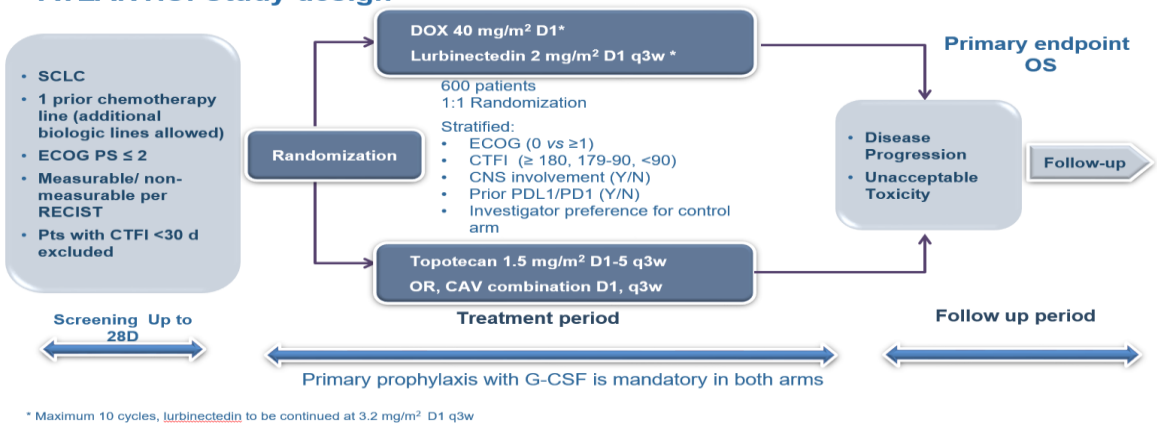
* Treatment discontinuation without any tumor assessment performed



Phase III ATLANTIS Trial

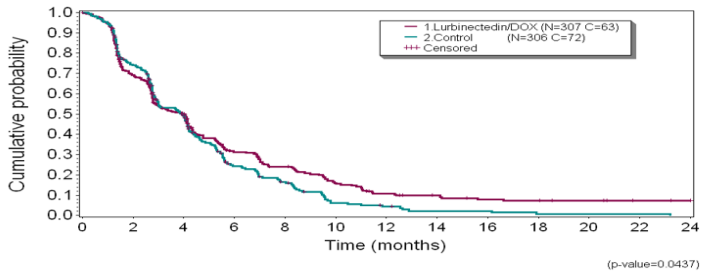
OS and PFS

ATLANTIS: Study design



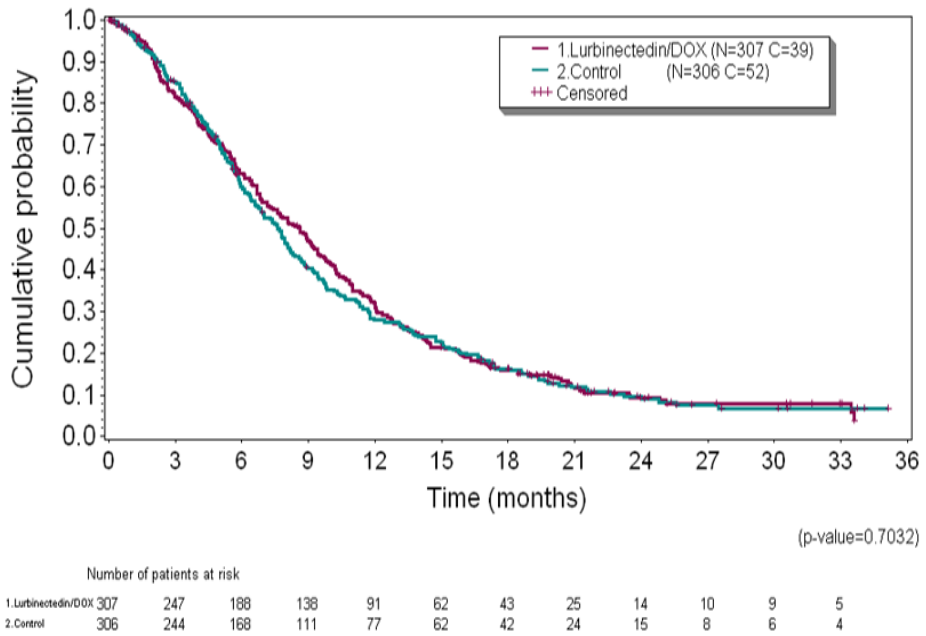
* Maximum 10 cycles, lurbinectedin to be continued at 3.2 mg/m² D1 q3w

PFS by IRC:



	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	244 (79.5)	234 (76.5)		
Censored, n (%)	63 (20.5)	72 (23.5)		
Median PFS (95% CI), months	**4.0 (2.8, 4.2)**	**4.0 (3.0, 4.1)**	**HR: 0.831 (0.693, 0.996)**	**0.0437**
Mean PFS, months	5.9	4.6		
PFS (%) at 6 months (95% CI)	31.3 (25.8, 36.9)	24.4 (19.1, 30.1)		0.0851
PFS (%) at 12 months (95% CI)	10.8 (7.1, 15.3)	4.4 (2.1, 8.1)		0.0129

Overall Survival (ITT population)



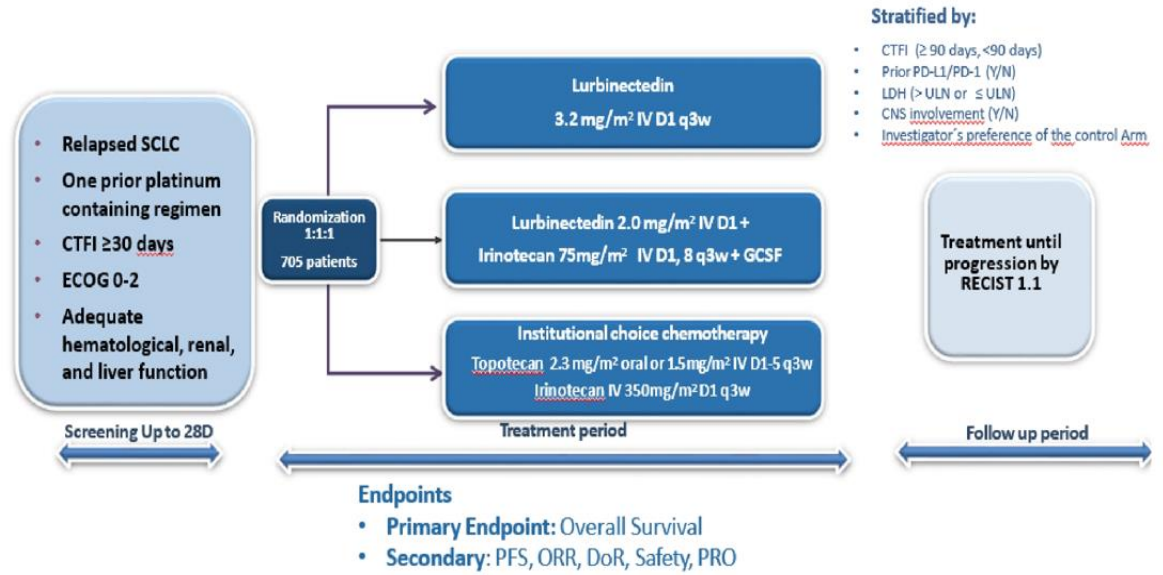
	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	268 (87.3)	254 (83.0)		
Censored, n (%)	39 (12.7)	52 (17.0)		
Median OS (95% CI), months	**8.6 (7.1, 9.4)**	**7.6 (6.6, 8.2)**	**HR : 0.967 (0.815, 1.148)**	**0.7032**
Mean OS, months	10.6	9.9		

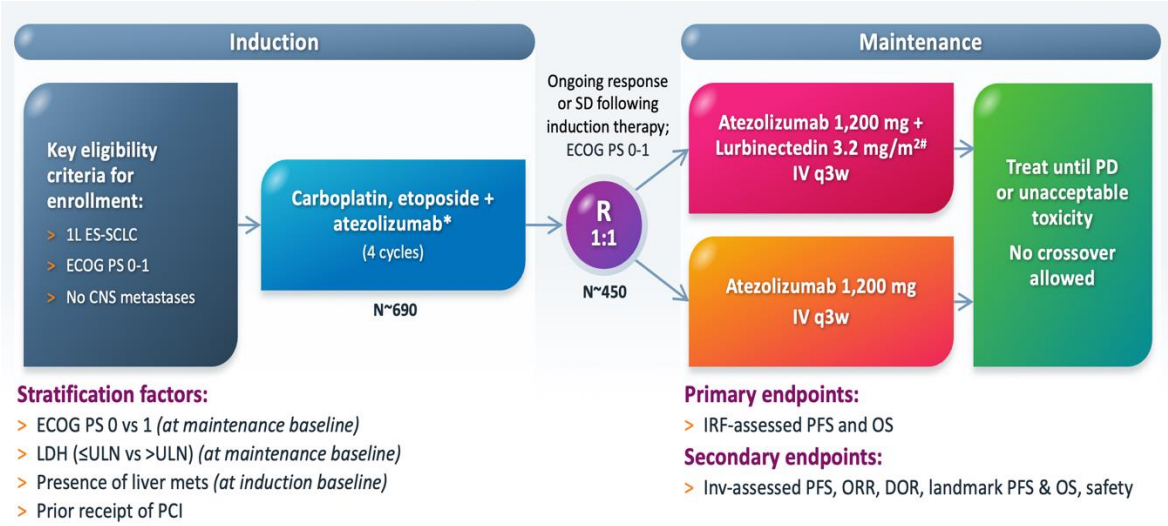
IASLC WCLC 2021 Plenary

Post ATLANTIS Trial
Lurbinectedin clearly active in SCLC

- **Lurbinectedin in Relapsed SCLC**
- Phase III LAGOON trial ongoing
  - Lurbinectedin vs irinotecan/topotecan vs combo of lurbinectedin + irinotecan

- **Maintenance lurbinectedin strategy ongoing (POSITIVE on Press Release)**
- Phase III IMforte trial
  - Randomized phase III study exploring maintenance lurbinectedin + atezolizumab (vs standard atezolizumab)





Limited and Extensive Stage SCLC:

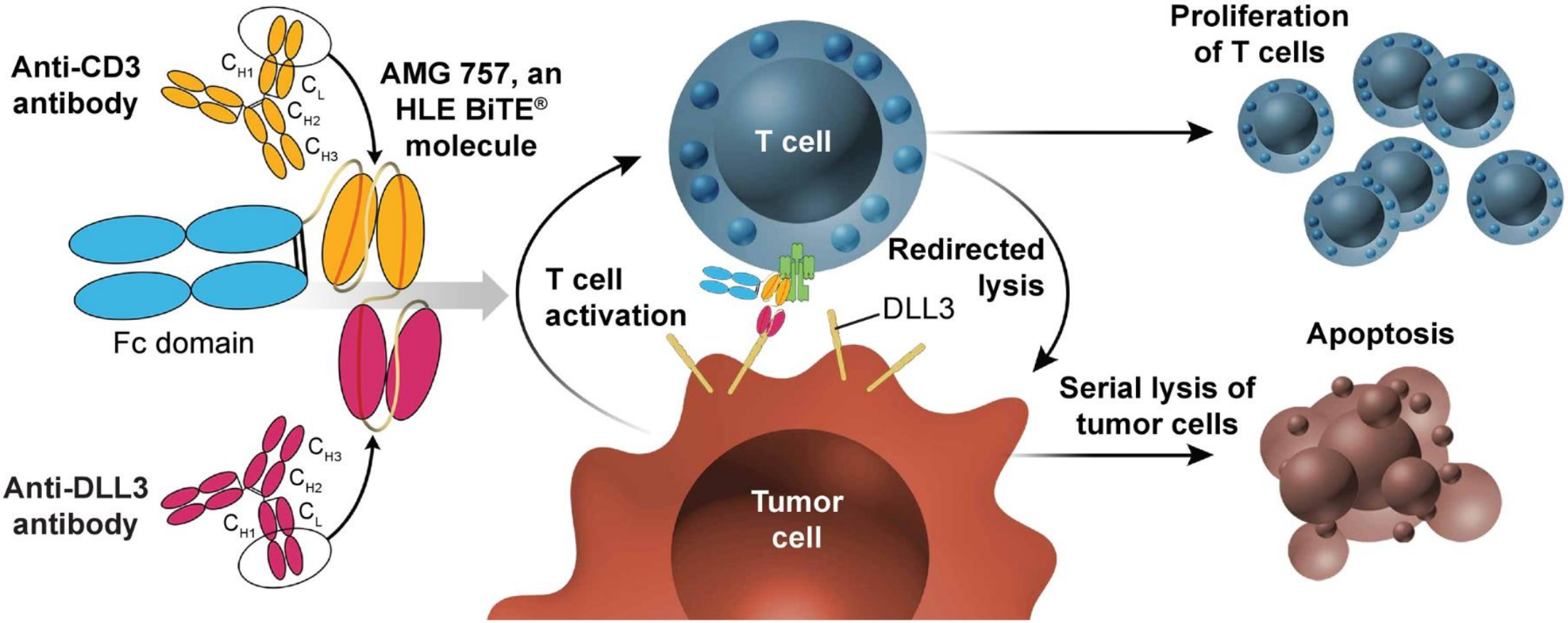
New Standard of Care and Novel Advances

T-CELL ENGAGERS

AMG 757

Half-life Extended DLL3-Directed Bispecific Antibody (BiTE)

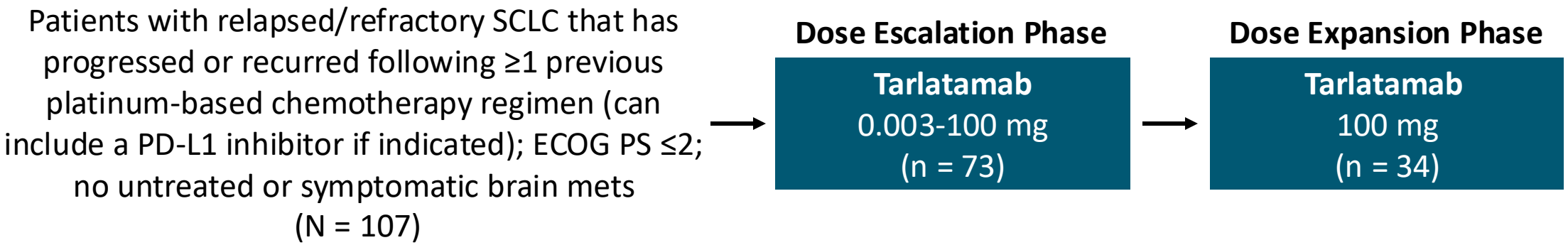
Figure 2. AMG 757 Is a Half-life Extended BiTE® Immuno-oncology Therapy



C_H, heavy chain constant domain; C_L, light chain constant domain; HLE BiTE®, half-life extended bispecific T-cell engager; CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, crystallizable fragment.

DeLLphi-300: Phase I Study of Tarlatamab in Patients With Relapsed/Refractory SCLC

- First-in-human, nonrandomized phase I dose exploration and expansion study
  - Data cutoff of July 19, 2022; median follow-up time of 8.7 mo (range: 0.2-31.8)



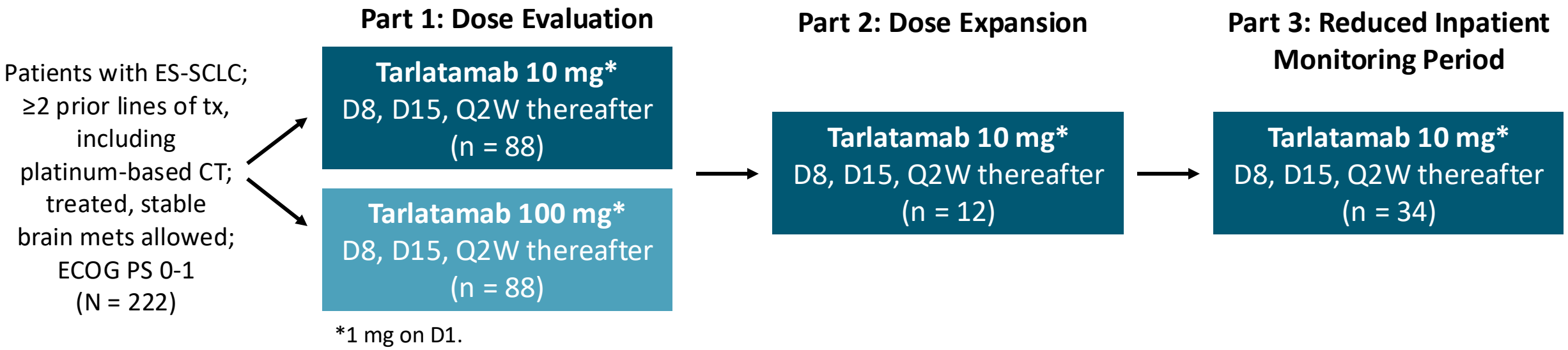
- **Primary Objectives**: Evaluate safety and tolerability in SCLC; determine MTD or RP2D
- **Secondary Objectives**: Characterize PK; evaluate preliminary antitumor activity*
- **Exploratory Objectives**: Evaluate immunogenicity of tarlatamab; assess biomarker expression

*Antitumor activity assessed using modified RECIST 1.1 every 8 wk (± 1 wk).

Paz-Ares. J Clin Oncol. 2023;[Epub].

DeLLphi-301: Tarlatamab in Relapsed ES-SCLC

- Open-label phase II study
  - Patients required to have received 1 platinum-based regimen and ≥1 other line of tx; median lines of tx: 2 (range: 1-8)

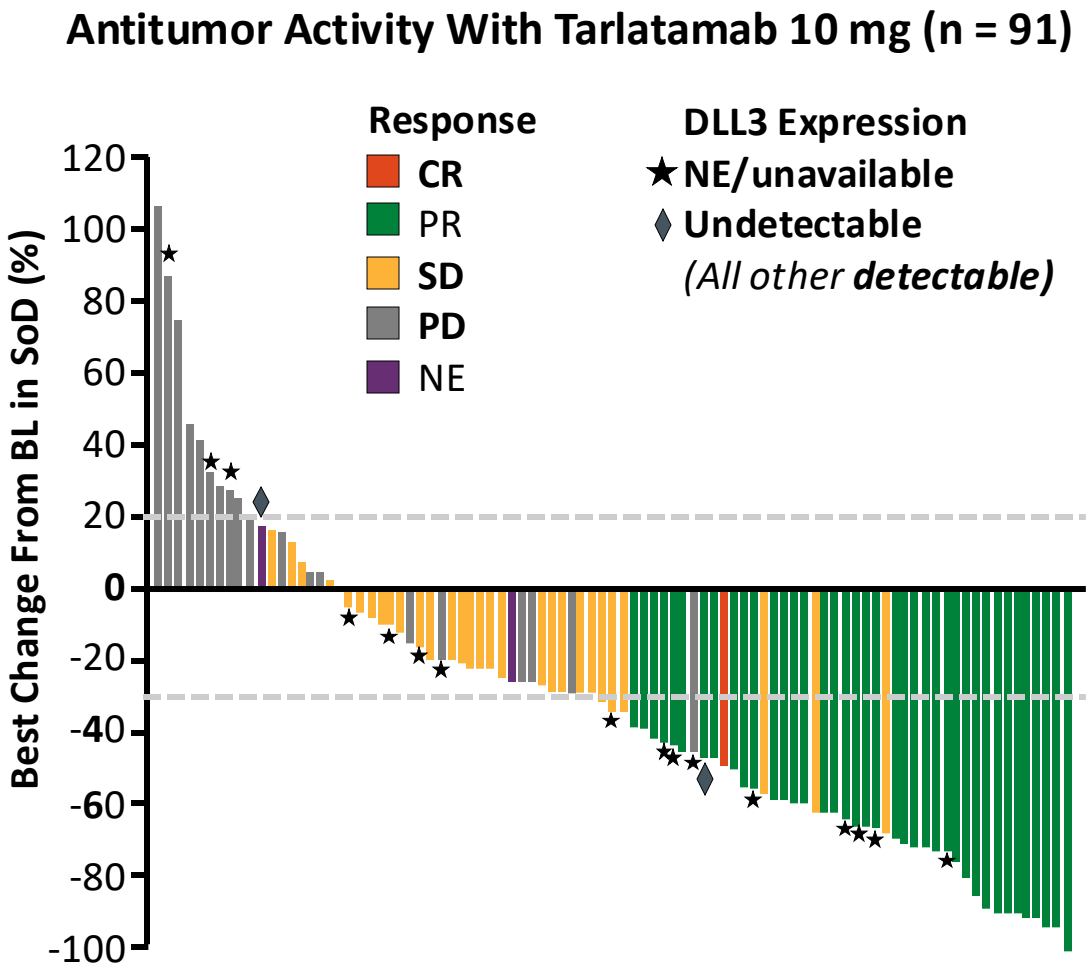


*1 mg on D1.

- **Primary endpoints:** ORR per RECIST v1.1 by BICR
- **Secondary endpoints:** DoR, DCR, PFS, OS, safety, drug serum concentration

Ahn. NEJM. 2023;389:2063. NCT05060016.

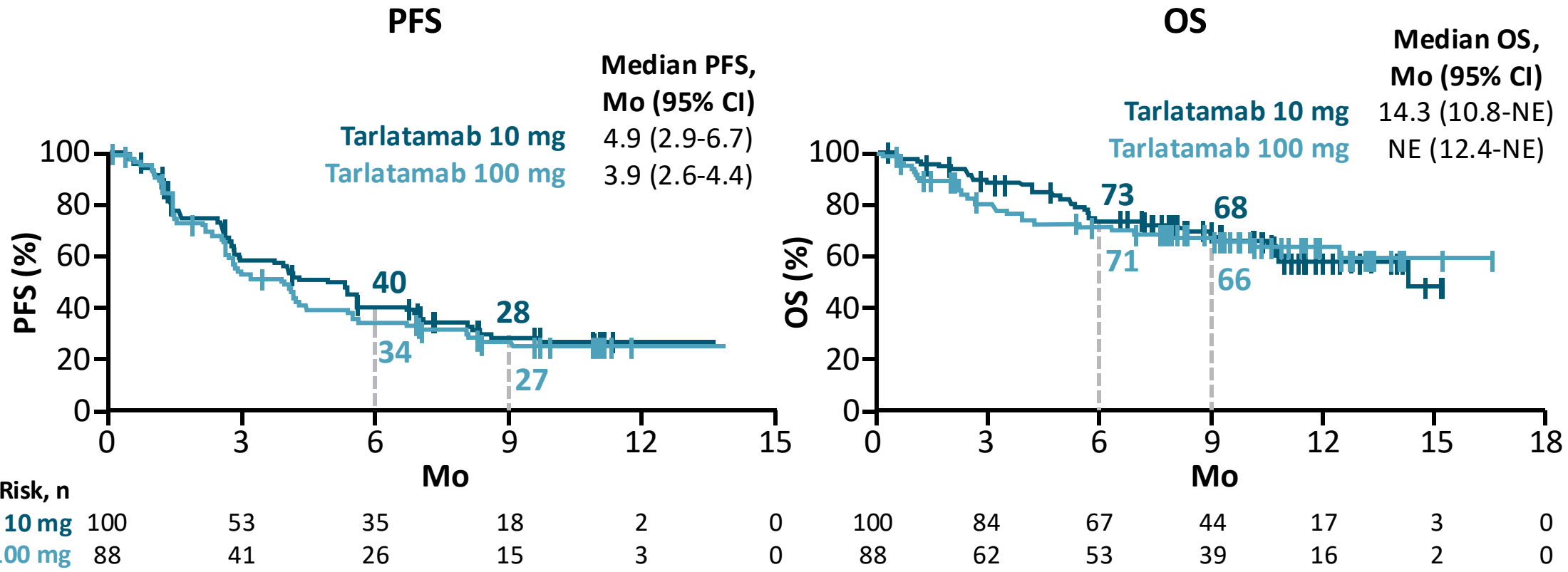
DeLLphi-301: Response



Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
ORR, % (97.5% CI) ▪ Confirmed CR, n (%) ▪ Confirmed PR, n (%)	40 (29-52) 1 (1) 39 (39)	32 (21-44) 7 (8) 21 (24)
SD, n (%)	30 (30)	27 (31)
PD, n (%)	20 (20)	13 (15)
Death before post-BL scan, n (%)	6 (6)	13 (15)
No post-BL scan, n (%)	2 (2)	3 (3)
Observed DoR, n/N (%) ▪ ≥3 mo ▪ ≥6 mo ▪ ≥9 mo	 35/40 (88) 23/40 (58) 10/40 (25)	 25/28 (89) 17/28 (61) 10/28 (36)
Median time to response, mo (range)	1.4 (1.1-2.8)	1.4 (1.2-9.6)
Ongoing response at data cutoff, n/N (%)	22/40 (55)	16/28 (57)
DCR, % (95% CI)	70 (60-79)	63 (52-73)
Median duration of disease control, mo (95% CI)	6.9 (5.4-9.7)	6.7 (4.2-NE)

Ahn. NEJM. 2023;389:2063.

DeLLphi-301: Survival



FDA accelerated approval May 16th, 2024

Ahn. NEJM. 2023;389:2063.

DeLLphi-300: Treatment-Related AEs

AE, n (%)	All Patients (N = 107)	
	Any Grade	Grade ≥3
Any AE	107 (100)	61 (57)
Any SAE	55 (51)	30 (28)
Any AE resulting in discontinuation*	4 (4)	3 (3)
Any TRAE	97 (91)	33 (31)
TRAEs ≥10%		
• CRS	56 (52)	1 (1)
• Pyrexia	40 (37)	2 (2)
• Dysgeusia	24 (22)	0
• Fatigue	23 (22)	3 (3)
• Nausea	21 (20)	0
• Decreased appetite	14 (13)	0
• Vomiting	13 (12)	0
• Anemia	12 (11)	1 (1)
• Asthenia	12 (11)	2 (2)
• Neutropenia	12 (11)	8 (7)
• Headache	11 (10)	0

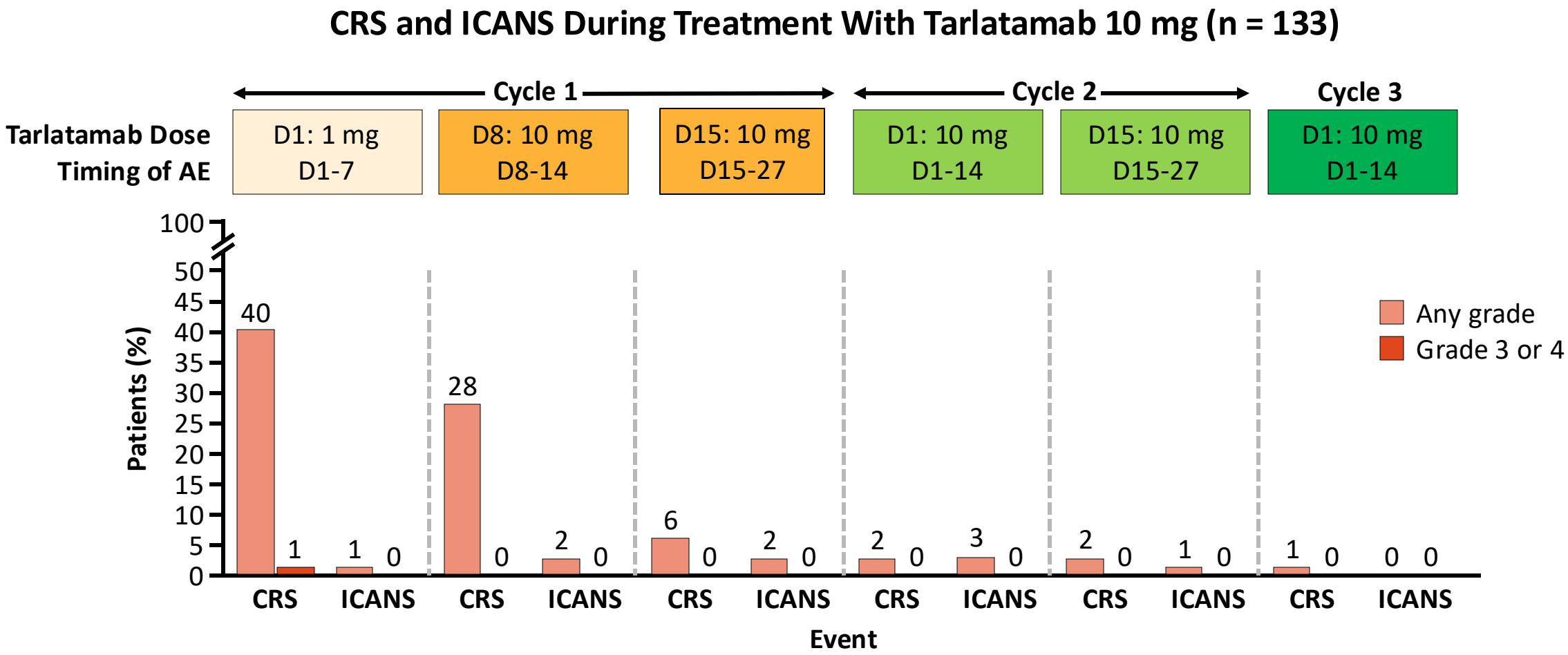
*Encephalopathy (n = 1), ICANS (n = 1), and pneumonitis (n = 2, including one grade 5 pneumonitis).

AEs of Interest, n (%)	All Patients (N = 107)	
	Any Grade	Grade ≥3
CRS	56 (52)	1 (1)
Neurologic events	53 (50)	7 (7)
Neutropenia	17 (16)	10 (9)

- CRS generally occurred in cycle 1 and rarely recurred in subsequent cycles
  - 8/107 patients (7.5%) required tocilizumab for CRS
- Neurologic events were predominantly grade 1 and presented as dysgeusia or headache
  - Most common grade ≥3 treatment-related NE: confusion (n = 5, 1 patient with grade 4)
- Grade 4 treatment-related neutropenia occurred in 4 patients (4%)
  - No treatment-related cases of febrile neutropenia

Paz-Ares. J Clin Oncol. 2023;[Epub].

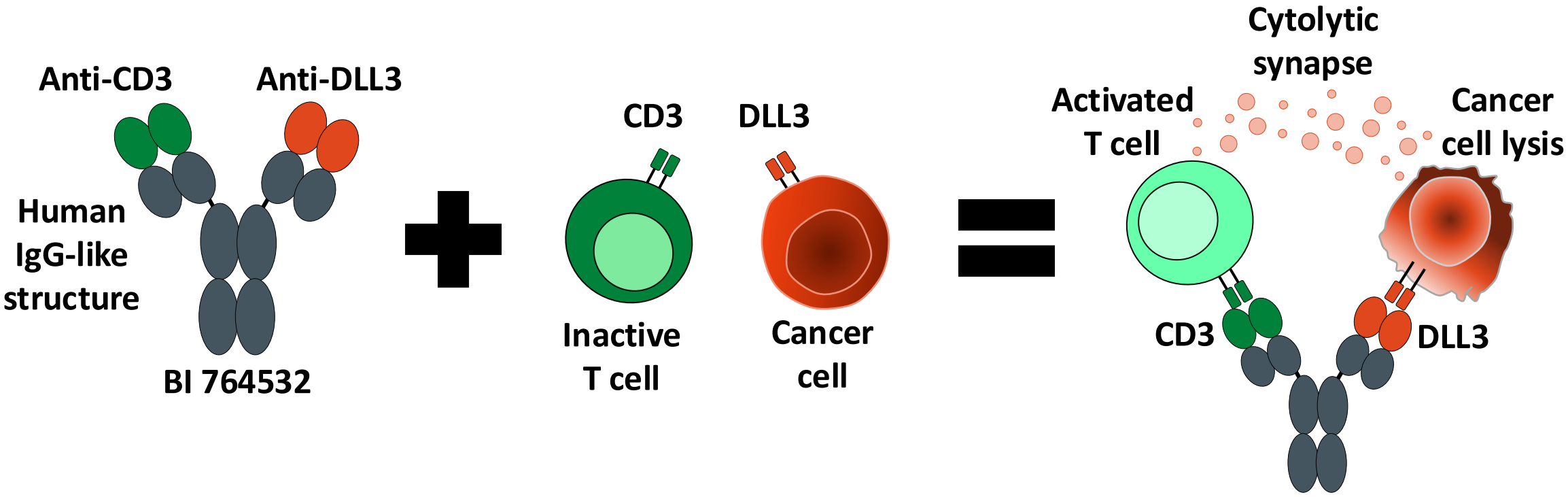
DeLLphi-301: Safety



Ahn. NEJM. 2023;389:2063.

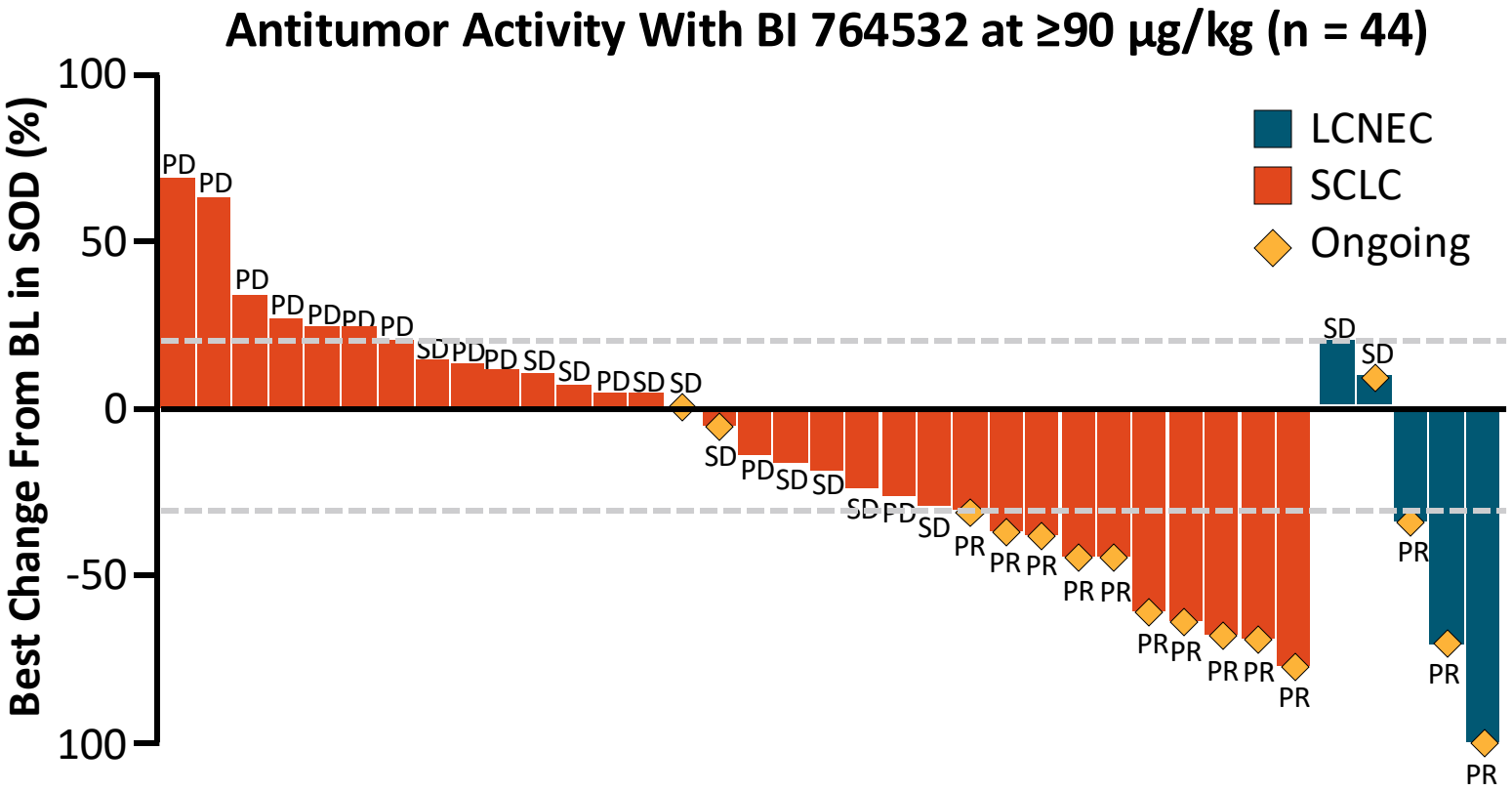
Emerging Therapies: BI 764532, a DLL3-targeted BiTE

- BI 764532 is a bispecific T-cell engager that binds DLL3 and CD3, leading to T-cell–mediated lysis of DLL3-expressing tumor cells



Wermke. WCLC 2023. Abstr OA01.05.

Phase I Study of BI 764532: Efficacy in SCLC and LCNEC

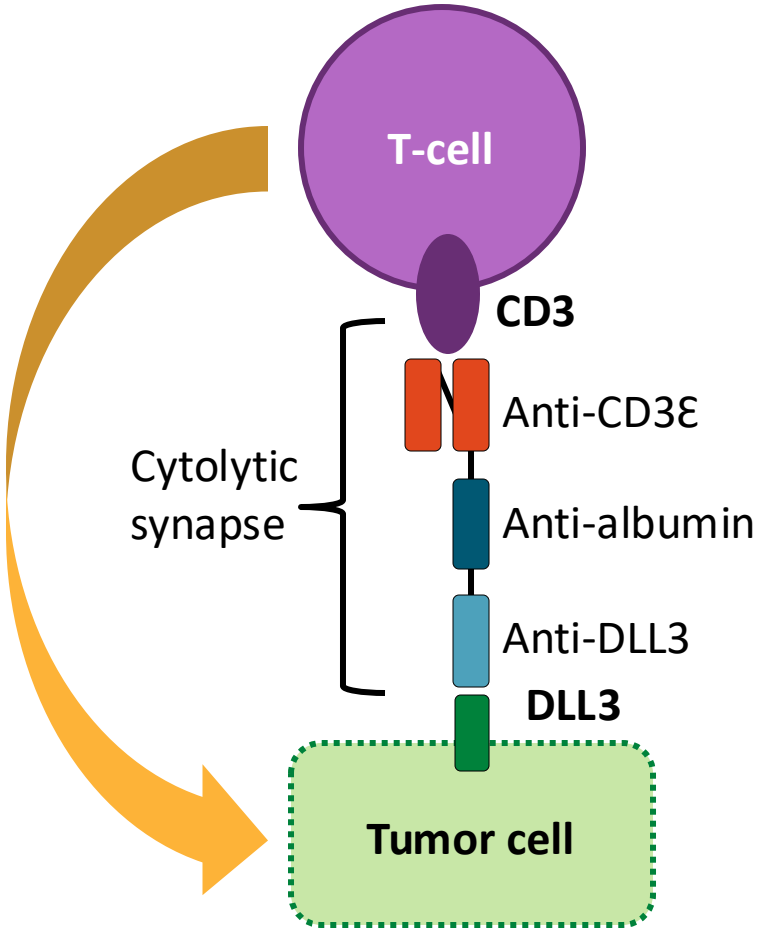


Response, n (%)	BI 764532 ≥90 µg/kg	
	SCLC (n = 39)*	LCNEC (n = 5)*
PR	10 (26)	3 (60)
SD	10 (26)	2 (40)
PD	12 (31)	0
DCR	20 (51)	5 (100)
NE†	7 (18)	0

(efficacy population). †d/c prior to tumor assessment.

HPN328: Mechanism of Action

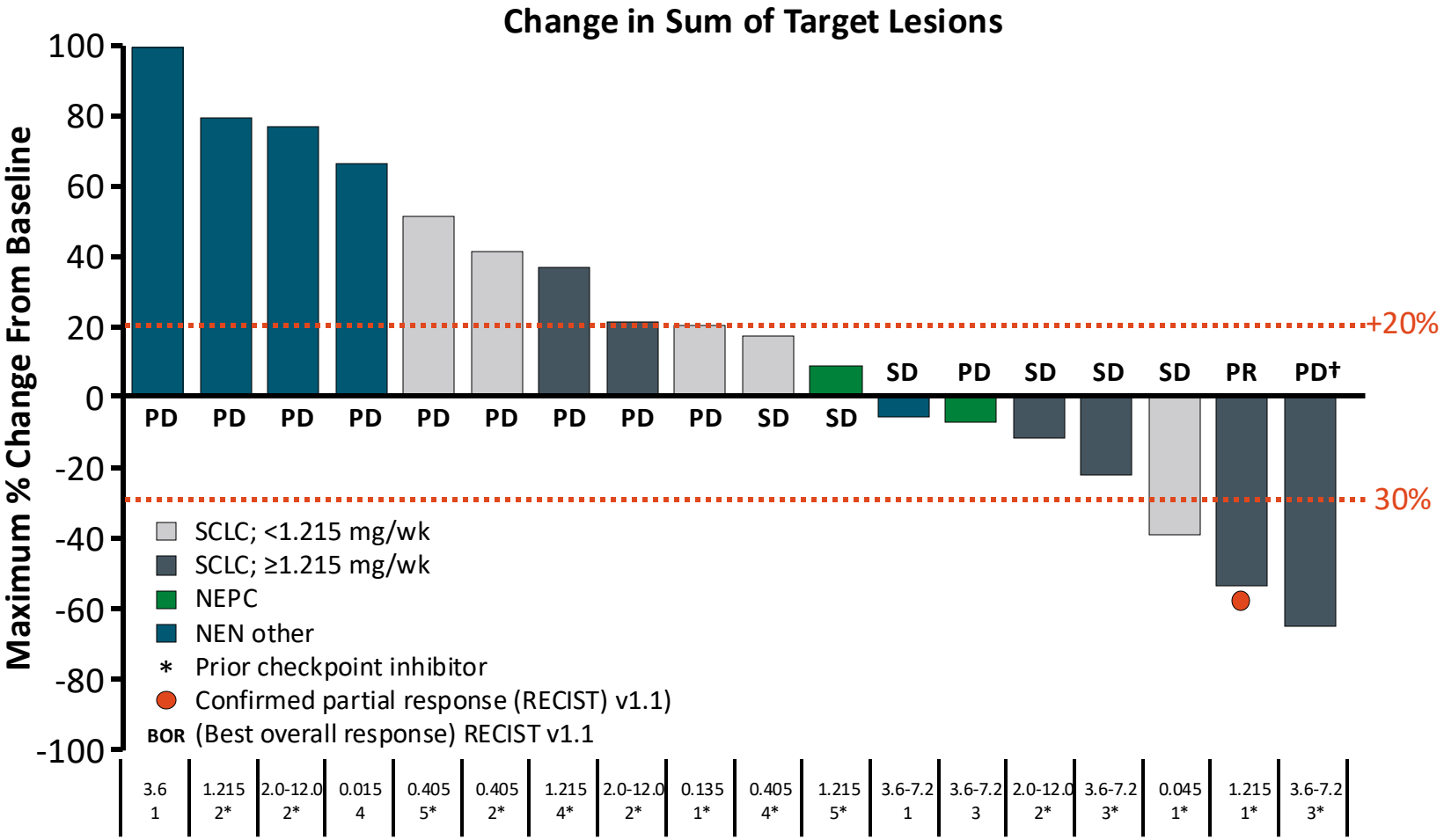
- HPN328 is a DLL3-targeted T-cell engaging agent with 3 binding domains
  - Anti-DLL3 (for target engagement)
  - Anti-albumin (for half-life extension)
  - Anti-CD3 (for T-cell engagement)



Johnson. ASCO 2022. Abstr 8566.

Phase I HPN328: Target Lesion Response

- 7/18 (39%): any decrease
  - (5 SCLC, 1 NEPC, 1 NEN [thymic atypical carcinoid])
- 1 confirmed PR (SCLC, 2L) ongoing treatment at 32 wk
- 3/11 (27%) SCLC patients had >30% decrease
- 4/6 (67%) SCLC patients treated with ≥1.215 mg/wk had any decrease



†New brain metastases identified at Wk 2. Overall response: PD; target lesion response: PR.

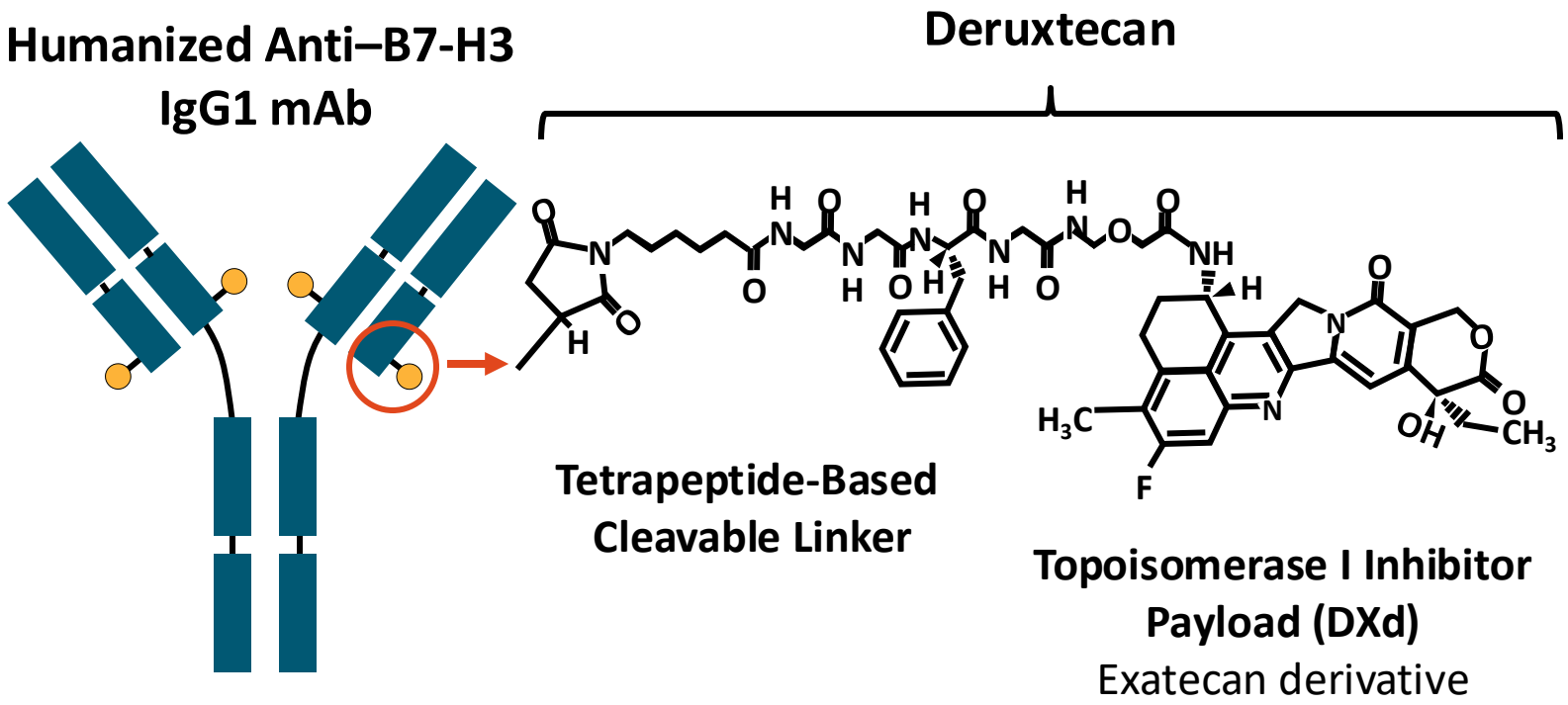
Johnson. ASCO 2022. Abstr 8566.

Limited and Extensive Stage SCLC:

New Standard of Care and Novel Advances

ANTIBODY DRUG CONJUGATES (ADC)

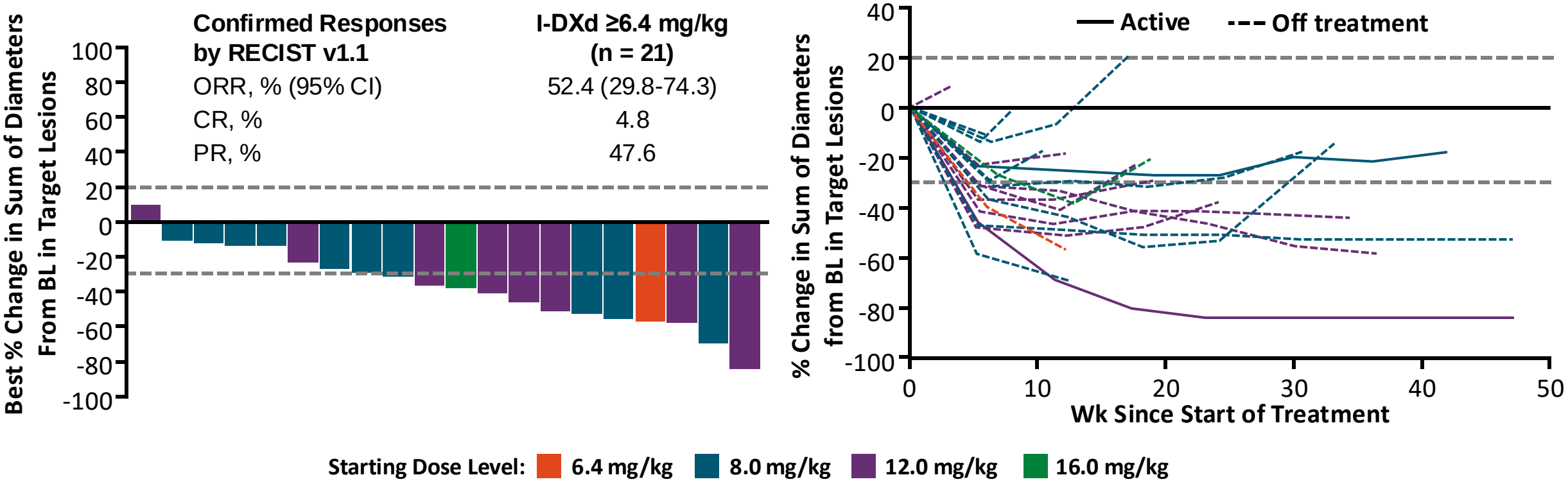
Emerging Therapies: Ifinatamab Deruxtecan, a B7-H3–Targeted Antibody–Drug Conjugate



- High-potency, membrane-permeable payload with short systemic half-life
- Optimized DAR: ~4:1
- Stable linker payload
- Tumor-selectable cleavable linker
- Bystander killing effect

Johnson. WCLC 2023. Abstr OA05.05.

Phase I/II Study of I-DXd in Refractory SCLC: Antitumor Activity



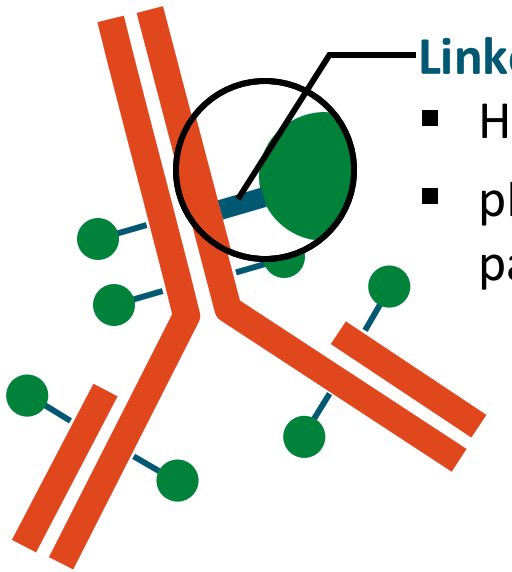
- Median follow-up: 11.7 mo (95% CI: 4.6-12.9)
- Median time to response: 1.2 mo (95% CI: 1.2-1.4)
- Median DoR: 5.9 mo (95% CI: 2.8-7.5)
- 2 patients remain on treatment

Johnson. WCLC 2023. Abstr OA05.05.

Emerging Therapies: Sacituzumab Govitecan, a TROP-2–Targeted Antibody–Drug Conjugate

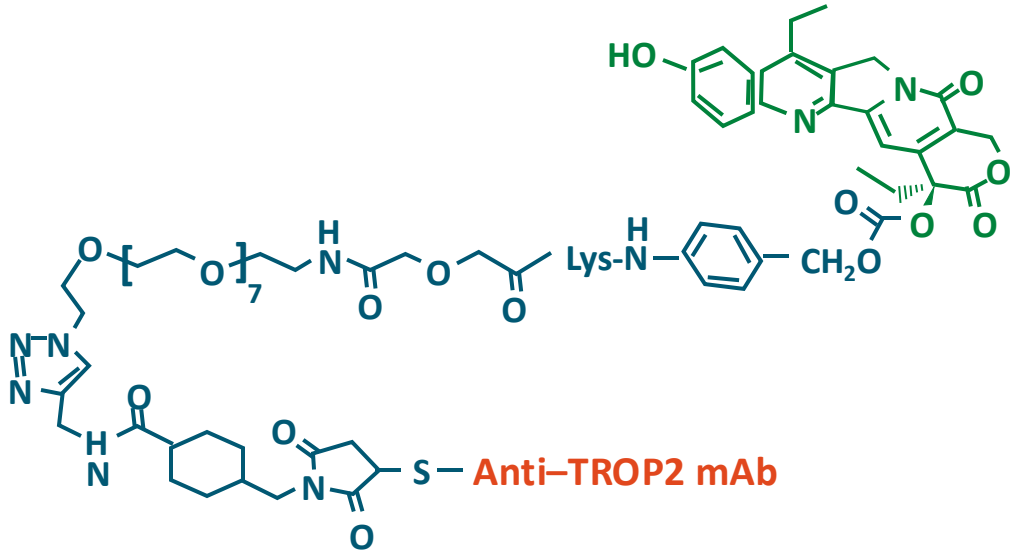
Humanized RS7 mAb

- Targets TROP2
- Type: hRS7 IgG1κ



Linker for SN-38

- High DAR (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor



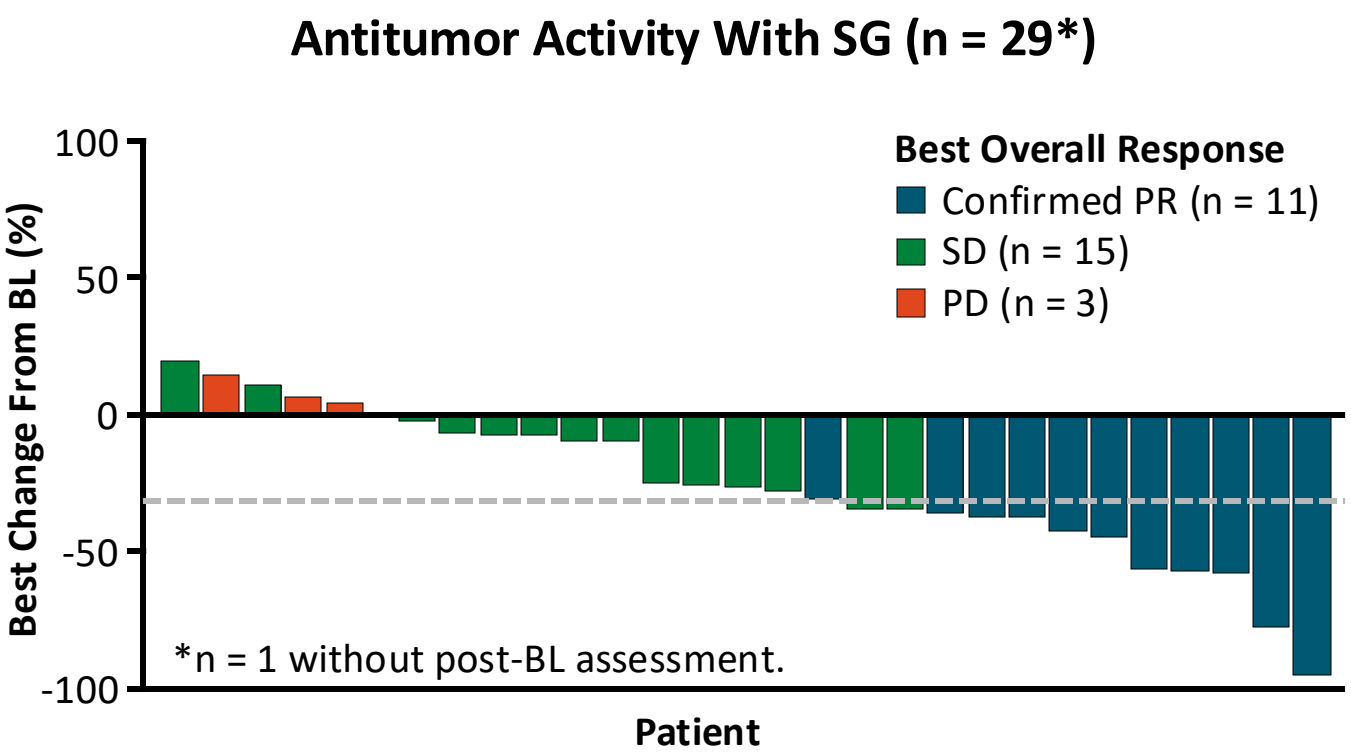
SN-38 Payload

- Delivers 136-fold more to tumors than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor

Bystander effect: In acidic tumor microenvironment, SN-38 is released from anti–TROP-2 antibody and diffuses into neighboring TROP-2–negative cells

Goldenberg. Oncotarget. 2015;6:22496. Goldenberg. MAbs. 2019;11:987. Sacituzumab govitecan PI.

TROPiCS-03: Response



Outcome	ES-SCLC (n = 30)
ORR,† % (95% CI)	37 (20-56)
Best overall response, n (%)	
▪ PR (confirmed)	11 (37)
▪ SD	15 (50)
▪ PD	3 (10)
CBR‡, % (95% CI)	40 (23-59)
Median DoR, mo (95% CI)	6.3 (2.7-NR)
▪ 6-mo DoR, % (95% CI)	63 (14-89)

†Confirmed CR + PR. ‡Confirmed CR + PR + SD ≥6 mo.

- 77% of patients (23/30) had any tumor reduction
- 43% of patients (13/30) had >30% tumor reduction

Dowlati. ESMO 2023. Abstr 199MO.

By investigator per RECIST v1.1. Includes patients enrolled on or before April 27, 2023.

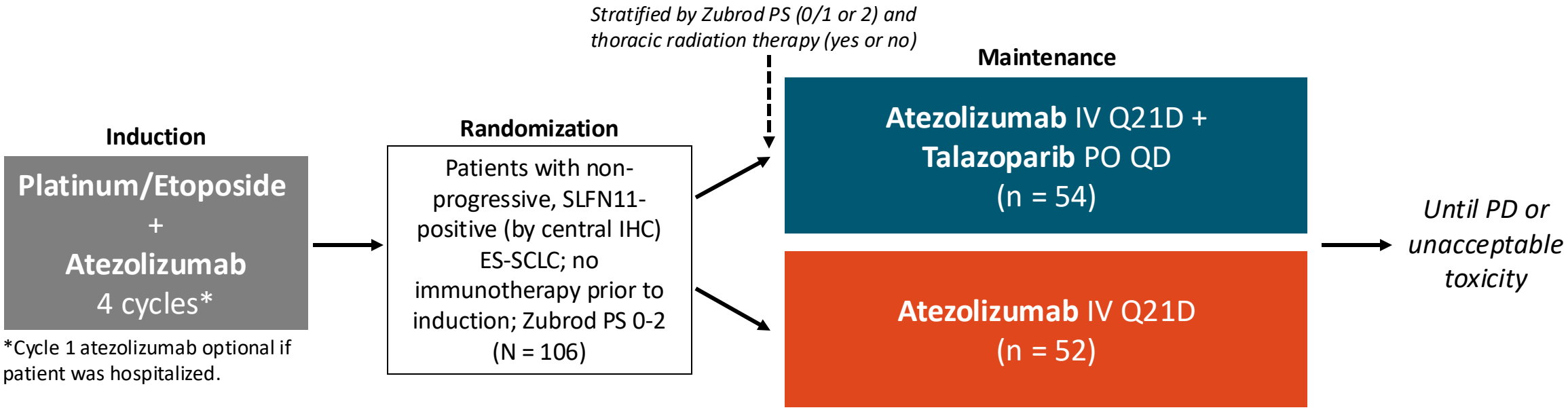
Limited and Extensive Stage SCLC:

New Standard of Care and Novel Advances

PATIENT SELECTION & BIOMARKERS

SWOG S1929: Study Design

- Randomized, open-label phase II trial

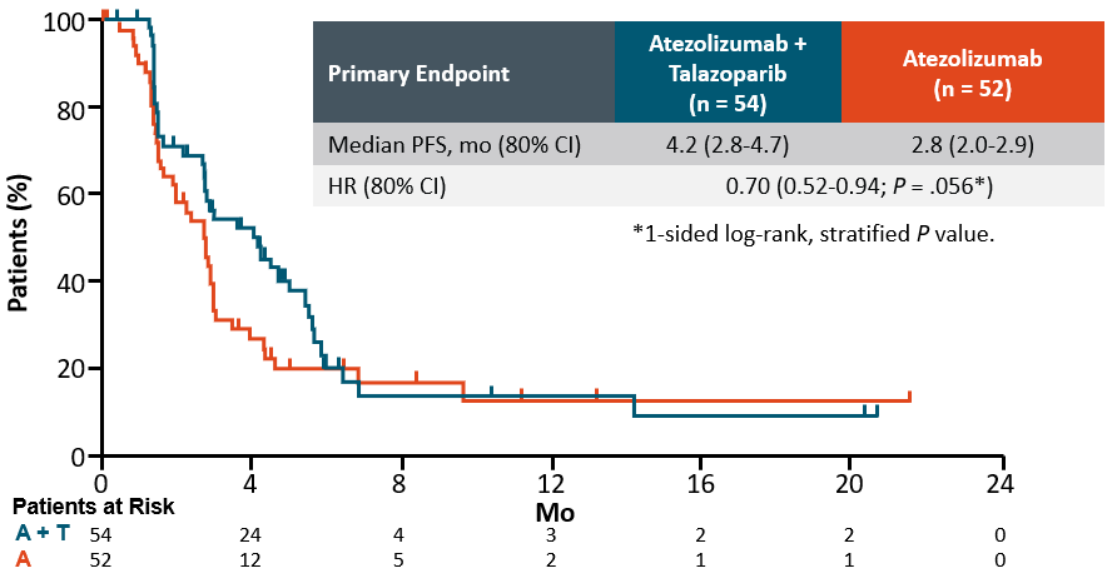


- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR, safety

Abdel Karim. ASCO 2023. Abstr 8504.

SWOG S 1929
Survival Outcomes

SWOG S1929: PFS



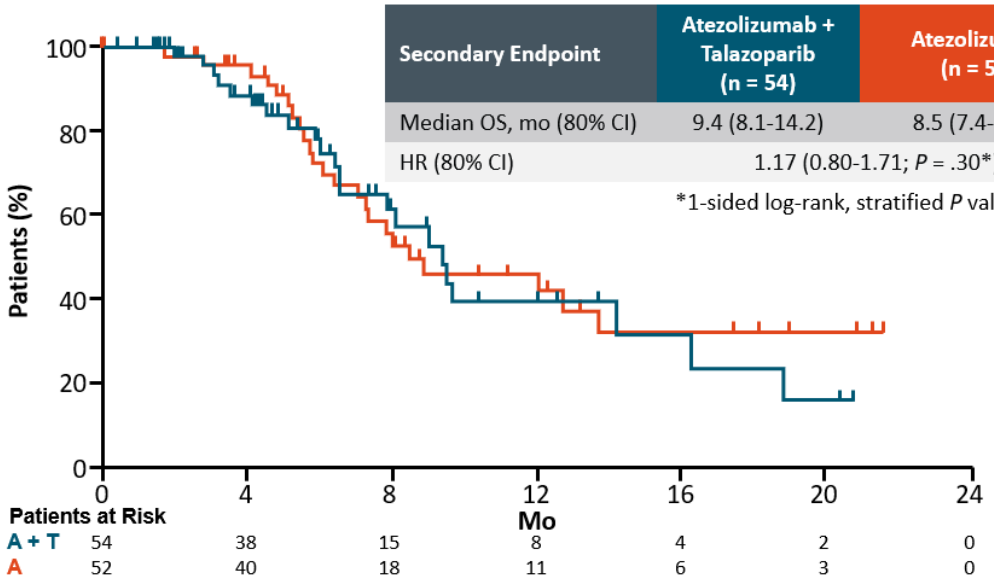
Primary Endpoint	Atezolizumab + Talazoparib (n = 54)	Atezolizumab (n = 52)
Median PFS, mo (80% CI)	4.2 (2.8-4.7)	2.8 (2.0-2.9)
HR (80% CI)	0.70 (0.52-0.94; *P* = .056*)	

*1-sided log-rank, stratified *P* value.

Median follow-up: 5 mo (range: 0-21.5)

Abdel Karim. ASCO 2023. Abstr 8504. Reproduced with permission.

SWOG S1929: Preliminary OS



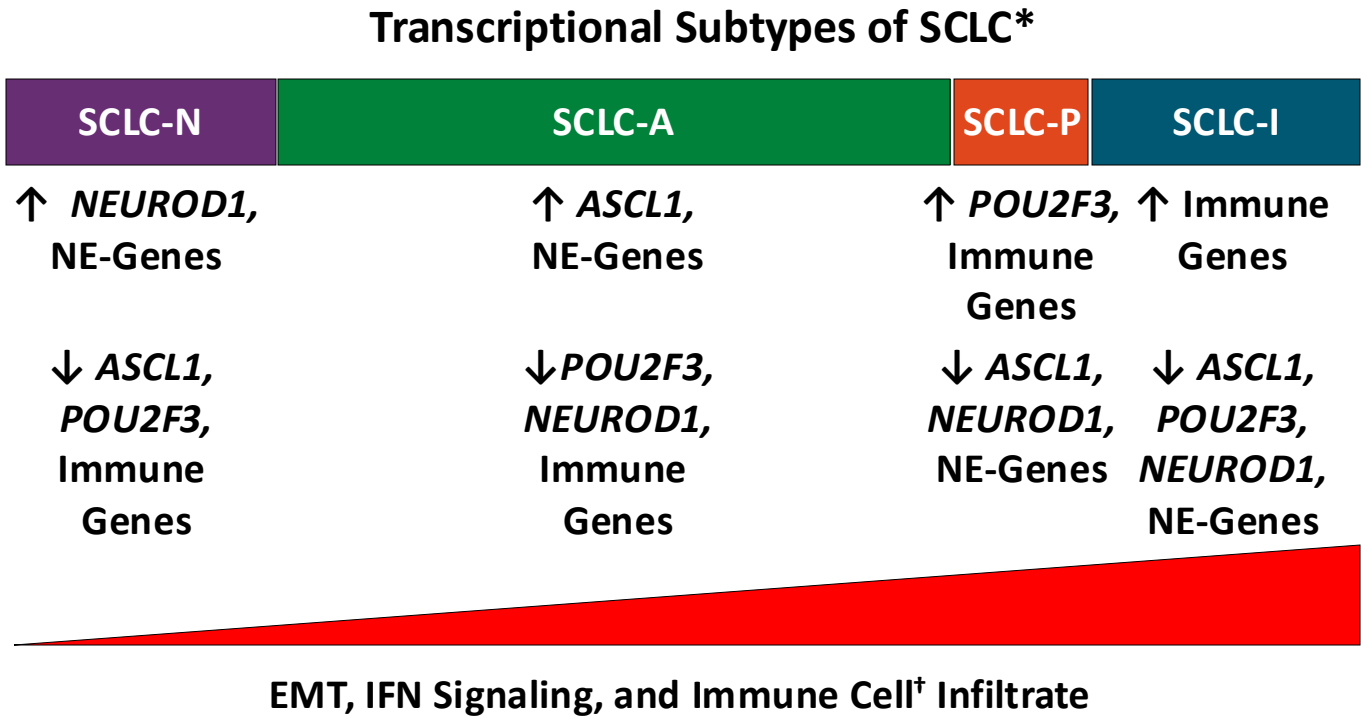
Secondary Endpoint	Atezolizumab + Talazoparib (n = 54)	Atezolizumab (n = 52)
Median OS, mo (80% CI)	9.4 (8.1-14.2)	8.5 (7.4-12.7)
HR (80% CI)	1.17 (0.80-1.71; *P* = .30*)	

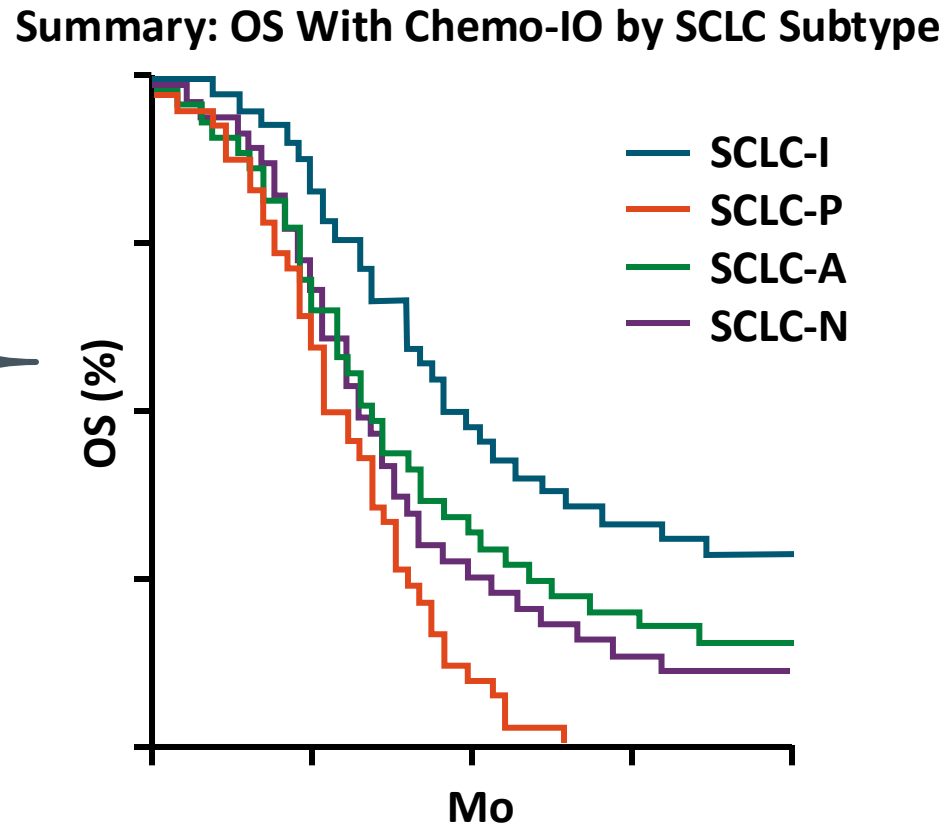
*1-sided log-rank, stratified *P* value.

Median follow-up: 5 mo (range: 0-21.5)

Abdel Karim. ASCO 2023. Abstr 8504. Reproduced with permission.

Lineage-Defining Transcription Factor Subsets of SCLC





- *ASCL1*, *NEUROD1*, and *POU2F3* expression defines SCLC subtypes with unique therapeutic vulnerabilities
  - Subtype switching associated with acquired resistance to CT

Inflamed, mesenchymal subtype predicts benefit with IO addition to CT

*NMF analysis of RNA-Seq data from 81 resected tumors, mostly LS-SCLC. **Width of box depicts** relative incidence. †T-cells, macrophages, NK cells, etc.

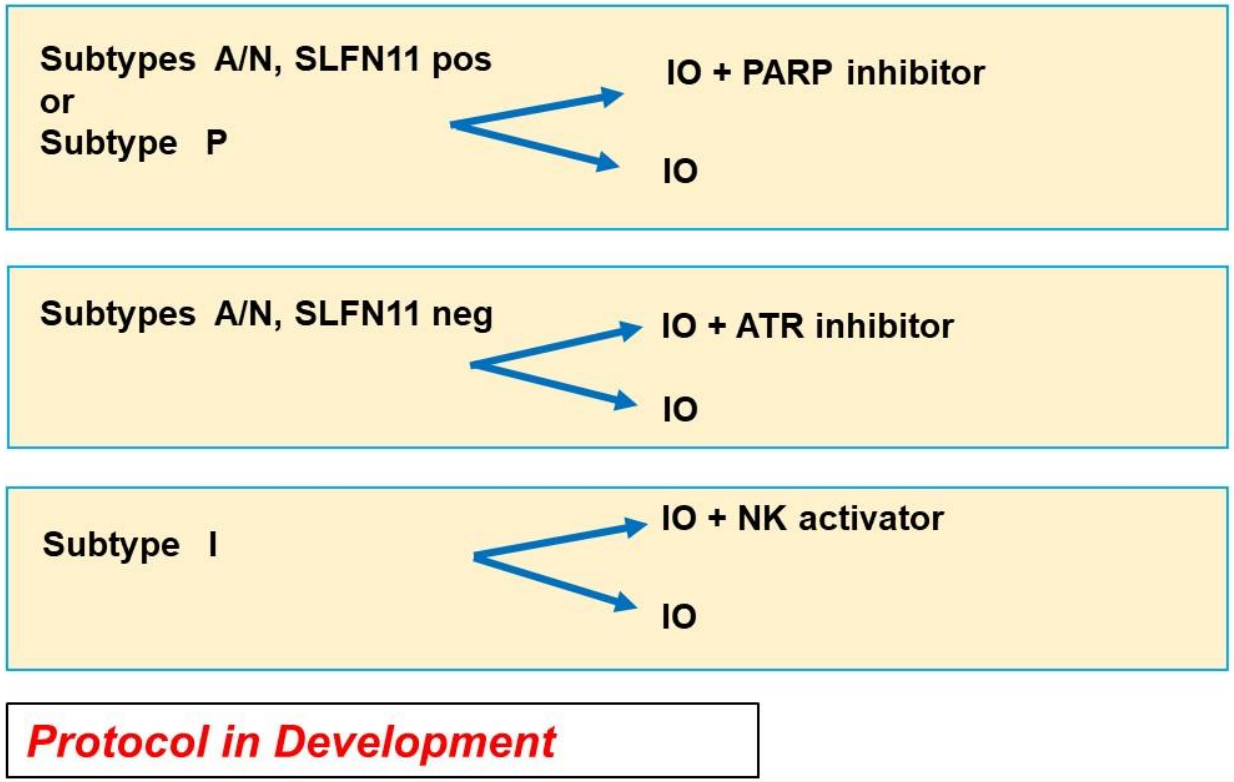
Gay. Cancer Cell. 2021;39:346.

S2409-PRISM: A Multicohort PRecIsion SCLC Subtype Maintenance Phase II Trial of Immunotherapy (IO) Versus Biomarker-Directed Novel Agents in Combination with IO in Extensive Stage Small Cell Lung Cancer

Step 1: Screening N=838

- ES-SCLC Screening
- Tissue available for testing
- Asymptomatic or Stable Treated Brain Lesions
- Allows consent after initial cycle for tissue screening

Step 2: Randomization N=312



Primary Endpoints: PFS

Secondary Endpoints: OS, Frequency, Severity of Adverse Events

Protocol in Development

PRESENTED BY: Anne Chiang MD PHD