Small cell lung cancer

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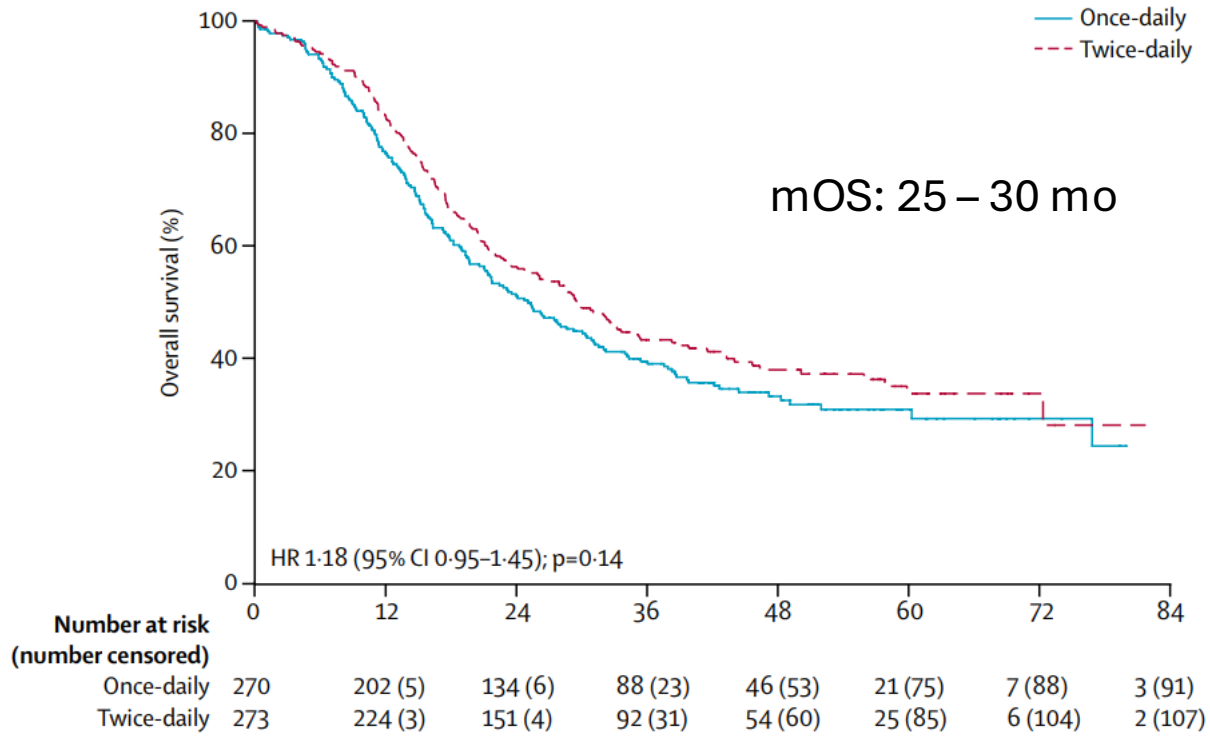
MLS Seattle

Small cell lung cancer (SCLC) overview

- Updates in treatment of limited stage SCLC (LS-SCLC)
- Updates in treatment of extensive stage SCLC (ES-SCLC)
- Therapies in development– targeting DLL3, antibody-drug conjugates, targeting SCLC subtypes

LS-SCLC- Background

- Concurrent chemoradiotherapy for LS-SCLC is associated with a median PFS of 14 – 15 mo, median OS of 25 – 30 mo, 5 year OS of 29 – 34% (Favre-Finn et al. Lancet, 2017; Bogart et al JCO 2023)



(CONVERT trial; Favre-Finn et al. Lancet, 2017)

2024 ASCO ANNUAL MEETING

ADRIATIC: durvalumab as consolidation treatment for patients with limited-stage small-cell lung cancer (LS-SCLC)

David R. Spigel, Ying Cheng, Byoung Chul Cho, Konstantin Laktionov, Jian Fang, Yuanbin Chen, Yoshitaka Zenke, Ki Hyeong Lee, Qiming Wang, Alejandro Navarro, Reyes Bernabe, Eva Buchmeier, John Wen-Cheng Chang, Isamu Okamoto, Sema Sezgin Goksu, Andrzej Badzio, Bethany Gill, Hema Gowda, Haiyi Jiang, Suresh Senan

PRESENTED BY: Dr David R. Spigel, Sarah Cannon Research Institute, Nashville, TN, USA

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.

PRESENTED BY: Dr David R. Spigel

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.

Courtesy of Dr. David Spiegel

Baseline characteristics

		Durvalumab (n=264)	Placebo (n=266)
Age, years	Median (range)	62.0 (28–84)	62.0 (28–79)
Sex, %	Male / Female	67.4 / 32.6	70.7 / 29.3
Race, %	White / Asian / Other	49.2 / 49.6 / 1.1	51.5 / 45.5 / 3.0
WHO performance status, %	0 / 1	50.0 / 50.0	47.4 / 52.6
Smoking status, %	Current / Former / Never	23.9 / 67.4 / 8.7	20.7 / 69.5 / 9.8
AJCC disease stage at diagnosis, %	I / II / III	3.0 / 9.5 / 87.5	4.1 / 8.6 / 87.2
Prior chemotherapy regimen, %*	Cisplatin-etoposide / Carboplatin-etoposide	65.5 / 34.5	66.9 / 33.1
Prior radiation schedule, %	Once daily / Twice daily	73.9 / 26.1	70.3 / 29.7
Best response to prior cCRT, %	CR / PR / SD	11.7 / 72.3 / 15.9	12.8 / 75.2 / 12.0
Prior PCI, %	Yes / No	53.8 / 46.2	53.8 / 46.2

*Based on the first cycle of chemotherapy.

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AJCC, American Joint Committee on Cancer; CR, complete response; PR, partial response; SD, stable disease.

Courtesy of Dr. David Spiegel

Patient disposition

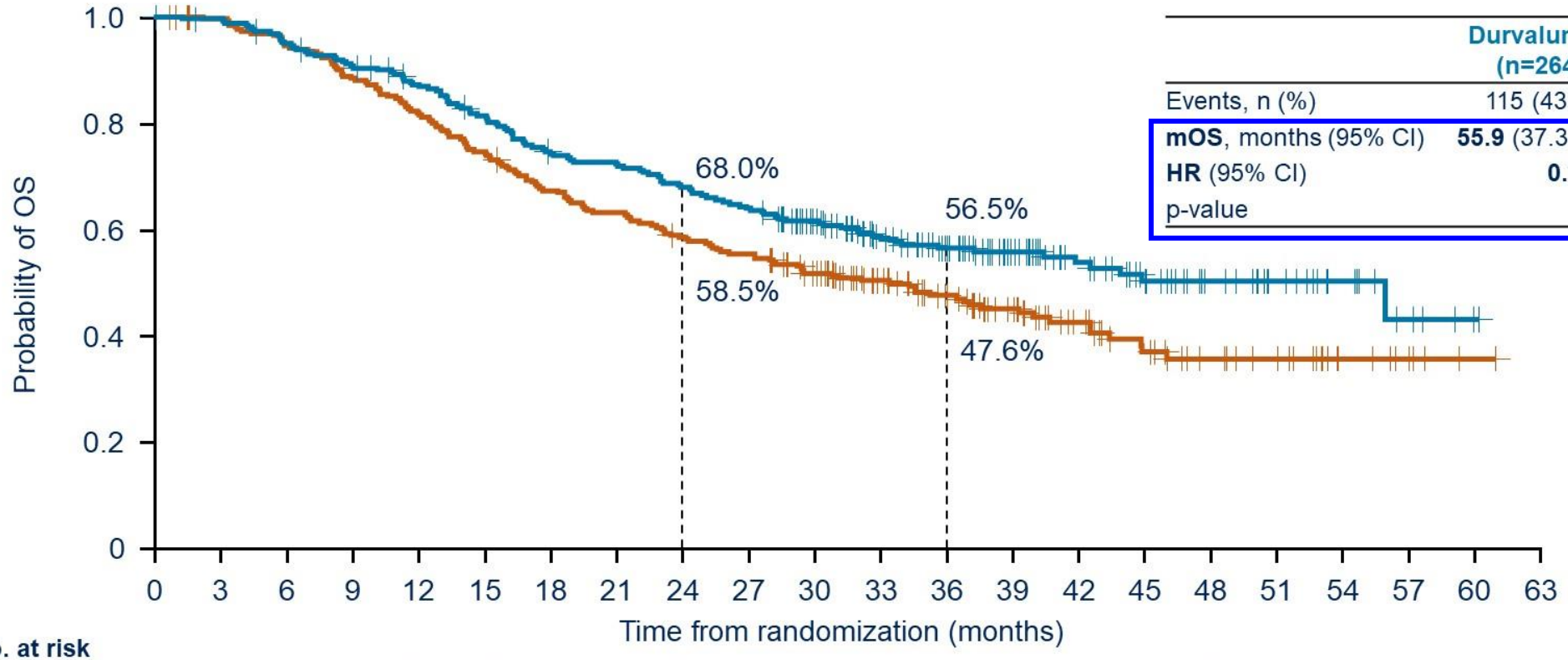
	Durvalumab (n=264)	Placebo (n=266)
Received treatment, n (%)	263* (99.6)	265 (99.6)
Ongoing study treatment at data cut-off†, n (%)	0	0
Completed the maximum 24 months of treatment, n (%)	88 (33.5)	70 (26.4)
Discontinued study treatment, n (%)	175 (66.5)	195 (73.6)
Disease progression	121 (46.0)	154 (58.1)
Adverse event	43 (16.3)	29 (10.9)
Patient decision	10 (3.8)	11 (4.2)
Other reason	1 (0.4)	1 (0.4)
Ongoing study (in follow-up) at data cut-off†, n (%)	140 (53.0)	111 (41.7)
Received subsequent systemic anticancer therapy, n	95	127
Received immunotherapy as first subsequent treatment	17	31

*One patient randomized to the durvalumab arm received tremelimumab in addition to durvalumab and will be included in the durvalumab + tremelimumab arm of the safety population. †Jan 15, 2024.

Courtesy of Dr. David Spiegel

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.

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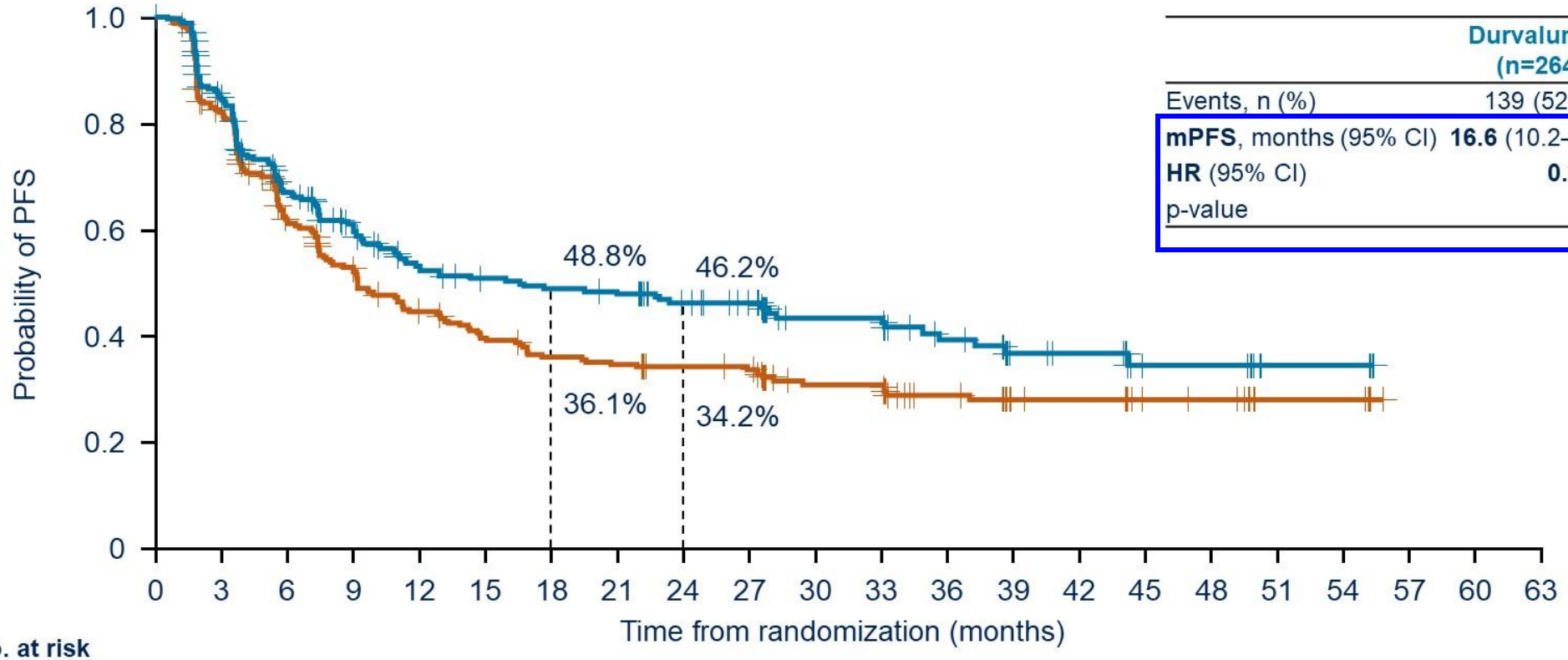
Progression-free survival* (dual primary endpoint)

- 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.

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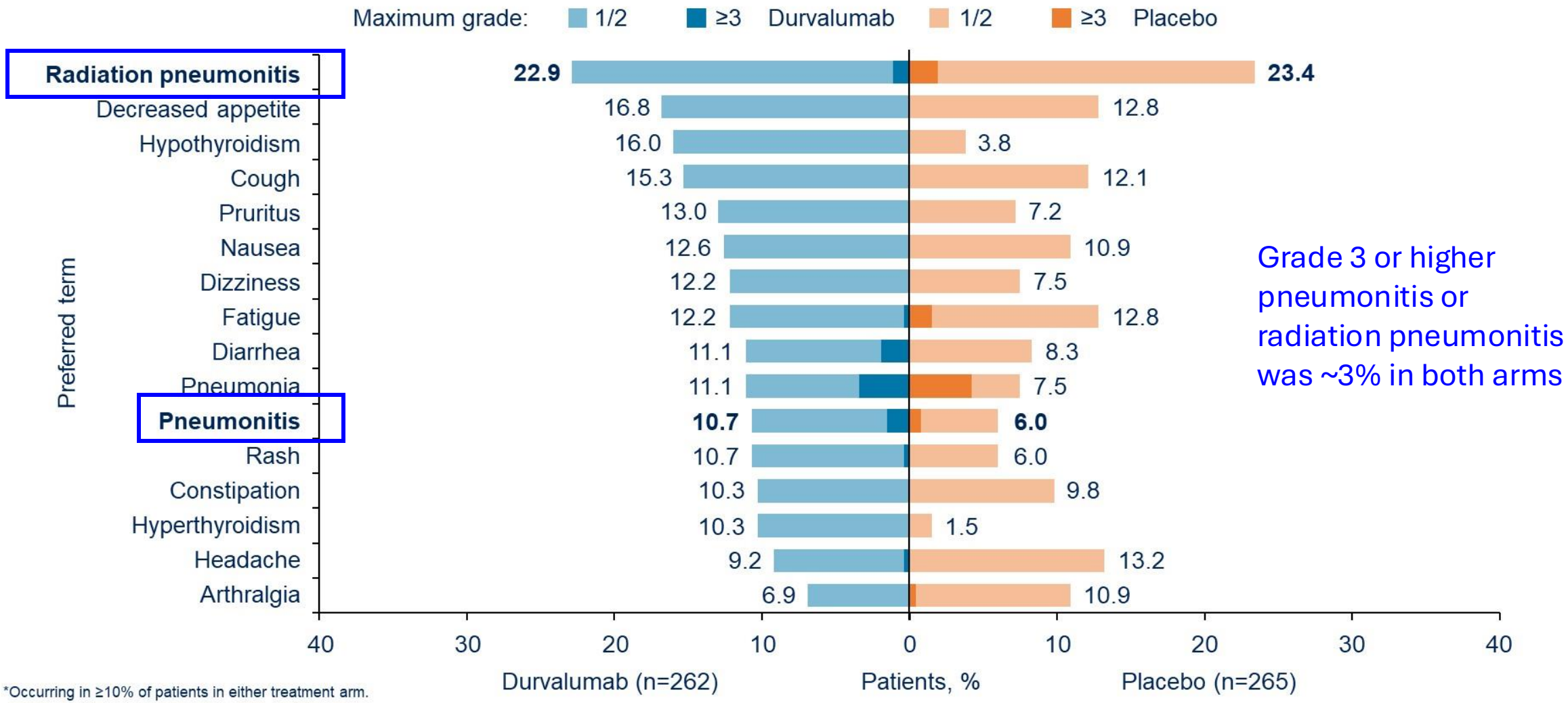
Exposure and safety summary

		Durvalumab (n=262)	Placebo (n=265)
Number of durvalumab or placebo doses	Median (range)	9.0 (1–26)	9.0 (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* AEs leading to death		2 (0.8)‡	0
Any-grade immune-mediated AEs†		84 (32.1)	27 (10.2)
Maximum grade 3/4 immune-mediated AEs		14 (5.3)	4 (1.5)

Includes AEs with an onset date following first dose of study treatment, or pre-treatment AEs that increased in severity following first dose of study treatment, through to 90 days after last dose or until start of the first subsequent systemic anticancer therapy (whichever occurred first).
*Assessed by investigator. †Defined as an AE of special interest (excluding infusion related/hypersensitivity/anaphylactic reaction) that is consistent with an immune-mediated mechanism that required treatment with systemic corticosteroids, other immunosuppressants, or endocrine therapy. ‡Causes of death were encephalopathy and pneumonitis.

Courtesy of Dr. David Spiegel

Most frequent AEs*



Grade 3 or higher pneumonitis or radiation pneumonitis was ~3% in both arms

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

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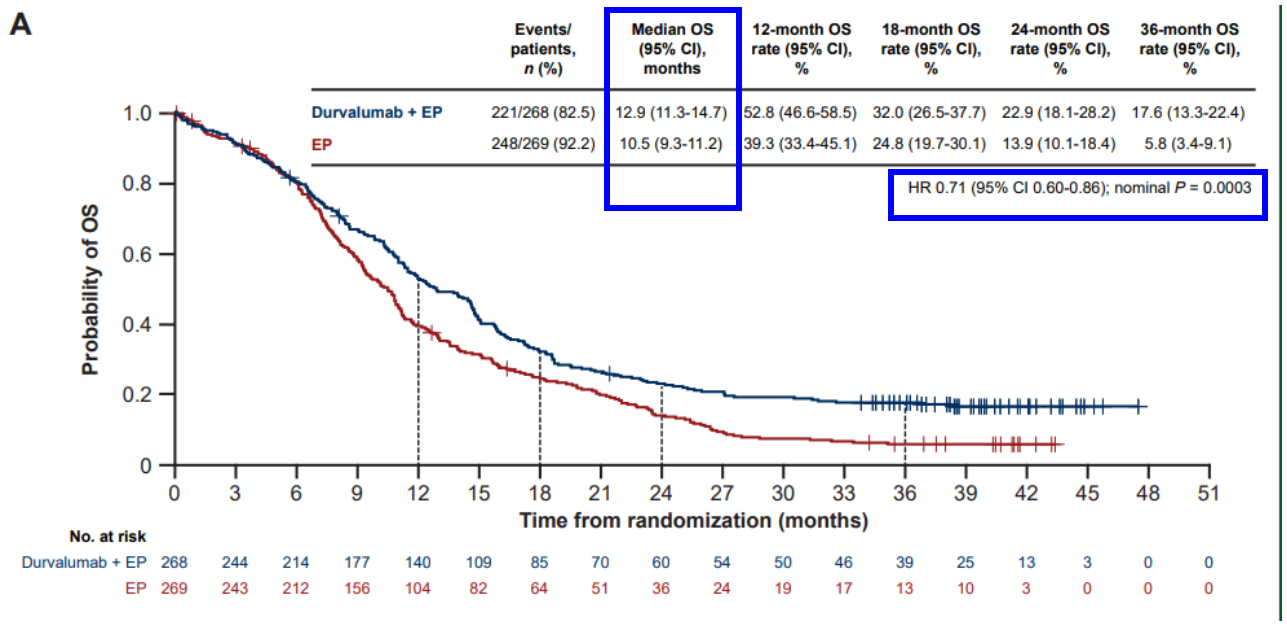
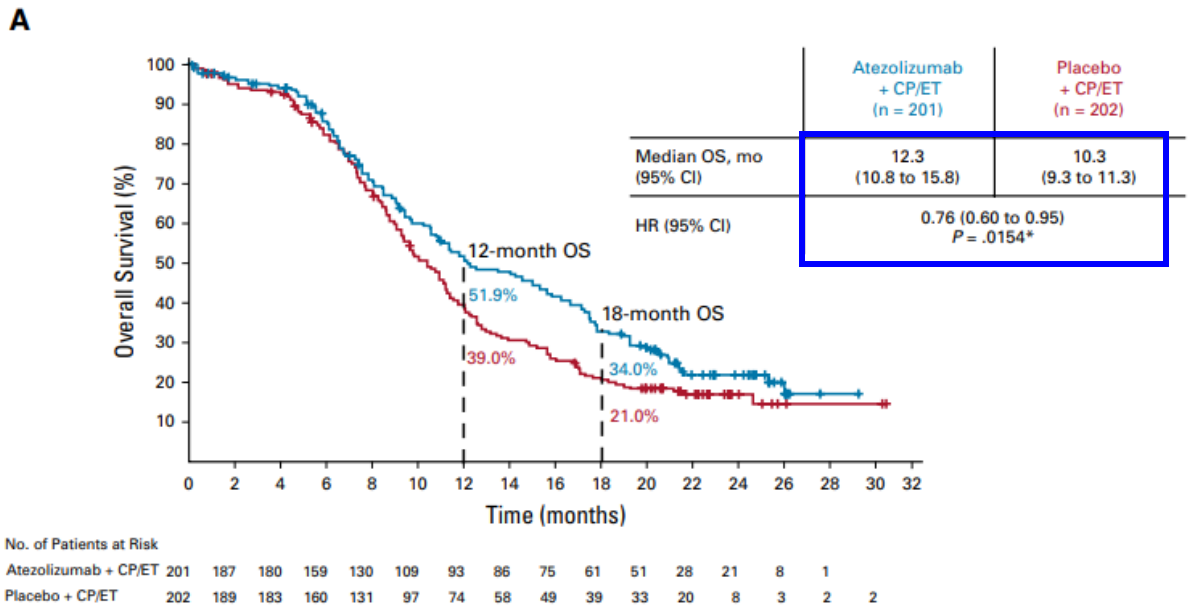
ES-SCLC: Background

CASPIAN (median follow-up 39.4 mo)



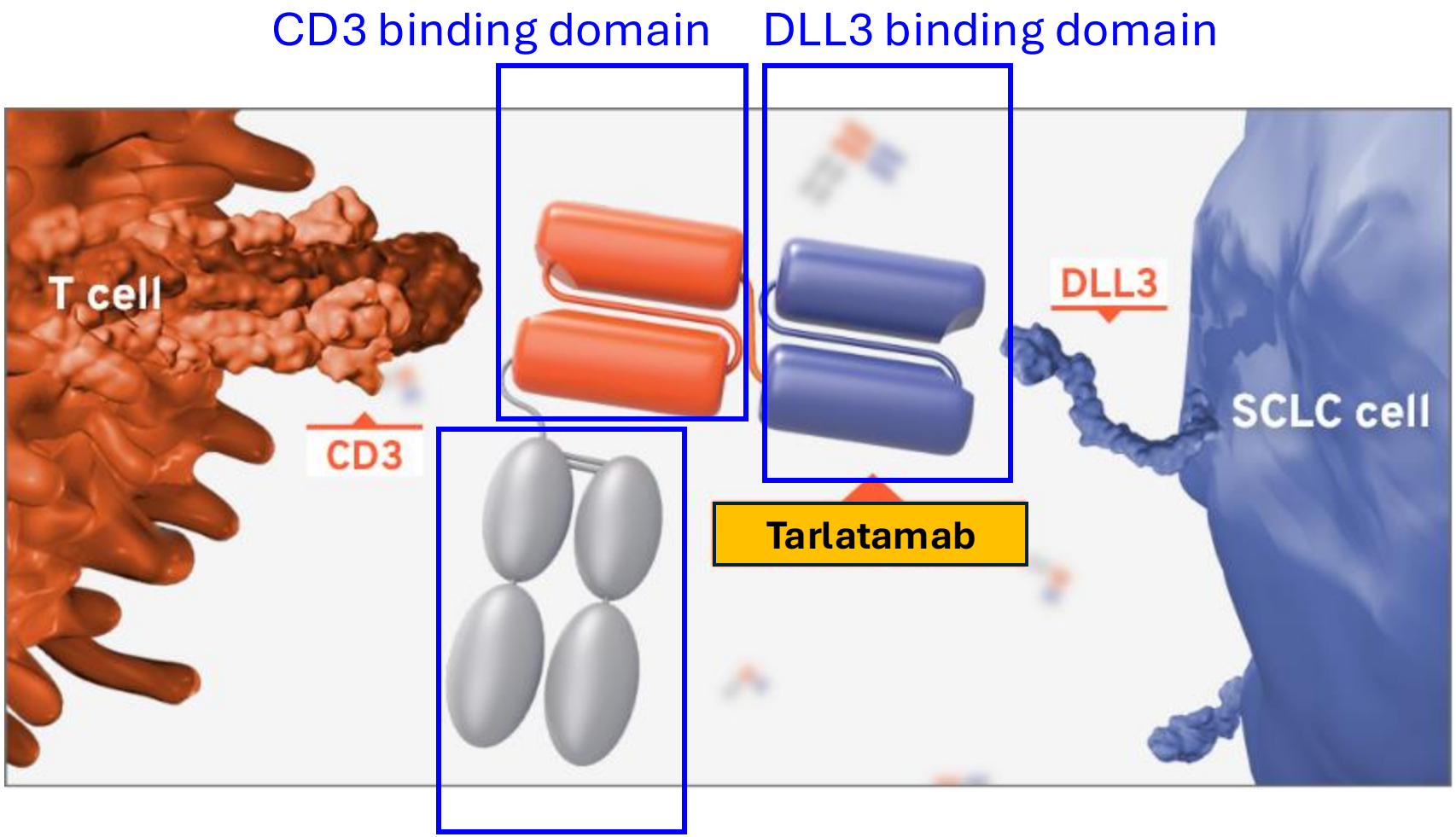
(Paz-Ares. ESMO Open 2022; Paz-Ares Lancet 2019)

IMpower133 (median follow-up 22.9 mo)



(Liu et al. JCO 2021, Horn et al NEJM 2018)

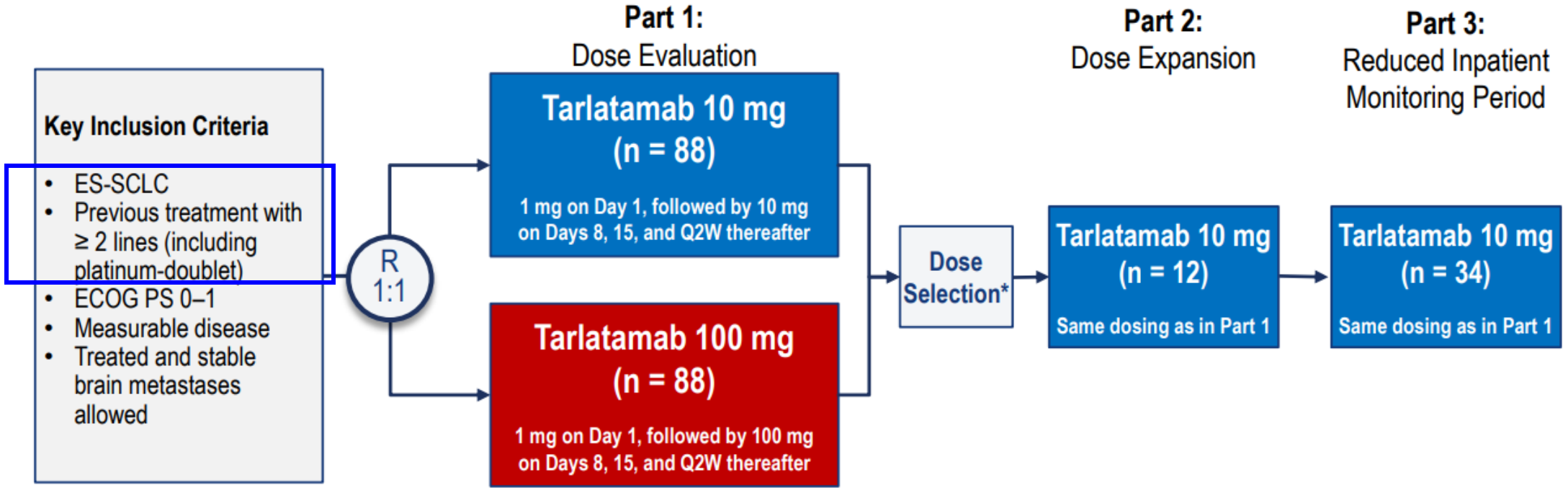
Tarlatamab: a novel bispecific T cell engager



Adapted from: https://www.imdelltrahcp.com/about-imdelltra/mechanism-of-action, Accessed Aug 21 2024

DeLLphi-301 Study Design

Phase 2, open-label study (NCT05060016)



Primary Endpoint: ORR per RECIST v1.1 by BICR, TEAEs, tarlatamab serum concentrations
Secondary Endpoints Included: DOR, DCR, PFS per RECIST v1.1 by BICR, OS

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*Once 30 patients per dose level had the opportunity to confirm an objective response after the first post-treatment scan or ≥ 13 weeks of follow-up, whichever occurred first.
BICR, blinded independent central review; **DCR**, disease control rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES-SCLC**, extensive stage-small cell lung cancer; **ITT**, intention-to-treat; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomization; **RECIST**, Response Evaluation Criteria in Solid Tumors; **TEAE**, treatment-emergent adverse event.

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Baseline Characteristics

	Part 1 + 2 Tarlatamab 10 mg (n = 100)	Part 1 Tarlatamab 100 mg (n = 88)	Part 3 Tarlatamab 10 mg (n = 34)
Median age, years (range)	64 (35–82)	62 (34–80)	66 (49–80)
Male, %	72	70	71
Asian / Black or African American / White,* %	41 / 0 / 58	41 / 0 / 58	6 / 3 / 91
Ever smoker / non-smoker, %	92 / 8	94 / 6	97 / 3
ECOG performance status: 0 / 1, %	26 / 74	27 / 73	29 / 71
Prior lines of therapy, median (range)	2 (1–6)	2 (1–8)	2 (2–6)
2 prior lines of therapy, %	65	55	65
≥ 3 prior lines of therapy, %	33	43	35
Prior anti-PD-(L)1 treatment, %	73	70	82
< 90 days to progression after first-line platinum therapy,† %	28	20	21
Brain / liver metastases, %	23 / 39	36 / 34	12 / 35
DLL3 expression (> 0%), n/N evaluable (%)	80/83 (96)	71/74 (96)	N/A‡

Data cutoff, June 27, 2023. Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg.
*No patients of American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander race were enrolled.
†Platinum sensitivity was calculated as end of first-line platinum therapy to date of first progression.
‡DLL3 sample analysis from Part 3 in progress.
DLL3, delta-like ligand 3; **ECOG**, Eastern Cooperative Oncology Group; **N/A**, not available; **PD-(L)1**, programmed death 1 / ligand 1.

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Tarlatamab Anti-Tumor Activity

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Objective response rate, n (%) (97.5% CI)	40 (40) (29, 52)	28 (32) (21, 44)
Complete response	1 (1)	7 (8)
Partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable / no post-baseline scan*	10 (10)	20 (23)
Observed duration of response ≥ 6 months, n/N (%)	23/40 (58)	17/28 (61)
Disease control rate, n (%) (95% CI)	70 (70) (60, 79)	55 (63) (52, 73)

Tarlatamab 10 mg demonstrated anti-tumor activity in heavily pre-treated SCLC with an objective response rate of 40%

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Data cutoff, June 27, 2023. Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 188). Part 3 did not have adequate follow-up for response analysis.

*Not evaluable and no post-baseline scan were considered non-responders for response analysis. **SCLC**, small cell lung cancer.

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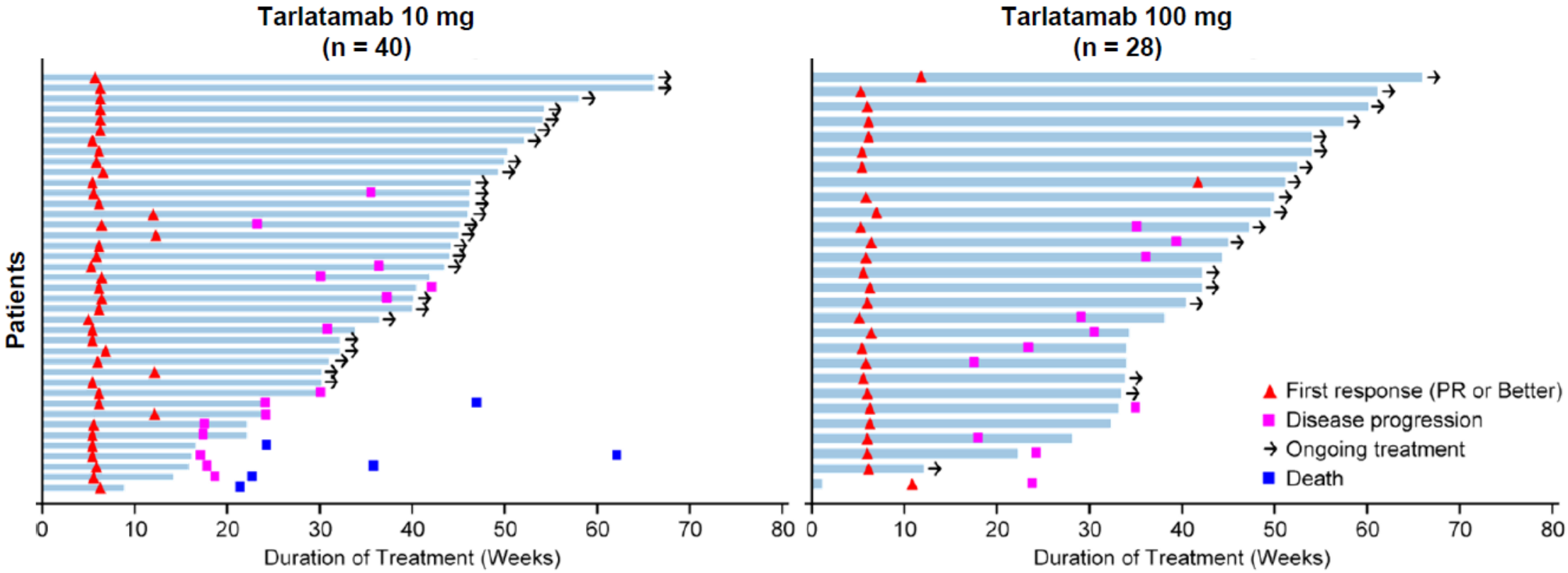
Duration of Response and Treatment



- Median TTR was 1.4 months (range, 1.1–9.6 months), and median DOR was not reached
- Of the 68 responders, the DOR was ≥ 6 months in 40 patients (59%)
- 56% of the responses were ongoing at data cutoff

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Median follow-up time for DOR, 9.5 months (95% CI; 8.3, 9.7 months).
DOR, duration of response; **PR**, partial response; **TTR**, time to objective response.

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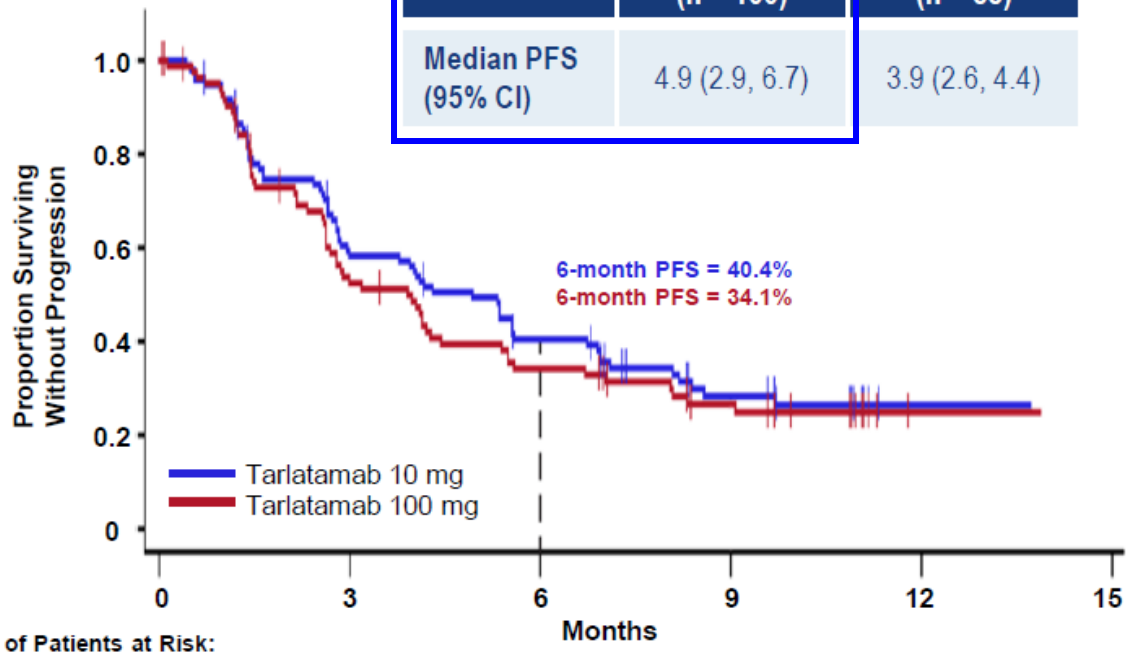
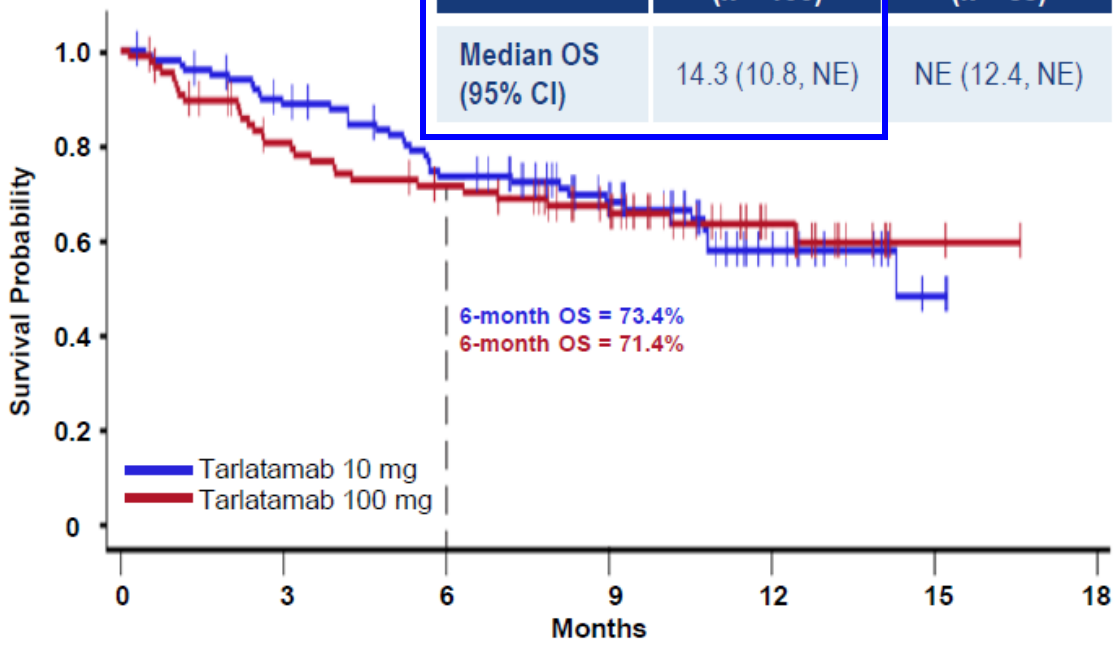
PFS and OS

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median PFS (95% CI)	4.9 (2.9, 6.7)	3.9 (2.6, 4.4)



Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median OS (95% CI)	14.3 (10.8, NE)	NE (12.4, NE)



Number of Patients at Risk:

Tarlatamab 10 mg	100	53	35	18	2	0	100	84	67	44	17	3	0
Tarlatamab 100 mg	88	41	26	15	3	0	88	62	53	39	16	2	0

OS data is not yet mature; at the last follow-up, 57% of patients in the tarlatamab 10 mg group and 51% of patients in the tarlatamab 100 mg group were still alive

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Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg.
NE, not estimable; **OS**, overall survival; **PFS**, progression-free survival.

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Summary of Adverse Events*

TEAEs, n (%)	Part 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 100 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
Any grade	96 (97)	87 (100)	34 (100)
≥ Grade 3	57 (58)	56 (64)	22 (65)
Related to tarlatamab, any grade	89 (90)	81 (93)	29 (85)
≥ Grade 3	29 (29)	29 (33)	5 (15)
Fatal	0	0	1 (3)†
Leading to dose interruption/reduction	14 (14)	25 (29)	3 (9)
Leading to discontinuation	4 (4)	3 (3)	0

Most Common TEAEs in ≥ 20% of Patients, n (%)	Part 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 100 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
CRS	49 (49)	53 (61)	19 (56)
Grade 1–2	49 (49)	48 (55)	18 (53)
≥ Grade 3	0	5 (6)	1 (3)
Decreased appetite	25 (25)	38 (44)	13 (38)
Pyrexia	38 (38)	29 (33)	8 (24)
Constipation	28 (28)	22 (25)	8 (24)
Anemia	26 (26)	22 (25)	9 (26)
Asthenia	20 (20)	21 (24)	10 (29)
Dysgeusia	24 (24)	12 (14)	14 (41)
Fatigue	21 (21)	17 (20)	9 (26)

- **Tarlatamab demonstrated a favorable safety profile, with a low rate of discontinuations due to treatment-related adverse events (TRAEs)**
- **Shorter inpatient monitoring (Part 3) did not alter the safety profile**

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*The safety analysis set includes all patients in Part 1, Part 2, and Part 3 who received at least one dose of tarlatamab (N = 220). †Fatal TRAE was respiratory failure.
CRS, cytokine release syndrome; **TEAE**, treatment-emergent adverse event.

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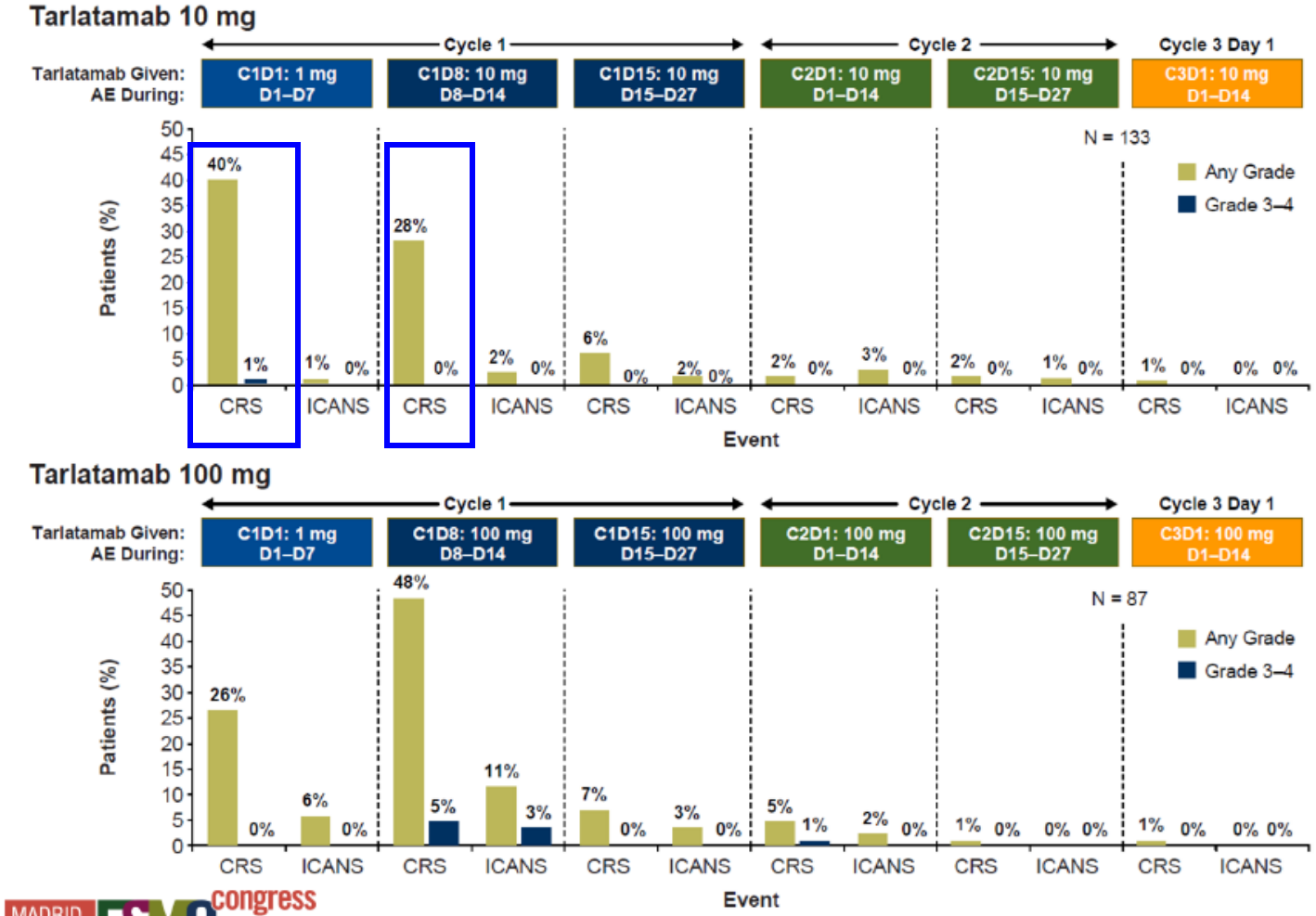
CRS and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)*



- CRS was largely confined to the first or second dose, primarily grade 1–2
- ICANS* occurred infrequently overall and was predominantly observed with tarlatamab 100 mg

Additional Interventions for CRS:

Patients receiving tarlatamab, n (%)	10 mg (n = 133)	100 mg (n = 87)
Tocilizumab	7 (5)	9 (10)
Supplemental oxygen	11 (8)	8 (9)
Vasopressor support	1 (1)	1 (1)

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*ICANS includes associated neurologic events based on a broad search using 61 selected preferred terms from MedDRA version 26.0.
AE, adverse event; **C**, cycle; **CRS**, cytokine release syndrome; **D**, day; **ICANS**, immune effector cell-associated neurotoxicity syndrome.

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DLL3 T-cell engagers: selected ongoing and future trials

LS-SCLC, 1L maintenance

Agent	NCT	Description
Tarlatamab	NCT06117774	DLL3/CD3 bispecific T cell engager

ES-SCLC, 1L maintenance

Agent	NCT	Description
Tarlatamab	NCT06211036	DLL3/CD3 bispecific T cell engager
BI 764532	NCT06077500	DLL3/CD3 bispecific T cell engager

Relapsed/refractory SCLC

Agent	NCT	Description
RO7616789	NCT05619744	Tri-specific targeting DLL3, CD3, CD137
BI 764532	NCT05990738	DLL3/CD3 bispecific T cell engager
PT217	NCT05652686	Anti-DLL3 x anti-CD47 bispecific
QLS31904	NCT05461287	Anti-DLL3 x anti-CD3 bispecific
HPN328	NCT04471727	Trispecific targeting DLL3, CD3, albumin

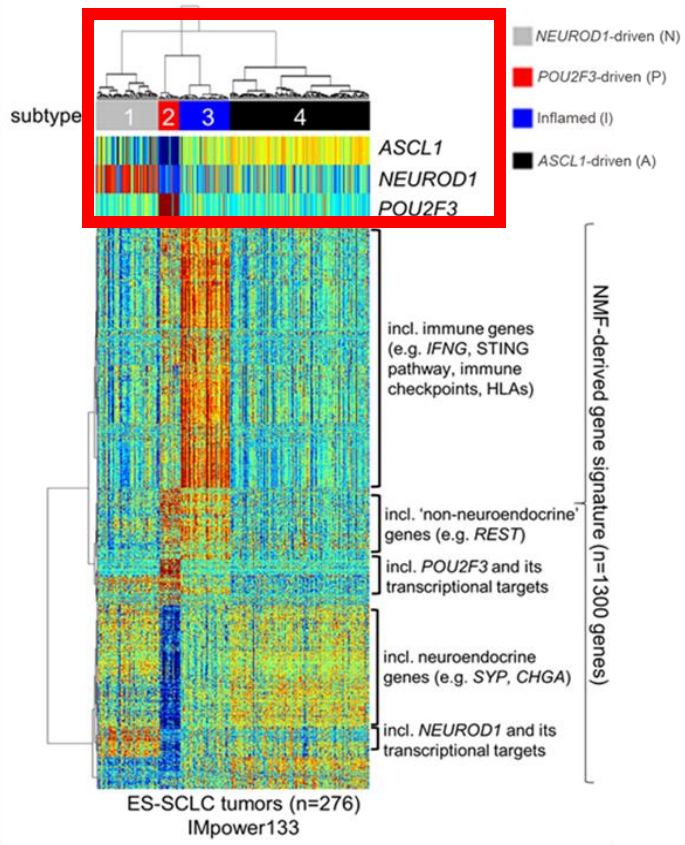
Antibody-Drug Conjugates in Development for SCLC

Agent	Target	Payload	NCT	Efficacy
Sacituzumab govitecan	TROP2	SN-38; topo I inhibitor	NCT01631552	ORR 37%; DOR 6.3 mo
Datopotamab deruxtecan	TROP2	Deruxtecan; topo I inhibitor	TRIOPION-PanTumor01 NCT03401385	NA
ABBV-011	SEZ6	Calicheamicin; induces DS breaks	NCT03639194 NCt05599984	19%
Ifinatamab deruxtecan	B7-H3	Deruxtecan; topo I inhibitor	NCT04145622	ORR 52.4%; DOR 5.9 mo
HS-20093	B7-H3	HS-9365 (proprietary target)	NCT05276609	57 – 58%

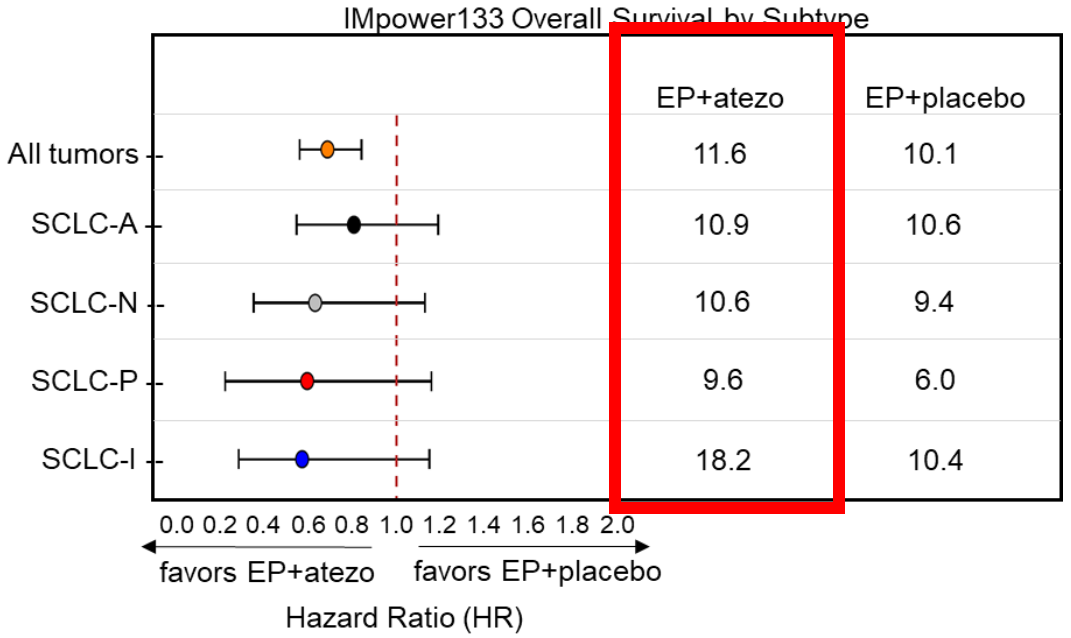
Adapted from Taofeek K. Owonikoko, MD, PhD TTLC 2024

SCLC subtypes experience variable benefit from frontline chemo-immunotherapy

Four subtypes defined by expression of transcription factors and inflammatory signature in IMP133.



Variable OS in IMP133 EP+atezo arm on subtype-by-subtype basis.



Gay et al., *Cancer Cell*, 2021

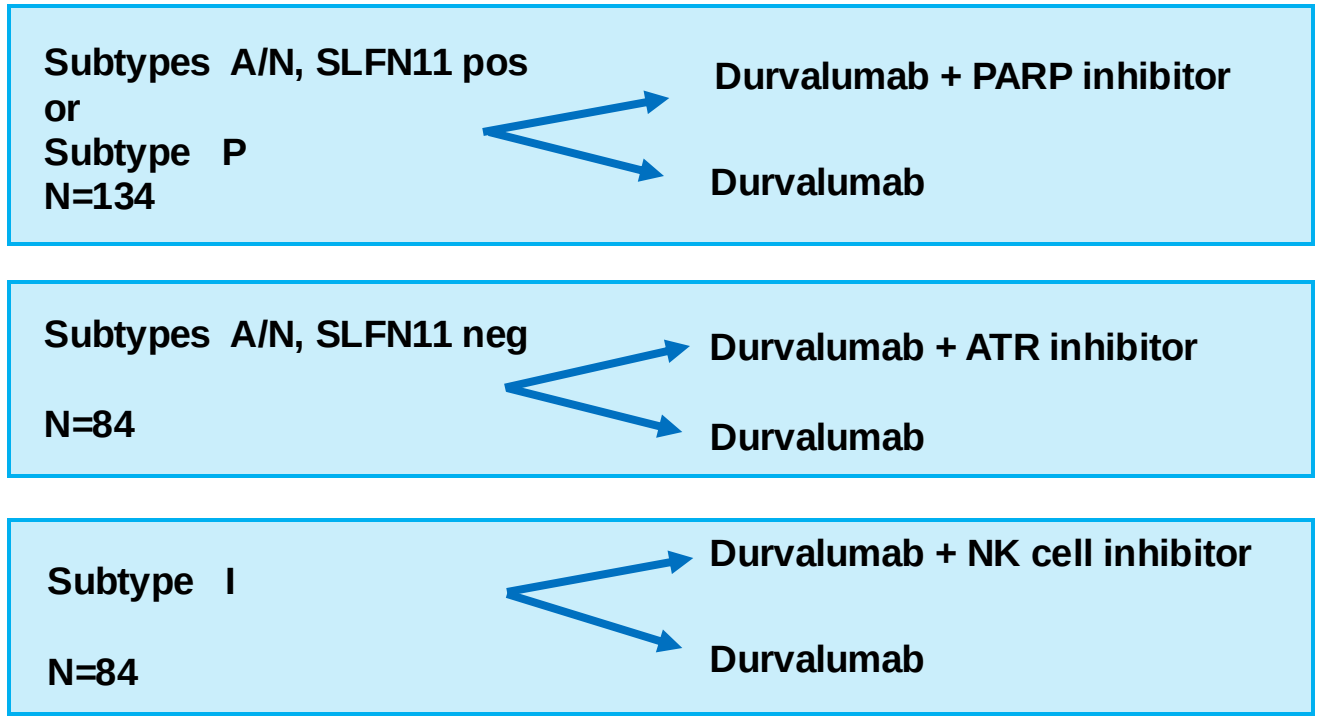
Courtesy of Anne Chiang MD PhD, TTLC 2024

S2409-PRISM: Overall Schema

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 Objective: PFS

Secondary Objectives: OS, Safety in AZD5305/durva run-in, AEs

Courtesy of Anne Chiang MD PhD, TTLC 2024

Conclusions

- Consolidation durvalumab is expected to become the new standard of care for patients with LS-SCLC who have not progressed after concurrent chemoradiation
- Tarlatamab 10 mg was associated with ORR 40% and 6-month OS was 73%. It is FDA approved as the first T cell engager for the treatment of ES-SCLC
- Novel DLL3-targeting agents, antibody drug conjugates targeting Trop2, SEZ6, and B7H3, and biomarker-directed immunotherapy combinations represent novel strategies in development for SCLC

Thank you

- Patients and their families who participate in clinical trials
- Thank you for your attention