T-Cell Engagers: Fighting Solid Tumors From Within

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Disclosures

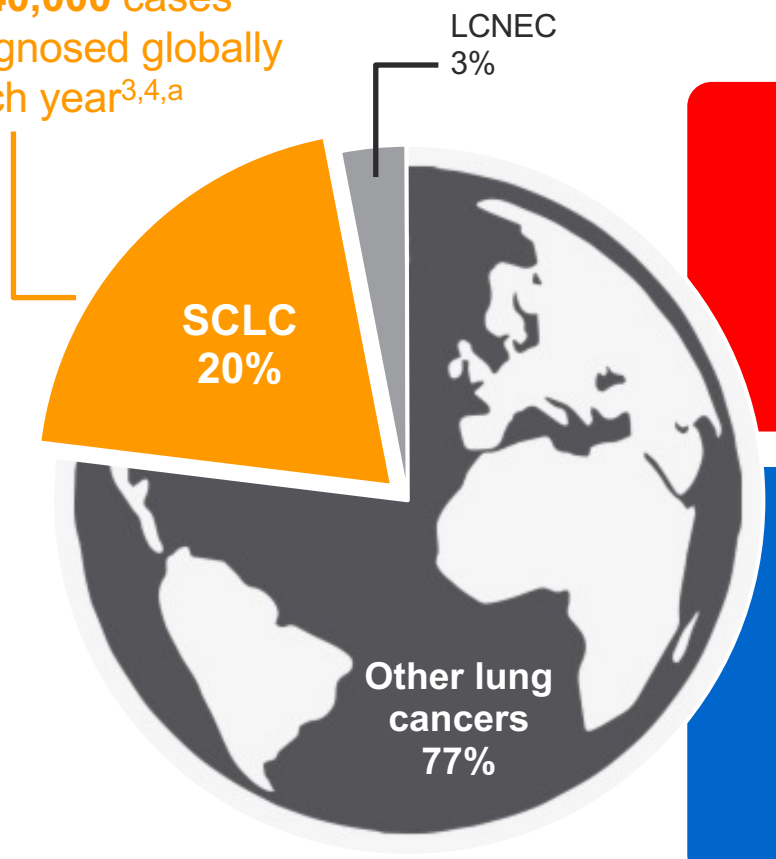
- I have consulted regarding oncology drug development with AbbVie, Amgen, Astra Zeneca, Boehringer Ingelheim, D2G, Daiichi Sankyo, Epizyme, Genentech/Roche, Ipsen, Jazz, Kowa, Lilly, Merck, and Syros.

- I serve on the scientific advisory boards of Auron, Boehringer Ingelheim, Bridge Medicines, DISCO, Earli, and Harpoon Therapeutics.

ESMO = European Society for Medical Oncology.

SCLC Is an Aggressive NEN of the Lung That Often Presents With Extensive Disease at Diagnosis[1,2]

≈440,000 cases diagnosed globally each year[3,4,a]



SCLC is characterized by[1,2]:

- Rapid growth
- Resistance to treatment after initial response
- Early development of widespread metastases

Prior to the immunotherapy era:

<7% of patients with SCLC (all stages) **will survive for ≥5 years[5]**

<5% of patients with extensive disease **will survive for >2 years[5]**

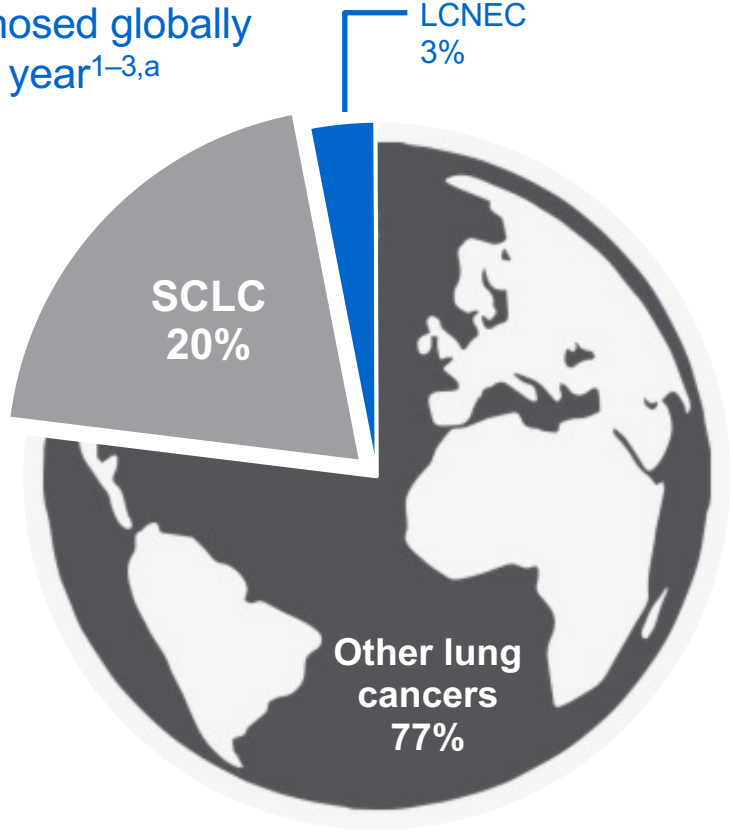
[a]Estimate based on a diagnosis of 2,206,771 new lung cancers globally in 2020,[3] with SCLC accounting for 20% of these.[4]

ESMO = European Society for Medical Oncology; NEN = neuroendocrine neoplasm; LCNEC = large cell neuroendocrine carcinoma; SCLC = small cell lung cancer.

1. National Comprehensive Cancer Network. NCCN Guidelines: Small Cell Lung Cancer, Version 3. 2023. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed June 2023; 2. Dingemans AMC, et al. *Ann Oncol.* 2021;32(7):839–853; 3. International Agency for Research on Cancer (IARC). Estimated number of new cases of cancer in 2020. https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf. Accessed July 2023; 4. Fernandez-Cuesta L, et al. *Am Soc Clin Oncol Educ Book*. 2023;43:e390794; 5. Byers LA, Rudin CM. *Cancer.* 2015;121(5):664–672.

LCNEC Is Another NEN of the Lung That Shares Key Clinical Features With SCLC[1,2]

≈66,000 cases diagnosed globally each year[1–3,a]



Like SCLC, LCNEC is a **high-grade NEN** with a **poor prognosis**[1,2]

diagnosed in advanced stages[2,4]

5-year OS

- **35%** in all stages[5]
- **15%–25%** in advanced stages[2]

[a]Estimate based on a diagnosis of 2,206,771 new lung cancers globally in 2020,[3] with LCNEC accounting for 3% of these.[1,2]

ESMO = European Society for Medical Oncology; LCNEC = large cell neuroendocrine carcinoma; NEN = neuroendocrine neoplasm; NSCLC = non–small cell lung cancer; OS = overall survival; SCLC = small cell lung cancer.

1. Fernandez-Cuesta L, et al. *Am Soc Clin Oncol Educ Book*. 2023;43:e390794; 2. Andrini E, et al. *J Clin Med*. 2022;11(5):1461; 3. International Agency for Research on Cancer (IARC). Estimated number of new cases of cancer in 2020. https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf. Accessed July 2023; 4. Lindsay CR, et al. *Br J Cancer*. 2021;125(9):1210–1216; 5. Ferrara MG, et al. *Front Oncol*. 2021;11:650293.

There Are Currently No Targeted Therapies Specific for LCNEC[1–3]

- Due to its rarity, there are **no clinical studies** focused specifically on LCNEC[1,2]
- The **LCNEC biomarker profile** has similarities with both **SCLC and NSCLC**[2,3]
  - As such, advanced LCNEC is commonly treated with systemic regimens for SCLC and NSCLC[2,3]
  - Results are modest with no clear indication of superiority of one regimen over another[1–4]

Summary of Responses of Advanced LCNEC to SCLC-Like or NSCLC-Like Regimens[4–9]

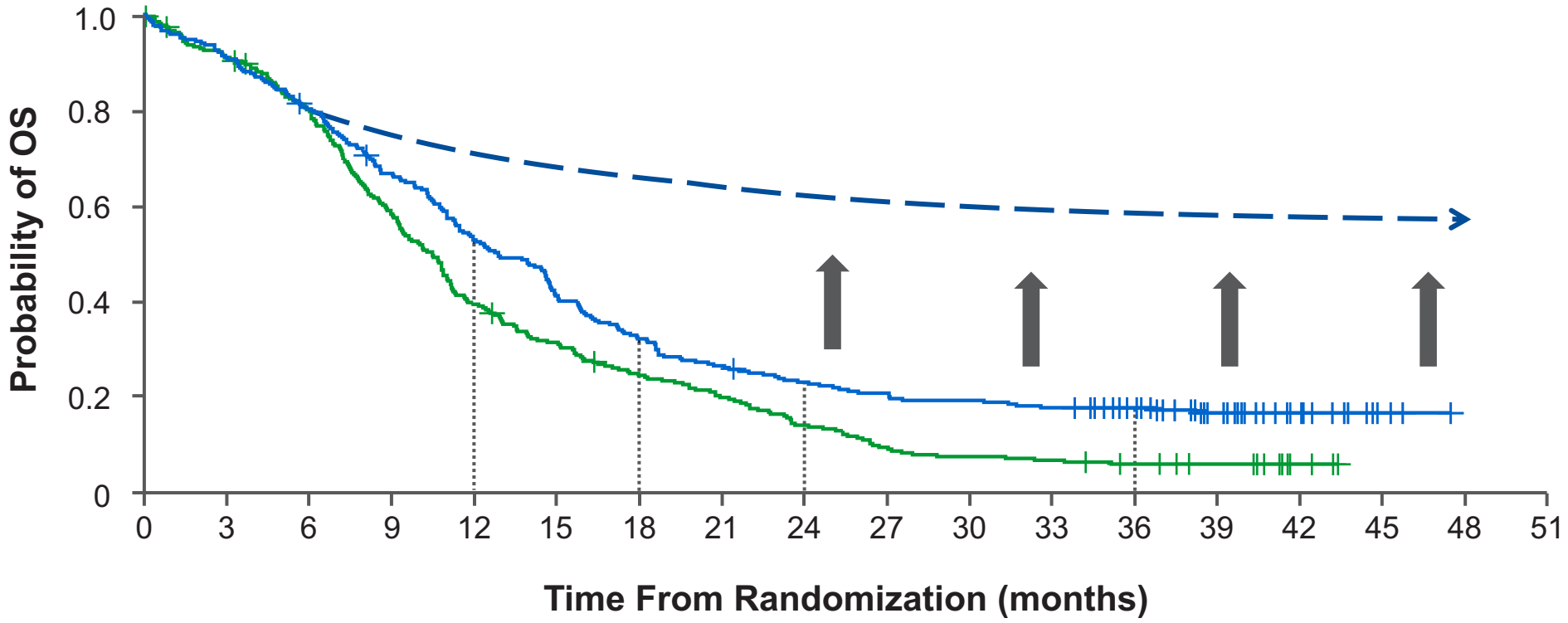
	SCLC-like Regimens	NSCLC-like Regimens
Treatments	• Platinum-etoposide[5,6,9] • Cisplatin-irinotecan[7]	• Carboplatin-paclitaxel-everolimus[8] • Gemcitabine, docetaxel, paclitaxel, or vinorelbine[4,9] • Pemetrexed only[4,9]
ORR	36.8%–46.7%	44.9%
mPFS	4.6–5.8 months	4.1–4.4 months
Median survival	6.7–12.6 months	5.9–9.9 months

ESMO = European Society for Medical Oncology; LCNEC = large cell neuroendocrine carcinoma; mPFS = median progression-free survival; NSCLC = non–small cell lung cancer; ORR = objective response rate; SCLC = small cell lung cancer.

1. Andrini E, et al. *J Clin Med*. 2022;11(5):1461; 2. Ferrara MG, et al. *Front Oncol*. 2021;11:650293; 3. Fernandez-Cuesta L, at al. *Am Soc Clin Oncol Educ Book*. 2023;43:e390794; 4. Jelli B, et al. *Lung Cancer*. 2023;181:107232; 5. Le Treut J, et al. *Ann Oncol*. 2013;24(6):1548–1552; 6. Naidoo J, et al. *Clin Lung Cancer*. 2016;17(5):e121–e129; 7. Niho S, et al. *J Thorac Oncol*. 2013;8(7):980–984; 8. Christopoulos P, et al. *Ann Oncol*. 2017;28(8):1898–1902; 9. Derks JL, et al. *Eur Respir J*. 2017;49(6):1601838.

How Do We Raise the Tail of This Curve?

- How do we induce immuno-responsiveness in the (90%?) of SCLC cases that are immuno-resistant?

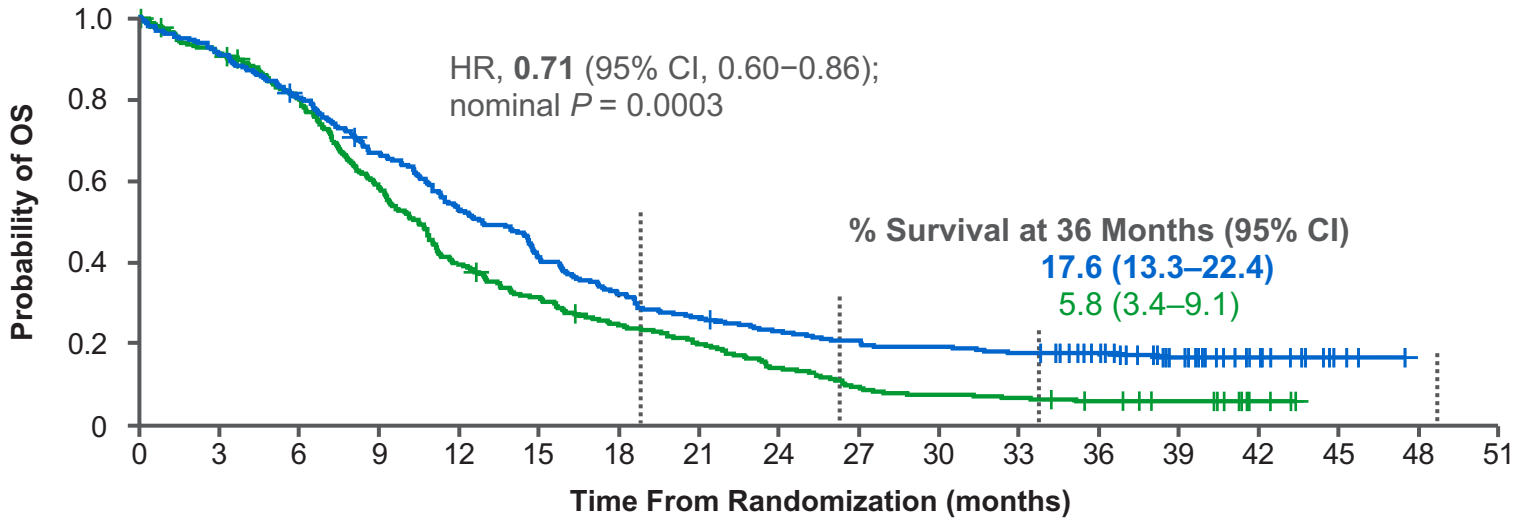


ESMO = European Society for Medical Oncology; OS = overall survival; SCLC = small cell lung cancer.
Paz-Ares L, et al. *ESMO Open.* 2022;7(2):100408.

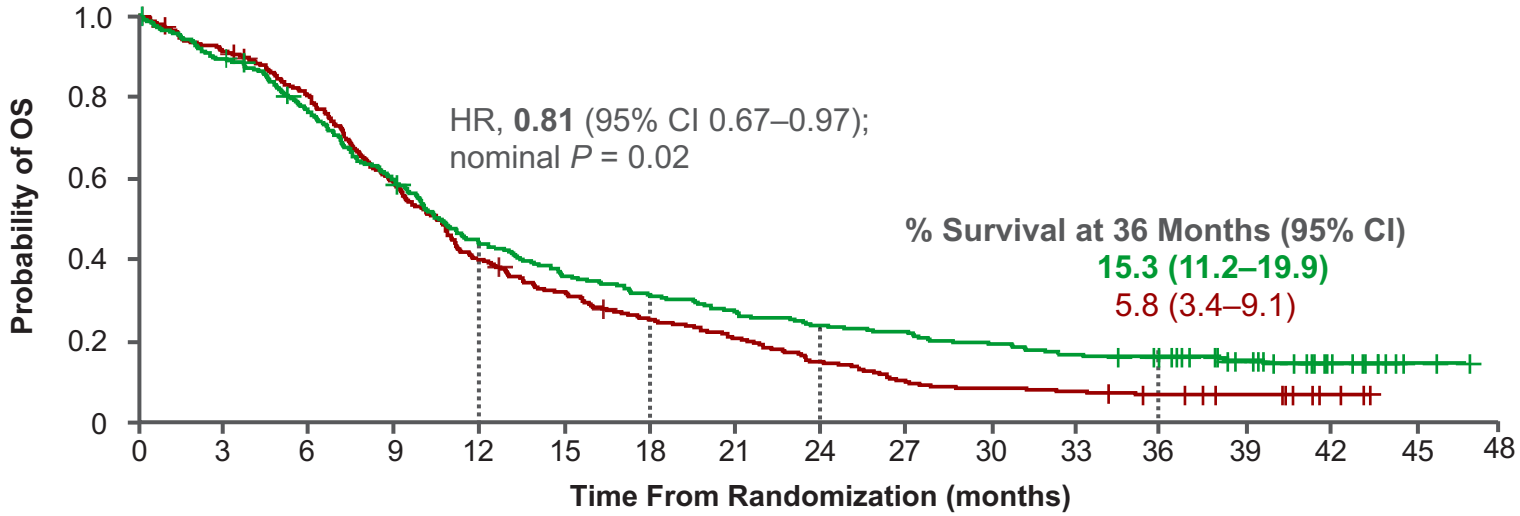
Blocking a Second T-Cell Checkpoint Doesn't Work (Yet)

CASPIAN

Etoposide ± durvalumab



Etoposide ± durvalumab/ tremelimumab

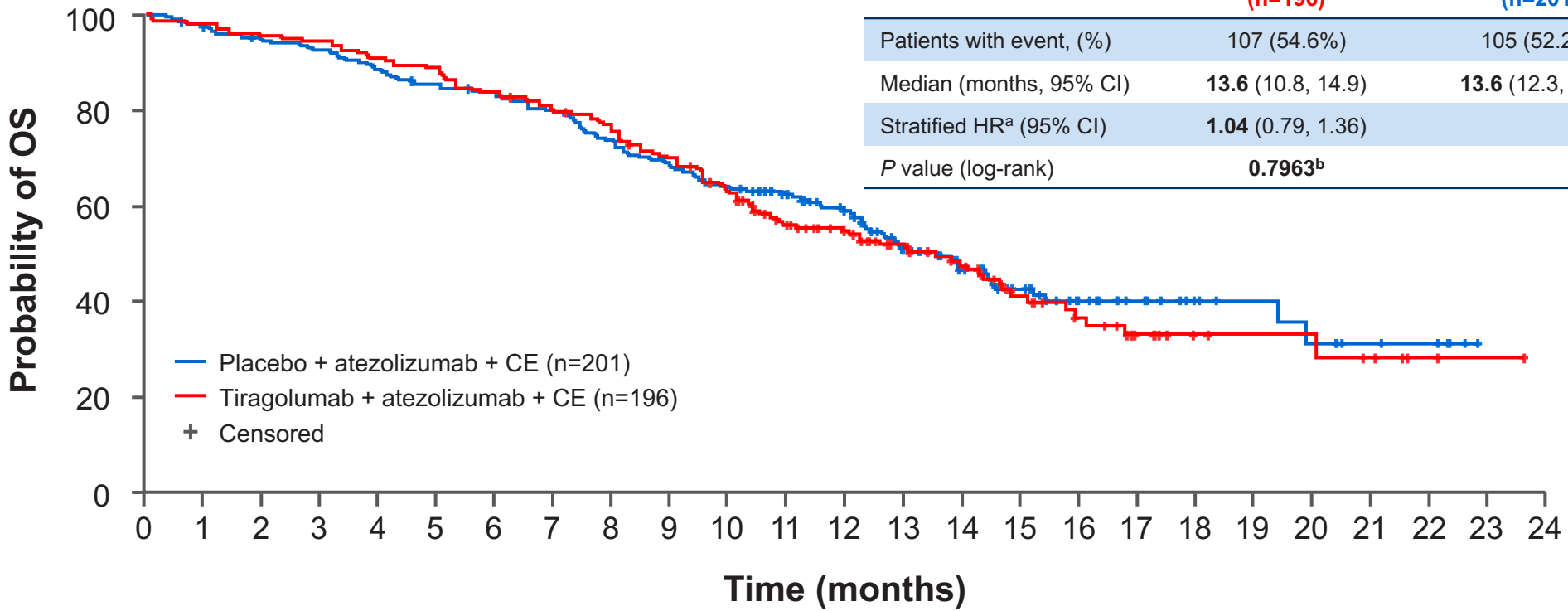


CI = confidence interval; ESMO = European Society for Medical Oncology; HR = hazard ratio; OS = overall survival.
Paz-Ares L, et al. *ESMO Open.* 2022;7(2):100408.

Blocking a *Third* T-cell Checkpoint Doesn't Work (Yet)

SKYSCRAPER-02

	Tiragolumab + atezolizumab + CE (n=196)	Placebo + atezolizumab + CE (n=201)
Patients with event, (%)	107 (54.6%)	105 (52.2%)
Median (months, 95% CI)	**13.6** (10.8, 14.9)	**13.6** (12.3, 15.2)
Stratified HR[a] (95% CI)	**1.04** (0.79, 1.36)	
P value (log-rank)	**0.7963**[b]	



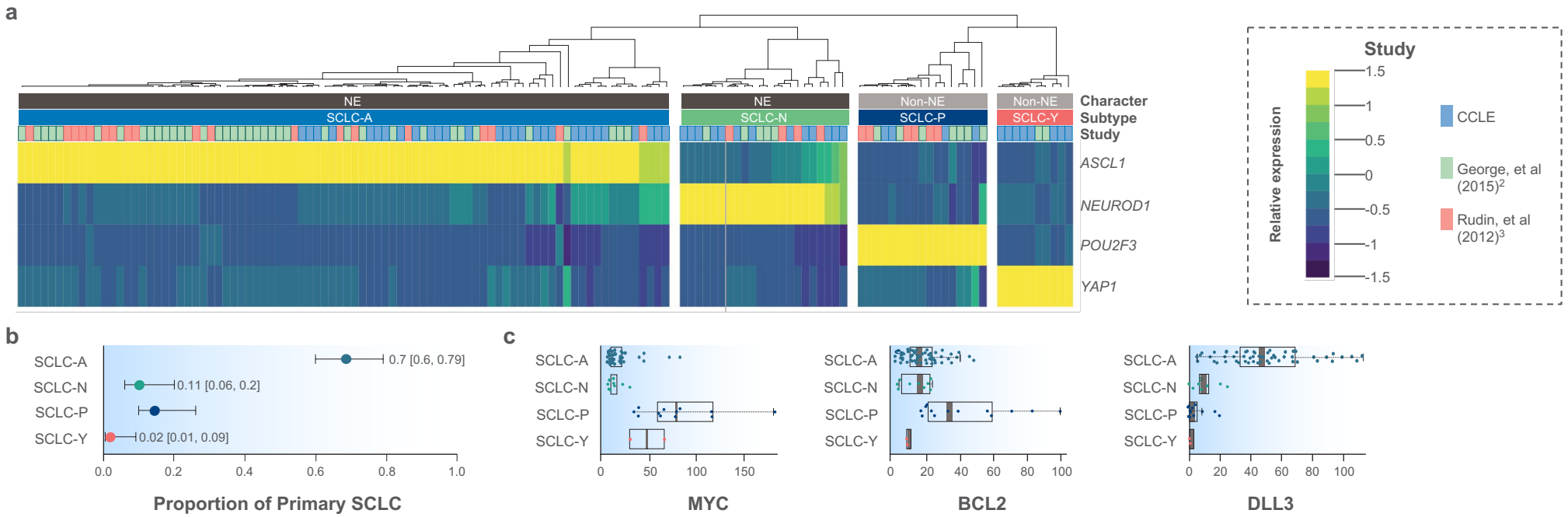
No. at risk																								
Placebo + atezolizumab + CE	201	195	188	183	175	168	164	156	144	134	125	115	97	70	47	36	26	19	12	9	7	5	4	NE	NE
Tiragolumab + atezolizumab + CE	196	191	186	184	177	172	162	154	146	133	116	93	80	62	51	32	21	14	9	7	7	5	2	1	NE

[a]Stratification factors are: ECOG, LDH. [b]Statistical boundary: 0.0175.
CE = carboplatin + etoposide; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ESMO = European Society for Medical Oncology; HR = hazard ratio; LDH = lactate dehydrogenase; OS = overall survival.
Rudin C, et al. *J Clin Oncol.* 2023 (in press).

Why Doesn't Blocking More IO Checkpoints in SCLC Work?

Hypotheses:

- A small subset of SCLC cases are immunoresponsive[1]
  - Most are inherently immunorefractory

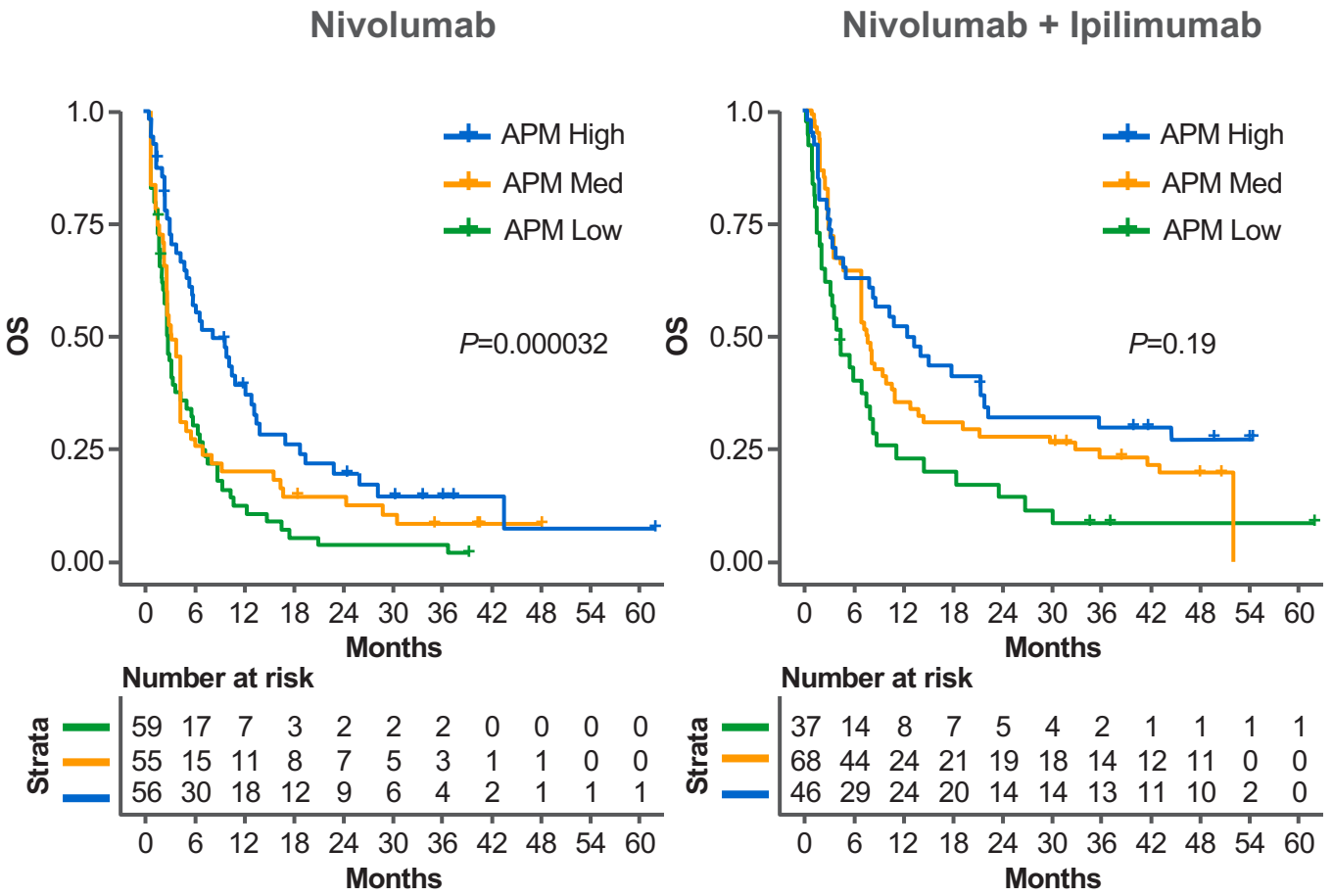


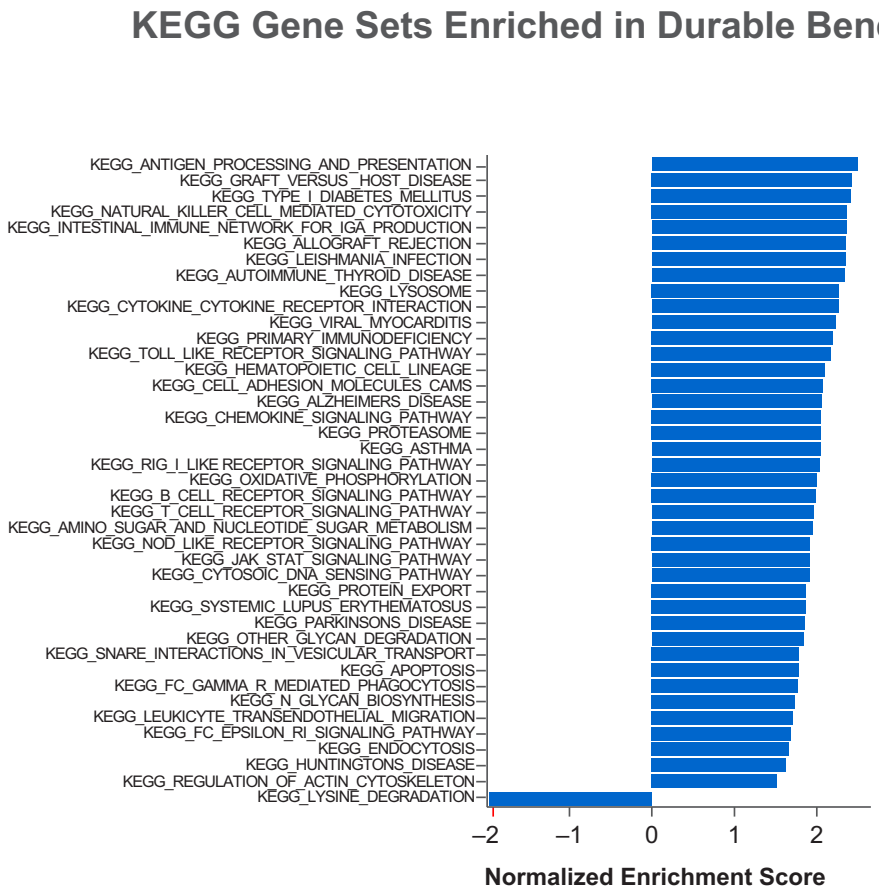
- A primary cause of "immunorefractory" status might be failure to express MHC class I[4]
  - MHC I is required for engagement of CD8+ cytotoxic T cells

ASCL1 = achaete-scute homologue 1; BCL2 = B-cell lymphoma 2; CCLE = Cancer Cell Line Encyclopedia; CD = cluster of differentiation; DLL3 = delta-like ligand 3; ESMO = European Society for Medical Oncology; IO = immuno-oncology; MHC = major histocompatibility complex; MYC = MYC proto-oncogene; NE = neuroendocrine; NEUROD1 = neurogenic differentiation factor 1; POU2F3 = POU class 2 homeobox 3; SCLC = small cell lung cancer; YAP1 = yes-associated protein.

1. Rudin CM, et al. *Nat Rev Cancer.* 2019;19(5):289–297; 2. George J, et al. *Nature*. 2015;524(7563):47–53; 3. Rudin C, et al. *Nat Genet.* 2012;44(10):1111–1116; 4. Mahadevan NR, et al. *Cancer Discov.* 2021;11(8):1952–1969.

Antigen Presentation Capacity as a Determinant of Outcome

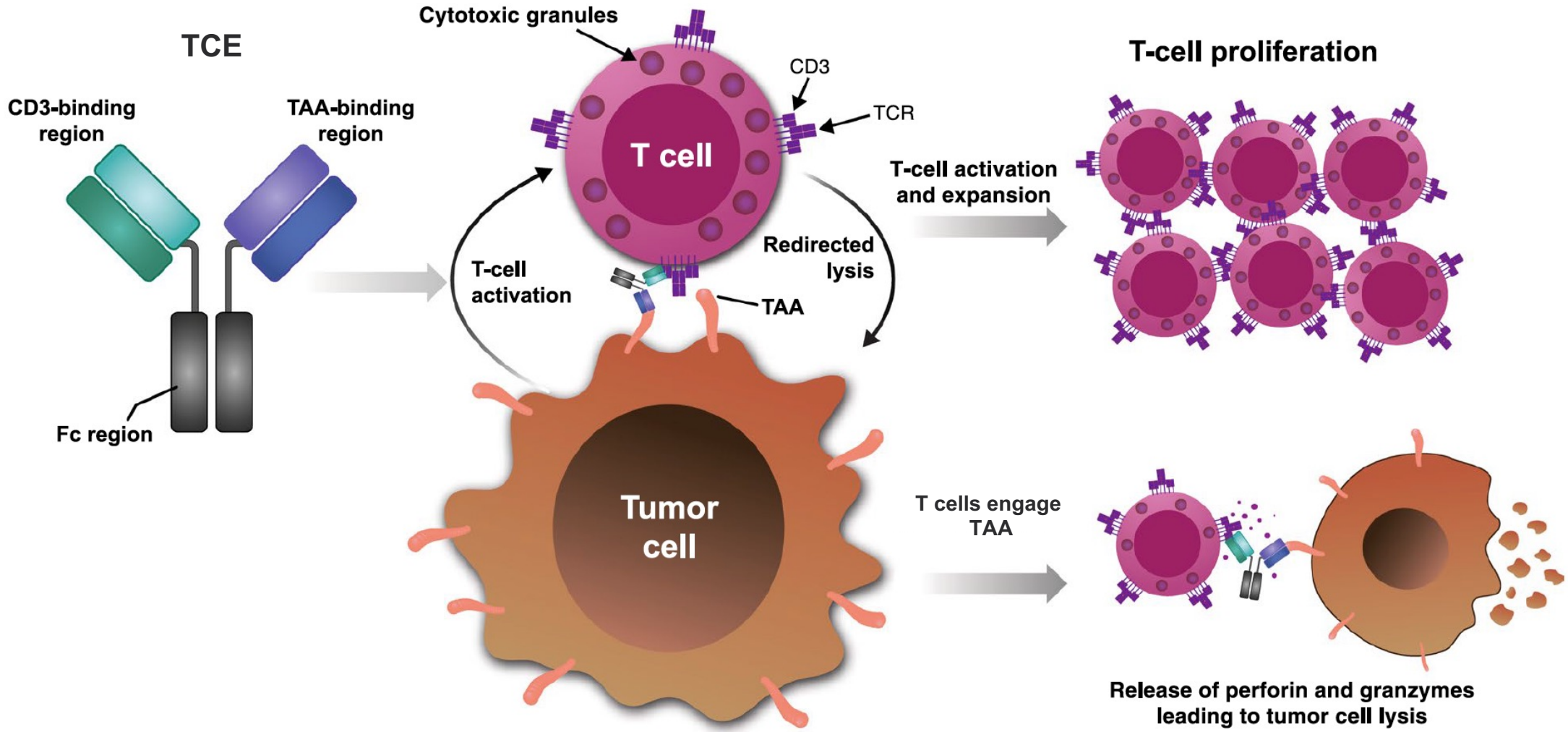




APM = antigen presentation machinery; ESMO = European Society for Medical Oncology; KEGG = Kyoto Encyclopedia of Genes and Genomes; OS = overall survival.

Rudin CM, et al. *J Thorac Oncol.* 2023;18(9):1222–1232.

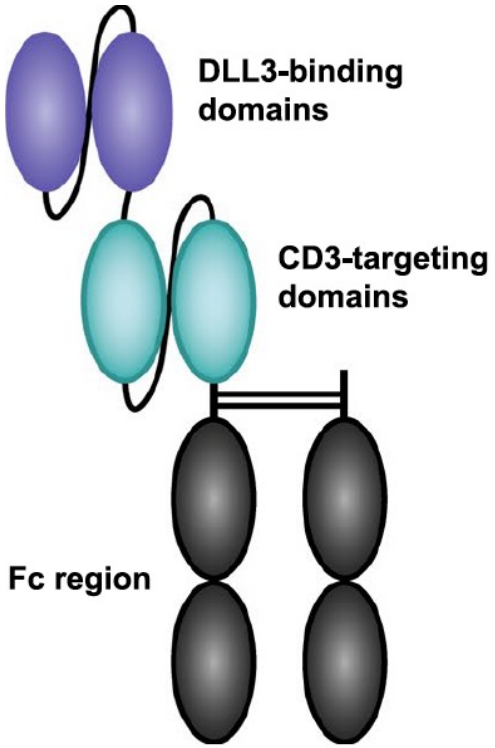
TCEs: Bringing the T Cell to the Tumor



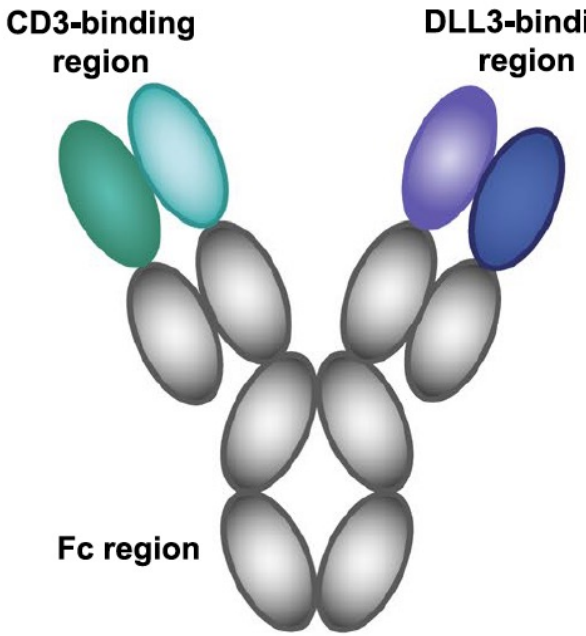
CD = cluster of differentiation; ESMO = European Society for Medical Oncology; Fc = fragment crystallizable; TAA = tumor-associated antigen; TCE = T-cell engager; TCR = T-cell receptor.
Rudin C, et al. *J Hematol Oncol.* 2023;16(1):66.

TCEs Exist in a Variety of Structures

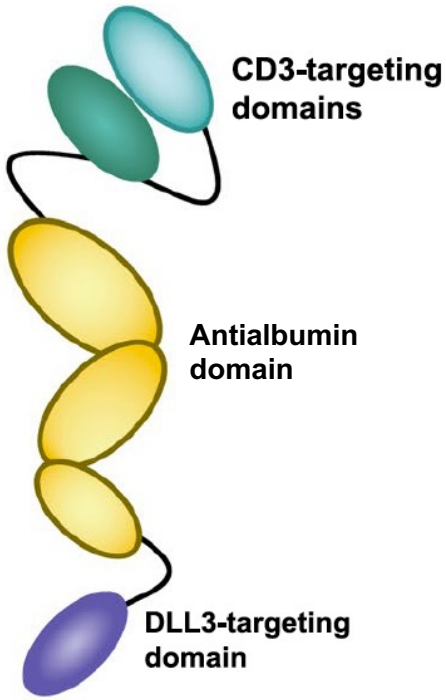
Tarlatamab
CD3/DLL3 BiTE®



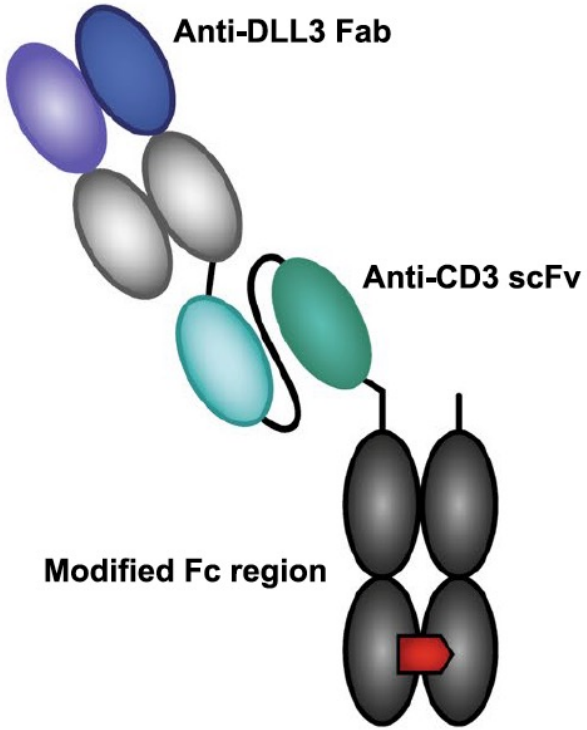
BI 764532
CD3/DLL3 IgG-like TCE



HPN328
CD3/DLL3/albumin TriTAC®



QLS31904
CD3/DLL3 bispecific antibody



BiTE = bispecific T-cell engager; CD3 = cluster of differentiation 3; DLL3 = delta-like ligand 3; ESMO = European Society for Medical Oncology; Fab = fragment antigen-binding; Fc = fragment crystallizable; IgG = immunoglobulin G; scFv = single-chain variable fragment; TCE = T-cell engager; TriTAC = tri-specific T-cell–activating construct.

Rudin C, et al. *J Hematol Oncol.* 2023;16(1):66.

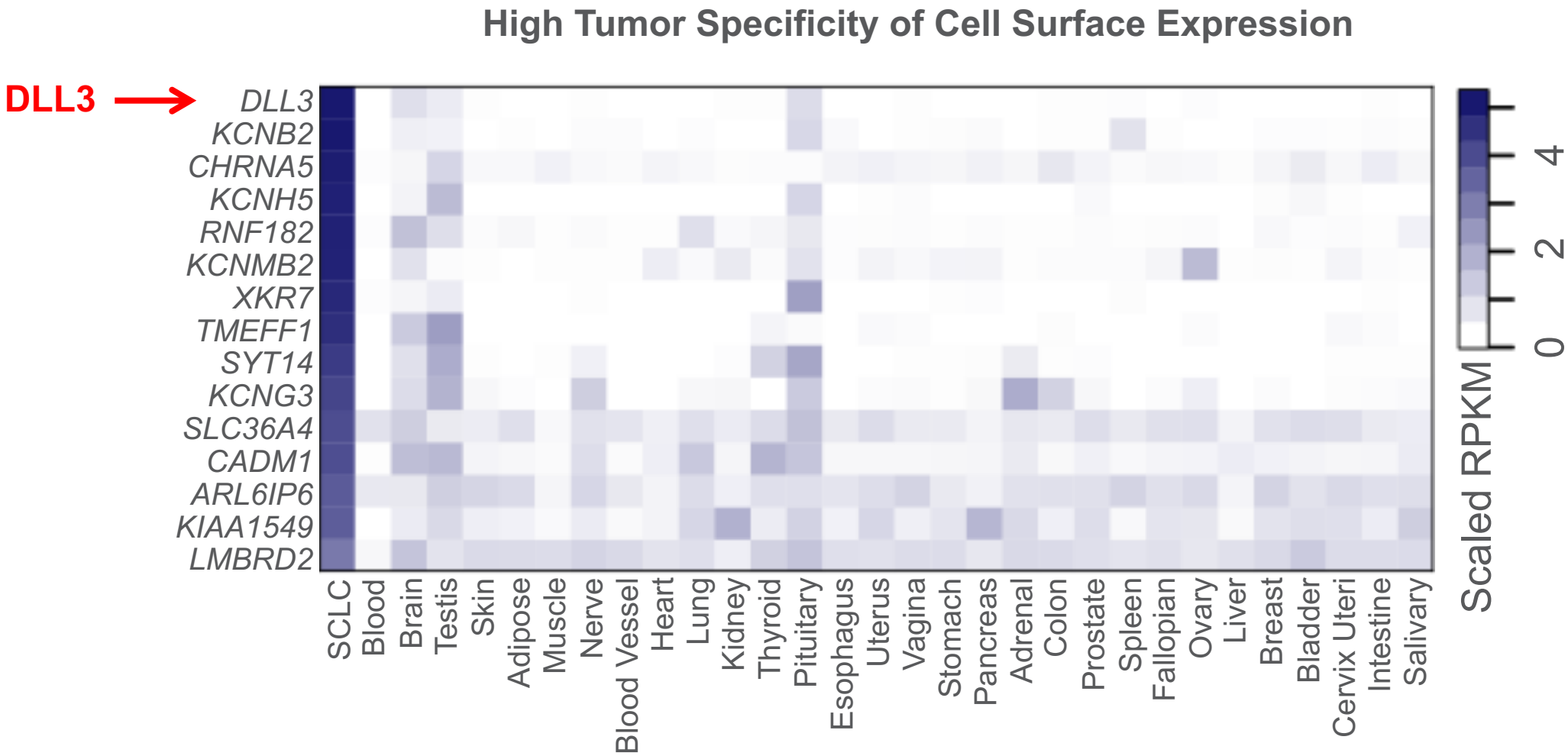
A Subset of DLL3-Targeted Therapies for SCLC

Agent	MoA	Status	Sponsor
ADCs[1]			
Rovalpituzumab tesirine	ADC targeting DLL3	Terminated	AbbVie/Stemcentrx
SC-002	ADC targeting DLL3	Terminated	Stemcentrx
CARs[1]			
DLL3-CAR-NK cells	Anti-DLL3-transduced natural killer cells	Recruiting (phase 1)	Tianjin Medical University Cancer Institute and Hospital
AMG 119	Anti-DLL3 transduced autologous T cells	Suspended (phase 1)	Amgen
TCEs[1]			
Tarlatamab	DLL3/CD3 BiTE®	Recruiting (phase 2)	Amgen
BI 764532	DLL3/CD3 IgG-like TCE[2]	Recruiting (phase 1)	Boehringer Ingelheim
HPN328	DLL3/CD3/Albumin TriTAC®[3]	Recruiting (phase 1/2)	Harpoon Therapeutics
RO7616789	DLL3/CD3/CD137 TriTAC®	Recruiting (phase 1)	Roche
PT217	DLL3/CD47 bispecific antibody[4]	Not yet recruiting	Phanes Therapeutics
QLS31904	DLL3/CD3 bispecific antibody[5]	Recruiting (phase 1)	Qilu Pharmaceutical

ADC = antibody-drug conjugate; BiTE = bispecific T-cell engager; CAR = chimeric antigen receptor; CD = cluster of differentiation; DLL3 = delta-like ligand 3; ESMO = European Society for Medical Oncology; MoA = mechanism of action; NK = natural killer; SCLC = small cell lung cancer; TCE = T-cell engager; TriTAC = tri-specific T-cell–activating construct.

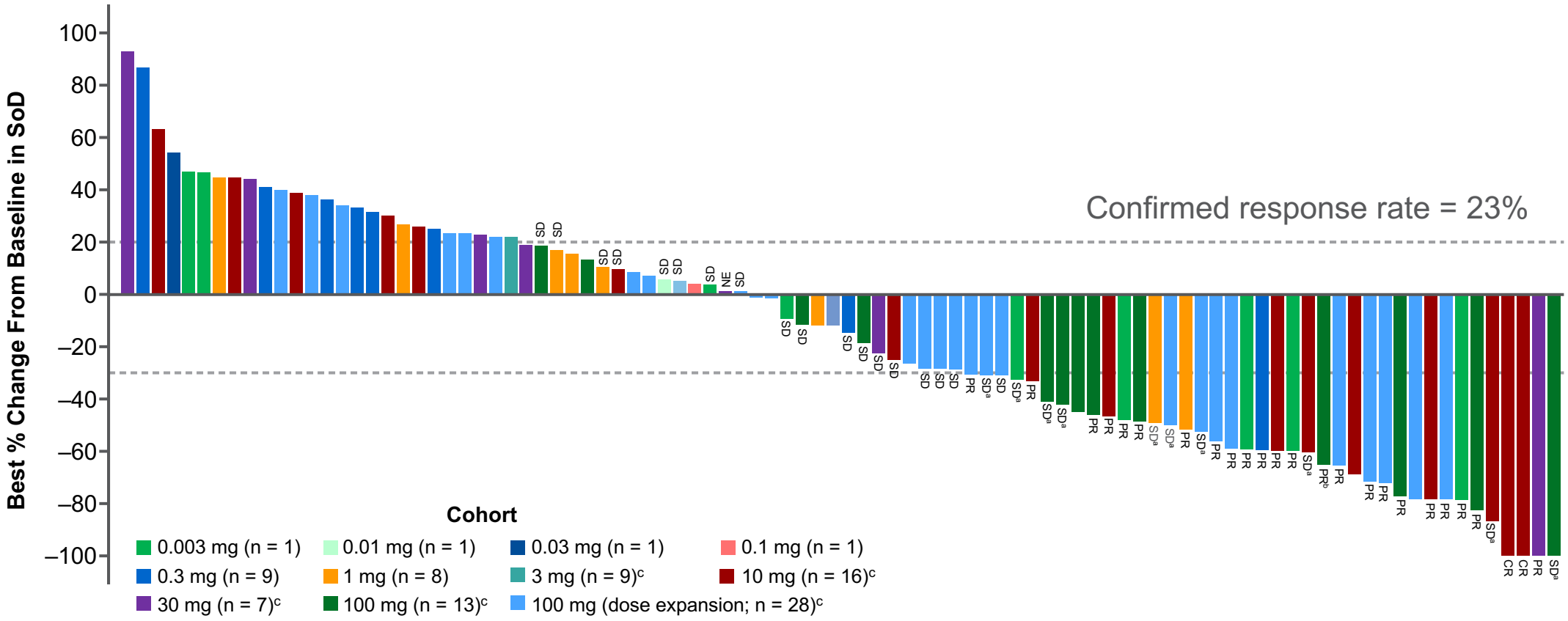
1. Rudin C, et al. *J Hematol Oncol.* 2023;16(1):66; 2. Wermke M, et al. *Future Oncol.* 2022;18(24):2639–2649; 3. Johnson ML, et al. *J Clin Oncol.* 2022;40(16 suppl):8566; 4. Jia H, et al. *Cancer Res.* 2022;82(12 suppl):2908; 5. Yang L, et al. *Cancer Res.* 2022;82(12 suppl):5550.

Why Such a Focus on DLL3?



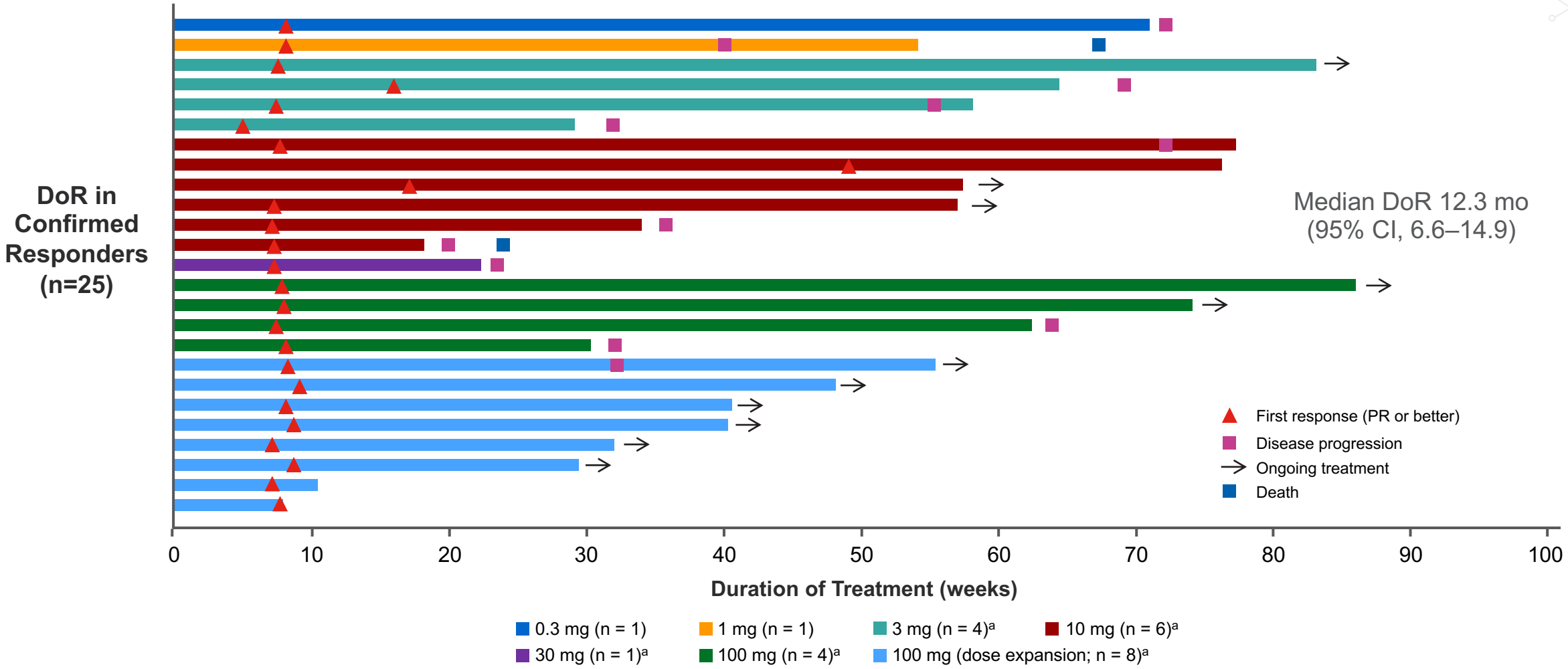
DLL3 = delta-like ligand 3; ESMO = European Society for Medical Oncology; RPKM = reads per kilobase of transcript per million mapped reads; SCLC = small cell lung cancer.
Sharma SK, et al. *Cancer Res.* 2017;77(14):3931–3941.

Tarlatamab Response in Patients With Treated SCLC



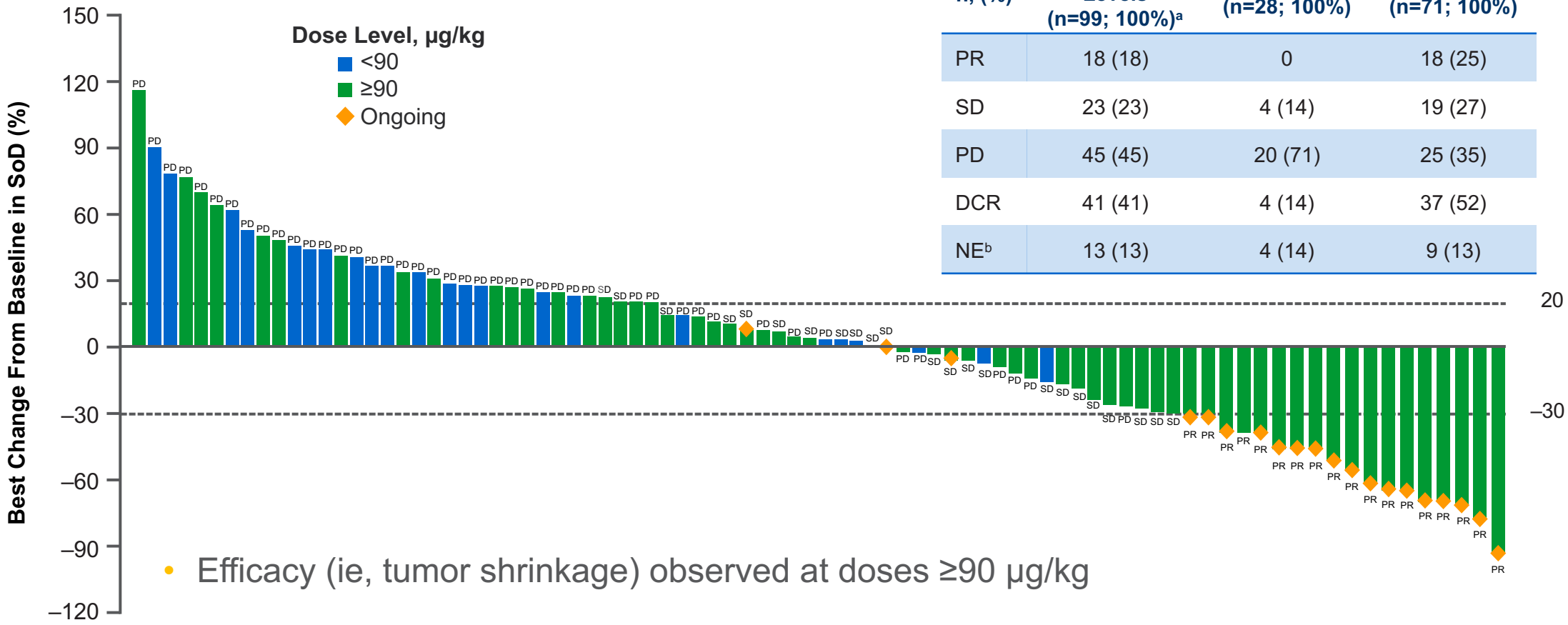
[a]SD: patients had an initial response but did not have confirmation of response on the subsequent scan. [b]PR: patients had an initial PR and still have potential for future confirmative scans. 1 confirmed patient in the 100-mg expansion cohort had missing SoD for lesion measurement and was not included in the plot. [c]Step dosing (ie, 1-mg run-in dose) was used in these cohorts.
ESMO = European Society for Medical Oncology; NE = not evaluable; PR = partial response; SCLC = small cell lung cancer; SD = stable disease; SoD = sum of diameters.
Paz-Ares L, et al. *J Clin Oncol.* 2023;41(16):2893–2903.

Durability of Tarlatamab Responses in SCLC



[a]Step dosing (ie, 1-mg run-in dose) was used in these cohorts.
CI = confidence interval; DoR = duration of response; ESMO = European Society for Medical Oncology; PR = partial response; SCLC = small cell lung cancer.
Paz-Ares L, et al. *J Clin Oncol.* 2023;41(16):2893–2903.

Early Efficacy Data With BI 764532 at Doses ≥90 µg/kg

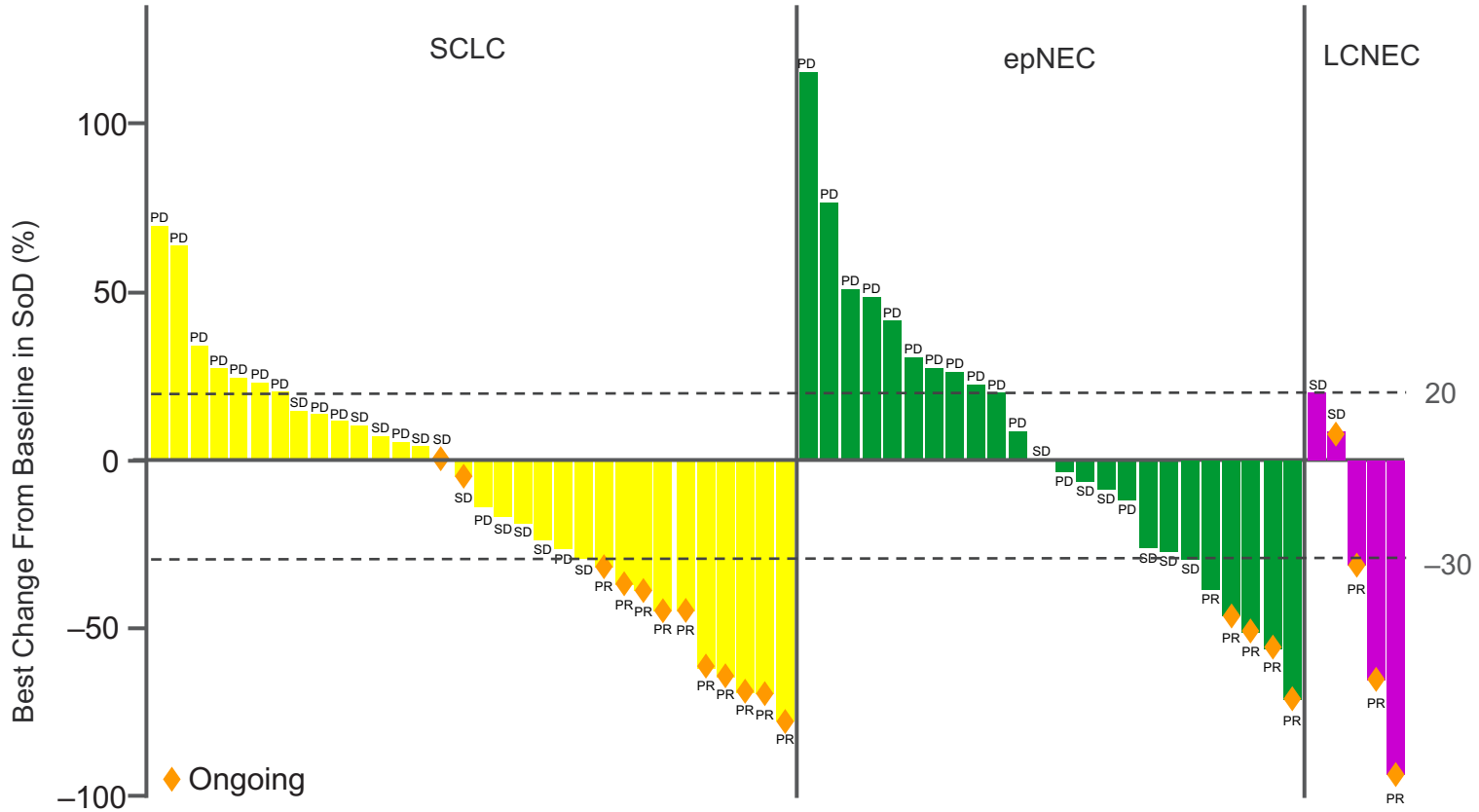


n, (%)	All Dose Levels (n=99; 100%)[a]	<90 µg/kg (n=28; 100%)	≥90 µg/kg (n=71; 100%)
PR	18 (18)	0	18 (25)
SD	23 (23)	4 (14)	19 (27)
PD	45 (45)	20 (71)	25 (35)
DCR	41 (41)	4 (14)	37 (52)
NE[b]	13 (13)	4 (14)	9 (13)

- Efficacy (ie, tumor shrinkage) observed at doses ≥90 µg/kg

[a]Efficacy populations: ≥1 postbaseline tumor assessment or permanently discontinued prior to tumor assessment; responses evaluated per RECIST v1.1 criteria. [b]Discontinued prior to tumor assessment.
DCR = disease control rate; ESMO = European Society for Medical Oncology; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease; SoD = sum of diameters.
Wermke M, et al. ASCO 2023. Abstract 8502.

Efficacy Data With BI 764532 in SCLC, LCNEC, and epNECs

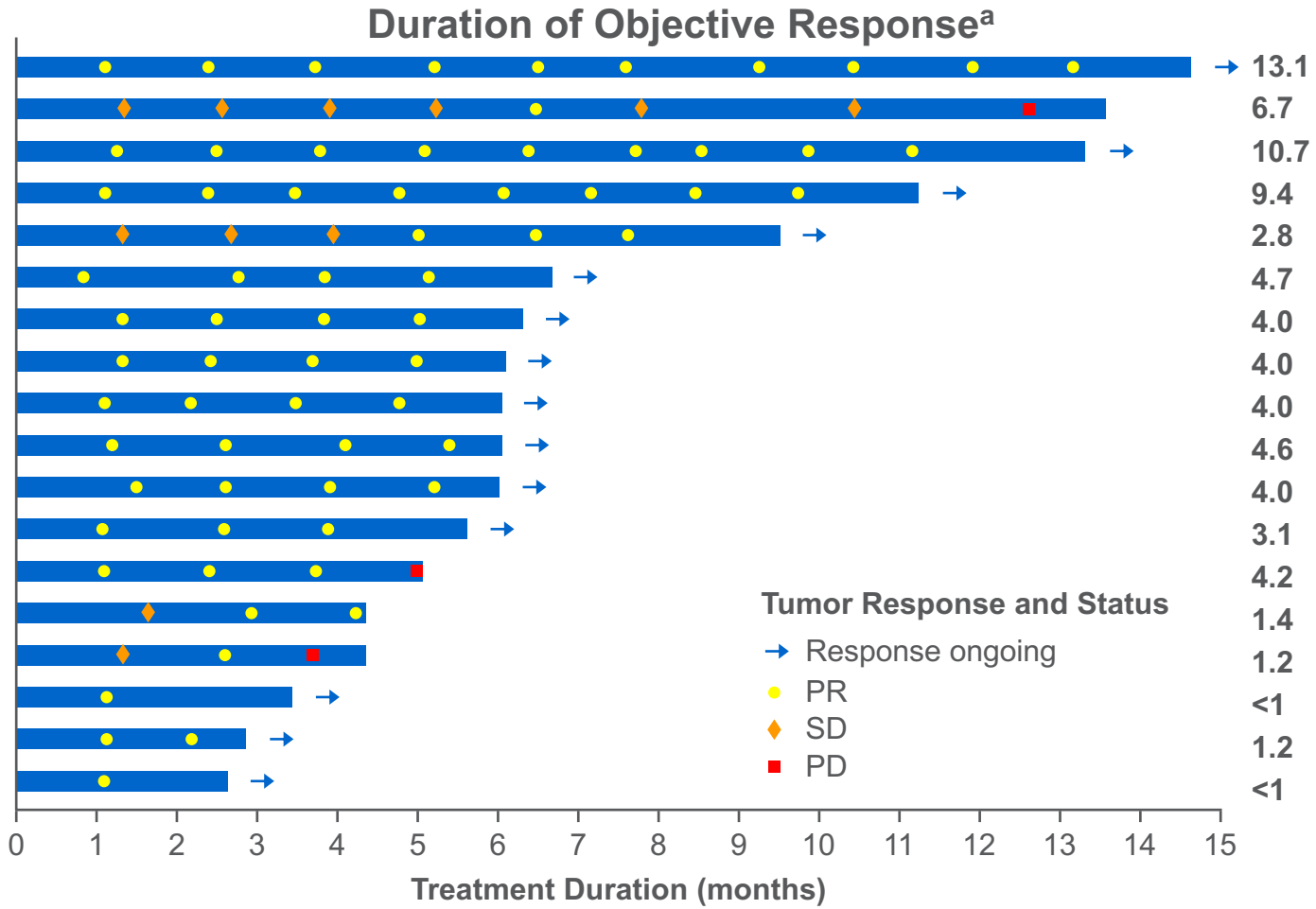


n, (%)	SCLC (n=39; 100%)[a]	epNEC (n=27; 100%)[a]	LCNEC (n=5; 100%)[a]
PR	10 (26)	5 (19)	3 (60)
SD	10 (26)	7 (26)	2 (40)
PD	12 (31)	13 (48)	0
DCR	20 (51)	12 (44)	5 (100)
NE[b]	7 (18)	2 (7)	0

- Efficacy (ie, tumor shrinkage) was observed across all enrolled tumor types

[a]Efficacy population: ≥1 postbaseline tumor assessment or permanently discontinued prior to tumor assessment; responses evaluated per RECIST v1.1 criteria. [b]Discontinued prior to tumor assessment.
DCR = disease control rate; epNEC = extrapulmonary neuroendocrine carcinoma; ESMO = European Society for Medical Oncology; LCNEC = large cell neuroendocrine carcinoma; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SCLC = small cell lung cancer; SD = stable disease; SoD = sum of diameters.
Wermke M, et al. ASCO 2023. Oral Presentation 8502.

Responses to BI 764532 Appear to Be Durable



- Responses are ongoing in 14/18 responders[b]
- Median DoR has not been reached

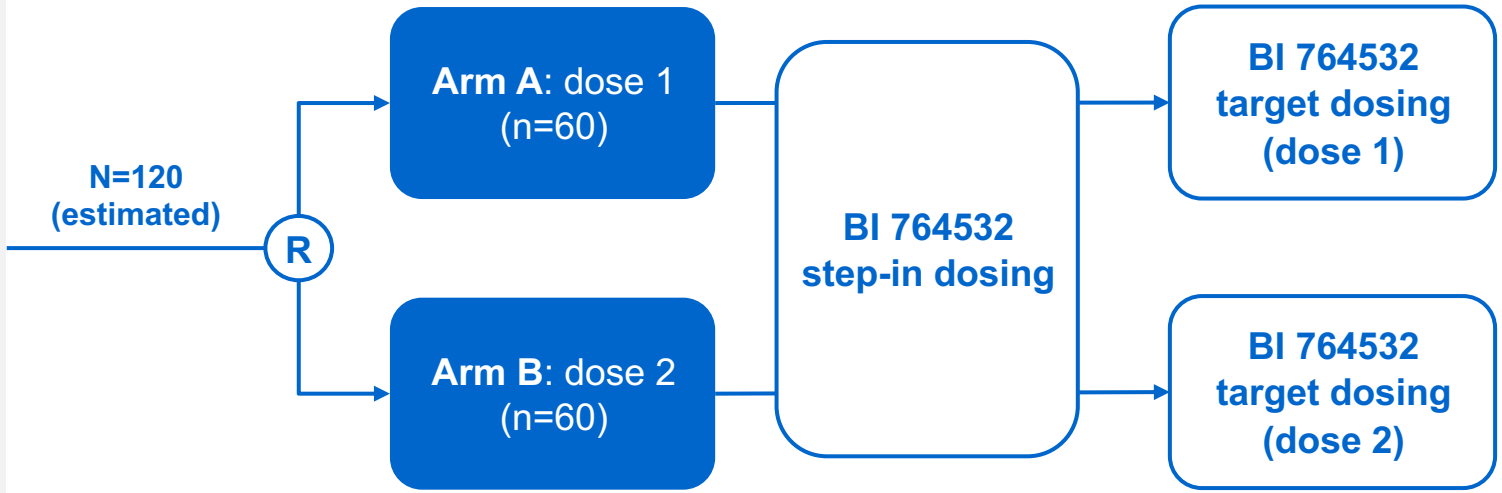
[a]Duration of objective response is defined as the time from first documented CR or PR until the earliest of disease progression or death among patients with objective response according to RECIST 1.1. [b]As of April 21, 2023.
CR = complete response; DoR = duration of response; ESMO = European Society for Medical Oncology; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease.
Wermke M, et al. ASCO 2023. Oral Presentation 8502.

BI 764532 Will Be Further Evaluated in DAREON™-5

DAREON-5™ is a phase 2, randomized, open-label, dose-selection study of BI 764532 in patients with relapsed/refractory ES-SCLC and in patients with other relapsed/refractory NECs[1,2]

Adults aged ≥18 years with:

- Histologically or cytologically confirmed relapsed/refractory SCLC (3L or later[a]), relapsed/refractory epNECs[b] (2L or later[a]), or LCNEC of the lung (2L or later[a])
- ECOG PS 0–1
- ≥1 measurable lesion per RECIST v1.1
- Adequate organ function
- No untreated or symptomatic brain metastases, leptomeningeal disease, or prior DLL3-targeting therapy



Endpoints

Primary: **OR; TEAEs during the on-treatment period**

Secondary: DoR, PFS, DC, OS, PROs, TEAEs leading to discontinuation

This compound is an investigational agent. Its safety and efficacy have not been established

[a]Prior therapy must include ≥1 platinum-based regimen. [b]Excluding Merkel cell carcinoma, medullary thyroid cancer, and neuroendocrine prostate cancer.
2L = second-line; 3L = third-line; DC = disease control; DLL3 = delta-like ligand 3; DoR = duration of objective response; ECOG PS = Eastern Cooperative Oncology Group performance status; epNEC = extrapulmonary neuroendocrine carcinoma; ESMO = European Society for Medical Oncology; ES-SCLC = extensive-stage SCLC; LCNEC = large cell neuroendocrine carcinoma; NEC = neuroendocrine carcinoma; OR = objective response; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SCLC = small cell lung cancer; TEAE = treatment-emergent adverse event.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05882058. Accessed September 2023; 2. Boehringer Ingelheim. https://pro.boehringer-ingelheim.com/inoncology/our-pipeline/dll3-cd3-t-cell-engager/dareon-5-1438.5. Accessed September 2023.

More Information About DAREON™-5 to Be Presented at This Congress

MADRID 2023 ESMO congress

MADRID SPAIN
20-24 OCTOBER 2023

Mini Oral Presentation 725MO. Valentina Gambardella.

Phase 1 trial of the DLL3/CD3 IgG-like T cell engager BI 764532 in patients (pts) with DLL3-positive (+) tumours: Focus on neuroendocrine carcinomas

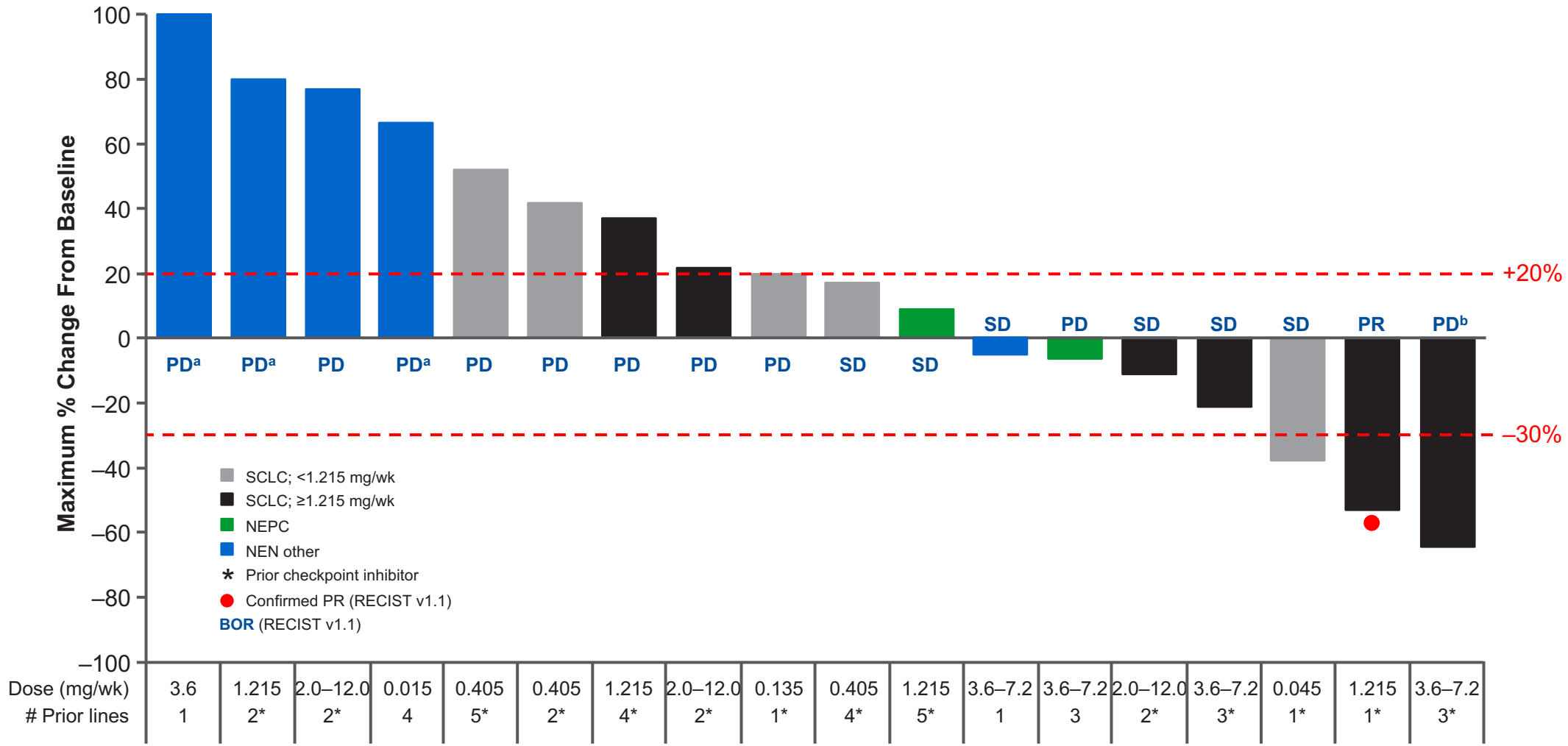
Sunday, 22 October 2023, 17:05–17:10

Burgos Auditorium – Hall 3

Mini oral session – NETs and endocrine tumors

CD = cluster of differentiation; DLL3 = delta-like ligand 3; ESMO = European Society for Medical Oncology; IgG = immunoglobulin G; NET = neuroendocrine tumor.

Very Early Efficacy Data With HPN328



[a]New asymptomatic brain metastases identified at week 2. Overall response = PD; target lesion response = PR. [b]Retrospective IHC analysis of archival biopsies demonstrated 0% cells positive for DLL3 in 3/5 patients with NEN.
BOR = best observed response; DLL3 = delta-like ligand 3; ESMO = European Society for Medical Oncology; IHC = immunohistochemistry; NEN = neuroendocrine neoplasm; NEPC = neuroendocrine prostate cancer; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SCLC = small cell lung cancer; SD = stable disease.
Johnson M, et al. ASCO 2022. Abstract 8566.

Updated Data on HPN328 to Be Presented Tomorrow

MADRID 2023 ESMO congress

MADRID SPAIN
20-24 OCTOBER 2023

Poster #1658. Noura Choudhury, et al.

Interim results from a phase 1/2 study of HPN328, a tri-specific, half-life extended DLL3-targeting T-cell engager in patients with small cell lung cancer and other neuroendocrine neoplasms

Saturday, 21 October 2023

Poster Session 17

DLL3 = delta-like ligand 3; ESMO = European Society for Medical Oncology.

Some Conclusions

- There is a cohort of patients with SCLC, small but real, who have durable benefit from ICB
  - Increasing the fraction of patients with SCLC who are ICB-responsive would be transformative

- Absence of MHC-I is implicated as a primary contributor to ICB failure in SCLC
  - One strategy to get around this might be MHC-independent T-cell engagement (eg, TCEs)

- DLL3 is a uniquely attractive target for SCLC and other high-grade NECs
  - Direct transcriptional target of ASCL1

- Exploring the expanding universe of immune effector strategies may offer alternative paths to durable IO response in patients with cancer

ASCL1 = achaete-scute homologue 1; DLL3 = delta-like ligand 3; ESMO = European Society for Medical Oncology; ICB = immune checkpoint blockade; IO = immuno-oncology; MHC-I = major histocompatibility complex class I; NEC = neuroendocrine carcinoma; SCLC = small cell lung cancer; TCEs = T-cell engagers.