IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Best of WCLC 2022: Small Cell Lung Cancer

Millie Das, MD

Stanford University

USA

DISCLOSURES

Company	**Relationship**
Genentech (uncompensated), Eurofins	Consulting
Astra Zeneca, Beigene, Sanofi/Genzyme, Janssen	Advisory Board
Merck, Genentech, CellSight, Novartis, Abbvie, United Therapeutics, Verily, Varian, Celgene	Research

Agenda

Novel therapies in 2nd line SCLC

- OA12.03: Ph II Talazoparib + Temozolomide
- OA12.04: Ph II Nivolumab + Temozolomide
- OA12.05: Ph I Tarlatamab (DLL-3 T-cell engager)

Real world clinical practice

- EP14.05: ChemoIO in ECOG PS 2-3 ES-SCLC

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Phase 2 study analysis of talazoparib (TALA) plus temozolomide (TMZ) for extensive-stage small cell lung cancer (ES-SCLC)

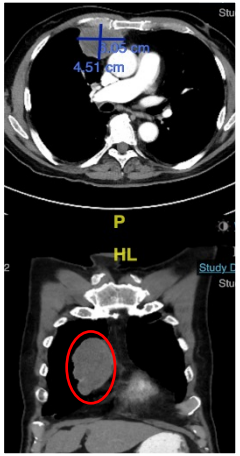
J. Goldman[1], A. Cummings[1], M. Mendenhall[1], M.A. Velez[1], S. Babu[2], T. Johnson[3], J. Alcantar[1], S. Dakhil[4], D. Kanamori[5], W. Lawler[6], S. Anand[1], J. Chauv[1], E.B. Garon[1], D. Slamon[1]

[1]David Geffen School of Medicine at UCLA, Los Angeles/CA/USA, [2]Fort Wayne Medical Oncology and Hematology, Ft. Wayne/IN/USA, [3]Orlando Health Cancer Institute, Orlando/FL/USA, [4]Cancer Center of Kansas, Wichita/KS/USA, [5]Comprehensive Blood & Cancer Center, Bakersfield/CA/USA, [6]Virginia K Crosson Cancer Center, Fullerton/CA/USA

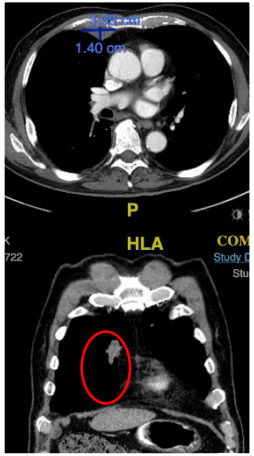
University of California, Los Angeles (UCLA), USA

Study Results

- Eleven of 28 evaluable patients ***(39.3%)*** achieved a confirmed partial response.
  - A 12th patient came off trial before the response could be confirmed.
- Median TTR was 1.8 months (m), DoR was 4.3 m, PFS was 4.3 m, and OS was 11.9 m.



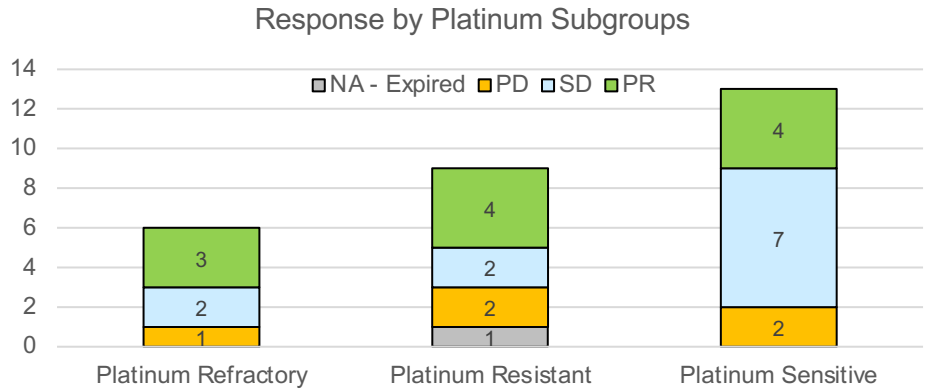
Baseline



At 2.0 m on treatment

Trial subject 1 with a 53% response per RECIST 1.1 at 2.0 m, until PD at 7.8 m.

- ORR was similar among platinum-refractory (3/6), -resistant (4/9), and -sensitive subgroups (4/13).
  - Platinum Refractory: Progressed while on treatment or within 28 days after last platinum-based therapy.
  - Platinum Resistant: Progressed between 28 and 90 days after last platinum-based therapy.
  - Platinum Sensitive: Progressed ≥ 90 days after last day of platinum-based therapy



Second-line PARPi-Temozolomide combinations

	Topotecan	Talazoparib + TMZ **37.5 mg/m² D1-5 28-day cycles**	Olaparib + TMZ 75 mg/m² D1-7 21-day cycles	Veliparib or PCB +TMZ 150-200 mg/m² D1-5 28-day cycles
n	444 All 2nd line, refractory 52%	28 **2nd line 93%** 3rd line 3%	50 2nd line 46%, 3rd line 34%, 4+ 20%	104 2nd line 67%, 3rd line 33% Refractory 59%
ORR All Plat-refractory Plat-resistant Plat-sensitive	21% ND ND ND	11/28 (**39.3%**) **3/6** **4/9** 4/13	41.7% 28.6% 47.1%	39%/14% 37%/15% 41%/11%
Median DOR	4.9 mo	4.3 mo	4.3 mo	4.6/3.7 mo
Median PFS	4.3 mo	4.3 mo	4.2 mo	3.8/2
Median OS	8.6 mo	**11.9 mo**	8.5 mo	8.2/7

Blackhall F, J Thorac Oncol 2021; Farago, Cancer Discovery 2019 (olaparib); Pietanza, J Clin Oncol 2018 (veliparib)

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n	**AEs**		**Grade 3/4**	104 2nd line 67%, 3rd line 33% Refractory 59%
	Anemia		53.6%	
	Neutrophil count decreased		32.1%	
	Platelet count decreased		60.7%	
ORR All				39%/14%
Plat-refractory	ND	**4/9**	28.6%	
Plat-resistant				37%/15%
Plat-sensitive	ND	4/13	47.1%	41%/11%
Median DOR	4.9 mo	4.3 mo	4.3 mo	4.6/3.7 mo
Median PFS	4.3 mo	4.3 mo	4.2 mo	3.8/2
Median OS	8.6 mo	**11.9 mo**	8.5 mo	8.2/7

Blackhall F, J Thorac Oncol 2021; Farago, Cancer Discovery 2019 (olaparib); Pietanza, J Clin Oncol 2018 (veliparib)

Conclusions

- Promising ORR=39% in patients treated with TALA + TMZ, responses seen in both platinum sensitive and resistant pts
- Adds to prior data of PARPi + TMZ
- Manageable mostly hematologic toxicities
- SLFN11 analysis not performed
- Supports further exploration in phase III trial

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Efficacy of nivolumab and temozolomide in extensive stage small cell lung cancer after chemo-immunotherapy

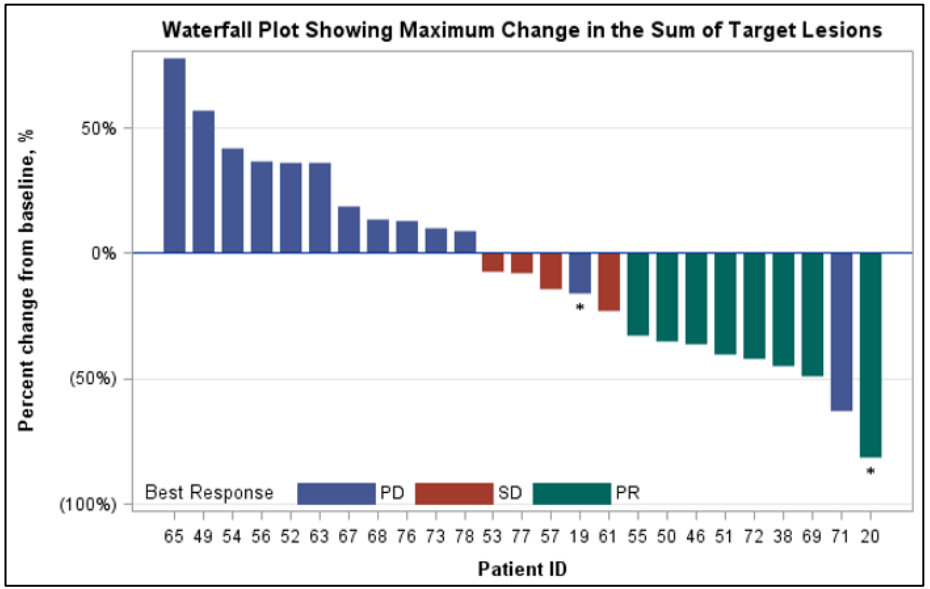
Dwight H. Owen, Lai Wei, Brooke Benner, Carly Pilcher, Gwen Christenson, Sarah Ferguson, Megan Jukich, Vineeth Sukrithan, Bhavana Konda, Manisha Shah, Himanshu Savardekar, Emily Schwarz, Ruthann Norman, Robert Wesolowski, William E. Carson III, Jacob Kaufman, Asrar Alahmadi, Regan Memmott, Peter Shields, Kai He, Erin M. Bertino, Carolyn J. Presley, David P. Carbone, Claire Verschraegen, Greg A. Otterson

The Ohio State University
USA

SCLC Efficacy

- Among 25 patients previously treated with first line chemo-immunotherapy, responses were seen in 7/25 (28%, 95% CI: 12-49%).

		ORR	95% CI	p-value
All patients		7/25 (28%)	12% - 49%	
Platinum resistant	Y	0/10 (0 %)	0 – 31%	0.057
	N	7/15 (47%)	21 – 73%	
Brain metastases	Y	2/10 (20%)	3% - 56%	0.659
	N	5/15 (33%)	12% - 62%	



* Patients not evaluable for primary endpoint due not receiving prior chemo-immunotherapy

Second-line Nivolumab-TMZ after chemo-immunotherapy

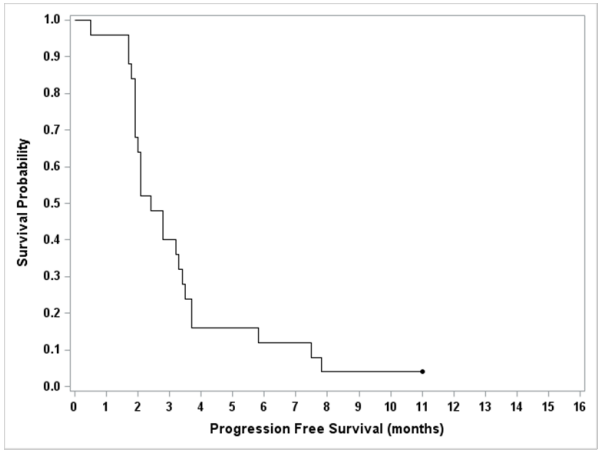
	Topotecan or amrubicin CM331	Nivolumab CM331	Nivolumab + TMZ 150 mg/m^2 D1-5 28-day cycles
N Plat sensitive 2nd/3rd line/4+	285 56.1% All 2nd line	284 57.4% All 2nd line	25 59% 3rd line 75%
ORR All Plat-refractory Plat-resistant Plat-sensitive	16.5%	13.7%	7/25 (**28%**) 0 7/15 (47%)
Median DOR	4.5 mo	8.3 mo	ND
Median PFS	3.8	1.4	2.4
Median OS	8.4	7.5	6.3

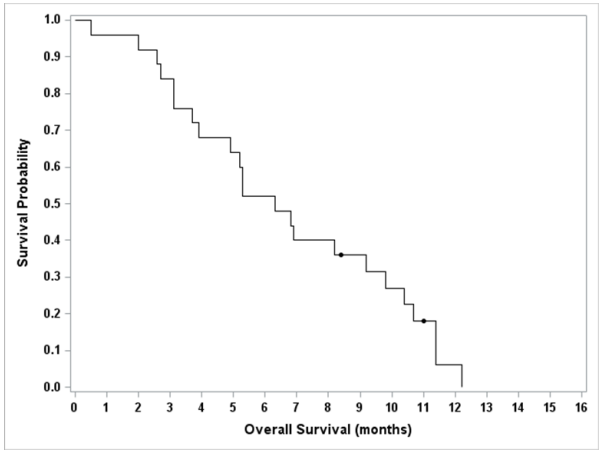
Spigel DR, Ann Oncol 2021

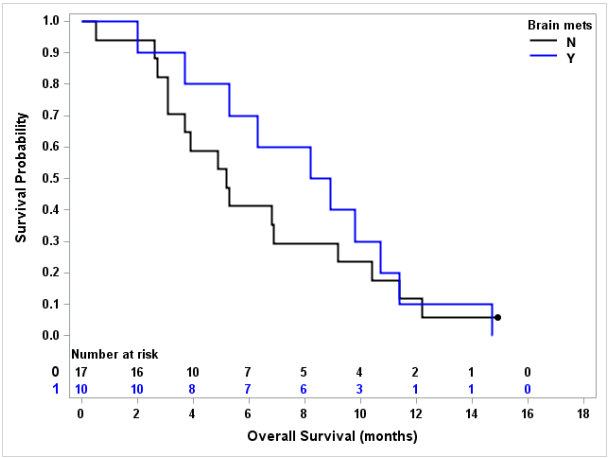
SCLC Efficacy: PFS and OS

- With a median follow up of 6.3 months, the median PFS of all 27 patients was 2.4 months (95% CI: 1.9, 3.4)

- The median OS for all patients was 6.3 months (95% CI 3.7, 9.2).







Safety and tolerability

- Most common treatment related toxicities included hematologic toxicities, fatigue, nausea, vomiting, and weight loss

- One treatment related death (COVID-19)

Adverse event	Gr<=2 (n, %)		Gr>= 3, (n, %)		All grade (n, %)	
Any TRAE	7 (26%)		19 (70%)		26 (96%)	
Lymphocyte count decreased	7	26%	10	37%	17	63%
Fatigue	11	41%	5	19%	16	59%
Anemia	9	33%	2	7%	11	41%
Vomiting	9	33%	2	7%	11	41%
Weight Loss	11	41%	0	0%	11	41%
Nausea	8	30%	1	4%	9	33%
Platelet count decreased	6	22%	3	11%	9	33%
Generalized muscle weakness	6	22%	2	7%	8	30%
Diarrhea	6	22%	1	4%	7	26%
Anorexia	6	22%	1	4%	7	26%
Constipation	5	19%	1	4%	6	22%
Rash	4	15%	0	0%	4	15%

Conclusions

- Nivolumab + TMZ has promising efficacy (ORR=28%)
- Responses not durable, only seen in platinum sensitive disease
- Correlative analyses ongoing, may provide insight into those patients most likely to respond

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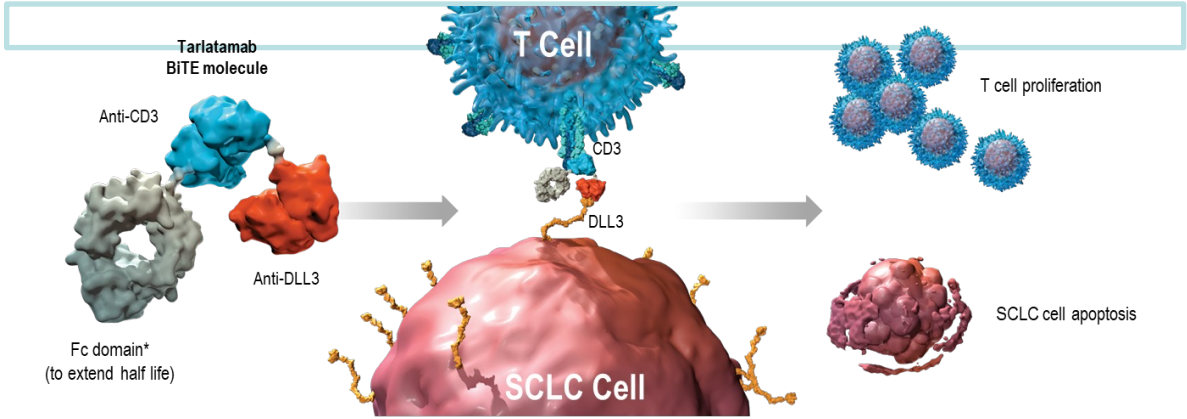
Phase 1 Updated Exploration and First Expansion Data for DLL3-Targeted T-cell Engager Tarlatamab in SCLC (DeLLphi-300 Study)

Hossein Borghaei,[1*] Luis Paz-Ares,[2] Melissa Johnson,[3] Stephane Champiat,[4] Taofeek Owonikoko,[5] Victoria Lai,[6] Michael Boyer,[7] Horst-Dieter Hummel,[8] Ramaswamy Govindan,[9] Neeltje Steeghs,[10] Fiona Blackhall,[11] Noemi Reguart,[12] Afshin Dowlati,[13] Yiran Zhang,[14] Nooshin Hashemi Sadraei,[14] Amanda Goldrick,[14] Hiroki Izumi[15]

* Presenter: Hossein Borghaei, Fox Chase Cancer Center, USA; Hossein.Borghaei@fccc.edu

Introduction

- Notch ligand delta-like ligand 3 (DLL3) is aberrantly expressed on the surface of SCLC cells[3,4]
- Tarlatamab is a bispecific T cell engager (BiTE®) immune therapy that binds DLL3 and CD3 leading to T cell-mediated tumor lysis[5]
  - Interim phase 1 dose exploration data show preliminary efficacy and acceptable safety in SCLC patients[6]



*Effector-functionless Fc domain; CD3, cluster of differentiation 3; DLL3, delta-like ligand 3; Fc, fragment crystallizable; SCLC, small cell lung cancer

1. Saba JD, et al. *Nat Rev Clin Oncol*. 2017;14:549-561. **2.** Mathieu L, et al. *Oncologist*. 2021;26:433-438. **3.** Leonetti A, et al. *Cell Oncol (Dordr)*. 2019;42:261-273. **4.** Saunders LR, et al. *Sci Transl Med*. 2015;7:302ra136. **5.** Giffin MJ, et al. *Clin Cancer Res*. 2021;27:1526-1537. **6.** Owonikoko TK, et al. Abstract 8510. Presented at: ASCO Annual Meeting; June 4–8, 2021; Virtual.

First-in-Human Study of Tarlatamab

Tarlatamab in Relapsed/Refractory SCLC

Dose Exploration (0.003-100 mg)

Optimization of dose & regimen

Dose Expansion (100 mg)

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 utility

- **Study design** – open-label, multi-center study of tarlatamab with dose escalation ranging from 0.003 mg to 100 mg and dose expansion at 100 mg administered by IV infusion every 2 weeks, with/without step dose
- Data cutoff of 15 June 2022, median follow-up time of 8.5 months (range, 0.2–30.7)
- **Disease assessment** – Antitumor activity assessed using modified RECIST 1.1 every 8 ± 1 weeks

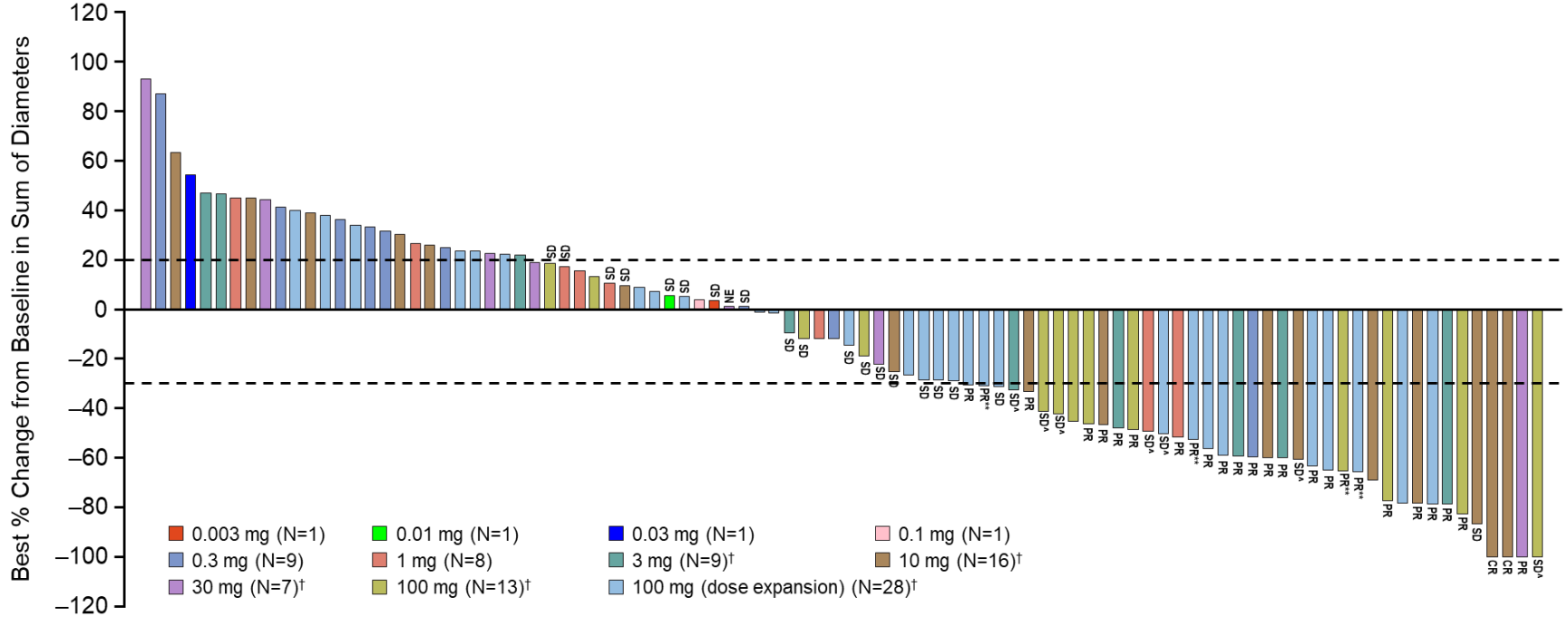
IV, intravenous; MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SCLC, small cell lung cancer

Treatment-related AEs (by preferred term)	Patients (N = 106)	
	All Grades, n (%)	Grade ≥ 3, n (%)*
Any treatment-related AE	97 (92)	33 (31)
Treatment-related AEs occurring in > 15% of patients (by preferred term)		
CRS	56 (53)	1 (1)
Pyrexia	40 (38)	2 (2)
Dysgeusia	24 (23)	0
Fatigue	23 (22)	3 (3)
Nausea	21 (20)	0

- 4/106 (4%) patients discontinued tarlatamab due to treatment-related AEs: encephalopathy (n=1), neurotoxicity (n=1), and pneumonitis (n=2, including one grade 5 AE)

Tarlatamab showed a manageable safety profile across evaluated doses

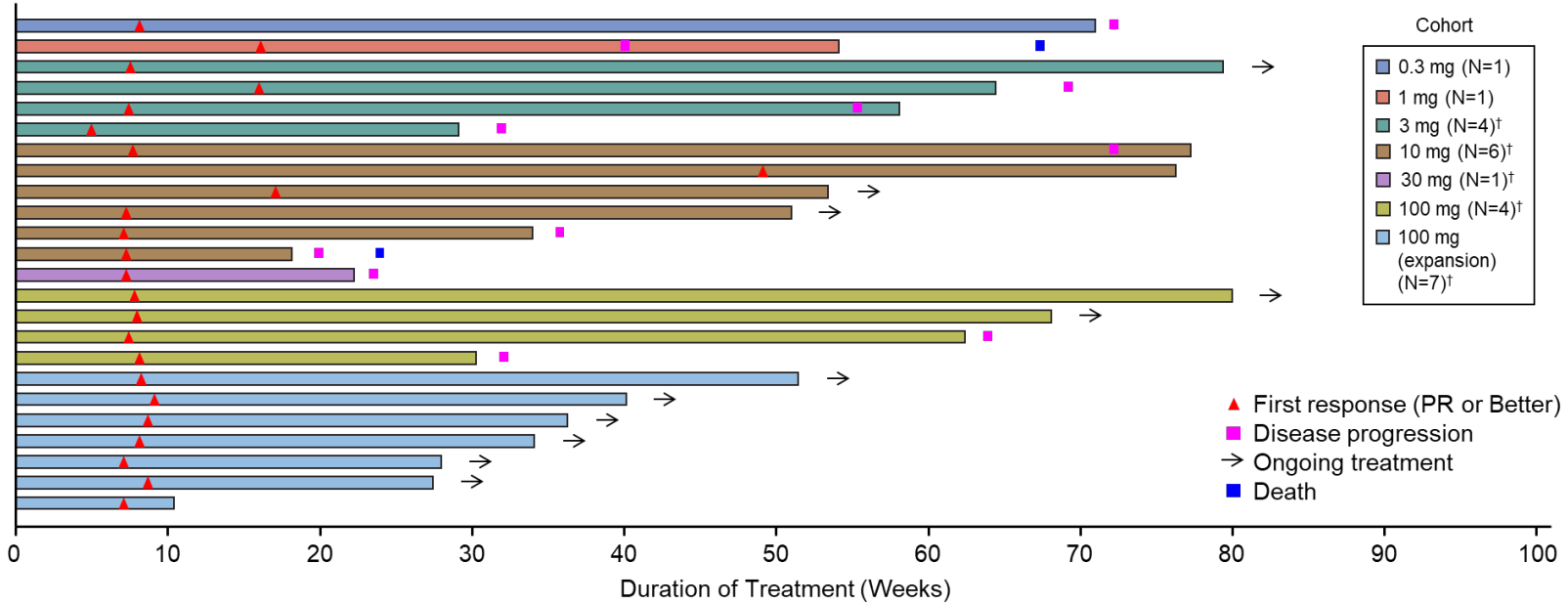
*Includes one patient with grade 5 pneumonitis; AE, adverse event; CRS, cytokine release syndrome.



Confirmed ORR, 23% (2 CRs, 22 PRs); 37% of patients with target lesion shrinkage ≥ 30%

† Indicates step dosing with 1 mg run-in dose. Plot includes patients who received ≥ 1 dose of tarlatamab, had at least 9 weeks follow-up after first dose of tarlatamab, and had sum of diameters available in post-baseline assessments. Unlabeled bars include confirmed and unconfirmed PD. CR, complete response; NE, not evaluable; ORR, objective response rate; PR, partial response; SD, stable disease. PR** indicates patients had an initial PR and still have potential for future confirmative scans; SD^ indicates patients had an initial response but did not have confirmation of response on the subsequent scan.

Duration of Response in Confirmed Responders (n=24)



- **Median duration of response was <u>13.0 months</u> (95% CI: 6.2, 14.9)***
  - 11 patients with evidence of response had treatment ongoing at data cutoff, including 2 complete responders
  - Median time to response was 1.8 months (range: 1.2–7.4)

Bar graph includes all patients with confirmed response (n = 24), with each bar representing 1 patient. *The interim time to event analysis set used in the duration of response analysis includes subjects whose data cut-off date is at least 6 months after first dose date (N=23). †Indicates step dosing with 1 mg run-in dose.

Targeting DLL3: bispecific T-cell engager compounds, efficacy

	Topotecan	RovaT	Tarlatamab	HPN328
n	129 2nd line refractory 52%	287 53%	106 2nd line 28%, 3rd line 42%, ≥4th 30%	11 56% 2nd and 3rd lines
ORR DCR	21% 43%	14.3% 35.3%	24/106 (23%) (2 CR) 52%	27%
Median DOR	4.9 mo	3.5 mo	**13 mo**	ND
Median PFS	4.3 mo	3 mo	3.7 months	ND
Median OS	8.6 mo	6.3 mo	**13.2 mo**	ND

Blackhall F, J Thorac Oncol 2021 (TAHOE); ASCO 2022, Abstract 8566 (HPN328)
Ongoing: BI764532 (Future Oncol 2022)

Conclusions

- Tarlatamab is first DLL3-targeted immune therapy to undergo clinical evaluation
- Promising response (ORR=23%) and durability (DOR=13 mos)
- Acceptable safety profile (CRS mainly gr 1, reversible)
- Phase II study underway

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Chemoimmunotherapy as the First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer and an ECOG PS of 2 or 3

Muskan Agarwal MD[1], Alex Liu MD[2], Blake T. Langlais MS[3], Konstantinos Leventakos MD[2], Nathan Y. Yu,MD[4], Daniel Almquist MD[2], Rami Manochakian MD[2], Vinicius Ernani MD[2]

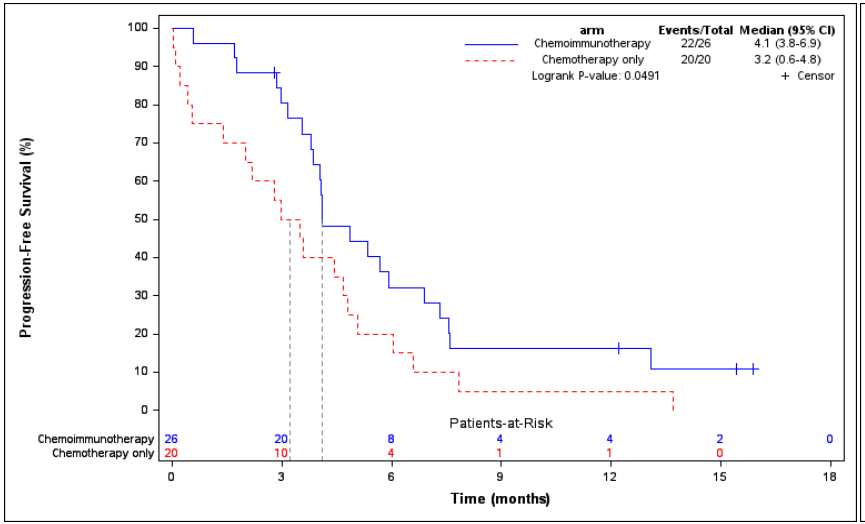
[1]Department of Internal Medicine, [2]Division of Hematology-Oncology, [3]Department of Quantitative Health Sciences, and [4]Department of Hematology-Oncology at Mayo Clinic Health Systems

- Retrospective analysis
- Patients seen at Mayo Clinic Health System from 2017 to 2020
- All adults with ES-SCLC and an ECOG PS 2 or 3 at the time of diagnosis who had not previously received any systemic therapy for SCLC in the past 5 years
- Treatment arms:

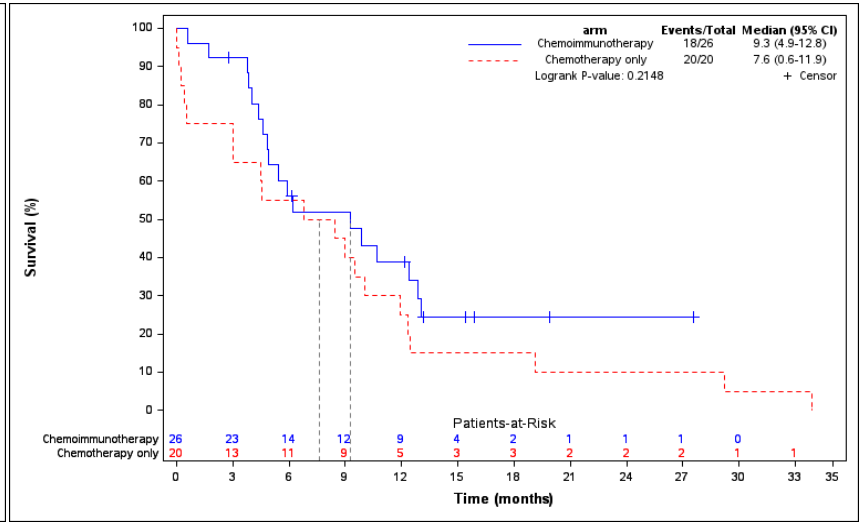
  Chemotherapy group: platinum-etoposide (20 patients)

  Chemoimmunotherapy: platinum/etoposide + atezolizumab (26 patients)
- Primary endpoint: OS
- Secondary endpoint: PFS

PFS by treatment group in patients with ECOG PS 2 or 3



OS by treatment group in patients with ECOG PS 2 or 3



Final thoughts

- Exciting new drugs and targets being explored in SCLC
- Lack of validated predictive biomarkers
- Goal of prospective trials with selection for molecular subtypes
- Need for more real world data