2024 World Conference on Lung Cancer

SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

Small Cell Lung Cancer

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Clinical Professor, Stanford University
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Agenda

- Antibody-drug conjugates
  - B7-H3: Ifinatamab deruxtecan (OA04.03)
  - TROP2: Sacituzumab govitecan (OA04.04)

- T-cell engagers
  - Tarlatamab (OA10.04)
  - MK-6070 (OA10.06)

Current options for relapsed disease?

Options at Relapse		
	ORR (%)	OS (months)
Topotecan	24	5.7
Irinotecan	19	7
Re- Platinum CTFI >3-6m	39	7.5
Lurbinectedin	35	9.3
Tarlatamab	40	14.3

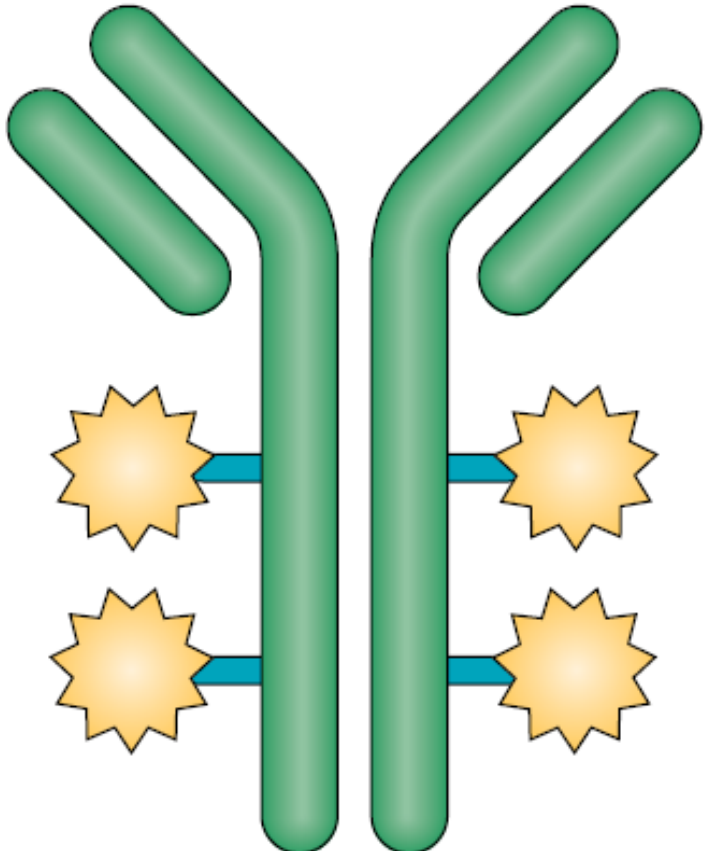
Poor ORR and OS especially in chemotherapy resistant patients

- ORR ~ 20%
- OS ~ 6 months
- Tarlatamab an option for select patients

Chemotherapy Free Interval ≤ 6 months Additional options per NCCN		
	ORR (%)	OS (months)
Oral etoposide	46	3.5
Gemcitabine	13	3.9
Nivolumab	10	4.4
CAV	18	5.7
Paclitaxel	24	5.8
Temozolomide	20	6
Pembrolizumab	19	7.7
Docetaxel	25	
Amrubicin (Japan)	31	7.5

von Pawel et al. JCO 1999 ; Edelman, et al. Lung Cancer 2022; O'Brien, et al. JCO 2006; Trigo et al. Lancet 2020; Ahn et al N EJM 2023; Yamamoto, et al. AntiCancer Res 2006; von Pawel et al. JCO 1999; van der Lee, et al. Ann of Onc 2001; Pietanza, et al. Clin Can Res 2012; Antonia, et al. Lancet Oncol 2016; Chung et al, JTO 2020; Johnson, et al. J Clin Oncol 1990

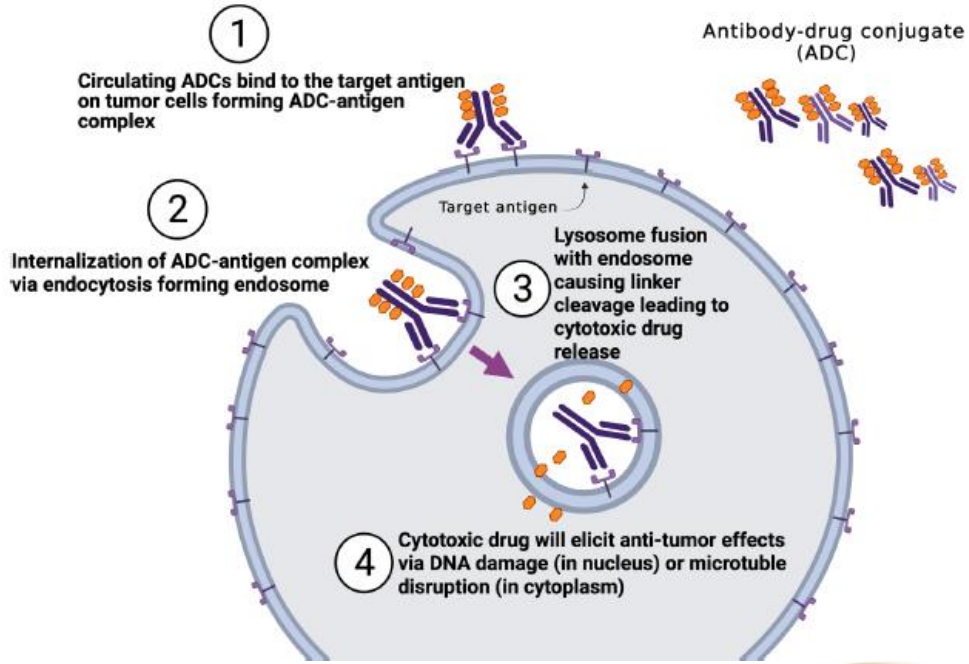
ADC: "Targeted Chemotherapy"



Green= Antibody

Blue= Linker

Yellow= Payload



Drago JZ, et al. Nat Rev Clin Oncol. 2021 Jun;18(6):327-344; Abuhelwa Z, et al. Cancer Treat Rev. 2022 May;106:102393; Fu Z, et al. Signal Transduction and Targeted Therapy. 20227:93

Ifinatamab deruxtecan (I-DXd) in extensive-stage small cell lung cancer (ES-SCLC): interim analysis of IDeate-Lung01

Charles M. Rudin,[1] Myung-Ju Ahn,[2] Melissa Johnson,[3] Christine L. Hann,[4] Nicolas Girard,[5] Makoto Nishio,[6] Ying Cheng,[7] Hidetoshi Hayashi,[8] Yu Jung Kim,[9] Alejandro Navarro,[10] Yuanbin Chen,[11] Tetsuya Sakai,[12] Meng Qian,[13] Juliette Godard,[14] Mei Tang,[13] Jasmeet Singh,[13] Luis Paz-Ares[15]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [5]Institut Curie, Paris, France; [6]The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [7]Jilin Cancer Hospital, Changchun, China; [8]Department of Medical Oncology, Kindai University, Osaka, Japan; [9]Seoul National University Bundang Hospital and Seoul National University College of Medicine, Seongnam, Republic of Korea; [10]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [11]Cancer and Hematology Centers, Grand Rapids, Michigan, MI, USA; [12]National Cancer Center Hospital East, Kashiwa, Japan; [13]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [14]Daiichi Sankyo, SAS, Paris, France; [15]Hospital Universitario 12 de Octubre, Madrid, Spain.

Phase 2 IDeate-Lung01 study (NCT05280470)

I-DXd: Humanized anti–B7-H3 IgG1 mAb with deruxtecan payload

Patient eligibility:

- Histologically or cytologically documented ES-SCLC
- Age ≥18 years[a]
- ≥1 prior line of PBC and ≤3 prior lines of systemic therapy
- Radiologically documented PD on or after most recent prior systemic therapy
- ECOG PS 0–1
- ≥1 measurable lesion per RECIST 1.1[b]
- Patients with asymptomatic brain metastases (untreated or previously treated) are eligible

R 1:1

Arm 1: I-DXd 8 mg/kg Q3W (n≈40)

Arm 2: I-DXd 12 mg/kg Q3W (n≈40)

Extended enrollment at RP3D (n≈70 3L+)

Stratification:

- 2L CTFI <90 days, 2L CTFI ≥90 days, 3L or 4L
- Prior anti–PD-(L)1 treatment (yes or no)

Primary endpoint:

- ORR by BICR[c]

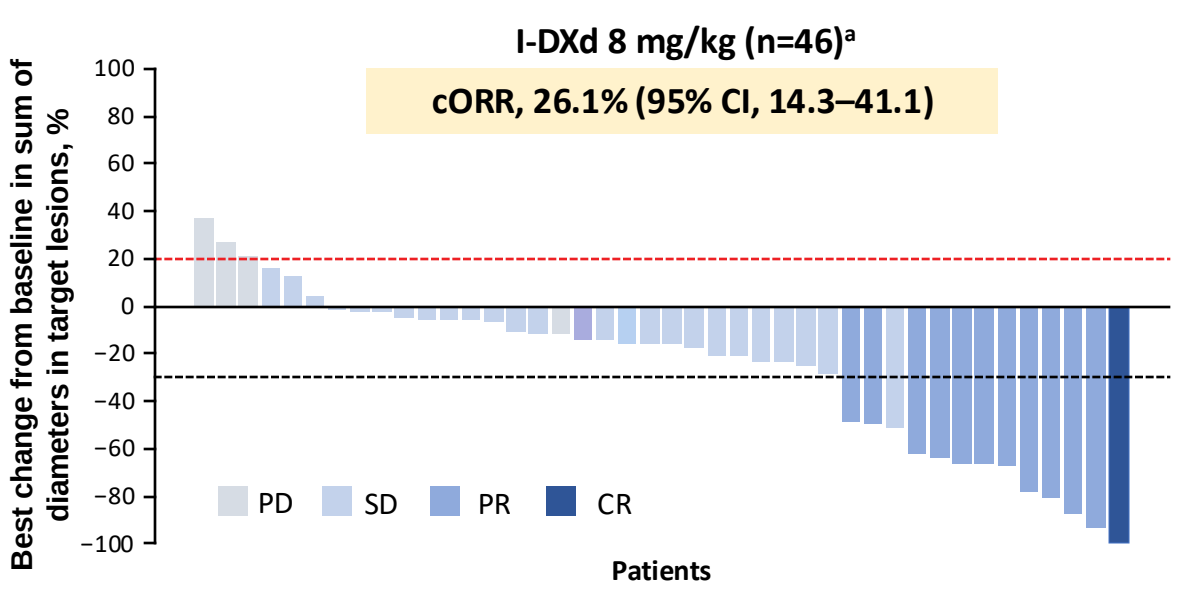
Secondary endpoints:

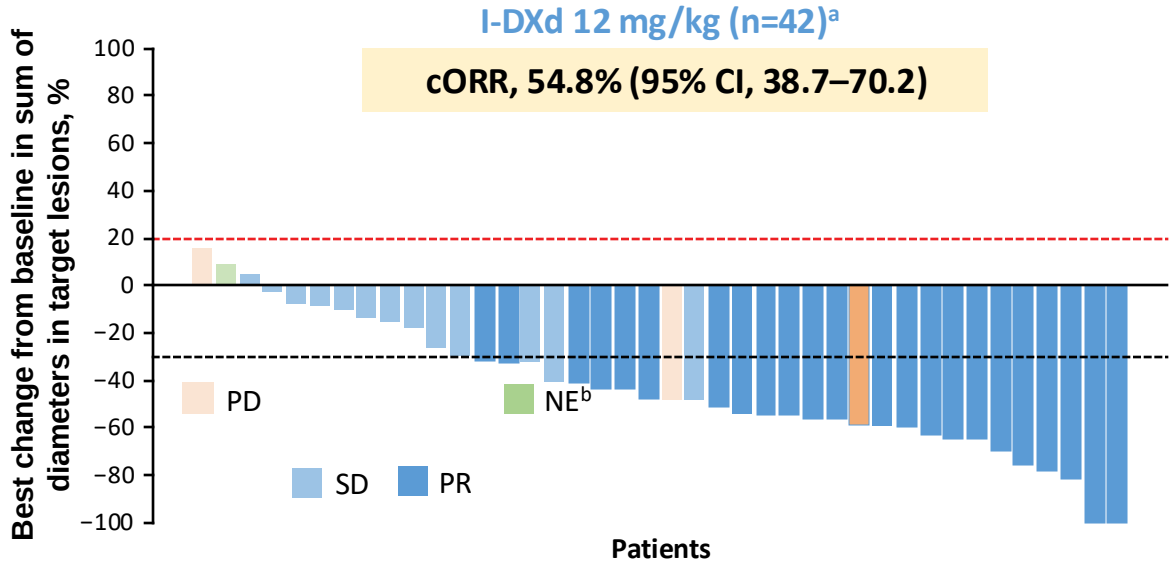
- DOR by BICR and inv[c]
- PFS by BICR and inv[c]
- OS
- DCR[c]
- TTR by BICR and inv[c]
- ORR by inv[c]
- Safety
- Pharmacokinetics
- Immmunogenicity

Exploratory analysis:

- Intracranial ORR by BICR[d]

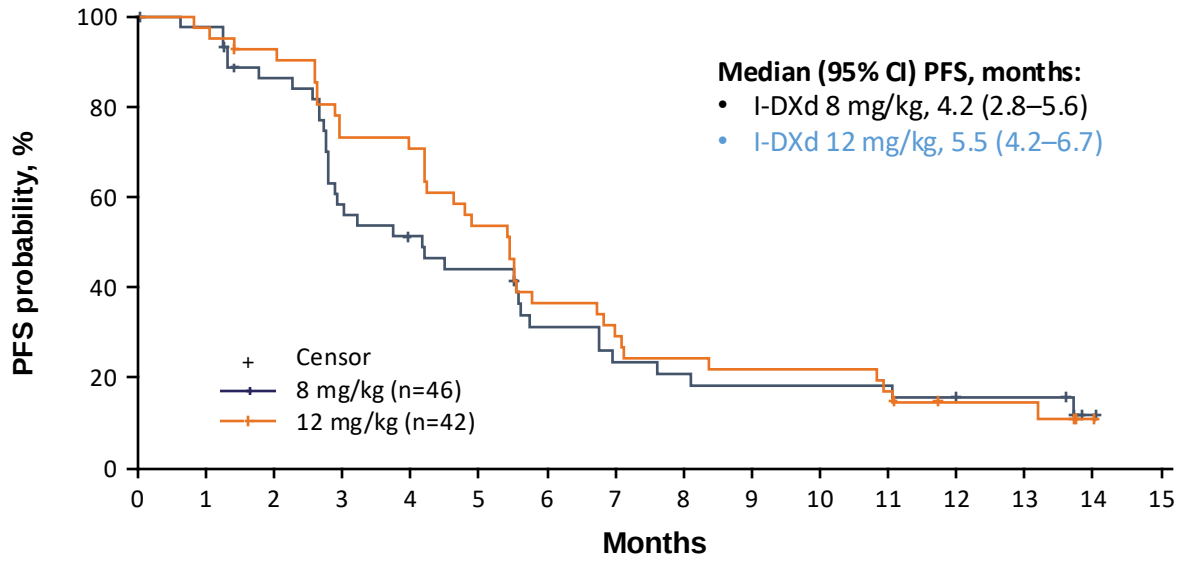
I-DXd has promising antitumor activity; patients treated with 12 mg/kg had a higher ORR than those treated with 8 mg/kg

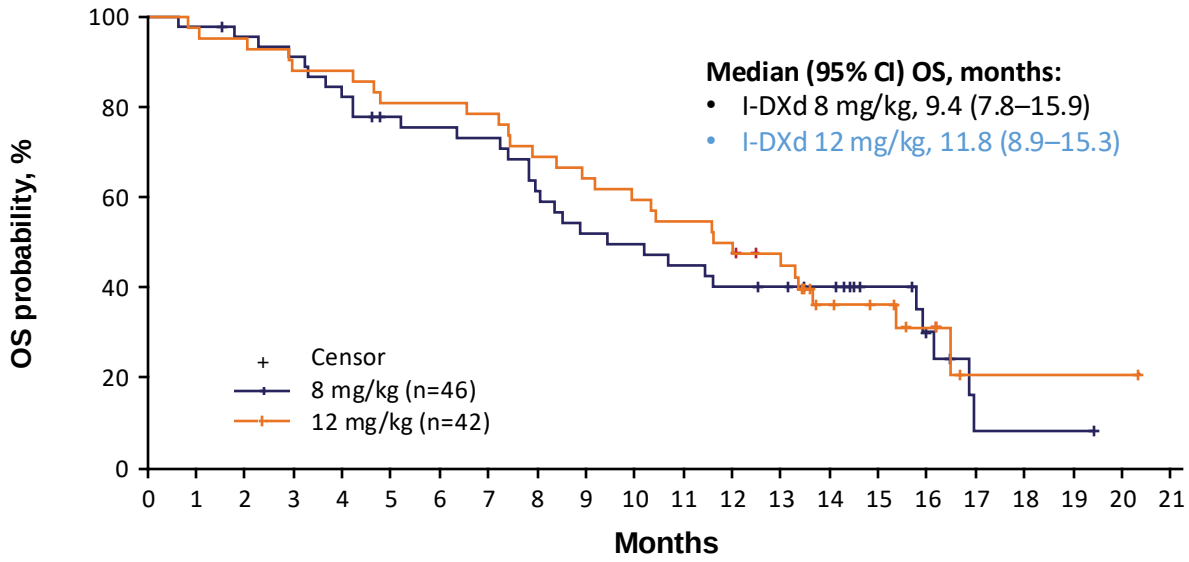




Confirmed response by BICR[c]	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
ORR, % (95% CI)	26.1 (14.3–41.1)	54.8 (38.7–70.2)
CR, n (%)	1 (2.2)	0
PR, n (%)	11 (23.9)	23 (54.8)
DCR, % (95% CI)	80.4 (66.1–90.6)	90.5 (77.4–97.3)

PFS and OS were similar between study arms, numerically favoring the I-DXd 12-mg/kg dose





Number of patients still at risk

8 mg/kg	46	44	37	25	21	18	12	9	8	7	7	7	5	5	1	0
12 mg/kg	42	41	38	30	29	22	15	12	10	9	9	7	4	4	1	0

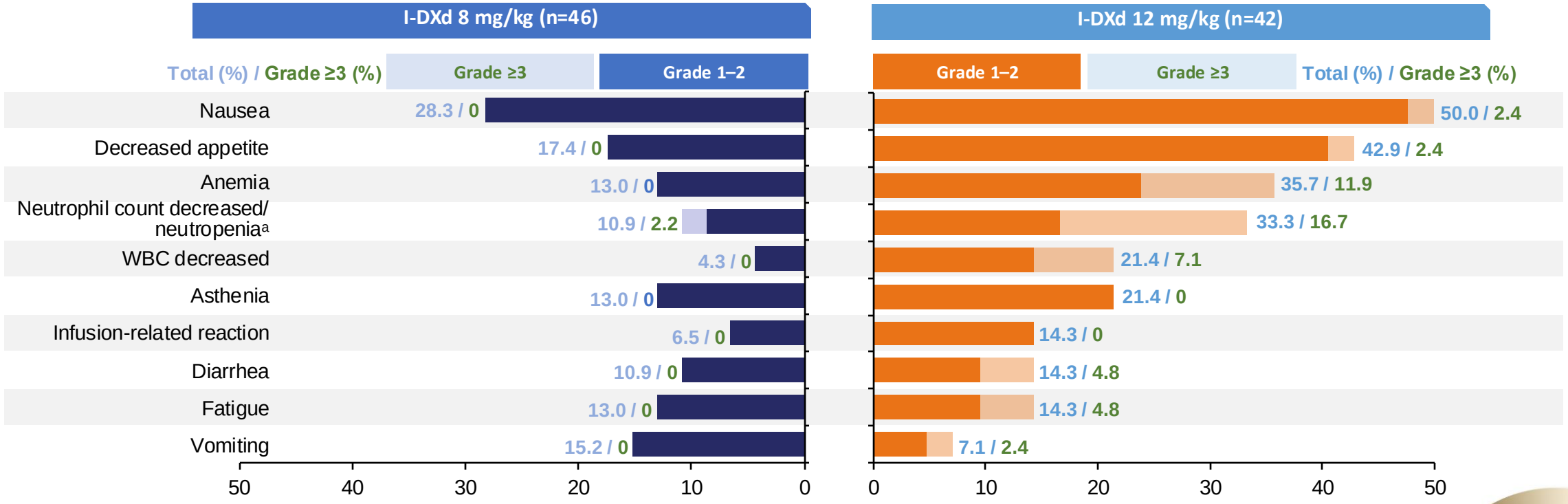
Number of patients still at risk

8 mg/kg	46	45	43	41	37	33	32	31	26	22	21	19	17	16	14	9	5	1	1	1	0	0
12 mg/kg	42	41	40	37	37	34	34	33	29	27	25	23	20	17	10	8	5	1	1	1	1	0

Efficacy summary in patients with brain metastases at baseline and in a subset of patients with brain target lesions at baseline

	Patients with brain metastases at baseline		Patients with brain target lesions at baseline			
	Systemic response[a]		Systemic response[a]		Intracranial response[b]	
	I-DXd 8 mg/kg n=19	I-DXd 12 mg/kg n=18	I-DXd 8 mg/kg n=6	I-DXd 12 mg/kg n=10	I-DXd 8 mg/kg n=6	I-DXd 12 mg/kg n=10
Confirmed ORR,[a] % (95% CI)	26.3 (9.1–51.2)	61.1 (35.7–82.7)	16.7 (0.4–64.1)	60.0 (26.2–87.8)	66.7 (22.3–95.7)	50.0 (18.7–81.3)
Best overall response,[a] n (%)						
CR	1 (5.3)	0	1 (16.7)	0	2 (33.3)	2 (20.0)
PR	4 (21.1)	11 (61.1)	0	6 (60.0)	2 (33.3)	3 (30.0)
SD	11 (57.9)	5 (27.8)	3 (50.0)	3 (30.0)	2 (33.3)	5 (50.0)
PD	2 (10.5)	2 (11.1)	2 (33.3)	1 (10.0)	0	0
NE	1 (5.3)	0	0	0	0	0

Most common treatment-related TEAEs (≥10% total population)



ILD/pneumonitis adjudicated as treatment-related was reported in:

- Four (8.7%) patients in the 8-mg/kg cohort (Grade 2, n=3; Grade 5, n=1)
- Five (11.9%) patients in the 12-mg/kg cohort (Grade, 1 n=1; Grade 2, n=3; Grade 3, n=1)
- No ILD events were pending adjudication at the time of data cutoff

My takeaways

- I-DXd has promising efficacy in previously treated SCLC patients
  - 12 mg/kg dosage showed improved efficacy compared with 8 mg/kg
- Safety profile was generally manageable, mostly GI and hematologic toxicities
- Potential for CNS activity noted in small number of patients with brain target lesions
- Phase III Ideate-Lung02 study underway utilizing 12 mg/kg dosing (NCT06203210)

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Sacituzumab Govitecan as Second-Line Treatment in Patients With Extensive-Stage Small Cell Lung Cancer

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TROPiCS-03 Study Design

SG: Humanized anti–TROP2 mAb with SN-38 payload

Key eligibility criteria
- Histologically confirmed ES-SCLC
- Disease progression after no more than 1 prior line of platinum-based chemo and anti–PD-(L)-1 therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0–1
- Stable, treated brain metastases allowed[a]

→ **ES-SCLC cohort** (N = 43)

→ **SG 10 mg/kg** IV on D1 and D8 21-day cycles (until PD or unacceptable toxicity)

→ **Survival follow-up**

Primary end points
- ORR (INV[b])

Secondary end points
- DOR, CBR, PFS (INV[b])
- ORR, DOR, CBR, PFS (BICR[b])
- OS
- Safety

Efficacy[a]	Platinum resistant (CTFI <90 days) (n = 20)	Platinum sensitive (CTFI ≥90 days) (n = 23)
ORR, % (95% CI)	35.0 (15.4–59.2)	47.8 (26.8–69.4)
BOR, n (%)		
Confirmed PR	7 (35.0)	11 (47.8)
SD	7 (35.0)	11 (47.8)
PD	4 (20.0)	0
Not assessed[b]	2 (10.0)	1 (4.3)
DCR (confirmed PR + SD), % (95% CI)	70.0 (45.7–88.1)	95.7 (78.1–99.9)
CBR (confirmed PR + SD for ≥6 months), % (95% CI)	40.0 (19.1–63.9)	56.5 (34.5–76.8)
Median DOR, months (95% CI)[c,d]	6.3 (1.5–6.9)	4.4 (3.0–NR)
DOR rate at 6 months, % (95% CI)[c]	57.1 (17.2–83.7)	41.6 (13.1–68.4)
Median PFS, months (95% CI)[c]	3.8 (1.4–7.6)	5.0 (4.1–7.4)
Median OS, months (95% CI)[c]	6.6 (4.7–17.7)	14.7 (7.7–NR)

SD duration was defined as the time from the date of first dose of study drug to the first documentation of PD or death from any cause.
[a]By investigator assessment. [b]Patients without any post-baseline assessments were counted as not assessed. [c]Based on Kaplan-Meier estimates. [d]Calculated for patients with confirmed PR.
BOR, best overall response; **CBR**, clinical benefit rate; **CTFI**, chemotherapy-free interval; **DCR**, disease control rate; **DOR**, duration of response; **NR**, not reached; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PR**, partial response; **SD**, stable disease.

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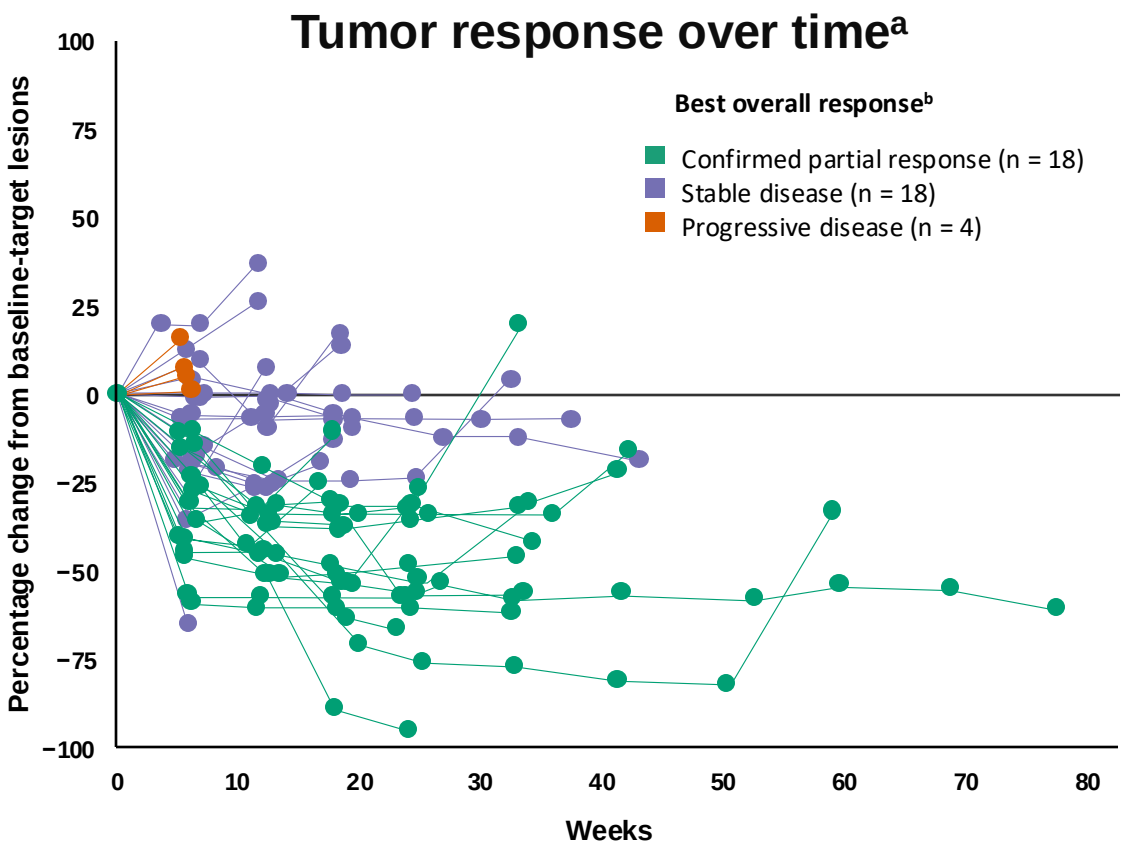
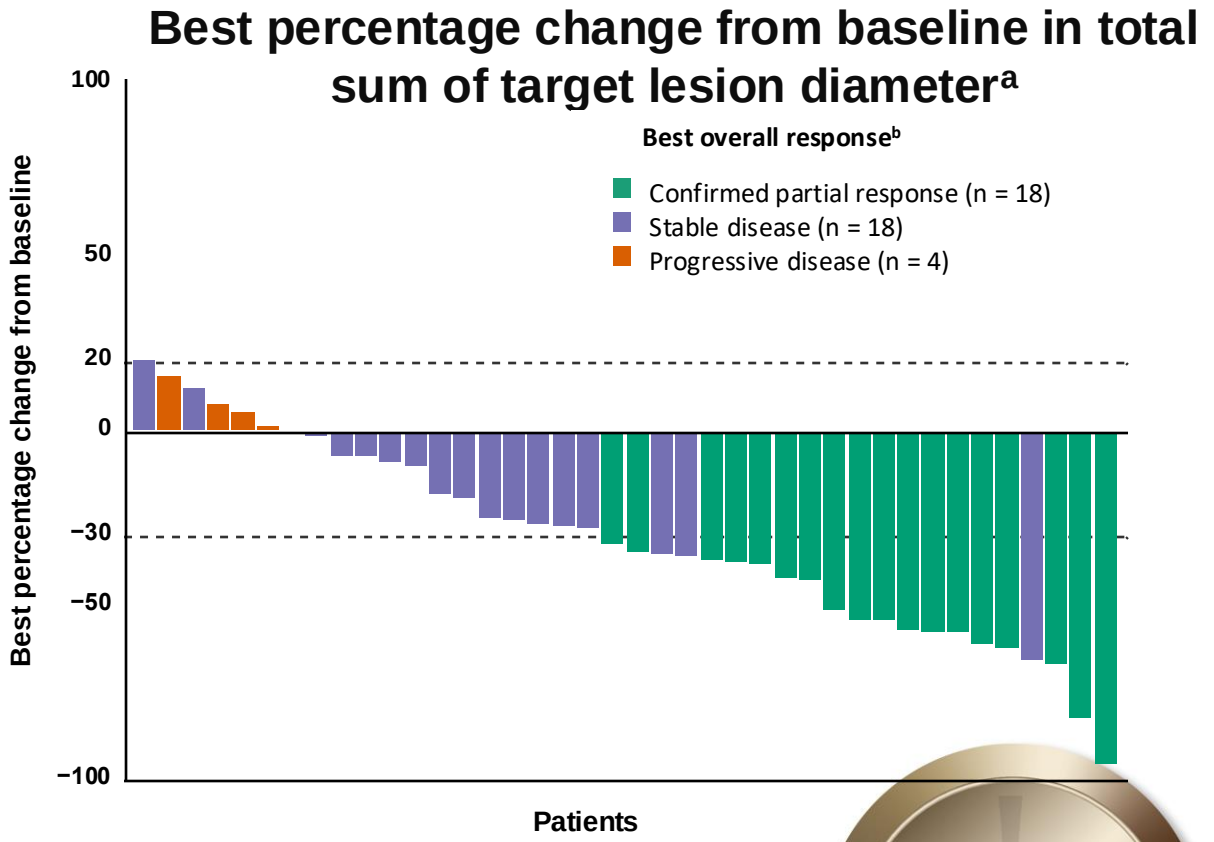
Efficacy Analyses

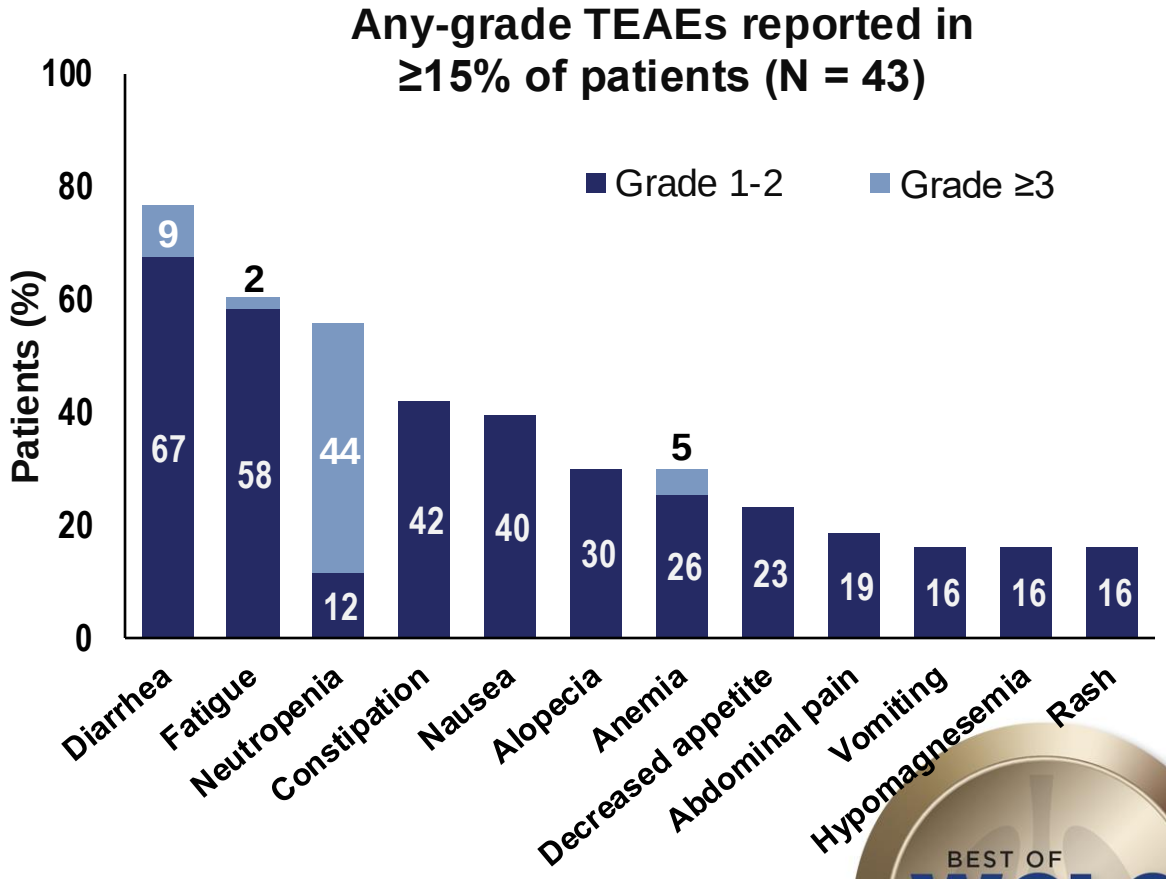




- 76.7% (33/43) of patients had tumor shrinkage
- 48.8% (21/43) of patients had a reduction of >30% in target lesion diameter

Safety Summary

Event, n (%)	ES-SCLC (N = 43)
Any-grade TEAEs	43 (100.0)
Grade ≥3 TEAEs	32 (74.4)
Serious TEAEs	22 (51.2)
TEAEs leading to dose reduction[a]	16 (37.2)
TEAEs leading to discontinuation	0
TEAEs leading to death[b]	3 (7.0)
Related to study drug[c]	1 (2.3)



My takeaways

- SG has promising efficacy in previously treated SCLC
- Activity seen in both platinum-sensitive and platinum-resistant patients
- Safety profile manageable, mostly GI and hematologic (44% grade 3 neutropenia)
- Phase III study in development?

DeLLphi 303

Tarlatamab with a PD-L1 Inhibitor as First-Line Maintenance After Chemo-Immunotherapy for ES-SCLC: DeLLphi-303 Phase 1b Study

Sally C. M. Lau[1], Myung-Ju Ahn, Mor Moskovitz, Michael Pogorzelski, Simon Häfliger, Kelly G. Paulson, Amanda Parkes, Yuyang Zhang, Ali Hamidi, Martin Wermke

[1] Department of Medicine, Perlmutter Cancer Center, NYU Grossman School of Medicine, New York, NY, USA

DeLLphi-303: Tarlatamab with PD-L1 Inhibitor as 1LM

DeLLphi 303

- Phase 1b, multicenter, open-label study (NCT05361395)

1L Chemo-IO

Platinum-etoposide
+
PD-L1 inhibitor

(4-6 cycles)

Enrollment

Key Inclusion Criteria

- No disease progression following 4-6 cycles of platinum-etoposide + PD-L1 inhibitor
- Eligible if no access to 1L PD-L1 inhibitor
- Prior treatment for LS-SCLC permitted
- ECOG PS 0-1
- Treated and asymptomatic brain metastases allowed
- DLL3 positivity not required

1L Maintenance

Non-randomized

Switching to different PD-L1 inhibitor permitted

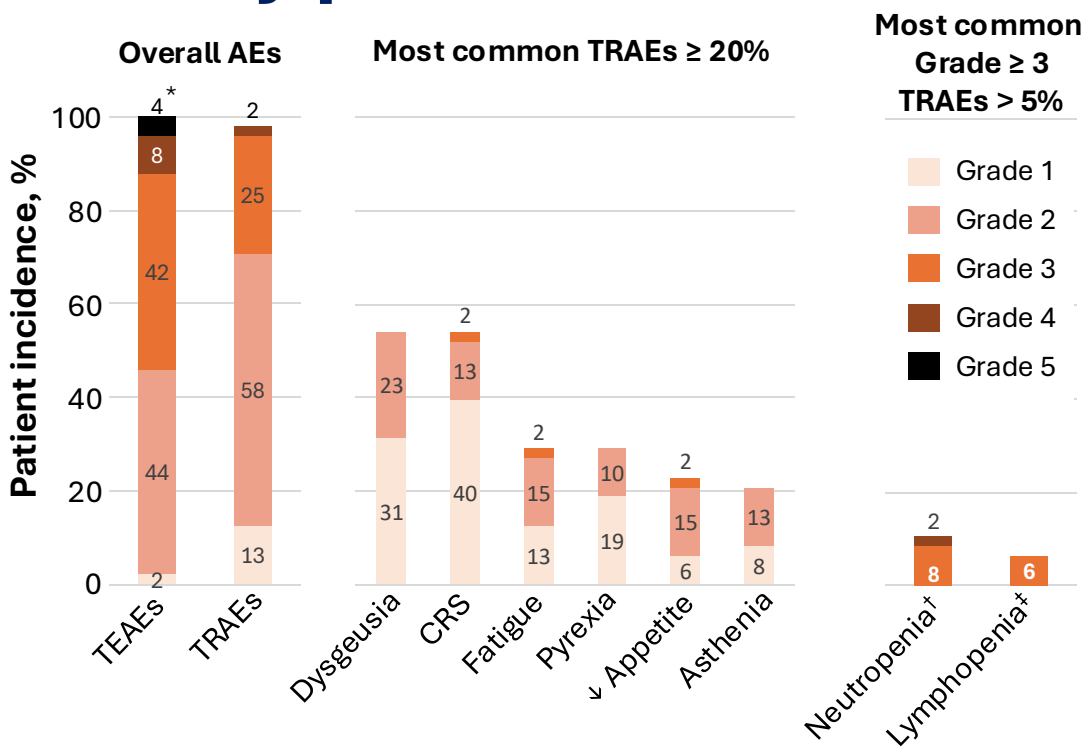
Tarlatamab (10 mg IV Q2W)* + Atezolizumab (1680 mg IV Q4W)

Tarlatamab (10 mg IV Q2W)* + Durvalumab (1500 mg IV Q4W)

- Must initiate C1D1 of maintenance phase within 8 weeks of the start of the last cycle of 1L chemo-immunotherapy
- Median follow-up time (N = 88): 10.0 months (range: 1.4+–20.4)

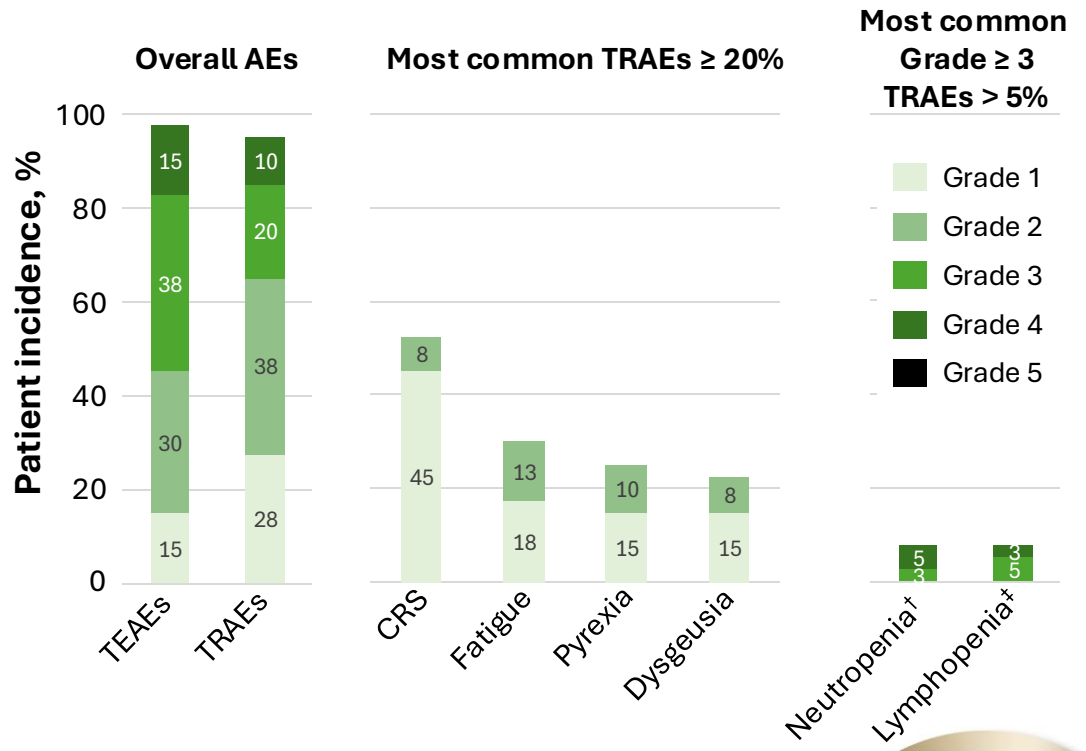
Primary Endpoints†: Dose-limiting toxicities, treatment-emergent / treatment-related adverse events (TEAEs, TRAEs)
Secondary Endpoints‡: Disease control and PFS per local RECIST 1.1 assessment, OS

Safety profile



Tarlatamab + Atezolizumab, n = 48

TRAEs led to dose interruption in 17% and tarlatamab discontinuation in 4% of patients§



Tarlatamab + Durvalumab, n = 40

TRAEs led to dose interruption in 15% and tarlatamab discontinuation in 8% of patients‖

- **Tarlatamab with a PD-L1 inhibitor as 1LM had a manageable safety profile with no DLTs and no fatal TRAEs**
- **There were no new or unexpected toxicities, and immune related adverse events (irAEs) were rare (2.3%)¶**

DeLLphi-303 Phase 1b Study: Efficacy in 1L Maintenance

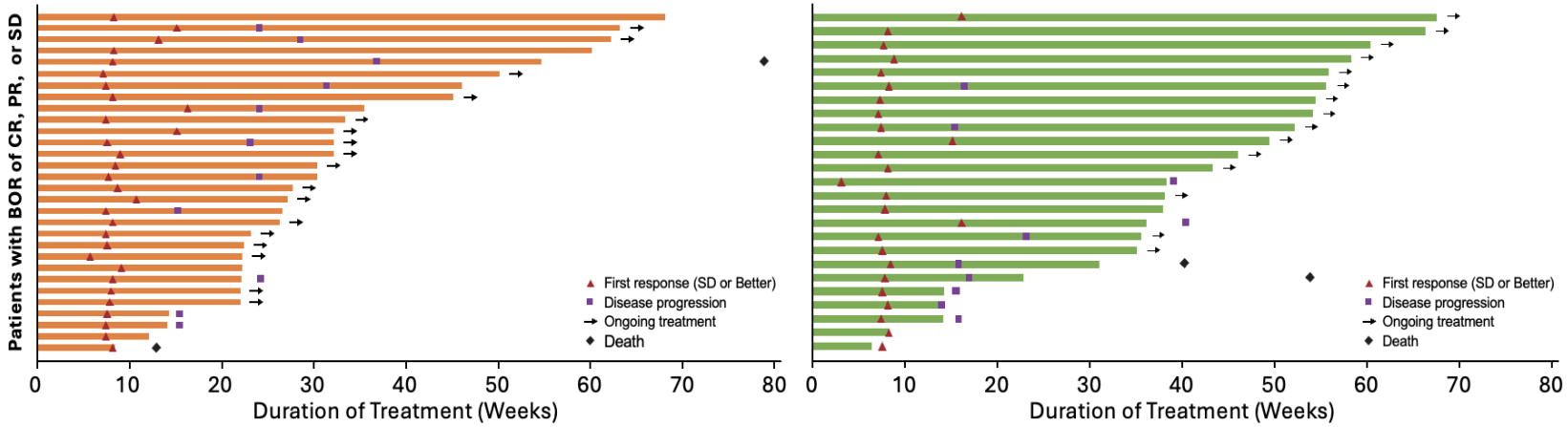
- For tarlatamab + PD-L1 inhibitor, DCR was 62.5% (95% CI: 51.5–72.6) and mDoDC was 9.3 months (95% CI: 5.6, NE)
- Median PFS: 5.6 months (compare to 2.6 mos for 1st line maintenance atezo)
- 9-mo OS: 89% (compare to ~60% for 1st line maintenance atezo)

Tarlatamab + Atezolizumab

- DCR: 30/48 = 62.5% (95% CI: 47.4-76.0)
- Median duration of DC = 7.2 months (95% CI: 5.6, NE)

Tarlatamab + Durvalumab, n = 25

- DCR: 25/40 = 62.5% (95% CI: 45.8, 77.3)
- Median duration of DC = NE (95% CI: 3.9, NE)



Reck M, et al. *J Thoric Oncol.* 2022; 17:1122-1129

Overview of ongoing tarlatamab trials in SCLC

Clinical trial name	Phase	Tarlatamab treatment	Status*
DeLLphi-300[1,2]	1	Tarlatamab in relapsed/refractory SCLC	Active, not recruiting
DeLLphi-301[3]	2	Tarlatamab in heavily pretreated† patients with SCLC†	Active, not recruiting
DeLLphi-302[4,5]	1b	Tarlatamab in combination with an anti-PD1 monoclonal antibody in SCLC (2L or later)	Active, not recruiting
DeLLphi-303[6,7]	1b	Tarlatamab in combination with SOC in 1L ES-SCLC	Recruiting
DeLLphi-304[8,9]	**3**	**Tarlatamab vs SOC chemotherapy in 2L SCLC**	**Recruiting**
DeLLphi-305[10]	**3**	**Tarlatamab + durvalumab vs. durvalumab in 1L maintenance**	**Recruiting**
DeLLphi-306[11]	3	Tarlatamab after chemoRT in LS-SCLC	Recruiting

- 1. ClinicalTrials.gov, NCT03319940 (accessed June 2023); 2. Paz-Ares L, et al. J Clin Oncol 2023;41:2893–903;
3. ClinicalTrials.gov, NCT05060016 (accessed June 2023); 4. ClinicalTrials.gov, NCT04885998 (accessed June 2023);
5. Dowlati A, et al. Ann Oncol 2021;32(suppl_5):S1164–74.10.1016; 6. ClinicalTrials.gov, NCT05361395 (accessed June 2023);
7. Gadgeel SM, et al. Ann Oncol 2022;33(suppl_7):S701–2.10.1016; 8. ClinicalTrials.gov, NCT05740566 (accessed June 2023);
9. Paz-Ares L, at al. ASCO 2023; poster 232a. 10. NCT06211036. 11. NCT06117774

My takeaways

- Promising activity of tarlatamab + IO in this phase I maintenance study in SCLC
- Phase III study underway (DeLLphi-305: NCT06211036)
- Is maintenance treatment early 2nd line treatment?
  - Are we curing patients?

Impact of Brain Metastases on Safety and Efficacy of MK-6070, a DLL3-Targeting T-Cell Engager, in Small Cell Lung Cancer

Noura J. Choudhury,[1] Himisha Beltran,[2] Melissa L. Johnson,[3] Erin L. Schenk,[4] Rachel E. Sanborn,[5] Jonathan R. Thompson,[6] Hirva Mamdani,[7] Afshin Dowlati,[8] Rahul R. Aggarwal,[9] Ann W. Gramza,[10] Prantesh Jain[11]

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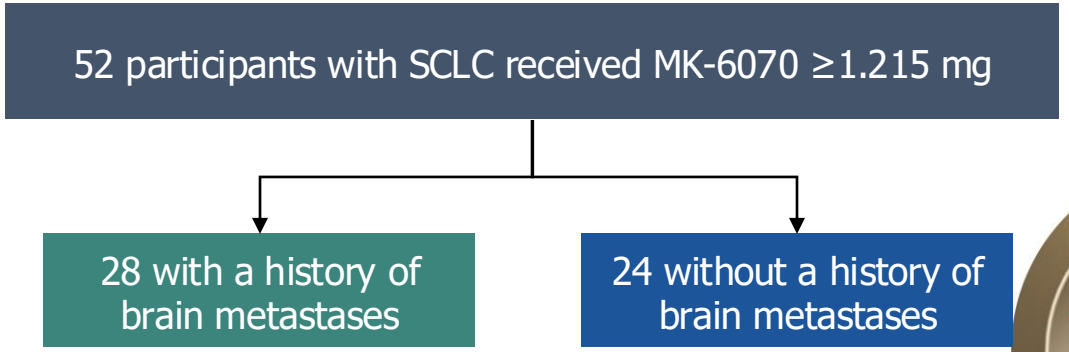
HPN328-4001 (MK-6070) Study Design and Analysis Considerations

- Trial design: 3 + 3 dose escalation
  - MK-6070 administered IV QW or Q2W with step dosing
- Key eligibility criteria for participants with SCLC
  - Age ≥18 years
  - ECOG PS 0 or 1
  - Measurable disease per RECIST v1.1
  - SCLC relapsed/refractory to ≥1 prior systemic therapy that included platinum-based chemotherapy
- Brain metastasis considerations
  - Present at baseline: participants eligible if brain metastases asymptomatic, previously treated, and radiologically stable for ≥2 weeks
  - Localized progression during study: radiotherapy permitted if participants otherwise benefitting from treatment

- Response assessment
  - ORR: assessed per RECIST v1.1
  - Extracranial ORR: assessed per modified RECIST v1.1 that includes participants with systemic responses and brain-only progression
- Analysis population: participants with SCLC who received ≥1 administration of MK-6070 monotherapy at a dose ≥1.215 mg



ClinicalTrials.gov identifier, NCT04471727. Data extraction date: June 3, 2024.

Antitumor Activity

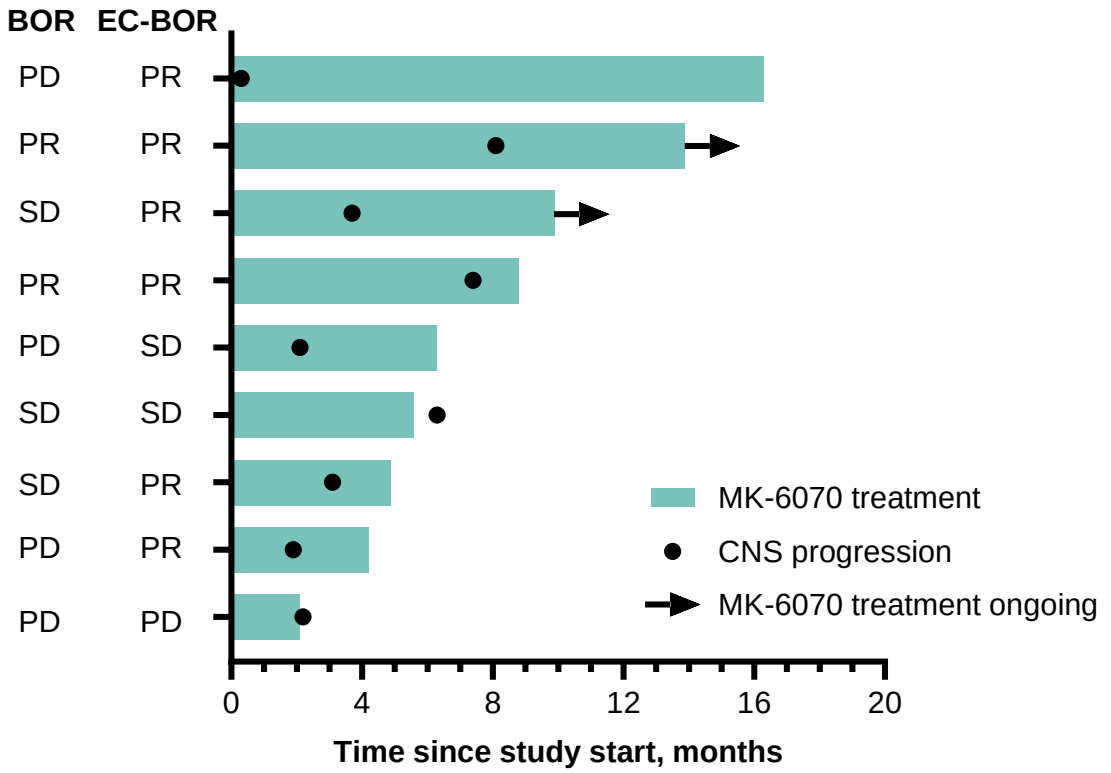
	Confirmed Response		Confirmed Extracranial Response	
	History of Brain Mets (n=28)	No History of Brain Mets (n=22[a])	History of Brain Mets (n=28)	No History of Brain Mets (n=22[a])
ORR, % (95% CI)	36% (19-56)	18% (5-40)	50% (31-69)	18% (5-40)
DCR, % (95% CI)	64% (44-81)	50% (28-72)	75% (55-89)	50% (28-72)
Best overall response, n (%)				
Complete response	1 (4%)	0	1 (4%)	0
Partial response	9 (32%)	4 (18%)	13 (46%)	4 (18%)
Stable disease	8 (29%)	7 (32%)	7 (25%)	7 (32%)
Progressive disease	10 (36%)	8 (36%)	7 (25%)	8 (36%)
Discontinued before assessment	0	3 (14%)	0	3 (14%)

[a]2 participants without a history of brain metastases were excluded from the efficacy population because they had not reached their first imaging assessment as of the data extraction date.
Data extraction date: June 3, 2024; PFS and OS data not mature at this time.

Intracranial Antitumor Activity

- Of 28 participants with a history of brain metastases:
  - 9 (32%) had CNS progression
    - Median time to CNS progression: 3.1 mo (range, 0.3-8.1)
    - Median time on treatment: 6.3 mo (range, 2.1-16.3)
  - 4 (14%) had extracranial PR but CNS progression
    - All 4 received radiotherapy to the brain
    - Median time on treatment: 7.4 mo (range, 4.2-16.3), with 1 participant remaining on treatment
- Of 20 participants with brain metastases at baseline:
  - 5 (25%) had complete response in the brain[a]
- Of 24 participants without a history of brain metastases:
  - None had CNS progression

Participants With a History of Brain Metastases Who Had CNS Progression (n=9)



[a]Based on the data collected, it is only possible to determine whether the brain metastases were present or absent at each imaging assessment.
Data extraction date: June 3, 2024.

My takeaways

- In the phase I study of MK-6070, there are no concerning safety signals and encouraging efficacy noted in SCLC patients with or without brain metastases
- Data suggests potential CNS activity, though further studies are needed
  - Prior radiation therapy details and RANO assessments needed

Overall Conclusions

- Exciting new drugs being explored in SCLC with encouraging efficacy
- B7-H3 and TROP-2 ADCs show promise
- Preliminary data indicates potential CNS activity for ADCs and T-cell engagers
- Small numbers of patients in trials presented today
- Await additional data from phase III trials