Best of WCLC 2023: Small Cell Lung Cancer

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Agenda

Advancing Immunotherapy in ES-SCLC

- **OA01.03: Ph III Benmelstobart + Anlotinib (ETER701)**
- **OA01.04: 5-year OS of pts treated with atezolizumab in IMpower133**

Novel therapies in 2nd line SCLC

- **OA01.05: Ph I of DLL3/CD3 T cell engager BI764532 in pts with DLL3+ tumors**
- **OA05.05: Ph I/II Ifinatamab deruxtecan (I-Dxd) in pts with refractory SCLC**

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Benmelstobart with Anlotinib plus Chemotherapy as First-line Therapy for ES-SCLC: A Randomized, Double-blind, Phase III Trial (ETER701)

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China

Study Design

- A multicenter, placebo-controlled, randomized phase III trial in first-line ES-SCLC.

Key Eligibility Criteria

- 18-75 years
- Pathologically confirmed diagnosis of ES-SCLC
- No prior systemic therapy
- Measurable lesion (RECIST1.1)
- Asymptomatic or treated and stable brain metastases permitted
- ECOG PS 0 or 1
- Adequate organ function

R (1:1:1)

N=738

	Induction (Four 21-day cycles)	*Maintenance**
	Benmelstobart (1200mg, d1) + **Anlotinib** (12mg, d1-14) + Etoposide + Carboplatin	Benmelstobart + Anlotinib
	Placebo + **Anlotinib** (12mg, d1-14) + Etoposide + Carboplatin	Placebo + Anlotinib
	Placebo + Placebo + **Etoposide** + **Carboplatin**	Placebo +Placebo

Primary Endpoints

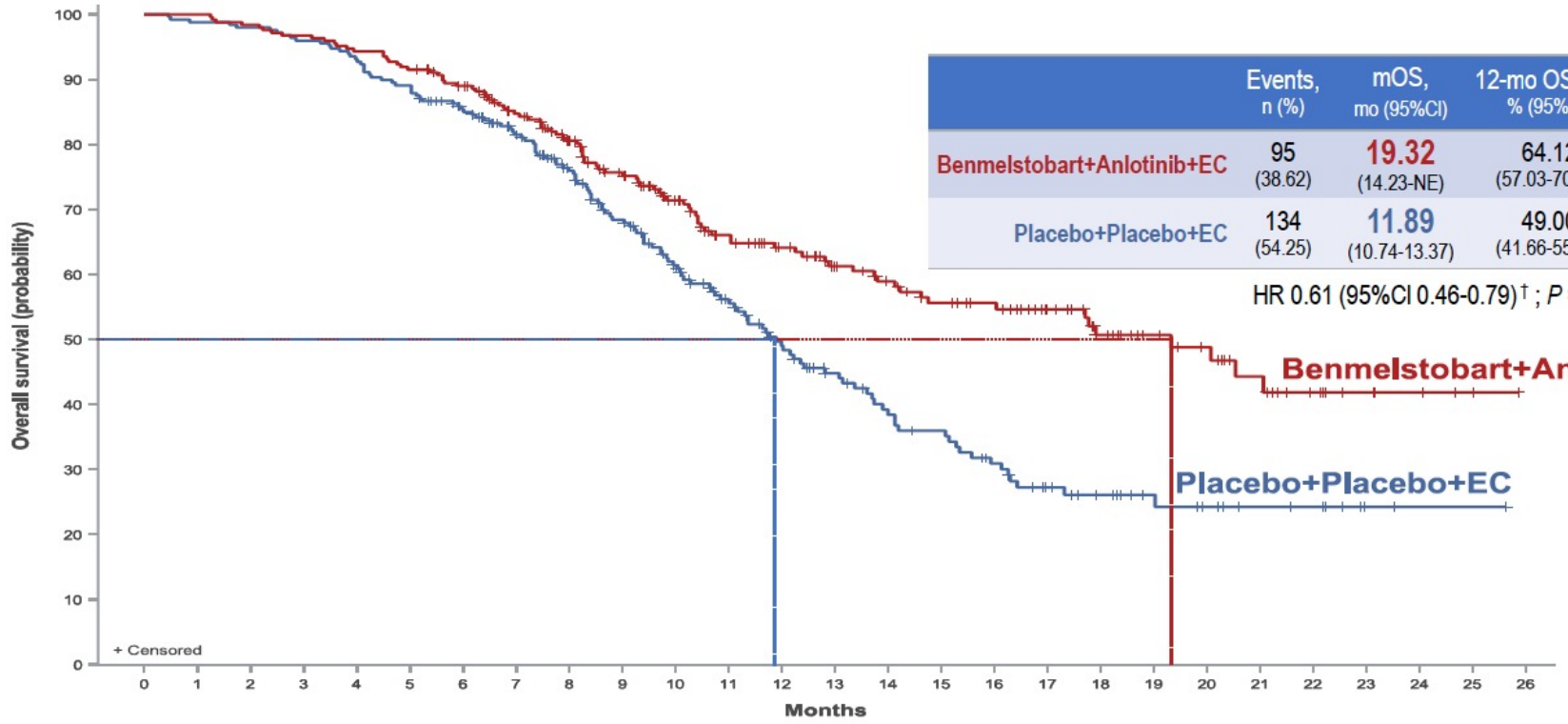
- OS (IRC, RECIST1.1)
- PFS (IRC, RECIST1.1)

Secondary Endpoints

- PFS (investigator, RECIST1.1 and iRECIST)
- ORR
- DCR
- DOR
- 6-mo/12-mo PFS rate
- 12-mo/18-mo OS rate
- Quality of Life
- Safety and tolerability

➢ **Stratified by:** ECOG PS (0/1); brain metastases (Y/N); liver metastases (Y/N).

Primary Endpoint: OS (ITT Population)



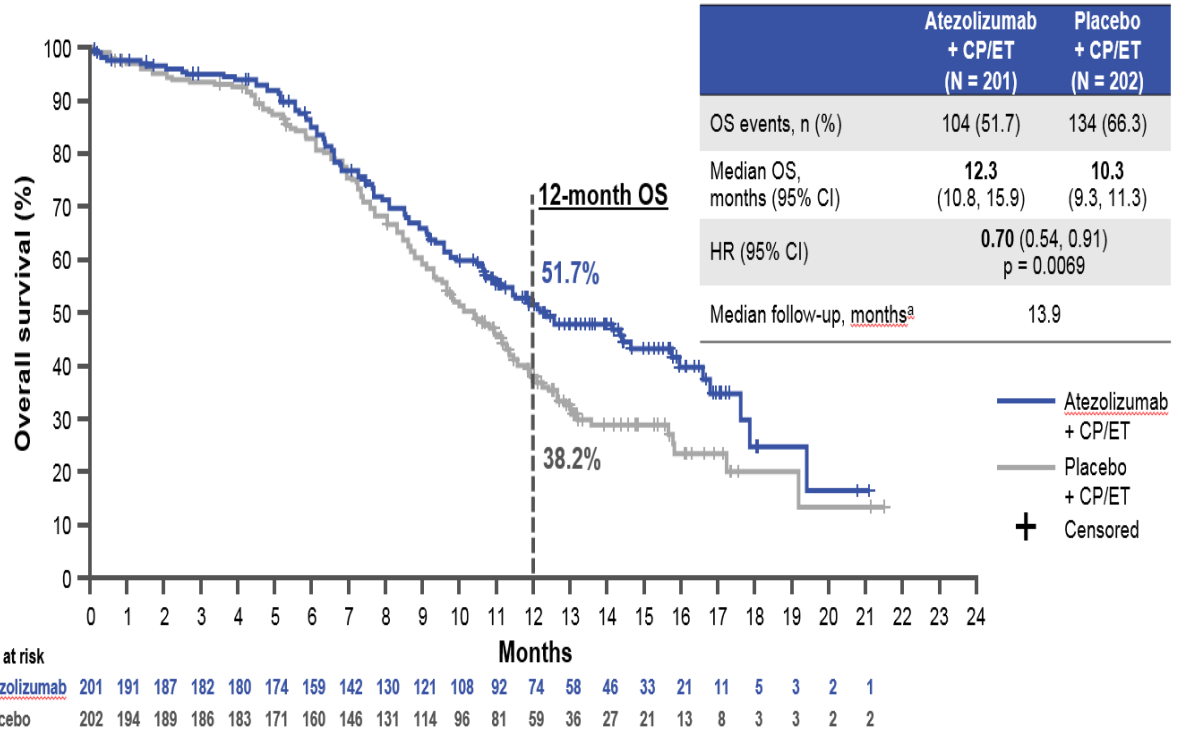
	Events, n (%)	mOS, mo (95%CI)	12-mo OS rate, % (95%CI)	24-mo OS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	95 (38.62)	19.32 (14.23-NE)	64.12 (57.03-70.34)	41.83 (31.30-52.00)
Placebo+Placebo+EC	134 (54.25)	11.89 (10.74-13.37)	49.00 (41.66-55.93)	24.24 (16.96-32.26)

HR 0.61 (95%CI 0.46-0.79)† ; *P* = 0.0002 *

No. at risk

Benmelstobart+Anlotinib+EC	246	246	242	238	232	225	214	192	168	149	123	106	93	81	73	64	58	46	36	28	24	18	11	7	5	2	0
Placebo+Placebo+EC	247	244	242	237	230	220	202	181	155	134	111	90	72	58	47	43	35	25	19	14	11	8	7	2	1	1	0

IMpower133 carboplatin/etoposide +/- atezolizumab

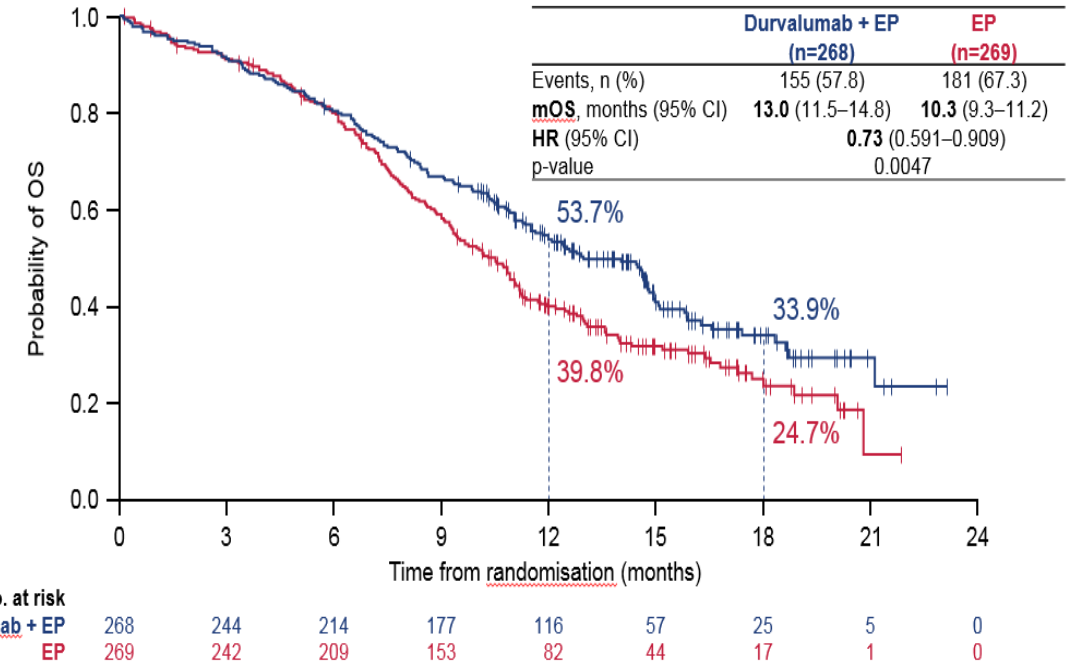


	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

Horn L et al. NEJM. 2018 Dec 6; 379(23):2220-2229

CASPIAN cis/carboplatin/etoposide +/- durvalumab

Overall Survival (Primary Endpoint)



	Durvalumab + EP (n=268)	EP (n=269)
Events, n (%)	155 (57.8)	181 (67.3)
mOS, months (95% CI)	**13.0** (11.5–14.8)	**10.3** (9.3–11.2)
HR (95% CI)	**0.73** (0.591–0.909)	
p-value	0.0047	

Paz-Aes L et al. Lancet. 2019 Nov 23;394(10212):1929-1939

Saftey Summary	Benmelstobart + Anlotinib + EC (N=246)		Placebo + Placebo + EC (N=246)*	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any TRAEs, n (%)	246 (100.0)	229 (93.1)	245 (99.6)	214 (87.0)
Leading to any dose reduction or interruption	124 (50.4)	83 (33.7)	57 (23.2)	39 (15.9)
Leading to any discontinuation	21 (8.5)	14 (5.7)	7 (2.8)	5 (2.0)
Leading to death	11 (4.5)	11 (4.5)	4 (1.6)	4 (1.6)
Any irAEs, n (%)	105 (42.7)	41 (16.7)	47 (19.1)	17 (6.9)
Leading to any dose reduction	16 (6.5)	13 (5.3)	5 (2.0)	3 (1.2)
Leading to any discontinuation	20 (8.1)	15 (6.1)	4 (1.6)	3 (1.2)
Leading to death	5 (2.0)	5 (2.0)	1 (0.4)	1 (0.4)
Any SAEs, n (%)	135 (54.9)	115 (46.7)	101 (41.1)	84 (34.1)
Benmelstobart-related ≥ Grade 3 SAEs	/	51 (20.7)	/	22 (8.9)
Anlotinib-related ≥ Grade 3 SAEs	/	56 (22.8)	/	33 (13.4)
Chemotherapy-related ≥ Grade 3 SAEs	/	92 (37.4)	/	63 (25.6)

Conclusions

- Benmelstobar + Anlotinib + EC improved PFS and OS as first-line therapy in ES-SCLC patients compared to Placebo + EC
- Tolerable and manageable safety profile
- Addition of anti-angiogenic agent to immunochemotherapy in the first-line treatment of ES-SCLC resulted in historically longest PFS and OS in Chinese population
- Would be good to test in other patient populations
- How does Benmelstobar + Anlotinib + EC compare to Benmelstobar + EC?

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Five-year survival in patients with ES-SCLC treated with atezolizumab in IMpower133: IMbrella A extension study results

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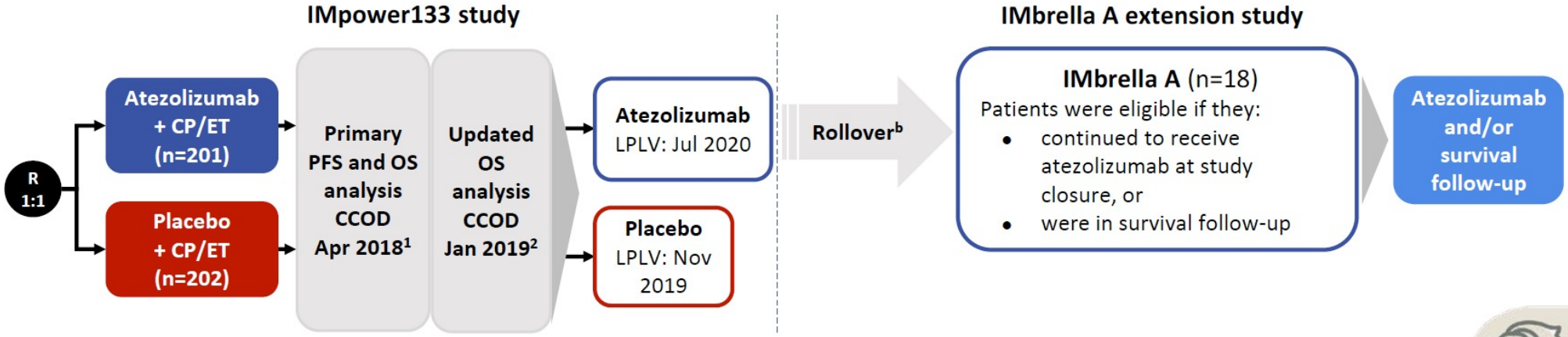
IMbrella A: an extension study of IMpower133[a]

- IMbrella A is an open-label, non-randomised, multicentre extension and long-term observational study
- Patients in the IMpower133 control arm were not eligible for enrollment in IMbrella A
- Rollover from IMpower133 to IMbrella A for patients treated with atezolizumab in IMpower133 occurred between December 2019 and July 2020
- We report a merged analysis from IMpower133 and IMbrella A with a CCOD of 16 March 2023

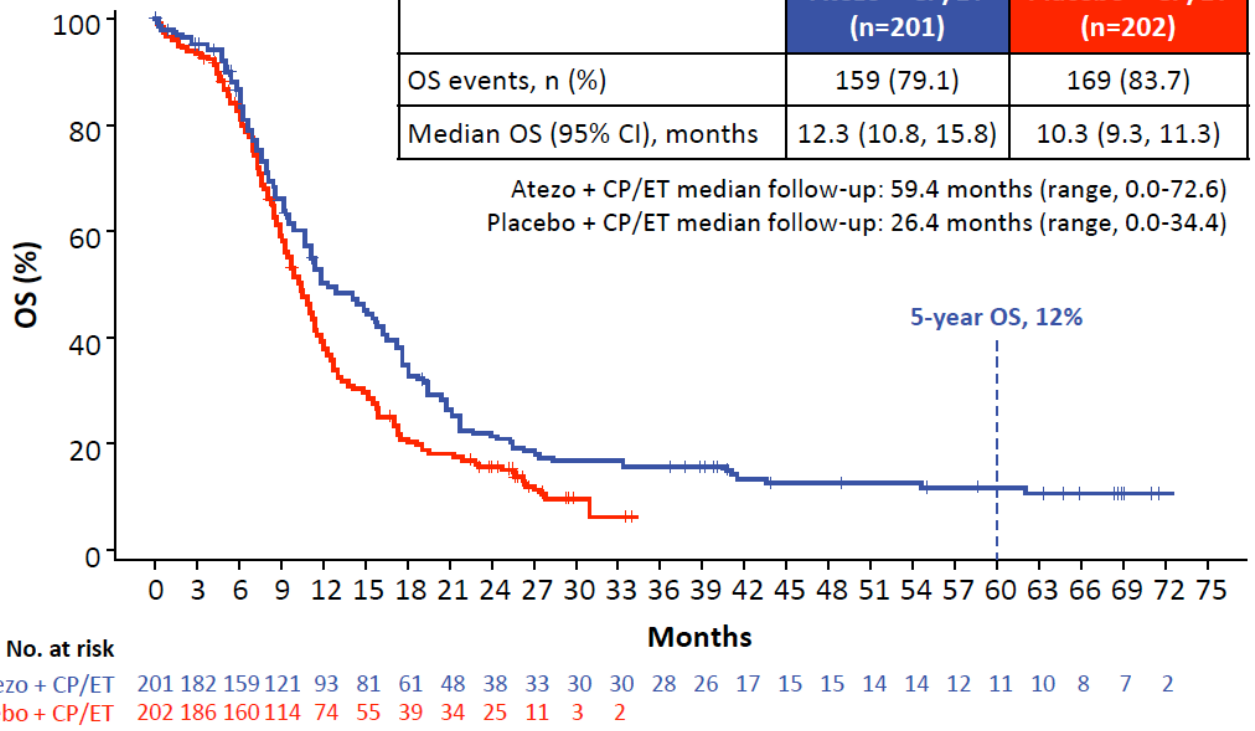


Atezolizumab, 1200 mg IV, Day 1; CP, AUC 5 mg/mL/min IV, Day 1; ET, 100 mg/m^2 IV, Days 1–3. CCOD, clinical cutoff date; LPLV, last patient, last visit. [a] IMbrella A (NCT03148418) allowed rollover from other Roche/Genentech-sponsored atezolizumab trials; only results from patients who rolled over from IMpower133 are reported. [b] Eight patients who were alive did not rollover to IMbrella A (censored). 1. Horn L, et al. N Engl J Med 2018;379:2220-92; 2. Liu SV, et al. J Clin Oncol 2021; 39:619-30.

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 (95% CI), months	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)

Atezo + CP/ET median follow-up: 59.4 months (range, 0.0-72.6)
Placebo + CP/ET median follow-up: 26.4 months (range, 0.0-34.4)



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

Conclusions

- First report of 5-year survival outcomes for patients who received first-line cancer immunotherapy with chemotherapy for ES-SCLC
- The OS data compare favorably with historical 5-year OS rates
- Long-term safety profile of atezolizumab + CP/ET in IMbrella A is encouraging
  - Late onset immune-mediated toxicities were rare and manageable
- Outcomes demonstrate the potential for durable survival benefit up to 5 years with atezolizumab + CP/ET
- What factors predict long term clinical benefit with immunotherapy?

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Phase I dose escalation trial of the DLL3/CD3 IgG-like T cell engager BI 764532 in patients with DLL3+ tumors: focus on SCLC and LCNEC

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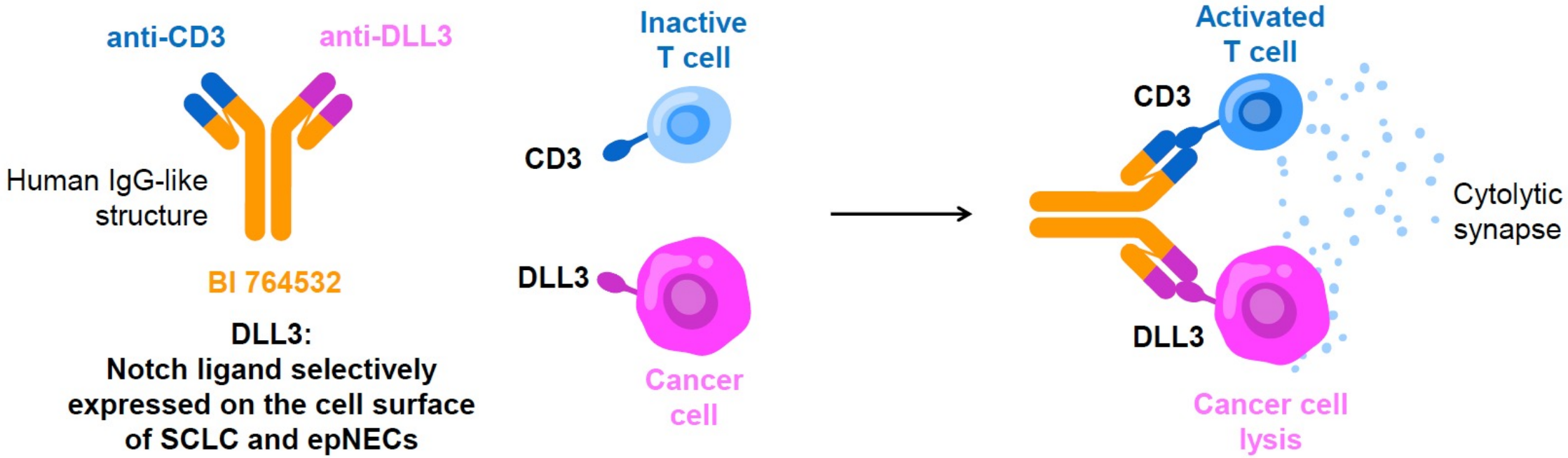
BI 764532: a novel DLL3-targeting T cell engager



- BI 764532 redirects the patient's own T cells to lyse DLL3-expressing cancer cells
- Potent preclinical antitumor activity against DLL3-positive cells and xenograft models[1]

Inclusion criteria and patient baseline characteristics

Key inclusion criteria

- Advanced SCLC, LCNEC, or epNEC
- DLL3-positive (archived tissue or in-study biopsy) according to central* review
- Failed/ineligible for available standard therapies (≥1 line of platinum-based chemotherapy)
- Adequate liver, bone marrow, and renal function
- ECOG PS 0/1

*Ventana DLL3 (SP347) assay at the Roche CDx CAP/CLIA laboratory

As of March 26 2023	N=107†
Median age, years (range)	60.0 (32–79)
Male, n (%)	61 (57)
Prior lines of therapy, n (%)	
1–2	72 (67)
≥3	33 (31)
ECOG PS 0/1, n (%)	28 (26)/78 (73)
Prior PD-1/PD-L1, n (%)	52 (49)
Brain/liver metastases, n (%)	41 (38)/60 (56)

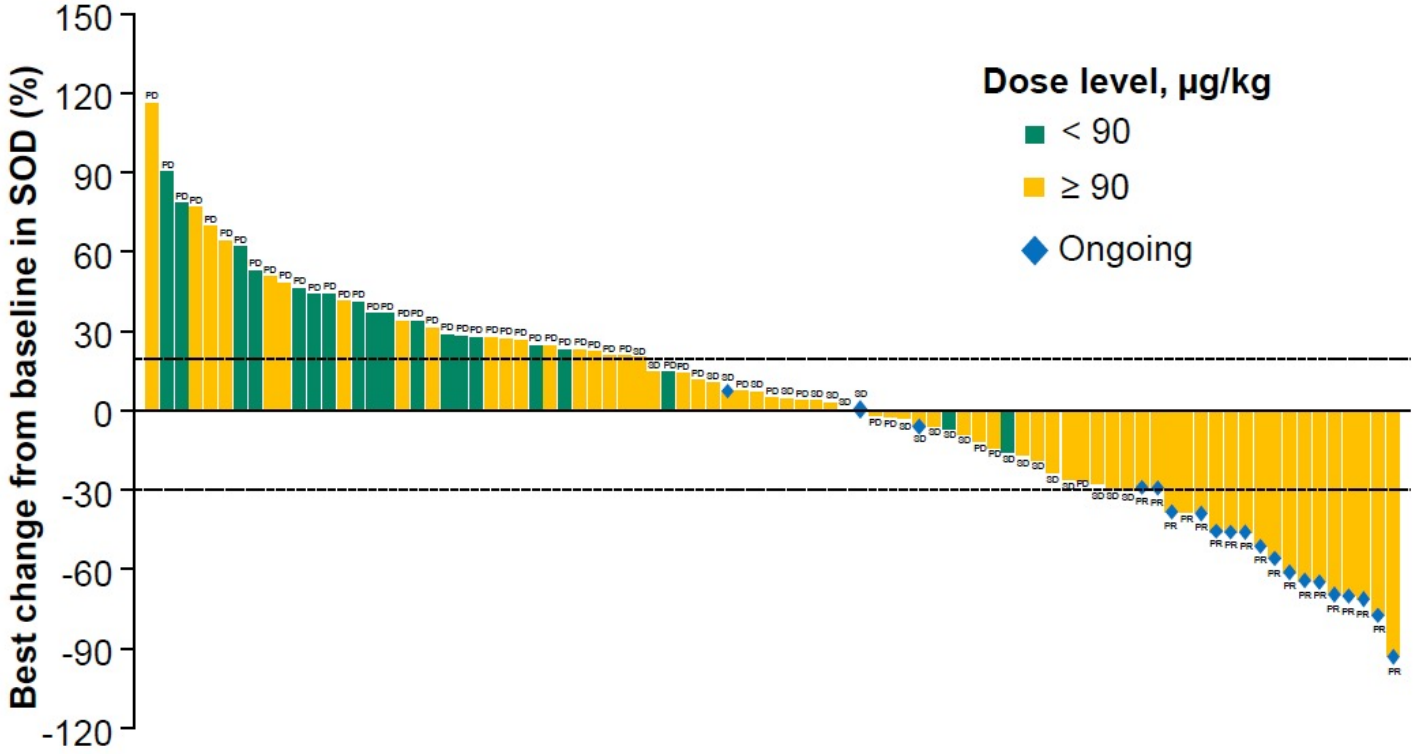
†Safety population: ≥1 dose of BI 764532

Most common all-cause AEs in pts with SCLC and LCNEC (>15% patients)

AE, n (%)	Patients (n=66)* All grade	Grade 1–2	Grade 3–5
Number of pts with ≥1 AE	**66 (100)**	**31 (47)**	**35 (53)**
CRS	32 (48)	31 (47)	1 (2)
Asthenia	21 (32)	19 (29)	2 (3)
Dysgeusia	18 (27)	18 (27)	0
Constipation	18 (27)	18 (27)	0
Lymphocyte count decreased	16 (24)	4 (6)	12 (18)
Nausea	15 (23)	14 (21)	1 (2)
Fatigue	13 (20)	12 (18)	1 (2)
Malignant neoplasm progression†	13 (20)	0	11 (17)
Decreased appetite	12 (18)	10 (15)	2 (3)
AST increased	12 (18)	11 (17)	1 (2)
Headache	12 (18)	12 (18)	0
Pyrexia	11 (17)	11 (17)	0

- **CRS managed with supportive care, corticosteroids, and/or anti-IL-6R antibodies**
- **Patients with AEs/TRAEs leading to discontinuation: 15 / 6%**

Overall efficacy (all patients)

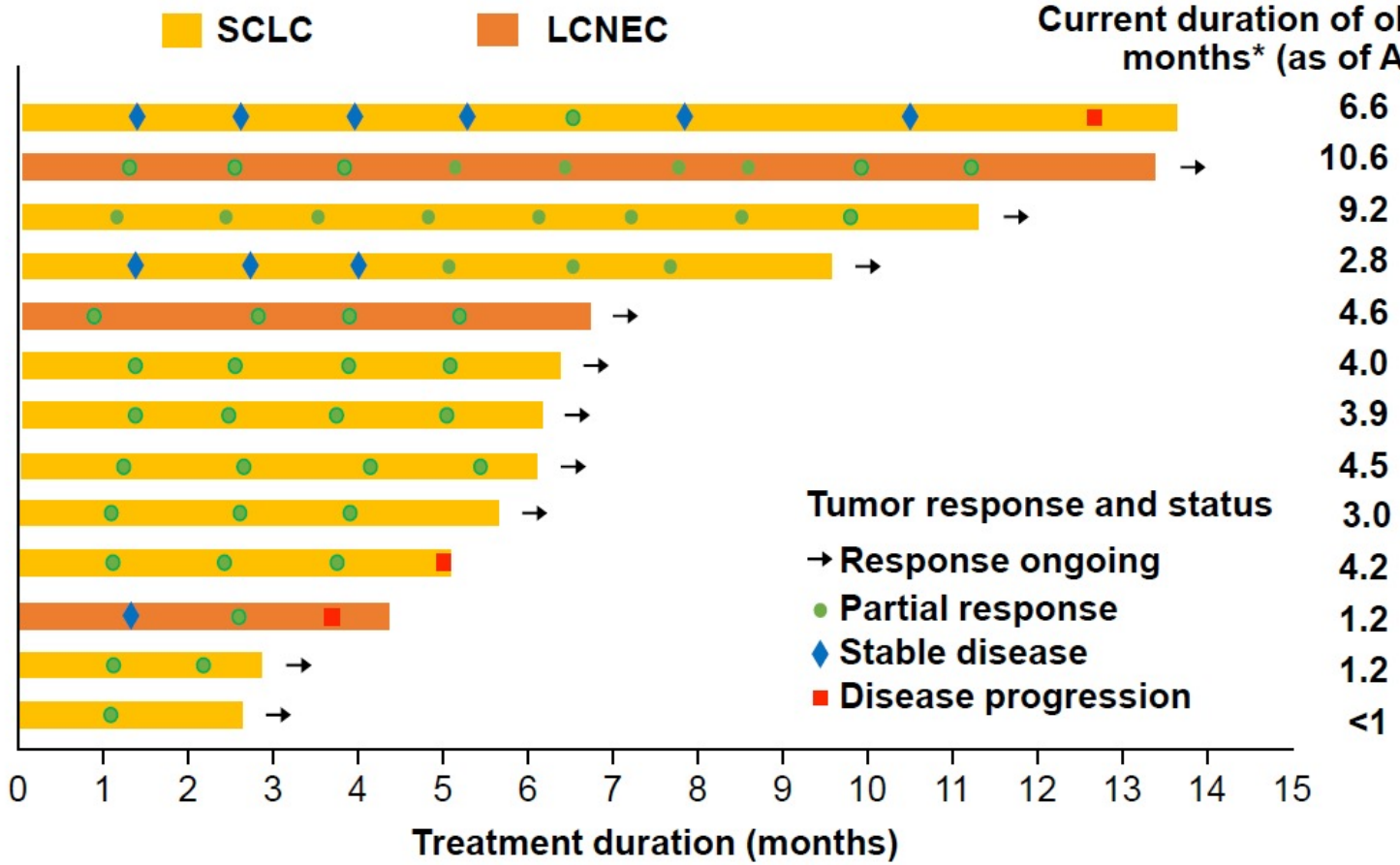


n, (%)	All tumors (n=99)*	SCLC (n=54)*	LCNEC (n=8)*
PR	18 (18)	10 (19)	3 (38)
SD	23 (23)	11 (20)	3 (38)
PD	45 (45)	23 (43)	2 (25)
DCR	41 (41)	21 (39)	6 (75)
NE†	13 (13)	10 (19)	0

*Efficacy population: ≥1 post-baseline tumor assessment or permanently discontinued prior to tumor assessment; responses evaluated per RECIST v1.1 criteria;
†Discontinued prior to tumor assessment

- **Efficacy, i.e. tumor shrinkage, observed at doses ≥ 90 µg/kg**

Response duration in patients with SCLC and LCNEC



- Responses are ongoing in 10/13 responders
- Although it is too early to assess median DoR, responses are ongoing in the majority of those who showed a response

Conclusions

- Safety profile of BI 764532 is acceptable and manageable at clinically efficacious dose levels in patients with SCLC and LCNEC
- CRS in 48% of patients with SCLC/LCNEC; mostly grade 1–2 and managed with standard supportive care
- Promising response rate in patients with SCLC/LCNEC (at doses ≥ 90 µg/kg): 26% and 60%
- Potential for durable responses
- Another promising DLL-3 targeting T-cell engager
  - Tarlatamab

Trials Targeting DLL3: Efficacy

	Topotecan	RovaT	Tarlatamab	HPN328
n	151 All 2nd line, Refractory excluded	287 53%	106 2nd line 28%, 3rd line 42%, ≥4th 30%	11 56% 2nd and 3rd lines
ORR DCR	21.9 % ND	14.3% 35.3%	24/106 (23%) (2 CR) 52%	27%
Median DOR	6.4 mo	3.5 mo	13 mo	ND
Median PFS	ND	3 mo	3.7 mo	ND
Median OS	8.7 mo	6.3 mo	13.2 mo	ND

Eckardt JR, et al. J Clin Oncol 2007 (topotecan); Blackhall F, J Thorac Oncol 2021 (RovaT); Borghaei H, et al. WCLC 2022 abstract OA12.05, Paz-Ares L, et al J Clin Oncol 2023 (tarlatamab); Johnson M, et al. ASCO 2022 abstract 8566 (HPN328)

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Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with refractory SCLC: a subgroup analysis of a phase 1/2 study

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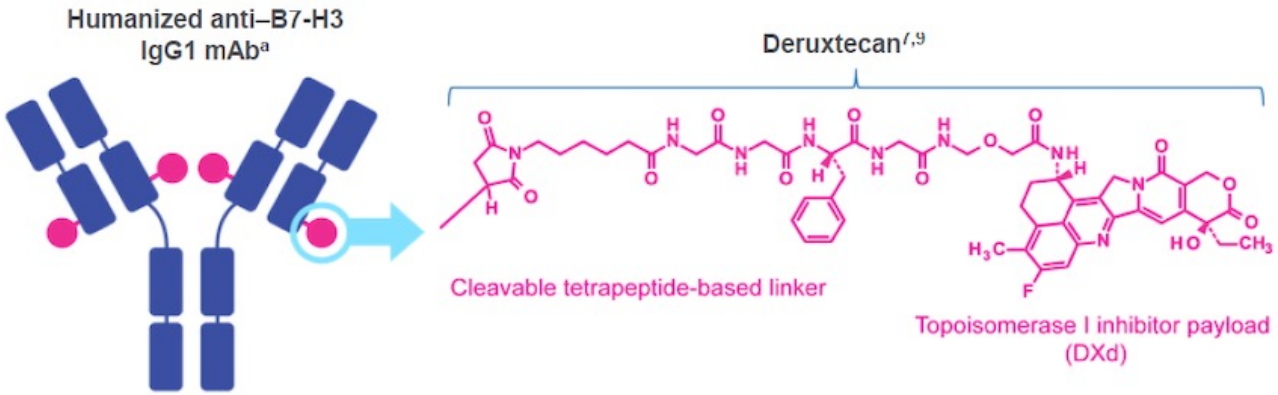
Ifinatamab Deruxtecan (I-DXd; DS-7300) Was Designed With 7 Key Attributes

- B7-H3 is overexpressed in a wide range of cancer types and is associated with disease progression and lower survival[1–5]
- I-DXd is a B7-H3 (CD276)-directed ADC composed of 3 parts:[6–9,11]
  - A humanized anti–B7-H3 IgG1 monoclonal antibody[9,11]
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[9,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[9,11,b,c]
Stable linker-payload[9,11,b]
Tumor-selective cleavable linker[9,11,b]
Bystander antitumor effect[7,10,11,b]

[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.
ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; CD276, cluster of differentiation 276; DXd, deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody.

1. Yamato M, et al. AACR-NCI-EORTC 2020. Abstract 28. 2. Dong P, et al. *Front Oncol*. 2018;8:264. 3. Picarda E, et al. *Clin Cancer Res*. 2016;22(14):3425–3431. 4. Bendell JC, et al. *J Clin Oncol*. 2020;39(15 suppl 1). Abstract TPS3646.
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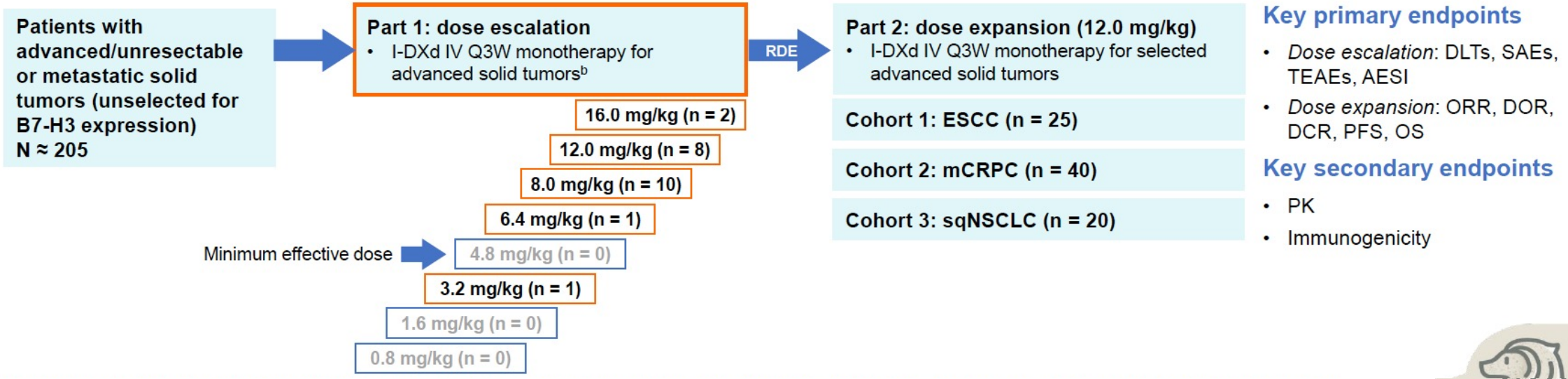
9. Yamato M, et al. *Mol Cancer Ther*. 2022;21(4):635–646.10. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039–1046. 11. Daiichi Sankyo. Data on file.

DS7300-A-J101 Study Design (NCT04145622)

- I-DXd is generally well tolerated with early signs of antitumor activity[1,2]
- **We present a subgroup analysis of patients with SCLC (N = 22[a]) from part 1 treated with I-DXd at all doses studied**
  - Patients dosed at ≥6.4 mg/kg (n = 21) were evaluable for efficacy
  - Baseline tumor biopsies were retrospectively examined for B7-H3 protein level by IHC and used for correlative analysis in biomarker-evaluable patients dosed at ≥6.4 mg/kg (n = 17)



Key primary endpoints

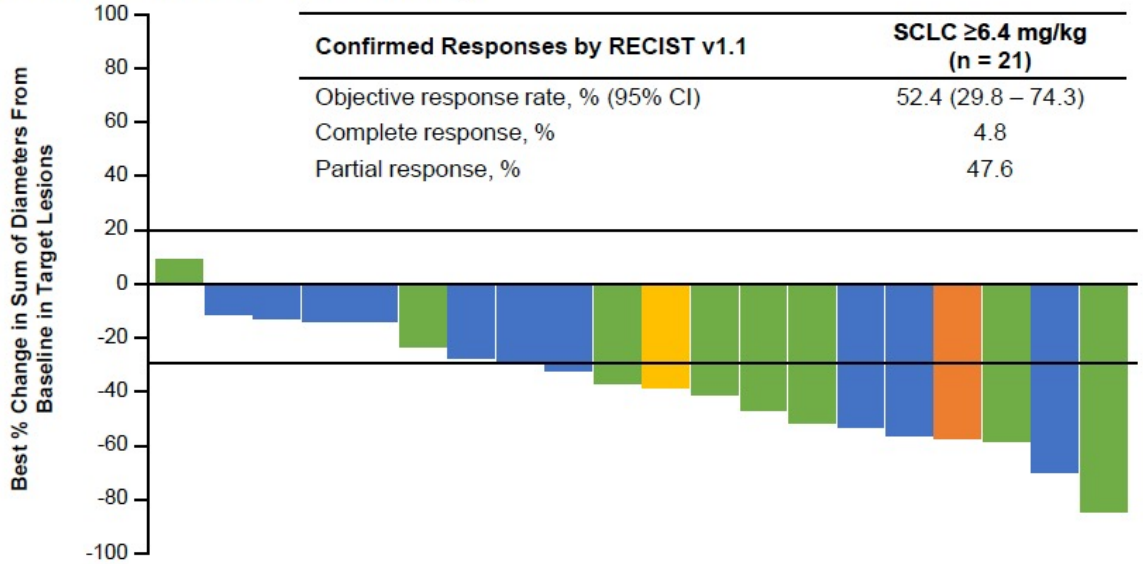
- *Dose escalation*: DLTs, SAEs, TEAEs, AESI
- *Dose expansion*: ORR, DOR, DCR, PFS, OS

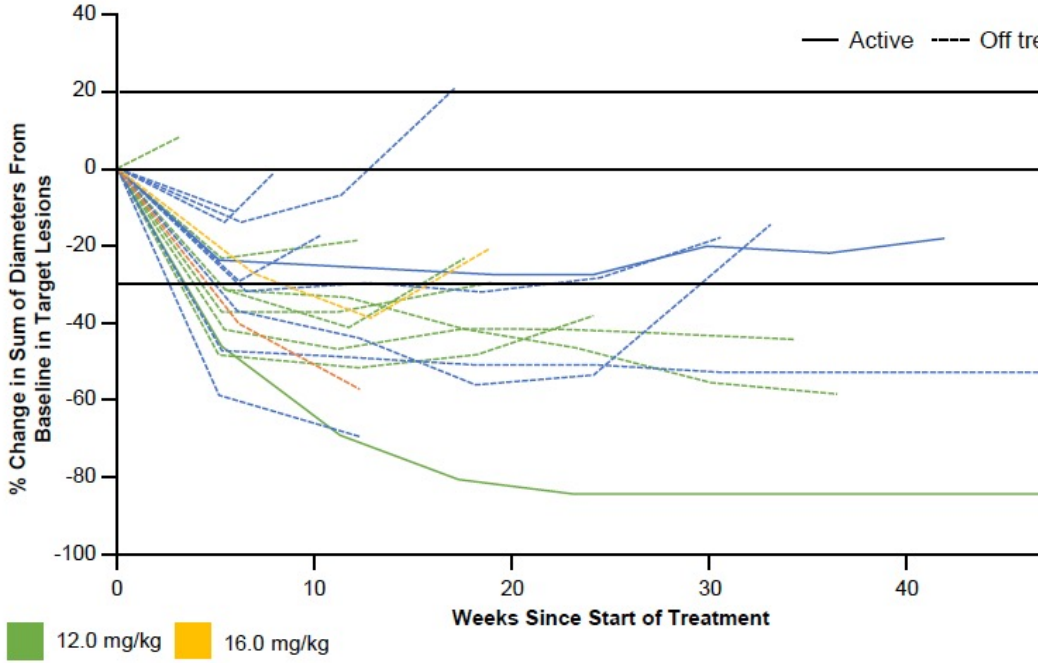
Key secondary endpoints

- PK
- Immunogenicity

Antitumor Activity[a]

Confirmed Responses by RECIST v1.1	SCLC ≥6.4 mg/kg (n = 21)
Objective response rate, % (95% CI)	52.4 (29.8 – 74.3)
Complete response, %	4.8
Partial response, %	47.6





Starting Dose Level: 6.4 mg/kg; 8.0 mg/kg; 12.0 mg/kg; 16.0 mg/kg

- Nearly all patients with post-baseline scans had a reduction in target lesions
- Median time to response was 1.2 months (95% CI, 1.2 – 1.4)
- Median duration of response was 5.9 months (95% CI, 2.8 – 7.5); two patients remain on treatment
- Median follow-up was 11.7 months (95% CI, 4.63 – 12.88)

Most Common (≥10%) All-Grade TEAEs Regardless of Causality

System Organ Class Preferred Term, n (%)	SCLC (N = 22)	
	Any Grade	Grade ≥3
Nausea	13 (59.1)	1 (4.5)
Fatigue	11 (50.0)	0 (0.0)
Anemia	6 (27.3)	1 (4.5)
Vomiting	6 (27.3)	0 (0.0)
Decreased appetite	5 (22.7)	1 (4.5)
Pyrexia	4 (18.2)	0 (0.0)
Constipation	4 (18.2)	1 (4.5)
IRR	3 (13.6)	0 (0.0)
Diarrhea	3 (13.6)	0 (0.0)
Dehydration	3 (13.6)	0 (0.0)
Dyspnea	3 (13.6)	0 (0.0)
Platelet count decreased	3 (13.6)	0 (0.0)
Arthralgia	3 (13.6)	0 (0.0)
Hyponatremia	3 (13.6)	0 (0.0)

- A total of three patients (13.6%) experienced an ILD or pneumonitis event (two Gr 1, one Gr 2)
  - All events were adjudicated by the ILD adjudication committee, of which one was adjudicated as drug-related ILD (Gr 2, 8.0 mg/kg) and discontinued treatment per protocol[a]
- Prophylactic premedication for nausea, vomiting, and IRR were not permitted for primary prophylaxis during cycle 1 of dose escalation

Conclusions

- I-DXd is a novel B7-H3–directed ADC that demonstrates robust and durable efficacy in patients with relapsed SCLC
- Generally well tolerated
- No apparent trend of correlation was observed between B7-H3 level and clinical efficacy parameters in the SCLC cohort
- Data support further clinical development of I-DXd, including a phase 2 study of patients with ES-SCLC following 1-3 prior lines of therapy (ongoing IDeate-1; NCT05280470)
- How will this ADC compare to others being evaluated in relapsed SCLC?

Other ADCs in SCLC

- IMMU-132 (Sacituzumab govitecan)
  - Anti-TROP-2 antibody linked with SN-38 (active metabolite of irinotecan)
  - TROP-2 high expression in 18% of high-grade NE tumors (incl 10% SCLC)
    - Associated with lower lung cancer-specific survival
  - 53 patients: 60% pts showed tumor shrinkage from baseline, ORR 14%
    - DOR 5.7 mos, PFS 3.7 mos, OS 7.5 mos, CBR 34%
  - TROPiCS-03 ongoing phase II trial

- ABBV-011
  - Seizure-related homolog protein (SEZ6)-targeting ADC, expressed in majority of SCLC
  - 98 patients: ORR=19%, CBR=69% (ORR=25% in SEZ6-positive patients)
  - ABBV-706 is next generation SEZ6-targeting ADC, phase I study underway

Overall Conclusions

- First line standard of care for ES-SCLC pts remains platinum/etoposide + PD-L1 inhibitor
  - Increased rate of 5-year responders with immunotherapy
  - Potential for improved efficacy with addition of antivascular agents
- Novel and emerging agents in relapsed SCLC patients
  - DLL-3 targeting T-cell engagers (BI 764532, Tarlatamab)
  - ADCs (I-Dxd, Sacituzumab govitecan, ABBV-011)