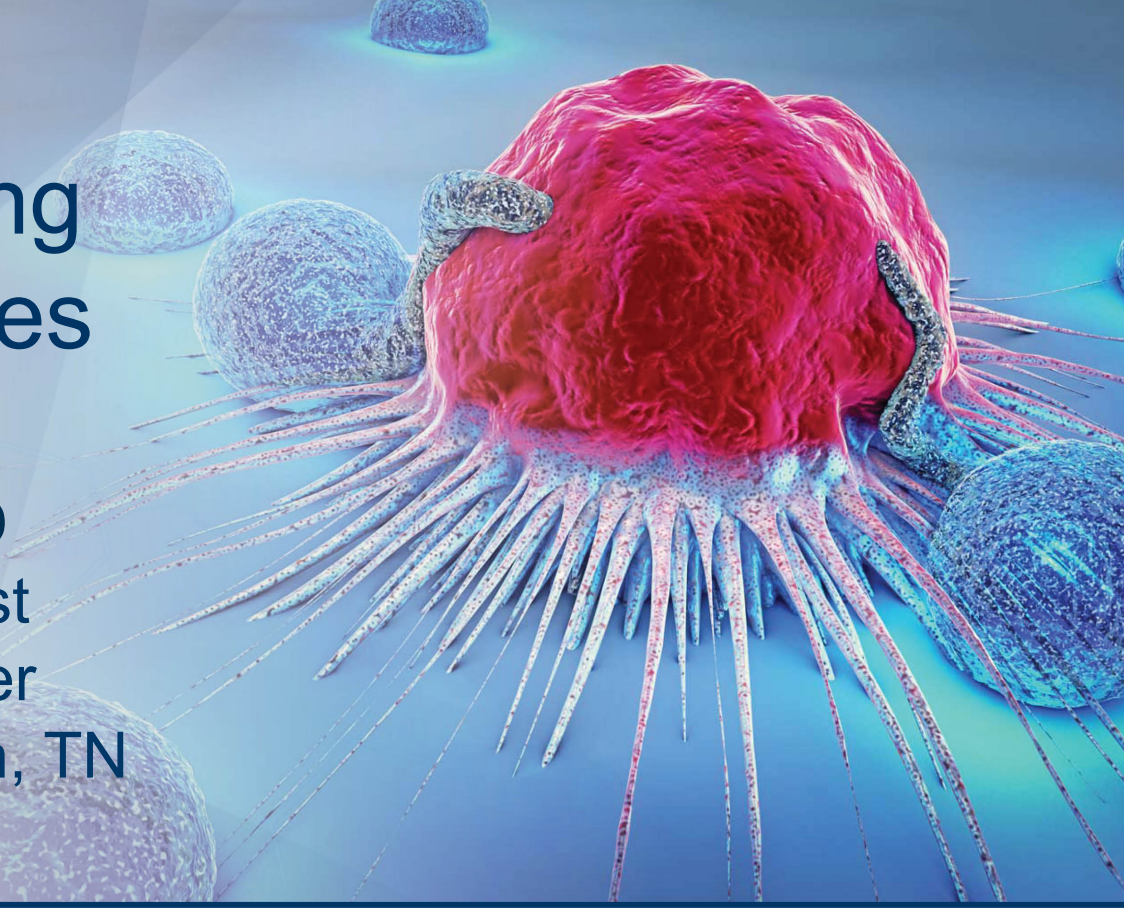
Small Cell Lung Cancer Updates



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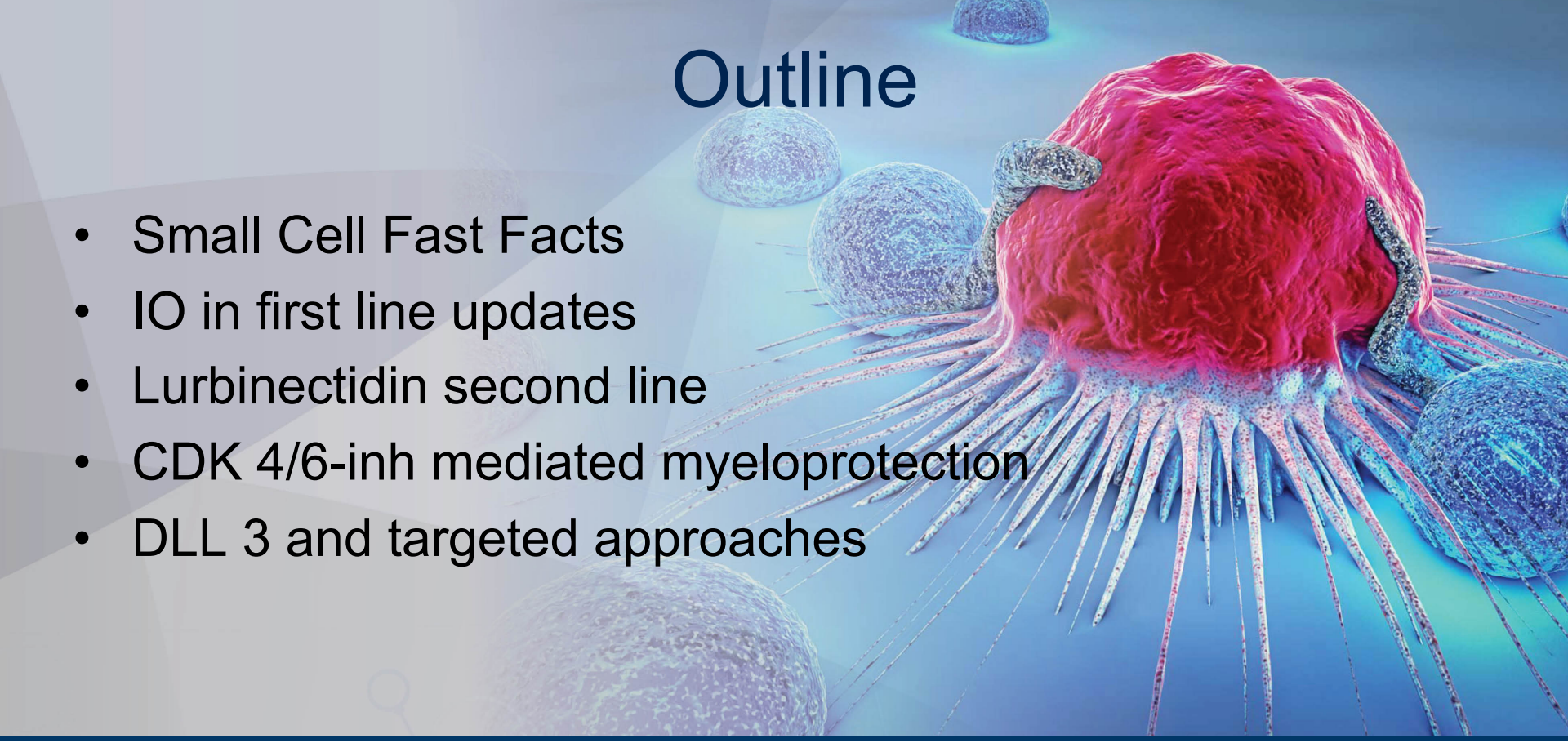
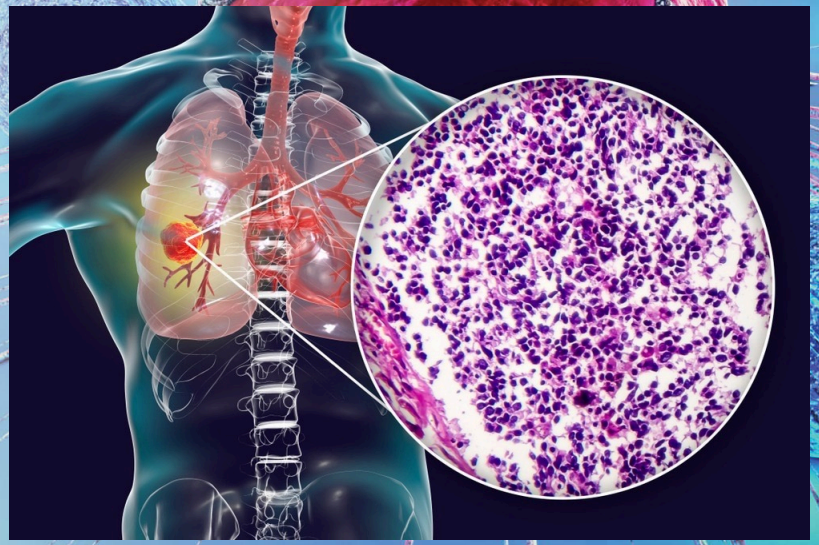
Memphis/Germantown, TN

Outline

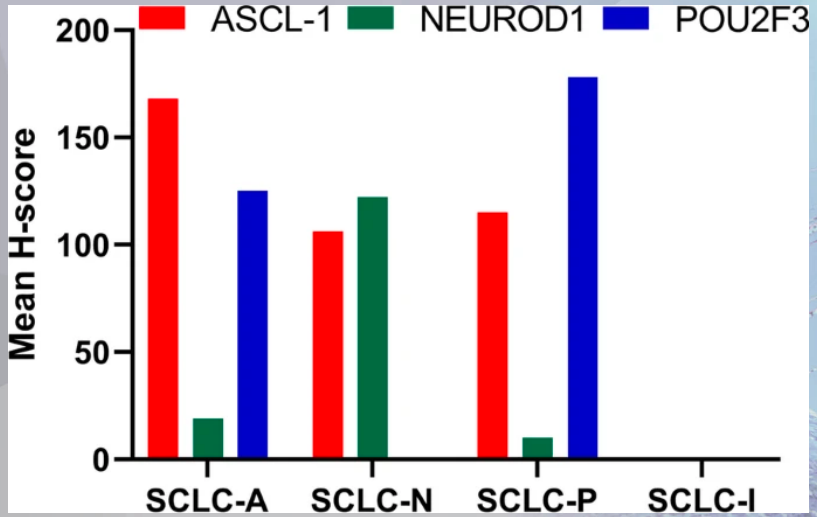
- Small Cell Fast Facts
- IO in first line updates
- Lurbinectidin second line
- CDK 4/6-inh mediated myeloprotection
- DLL 3 and targeted approaches

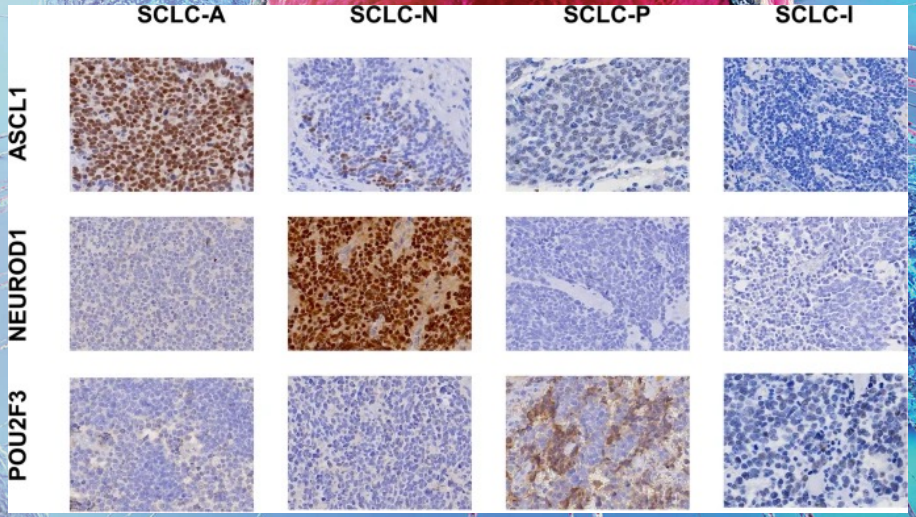


- Aggressive NE tumor originating from type II alveolar cells
- ~12-15% of lung cancers
- High proliferation rate
- Early metastases
- High morbidity & mortalilty
- High unmet need for new tx’s



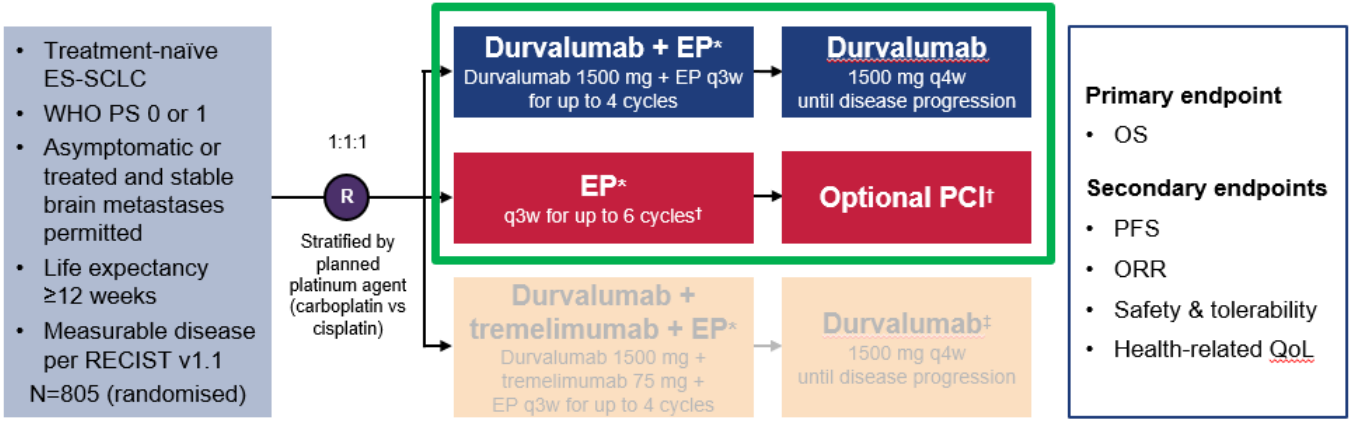
Sub-typing: Prognostics and Therapeutics





CASPIAN Study Design

Phase 3, global, randomised, open-label, sponsor-blind multicentre study

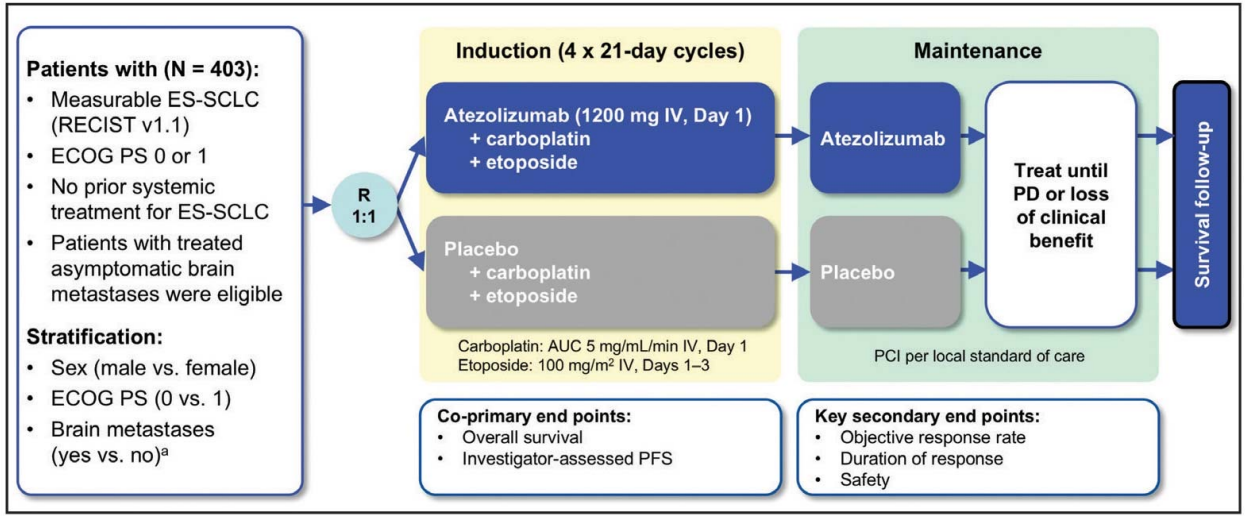


The durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

*EP consists of etoposide 80–100 mg/m² with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m²
†Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion
‡Patients received an additional dose of tremelimumab post-EP

AUC, area under the curve; ORR, objective response rate; PCI, prophylactic cranial irradiation; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; WHO, World Health Organization

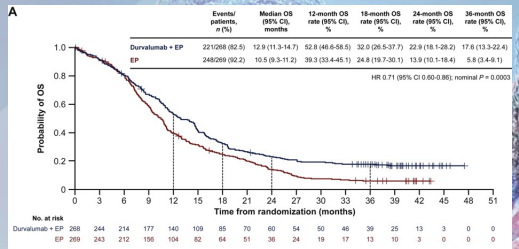
Fig. 1. Study Design of IMpower133



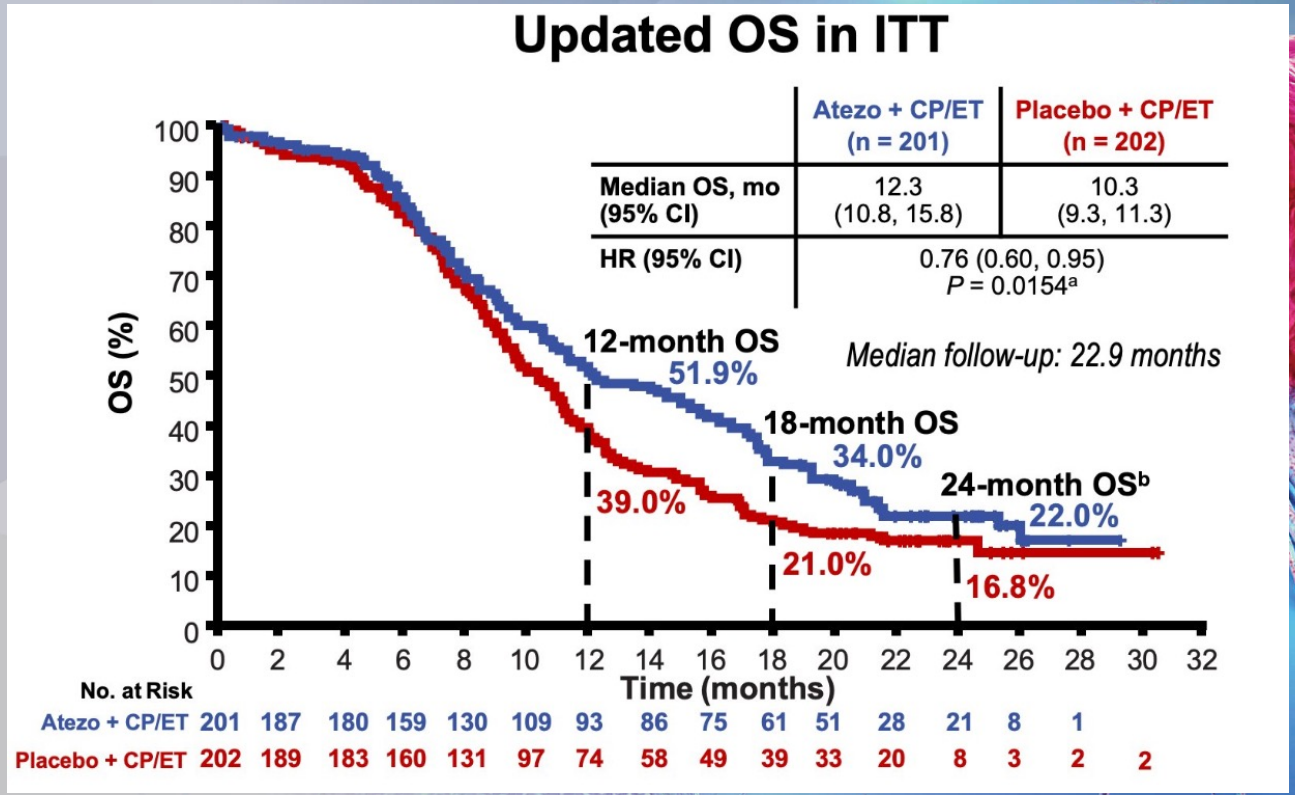
[a]Only patients with treated brain metastases were eligible.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

CASPIAN: updated OS data

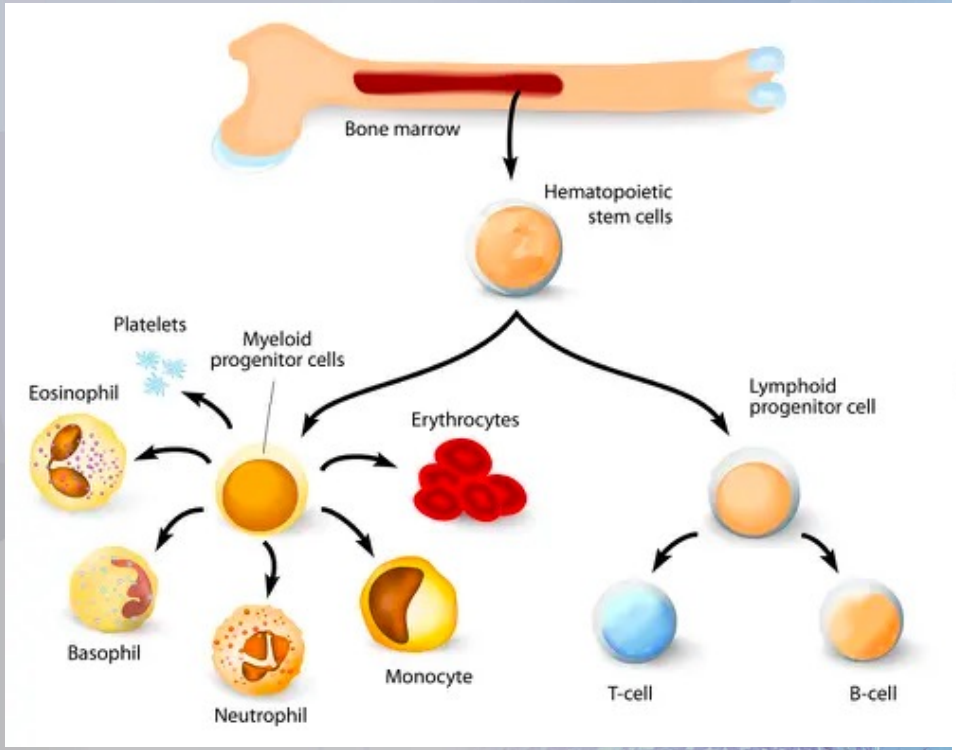


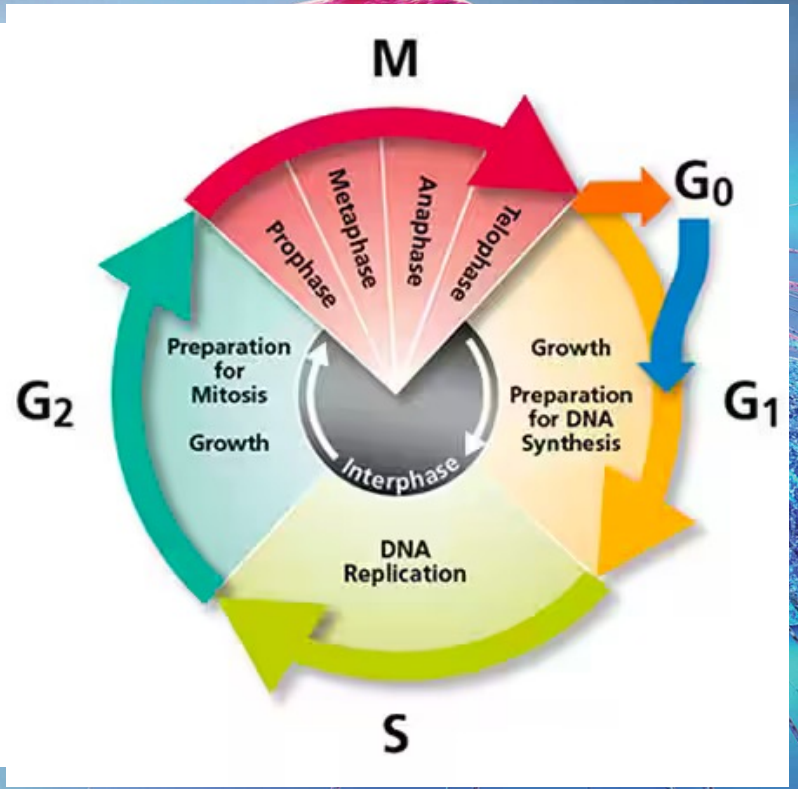
Updated OS in ITT



Primary Toxicity in ES-SCLC Treatment: Myelosuppression

	Atezolizumab (n = 198)			Placebo (n = 196)		
	Grade 1/2	Grade 3/4	Grade 5	Grade 1/2	Grade 3/4	Grade 5
Any AE	73 (36.9)	112 (56.6)	3 (1.5)	68 (34.7)	110 (56.1)	3 (1.5)
AE with incidence ≥10% or ≥2% incidence of grade 3/4 in either group						
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0
Alopecia	69 (34.8)	0	0	66 (33.7)	0	0
Nausea	62 (31.3)	1 (0.5)	0	58 (29.6)	1 (0.5)	0
Fatigue	39 (19.7)	3 (1.5)	0	37 (18.9)	1 (0.5)	0
Decreased neutrophil count	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Decreased appetite	39 (19.7)	2 (1.0)	0	26 (13.3)	0	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Decreased platelet count	17 (8.6)	7 (3.5)	0	21 (10.7)	7 (3.6)	0
Vomiting	25 (12.6)	2 (1.0)	0	19 (9.7)	3 (1.5)	0
Constipation	19 (9.6)	1 (0.5)	0	25 (12.8)	0	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
Decreased white-cell count	10 (5.1)	6 (3.0)	0	16 (8.2)	9 (4.6)	0
Diarrhea	15 (7.6)	4 (2.0)	0	18 (9.2)	1 (0.5)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0
Infusion-related reaction	6 (3.0)	4 (2.0)	0	9 (4.6)	1 (0.5)	0


Bone marrow
Hematopoietic stem cells
Platelets
Myeloid progenitor cells
Eosinophil
Erythrocytes
Lymphoid progenitor cell
Basophil
Neutrophil
Monocyte
T-cell
B-cell


M
G0
G1
S
G2
Prophase
Metaphase
Anaphase
Telophase
Interphase
Preparation for Mitosis
Growth
Growth
Preparation for DNA Synthesis
DNA Replication

1L ES-SCLC: TRILACICLIB ADMINISTERED PRIOR TO E/P

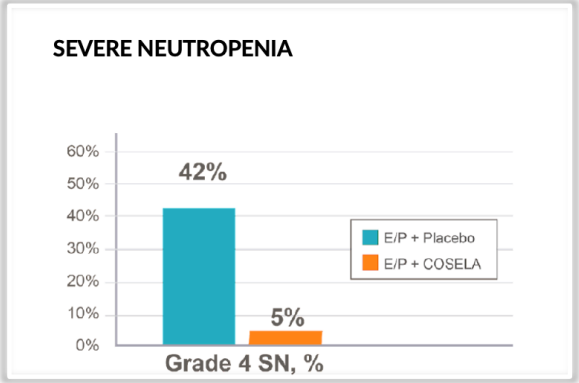
Newly diagnosed ES-SCLC

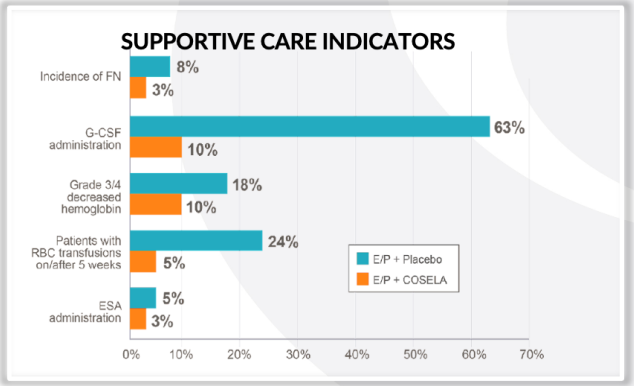
DAY 1

All patients received **carboplatin (AUC 5**

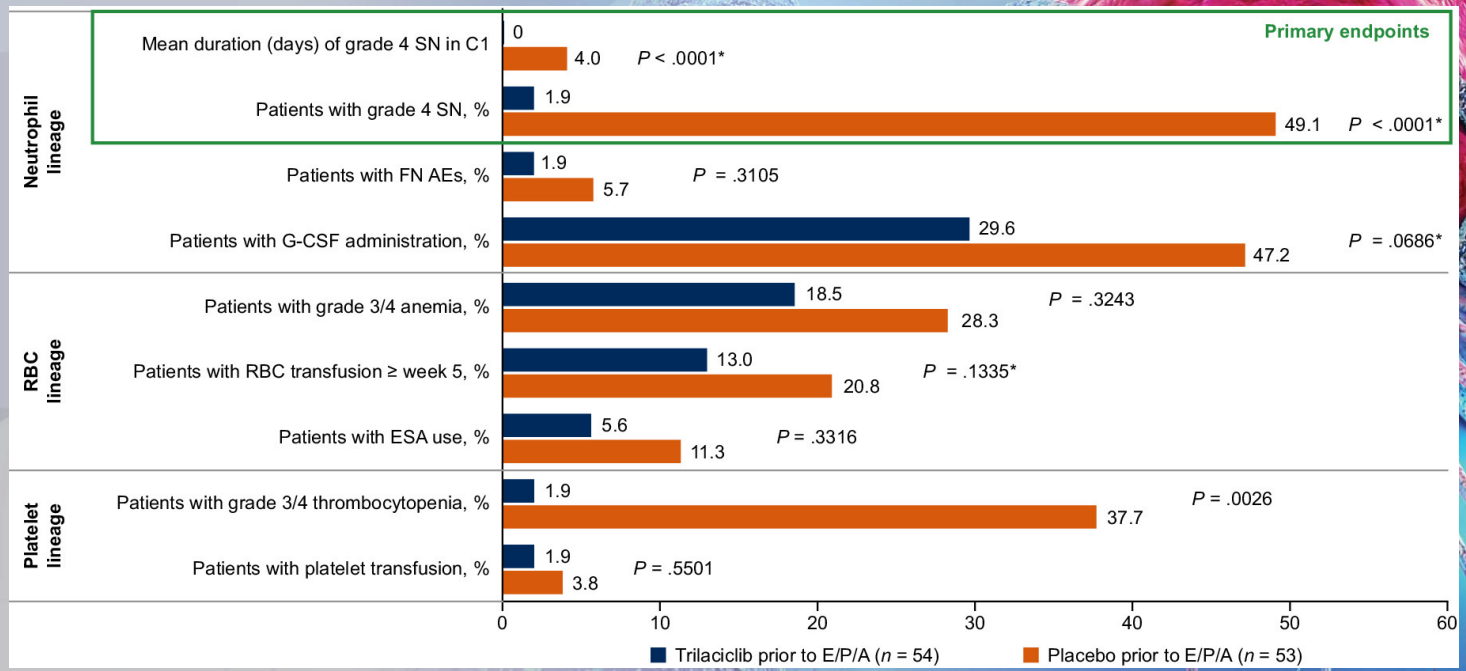
DAYS 1–3

All patients received **etoposide 100 mg/m²** and **trilaciclib 240 mg/m²** OR **placebo**

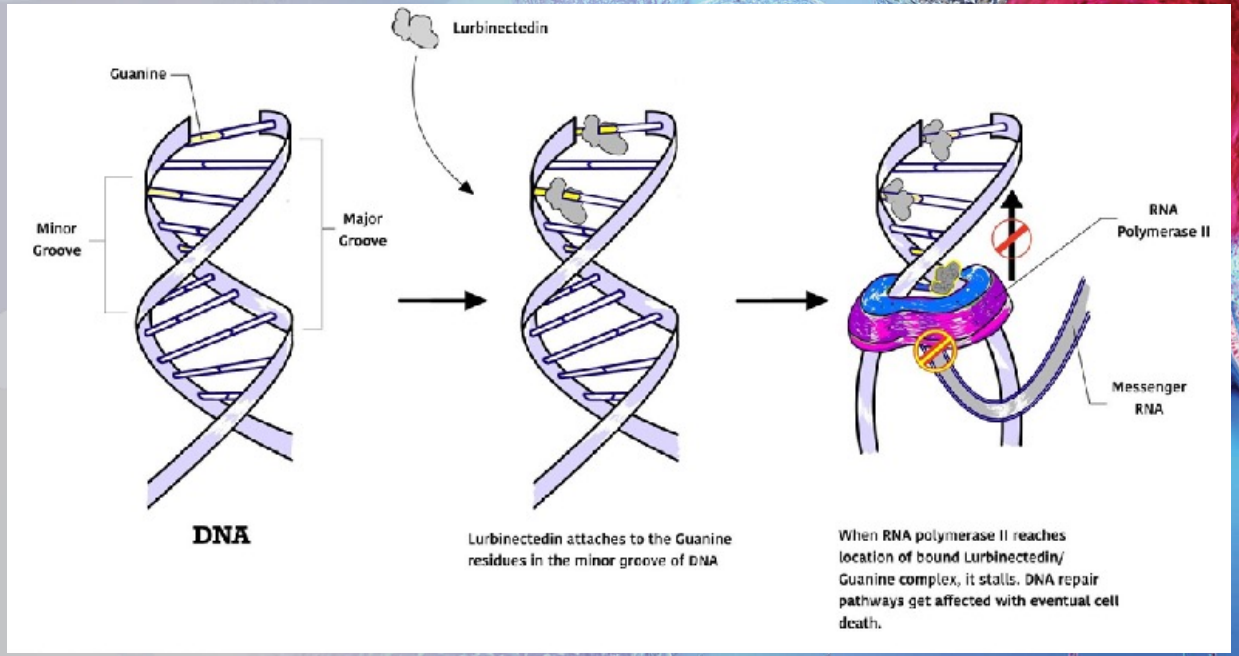




Daniel D, et al. *Int J Cancer*. 2020

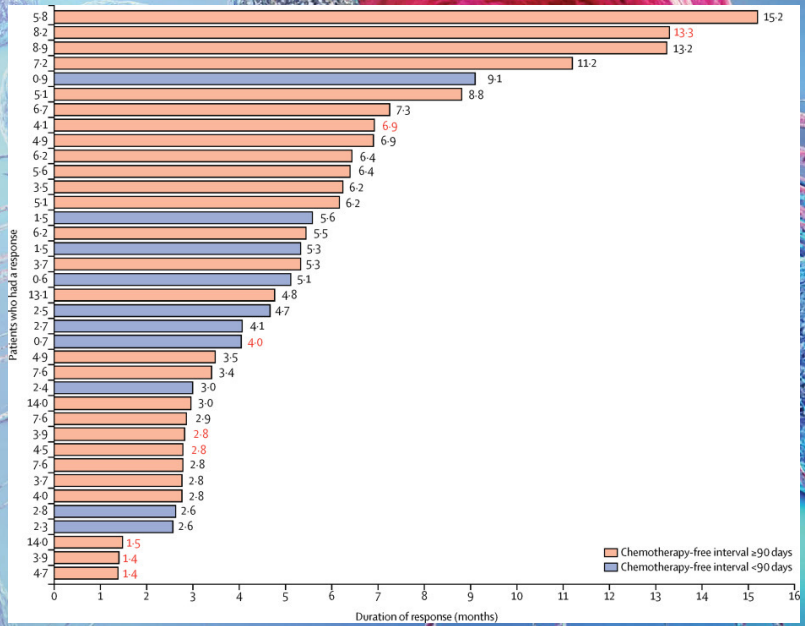

Neutrophil lineage
RBC lineage
Platelet lineage
Primary endpoints
Mean duration (days) of grade 4 SN in C1
0
4.0
P < .0001*
Patients with grade 4 SN, %
1.9
49.1
P < .0001*
Patients with FN AEs, %
1.9
5.7
P = .3105
Patients with G-CSF administration, %
29.6
47.2
P = .0686*
Patients with grade 3/4 anemia, %
18.5
28.3
P = .3243
Patients with RBC transfusion ≥ week 5, %
13.0
20.8
P = .1335*
Patients with ESA use, %
5.6
11.3
P = .3316
Patients with grade 3/4 thrombocytopenia, %
1.9
37.7
P = .0026
Patients with platelet transfusion, %
1.9
3.8
P = .5501
0
10
20
30
40
50
60
Trilaciclib prior to E/P/A (n = 54)
Placebo prior to E/P/A (n = 53)

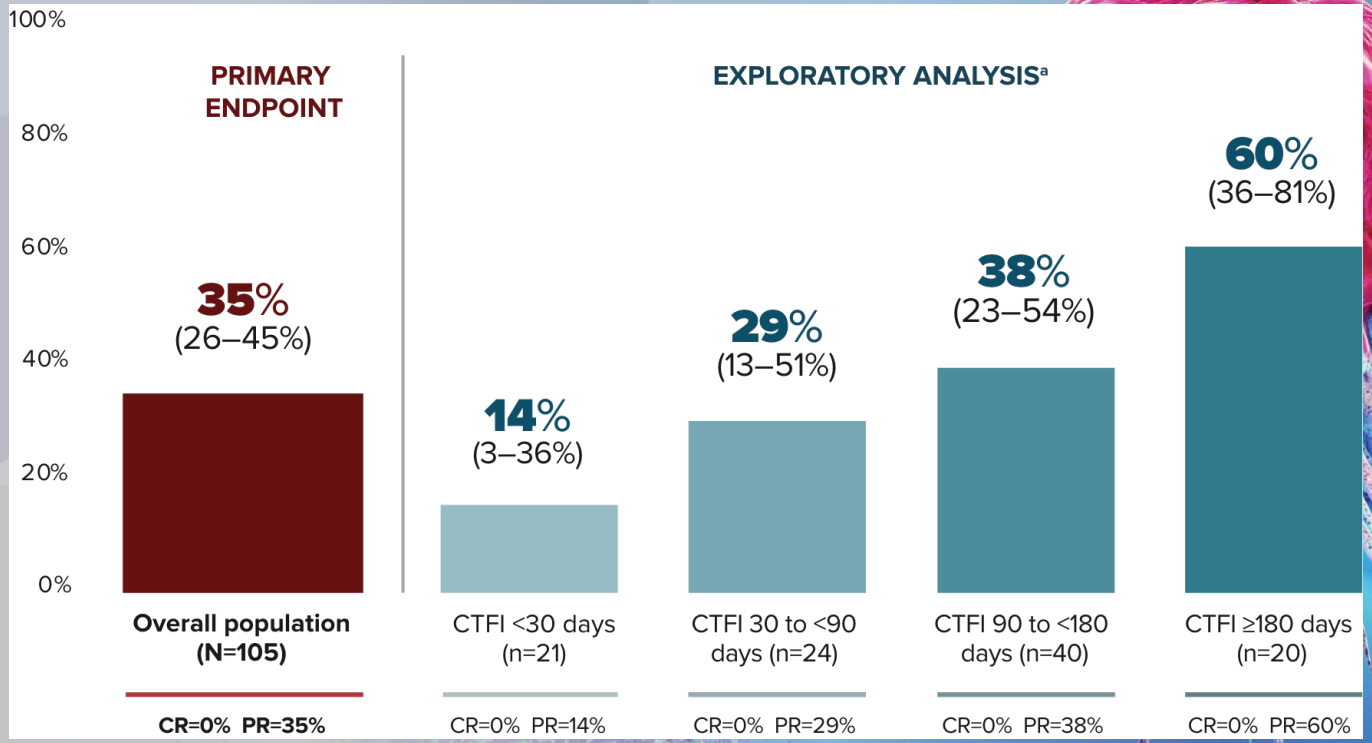
Lurbinectin in Relapsed Small Cell



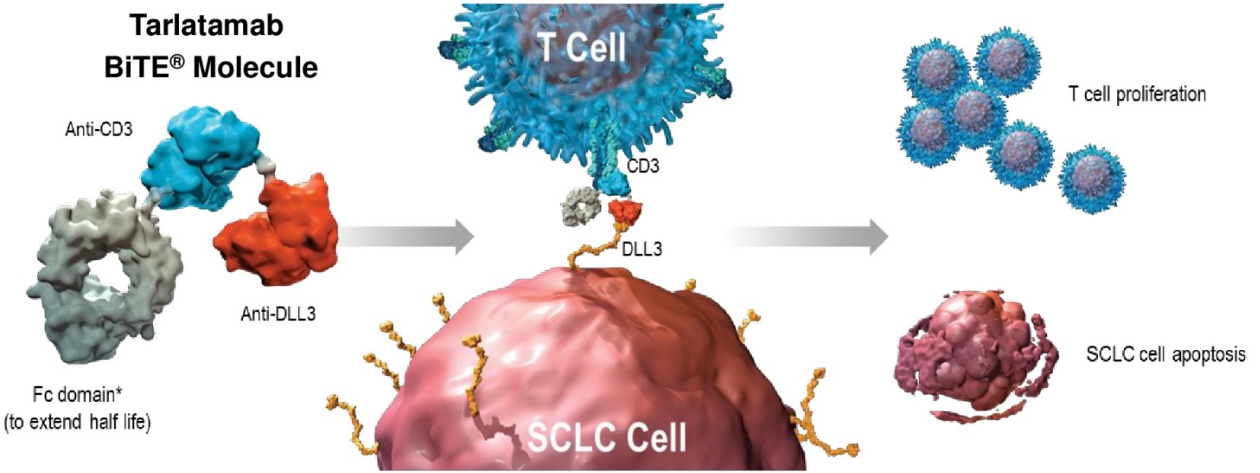
Lurbinectidin Efficacy

- Single-arm, open-label, phase 2 basket trial
- Overall response by investigator assessment was seen in 37 patients (35·2%; 95% CI 26·2–45·2)




100%
80%
60%
40%
20%
0%
PRIMARY ENDPOINT
EXPLORATORY ANALYSIS[a]
35% (26–45%)
14% (3–36%)
29% (13–51%)
38% (23–54%)
60% (36–81%)
Overall population (N=105)
CTFI <30 days (n=21)
CTFI 30 to <90 days (n=24)
CTFI 90 to <180 days (n=40)
CTFI ≥180 days (n=20)
CR=0% PR=35%
CR=0% PR=14%
CR=0% PR=29%
CR=0% PR=38%
CR=0% PR=60%

- Small cell lung cancer (SCLC) is an aggressive neuroendocrine tumor with poor prognosis and limited treatment options[1,2]
- Delta-like ligand 3 (DLL3) is a Notch ligand aberrantly expressed on the surface of up to 85% of SCLC cells but rarely expressed on normal tissues[3,4]
- Tarlatamab is a half-life extended BiTE® (bispecific T cell engager) molecule designed to bind DLL3 on SCLC cells and CD3 on T cells, leading to T-cell mediated tumor lysis[5]
- DeLLphi-304 is a randomized, open-label, phase 3 study to evaluate the efficacy and safety of tarlatamab compared with standard of care (SOC) in patients with relapsed SCLC after platinum-based first-line chemotherapy



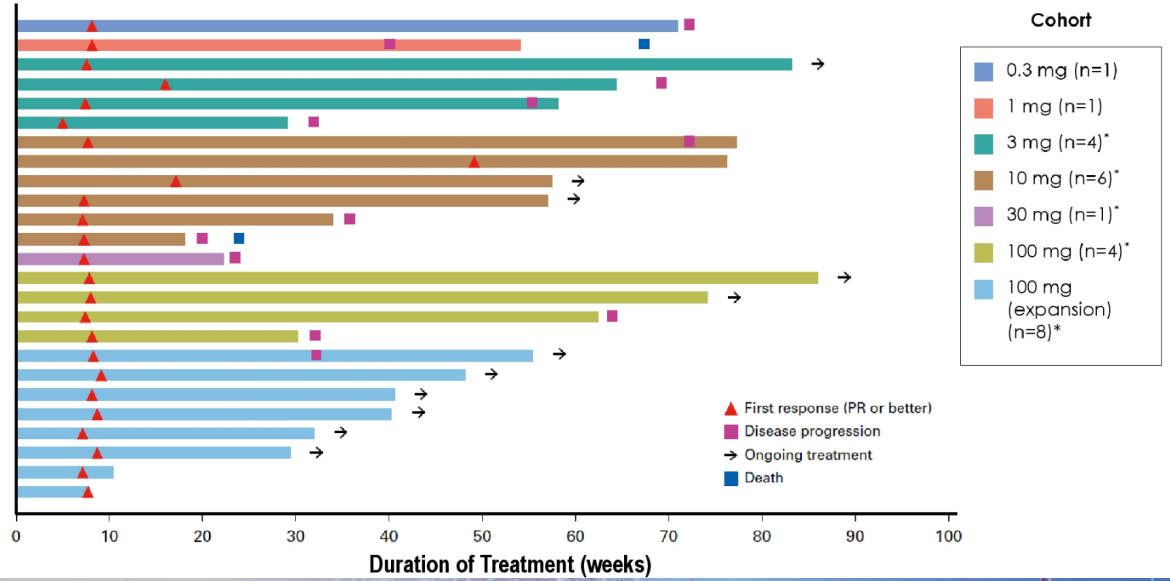
*Effector-functionless Fc domain; CD3, cluster of differentiation 3; DLL3, delta-like ligand 3; Fc, fragment crystallizable; SCLC, small cell lung cancer.

1. Sabari JK, 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.

Tarlatamab in Relapsed/Refractory SCLC

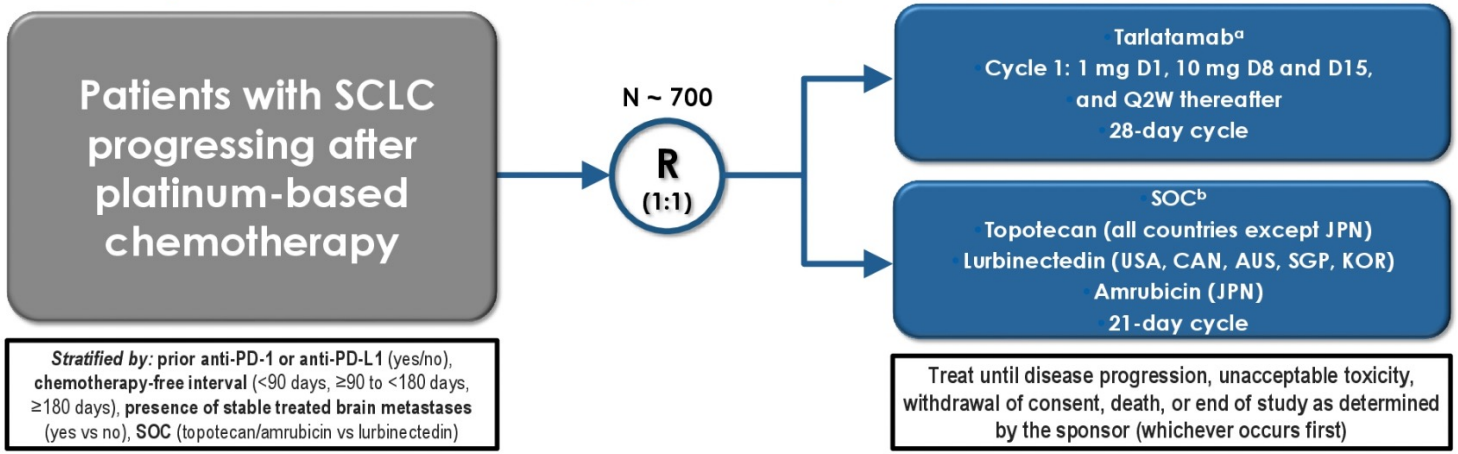
Phase 1 dose exploration/expansion study (NCT03319940) demonstrated antitumor activity with durable responses and a manageable safety profile in patients with relapsed/refractory SCLC

Time to and Duration of Response Among Confirmed Responders



Study Design

Phase 3, open-label, randomized, multi-center study evaluating efficacy and safety of tarlatamab compared with SOC in patients with SCLC who have progressed after 1 prior line of platinum-based chemotherapy



Pre- and post-infusion medication requirements include dexamethasone administered within 1 hour prior to cycle 1 tarlatamab infusion on D1 and D8 and IV hydration following cycle 1 tarlatamab doses on D1, D8, and D15

[a]Tarlatamab will be administered as a 60-minute IV infusion

[b]Standard of care (21-day cycle): Lurbinectedin (USA, Canada, Australia, Singapore, and Korea) will be administered as 3.2 mg/m^2 IV on day 1 every 3 weeks. Topotecan (all countries, except Japan and China) will be administered as IV at 1.5 mg/m^2 or oral at 2.3 mg/m^2/day on days 1, 2, 3, 4, and 5 every 3 weeks. Topotecan (China) will be administered as IV at 1.25 mg/m^2 or oral at 2.3 mg/m^2/day on days 1, 2, 3, 4, and 5 every 3 weeks. Amrubicin (Japan) will be administered as 40 mg/m^2 IV on days 1 to 3 every 3 weeks.

PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SCLC, small cell lung cancer; SOC, standard of care.

Primary Endpoint:

- OS

Key Secondary Endpoints:

- PFS
- PRO (disease-related symptoms, physical function, global health status of QOL)

Secondary Endpoints*:

- ORR, DCR, DOR, Pharmacokinetics, TEAEs

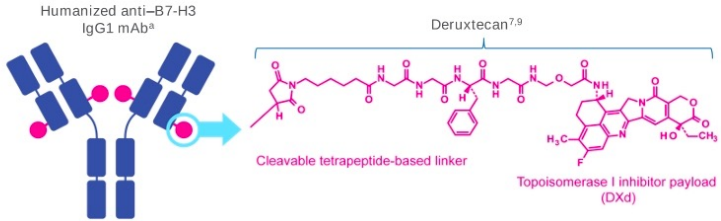
Exploratory Endpoints:

- Quantification of relevant SCLC biomarker expression

- Phase 1 study (DeLLphi-300) of tarlatamab demonstrated manageable safety with encouraging response durability in heavily pretreated patients with relapsed/refractory SCLC
- The encouraging safety and efficacy findings from DeLLphi-300 is being further evaluated in a phase 2 open-label study (DeLLphi-301; NCT05060016) in patients with relapsed/refractory SCLC after ≥2 lines of prior treatment
- DeLLphi-304 (NCT05740566) is a randomized, open-label, phase 3 study of tarlatamab compared with standard of care (SOC) in ~700 patients with relapsed SCLC after platinum-based first-line chemotherapy that is actively recruiting study participants

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



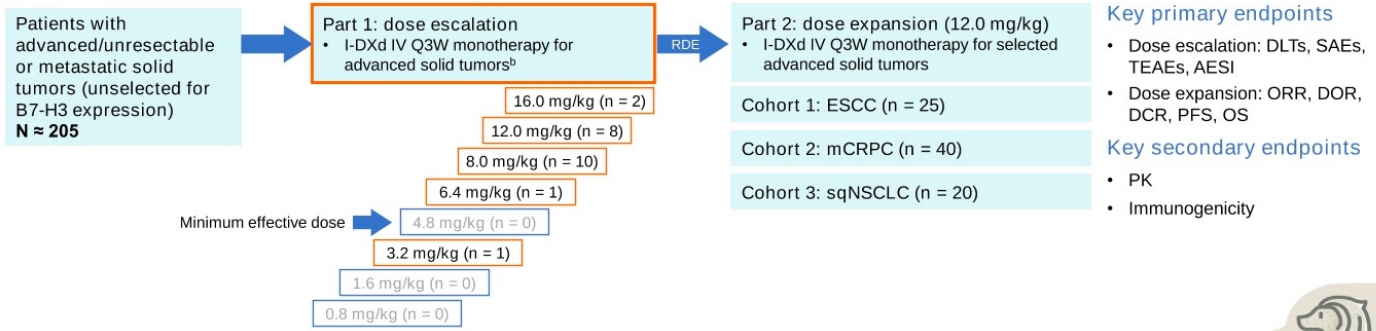
Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[9,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[9,11,b,c]
Stable linker-payload[9,11,b]
Tumor-selective cleavable linker[9,11,b]
Bystander antitumor effect[7,10,11,b]

[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.
5. Kontos F, et al. Clin Cancer Res. 2021;27(5):1227–1235. 6. Okajima D, et al. Mol Cancer Ther. 2021;20(12):2329–2340. 7. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173–185. 8. Ogitani Y, et al. Clin Cancer Res. 2016;22(20):5097–5108.
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)



[a]Number of patients with SCLC in parentheses of each dose cohort. [b]Tumor types included advanced/unresectable or metastatic HNSCC, ESCC, mCRPC, sqNSCLC, SCLC, bladder cancer, sarcoma, endometrial cancer, melanoma, and breast cancer.
AESI, adverse event of special interest; B7-H3, B7 homolog 3; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ESCC, esophageal squamous cell carcinoma; IHC, immunohistochemistry; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RDE, recommended dose for expansion; SAE, serious adverse event;; SCLC, small cell lung cancer; sqNSCLC, squamous non-small cell lung cancer; TEAE, treatment-emergent adverse event.
1. Johnson ML, et al. ESMO. 2021. Abstract 513O. 2. Doi T, et al. ESMO. 2022. Abstract 453O.

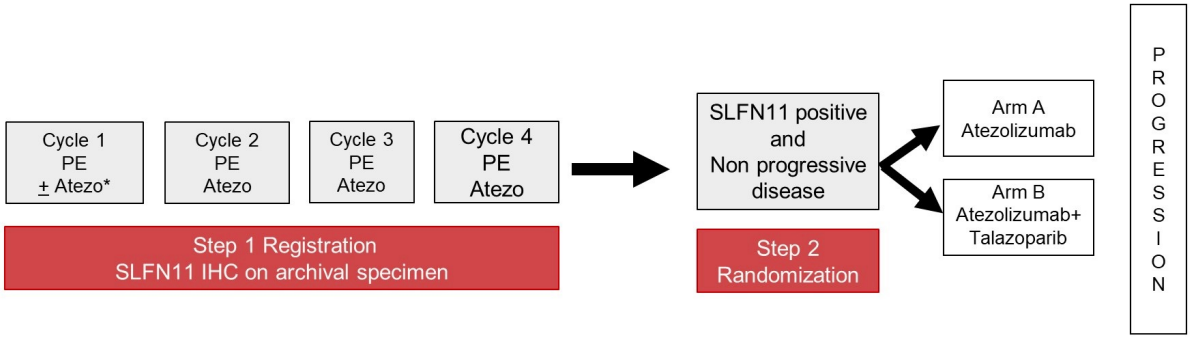
Conclusions

- I-DXd, a novel B7-H3–directed DXd-ADC, continues to demonstrate robust and durable efficacy in patients with heavily pretreated SCLC
  - Including 52% ORR, 5.9 months mDOR, 5.6 months mPFS, and 12.2 months mOS
- I-DXd was generally well tolerated; no new safety signals were observed, and the safety profile was consistent with previous reports[1,2]
  - Nausea was the most common TEAE, and antiemetic prophylaxis is now required for all I-DXd studies
- No apparent trend of correlation was observed between B7-H3 level and clinical efficacy parameters in the SCLC cohort
- These data support further clinical development of I-DXd, including a phase 2 study of patients with extensive stage SCLC following 1 – 3 prior lines of therapy (IDeate-1; NCT05280470)
  - TiP Poster #1561 at this meeting describes the design of this study

ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; DXd, deruxtecan; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event; TiP, trial in progress.

1. Johnson ML, et al. ESMO. 2021. Abstract 513O. 2. Doi T, et al. ESMO. 2022. Abstract 453O.

S1929: Phase II Study of Maintenance Atezolizumab Versus Atezolizumab in Combination with Talazoparib in Patients with SLFN11 Positive Extensive Stage Small Cell Lung Cancer (ES-SCLC) NCT04334941



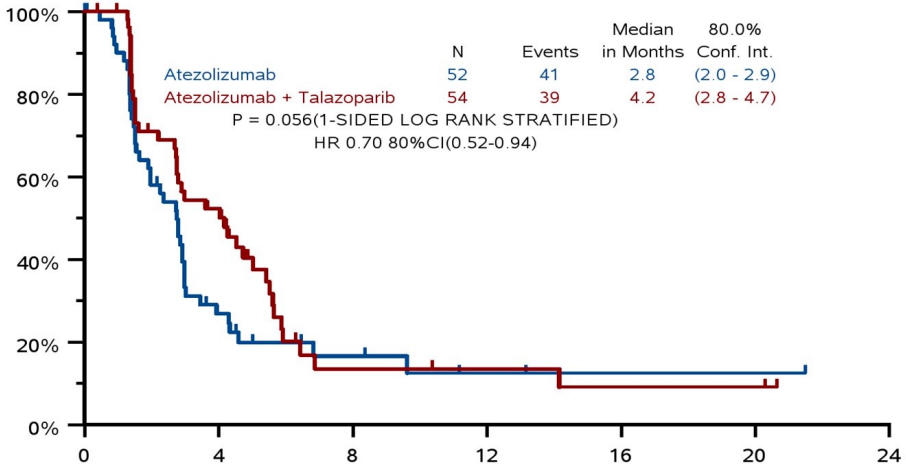
Hypothesis: The addition of talazoparib to maintenance atezolizumab will improve PFS in SLFN11+ SCLC.

Primary Endpoint: PFS
Secondary endpoints: OS, ORR, AE.
TM Objective: To bank specimens for future correlative studies.

**Atezolizumab was optional if the patient is hospitalized for cycle 1*
A maximum of 9 weeks after the end of cycle 4 was allowed prior to randomization

PRESENTED BY: Nagla Abdel Karim, MD

Progression Free Survival



	N	Events	Median in Months	80.0% Conf. Int.
Atezolizumab	52	41	2.8	(2.0 - 2.9)
Atezolizumab + Talazoparib	54	39	4.2	(2.8 - 4.7)

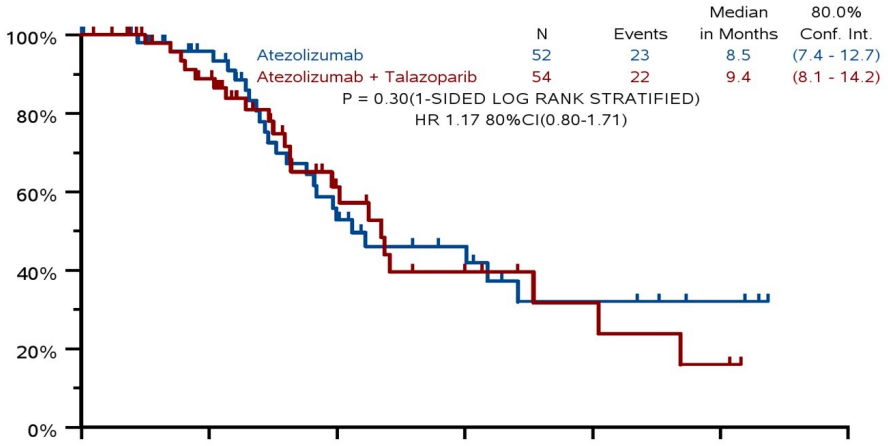
P = 0.056(1-SIDED LOG RANK STRATIFIED)
HR 0.70 80%CI(0.52-0.94)

Patients at Risk							
Atezolizumab	52	12	5	2	1	1	0
Atezolizumab + Talazoparib	54	24	4	3	2	2	0

Median FU time among patients who are alive is 5 months with a range of (0, 21.5M)

PRESENTED BY: Nagla Abdel Karim, MD

Preliminary OS



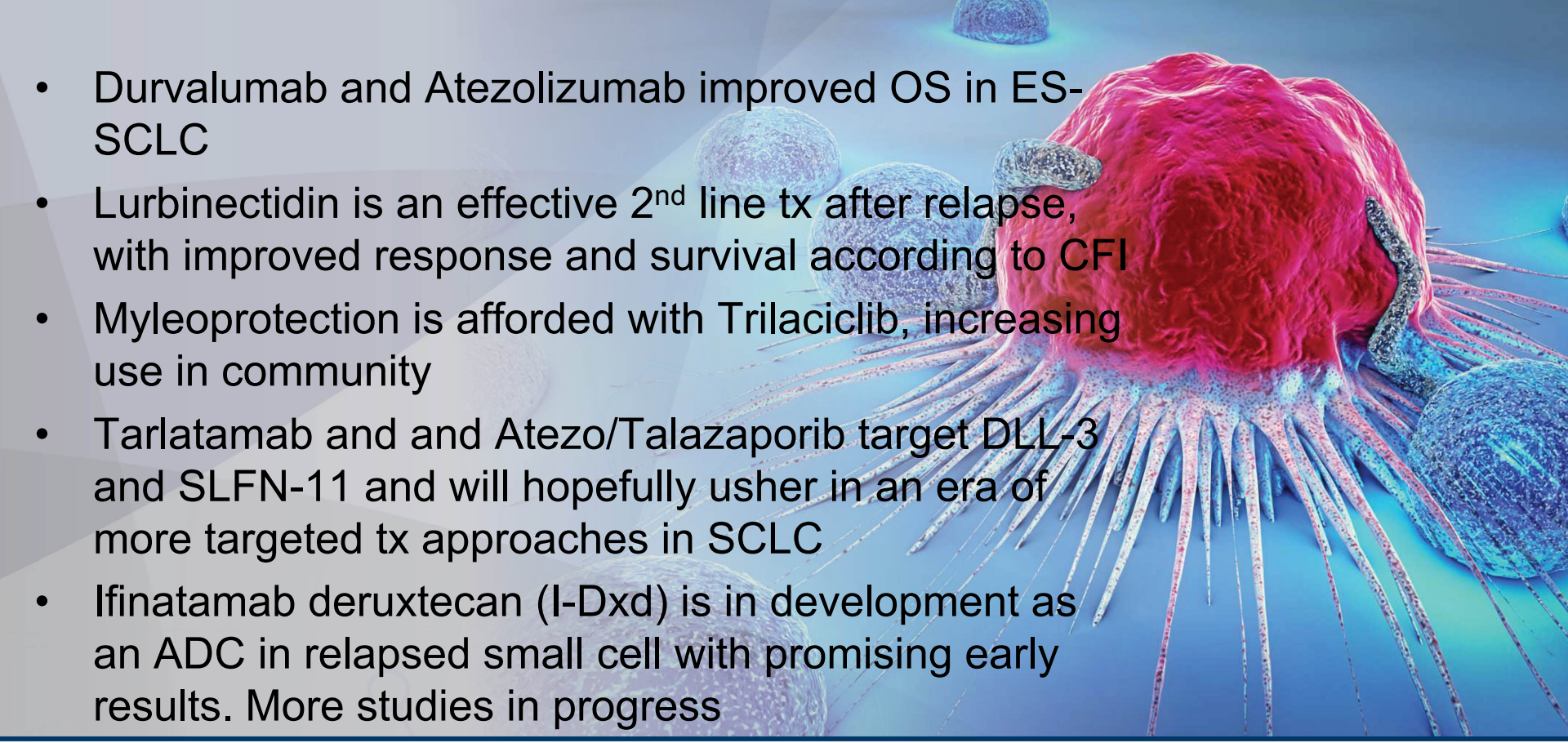
	N	Events	Median in Months	80.0% Conf. Int.
Atezolizumab	52	23	8.5	(7.4 - 12.7)
Atezolizumab + Talazoparib	54	22	9.4	(8.1 - 14.2)

P = 0.30(1-SIDED LOG RANK STRATIFIED)
HR 1.17 80%CI(0.80-1.71)

Patients at Risk							
Atezolizumab	52	40	18	11	6	3	0
Atezolizumab + Talazoparib	54	38	15	8	4	2	0

Median FU time among patients who are alive is 5 months with a range of (0, 21.5M)

PRESENTED BY: Nagla Abdel Karim, MD



- Durvalumab and Atezolizumab improved OS in ES-SCLC
- Lurbinectidin is an effective 2nd line tx after relapse, with improved response and survival according to CFI
- Myleoprotection is afforded with Trilaciclib, increasing use in community
- Tarlatamab and and Atezo/Talazaporib target DLL-3 and SLFN-11 and will hopefully usher in an era of more targeted tx approaches in SCLC
- Ifinatamab deruxtecan (I-Dxd) is in development as an ADC in relapsed small cell with promising early results. More studies in progress

Thank you!