Lung Cancer UPDATES
IASLC HIGHLIGTHS
28-31 ENERO 2021
VIRTUAL

Iniciativa científica de:
GECP lung cancer research

Carcinoma microcítico Pulmón

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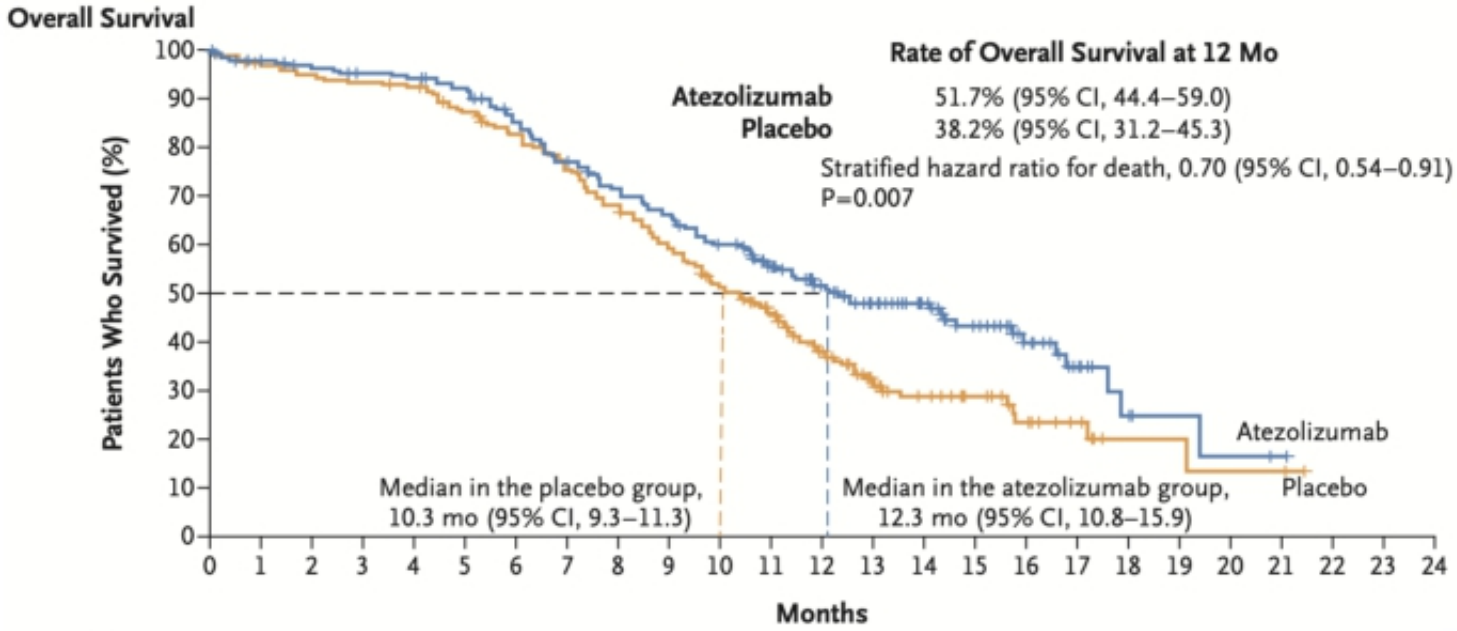
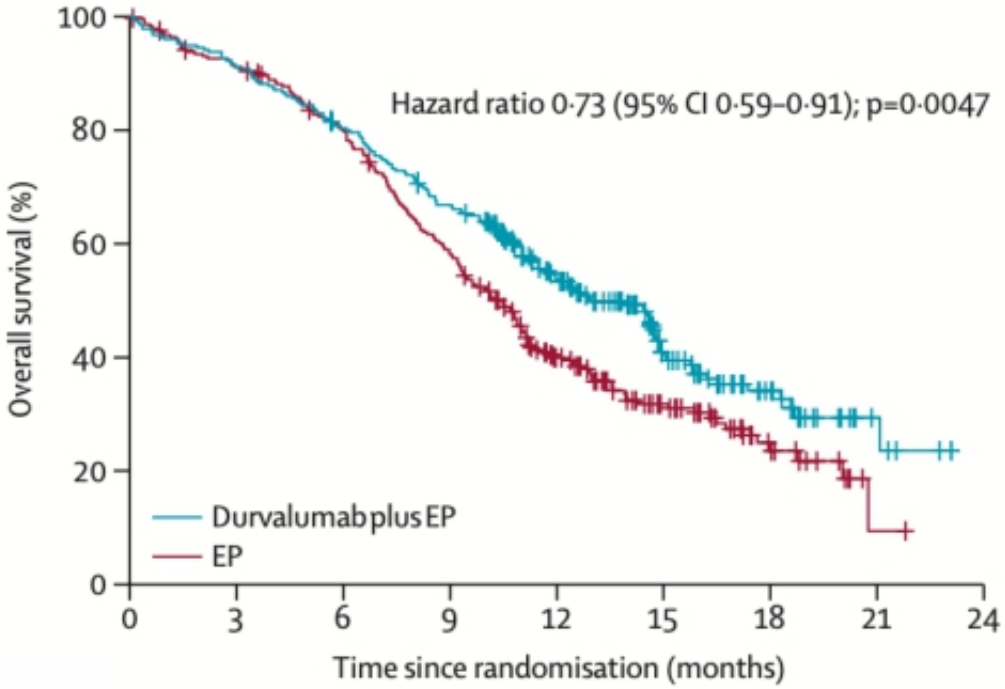
Progress in SCLC

- Addition of a PD-L1 inhibitor to chemotherapy improves survival
  - IMpower 133: atezolizumab + carboplatin + etoposide, approved March 2019
  - CASPIAN: durvalumab + platinum + etoposide, approved March 2020





Horn, NEJM 2018; Paz-Ares, Lancet 2019

Progress in SCLC

Drug	Positives
Atezolizumab	FDA approval 1st line based on IMpower 133
Durvalumab	FDA approval 1st line based on CASPIAN
Lurbinectedin	Accelerated FDA approval 2nd line based on single arm phase II trial
Nivolumab	Accelerated FDA approval 3rd line based on CheckMate 032
Pembrolizumab	Accelerated FDA approval 3rd line based on KEYNOTE 028/158

Progress in SCLC

Drug	Positives	Negatives
Atezolizumab	FDA approval 1st line based on IMpower 133	2nd line IFCT-1603 with RR only 2%
Durvalumab	FDA approval 1st line based on CASPIAN	Durvalumab plus tremelimumab in CASPIAN negative for OS
Lurbinectedin	Accelerated FDA approval 2nd line based on single arm phase II trial	Confirmatory phase III ATLANTIS trial (with doxorubicin) negative for OS
Nivolumab	Accelerated FDA approval 3rd line based on CheckMate 032	2nd line (CheckMate 331) and maintenance trials (Checkmate 451) negative for OS
Pembrolizumab	Accelerated FDA approval 3rd line based on KEYNOTE 028/158	1st line trial (KEYNOTE 604) negative for OS

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CONQUERING THORACIC CANCERS WORLDWIDE

IMpower133: exploratory analysis of maintenance therapy in patients with extensive-stage small cell lung cancer

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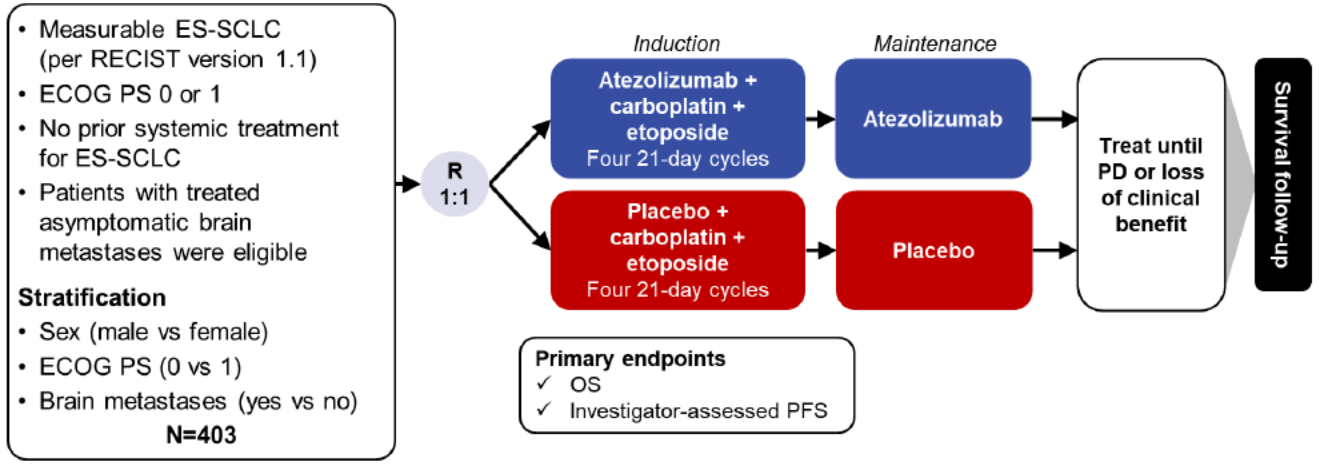
OA11.06

Methods

IMpower133 study design



Maintenance population: *patients who received at least the first dose of maintenance therapy, regardless of the number of chemotherapy cycles received*

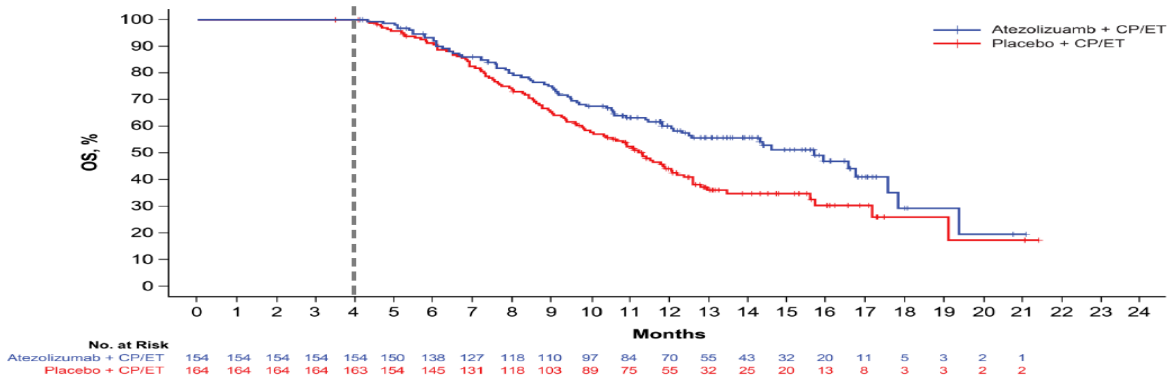
Characteristic	Atezolizumab + CP/ET (n=201)	Placebo + CP/ET (n=202)
Maintenance, n (%)	**154 (77)**	**164 (81)**
95% CI	70, 82	75, 86
Non-maintenance, n (%)	47 (23)	38 (19)
95% CI	18, 30	14, 25

- A generalised linear model was used to identify patient and disease characteristics that could be prognostic or predictive of reaching the maintenance phase
- A multivariate Cox model from the start of maintenance treatment was used to evaluate the treatment effect on OS and PFS to account for potential lead-time bias

Atezolizumab, 1200 mg IV, day 1; carboplatin, AUC 5 mg/mL/min IV, day 1; etoposide, 100 mg/m^2 IV, days 1-3.
NCT02763579. Data cutoff: 24 April 2018.

Results

OS in the maintenance population

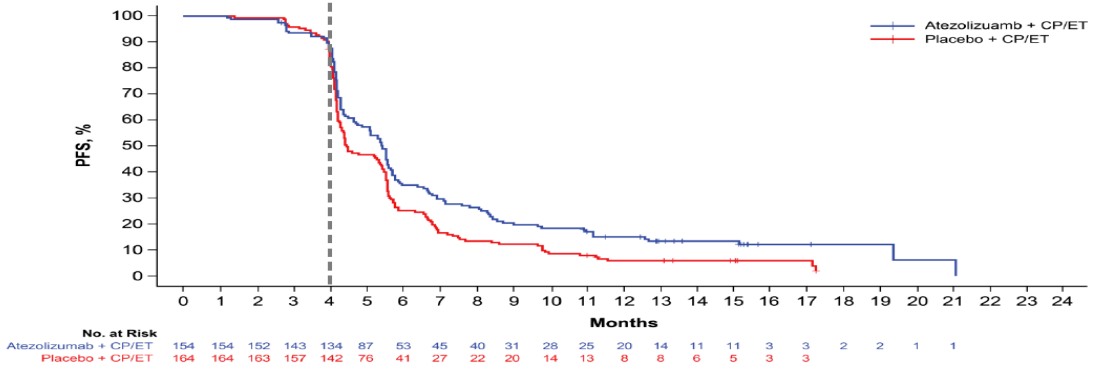


	Atezolizumab + CP/ET (n=154)	Placebo + CP/ET (n=164)
OS HR[a] from start of maintenance (95% CI)	0.59 (0.43, 0.81)	
Median OS from start of maintenance (95% CI), mo	12.5 (9.0, 14.5)	8.4 (7.0, 9.4)
Median OS from randomisation (95% CI), mo	15.7 (12.3, 17.6)	11.3 (10.1, 12.2)

- Among patients in the maintenance population, median OS was longer in the atezolizumab + CP/ET vs placebo + CP/ET arm

[a] Covariates used in the multivariate model: ECOG PS, LDH, SLD, age, number of metastatic sites, sex and presence of brain metastases.
Grey dotted line represents approximate start of maintenance therapy. Data cutoff: 24 April 2018.

PFS in the maintenance population



	Atezolizumab + CP/ET (n=154)	Placebo + CP/ET (n=164)
PFS HR[a] from start of maintenance (95% CI)	0.64 (0.50, 0.82)	
Median PFS from start of maintenance (95% CI), mo	2.6 (2.3, 2.9)	1.8 (1.4, 2.3)
Median PFS from randomisation (95% CI), mo	5.5 (4.9, 5.6)	4.5 (4.3, 5.4)

- Among patients in the maintenance population, median PFS was longer in the atezolizumab + CP/ET vs placebo + CP/ET arm

[a] Covariates used in the multivariate model: ECOG PS, LDH, SLD, age, number of metastatic sites, sex and presence of brain metastases.
Grey dotted line represents approximate start of maintenance therapy. Data cutoff: 24 April 2018.

SAFETY

n (%)	From randomisation (induction and maintenance)		From start of maintenance[a]	
	Atezolizumab + CP/ET (n=155)	Placebo + CP/ET (n=163)	Atezolizumab + CP/ET (n=155)	Placebo + CP/ET (n=163)
Patients with ≥1				
Any AE	155 (100)	159 (98)	127 (82)	118 (72)
Treatment-related AE	151 (97)	153 (94)	76 (49)	61 (37)
Atezolizumab/placebo	100 (65)	86 (53)	64 (41)	41 (25)
Grade 3/4 AE	105 (68)	105 (64)	43 (28)	37 (23)
Treatment-related Grade 5 AE	0	1 (<1)	0	1 (<1)
Serious AE	52 (34)	47 (29)	24 (15)	19 (12)
AE leading to dose modification or interruption	111 (72)	100 (61)	30 (19)	17 (10)
Atezolizumab/placebo	96 (62)	85 (52)	28 (18)	17 (10)
Immune-related AE	64 (41)	46 (28)	41 (26)	24 (15)

[a] Any, Grade 3/4, serious and immune-related AEs previously reported in Mansfield AS, et al. Annal Oncol. 2020;31:310-7.
Data cutoff: 24 April 2018.

Immune-related AEs in the maintenance population

n (%)[b]	From randomisation (induction and maintenance)				From start of maintenance[a]			
	Atezolizumab + CP/ET (n=155)		Placebo + CP/ET (n=163)		Atezolizumab + CP/ET (n=155)		Placebo + CP/ET (n=163)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Rash	34 (22)	3 (2)	19 (12)	0	21 (14)	2 (1)	6 (4)	0
Hypothyroidism	24 (16)	0	1 (<1)	0	16 (10)	0	1 (<1)	0
Pneumonitis	3 (2)	1 (<1)	5 (3)	2 (1)	1 (<1)	1 (<1)	5 (3)	2 (1)
Pancreatitis	1 (<1)	1 (<1)	2 (1)	2 (1)	0	0	2 (1)	2 (1)

- Grade 3/4 immune-related AEs were not commonly reported; no Grade 5 immune-related events occurred

[a] Any grade immune-related AEs previously reported in Mansfield AS, et al. Annal Oncol. 2020;31:310-7.
[b] Events of any grade occurring in ≥10% of patients and Grade 3/4 events occurring in ≥1%. Data cutoff: 24 April 2018.

CONCLUSIONES

- Impower133 recibieron una proporción de tratamiento de mantenimiento similar en el brazo de atezolizumab + CB/ET (77%) y placebo + CB/ET (81%)

- Se observó un beneficio significativo en la población de mantenimiento en pacientes que recibieron atezolizumab + CB/ET vs placebo + CB/ET tanto en 0S(HR 0.59) como en PFS (0.64)

- Seguridad comparable a pesar de la continuación de atezolizumab de mantenimiento

- Tanto el tratamiento de inducción como el del mantenimiento contribuyen al beneficio en OS observado en el IMpower133

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CONQUERING THORACIC CANCERS WORLDWIDE

P48.03: First-line durvalumab plus platinum-etoposide in extensive-stage (ES)-SCLC: exploratory analyses based on extent of disease in CASPIAN

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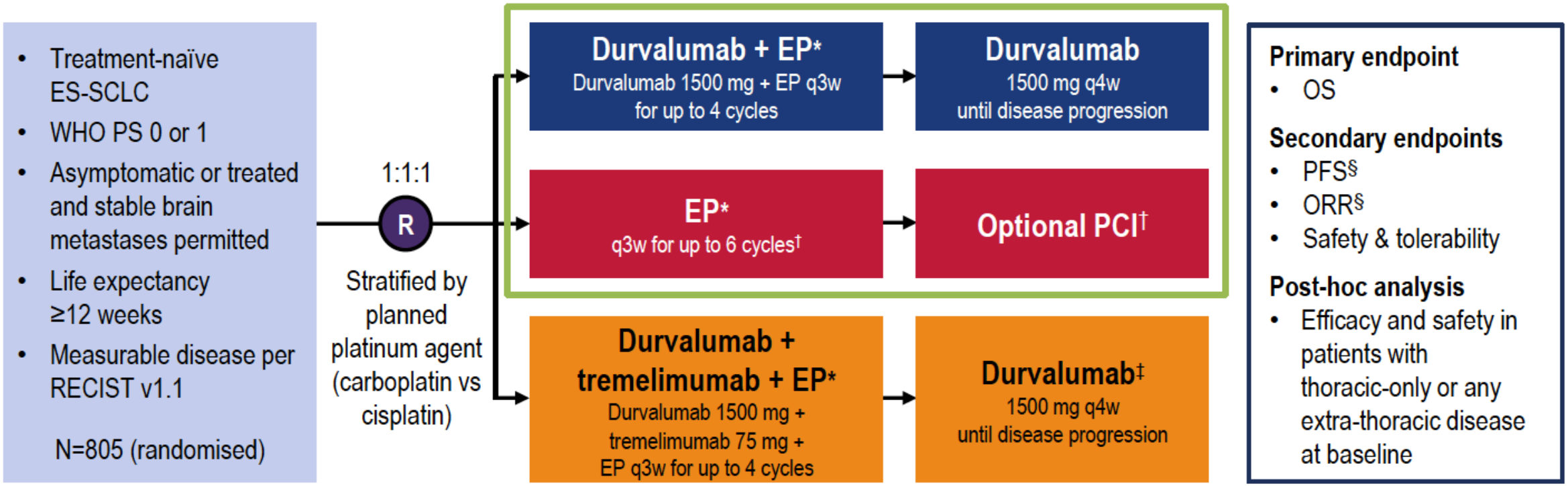
- CASPIAN is a Phase 3, global, randomised, open-label, sponsor-blind, multicentre study



*EP consists of etoposide 80–100 mg/m^2 with either carboplatin area under the curve 5–6 or cisplatin 75–80 mg/m^2;
†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; §By investigator assessment per RECIST v1.1

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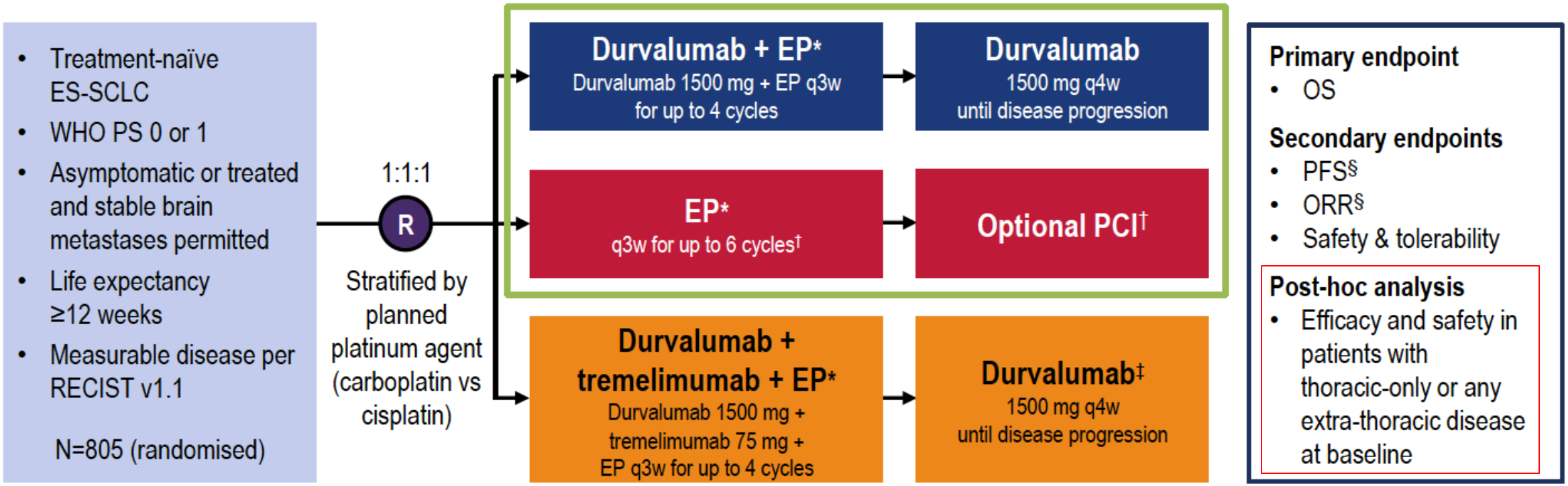

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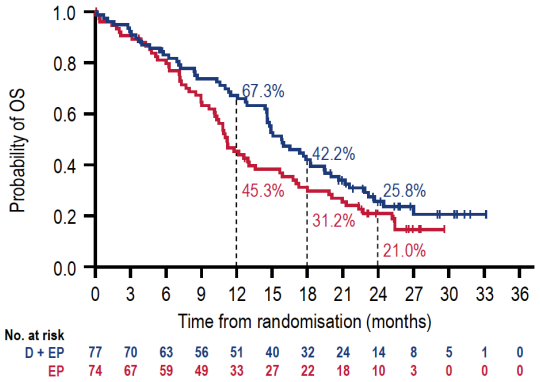
‡Patients received an additional dose of tremelimumab post-EP; §By investigator assessment per RECIST v1.1

Results

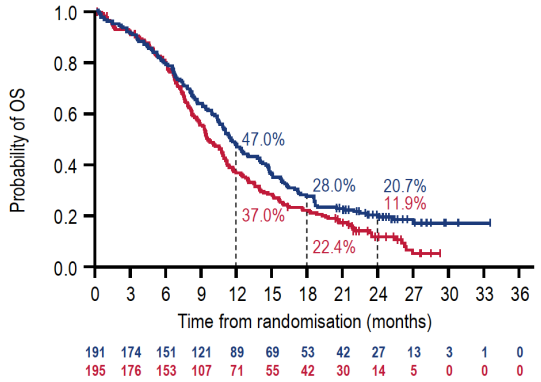
Thoracic-only disease at baseline

	Durvalumab + EP	EP
Events, n/N (%)	57/77 (74.0)	60/74 (81.1)
mOS, months (95% CI)	15.9 (14.6–19.5)	11.2 (9.7–13.6)
HR (95% CI)	**0.73** (0.51–1.06)	



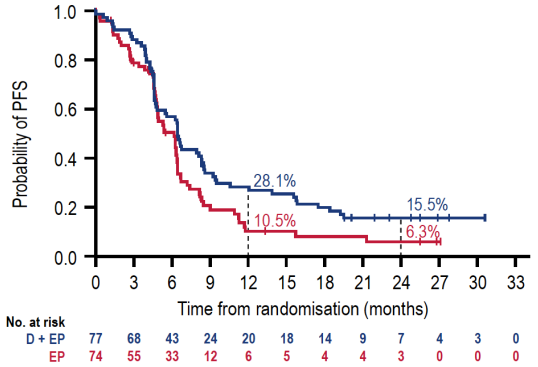
Extra-thoracic disease at baseline

	Durvalumab + EP	EP
Events, n/N (%)	153/191 (80.1)	171/195 (87.7)
mOS, months (95% CI)	11.5 (10.4–13.8)	9.7 (8.8–10.9)
HR (95% CI)	**0.77** (0.62–0.96)	



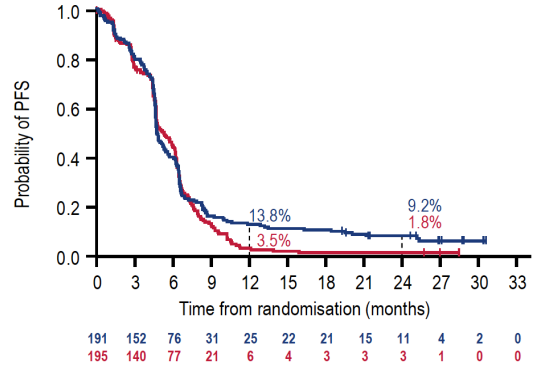
Thoracic-only disease at baseline

	Durvalumab + EP	EP
Events, n/N (%)	63/77 (81.8)	61/74 (82.4)
mPFS, months (95% CI)	6.5 (4.8–8.3)	6.2 (4.9–6.4)
HR (95% CI)	**0.70** (0.49–1.00)	



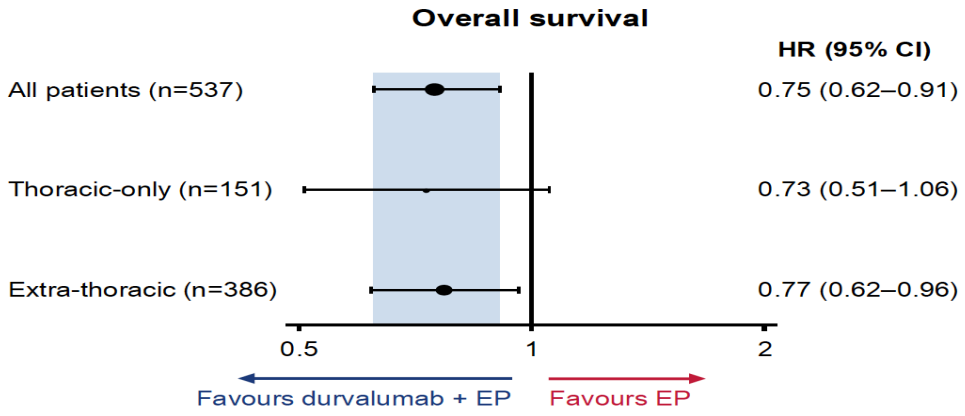
Extra-thoracic disease at baseline

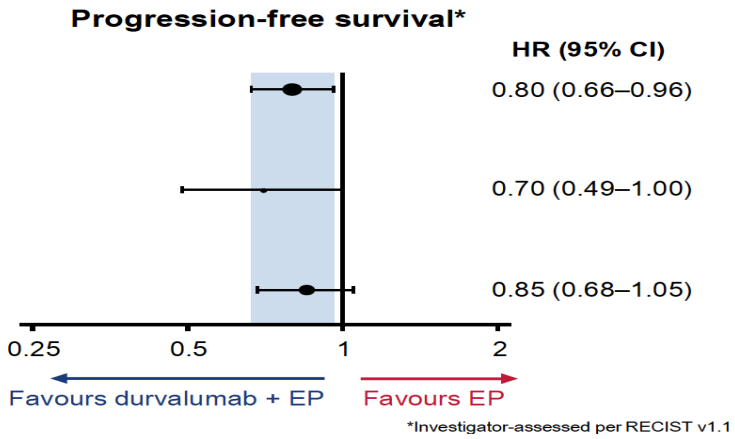
	Durvalumab + EP	EP
Events, n/N (%)	171/191 (89.5)	175/195 (89.7)
mPFS, months (95% CI)	4.8 (4.6–5.4)	5.3 (4.7–6.1)
HR (95% CI)	**0.85** (0.68–1.05)	



*Investigator-assessed per RECIST v1.1

- HRs for OS and PFS consistently favoured durvalumab + EP versus EP, regardless of the extent of disease at baseline





*Investigator-assessed per RECIST v1.1

OS, PFS, and ORR were improved with durvalumab+ EP versus EP, regardless of whether patients had thoracic-only or any extra-thoracic disease at baseline, consistent with the ITT analyses

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CONQUERING THORACIC CANCERS WORLDWIDE

Safety of BMS-986012, an Anti–Fucosyl-GM1 Monoclonal Antibody, Plus Platinum/Etoposide in Untreated Extensive-Stage SCLC

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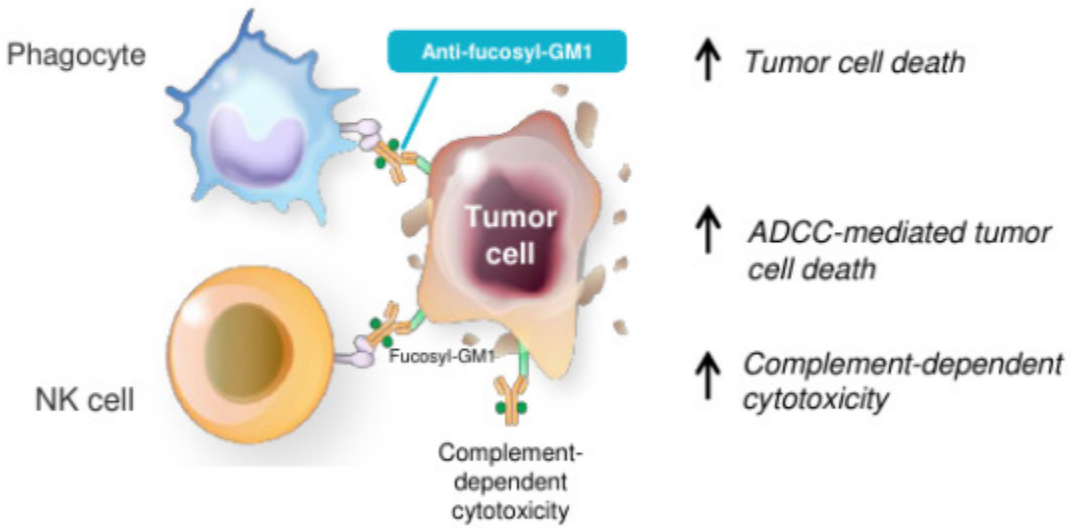
[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Spain; [3]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [4]Bristol Myers Squibb, Lawrenceville, NJ, USA; [5]Vall d´Hebron University Hospital, Barcelona, Spain

Introduction

- Fucosyl-GM1 is a monosialoganglioside with limited expression in normal tissues but high expression on the surface of tumor cells in SCLC[1-3]
- BMS-986012 is a nonfucosylated, first-in-class, fully human IgG1 mAb that binds to fucosyl-GM1 with high affinity and specificity[3]
  - Lack of fucosylation is associated with higher binding on NK cells and increased ADCC[3]
- The current study presents the preliminary safety findings from a phase 1/2 trial of BMS-986012 combined with platinum/etoposide, followed by BMS-986012 monotherapy maintenance in previously untreated patients with extensive-stage SCLC



ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; SCLC, small-cell lung cancer.

1. Zhang S, et al. *Int J Cancer* 1997;73:42–49. 2. Brezicka FT, et al. *Cancer Res* 1989;49:1300–1305. 3. Ponath P, et al. *Clin Cancer Res* 2018;24:5178–5189.

Study Design and Methods

This was a phase 1/2 trial of the combination of BMS-986012 and platinum/etoposide followed by BMS-986012 monotherapy maintenance in previously untreated patients with extensive-stage SCLC (NCT02815592)

Key Eligibility Criteria[a]

- Age ≥ 18 years old
- Chemotherapy-naive patients with extensive-stage SCLC
- ECOG PS 0 or 1
- Any prior radiotherapy, including radiosurgery to CNS metastases, must have been completed ≥2 weeks prior to enrollment

Combination therapy	Maintenance
Part 1 **BMS-986012:** 400 or 1000 mg IV on day 1 ***plus*** **Cisplatin:** 80 mg/m2 IV on day 1 ***and*** **Etoposide:** 100 mg/m^2 IV on days 1, 2, and 3 of each of four 21-day cycles	BMS-986012 monotherapy until unacceptable toxicity[b] or disease progression
Part 2 **BMS-986012:** 400 or 1000 mg IV on day 1 ***plus*** **Carboplatin:** AUC 5 on day 1 ***and*** **Etoposide:** 100 mg/m^2 IV on days 1, 2, and 3 of each of four 21-day cycles	BMS-986012 monotherapy until unacceptable toxicity[b] or disease progression

Primary Objective: safety/tolerability

Data cutoff: February 6, 2020

[a]Patients with symptomatic CNS metastases, uncontrolled pleural effusion, carcinomatous meningitis, evidence of uncontrolled and active infection, autoimmune disease requiring systemic treatment, or prior systemic therapy for lung cancer, including but not limited to chemotherapy, vaccines, and other targeted therapies, were excluded. [b]Toxicity evaluated according to NCI CTCAE version 4.03

AUC, area under the concentration-time curve, CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NCI, National Cancer Institute; SCLC, small-cell lung cancer

BMS-986012-Related Adverse Events

	BMS-986012 (400 mg) + Cis/Carbo + etoposide[a] n=12		BMS-986012 (1000 mg) + Cis/Carbo + etoposide[a] n=2		All patients N=14	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Patients with any TRAE, n (%)	11 (92)	3 (25)	1 (50)	0	12 (86)	3 (21)
Pruritus	11 (92)	1 (8)	1 (50)	0	12 (86)	1 (7)
Urticaria	1 (8)	1 (8)	0	0	1 (7))	1 (7)
Neutropenia	1 (8)	1 (8)	0	0	1 (7)	1 (7)
Infusion-related reaction	1 (8)	0	0	0	1 (7)	0
Dizziness	1 (8)	0	0	0	1 (7)	0
Conjunctivitis	1 (8)	0	0	0	1 (7)	0
Xerosis	1 (8)	0	0	0	1 (7)	0

- Pruritus was primarily grade 1–2 and most cases self-resolved
- Grade 3–4 TRAEs were experienced by 3 of 14 patients (21%)
- No treatment-related SAEs were reported
- No dose-limiting toxicities were reported
- There were no treatment-related deaths

carbo, carboplatin; cis, cisplatin; SAE, serious adverse event; TRAE, treatment-related adverse event.

Conclusions

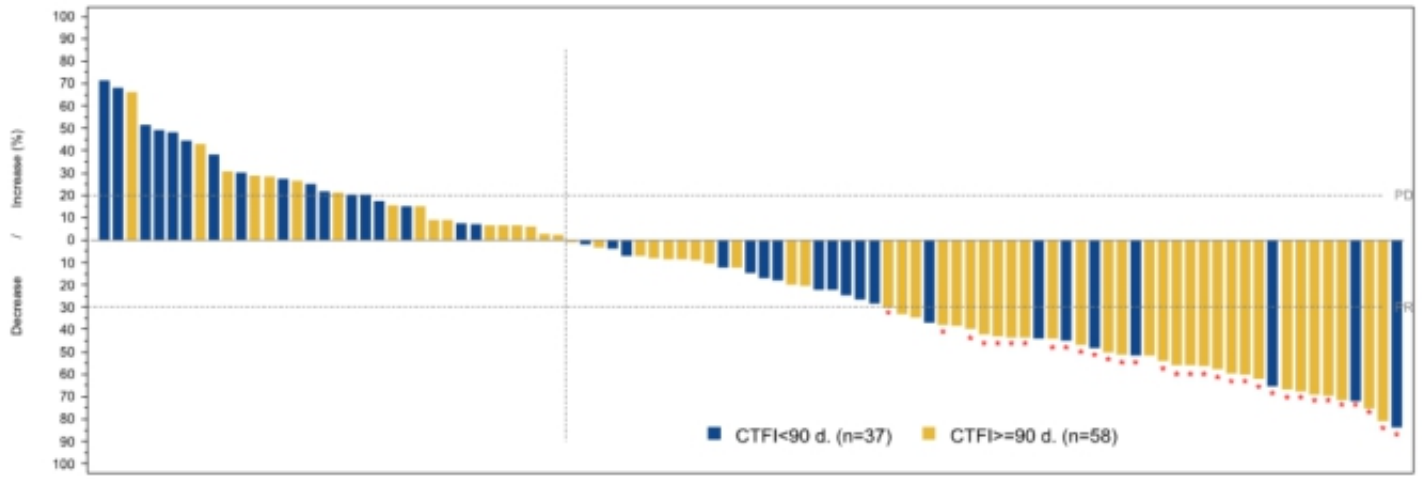
- BMS-986012 in combination with platinum/etoposide demonstrated a tolerable safety profile in a small treatment-naive patient population with extensive-stage SCLC
  - The safety profile was reported in the 400-mg cohort; safety data in the 1000-mg cohort were limited
  - Pruritus was the most common TRAE (86%)
    - In nearly all cases, pruritus self-resolved after the first 2 cycles of therapy and did not recur
  - No dose-limiting toxicities were reported
- These safety findings support the ongoing evaluation of BMS-986012 as first-line therapy for patients with extensive-stage SCLC. A phase 2 randomized study of BMS-986012 in combination with carboplatin, etoposide, and nivolumab will start enrollment in early 2021 (NCT04702880)[a]

Please see poster **#3396** where we present updated clinical and safety data from a study of BMS-986012 + nivolumab in patients with relapsed/refractory SCLC

[a]CA001-050: A Randomized, Open Label Phase II Clinical Trial of BMS-986012 in Combination with Carboplatin, Etoposide and Nivolumab as First-line Therapy in Extensive-Stage Small Cell Lung Cancer (ES-SCLC).
SCLC, small cell lung cancer; TRAE, treatment-related adverse event.

What's Next?

- First line chemo-immunotherapy is our standard of care
  - Most patients unfortunately relapse
- Second line options:
  - Topotecan
  - Lurbinectedin (FDA accelerated approval, single arm phase II RR 35.2%)



Confirmatory phase III ATLANTIS trial of lurbinectedin plus doxorubicin did **not** improve OS vs topotecan/CAV

Trigo, Lancet Oncol 2020

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EFFICACY AND SAFETY PROFILE OF LURBINECTEDIN-IRINOTECAN IN PATIENTS WITH RELAPSED SCLC

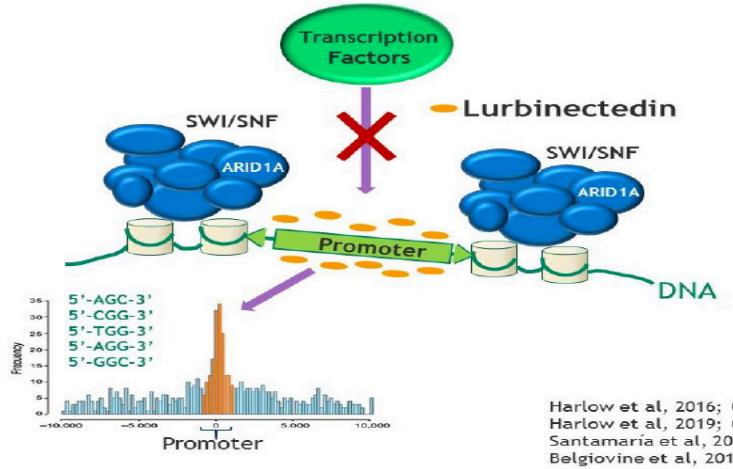
Results from a phase Ib-II trial

Santiago Ponce[1], Gregory M. Coté[2], Alejandro Falcón[3], Elizabeth Jimenez-Aguilar[1], Jessica J Lin[2], Inmaculada Sánchez Simón[3], María José Flor[3], Rafael Núñez[4], Ana M Jiménez[4], Eva Jiménez[4], Sonia Extremera[4], Carmen Kahatt[4], Ali Zeaiter[4], Luis Paz-Ares[1]

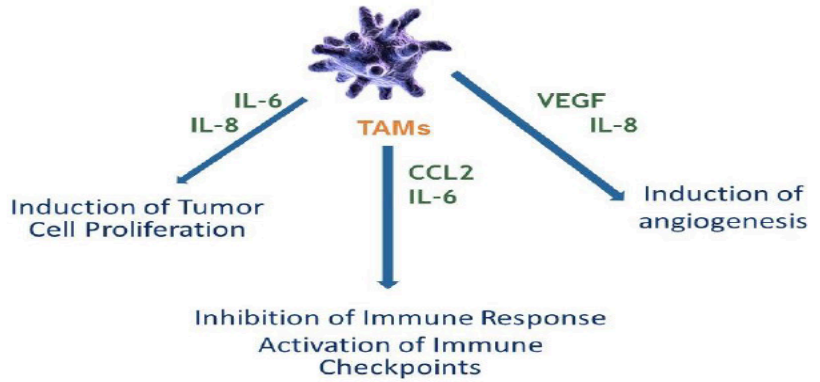
[1]Hospital Universitario 12 de Octubre, Madrid, Spain. [2]Massachusetts General Hospital, Boston, MA, U.S.A. [3]Hospital Universitario Virgen del Rocío, Sevilla, Spain. [4]Pharma Mar, S.A., Colmenar Viejo, Madrid, Spain.

Lurbinectedin – a Selective Inhibitor of Oncogenic Transcription

CANCER IS FREQUENTLY A TRANSCRIPTIONAL DISEASE CAUSED BY DEREGULATED ONCOGENIC TRANSCRIPTION FACTORS

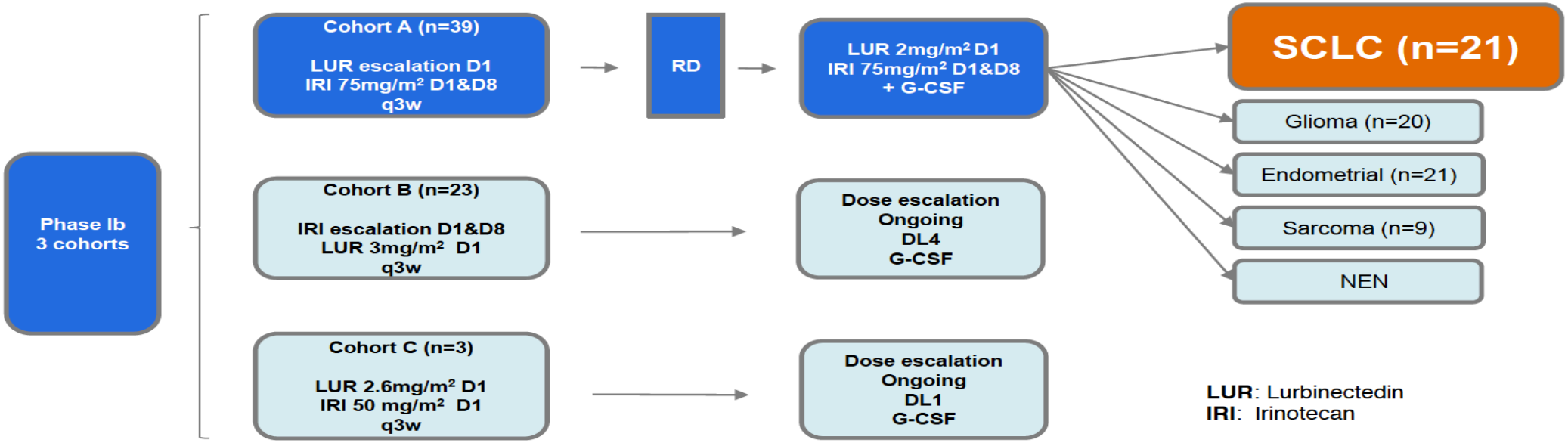


BY INHIBITING ACTIVE TRANSCRIPTION IN TUMOR ASSOCIATED MACROPHAGES (TAMS), LURBINECTEDIN DOWNREGULATES IL-6, IL-8, CCL2 AND VEGF



Harlow et al, 2016; Cancer Res 72: 6657-68
Harlow et al, 2019; Clin Cancer Res doi: 10.1158/1078-0432.CCR-18-3511
Santamaria et al, 2016. Mol Cancer Ther 15:2399-412
Belgiovine et al, 2017 Br J Cancer 117:628-38

Study Design



RESPONSE RATE

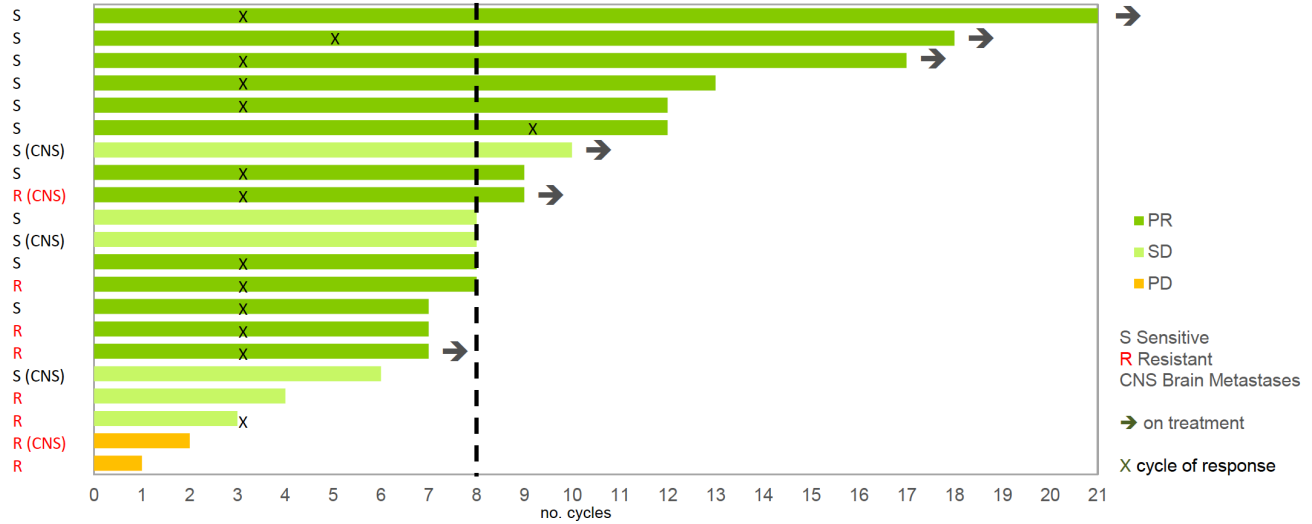
SCLC cohort, efficacy table (n=21)

	All patients (n=21)	CTFI		Setting	
		≥90 days (n=13)	<90 days (n=8)	2nd line (n=13)	3rd line (n=8)
Median number of cycles (range)	8+ (1-20)	10+ (6-20)	6+ (1-8)	8+ (3-21)	8+ (1-18)
Objective Response Rate (PR)	**62%**	**69%**	**50%**	**77%**	**38%**
Clinical Benefit Rate (PR+SD>4m)	81%	92.3%	62.5%	92.3%	62.5%
Disease Control Rate (PR+SD)	90%	100%	75%	100%	75%
Median DOR (m) (95% CI)	6.7+ (3.0-N.R)	7.5+ (3.0-N.R)	3.7+ (2.8-3.7)	6.7+ (3.0-N.R)	3.0+ (3.0-N.R)
Median PFS (m) (95% CI)	**6.2+ (4.3-8.5)**	**8.1+ (4.3-N.R)**	**4.8+ (0.7-5.0)**	**8.5+ (4.8-N.R)**	**4.2+ (0.7-7.2)**

N.R not reached

SCLC cohort, waterfall plot (n=21)

SCLC cohort, swimmer plot (n=21)



SCLC cohort, Safety (n=21)

Adverse Events and Laboratory abnormalities		LUR 2 mg/m2 D1 + IRI 75 mg/m2 D1¬8 + G-CSF (n=21 patients)	
		Grade 1-2, %	Grade 3-4, %
Treatment- related adverse events	Fatigue	66.7	23.8*
	Nausea	57.1	-
	Vomiting	38.1	4.8
	Diarrhea	33.3	28.6**
	Constipation	19	-
	Abdominal pain	4.8	-
	Anorexia	52.4	-
	Febrile neutropenia	-	9.5
Laboratory abnormalities	Anemia	81	19
	Neutropenia	33.3	61.9***
	Thrombocytopenia	66.7	9.5
	ALT increase	57.1	4.8
	AST increase	61.9	4.8

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRI, irinotecan; LUR, lurbinectedin.

*1 episode per patient (n=5 pts) **All were grade 3. 1 episode per patient, except in 1 patient (2 episodes of 1 day of duration each)

*** 6/21 pts (28.6 %) neutropenia grade 4

Related AEs summary / dose modifications / supportive treatment	n (%)
Any AE	21 (100)
AE ≥ grade 3	16 (76.2)
SAEs	6 (28.5)
Related AEs leading to death	**0 (0.0)**
Related AEs leading to treatment discontinuation	**0 (0.0)**
Dose delays treatment related	6 (28.6)
Dose reductions	11 (52.4)
Transfusions (red blood)	7 (33.3)

Lurbinectedin + Irinotecan

- ORR 62% and PFS 6.2 months
  - Chemo-sensitive (≥ 90d CTFI): ORR 69%, PFS 8.1m
  - Chemo-resistant (< 90d CTFI): ORR 50%, PFS 4.8m

Reference	Drug	RR	Sample Size	Sens / Res
Trigo, 2020	Lurbinectedin	35%	37/105	45% / 22%
Masuda, 1992	Irinotecan	47%	7/15	
Onada, 2006	Amrubicin	50%	30/60	52% / 50%
Inoue, 2015	Amrubicin	67%	18/27	67% / ------
von Pawel, 2014	Amrubicin	31%	132/424	41% / 20%

Lurbinectedin + Irinotecan

- Impressive responses in sensitive and resistant populations
- Promising combination
- Not yet practice changing
  - Notable toxicity with the combination
  - Larger, randomized trials needed
  - Improved survival is the goal and response does not always correlate
- Irinotecan liposome formulation under investigation
  - Granted fast-track designation by FDA
  - Ongoing phase 2/3 RESILIENT trial (NCT03088813)

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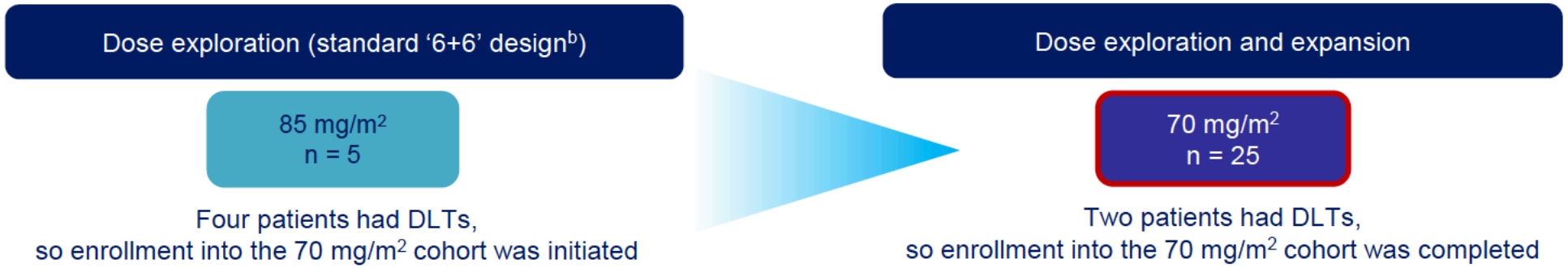
RESILIENT part 1: a phase II dose-exploration and dose-expansion study of second-line liposomal irinotecan monotherapy in adults with small cell lung cancer

Luis G Paz-Ares,[1] David R Spigel,[2] Yuanbin Chen,[3] Maria Jove,[4] Oscar Juan-Vidal,[5] Patricia Rich,[6] Theresa Hayes,[7] Vanesa Gutiérrez Calderón,[8] Reyes Bernabe Caro,[9] Alejandro Navarro,[10] Afshin Dowlati,[11] Bin Zhang,[12] Yan Moore,[12] Xiaopan Valerie Yao,[12] Jaba Kokhreidze,[12] Santiago Ponce,[1] Paul Bunn[13]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [3]Cancer & Hematology Centers of Western Michigan, Grand Rapids, MI, USA; [4]Institut Català d'Oncologia, Hospital Duran i Reinals, Barcelona, Spain; [5]Hospital Universitari i Politècnic La Fe, Valencia, Spain; [6]Cancer Treatment Centers of America, Atlanta, GA, USA; [7]South West Healthcare, VIC, Australia; [8]Hospital Regional Universitario de Malaga, Spain; [9]Hospital Universitario Virgen del Rocio, Seville, Spain; [10]Hospital Universitari Vall d'Hebron, Spain; [11]Case Western Reserve University, Cleveland, OH, USA; [12]Ipsen, Cambridge, MA, USA; [13]University of Colorado, Cancer Center and Department of Medicine, Denver, CO, USA



SAFETY

Treatment exposure and safety

	85 mg/m² n = 5	70 mg/m² n = 25	All patients N = 30
Duration of treatment, weeks, mean (SD)	12.3 (9.19)	17.7 (14.94)	16.8 (14.17)
Total dose received, mg, median (range)	687.0 (160.0–1109.4)	714.0 (148.0–2295.8)	696.0 (148.0–2295.8)
Any TEAE, n (%)	**5 (100)**	**25 (100)**	**30 (100)**
Leading to discontinuation of treatment	1 (20.0)	2 (8.0)	3 (10.0)
Leading to dose reduction	4 (80.0)	7 (28.0)	11 (36.7)
Any treatment-related TEAE, n (%)	**5 (100)**	**24 (96.0)**	**29 (96.7)**
Grade ≥3	5 (100)	10 (40.0)	15 (50.0)
Any treatment-related serious TEAE, n (%)	**2 (40.0)**	**3 (12.0)[a]**	**5 (16.7)**
Grade ≥3 treatment-related TEAEs occurring in ≥5% of patients, n (%)			
Diarrhea	3 (60.0)	5 (20.0)	8 (26.7)
Neutropenia	1 (20.0)	4 (16.0)	5 (16.7)
Abdominal sepsis	0	2 (8.0)[a]	2 (6.7)
Anemia	0	2 (8.0)	2 (6.7)
Asthenia	0	2 (8.0)	2 (6.7)
Thrombocytopenia	0	2 (8.0)	2 (6.7)
Fatigue	1 (20.0)	1 (4.0)	2 (6.7)
Hypokalemia	1 (20.0)	1 (4.0)	2 (6.7)
Hypomagnesemia	1 (20.0)	1 (4.0)	2 (6.7)

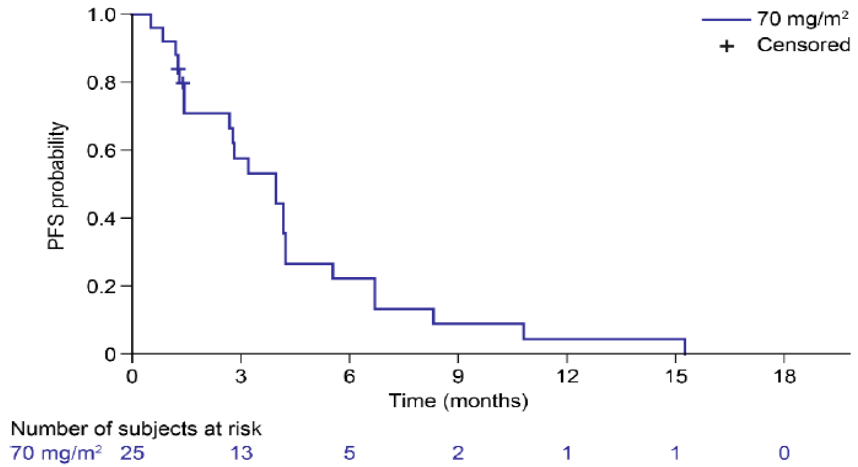
[a]Abdominal sepsis related to treatment led to death in two patients. SD, standard deviation; TEAE, treatment-emergent adverse event

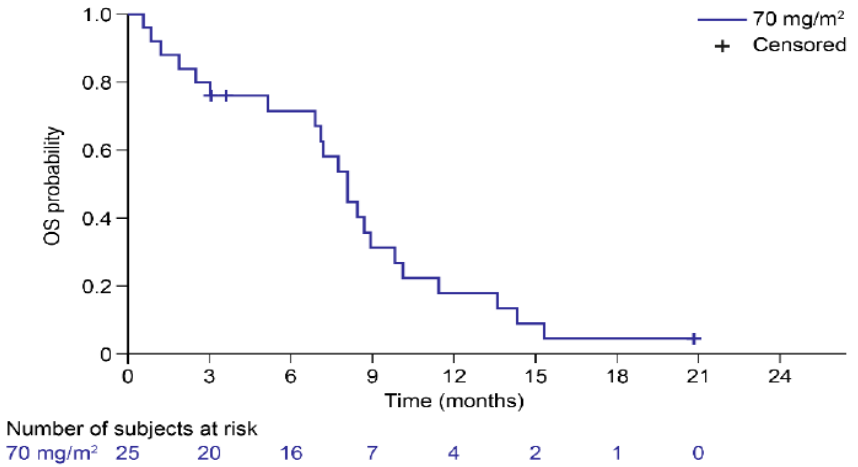
CLINICAL EFFICACY

Clinical efficacy (1/2)

	85 mg/m² n = 5	70 mg/m² n = 25	All patients N = 30
Best overall response, n (%)			
Complete response	0	1 (4.0)	1 (3.3)
Partial response	2 (40.0)	10 (40.0)	12 (40.0)
Stable disease	1 (20.0)	7 (28.0)	8 (26.7)
Progressive disease	1 (20.0)	5 (20.0)	6 (20.0)
Non-evaluable	1 (20.0)	2 (8.0)	3 (10.0)
Objective response, % (95% CI)			
Complete response + partial response	40.0 (5.27–85.34)	44.0 (24.40–65.07)	43.3 (25.46–62.57)
Duration of response			
Median, months (95% CI)	8.80 (4.11–NE)	2.99 (2.37–7.03)	3.78 (2.43–7.03)

Clinical efficacy (2/2)





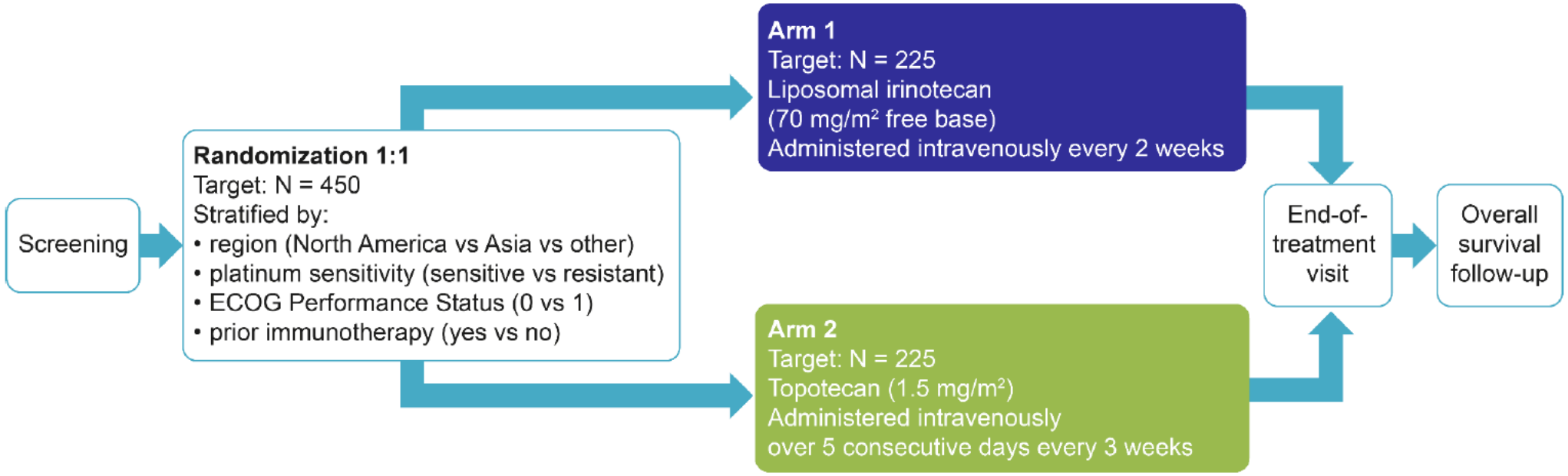
Median PFS: 3.98 months (95% CI: 1.45–4.24)

Median OS: 8.08 months (95% CI: 5.16–9.82)

CI, confidence interval; OS, overall survival; PFS, progression-free survival

RESILIENT part 2: Design

- An open-label, randomized, multicenter, phase III study comparing second-line liposomal irinotecan (arm 1) with second-line topotecan (arm 2) in adults with SCLC



ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung cancer

Lurbinectedin (PM01183) in Combination with Pembrolizumab for Patients with Relapsed Small Cell Lung Cancer. The LUPER Study

Maria José de Miguel Luken[1], Bernard Gaston Doger Speville Uribe[2], Alejandro Navarro Mendivil[3,4], Roldan Cortés[4], Antonio Calles Blanco[5]

[1]Centro Integral Oncologico Clara Campal, Madrid, Spain; Hospital Universitario HM Sanchinarro, Madrid, Spain. [2]Fundacion Jimenez Diaz, Madrid, Spain. [3]Vall d'Hebron University Hospital, Barcelona, Spain. [4]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain. [5]Hospital General Universitario Gregorio Marañón, Madrid, Spain.

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Figure 1: LUPER Study Design

Dose Escalation Part I
Lurbinectedin (PM01183)
2.4 mg/m² (starting dose), IV, D1 Q3W
+
Pembrolizumab
200 mg (fixed dose), IV, D1 Q3W

→ RP2D →

Dose Expansion Part II
Lurbinectedin (PM01183)
RP2D, IV, D1 Q3W
+
Pembrolizumab
200 mg (fixed dose), IV, D1 Q3W

N= 3/6 patients per cohort		
ENDPOINTS PART I	Primary:	• MTD and RP2D
	Secondary:	• Safety as per NCI-CTCAE 5.0 • Preliminary efficacy by RECIST 1.1 • Pharmacokinetics and Pharmacogenetics

N≈ 30 patients per cohort		
ENDPOINTS PART II	Primary:	• ORR as per RECIST 1.1
	Secondary:	• Safety as per NCI-CTCAE 5.0 • CBR, DoR, PFS by RECIST 1.1 and OS • Pharmacokinetics and Pharmacogenetics

Abbreviations: CBR, clinical benefit rate; D1: day 1; DoR: duration of response; IV, intravenously; MTD, maximum tolerated dose; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; OS: overall survival; PFS, progression-free survival; Q3W, every three weeks; RP2D, recommended phase 2 dose

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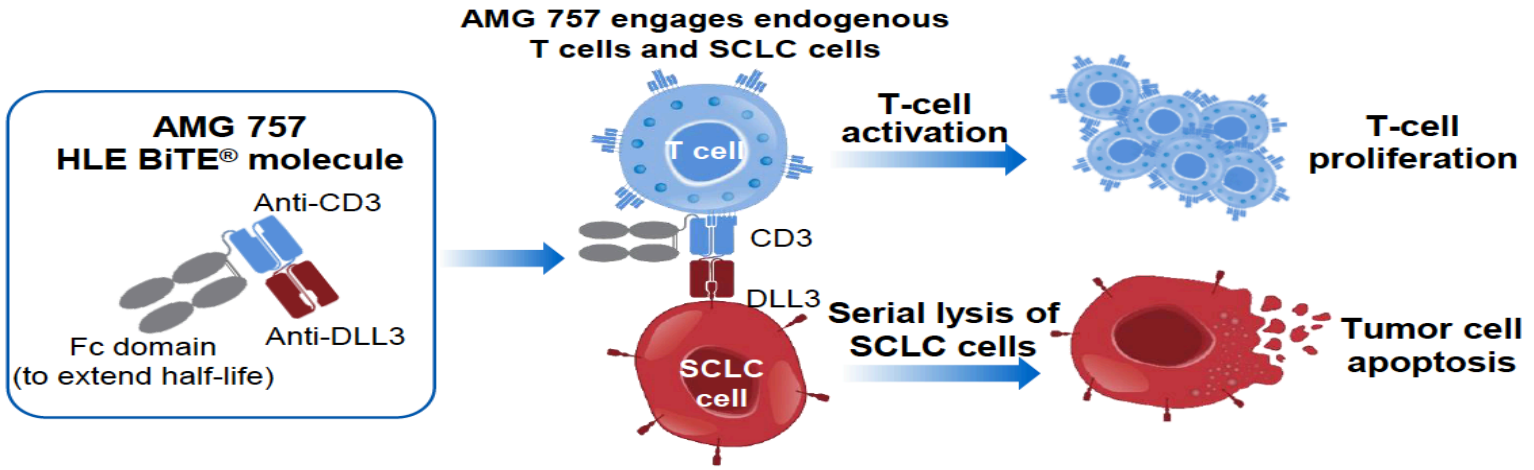
A phase 1 study of AMG 757, a half-life extended bispecific T-cell engager (BiTE®) immuno-oncology therapy against DLL3, in SCLC

Taofeek K. Owonikoko,[1] Michael Boyer,[2] Melissa Johnson,[3] Ramaswamy Govindan,[4] Luis Paz-Ares Rodrigues, [5] Fiona H. Blackhall,[6] Rene J. Boosman,[7] Stéphane Champiat,[8] Horst-Dieter Hummel,[9] W. Victoria Lai,[10] Hibiki Udagawa, [11] Anne C. Chiang,[12] Afshin Dowlati,[13] Christine L. Hann,[14] Ravi Salgia,[15] Everett E. Vokes,[16] Mukul Minocha,[17] Nooshin Hashemi Sadraei,[17] Aditya Shetty,[17] Marie-Anne Damiette Smit,[17] Yiran Zhang,[17] Amrita Pati,[17] Sumi Roy,[17] Beate Sable,[17] Hossein Borghaei[18]

[1]Emory University School of Medicine, Atlanta, GA, USA; [2]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [3]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [4]Washington University Medical School, St. Louis, MO, USA; [5]Hospital Universitario 12 de Octubre, Universidad Complutense & Ciberonc, Madrid, Spain; [6]The Christie NHS Foundation Trust, University of Manchester, Manchester, UK; [7]The Netherlands Cancer Institute, Amsterdam, Netherlands; [8]Gustave Roussy, Paris-Saclay University, Villejuif, France; [9]Comprehensive Cancer Center Mainfranken, University Hospital Wuerzburg, Wuerzburg, Germany; [10]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [11]National Cancer Center Hospital East, Kashiwa, Chiba, Japan; [12]Yale School of Medicine, New Haven, CT, USA; [13]University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; [14]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [15]City of Hope Hospital, Duarte, CA, USA; [16]University of Chicago Medicine and Biological Sciences, Chicago, IL, USA; [17]Amgen Inc., Thousand Oaks, CA, USA; [18]Fox Chase Cancer Center, Philadelphia, PA, USA

JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT

AMG 757: A Half-life Extended Bispecific T-cell Engager (BiTE®) Targeting DLL3 for SCLC



CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; SCLC, small cell lung cancer.

- BiTE molecules engage a patient's own T cells to attack and eradicate cancer cells[1,2]

1. Stieglmaier J, et al. *Expert Opin Biol Ther.* 2015;15:1093-1099.
2. Einsele H, et al. *Cancer.* 2020;126:3192-3201.

First-In Human Dose Exploration Study of AMG 757

AMG 757 in Relapsed/Refractory SCLC

Dose Exploration
(n = 1–4 per dose cohort)

Optimization of dose & regimen

Dose Expansion

Primary Objectives	▪ Evaluate safety and tolerability in SCLC ▪ Determine MTD or RP2D
Secondary Objectives	▪ Characterize PK ▪ Evaluate preliminary antitumor activity
Exploratory Objectives	▪ Evaluate immunogenicity, biomarkers, and target protein & outcomes

- **Study design** – NCT03319940: open-label, multi-center study of AMG 757 (dose escalation ranging from 0.003 mg to 30 mg as of data cutoff [***3 November 2020***]), administered by IV infusion every 2 weeks, with/without step dose
- **Disease assessment** – Antitumor activity assessed using modified RECIST 1.1 every 8 ± 1 weeks

Adverse Events (AEs)

Treatment-related AEs	Patients (N = 52)	
	All Grades, n (%)	Grade ≥ 3, n (%)*
Any treatment-related AE	41 (79)	12 (23)
Treatment-related AEs in ≥ 10% of patients		
CRS	**23 (44)**	**1 (2)†**
Pyrexia	10 (19)	0
Fatigue	7 (14)	0
Anemia	5 (10)	1 (2)
Nausea	5 (10)	0

*Includes one patient with grade 5 pneumonitis; † Grade 3 CRS, more detail presented on next slide.
AE, adverse event; CRS, cytokine release syndrome; DLT, dose limiting toxicity.

- Treatment-emergent AEs occurred in 51/52 (98%) patients
  - Grade ≥ 3 occurred in 27 (52%) patients
- Treatment-related AEs occurred in 41 (79%) patients, resulting in discontinuation in 1 (2%) patient
  - The one DLT was grade 5 pneumonitis and occurred in 1 (2%) patient

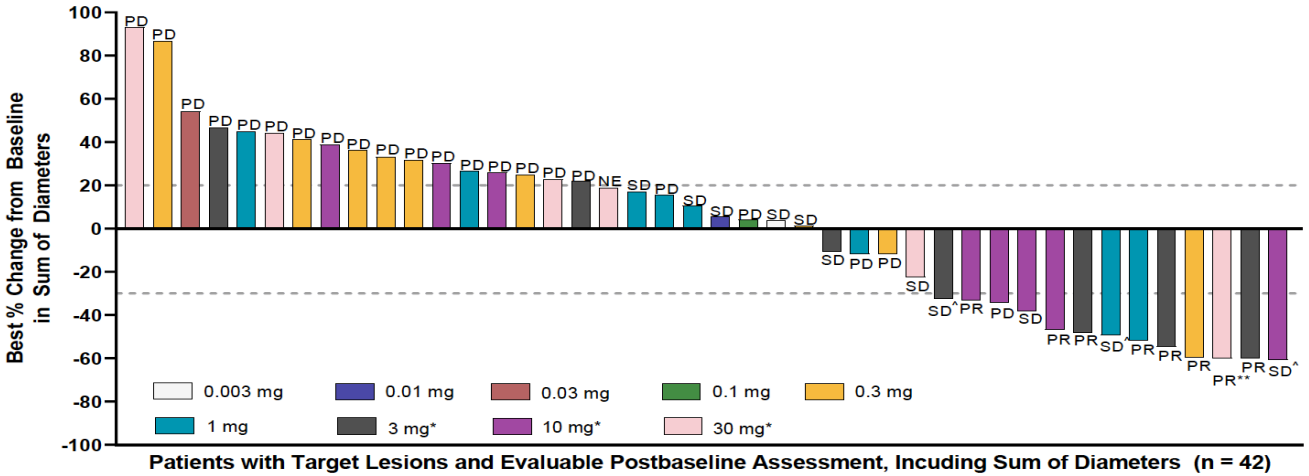
Characteristics of Cytokine Release Syndrome (CRS)

- CRS was typically reversible, manageable, and associated with fever ± tachycardia and nausea (Lee 2014 grading)
  - No CRS events led to treatment discontinuations
- CRS typically occurred in cycle 1 and did not recur in subsequent cycles
  - CRS was managed with supportive care and prophylactic corticosteroids

CRS Grading (Lee 2014) and On-Study Incidence			
Grade 1	Grade 2	Grade 3	Grade 4
Symptoms include fever, nausea, fatigue, headache, myalgias, and malaise, requiring symptomatic treatment only	Grade 1 CRS symptoms and • O_2 requirement < 40% • Intravenous fluids or low-dose vasopressor for hypotension • Grade 3 elevated aminotransferases	Grade 1 CRS symptoms and • O_2 requirement ≥ 40% • High-dose or multiple vasopressors for hypotension • Grade 4 elevated aminotransferases	Grade 1 CRS symptoms and • Requirement for ventilator • Grade 4 organ toxicity (excluding elevated aminotransferases)
CRS Incidence (worst grade), n (%)			
17 (33)	**5 (10)**	**1 (2)**	**0 (0)**

Efficacy

AMG 757 Demonstrates Anti-Tumor Activity in Patients with SCLC



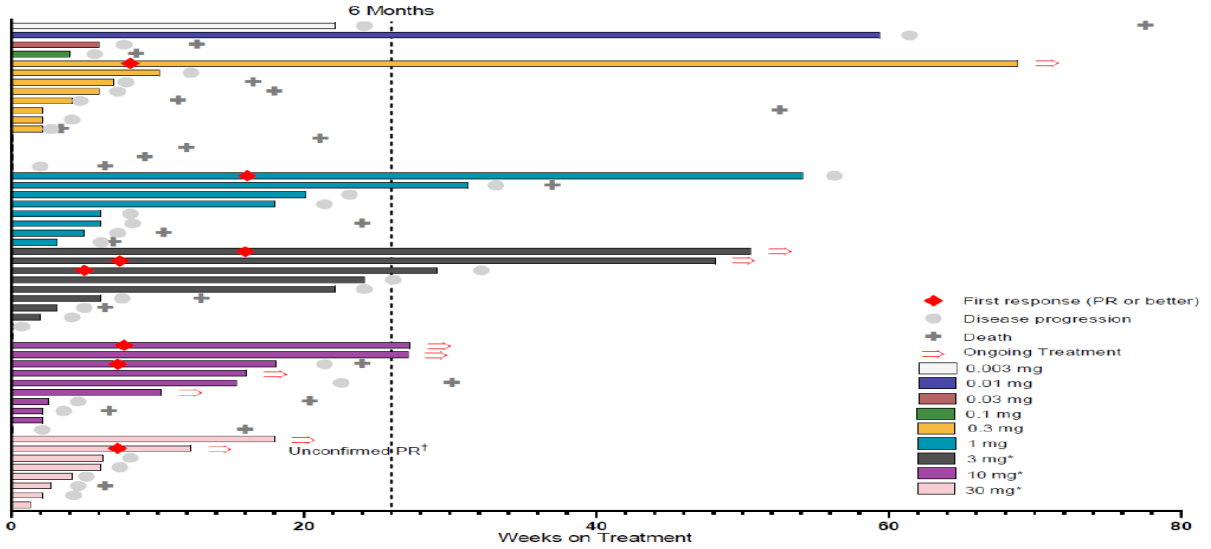
Patients with Target Lesions and Evaluable Postbaseline Assessment, Incuding Sum of Diameters (n = 42)

Modified RECIST 1.1 Response, n (%)	Patients† (N = 51)
PR, confirmed	7 (14)
0.3 mg target dose	1/12 (8)
1 mg target dose	1/8 (13)
3 mg target dose	3/9 (33)
10 mg target dose	2/10 (20)
PR, unconfirmed	1 (2)
30 mg target dose	1 (2)
SD	11 (22)
Disease control rate, %	37

PR** indicates the PR is unconfirmed. SD^ indicates patients who had an initial PR, but did not have confirmation of PR on the subsequent scan. NE indicates PD in the post-baseline scan and came off study without further confirmation scan.
*Step dosing. †Includes patients who received ≥ 1 dose of AMG 757 and had at least 8 weeks follow-up. NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Duration of Treatment and Response

- **10/52 (20%) patients have completed ≥ 6 months (≥ 24 weeks) of treatment**
  - 4/7 patients with confirmed PR are still receiving therapy and have on-going response
- **For patients with confirmed PR (n = 7)**
  - Median time to response was 1.8 months
  - Median duration of response was 6.2 months
  - Median follow-up was 11.5 months



Includes all patients who received ≥ 1 dose of AMG 757. *Step dosing. †No follow-up confirmation scan at cutoff.

Conclusions

- The results presented herein support AMG 757 as the first half-life extended BiTE® immuno-oncology therapy with a favorable safety profile and a durable response profile
  - Grade 3 treatment-related AEs occurred in 12 (23%) patients
  - CRS events were primarily grade 1 or 2 with only 1 case (2%) of grade 3 CRS
  - Only 1 discontinuation of treatment due to treatment-related AEs
  - Encouraging efficacy was observed during dose exploration, with confirmed PR in 14% of patients; response was durable, with a median duration of 6.2 months
- Dose optimization for monotherapy is ongoing

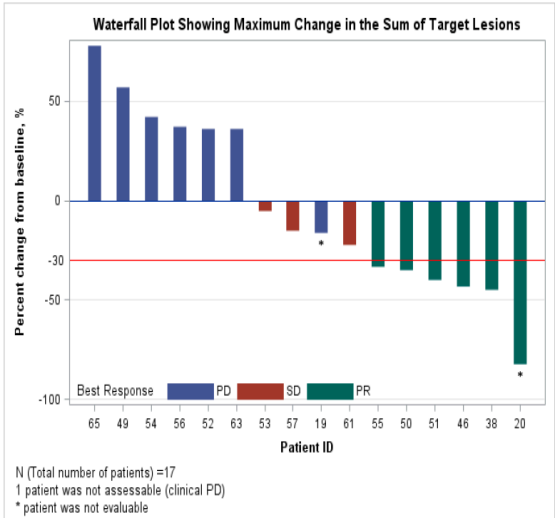
A Phase 2 Trial of Nivolumab and Temozolomide in Extensive Stage Small Cell Lung Cancer: Interim Efficacy Analysis.

Dwight H Owen, Lai Wei, Carly Pilcher, Sandip H Patel, Bhavana Konda, Manisha Shah, Sarah Ferguson, Brooke Benner, Ruthann Norman, William E Carson, Michael Smith, Sherry Mori Vogt, Claire Verschraegen, Kai He, Erin M Bertino, Carolyn J Presley, Peter G. Shields, David P. Carbone, Gregory A. Otterson.

The Ohio State University – James Comprehensive Cancer Center, Columbus, OH, USA

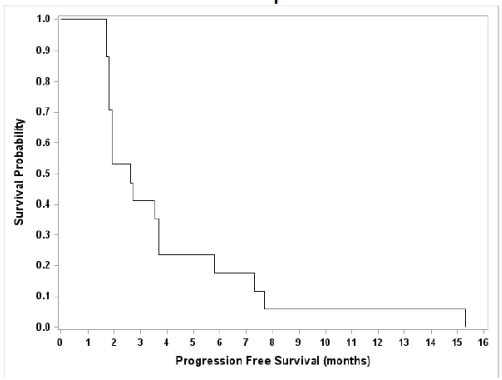
Results: Response rate (primary objective)

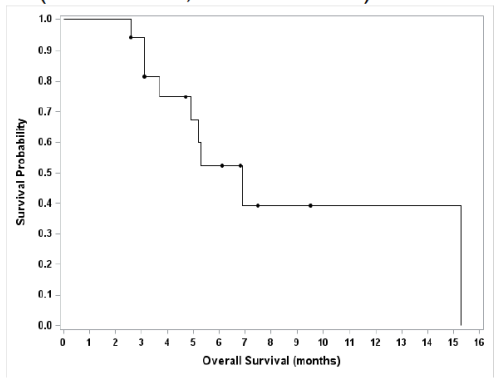
- Of 15 evaluable patients treated after progression on first line chemo-IO, response rate was 33% (n=5)
- Responses were seen in 2nd and 3rd line setting and in platinum sensitive and resistant patients



Results: Progression-free and overall survival

- Median PFS in evaluable patients was 2.6 months (95% CI: 1.8, 3.7)
- Median OS in evaluable patients was 6.9 months (95% CI 3.1, Not Reached)





Results: Safety and toxicity

- No treatment related deaths occurred during study therapy in either cohort
- One patient had grade 5 infection (COVID-19) greater than 100 days after last study treatment.
- In SCLC cohort, one grade 3 irAE occurred (colitis)
- Treatment related SAE included grade 3 lung infection (n=1), constipation (n=1), wound infection (n=1), anemia (n=1), GI bleeding (n=1), nausea (n=1), COVID-19 (n=1), and grade 4 thrombocytopenia (n=1).
- No patients permanently discontinued treatment due to toxicity.

NRG Oncology/Alliance LU005: A Phase II/III Randomized Clinical Trial of Chemoradiation Versus Chemoradiation Plus Atezolizumab in Limited Stage Small Cell Lung Cancer

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STUDY DESIGN

PATIENT POPULATION	STRATIFY	RANDOMIZE*	
Limited stage (Tx, T1-T4, N0-3, M0) small cell lung cancer (LS-SCLC)	• Radiation schedule, BID (3 weeks) vs daily (6.5 weeks) • Chemotherapy (cisplatin vs carboplatin) • Sex (male vs female) • ECOG Performance Status (0/1 vs 2)		**Arm 1** Platinum**/etoposide q3 weeks x 4 cycles + **Thoracic RT 45 Gy bid or 66 Gy daily** beginning with cycle 2 of chemotherapy*** **Arm 2** Platinum**/etoposide q3 weeks x 4 cycles + Thoracic RT 45 Gy bid or 66 Gy daily beginning with cycle 2 of chemotherapy*** + Atezolizumab q3 weeks x 1 year, beginning with cycle 2 of chemotherapy

TAKE HOME POINTS

- First line chemo-immunotherapy is our standard
  - Concurrent and maintenance immunotherapy
  - We need new combinations of immunotherapy to improve the efficacy
- Promising salvage regimens emerging
  - Lurbinectedin + irinotecan, irinotecan liposomal and AMG 757 show promise but also have important toxicity profiles
  - High response rates are nice but improving survival is our objective
  - Future studies should consider prospective clinical trial designs with selection for specific molecular subtypes

Takeaway Points

- First line chemo-immunotherapy is our standard
  - Concurrent and maintenance immunotherapy
- Promising salvage regimens emerging
  - Lurbinectedin + irinotecan, liposomal irinotecan and AMG 757 show promise but also have important toxicity profiles
  - High response rates are nice but improving survival is our goal
- Substantial gains will only be made with a commitment to biomarker development and identification of unique subsets within SCLC