Lung Cancer UPDATES
IASLC HIGHLIGHTS
09-12 SEPTIEMBRE 2023
Singapore

Iniciativa científica de:
GECP
lung cancer research

Mesotelioma y SCLC

Juan Coves Sarto

H. Universitario Son Llàtzer

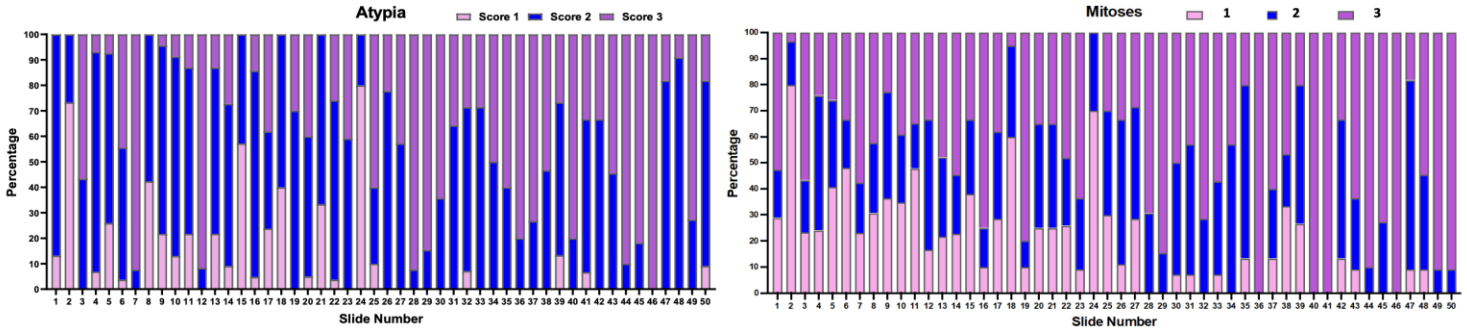
IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

Variance in Pathologists' Grading of Pleural Mesothelioma

Sarita Prabhakaran
Flinders University
Australia

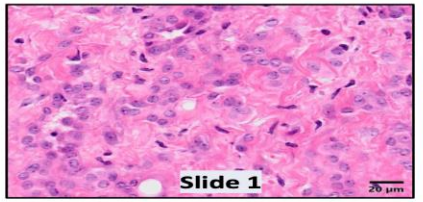
Variances between pathologists grading of 50 epithelioid mesothelioma					
Histological scoring	**Method**	**Cases**	**Kappa**	**Confidence Interval**	**p value**
Nuclear grade	Complete case analysis	14	0.419	0.253-0.584	<0.001
	Multiple imputation	50	0.431	0.343-0.518	<0.001
Atypia	Complete case analysis	21	0.239	0.187-0.291	<0.001
	Multiple imputation	50	0.299	0.263-0.335	<0.001
Mitotic count	Complete case analysis	25	0.289	0.212-0.367	<0.001
	Multiple imputation	50	0.141	0.089-0.192	<0.001
Necrosis	Complete case analysis	14	0.345	0.180-0.511	<0.001
	Multiple imputation	50	0.206	0.119-0.294	<0.001
Myxoid stroma	Complete case analysis	21	0.539	0.468-0.610	<0.001
	Multiple imputation	50	0.406	0.360-0.452	<0.001

Results of scores on nuclear atypia and mitotic counts

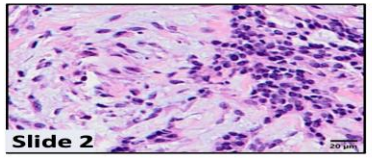


Possible explanations of our findings/Limitations

- Use of virtual slides
- Heterogenous morphology
- Difficulty choosing hotspots in tumours
- Format of survey- technical difficulties



Low grade



Myxoid stroma

Full concordance when morphology is typical

Phase 1/2 Randomized Trial of Anetumab Ravtansine and Pembrolizumab Compared to Pembrolizumab for Pleural Mesothelioma

Aaron Mansfield

Study Design

Phase 1 Safety Lead-In
- anetumab ravtansine (6.5 mg/kg iv) and pembrolizumab (200 mg iv) q3weeks

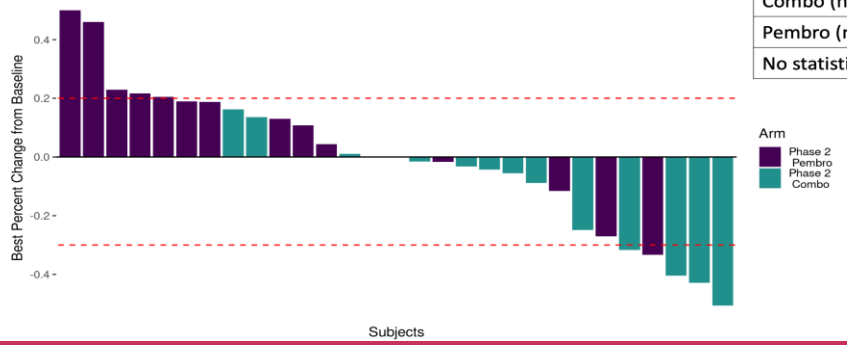
Phase 2 Randomization
- anetumab ravtansine and pembrolizumab
- pembrolizumab

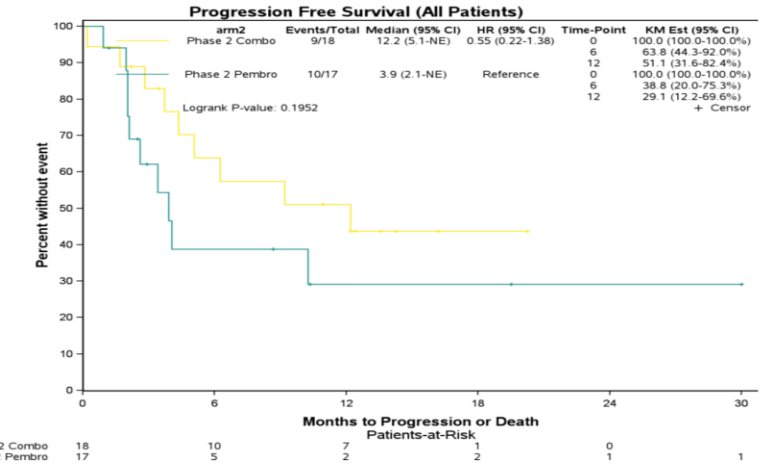
Phase 1
- No prior immunotherapy
- No significant comorbidities or auto-immune conditions
- Epithelioid mesothelioma
- Measurable disease not required

Phase 2
- No prior immunotherapy
- No significant comorbidities or auto-immune conditions
- ≥30% mesothelin expression by tumor cells
- Measurable disease

Phase 2 – Best change from baseline

Arm	PR	SD
Combo (n=18)	2	9
Pembro (n=17)	1	5
No statistical difference in ORR		





Group 1: Anetumab ravtansine and Pembrolizumab
Group 2: Pembrolizumab

Hazard ratio: 0.55
P value = 0.1952

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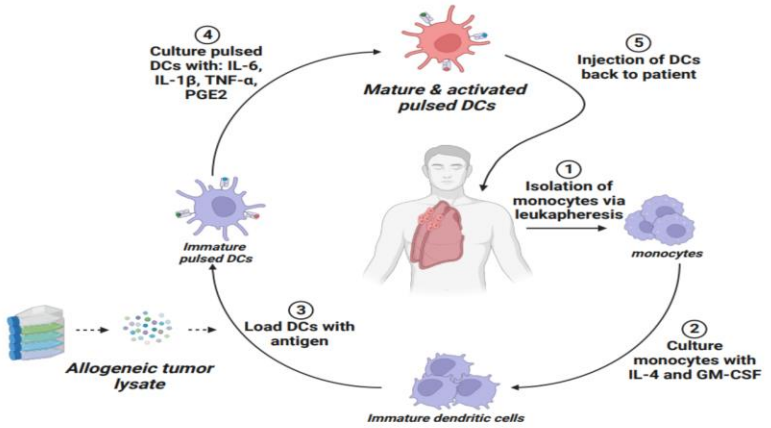
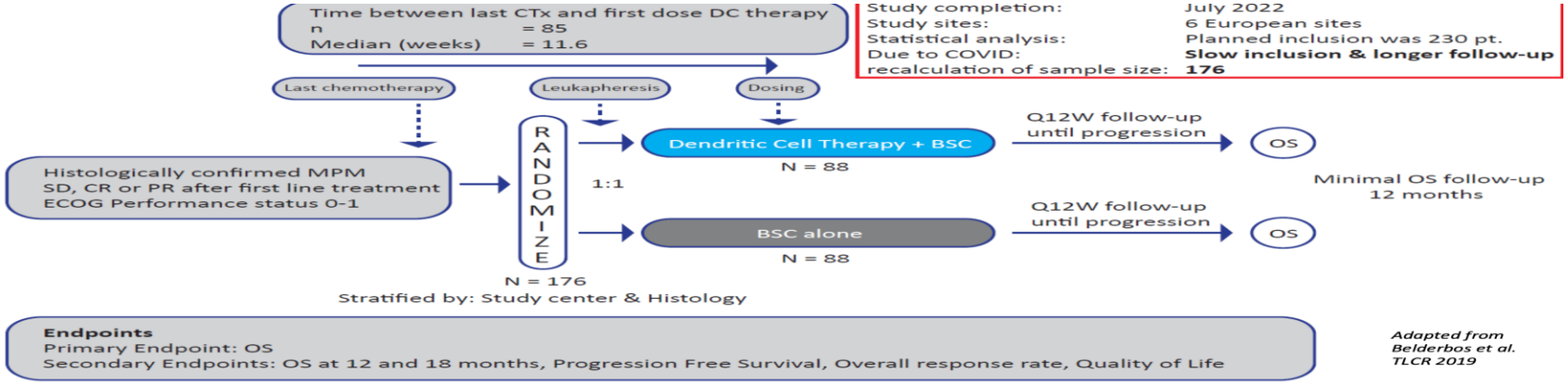
A multicenter, randomized, phase II/III study of dendritic cells (DC) loaded with allogeneic tumor cell lysate in subjects with mesothelioma as maintenance therapy after chemotherapy: DENdritic cell Immunotherapy for Mesothelioma (DENIM) trial

J.G.J.V. Aerts, MD PhD
Erasmus MC University Hospital Rotterdam the Netherlands
On behalf of the DENIM study group



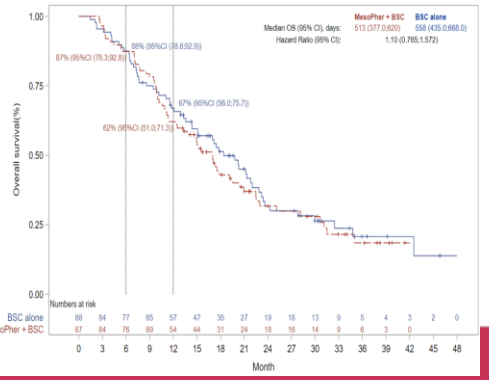


Study completion:	July 2022
Study sites:	6 European sites
Statistical analysis:	Planned inclusion was 230 pt.
Due to COVID:	**Slow inclusion & longer follow-up**
recalculation of sample size:	**176**

Adapted from Belderbos et al. TLCR 2019

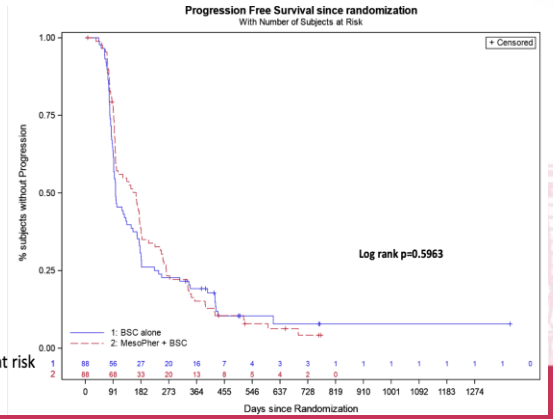
Overall Survival (Intention to treat analysis)

	DC + BSC (n=88)	BSC alone (n=88)
Median OS (95% CI), months	16,9 (12.4; 20.4)	18,3 (14.3; 21.9)



Progression Free Survival (intention to treat analysis)

	DC+ BSC (n=88)	BSC alone (n=88)
Median PFS (95% CI), days	166 (99-178)	99 (93-136)



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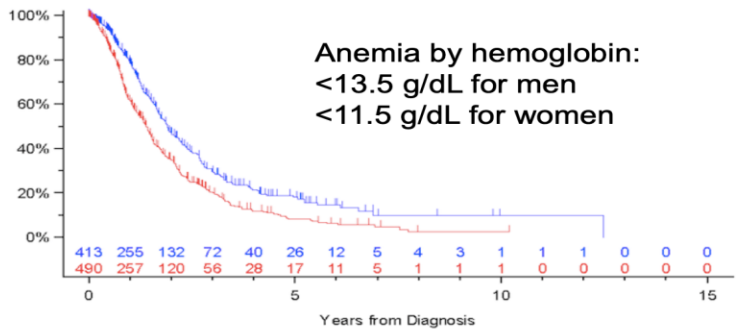
The IASLC Pleural Mesothelioma Staging Project: Updated Modeling of Prognostic Factors in Pleural Mesothelioma

Andrea S. Wolf, MD, MPH
New York Mesothelioma Program
The Icahn School of Medicine at Mount Sinai
United States of America

Results: Univariate analysis overall survival

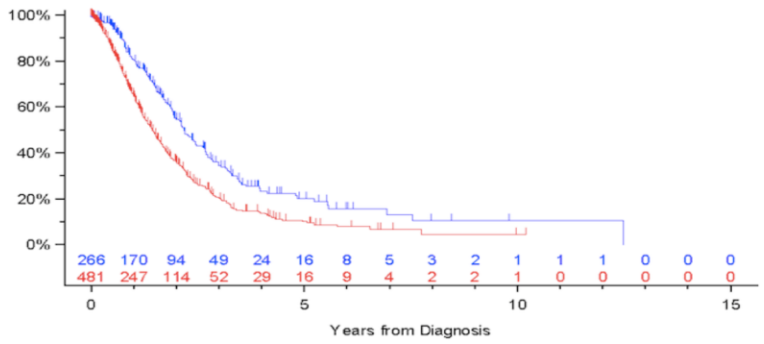
Overall Survival by Anemia



	Deaths / N	Median in Years	3-Year Estimate
No Anemia	247 / 413	1.9 (1.7, 2.2)	30% (24, 35)
Anemia	358 / 490	1.4 (1.2, 1.5)	20% (16, 24)

Log-rank p-value < .0001

Overall Survival by Serum Mesothelin



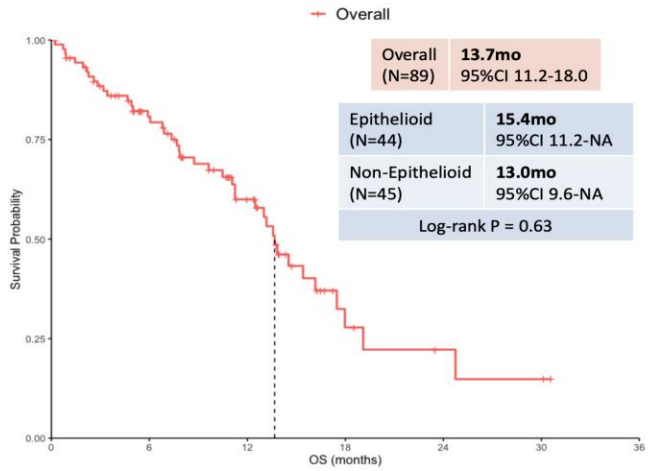
	Deaths / N	Median in Years	3-Year Estimate
Serum Mesothelin < 6.7 nmol/L	149 / 266	2.2 (1.9, 2.6)	34% (27, 42)
Serum Mesothelin >= 6.7 nmol/L	319 / 481	1.4 (1.3, 1.6)	20% (16, 25)

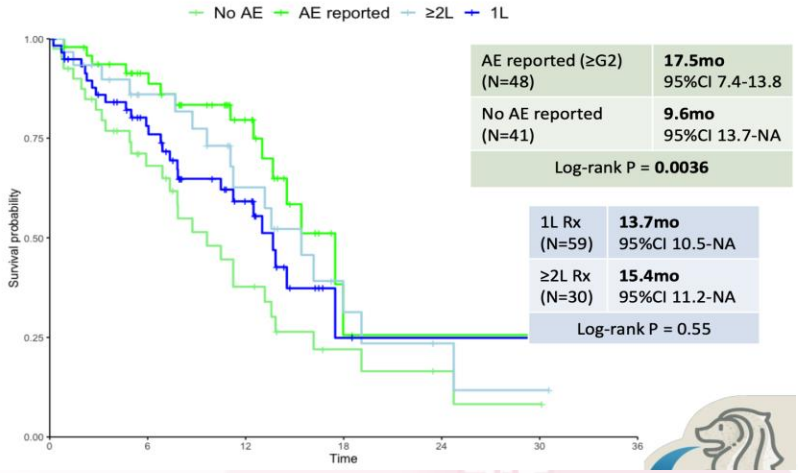
Log-rank p-value < .0001

RIOMeso - Real World Outcomes of Immunotherapy (IO) for Pleural MESOthelioma in Australia

Table 1 – Patient Demographics		*CM 743 - IO*
No. of patients	89	303
Age, median (range)	73 (19 - 89)	69
Male	70 (83%)	77%
ECOG ≤1	70 (91%)	100%
Current / past smoking	47 (53%)	57%
Known asbestos exposure	66 (73%)	-
Histology		
Epithelioid	49%	76%
Non-epithelioid	51%	24%
Sarcomatoid	*17%*	*12%*
Biphasic	*16%*	*13%*
Other / Unavailable	*18%*	-
Treatment line		
1L	59 (66%)	100%
≥2L	30 (34%)	-

Results - Survival

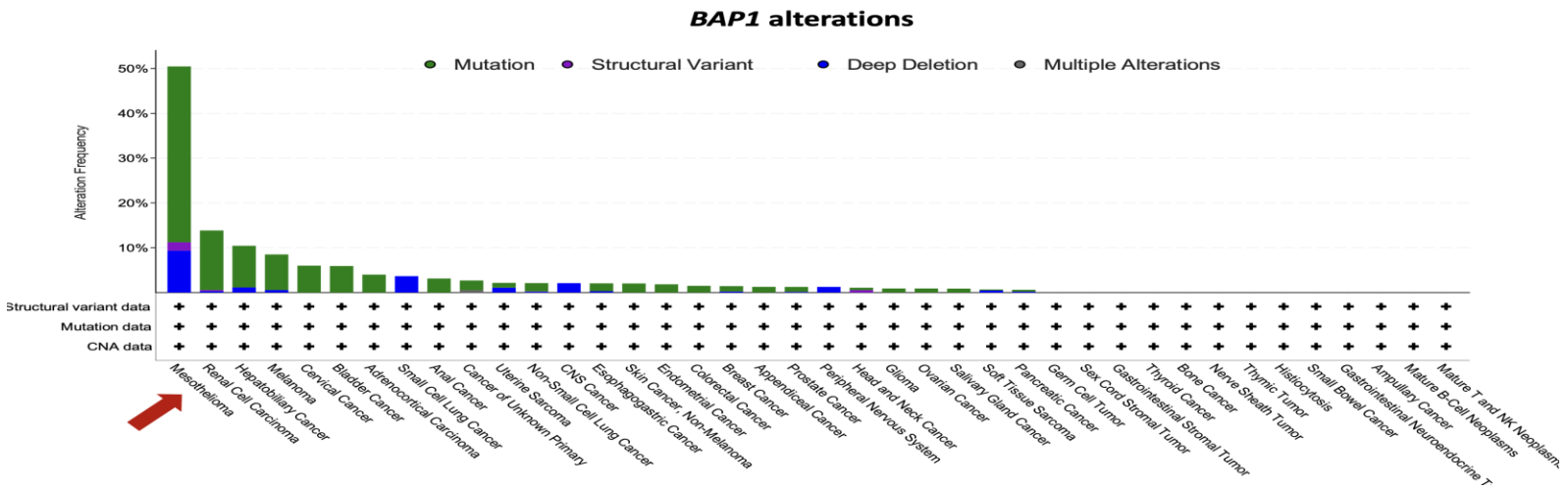




BAP1 Deficiency Inflames TIME: A Promising Biomarker for Enhanced Immunotherapy in Malignant Pleural Mesothelioma

Yongqian Shu

Genomic feature: tumor suppressor gene BAP1 loss in MPM



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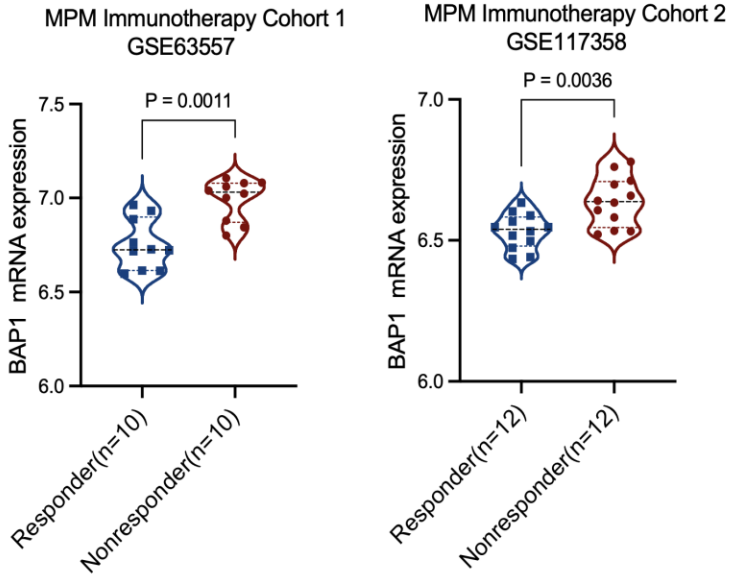

***BAP1*-loss MPM tends to respond better to immunotherapy**

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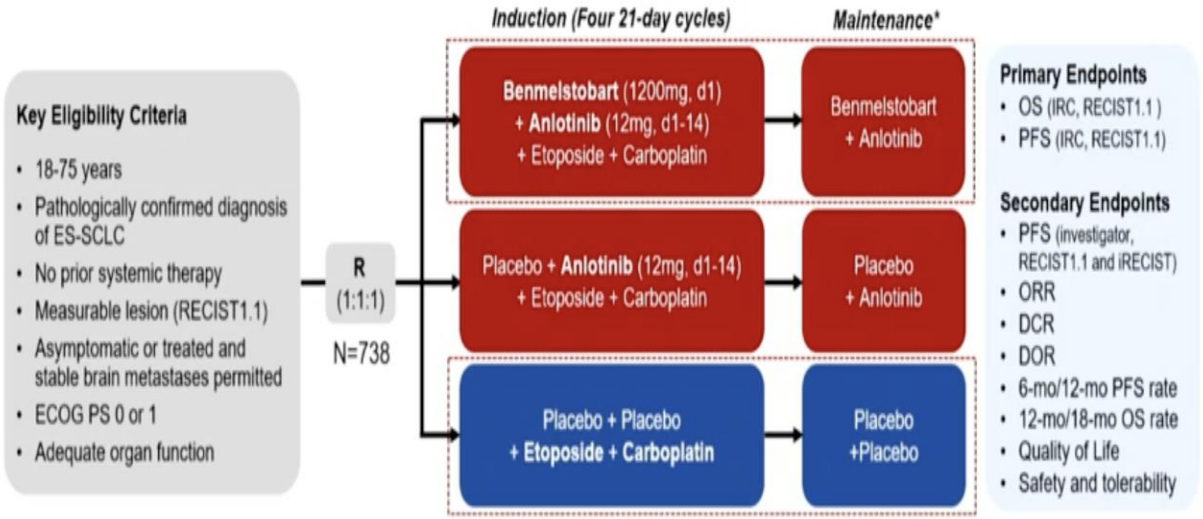
Benmelstobart with Anlotinib plus Chemotherapy as First-line Therapy for ES-SCLC: A Randomized, Double-blind, Phase III Trial (ETER701)

Ying Cheng[1], R. Yang[2], J. Chen[3], W. Zhang[4], C. Xie[5], Q. Hu[6], N. Zhou[7], C. Huang[8], S. Wei[9], H. Sun[10], X. Li[11], Y. Yu[12], J. Lai[13], H. Yang[14], H. Fang[15], H. Chen[16], P. Zhang[17], K. Gu[18], Q. Wang[19], J. Shi[20], T. Yi[21], X. Xu[22], X. Ye[23], D. Wang[24], C. Xie[25], C. Liu[26], Y. Zheng[27], D. Lin[28], W. Zhuang[29], P. Lu[30], G. Yu[31], J. Li[32], Y. Gu[33], B. Li[34], R. Wu[35], O. Jiang[36], Z. Wang[37], G. Wu[38], H. Lin[39], D. Zhong[40], Y. Xu[41], Y. Shu[42], D. Wu[43], X. Chen[44], J. Wang[45], M. Wang[46]

Study Design

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

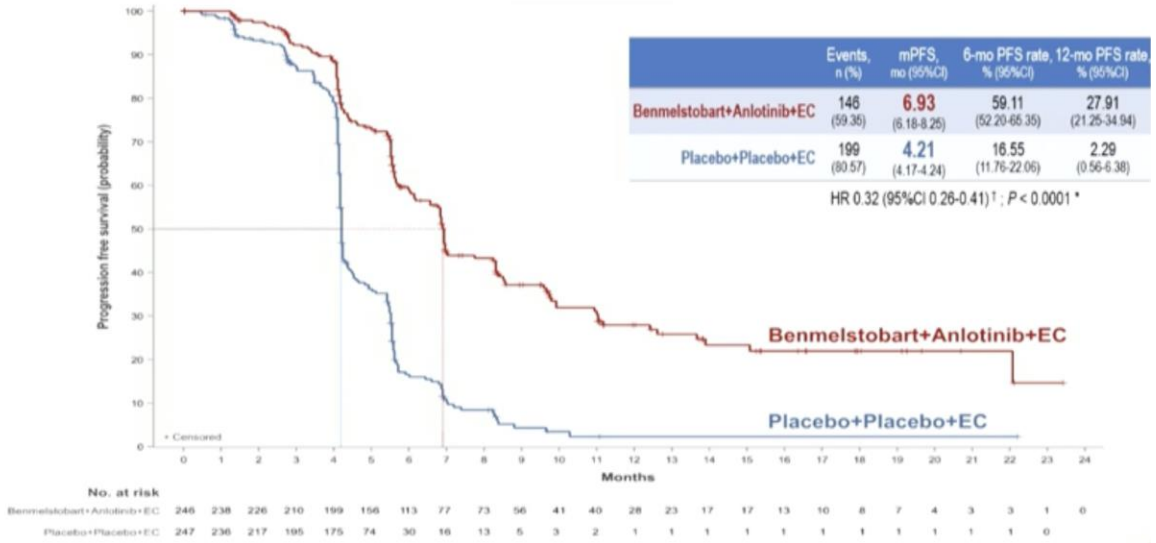


› **Stratified by:** ECOG PS (0/1); brain metastases (Y/N); liver metastases (Y/N).

Baseline Characteristics (ITT Population)

	Benmelstobart+Anlotinib+EC (N=246)	Placebo + Placebo + EC (N=247)
Median Age (range), years	62.0 (36-75)	63.0 (30-75)
Gender, n (%)		
Male	209 (85.0)	207 (83.8)
ECOG PS, n (%)		
0 / 1	47 (19.1) / 199 (80.9)	48 (19.4) / 199 (80.6)
Smoking status, n (%)		
Never	59 (24.0)	54 (21.9)
Former / Current	154 (62.6) / 33 (13.4)	158 (64.0) / 35 (14.2)
Clinical stage*, n (%)		
Limited-stage	1 (0.4)	7 (2.8)
Extensive-stage	245 (99.6)	240 (97.2)
Disease stage# (AJCC 8th), n (%)		
II	0 (0.0)	1 (0.4)[a]
III	30 (12.2)	21 (8.5)
IV	216 (87.8)	225 (91.1)
Brain / Liver / Bone metastases, n (%)	25 (10.2) / 79 (32.1) / 69 (28.0)	26 (10.5) / 79 (32.0) / 69 (27.9)

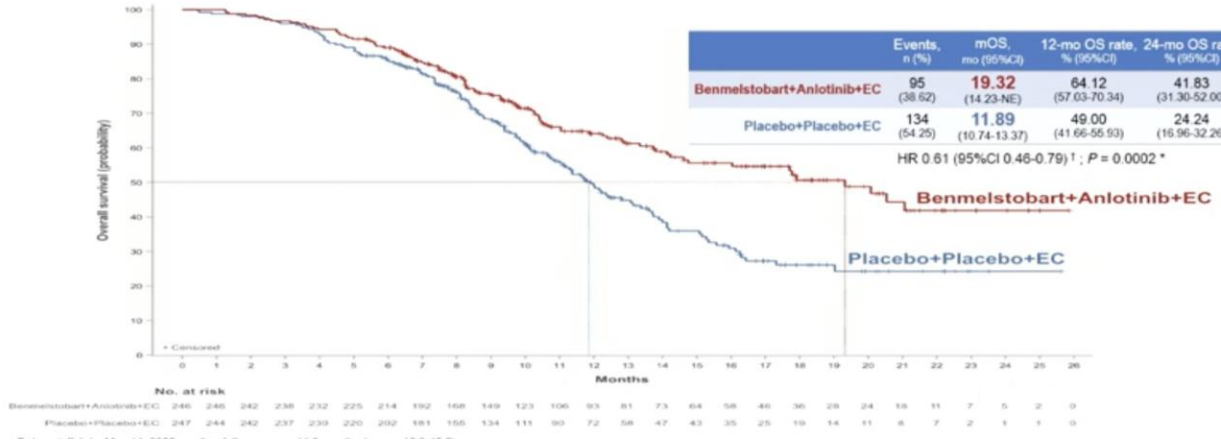
Primary Endpoint: PFS (ITT Population)



	Events, n (%)	mPFS, mo (95%CI)	6-mo PFS rate, % (95%CI)	12-mo PFS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	146 (59.35)	6.93 (6.18-8.25)	59.11 (52.20-65.35)	27.91 (21.25-34.94)
Placebo+Placebo+EC	199 (80.57)	4.21 (4.17-4.24)	16.55 (11.76-22.06)	2.29 (0.56-6.38)

HR 0.32 (95%CI 0.26-0.41)† ; *P* < 0.0001 *

Primary Endpoint: OS (ITT Population)



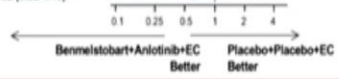
	Events, n (%)	mOS, mo (95%CI)	12-mo OS rate, % (95%CI)	24-mo OS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	95 (38.62)	19.32 (14.23-NE)	64.12 (57.03-70.34)	41.83 (31.30-52.00)
Placebo+Placebo+EC	134 (54.25)	11.89 (10.74-13.37)	49.00 (41.66-55.93)	24.24 (16.96-32.26)

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

PFS and OS in Subgroups

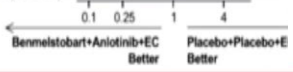
OS

Subgroups	N (Events)	Benmelstobart+Anlotinib+EC vs. Placebo+Placebo+EC Harzard Ratio for Death (95%CI)
All the patients	493 (229)	0.61 (0.47-0.79)
ECOG PS, n (%)		
0	95 (35)	0.49 (0.24-0.98)
1	398 (194)	0.63 (0.47-0.84)
Brain metastases		
Yes	51 (27)	0.64 (0.29-1.41)
No	442 (202)	0.60 (0.45-0.79)
Liver metastases		
Yes	158 (96)	0.79 (0.53-1.18)
No	335 (133)	0.51 (0.36-0.72)
Bone metastases		
Yes	138 (73)	0.55 (0.34-0.88)
No	355 (156)	0.62 (0.45-0.86)
Age		
≥65	196 (96)	0.54 (0.35-0.81)
<65	297 (133)	0.65 (0.46-0.92)
Lactate Dehydrogenase (LDH)		
≥ULN	232 (127)	0.61 (0.43-0.87)
<ULN	259 (102)	0.55 (0.37-0.82)
Clinical stage' at first diagnosis		
Limited-stage	8 (5)	0.62 (0.47-0.80)
Extensive-stage	485 (224)	
Gender		
Male	416 (201)	0.64 (0.48-0.85)
Female	77 (28)	0.30 (0.12-0.75)
Disease stage#		
IV	441 (209)	0.63 (0.48-0.83)
II/III	52 (20)	0.43 (0.18-1.07)
Smoking status		
Former	312 (150)	0.67 (0.49-0.93)
Never	113 (41)	0.38 (0.20-0.74)
Current	68 (38)	0.62 (0.32-1.19)

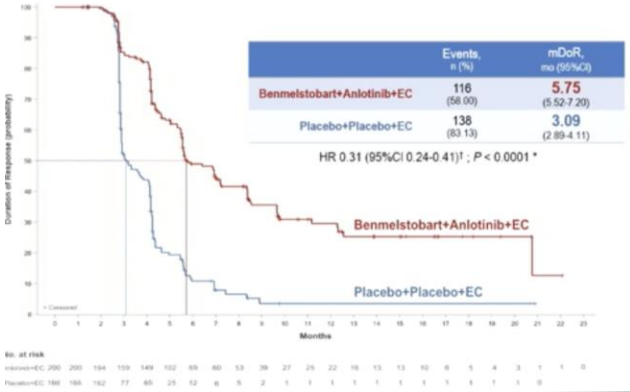


PFS

Subgroups	N (Events)	Benmelstobart+Anlotinib+EC vs. Placebo+Placebo+EC Harzard Ratio for Disease Progression or Death (95%CI)
All the patients	493 (345)	0.32 (0.26-0.41)
ECOG PS, n (%)		
0	95 (60)	0.22 (0.12-0.40)
1	398 (285)	0.36 (0.30-0.49)
Brain metastases		
Yes	51 (40)	0.59 (0.30-1.16)
No	442 (305)	0.33 (0.26-0.42)
Liver metastases		
Yes	158 (123)	0.36 (0.24-0.53)
No	335 (222)	0.31 (0.23-0.41)
Bone metastases		
Yes	138 (100)	0.39 (0.26-0.60)
No	355 (245)	0.33 (0.25-0.44)
Age		
≥65	196 (136)	0.31 (0.22-0.45)
<65	297 (209)	0.37 (0.28-0.50)
Lactate Dehydrogenase (LDH)		
≥ULN	232 (167)	0.35 (0.25-0.48)
<ULN	259 (177)	0.33 (0.24-0.46)
Clinical stage' at first diagnosis		
Limited-stage	8 (7)	0.78 (0.09-6.88)
Extensive-stage	485 (338)	0.35 (0.28-0.44)
Gender		
Male	416 (296)	0.34 (0.27-0.43)
Female	77 (49)	0.32 (0.17-0.60)
Disease stage#		
IV	441 (310)	0.34 (0.27-0.43)
II/III	52 (35)	0.40 (0.20-0.80)
Smoking status		
Former	312 (227)	0.40 (0.30-0.52)
Never	113 (70)	0.26 (0.15-0.44)
Current	68 (48)	0.26 (0.13-0.49)



Secondary Endpoints: DoR, ORR, DCR (ITT Population)



	Events, n (%)	mDoR, mo (95%CI)
Benmelstobart+Anlotinib+EC	116 (58.00)	5.75 (5.52-7.20)
Placebo+Placebo+EC	138 (83.13)	3.09 (2.89-4.11)

HR 0.31 (95%CI 0.24-0.41)† ; *P* < 0.0001 *

Tumor response (IRC, RECIST 1.1)

	Benmelstobart + Anlotinib + EC (N=246)	Placebo + Placebo + EC (N=247)
Objective confirmed response, n (%) [95%CI]	200 (81.30) [75.86-85.97]	165 (66.80) [60.55-72.64]
Complete Response, n (%)	3 (1.22)	0 (0.00)
Partial Response, n (%)	197 (80.08)	165 (66.80)
Stable Disease, n (%)	23 (9.35)	50 (20.24)
Progressive Disease, n (%)	8 (3.25)	16 (6.48)
Not Evaluable*, n (%)	15 (6.10)	16 (6.48)
P	0.0001	
Disease Control Rate, n (%) [95%CI]	223 (90.65) [86.30-93.98]	215 (87.04) [82.21-90.97]
P	0.2003	

* The best overall response could not be evaluated for patients who had no baseline or no postbaseline tumor assessments, and at least one lesion that could not be evaluated.
IRC= Independent Review Committee

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)

TRAEs	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)
TRAEs reported in ≥10% of patients, n (%)				
Neutrophil count decreased	224 (91.1)	171 (69.5)	223 (90.7)	169 (68.7)
Platelet count decreased	219 (89.0)	122 (49.6)	201 (81.7)	88 (35.8)
White-cell count decreased	223 (90.7)	94 (38.2)	225 (91.5)	85 (34.6)
Anemia	192 (78.0)	59 (24.0)	207 (84.2)	58 (23.6)
Nausea	99 (40.2)	1 (0.4)	108 (43.9)	0 (0.0)
Hypertension	77 (31.3)	38 (15.5)	18 (7.3)	4 (1.6)
Hypothyroidism	75 (30.5)	1 (0.4)	13 (5.3)	0 (0.0)
ALT increased	68 (27.6)	2 (0.9)	73 (29.7)	5 (2.0)
Hypertriglyceridemia	67 (27.2)	8 (3.3)	46 (18.7)	2 (0.8)
AST increased	66 (26.8)	3 (1.2)	60 (24.4)	1 (0.4)
Hypoalbuminemia	60 (24.4)	0 (0.0)	37 (15.0)	1 (0.4)
Proteinuria	59 (24.0)	2 (0.8)	28 (11.4)	1 (0.4)
Hypercholesterolemia	48 (19.5)	1 (0.4)	24 (9.8)	0 (0.0)
Weight loss	45 (18.3)	3 (1.2)	17 (6.9)	1 (0.4)
TSH increased	33 (13.4)	1 (0.4)	8 (3.3)	0 (0.0)
Occult blood positive	29 (11.8)	0 (0.0)	17 (6.9)	2 (0.8)
Lymphocyte count decreased	29 (11.8)	8 (3.3)	24 (9.8)	7 (2.9)
Total bilirubin increased	29 (11.8)	2 (0.8)	17 (6.9)	2 (0.8)
Palmar-plantar erythrodysesthesia syndrome	28 (11.4)	6 (2.4)	3 (1.2)	0 (0.0)
γ-GT increased	27 (11.0)	4 (1.6)	28 (11.4)	3 (1.2)

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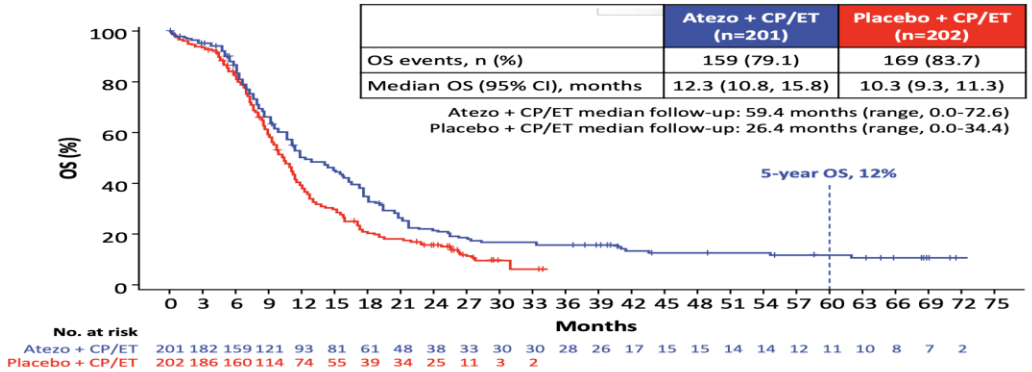
Five-year survival in patients with ES-SCLC treated with atezolizumab in IMpower133: IMbrella A extension study results

Stephen V. Liu,[1] Rafal Dziadziuszko,[2] Shunichi Sugawara,[3] Steven Kao,[4] Maximilian Hochmair,[5] Florian Huemer,[6] Gilberto de Castro, Junior,[7] Libor Havel,[8] Reyes Bernabé Caro,[9] György Losonczy,[10] Jong-Seok Lee,[11] Dariusz Kowalski,[12] Zoran Andric,[13] Raffaele Califano,[14] Andrea Veatch,[15] Gregory Gerstner,[16] Marta Batus,[17] Stefanie Morris,[18] Monika Kaul,[19] Madeena Siddiqui,[19] Huafei Li,[20] Wei Zhang,[19] Barzin Nabet,[19] Martin Reck[21]

Characteristic	IMpower133 Atezo + CP/ET (n=201)[1]	IMbrella A (n=18)[a]
Median age (range), year	64.0 (28-90)	60.5 (46-80)
Age < 65 years, n (%)	111 (55.2)	14 (77.8)
Male, n (%)	129 (64.2)	11 (61.1)
White, n (%)	163 (81.1)	14 (77.8)
Asian, n (%)	33 (16.4)	3 (16.7)
Never used tobacco, n (%)	9 (4.5)	1 (5.6)
ECOG PS 0, n (%)	73 (36.3)	12 (66.7)
Brain metastases, n (%)	17 (8.5)	2 (11.1)
Liver metastases, n (%)	77 (38.3)	2 (11.1)

IMpower133 and IMbrella A: long-term OS

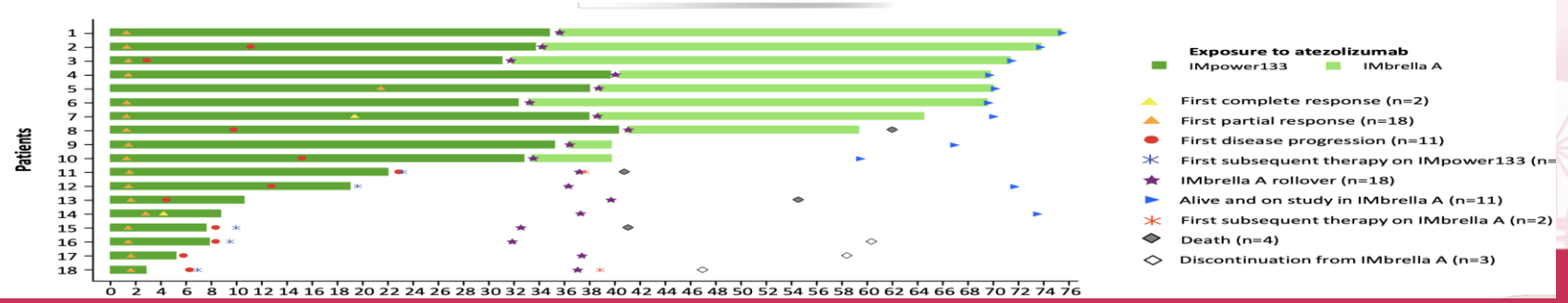


	Atezo + CP/ET (n=201)	Placebo + CP/ET (n=202)
OS events, n (%)	159 (79.1)	169 (83.7)
Median OS (95% CI), months	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)

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]

Patients from IMpower133 who enrolled in IMbrella A (n=18)



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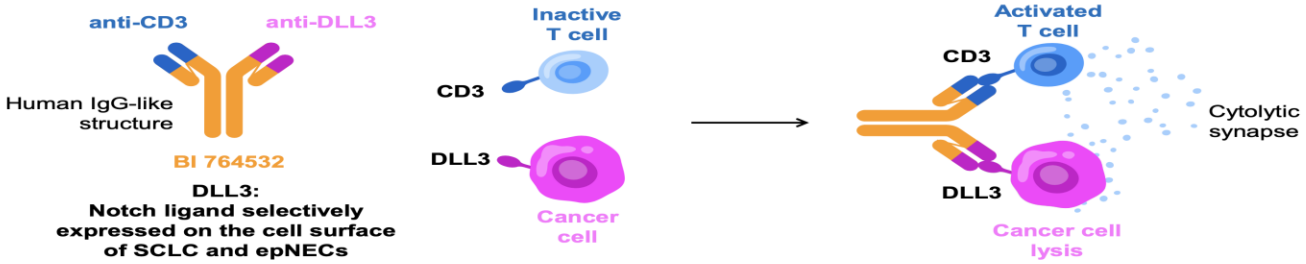
Phase I dose escalation trial of the DLL3/CD3 IgG-like T cell engager BI 764532 in patients with DLL3+ tumors: focus on SCLC and LCNEC

Martin Wermke[1], Yasutoshi Kuboki[2], Enriqueta Felip[3], Olatunji B. Alese[4], Daniel Morgensztern[5], Cyrus Sayehli[6], Edurne Arriola[7], Miguel F. Sanmamed[8], Zohra Oum' Hamed[9], Eric Song[10], Matus Studeny[11], Valentina Gambardella[12]

BI 764532: a novel DLL3-targeting T cell engager



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

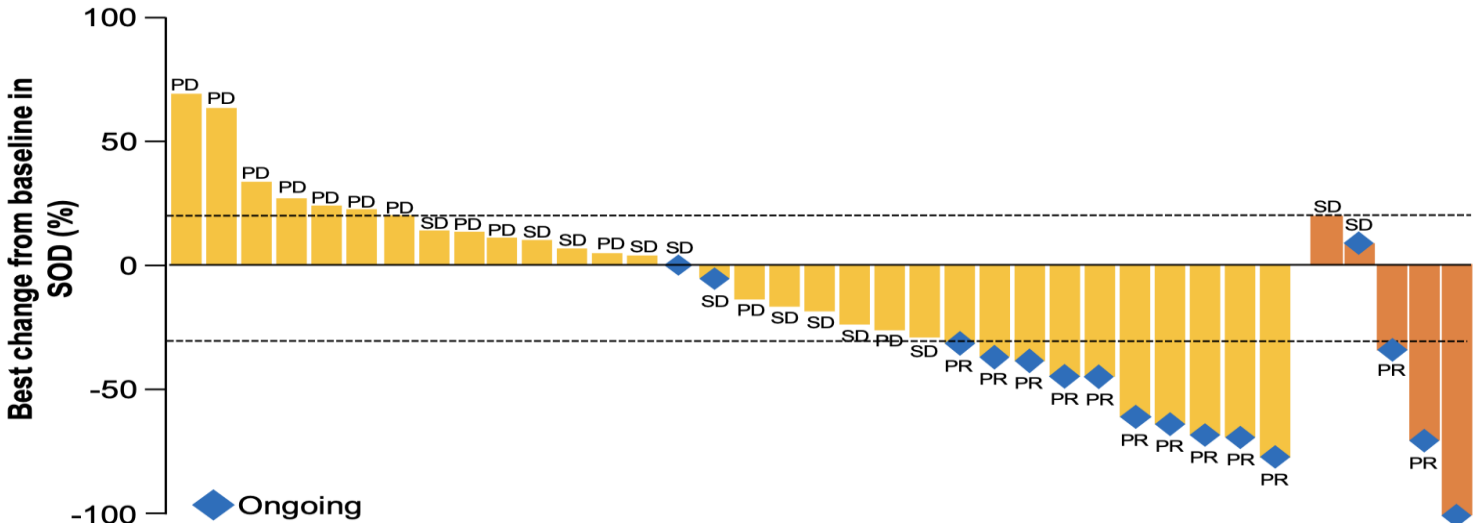
As of March 26 2023	N=107†
Median age, years (range)	60.0 (32–79)
Male, n (%)	61 (57)
Prior lines of therapy, n (%)	
1–2	72 (67)
≥3	33 (31)
ECOG PS 0/1, n (%)	28 (26)/78 (73)
Prior PD-1/PD-L1, n (%)	52 (49)
Brain/liver metastases, n (%)	41 (38)/60 (56)

†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

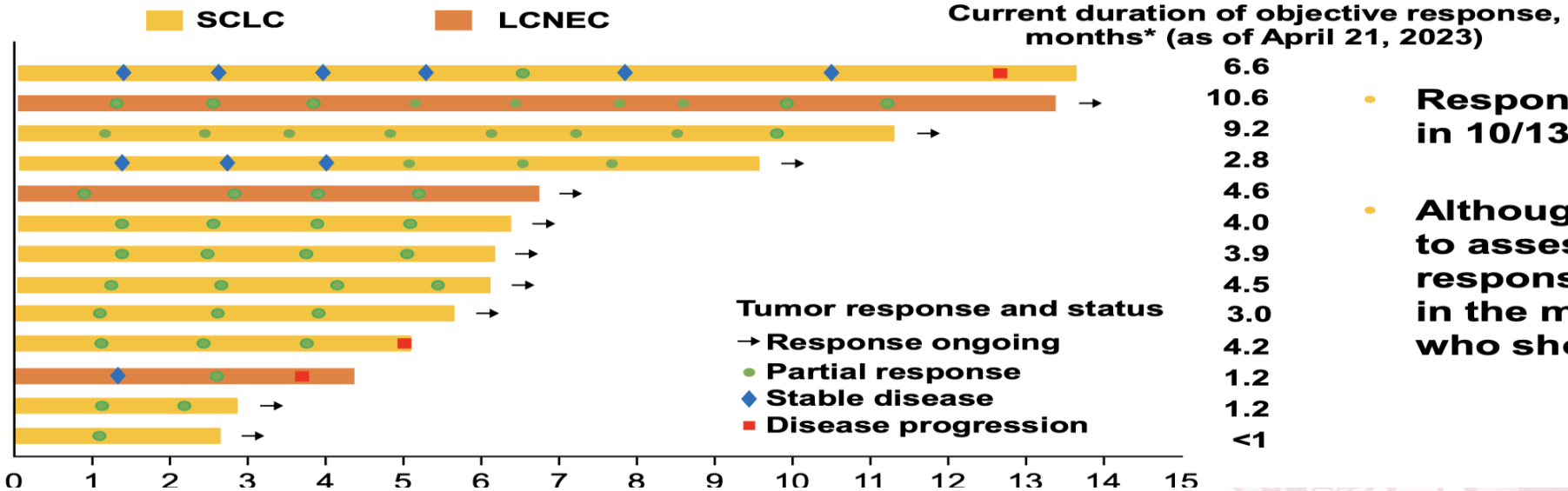
Efficacy in patients with SCLC and LCNEC (doses ≥ 90µg/kg)



n, (%)	SCLC (n=39)*	LCNEC (n=5)*
PR	10 (26)	3 (60)
SD	10 (26)	2 (40)
PD	12 (31)	0
DCR	20 (51)	5 (100)
NE†	7 (18)	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

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

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First-line Chemotherapy With or Without Tislelizumab for Extensive-stage Small Cell Lung Cancer: RATIONALE-312 Phase 3 Study

Ying Cheng,[1*] Yun Fan,[2] Yanqiu Zhao,[3] Dingzhi Huang,[4] Xingya Li,[5] Peng Zhang,[6] Mafei Kang,[7] Nong Yang,[8] Diansheng Zhong,[9] Zhen Wang,[10] Yan Yu,[11] Yu Zhang,[12] Jun Zhao,[13] Tai Qin,[14] Chenqi Chen,[15] Shiangjiin Leaw,[15] Wenjuan Zheng,[14] and Yong Song,[16] on behalf of the RATIONALE-312 Study Group

Study Design

Randomized, double-blind, placebo-controlled, multicenter, phase 3 study (NCT04005716)

Key eligibility criteria
- Patients aged ≥18 years with histologically/cytologically confirmed ES-SCLC
- No prior systemic treatment for ES-SCLC
- ECOG PS ≤1

R 1:1

Induction treatment (Q3W, four cycles)
- Tislelizumab 200 mg D1 + carboplatin (AUC 5) or cisplatin (75 mg/m²), D1 + etoposide (100 mg/m²), D1-3
- Placebo D1 + carboplatin (AUC 5) or cisplatin (75 mg/m²), D1 + etoposide (100 mg/m²), D1-3

Maintenance treatment
- Tislelizumab 200 mg Q3W
- Placebo Q3W

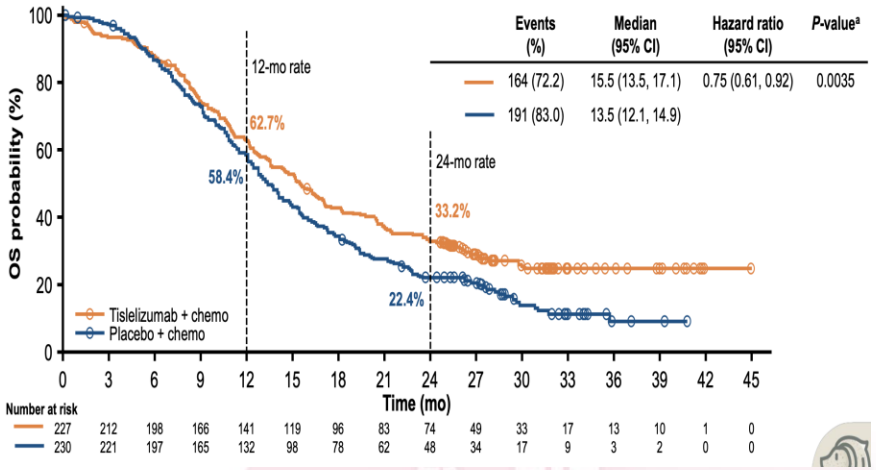
Continue until disease progression or intolerable toxicity

Stratification factors
- ECOG PS (0 vs 1)
- Cisplatin vs carboplatin
- Brain metastasis (yes vs no)

Primary endpoint: OS
Key secondary endpoints:
- PFS, ORR, and DoR (INV-assessed)
- Safety and tolerability

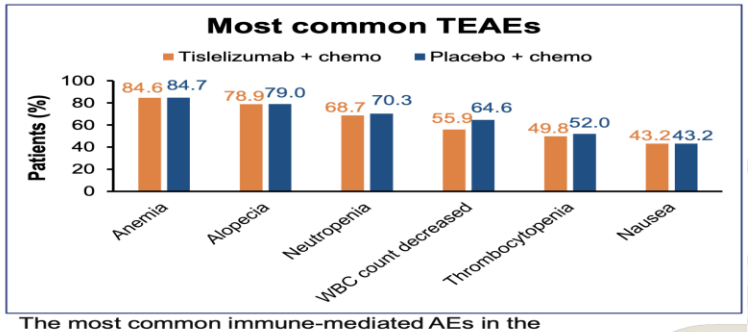
Statistical methods
- Planned to enroll 455 pts; 80% power to detect HR 0.74 with 353 OS events
- Hierarchical testing on PFS: only when OS demonstrates significance[a]

Overall Survival (OS)



Safety Summary

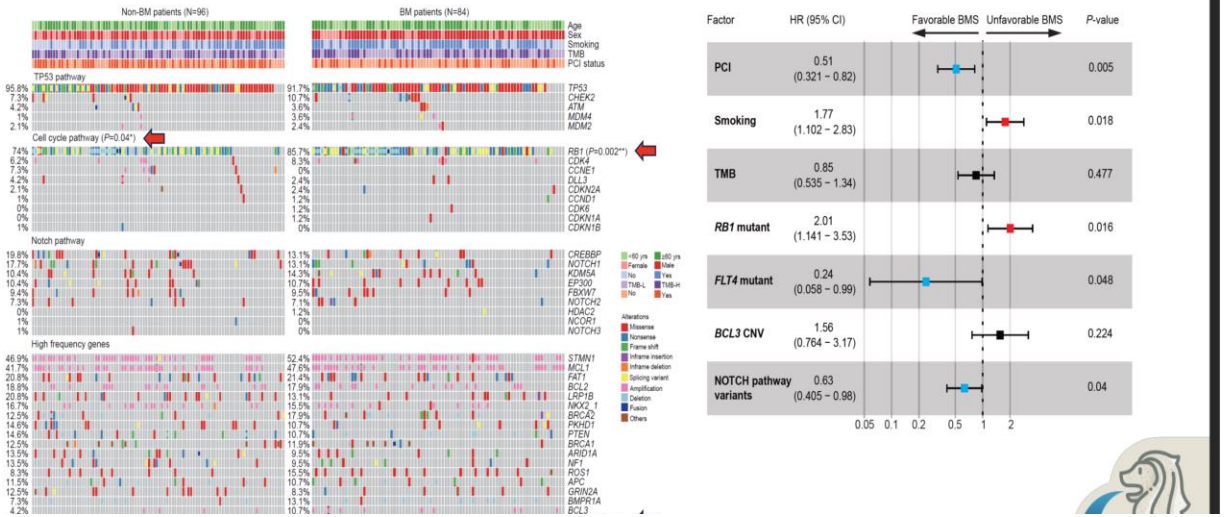
	Tislelizumab + chemo (n=227)	Placebo + chemo (n=229)
Tislelizumab/placebo cycles		
Mean	11.8	7.3
Median (range)	6.0 (1-59)	6.0 (1-48)
>16 cycles, n (%)	44 (19.4%)	10 (4.4%)
Chemotherapy cycles, median, n (range)	4 (1-4)	4 (1-4)
TEAEs, n (%)	226 (99.6)	228 (99.6)
Treatment-related[a]	226 (99.6)	228 (99.6)
Grade ≥3	201 (88.5)	206 (90.0)
Serious	94 (41.4)	69 (30.1)
Leading to discontinuation[b]	30 (13.2)	7 (3.1)
Leading to death[c]	14 (6.2)	4 (1.7)
Tislelizumab/placebo-related	7 (3.1)	0 (0.0)
Chemotherapy-related	6 (2.6)	0 (0.0)
Immune-mediated AEs, n (%)	87 (38.3)	41 (17.9)
Leading to death	1 (0.4)	0 (0.0)
Infusion-related reactions, n (%)	8 (3.5)	5 (2.2)



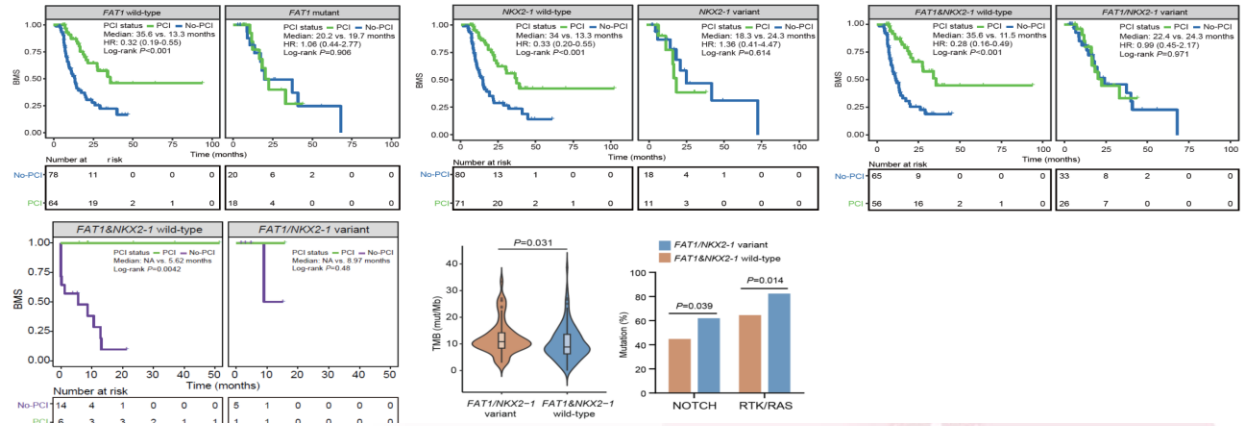
The most common immune-mediated AEs in the tislelizumab plus chemo arm were hypothyroidism (13.7%), rash (13.2%), hyperthyroidism (5.7%)

Biomarkers for Brain Metastases Risk and Survival Benefit of Prophylactic Cranial Irradiation in Limited-Stage Small-Cell Lung Cancer

Genomic alterations associated with BM risk in LS-SCLC



Potential predictive genomic signatures for PCI response



1. Genomic profiling revealed significant differences between LS-SCLC patients with and without brain metastases.
2. Five clinical/genomic features were independently associated with BM risk in LS-SCLC.
3. *FAT1* and *NKX2-1* mutational status effectively predicts PCI treatment response in LS-SCLC.

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A Phase 1b/2 Study of Senaparib in Combination with Low-dose Temozolomide: Updated Results in Relapsed ES-SCLC Patients

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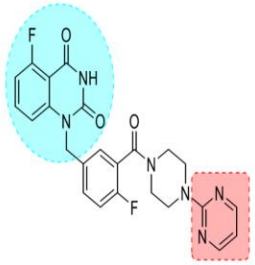
Min Hee Hong[1], Bo Gao[2], Ying Cheng[3], Byoung Yong Shim[4], Melissa Johnson[5], Cheng-Ying Liu[6], Sang-We Kim[7], Ki Hyeong Lee[8], Robert Zielinski[9], Richard Eek[10], Sheng Hu[11], Chia-Chi Lin[12], Wei-Pang Chung[13], Chih-Yi Hsieh[14], Sui Xiong Cai[14], Ye Edward Tian[14], Lan Liu[14], Tiantian Niu[14], Clare Halcro[15], Baoyue Li[14], Ming Zhang[14], Congcong Zhang[14], Huiyun Li[14], Li Xu[14], Hsin-Tien Hung[15]

Introduction of senaparib



IMP4297, Senaparib

- There are very limited treatment options for relapsed ES-SCLC.
- Senaparib is a novel PARP1/2 inhibitor with improved efficacy combined with temozolomide in SCLC model[1,2].

Potential synergism of senaparib and temozolomide[3]

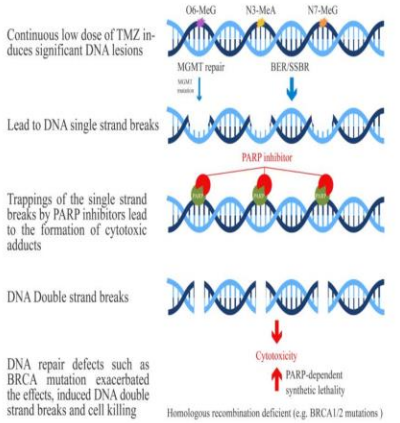
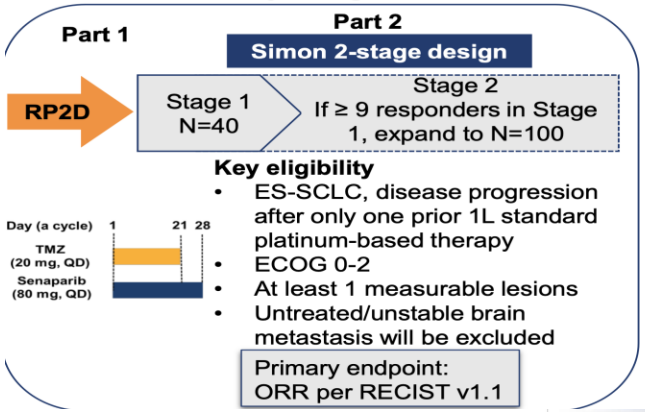


Figure 1. Mechanism of PARP inhibitors in combination with low dose temozolomide

Study design



Key eligibility

- ES-SCLC, disease progression after only one prior 1L standard platinum-based therapy
- ECOG 0-2
- At least 1 measurable lesions
- Untreated/unstable brain metastasis will be excluded

Primary endpoint:
ORR per RECIST v1.1

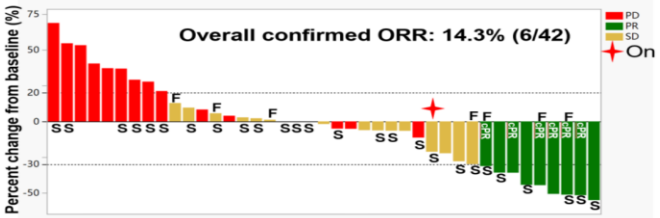
Baseline characteristics in Part 2

N=45		n (%)
Gender	Female/Male	11 (24.4)/34 (75.6)
Age (years)	Median	67.0 (39.0, 83.0)
Race	Asian/White	34 (75.6)/11 (24.4)
Smoking	Yes	41 (91.1)
History	No	4 (8.9)
Platinum	Resistant	18 (40.0)
sensitivity*	Sensitive	27 (60.0)
ECOG	≤1/2	43 (95.5)/2 (4.4)
Brain	Yes	11 (24.4)
metastasis	No	34 (75.6)
Prior IO	Yes/No	36 (80.0)/9 (20.0)

* Platinum sensitive: chemotherapy-free interval (CFI) exceeds 90 days. Platinum resistant: CFI within 90 days.

Efficacy

Best change from baseline in Target lesions



S: platinum-sensitive; F: FANC mut; one patient was not shown as the target lesions were not evaluable post-baseline.

	FANC WT (n=38)	FANC mut (n=7)
Confirmed ORR	8.6% (3/35)	42.9% (3/7)
mDOR (months) (95% CI)	4.0 (3.4, NR)	5.6 (3.9, NR)

- FANC WT: no pathogenic mutation in FANC genes;
- FANC mut: at least one pathogenic mutation in FANC genes, including FANCA, FANCD1(BRCA2), FANCL, FANCM, et al.

- Median follow-up: 8.3 months (0.6-18.7)
- Median time to response: 1.8 months (1.7-2.0)
- Median duration of response: 4.8 months (95% CI, 3.9- NR)

Conclusiones

- Mesotelioma:
  - Sigue siendo una entidad de difícil diagnóstico y consenso anatomopatológico.
  - La anemia y los niveles de mesotelina son factores pronósticos.
  - Los anticuerpos conjugados combinados con IO y las células dendriticas en monoterapia no han aportado avances.
  - La pérdida de BAP1 se asocia a mejor respuesta a IO
  - Estudios de vida real reflejan datos similares y muestran la asociación de toxicidad con incremento en OS.
- SCLC:
  - Benmelstobart + anlotinib: Muestran excelentes resultados en supervivencia con toxicidad manejable: PERO EN POBLACIÓN ASIATICA.
  - Se mantiene hasta un 12% de largos supervivientes con Atezolizumab a 5 años en el estudio Imbrella.
  - Datos prometedores en fase I del anticuerpo dual CD3/DLL3 en segundas líneas con tasas de respuesta de 50% y respuestas duraderas.
  - Se confirma con tislelizumab la eficacia de tratar el eje PD1-PDL1 en SCLC.
  - Estudios genómicos muestran posibles biomarcadores para el beneficio de la PCI: FAT1 y NKX2
  - Senaparib (iPARP) muestra datos de eficacia en pacientes previamente tratados especialmente en paciente con mutaciones en FANC