

Cáncer de pulmón de célula pequeña, mesotelioma pleural y otros tumores

Rafael López Castro

Hospital Clínico Universitario de Valladolid



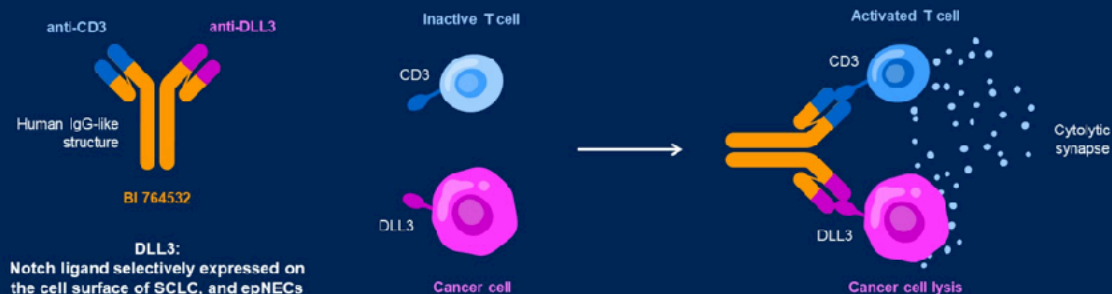
Cáncer de pulmón de célula pequeña



#8502: First-in-human dose-escalation trial of BI 764532, a delta-like ligand 3 (DLL3)/CD3 IgG-like T-cell engager in patients (pts) with DLL3-positive (DLL3+) small-cell lung cancer (SCLC) and neuroendocrine carcinoma (NEC)

Martin Wermke, Enriqueta Felip, Yasutoshi Kuboki, Daniel Morgensztern, Cyrus Sayehli, Miguel F. Sanmamed, Edurne Arriola, Zohra Oum'Hamed, Eric Song, Matus Studeny, Valentina Gambardella

BI 764532: a novel DLL3-targeting T cell engager



- BI 764532 redirects the patient's own T cells to lyse DLL3-expressing cancer cells

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

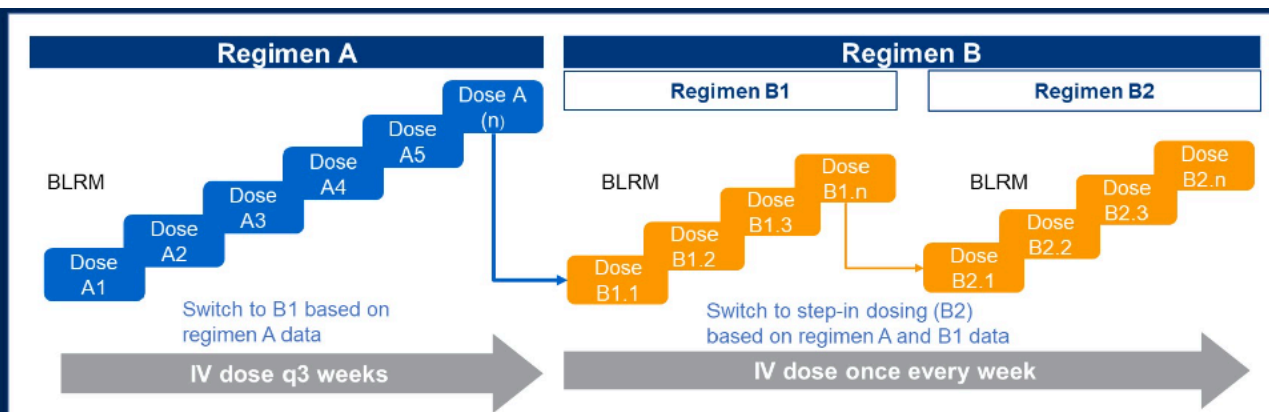
As of March 2023†	N=107‡
Median age, years (range)	60.0 (32–79)
Male, n (%)	61 (57)
Prior lines of therapy, n (%)	
1–2	72 (67)
≥3	33 (31)
ECOG PS 0/1, n (%)	28 (26)/78 (73)
Prior PD-1/PD-L1, n (%)	52 (49)
Brain/liver metastases, n (%)	41 (38)/60 (56)



†Data snapshot: 26th March 2023

‡Safety population: ≥1 dose of BI 764532

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



Primary endpoints

- MTD
- DLTs in the MTD evaluation period

Secondary endpoints

- Objective response (RECIST 1.1)
- PK parameters

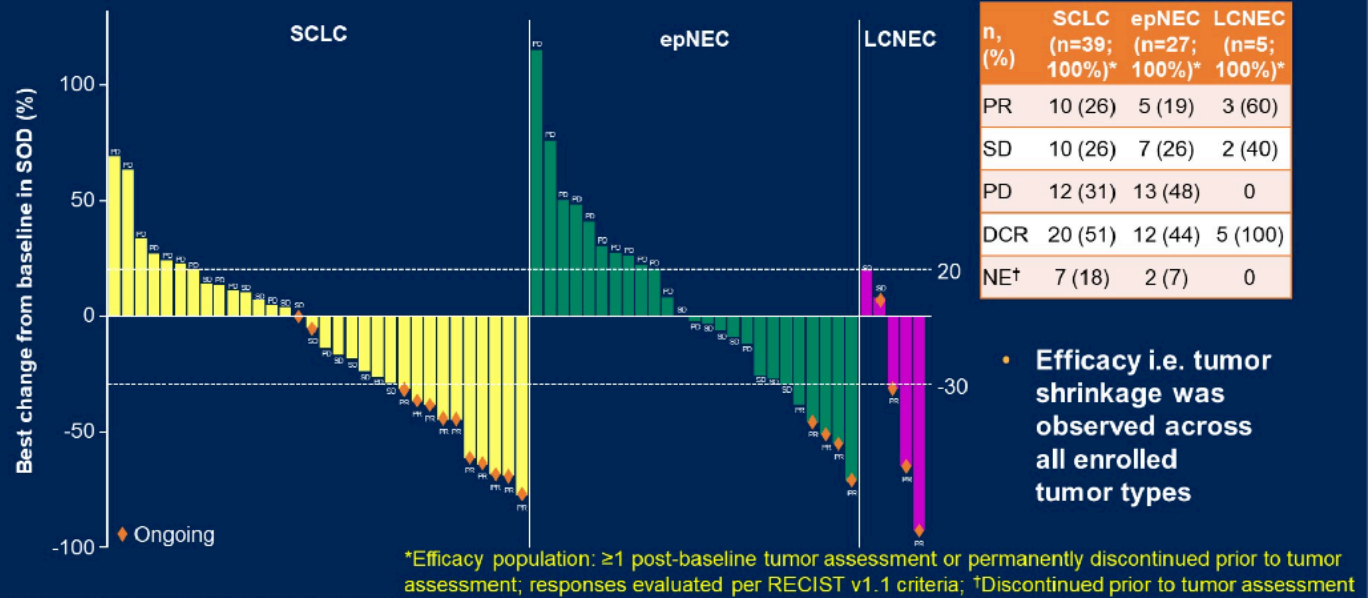
Most common treatment-related AEs (>10% patients)

TRAE, n (%)	Total (N=107; 100%)*		
	All grade	Grade 1–2	Grade 3–5
Number of pts with ≥1 TRAE	92 (86)	63 (59)	29 (27)
CRS	63 (59)	61 (57)	2 (2)
Lymphocyte count decreased	21 (20)	4 (4)	17 (16)
Dysgeusia	21 (20)	21 (20)	0
Asthenia	20 (19)	19 (18)	1 (<1)
Pyrexia	19 (18)	19 (18)	0
AST increased	15 (14)	13 (12)	2 (2)
Fatigue	15 (14)	14 (13)	1 (<1)
Nausea	13 (12)	13 (12)	0

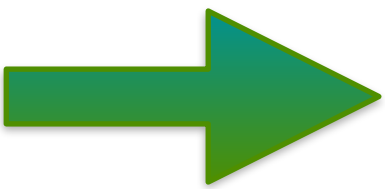
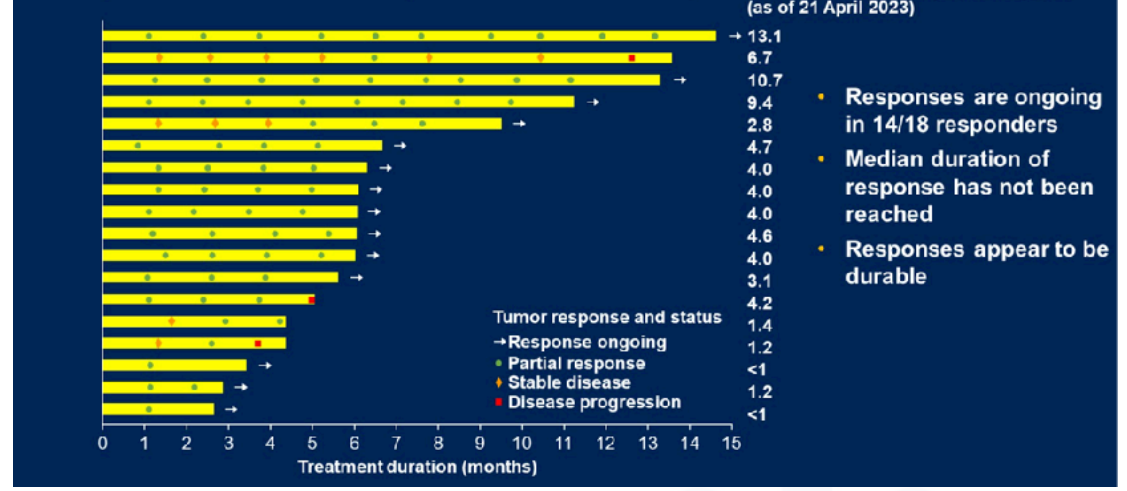
- CRS managed with supportive care, corticosteroids, and/or anti-IL-6R antibodies
- Patients with AEs/TRAEs leading to discontinuation: 13%/4%

*Safety population: ≥1 dose of BI 764532

Efficacy by tumor type (doses $\geq 90 \mu\text{g/kg}$)



Response duration (all indications)



- Promising efficacy (doses $\geq 90 \mu\text{g/kg}$: ORR 25% (SCLC 26%, epNEC 19%, LCNEC 60%)
- Responses appear to be durable
- CRS 59% patients, mostly Grade 1-2 and manageable

#8503: Exploratory biomarker analysis of the phase 3 KEYNOTE-604 study of pembrolizumab plus etoposide for extensive-stage SCLC

Charles M. Rudin, Hye Ryun Kim, Alejandro Navarro, Maya Gottfried, Solange Peters, Tibor Csozsi, Parneet Kaur Cheema, Delvys Rodriguez-Abreu, Mira Wollner, James Chih-Hsin Yang, Julien Mazieres, Terufumi Kato, Gregory Peter Kalemkerian, Elisha Dettman, Mackenzie Edmondson, Amir Vajdi, Andrey Loboda, Hazem Edmond El-Osta, Bin Zhao, Mark M. Awad

453 patients randomly allocated in KEYNOTE-604

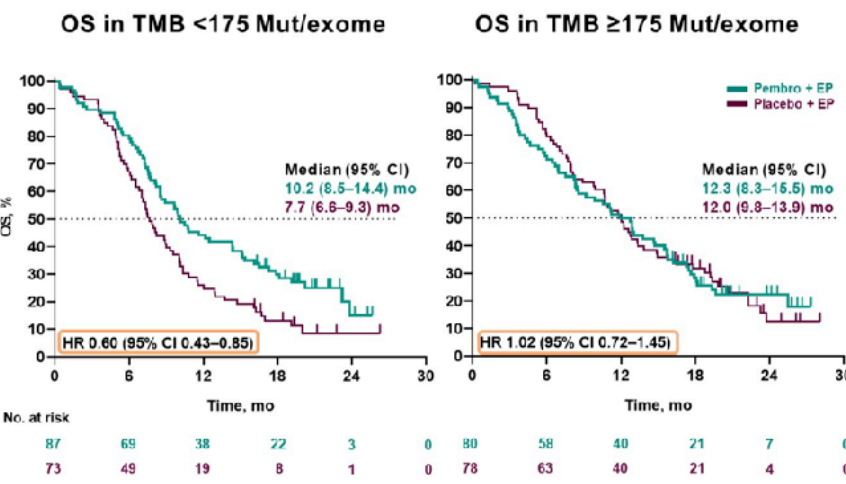
Pembrolizumab + EP
 • 228 allocated
 • 223 treated^a

Placebo + EP
 • 225 allocated
 • 223 treated^a

Biomarker Evaluable Population
 • 167 (74.9%) TMB
 • 159 (71.3%) Tcell_{inf}GEP

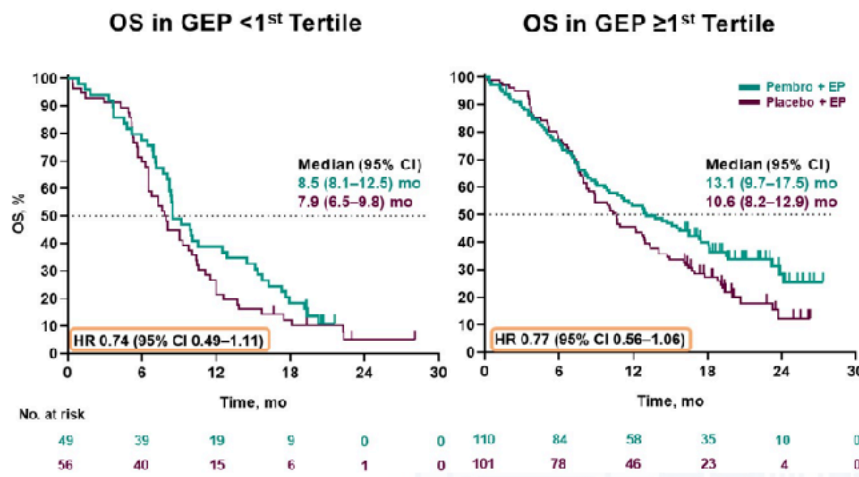
Biomarker Evaluable Population
 • 151 (67.7%) TMB
 • 157 (70.4%) Tcell_{inf}GEP

Biomarker	Pembrolizumab + EP			Placebo + EP		
	n	OS P-value	PFS P-value	n	OS P-value ^a	PFS P-value ^a
TMB (log ₁₀ transformed) ^b	167	0.450	0.362	151	0.005	0.141
Tcell _{inf} GEP ^b	159	0.003	0.002	157	2.19 x 10⁻⁴	0.001



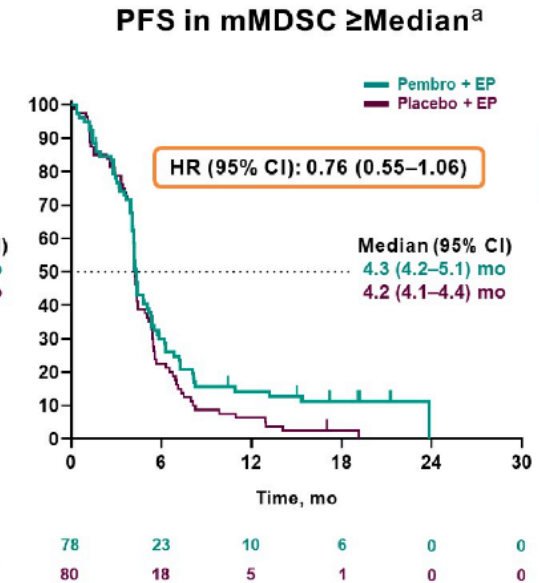
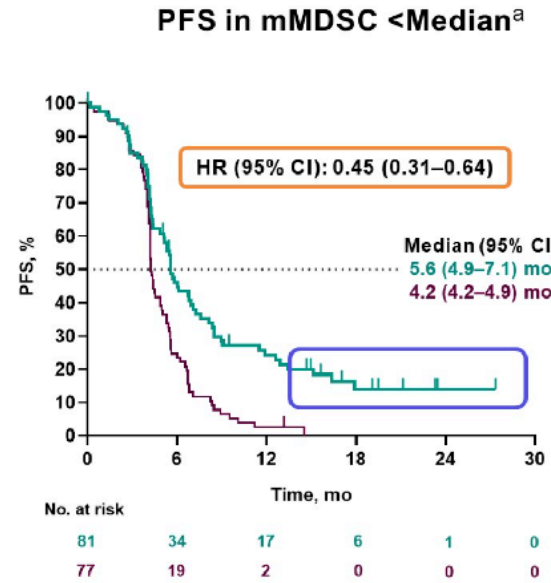
Association of PFS with TMB

	Pembro + EP	Placebo + EP
TMB <175 Mut/exome		
Median PFS (95% CI), mo	4.9 (4.3–5.5)	4.1 (3.9–4.2)
HR (95% CI)	0.55 (0.39–0.76)	
TMB ≥175 Mut/exome		
Median PFS (95% CI), mo	4.4 (4.2–5.6)	4.5 (4.2–5.4)
HR (95% CI)	0.79 (0.57–1.10)	



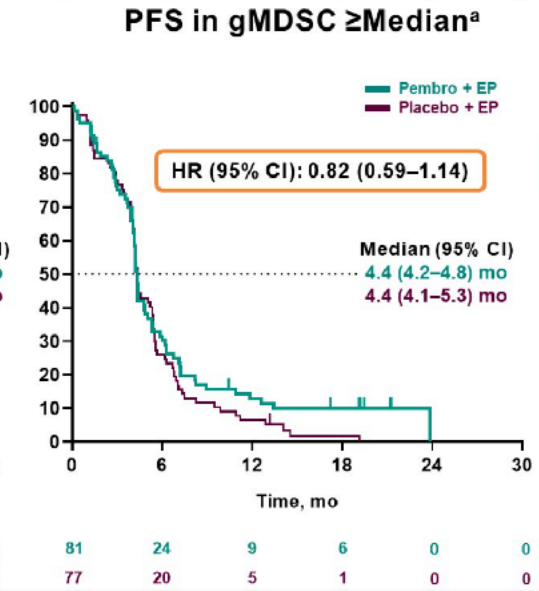
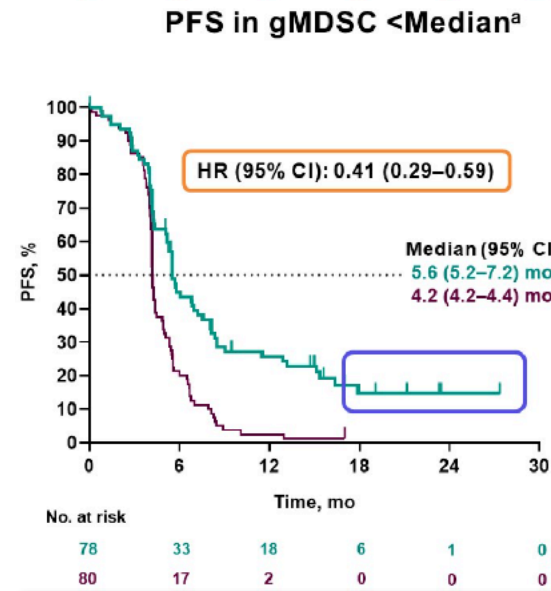
Association of PFS with Tcell_{inf}GEP

	Pembro + EP	Placebo + EP
GEP <1st Tertile		
Median PFS (95% CI), mo	4.4 (4.2–5.2)	4.2 (4.0–4.2)
HR (95% CI)	0.58 (0.38–0.88)	
GEP ≥1st tertile		
Median PFS (95% CI), mo	5.4 (4.3–6.3)	4.4 (4.2–5.1)
HR (95% CI)	0.62 (0.46–0.83)	



Association of OS with mMDSC

	Pembro + EP	Placebo + EP
mMDSC <Median		
Median OS (95% CI), mo	15.5 (11.2–19.4)	10.6 (8.2–12.9)
HR (95% CI)	0.64 (0.44–0.93)	
mMDSC ≥Median		
Median OS (95% CI), mo	8.3 (6.9–11.1)	8.0 (7.3–10.4)
HR (95% CI)	0.83 (0.59–1.17)	



Association of OS with gMDSC

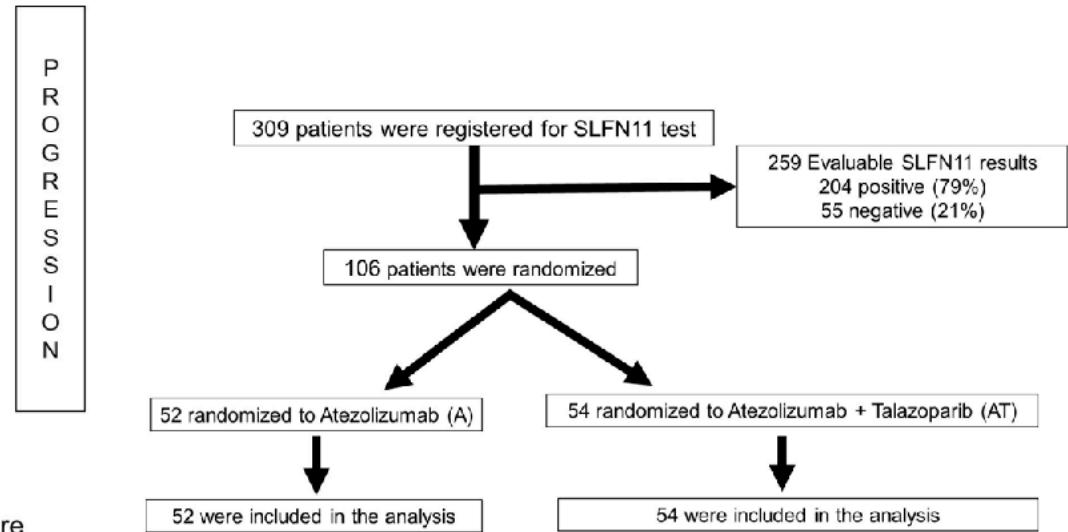
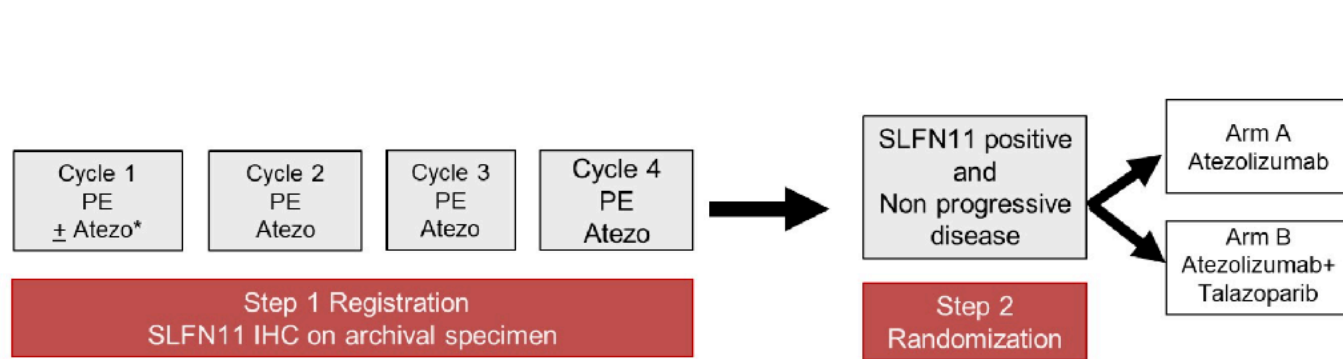
	Pembro + EP	Placebo + EP
gMDSC <Median		
Median OS (95% CI), mo	16.3 (10.5–18.2)	9.0 (7.7–11.1)
HR (95% CI)	0.59 (0.41–0.86)	
gMDSC ≥Median		
Median OS (95% CI), mo	8.3 (6.5–11.6)	9.8 (7.3–11.6)
HR (95% CI)	0.87 (0.62–1.23)	



- TMB sin correlación positiva (baja TMB mayor beneficio con pembro)
- Tcell_{inf}GEP asociación positiva con OS y PFS en ambos grupos; bajo mMDSC y gMDSC potencial asociación con PFS con pembro

#8504: SWOG S1929: Phase II randomized study of maintenance atezolizumab (A) versus atezolizumab + talazoparib (AT) in patients with SLFN11 positive extensive stage small cell lung cancer (ES-SCLC)

Nagla Fawzy Abdel Karim, Jieling Miao, Karen L. Reckamp, Carl Michael Gay, Lauren Averett Byers, Yingqi Zhao, Mary Weber Redman, Daniel R. Carrizosa, Wei-Lien Wang, William J. Petty, Kathan Mehta, Bryan A. Faller, Edem S. Agamah, Samer S. Kasbari, Rajini Katipamula Maliseti, Atul Kumar, John Schallenkamp, Krishna Chaitanya Alluri, Jhanelle Elaine Gray, Karen Kelly



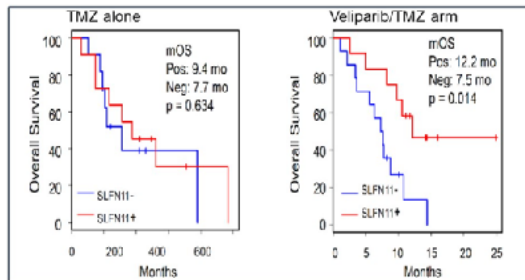
P
R
O
G
R
E
S
S
I
O
N

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*

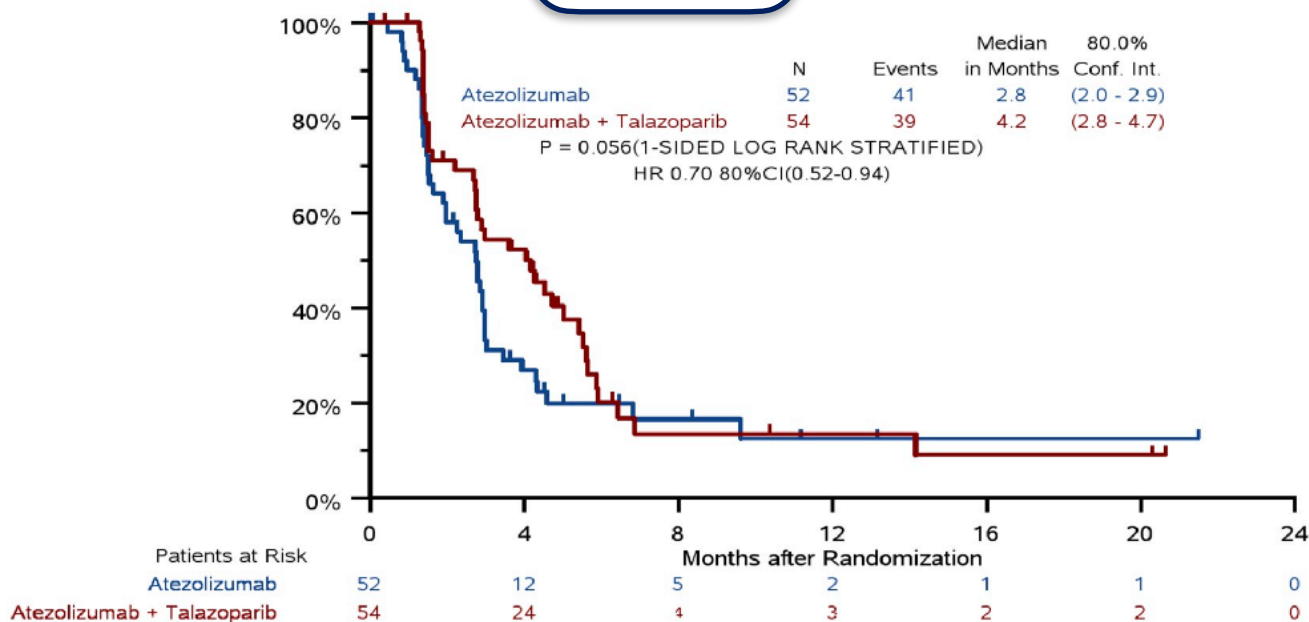


High SLFN11 predicts improved outcomes in the Veliparib/TMZ arm (Interaction p-value 0.009)

Pietanza et al. J Clin Oncol. 2018 Aug 10; 36(23): 2386-2394

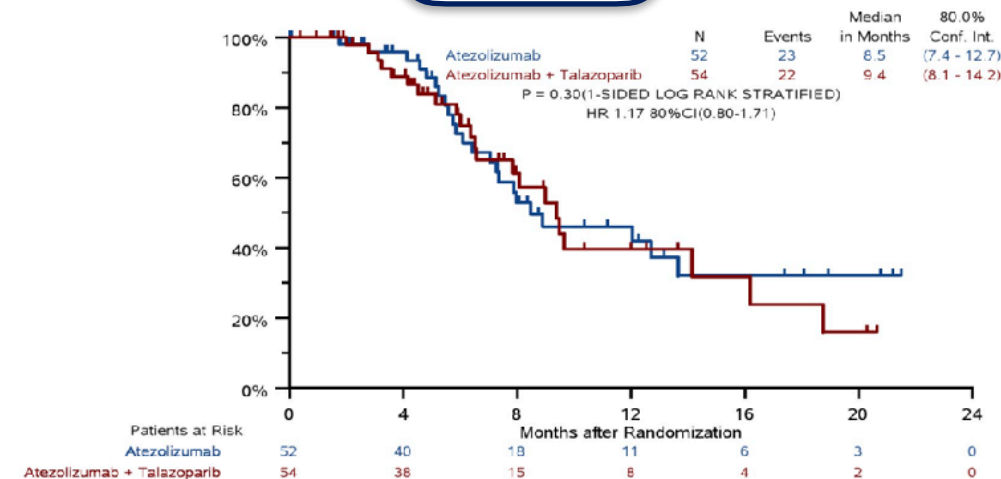
	Atezolizumab (N = 52)	Atezolizumab Talazoparib (N = 54)	Total (N = 106)
Age: Median (Range)	66.9 (44.6, 84.0)	66.7 (46.1, 82.9)	66.8 (44.6, 84.0)
Female	27 (52%)	24 (44%)	51 (48%)
Male	25 (48%)	30 (56%)	55 (52%)
White	47 (90%)	47 (87%)	94 (89%)
Black	3 (6%)	3 (6%)	6 (6%)
Hispanic	4 (8%)	2 (4%)	6 (6%)
PS (0-1)	50 (96%)	52 (96%)	102 (96%)
Prior Thoracic Radiation Therapy	13 (25%)	13 (26%)	26 (25%)

PFS



	A	AT	PFS HR (80% CI)	P-value (1-sided)
Prior Radiation				
No Prior RT	32/39	32/41	0.74 (0.53,1.02)	0.116
Prior RT	9/13	7/13	0.54 (0.27,1.07)	0.12
Brain Mets				
No Brain Mets	32/41	30/41	0.75 (0.54,1.05)	0.135
Brain Mets	9/10	9/13	0.42 (0.22,0.81)	0.04
Liver Mets				
No Liver Mets	30/38	27/40	0.6 (0.42,0.86)	0.031
Liver Mets	11/13	12/14	0.77 (0.43,1.36)	0.284
Bone Mets				
No Bone Mets	30/38	29/42	0.61 (0.43,0.87)	0.035
Bone Mets	11/13	10/12	0.93 (0.51,1.69)	0.433
Overall	41/52	39/54	0.7 (0.52,0.93)	0.056

OS



Hematologic toxicities

No. (%)	Atezolizumab (n=47)				Atezolizumab + Talazoparib (n=52)			
	1-2	3	4	5	1-2	3	4	5
Anemia	9 (19)	1 (2)	0	0	8 (15)	19 (37)	0	0
CD4 lymphocytes decreased	0	0	0	0	1 (2)	0	0	0
Lymphocyte count decreased	4 (9)	1 (2)	0	0	11 (21)	3 (6)	0	0
Neutrophil count decreased	0	0	0	0	10 (19)	0	1 (2)	0
Platelet count decreased	2 (4)	0	0	0	19 (37)	9 (17)	4 (8)	0
White blood cell decreased	1 (2)	0	0	0	17 (33)	2 (4)	1 (2)	0
Max. Grade All Hem Toxicities	12 (26)	2 (4)	0	0	14 (27)	22 (42)	4 (8)	0

S1929 met its primary endpoint demonstrating that maintenance AL improved PFS in SLF11-positive patients with ES-SCLC

CPCP, mesotelioma y otros tumores

Lung Cancer Updates - ASCO'23

Mesotelioma pleural maligno



#LBA8505: IND227 phase III (P3) study of cisplatin/pemetrexed (CP) with or without pembrolizumab (pembro) in patients (pts) with malignant pleural mesothelioma (PM): A CCTG, NCIN, and IFCT trial

Quincy S. Chu, Maria Carmela Piccirillo, Laurent Greillier, Federica Grosso, Giuseppe Lo Russo, Marie Florescu, Manlio Mencoboni, Penelope Ann Bradbury, Alessandro Morabito, Fabiana Letizia Cecere, Sara Delfanti, Arnaud Scherpereel, Myriam Locatelli-Sanchez, Gerard Zalcman, David E Dawe, Joana Sederias, Scott A. Laurie, Christopher W. Lee, Wei Tu, Lesley Seymour

Phase III, open label

Chemotherapy naïve pts with PM
N=440

Stratified by histology
Primary endpoint OS

Randomize (1 : 1)

Platinum-pemetrexed* q3w x 6 cycles

Platinum-pemetrexed* q3w x 6 cycles
+ Pembrolizumab q3w for 2 years

Objectives

PRIMARY:

- Overall Survival

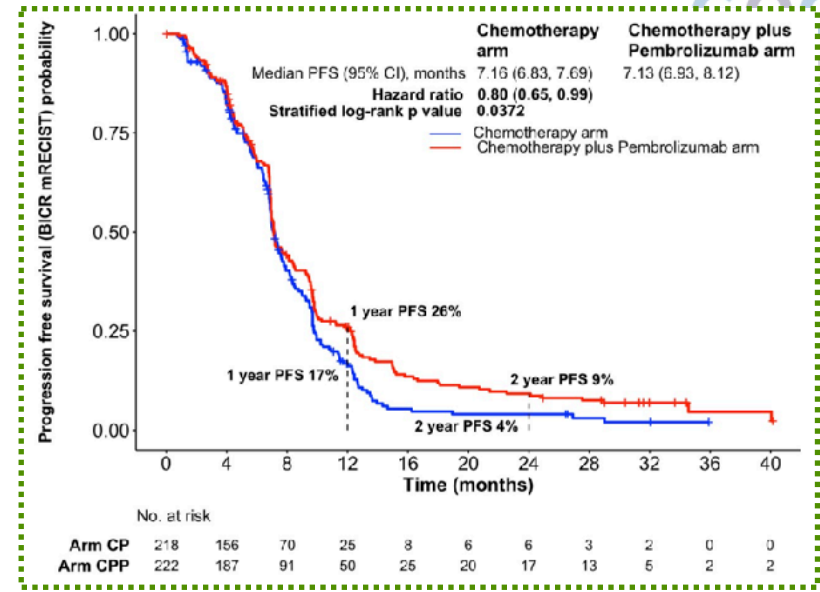
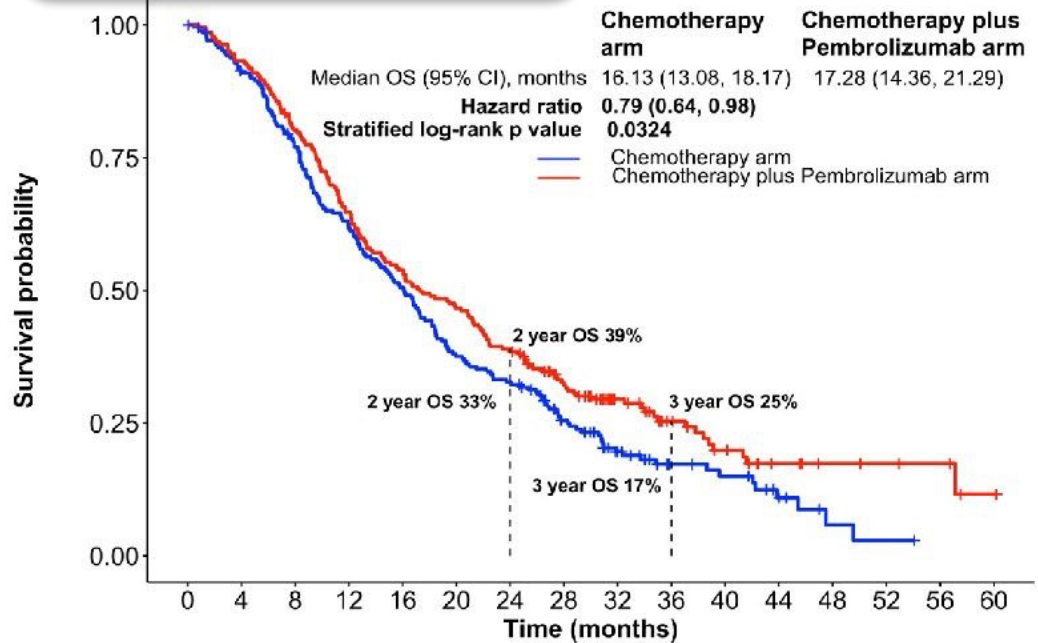
SECONDARY:

- Tolerability
- Response (mRECIST, central review, imaging - 6, 12, 18 wks then every 12 wks)
- PFS
- QoL
- Health economics

EXPLORATORY:

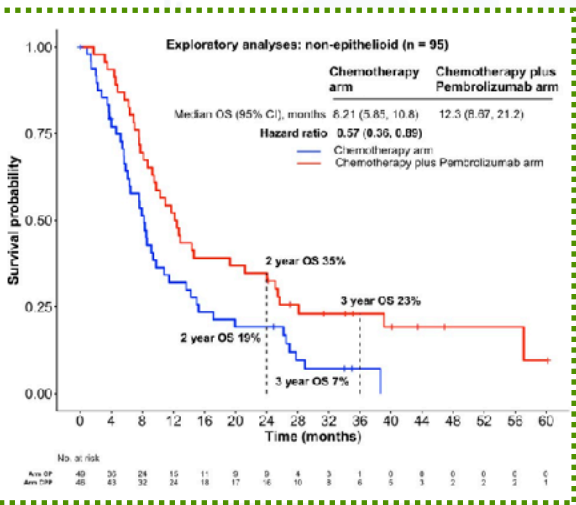
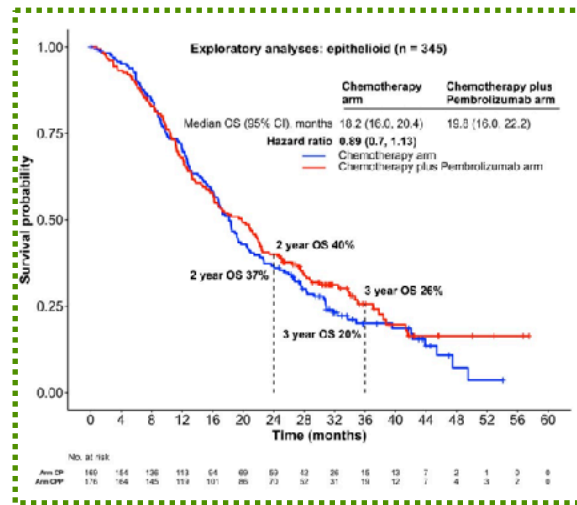
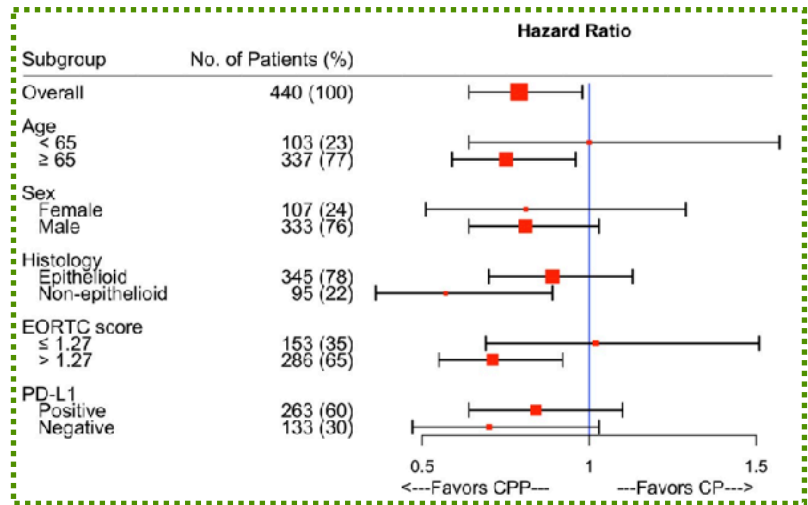
- Predictive and prognostic value of PD-L1 (Dako 22C3 platform; combined positive score (CPS))
- iRECIST
- Other Correlatives

Overall survival



Patients enrolled Jan 2017-Sept 2020
Median follow up 16.16 months
All pts discontinued all study drugs

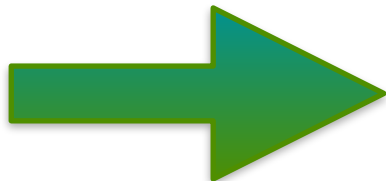
No. at risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Arm CP	218	190	160	128	105	78	68	46	29	16	13	7	2	1	0	0
Arm CPP	222	207	177	143	119	103	86	62	39	25	17	10	6	5	4	1



Best Overall Response (mRECIST, Central Review)

Response	CP (N=218)	CPP (N=222)	P-value	
Complete Response	0	2 (1%)	P < 0.0001	
Partial Response	83 (38%)	136 (61%)		
Stable disease/non-CR/PD	103 (47%)	70 (32%)		
Disease Progression	11 (5%)	9 (4%)		
Response could not be assigned	Total	21 (10%)	5 (2%)	
	Never treated/WOC ¹	7 (3%)	0	
	Other reasons ²	9 (4%)	3 (1%)	
	No baseline images uploaded	5 (2%)	2 (1%)	
Duration of CR/PR (mths)	Median (95% CI)	5.5m (4.2-6)	5.8m (5.5-7)	P=0.185
	Range	0.03, 25.1	0.03, 38.9	

Pooled AE term	CP N=211 : All Causality		CPP N = 222			
	All (%)	≥ grade 3 (%)	All (%)		≥ grade 3 (%)	
			All Causality	Related to Pembro	All Causality	Related to Pembro
Skin toxicity	18%	<1%	36%	26%	1%	1%
Diarrhea/colitis	14%	1%	32%	22%	3%	3%
Chills/fever	12%	<1%	31%	8%	-	-
Sensory neuropathy	15%	-	24%	8%	-	-
Abdominal Pain	9%	<1%	18%	6%	3%	1%
Joint Pain/Inflammation	2%	-	13%	8%	1%	1%
Ototoxicity	11%	<1%	13%	2%	<1%	0%
Myositis, muscle	5%	-	10%	4%	1%	<1%
Hypothyroidism	2%	-	9%	7%	-	-
Cognitive	7%	<1%	7%	1%	<1%	0%
Infusion reactions	1%	-	5%	3%	-	-
Pneumonitis	-	-	5%	5%	2%	2%
Nephritis/AKI	1%	-	4%	3%	2%	1%
Hepatitis	-	-	2%	2%	2%	2%
Thrombocytopenia	<1%	<1%	2%	0%	2%	0%
Motor neuropathy	<1%	-	2%	1%	<1%	<1%

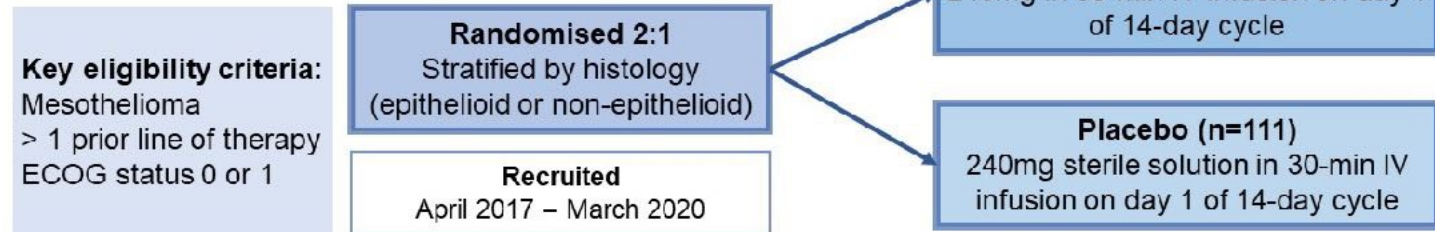


Platinum/pemetrexed and pembrolizumab is a new therapeutic option in this patient population

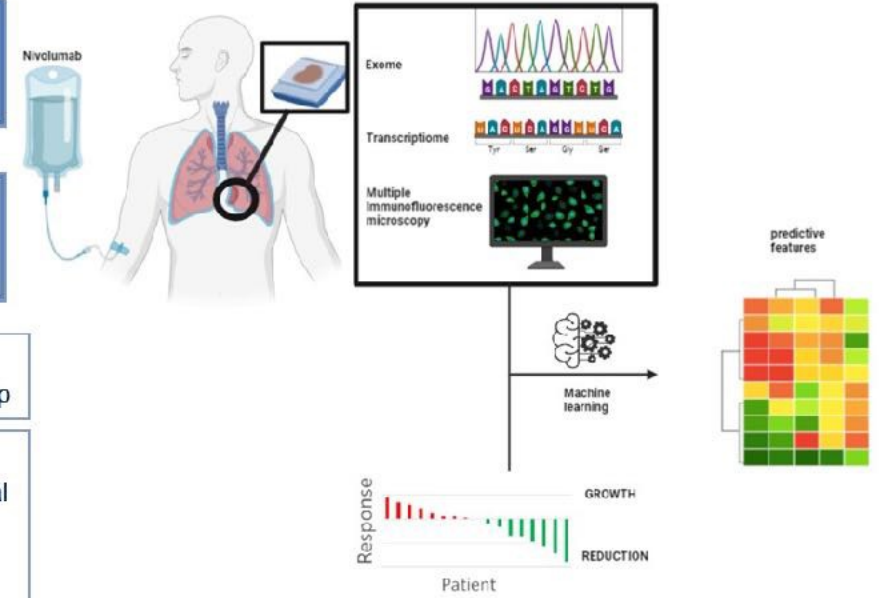
#8506: Efficacy, cellular and molecular determinants of PD-1 checkpoint inhibition in relapsed mesothelioma

Dean Anthony Fennell, Sean Ewings, Kayleigh Hill, Charlotte Poile, Essa Baitei, Zisen Zhou, James Harber, Tamihito Kamata, Hongji Yang, Joanna Dzialo, Daniel Faulkner, Christian H.H Ottensmeier, Sarah Danson, Nicola Steele, Kim Mallard, Peter Wells-Jordan, Catherine Jane Richards, Min Zhang, Jason Lester, Gareth Owen Griffiths

Administered until progression, unacceptable toxicity, withdrawal or 12m



- **Blinded** multi-omic analysis
- Evaluation of exome, transcriptome and tumour microenvironmental correlates in *extreme* responders versus treatment refractory mesotheliomas



Target sample size: 336
 Study halted recruitment at n=332 due to the COVID-19 pandemic, however with sufficient events/follow up

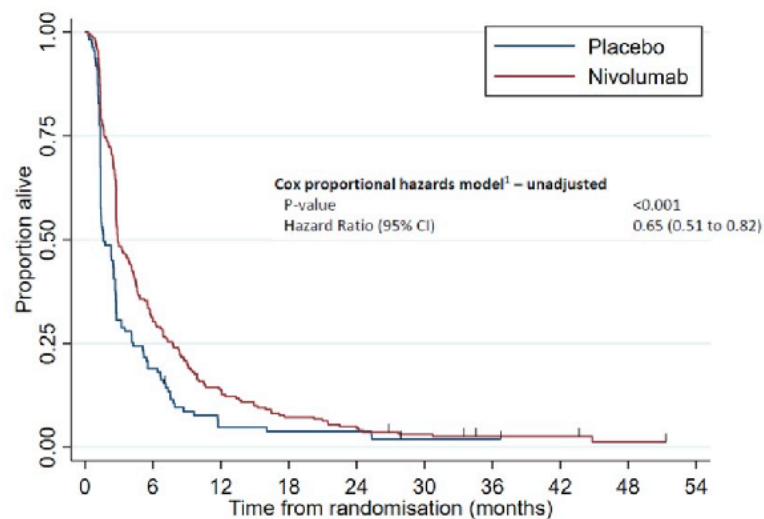
Co-primary outcomes:

- Investigator-reported progression-free survival
- Overall survival

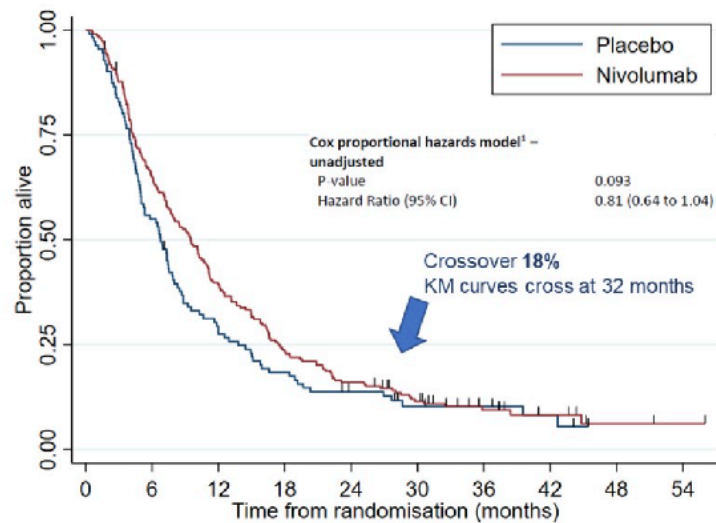
Secondary outcomes:

- RECIST-determined progression-free survival
- Response rate
- EQ-5D
- Safety

Investigator Assessed Progression-free survival



Overall survival



Characteristic	Nivolumab (n=221)	Placebo (n=111)
Age - years (median, IQR)	70 (65-74)	71 (65-76)
Sex – male	167 (76%)	86 (77%)
ECOG Status 0	44 (20%)	22 (20%)
PD-L1 TPS ≥ 1%*	56 (37%)	24 (29%)
Epithelioid	195 (88%)	98 (88%)
Pleural site	213 (96%)	105 (95%)
Asbestos exposure	150 (68%)	80 (72%)
Ever smoker	120 (54%)	58 (52%)
Time since diagnosis – months (median, IQR)	17.8 (11.7 to 27.4)	17.1 (10.4 to 25.7)
Line of treatment – 2 nd	63 (29%)	37 (33%)
Line of treatment – 3 rd	124 (56%)	66 (59%)
T3/4 stage	150 (68%)	84 (76%)
N1/2/3 stage	115 (52%)	67 (60%)
M1 stage	47 (21%)	24 (22%)

Number at risk

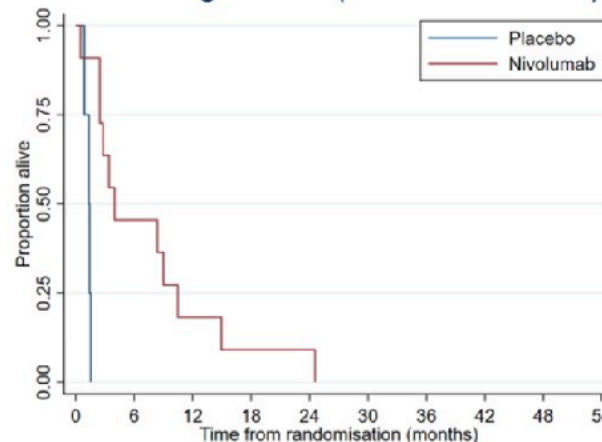
Time (months)	0	6	12	18	24	30	36	42	48	54
Placebo	111	21	5	4	4	1	1	0	0	0
Nivolumab	221	67	31	16	11	6	3	3	1	0

Number at risk

Time (months)	0	6	12	18	24	30	36	42	48	54
Placebo	111	61	30	20	13	7	6	3	0	0
Nivolumab	221	142	86	52	35	22	11	6	2	1

Characteristic and Subgroup	Nivolumab events / patients	Placebo events / patients	Nivolumab median (95% CI)	Placebo median (95% CI)	HR (95% CI)	P-value	
Total	332	219/221	108/111	2.9 (2.8, 4.1)	1.6 (1.4, 2.8)	0.65 (0.51, 0.82)	0.09
Asbestos exposure							
No	95	63/85	30/30	2.9 (2.5, 4.3)	1.4 (1.3, 4.1)	0.67 (0.43, 1.04)	
Yes	230	147/150	77/80	3.3 (2.8, 4.5)	1.6 (1.4, 2.8)	0.64 (0.48, 0.85)	
Smoking status							
Non-smoker	152	98/100	52/52	2.9 (2.8, 4.3)	1.6 (1.4, 2.8)	0.70 (0.50, 0.98)	
Ex-smoker	157	104/105	51/52	2.9 (2.8, 4.4)	1.6 (1.3, 2.8)	0.53 (0.38, 0.78)	0.41
Current smoker	21	13/15	4/9	5.7 (1.6, 15.2)	1.4 (1.4, .)	0.90 (0.26, 2.82)	0.46
Extra-thoracic metastases							
No	305	198/203	99/102	2.9 (2.8, 4.1)	2.3 (1.4, 2.7)	0.67 (0.53, 0.86)	0.17
Yes	24	15/15	9/9	3.2 (1.9, 4.8)	1.4 (0.7, 1.5)	0.32 (0.13, 0.79)	
LDH level							
Below median	146	103/104	41/42	2.9 (2.8, 4.3)	2.4 (1.4, 2.8)	0.64 (0.44, 0.93)	0.43
Above median	152	94/98	53/54	2.9 (2.7, 4.5)	1.4 (1.3, 2.8)	0.56 (0.40, 0.79)	
Neutrophil-lymphocyte ratio							
Below median	166	102/108	58/60	4.3 (3.0, 5.6)	2.7 (1.6, 2.8)	0.67 (0.48, 0.92)	0.30
Above median	165	113/114	50/51	2.8 (2.5, 2.9)	1.4 (1.3, 1.6)	0.56 (0.40, 0.79)	
PD-L1							
<1% Positive	170	102/105	64/65	2.9 (2.7, 4.3)	1.6 (1.4, 2.8)	0.60 (0.44, 0.83)	
1-50% Positive	73	46/90	21/23	3.3 (2.8, 5.5)	2.7 (1.3, 5.4)	0.68 (0.53, 1.48)	0.14
>50% Positive	15	11/11	4/4	4.0 (2.5, 10.5)	1.3 (0.9, .)	0.66 (0.01, 0.54)	0.04

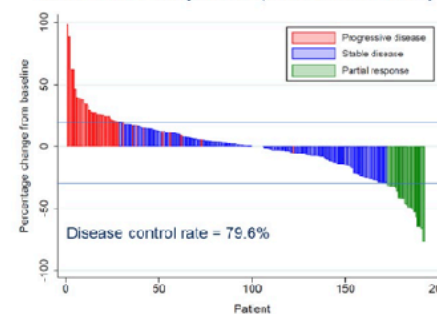
PFS in high PD-L1 (>50% TPS 22C3)



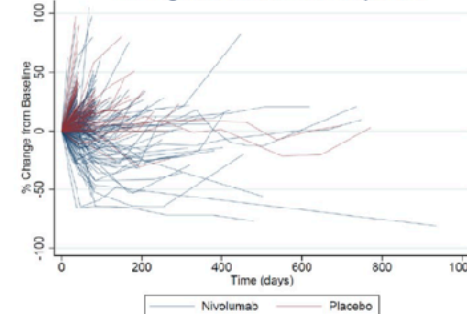
Number at risk

Time (months)	0	6	12	18	24	30	36	42	48	54
Placebo	4	0	0	0	0	0	0	0	0	0
Nivolumab	11	5	2	1	1	0	0	0	0	0

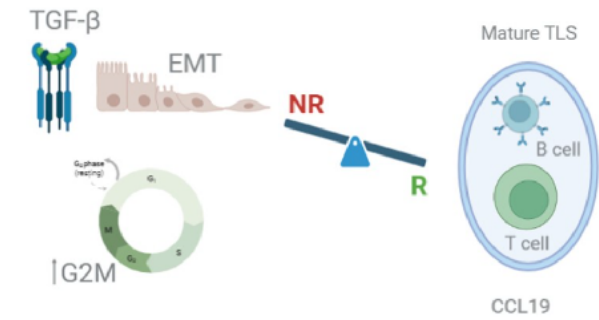
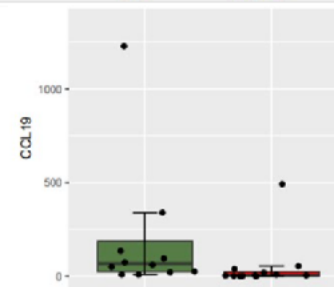
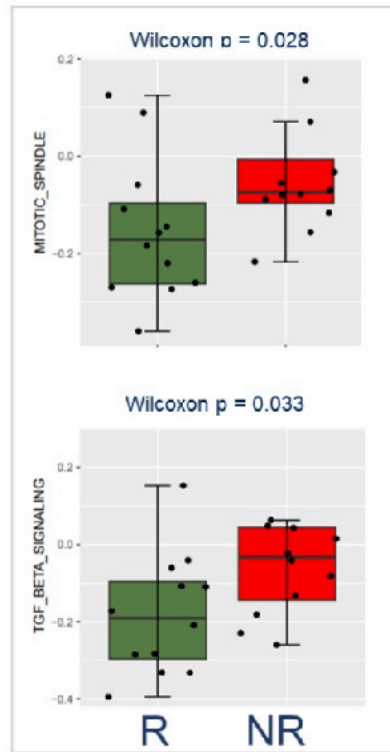
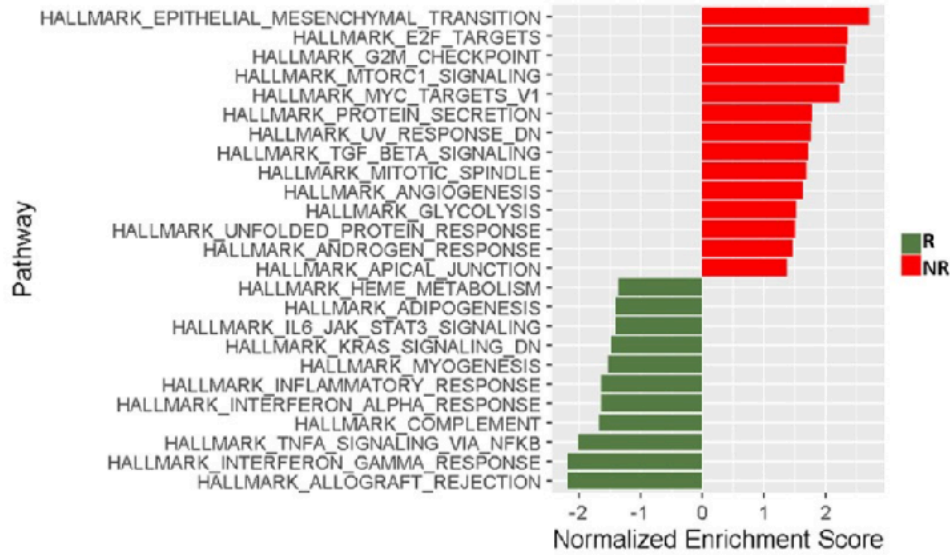
mRECIST response (Nivolumab arm)



Timing & duration of response



Responders exhibit Inflammatory response signalling

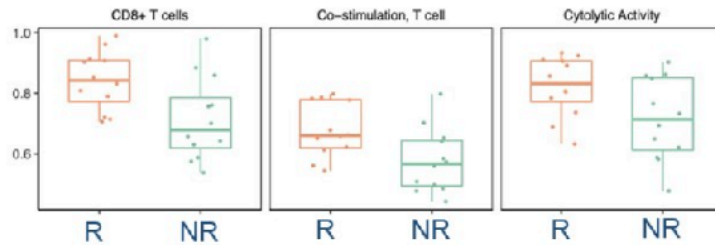


Responders

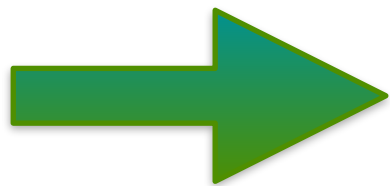
- CD8+ T-cell infiltration (deconvolution of RNAseq)
- inflammatory pathway upregulation
- T cell co-stimulation and cytolytic activity.

Non-responders

- epithelial mesenchymal transition (EMT)^{1,2}
- TGF- β signalling
- Mitotic spindle, G2M and E2F transcription.



R , partial responder; NR , progression as best response

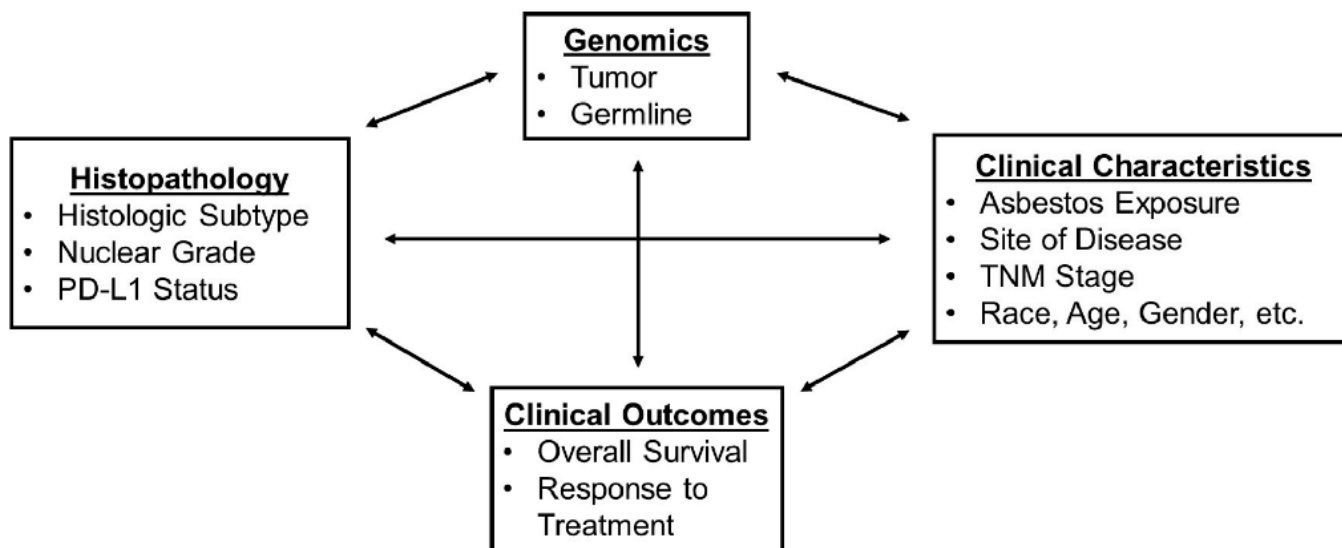


- Nivolumab-responsive mesotheliomas harbour an inflamed tumour microenvironment, enriched with mature tertiary lymphoid structures and CCL19 expression
- Epithelial mesenchymal transition, TGF-beta signalling, and mitotic spindle transcription are associated with resistance to nivolumab

#8507: Association of somatic mutations and histologic subtype/grade on prognosis and PD-L1 expression in mesothelioma

Allen Zhu, Aliya N. Husain, Andrew Hermina, Owen Mitchell, Jeffrey S. Mueller, Michael William Drazer, Hedy L. Kindler, Jung Woo Kwon

Objectives: Identify how features in histopathology and genetics correlate with one another and with clinical outcomes

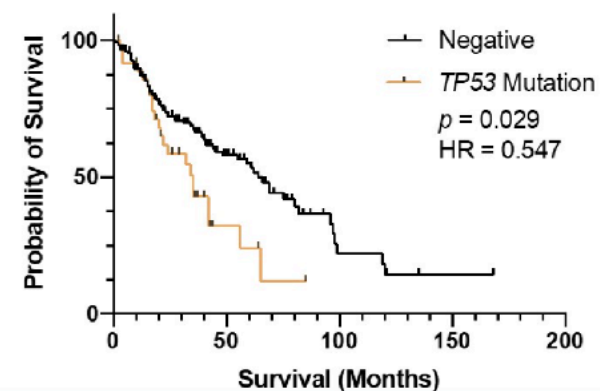
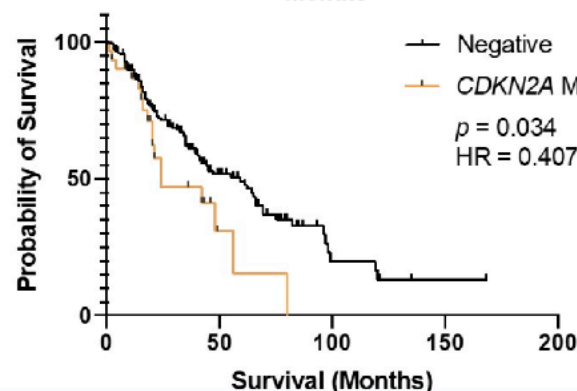
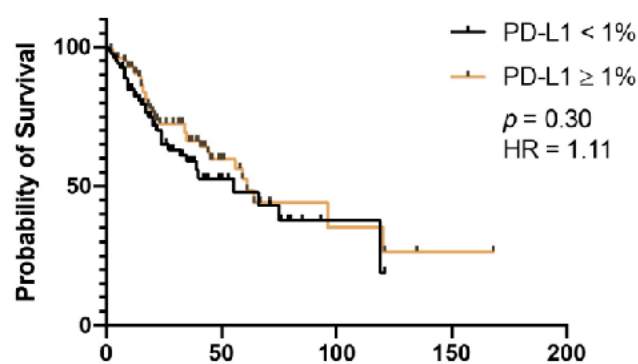
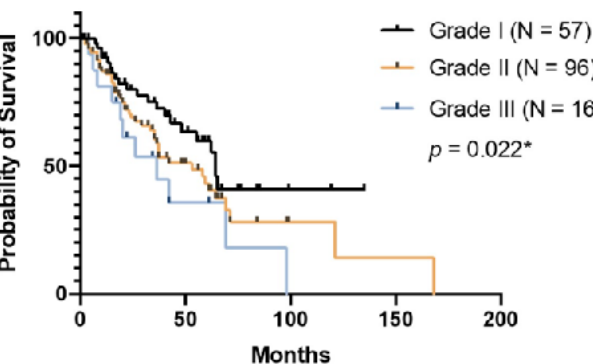
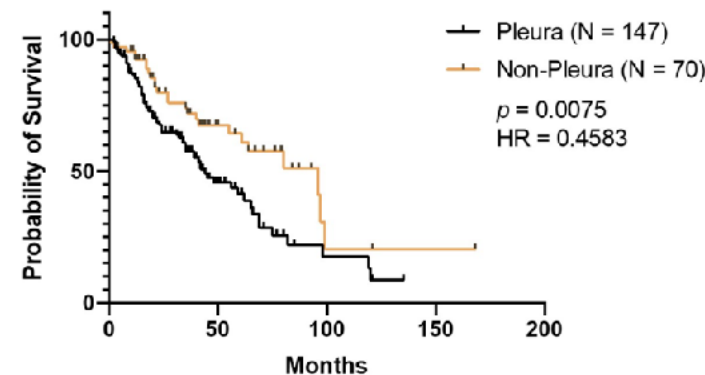
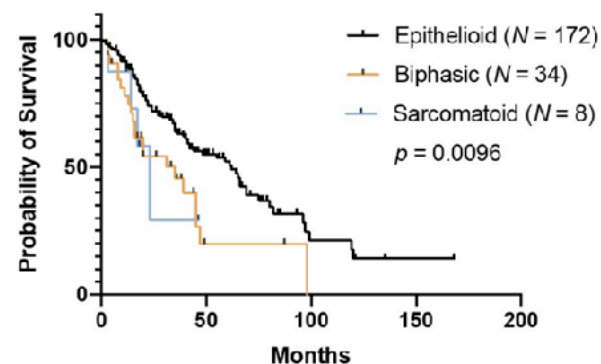
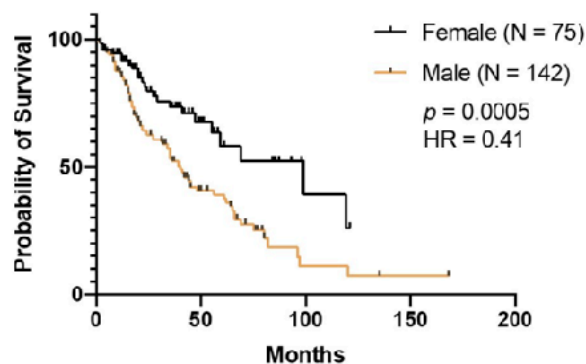


Characteristic		N (%)
Age at Diagnosis (years)	Median (range)	66 (16-89)
Gender	Male	142 (65)
	Female	75 (35)
Race	White, non-Hispanic	205 (95)
	White, Hispanic	5 (2)
	Black	4 (2)
	Asian	3 (1)
Self-reported asbestos exposure	Definite	83 (39)
	Probable	56 (26)
	Possible	64 (30)
Personal cancer history	No known exposure	13 (6)
	Present	54 (25)
Family cancer history	Present	151 (70)

Characteristic	Categories	N = 217 (%)
Site of Disease	Pleural	147 (68)
	Peritoneal	63 (29)
	Bicavitary	4 (2)
	Tunica vaginalis testis	3 (1)
Germline Mutation	Present	34 (16)
Status at Follow-up	Alive	111 (51)
	Deceased	106 (49)

Characteristic	Categories	N (%)
Histologic Subtype N = 217	Epithelioid	172 (79)
	Sarcomatoid	8 (4)
	Biphasic	33 (15)
	Other	4 (2)
Nuclear Grade N = 166	I	55 (33)
	II	96 (58)
	III	15 (9)
Tumor Stage* N = 50	pT1	12 (24)
	pT2	12 (24)
	pT3	18 (36)
	pT4	8 (16)
Lymph Node Stage* N = 50	pN0	32 (64)
	pN1	18 (36)

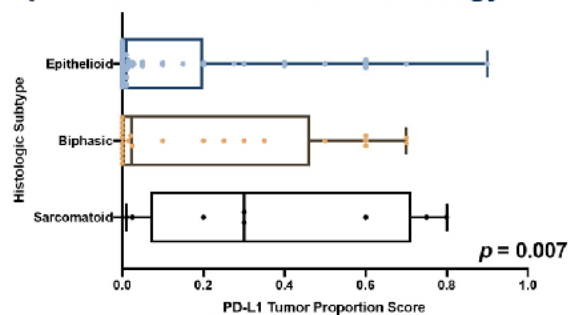
*staged only in resected tumors



Epithelioid histology has lower PD-L1 expression than biphasic or sarcomatoid histology

In epithelioid mesothelioma, PD-L1 expression is not associated with nuclear grade

PD-L1 expression is not associated with common somatic mutations



	Nuclear Grade – N (%)			p-value
	I	II	III	
PD-L1 < 1%	24 (47)	43 (50)	4 (36)	0.69
PD-L1 ≥ 1%	27 (53)	43 (50)	7 (64)	

	N (%)		p-value
	PD-L1 (+)	PD-L1 (-)	
BAP1	40 (48.8)	38 (37.3)	0.13
TP53	15 (18.3)	15 (14.7)	0.51
NF2	14 (17.1)	26 (25.5)	0.17
CDKN2A	14 (17.1)	12 (11.8)	0.31
TERT	6 (7.3)	11 (10.8)	0.42



- Epithelioid histology, TP53 somatic mutation and gender are the strongest predictors of survival
- Nuclear grade is useful for prognosis but somatic mutations should be taken into consideration

#8511: Bemcentinib and pembrolizumab in patients with relapsed mesothelioma: MIST3, a phase IIa trial with cellular and molecular correlates of efficacy

Matthew G Krebs, Amy Branson, Shaun Barber, Charlotte Poile, Amy King, Alastair Greystoke, Sam Moody, Luke Nolan, Molly Scotland, Liz Darlison, Amrita Bajaj, Bruno Morgan, Cassandra Brookes, Peter Wells-Jordan, Catherine Jane Richards, Anne L. Thomas, Dean Anthony Fennell

Key inclusion criteria

- Histologically confirmed pleural mesothelioma
- ECOG PS 0-1
- Prior platinum-based systemic therapy (max 2 lines)
- Measurable disease by mRECIST1.1
- Adequate hematological and biochemical status
- Willingness to undergo a fresh biopsy (optional)

Pre-treatment biopsy

Treatment

- Bemcentinib 400mg po for 3 days then 200mg OD every 3 weeks
- Pembrolizumab 200mg IV every 3 weeks

Treatment until disease progression

Re-biopsy on progression

Correlative Research

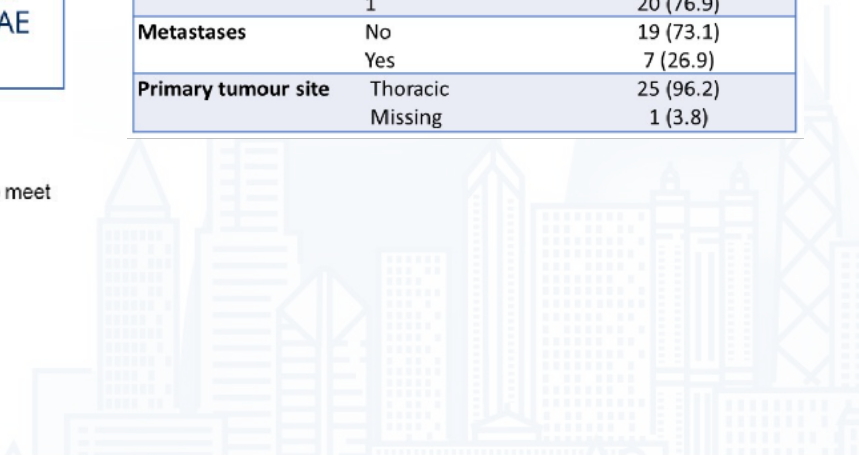
- Baseline and relapsed DNA and RNA sequencing
- Gut 16s RNA sequencing
- Tissue microarray & ultradeep multiplex immunofluorescence
- AXL IHC and sAXL

Primary endpoint:
 Disease control rate at 12 weeks (DCR12w).*

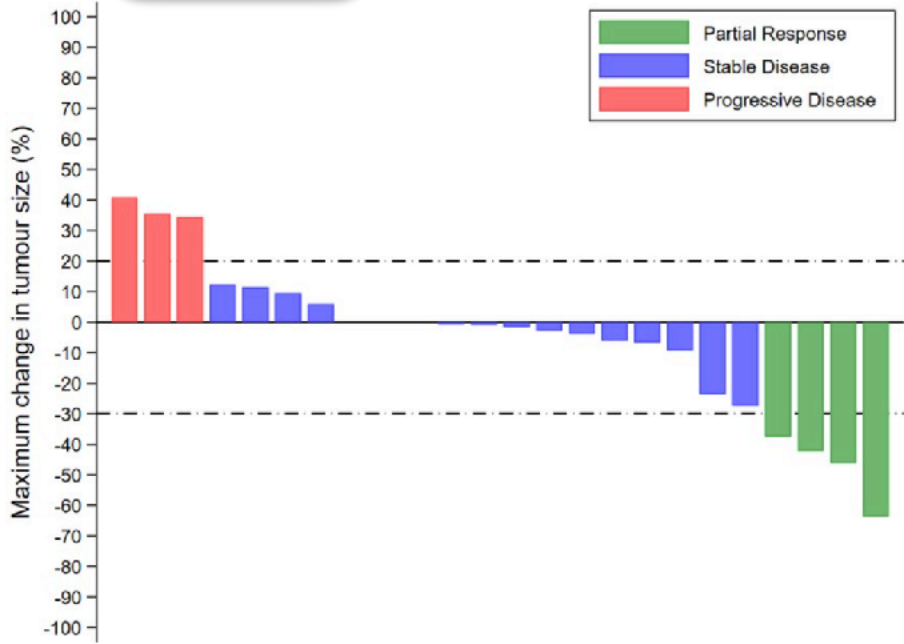
Secondary endpoints:
 DCR at 24 weeks (DCR24w),
 Best objective response rate (ORR) and toxicity (NCI CTCAE 4.03).

*minimum 11/26 patients with DCR needed to meet threshold for further evaluation

Characteristic (n=26)		N (%)
Age (years)	Median (range)	73 (55-85)
Gender	Male	23 (88.5)
	Female	3 (11.5)
Mesothelioma subtype	Epithelioid	23 (88.5)
	Biphasic	2 (7.7)
	Sarcomatoid	1 (3.8)
History of asbestos	Yes	20 (76.9)
	Unknown	6 (23.1)
ECOG status	0	6 (23.1)
	1	20 (76.9)
Metastases	No	19 (73.1)
	Yes	7 (26.9)
Primary tumour site	Thoracic	25 (96.2)
	Missing	1 (3.8)

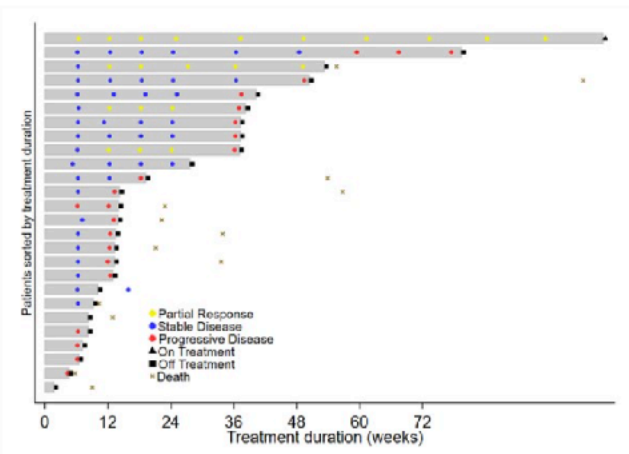


Efficacy



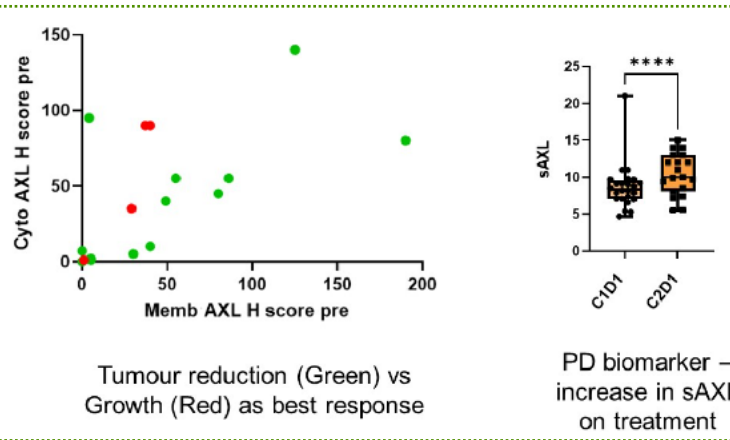
Waterfall plot of best responses of patient within 24 weeks (N = 24[^])
Tumour assessment was not available for two patients

Outcome	n (%)
DCR12weeks	12/26 (46.2%)
DCR24weeks	10/26 (38.5%)
ORR	15.4%
PR	4/26 (15.4%)
CR	0/26 (0%)
SD	15/26 (57.7%)
PD	7/26 (27%)



Safety

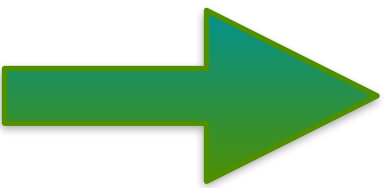
ADVERSE EVENT	Total N (%)	G1/2 N(%)	G3 N (%)
Fatigue	12 (46)	11 (42)	1 (4)
Nausea	11 (42)	11 (42)	0 (0)
Diarrhoea	7 (27)	6 (23)	1 (4)
Weight loss	7 (27)	6 (23)	1 (4)
Constipation	6 (23)	6 (23)	0 (0)
Raised creatinine	6 (23)	6 (23)	0 (0)
Anaemia	5 (19)	5 (19)	0 (0)
Increased ALT	5 (19)	5 (19)	0 (0)
Increased AST	5 (19)	5 (19)	0 (0)
Fever	5 (19)	5 (19)	0 (0)
Peripheral oedema	5 (19)	5 (19)	0 (0)



Tumour reduction (Green) vs Growth (Red) as best response

PD biomarker – increase in sAXL on treatment

MiST3 met its primary endpoint por DCR and warrants further evaluation in patients who are refractory or who have relapsed following prior standard chemotherapy



Conclusiones

Iniciativa científica de:

