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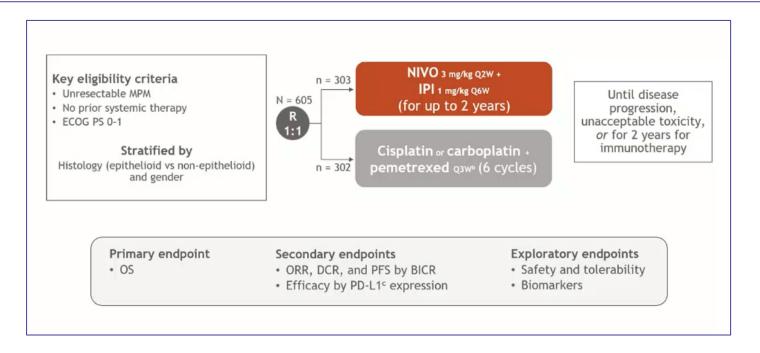


 CheckMate 743: 3-year update. First-line nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) in patients (pts) with unresectable malignant pleural mesothelioma (MPM)

 PEMBIB phase 1b: Pembrolizumab and Nintedanib for Patients with Advanced Mesothelioma

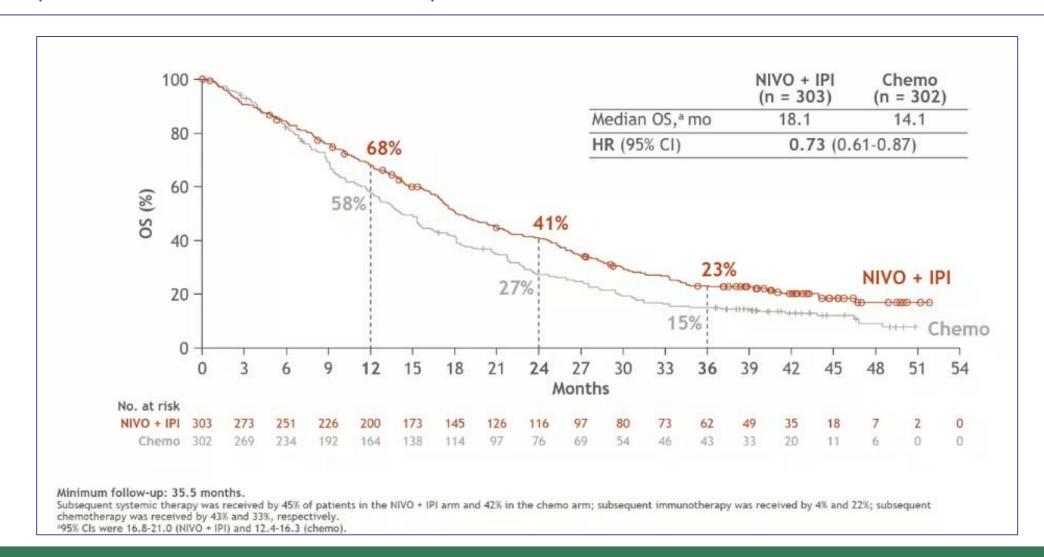
LBA65. Solange Peters, et al.

- Dual immunotherapy with nivolumab (NIVO) + ipilimumab (IPI), which have distinct but complementary mechanism of action, has improved long-term OS in multiple tumor types
- CheckMate 743: study design



- 1L NIVO + IPI significantly prolonged OS vs chemotherapy (chemo) in patients with unresectable MPM
- This regimen is now approved in EU, US, and other countries as 1L treatment for adults with unresectable MPM

3-year update: overall survival in all randomized patients



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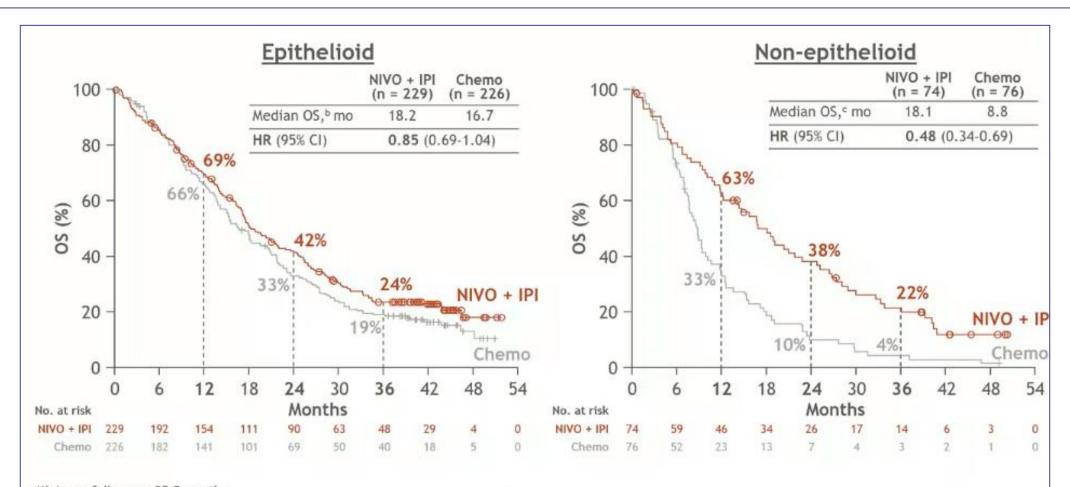
• 3-year update: overall survival subgroup analysis

	Median	OS, mo		
Subgroup	NIVO + IPI (n = 303)	Chemo (n = 302)	Unstratified HR	Unstratified HR (95% CI)
All randomized (N = 605)	18.1	14.1	0.75a	
< 65 years (n = 167)	17.2	13.3	0.78	
≥ 65 to < 75 years (n = 281)	20.3	14.5	0.67	
≥ 75 years (n = 157)	16.9	15.5	0.91	
Male (n = 467)	17.5	13.7	0.73	<b>→</b>
Female (n = 138)	21.1	18.0	0.82	<u>-</u>
ECOG PS 0 (n = 242)	20.7	19.5	0.90	
ECOG PS ≥ 1 <sup>b</sup> (n = 363)	17.0	11.6	0.66	
Never smoker (n = 249)	17.9	14.1	0.74	
Former smoker <sup>c</sup> (n = 318)	17.6	14.9	0.79	
Epithelioid (n = 455)	18.2	16.7	0.85	
Non-epithelioid <sup>d,e</sup> (n = 150)	18.1	8.8	0.48	
PD-L1 < 1% (n = 135)	17.3	16.6	0.99	
$PD-L1 \ge 1\%^f (n = 451)$	18.0	13.3	0.71	<b>→</b> i

Bold text indicates study stratification factors.

<sup>\*</sup>Stratified HR, 0.73; \*One patient in the chemotherapy group had a baseline ECOG PS of 2 (protocol deviation); \*26 patients were current smokers; smoking status of 12 patients was unknown; discludes sarcomatoid, mixed, and other; \*One patient was changed from epithelioid to non-epithelioid after the primary analysis; PD-L1 expression level was not reported for 19 patients.

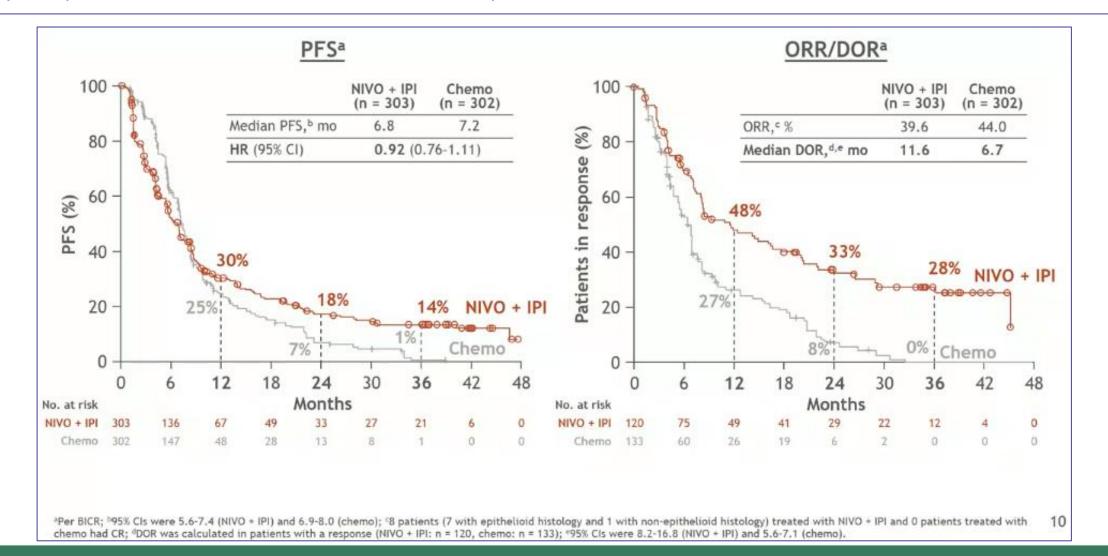
3-year update: overall survival by histology



Minimum follow-up: 35.5 months.

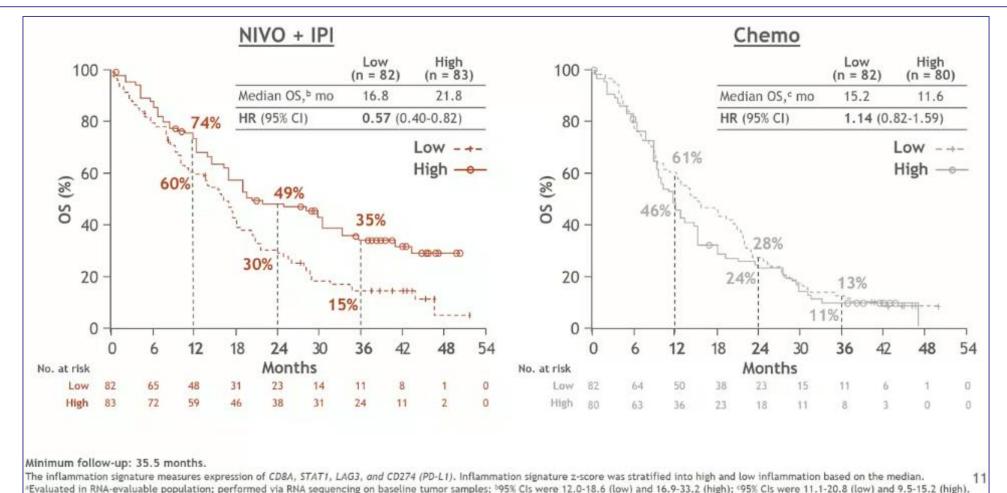
In patients with epithelioid histology, subsequent systemic therapy was received by 47% in the NIVO + IPI arm vs 44% in the chemo arm; subsequent immunotherapy was received by 45% vs 35%, respectively. In patients with non-epithelioid histology, subsequent systemic therapy was received by 39% in the NIVO + IPI arm vs 37% in the chemo arm; subsequent immunotherapy was received by 5% vs 20%; subsequent chemotherapy was received by 38% vs 26%, respectively.

3-year update: PFS, ORR and DOR in all randomized patients



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- Exploratory biomarker analyses: OS by 4-gene inflammatory signature score
  - 4-gene inflammatory signature score includes CD8A, STAT1, LAG3 and CD274 (PD-L1) genes
  - Performed via RNA sequencing on baseline formalin-fixed, paraffin-embedded tumor samples



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- Exploratory biomarker analyses: OS by TMB and LIPI score
  - Tumor mutational burden (TMB)
    - TMB is the total number of somatic missense mutations, excluding variants, in the gnomaAD database
    - . Tissue TMB was evaluated using whole-exome sequencing of matched tumor and normal samples and characterized in low, intermediate, or high tertiles based on number of mutations
  - Lung immune prognostic index (LIPI)
    - LIPI scores (poor, intermediate, and good) were assessed by LDH levels and derived neutrophil-to-lymphocyte ratio (dNLR) from peripheral blood samples

	Median	OS, mo	Unstratified	Unstratified
Subgroup	NIVO + IPI	Chemo	HR	HR (95% CI)
Tissue TMB tertile <sup>a</sup>				
Low <sup>b</sup> (n = 103)	19.3	18.0	0.74	
Intermediate <sup>c</sup> (n = 97)	17.9	9.9	0.48	
$High^d (n = 95)$	17.1	14.1	0.70	
LIPI score <sup>e</sup>				
$Good^f (n = 293)$	21.6	16.3	0.78	
Intermediate <sup>g</sup> (n = 233)	17.1	14.1	0.76	
$Poor^h (n = 47)$	6.1	6.0	0.83	
			0	0.5 1 1.5 NIVO + IPI ← → Chemo

Minimum follow-up: 35.5 months.

a TMB was determined using whole-exome sequencing; 160 patients in the NIVO + IPI arm and 135 in the chemo arm were evaluable for TMB; median TMB was 35 total mutations (1.75 mut/Mb); 5 < 32 total mutations (< 1.60 mut/Mb); 32-41 total mutations (1.60-2.05 mut/Mb); 41 total mutations (> 2.05 mut/Mb); LIPI score was based on baseline dNLR (neutrophils / [WBC - neutrophils]) and LDH levels; 296 patients in the NIVO + IPI arm and 277 patients in the chemo arm were evaluable for LIPI; ANLR < 3 and LDH < ULN; ANLR < 3 or LDH < ULN; ANLR < 3 and LDH < ULN;

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• 3-year update: treatment-related AEs in all treated patients

	NIVO + IPI <sup>a</sup> Chemo <sup>b</sup> (n = 300) (n = 284)			
TRAE, %	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE <sup>c</sup>	80	31	82	32
TRAEs leading to discontinuation of any component of the regimen <sup>c</sup>	23	15	16	7
TRAEs leading to discontinuation of all components of the regimen	17	13	8	5
Serious TRAEs <sup>c</sup>	21	16	8	6
Treatment-related deaths	1	d	<	1 <sup>e</sup>

- With 12 additional months of follow-up, safety was consistent with the previous report with no change in the overall rate of TRAEs
- Incidence of exposure-adjusted TRAEs per 100 person-years were 503.4 with NIVO + IPI and 1354.1 with chemo

Person-years of exposure: NIVO + IPI, 220.7; chemo, 94.6.

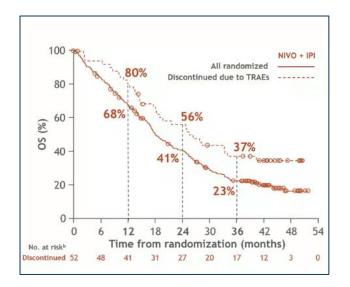
Median (IQR) doses for treated patients: NIVO 12.0 (5.0-23.5); IPI 4.0 (2.0-7.0); Median (IQR) doses for treated patients: pemetrexed 6.0 (4.0-6.0), cisplatin 5.0 (3.0-6.0), carboplatin 6.0 (4.0-6.0); Clock of the sevents reported between first dose and 30 days after last dose of study drug; 3 deaths due to NIVO + IPI; pneumonitis, encephalitis, acute heart failure; 4 death due to chemo:

Efficacy in patients who discontinued NIVO + IPI due to TRAEs

	NIVO + IP (n = 52)
From randomization	·
Median OS,c mo	25.4
3-year OS rate, %	37
ORR,d n (%)	35 (67)
After treatment discontinuation	
Median DOR,e mo	20.0
Ongoing response for ≥ 3 years, f %	34e

Among patients who discontinued all components of NIVO + IPI due to TRAEs

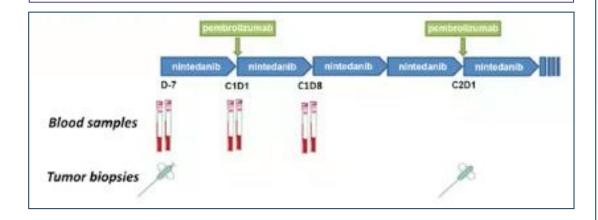
- Median (range) number of doses was 9 (1-47) for NIVO and 3 (1-16) for IPI
- Median (range) duration of treatment was 4.3 (0.0-22.5) months



- These results from CheckMate 743 represent the first 3-year survival data with immunotherapy in 1L MPM;
   NIVO + IPI continued to provide durable and long-term benefit versus chemo with no new safety signals,
   despite patients being off therapy for 1 year
  - 3-year OS rates: 23% vs 15%, respectively
  - 28% of responders have ongoing response at 3 years
- In exploratory biomarker analyses, a high score of the 4-gene inflammatory signature appeared to correlate with improved survival benefit with NIVO + IPI
  - OS showed a trend favoring NIVO + IPI vs chemo across all LIPI scores; TMB did not correlate with survival benefit
- In a post hoc analysis, discontinuation of NIVO + IPI due to TRAEs did not have a negative impact on the long-term benefits seen in all randomized patients
  - 34% of responders who had a TRAE leading to treatment discontinuation maintained their responses for
     ≥ 3 years after discontinuation
- With additional 12 months follow-up, these data from CheckMate 743 confirm NIVO + IPI as a standard of care for unresectable MPM regardless of histology

1732MO. Francois-Xavier Danlos, et al.

- Expansion cohort of PEMBIB phase 1b clinical trial
- Pleural Mesothelioma Relapsing/Refractory
- Nintedanib 150mg BID with 7 days lead-in
- Pembrolizumab 200mg IV Q3W
- Blood and Tumor samples
- RECIST v1.1 assessments



#### Clinical characteristics

	Total (n=30)
Male	20 (67%)
Mean age, years [SD]	69 [11]
Body mass index, kg/m², mean [SD]	25 [4.9]
ECOG performans status 0 1	9 (30%) 20 (67%)
Histology subtypes Epithelioid Biphasic Sarcomatoid	25 (83%) 4 (13%) 1 (3.3%)
TNM UICC (v.8) III IV	20 (67%) 10 (33%)
Previous systemic anticancer treatment 1 2 ≥3	23 (77%) 5 (17%) 2 (6.7%)
Previous treatment with Bevacizumab No Yes	18 (60%) 12 (40%)
BAP1 expression status (IHC) Loss Normal Not done	9 (30%) 3 (10%) 12 (40%)

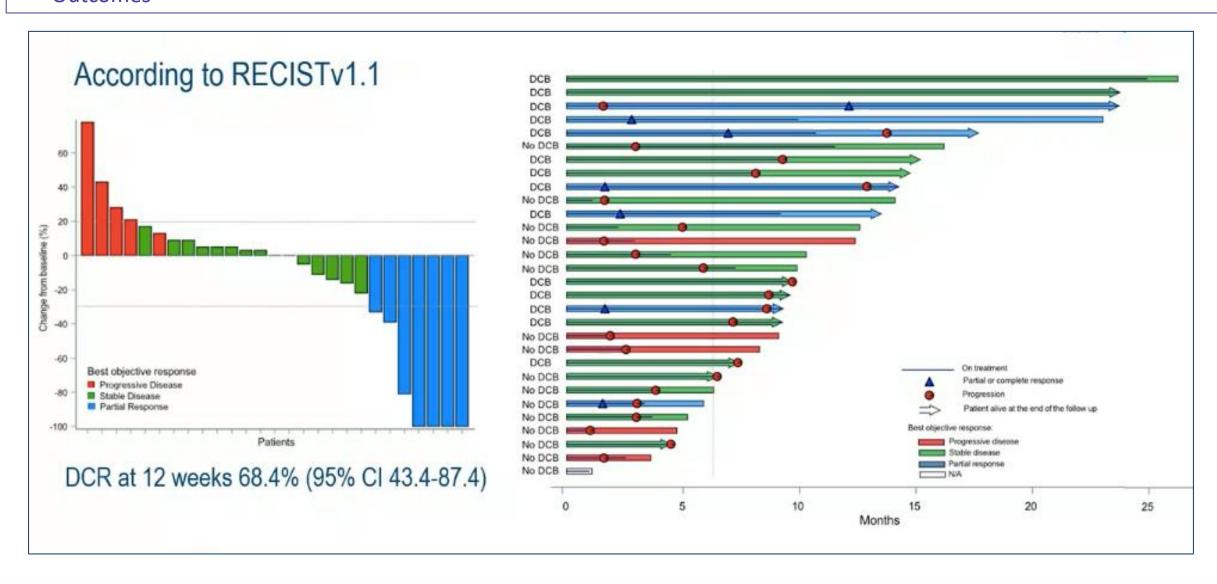
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Adverse events (frequence ≥ 10%)

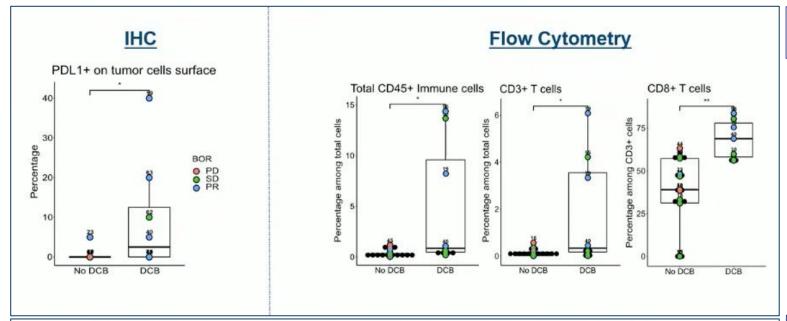
	Grade 1-2	Grade 3	Grade 4	Grade 5
Myocarditis & cardiac disorder	1 (3.3%)	1 (3.3%)	0	1 (3.3%)
Diarrhea	18 (60%)	1 (3.3%)	0	0
Fatigue	14 (46.7%)	2 (6.7%)	0	0
Dyspnea	11 (36.7%)	2 (6.7%)	0	0
Skin disorder (including rash & pruritis)	6 (20%)	2 (6.7%)	0	0
Nausea	7 (23.3%)	1 (3.3%)	0	0
Vomiting	10 (30%)	0	0	0
Arthralgia	6 (20%)	0	0	0
Fever	6 (20%)	0	0	0
Hypomagnesemia	5 (16.7%)	0	0	0
Central nervous system disorder	5 (16.7%)	0	0	0
Anemia	4 (13.3%)	0	0	0
Hypothyroidism	4 (13.3%)	0	0	0
Lipase increased	1 (3.3%)	2 (6.7%)	1 (3.3%)	0
Transaminases increased	3 (10%)	0	0	0
Pneumonitis	3 (10%)	0	0	0
Colitis	0	1 (3.3%)	0	0

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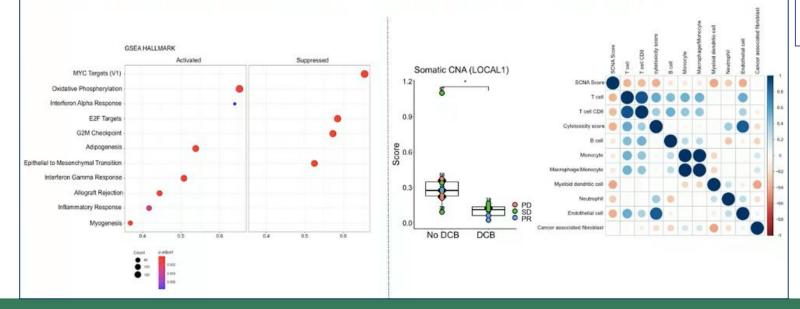
Outcomes



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 PDL1+ on tumor cells and CD8+ T lymphocytes infiltrates were higher in patients with benefit to treatment



 Oncogenic pathways led to primary resistance and aneuploidy (SCNA) shaped tumoral immune infiltration

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- Nintedanib 150mg bid + Pembrolizumab 200mg Q3W were tolerated in patients with unresectable pleural mesothelioma after resistance to platinum-based chemotherapy with pemetrexed.
- Disease control rate at 12 weeks: 68.4% (95% CI 43.4-87.4).
- Anti-angiogenic + anti-PD1 have same pharmacodynamic impacts on all patients.
- PDL1 expression by cancer cells and tumor infiltrating CD8+ T-cells at baseline are predictive of anti-angiogenic + anti-PD1 efficacy.
- SCNA due to accumulation of oncogenic mutations lead to IL6 mediated immunosuppression and resistance to antiangiogenic + anti-PD1.

## Analysis of chemotherapy (Ct) efficacy according to histology in malignant pleural mesothelioma (MPM) patients (p)

#### Abstract 1733P





#### 1733P\_Analysis of chemotherapy (Ct) efficacy according to histology in malignant pleural mesothelioma (MPM) patients

Cedrés S', Asaf JD', Iranzo P', Callejo A', Pardo-Aranda N', Navarro A', Marmolejo D', Rezgallah A', Pedrola A', Gonzalo J', Frigola J', Carbonell C', Amat R', Dienstmann R', Felip E'

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#### Background:

 MPM is a highly aggressive pleural tumor with limited survival. CheckMate-743 demonstrated survival benefit of immunotherapy over Ct in 1st line with some differences in the efficacy according to histology. The objective of this study is to characterize the impact of chemotherapy according to histology in patients (p) diagnosed with MPM at our institution.

#### Methods and patients:

•Review of 189 MPM p between November 2002 and April 2020. Associations between clinical variables and outcome were assessed with Cox regression models and survival data were calculated by the Kaplan-Meier method.

#### Results:

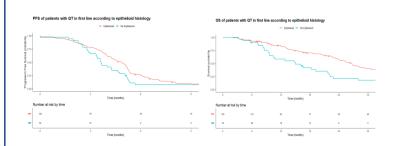
- Median age 68 years (y) (45-88 y)
- 1<sup>st</sup> line chemo: 85% of p (66% cisplatin-pemetrexed and 27% carboplatin-pemetrexed)
- Median survival (OS) in overall population was 21.3 m (95%CI17.2-24.3).
- Epithelioid histology, PS 0, neutrophil-lymphocyte ratio >5 and treatment with cisplatin vs carboplatin were associated with significant improvements in
- For patients treated with chemotherapy in first line the progression free survival (PFS) was 4.4 m and the OS 23.1 m.
- Patients with epithelioid tumors had better PFS and
- Median progression PFS for p with epithelioid tumors treated with chemotherapy in first line was 4.8 m versus 3.6 months in no epithelioid tumors (HR 1.5 CI95% 1.0-2.3; p=0.03).
- OS for epithelioid patients treated with first line chemotherapy was 26.7 m versus 15.0 m in no epithelioid patients (HR2.25 CI95% 1.4-3.4; p<0.001).

BASELINE PATI	ELINE PATIENTS CHARACTERISTICS		
Characteristic	Number	Percentage	
Median age	68 y (45-88)		
Gender			
Males	57	70	
Females	132	30	
PS			
0	44	23	
1	131	69	
2	14	13	
Asbestos			
Yes	141	74	
No	47	26	
Histology			
Epithelioid	145	76	
No-epithelioid	44	24	
First line chemo			
Yes	161	85	
No	28	15	
Type of chemo			
Cisplatin-pem	108	66	
Carboplatin-pem	32	27	

## PROGNOSTIC FACTORS Global survival according to PS Legend + PS = 0 + PS = 1 + PS = 2 Global survival according to epithelioid histology Global survival according NLR

#### SURVIVAL ACCORDING HISTOLOGY

	PFS			OS		
	Overall	Cisplatin	Carboplati	Overall	Cisplatin	Carbopla
			n			tin
EPITHELIOID	4.8	5.1	4.5	26.7	30.7	26.7
NON-EPITHELIOID	3.6	3.6	3.6	15.0	17.2	14.8
	HR 1.5	HR 1.4	HR 1.99	HR 2.25	HR 2.7	HR 2.7
	CI95%	CI95%	CI95%	CI95%	CI95%	CI95%
	1.1-2.3;	0.91-2.3;	0.96-4.1;	1.4-3.4;	1.6-4.5;	1.3-5.8;
	p=0.03	p=0.06	p=0.06	p<0.001	p<0.001	p=0.008



In our series, patients with no epithelioid tumors presented worse prognosis. Although epithelioid tumors exposed to cisplatin had higher PFS, histology was not a clear predictor of Ct efficacy.

#### **CONCLUSION:**

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### Genomic landscape of pleural and peritoneal mesothelioma tumors

### Abstract 1734P

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## University of Zurich<sup>uzh</sup> 1734P

### Genomic Landscape of Pleural and Peritoneal Mesothelioma Tumors

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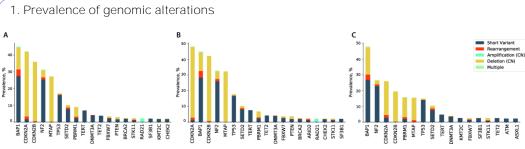
#### Background

Malignant pleural and peritoneal mesotheliomas are rare malignancies with an unacceptably poor prognosis and limited treatment options. The genomic landscape is mainly characterized by loss of tumor suppressor genes and mutations in DNA repair genes. Currently, data from next-generation sequencing (NGS) of mesothelioma tumors is restricted to a limited number of cases; moreover, data comparing molecular features of mesothelioma from pleural and peritoneal origin with NGS are lacking. Here, we have analyzed the largest cohort of patients with mesothelioma so far, for molecular alterations by NGS. These results indicate that molecular analysis for mesothelioma may inform clinical routine.

#### Materials and Methods

We analyzed 1113 pleural mesothelioma and 355 peritoneal mesothelioma samples from patients sequenced through December 2020. All tumors were sequenced with the FoundationOne® or FoundationOne®CDx test for detection of substitutions, insertion-deletions, copy-number alterations and selected rearrangements in at least 324 cancer genes. Microsatellite instability was called on at least 95 loci and tumor mutational burden (TMB) was calculated on 0.8-1.2 Mb.

#### Results



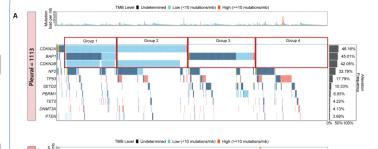
This analysis revealed 19 genes with an overall prevalence of at least 2%. Alterations in *BAP1, CDKN2A, CDKN2B, NF2, MTAP, TP53*, and *SETD2* occurred with a prevalence of at least 10%. A) prevalence of alterations in the entire cohort, B) in pleural mesothelioma and C) in peritoneal mesothelioma. The alterations include short variants (short nucleotide variants (SNV) and insertion-deletions (indels)), gene rearrangements, copy number variations and multiple alterations.

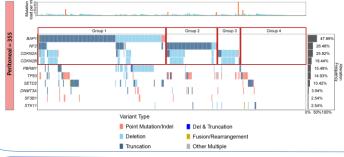
#### Disclosure and contact information

SH, EFB, ACF: No conflict of interest related to this work ZF, ESS: Employees of Foundation Medicine and Shareholders in Roche

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2. Overview on genomic subgroups according to **CDKN2A/B** and **BAP1** expression





Based on the most common alterations occurring, four distinct subgroups in pleural and peritoneal mesothelioma were identified. Due to large differences in the prevalence of the genomic alterations between pleural and peritoneal mesothelioma, the subgroups in pleural and peritoneal mesothelioma are defined by their different genomic makeup. In pleural mesothelioma, group 1 had alterations in CDKN2A/B and BAP1, group 2 in CDKN2A/B, group 3 in BAP1 only and group 4 neither in BAP1 nor in CDKN2A/B but in TP53. NF2 alterations were identified across all four groups. In peritoneal mesothelioma. group 1 was characterized by BAP1 expression, group 2 by NF2, group 3 by no expression of BAP1 and NF2. CDKN2A/B is expressed homogenously throughout group 1-3. Group 4 had none of the major alterations. CDKN2A/B was expressed homogenously throughout group 1-3. Group 4 had non of the major alterations.





#### Conclusion

Precision medicine including comprehensive genomic profiling has tremendously improved the outcome of patients, especially in lung cancer, breast cancer and melanoma. Nevertheless, rare malignancies and in malignancies with a low numbers of somatic mutations need to be analyzed to identify new therapeutic options for these difficult to treat cancers.

## Prognostic factors predicting survival in malignant pleural mesothelioma: A retrospective study in two Spanish hospitals

Abstract 1736P

#1736P: Prognostic factors predicting survival in malignant pleural mesothelioma:

A retrospective study in two Spanish hospitals

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Disclosure: The authors have no conflicts of interest to declare

#### Background

Malignant pleural mesothelioma (MPM) is a rare, aggressive tumor, with poor prognosis. Its well-known association to aspector exposure helps to identify the population mostly affected by this disease. The aim of this study is to characterize patients with MPM in two Spanish hospitals, as well as define prognostic variables which may influence outcomes and survival.

#### Methods

A descriptive, retrospective analysis of 97 patients diagnosed of MPM from November 2004 to December 2020 in Regional University and Virgen de la Victoria hospitals located in Málaga, Spain, was carried out. Qualitative variables were analyzed under frequency tables, and quantitative variables in the form of mean, median, maximum, minimum and standard deviation. Overall survival (OS) was calculated from the start of therapy to death from any cause or latest check-up. Survival curves were estimated with the Kaplan–Meier method and the differences between survival curves were evaluated with log-rank test.



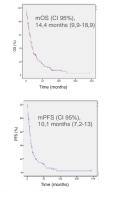
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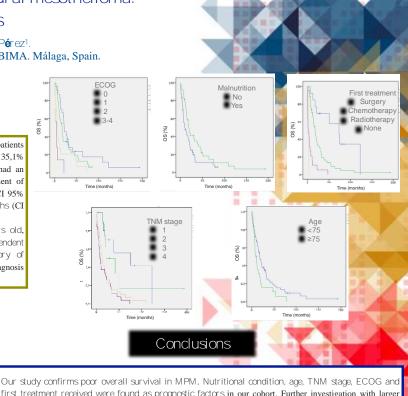
#### Results

With a median follow-up of 14 months (range 0-193), a total of 97 patients were analyzed, median age 70 (range 23-91) 71,1% (n=69) males. A 35,1% (n=34) had a known history of asbestos exposure, 74,5% (n=70) had an ECOG 0-1, and 80,4% (n=78) had advanced disease at the moment of diagnosis, defined by TNM III-IV. Median OS was 14,4 months (CI 95% 9,9-18,9), and median progression free survival (PFS) 10,1 months (CI 95% 7,2-13).

Univariate analysis demonstrated TNM stage, age over 75 years old, malnutrition, poor ECOG and first treatment received were independent prognostic factors that predicted poor survival (p<0.05). History of smoking was found to be associated with advanced stage at diagnosis (p<0.05).

General characteristics	% (n)
Median age (range)	70 (23-91)
Sex % (n) Men Women	71,1 (69) 28,9 (28)
ECOG 0-1 ≥2	72,1 (70) 27,9 (24)
Histology Epithelioid Non epithelioid Unknown	71,1% (n=69) 12,4% (n=12) 16,5% (n=16)
TNM stage I II III IV	10,3% (n=10) 9,3% (n=9) 47,4% (n=46) 33% (n=32)
First treatment received Surgery Chemotherapy Radiotherapy No treatment	13,7 (13) 65,3 (62) 1,1 (1) 20 (19)
Number of chemotherapy lines 0-2 3-4 ≥5	73,2 (60) 24,4 (20) 2,4(2)





first treatment received were found as prognostic factors in our cohort. Further investigation with larger samples should be carried out to verify this findings.

References

Ringgaard Petersen T, Panou V, Meristoudis C, Weinreich UM, Ree CD. Cinical prognessis factors mesothelioma: best supportive care and anti-tumor treatments in a real-life setting, Acta Oncologica. 2 2021;1-7.

 Consiliate S, Lodge D, Neville D, Jones T, Fogg C, Basselt P, et al. Predicting service in malignant please
mesorbhiloms using routine client and laboratory brancherisines. BMD Open Regis Res. 7, January 2017, 8(1)
 Guzmán-Casta, Carrasco-Canchards, Guzmán-Hissos et al. Prognostis factors for progression free and overal survival in malignant plearul mesorbhiloms. Thoracic Cancer - Wiley Online Jatersys Memory 202
 Nadal E, Bosch-Barrera J, Cedrés S, Coves J, García-Campelo R, Giljado M, et al. SEOM clinical guidelines for the reatment of malignant plearul mesorbelioms (2020). Clin Transl Oncol 4 de febrero of 2021.
 S. Accids R, Neesth G, Najib M. Update on biology and management of mesorbicome. THORACIG ONCOLOGY-18. 2 Oct. 2020.





## Gracias por su atención