REGIONE AUTONOMA FRIULI VENEZIA GIULIA

Comune di Monfalcone

I SESSIONE

Il trattamento multidisciplinare del mesotelioma pleurico

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Aviano

Nuovi orizzonti per il Mesotelioma pleurico

IMMUNOTERAPIA

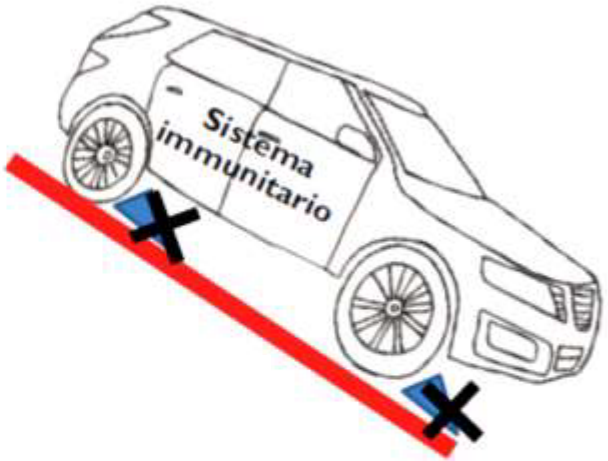
REGIONE AUTONOMA FRIULI VENEZIA GIULIA

Comune di Monfalcone

... il vero "farmaco" non è l'inibitore dei checkpoints immunitari, ma il sistema immunitario stesso

(A) Approcci storici convenzionali
Attivare il sistema immunitario
Vaccini
Citochine (IL2, interferon)

(B) Nuovo approccio
Rimuovere i freni del sistema immunitario
Immune-checkpoints inibitori



Azione sul sistema immunitario dell'ospite e non contro le cellule tumorali

Azione indiretta

(A) Approcci storici convenzionali
Attivare il sistema immunitario
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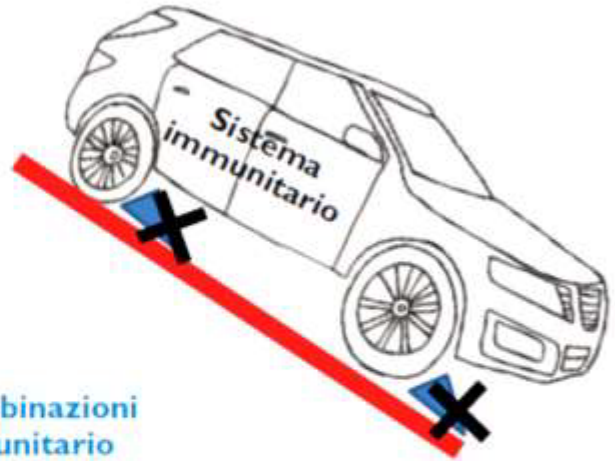
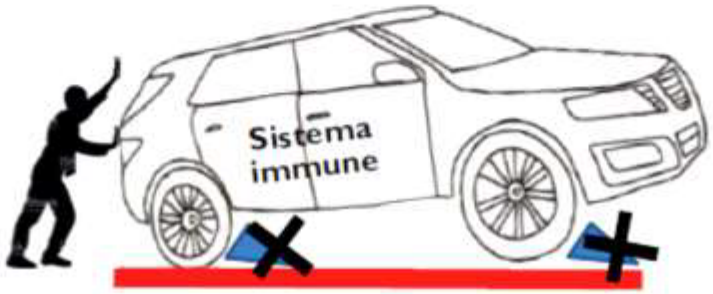
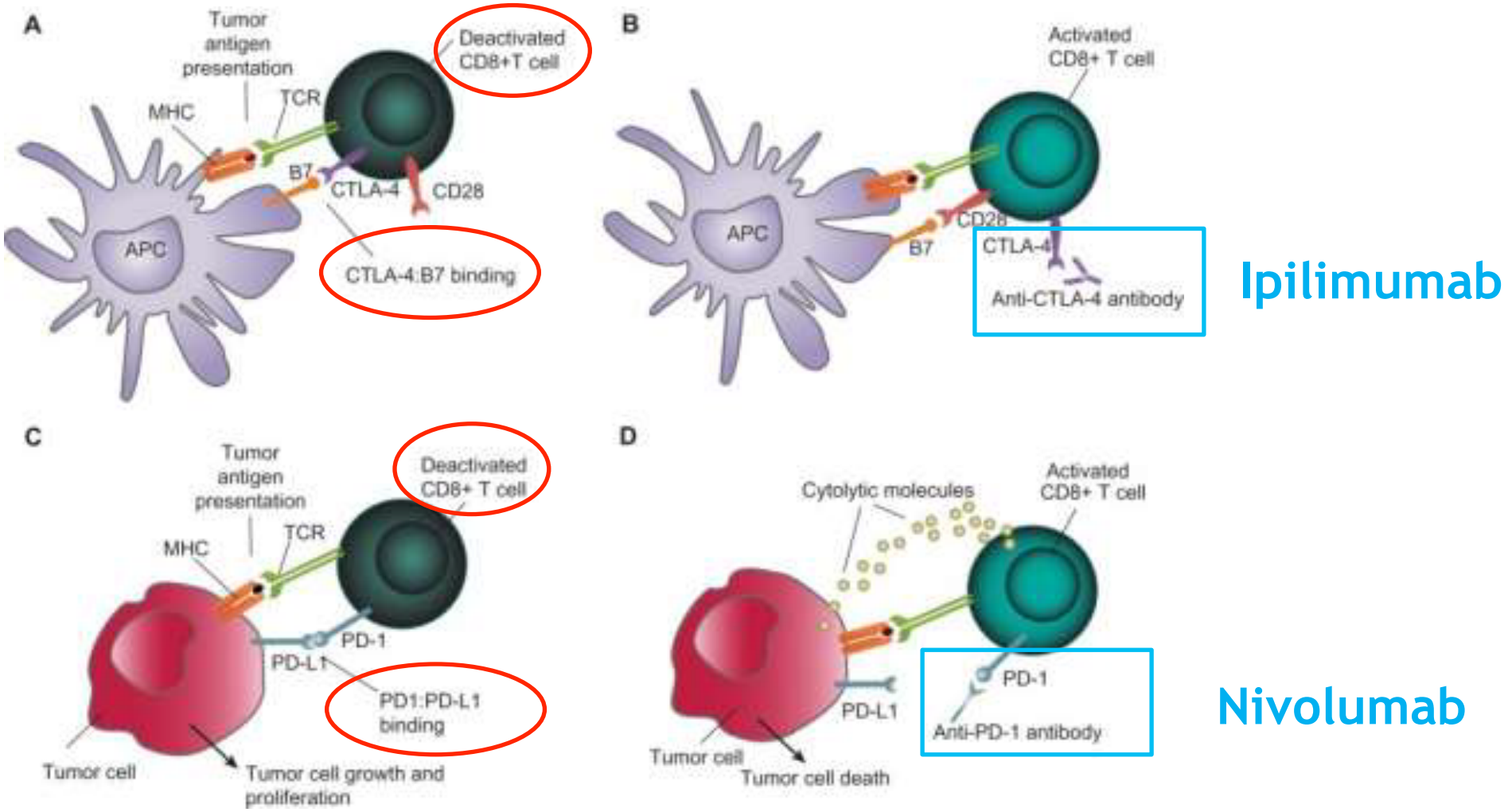


Azione sul sistema immunitario dell'ospite e non contro le cellule tumorali

(C) Il futuro prossimo: le combinazioni
Attivare il sistema immunitario
e rimuoverne i freni

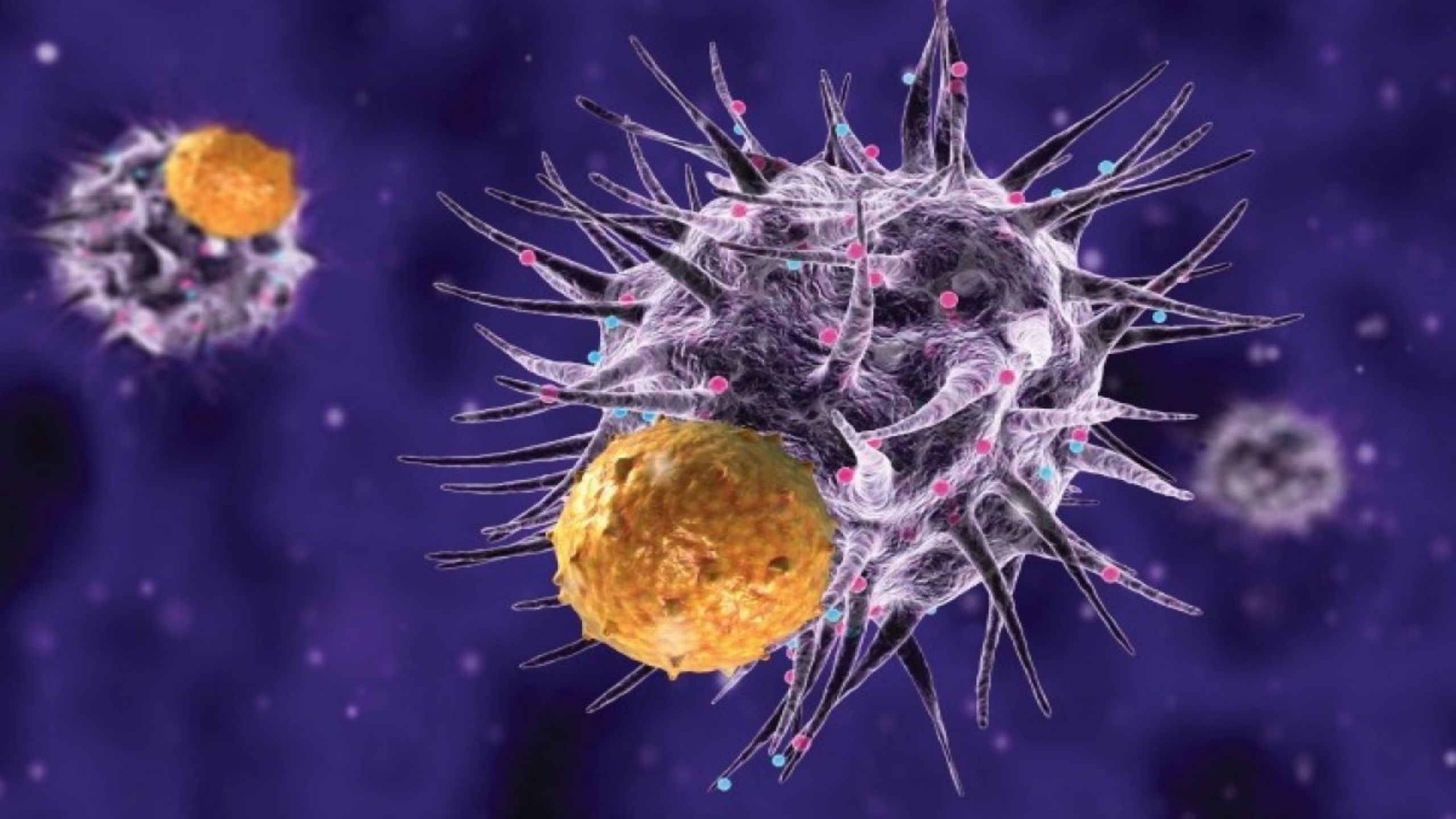


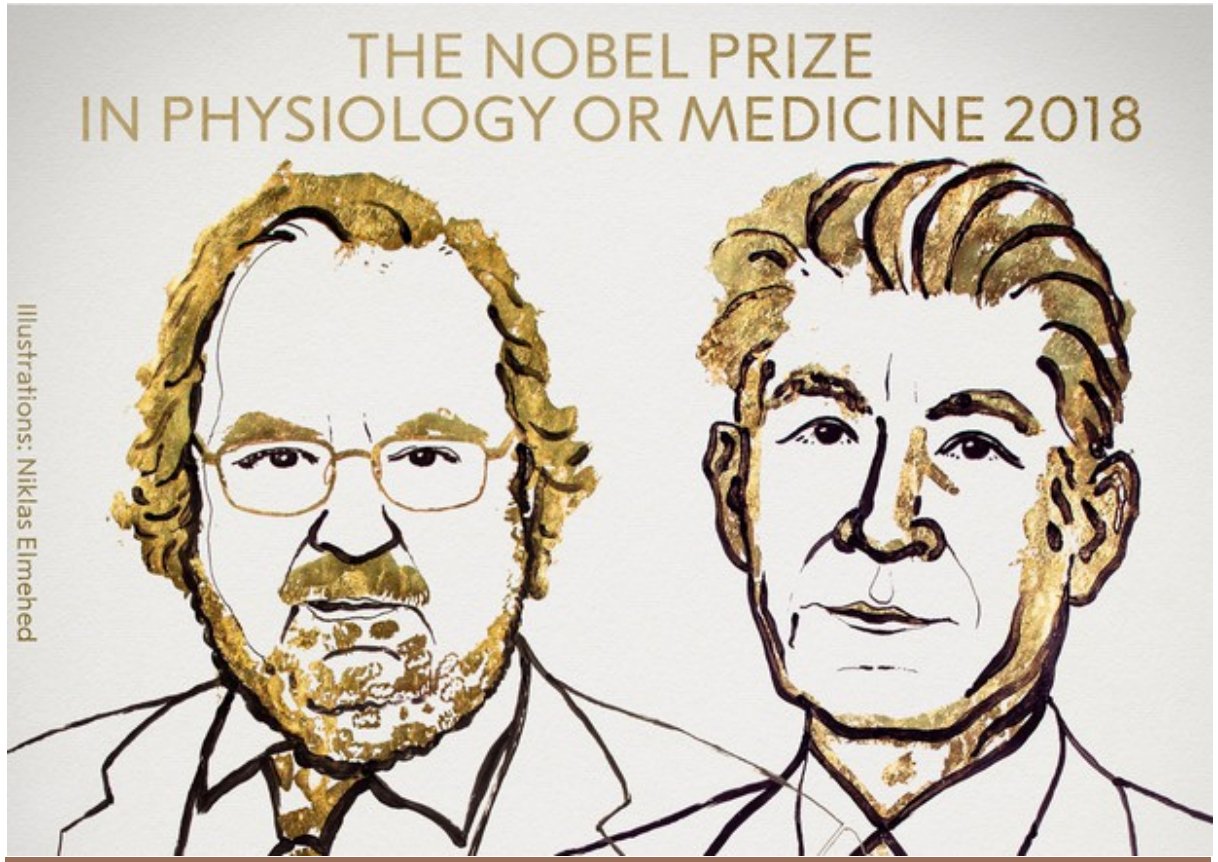
Azione indiretta



Ipilimumab

Nivolumab





James P. Allison Tasuku Honjo

"for their discovery of cancer therapy by inhibition of negative immune regulation"

La risposta infiammatoria cronica alle fibre di **ASBESTO** osservata nella carcinogenesi del MPM porta ad un **MICROAMBIENTE TUMORALE IMMUNOSOPPRESSIVO**

Table 1 Single Arm Studies of immunotherapy in Mesothelioma

Study	Drugs & Schedule	N	Phase	Line of Treatment	Response Rate	PFS (mon)	OS (mon)
KEYNOTE028[51]	Pembrolizumab 10mg/kg q2 weekly	25	Ib	2+	20%	5.4	18
IRB14-1381[52]	Pembrolizumab 200mg q3 weekly	65	2	2	19%	4.5	11.5
KEYNOTE158[53]	Pembrolizumab 200mg q3 weekly	118	2	2+	8%	2.1	10.0
MERIT[54]	Nivolumab 240mg q2 weekly	34	2	2	29%	6.1	17.3
INITIATE[55]	Nivolumab 240mg q 2weekly + ipilimumab 1mg/kg q 6weekly	38	2	2+	29%	6.2	NR
NIBIT-MESO-1[56]	Tremelimumab 1mg/kg + durvalumab 20mg/kg q4 weekly	40	2	1–2	28%	5.7	16.6
DREAM[57]	Cisplatin 75mg/m2 + pemetrexed 500mg/m2 + durvalumab 1125mg q3weekly	54	2	1	48%	6.9	18.4
PrE0505[58]	Cisplatin 75mg/m2 + pemetrexed 500mg/m2 + durvalumab 1120mg q3 weekly	55	2	1	56%	6.7	21.1

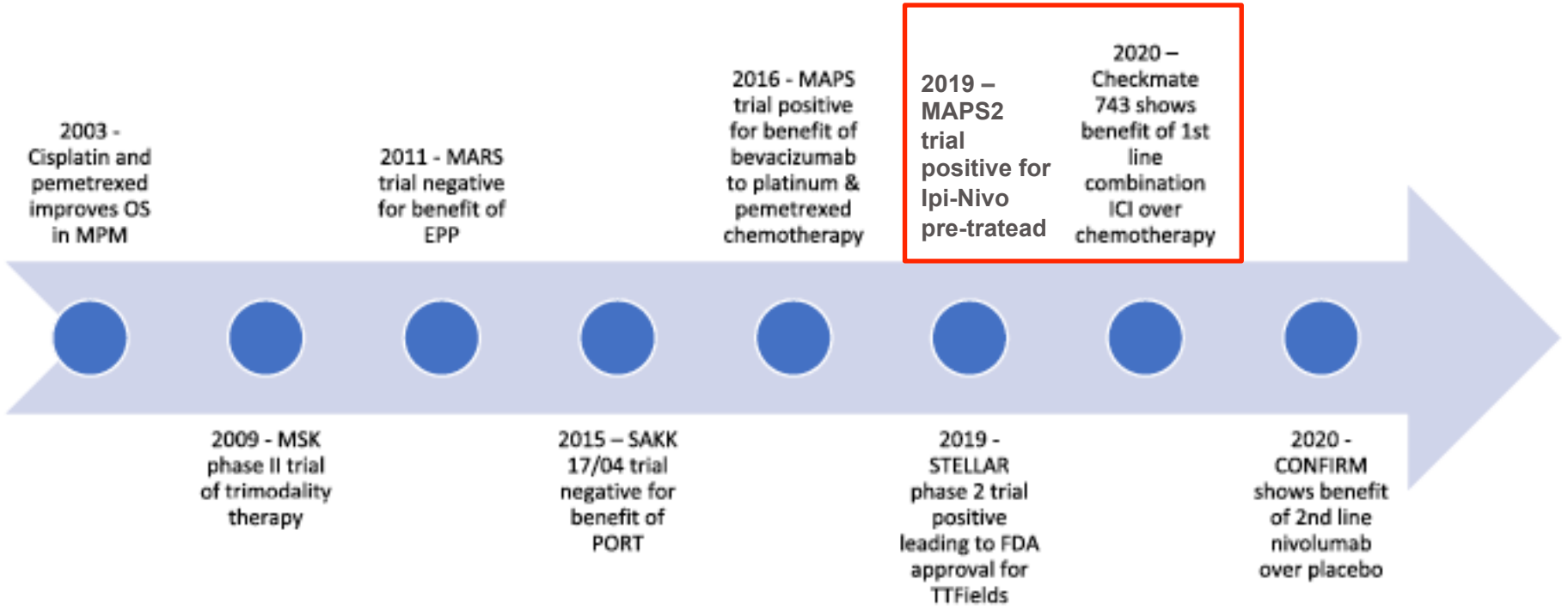
Abbreviations: OS, overall survival; PFS, progression free survival; NA, not available; NR, not reached.

Table 2 Randomised Studies of immunotherapy in Mesothelioma

Study	Drugs & Schedule	N	Phase	Line of Treatment	Response Rate	PFS (mon)	OS (mon)
PROMISE-Meso[59]	Pembrolizumab 200mg q3 weekly versus chemotherapy	144	3	2	22% versus 6%*	2.5 versus 3.4	10.7 versus 12.4
CONFIRM[60]	Nivolumab 3mg/kg q2 weekly versus placebo	332	3	2	NA	3.0 versus 1.8*	9.2 versus 6.6*
MAPS2[61]	Nivolumab 3mg/kg q2 weekly + Ipilimumab 1mg/kg q6weekly versus Nivolumab 3mg/kg q2weekly	125	2	2–3	28% versus 19%	5.6 versus 4.0	15.9 versus 11.9
CHECKMATE743[14]	Nivolumab 3mg/kg q 2weekly + ipilimumab 1mg/kg q6 weekly versus platinum + pemetrexed chemotherapy	605	3	1	40% versus 43%	6.8 versus 7.2	18.1 versus 14.1*
DETERMINE[62]	Tremelimumab 10mg/kg q3weekly versus placebo	571	2b	2+	4.5% versus 1.1%	2.8 versus 2.7*	7.7 versus 7.3 months

Note: * denotes statistically significant.
Abbreviations: OS, overall survival; PFS, progression free survival; NA, not available; NR, not reached.

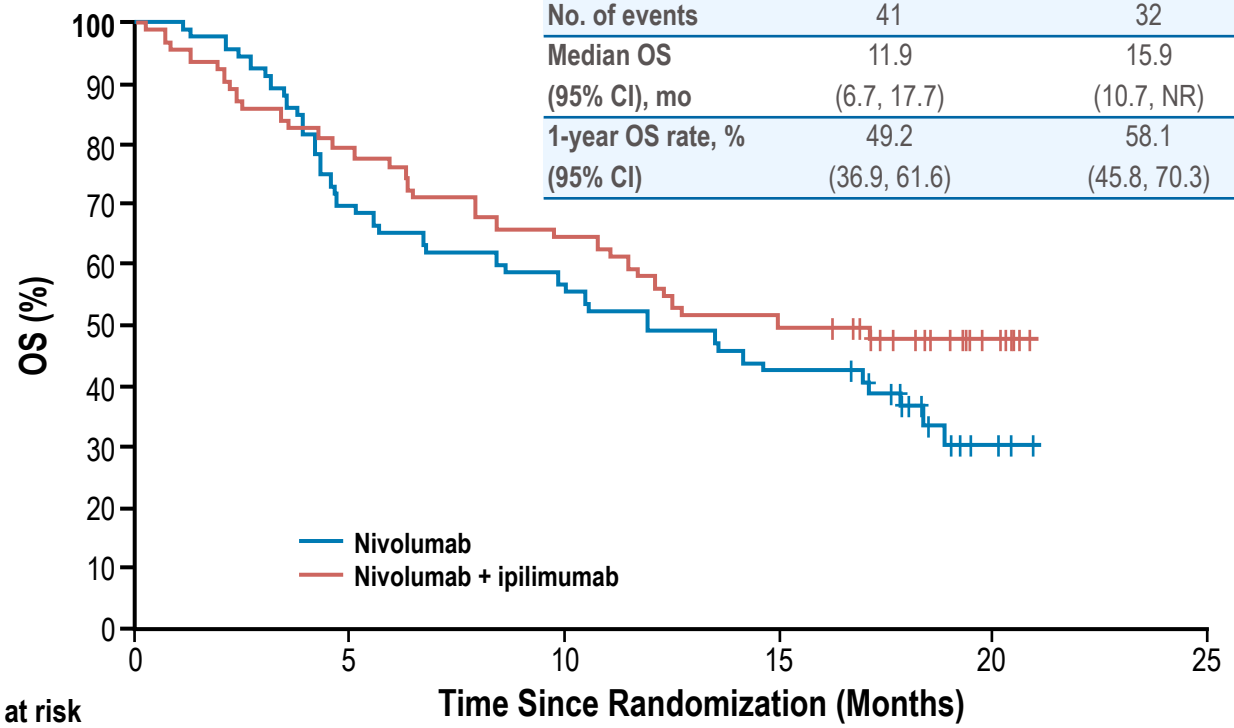
Davis A. et al. Lung cancer: Targets and Therapy 02 Mar 2022



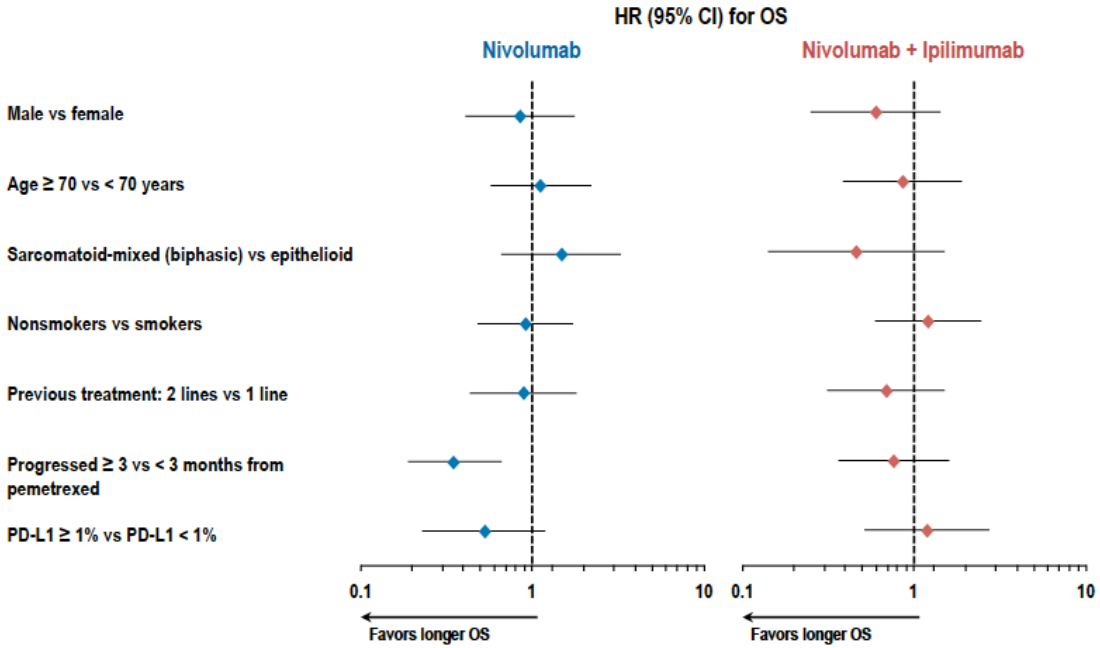
Davis A. et al. Lung cancer: Targets and Therapy 02 Mar 2022

MAPS2 trial positive for Ipi-Nivo pre-treated

	Nivolumab (n = 63)	Nivolumab + Ipilimumab (n = 62)
No. of events	41	32
Median OS	11.9	15.9
(95% CI), mo	(6.7, 17.7)	(10.7, NR)
1-year OS rate, %	49.2	58.1
(95% CI)	(36.9, 61.6)	(45.8, 70.3)



No. at risk (no. censored)						
Nivolumab	63 (0)	44 (0)	35 (0)	27 (0)	5 (17)	0 (22)
Nivolumab + ipilimumab	62 (0)	49 (0)	40 (0)	32 (0)	8 (22)	0 (30)



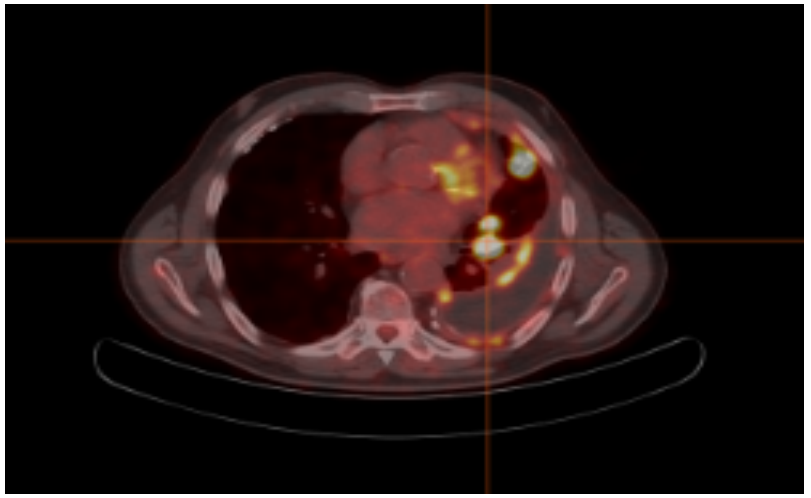
Scherpereel A et al. Lancet Oncol 2019,20(2):239-253

MAPS2 trial positive for Ipi-Nivo pre-treated

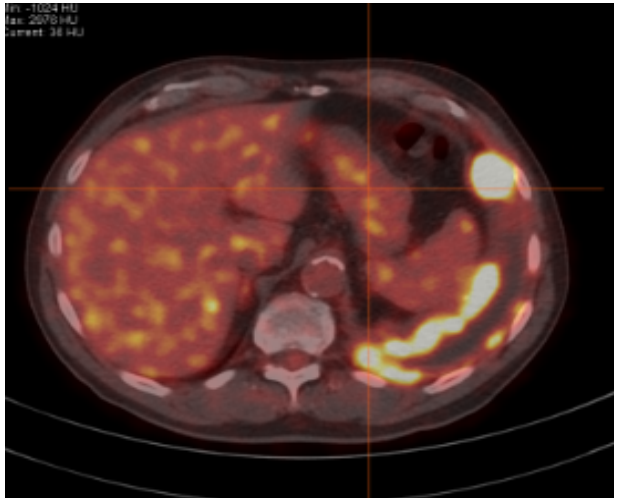
Uso compassionevole di Ipilimumab-Nivolumab nei pazienti pre-trattati

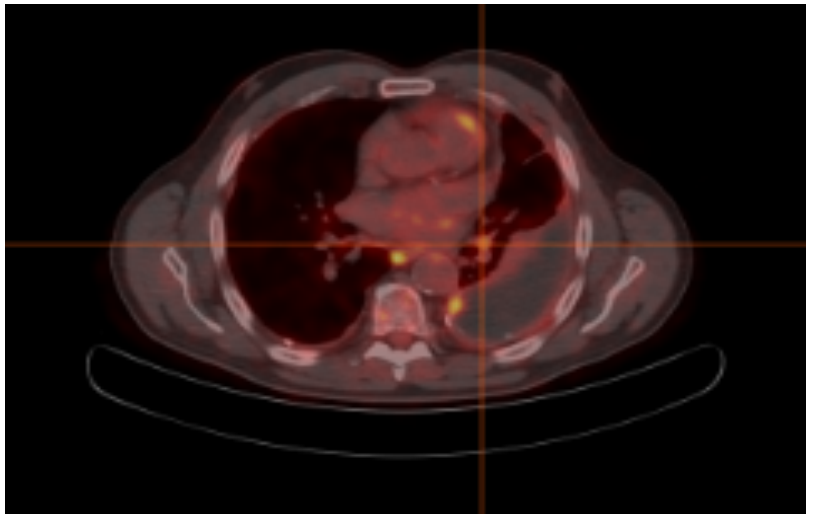
Scherpereel A et al. Lancet Oncol 2019,20(2):239-253

Uso compassionevole di Ipilimumab-Nivolumab - 2° linea

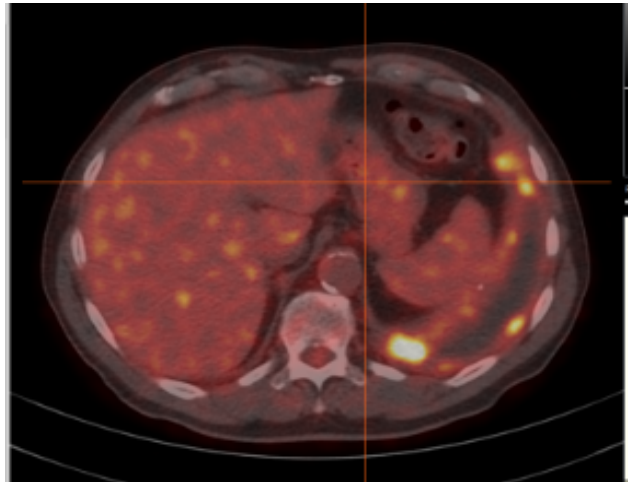


Basale





Dopo 3 mesi



CHECKMATE 743 - Ipilimumab-Nivolumab - 1° linea

Key eligibility criteria
- Unresectable MPM
- No prior systemic therapy
- ECOG PS 0–1

Stratified by
Histology (epithelioid vs non-epithelioid) and gender

N = 605
R 1:1

n = 303
NIVO 3 mg/kg Q2W + **IPI** 1 mg/kg Q6W (for up to 2 years)

n = 302
Cisplatin or **carboplatin** + **pemetrexed** Q3W[b] (6 cycles)

Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

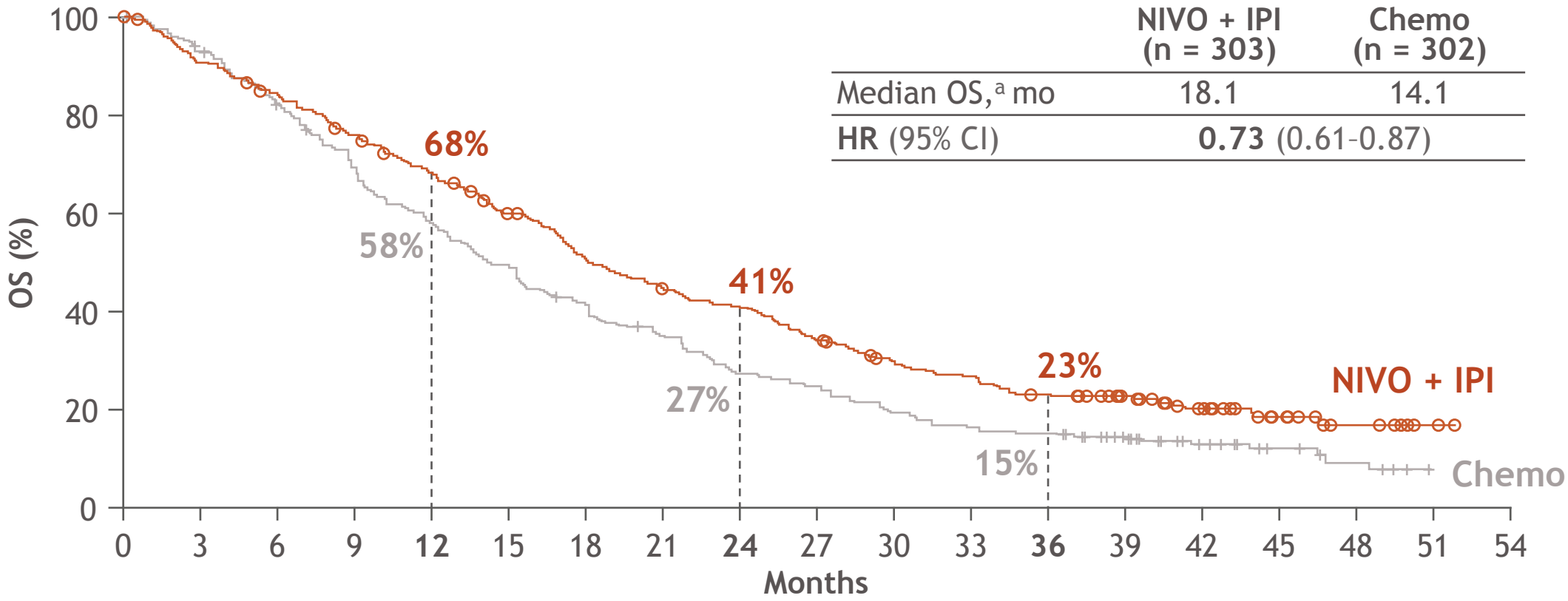
Secondary endpoints
- ORR, DCR, and PFS by BICR
- Efficacy by PD-L1[c] expression

Exploratory endpoints
- Safety and tolerability
- Biomarkers

Baas P. et al. The Lancet 2021;397(10272):375-386

3-year update: overall survival in all randomized patients

	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS,[a] mo	18.1	14.1
HR (95% CI)	**0.73** (0.61–0.87)	

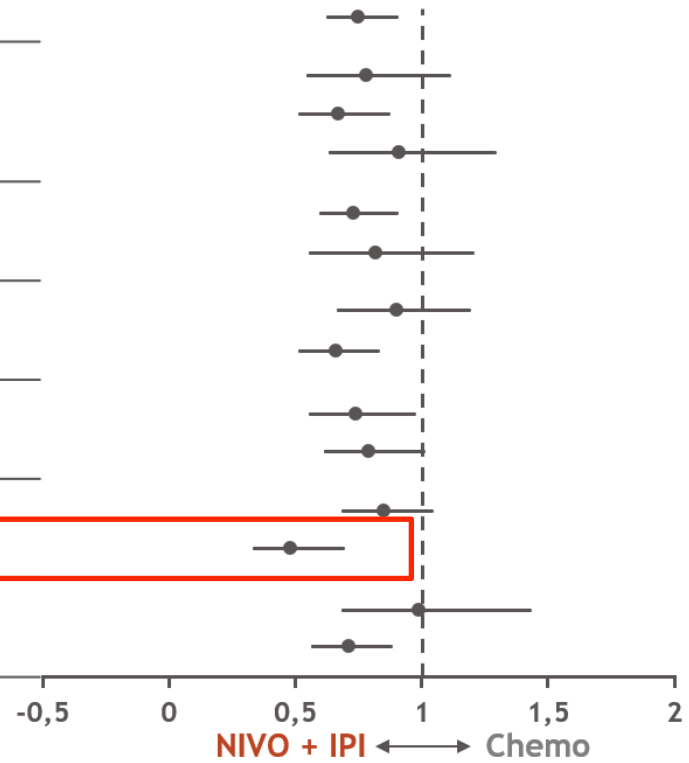


No. at risk

NIVO + IPI	303	273	251	226	200	173	145	126	116	97	80	73	62	49	35	18	7	2	0
Chemo	302	269	234	192	164	138	114	97	76	69	54	46	43	33	20	11	6	0	0

3-year update: OS subgroup analysis

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI (n = 303)	Chemo (n = 302)	
All randomized (N = 605)	18.1	14.1	0.75[a]
< 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**
Female (n = 138)	**21.1**	**18.0**	**0.82**
ECOG PS 0 (n = 242)	20.7	19.5	0.90
ECOG PS ≥ 1[b] (n = 363)	17.0	11.6	0.66
Never smoker (n = 249)	17.9	14.1	0.74
Former smoker[c] (n = 318)	17.6	14.9	0.79
Epithelioid (n = 455)	**18.2**	**16.7**	**0.85**
Non-epithelioid[d,e] (n = 150)	**18.1**	**8.8**	**0.48**
PD-L1 < 1% (n = 135)	17.3	16.6	0.99
PD-L1 ≥ 1%[f] (n = 451)	18.0	13.3	0.71

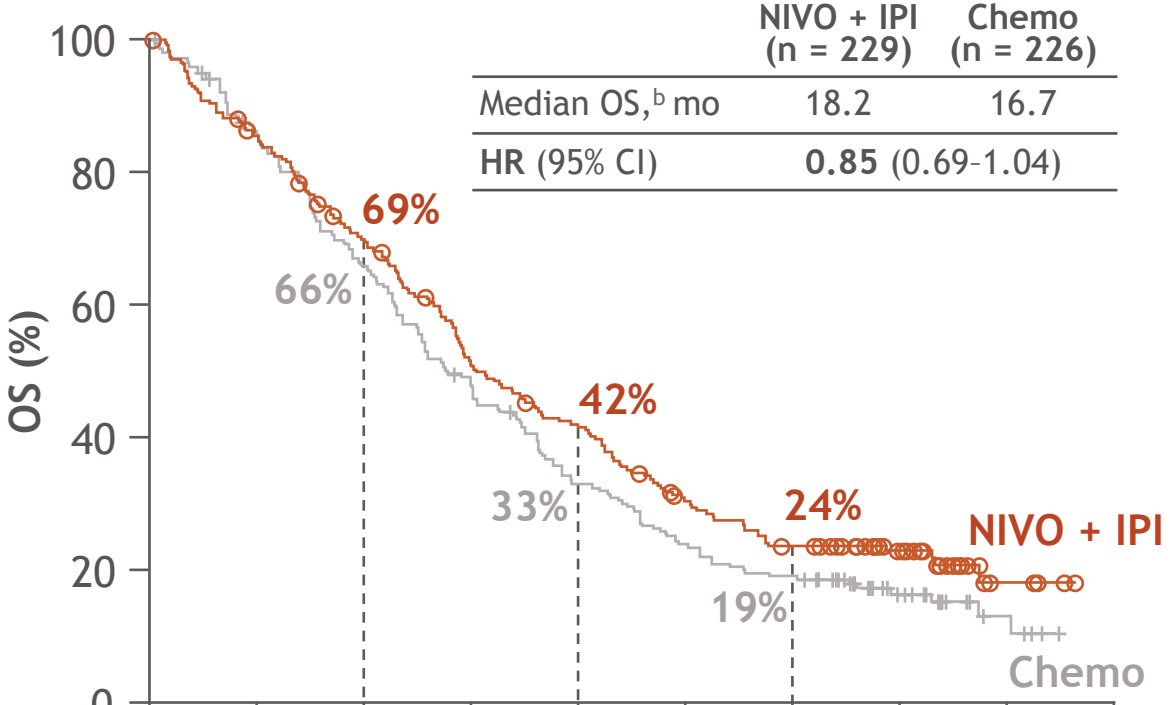


Minimum follow-up: 35.5 months. Bold text indicates study stratification factors.
[a]Stratified HR, 0.73; [b]One patient in the chemotherapy group had a baseline ECOG PS of 2 (protocol deviation); [c]26 patients were current smokers; smoking status of 12 patients was unknown; [d]Includes sarcomatoid, mixed, and other; [e]One patient was changed from epithelioid to non-epithelioid after the primary analysis; [f]PD-L1 expression level was not reported for 19 patients.

3-year update: OS by histology

Epithelioid

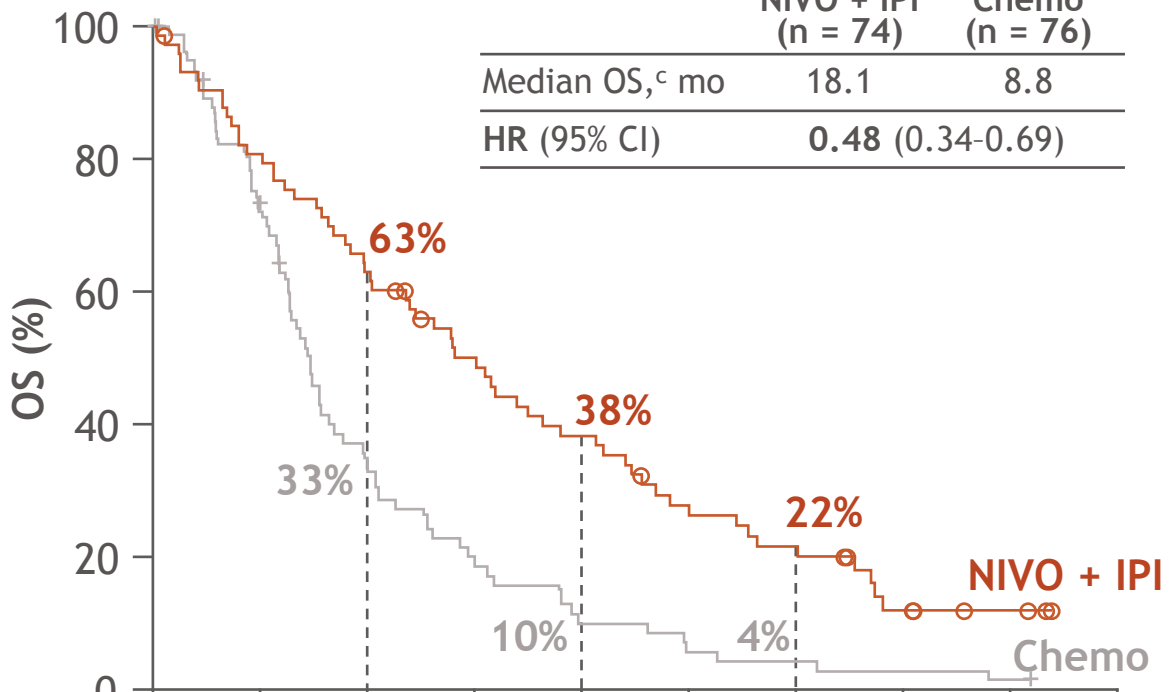
	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS,[b] mo	18.2	16.7
HR (95% CI)	**0.85** (0.69-1.04)	



No. at risk										
NIVO + IPI	229	192	154	111	90	63	48	29	4	0
Chemo	226	182	141	101	69	50	40	18	5	0

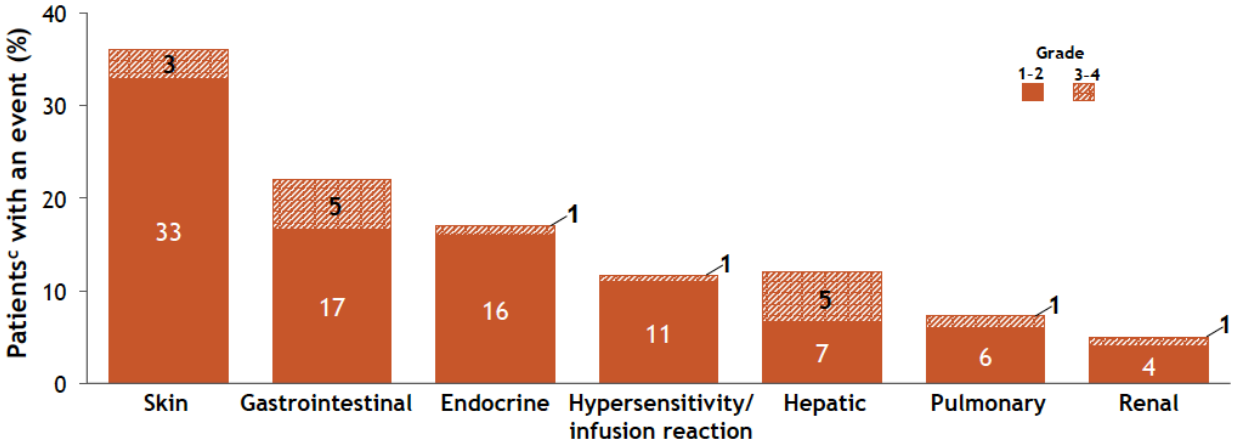
Non-epithelioid

	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS,[c] mo	18.1	8.8
HR (95% CI)	**0.48** (0.34-0.69)	

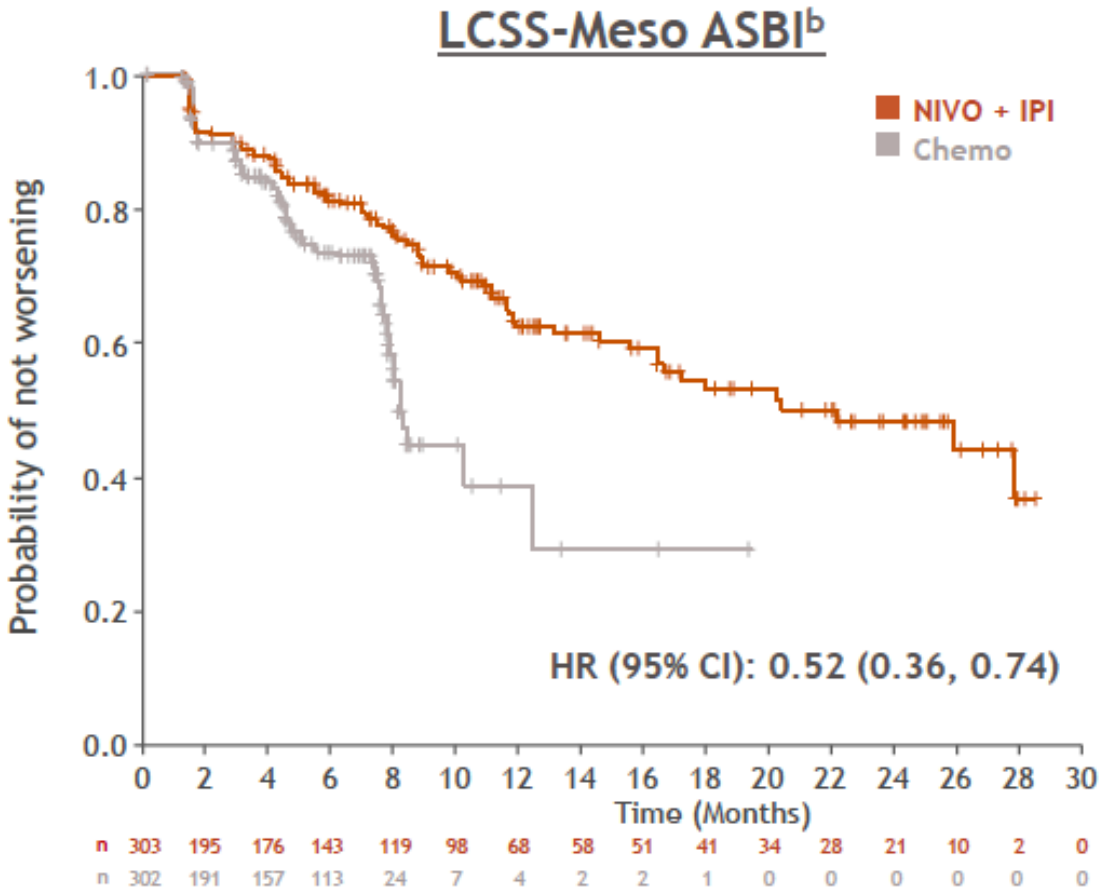


No. at risk										
NIVO + IPI	74	59	46	34	26	17	14	6	3	0
Chemo	76	52	23	13	7	4	3	2	1	0

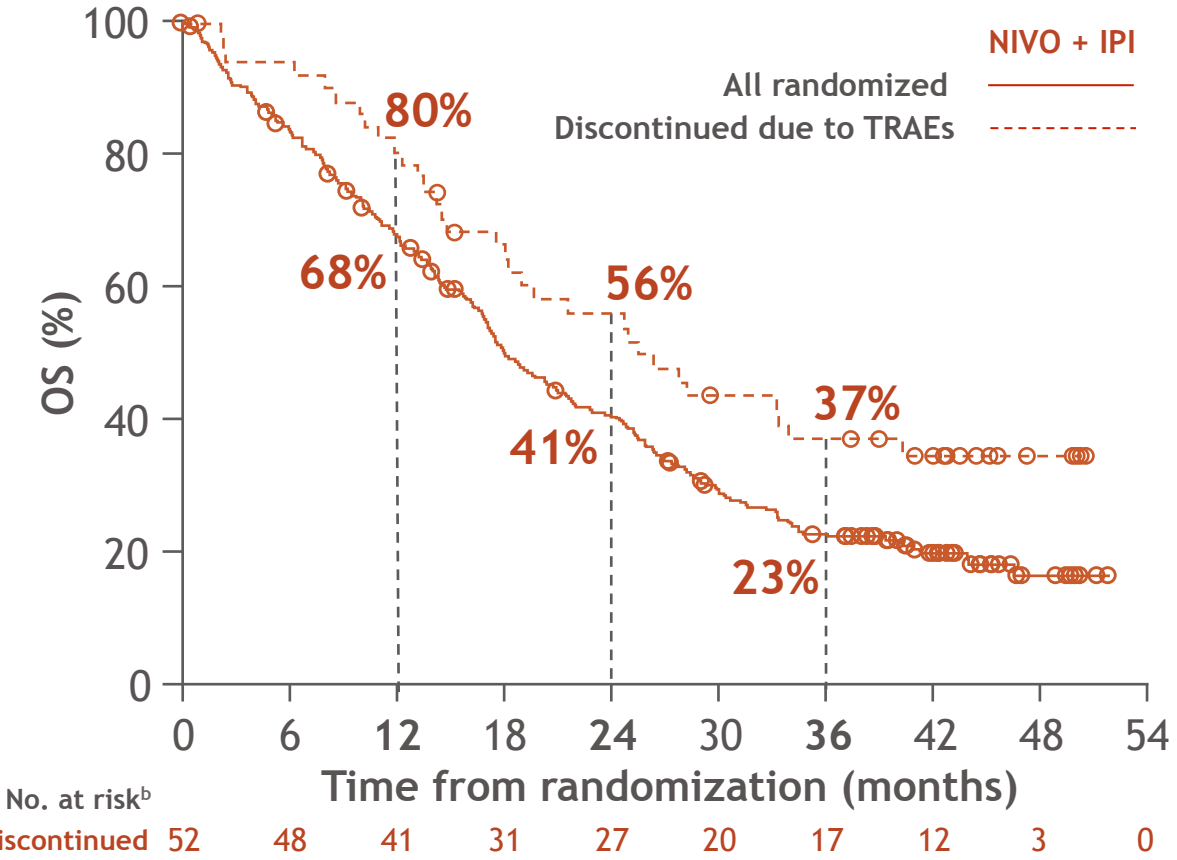
Treatment-related AEs with NIVO + IPI



Time to definitive deterioration



Efficacy in patients who discontinued NIVO + IPI due to TRAEs[a]



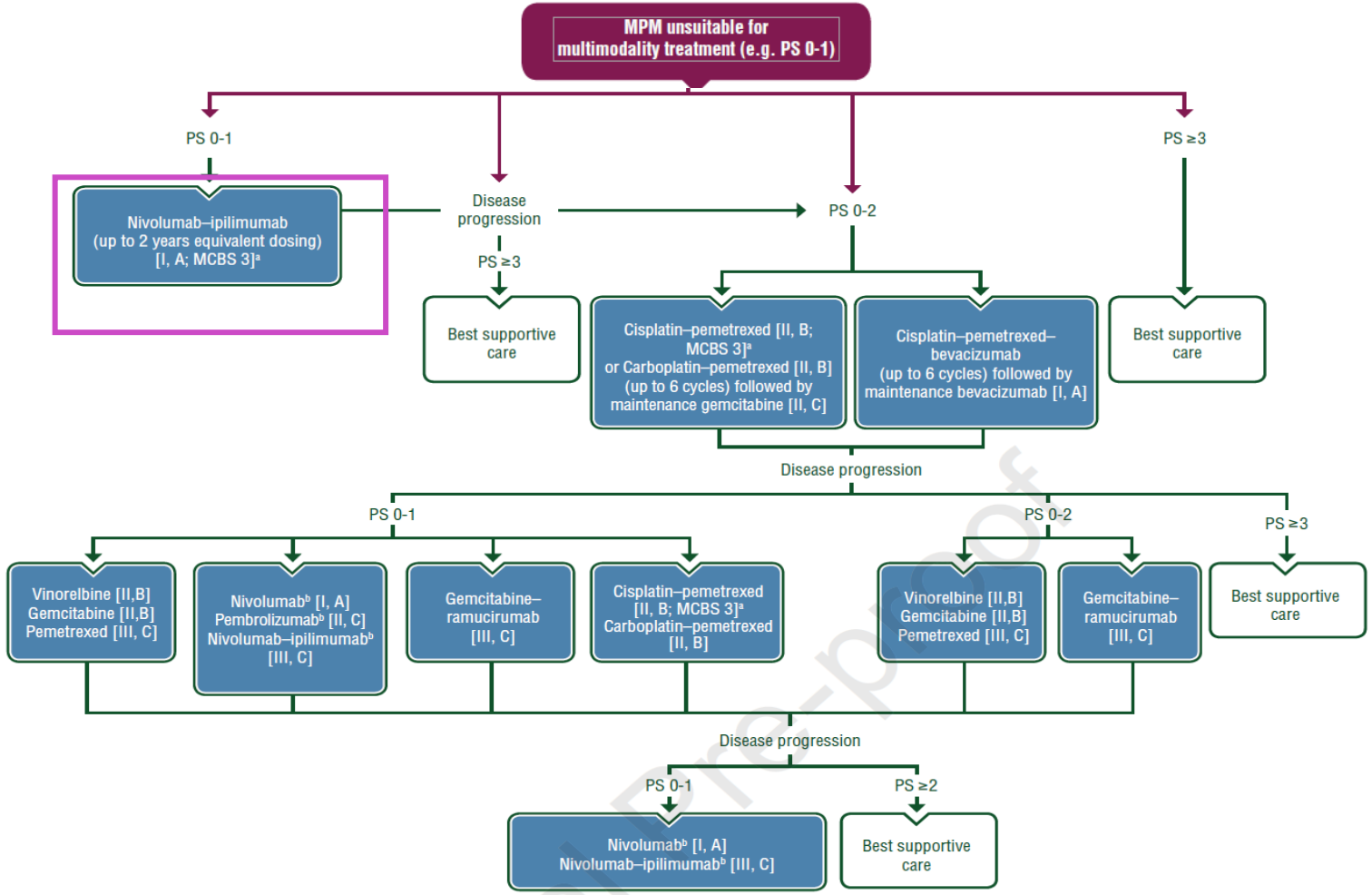
Patients who discontinued all components of NIVO + IPI due to TRAEs

	NIVO + IPI (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] %	34[e]

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

ESMO Guidelines for 2021: MPM unresectable



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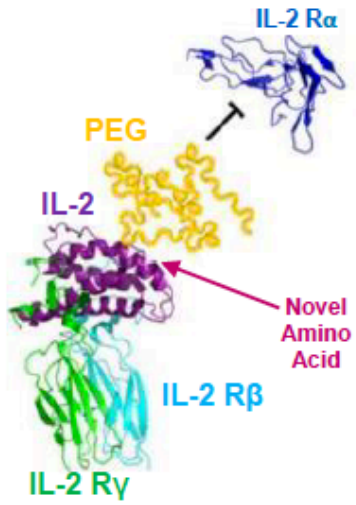
ESMO Guidelines for 2021: MPM unresectable

In Italia
Siamo in attesa dell'approvazione AIFA
……
verosimilmente in estate 2022

Studio ACT 16849 –THOR 707

SAR'245 'non-alpha' IL-2



- PEG blocks engagement of IL-2R α chain
- Selectively expands anti-tumor CD8+ T and NK cells
- No expansion of immune-suppressive CD4+ reg T cells
- No activation of eosinophils responsible for VLS

	SAR'245[3]
	Site-specific pegylation
Dose	24 µg/kg
Schedule	Q3W
Non-Alpha	✓
Expansion of CD8+T-cells[4]	✓✓
Expansion of NK cells[5]	✓✓
No expansion of CD4-Tregs	✓
No meaningful increase in EOS	✓
No anti-drug antibodies	✓

+ Pembrolizumab
o
+ Pembrolizumab+CT

Studio ACT 16849 –THOR 707

Thoracic

Non-small cell lung cancer

Indications	Experimental treatment
1L PD-1 naïve	SAR'245 + pembro
1L PD-1 naïve (Non-Sq)	SAR'245 + pembro + carbo-/cis-platin + pemetrexed
2-3L PD-1 Progressors	SAR'245 + pembro w / or w/ out nab-paclitaxel

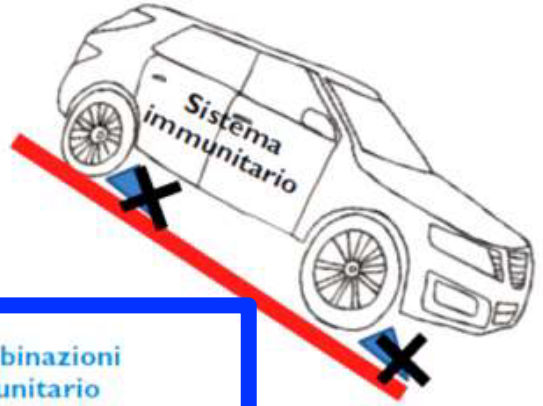
Mesothelioma

Indications	Experimental treatment
2-3L PD-1 naïve	SAR'245 + pembro

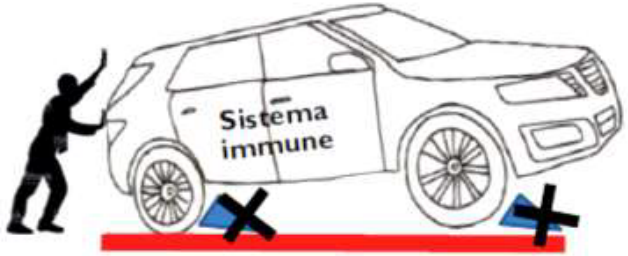
ARRUOLAMENTO SOSPESO per MPM

(A) Approcci storici convenzionali
Attivare il sistema immunitario
Vaccini
Citochine (IL2, interferon)

(B) Nuovo approccio
Rimuovere i freni del sistema immunitario
Immune-checkpoints inibitori



(C) Il futuro prossimo: le combinazioni
Attivare il sistema immunitario
e rimuoverne i freni



IN PRATICA.....

Per linee successiva alla 1°:

- Uso compassionevole Nivo-Ipi SOLO NON EPITELIALI
- In attesa di riapertura arruolamento studio ACT16849 per qualsiasi istologia (?)

Per 1° linea:

- In attesa di approvazione/rimborsabilità AIFA di Nivo-Ipi (estate 2022 ?)

Prospettive future

1) Oltre ICI: CAR-T targettanti mesotelina; approcci oncovirali o con cellule dendritiche

2) Terapie molecolari target: gene BAP1, gene ASS1

3) Chemio-immunoterapia (DREAMER3R study, BEAT-MESO study, NCT02784171)

4) Sistema NovoTTF-100L (TTF, Tumor Treating Fields)

Sequenza di IO-IO o CT-IO e poi SBRT (ipotesi di lavoro)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