UCSF
University of California
San Francisco

Mesothelioma

Best of IASLC World Conference on Lung Cancer 2020

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March 27, 2021

Disclosures

- Consulting
  - AstraZeneca, Sanofi
- Research Funding (to institution)
  - Amgen, Celgene, JNJ, Merck, Novartis, OncoMed, Trizell

- I will discussing non-FDA approved treatment/ indications during my presentation today (research findings)

Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma

By Nicholas J. Vogelzang, James J. Rusthoven, James Symanowski, Claude Denham, E. Kaukel, Pierre Ruffie, Ulrich Gatzemeier, Michael Boyer, Salih Emri, Christian Manegold, Clet Niyikiza, and Paolo Paoletti

Purpose: **Patients with malignant pleural mesothelioma, a rapidly progressing malignancy with a median survival time of 6 to 9 months, have previously responded poorly to chemotherapy. We conducted a phase III trial to determine whether treatment with pemetrexed and cisplatin results in survival time superior to that achieved with cisplatin alone.**

Patients and Methods: **Chemotherapy-naive patients who were not eligible for curative surgery were randomly assigned to receive pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 on day 1, or cisplatin 75 mg/m^2 on day 1. Both regimens were given intravenously every 21 days.**

Results: **A total of 456 patients were assigned: 226 received pemetrexed and cisplatin, 222 received cisplatin alone, and eight never received therapy. Median survival time in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the control arm (P = .020, two-sided log-rank test). The hazard ratio for death of patients in the pemetrexed/cisplatin arm versus those in the control arm was 0.77. Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months (P = .001). Response rates were 41.3% in the pemetrexed/cisplatin arm versus 16.7% in the control arm (P < .0001). After 117 patients had enrolled, folic acid and vitamin B$_{12}$ were added to reduce toxicity, resulting in a significant reduction in toxicities in the pemetrexed/cisplatin arm.**

Conclusion: **Treatment with pemetrexed plus cisplatin and vitamin supplementation resulted in superior survival time, time to progression, and response rates compared with treatment with cisplatin alone in patients with malignant pleural mesothelioma. Addition of folic acid and vitamin B$_{12}$ significantly reduced toxicity without adversely affecting survival time.**

J Clin Oncol 21:2636-2644.

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Then 2004-2016…

Then 2004-2016…

2016: MAPS trial

Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial

Gérard Zalcman, Julien Mazieres, Jacques Margery, Laurent Greillier, Clarisse Audigier-Valette, Denis Moro-Sibilot, Olivier Molinier, Romain Corre, Isabelle Monnet, Valérie Gounant, Frédéric Rivière, Henri Janicot, Radj Gervais, Chrystèle Locher, Bernard Milleron, Quan Tran, Marie-Paule Lebitasy, Franck Morin, Christian Creveuil, Jean-Jacques Parienti, Arnaud Scherpereel, on behalf of the French Cooperative Thoracic Intergroup (IFCT)

Summary

Background Malignant pleural mesothelioma is an aggressive cancer with poor prognosis, linked to occupational asbestos exposure. Vascular endothelial growth factor is a key mitogen for malignant pleural mesothelioma cells, therefore targeting of vascular endothelial growth factor might prove effective. We aimed to assess the effect on survival of bevacizumab when added to the present standard of care, cisplatin plus pemetrexed, as first-line treatment of advanced malignant pleural mesothelioma.

Lancet 2016; 387: 1405–14

Published Online
December 21, 2015
http://dx.doi.org/10.1016/
S0140-6736(15)01238-6

This online publication has

OS benefit: 18.8 vs 16.1 mo, HR 0.77, p=0.0167

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Never FDA approved

OS benefit: 18.8 vs 16.1 mo, HR 0.77, p=0.0167

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2016-2021: Not quite a desert

- Immunotherapy
  - Salvage PD-(L)1 inhibition
    - KEYNOTE-028, pembro in PD-L1+: PR 20%
    - Nivo-Meso, nivo in PD-L1 unselected: PR 15%
    - JAVELIN meso cohort, avelumab in PD-L1 unselected: PR 9.4%
  - Salvage CTLA4 inhibition
    - DETERMINE, tremelimumab (DETERMINE): RP2b study negative
  - Salvage combination
    - MAPS-2, nivo+ipi: PR 24%
    - INITIATE,nivo+ipi: PR 27%
    - NIBIT-Meso, durva+treme PR 28%

2020 WCLC in “Singapore”

2020 WCLC in "Singapore"

First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial

Paul Baas, Arnaud Scherpereel, Anna K Nowak, Nobukazu Fujimoto, Solange Peters, Anne S Tsao, Aaron S Mansfield, Sanjay Popat, Thierry Jahan, Scott Antonia, Youssef Oulkhouir, Yolanda Bautista, Robin Cornelissen, Laurent Greillier, Francesco Grossi, Dariusz Kowalski, Jerónimo Rodríguez-Cid, Praveen Aanur, Abderrahim Oukessou, Christine Baudelet, Gérard Zalcman

Summary

Background Approved systemic treatments for malignant pleural mesothelioma (MPM) have been limited to chemotherapy regimens that have moderate survival benefit with poor outcomes. Nivolumab plus ipilimumab has shown clinical benefit in other tumour types, including first-line non-small-cell lung cancer. We hypothesised that this regimen would improve overall survival in MPM.

Lancet 2021; 397: 375–86

Published Online January 21, 2021 https://doi.org/10.1016/S0140-6736(20)32714-8

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FDA approved 10/2/20

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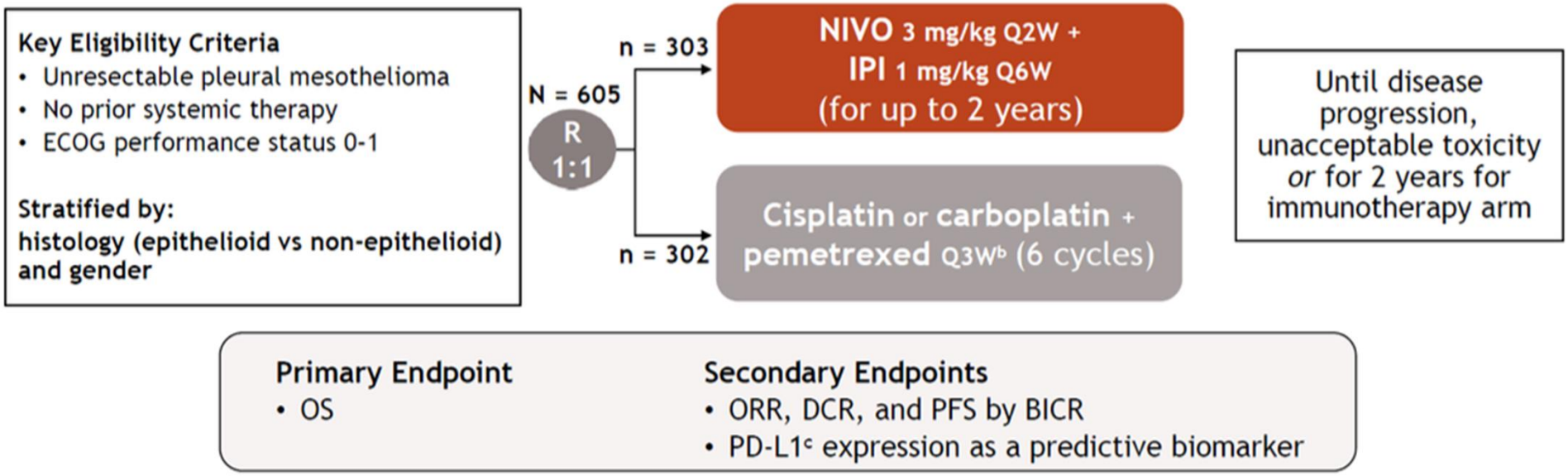
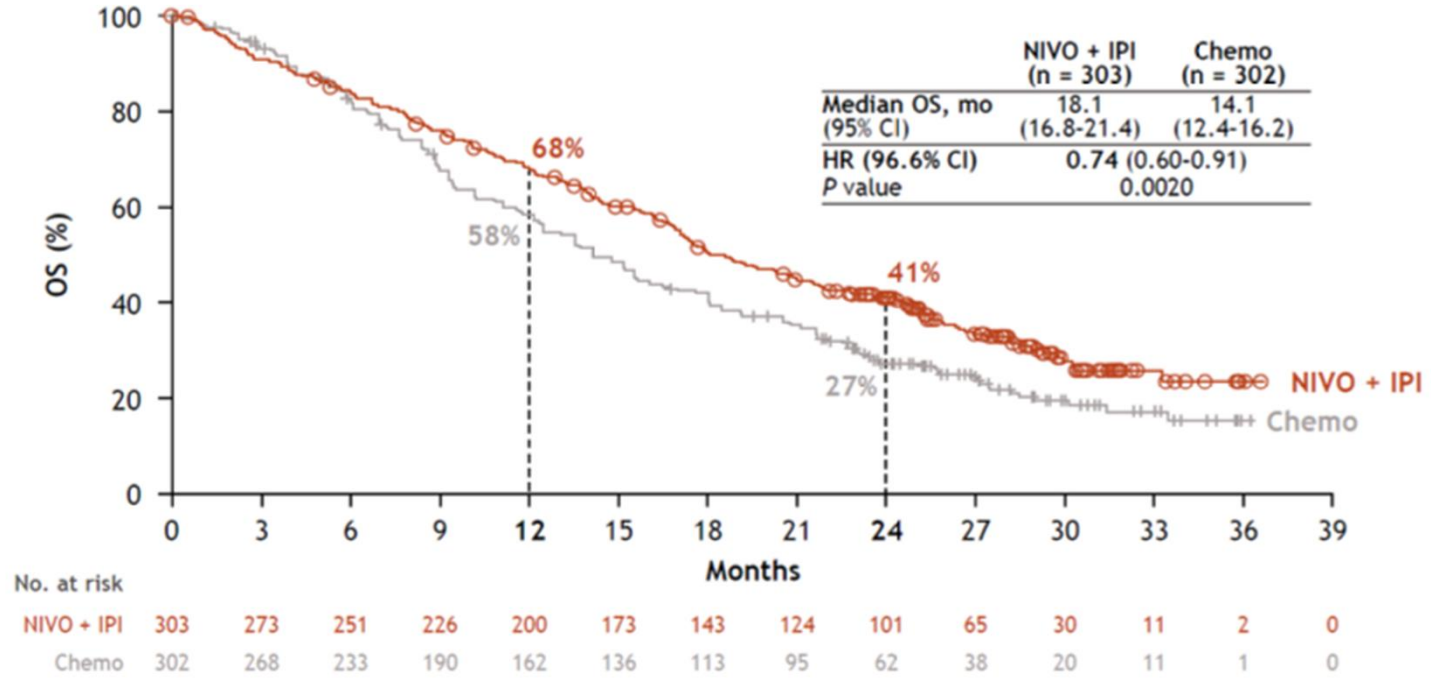
CheckMate 743: Nivolumab + ipilimumab

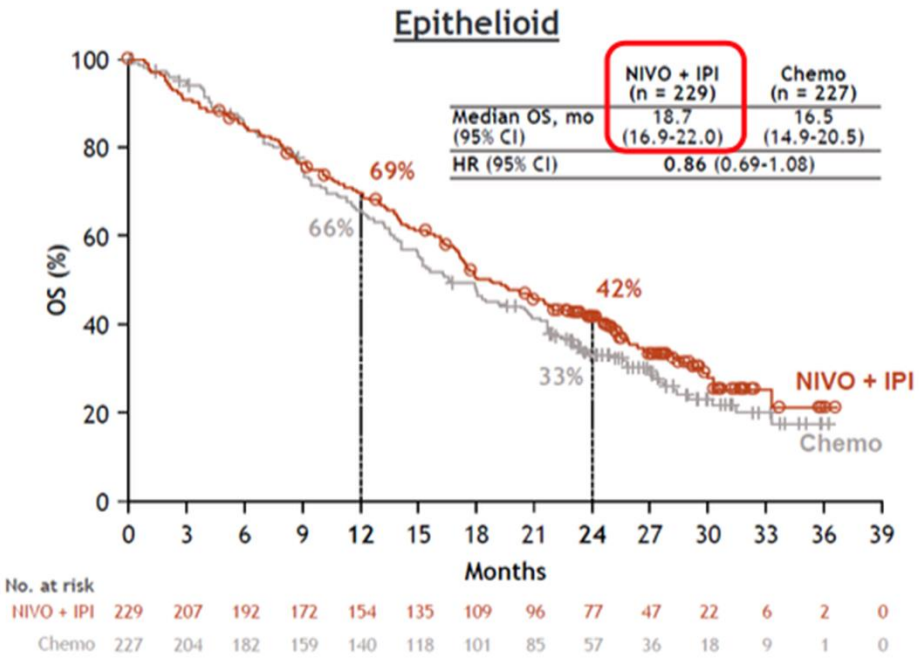


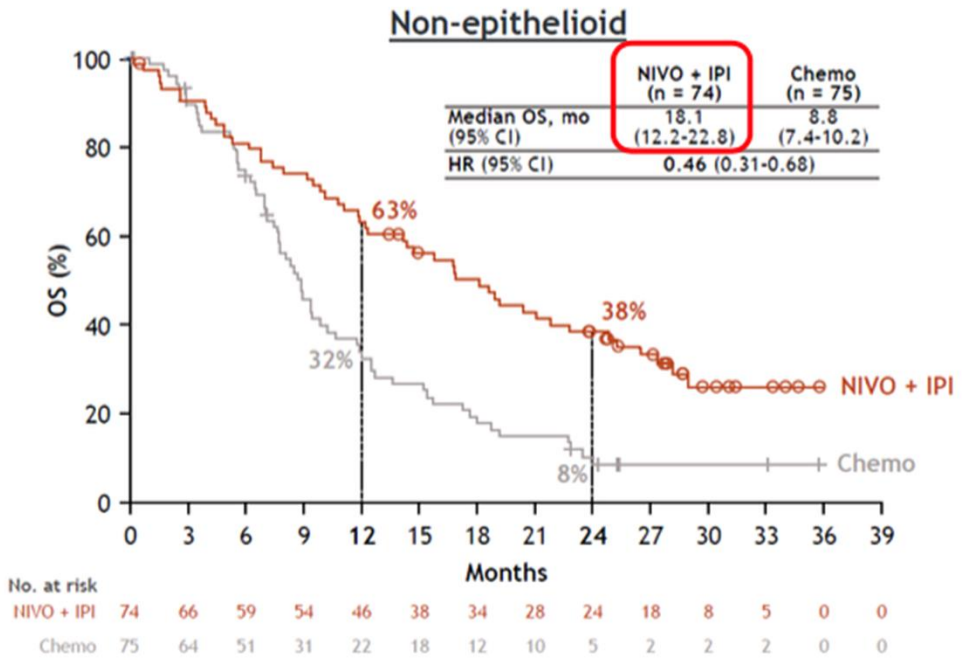
CheckMate 743: Nivolumab + ipilimumab



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS, mo (95% CI)	18.1 (16.8-21.4)	14.1 (12.4-16.2)
HR (96.6% CI)	0.74 (0.60-0.91)	
P value	0.0020	

CheckMate 743: Nivolumab + ipilimumab





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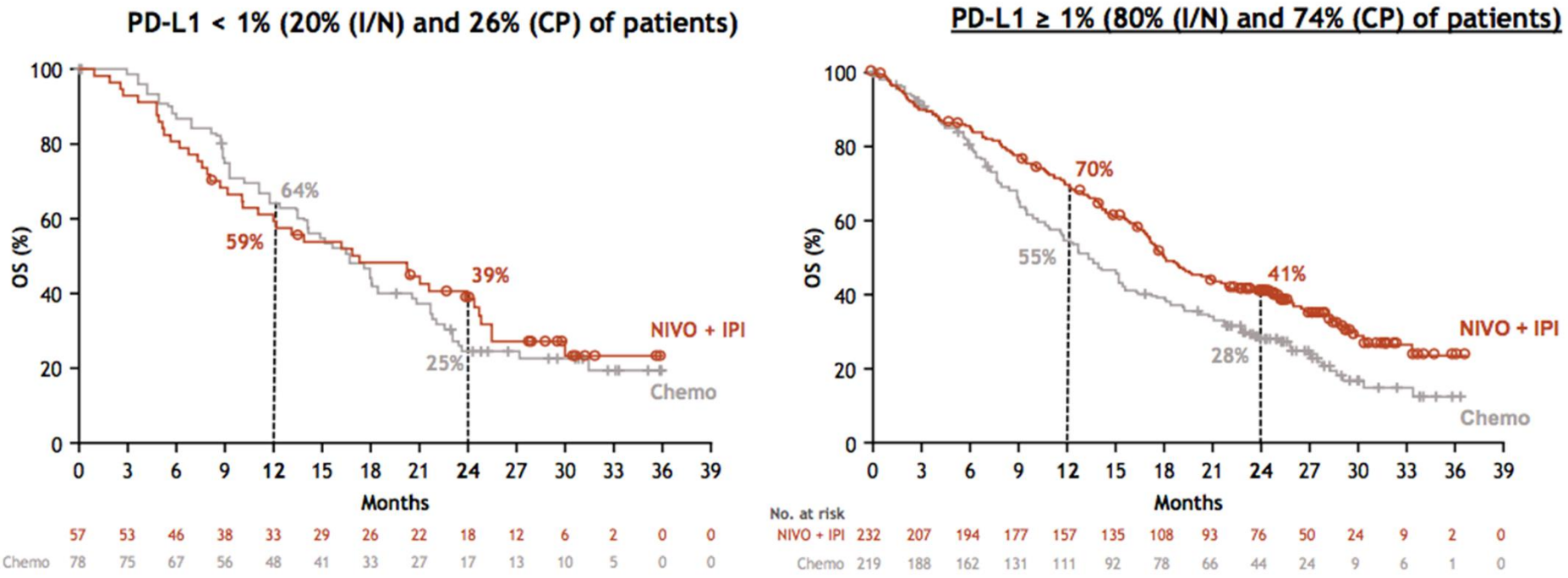
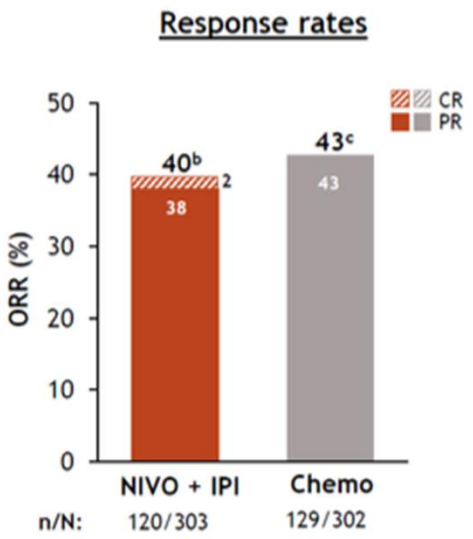
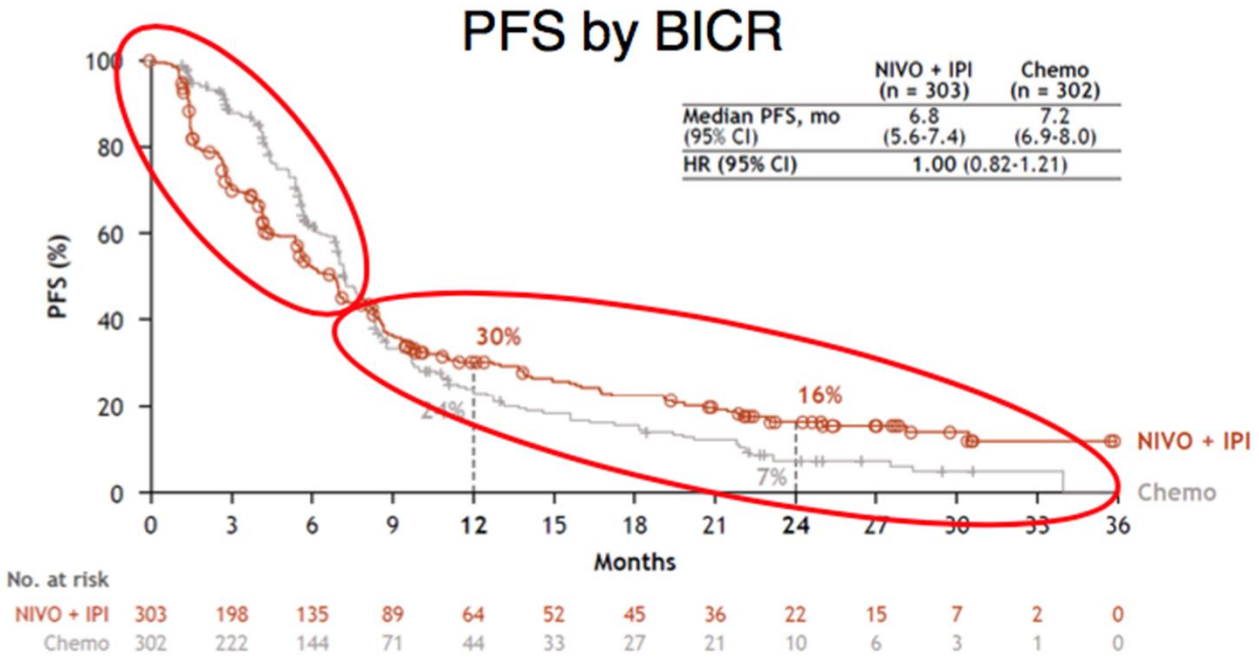


Patients were not stratified by PD-L1 expression level.
OS HR (95% CI) for PD-L1 ≥ 1% vs < 1% were: NIVO + IPI, 0.87 (0.61-1.23); chemo, 1.18 (0.87-1.60).

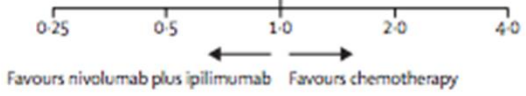
CheckMate 743: Nivolumab + ipilimumab





CheckMate 743: Nivolumab + ipilimumab

	Number of patients	Median overall survival (months)		Unstratified hazard ratio for death (95% CI)
		Nivolumab plus ipilimumab group (n=303)	Chemotherapy group (n=302)	
All randomly assigned	**605**	**18·1**	**14·1**	**0·75 (0·62–0·91)**
Age, years				
<65	167	17·2	13·3	0·76 (0·52–1·11)
65 to <75	281	20·3	14·9	0·63 (0·48–0·83)
≥75	157	16·9	15·4	1·02 (0·70–1·48)
Sex				
Male	467	17·5	13·7	0·74 (0·60–0·92)
Female	138	21·4	18·0	0·76 (0·50–1·16)
ECOG performance status*				
0	242	20·7	19·5	0·87 (0·64–1·19)
1	363	17·0	11·6	0·66 (0·52–0·85)
Tumour histology				
Epithelioid	456	18·7	16·5	0·86 (0·69–1·08)
Non-epithelioid	149	18·1	8·8	0·46 (0·31–0·68)
Stage of cancer				
3	209	23·9	16·3	0·61 (0·44–0·86)
4	309	16·7	10·8	0·67 (0·52–0·87)
PD-L1 expression subgroups				
PD-L1 <1%	135	17·3	16·5	0·94 (0·62–1·40)
PD-L1 ≥1%	451	18·0	13·3	0·69 (0·55–0·87)



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CheckMate 743: Nivolumab + ipilimumab

	Nivolumab plus ipilimumab group (n=300)			Chemotherapy group (n=284)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any	148 (49%)	79 (26%)	12 (4%)	141 (50%)	73 (26%)	18 (6%)
Diarrhoea	52 (17%)	10 (3%)	0	19 (7%)	2 (1%)	0
Pruritus	46 (15%)	3 (1%)	0	1 (<1%)	0	0
Rash	40 (13%)	3 (1%)	0	15 (5%)	0	0
Fatigue	38 (13%)	3 (1%)	0	50 (18%)	5 (2%)	0
Hypothyroidism	32 (11%)	0	0	0	0	0
Nausea	29 (10%)	1 (<1%)	0	97 (34%)	7 (2%)	0
Anaemia	5 (2%)	1 (<1%)	0	70 (25%)	32 (11%)	0
Decreased appetite	27 (9%)	2 (1%)	0	48 (17%)	2 (1%)	0
Constipation	12 (4%)	0	0	41 (14%)	1 (<1%)	0
Vomiting	8 (3%)	0	0	35 (12%)	6 (2%)	0
Asthenia	25 (8%)	0	0	32 (11%)	12 (4%)	0
Increased lipase	7 (2%)	11 (4%)	2 (1%)	0	1 (<1%)	0
Colitis	3 (1%)	7 (2%)	0	1 (<1%)	1 (<1%)	0
Increased amylase	10 (3%)	6 (2%)	1 (<1%)	1 (<1%)	0	0
Thrombocytopenia	0	2 (1%)	0	16 (6%)	4 (1%)	6 (2%)
Neutropenia	0	1 (<1%)	1 (<1%)	28 (10%)	31 (11%)	12 (4%)

Data are n (%). Safety was assessed in all patients who received at least one dose of study drug. Treatment-related adverse events with an incidence of ≥10% in any group or grade 3 or 4 severity with an incidence of ≥2% in any group are shown. All grade 3 and 4 events are listed in the appendix (pp 13-16). Treatment-related adverse events included those reported between the first dose of study drug and 30 days after the last dose of study drug. *Only events that led to death within 24 h were documented as grade 5 and reported as deaths. Events leading to death >24 h after onset are reported with the worst grade before death.

Table 3*: Summary of treatment-related adverse events in all treated patients

Discontinuation rate for any-grade treatment-related adverse events:

- Nivo/ipi: 23%
- Chemo: 16%

For gr3-4 events

- Nivo/ipi: 15%
- Chemo: 7%

Future WCLC?

- Chemoimmunotherapy
  - DREAM3R phase 3: Cis/pemetrexed +/- durva
  - ETOP 13-18 BEAT Meso: Carbo/pemetrexed/bev +/- atezo
  - CCTG IND227/IFCT1901: Platinum/pemetrexed +/- pembro
- Other immunotherapy
  - Cellular therapies…

Intra-pleural mesothelin-directed CARs: MSKCC experience

iCasM28z CAR

Fully human mesothelin CAR to reduce immunogenicity

No adverse events >Grade 2
No on-target, off-tumor toxicity

Monitored by	Method
Clinical	Pleuritis Pericarditis Peritonitis
Laboratory	Serum Troponin level
Cardiac	EKG, Echocardiogram
Imaging	CXR, CT, PET
Pathology	Biopsy

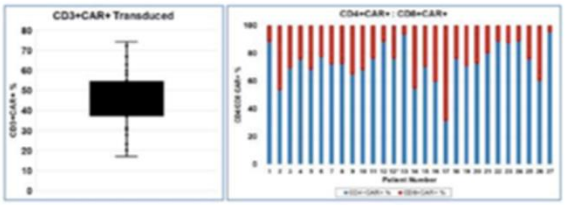
NCT02414269

Intrapleural administration

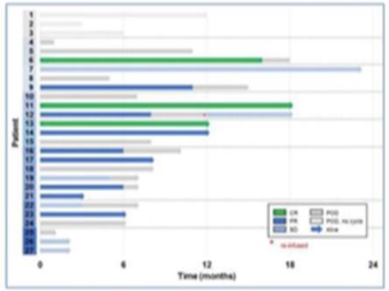
29 patients treated
(3 patients re dosed)

Mesothelioma, pleural metastatic lung and breast cancers

CAR transduction is successful in all patients in both CD4 and CD8 T cells



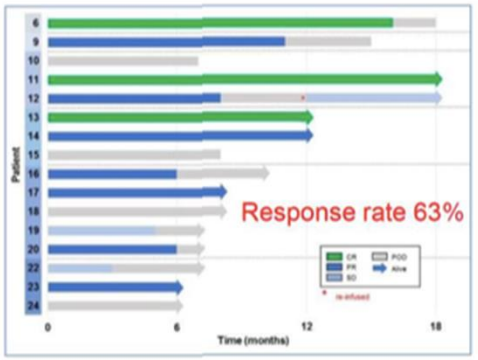
Responses of all patients (n=27)



PD-L1: 0-5% in 22 patients,
≥10% in 4 patients

CR – Complete response
PR – Partial response
SD – Stable disease
POD – Progression of disease

Responses of mesothelioma patients (n=16) that received Cyclophosphamide and CAR T-cells and at least 3 doses of anti-PD1 antibody with minimum 3 months follow-up



Adusumilli et al. AACR (2019), ASCO (2019), WCLC (2109)

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- Other immunotherapy
  - Cellular therapies…
    - Intra-pleural mesothelin-directed CARs
    - Intra-pleural FAP-directed CARs
    - Dendritic cell therapy

Summary

- CheckMate 743 establishes nivolumab+ipilimumab as a 1st line standard of care
  - Clear advantage for sarcomatoid
  - Likely comparable to chemo for epithelioid
  - PD-L1 not really an effective predictive biomarker
- Immunotherapy at *least* in 2nd line warranted
  - CONFIRM phase 3 trial: Nivo > placebo
  - But I'd still try for nivolumab+ipilimumab
- Stay tuned for
  - Chemo+IO combinations
  - Other immunotherapy, potentially CAR-T
- Refer for trials!