City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

PLEURAL & PERITONEAL MESOTHELIOMA

Update on Treatment Approaches to Pleural Mesothelioma

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City of Hope

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- Consultant for AstraZeneca and Sanofi.
- On the Speakers Bureau for AstraZeneca and Sanofi.

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This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

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Malignant mesothelioma is an aggressive cancer with poor prognosis

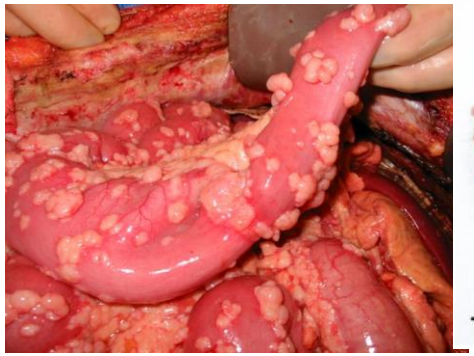
- 3,000 new cases in US each year
- Majority of patients not candidates for surgery
- Staging and radiologic assessment difficult
- Pemetrexed plus cisplatin FDA approved, 2004
- Nivolumab plus Ipilimumab FDA approved, 2020

Median overall survival ~18 months

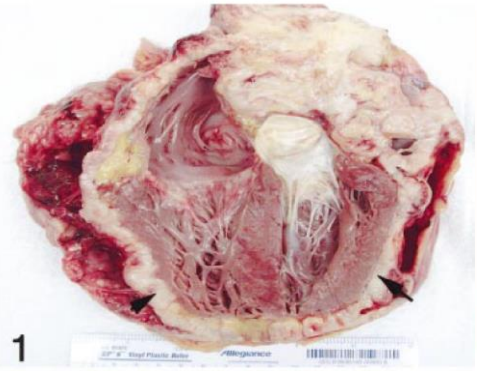
Kindler H,…Hassan R, *J Clin Oncol*., 2018
Rusch VW et. al., *J Thorac Oncol*., 2016
Vogelzang NJ et. al., *J Clin Oncol*., 2003
Baas P et. al., *Lancet*, 2021

Mesothelioma arises at sites that are lined by mesothelial cells

Pleural



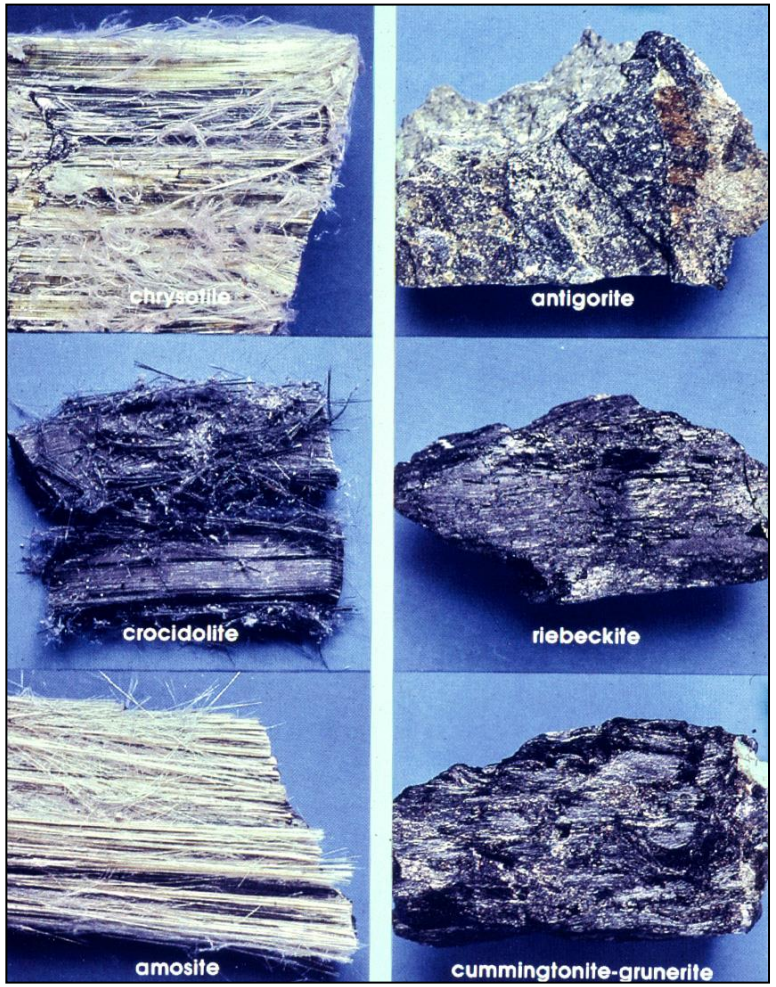
Peritoneal



Pericardial

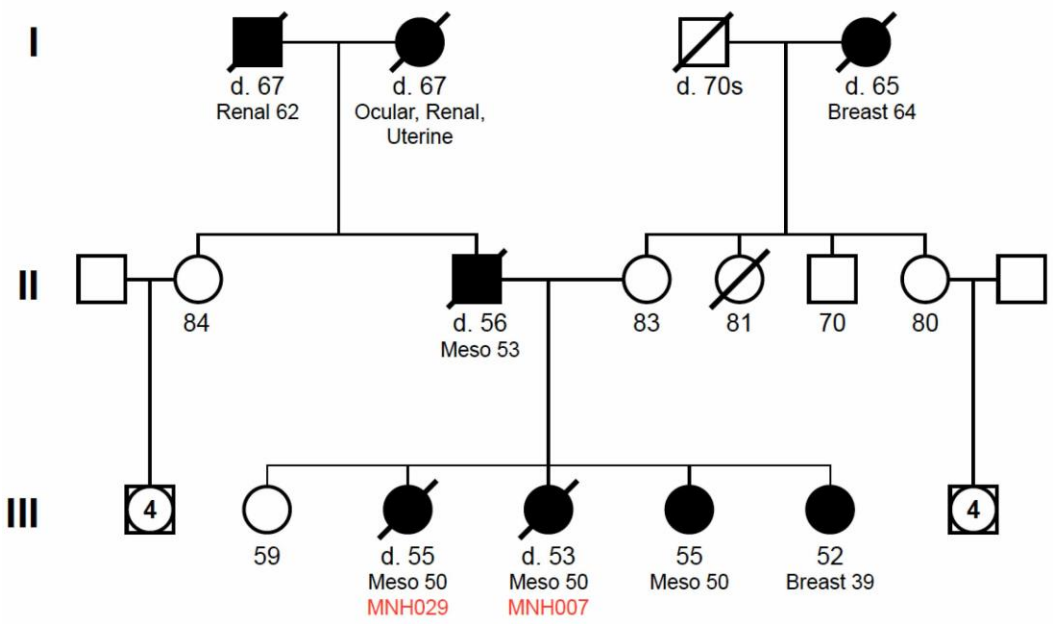
Tunica vaginalis

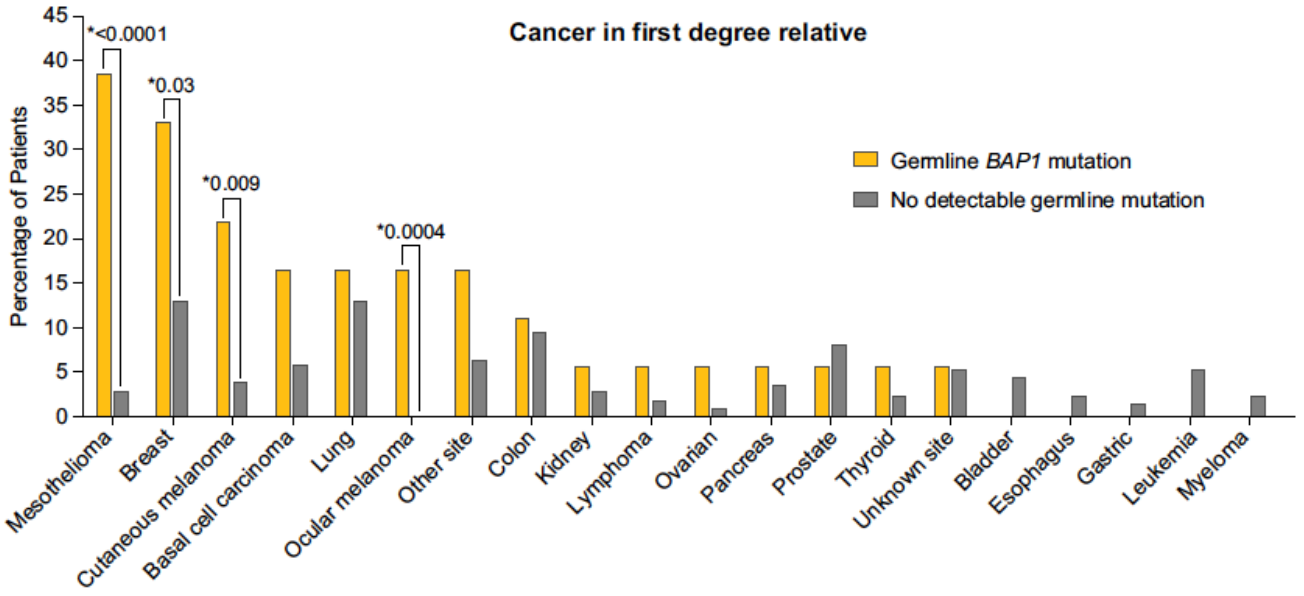
Malignant mesothelioma - causes



- Asbestos is the primary cause of mesothelioma
- Patients with Hodgkin's disease and NHL that have received XRT have an increased risk of developing mesothelioma
- Mesothelioma risk also increased in patients with germline mutations in the *BAP1* gene

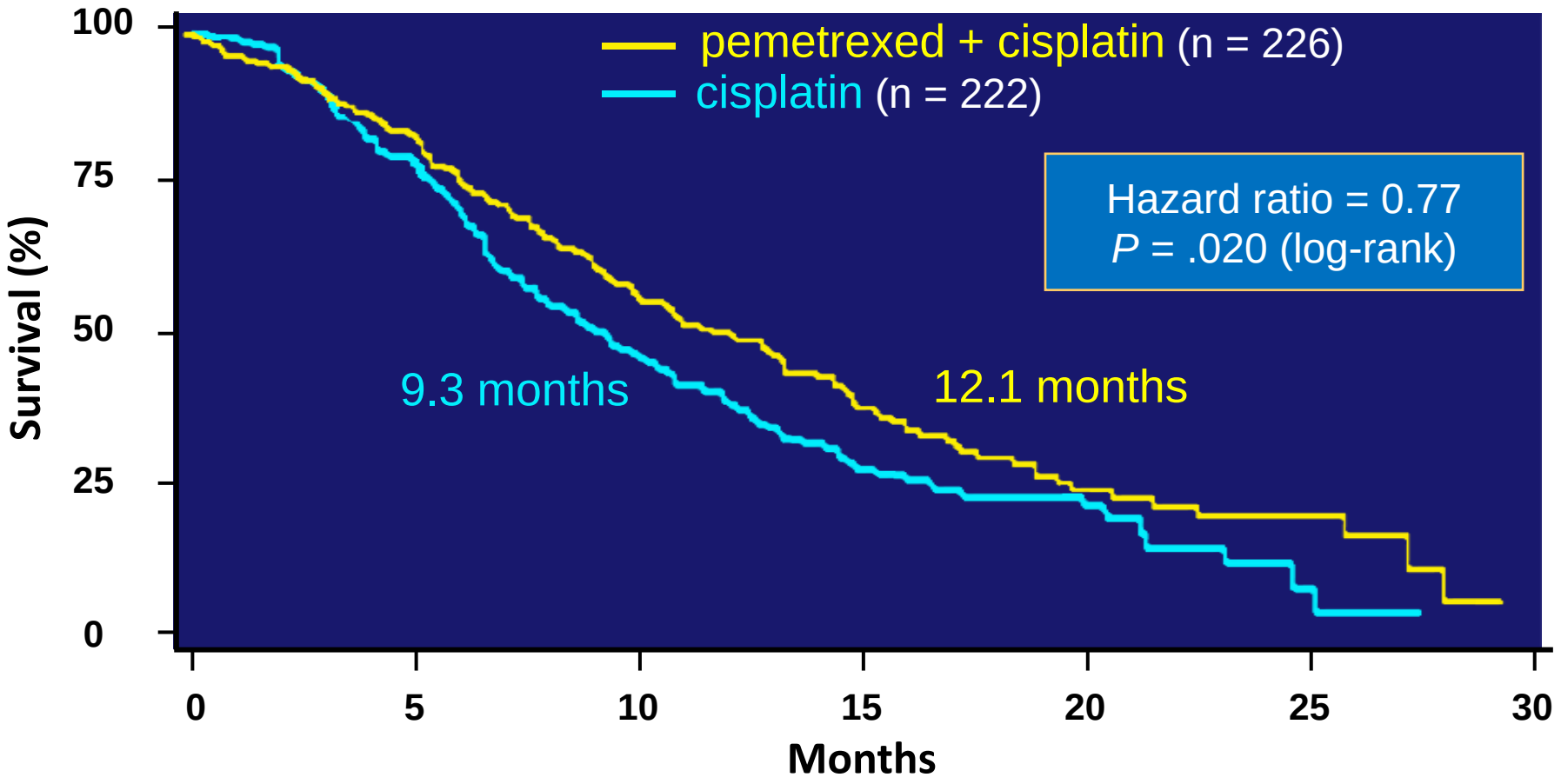
Patients and their family members with germline BAP1 mutations are at increased risk for mesothelioma and other cancers





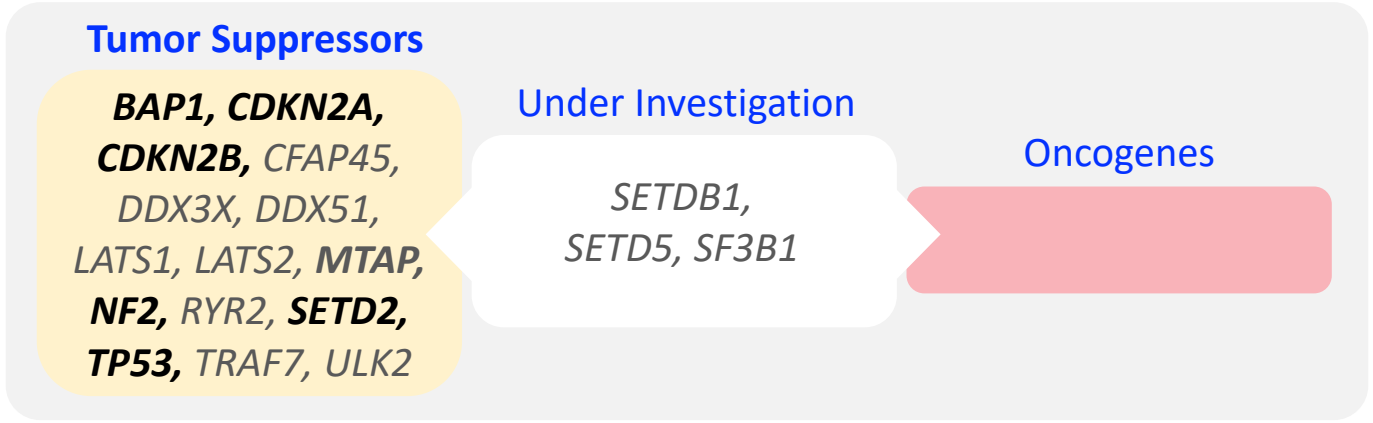
Hassan R et. al. PNAS, 2019

Phase III Study of Pemetrexed plus Cisplatin in MPM



Vogelzang NJ et al. *J Clin Oncol* 2003

Frequently mutated genes in MPM



bold = mutation frequency >5%

Illei Clin Cancer Res. 2003; Bueno R. *et al*. *Nat Genet* 2016; Hmeljak J. *et al*. *Cancer Discov* 2018.

Targets for Current and Future Approaches

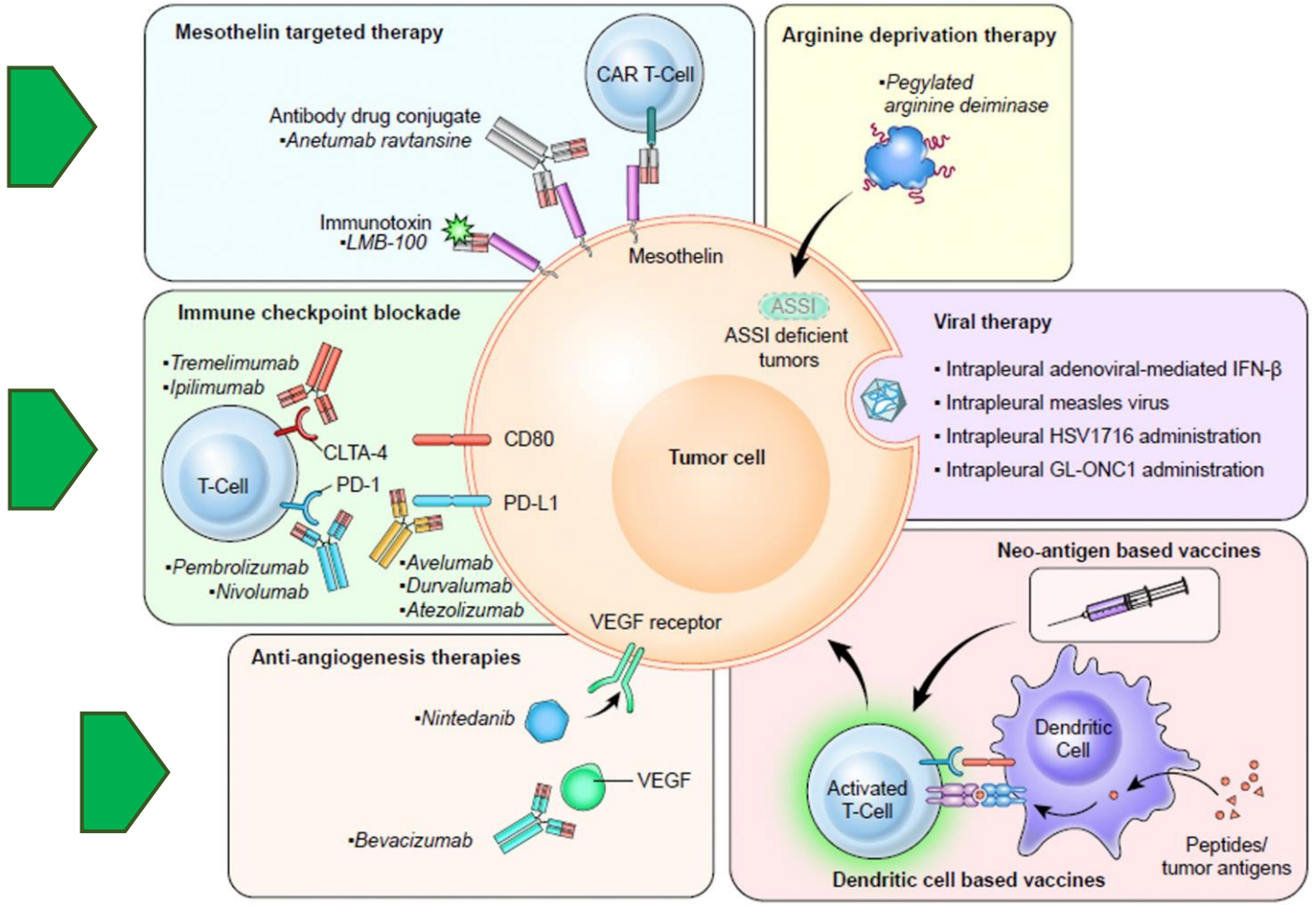
Phenotypic Histologic Subtypes	
Epithelioid (50–60% of cases)	
Biphasic (30–40% of cases)	
Sarcomatoid (10% of cases)	

Current and Future Systemic Approaches
Chemotherapy
Antibody-drug conjugates
Immune checkpoint inhibition (PD-1 or PD-L1 inhibition)
Ferroptosis inducers
Cellular therapy (CAR-T cells targeting mesothelin)
Angiogenesis inhibition

Genomic or Epigenomic Landscape	
Mutation	**Therapeutic Targets**
BAP1	EZH2; PARP
CDKN2A	p16
NF2	FAK; YAP-TEAD; mTOR and PI3K
ASS1	Arginine

Janes SM et al N Engl J Med 2021

Selected examples of different strategies currently in clinical trials for therapy of malignant mesothelioma



Luciano M,…Hassan, R. JTO, 2018

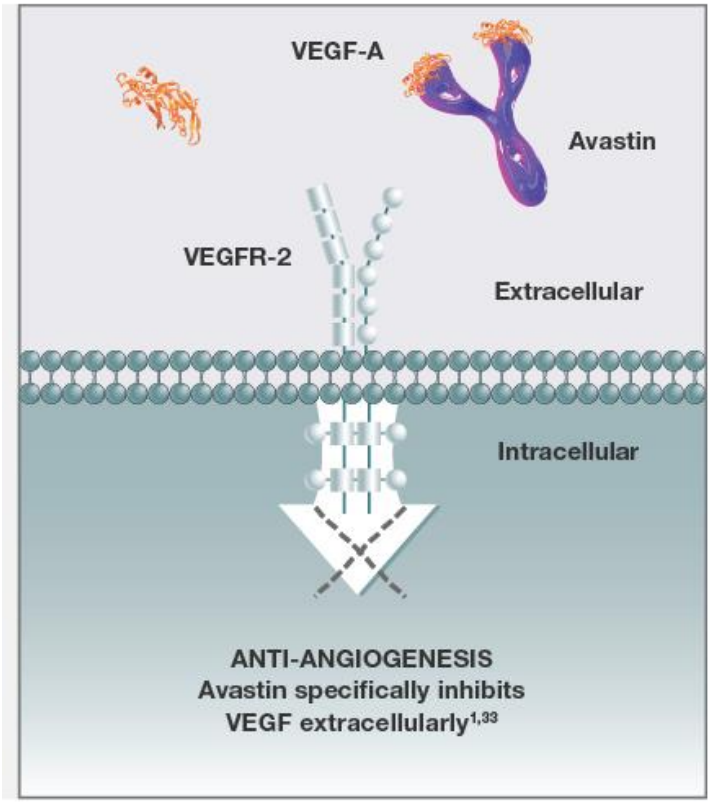
Anti-angiogenic agents for treatment of mesothelioma

Anti-angiogenic therapies

- Limited activity of cediranib, sorafenib and sunitinib
- The following two agents show some activity when combined with chemotherapy
  - Bevacizumab, an anti-VEGF antibody
  - Nintedanib, a multi-kinase inhibitor that targets VEGF receptors 1, 2, 3; PDGFR, FGF receptors

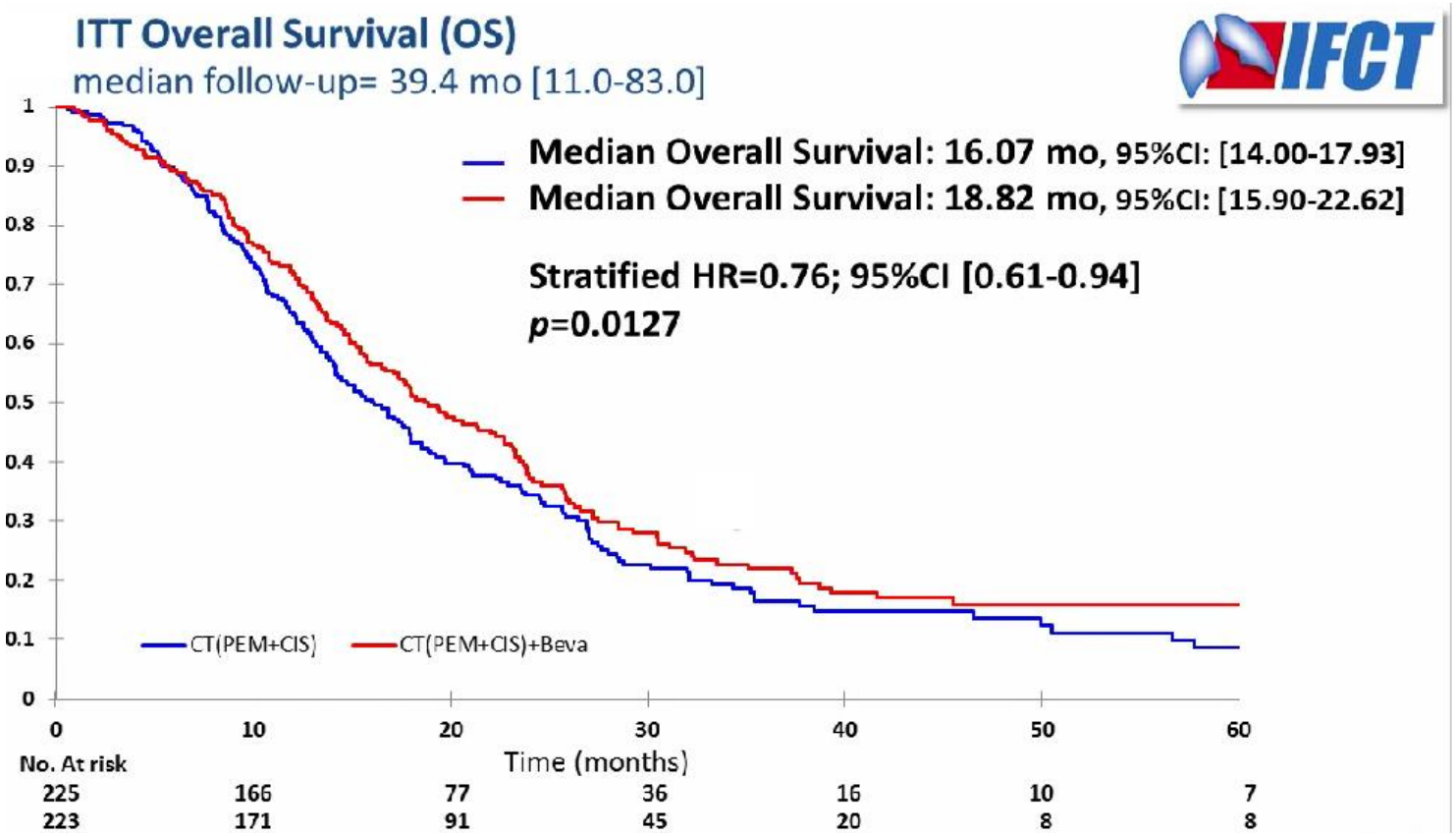
IFCT-GFPC-0701 trial: MAPS

IFCT-sponsored, open-label, multi-center randomized phase II-III trial



Zalcman G et al. ASCO 2015

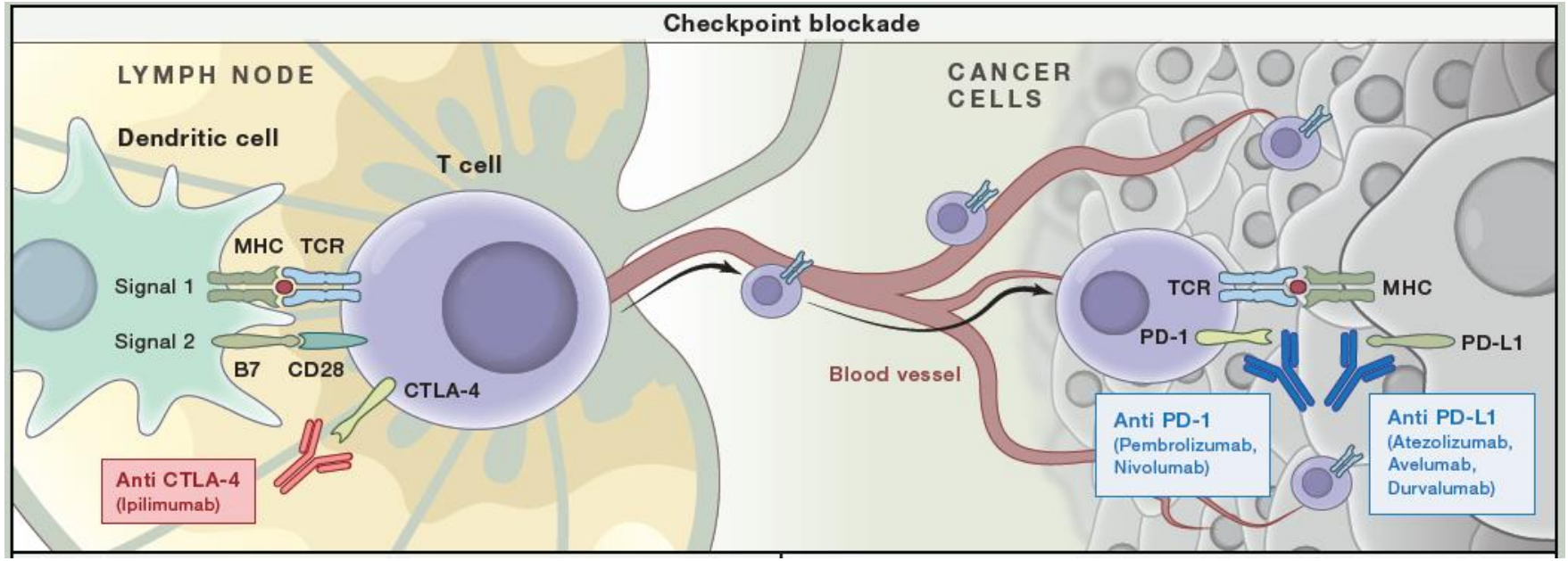
Increased overall survival in patients receiving bevacizumab plus pemetrexed and cisplatin



Zalcman G et al. *Lancet* 2015

Immune checkpoint blockade in mesothelioma

Immune-Checkpoints



Abril-Rodriguez G, Ribas A. *Cancer Cell*, 2017

Clinical trials of immune checkpoints in mesothelioma

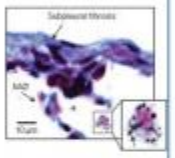
- Anti-CTLA-4 antibodies: Tremelimumab, Ipilimumab
- Anti-PDL1 antibodies: Avelumab, Durvalumab
- Anti-PD-1 antibodies: Pembrolizumab, Nivolumab

Pleural mesothelioma tumor immune microenvironment

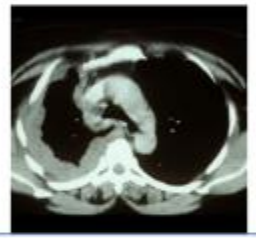
Pleural trapping of inhaled fibers

Frustrated phagocytosis

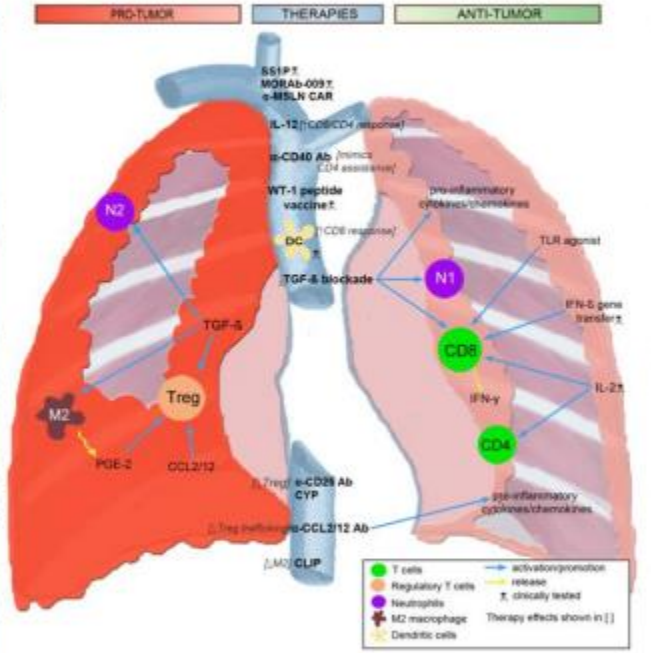
Pleural immune response



MPM



Author/Journal	# pts	Stages	Histology
Yamada		I - 7%	Epi 59%
Cancer Immunol Immunother 2010	44	II - 39%	Bi 32%
		III - 48%	Sarc 9%
		IV - 7%	
Ali		I -2%	Epi 77%
J Thorac Oncol 2009	60	II - 25%	Bi 15%
		III - 73%	Sarc 8%
Anraku		II - 22%	Epi 78%
J Thorac Cardiovasc Surg 2008	32	III - 72%	Bi 3%
		IV - 6%	Sarc 19%
Mudhar	15		Epi
ESJO 2002			
Leigh	58	NA	NA
S. Afr. Med. 1982			



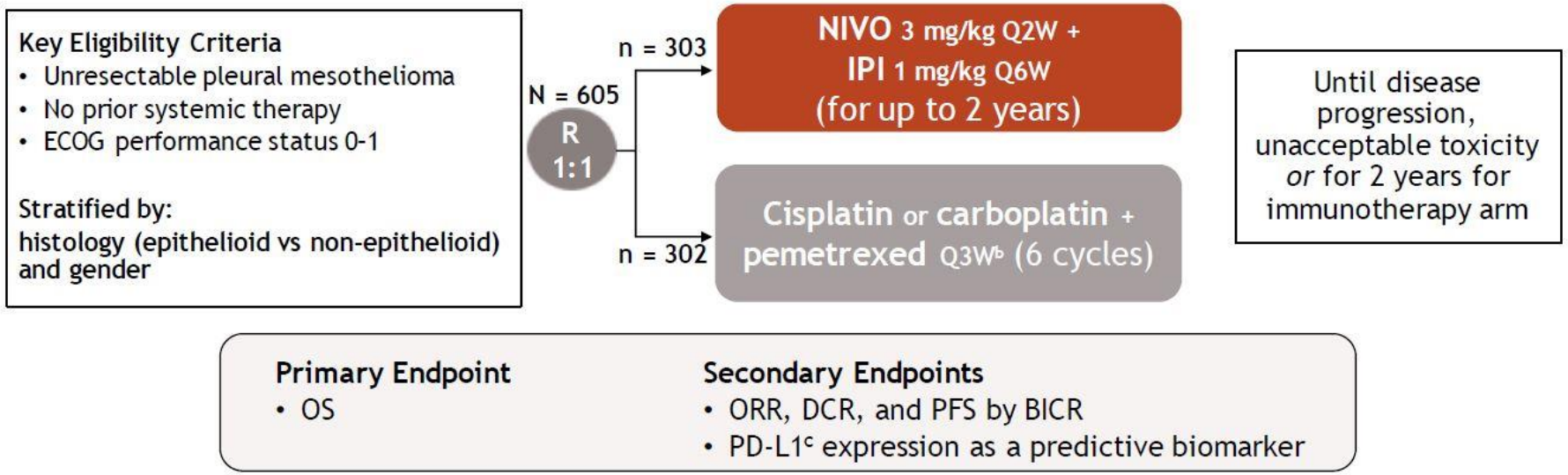
Bograd A, Adusumilli PS. *Cancer Immunol Immunother* 2011 Nov

Efficacy of immune checkpoints in mesothelioma

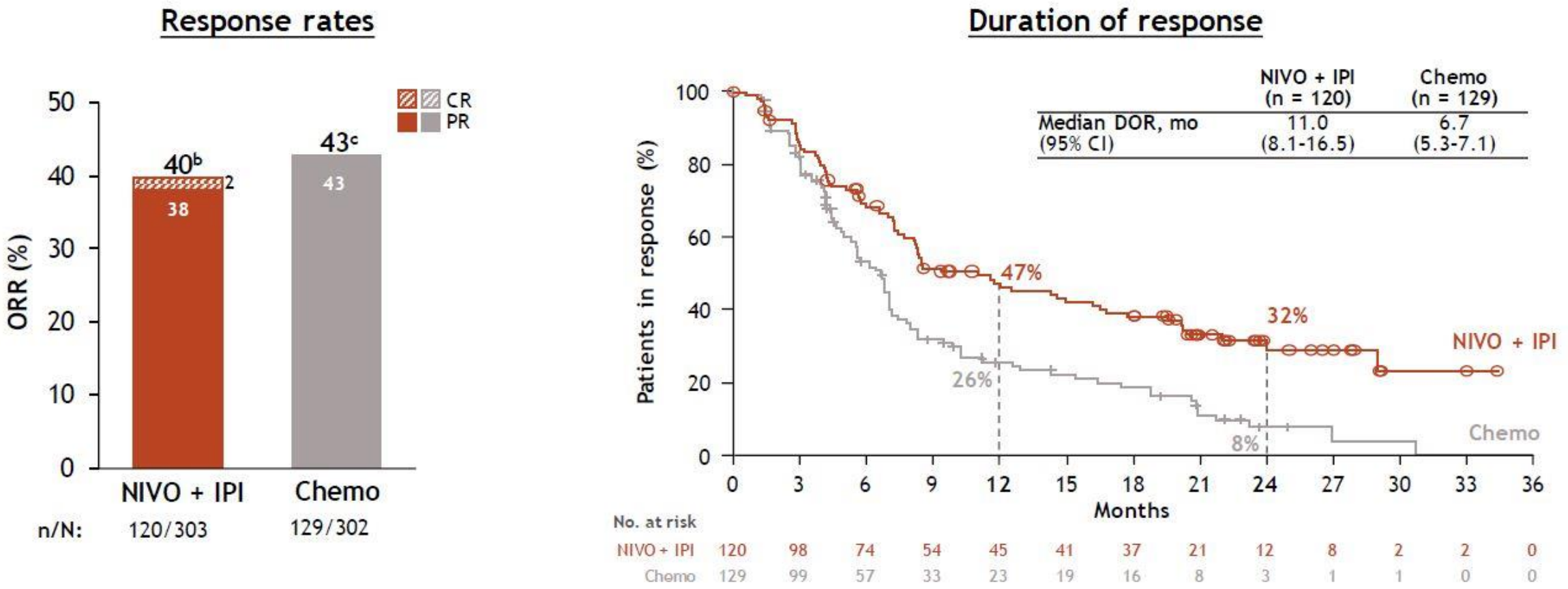
Checkpoint Inhibitor (Target)	Clinical Trials	Objective Response Rate (No. of Responders/ Total No. Enrolled)	References
Pembrolizumab (Anti-PD-1)	KEYNOTE-028: Ph 1b, 10 mg/kg every 2 wk up to 2 y	PR: **20%** (5/25)	Alley et al., 2017, Lancet Oncol
	Ph 2, 200 mg every 21 d	PR: **19%** (12/65)	Desai et al., 2018, J of Clin Oncol
Nivolumab (Anti-PD-1)	Ph 2, 3mg/kg every 2 wk	PR: **24%** (8/34)	Quispel-Janssen et al., 2018, J Thorac Oncol
	MERIT: Ph 2, 240 mg every 2 wk	ORR: **29%** (10/34)	Okada et al., 2019, Clin Cancer Res
Avelumab (Anti-PD-L1)	JAVELIN: Ph 1b, 10 mg/kg every 2 wks	1CR, 4PR: **9%** (5/53)	Hassan et al., 2019, JAMA Oncol
Tremelimumab (Anti-CTLA-4)	Ph 2, 15 mg/kg every 90 d	PR: **7%** (2/29)	Calabro et al., 2013, Lancet Oncol
	Ph 2, 10 mg/kg every 4 wk for 6 doses then every 12 wk	PR: **3%** (1/29)	Calabro et al., 2015, Lancet Respir Med
	DETERMINE: Ph 2b, same dose and schedule as above, treated (n=382) vs placebo (n=189)	**No benefit in OS**	Maio et al., 2017, Lancet Oncol

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

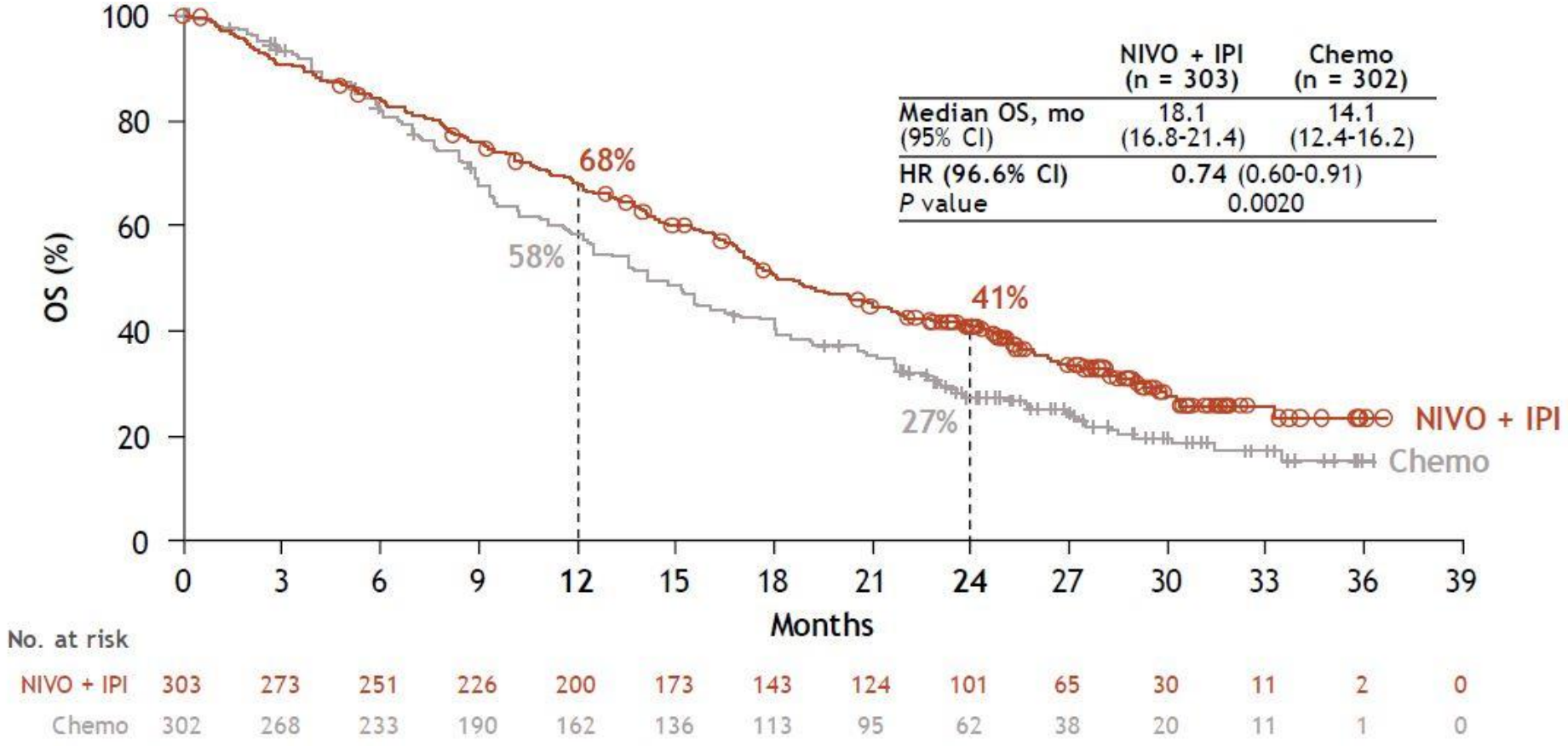


Response rate



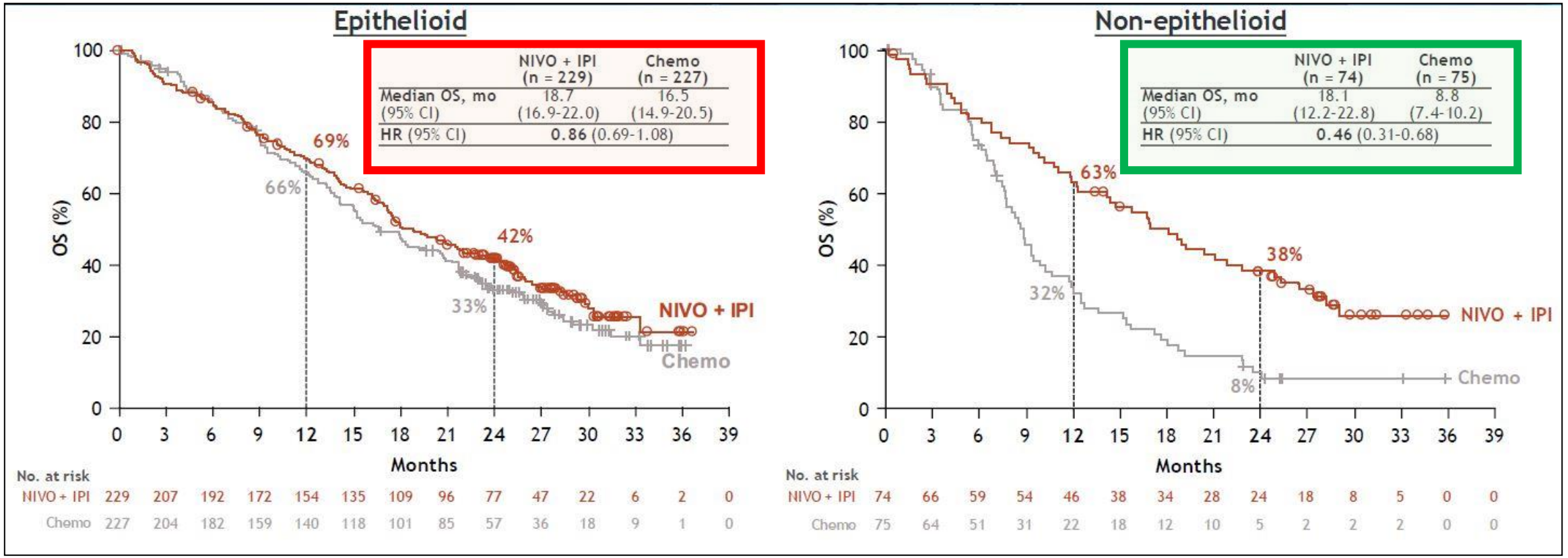
- Disease control rate was 76.6% with NIVO + IPI and 85.1% with chemo

Overall survival



	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	

Overall survival by histology



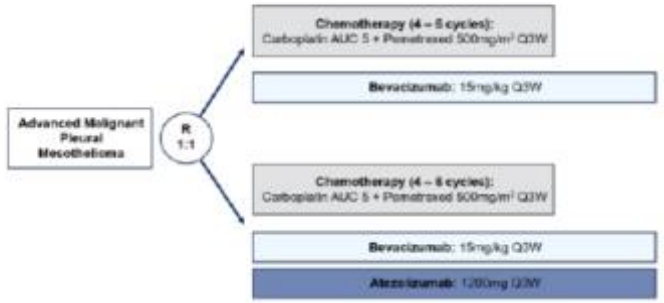
Adverse events

	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%)

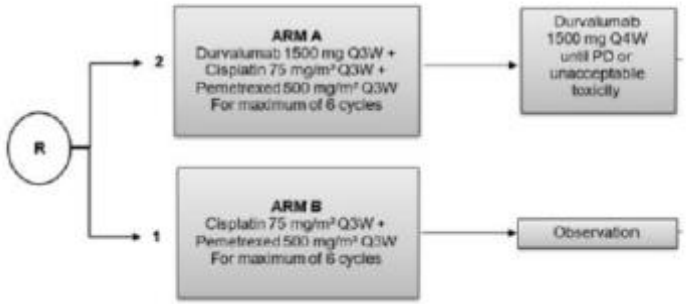
Data are n (%). Safety was assessed in all patients who received at least one dose of study drug. Treatment-related adverse events with an incidence of ≥10% in any group or grade 3 or 4 severity with an incidence of ≥2% in any group are shown. All grade 3 and 4 events are listed in the appendix (pp 13–16). 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.

Bringing IO to Frontline Treatment

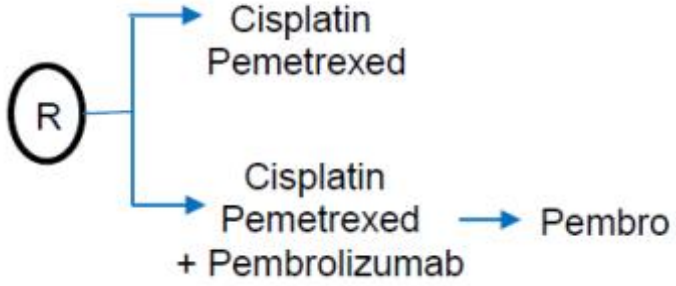
BEAT-meso: 1L
Carboplatin/Pemetrexed/Bevacizumab
+/- Atezolizumab



DREAM3R: 1L
Carboplatin/Pemetrexed
+/- Durvalumab

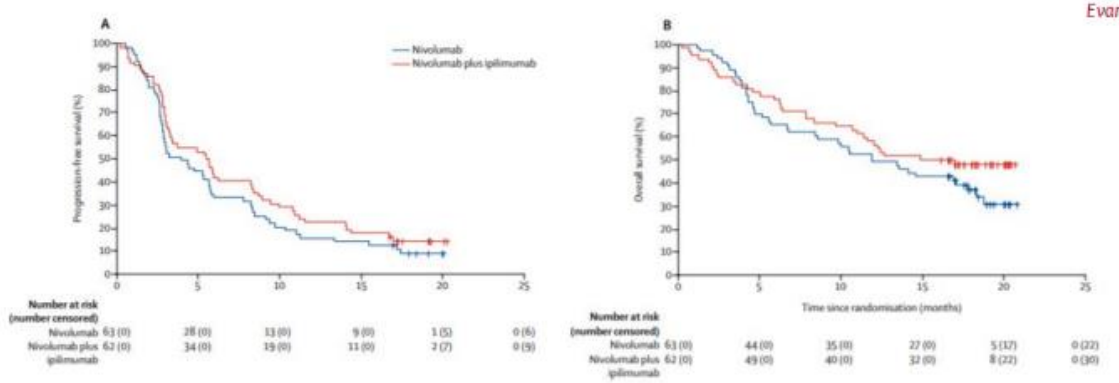


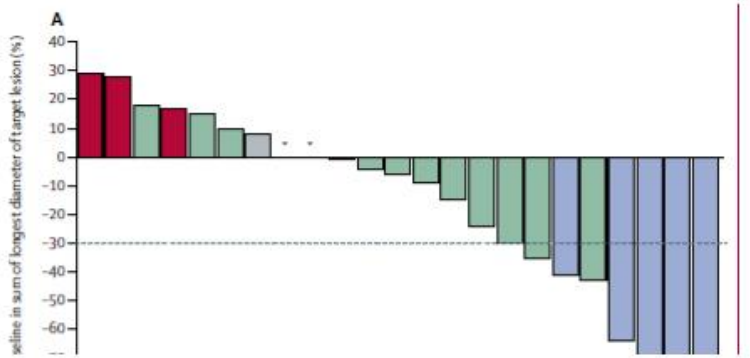
IND.227: 1L
Cisplatin/Pemetrexed
+/- Pembrolizumab



Pleural Mesothelioma Second-line Options

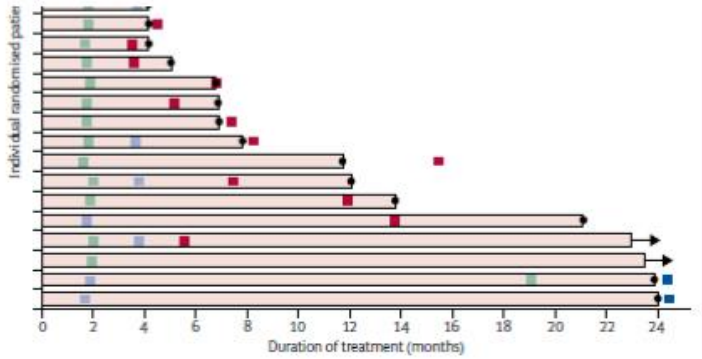
- Chemotherapy
  - Gemcitabine (ORR ~31%)
  - Vinorelbine (ORR 16%, mOS 9.6 mo)
- Immunotherapy
  - Pembrolizumab or nivolumab
  - Nivolumab/Ipilimumab (if prior Pem/DDP +/- Bev)





Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial

Evan W Alley, Juanita Lopez, Armando Santoro, Anne Morosky, Sanatan Saraf, Bilal Piperdi, Emilie van Brummelen

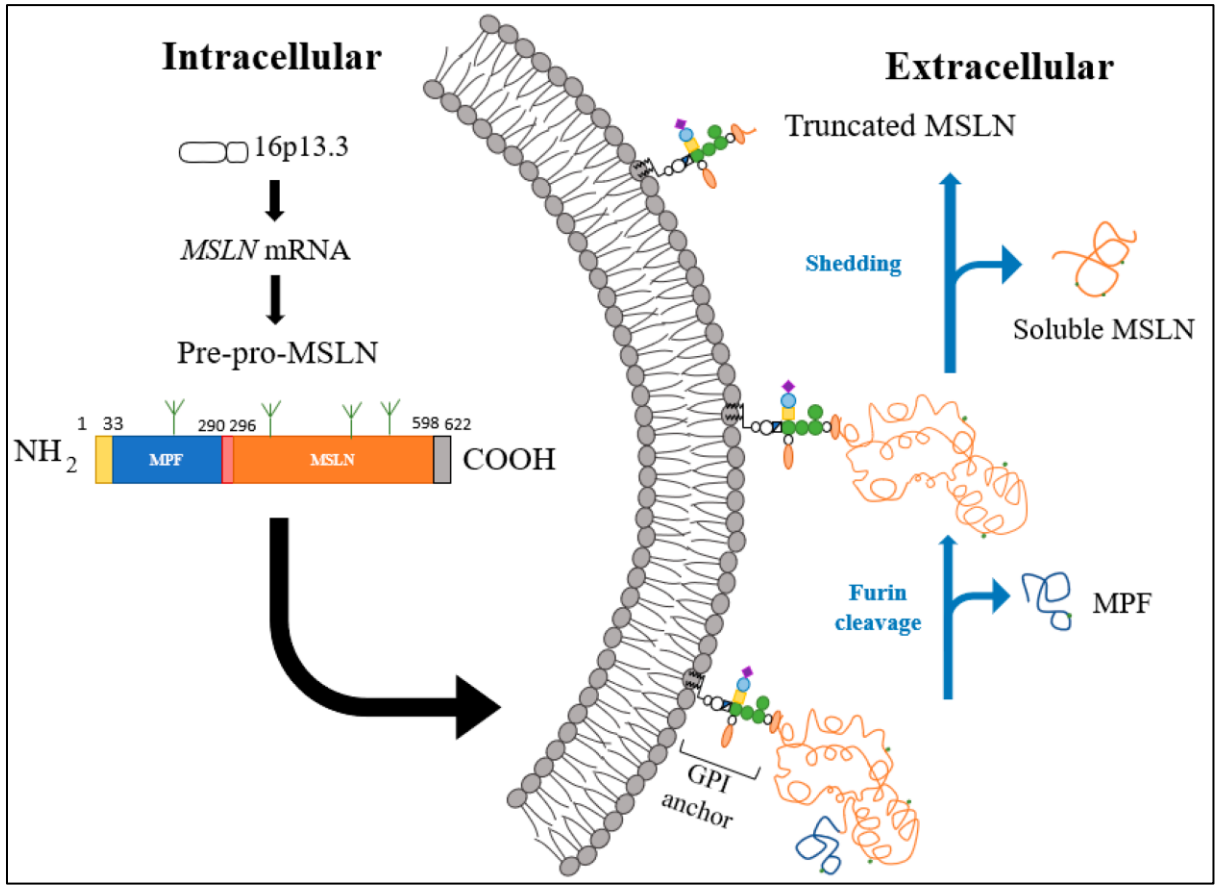


Janne, Clin Lung Cancer 2003; Stebbing, Lung Cancer 2009; Sherpereel Lancet 2019

Mesothelin targeted therapies for mesothelioma

Mesothelin

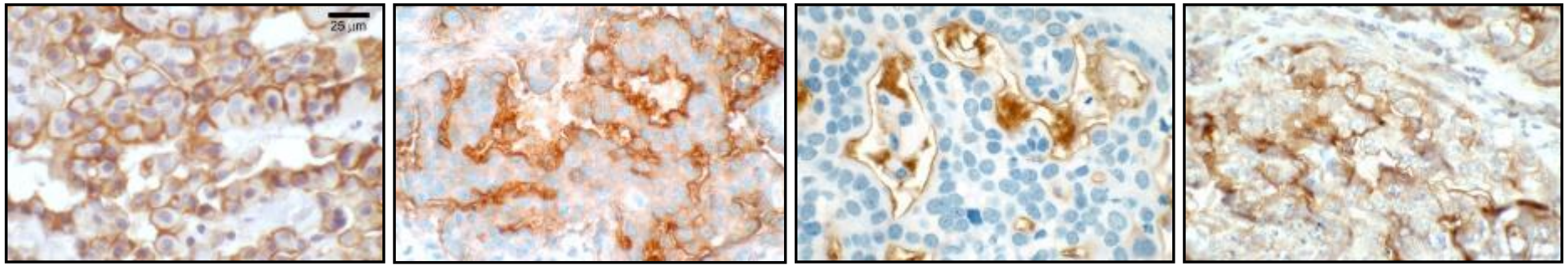
- Cell surface glycoprotein
- Expression in normal human tissues limited to mesothelial cells lining pleura, peritoneum and pericardium
- Mesothelin binds MUC16 and may play a role in tumor metastases



Chang K, Pastan I., PNAS 1996; Hassan R. et al. Clin Cancer Res. 2004; Pastan I, Hassan R., Cancer Res. 2014; Faust J.R et al. Cancers 2022

Mesothelin is highly expressed in many solid tumors

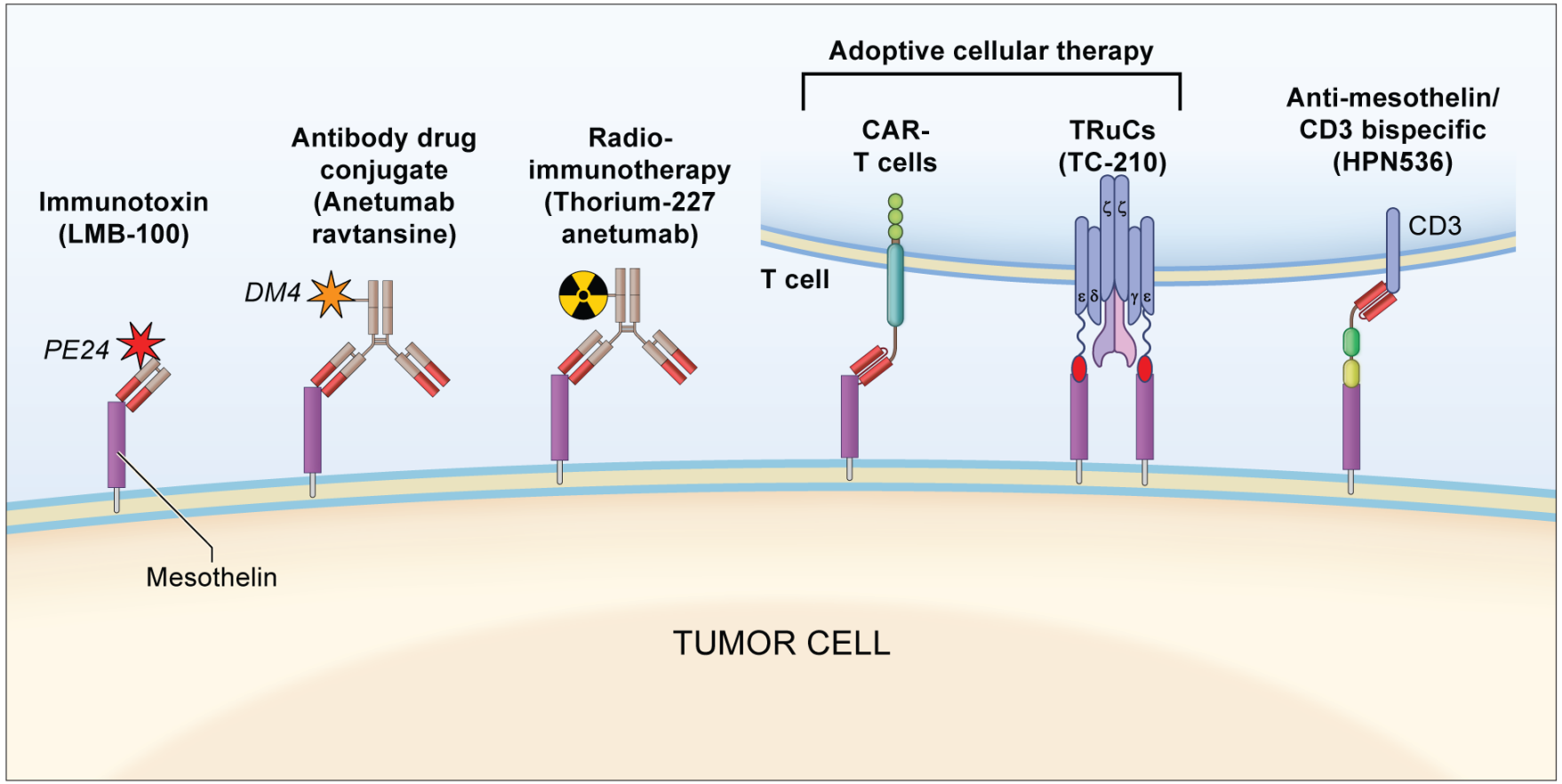
- Mesothelioma (epithelial) ~ 100%
- Pancreatic Cancer ~ 80%
- Ovarian Cancer 67-71%
- Lung adenocarcinoma 41-53%
- Gastric cancer, synovial sarcomas, TNBC, biliary cancers, thymic



Mesothelioma Ovarian Cancer Pancreatic Cancer Lung Cancer

Hassan et al. Clin. Cancer Res., 2004 Ordonez NG. Am J Surg Pathol, 2003

Mesothelin targeted therapies currently in clinical trials



Hassan R et. al. *Journal of Clinical Oncology*, 2016; Hassan R et. al. *Cancer, 2020;* Hassan R et. al. *Journal of Clinical Oncology*, 2020; Hassan R et. al. *Clin Cancer Res*., 2019; Jiang Q…Hassan R. *Science Transl. Medicine,* 2020

Summary

- Prognoses for patients diagnosed with mesothelioma remains poor
- Targeted approaches that take advantage of the mutational profile in mesothelioma have not come to fruition
- Frontline IO therapy with ipilimumab plus nivolumab increased overall survival in particular for patients with sarcomatoid mesothelioma
- There is a need for more biomarker-driven trials in mesothelioma