Malignant Pleural Mesothelioma

Bernardo Goulart MD, MS
Associate Professor
2020 UW/SCCA Oncology Board Review Course

Definition & Epidemiology

- **Malignant neoplasm arising from mesothelial cells.**
- **80% pleural; 20% from peritoneum, pericardium, tunica vaginalis testis.**
- **Rare: 2,400 incident cases/year.**
- **Median age = 72 years.**
- **Male predominance.**
- **Risk factors: Asbestos (60%); ionizing radiation; erionite; Germline mutations (12%).**
- **Median OS = 12 to 18 months.**

2015 WHO Classification of Pleural Tumors

Diffuse MPM

- Epithelioid (60%)
- Sarcomatoid (20%)
- Biphasic (20%)

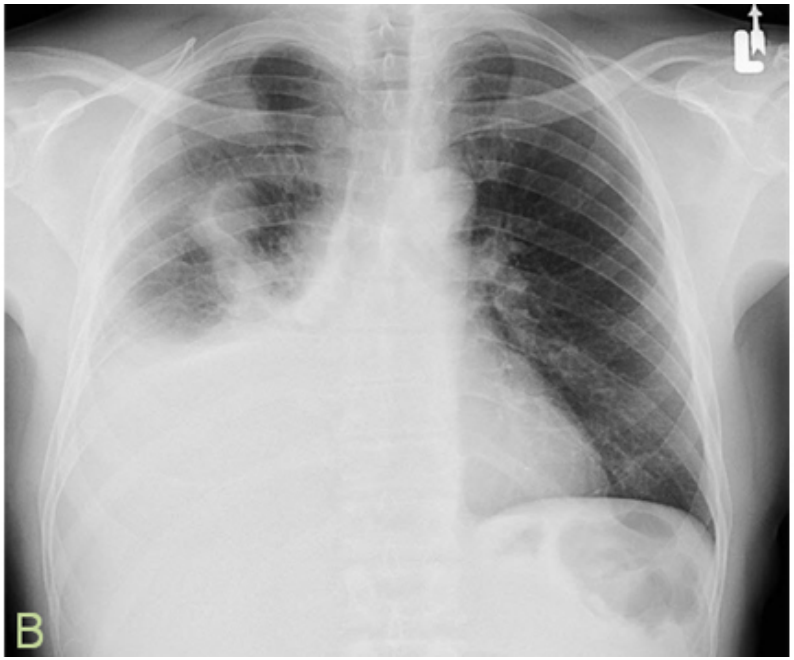
Other

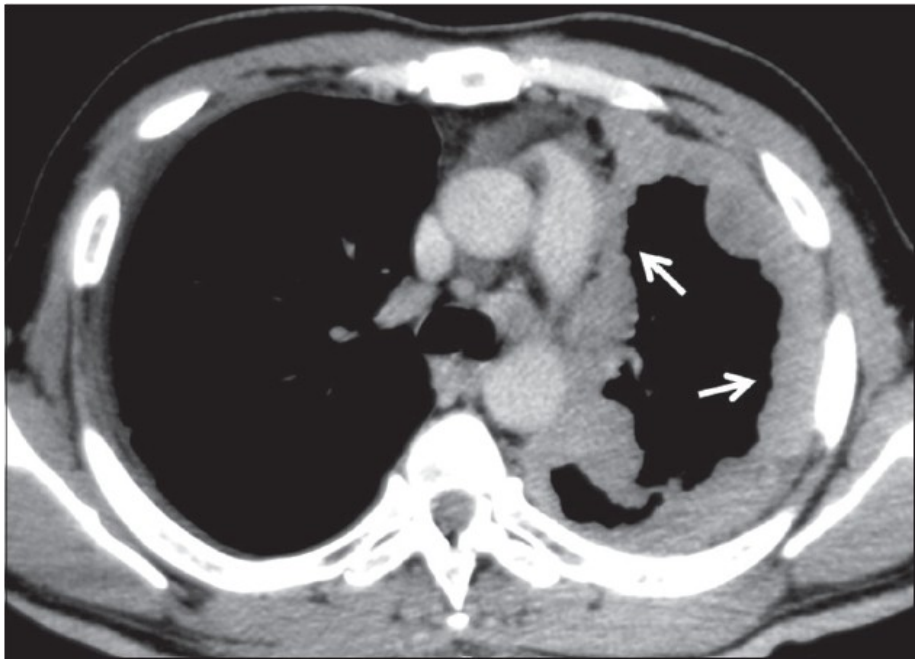
- Localized MPM
- Well differentiated papillary mesothelioma

Journal of Thoracic Oncology Vol. 11 No. 2: 142-154

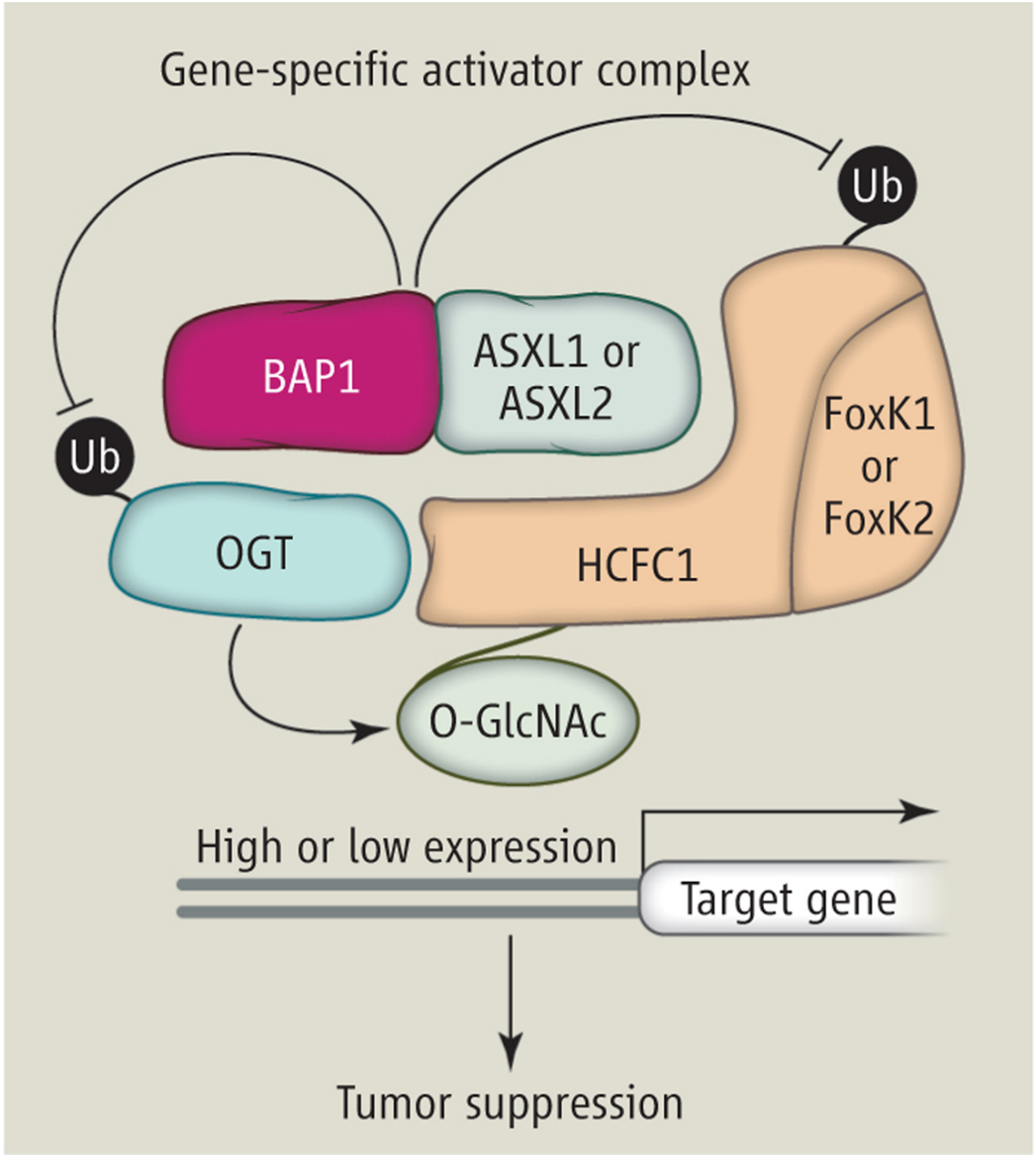
Clinical and Radiographic Presentation

- **Dyspnea; chest pain.**
- **Pleural effusion on initial chest x-ray.**
- **Chest CT: loculated effusion with pleural nodularities.**



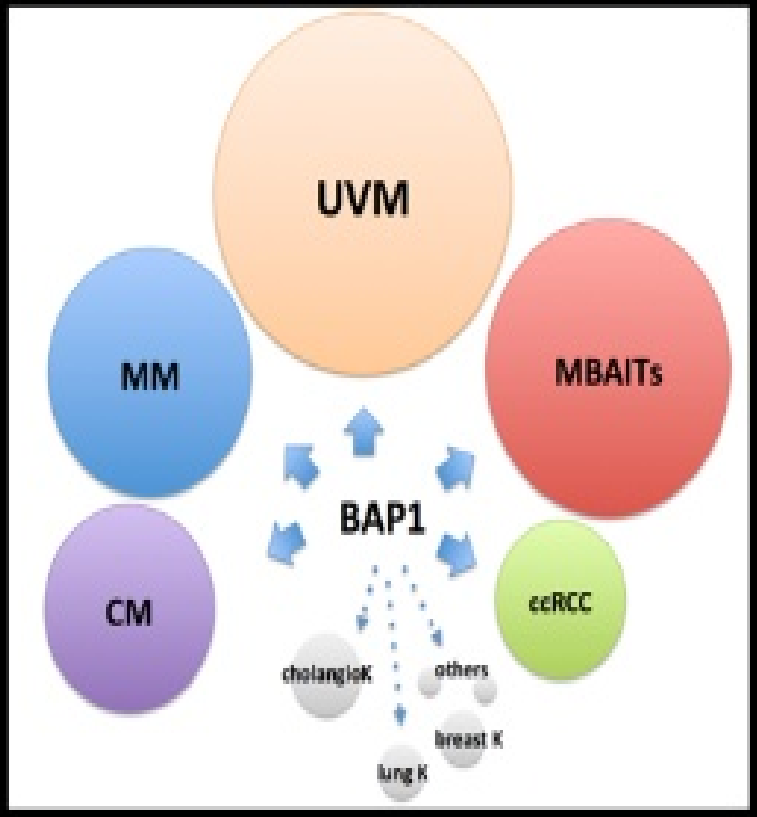


BAP-1



White AE; Harper JW. Science; Sep 2012; 337:1463-4

The BAP1 Cancer Syndrome



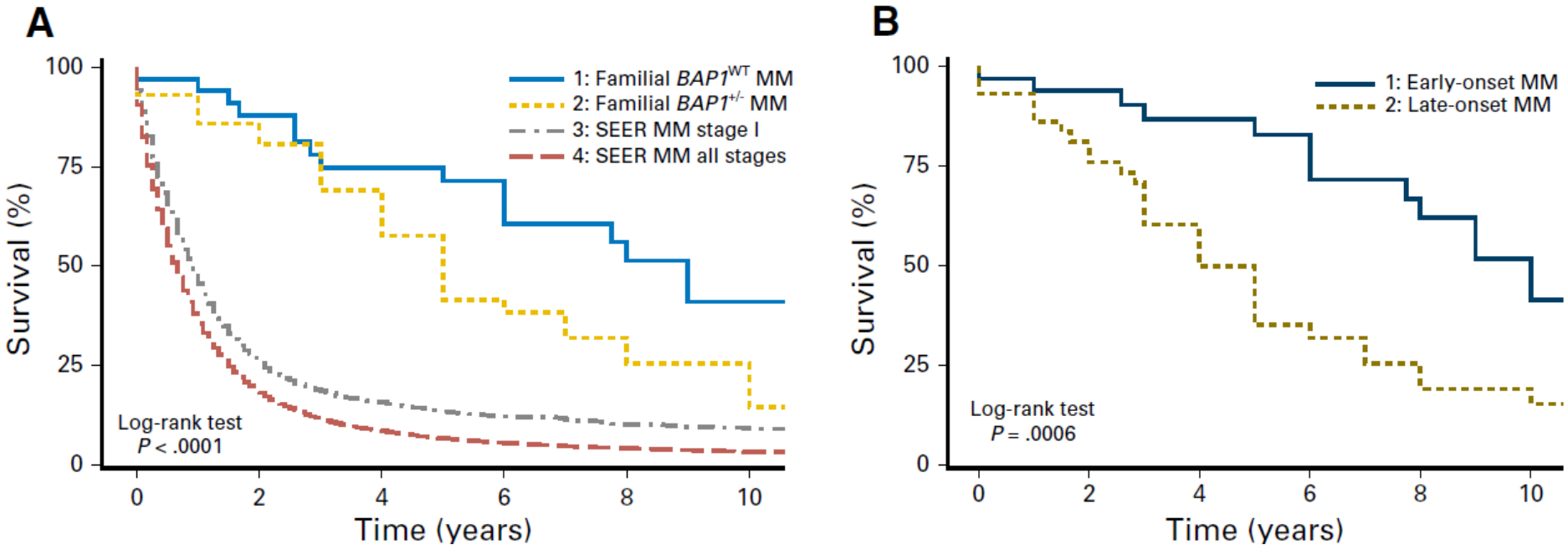
Carriers of BAP1 mutations are predisposed to different tumors:

- Malignant mesothelioma
- Uveal and cutaneous melanoma
- Renal Cell carcinoma, clear cell type
- Basal cell and squamous carcinomas
- Cholangioca and other cancers
- MBAITS (benign melanocytic tumors)

- Nature Reviews Cancer, Progess: BAP1 and Cancer, March 2013, Carbone M, et al.
- Journal of Translational Medicine, BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITS, August 2012, Carbone M, ..., Harvey I Pass and Yang H

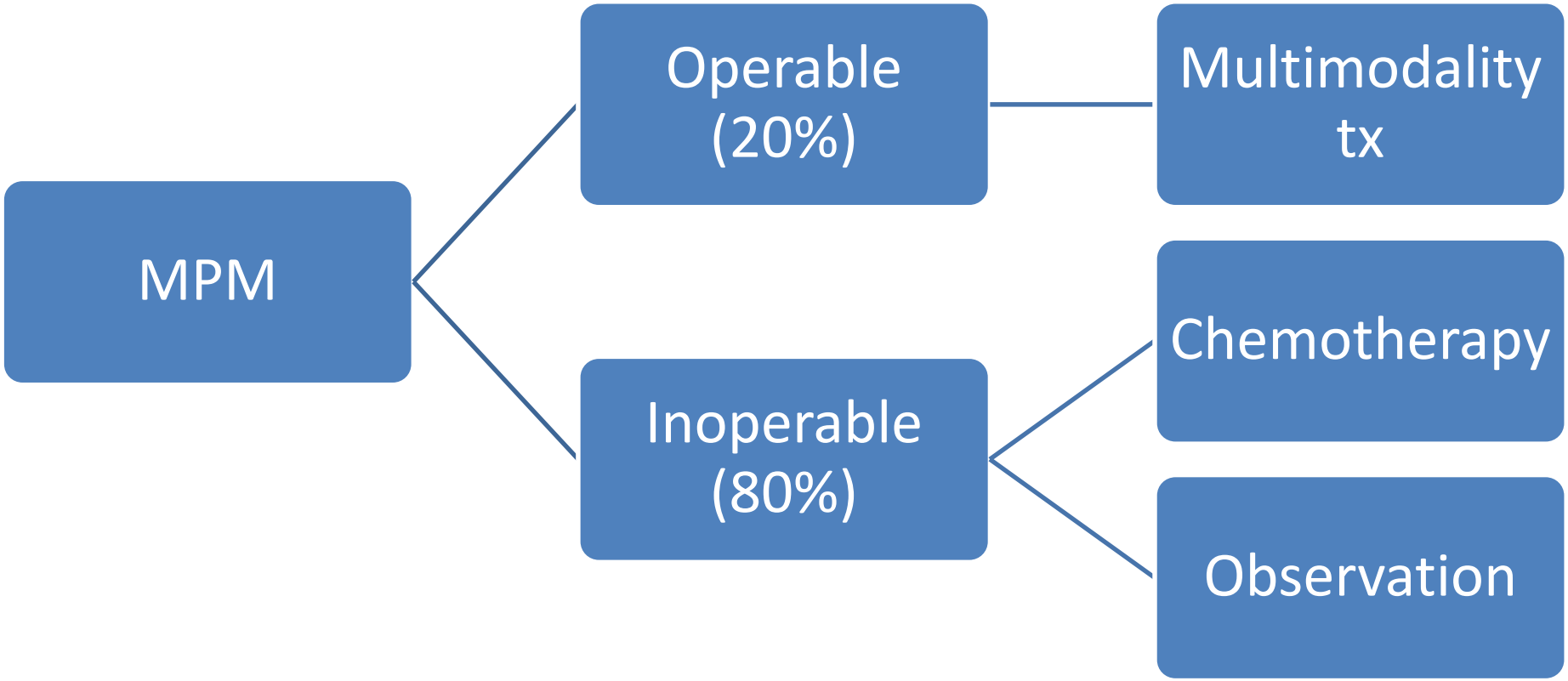
A Subset of Mesotheliomas With Improved Survival Occurring in Carriers of *BAP1* and Other Germline Mutations

Sandra Pastorino, Yoshie Yoshikawa, Harvey I. Pass, Mitsuru Emi, Masaki Nasu, Ian Pagano, Yasutaka Takinishi, Ryuji Yamamoto, Michael Minaai, Tomoko Hashimoto-Tamaoki, Masaki Ohmuraya, Keisuke Goto, Chandra Goparaju, Kavita Y. Sarin, Mika Tanji, Angela Bononi, Andrea Napolitano, Giovanni Gaudino, Mary Hesdorffer, Haining Yang, and Michele Carbone



J Clin Oncol 36:3485-3494.

Treatment Stratification



Important for Board Exam!

How to Define Inoperable MPM?

- Stage IV (M1)
- Sarcomatoid histology.
  Biphasic?
- Poor candidates for surgery.

Operable MPM: Principles

Treatment intent is "curative".

Survival benefit from surgery is uncertain.

- **Extrapleural pneumonectomy (EPP).**
- **Pleurectomy with decortication (P/D).**

Surgical goal: macroscopic complete resection (MCR).

Three potential strategies:

- **Surgery → Adjuvant chemotherapy → Hemithoracic Radiation (if EPP).**
- **Neoadjuvant chemotherapy → Surgery → Hemithoracic Radiation (if EPP).**
- **IMRT → EPP (investigational).**

Operable MPM: Principles

EPP vs. P/D:

- EPP: higher morbidity, higher likelihood of MCR.
- Optimal surgery is unclear.
- BOARD: Both EPP and P/D are acceptable.

Cisplatin and Pemetrexed.

- Regimen of choice in the neoadjuvant and adjuvant settings (BOARD).

Inoperable MPM

Observation

Minimally symptomatic.

Small tumor burden.

Favorable prognosis. Examples:

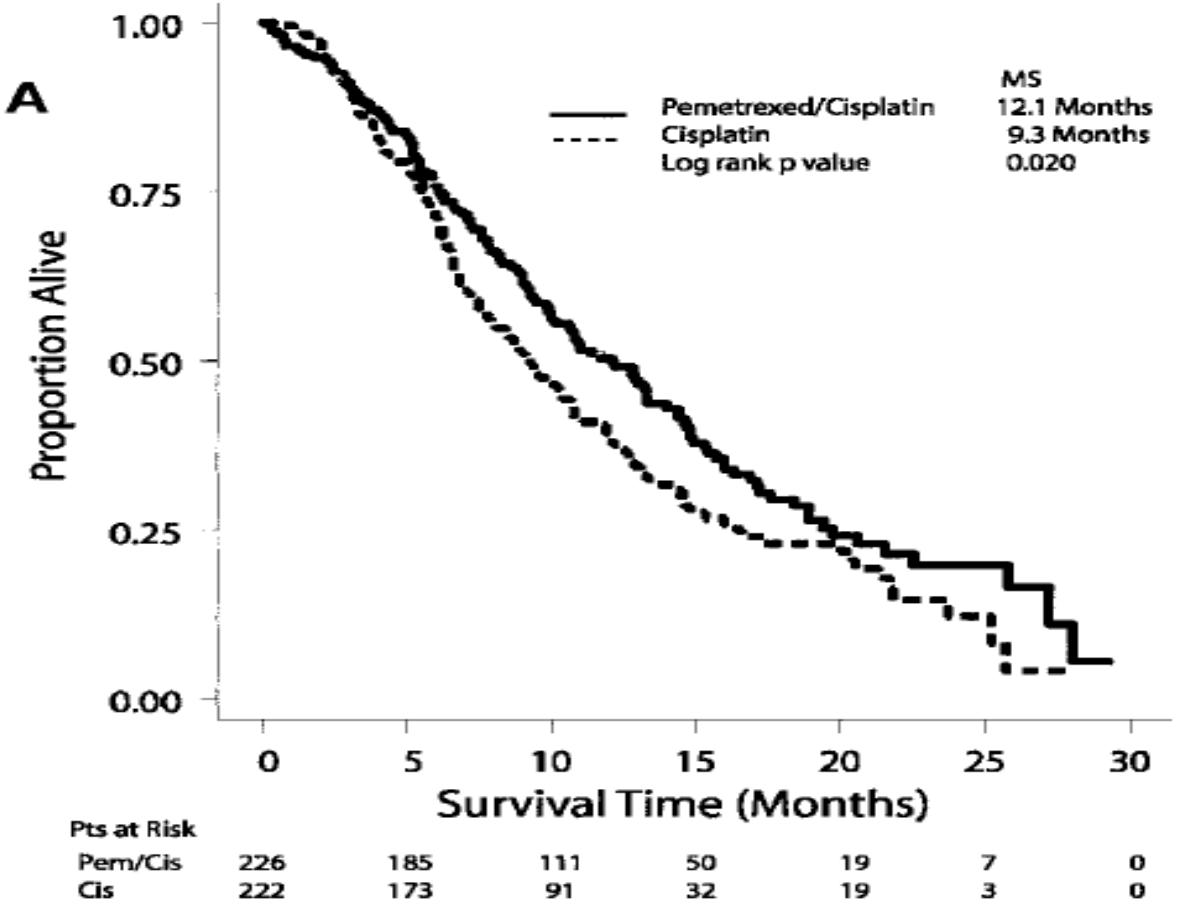
- Germline BAP-1+.
- Other familial MPM.

Older age w/ borderline PS.

First-Line Chemotherapy

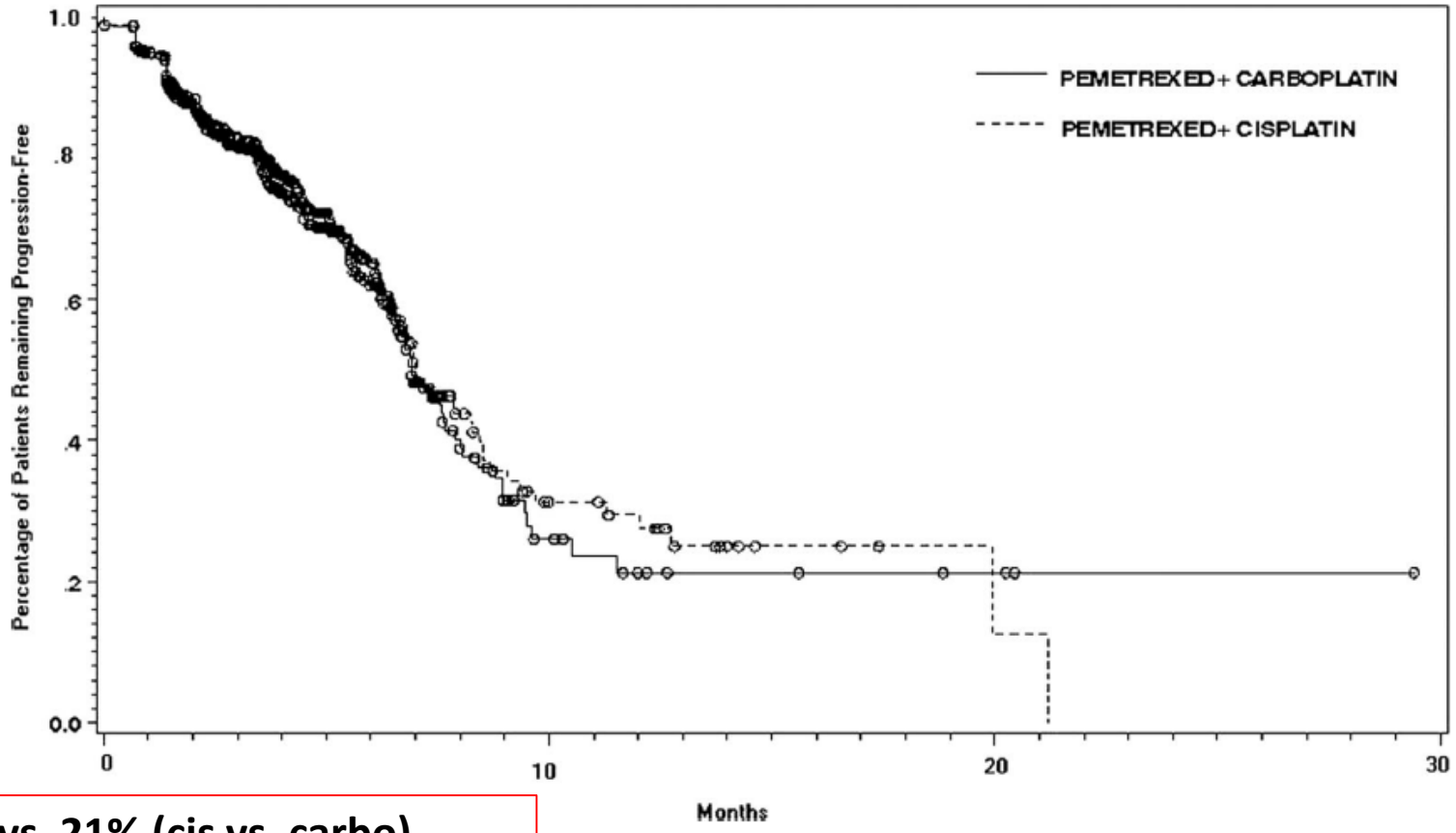
Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma

- N=448
- RR 41% vs. 17%.
- N/V and fatigue.



Journal of Clinical Oncology, Vol 21, No 14 (July 15), 2003: pp 2636-2644

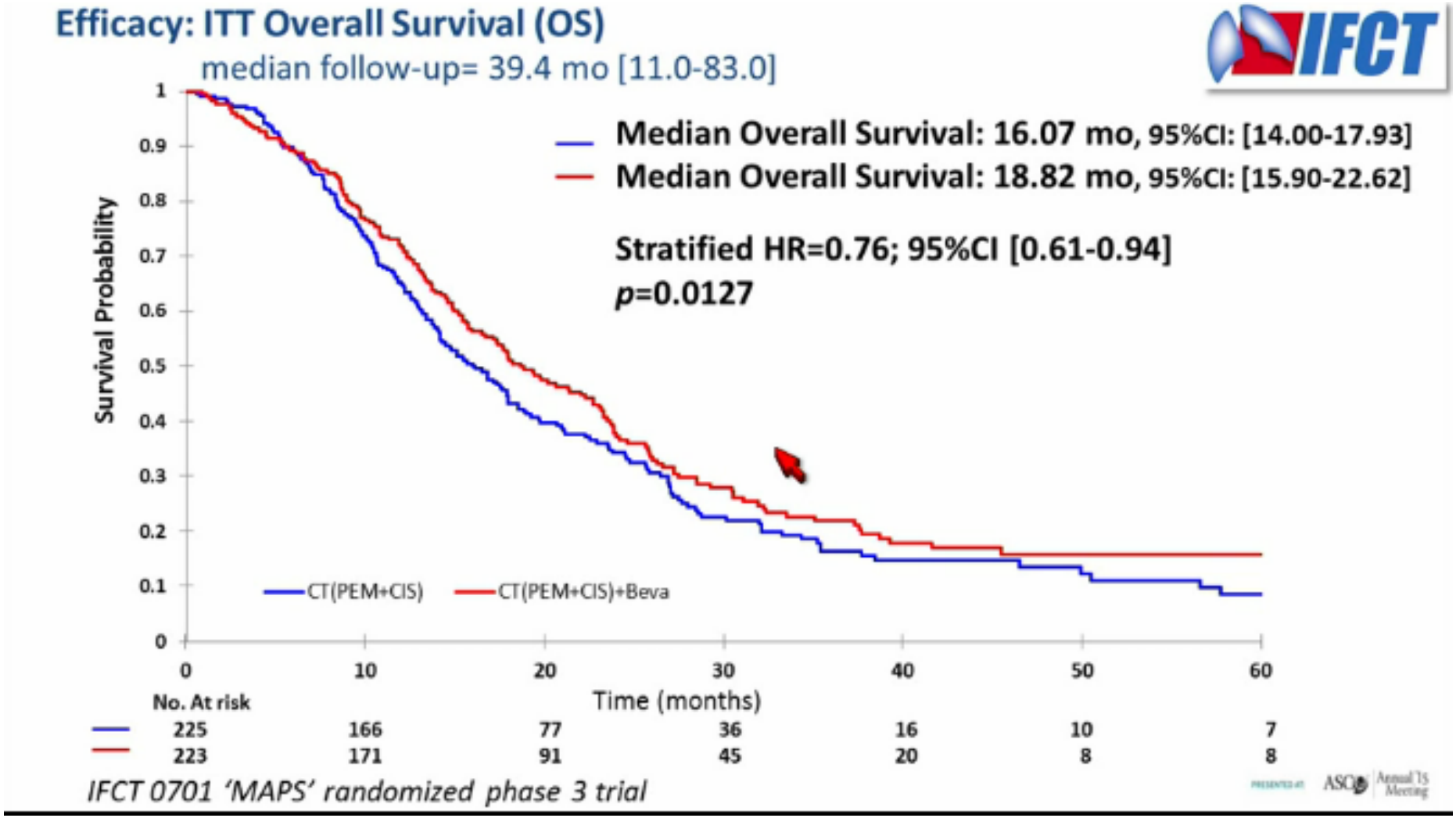
Pemetrexed Plus Cisplatin or Pemetrexed Plus Carboplatin for Chemonaïve Patients with Malignant Pleural Mesothelioma: Results of the International Expanded Access Program



RR: 26% vs. 21% (cis vs. carbo).
1-yr OS: 63% vs. 64% (cis vs. carbo).

(*J Thorac Oncol.* 2008;3: 756–763)

MAPS Trial



2015 ASCO meeting; abstract 7500

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

- Pemetrexed* 500 mg/m² day 1
  Cisplatin 75 mg/m² day 1
  Administered every 3 weeks (category 1)[1]

- Pemetrexed 500 mg/m² day 1
  Cisplatin 75 mg/m² day 1
  Bevacizumab 15 mg/kg day 1
  Administered every 3 weeks for 6 cycles followed by maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression (category 1)[2,**]

- Pemetrexed* 500 mg/m² day 1
  Carboplatin AUC 5 day 1
  Administered every 3 weeks[3-5,†]

- Gemcitabine 1000–1250 mg/m² days 1, 8, and 15
  Cisplatin 80–100 mg/m² day 1
  Administered in 3- to 4-week cycles[6,7]

- Pemetrexed* 500 mg/m² every 3 weeks[8]

- Vinorelbine 25–30 mg/m² weekly[9]

"Board" 1st-line regimens

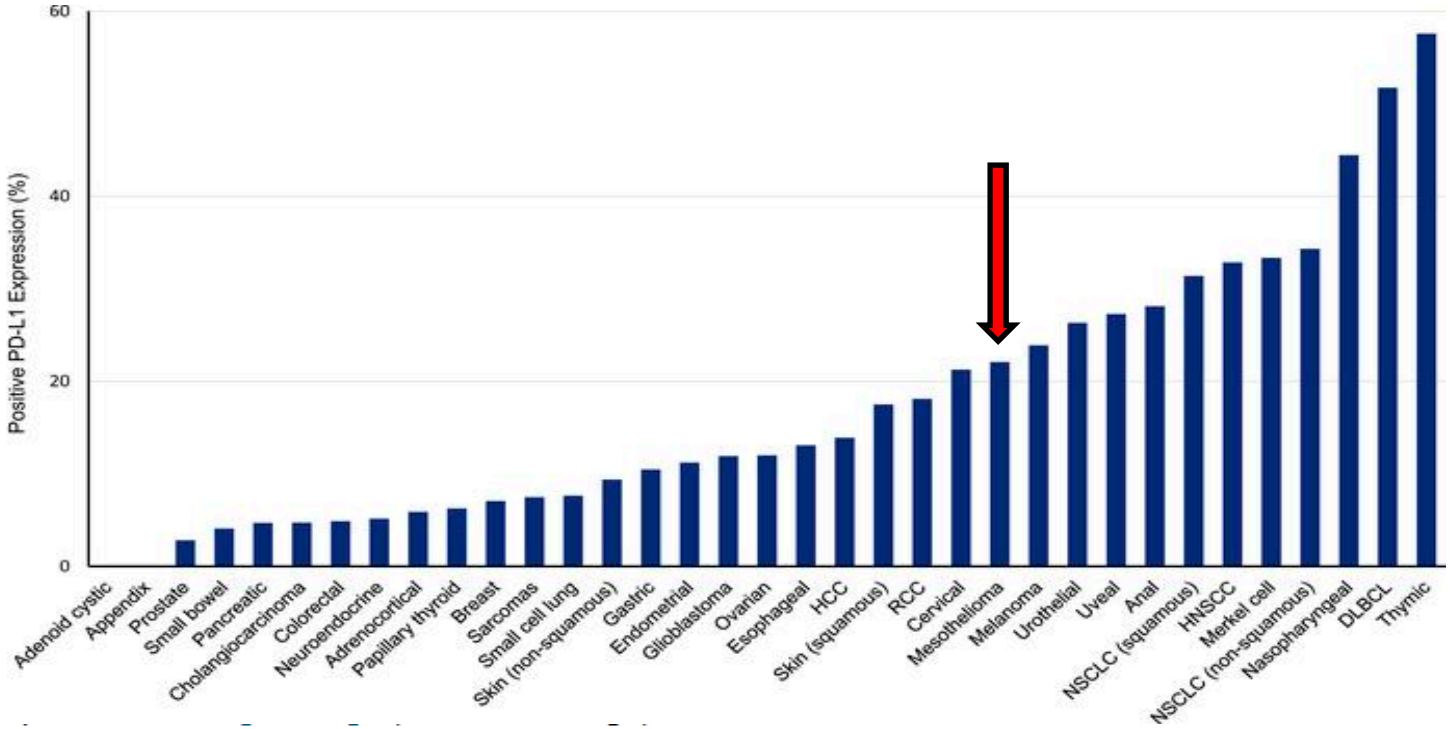
NovoTTF™-100L System - H180002

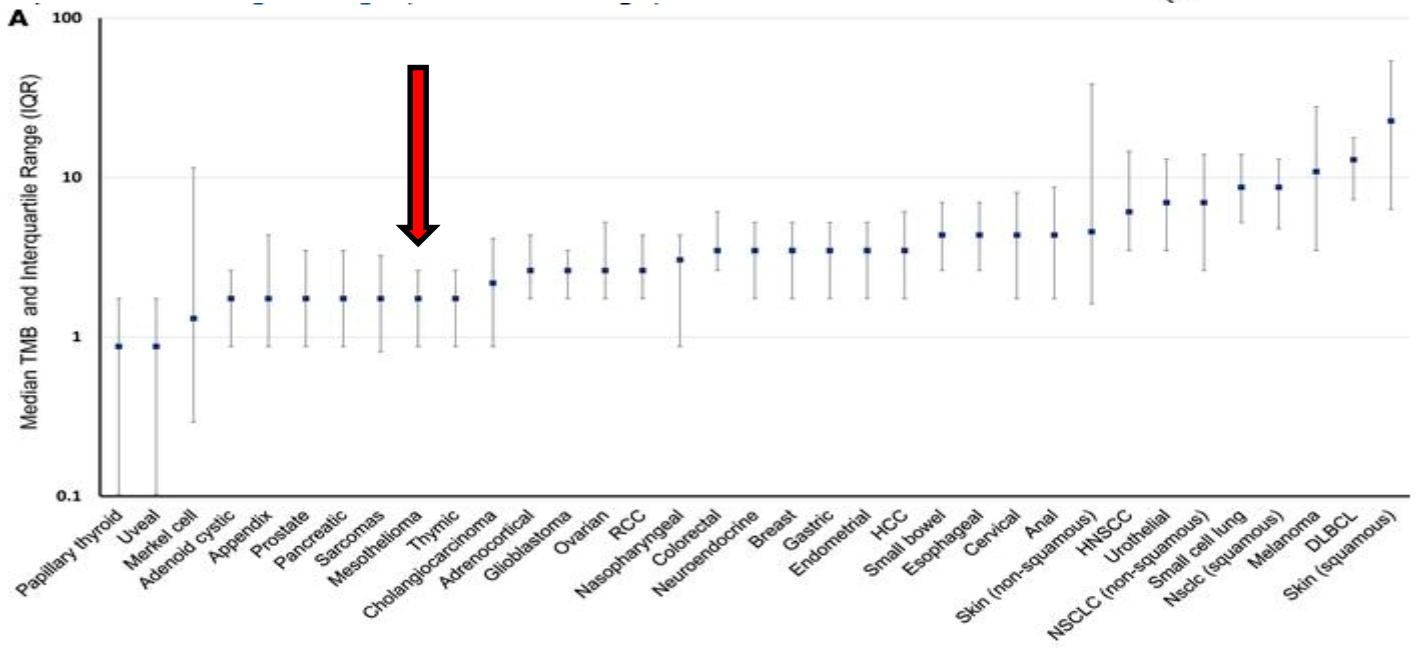
?

Stellar phase II trial with cisplatin and pemetrexed: Median OS = 18 months.

https://www.fda.gov/medical-devices/recently-approved-devices/novottftm-100l-system-h180002

Immune Checkpoint Inhibitors in 1st Line Systemic Therapy





JCI Insight. 2019;4(6):e126908. https://doi.org/10.1172/jci.insight.126908.

Abstract 9003

PrE0505

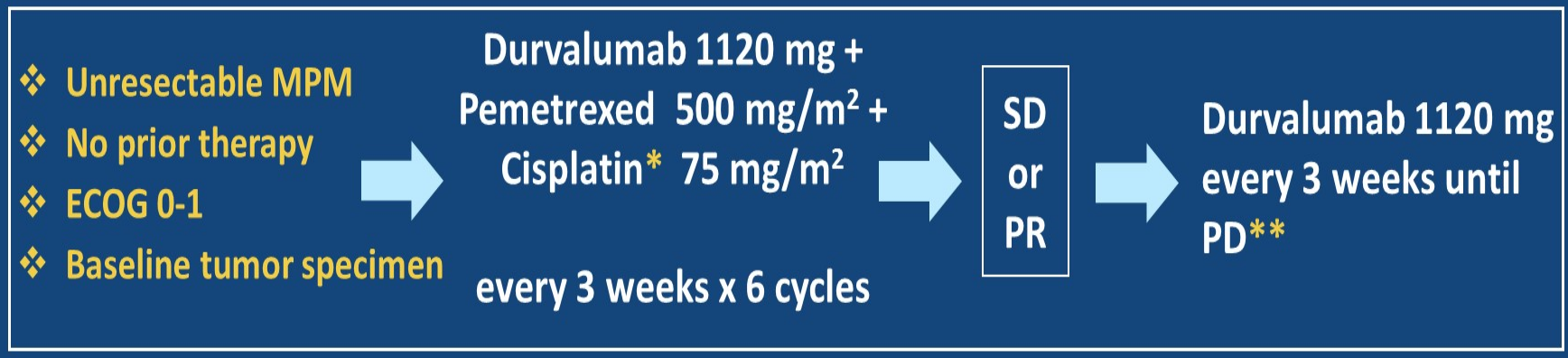
Phase 2 Multi-Center Study of anti-PD-L1 Durvalumab, in Combination with Cisplatin and Pemetrexed for the First-Line Treatment of Unresectable Malignant Pleural Mesothelioma (MPM)

Patrick Forde[1], Zhuoxin Sun[2] , Valsamo Anagnostou[1], Hedy Kindler[3], Thomas Purcell[4], Bernardo Goulart[5], Arkadiusz Z. Dudek[6], Hossein Borghaei[7], Julie Brahmer[1], Suresh Ramalingam[8]

[1]Johns Hopkins University; [2]Dana-Farber Cancer Institute; [3]University of Chicago; [4]University of Colorado; [5]University of Washington; [6]Metro-Minnesota Community Oncology Research Consortium; [7]Fox Chase Cancer Center; [8]Winship Cancer Institute of Emory University

Patients and Methods

Between June 2017 and June 2018, 55 patients were enrolled at 15 US sites

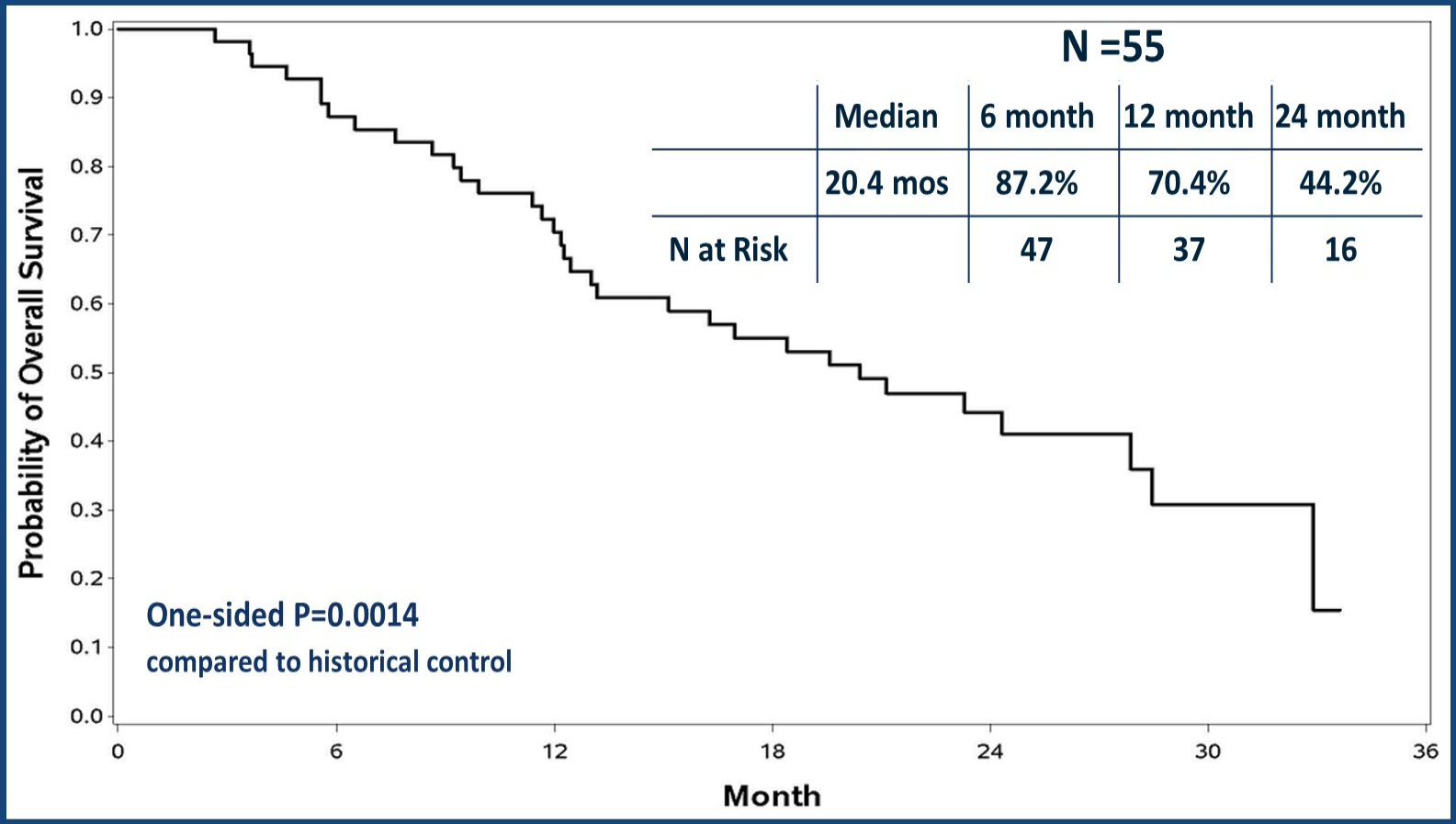


- 90% power to detect a 37% reduction in the OS hazard rate of 0.058 to 0.037 based on Wald test for the log failure rate parameter (one-sided type I error rate of 10%)
- To correspond to a 58% improvement in the median OS from 12 months (historical control) to 19 months (goal)
- Pre-specified safety review after enrollment of the first 6 and 15 patients. No DLTs noted for the combination with durvalumab 1120 mg

* Carboplatin was substituted if cisplatin was contraindicated, or due to toxicity during treatment

** Max duration 1 year from start of study

Results: Overall Survival



CheckMate-743 Trial of Nivolumab, Ipilimumab Meets Primary Endpoint in Mesothelioma Trial

April 21, 2020
Hannah Slater

The trial evaluating nivolumab in combination with ipilimumab in previously untreated malignant pleural mesothelioma met its primary endpoint of overall survival.

The CheckMate-743 trial evaluating nivolumab (Opdivo) in combination with ipilimumab (Yervoy) in previously untreated malignant pleural mesothelioma met its primary endpoint of overall survival (OS), according to Bristol-Myers Squibb, the agent's developer.[1]

Based on a pre-specified interim analysis conducted by an independent data monitoring committee, the combination treatment was also found to result in a statistically significant and clinically meaningful improvement in OS compared to chemotherapy (pemetrexed and cisplatin or carboplatin). Additionally, the safety profile of nivolumab plus ipilimumab observed in the trial reflects the known safety profile of the combination.

"Malignant pleural mesothelioma is a devastating disease that has seen limited treatment advances over the past decade," Sabine Maier, MD, development lead of thoracic cancers at Bristol Myers Squibb, said in a press release. "These topline results from the CheckMate-743 trial demonstrate the potential of Opdivo plus Yervoy in previously untreated patients with malignant pleural mesothelioma and is another example of the established efficacy and safety of the dual immunotherapy combination seen in multiple tumor types."

"We would like to thank the patients who participated in this trial, as well as the investigators and site personnel for their perseverance during the conduct of this study and in delivering this important result for patients in the midst of the COVID-19 pandemic," Maier added. "We look forward to working with investigators to present the results at a future medical meeting, and to discussing them with health authorities."

First-Line Therapy: Key Points

Standard

- Cisplatin/Carboplatin + Pemetrexed ± Bevacizumab.

Consider Observation

- Minimally symptomatic, low disease burden, favorable prognosis (e.g., germline BAP-1 germline +)

Evolving role for ICIs.

- DREAM3R: Cis/Pem/Durva vs. Cis/Pem. Ongoing.
- Promising role of Nivo/Ipi, data release pending.

Second-Line therapy

NO FDA APPROVED 2L REGIMENS (BOARD)

Chemotherapy	Evolving Role of ICIs	Evolving role for anti-VEGF MoAb
• Vinorelbine • Gemcitabine • Repeat pemetrexed • RR ≈ 10%	• Pembrolizumab • Nivolumab ±Ipilimumab	• Gemcitabine + Ramucirumab. • 2020 ASCO abst #9004.

Pembrolizumab

Keynote 028

	Full-analysis set (n=25)
Objective response	5 (20%; 95% CI 6·8–40·7)
Complete response	0
Partial response	5 (20%)
Stable disease	13 (52%)
Progressive disease	4 (16%)
Not evaluable or no assessment*	3 (12%)
Duration of follow-up (months)	18·7 (10·4–24·0)
Time to response (months)	1·9 (1·7–3·8)
Duration of response (months)	12 (3·7–NR)
Duration of stable disease (months)	5·6 (3·6–12·0)
Clinical benefit (complete response + partial response + stable disease ≥6 months)	40% (21·1–61·3)
Progression-free survival	
Events	21 (84%)
Median (months)	5·4 (3·4–7·5)
6 months	45·8% (25·6–64·0)
12 months	20·8% (7·6–38·5)
Overall survival	
Deaths	14 (56%)
Median (months)	18 (9·4–NR)
6 months	83·5% (61·7–93·5)
12 months	62·6% (40·4–78·5)

Lancet Oncol 2017; 18: 623–30

Popat et al, 2019 ESMO

2L Phase III trial Pembro vs. Gemcitabine or Vinorelbine		
	Pembro	**Gem or Vin**
PFS (months)	2.5	3.4
OS (months)	10.7	11.7

NCCN category 2A

Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial

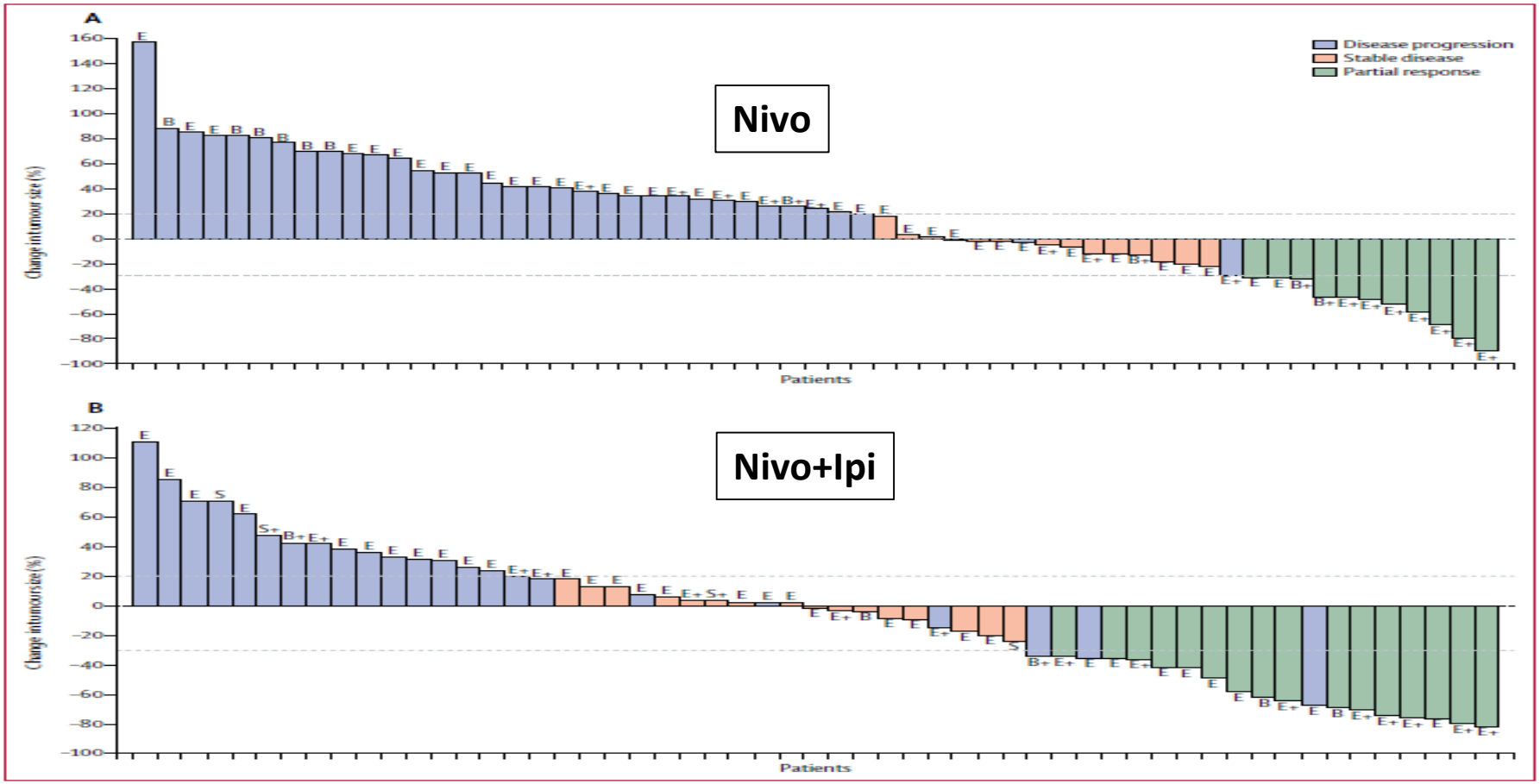
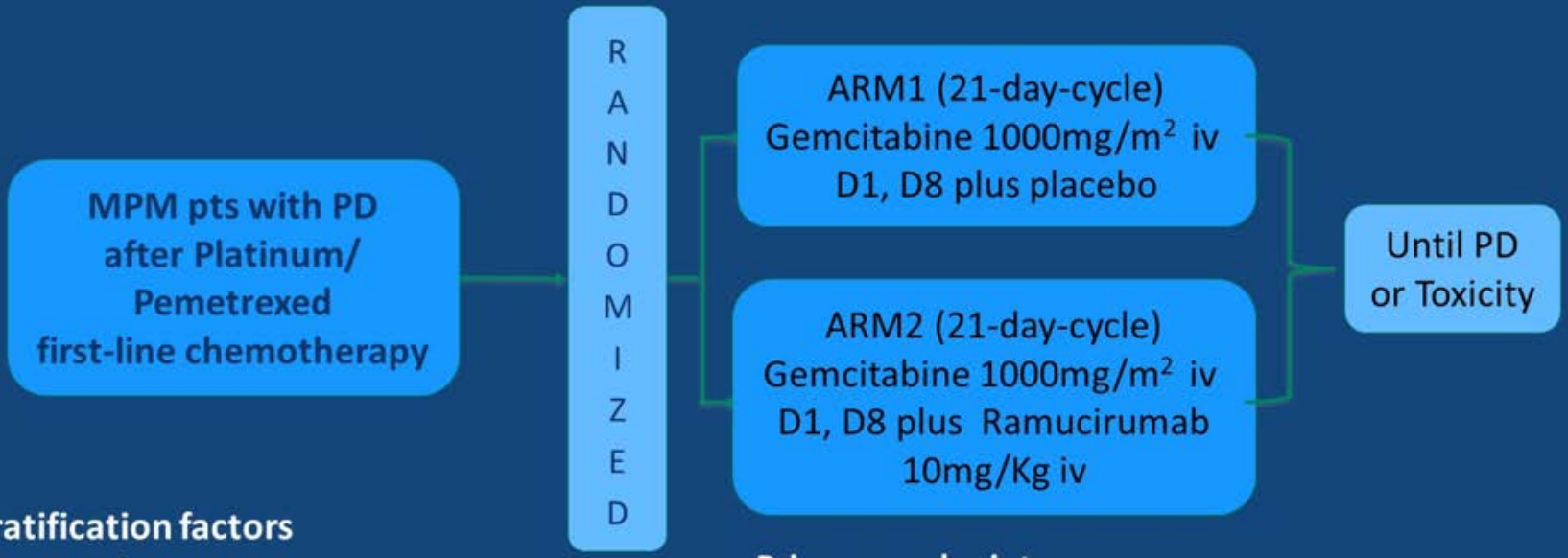


Figure 2: Percentage changes in tumour size, baseline to week 12

Lancet Oncol 2019; 20: 239–53

RAMES Study: Phase II comparative design



Stratification factors

- ECOG/PS 0-1 vs 2
- Age ≤ 70 vs > 70
- Histological subtype
- TTP

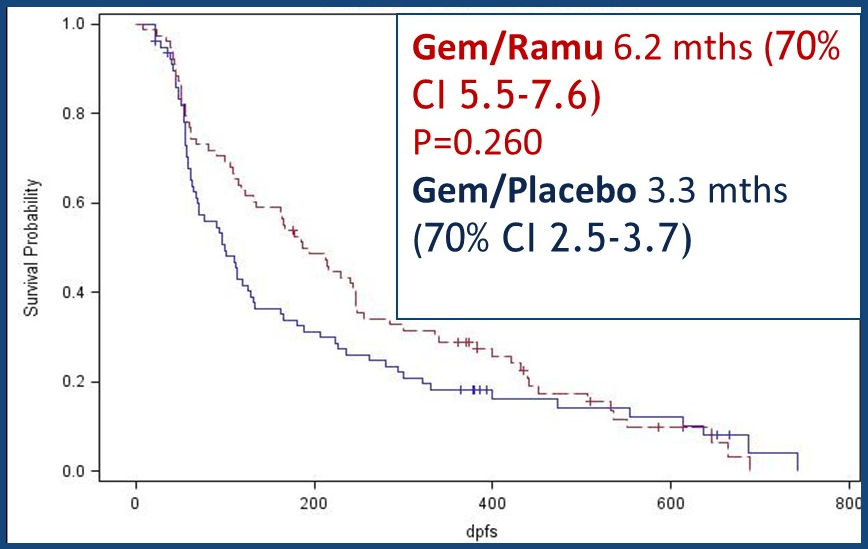
Primary endpoint

- OS

Secondary endpoints

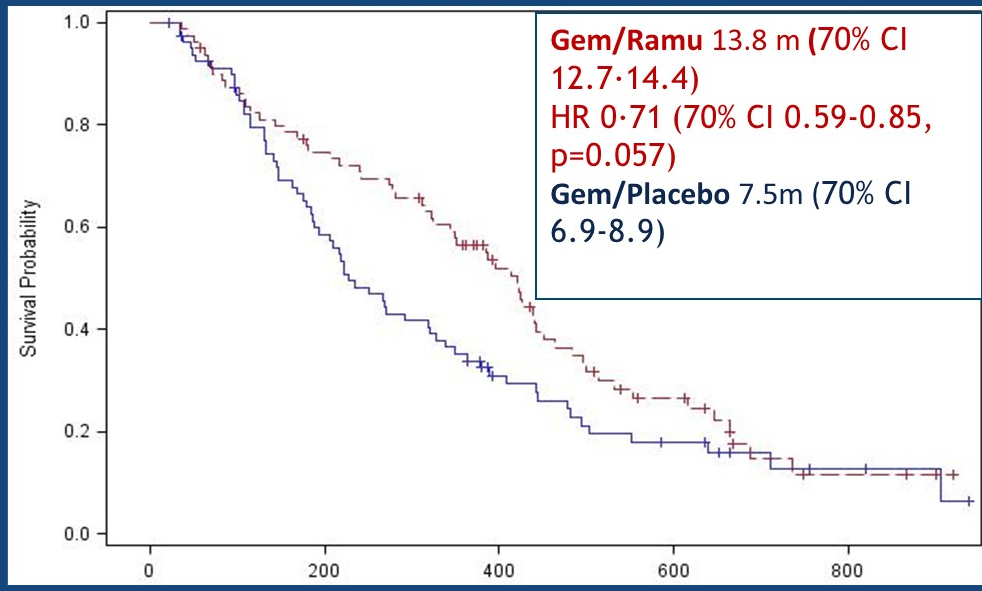
- PFS, ORR, Safety, QoL
- Predictive markers

PFS



Gem/Ramu 6.2 mths (70% CI 5.5-7.6)
P=0.260
Gem/Placebo 3.3 mths (70% CI 2.5-3.7)

OS



Gem/Ramu 13.8 m (70% CI 12.7·14.4)
HR 0·71 (70% CI 0.59-0.85, p=0.057)
Gem/Placebo 7.5m (70% CI 6.9-8.9)

2L Therapy: Keypoints

Main message

No FDA-approved 2nd line therapies (Board).

Chemotherapy

Vinorelbine, gemcitabine, pemetrexed

- RR ≈ 10%.

Checkpoint inhibitors

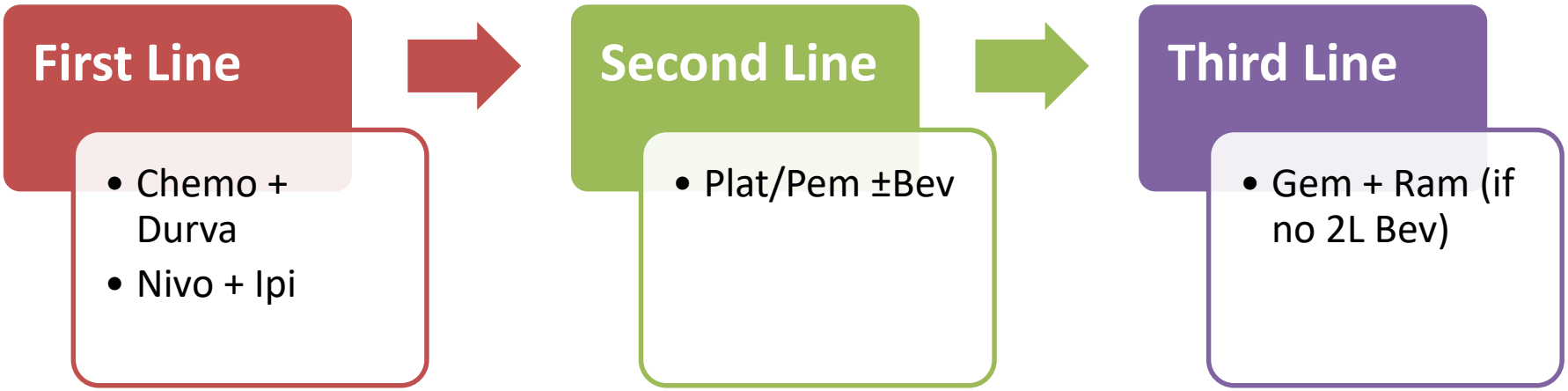
Evolving role of PDL1 CIs.

- Consider 2L pembrolizumab, gemcitabine, vinorelbine, or re-challenge pemetrexed*.
- Data is immature for nivo or nivo/ipi.

Gem/Ram

Deserves at least a phase III. Stay tuned.

Final Thoughts on Future Directions



Questions