Emerging role of immune checkpoint inhibitors and ongoing clinical trials in malignant pleural mesothelioma (MPM)

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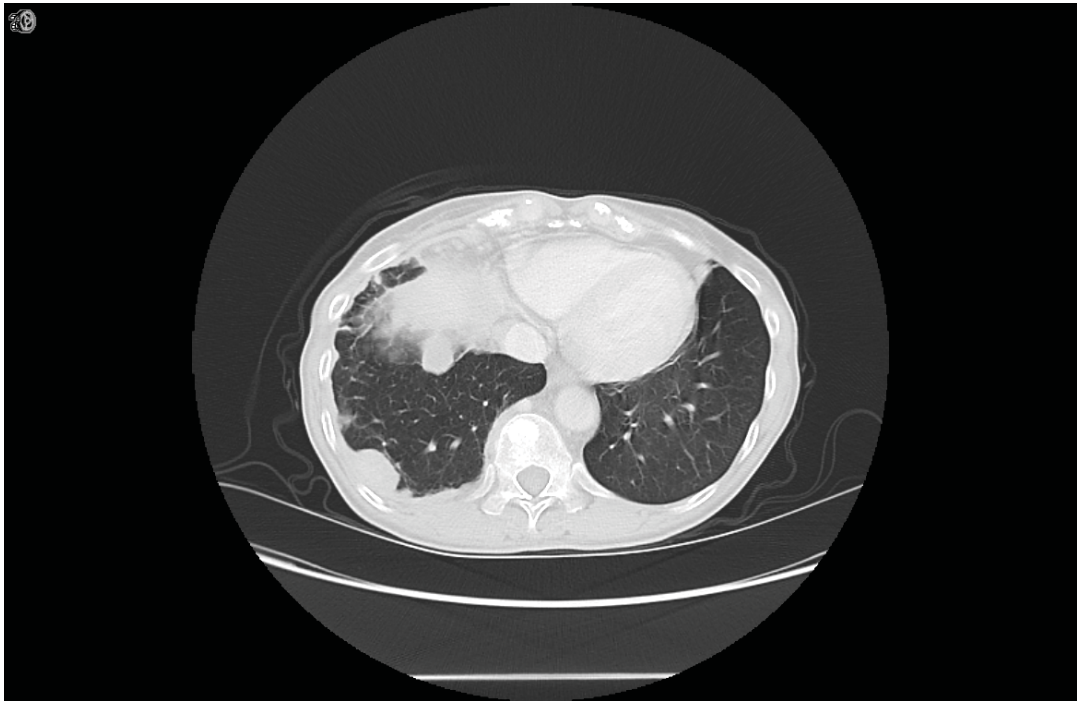
Mesothelioma Case

- 67 yo woman, never-smoker, diagnosed with epithelioid mesothelioma. Presented with right chest wall pain, anorexia and weight loss. Imaging showed right lung and pleural masses with mets to bone and liver
- She received RT to the T4 and T12 vertebral bodies and had chemotherapy with 6 cycles of carboplatin/pemetrexed/ bevacizumab completed (8/2016) then maintenance pemetrexed/bevacizumab
- Subsequent POD and referred for a clinical trial



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PD-L1 expression in malignant pleural mesothelioma

	Mansfield et al[1]	Cedrés et al[2]	Thapa et al[3]	Combaz-Lair[4]
N	106	77	311	58
Antibody used	5H1	E1L3N	E1L3N	E1L3N
Criteria of positivity	>5% membranous and/or cytoplasmic staining	≥ 1% membranous and/or cytoplasmic staining	>5% membranous staining	≥ 1% membranous and/or cytoplasmic staining
PD-L1 positivity All	40%	20.7%	41.7%	29%
Epitheloid	33%	20%	33%	23%
Non-epitheloid	38%	73%	42%*	37%

*Strong positivity predominantly in non-epitheloid tumors

*97% percent (58/60 cases) of the MPM showed a mixed infiltrate of lymphocytes, macrophages, and plasma cells (Combaz-Lair, Human Pathol 2016)

[1]Mansfield, JTO 2014, [2]Cedres, Plos One 2015, [3]Thapa, ASCO 2016, [4]Combaz-Lair, Human Pathol 2016

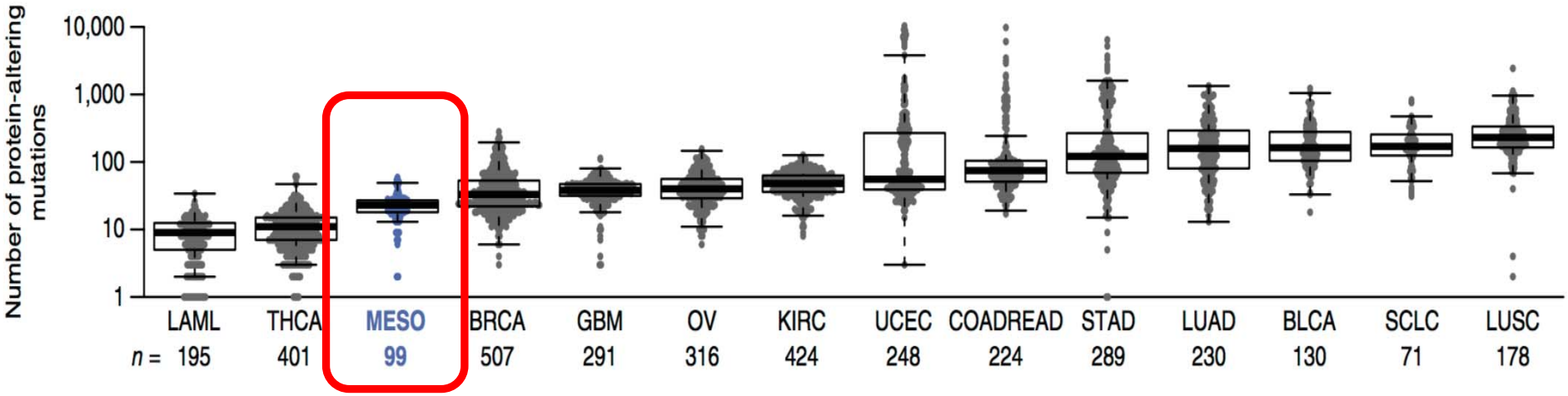
Courtesy of Solange Peters

Correlation of PD-L1 expression with immune cell infiltrates, genome-wide copy number aberrations and survival in mesothelioma

- **Methods**
  - Tissue microarray constructed from 329 patients with MPM
  - Immunohistochemistry performed for CD8, CD4, FoxP3 and PD-L1
- **Key results**
  - PD-L1+ in 41.7% of patients with high expression in only 9.6% (defined as >50% of tumour having ≥2+ intensity membranous staining)
  - PD-L1+ correlated with non-epithelioid histology and increased infiltration with CD4, CD8 and FoxP3 lymphocytes
  - High PD-L1 expression correlated with worse prognosis (5.3 months vs. 13.5 months for PD-L1 negative and 11.3 months for weak PD-L1 expression; p=0.0001)
  - Increased genomic alterations did not correlate with PD-L1 expression, but was associated with poorer survival

Thapa, ASCO 2016

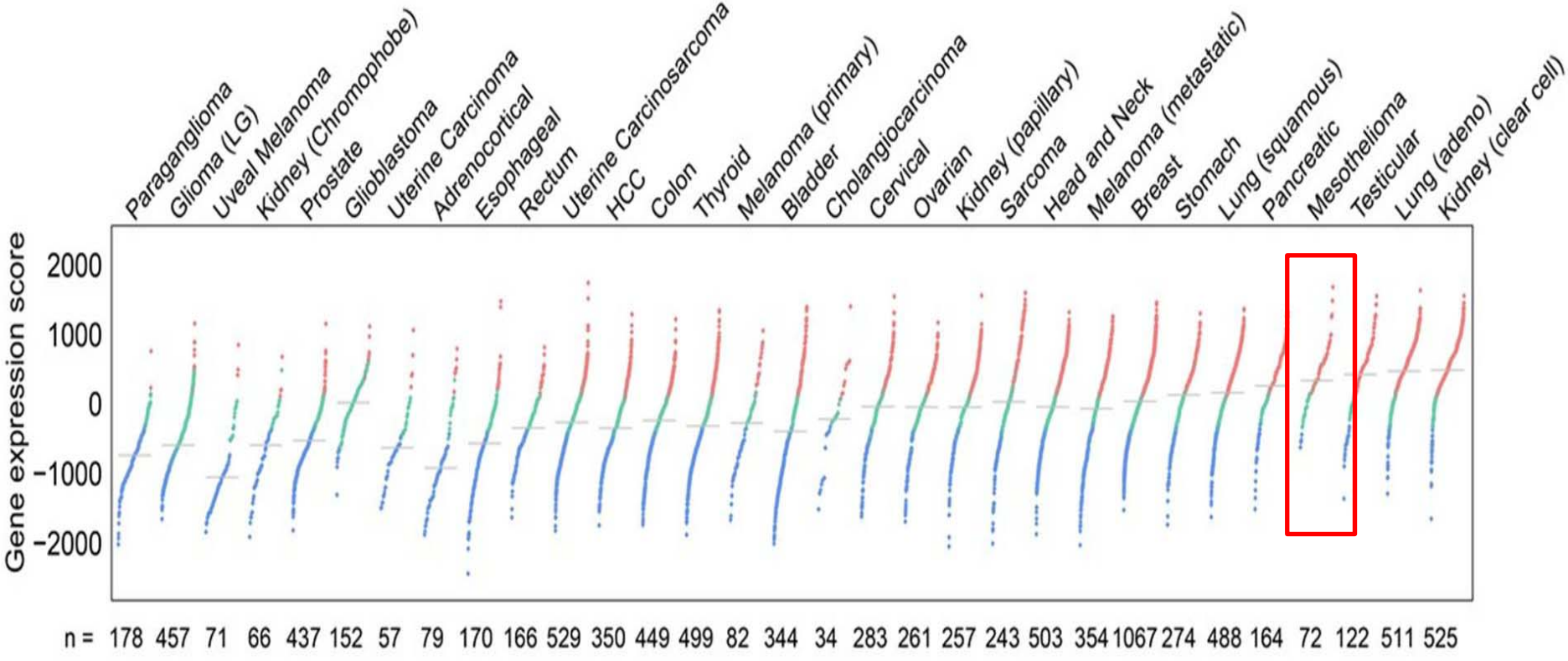
Mesothelioma – mutational load



- Whole-exome sequencing on DNA from 22 MPMs and matched blood samples. Identification of 517 somatic mutations across 490 mutated genes
- Mesothelioma contain an average of 24 protein coding alteration per sample, a rate considerably lower than other types malignancies

Bueno, Nat Gen 2016

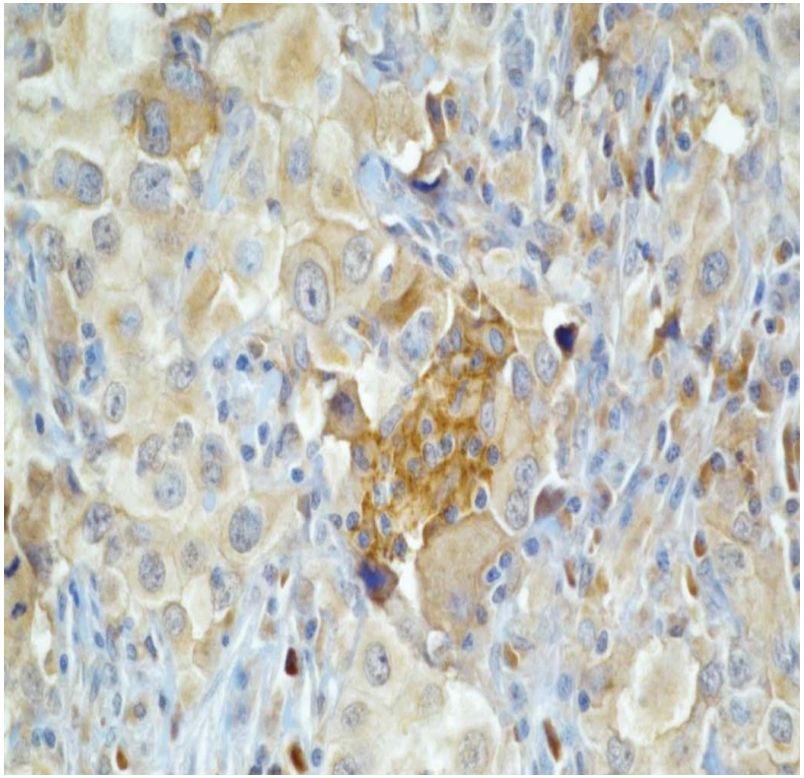
T-cell inflamed microenvironment by tumor entity across TCGA solid tumors



Luke, ASCO 2016

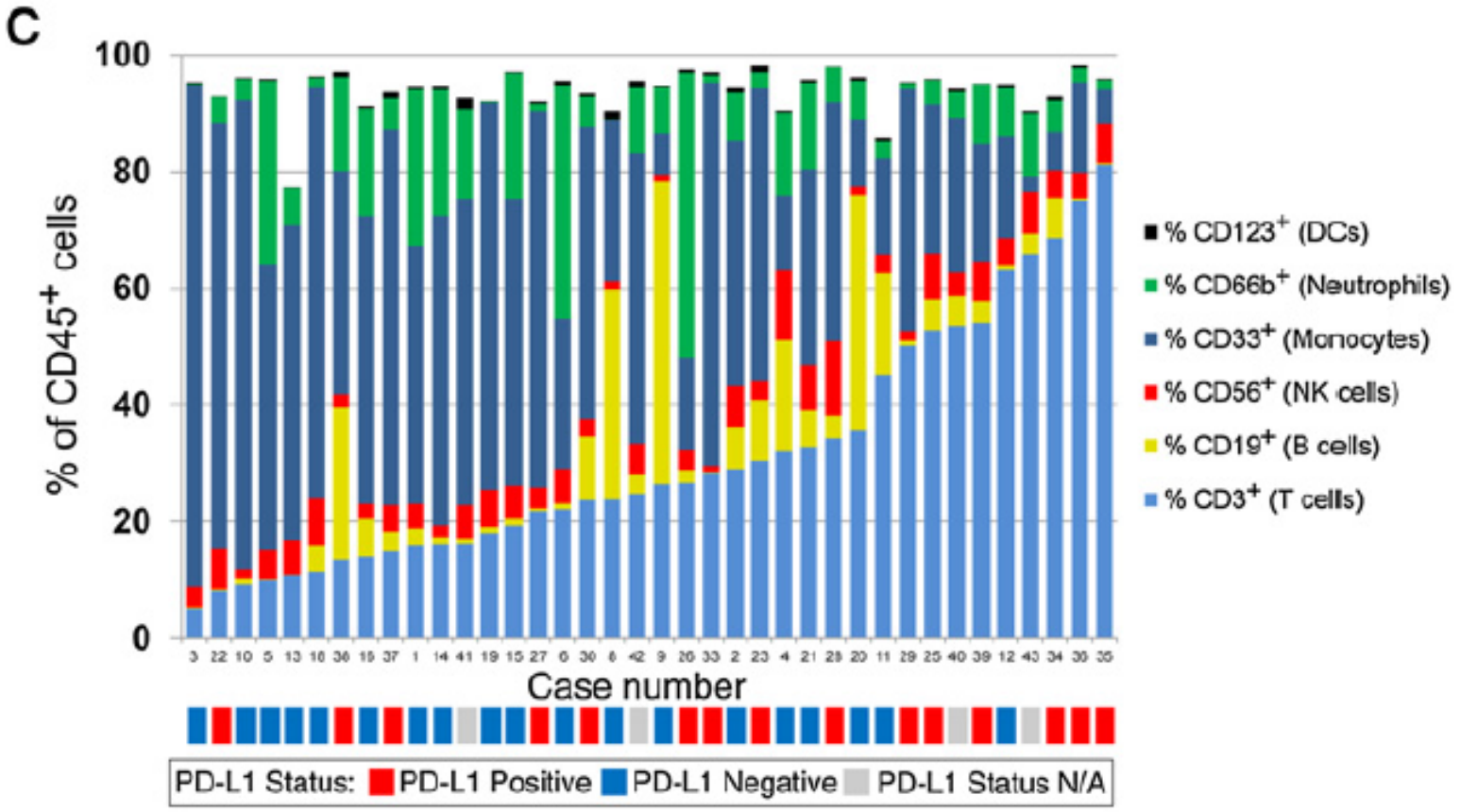
TILs

- 97% percent (58/60 cases) of the MPM showed a mixed infiltrate of lymphocytes, macrophages, and plasma cells.



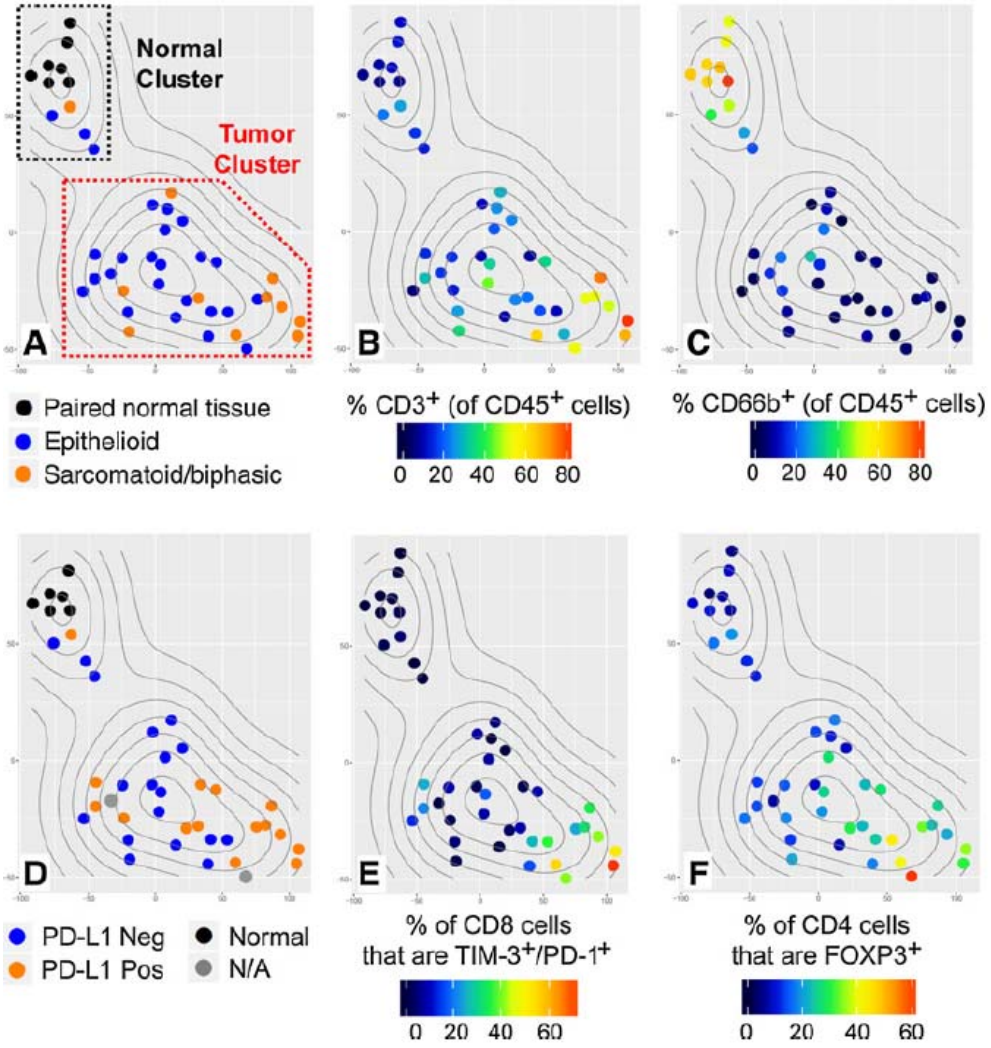
Combaz-Lair, Human Pathology 2016

Immune profiling of MPM



Awad et al, Cancer Immunol Res 2016

Immune profiling of MPM



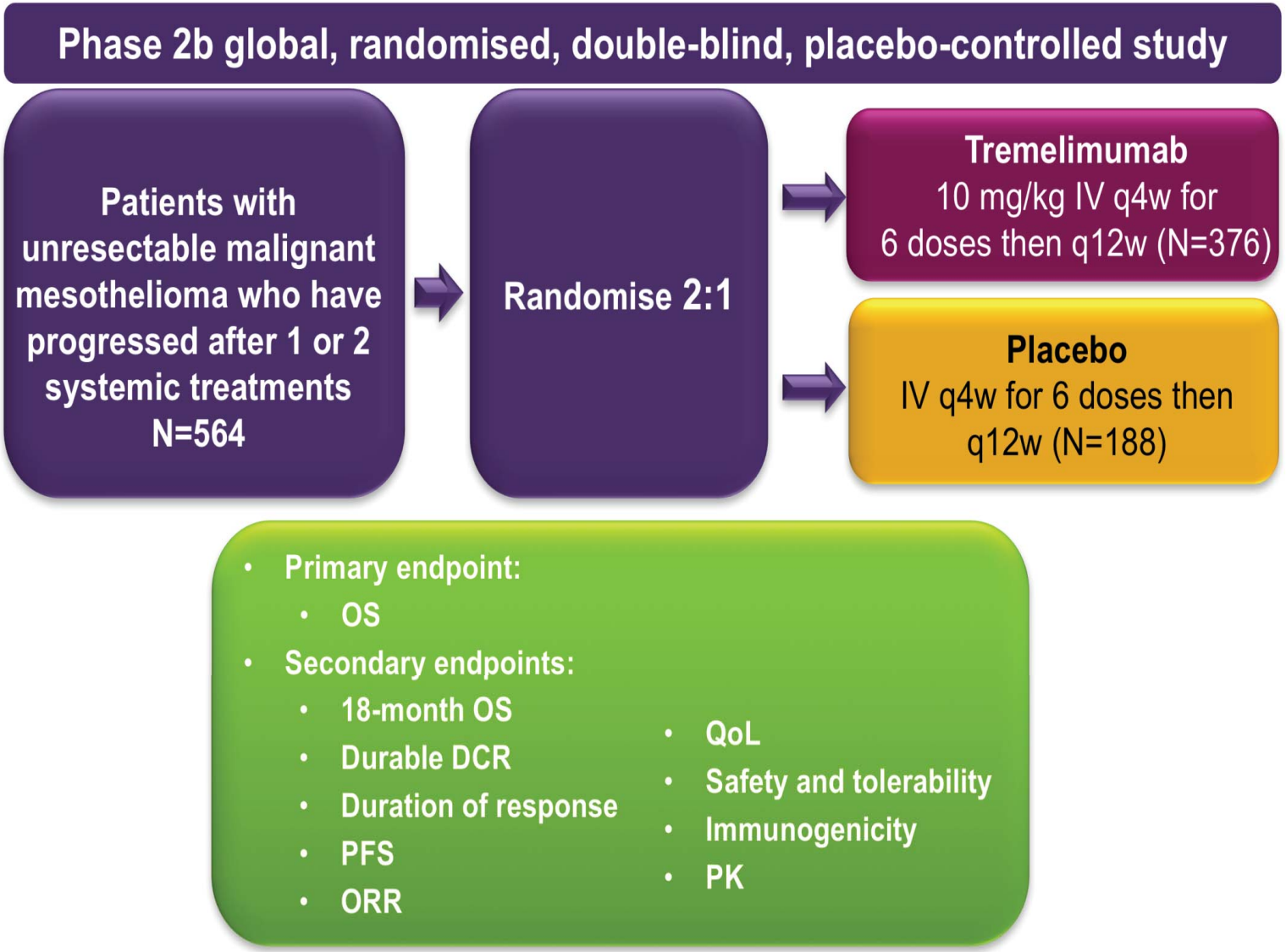
Awad et al, Cancer Immunol Res 2016

Tremelimumab
MESOT-TREM-2008 and -2012 (IIS)

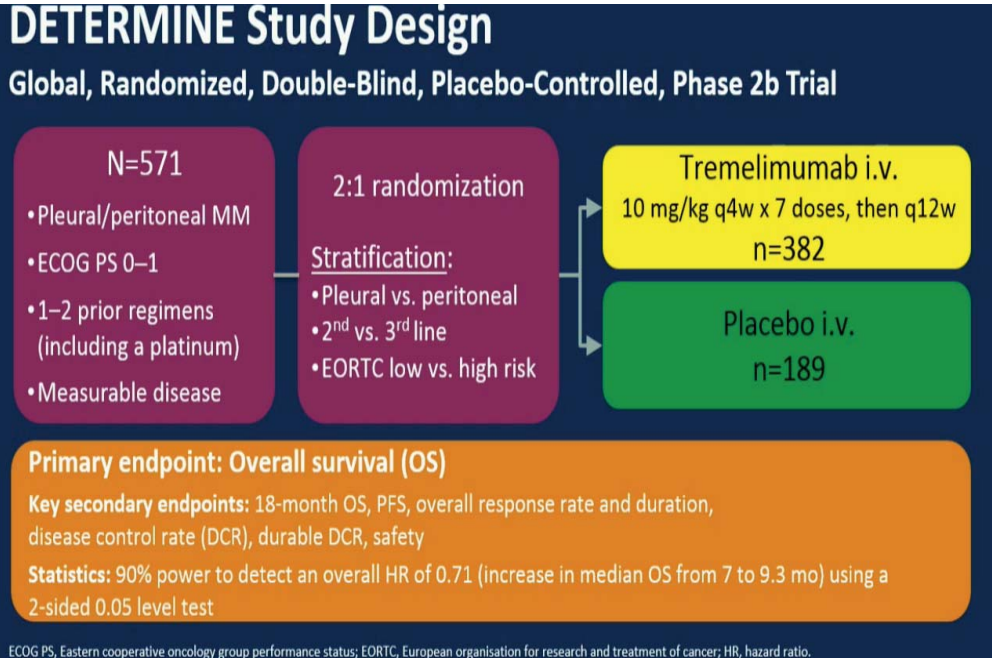
Best tumour response	MESOT-TREM-2008* 15 mg/kg q12w, N=29[1]	MESOT-TREM-2012† 10 mg/kg q4w/q12w, N=29[2]
ORR, % (95% CI) CR PR	6.9 (0.0–16.1) 0 6.9 (0.0–16.1)	13.8 (3.9–31.7) 0 13.8 (3.9–31.7)
SD, % (95% CI)	24.1 (8.6–39.7)	38 (20.7–57.7)
DCR, % (95% CI)	31.0 (14.2–47.9)	51.7 (32.5–70.6)
1-year survival, % (95% CI)	48.3 (30.1–66.5)	48.3 (30.1–66.5)
2-year survival, % (95% CI)	36.7 (18.7–54.7)	–
Median OS, months (95% CI)	10.7 (0.0–21.9)	11.3 (3.4–19.2)
Median PFS, months (95% CI)	6.2 (1.3–11.1)	6.2 (5.7–6.7)

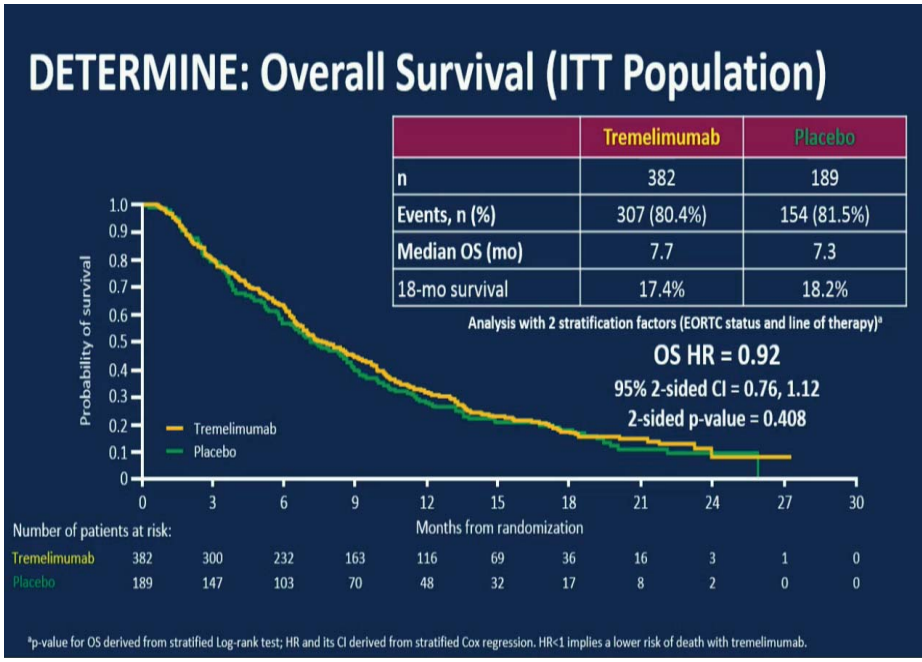
[1]Calabro L, et al. Lancet Oncol 2013;14:1104–11;
[2]Calabro L, et al. Lancet Resp Med 2015;3:301–9

DETERMINE: study design



Tremelimumab in second or third line versus placebo in malignant mesothelioma





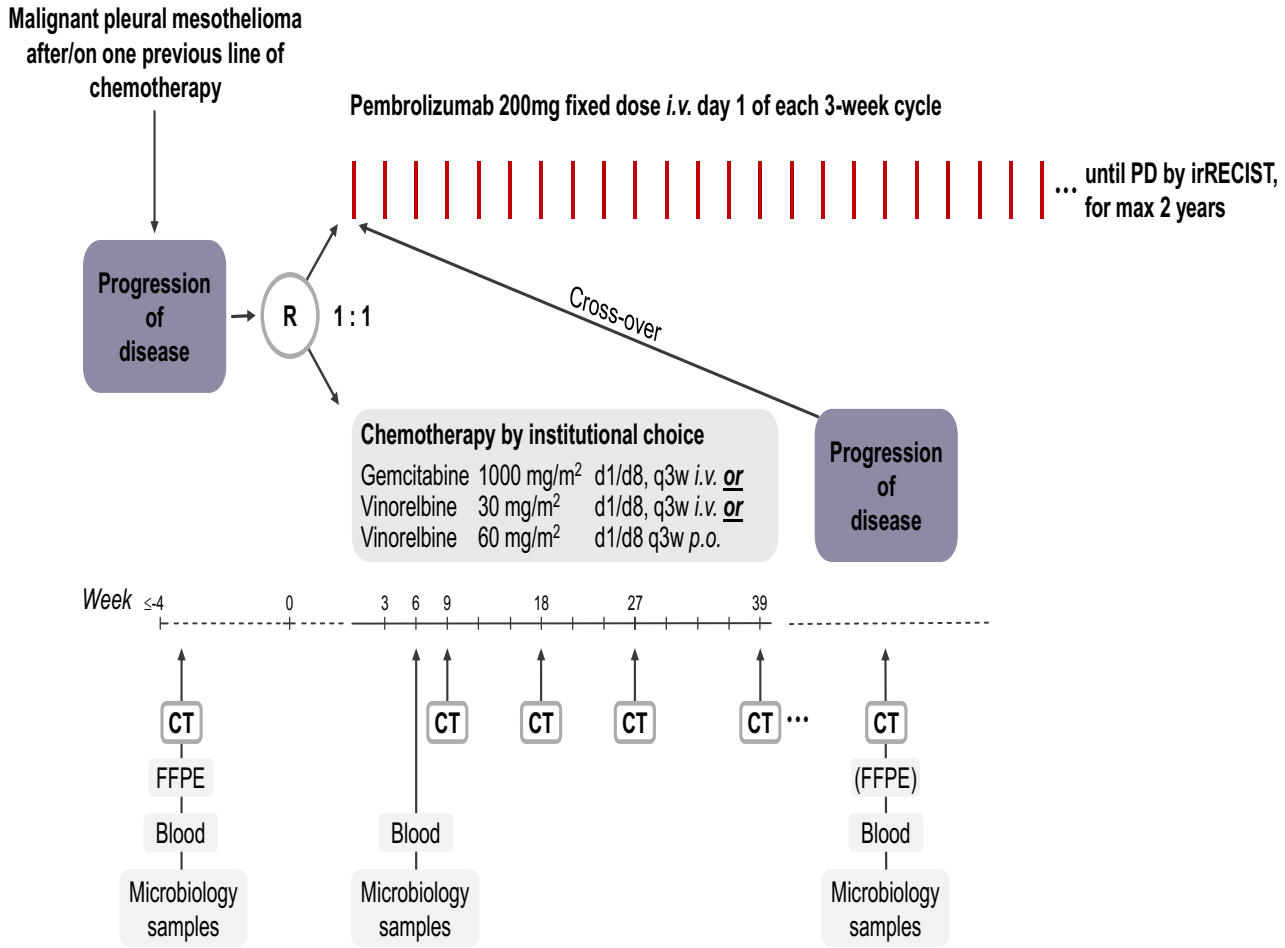
Kindler ASCO 2016

Anti-PD-1 antibody results

Study	Keynote-028 PD-L1+	NivoMes Unselected	Avelumab Unselected
Patient Number	25	18	53
PR	7 (28%)	5 (27%)	5 (9.4%)
SD	12 (48%)	4 (22%)	27 (47.2%)
PD	4 (16%)	9 (50%)	18 (34%)
Not assessed	2 (8%)		

Level of PD-L1 expression in Keynote-028 did not correlate with response
Both PD-L1 positive and negative patients responded to Avelumab
Response to Avelumab was not associated with TIL or tumour PD-L1 staining

PROMISE-meso: Pembrolizumab in advanced pretreated malignant pleural mesothelioma



Study design:

- Multicentre, randomised, phase III trial, ETOP sponsored

Primary objectives:

- To assess safety and efficacy of pembrolizumab versus standard chemotherapy in MPM

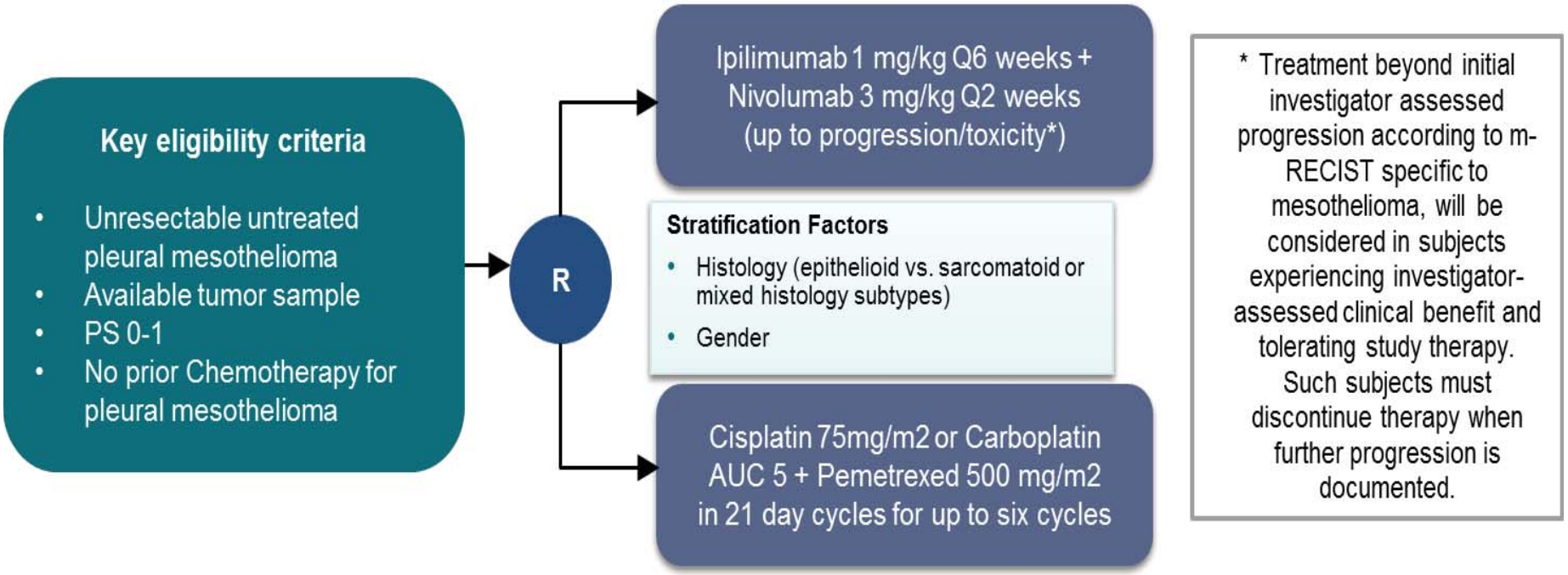
Primary endpoint:

- Progression-free survival (based on independent radiological review)

Sample size:

- 142 randomized patients

CA209-743: A phase III NIVO/IPI vs. chemotherapy first line trial in mesothelioma



- **Primary Outcome Measures:**
  - OS / PFS
- **Secondary/exploratory Outcome Measures:**
  - ORR, DCR, PRO, association between PD-L1 expression and efficacy measures, safety, PK/ immunogenicity

ClinicalTrials.gov Identifier: NCT02899299

Summary

- CTLA-4 blockade phase 3 trial in MPM with tremelimumab: negative trial
- Complex TME in MPM
- Single agent activity of anti-PD-1 Ab does not correlate well with PD-L1 expression
- Phase 3 trials with immune checkpoint blockade are ongoing

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