Immunotherapy- What is in the Future?

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Disclosure

Advisory Board and Honorarium:

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Agenda

- Review of novel immunotherapy targets in mesothelioma
  - Mesothelin
  - Tumour associated macrophages, myeloid derived suppressor cells and Treg
  - Immune checkpoint including PD(L)1.

Mesothelin

- Mesothelin is 40 KDa glycoprotein expressed in
  - Mesothelioma
  - Adenocarcinoma of the lung
  - Pancreatic cancer
  - Ovarian cancer
  - Gastric cancer.
    - Limited expression in normal cells, including pleura, peritoneum and pericardium
    - Of unknown biological function
    - A 32KDa cleavage NH2-terminal of unknown function.

Hassan R et al. Clin Cancer Res 2004;10:3937-3942.

Mesothelin

- Soluble mesothelin is a 41-45 KDa with NH2-terminal amino acid sequence identical to that of the membrane-bound portion of mesothelin.

Table 2. Studies assessing treatment response or survival using serial serum SM during treatment

Author (year)	Treatment (no. of patients)	Outcome measure	Threshold for SM change	Results
Hooper *et al* (2015)	P/C – 58, BSC – 15	Mod RECIST CT OS, TTP	0%	Chemotherapy group; a falling serum SM at 6–8 weeks was associated with longer time to progression ($P<0.001$), and a falling SM post chemotherapy was associated with improved OS ($P=0.031$)
Hassan *et al* (2014)	P/C and Im – 20	Mod RECIST CT	15%	Fall in serum SM correlated with radiological response with 70% accuracy ($P=0.003$)
Nowak *et al* (2013)	Bio – 53	Mod RECIST CT FDG-PET OS, TTP	0%	Median change in serum SM correlated with sum change in tumour bulk on FDG-PET ($P<0.05$). % change in serum SM was associated with TTP ($P<0.001$) but not OS
Franko *et al* (2012)	G/C – 56, P/C – 8, BSC – 4, Surg – 10	Mod RECIST CT	n/a	Significantly lower mean serum SM in partial response or stable disease compared to progressive disease ($P=0.001$)
Hollevoet *et al* (2011)	P/C – 57, Surg – 5	Mod RECIST CT	15%	Partial response to chemotherapy correlated with a 34% fall in SM ($P=0.010$) compared with a 54% rise in progressive disease ($P<0.001$)
Creaney *et al* (2011)	Chemo – 61, BSC – 25, Surg – 8	Mod RECIST CT FDG-PET OS	25%	Chemotherapy group; correlation between change in serum SM and CT ($P=0.023$) and FDG-PET ($P<0.001$) Also, a falling SM was associated with better OS (19 months) compared with static (13 months) or rising levels (15 months). ($P=0.001$)
Wheatley-Price *et al* (2010)	Chemo – 21, BSC – 13, Surg – 8	Mod RECIST CT RECIST CT CT report	10% or 5 nmol l^{-1}	Chemotherapy and BSC groups; relative change in serum SM from baseline significantly associated with disease progression ($P<0.010$)
Grigoriu *et al* (2009)	Chemo – 20, Im – 16, BSC – 4	Mod RECIST CT	10%	In patients with raised SM at baseline (>1 nM l^{-1}), rising level correlated with progressive disease in 12 out of 16 patients. OS higher in patients with stable SM compared with increasing ($P=0.012$)

Abbreviations: Bio = biological therapy; BSC = best supportive care; C = cisplatin; Chemo = chemotherapy (not specified); G = gemcitabine; Im = immunotherapy; Mod RECIST CT = modified response evaluation criteria in solid tumors CT; OS = overall survival; P = pemetrexed; Surg = surgery; TTP = time to progression.

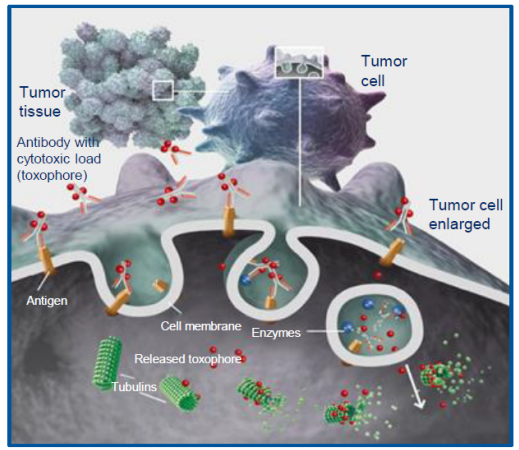
Arnold DT et al. Br J Cancer 2017;116:731-741.

Mesothelin- antibody drug conjugate

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 → DENVER, COLORADO, USA

Anetumab ravtansine (BAY 94-9343): an anti-mesothelin antibody-drug conjugate



- Mesothelin is a membrane-associated differentiation antigen that is overexpressed in a number of solid tumors, including the vast majority of mesotheliomas[1,2]
- Anetumab ravtansine (BAY 94-9343) is a novel, fully humanized anti-mesothelin immunoglobulin G1 antibody conjugated to a ravtansine, a maytansine-derivative DM4 anti-tubulin cytotoxic agent

Mode of action:

- Targeted delivery of the potent anti-proliferative toxophore DM4 (tubulin inhibitor) to cancer cells expressing the tumor-associated antigen mesothelin

Here we report results from a Phase I open-label study of anetumab ravtansine in patients with advanced solid tumors, with a particular focus on patients with mesothelioma

PK, pharmacokinetics

1. Hassan et al. *Clin Cancer Res* 2004; 10: 3937-3942; 2. Hassan, Ho. *Eur J Cancer* 2008; 44: 46-53

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October 15–18, 2017 | Yokohama, Japan
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Randomized Phase II Study of Anetumab Ravtansine or Vinorelbine in Patients with Malignant Pleural Mesothelioma

HL Kindler,[1] S Novello,[2] D Fennell,[3] G Blumenschein, Jr.,[4] A Bearz,[5] GL Ceresoli,[6] JG Aerts,[7] J Spicer,[8] P Taylor,[9] A Greystoke,[10] K Nackaerts,[11] L Calabrò,[12] S Burgers,[13] R Jennens,[14] AF Sporchia,[15] A Walter,[16] J Siegel,[17] BH Childs,[17] C Elbi,[17] R Hassan[18]

[1]University of Chicago, Chicago, IL, USA; [2]University of Turin, San Luigi Hospital, Orbassano, Italy; [3]University of Leicester and Leicester University Hospitals, Leicester, UK; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]IRCCS Centro di Riferimento Oncologico – CRO, Pordenone, Italy; [6]Cliniche Humanitas Gavazzeni, Bergamo, Italy; [7]Erasmus Medisch Centrum, Rotterdam, Netherlands; [8]King's College London, Guy's Hospital, London, UK; [9]University Hospital of South Manchester, Manchester, UK; [10]Freeman Hospital, Newcastle Upon Tyne, UK; [11]KU Leuven, University Hospitals, Leuven, Belgium; [12] University Hospital of Siena, Siena, Italy; [13]Nederlands Kanker Instituut, Amsterdam, Netherlands; [14]Epworth Healthcare, Richmond, Victoria, Australia; [15]Bayer, Milan, Italy; [16]Bayer AG, Berlin, Germany; [17]Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA; [18]National Cancer Institute, Bethesda, MD, USA.

IASLC 2017

Trial Design

Patient selection criteria

- Unresectable/ metastatic MPM
- One prior line of chemotherapy
- Mesothelin-overexpression (≥30% of cells medium and strong) by central lab
- ECOG PS 0–1
- Age ≥18 years
- No/mild corneal epitheliopathy

N=248

RANDOMIZATION

2:1

Anetumab ravtansine 6.5 mg/kg Q3W (n=166)

Stratification factors:

- **Geographical region**
- **TTP on 1L therapy**

Vinorelbine 30 mg/m^2 QW (n=82)

Endpoints

Primary

- PFS (central review; HR 0.50, 90% power)

Secondary

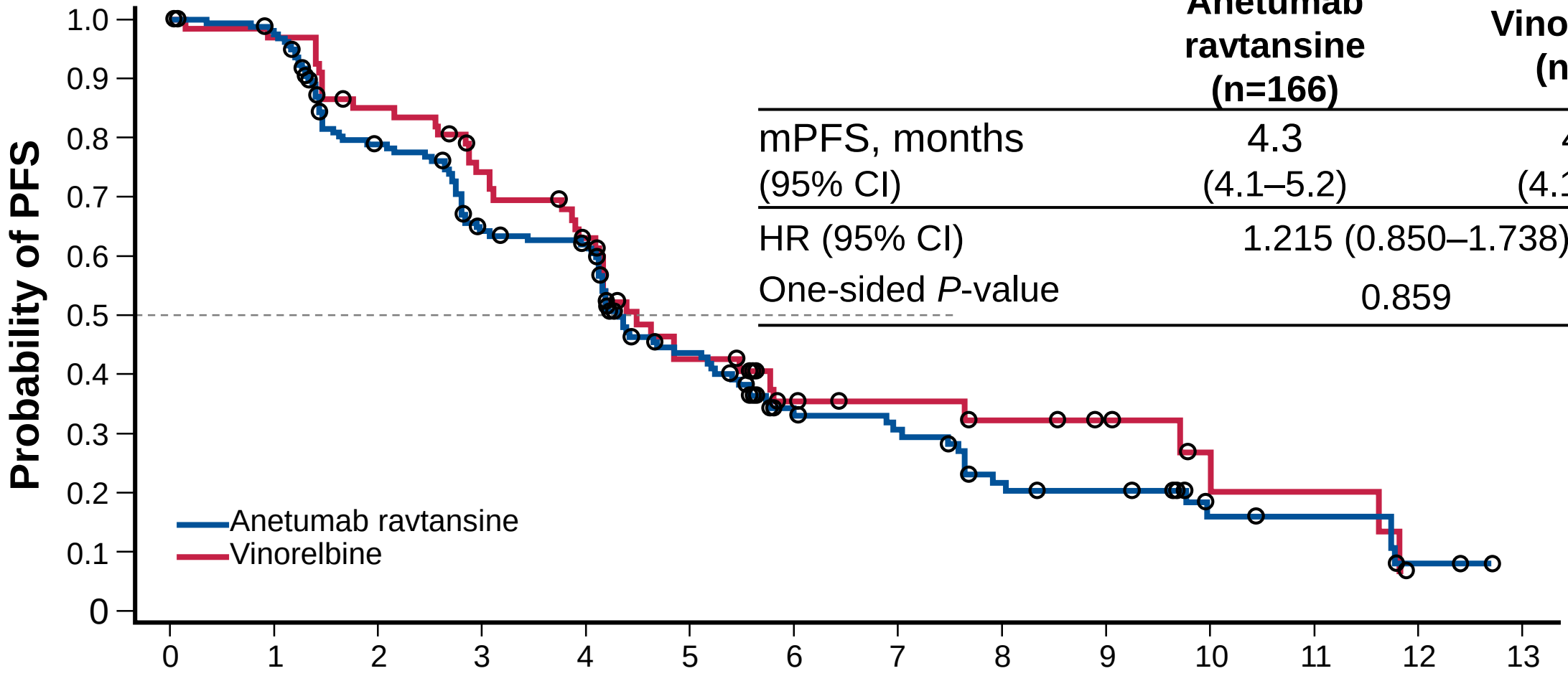
- OS
- Response (ORR, DCR, DOR)
- PROs
- Safety and tolerability

Other

- Pharmacokinetics
- Immunogenicity
- Biomarkers

1L, first line; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PROs, patient-reported outcomes; Q3W, once every 3 weeks; QW, once weekly; TTP, time to progression.

Primary Endpoint: PFS



	Anetumab ravtansine (n=166)	Vinorelbine (n=82)
mPFS, months (95% CI)	4.3 (4.1–5.2)	4.5 (4.1–5.8)
HR (95% CI)	1.215 (0.850–1.738)	
One-sided *P*-value	0.859	

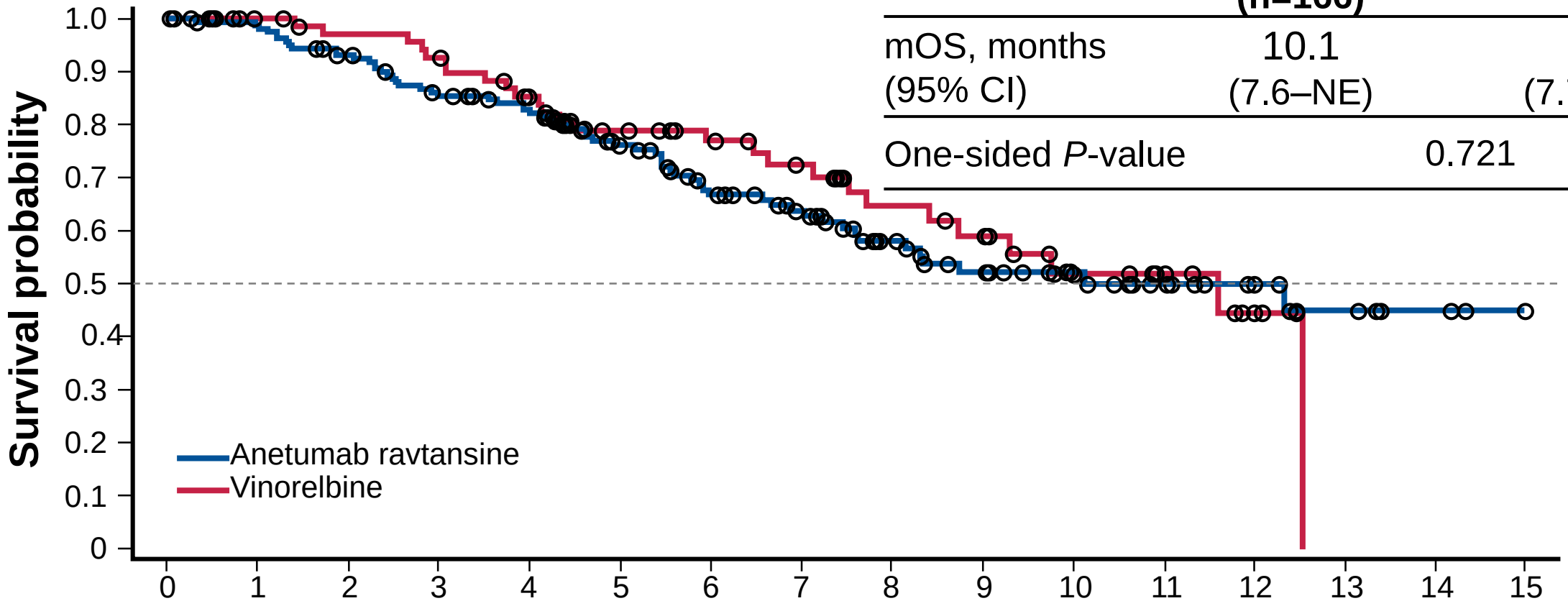
Number of patients at risk

AR	**166**	**152**	**114**	**89**	**83**	**49**	**28**	**25**	**16**	**14**	**7**	**6**	**2**	**0**
V	**82**	**65**	**56**	**47**	**37**	**22**	**13**	**11**	**9**	**7**	**3**	**3**	**0**	**0**

AR, anetumab ravtansine; CI, confidence interval; mPFS, median progression-free survival; V, vinorelbine.

OS – Interim Analysis*

	Anetumab ravtansine (n=166)	Vinorelbine (n=82)
mOS, months (95% CI)	10.1 (7.6–NE)	11.6 (7.7–12.5)
One-sided *P*-value	0.721	



Number of subjects at risk

AR	**166**	**160**	**147**	**132**	**124**	**95**	**74**	**61**	**44**	**33**	**23**	**17**	**11**	**6**	**3**	**0**
V	**82**	**71**	**67**	**64**	**55**	**45**	**38**	**31**	**24**	**20**	**12**	**9**	**3**	**0**	**0**	**0**

mOS, median overall survival; NE, not estimable.

*87 of 159 target events for OS analysis had occurred at the time of primary PFS analysis.

Response

Best overall response, n (%)	Anetumab ravtansine (n=166)	Vinorelbine (n=82)
Complete response	0 (0)	0 (0)
Partial response	14 (8)	5 (6)
Stable disease	108 (65)	51 (62)
Progressive disease	24 (14)	9 (11)
Not available	20 (12)	17 (21)
Overall response rate	14 (8)	5 (6)
Disease control rate	122 (73)	56 (68)

ORR = CR + PR; DCR = CR + PR + SD.
CR, complete response; PR, partial response; SD, stable disease.

Most Frequent Treatment-Emergent Adverse Events

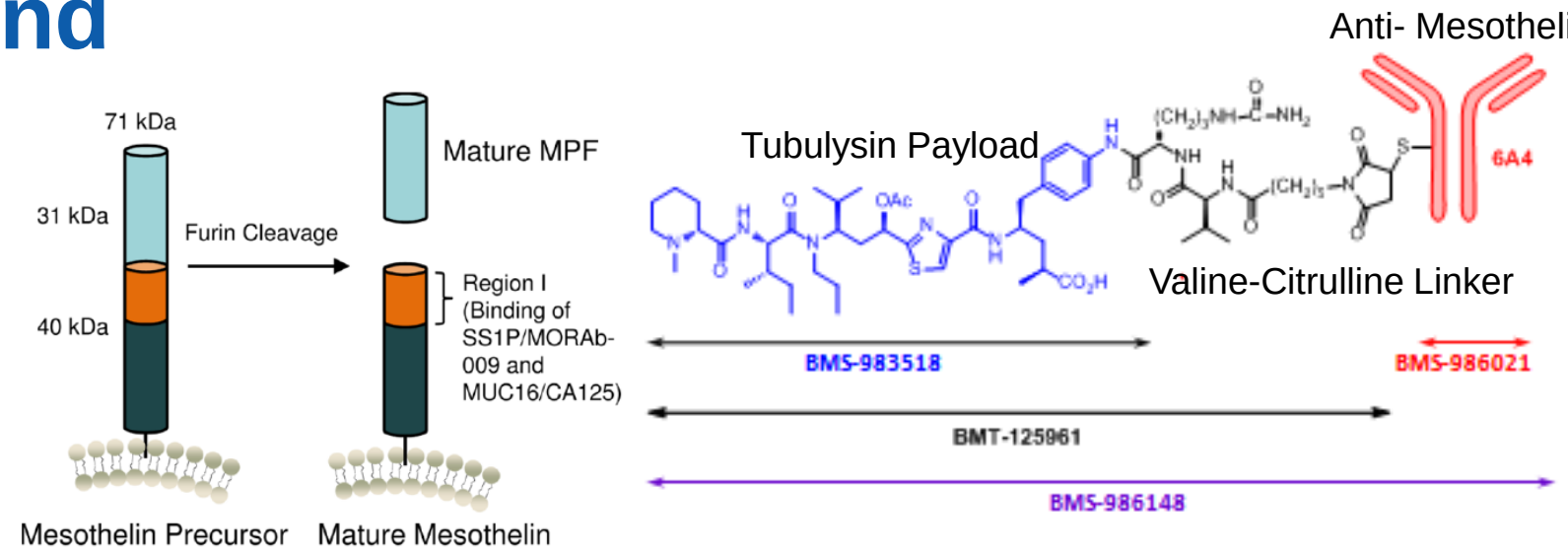
TEAE, %	Anetumab ravtansine (n=163)		Vinorelbine (n=72)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Nausea	41.1	0	31.9	0
Corneal epitheliopathy	39.3	1.8	0	0
Fatigue	35.0	4.3	30.6	5.6
Decreased appetite	34.4	1.8	23.6	2.8
Diarrhea	33.1	2.5	18.1	1.4
Vomiting	20.9	0	6.9	0
Asthenia	20.2	4.3	22.2	1.4
Dyspnea	19.6	4.3	29.2	4.2
Chest pain	17.2	2.5	15.3	1.4
Constipation	16.0	0.6	48.6	1.4
Peripheral neuropathy	15.3	3.7	6.9	0
Fever	14.1	0.6	18.1	1.4
Anemia	9.2	1.8	27.8	6.9
Neutropenia	2.5	0.6	51.4	38.9

≥15% in either cohort. Three patients in the anetumab ravtansine group and 10 patients in the vinorelbine group did not receive study drug and were not included in the safety population.

BMS-986148, an Anti-Mesothelin Antibody-Drug Conjugate (ADC), Alone or in Combination with Nivolumab Demonstrates Clinical Activity in Patients with Select Advanced Solid Tumors

Lolkema et al. ACR-NCI-EORTC meeting 2019:B057.

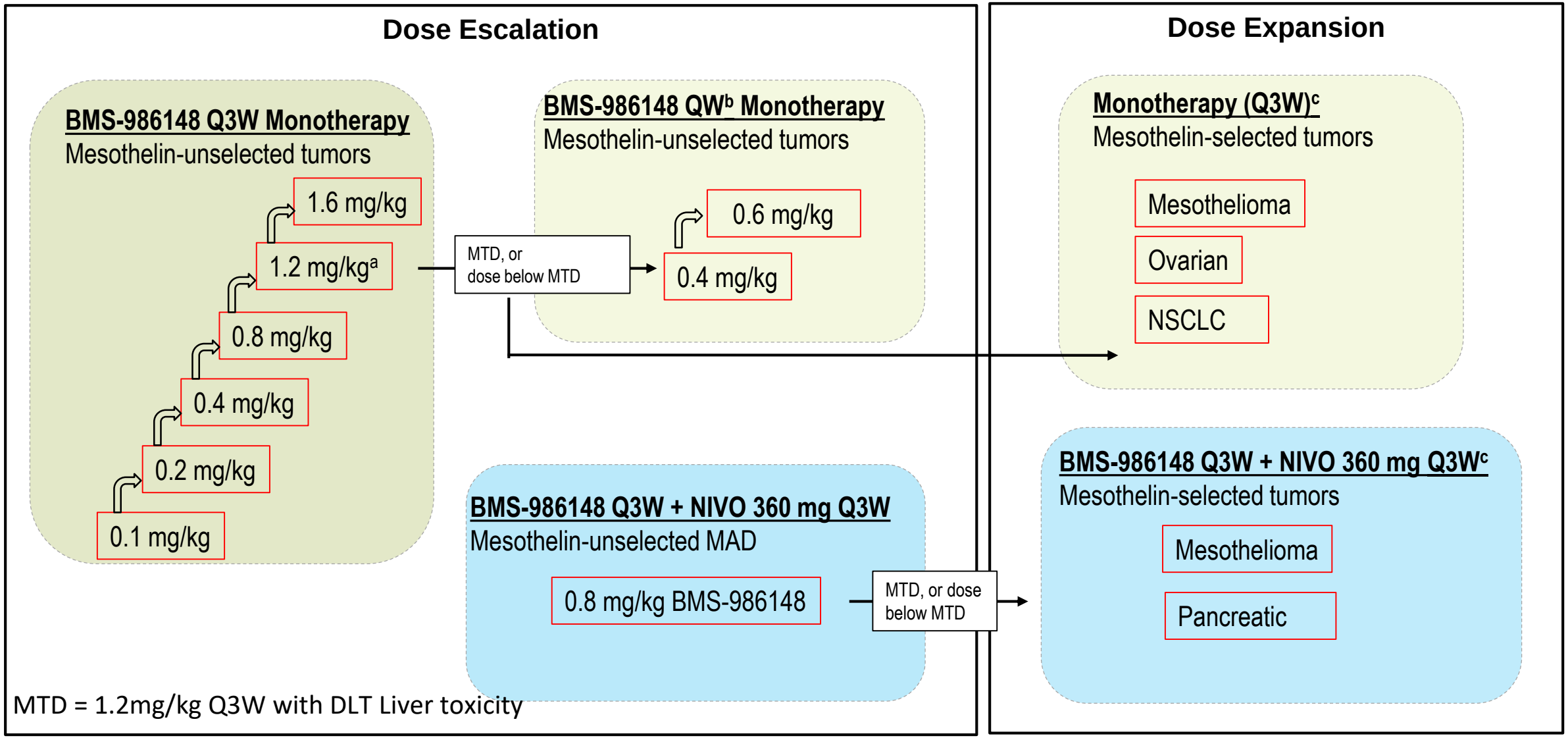
Background



- Traditional cancer chemotherapy is often accompanied by systemic toxicity to the patient
  - Antibody–drug conjugates (ADCs) use antibodies to deliver a potent cytotoxic compound selective to tumor cells, thus improving the therapeutic index of chemotherapeutic agents[5]
- BMS-986148 is a fully human IgG1 anti-mesothelin monoclonal ab conjugated to tubulysin to promote selective cytotoxic delivery to tumor cells
  - Tubulysins disrupt microtubule assembly, leading to impaired cell division and subsequent apoptosis[6]
  - In preclinical models, combination of anti–mesothelin-tubulysin with anti–PD-1 promoted a synergistic antitumor response and influx of tumor-infiltrating lymphocytes[7]
- Here, we present initial data for BMS-986148 ± nivolumab (NIVO; anti–PD-1) from a phase 1/2a trial in a biomarker-defined population of patients (pts) with select advanced solid tumors (NCT02341625)[8]

5. Hedrich WD, et al. *Clin Pharmacokinet*. 2018;57(6):687-703. 6. Khalil MW, et al. *Chembiochem*. 2006;7(4):678-83. 7. Data on file. Bristol-Myers Squibb Company. 8. NCT2341625 Available at https://clinicaltrials.gov/ct2/show/NCT02341625.

Study Design



[a]Intermediate dose; [b]QW for 3 weeks followed by 1 week off; [c]Cohorts clinically evaluated.

Best Overall Response

	Monotherapy				Combination	
	All Escalation (n = 45)	All Expansion (n = 51)	Meso Expansion (n = 25)	Ovarian Expansion (n = 22)	All (n = 30)[a]	Meso (n = 13)[b]
ORR, n (%) [95% CI]	1 (2)[c] [NA]	3 (6)[d] [1, 16]	1 (4) [0, 20]	2 (9) [1, 29]	6 (20) [NA]	3 (23)[e] [5, 54]
Best overall response, n (%)						
CR	0	0	0	0	0	0
PR	1 (2)	3 (6)	1 (4)	2 (9)	6 (20)	3 (23)
SD	12 (27)	24 (47)	12 (48)	11 (50)	13 (43)	8 (61.5)
PD	27 (60)	16 (31)	8 (32)	6 (27)	6 (20)	1 (8)
Not evaluable	0	0	0	0	0 (0)	0
Not reported	5 (11)	8 (16)	4 (16)	3 (14)	5 (17)	1 (8)
DCR, n (%)	13 (29)	27 (53)	13 (52)	13 (59)	19 (63)	11 (85)
PFS, median, mo [95%CI]	NA	3 [2, 4]	4 [1, 9]	3 [1, 4]	NA	7 [3, 12]

CR, complete response; DCR, disease control rate; NA, not available; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]Includes patients from dose escalation and expansion groups. [b]Includes only patients from expansion group. An additional n=3 mesolthelioma patients were treated in escalation, with n=2 reporting a confirmed partial response lasting 9.69 and 10.41 months, respectively. [c]N=1 with mesothelioma assigned to 0.8 mg/kg Q3W had a confirmed partial response lasting 10.22 months. [d]ORR was 0% for NSCLC. [e]Mean ORR was 31% with combo in escalation and expansion cohorts with mesothelioma (n= 16).

Treatment-Related Adverse Events

	Mono Q3W[a] (n = 84)		Mono QW[a,b] (n = 12)		Combo Q3W (n = 30)	
	Any Gr	Gr 3-4	Any Gr	Gr 3-4	Any Gr	Gr 3-4
Any TRAE, n (%)	72 (86)	42 (50)	11 (92)	3 (25)	27 (90)	10 (33)
TRAEs in ≥ 10% of all pts, n (%)						
AST increased	41 (49)	20 (24)	4 (33)	1 (8)	9 (30)	1 (3)
ALT increased	39 (46)	17 (20)	5 (42)	2 (17)	8 (27)	1 (3)
Fatigue	34 (40)	6 (7)	5 (42)	0	8 (27)	0
Nausea	27 (32)	0	2 (17)	0	7 (23)	0
Decreased appetite	22 (26)	1 (1)	2 (17)	0	4 (13)	0
Blood alkaline phosphatase increased	20 (24)	5 (6)	1 (8)	0	2 (7)	0
Diarrhea	14 (17)	2 (2)	2 (17)	0	2 (7)	0
Vomiting	15 (18)	0	0	0	2 (7)	0
Abdominal pain	11 (13)	1 (1)	2 (17)	0	2 (7)	0
Pleuritic pain	9 (11)	2 (4)	2 (17)	1 (8)	3 (10)	1 (3)
Dyspnea	10 (12)	2 (2)	2 (17)	0	0	0
Dysgeusia	6 (7)	0	3 (25)	0	3 (10)	0
TRAEs leading to treatment discontinuation, n (%)	15 (18)	11 (13)	0	0	4 (13)	3 (10)

- Serious TRAEs were reported in 15 patients (18%) in the mono Q3W group, 2 patients (17%) in the mono QW group, and 7 patients (23%) in the combination group
- One treatment-related death occurred in the mono Q3W group (1.2 mg/kg Q3W; pneumonitis)
- The majority of ophthalmic AEs were mild and manageable with topical treatments when indicated:
  - One subject in the mono Q3W group (1.2 mg/kg Q3W) experienced Grade 3 keratopathy and Grade 3 reduced visual acuity
  - One subject in the mono Q3W group (1.2 mg/kg Q3W) experienced Grade 3 cataracts (left and right eyes)

[a]All dose-escalation levels combined; [b]QW for 3 weeks followed by 1 week off.

Mesothelin antibody drug conjugate

- Other agents in development:
  - LMB-100:
    - Mesothelin antibody with an immunotoxin.

Mesothelin CAR-T cell Therapy

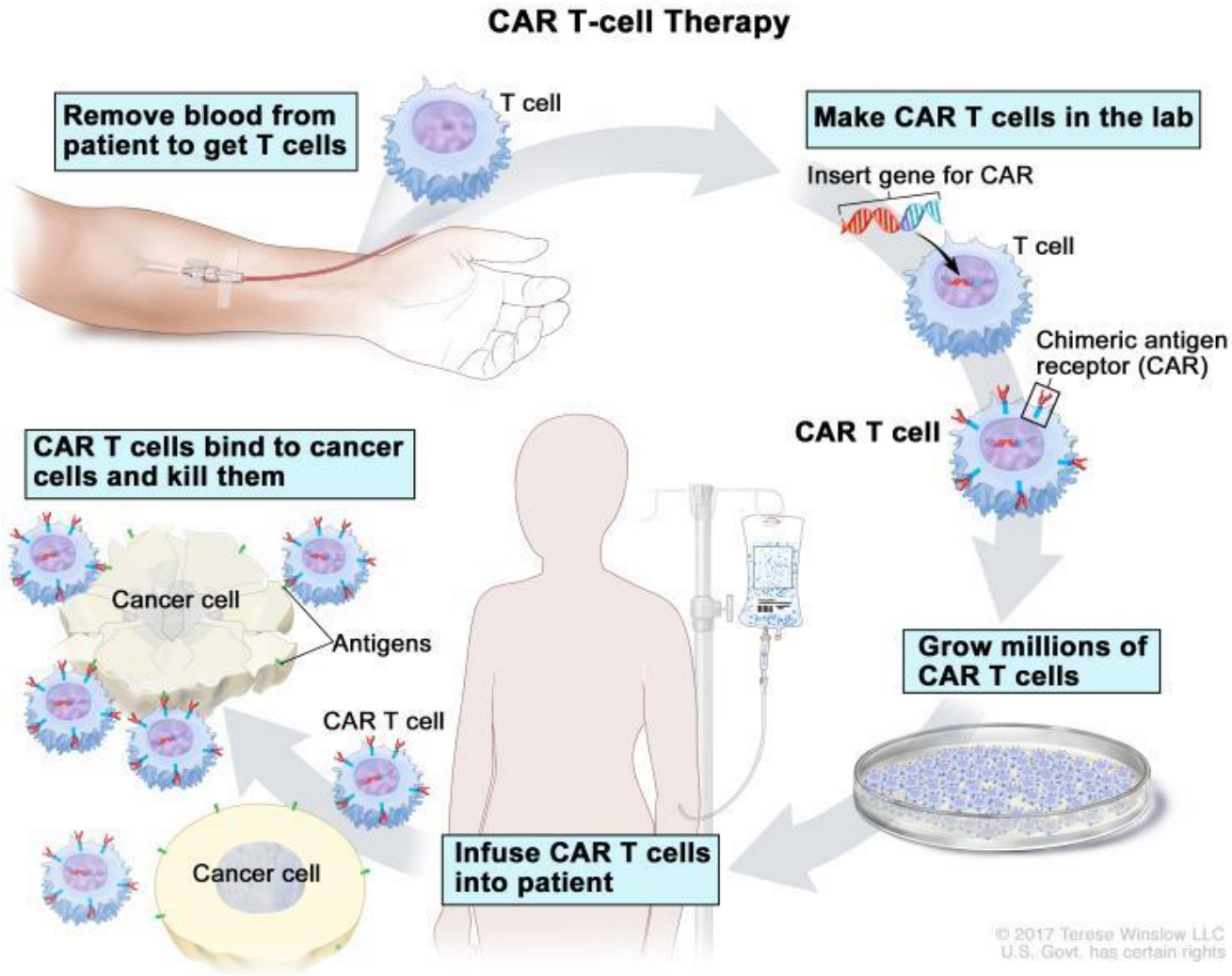


Image of courtesy of the National Cancer Institute

Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- T-regs, myeloid derived suppressor cells and tumour associated macrophages in the tumour stroma induce CD8 cells apoptosis and tolerance.
- TAMs can be divided into 2 groups:
  - M1 in the tumour islets:
    - Anti-tumour
    - Induces TH1 response.
  - M2 in the tumour stroma:
    - Promotes scavenging of debris
    - Promotes angiogenesis
    - Remodels and repairs.
    - High expression of
      - Cytokines: IL-10, CCL17, CCL22 and CCL2
      - MMP
      - CD206 (mannose receptor), CD163 (scavenger receptor), and galactose type receptor
    - Loss of antigen presentation function.

1. Lievense et al. Lung Cancer 2013;80:250-62.

Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- Ujiie et al. examined 8 infiltrating immune cells and 5 cytokines and receptors in tumours and stroma:
  - Univariate analysis found
    - High CD4 T cell and CD20 B-Cell are associated with good prognosis
    - High IL-17R on CD8 T cell is associated with poor prognosis.
  - Multivariate analysis found
    - CD20 (Mature B-cell) is associated with good prognosis
    - High CD163 (M2) is associated with poor prognosis.
  - TAMs lead to increase IL10 and B7-H3 expression on tumour cells which inhibit T-cell immune response.[1, 2]

1. Ujiie et al. Oncoimmunology 2015;19:e1009285
2. Chen et al. Exp Cell Res 2013;319:96-102.

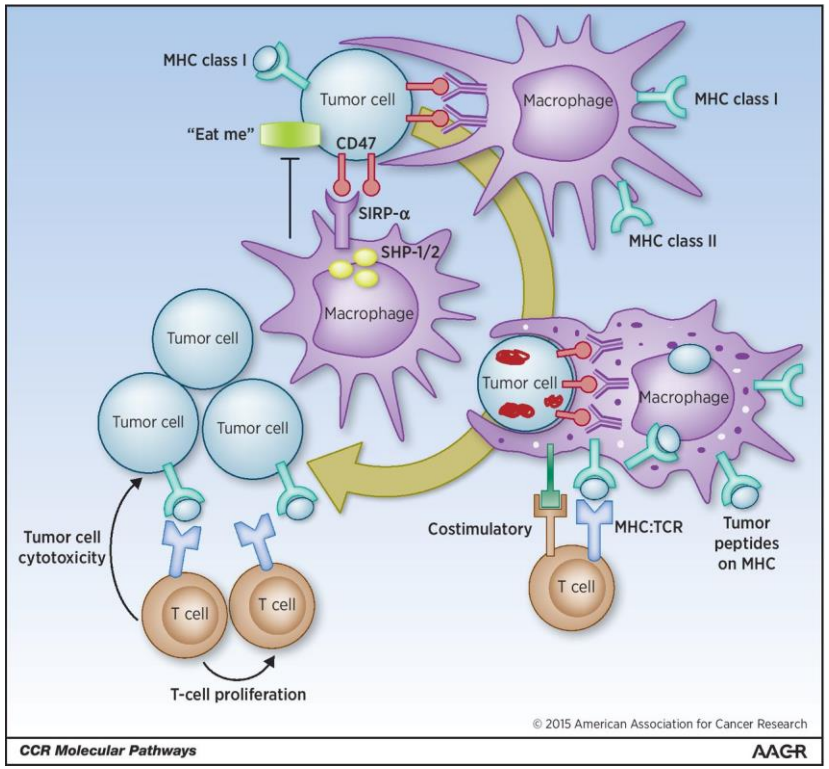
Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- In hypoxic environment, M1 is converted to M2, leading to angiogenesis and lymphogenesis via VEGF and MMP-9 overexpression.
- Mesothelioma cells secrete prostaglandin E2 which activates macrophages to M2 and, in turn, leads to differentiation of T-cell to T-reg and decrease in CD8 cells proliferation.[1, 2, 3]

1. Lievense et al. JTO 2016;11:1755-64
2. Izzi et al. Cancer Lett 2012;322:18-34
3. Izzi et al. Int J Oncol 2009;34:543-50

Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- CD47 or SIRP-alpha:



- Inhibition of CD47 or SIPR-alpha leads to activation of M1, and anti-tumour activity.[1]

McCracken MN et al. Clin cancer Res 2015;3597-3601.

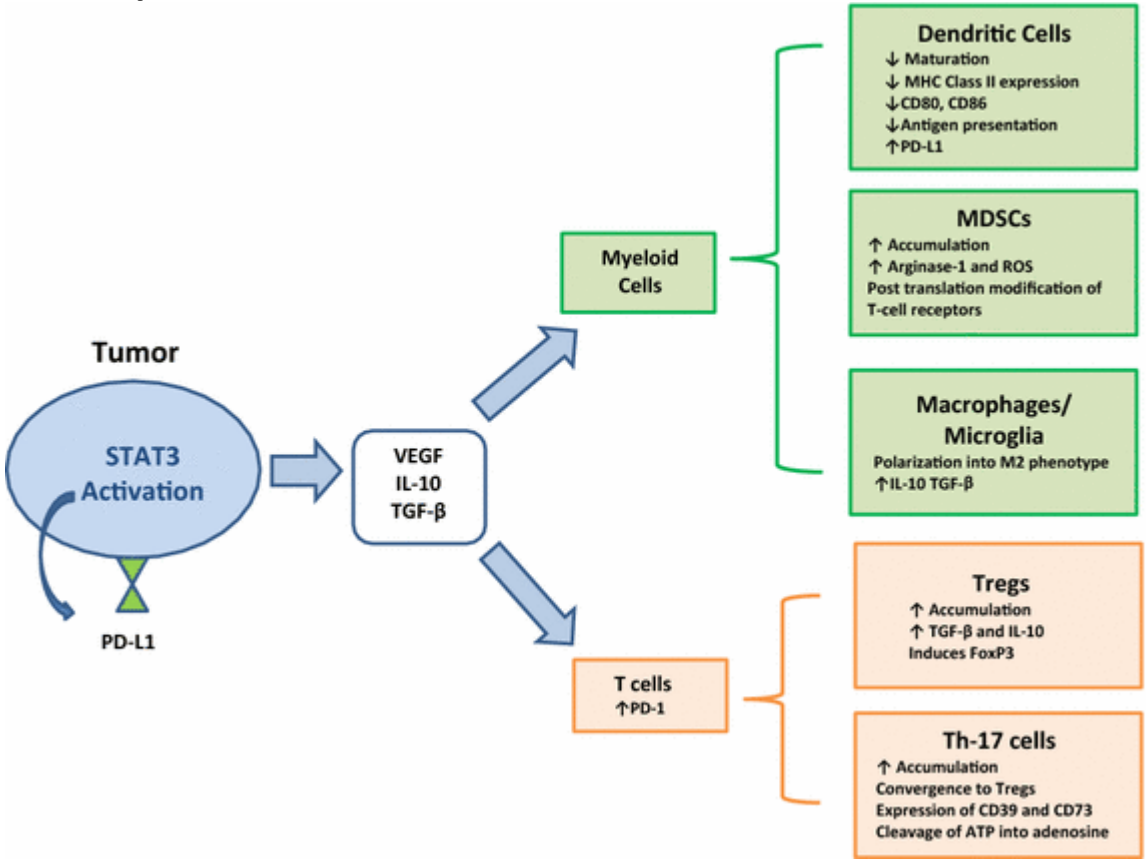
Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- CSF-1:
  - Responsible for recruitment of TAMs and MDSC
  - Inhibition of CSF-1 leads to reprogramming of TAMs and thus anti-tumour inflammatory response and CD8 activation.[1]

1. Hores et al. J Exp Med 2018;215:859-76.

Tumour Associated Macrophages and Myeloid Derived Suppressor Cells

- IL6/IL6-R and STAT3



- Responsible for MDSC proliferation, increase in Treg, decrease in CD8 cells and maturation of dendritic cell.[1]
- Increase in PDL-1 expression on tumour cells and Treg
- Increase in IDO1 and thus kynurenine and other immunosuppressive secretory factors: Arginine and adenosine[1,2,3]
- Associated with increase phosphoesterase 5 expression.[4]

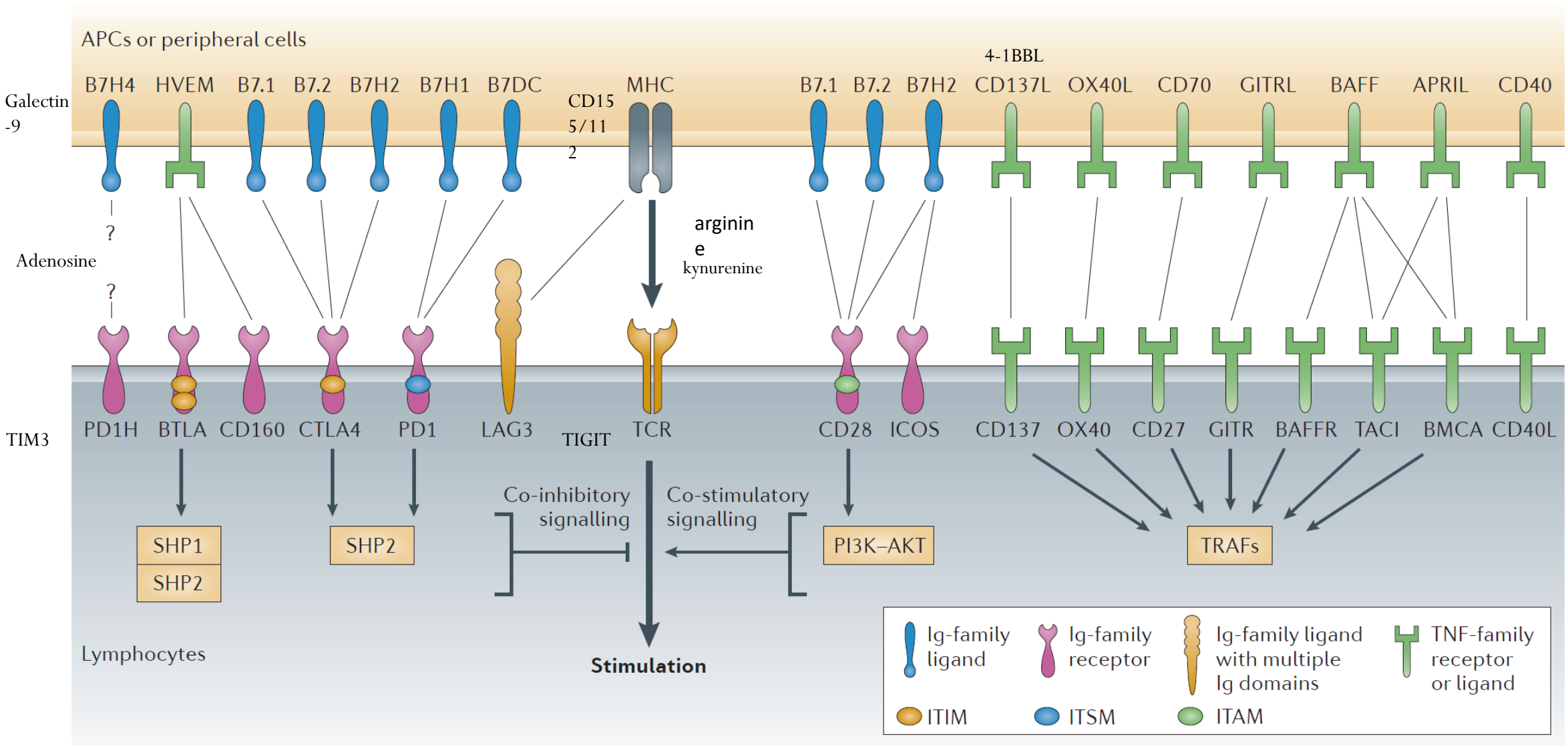
1. Caetano et al. Cancer Res 2016;76:3189-99.
2. Chen MF et al. Oncotarget 2014;5:8716-28.
3. Yu et al. K Immunol 2014;193:2574-86.
4. Isiam BN et al. Cancer Prev Res 2017;10:377-388
5. Ferguson J Neuro-Oncol 2015; 123:381-394.

Tumour Associated Macrophages and Myeloid Derived Suppressor Cells-

- CCR5:
  - Increase in CCR5 expression on MDSC by upregulation of CCR5 ligands, IL6, GM-CSF and other inflammatory factors and increase infiltration of MDSC.[1]
  - Important for Treg differentiation and its migration to inflammatory sites[2]
  - Increase resistance to DNA damaging agents and thus increase in metastases and stemness of cancer cells. [2]

1. Umansky et al. Cancer Immunol Immunother 2017;60:1015-23
2. Jiao X et al. Cancer Res 2019;79:4801-7.

Immune Checkpoints



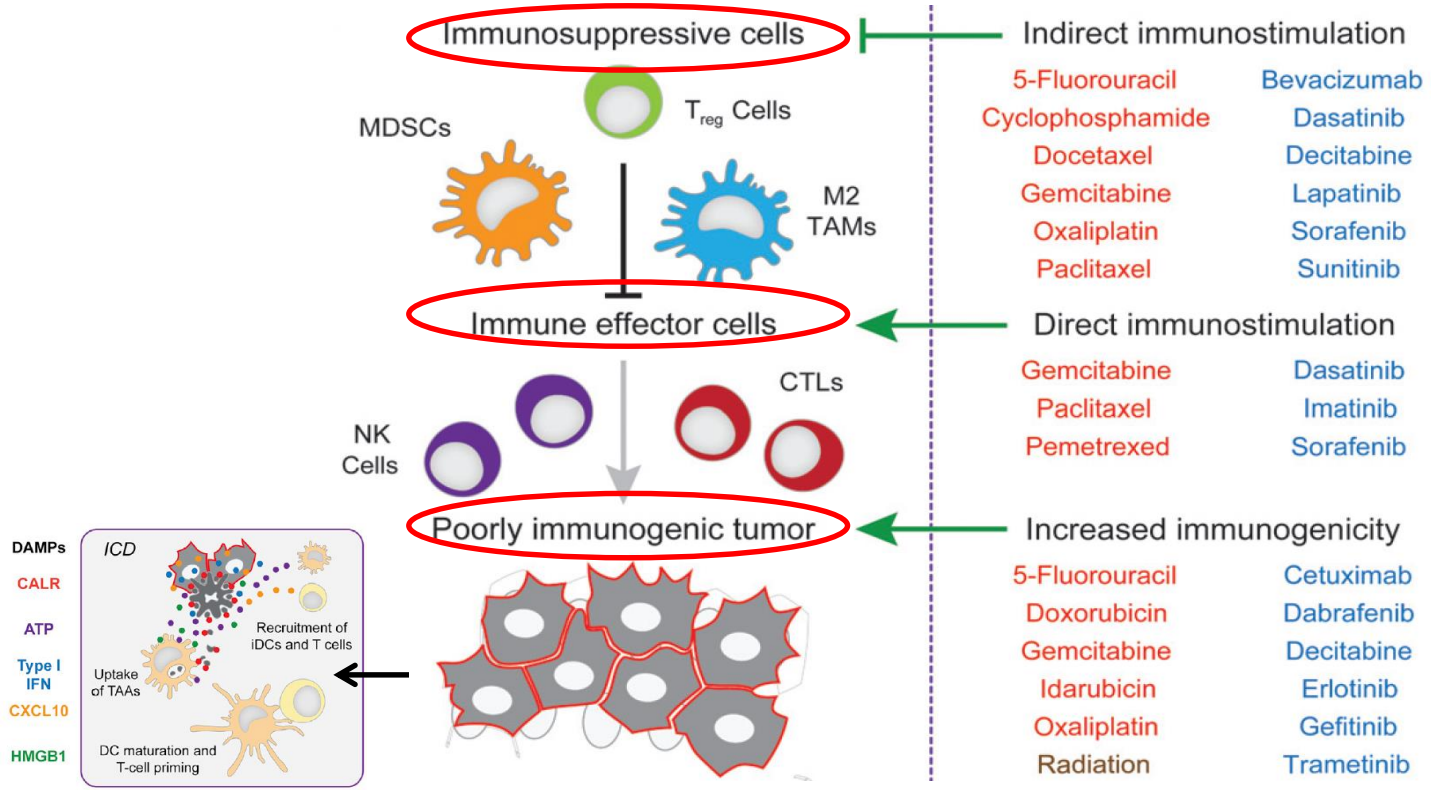
Mayes Nat Rev Drug Discov 2018;17:130-145

PD1/PDL-1 and Chemotherapy

Chemotherapy can promote tumor immunity in two major ways

1. Inducing immunogenic cell death as part of its intended therapeutic effect

2. Disrupting strategies that tumors use to evade the immune response



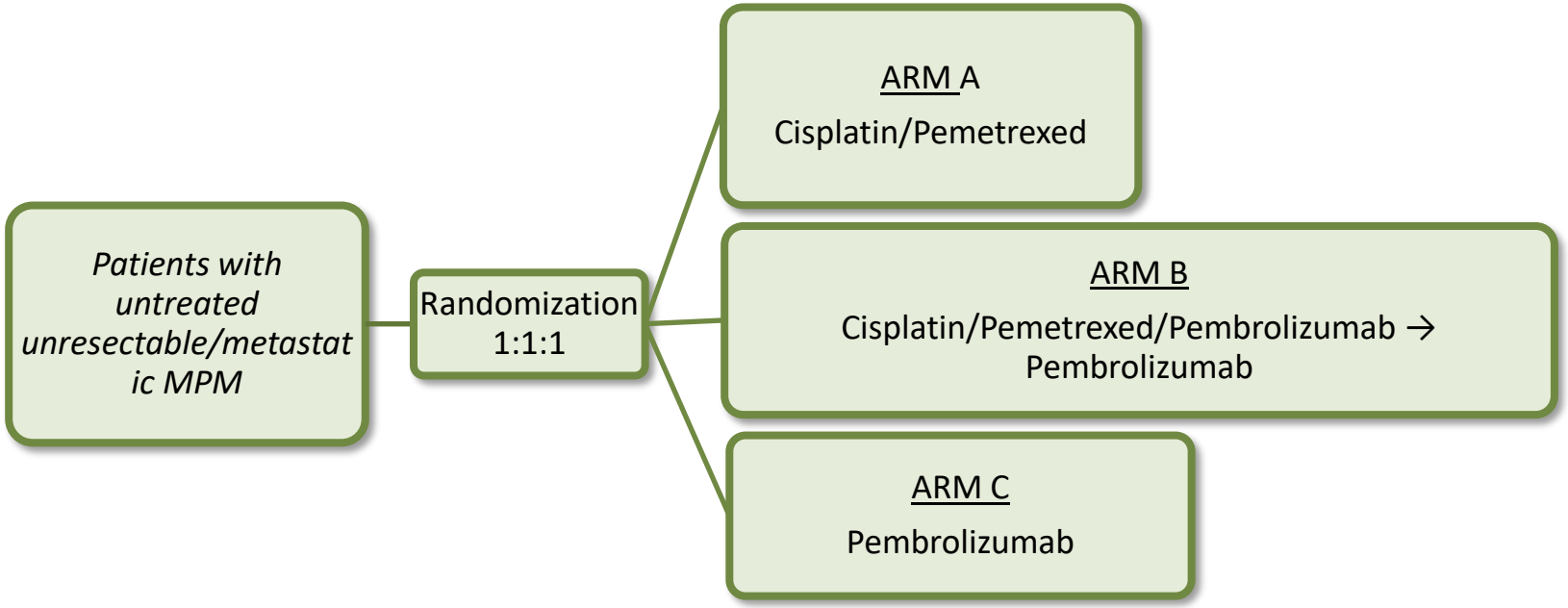
TL, CD8 cytotoxic T lymphocyte; MDSC, myeloid-derived suppressor cell; NK, natural killer; TAM, tumor-associated macrophage

Lorenzo Galluzzi et al, cancer Immuno Res 2016

IND 227 Trial Schema

- This is an academic open-label, multicentre, phase II randomized study in patients with malignant pleural mesothelioma (MPM) receiving first-line treatment for incurable advanced or metastatic disease.

- Patients will be stratified by histological subtype (epithelioid vs. other histology). PD-L1 tumour status will be used retrospectively at the time of clinical outcome analysis.



Canadian Cancer Trials Group

Phase 3

Primary Objective

- To evaluate whether pembrolizumab improves overall survival when added to standard chemotherapy in malignant pleural mesothelioma compared to standard chemotherapy.

Secondary Objectives

- To evaluate the tolerability of pembrolizumab, alone and given to patients receiving standard chemotherapy.
- To assess antitumour activity of pembrolizumab given to patients receiving standard chemotherapy.
- To evaluate whether pembrolizumab improves progression-free survival when added to standard chemotherapy.
- To evaluate the quality of life impact of pembrolizumab given to patients receiving chemotherapy.
- To explore predictive and prognostic value of PDL-1 expression and presence of T-cells subsets within the tumour microenvironment.
- To explore health economics when adding pembrolizumab to standard chemotherapy.

Exploratory Objective

- To explore predictive and prognostic value of exploratory blood based biomarkers.
- To explore predictive and prognostic value of other immune cells in tumour microenvironment.

First IND International Phase 2/3 Trial

ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale

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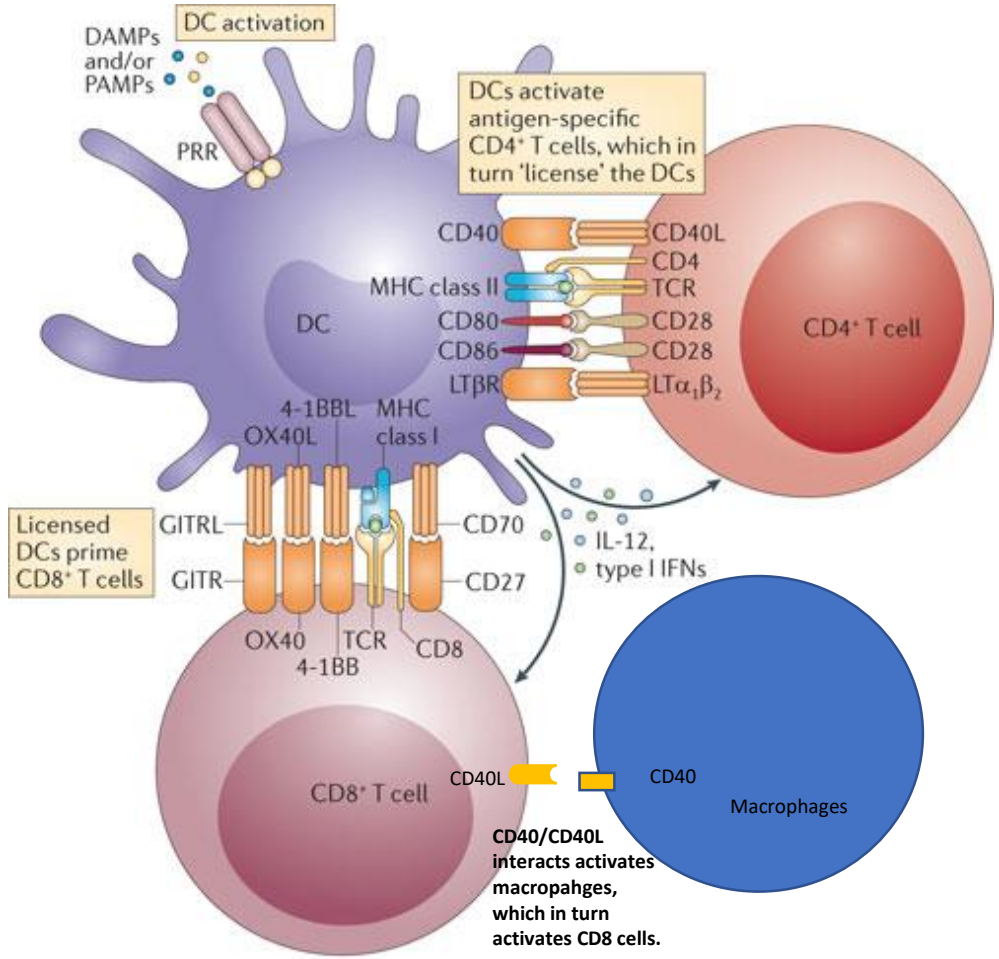
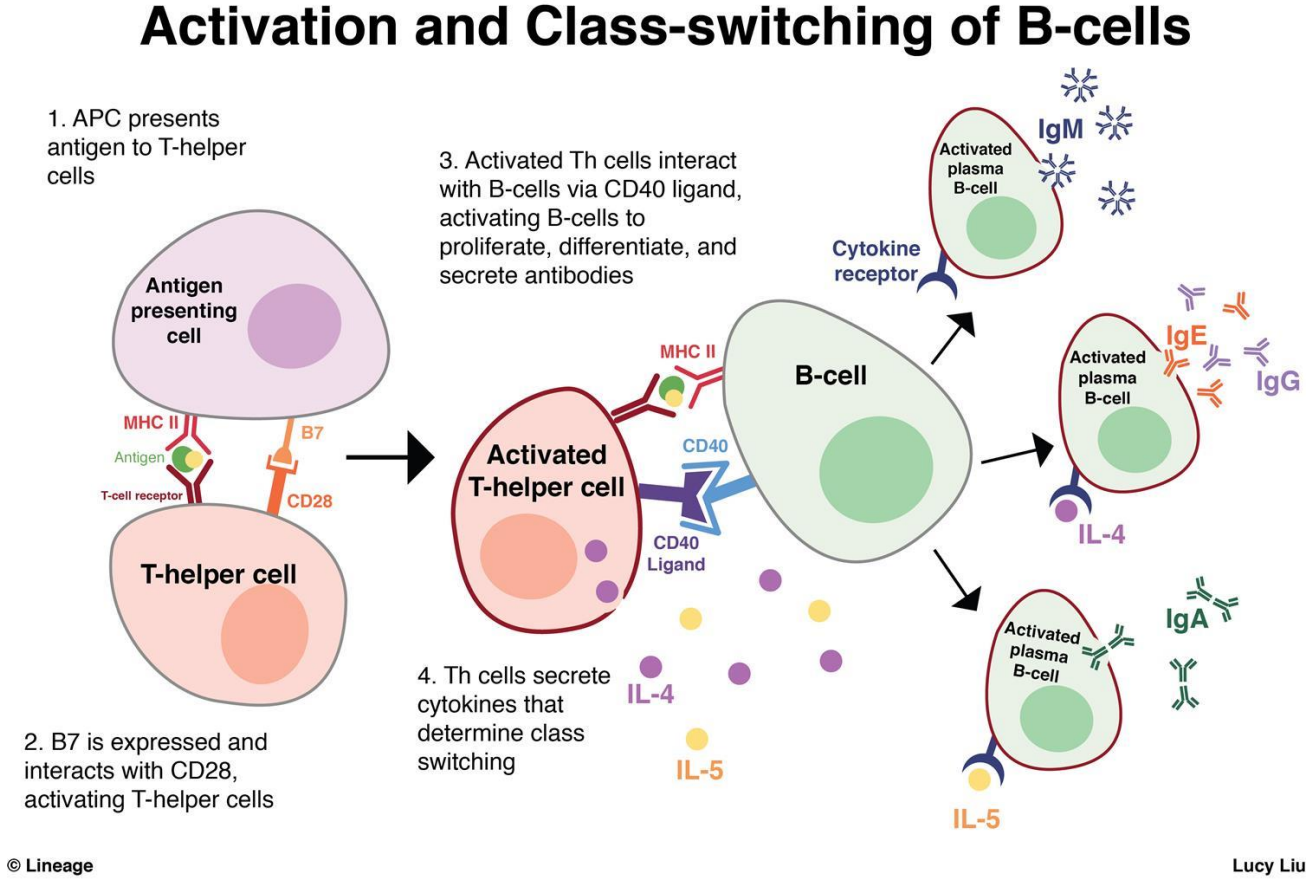
CD40





1. DeLuca LS et al. Nat Rev Immunol. 2012;12:339-351
2. Hores et al. J Exp Med 2018;215:859-76
3. Jackaman C et al. Immunol Cell Biol 2011;89:255-67.
4. Jackaman et al. Int Immunol 2012; 245:357-68.

Immune Checkpoints

- Salaroglio et al. demonstrated increase in
  - Treg and MDSC (granulocyte or macrophage derived) which is a negative predictor for PFS and OS
  - Increase in LAG3 and TIM3 expression on CD8 cells associated to negative OS.
  - MHC1 mutation in 59% of mesothelioma associated dendritic cells or antigen presenting cells.[1]
- B7-H3:
  - A member of B7 family, which interacts with CD28 family molecules such as PD1, CD28, CTLA4 and ICOS, as a co-inhibitory signal leading to immune suppression.[2]
  - Expressed on antigen presenting cells and mesothelioma cell lines
  - High expression in 54% of epithelioid subtype of mesothelioma and uncommon in sarcomaotid subtypes.[3]

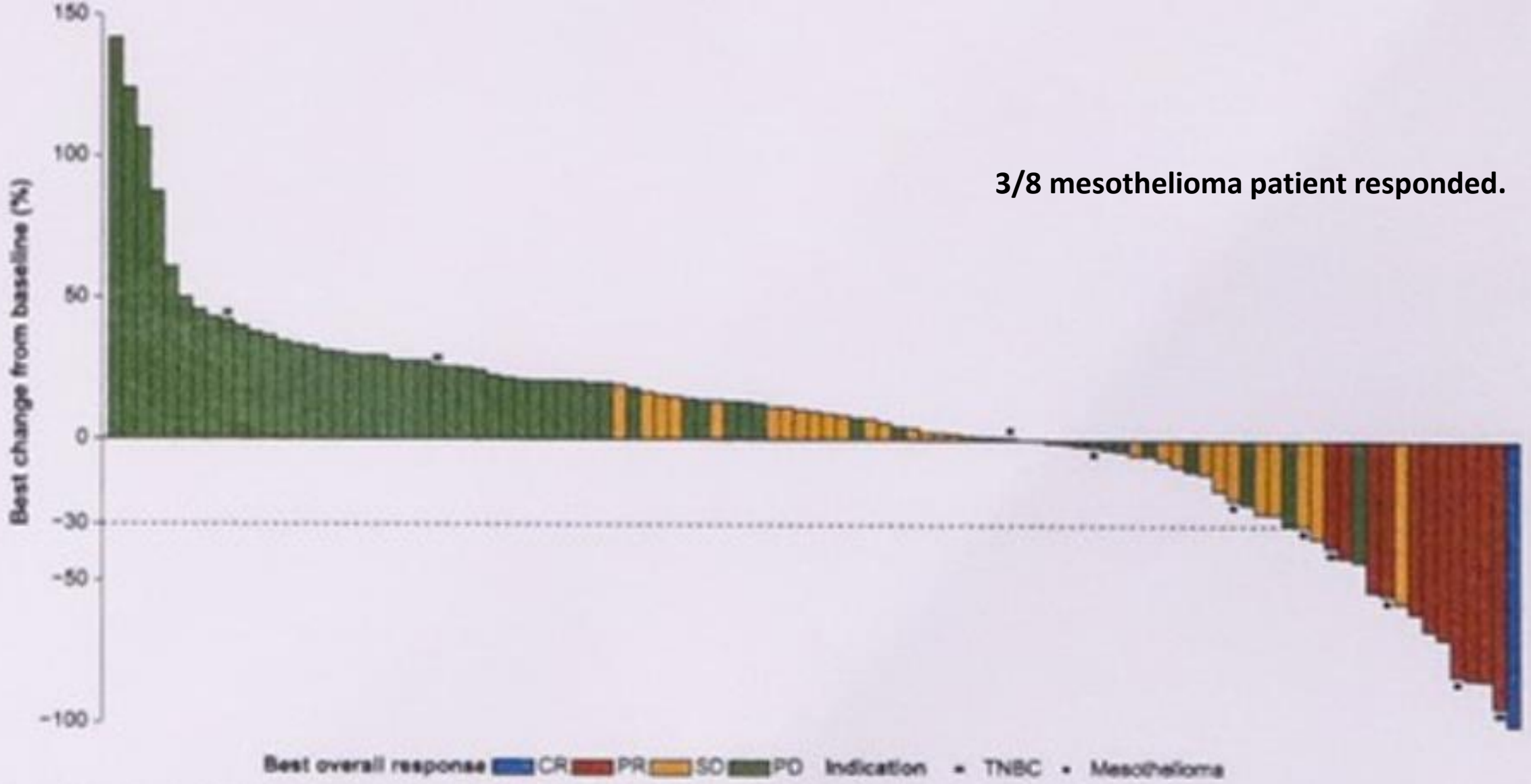
1. Salaroglio et al. JTO 2019;44:1458-71.
2. Castellanos JR et a;. Am J Clin Exp Immunol 2017;6:66-75.
3. Calabro L, et al. J Cell Physiol 2011;226:2595-600.

Study design

LAG525X2101C is an open-label, Phase I/II study of cohorts with single-agent LAG525 or the combination of LAG525 and spartalizumab (NCT02460224; **Figure 2**).

Figure 2. LAG525X2101C Study Design

Hing D et al. PASCO 2018:A3012.



3/8 mesothelioma patient responded.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.
[a]The additional PR reported in a patient with mesothelioma after the data cut-off is color coded as SD in this figure. N=10[a] evaluable. 20 patients (including 2 with mesothelioma and 1 with TNBC) were not evaluable due to postbaseline assessment not yet performed, discontinuation prior to first postbaseline assessment, or missing tumor measurements.

Immune Checkpoints

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TGF-Beta

- Exposure to chrysotile leads to activation of the MAPK/ERK pathway and thus p38, which in turn leads to increase in TGF-B1 expression and Treg infiltration and immune suppression.[1]
- Loss of NF2 or other component of the Hippo pathway is common in mesothelioma which leads to over-expression and activation of TGF-beta 1 receptor and thus mesothelioma formation.[2, 3]
- In part leads to infiltration of CD8+, CD4+ and FOXP3+/CD4+/CD25+ Treg into the tumour and thus immune suppression.[4]

1. Maeda M et al. Int J Oncol 2014;45:2522-32.
2. Cho JH et al. Mol cancer Ther 2018;17:2271-2284.
3. Fujii M et al. J Exp Med 2012;209:479-94.
4. Hegamns JP et al. Eur Resp J 2006;27:10866-95.

Conclusions

- With further understanding of the mutational and immune landscapes of mesothelioma:
  - Biology
  - Targets
  - Therapeutics.
- Mesothelioma may
  - A collection of different subtypes
  - Novel therapeutics should be moving forward based on biology and efficacy in preclinical models, particularly immune competent mouse models.
  - Novel clinical trial designs with international collaboration will be needed.

Thank you