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Early Phase 1 Clinical Trials

Aung Naing, MD

Lead, Immunotherapy Working Group

Dept. of Investigational Cancer Therapeutics

The University of Texas MD Anderson Cancer Center

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Disclosure

The following relationships exist related to this presentation:

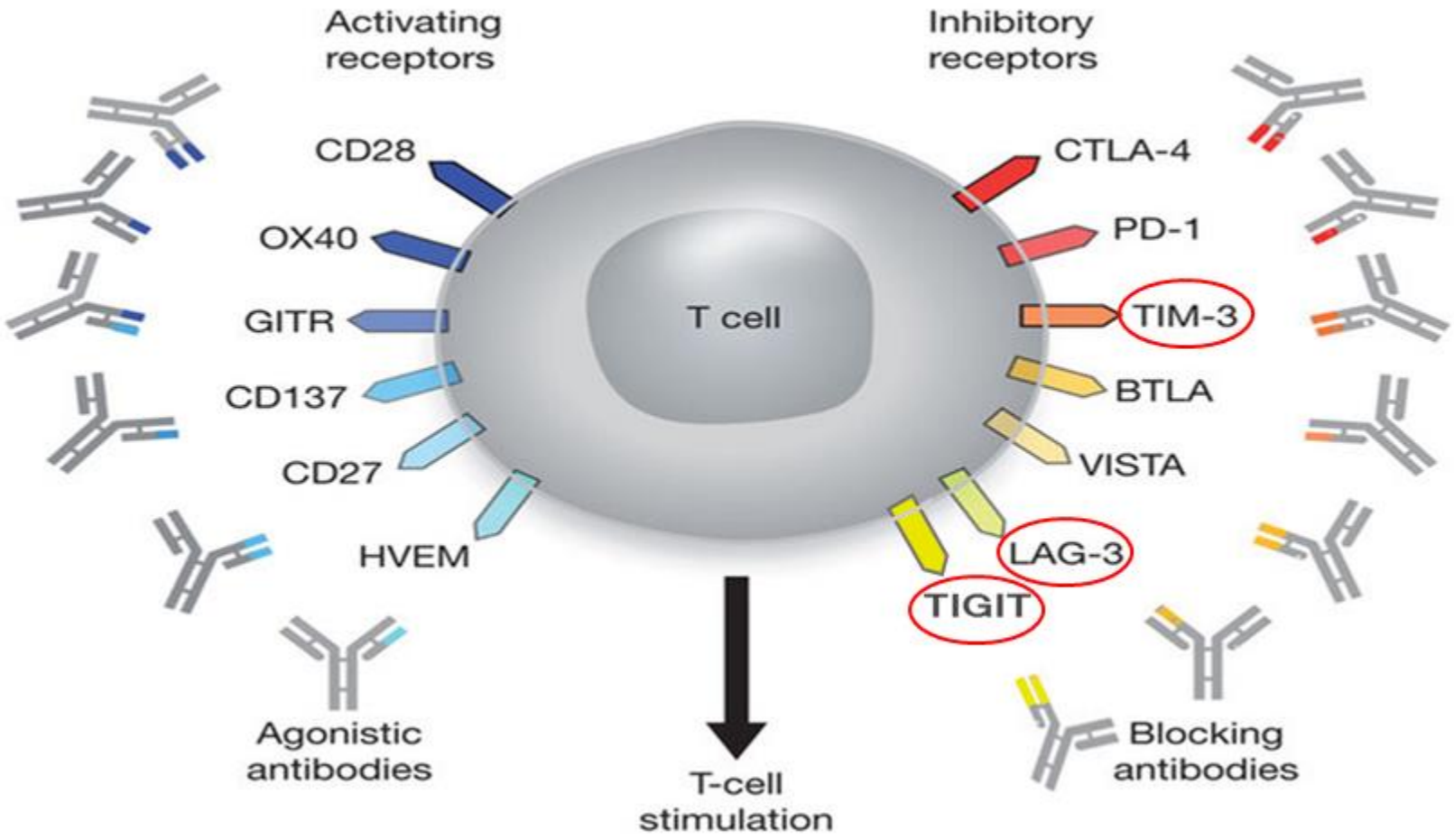
- **Research funding from NCI; EMD Serono; MedImmune; Healios Onc. Nutrition; Atterocor; Amplimmune; ARMO BioSciences; Karyopharm Therapeutics; Incyte; Novartis; Regeneron; Merck; BMS; Pfizer, CytomX Therapeutics; Neon Therapeutics; Calithera Biosciences; TopAlliance Biosciences; Immune Deficiency Foundation (Spouse)**
- **On advisory board of CytomX Therapeutics and Novartis**
- **Travel and accommodation expense from ARMO BioSciences**

Strategies to Improve Efficacy of ICPis

- Durable responses have been achieved with anti-CTLA-4 and anti-PD-1/PD-L1 agents
- Efficacy of ICPis can be further improved by effective modulation of:
  - Hot tumors: to enhance tumor responsiveness in the immuno-oncology naïve population
  - Cold tumors: to "turn on" their sensitivity to immune stimulation
  - Resistant tumors: to reverse refractoriness to immune stimulation
- Achieved using combination strategies
- But, responses have been at the cost of increased toxicity
- Clinical trials must therefore be guided by shared knowledge from pre-clinical, translational and early clinical data
- Current approaches are experimental and no definite data exists beyond those for ipilimumab in combination with nivolumab

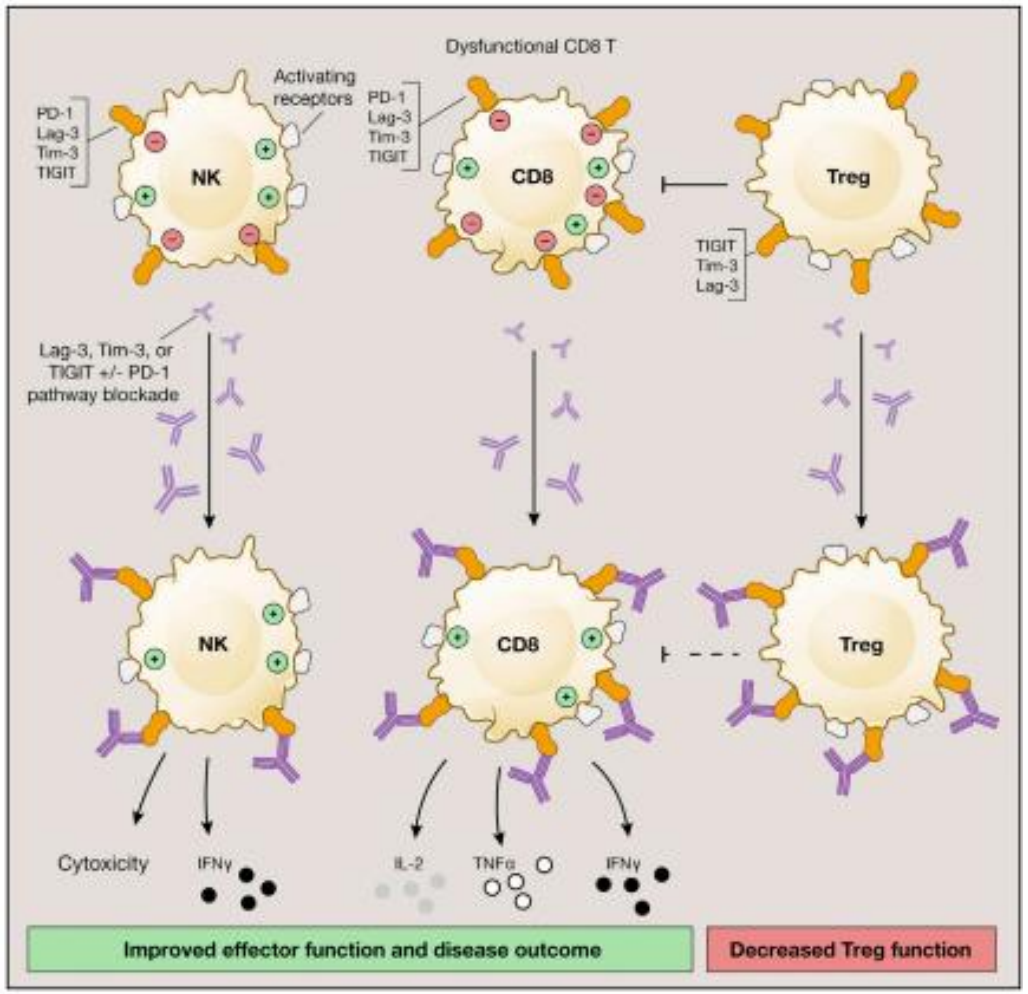
Naing A: Being realistic and optimistic in curing cancer. Journal of Immunotherapy and Precision Oncology 1:53-55, 2018.

T Cell Targets for Immunotherapy



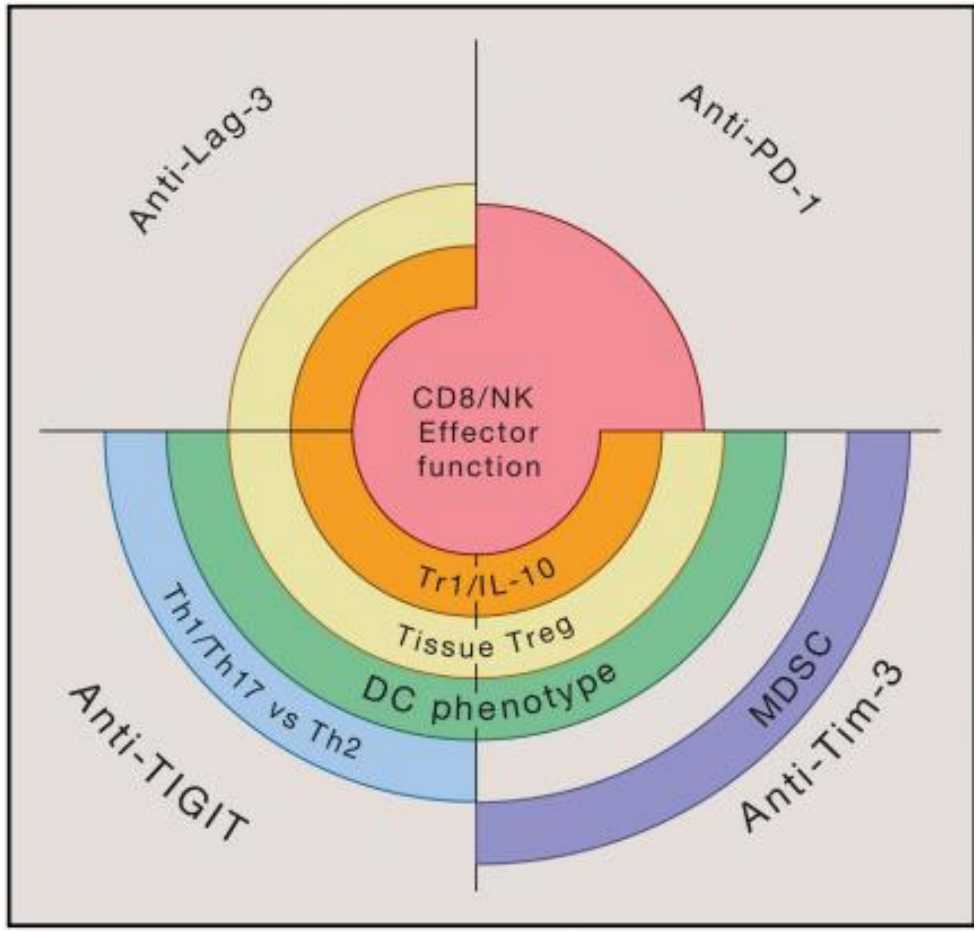
Modified from: Mellman I, Coukos G, Dranoff G: Cancer immunotherapy comes of age. Nature 480:480-9, 2011.

Role of Combinatorial Receptor Blockade



Anderson AC, Joller N, Kuchroo VK: Lag-3, Tim-3, and TIGIT: Co-inhibitory Receptors with Specialized Functions in Immune Regulation. Immunity 44:989-1004, 2016.

Impact of Receptor Blockade



Anderson AC, Joller N, Kuchroo VK: Lag-3, Tim-3, and TIGIT: Co-inhibitory Receptors with Specialized Functions in Immune Regulation. Immunity 44:989-1004, 2016.

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A Phase 1 Study of TSR-022, an Anti-TIM-3 Monoclonal Antibody, in Combination with TSR-042 (Anti-PD-1) in Patients with Colorectal Cancer and Post-PD-1 NSCLC and Melanoma

Diwakar Davar, Peter Boasberg, Zeynep Eroglu, Gerald Falchook, Justin Gainor, Erika Hamilton, J. Randolph Hecht, Jason Luke, Michael Pishvaian, Antoni Ribas, Judy Wang, Kristen McEachern, Angela Waszak, Sharon Lu, Yong Li, Ying Wang, Patricia LoRusso

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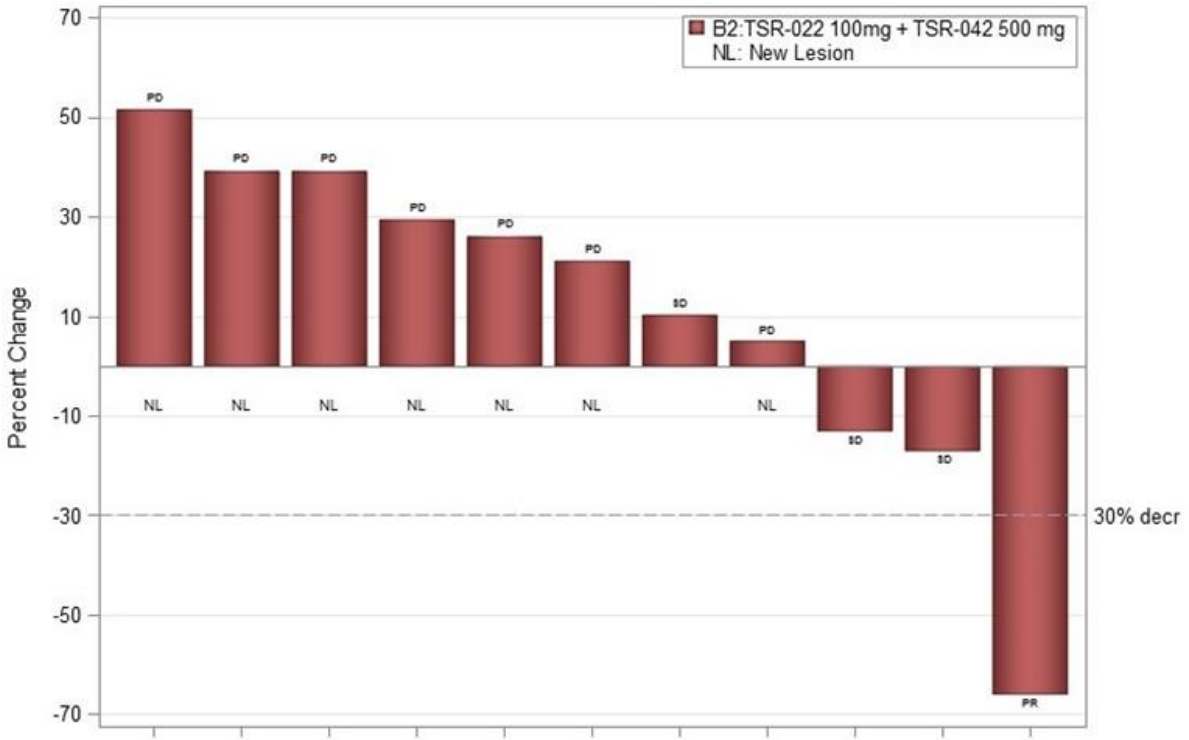
TSR-022, an Anti-TIM-3 Monoclonal Antibody, in Combination with TSR-042 (Anti-PD-1)

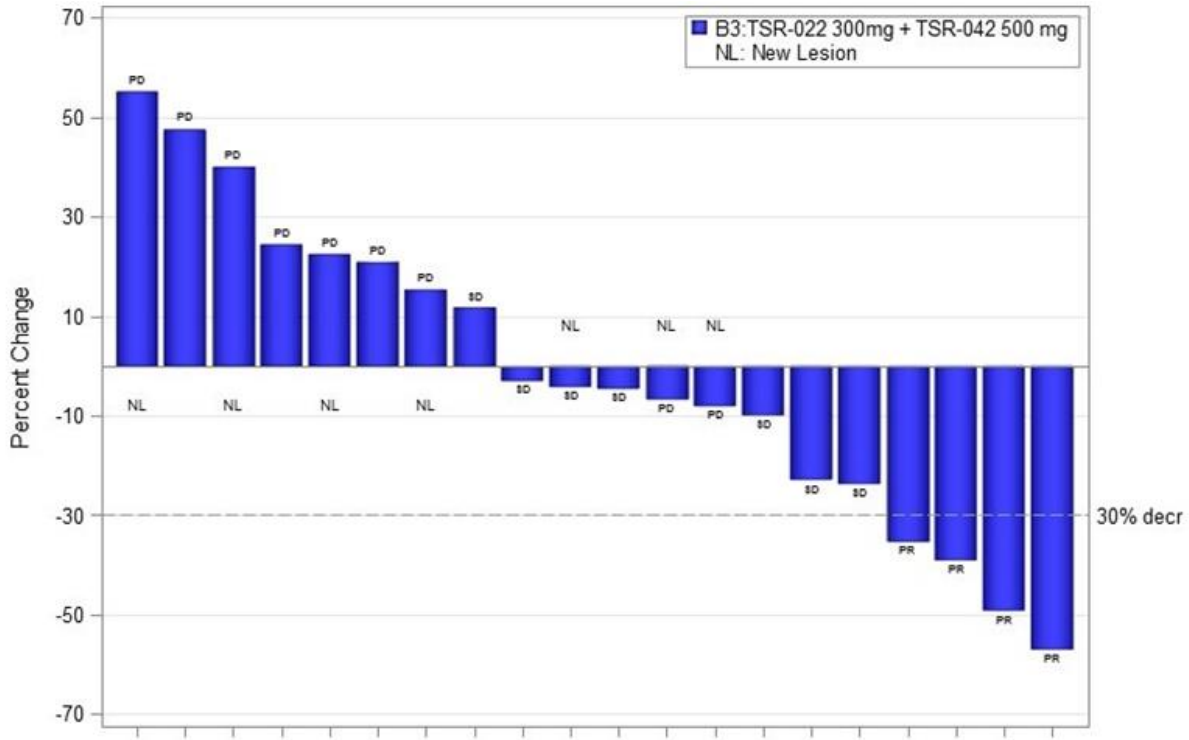
- **TSR-022 is a humanized anti-TIM-3 IgG4 monoclonal antibody**
- **TSR-022, when combined with anti-PD-1, increased the proliferation and production of IL-2 by human T cells**

AMBER STUDY

- **First-in-human study**
- **Part 1 (n=98): all comers, includes immuno-oncology–naïve patients.**
  - **Dose escalation of TSR-022 as a monotherapy**
  - **And, in combination with TSR-042, an anti-PD-1 antibody (metastatic disease with no remaining treatment options)**
- **Part 2 (n=104): TSR-022 in combination with TSR-042 is being evaluated in post-PD-1 melanoma, and post-PD-1 NSCLC (ongoing).**

Part 2: Emerging Evidence for Dose Response: NSCLC Cohort (n=39)



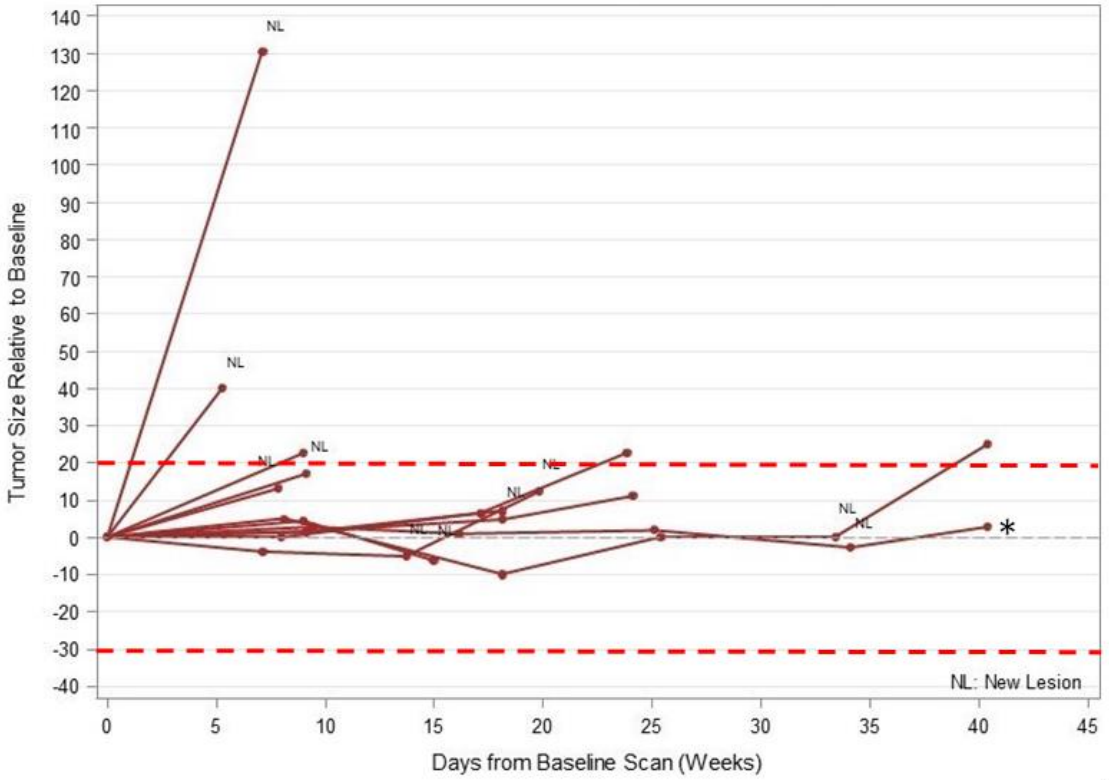


*One patient with scan was not evaluable and hence not included in Figure.
SD=stable disease.

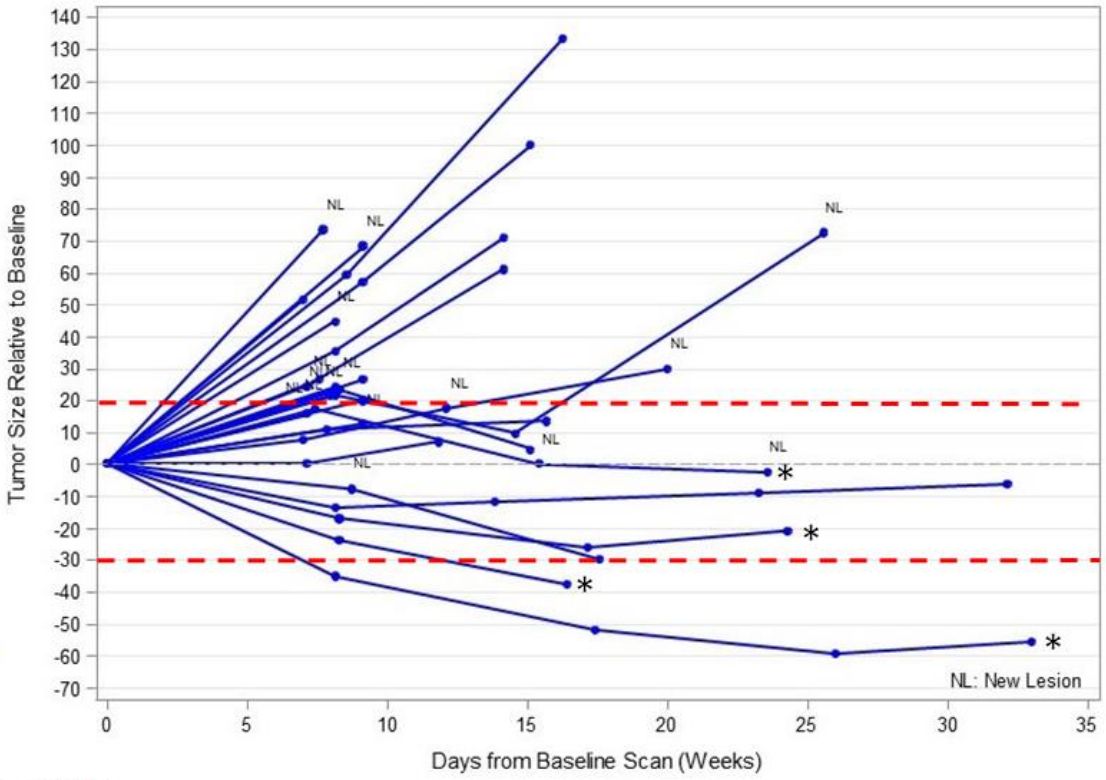
- Objective Responses (PR, n=5) were all in PD-L1 positive patients (Tumor Proportion Score ≥1%)
- But not all PD-L1 positive patients responded.

Part 2: Emerging Evidence for Dose Response: Melanoma Cohort

TSR-022 100 mg + TSR-042



TSR-022 300 mg + TSR-042



* = ongoing

Toxicity & PK

- **Grade ≥3 treatment-related adverse events in combination therapy was 6.7%.**
- **Grade ≥3 treatment-related adverse events in combination therapy were increased lipase, rash maculo-papular, and fatigue**
- **irAEs observed in Part 2 NSCLC Cohort: hypothyroidism and pancreatitis.**
- **PK: There was a dose-proportional increase in TSR-022 exposure and receptor occupancy. A 900 mg dose is required to maintain maximal receptor occupancy throughout the dosing interval.**

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The Anti–LAG-3 Antibody MK-4280 as Monotherapy and In Combination With Pembrolizumab for Advanced Solid Tumors: First-in-Human Phase 1 Dose-Finding Study

Nehal Lakhani,[1] Todd M. Bauer,[2] Anson Abraham,[3] John Luddy,[3] John Palcza,[3] Elliot Chartash,[3] Jane A. Healy,[3] Amita Patnaik[4]

[1]START Midwest, Grand Rapids, MI, USA; [2]Sarah Cannon Research Institute/Tennessee Oncology, PLLC., Nashville, TN, USA; [3]Merck & Co., Inc., Kenilworth, NJ, USA; [4]START, San Antonio, TX, USA

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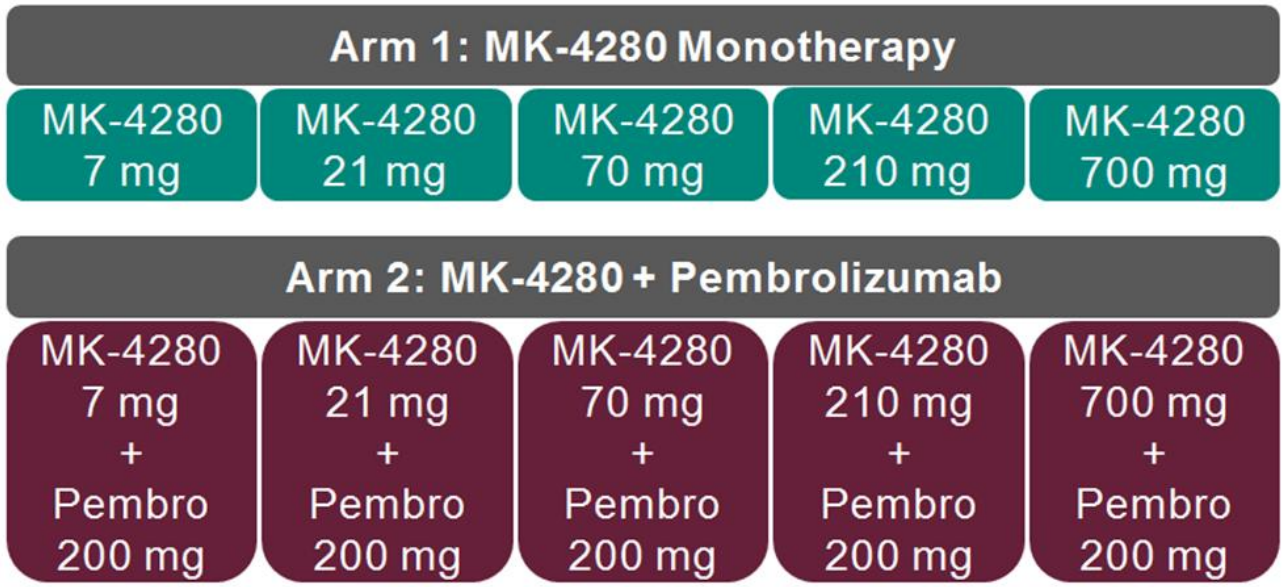
Trial Design & PK



Primary Cancer, n (%)	MK-4280 Monotherapy N = 18	MK-4280 + Pembro N = 15
Sarcoma	4 (22%)	0
Appendiceal	2 (11%)	1 (7%)
Biliary	2 (11%)	0
Colorectal	2 (11%)	5 (33%)
Adrenocortical	1 (6%)	1 (7%)
Breast	1 (6%)	2 (13%)
Small intestinal	1 (6%)	1 (7%)
RCC	0	2 (13%)
Other	5 (28%)[a]	3 (20%)[b]

[a]Includes cervical, endometrial, head & neck, NSCLC, and pancreatic cancer (n=1 each). [b]Includes fallopian tube, gastroesophageal junction, and ovarian cancer (n=1 each)

- **Standard 3+3 design, Treatment: IV Q3W**
- **Crossover from monotherapy to combination therapy was not permitted**
- **MK-4280 dose escalation proceeded to 700 mg Q3W for both monotherapy and combination therapy without any DLTs.**
- **Exposure increased with increasing dose, and target-mediated drug disposition was observed at low doses.**

Adverse Events

MK-4280 Monotherapy

Occurred in ≥1 patient, n (%)	N = 18
Fatigue	3 (17%)
Arthralgia	2 (11%)
Dermatitis acneiform	1 (6%)
Diarrhea	1 (6%)
Dry skin	1 (6%)
Flatulence	1 (6%)
Influenza like illness	1 (6%)
Infusion related reaction	1 (6%)
Hypokalemia	1 (6%)
Hypomagnesemia	1 (6%)
Milia	1 (6%)
Paraesthesia	1 (6%)
Peripheral sensory neuropathy	1 (6%)
Photosensitivity reaction	1 (6%)
Pneumonitis	1 (6%)
Pruritus	1 (6%)
Vomiting	1 (6%)

- 1 grade 3 event: pneumonitis
- 0 grade 4 or 5 events

MK-4280 + Pembrolizumab

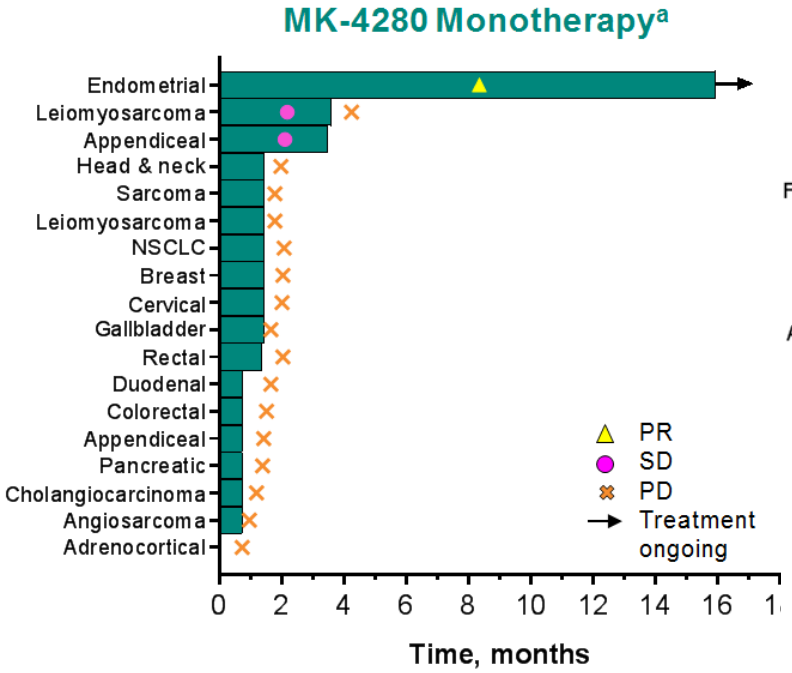
Occurred in ≥1 patient, n (%)	N = 15
Fatigue	3 (20%)
Pyrexia	3 (20%)
Pruritus	2 (13%)
Rash maculopapular	2 (13%)
Arthralgia	1 (7%)
Dermatitis aceniform	1 (7%)
Diarrhea	1 (7%)
Dry mouth	1 (7%)
Hyperglycemia	1 (7%)
Hyperthyroidism	1 (7%)
Hypophysitis	1 (7%)
Hypothyroidism	1 (7%)
Influenza like illness	1 (7%)
Infusion related reaction	1 (7%)
Myalgia	1 (7%)
Pneumonitis	1 (7%)
Vitiligo	1 (7%)

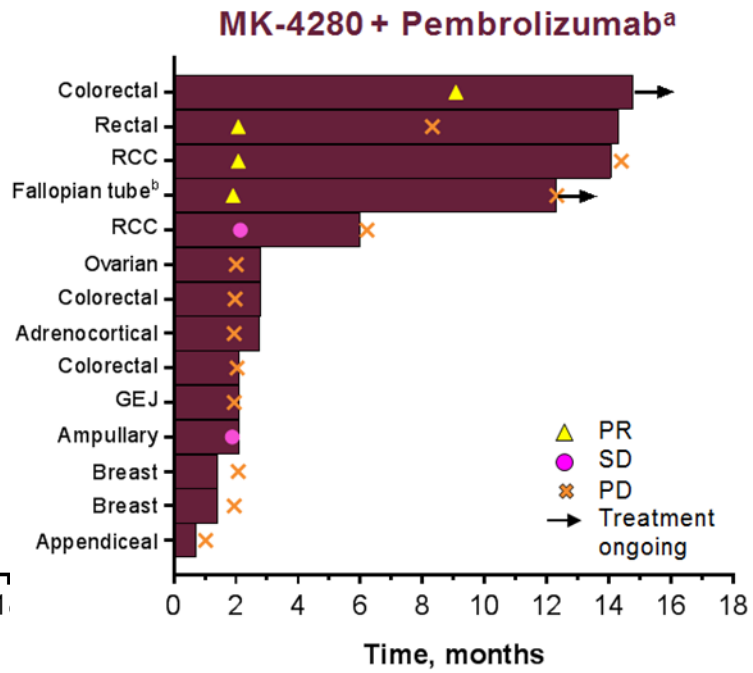
- 5 grade 3 events: arthralgia, hyperglycemia, hypophysitis, infusion-related reaction, pneumonitis (n = 1 each)
- 0 grade 4 or 5 events

Response

Response	MK-4280 Monotherapy N = 18	MK-4280 + Pembrolizumab N = 15
ORR,[a] % (95% CI)	6% (<1–27)	27% (8–55)
DCR,[a] % (95% CI)	17% (4–41)	40% (16–68)
Best response, n (%)		
Complete response	0	0
Partial response[a]	1 (6%)	4 (27%)
Stable disease	2 (11%)	2 (13%)
Progressive disease	15 (83%)	8 (53%)
Not assessed[b]	0	1 (7%)

Response by RECIST v1.1, Investigator Review
[a]All responses were confirmed.
[b]No post-baseline assessment as of data cutoff date





[a]Only those patients who had ≥1 post-baseline imaging assessment are included (n = 18 for MK-4280 monotherapy, n = 14 for MK-4280 + pembrolizumab).
[b]Patient discontinued treatment on Jun 18, 2018 because of an adverse event (persistent grade 1 pneumonitis despite corticosteroids).

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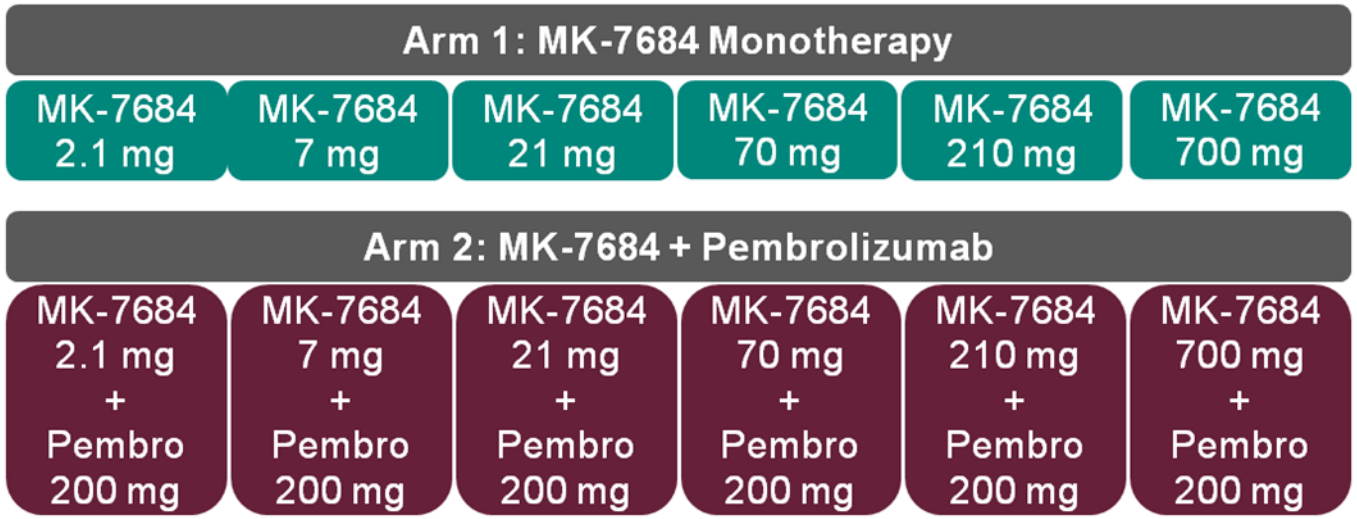
Phase 1 Dose-Finding Study of the Anti–TIGIT Antibody MK-7684 as Monotherapy and In Combination With Pembrolizumab in Patients With Advanced Solid Tumors

Talia Golan,[1] Todd M. Bauer,[2] Antonio Jimeno,[3] Ruth Perets,[4] Jiaxin Niu,[5] James J. Lee,[6] Patricia LoRusso,[7] Mallika Lala,[8] Sybil M.G. Williams,[8] Mingmei Cai,[8] Jennifer Garrus,[8] Zhen Zeng,[8] Elliot Chartash,[8] Jane A. Healy,[8] Drew Rasco[9]

[1]Sheba Medical Center, Tel Hashomer, Israel; [2]Sarah Cannon Research Institute/Tennessee Oncology, PLLC., Nashville, TN, USA; [3]University of Colorado, Aurora, CO, USA; [4]Rambam Medical Center, Haifa, Israel; [5]Banner MD Anderson Cancer Center, Gilbert, AZ; [6]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [7]Yale Cancer Center, New Haven, CT, USA; [8]Merck & Co., Inc., Kenilworth, NJ, USA; [8]START, San Antonio, TX, USA

Trial Design & PK



Primary Cancer, n (%)	MK-7684 Monotherapy N = 34	MK-7684 + Pembro N = 34
NSCLC	7 (21%)	7 (21%)
Colorectal	6 (18%)	4 (12%)
Ovarian	4 (12%)	2 (6%)
Gastric/GEJ	3 (9%)	5 (15%)
Head and neck	3 (9%)	0
Thymic	2 (6%)	1 (3%)
Pancreatic	1 (3%)	2 (6%)
Urothelial	1 (3%)	2 (6%)
Breast	0	2 (6%)
Sarcoma	0	2 (6%)
Other	5 (15%)[a]	5 (15%)[b]
Missing/unknown	2 (6%)	2 (6%)

[a]Includes 1 patient each with esophageal, gallbladder, intestinal, mesothelioma, SCLC.
[b]Includes 1 patient each with melanoma, Merkel cell, RCC, squamous, and uterine.

- First-in-human study, treatment: IV once every 3 weeks
- MK-7684 is Humanized, IgG1 monoclonal antibody that binds TIGIT and prevents it from interacting with CD112 and CD155
- Crossover from monotherapy to combination therapy upon PD was permitted for eligible patients
- Dose escalation completed for each pre-specified dose level for both monotherapy and combination therapy without any DLTs
- Exposure increased with increasing dose, target-mediated drug disposition observed at low doses

Adverse Events

MK-7684 Monotherapy

Occurred in ≥2 patients, n (%)	N = 34
Fatigue	5 (15%)
Pruritus	4 (12%)
Anemia	3 (9%)
Infusion-related reaction	3 (9%)
Arthralgia	2 (6%)
Decreased appetite	2 (6%)
Dermatitis acneiform	2 (6%)
Diarrhea	2 (6%)
Headache	2 (6%)
Nausea	2 (6%)
Rash	2 (6%)
Rash maculopapular	2 (6%)

- 2 grade 3: anemia and diarrhea (n = 1 each)
- 0 grade 4

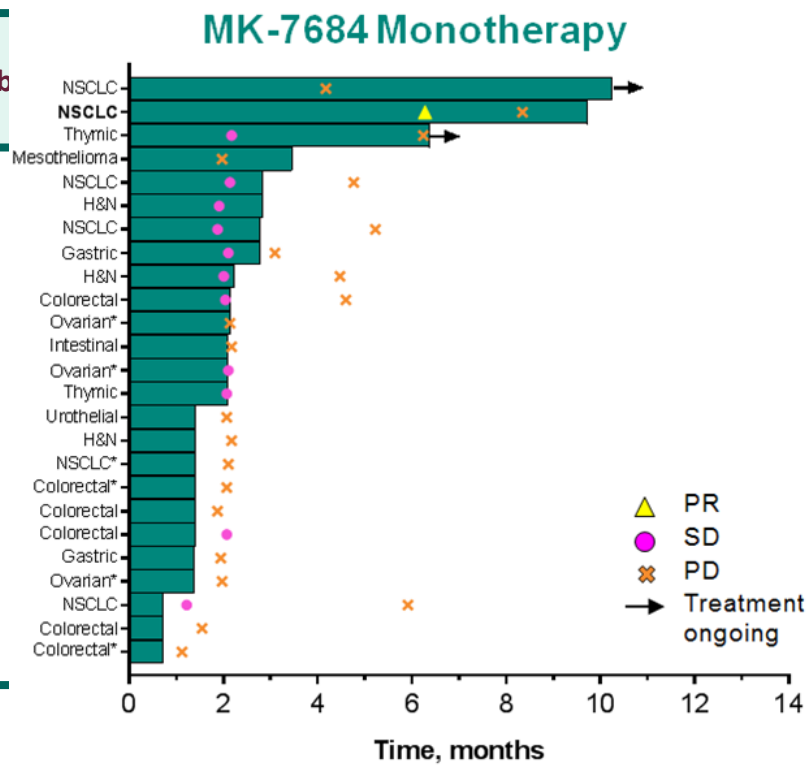
MK-7684 + Pembrolizumab

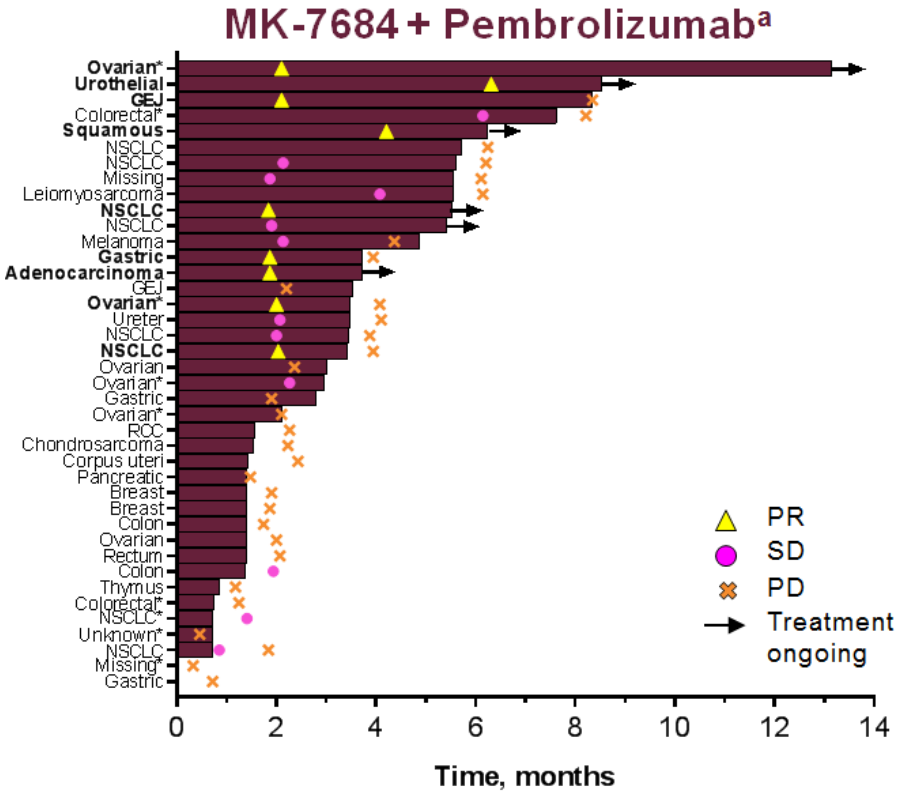
Occurred in ≥2 patients, n (%)	N = 47
Pruritus	10 (21%)
Fatigue	4 (9%)
Nausea	4 (9%)
Rash	4 (9%)
Decreased appetite	3 (6%)
Diarrhea	3 (6%)
ALT increased	2 (4%)
Dyspnea	2 (4%)
Hypophosphatemia	2 (4%)
Neuropathy peripheral	2 (4%)
Pyrexia	2 (4%)
Rash maculopapular	2 (4%)

- 5 grade 3: ALT increased, colitis, γGT increased, hypersensitivity, and rash maculopapular (n = 1 each)
- 0 grade 4

Response

Response	MK-4280 Monotherapy N = 34	MK-4280 + Pembrolizumab N = 43[b]
ORR,[a] % (95% CI)	3% (<1-15)	19% (8-33)
DCR,[a] % (95% CI)	35% (20-54)	47% (31-62)
Best response, n (%)		
Complete response	0	0
Partial response	1 (3%)	8 (19%)
Stable disease	11 (32%)	12 (28%)
Progressive disease	13 (38%)	20 (47%)
Not assessed[c]	9 (26%)	3 (7%)





Response by RECIST v1.1, Investigator Review

[a]Evaluated in patients with measurable disease at baseline. Includes confirmed and unconfirmed responses

[b]Includes the 34 patients originally allocated to the combination and the 13 who crossed over from MK-7684 monotherapy

[c]No post-baseline assessment as of data cutoff date

*Patients who crossed over.

[a]Includes 32 patients originally allocated to the combination and 9 who crossed over from MK-7684 monotherapy. Data cutoff date: Aug 16, 2018.

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Results from a Phase I dose escalation trial (TACTI-mel) with the soluble LAG-3 protein (IMP321, eftilagimod alpha) together with pembrolizumab in unresectable or metastatic melanoma

Adnan Khattak[1], Victoria Atkinson[2], Andrew Haydon[3], Melissa Eastgate[4], Amitesh Roy[5], Christian Mueller[6], Chrystelle Brignone[7], Frederic Triebel[7]

[1] Fiona Stanley Hospital, Perth [2] Princess Alexandra Hospital, Brisbane
[3] Alfred Hospital, Melbournen [4] Royal Brisbane Womens Hosital, Brisbane
[5] Flinders Centre for Innovation in Cancer, Adelaide
[6] Clinical Development Immutep, GmbH, Berlin [7] R&D Immutep, Paris

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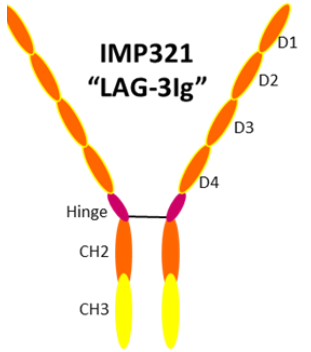
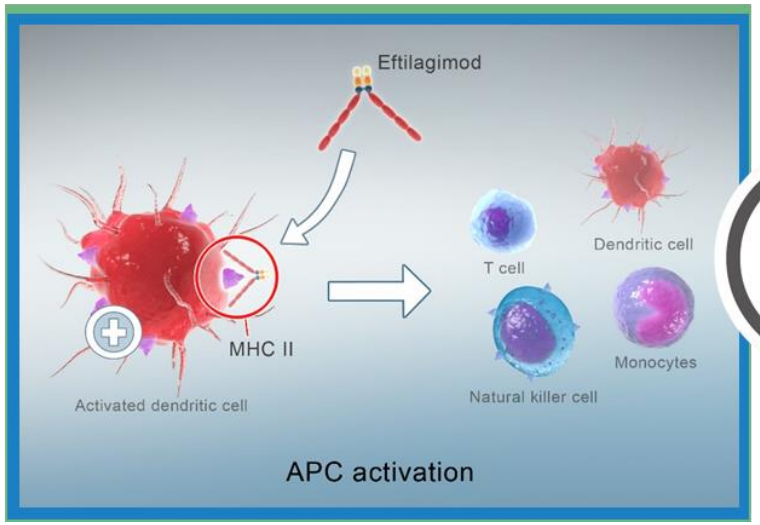
Eftilagimod alpha (efti, IMP321)

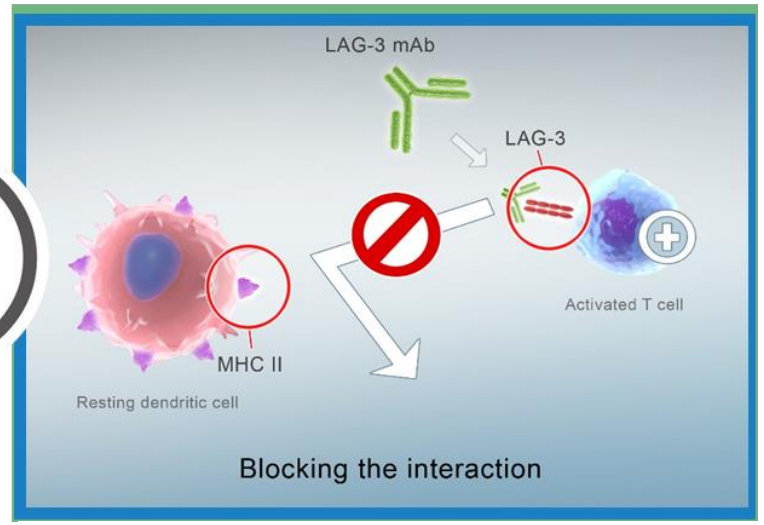
- **Is a recombinant soluble LAG-3Ig fusion protein binding to MHC class II molecules**
  - **Is an APC activator and a T cell recruiter at the tumor site (not ICPi)**
  - **Is an MHC II agonist: a few ng/ml in the blood is enough to see sustained APC activation**



"PUSHING THE ACCELERATOR ON IMMUNE RESPONSES"



"RELEASING THE BRAKE ON THE T CELL"



Eftilagimod alpha (efti, IMP321):

APC activator

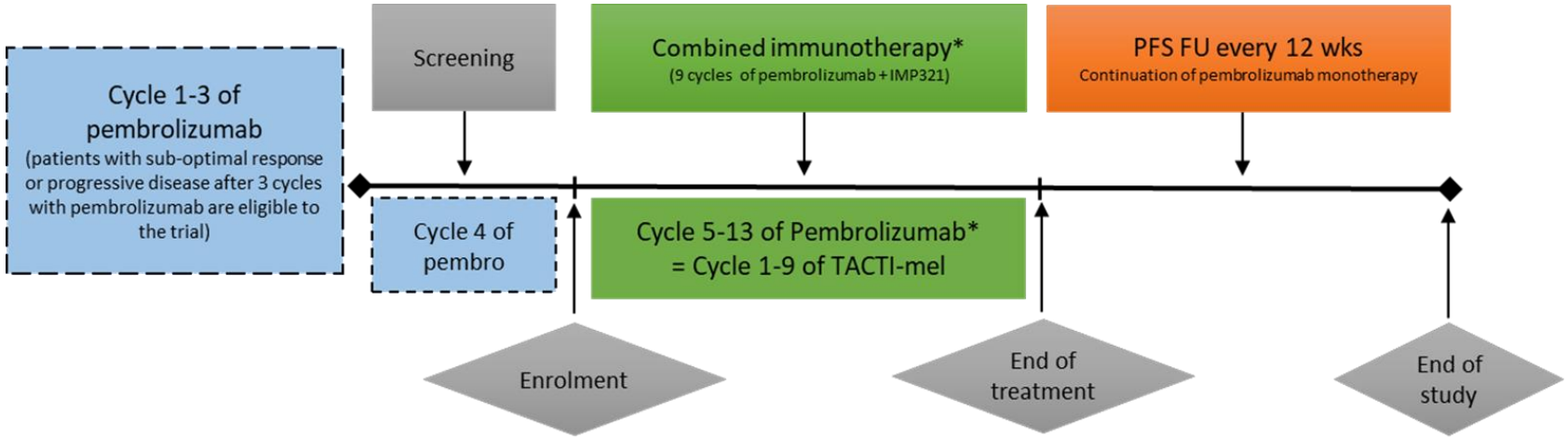
- Boost and sustain the $CD8^+$ T cell responses
- Activate multiple immune cell subsets

LAG-3 antagonist antibodies:

Immune checkpoint inhibitor (ICPi)

- Increase cytotoxicity of the pre-existing CD8 T cell response

TACTI-mel: Trial Design



- **N=18 patients (6 pts per efti dose group)**
- **Patients received:**
  - **2 mg/kg pembrolizumab i.v. every 3 weeks**
  - **1, 6, 30 mg efti s.c. every 2 weeks for up to 6 months**
- **Imaging was done every 12 weeks**
- **11 of 18 patients (61%) had irPD/irSD to pembrolizumab after 3 cycles (? Role of PsP)**

Grade 3 / 4 Drug-Related Adverse Events

Preferred term	Grade 3 N (%)	Grade 4 N (%)	Rel to efti / pembro
Maculo-papular rash	1 (6 %)	-	No / Yes
Decreased renal function	1 (6 %)	-	Yes / No
Colitis	1 (6 %)	-	No / Yes
Altered liver functions	1 (6 %)	-	No / Yes

- No DLT
- Most common AEs were fatigue (44 %), rash (33 %), diarrhea (28 %), nausea (28 %), arthralgia (17 %) and colitis (11 %).
- 1 patient died due to an AE (grade 4 intercranial hemorrhage, not related.)
- 3 patients had treatment delay due to an AE; 1 patient discontinued due to an AE

Response

Best Overall Response acc. to irRC	N = 18 (%)
irCR	1 (6 %)
irPR[#]	5 (28 %)[#]
irSD	6 (33 %)
irPD	6 (33 %)
Best overall response rate (ORR)[§]	**6 (33 %)**
Patients with tumor shrinkage	**10 (56 %)**
Disease control rate	**12 (66 %)**

- [#]Including 1 patient with complete disappearance of all target lesions
- [§]Taking cycle 5 of pembrolizumab as baseline
- If response is calculated from pre-pembrolizumab time point: ORR is 66 % by irRC

Future Directions

- **Development of proof-of concept studies**
  - **Determine the expression levels of TIM3, LAG-3, and TIGIT receptors in different tumor types**
  - **Correlate expression levels to response/resistance**
- **Better understand the underlying mechanism of response and resistance**
- **Identify biomarkers of response/resistance**
- **Studies to evaluate optimal administration of drugs**
  - **Concurrent or sequential administration**
  - **If sequential, which drug first**
  - **Optimal run-in time?**

Lessons and Take Home Messages

- Combination of anti-PD-1 inhibitors with anti-TIM-3/LAG-3/TIGIT agents well tolerated
- Promising antitumor activity observed in a heavily pretreated population and in patients who have progressed on or after prior anti-PD(L)-1 treatment
- Optimal trial design guided by shared knowledge from pre-clinical, translational and early clinical data needed
- Further translational studies warranted to better understand mechanisms of response/resistance/toxicity

Thank You

Email: anaing@mdanderson.org

Twitter: @AnaingMD