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

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Disclosures

- Nehal Lakhani reports relationships with the following:
  - ALX Therapeutics; Amgen; Arqule; Ascentage; Apexian; Asana Biosciences; Formation Biologics; Beigene; Constellation Pharma; CytomX; Daiichi Sankyo; Forth Seven, Inc.; InhibRx; Incyte; Macrogenics; Loxo; Livzon Mabpharm; Merck & Co., Inc.; Northern Biologics; Pfizer; Regeneron; Symphogen; and TaiRx

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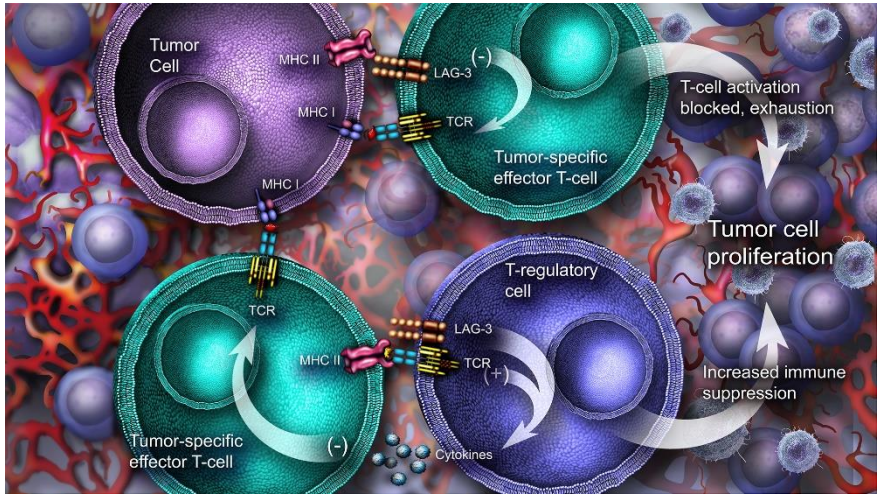
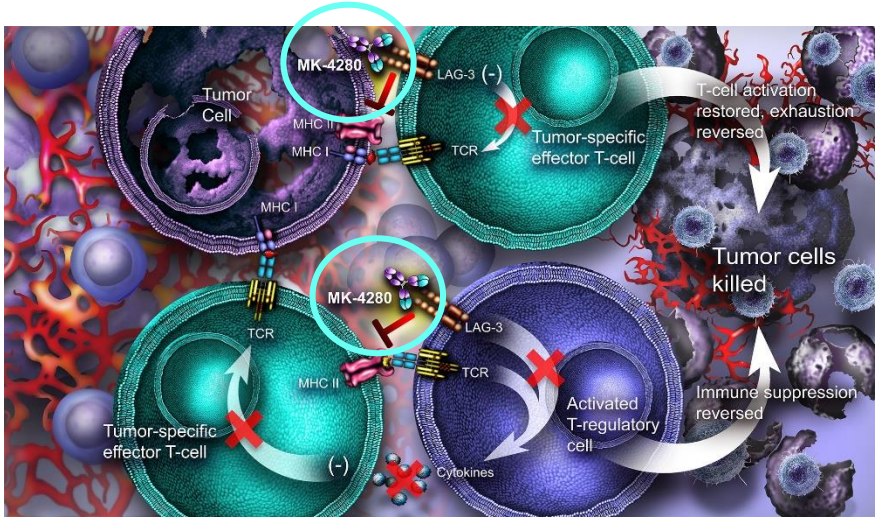
LAG-3 and MK-4280

- LAG-3: immune checkpoint expressed on $CD4^+$ and $CD8^+$ T cells and NK cells that binds to MHC class II
- In cancer, prevents genesis of an effective anti-tumor immune response
- Preventing LAG-3 from binding to MHC II could help restore anti-tumor immunity
- MK-4280: humanized, IgG4 monoclonal antibody that binds LAG-3 and prevents it from interacting with MHC class II

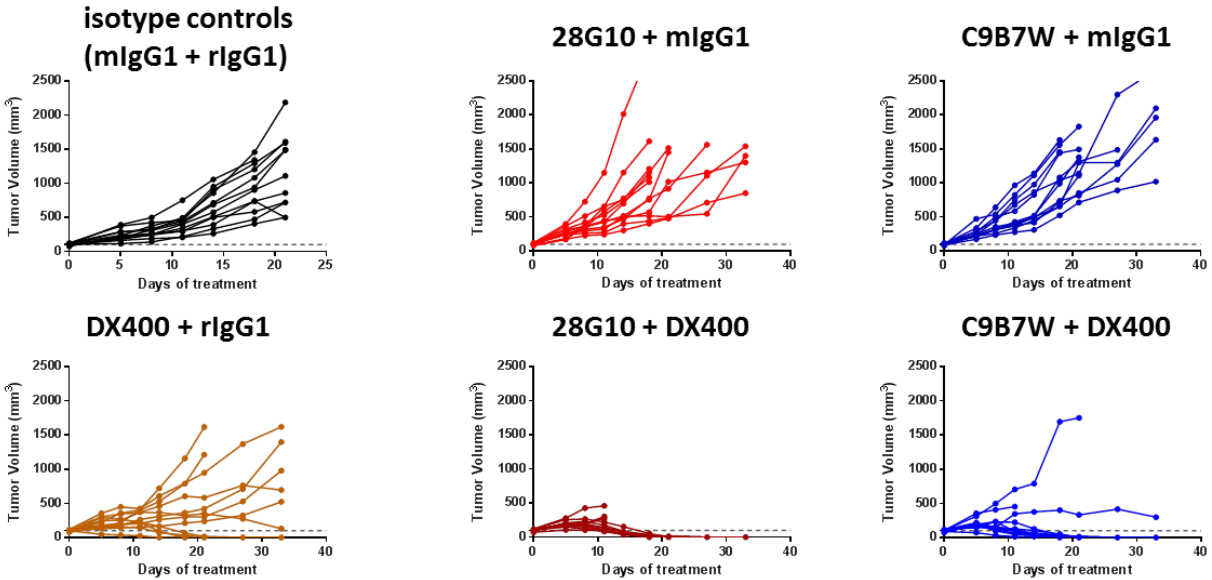




LAG-3, lymphocyte-activation gene 3.

Goldberg MV and Drake CG. *Curr Top Microbiol Immunol* 2011;344:269-78.

RenCa Mouse Model: Strongly Additive Antitumor Activity for Combined LAG-3 and PD-1 Inhibition



- **28G10**: anti–LAG-3 antibody that blocks the interaction between LAG-3 and MHCII
- **C9B7W**: anti–LAG-3 antibody that does not block the interaction between LAG-3 and MHCII
- **DX400**: anti–PD-1 antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2

mIgG1, mouse IgG1; rIgG1, rat IgG1.

de Waal Malefyt R et al. Poster 298. Presented at: 28th EORTC-NCI-AACR Symposium; Nov 29-Dec 3, 2016; Munich, Germany. Figure shown with permission of R. de Waal Malefyt.

Study 4280-001

- First-in-human, phase 1 dose-finding study of MK-4280 as monotherapy and in combination with the anti–PD-1 monoclonal antibody pembrolizumab in patients with advanced solid tumors (ClinicalTrials.gov, NCT02720068)
  - Part A: dose escalation
  - Part B: dose confirmation to estimate the recommended phase 2 dose

Study Design: Part A

- Standard 3+3 dose escalation
  - DLT evaluation period: cycle 1
  - Patients per dose level: minimum of 3, maximum of 6
- Treatment: IV once every 3 weeks for up to 35 cycles or until PD, intolerable toxicity, physician decision, or consent withdrawal
- Intrapatient dose escalation and crossover from monotherapy to combination therapy were not permitted

Arm 1: MK-4280 Monotherapy

MK-4280 7 mg	MK-4280 21 mg	MK-4280 70 mg	MK-4280 210 mg	MK-4280 700 mg

Arm 2: MK-4280 + Pembrolizumab

MK-4280 7 mg + Pembro 200 mg	MK-4280 21 mg + Pembro 200 mg	MK-4280 70 mg + Pembro 200 mg	MK-4280 210 mg + Pembro 200 mg	MK-4280 700 mg + Pembro 200 mg

DLT, dose-limiting toxicity.
ClinicalTrials.gov, NCT02720068.

Study Design: Part A

- Key inclusion criteria
  - Age ≥18 years
  - Confirmed metastatic solid tumor
  - Failure of standard treatment options
  - ECOG PS 0 or 1
  - Measurable disease per irRECIST v1.1
- Key exclusion criteria
  - Prior anti–LAG-3 therapy
  - Discontinuation of prior anti–PD-1, PD-L1, or CTLA-4 therapy for grade ≥3 immune-related AE
  - Prior anti-cancer therapy, including radiation, within 4 weeks
  - Known active CNS metastases

- Key study objectives
  - Primary
    - Safety and tolerability of MK-4280 monotherapy
    - Safety and tolerability of MK-4280 + pembrolizumab
  - Secondary
    - Pharmacokinetics of MK-4280 given as monotherapy and with pembrolizumab
    - Antitumor activity of MK-4280 monotherapy
    - Antitumor activity of MK-4280 + pembrolizumab

ClinicalTrials.gov, NCT02720068.

Baseline Characteristics

Characteristic, n (%)	MK-4280 Monotherapy N = 18	MK-4280 + Pembro N = 15
Age, median (range)	55.5 (36-82)	62.0 (40-79)
Male sex	7 (39%)	8 (53%)
ECOG PS		
0	4 (22%)	7 (47%)
1	14 (78%)	8 (53%)
Prior therapy		
Neoadjuvant	1 (6%)	0
Adjuvant	3 (17%)	4 (27%)
1	2 (11%)	0
2	5 (28%)	2 (13%)
3	3 (17%)	1 (7%)
4	0	3 (20%)
≥5	4 (22%)	5 (33%)

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 1 patient each with cervical, endometrial, head & neck, NSCLC, and pancreatic cancer.
[b]Includes 1 patient each with fallopian tube, gastroesophageal junction, and ovarian cancer.
Data cutoff date: Jun 12, 2018.

Dose Finding and Disposition

MK-4280 monotherapy

- **Dose escalation completed for each prespecified dose level**
- **No DLTs observed**
- Disposition
  - On treatment: n = 1
  - Discontinued: n = 17
    - Radiographic PD: n = 15
    - AE: n = 1
    - Physician decision: n = 1
    - Clinical PD: n = 0
    - Withdrawal: n = 0

MK-4280 + Pembrolizumab

- **Dose escalation completed for each prespecified dose level**
- **No DLTs observed**
- Disposition
  - On treatment: n = 2
  - Discontinued: n = 13
    - Radiographic PD: n = 8
    - AE: n = 2
    - Physician decision: n = 1
    - Clinical PD: n = 1
    - Withdrawal: n = 1

Data cutoff date: Jun 12, 2018.

Adverse Event Summary

Adverse Event, n (%)	MK-4280 Monotherapy N = 18	MK-4280 + Pembrolizumab N = 15
Any attribution		
Any grade	17 (94%)	15 (100%)
Grade 3	9 (50%)	9 (60%)
Grade 4	0	0
Grade 5	0	0
Led to discontinuation	1 (6%)	3 (20%)
Treatment related		
Any grade	11 (61%)	8 (53%)
Grade 3	1 (6%)	3 (20%)
Grade 4	0	0
Grade 5	0	0
Led to discontinuation	1 (6%)	2 (13%)

Data cutoff date: Jun 12, 2018

Treatment-Related 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

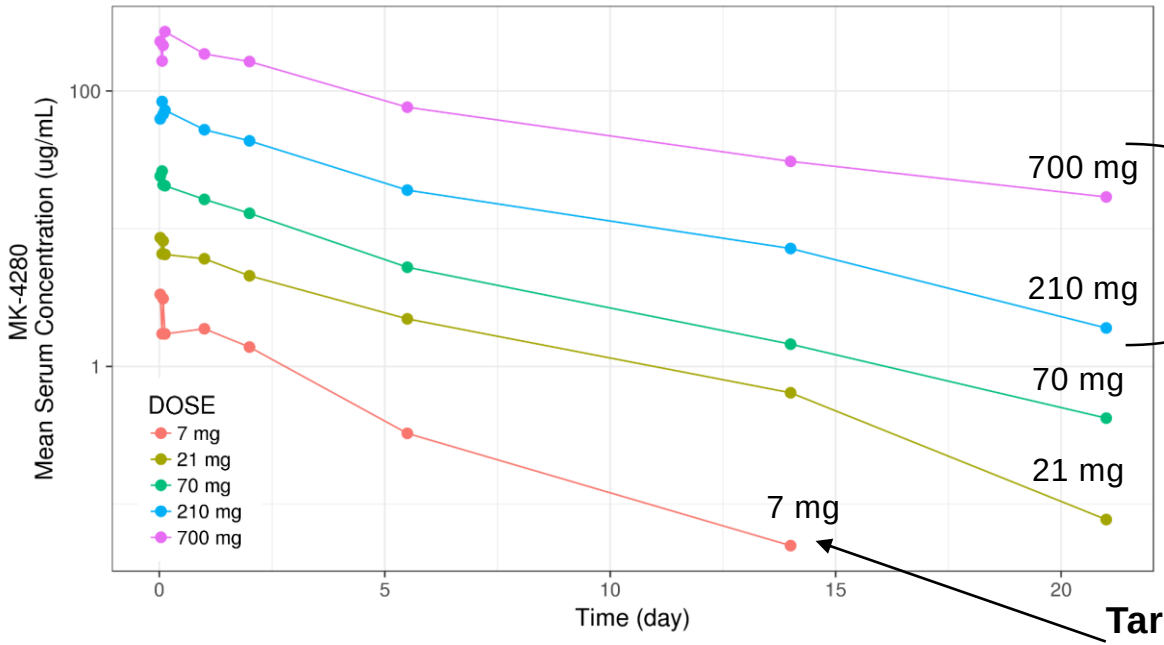
MK-4280 + Pembrolizumab

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 in 3 patients: arthralgia and hypophysitis in 1 patient, hyperglycemia and pneumonitis in 1 patient, and infusion-related reaction in 1 patient
- 0 grade 4 or 5 events

Data cutoff date: Jun 12, 2018

Pharmacokinetics of MK-4280: Dose Escalation



Linear clearance with doses of 210 mg and 700 mg

Target-mediated clearance at low doses

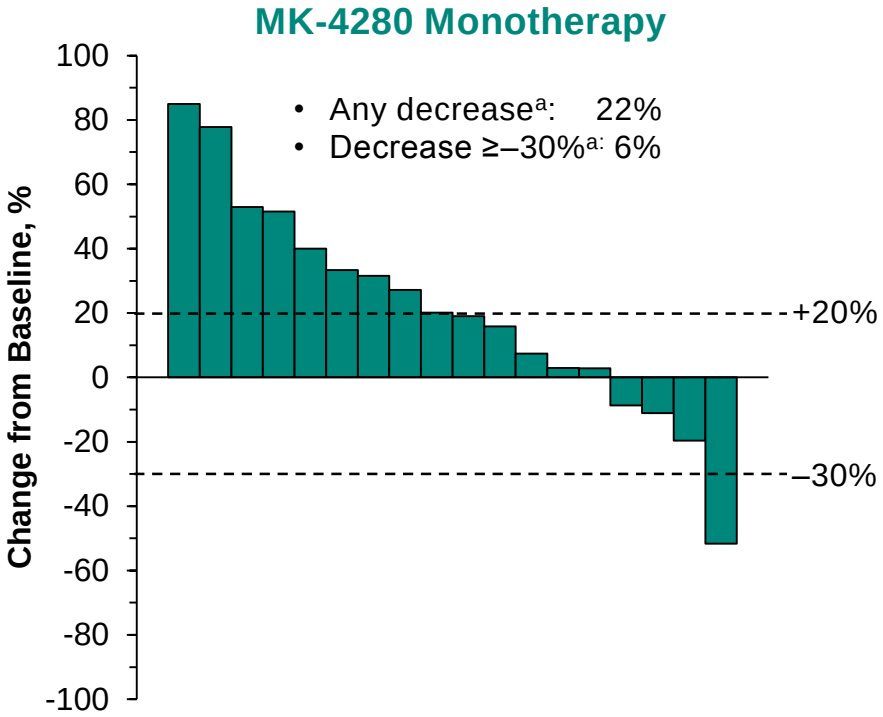
Arithmetic mean concentrations plotted using nominal sampling times.

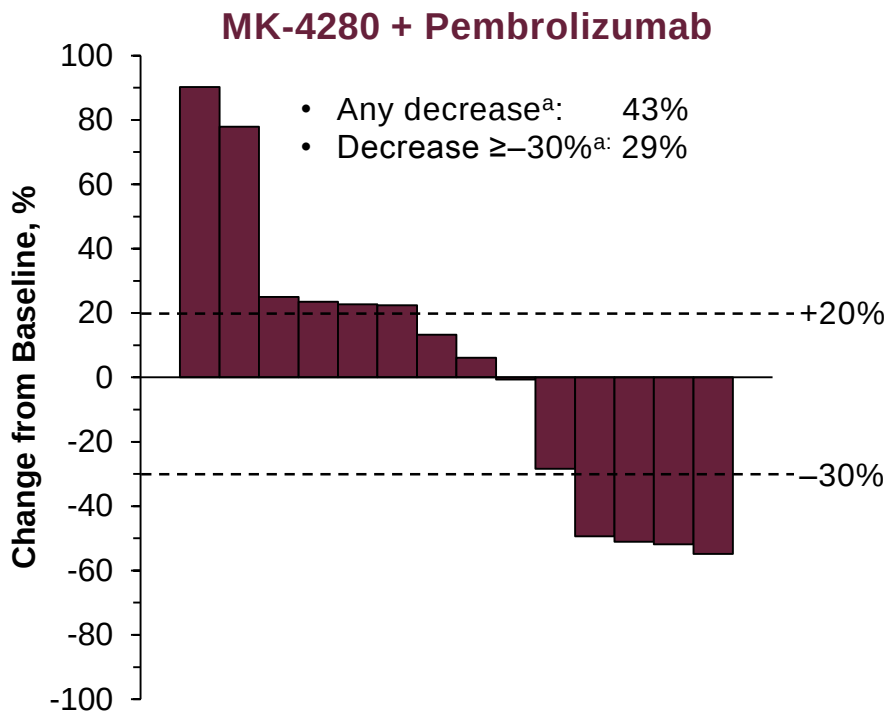
Antitumor Activity
(RECIST v1.1, Investigator Review)

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%)

[a]All responses were confirmed.
[b]No post-baseline assessment as of data cutoff date.
Data cutoff date: Jun 12, 2018

Best Percentage Change from Baseline in Target Lesions[a] (RECIST v1.1, Investigator Review)



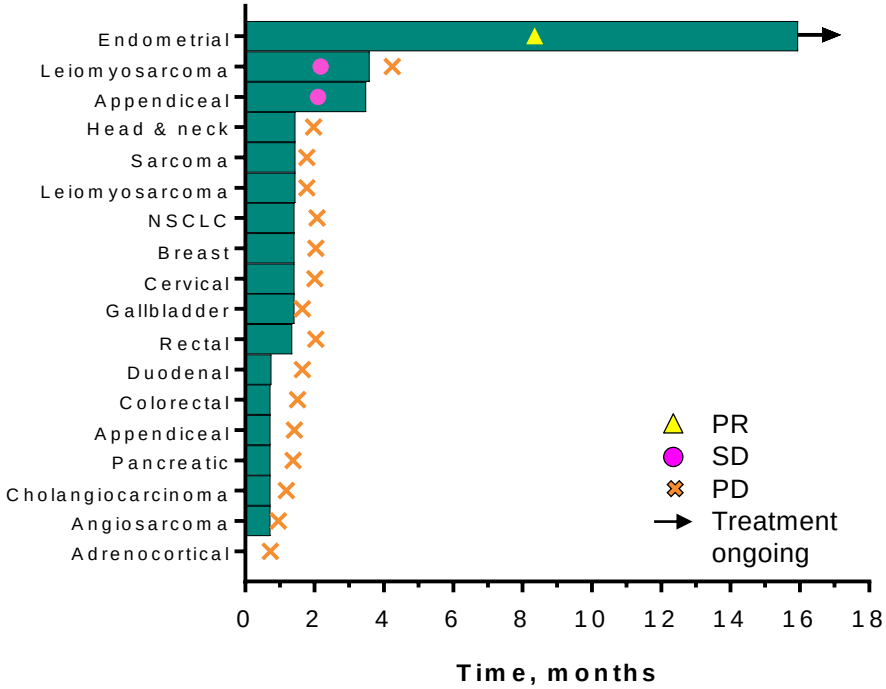


[a]Evaluated in patients with measurable disease at baseline and ≥1 evaluable post-baseline imaging assessment (n = 18 for MK-4280 monotherapy, n = 14 for MK-4280 + pembrolizumab).
Data cutoff date: Jun 12, 2018

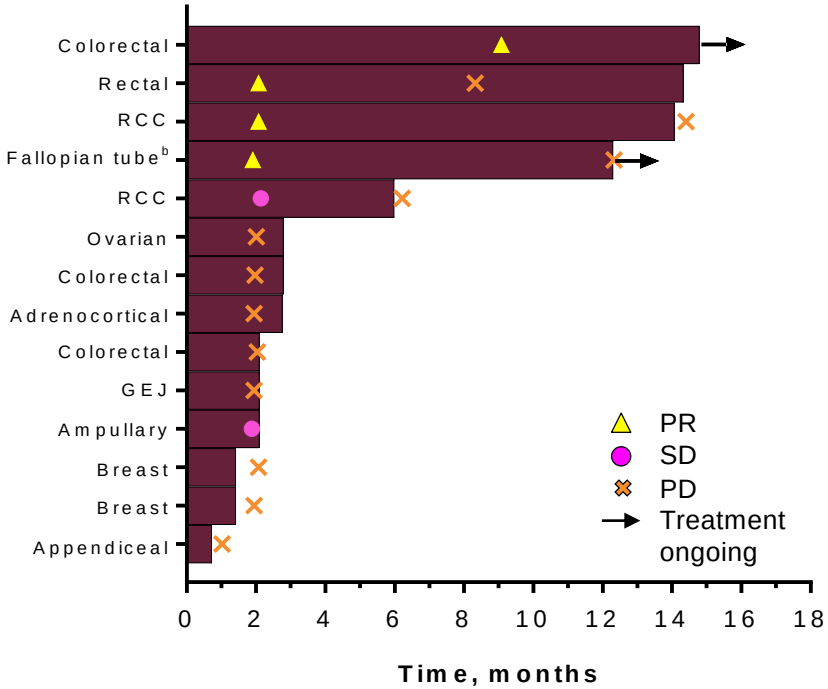
Treatment Duration and Response

(RECIST v1.1, Investigator Review)

MK-4280 Monotherapy[a]



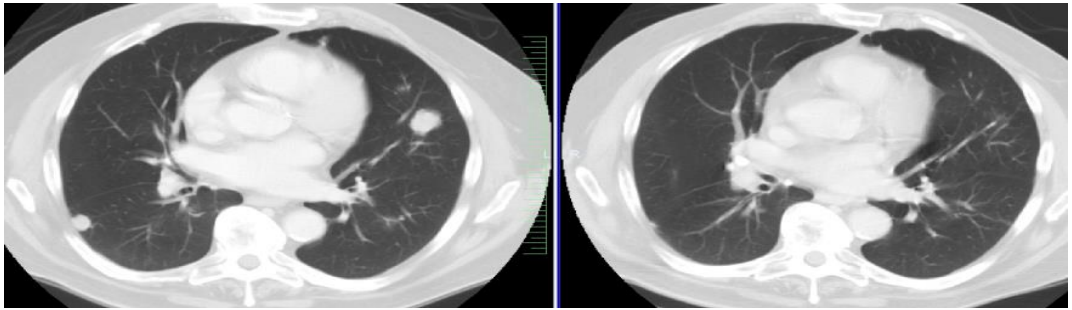
MK-4280 + Pembrolizumab[a]



Line length represents the time to the last dose of study treatment. Time to best response and subsequent progression are shown for each patient.
[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).
Data cutoff date: Jun 12, 2018

Partial Response: 72-year-old Male With MMR Proficient and *KRAS*, *NRAS*, and *BRAF*–Negative Rectal Cancer and Metastases to Lung

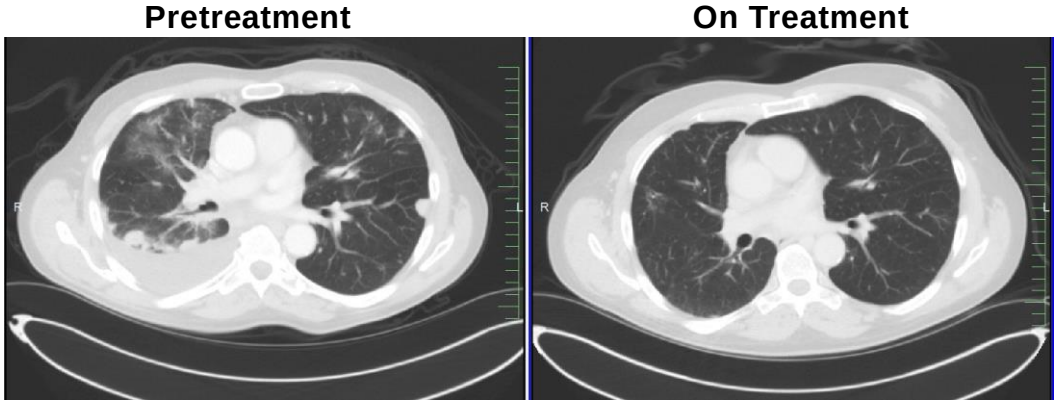
Lung Metastases



- 5 prior lines of chemotherapy, no prior anti–PD-1 or anti–PD-L1 therapy
- Received MK-4280 21 mg plus pembrolizumab
- Partial response first observed at 9 weeks, confirmed at 18 weeks
  - 45% reduction in tumor volume
  - Tumor volume reduction in lung lesions and lymph nodes, stable presacral mass

Partial Response: 60-year-old Male With Renal Cell Carcinoma and Metastases to Lung and Bone

Lung Metastases



- 3 prior lines of therapy, including 3 cycles of anti–PD-1 therapy with nivolumab
- Received MK-4280 7 mg plus pembrolizumab after active, confirmed PD at multiple sites while on nivolumab
- Partial response first observed at 9 weeks, confirmed at 18 weeks
  - 49% reduction in tumor volume
  - Tumor volume reduction noted at all visible disease sites including the lung and multiple lymph nodes
  - Response lasted for 15 months before disease progression

Summary and Conclusions

- In this first-in-human study, MK-4280 given as monotherapy and in combination with pembrolizumab 200 mg was well tolerated and had a manageable safety profile across all doses tested
  - Dose escalation proceeded to the maximum dose of 700 mg without any DLTs
  - No treatment-related deaths
- Promising antitumor activity observed across multiple tumor types, particularly for the combination of MK-4280 and pembrolizumab
  - 6% ORR and 17% DCR for MK-4280 alone
  - 27% ORR and 40% DCR for the combination
- Ongoing studies of MK-4280
  - Part B of current study: dose confirmation and efficacy evaluation of MK-4280 alone and in combination with pembrolizumab ± chemotherapy in select advanced solid tumors
  - Study 4280-003: phase 1/2 study of MK-4280 + pembrolizumab in patients with select hematological malignancies (see poster P315 by Gregory et al for trial design)

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[a]Includes investigators participating in dose confirmation.