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

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Disclosures

- Talia Golan
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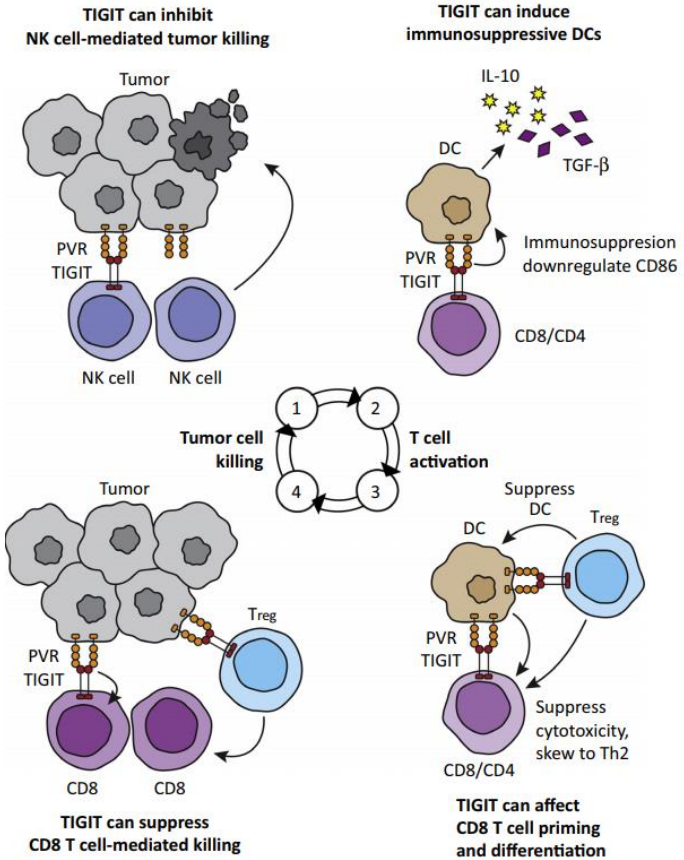
TIGIT: T-Cell Immunoreceptor With Ig and ITIM Domains

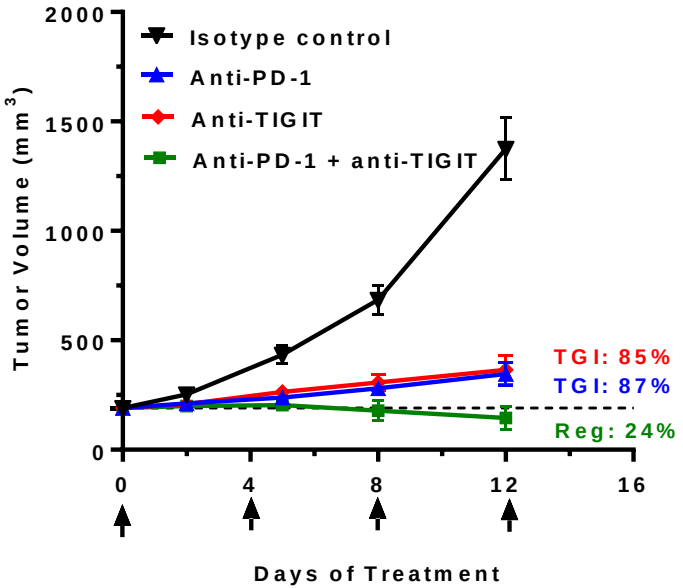
- Immunomodulatory receptor expressed on lymphocytes, most commonly on effector $CD4^+$ and $CD8^+$ T cells, regulatory $CD4^+$ T cells, and NK cells
- Competes with CD226 for binding to its ligands CD155/PVR/Nec15/Tage4 and CD112/PVRL-2
- Binding of TIGIT to CD155 and CD112 on tumor cells and tumor-associated macrophages prevents initiation of an effective antitumor immune response
- Preventing TIGIT from binding to its ligands could restore antitumor immunity



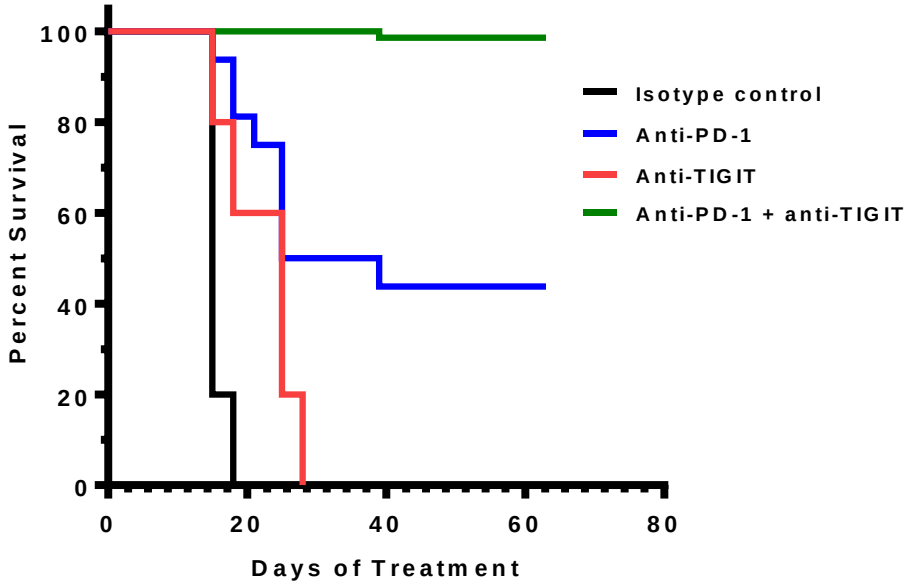
Manieri NA et al. *Trends Immunol* 2017;38:20-28.

MC38 Mouse Model: TIGIT Inhibition Shows Antitumor Activity as Monotherapy and in Combination With PD-1 Inhibition

Change in Tumor Volume



Survival



REG, regression; TGI, tumor growth inhibition.
MSD, data on file.

MK-7684

- Humanized, IgG1 monoclonal antibody that binds TIGIT and prevents it from interacting with CD112 and CD155
- Study 7684-001: first-in-human, phase 1 dose-finding study of MK-7684 as monotherapy and in combination with the anti–PD-1 monoclonal antibody pembrolizumab in patients with advanced solid tumors (ClinicalTrials.gov, NCT02964013)
  - Part A: dose escalation
  - Part B: dose confirmation to estimate the recommended phase 2 dose

Study Design: Part A

- Modified toxicity probability design
  - DLT evaluation period: cycle 1
  - Target DLT rate: ~30%
  - Patients per dose level: minimum of 3, maximum of 14
- Treatment: IV once every 3 weeks for up to 35 cycles or until PD, intolerable toxicity, physician decision, or consent withdrawal
- Crossover from MK-7684 monotherapy to combination therapy upon PD was permitted for eligible patients

Arm 1: MK-7684 Monotherapy

MK-7684 2.1 mg	MK-7684 7 mg	MK-7684 21 mg	MK-7684 70 mg	MK-7684 210 mg	MK-7684 700 mg

Arm 2: MK-7684 + Pembrolizumab

MK-7684 2.1 mg + Pembro 200 mg	MK-7684 7 mg + Pembro 200 mg	MK-7684 21 mg + Pembro 200 mg	MK-7684 70 mg + Pembro 200 mg	MK-7684 210 mg + Pembro 200 mg	MK-7684 700 mg + Pembro 200 mg

DLT, dose-limiting toxicity.
ClinicalTrials.gov, NCT02964013.

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 RECIST v1.1
- Key exclusion criteria
  - Prior anti-TIGIT 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-7684 monotherapy
    - Safety and tolerability of MK-7684 + pembrolizumab
  - Secondary
    - Pharmacokinetics of MK-7684 given as monotherapy and with pembrolizumab
    - Antitumor activity of MK-7684 monotherapy
    - Antitumor activity of MK-7684 + pembrolizumab

ClinicalTrials.gov, NCT02964013.

Baseline Characteristics

Characteristic, n (%)	MK-7684 Monotherapy N = 34	MK-7684 + Pembro N = 34
Age, median (range)	67.5 (33-82)	62.5 (24-79)
Male sex	16 (47%)	22 (65%)
ECOG PS 1	17 (50%)	22 (65%)
Prior therapy		
Neoadjuvant	1 (3%)	0
Adjuvant	2 (6%)	3 (9%)
1	3 (9%)	2 (6%)
2	9 (26%)	15 (44%)
3	5 (15%)	5 (15%)
4	8 (24%)	3 (9%)
≥5	5 (15%)	4 (12%)
Missing	1 (3%)	2 (6%)

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, and SCLC. [b]Includes 1 patient each with melanoma, Merkel cell, RCC, squamous, and uterine.
Data cutoff date: Aug 16, 2018.

Dose Finding and Disposition

MK-7684 monotherapy

- **Dose escalation completed for each prespecified dose level**
- **No DLTs observed**
- Disposition
  - On treatment: n = 2
  - Discontinued: n = 32
    - PD: n = 27
    - Physician decision: n = 2
    - Withdrawal: n = 3
- Crossed over to MK-7684 + pembrolizumab: n = 13

MK-7684 + Pembrolizumab

- **Dose escalation completed for each prespecified dose level**
- **No DLTs observed**
- Disposition
  - On treatment: n = 7
  - Discontinued: n = 27
    - PD: n = 25
    - Physician decision: 1
    - Withdrawal: 1

Data cutoff date: Aug 16, 2018.

Adverse Event Summary

Adverse Event, n (%)	MK-7684 Monotherapy N = 34	MK-7684 + Pembrolizumab N = 47[a]
Any attribution		
Any grade	33 (97%)	45 (96%)
Grade 3-5	13 (38%)	20 (43%)
Grade 5	1 (3%)	3 (6%)
Led to discontinuation	0	1 (2%)
Treatment related		
Any grade	19 (56%)	28 (60%)
Grade 3	2 (6%)	5 (11%)
Grade 4	0	0
Grade 5	0	0
Led to discontinuation	0	0

[a]Includes the 34 patients originally allocated to the combination and the 13 who crossed over from MK-7684 monotherapy.
Data cutoff date: Aug 16, 2018.

Treatment-Related 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 or 5

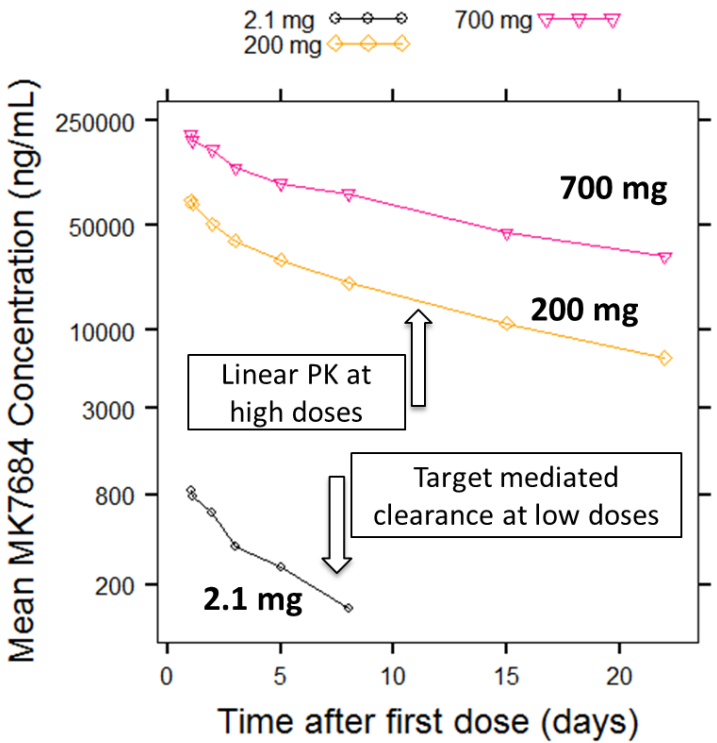
MK-7684 + Pembrolizumab

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 or 5

[a]Includes the 34 patients originally allocated to the combination and the 13 who crossed over from MK-7684 monotherapy.
Data cutoff date: Aug 16, 2018.

Pharmacokinetics of MK-7684: Dose Escalation



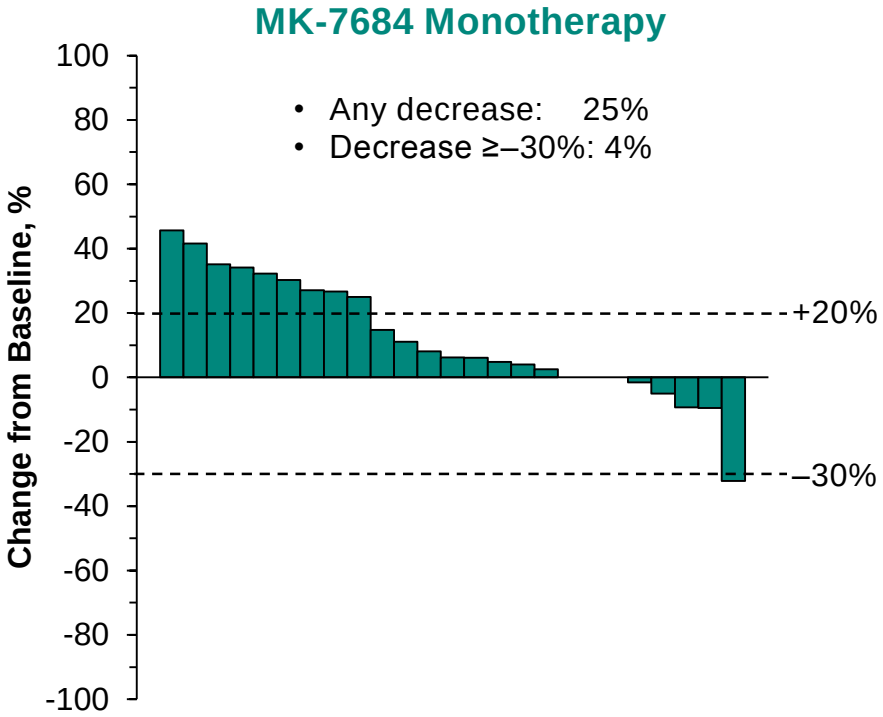
Plot generated pooling MK-7684 PK data from both the monotherapy and combination therapy arms. Arithmetic mean concentrations plotted using nominal sampling times.

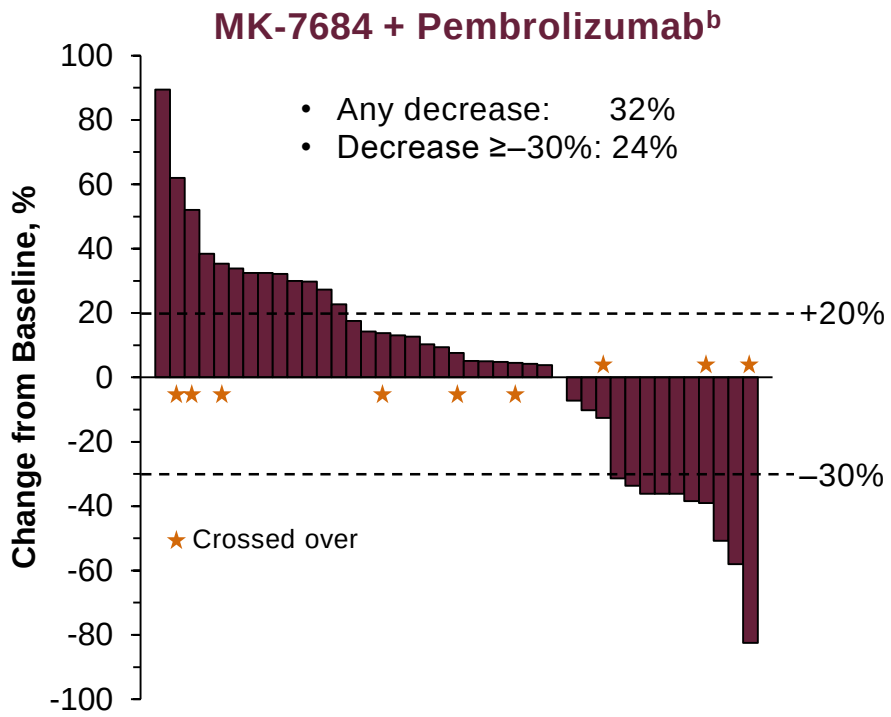
Antitumor Activity[a]
(RECIST v1.1, Investigator Review)

Response	MK-7684 Monotherapy N = 34	MK-7684 + Pembrolizumab N = 43[b]
ORR, % (95% CI)	3% (<1-15)	19% (8-33)
DCR, % (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%)

[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.
Data cutoff date: Aug 16, 2018.

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



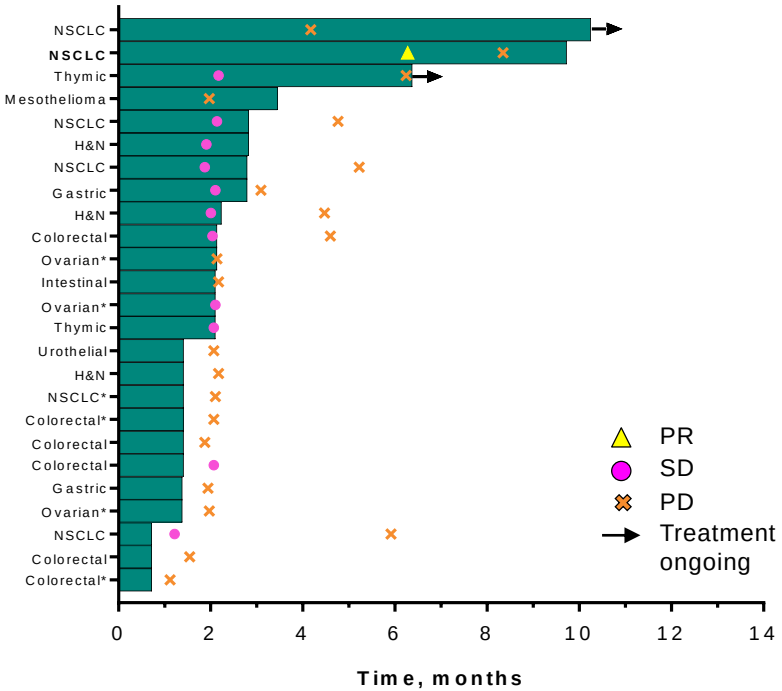


[a]Evaluated in patients with measurable disease at baseline and ≥1 evaluable post-baseline imaging assessment (n = 25 for MK-7684 monotherapy, n = 41 for MK-7684 + pembrolizumab).
[b]Includes 32 patients originally allocated to the combination and 9 who crossed over from MK-7684 monotherapy
Data cutoff date: Aug 16, 2018.

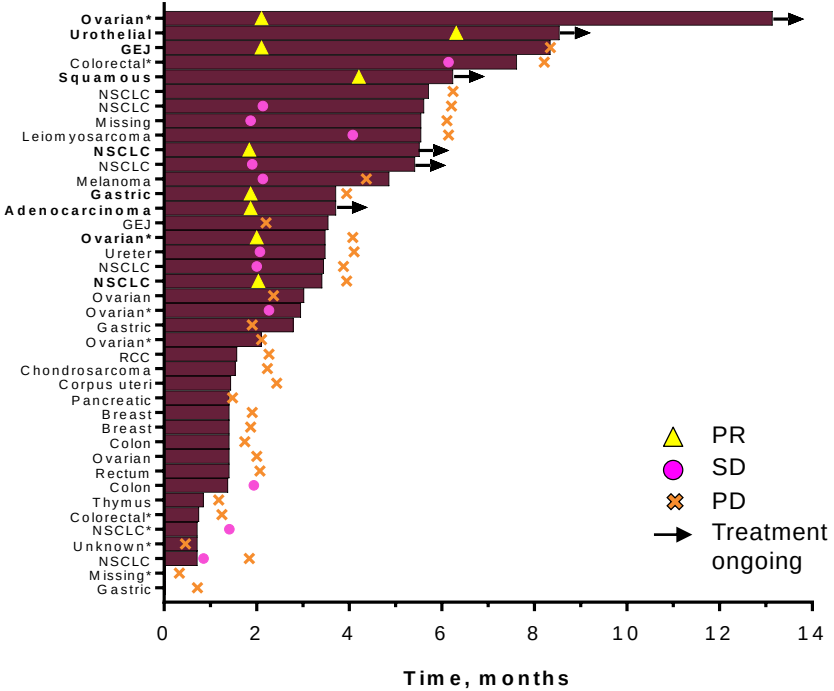
Treatment Duration and Response

(RECIST v1.1, Investigator Review)

MK-7684 Monotherapy



MK-7684 + Pembrolizumab[a]



Line length represents the time to the last dose of study treatment. Time to best response and subsequent PD or death, whichever occurred first, are shown for each patient. Only those patients who had ≥1 post-baseline imaging assessment are included.

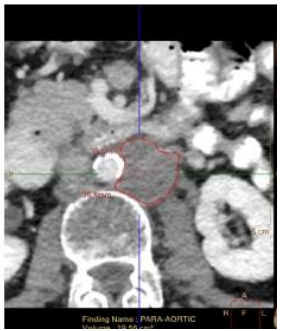
*Patients who crossed over.

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

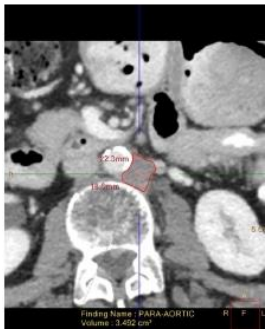
Partial Response in a 75-year-old Female with *BRCA* Wild-Type Ovarian Cancer

Para-aortic Lymph Node

Pretreatment

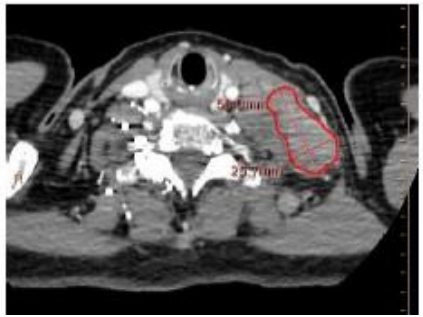


On Treatment

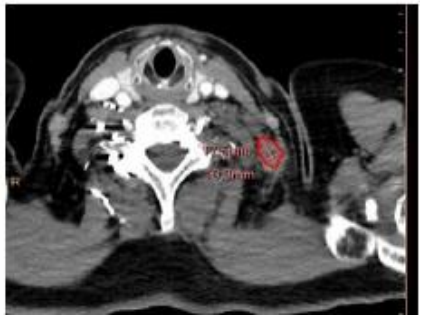


Cervical Lymph Node

Pretreatment



On Treatment



- 4 prior lines of chemotherapy, no prior anti–PD-1 or anti–PD-L1 therapy
- Received MK-7684 2.1 mg monotherapy with document PD per RECIST, then crossed over to MK-7684 2.1 mg plus pembrolizumab
- Partial Response at 9 weeks after crossover
  - 85% reduction in tumor volume
  - Reduction in size of all lesions: mesenteric deposits, lymph nodes (para-aortic, iliac, cervical)
  - Response is ongoing at 13 months
  - Treatment discontinued because of rash

Summary and Conclusions

- In this first-in-human study, MK-7684 given as monotherapy and in combination with pembrolizumab 200 mg was well tolerated and had a manageable safety profile across all doses tested
  - Dose finding proceeded to completion without DLTs
  - No treatment-related deaths
- Promising antitumor activity observed in a heavily pretreated population across multiple tumor types, particularly for MK-7684 + pembrolizumab
  - 3% ORR and 35% DCR for MK-7684 alone
  - 19% ORR and 47% DCR for the combination
  - Responses observed in patients who crossed over from monotherapy to combination therapy
- Dose confirmation and efficacy evaluation of MK-7684 alone and in combination with pembrolizumab is ongoing in patients with select advanced solid tumors

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[a]Includes investigators participating in dose confirmation.