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A Phase 1b Study of Pembrolizumab (Pembro; MK-3475) in Patients With Advanced Urothelial Cancer

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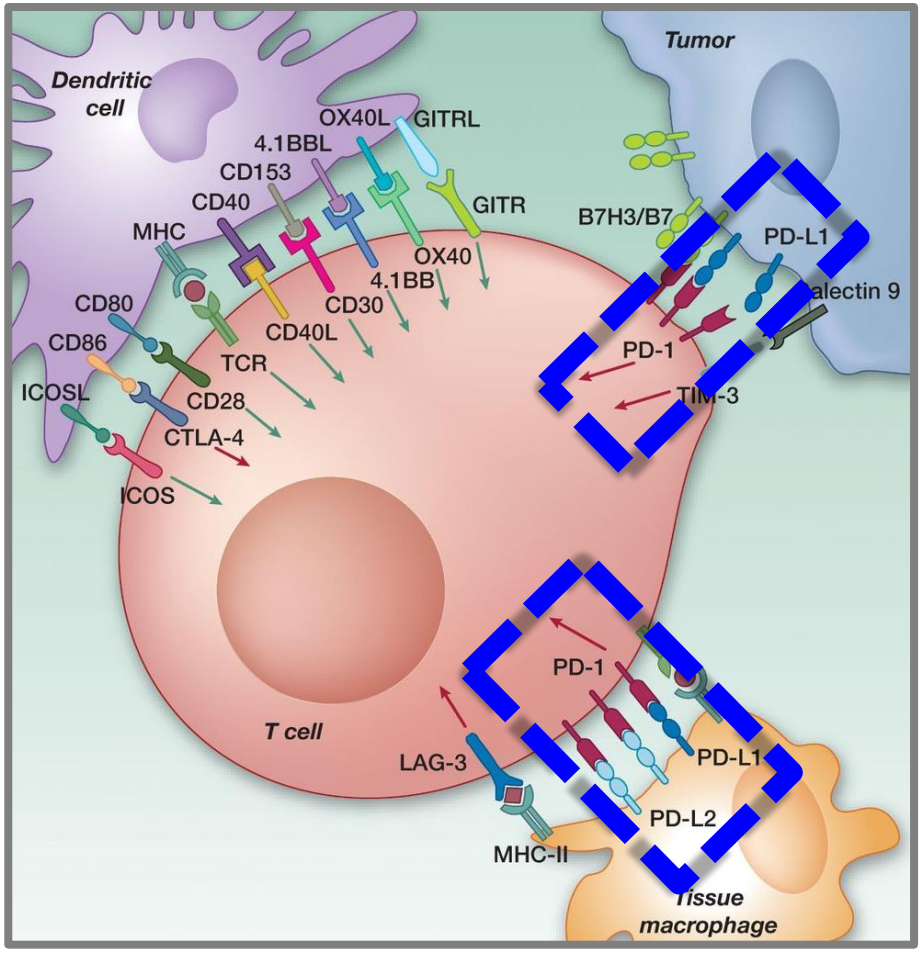
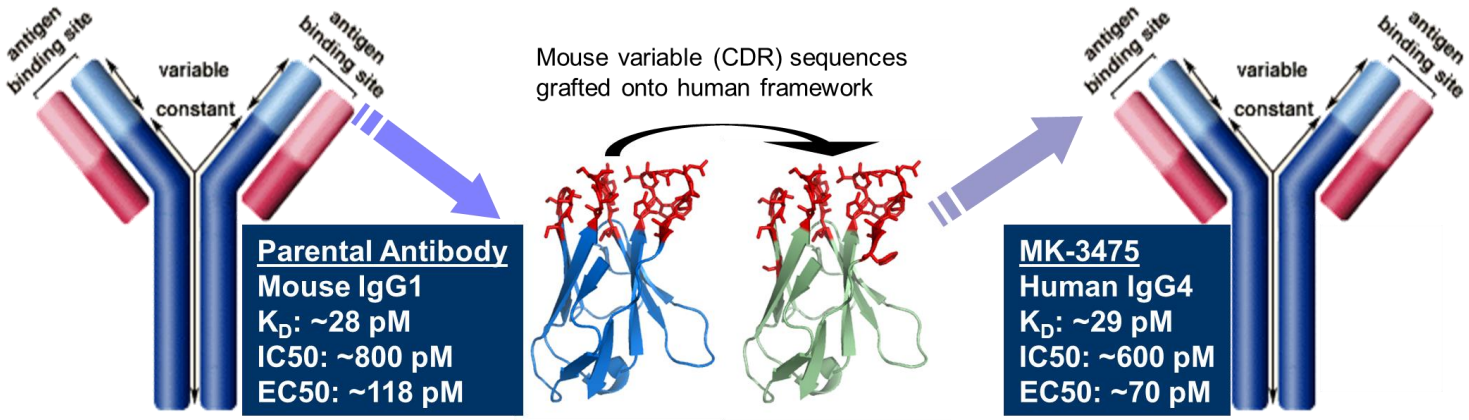
PD-1 Pathway and Immune Surveillance



- PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells
- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function
- Expression of PD-L1 on tumor cells and macrophages can suppress immune surveillance and permit neoplastic growth

Figure used with permission of Melero I et al. *Clin Cancer Res.* 2013;19:997-1008.
Keir ME et al. *Annu Rev Immunol*. 2008;26:677-704; Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64; Hirano F et al. *Cancer Res*. 2005;65:1089-96.

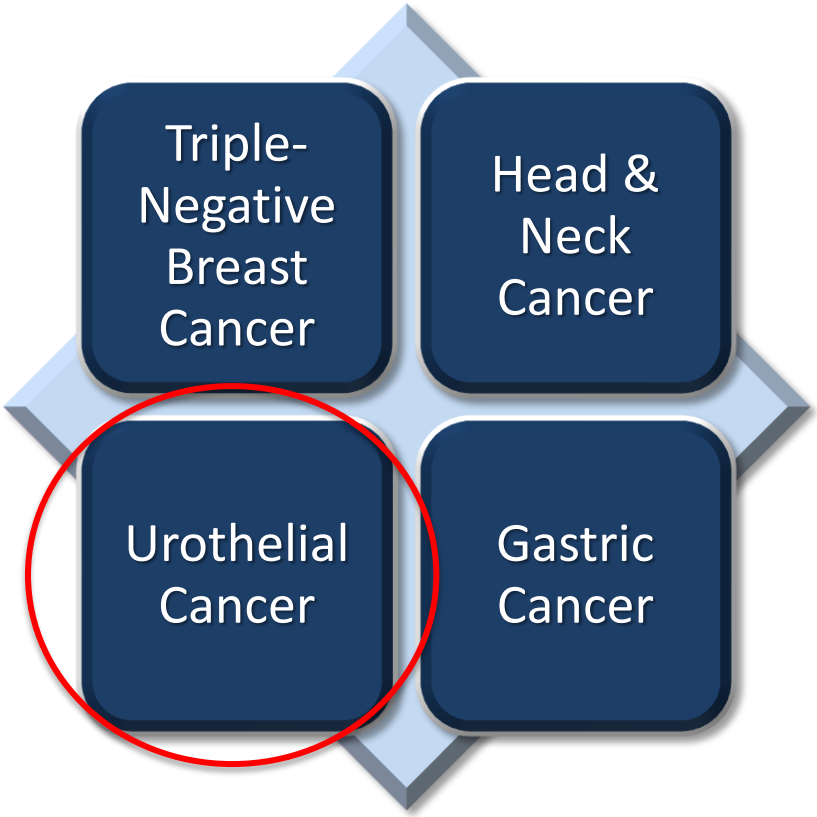
Pembrolizumab (MK-3475) Is a Humanized IgG4, High-Affinity, Anti-PD-1 Antibody



- Dual blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- Pharmacokinetics support dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Low occurrence of anti-drug antibodies, which have no impact on pharmacokinetics
- Demonstrated clinical activity in multiple tumor types[1-5]
- Recently approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if *BRAF* V600 mutation positive, a BRAF inhibitor

1. Ribas A et al. *J Clin Oncol*. 2014;32(suppl 5):abstr LBA9000; 2. Rizvi N et al. *J Clin Oncol*. 2014;32(suppl 5): abstr 8007; 3. Garon EB et al. *J Clin Oncol*. 2014;32(suppl 5): abstr 8020; 4. Seiwert TY et al. *J Clin Oncol*. 2014;32(suppl 5):abstr 6011. Plimack E et al. Abstr. LBA23. Presented at 2014 ESMO Congress, September 26-30, Madrid, Spain.

KEYNOTE-012 (NCT01848834): Phase Ib Multi-Cohort Study of Pembrolizumab in Patients With PD-L1^{+} Advanced Solid Tumors



Seiwert T et al. *J Clin Oncol*. 2014;32(suppl 5):abstr L6011. 2. Chow LQM et al. Abstr. LBA31. Presented at: 2014 ESMO Congress, September 26-30, 2014, Madrid, Spain. Muro K et al. Abstr. LBA15. Presented at 2014 ESMO Congress, September 26-30, Madrid, Spain.

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KEYNOTE-012: Urothelial Cohort

- Recurrent or metastatic cancer of the renal pelvis, ureter, bladder, or urethra
- Transitional or non-transitional cell histology
- ECOG PS 0-1
- No systemic steroid therapy
- No autoimmune disease
- No active brain metastases
- PD-L1-positive tumor

→ Pembro 10 mg/kg IV Q2W

- Complete Response → Discontinuation Permitted
- Partial Response or Stable Disease → Treat for 24 months or until progression or intolerable toxicity
- Confirmed Progressive Disease → Discontinue

Screening for PD-L1

- PD-L1 positivity was defined as any staining in the stroma or in ≥1% of tumor cells using a prototype IHC assay and the 22C3 antibody clone
- 61 of 95 (64.2%) patients screened were found to be PD-L1 positive

Patients: 33 enrolled and treated

Treatment: 10 mg/kg IV Q2W

Response assessment: Performed every 8 weeks per RECIST v1.1

At the discretion of the investigator, patients who received pembrolizumab for ≥24 weeks and for ≥2 treatments beyond confirmed complete response may discontinue therapy. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy was received. If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later.

Baseline Characteristics

Characteristic	Total (N = 33) n (%)
Age, yr, median (range)	70 (44-85)
Male	23 (70)
ECOG performance status	
0	9 (27)
1	23 (70)
Unknown	1 (3)
Histology	
Transitional cell	30 (91)
Non-transitional cell/mixed	3 (9)
Location of metastasis	
Liver	7 (21)
Lymph node only	2 (6)

Characteristic	Total (N = 33) n (%)
No. of prior therapies for advanced disease	
0	8 (24)
1	8 (24)
2	6 (18)
≥3	9 (33)
Prior platinum-based therapy[a]	
Neoadjuvant setting	9 (27)
Adjuvant setting	10 (30)
Metastatic setting	22 (67)

[a]Patients may have received platinum-based therapy in ≥1 setting.

Analysis cut-off date: August 6, 2014.

Treatment-Related Adverse Events

Any Grade Observed in ≥2 Patients

Adverse Event, n (%)	N = 33
Any	**20 (61)**
Fatigue	6 (18)
Peripheral edema	4 (12)
Nausea	3 (9)
ALT increased	2 (6)
AST increased	2 (6)
Dry mouth	2 (6)
Face edema	2 (6)
Headache	2 (6)
Muscle spasms	2 (6)
Pruritus	2 (6)
Pyrexia	2 (6)
Rash	2 (6)

Grade 3-4 Observed in ≥1 Patient

Adverse Event, n (%)	N = 33
Any	**4 (12)**
AST increased	1 (3)
Dehydration	1 (3)
Neuromyopathy	1 (3)
Rash maculopapular	1 (3)
Rash pruritic	1 (3)
Rhabdomyolysis	1 (3)
Thrombocytopenia	1 (3)
Toxic encephalopathy	1 (3)

- No treatment-related deaths
- 1 infusion-related reaction
- 1 discontinuation due to a treatment-related AE

Analysis cut-off date: August 6, 2014.

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Antitumor Activity (RECIST v1.1, Central Review)

	Patients Evaluable For Response[a] (n = 29)		
	n	%	95% CI
Overall response rate	7	24.1	10.3-43.5
Best overall response			
Complete response	3	10.3	2.2-27.4
Partial response	4	13.8	3.9-31.7
Stable disease	4	13.8	3.9-31.7
Progressive disease	14	48.3	29.4-67.5
No assessment	4	13.8	3.9-31.7

[a]Patients evaluable for response were those with measurable disease by central review at baseline who received ≥1 pembrolizumab dose and who had ≥1 post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE. "No assessment" signifies patients who discontinued therapy before the first scan due to progressive disease or a treatment-related AE.
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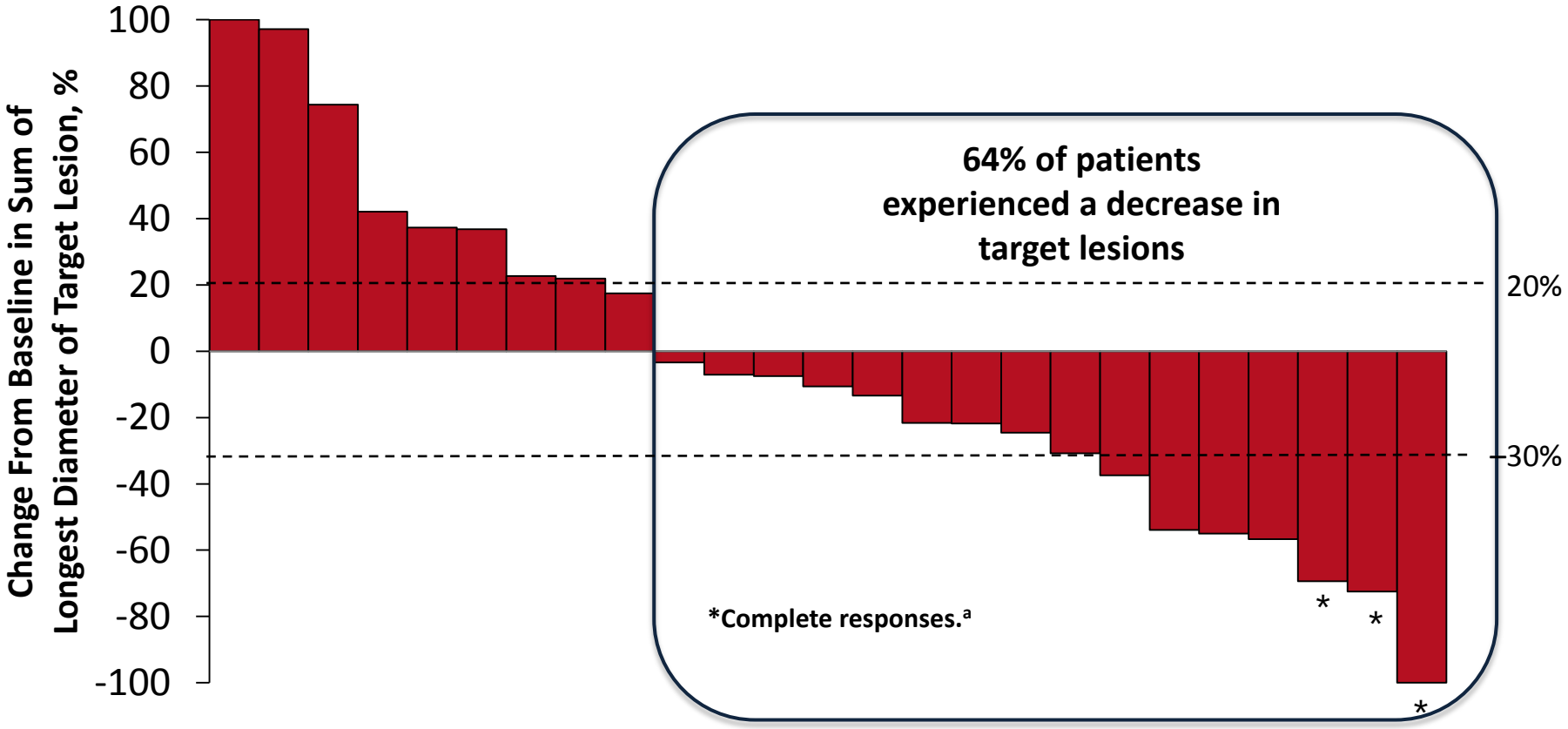
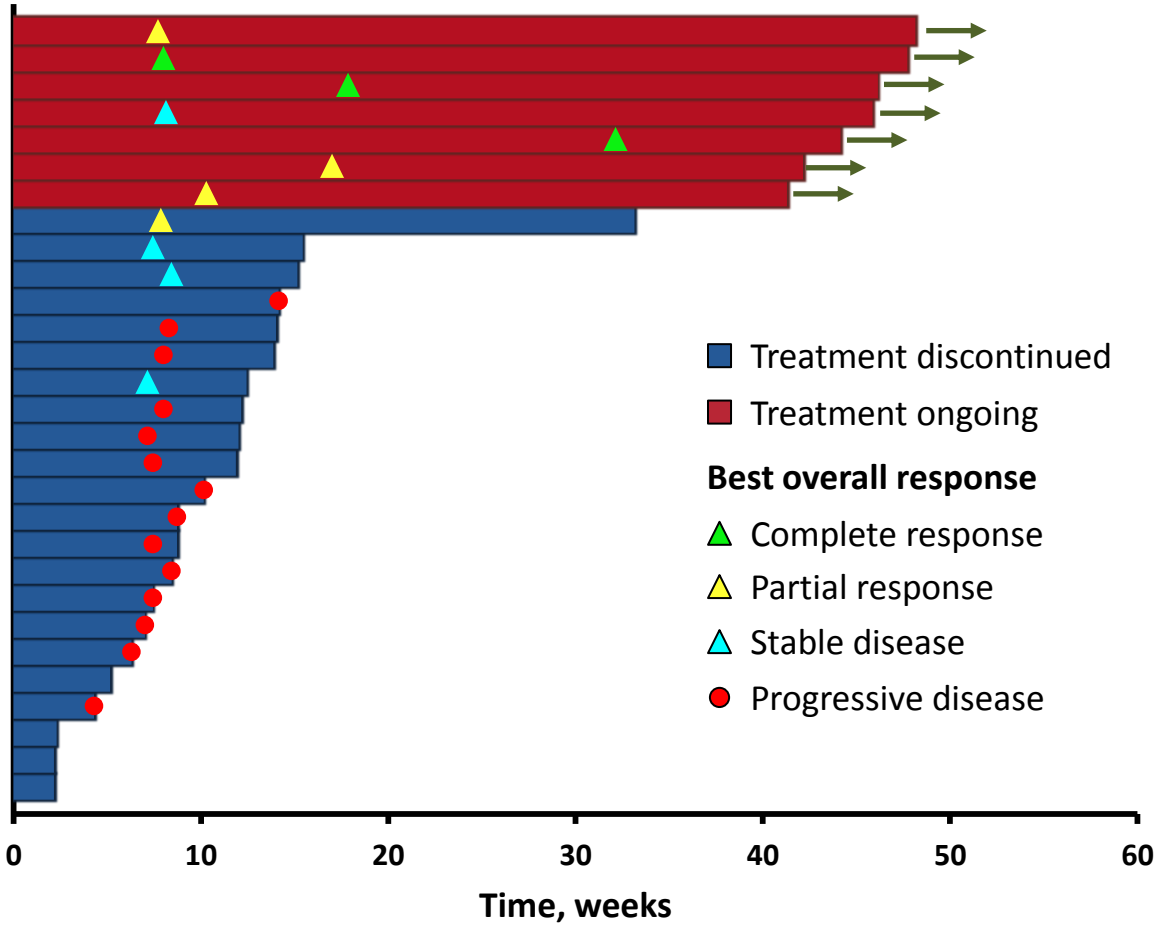
Maximum Percent Change From Baseline in Target Lesions (RECIST v1.1, Central Review)



[a]2 of 3 patients with complete response had <100% reduction due to the use of lymph nodes as target lesions. All lymph nodes returned to normal size per RECIST v1.1.
Analysis includes patients with measurable disease per central review at baseline who received ≥1 pembro dose and had ≥1 post-baseline tumor assessment (n = 25).
Analysis cut-off date: August 6, 2014.

Treatment Exposure and Response Duration



- Median follow-up duration: 11 months (range, 10-13)
- 7 (21%) patients remain on therapy
- 22 (67%) patients received ≥3 pembrolizumab doses
- Median time to response: 8 weeks (range, 8-17)
- 6 of 7 responses are ongoing
- Response duration: 16 to 40+ weeks (median not reached)

Analysis performed in patients with measurable disease by central review at baseline who received ≥1 pembro dose and had ≥1 post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE (n = 29).
Analysis cut-off date: August 6, 2014.

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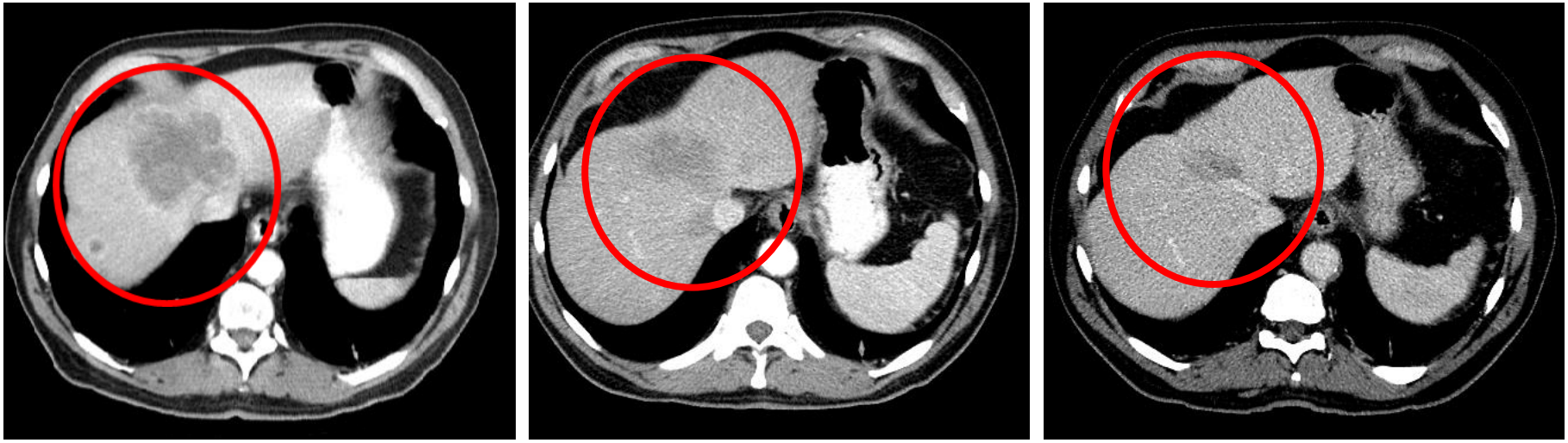
Partial Response In a Patient With Liver Metastases

Baseline **Week 8** **Week 16**

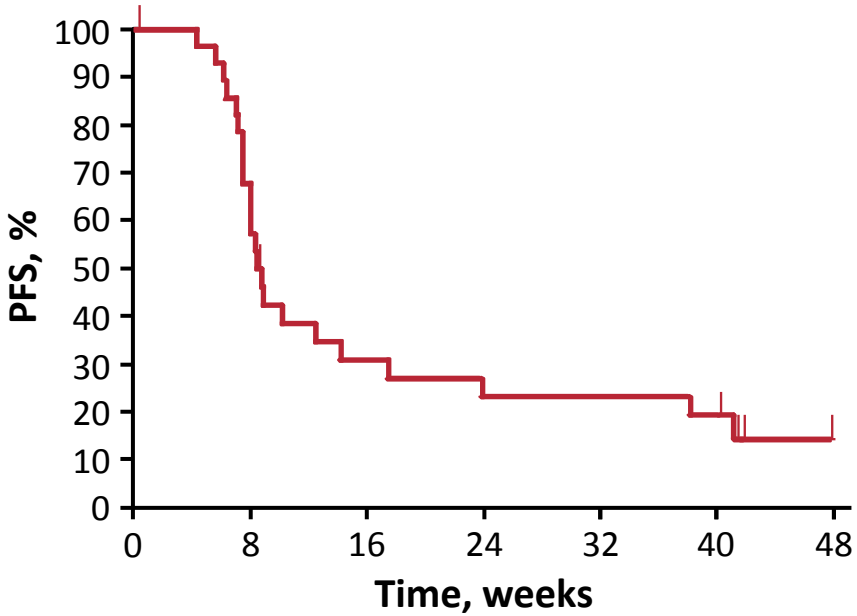


- Patient experienced progressive disease at week 24 due to increased size of non-target lesions
- Patient alive with response in liver maintained through week 40

Case courtesy of Dr. Aymen Elfiky, Dana Farber Cancer Institute, Boston, MA, USA.

Survival

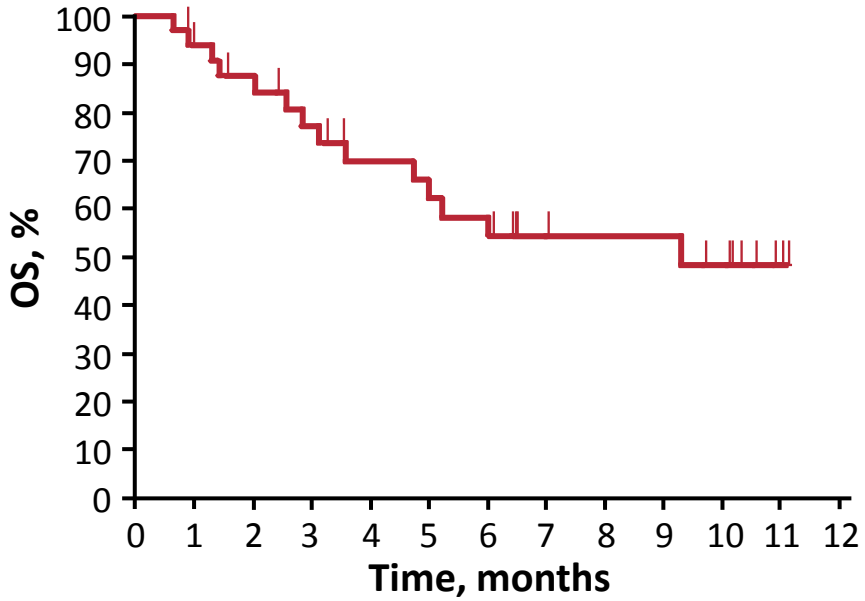
Progression-Free Survival (n = 29)



N at risk	29	19	8	6	6	5	0

- Median PFS: 8.6 weeks (95% CI, 7.4-14.1)
- PFS rate at 6 months: 23.1%

Overall Survival (N = 33)



N at risk	33	29	26	22	18	16	15	9	9	9	7	2	0

- Median OS: 9.3 months (95% CI, 3.6-NR)
- OS rate at 6 months: 58.0%

PFS analysis performed in patients with measurable disease by central review at baseline who received ≥1 pembro dose and had ≥1 post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE (n = 29).
OS analysis performed in all enrolled patients (n = 33).
Analysis cut-off date: August 6, 2014.

Summary and Conclusions

- Pembrolizumab was generally well tolerated in patients with advanced urothelial cancer that expressed PD-L1 in the stroma or ≥1% of tumor cells
- Overall response rate in this mostly pretreated population was 24.1%, including a complete response rate of 10.3%
- Responses are durable, with 6 of 7 responses ongoing (median duration of response not reached after 11-month median follow-up)
- 58.0% of patients were alive at 6 months, and median OS was 9.3 months
- 64.2% of patients screened expressed PD-L1 in the stroma or ≥1% of tumor cells. Analysis of the relationship between PD-L1 expression with clinical outcomes is ongoing
- These results support the ongoing development of pembrolizumab in urothelial cancer
- KEYNOTE-045, a randomized phase 3 study of pembrolizumab in advanced urothelial cancer, will be initiated by the end of 2014

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