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IMMUNE CHECKPOINT THERAPY FOR GENITOURINARY CANCERS: KIDNEY CANCER AND TRANSITIONAL CELL CARCINOMA

Kathleen Mahoney, M.D., Ph.D.
Instructor of Medicine, Harvard Medical School
Attending, Beth Israel Deaconess Medical Center
Research Fellow, Dana Farber Cancer Institute

Thursday, September 8, 2016

Cancer Center

Disclosures

- No relevant financial relationships
- There will be discussion about the use of products for non-FDA approved indications in this presentation

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Immune checkpoint therapies

- **How does PD-1 antibody therapy mediate its antitumor effect?**

A. Kills lymphocytes that express PD-1 protein
B. Kills tumor cells that express the PD-L1 protein
C. Blocks the interaction between PD-L1 and PD-1 on lymphocytes that prevents lymphocytes from killing tumor cells
D. Kills rapidly dividing tumor cells by binding DNA inside the tumor cell

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Immune checkpoint therapies

- **What are risks/side effects unique to immune checkpoint therapies?**

A. hair loss
B. neutropenic fever due to profound cytopenias
C. shinges due to lymphocyte dysfunction
D. immune-related adverse effects

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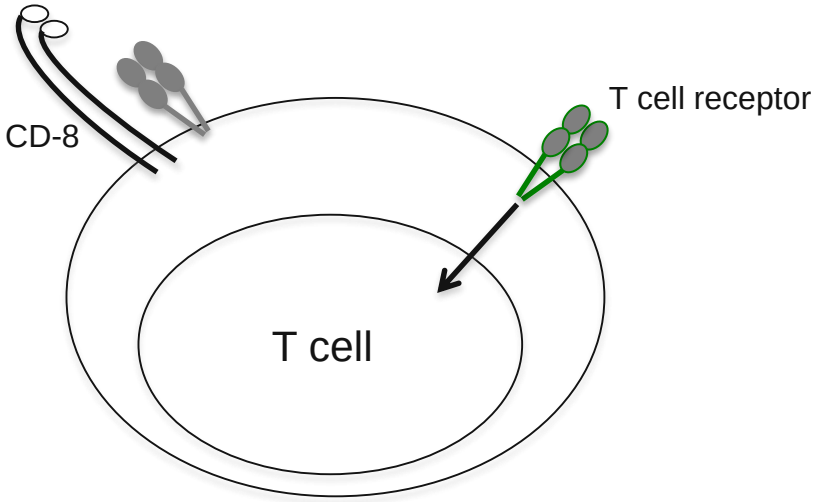
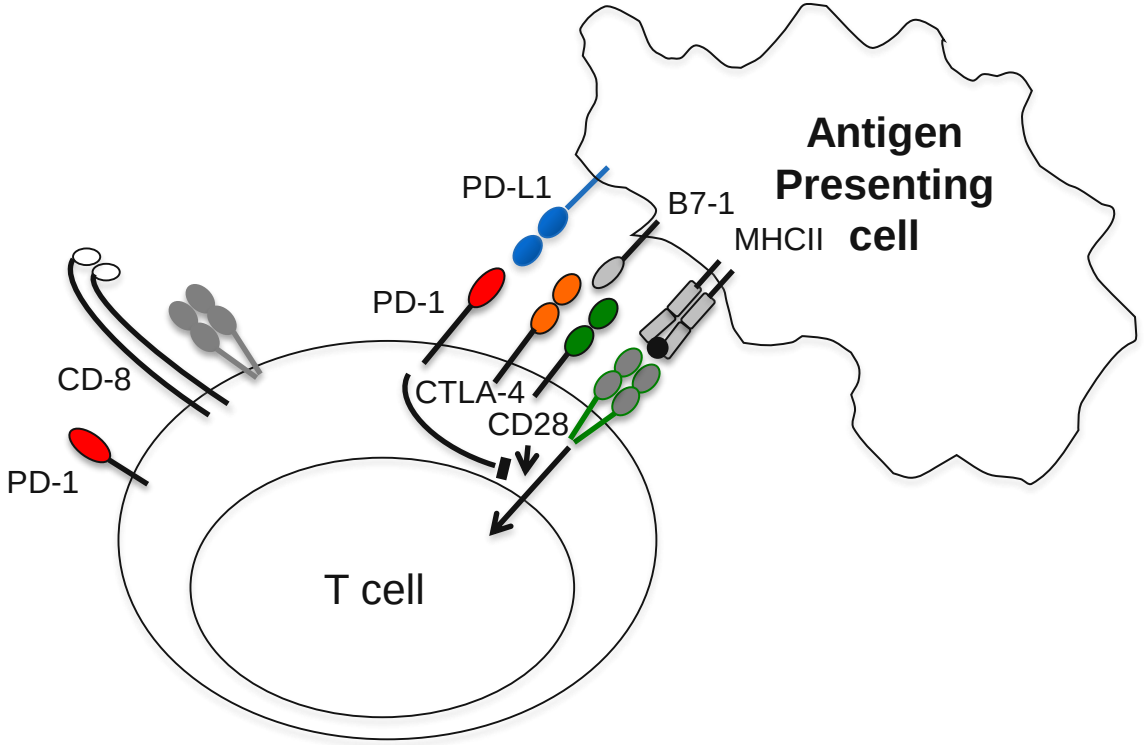
Overview of approved immune checkpoint therapies



Adapted from Mahoney et al. Kidney Cancer, 2nd ed. 2015

Overview of approved immune checkpoint therapies

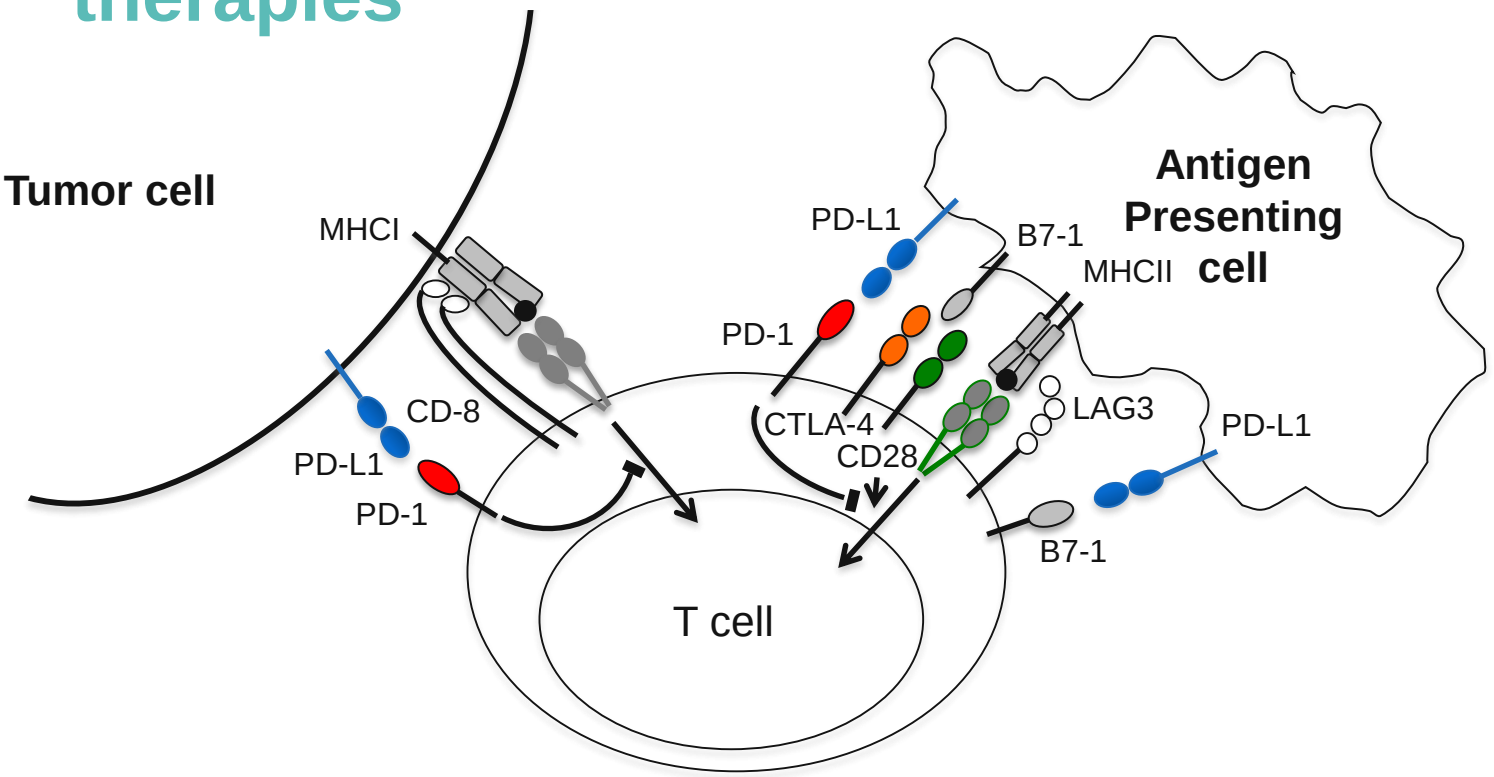


Ipilimumab – initial FDA approved 2011

Melanoma

Adapted from Mahoney et al. Kidney Cancer, 2nd ed. 2015

Overview of approved immune checkpoint therapies



Ipilimumab – initial FDA approved 2011 — Melanoma

Pembrolizumab – initial FDA approved 2014 — Melanoma, NSCLC

Nivolumab – initial FDA approved 2014 — Melanoma, **Kidney**, Hodgkin lymphoma

Atezolizumab – initial FDA approved 2016 — **Bladder cancer**

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Adapted from Mahoney et al. Kidney Cancer, 2nd ed. 2015

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Overview

- Clinical vignettes
- Activity of immune checkpoint inhibitors in advanced genitourinary cancer:
  - *transitional cell carcinoma*
  - *renal cell carcinoma*
- Learning points and clinical considerations
- Questions

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Case presentation 1.1

- 64-year-old gentleman presented with worsening urinary symptoms (urgency, hematuria, and dysuria) and a large ill-defined mass in the bladder.

  TURBT showed invasive high-grade urothelial carcinoma.

  Neoadjuvant platinum-based combination x 2 cycles

  Radical cystoprostatectomy due to urinary obstruction and elevated creatinine: pT3bN3Mx

- **What is the your treatment plan after cystectomy?**

A. 4 cycles of adjuvant chemotherapy
B. follow up with surveillance imaging in 3 months
C. atezolizumab
D. clinical trial

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Case presentation 1.2 (prior to approval of atezolizumab)

Ineligible for atezolizumab clinical trial (chronic hepatitis B)

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Case presentation 1.2 (prior to approval of atezolizumab)

Ineligible for atezolizumab clinical trial (chronic hepatitis B)

- He developed enlarged aortocaval lymphadenopathy 6 months later.
- He started pemetrexed,
  but progressed after 3 cycles.

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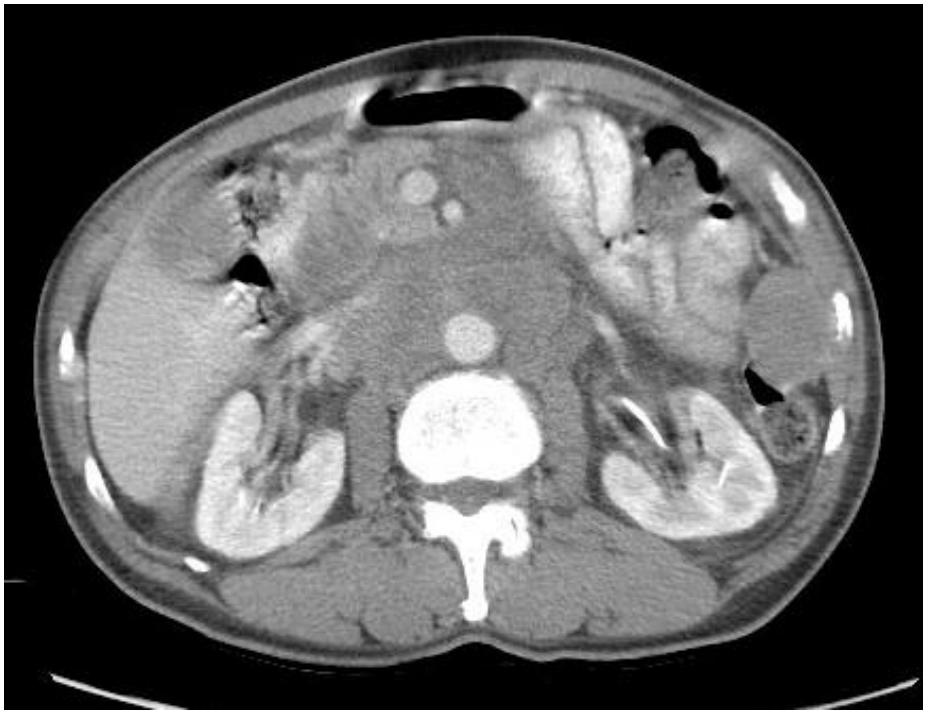
Case presentation 1.2 (prior to approval of atezolizumab)

Ineligible for atezolizumab clinical trial (chronic hepatitis B)

- He developed enlarged aortocaval lymphadenopathy 6 months later.
- He started pemetrexed, but progressed after 3 cycles.
- He was changed to paclitaxel, but developed additional peritoneal masses and progressive of lymphadenopathy encompassing aorta.



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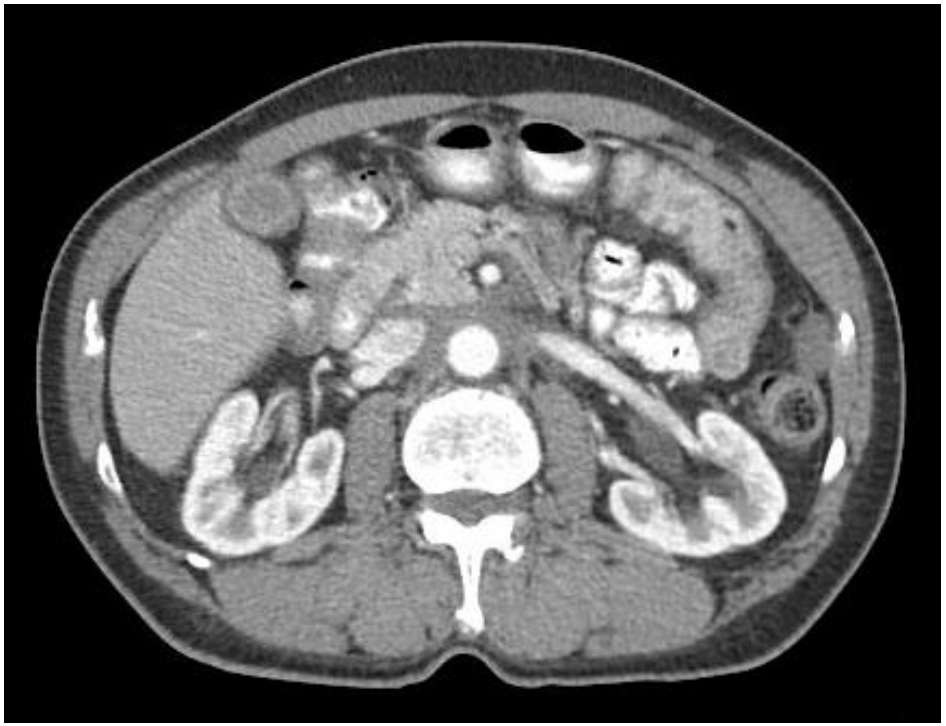
Case presentation 1.3 (prior to approval of atezolizumab)

Ineligible for atezolizumab clinical trial (chronic hepatitis B)

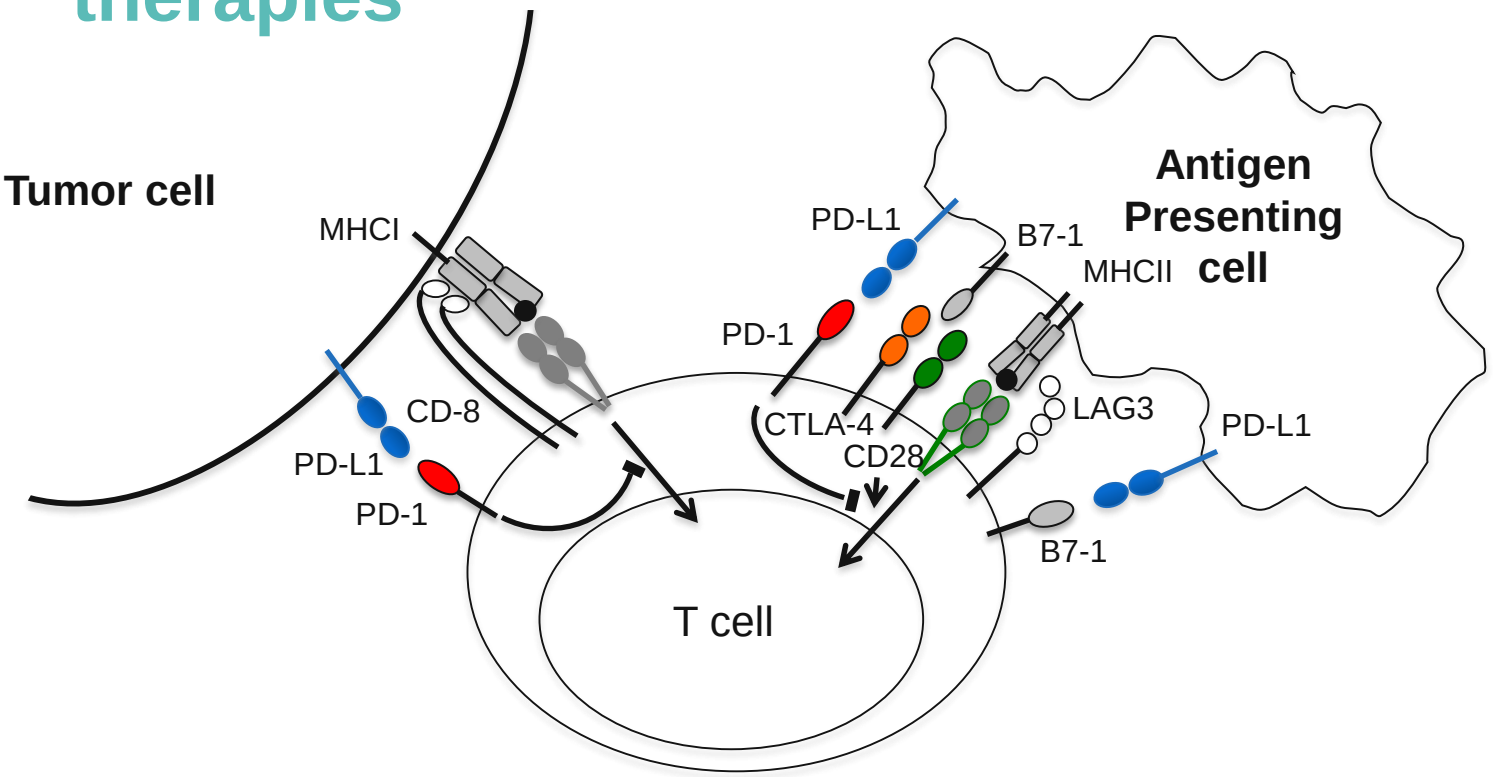
- He had undetectable hepatitis B viral load on treatment.
- Given Phase II data showing efficacy of the PD-1 blocking antibody pembrolizumab in patients with advanced bladder cancer, he started pembrolizumab (off-label).

- He continues to response to treatment after >10 cycles.

He is tolerating it well,
except for developing macular rash
(managed with topical steroids).



Overview of approved immune checkpoint therapies



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Atezolizumab – initial FDA approved 2016 — **Bladder cancer**

Adapted from Mahoney et al. Kidney Cancer, 2nd ed. 2015

Phase I. Atezolizumab is well tolerated.

doi:10.1038/nature13954

MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

Thomas Powles[1], Joseph Paul Eder[2], Gregg D. Fine[3], Fadi S. Braiteh[4], Yohann Loriot[5], Cristina Cruz[6], Joaquim Bellmunt[7], Howard A. Burris[8], Daniel P. Petrylak[2], Siew-leng Teng[3], Xiaodong Shen[3], Zachary Boyd[3], Priti S. Hegde[3], Daniel S. Chen[3] & Nicholas J. Vogelzang[9]

Table 2 | Treatment-related adverse events occurring in two or more patients (grade 1–2) or in one patient (grade 3–4)

Treatment-related adverse events* ($n = 68$)	All grades (n (%))	Grade 3–4 (n (%))
All	39 (57.4)	3 (4.4)
Decreased appetite	8 (11.8)	0
Fatigue	8 (11.8)	0
Nausea	8 (11.8)	0
Pyrexia	6 (8.8)	0
Asthenia	5 (7.4)	1 (1.5)
Chills	3 (4.4)	0
Influenza-like illness	3 (4.4)	0
Lethargy	3 (4.4)	0
Anaemia	2 (2.9)	0
Arthralgia	2 (2.9)	0
Bone pain	2 (2.9)	0
Hyperthermia	2 (2.9)	0
Pain	2 (2.9)	0
Platelet count decrease	2 (2.9)	0
Pruritus	2 (2.9)	0
Thrombocytopaenia	2 (2.9)	1 (1.5)
Vomiting	2 (2.9)	0
Blood phosphorus decrease	1 (1.5)	1 (1.5)

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Nature 2014; 515,558.

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Phase I. Atezolizumab is effective.

MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

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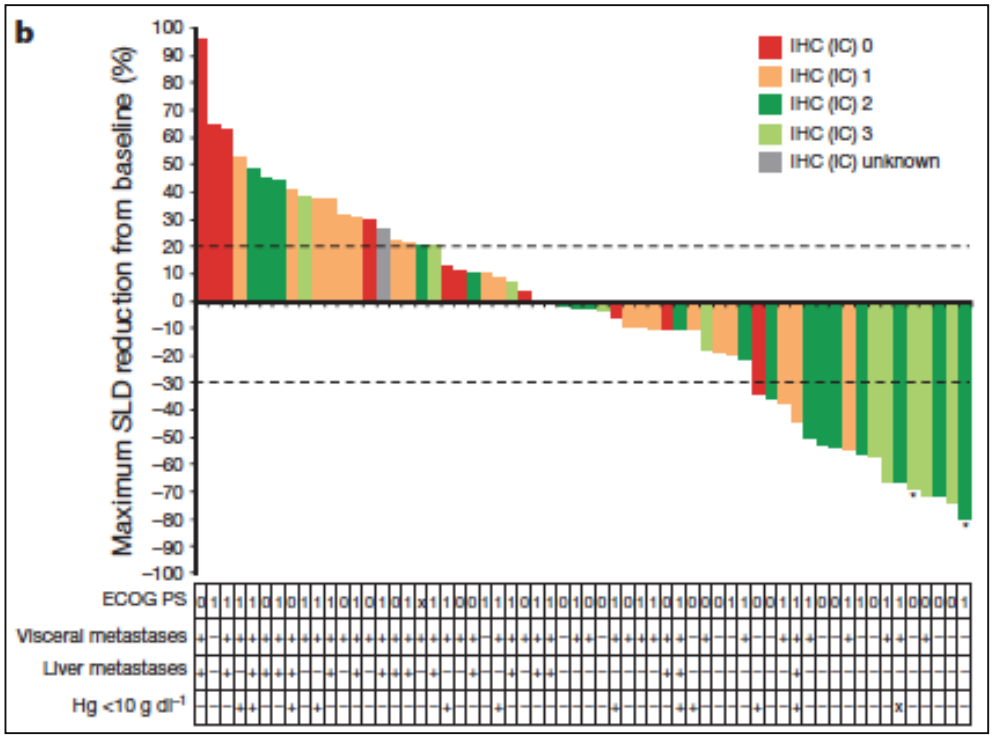
Initially the trial enrolled patients with tumors that expressed higher levels of the PD-L1 protein, then expanded enrollment to patients with no/low levels PD-L1 protein.



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Nature 2014; 515,558.

Phase II. Atezolizumab for Bladder cancer

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial

Jonathan E Rosenberg, Jean Hoffman-Censits, Tom Powles, Michiel S van der Heijden, Arjun V Balar, Andrea Necchi, Nancy Dawson, Peter H O'Donnell, Ani Balmanoukian, Yohann Loriot, Sandy Srinivas, Margitta M Retz, Petros Grivas, Richard W Joseph, Matthew D Galsky, Mark T Fleming, Daniel P Petrylak, Jose Luis Perez-Gracia, Howard A Burris, Daniel Castellano, Christina Canil, Joaquim Bellmunt, Dean Bajorin, Dorothee Nickles, Richard Bourgon, Garrett M Frampton, Na Cui, Sanjeev Mariathasan, Oyewale Abidoye, Gregg D Fine, Robert Dreicer

- Progressed on platinum-based therapy
- 1200mg every 3 weeks
- Primary endpoint: ORR (Compare to historical control rate of 10%)

Lancet 2014; 387:1909.

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  Objective Response Rate in all patients 15% [95% CI 11–20], p=0.0058

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- Progressed on platinum-based therapy
- 1200mg every 3 weeks
- Primary endpoint: ORR (Compare to historical control rate of 10%)
  Objective Response Rate in all patients 15% [95% CI 11–20], p=0.0058
- PDL1 status (on immune cells) assessed on tissue from all patients

ORR in PD-L1 IC2/3 = 26% (95% CI 18–36)

Lancet 2014; 387:1909.

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Atezolizumab is the first immune checkpoint therapy approved for patients with bladder cancer

- Given the unmet need for therapies for patients with bladder cancer, PD-L1 therapy with atezolizumab has been approved for platinum-refractory disease regardless of the expression of PD-L1 in the tumor.

- Single agent and combination trials with PD-1/PD-L1 therapies for patients with advanced bladder cancer are ongoing.

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Case presentation 2.1

- 60 year old gentleman presented with hematuria. Workup revealed a 6 centimeter renal mass and 1 centimeter lung nodule.
- He underwent radical nephrectomy and concurrent left lower lobe wedge resection, clear cell renal cell carcinoma, grade 3.

  pT3BN0M1

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- He underwent radical nephrectomy and concurrent left lower lobe wedge resection, clear cell renal cell carcinoma, grade 3.

  pT3BN0M1
- After 2 years, he developed hilar and mediastinal lymph node disease.

- **What is the your treatment plan?**

A. high dose interleukin-2
B. pazopanib
C. nivolumab
D. clinical trial

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Case presentation 2.2

- 60 year old gentleman presented with hematuria. Workup revealed a 6 centimeter renal mass and 1 centimeter lung nodule.
- He underwent radical nephrectomy and concurrent left lower lobe wedge resection, clear cell renal cell carcinoma, grade 3.

  pT3BN0M1

- After disease recurred, he underwent high dose interleukin-2, but his disease progressed after his first cycle.

- **What is the your treatment plan?**

A. cabozantinib
B. pazopanib
C. nivolumab
D. clinical trial

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Case presentation 2.3

- 60 year old gentleman presented with hematuria. Workup revealed a 6 centimeter renal mass and 1 centimeter lung nodule.
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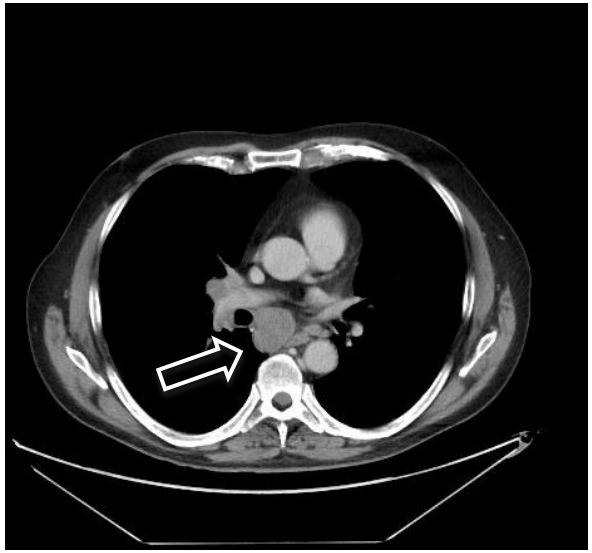
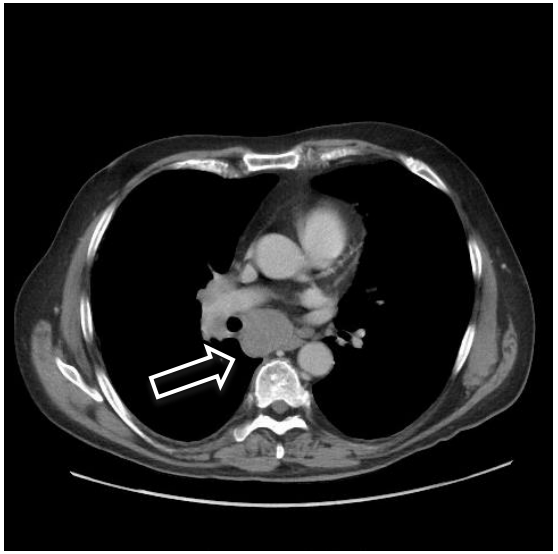
- He enrolled on the Phase I clinical trial with MDX-106 (nivolumab).

Case presentation 2.4

- He enrolled on the Phase I clinical trial with MDX-106 (nivolumab).
- At 2 months, his hilar lymph node was slightly larger.



Pretreatment



2 months on treatment

Adapted from Mahoney et al. Kidney Cancer, 2nd ed. 2015

Case presentation 2.4

- He enrolled on the Phase I clinical trial with MDX-106 (nivolumab).
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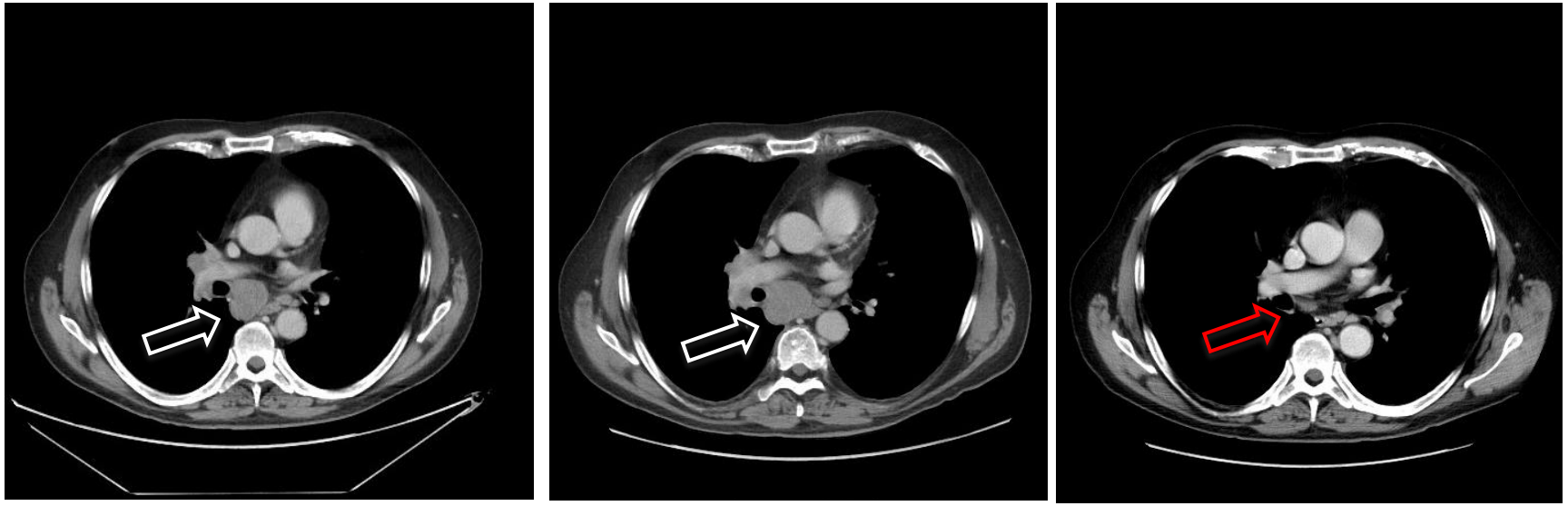

Pretreatment | 2 months on treatment | 14 months on treatment

- He developed an **atypical response** to therapy.

Adapted from Mahoney et al. Kidney Cancer, 2nd ed. 2015

Case presentation 2.5

- He enrolled on the Phase I clinical trial with MDX-106 (nivolumab).
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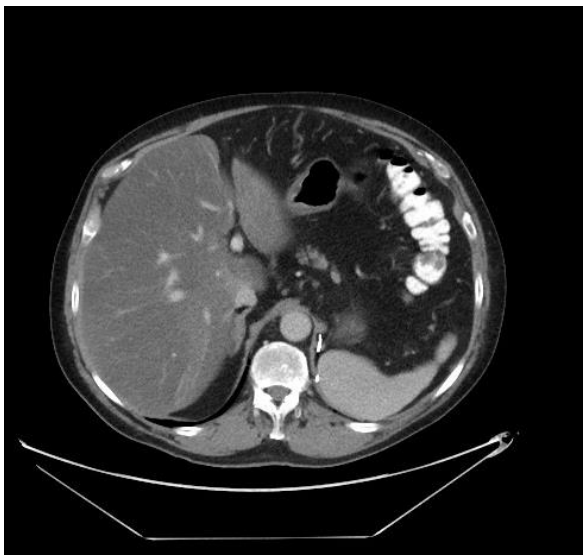

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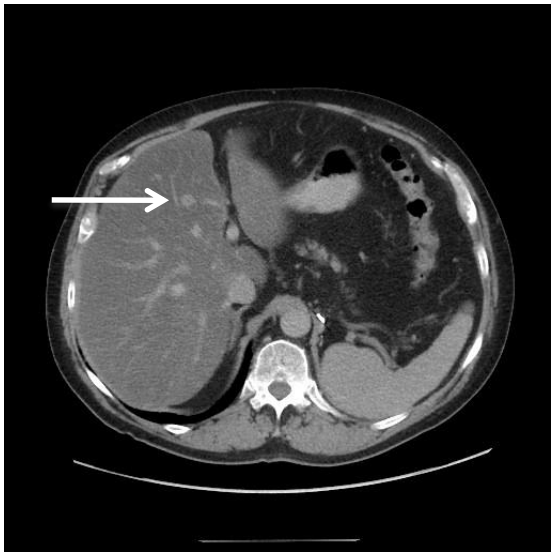
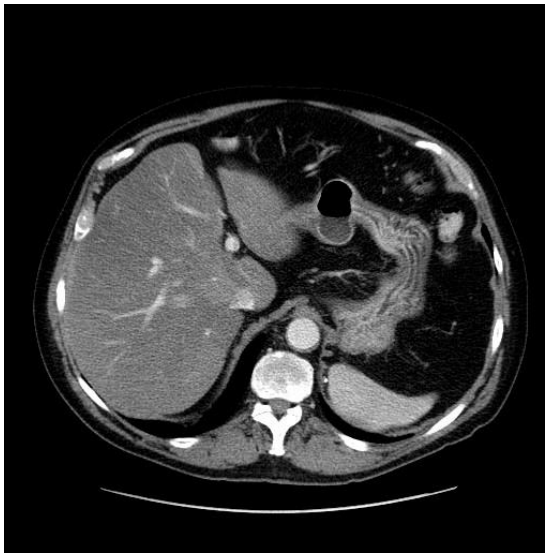


2 months on treatment



14 months on treatment

- He developed an **atypical response** to therapy
  with new asymptomatic lesions in the liver,
  which also resolved on continued PD-1 therapy.

Adapted from Mahoney et al. Kidney Cancer, 2nd ed. 2015

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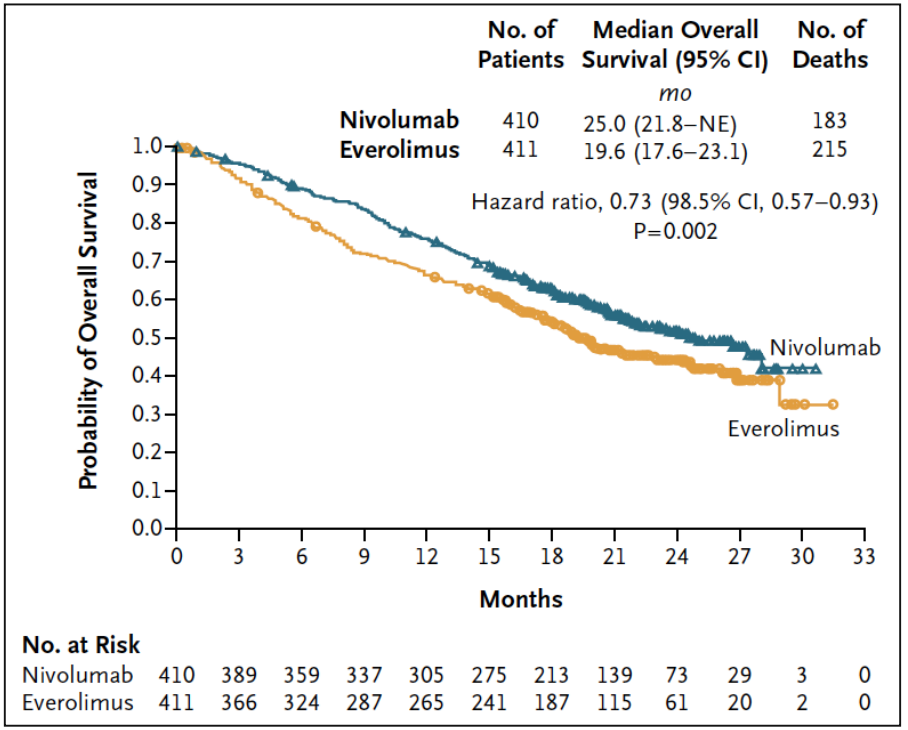
Phase III. Nivolumab has improved overall survival in patient with treated kidney cancer

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Enrolled patients previously treated with VEGFR-tyrosine kinase inhibitor



NEJM 2015; 373:1803.

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Phase III. Nivolumab is effective in kidney cancer regardless of prognostic risk

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A Subgroup Analyses of Overall Survival

Subgroup	Nivolumab	Everolimus	Unstratified Hazard Ratio for Death (95% CI)
	no. of events/total no.		
Overall	183/410	215/411	0.76 (0.62–0.92)
MSKCC prognostic score			
Favorable	45/145	52/148	0.89 (0.59–1.32)
Intermediate	101/201	116/203	0.76 (0.58–0.99)
Poor	37/64	47/60	0.47 (0.30–0.73)
Previous antiangiogenic regimens			
1	128/294	158/297	0.71 (0.56–0.90)
2	55/116	57/114	0.89 (0.61–1.29)

NEJM 2015; 373:1803.

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Combination therapy may improve outcomes

- NCT01472081 Phase 1 combination of nivolumab and ipilimumab:

  Arm 1: Nivolumab 3mg/kg and Ipilimumab 1mg/kg x 4 cycles, then Nivolumab maintenance every 2 weeks

  Arm 2: Nivolumab 1mg/kg and ipilimumab 3mg/kg x 4 cycles, then Nivolumab maintenance every 2 weeks

	N3 +I1 (n=21)	N1 + I3 (n=23)
Confirmed ORR, 95% Confidence interval	**9 (43%)** 21.8-66.0	11**(48%)** 26.8-69.4
Median duration of response	31.1 weeks (4.1-42.1)	NR (12.1-35.1)
Best ORR CR/PR SD PD	 9 (43%) 5 (24%) 5 (24%)	 11(47%) 8 (35%) 3 (13%)

Adapted from Hammers ASCO 2014

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Summary and clinical considerations

- PD-L1 blockade with atezolizumab is approved for patients with platinum-refractory advanced urothelial carcinoma.
- PD-1 blockade with nivolumab is approved for patients with advanced kidney cancer who have been previously treated with VEGFR-tyrosine kinase inhibitors.
- Combination trials with PD-1/PD-L1 based immunotherapy are currently ongoing for patients with bladder and kidney cancer.

  PD-1/PD-L1 single agent therapeutic clinical trial are expected to open for patient with kidney cancer, including patients with untreated metastatic cancer or high risk disease (adjuvant setting).

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Additional clinical considerations

- There have been few patients with chronic viral illness enrolled and treated on PD-1/PD-L1 clinical trials.

  Caution should be used when treating patients with chronic viral illnesses, such as hepatitis and HIV.

- A small fraction of patients may benefit from immune checkpoints despite “psuedo-progression” on imaging.

  Continuation of therapy should be considered in patients who are asymptomatic in the setting of new lesions.

- Combinations with immune checkpoint blocking therapies are associated with increased side effects.

  Side effects from immune checkpoints should be monitored for months after stopping therapy.

Of note, nivolumab is detectable bound to immune cells longer than the half life of the unbound drugs.

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Questions?

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Immune checkpoint therapies

- **How does PD-1 antibody therapy mediate its antitumor effect?**

A. Kills lymphocytes that express PD-1 protein
B. Kills tumor cells that express the PD-L1 protein
C. Blocks the interaction between PD-L1 and PD-1 on lymphocytes that prevents lymphocytes from killing tumor cells
D. Kills rapidly dividing tumor cells by binding DNA inside the tumor cell

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Immune checkpoint therapies

- **How does PD-1 antibody therapy mediate its antitumor effect?**

A. Kills lymphocytes that express PD-1 protein
B. Kills tumor cells that express the PD-L1 protein
C. **Blocks the interaction between PD-L1 and PD-1 on lymphocytes that prevents lymphocytes from killing tumor cells**
D. Kills rapidly dividing tumor cells by binding DNA inside the tumor cell

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Immune checkpoint therapies

- **What are risks/side effects unique to immune checkpoint therapies?**

A. hair loss
B. neutropenic fever due to profound cytopenias
C. shinges due to lymphocyte dysfunction
D. immune-related adverse effects

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