ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Genitourinary Cancers

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Disclosures

- I will be discussing approved and non-FDA approved indications during my presentation.
- Slides originally part of SITC "Advances in Immunotherapy Conference"

Learning Objectives:

- ***Describe the rationale for common approaches to cancer immunotherapy, particularly with respect to prostate cancer and bladder cancer***
- ***Familiarize the learner with clinical data on the efficacy of approved therapies***
- ***Recognize patient selection criteria for approved therapies***
- ***Select appropriate sequencing of approved therapies***

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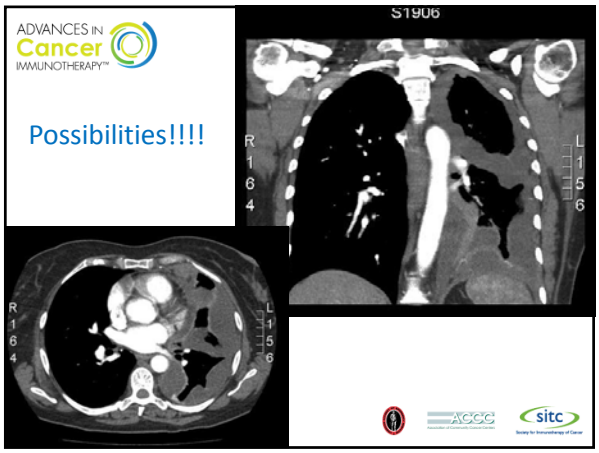
Possibilities!!!!



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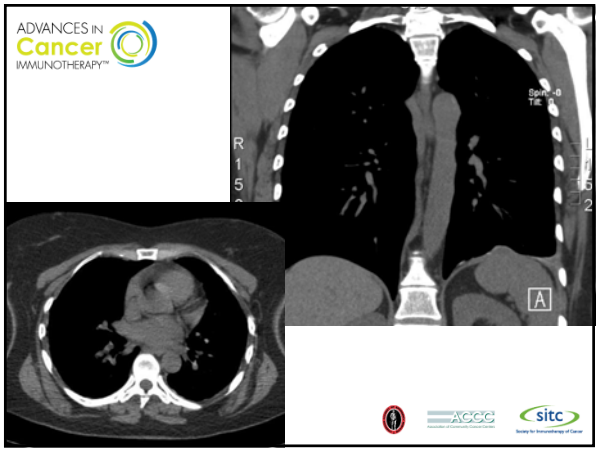

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Prostate Cancer – Case #1:

You are seeing a 68 y/o man who was diagnosed with a Gleason 5+4 prostate cancer 5 years ago. He had evidence of metastases to the bone and retroperitoneal lymph nodes, and was started on treatment with leuprolide and bicalutamide. His PSA initially declined, but then began rising two years ago, and the bicalutamide was discontinued. His PSA continued to rise, and is currently 5 ng/mL. Bone scan shows new metastases, but he remains asymptomatic. What are appropriate immunotherapy treatment options for him?

A) Nivolumab
B) Sipuleucel-T
C) Pembrolizumab
D) B or C

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Sipuleucel-T:

Approval indications:
Patients with asymptomatic to minimally symptomatic castration-resistant metastatic prostate cancer. **Showed 4 month survival advantage in metastatic setting.**

Drug: Autologous Antigen Presenting Cells activated ex vivo with a recombinant fusion protein of a prostate antigen(prostatic acid phosphatase) linked to GMCSF, an immune cell activator.

Dosing: Collection and infusion every 2 weeks x 3

Common adverse reactions:
Chills, fatigue, fever, back pain, nausea, joint aches, headache
Warnings:
Infusion reactions, not tested for transmissible infectious diseases, syncope/hypotension, myocardial infarction, thromboembolic events

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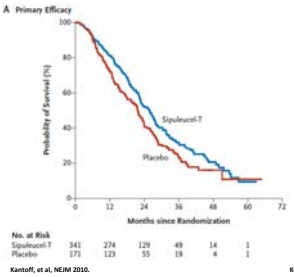
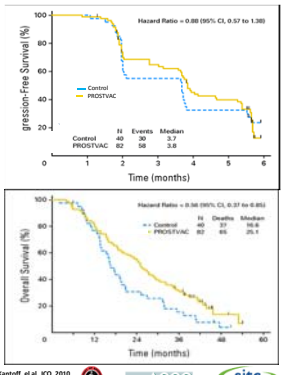
Vaccines in Prostate Cancer



Kantoff, et al, NEJM 2010.



Kantoff, et al, JCO 2010

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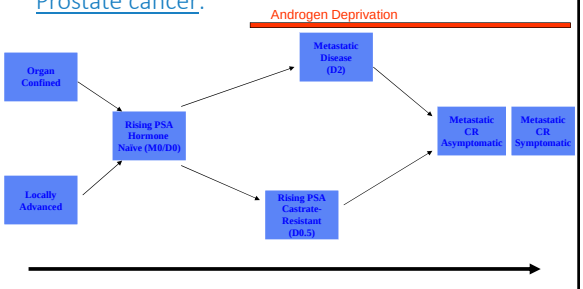
Prostate cancer:



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Lessons learned: Prostate cancer immunotherapy trials

- Prostate *not* an "inflamed" solid tumor like melanoma, renal, lung, bladder
- *Not* significantly hyper-mutated
- For vaccines ↑ doses of vaccine ≠ augmentation of immunity
- *Limited efficacy* of checkpoint inhibitors, anti-CTLA-4, anti-PD1
- No evidence of disease pseudo-progression before response
- No abscopal effects

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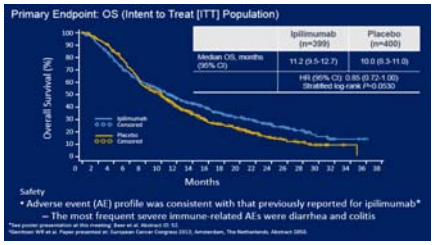
Ipilimumab CTLA-4

Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043)1



Kwon et al Lancet Onc 2014 15:700

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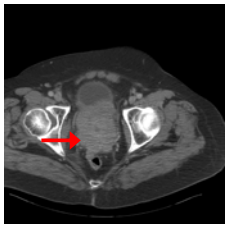
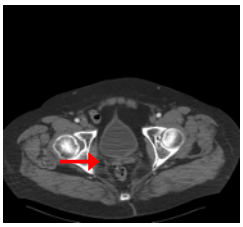
Resolution of Prostate Mass

Screening



14 months



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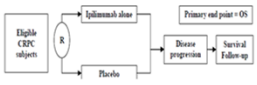
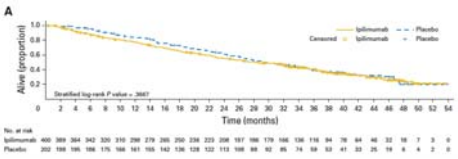
Ipilimumab CTLA-4



Patients:

- Asymptomatic/minimally symptomatic, chemotherapy-naïve castration resistant prostate carcinoma (CRPC)
- No visceral metastases



mOS 28.7 vs. 29.7 mos (HR 1.11; 0.88 – 1.39)

Beer et al JCO 2016

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PD-1/PD-L1 blockade in mCRPC

- Phase I trials with nivolumab
  - No evidence of single-agent activity in mCRPC
- Phase I trials with pembrolizumab
  - Small percentage response rate in patients with advanced mCRCP
  - Pembrolizumab now approved (May 2017) for MSI-high and mismatch repair deficient tumors – hence data exists to support this in the small percentage of prostate cancer that are MSI^{high}
- Multiple combinations are underway with ipilimumab or PD-pathway inhibitors with vaccines (including sipuleucel-T), chemotherapy, androgen deprivation, and radiation therapy

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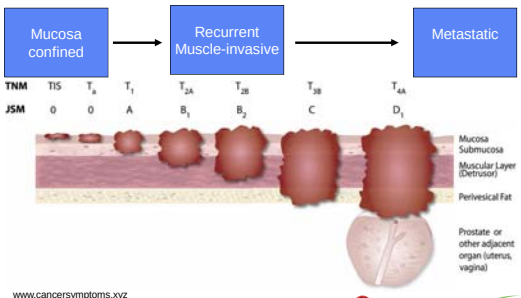
Bladder Cancer:

Mucosa confined → Recurrent Muscle-invasive → Metastatic



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Bladder Cancer – Case #2:

You are seeing a 60 y/o man who was diagnosed with superficial bladder cancer 5 years ago. After several courses of resection and intravesical BCG therapy, he developed muscle-invasive disease 2 years ago and underwent radical cystoprostatectomy. He then did well until 4 months ago when he was found to have lung and liver metastases. He started treatment with gemcitabine and cisplatin chemotherapy, but unfortunately had progressive disease after 3 cycles of therapy. What is the best immunotherapy treatment option for him?

A) IL-2

B) Atezolizumab

C) Pembrolizumab

Prognosis for Bladder Cancer by Stage

Stage	Relative 5-year Survival Rate[8]
0	98%
I	88%
II	63%
III	46%
IV	15%

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The new bladder landscape: new drug approvals

- Durvalumab – anti-PDL1
- Atezolizumab – anti-PDL1
- Avelumab – anti-PDL1
- Nivolumab – anti-PD1
- Pembrolizumab – anti-PD1

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Atezolizumab: PD-L1

Atezolizumab – IMvigor 210 Study

- Open-label, multilabel, two cohort Phase II Study
  - Cohort 1: cisplatin-ineligible (N=119)
  - Cohort 2: progression after platinum-containing chemo (N=310)
    - Assessed PD-L1 expression on tumor infiltrating immune cells

ORR all patients 15%

Median OS 7.9 months

PD-L1 Expression	ORR
≥ 5%	26%
1 – 5%	10%
< 1%	8%

ACCC sitc

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Atezolizumab: PD-L1

Atezolizumab – IMvigor 210 Study

- May 2016: Accelerated approval for patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-based chemotherapy (or whose disease has worsened within 12 months of receiving platinum-based neoadjuvant or adjuvant chemotherapy).
- Expanded approval as a first-line treatment in cisplatin-ineligible patients (IMvigor 210 Cohort 1).
  - ORR 23.5% (CR in 6.7%, PR in 16.8%)
- Approved regardless of PD-L1 status

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Atezolizumab: PD-L1

IMvigor 211 trial

- Open-label, multicenter, randomized Phase III study (atezolizumab vs. physician's choice)
- 931 patients
- Primary endpoint: Overall survival
- **Primary endpoint not met**
- ORR 14.8%, 26% in patients with high PD-L1 expression
- mPFS 2.7 months
- OS 15.9 months

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Nivolumab – Checkmate 275 Study

- Phase II Study in locally advanced/metastatic disease following platinum chemotherapy (N=270)
  - Stratified by PD-L1 expression ≥ 5% or < 5%

ORR all patients 19.6%

Median OS 8.7 months

PD-L1 Expression	ORR
≥ 5%	28.4%
< 5%	15.8%

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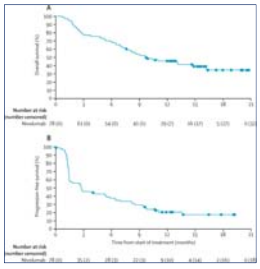
Checkmate 032 Study



Kaplan-Meier curves of overall survival (A) and progression-free survival (B); circles are censored patients.

	Nivolumab (n=78)	PD-L1 <1% (n=42)	PD-L1 ≥1% (n=25)
Confirmed objective response	19 (24·4%, 15·3–35·4)	11 (26·2%, 13·9–42·0)	6 (24·0%, 9·4–45·1)
Best overall response			
Complete response	5 (6%)	1 (2%)	4 (16%)
Partial response	14 (18%)	10 (24%)	2 (8%)
Stable disease	22 (28%)	11 (26%)	8 (32%)
Progressive disease	30 (38%)	18 (43%)	8 (32%)
Unable to establish	7 (9%)	2 (5%)	3 (12%)

Antitumour activity

Sharma, et al., Lancet Onc , 17: 1590-1598, 2016

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Nivolumab

Nivolumab:

- February 2017: FDA approval for patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-based chemotherapy (or whose disease has worsened within 12 months of receiving platinum-based neoadjuvant or adjuvant chemotherapy).
- Approved regardless of PD-L1 status

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Avelumab/Durvalumab

- Locally advanced or metastatic bladder cancer whose disease has progressed during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy.
- Avelumab: Approval based on single-arm, open-label JAVELIN trial in which ORR was 13.3% among 226 patients. Median duration of response not reached (1.4+ to 17.4+ months)
- Durvalumab: Phase I/II trial evaluated the safety and efficacy of durvalumab in patients with locally advanced or metastatic urothelial carcinoma of the bladder (N=191). RR-17.8% (2nd line); 27.6% and 5.1% in PD-L1 high and low group, respectively.

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Pembrolizumab

- Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; accelerated approval for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.
- Based on **Trial KEYNOTE-045 (2nd line)**, a multicenter, randomized, active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. **Improved OS**.
- Accelerated approval for the **first-line** indication was based on data from **KEYNOTE-052**, a single-arm, open-label trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were deemed not eligible for cisplatin-containing chemotherapy. Patients received pembrolizumab 200 mg every 3 weeks. With a median follow-up time of 7.8 months, the ORR was 28.6% (95% CI 24, 34) and the median response duration was not reached (range 1.4+, 17.8+ months).

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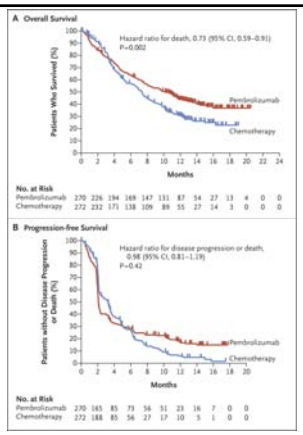
KEYNOTE-045

OS: Median 10.3 months versus 7.4 months

PFS: Not significantly different

AE: Fewer TRAE of any grade in the pembrolizumab group (60.9% versus 90.2%)



Bellmunt, et al., NEJM, 376: 1015-1026, 2017

Trial Data for Checkpoint Inhibitors in Urothelial Carcinoma

	Clinical Trial	Phase	Patient #	ORR %	CR %	Median OS months	Grade 3-4 irAE%
Atezolizumab 2nd Line	Imvigor 210(co-2)[1]	II	310	14.5	5.0	7.9	16.0
Pembrolizumab 2nd line	KEYNOTE-045[3]	III	521	21.1	6.0	10.3	15.0
Nivolumab 2nd line	Checkmate-275[5]	II	265	19.6	2.3	8.7	18.0
Durvalumab 2nd line	NCT01693562[6]	I/II	191	17.8	3.7	18.2	6.8
Avelumab 2nd line	NCT01772004[7]	Ib	249	17.0	6.0	6.5	8.0
Atezolizumab 1st line	Imvigor 210(co-1)[2]	II	119	23.0	9.2	15.9	16.0
Pembrolizumab 1st line	KEYNOTE-052[4]	II	370	24.0	5.0	-	15.0

Trial Data for Checkpoint Inhibitors in Urothelial Carcinoma

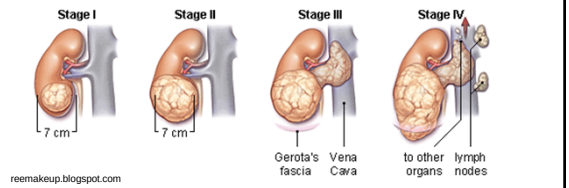
	Clinical Trial	Phase	Patient #	ORR %	CR %	Median OS months	Grade 3-4 irAE%	What were toxicities ????
Atezolizumab 2nd Line	Imvigor 210(co-2)[1]	II	310	14.5	5.0	7.9	16.0	**Fatigue 2%** Pneumonitis 1% Colitis 1%
Pembrolizumab 2nd line	KEYNOTE-045[3]	III	521	21.1	6.0	10.3	15.0	**Pneumonitis 2.3%** Fatigue 1.1% Nephritis 0.8%
Nivolumab 2nd line	Checkmate-275[5]	II	265	19.6	2.3	8.7	18.0	**Hepatitis 2%** Fatigue 2% Colitis 2%
Durvalumab 2nd line	NCT01693562[6]	I/II	191	17.8	3.7	18.2	6.8	**AST Rise 1.6%** Colitis 0.5%
Avelumab 2nd line	NCT01772004[7]	Ib	249	17.0	6.0	6.5	8.0	**Fatigue 2%** Low phosphate 1%
Atezolizumab 1st line	Imvigor 210(co-1)[2]	II	119	23.0	9.2	15.9	16.0	Fatigue 3% ALT/AST rise 3% **Renal Failure 2%**
Pembrolizumab 1st line	KEYNOTE-052[4]	II	370	24.0	5.0	-	15.0	Fatigue 2% **DKA 1%** Pneumonitis 1%

Trial Data for Checkpoint Inhibitors in Urothelial Carcinoma

	Clinical Trial	Phase	Patient #	ORR %	CR %	Median OS months	Grade 3-4 irAE%	Cost Per Year Therapy
Atezolizumab 2nd Line	Imvigor 210(co-2)[1]	II	310	14.5	5.0	7.9	16.0	$191,820
Pembrolizumab 2nd line	KEYNOTE-045[3]	III	521	21.1	6.0	10.3	15.0	$200,865
Nivolumab 2nd line	Checkmate-275[5]	II	265	19.6	2.3	8.7	18.0	$169,911
Durvalumab 2nd line	NCT01693562[6]	I/II	191	17.8	3.7	18.2	6.8	$227,118
Avelumab 2nd line	NCT01772004[7]	Ib	249	17.0	6.0	6.5	8.0	$200,810[13]
Atezolizumab 1st line	Imvigor 210(co-1)[2]	II	119	23.0	9.2	15.9	16.0	
Pembrolizumab 1st line	KEYNOTE-052[4]	II	370	24.0	5.0	-	15.0	

Kidney Cancer:

Surgically resectable → Oligo-metastatic → Metastatic

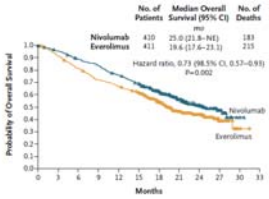


reemakeup.blogspot.com

Nivolumab

- Phase III CheckMate 025 trial – 821 patients with previously treated mRCC (1-2 VEGF TKI):
  Nivolumab (anti-PD-1) 3 mg/kg q 2 wk
  versus everolimus 10 mg per day

- Median OS: 25m vs 19.6m
- ORR: 25% vs 5%
- Median PFS: 4.6m vs 4.4m
- Median duration: 23m vs 13.7m
- Grade 3/4 AE: 19% vs 37%
- Most common AE with nivolumab was fatigue (2%)



Approved by FDA in 2015

Motzer (2015) N Engl J Med 373:1803

Nivolumab:

Approval indications:
Patients with metastatic renal cell cancer who have received prior anti-angiogenic therapy

Dosing: 240 mg IV every 2 weeks and now 480 mg IV every 4 weeks

Common adverse reactions:
Asthenia, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, arthralgia

Warnings:
Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, rash, encephalitis, others

Risk Stratification

The Memorial Sloan-Kettering Cancer Center(MSKCC)/Motzer Score has been used to prognosticate survival based on lab values in the setting of newly diagnosed metastatic RCC.

This scoring system has been updated to evaluate patients in the setting of TKI therapy:

The *International Metastatic Renal Cell Carcinoma Database Consortium* (IMDC) model/Heng Score

IMDC/Heng Score

- Patients are stratified according to presence of 6 risk factors:

- Karnovsky performance status (KPS) < 80%
- Hemoglobin less than lower limit normal
- Time from diagnosis to treatment < 1 year
- Corrected calcium above the upper limit normal (ULN)
- Platelets greater than ULN
- Neutrophils greater than ULN

IMDC/Heng Score

Number of Risk Factors	Risk Group	Median Overall Survival (months)	Two-year overall survival (%)
0	Favorable	Not reported	75
1-2	Intermediate	27	53
3-6	Poor	8.8	7

Heng, DY et al. External validation and comparison with other models of the IMDC prognostic model: a population-based study. Lancet Oncology. 14(2), 141-148(2013)

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Checkmate 214

- The Checkmate 214 Trial randomized 1096 patients with newly diagnosed metastatic renal cell carcinoma to upfront:

ipilimumab/nivolumab (checkpoint inhibitors)

vs.

Sunitinib (TKI)

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Overall survival and response rate were higher for **intermediate/poor risk patients** in the ipilimumab/nivolumab arm.

…BUT

In the **favorable risk** patients, exploratory analyses showed that response rate and progression free survival favored the sunitinib arm.

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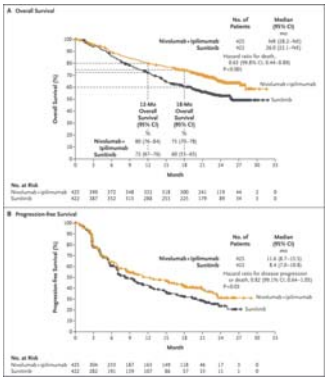

Motzer, RJ et al. Nivolumab plus Ipilimumb versus Sunitinib in Advanced Renal Cell Carcinoma; NEJM April 5 2018.

Other PD-1/PD-L1 Inhibitors:

- Phase III – Atezolizumab (anti-PD-L1) + Bevacizumab vs. Sunitinib
  - Previously untreated mRCC
- Phase II – Nivolumab pre-surgical resection for mRCC (ADAPTeR)
- Phase I – Nivolumab + Sunitinib or Pazopanib or Ipilimumab
  - Previously untreated mRCC (CheckMate 016)
- Different combinations with chemotherapy, IFNα, etc
- Multiple combinations with pembolizumab

Questions???

References(not cited in text)

1.Rosenberg, J.E., et al., *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.* Lancet, 2016. **387**(10031): p. 1909-20.

2.Balar, A.V., et al., *Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial.* Lancet, 2017. **389**(10064): p. 67-76.

*3.Bellmunt, J., et al., Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med, 2017. **376**(11): p. 1015-1026.*

4.Balar, A.V., et al., First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol, 2017. 18(11): p. 1483-1492.

5.Sharma, P., et al., Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol, 2017. 18(3): p. 312-322.

6.Powles, T., et al., Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma: Updated Results From a Phase 1/2 Open-label Study. JAMA Oncol, 2017. 3(9): p. e172411.

7.Patel, M.R., et al., Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol, 2018. 19(1): p. 51-64.

8.Ries LAG, Young JL, Keel GE, et al. SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. National Cancer Institute, SEER Program, NIH Pub. No. 07-6215, Bethesda, MD, 2007.