Immunotherapy for the Treatment of Genitourinary Malignancies

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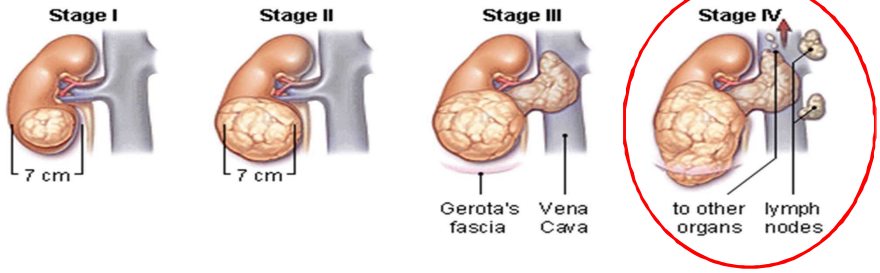
Disclosures

- Receipt of Intellectual Property Rights/Patent Holder: Madison Vaccines Inc. (for pTVG-HP and pTVG-AR
- Consulting Fees: Madison Vaccines Inc.
- Contracted Research: Madison Vaccines Inc, Merck, BMS, Janssen, Pfizer, Novartis
- Ownership Interest Greater Than 5 Percent: Madison Vaccines Inc.
- I will be discussing non-FDA approved indications during my presentation.

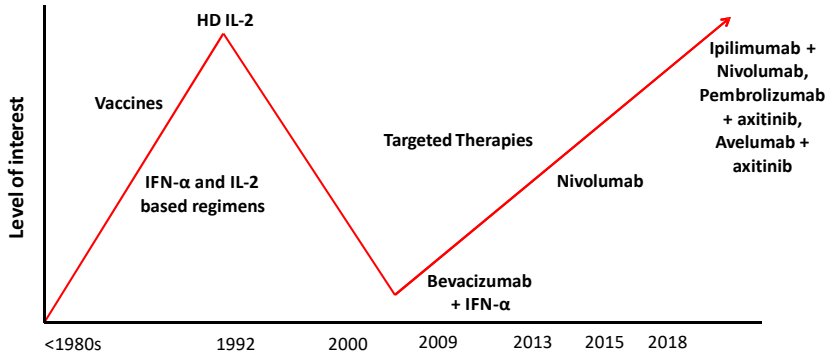
Immunotherapy for Metastatic Kidney Cancer (Renal Cell Carcinoma; RCC)

Surgically resectable → Oligo-metastatic → Metastatic



reemakeup.blogspot.com

History of Immunotherapy in mRCC



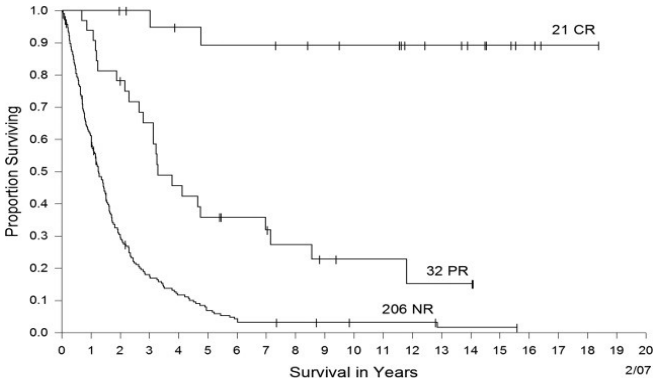
Resurgence of interest in immunotherapy

FDA-approved Immunotherapies for mRCC

Drug	Approved	Indication	Dose
High dose Interleukin-2	1992	Metastatic RCC	600,000 International Units/kg (0.037 mg/kg) IV q8hr infused over 15 minutes for a maximum 14 doses, THEN 9 days of rest, followed by a maximum of 14 more doses (1 course)
Interferon-a + bevacizumab	2009	Clear cell RCC	IFN 9 MIU s.c. three times a week + bev 10 mg/kg Q2W
Nivolumab	2015	Clear cell RCC refractory to prior VEGF targeted therapy	3mg/kg or 240mg IV Q2W or 480mg IV Q4W
Nivolumab +ipilimumab	2018	Clear cell RCC, treatment naïve	3mg/kg nivo plus 1mg/kg ipi Q3W x 4 doses then nivo maintenance at flat dosing
Pembrolizumab + axitinib	2019	Advanced RCC, Treatment naïve	200 mg pembro Q3W + 5 mg axitinib twice daily
Avelumab + axitinib	2019	Advanced RCC, Treatment naïve	800 mg avelumab Q2W + 5 mg axitinib twice daily

High Dose IL-2 in mRCC

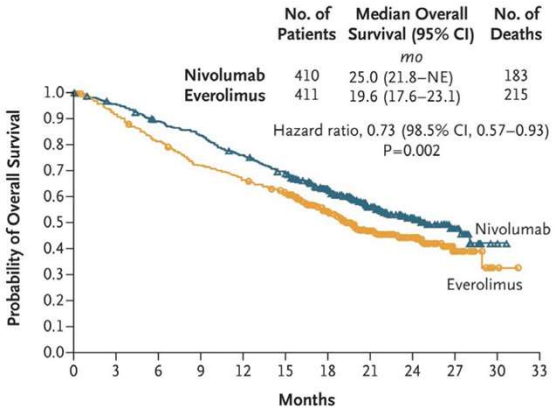
- 20 year analysis of 259 patients
- ORR = 20%
  - 9% CR (n = 23)
  - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months



Klapper et al. Cancer 2008

Second-Line Nivolumab in mRCC

- CheckMate 025 Phase III trial
- Metastatic, clear-cell disease
- One or two previous antiangiogenic treatments
- Nivolumab (3 mg/kg IV Q2W) vs everolimus (10 mg daily)

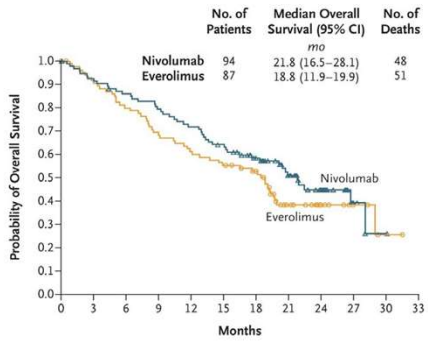


Motzer et al. NEJM 2015

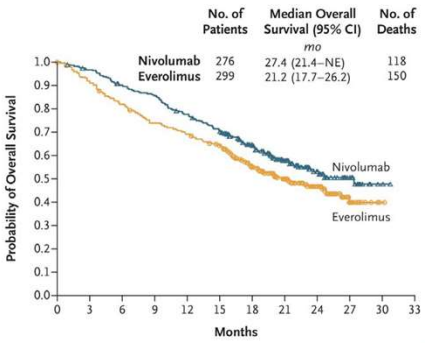
Second-Line Nivolumab in mRCC

PD-L1 subgroups

PD-L1 ≥ 1%

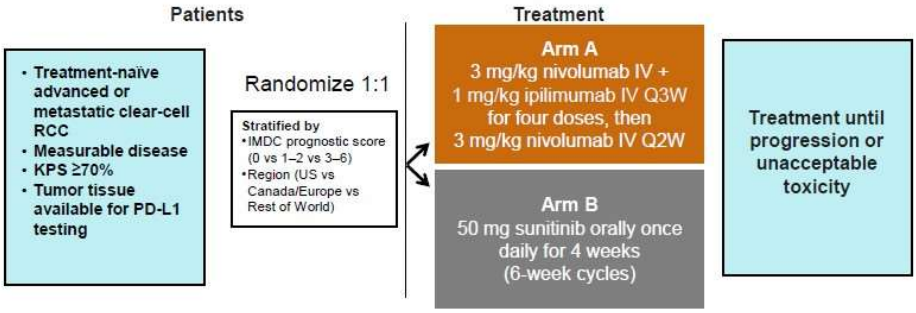


PD-L1 < 1%



Motzer et al. NEJM 2015

First-line Nivolumab + Ipilimumab in mRCC



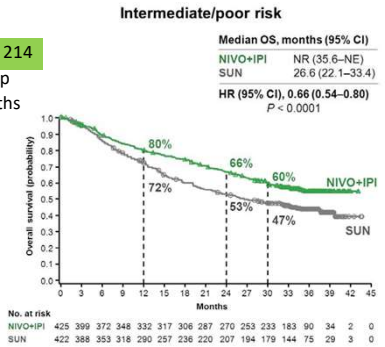
Nivolumab = anti-PD-1 antibody Ipilimumab = anti-CTLA-4 antibody

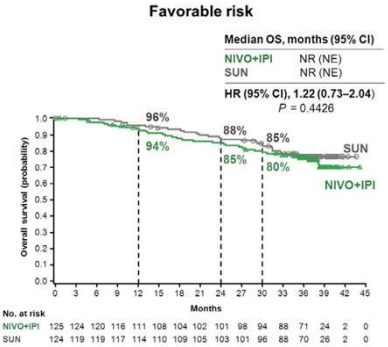
IMDC = International Metastatic RCC Database Consortium

Motzer et al. NEJM 2018, 378:1277

First-line Nivolumab + Ipilimumab in mRCC by IMDC Risk: overall survival

CheckMate 214
Follow-up
= 30 months

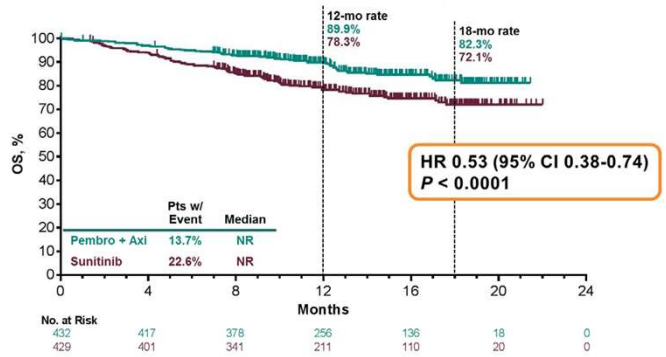




Tannir et al. ASCO GU 2019

First-line Pembrolizumab + axitinib in advanced RCC: overall survival

KEYNOTE-426: OS in the ITT Population

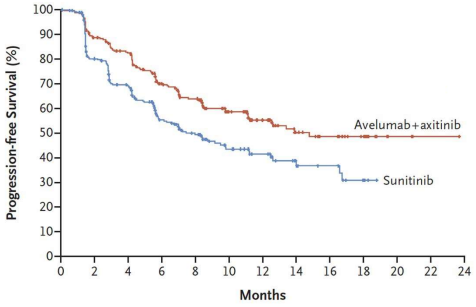


Rini, ASCO 2019
Rini et al. NEJM 2019, 380:1116

First-line avelumab + axitinib in mRCC: progression-free survival

- 2 Independent Primary Endpoints: PFS and OS in PD-L1+
- Median PFS – 13.8 mo vs 7.2 mo (HR 0.61; 95% CI, 0.47–0.79)
- ORR: 51.4% vs 25.7% overall
- OS data: immature

JAVELIN 101 : PFS in the PD-L1+ Population



Motzer, NEJM 2019, 380:1103

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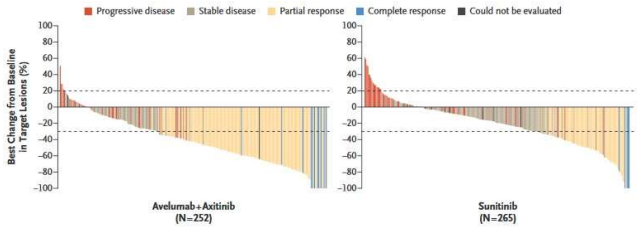
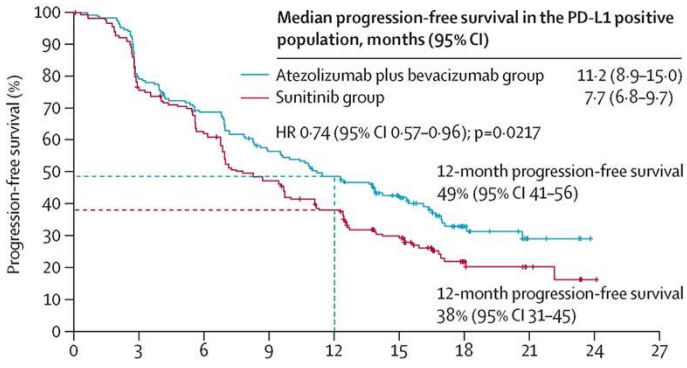


Motzer, NEJM 2019, 380:1103

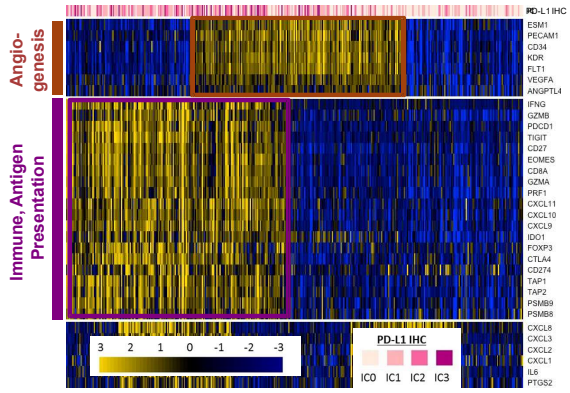
In Development: First-line atezolizumab + bevacizumab in PD-L1+ mRCC

Immotion151



Rini, The Lancet 2019, 393:2404

In Development: First-line atezolizumab + bevacizumab: molecular signatures

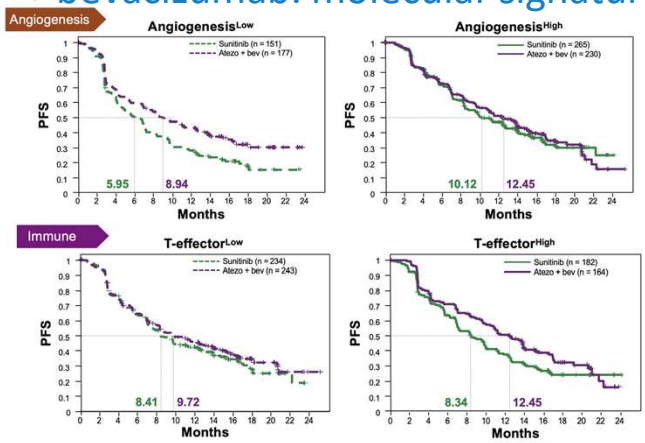


Identification of gene signatures based on association with clinicaloutcome

- T_{eff}: *CD8a*, *IFNG*, *PRF1*, *EOMES*, *CD274*
- Angio: *VEGFA*, *KDR*, *ESM1*, *PECAM1*, *CD34*, *ANGPTL4*

Rini et al, ESMO 2018

In Development: First-line atezolizumab + bevacizumab: molecular signatures



Rini et al, ESMO 2018

Front-line phase 3 trials with immunotherapy agents (efficacy summary)

	CheckMate 214	KEYNOTE-426	JAVELIN 101	IMmotion151
Intervention	Ipilimumab + Nivolumab	Pembrolizumab + Axitinib	Avelumab + Axitinib	Atezolizumab + Bevacizumab
Comparator	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Primary Endpoint	OS, PFS, ORR in int/poor risk	OS, PFS	PFS, OS in PD-L1+	PFS in PD-L1+; OS
mOS, months	NR vs 37.9 (30 mo min followup)	NR vs NR (median 12.8 mo followup)	Not reported	33.6 vs 34.9 (median 24 mo followup)
PFS, months	9.7 vs 9.7	15.1 vs 11.1	13.8 vs 7.2	11.2 vs 7.7
ORR (ITT), %	41% vs 34%	59.3% vs 35.7%	51.4% vs 25.7%	37% vs 33%
CR rate (ITT)	10.5% vs 1.8%	5.8% vs 1.9%	3.4% vs 1.8%	5% vs 2%

IIT: Intent-to-Treat; PFS: progression-free survival; ORR: overall response rate; OS: overall survival

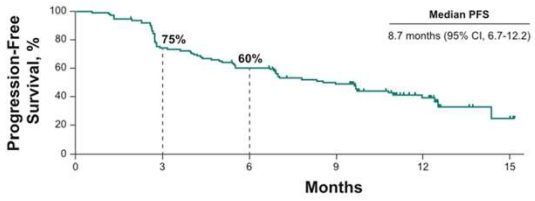
Tannir, ASCO GU 2019.
Rini, NEJM 2019.
Motzer, NEJM 2019.
Rini, Lancet 2019.

Ongoing front-line phase 3 trials with immunotherapy agents for front-line ccRCC

Trial number	Trial Name	Treatment Arm	Comparator Arm	Population Size	Primary End Point
NCT03141177	CheckMate 9ER	Cabozantinib + Nivolumab	Sunitinib	630	PFS
NCT02811861	CLEAR	Lenvatinib + Pembrolizumab or Everolimus	Sunitinib	1050	PFS
NCT03729245	CA045002	NKTR-214 + Nivolumab	Sunitinib (or cabozantinib)	600	ORR, OS
NCT03937219	COSMIC-313	Cabozantinib + Ipilimumab + Nivolumab	Ipilimumab + Nivolumab	676	PFS

PFS: progression-free survival; ORR: overall response rate; OS: overall survival

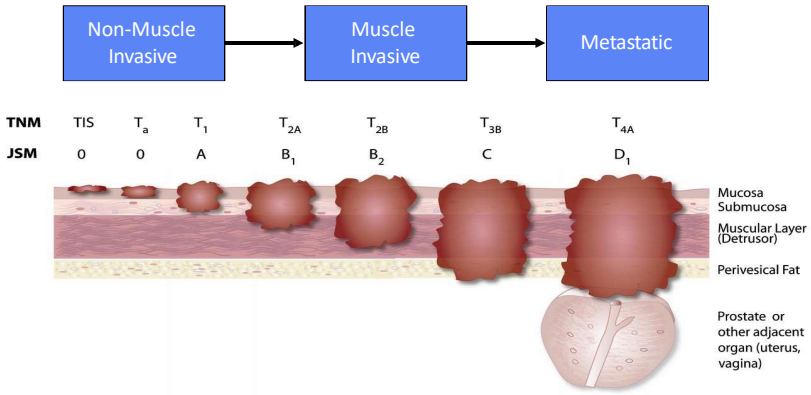
In Development: First-line pembrolizumab monotherapy in mRCC KEYNOTE - 427



	N = 110
Confirmed ORR, % (95% CI)	36.4
CR, %	3 (3)
PR, %	37 (34)
DCR, %	57 (47-67)
DOR, median (range), mo	Not Reported
DOR ≥ 6 mo (responders), %	77

Donskov et al. ESMO 2018
Tykodi et al, ASCO 2019

Immunotherapy for Metastatic Bladder Cancer (Urothelial Carcinoma; UC)



Approved checkpoint inhibitor for non-muscle invasive bladder cancer

Drug	Approved	Indication	Dose
Pembrolizumab	January 2020	BCG-unresponsive, high-risk NMIBC, with or without papillary tumors and ineligible for cystectomy	200 mg Q3W

Response, n (%)	KEYNOTE-057 cohort A (n=97)
Complete response	40 (41.2)
Non-complete response	56 (57.7)
Persistent	40 (41.2)
Recurrent	6 (6.2)
NMIBC stage progression	9 (9.3)
Progression to T2	0
Extravesical disease	1 (1.0)
Non-evaluable	1 (1.0)

FDA Advisory Committee Briefing Document, 2019.

Approved checkpoint inhibitors for mUC – *cisplatin refractory*

Drug	Approved	Indication	Dose
Atezolizumab	2016 (2018)	Advanced/metastatic UC	1200 mg Q3W
Avelumab	2017 2020	Advanced/metastatic UC Maintenance therapy after FL platinum	10 mg/kg Q2W
Durvalumab	2017	Advanced/metastatic UC	10 mg/kg Q2W
Nivolumab	2017	Advanced/metastatic UC	240 mg Q2W or 480 mg Q4W
Pembrolizumab	2017 (2018)	Advanced/metastatic UC	200 mg Q3W

Approved checkpoint inhibitors for mUC – *cisplatin ineligible*

Drug	Approved	Indication	Dose
Atezolizumab	2016 (2018)	Advanced/metastatic UC (PD-L1 ≥5%)	1200 mg Q3W
Pembrolizumab	2017 (2018)	Advanced/metastatic UC (PD-L1 CPS ≥10)	200 mg Q3W

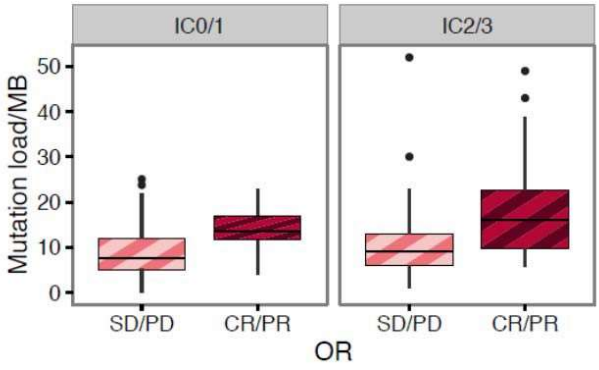
June 2018

FDA limits the use of Atezolizumab and Pembrolizumab for some urothelial cancer patients

- Locally advanced or metastatic urothelial carcinoma and ineligible for cisplatin-based chemo and tumor PD-L1 (CPS ≥ 10, pembro; IC ≥ 5% tumor area, atezo)
- Patients ineligible for any platinum-containing chemotherapy regardless of PD-L1 status

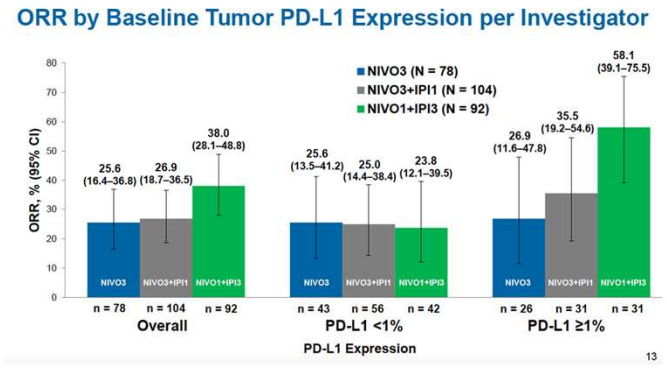
Tumor Mutational Burden (TMB) May Signal Responses with PD-1 Blockade

Atezolizumab in mUC



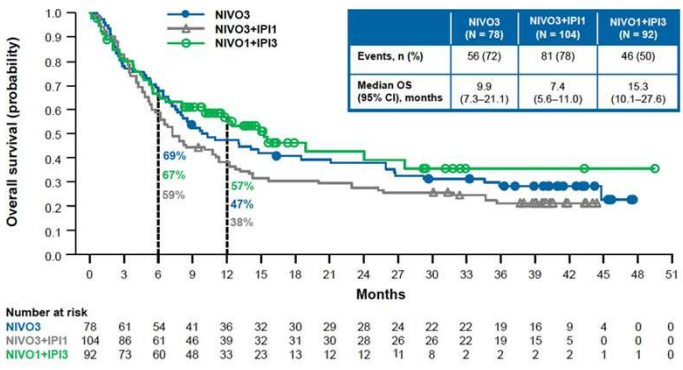
Rosenberg et al. Lancet 2016 387:1909

In development: Ipilimumab + Nivolumab CheckMate 032



Rosenberg, ESMO 2018

In development: Ipilimumab + Nivolumab CheckMate 032



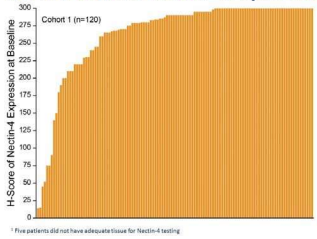
	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Events, n (%)	56 (72)	81 (78)	46 (50)
Median OS (95% CI), months	9.9 (7.3–21.1)	7.4 (5.6–11.0)	15.3 (10.1–27.6)

Rosenberg, ESMO 2018

Approved antibody-drug conjugate for mUC

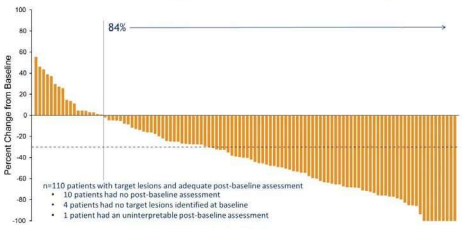
Drug	Approved	Indication	Dose
Enfortumab vedotin	December 2019	Locally advanced/metatstatic UC with previous αPD-1/PD-L1 and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

EV-201: Cohort 1 Nectin-4 Expression



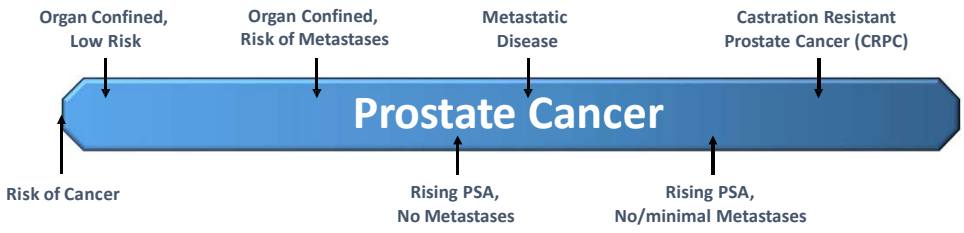
[1] Five patients did not have adequate tissue for Nectin-4 testing

EV-201: Cohort 1 Change in Tumor Measurements per BICR



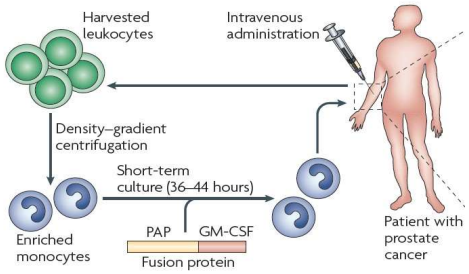
Petrylak. ASCO 2019.

The Spectrum of Prostate Cancer

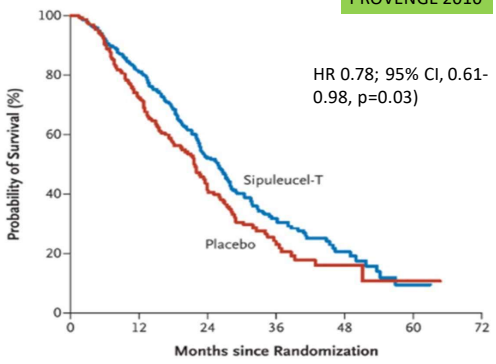


Sipuleucel-T in mCRPC

First anti-cancer therapeutic vaccine



PROVENGE 2010



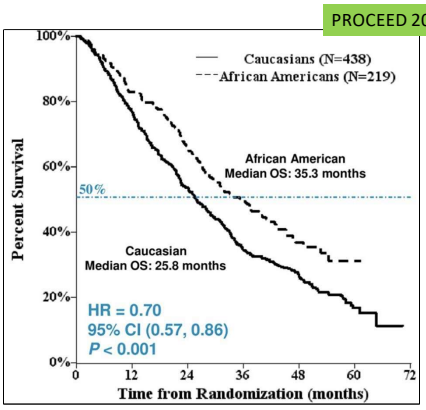
HR 0.78; 95% CI, 0.61-0.98, p=0.03)

Drake et al. Curr Opin Urol 2010
Kantoff et al. NEJM 2010

Sipuleucel-T in mCRPC

- Post-hoc analysis of Phase 3 trial PROCEED (N = 1902 mCRPC patients)
- African-Americans (AA) = 438; Caucasians (CAU) = 219
- Median OS = 35.2 (AA) vs 29.9 mo (CAU); HR 0.81, 95% CI 0.68–0.97; p = 0.03.
- AA race was independently associated with prolonged OS on multivariate analysis (HR 0.60, 95% CI 0.48–0.74; p < 0.001)

PROCEED 2019

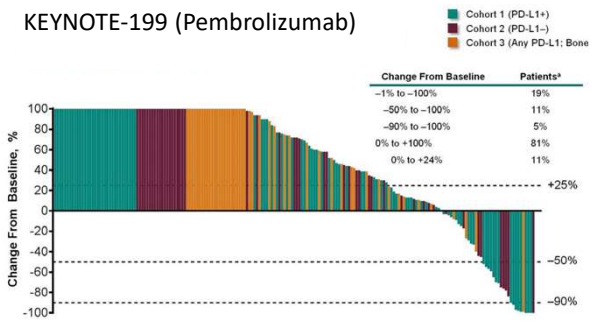


Sartor et al. ASCO 2019

Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

KEYNOTE-199 (Pembrolizumab)



- Pembrolizumab is approved for all Microsatellite Instability-High (MSI-H) solid tumors
- MSI-H incidence is low in PC
  - Localized PC ~2%
  - Autopsy series of mCRPC ~12%
- MSI testing may offer pembrolizumab as an option

Antonarakis JCO 2020 38:395

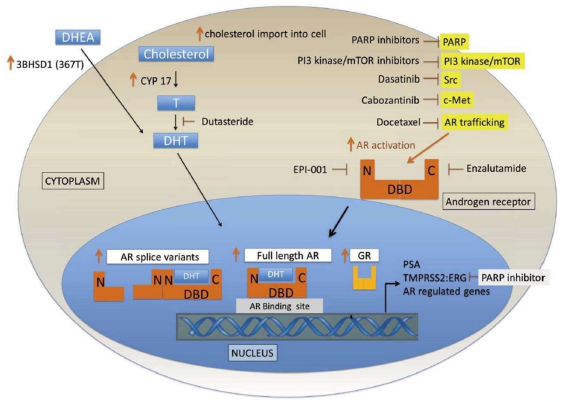
In development: nivolumab + ipilimumab in mCRPC

- Checkmate 650
- Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 doses, then Nivo 480 mg Q4W
- Progressed after 2nd-gen hormonal: 26% response @ 11.9 mo, 2 CR
- Progressed after chemo+hormonal: 10% response @ 13.5 mo, 2 CR
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

Sharma, GU Cancer Symp 2019.

Future Combinations in mCRPC to Engage Immune System

- Hormonal therapy
- Radiation
- Radium-223
- PARP inhibitors
- Chemotherapy
- Vaccines
- Bi-specific T-cell engagers



Stein et al. Asian J Andrology 2014

irAEs with Immune Checkpoint Inhibitors in GU Cancers - Meta-analysis of 8 studies

Similar incidence overall

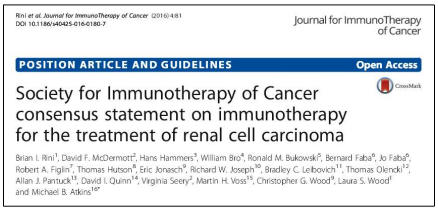
Adverse event	Incidence, any grade (GU only trials) (%)	Incidence, grades 3–5 (GU only trials) (%)	Incidence any grade (non-GU clinical trials) (%)	Incidence, grades 3–5 (non-GU clinical trials) (%)
Hypothyroid/ thyroiditis	0.8–9	0–0.6	3.9–12	0–0.1
Diabetes/DKA	0–1.5	0–0.7	0.8–0.8	0.4–0.7
LFT changes/ hepatitis	1.5–5.4	1–3.8	0.3–3.4	0.3–2.7
Pneumonitis	2–4.4	0–2	1.8–3.5	0.25–1.9
Encephalitis	NR	NR	0.2–0.8	0.0–0.2
Colitis/diarrhea	1–10	1–10	2.4–4.1	1.0–2.5
Hypophysitis	0–0.5	0–0.2	0.2–0.9	0.2–0.4
Renal Dysfunction/ nephritis	0.3–1.6	0–1.6	0.3–4.9	0.0–0.5
Myositis	0.8–5	0–0.8	NR	NR

Maughan et al. Front Oncol 2017

Conclusions

- The role of immunotherapy in GU malignancies is increasing
- In RCC, many front-line checkpoint inhibitor options are approved
- Multiple checkpoint inhibitors approved for advanced/metastatic urothelial carcinoma
- T-cell checkpoint blockade used as monotherapies have demonstrated little activity in prostate cancer
- Current challenges include choice of optimal agents/combinations and sequence of these therapies with other agents

Additional Resources

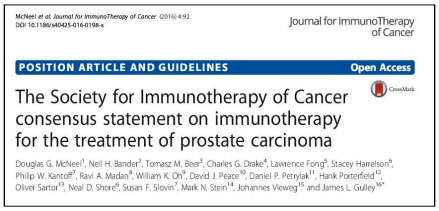

Rini et al. Journal for ImmunoTherapy of Cancer (2016) 4:81
DOI 10.1186/s40425-016-0180-7

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of renal cell carcinoma

Brian I. Rini[1], David F. McDermott[2], Hans Hammers[3], William Bro[4], Ronald M. Bukowski[5], Bernard Faba[6], Jo Faba[6], Robert A. Figlin[7], Thomas Hutson[8], Eric Jonasch[9], Richard W. Joseph[10], Bradley C. Leibovich[11], Thomas Olencki[12], Allan J. Pantuck[13], David I. Quinn[14], Virginia Seery[4], Martin H. Voss[15], Christopher G. Wood[9], Laura S. Wood[1] and Michael B. Atkins[16*]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The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of prostate carcinoma

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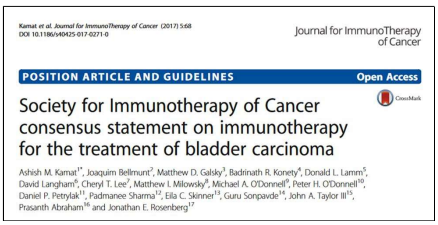
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Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma

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Case Studies

Case Study 1

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. These were biopsied and sent for further analysis that showed high tumor mutational burden, and no discernible PD-L1 staining. He feels well, has no other major medical health problems, and his basic laboratory studies are all within normal limits. Which of the following would be the most appropriate treatment?

A. Atezolizumab
B. Gemcitabine and cisplatin
C. Pembrolizumab
D. Enfortumab vedotin

Case Study 1

The patient goes on to receive cisplatin and gemcitabine for 6 cycles, and has an excellent response with a near complete response. Which of the following would you now propose:

A. Maintenance therapy with avelumab
B. Maintenance therapy with pembrolizumab
C. Maintenance therapy with docetaxel
D. No further therapy – begin surveillance

Case Study 2

You are seeing a 65 y/o woman, in otherwise good health, who underwent nephrectomy 2 years ago for what was found to be a T2 renal cell cancer, Fuhrman grade 2. Staging studies completed prior to hospital discharge at that time showed multiple small pulmonary nodules suspicious for metastatic disease. She entered radiographic surveillance, and 1 month ago was found to have increase in the size of several of the pulmonary nodules. Biopsy confirmed the presence of metastatic renal cell cancer. What are potential treatment options for her at this time?

A. Nivolumab and ipilimumab
B. High dose IL-2
C. Pembrolizumab and axitinib
D. All of the above

Case Study 2

Which choice would you make if this patient had multiple high-risk features, including an IMDC score of 6, and multiple sites of rapidly progressive, symptomatic metastases occurring within 4 months of her original diagnosis?

A. Nivolumab and ipilimumab
B. High dose IL-2
C. Pembrolizumab and axitinib
D. All of the above

Case Study 2

After discussion, she elects to start pazopanib, and has a treatment response. She remains on pazaopanib for several years until she develops new liver and pancreatic metastases. What are potential treatment options for her at this time?

A. Atezolizumab
B. Nivolumab
C. Ipilimumab
D. All of the above