Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Renal Cell Carcinoma

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

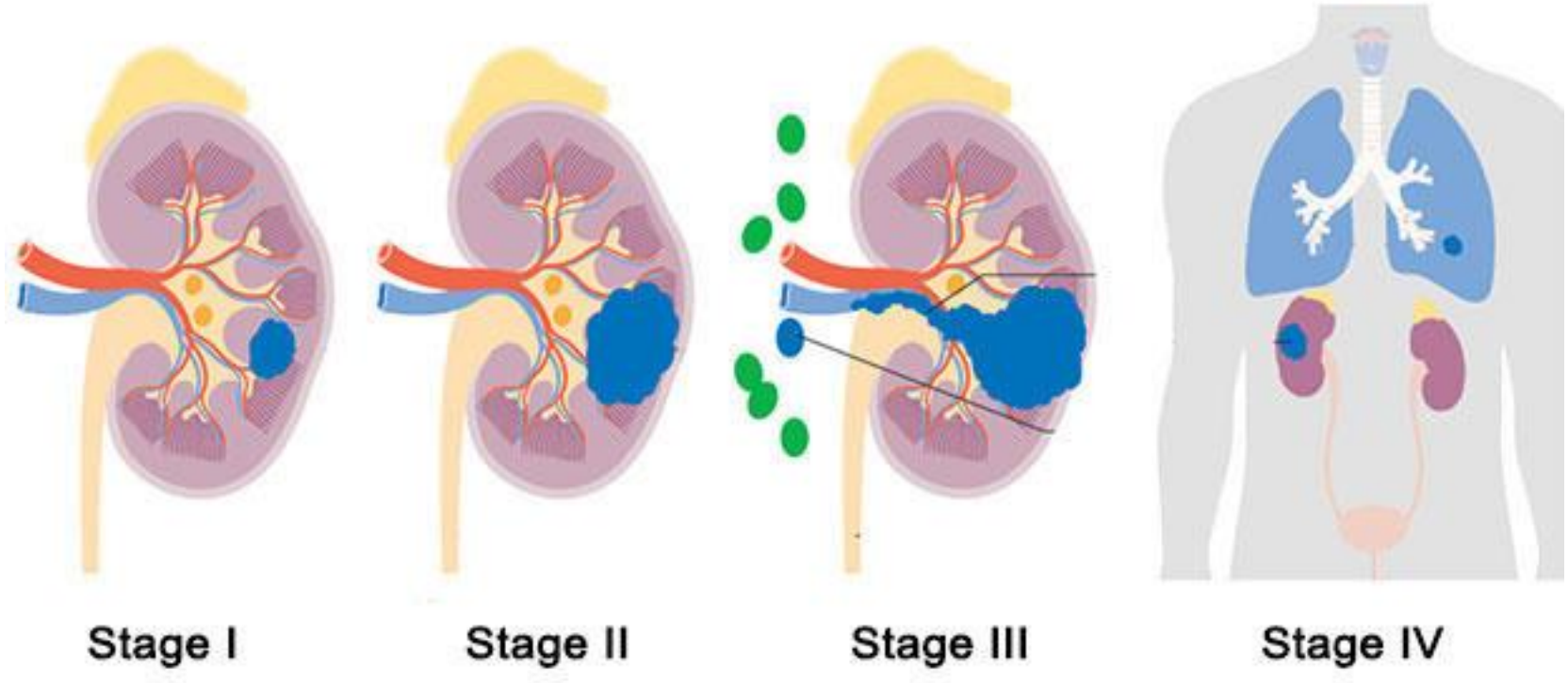
sitc Society for Immunotherapy of Cancer

Disclosures

- **Receipt of Intellectual Property Rights/Patent Holder:** Binding proteins specific for 5T4 and uses
- **Consulting Fees:** Bristol-Myers Squibb, Intellisphere LLC, Merck, Natera
- **Contracted Research:** Bristol-Myers Squibb, Calithera Biosciences, Clinigen, Exelixis, Genentech, Jounce Therapeutics, Merck, Nektar Therapeutics, Peloton Therapeutics, Pfizer

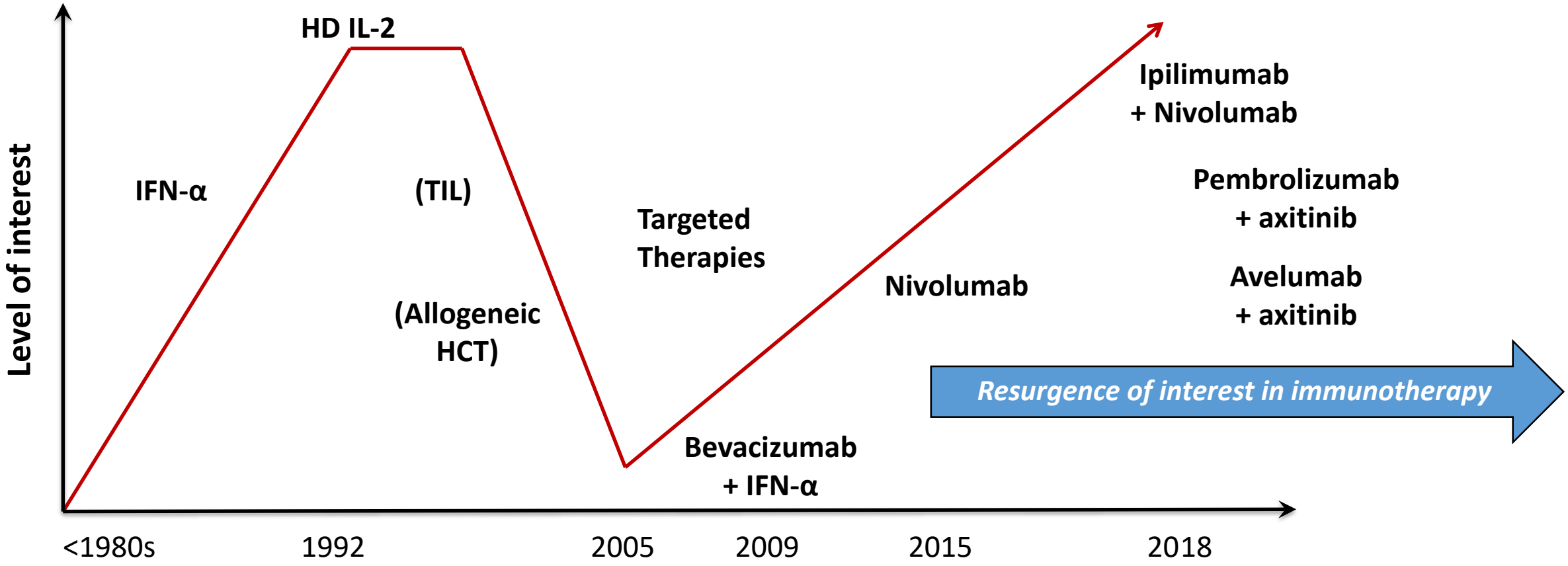
Immunotherapy for Metastatic Renal Cell Carcinoma (mRCC)

Surgically resectable → Metastatic



https://www.moderncancerhospital.com.cn/cancer-staging/kidney-cancer-staging/

History of Immunotherapy in mRCC

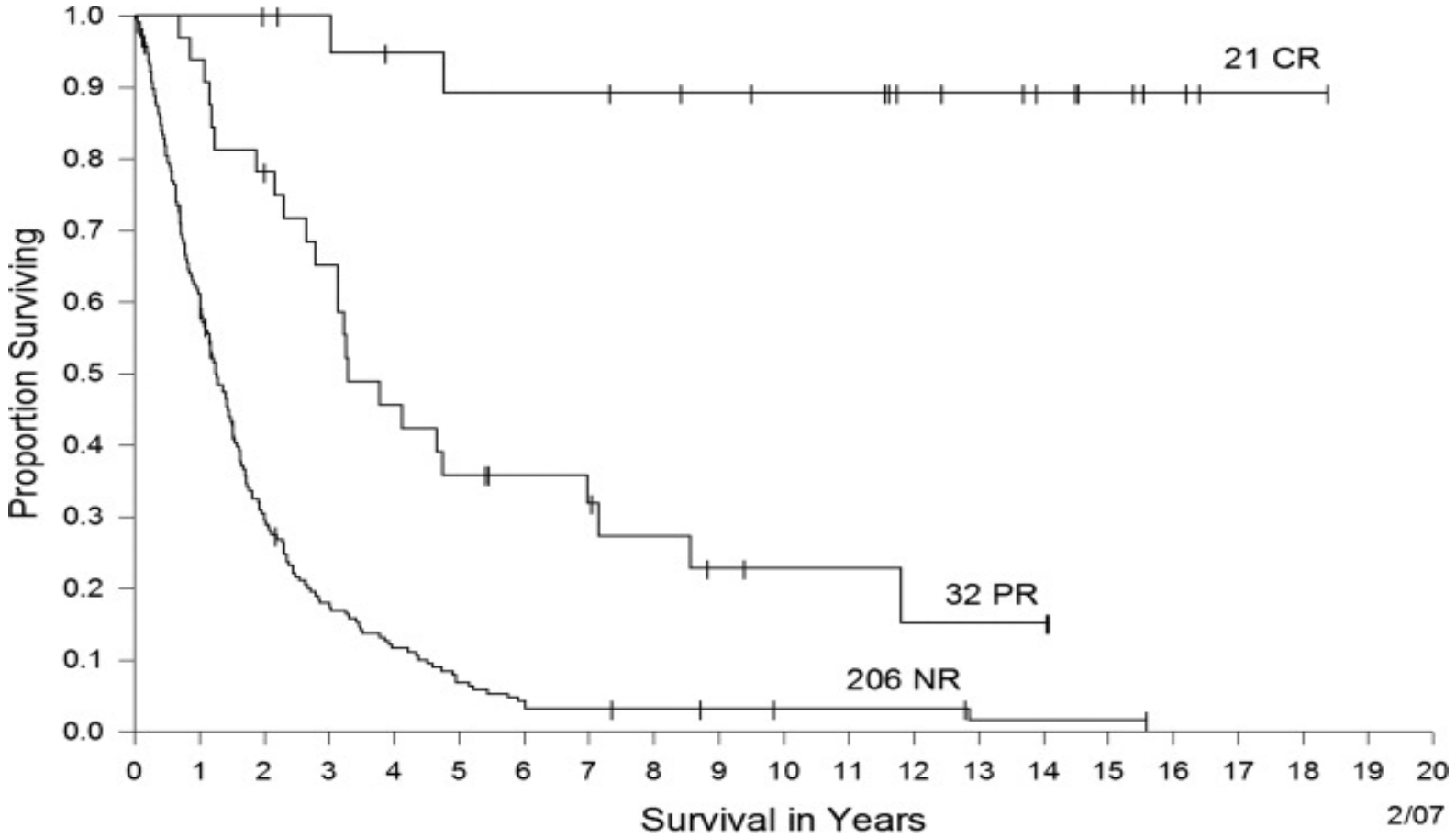


FDA-approved Immunotherapies for mRCC

Drug	Approved	Indication	Line of Therapy	Comparator
High dose Interleukin-2	1992	Advanced/Metastatic RCC	First line	None
Interferon-α + bevacizumab	2009	Advanced/Metastatic RCC	First line	IFN-α
Nivolumab	2015	Advanced/Metastatic RCC refractory to prior VEGF targeted therapy	2nd to 4th line	Everolimus
Nivolumab + ipilimumab	2018	Intermediate/Poor risk Advanced/Metastatic RCC	First line	Sunitinib
Pembrolizumab + axitinib	2019	Advanced/Metastatic RCC	First line	Sunitinib
Avelumab + axitinib	2019	Advanced/Metastatic RCC	First line	Sunitinib

High Dose IL-2 in mRCC

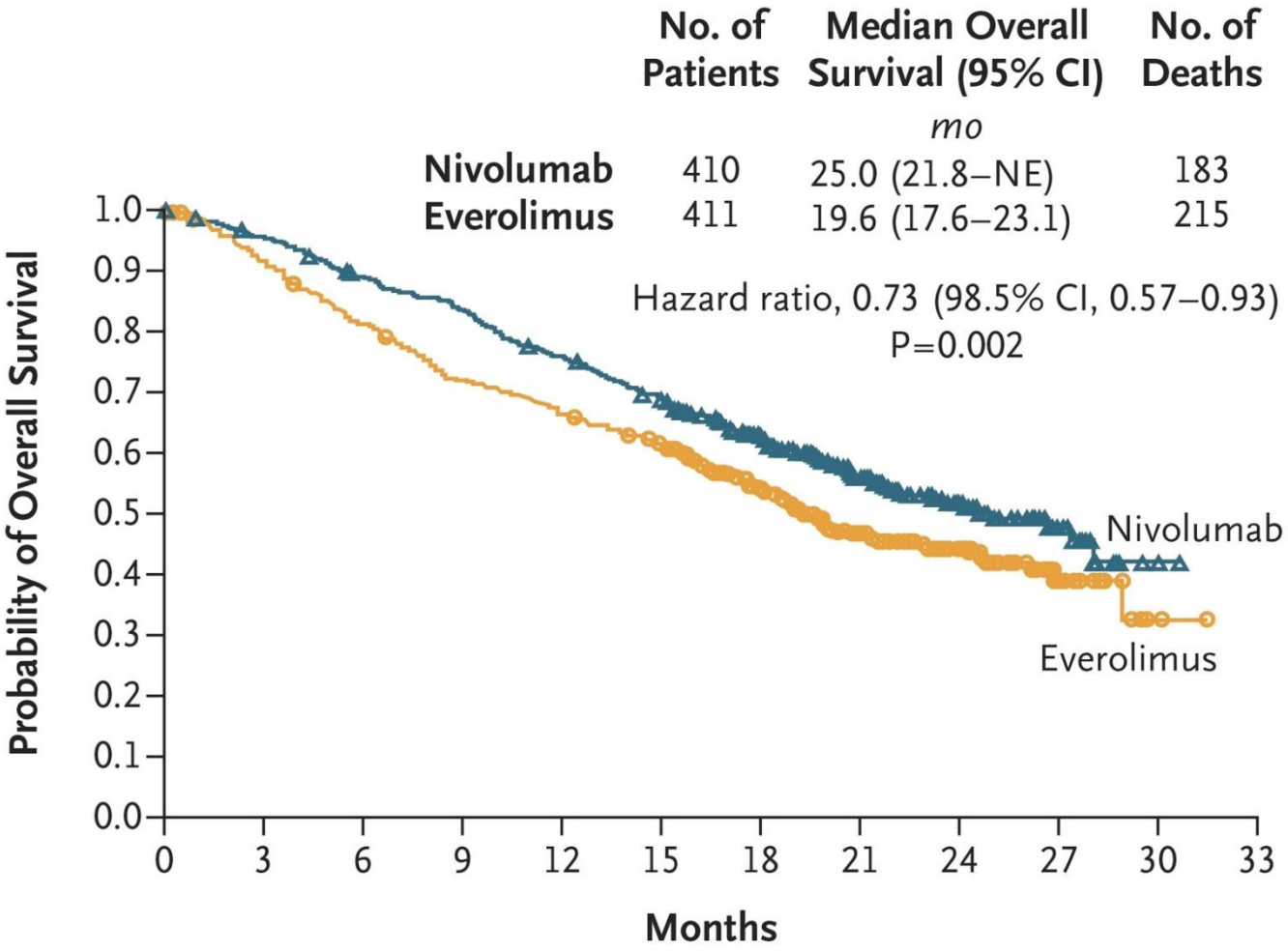
- 20 year analysis of 259 patients
- ORR = 20%
  - 9% CR (n = 23)
  - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months



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)

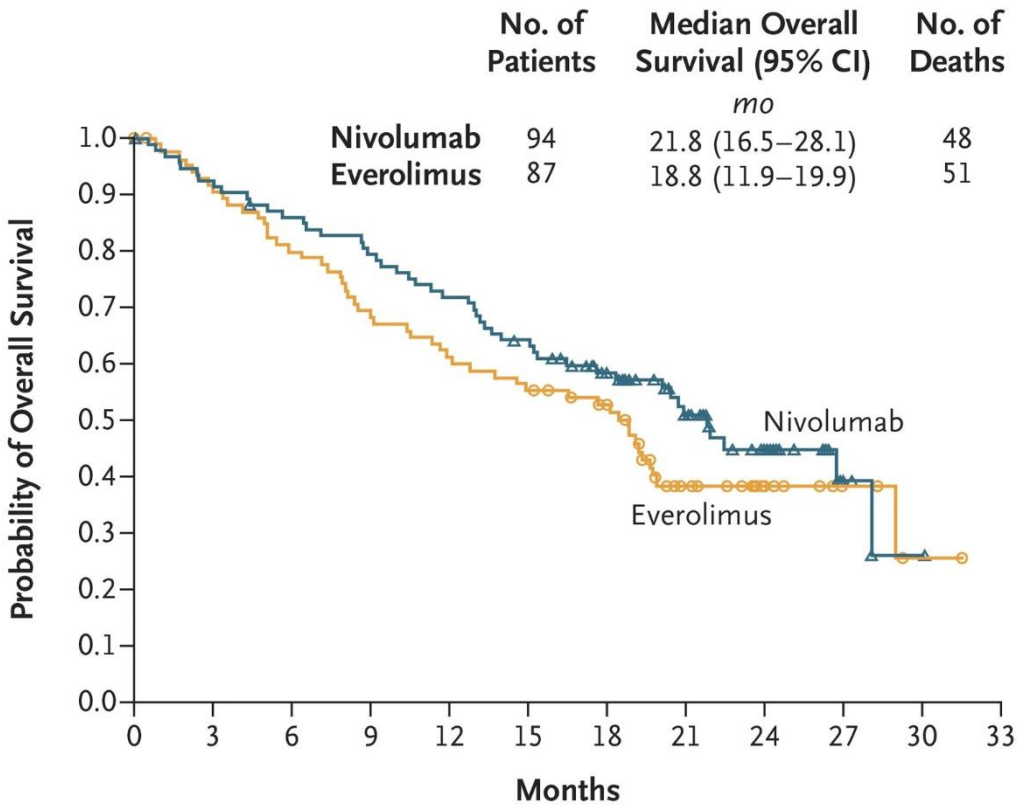


Motzer et al. NEJM 2015

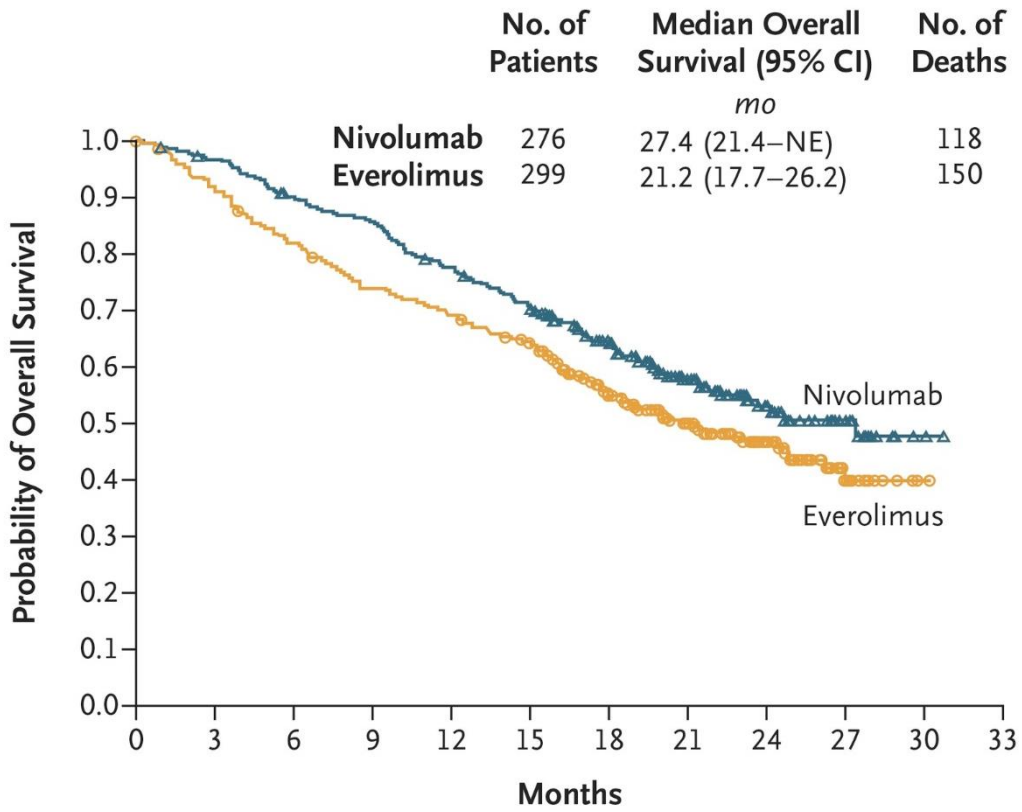
Second-Line Nivolumab in mRCC

PD-L1 subgroups

PD-L1 ≥ 1% (23%)

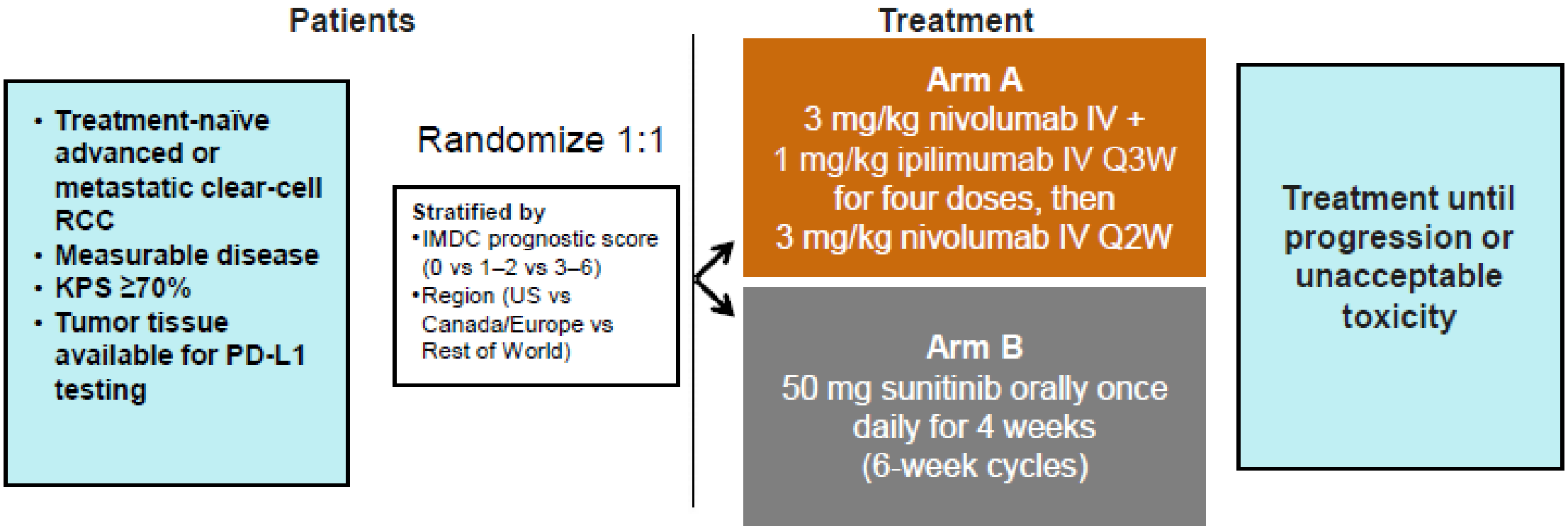


PD-L1 < 1% (67%)



Motzer et al. NEJM 2015

First-line Nivolumab + Ipilimumab in mRCC – CheckMate 214



Co-primary endpoints:
ORR, PFS and OS <u>in I/P risk</u> patients

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

Escudier et al. ESMO 2017

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

CheckMate 214

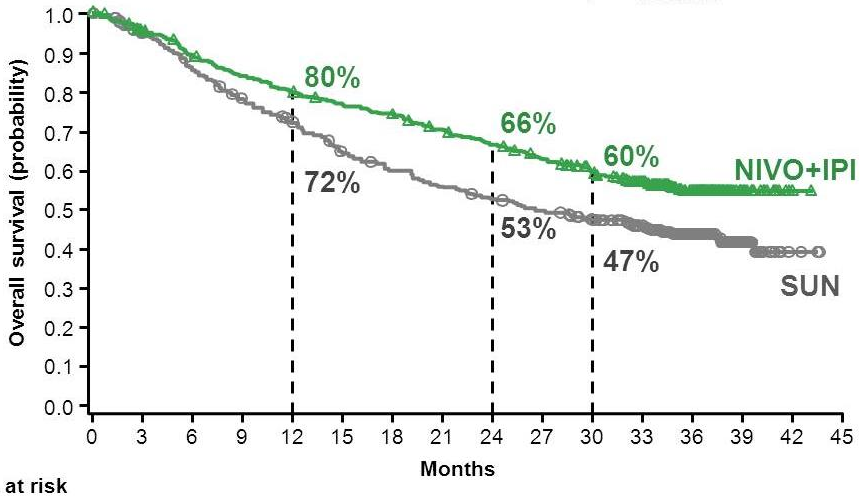
Follow-up
= 30 months

Intermediate/poor risk

Median OS, months (95% CI)

NIVO+IPI	NR (35.6–NE)
SUN	26.6 (22.1–33.4)

HR (95% CI), 0.66 (0.54–0.80)
P < 0.0001



No. at risk

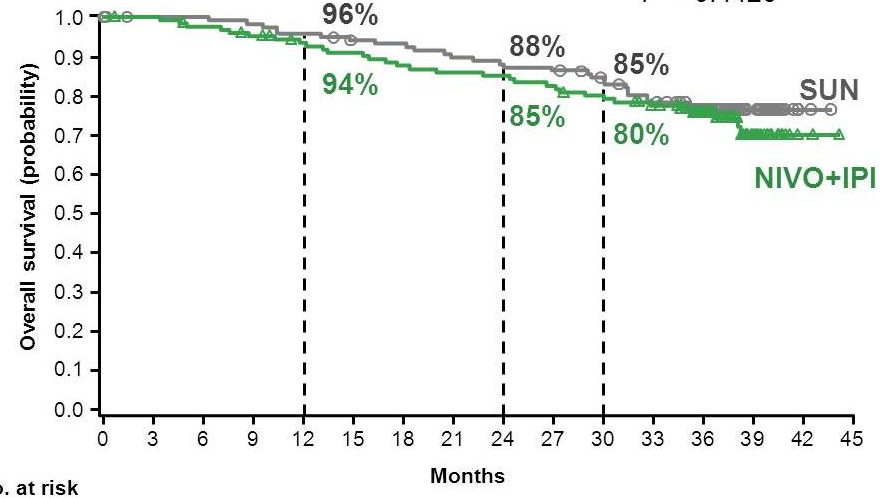
NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

Favorable risk

Median OS, months (95% CI)

NIVO+IPI	NR (NE)
SUN	NR (NE)

HR (95% CI), 1.22 (0.73–2.04)
P = 0.4426



No. at risk

NIVO+IPI	125	124	120	116	111	108	104	102	101	98	94	88	71	24	2	0
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

Tannir et al. ASCO GU 2019

CheckMate 214 (RCC): Key Clinical Outcomes by IMDC Risk Group

42 Month Minimum Follow-up:

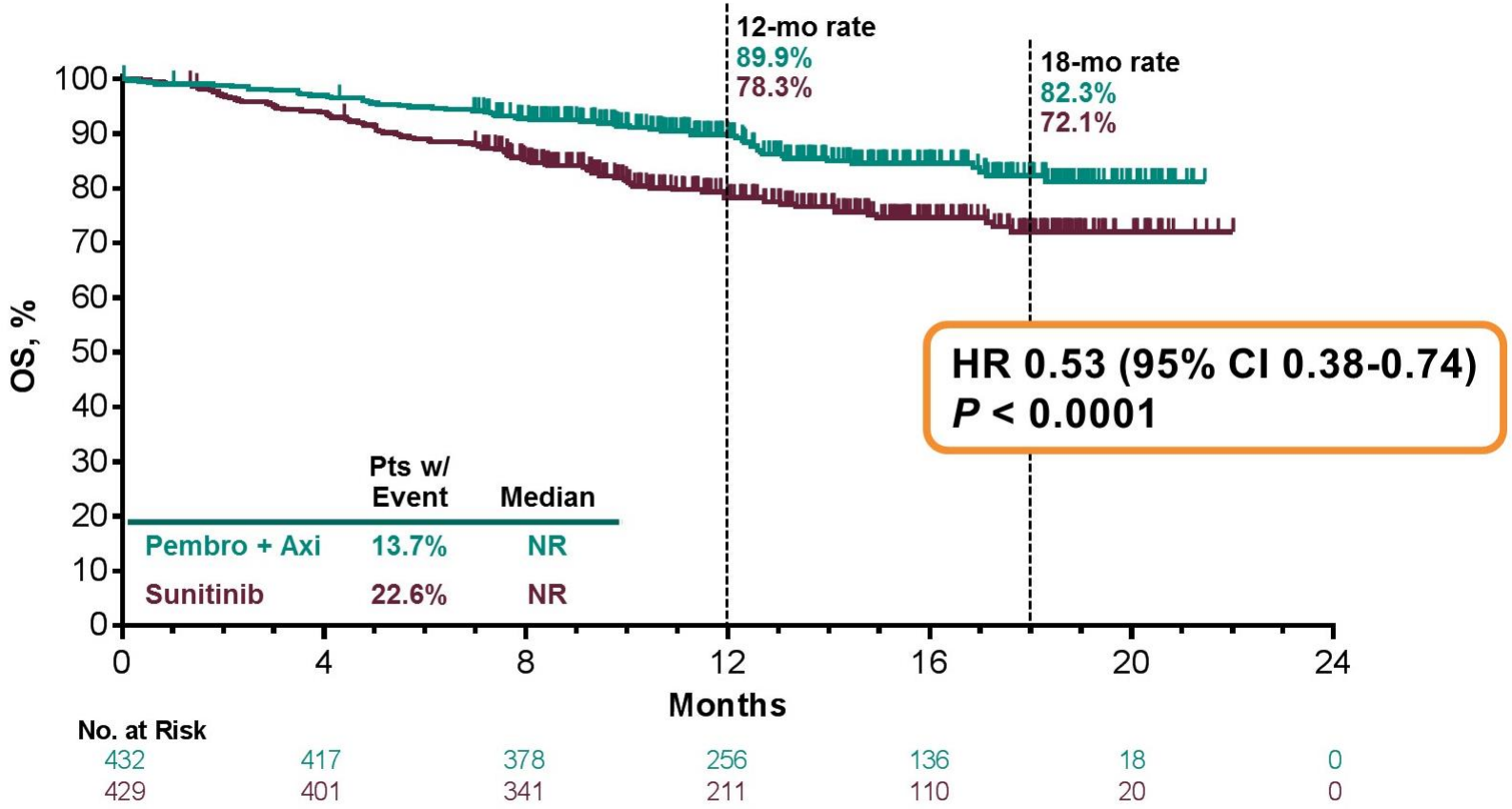
Patient Subset	Better Treatment		
	ORR[1]	PFS	OS
ITT	Ipi/Nivo 39 v 33%	No Diff 12.5 v 12.3 mo	Ipi/Nivo NR v 38.4 mo
IMDC Good Risk	Sunitinib 54 v 29%	Sunitinib 27.7 v 17.8 mo	NR v NR
IMDC Int/Poor Risk	Ipi/Nivo 42 v 26%	Ipi/Nivo 12 v 8.3 mo	Ipi/Nivo 47 v 26.6 mo

[1]per IRRC (Independent Radiology Review Committee)

Tannir, NM et al. GU ASCO 2020.

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

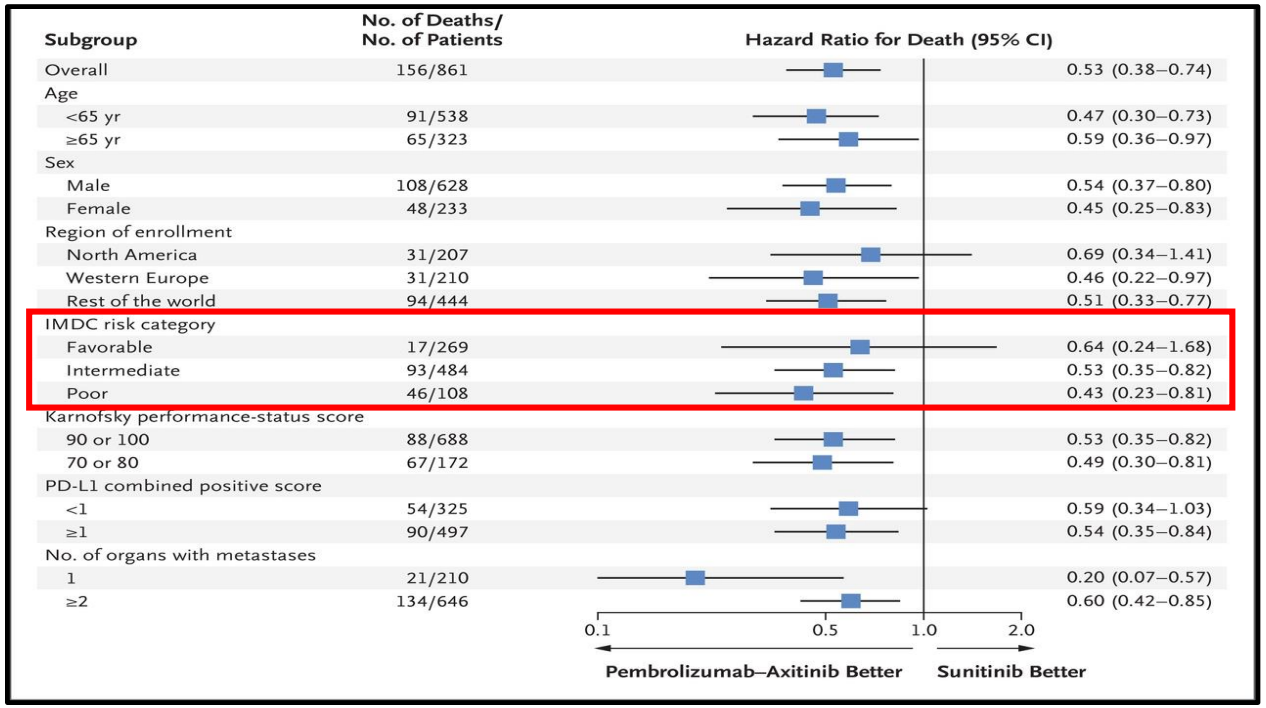
KEYNOTE-426: OS in the ITT Population



Rini, ASCO 2019

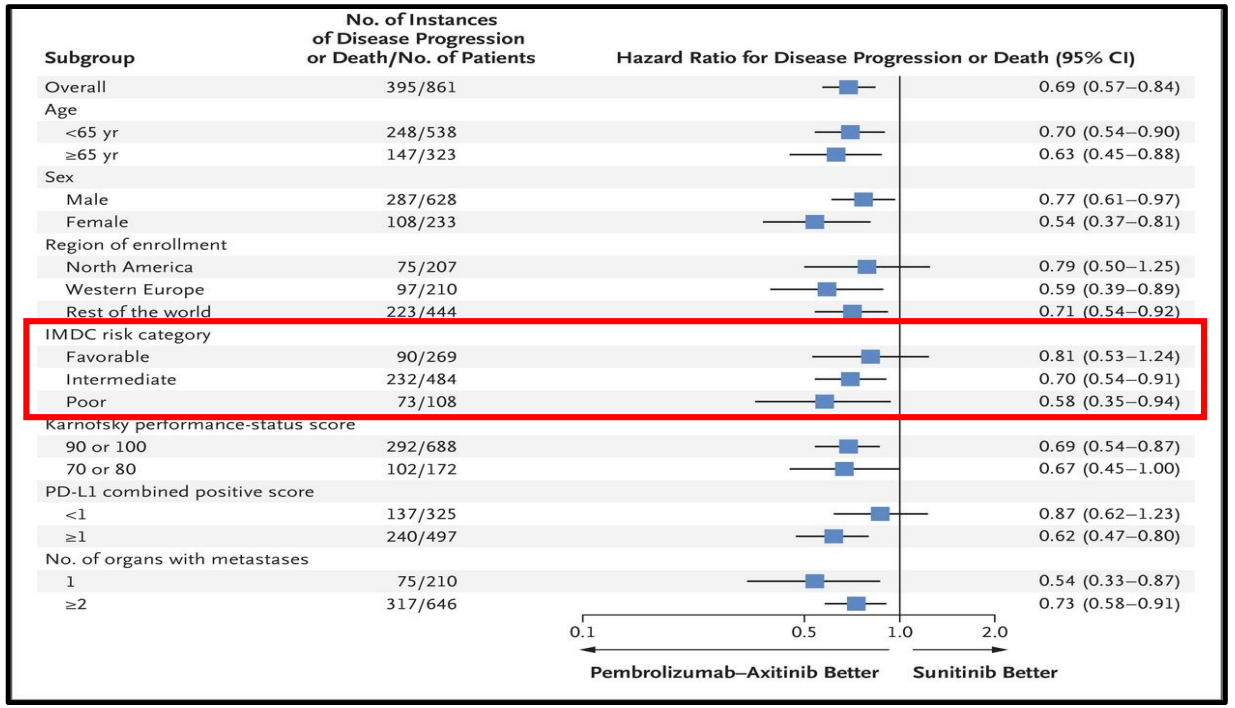
KeyNote 426: Outcomes by Clinical Subsets

OS



Subgroup	No. of Deaths/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	156/861	0.53 (0.38–0.74)
Age		
<65 yr	91/538	0.47 (0.30–0.73)
≥65 yr	65/323	0.59 (0.36–0.97)
Sex		
Male	108/628	0.54 (0.37–0.80)
Female	48/233	0.45 (0.25–0.83)
Region of enrollment		
North America	31/207	0.69 (0.34–1.41)
Western Europe	31/210	0.46 (0.22–0.97)
Rest of the world	94/444	0.51 (0.33–0.77)
IMDC risk category		
Favorable	17/269	0.64 (0.24–1.68)
Intermediate	93/484	0.53 (0.35–0.82)
Poor	46/108	0.43 (0.23–0.81)
Karnofsky performance-status score		
90 or 100	88/688	0.53 (0.35–0.82)
70 or 80	67/172	0.49 (0.30–0.81)
PD-L1 combined positive score		
<1	54/325	0.59 (0.34–1.03)
≥1	90/497	0.54 (0.35–0.84)
No. of organs with metastases		
1	21/210	0.20 (0.07–0.57)
≥2	134/646	0.60 (0.42–0.85)

PFS



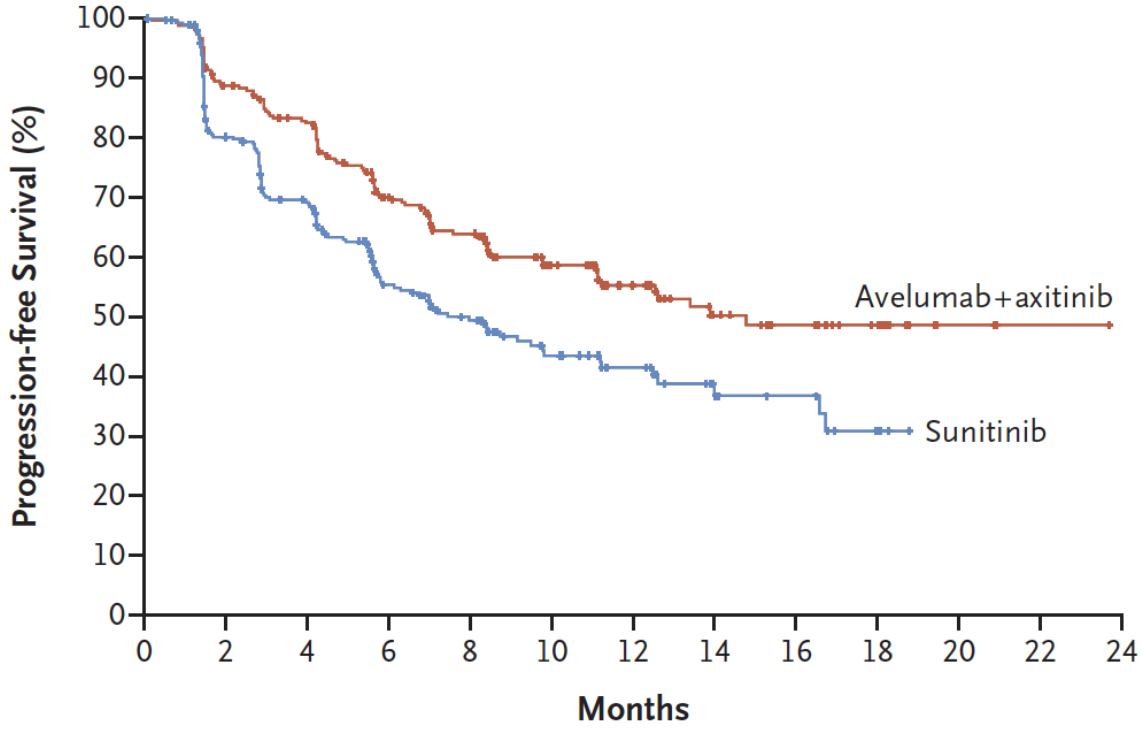
Subgroup	No. of Instances of Disease Progression or Death/No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	395/861	0.69 (0.57–0.84)
Age		
<65 yr	248/538	0.70 (0.54–0.90)
≥65 yr	147/323	0.63 (0.45–0.88)
Sex		
Male	287/628	0.77 (0.61–0.97)
Female	108/233	0.54 (0.37–0.81)
Region of enrollment		
North America	75/207	0.79 (0.50–1.25)
Western Europe	97/210	0.59 (0.39–0.89)
Rest of the world	223/444	0.71 (0.54–0.92)
IMDC risk category		
Favorable	90/269	0.81 (0.53–1.24)
Intermediate	232/484	0.70 (0.54–0.91)
Poor	73/108	0.58 (0.35–0.94)
Karnofsky performance-status score		
90 or 100	292/688	0.69 (0.54–0.87)
70 or 80	102/172	0.67 (0.45–1.00)
PD-L1 combined positive score		
<1	137/325	0.87 (0.62–1.23)
≥1	240/497	0.62 (0.47–0.80)
No. of organs with metastases		
1	75/210	0.54 (0.33–0.87)
≥2	317/646	0.73 (0.58–0.91)

Rini, BI *et al*. NEJM (2019) 380:1116-1127

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

- Primary Endpoint: 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: 61.9% vs 29.7
- OS data: immature

JAVELIN 101 : PFS in the PD-L1+ Population



Motzer, NEJM 2019.

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

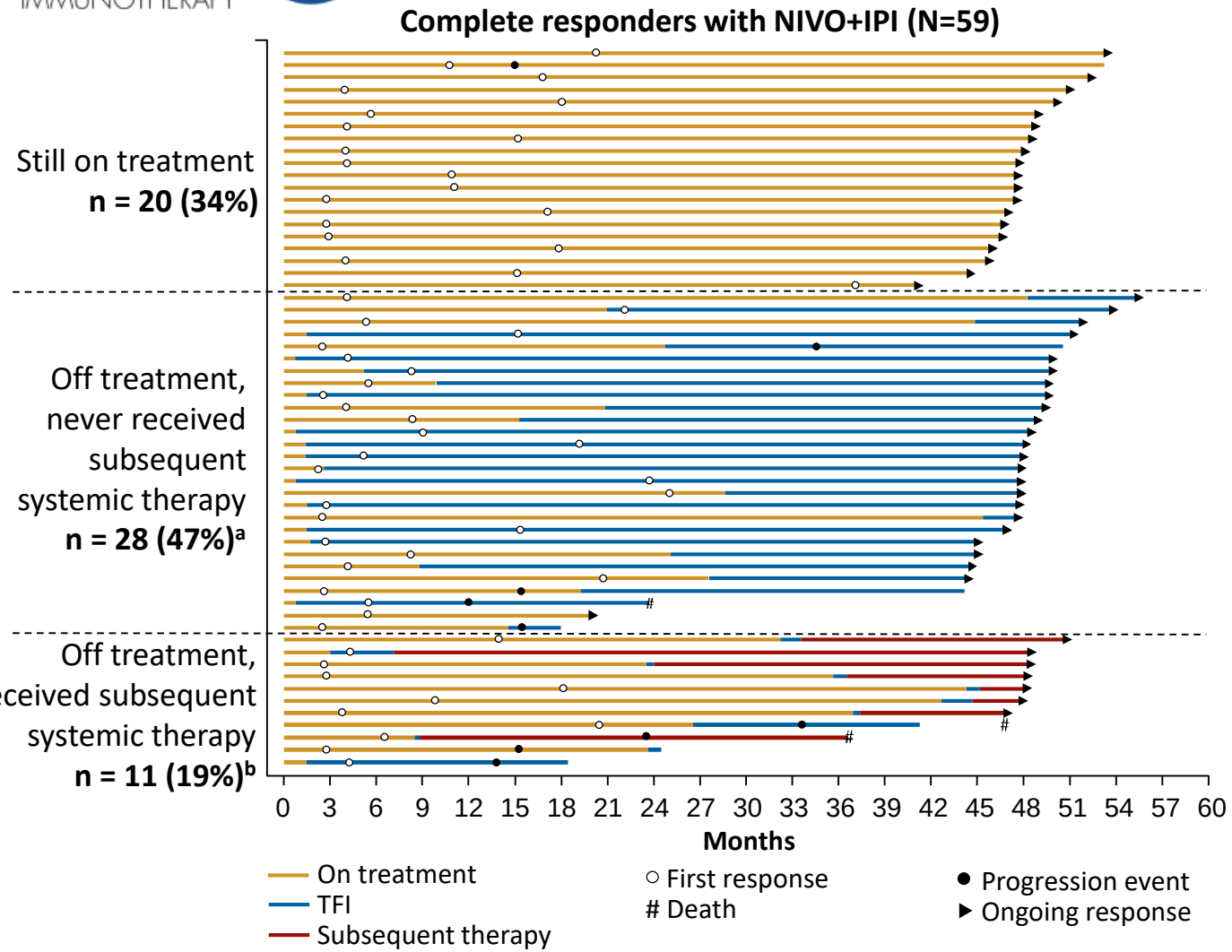
	CheckMate 214	KEYNOTE-426	JAVELIN 101
Intervention	Nivolumab + Ipilimumab	Pembrolizumab + Axitinib	Avelumab + Axitinib
Comparator	Sunitinib	Sunitinib	Sunitinib
Primary Endpoint	OS, PFS, ORR in int/poor risk	OS, PFS	PFS, OS in PD-L1+
mOS (ITT), months	NR vs 38.4 (42 mo min followup)	NR vs NR (median 12.8 mo followup)	Not reported
PFS (ITT), months	12.5 vs 12.3	15.1 vs 11.1	13.8 vs 8.4
ORR (ITT), %	39% vs 33%	59% vs 36%	51% vs 26%
CR rate (ITT)	11% vs 2%	6% vs 2%	3% vs 2%

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

Tannir, ASCO GU 2020.
Rini, NEJM 2019.
Motzer, NEJM 2019.

Durability of Complete Response per IRRC

Post hoc analysis in the NIVO+IPI arm: ITT population



NIVO+IPI	Complete responders N = 59
Median time to response in complete responders, months (range)[c]	2.8 (0.9–9.8)
Median duration of response in complete responders, months (95% CI)	NR (NE)
Complete responders with ongoing response, n (%)[d]	**51 (86)**
Median duration of TFI in patients with complete response with no subsequent systemic therapy, months (range)[a]	N = 28 34.6 (0.5–49.7)

[a]TFI was defined as time from end of study therapy until last known date alive. [b]TFI was defined as time from end of study therapy until subsequent systemic therapy initiation. [c]75% of all responses occurred within 2.9 months among complete responders. [d]One additional patient was included in the calculation of ongoing response due to censoring (had not progressed per IRRC at the time of subsequent systemic therapy initiation).
Bar indicates time on treatment/TFI. Time zero corresponds to first treatment date.
TFI, treatment-free interval in patients who are off study treatment.

Adapted from Tannir, NM et al. GU ASCO 2020.

In Development: Ongoing front-line phase 3 trials with I/O agents for advanced ccRCC

Trial number	Trial Name	Treatment Arm	Comparator Arm	Population Size	Primary End Point
NCT03141177	CheckMate 9ER	Cabozantinib + Nivolumab	Sunitinib	638	PFS
NCT02811861	CLEAR	Lenvatinib + Pembrolizumab or Everolimus	Sunitinib	1069	PFS
NCT03729245	CA045002	NKTR-214 + Nivolumab	Sunitinib or Cabozantinib	600	ORR, OS
NCT03937219	COSMIC-313	Cabozantinib + Nivolumab + Ipilimumab	Nivolumab + Ipilimumab	676	PFS

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

www.clinicaltrials.gov

Exploratory: Derivation of the 26-gene JAVELIN Renal 101 signature

- Whole transcriptomic data from 720 baseline tumor samples (350 in the avelumab + axitinib arm, 370 in the sunitinib arm) were filtered for informative genes

  Genes with low or invariant expression were removed

  4,622 genes remained after initial filtering

- Blinded to clinical outcome, co-expression analysis identified a module of 306 genes
- High expression of a 306-gene signature was associated with better PFS in the avelumab + axitinib arm but not in the sunitinib arm
- Further filtering of the co-expressed 306 genes based on immune-related functionality and most significant association with PFS in the avelumab + axitinib arm identified a 26-gene subset

T-cell receptor signaling	•*CD3G, CD3E, CD8B, THEMIS, TRAT1, GRAP2, CD247*
T-cell activation, proliferation, and differentiation	•*CD2,* CD96,* PRF1,* CD6, IL7R, ITK, GPR18, EOMES, SIT1, NLRC3*
NK cell–mediated cytotoxicity	•*CD2,* CD96,* PRF1,* CD244, KLRD1, SH2D1A*
Chemokine	• *CCL5, XCL2*
Other immune response genes	• *CST7, GFI1, KCNA3, PSTPIP1*

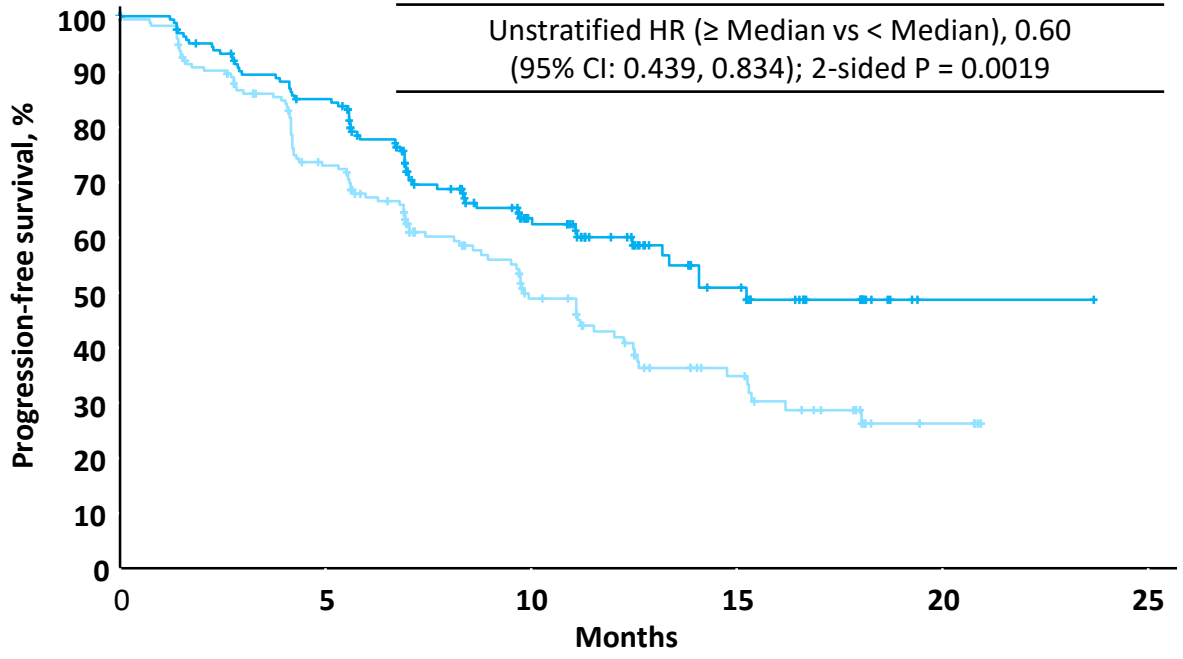
* Genes included in > 1 functional group

Choueiri, TK et al. ASCO 2019

Exploratory: PFS according to 26-gene JAVELIN Renal 101 signature

Avelumab + axitinib	Median PFS (95% CI), mo
≥ Median value	15.2 (12.5, NE)
< Median value	9.8 (8.6, 12.2)

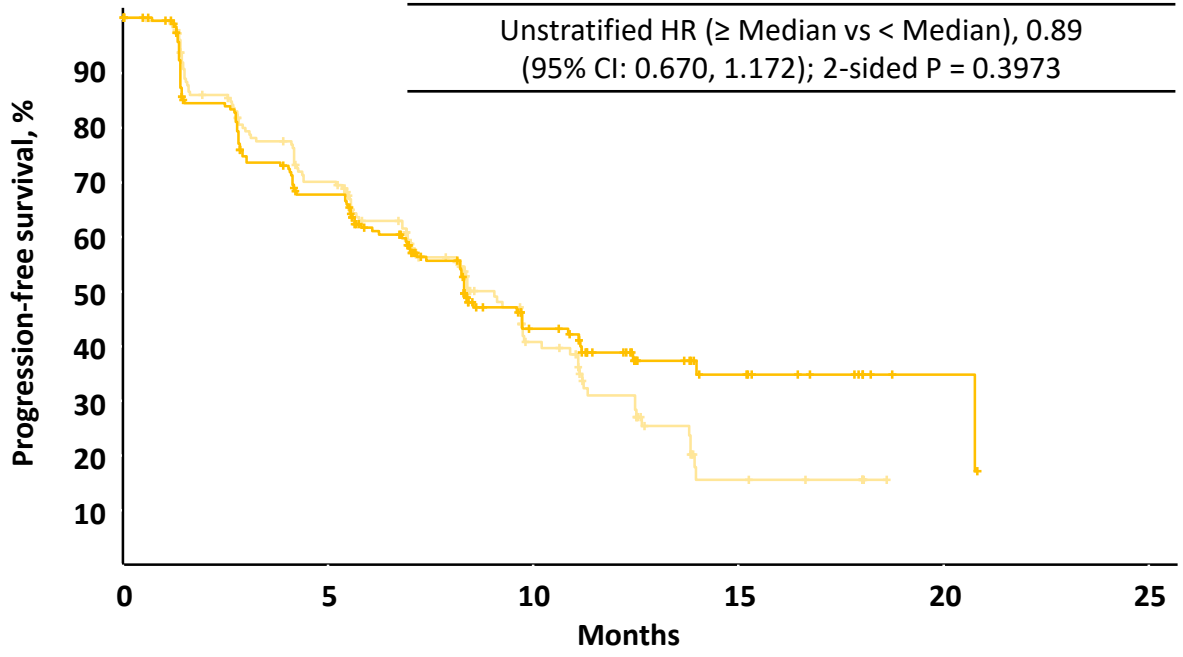
Unstratified HR (≥ Median vs < Median), 0.60 (95% CI: 0.439, 0.834); 2-sided P = 0.0019



≥ Median	170	136	60	25	1	0
< Median	180	116	53	24	4	0

Sunitinib	Median PFS (95% CI), mo
≥ Median value	8.3 (7.0, 11.1)
< Median value	9.0 (7.1, 9.8)

Unstratified HR (≥ Median vs < Median), 0.89 (95% CI: 0.670, 1.172); 2-sided P = 0.3973



≥ Median	191	115	43	13	2	0
< Median	179	114	37	7	0	0

NE, not estimable; **PFS**, progression-free survival.

Choueiri, TK et al. ASCO 2019

Selecting Between First-Line Checkpoint Containing Regimens

- Nuances for selecting between checkpoint regimens:
  - ✓IMDC risk category
  - – ORR and time to response
  - – Depth of response (CR)
  - – Treatment free survival
  - – Toxicity / discontinuation rate
  - – Medical comorbidities
  - – Frequency of visits
- Await more mature OS data
- No consensus for “best choice”

Immunotherapy for the Treatment of Urothelial and Prostate Cancers

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Disclosures (within 1 year)

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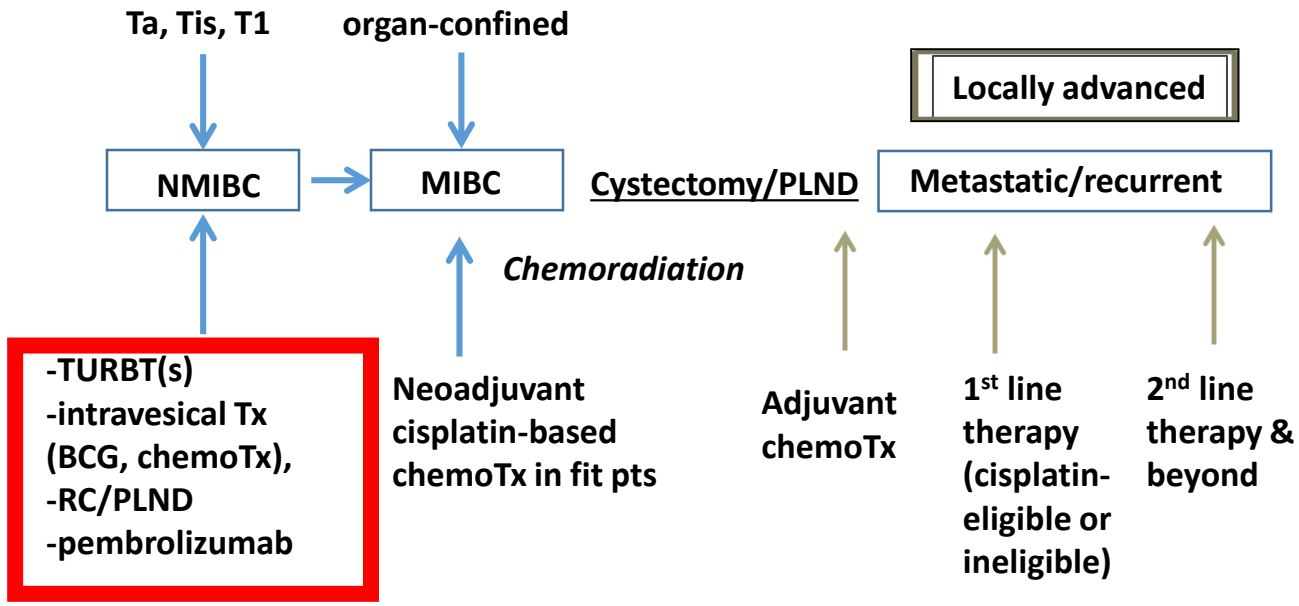
Institutional research funding: Bavarian Nordic; Bristol-Myers Squibb; Clovis Oncology; Debiopharm; Immunomedics; Pfizer; Merck; QED Therapeutics; GlaxoSmithKline; Kure It Cancer Research

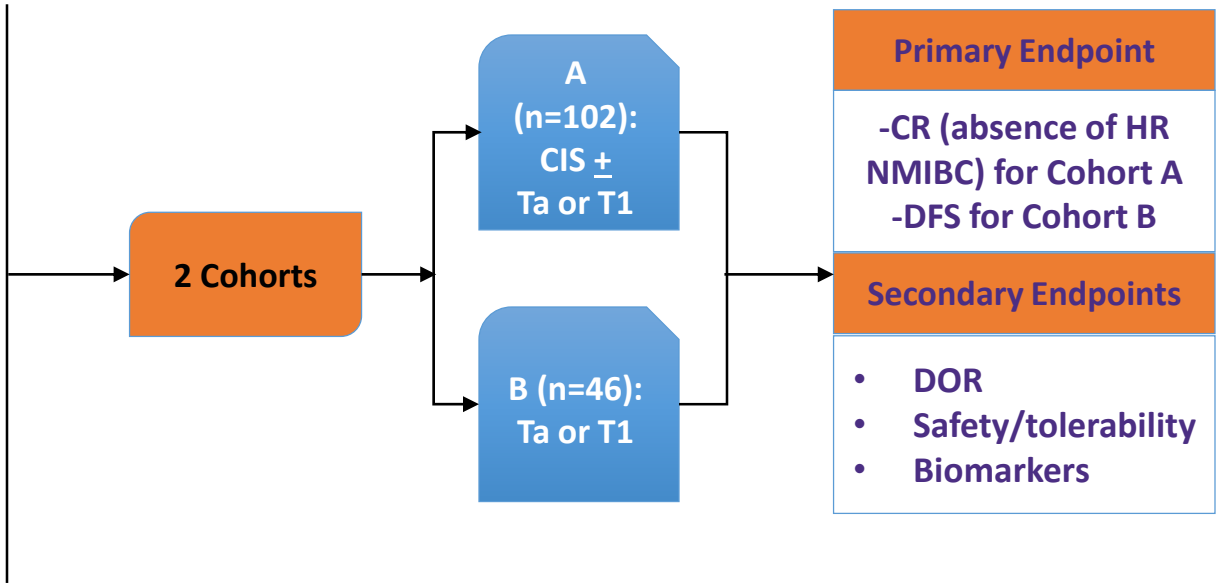
Disease / treatment settings



Systemic Immune-Oncology Therapy for NMIBC after BCG: KEYNOTE-057 with Pembrolizumab

Eligibility

- **High risk NMIBC**
- **BCG-unresponsive**
- **Papillary disease must be fully resected**
- **Refuse or ineligible for radical cystectomy**



Pembrolizumab 200 mg every 3 weeks for 2 years or until recurrence

Systemic Immune-Oncology Therapy for NMIBC after BCG: KEYNOTE-057 with Pembrolizumab

Summary of Best Overall Response Rate in Cohort A

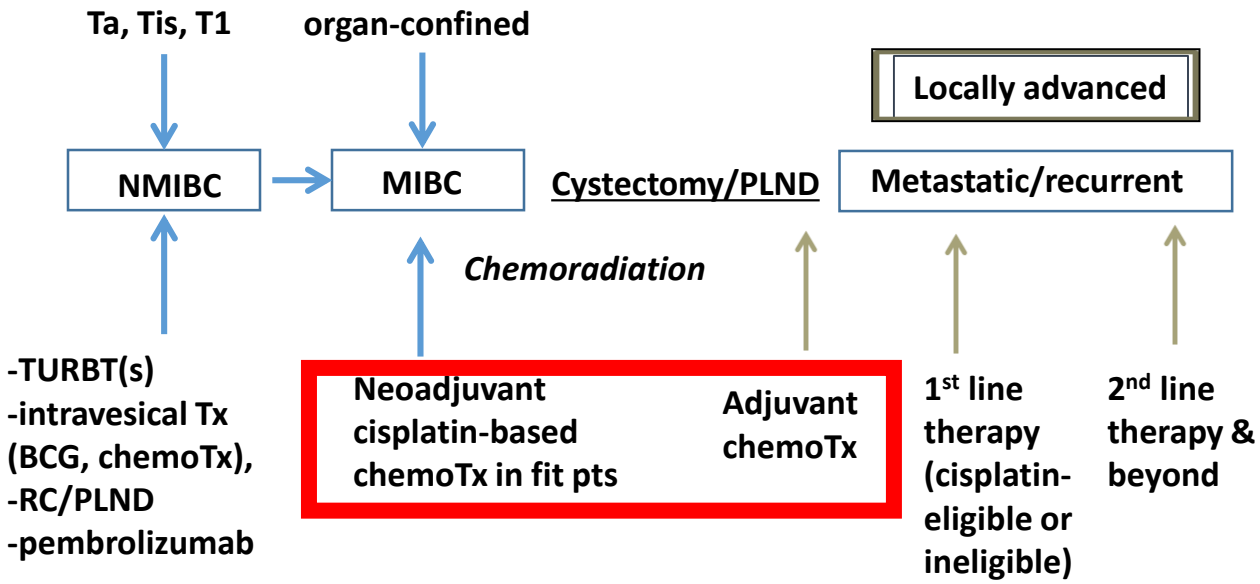
Response	N = 102		
	N	%	95% CI
CR	**42**	**41.2**	**31.5–51.4**
Non–CR	**58**	**56.9**	**46.7–66.6**
Persistent[b]	41	40.2	30.6–50.4
Recurrent	7	6.9	2.8-13.6
NMIBC stage progression[c]	9	8.7	4.1–16.1
Extravesical disease[d]	1	1.0	0.0–5.3
Progression to T2	0	0	–
Nonevaluable[e]	**2**	**2.0**	0.2–6.9

- [a]Summary of overall responses of high-risk NMIBC per central assessment at month 3 in all patients who received ≥1 dose of trial treatment, had baseline evaluations, and also had ≥1 post-baseline disease assessment. [b]Defined as patients with CIS at baseline who at month 3 also had CIS +/- papillary tumor. [c]Increase in stage from CIS and/or high-grade Ta at baseline to T1 disease. [d]Defined as presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging. [d]Patient developed new liver lesions on imaging and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. [e]Patients missing protocol-specified efficacy assessments or have discontinued from the trial for reasons other than PD are considered not evaluable for efficacy

January 2020: FDA approved pembrolizumab for BCG-unresponsive CIS with or without papillary tumors who are ineligible for or have not elected to undergo cystectomy

De Wit, et al. *Ann Oncol ESMO* 2018
Balar A, et al. ASCO GU 2019
Additional updates prior to FDA approval

Disease / treatment settings



Neoadjuvant & Adjuvant Immunotherapy Trial Landscape is rapidly evolving

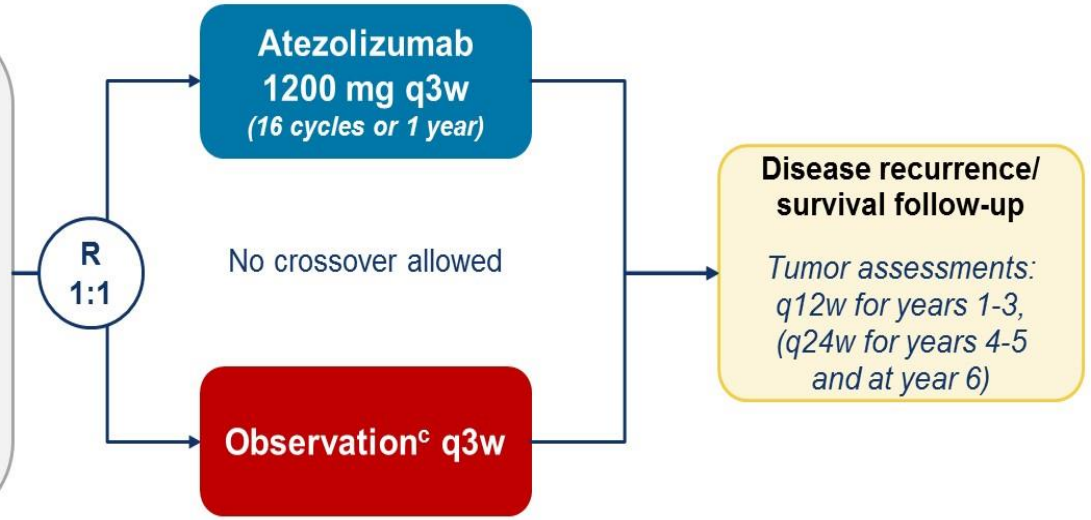
	N	Site	Phase	Neoadjuvant Trials	UTUC
NCT03294304	41	Minnesota	II	Nivolumab + Gemcitabine / Cisplatin	
NCT02845323	44	Hopkins	II	Nivolumab +/- Urelumab (cisplatin ineligible)	
Precog0807	*36*	*PreCOG (~ 8 US sites)*	*Ib*	*Nivolumab +/- Lirilumab*	
NCT03387761	24	Netherlands	Ib	Nivolumab + Ipilimumab (NABUCCO)	
NCT02736266	90	Italy	II	Pembrolizumab (PURE-01)	x
NCT03212651	40	France	II	Pembrolizumab (PANDORE)	
NCT02365766	81	HCRN	II	Pembrolizumab + Gemcitabine (cisplatin ineligible) or + Gemcitabine / Cisplatin	x
NCT02690558	39	UNC	II	Pembrolizumab + Gemcitabine / Cisplatin	
NCT03406650	61	Switzerland	II	Durvalumab NA+A	x
NCT02812420	15	MDACC	II	Durvalumab + Tremelimumab (cisplatin ineligible)	
NCT03472274	99	Spain	II	Durvalumab + Tremelimumab vs chemotherapy (DUTRENEO)	x
NCT03234153	68	Switzerland	II	Durvalumab + Tremelimumab (cisplatin ineligible)	
NCT03498196	10	Baylor	II	Avelumab (cisplatin ineligible)	
NCT02451423	42	UCSF	II	Atezolizumab (cisplatin ineligible) includes <cT2	
Phase III Adjuvant Trials					
NCT02450331	800		III	Atezolizumab Vs Observation	x
NCT03244384	739		III	Pembrolizumab Vs Observation	x
NCT02632409	640		III	Nivolumab Vs Placebo	x

~ 6 phase III peri-operative IO trials (in cisplatin fit & in unfit pts)

IMvigor010 Study Design

Key eligibility[a]

- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤ 14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC[b]**
  - **pT3-T4a or pN+** for patients **not treated with NAC[b]**
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**



Stratification factors

- Number of LNs resected (< 10 vs ≥ 10)
- Prior NAC (Yes vs No)
- LN status (+ vs –)
- Tumor stage (≤ pT2 vs pT3/pT4)
- PD-L1 status[a] (IC0/1 vs IC2/3)

- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.

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sitc Society for Immunotherapy of Cancer

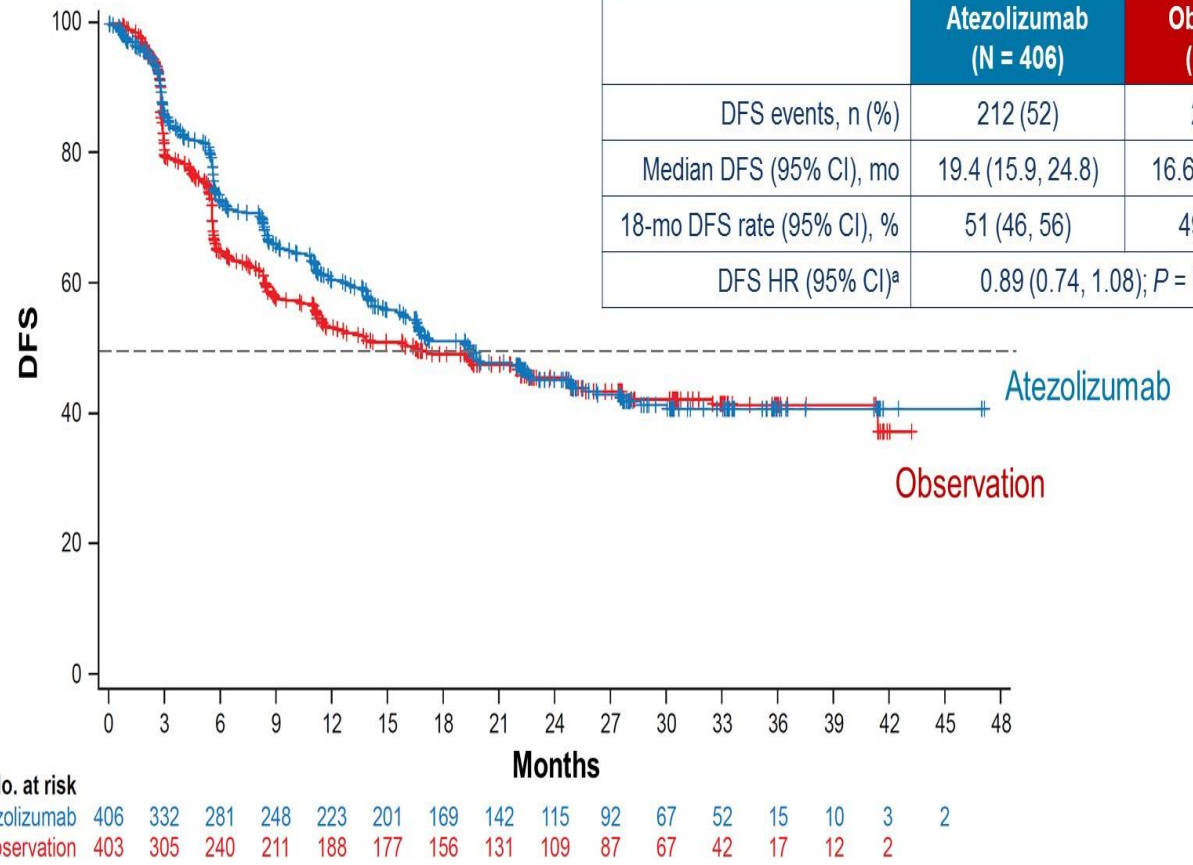
ADVANCES IN Cancer IMMUNOTHERAPY™

Press Release (09/24/20)

Nivolumab Significantly Improved DFS vs. Placebo as Adjuvant Therapy for Pts with High-Risk, Muscle-Invasive Urothelial Carcinoma in Phase 3 CheckMate -274 (OS data probably immature)

DFS in ITT Population

	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	



Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author, permission required for reuse.

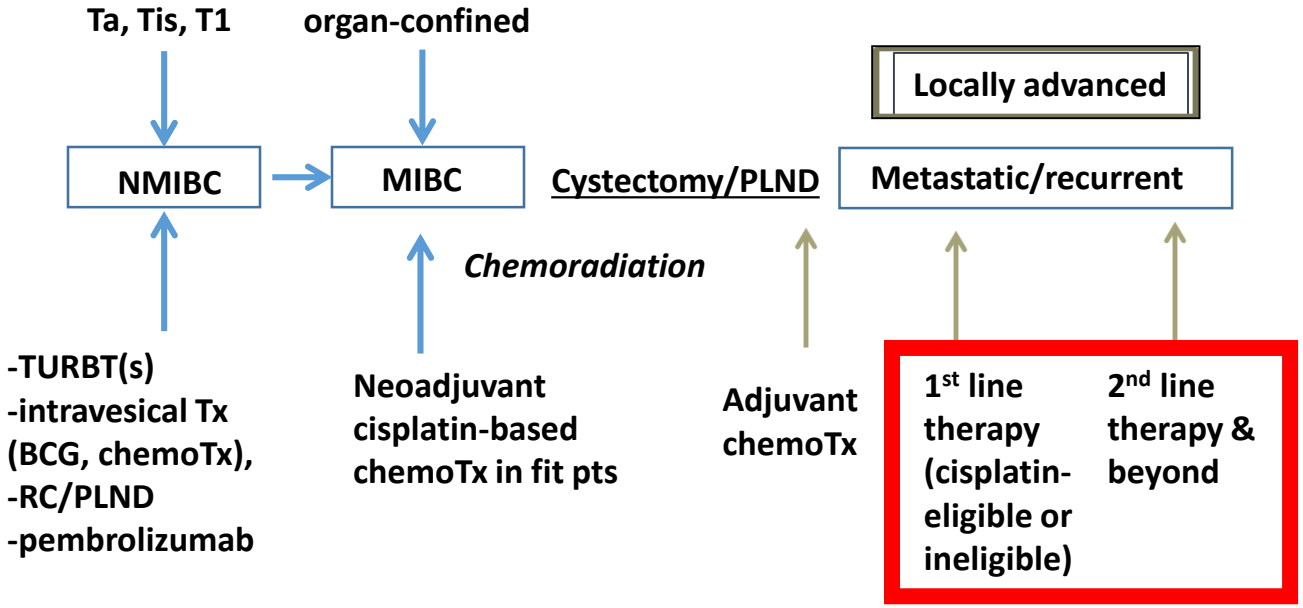
PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000].

https://bit.ly/2SKSAD3

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE ACCC Association of Community Cancer Centers HOPA Hematology/Oncology Pharmacy Association sitc Society for Immunotherapy of Cancer

Presented By Maha Hussain at TBD

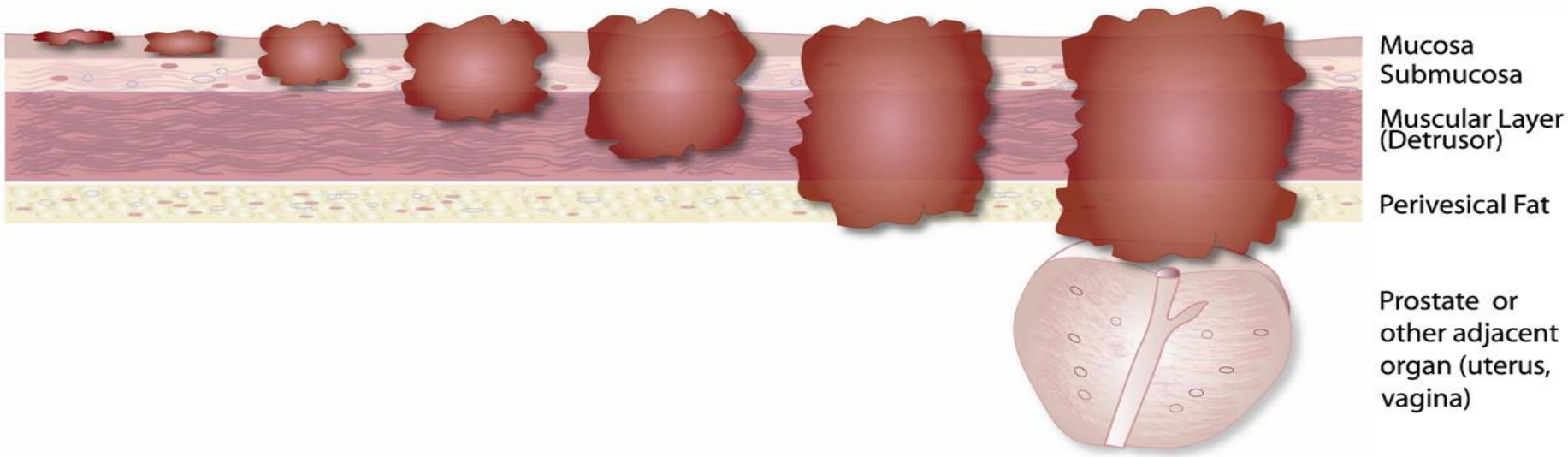
Disease / treatment settings



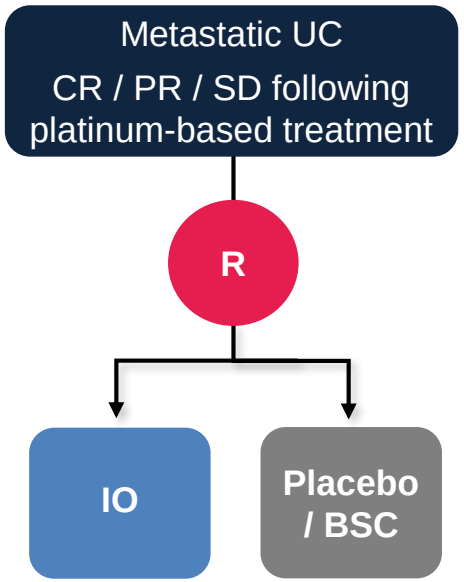
Immunotherapy for Metastatic Urothelial Carcinoma (UC)

Non-Muscle Invasive → Muscle Invasive → Metastatic

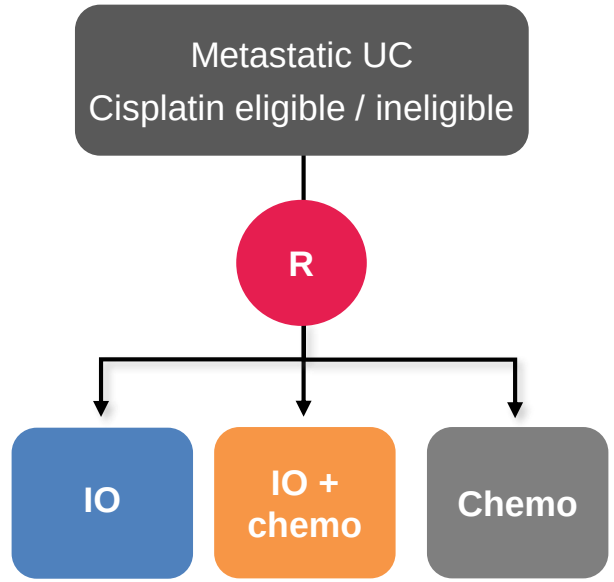
TNM	TIS	T_a	T_1	T_{2A}	T_{2B}	T_{3B}	T_{4A}
JSM	0	0	A	B_1	B_2	C	D_1



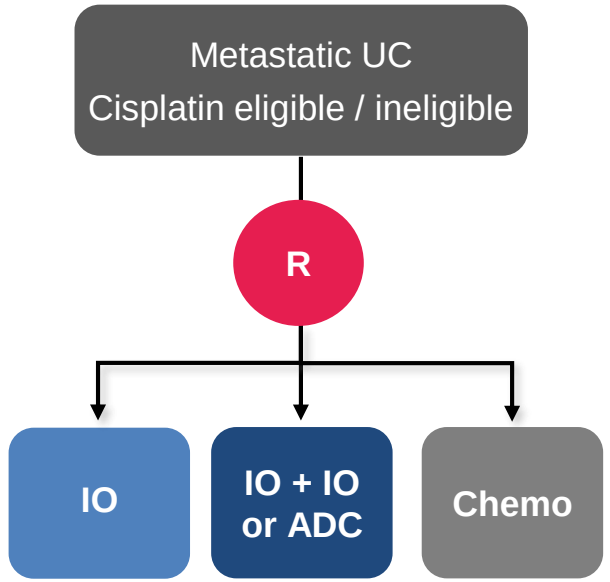
Different strategies impacting 1L SoC



JB100 [NCT02603432]	avelumab	BSC	OS
HOOSIER [NCT02500121]	pembro	placebo	6-mo PFS



KN361 [NCT02853305]	pembro	pembro + chemo	chemo	OS, PFS
CM901 [NCT03036098]	--	nivo + chemo*	chemo	OS, PFS
IMvigor130 [NCT02807636]	atezo	atezo + chemo	chemo	OS, PFS, safety



DANUBE [NCT02516241]	durva	durva + treme	chemo	OS
CM901 [NCT03036098]	--	nivo + ipi	chemo	OS, PFS
EV-302 [NCT04223856]	--	pembro + EV	chemo	OS, PFS

*For cisplatin-eligible patients only

1L, first-line; ADC, antibody-drug conjugate; atezo, atezolizumab; BSC, best supportive care; EV, enfortumab vedotin; chemo, chemotherapy; CR, complete response; durva, durvalumab; IO, immuno-oncology; ipi, ipilimumab; OS, overall survival; nivo, nivolumab; pembro, pembrolizumab; PFS, progression-free survival; PR, partial response; R, randomisation; SD, stable disease; SoC, standard of care; treme, tremelimumab; UC, urothelial carcinoma. NCT entries available at https://clinicaltrials.gov/ [Accessed August 2020].

Approved immune checkpoint inhibitors for mUC in cisplatin-ineligible pts in 1L

Drug	Approved	Indication	Dose
Atezolizumab	2017 (2018)	Advanced/metastatic UC (PD-L1 ≥5% IC)	1200 mg Q3W
Pembrolizumab	2017 (2018)	Advanced/metastatic UC (PD-L1 CPS ≥10)	200 mg Q3W or 400 mg Q6W

June 2018

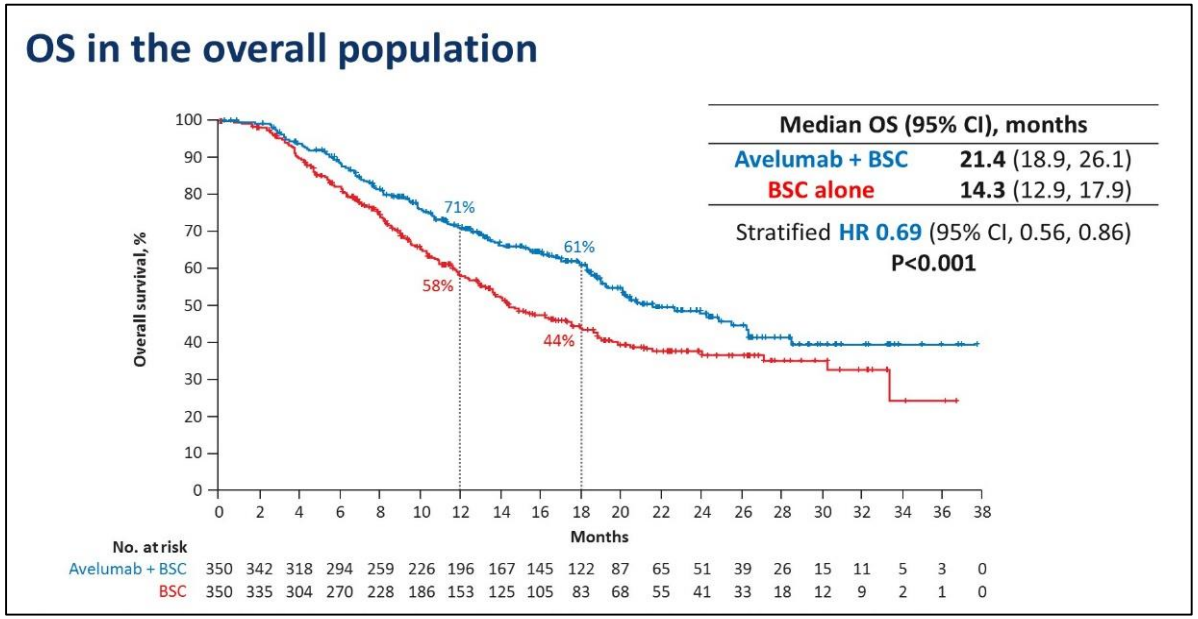
FDA limits the use of Atezolizumab & Pembrolizumab in 1L in PD-L1-high cisplatin-unfit or all platinum-unfit pts

- **Locally advanced/unresectable or metastatic UC in pts ineligible for cisplatin-based chemoTx and tumor PD-L1 (CPS ≥ 10, pembro; IC ≥ 5% IC, atezo)**
- **Pts ineligible for any platinum-containing chemotherapy regardless of PD-L1 status (US only)**

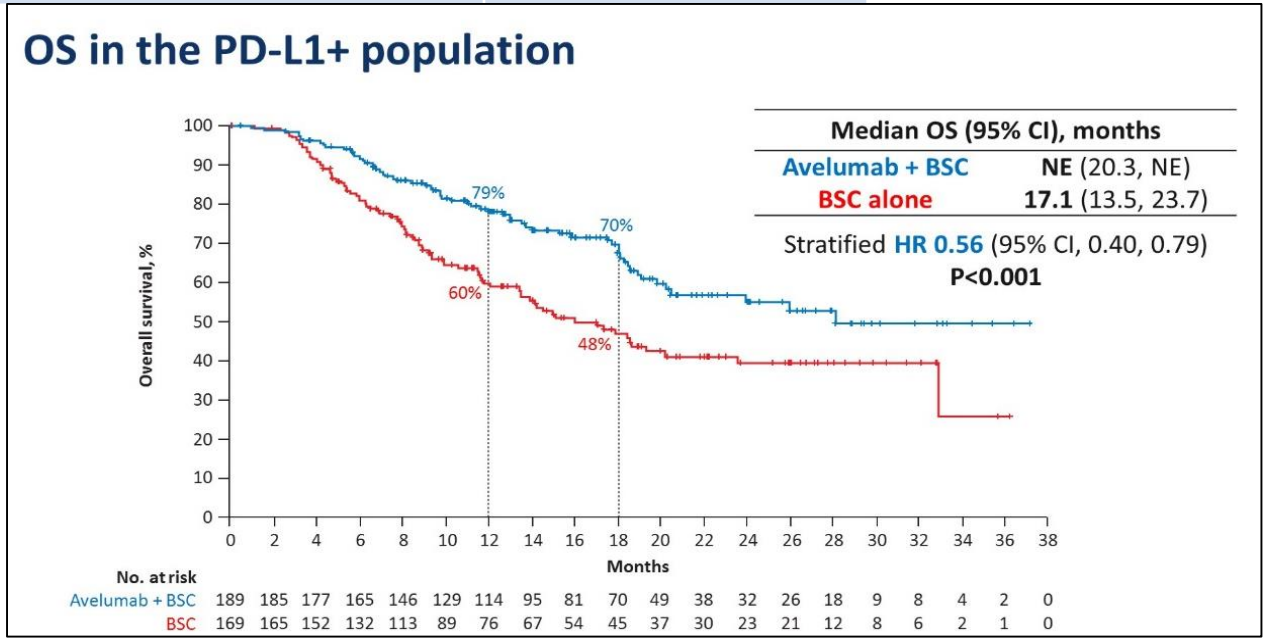
Approved immune checkpoint inhibitor for switch maintenance treatment in 1L

Drug	Indication	Dose
Avelumab	**Maintenance of locally advanced/metastatic UC without progression on first-line Pt chemotherapy**	**800 mg Q2W**

OS in the overall population



OS in the PD-L1+ population



Powles, ASCO 2020.

#LearnACI

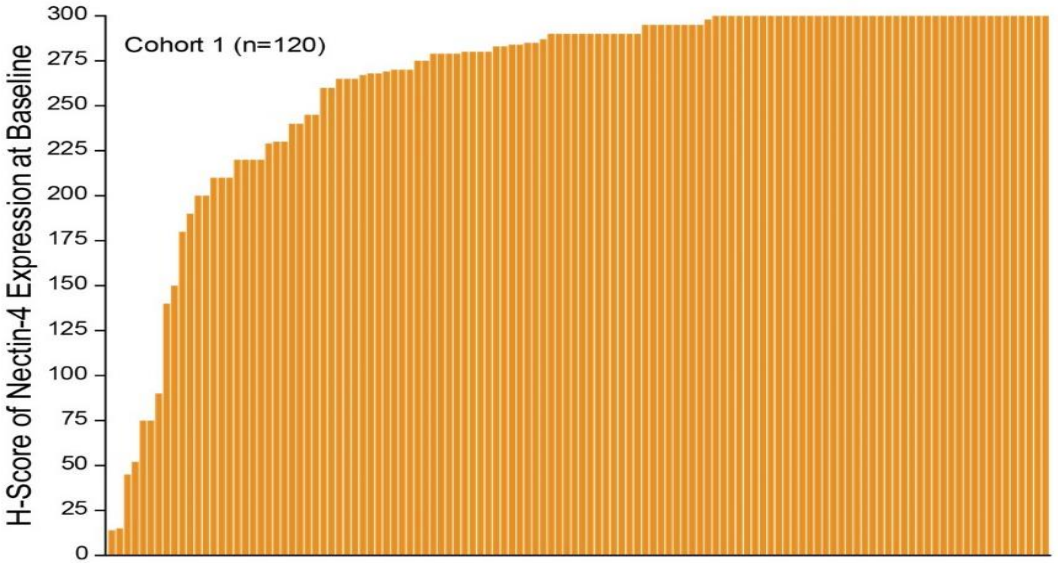
Approved immune checkpoint inhibitors for *platinum-refractory mUC*

Drug	Approved	Indication	Dose
Atezolizumab	2016 (2018)	Advanced/metastatic UC	1200 mg Q3W
Avelumab	2017	Advanced/metastatic UC	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 or 400 mg Q6W

Approved antibody-drug conjugate for mUC after prior platinum, prior ICI

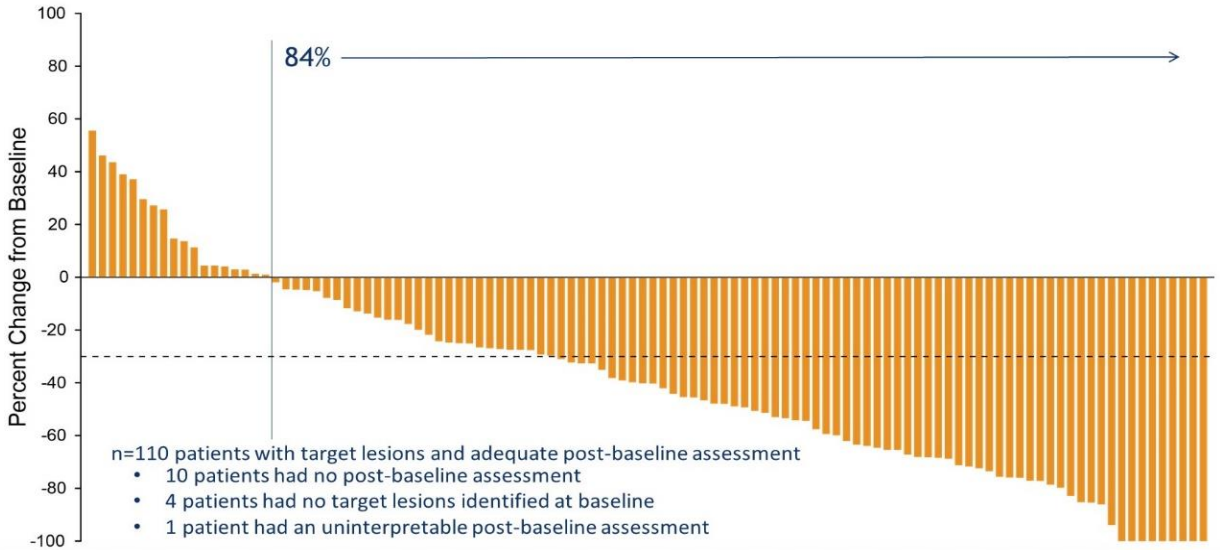
Drug	Approved	Indication	Dose
Enfortumab vedotin	December 2019	Locally advanced/metatstatic UC after anti-PD-(L)1 & platinum-based chemoTx	1.25 mg/kg IV on days 1, 8, 15 of each 28-day cycle

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



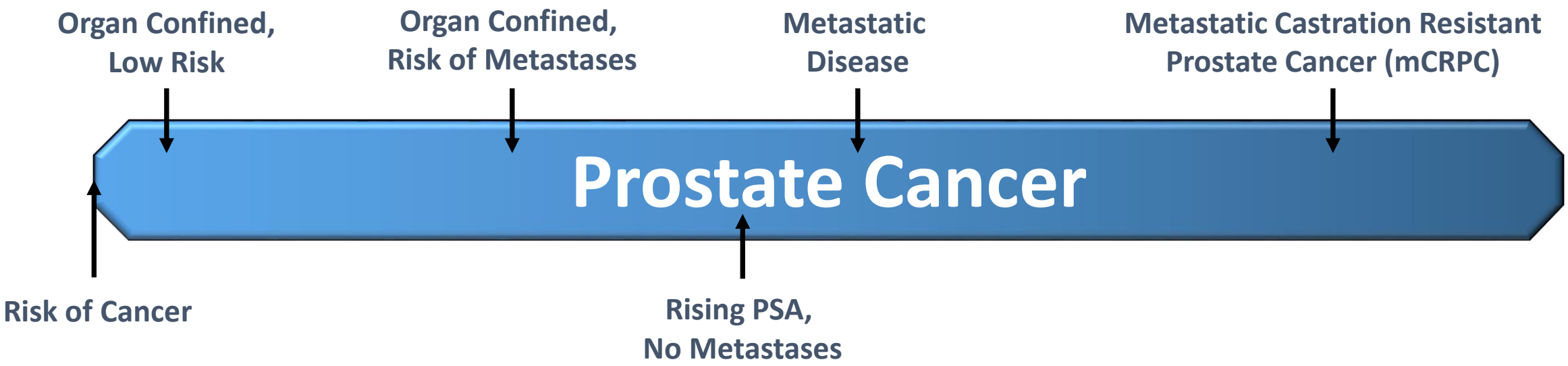
Petrylak, ASCO 2019.

Advanced Urothelial Ca Treatment Algorithm (updates highlighted)

Disease State	Setting	Preferred Option	Standard Options
Metastatic, no prior chemotherapy	Cisplatin-eligible	Cisplatin/gemcitabine f/b avelumab maintenance	Cisplatin-based combination chemotherapy f/b avelumab maintenance
Metastatic, no prior chemotherapy	Cisplatin-ineligible	Gemcitabine/Carboplatin -PD-L1 low tumors -carboplatin-fit patients f/b avelumab maintenance	Gemcitabine/Carboplatin (any PD-L1 status) f/b avelumab maintenance *Pembrolizumab* *Atezolizumab* Single agent chemotherapy
Metastatic, prior plati chemotherapy or rela within 1 year of perio cisplatin-based therapy		FGFR2/3 alterations)	mab ab Nivolumab
Metastatic, prior chemotherapy & immunotherapy		Enfortumab vedotin OR Erdafitinib (tumors with FGFR2/3 alterations)	Taxane (US) Vinflunine (EU)

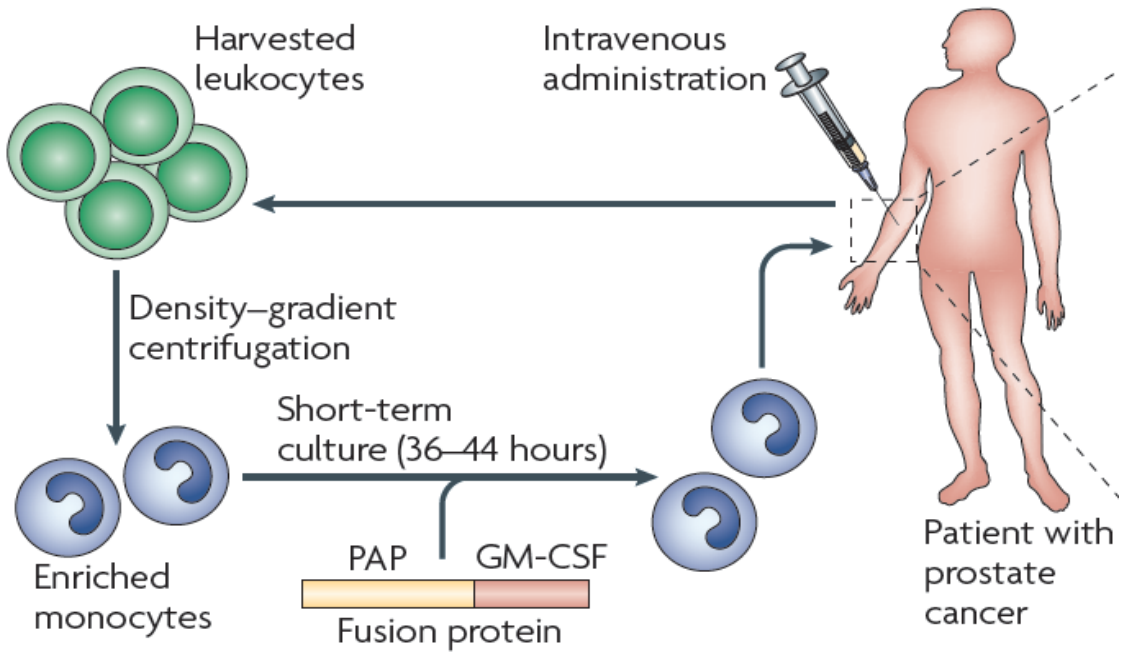
Clinical trials are critical throughout disease spectrum & treatment settings!

The Spectrum of Prostate Cancer



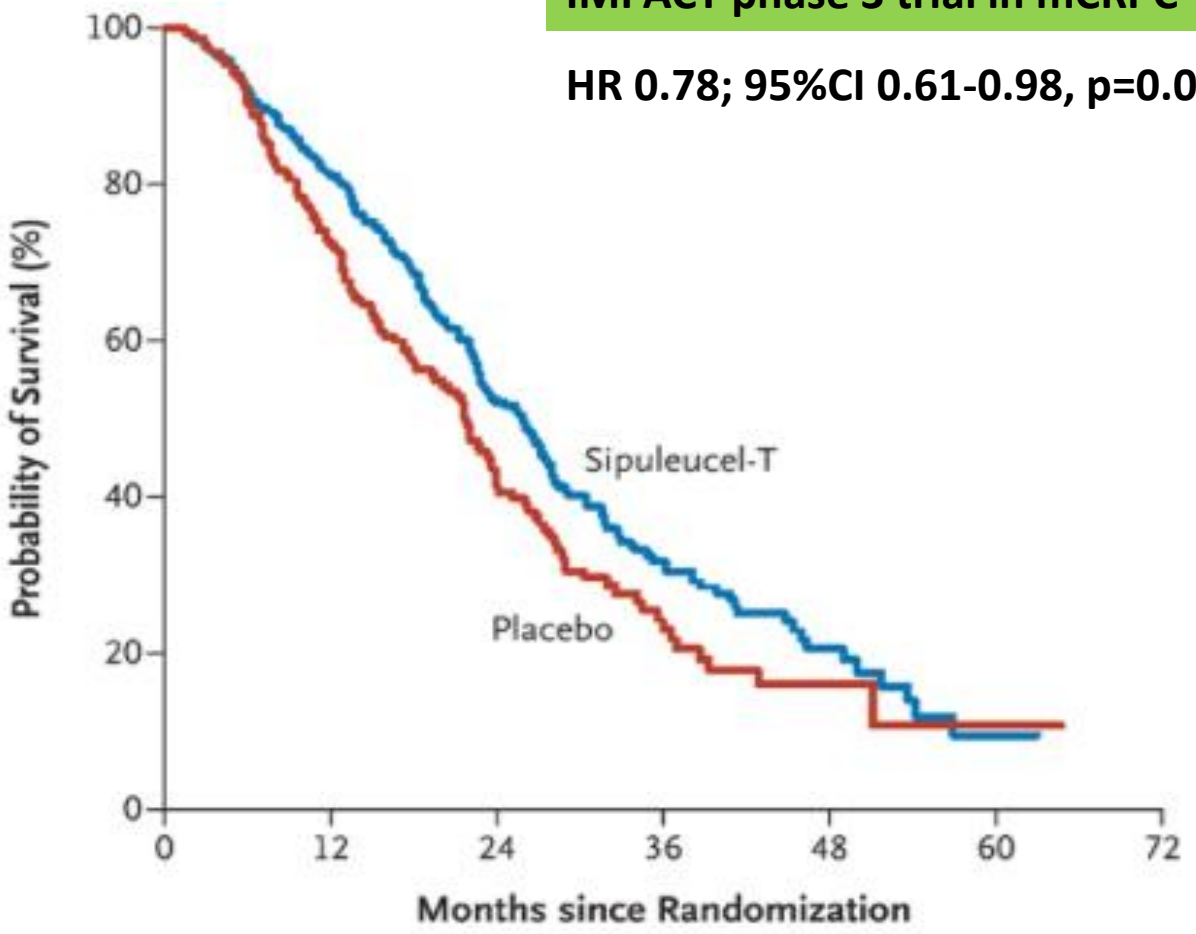
Sipuleucel-T in mCRPC

First anti-cancer therapeutic vaccine



IMPACT phase 3 trial in mCRPC

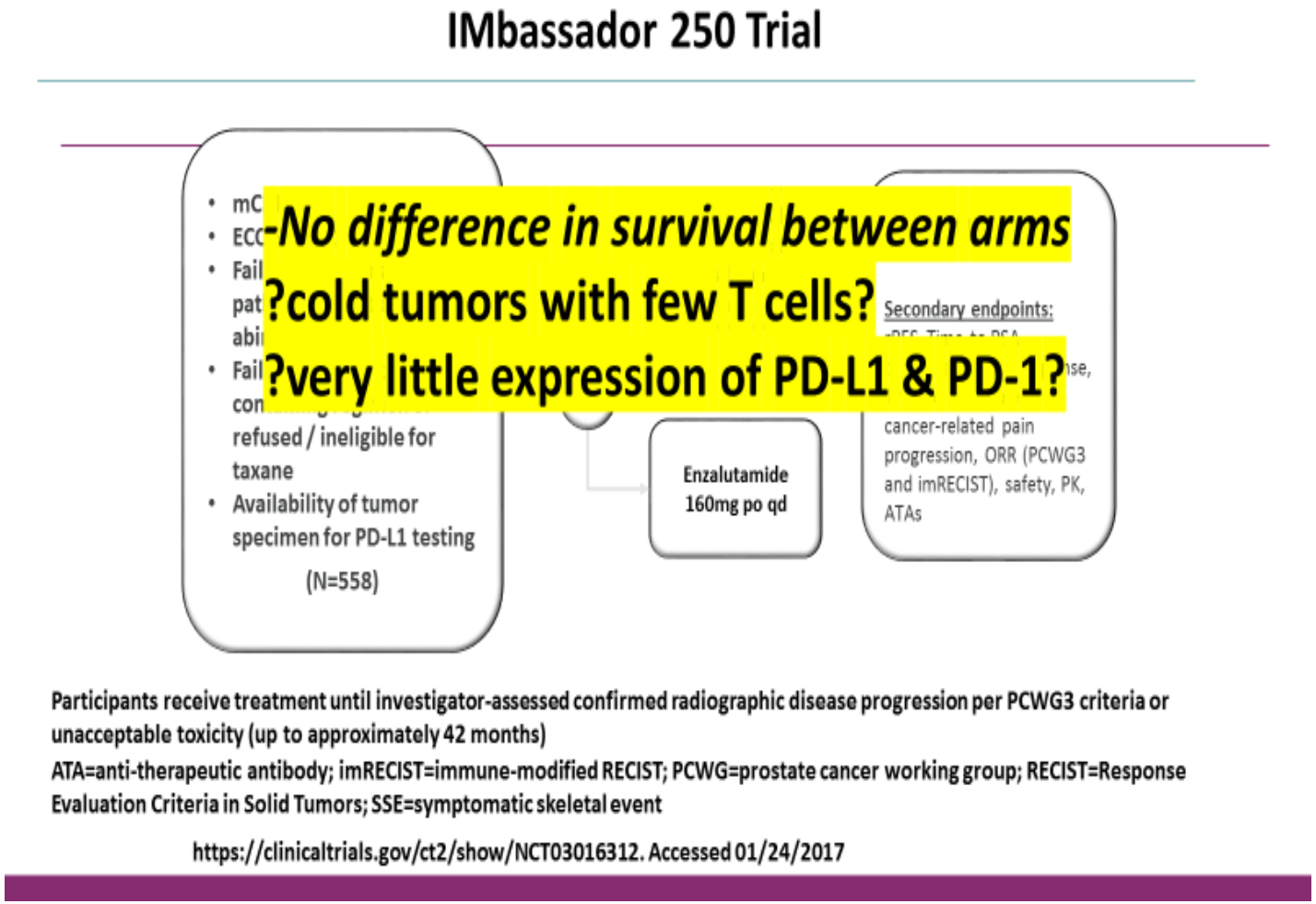
HR 0.78; 95%CI 0.61-0.98, p=0.03



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

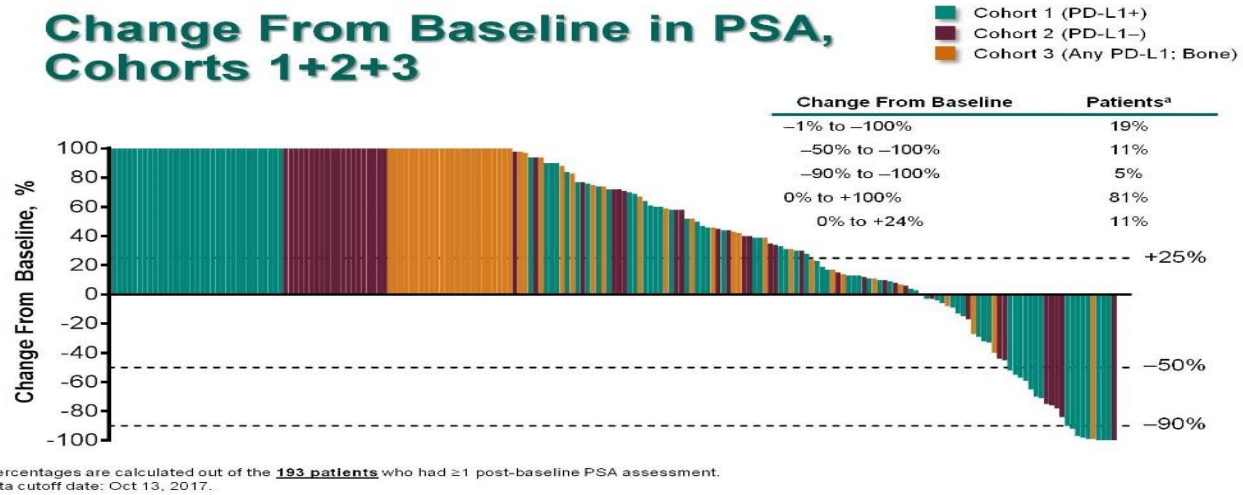
Limited efficacy of Immune Checkpoint Inhibitors in mCRPC

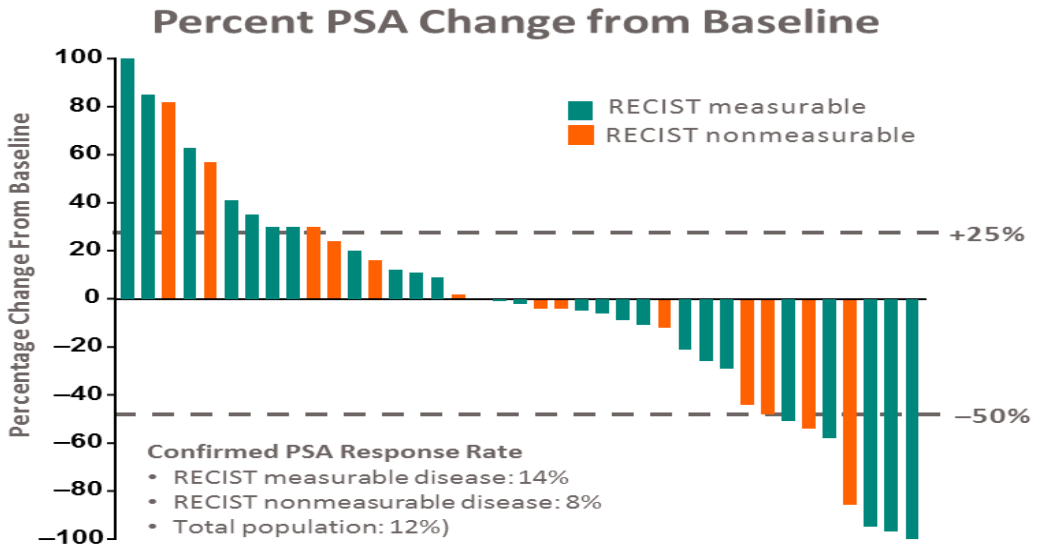
No FDA-approved ICIs for mCRPC



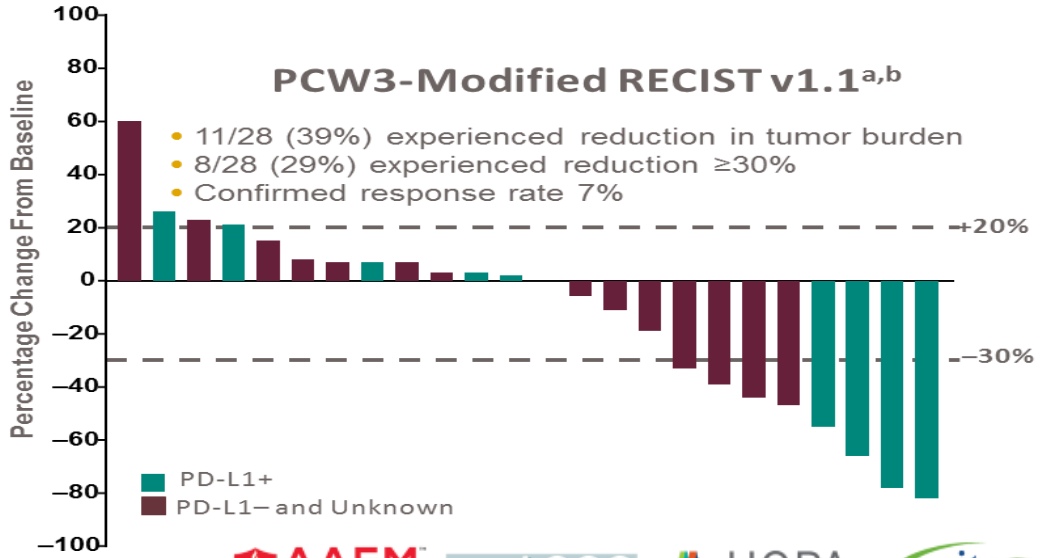
- **Pembrolizumab approved for all Microsatellite Instability-High (MSI-H) refractory solid tumors**
- **MSI-H incidence low in prostate Ca**
  - **Localized ~2%**
  - **Autopsy series of mCRPC ~12%**
- **Pembrolizumab approved for refractory solid tumors (TMB-H; ≥ 10 mutations/Mb) as determined by FDA-approved test (TMB-H seems rare in prostate Ca)**
- ***MSI & TMB testing may offer pembrolizumab as an option***

Pembrolizumab KEYNOTE-199 & KEYNOTE-365





KEYNOTE-199: Post-docetaxel single agent Pembrolizumab



KEYNOTE-365 Cohort A: Post-docetaxel Pembrolizumab + Olaparib

Yu EY et al. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 145)

De Bono J et al. *J Clin Oncol* 36, 2018 (suppl; abstr 5007)

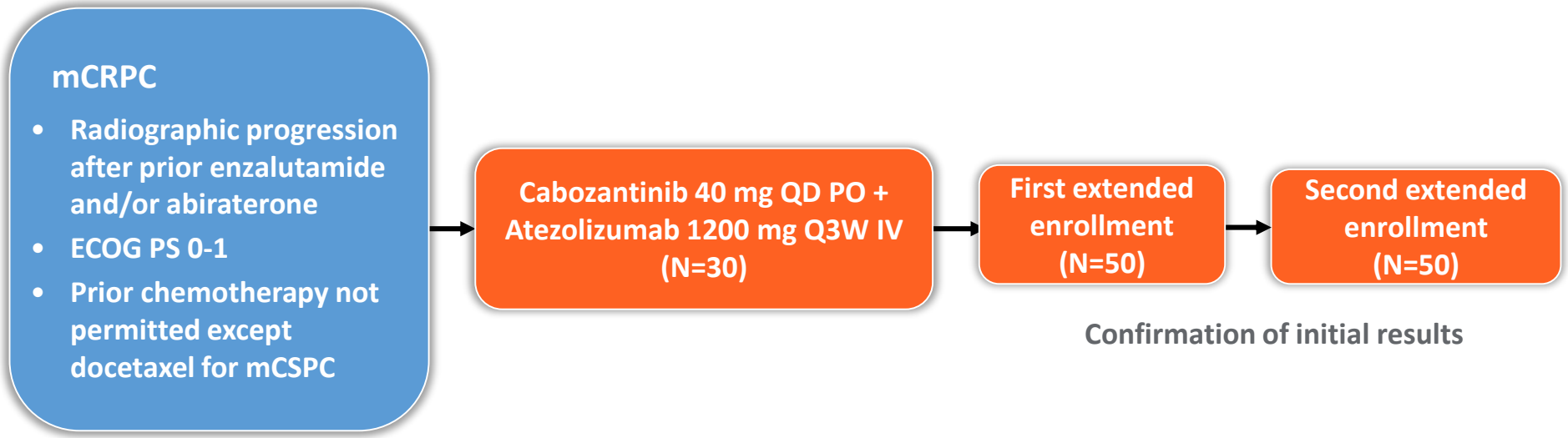
Combination Immunotherapy: Checkmate 650

- Open-label, multicenter phase II trial of combination
- **25% ORR in pre-chemo cohort 1 & 10% ORR in post-chemo cohort 2**
  - Cohort 1: Asymptomatic, chemotherapy naïv
- **5.5 & 3.8 mo median rPFS; 19.0 & 15.2 mo median OS**
  - Grade 3-5 adverse events: 42%
- **Exploratory analyses identify potential biomarkers of response**
  - ORR: 10%
  - Grade 3-5 adverse events: 53%
- **G 3–4 TRAEs ~42%–53%, with 4 treatment-related deaths; dose/schedule mods have been implemented**
- **Study expansion needed to assess other dosing regimens**

		Cohort 1	Cohort 2
		26 (10–48), 6/23	10 (2–27), 3/30
			2/8 (25)
			0/20 (0)
DDR[b]	+	2/5 (40)	2/5 (40)
		4 (29)	1/9 (11)
	+	2/3 (67)	1/2 (50)
	-	4/16 (25)	2/12 (17)
TMB[b,c]	High	6/10 (60)	3/6 (50)
		0/9 (0)	0/8 (0)
PSA response[d]		6/28 (21)	5/40 (13)

Sharma et al. ASCO Annual Meeting, 2019

COSMIC-021: Expansion for CRPC Cohort 6

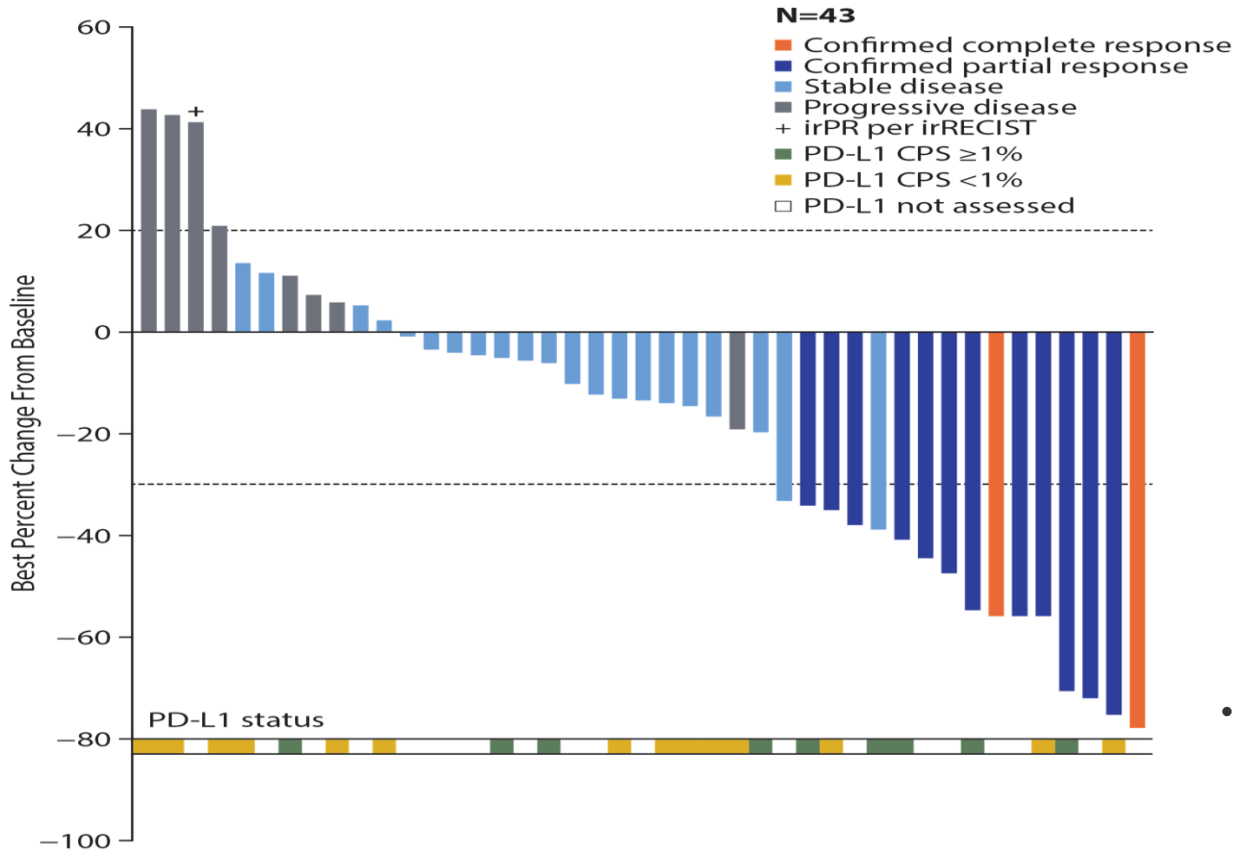


Pts receive study treatment as long as they continue to experience clinical benefit as assessed by the investigator or until unacceptable toxicity

ECOG, Eastern Cooperative Oncology Group; m, metastatic; CRPC, castration-resistant prostate cancer; CSPC, castration-sensitive prostate cancer; PO, orally; PS, performance status; Q3W, once every 3 weeks; QD, once daily

Agarwal N, et al. ASCO GU. 2020 (abstr 139)

Best Change From Baseline in Sum of Target Lesions per Investigator by RECIST v1.1



	N=44
ORR (80% CI), %	32 (23–42)
BOR, n (%)	
Confirmed CR	2 (4.5)
Confirmed PR	12 (27)
SD	21 (48)
PD	8 (18)[+]
Missing	1 (2.3)
DCR, n (%)	35 (80)

- ORR was 32% among all 44 CRPC pts and 33% among 36 pts with high-risk clinical features (visceral and/or extra-pelvic lymph node metastases)

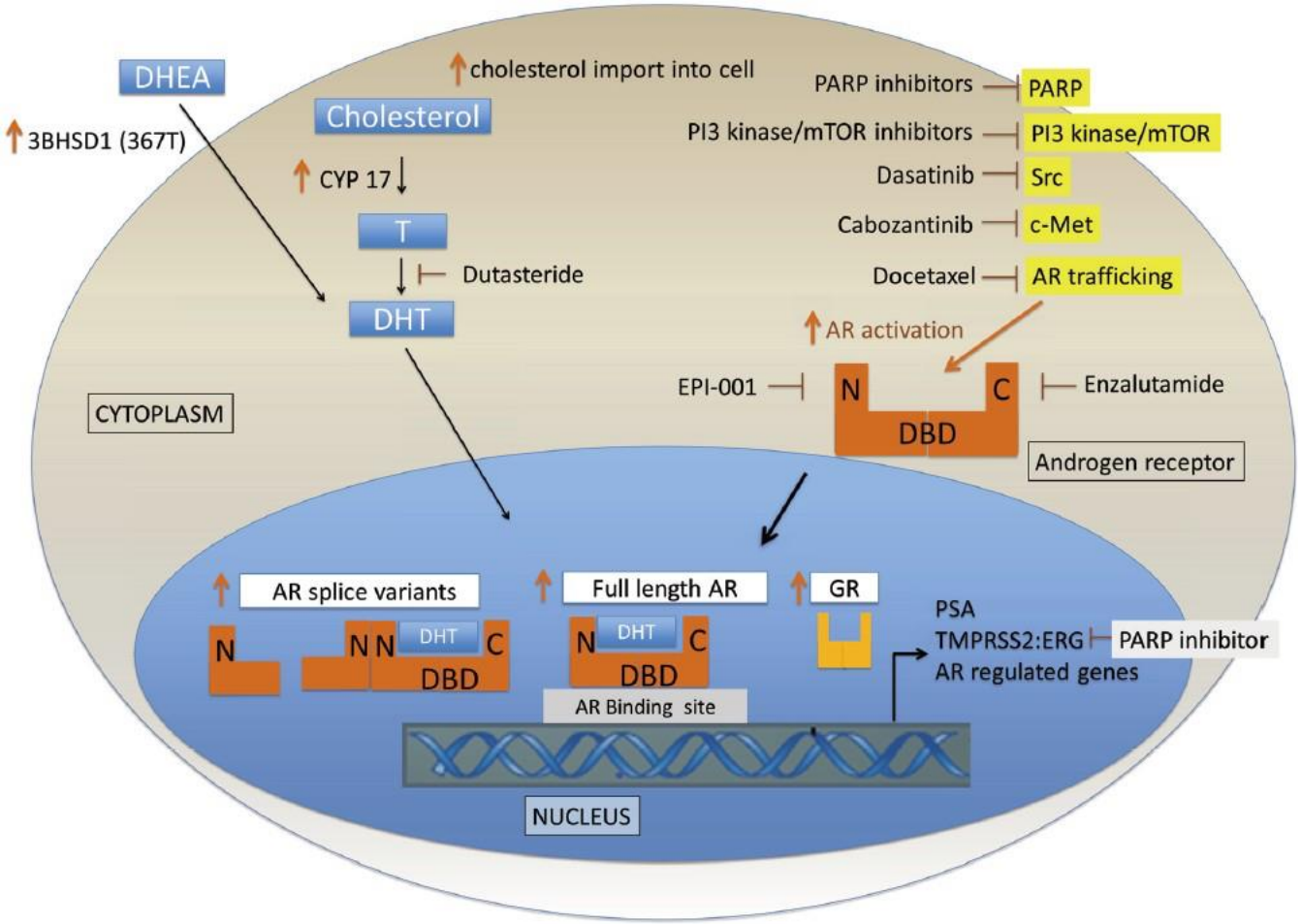
43 out of 44 pts had at least 1 post-baseline tumor assessment. The two patients with CRs had lymph node metastases as target lesions; [+]One patient (noted above) had an irPR per irRECIST with reduction in target lesions from baseline of ~60% after initial PD. PD-L1 status is shown for pts with known PD-L1 status; analysis of PD-L1 is ongoing. Disease control rate (DCR) = complete response + partial response + stable disease.

CR, complete response; CRPC, castration-resistant prostate cancer; ir, immune related; ORR, objective response rate; RECIST, Response Evaluation Criteria In Solid Tumors; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors

Agarwal N, et al. ASCO GU. 2020 (abstr 139)

Future Combinations in mCRPC to Engage Immune System

- **Anti-androgen therapy**
- **Radiation**
- **Radium-223**
- **PARP inhibitors**
- **Chemotherapy**
- **New/other targets**



Stein et al. Asian J Andrology 2014

	CAR T cell : Chimeric antigen receptors	BiTE : Bispecific T cell engagers
Structure	A synthetic gene encoding an scFv against tumor antigen linked to activation and costimulatory motifs	A recombinant protein: of two linked scFVcs: one binds to CD3 on T cells and one to a tumor antigen on tumor cells
Effector cell types	Engineered CD8+ and CD4+T cell. Less differentiated subsets, better antitumor activity in vivo (T_{SCM} and T_{CM})	Endogenous CD8+ and CD4+T cells. Antigen experienced T_{EM} but not T_{N} effective
Immune synapse	Atypical	Typical
Serial Killing	Yes	Yes
Killing mechanisms	Perforin and granzyme B, FAS/Fas-L, or TNF/TNF-R	Perforin and granzyme B
Trafficking	Active	Passive
Toxicity	CRS, neurotoxicity, B-cell aplasia	CRS, neurotoxicity, B-cell aplasia
Clinical applications	Pretreatment lympho depletion required- cyclophosphamide and fludarabine, 1 infusion	No lymphodepletion, repeat administration required

https://www.urotoday.com/conference-highlights/esmo-2020/prostate-cancer/124635-esmo-virtual-congress-2020-novel-immunotherapy-for-prostate-cancer-amg-160-psma-targeted-bispecific-t-cell-engager-bite-immune-therapy-for-metastatic-castration-resistant-prostate-cancer.html (accessed 10/3/2020)

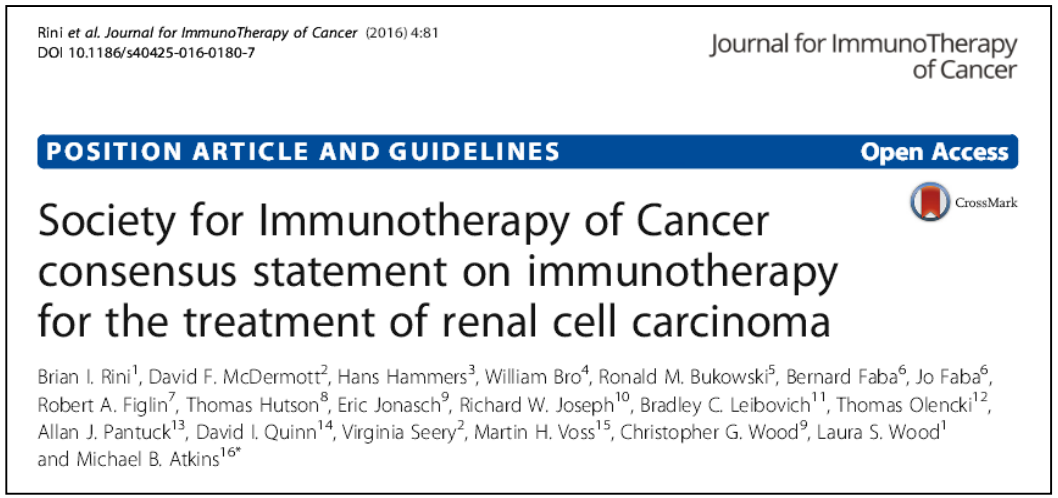
irAEs with Immune Checkpoint Inhibitors in GU Cancers - Meta-analysis of 8 studies

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

Additional Resources



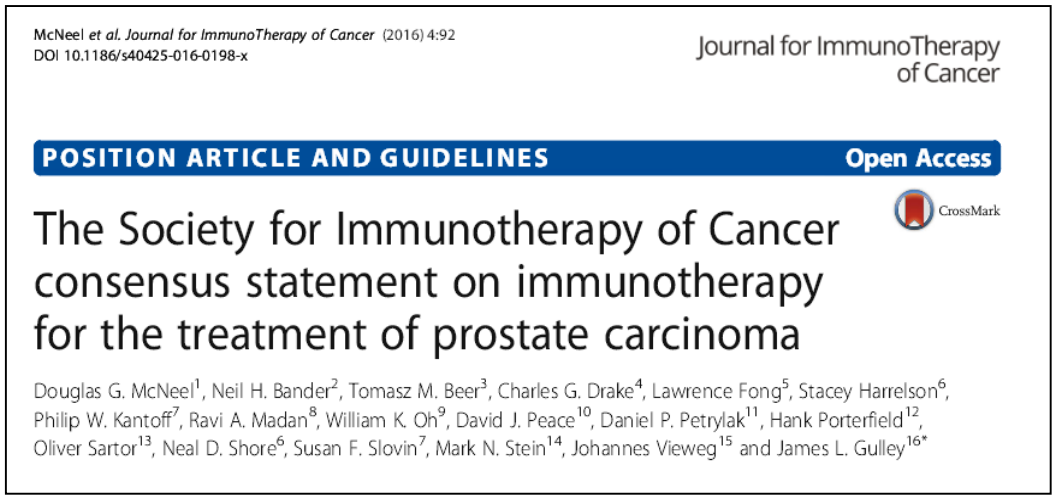
Rini *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:81
DOI 10.1186/s40425-016-0180-7

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[2], Martin H. Voss[15], Christopher G. Wood[9], Laura S. Wood[1] and Michael B. Atkins[16*]



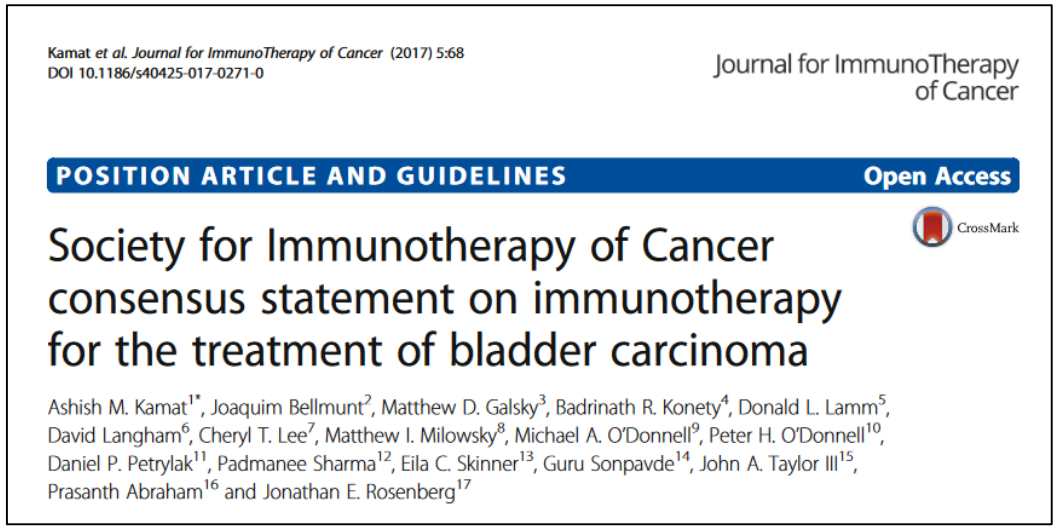
McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

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

Douglas G. McNeel[1], Neil H. Bander[2], Tomasz M. Beer[3], Charles G. Drake[4], Lawrence Fong[5], Stacey Harrelson[6], Philip W. Kantoff[7], Ravi A. Madan[8], William K. Oh[9], David J. Peace[10], Daniel P. Petrylak[11], Hank Porterfield[12], Oliver Sartor[13], Neal D. Shore[6], Susan F. Slovin[7], Mark N. Stein[14], Johannes Vieweg[15] and James L. Gulley[16*]



Kamat *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:68
DOI 10.1186/s40425-017-0271-0

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

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

Ashish M. Kamat[1*], Joaquim Bellmunt[2], Matthew D. Galsky[3], Badrinath R. Konety[4], Donald L. Lamm[5], David Langham[6], Cheryl T. Lee[7], Matthew I. Milowsky[8], Michael A. O'Donnell[9], Peter H. O'Donnell[10], Daniel P. Petrylak[11], Padmanee Sharma[12], Eila C. Skinner[13], Guru Sonpavde[14], John A. Taylor III[15], Prasanth Abraham[16] and Jonathan E. Rosenberg[17]

Conclusions

- The role of immunotherapy in GU cancers is expanding
- Biomarkers being explored, but validation & clinical utility is a high bar

- RCC: IPI/NIVO; CABO/NIVO; PEMBRO/AXI are 1L therapy options

- Sipuleucel-T: approved in relatively asymptomatic mCRPC (OS benefit)
- Ongoing trials evaluating anti-PD(L)1 + (PARPi or docetaxel or cabozantinib)
- CTLA4 or anti-PD(L)1 monotherapy in all comers has no role in prostate Ca; role of combo in selected pts?
- Atezo/enza vs enza phase 3 trial did not show survival difference

Take home messages for urothelial Ca

- **Pembrolizumab FDA approved for BCG-unresponsive CIS (with or without papillary tumors) in pts who refuse or can't get radical cystectomy, which is SOC in this setting (KN057 trial)**
- **Clinical trials or cisplatin-based chemoTx for cisplatin-eligible pts**
- **Adjuvant atezolizumab did not prolong DFS vs observation, but adjuvant nivolumab prolonged DFS vs placebo: await *Ambassador***
- **Atezolizumab & pembrolizumab: similar level of evidence in 1L cisplatin-ineligible for *PD-L1+ (or* 'platinum-unfit' *pts in US only)***
- **Javelin Bladder 100 trial met primary endpoint of OS with switch maintenance avelumab/BSC vs BSC and changed practice after CR/PR/SD after 1L platinum based chemoTx!**
- **Level I evidence *for pembrolizumab in* platinum refractory setting (KN045 trial); the role of anti-CTLA4 is only experimental in UC**

Case Studies

Case Presentation

- 83 yo woman with severe medical comorbidities initially presented with gross hematuria
- She was found on cystoscopy & subsequent TURBT to have extensive, multifocal CIS; staging with no extravesical disease
- She received full course (6 doses) of induction BCG with cCR; then underwent 3 doses maintenance BCG surveillance
- Surveillance initially negative but within 6 months she was found to have multifocal CIS & high-grade T1 tumor. She has PS ECOG 2 and high comorbidity index and was deemed not a candidate for cystectomy

What are reasonable treatment options for this patient?

A. Intravesical chemotherapy
B. Intravenous pembrolizumab
C. Clinical trial
D. All the above

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Case Presentation

73 yo man with metastatic urothelial cancer during investigation of dysuria & hematuria. Somatic tumor testing did not show FGFR2 or FGFR3 alterations.

-No other known past medical history; PS ECOG 1, GFR 70 cc/min

-CT chest, abdomen, pelvis: diffuse liver & lung metastases, PD-L1: CPS 20

-He received the last of 4 cycles gemcitabine/cisplatin with partial response but has developed significant neuropathy & fatigue and does not want more chemoTx

->Which option below has level I evidence & FDA approval?

A. Avelumab till progression or unacceptable toxicity (correct)

B. Avelumab for 2 years

C. Pembrolizumab till progression or unacceptable toxicity

D. Pembrolizumab for 2 years

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Case Presentation

77 yo man with metastatic urothelial cancer. Somatic tumor testing did not show FGFR2 or FGFR3 alterations. No other known past medical history; PS ECOG 0, GFR 60 cc/min.

-CT chest, abdomen, pelvis: pelvic lymph node & lung metastases, PD-L1: CPS 10

-He received 3 cycles gemcitabine/cisplatin with disease progression

->Which option below has level I evidence based on OS benefit as a primary endpoint in a phase III trial in this setting?

A. Atezolizumab
B. Avelumab
C. Durvalumab
D. Nivolumab
E. Pembrolizumab (correct)

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Case Studies - mRCC

Case Study 1

A 55 yo man with past hx of HTN and a former 20 pk-yr smoker was evaluated for right sided chest pain:

- CT imaging showed an 8 cm left renal mass and a lytic lesion in his right 4th rib.
- He underwent L radical nephrectomy showing ccRCC followed by resection of the right rib lesion confirming metastatic disease.

His follow-up plan was surveillance, however 6 months later he developed new back pain.

- Restaging showed new findings including a destructive lesion in T4, an enlarged right subpectoral LN and lesion in the head of the pancreas.
- He completed palliative XRT to T4 and presents to discuss systemic treatment options.
- You rate his performance status to be very good; ECOG PS of 1
- Baseline labs are all WNL.

Case Study 1

Question 1

His IMDC Risk Category is:

(A) Good Risk

(B) Intermediate Risk

(C) Poor risk

(D) Cannot be determined

Case Study 1

Question 2

I/O treatment options with an overall survival (OS) benefit versus targeted agents for this patient include:

(A) IL-2

(B) Ipilimumab + nivolumab

(C) Pembrolizumab + Axitinib

(D) Avelumab + Axitinib

(E) B + C only

(F) All of these

Case Study 1

The patient was treated with Ipi + Nivo. Two weeks after the second dose, he presented to an outside ED reporting fever and all over body aches. He denied chest pain or shortness of breath.

- Pertinent labs findings included elevated troponin 7.35, also elevated transaminases AST 465 and ALT 224.
- Creatine kinase was 7969.
- EKG was normal.

He was treated emergently with solumedrol 125 mg pending admission and further cardiac evaluation.

- TTE was WNL.

Case Study 1

Question 3

In collected case series of immune checkpoint inhibitor associated myocarditis, the observed mortality rate is closest to:

(A) 2%

(B) 15%

(C) 45%

(D) 100%

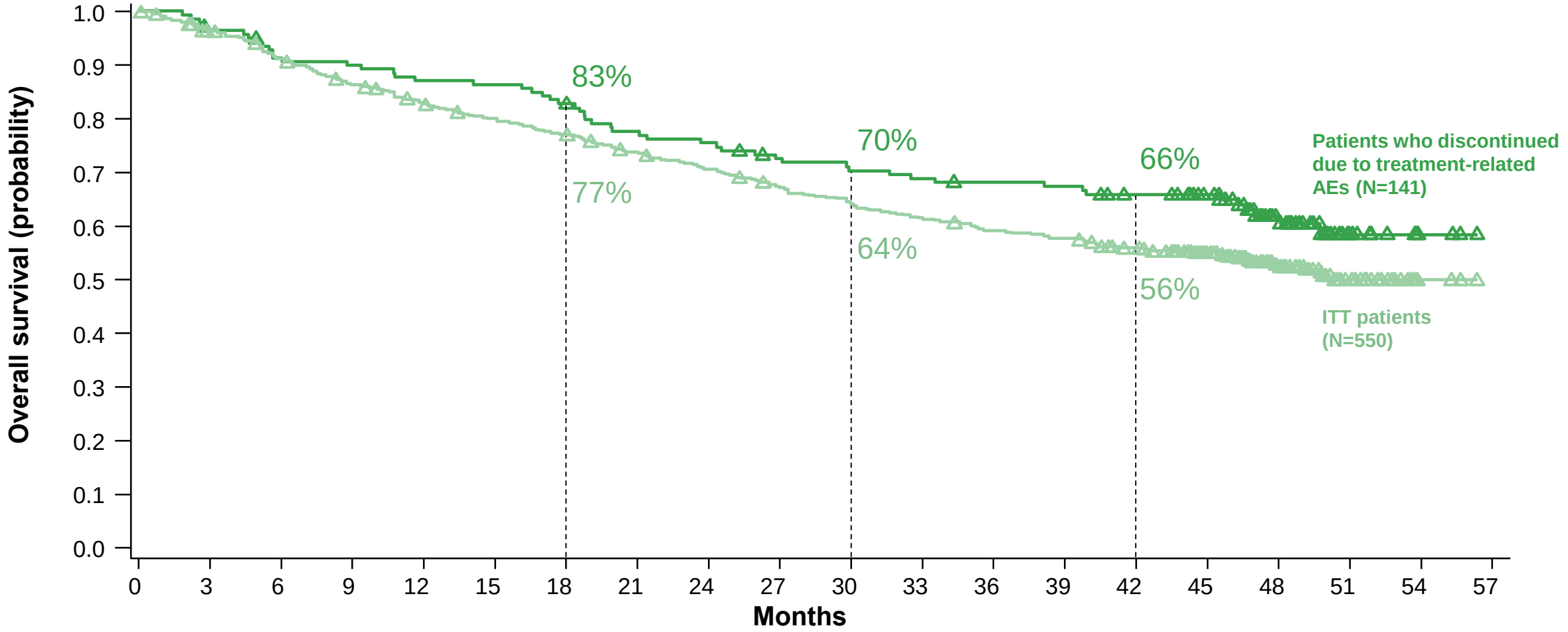
Case Study 1

The patient was counseled it was unsafe to attempt to resume immune checkpoint inhibitor treatments.

- Abnormal labs responded briskly to corticosteroids and had normalized at 2 week follow up.
- He completed a steroid taper over 6 weeks with no re-emergence of abnormal lab findings and no new symptoms.
- Restaging on completion of steroid taper showed a radiographic response. The patient was monitored with surveillance imaging without further systemic therapy.
- The patient remains a CR of his non-bony disease 10 months after discontinuation of treatment.

OS in Patients Who Discontinued Due to Treatment-Related AEs

Post hoc analyses in the NIVO+IPI arm (CheckMate 214)



Adapted from Tannir, NM et al. GU ASCO 2020.