Immunotherapy in Kidney and Bladder Cancers

Master Lecture Series: Evolving Treatments in Immunotherapy & Target Therapy

Pedro C. Barata MD MSc
Assistant Professor of Medicine
Tulane University Medical School
Genitourinary Cancers

Tulane University
SCHOOL OF MEDICINE
Tulane Cancer Center

NRG ONCOLOGY
Advancing Research. Improving Lives.™

SWOG
Leading cancer research. Together.

Disclosures

Bayer, Bristol-Myers Squibb, Eisai, Pfizer, EMD Serono, Clovis, Caris, BlueEarth Diagnostics, Astellas

(Consulting/Research)

PracticeUpdate

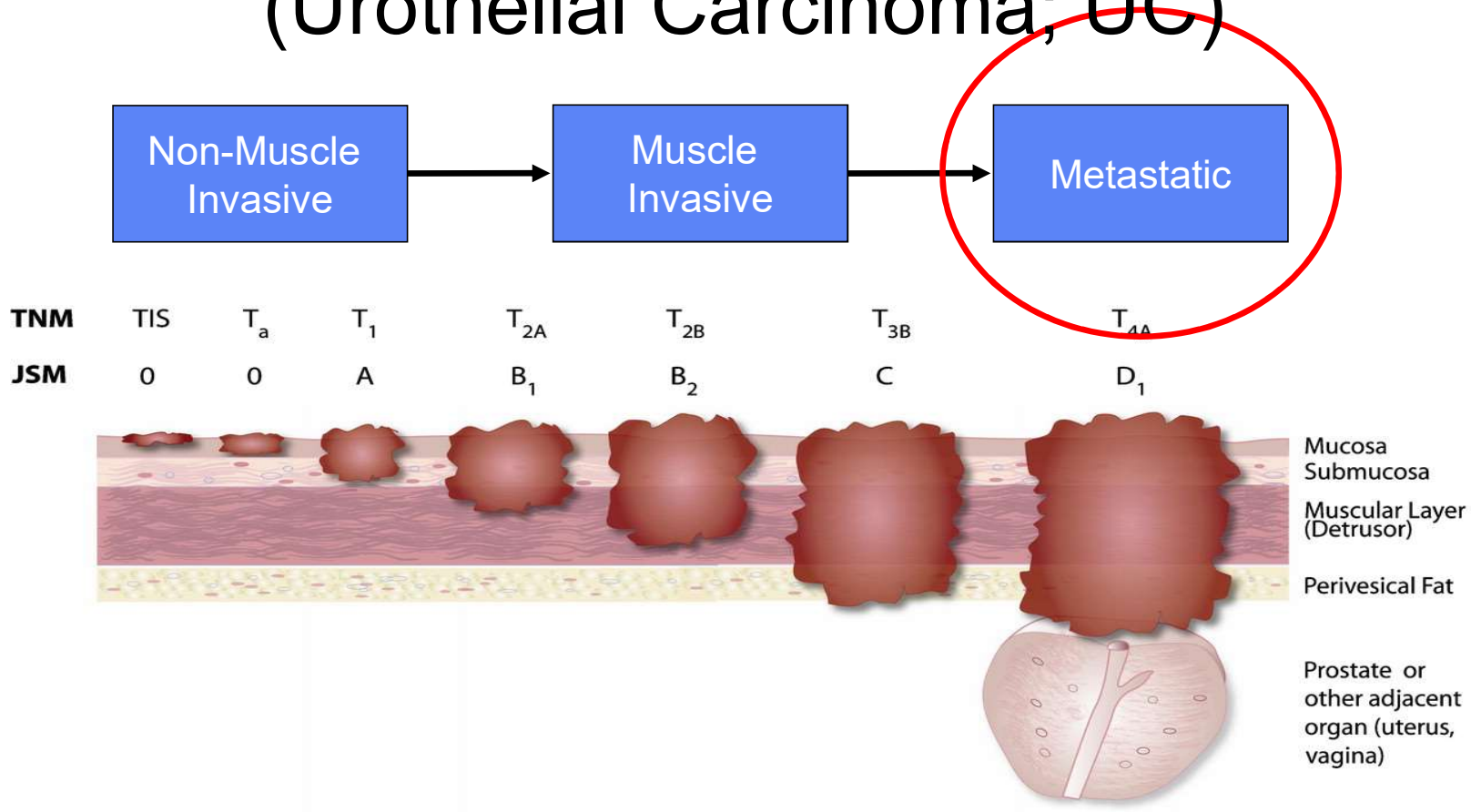
NRG and SWOG member

Tulane University

UROTHELIAL CARCINOMA

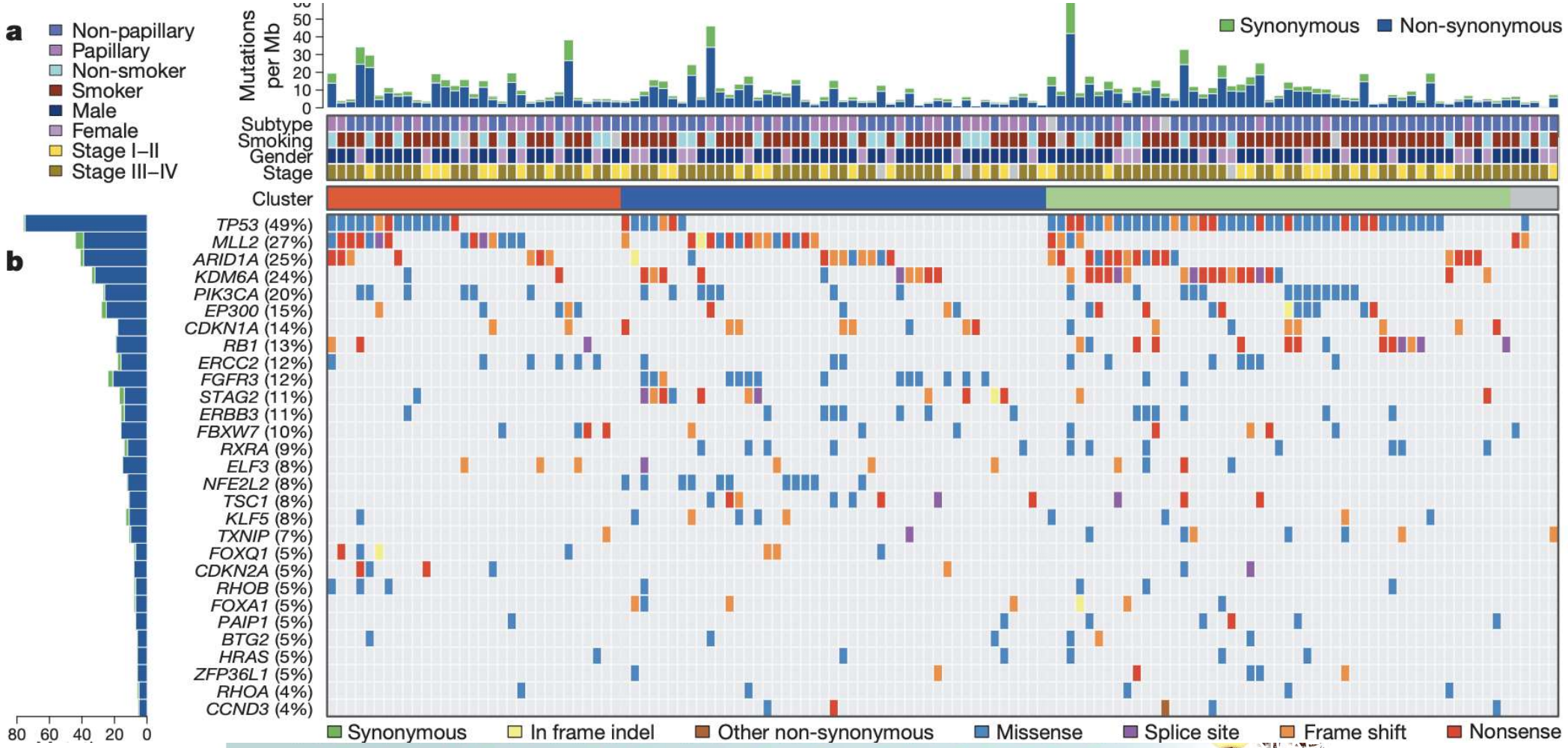
Tulane University

Immunotherapy for Metastatic Bladder Cancer (Urothelial Carcinoma; UC)



Tulane University

Tumor Cancer Genome Atlas (TCGA): Urothelial Ca



TCGA, Nature 2014

Approved checkpoint inhibitors for mUC – *cisplatin refractory*

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

Tulane University

Approved checkpoint inhibitors for mUC – *cisplatin ineligible*

Drug	Approved	Indication	Dose
Atezolizumab	2017 (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

Tulane University

BARCELONA 2019 ESMO congress

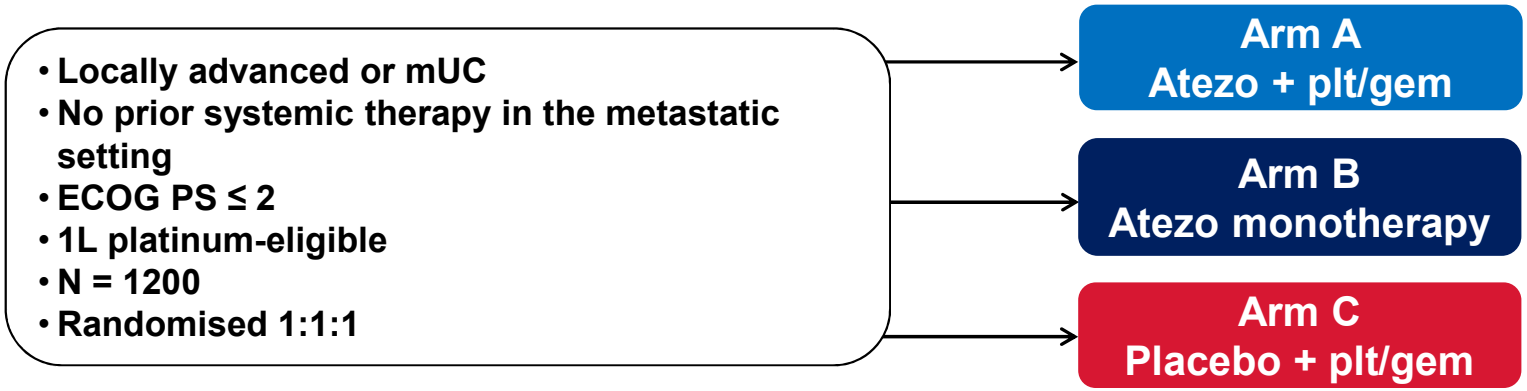
IMvigor130: a phase III study of atezolizumab with or without platinum-based chemotherapy in previously untreated metastatic urothelial carcinoma

Enrique Grande,[1] Matthew D Galsky,[2] José Ángel Arranz Arija,[3] Maria De Santis,[4] Ian D Davis,[5] Ugo De Giorgi,[6] Marina Mencinger,[7] Eiji Kikuchi,[8] Xavier García-del-Muro,[9] Mahmut Gumus,[10] Mustafa Özgüroğlu,[11] Arash Rezazadeh Kalebasty,[12] Se Hoon Park,[13] Boris Alekseev,[14] Fabio Augusto Schutz,[15] Jian-Ri Li,[16] Almut Mecke,[17] Sanjeev Mariathasan,[18] AnnChristine Thåström,[18] Aristotelis Bamias[19]

[1]MD Anderson Cancer Center Madrid, Madrid, Spain; [2]Icahn School of Medicine at Mount Sinai/Tisch Cancer Institute, New York, NY, USA; [3]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [4]Charité University Hospital, Berlin, Germany, and Department of Urology, Medical University, Vienna, Austria; [5]Eastern Health/Monash University, Melbourne, Australia; [6]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), IRCCS, Meldola, Italy; [7]Institute of Oncology Ljubljana, Ljubljana, Slovenia; [8]Keio University, Tokyo, Japan; [9]Catalan Institute of Oncology, IDIBELL, University of Barcelona, Barcelona, Spain; [10]Istanbul Medeniyet University, Goztepe Research Hospital, Istanbul, Turkey; [11]Istanbul University-Cerrahpaşa, Cerrahpasa School of Medicine, Istanbul, Turkey; [12]Norton Cancer Institute, Louisville, KY, USA; [13]Sungkyunkwan University Samsung Medical Center, Seoul, Korea; [14]P. Herzen Oncology Research Institute, Moscow, Russia; [15] Beneficência Portuguesa de São Paulo, São Paulo, Brazil; [16]Taichung Veterans General Hospital/Hungkuang University, Taichung, Taiwan; [17]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [18]Genentech, Inc., South San Francisco, CA, USA; [19]National and Kapodistrian University of Athens, Athens, Greece

Tulane University

IMvigor130 study design



Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases)
- Investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)

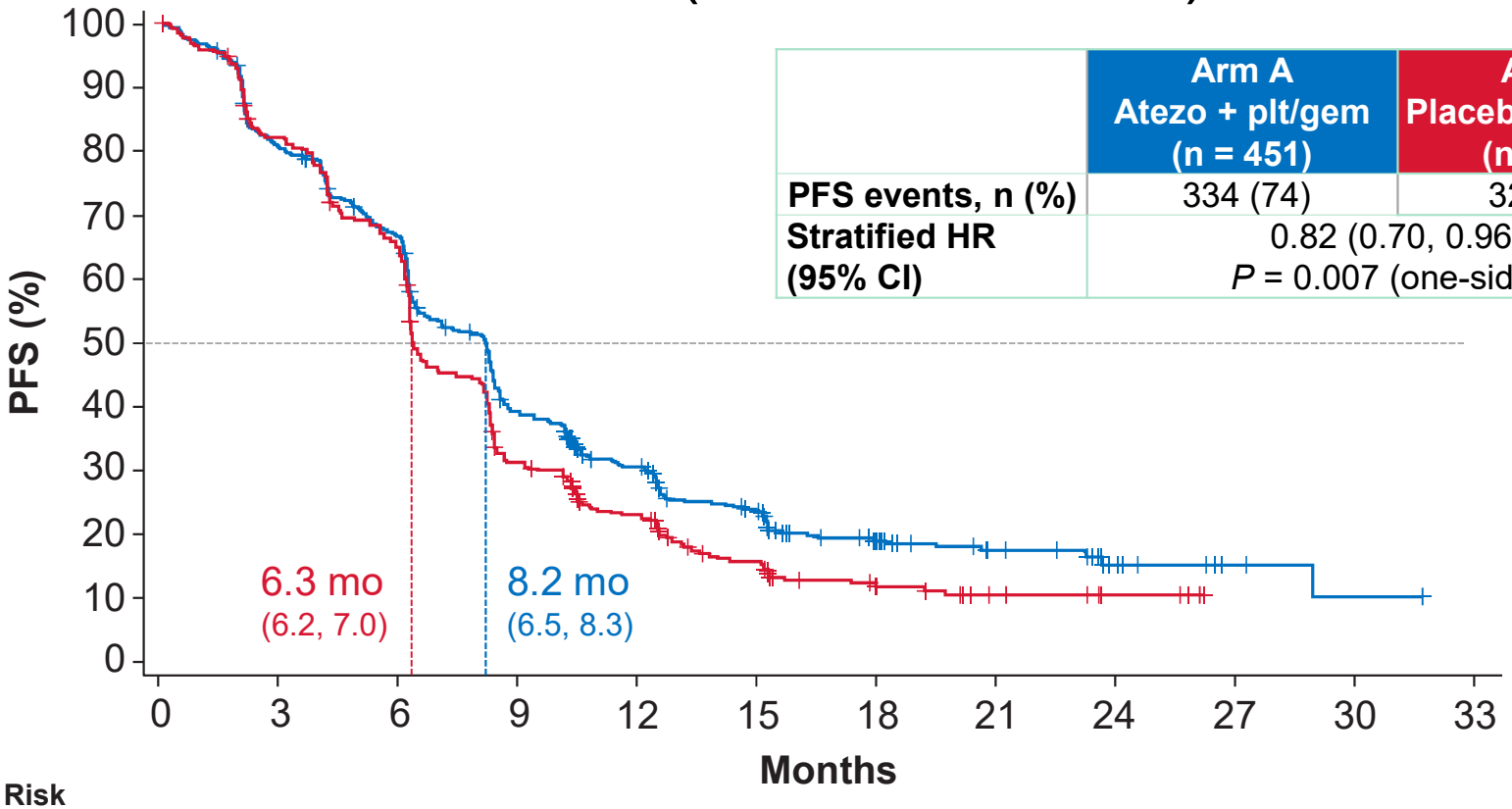
Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[a] and DOR
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

[a] per RECIST 1.1.

Tulane University

Final PFS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

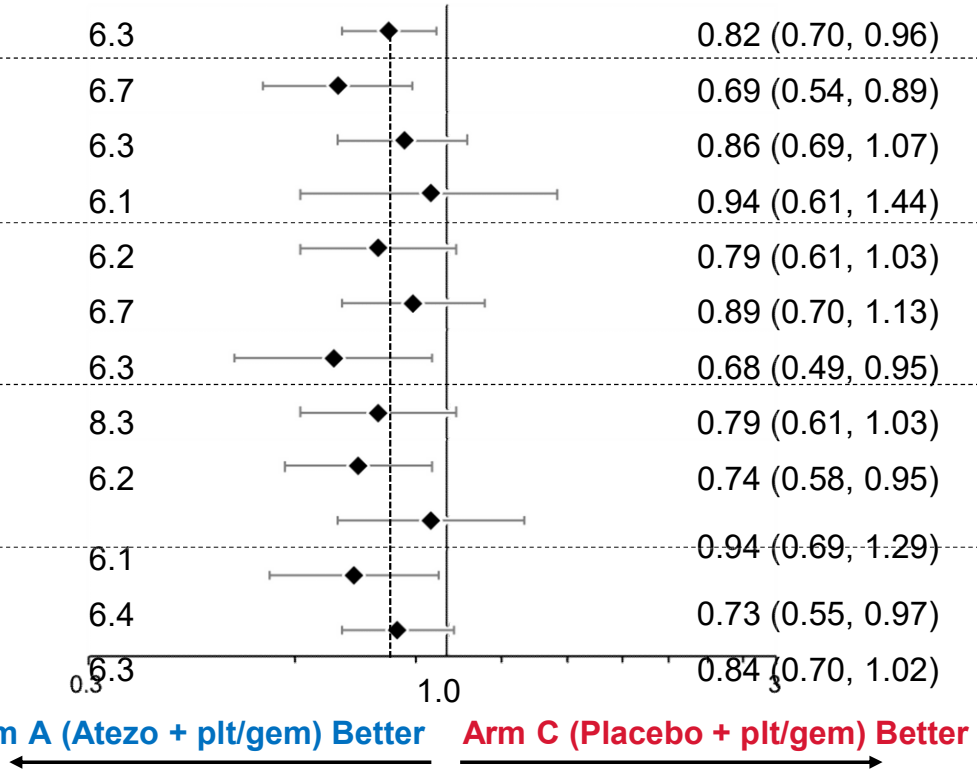
No. at Risk												
Atezo + plt/gem	451	345	282	160	111	74	42	22	10	4	2	NE
Placebo + plt/gem	400	317	246	116	73	40	18	11	4	NE	NE	NE

NE, not estimable. Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

Tulane University

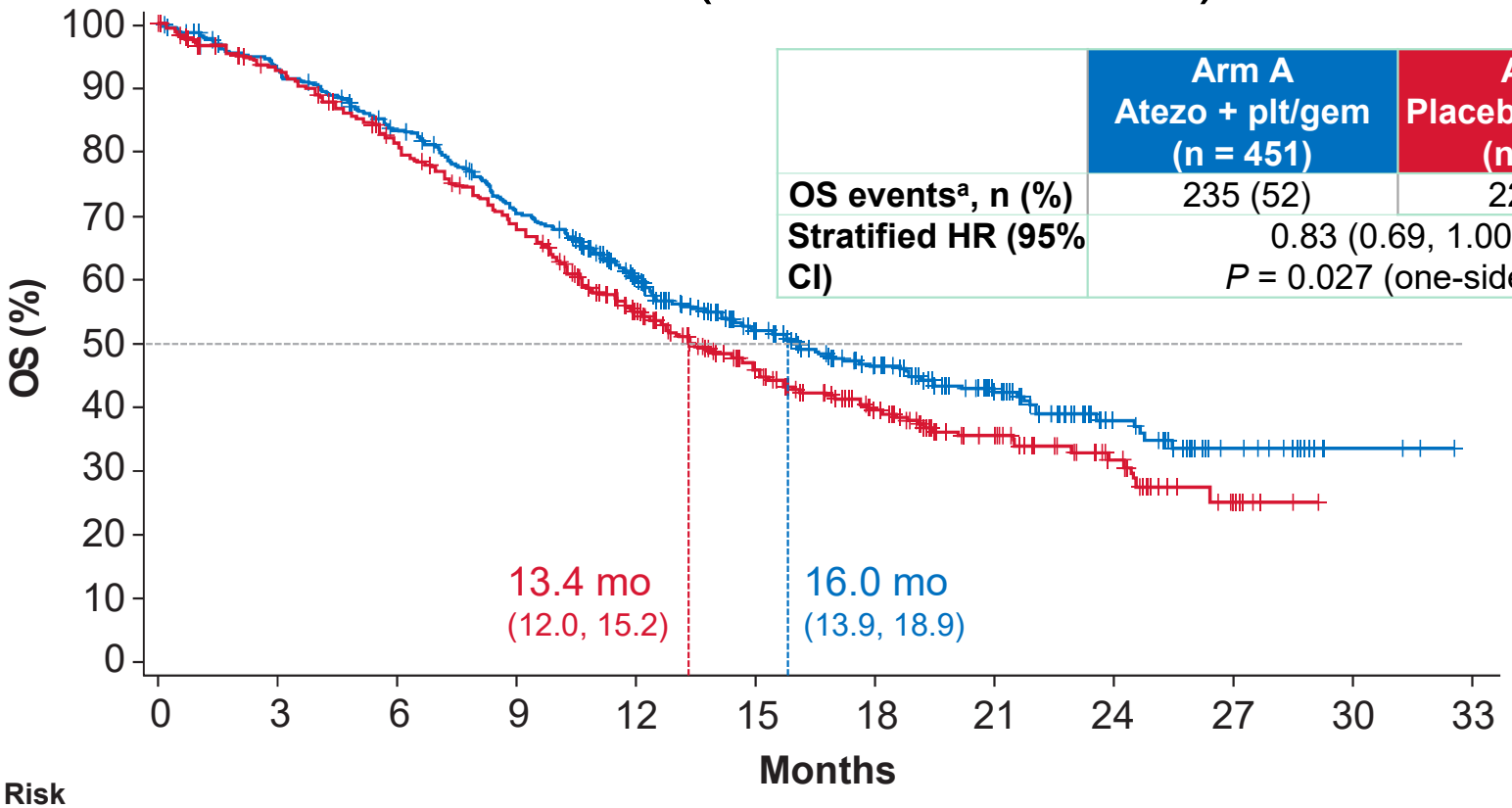
PFS subgroups: ITT (Arm A vs Arm C)

Characteristic		Patients (n)	Arm A mPFS, mo (n = 451)	Arm C mPFS, mo (n = 400)	HR (95% CI)[a]
All patients		851	8.2	6.3	0.82 (0.70, 0.96)
ECOG PS	0	355	9.4	6.7	0.69 (0.54, 0.89)
	1	396	6.8	6.3	0.86 (0.69, 1.07)
	2	100	4.8	6.1	0.94 (0.61, 1.44)
PD-L1 status	0	278	6.5	6.2	0.79 (0.61, 1.03)
	1	374	8.1	6.7	0.89 (0.70, 1.13)
	2/3	199	8.6	6.3	0.68 (0.49, 0.95)
Bajorin risk factor score	0	338	9.8	8.3	0.79 (0.61, 1.03)
	1	318	8.2	6.2	0.74 (0.58, 0.95)
	2 and/or liver mets	195	5.0	6.1	0.94 (0.69, 1.29)
Investigator choice of chemo	Cisplatin	273	8.8	6.4	0.73 (0.55, 0.97)
	Carboplatin	578	7.1	6.3	0.84 (0.70, 1.02)



[a] Unstratified HR shown for all characteristics except for 'All Patients', where stratified HR is shown.

Interim OS: ITT (Arm A vs Arm C)



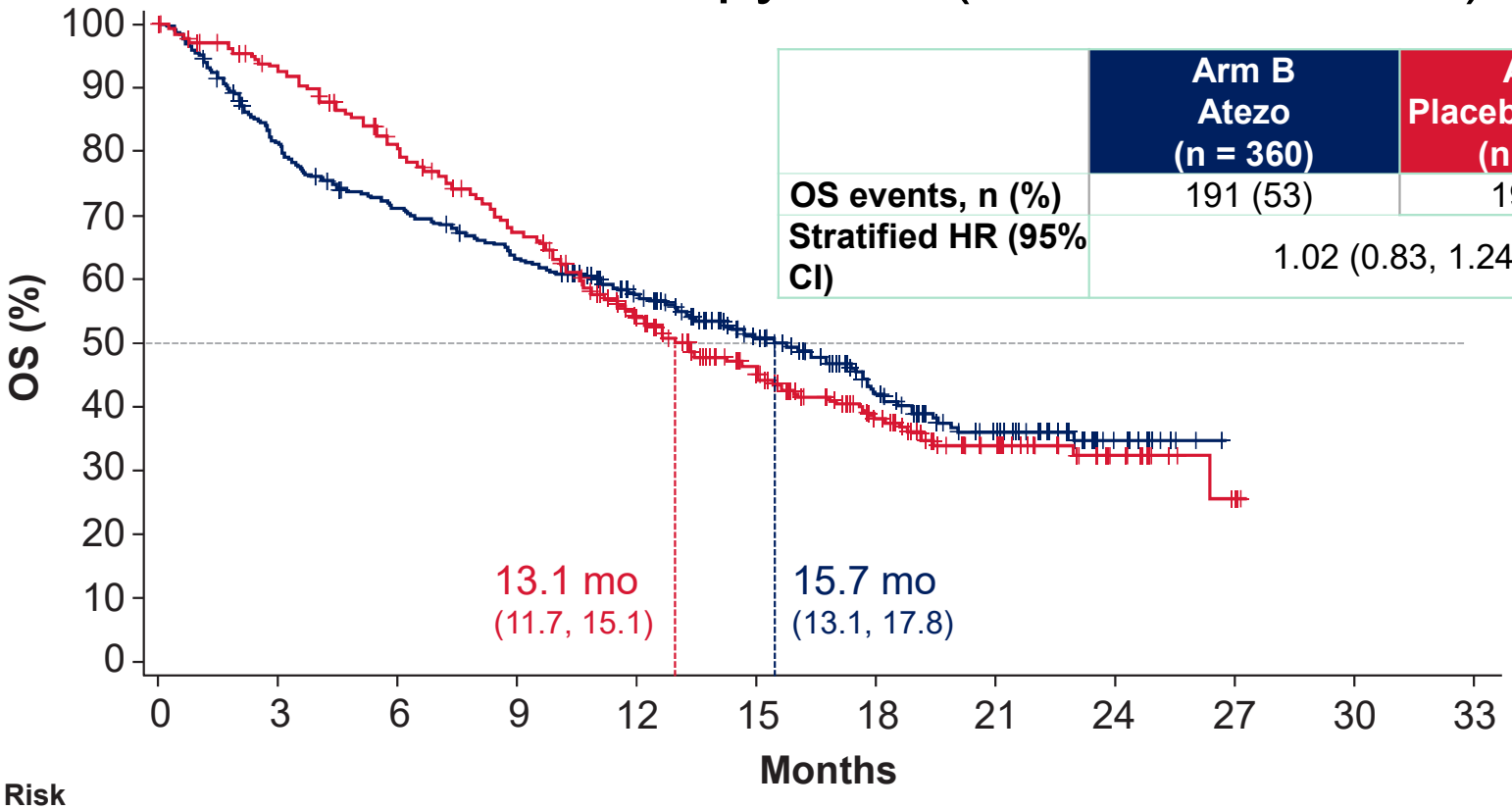
	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

No. at Risk												
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] 5% of patients from Arm A and 20% of patients from Arm C received non-protocol immunotherapy. [b] Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

Tulane University

Interim OS for Monotherapy: ITT (Arm B vs Arm C)



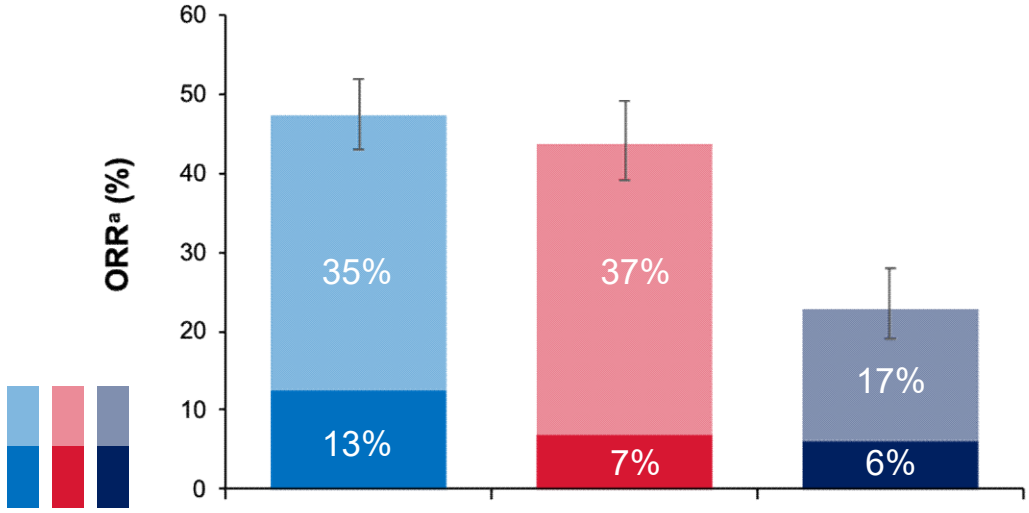
	Arm B Atezo (n = 360)	Arm C Placebo + plt/gem (n = 359)[a]
OS events, n (%)	191 (53)	198 (55)
Stratified HR (95% CI)	1.02 (0.83, 1.24)	

No. at Risk												
Atezo	360	285	245	216	173	120	72	42	16	NE	NE	NE
Placebo + plt/gem	359	322	274	224	158	103	62	35	15	3	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] Comparison only includes patients concurrently enrolled with Arm B.

Tulane University

Confirmed ORR and DOR



	Atezo + plt/gem	Placebo + plt/gem	Atezo
DOR[b], median (95% CI), mo	8.5 (7.2,10.4)	7.6 (6.3, 8.5)	NE (15.9, NE)

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

[a] Objective response–evaluable patients: n = 447 in atezo + plt/gem, n = 397 in placebo + plt/gem, n = 359 in atezo.

[b] n = 212 in atezo + plt/gem, n = 174 in placebo + plt/gem, n = 82 in atezo.

Tulane University

Safety summary

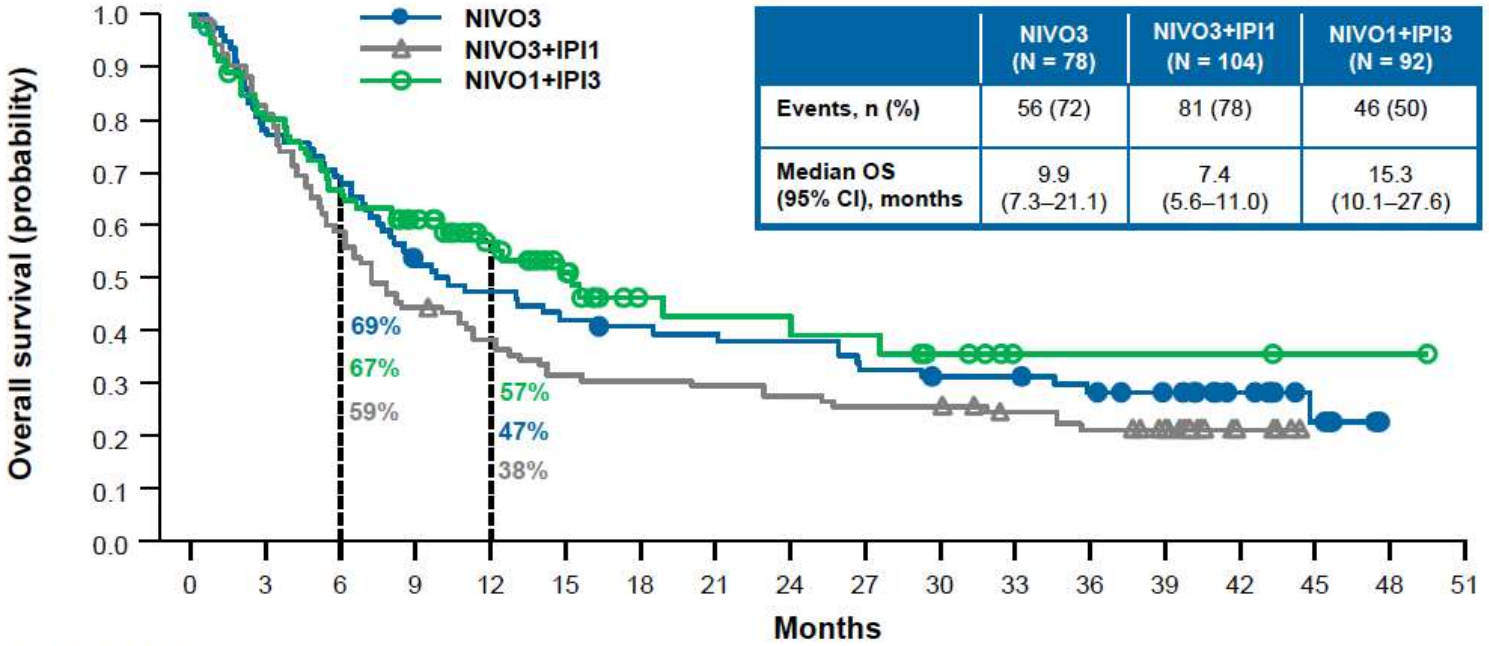
AE, n (%)	Atezo + plt/gem (n = 453)	Placebo + plt/gem (n = 390)	Atezo (n = 354)
Any grade, all cause	451 (100)	386 (99)	329 (93)
Grade 3-4	383 (85)	334 (86)	148 (42)
Grade 5	29 (6)	20 (5)	28 (8)
Any grade, treatment related	434 (96)	373 (96)	211 (60)
Grade 3-4	367 (81)	315 (81)	54 (15)
Grade 5	9 (2)	4 (1)	3 (1)
Any grade, serious	234 (52)	191 (49)	152 (43)
Treatment-related serious AEs	144 (32)	101 (26)	44 (12)
Any grade leading to any treatment discontinuation	156 (34)	132 (34)	22 (6)
Atezo or placebo discontinuation	50 (11)	27 (7)	21 (6)
Cisplatin discontinuation	53 (12)	52 (13)	0
Carboplatin discontinuation	90 (20)	79 (20)	1 (< 1)[a]
Gemcitabine discontinuation	117 (26)	100 (26)	1 (< 1)[a]
Any grade leading to any dose reduction or interruption	363 (80)	304 (78)	112 (32)

AE, adverse event. Safety-evaluable population.

Data cutoff, 31 May 2019; median survival follow-up 11.8 months (all patients).

[a] This patient was randomised to atezo + plt/gem and received atezo; they had an AE of pyrexia that day, and gemcitabine and carboplatin were marked as ‘drug withdrawn’. Since no chemotherapy was given, this patient was included in the atezo monotherapy arm for safety analysis.

In development: Ipilimumab + Nivolumab CheckMate 032

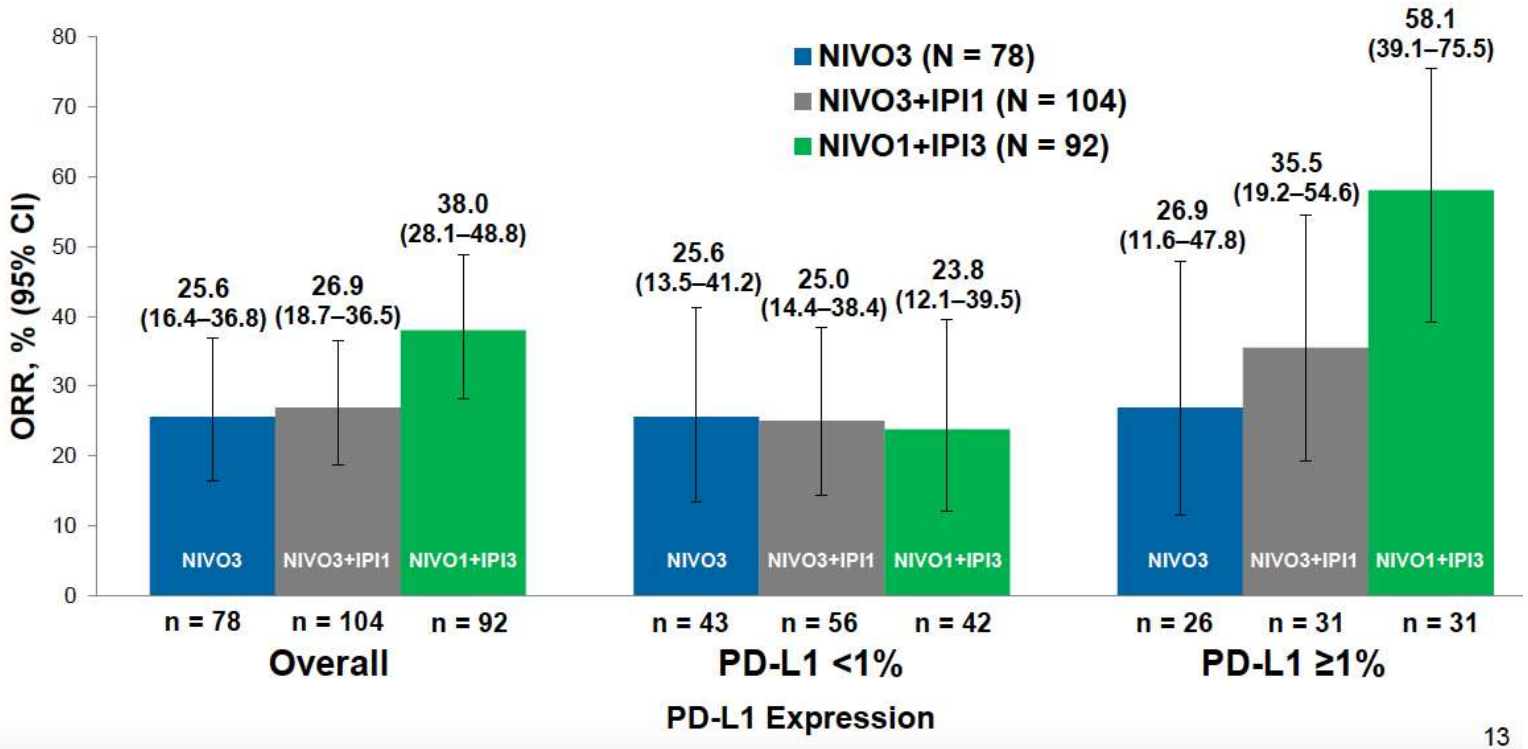


	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Events, n (%)	56 (72)	81 (78)	46 (50)
Median OS (95% CI), months	9.9 (7.3–21.1)	7.4 (5.6–11.0)	15.3 (10.1–27.6)

Tulane University

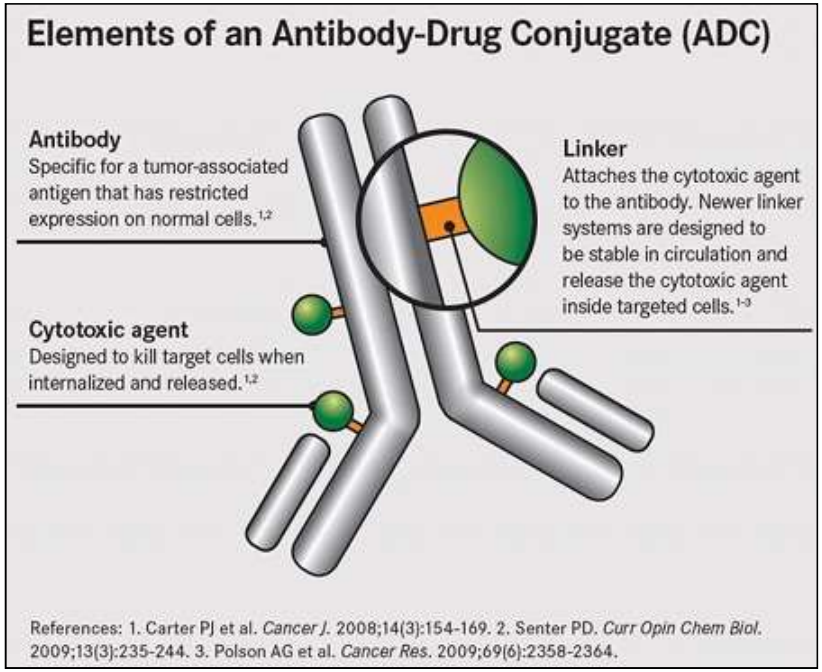
In development: Ipilimumab + Nivolumab CheckMate 032

ORR by Baseline Tumor PD-L1 Expression per Investigator



Tulane University

Key Elements of an ADC



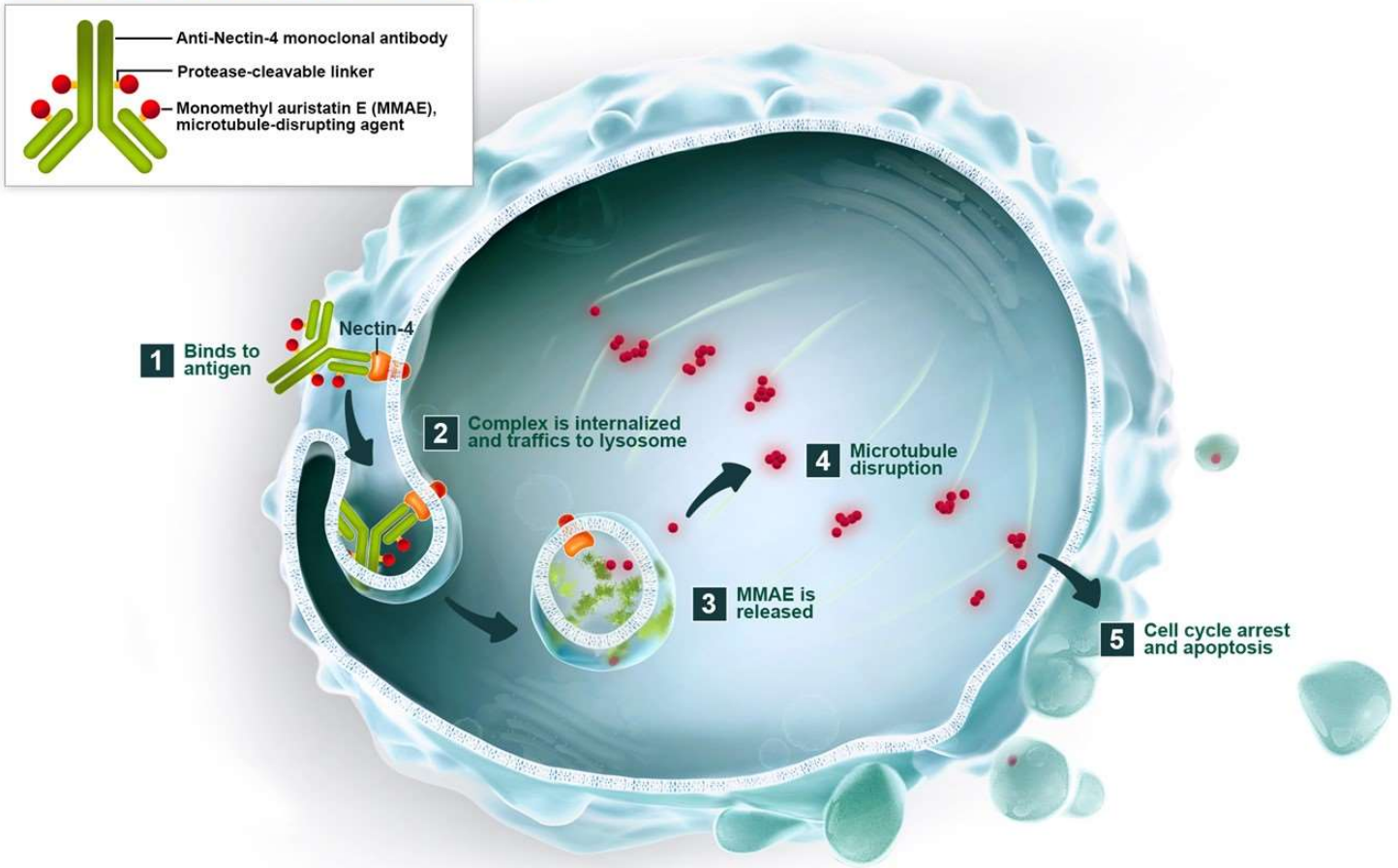
Carter PJ, Cancer Journal 2008;
Senter PD, Cur Opinion Chemo Biol 2009

ADC binds to a specific antigen on the surface of cancer cells, is internalized by endocytosis and the cytotoxic payload is released after lysosomal degradation

Tulane University

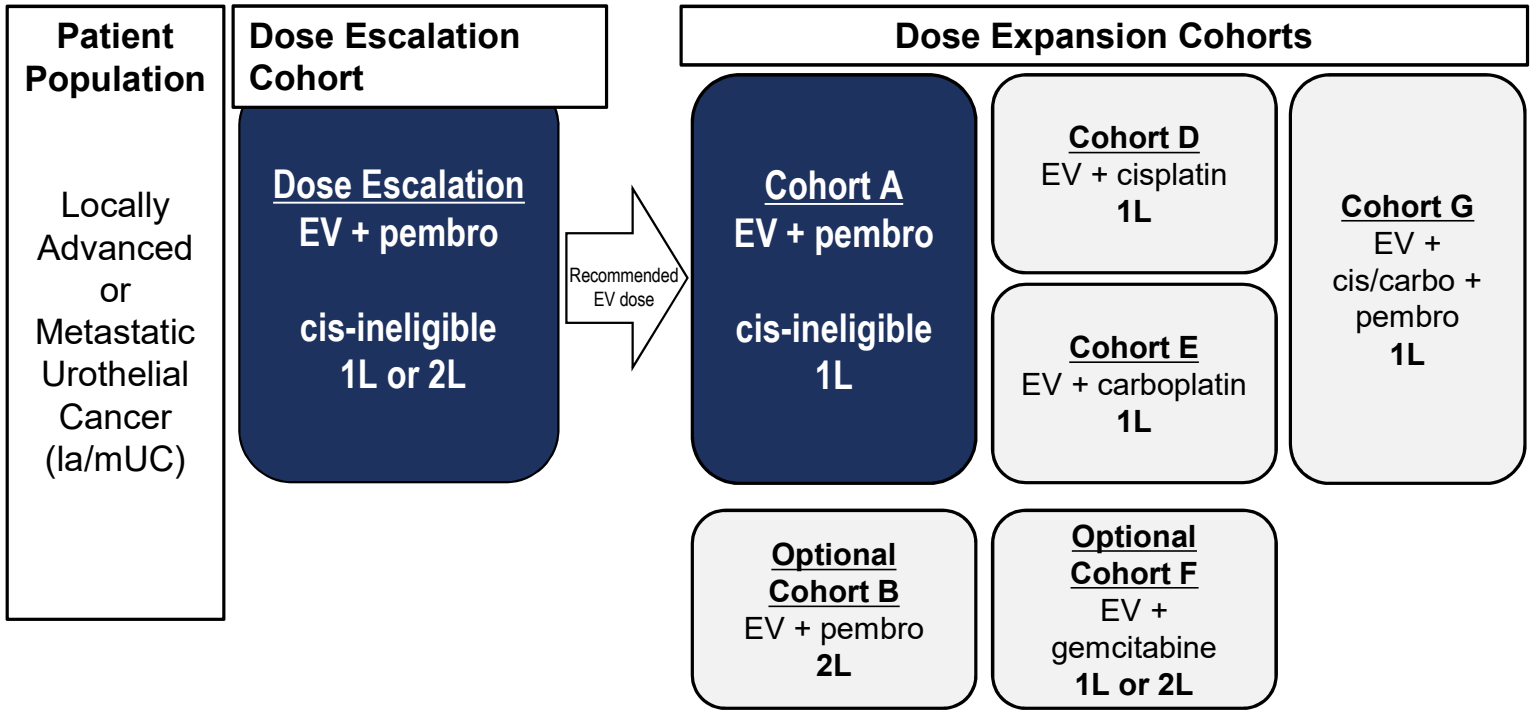
Enfortumab Vedotin: Nectin-4 Targeted Therapy

Proposed Mechanism of Action



Enfortumab vedotin (ASG-22ME) is an investigational agent, and its safety and efficacy have not been established.
Enfortumab vedotin is being developed in collaboration with Astellas Pharma Inc.

Study Design



Hoimes C, S ESMO 2019

Tulane University

ORR per RECIST v1.1 by investigator 18 Jun 2019 data cut-off	Patients (N=45) n (%)
Confirmed Objective Response Rate (ORR) 95% confidence interval	32 (71) (55.7, 83.6)
Best Overall Response per RECIST v. 1.1	
Complete response	6 (13)
Partial response	26 (58)
Stable disease	10 (22)
Progressive disease	1 (2)
Not evaluable[1]	2 (4)

Hoimes C, S ESMO 2019

Tulane University

Take-home points (I)

- There are 5 different PD1/PD-L1 Inhibitors approved for mUC
- IMvigor130 is the first immune checkpoint inhibitor study to demonstrate an improvement in PFS over standard of care in 1L mUC
- Erdafitinib (recently approved) in combination with pembrolizumab has demonstrated very promising promising results

- Many unanswered questions…

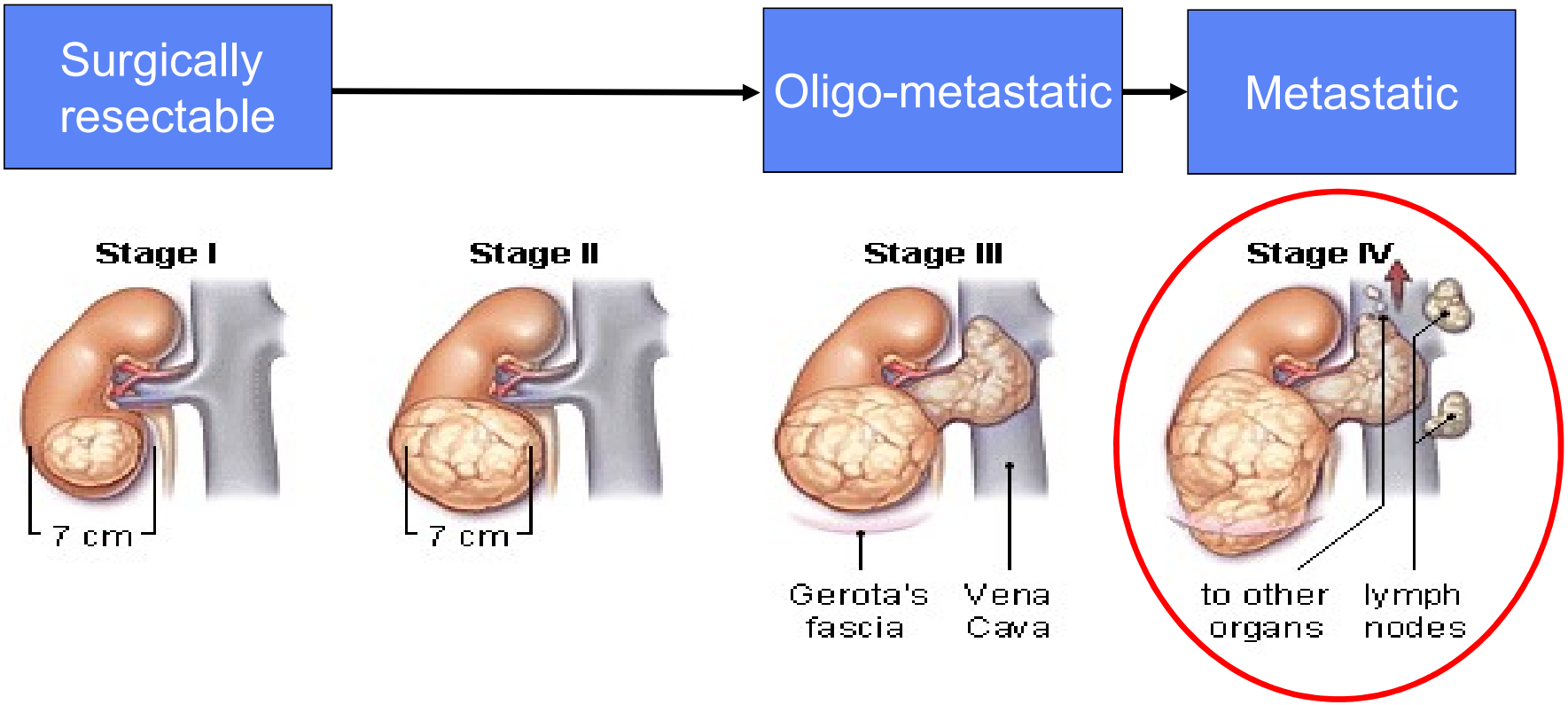
1 – Optimal treatment sequence (Pre/post checkpoint inhibitors? Combination? monotherapy?)
2 – Mechanisms of Resistance

Tulane University

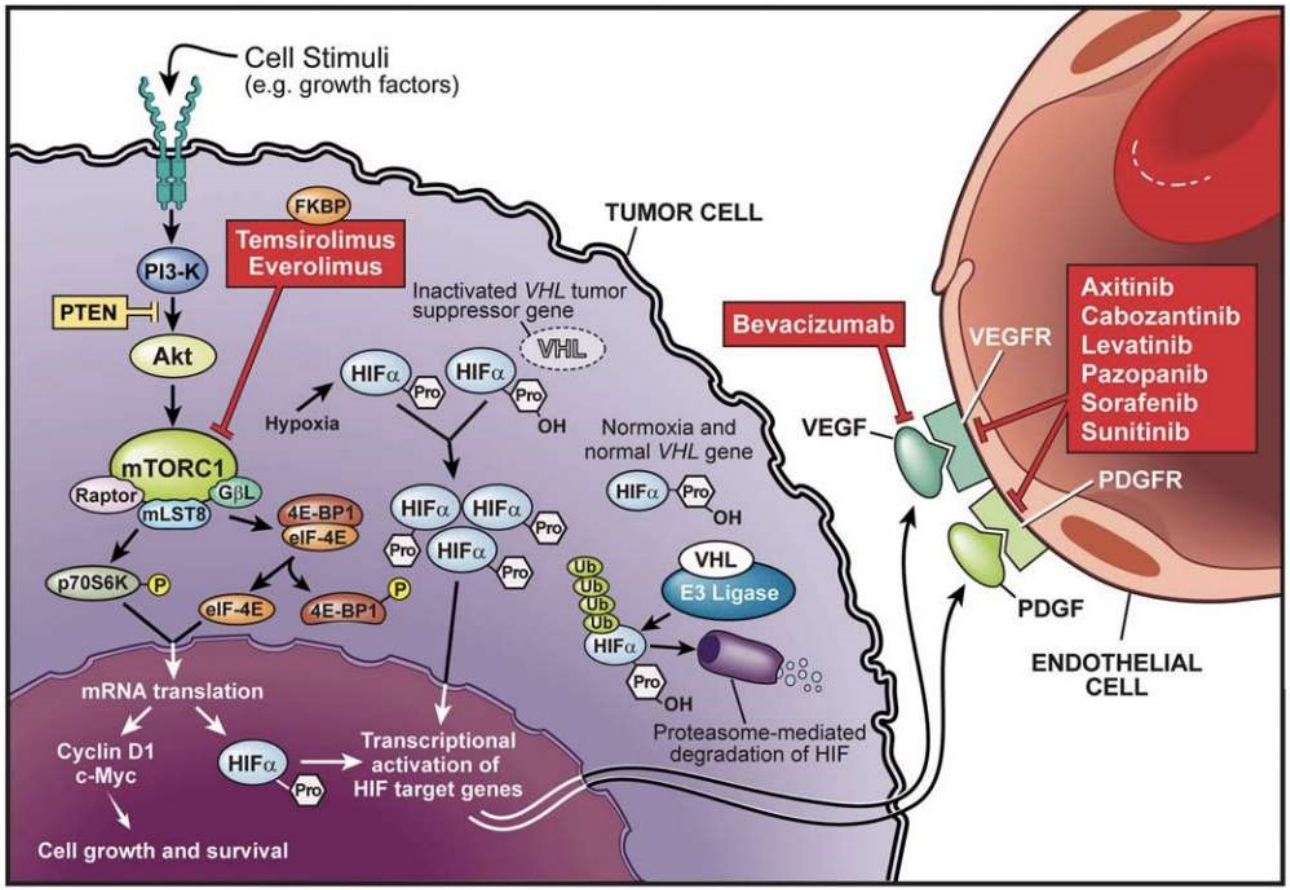
RENAL CELL CARCINOMA

Tulane University

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



Kidney Cancer – Treatment Options

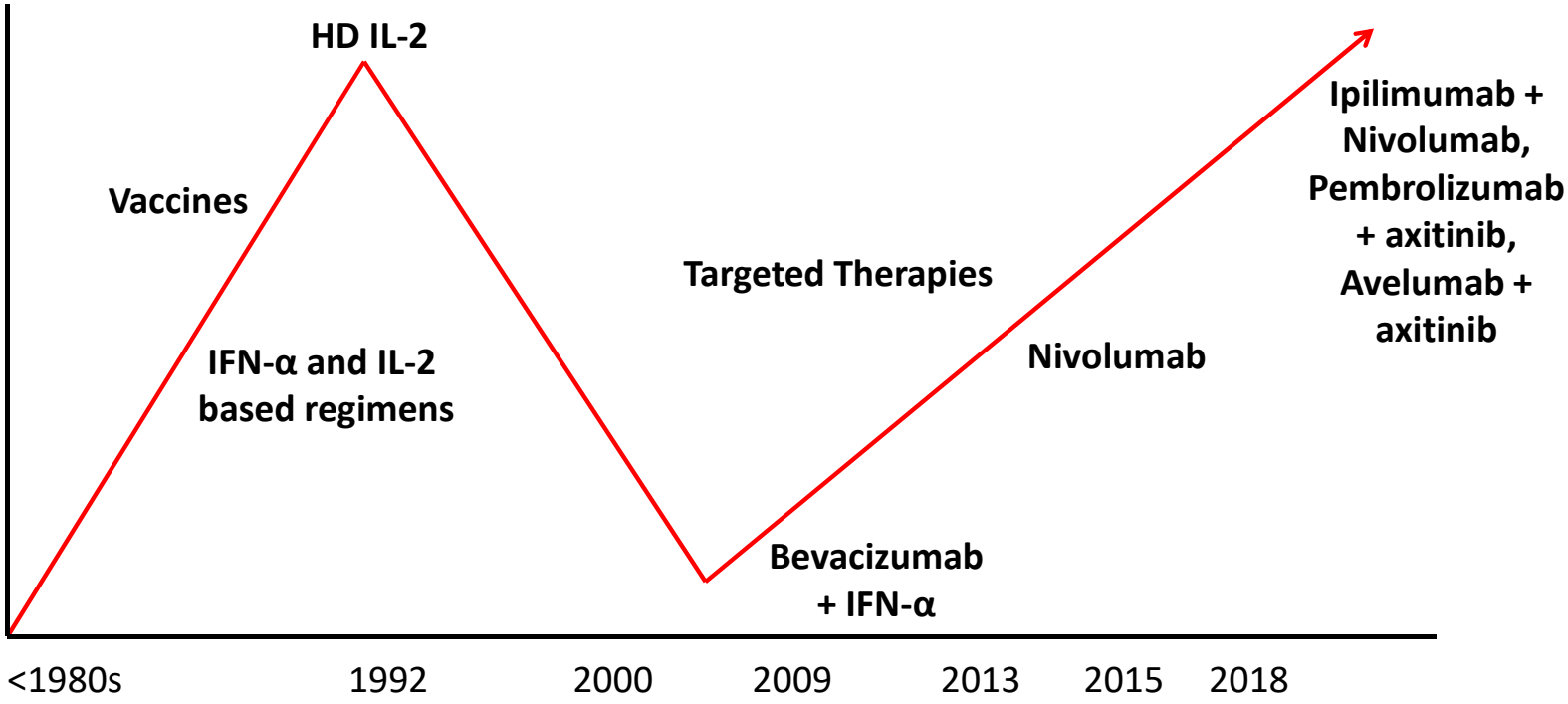


- Targeted Therapies
- Anti-VEGFR
- mTOR inhibitors

Barata et al, Ca J Clinicians 2017

Tulane University

History of Immunotherapy in mRCC



Resurgence of interest in immunotherapy

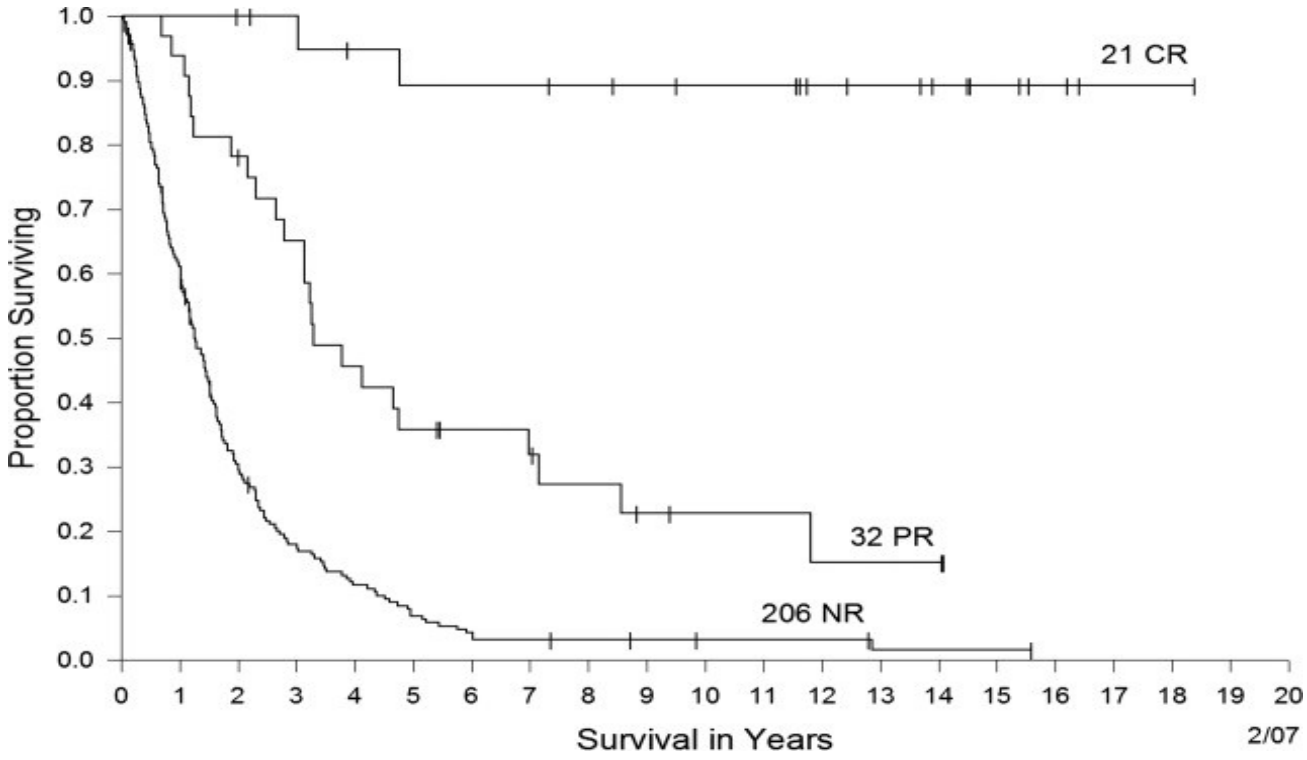
Tulane University

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

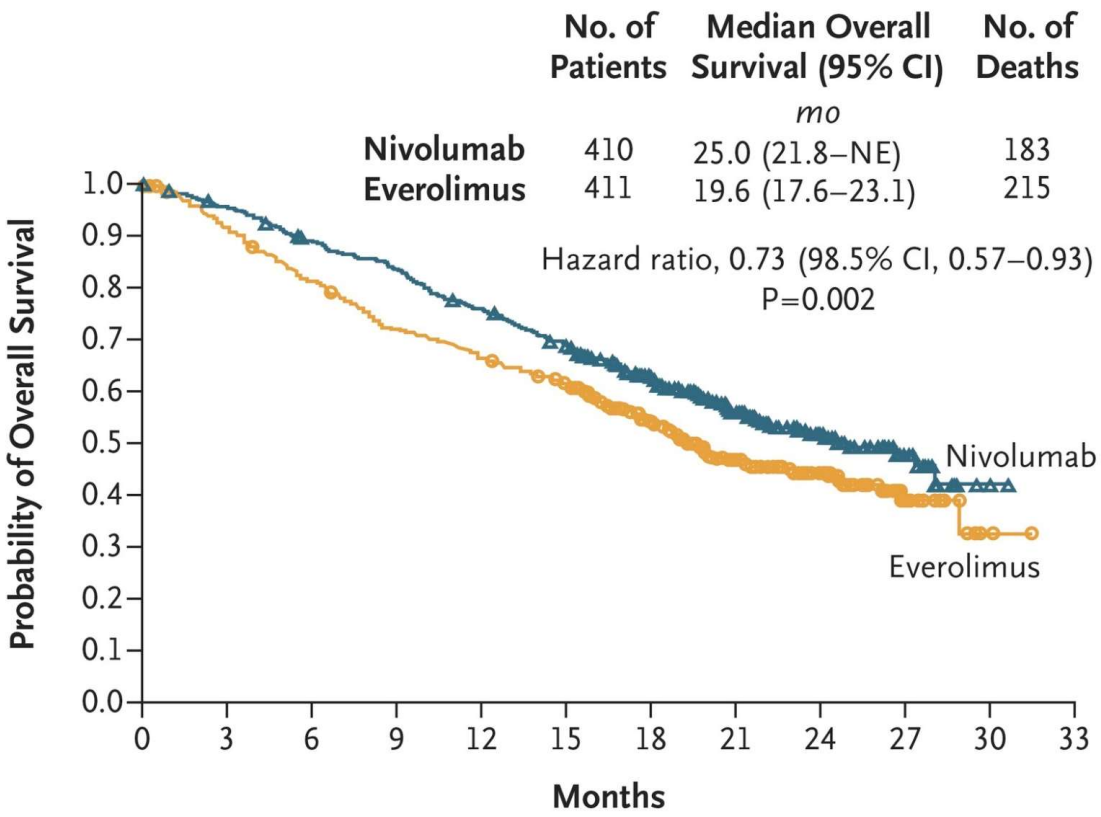


Klapper et al. Cancer 2008

Tulane University

Second-Line Nivolumab in mRCC

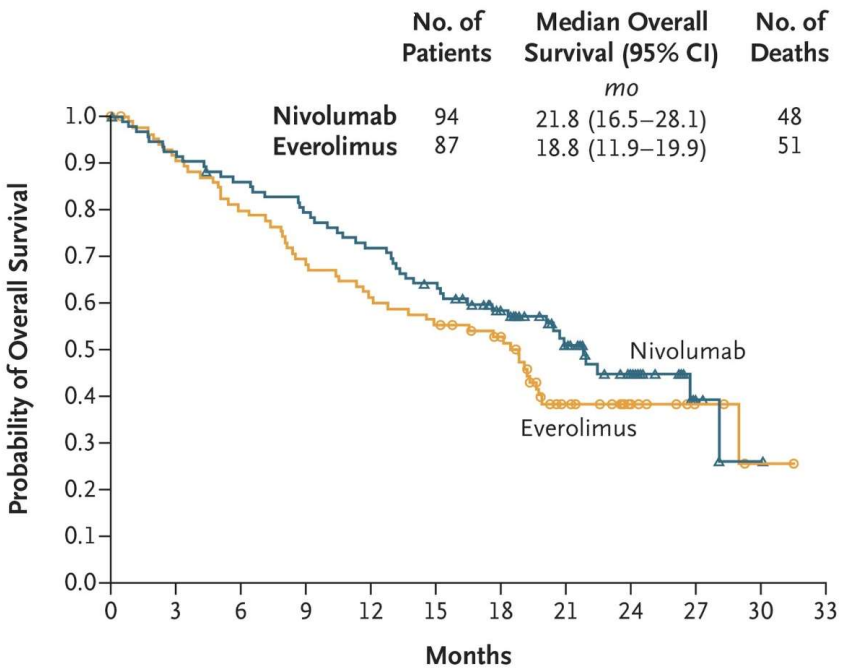
- CheckMate 025 Phase III trial
- Metastatic, clear-cell disease
- One or two previous antiangiogenic treatments
- Nivolumab (3 mg/kg IV Q2W) vs everolimus (10 mg daily)

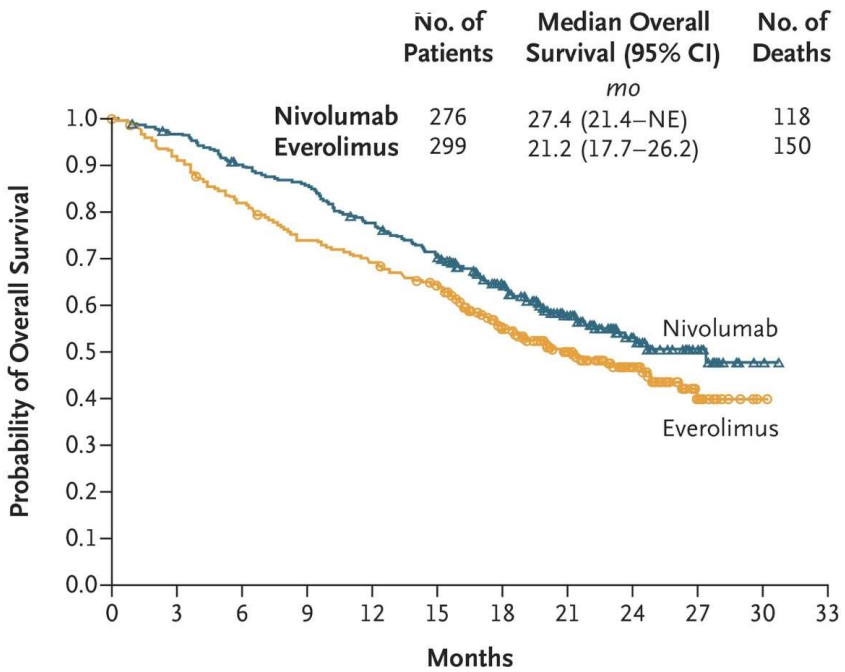


Motzer et al. NEJM 2015

Tulane University

Second-Line Nivolumab in mRCC
PD-L1 subgroups

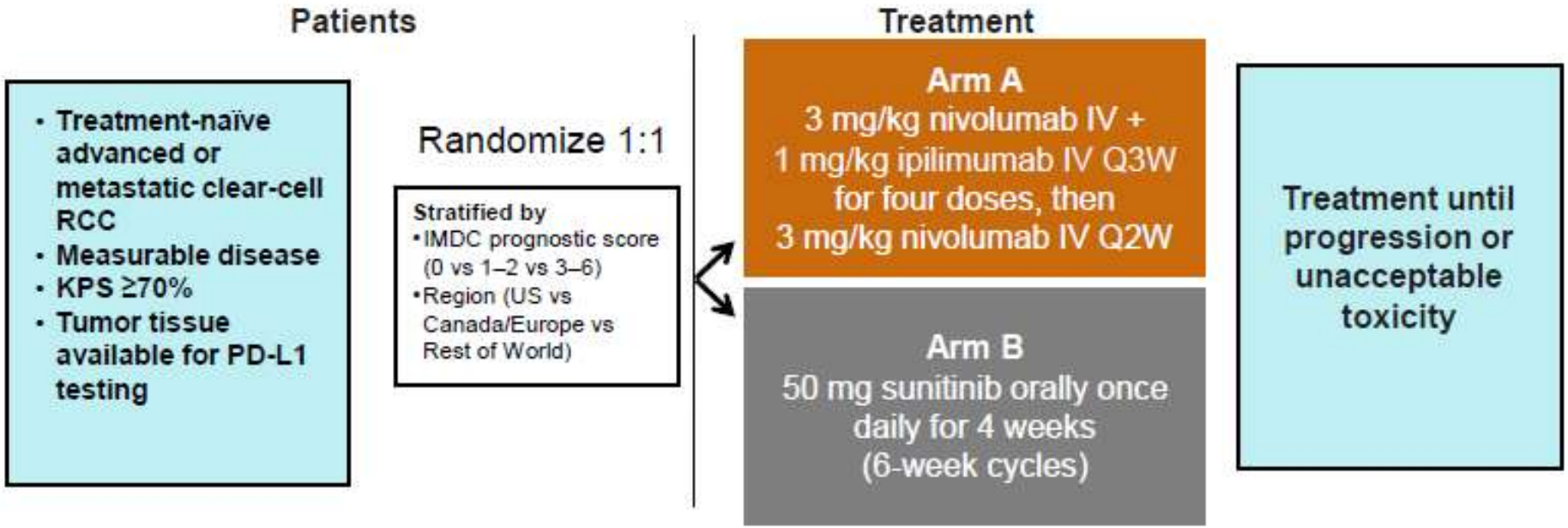




Motzer et al. NEJM 2015

Tulane University

First-line Nivolumab + Ipilimumab in mRCC

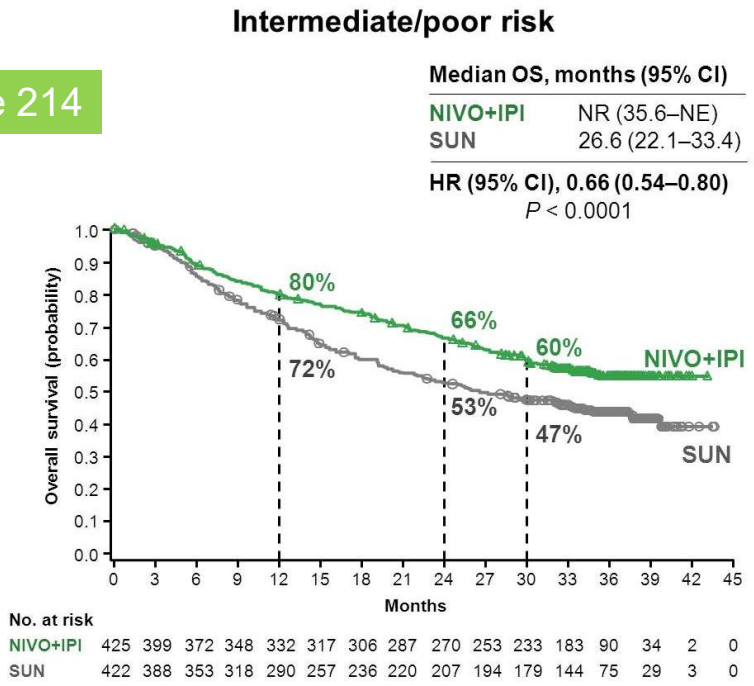


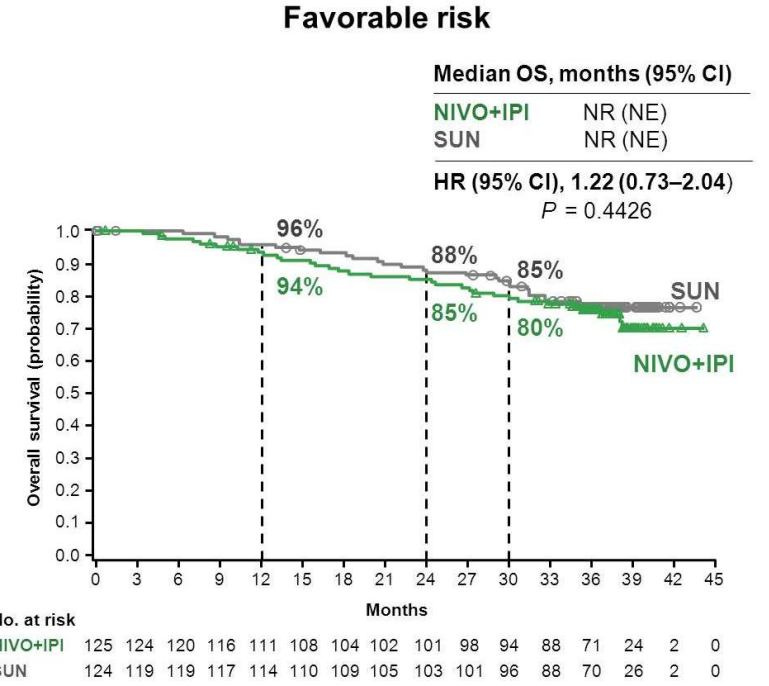
Escudier et al. ESMO 2017

Tulane University

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

CheckMate 214

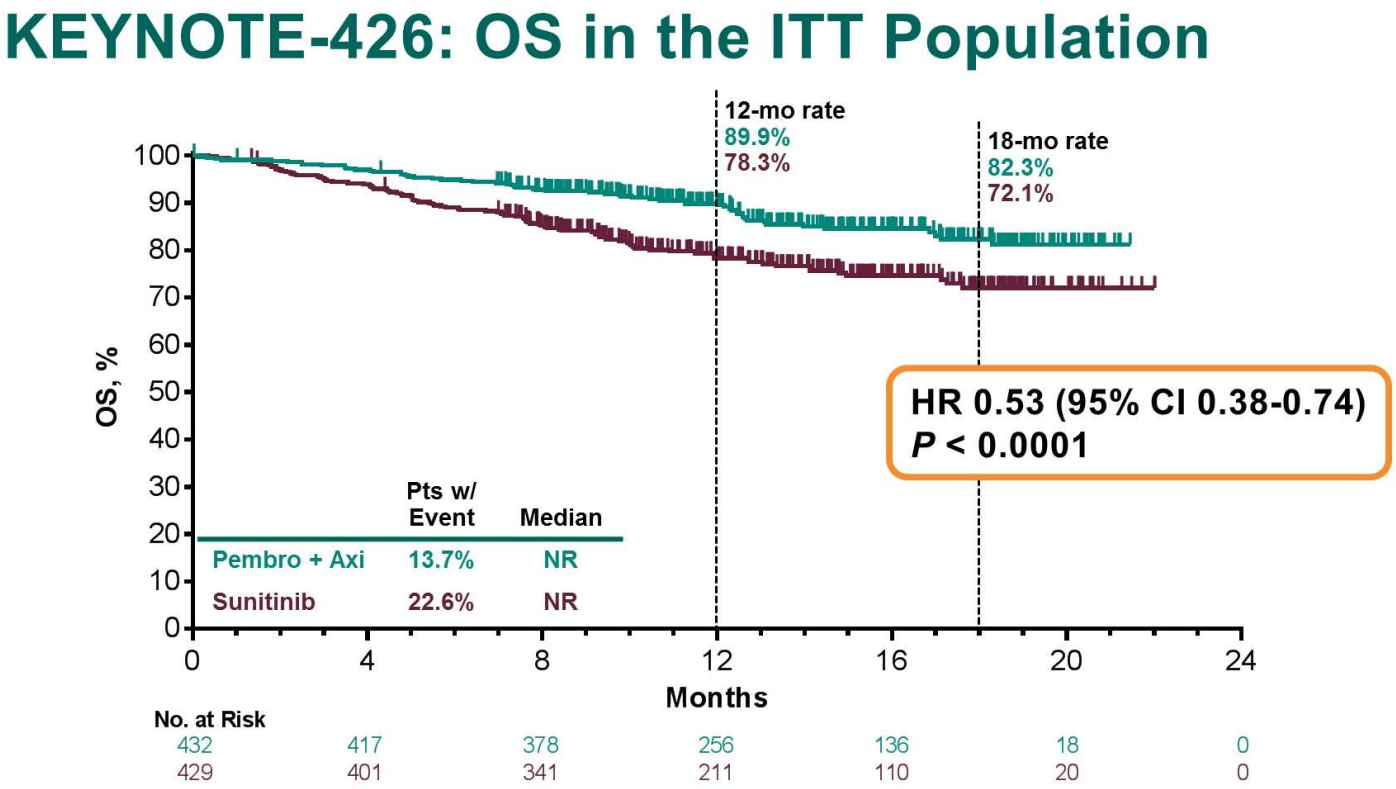




Tannir et al. ASCO GU 2019

Tulane University

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



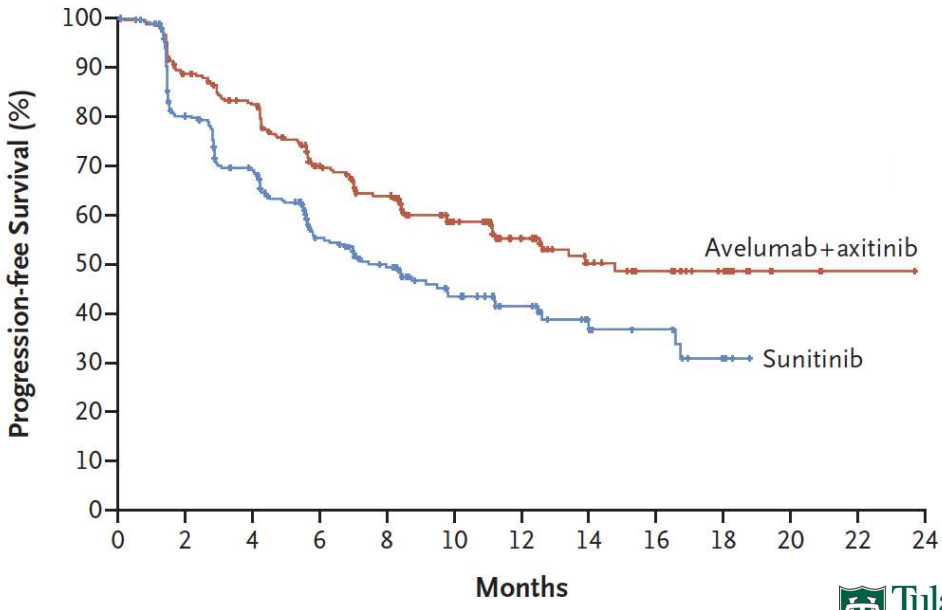
Rini, ASCO 2019

Tulane University

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

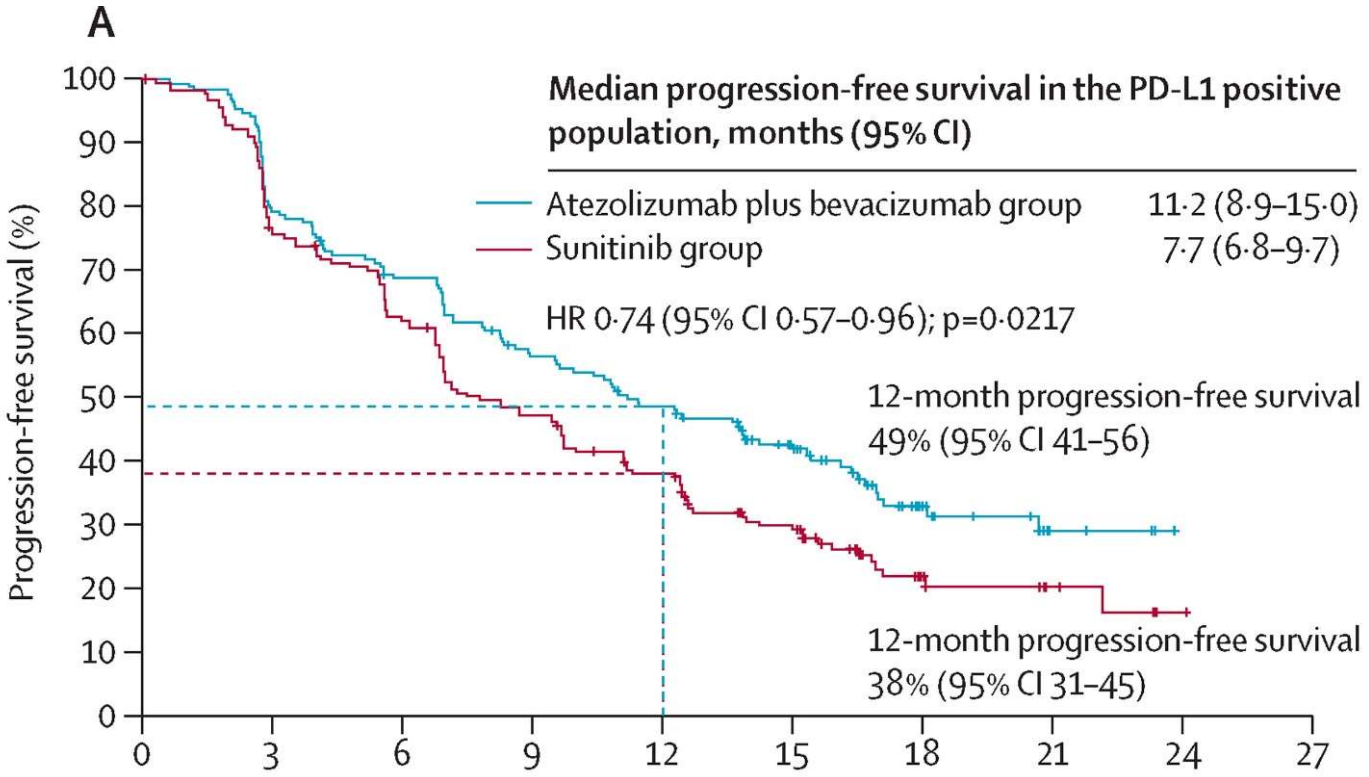


Motzer, NEJM 2019.

Tulane University

First-line atezolizumab + bevacizumab in PD-L1+ mRCC

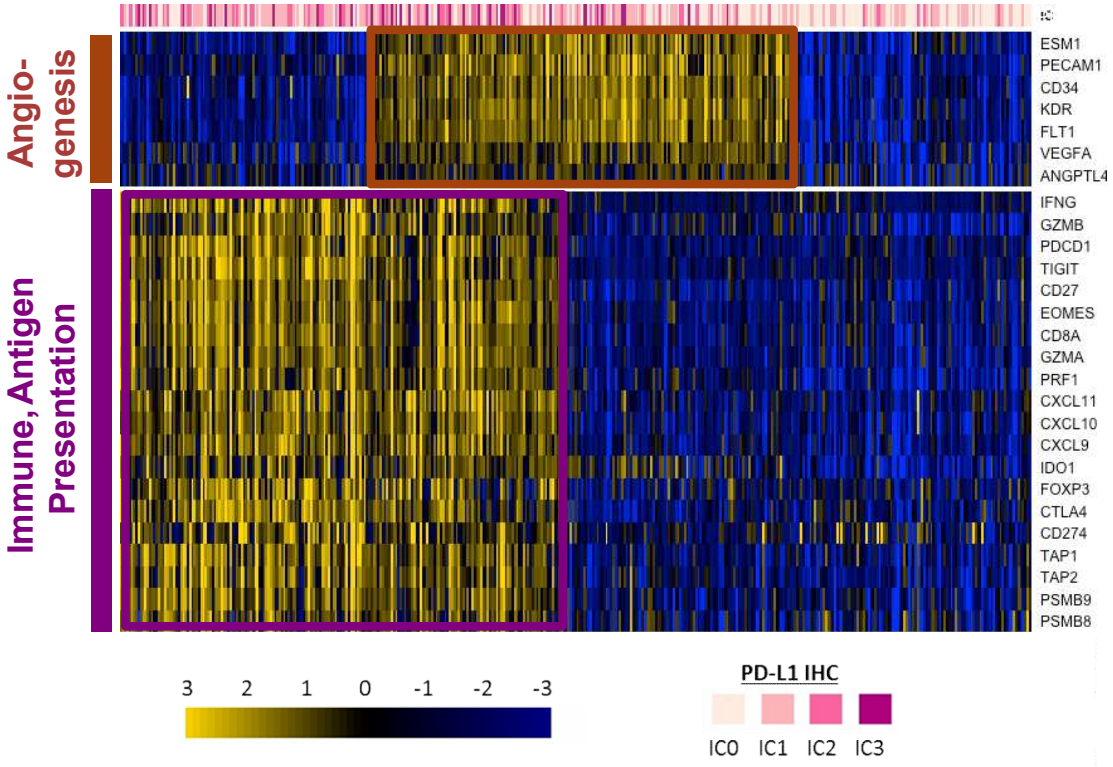
Immotion151



Rini, The Lancet 2019.

Tulane University

First-line atezolizumab + bevacizumab: molecular signatures



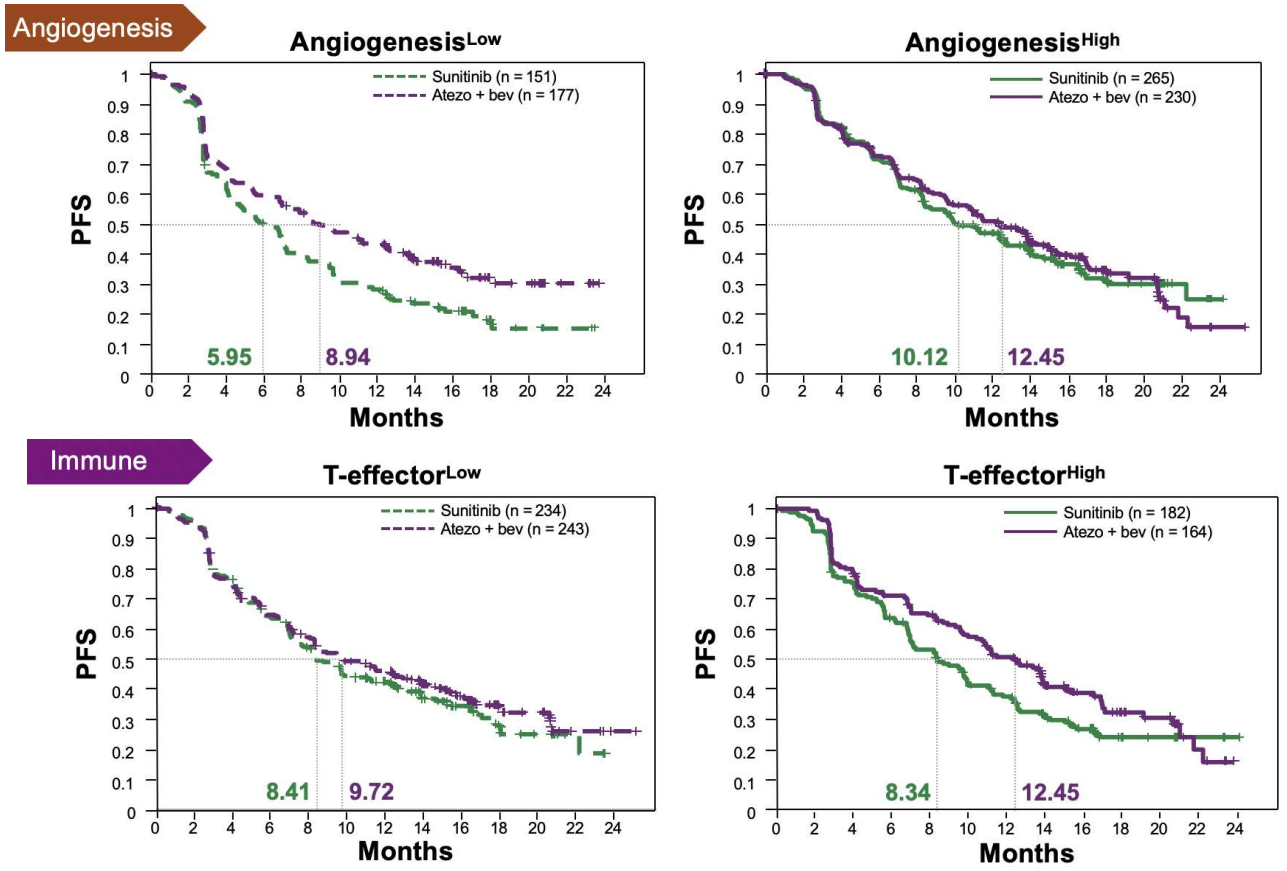
Identification of gene signatures based on association with clinical outcome

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

Rini et al, ESMO 2018

Tulane University

First-line atezolizumab + bevacizumab: molecular signatures



Rini et al, ESMO 2018

Tulane University

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

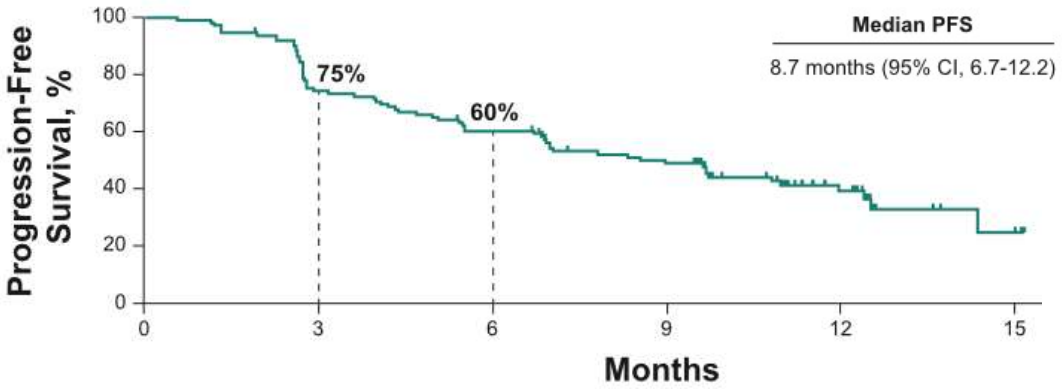
Tannir, ASCO GU 2019.
Rini, NEJM 2019.
Motzer, NEJM 2019.
Rini, Lancet 2019.

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	600	ORR, OS
NCT03937219	COSMIC-313	Cabozantinib + Ipilimumab + Nivolumab	Sunitinib	676	PFS

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

First-line pembrolizumab monotherapy in mRCC - KEYNOTE – 427 (cohort A, B) Cohort A



	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

Tulane University

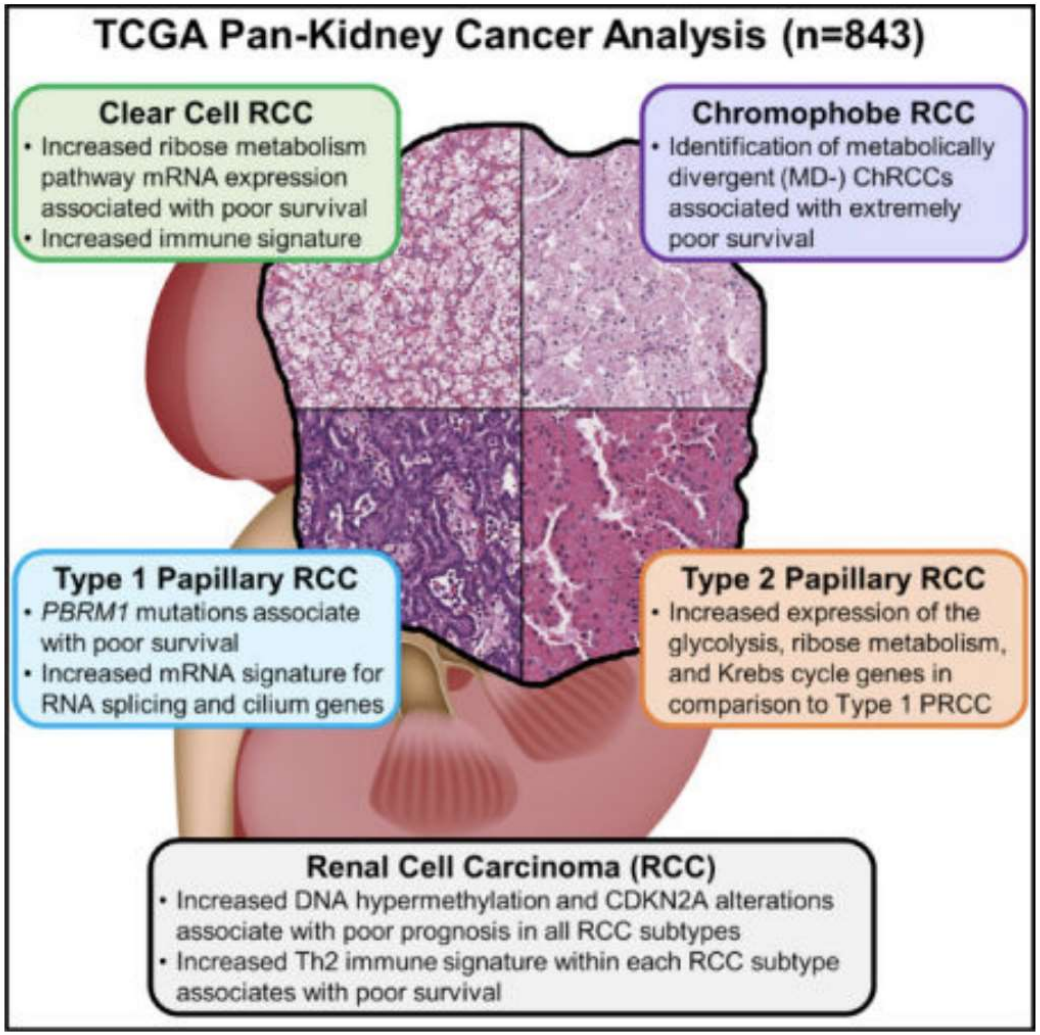
Non-clear cell RCC ≠ clear cell RCC

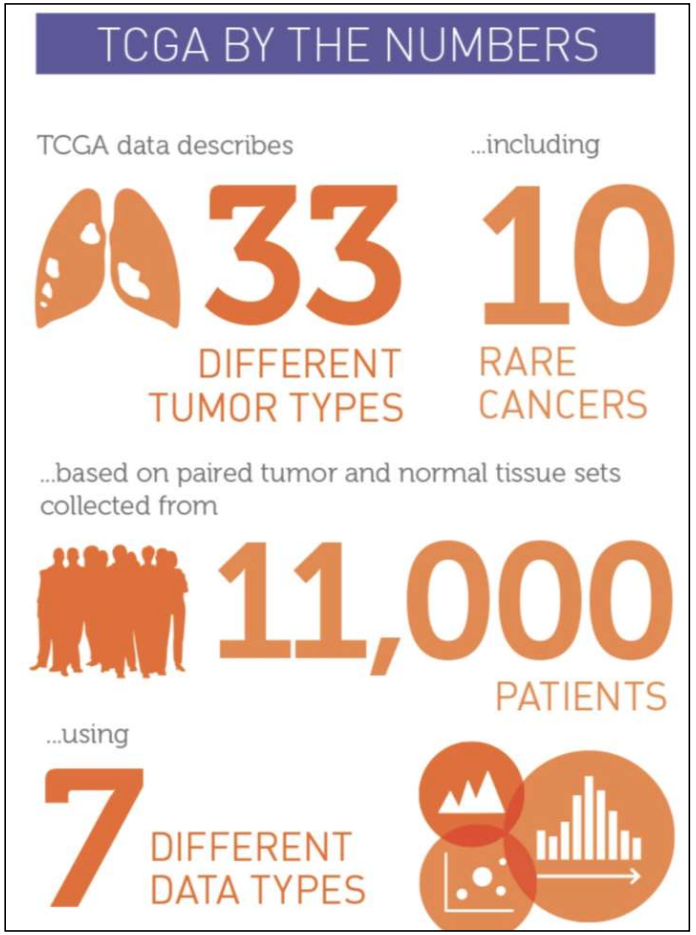
- Non-clear cell RCC is typically treated with agents investigated in ccRCC studies such as VEGF tyrosine kinase inhibitors (TKI) or immune checkpoint inhibitors

- Clinical studies often exclude non-clear cell histologies or lump all non-ccRCC together, making conclusions based on specific subtypes difficult

Tulane University

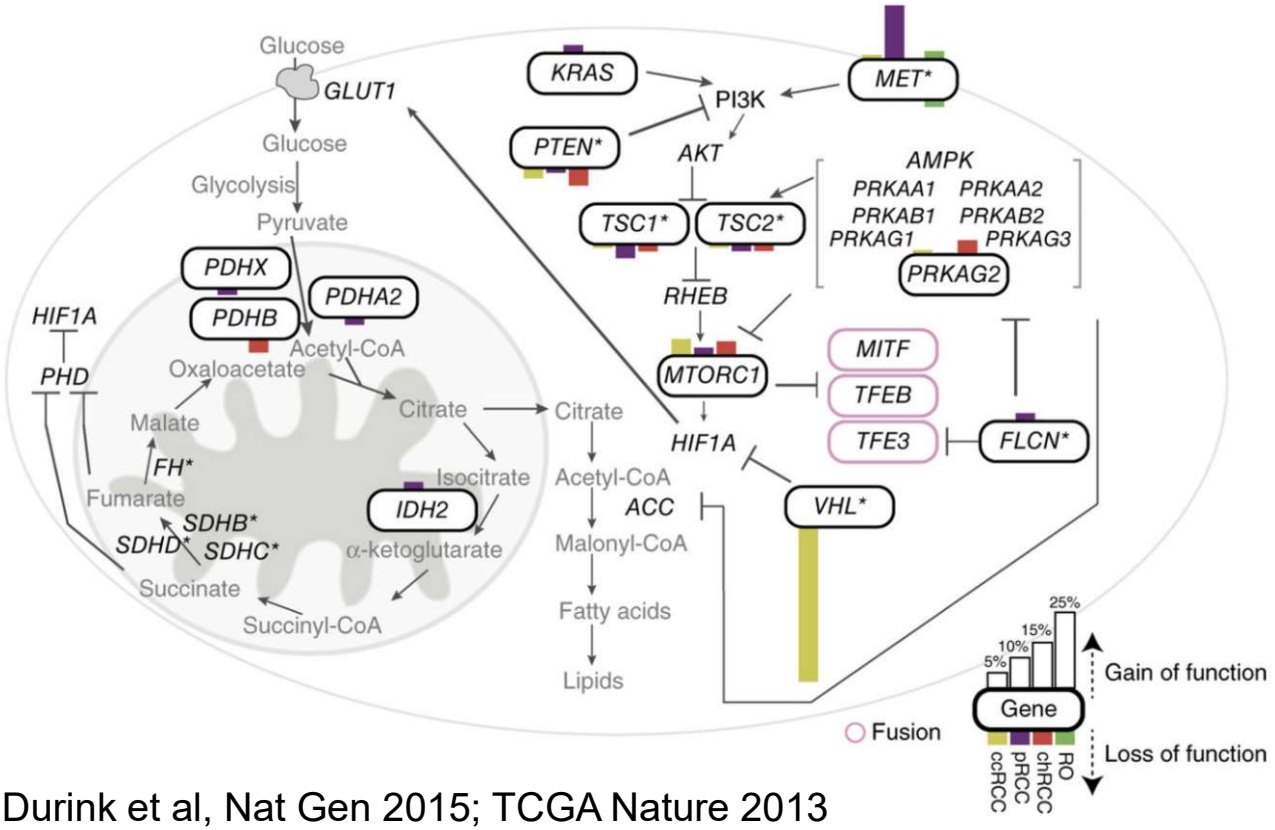
Tumor Cancer Genome Atlas (TCGA): RCC



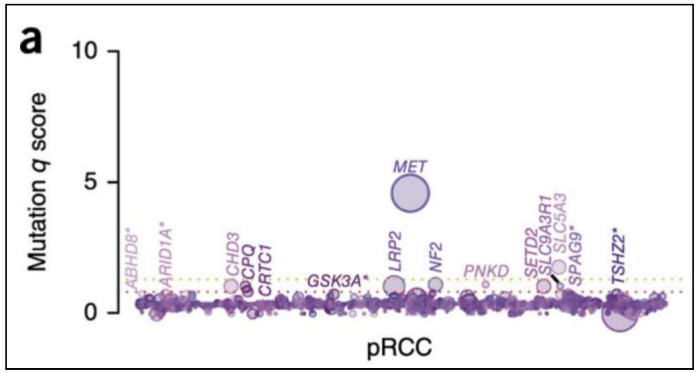


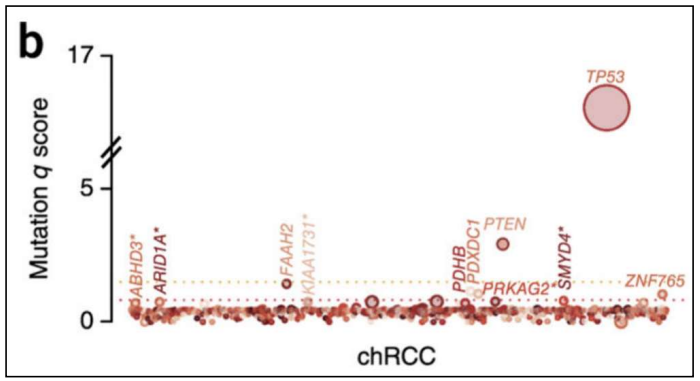
Tulane University

Alteration in Key Pathways in nccRCC



Durink et al, Nat Gen 2015; TCGA Nature 2013



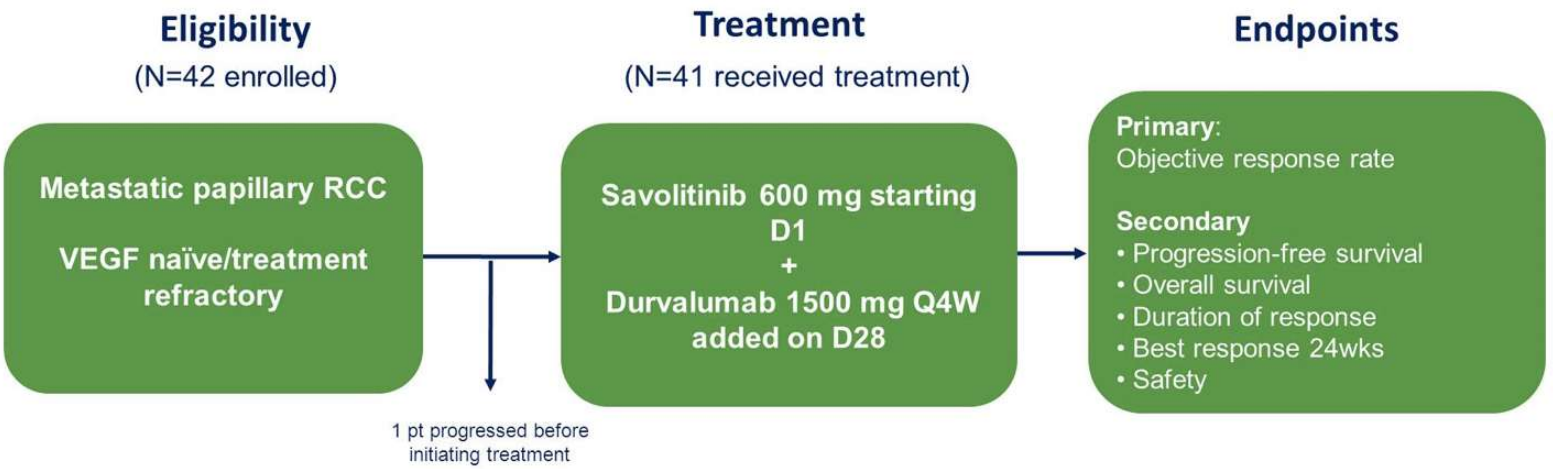


Tulane University

Savolitinib + Durvalumab Study (CALYPSO)

Study Design: Papillary Cohort

Trial Sponsor: Queen Mary University of London



- Treatment until progression/loss of clinical benefit or unacceptable toxicity
- **Median follow-up: 6.9 months** (95% CI: 4.7 – 10.0) as of 25Sep2018

Statistical considerations:
RR≤30% not worthy of further investigation
RR≥50% treatment developed further
80% power at 5% significance
17 responses / 39 patients to further study drug

Suarez et al, ASCO GU 2019

Tulane University

Savolitinib + Durvalumab Study (CALYPSO)

	N=41
Age (years), median (IQR)	62 (49 – 68)
ECOG status, n (%)	
0	16 (39)
1	25 (61)
IMDC, n (%)	
Good (0-1 points)	12 (29)
Intermediate (1-2 points)	26 (63)
Poor (>3 points)	3 (7)
Metastatic sites, n (%)	
Bone	7 (17)
CNS	2 (5)
Liver	8 (20)
Lung	18 (44)
Nephrectomy performed, n (%)	
Yes	35 (85)
Previous anti-tumour treatments*, n (%)	
0	28 (68)
1	9 (22)
2	4 (10)
3 or more	0

Best overall response	All patients (N=41)		Previously untreated (N=28)	
	n (%)	95% CI for %	n (%)	95% CI for %
PR	11 (27)	(14 - 43)	9 (32)	(16 - 52)
SD	16 (39)	(24 - 55)	12 (43)	(24 - 63)
PD	11 (27)	(14 - 43)	5 (18)	(6 – 37)
NA*	3 (7)	(2 – 20)	2 (7)	(1 – 24)

*Only baseline scan available.

Suarez et al, ASCO GU 2019

Tulane University

Savolitinib + Durvalumab Study (CALYPSO)

Best Overall Response Rate by PD-L1 & MET status

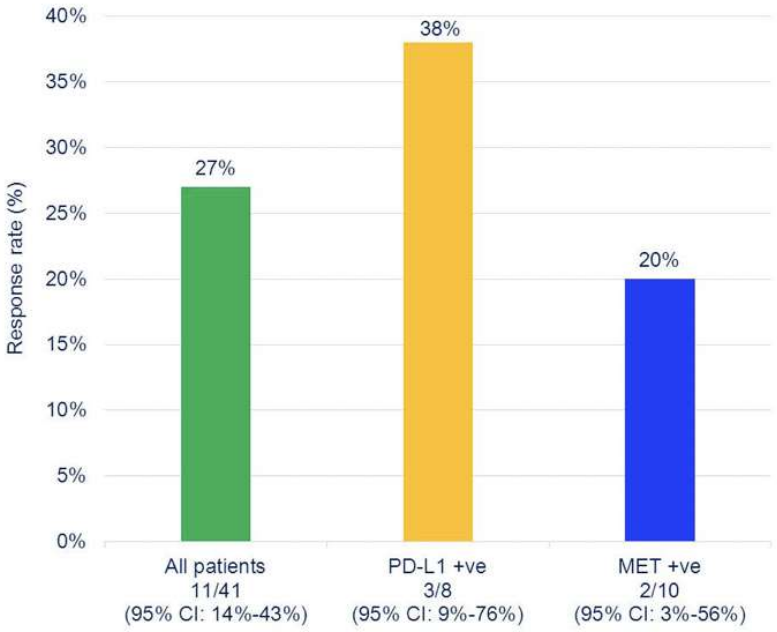
Best overall response	PD-L1+ (N=8/35) n (%)	MET+ (N=10/35) n (%)
PR	3 (38)	2 (20)
SD	1 (13)	5 (50)
PD	3 (38)	2 (20)
NA*	1 (13)	1 (10)

*Only baseline scan available.

8/41 PD-L1 +ve (>25% immune component with SP263 Ab). 27 PD-L1-ve.

10/41 patients MET +ve (≥ 3+ in ≥ 50% tumour cells with IHC). 25 MET -ve.

6 patients not assessable/available for both biomarkers



Suarez et al, ASCO GU 2019

Tulane University

Take-home points (II)

Therapies for nccRCC derive from research conducted on ccRCC

NGS may have therapeutic implications. MET is the best example with different anti-MET drugs now under investigation

Combination strategies are currently ongoing and may change the treatment landscape of nccRCC in the near future

Clinical Trials!!!

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

Thank You!!

pbarata@tulane.edu

Tulane University