Updates in renal and bladder cancer for the internist

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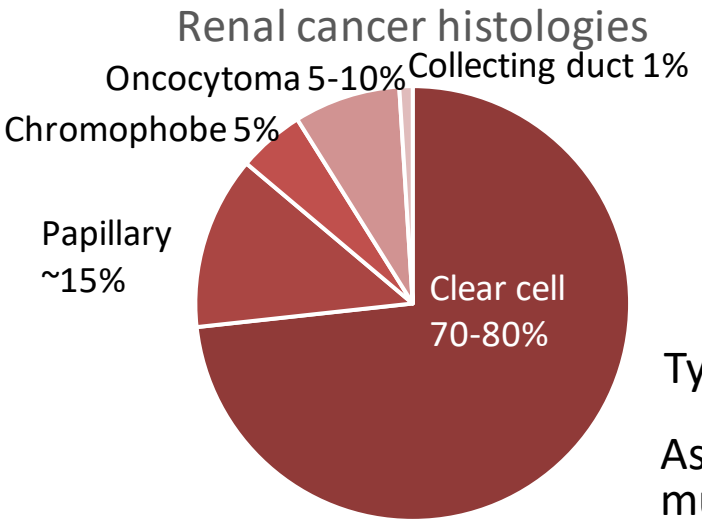
Disclosures/Confluence of Interests

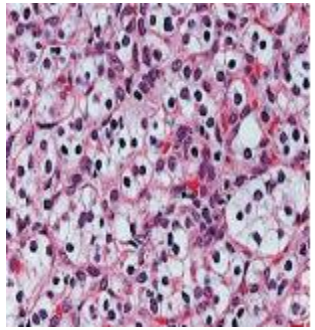
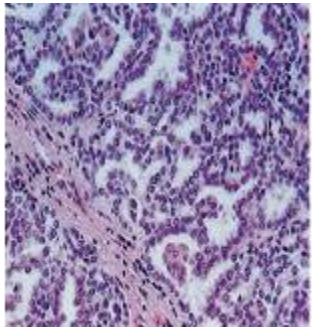
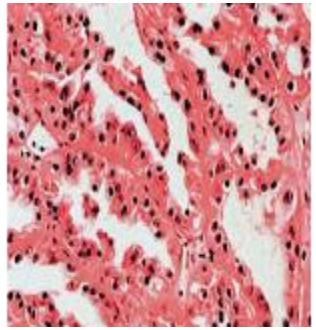
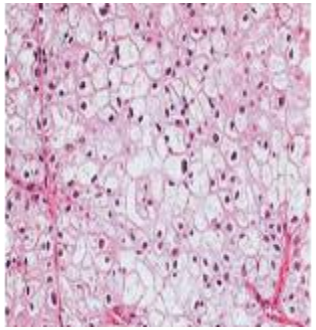
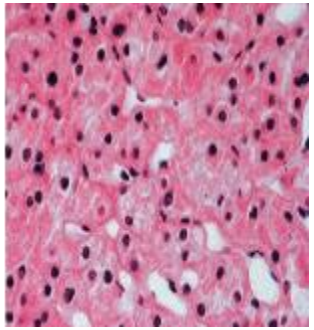
- PI/research funding - Acerta, Novartis, Merrimack, Abbvie/StemCentrx, Merck, Regeneron, Mirati Therapeutics, Janssen, Astra Zeneca, Pfizer, OmniSeq, Personal Genome Diagnostics, Astellas
- Advisory Board – Merck, Exelixis, Sanofi-Aventis, Janssen, Astra Zeneca, Pfizer, Amgen, BMS, Pharmacyclics, SeaGen, Calithera, Dendreon, QED Therapeutics, Eisai, Aveo Pharmaceuticals, Bayer, Eli Lilly
- Consultant – Pfizer, MJH Associates, Vaniam, Aptitude Health, PeerView, Clinical Care Options

Outline

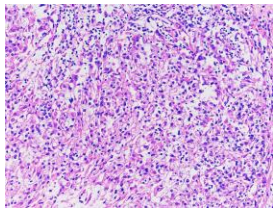
- Renal cell carcinoma
  - Combining immunotherapy and anti-angiogenic agents
  - Adjuvant and first-line metastatic treatment landscape
- Urothelial cancer
  - Immunotherapy, targeted therapies, antibody drug conjugates
  - Toxicities

Renal cell histologies: clear cell and non clear cell



Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
Associated mutations	*VHL, SDH, BAP1*	*MET*	*FH*	*BHD*	*BHD*
Incidence (%)	*75*	*5*	*10*	*5*	*5*
Locus	3p25	7q31	1q42	17p11	17p11

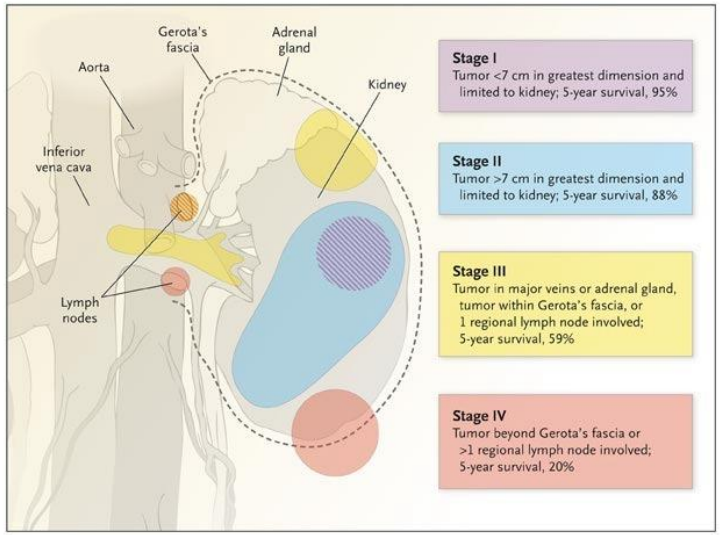


- Sarcomatoid differentiation present ~5% of RCCs
  - Can occur with any histologic subtype
  - Spindle-like cells, high cellularity, and cellular atypia
  - More aggressive

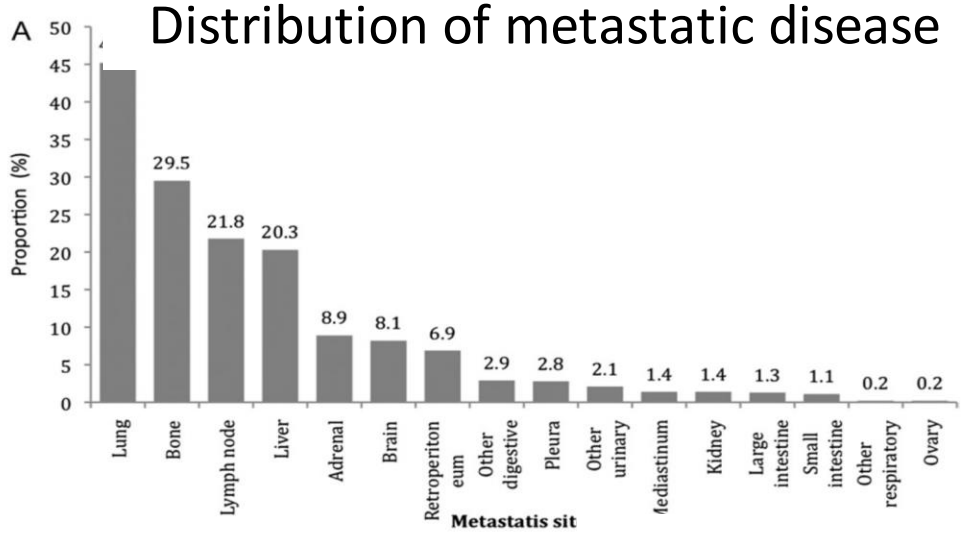
BHD=Birt-Hogg-Dubé;
FH=fumarate hydratase;
VHL=von Hippel-Lindau.

1. Modified from Linehan WM et al. *J Urol*. 2003;170:2163-2172.
2. Kim WY. *J Clin Oncol*. 2004;22:4991-5004.

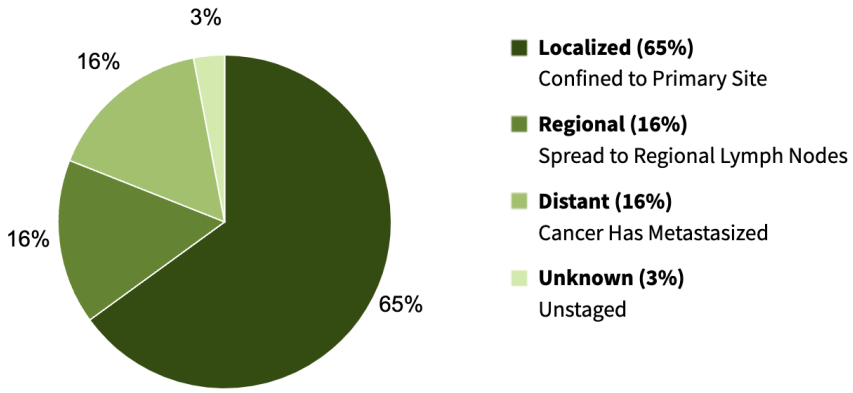
Staging and natural history



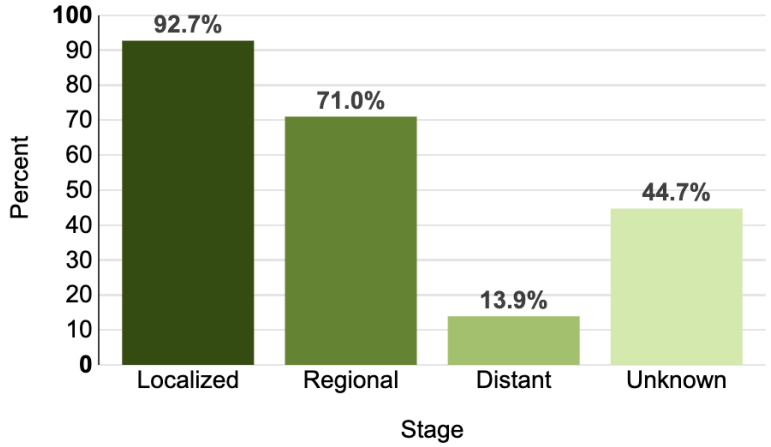
Distribution of metastatic disease



Percent of cases by stage

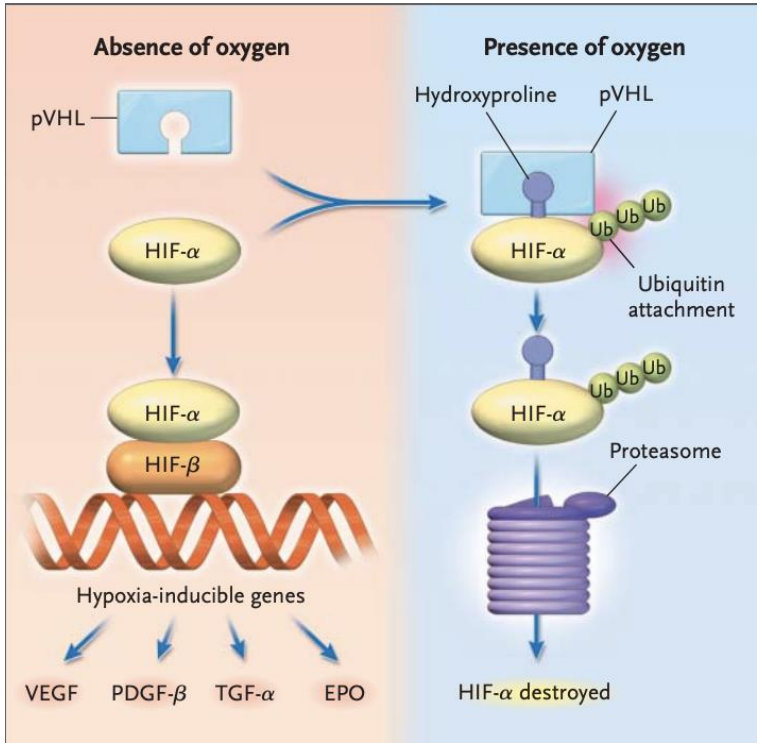


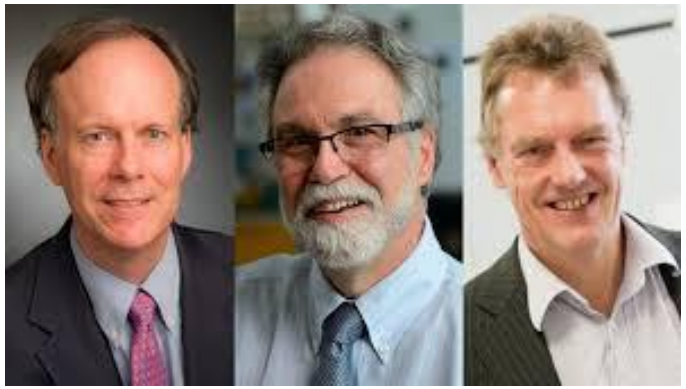
5-year relative survival



SEER Cancer of the Kidney and Renal Pelvis Fact Sheet 2021
Bianchi, M. et al. Ann Oncol 2012

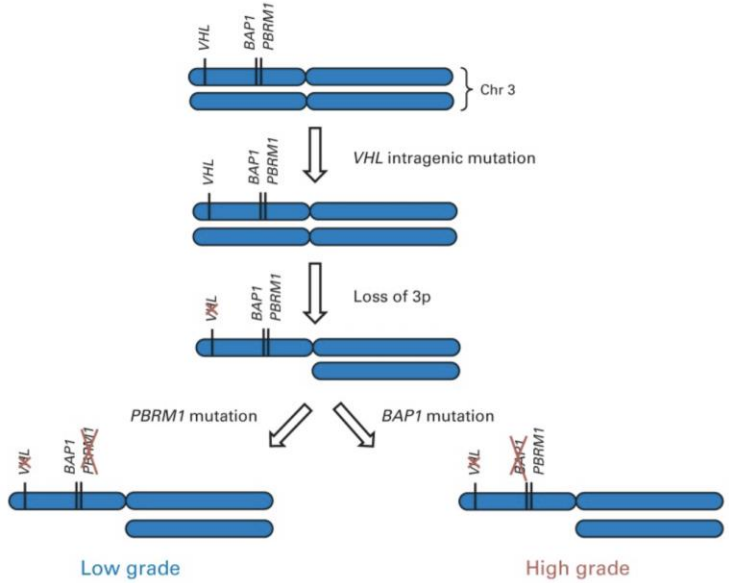
Renal cell carcinoma biology: angiogenesis and molecular pathogenesis





Kaelin Semenza Ratcliffe

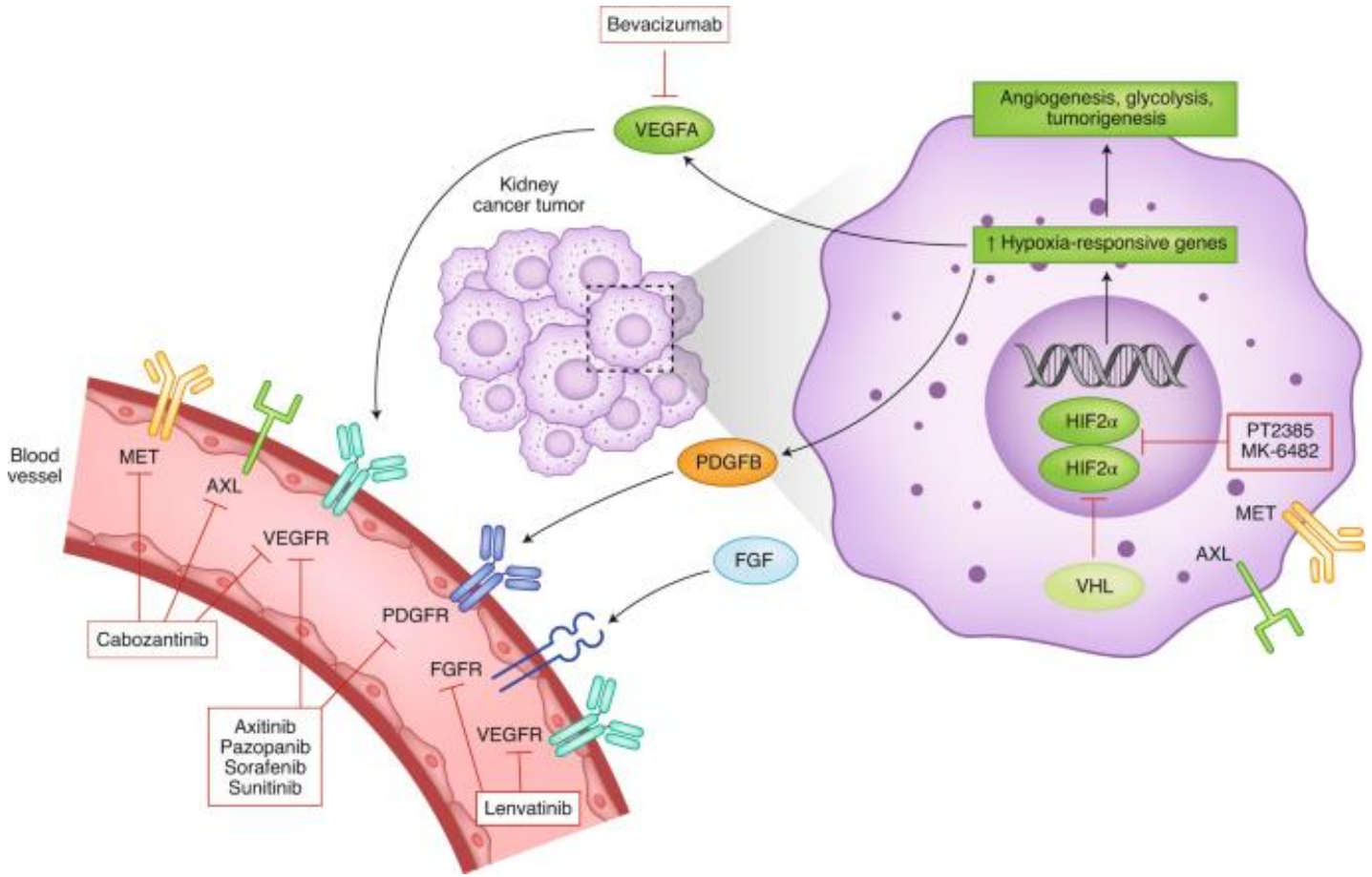
2019 Nobel Prize in Physiology or Medicine



Brugarolas

George DJ & Kaelin WG, *NEJM*, 2003; Brugarolas J, *JCO*, 2014

Treatments targeting VEGF axis/angiogenesis



Targeting angiogenesis:

Small molecule tyrosine kinase inhibitors of VEGFR:
Sunitinib
Pazopanib
Sorafenib
Axitinib

Cabozantinib (off-target effects on MET and Axl)
Lenvatinib (off-target effects on FGFRs)

Monoclonal antibodies:
Bevacizumab

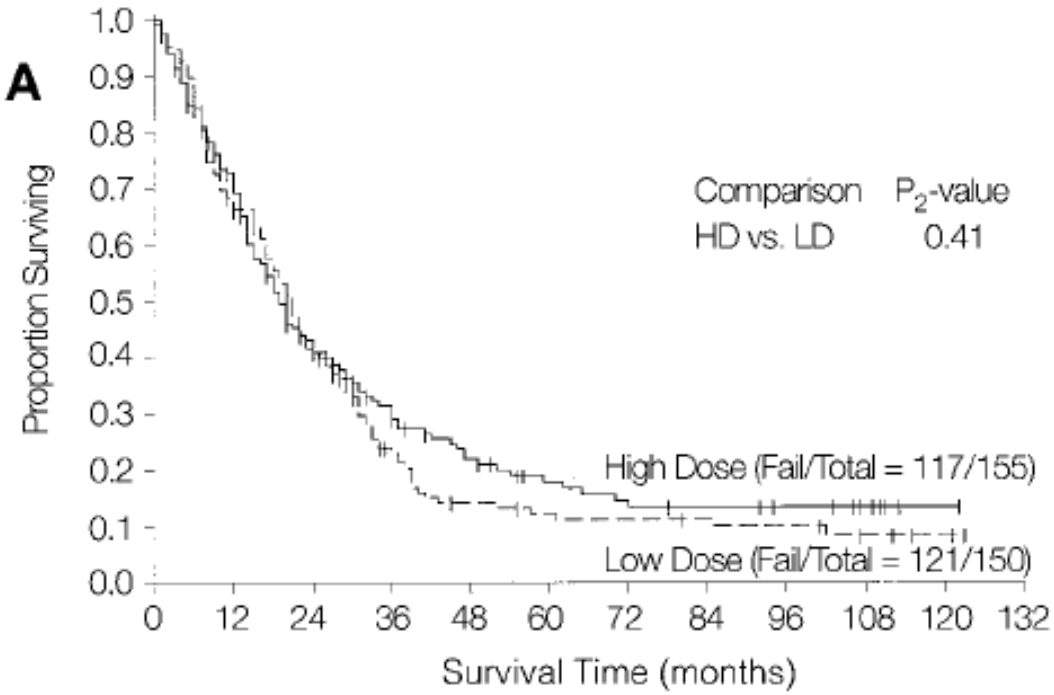
Small molecule inhibitors of HIF2a:
PT2385
Belzutifan (MK-6482)

Choueiri TK & Kaelin WG, *Nature Medicine*, 2020

Cytokine therapy era of 1990s-2000s

	No. of Patients		
	High-Dose IL-2	Low-Dose IL-2	Subcutaneous IL-2
Two-arm study			
Evaluable patients	155	149	
CR	11	6	
PR	22	13	
Major response rate, %	21	13*	
Three-arm study			
Evaluable patients	96	92	93
CR	6	1	2
PR	14	9	7
Major response rate, %	21	11	10†

Abbreviations: IL-2, interleukin-2; CR, complete response; PR, partial response.
*$P = .048$ by χ^2 test; $P = .067$ by Fisher's exact test *v* high-dose IL-2.
†$P = .033$ by χ^2 test; $P = .043$ by Fisher's exact test *v* high-dose IL-2 (unadjusted).



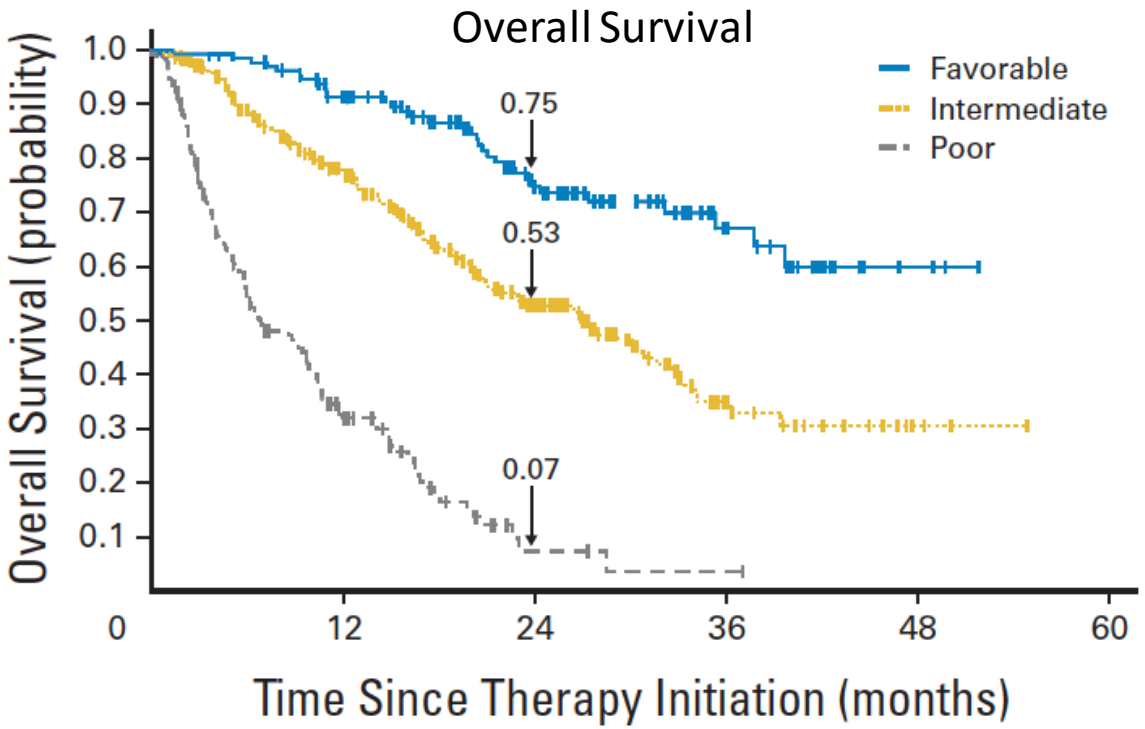
- High dose IL-2 very toxic but durable responses

Yang JC et al, *JCO*, 2003

International metastatic renal cell carcinoma database consortium (IMDC) prognostication

Heng/IMDC Criteria	
Karnofsky Performance Status < 80%	
Time from diagnosis to treatment < 1 year	
Hypercalcemia	
Anemia	Markers of inflammation
Neutrophilia	
Thrombocytosis	

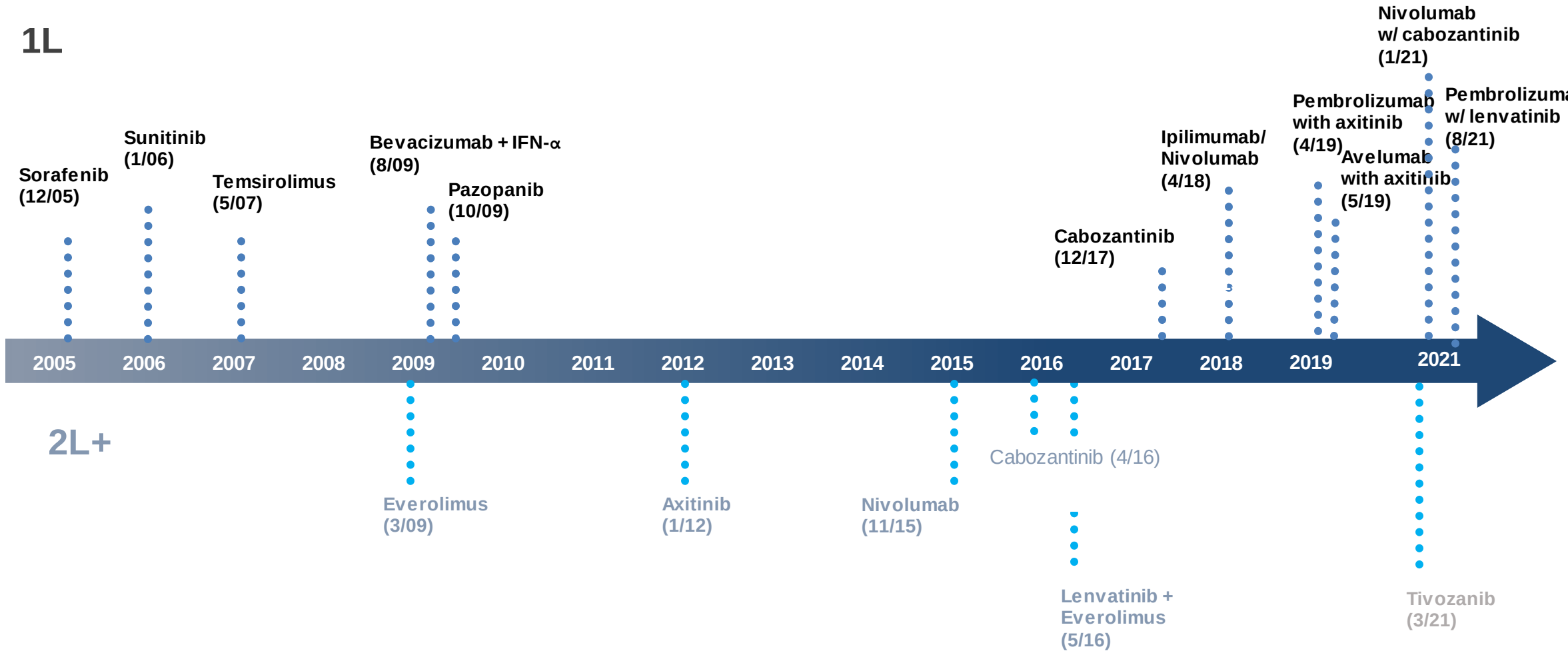
IMDC categories
Favorable (0 risk factors)
Intermediate (1-2 risk factors)
Poor (≥3 risk factors)



Initial prognosis publication 2009.
Used as stratification & selection in trials,
now strong implication for treatment selection

Heng DY, et al. *J Clin Oncol.* 2009.

Timeline of US FDA approved therapies in metastatic ccRCC



First-line metastatic renal cell carcinoma phase 3 trial designs ~2014-2018

- Clear cell renal cell carcinoma
- Measurable metastatic disease, by RECIST criteria
- No prior systemic treatments
- Good performance status
- Archival tissue available

Stratification factors:
IMDC criteria
(favorable, intermediate, poor)
Region (US vs outside US)
Performance status

RANDOMIZATION

Common control cohort in all trials	Sunitinib 50mg PO daily 4weeks on, 2 weeks off
Checkmate 214, phase 3 n= 1096	Ipilimumab 1mg/kg IV q3wk Nivolumab 3mg/kg IV q3wk x4 cycles Then nivolumab 3mg/kg IV q2wk
Javelin Renal 101, phase 3 n= 886	Axitinib 5mg PO BID Avelumab 10mg/kg IV q2wk
Keynote 426, phase 3 n= 861	Axitinib 5mg PO BID Pembrolizumab 200mg IV q3wk
IMMotion 151, phase 3 n= 915	Bevacizumab 15mg/kg IV q3wk Atezolizumab 1200mg IV q3wk
Checkmate 9ER n= 638	Cabozantinib 40mg PO daily Nivolumab 240mg IV q2wk
CLEAR n= 1069	Lenvatinib 20mg PO daily Pembrolizumab 200mg IV q3wk

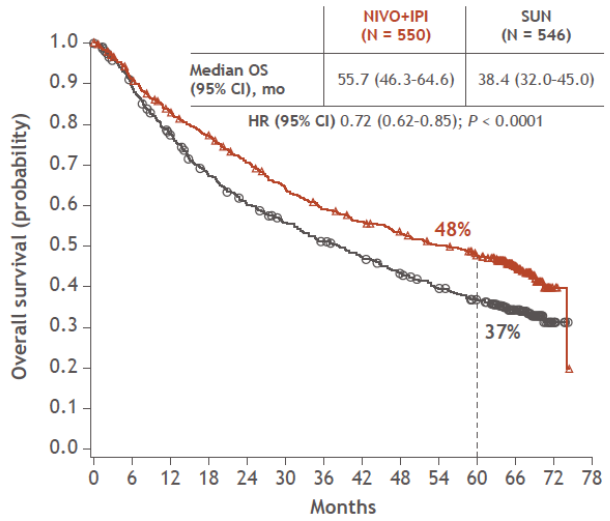
Treat until disease progression or unacceptable toxicity

Primary endpoints:
Overall survival
Progression free survival

Secondary endpoints:
Objective response rates
Duration of responses
Patient-reported quality of life
Safety of combinations

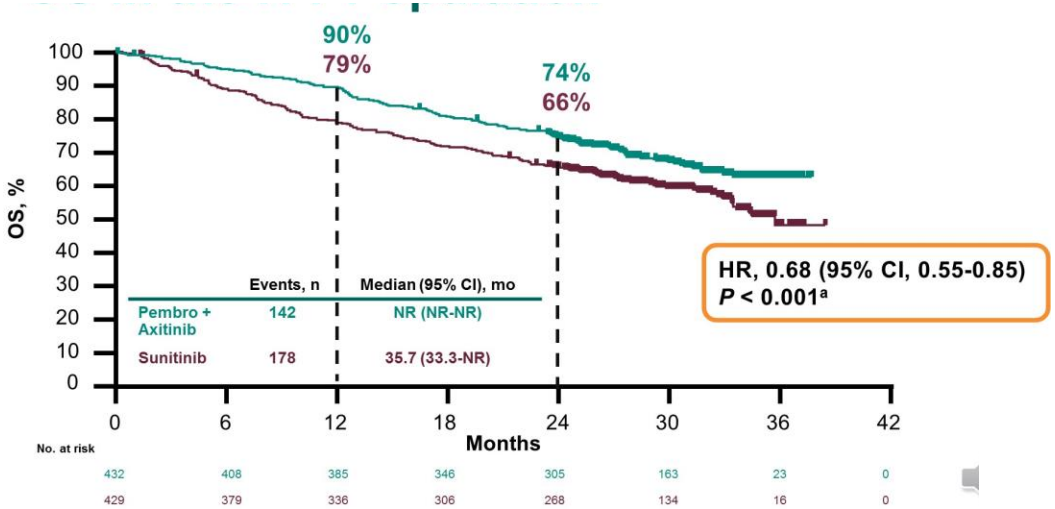
First-line metastatic renal cell carcinoma trials: Overall Survival

Checkmate 214: Overall Survival ITT (60-mo follow up)

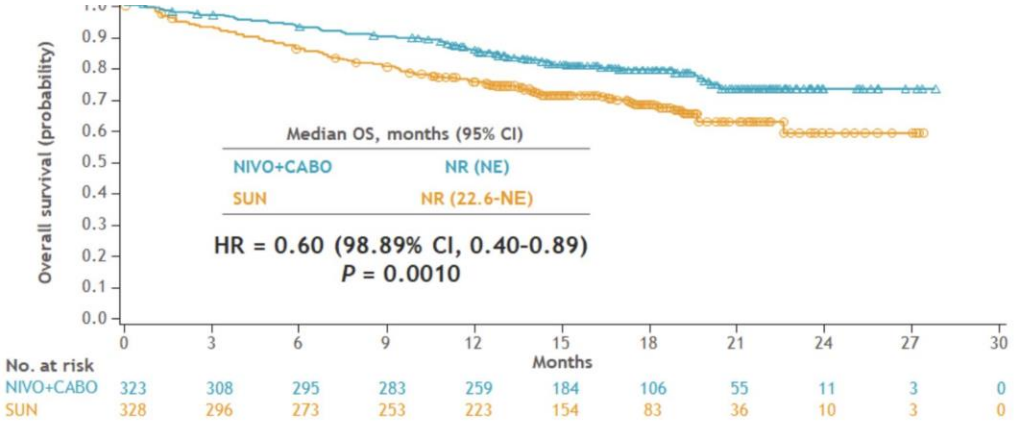


HR, 0.72 (95% CI, 0.61-0.86)
P<0.0001

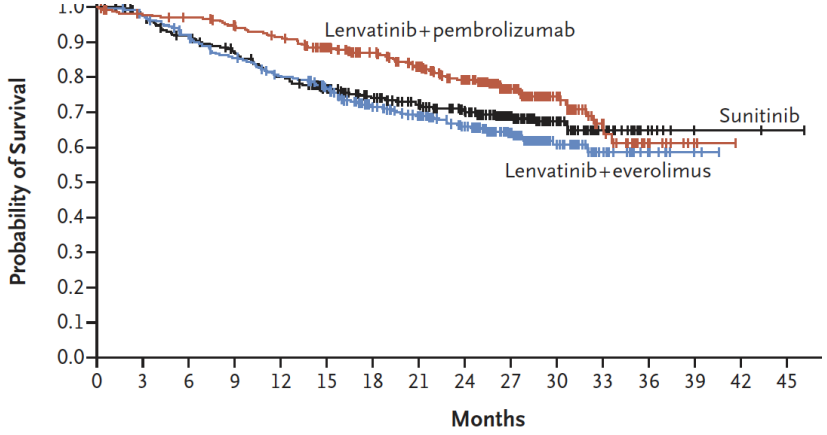
Keynote 426: Overall Survival ITT



Checkmate 9ER: Overall Survival



CLEAR/Keynote 581: Overall Survival ITT



Tannir N et al, GU ASCO 2020; Choueiri TK et al, *NEJM*, 2021
Powles T et al, *Lancet Oncol*, 2020; Motzer RJ et al, *NEJM*, 2021

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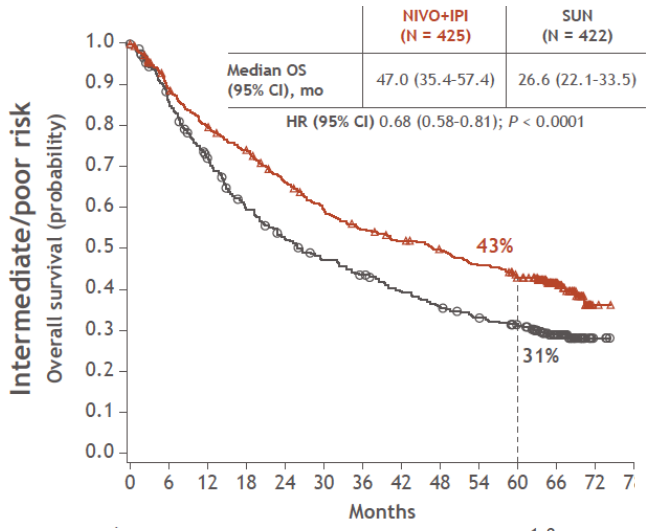
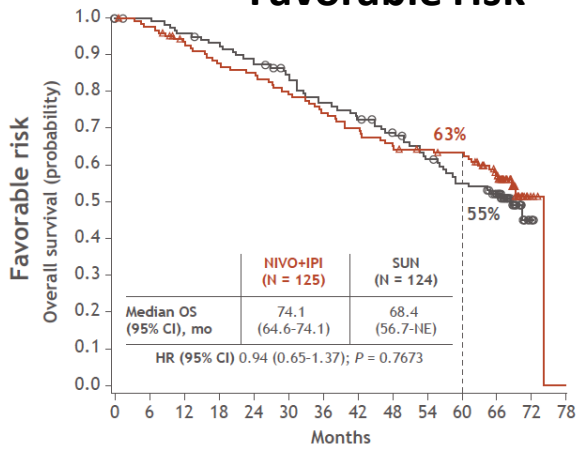
Survival benefit driven by patients with IMDC intermediate-poor risk/ “clinically inflamed” disease

Checkmate 214 Overall survival by IMDC risk 60 mo followup

Intermediate/Poor risk

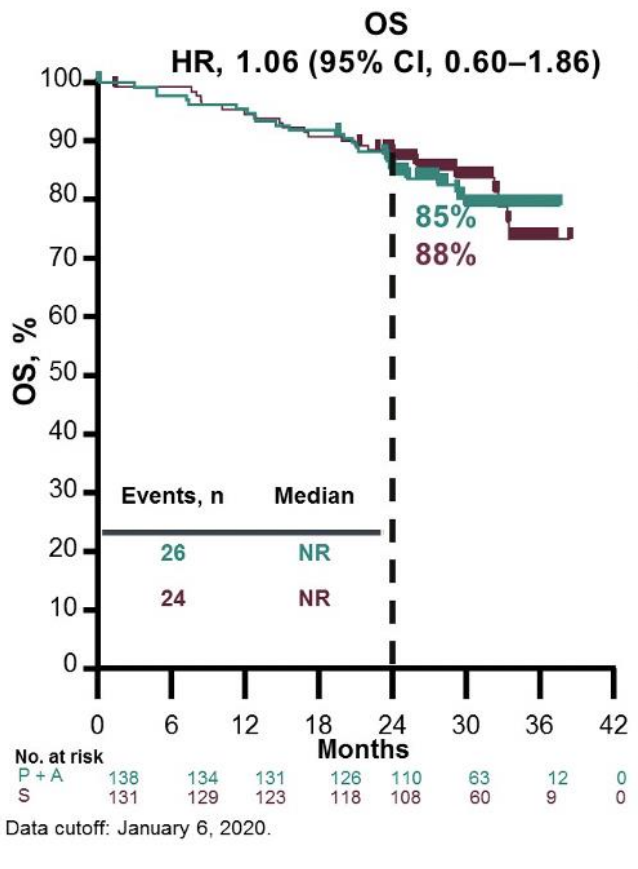


Favorable risk

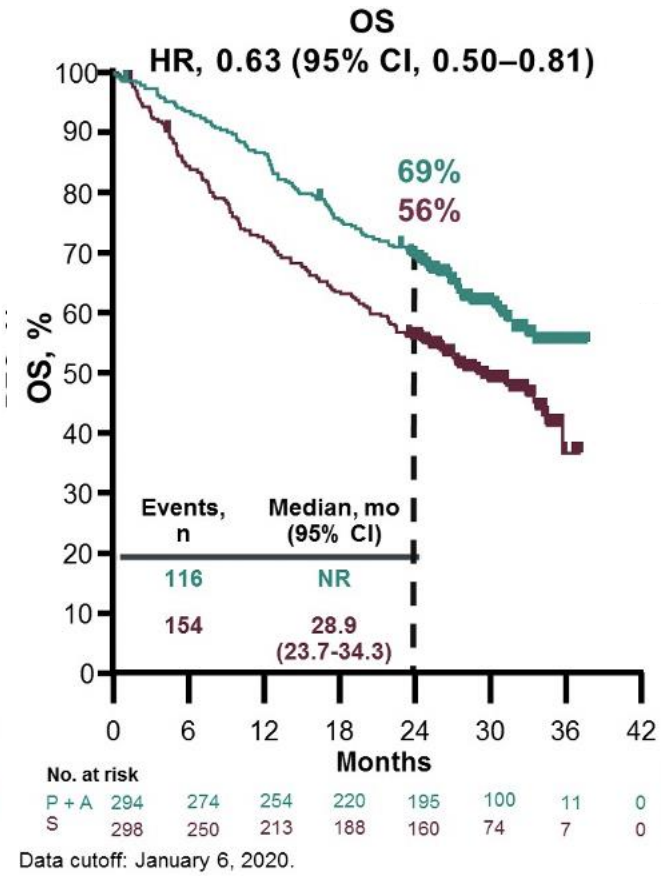


Keynote 426: Overall survival by IMDC risk

Favorable risk



Intermediate/Poor risk



Tannir N et al, *GU ASCO*, 2020

Powles T et al, *Lancet Oncol*, 2020

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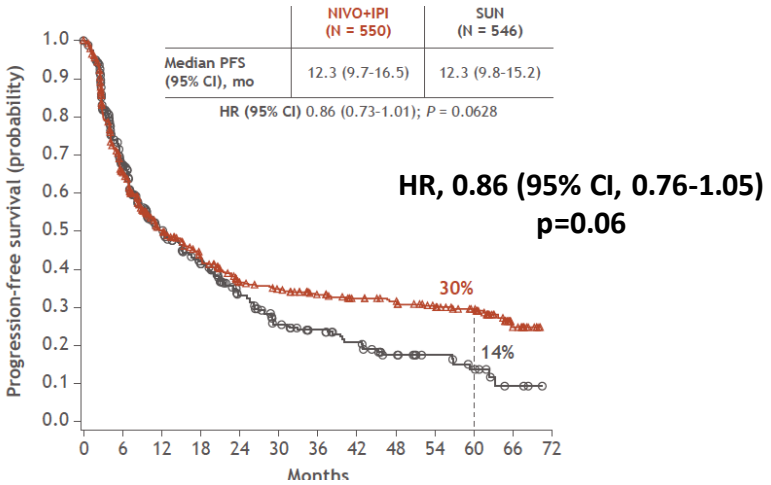
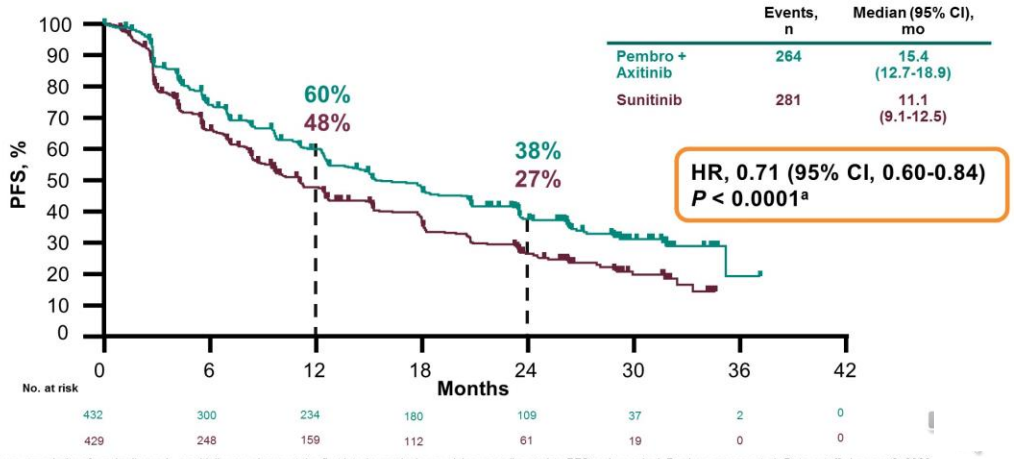
PFS for ipilimumab-nivolumab – some responses durable
PFS for axitinib-pembrolizumab, axitinib-avelumab, cabozantinib-nivolumab, Lenvatinib-pembrolizumab significantly improved

Checkmate 214 Progression free survival 60-month update

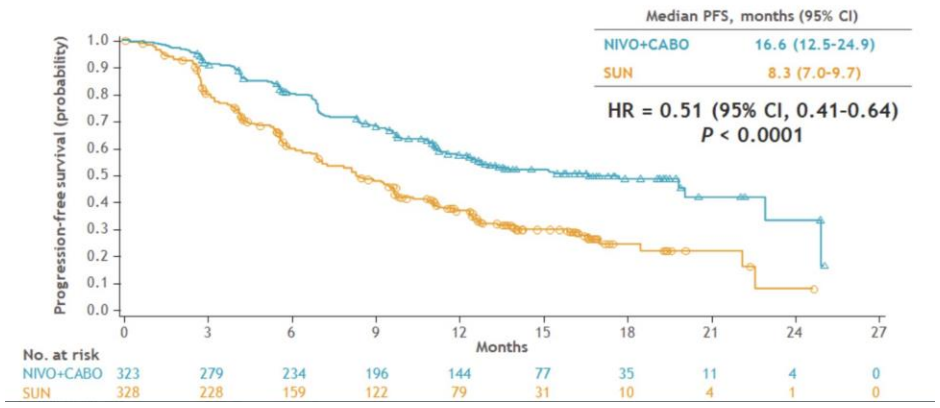


HR, 0.86 (95% CI, 0.76-1.05)
p=0.06

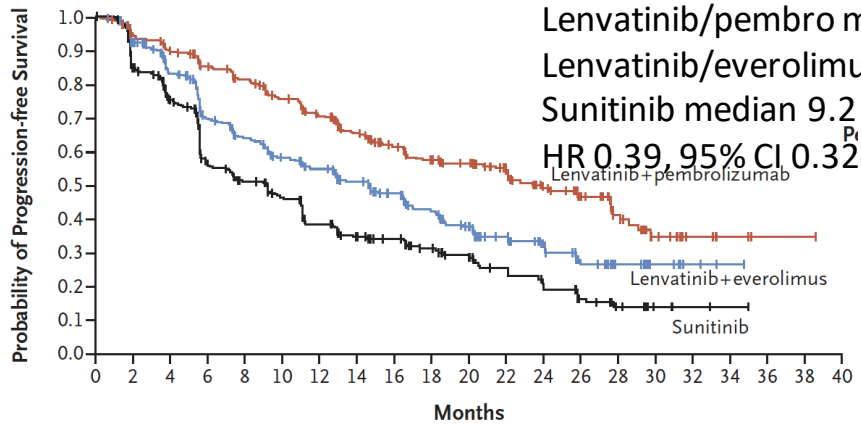
Keynote 426 Progression free survival



Checkmate 9ER Progression free survival



CLEAR/Keynote 581 Progression free survival



Lenvatinib/pembro median 23.9mo
Lenvatinib/everolimus median 14.7 mo
Sunitinib median 9.2 mo
HR 0.39, 95% CI 0.32-0.49, p<0.001

Motzer RJ et al, ESMO, 2021
Powles T et al, *Lancet Oncol*, 2020

Motzer RJ et al, *NEJM*, 2021
Choueiri TK et al, *NEJM*, 2021

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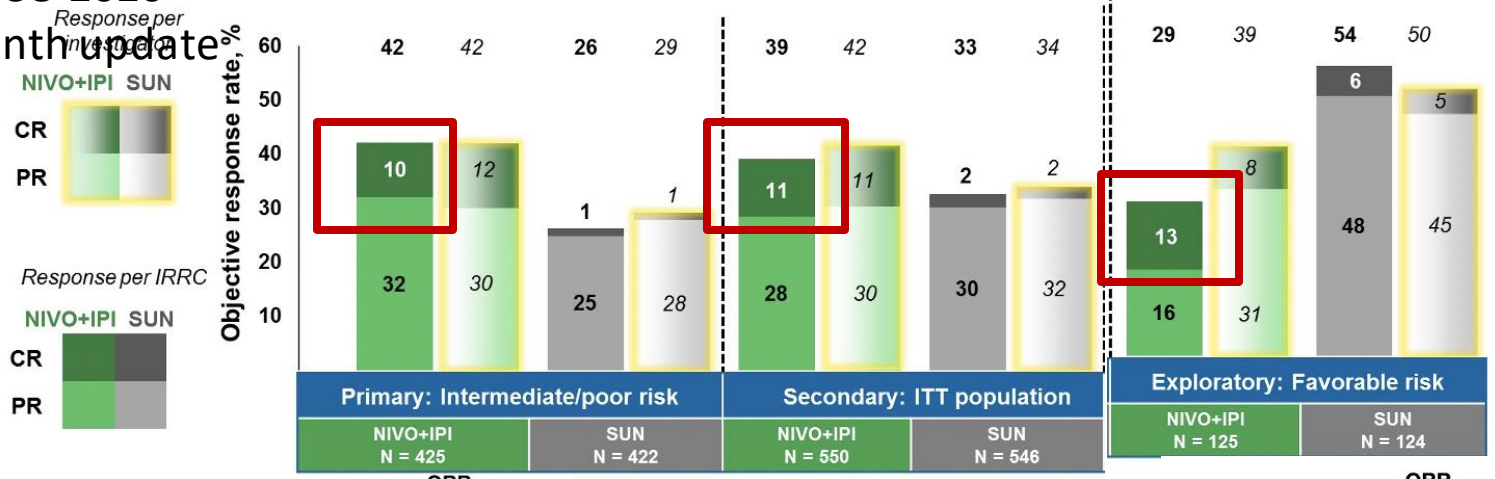
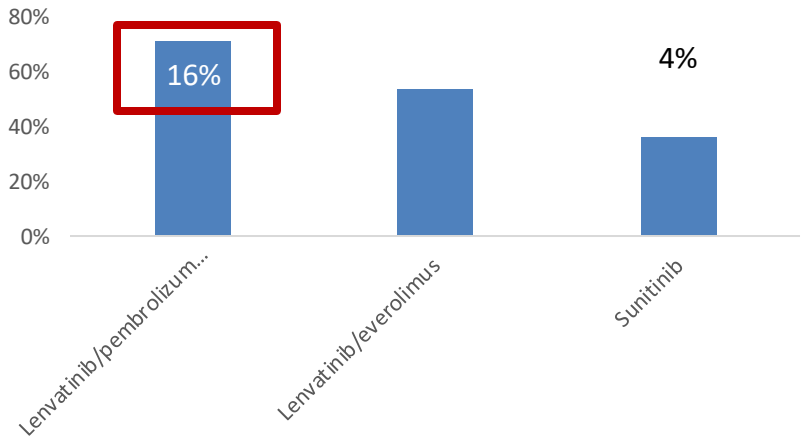
Objective responses – 8-16% complete responders, some delayed responses

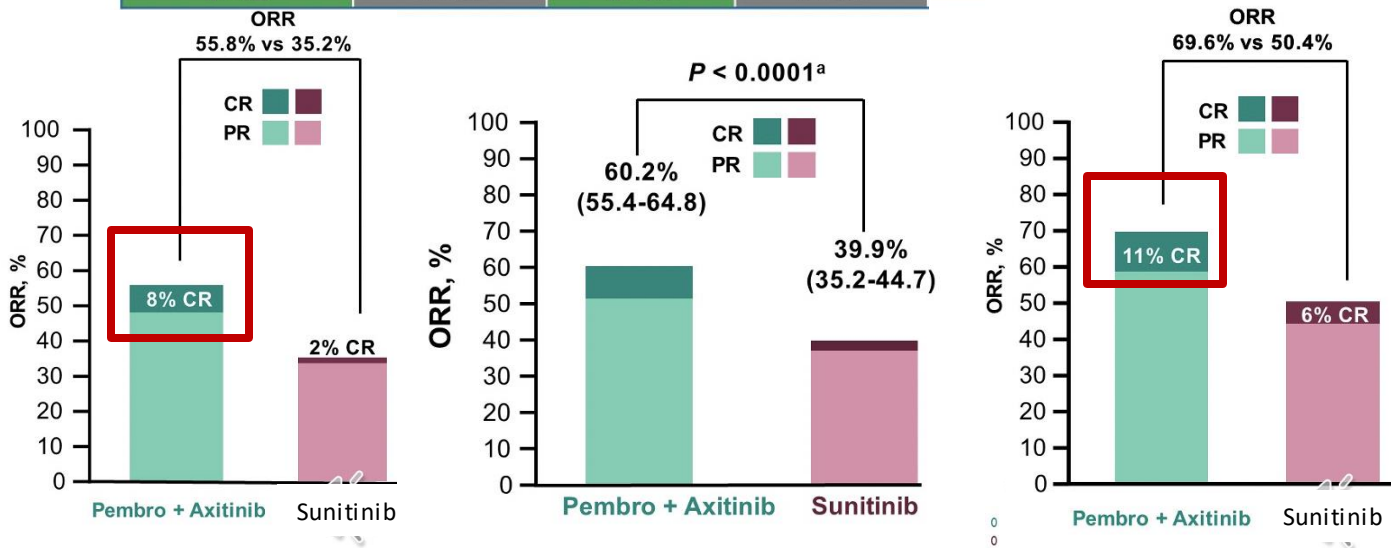
Checkmate 214
GU ASCO 2020
48 month update



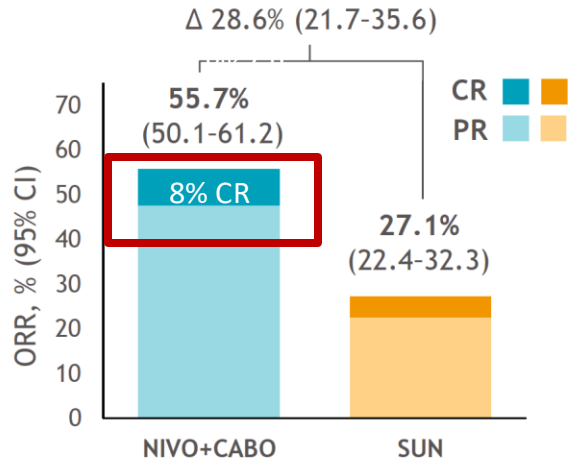
CLEAR Intention to treat



Keynote 426
ASCO 2020
24-month update



Checkmate 9ER $P < 0.0001$



Tannir N et al, *GU ASCO*, 2020; Motzer RJ et al, *NEJM*, 2021
Powles T et al, *Lancet Oncol*, 2020; Choueiri TK et al, *NEJM*, 2021

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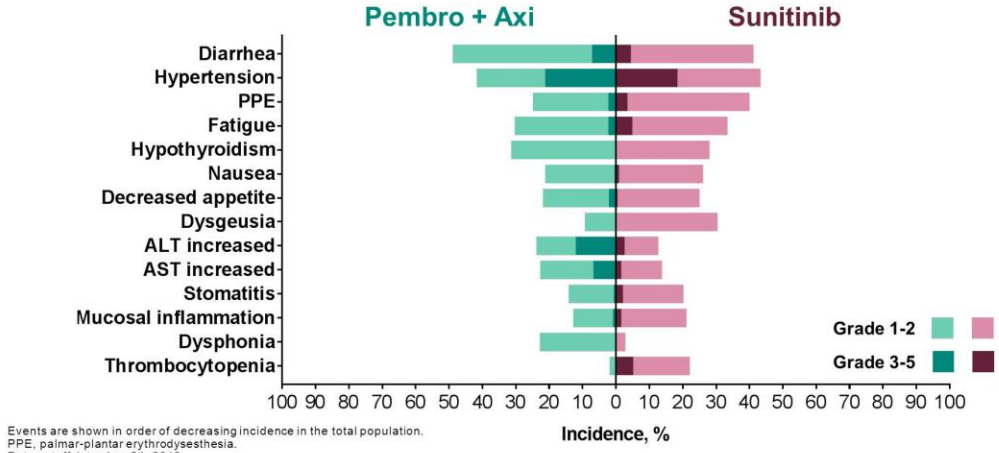
Safety data: immune mediated adverse events

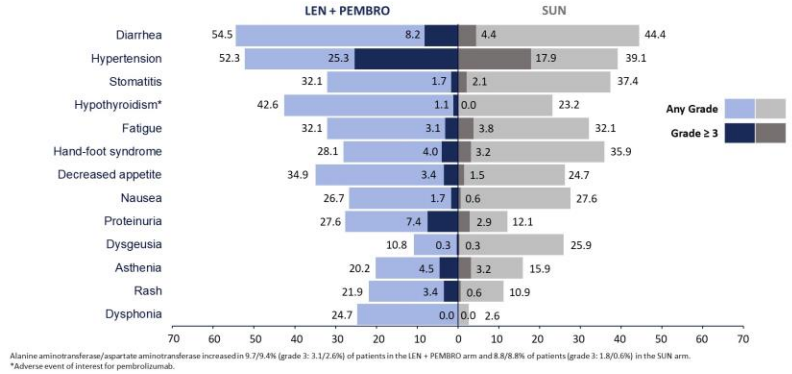
Checkmate 214: ipilimumab-nivolumab adverse events

	NIVO + IPI N = 547	
Category, %	Any grade	Grade 3–4
Rash	17	3
Diarrhea/colitis	10	5
Hepatitis	7	6
Nephritis and renal dysfunction	5	2
Pneumonitis	4	2
Hypersensitivity/infusion reaction	1	0
Hypothyroidism	19	<1
Hyperthyroidism	12	<1
Adrenal insufficiency	8	3
Hypophysitis	5	3
Thyroiditis	3	<1
Diabetes mellitus	3	1

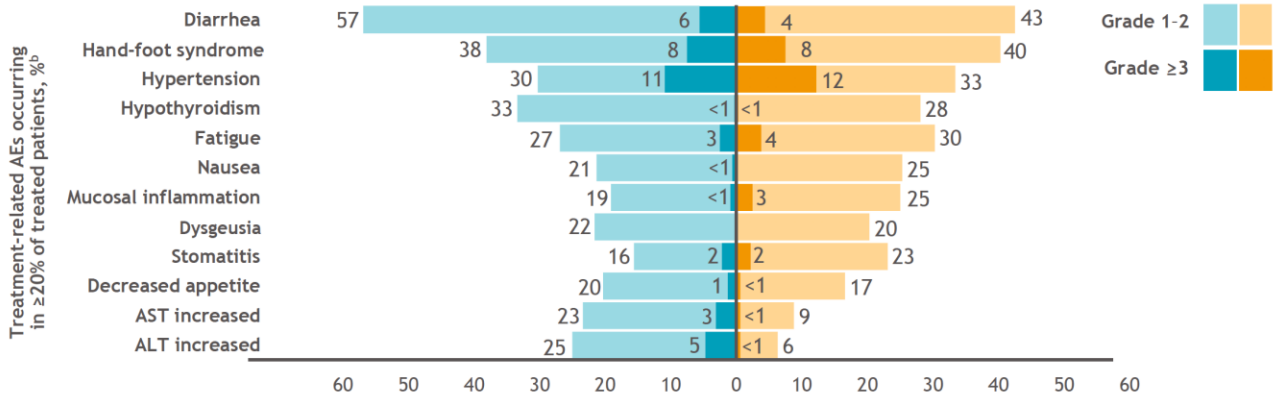
Keynote 426: Axitinib-pembrolizumab adverse events



CLEAR: Lenvatinib-pembrolizumab adverse events



Checkmate 9ER: cabozantinib-nivolumab adverse events



Motzer RJ et al, *Lancet Oncol*, 2019; Choueiri TK et al, *NEJM*, 2021
Rini BI et al, *NEJM*, 2019; Motzer RJ et al, *NEJM*, 2021

CheckpointNow MD

Episode 2

Immune Related Thyroid Toxicities

Hosts: Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss challenges encountered in the diagnosis and management of commonly encountered Immune Related Thyroid Toxicities.

Episode 3

Breaking down the diagnosis and management of Immune Hypophysitis

Hosts: Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss all things Immune Hypophysitis and all you need to know to get better at managing this complex toxicity

Episode 4

Immune mediated Inflammatory Arthritis: Challenges in diagnosis and management

Hosts: Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss with guest expert and Rheumatologist Dr. Sophia Weinmann about the complex and challenging diagnosis of Immune mediated Inflammatory Arthritis.

Episode 6

Rheumatic adverse events: Discussions on pre-existing rheumatic disease, biomarkers, collaborations and more.

Hosts: Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss with guest experts and rheumatologists Dr. Leonard Calabrese and Dr. Cassandra Calabrese from Cleveland Clinic and Dr. Alexa Meara from Ohio State University about budding collaborations and scientific discovery in Immune Mediated Rheumatic Adverse Events

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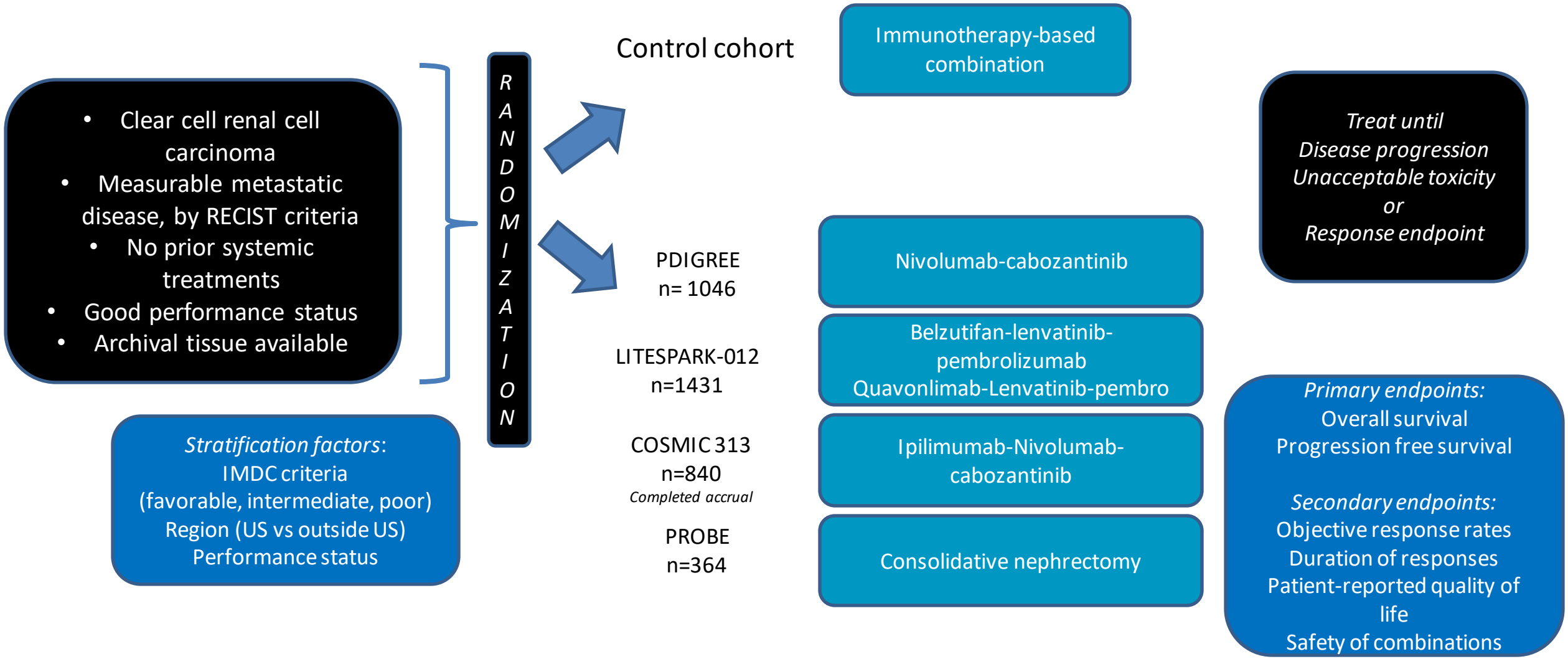
Episode 7

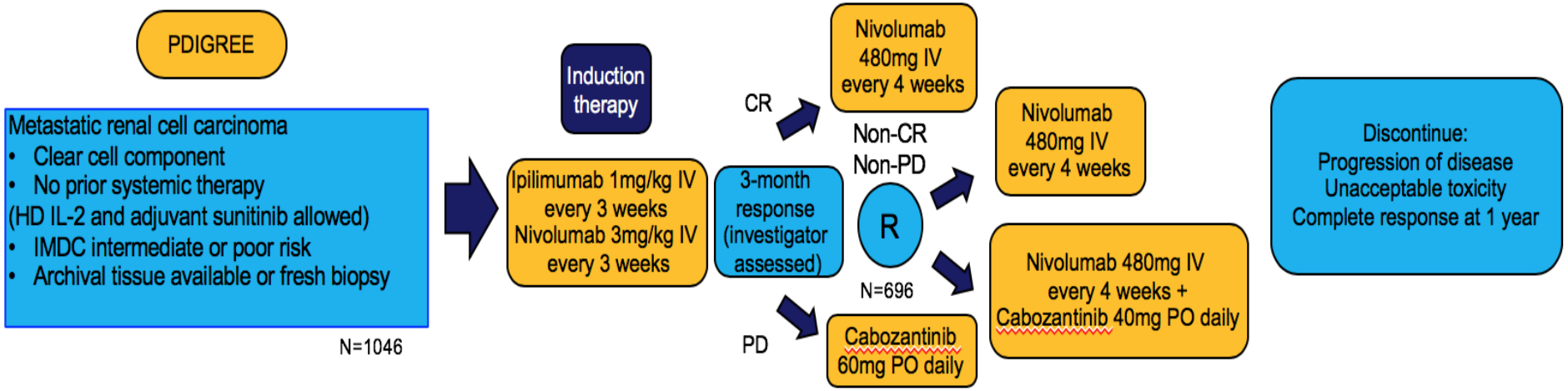
Immune Mediated Colitis and lessons learnt from multidisciplinary team based management.

Hosts: Learn from the experts about the clinical diagnosis and multidisciplinary management of Immune Mediated Colitis. Join our hosts Dr. Afreen Shariff and Dr. Tian Zhang as they discuss with guest experts- medical Oncologist Dr. Kerry Reynolds and Gastroenterologist/ Immunologist Dr. Micheal Dougan from Massachusetts General Hospital for an informative and high yield discussion.

Next Generation First-line phase 3 trial designs in mRCC



PD-Inhibitor nivolumab and Ipilimumab followed by nivolumab vs VEGF TKI cabozantinib with nivolumab (PDIGREE, A031704) – schema



1º endpoint:
3-year OS
(60% nivo vs 70% nivo-cabo, HR 0.70
85% power, 2-sided α =0.05)

Key 2º endpoints:
-- 1-year CR rate
-- PFS
-- ORR by RECIST
-- Toxicity of nivo-cabo


Study chairs: Zhang & Choueiri

Study activated in NCTN May 2019
Active enrollment across sites

PDIGREE: Alliance trial A031704
Clinicaltrials.gov: NCT03793166

Two patients, same treatment, different outcomes

47yo man

Treatment break: 15 months

Treatment break: Ongoing

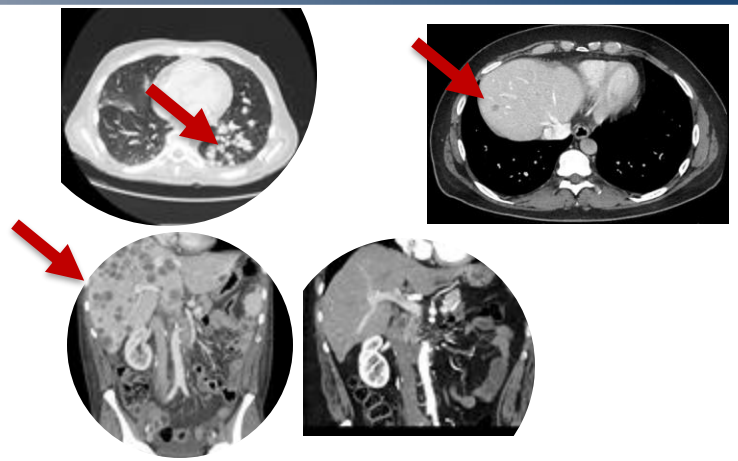
Ipilimumab/ Nivolumab 9/2017-11/2018

Held for hematoma

Nivolumab 2/2020-7/2021

Held for Immune-mediated diabetes 8/2021

2017 2019 2021



Innumerable symptomatic liver and lung mets,
Hgb 8.6, plt 550, <1 year from nephrectomy

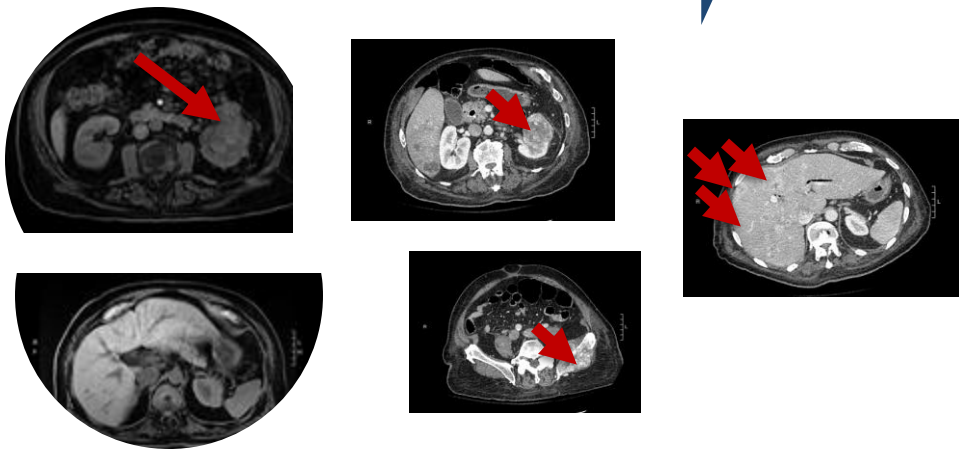
70yo man

Ipilimumab/nivolumab 6/2019-9/2019

Liver abscess, sepsis hospice 10/2019

Death 11/2019

2019 2020

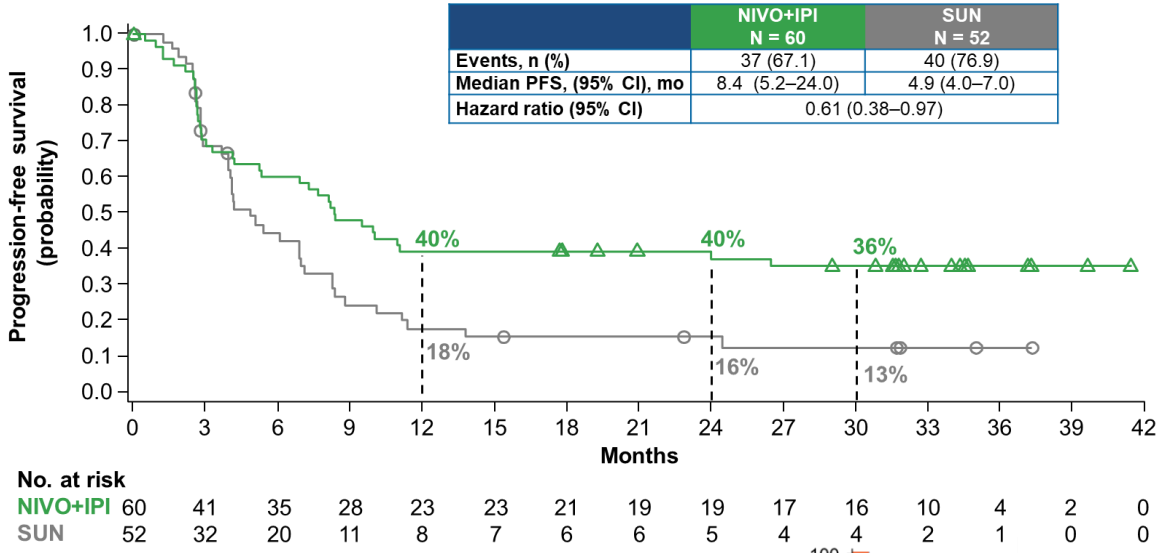


Hgb 9.0, plt 500
De novo metastatic to lungs and liver

Sarcomatoid differentiation may predict for immunotherapy response – Progression Free Survival

CheckMate 214

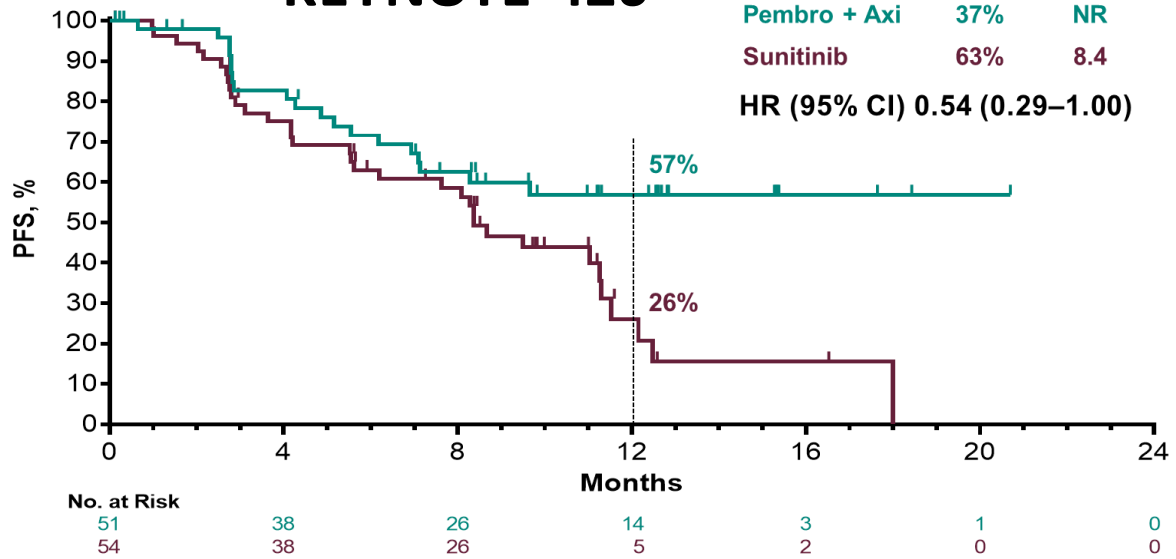
	NIVO+IPI N = 60	SUN N = 52
Events, n (%)	37 (67.1)	40 (76.9)
Median PFS, (95% CI), mo	8.4 (5.2–24.0)	4.9 (4.0–7.0)
Hazard ratio (95% CI)	0.61 (0.38–0.97)	



KEYNOTE-426

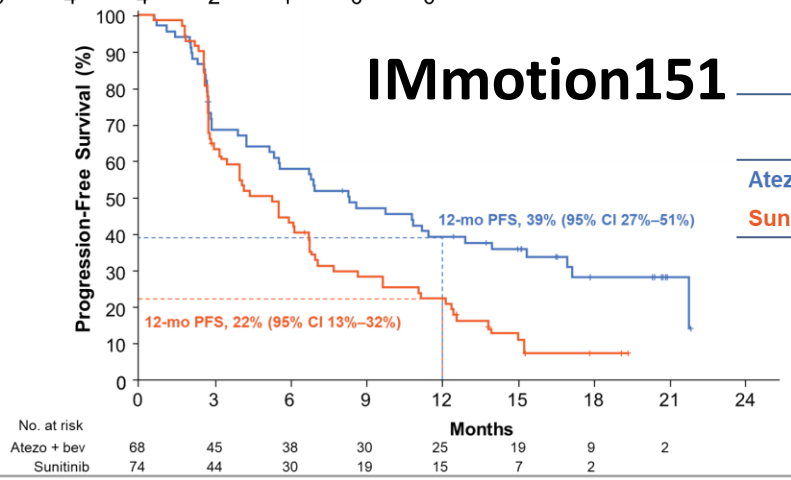
	Pts w/ Event	Median
Pembro + Axi	37%	NR
Sunitinib	63%	8.4

HR (95% CI) 0.54 (0.29–1.00)



IMmotion151

	Median PFS (95% CI)
Atezo + bev	8.3 mo (5.4, 12.9)
Sunitinib	5.3 mo (3.3, 6.7)



Rini BI et al, Eur Urol, 2020; S0302-2838(20)30450-4.
Tannir NM et al, *Clin Cancer Res*, 2020

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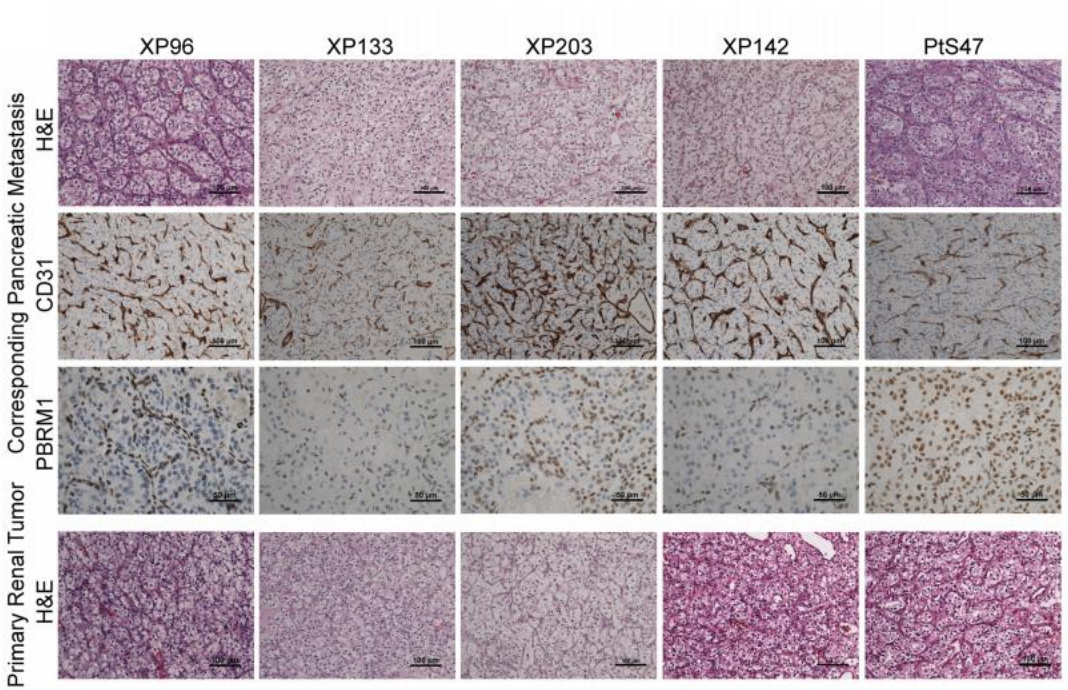
Sarcomatoid RCC: response to immunotherapy combinations

	Ipilimumab/Nivolumab Checkmate 214 (N=74)	Axitinib/Pembrolizumab Keynote 426 (N=51)	Axitinib/Avelumab Javelin Renal 101 (N=47)	Atezolizumab/Bevacizumab Immotion 151 (N=68)
ORR	61%	59%	47%	49%
CR	19%	12%	4%	10%
Median PFS HR (95% CI) vs sunitinib	26.5 months 0.54 (0.3-0.9)	NR 0.54 (0.29-1.00)	7.0 months 0.57 (0.33-1.00)	8.3 months 0.52 (0.34-0.79)
12 month PFS	57% (est.)	57%	35% (est.)	39%
Median OS HR (95% CI) vs sunitinib	NR 0.45 (0.3-0.7)	NR 0.58 (0.21-1.59)	NA	21.7 months 0.64 (0.41-1.01)
12 month OS	84% (est.)	83%	83%	56%

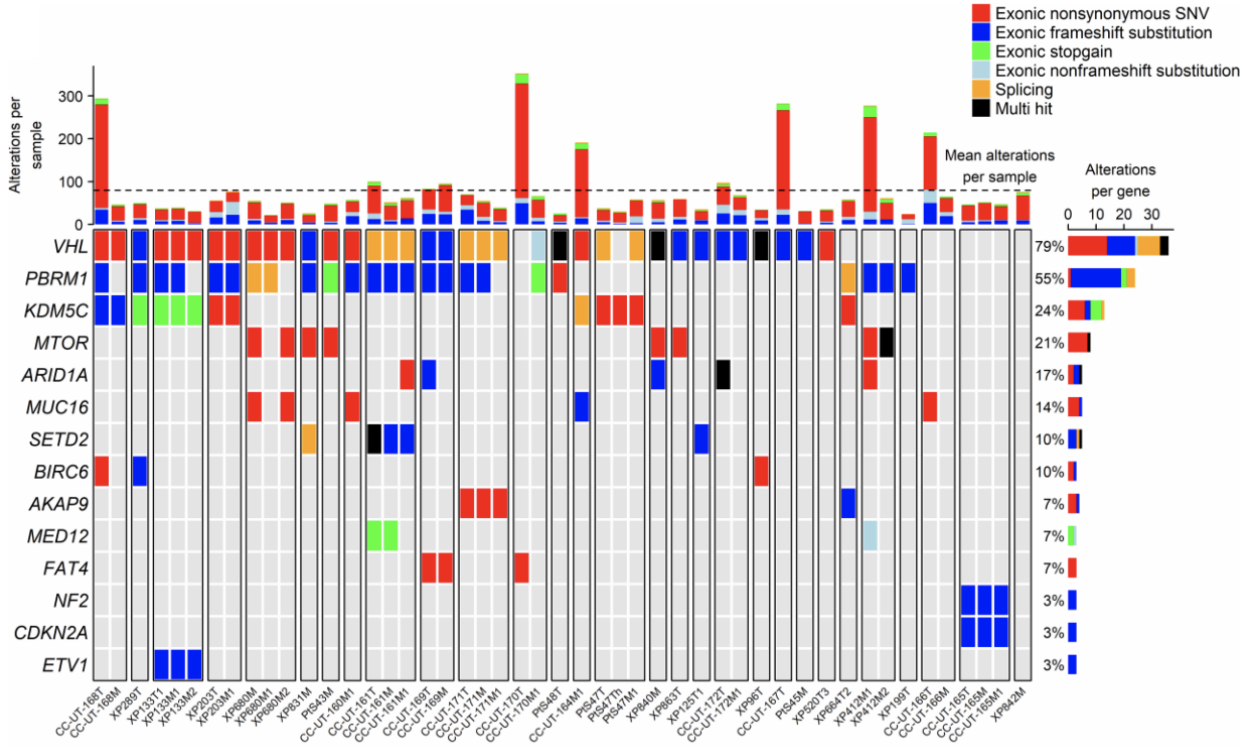
Rini BI et al, *Eur Urol*, 2020; S0302-2838(20)30450-4.
Tannir NM et al, *Clin Cancer Res*, 2020; Hwang JK et al, *Clin Cancer Res*, 2020

Pancreatic metastases: dependent on angiogenesis



- Highly vascular, looks like primary tumors

- Gene mutation panels with high proportion with loss of *VHL* and other angiogenesis pathways



Singla N et al, *JCI Insight*, 2020

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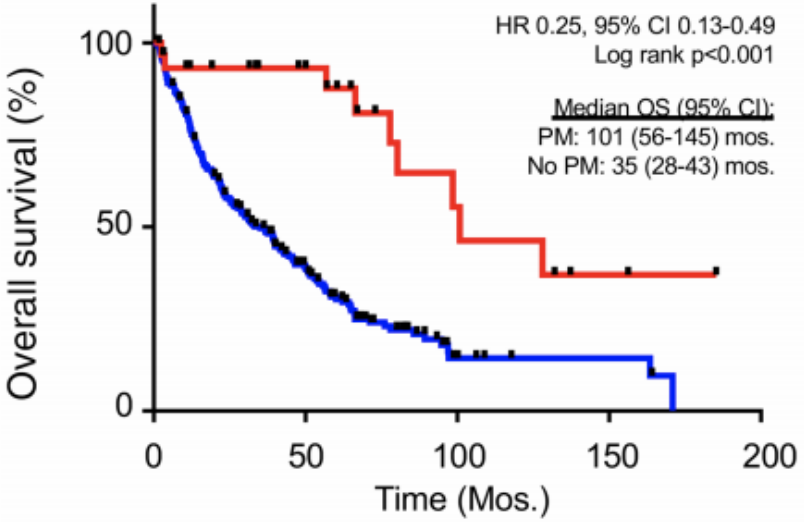
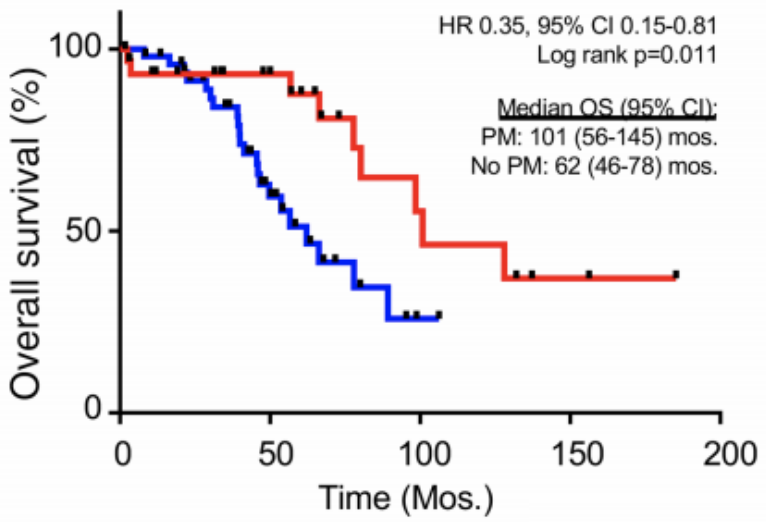
Pancreatic metastases dependent on angiogenesis, respond to VEGF-targeted treatments, not to nivolumab

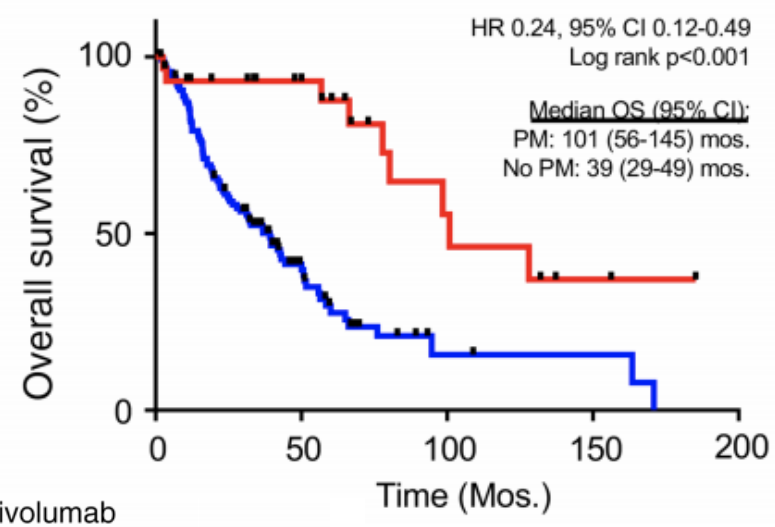
Metastatic RCC All patients



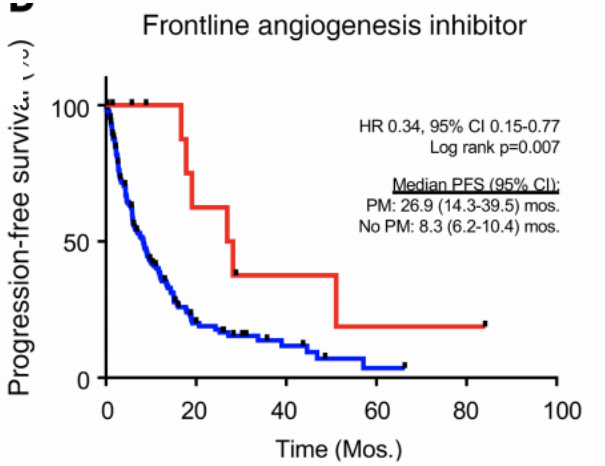
metastatic RCC IMDC favorable



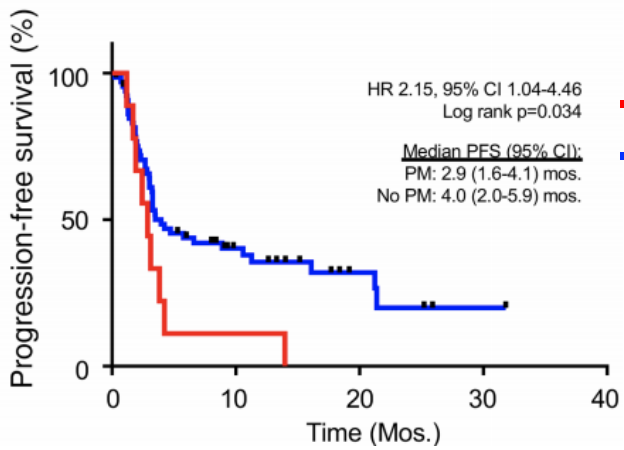
metastatic RCC IMDC intermediate/poor



Frontline angiogenesis inhibitor



Nivolumab



Pancreas mets

No pancreas mets

Singla N et al, *JCI Insight*, 2020

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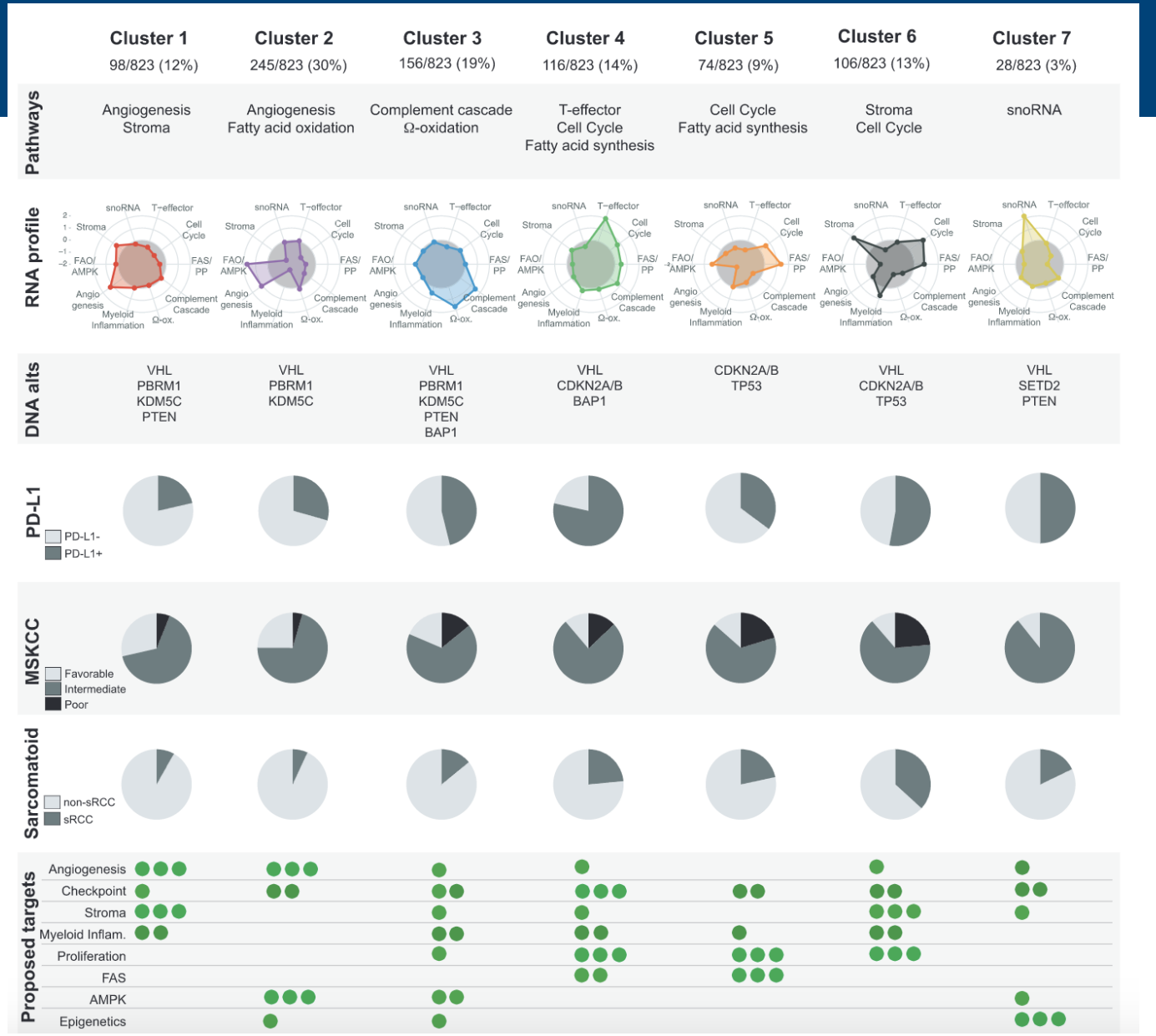
Gene expression clustering of 7 molecular subtypes from IMMotion 151 trial (atezolizumab-bevacizumab vs sunitinib)

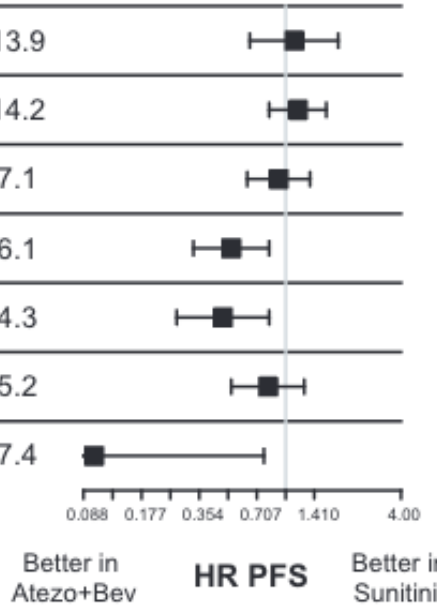


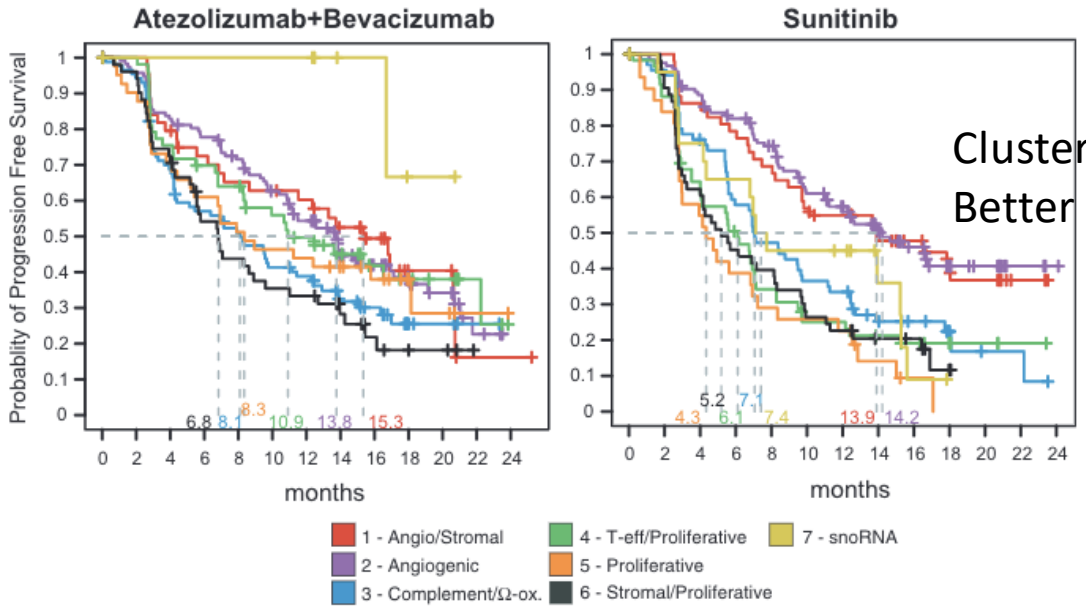
Motzer et al, *Cancer Cell*, 2020

UTSouthwestern Medical Center

Molecular clusters have differing responses to sunitinib vs atezolizumab/ bevacizumab

Cluster	PFS HR (95% CI)	p-value	A/B mPFS	Sunitinib mPFS
1 - Angio/stromal	1.11 (0.65−1.88)	0.708	15.3	13.9
2 - Angiogenic	1.16 (0.82−1.63)	0.397	13.8	14.2
3 - Complement/Ω-ox.	0.92 (0.63−1.34)	0.666	8.1	7.1
4 - T-eff/Proliferative	0.52 (0.33−0.82)	0.005	10.9	6.1
5 - Proliferative	0.47 (0.27−0.82)	0.007	8.3	4.3
6 - Stromal/Proliferative	0.81 (0.52−1.25)	0.331	6.8	5.2
7 - snoRNA	0.10 (0.01−0.77)	0.028	NR	7.4

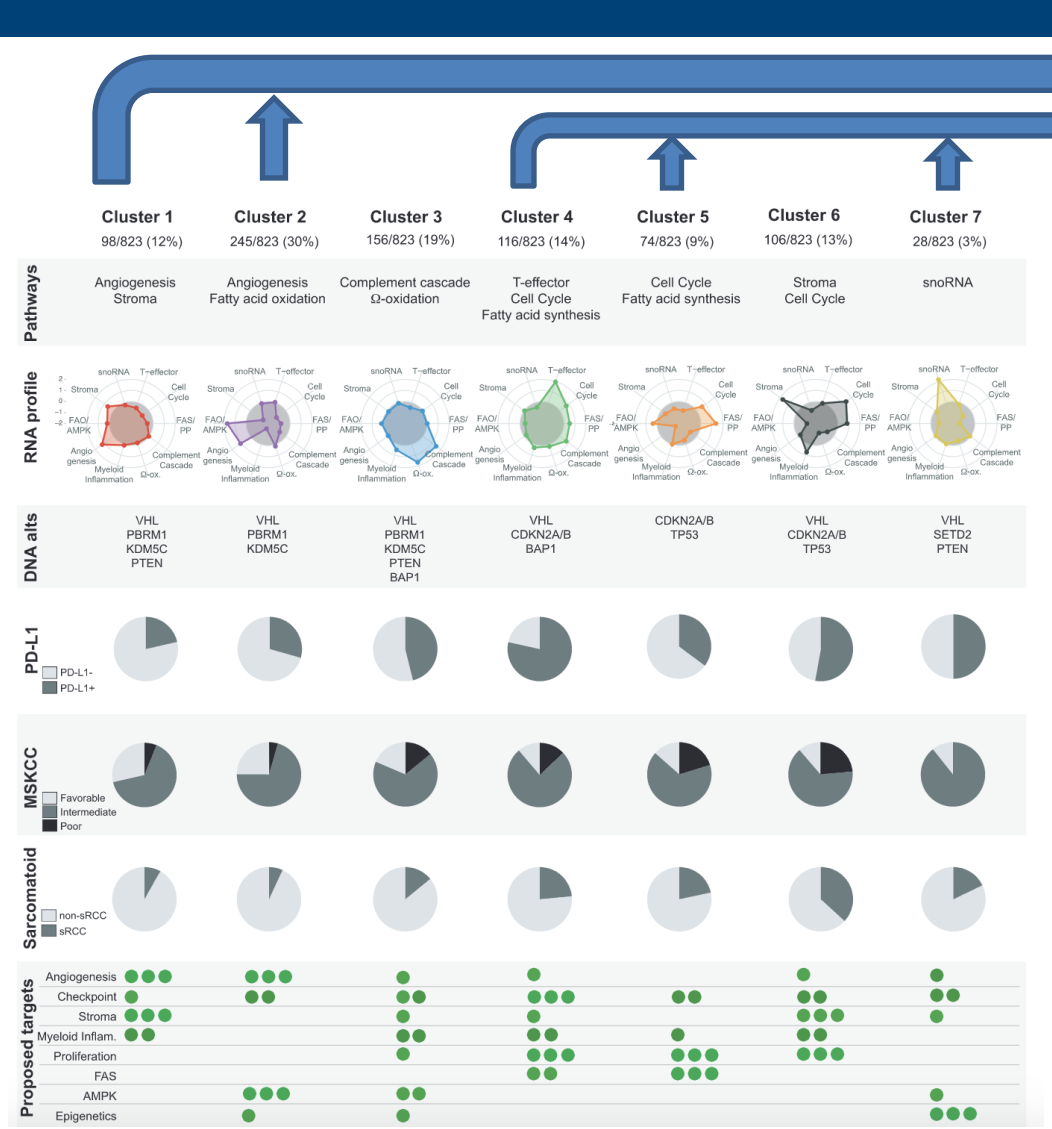




Clusters 1/2:
Better PFS with sunitinib

Motzer et al, *Cancer Cell*, 2020

Future trials with molecular selection



Proposed trial from Rini et al
Multicenter study from Vanderbilt

Need strategies for rapid gene expression testing to improve clinical utility

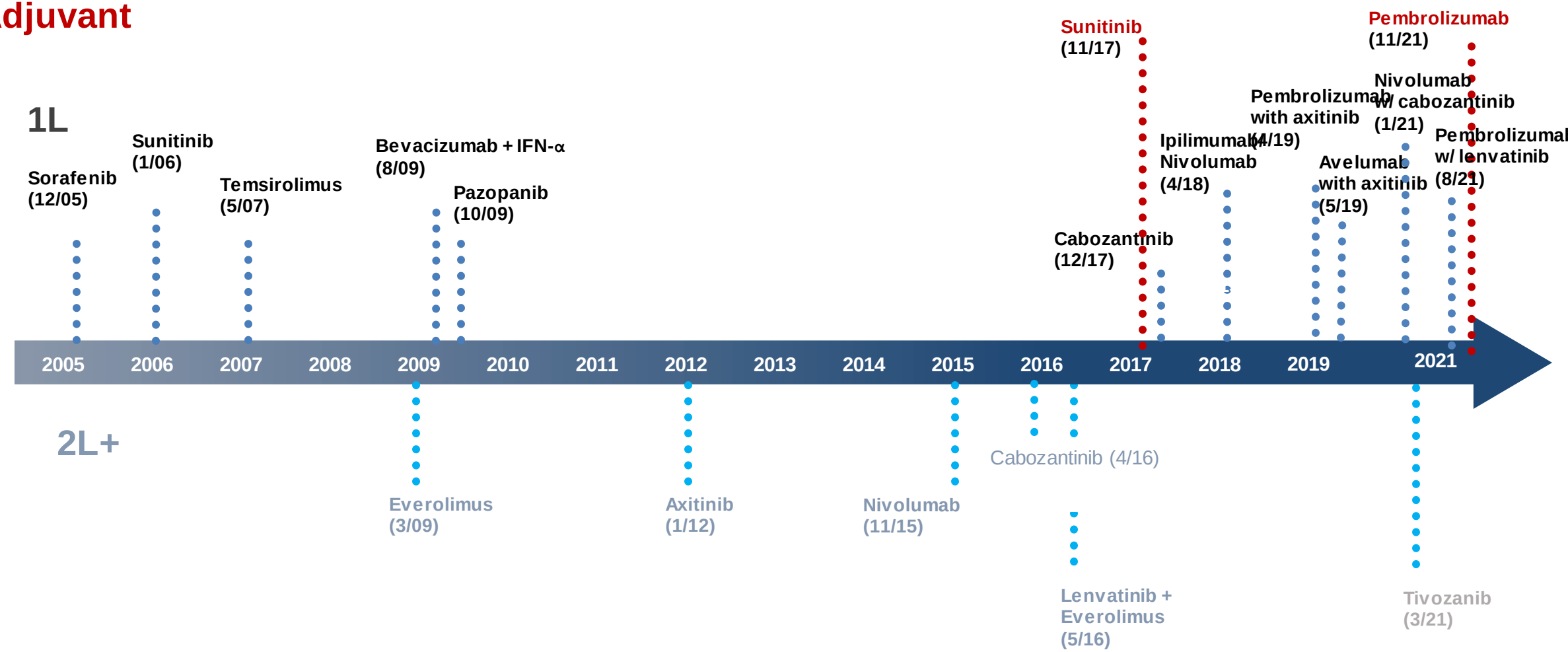
Rini BI et al, IKCS, 2021

First-line metastatic clear cell RCC treatment summary

- Overall survival benefit for ipilimumab-nivolumab, pembrolizumab-axitinib, cabozantinib-nivolumab, and lenvatinib-pembrolizumab
  - No head-to-head trial of VEGF-IO combinations versus ipilimumab-nivolumab
  - Better outcomes of VEGF-IOs vs sunitinib in favorable risk disease
- Treatment selection depends on patient in front of us:
  - IMDC status
  - Prior nephrectomy?
  - Bone metastases?
  - Symptomatic disease?
  - Burden of metastatic disease?
  - Goals of treatment?
- Opportunities in molecular patient selection and treatment sequencing

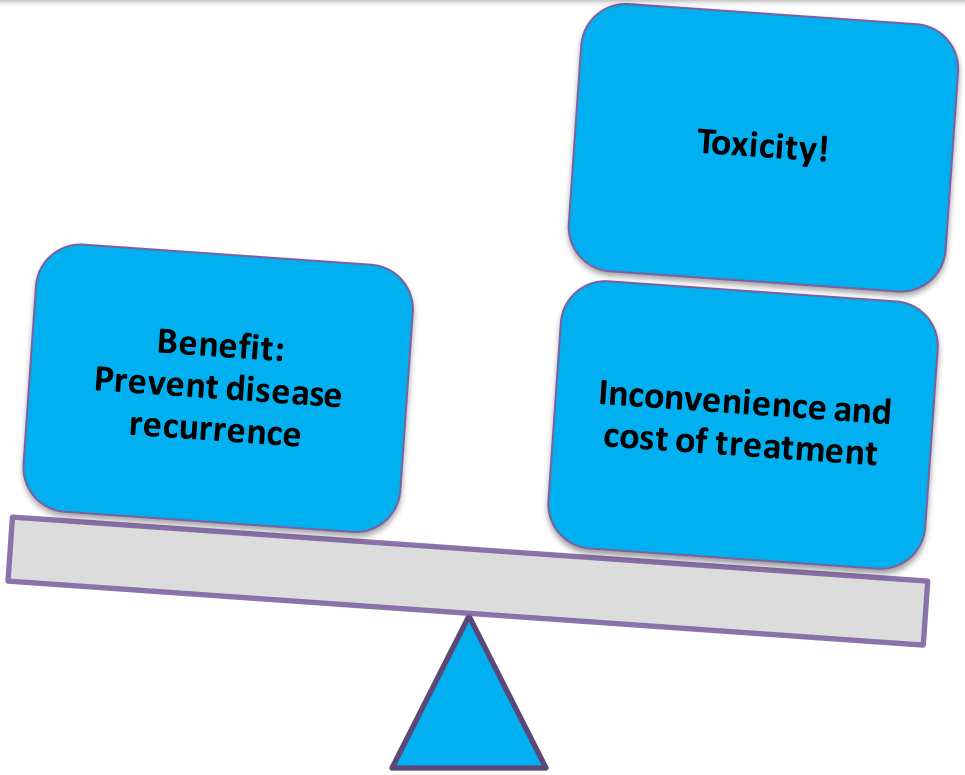
Timeline of US FDA approved therapies

Adjuvant



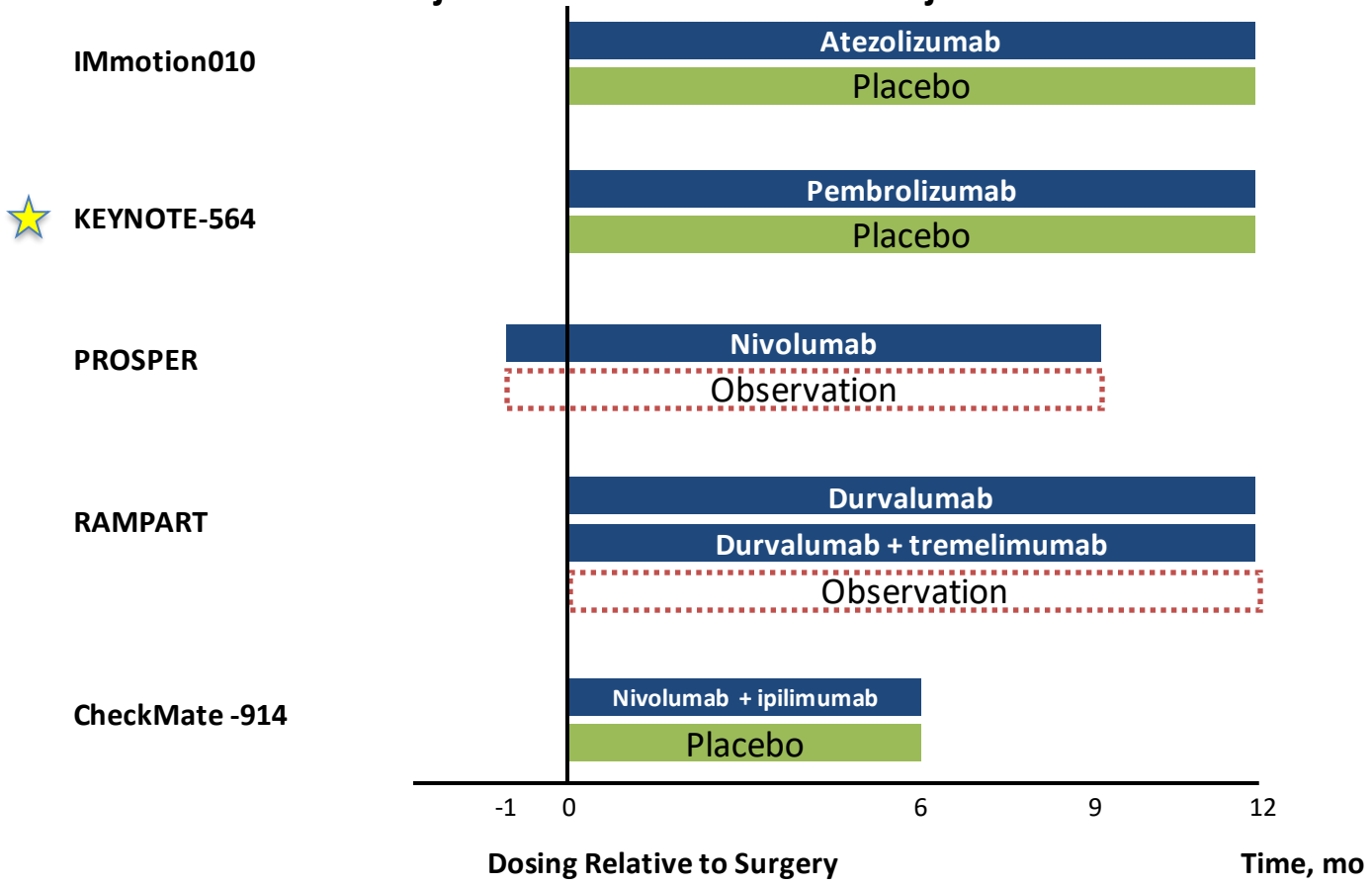
Balancing Risk/Benefit: Sunitinib in the Adjuvant Setting

November 16, 2017: FDA approved 1 year of sunitinib in the adjuvant setting
Not used often in clinical care because toxicity outweighs potential benefit



If/when recommended, adjuvant sunitinib likely more for younger patients with a high anxiety about disease recurrence and a high threshold for toxicity

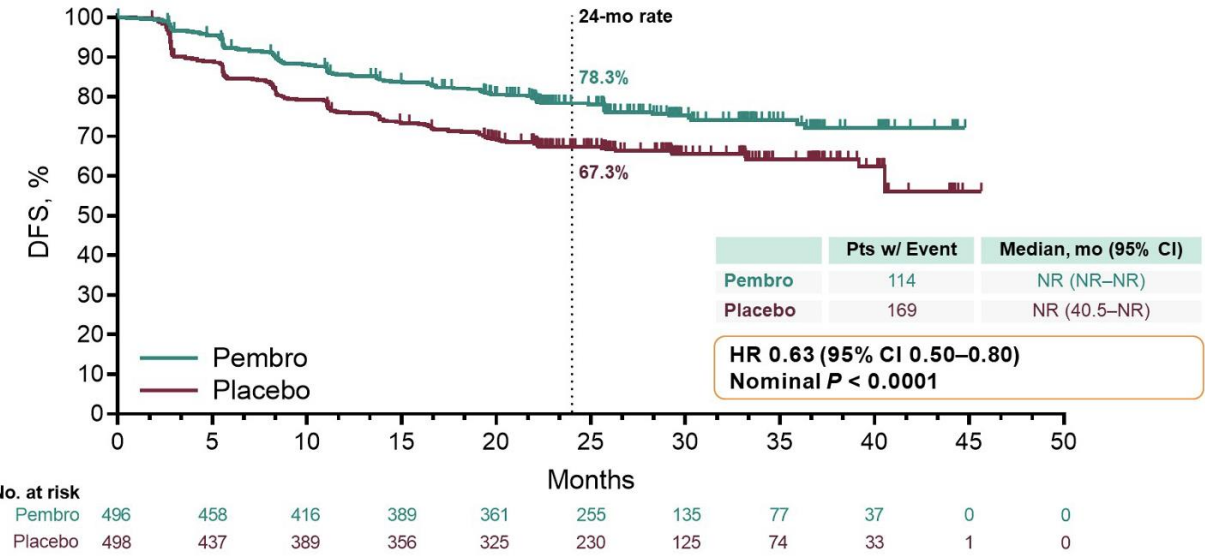
Completed and Ongoing Phase 3 Adjuvant Trials With Immune Checkpoint Inhibitors



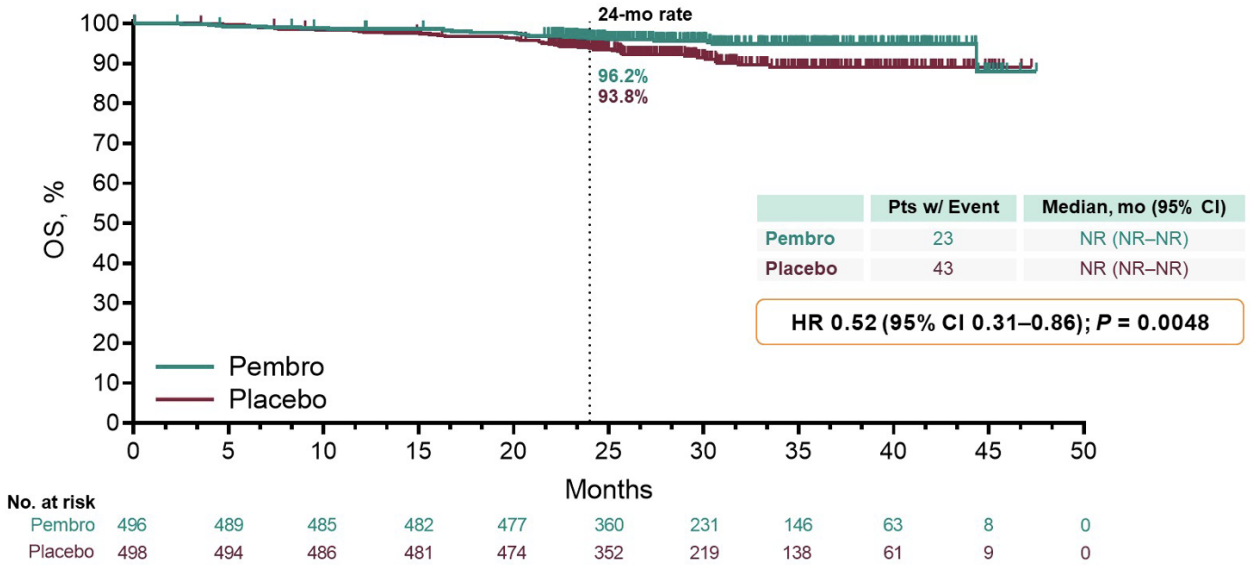
	Eligible Histology	Primary Endpoint	Enrollment
IMmotion010	ccRCC	DFS	778 (actual)
★ KEYNOTE-564	ccRCC	DFS	994 (actual)
PROSPER	ccRCC, nccRCC	EFS	766 (estimated)
RAMPART	ccRCC, nccRCC	DFS, OS	1,750 (estimated)
CheckMate -914	ccRCC	DFS	1,600 (estimated)

Phase 3 KEYNOTE-564 – 30-month follow up

Disease free survival



Overall Survival



- With a median follow-up of 24 months, the primary endpoint of DFS was met; ongoing DFS benefit at 30-mo follow up (HR 0.63; GU ASCO 2022)
- Not enough events for OS - Additional follow-up planned for key secondary endpoint of OS
- Safety results as expected for immune checkpoint inhibitors, and no new safety signals were observed
- No clinically meaningful changes from baseline in HRQOL or symptom scores were observed

Choueiri TK et al, GU ASCO 2022

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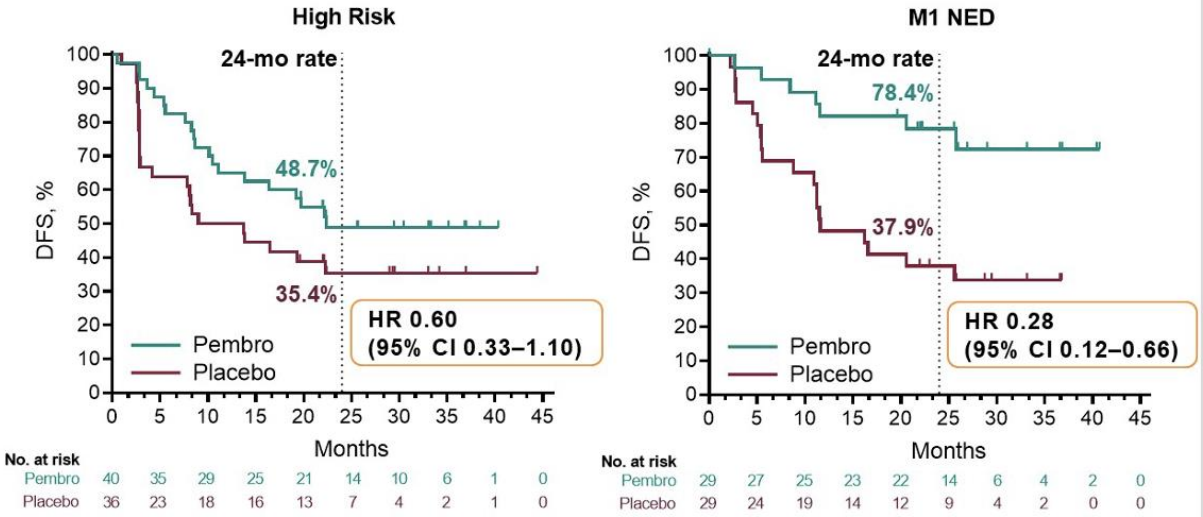
Keynote 564: pre-specified subsets with DFS benefit

Disease free survival

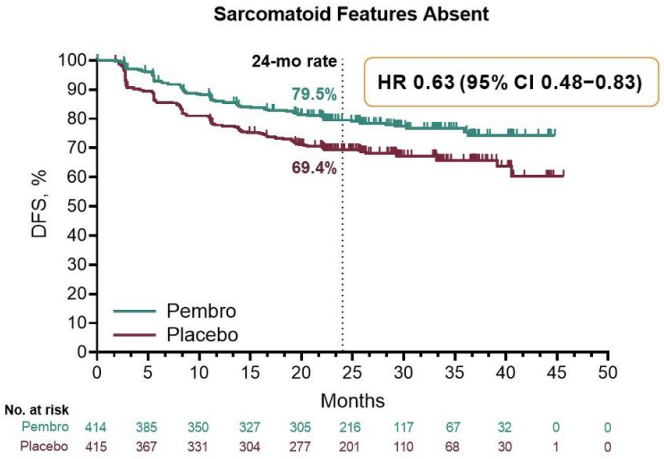


	Pts w/ Event	Median, mo (95% CI)
Pembro	20	22.4 (11.1–NR)
Placebo	23	11.4 (2.9–NR)

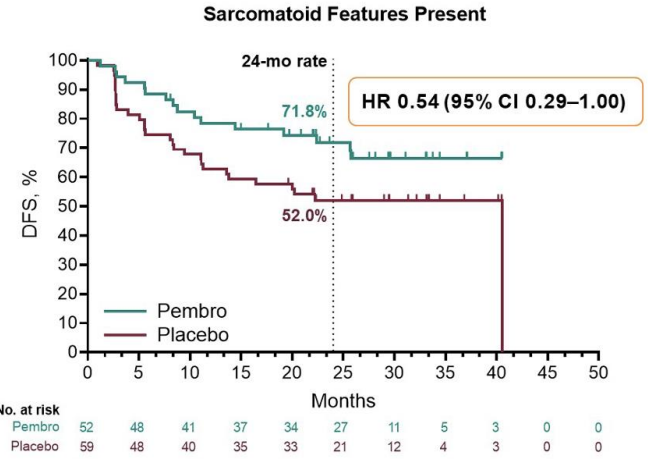
	Pts w/ Event	Median, mo (95% CI)
Pembro	7	NR (25.7–NR)
Placebo	19	11.6 (5.6–NR)

High risk: pT4, any grade, N0, M0 or any T/grade, N+, M0
M1 NED: s/p metastasectomy within 1 year nephrectomy

Sarcomatoid features – smaller group overall
Disease free survival



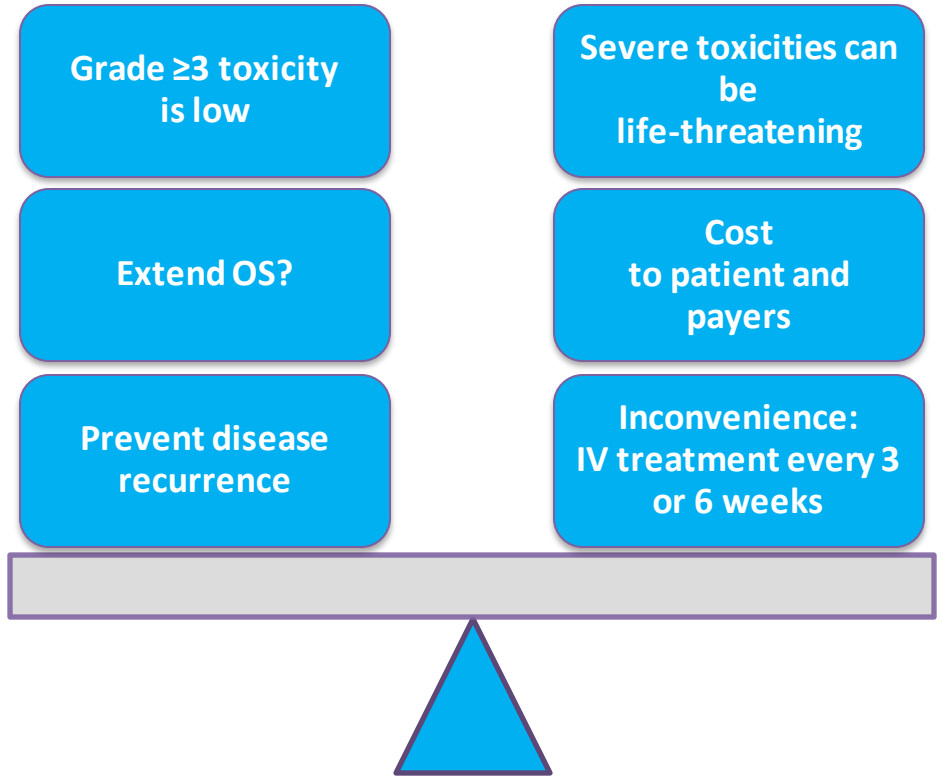
	Pts w/ Event	Median, mo (95% CI)
Pembro	88	NR (NR–NR)
Placebo	133	NR (NR–NR)



	Pts w/ Event	Median, mo (95% CI)
Pembro	16	NR (NR–NR)
Placebo	29	40.5 (11.3–NR)

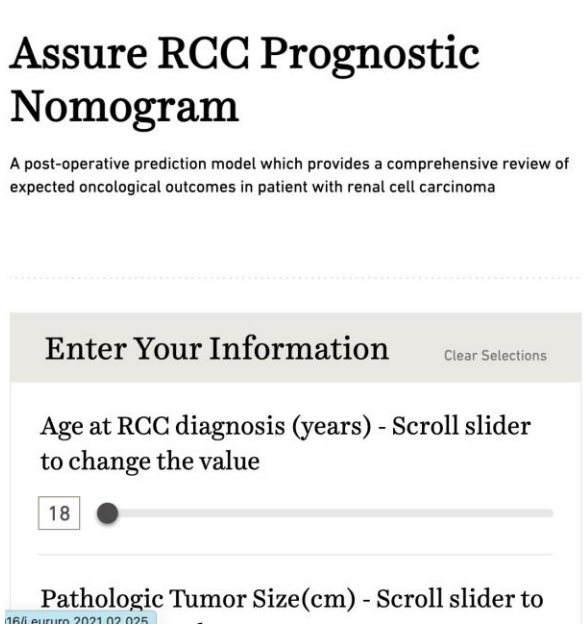
Balancing Risk/Benefit: Pembrolizumab in the Adjuvant Setting

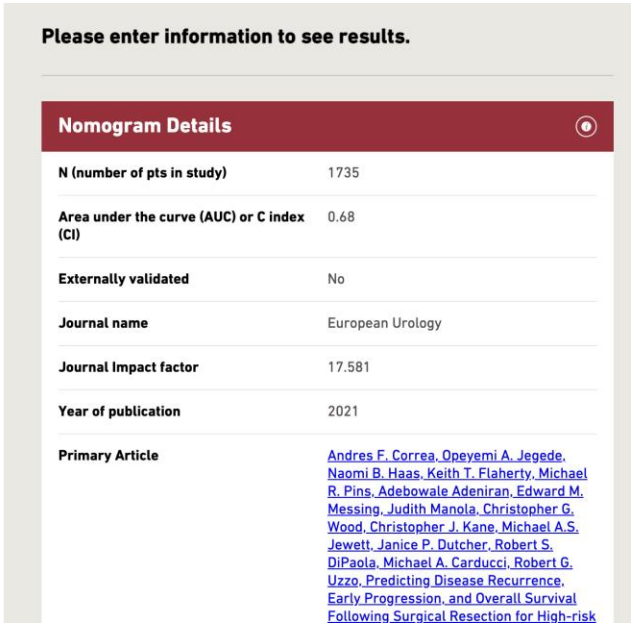
November 17, 2021: FDA approved pembrolizumab for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions

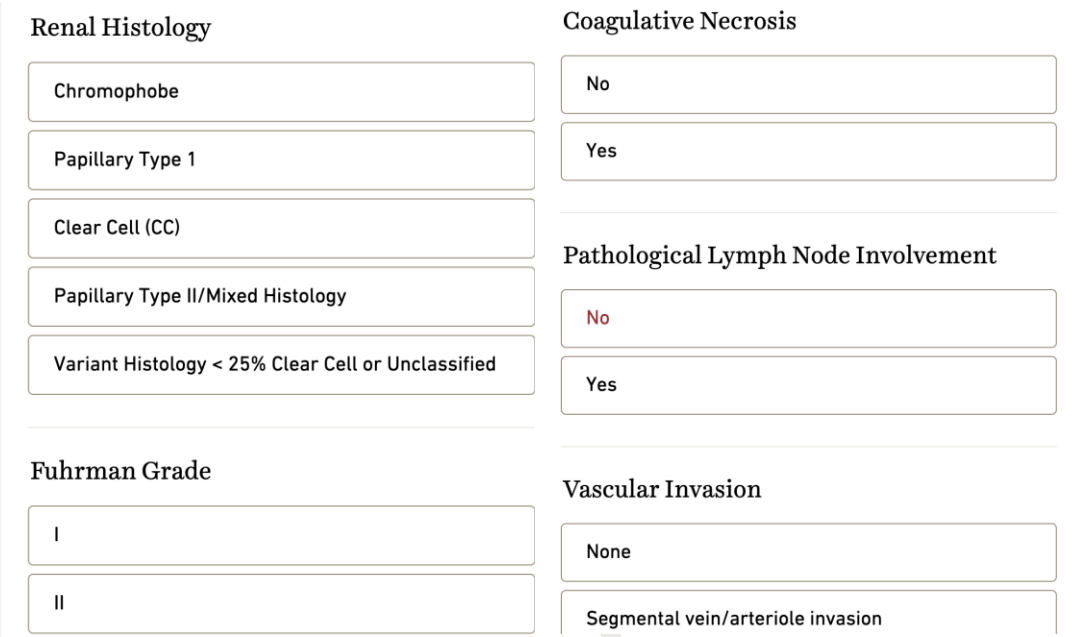


Depends on patient preferences/priorities, tolerance for toxicity, and goals for treatment—shared decision-making

Recurrence prediction: ASSURE nomogram

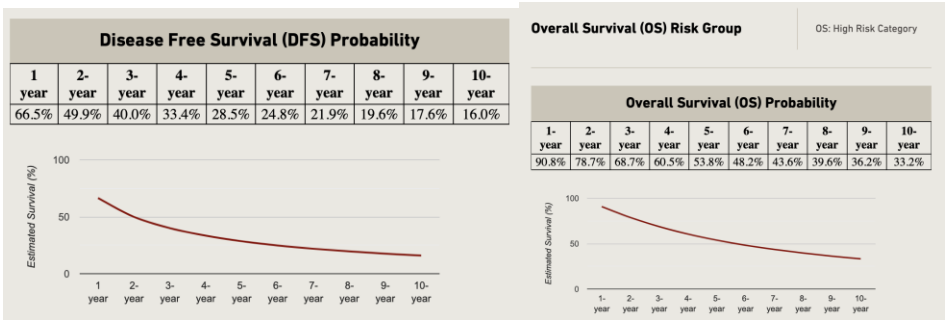






Main features:

Age	Necrosis
Tumor size	LN involvement
Histology	Vascular invasion
Grade	Sarcomatoid features



Output:
Landmark disease free survival & overall survival (1-10yr) rates

https://studies.fccc.edu/nomograms/492

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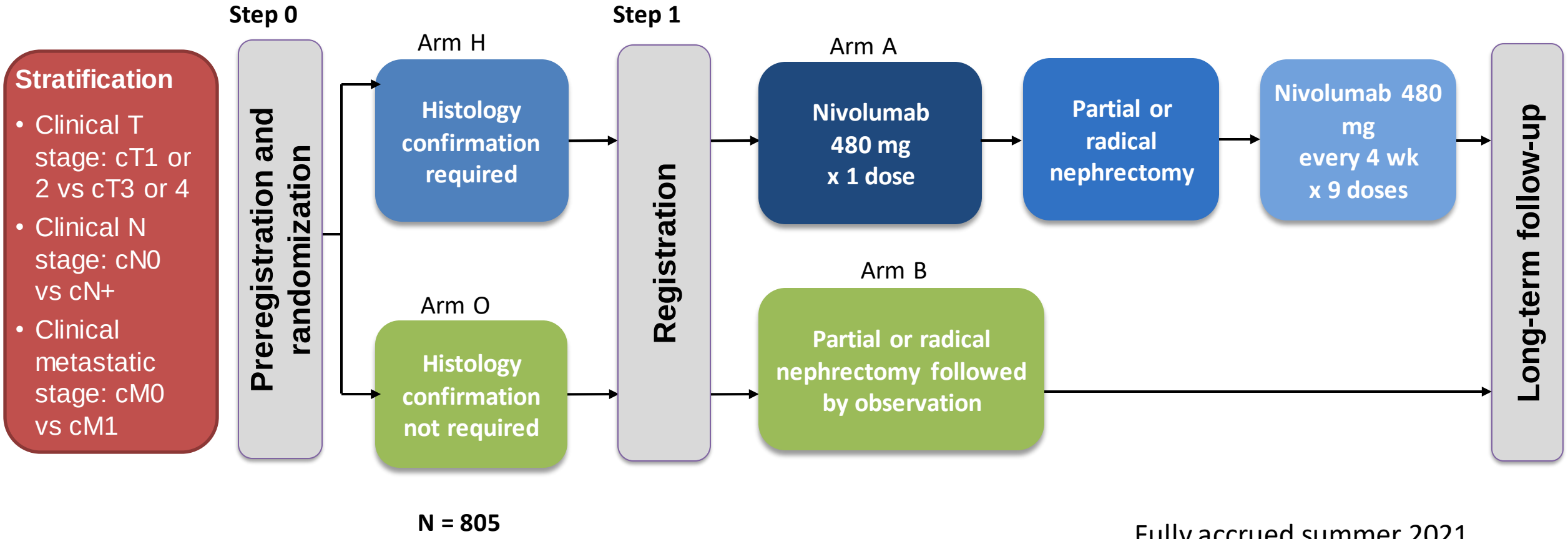
Completed accrual: PROSPER Study



Fully accrued summer 2021

Allaf ME et al. ASCO 2021. Abstract TPS4596

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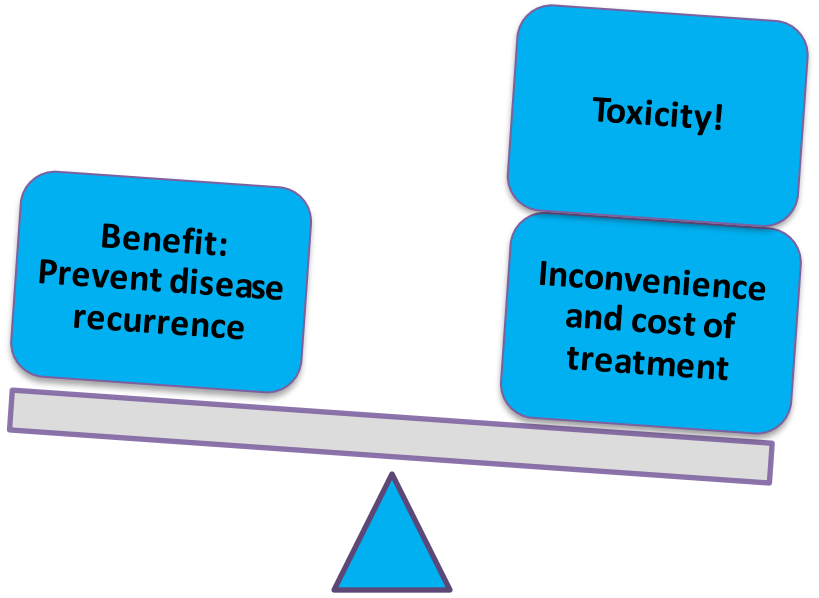
Adjuvant clear cell RCC takeaways

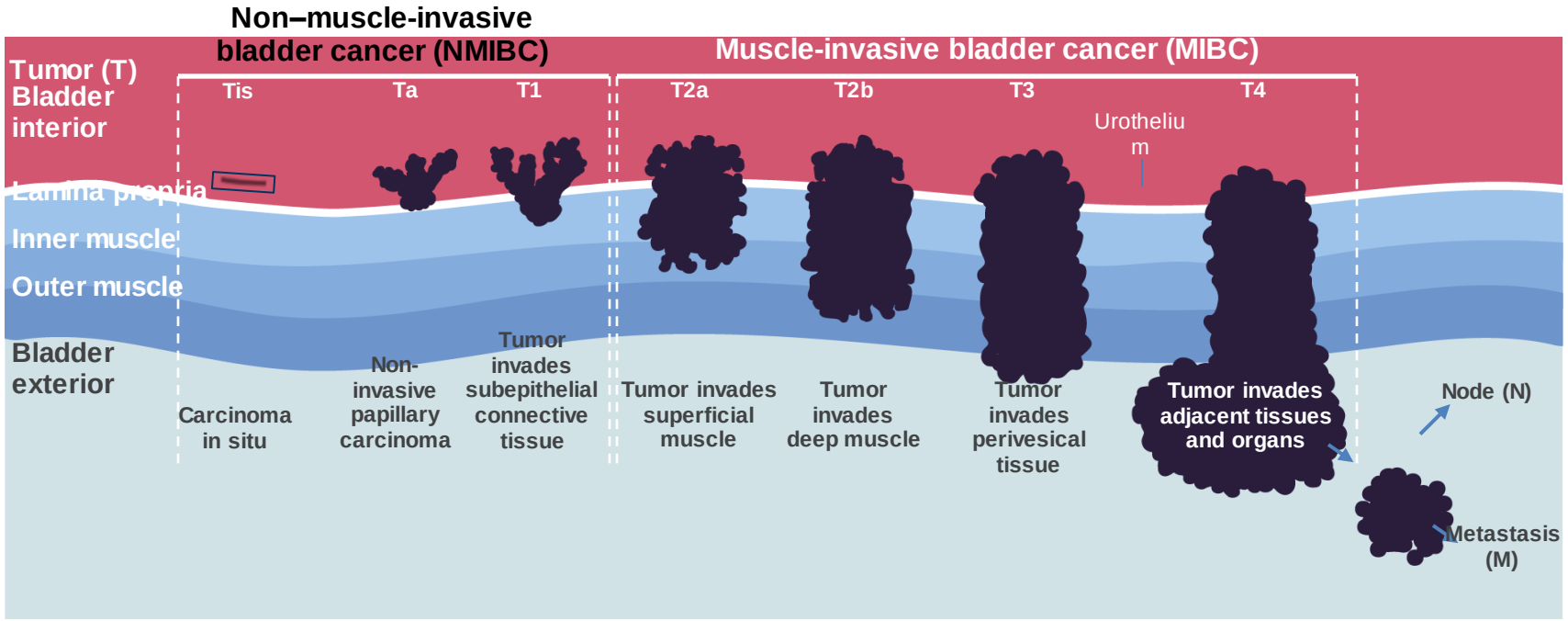
- Pembrolizumab now approved as adjuvant option with tolerable toxicity profile
- Balancing risks of toxicities with decreasing recurrence risk
- Depends on patient in front of us:
    - Pathologic features at time of nephrectomy, risk of recurrence
    - Discussion point whether benefit is meaningful for that patient



Outline

- Renal cell carcinoma
  - Combining immunotherapy and anti-angiogenic agents
  - Adjuvant and first-line metastatic treatment landscape
- Urothelial cancer
  - Immunotherapy, targeted therapies, antibody drug conjugates
  - Toxicities

Urothelial cancer staging and prognosis



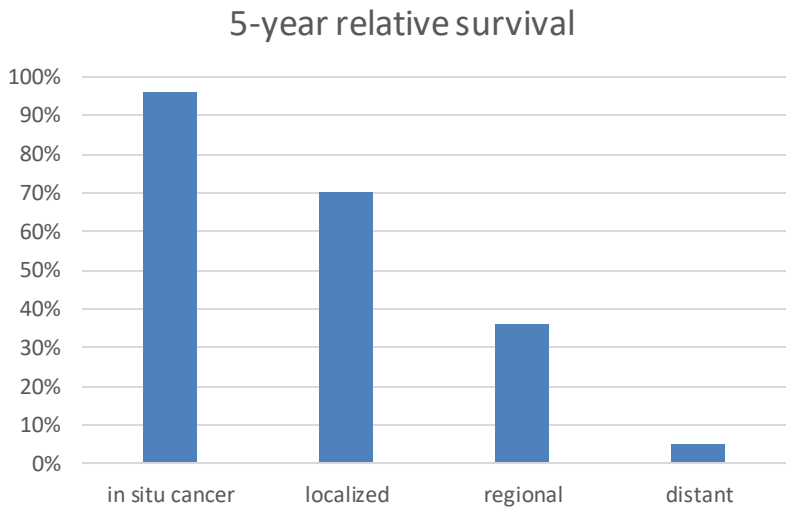


Image: Adapted from Macmillan Publishers Ltd: Knowles MA, Hurst CD. *Nat Rev Cancer*. 2015;15(1):25-41. ©2017.

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Treatment landscape for metastatic urothelial cancer: July 2014

Platinum-based chemotherapy

MVAC

Gem/cis

Gem/carbo

Refractory chemotherapy

Paclitaxel

Docetaxel

Pemetrexed

Clinical trials:

Immune checkpoint inhibitors

Enfortumab vedotin

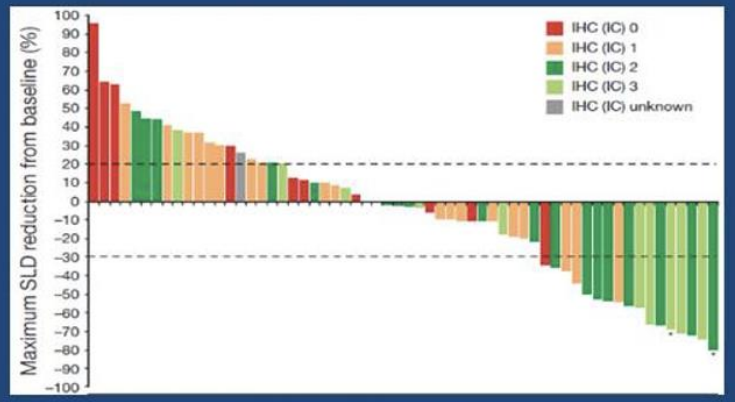
Sacituzumab govitecan

Novel targets, immunomodulating agents

Zhang T, adapted from discussion, ASCO Annual Meeting, 2020

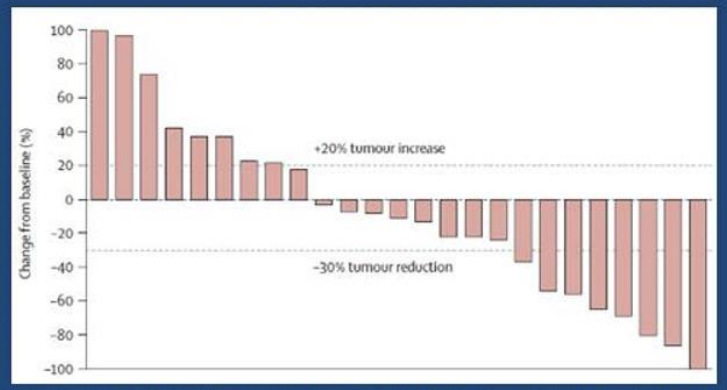
Phase 1/2 PD-1 inhibitors

Atezolizumab



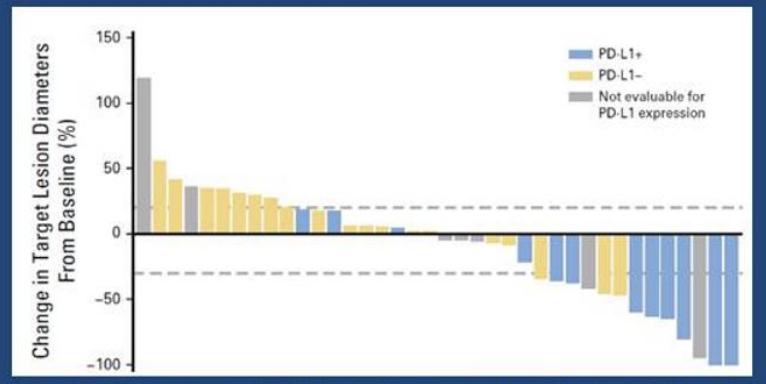
Powles T et al., Nature. 2014;515:558-562.

Pembrolizumab



Plimack ER, et al. Lancet Oncol 2017 Feb;18(2):212-220

Avelumab

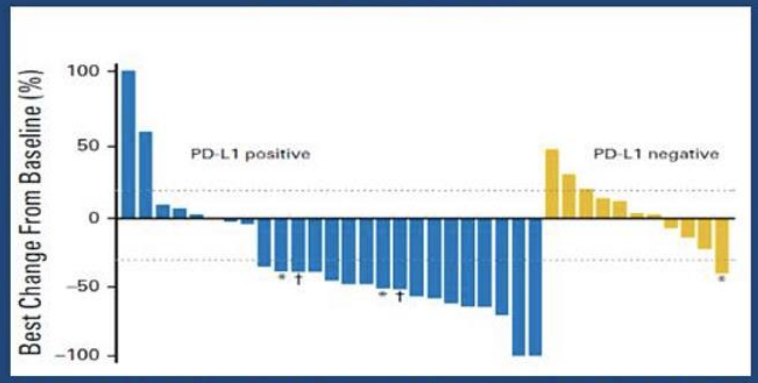


Apolo, AB., et al. (2017) J Clin Oncol 1;35(19):2117-2124

Nivolumab

Sharma, P., et al. (2016). Lancet Oncol 17: 1590-1598

Durvalumab



Massard, C., et al. (2016). J Clin Oncol 34(26):3119-25

Pivotal trials Immune checkpoint inhibitors

- Urothelial cancer
- Measurable metastatic disease, by RECIST criteria
- Prior platinum-based chemotherapy
- Good performance status
- Archival tissue available

Stratification factors:
IMDC criteria
(favorable, intermediate, poor)
Region (US vs outside US)
Performance status

RANDOMIZATION

Common control cohort in all trials → Chemotherapy

Keynote 045, phase 3
n= 542 → Pembrolizumab 200mg IV q3 weeks

IMVigor 211, phase 3
n= 931 → Atezolizumab 1200mg IV q3 weeks

Checkmate 275, phase 3
n= 270 → Nivolumab 3mg/kg IV q2 weeks

DANUBE, phase 3
n= 1032 → Durvalumab 10mg/kg IV q2 weeks
Durvalumab with temelimumab

Javelin, Phase 2
n= 44 → Avelumab 10mg/kg IV q2 weeks

Treat until disease progression or unacceptable toxicity

Primary endpoints:
Overall survival
Progression free survival

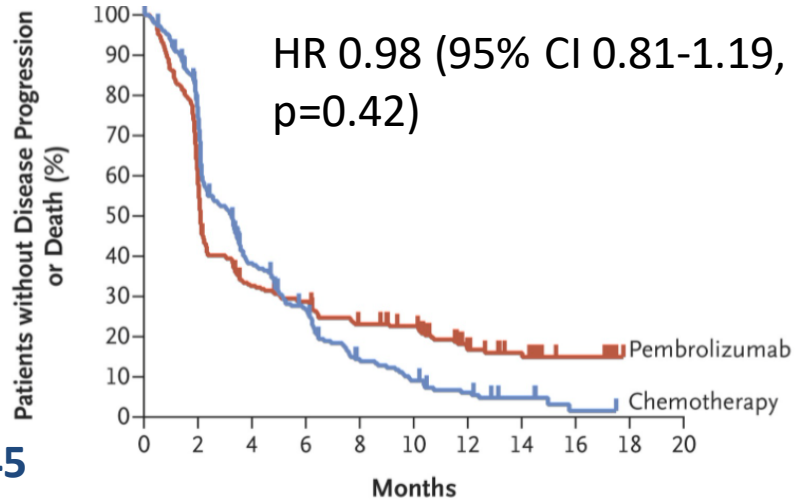
Secondary endpoints:
Objective response rates
Duration of responses
Patient-reported quality of life
Safety of combinations

Bellmunt J et al, *NEJM*, 2017
Powles T et al, *Lancet*, 2017
Sharma P et al, *Lancet Oncol*, 2017
Powles T et al, *JAMA Oncol*, 2017
Apolo AB et al, JCO, 2017

Phase 3 Immune checkpoint inhibitors

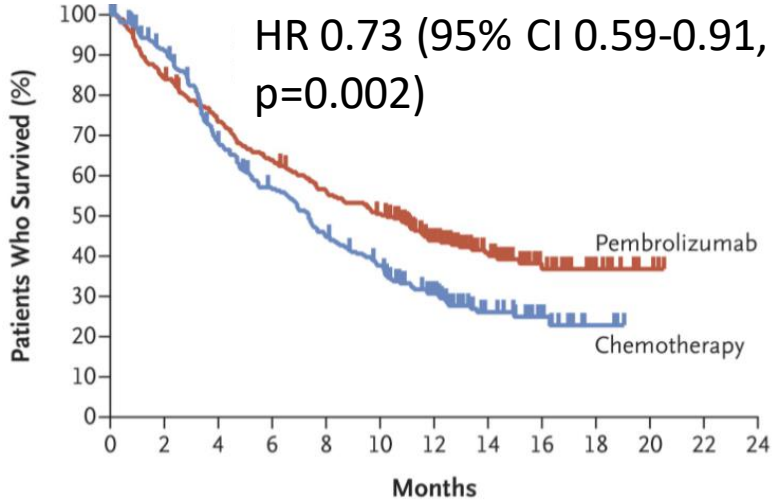
Keynote 045
Pembro v chemo

Progression Free Survival



HR 0.98 (95% CI 0.81-1.19, p=0.42)

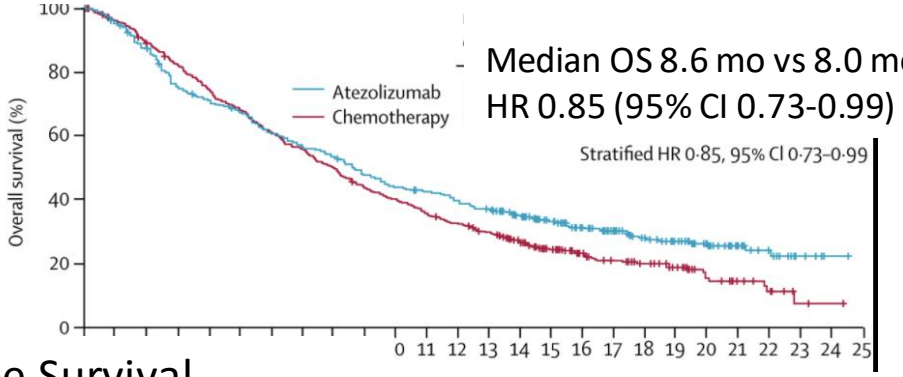
Overall survival



HR 0.73 (95% CI 0.59-0.91, p=0.002)

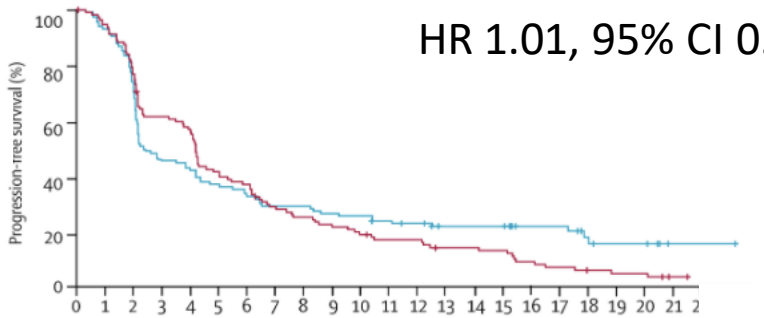
IMVigor 211
Atezolizumab vs chemo

Overall survival



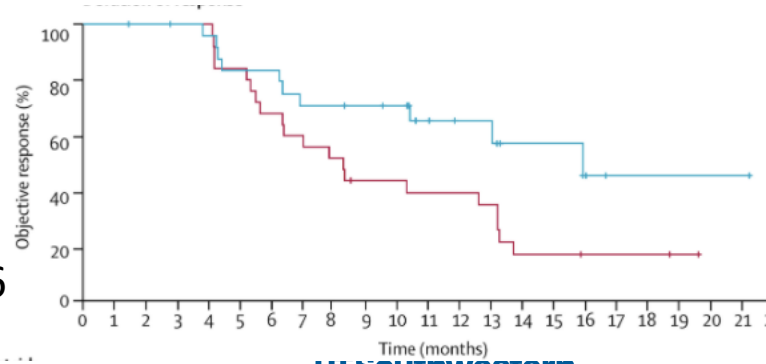
Median OS 8.6 mo vs 8.0 mo
HR 0.85 (95% CI 0.73-0.99)

Progression Free Survival



HR 1.01, 95% CI 0.75-1.34

Duration of responses



mDOR 15.9mo vs 8.3 mo
HR 0.57, 95% CI 0.26-1.26

Bellmunt J et al, *NEJM*, 2017

Powles T et al, *Lancet*, 2017

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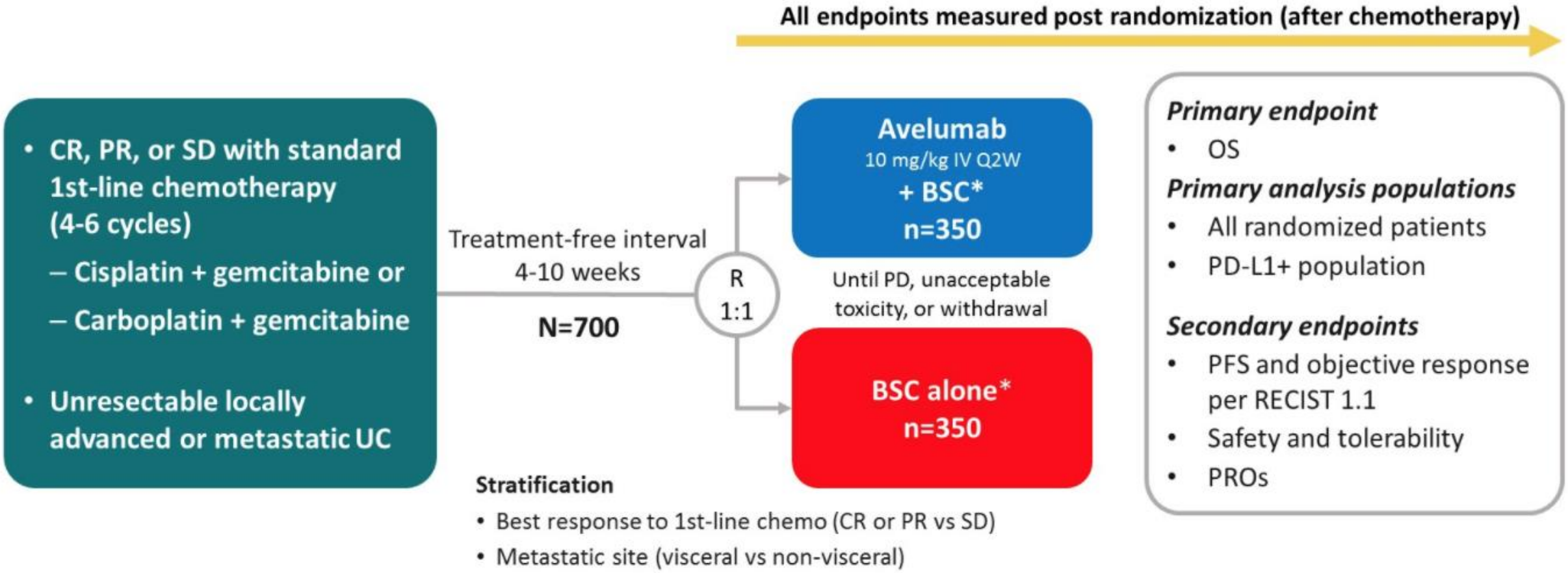
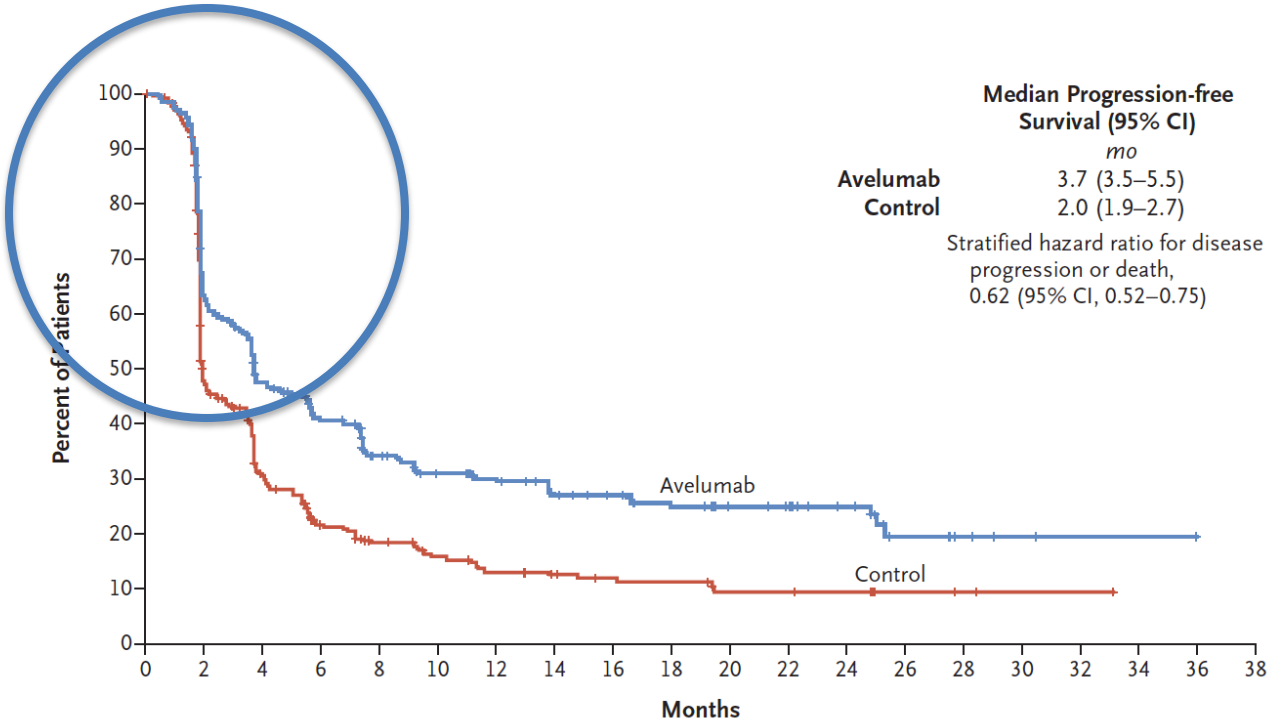
Maintenance avelumab for mUC



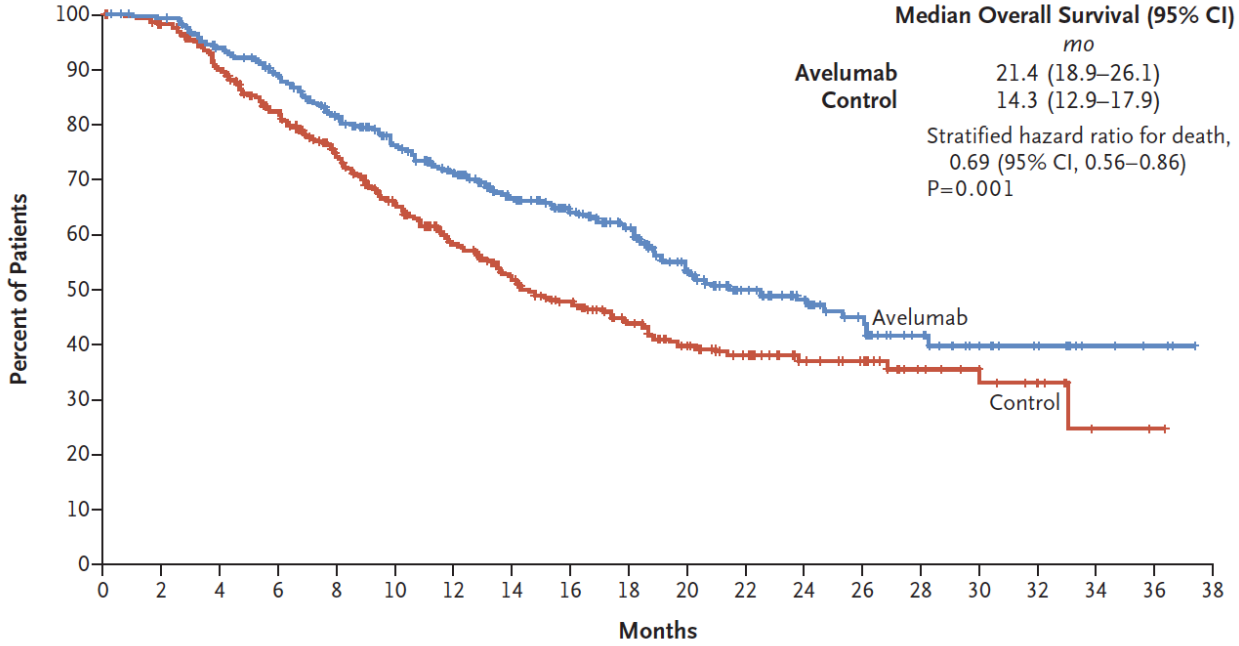
Powles T et al, *NEJM*, 2020

Maintenance avelumab for mUC

Progression free survival



Overall survival



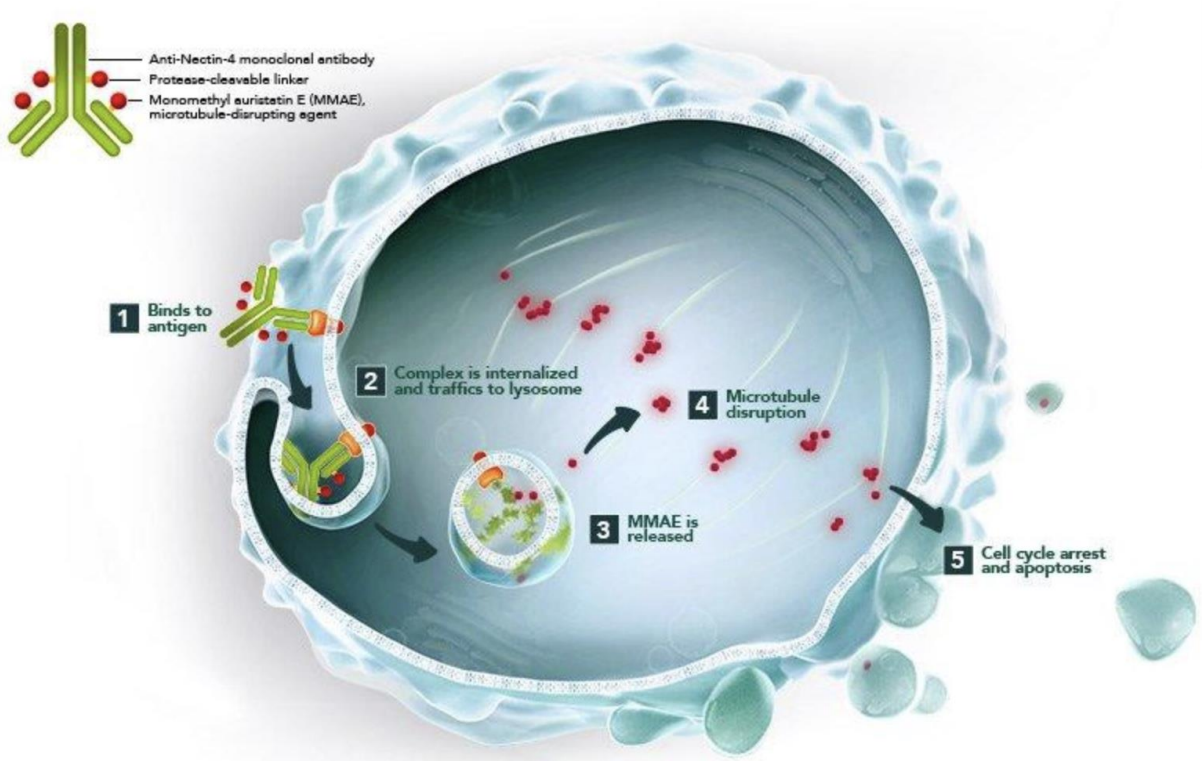
Powles T et al, *NEJM*, 2020

Antibody drug conjugates (ADCs) in mUC

Enfortumab vedotin

Target: Nectin 4

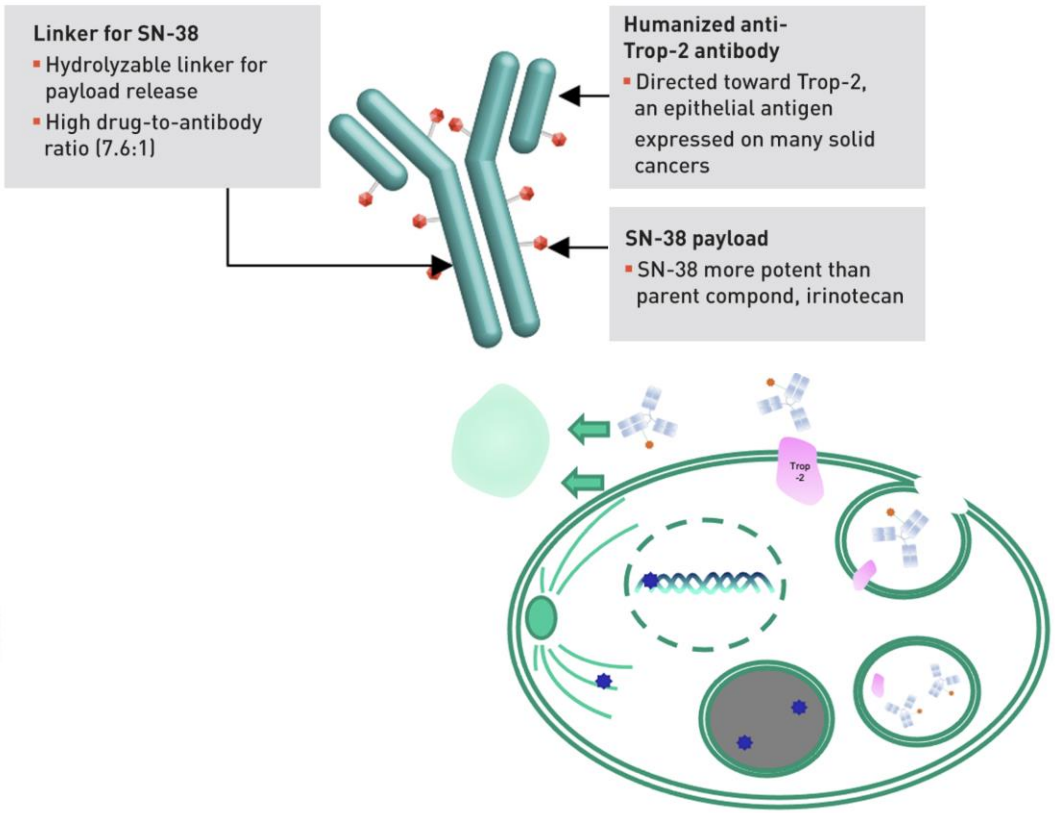
Payload: MMAE – microtubule disrupter



Sacituzumab govitecan

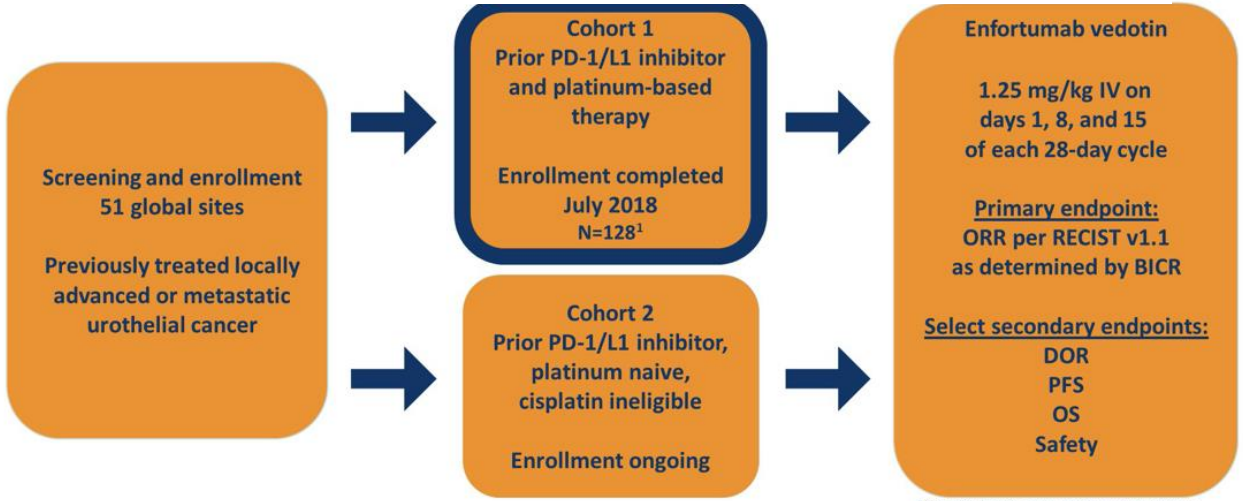
Target: Trop 2

Payload: SN38



Enfortumab vedotin for mUC post-platinum & post- checkpoint inhibitor

EV-201: Single-arm, 2-cohort Phase 2 trial



[1] 3 patients did not receive enfortumab vedotin treatment: one each due to clinical deterioration, patient decision, and low hemoglobin after enrollment

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

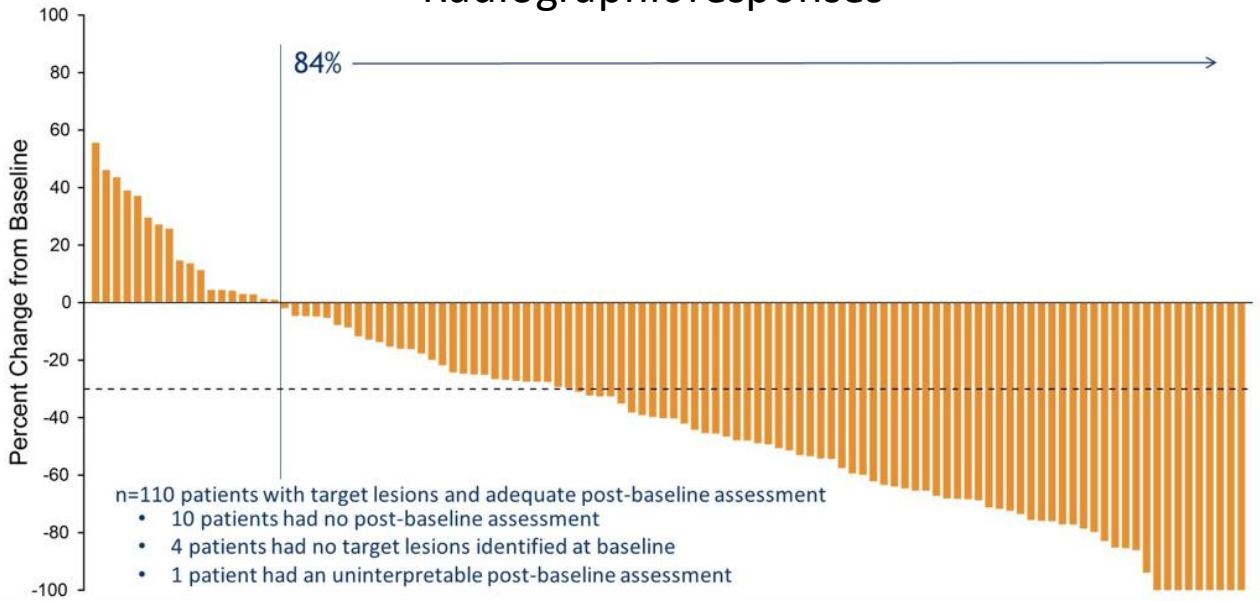
Patient characteristics

	Patients (N=125)
Male sex, n (%)	88 (70)
Age, years	
Median (min, max)	69 (40, 84)
≥75 years, n (%)	34 (27)
ECOG PS of 1, n (%)	85 (68)
Primary tumor location, n (%)	
Bladder/other	81 (65)
Upper tract	44 (35)
Number of prior systemic therapies[1], median (range)	3 (1, 6)
≥2 Bellmunt adverse prognostic factors	52 (42)
Metastasis sites, n (%)	
Lymph nodes only	13 (10)
Visceral disease	112 (90)
Liver	50 (40)
PD-L1 status by combined positive score[2]	
<10	78/120 (65)
≥10	42/120 (35)

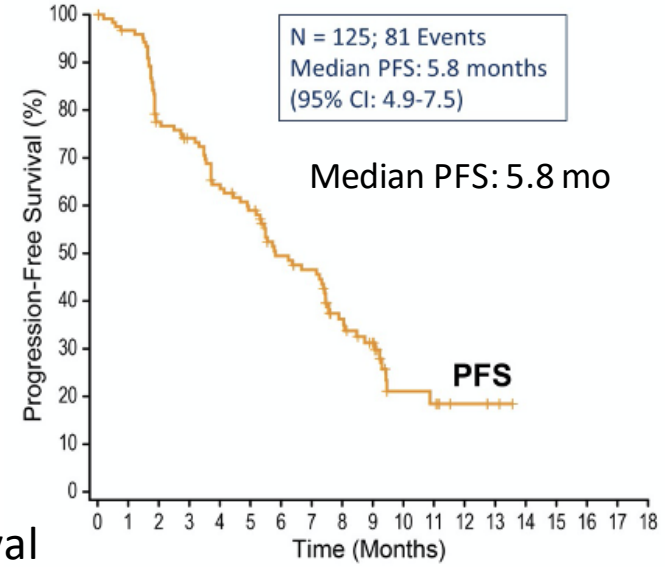
Rosenberg JE, *J Clin Oncol*, 2019

Enfortumab vedotin for mUC post-platinum

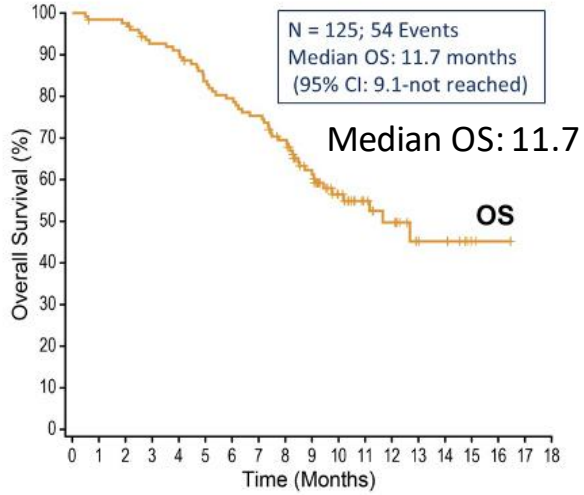
Radiographic responses



Progression free survival

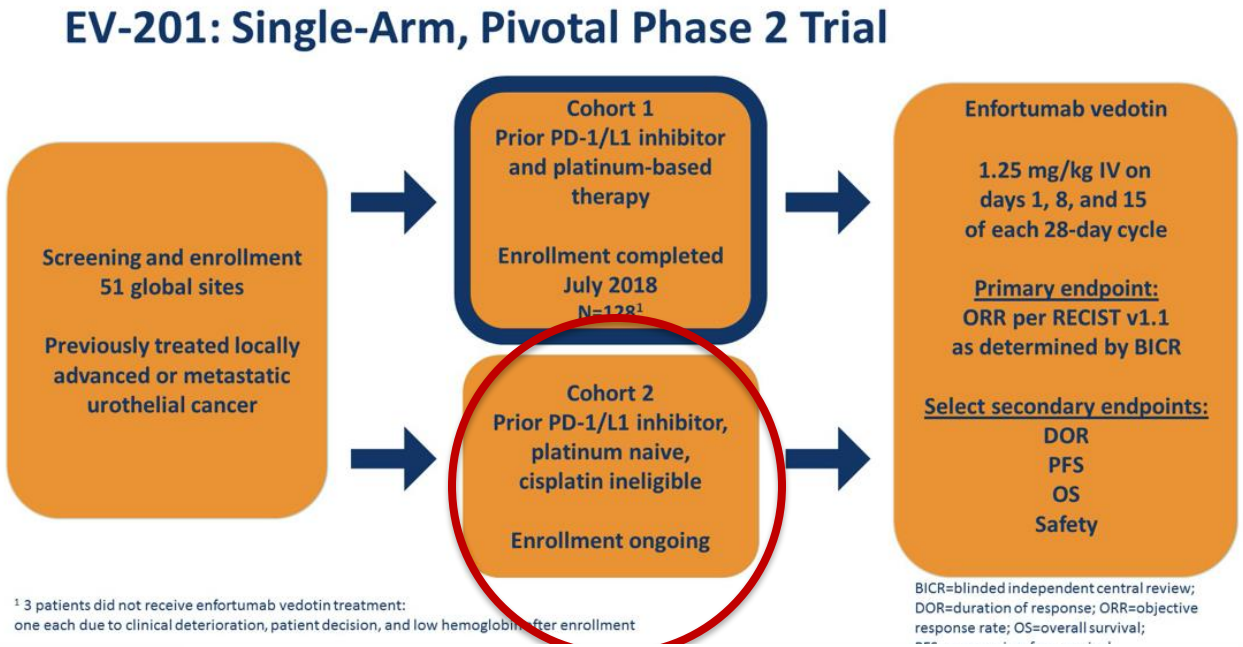


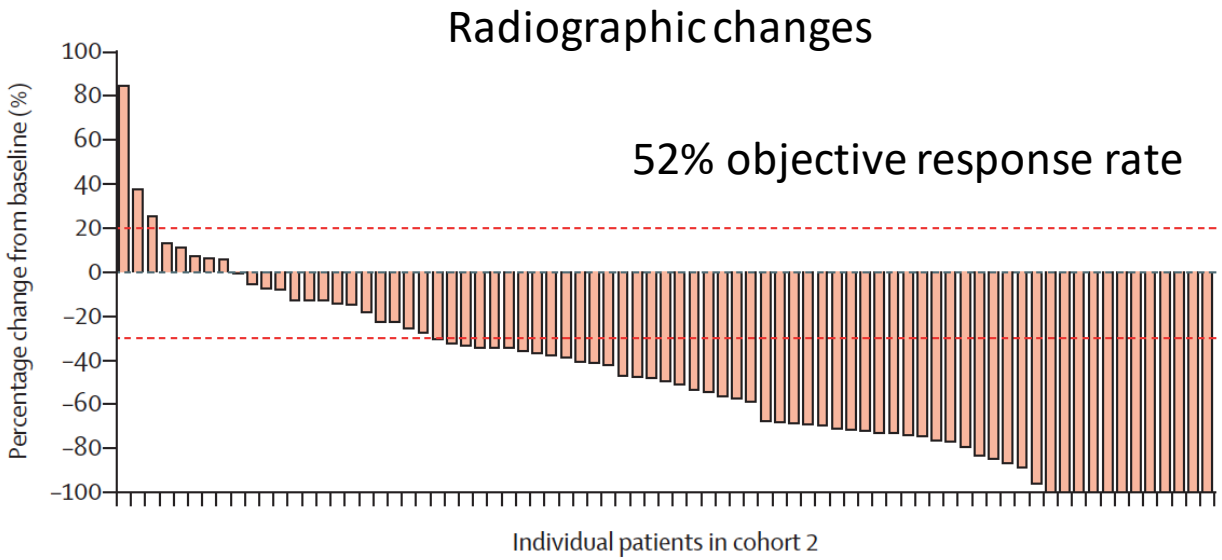
Overall Survival

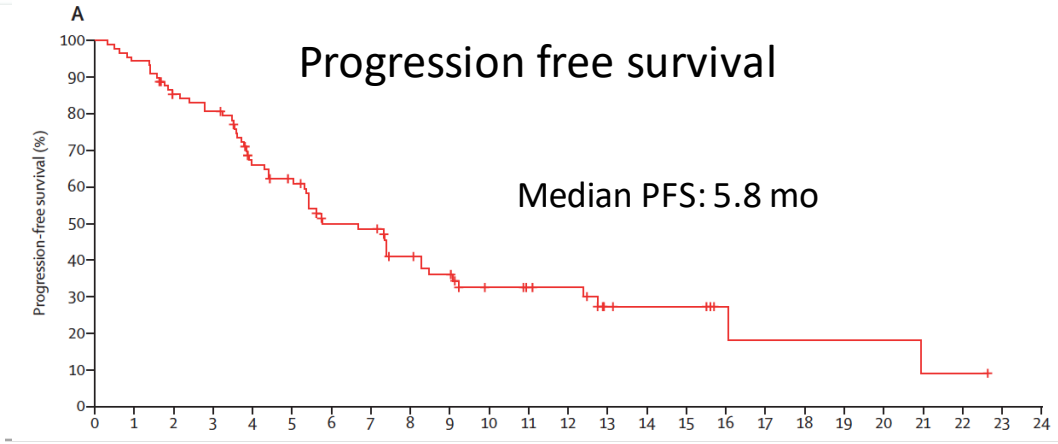


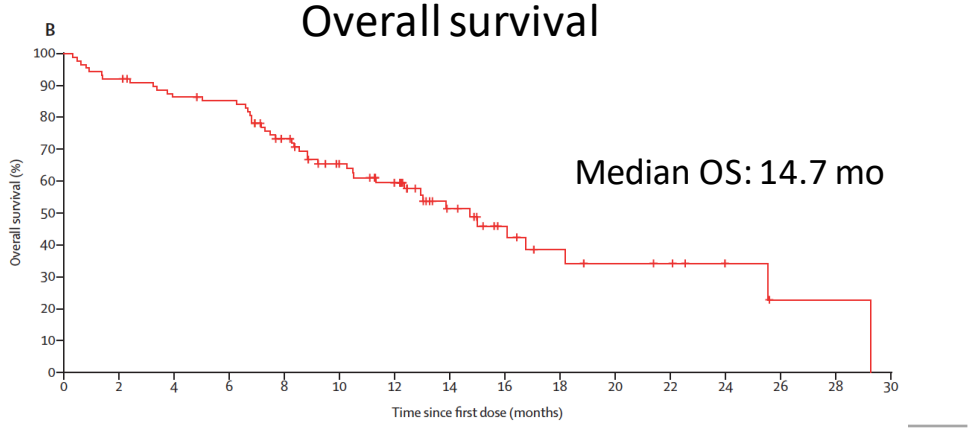
 Rosenberg JE, *J Clin Oncol*, 2019

Enfortumab vedotin for mUC post-IO (cisplatin-ineligible)









Yu EY et al, *Lancet Oncol*, 2020

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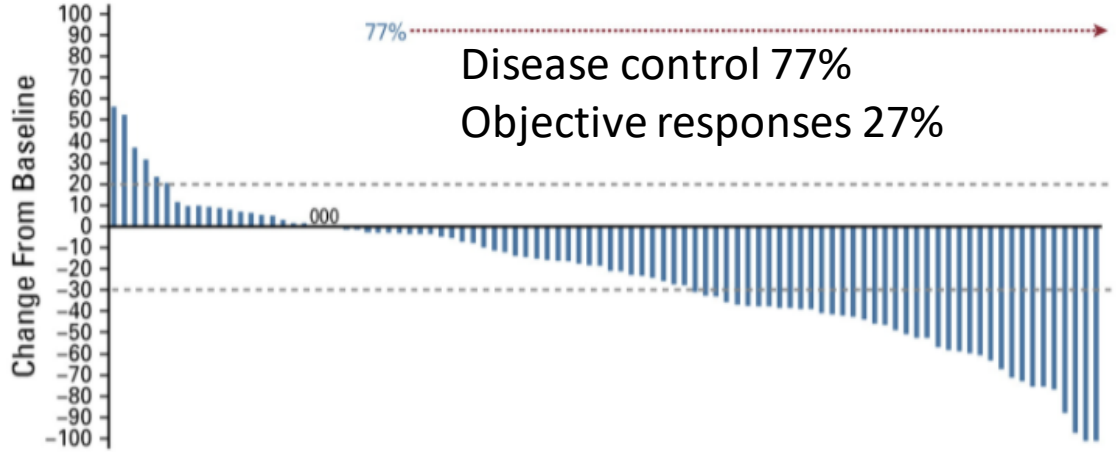
Sacituzumab govitecan phase 2 post-platinum

- Urothelial cancer
- Measurable metastatic disease, by RECIST criteria
- Prior platinum-based chemotherapy
- Prior immune checkpoint inhibitors
- Good performance status
- Archival tissue available

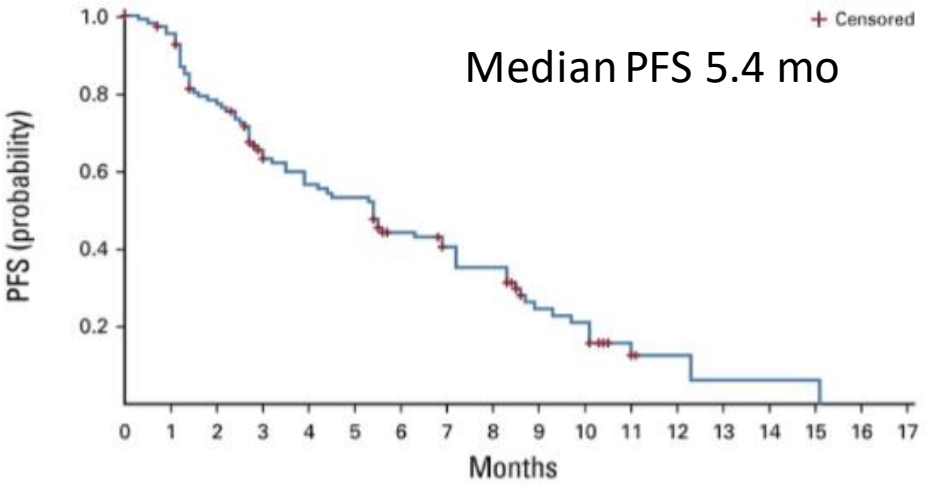
N=113

Sacituzumab govitecan 10mg/kg IV d1/d8 every 3 weeks



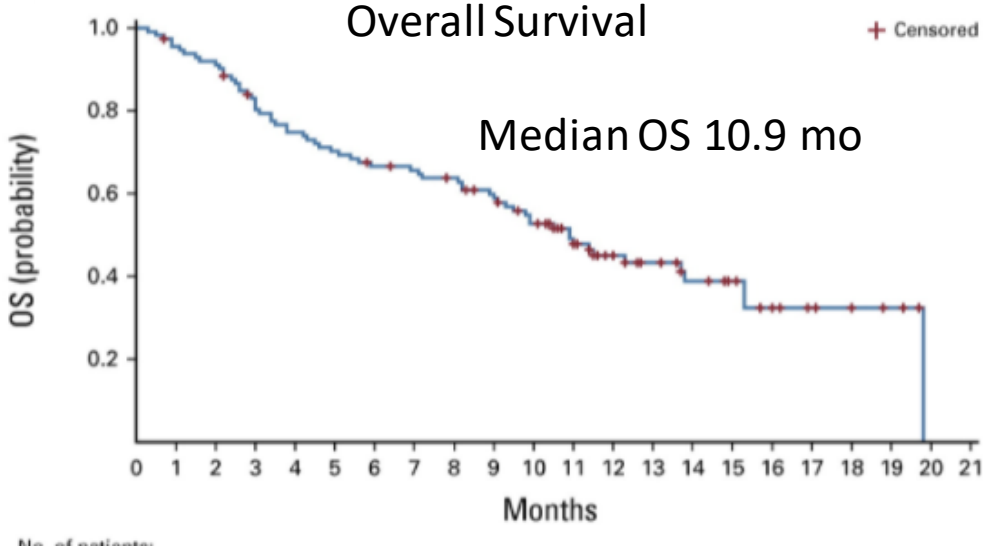
Disease control 77%
Objective responses 27%

Progression Free Survival



Median PFS 5.4 mo

Overall Survival

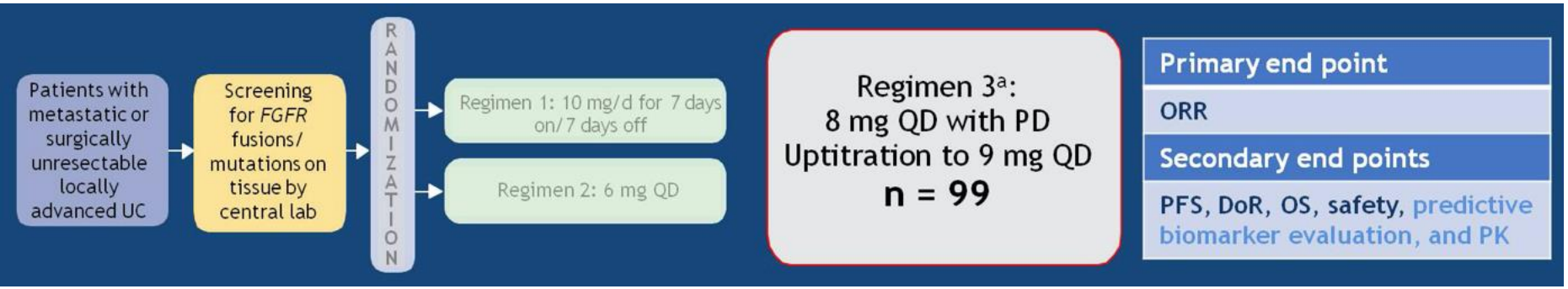


Median OS 10.9 mo

Tagawa ST et al, *JCO*, 2021

UTSouthwestern Medical Center

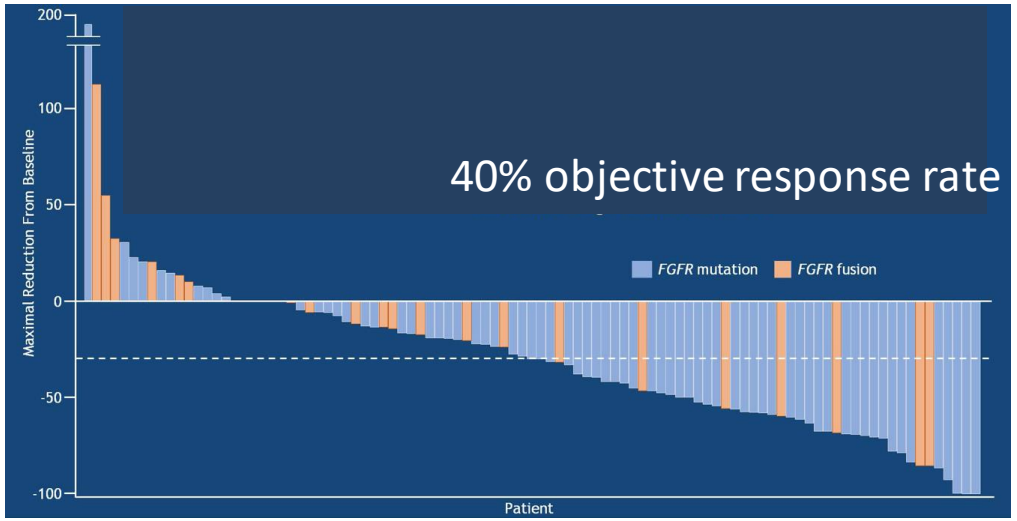
Targeted: Erdafitinib for FGFR-altered mUC



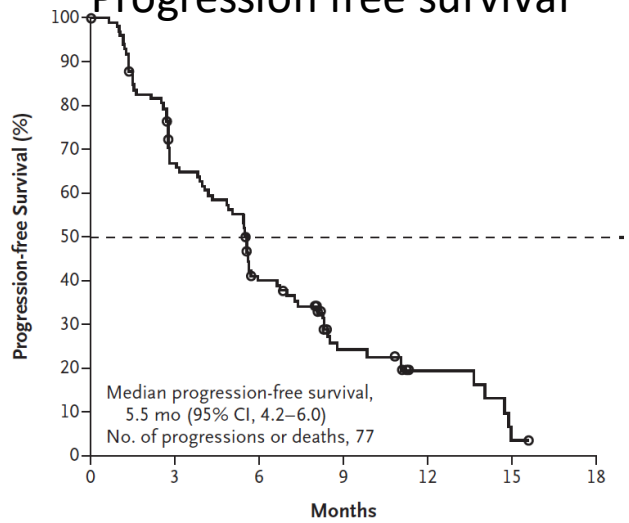
Baseline patient characteristics

Patients, n (%)		8 mg continuous dose (n = 99)
Age, median years (range)		68 (36-87)
ECOG performance status	0	50 (51)
	1	42 (42)
	2	7 (7)
Pre-treatment	Progressed or relapsed after chemo	87 (88)
	Chemo-naïve	12 (12)
	Prior immunotherapy	22 (22)
Number of lines of prior treatment	0	11 (11)
	1	45 (46)
	2	29 (29)
	≥ 3	14 (14)
Visceral metastases	Present	78 (79)
	Absent	21 (21)
Hemoglobin Level	≥10	84 (85)
	<10	15 (15)
Tumor location	Upper tract	23 (23)
	Lower tract	76 (77)
Creatinine clearance rate	< 60 mL/min	52 (53)
	≥ 60 mL/min	47 (47)
FGFR alterations	*FGFR2* or *FGFR3* fusion	25 (25)
	FGFR3 mutation	74 (75)

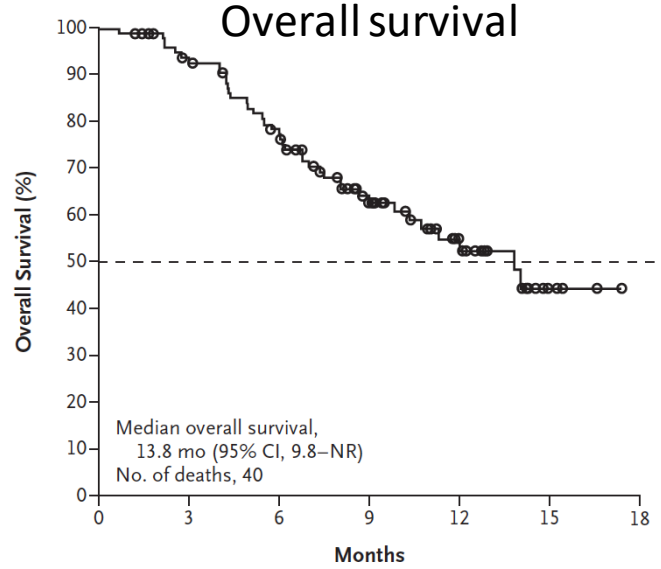
Radiographic responses



Progression free survival



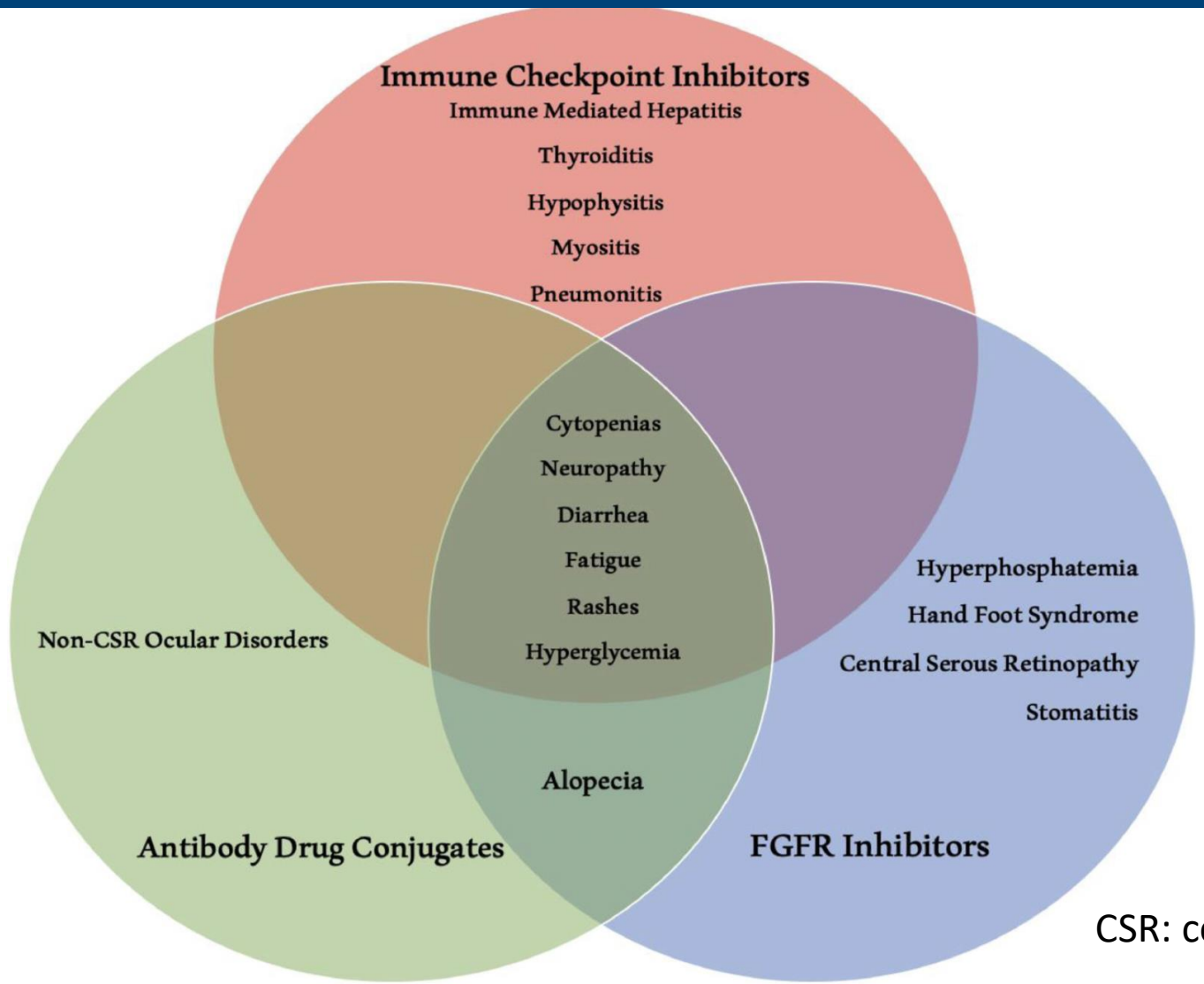
Overall survival



Loriot Y et al, *NEJM*, 2019

UTSouthwestern Medical Center

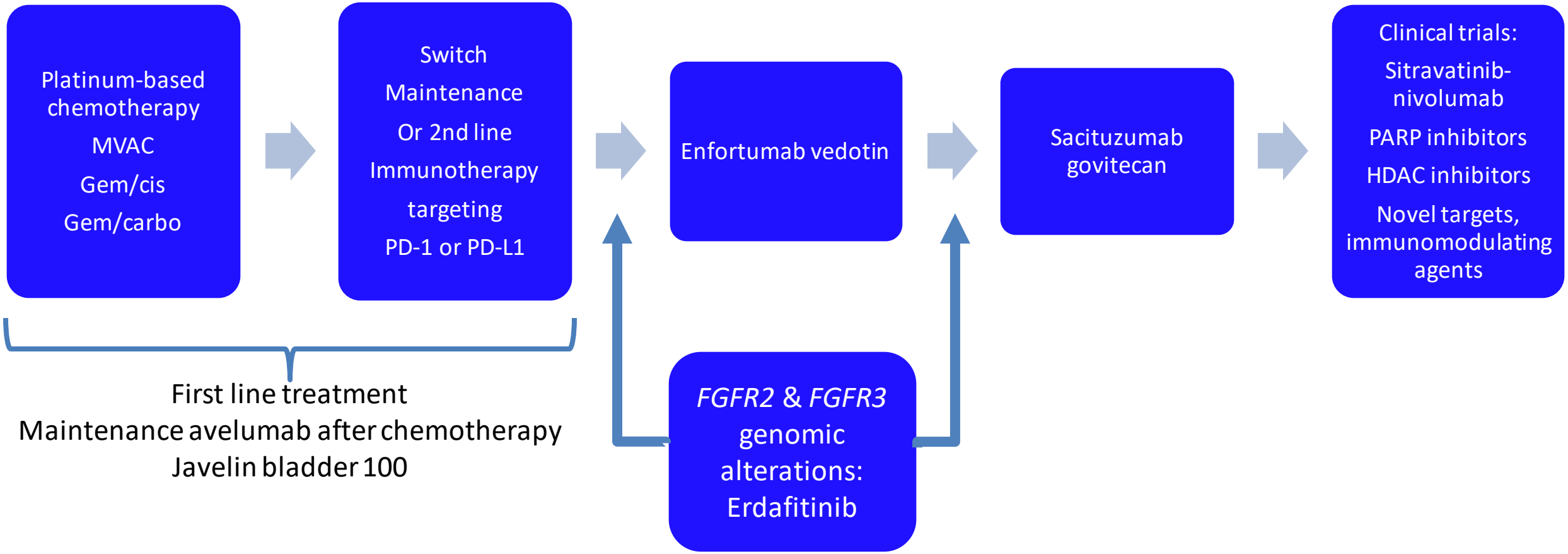
Overlapping Toxicities of mUC treatments



CSR: central serous retinopathy

Atiq S et al, *Urol Oncol*, 2021

The current treatment landscape for mUC: April 2022



Zhang T, adapted from discussion, ASCO Annual Meeting, 2020

Additive benefit of sequential treatment

Treatment break: 5 months

Treatment break: 13 months for skin/nail toxicities

Gemcitabine/ cisplatin 9/2015-1/2016

Atezolizumab 6/2016-9/2017

Pembrolizumab 9/2017-11/2017

Trial: FGFR inhibitor 12/2017-8/2018

Erdafitinib 6/2019-11/2019

Expanded access Enfortumab vedotin 12/2019-9/2020

Trial: Sitravatinib-nivolumab 9/2020-5/2021

Sacituzumab govitecan 5/2021-7/2021

Death 8/2021

65yo man, Professor

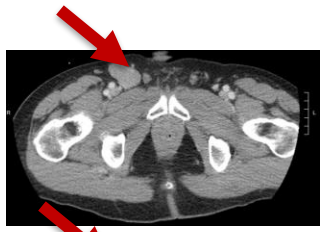
71yo

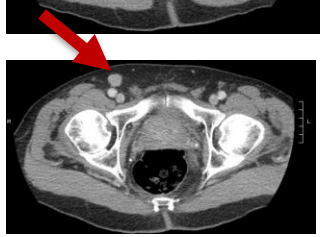
Grandson born

Daughter Oscars nomination

Another grandbaby

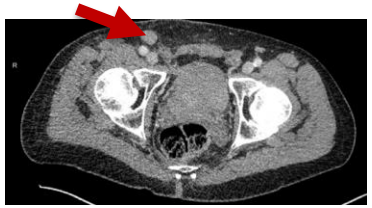
2015 2016 2017 2018 2019 2020 2021

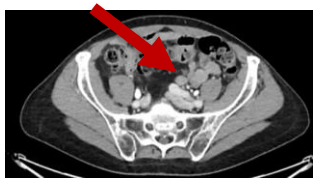


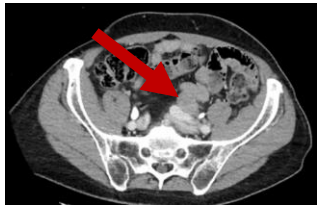


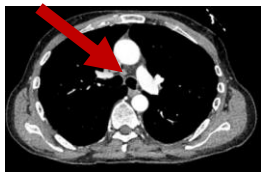
R inguinal LN: metastatic urothelial cancer

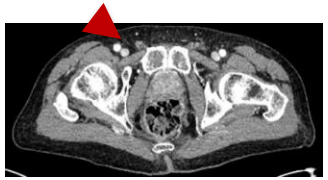
NGS testing from LN biopsy:
FGFR3 S249C
PI3K, *MLL2*, *CDKN2A/B* loss, *NOTCH* amp, *TERT* alteration

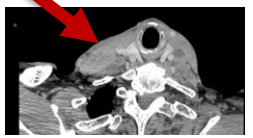


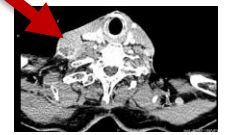


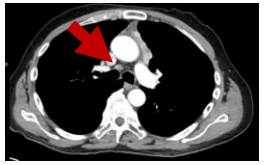


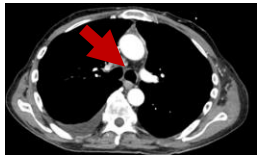


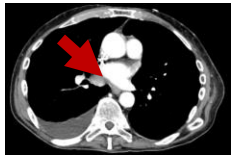


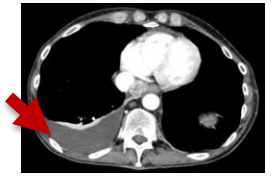












Oncology Goals:
Live longer, while maintaining quality of life

Takeaways from urothelial cancer

- New advances in immunotherapies, ADCs, and FGFR targeted therapies
  – Maintenance avelumab, enfortumab vedotin, sacituzumab govitecan, & erdafitinib (first genomically selected treatment)
  – All improving clinical outcomes in mUC

- Learning from our patients - cohorts and the individual
  – Unanswered questions in treatment resistance, novel combinations, sequencing
  – As long as good performance status, novel treatments and trials should be available

- To cure sometimes, to relieve often, to comfort always

~ Edward Trudeau

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Hans Hammers
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Waddah Arafat
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Petros Grivas
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Felix Feng

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NCI National Clinical Trials Network
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Thank you for your attention!

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