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Controversies in Cancer Care: Evidence, Interpretation, & Clinical Decision Making

Renal Cancer: Which Drug(s), When, and For Whom?

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Disclosures

- Consultant for AstraZeneca, Aveo, Bayer, Caremark, EMD Serono, Merck, Pfizer, & Xencor.

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This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Investigational HIF inhibitors and PD1-VEGFR bispecific antibodies will be addressed.

WHO Renal Cancer Classification (2022)

- Clear cell renal tumors
  - Clear cell RCC
  - Multilocular cystic renal neoplasm of LMP
- Papillary renal tumors
  - Renal papillary adenoma
  - Papillary RCC
- Collecting duct carcinoma
- Oncocytic and chromophobe renal tumors
  - Oncocytoma
  - Chromophobe RCC
  - Other Oncocytic tumors
- Renal cell carcinoma, unclassified
- Other renal tumors
  - Mucinous tubular and spindle cell carcinoma
  - Clear cell papillary renal cell carcinoma
  - Tubulocystic renal cell carcinoma
  - Acquired cystic disease associated renal carcinoma
  - Eosinophilic solid and cystic renal cell carcinoma
- Molecularly defined renal carcinomas
  - Succinate dehydrogenase deficient RCC
  - Fumarate hydratase deficient RCC
  - MiT family translocation renal cell carcinomas
    - TFE3 rearranged
    - TFEB altered
  - ELOC (TCEB1) mutated
  - ALK rearranged RCC
  - SMARCB1 deficient renal medullary carcinoma

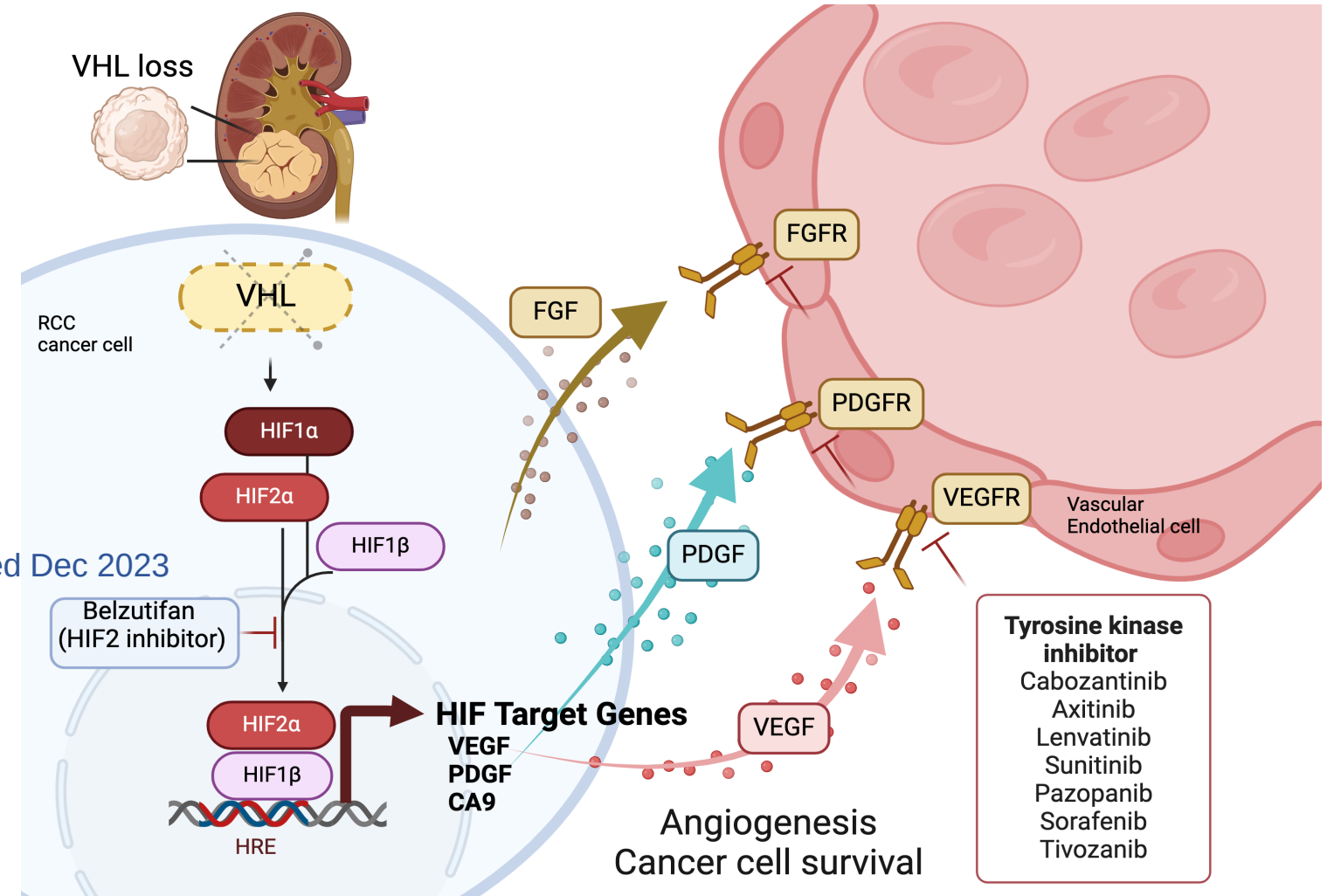
Metanephric, Mixed epithelial & stromal renal tumors, renal mesenchymal tumors, embryonal neoplasms excluded

ccRCC Pathophysiology and Therapeutic Targets

VHL gene inactivation leads to **constitutive activation** of the **HIF pathway**

VHL loss (90% cases)

FDA-approved Dec 2023



Courtesy J. Trujillo

Ethnic and Social Diversity in Renal Cancer

SMARCB1 Deficient Renal Cancer

- Closely associated with sickle cell disease and trait & thus more common in Black population
- Arises in the renal medulla from the distal segment of the collecting ducts
- May be triggered by the chronic medullary hypoxia and hypertonic environment resulting from sickled red cells and microvascular occlusion
- Hypoxic environment
    - Promotes double strand DNA breaks
    - Repression of the RAD51 and BRCA1 pathways
    - Induction of nonhomologous end joining (NHEJ) repair pathways, more likely to produce deletions and translocations
- Translocations and deletions are the most common causes of SMARCB1 inactivation
- Considered to be the seventh sickle cell nephropathy (others: unilateral hematuria, papillary necrosis, renal infarct, nephrotic syndrome, pyelonephritis, inability to concentrate urine)

VEGF Pathway Inhibitors in Renal Cancer

Agent(s)	Context of Definitive Trial(s)				
	Comparator	No Prior Therapy	Prior IL2 or IFNA	Prior VEGF Pathway	Outcome
Bevacizumab/IFNA	IFNA	X			PFS (bev)
Sunitinib	IFNA	X			OS (sun)
Sorafenib	Placebo		X		PFS (sor)
Pazopanib	Placebo	X	X		PFS (paz)
Axitinib	Sorafenib			X	PFS (ax)
Axitinib	Sorafenib	X			None
Pazopanib	Sunitinib	X			None
Tivozanib	Sorafenib	X	X		OS (sor)
Tivozanib	Sorafenib			X	PFS (tivo)
Dovitinib	Sorafenib			X	None
Cabozantinib	Sunitinib	X			PFS (cabo)

Without single agent comparative data

- Lenvatinib
- Zanzalintinib

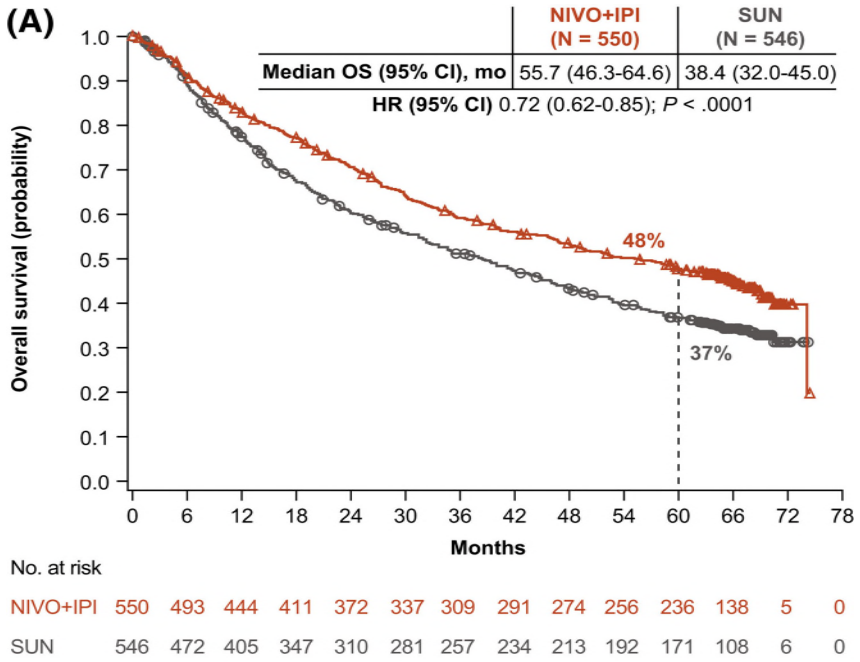
VEGF Pathway Inhibitor Toxicities

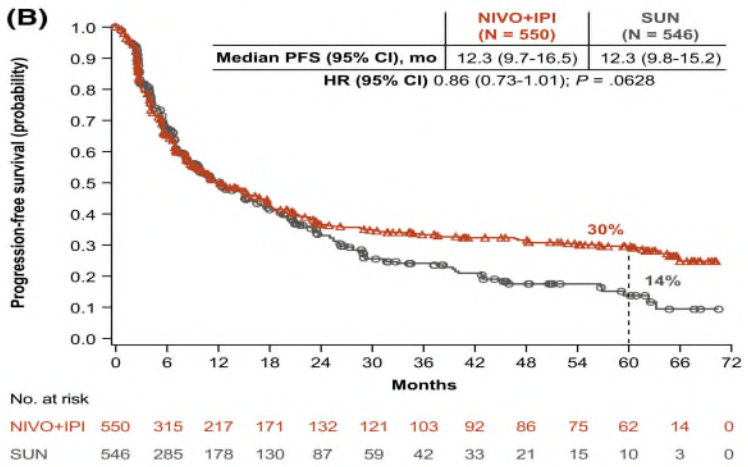
- Cardiac (~73%)
  - Hypertension
    - Reversible Posterior Leukoencephalopathy
    - MI
    - CVA
  - CHF
- Integument
  - Hand/Foot
  - Mucositis
  - Diarrhea
- Systemic
  - Fatigue
  - Dysgeusia
- Metabolic
  - Liver toxicity
- Hypothyroidism

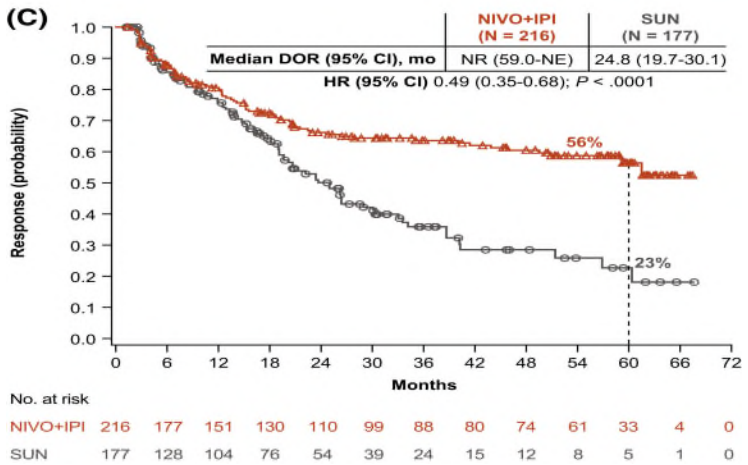
Take Home Points: VEGFR Inhibitors

- There is no definitive data as to a “preferred” VEGF pathway inhibitor
  - Not all VEGFRi play well with PD1 pathway inhibitors
  - Single agent VEGFRi still appropriate for patients with contraindications to PD1 checkpoint inhibitor therapy or post-CPI therapy
  - Dose intensity probably matters
- VEGF pathway inhibitors can be used sequentially
  - Is there an advantage to intermittent therapy?
  - Long term “minor” toxicities are clinically significant
- Every drug company has at least one VEGFR inhibitor (The Lemming Principle)
  - There are pharmacologic, but minimal clinical differences between the agents

Ipilimumab/Nivolumab Long Term Outcomes







Predictors of benefit:

- PD1/PDL1 expression (minimal impact)
- Sarcomatoid differentiation
- T-cell infiltration
- BAP1 loss?

None clinically useful to decide between combined immunotherapy and PD1/VEGFR therapy

Motzer, et al, Cancer, 2022

Treatment-Related Adverse Events

	NIVO + IPI N = 547		SUN N = 535	
Event, %	Any grade	Grade 3–5	Any grade	Grade 3–5[a]
Treatment-related adverse events in ≥25% of patients	**93**	**46**	**97**	**63**
Fatigue	**37**	**4**	**49**	**9**
Dysgeusia	**6**	**0**	**33**	**<1**
Stomatitis	**4**	**0**	**28**	**3**
Hypertension	**2**	**<1**	**40**	**16**
Mucosal inflammation	**2**	**0**	**28**	**3**
Palmar-plantar erythrodysesthesia syndrome	**1**	**0**	**43**	**9**
Treatment-related AEs leading to discontinuation, %	**22**	**15**	**12**	**7**
Treatment-related deaths	**n = 7[b]**		**n = 4[c]**	

60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event

[a]Two patients had grade 5 cardiac arrest. [b]Pneumonitis, immune mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c]Cardiac arrest (n = 2), heart failure, multiple organ failure

Escudier B, et al. Proceedings from the 2017 ESMO Congress; S. Abstract LBA5.

Efficacy and Safety Summary 1st Line Therapy

	VARIABLE	CHECKMATE 214 PHASE III NIVO+IPI VS. SUN (N=425 VS 422)	KEYNOTE 426 PHASE III PEMBRO+AXITINIB VS. SUN (N=432 VS 429)	CHECKMATE 9ER PHASE III NIVO+CABO VS SUN (N=323 VS 328)	CLEAR PHASE III LEN + PEMBRO VS LEN + EVE VS SUN (N = 355 VS 357 VS 357)
EFFICACY	**Median OS, months** **HR (95% CI); *P* value**	47.0 vs 26.6 0.66 (0.55-0.80); <0.0001	NR vs 35.7 0.68 (0.55-0.85)	NR vs. NR 0.60 (0.40-0.89); 0.0010	NR vs. NR vs. NR 0.66 (0.49-0.88); 0.005 L+P 1.15 (0.88-1.50); 0.3 L+E
EFFICACY	**Median PFS†, months** **HR (95% CI); *P* value**	–	15.4 vs 11.1 0.71 (0.60-0.84); <.0001	16.6 vs 8.3 0.51 (0.41-0.64); <.0001	23.9 vs 14.7 vs. 9.2 0.39 (0.32, 0.49); *P* <.001 L+P **0.65 (0.53, 0.80); *P* <.001 L+E**
EFFICACY	**ORR†, %**	42 vs 26	60.2 vs 39.9	55.7 vs. 27.1	71 vs 53.5 vs 35.1
EFFICACY	**PD, %**	19 vs 16	11.3 vs 17.2	5.6 vs. 13.7	5.4 vs 7.3 vs 14
EFFICACY	**Median DOR†, months**	NR vs 19.7	23.5 vs. 15.9	20.2 vs 11.5	25.8 vs 16.6 vs 14.6
SAFETY	**Any grade AEs, %**	93 vs 97	98.4.3 vs 99.3	100 vs. 99	99.7 vs 99.7 vs 98.5
SAFETY	**Grade 3/4 AEs, %**	46 vs 63	75.8 vs 70.6	75 vs. 71	82.4 vs 83.1 vs 71.8
SAFETY	**AEs Leading to Discontinuation, %**	22 vs 12	10.7 vs. 13.9	3.1 vs. 8.8	13.4 vs 18.9 vs 14.4

Motzer RJ et al. *N Engl J Med.* 2018;378:1277-1290; Tannir MN et al. 2020ASCO GU. Abstract 609; Rini BI et al. 2021 ASCO. Abstract 4500; Choueiri TK et al. *N Engl J Med*. 2021;384(9):829-841; Motzer RJ et al. *N Engl J Med*. 2021;384(14):1289-1300.

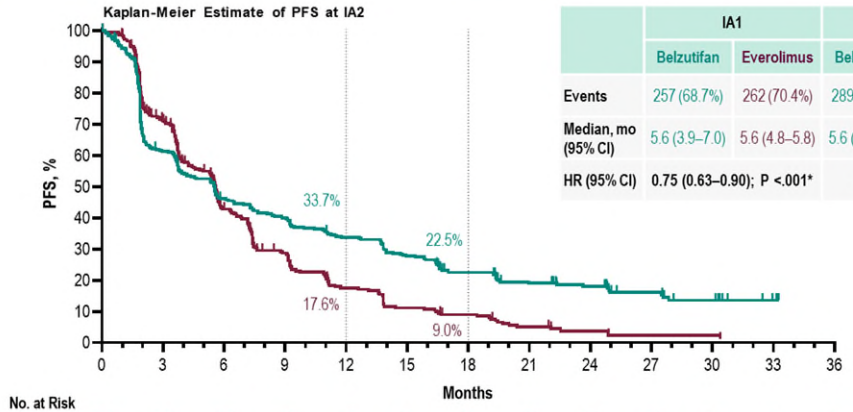
ccRenal Cancer: Initial Therapy Guidelines

- Good prognosis patients
  - Surveillance or oligometastatic directed therapy
  - Single agent therapy (VEGFRi or PD1 pathway inhibitor?)
  - Combination PD1/VEGFRi therapy
- Intermediate & poor prognosis patients
  - Ipilimumab/nivolumab
  - Combination PD1/VEGFRi therapy
- Which PD1/VEGFRi combination
  - Doesn’t matter
  - MD familiarity, patient financial toxicity, and cost are paramount

HIF Inhibitor Belzutifan Ph 3 Study

Albiges LS005 ESMO 2023

Primary Endpoint: PFS per RECIST 1.1 by BICR

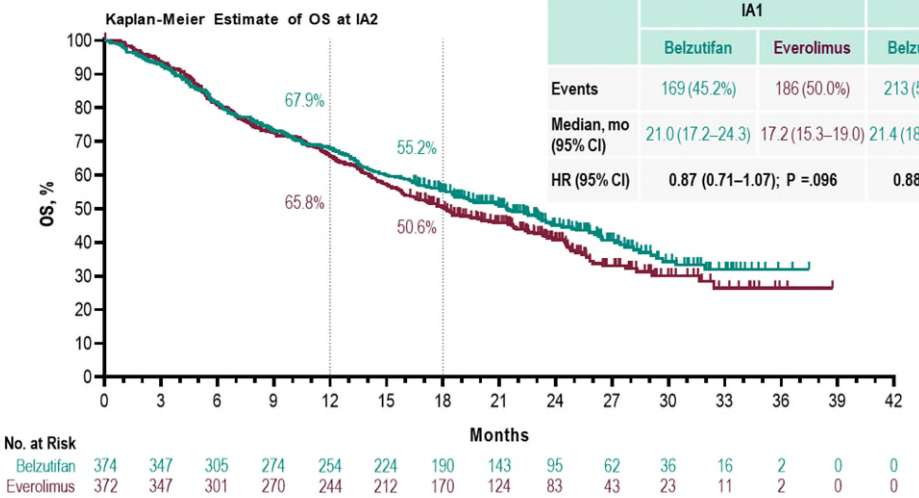


	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

* denotes statistical significance. Primary PFS endpoint was met at IA1 and was not formally statistically tested at IA2. Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

Albiges LS005 ESMO 2023

Primary Endpoint: OS



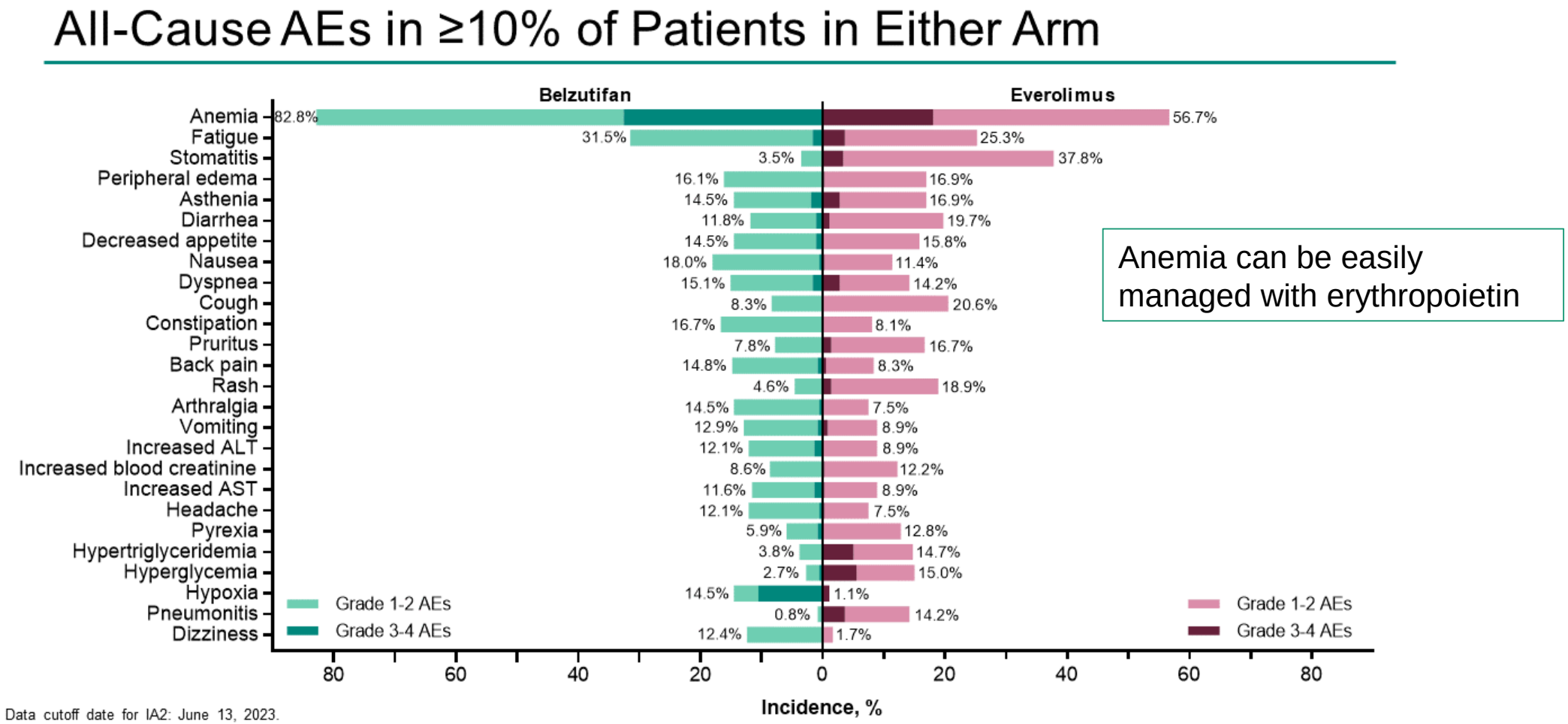
	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.0 (17.2–24.3)	17.2 (15.3–19.0)	21.4 (18.2–24.3)	18.1 (15.8–21.8)
HR (95% CI)	0.87 (0.71–1.07); P =.096		0.88 (0.73–1.07); *P* =.099	

Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

Choueri, et al. NEJM 391:710, 2024

Belzutifan Toxicities

Albiges LS005 ESMO 2023

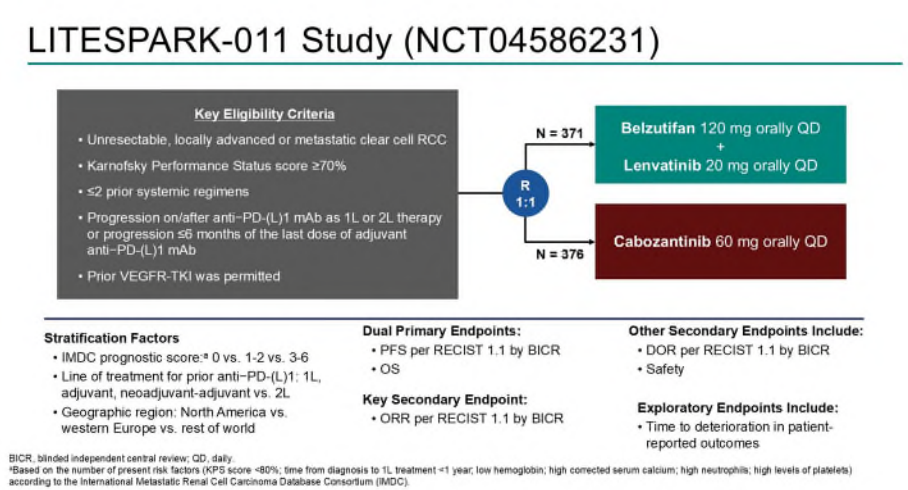


Anemia can be easily managed with erythropoietin

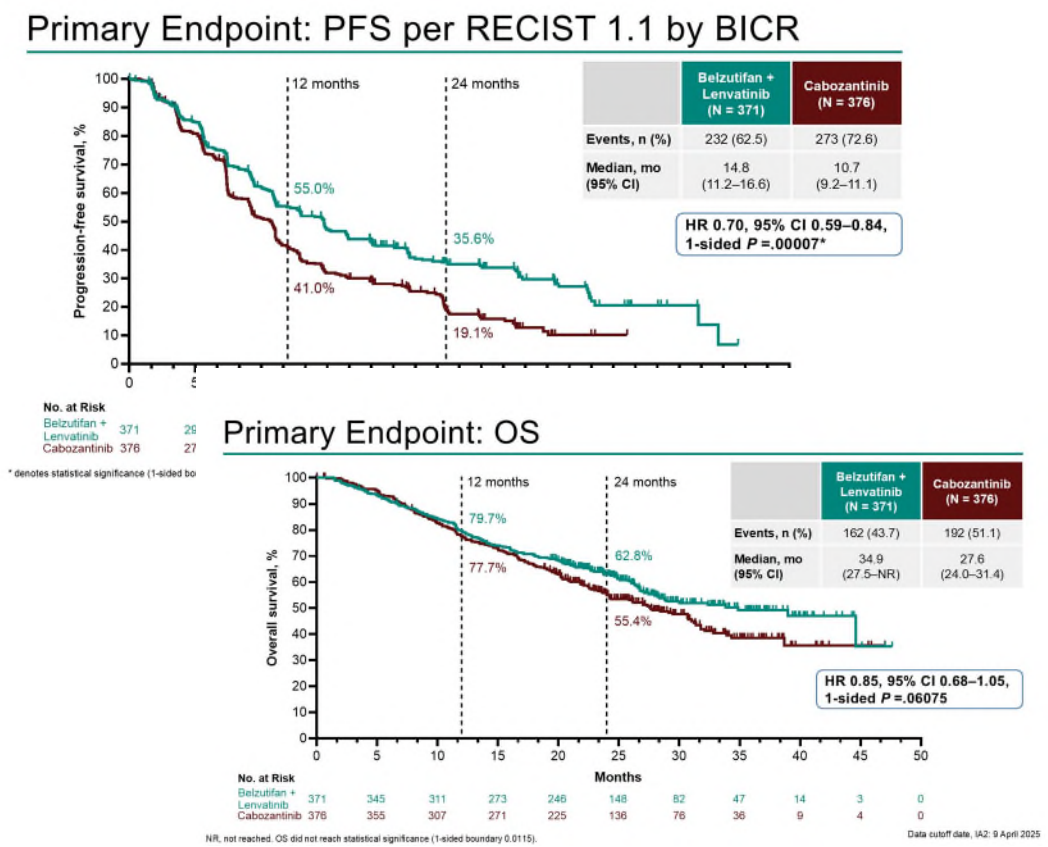
Data cutoff date for IA2: June 13, 2023.

HIF Inhibitor Combinations

- First line pembrolizumab/belzutifan/lenvatinib vs pembrolizumab/lenvatinib: “missed primary endpoint”
- “Second line” Len/Bev interesting:



43% without prior VEGFRi



- Cabozantinib w/wo Casdatifan phase 3: ongoing

Motzer, et al, ASCO GU 2026

mTOR inhibitors

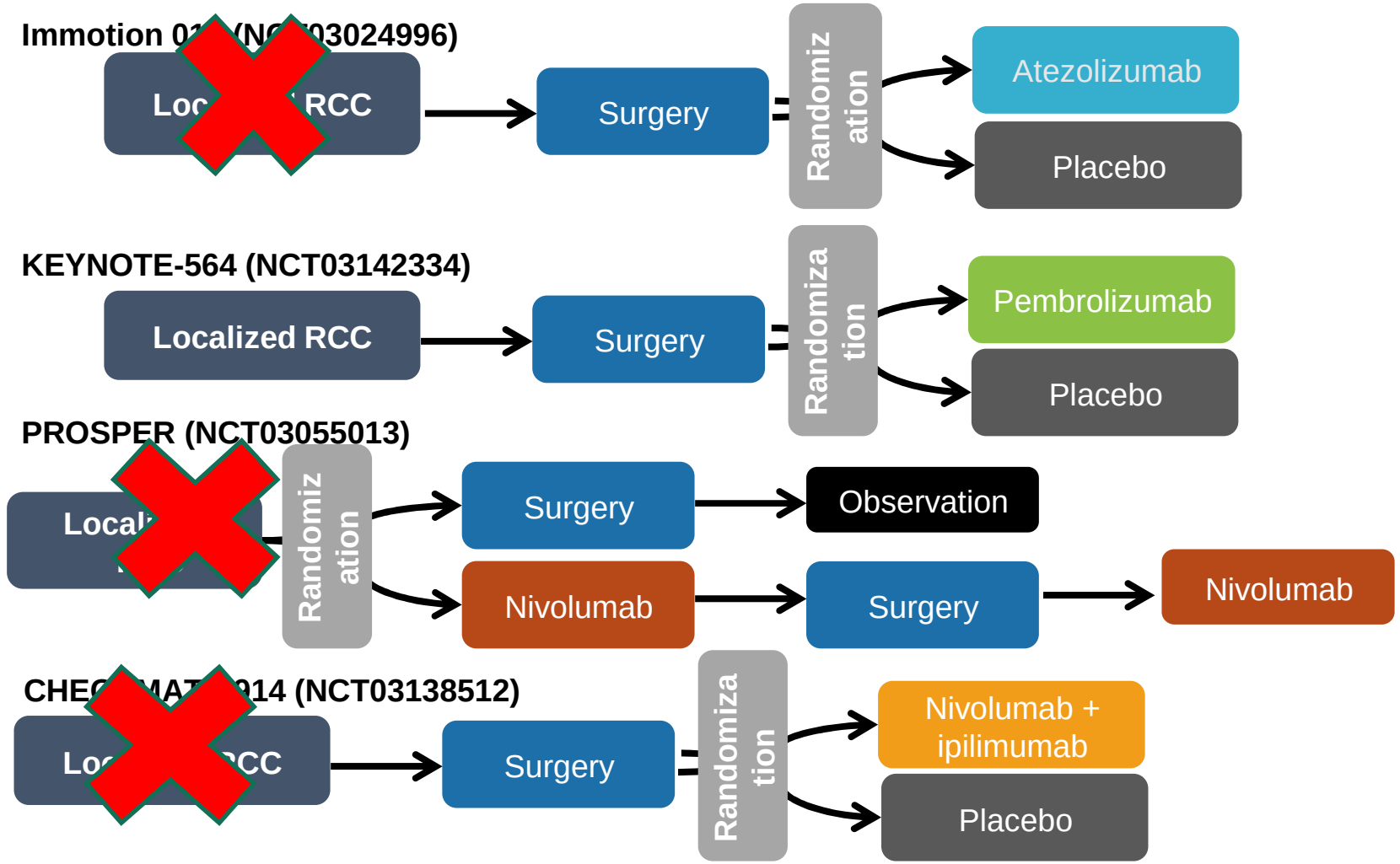
Agent	Context of Definitive Trial			
	Comparator	No Prior Therapy	Prior VEGF Pathway	Outcome
Temsirolimus*	IFNA	X		OS (tem)
Everolimus	Placebo		X	PFS (ev)
Temsirolimus	Sorafenib		X	OS (sor)
Everolimus	Sunitinib	X		OS (sun)
Everolimus	Cabozantinib		X	OS (cabo)
Everolimus	Lenvatinib/Everolimus		X	OS (combo, not len alone)

*Poor prognosis only, included non-clear cell

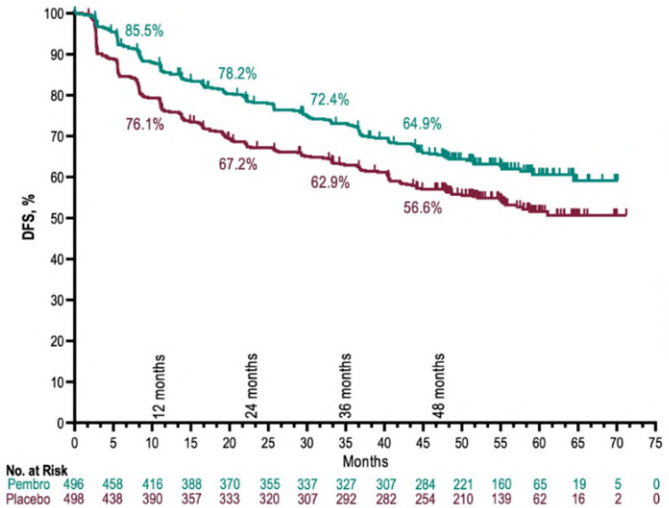
Adjuvant Therapy: VEGF & mTOR Pathway Inhibitors

Trial	N	Patient Characteristics	Treatment Arms	Treatment Duration	Primary Endpoint
S-TRAC: Sunitinib Trial in Adjuvant Renal Cancer Treatment [1]	615	High-risk patients according to UISS	Sunitinib Placebo	1 year	DFS HR 0.76; P = .03
ASSURE: Adjuva[illegible]nib or Sunitinib for Unfavorable R[illegible]	1,943	Non-metastatic RCC; disease stage II–IV selected by UISS	Sunitinib Sorafenib Placebo	1 year	DFS HR 1.02
SOR[illegible]b in Patients with Resected Prima[illegible]t High/Intermediate Risk of Rel[illegible]	1,656	Patients with Leibovich high- and intermediate-risk resected RCC	Sorafenib Sorafenib/ placebo Placebo	1 year 3 years	10-year OS (69% vs 69% vs 70%)
EVEREST: Everoli[illegible]enal Cancer Ensuing Surgical[illegible]	1,537	Pathological stage intermediate or very high–risk patients with full or partial nephrectomy	Everolimus Placebo	9 treatment cycles	5-year RFS (63% vs 67%, p = 0.05)
PROTE[illegible]panib as an Adjuvant Treat[illegible]calized RCC[5]	1,540	Patients with moderately high or high risk after nephrectomy of localized or locally advanced RCC by AJCC TNM v.2010	Pazopanib Placebo	1 year	DFS HR 0.862; P = .165
ATLAS: Adjuvant[illegible]herapy of Renal Cell Cancer in H[illegible]tients[6]	700	High-risk, non-metastatic RCC with nephrectomy by AJCC TNM v.2010	Axitinib Placebo	3 years	DFS Stopped by DSMC for futility

Adjuvant Therapy: Immunotherapy



Adjuvant Therapy – The Pembrolizumab Story



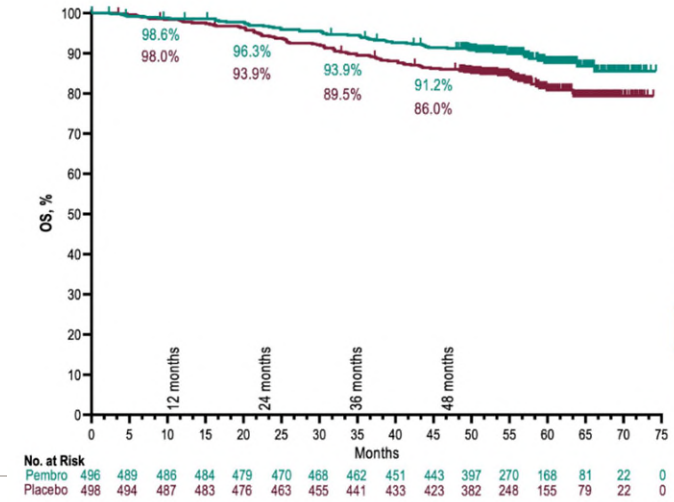
	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)

Median follow-up was 57.2 months (range, 47.9–74.5)

HR 0.72 (95% CI 0.59–0.87)

Primary DFS endpoint was met at IA1 and was not formally statistically tested thereafter.

Data cutoff date: September 15, 2023.



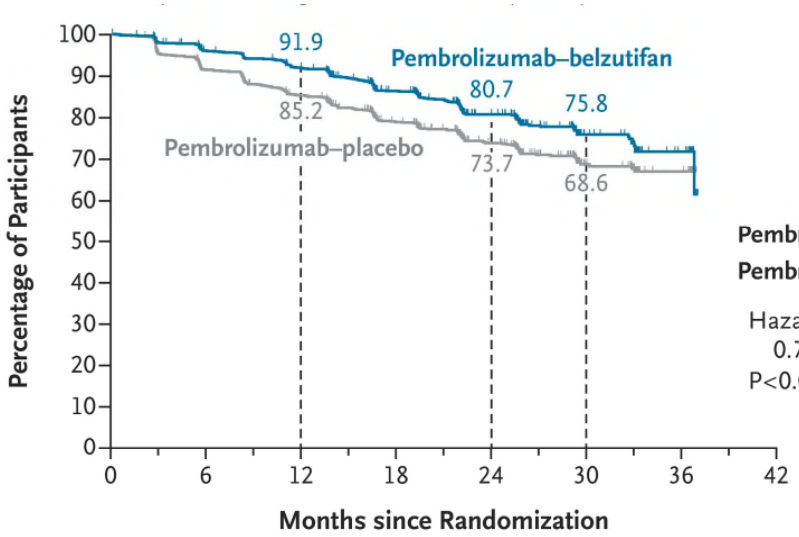
	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

Median follow-up was 57.2 months (range, 47.9–74.5)

HR 0.62 (95% CI 0.44–0.87); *P* =.002*

*** denotes statistical significance.** P-value boundary for OS at IA3 was 0.0072 (1-sided) per Lan-DeMets O'Brien-Fleming spending approximation α-spending function. As this key secondary endpoint was formally met, any future OS analyses will be descriptive only.

Data cutoff date: September 15, 2023.



No. of Participants with an Event	
Pembrolizumab–Belzutifan	186
Pembrolizumab–Placebo	246

Hazard ratio for recurrence or death, 0.72 (95% CI, 0.59–0.87)
P<0.001

Choueiri, et al, ASCO GU 2024; Choueiri, et al NEJM 2026

What About "Non-Clear Cell" Renal Cancer?

- Typically follow clear cell therapy standards due to lack of definitive data
- Classic Papillary:
    1. Cabozantinib
    2. PD1i/VEGFRi OR ipilimumab/nivolumab
    3. Nivolumab/zanzalintinib vs sunitinib phase 3 pending
- Chromophobe:
    1. Lenvatinib/everolimus OR everolimus
    2. PD1i/VEGFRi
    3. Ipilimumab/nivolumab for "sarcomatoid" differentiation
- MiT Translocation associated:
    1. Pembrolizumab/lenvatinib
    2. Other PD1i/VEGFRi combinations

Prado, et al. JCO Onc Practice https://doi.org/10.1200/OP-25-0064

What About “Non-Clear Cell” (part 2)?

- SMARCB1 deficient/Collecting duct
    1. Platinum based therapy
    2. ???
- FH germline mutation:
    1. Bevacizumab/erlotinib
    2. PD1i/VEGFRi
- ALK rearranged: alectinib or other ALKi
- “Sarcomatoid” NOS: ipilimumab/nivolumab

Prado, et al. JCO Onc Practice https://doi.org/10.1200/OP-25-0064

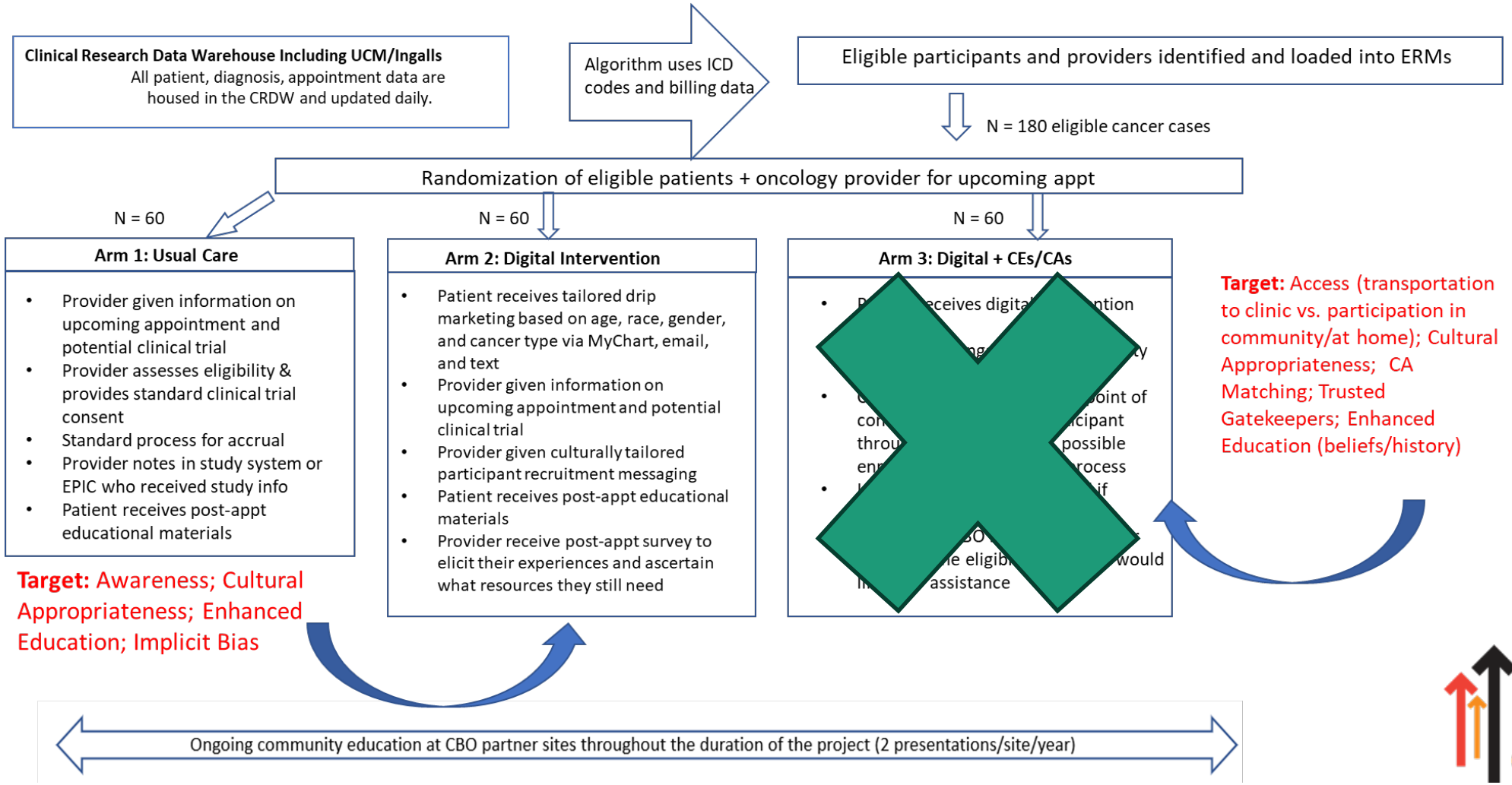
What's New

- NEO-811: "molecular glue" binding cereblon E3 ubiquitin ligase to ARNT (HIF-1beta)
- Bispecific Ab
  - PD1-VEGFR bispecifics: multiple agents, interesting preliminary data in refractory patients
  - REGN15505: PSMAxCD3 bispecific (Regeneron)
  - ENPP3-CD3 bispecific (Xencor)
- Cellular therapy (CAR-T, NK, ….): targeting CD70/CAIX
- Microbiome modulation of PD1 checkpoint:
  - CBM588 (oral live bacteria/probiotic)
  - EXL01
  - Etc

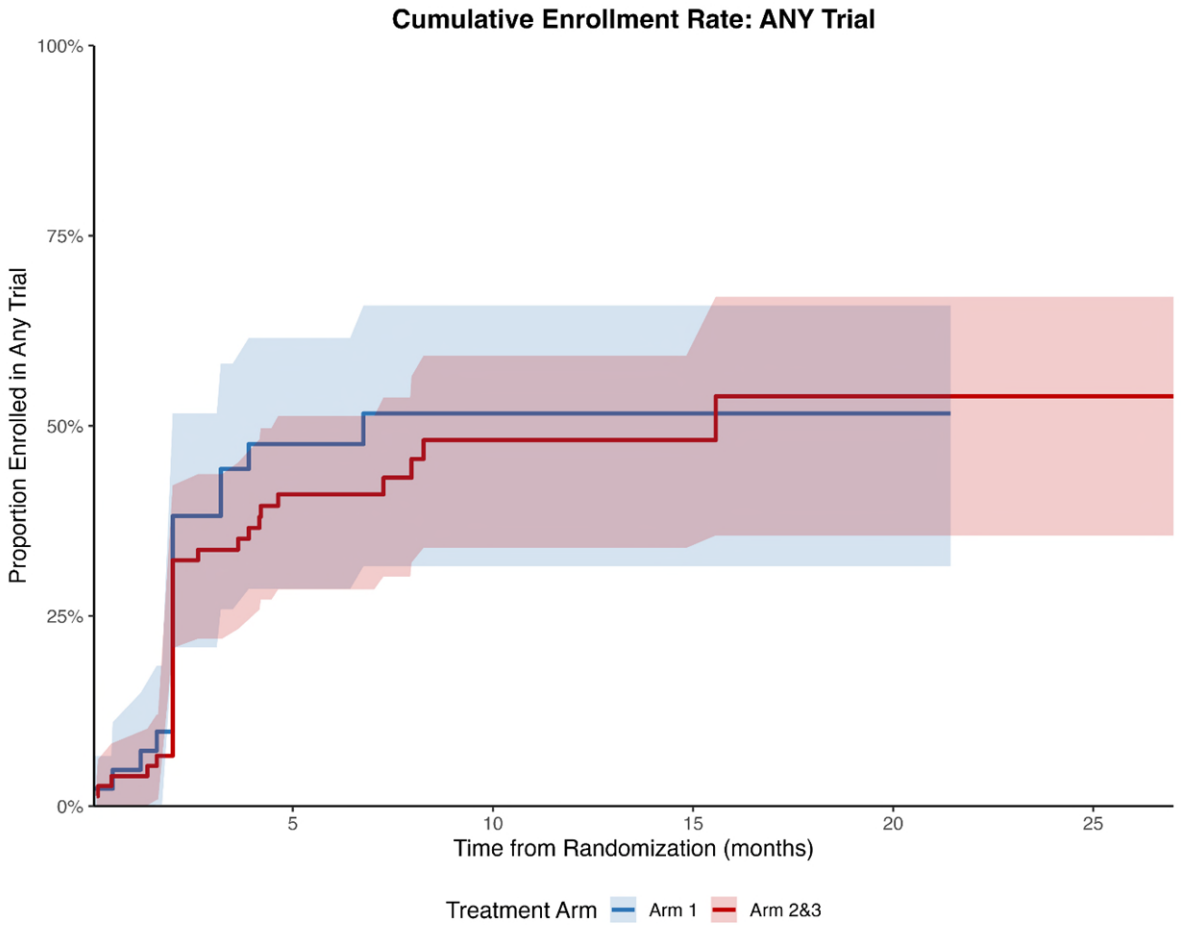
The Health Equity Question

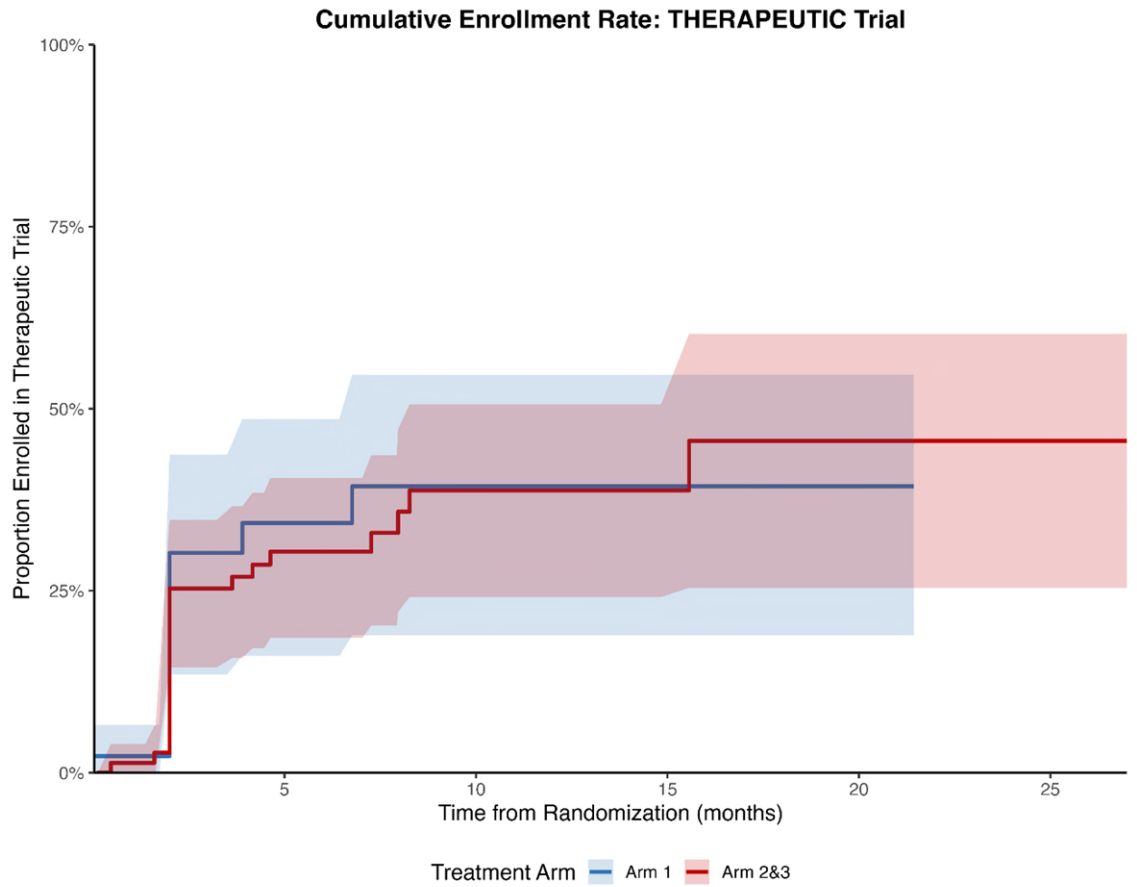
- Frequent visits for infusions are burdensome and difficult
- Chronic “grade 1 and 2” toxicities are burdensome (e.g. diarrhea)
  - And especially if there are limited family caregivers
  - And especially if limited health literacy
- “Small” copays (e.g. 10%) have major financial toxicity
- Providers for underserved communities are overburdened
  - Insufficient detailed disease knowledge
  - Insufficient support from pharmacy, social work, pre-approvals, etc

Implicit Bias: Enhancing Trial Accrual For Underserved Pts



Recruitment Trial Outcomes





RCC Conclusions

- Nephrectomy in metastatic patients: very good risk patients only
- Consider adjuvant pem/belzutifan for high risk localized disease
- Ipilimumab/Nivolumab OR pembro/axitinib OR nivo/cabozantinib OR pembro/lenvatinib are a first line standard
  - Surveillance, oligometastatic directed therapy, single agent therapy for good prognosis pts
  - Sequential use of VEGFRi is appropriate
- Triplet ipi/nivo/cabo OR pembro/len/belzutifan not useful
- Immunotherapy retreatment not useful
- Belzutifan (w lenvatinib?) is a 2nd/3rd line standard
- mTOR inhibitors have a minimal role
- Multiple combinations are being tested
- Therapy for non-clear cell renal cancer is unclear

Therapy sequencing is very confusing

Clinical Trial Accrual Is The Most Appropriate Standard – Always