Inaugural Southern California Genitourinary Cancer Research Forum

Key Updates in Kidney Cancer

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Disclosures

- Grant/Research Support from AstraZeneca, Bayer, Bristol-Myers Squibb, Exelixis, Oncternal, and Tempus.
- Consultant for AstraZeneca, Aveo, Bayer, Bristol-Myers Squibb, Calithera, Caris, Dendreon, Eisai, Exelixis, Johnson & Johnson, Lilly, Merck, Myovant, Novartis, Pfizer, Sanofi, SeaGen, Sorrento Therapeutics, Telix, and Tempus.

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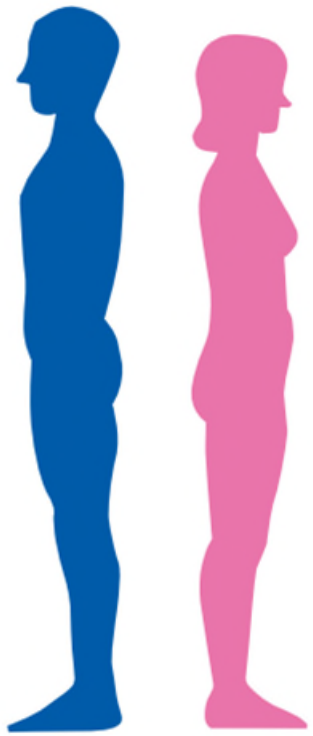
This presentation has been peer-reviewed and no conflicts were noted.

Renal Cell Carcinoma is a Common Malignancy

Estimated New Cases

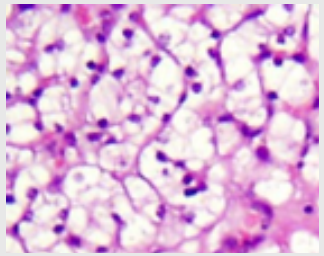
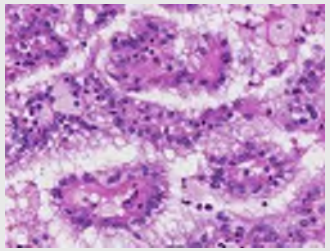
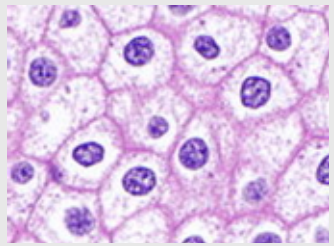
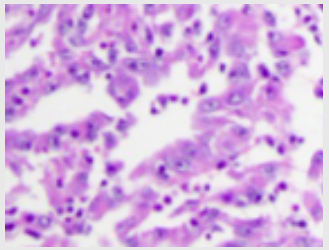
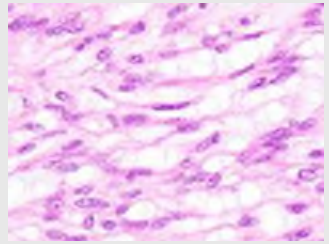
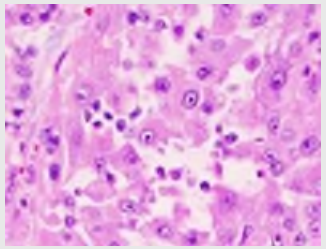
Males			Females		
Prostate	288,300	29%	Breast	297,790	31%
Lung & bronchus	117,550	12%	Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%	Colon & rectum	71,160	8%
Urinary bladder	62,420	6%	Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%	Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%	Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%	Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%	Pancreas	30,920	3%
Leukemia	35,670	4%	Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%	Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**	**All Sites**	**948,000**	**100%**



Global incidence increased over the past two decades by 2% per year

Siegel et al, Cancer Statistics, 2023

Renal Cell Carcinoma Histologies

Clear Cell	Papillary	Chromophobe	Collecting Duct	Mucinous Tubular	Unclassified
					
Proximal Tubule	Proximal and Distal Tubules	Distal Tubule Intercalated Cells	Collecting Duct	Proximal Tubule	-
80%	15-20%	5%	1-2%	<1%	4-5%
VHL, chr 3p	MET, chr 7, FH	PTEN, TP53, MTOR, TSC 1/2	NF2, CDKN2A/B, SMARCB1	chr loss and gain	NF2,SETD2, BAP1
5-year OS 81%	5-year OS 82%	5-year OS 91%	5-year OS 44%	Favorable	5-year OS 60%

OS=Overall survival. *5-year OS for patients with localized disease.

Moch et al, Eur Urol, 2022

Expanding List of Renal Cell Tumors

2022 World Health Organization Classification of Renal Cell Tumors

Table 1 – ICD-O coding of tumours of the kidney

ICD-O-3.2		ICD-O label (subtypes are indicated in grey text, with the label indented)
Renal cell tumours		
Clear cell renal tumours		
8310/3		Clear cell renal cell carcinoma
8316/1		Multilocular cystic renal neoplasm of low malignant potential
Papillary renal tumours		
8260/0		Papillary adenoma
8260/3		Papillary renal cell carcinoma [a]
Oncocytic and chromophobe renal tumours		
8290/0		Oncocytoma
8317/3		Chromophobe cell renal carcinoma
		Other oncocytic tumours of the kidney
Collecting duct tumours		
8319/3		Collecting duct carcinoma
Other renal tumours		
8323/1		Clear cell papillary renal cell tumour[a]
8480/3		Mucinous tubular and spindle cell carcinoma
8316/3		Tubulocystic renal cell carcinoma
8316/3	★	Acquired cystic disease–associated renal cell carcinoma
8311/3	★	Eosinophilic solid and cystic renal cell carcinoma
8312/3		Renal cell carcinoma, NOS
Molecularly defined renal carcinomas		
8311/3	★	*TFE3*-rearranged renal cell carcinomas
8311/3	★	*TFEB*-altered renal cell carcinomas
8311/3	★	*ELOC* (formerly *TCEB1*)-mutated renal cell carcinoma
8311/3	★	Fumarate hydratase–deficient renal cell carcinoma
8311/3		Hereditary leiomyomatosis and renal cell carcinoma syndrome–associated renal cell carcinoma
8311/3		Succinate dehydrogenase–deficient renal cell carcinoma
8311/3	★	*ALK*-rearranged renal cell carcinomas
8510/3		Medullary carcinoma, NOS
8510/3	★	SMARCB1-deficient medullary-like renal cell carcinoma
8510/3		SMARCB1-deficient undifferentiated renal cell carcinoma, NOS
8510/3		SMARCB1-deficient dedifferentiated renal cell carcinomas of other specific subtypes

Removal of Papillary Type 1 and 2

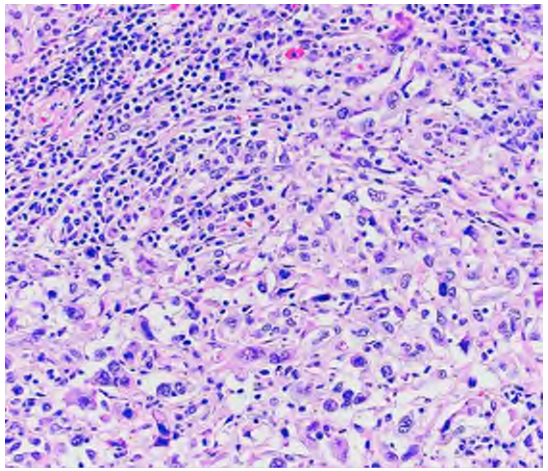
★ **Newly Defined Entities**

Molecularly Defined Entities

Moch et al, Eur Urol, 2022

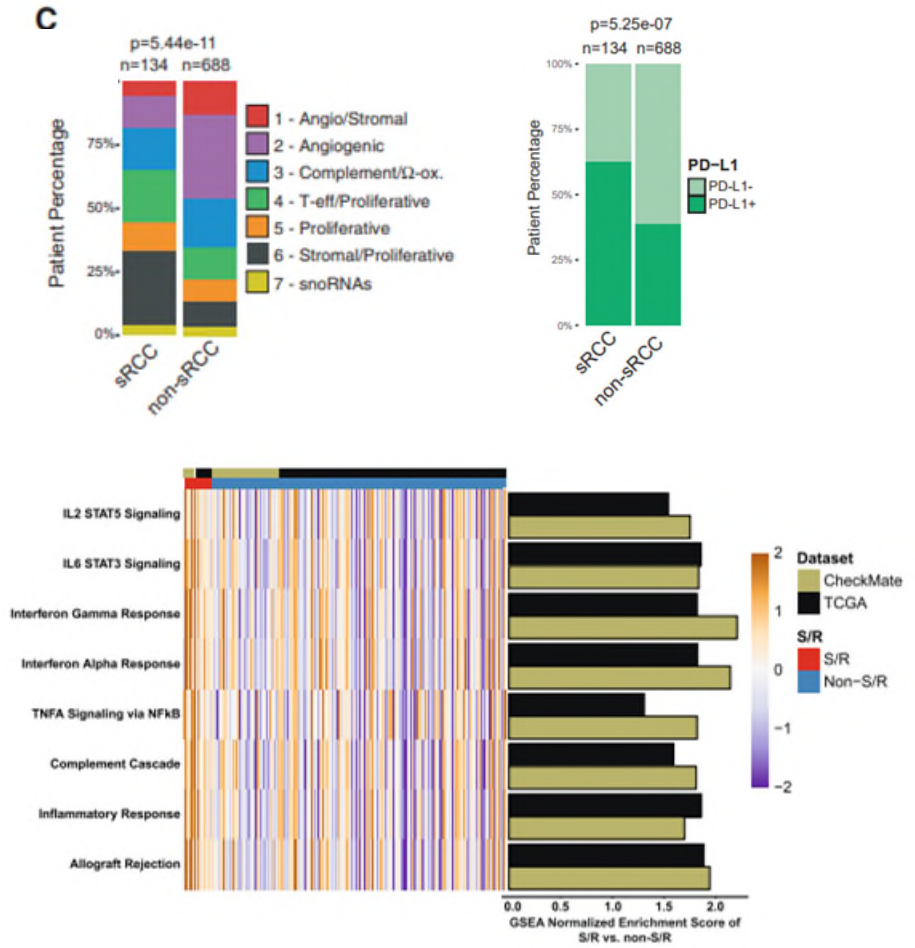
Sarcomatoid Dedifferentiation

Sarcomatoid Dedifferentiation in ccRCC



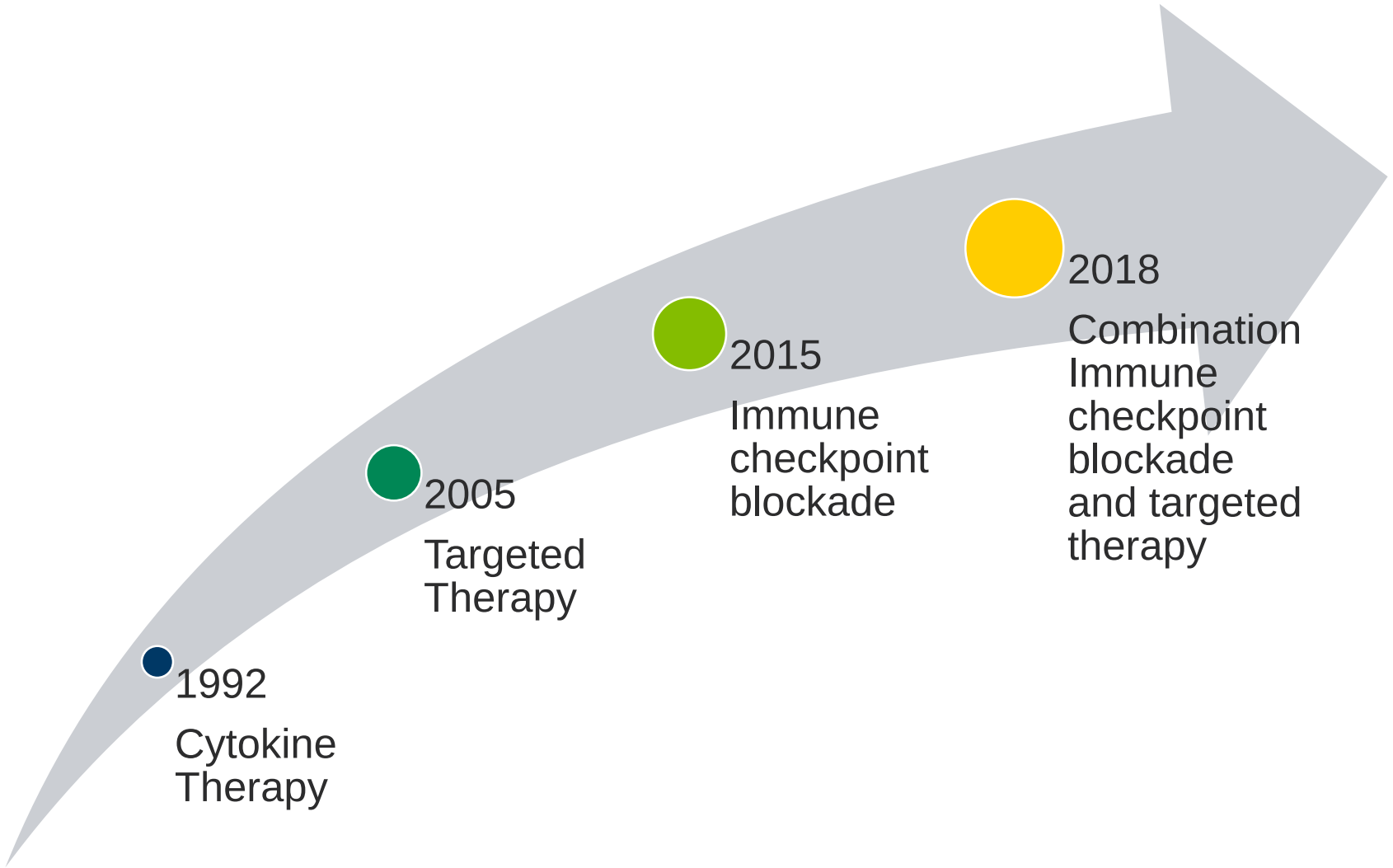
- Can occur in any RCC histology, 20% stage IV
- Occurs as a result of EMT
- Enrichment BAP1 alterations, NF2 alteration, EZH2 amplifications, CDKN2A/B deletions, and MYC transcriptional programs
- Immune-inflamed phenotype – activation of immune pathways, increased expression of antigen presentation machinery genes, increased cytotoxic immune infiltration, and high PDL1 protein expression on tumor cells

Molecularly and Immunologically Distinct



Motzer et al, Cancer Cell, 2020; Bakouny et al, Nature Communications, 2021

Renaissance of Treatment Options for Renal Cell Carcinoma

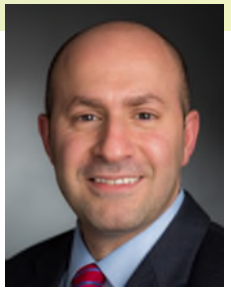


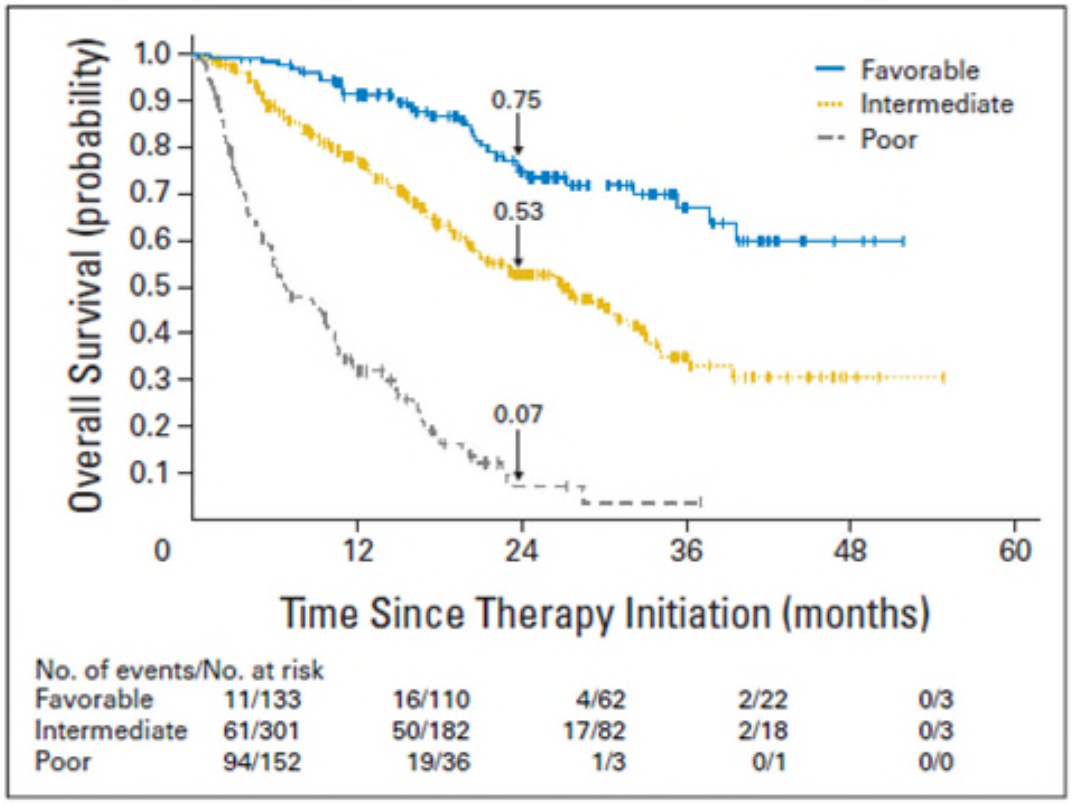
Phase 3 Trials of VEGF Targeted Therapies in RCC

	Treatment	Control	Line	N	ORR	PFS (mos)	OS (mos)
Avoren	Bevacizumab + IFNα	IFNα	1	649	31% vs. 13%	10.2 vs. 5.4	NR vs. 19.8
NCT00083889	Sunitinib	IFNα	1	750	31% vs. 6%	11.0 vs. 5.0	NR vs. NR
NCT00334282	Pazopanib	Placebo	1, 2	435	30% vs. 3%	9.2 vs. 4.2	22.9 vs. 20.5
COMPARZ	Pazopanib	Sunitinib	1	1110	31% vs. 24%	8.4 vs. 9.5	28.4 vs. 29.3
Tivo-1	Tivozanib	Sorafenib	1	517	33% vs. 23%	11.9 vs. 9.1	29.8 vs. 29.3
TARGET	Sorafenib	Placebo	≥2	903	10% vs. 2%	5.5 vs. 2.8	NR vs. 14.7
AXIS	Axitinib	Sorafenib	≥2	723	19% vs. 9%	6.7 vs. 4.7	20.1 vs. 19.2
METEOR	Cabozantinib	Everolimus	≥2	658	21% vs. 5%	7.4 vs. 3.8	21.4 vs. 16.5
Tivo-3	Tivozanib	Sorafenib	3-4	350	15% vs. 8%	11.1 vs. 6.0	16.4 vs. 19.7

ORR=Objective response rate; PFS=Progression-free survival; OS=Overall survival; mos=Months; NR=Not reached.

Development of IMDC Prognostic Model in the TKI Era





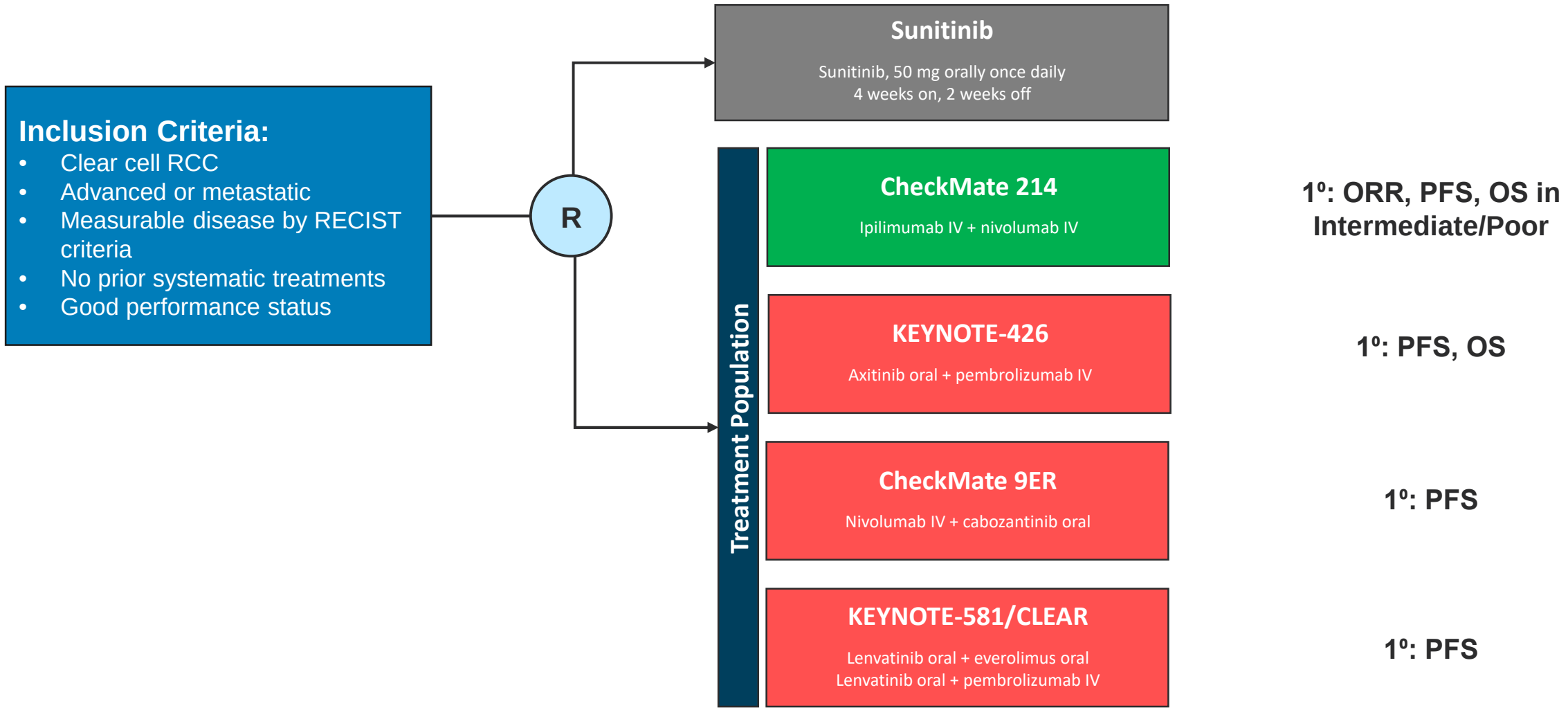
- KPS <80
- Time from original diagnosis to initiation of targeted therapy <1 year
- Hemoglobin less than the lower limit of normal
- Serum calcium, neutrophil count, or platelet count greater than the upper limit of normal

	Median Survival (months)	2-Year Overall Survival
Favorable (0)	NR	75%
Intermediate (1-2)	27	53%
Poor (3-6)	8.8	7%

Initial model developed in treatment naïve patients initiating targeted therapy

Heng et al, JCO, 2009

Landmark Combination Frontline Studies in RCC



Frontline Immunotherapy Combination Studies

Baseline Characteristics

Variable		Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib Clear n=1096
IMDC Risk Group	Favorable, %	23%	33%	23%	32%
	Intermediate, %	61%	56%	58%	54%
	Poor, %	17%	13%	19%	10%
Previous Nephrectomy, %		81%	83%	69%	73%
Sarcomatoid Features, %		14%	18%	11%	8%
Bone Metastases, %		20%	24%	24%	24%
Liver Metastases, %		18%	15%	23%	17%
PD-L1 Expression ≥1%, %		24% (Dako PD-L1 28-8; Tumor)	60% (Agilent Tech PD-L1 22C3; CPS)	25% (Dako PD-L1 28-8; Tumor)	31% (Agilent Tech PD-L1 22C3; CPS)

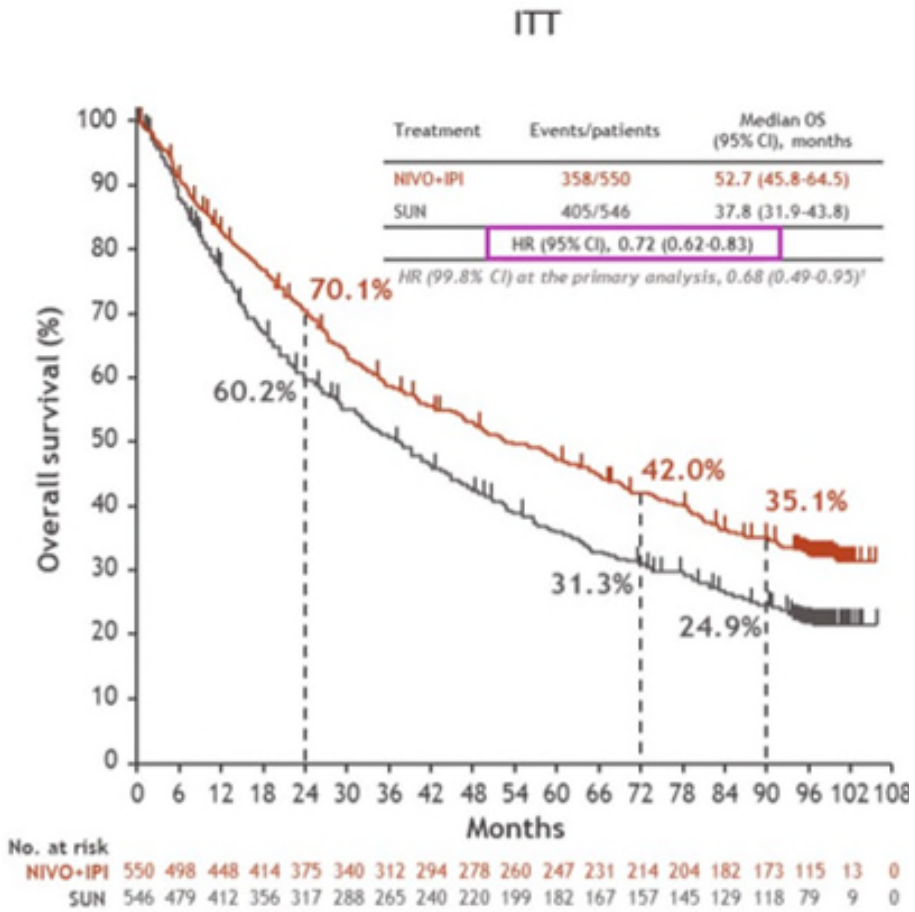
IMDC=International Metastatic RCC Database Consortium; PD-L1=Programmed Death Ligand 1; CPS=Combined positive score (TC+IC positive/TC all); ORR=Objective response rate; PFS=Progression-free survival; OS=Overall survival.

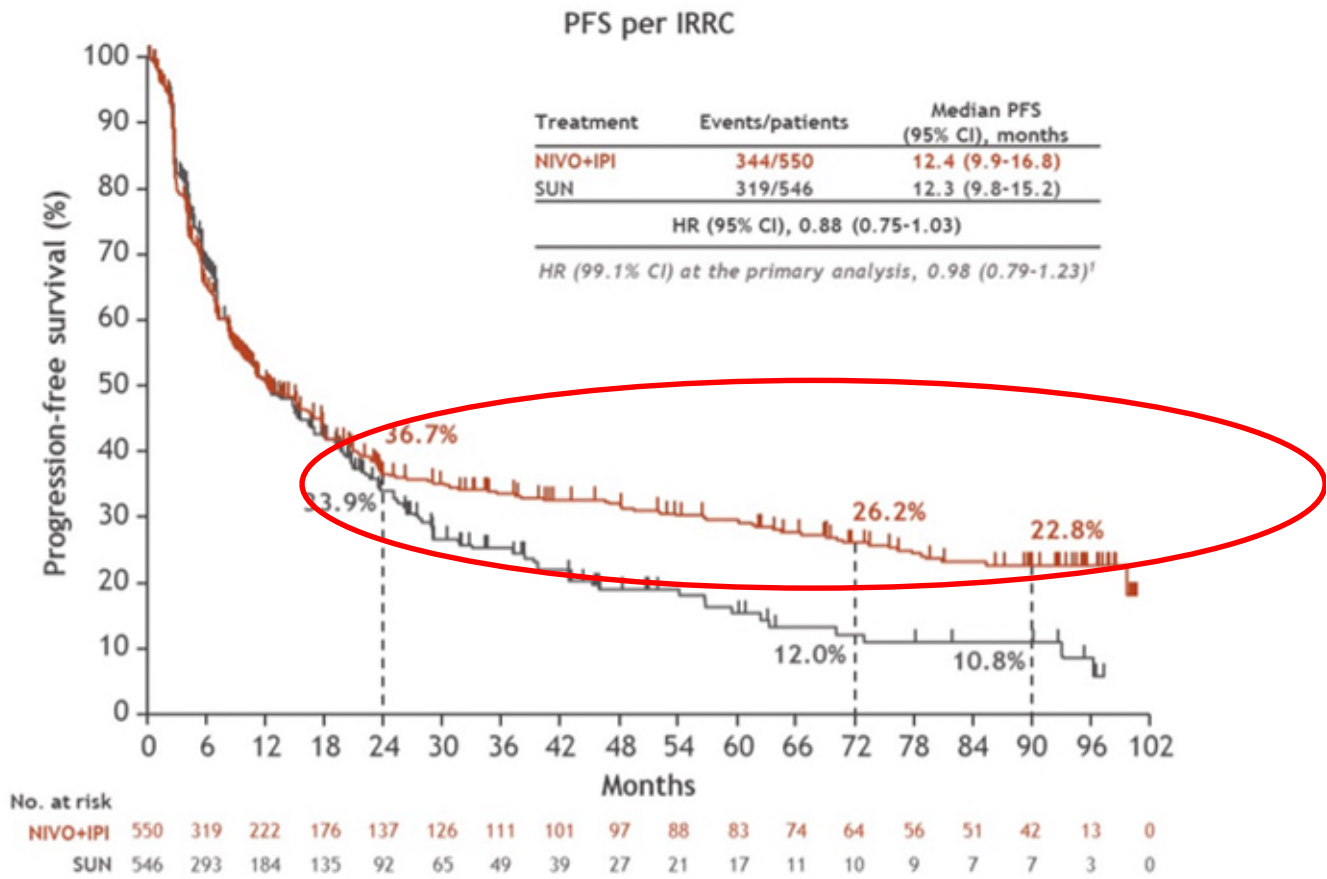
Motzer et al, NEJM, 2018; Rini et al, NEJM, 2019; Choueiri et al, NEJM, 2021; Motzer et al, NEJM, 2021

Outcomes of Immune Combinations – ITT

	Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib Clear n=1096
Follow-up, mo	99.1 (median)	67.2 (median)	55.6 (median)	49.8 (median)
Median PFS, mo	12.4	15.7	16.4	23.9
PFS HR	0.88	0.69	0.58	0.47
Landmark PFS	90-month 21%	60-month 18%	48-month 17%	36-month 37%
Median OS, mo	52.7	47.2	46.5	53.7
Landmark OS	90-month 35%	60-month 42%	48-month 49%	36-month 66%
OS HR	0.72	0.84	0.77	0.79
ORR, %	39	61	57	71
CR, %	12	12	14	18
PD, %	18	12	7	5
Quality of Life	Improved	Similar	Improved	Similar-Improved

Nivolumab + Ipilimumab Associated with Durable Survival

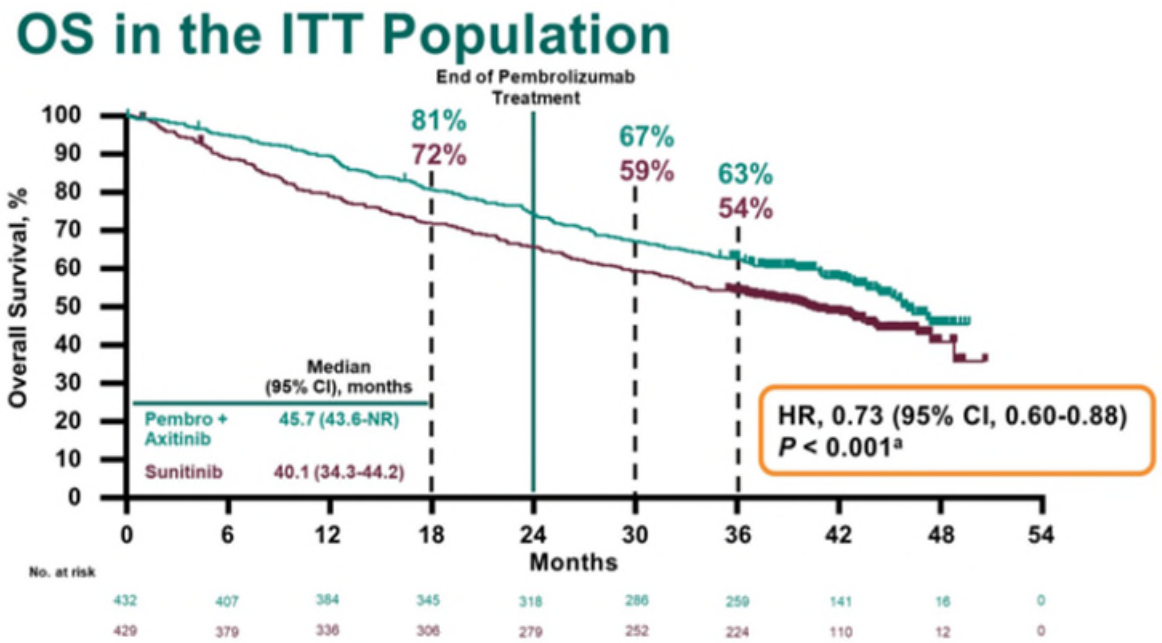


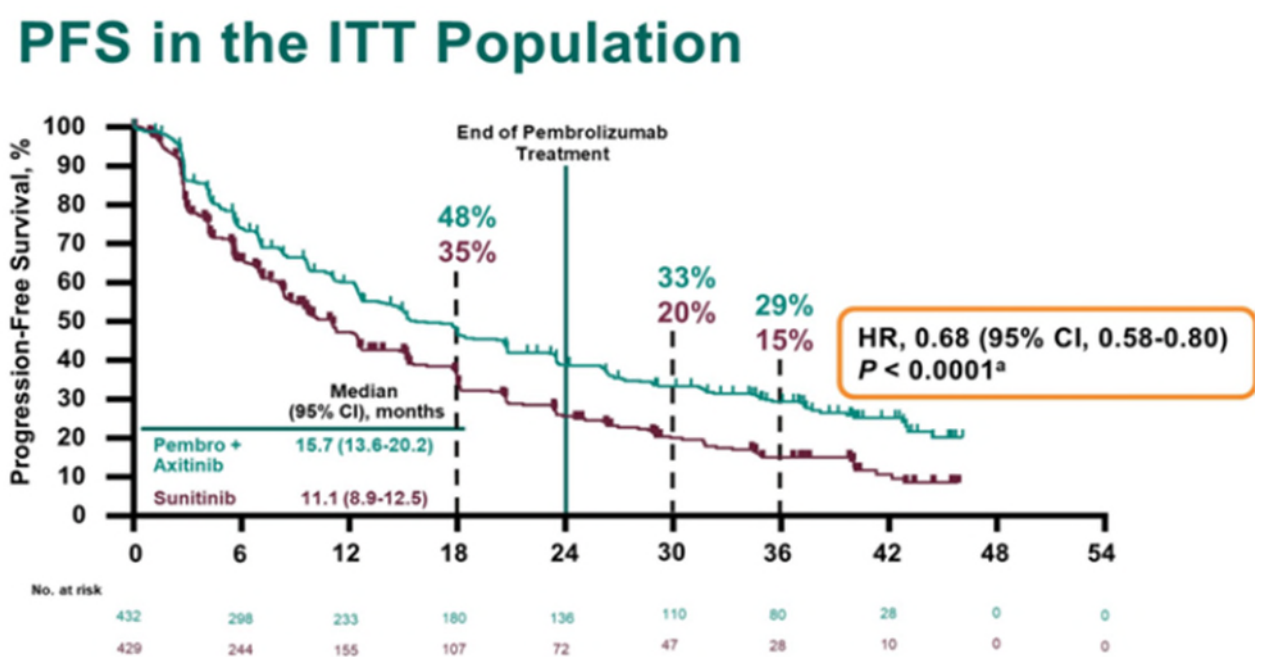


Median 8 year follow up
ITT Population

Tannir et al, GU ASCO, 2024

Durable Benefit with IO + VEGF in RCC

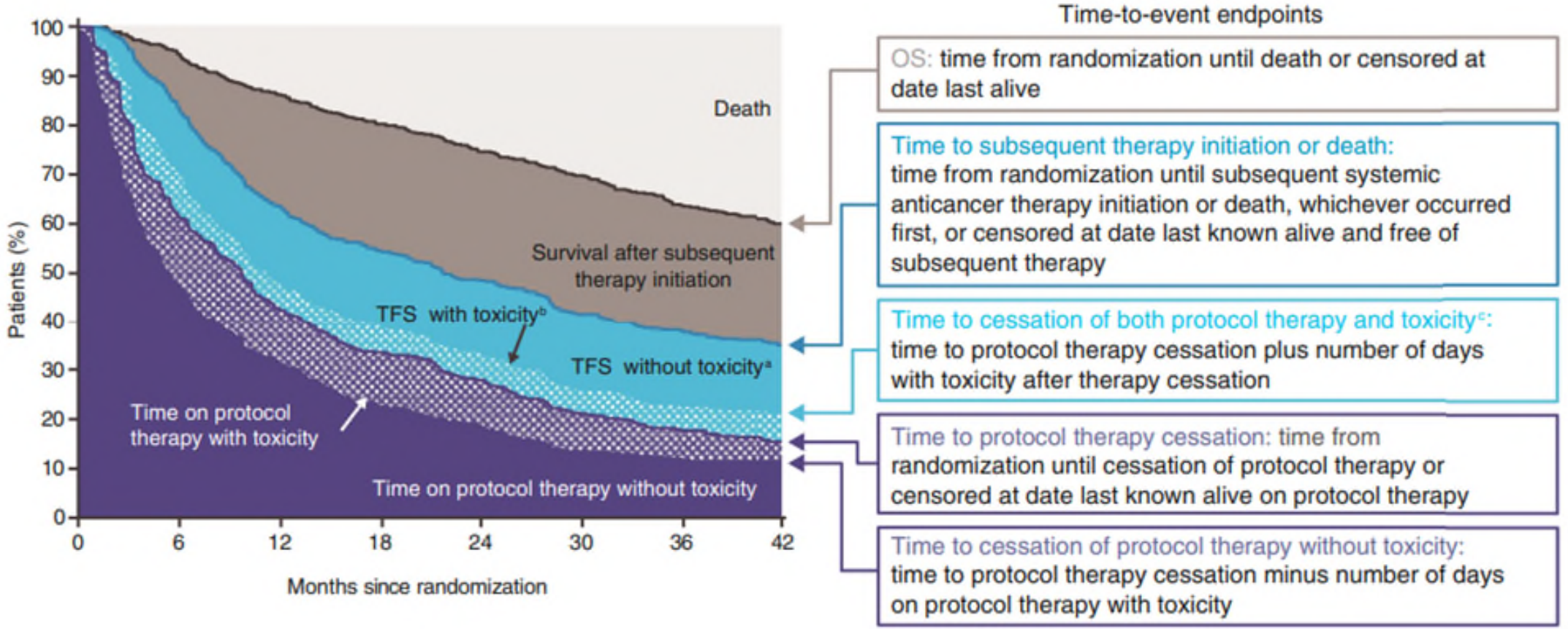




Minimum 42 month follow up
ITT Population

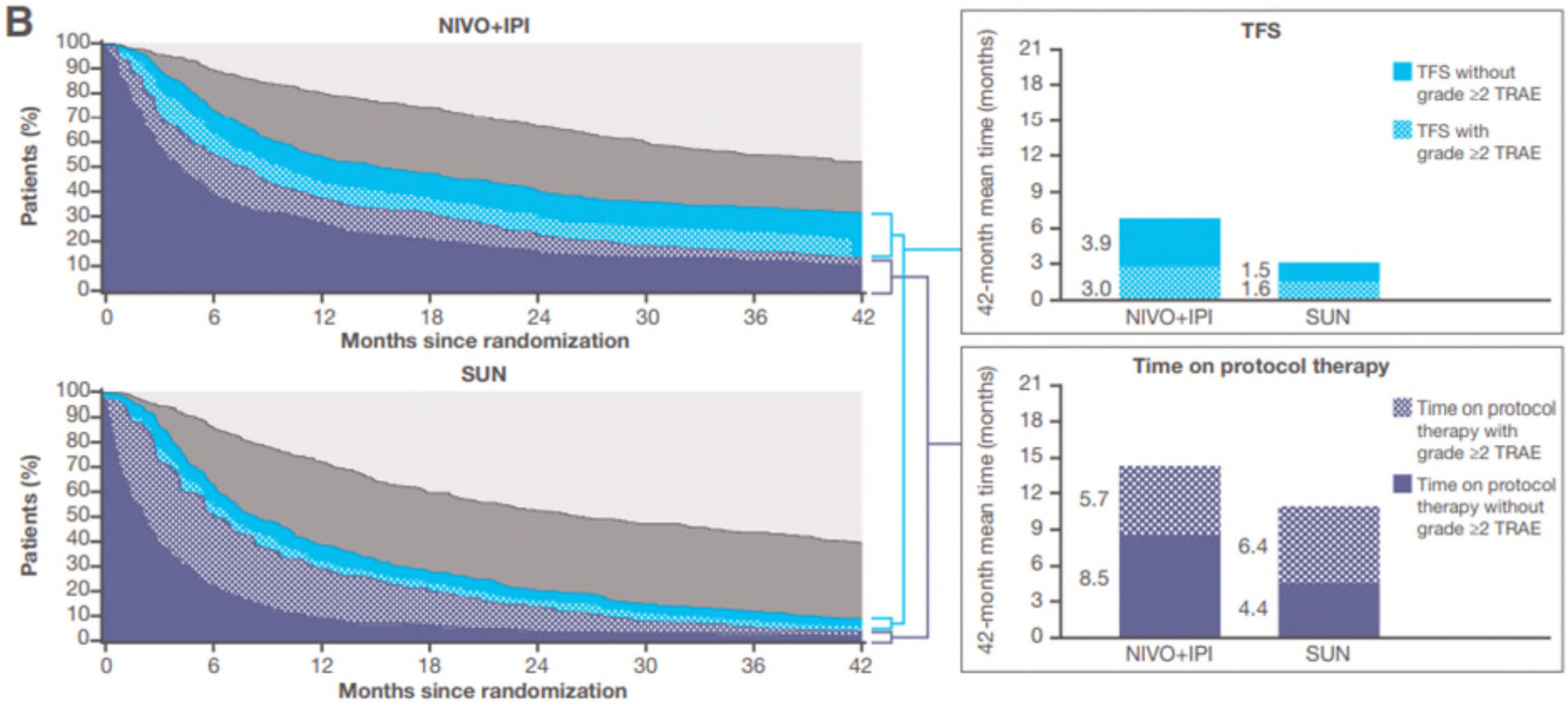
Powles et al, Lancet Oncol, 2020

Defining New Endpoints – Treatment Free Survival



Regan et al, Clin Cancer Res, 2021

Defining New Endpoints – Treatment Free Survival



Minimum 42 month follow up
Intermediate and Poor Risk Population

Regan et al, Clin Cancer Res, 2021

IO Combinations – Intermediate/Poor Risk Disease

	Nivolumab + Ipilimumab n=1096	Pembrolizumab + Axitinib n=861	Nivolumab + Cabozantinib n=651	Pembrolizumab + Lenvatinib n=1096
Int/Poor, %	78	68	77	58/9
Median f/u, mo	99.1	67.2	55.6	49.8
OS HR (CI)	46.7 vs 26.0 0.69 (0.59-0.81)	42.2 vs 29.3 0.76 (0.62-0.93)	43.9 vs 29.3 0.73 (0.58-0.91)	47.9 vs. 34.3 0.74 (0.57-0.96)
PFS HR (CI)	12.4 vs 8.5 0.73 (0.61-0.87)	13.8 vs 8.3 0.68 (0.56-0.82)	15.4 vs 7.1 0.56 (0.45-0.68)	22.1 vs 5.9 0.43 (0.34-0.55)
ORR, %	42 v 27	57 vs 35	53 vs 23	72 vs 30*
CR, %	12 vs 3	11 vs 3	13 vs 4	14 vs 4*

Benefit across all regimens in patients with intermediate and poor risk disease

Int=Intermediate; f/u=Follow-up; mo=months; OS=Overall survival; HR=Hazard ratio; CI=Confidence interval; PFS=Progression-free survival; ORR=Objective response rate; CR=Complete response; NR=Not reached. *At 33.7 month follow up.

Motzer et al, Cancer, 2022; Rini et al, ASCO, 2023; Burotto et al, GU ASCO, 2023

IO Combinations – Favorable Risk Disease

	Nivolumab + Ipilimumab n=1096	Pembrolizumab + Axitinib n=861	Nivolumab + Cabozantinib n=651	Pembrolizumab + Lenvatinib n=1096
Favorable, %	23	32	23	31
Median f/u, mo	99.1	67.2	55.6	49.8
OS HR (CI)	77.9 vs 66.7 0.82 (0.60-1.13)	NR vs NR 1.10 (0.79-1.54)	52.9 vs 58.9 1.10 (0.69-1.75)	NR vs NR 0.94 (0.58-1.52)
PFS HR (CI)	12.4 vs 28.9 1.76 (1.25-2.48)	20.7 vs 17.9 0.76 (0.57-1.02)	21.4 vs 12.8 0.69 (0.48-1.00)	28.6 vs 12.9 0.50 (0.35-0.71)
ORR, %	30 vs 52	69 vs 50	66 vs 44	68 vs 51*
CR, %	13 vs 6	13 vs 6	16 vs 8	21 vs 5*

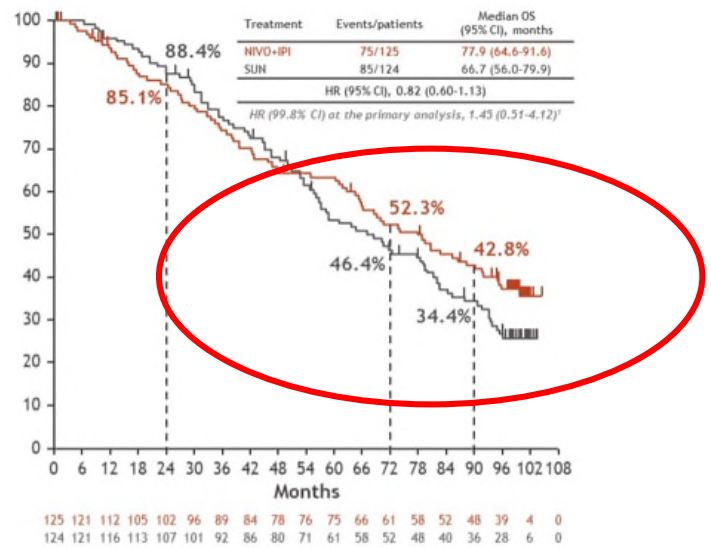
Many options for favorable risk patients
Many patients received post front line treatment

Fav=Favorable; f/u=Follow-up; mo=months; OS=Overall survival; HR=Hazard ratio; CI=Confidence interval; PFS=Progression-free survival; ORR=Objective response rate; CR=Complete response; NR=Not reached. *At the 33.7 month follow-up.

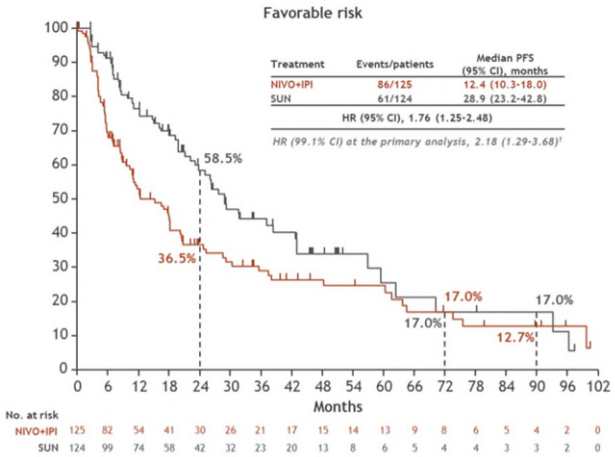
IO Combinations – Favorable Risk Disease

Nivolumab + Ipilimumab

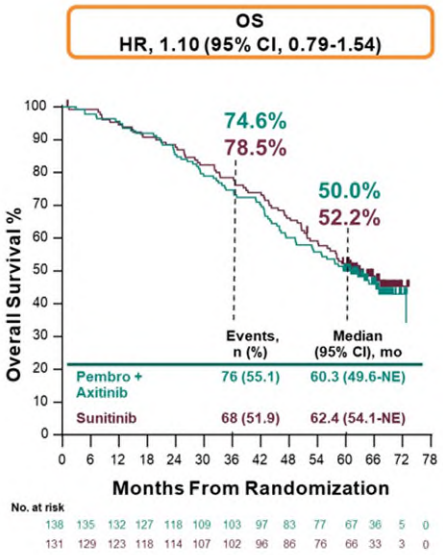
OS

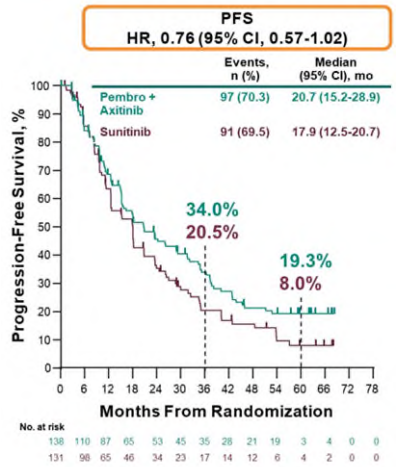


PFS

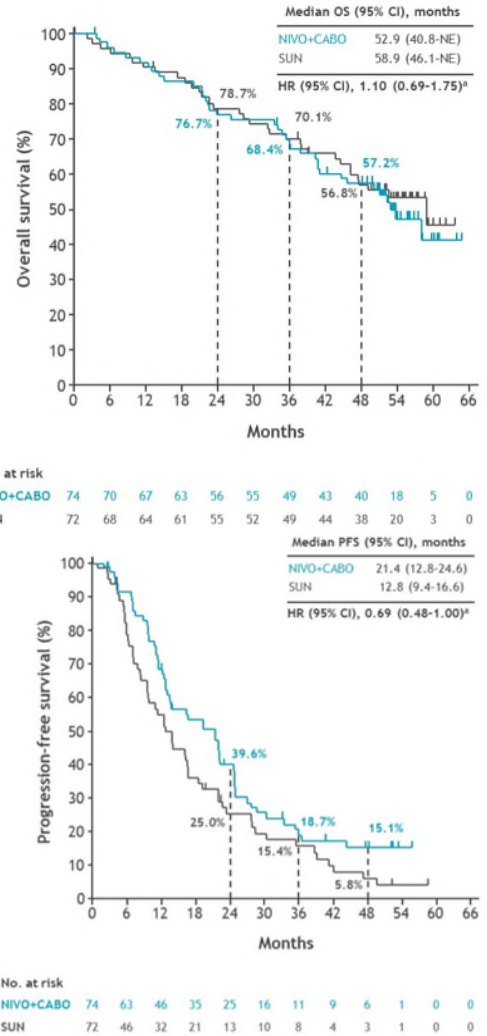


Pembrolizumab + Axitinib





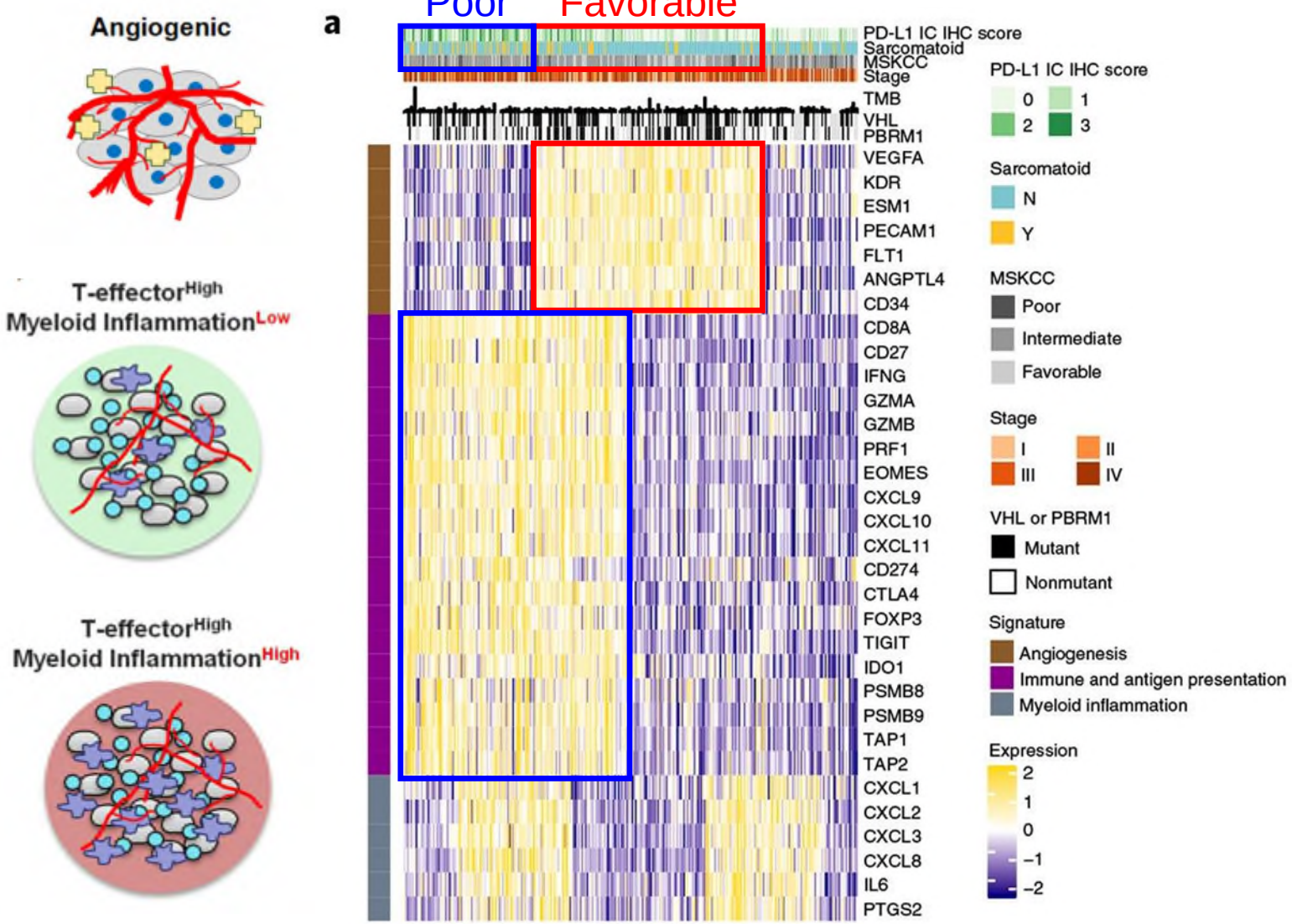
Nivolumab + Cabozantinib



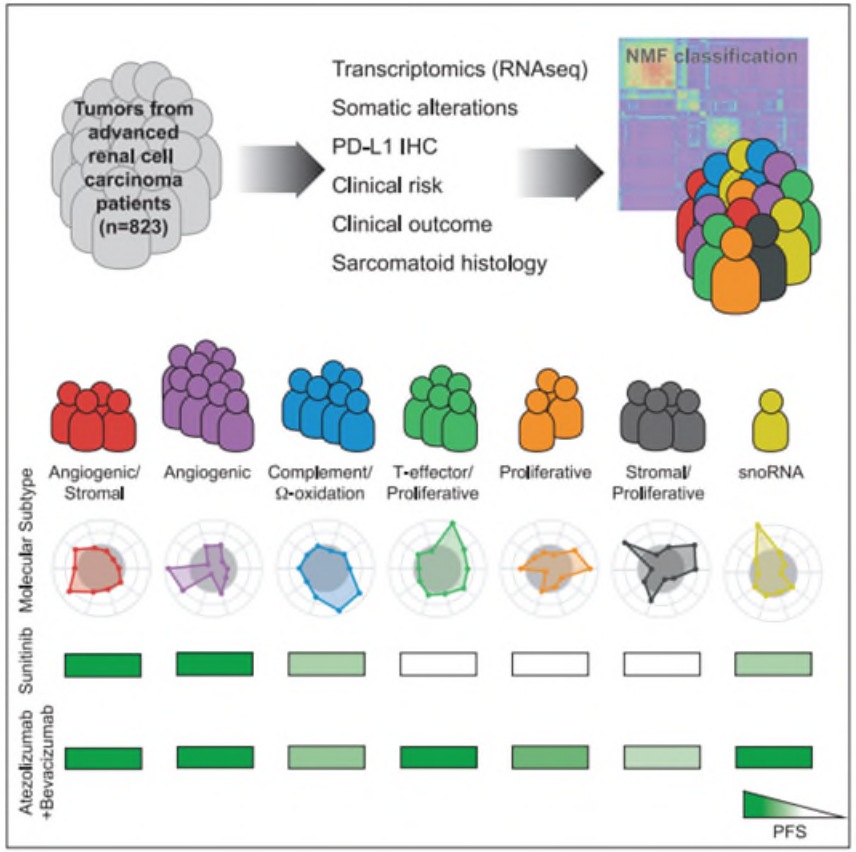
Tannir, GU ASCO, 2024; Rini, ASCO, 2023; Bourlon, GU ASCO, 2024

Transcriptomic Signatures Elucidate Heterogeneous Outcomes

IMMotion150

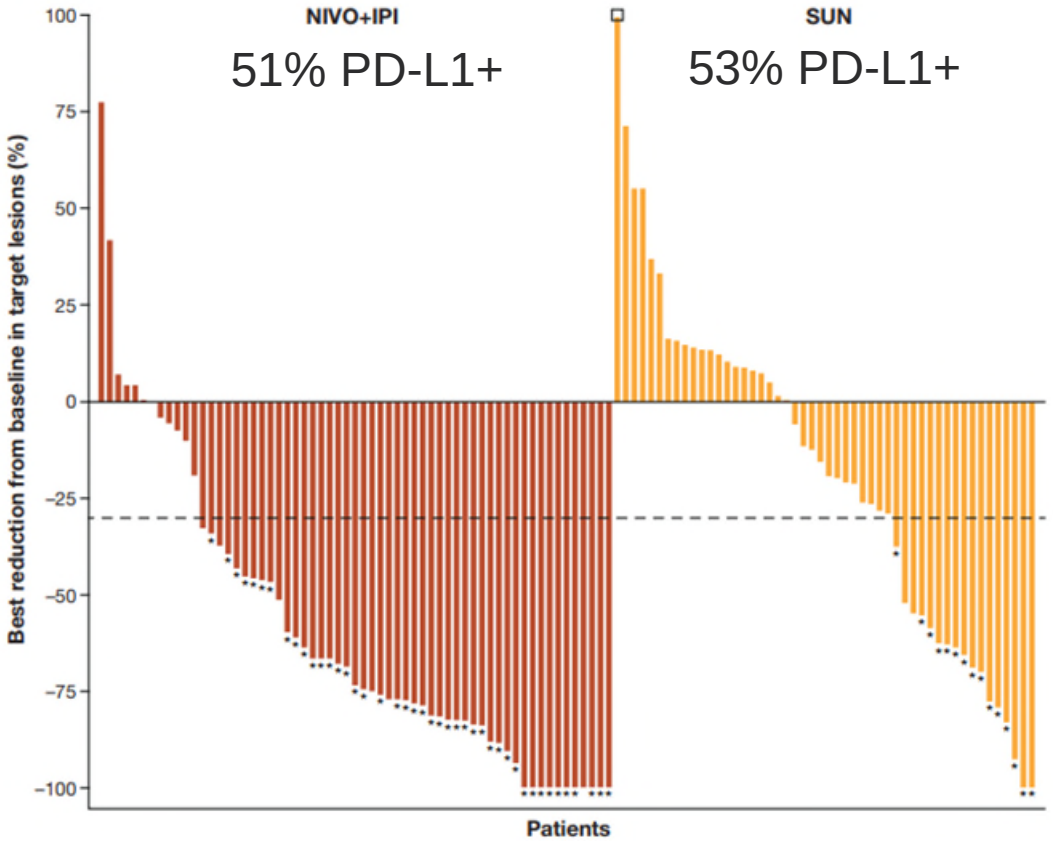


IMMotion151



McDermott et al, Nature Medicine, 2018
Motzer et al, Cancer Cell, 2020

Nivolumab and Ipilimumab for Sarcomatoid RCC



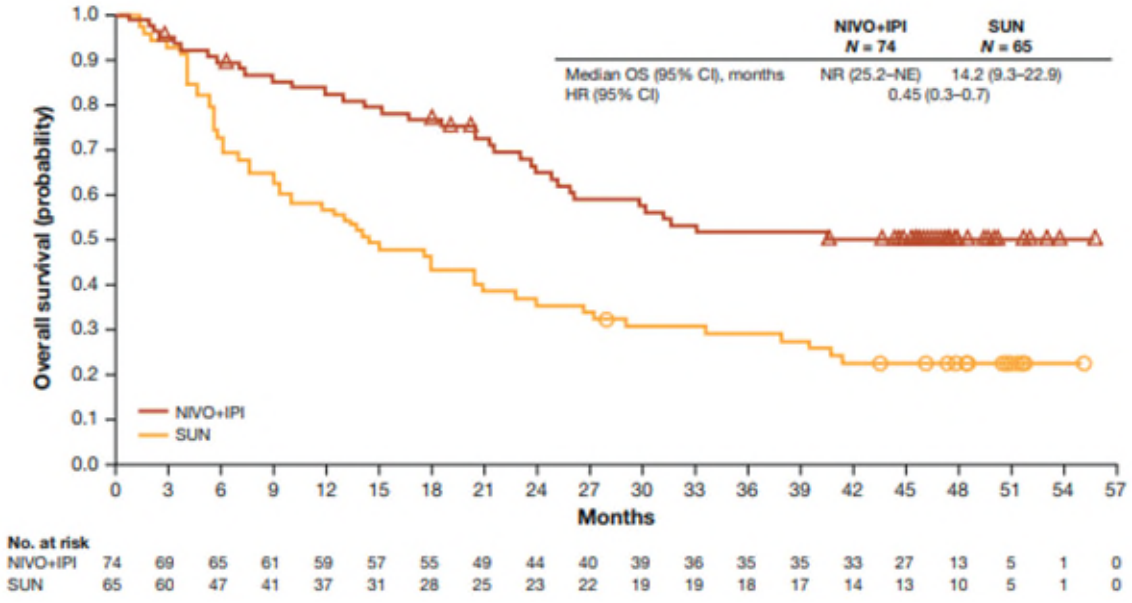
Outcome	N (n=74 Nivo + Ipi)
ORR	61%
CR	19%
PR	42%
SD	11%
PD	20%
NE	8%

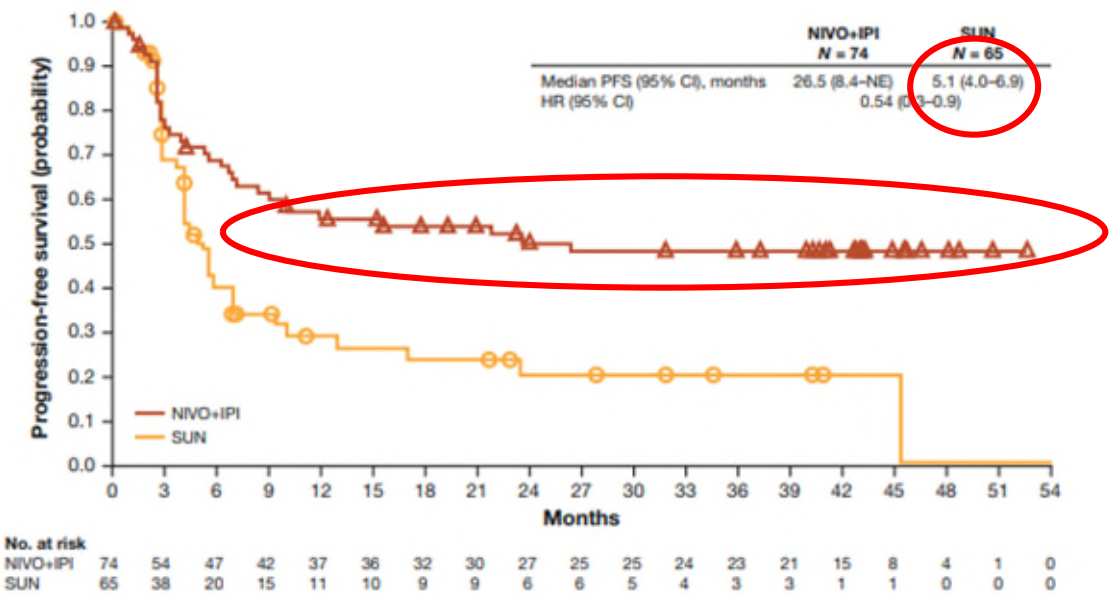
Identified as having a sarcomatoid-positive RCC by local pathology reports and/or independent central review (n=85/145)

ORR=Objective response rate; CR=Complete response; PR=Partial response; SD=Stable disease; PD=Progressive disease; NE=Not evaluable.

Tannir et al, CCR, 2020

Nivolumab and Ipilimumab for Sarcomatoid RCC





Minimum 42 month follow up
Intermediate and Poor Risk Population

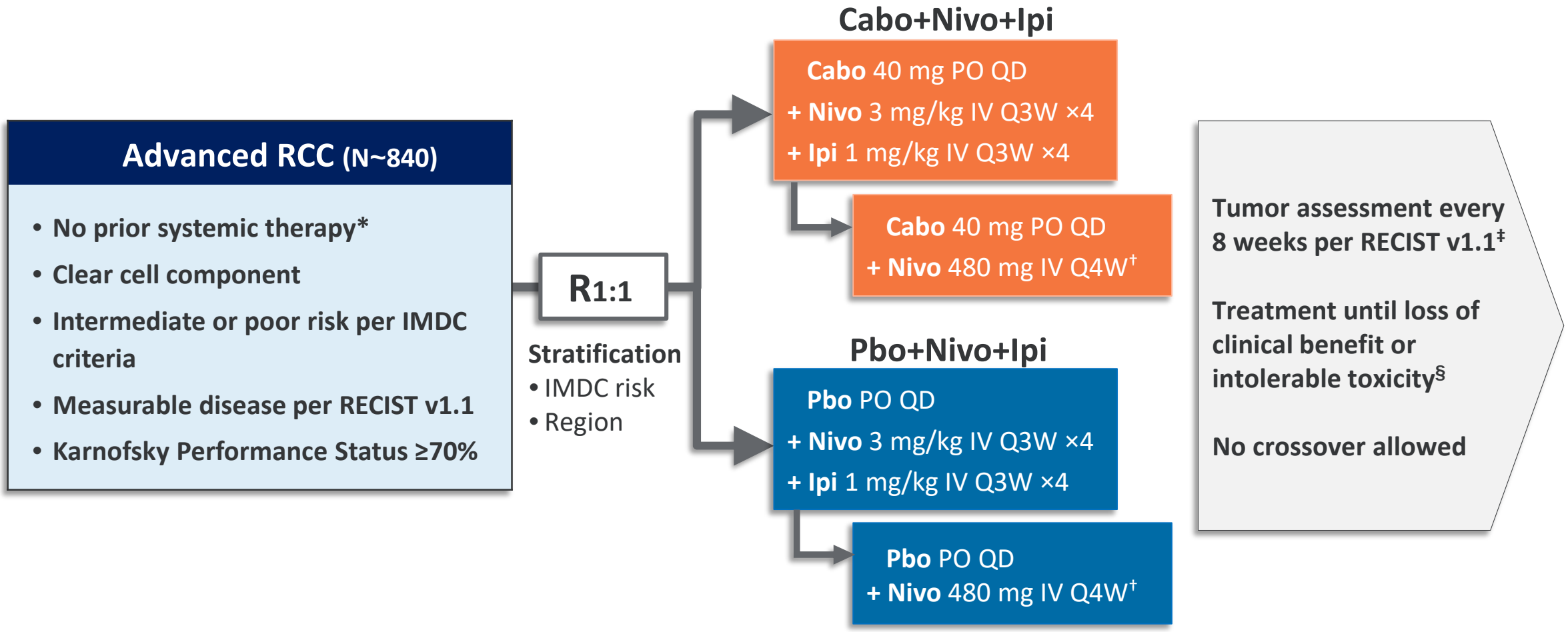
Tannir et al, CCR, 2020

IO-VEGF Combinations for Sarcomatoid RCC

Trial	Phase	Histology	Sarcomatoid	ORR	PFS	OS
IMmotion-151 – Atezo + Bevacizumab	III	cc	142/915 (15.5%)	49%	8.3 months	21.7 months
Javelin 101 – Avelumab + Axitinib	III	cc	108/886 (12.2%)	46.8%	7.0 months	NR
Keynote-426 – Pembro + Axitinib	III	cc	105/861 (12.2%)	58.8%	Not reached	Not reached
Checkmate-9ER – Nivo + Cabozantinib	III	cc	75/651 (11.5%)	55.9%	10.9 months	Not reached
Clear – Pembrolizumab + Lenvatinib	III	cc	49/712 (6.8%)	60.7%	11 months	Not reached
Atezo + Bevacizumab	II	cc + ncc	26/60 (43%)	cc 50%/ncc 38%	NR	NR

Ncc=Non-clear cell; cc=Clear cell; ORR=Objective response rate; PFS=Progression free survival; OS=Overall survival; NR=Not recorded.

Moving into Triple Therapy: Cosmic 313



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

Choueiri et al, ESMO Annual Congress, 2022

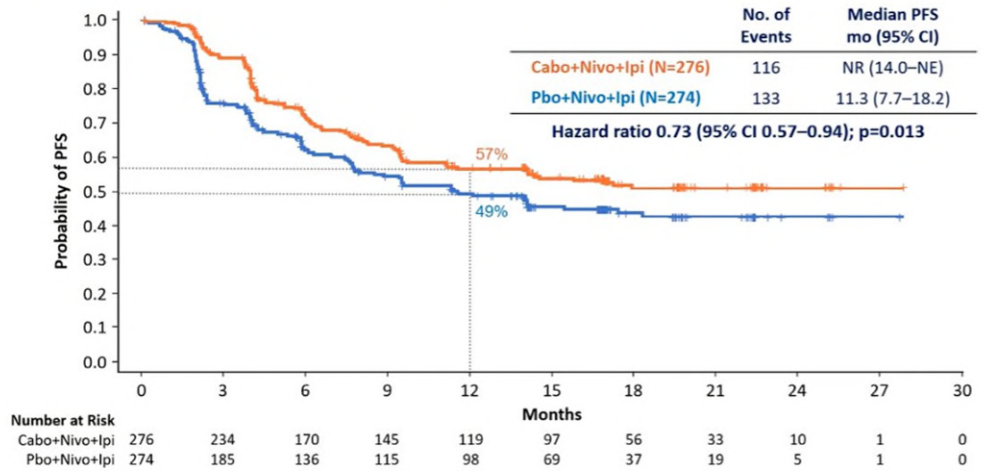
Understanding the COSMIC 313 Patient Population

Variable		Nivolumab + Ipilimumab n=1096	Pembrolizumab + Axitinib n=861	Nivolumab + Cabozantinib n=651	Pembrolizumab + Lenvatinib n=1096	Nivolumab + Ipilimumab + Cabozantinib N=855
IMDC Risk Group	Favorable, %	23%	33%	23%	32%	0%
	Intermediate, %	61%	56%	58%	54%	75%
	Poor, %	17%	13%	19%	10%	25%
Previous Nephrectomy, %		81%	83%	69%	73%	65%
Sarcomatoid Features, %		14%	18%	11%	8%	6.4%*
Bone Metastases, %		20%	24%	24%	24%	19%
Liver Metastases, %		18%	15%	23%	17%	20%
PD-L1 Expression ≥1%, %		24% (Dako PD-L1 28-8; Tumor)	60% (Agilent Tech PD-L1 22C3; CPS)	25% (Dako PD-L1 28-8; Tumor)	31% (Agilent Tech PD-L1 22C3; CPS)	21% (Dako PD-L1 28-8; Tumor)

*35/550 in the PITT population.

COSMIC 313 Outcomes

Progression-Free Survival: Final Analysis (PITT Population)



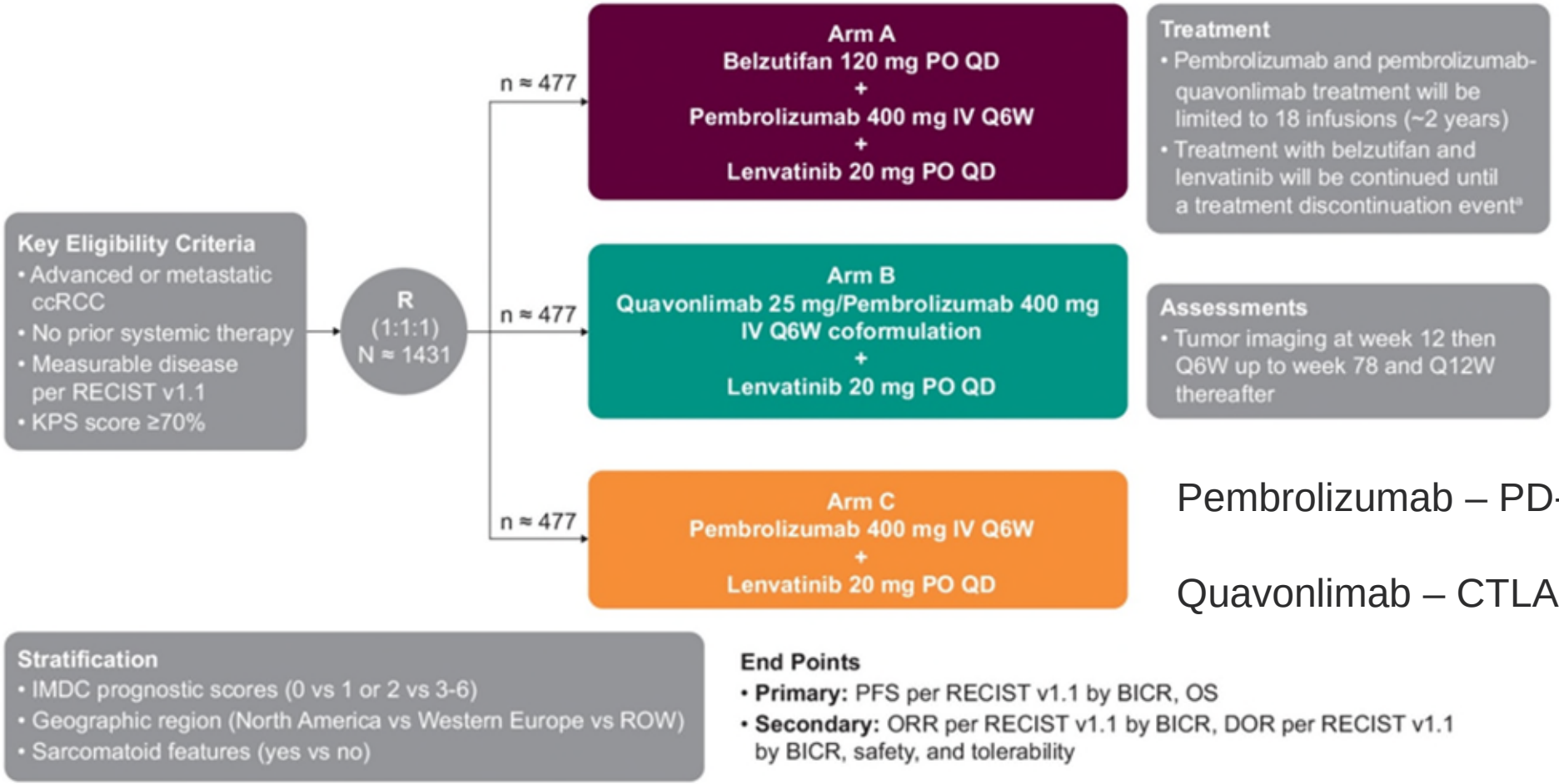
	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

	Cabo+Nivo+Ipi (N=426)	Pbo+Nivo+Ipi (N=424)
Median duration of exposure of study treatment (range), mo	10.9 (0.2–28.5)	10.3 (0.1–28.1)
Median average daily dose (range) of Cabo or Pbo, mg	23.2 (3.6–40.0)	36.1 (0.8–40.0)
Median Nivo infusions (range) received, no	10 (1–27)	9 (1–27)
Doses of Ipi received, %		
4	58	73
3	13	14
2	22	7
1	7	6
Any dose hold due to an AE, %	90	70
Any dose reduction of Cabo or Pbo due to an AE, %	54	20
Treatment-related AE leading to discontinuation, %		
Any study treatment	45	24
Cabo or Pbo	28	14
Nivo	26	18
Ipi	30	12
All treatment components (due to the same AE)	12	5

	Cabo+Nivo+Ipi (N=426)		Pbo+Nivo+Ipi (N=424)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse events				
Any event,* %	99	73	91	41
Alanine aminotransferase increased	46	26	17	6
Aspartate aminotransferase increased	44	20	16	5
Diarrhea	41	4	18	3
Palmar-plantar erythrodysesthesia	28	3	4	0
Hypothyroidism	24	<1	15	0
Hypertension	23	8	5	2
Fatigue	22	2	21	1
Lipase increased	22	9	13	6
Amylase increased	20	5	12	2
Rash	20	2	20	1
Pruritus	20	0	26	<1

On the Horizon: Additional Triple Therapy Combinations

MK6482-012



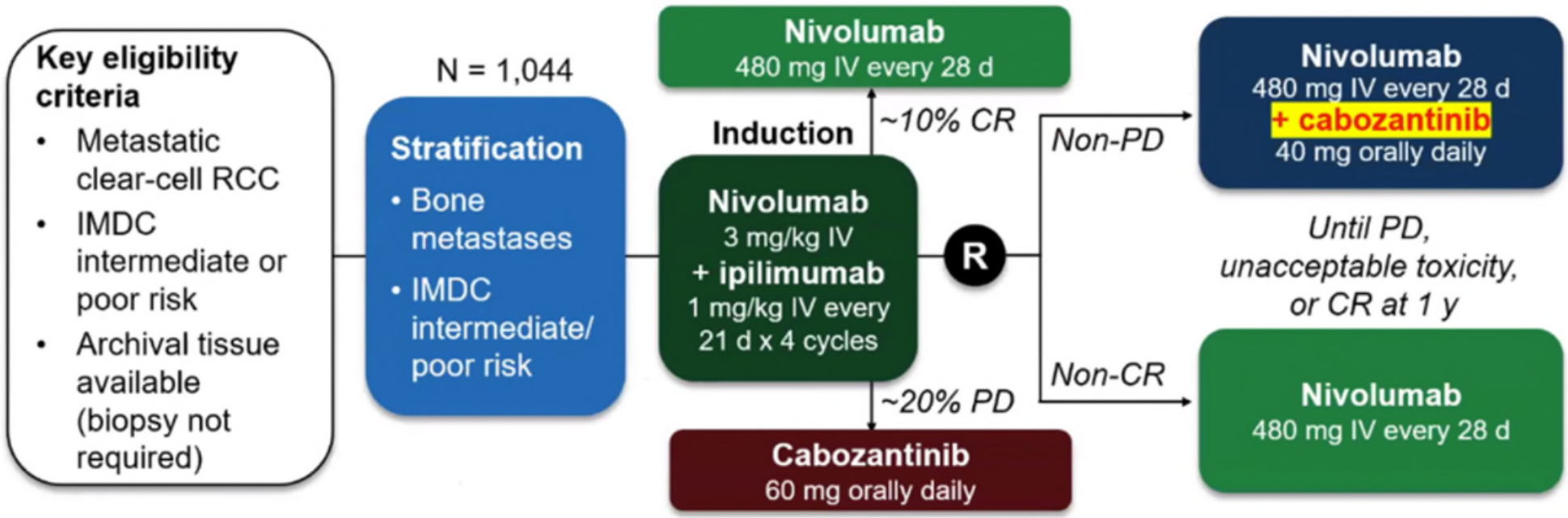
Pembrolizumab – PD-1 inhibitor

Quavonlimab – CTLA-4 inhibitor

On the Horizon: Maintenance IO-VEGF

PDIGREE (Alliance A031704)

Nivolumab + Ipilimumab Followed by Nivolumab or Nivolumab + Cabozantinib



Endpoints

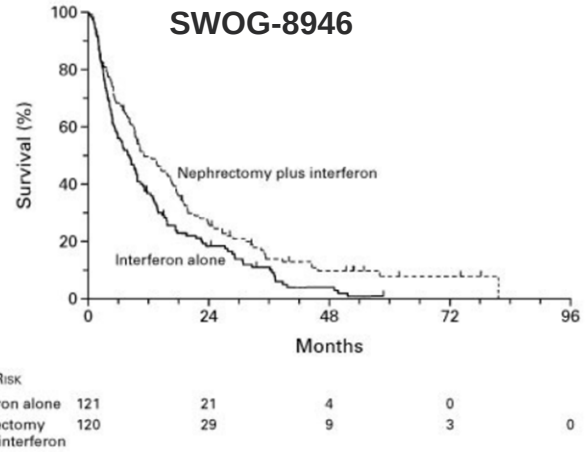
- **Primary:** OS
- **Key secondary:** PFS, 1-y CR rate, ORR by RECIST, toxicity, and correlatives

Principal Investigator: Tian Zhang

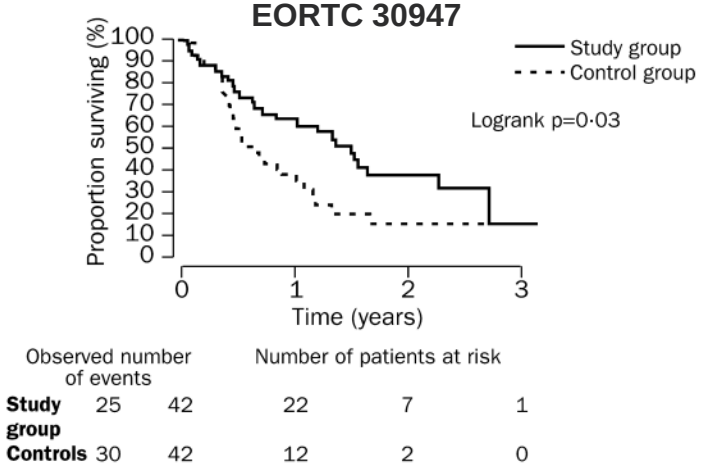
Evolving Role of Cytoreductive Nephrectomy

Cytokine Era

SWOG-8946

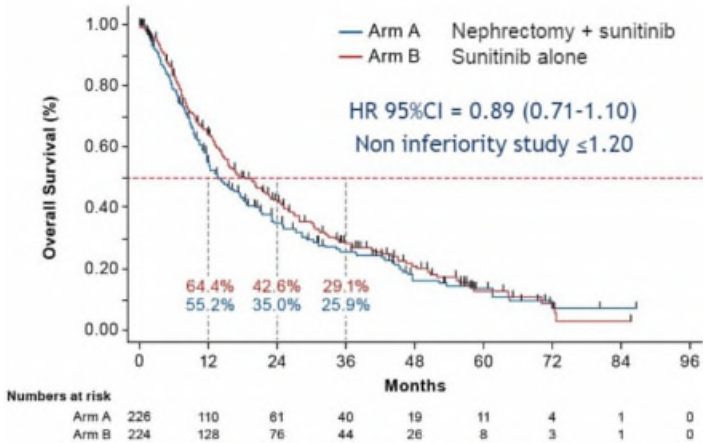


EORTC 30947



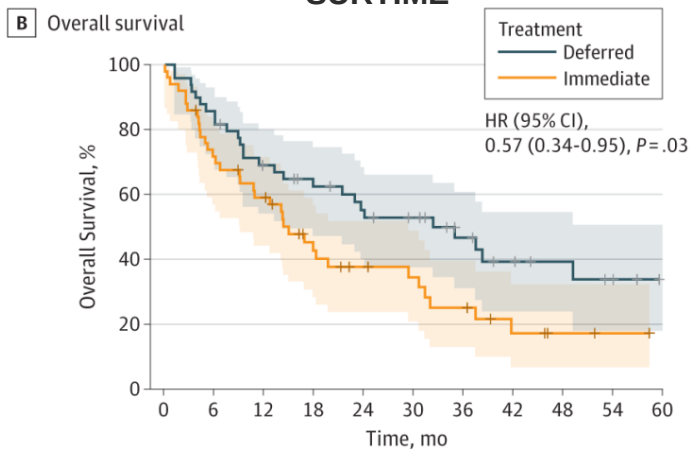
Targeted Therapy Era

CARMENA



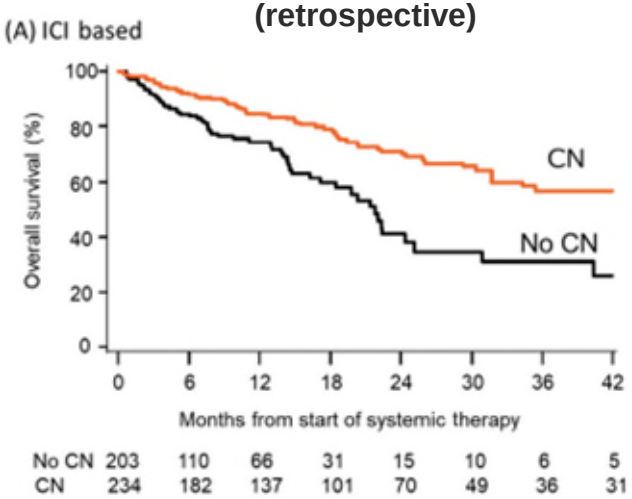
Median follow-up was 50.9 months (range 0.0-86.6)

SURTIME



IO Combination Era

IMDC (retrospective)



Flanigan et al, NEJM, 2001; Mickisch et al, Lancet, 2001; Mejean et al, NEJM, 2018; Bex et al, JAMA Oncology, 2018

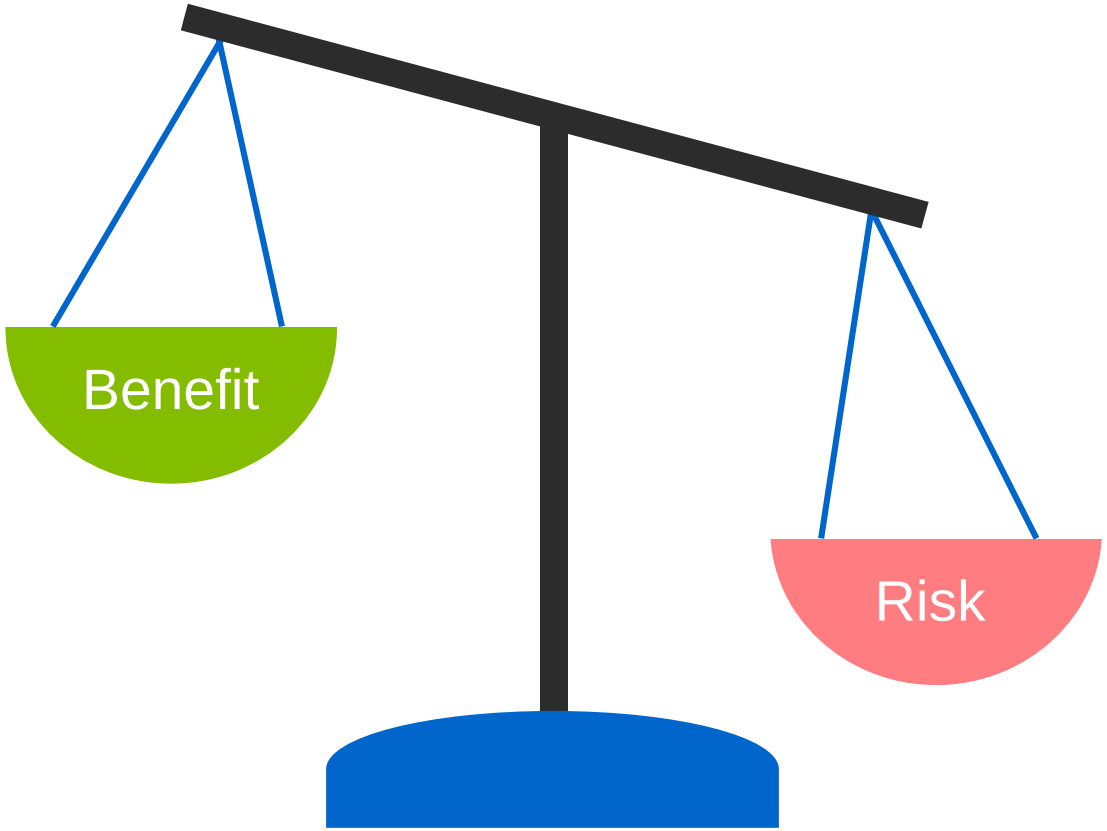
Treatment Options for Non-Clear Cell RCC

Study	Phase	Agent	N	Histology	ORR (%)	PFS (months)
VEGF Monotherapy						
PapMet	2	Cabozantinib vs Sunitinib	147	Papillary	23% vs 4%	9.0 vs 5.6
Savior	3	Savolitinib vs Sunitinib	60	Met-driven RCC	27% vs 7%	7.0 vs 5.6
Immunotherapy						
Keynote-427	2	Pembrolizumab	165	Papillary, chromophobe, unclassified	26.7%	4.2
HCRN GU16-260	2	Nivolumab	35	Papillary, chromophobe, unclassified	14.3%	4.0
Checkmate-920	2	Nivolumab + Ipilimumab	52	Non-clear cell RCC	19.6%	3.7
Immunotherapy + VEGF						
Cosmic-021	1b	Cabozantinib + Atezolizumab	32	Non-clear cell RCC	31%	9.5
Lee, JCO, 2022	2	Nivolumab + Cabozantinib	47	Cohort 1) Papillary, unclassified, or translocation; 2) Chromophobe	1) 47.5%; 2) 0%	1) 12.5
Keynote-B61	2	Pembrolizumab + Lenvatinib	82	Non-clear cell RCC	47.6%	72.3%*
McGregor, JCO, 2020	2	Atezolizumab + Bevacizumab	60	Non-clear cell RCC; >20% Sarcomatoid	33%	8.3

*6-month progression-free survival. ORR=Objective response rate; PFS=Progression free survival.

Balancing Goals for Selection of Therapy

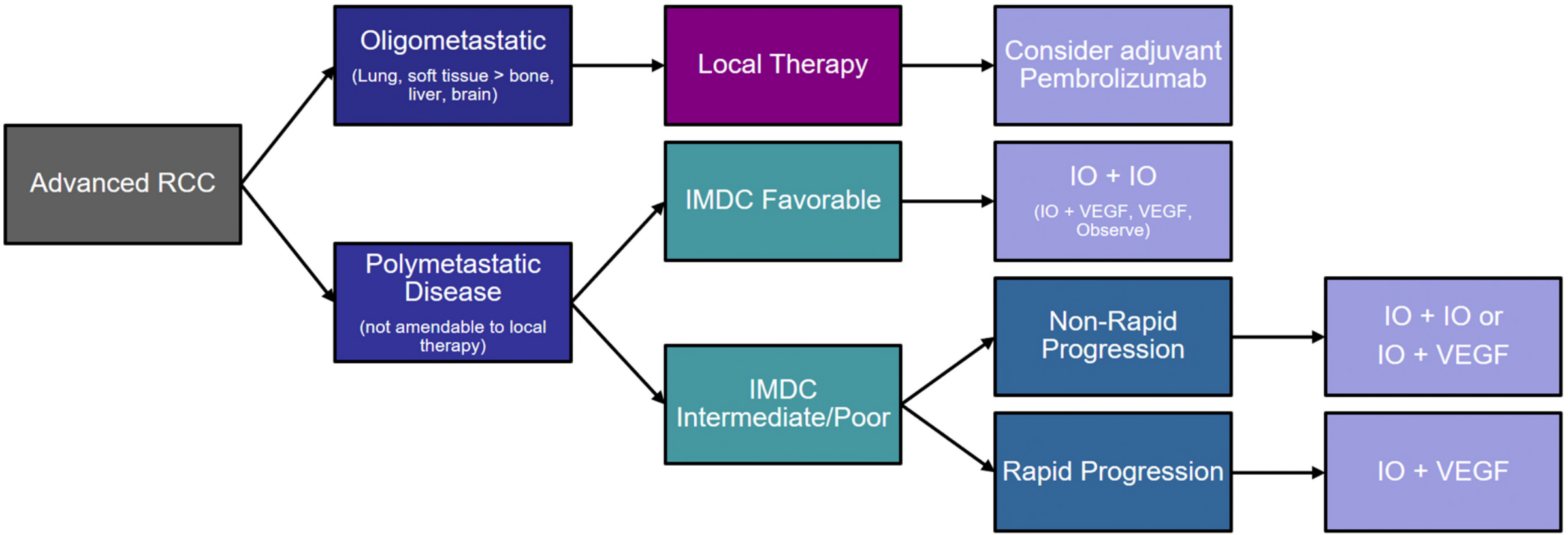
Improved OS
Improved PFS
Improved response rate
Limited PD rate
Durability of response
Depth of response
Complete response
Treatment-free survival
Improved QOL



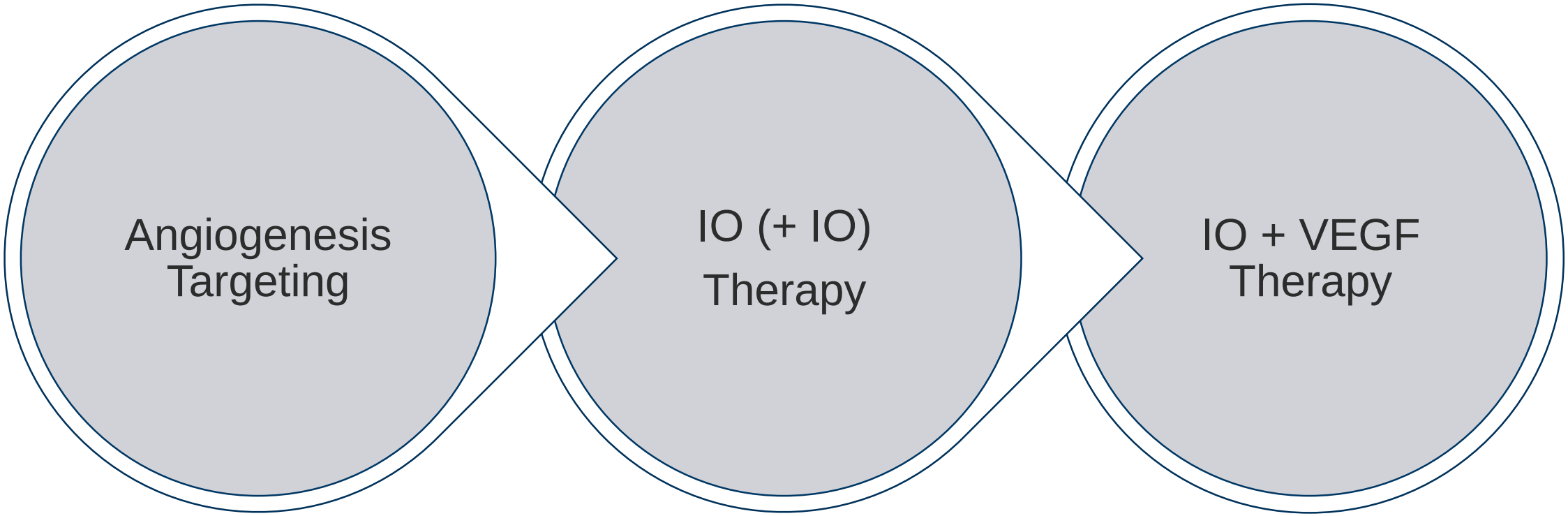
Immune-mediated AE
Chronic TKI toxicity
Limited durability of response
Primary PD rate
No benefit in QOL

OS=Overall survival; PFS=Progression-free survival; PD=Progressive disease; QOL=Quality of life; AE=Adverse event; TKI=Tyrosine kinase inhibitor.

Practical Approach for Treatment – 2/2024



Systemic Treatments in the Refractory Setting



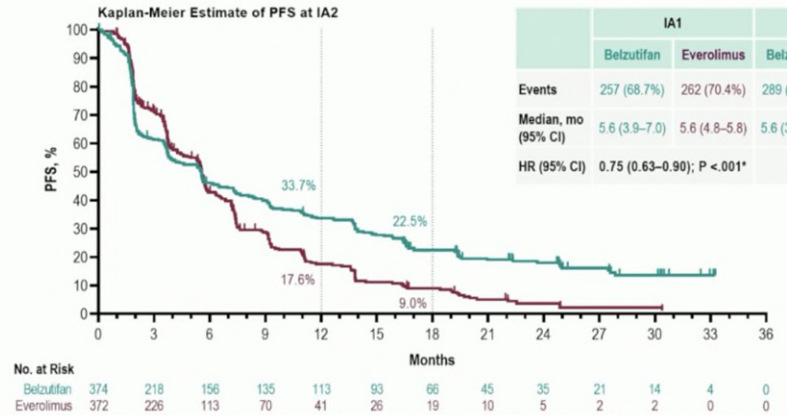
VEGF Therapy in the Refractory Setting

	Axitinib (AXIS)	Cabozantinib (METEOR)	Lenvatinib + Everolimus	Tivozanib (Tivo-3)	Cabozantinib + Telaglenastat (CANTATA)
Phase, N	3, 723	3, 658	2, 153	3, 350	2, 444
Treatment line	2	≥2	2	3-4	≥2
Comparator(s)	Sorafenib	Everolimus	Lenvatinib vs everolimus	Sorafenib	Cabozantinib
Prior CPI	0%	5%	0%	26%	62%
ORR	19% vs 9%	17% vs 3%	43% vs 27% vs 6%	18% vs 8%	31% vs 28%
PFS, months HR (95% CI)	6.7 vs 4.7 0.67 (0.54-0.81)	7.4 vs 3.9 0.52 (0.42-0.62)	14.6 vs 7.4 vs 5.5 0.40 (0.24-0.68) 0.66 (0.39-1.10)	5.6 vs 3.9 0.73 (0.56-0.94)	9.2 vs 9.3 0.94 (0.74-1.21)
OS, months HR (95% CI)	20.1 vs 19.2 0.97 (0.80-1.17)	21.4 vs 16.5 0.66 (0.53-0.83)	25.5 vs 19.1 vs 15.4 0.51 (0.30-0.88) 0.75 (0.43-1.30)	16.4 vs 19.1 0.89 (0.70-1.14)	22.2 vs 24.8
Approval date	2012	2016	2016	2021	Not Approved

Belzutifan in Refractory Clear Cell RCC – LITESPARK-005

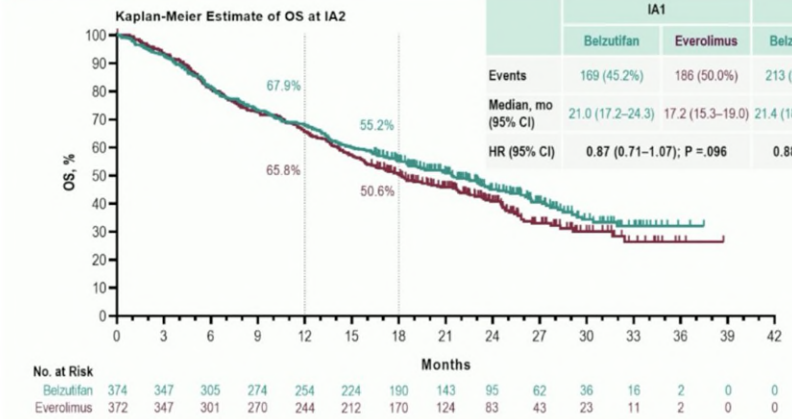
FDA Approved 12/2023

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)	

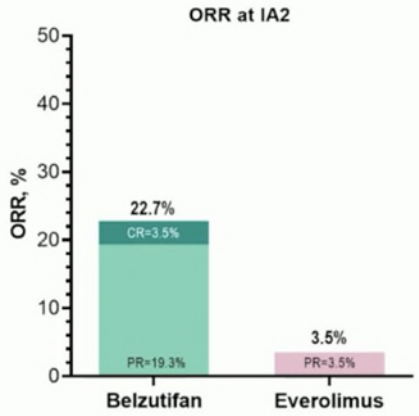
Primary Endpoint: OS



	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	

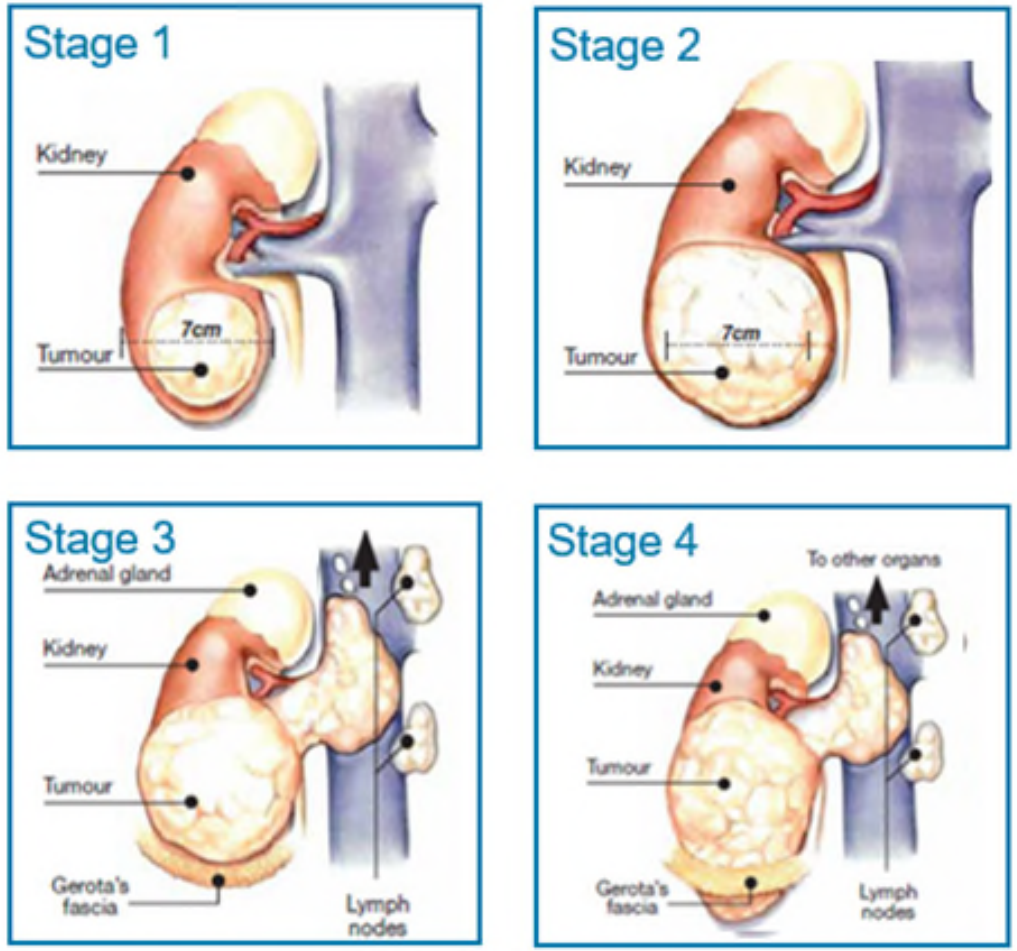
Key Secondary Endpoint: ORR by BICR per RECIST 1.1

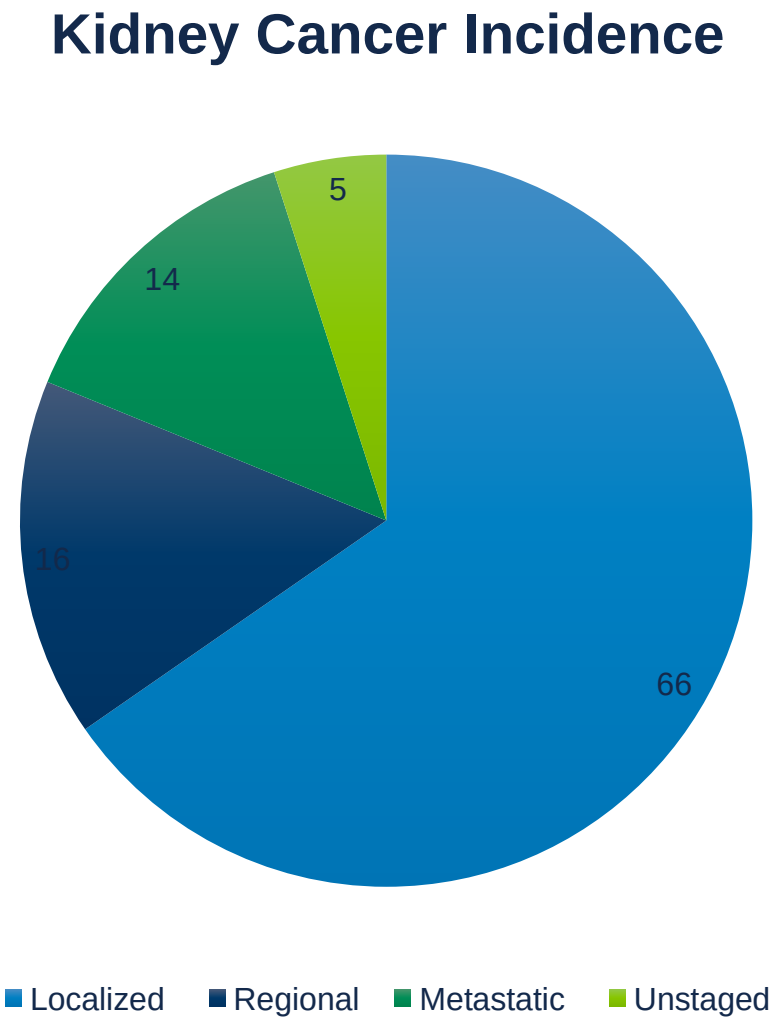
	Belzutifan (N = 374)	Everolimus (N = 372)
	IA1	
ORR, % (95% CI)	21.9% (17.8–26.5)	3.5% (1.9–5.9)
Estimated difference in % (95% CI)	18.4 (14.0–23.2); P <.00001*	
CR	2.7%	0
PR	19.3%	3.5%
SD	39.3%	65.9%
PD	33.7%	21.5%
Non-evaluable[a]	1.3%	2.2%
No assessment[b]	3.7%	7.0%
	IA2	
ORR, % (95% CI)	22.7% (18.6–27.3)	3.5% (1.9–5.9)
Estimated difference in % (95% CI)	19.2 (14.8–24.0)	



Albiges et al, ESMO, 2023

Risk of Recurrence Increases with Stage





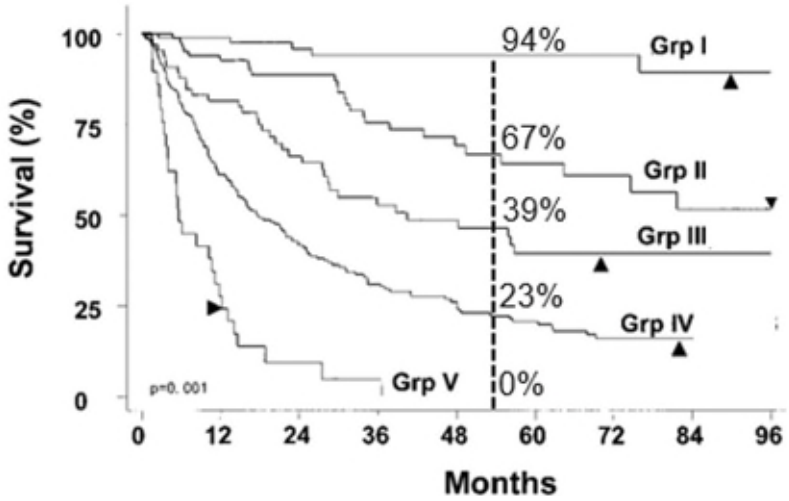
Risk Stratification Tools in Localized RCC

Model	Parameters	Outcome	Type
UISS	TNM, grade, ECOG PS	OS	KM Analysis
SSIGN	TNM, pN+, pM+, tumor size, grade, tumor necrosis	CSS	Algorithm
Leibovich	TNM, pN+, tumor size, grade, tumor necrosis	MFS	Algorithm
MSKCC	TNM, tumor size, grade, tumor necrosis, symptoms	RFS	Nomogram
Kattan	TNM, tumor size, histology, symptoms	RFS	Nomogram
Yaycioglu	Tumor size, symptoms	RFS	Formula
Karakiewic	TNM, age, sex, + margin, tumor size, symptoms	CSS	Nomogram
Cindolo	Tumor size, symptoms	RFS	Formula

UISS=University of California at Los Angeles Integrated Staging System; SSIGN=Stage, Size, Grade, and Necrosis Score; MSKCC=Memorial Sloan Kettering Cancer Center; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=Overall survival; CSS=Cancer-specific survival; MFS=Metastasis-free survival; RFS=Recurrence-free survival; KM=Kaplan-Meier.

UCLA Integrated Staging System

pTNM Stage, Grade, Performance status



Zisman et al, J Clin Oncol, 2002; Frank et al, J Urol, 2002; Leibovich et al, Cancer, 2003; Sorbellini et al, J Urol, 2005; Kattan et al, J Urol, 2001; Yaycioglu et al, Urology, 2001; Karakiewicz et al, JCO, 2007; Cindolo et al, BJU Int, 2003

Adjuvant Cytokine Therapy Did NOT Improve Survival

Trial	Population	Arms	N	Primary	Outcome
Porzsolt et al (1992)	pT3-4N0 or pTxN1-3	IFN-α vs. Observation	270	TTF/Survival	No Difference
Trump et al (1996)	pT3-4aN0 or pTxN1-3	L-IFN vs. Observation	294	Recurrence	No Difference
Pizzocaro et al (2001)	pT3-4aN0 or pTxN1-3	IFN-α vs. Observation	247	5-year DFS	No Difference
Messing et al (2003)	pT3-4aN0 or pTxN1-3	IFN-α vs. Observation	283	5-year OS	No Difference
Clark et al (2003)	pT3b-4Nx or pTxN1-3	IL-2 vs. Observation	138	2-year DFS	No Difference
Atzpodien et al (2005)	pT3b-4Nx or pTxN1-3	IL-2/IFN-α/5-FU vs. Observation	203	2-year DFS	No Difference
Aitchison et al (2014)	pT3b-4Nx or pTxNa-2 or +margin/vascular invasion	IL-2/IFN-α/5-FU vs. Observation	309	3-year DFS	No Difference

IFN-α=Interferon alpha; L-IFN=Lymphoblastoid interferon; IL-2=Interleukin 2; 5-FU=5-Fluorouracil; TTF= Time to treatment failure; DFS=Disease-free survival; OS=Overall survival.

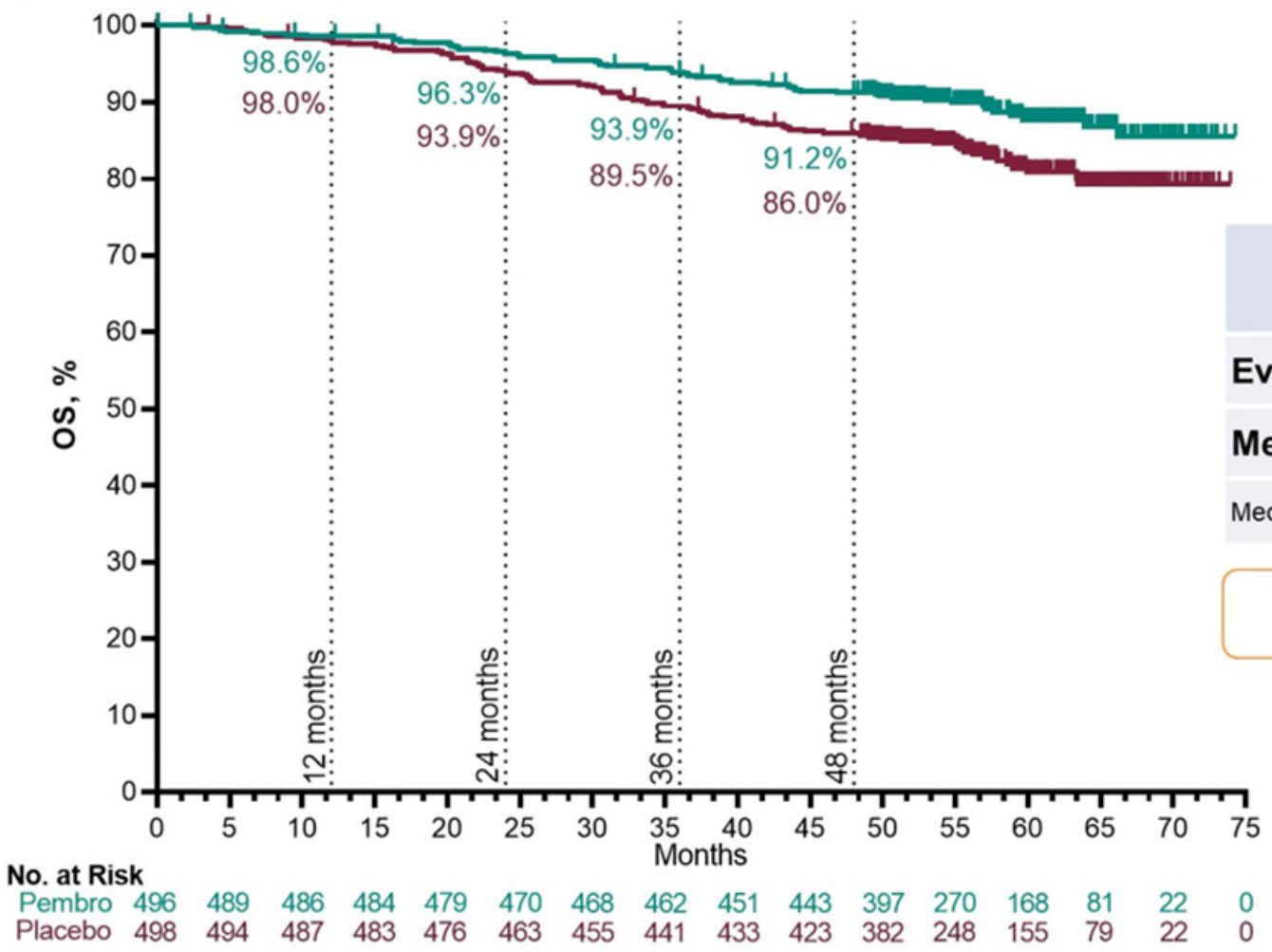
Porzsolt et al, Proceedings of ASCO, 1992; Trump et a;, Proceedings of ASCO, 1996; Pizzacaro et al, JCO, 2001; Messing et al, NEJM, 2003; Clark et al, JCO, 2003; Atzpodien et al Br J Cancer, 2005; Aitchizon et al, EJC, 2014

Adjuvant Targeted Therapy with Mixed Results

Trial	Arms	Years	N	Primary Endpoint	CC Only	Eligibility	Hazard Ratio Confidence Interval
ASSURE (Haas, Lancet, 2016)	Sunitinib vs. Sorafenib vs. Placebo*	1	1943	DFS	No	pT1bG3-4N0, pT2-4GxN0, TxGxN+	Sunitinib – 1.02 (97.5% CI 0.85-1.23) Sorafenib – 0.97 (97.5% CI 0.80-1.17)
STRAC (Ravaud, NEJM, 2016)	Sunitinib vs. Placebo	1	615	DFS	Yes	pT3-4GxN0-x, TxGxN1-2	0.76 (95% CI 0.59-0.98)
PROTECT (Motzer, JCO, 2017)	Pazopanib vs. Placebo*	1	1538	DFS	Yes	pT2G3-4N0, pT3-4N0, pTxN1	0.86 (95% CI 0.70-1.06)
ATLAS (Gross-Goupil, Ann Oncol, 2018)	Axitinib vs. Placebo	1-3	724	DFS	Yes	pT2-4GxN0, pTxN1	0.870 (95% CI 0.66-1.147)
SORCE (Eisen, JCO, 2020)	Sorafenib vs. Placebo)*	1-3	1711	DFS	No	Leibovich score 3-11	1.01 (95% CI 0.83-1.23)
EVEREST (Ryan, Lancet, 2023)	Everolimus vs. Placebo	1	1545	RFS	No	pT1bG3-4N0, pT2-4N1	0.85 (95% CI 0.72-1.00)

*Starting dose change during study; DFS=Disease-free survival; CC=Clear cell; RFS=Recurrence-free survival; CI=Confidence Interval.

Keynote-564 Outcomes



First Adjuvant IO Therapy to Improve OS in Any Malignancy

	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)		

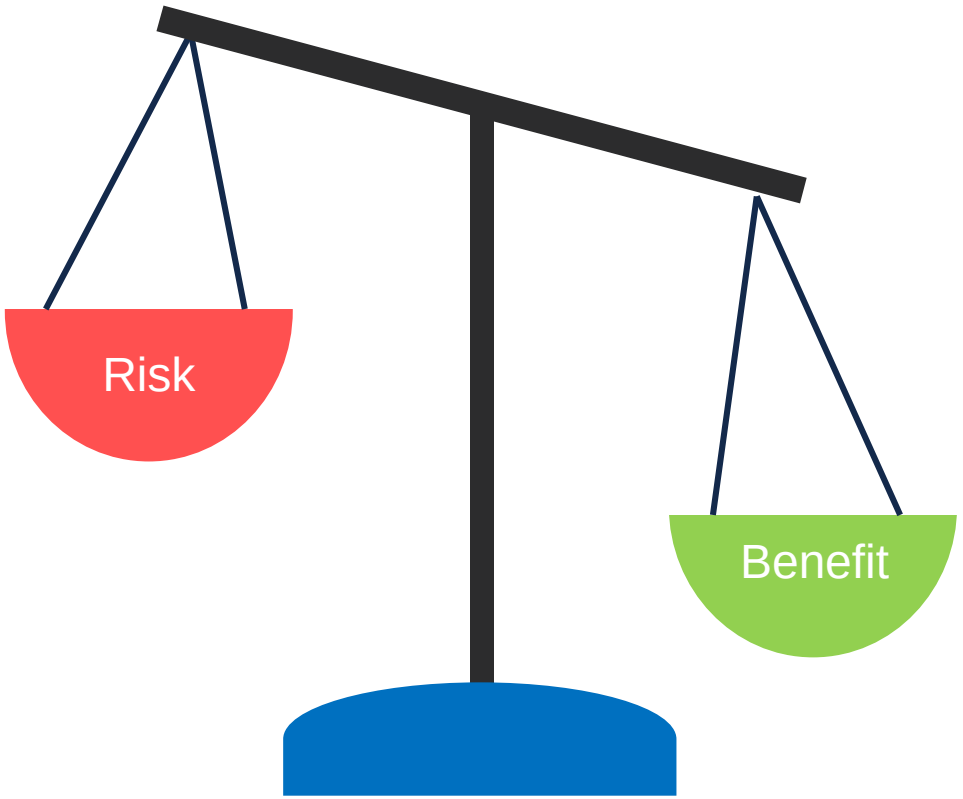
HR 0.62 (95% CI 0.44–0.87); *P* =.002*

*** 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.

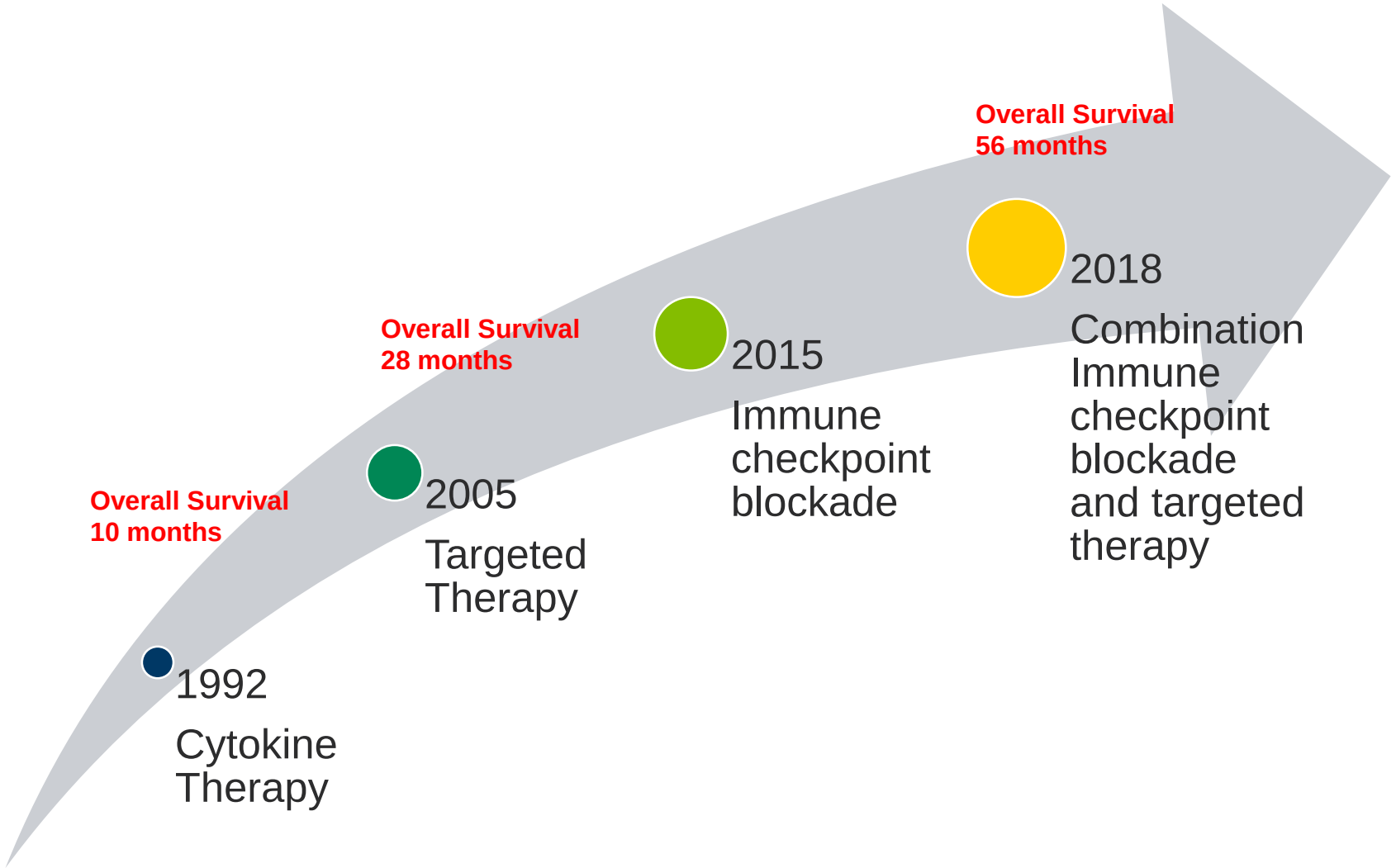
Choueiri, GU ASCO, 2024

Decision for Adjuvant Therapy



- Disease-free survival
- Overall survival
- Risk of over treatment
- Side effects of therapy
- Quality of life
- Financial cost

Decades of Progress



Conclusions

- Significant advances in our understanding of cancer and RCC tumor biology has resulted in improved therapeutic options for patients in the clinical
- Survival has dramatically improved for patients with RCC over the past decade and approaches 5 years in the modern era
- Additional studies designed to test novel treatments, radiation therapy, surgery and biomarker based strategies are underway and will certainly impact the future landscape of RCC