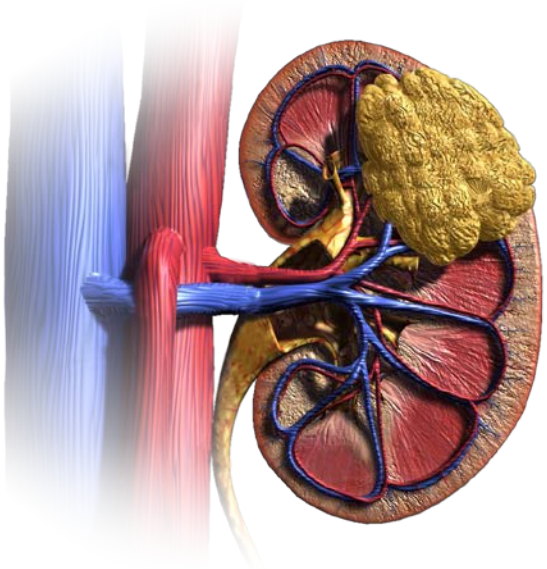
Comprehensive HemOnc Review:
Renal Cell Carcinoma



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October 4, 2020

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Disclosures

- **Research Funding**
  - Bristol-Myers Squibb
  - Clinigen
  - Exelixis
  - Jounce Therapeutics
  - Merck
  - Nektar Therapeutics
  - Pfizer
- **Consulting**
  - Merck

Learning Objectives

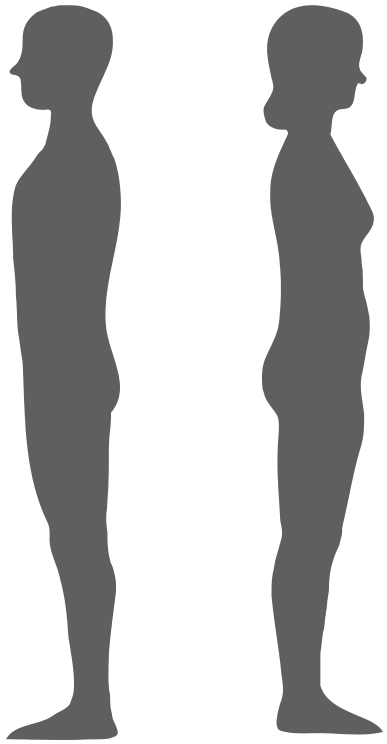
- RCC Epidemiology
- Hereditary RCC cancer syndromes
- Risk Stratification
- Cytoreductive Nephrectomy
- Systemic Treatments Overview
  - Local RCC - Adjuvant therapy
  - Metastatic RCC
    - → 1st line
    - → 2nd line
    - → Clinical subsets

Epidemiology

2020 - Estimated US New Cancer Cases*

2020 US Estimates:
- **73,750 new cases**
- **14,830 deaths**

Men 893,660		Women 912,930	
Prostate	21%	30%	Breast
Lung & bronchus	13%	12%	Lung & bronchus
Colon & rectum	9%	8%	Colon & rectum
Urinary bladder	7%	7%	Uterine corpus
Melanoma of skin	7%	4%	Melanoma of skin
Kidney & renal pelvis	5%	4%	Thyroid
Non-Hodgkin lymphoma	5%	4%	Non-Hodgkin lymphoma
Oral cavity & pharynx	4%	3%	Kidney & renal pelvis
Pancreas	3%	3%	Pancreas
Liver and bile duct	3%	2%	Ovary
All Other Sites	23%	23%	All Other Sites



*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
American Cancer Society: www.cancer.org.

Why Me?

Associations and Risk Factors for RCC

- **Male > female 2:1**
- **Age – median 64**
- **Genetic predisposition**
- **Smoking**
- **Obesity**
- **Uncontrolled hypertension**

3 modifiable RF's associated with 49% of cases

- Occupational exposure to toxins - Organic solvents (Benzene, TCE), cadmium, asbestos
- Disease associations: Long-term dialysis for acquired renal cystic disease; Chronic Hepatitis C; Sickle cell anemia (medullary carcinoma of the kidney); Solid organ transplant recipient
- Drug associations: Phenacetin, aspirin abuse (renal pelvis tumors); Prior cytotoxic chemotherapy (translocation RCC)

Staging system for RCC

AJCC 8th ed., 2017

Stage I
Tumor < 7 cm in greatest dimension and limited to kidney

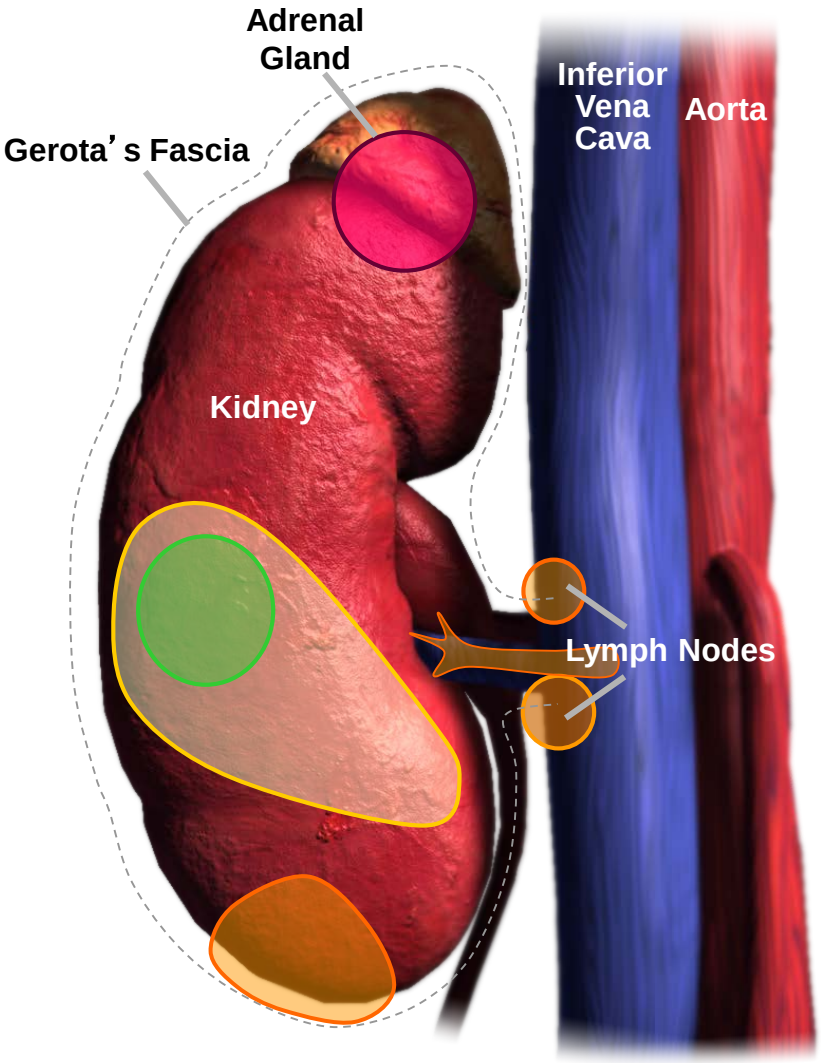
- **Ia** < 4 cm
- **Ib** > 4 to < 7 cm

Stage II
Tumor > 7 cm in greatest dimension and limited to kidney

- **IIa** > 7 to < 10 cm
- **IIb** > 10 cm

Stage III
Tumor major veins, tumor within Gerota's fascia, or regional lymph node involved

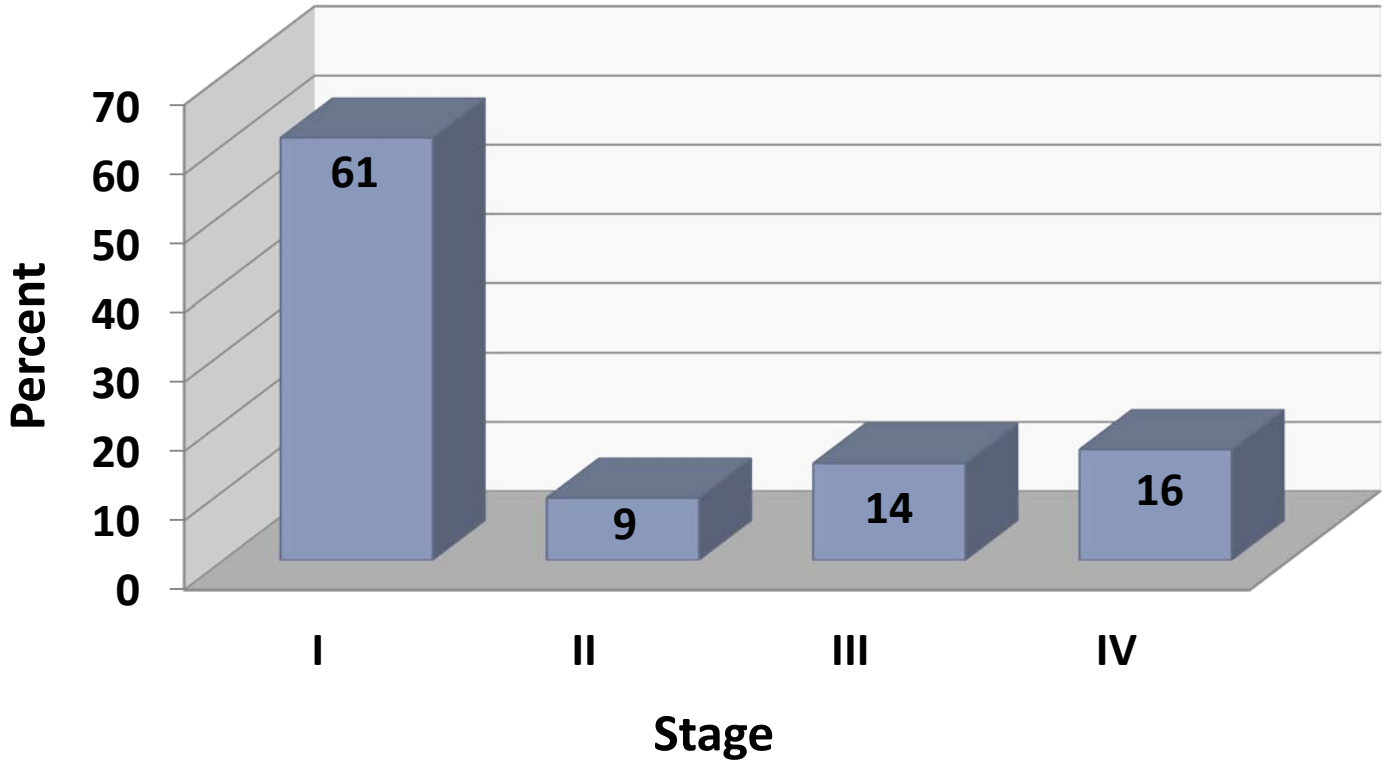
Stage IV
Tumor invasion beyond Gerota's fascia, adrenal or distant metastases



AJCC Cancer Staging Manual, 8th edition. New York: Springer; 2017.

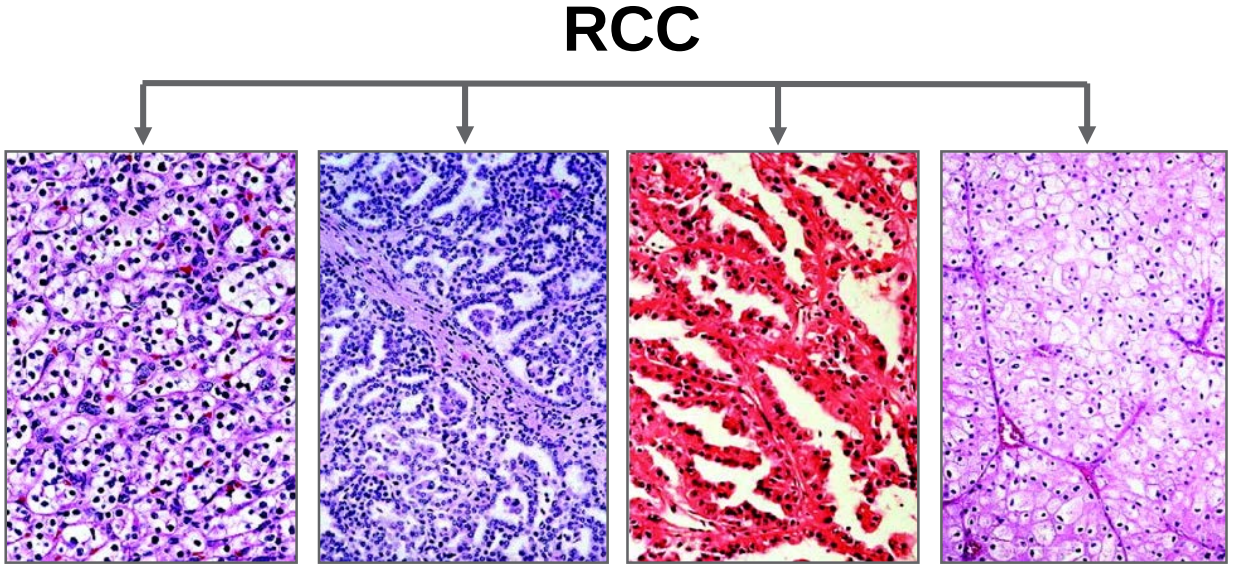
RCC Stage at Diagnosis, 2004-2014

National Cancer Database (NCDB),
1442 hospitals; N=371,851



https://oliver.facs.org/BMPub/Docs/

Common histologic subtypes of RCC



Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	*Unclassified*
Incidence	75%	5%	10%	5%	2-6%
Associated Germline Mutations	*VHL* *SDH* *BAP1* *TSC1/2*	*Met*	*FH*	*FLCN* *TSC1/2* *PTEN*	

Plus

- Translocation RCC
- Medullary
- Collecting Duct

VHL = von Hippel-Lindau;
SDH = succinate dehydrogenase;
FH = fumarate hydratase;
FLCN = folliculin;
TSC = tuberous sclerosis complex

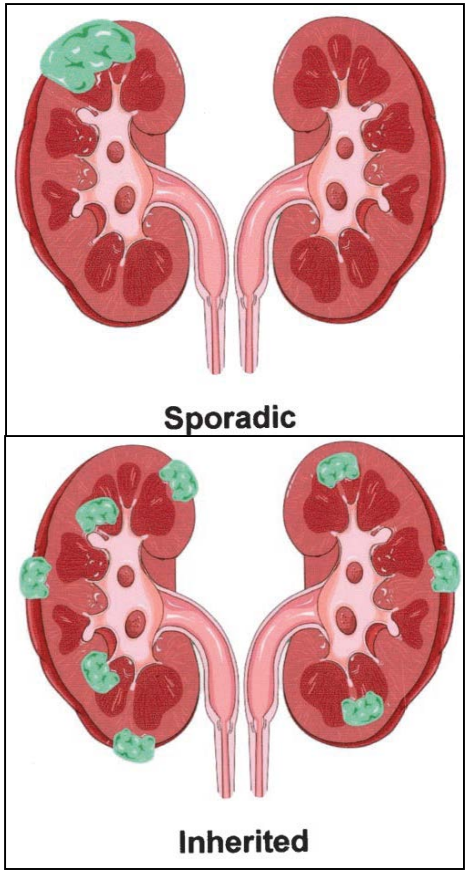
Modified from Linehan *et al*. J Urol. (2003) 170:2163-2172.
Ho and Jonasch. JNCCN. (2014) 12:1347.

Hereditary RCC

Referral criteria for genetic counseling

- All common histologic subtypes of RCC can be associated with a hereditary syndrome
- Kidney cancer age of onset ≤ 46 years (mean 37 years)
- Bilateral/multifocal kidney tumors
- Family history of kidney cancer
- Association with other clinical features of a recognized cancer syndrome

- Germline mutation incidence in unselected RCC patients with advanced disease – 16%



Linehan *et al*. J Urol. (2003) 170:2163-2172.
Carlo, MI *et al*. JAMA Oncol. (2018) 4:1228-1235.

Risk Stratification

(for Newly Diagnosed Metastatic RCC)

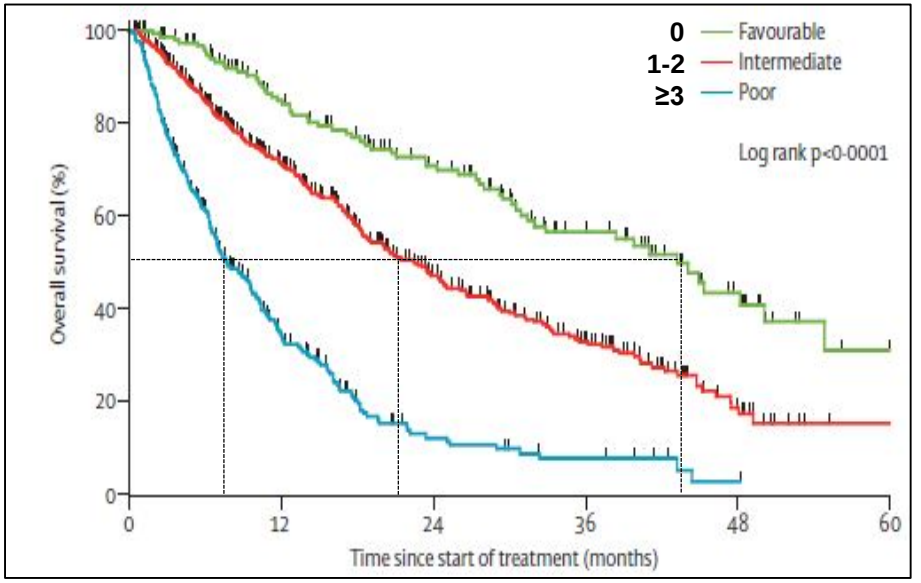
IMDC (Heng) Risk Model for mRCC Treated by Targeted Therapy

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Risk Model:

6 Baseline Risk Factors Predict Diminished Overall Survival (OS) in mRCC:

- Diagnosis to systemic treatment < 1 year* (DxTx<1yr)
- Diminished performance status (PS)*
- Elevated corrected calcium*
- Anemia*
- Elevated neutrophils (new)
- Elevated platelets (new)

*Same as MSKCC risk model[3]



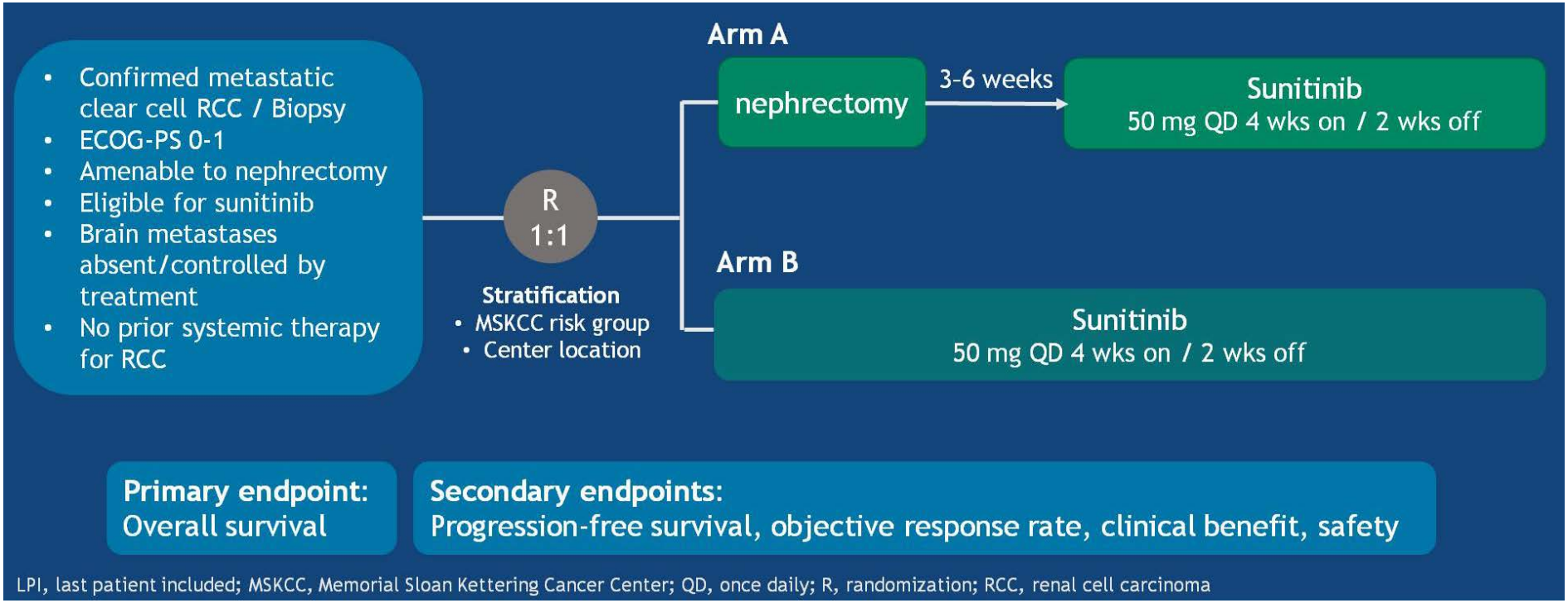
Median OS by IMDC risk group:

- Favorable risk: 43 months
- Intermediate risk: 22.5 months
- Poor risk: 7.8 months

1. Heng, D *et al*. JCO (2009) 27:5794
2. Heng, D *et al*. Lancet Oncology. (2013) 14:141
3. Motzer, RJ *et al*. JCO (2002) 20:289-296

Cytoreductive Nephrectomy (CN)

CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study

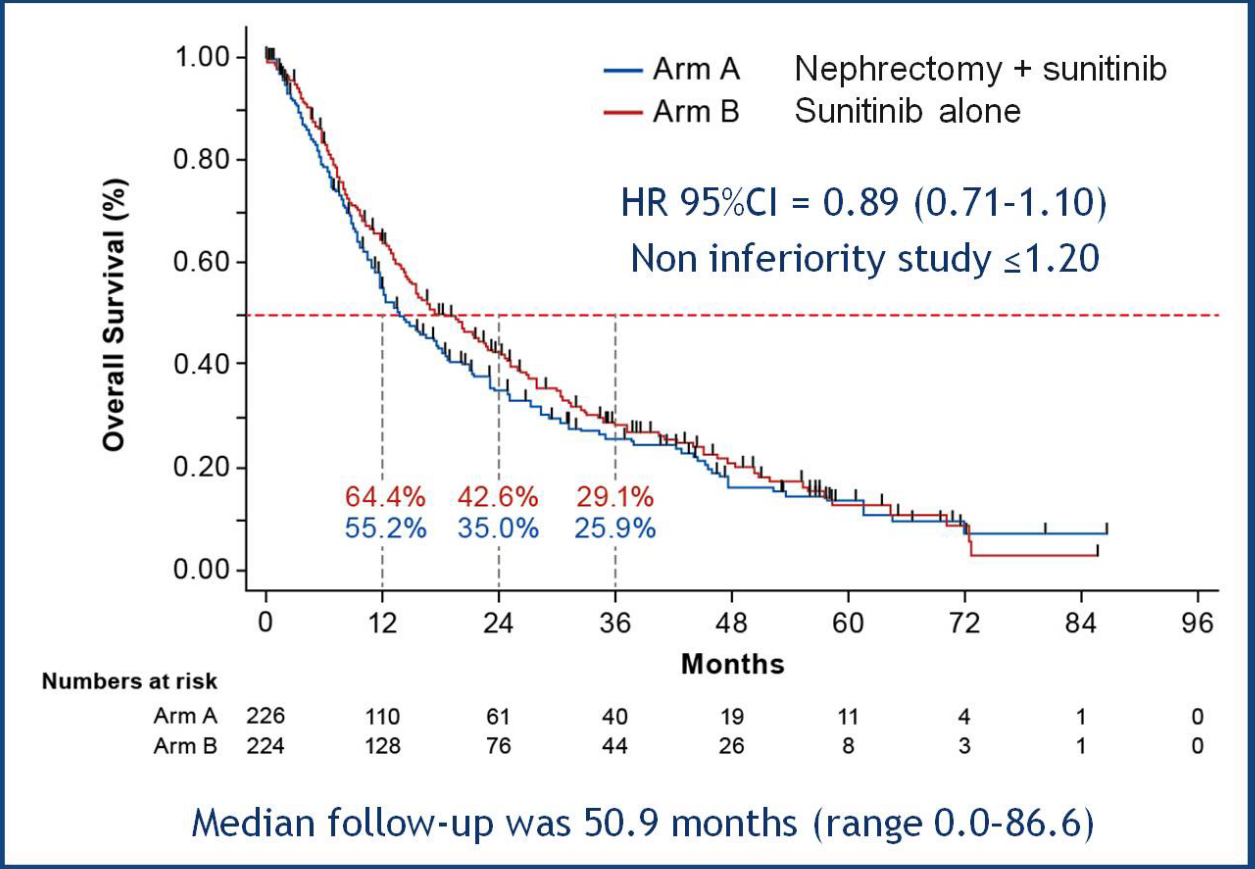


LPI, last patient included; MSKCC, Memorial Sloan Kettering Cancer Center; QD, once daily; R, randomization; RCC, renal cell carcinoma

CARMENA – Primary Endpoint

Overall survival (ITT)

Total enrollment = 450



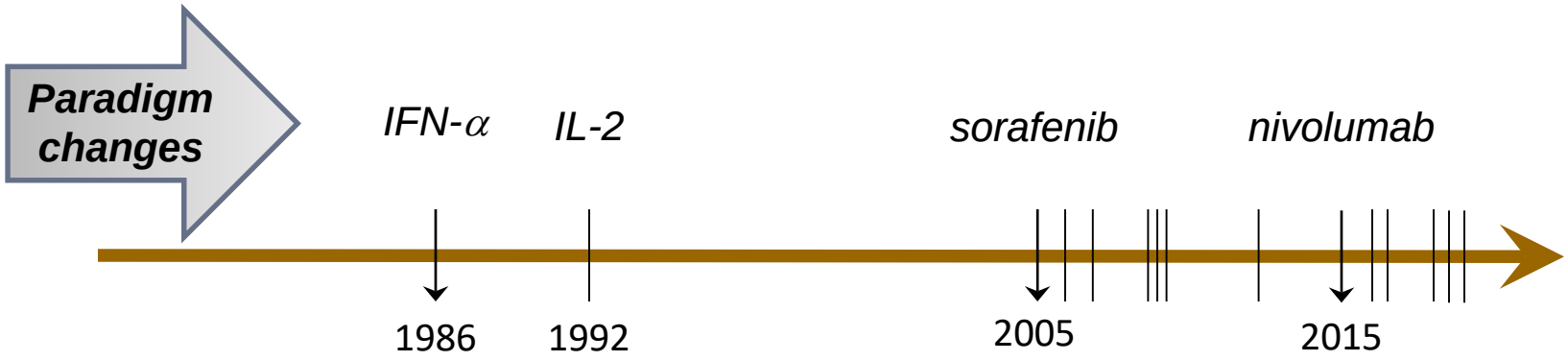
Post CARMENA Role for Initial CN with mRCC?

NO	YES
▪ Patients with similar clinical profile to CARMENA population	▪ Palliation – Hematuria – Flank pain – LUQ mass and weight loss – IVC thrombus ▪ With metastatectomy to surgical NED status

- Can we extrapolate to immune checkpoint blockade?
- ***Consider Multispecialty consultation***

Systemic Therapy Overview

Timeline of Systemic RCC Therapies



No Standard Therapy	Cytokine Immunotherapy	Targeted Therapy	Checkpoint Immunotherapy
cytotoxics	Interferon alfa Interleukin-2	TKI's Sorafenib (2005) Sunitinib (2006) Pazopanib (2009) Axitinib (2012) Cabozantinib (2016) Lenvatinib (2016) Bevacizumab mTOR-Inhibitors	Immune Checkpoint-Blocking Abs Nivolumab (2015) Ipilimumab (2018) Pembrolizumab (2019) Avelumab (2019)

Tools in the Tool Box:
15 FDA-Approved Drugs for Metastatic RCC

Immunotherapy		Targeted Therapy		
		VEGF-Pathway		
Cytokines	Immune Checkpoint Blocking Abs	Antibody	Tyrosine-kinase Inhibitor (TKI)	mTOR Inhibitor
IFN-α (1986) IL-2 (1992)	Nivolumab (2015) Ipilimumab* (2018) Pembrolizumab* (2019) Avelumab* (2019)	Bevacizumab* (2009)	Sorafenib (2005) Sunitinib (2006) Pazopanib (2009) Axitinib (2012) Cabozantinib (2016) Lenvatinib* (2016)	Temsirolimus (2007) Everolimus (2009)

*FDA approval as part of combination therapy

Adjuvant Therapy

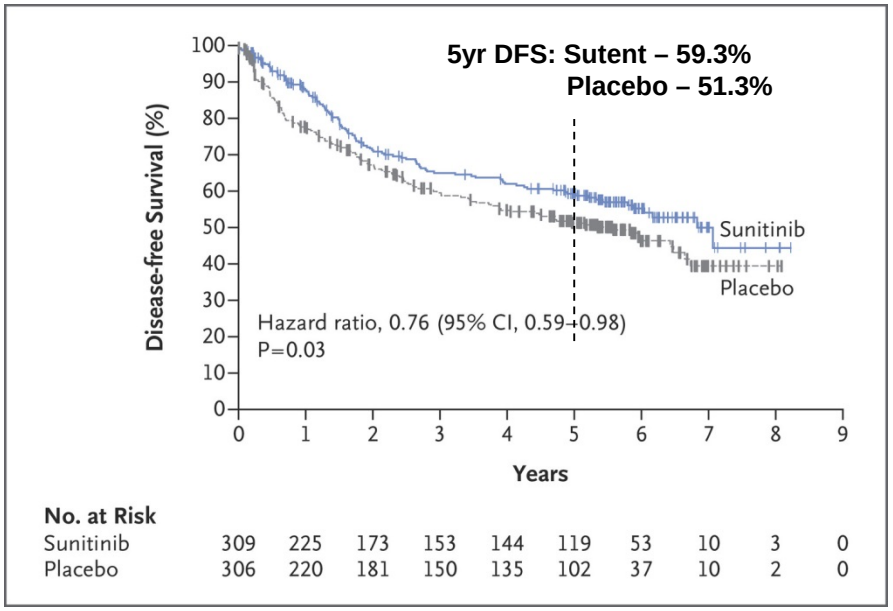
Key Comparisons for Reported Adjuvant Targeted Therapies

Trial	N	Drug	Patients	Histology	DFS	OS
ASSURE	1943	Sunitinib Sorafenib Placebo	pT1b,N0,Gr>2, M0 pT2-4,N0,G(any), M0 pT(any),N1,G(any), M0	80% cc	5.8 yr 6.1 yr 6.6 yr	5yr 77.9% 5yr 80.5% 5yr 80.3%
S-TRAC	720	Sunitinib Placebo	≥ Stage 3, M0	100% cc	6.8 yr 5.6 yr *HR 0.76, P=0.03*	5.4yr 79.3% 5.4yr 79.1%
PROTECT	1500	Pazopanib Placebo	pT2,N0,Gr>2, M0 pT3-T4 N0, G(any), M0 pT(any),N1,G(any), M0	100% cc	ITT_{600mg} *HR 0.862* *P=0.1649*	*HR 0.79* *P=0.16*
ATLAS	722	Axitinib Placebo	≥pT2, any N, M0	100% cc	*Stopped for futility*	NA

Haas, NB *et al*. Lancet (2016) 387:2008–16.
Ravaud, A *et al*. NEJM (2016) 375:2246-54.
Motzer, RJ et al. JCO (2017) 35:3916-3923.
www.clinicaltrials.gov

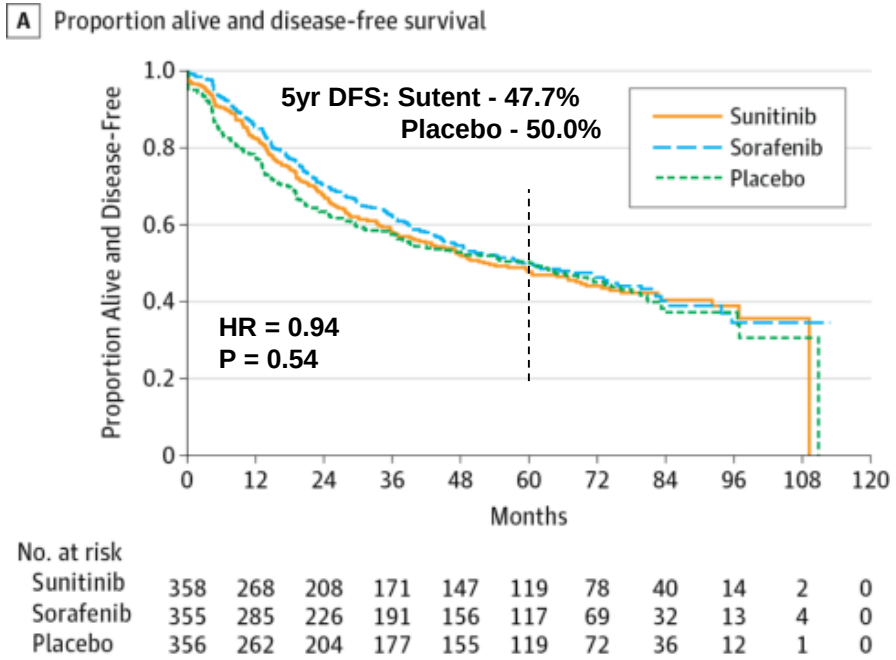
S-TRAC vs ASSURE Subset - DFS Outcomes

S-TRAC



Median DFS: Sutent - 6.8 yrs
Placebo - 5.6 yrs

ASSURE High Risk ccRCC (≥ Stage 3)



Ravaud, A *et al*. NEJM (2016) 375:2246-54.
Haas, NB *et al*. JAMA Oncol. (2017) 3:1249-1252.

First FDA Approval of Adjuvant Treatment for RCC

- Based on S-TRAC results, FDA approved adjuvant Sunitinb November 16, 2017
- Package Insert language - “SUTENT is indicated for the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy.”

  (underlining added for emphasis – no FDA stage or histology requirement)

What are we Doing with Adjuvant Sunitinib in 2020?

- Discordant randomized trials, no OS endpoint, and no data for non-clear cell histology or stage IV NED
- NCCN Category 2B indication for stage III, clear cell RCC

Yes?	No?

• Young patients
• Highest risk
  – Poor prognostic variables
• Good PS (ECOG 0)
	• Elderly
	• Unlikely to maintain dose intensity
	  – Renal dysfunction
	  – Heart disease
	  – GI syndromes
	  – Poor PS
	• ? Non-clear cell histology

Front-Line Systemic Therapy

CheckMate 214 (RCC): Pivotal Phase III Study of IPI + NIVO vs Sunitinib

Key Eligibility Criteria

- Clear cell histology
- No prior treatment
- Tumor tissue available for PD-L1 testing
- Stratification
  - IMDC Risk
  - Geographic location

1:1

N=550

NIVO 3 mg/kg + IPI 1 mg/kg Q3W x 4 doses Followed by NIVO 3 mg/kg Q2W

N=546

Sunitinib 50 mg PO daily, d1-28 Q6W

IMDC RFs (6)

- Diagnosis to tx < 1yr
- PFS < 70%
- Elevated Ca
- Elevated neutrophil
- Anemia
- Elevated plt

IMDC Risk Group

- Good (0 RF)
- Intermediate (1-2 RF)
- Poor (≥ 3 RF)

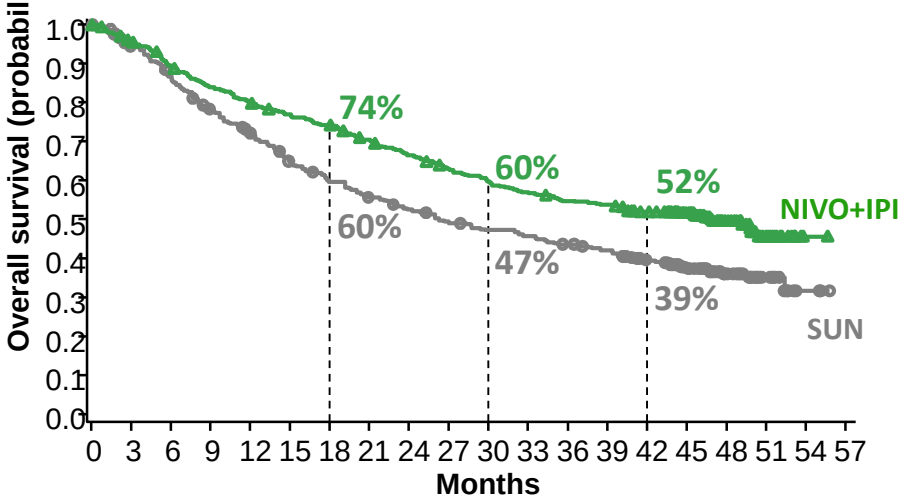
– **Co-primary end points: OS, ORR, PFS in Intermediate and Poor Risk patients**

Motzer, RJ *et al*. NEJM (2018) 378:1277-90.

CheckMate 214: Overall Survival by IMDC Risk

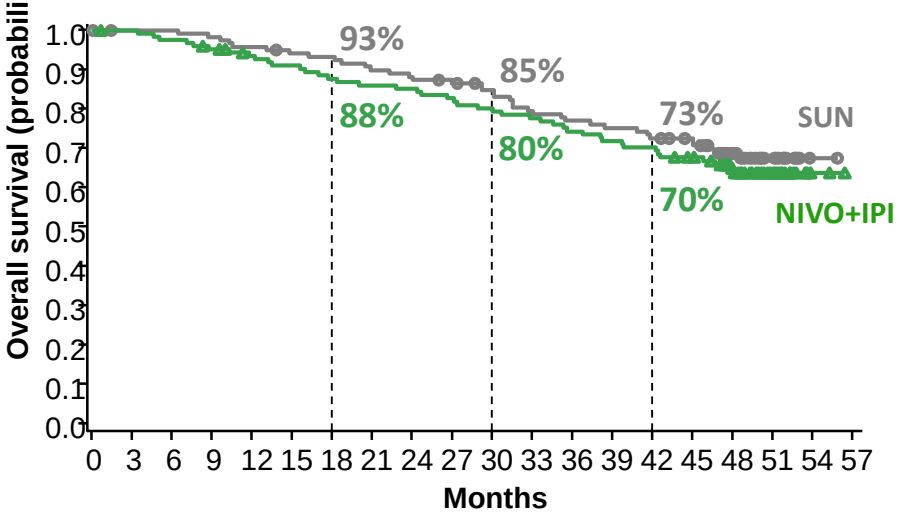
42-Month Follow-Up

Intermediate/poor risk



Minimum follow-up	OS	NIVO+IPI N = 425	SUN N = 422
42 mo	Median, mo (95% CI)	47.0 (35.6–NE)	26.6 (22.1–33.5)
	HR (95% CI)	0.66 (0.55–0.80) *P* < 0.0001	

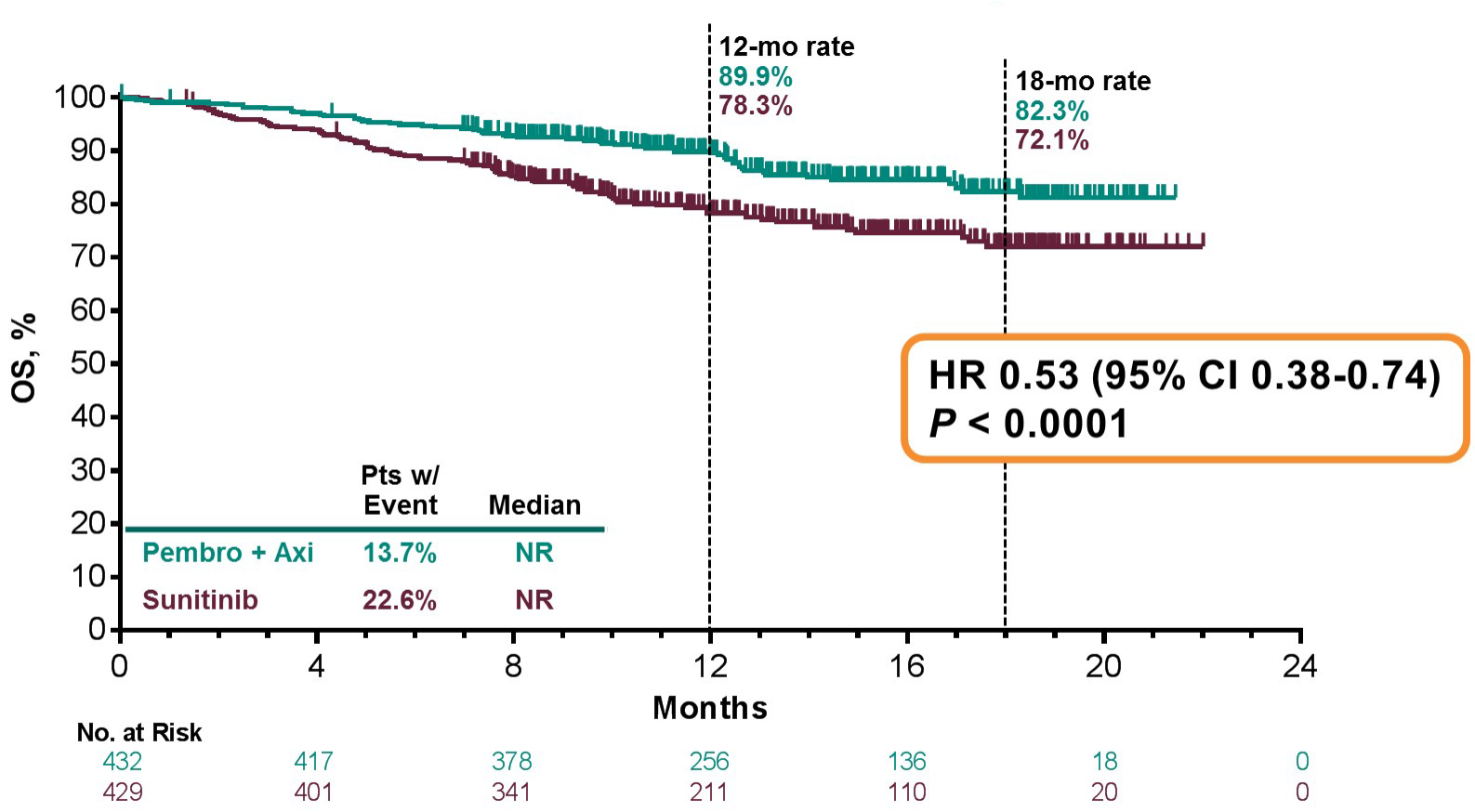
Favorable risk



Minimum follow-up	OS	NIVO+IPI N = 125	SUN N = 124
42 mo	Median, mo (95% CI)	NR (NE)	NR (NE)
	HR (95% CI)	1.19 (0.77–1.85) *P* = 0.4383	

Presented By Nizar Tannir at 2020 Genitourinary Cancers Symposium

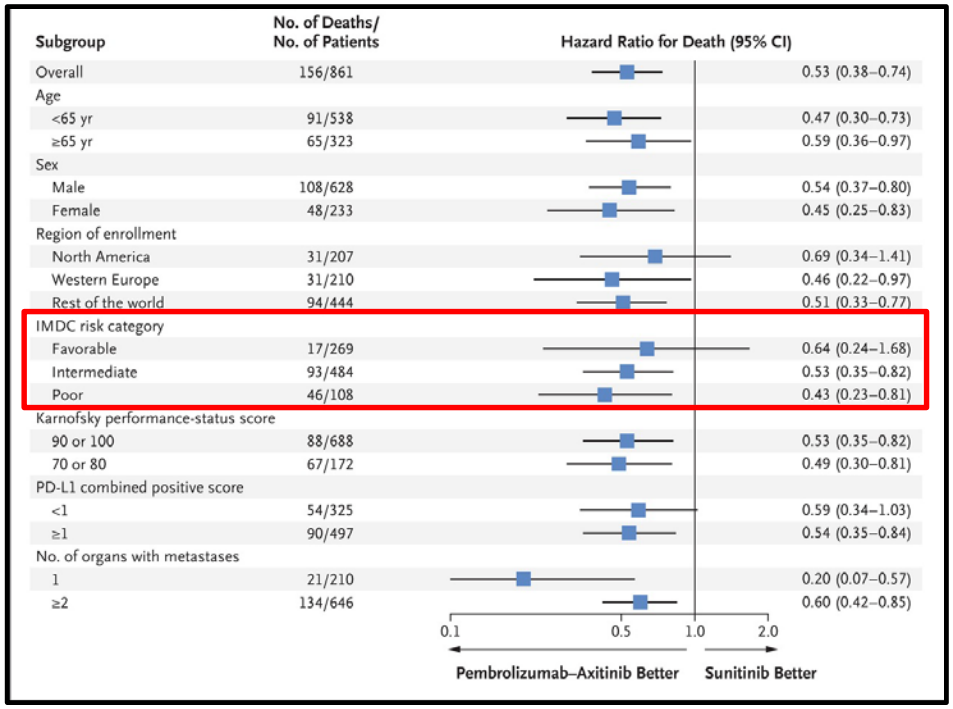
KeyNote 426: Axitinib + Pembrolizumab Survival Outcomes



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

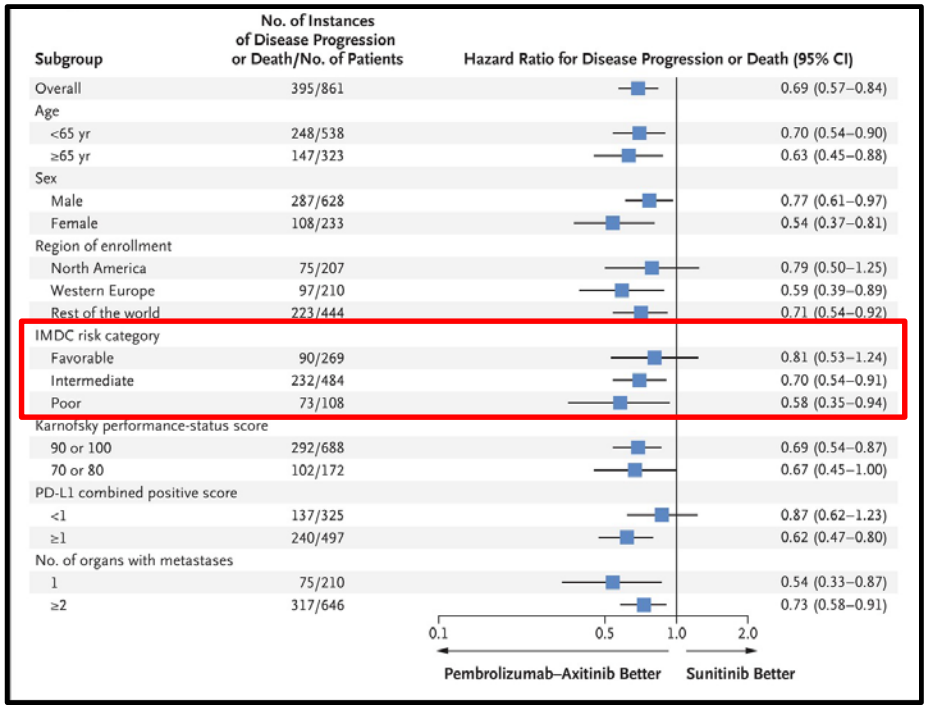
KeyNote 426:
Outcomes by Clinical Subsets

OS



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

PFS



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

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

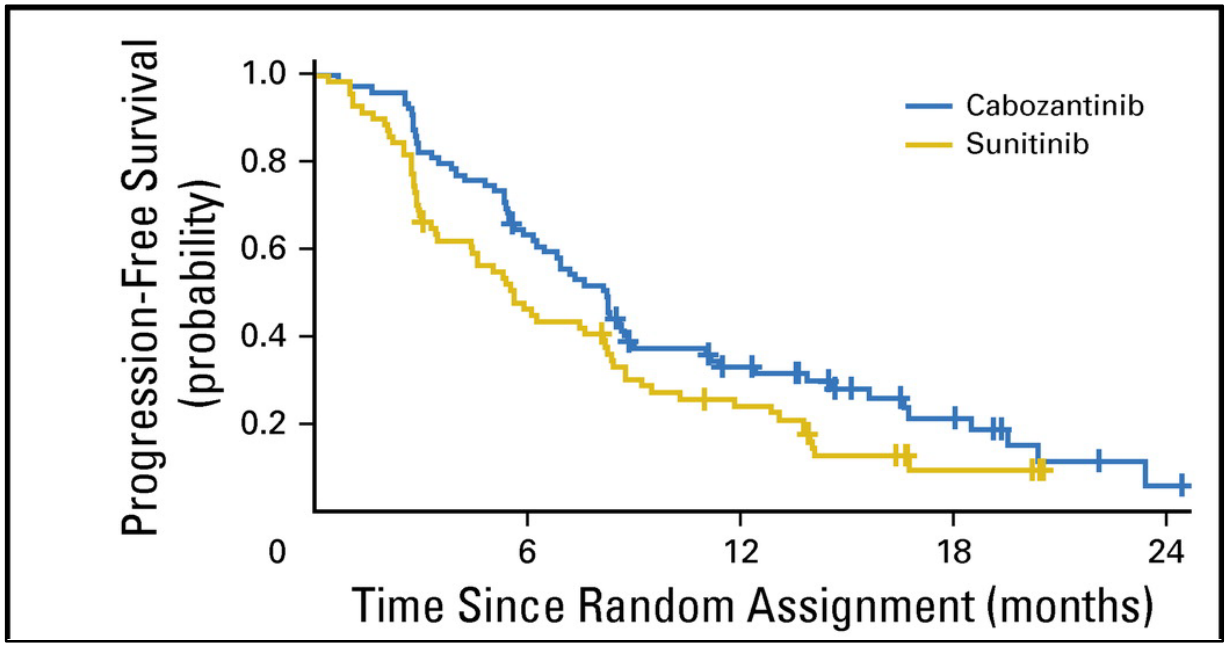
Summary – PD-L1 as Biomarker for Selecting Immune Checkpoint Blocking Therapy

PD-L1 Expression in Tumor	RCC
Prognostic	Unfavorable
Association with ICI treatment – OS ▪ Ipi+Nivo vs SUN ▪ Axi+Pembro vs SUN	No comparative outcome difference for OS
Companion Diagnostic	No
Clinical role for testing	No

Selecting Between First-Line Checkpoint Containing Regimens

- **Nuances between checkpoint regimens**
  - ORR
  - Depth of response (CR)
  - Treatment free survival
  - Toxicity / discontinuation rate
  - Frequency of visits
- **Await more mature OS data**
- **No consensus for “best choice”**

CABOSUN (Randomized, phase II) – Front-line Treatment of Intermediate and Poor Risk ccRCC



Endpoint	CABO	SUN	HR (P)
PFS	8.2 mo	5.6 mo	0.66 (P=0.012)
OS	30.3 mo	21.8 mo	0.80 (NS)
ORR	46%	18%	Not stated

Choueiri, T.K. *et al*. JCO (2017) 35, 591-597.

Current NCCN Guidelines for First-Line Therapy for clear cell RCC

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred regimens**	Other recommended regimens	Useful in certain circumstances
Favorable[a]	• **Axitinib + pembrolizumab**[b] • **Pazopanib** • **Sunitinib**	• Ipilimumab + nivolumab[b] • Axitinib + avelumab[b] • Cabozantinib (category 2B)	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d]
Poor/ intermediate[a]	• **Ipilimumab + nivolumab**[b] **(category 1)** • **Axitinib + pembrolizumab**[b] **(category 1)** • **Cabozantinib**	• Pazopanib • Sunitinib • Axitinib + avelumab[b]	• Axitinib (category 2B) • High-dose IL-2[d] • Temsirolimus[e]

What's Coming to First-Line Therapy?

- Axitinib + avelumab
  - FDA approval May, 2019
  - Await OS data
- Nivolumab + cabozantinib (CheckMate 9ER)
  - Press release - study was positive for PFS, OS, ORR versus sunitinib

www.nccn.org – Kidney Cancer Guidelines version 1.2021

Second-Line Systemic Therapy and Select Clinical Subsets

Comparison of Current Second-Line Treatment Options for RCC

	Axitinib	Nivolumab	Cabozantinib	Lenvatinib/Eve
Patient Population	TKI refractory*	TKI refractory	TKI refractory	TKI refractory
Comparator	Sorafenib	Everolimus	Everolimus	Everolimus
ORR	9%*	22%	17%	35%
PFS, months	6.5*	4.6	7.4	12.8
OS, months	15.2*	25.0	21.4	25.5
Dose reductions	30%	n/a	60%	71%
D/C due to AE	7%	8%	9%	29%
Toxicity	G3 50%	18%	63%	57%
	G4 6%	1%	8%	14%

Modified from B. Rini, 2016 ASCO Annual Meeting

Rini, BI et al. Lancet. (2011) 378:1931. Motzer, RJ et al. NEJM. (2015) 373:1803.
Choueiri, T et al. NEJM (2015) 373:1814.
Motzer, RJ et al. Lancet Oncol. (2015) 16:1473.

Clinical Outcomes for Sarcomatoid RCC

Treatment	Chemo	Targeted Tx	Immunotherapy			
Regimen (N)	**Dox+Gem[1] 39**	**Sun+Gem[2] 39**	**Ipi/Nivo[3] 60**	**Atezo/Bev[4] 68**	**Pembro/Axi[5] 51**	**Pembro[6] 11**
ORR, %	16	26	57	49	59	64
CR, %	3	3	18	10	12	0
PR, %	13	23	38	39	47	64
Median PFS, mo	3.5	5	8.4	8.3	NR	—
Median OS, mo	8.8	10	31.2	NR	NR	—

[1]Haas, NB *et al*. Med Oncol (2012) 29:761-7
[2]Michaelson, MD *et al*. Cancer (2015) 121:3435-43
[3]ASCO 2019, abstr #4513
[4]ASCO 2019, abstr #4512
[5]ASCO 2019, abstr #4500
[6]ASCO 2019, abstr #4570

KeyNote 427: First-Line Pembrolizumab for non-clear cell RCC

Group (N)	TOTAL 165	Papillary 118	Chromophobe 21	Unclassified 26	Sarcomatoid 38
ORR, %	25	25	10	35	45
CR, %	5	—	—	—	—
PR, %	20	—	—	—	—
12-mo PFS, %	23	—	—	—	—
12-mo OS, %	72	—	—	—	—
Median DOR	NR[1]	NR	NR	NR	NR

[1]Median follow-up 11.1 mo

Conclusions

- Immune checkpoint inhibitors appear to be the drug class of choice for sarcomatoid RCC tumors
- Immune checkpoint inhibitors have clinically significant activity in most subtypes of non clear cell RCC

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Thank you for your attention