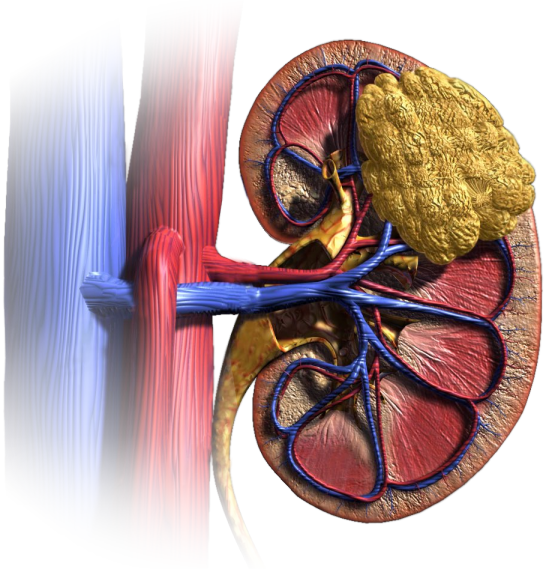
Comprehensive HemOnc Review:
Renal Cell Carcinoma



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2021

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**
  - Bristol-Myers Squibb
  - Exelixis
  - Intellisphere, LLC
  - Merck

Learning Objectives

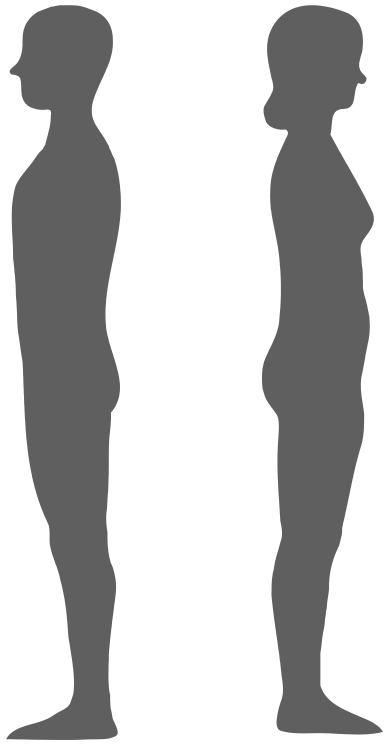
- RCC Epidemiology
- Hereditary RCC cancer syndromes
- Risk Stratification
- Cytoreductive Nephrectomy
- Systemic Treatments Overview
  - Local RCC - Adjuvant therapy
  - Metastatic RCC
    - → 1st line, clear cell
    - → 1st line, other histologies
    - → 2nd line/salvage

Epidemiology

2021 - Estimated US New Cancer Cases*

2021 US Estimates:
- **76,080 new cases**
- **13,780 deaths**

Men 970,250		Women 927,910	
Prostate	26%	30%	Breast
Lung & bronchus	12%	13%	Lung & bronchus
Colon & rectum	8%	8%	Colon & rectum
Urinary bladder	7%	7%	Uterine corpus
Melanoma of skin	6%	5%	Melanoma of skin
Kidney & renal pelvis	5%	4%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	5%	3%	Thyroid
Oral cavity & pharynx	4%	3%	Pancreas
Leukemia	3%	3%	Kidney & renal pelvis
Pancreas	3%	3%	Leukemia
All Other Sites	21%	21%	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 (trichloroethylene), cadmium, asbestos
- Disease associations: Polycystic kidney disease; Chronic Hepatitis C; **Sickle cell anemia (medullary carcinoma of the kidney)**; Solid organ transplant recipient
- Drug associations: 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

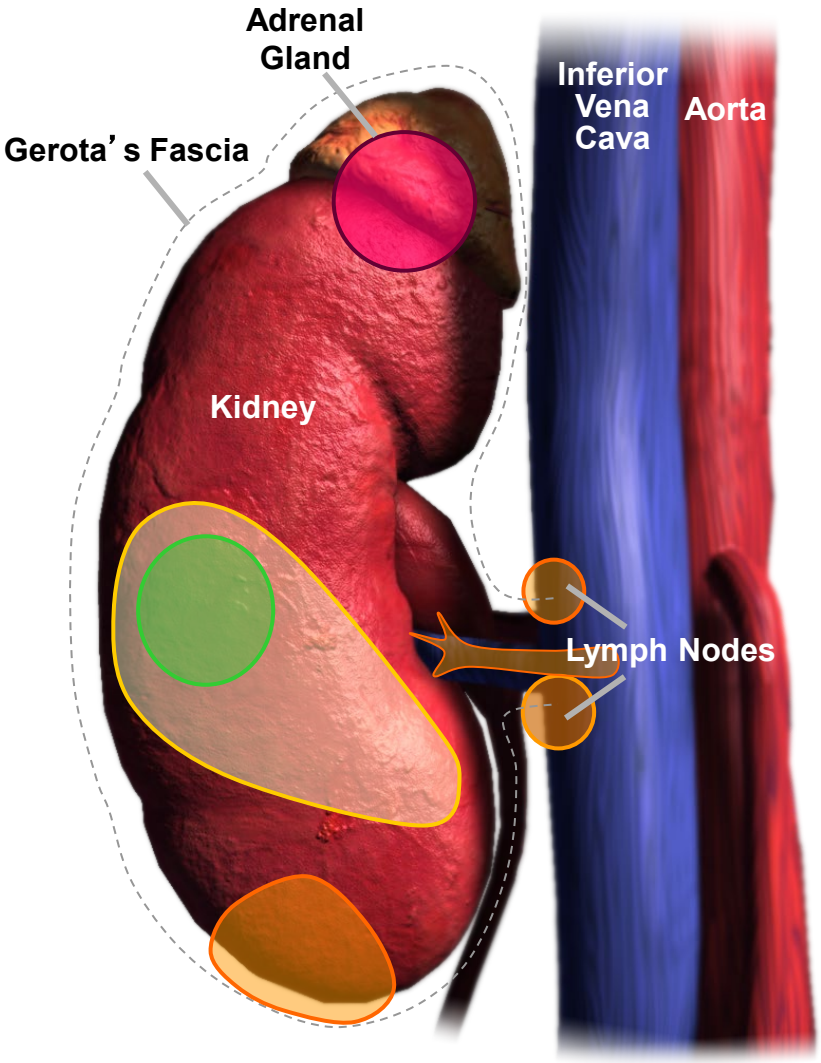
- **Ia** < 4 cm
- **Ib** > 4 to < 7 cm

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

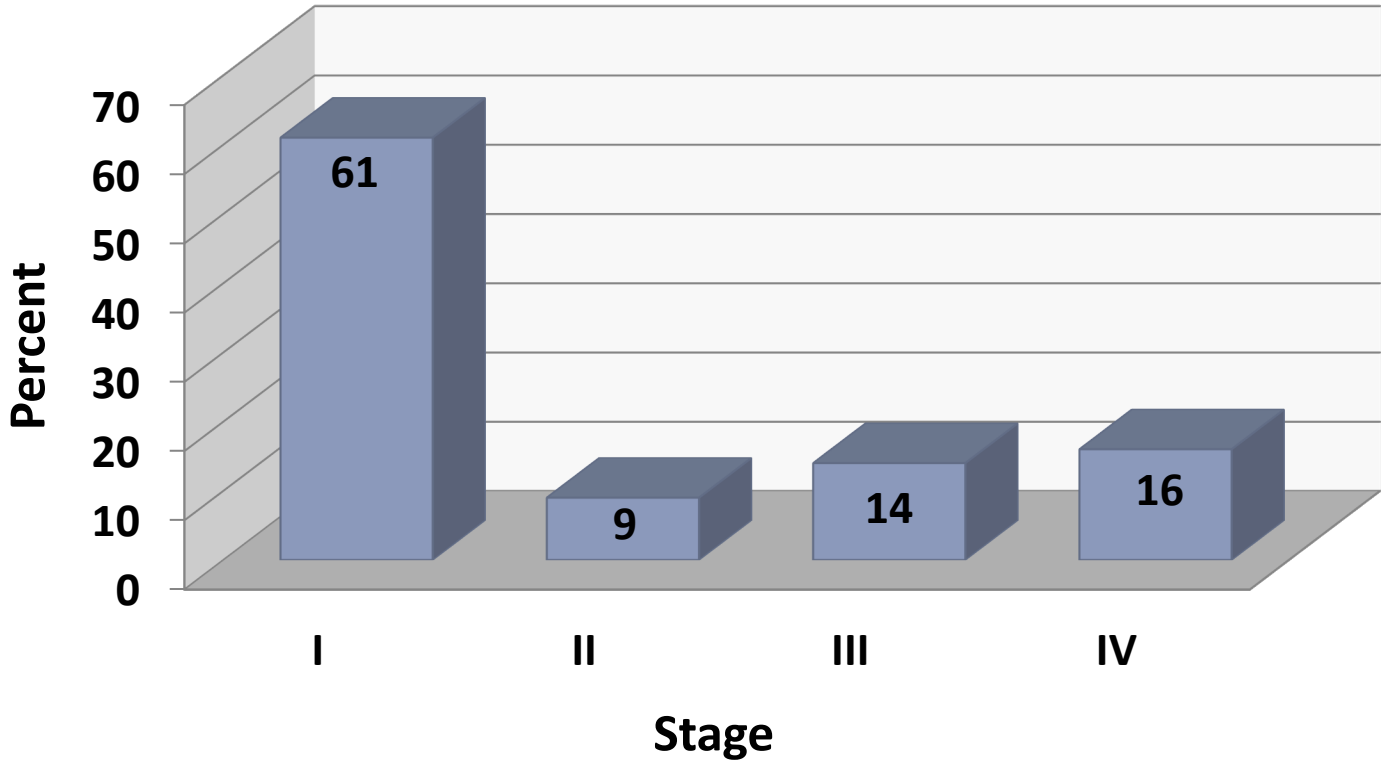
Stage IV
Tumor invasion beyond Gerota's fascia, adrenal or distant metastases



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

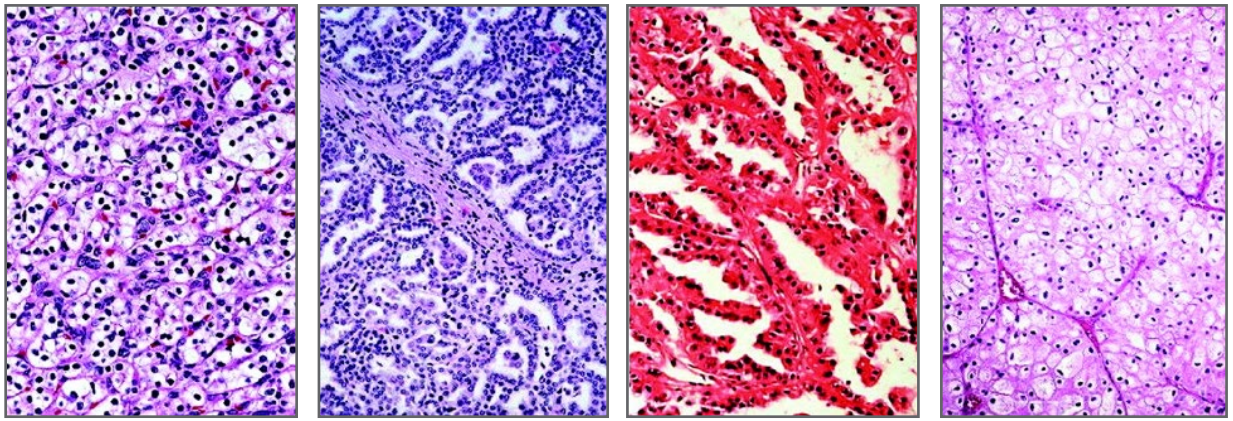
RCC Stage at Diagnosis, 2004-2014

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

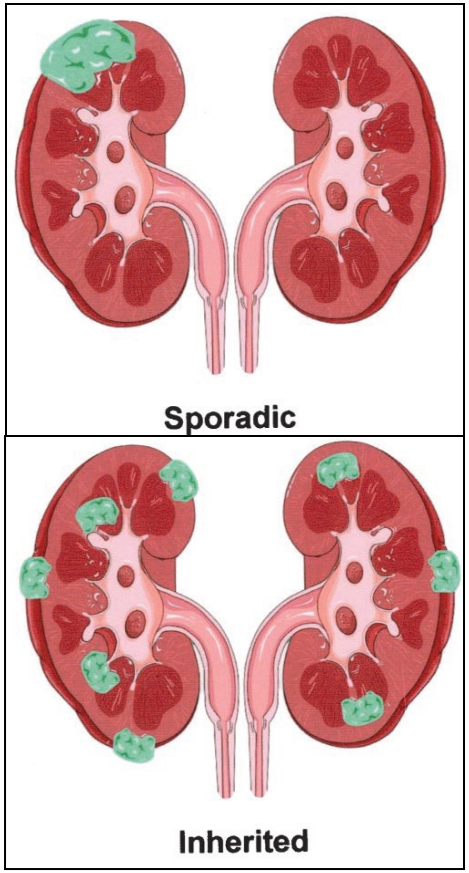
Modified from Linehan *et al*. J Urol. (2003) 170:2163-2172.
Ho and Jonasch. JNCCN. (2014) 12:1347.

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

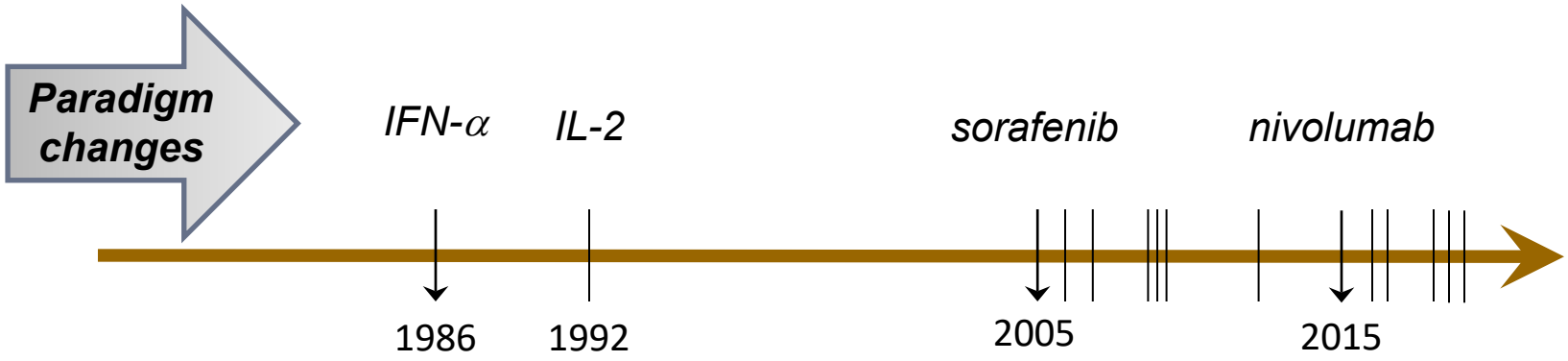
- Germline mutation incidence in unselected RCC patients with advanced disease – 16%



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

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) Tivozanib (2021) **Bevacizumab** **mTOR- Inhibitors**	**Immune Checkpoint-Blocking Abs** Nivolumab (2015) Ipilimumab (2018) Pembrolizumab (2019) Avelumab (2019)

Risk Stratification

(for Newly Diagnosed Metastatic RCC)

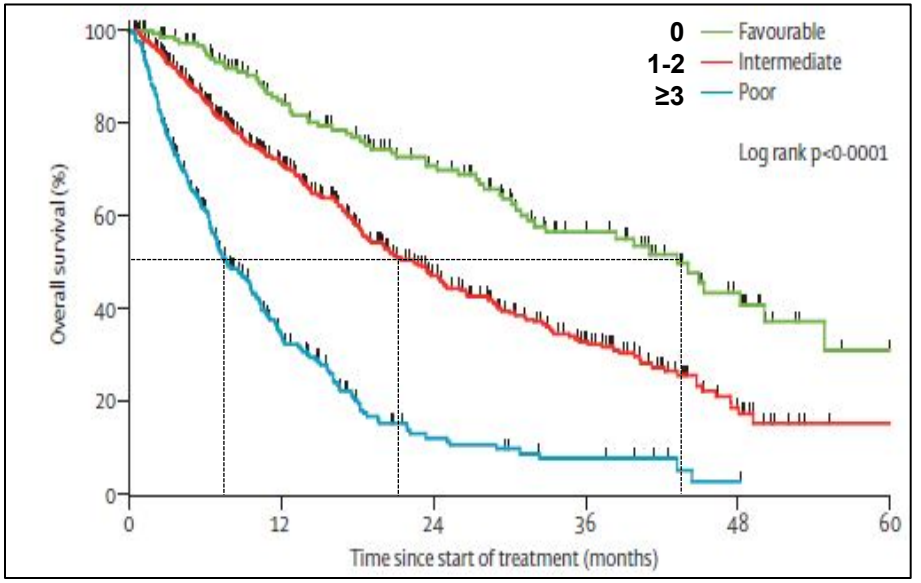
IMDC (Heng) Risk Model for mRCC Treated by Targeted Therapy

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

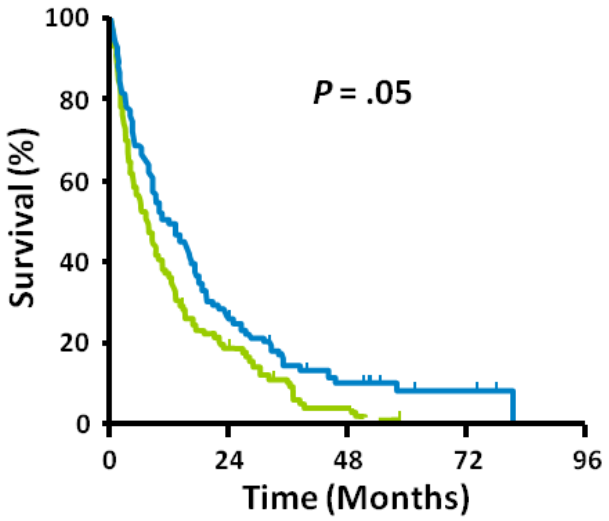
Cytoreductive Nephrectomy (CN)

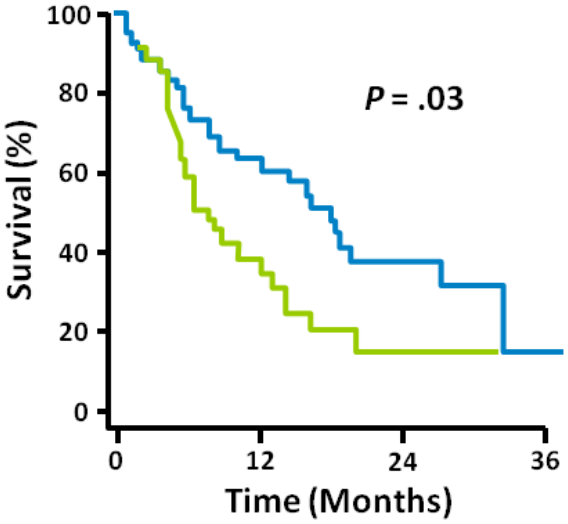
Survival Benefit for Initial CN plus IFN-α

Cytoreductive Nephrectomy

SWOG[a]	Median Survival
IFN-α + nephrectomy (N=120)	11.1 mo
IFN-α (N=121)	8.1 mo

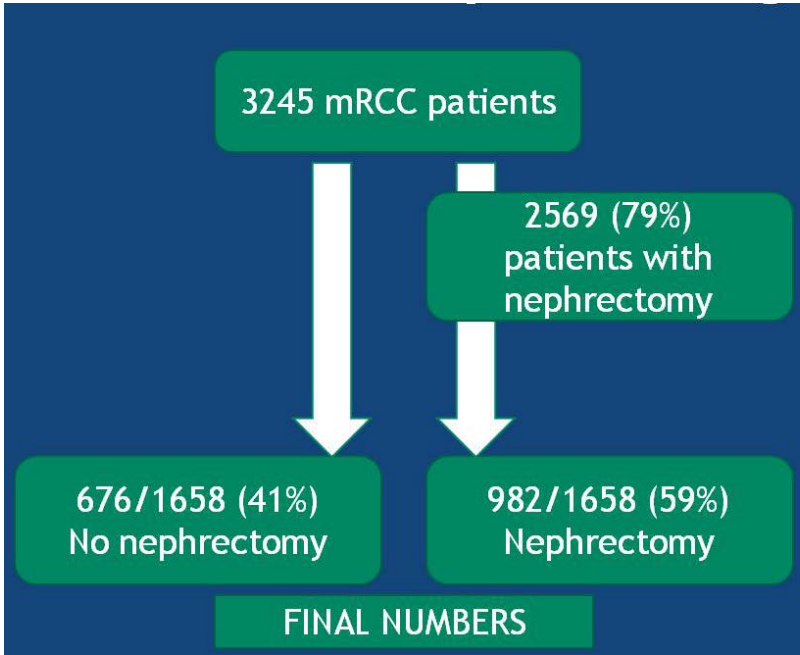
EORTC[b]	Median Survival
IFN-α + nephrectomy (N=42)	17.0 mo
IFN-α (N=43)	7.0 mo

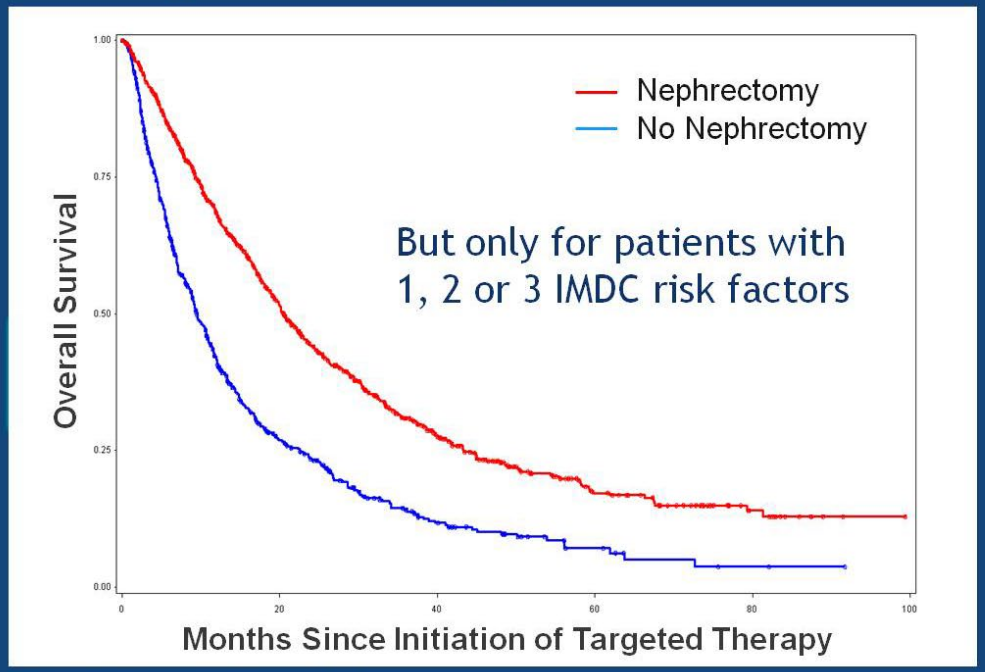




a. Flanigan RC, et al. *N Engl J Med.* 2001;345:1655-1659.
b. Mickisch GHJ, et al. *Lancet*. 2001;358:966-970.

(IMDC) Retrospective Database Study Associated Better Survival with Nephrectomy

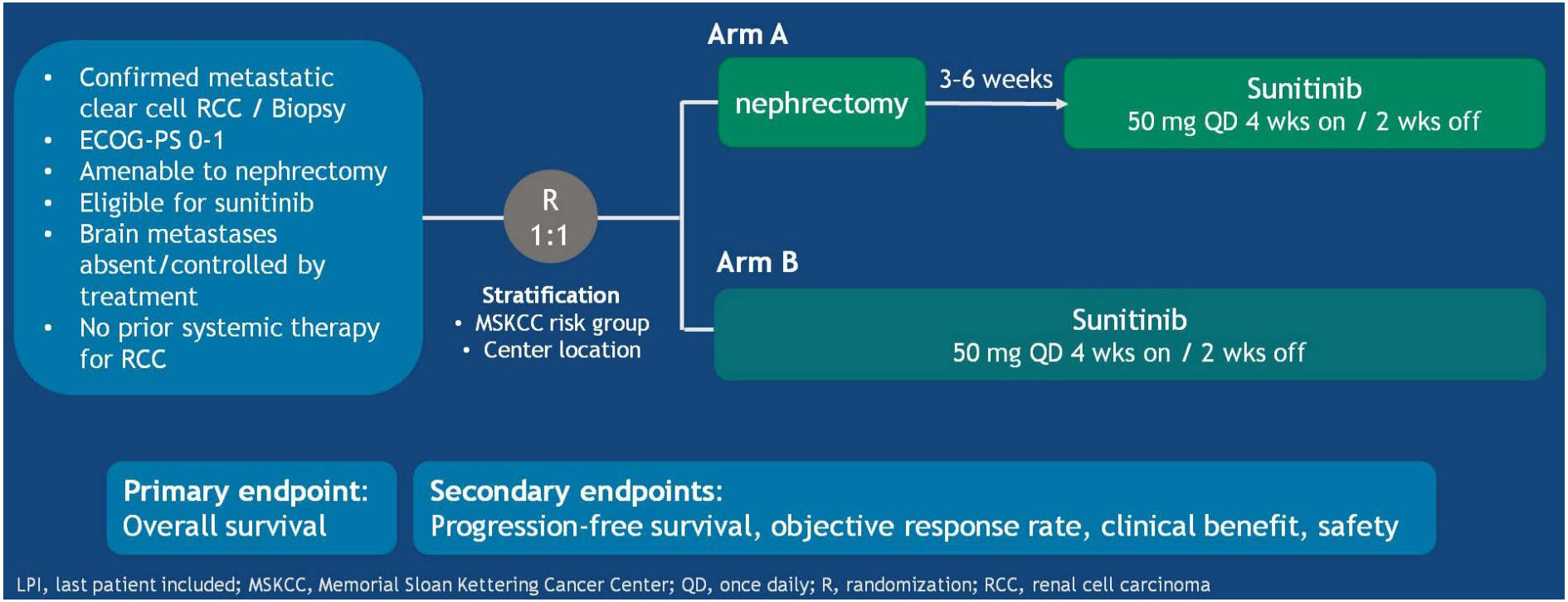




IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma
Heng D, et al, *Eur Urol* 2014;66:704.

Median OS: 20.6 vs 9.6 mo
Adjusted HR 0.60, $p < 0.0001$

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

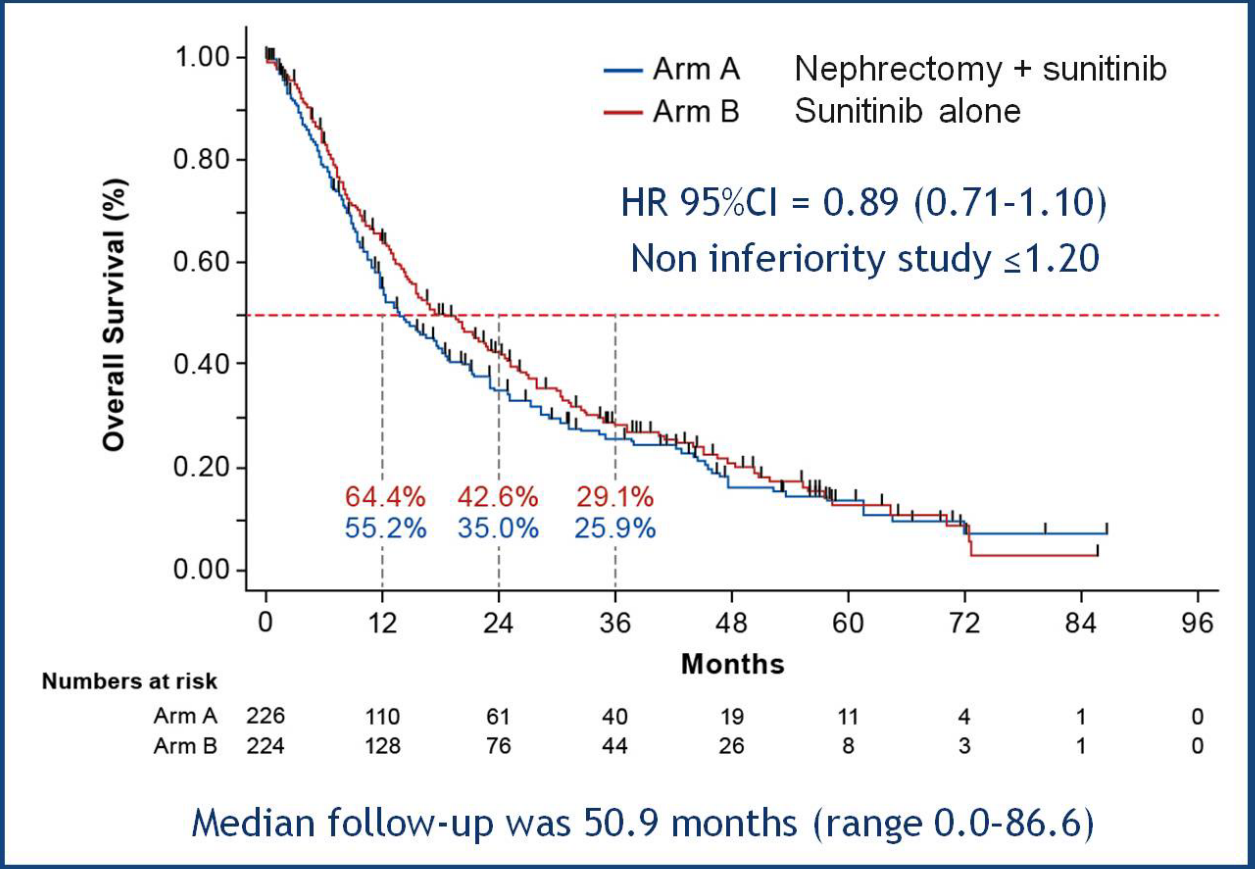


LPI, last patient included; MSKCC, Memorial Sloan Kettering Cancer Center; QD, once daily; R, randomization; RCC, renal cell carcinoma

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***

Adjuvant Therapy

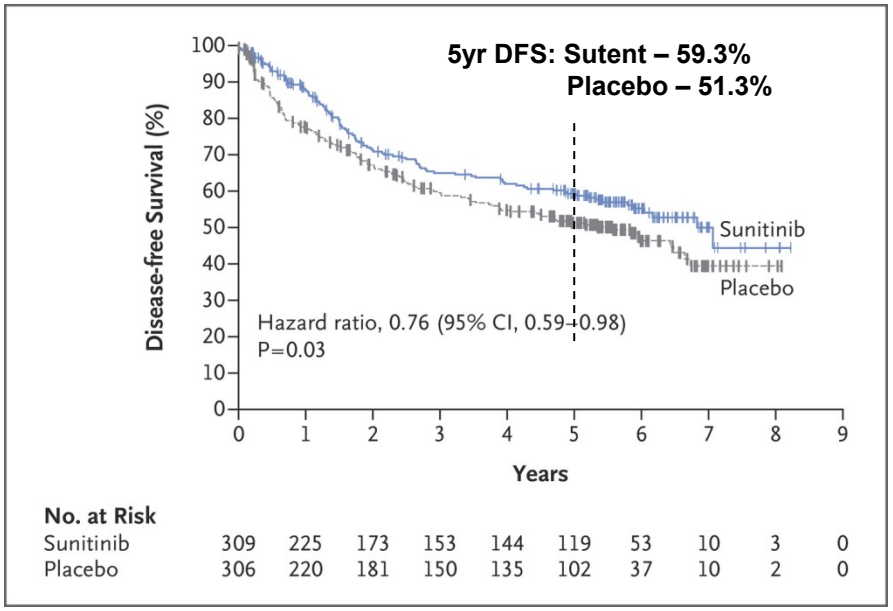
Key Comparisons for Reported Adjuvant Targeted Therapies

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	724	Axitinib Placebo	≥pT2, any N, M0	100% cc	*HR 0.870* *P=0.3211*	NA
SORCE	1711	Placebo 1yr Sorafenib 3yr Sorafenib	Leibovich score intermediate or high, M0	84% cc	*HR 0.94, P=.509* *HR 1.01, P=.946*	*HR 0.92; P=0.541* *HR 1.06, P=.638*

Haas, NB *et al*. Lancet (2016) 387:2008–16. Motzer, RJ *et al*. JCO (2017) 35:3916-3923. Eisen, T *et al*. JCO (2020) 38:4064-75
Ravaud, A *et al*. NEJM (2016) 375:2246-54. Gross-Goupil, M *et al*. Ann Oncol (2018) 29:2371-8

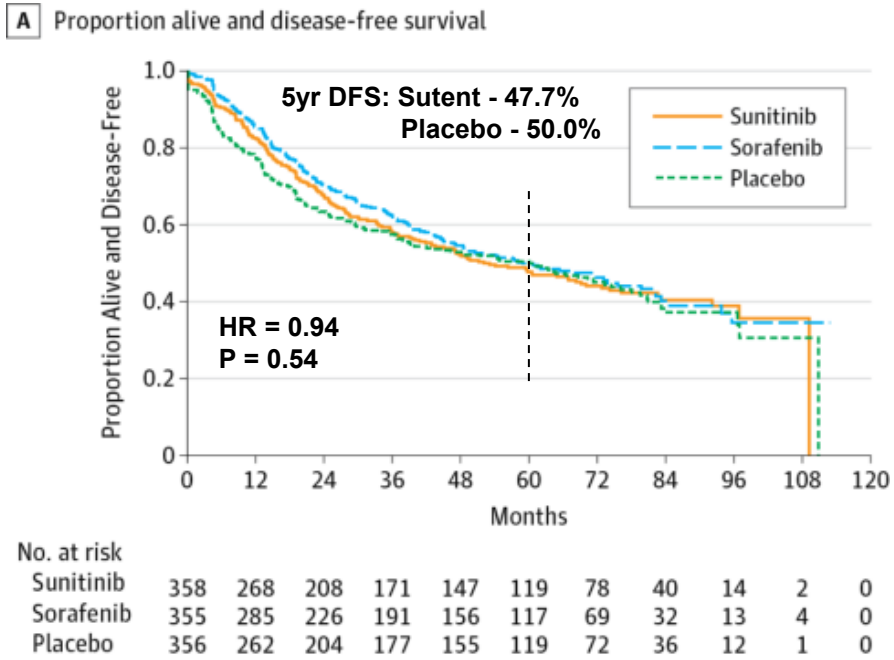
S-TRAC vs ASSURE Subset - DFS Outcomes

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
- Discordant randomized trials, no OS endpoint, and no data for non-clear cell histology or stage IV NED
- NCCN Category 3 indication for stage III, clear cell RCC

What are we doing with adjuvant Sunitinib?

Yes?	No?

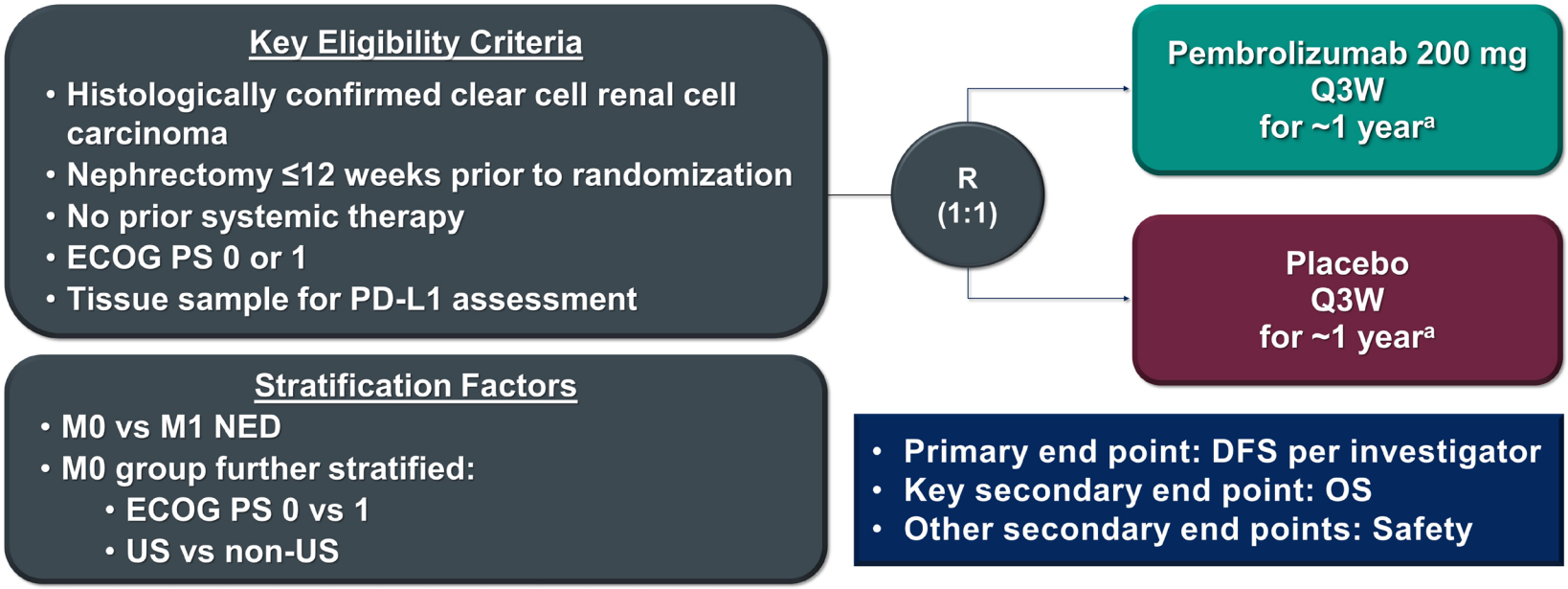
• Young patients
• Highest risk
  – Poor prognostic variables
• Good PS (ECOG 0)
	• Elderly
	• Unlikely to maintain dose intensity
	  – Renal dysfunction
	  – Heart disease
	  – GI syndromes
	  – Poor PS
	• Non-clear cell histology

5 Competing Phase III Adjuvant Trials for RCC with Checkpoint Blocking Antibodies

Phase III Adjuvant Studies of PD1 Pathway Antibodies				
Study Name	**Start Date**	**N**	**Therapy**	**Enrollment**
Keynote 564	**2017**	**950**	**Pembrolizumab vs placebo**	**complete**
Immotion 010	2017	664	Atezolizumab vs placebo	complete
PROSPER	2017	766	Nivolumab vs placebo	complete
CheckMate 914	2017	1600	Nivolumab plus Ipilimumab vs Nivolumab vs placebo	ongoing
RAMPART	2018	1750	Durvalumab plus Tremelimumab vs Durvalumab vs observation	ongoing

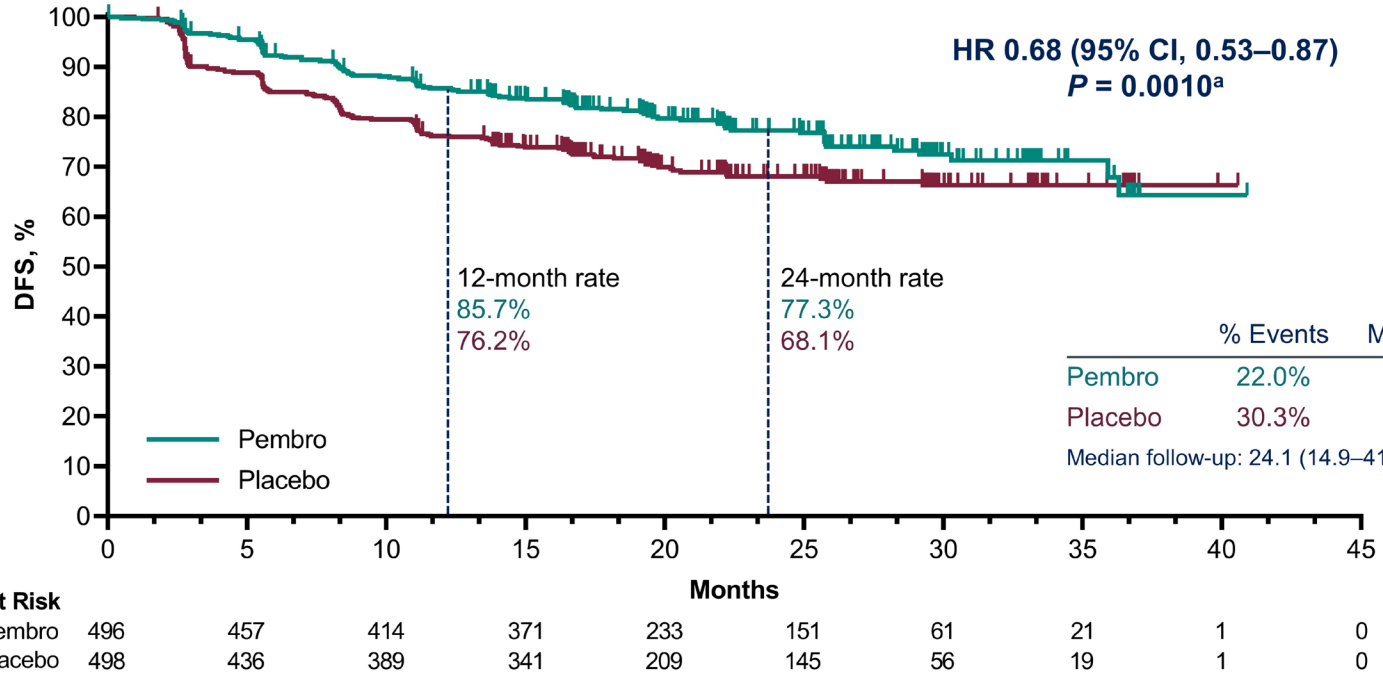
www.clinicaltrials.gov

KEYNOTE-564 Study Design



DFS, disease-free survival; Q3W, every 3 weeks.
[a]≤17 cycles of treatment were equivalent to ~1 year.

DFS by Investigator, ITT Population



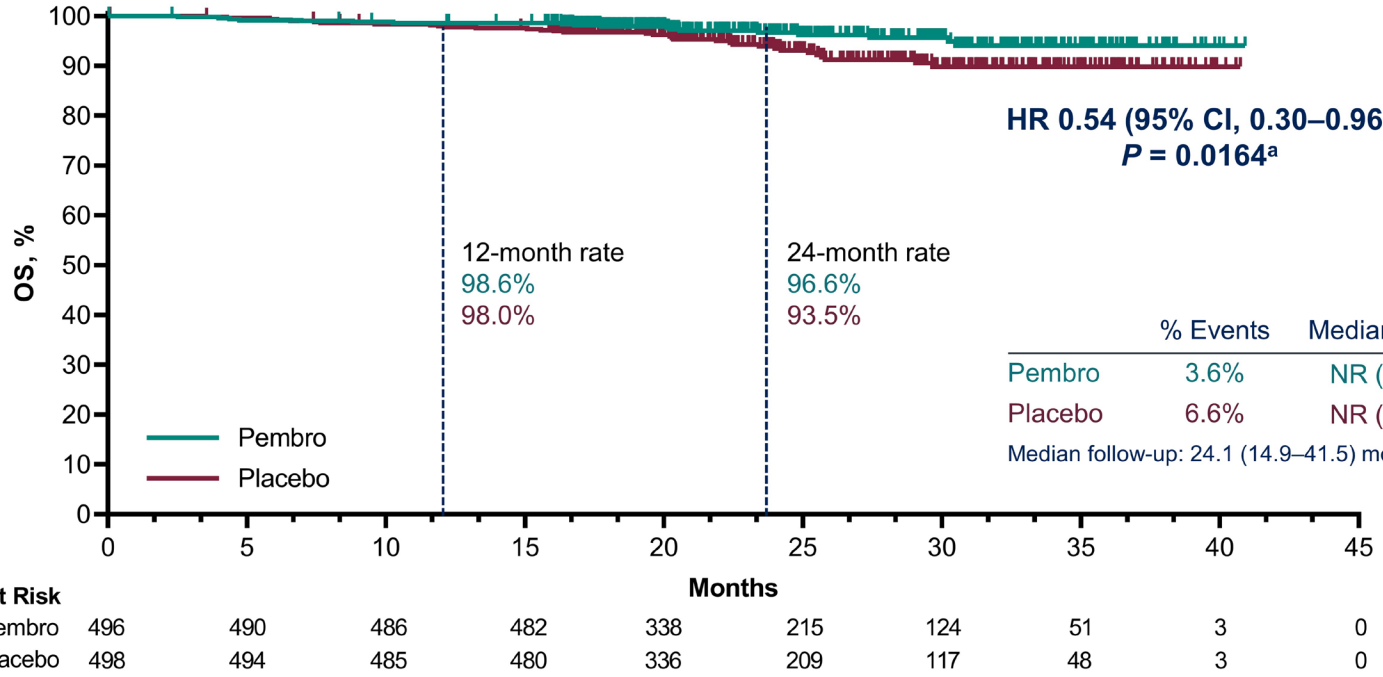
	% Events	Median (95% CI)
Pembro	22.0%	NR (NR–NR)
Placebo	30.3%	NR (NR–NR)

Median follow-up: 24.1 (14.9–41.5) months.

No. at Risk										
Pembro	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

[a]Crossed prespecified p-value boundary for statistical significance of 0.0114.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

Interim OS Results, ITT Population



[a]Did not cross prespecified p-value boundary for statistical significance of 0.0000093 for 51 events. Final analysis for OS to occur after approximately 200 OS events.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

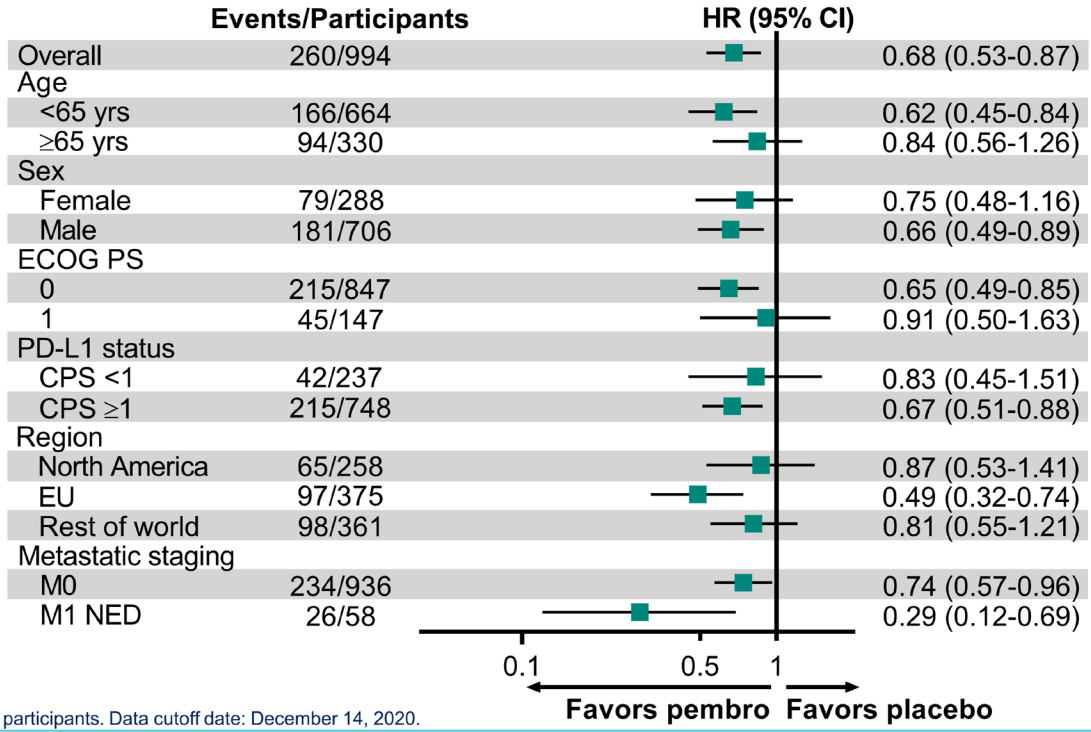
KEYNOTE-564 – Eligible Patients

Intermediate-High Risk		High Risk		M1 NED
pT2 Grade 4 or sarcomatoid N0 M0	pT3 Any grade N0 M0	pT4 Any grade N0 M0	Any pT Any grade N+ M0	NED after resection of oligometastatic sites ≤1 year from nephrectomy
80% 5-year DFS UISS	55-80% 5-year DFS UISS	55% 5-year DFS UISS	32% 5-year DFS UISS	20% 3-year DFS E2810

NED=No evidence of disease; DFS=Disease-free survival; UISS=University of California at Los Angeles Integrated Staging System.

Zisman et al, J Clin Oncol, 2002; Appleman et al, Presented at ASCO Annual Meeting, 2019

DFS by Investigator in Subgroups, ITT Population



ITT population included all randomized participants. Data cutoff date: December 14, 2020.

Front-Line Systemic Therapy
Clear Cell

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)

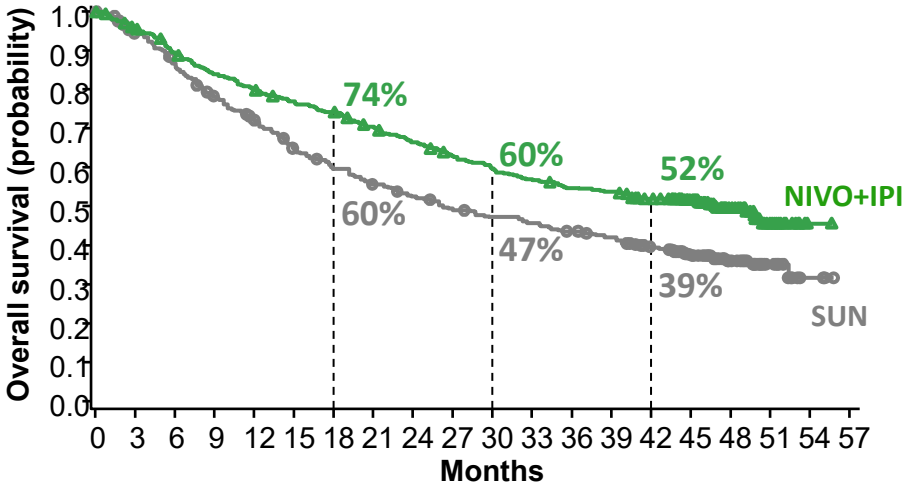
– **Co-primary end points: OS, ORR, PFS in Intermediate and Poor Risk patients**

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

CheckMate 214: Overall Survival by IMDC Risk

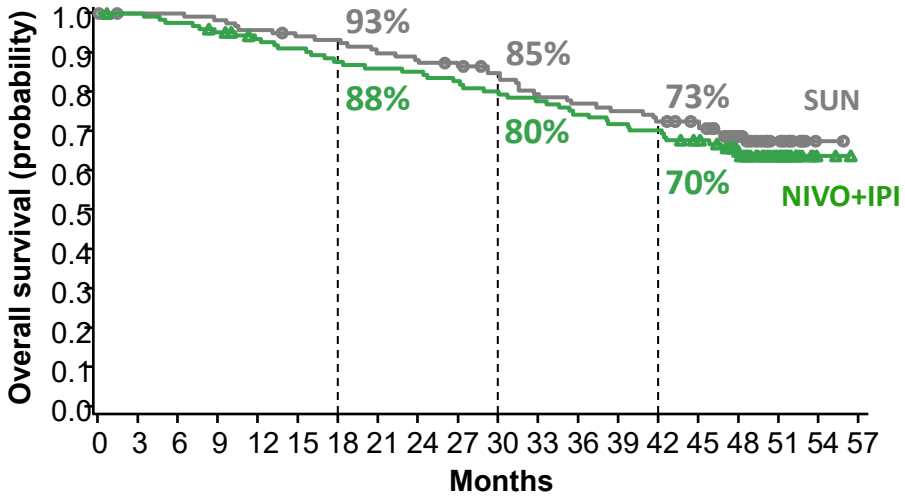
42-Month Follow-Up

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

CheckMate 214 (RCC): Key Clinical Outcomes by IMDC Risk Group

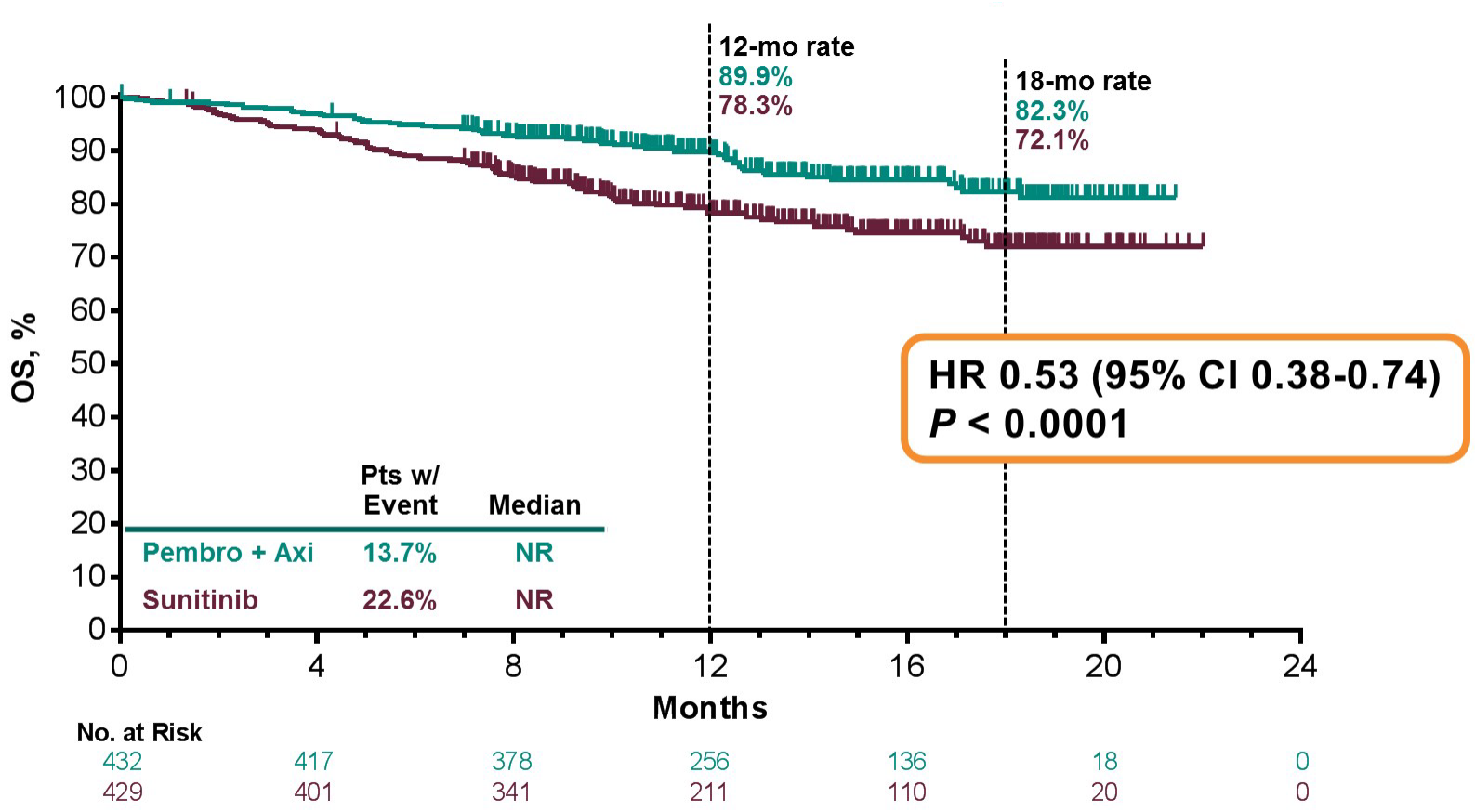
42 Month Minimum Follow-up:

Patient Subset	Better Treatment		
	ORR[1]	PFS	OS
ITT	Ipi/Nivo 39 v 33%	No Diff 12.5 v 12.3 mo	Ipi/Nivo NR v 38.4 mo
IMDC Good Risk	Sunitinib 54 v 29%	Sunitinib 27.7 v 17.8 mo	NR v NR
IMDC Int/Poor Risk	Ipi/Nivo 42 v 26%	Ipi/Nivo 12 v 8.3 mo	Ipi/Nivo 47 v 26.6 mo

[1]per IRRC (Independent Radiology Review Committee)

Tannir, NM *et al*. GU ASCO 2020.

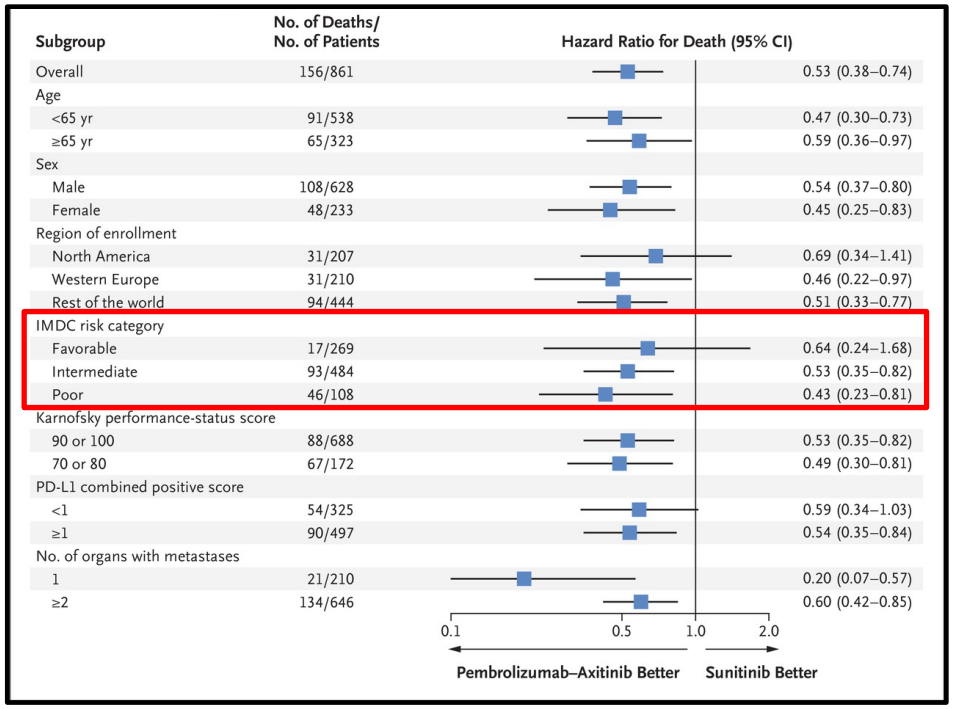
KeyNote 426: Axitinib + Pembrolizumab Survival Outcomes



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

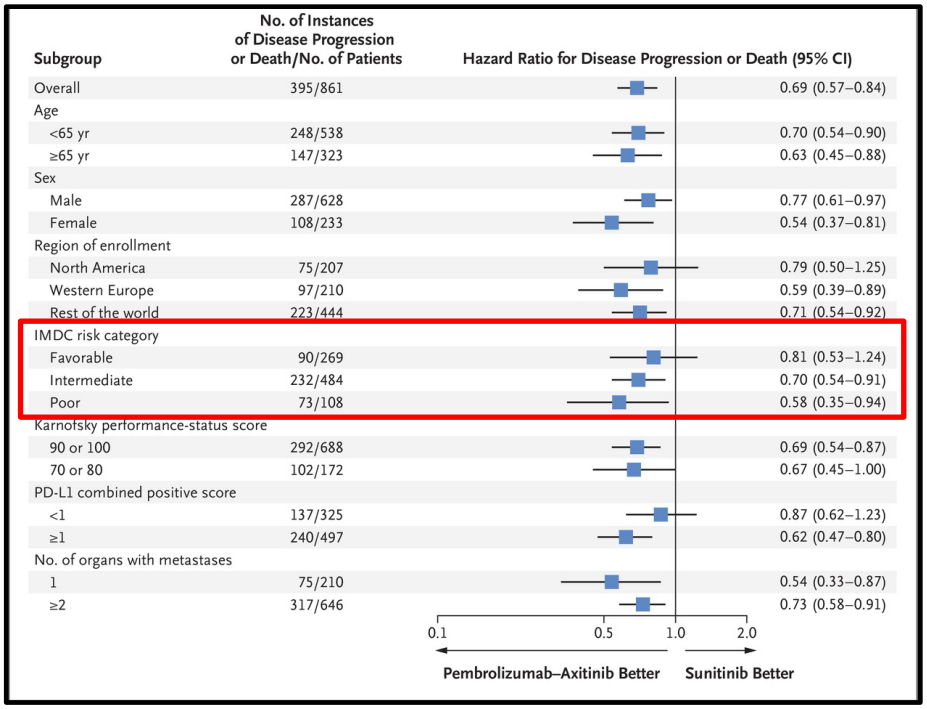
KeyNote 426:
Outcomes by Clinical Subsets

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

Front-line phase 3 trials with immunotherapy agents (efficacy summary)

	CheckMate 214	KEYNOTE-426	CheckMate 9ER	CLEAR
Intervention	Nivolumab + Ipilimumab	Pembrolizumab + Axitinib	Nivolumab + Cabozantinib	Pembrolizumab + Lenvatinib
Comparator	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Primary Endpoint	OS, PFS, ORR in int/poor risk	OS, PFS	PFS	PFS
mOS (ITT), months	(minimum 42 mo FU) NR vs 38.4 HR 0.72	(median 30.6 mo FU) NR vs 35.7 HR 0.68	(median 18.1 mo FU) NR vs NR HR 0.60	(median 26.6 mo FU) NR vs NR HR 0.66
PFS (ITT), months	12.4 vs 12.3 HR 0.88	15.4 vs 11.1 HR 0.71	16.6 vs 8.3 HR 0.51	23.9 vs 9.2 HR 0.39
ORR (ITT), %	39% vs 33%	60% vs 40%	56% vs 27%	71% vs 36%
CR rate (ITT)	11% vs 2%	9% vs 3%	8% vs 5%	16% vs 4%
Primary PD	18% vs 15%	11% vs 17%	6% vs 14%	5% vs 14%

Motzer, RJ *et al*. JITC (2020)
Powles, T *et al*. Lancet Oncol (2020)
Choueiri, TK *et al*. NEJM (2021)
Motzer, RJ *et al*. NEJM (2021)

Selecting Between First-Line Checkpoint Containing Regimens

- **Nuances between checkpoint regimens**
  - Risk category
  - ORR / disease control rate
  - Toxicity / discontinuation rate
  - Treatment free survival
  - Frequency of visits
- **Await more mature OS data**
- **No consensus for “best choice”**

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

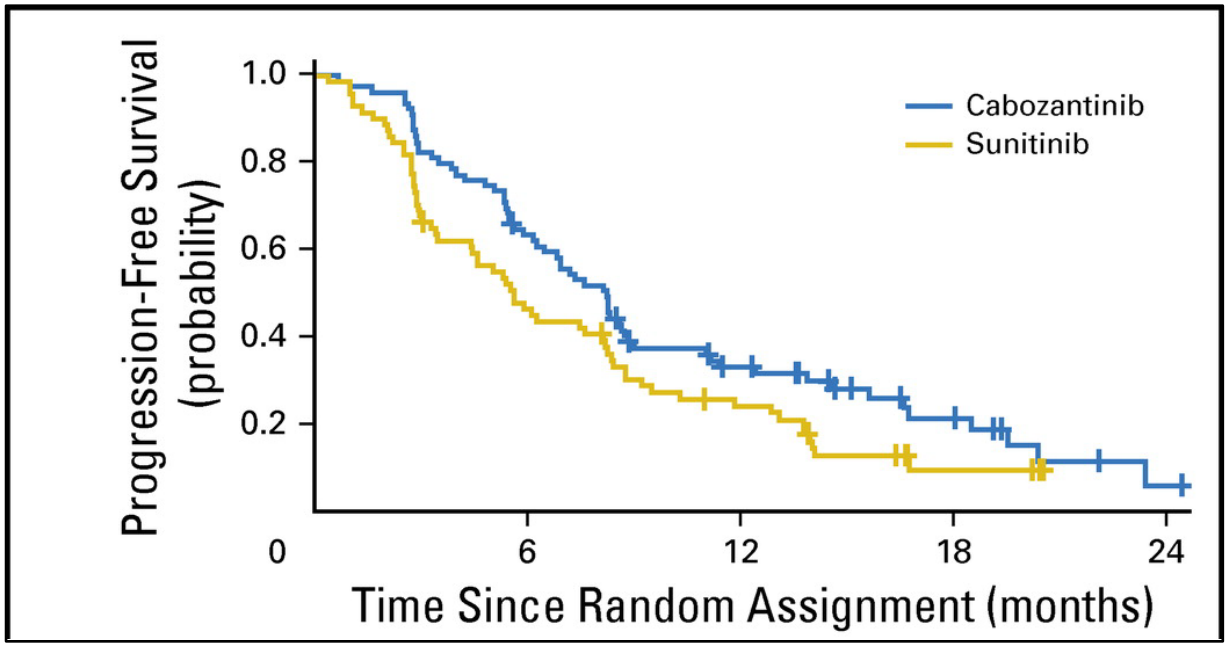
PD-L1 Expression in Tumor	RCC
Prognostic	Unfavorable
Association with ICI treatment – OS ▪ Ipi+Nivo vs SUN ▪ Axi+Pembro vs SUN	No comparative outcome difference for OS
Companion Diagnostic	No
Clinical role for testing	No

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] • **Cabozantinib + nivolumab**[b] **(category 1)** • **Lenvatinib + pembrolizumab**[b] **(category 1)** • **Pazopanib** • **Sunitinib**	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b]	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d]
Poor/ intermediate[a]	• **Axitinib + pembrolizumab**[b] **(category 1)** • **Cabozantinib + nivolumab**[b] **(category 1)** • **Ipilimumab + nivolumab**[b] **(category 1)** • **Lenvatinib + pembrolizumab**[b] **(category 1)** • **Cabozantinib**	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] • Temsirolimus[e]

www.nccn.org – Kidney Cancer Guidelines version 4.2021

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.

Front-Line Systemic Therapy

Non clear cell subets

Clinical Outcomes for Sarcomatoid ccRCC

Treatment	Chemo	Targeted Tx	Immunotherapy			
Regimen (N)	**Dox+Gem[1] 39**	**Sun+Gem[2] 39**	**Ipi/Nivo[3] 74**	**Avelumab/Axi[4] 47**	**Pembro/Axi[5] 51**	**Pembro[6] 11**
ORR, %	16	26	61%	47%	59%	64%
CR, %	3	3	19%	4%	12%	0%
PR, %	13	23	42%	43%	47%	64%
Median PFS, mo	3.5	5	26.5	7.0	NR	16.3
Median OS, mo	8.8	10	NR	NR	NR	32.2

[1]Haas, NB *et al*. Med Oncol (2012)
[2]Michaelson, MD *et al*. Cancer (2015)
[3]Tannir, NM *et al*. ClinCaRes (2021)
[4]Chouriri, TK *et al*. ESMO Open (2021)
[5]ASCO 2019, abstr #4500
[6]McDermott, DF *et al*. JCO (2021)

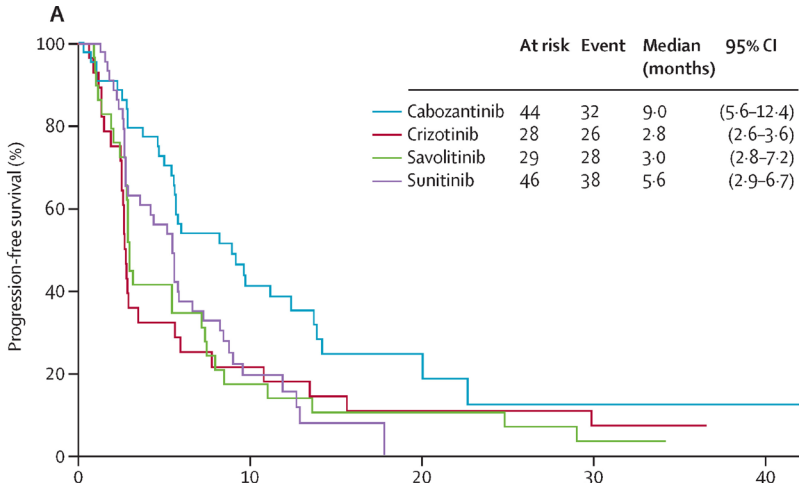
KeyNote 427: First-Line Pembrolizumab for non-clear cell RCC

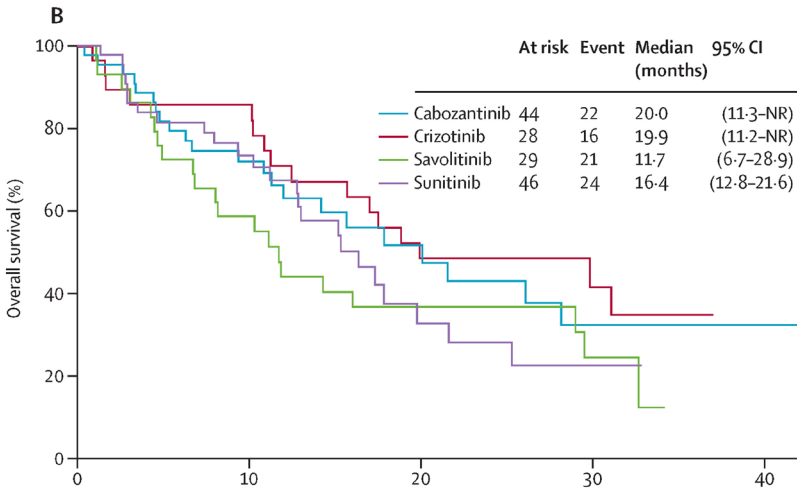
Group (N)	TOTAL 165	Papillary 118	Chromophobe 21	Unclassified 26	Sarcomatoid 38
ORR, %	25	29%	10%	32%	42%
CR, %	5	6%	5%	12%	10%
PR, %	20	23%	5%	19%	32%
Median PFS	4.2 mo	5.5 mo	3.9 mo	2.8 mo	6.9 mo
Median OS	28.9 mo	31.5 mo	23.5 mo	17.6 mo	25.5 mo
Median DOR	29.0 mo	NR	NR	NR	NR

Median follow-up 31.5 mo

McDermott, DF *et al*. JCO (2021)

SWOG 1500 (Randomized, phase II) – Comparison of sunitinib versus cabozantinib, crizotinib or savolitinib for advanced papillary RCC (no prior targeted therapy)





Endpoint	CABO N=44	SUN N=46	HR (P)
PFS	9.0 mo	5.6 mo	0.60 (P=0.019)
OS	20.0 mo	16.4 mo	0.84 (NA)
ORR	23%	4%	NA

Pal, SK. *et al.* Lancet Oncol (2021).

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
- Cabozantinib had better activity by PFS and ORR versus sunitinib for advanced papillary RCC

Second-Line/Salvage Systemic Therapy

Comparison of Current Second-Line Treatment Options for RCC

	Axitinib	Nivolumab	Cabozantinib	Lenvatinib/ Everolimus	Tivozanib
Patient Population	TKI refractory*	TKI refractory	TKI refractory	TKI refractory	TKI refractory
Comparator	Sorafenib	Everolimus	Everolimus	Everolimus	Sorafenib
ORR	9%*	22%	17%	35%	18%
PFS, months	6.5*	4.6	7.4	12.8	5.6
OS, months	15.2*	25.0	21.4	25.5	16.4
Dose reductions	30%	n/a	60%	71%	24%
D/C due to AE	7%	8%	9%	29%	NS
Toxicity	G3 50%	18%	63%	57%	NS
	G4 6%	1%	8%	14%	NS

Rini, BI *et al*.. Lancet (2011)
Choueiri, TK *et al*. NEJM (2015)
Motzer, RJ *et al*. Lancet Oncol (2015)
Motzer, RJ *et al*. NEJM (2015)
Rini, BI *et al*. Lancet Oncol (2020)

Selected "Emerging" Experience With "RCC" Drugs Post IO

Author (Journal, Year)	Study	Agents	N	ORR	PFS/TTF
Albiges (EJC, 2015)	Retrospective	VEGF TKI/mTOR (axi/eve++)	56	13%	6.6 mo
Nadal (Ann Oncol, 2016)	Retrospective	VEGF TKI	70	28%	6.4 mo
Derosa (ESMO, 2017)	Retrospective	VEGF TKIs (cabo/axi)	56	33%	8 mo
McGregor (EJC, 2020)	Retrospective	Cabozantinib	86	36%	6.5 mo
Auvray (EJC, 2019)	Retrospective	TKIs (post combo nivo/ipi)	33	36%	8 mo
Shah (EJC, 2019)	Retrospective	TKIs	70	41%	13.2 mo
Powles (BJC, 2018)	Subgroup (Ph III, METEOR)	Cabozantinib/everolimus	32	22%	NR/4.1
Ornstein (Lancet Oncol, 2019)	Prospective	Axitinib, dose titrated	38	45%	8.8 mo

Preliminary safety data show no concerning signals of "amplified" or unusual toxicities

Summary: post-IO (PD-1/L1) therapy choices

	VEGF TKI	IO	IO+IO (nivo+ipi)	IO→IO (nivo followed by ipi)	IO+VEGF
Evidence	Moderate	Low	Moderate	Moderate (to not do)	Moderate

- **Low:** few retrospective studies
- **Moderate:** retrospective, subgroups of phase 3, prospective non-randomized
- **High:** randomized studies

NEW TARGETS ALWAYS WELCOME

SEATTLE CANCER CARE ALLIANCE, UW MEDICINE and FRED HUTCH

Thank you for your attention