
بسم الله الرحمن الرحيم

METASTATIC RCC (PAST)

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HEMATOLOGIST/ONCOLOGIST;GUMS;AUG-8-2019

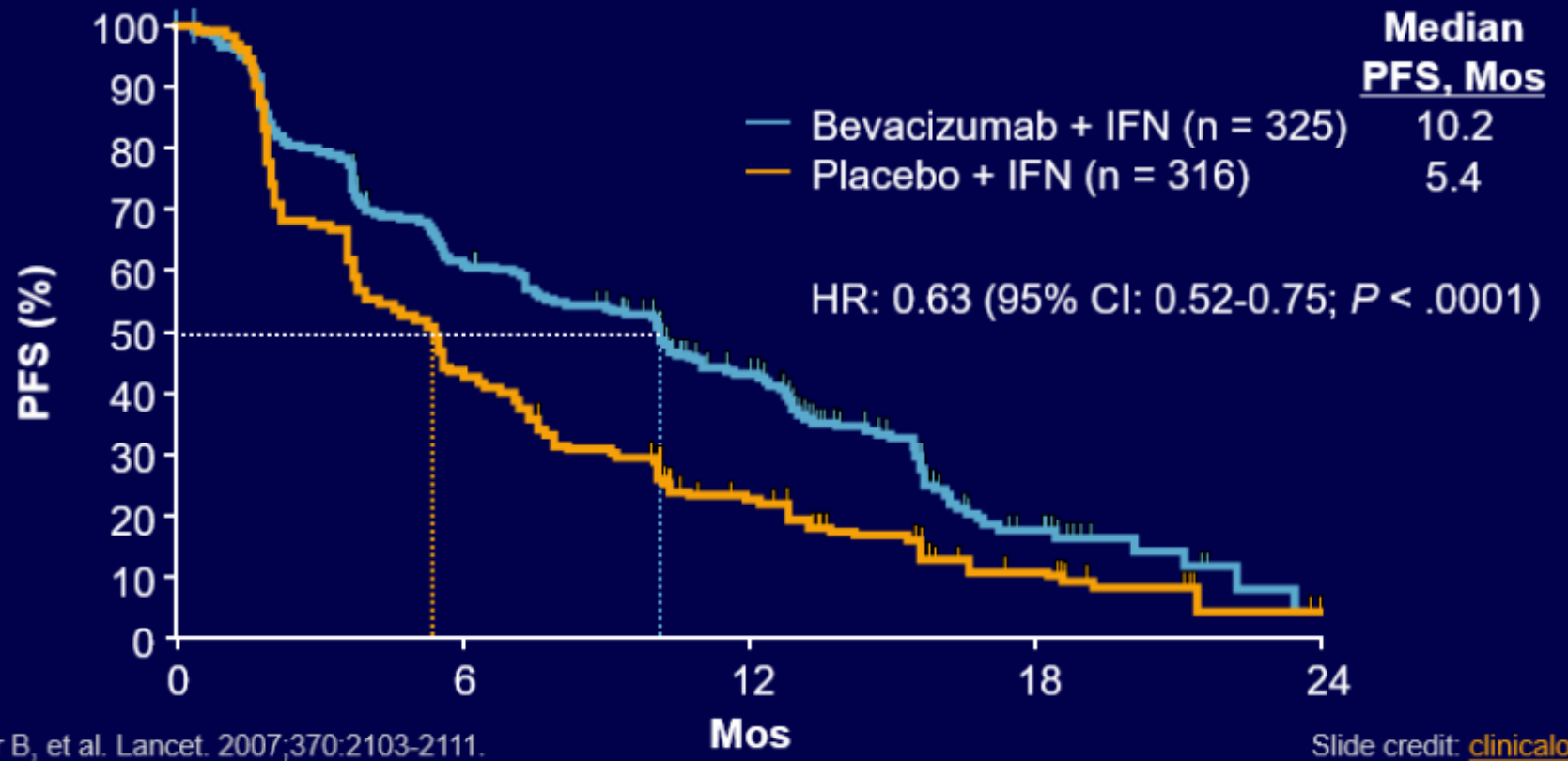
VHL Pathway in RCC

- VHL gene product: involved in regulation of oxygen sensing in renal tubular cells
- Majority of clear-cell RCC characterized by biallelic VHL loss
- Loss of VHL function leads to upregulation of downstream targets
  - Direct target: **HIF**
  - Through HIF: upregulation of **VEGF**, **PDGF**, others
- Classic tumor suppressor gene

Clark PE, et al. Cancer. 2008;113:1768-1778.
Shenoy N, et al. Ann Oncol. 2016;27:1685-1695.

Phase III AVOREN Trial: PFS

- A randomized, double-blind, phase III trial in patients with previously untreated metastatic RCC

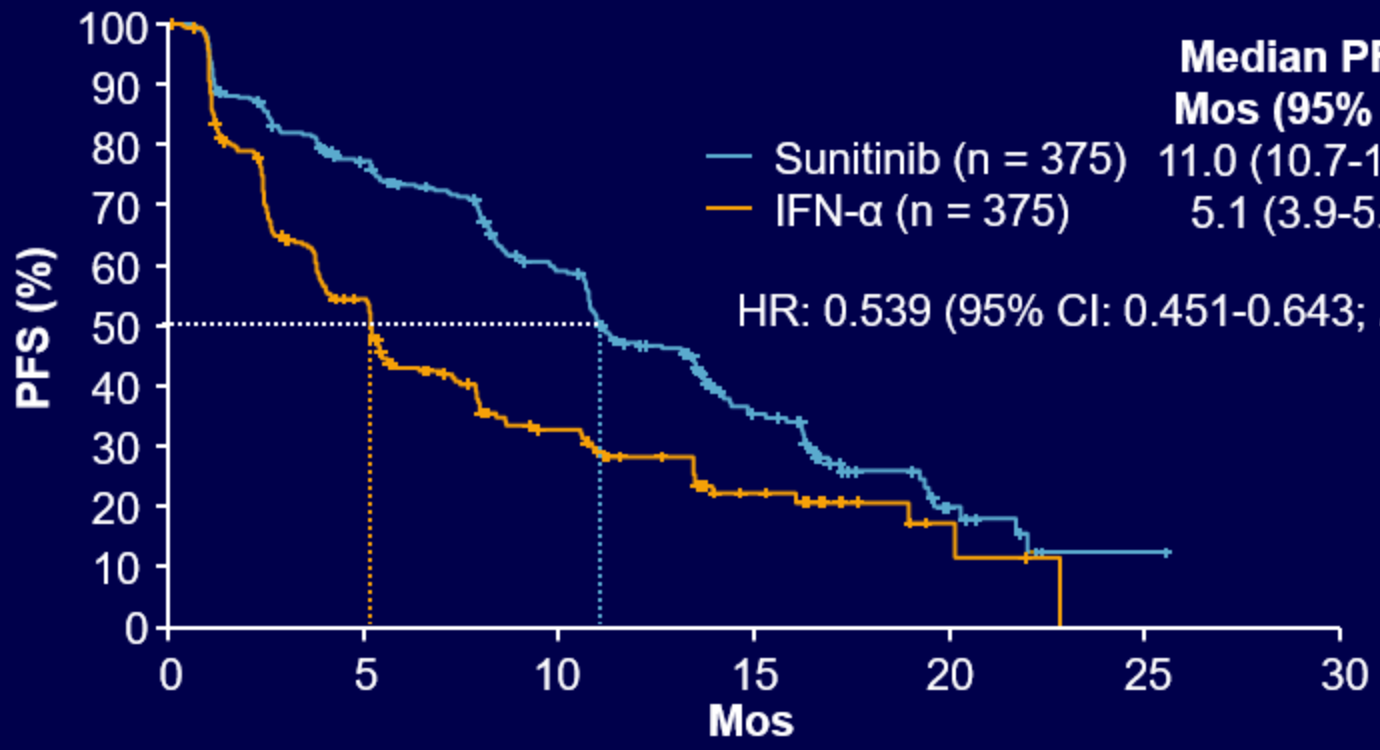


Escudier B, et al. Lancet. 2007;370:2103-2111.

Slide credit: clinicaloptions.com

Phase III Trial of Sunitinib vs IFN-α as First-line Treatment in Pts With Metastatic RCC: PFS

- A randomized phase III trial in previously untreated metastatic RCC with clear-cell component



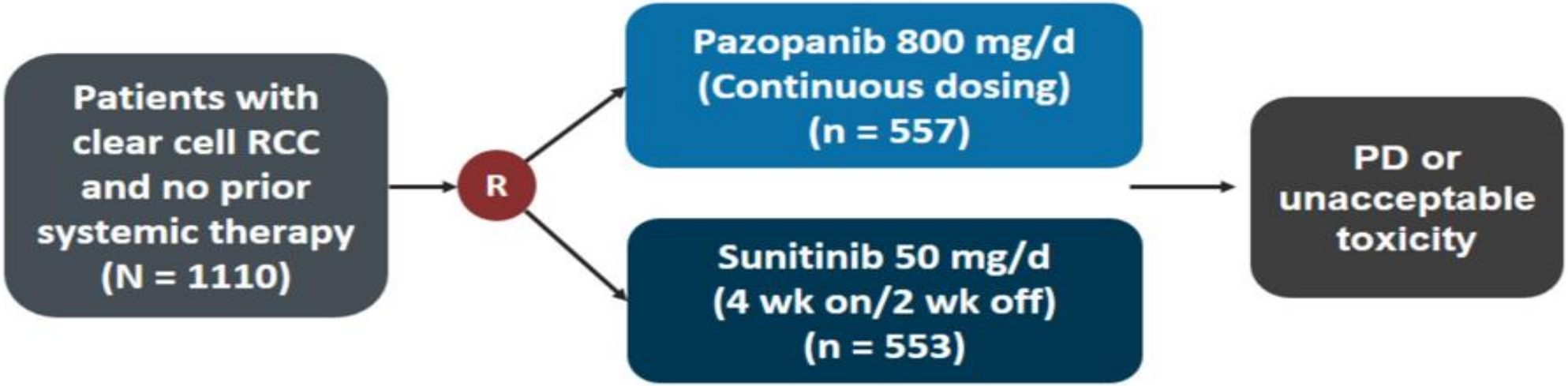
Figlin RA, et al. ASCO 2008. Abstract 5024. Motzer RJ, et al. J Clin Oncol. 2009;27:3584-3590.

Slide credit: clinicaloptions.com

Pazopanib vs Sunitinib in Untreated mRCC

COMPARZ Trial

- Randomized, phase 3, open-label, noninferiority trial



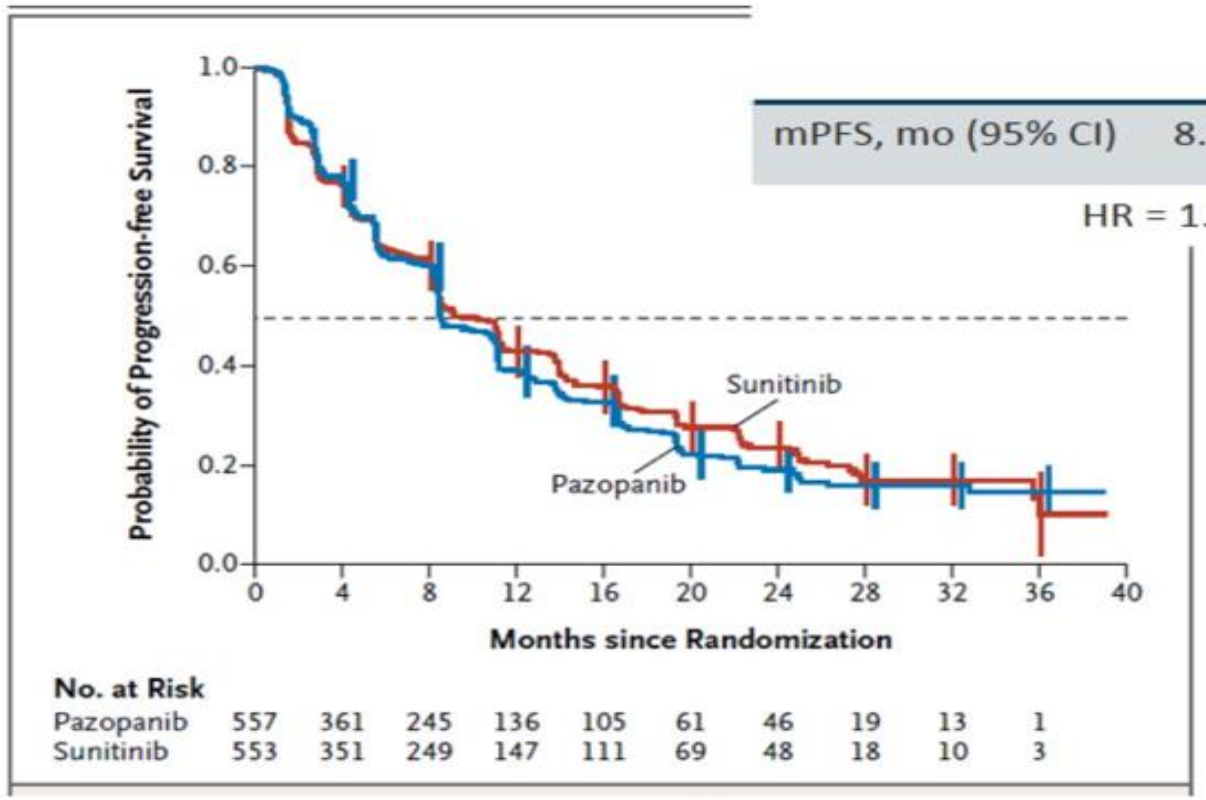
- Primary endpoint: PFS by independent review

Motzer RJ, et al. *N Engl J Med*. 2013;369:722-731.

Medscape EDUCATION

Phase 3 COMPARZ Trial

Progression-Free Survival



	Pazopanib (n = 557)	Sunitinib (n = 553)
mPFS, mo (95% CI)	8.4 (8.3, 10.9)	9.5 (8.3, 11.1)

HR = 1.05 (95% CI: 0.90, 1.22)

- Pazopanib is noninferior to sunitinib for efficacy by independent review

From N Engl J Med, Motzer RJ, Hutson TE, Cella D, et al, Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma, 369., 722-731. Copyright © 2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Medscape EDUCATION

Phase 3 COMPARZ Trial

Treatment-Emergent Adverse Events

Increased risk with sunitinib*

- Fatigue
- HFS, rash, stomatitis, mucosal inflammation, yellow skin
- Dysgeusia, constipation, dyspepsia, GERD
- Hypothyroidism, increased LDH, increased thyrotropin
- Pain in limb, edema, epistaxis
- Various hematologic and other lab abnormalities

Increased risk with pazopanib*

- Changes in hair color
- Weight loss
- Alopecia
- Increased AST/ALT
- Increased total bilirubin
- Increased alkaline phosphatase
- Hypoglycemia

*Events listed occurred in >10% of patients taking either sunitinib or pazopanib.

Motzer RJ, et al. *N Engl J Med*. 2013;369:722-731.

Medscape EDUCATION

Cabozantinib

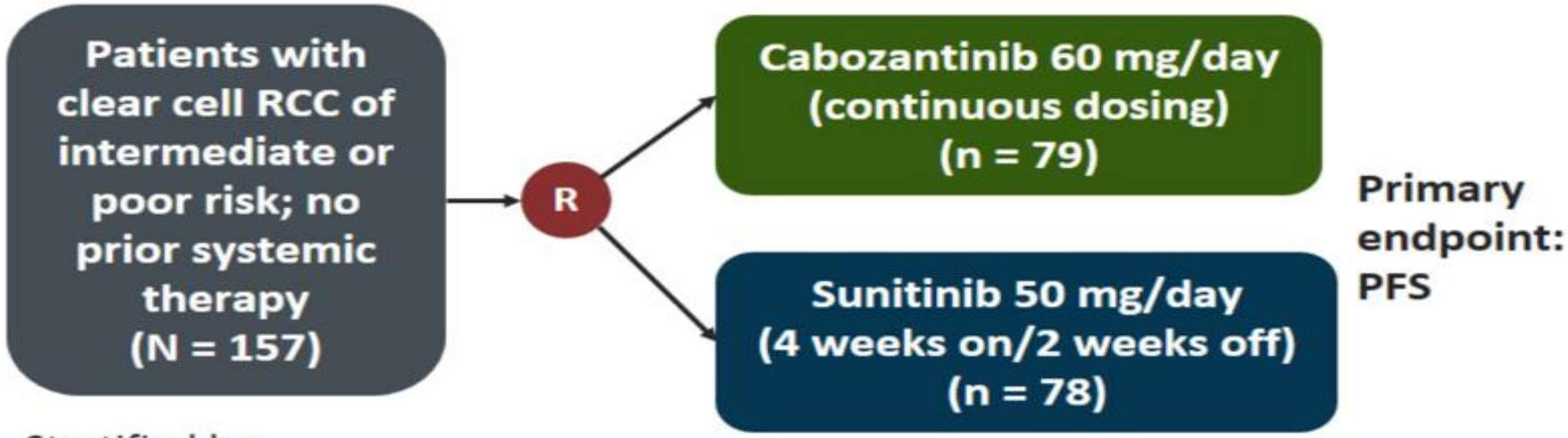
- Small molecule inhibitor of MET, VEGFR-2, RET, KIT, AXL, and FLT3[a]
- MET pathway acts synergistically with VEGF to promote angiogenesis[a]
- Inhibition of these targets inhibits tumor angiogenesis, tumor cell proliferation, cellular migration, and invasion[a]
- FDA approved (April 2016) for patients with advanced RCC who have received prior antiangiogenic therapy[b]
- Results from phase 2 study (CABOSUN) of cabozantinib vs sunitinib in first-line treatment of RCC were recently published

a. Yakes MF, et al. *Mol Cancer Ther*. 2011;10:2298-2308; b. Cabometyx™ PI 2016.

Medscape EDUCATION

Cabozantinib vs Sunitinib in Untreated Clear Cell RCC: CABOSUN Study

- Multicenter, randomized, phase 2 study



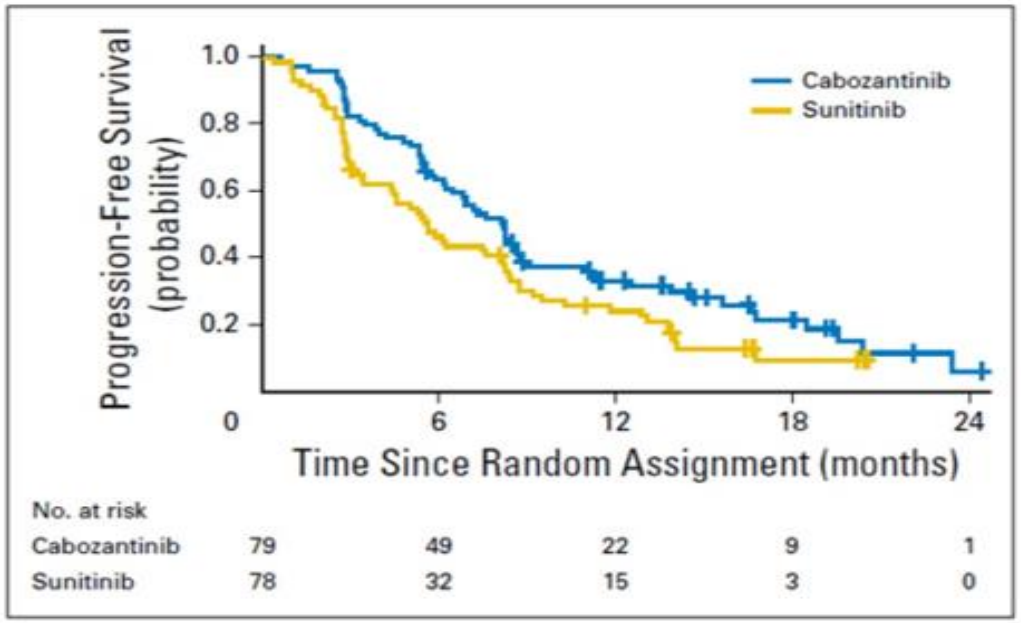
Stratified by:

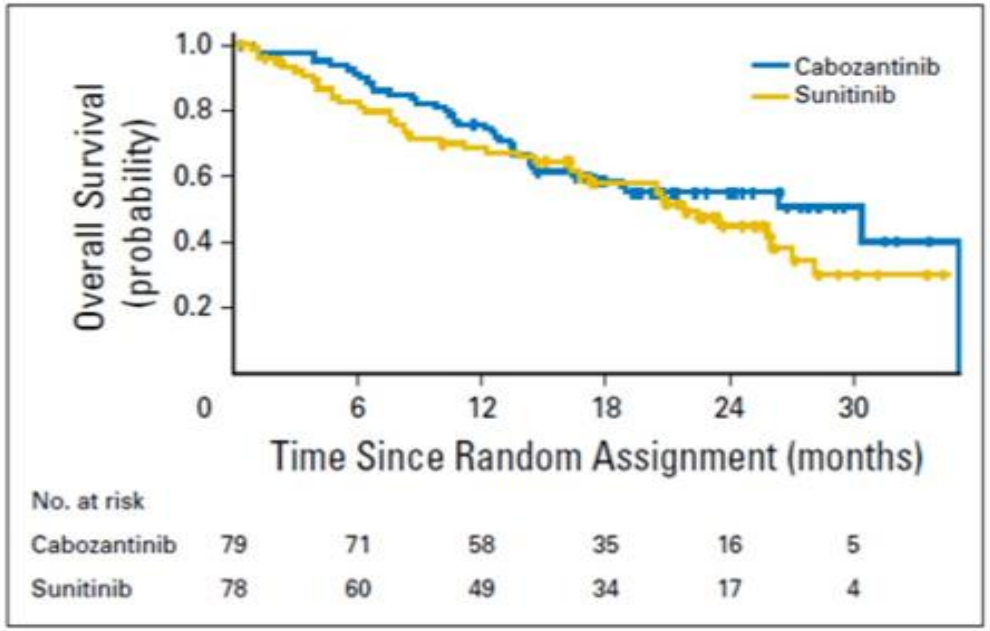
- IMDC risk group (intermediate vs poor)
- Bone metastasis (yes/no)

Choueiri TK, et al. *J Clin Oncol*. 2017;35:591-597.

Medscape EDUCATION

CABOSUN Study
Efficacy Results





- Cabozantinib improved PFS vs sunitinib (8.2 months vs 5.6 months; HR, 0.66; *P* = .012)
- 34% reduction in median rate of progression
- ORR: 46% vs 18% for cabozantinib vs sunitinib, respectively

Medscape EDUCATION

ASPEN: Everolimus vs Sunitinib in Nonclear-Cell RCC

Stratified by histology (papillary vs chromophobe vs unclassified), MSKCC risk group

Untreated pts with metastatic nonclear-cell RCC, KPS ≥ 60 (N = 108)

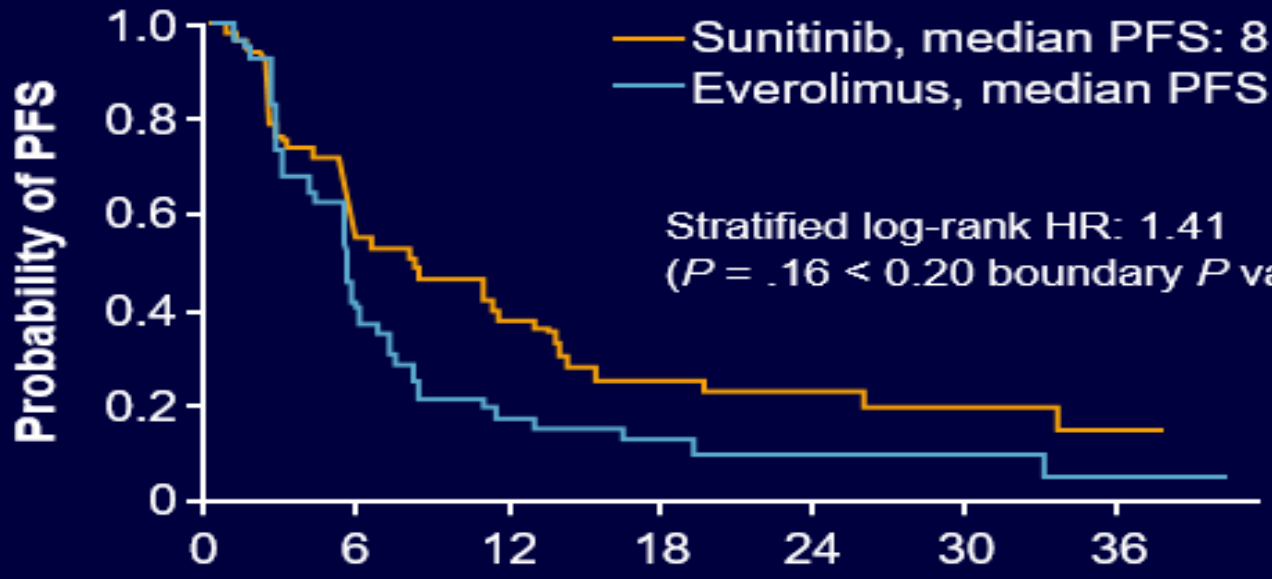
Everolimus 10 mg QD
daily in 6-wk cycles
(n = 57)

Sunitinib 50 mg QD
Days 1-28 in 6-wk cycles
(n = 51)

- Primary endpoint: radiographic PFS
- Secondary endpoints: OS; PFS at 6, 12, 24 mos; ORR; CBR; time to metastasis; QoL

Armstrong AJ, et al. ASCO 2015. Abstract 4507.

ASPEN: Progression-Free Survival

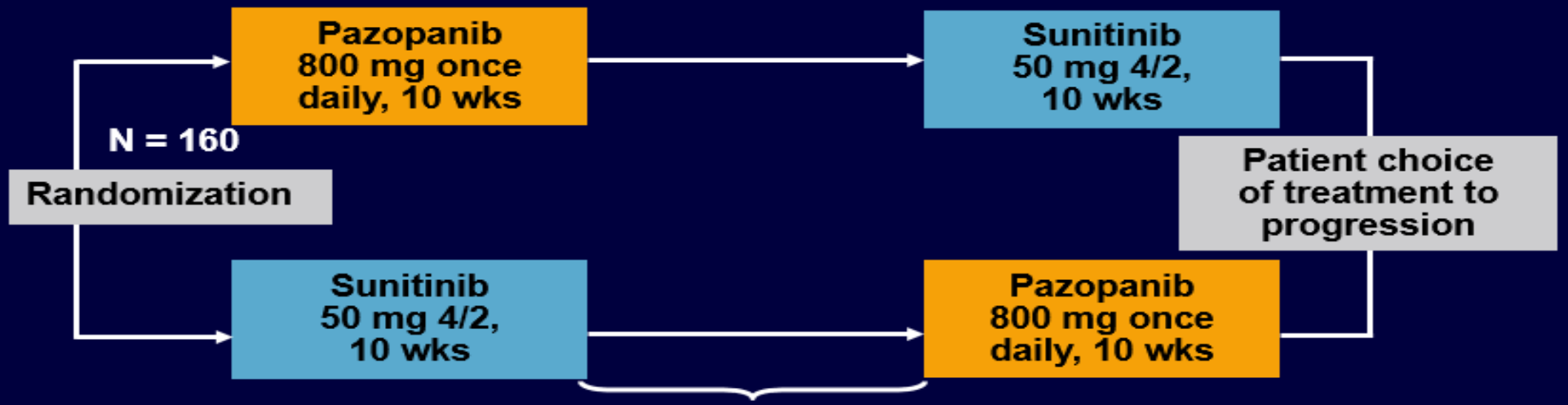


Pts at Risk, n							
Sunitinib	51	26	17	10	8	4	1
Everolimus	57	21	8	4	3	2	1

- Median OS: sunitinib vs everolimus: 32 (95% CI: 15-NR) vs 13 mos (95% CI: 10-38) (HR: 1.12; *P* = .60)

Armstrong AJ, et al. ASCO 2015. Abstract 4507. Reprinted with permission.

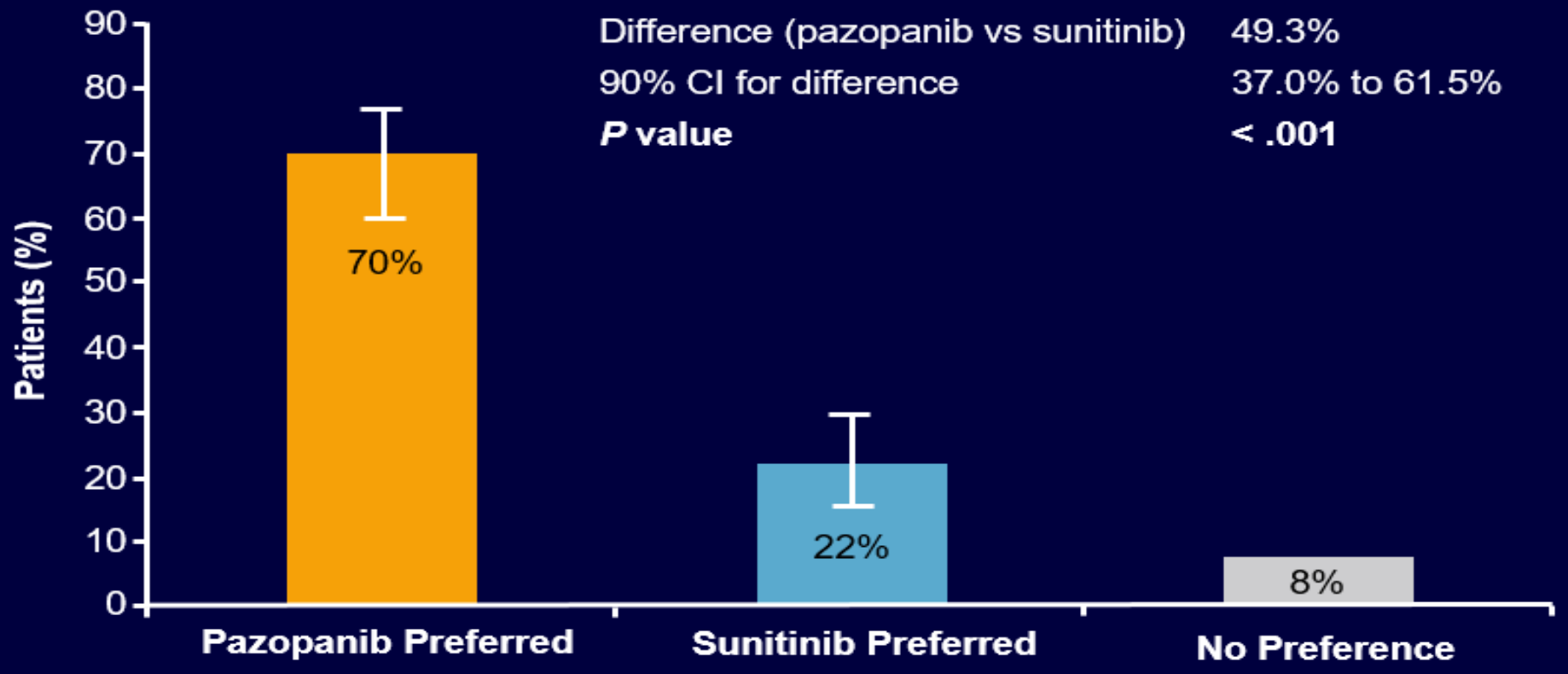
PISCES Patient Preference Study Design



- Primary endpoint
  - Patient preference
- Secondary endpoints
  - Quality of life (EQ-5D)
  - Safety (FACIT-Fatigue)
  - Pharmacokinetics
  - Biomarkers

ClinicalTrials.gov. NCT01064310.

Primary Endpoint: Patient Preference Primary Analysis Population



Escudier BJ, et al. ASCO 2012. Abstract CRA4502.

TIVO-1: Phase III Study of First-Line Tivozanib vs Sorafenib for mRCC

Key Eligibility Criteria:
- Advanced RCC
- Clear-cell histology
- Measurable disease
- Previous nephrectomy
- 0-1 previous therapy for mRCC
- No previous VEGF or mTOR therapy
- ECOG PS 0-1

Stratification factors:
- Geographic region
- Previous treatments for mRCC
- Number of metastatic lesions

RANDOMIZE

1:1

Tivozanib* 1.5 mg/day PO, 3 wks on/1 wk off

Sorafenib 400 mg PO BID, continuous

Progression

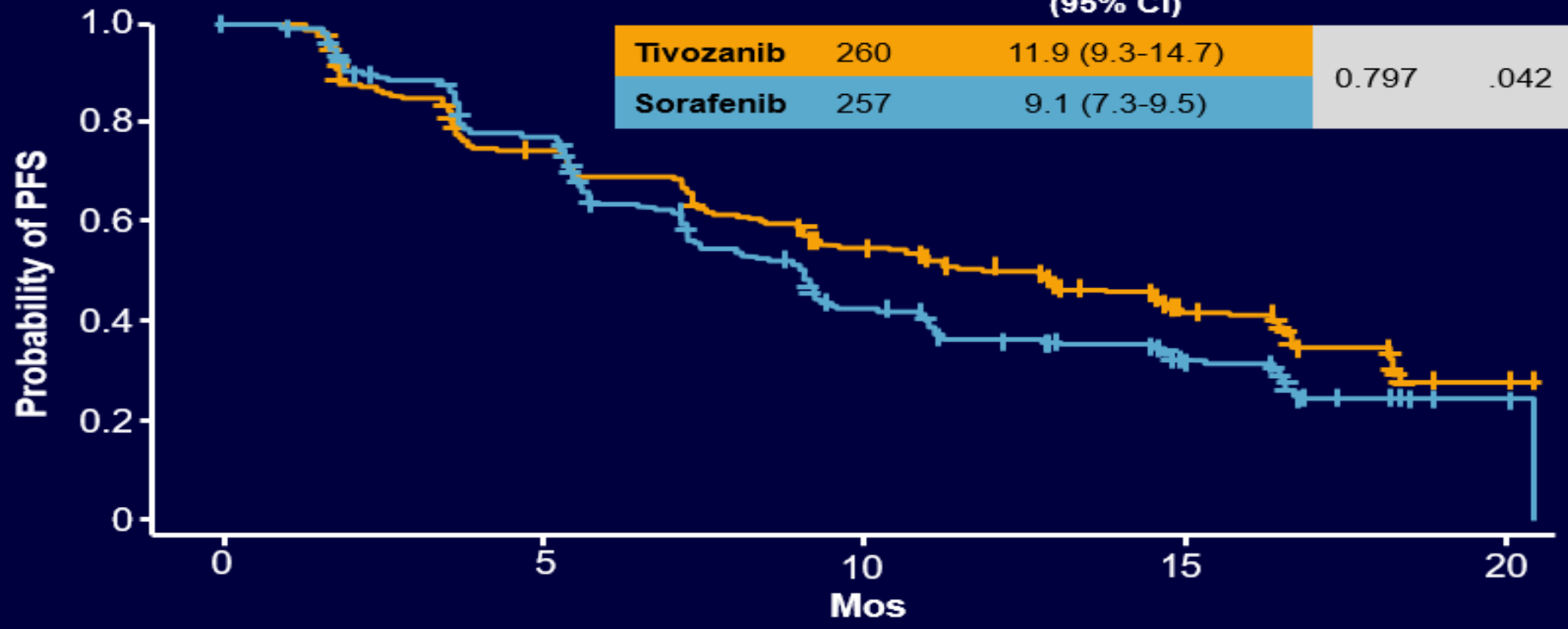
Crossover to tivozanib via separate protocol

*Investigational agent

Motzer R, et al. ASCO 2012. Abstract 4501.

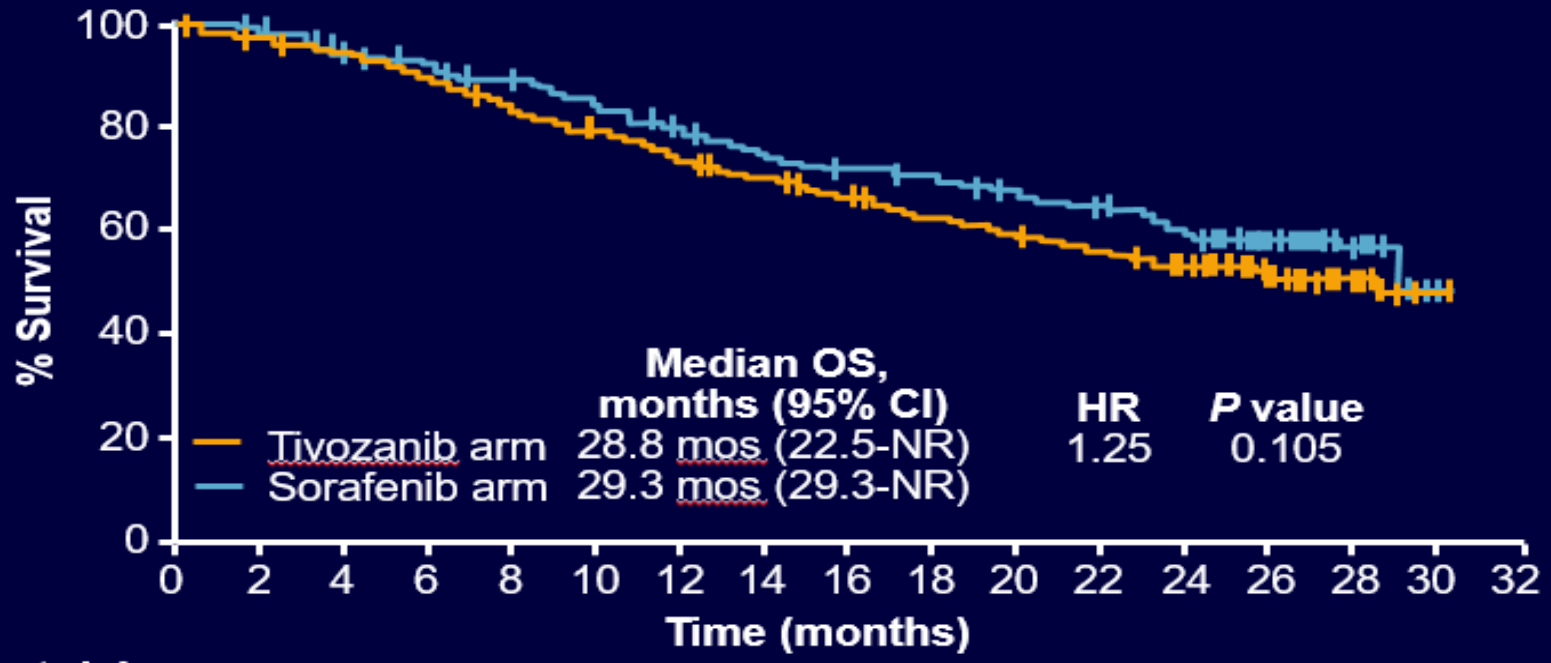
Primary Endpoint: PFS (Independent Review)

	N	Median PFS, Mos (95% CI)	HR	*P* Value
Tivozanib	260	11.9 (9.3-14.7)	0.797	.042
Sorafenib	257	9.1 (7.3-9.5)		



Motzer R, et al. ASCO 2012. Abstract 4501.

Tivo-1: Protocol-Specified, Final Overall Survival Analysis



Patients at risk:

Tivozanib arm	260	256	241	227	211	198	183	170	159	148	142	133	125	89	39	2	0
Sorafenib arm	257	249	241	232	218	208	194	181	170	167	157	151	137	98	43	3	0

Motzer et al. ASCO GU 2013

SWITCH: Phase III Sequential Study of Sorafenib and Sunitinib

Eligibility
- mRCC with all histologies (N = 346)

Stratification
- ECOG PS 0 or 1
- No previous systemic therapy for advanced or mRCC

RANDOMIZATION

Sorafenib 400 mg BID → **Sunitinib 50 mg/day (schedule 4/2)**

Sunitinib 50 mg/day (schedule 4/2) → **Sorafenib 400 mg BID**

Discontinuation (due to progressive disease/toxicity)

- Primary endpoints: overall PFS
- Secondary endpoints: total time to progression, OS, disease control rate and cardiotoxicity

ClinicalTrials.gov. NCT00732914.

RECORD-3: Phase II Sequential Study of Sunitinib and Everolimus

Eligibility
- Patients with advanced RCC (N = 390)

Stratification
- KPS ≥70%
- No previous systemic therapy for advanced or mRCC

RANDOMIZATION

Everolimus 10 mg/day → **Sunitinib 50 mg/day (schedule 4/2)**

Sunitinib 50 mg/day (schedule 4/2) → **Everolimus 10 mg/day**

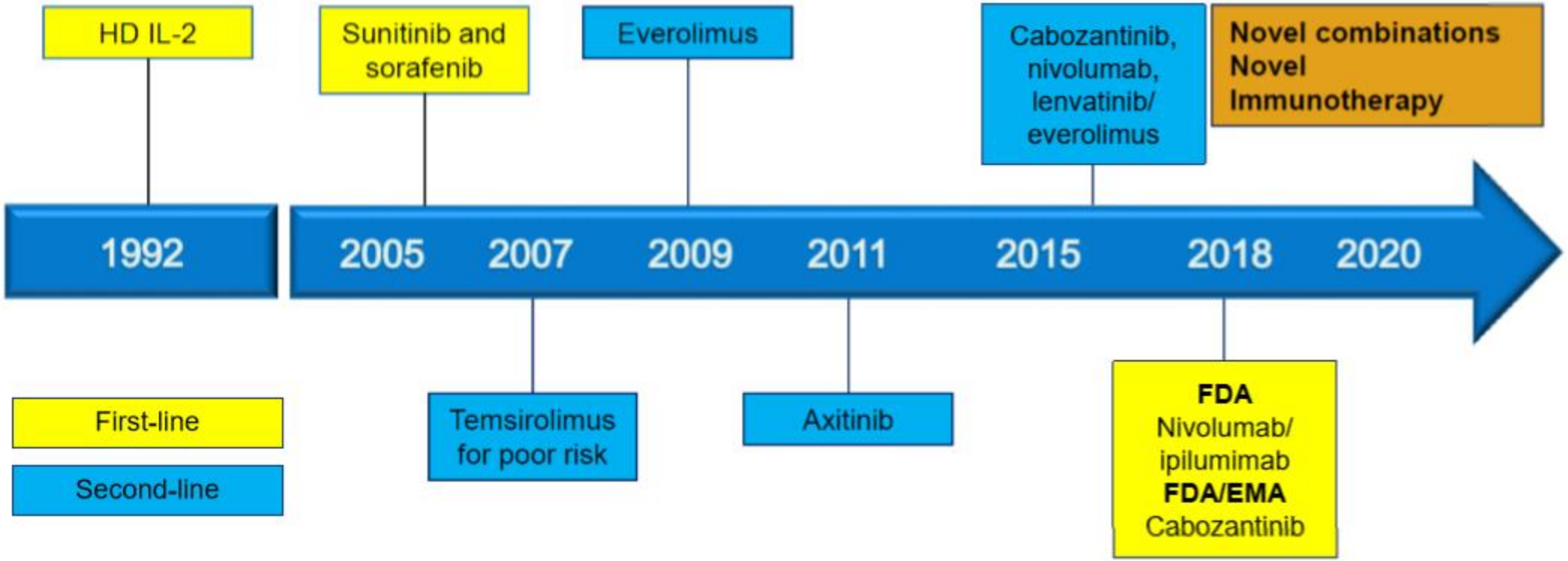
Discontinuation (due to progressive disease/toxicity)

- Primary endpoints: first PFS
- Secondary endpoints: second PFS, ORR, duration of response, patient-reported outcomes, OS

ClinicalTrials.gov. NCT01784978.

METASTATIC RCC (PRESENT)

Increasing Treatment Options in RCC



EMA, European Medicines Agency; FDA, [United States] Food & Drug Administration; HD IL-2, high-dose interleukin-2

Pal SK, et al. Presented at: 2018 Genitourinary Cancers Symposium; February 8-10, 2018: San Francisco, California, United States. Abstract 584.

DISCUSSION ON REVIEWS & ARTICLES

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Kidney Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab (category 3)	• Bevacizumab or biosimilar[e] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[c] (category 2B) • Temsirolimus[d] (category 2B)

[a] See Risk Models to Direct Treatment (IMDC criteria) (KID-D).
[b] Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol 2016;17:1317-1324.
[c] Patients with excellent performance status and normal organ function.
[d] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium greater than 10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.
[e] Biosimilar options include: bevacizumab-awwb.

DISCUSSION ON REVIEWS & ARTICLES

National Comprehensive Cancer Network®

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Kidney Cancer

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Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

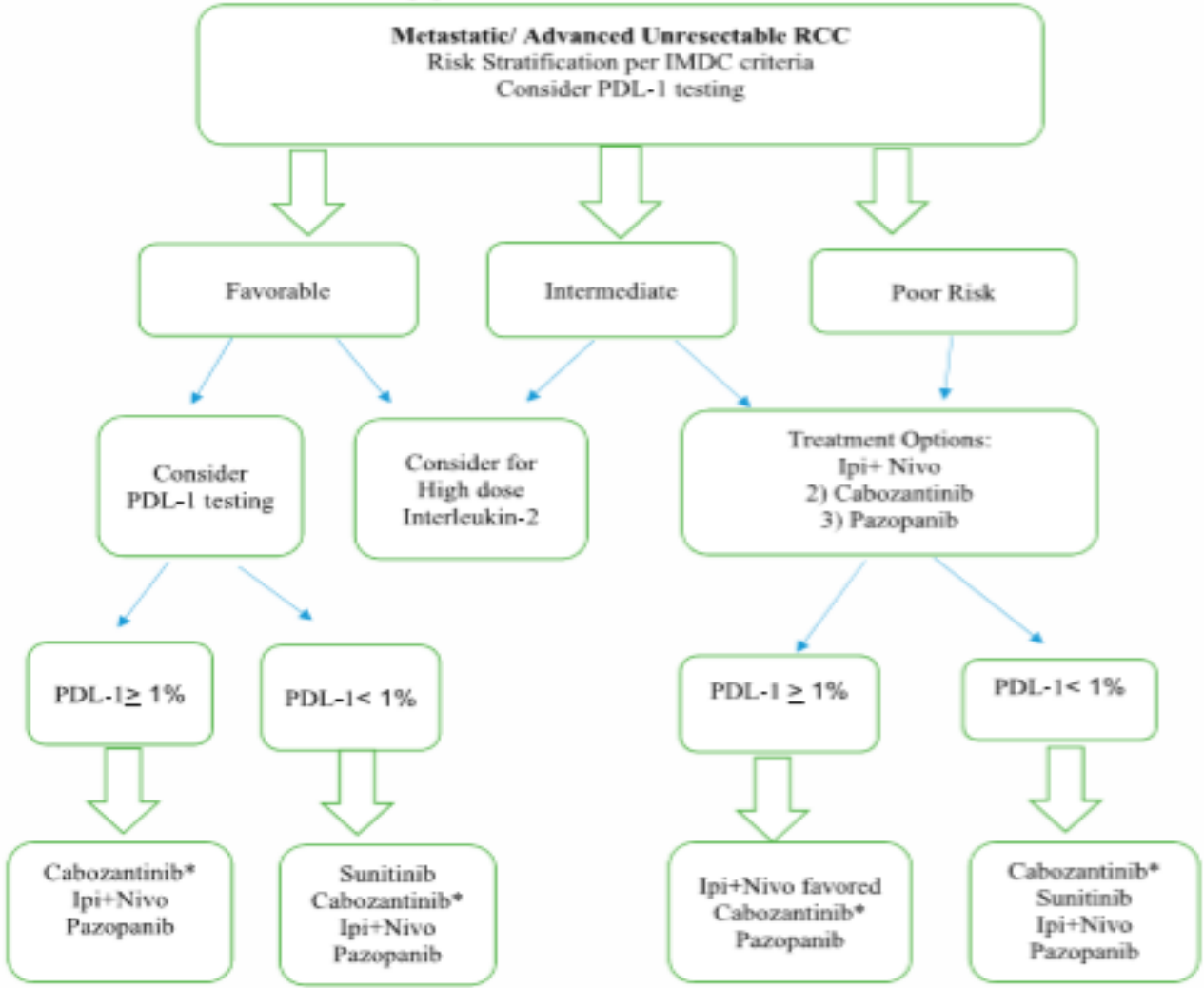
SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[f]		
Preferred regimens	**Other recommended regimens**	**Useful under certain circumstances**
• Clinical trial • Sunitinib	• Cabozantinib • Everolimus	• Axitinib • Bevacizumab or biosimilar[e] • Erlotinib • Lenvatinib + everolimus • Nivolumab • Pazopanib • Bevacizumab or biosimilar[e] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) • Bevacizumab or biosimilar[e] + everolimus • Temsirolimus[d] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

[d] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium greater than 10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.

[e] Biosimilar options include: bevacizumab-awwb.

[f] For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas. Oral targeted therapies generally do not produce responses in patients with renal medullary carcinoma. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred therapy for renal

FIGURE 1. Personalized Frontline Therapy of Renal Cell Carcinoma



Asterisks indicate that cabozantinib should be considered for patients with bone metastases. The recommendation for PD-L1 testing for treatment decisions is based on subset analysis of CheckMate 214.

Abbreviations: RCC, renal cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; Ipi+Nivo, ipilimumab/nivolumab.

Risk Assessment

Similarities and Differences Between Risk Factor Models for aRCC

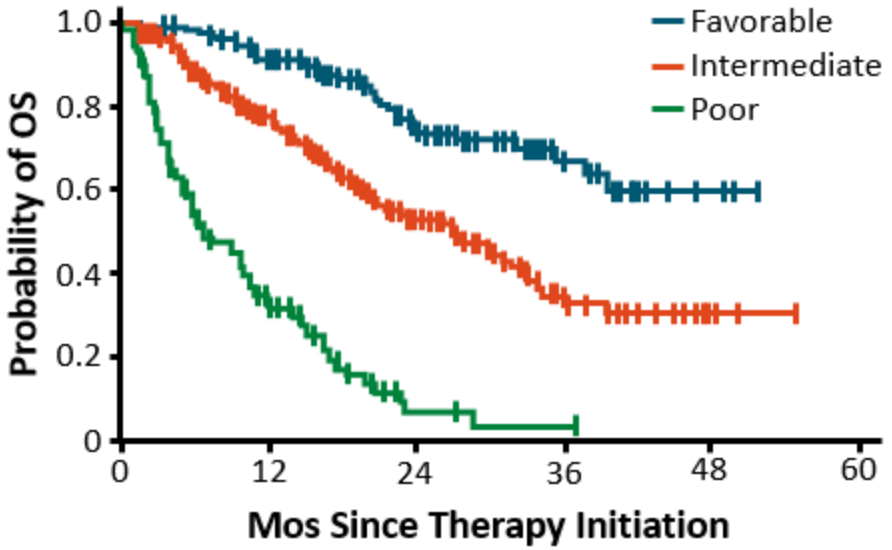
Variable	IMDC	CCF	French	IKCWG	MSKCC
PS	√	√	√	√	√
Time from diagnosis to therapy	√	√		√	√
Time from diagnosis to metastasis			√		
Number of metastatic sites			√	√	
Liver metastasis			√		
Previous immunotherapy				√	
Hg level	√			√	√
Uncorrected Ca+ level	√	√		√	√
Neutrophil count	√	√			
Platelet count	√	√			
LDH level				√	√
WBC count				√	
Alkaline phosphatase level				√	

*The cutoff values for the risk groups (–2·78 and –1·25) are the 25th and 75th percentiles of the distribution of risk scores from the IKCWG model

Ca+, calcium; CCF, Cleveland Clinic Foundation; Hg, hemoglobin; IKCWG, *International Kidney Cancer Working Group*; LDH, lactate dehydrogenase; MSKCC, Memorial Sloan-Kettering Cancer Center; ECOG PS, Eastern Cooperative Oncology Group performance score; WBC, white blood cell

IMDC Prognostic Criteria

- Clinical
  - KPS < 80% (*P* < .0001)
  - Time from diagnosis to tx < 1 yr (*P* = .01)
- Laboratory
  - Hemoglobin < LLN (*P* < .0001)
  - Calcium > ULN (*P* = .0006)
  - Neutrophil count > ULN (*P* < .0001)
  - Platelet count > ULN (*P* = .01)



No. of Events/No. at Risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

Favorable: 0 risk factors; intermediate: 1-2 risk factors; poor: 3+ risk factors

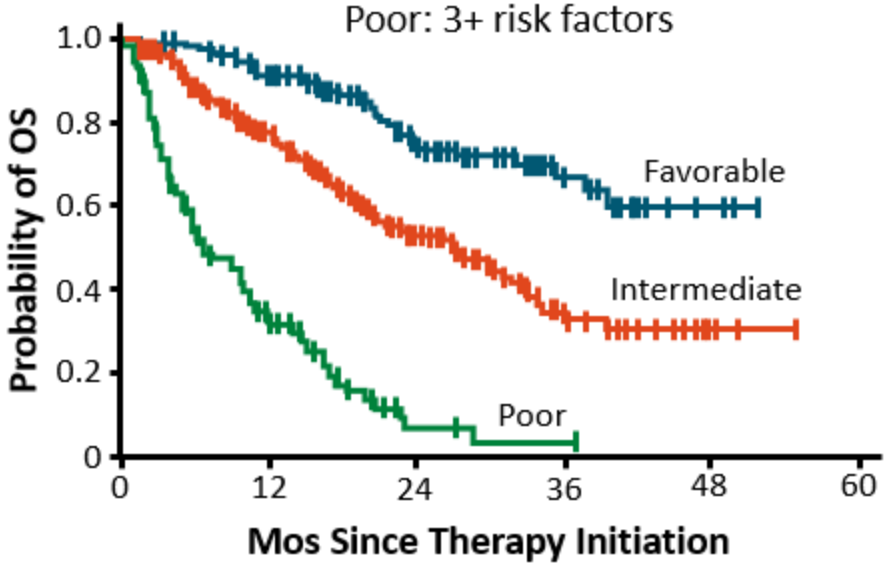
Heng. JCO. 2009;27:5794.

Slide credit: clinicaloptions.com

IMDC (Heng) Prognostic Criteria

- Clinical
  - KPS < 80% (*P* < .0001)
  - Time from diagnosis to tx < 1 yr (*P* = .01)
- Laboratory
  - Hemoglobin < LLN (*P* < .0001)
  - Calcium > ULN (*P* = .0006)
  - Neutrophil count > ULN (*P* < .0001)
  - Platelet count > ULN (*P* = .01)

Favorable: 0 risk factors; Intermediate: 1-2 risk factors; Poor: 3+ risk factors



75% to 80% of patients selecting first-line mRCC Tx options have ≥ 1 of these risk factors, classifying their mRCC as intermediate or poor risk

Risk classification may change over time and may help in selecting treatments such as immunotherapy

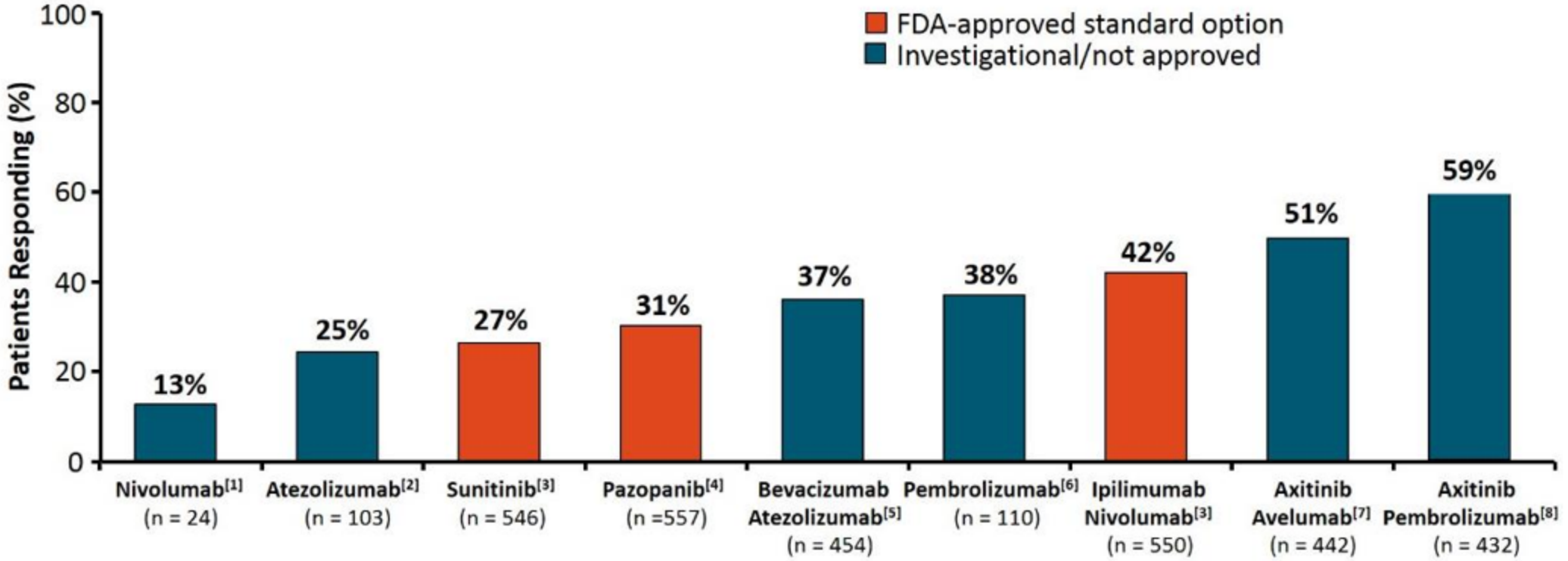
Heng. JCO. 2009;27:5794.

Slide credit: clinicaloptions.com

IMDC Risk Factor[10]

Risk Factor	Classification
KPS < 80%	Good (0)
Neutrophil > ULN	2-year OS, 75%
Hemoglobin < LLN	Intermediate (1–2)
Calcium > ULN	2-year OS, 53%
Time from diagnosis to treatment < 1 year	Poor (> 2)
Platelet > ULN	Median OS, 8.8 months

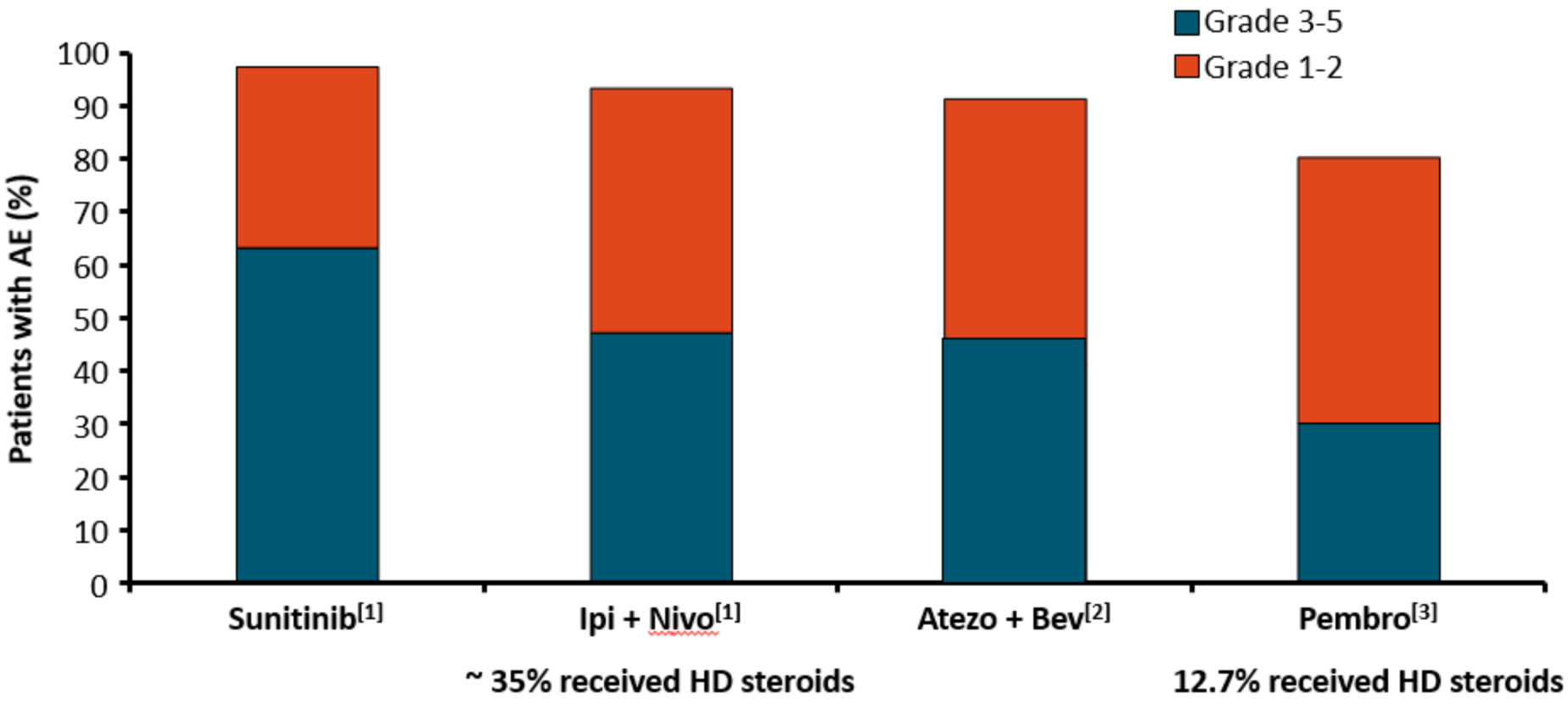
Response Rates in Frontline Metastatic ccRCC (All Risk Groups)



1. Choueiri. Clin Cancer Res. 2016;15:5461. 2. McDermott. ASCO GU 2017. Abstract 431. 3. Motzer. NEJM. 2018;378:1277.
4. Motzer. NEJM. 2013;369:722. 5. Escudier. ASCO 2018. Abstract 4511. 6. McDermott. ASCO 2018. Abstract 4500.
7. Motzer. ESMO 2018. Abstract LBA6. 8. Powles. Genitourinary Cancers Symposium 2019. Abstr 543.

Slide credit: clinicaloptions.com

Treatment-Related Adverse Events in Frontline Metastatic ccRCC (All Risk)



1. Motzer. NEJM. 2018;378:1277. 2. Escudier. ASCO 2018. Abstract 4511. 3. McDermott. ASCO 2018. Abstract 4500.

Slide credit: clinicaloptions.com

Systemic Therapy Options for mRCC 2019

Treatment
Ipilimumab + Nivolumab
Nivolumab
Cabozantinib
Axitinib
Lenvatinib + Everolimus
Pazopanib
Sunitinib
Bevacizumab
(Sorafenib, HD IL-2, Temsirolimus)

Slide credit: clinicaloptions.com

How to Select Treatment for Metastatic RCC in Different Patient Populations

Slide credit: clinicaloptions.com

Decision Making in First-Line Therapy for mRCC

Patient Factors

- Age
- Organ function
- Immune status
- Comorbid conditions
- IMDC risk
- Neutrophil-lymphocyte ratio
- Urgency of response

Disease Factors

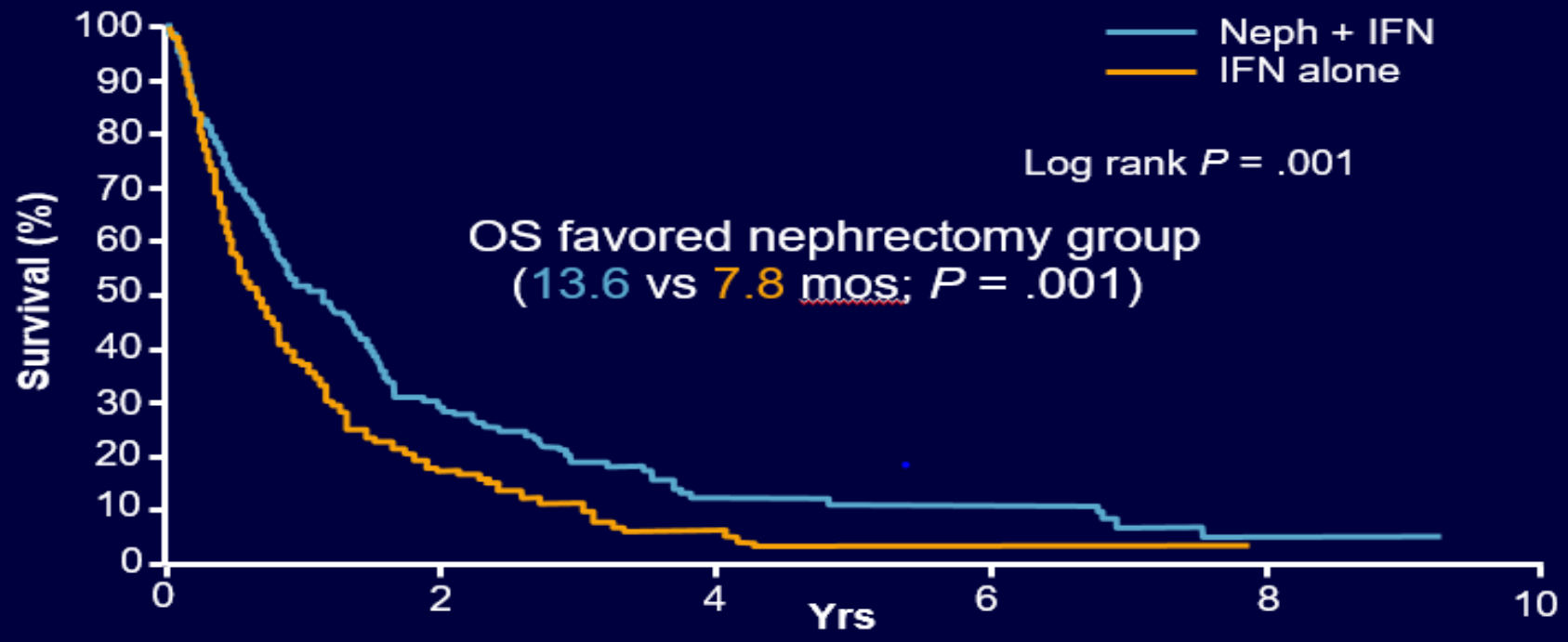
- Histology
- Tumor biology
- Presentation
  - Synchronous/metachronous
- Symptomatic/not symptomatic
- Sites of metastases
- IMDC risk
- PD-L1 status

mRCC, metastatic RCC

Vaishampayan U, et al. *J Clin Oncol*. 2018;36(suppl): Abstract 4510.

DEBULKING (CRN)

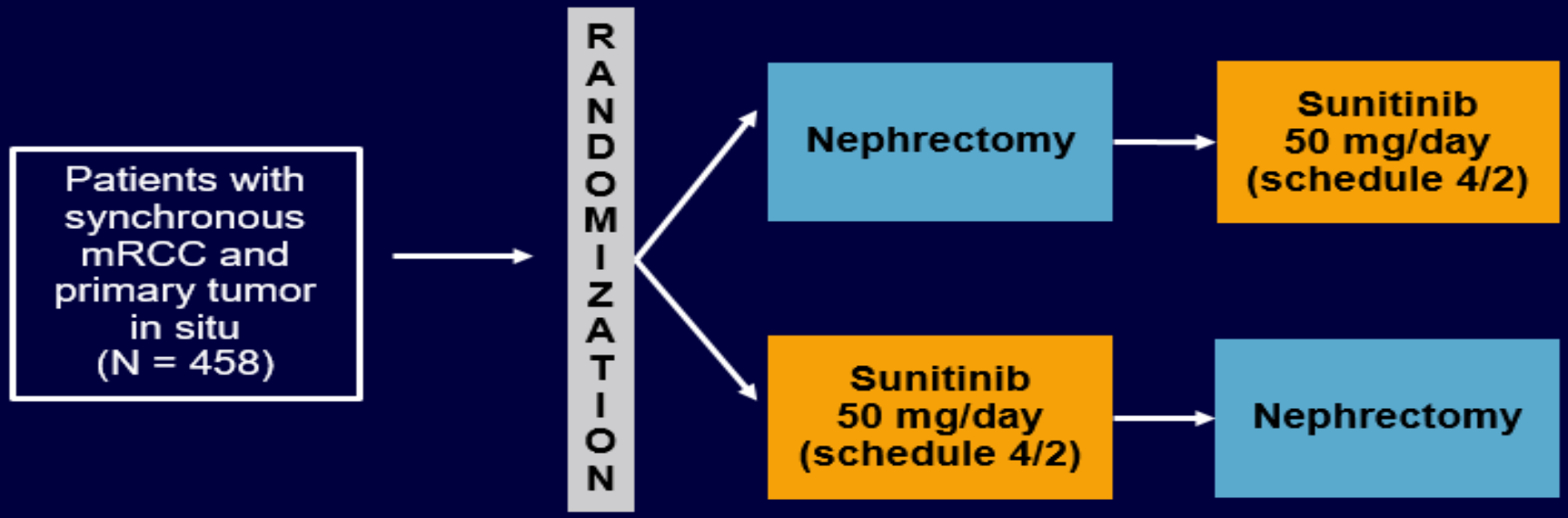
Interferon ± Debulking Nephrectomy



O	N	Patients at Risk, n:			
141	161	46	13	9	3
152	163	26	7	1	0

Flanigan R, et al. J Urol. 2004;171:1071-1076.

SURTIME: EORTC-GU 30073 Phase III Study of Nephrectomy and Sunitinib

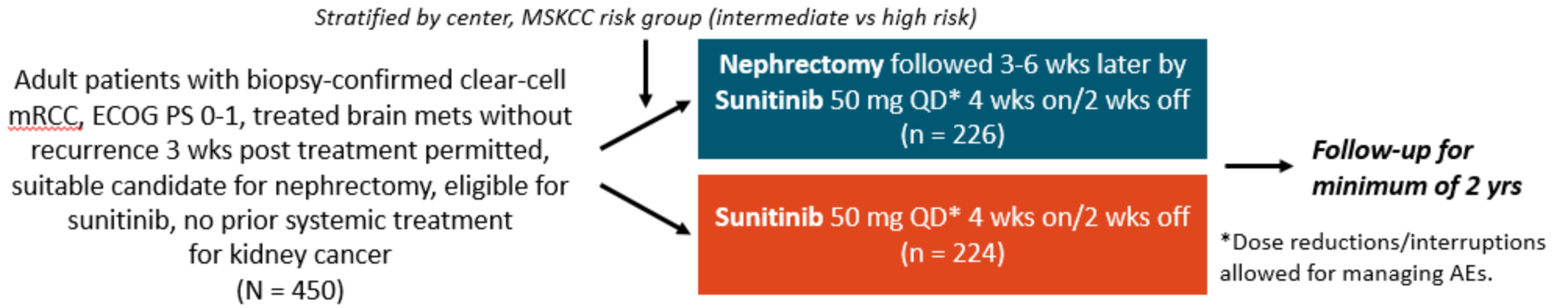


- Primary endpoint: PFS
- Secondary endpoints: OS, association with prognostic gene and protein expression profiles

CinicalTrials.gov. NCT01099423

CARMENA: Study Design

- Final analysis of multicenter, randomized, open-label noninferiority phase III trial
  - Steering committee closed trial after second interim analysis (prespecified at 326 events) due to slow recruitment; second interim analysis deemed sufficient to meet trial objectives



- Primary endpoint: OS
  - Trial designed to have 80% power with 1-sided $\alpha = 0.05$ to show noninferiority with 576 patients enrolled (observed deaths, n = 456)
- Secondary endpoints: PFS, ORR (RECIST v1.1), clinical benefit, treatment adherence, nephrectomy in sunitinib-only arm, postoperative morbidity and mortality, safety

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

CARMENA: Baseline Characteristics

- Median follow-up of 50.9 mos at data cutoff (December 12, 2017)

Characteristic, n (%)	Nephrectomy → Sunitinib (n = 226)	Sunitinib (n = 224)
Median age, yrs (range)	63 (33-84)	62 (30-87)
Male	169 (74.8)	167 (74.6)
MSKCC risk category	n = 225	n = 224
▪ Intermediate	125 (55.6)	131 (58.5)
▪ Poor	100 (44.4)	93 (41.5)
ECOG PS		
▪ 0	130 (57.5)	122 (54.5)
▪ 1	96 (42.5)	102 (45.5)
Fuhrman grade of RCC	n = 150	n = 156
▪ 1 or 2	77 (51.3)	82 (52.6)
▪ 3 or 4	73 (48.7)	74 (47.4)
Tumor stage	n = 67	n = 49
▪ T1	5 (7.5)	7 (14.3)
▪ T2	13 (19.4)	13 (26.5)
▪ T3 or T4	47 (70.1)	25 (51.0)
▪ Tx	2 (3.0)	4 (8.2)

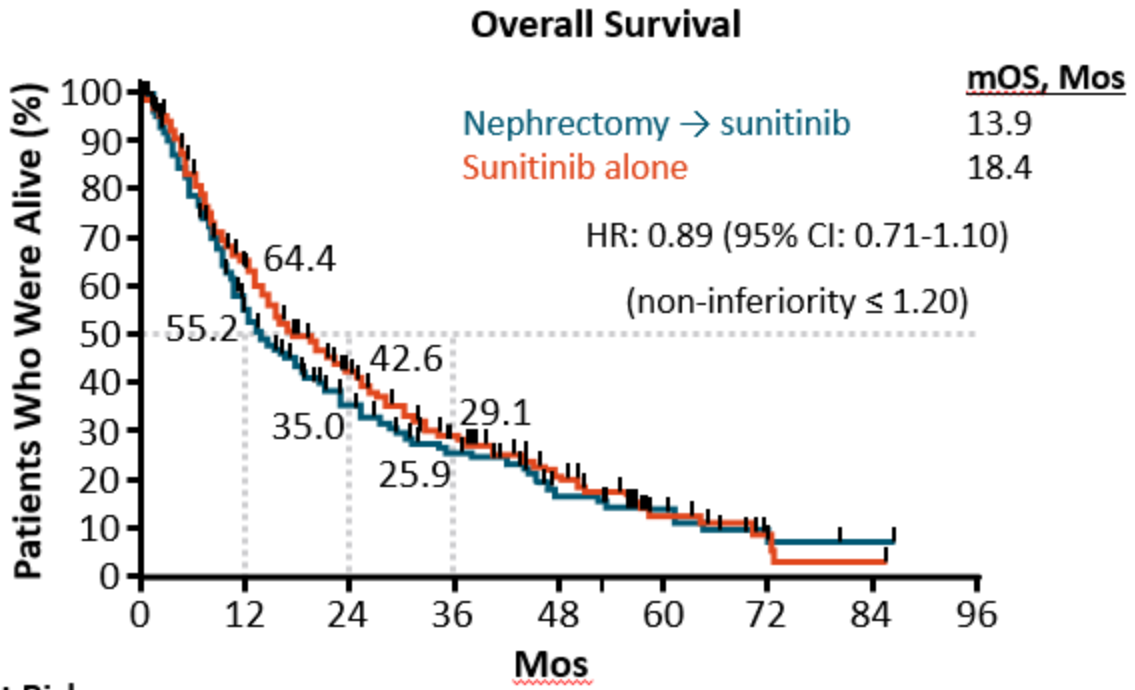
Characteristic, n (%)	Nephrectomy → Sunitinib (n = 226)	Sunitinib (n = 224)
Node stage	n = 66	n = 49
▪ N0	23 (34.8)	18 (36.7)
▪ N1	13 (19.7)	6 (12.2)
▪ N2	7 (10.6)	13 (26.5)
▪ Nx	23 (34.8)	12 (24.5)
Median primary tumor size, mm (range)	88 (6-200)	86 (12-190)
Median no. mets (range)	2 (1-5)	2 (1-5)
Median tumor burden, mm (range)	140 (23-399)	144 (39-313)
Location of mets	n = 217	n = 221
▪ Lung	172 (79.3)	161 (72.9)
▪ Bone	78 (35.9)	82 (37.1)
▪ LN	76 (35.0)	86 (38.9)
▪ Other	78 (35.9)	90 (40.7)

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

CARMENA: Overall Survival

- Sunitinib alone not inferior to nephrectomy → sunitinib (upper boundary of 95% CI ≤ 1.20)
- mOS longer with sunitinib alone vs nephrectomy → sunitinib:
  - MSKCC intermediate-risk: 23.4 vs 19.0 mos (HR: 0.92)
  - MSKCC poor-risk: 13.3 vs 10.2 mos (HR: 0.86)



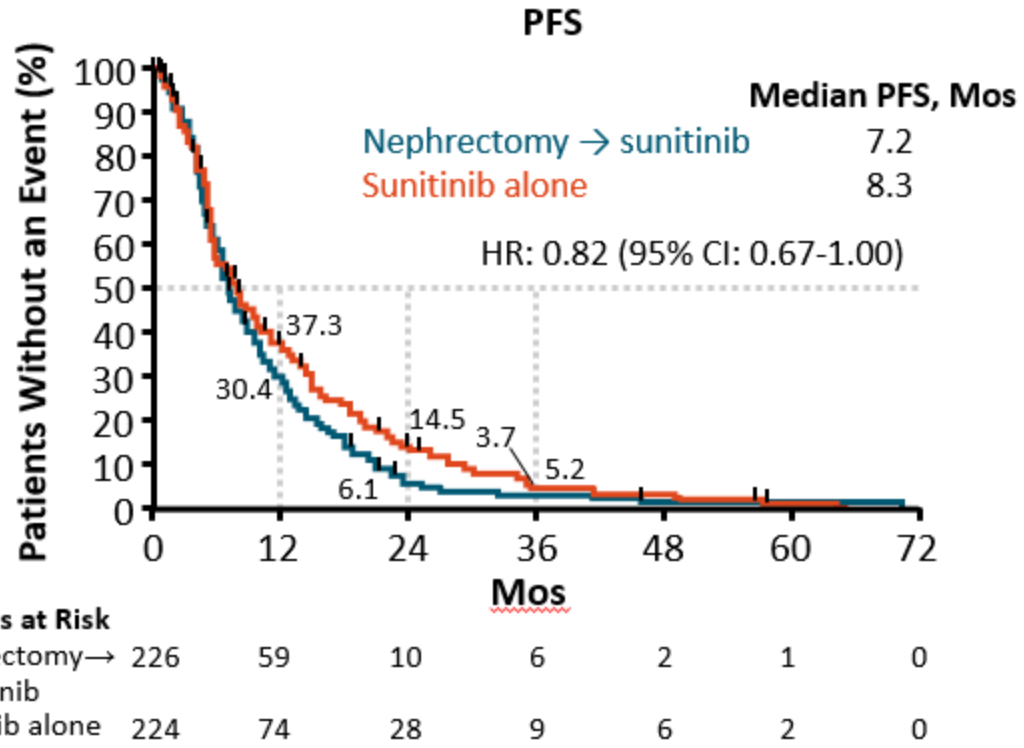
Patients at Risk

Nephrectomy→ sunitinib	226	110	61	40	19	11	4	1	0
Sunitinib alone	224	128	76	44	26	8	3	1	0

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

CARMENA: PFS, Response, and Clinical Benefit



Response	Nephrectomy → Sunitinib (n = 186)	Sunitinib (n = 213)
Best overall response, n (%)	n = 178	n = 208
▪ CR	1 (0.6)	0
▪ PR	50 (28.1)	62 (29.8)
▪ SD	64 (36.0)	97 (46.6)
▪ PD	49 (27.5)	40 (19.2)
▪ NE	14 (7.9)	9 (4.3)
ORR, %	27.4	29.1
DCR,* %	61.8	74.6
Clinical benefit,† n (%)	68 (36.6)‡	102 (47.9)‡

*Disease control defined as CR, PR, or SD. †Defined as disease control beyond 12 wks. ‡P = .02

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

CARMENA: Safety, Nephrectomy Outcomes

Severe (Grade 3/4) AEs in Sunitinib-Treated Patients,* n (%)	Nephrectomy → Sunitinib (n = 186)	Sunitinib (n = 213)
Any	61 (32.8)*	91 (42.7)*
Asthenia	16 (8.6)	21 (9.9)
Hand–foot syndrome	8 (4.3)	12 (5.6)
Anemia	5 (2.7)	11 (5.2)
Neutropenia	5 (2.7)	10 (4.7)
Kidney or urinary tract disorder	1 (0)	9 (4)

*$P = .04$

- In nephrectomy → sunitinib arm, 95% underwent nephrectomy with most (58%) having open surgery
  - Postop mortality within 1 mo of surgery: 2%
  - Postop morbidity: 82 pts (39%)
    - Clavien-Dindo grade 3: 11% of those with postoperative morbidity
    - Clavien-Dindo grade > 3: 5% of those with postoperative morbidity
- In sunitinib-alone arm, 38 patients needed secondary nephrectomy (7 for emergency treatment of primary tumor); 31.3% restarted sunitinib

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

CARMENA: Conclusions

- In final analysis of CARMENA, sunitinib alone not inferior to cytoreductive nephrectomy followed by sunitinib in patients with mRCC
  - HR for death: 0.89 (95% CI: 0.71-1.10; noninferior if upper boundary ≤ 1.20)
  - Median OS longer in sunitinib-alone arm for all patients and in intermediate-risk and poor-risk subgroups
- Clinical benefit rate significantly higher in sunitinib-alone arm (47.9% vs 36.6% with nephrectomy followed by sunitinib; *P* = .02)
- Investigators concluded that nephrectomy should no longer be part of standard of care for patients with mRCC requiring medical treatment

Méjean A, et al. ASCO 2018. Abstract LBA3. Méjean A, et al. N Engl J Med. 2018;[Epub ahead of print].

Debulking Nephrectomy

- CARMENA trial: phase 3 trial comparing nephrectomy + sunitinib vs sunitinib alone in patients with advanced RCC (N=450)
  - Sunitinib alone was not inferior to sunitinib + nephrectomy
  - mOS: 18.4 mo with sunitinib alone vs 13.9 mo with sunitinib + nephrectomy

Méjean A, et al. *N Engl J Med*. 2018;379:417-427.

Debulking Nephrectomy (cont)

- Update looked at results in intermediate-risk disease by risk factors and number of metastatic sites

mOS, mo	Nephrectomy + sunitinib (n=127)	Sunitinib alone (n=139)
IMDC 1 risk factor	(n=63) 31.4	(n=63) 25.2
IMDC 2 risk factors	(n=64) 17.6	(n=76) 31.2

Méjean A, et al. ASCO 2019. Abstract 4508.

ADJUVANT

Published Tyrosine Kinase Inhibitor Adjuvant Trials

Trial	Therapy	N	Histology	Stage	Starting Dose	Minimum Dose	DFS	OS
ASSURE[1]	Sunitinib Sorafenib Placebo	1943	**79% ccRCC**	> pT1b, G3-4, or N+	50 or 37.5 mg (Su)/ 400 mg (So)	25 mg (Su)/40 mg (So)	No	No
S-TRAC[2]	Sunitinib Placebo	615	ccRCC	> pT3b or N+	**50 mg**	**37.5 mg**	Yes	No
PROTECT[3]	Pazopanib Placebo	1538	ccRCC or mostly ccRCC	pT2 (G3-4), ≥ pT3, or N+	600 mg	400 mg	No	No

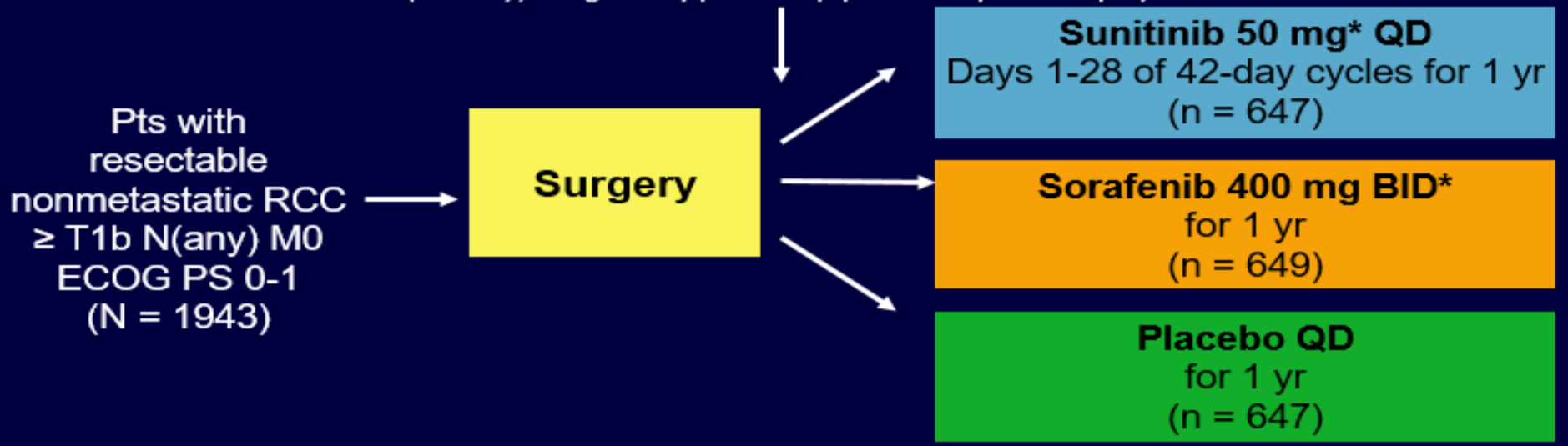
1. Haas. Lancet. 2016;387:2008. 2. Ravaud. NEJM. 2016;375:2246. 3. Motzer. JCO. 2017;35:3916.

Slide credit: clinicaloptions.com

ASSURE: Study Design

- Double-blind, randomized phase III trial

Stratified by: risk (intermediate high vs very high); histology (clear cell vs nonclear cell); ECOG PS (0 vs 1); surgical approach (open vs laparoscopic)



*Revised dose: sunitinib 37.5 mg/day; sorafenib 400 mg QD.

- Endpoints: DFS, OS, AEs, correlative studies

Haas NB, et al. ASCO 2015. Abstract 4508.

ASSURE: Subgroup Analysis

- As previously reported, no improvement in DFS or OS with either sunitinib or sorafenib compared with placebo
- DFS not affected by longer time on treatment or time after treatment with either study drug
- Subgroup analysis revealed sex differences in outcome
  - Significantly longer median DFS in women compared with men (83.0 vs 62.1 mos; *P* = .002)
  - No DFS increase in women receiving either drug vs placebo
  - Women received less study drug than men

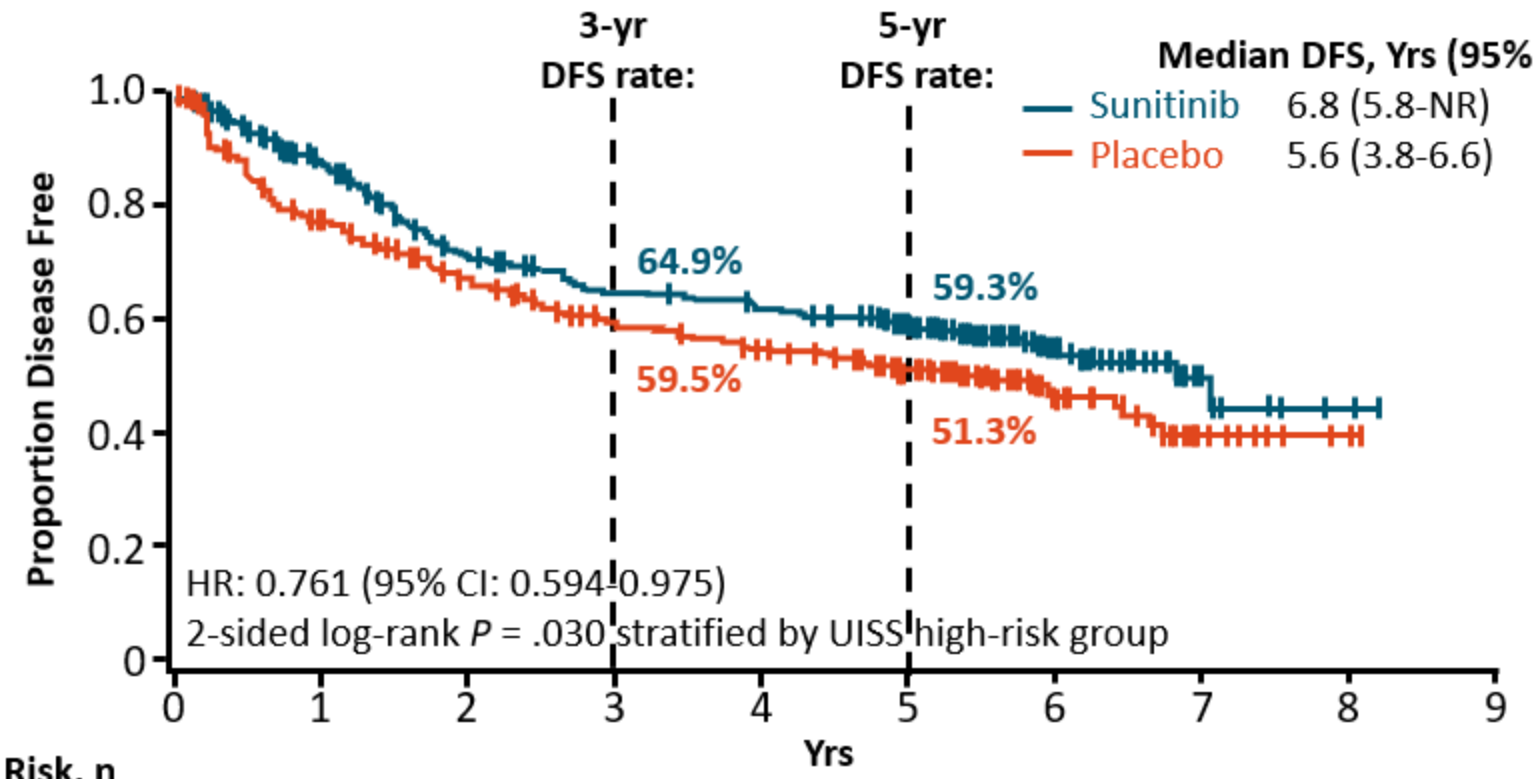
Haas NB, et al. ASCO 2015. Abstract 4508.

ASSURE: Investigator Conclusions

- Neither sunitinib nor sorafenib improved DFS for pts with advanced renal cell carcinoma after resection
- Both agents associated with high levels of toxicity that were only partly manageable through dose reductions
  - Pts received lower-than-planned doses of drug in both active treatment arms
- Longer treatment was not associated with improved clinical outcome
- Investigators suggest that pts with locally advanced renal cell carcinoma should not receive adjuvant sorafenib or sunitinib

Haas NB, et al. ASCO 2015. Abstract 4508.

S-TRAC Phase III Trial: DFS With Sunitinib vs Placebo in Patients With Locoregional, High-Risk ccRCC



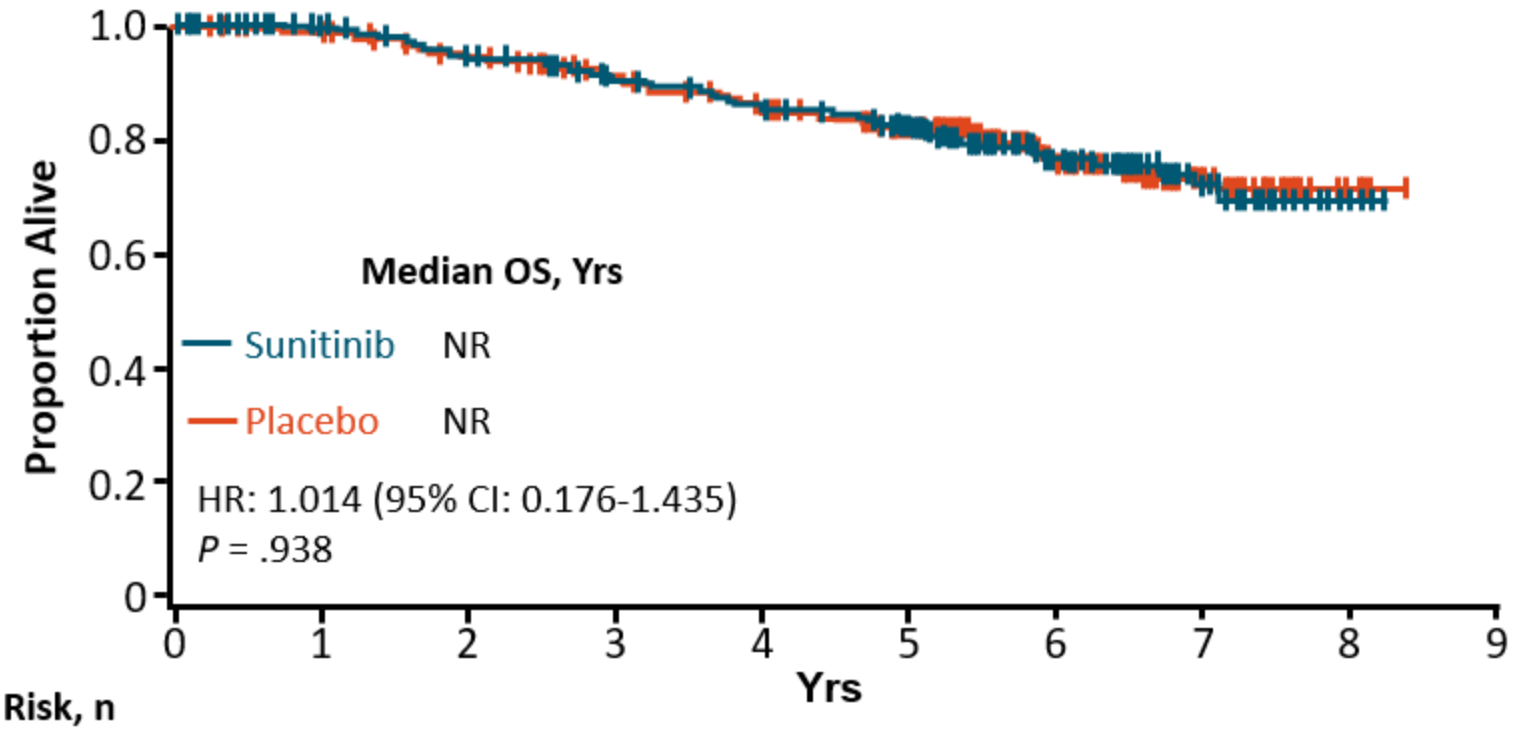
Patients at Risk, n

Sunitinib	309	225	173	153	144	119	53	10	3	0
Placebo	306	220	181	150	135	102	37	10	2	0

Ravaud. NEJM. 2016;375:2246.

Slide credit: clinicaloptions.com

S-TRAC Phase III Trial: OS With Sunitinib vs Placebo in Patients With Locoregional, High-Risk ccRCC



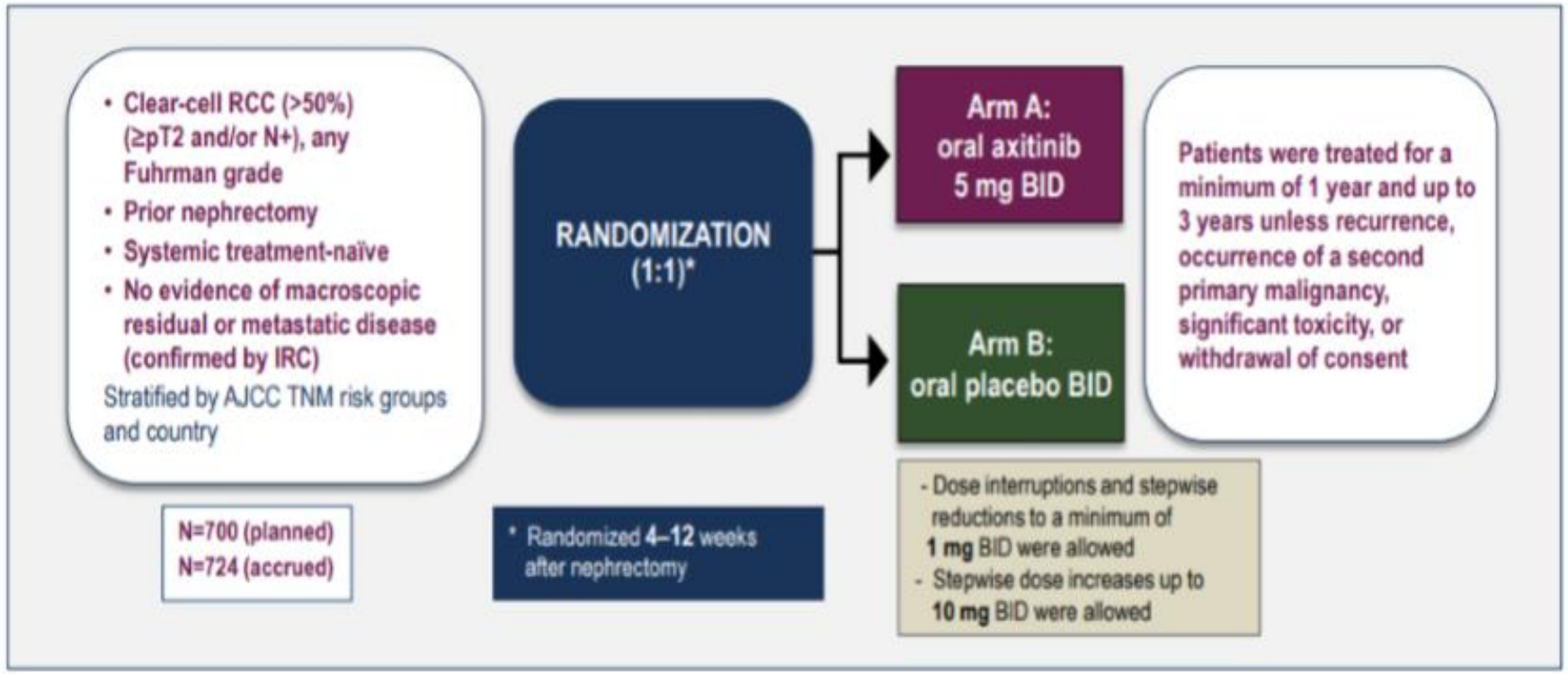
Patients at Risk, n

Sunitinib	309	278	258	236	222	196	98	31	4	0
Placebo	306	289	269	250	231	197	96	40	4	0

Ravaud. NEJM. 2016;375:2246.

Slide credit: clinicaloptions.com

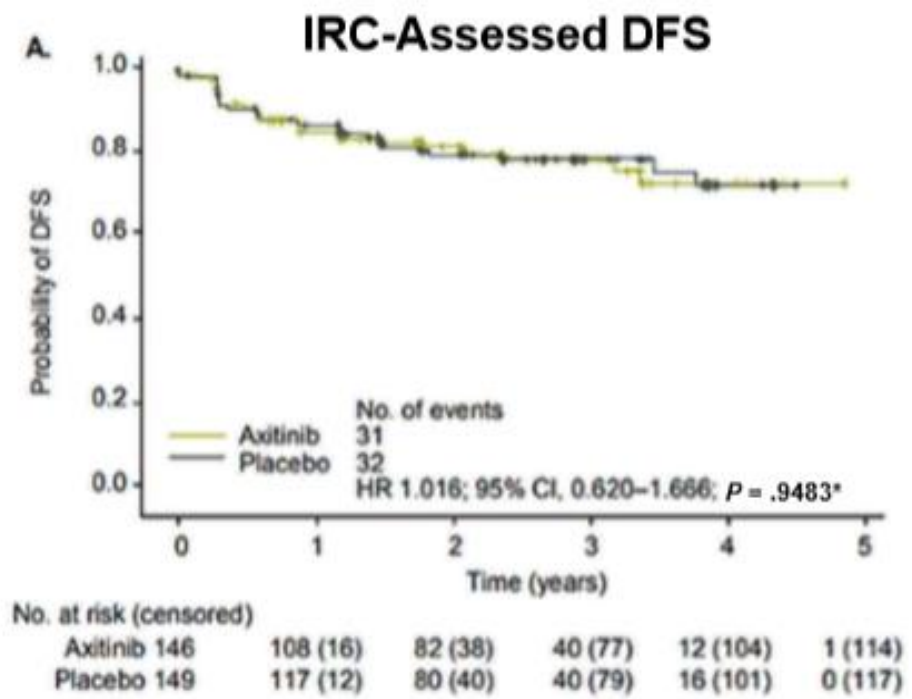
ATLAS Trial: Study Design

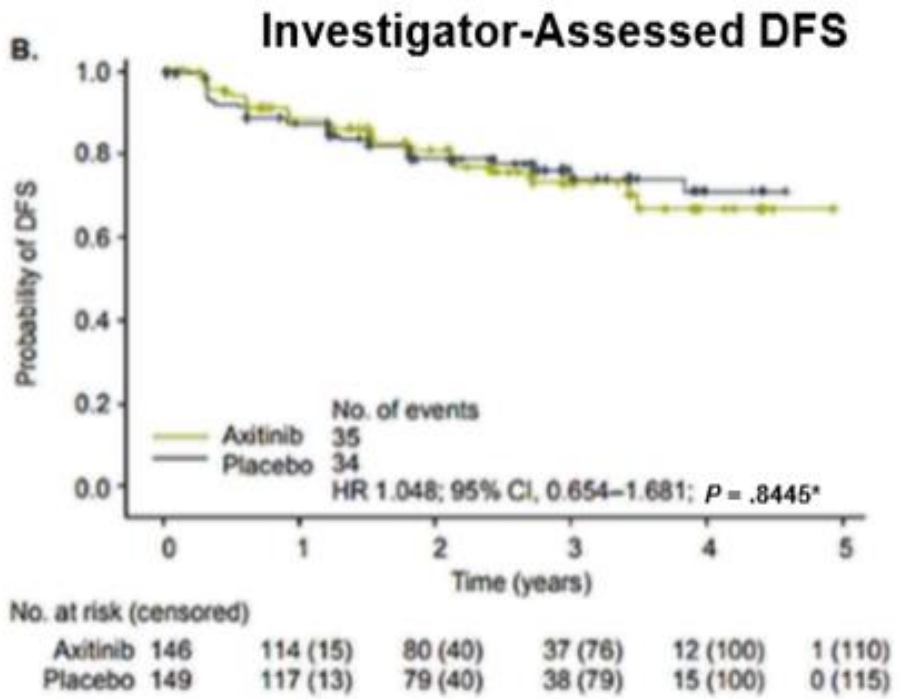


AJCC, American Joint Committee on Cancer; IRC, independent review committee; TNM, tumor, lymph nodes, and metastasis

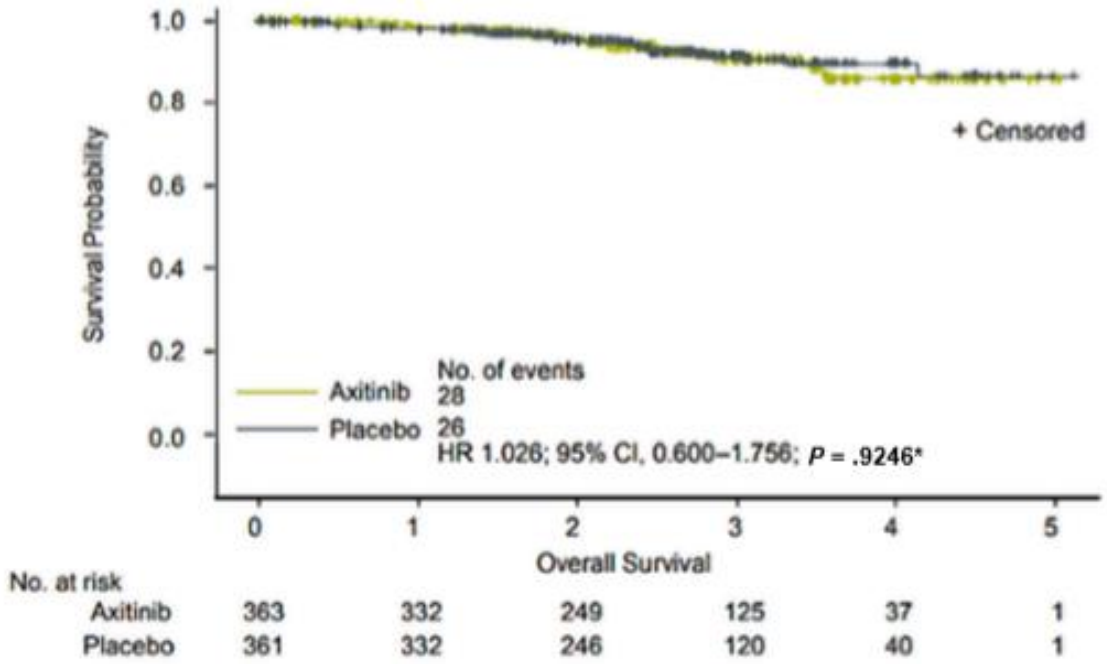
Gross-Goupil M, et al. *Ann Oncol.* 2018;29(Suppl 8): Abstract 863O. Gross-Goupil M, et al. *Ann Oncol.* 2018 Oct 20. [Epub ahead of print].

Subgroup Analysis: DFS—Lowest-Risk Subpopulation





Overall Survival: ITT Population



Conclusions

- The ATLAS trial was stopped due to futility at a preplanned interim analysis that showed no significant difference in DFS per IRC
- The safety profile of axitinib in ATLAS was consistent with previous trials in advanced RCC setting and no new safety signals were detected
- A reduction in risk of DFS event was observed in subpopulation at highest risk of recurrent RCC (pT3 with FG ≥3 or pT4 and/or N+, any T, any FG), but not in the lower-risk subpopulation
- The DFS improvement seen in the subgroup analysis of patients at the highest risk of recurrence further supports the importance of selecting patients most likely to benefit from treatment in the adjuvant RCC setting

Ongoing Phase III Adjuvant Trials: Immunotherapy vs Placebo

Parameter	IMmotion010[1] (NCT03024996)	PROSPER[2] (NCT03055013)	KEYNOTE-564[3] (NCT03142334)	CheckMate 914[4] (NCT03138512)
Drug	Atezolizumab	Nivolumab	Pembrolizumab	Nivolumab + ipilimumab
Histology	Clear-cell ± sarcomatoid histology	RCC of any histology	Clear-cell ± sarcomatoid features	Clear-cell ± sarcomatoid features
Dose duration	1 yr	2 doses prior to surgery and adjuvant nivolumab for 9 mos	1 yr	6 mos
Risk classification	T2 grade 4, T3a grade 3/4, T3b/c any grade, T4 any grade, or TxN+ any grade	Clinical stage ≥ T2 or any N+	pT2, grade 4; pT3/4, any grade; N+ M0; M1 NED	pT2aN0, grade 3-4; pT2b-T4; N+
Primary endpoint	DFS	RFS at 5 yrs	DFS	DFS
BICR	Yes	Yes	Yes	Yes
Status	Active, recruiting	Active, recruiting	Active, recruiting	Active, recruiting

1. Uzzo. ASCO 2017. Abstr TPS4598. 2. Harshman. ASCO 2018. Abstr TPS4597.
3. Choueiri. ASCO 2018. Abstr TPS4599. 4. Bex. ESMO 2018. Abstr 927TiP.

OBSERVATION

Prospective Phase II Study: Active Surveillance in Metastatic RCC

Pts with metastatic RCC, no prior systemic treatment in metastatic or neo/adjuvant setting, no disease symptoms, prior XRT and nephrectomy or metastasectomy permitted (N = 52)

→

CT Scans
Every 3 mos in Yr 1
Every 4 mos in Yr 2
Every 6 mos after Yr 2

QoL (FKSI-DRS) and anxiety/depression (HADS) assessed at baseline and each CT scan
Peripheral blood for immune cell quantification drawn at baseline and every CT scan

→

Systemic treatment, per physician and patient discretion

- Primary endpoint: time to initiation of systemic therapy

Rini BI, et al. Lancet Oncol. 2016;17:1317-1324.

Slide credit: clinicaloptions.com

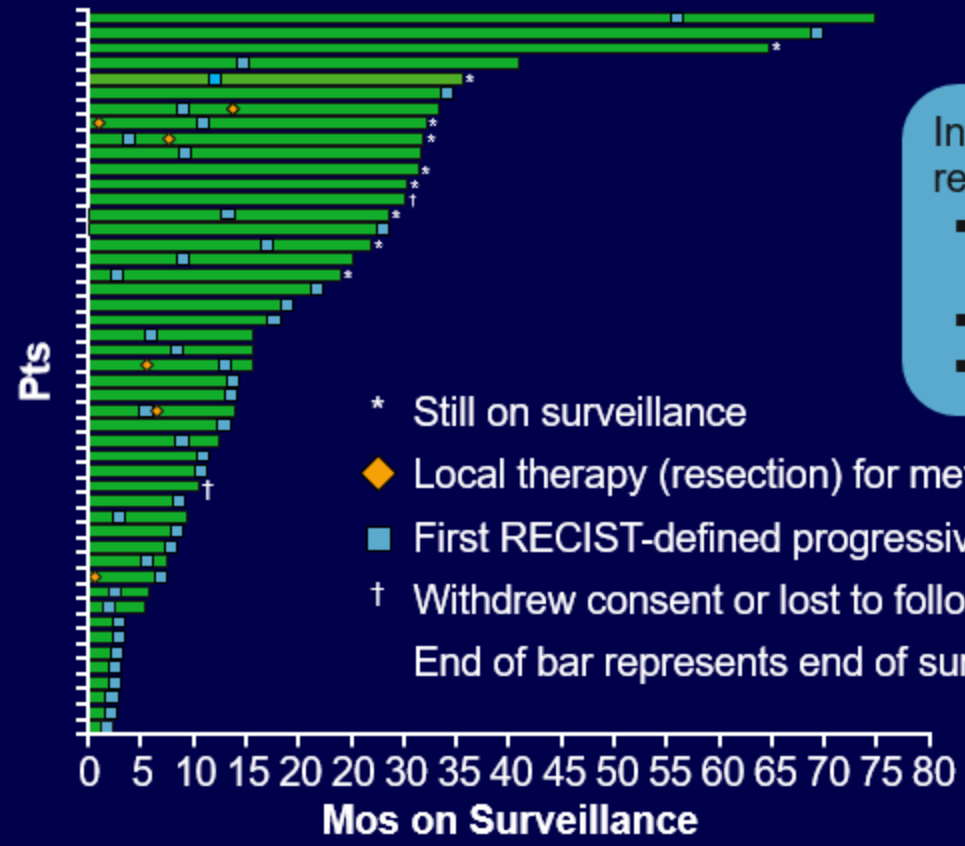
Active Surveillance Study in Metastatic RCC: Baseline Characteristics

Characteristic	Pts (N = 48)
Age, median (range)	67 (62-75)
Male/female, %	75/25
Clear-cell histology, n (%)	46 (96)
KPS, n (%) ▪ 100% ▪ 90% ▪ 80%	 30 (63) 15 (31) 3 (6)
Interval from diagnosis to metastases, mos (IQR)	5.1 (0.7-25.7)
IMDC risk group, favorable/intermediate/poor, %	23/75/2
Metastatic sites, n (%) ▪ Lung ▪ Lymph nodes ▪ Adrenal ▪ Bone	 34 (71) 12 (25) 6 (13) 10 (21)
Median tumor burden at baseline, cm (IQR)	3.2 (1.5-6.7)
Prior nephrectomy, n (%)	47 (98)

Rini BI, et al. Lancet Oncol. 2016;17:1317-1324.

Slide credit: clinicaloptions.com

Active Surveillance Study in Metastatic RCC: Time on Surveillance



* Still on surveillance

◆ Local therapy (resection) for metastatic site

■ First RECIST-defined progressive disease

† Withdrew consent or lost to follow-up

End of bar represents end of surveillance

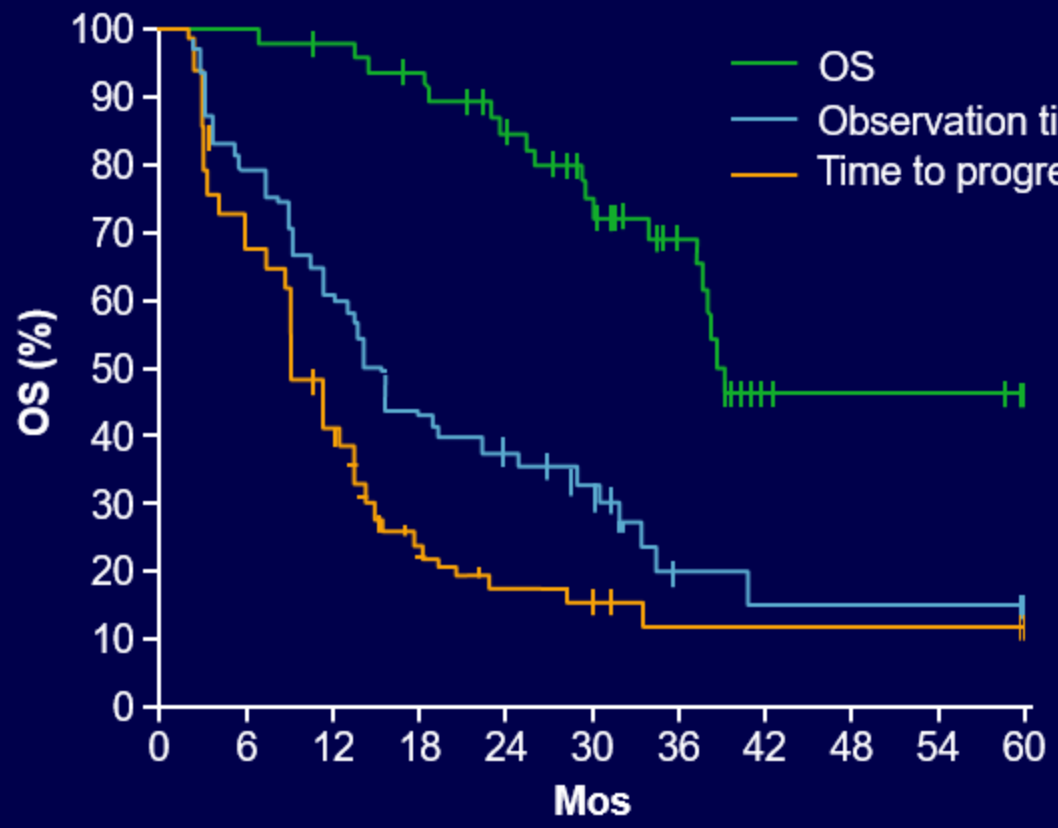
In the 42 pts who did not undergo resection during the surveillance period:

- Median absolute change in tumor burden during surveillance: 1.3 cm
- Relative change: 31%
- Median growth rate: 0.09 cm/mo

Rini BI, et al. Lancet Oncol. 2016;17:1317-1324.

Slide credit: clinicaloptions.com

Active Surveillance Study in Metastatic RCC: Outcomes



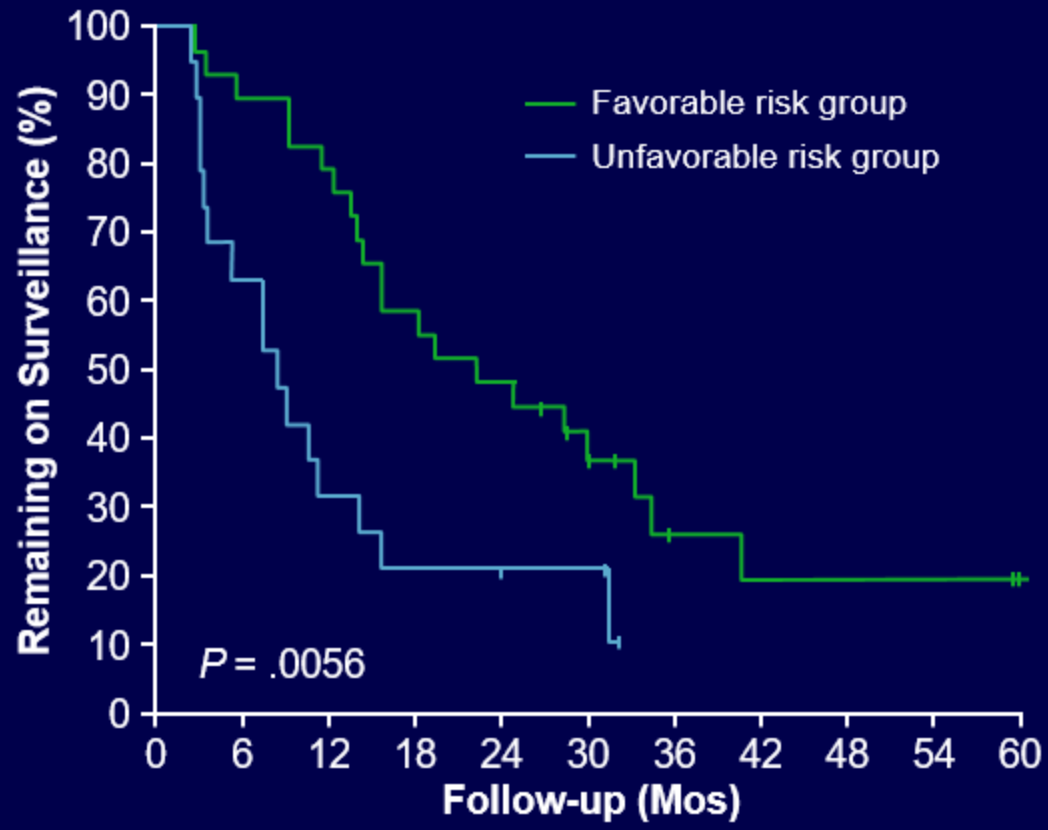
	Median, Mos
OS	38.6
Observation time	14.9
Time to progression	9.4

- 23/43 (53%) of pts with PD immediately started systematic therapy after progression
- 20/43 (47%) of pts with PD continued on surveillance
- Median additional surveillance period for these pts: 15.8 mos

Rini BI, et al. Lancet Oncol. 2016;17:1317-1324.

Slide credit: clinicaloptions.com

Active Surveillance Study in Metastatic RCC: Outcome by Risk Group



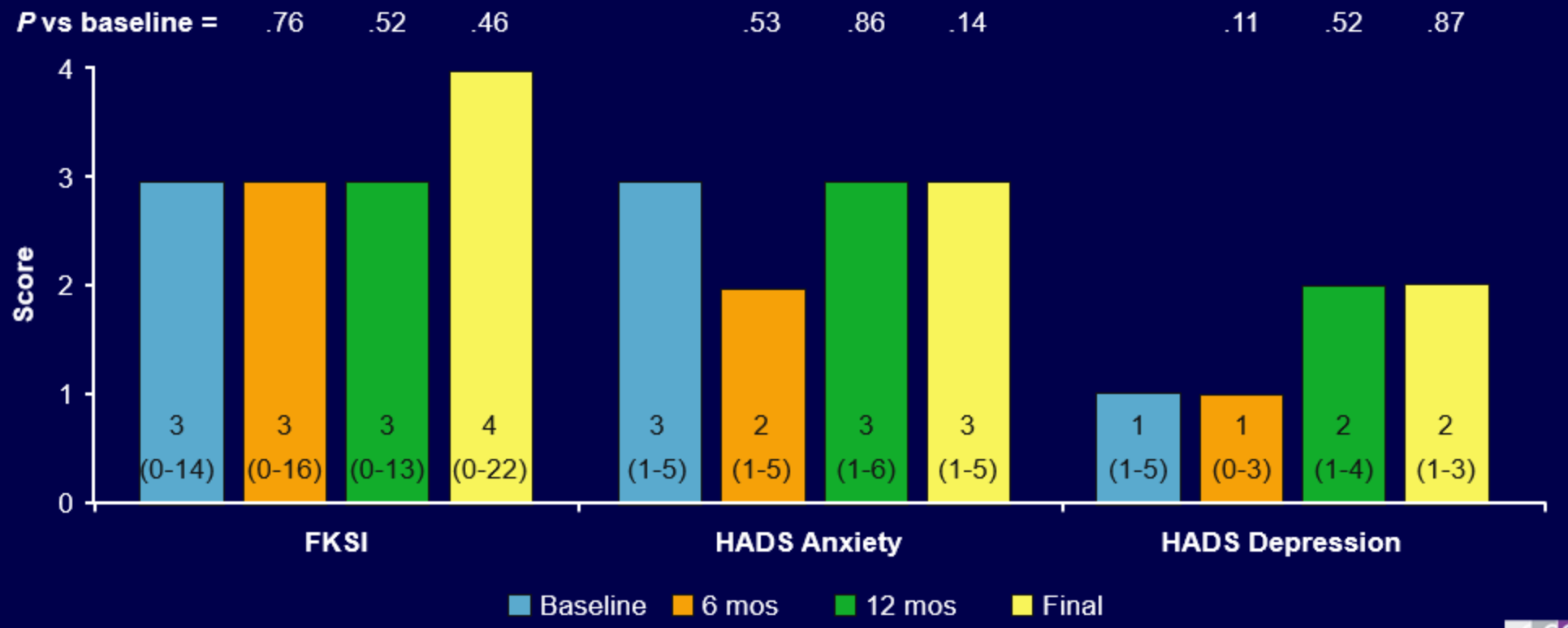
Favorable group (60% of pts)
0 or 1 IMDC risk factors and ≤ 2 organs involved with metastatic disease
- Estimated median surveillance time: **22.2 mos**

Unfavorable group (40% of pts)
All others (ie, > 1 IMDC risk factor and/or > 2 organ sites of metastases)
- Estimated median surveillance time: 8.4 **mos**

Rini BI, et al. Lancet Oncol. 2016;17:1317-1324.

Slide credit: clinicaloptions.com

Active Surveillance Study in Metastatic RCC: Depression/Anxiety and QoL



Rini BI, et al. Lancet Oncol. 2016;17:1317-1324.

Slide credit: clinicaloptions.com

Prospective, Phase II Observation Study in Patients With Asymptomatic mRCC

- Clinically evident metastatic RCC of any histologic subtype
- First documentation (radiographic or histologic) of metastatic RCC up to 12 mos prior to registration on study
- No prior systemic therapy for RCC in the metastatic or neo/adjuvant setting
- Prior XRT (including for CNS metastases) and prior nephrectomy/metastasectomy permitted but not required
- No disease-related symptoms
- Measurable/evaluable disease per RECIST v1.0

CT every 3 mos in Yr 1; every 4 mos in Yr 2; then every 6 mos

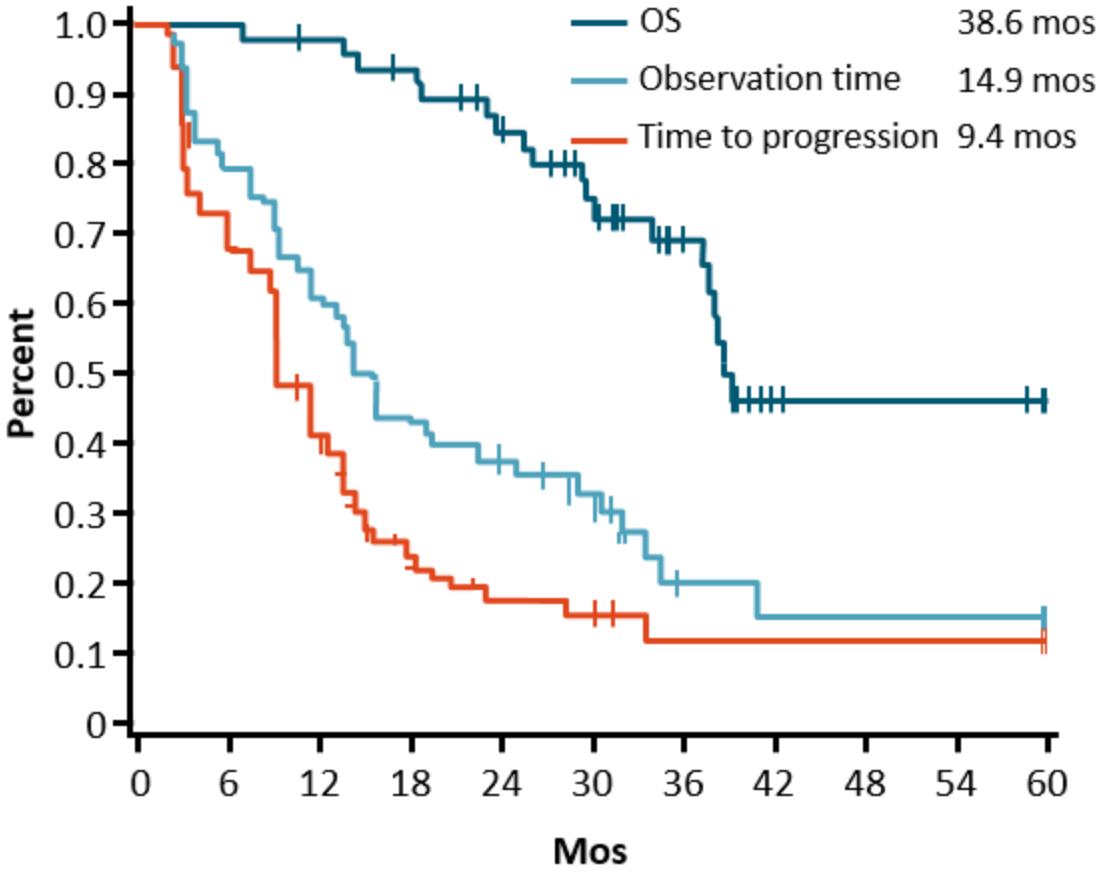
Initiation of systemic treatment per doctor/ patient discretion

- FKSI-DRS (QoL) and HADS (anxiety/depression) assessments administered at baseline and at every CT scan timepoint
- Peripheral blood for immune cell quantification drawn at baseline and at every CT scan time point

Rini. Lancet Oncol. 2016;17:1317.

Slide credit: clinicaloptions.com

Prospective Observation Study: Outcomes



- Median absolute change in tumor burden during surveillance: 1.3 cm
  - Relative change: 31%
  - Median growth rate: 0.09 cm/mo
- 23/43 (53%) patients with PD immediately started systematic therapy after progression and 20/43 (47%) continued on surveillance
  - Median additional surveillance period for these patients: 15.8 mos

Rini. Lancet Oncol. 2016;17:1317.

Slide credit: clinicaloptions.com

How to Choose Among Expanding Systemic Options in mRCC

What Does the Patient Want at Initial Presentation?

1. Cured of disease, preferably with limited toxicity during/after therapy and the ability to stop therapy

2. To live longer

3a. Disease control

3b. Quality of life maintained

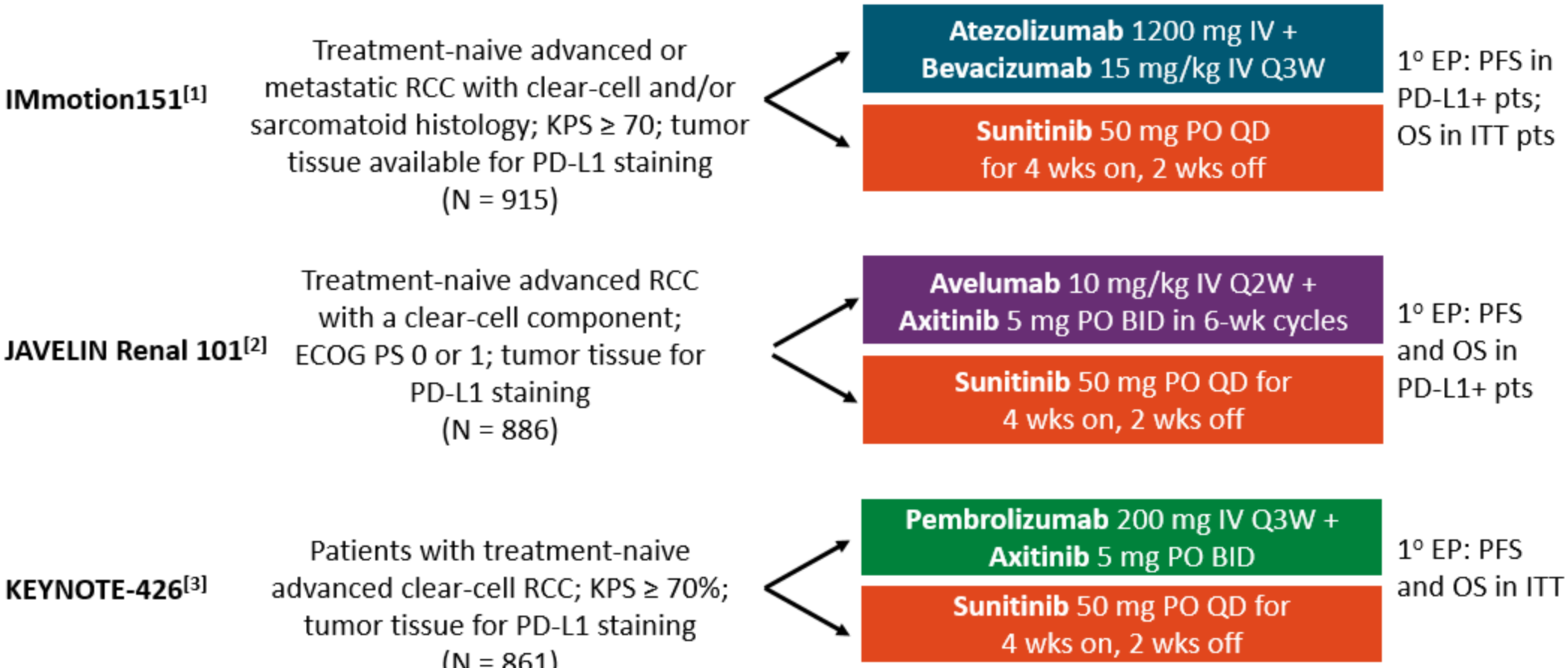
Slide credit: clinicaloptions.com

Rationale for Combining Immunotherapy With VEGF-Targeted Therapy

- T-cell–mediated cancer cell killing may be enhanced through various mechanisms, including
  - Reversal of VEGF-mediated immunosuppression
  - Promotion of T-cell priming and activation via dendritic cell maturation[1-2]
  - Normalization of the tumor vasculature for increased T-cell tumor infiltration[3-6]
  - Establishment of an immune-permissive tumor microenvironment by decreasing MDSC and Treg populations[6-10]

1. Gabrilovich DI. Nat Med. 1996;2:1096. 2. Oyama. J Immunol. 1998;160:1224. 3. Goel. Physiol Rev. 2011;91:1071. 4. Motz. Nat Med. 2014;20:607. 5. Hodi. Cancer Immunol Res. 2014;2:632. 6. Wallin. Nat Commun. 2016;7:12624. 7. Gabrilovich. Nat Rev Immunol. 2009;9:162. 8. Roland. PLoS One. 2009;4:e7669. 9. Facciabene. Nature. 2011;475:226. 10. Voron. J Exp Med. 2015:212:139. Figure adapted from Chen. Immunity. 2013;39:1.

Randomized Phase III Study Designs for Combination Tx

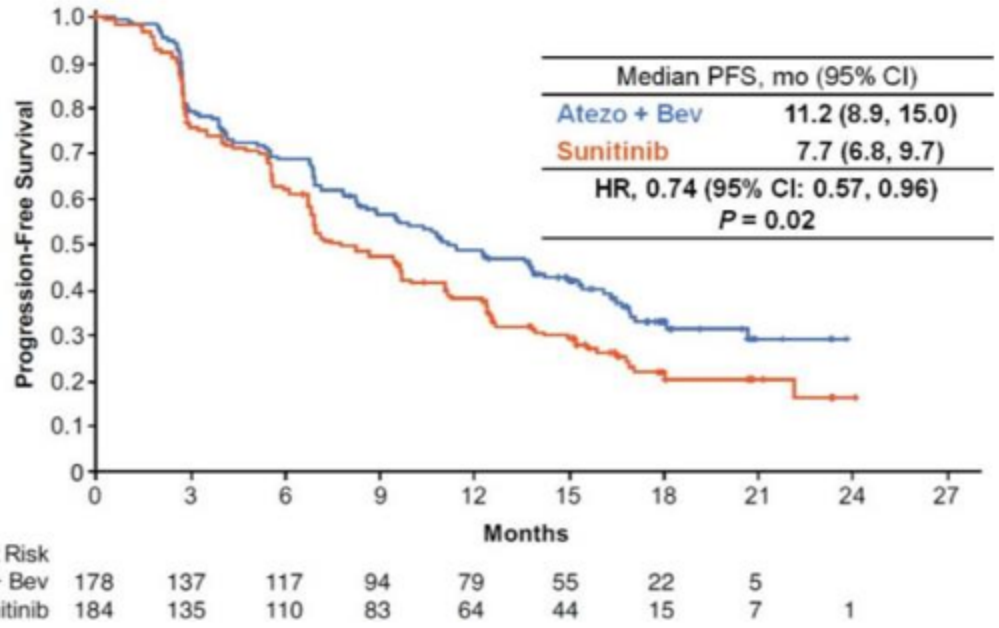


1. Motzer. Genitourinary Cancers Symposium 2018. Abstr 578. 2. Motzer. ESMO 2018. Abstract LBA6. 3. Powles. Genitourinary Cancers Symposium 2019. Abstr 543.

Slide credit: clinicaloptions.com

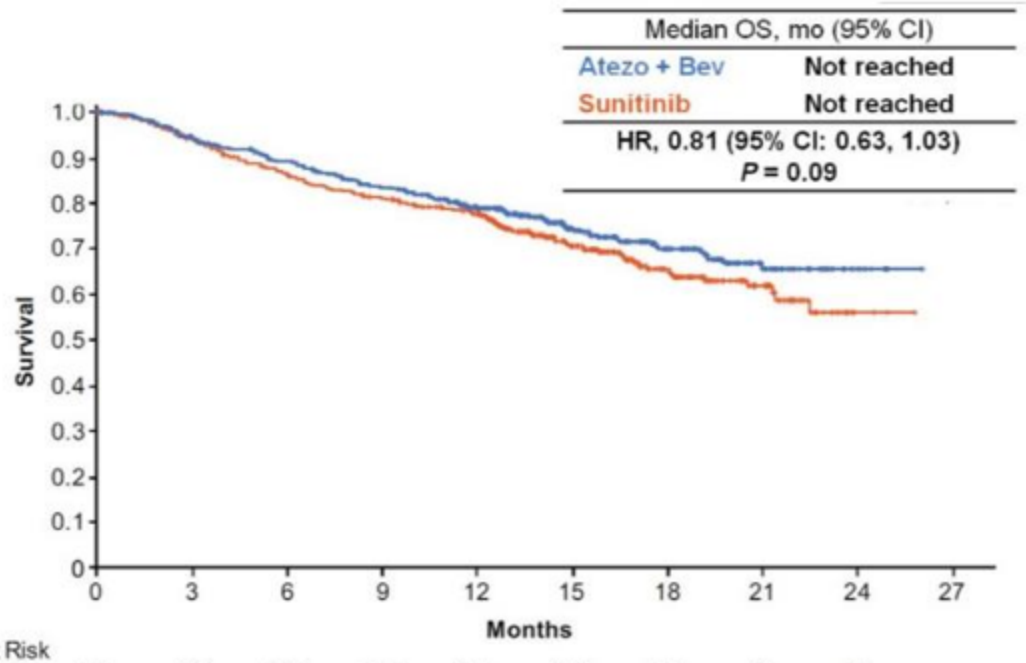
IMmotion151: Atezolizumab + Bevacizumab in Treatment-Naive Advanced RCC

PFS in PD-L1+ Cohort



No. at Risk									
Atezo + Bev	178	137	117	94	79	55	22	5	
Sunitinib	184	135	110	83	64	44	15	7	1

OS in ITT Cohort



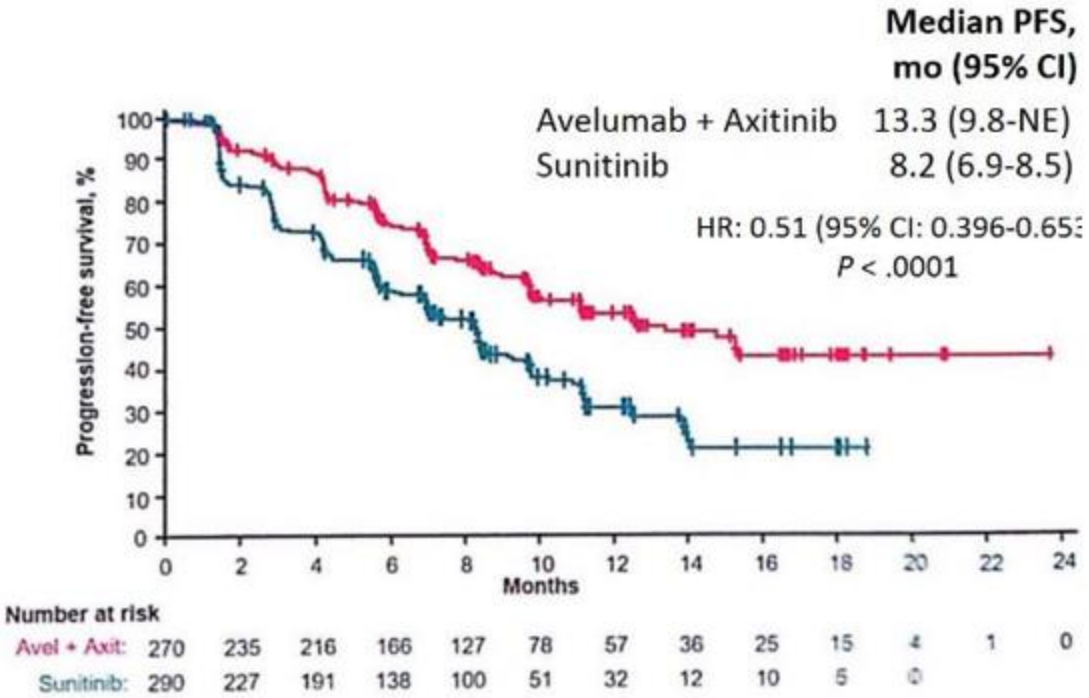
No. at Risk									
Atezo + Bev	454	428	398	371	341	246	141	69	18
Sunitinib	461	422	384	357	331	227	126	65	15

Motzer. Genitourinary Cancers Symposium 2018. Abstr 578.

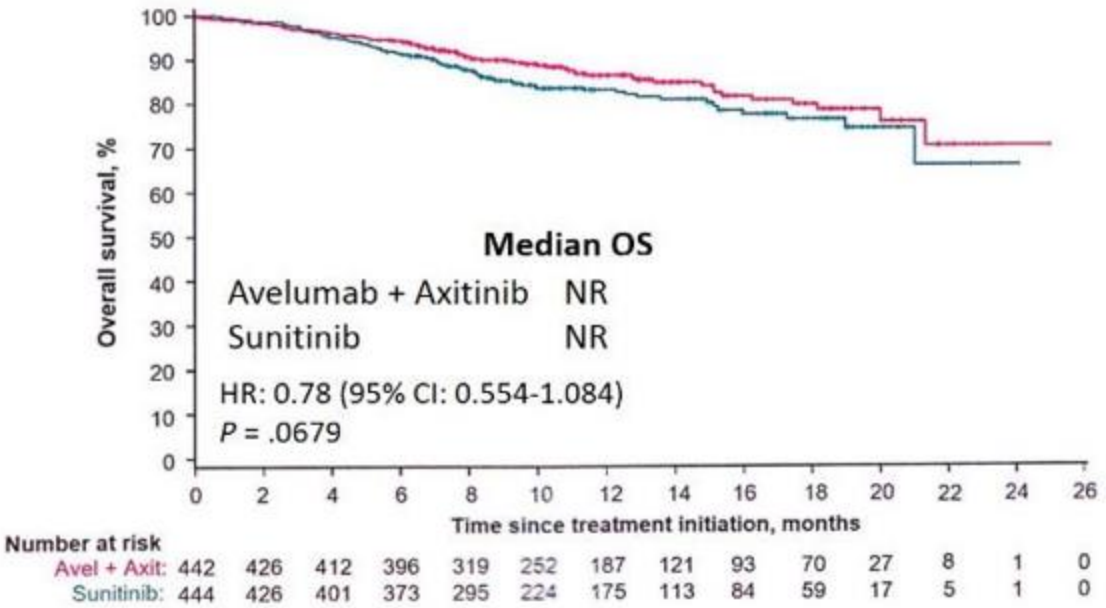
Slide credit: clinicaloptions.com

JAVELIN Renal 101: Avelumab + Axitinib in Treatment-Naive Advanced RCC

PFS in PD-L1+ Cohort



OS in ITT Cohort (Data Immature)

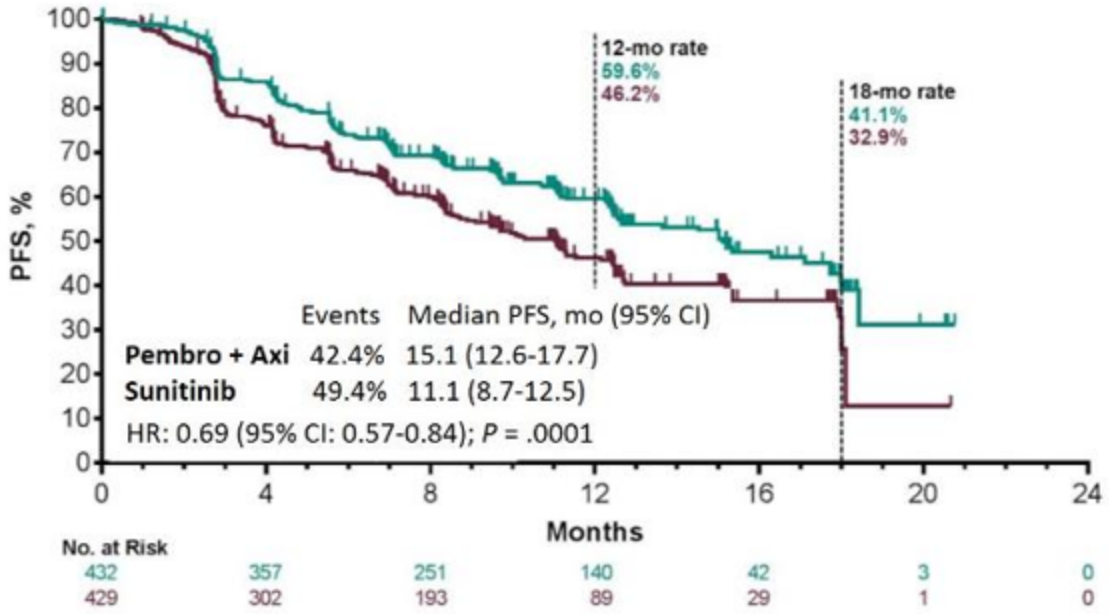


Motzer. ESMO 2018. Abstract LBA6.

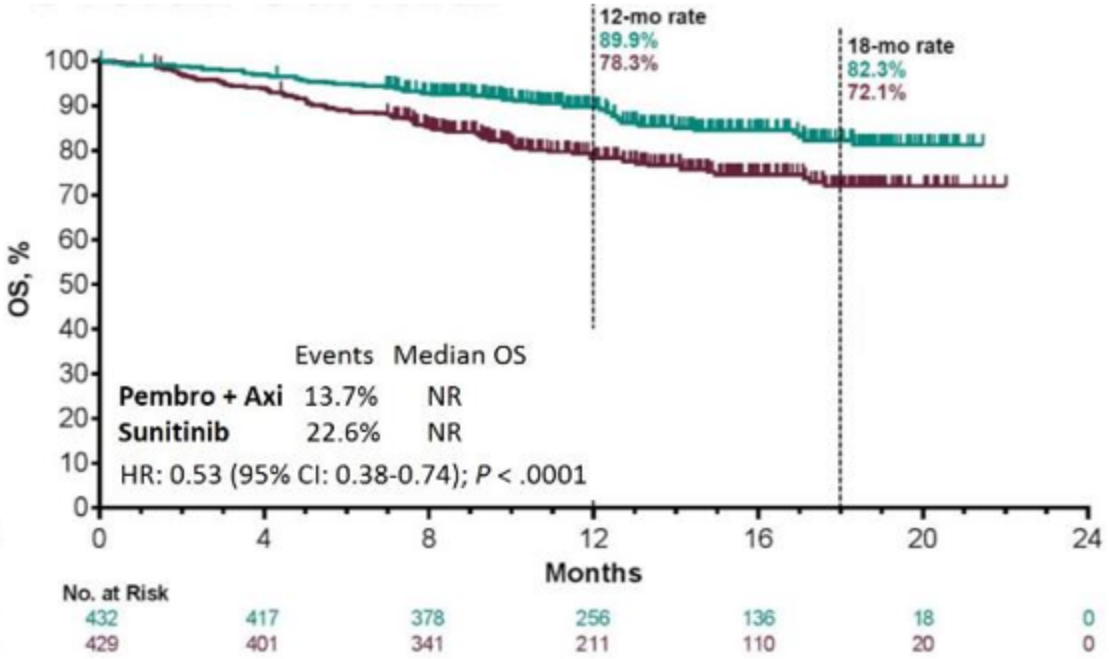
Slide credit: clinicaloptions.com

KEYNOTE-426: Pembrolizumab + Axitinib in Treatment-Naive Advanced RCC

PFS in ITT Population



OS in ITT Population



UPDATED AT ASCO GU 2019.

Powles. Genitourinary Cancers Symposium 2019. Abstr 543.

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Phase III IO-Based Combinations in RCC

Control	Comparator(s)	PFS (HR)	OS (HR)
Sunitinib	Nivolumab/ipilimumab[1]	No* (0.98)	Yes (0.68)
Sunitinib	Bevacizumab + atezolizumab[2]	Yes (0.83)	No (0.81)
Sunitinib	Axitinib + avelumab[3]	Yes (0.69)	No (0.78)
Sunitinib	Axitinib + pembrolizumab[4]	Yes (0.69)	Yes (0.53)
Sunitinib	Lenvatinib + everolimus *vs* lenvatinib/pembro	Pending	Pending
Sunitinib	Cabozantinib/nivolumab	Pending	Pending

1. Motzer. NEJM. 2018;378:1277. 2. Motzer. Genitourinary Cancers Symposium 2018. Abstr 578.
3. Motzer. ESMO 2018. Abstract LBA6. 4. Powels. Genitourinary Cancers Symposium 2019. Abstr 543.

Remission Rates for Major Regimens in mRCC

Regimen	Study	Efficacy Population	IRC-Assessed CR Rate	CR Rate in Selected Patients	PR Rate	Remission Rate
Nivolumab + ipilimumab	CheckMate 214[1]	IMDC intermediate/poor risk	9.0%	PD-L1 ≥ 1%: 16% Sarcomatoid: 18%	32%	?
Atezolizumab + bevacizumab	IMmotion151[2]	ITT	5.0%	PD-L1 ≥ 1%: 9%	31%	?
Avelumab + axitinib	JAVELIN Renal 101[3]	ITT	3.0%	PD-L1+: 4%	48%	?
Pembrolizumab + axitinib	Phase I[4]	All patients	7.7%	--	65.4%	?
Pembrolizumab monotherapy	KEYNOTE-427[5]	Cohort A (ccRCC)	2.7%	PD-L1 CPS ≥ 1: 6.5%	35.5%	?
TKIs			< 5%	?	30% to 40%	~ 0

1. Motzer. NEJM. 2018;378:1277. 2. Motzer. Genitourinary Cancers Symposium 2018. Abstr 578.
3. Motzer. ESMO 2018. Abstract LBA6. 4. Atkins. Lancet Oncology. 2018;19:405.
5. McDermott. ASCO 2018. Abstr 4500.

Conclusions

- Adjuvant VEGF therapy, when adequately dosed, can offer modest benefit balanced against toxicity

- The goal of a patient with newly metastatic RCC is cure; therefore, regimens with the highest chance of cure/durable response, balanced against acceptable toxicity/time off of treatment, should be prioritized

- Immunotherapy-based regimens offer the best chance of achieving patient goals
  - Whether immunotherapies in combination with one another or with VEGF therapies most effectively achieves these goals is as yet undefined

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TYSUNA®

- Dosing:

  - ✓ ***Gastrointestinal stromal tumor (GIST):*** Oral: 50 mg once daily for 4 weeks of a 6-week treatment cycle (4 weeks on, 2 weeks off)

  - ✓ ***Pancreatic neuroendocrine tumors, advanced (PNET):*** Oral: 37.5 mg once daily, continuous daily dosing

  - ✓ ***Renal cell cancer, adjuvant treatment:*** Oral: 50 mg once daily for 4 weeks of a 6-week treatment cycle (4 weeks on, 2 weeks off) for 9 cycles

  - ✓ ***Renal cell cancer, advanced:*** Oral: 50 mg once daily for 4 weeks of a 6-week treatment cycle (4 weeks on, 2 weeks off)

خدانگهدار