Advances in the Treatment of Renal Cell Carcinoma

Developed in collaboration

Med-IQ DukeHealth

Learning Objectives

Upon completion, participants should be able to:

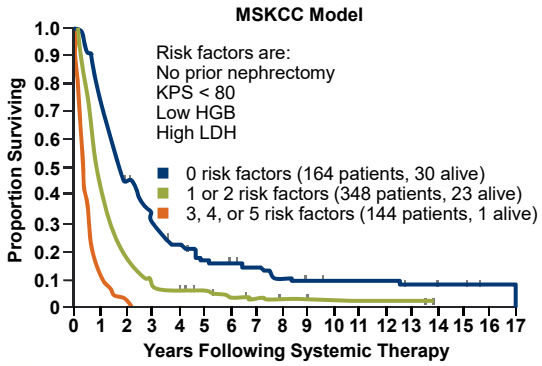
- Identify patients with metastatic renal cell carcinoma who may benefit from cytoreductive nephrectomy
- Discuss the impact of adjuvant sorafenib on outcomes in oligometastatic renal cell carcinoma patients

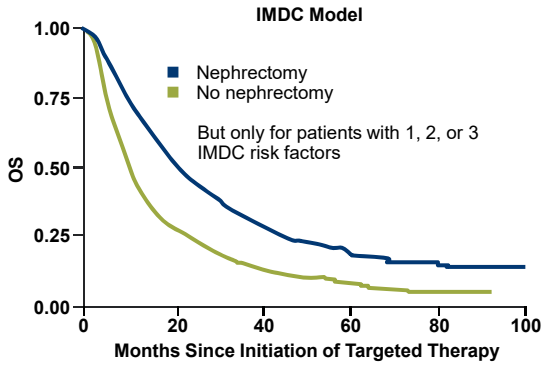
Highlights From ASCO 2018

Tian Zhang, MD

Cytoreductive Nephrectomy

- Independent predictor of survival in MSKCC and IMDC prognostic models



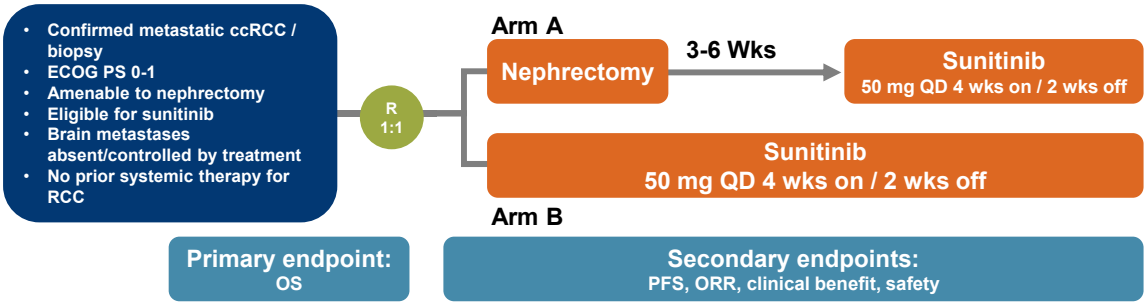


IMDC risk factors: anemia, thrombocytopenia, neutrophilia, hypercalcemia, KPS < 80, < 1 year to systemic therapy.

Heng DYC, et al. *Eur Urol.* 2014;66:704-10; Motzer RJ, et al. *J Clin Oncol.* 1999;17:2530-40; Mejean A, et al. *J Clin Oncol.* 2018;36(suppl;abstr LBA3).

CARMENA

- Prospective, multicenter, open-label, randomized, phase 3 noninferiority study



Mejean A, et al. *J Clin Oncol*. 2018;36(suppl;abstr LBA3).
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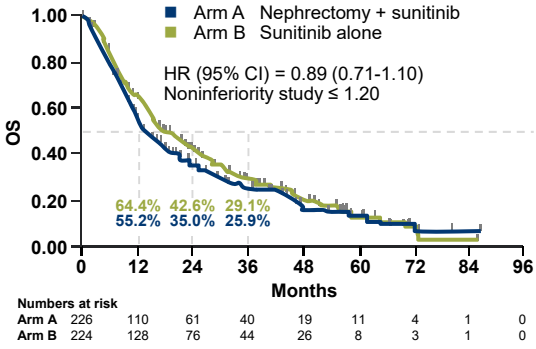
CARMENA: Patient Characteristics and OS

Characteristic	Arm A: Nephrectomy + Sunitinib (n = 226)	Arm B: Sunitinib Alone (n = 224)
Median age (range), years	63 (33-84)	62 (30-87)
Male sex, n (%)	169 (75)	167 (75)
MSKCC score, n (%)		
Intermediate	125 (56)	131 (59)
Poor	100 (44)	93 (41)
Missing	1	0
ECOG PS, n (%)		
0	130 (57)	122 (54)
1	96 (42)	102 (45)

Characteristic	Arm A: Nephrectomy + Sunitinib (n = 226)	Arm B: Sunitinib Alone (n = 224)
Median size of primary tumor, mm (range)	88 (6-200)	86 (12-190)
Median number of metastatic sites, n (range)	2 (1-5)	2 (1-5)
Tumor burden by RECIST v1.1, mm (range)	140 (23-399)	144 (39-313)
Location of metastases, n (%)		
Lung	172 (79)	161 (73)
Bone	78 (36)	82 (37)
Lymph nodes	76 (35)	86 (39)
Other	78 (36)	90 (40)



Median follow-up was 50.9 months (range 0.0-86.6)
40 patients in Arm A did not receive sunitinib
38 patients in Arm B received secondary nephrectomy

Mejean A, et al. *J Clin Oncol*. 2018;36(suppl;abstr LBA3).

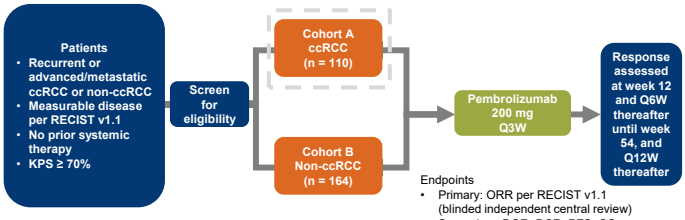
CARMENA: Nephrectomy for Which mRCC Patients?

- Patients who may benefit from nephrectomy are those with a small metastatic burden (< 10%-15% of total tumor burden) with large primary and excellent PS
- Systemic therapies should be attempted before nephrectomy in patients with more metastatic burden or worse PS

Mejean A, et al. *J Clin Oncol*. 2018;36(suppl;abstr LBA3).

Immunotherapy in mRCC: KEYNOTE-427

Keynote-427: (NCT02853344)



Endpoints
- Primary: ORR per RECIST v1.1 (blinded independent central review)
- Secondary: DOR, DCR, PFS, OS, safety, and tolerability
- Exploratory: tissue based biomarkers (eg, IHC, RNA sequencing)

Confirmed ORR by Blinded Independent Central Review

	n = 110		
	n	%	95% CI
ORR	42	38.2	29.1-47.9
DCR (CR + PR + SD ≥ 6 mo)	65	59.1	49.3-68.4
Best overall response			
CR	3	2.7	
PR	39	35.5	
SD	35	31.8	
PD	31	28.2	
No assessment	2	1.8	

Database cutoff: March 12, 2018.

- Pembrolizumab* shows promising antitumor activity as monotherapy in first-line ccRCC across IMDC risk groups
- Forms basis for adjuvant studies and combination studies in metastatic setting

*Off-label use.
McDermott DF, et al. *J Clin Oncol*. 2018;36(suppl;abstr 4500); Motzer RJ, et al. *N Engl J Med*. 2018;378:1277-90.
Please see full prescribing information for warnings, efficacy, risk, and safety.

Immunotherapy in mRCC

Immunotherapy	Phase	N	IMDC Poor	ORR	CR	ORR (PD-L1 +)	mPFS	Trt Disc Due to AEs
Nivolumab	1b (CA209-009)	24	NA	13%	8%	NA	6 m	NA
Atezolizumab*	2 (IMmotion150)	103	8%	25%	11%	28%	6.1 m	3%
Pembrolizumab*	2 (KEYNOTE-427)	110	15.5%	38%	2.7%	50%	8.7 m	10.9%
Nivo+Ipi (ITT)	3 (Checkmate 214)	550	17%	39%	9.8%	53%	12.4 m	22%

- Pembrolizumab monotherapy better tolerated with fewer treatment discontinuations but lower CR rates
  - 10.9% of patients discontinued pembrolizumab due to AE

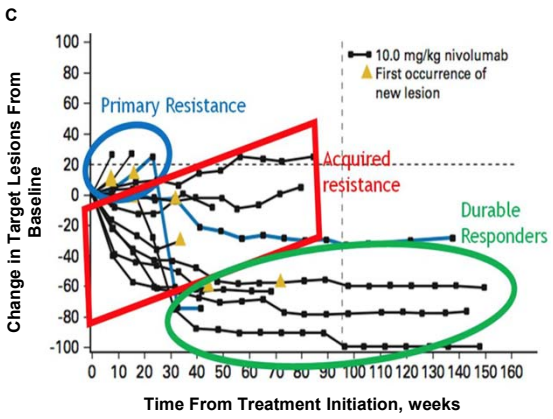
*Off-label use.

Choueiri TK, et al. *Clin Cancer Res.* 2016;22:5461-71; Atkins MB, et al. *J Clin Oncol*. 2017;35(suppl;abstr 4505); McDermott DF, et al. *J Clin Oncol*. 2018;36(suppl;abstr 4500); Motzer RJ, et al. *N Engl J Med*. 2018;378:1277-90; Choueiri TK, et al. *J Clin Oncol.* 2018;36(suppl;abstr TPS4599).

Please see full prescribing information for warnings, efficacy, risk, and safety.

Biomarkers to Predict Immunotherapy Response

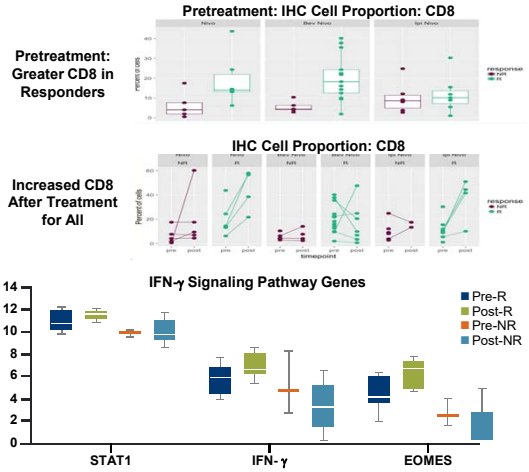
- Systemic therapies are improving, and better biomarkers are needed to identify patients who would benefit as well as those who are resistant to immunotherapies
- Promising biomarkers from ASCO 2018 include:
  - Tumor infiltrating T cells
  - Insertion-and-deletion (indel) burden
  - Gut microbiome



Gao JJ, et al. *J Clin Oncol.* 2018;36(suppl;abstr 4520); Voss MH, et al. *J Clin Oncol.* 2018;36(suppl;abstr 4518); Derosa L, et al. *J Clin Oncol.* 2018;36(suppl;abstr 4519).

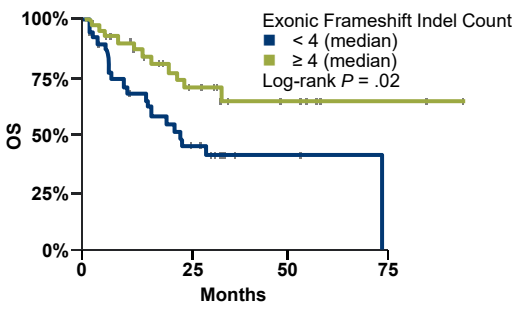
Biomarker: Tumor-Infiltrating T Cells

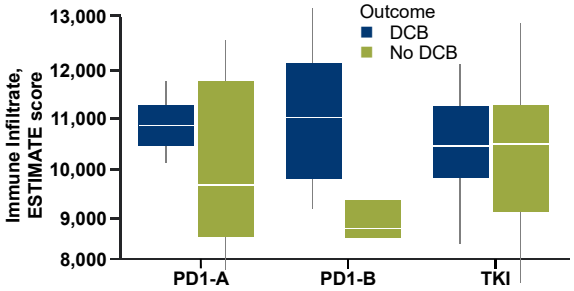
- Infiltrating CD8+ T cells correspond with immunotherapy response
- T cells increase on treatment
- IFN-γ signaling higher in responders



Gao JJ, et al. *J Clin Oncol.* 2018;36(suppl;abstr 4520).

Biomarker: Indels



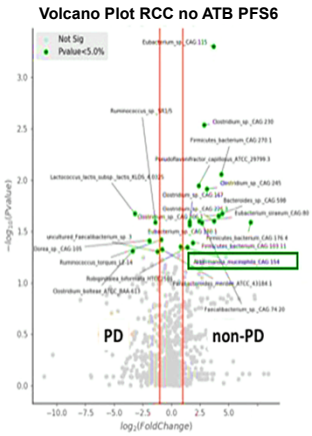


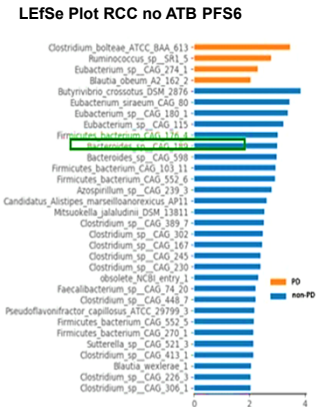
- Indels correspond with OS
- T cells and macrophages in the tumor microenvironment correspond with response to immunotherapy

Voss MH, et al. *J Clin Oncol.* 2018;36(suppl;abstr 4518).

Biomarker: Gut Microbiome

- Fecal microbiota diversity does not differ between responders and nonresponders
- *Akkermansia muciniphila* and *Bacteroides* species are more abundant in responders to immunotherapy





Derosa L, et al. *J Clin Oncol*. 2018;36(suppl;abstr 4519).

Conclusion

- CARMENA showed importance of careful selection of patients for cytoreductive nephrectomy
  - Large primary tumors, low metastatic burden, excellent PS
- In Keynote-427, pembrolizumab* monotherapy well tolerated and has disease activity for mRCC
  - Basis for ongoing adjuvant and combination trials
- Better biomarkers are needed to predict for immunotherapy sensitivity and resistance
  - Promising biomarkers from ASCO: tumor-infiltrating CD8+ T cells, indel burden, and gut microbiome

*Off-label use.

Radiation Therapy Approaches

Joseph K. Salama, MD

Oligometastases

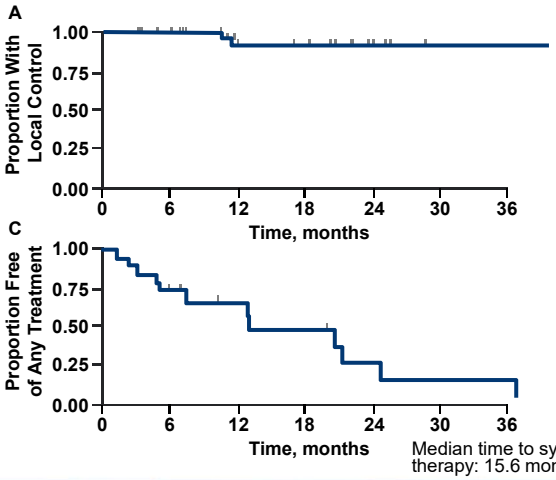
- Distinct clinical state
- Metastases limited in number and/or destination organ
- More indolent biology earlier in the metastatic cascade

"An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy."

Hellman S, et al. *J Clin Oncol.* 1995;13:8-10.

Ablative Radiation for the Treatment of Oligometastatic RCC

- SBRT can control oligometastases, including "radioresistant" tumors
- 18 patients with RCC and limited metastases were treated using SBRT
- At 2 years' follow-up, LeC was 91.4%, OS 85%
  - Patients who underwent treatment for all metastatic sites had a 2-year LeC of 100%
- SBRT treatment was well tolerated
  - Most common toxicity was fatigue (61.1%)
- Freedom from any post-SBRT therapy was 64.2% at 1 year



Median time to systemic therapy: 15.6 months

Ranck MC, et al. *Am J Clin Oncol.* 2013;36:589-95.

Identifying Oligometastatic Patients Who May Benefit From Ablative Radiation

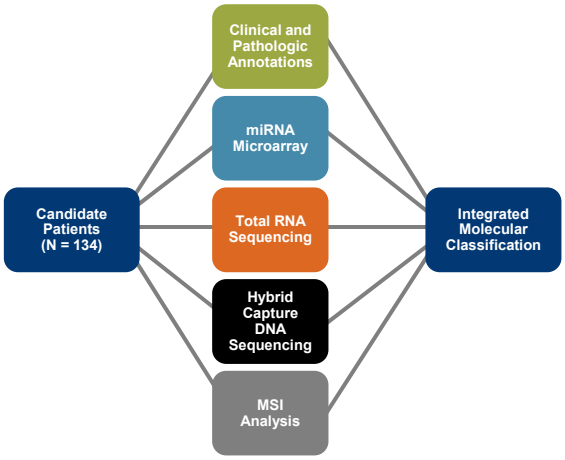
- Analysis of 361 exclusively extracranial oligometastatic patients treated with HIGRT
- RPA used to stratify patients into 5 classes
- OS and PFS were well stratified based on RPA class
- Patients with BKP or long disease-free intervals have promising overall outcomes

Class	3-Year OS	3-Year PFS*
1: All BKP patients	75% (95% CI, 66%-85%)	44% (95% CI, 32%-57%)
2: Patients with non-BKP diseases and a disease-free interval of ≥ 75 months	85% (95% CI, 67%-100%)	17% (95% CI, 13%-23%)
3: Patients with non-BKP diseases, disease-free interval of < 75 months, and ≤ 2 metastases	55% (95% CI, 48%-64%)	
4: Patients with non-BKP diseases, disease-free interval of < 75 months, ≥ 3 metastases, and age < 62 years	38% (95% CI, 24%-60%)	
5: All remaining patients	13% (95% CI, 5%-35%)	

*For PFS analysis, RPA allowed stratification of patients into two prognostic classes.
Hong JC, et al. *PLoS One.* 2018;13:e0195149.

Molecular Subtyping of Colorectal Liver Metastases

- 134 patients with liver metastases from colorectal cancer
  - Molecular analysis of limited de novo liver metastases
- Patients were uniformly treated with perioperative chemotherapy, definitive treatment of primary cancer, and partial hepatectomy for resection of liver metastases
- 113-gene signature validated in independent MSKCC dataset



Pitroda SP, et al. *Nat Commun*. 2018;9:1793.

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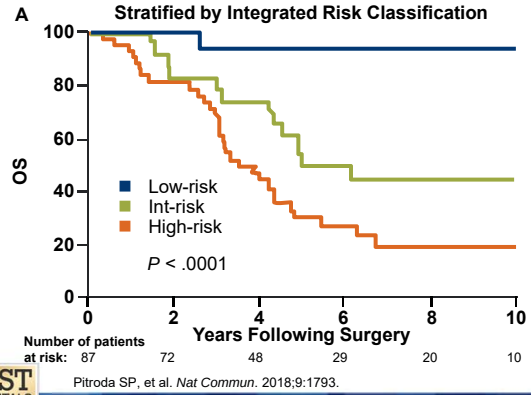
Integration of Intrinsic Molecular Subtypes and Clinical Risk Stratification

- Molecular subtypes of CRCLM significantly improve clinical risk stratification for identifying patients with favorable prognoses after hepatic resection of limited de novo CRCLM



	SNF1 Canonical	SNF2 Immune	SNF3 Stromal
Frequency	33%	28%	39%
Molecular signatures	↓immune and stroma E2F/MYC signaling DNA damage and cell cycle	↓immune interferon signaling p53 pathway	↑stroma KRAS signaling EMT and angiogenesis
Specific mutations	*NOTCH1* and *PIK3C2B*	*NRAS*, *CDK12*, and *EBF1*	*SMAD3*
Metastatic recurrences	Intermediate	Few	Many
OS	Intermediate	Favorable	Unfavorable

Pitroda SP, et al. *Nat Commun*. 2018;9:1793.

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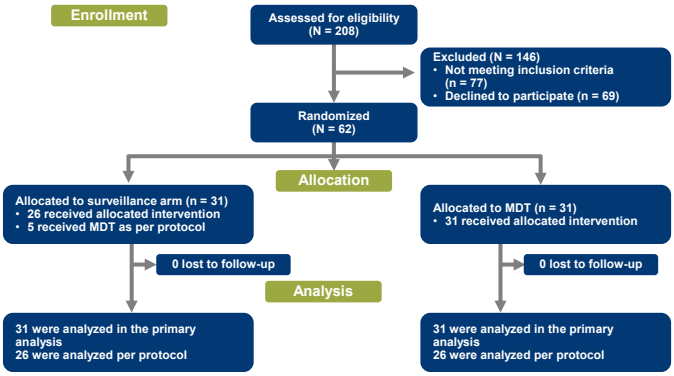
DukeHealth

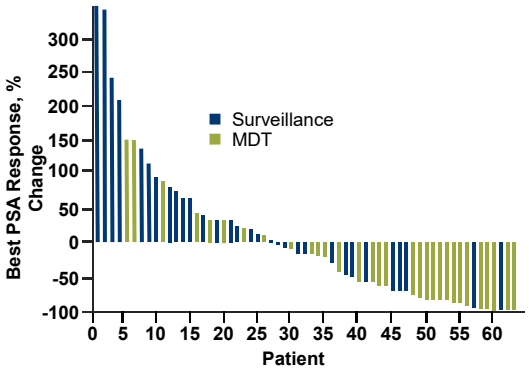
STOMP Study: Phase 2 RCT

- Primary endpoint
  - Time to ADT
- Stratification
  - PSA DT
  - Location of metastases
- Reason to start ADT
  - Symptoms
  - Local progression
  - Polymetastatic progression

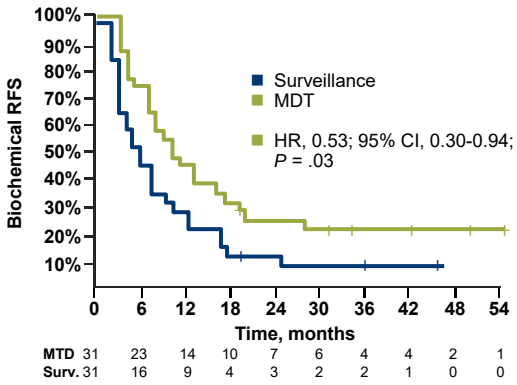


Ost P, et al. *J Clin Oncol*. 2018;36:446-53.

STOMP Study: Biochemical Progression



Surveillance: PSA decline in 35% of patients
MDT: PSA decline in 75% of patients



ADT-free survival longer with MDT than with surveillance alone (*P* = .03)

Ost P, et al. *J Clin Oncol*. 2018;36:446-53.

RESORT: Study Design

Key Eligibility Criteria
- Histologic diagnosis of predominantly ccRCC
- Maximum 3 metastatic lesions (independently of the site)
- Absence of radiological residual lesions following surgical removal of metastatic disease
- Histologically proven disease-free margins of resected surgical specimen
- No more than 3 months from radical resection of metastases
- ECOG PS of 0-2

Randomized 1:1
Stratification according to:
- Time from nephrectomy (> or < 12 months)
- Site of disease (lung vs other)
- Number of lesions (single vs multiple)

Sorafenib* for 52 weeks

Observation for 52 weeks

Primary endpoint: RFS
Secondary endpoints: OS, safety profile
Exploratory endpoints: Translational analyses on blood and tumor samples

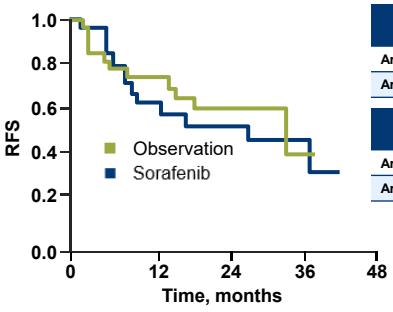
*Starting dose: Sorafenib 400 mg once a day for 3 weeks. After 21 days the dose should be increased to the standard dose (400 mg bid) if the patient has not experienced greater than grade I skin toxicity or greater than grade II of any other toxicity.

Procopio G, et al. *J Clin Oncol.* 2018;36(suppl;abstr 4502).
Please see full prescribing information for warnings, efficacy, risk, and safety.

RESORT: Sorafenib and mRFS

- Adjuvant sorafenib not associated with improved outcomes

mRFS in the Two Treatment Arms



	N. of Pts	N. of Events	Median (Months)
Arm = OBS	36	12	35.0
Arm = Sorafenib	32	14	29.0

	12-Month RFS (%, 95% CI)	24-Month RFS (%, 95% CI)
Arm = OBS	74 (59-91)	59 (42-82)
Arm = Sorafenib	62 (46-84)	52 (35-76)

Procopio G, et al. *J Clin Oncol.* 2018;36(suppl;abstr 4502).
Please see full prescribing information for warnings, efficacy, risk, and safety.

Conclusion

- Increased understanding of the molecular underpinnings of oligometastatic disease
- Favorable outcomes in patients with oligometastatic prostate and kidney cancer
- Improved biochemical RFS in the treatment of oligometastatic prostate cancer
- Adjuvant sorafenib is not associated with improved outcomes for oligometastatic RCC patients

Contact Information

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Renal Cell Carcinoma: Abbreviations and Acronyms

ADT = androgen deprivation therapy
AE = adverse event
ATB = antibiotics
BKP = breast, kidney, or prostate cancers
ccRCC = clear cell renal cell carcinoma
CR = complete response
CRCLM = colorectal cancer liver metastases
DCB = durable clinical benefit
DCR = disease control rate
DOR = duration of response
DT = doubling time
ECOG = Eastern Cooperative Oncology Group
EOMES = eomesodermin
EMT = epithelial-mesenchymal transition
HGB = hemoglobin
HIGRT = hypofractionated image-guided radiotherapy
IFN =interferon gamma
IHC = immunohistochemistry
indel = insertion-and-deletion
ITT = intention to treat
IMDC = International Metastatic Renal Cell Carcinoma Database Consortium
KPS = Karnofsky Performance Score
LDH = lactate dehydrogenase
LeC = lesion control
MDT = metastasis-directed therapy
mPFS = median progression-free survival
mRCC = metastatic renal cell carcinoma
mRFS = median recurrence-free survival
MSI = microsatellite instability
MSKCC = Memorial Sloan Kettering Cancer Center
NA = not available
NR = nonresponder
OBS = observation
ORR = objective response rate
OS = overall survival
PD = progressive disease
PD1 = programmed death 1
PD-L1 = programmed death-ligand 1
PFS = progression-free survival
PR = partial response
PS = Performance Status
PSA = prostate-specific antigen
R = responder
RCC = renal cell carcinoma
RCT = randomized controlled trial
RFS = recurrence-free survival

RPA = recursive partitioning
SBRT = stereotactic body radiotherapy
SD = stable disease
SNF = similarity network fusion
TKI = tyrosine kinase inhibitor