Memorial Sloan Kettering Cancer Center

RENAL CELL CARCINOMA

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Disclosures
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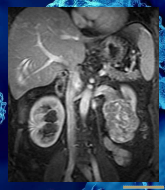


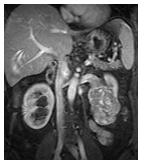
HEMATOLOGY ONCOLOGY BEST PRACTICES

GW

1

Renal Cell Carcinoma

Epidemiology
Pathology/Biology
Genetic Syndromes



GW 2

Renal Cortical Tumors Epidemiology

- Malignant tumors of the kidney account for 2% of all cancers in USA each year
- Median age at diagnosis is 66 years and median age at death is 70 years
- Autopsy incidence is ~ 2-5%
- Incidental tumor detection: 70%
- Median tumor size: 3.5 cm
- 30-40% of patients will present with or eventually develop metastatic disease

Associated Risk Factors

Smoking (2X risk, history in 20-30% of patients)
Obesity (particularly women): linear relation w/ body weight
Hypertension
Unopposed estrogen therapy
Occupational exposure to: petroleum products, heavy metals, asbestos
? Carcinogenic effects of chronic kidney disease (CKD).

GW 3

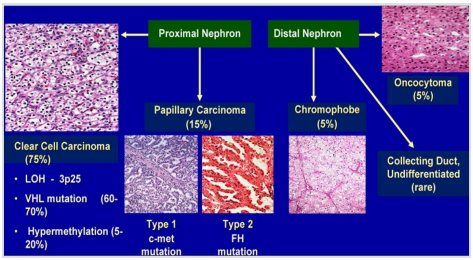
Renal Cortical Tumors:

- **Malignant Parenchymal Neoplasms**
  - Conventional (Clear Cell)
  - Papillary
  - Chromophobe
  - Collecting duct carcinoma
  - Medullary carcinoma of the kidney
  - Unclassified
- **Benign Parenchymal Neoplasms**
  - Metanephric Adenoma
  - Metanephric adenofibroma
  - Papillary renal cell adenoma
  - Renal Oncocytoma
- **Benign renal masses:** angiomyolipoma, hemorrhagic cyst, cystic nephroma, AVM, leiomyoma, oncocytoma
- **Other malignant renal tumors:** UC of renal pelvis; Wilm's tumor (children and adults); metastatic tumors (rare); renal or peri-renal sarcoma; lymphoma

Kovacs, G., Akhtar, M., and Beckwith, B. J.: The Heidelberg Classification of renal cell tumors. *J Pathol*, 183: 131, 1997

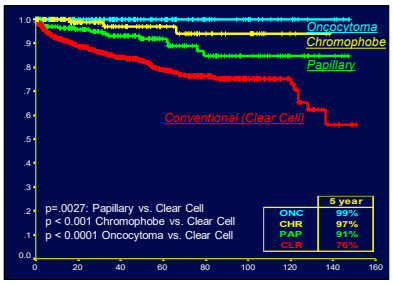
GW 4

Genetic Findings in RCC Subtypes



GW 5

Progression Free Probability by Histological Subtype



GW 6

Genetic Findings in RCT Subtypes

Histological Subtype	%	Genetic/Molecular Defects	Associated Syndromes
Conventional Clear Cell	75	**LOH 3p Mutation of 3p25 (VHL)**	**Von Hippel-Lindau** Sporadic RCC Hereditary RCC
Papillary 1	5	C-Met Gene mutation 7q31	Hereditary Papillary (HPRCC)
Papillary 2	10	Fumarate hydratase 1q42	Sporadic Papillary
Chromophobe	5	Birt-Hogg Dube 17p11	Birt-Hogg Dube
Oncocytoma	9.7	Birt-Hogg Dube 17p11	Familial Oncocytoma Birt-Hogg Dube
Collecting Duct	0.4	-18, -Y	Renal Medullary Carcinoma

*Zambrano N., Histopathology and Molecular Genetics of Renal Tumors. *J. Urol*, Oct 1999

GW 7

Von Hippel Lindau Syndrome

- Autosomal dominant mutation in 3p25 (VHL)
- 40% VHL patients have RCC with retinal and CNS findings usually preceding discovery of renal involvement
- Multicentric, bilateral renal involvement in ~ 75% patients
- MSKCC: 5 VHL patients / 2002 RCC patients operated on between 1989 and 2005
- Renal cancer and renal insufficiency are now the leading cause of death in VHL

GW 8

Von Hippel Lindau Syndrome

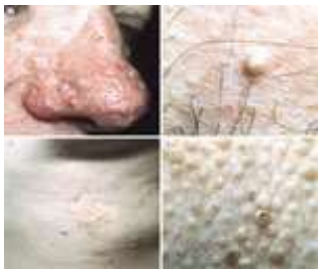
- VHL: Familial multiple cancer syndrome
  - Hemangiomas
  - Hemangioblastomas (brain, spinal cord, retina)
  - Pheochromocytomas
  - Pancreatic carcinomas
  - Epididymal cysts
  - RCC (40% of VHL patients)
  - Renal cysts multiple/bilateral (49-85%)

GW 9

Birt-Hogg-Dubé Syndrome (BHD)

- Hereditary hair follicle tumors located on face and neck
- Kidney tumors of multiple tumor histologies develop in 20-30% of patients (chromophobe commonest)
- Bilateral, multi-focal renal tumors (chromophobe, oncocytoma, clear cell)
- Lung cysts occur in 90%
- Spontaneous pneumothorax (20%)
- Genetic linkage analysis places the BHD on chromosome 17
- FLCN gene (folliculin- ?tumor suppressor)

Birt-Hogg-Dubé Syndrome



BHDSyndrome.org; Courtesy of Urologic Oncology Branch, NCI, NIH

Hereditary Syndromes: Clinical Features

Hereditary Papillary Renal Cell Carcinoma (HPRC)

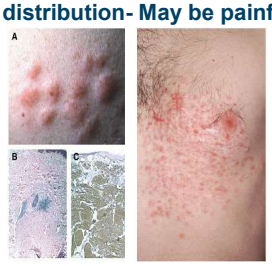
- Risk of bilateral, multifocal papillary RCC
- Patients develop papillary RCC (type 1)
- Mutations in c-MET

Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC)

- Uterine leiomyomas (more common) or leiomyosarcoma (rare)
- Cutaneous nodules (leiomyomas)
- Type 2 papillary RCC, frequently solitary, aggressive
- Germline mutation in gene recently identified is fumarate hydratase (FH) codes for a Krebs cycle enzyme

Cutaneous Leiomyomas

Found on both extremity and trunk Isolated or disseminated in distribution- May be painful



http://www.vhl.org/hlrcc

GW 13

When to refer for Genetic Counseling? ACMG Practice Guidelines

• RCC with clear cell histology, if any of the following criteria are met:	VHL, OMIM 193300; BHD, OMIM 135150
–dx at age <50	
–Bilateral or multifocal tumors	
–≥1 close relative with clear cell RCC	
• RCC with papillary type 1 histology	HPRC, OMIM 605074
• RCC with papillary type 2 histology	HLRCC, OMIM 605839, 150800
• RCC with collecting duct histology	HLRCC, OMIM 605839, 150800
• RCC with tubulopapillary histology	HLRCC, OMIM 605839, 150800
• RCC with BHD-related histology (chromophobe, oncocytoma, oncocytic hybrid)	BHD, OMIM 135150
• Urothelial carcinoma (or transitional cell carcinoma) and 2 additional cases of any LS-associated cancer (Table 6) in the same person or in relatives	LS, OMIM 120435, 120436
• RCC and 2 additional Cowden syndrome criteria (Table 4) in the same person	Cowden, OMIM 158350
• Angiomyolipomas of the kidney and one additional TSC criterion (Table 8) in the same person	TSC, OMIM 191100

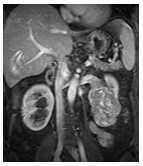
OMIM - Online Mendelian Inheritance in Man
https://www.omim.org

Hampel et al. *Genetics in Medicine* 2014

GW 14

Renal Cell Carcinoma

Staging and Prognosis
Surgical Concepts
Peri-operative Therapy



GW 15

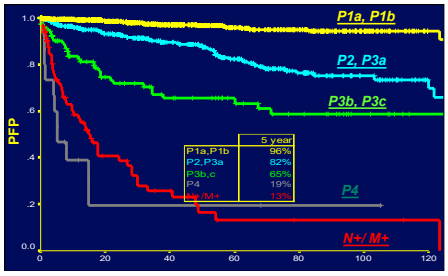
Renal Cell Carcinoma
Primary Tumor (T) AJCC/UICC Staging

- pTx Primary tumor cannot be assessed
- pT0 No evidence of primary tumor
- pT1 Tumor 7 cm or less confined to kidney
  - pT1a 4 cm or less
  - pT1b > 4 cm but not greater than 7 cm
- pT2 > 7 cm but confined to kidney
- pT3 Tumor involves major veins, adrenal, or perinephric tissue but not beyond Gerota's fascia
  - pT3a adrenal or perinephric tissue
  - pT3b renal vein or vena cava below diaphragm
  - pT3c vena cava above diaphragm
- pT4 Beyond Gerota's fascia

TNM Classification of Malignant Tumours, Sixth Ed, UICC, 2002 p. 193 – 196.

GW 16

Progression Free Probability by Pathological Stage



Months From Nephrectomy

GW 17

Changing Landscape Leads to Expansion in Partial Nephrectomy

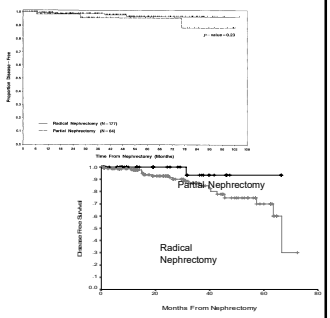
- 70% of tumors now discovered incidentally
- New concerns for long term renal health of patients subjected to radical nephrectomy
- Partial nephrectomy is equally effective to radical nephrectomy for tumors of 7cm or less
- Small but real risk (5%) of contralateral tumor formation in patient's lifetime

GW 18

Disease-Free Survival Partial and Radical Nephrectomy:
Tumors 4cm or less

Expansion of Surgery to Partial Nephrectomy

Conventional (Clear Cell) tumors
4 to 7cm in greatest diameter.



McKiernan et al. *Urology* 59:816-820, 2002
Dash et al, *BJU*, 97:939, 2006

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Impact on Renal Function
Partial compared to Radical Nephrectomy (N=662)

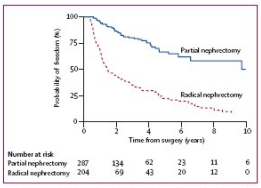

Figure 2: Probability of freedom from new onset of GFR lower than 60 mL/min per 1·72 m^2, by operation type

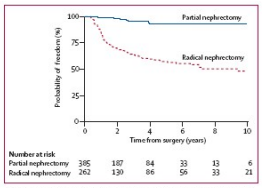

Figure 3: Probability of freedom from new onset of GFR lower than 45 mL/min per 1·72 m^2, by operation type

Huang et al. *Lancet Oncol* 2006; 7: 735–40

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RCC: Adjuvant Trials Seeking Benefit

Historic Trials	Number	Benefit?
IFN vs Surveillance	264	No
IFN vs Surveillance	270	No
IFN vs Surveillance	283	No
HD-IL-2 vs surveillance	69	No
IL-2, IFN & 5-FU vs surveillance	200	No
IL-2, IFN & 5-FU vs surveillance	309	No
HSP vaccine vs surveillance	818	No

Adjuvant Randomized Phase III trials with modern TKI's:

S-TRAC – Sunitinib- FDA approved based on benefit
ASSURE – Sorafenib vs Sunitinib vs placebo - NB
PROTECT – Pazopanib- NB
ATLAS – Axitinib–terminated early by DSMC-NB (Annals Oncol 2018)
SORCE – Sorafenib- no benefit (1 yr vs 3 yrs vs surveillance) (ESMO 2019)

Adjuvant Randomized Phase III trials with Checkpoint Blockade Inhibition

Keynote 564 – Pembrolizumab (1 yr) vs Placebo - Benefit

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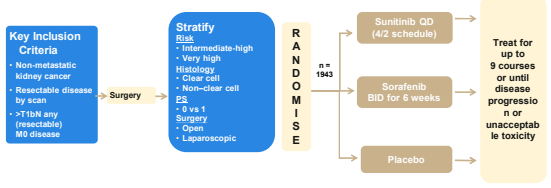
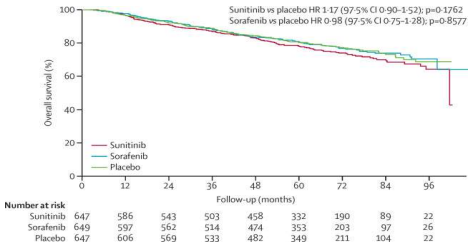
Adjuvant Sorafenib vs Sunitinib vs Placebo Phase III ASSURE Trial (ECOG E2805)



Primary endpoint: DFS
Secondary endpoints: OS, DFS (ccRCC only), biomarker analysis, LVEF changes, incidence of CHF, QoL, safety

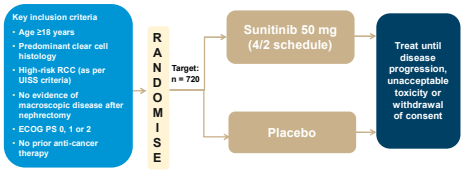
Hass NB et al., 2015 ASCO Annual Meeting

ASSURE – No Difference in Disease-free Survival was seen between Treatment Arms



Haas NB, et al. *Lancet* 2016; 387:2008-16

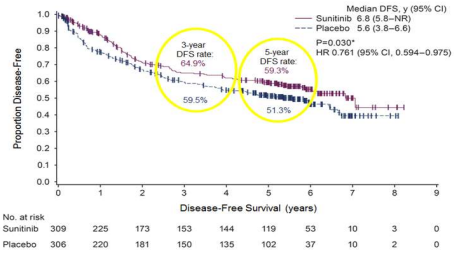
Phase III S-TRAC trial – Adjuvant Sunitinib vs. Placebo



Primary end point: DFS
Secondary end points: OS, PRO, safety

Ravaud et al. Presented at: 2016 ESMO Annual Meeting

S-TRAC- Superior Disease-free Survival for Sunitinib-treated Patients



Ravaud A et al. ESMO 2016
Ravaud A et al. *N Engl J Med* 2016 Oct 9

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ASSURE & S-TRAC– Subtle Differences

	S-TRAC	ASSURE (sunitinib arm)
Numbers total	615	1294
Sponsor	Pfizer	ECOG, SWOG, CLGB, NCI
T-stages(n) - T1-2 - T3-4	 - 615 (100%)	 469 (36.3%) 824 (63.7%)
Histology - Clear cell - Non clear-cell	 99.0% 1%	 79% (=1021 patients) 21%
Completion of 1 year sunitinib (%)	55,6%	59%
Discontinuation of therapy in the sunitinib arm - total - AE	 44.4% 28.1%	 Full dose: 193/438 (44%)[$] Reduced: 65/191 (34%) Total: 258/629 (41%)
Starting dose sunitinib at 50 mg/d	306 (100%)	438/647 (67.7%)

Adapted from Bex A, ESMO Annual Meeting 2016

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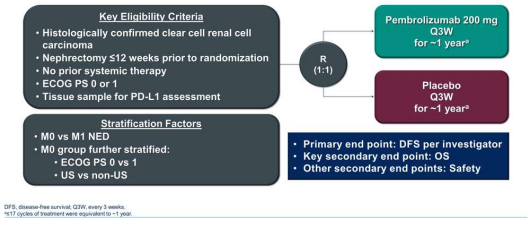
KEYNOTE-564 Study Design



Choueiri et al. ASCO 2021.

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KEYNOTE-564: Pre-specified Disease Risk Categories

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	

Choueiri et al. ASCO 2021.

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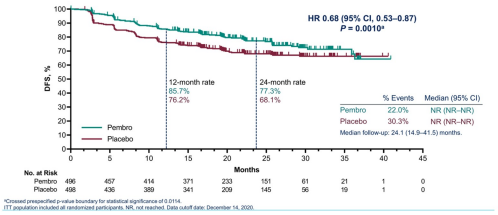
KEYNOTE 564: DFS by Investigator, ITT Population



Choueiri et al. ASCO 2021.

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KEYNOTE-564: Interim OS Results, ITT Population

Choueiri et al. ASCO 2021.

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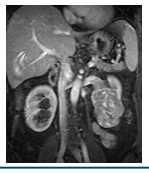
Renal Cell Carcinoma
Advanced Disease Management

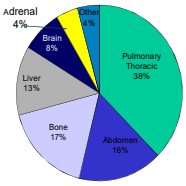
Metastasectomy
Nephrectomy in metastatic disease
Tyrosine Kinase Inhibitors



GW 31

Metastatic RCC

Patterns of Metastases: Organ Sites



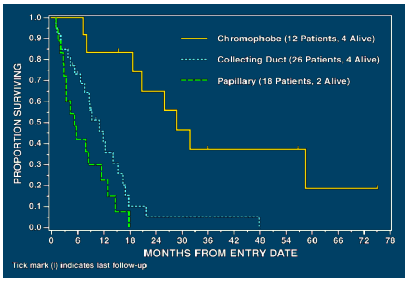
Prognostic Factors: Cytokine era, Prior to TKI's

	p-value	Risk Ratio
LDH (>1.5 x nl)	0.00001	2.5
Hemoglobin (< Normal)	0.00001	1.7
Corrected Calcium (>10)	0.00001	1.7
Karnofsky Perf. Status (< 80)	0.00001	1.5
Nephrectomy (None)	0.001	1.4

J Clin Oncol 17: 2530, 1999

GW 32

Non-Clear Cell Histology: Survival by Cell Type



Motzer et al. *J Clin Oncol.* 2002 ;20:2376-81.

GW 33

Renal Cell Carcinoma
Surgical Resection of Metastasis

- 278 Patients with recurrent RCC 1980-1993
  - 141 (51%) underwent curative metastasectomy
  - 70 (25%) underwent non-curative resection
  - 67 (24%) received non-surgical treatment
- Variables:
  - Site and number of metastatic deposits
  - Performance status of the patient
  - Disease-free interval from treatment of primary tumor to diagnosis of metastatic disease

Kavolus et al *J Clin Oncol.* 1998 16:2261-6.

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Renal Cell Carcinoma
Surgical Resection of Metastasis

	Five-year Survival
Surgical Resection (n=141)	
Non-curative	14%
Curative intent	44%
Solitary (n=94)	
Lung Only	50%
Brain	18%
Non-surgical therapy (n=67)	11%
Prognostic factors	
DFI > 12 ms	55% vs 9%
Solitary vs multiple	54% vs 29%
Age < 60 yrs	49 vs 35%

Kavolus et al J Clin Oncol. 1998 16:2261-6.

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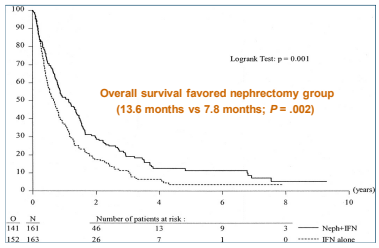
Debulking Nephrectomy: Prospective trial of Pre-treatment Nx from the cytokine era

Cytoreductive Nephrectomy Plus Interferon-α2b Versus Interferon α2b Alone



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

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Poor Risk Factors in Advanced Untreated RCC

MSKCC Criteria	
Karnofsky Performance Status	<80%
Time from diagnosis to treatment with IFN-α	<12 months
Hemoglobin	<LLR
LDH	>1.5 x ULR
Corrected serum calcium	>10.0 mg/dL

IMDC Criteria	
Karnofsky Performance Status	<80%
Time from diagnosis to treatment with TKI	<12 months
Hemoglobin	<LLR
Neutrophils	> ULR
Platelets	> ULR
Corrected serum calcium	>10.0 mg/dL

Risk Group by No. of Risk Factors	
Favorable	0
Intermediate	1 or 2
Poor	3-5

IFN = interferon; KPS = Karnofsky PS; LDH = lactate dehydrogenase;
LLR = lower limit of laboratory's reference range;
MSKCC = Memorial Sloan-Kettering Cancer Center;
ULR = upper limit of laboratory's reference range.
IIMDC (International Metastatic RCC Database Consortium)

Motzer RJ et al. *J Clin Oncol.* 2002;20:289-296. Heng DY, et al. *J Clin Oncol.* 2009;27:5794-5799.

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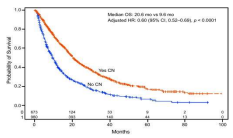
Debulking Nephrectomy: Retrospective Data from the Targeted era – IMDC cohort (n=1,633)



IMDC RF	No CN OS, mo (n)	CN OS, mo (n)	p value
0	insufficient number to compare		
1	22.5 (n = 72)	30.4 (n = 178)	0.002
2	10.2 (n = 143)	20.2 (n = 253)	<0.001
3	10.0 (n = 113)	15.9 (n = 106)	<0.001
4	5.4 (n = 103)	6.0 (n = 67)	0.166
5	3.6 (n = 36)	2.8 (n = 14)	0.504
6	insufficient number to compare		

Heng et al., *Eur Urol* 2014 Oct;66(4):704-10

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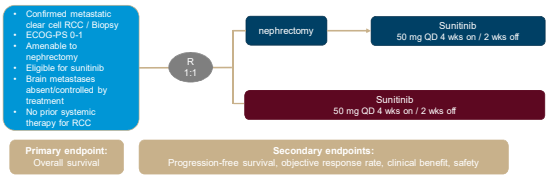
CARMENA: Prospective, Multicenter, Open-label, Randomized, Phase III Non-inferiority Study



The study was designed to have 80% power at a 1-sided significance level of 5% (risk alpha)
Non-inferiority margin of HR: upper 95% CI ≤1.20 for sunitinib alone

Arnaud Méjean et al. ASCO 2018 and *NEJM*

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Patient Characteristics

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)**

Arnaud Méjean et al. ASCO 2018 and *NEJM*

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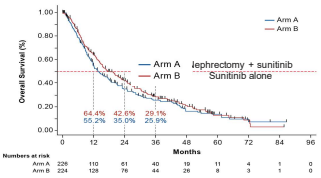
Overall Survival (ITT)

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

HR 95%CI = 0.89 (0.71–1.10)

Non inferiority study ≤1.20



Median OS, months (95% CI)	Arm A: Nephrectomy + Sunitinib (n = 226)	Arm B: Sunitinib alone (n = 224)	HR (95% CI)
Overall	13.9 (11.8–18.3)	18.4 (14.7–23.0)	0.89 (0.71–1.10)
MSKCC intermediate risk	**19.0 (12.0–28.0)**	**23.4 (17.0–32.0)**	**0.92 (0.6–1.24)**
MSKCC poor risk	**10.2 (9.0–14.0)**	**13.3 (9.0–17.0)**	**0.86 (0.62–1.17)**

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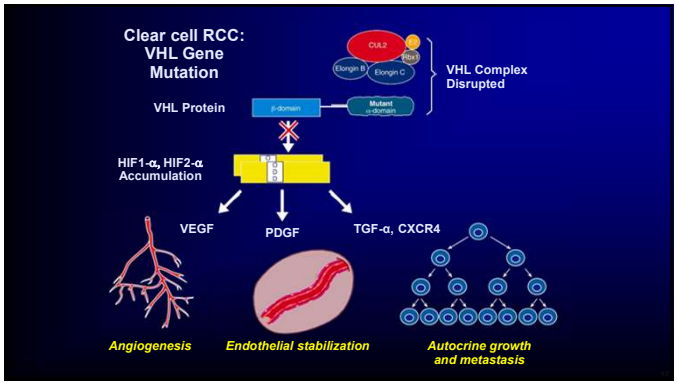
RCC: rIL-2 High-dose Bolus

Author	Patients	CR (%CR+PR)
Atkins	71	4 (17%)
Fyfe	255	12 (14%)
Yang	65	2 (20%)
Rosenberg	149	10 (20%)
Rosenberg	48	4 (21%)
Taneja	28	1 (18%)
Bukowski	41	1 (15%)
Abrams	16	0
All	**673**	**34 (17%)**

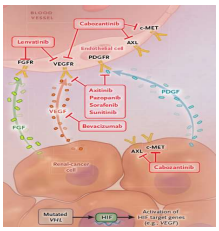
*Approved due to durable CR's

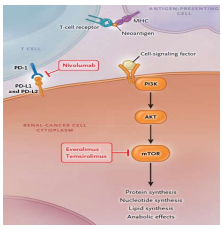
J Urol 163: 308, 1999

42



Overview – Targeted Therapies for Advanced Renal Cell Cancer





GW 44

Poor Risk Factors in Advanced Untreated RCC

MSKCC Criteria	
Karnofsky Performance Status	<80%
Time from diagnosis to treatment with IFN-α	<12 months
Hemoglobin	<LLR
LDH	>1.5 x ULR
Corrected serum calcium	>10.0 mg/dL

IMDC Criteria	
Karnofsky Performance Status	<80%
Time from diagnosis to treatment with TKI	<12 months
Hemoglobin	<LLR
Neutrophils	> ULR
Platelets	> ULR
Corrected serum calcium	>10.0 mg/dL

Risk Group by No. of Risk Factors	
Favorable	0
Intermediate	1 or 2
Poor	3-5

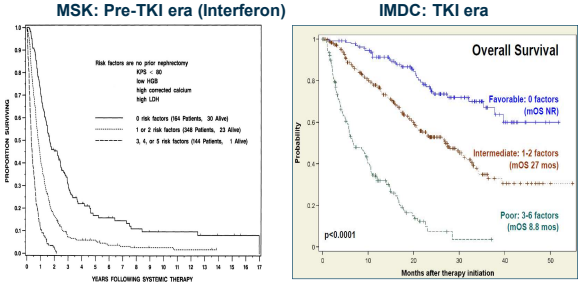
IFN = interferon; KPS = Karnofsky PS; LDH = lactate dehydrogenase; LLR = lower limit of laboratory's reference range; MSKCC = Memorial Sloan-Kettering Cancer Center; ULR = upper limit of laboratory's reference range. IMDC (International Metastatic RCC Database Consortium)

Motzer RJ et al. *J Clin Oncol.* 2002;20:289-296. Heng DY, et al. *J Clin Oncol.* 2009;27:5794-5799.

GW 45

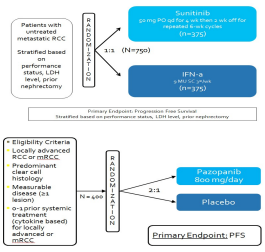
Improved Survival with the Targeted Therapies

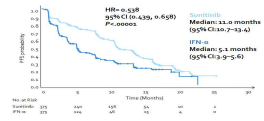
MSK: Pre-TKI era (Interferon) IMDC: TKI era

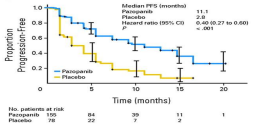


J Clin Onc 1999,2002 and 2009

Sunitinib and Pazopanib are Standards in First-line RCC



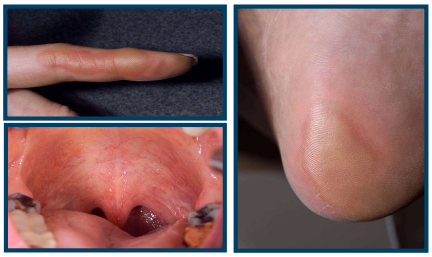




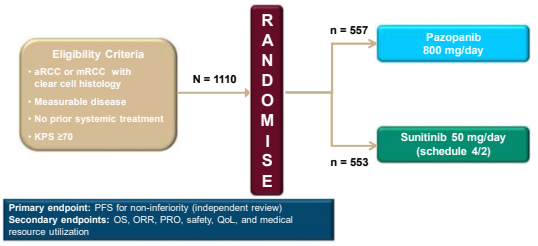
Motzer RJ, et al. *N Engl J Med.* 2007;356:115–124;
Sternberg CN, et al. *J Clin Oncol.* 2010;28:1061-1068.

Sunitinib Skin Adverse Events:

Palmar - Plantar Erythrodysesthesia (21%) and Mucositis (43%)



COMPARZ: Phase III Non-Inferiority Trial of Pazopanib vs Sunitinib: Study Design

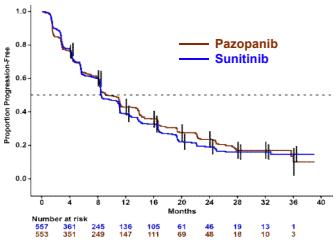


KPS, Karnofsky performance status; QoL, quality of life.

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

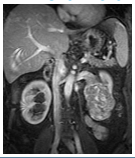
Pazopanib versus Sunitinib (COMPARZ) Progression-free Survival (independent review)

	N	Median PFS (95% CI)
Pazopanib	557	8.4 mo (8.3, 10.9)
Sunitinib	553	9.5 mo (8.3, 11.1)
HR (95% CI) = 1.047 (0.898,1.220)		

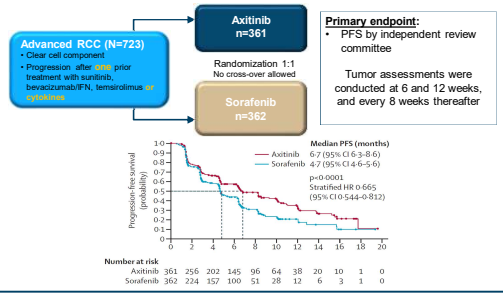


2nd Line Therapy after initial TKI Treatment

Axitinib
Cabozantinib
Lenvatinib + Everolimus
Nivolumab

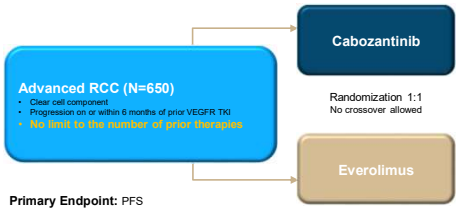


AXIS: Phase III Study of Axitinib vs. Sorafenib



Rini BI, et al. *Lancet.* 2011;378:1931-9.

METEOR: Phase III Cabozantinib vs Everolimus



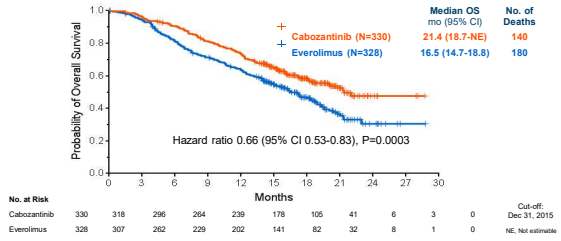
Primary Endpoint: PFS

Tumor assessment by RECIST 1.1 every 8 weeks

Treatment until loss of clinical benefit or intolerable toxicity

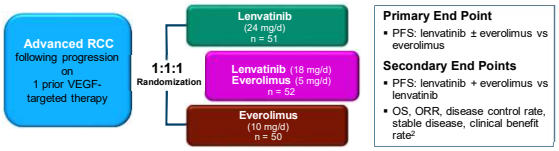
1 Choueiri TK, et al. *N Engl J Med.* 2015;373:1814-1823
2 Choueiri TK et al. *Lancet Oncol* 2016;7:917–927

Overall Survival for Cabozantinib vs Everolimus (METEOR)



Lancet Oncol. 2016;17:917-27

Study 205: Phase II Lenvatinib+Everolimus



Primary End Point
- PFS: lenvatinib ± everolimus vs everolimus

Secondary End Points
- PFS: lenvatinib + everolimus vs lenvatinib
- OS, ORR, disease control rate, stable disease, clinical benefit rate[2]

Motzer RJ, et al. *Lancet Oncol.* 2015;16(15):1473-1482.

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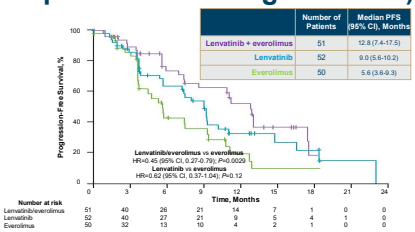
Lenvatinib/Everolimus Phase II Study: PFS (Independent Radiologic Review)



Motzer R, et al. *Lancet Oncol.* 2015;16:1473-1482

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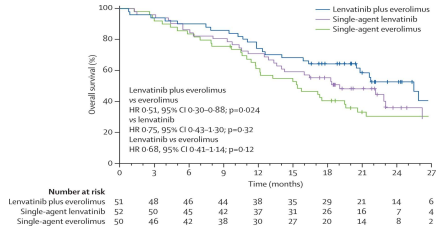
Lenvatinib/Everolimus Phase II Study: Overall Survival in the Post-hoc Updated Analysis



Motzer R, et al. *Lancet Oncol.* 2015;16:1473-1482

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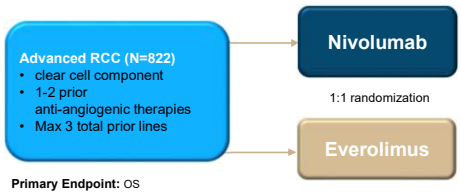
CheckMate 025: Phase III Nivolumab vs. Everolimus

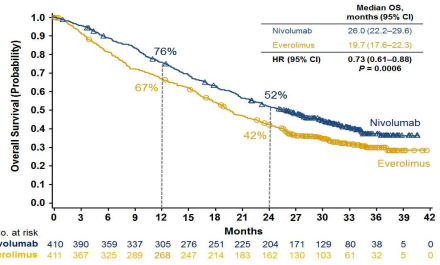


Primary Endpoint: OS

Tumor assessments were conducted every 8 weeks for the first year

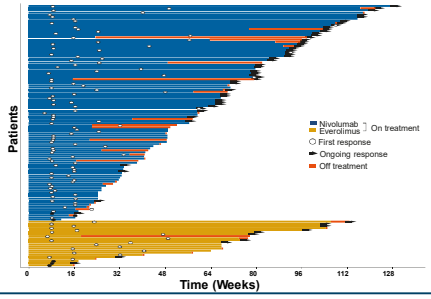
Study therapy continued if clinical benefit and acceptable side effect profile were seen

CheckMate 025: Overall Survival



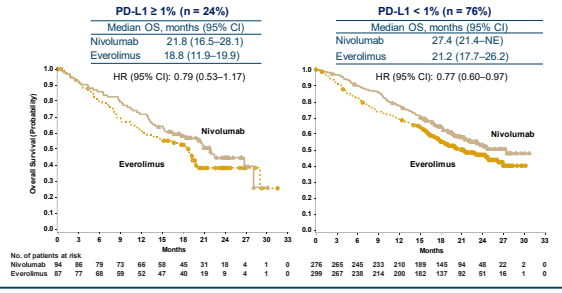
Plimack ER, et al. 15th Intl Kidney Cancer Symposium. Nov 2016, Miami, FL.

Response Characteristics



Motzer RJ, et al. *NEJM*. 2015;373:1803-1813.

Overall Survival by PD-L1 Expression



Motzer RJ, et al. *NEJM*. 2015;373:1803-1813.

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	AXIS[1,2]	CheckMate 025[3,4]	METEOR[5,6]	Study 205[7]
Phase	Phase III	Phase III	Phase III	Phase II
PFS	AXI: 6.7 mo SOR: 4.7 mo	NIV: 4.6 mo EVE: 4.4 mo	CAB: 7.4 mo EVE: 3.8 mo	LEN/EVE: 14.6 mo LEN: 7.4 mo EVE: 5.5 mo
Tumor responses	CR: 0% vs 0% PR: 19% vs 9% SD: 50% vs 54% PD: 22% vs 21%	CR: 1% vs 1% PR: 24% vs 5% SD: 34% vs 55% PD: 35% vs 28%	CR: 0% vs 0% PR: 21% vs 5% SD: 62% vs 62% PD: 14% vs 27%	CR: 2% vs 0% vs 0% PR: 41% vs 27% vs 6% SD: 41% vs 52% vs 62% PD: 4% vs 6% vs 24%
OS	AXI: 20.1 mo SOR: 19.2 mo HR 0·96 (0·80–1·17)	NIV: 25.0 mo EVE: 19.6 mo HR 0.73 (0.57-0.93)	CAB: 21.4mo EVE 16.5mo HR 0.66 (0.53-0.83)	LEN/EVE: 25.5 mo LEN: 19.1 mo EVE: 15.4 mo HR 0.51 (0.3-0.88)
PFS/OS by prior therapy	PFS 1 prior TKI: 4.8 vs 3.4 mo	OS 1 prior anti-VEGF (any): 23.6 vs 19.9 mo 2 prior anti-VEGF (any): NE vs 18.4 mo	PFS Prior SUN: 9.1 vs 3.7 mo	PFS 1 prior TKI: LEN/EVE: 14.6 mo LEN: 7.4 mo EVE: 5.5 mo

References: 1. Rini BI et al. *Lancet*. 2011;378(9807):1931-1939. 2. Motzer RJ et al. *Lancet Oncol*. 2013;14(6):552-562.. 3. Motzer RJ et al. *N Engl J Med*. 2015;373(19):1803-1813. 4. Motzer RJ et al. Poster presented at: 2016 Genitourinary Cancers Symposium. *J Clin Oncol* 34, 2016 (suppl 2S; abstr 498). 5. Choueiri TK et al. *N Engl J Med*. 2015;373(19):1814-1823. 6. Escudier BJ et al. Poster presented at: 2016 Genitourinary Cancers Symposium. *J Clin Oncol* 34, 2016. (suppl 2S; abstr 499). 7. Motzer RJ et al. *Lancet Oncol*. 2015;16(15):1473-1482.

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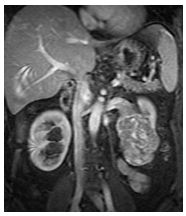
Moving active 2nd-Line Drugs into 1st-Line Combination Therapy

Axitinib plus Avelumab

Nivolumab plus Ipilimumab
Axitinib plus Pembrolizumab
Cabozantinib plus Nivolumab
Lenvatinib + Pembrolizumab



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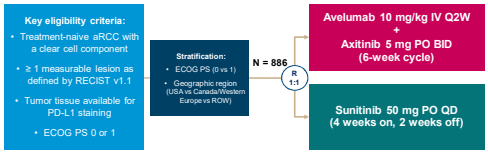
JAVELIN Renal 101: Study Design



BID, twice per day; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PO, orally; Q2W, every 2 weeks; QD, once per day; ROW, rest of the world.

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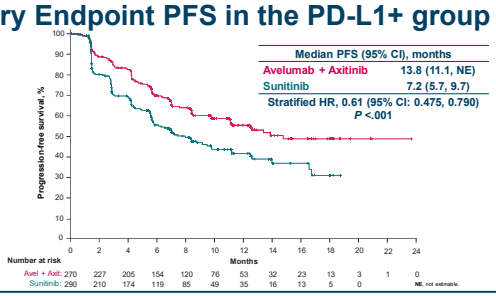
Javelin101: Axitinib + Avelumab vs Sunitinib Primary Endpoint PFS in the PD-L1+ group



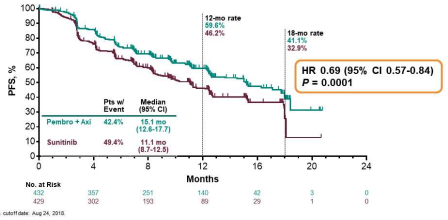
Motzer RJ, et al. *N Engl J Med.* 2019; 380:1103-15.

65

Keynote 426: Axitinib plus Pembrolizumab vs Sunitinib: OS

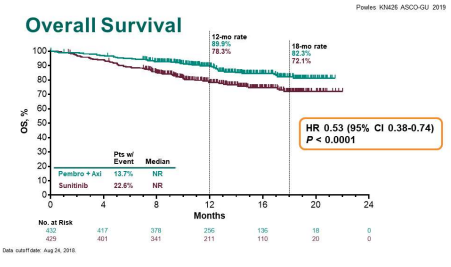
Powles KN426 ASCO-GU 2019

Progression-Free Survival



66

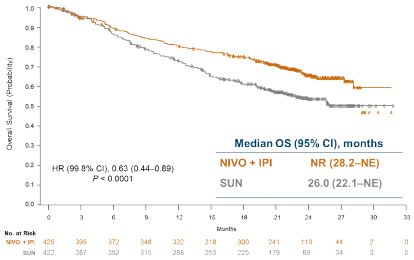
Keynote 426: Axitinib plus Pembrolizumab vs Sunitinib: OS



Rini BI, et al. *N Engl J Med.* 2019;380:1116-27.

67

Checkmate-214: Nivo/Ipi vs Sunitinib: Overall Survival in Intermediate/Poor Risk



Escudier B, et al. ESMO 2017. Abstract LBA5; Motzer RJ, et al. *N Engl J Med.* 2018;378(14):1277–1290.

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Patients With Intermediate-/Poor-Risk mRCC

Keynote 426[1]	Intermediate/Poor Risk	
	Pembro+Axi (n=294)	Sunitinib (n=298)
ORR*	55.8%	29.5%
P value	-	
CR	4.8%	0.7%
Median PFS, months	12.6	8.2
Hazard Ratio (95% CI)	0.67 (0.53-0.85)	
P value	-	
12-month OS	87%	71%
Hazard Ratio (95% CI)	0.52 (0.37-0.74)	
P value	-	

CheckMate 214[2]	Intermediate/Poor Risk	
	Nivo+Ipi (n=425)	Sunitinib (n=422)
ORR*	42%	27%
P value	<0.001	
CR	9%	1%
Median PFS, months	11.6	8.4
Hazard Ratio (99.1% CI)	8.2 (0.64-1.05)	
P value	0.03	
12-month OS	80%	72%
Hazard Ratio (99.8% CI)	0.63 (0.44-0.89)	
P value	<0.001	

*Per blinded independent radiology review committee by RECIST version 1.1.
Pembro+Axi=Pembrolizumab + axitinib; Nivo+Ipi=Nivolumab + ipilimumab; ORR=Objective response rate; CR=Complete response; PFS=Progression-free survival; CI=Confidence interval; OS=Overall survival.

1. Rini BI, et al. *N Engl J Med.* 2019;380:1116-1127; 2. Motzer RJ, et al. *N Engl J Med.* 2018;378(14):1277–1290.

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Patients With Favorable-Risk mRCC

Keynote 426	Favorable Risk	
	Pembro+Axi (n=138)	Sunitinib (n=131)
ORR*	66.7%	49.6%
P value	-	
CR	-	-
Median PFS, months	17.7	12.7
Hazard Ratio (95% CI)	0.81 (0.53-1.24)	
P value	-	
12-month OS	95%	94%
Hazard Ratio (95% CI)	0.64 (0.24-1.68)	
P value	-	

CheckMate 214	Favorable Risk	
	Nivo+Ipi (n=125)	Sunitinib (n=124)
ORR*	29%	52%
P value	<0.001	
CR	11%	6%
Median PFS, months	15.3	25.1
Hazard Ratio (95% CI)	2.18 (1.29-3.68)	
P value	<0.001	
12-month OS	94%	96%
Hazard Ratio (99.8% CI)	1.45 (0.51-4.12)	
P value	0.27	

*Per blinded independent radiology review committee by RECIST version 1.1.
Pembro+Axi=Pembrolizumab + axitinib; Nivo+Ipi=Nivolumab + ipilimumab; ORR=Objective response rate; CR=Complete response; PFS=Progression-free survival; CI=Confidence interval; OS=Overall survival.

1. Rini BI, et al. *N Engl J Med.* 2019;380:1116-1127; 2. Motzer RJ, et al. *N Engl J Med.* 2018;378(14):1277–1290.

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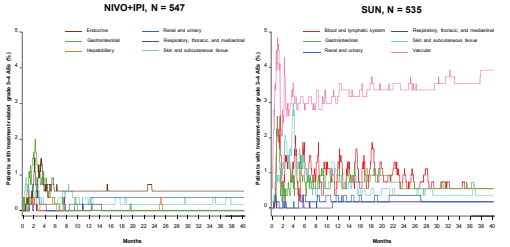
Checkmate 214: Treatment-Related AEs Over Time



- In the NIVO+IPI arm, 35% of patients received high-dose glucocorticoids (≥40 mg prednisone/d or equivalent) for select treatment-related AE management
- No additional treatment-related deaths occurred

Tannir NM, et al. GU Ca Symp 2019. Abstract 547; Motzer RJ, et al. *Lancet Oncol.* 2019; 20: 1370–85.

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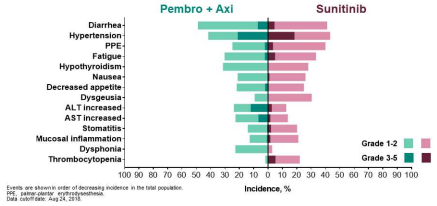
KEYNOTE-426: Treatment-Related AEs (≥20%)

Powles KN426 ASCO-GU 2019

Treatment-Related Adverse Events: Incidence ≥20%



Events are shown in order of decreasing incidence in the total population.
PPE, palmar-plantar erythrodysesthesia.
Data cutoff date: Aug 24, 2018.

Powles T, et al. GU Ca Symp 2019. Abstract 543.

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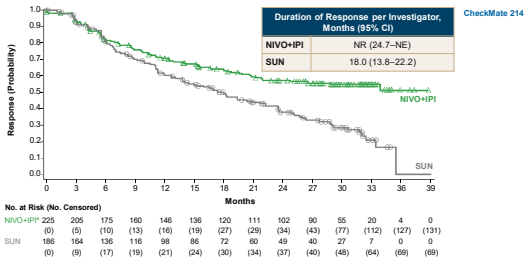
Duration of Response in the Nivolumab Plus Ipilimumab and Sunitinib Groups (ITT Patients)



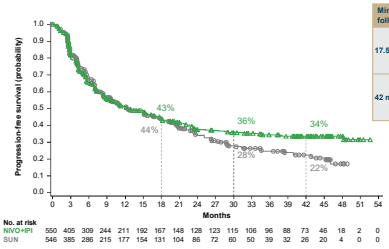
Duration of Response per Investigator, Months (95% CI)	
NIVO+IPI	NR (24.7–NE)
SUN	18.0 (13.8–22.2)

CheckMate 214

No. at Risk (No. Censored)														
NIVO+IPI[a]	225	205	175	160	146	136	120	111	102	90	55	20	4	0
	(0)	(5)	(10)	(13)	(16)	(19)	(27)	(29)	(34)	(43)	(77)	(112)	(127)	(131)
SUN	186	164	136	116	98	86	72	60	49	40	27	7	0	0
	(0)	(9)	(17)	(19)	(21)	(24)	(30)	(34)	(37)	(40)	(48)	(64)	(69)	(69)

[a] Characterization of response kinetics could not be calculated for 2 intermediate/poor-risk partial responders to NIVO+IPI due to missing date of partial response. Motzer RJ et al. *Lancet Oncol* 2019;20:1370–1385.

Nivo/IPI vs Sunitinib Long-term Follow-up PFS by IRRC in ITT Patients



No. at risk															
NIVO+IPI	550	405	309	244	211	192	167	148	128	123	115	106	96	88	73	46	18	2	0
SUN	546	385	286	215	177	154	131	104	86	72	60	50	39	32	26	20	4	0	0

Minimum follow-up	PFS	NIVO+IPI N = 550	SUN N = 546
17.5 mo[1]	Median, mo (95% CI)	12.4 (9.9–16.5)	12.3 (9.8–15.2)
	HR (99.1% CI)	0.98 (0.79–1.23) *P* = 0.85	
42 mo	Median, mo (95% CI)	12.5 (9.8–17.0)	12.3 (9.8–16.6)
	HR (95% CI)	0.89 (0.76–1.05) *P* = 0.16	

Motzer RJ, et al. *N Engl J Med* 2018;378:1277–1290.

VIRTUAL 2020 ESMO congress

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

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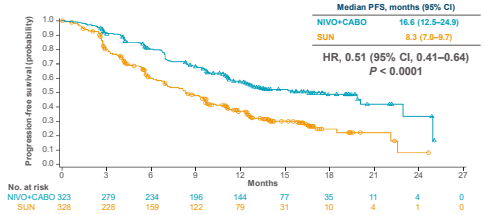
Presentation Number:696O

Progression-Free Survival per BICR



Minimum study follow-up, 10.6 months.

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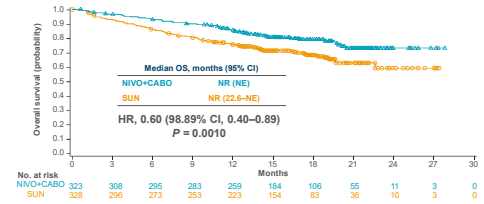
Checkmate 9ER Nivolumab plus Cabozantinib vs Sunitinib Overall Survival



Minimum study follow-up, 10.6 months.
NE, not estimable; NR, not reached.

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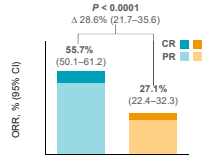
Objective Response and Best Overall Response per BICR



Outcome, %	NIVO+CABO (n = 323)	SUN (n = 328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1
Median time to response (range), months[b]	2.8 (1.0–19.4)	4.2 (1.7–12.3)
Median duration of response (95% CI), months[b]	20.2 (17.3–NE)	11.5 (8.3–18.4)

- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥ 1% vs < 1%), and bone metastases

BICR-assessed ORR and BOR by RECIST v1.1.
aIncludes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified; bMedian time to and duration of response were calculated for patients who had a complete or partial response (n = 180 with NIVO+CABO, n = 89 patients with SUN).

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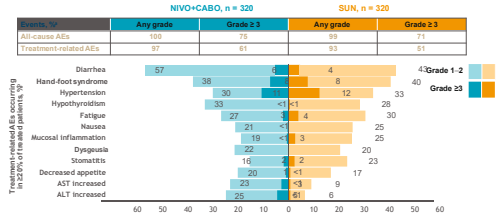
Safety Summary



a Includes events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients. Treatment-related deaths per investigator: NIVO+CABO n = 1 (small intestine perforation), SUN n = 2 (pneumonia, respiratory distress); bTotal bar represents treatment-related AEs of any grade ≥ 20% in either treatment arm; of these events, none were grade 5.

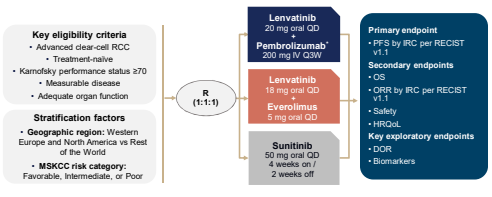
Phase 3 trial of lenvatinib plus pembrolizumab or everolimus versus sunitinib monotherapy as a first-line treatment for patients with advanced renal cell carcinoma (CLEAR study)

Robert Motzer[1], Camillo Porta[2], Masatoshi Eto[3], Thomas Powles[4], Viktor Grünwald[5], Thomas E. Hutson[6], Boris Alekseev[7], Sun Young Rha[8], Evgeny Kopyltsov[9], María José Méndez-Vidal[10], Sung-Hoo Hong[11], Anil Kapoor[12], Teresa Alonso Gordoa[13], Jeffrey C. Goh[14], Jaime R. Merchan[15], Alan D. Smith[16], Kalgi Mody[17], Rodolfo F. Perini[18], Dongyuan Xing[17], and Toni K. Choueiri[19]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]San Matteo University Hospital Foundation, Pavia, Italy; [3]Kyushu University, Fukuoka, Japan; [4]The Royal Free NHS Trust, London, England, UK; [5]University Hospital Essen, Essen, Germany; [6]Texas Oncology, Dallas, TX, USA; [7]P.A. Herbeni Moscow Cancer Research Institute, Moscow, Russia; [8]Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; [9]State Institution of Healthcare "Regional Clinical Oncology Dispensary", Omsk, Russia; [10]Maimonides Institute for Biomedical research of Cordoba (IMIBIC) Hospital Universitario Reina Sofía, Medical Oncology Department, Córdoba, Spain; [11]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [12]McMaster University Hamilton, Ontario, Canada; [13]Hospital Universitario Ramón y Cajal, Madrid, Spain; [14]ICON Research, South Brisbane & University of Queensland, St Lucia, Queensland, Australia; [15]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [16]Eisai Ltd., Hatfield, UK; [17]Eisai Inc., Woodcliff Lake, NJ, USA; [18]Merck & Co., Inc., Kenilworth, NJ, USA; [19]Dana-Farber Cancer Institute, Boston, MA, USA

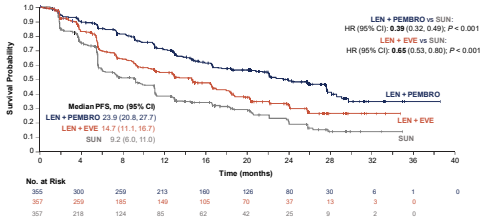
Abstract #269

Study Design



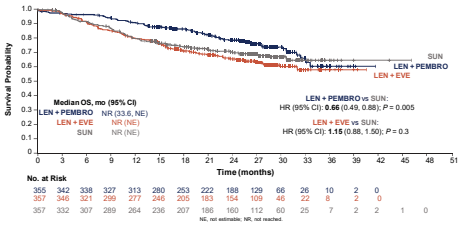
*Patients could receive a maximum of 35 pembrolizumab treatments.
DOR, duration of response; HRQoL, Health-related quality of life; IRC, Independent Review Committee; MKSCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; R, randomization.

Progression-free Survival*



*By Independent Review Committee per RECIST v1.1.

Overall Survival

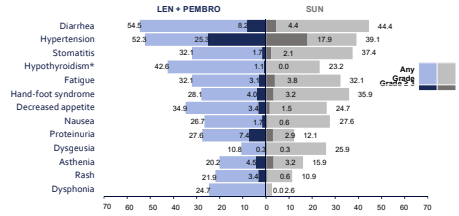


Confirmed Objective Response Rate*

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Objective response rate (95% CI) — %	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Best overall response — %			
Complete response	16.1	9.8	4.2
Partial response	54.9	43.7	31.9
Stable disease	19.2	33.6	38.1
Progressive disease	5.4	7.3	14.0
Unknown / not evaluable	4.5	5.6	11.8
Relative risk versus SUN (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	--
P-value	< 0.001	< 0.001	--

*By Independent Review Committee per RECIST v1.1.

TRAEs With Frequency ≥20%



Alanine aminotransferase/aspartate aminotransferase increased in 9.7/9.4% (grade 3: 3.1/2.6%) of patients in the LEN + PEMBRO arm and 8.8/8.8% of patients (grade 3: 1.8/0.6%) in the SUN arm.
*Adverse event of interest for pembrolizumab.

Randomized Phase III First-Line Combination Studies in RCC with Sunitinib as the SOC Comparator arm

	Nivolumab + Ipilimumab CheckMate 214[1] N=1096	Pembrolizumab + Axitinib Keynote 426[2] N=861	Cabozantinib + Nivolumab Checkmate-9ER[3] N=652	Lenvatinib + Pembrolizumab arm ** CLEAR[4] (N=1068*)
PFS (ITT) HR (95% CI)	12.4 vs 12.3 0.88 (.75-1.04)	15.7 vs 11.1 0.68 (0.58-0.80)	17.0 vs 8.3 0.56 (0.43-0.64)	23.9 vs 9.2 0.39 (0.32-0.49)
Favorable	23%	31%	23%	32%
Intermediate	61%	56%	57%	60%
Poor	17%	13%	20%	9%
OS vs SUT (mos) HR (95% CI)	NR vs 38.4 0.72 (0.61-0.86)	57.5 vs 48.5 0.73 (0.60-0.88)	NR vs 29.5 0.66 (0.50-0.87)	NR vs NR 0.66 (0.49-0.88)

1. Motzer RJ, et al. *N Engl J Med.* 2018;378(14):1277–1290, *JITC* 2020. 2. Rini BI, et al. *N Engl J Med.* 2019;380:1116-27; ASCO 2021; 3. Apolo 2021 et al. ASCO 2021; Grunwald et al. ASCO 2021.

Non-Clear Cell RCC

	SUPAP	ASPEN	ESPN	RECORD -3
PFS (mo.)	6.6 vs 5.5	8.3 vs 5.6	6.1 vs 4.1	7.2 vs 5.1
ORR	12%	18% vs 9%	9% vs 3%	NR
CBR	70%	77% vs 62%	73% vs 77%	NR
DCR/CBR @12 wks	37%	37% vs 16%	NR	NR
PD	30%	20 vs 23%	27% vs 23%	NR
Median OS (mo.)	17.8 vs 12.4	31.5 vs 13.2	16.2 vs 14.9	NR

Sunitinib demonstrated modest benefit over everolimus

Deepak Kilari
Presented By: Dr. Toni K. Choueiri

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Non-Clear Cell RCC Cabozantinib Studies

	Campbell et al.[1]	Chanza et al.[2]	SWOG PAPMET [3]
N	30	112	147(100)
Type	Retrospective	Retrospective	Randomized
Histology	All non–clear cell	All non–clear cell	Papillary
PFS (months)	8.6	7.0	9.0 vs 5.6
ORR	14.3%	27%	23% vs 4%
DCR	78.6	74%	80% vs 56
OS (months)	25.4	12.0	20.0 vs 16.4

Cabozantinib new standard of care

Presented By: Deepak Kilari

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1 Campbell et al *Eur J Ca* 2018; 2 Chanza et al. *Lancet Oncology* 2019; 3 Pal et al. *Lancet* 2021

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Cabozantinib + Nivolumab in Non-Clear Cell RCC

Study Treatment

Key Inclusion Criteria
- Advanced or metastatic ncRCC
- Measurable disease per RECIST v1.1
- 0–1 prior lines of systemic therapy

Cabozantinib
40 mg PO daily
+
Nivolumab
240 mg IV every 2 weeks
(or 480 mg IV 4 weeks)

Primary Endpoint
- ORR by RECIST

Secondary Endpoints
- PFS by RECIST
- PFS by irRECIST
- OS
- Safety and tolerability

- This is a single center, open-label, phase 2 study (NCT03635892) including patients treated with 0 or 1 prior systemic therapies in non-clear cell RCC with select histologies[1]:
  - Cohort 1: papillary[2], unclassified, or translocation-associated RCC (N=40)
  - Cohort 2: chromophobe RCC (N=7)
- Cohort 1 was a single-stage design that met its primary endpoint (N=20) and was expanded to produce more precise estimates of ORR (total N=40). Cohort 2 was a Simon two-stage design that closed early.

1 Histopathology was prospectively reviewed at MSKCC and retrospectively reviewed/confirmed by dedicated GU pathologist (YC)
2 Papillary included unclassified with papillary features, high grade/type 1 papillary, and FH-deficient/type 2 papillary
ncRCC, non-clear cell renal cell carcinoma, ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors v1.1; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; PO, orally; IV, intravenously; PFS, progression-free survival; OS, overall survival

Presented By: Chung-Han Lee

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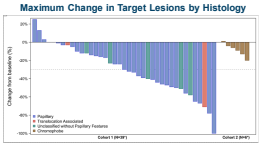
Cabozantinib + Nivolumab in Non-Clear Cell RCC

Summary of Efficacy Outcomes

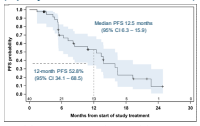
	Cohort 1 (N=40)	Cohort 2 (N=7)
Objective response rate (95% CI)	47.5% (31.5, 63.9)	0% (0, 41.0)
Best response – n (%)		
Partial response	19 (47%)	0 (0%)
Stable disease	20 (50%)	5 (71%)
Progressive disease	1 (3%)	1 (14%)
Not Evaluable	0 (0%)	1 (14%)
Disease control rate (95% CI)	97.5% (86.8, 99.9)	71.4% (29.0, 96.3)
Clinical benefit rate (95% CI)	75.0% (58.8, 87.3)	57.1% (18.4, 90.1)
Median progression-free survival, months (95% CI)	12.5 (6.3, 15.9)	*
Median duration of response, months (95% CI)	13.6 (9.7, 19.8)	†

*Median PFS not calculated due to small numbers of patients. †No responders in cohort to calculate DOR

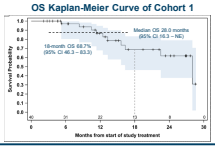
Maximum Change in Target Lesions by Histology



PFS by RECIST Kaplan-Meier Curve of Cohort 1 (Papillary/unclassified/translocation-associated)



OS Kaplan-Meier Curve of Cohort 1



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