CENTER FOR SPECIALTY PHARMACY EDUCATION

A Review in the Treatment Options for Renal Cell Cancer

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NASP NATIONAL ASSOCIATION OF SPECIALTY PHARMACY

ProCE

RENAL CELL CANCER (RCC) INCIDENCE

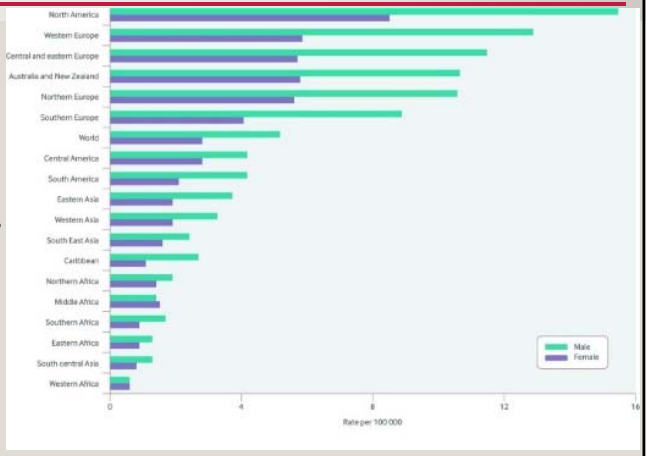
Worldwide, RCC is the ninth most common cancer, with about 337 860 new cases diagnosed in 2012.

In 2013, cancers of the kidney and renal pelvis were estimated to occur in 65 150 patients in the United States, resulting in 13 680 deaths.

In the World Health Organization Europe region, an estimated 121 629 new cases of RCC occurred in 2012, of which 75 676 affected men.

The incidence of RCC varies geographically with the highest incidence in developed countries.

In a recent review of 3001 patients without symptoms being imaged for computed tomography colonography, 14% of patients harbored a renal mass greater than 1 cm in size.



BMJ. 2014; 349. Taken with Permission.

RISK FACTORS

- Social factors
  - Cigarette smoking
  - Obesity
  - Hypertension
  - End Stage Renal Disease (ESRD)
- Environmental/Occupational factors
  - Know to increase risk factors
    - Trichloroethylene
    - Phenacetin-containing analgesia
  - Associated with increase in development
    - Asbestos
    - Polycyclic aromatic Hydrocarbons
- Acquired Cystic Kidney Disease

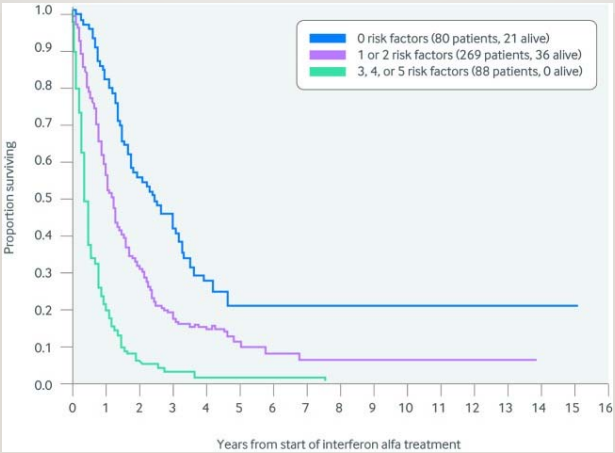
GENETIC RISK FACTORS

- Von-Hippel Lindau (VHL) syndrome
  - 23-45% lifetime risk of RCC with VHL disease
  - Abnormality on chromosome 3p in the VHL gene
- Hereditary papillary renal carcinoma (HPRC)
- Hereditary leiomyomatosis renal cell carcinoma (HLRCC)
- Birt-Hogg-Dube (BHD)

CLINICAL PRESENTATION

- Many are asymptomatic until disease is advanced
- Classic Triad
  - Hematuria
  - Flank pain
  - Palpable mass
- Non-specific symptoms
- Paraneoplastic syndromes
- Systemic symptoms

MEMORIAL SLOAN KETTERING RISK CRITERIA



Motzer RJ et al. JCO 2002;20:289-296. Taken with permission

STAGING AND PROGNOSIS

AMERICAN JOINT COMMITTEE ON CANCER

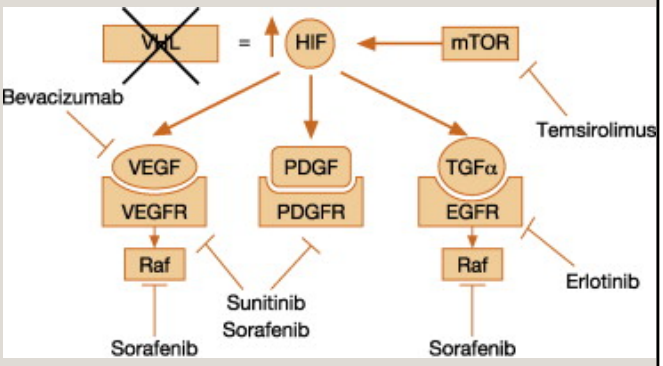
- Many are asymptomatic until disease is advanced
- Classic Triad
  - Hematuria
  - Flank pain
  - Palpable mass
- Non-specific symptoms
- Paraneoplastic syndromes
- Systemic symptoms

SURVIVAL BY STAGE

Stage	5-year Survival
I	96%
II	82%
III	64%
IV	23%

MANAGEMENT OF RCC

- Stage I – III (Localized disease)
  - Nephrectomy
  - No established role for adjuvant therapy
- Stage IV (Metastatic disease)
  - Surgery – nephrectomy / Immunotherapy
    - HD Interleukin-2
    - Interferon-alfa
    - Nivolumumab
  - Targeted therapies



CYTOREDUCTIVE NEPHRECTOMY

- Patients with stage IV disease are also candidates for surgery
  - Minimal regional adenopathy
  - Primary RCC and a solitary site of metastasis
  - Develop a solitary recurrence after nephrectomy
  - Symptoms related to primary tumor
- Cytoreductive nephrectomy before systemic therapy is recommended
- Radiation therapy may be administered for bone metastasis

THERAPIES IN RCC

FIRST-LINE THERAPY

- Pazopanib
- Sunitinib
- Bevacizumab + IFN
- Temsirolimus
- Axitinib
- High-dose Il-2

SECOND-LINE THERAPIES

- Cabozatinib
- Nivolumumab
- Axitinib
- Lenvatinib + everolimus
- Everolimus
- Pazopanib
- Sorafenib
- Sunitinib
- Bevacizumab
- High-dose Il-2
- Temsirolimus

NCCN Guidelines Version 2.2017

INTERLEUKIN-2

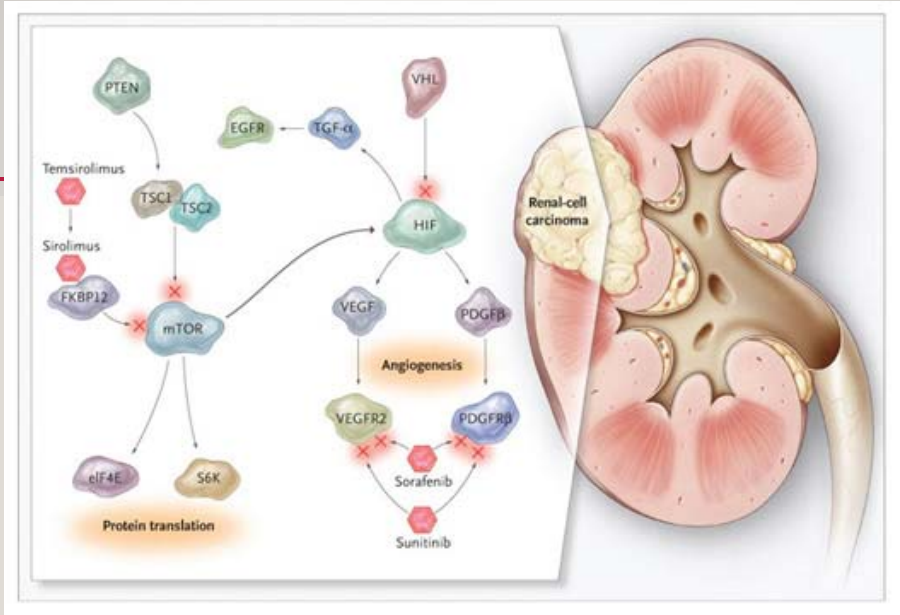
FDA approved for the treatment of RCC

- MOA: induces T-lymphocyte and natural killer cell activity
- Dosing
  - 600,000 IU/kg Q8 hours IV over 15 minutes x 5 days, then repeat 6-10 days off therapy
  - Also Given CIVI and subcutaneously
- Complete response of 5-9% with many patients not relapsing for up to 17 years
- Used in combination with other agents but clinical benefit unknown

INTERLEUKIN-2

Adverse Effects:

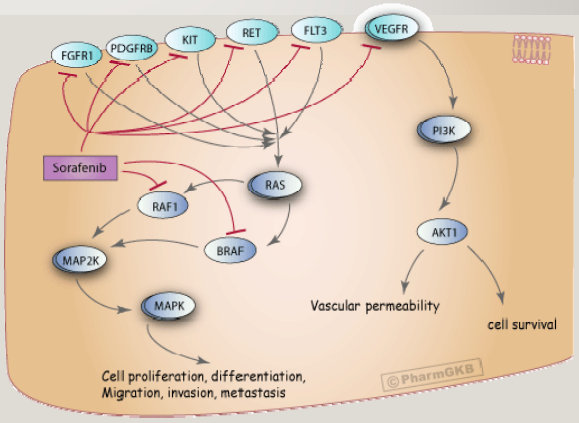
- Capillary leak syndrome
- Hypotension
- Oliguria or anuria
- Arrhythmias
- Mental status changes
- Electrolyte abnormalities
- Increased LFT
- Rash
- Flushing



N Engl J Med 2007;356:185-187 Taken with permission

SORAFENIB

- Mechanism of action
  - Inhibits tumor cell proliferation by targeting the Raf/MEK/ERK pathway at the level of Raf kinase
  - Exhibits anti-angiogenic effects by targeting receptor tyrosine kinases VEGFR-2 and PDGFR and associated signaling cascades



Clinical Pharmacology & Therapeutics 2012 92: 414-417 Taken with Permission

SORAFENIB

- FDA approved for the treatment of RCC and hepatocellular cancer
- Dosing:
  - 400mg BID on an empty stomach
  - 1 hour before or 2 hours after a meal
- Dosage adjustment for skin toxicity
- Continue treatment until:
  - Clinical benefit is no longer evident
  - Unacceptable toxicity

SORAFENIB

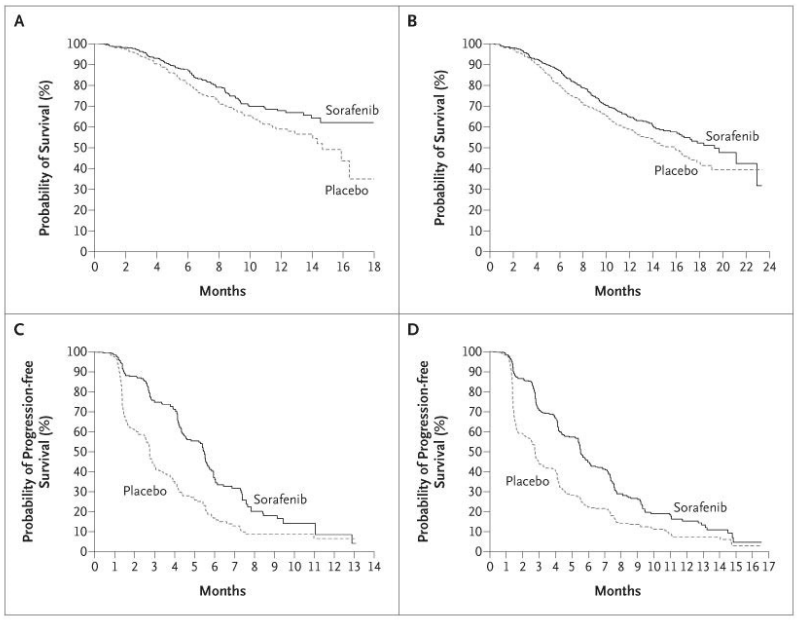
- Phase II discontinuation trial
- 202 patients with advanced RCC received 12 weeks of sorafenib 400mg BID, if response then randomized to sorafenib or placebo
- 65 patients included in randomization
- Results:
  - 24 wks: 50% sorafenib group vs. 18% placebo group were progression free
  - PFS longer in sorafenib group 163 days vs. 41 days for placebo (p=0.0001)

SORAFENIB

- Phase III placebo-controlled trial - TARGET
- Randomized trial in patients with advanced RCC who had received one prior systemic therapy
- Primary endpoint: overall survival
- Sorafenib 400mg po BID or placebo
- Results:
  - Median overall survival 19.3 vs. 14.3 months
  - Median progression free survival (PFS) 167 vs. 84 days for sorafenib vs. placebo ($p<0.01$)
  - Reduced risk of death with sorafenib
  - Crossover patients had 30% improvement in survival

N Engl J Med 2007; 356:125-134

SORAFENIB



N Engl J Med 2007; 356:125-134. Taken with Permission

SORAFENIB

- Hand-foot skin reaction
- Emergent hypertension
  - Monitor BP weekly during the first 6 wks
- Hemorrhage
- Cardiac ischemia
- Warfarin co-administration
  - Increase in INR

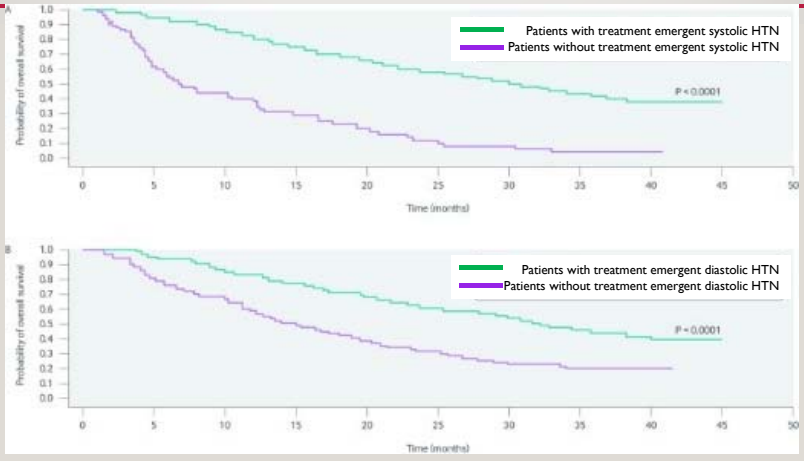
Table 3. Adverse Events.*

Adverse Event	Sorafenib (N=451)			Placebo (N=451)			P Value (Grade 3 or 4)†	P Value (Grade 2)‡
	Any Grade	Grade 2	Grade 3 or 4	Any grade	Grade 2	Grade 3 or 4		
	number (percent)							
Cardiac — hypertension§	76 (17)	44 (10)	16 (4)	8 (2)	3 (<1)	2 (<1)	0.001	<0.001
Hematologic — decreased hemoglobin	34 (8)	14 (3)	12 (3)	33 (7)	8 (2)	20 (4)	0.21	0.28
Constitutional								
Fatigue	165 (37)	54 (12)	22 (5)	125 (28)	39 (9)	16 (4)	0.41	0.12
Other symptoms	46 (10)	9 (2)	6 (1)	27 (6)	8 (2)	6 (1)	1.00	1.00
Weight loss	46 (10)	23 (5)	3 (<1)	25 (6)	8 (2)	0	0.25	0.009
Gastrointestinal								
Diarrhea	195 (43)	56 (12)	11 (2)	58 (13)	13 (3)	3 (1)	0.06	<0.001
Nausea	102 (23)	27 (6)	3 (<1)	87 (19)	21 (5)	3 (1)	1.00	0.46
Anorexia	73 (16)	24 (5)	3 (<1)	57 (13)	16 (4)	5 (1)	0.73	0.26
Vomiting	73 (16)	25 (6)	4 (1)	53 (12)	20 (4)	6 (1)	0.76	0.54
Constipation	68 (15)	22 (5)	3 (1)	49 (11)	19 (4)	3 (1)	1.00	0.75
Neurologic — sensory neuropathy	59 (13)	13 (3)	2 (<1)	29 (6)	4 (1)	3 (1)	1.00	0.05
Pain								
Abdominal	49 (11)	22 (5)	7 (2)	41 (9)	16 (4)	9 (2)	0.80	0.41
Headache	47 (10)	18 (4)	1 (<1)	27 (6)	7 (2)	2 (<1)	1.00	0.04
Joint	45 (10)	13 (3)	7 (2)	29 (6)	14 (3)	1 (<1)	0.07	1.00
Bone	34 (8)	18 (4)	3 (1)	35 (8)	12 (3)	15 (3)	0.007	0.35
Tumor	29 (6)	9 (2)	13 (3)	24 (5)	11 (2)	8 (2)	0.38	0.82
Pulmonary								
Cough	60 (13)	21 (5)	1 (<1)	64 (14)	19 (4)	1 (<1)	1.00	0.87
Dyspnea	65 (14)	25 (6)	16 (4)	52 (12)	18 (4)	11 (2)	0.44	0.35
Dermatologic								
Rash or desquamation	180 (40)	59 (13)	4 (1)	70 (16)	9 (2)	1 (<1)	0.37	<0.001
Hand–foot skin reaction	134 (30)	55 (12)	25 (6)	30 (7)	5 (1)	0	<0.001	<0.001
Alopecia	122 (27)	17 (4)	1 (<1)	15 (3)	2 (<1)	0	1.00	<0.001
Pruritus	85 (19)	21 (5)	1 (<1)	29 (6)	2 (<1)	0	1.00	<0.001

* Listed are adverse events of any grade occurring in at least 10% of patients (with a breakdown of grade 2 events) and adverse events of grade 3 or 4 occurring in at least 2% of patients.
† P values are for the comparison between the sorafenib group and the placebo group with respect to grade 3 or 4 adverse events.
‡ P values are for the comparison between the sorafenib group and the placebo group with respect to grade 2 adverse events.
§ Cardiac ischemia or infarction occurred in 12 patients (3%) in the sorafenib group and 2 patients (<1%) in the placebo group (P=0.01).

N Engl J Med 2007; 356:125-134. Taken with Permission

OVERALL SURVIVAL



J Natl Cancer Inst 2011;103:763-73. Taken with Permission

SUNITINIB

- Mechanism of action
  - Selective inhibitor of multiple tyrosine kinases
    - PDGFR, VEGFR, KIT, FLT3, CSF-1R, and RET
  - Anti-tumor activity I
    - Inhibition of angiogenesis
    - Direct anti-proliferative effects

SUNITINIB

- FDA approved for advanced RCC and Gastrointestinal stromal tumors (GIST) after disease progression on or intolerance to imatinib mesylate (Gleevac®)
- Dosing:
  - 50 mg PO daily x 4 weeks, then 2 weeks off
  - May be taken with or without food
- Dosing adjustments should be made in increments of 12.5mg

SUNITINIB

- Phase II trials of sunitinib as second line therapy in cytokine refractory RCC
- Study I (n=63) 37% Overall response rate (ORR)
  - Duration of response (DR) 54 weeks (12.5 months)
  - 27% patients – stable disease (SD) lasting ≥3 months
  - Median time to progression (TTP) - 8.7 months
- Study II (n=106) 34% ORR
  - DR 27.1 weeks
    - Premature due to only 15% of responders had experienced disease progression

SUNITINIB

- Phase III trial in previously untreated metastatic RCC patients
- Randomized 750 patients to receive sunitinib vs. INFα
- Primary endpoint: progression free survival
- Results:
  - Median PFS 11 months for sunitinib vs. 5 months for INFα
  - Objective response rate (ORR) 31% for sunitinib vs. 6% for INFα
  - Similar rates of stable disease in both groups (48% sunitinib vs. 49% INFα)
  - Overall survival was longer with sunitinib (26.4 months vs. 21.8 months)

SUNITINIB– ADVERSE EFFECTS

- Cardiovascular
  - HTN 15%
- GI
  - Diarrhea 40%
  - Nausea 31%
  - Mucositis/stomatitis 29%
- Dermatological
  - Rash 14%
  - Skin discoloration 30%
  - Hand-Foot Syndrome 14%
- Neurology
  - Altered taste 21%
  - Headache 13%
- Pulmonary
  - Dyspnea 10%
  - Cough 8%
- Bleeding 18%
- Hypophosphatemia
- Musculoskeletal
  - Arthralgia 12%
  - Back pain 11%

SUNITINIB

PRECAUTIONS

- Heart failure
  - Consider baseline and periodic evaluations of LVEF
- Emergent hypertension
  - Monitored carefully and started on appropriate antihypertensive medications
- Adrenal Function
  - Monitor for adrenal insufficiency in patients who experience stress
- Hemorrhagic Events

DRUG INTERACTIONS

- Increase sunitinib concentrations
  - Strong CYP3A4 inhibitors
    - Reduce dose to 37.5mg daily
  - Grapefruit
- Decrease sunitinib concentrations
  - CYP3A4 inducers
    - Select an alternative medication
    - Increase dose to 87.5mg daily

PAZOPANIB

- Pazopanib, an oral angiogenesis inhibitor, has high affinity for PDGFR and VEGFR 1, 2 and 3 and also targets C-kit
- Clinical efficacy of pazopanib demonstrated in a Phase II trial in patients with advanced renal cell carcinoma (RCC) ORR, 34.7%
  - PFS, 11.9 mos vs 6.2 mos (placebo)

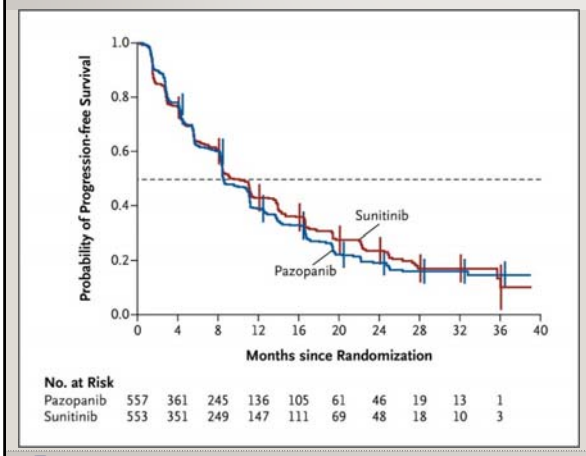
.Expert Opin Investig Drugs 2008;17:253-261

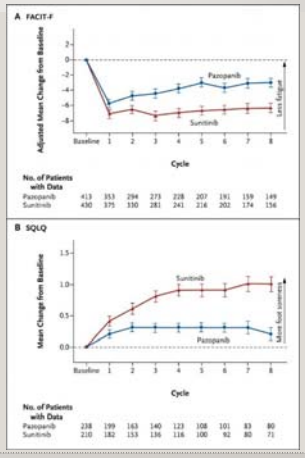
PAZOPANIB

- The study was a randomized, open-label, phase 3 trial of pazopanib versus sunitinib.
- Randomization was stratified according to Karnofsky performancestatus score (70 or 80 vs. 90 or 100), level of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), and nephrectomy (yes vs. no).
- Patients were randomly assigned to one of the two study drugs in a 1:1 ratio in permuted blocks of four.
- Pazopanib was administered orally at a once-daily dose of 800 mg, with continuous dosing.
- Sunitinib was administered orally in 6-week cycles at a once-daily dose of 50 mg for 4 weeks, followed by 2 weeks without treatment.
- Dose reductions for pazopanib (to 600 mg and then to 400 mg) and sunitinib (to 37.5 mg and then to 25 mg) were determined according to the severity of adverse events.
- Patients were treated until progression of disease, the occurrence of unacceptable toxic effects, or withdrawal of consent

N Engl J Med. 2013;369:722-31

PAZOPANIB





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PAZOPANIB ADVERSE EVENTS

Table 1. Adverse Events and Laboratory Abnormalities during Treatment for Which the Relative Risk Differed Significantly between Groups.*

Event	Pazopanib (N=554)			Sunitinib (N=548)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse events						
Increased risk with sunitinib — no. of patients (%)†						
Fatigue‡	302 (55)	58 (10)	1 (<1)	344 (63)	92 (17)	2 (<1)
Hand–foot syndrome‡	163 (29)	32 (6)	0	275 (50)	62 (11)	2 (<1)
Dysgeusia	143 (26)	1 (<1)	0	198 (36)	0	0
Rash	97 (18)	4 (1)	0	125 (23)	4 (1)	0
Constipation	94 (17)	4 (1)	0	130 (24)	5 (1)	0
Dyspepsia	78 (14)	0	0	133 (24)	3 (1)	0
Stomatitis	77 (14)	4 (1)	0	150 (27)	8 (1)	0
Hypothyroidism	67 (12)	0	0	133 (24)	2 (<1)	0
Pain in a limb	67 (12)	2 (<1)	0	91 (17)	6 (1)	0
Mucosal inflammation‡	61 (11)	3 (1)	0	141 (26)	16 (3)	0
Peripheral edema	59 (11)	1 (<1)	0	91 (17)	2 (<1)	0
Epistaxis	48 (9)	1 (<1)	0	97 (18)	6 (1)	0
Pyrexia	48 (9)	2 (<1)	0	88 (16)	6 (1)	0
Increased blood LDH	39 (7)	2 (<1)	0	58 (11)	3 (1)	0
Increased blood thyrotropin	31 (6)	0	0	66 (12)	0	0
Gastroesophageal reflux disease	19 (3)	1 (<1)	0	56 (10)	2 (<1)	0
Yellow skin	4 (1)	0	0	83 (15)	0	0
Increased risk with pazopanib — no. of patients (%)§						
Changes in hair color	168 (30)	0	0	53 (10)	1 (<1)	0
Weight loss	84 (15)	5 (1)	0	33 (6)	1 (<1)	0
Alopecia	75 (14)	0	0	45 (8)	0	0
Hematologic and other laboratory abnormalities						
Increased risk with sunitinib — no. of patients/total no. (%)¶						
Leukopenia‡	237/548 (43)	8/548 (1)	0/548	423/542 (78)	34/542 (6)	0/542
Thrombocytopenia‡	227/548 (41)	17/548 (3)	3/548 (1)	421/542 (78)	95/542 (18)	22/542 (4)
Lymphocytopenia‡	208/548 (38)	29/548 (5)	0/548	300/542 (55)	76/542 (14)	1/542 (<1)
Neutropenia‡	203/548 (37)	20/548 (4)	5/548 (1)	370/542 (68)	103/542 (19)	6/542 (1)
Anemia‡	171/548 (31)	7/548 (1)	5/548 (1)	326/542 (60)	34/542 (6)	6/542 (1)
Hypophosphatemia‡	193/539 (36)	24/539 (4)	0/539	279/533 (52)	44/533 (8)	5/533 (1)
Hypoalbuminemia	179/544 (33)	4/544 (1)	0/544	225/539 (42)	9/539 (2)	0/539
Increased creatinine	177/548 (32)	4/548 (1)	0/548	250/542 (46)	5/542 (1)	3/542 (1)
Hypomagnesemia‡	125/539 (23)	1/539 (<1)	0/539	128/535 (24)	6/535 (1)	1/535 (<1)
Hypermagnesemia‡	62/539 (12)	13/539 (2)	0/539	97/535 (18)	25/535 (5)	0/535
Increased risk with pazopanib — no. of patients/total no. (%)						
Increased AST‖	333/547 (61)	62/547 (11)	7/547 (1)	323/541 (60)	15/541 (3)	0/541
Increased ALT‖	326/547 (60)	84/547 (15)	12/547 (2)	234/540 (43)	19/540 (4)	2/540 (<1)
Increased total bilirubin¶	199/546 (36)	16/546 (3)	2/546 (<1)	144/541 (27)	11/541 (2)	2/541 (<1)
Increased alkaline phosphatase‖	154/547 (28)	17/547 (3)	0/547	131/540 (24)	5/540 (1)	0/540
Hypoglycemia‖	83/548 (15)	2/548 (<1)	0/548	57/541 (11)	3/541 (1)	0/541

* Events listed are those that occurred in more than 10% of patients. A difference in relative risk was considered to be significant when the 95% confidence interval for relative risk did not include unity. These confidence intervals were not corrected for multiple comparisons. Increased levels of blood lactate dehydrogenase (LDH) and blood thyrotropin are not graded according to the Common Terminology Criteria for Adverse Events and were reported as adverse events when the investigator considered them clinically significant. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

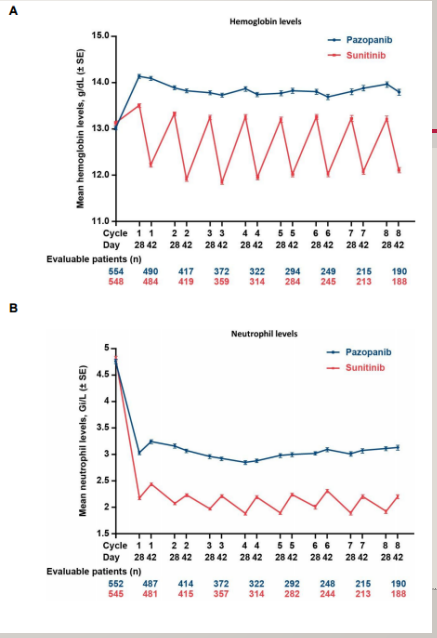
† The relative risk of an event of any grade was significantly higher with sunitinib than with pazopanib.

‡ The relative risk of a grade 3 or 4 event was significantly higher with sunitinib than with pazopanib.

§ The relative risk of an event of any grade was significantly higher with pazopanib than with sunitinib.

¶ Except for hypomagnesemia, the relative risk of an event of any grade was significantly higher with sunitinib than with pazopanib.

‖ The relative risk of a grade 3 or 4 event was significantly higher with pazopanib than with sunitinib.



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SECOND-LINE TREATMENT OPTIONS

- Axitinib
- Cabozatinib
- Nivolumuab

AXITINIB

Most Selective for VEGFR -1, -2, and -3

	Target Selectivity			
	Axitinib[1]	Sorafenib[2]	Sunitinib[3]	Pazopanib[4]
VEGFR-2	+	+	+	+
PDGFR b		+	+	+
c-kit		+	+	+
FLT-3		+	+	
CSF-1R		ND	+	+
Raf-1	ND	+	ND	ND

+: inhibition of receptor kinase comparable (≤ 5 times) to potency for VEGFR-2
ND: not determined

. Kumar R, et al. Mol Cancer Ther. 2007;6:2012-2021.

PHASE III AXIS STUDY :AXITINIB VS SORAFENIB AS SECOND-LINE THERAPY FOR MRCC

Stratified by previous regimen, ECOG PS (0 vs 1)

Patients with clear-cell mRCC, refractory to 1 previous first-line therapy (N = 723)

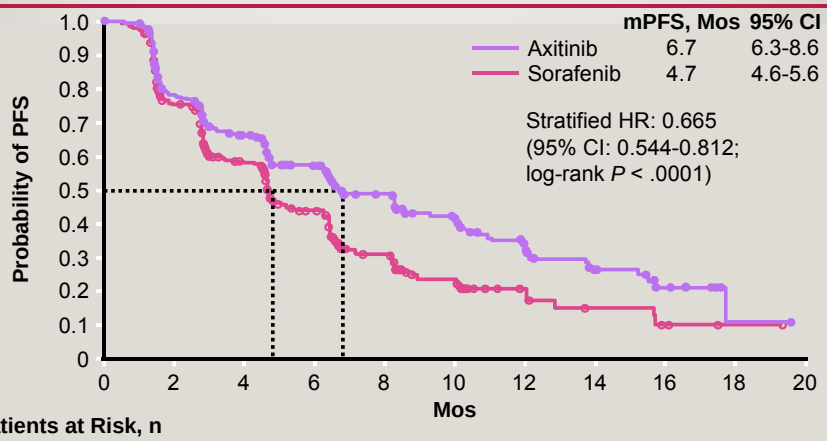
- **Axitinib*** 5 mg BID (n = 361)
- **Sorafenib** 400 mg BID (n = 362)

*Starting dose 5 mg BID with option for dose titration to 10 mg BID.

- Primary endpoint: PFS (independent review committee [IRC])
- Secondary endpoints: OS, ORR (RECIST), duration of response, safety, QoL

Rini BI, et al. Lancet. 2011;378:1931-1939

AXIS TRIAL



Patients at Risk, n

Axitinib	361	256	202	145	96	64	38	20	10	1	0
Sorafenib	362	224	157	100	51	28	12	6	3	1	0

AXIS TRIAL: EFFICACY RESULTS

PFS by Previous Regimen

Previous Treatment Regimen	Axitinib (n = 361)	Sorafenib (n = 362)	HR	PValue*
Cytokines (n = 251)				
▪ IRC	12.1	6.5	0.464	< .0001
▪ Investigator	12.0	8.3	0.636	.0049
Sunitinib (n = 389)				
▪ IRC	4.8	3.4	0.741	.0107
▪ Investigator	6.5	4.5	0.636	.0002
Temsirolimus (n = 24)				
▪ IRC	10.1	5.3	0.511	.1425
▪ Investigator	2.6	5.7	1.210	.6342
Bevacizumab (n = 59)				
▪ IRC	4.2	4.7	1.147	.6366
▪ Investigator	6.5	4.5	0.753	.2126

*1-sided log-rank test stratified by ECOG PS.

Rini BI, et al. Lancet. 2011;378:1931-1939.

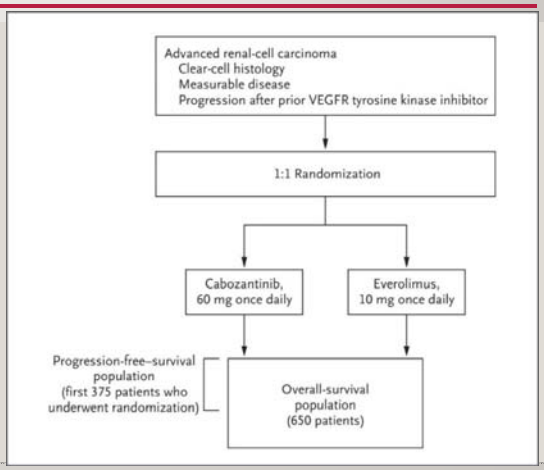
CABOZATINIB

- Inhibitor of MET and VEGF receptor
- Striking response seen in bone of patients with prostate cancer
- Agent is being explored in multiple other cancers, including RCC
- Currently FDA approved for use in patients with progressive, metastatic medullary thyroid cancer

OncoTarets and Therapy 2016;9:5825—5837

CABOZATINIB STUDY DESIGN

- Patients were randomly assigned in a 1:1 ratio to receive either cabozantinib or everolimus.
- Randomization was stratified according to the number of previous VEGFR-targeting tyrosine kinase inhibitors (1 or ≥2) and prognostic risk category (favorable, intermediate, or poor)
- Cabozantinib was administered orally at a dose of 60 mg once daily, and everolimus was administered orally at a dose of 10 mg once daily.
- Treatment was continued as long as clinical benefit was observed by the investigator or until the development of unacceptable toxic effects. Crossover between treatment groups was not allowed.



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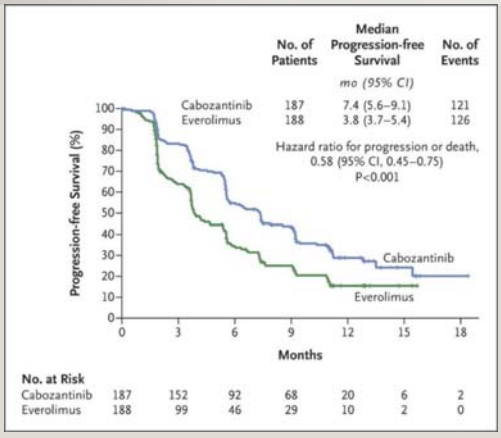
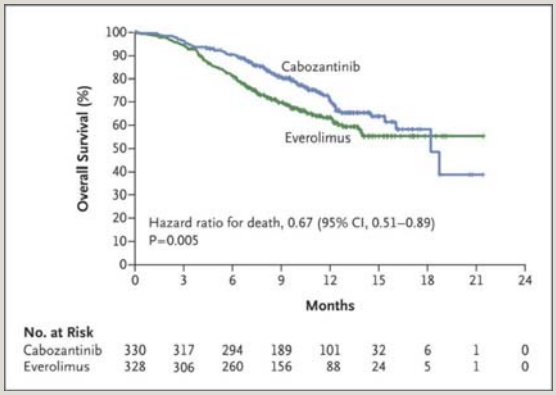
CABOZATINIB OUTCOMES





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CABOZATINIB SIDE EFFECTS

Table 2. Adverse Events.*

Event	Cabozantinib (N=331)		Everolimus (N=322)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any adverse event	331 (100)	226 (68)	321 (>99)	187 (58)
Diarrhea	245 (74)	38 (11)	88 (27)	7 (2)
Fatigue	186 (56)	30 (9)	148 (46)	22 (7)
Nausea	165 (50)	13 (4)	90 (28)	1 (<1)
Decreased appetite	152 (46)	8 (2)	108 (34)	3 (<1)
Palmar–plantar erythrodysesthesia syndrome	139 (42)	28 (8)	19 (6)	3 (<1)
Hypertension	122 (37)	49 (15)	23 (7)	10 (3)
Vomiting	106 (32)	7 (2)	45 (14)	3 (<1)
Weight decreased	102 (31)	6 (2)	40 (12)	0
Constipation	83 (25)	1 (<1)	60 (19)	1 (<1)
Dysgeusia	78 (24)	0	30 (9)	0
Stomatitis	73 (22)	8 (2)	77 (24)	7 (2)
Hypothyroidism	67 (20)	0	1 (<1)	0
Dysphonia	65 (20)	2 (<1)	12 (4)	0
Mucosal inflammation	63 (19)	3 (<1)	73 (23)	11 (3)
Asthenia	62 (19)	14 (4)	50 (16)	7 (2)
Dyspnea	62 (19)	10 (3)	90 (28)	13 (4)
Cough	61 (18)	1 (<1)	107 (33)	3 (<1)
Back pain	56 (17)	7 (2)	47 (15)	7 (2)
Abdominal pain	53 (16)	12 (4)	31 (10)	4 (1)
Rash	50 (15)	2 (<1)	89 (28)	2 (<1)
Pain in arms or legs	47 (14)	3 (<1)	26 (8)	1 (<1)
Muscle spasms	41 (12)	0	16 (5)	0
Dyspepsia	40 (12)	1 (<1)	15 (5)	0
Dry skin	37 (11)	0	32 (10)	0
Headache	37 (11)	1 (<1)	38 (12)	1 (<1)
Arthralgia	36 (11)	1 (<1)	45 (14)	4 (1)
Dizziness	36 (11)	0	21 (7)	0
Peripheral edema	31 (9)	0	72 (22)	5 (2)
Pyrexia	28 (8)	2 (<1)	51 (16)	1 (<1)
Pruritus	25 (8)	0	47 (15)	1 (<1)
Epistaxis	12 (4)	0	46 (14)	0
Pneumonitis	0	0	33 (10)	6 (2)
Laboratory abnormality				
Aspartate aminotransferase increased	58 (18)	6 (2)	18 (6)	1 (<1)
Anemia	56 (17)	18 (5)	122 (38)	50 (16)
Alanine aminotransferase increased	53 (16)	8 (2)	19 (6)	1 (<1)
Hypomagnesemia	52 (16)	16 (5)	5 (2)	0
Proteinuria	41 (12)	8 (2)	30 (9)	1 (<1)
Hypokalemia	38 (11)	15 (5)	21 (7)	6 (2)
Hypophosphatemia	33 (10)	12 (4)	18 (6)	7 (2)
Hypertriglyceridemia	20 (6)	5 (2)	40 (12)	9 (3)
Serum creatinine increased	15 (5)	1 (<1)	35 (11)	0
Hyperglycemia	15 (5)	2 (<1)	62 (19)	16 (5)

* Shown are adverse events that were reported in at least 10% of the patients in either study group, regardless of whether the event was considered by the investigator to be related to the study treatment. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[19]

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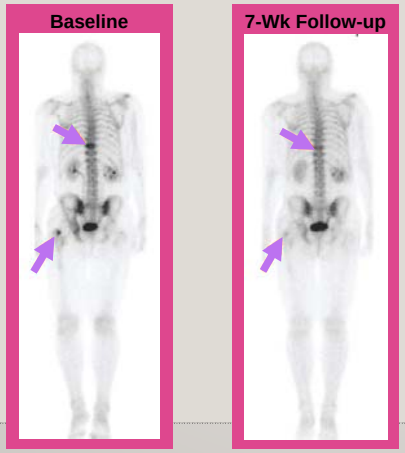
PARTIAL BONE SCAN RESOLUTION/PAIN RELIEF IN SYMPTOMATIC PATIENT WITH BONE METS

Previous therapies include sorafenib, everolimus, and sunitinib



- Patient substantially reduced narcotic use by 7 wks; continued on reduced narcotics until Wk 25
- Another patient with bone metastases and pain at baseline reported complete resolution of pain by 4 wks
  - Pain free 90+ wks on study

Choueiri TK, et al. ASCO 2012. Abstract 4504

NIVOLUMUMAB

Enrolled patients

- Previously treated advanced or metastatic clear-cell RCC
- 1 or 2 prior anti-angiogenic treatments

Randomize 1:1

Nivolumab
(N = 410)
3 mg/kg every 2 weeks
intravenous

Everolimus
(N = 411)
10 mg/day
oral

- Treat until progression or intolerable toxicity
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

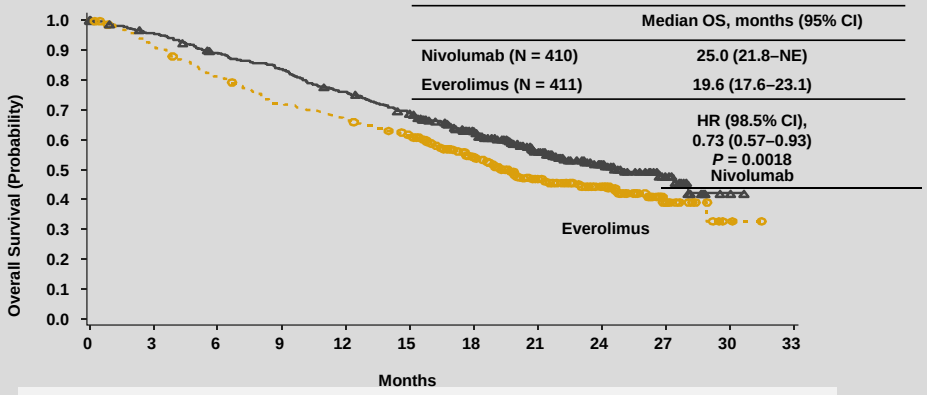
Disease assessments

- Every 8 weeks from randomization through 12 months
- Then every 12 weeks until progression or treatment discontinuation

Primary endpoint

- Overall survival (OS)

NIVOLUMUMAB



- **The risk of death was reduced by 27% in patients in the nivolumab treatment group compared with those in the everolimus group**
- **Study stopped after planned interim analysis (398 deaths) because assessment by an independent data monitoring committee concluded that the study met its primary endpoint, demonstrating superior OS for nivolumab**

HR, hazard ratio; NE, not estimable.

N Engl J Med 2015; 373:1803-1813

NIVOLUMUMAB ADVERSE EVENTS

- Grade 3 or 4 treatment-related AEs were less frequent with nivolumab than with everolimus and treatment-related adverse events leading to discontinuation were experienced by fewer patients treated with nivolumab
- The most common treatment-related AEs of any grade reported in the nivolumab arm were fatigue (33%), nausea (14%), and pruritus (14%), and in the everolimus arm, fatigue (34%), stomatitis (29%), and anemia (24%)
- There were no treatment-related deaths in the nivolumab treatment arm

AE, adverse event; mRCC, metastatic renal cell carcinoma.

SELECTED CLINICAL TRIALS SECOND-LINE THERAPY

Agent	Mechanism	Trial arms	ORR (%)	PFS (Months)	OS (Months
Axitinib	VEGFR inhibitor	Axitinib *versus* sorafenib	19 *versus* 9 P=0.0001	6.7 *versus* 4.7 P<0.0001	20.1 *versus* 19.2 P=0.3744 NS
Cabozantinib	VEGF, MET and AXL inhibitor	Cabozantinib *versus* everolimus	21 *versus* 5 P<0.001	7.5 *versus* 3.9 P<0.001	21.4 *versus* 16.5 P<0.001
Nivolumab	PD-1 inhibitor	Nivolumab *versus* everolimus	25 *versus* 5 P<0.001	4.6 *versus* 4.4 P=0.11 NS	25.0 *versus* 19.6 P=0.002

SUMMARY

- Current therapies continue to emerge in Renal Cell Cancer
- Second line strategies are emerging, especially with the advent of Checkpoint Inhibitors
- Patient specific treatments need to be mitigated based on a therapies adverse outcome profile