Edelleen uutta munuaissyövän hoidossa?

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29.8.2014 Onkologiapäivät

Approved Therapies in RCC

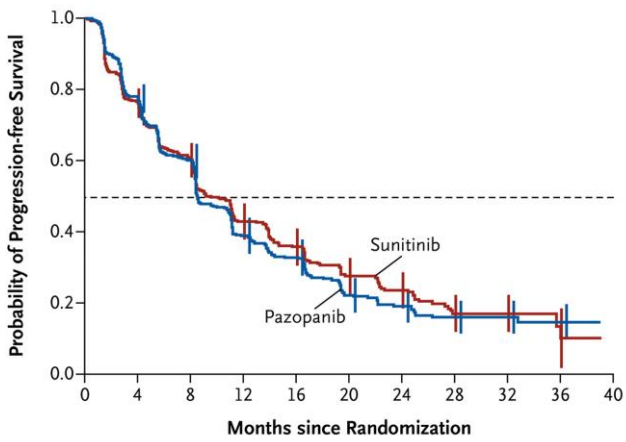
- Pivotal trials have led to approval of multiple targeted agents for the treatment of mRCC

Year of Publication	Agent	First Author
2003	Bevacizumab*	Yang[1]
2007	Sorafenib*	Escudier[2]
2007	Sunitinib†	Motzer[3]
2007	Temsirolimus†	Hudes[4]
2007	Bevacizumab + IFN-α†	Escudier[5]
2008	Bevacizumab + IFN-α†	Rini[6]
2008	Everolimus*	Motzer[7]
2010	Pazopanib*	Sternberg[8]
2011	Axitinib‡	Rini[9]

IFN-α, interferon α.
*Versus placebo; †Versus IFN-α; ‡Versus sorafenib.

1. Yang JC et al. *N Engl J Med.* 2003;349:427-434. 2. Escudier B et al. *N Engl J Med.* 2007;356:125-134.
3. Motzer RJ et al. *N Engl J Med.* 2007;356:115-124. 4. Hudes G et al. *N Engl J Med.* 2007;356:2271-2281.
5. Escudier B et al. *Lancet.* 2007;370:2103-2111. 6. Rini BI et al. *J Clin Oncol.* 2008;26:5422-5428.
7. Motzer RJ et al. *Lancet.* 2008;372:449-456. 8. Sternberg CN et al. *J Clin Oncol.* 2010;28:1061-1068.
9. Rini BI et al. *Lancet.* 2011;378:1931-1939.

COMPARZ: patsopanib vs sunitinib



No. at Risk

Pazopanib	557	361	245	136	105	61	46	19	13	1
Sunitinib	553	351	249	147	111	69	48	18	10	3

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

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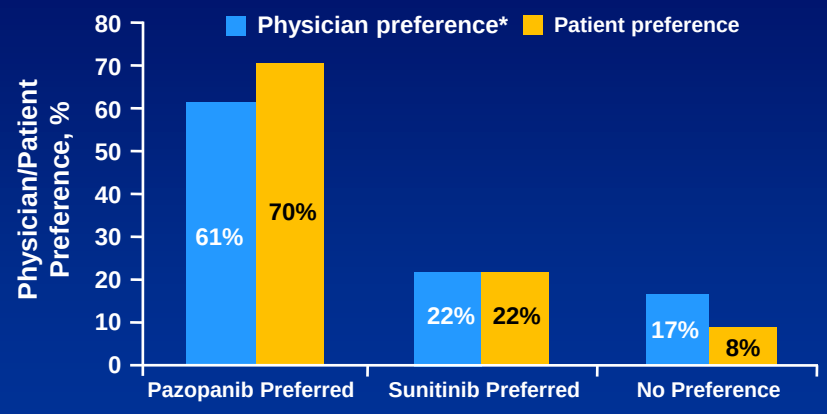
PISCES Study: Patient and Physician Preference (Primary Analysis Population)[1]



*Completed while patient was still blinded.

1. Escudier B et al. *J Clin Oncol*. 2014, 32: 1412-8

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Yhteenveto: RECORD-3 and SWITCH

RECORD-3[1]

Eve. → Sun vs. Sun. → Eve	1st-line mPFS, months (95% CI)		1st-line ORR, % (95% CI)		Combined mPFS, Months (95% CI)		mOS (95% CI, months)	
	Eve	Sun	Eve	Sun	Eve → Sun	Sun → Eve	Eve → Sun	Sun → Eve
	7.9 months (5.6, 8.2)	10.7 months (8.2,11.5)	8.0% (4.9,12.2)	26.6% (21.1,32.8)	21.13	25.79	22.4 (17.9,NA)	32.0 (20.5,NA)

SWITCH

Sor. → Sun. vs. Sun. → Sor.	1st-line mPFS, months (95% CI)		1st-line ORR,%		Combined mPFS, Months (95% CI)		mOS, months (95% CI)	
	Sor	Sun	Sor	Sun	Sor → Sun	Sun → Sor	Sor → Sun	Sun → Sor
	5.9 (>5.5, >7.9)	8.5 (>7.1, <11.2)	31	29	12.5 (>11.5, <15.0)	14.9 (>10.5 ,<17.2)	31.5 (>23.3 ,<36.9)	30.2 (>23.6, <50.1)

1. Motzer *et al*. JCO Jul 21 2014; 2. Michel *et al*. ASCO GU 2014

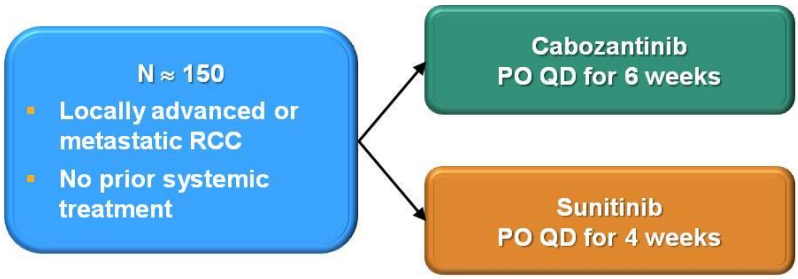
A phase I study of cabozantinib (XL 184) in patients with renal cell cancer

- VEGFR 2 ja c-MET inhibitor
- 25 prior anti VEGF treated patients
- 28% PR response
- Median PFS 12,9 months
- OS 15,0 months

- Choueiri et al. Ann Oncol 2014, Aug 25: 1603-8

Cabozantinib (CaboSun)

Ongoing phase 2 study in RCC in Alliance



Primary endpoint: PFS

Secondary endpoints: OS, ORR, safety

Choueiri TK, PI

Estimated study completion date: late 2014.

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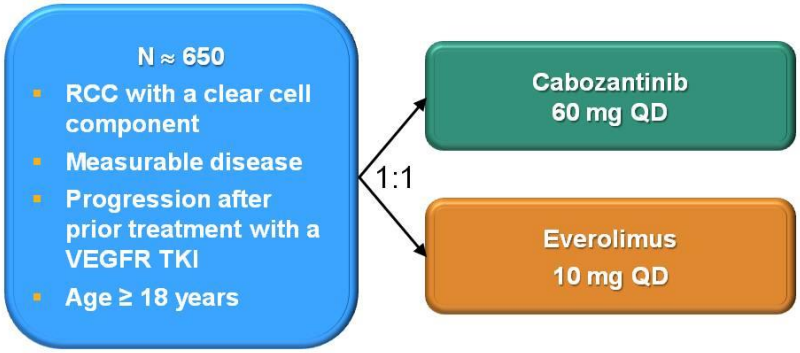
Presented By Michael Atkins at 2014 ASCO Annual Meeting

Cabozantinib

Ongoing phase 3 study in RCC



Primary endpoint: PFS

Secondary endpoints: OS, ORR

Estimated study completion date: September 2017.

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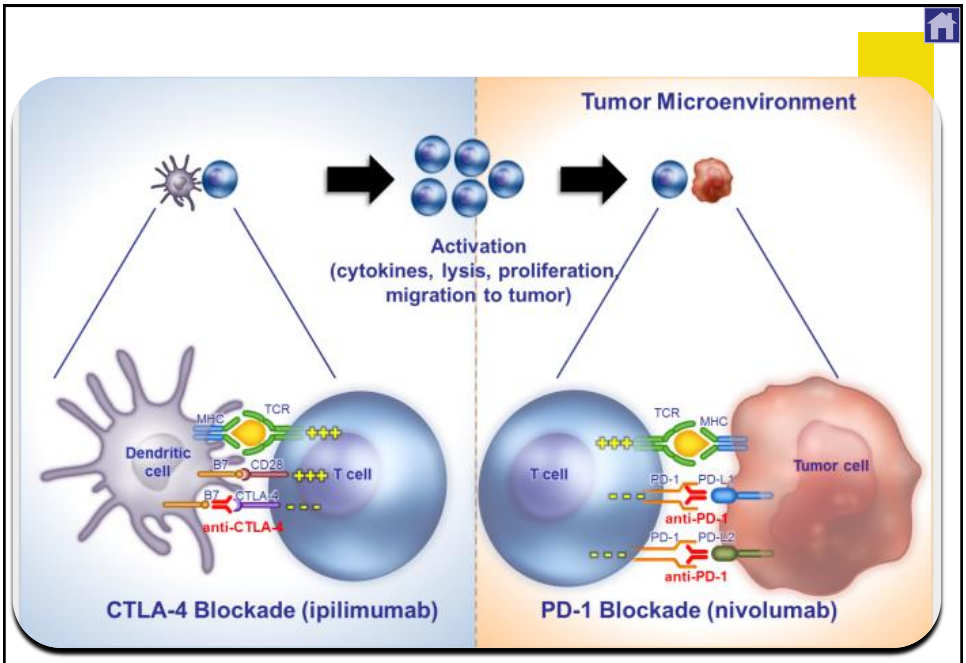
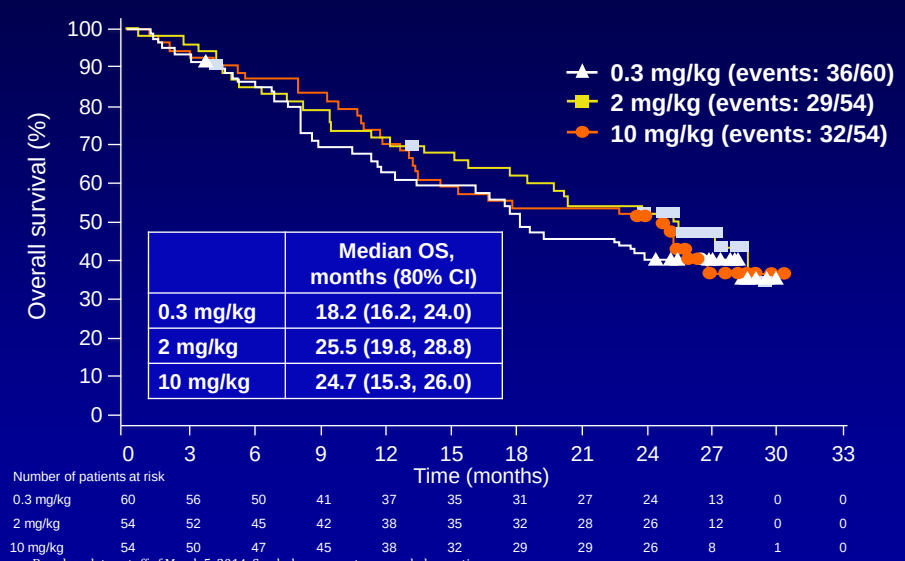
Presented By Michael Atkins at 2014 ASCO Annual Meeting



H. Hammers, ASCO 2014

Nivolumab for metastatic renal cell carcinoma (mRCC): results of a randomized, dose-ranging phase II trial



	Median OS, months (80% CI)
0.3 mg/kg	18.2 (16.2, 24.0)
2 mg/kg	25.5 (19.8, 28.8)
10 mg/kg	24.7 (15.3, 26.0)

Number of patients at risk

0.3 mg/kg	60	56	50	41	37	35	31	27	24	13	0	0
2 mg/kg	54	52	45	42	38	35	32	28	26	12	0	0
10 mg/kg	54	50	47	45	38	32	29	29	26	8	1	0

Based on data cutoff of March 5, 2014; Symbols represent censored observations.

R. Motzer, ASCO 2014

Overall survival in phase III trials and nivolumab phase II study

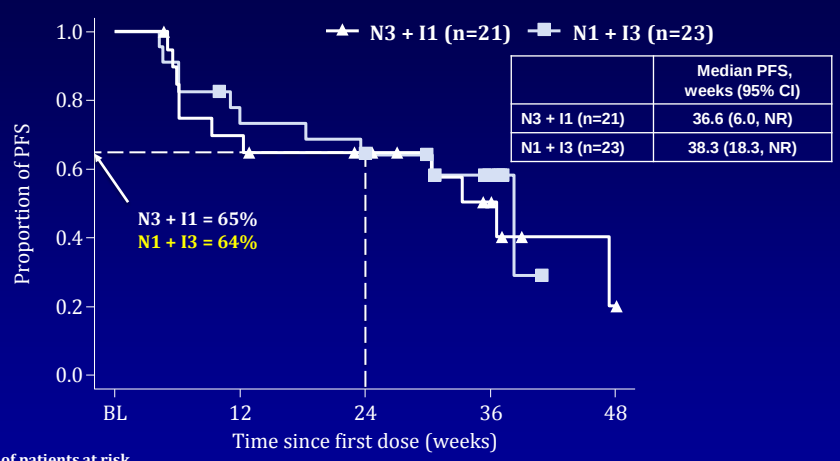
	AXIS[1,a]	INTORSECT[2]	RECORD-1[3]	GOLD[4]	Nivolumab study
Drug	Axitinib; sorafenib	Temsirolimus; sorafenib	Everolimus; placebo	Dovitinib; sorafenib	**Nivolumab; 0.3; 2; 10 mg/kg**
Patients, n	389	512	416	570	168
Risk group, %[b]					
Favorable	Not stated	19	29	20	33
Intermediate		69	56	58	42
Poor		12	14	22	25
Prior therapy	Sunitinib	Sunitinib	VEGF	VEGF + mTOR	VEGF ± mTOR
Line of therapy	2nd	2nd	2nd or higher	3rd or higher	2nd to 4th
Median OS, months	15.2; 16.5	12.3; 16.6	14.8; 14.4	11.1; 11.0	**18.2; 25.5; 24.7**
CI	12.8, 18.3[c] 13.7, 19.2[c]	10.1,14.8[c] 13.6, 18.7[c]	Not stated	9.5, 13.4[c] 8.6, 13.5[c]	16.2, 24.0[d] 19.8, 28.8[d] 15.3, 26.0[d]

[a]Post TKI subset; [b]Total ≠100% due to rounding; [c]95% CI; [d]80% CI.

1. Motzer R, et al. *Lancet Oncol.* 2013;14:552-62; **2.** Hutson TE, et al. *J Clin Oncol.* 2014;32:760-7; **3.** Motzer R, et al. *Cancer.* 2010;116:4256-65; **4.** Motzer R, et al. *Lancet Oncol.* 2014;15:286-96.

R. Motzer, ASCO 2014

CA209-016 (NCT01472081): phase I study design (N + I cohort)



Number of patients at risk

N3 + I1	21	14	11	6	1
N1 + I3	23	17	14	7	0

Symbols represent censored observation. Number of patients at risk listed is number at risk before entering the time period. NR, not reached.

H. Hammers, ASCO 2014

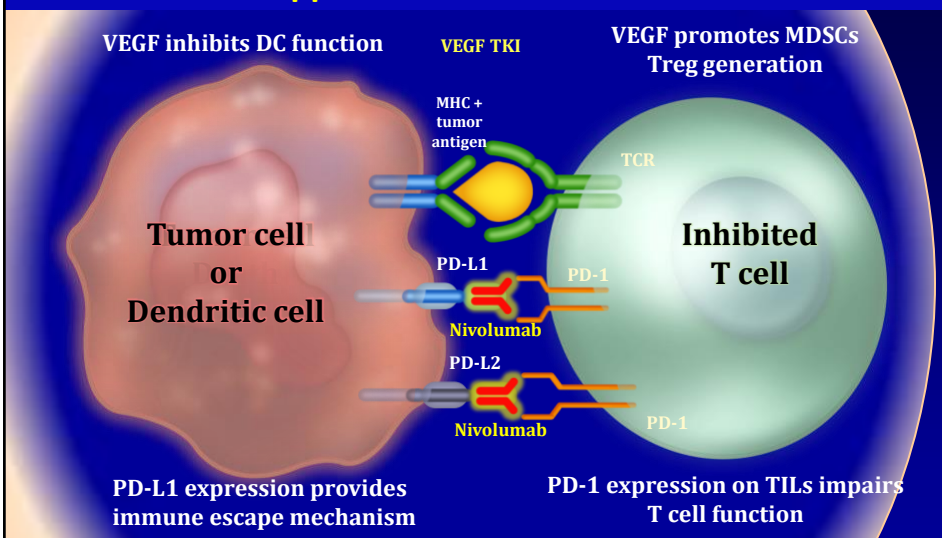
Treatment-related select AE categories

Category, n (%)	N3 + I1 (n=21)		N1 + I3 (n=23)	
	All	Grade 3-4	All	Grade 3-4
Endocrinopathy	3 (14.3)	0	8 (34.8)	0
Gastrointestinal disorder	6 (28.6)	1 (4.8)	9 (39.1)	4 (17.4)
Hepatic	1 (4.8)	0	9 (39.1)	6 (26.1)
Infusion reaction	2 (9.5)	0	2 (8.7)	0
Pulmonary	1 (4.8)	0	2 (8.7)	0
Renal disorder	2 (9.5)	0	3 (13.0)	0
Skin disorder	8 (38.1)	0	9 (39.1)	0

- **No high-grade pulmonary AEs, including pneumonitis, were observed**

H. Hammers, ASCO 2014

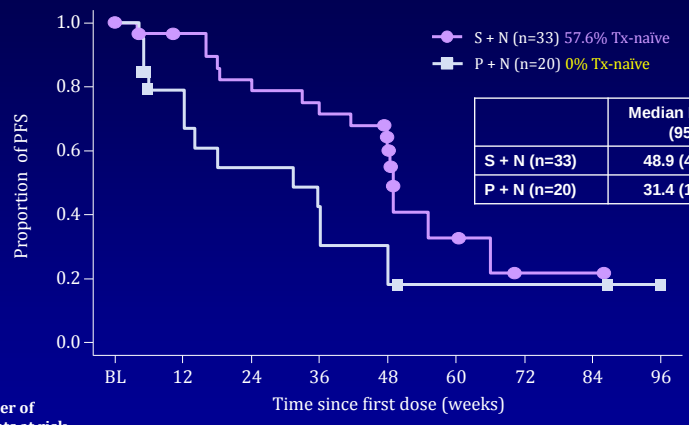
Immunosuppressive tumor microenvironment



PD-1, programmed death-1; PD-L1, programmed death ligand-1.
Gabrilovich D, et al. *Nat Med.* 1996;2:1096-103; Gabrilovich D, et al. *Nat Rev Immunol.* 2009;9:162-74; Bronte V, et al. *J Immunother.* 2001;24:431-46; Finke JH, et al. *Clin Cancer Res.* 2008;14:6674-82; Ko JS, et al. *Clin Cancer Res.* 2009;15:2148-57; Thompson RH, et al. *Clin Cancer Res.* 2007;13:1757-61; Thompson RH, et al. *Proc Natl Acad Sci U S A.* 2004;101:17174-9.

A. Amin, ASCO 2014

Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC)

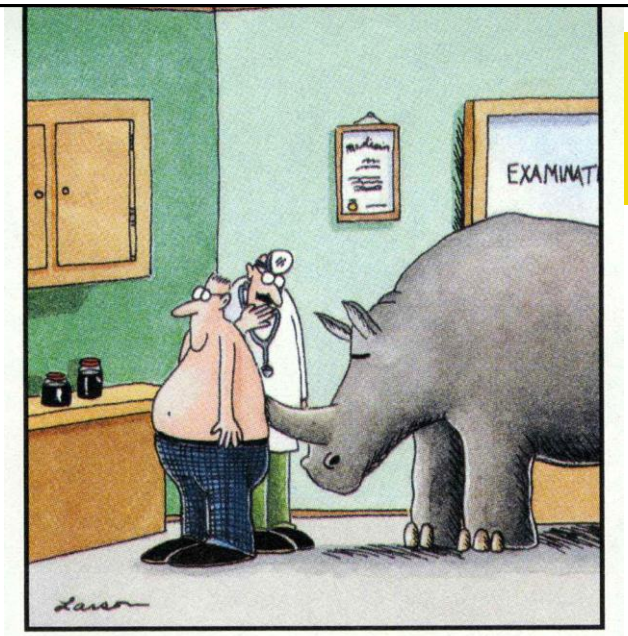


	Median PFS, weeks (95% CI)
S + N (n=33)	48.9 (41.6-66.0)
P + N (n=20)	31.4 (12.1-48.1)

Number of patients at risk									
S + N	33	27	23	21	16	4	1	1	0
P + N	20	13	9	7	5	2	2	2	1

Symbols represent censored observation. Number of patients at risk listed is number at risk before entering the time period.
Tx, treatment

A. Amin, ASCO 2014



"Wait a minute here, Mr. Crumbley. ... Maybe it isn't kidney stones after all."