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Incontri
di aggiornamento
del Dipartimento
Oncologico

Responsabile Scientifico:
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6° INCONTRO - Martedì 29 novembre 2016

Oncologia traslazionale - 2ª edizione

La via del segnale PI3K/Akt/mTOR:

Inibitori di mTOR nel carcinoma renale

Alessandro Inno

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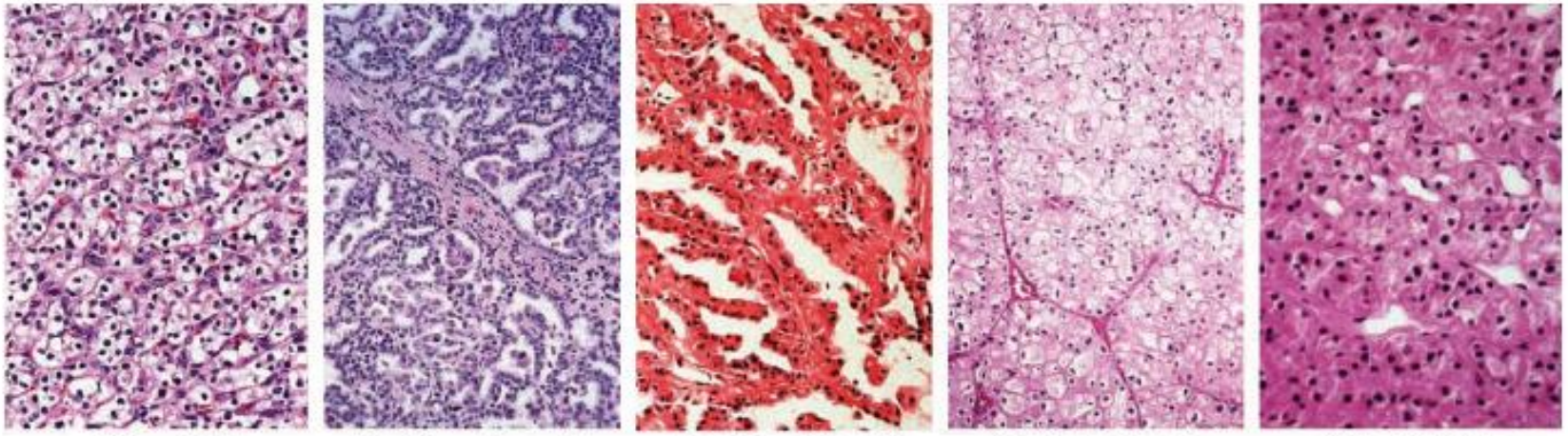
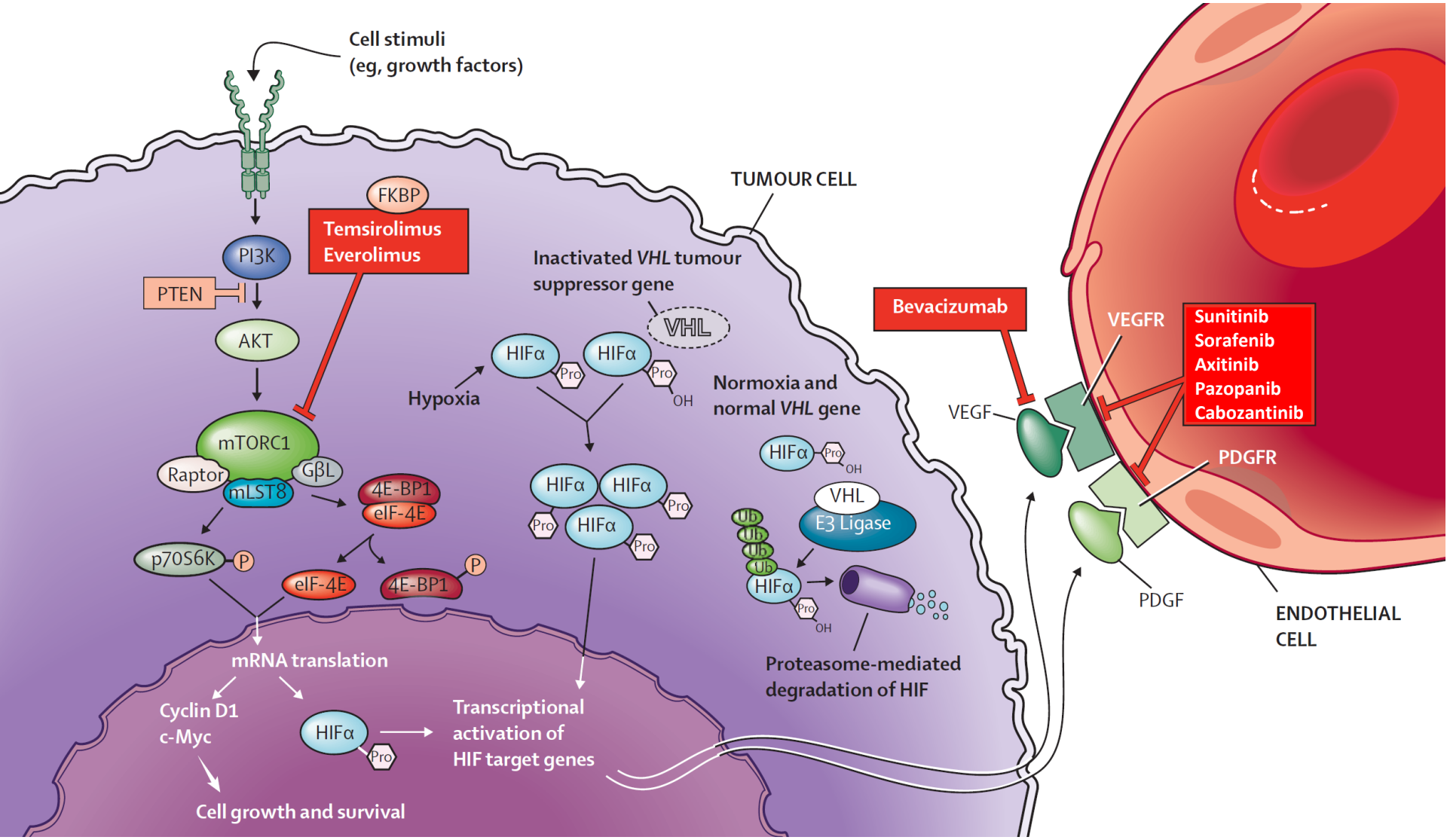
Human renal epithelial neoplasms



Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
Frequency	75%	5%	10%	5%	5%
Gene	*VHL*	*c-Met*	*FH*	*BHD*	*BHD*

Linehan WM, et al. J Urol. 2003;170:2163-2172

RCC therapy: Targeting VEGF at Multiple Levels

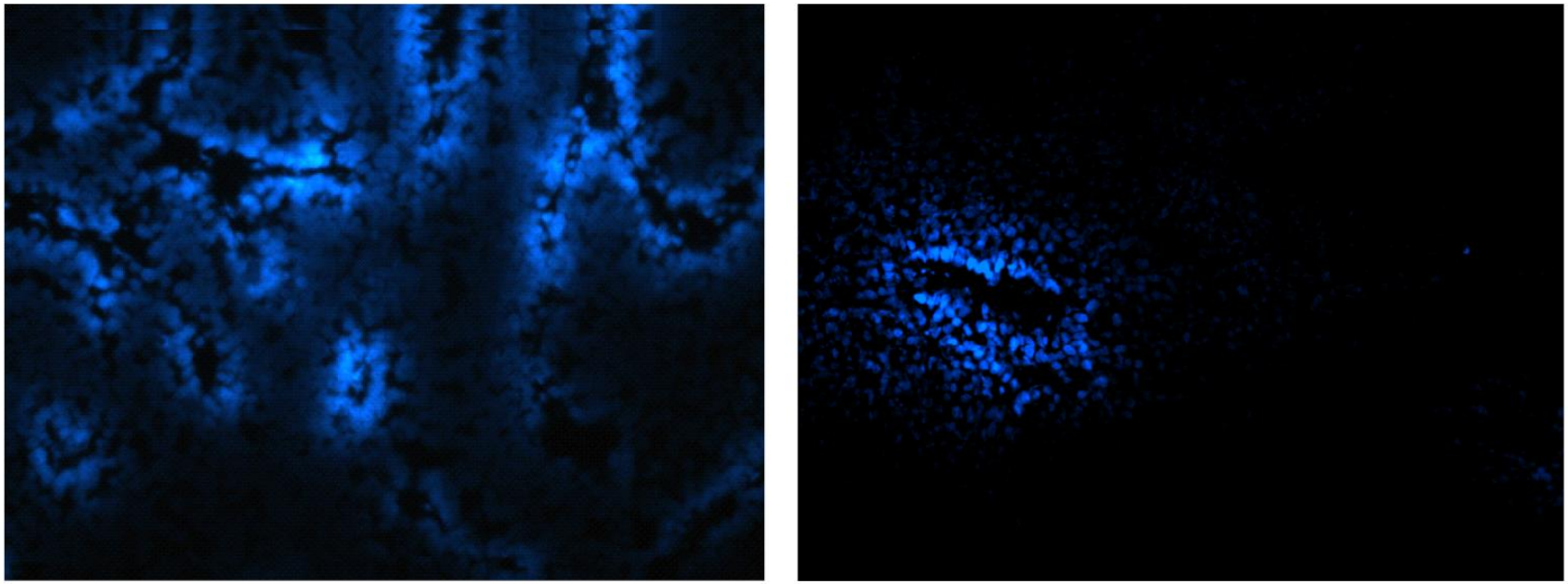


Modified from: Rini BI and Atkins MB. Lancet Oncol 2009; 10:992-1000

Angiogenesis Inhibition Through mTOR Blockade

Vehicle controls

Everolimus

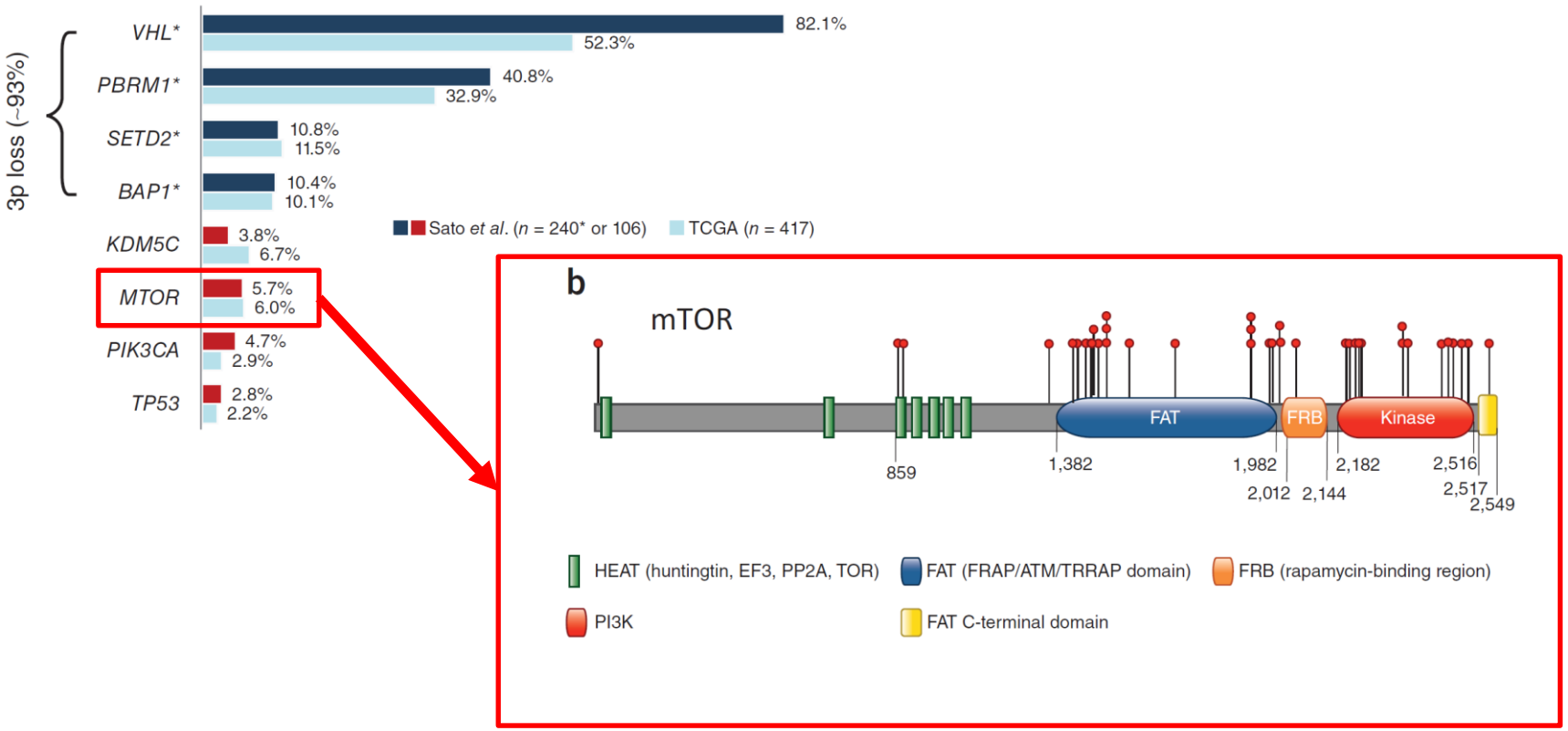


KB-31 (epidermoid carcinoma) xenografts

Significant reduction in microvessel density following Everolimus treatment in a primary human tumour (tumour edges shown) in a xenograft model

Lane HA, et al. Clin Cancer Res 2009; 15:1612-1622

mTOR is one of the most commonly mutated genes



The mutations in *mTOR* clustered in regions encoding the conserved FAT and kinase domains of the mTOR protein, where they likely destabilize the intrinsecally restricted conformation of the protein, thus leading to increased mTORC1 signalling

Hakimi AA, et al. Nat Genet 2013; 45:849-850

RCC is also a metabolic disease

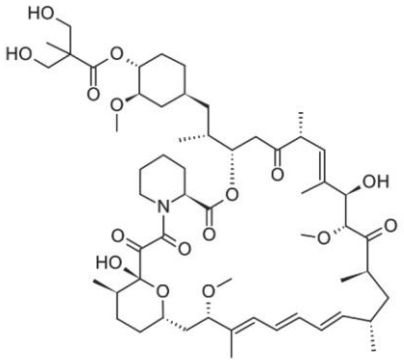
Integrated mRNA expression and proteomic data suggested a global metabolic shift that involved:
- **increased dependence on the pentose phosphate shunt,**
- **decreased activity of AMP-activated protein kinase (AMPK) and the Krebs cycle,**
- **increased glutamine transport and**
- **higher fatty acid production,**

which all correlate with disease aggressiveness

Allosteric mTORC1 inhibitors (i.e., Temsirolimus and Everolimus) thus affect this global metabolic shift

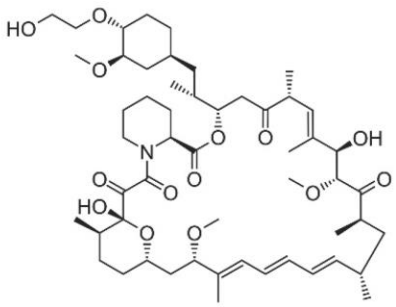
Hakimi AA, et al. Nat Genet 2013; 45:849-850

mTOR inhibitors for RCC



Temsirolimus

I linea nei pazienti «poor risk»



Everolimus

Dopo fallimento di terapia mirata anti-VEGF

1st line Temsirolimus in Poor-Risk RCC*

3/6 Poor-Risk Features:
- LDH > 1.5 x ULN
- Hb < LLN
- Ca^{++} (corrected) > 10 mg/dL
- KPS 60-70
- Initial diag to random < 1 yr
- Multiple sites of metastases mRCC

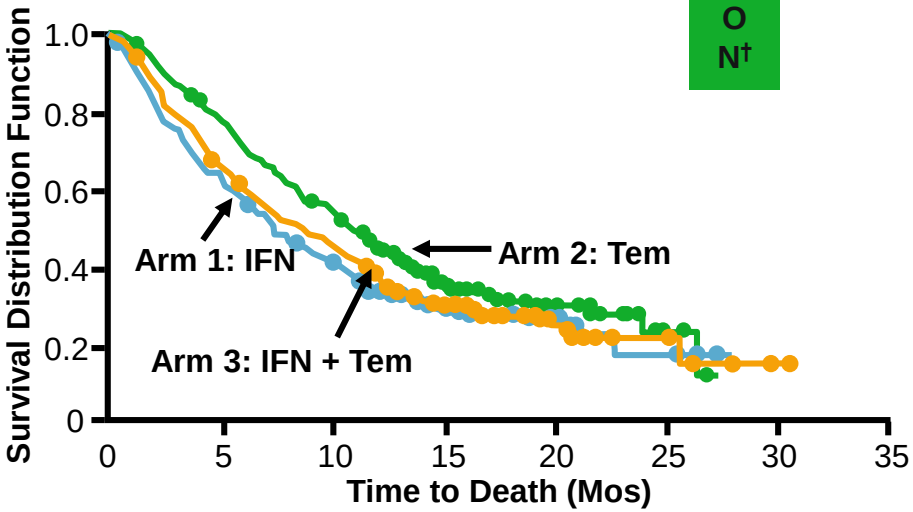
(N = 626)

RANDOMIZATION†

IFN-α 3 MU-18 MU (n = 207)
CR + PR: 4.8%
CR + PR + SD‡: 15.5%

Tem 25 mg QW (n = 209)
CR + PR: 8.6%
CR + PR + SD: 32.1%

IFN-α 3 MU-6 MU + **Tem** 15 mg QW (n = 210)
CR + PR: 8.1%
CR + PR + SD: 28.1%



Parameter	IFN Arm 1 (n = 207)	Tem Arm 2 (n = 209)	Tem + IFN Arm 3 (n = 210)
Median survival, Mos	7.3	10.9	8.4
Comparisons		Arm 2 to Arm 1	Arm 3 to Arm 1
Stratified log-rank *P*		.008	.70

*Modified MSKCC poor risk. †Stratified by country and nephrectomy status. ‡SD ≥ 24 wks.

Hudes G, et al. N Engl J Med. 2007; 356:2271-2281

Everolimus vs Placebo in Pretreated pts: RECORD-1

Patients with clear-cell mRCC progressing on or ≤ 6 mos after sorafenib and/or sunitinib (N = 410)

Randomized 2:1; stratified by MSKCC risk criteria and previous VEGFr-TKI therapy (1 vs 2)

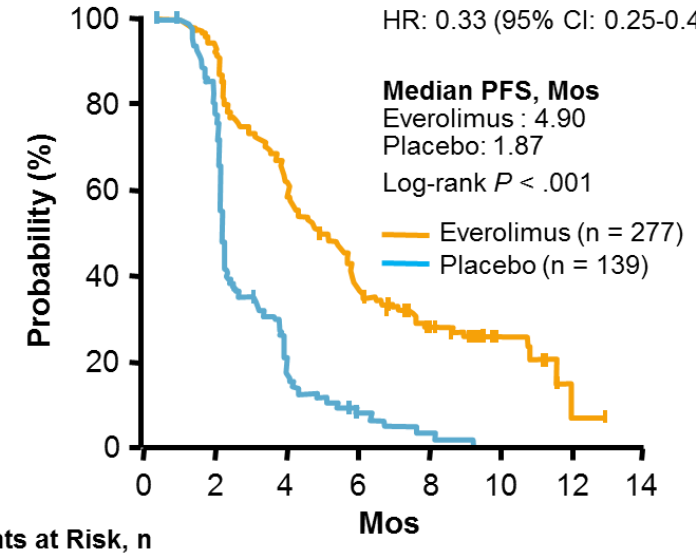
Everolimus 10 mg/day PO + **BSC** (n = 272)

Placebo + **BSC** (n = 138)

Treatment until progression or intolerance

- Treatment given in 28-day cycles
- Dose reduction for toxicity allowed

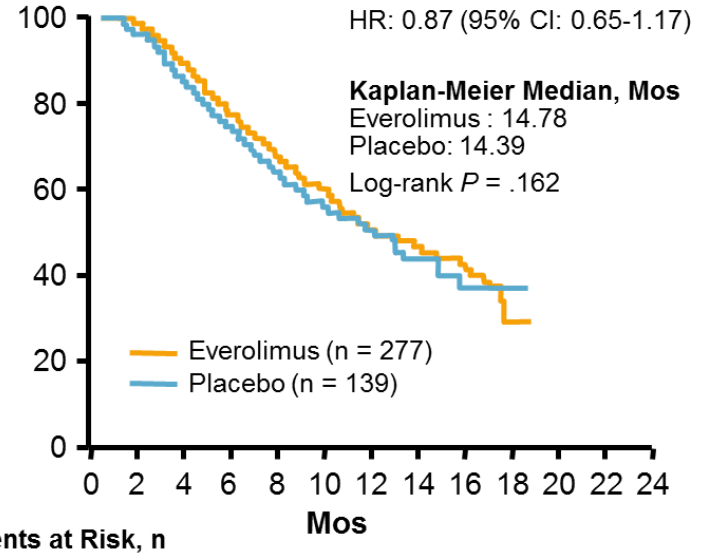
PFS
Central Radiology Review



Patients at Risk, n

Everolimus	277	192	115	51	26	10	1	0
Placebo	139	47	15	6	2	0	0	0

OS



Patients at Risk, n

Everolimus	277	267	240	204	164	155	131	101	61	30	6	0	0
Placebo	139	131	117	100	88	74	56	43	27	13	3	0	0

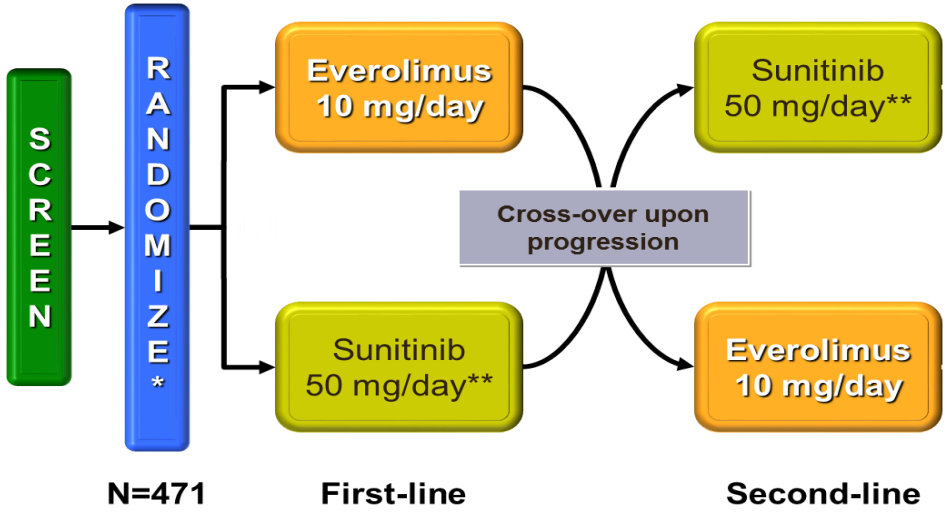
Motzer RJ, et al. Cancer 2010; 116:4256-4265

Main Adverse Events with mTOR Inhibitors

	Everolimus ($n = 274$) [33]		Temsirolimus ($n = 208$) [5]	
	All grades	Grades 3/4	All grades	Grade 3 or 4
Pulmonary				
Cough	30	0.7/0	26	1
Dyspnoea	24	6.2/1.5	28	9
NIP	9.9	2.6/0	2[a]	1[a]
Non-pulmonary				
Stomatitis	38	4.0/0.4	20	1
Asthenia	33	2.6/0.7	51	11
Fatigue	31	5.5/0	NA	NA
Diarrhoea	30	1.5/0	27	1
Rash	29	1.1/0	47	4
Nausea	26	1.5/0	37	2
Anorexia	25	1.5/0	32	3
Peripheral oedema	25	0.7/0	27	2
Vomiting	20	2.2/0	19	2
Pyrexia	20	0.7/0	24	1
Mucosal inflammation	19	1.5/0	NA	NA
Headache	19	0.7/0.4	15	1
Abdominal pain	9.5	3.3/0	21	4
Laboratory investigations				
Anaemia (decreased haemoglobin)	38	9.5/0.7	45	20
Hypercholesterolaemia	20	3.3/0	24	1
Hypertriglyceridaemia	15	1.1/0	27	3
Hyperglycaemia	12	6.2/0	26	11
Raised creatinine	9.5	1.1/0	14	3
Thrombocytopaenia	6.6	1.5/0	14	1

Hudes G, et al. N Engl J Med. 2007; 356:2271-2281
Motzer RJ, et al. Cancer 2010; 116:4256-4265

VEGFR-TKI/mTORi Sequence: RECORD-3 trial



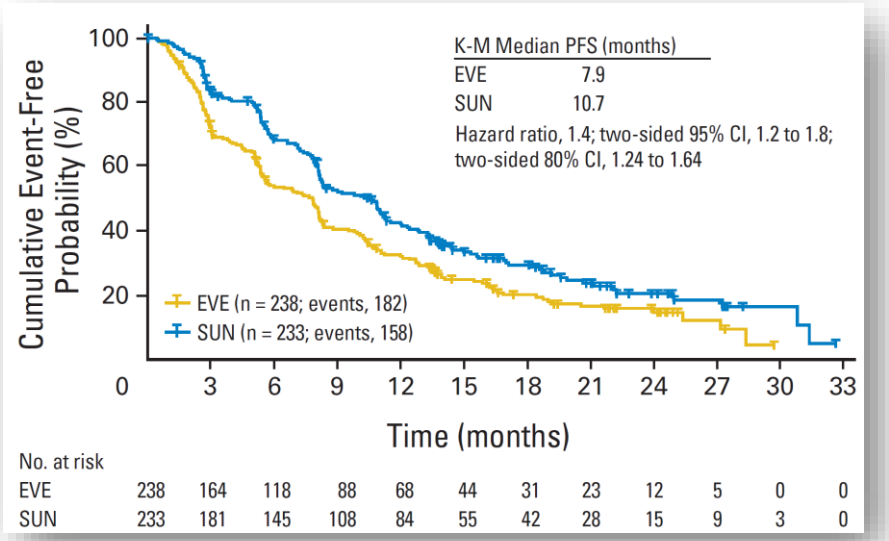
Study endpoints

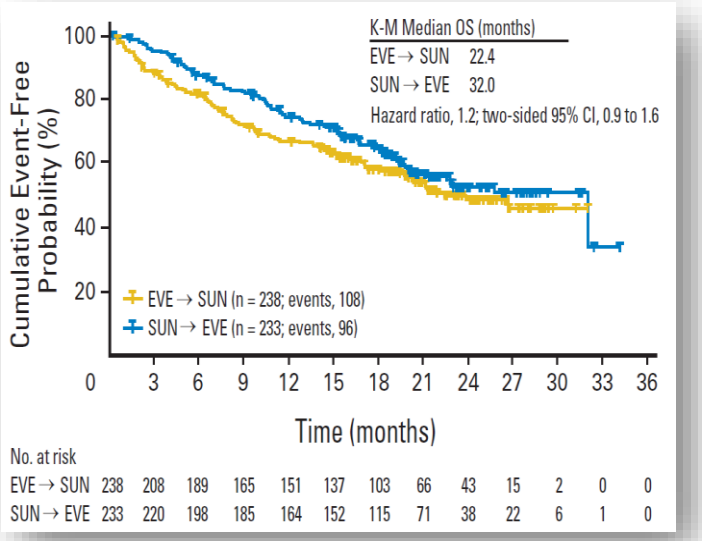
Primary
- PFS 1st-line

Secondary
- Combined PFS
- ORR 1st-line
- OS
- Safety

Median follow-up 22.7 months

*Stratified by MSKCC prognostic factors; **4 weeks on, 2 weeks off.





Motzer RJ, et al. J Clin Oncol 2014; 32:2765-2772

2nd line Temsirolims vs Sorafenib: INTORSECT trial

Patients with mRCC and PD on 1st-line sunitinib

(N=512)

Stratification factors:

- Duration of sunitinib therapy (≤ or >6 mo)
- MSKCC risk group
- Histology (clear cell or non–clear cell)
- Nephrectomy status

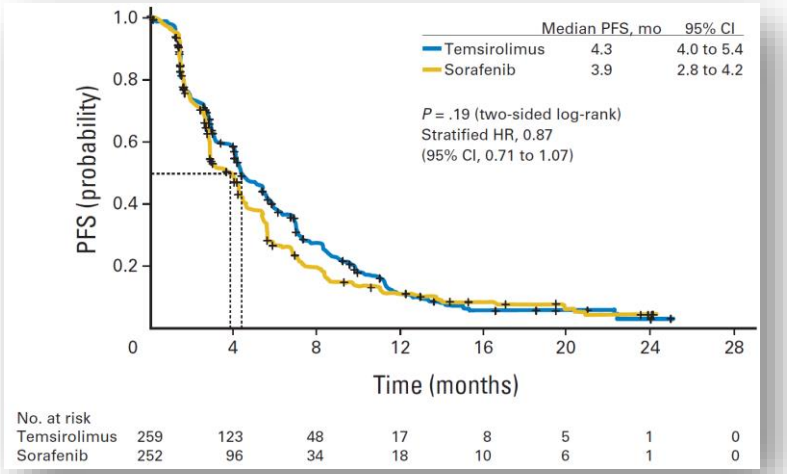
→ RANDOMIZE (1:1)

- **Temsirolimus** 25 mg IV weekly (n=259)
- **Sorafenib** 400 mg oral BID (n=253)

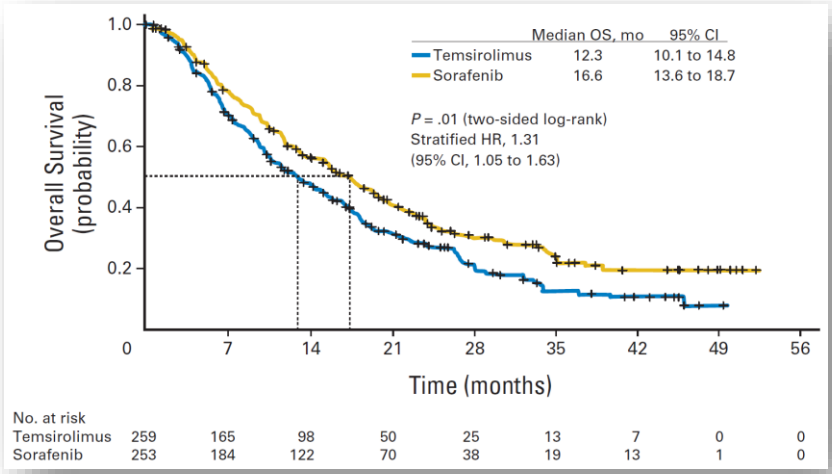
→ Treat until PD, unacceptable toxicity, or discontinuation for any other reason

N=512
112 sites in 20 countries

PFS



OS



Motzer RJ, et al. Cancer 2010; 116:4256-4265

The NEW ENGLAND JOURNAL of MEDICINE

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Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

ABSTRACT

BACKGROUND

Nivolumab, a programmed death 1 (PD-1) checkpoint inhibitor, was associated with encouraging overall survival in uncontrolled studies involving previously treated patients with advanced renal-cell carcinoma. This randomized, open-label, phase 3 study compared nivolumab with everolimus in patients with renal-cell carcinoma who had received previous treatment.

METHODS

A total of 821 patients with advanced clear-cell renal-cell carcinoma for which they had received previous treatment with one or two regimens of antiangiogenic therapy were randomly assigned (in a 1:1 ratio) to receive 3 mg of nivolumab per kilogram of body weight intravenously every 2 weeks or a 10-mg everolimus tablet orally once daily. The primary end point was overall survival. The secondary end points included the objective response rate and safety.

RESULTS

The median overall survival was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The hazard ratio for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; P=0.002), which met the prespecified criterion for superiority (P≤0.0148). The objective response rate was greater with nivolumab than with everolimus (25% vs. 5%; odds ratio, 5.98 [95% CI, 3.68 to 9.72]; P<0.001). The median progression-free survival was 4.6 months (95% CI, 3.7 to 5.4) with nivolumab and 4.4 months (95% CI, 3.7 to 5.5) with everolimus (hazard ratio, 0.88; 95% CI, 0.75 to 1.03; P=0.11). Grade 3 or 4 treatment-related adverse events occurred in 19% of the patients receiving nivolumab and in 37% of the patients receiving everolimus; the most common event with nivolumab was fatigue (in 2% of the patients), and the most common event with everolimus was anemia (in 8%).

CONCLUSIONS

Among patients with previously treated advanced renal-cell carcinoma, overall survival was longer and fewer grade 3 or 4 adverse events occurred with nivolumab than with everolimus. (Funded by Bristol-Myers Squibb; CheckMate 025 ClinicalTrials.gov number, NCT01668784.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Motzer at Memorial Sloan Kettering Cancer Center, Memorial Hospital, 1275 York Ave., New York, NY 10021, or at motzerr@mskcc.org; or to Dr. Sharma at M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or at padsharma@mdanderson.org.

*A complete list of investigators in the CheckMate 025 study is provided in the Supplementary Appendix, available at NEJM.org

This article was published on September 25, 2015, and updated on January 14, 2016, at NEJM.org.

N Engl J Med 2015;373:1803-13.
DOI: 10.1056/NEJMoa1510665

ORIGINAL ARTICLE

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*

ABSTRACT

BACKGROUND

Cabozantinib is an oral, small-molecule tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) as well as MET and AXL, each of which has been implicated in the pathobiology of metastatic renal-cell carcinoma or in the development of resistance to antiangiogenic drugs. This randomized, open-label, phase 3 trial evaluated the efficacy of cabozantinib, as compared with everolimus, in patients with renal-cell carcinoma that had progressed after VEGFR-targeted therapy.

METHODS

We randomly assigned 658 patients to receive cabozantinib at a dose of 60 mg daily or everolimus at a dose of 10 mg daily. The primary end point was progression-free survival. Secondary efficacy end points were overall survival and objective response rate.

RESULTS

Median progression-free survival was 7.4 months with cabozantinib and 3.8 months with everolimus. The rate of progression or death was 42% lower with cabozantinib than with everolimus (hazard ratio, 0.58; 95% confidence interval [CI] 0.45 to 0.75; P<0.001). The objective response rate was 21% with cabozantinib and 5% with everolimus (P<0.001). A planned interim analysis showed that overall survival was longer with cabozantinib than with everolimus (hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P=0.005) but did not cross the significance boundary for the interim analysis. Adverse events were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib and in 25% of those who received everolimus. Discontinuation of study treatment owing to adverse events occurred in 9% of the patients who received cabozantinib and in 10% of those who received everolimus.

CONCLUSIONS

Progression-free survival was longer with cabozantinib than with everolimus among patients with renal-cell carcinoma that had progressed after VEGFR-targeted therapy. (Funded by Exelixis; METEOR ClinicalTrials.gov number, NCT01865747.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Choueiri at the Dana–Farber Cancer Institute, 450 Brookline Ave. (DANA 1230), Boston, MA 02215, or at toni_choueiri@dfci.harvard.edu.

*A complete list of investigators in the Metastatic RCC Phase 3 Study Evaluating Cabozantinib versus Everolimus (METEOR) is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 25, 2015, at NEJM.org

N Engl J Med 2015;373:1814-23.
DOI: 10.1056/NEJMoa1510016

Cabozantinib vs Everolimus: METEOR

Advanced RCC (N=658)
- Clear cell component
- Progression within 6 months of prior VEGFR TKI
- No limit to the number of prior therapies
- PD-1 checkpoint inhibitors allowed
- Treated brain metastases allowed

1:1

Stratification
- MSKCC[1] risk groups: favorable, intermediate, poor
- Prior VEGFR TKIs: 1 or ≥2

Cabozantinib
60 mg qd PO

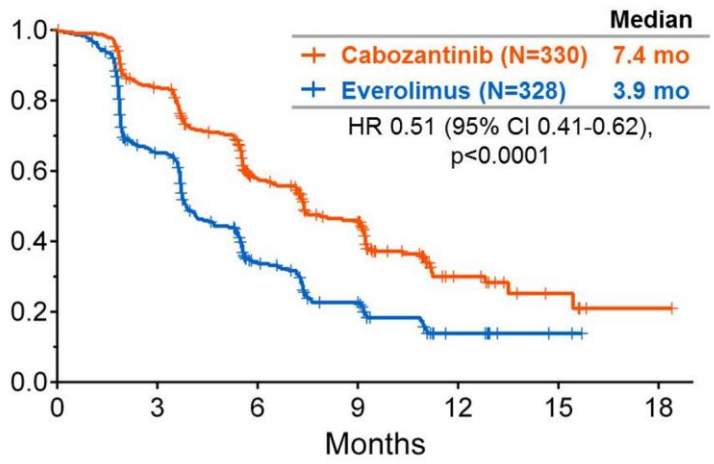
Everolimus
10 mg qd PO

Tumor assessment every 8 weeks (RECIST v1.1)

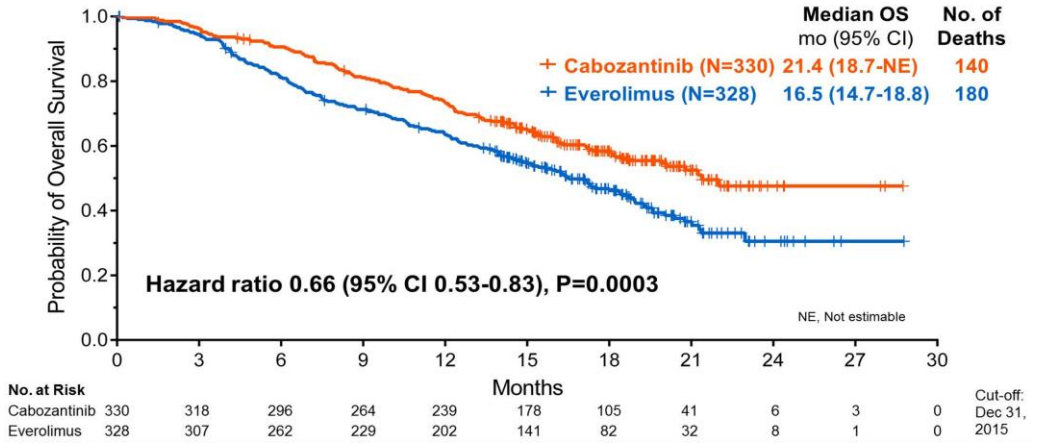
Treatment until loss of clinical benefit or intolerable toxicity

No crossover allowed

Progression-Free Survival per IRC[1]



Overall Survival



Chouieri TK, et al. Lancet Oncol 2016; 17:917-927

Nivolumab vs Everolimus: Checkmate 025

Enrolled patients

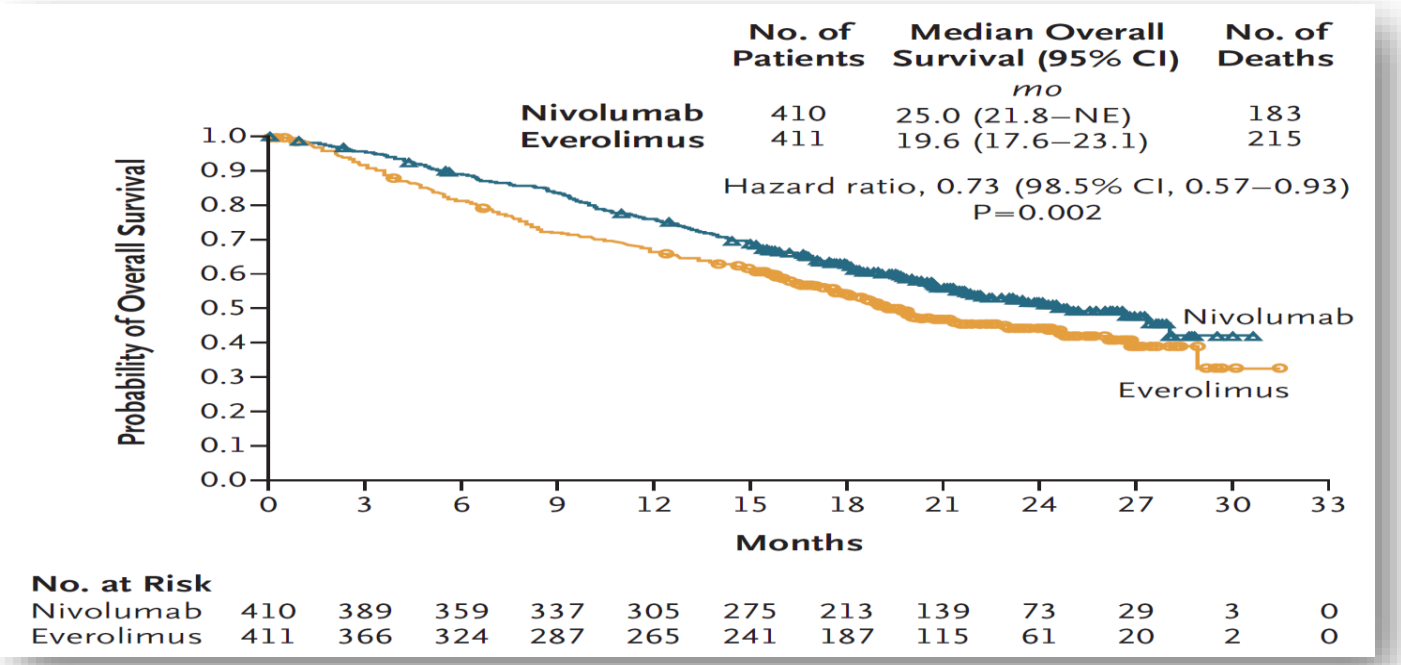
- Previously treated advanced or metastatic clear-cell RCC
- 1 or 2 prior anti-angiogenic treatments

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



Motzer RJ, et al. N Engl J Med 2015; 373:1803-1813

mTOR Inhibitors: Future Perspectives in RCC

1. Investigation in Other Histologies
2. Molecular Predictive Factors
3. Combination with Other Agents

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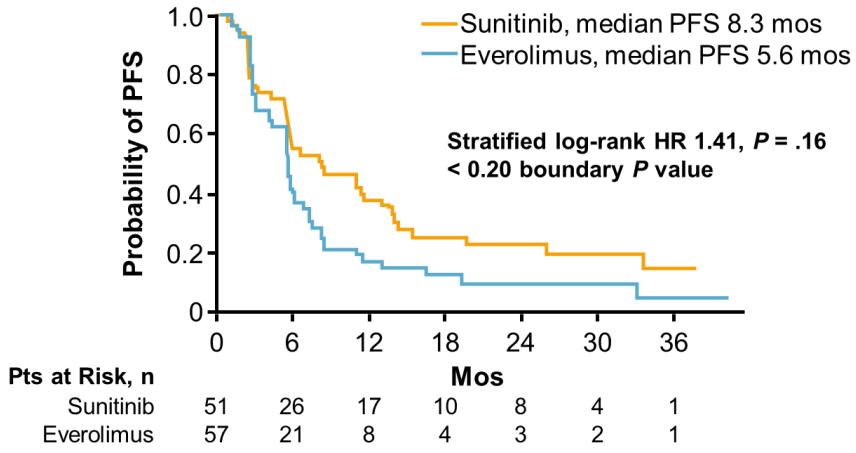
Non Clear-Cell Histology: the ASPEN trial

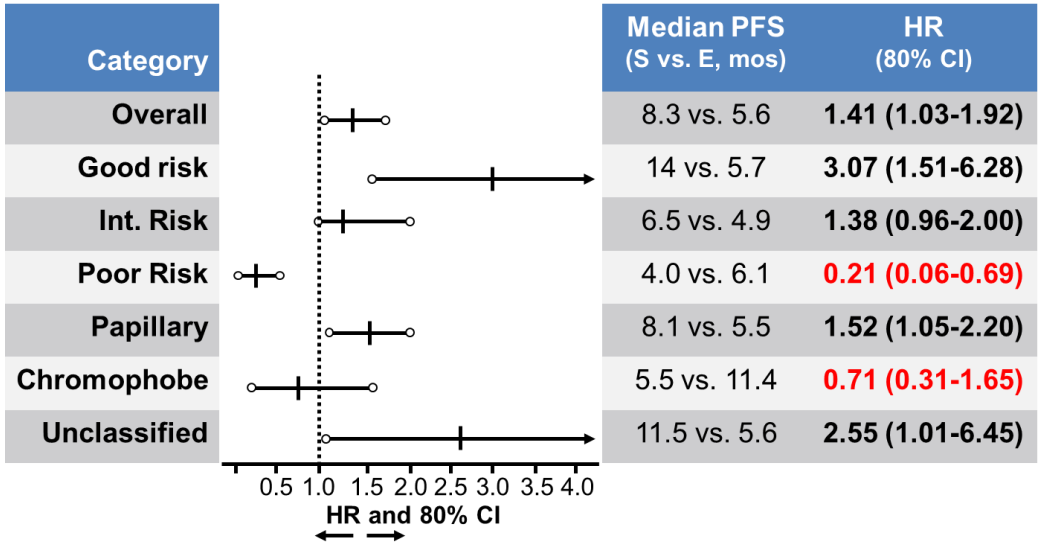
Stratified by histology (papillary vs chromophobe vs unclassified), MSKCC risk group

Untreated pts with metastatic NCRCC, KPS ≥ 60 (N = 108)

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

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



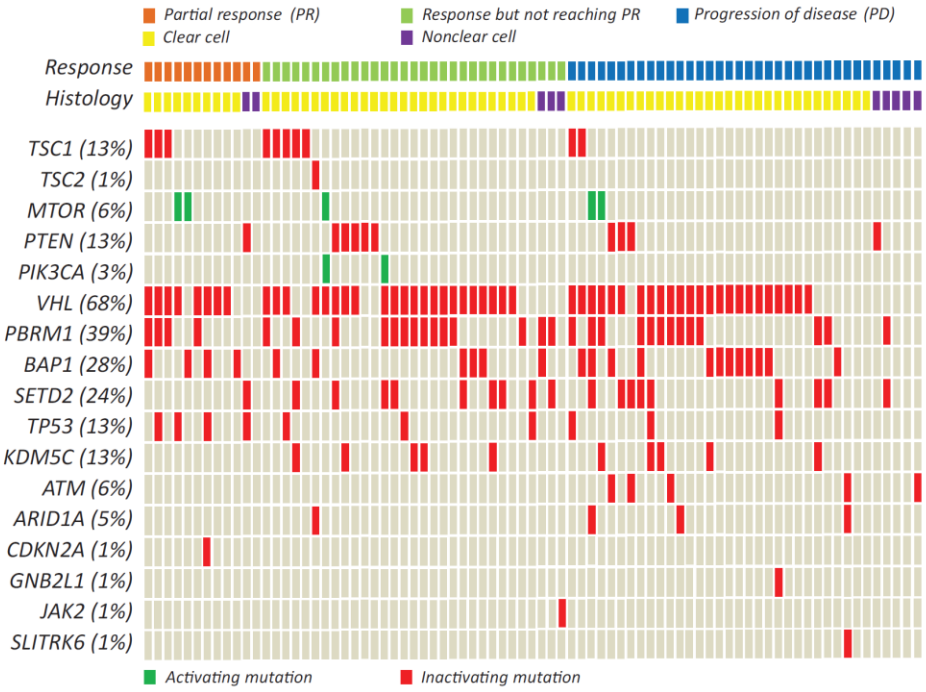


Armstrong AJ, et al. Lancet Oncol 2016; 17:378-388

mTOR Inhibitors: Future Perspectives in RCC

1. Investigation in Other Histologies
2. Molecular Predictive Factors
3. Combination with Other Agents

Looking for Predictive Factors



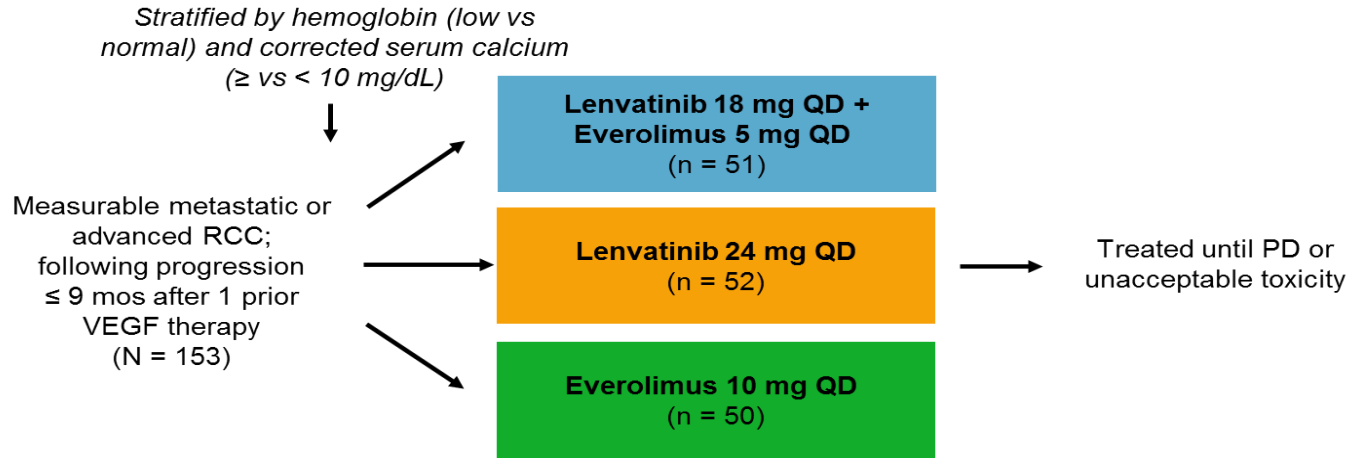
Patients, %	MTOR, TSC1 and TSC2 mutation status			
	CR/PR >6 months, n=12	Primary refractory, n=36	P value	OR
Mutation detected	42	11	0.03	5.28
Mutation not detected	58	89		

Kwiatkowski DJ, et al. Clin Cancer Res 2016; 22:2445-2452

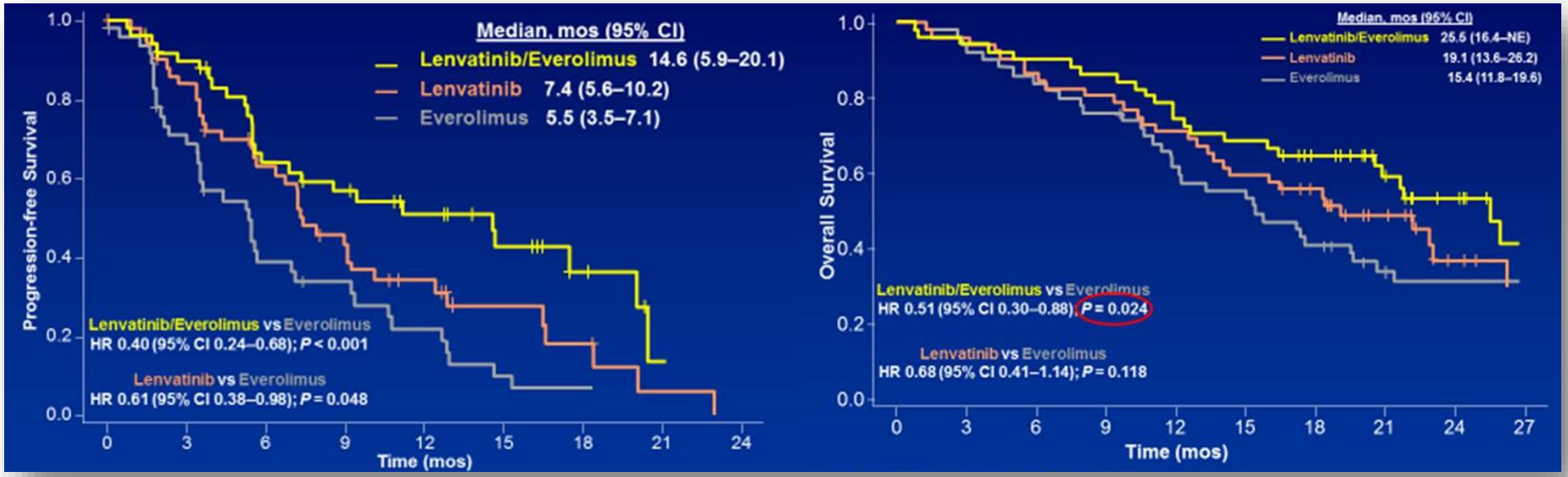
mTOR Inhibitors: Future Perspectives in RCC

1. Investigation in Other Histologies
2. Molecular Predictive Factors
3. Combination with Other Agents

Combination: Everolimus + Lenvatinib



- Primary endpoint: PFS with lenvatinib ± everolimus vs everolimus alone
- Secondary endpoints: PFS with combination vs lenvatinib alone, ORR, OS, safety/tolerability



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

Combination: Everolimus + Lenvatinib

	Nivolumab[1]	Cabozantinib[2]	Lenvatinib[3]
RR (%)	25	21	35
PFS (mos)	4.6	7.4	12.8
OS (mos)	25	21.4	25.5
Dose reductions (%)	NA	60	71
Discontinuation due to AEs (%)	8	9	24
Toxicity	G3 18% G4 1%	G3/4 68%	G3 57% G4 14%

1. Motzer RJ, et al. N Engl J Med 2015; 373:1803-1813.
2. Chouieri TK, et al. Lancet Oncol 2016; 17:917-927.
3. Motzer RJ, et al. Lancet Oncol 2015; 16:1473-1482.

Sacro Cuore Don Calabria

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Numero per la Cura del Tumore

Cancer Care Center Negrar - Verona

GRAZIE PER L'ATTENZIONE

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