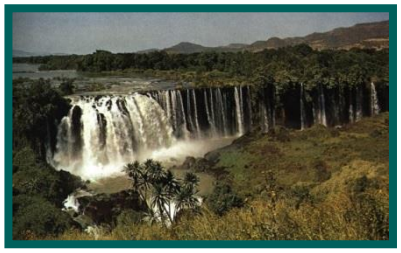
SISTEMA SANITARIO REGIONALE

ASL ROMA 2



LA CHIRURGIA UROLOGICA ROMANA 2018

27 anni di chirurgia urologica all'Ospedale Sandro Pertini

TUMORI DEL RENE

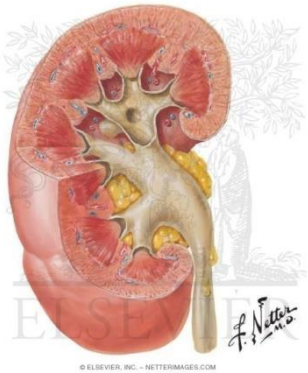
TRATTAMENTO ONCOLOGICO

GIULIANA D'AURIA

UOC Oncologia Ospedale Pertini

Roma, 26 – 27 Gennaio 2018

I NUMERI DELLA PATOLOGIA

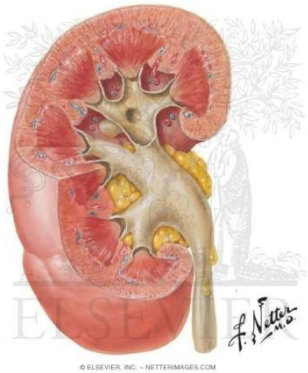


- ✓10° posto in termini di frequenza
- ✓Piu frequente negli uomini
- ✓Circa 13000 nuovi casi nel 2017
- ✓Sopravvivenza a 5 anni intorno al 70%
- ✓Prevalenza anamnestica circa 130000 persone (4 posto)

20-30% circa metastasi sincrone o metacrone

25-50% dei pazienti con ricaduta dopo chirurgia

I NUMERI DELLA PATOLOGIA



- ✓**SITI di metastasi:** polmoni, LN, fegato, SNC, osso
- ✓**5-years Survival:** 57% tra 1987-89
  74% tra 2006-12

Diagnosi precoce

Aumento possibilità terapeutiche

LA TERAPIA DELLA MALATTIA AVANZATA

RUOLO DELLA NEFRECTOMIA

✓**Chirurgia vs chirurgia + IFN: OS 11.1 mesi vs 8.1 mesi**

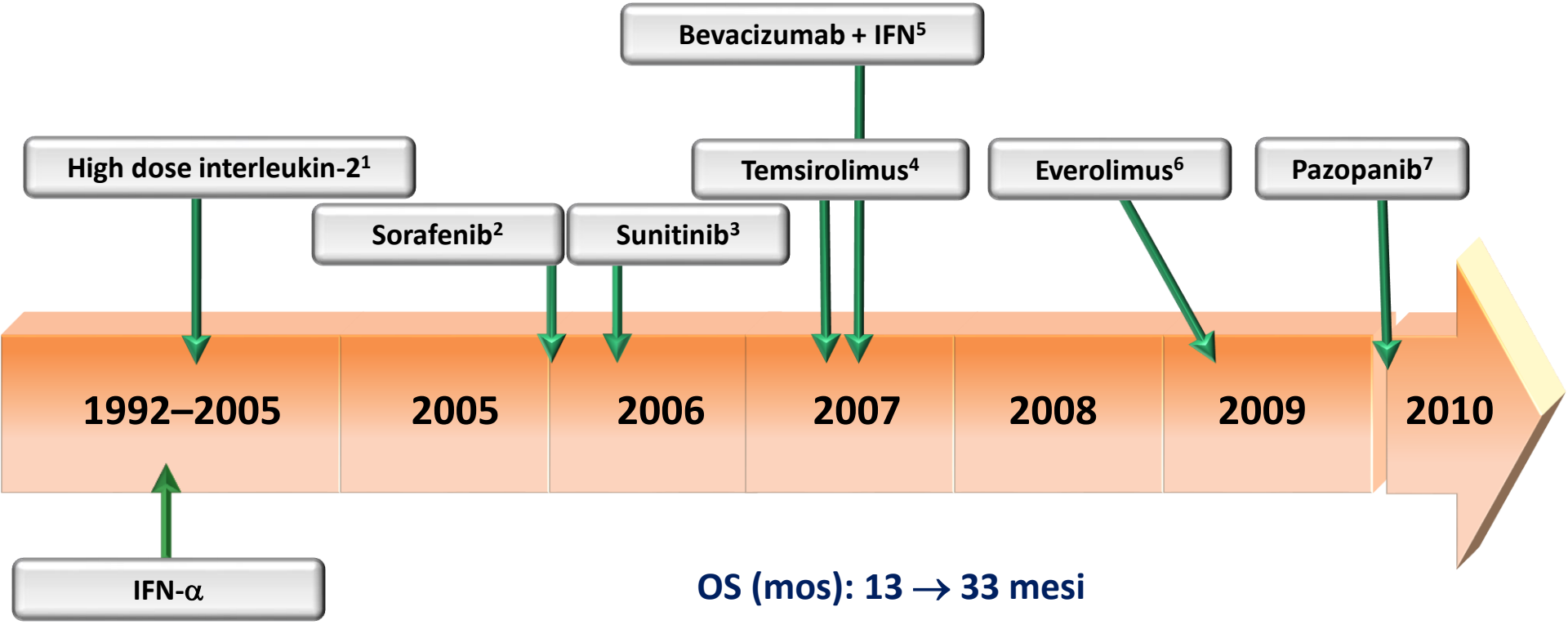
Flanigan, NEJM 2011
Mickisch, Lancet 2001

✓**Chirurgia vs chirurgia + nuovi farmaci: OS 17.1 mesi vs 7.7 mesi**

Hanna, JCO 2016
Heng Eur Urol 2014

CHIRURGIA DELLE METASTASI

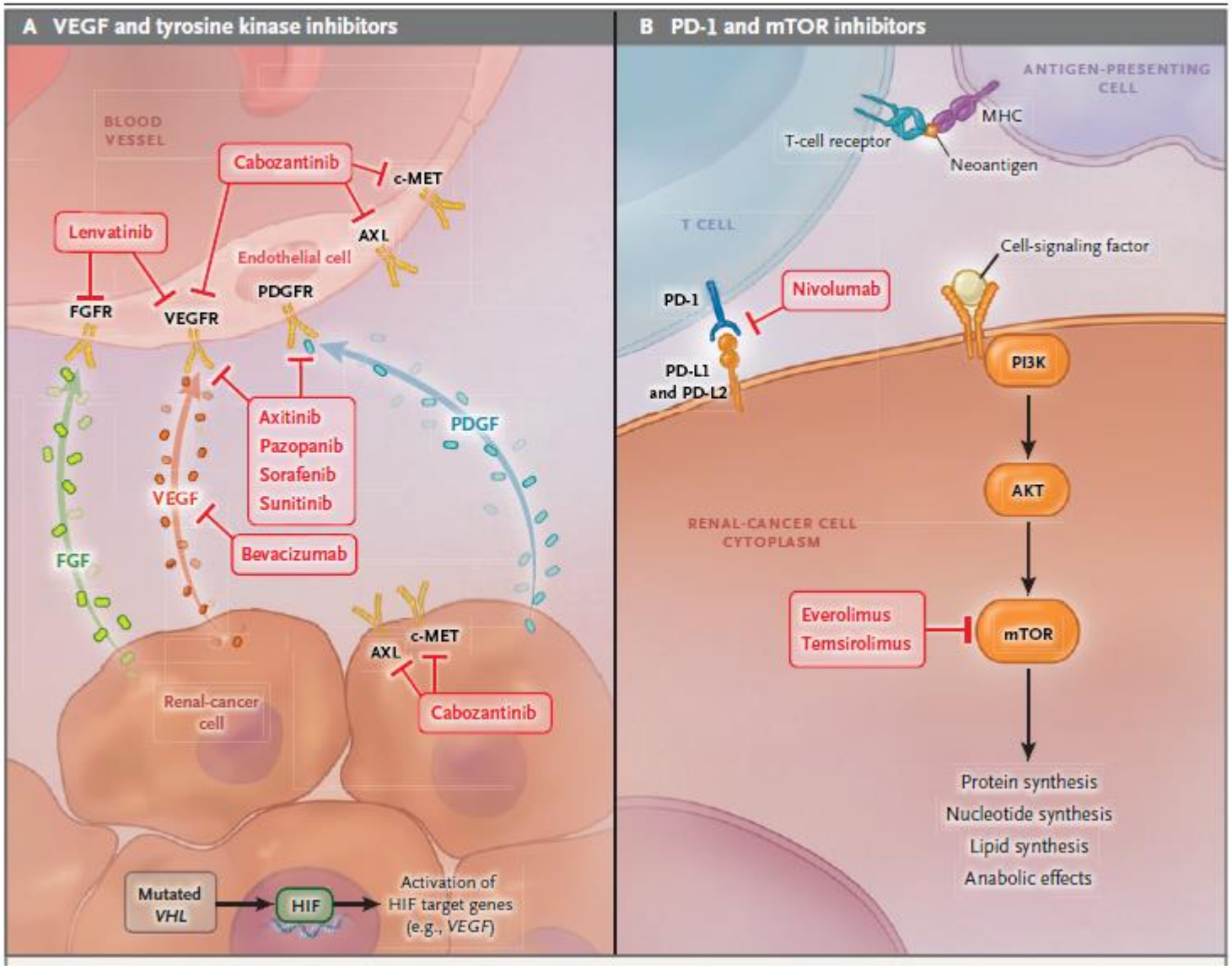
Treatment options for RCC have been revolutionized in a short period of time…



OS (mos): 13 → 33 mesi

1. Fyfe G *et al. J Clin Oncol* 1995; 13: 688-696.
2. Escudier B *et al. N Engl J Med* 2007; 356: 125-134.
3. Sutent. Summary of Product Characteristics. 2010.
4. Hudes G *et al. N Engl J Med* 2007; 356: 2271-2281.
5. Escudier B *et al. Lancet* 2007; 370: 2103-2211.
6. Afinitor. Summary of Product Characteristics. 2010.
7. Sternberg CN *et al. J Clin Oncol* 2010; 28: 1061-1068

MECCANISMI MOLECOLARI

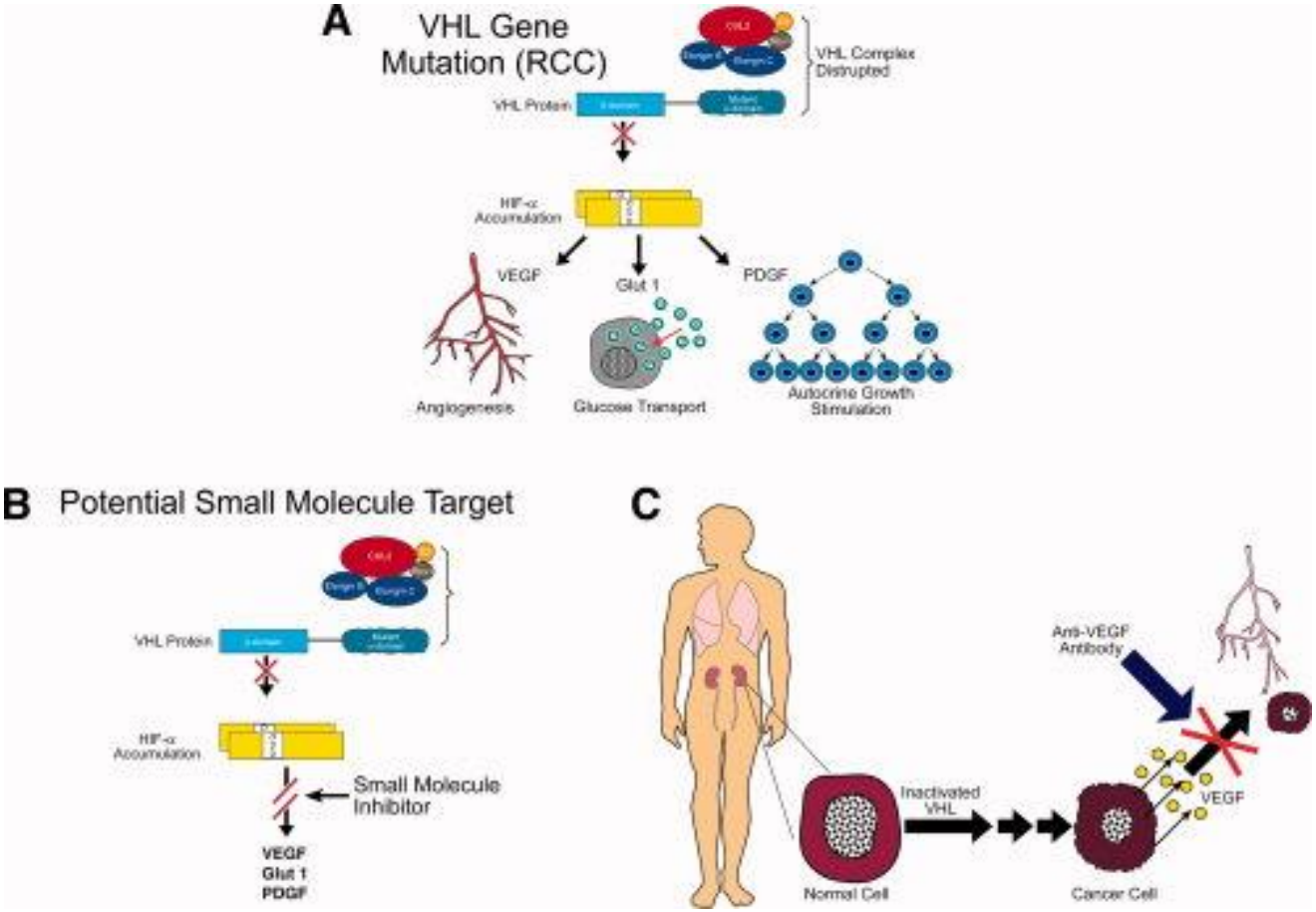


Motzer, NEJM 2017

MECCANISMI MOLECOLARI

Clear cell

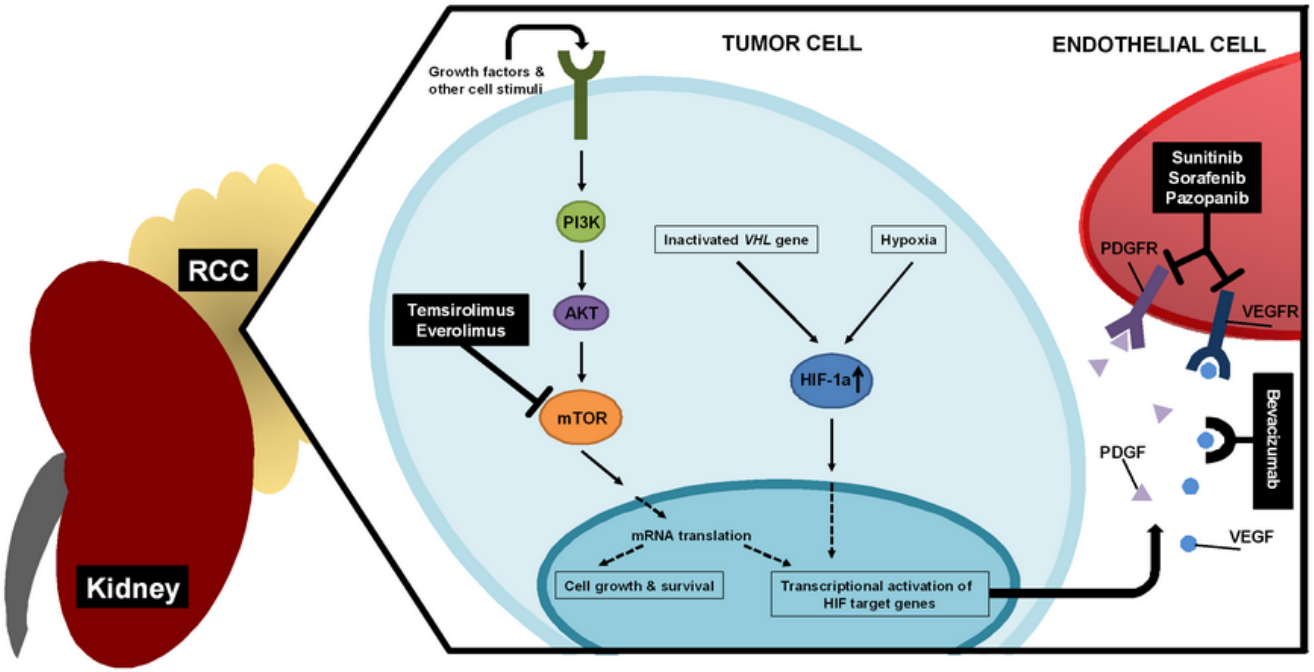
Von Hippel Lindau gene Mutation ~50%



MECCANISMI MOLECOLARI

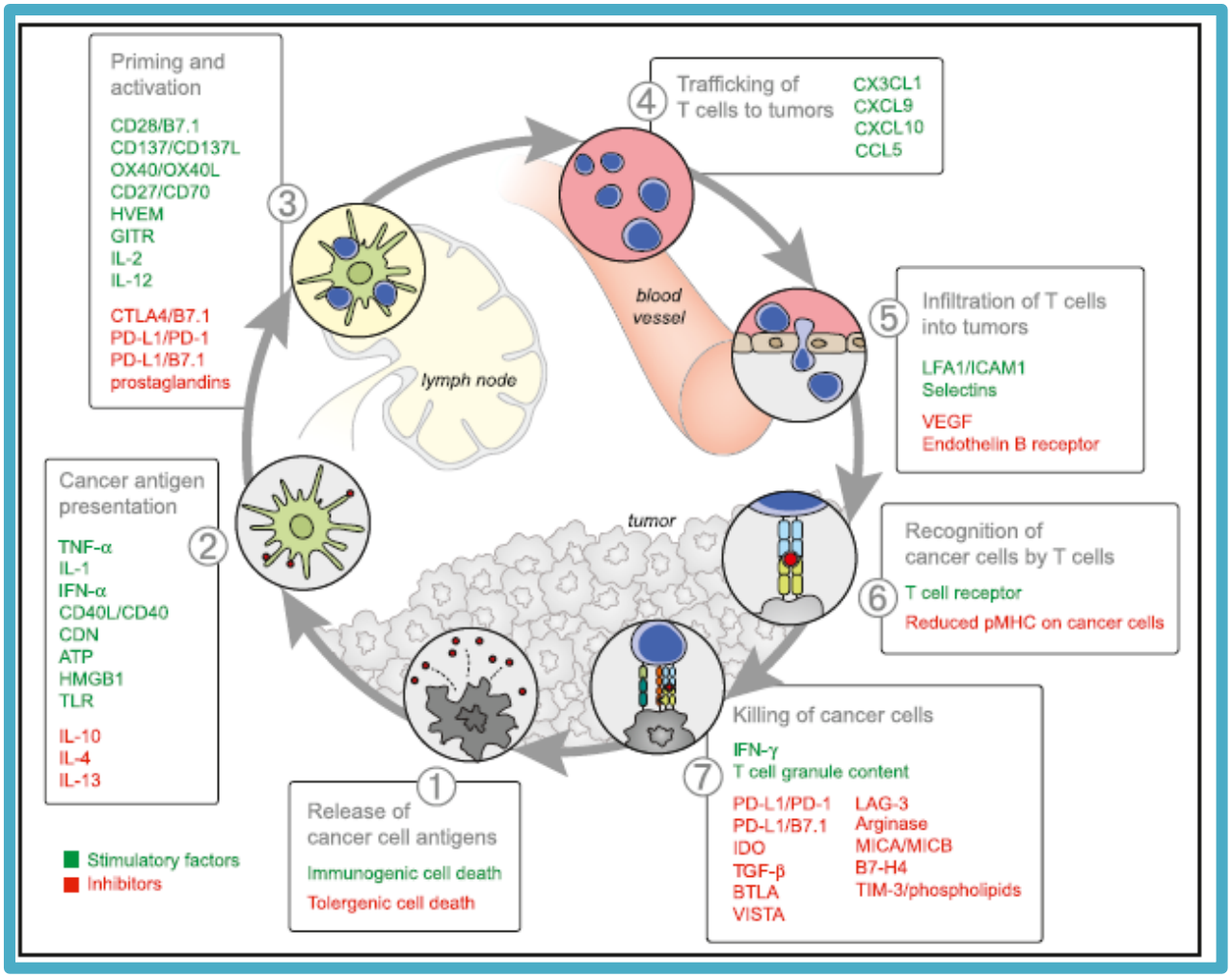
Clear cell

mTOR mutation



MECCANISMI MOLECOLARI

IMMUNOTERAPIA

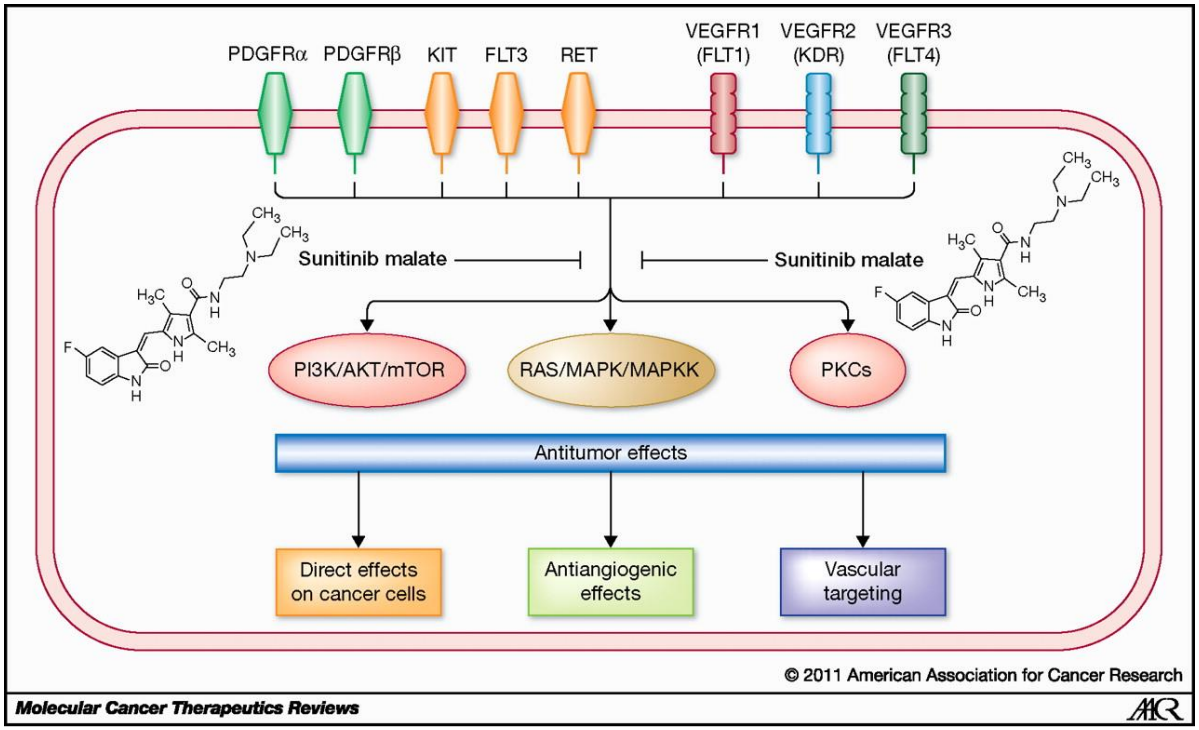


LA TERAPIA DI I LINEA

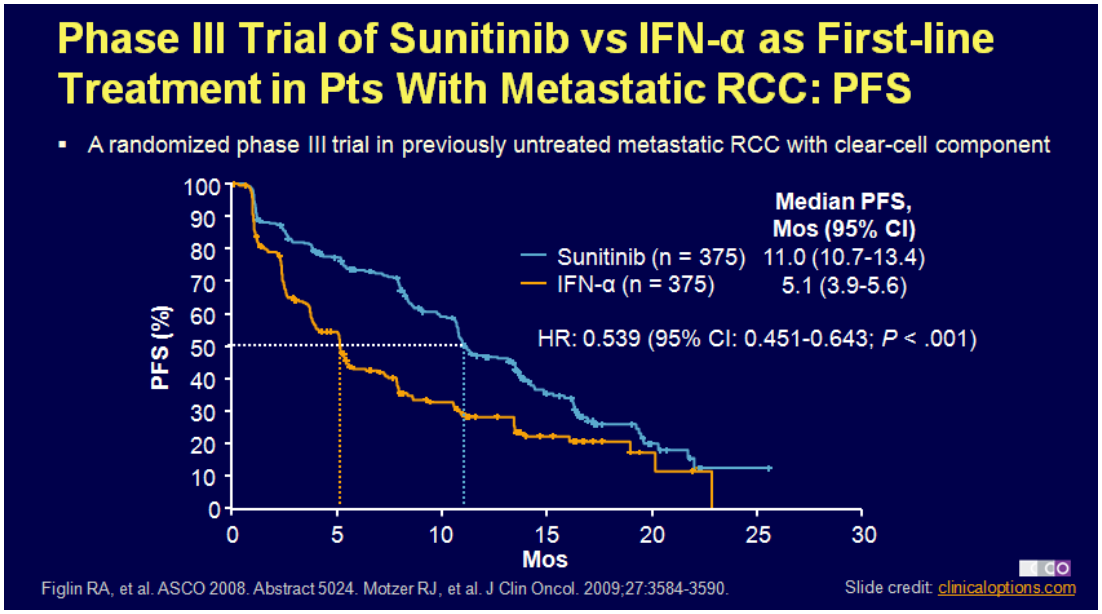
- ✓SUNITINIB
- ✓PAZOPANIB
- ✓TEMSIROLIMUS
- ✓BEVACIZUMAB+ IFN

LA TERAPIA DI I LINEA

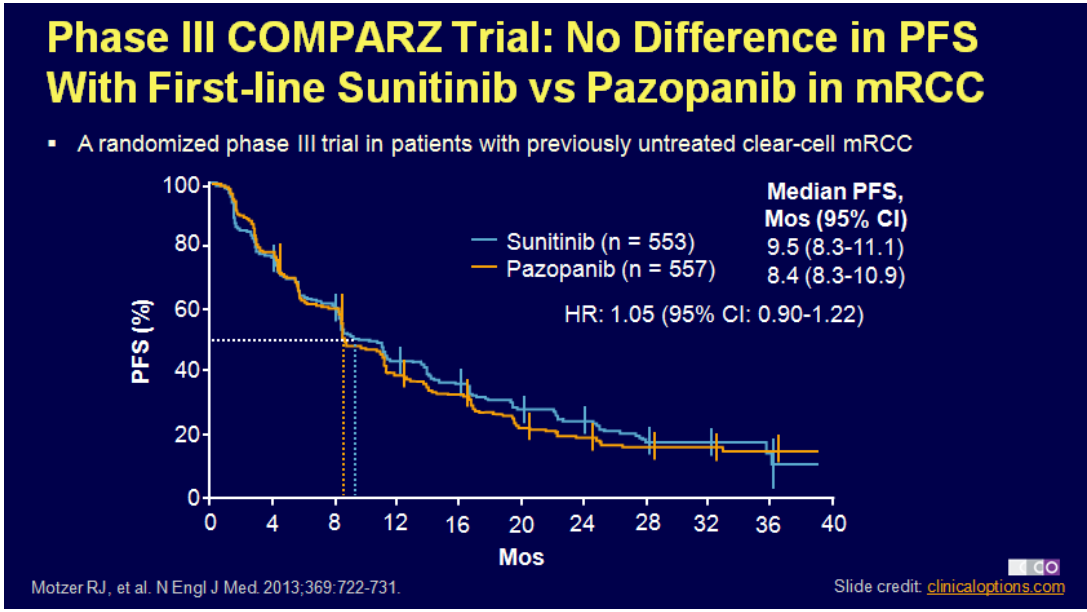
- ✓SUNITINIB
- ✓PAZOPANIB



LA TERAPIA DI I LINEA



Overall survival ~28 months



TOSSICITA'

Table 2. Selected Toxic Effects from Approved Systemic Therapies in Advanced Renal-Cell Carcinoma.

Class and Drug*	Toxic Effects
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Motzer, NEJM 2017

LA TERAPIA DI II LINEA

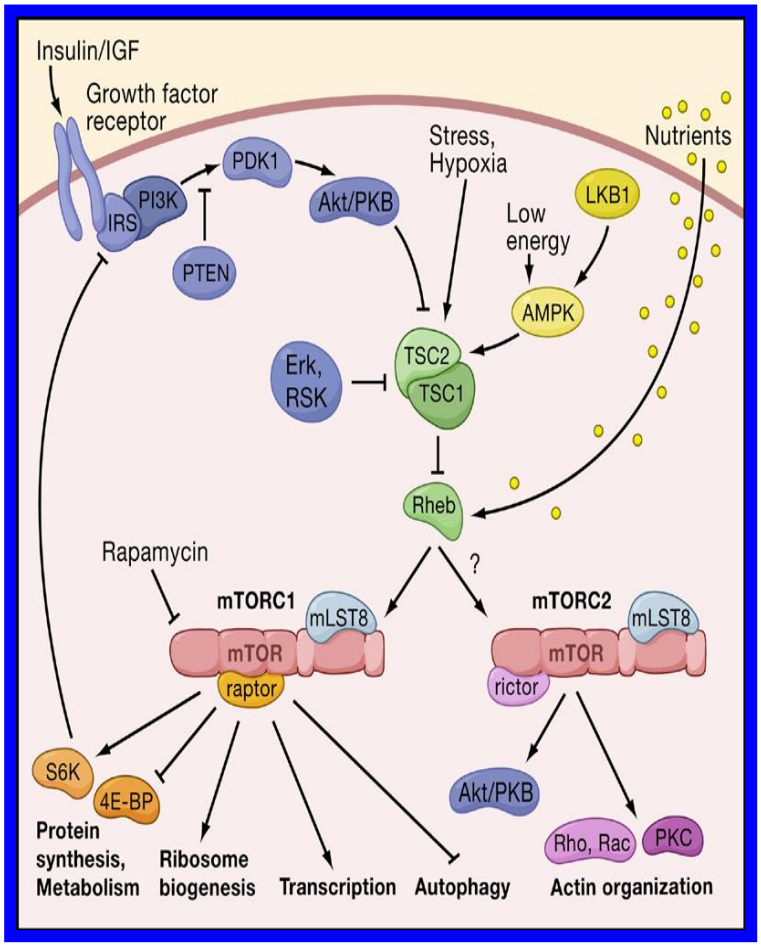
2017

- ✓Everolimus
- ✓Axitinib
- ✓Nivolumab

→

- TKI targeting VEGF + others (cabozantinib)
- VEGFi + mTORi (lenvatinib + everolimus)

mTOR e angiogenesi

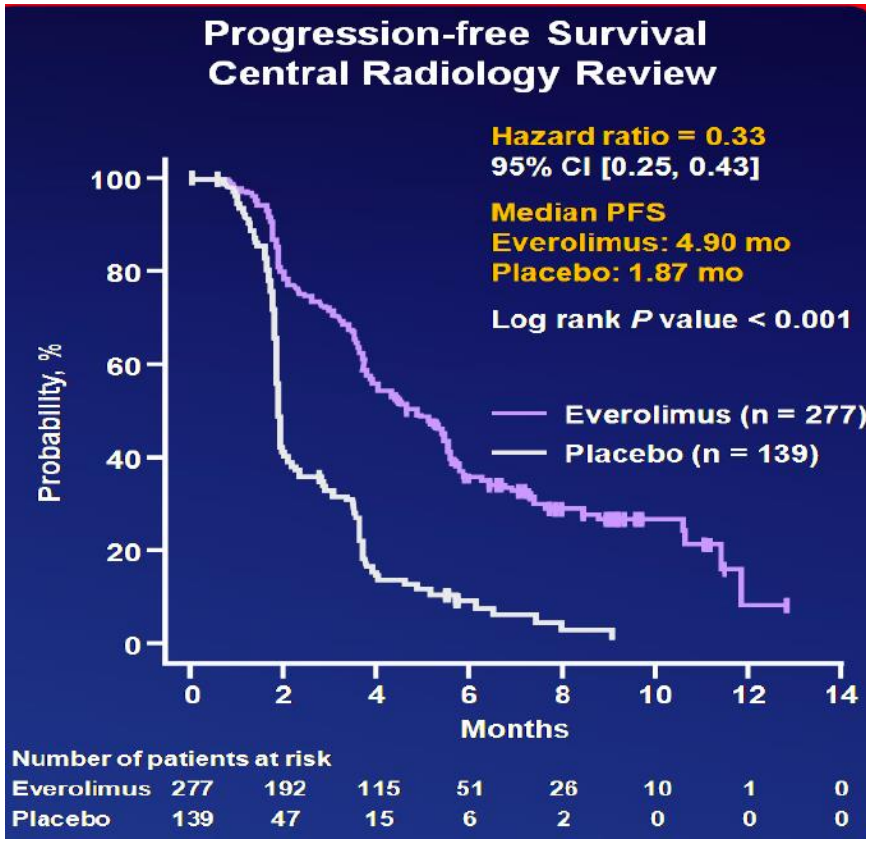


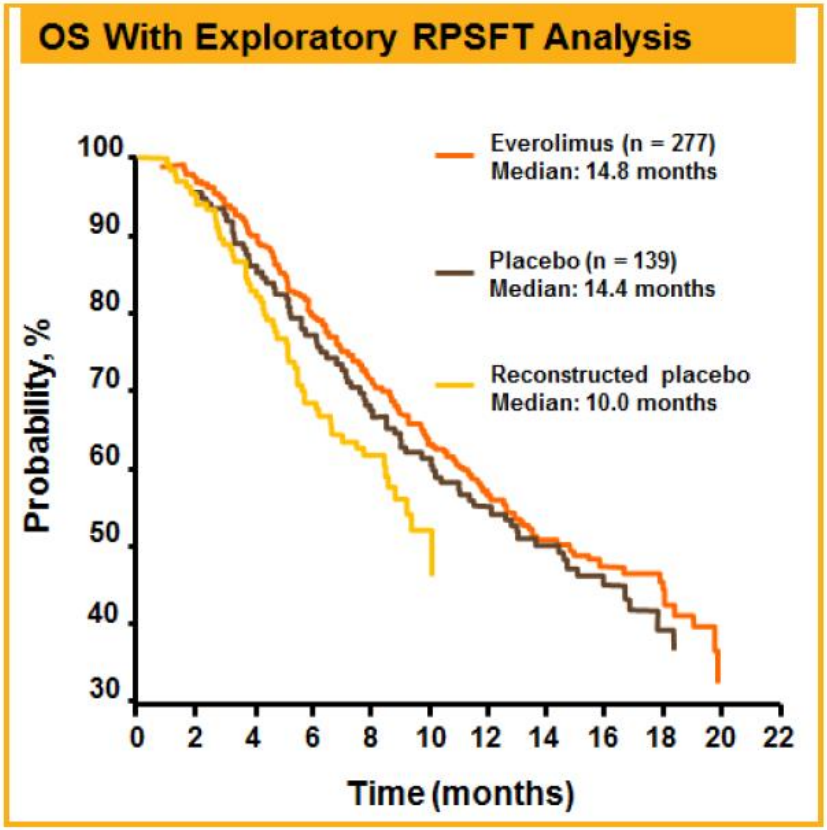
- mTOR controls the protein synthesis of HIF-1/2
- Thus, inhibiting mTOR means also inhibiting angiogenesis[1,2]
- Thus, in renal cancer – which is so heavily dependant on angiogenesis – the inhibition of the mTOR pathway may result just in a 'different' (someone would say 'weaker') inhibition of angiogenesis[3]

Keefe SM et al. Semin Oncol,. 2013 Aug;40(4):421-8

Hager M et al. *J Cell Mol Med*. 2009;13:2181-2188

LA TERAPIA DI II LINEA
RECORD-1 TRIAL:EVEROLIMUS





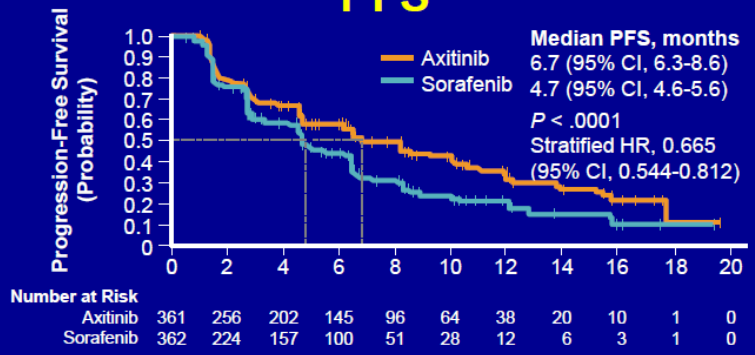
Motzer, Lancet 2008
Morzer, Cancer 2010

LA TERAPIA DI II LINEA
AXIS TRIAL: AXITINIB

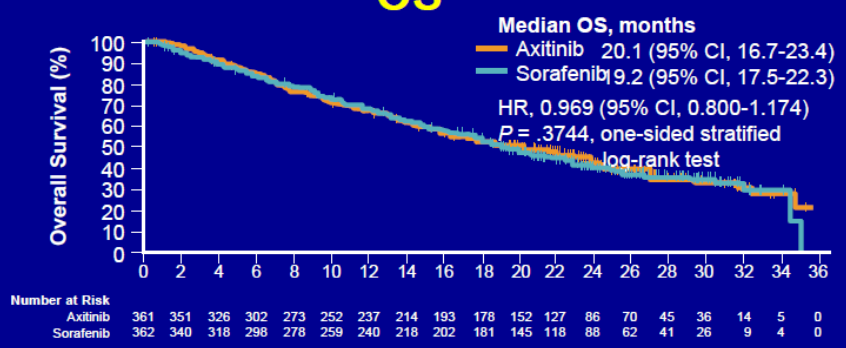
AXIS: Results on PFS and OS of Axitinib Vs Sorafenib in Second-Line Metastatic RCC

Intent to treat analysis

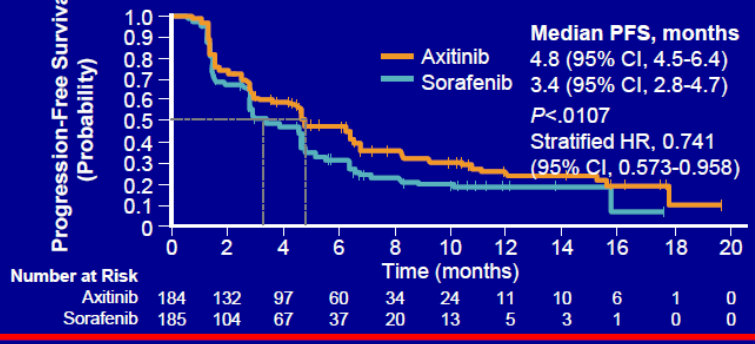
PFS

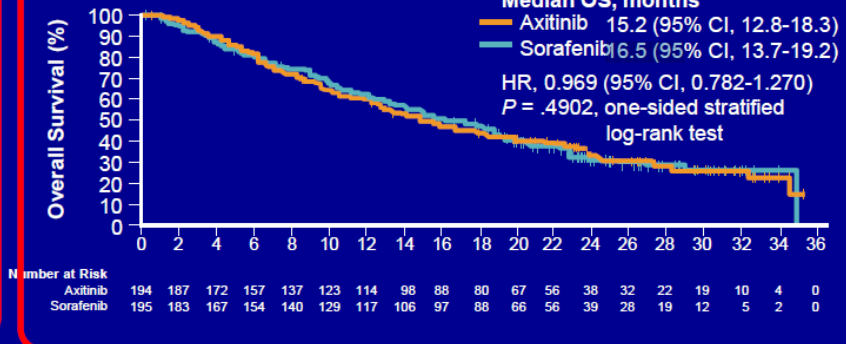


OS



Prior sunitinib





1. Rini BI, et al. *Lancet*. 2011;378(9807):1931-1939. 2. Motzer RJ, et al, *Lancet Oncol*. 2013;14(6):552-562.

Rini, Lancet 2011

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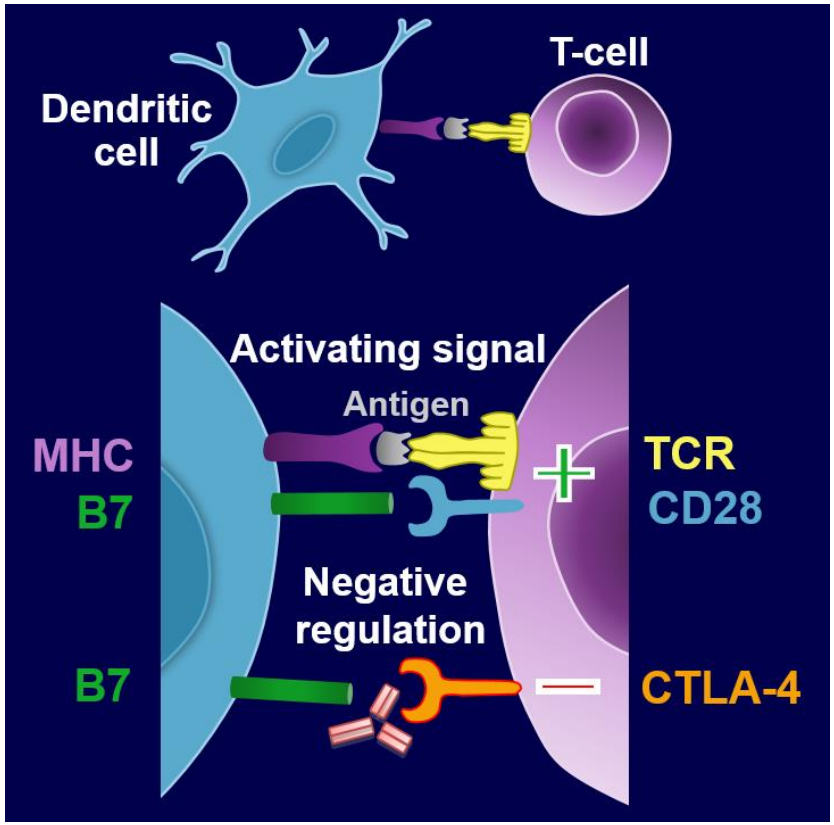
Motzer, NEJM 2017

LA TERAPIA DI II LINEA
IMMUNOTERAPIA

Lymph Node

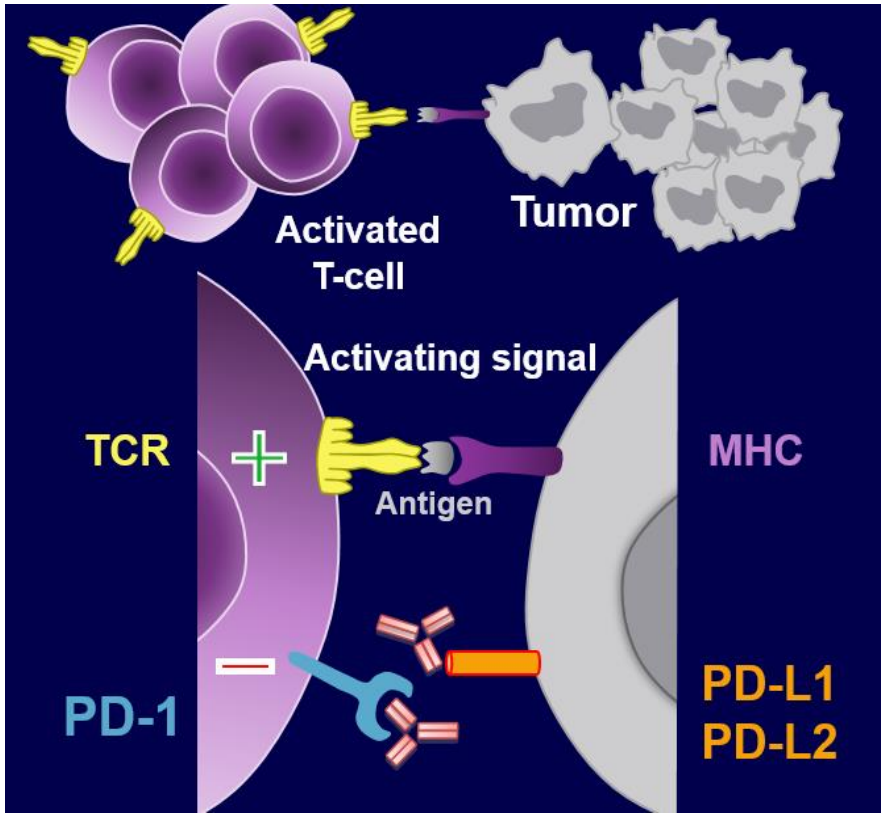
Priming Phase



Inhibitory signal blocked by antibody binding

Tumor Microenvironment

Effector Phase



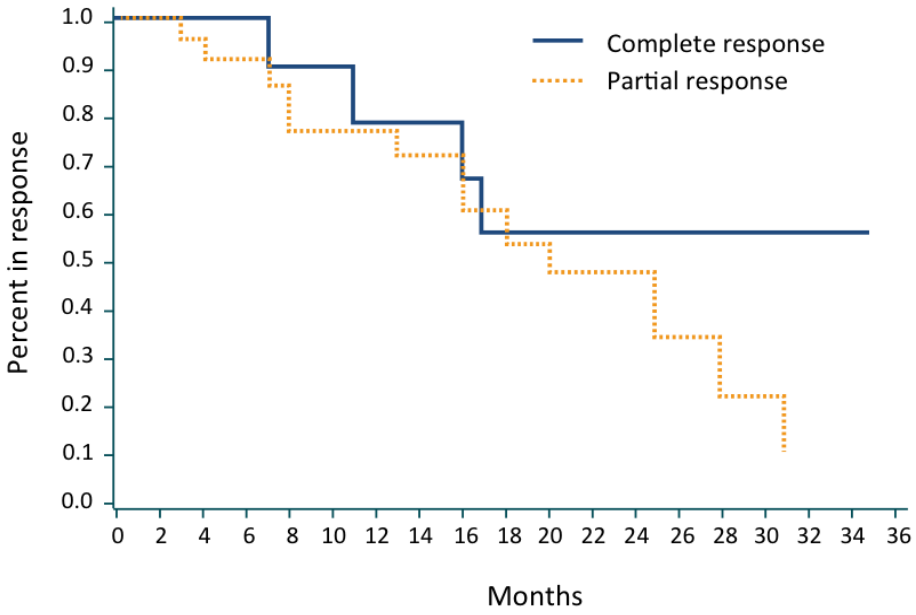
Negative regulation blocked by antibody binding

LA TERAPIA DI II LINEA IMMUNOTERAPIA

- mRCC is considered as an immunogenic tumour type[1,2]
  - Spontaneous regressions have been observed in mRCC and could be explained by the involvement of the immune system[1,2]

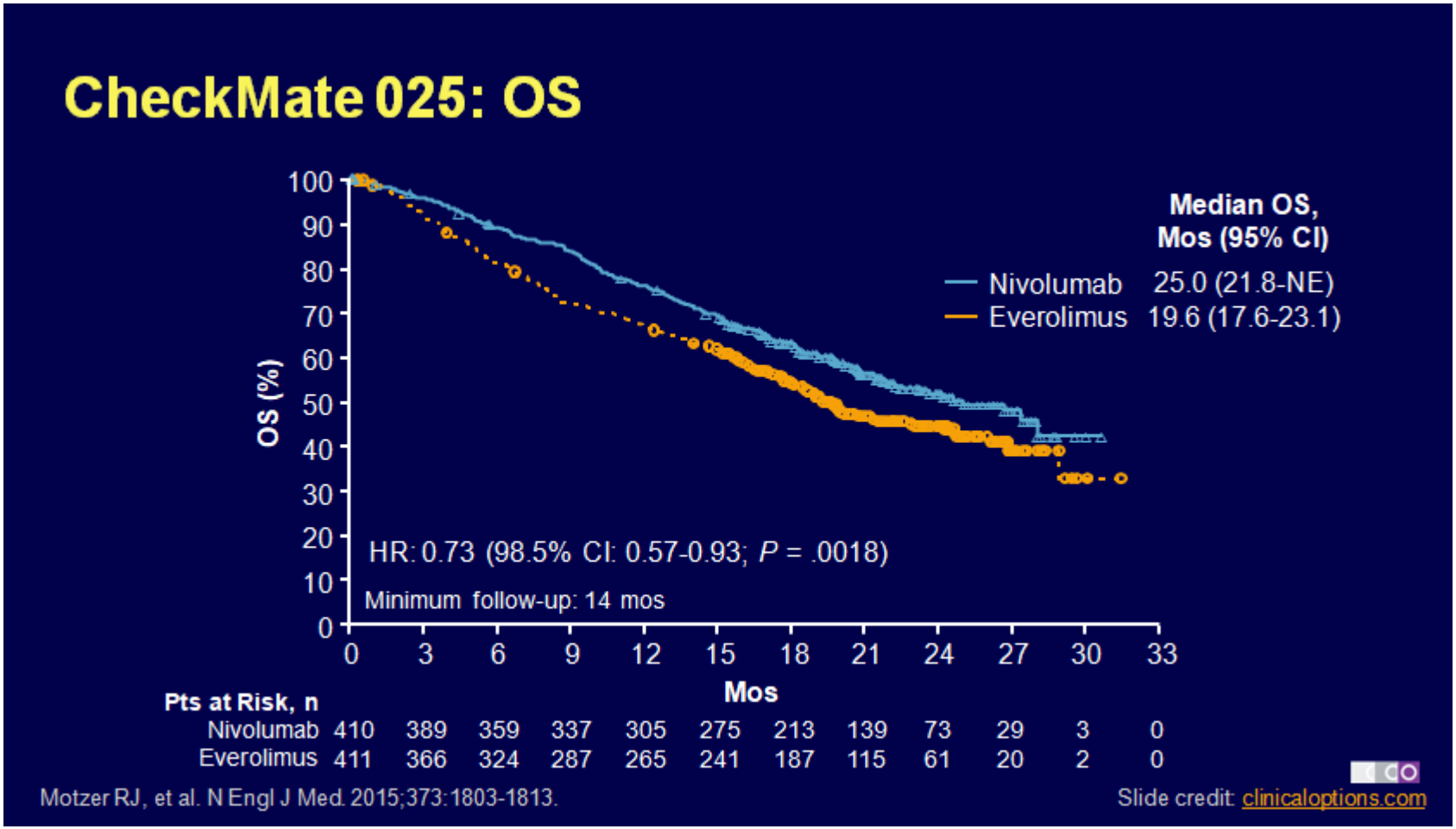
- Cytokine therapy in mRCC
  - Treatment with IFN-α and IL-2 have both shown clinical activity in mRCC[3]
  - Patients who responded to treatment with IL-2 had durable responses (ORR: 14% with 5% complete responses and 9% partial responses) but this was associated with substantial toxicity[4]

Response duration in all responders to IL-2 treatment[4]

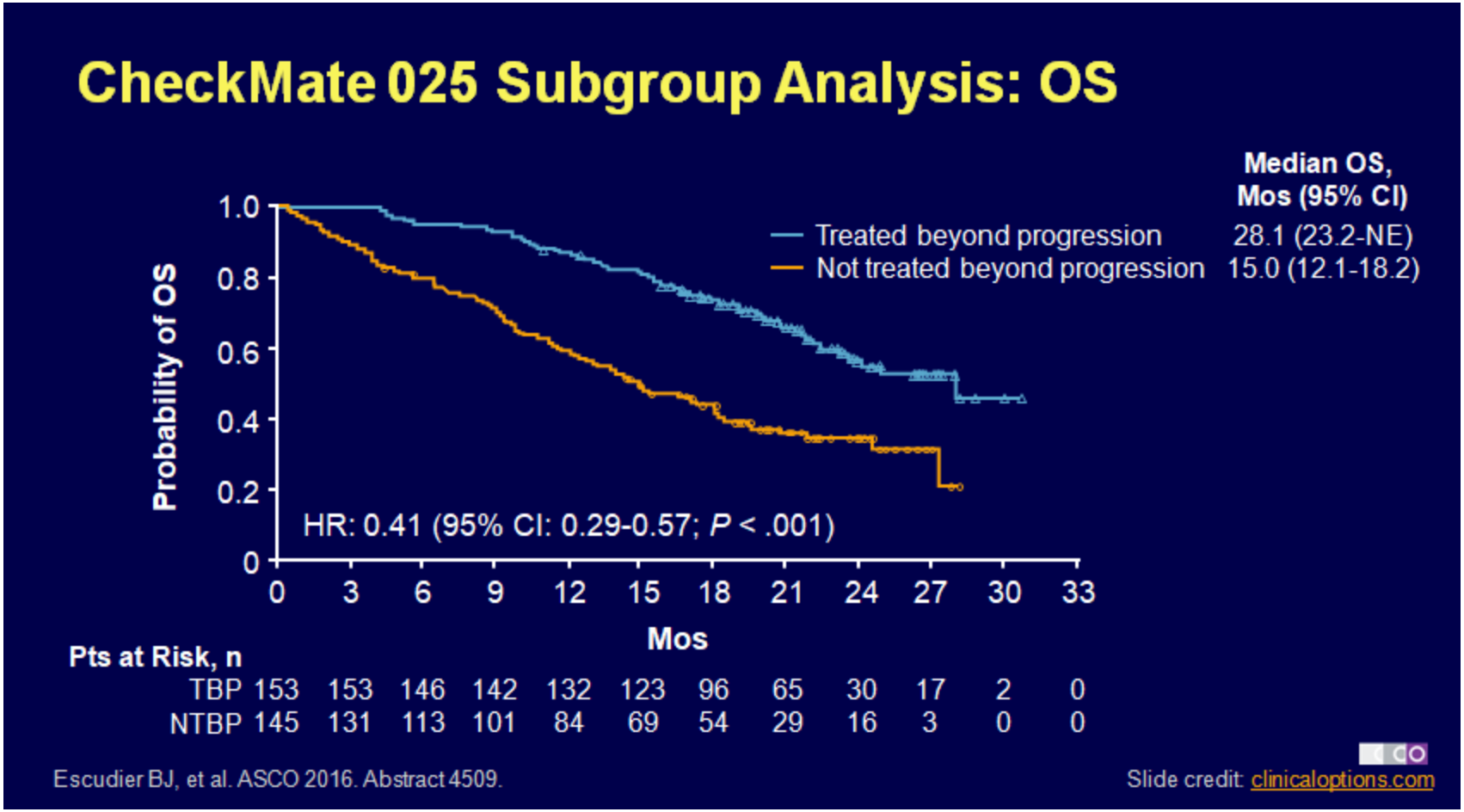


1. Oliver RT, Br J Urol 1989;. Vogelzang NJ, J Urol 1992;
2. 3. McDermott D, Cancer 2009; 4. Fyfe G. J Clin Oncol 1995

LA TERAPIA DI II LINEA
NIVOLUMAB



LA TERAPIA DI II LINEA
NIVOLUMAB: TREATMENT BEYOND PD



TOSSICITA'

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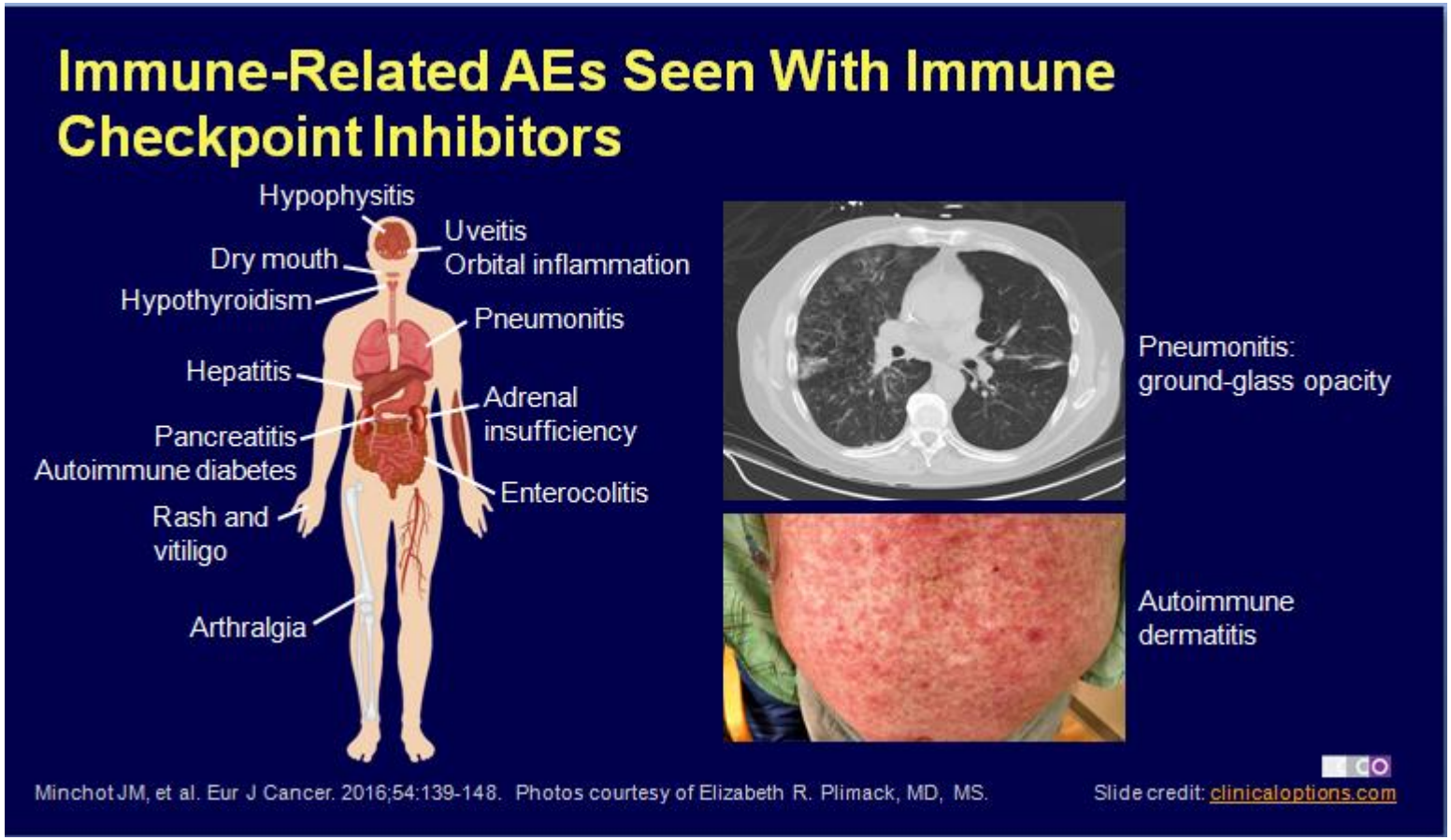
Motzer, NEJM 2017

LA TERAPIA DI II LINEA IMMUNOTERAPIA



LA TERAPIA DI II LINEA CABOZANTINIB

Cabozantinib main Targets:

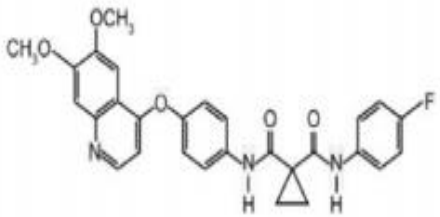
- ***VEGFR***
- ***MET***
- ***AXL***

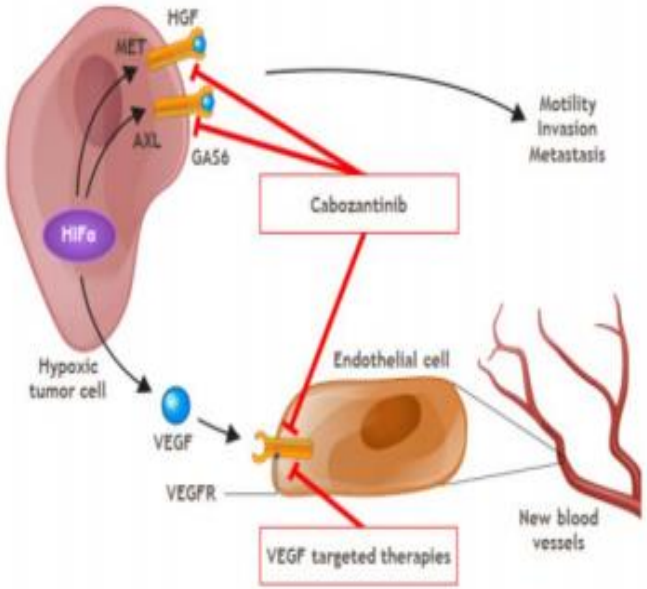
Cabozantinib: Targeting Multiple Distinct Pathways

Cabozantinib is an oral small molecule inhibitor of receptors, including MET, AXL, and VEGFR-1, -2, -3. These receptors are involved in both normal cellular function and pathologic processes. Cabozantinib was rationally designed to target more than just the VEGF pathway.

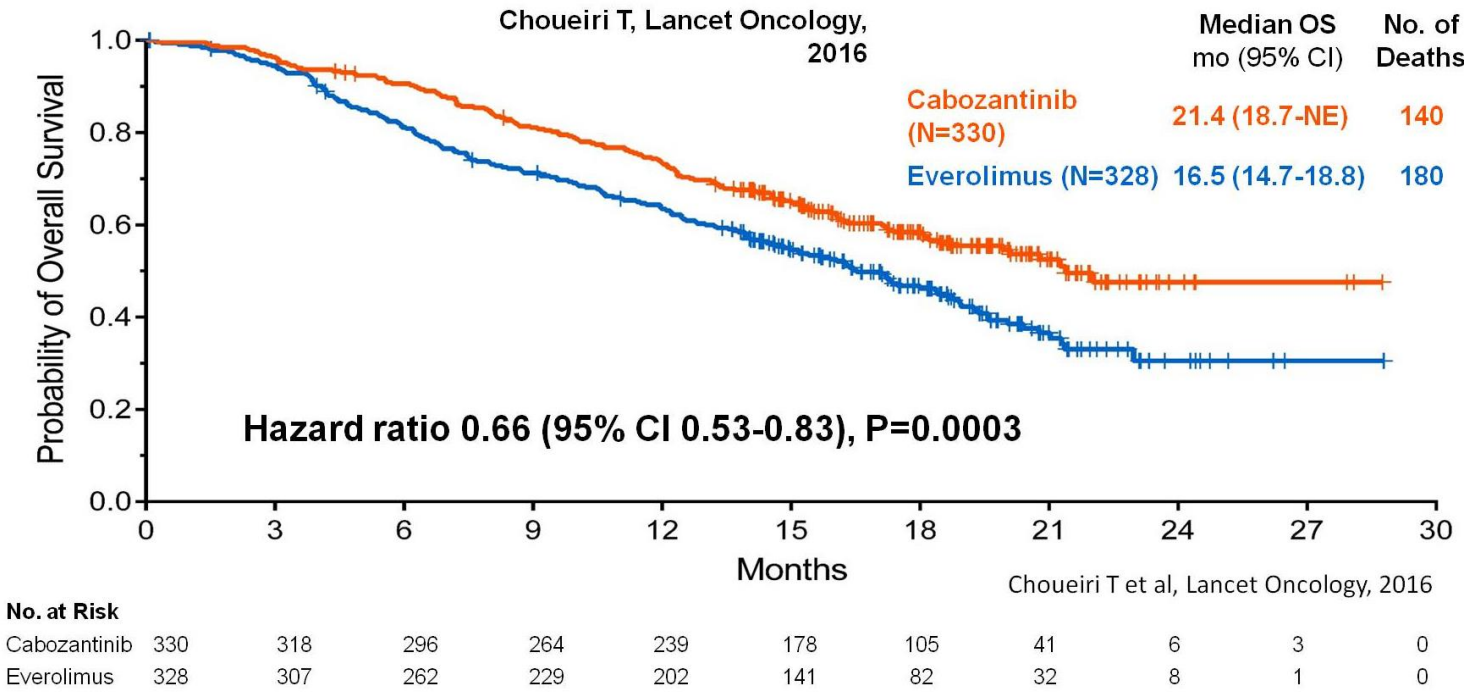
In preclinical models of renal cell carcinoma, cabozantinib has been shown to inhibit the activity of these receptors which includes tumor angiogenesis, invasiveness, metastasis, and drug resistance.

Cabozantinib, by targeting these 3 distinct molecular pathways, among others, provides a multitargeted approach for the treatment of renal cell carcinoma.



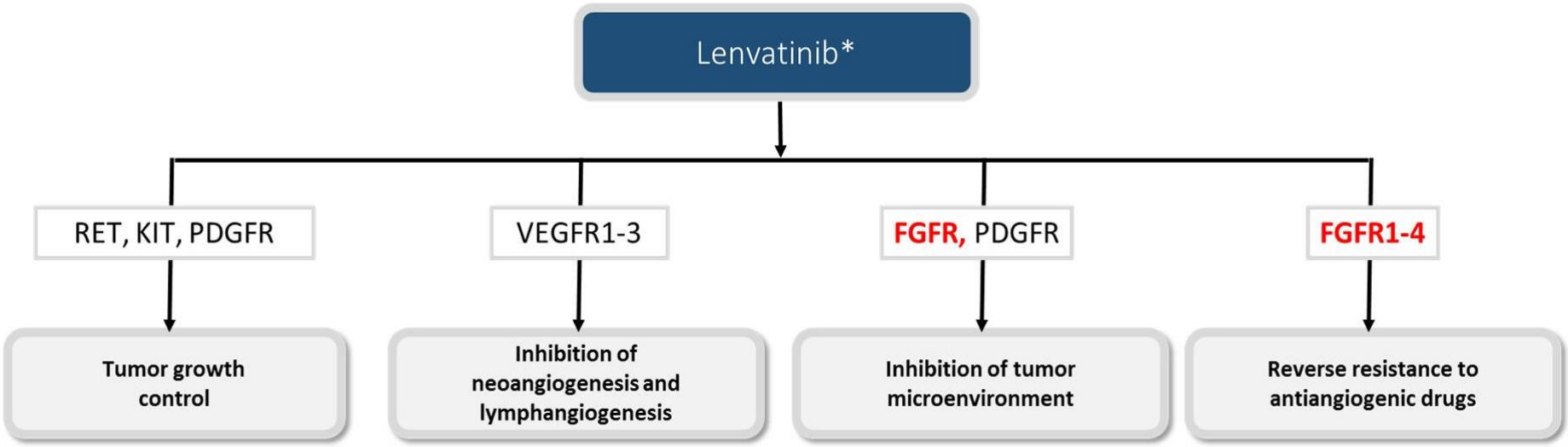


LA TERAPIA DI II LINEA
METEOR TRIAL: CABOZANTINIB



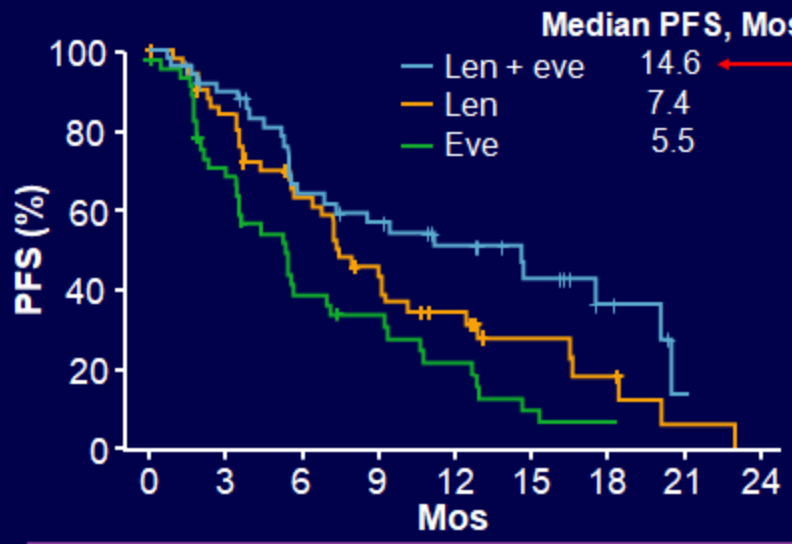
Choueiri, NEJM 2015
Choueiri, Lancet Onc 2016

LA TERAPIA DI II LINEA
LEVANTINIB



LA TERAPIA DI II LINEA
LEVANTINIB

Lenvatinib ± Everolimus in Metastatic RCC: PFS



Median treatment duration: 7.6 mos

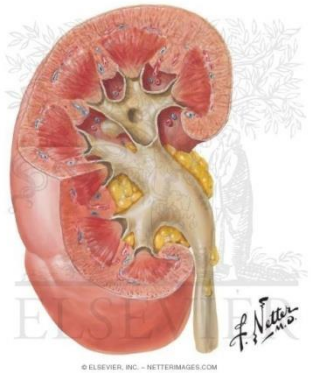
- PFS significantly longer in pts receiving lenvatinib + everolimus vs everolimus alone
- Len + eve vs eve: HR: 0.40 (95% CI: 0.24-0.68; *P* = .0005)
- Len vs eve: HR: 0.61 (95% CI: 0.38-0.98; *P* = .048)

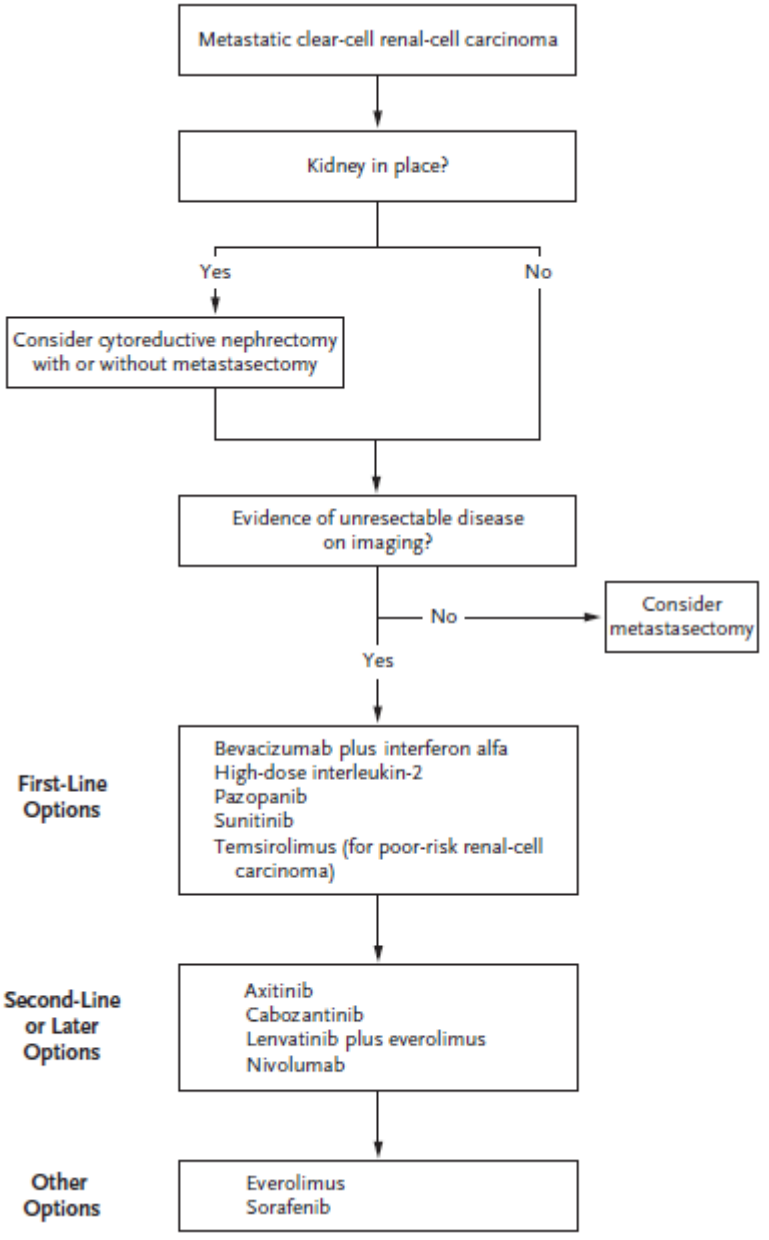
	Lenvatinib/Everolimus	Lenvatinib	Everolimus
ORR, %	35	39	0
95% CI	22-50	25-53	0-7

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

Slide credit: clinicaloptions.com

DECISION MAKING





Motzer, NEJM 2017

NEW DIRECTIONS

Table 3. Selected Ongoing Phase 3 Trials of Combination Therapy with Immune Checkpoint Blockers and Vaccines as First-Line Treatment for Advanced Renal-Cell Carcinoma.

Treatment	Primary End Point	Estimated No. of Patients Enrolled	Trial	ClinicalTrials.gov No.
Pembrolizumab–lenvatinib vs. everolimus–lenvatinib vs. sunitinib	Progression-free survival	735	CLEAR	NCT02811861
Nivolumab–ipilimumab vs. sunitinib	Progression-free survival and overall survival	1070	CheckMate 214	NCT02231749
Atezolizumab–bevacizumab vs. sunitinib	Progression-free survival and overall survival in PD-L1–detectable tumors	900	IMmotion151	NCT02420821
Avelumab–axitinib vs. sunitinib	Progression-free survival	583	JAVELIN Renal 101	NCT02684006
Pembrolizumab–axitinib vs. sunitinib	Progression-free survival and overall survival	840	KEYNOTE-426	NCT02853331
Autologous dendritic-cell immunotherapy–sunitinib vs. sunitinib	Overall survival	450	ADAPT	NCT01582672

Motzer, NEJM 2017

CONCLUSION

- ✓ Numerous new treatment options with proven role in advanced RCC now available
- ✓ Checkpoint inhibition has proven survival benefit in RCC in second-line therapy and beyond
  - ✓ However, VEGF and mTOR pathways remain important targets in this disease
- ✓ Immune-based combination therapies under active investigation for frontline therapy
  - ✓ Substantial percentage of patients may have durable benefit with minimal toxicity

CONCLUSION

- ✓ Multiple frontline trials may imminently change treatment landscape
  - ✓ Dual checkpoint inhibition (ipilimumab/nivolumab)
  - ✓ VEGF/checkpoint inhibitor combinations
- ✓ If checkpoint inhibitors move to frontline therapy, what is the optimal strategy for second-line therapy?
  - ✓ Current frontline TKIs: sunitinib, pazopanib
  - ✓ Next-generation TKIs: cabozantinib, axitinib
  - ✓ Combination VEGFR/mTOR inhibition
- ✓ Ultimate goal: frontline therapy curative, no need for second line