



 IX Congresso Internacional de
Uro-Oncologia

**IV SIMPÓSIO MULTIPROFISSIONAL
DE URO-ONCOLOGIA**

02 e 03 de março de 2018
SHERATON SÃO PAULO WTC HOTEL

TERAPIA COM INIBIDORES DE TIROSINA KINASE

Felipe Feistauer
CRF 8794

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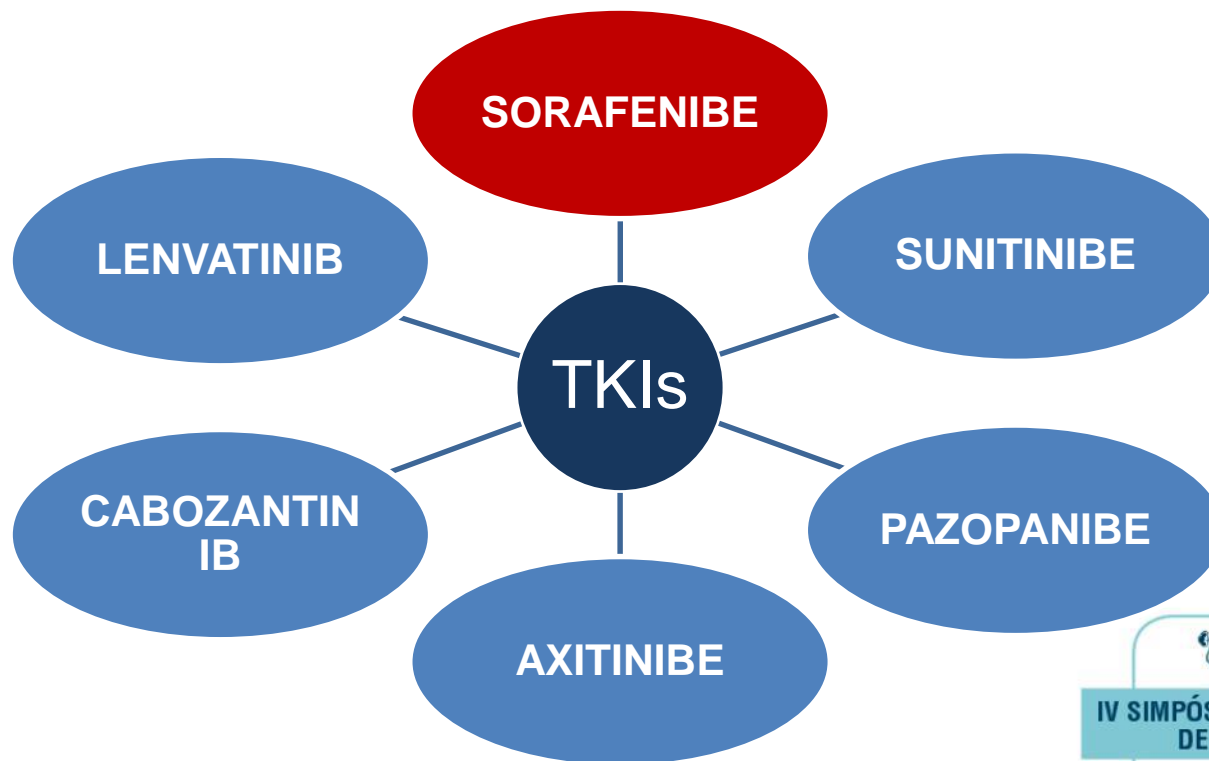
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TERAPIA COM INIBIDORES DE TIROSINA KINASE

Carcinoma Renal \geq 2005

Approval	Agent	FDA Indication
2005	Sorafenib 	Advanced
2006	Sunitinib 	Advanced
2007	Temsirolimus	Advanced
2009	Bevacizumab + IFN- α	Metastatic
2009	Everolimus	After failure of sunitinib or sorafenib
2009	Pazopanib 	Advanced
2012	Axitinib 	Failure of prior systemic therapy
2015	Nivolumab	After failure of anti-angiogenic drug(s)
2016	Cabozantinib	Prior anti-angiogenic therapy
2016	Lenvatinib (+ everolimus)	Following 1 prior anti-angiogenic therapy

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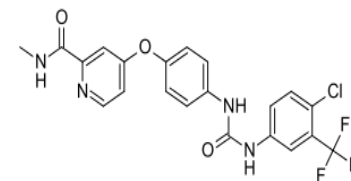
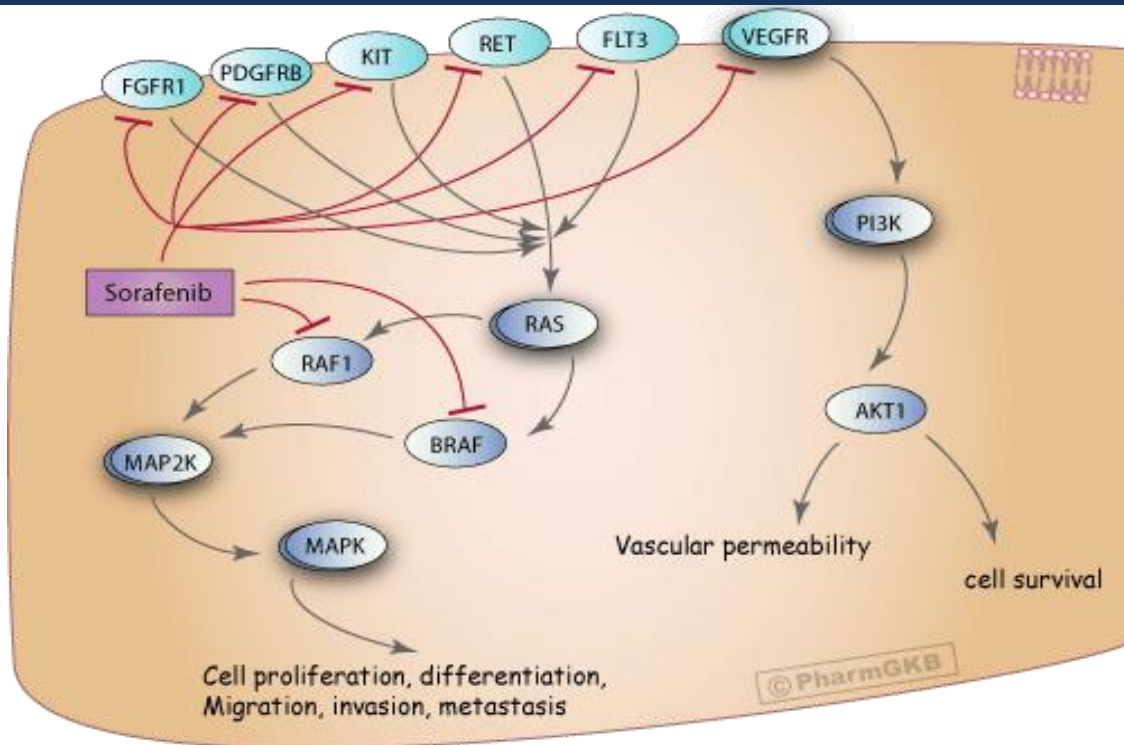
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SORAFENIBE



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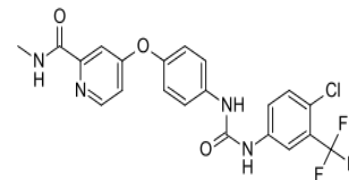
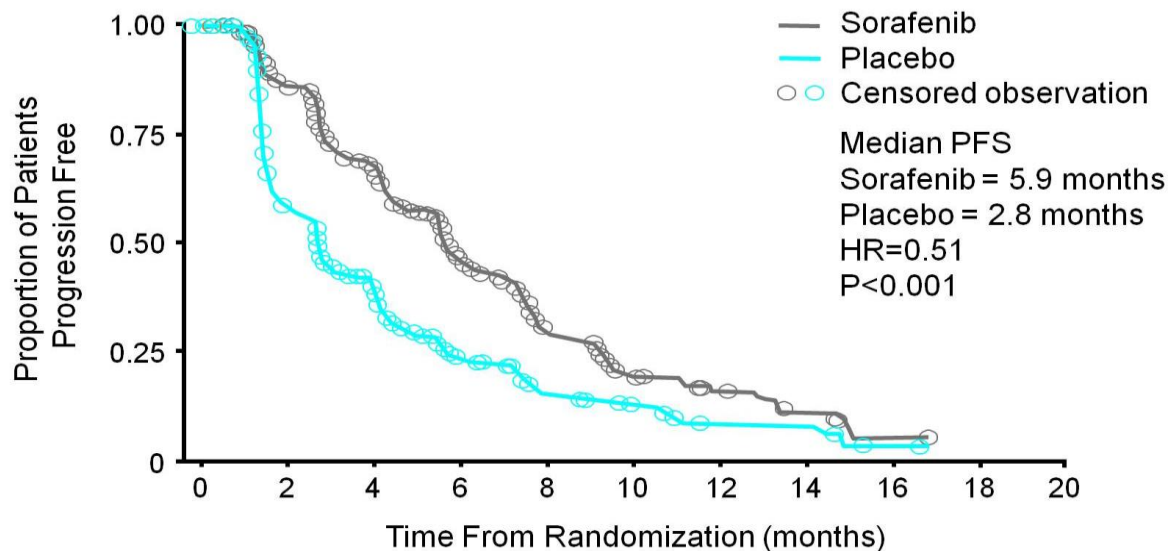
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SORAFENIBE

Sorafenib versus Placebo (TARGETS)



PFS by investigator assessment.

N Engl J Med 2007;356:125–134.

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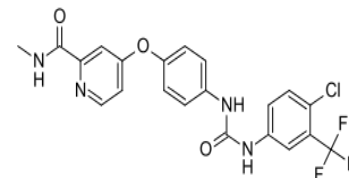
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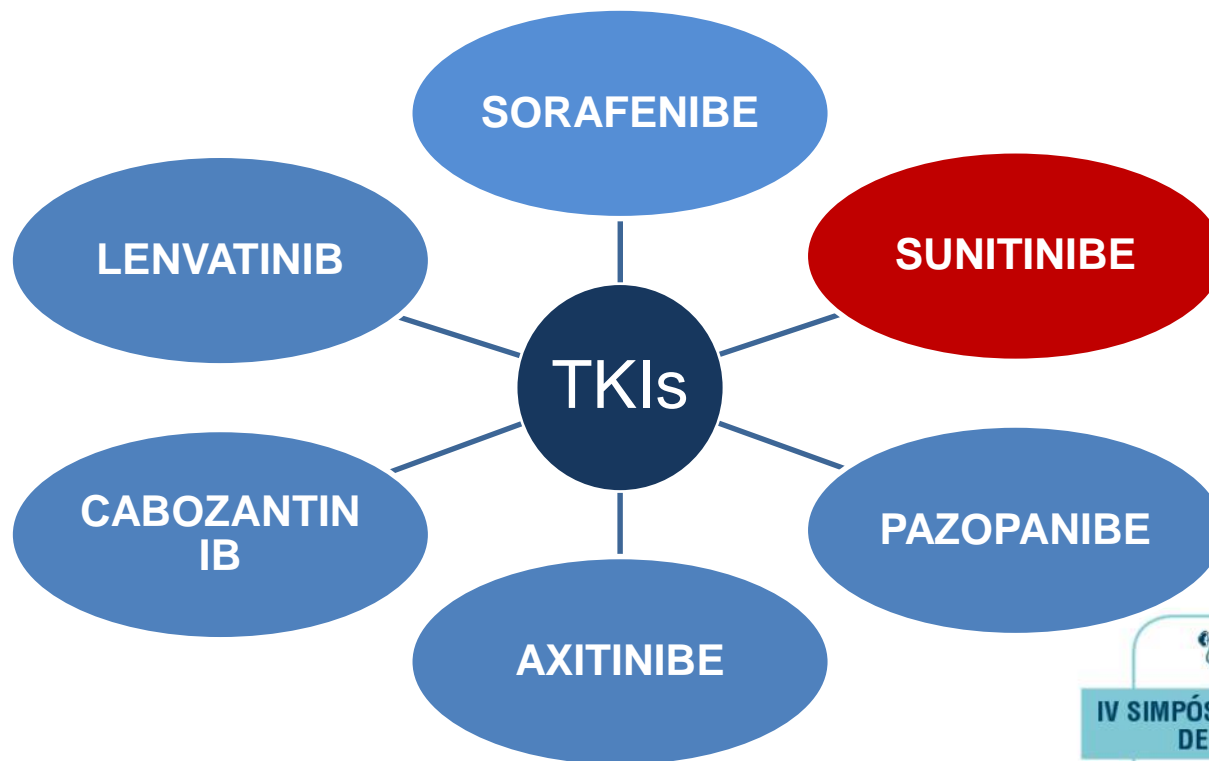
TERAPIA COM INIBIDORES DE TIROSINA KINASE

SORAFENIBE

- **Indicação em câncer renal:** avançado 1ª linha
- **Posologia:** 400 mg 2 vezes ao dia, 1 hora antes ou 2 horas após alimentação
- **Meia vida:** 25-48 horas
- **Manejo da dose:**
 - **Renal:** L (400 mg 2x/dia); M. (200mg 2x/dia); G (?)
 - **Hepático:** **L.** (400 mg q12h); **M.** (200 mg q12h) **G.** (200 mg/dia??)



TERAPIA COM INIBIDORES DE TIROSINA KINASE



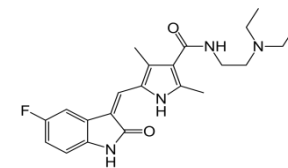
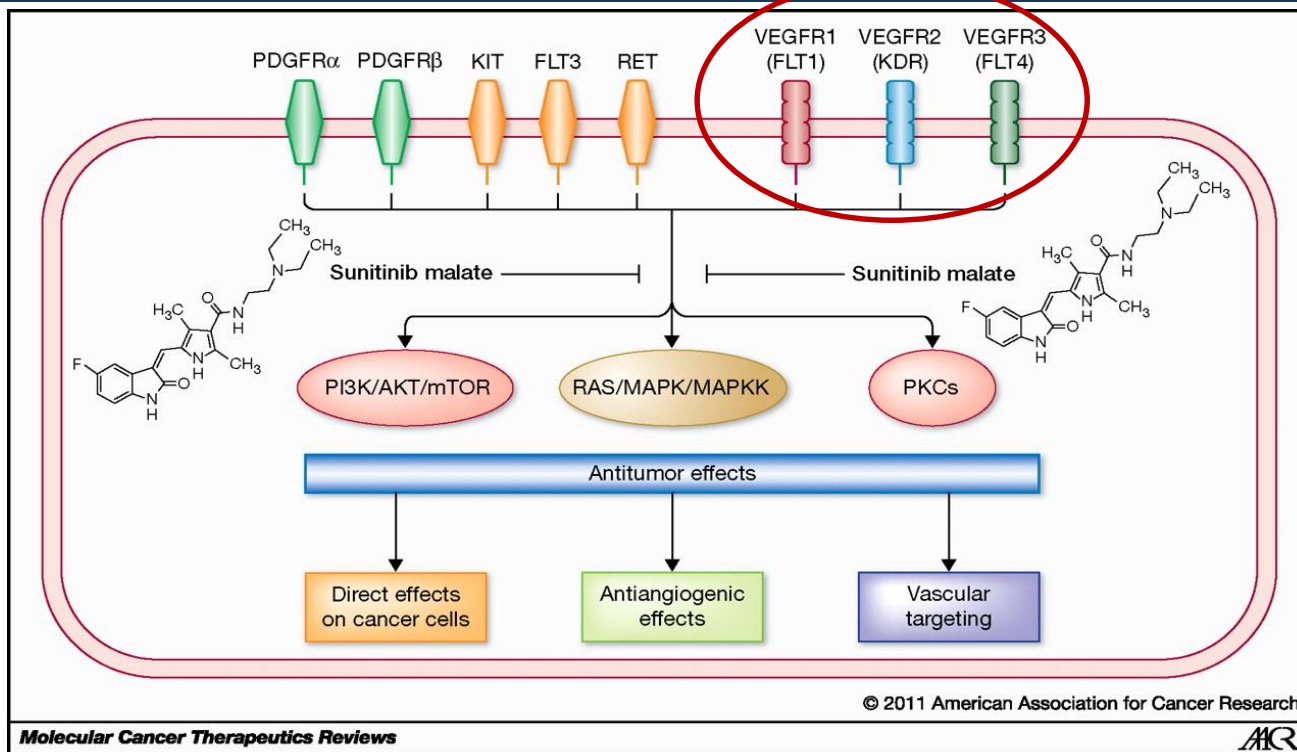
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SUNITINIB



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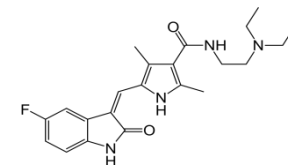
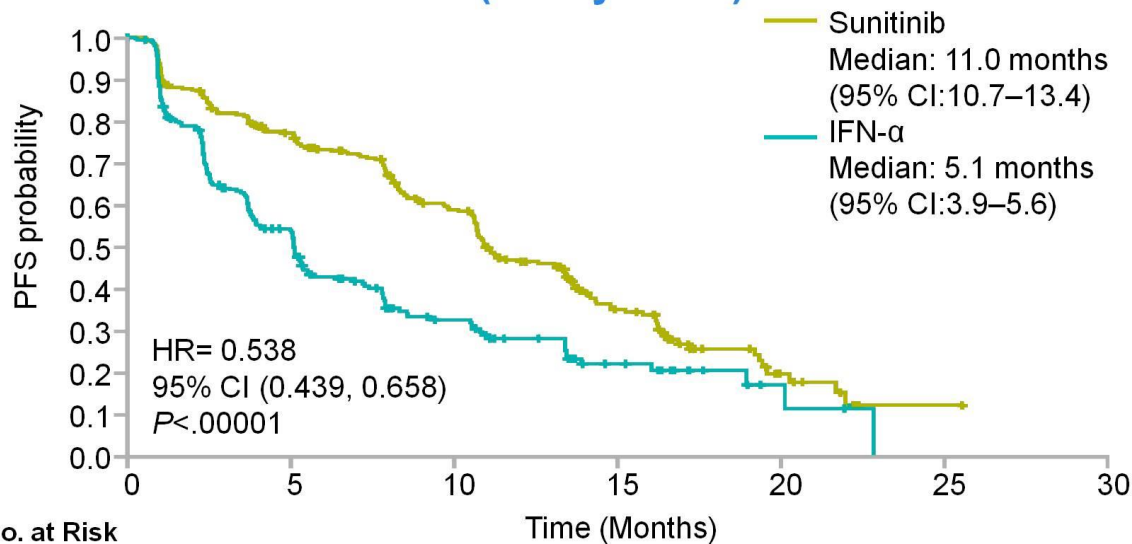
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SUNITINIB

Sunitinib vs Interferon- α (Study 1034)



PFS by on central review

N Engl J Med. 2007;356:115–124

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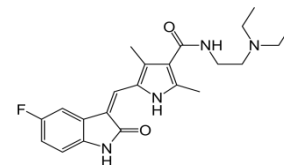
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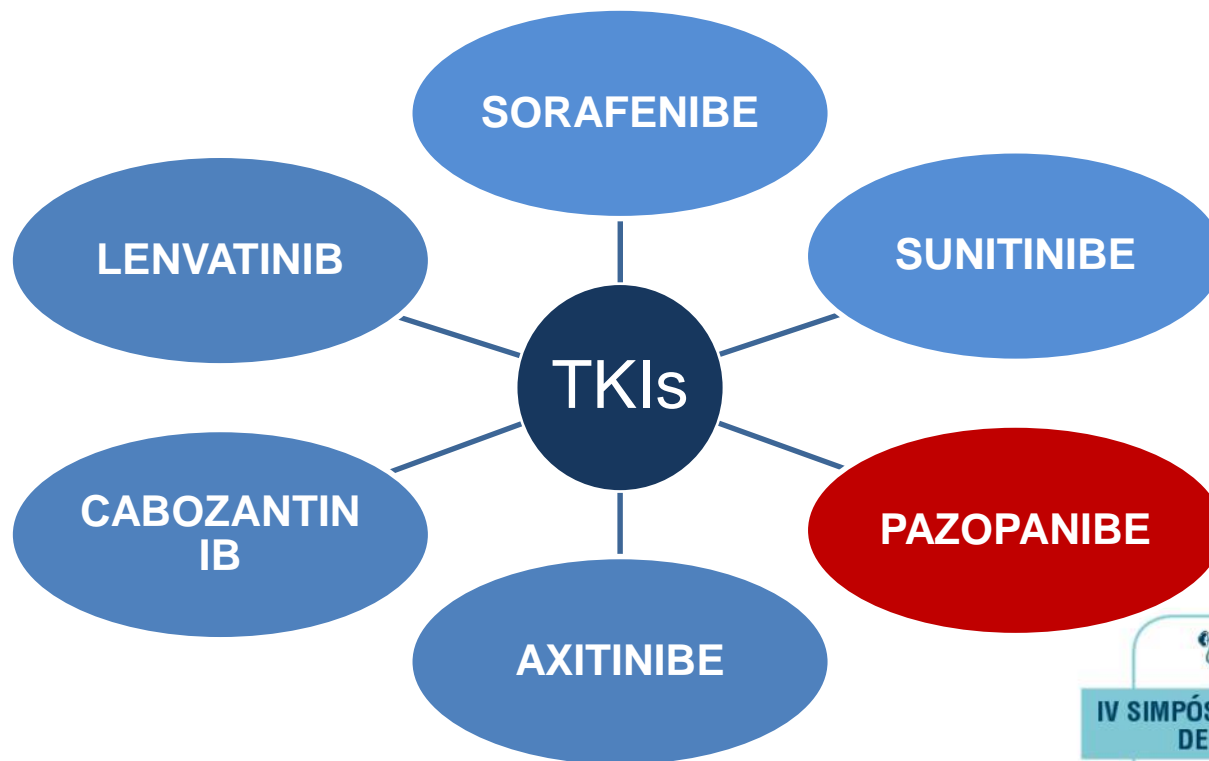
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SUNITINIB

- **Indicação em câncer renal:** avançado 1ª linha
- **Posologia:** 50 mg/dia 4 semanas *on* 2 semanas *off*
- **Meia vida:** 40-60 h ; 80-110 h
- **Manejo da dose:**
 - **Renal:** sem ajuste
 - **Hepático:** Leve e Moderado sem ajuste; **Grave ?**

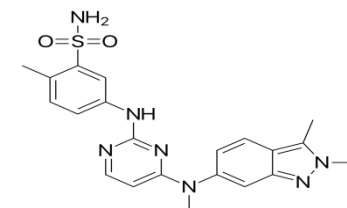
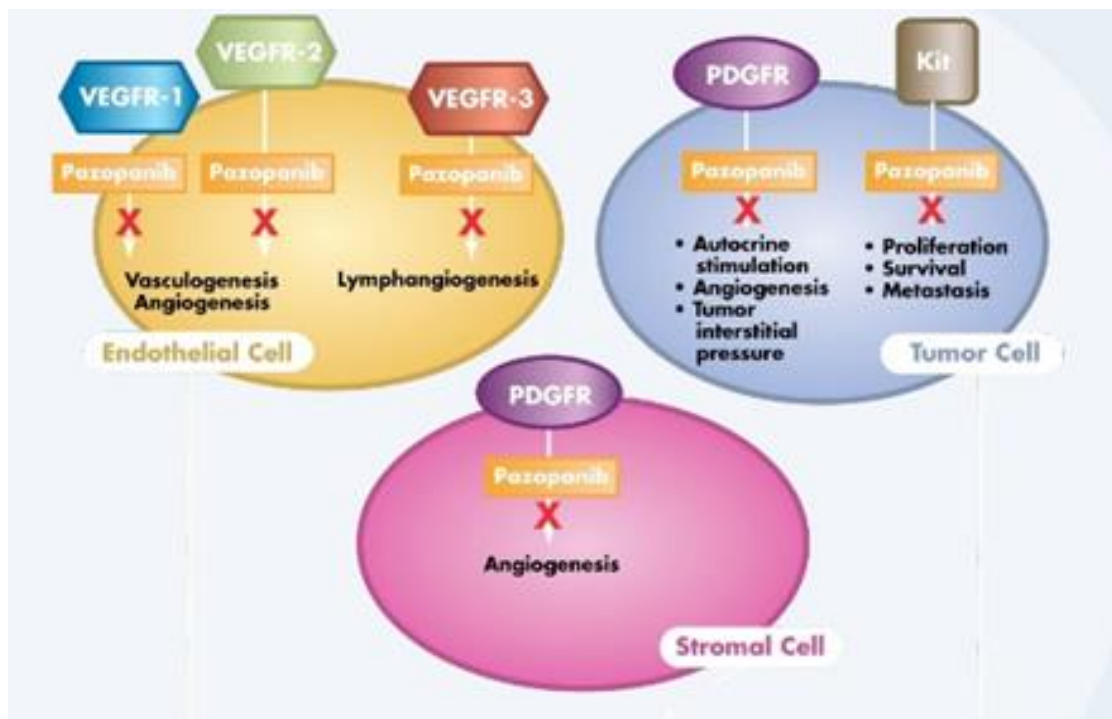


TERAPIA COM INIBIDORES DE TIROSINA KINASE



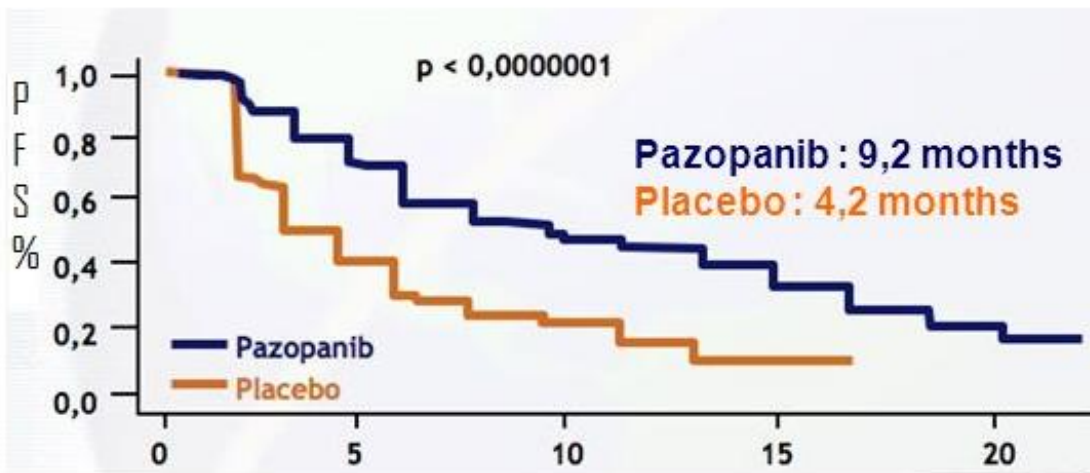
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PAZOPANIBE

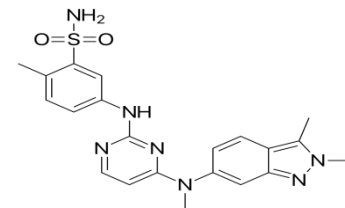


TERAPIA COM INIBIDORES DE TIROSINA KINASE

PAZOPANIBE



Cora N. Sternberg A randomized, double-blind phase III study of pazopanib in treatment-naive and cytokine-pretreated patients with advanced renal cell carcinoma, 2009



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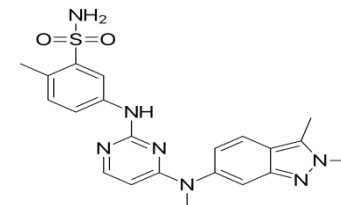
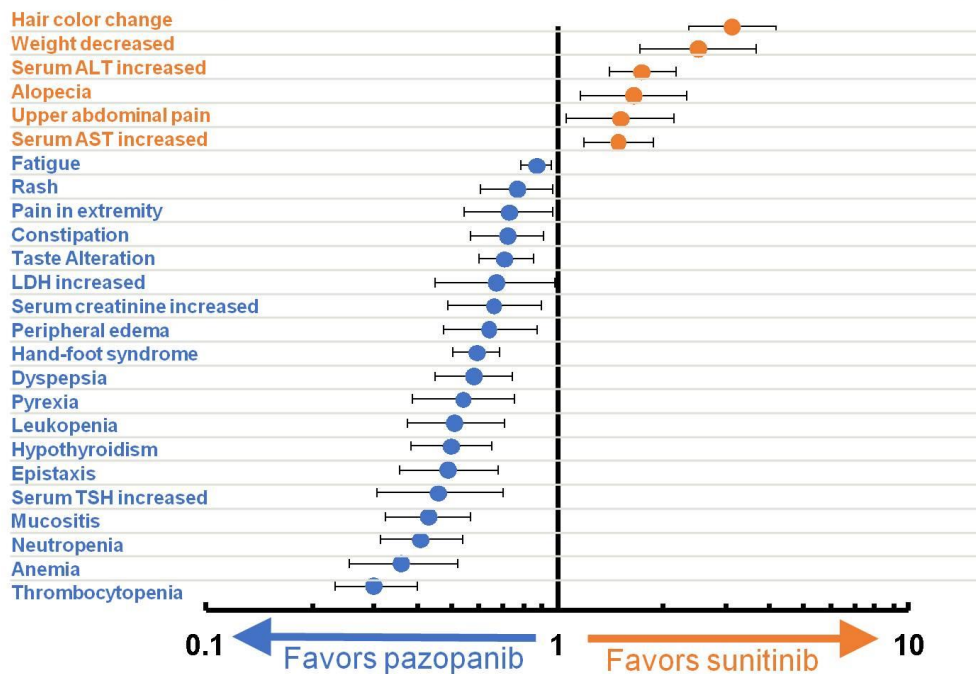
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PAZOPANIBE

Pazopanib vs Sunitinib (COMPARZ) Adverse Events (NEJM 2013)

AE occurrence
 ≥10% in either
 arm; 95% CI for
 RR does not
 cross 1



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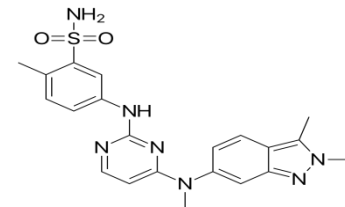
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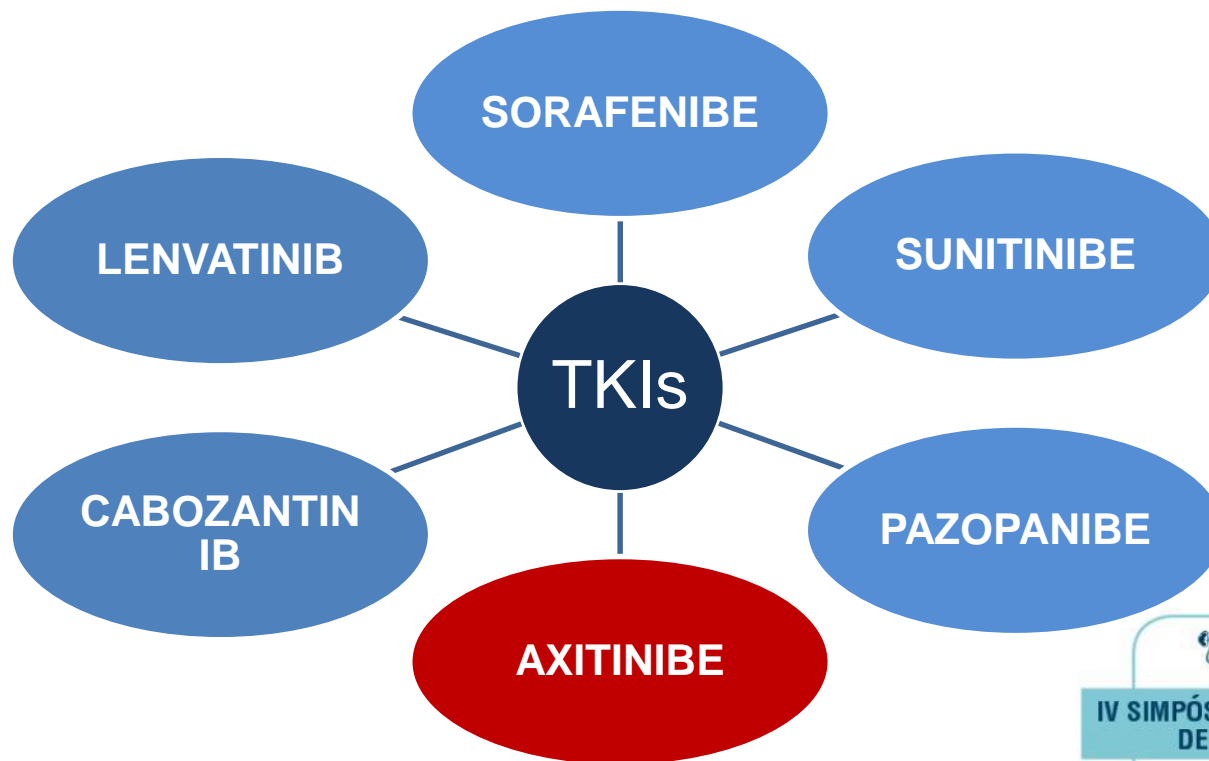
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PAZOPANIBE

- **Indicação em câncer renal:** avançado 1ª linha
- **Posologia:** 800 mg ao dia, 1 hora antes ou 2 horas após alimentação
- **Meia vida:** ~ 31 horas
- **Manejo da dose:**
 - **Renal:** ClCr \geq 30 mL/min (sem ajuste); ClCr < 30 mL/min (?)
 - **Hepático:** **L** (sem ajuste); **M** (200 mg/dia); **G** (contraindicado)



TERAPIA COM INIBIDORES DE TIROSINA KINASE



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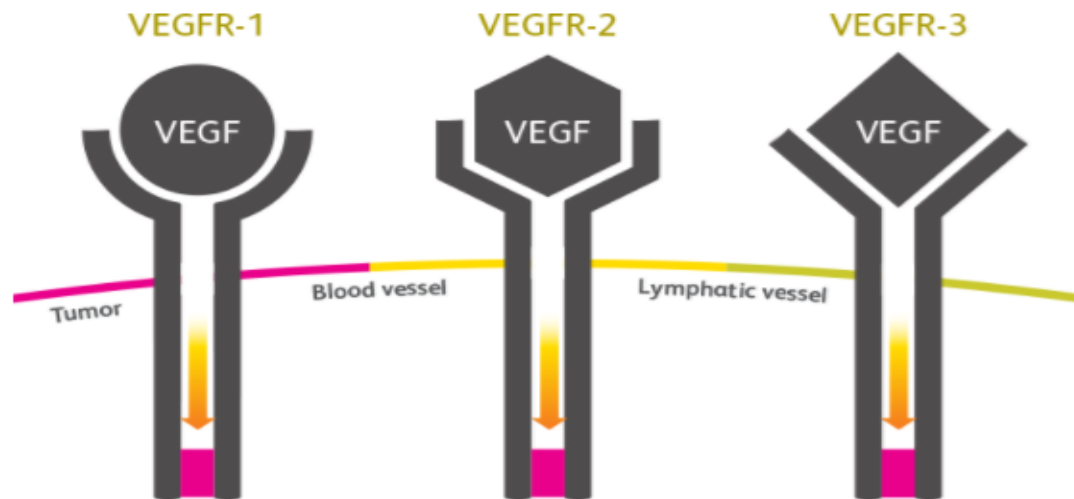
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AXITINIBE

INLYTA was designed to inhibit tyrosine kinases, including VEGFR-1, -2, and -3



INLYTA has been shown to inhibit receptor tyrosine kinases, including VEGFR-1, -2, and -3, in vitro and in preclinical models

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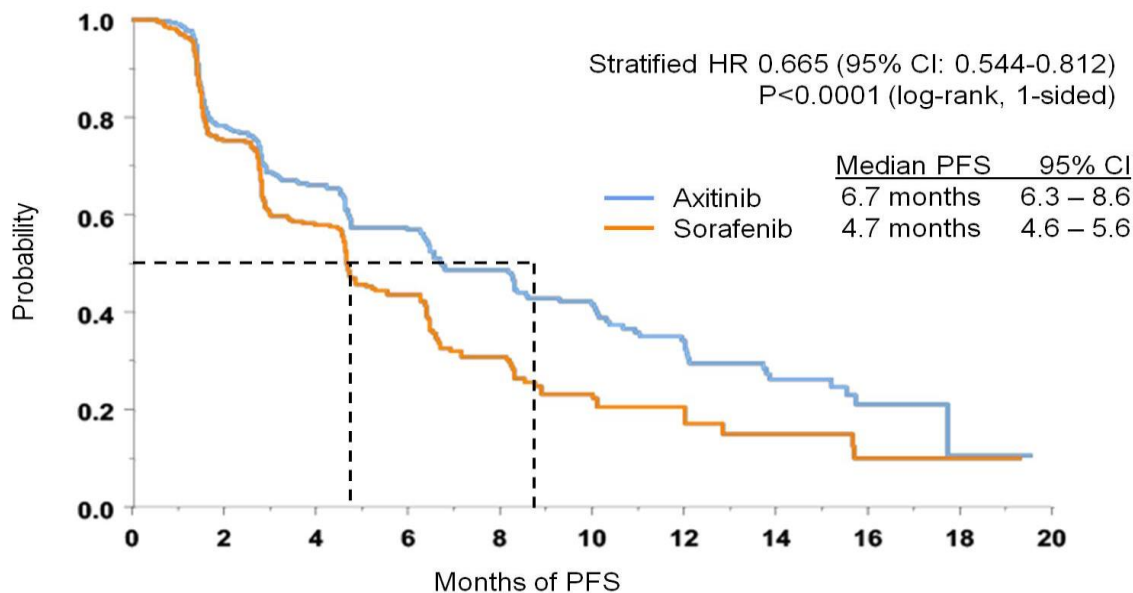
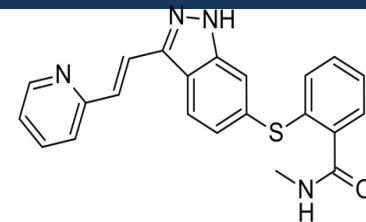
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AXITINIBE

Axitinib vs Sorafenib as 2nd line (AXIS)



PFS Based on central review

Lancet 378; 1931, 2011

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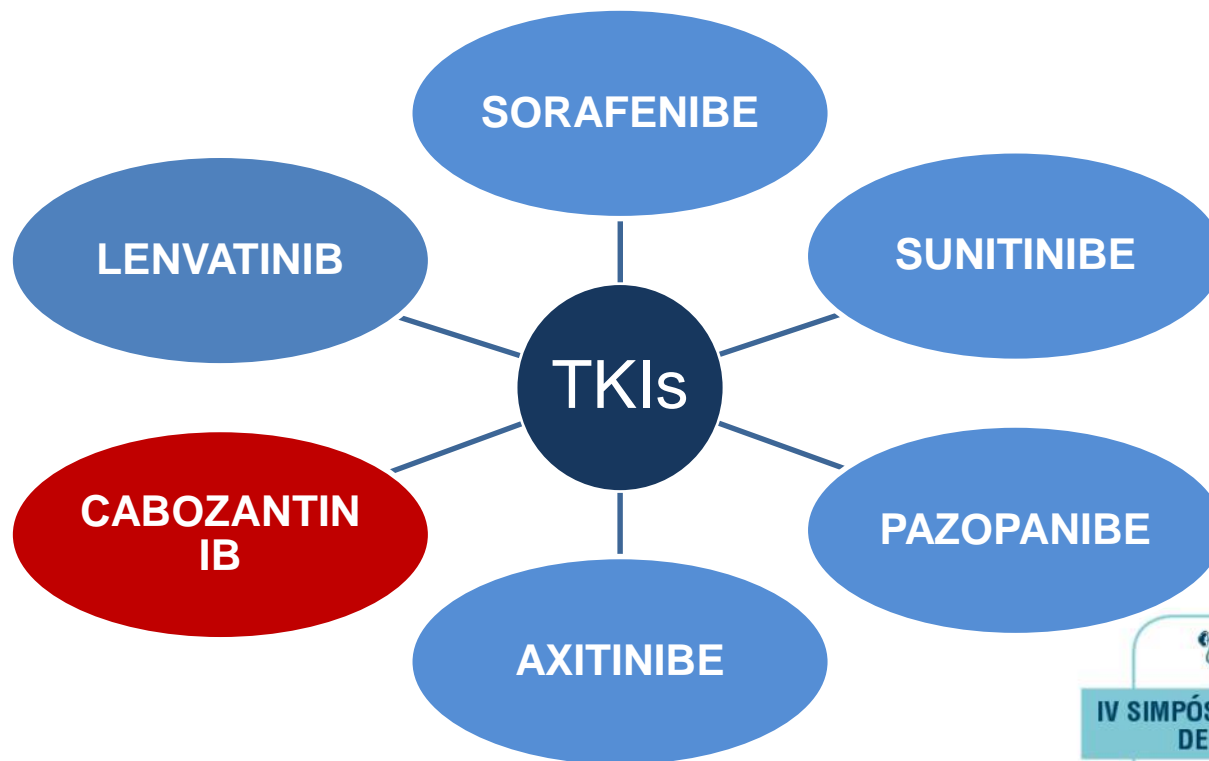
TERAPIA COM INIBIDORES DE TIROSINA KINASE

AXITINIBE

- **Indicação em câncer renal:** avançado 2ª linha (Br) e 1ª linha (EUA)
- **Posologia:** 5 mg 2 vezes ao dia → 10 mg 2 vezes ao dia, com ou sem alimentos
- **Meia vida:** 2,5 – 6,1 h
- **Manejo da dose:**
 - **Renal:** Sem ajuste
 - **Hepático:** Leve e Moderado sem ajuste; **Grave ?**



TERAPIA COM INIBIDORES DE TIROSINA KINASE



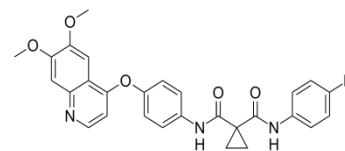
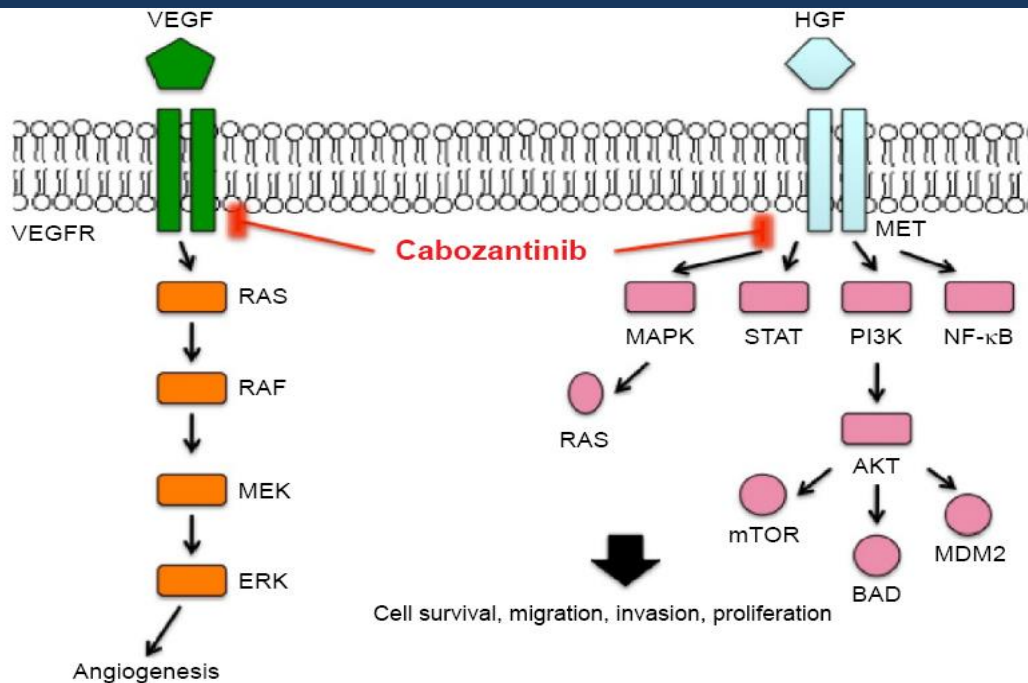
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CABOZANTINIB



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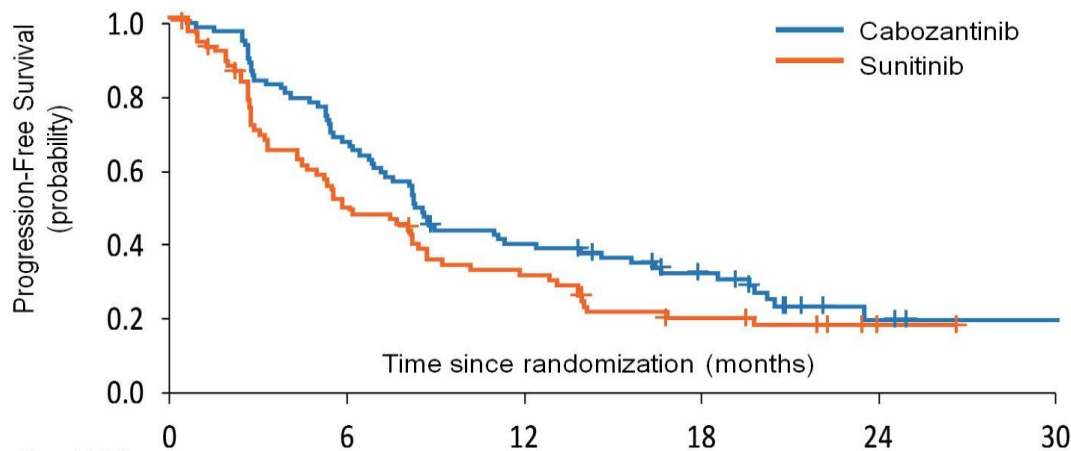
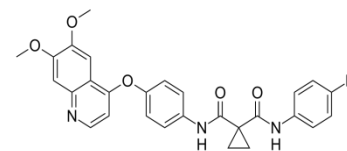
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Steven S Yu, David I Quinn, Tanya B Dorff. Clinical use of cabozantinib in the treatment of advanced kidney cancer: efficacy, safety, and patient selection, 2016

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CABOZANTINIB

Cabozantinib vs Sunitinib First-line (CABOSUN)



Time (months)	Cabozantinib No. at Risk	Sunitinib No. at Risk
0	79	78
6	50	32
12	26	17
18	1	7
24	15	0
30	15	0

Arm	PFS Events	Median PFS (95% CI), mo	HR (95% CI)*
Cabozantinib	64	8.2 (6.2, 9.0)	0.69 (0.48-0.99)
Sunitinib	61	5.6 (3.4, 8.1)	p-value (one-sided) = 0.012

* Adjusted for bone metastases and IMDC risk group

J Clin Oncol 2017

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CABOZANTINIB

➤ Indicação em câncer renal: **avançado 1ª linha EUA**

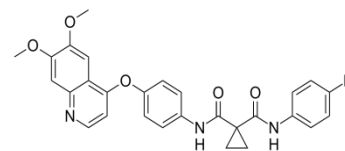
➤ Posologia: 60 mg/dia 1 hora antes ou 2 horas após

➤ Meia vida: 120 h

➤ Manejo da dose:

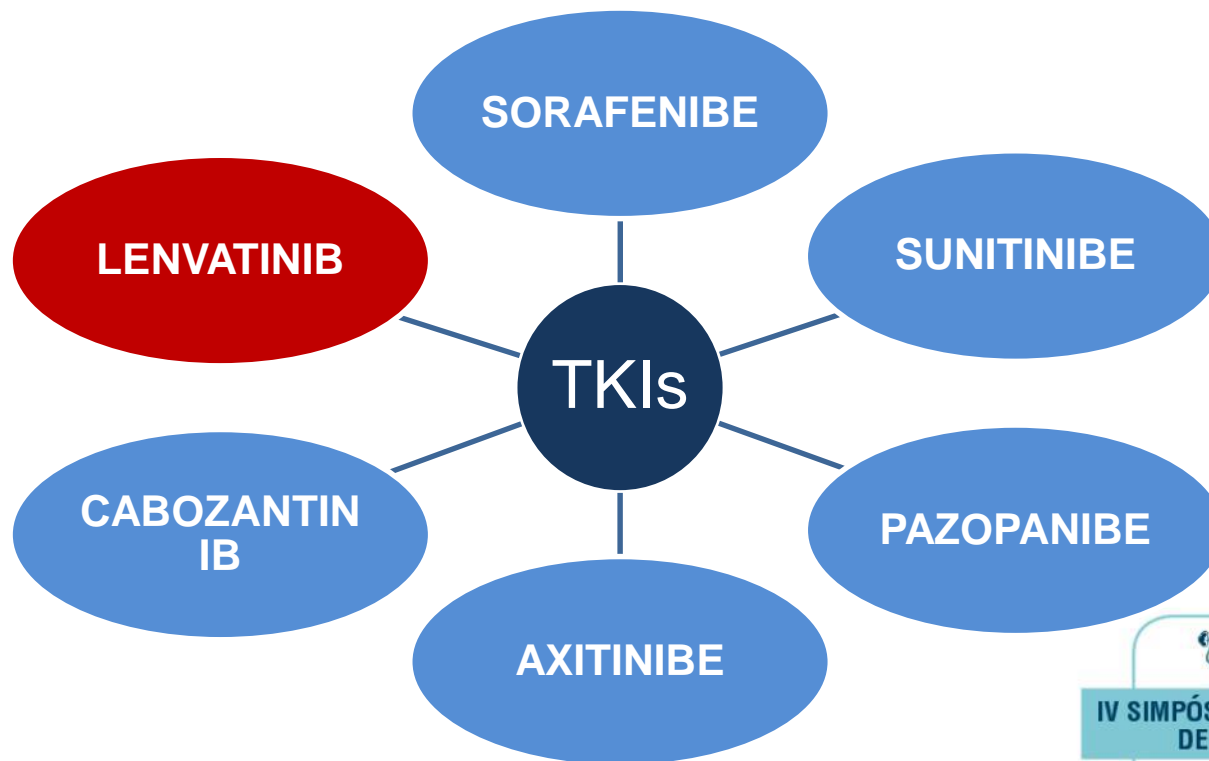
- **Renal**: Leve e Moderado sem ajuste; **Grave**:
contraindicado

- **Hepático**: Leve e Moderado sem ajuste; **Grave**:
contraindicado



FIRST-LINE THERAPY
(alphabetical by category and preference)

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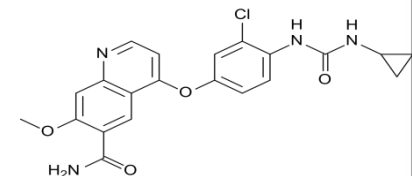
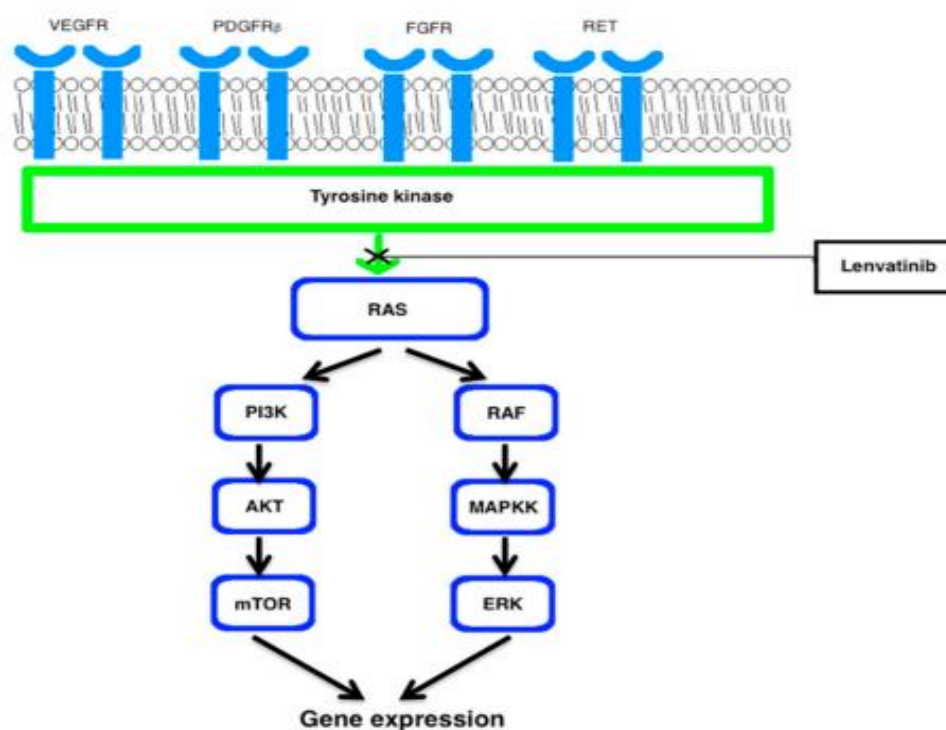
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LENVATINIB

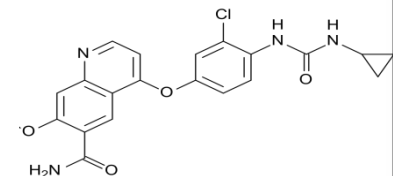


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LENVATINIB

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

Dr Robert J Motzer, MD  , Thomas E Hutson, DO, Hilary Glen, MD, M Dror Michaelson, MD, Ana Molina, MD, Prof Timothy Eisen, FRCP, Prof Jacek Jassem, MD, Jakub Zolnierek, MD, Jose Pablo Maroto, MD, Begoña Mellado, MD, Prof Bohuslav Melichar, MD, Jiri Tomasek, MD, Alton Kremer, MD, Han-Joo Kim, PhD, Karen Wood, PhD, Corina Dutcus, MD, James Larkin, FRCP



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LENVATINIB

➤ **Indicação em câncer renal:** avançado 2ª linha

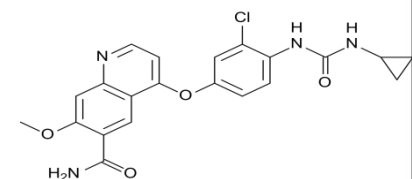
➤ **Posologia:** 18 mg/dia + Everolimus 5 mg/dia

➤ **Meia vida:** 28 horas

➤ **Manejo da dose:**

- **Renal:** Leve e moderado: sem ajuste; **Grave: 14 mg/dia**

- **Hepático:** Leve e moderado: sem ajuste; **Grave: 14 mg/dia**



TERAPIA COM INIBIDORES DE TIROSINA KINASE




National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 3.2018 Kidney Cancer

SUBSEQUENT THERAPY^m (alphabetical by category and preference)

Relapse or
Stage IV and
surgically
unresectable

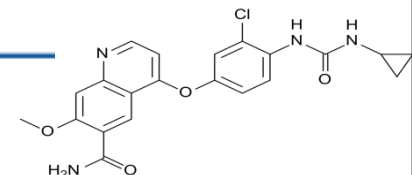
Predominant
clear cell
histology

- Clinical trial
- Cabozantinib (category 1, preferred)ⁿ
- Nivolumab (category 1, preferred)ⁿ
- Axitinib (category 1)
- Lenvatinib + everolimus (category 1) 
- Everolimus
- Pazopanib
- Sorafenib
- Sunitinib
- Bevacizumab (category 2B)
- High-dose IL-2 for selected patients^l (category 2B)
- Temsirolimus (category 2B)

and

Best supportive care:^l

[See NCCN Guidelines for Palliative Care](#)



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TKIs - TOXICIDADES

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TKIs - TOXICIDADES

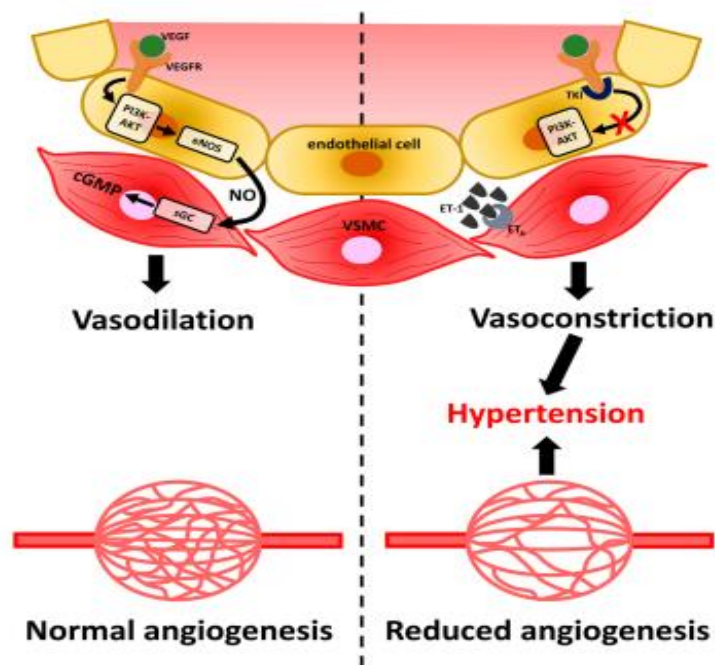
HIPERTENSÃO

↓ VEGF

↓ Oxido nítrico

↑ Vasoconstricção

↑ Resistencia Periférica



Manejo?
Anti-hipertensivos
orais

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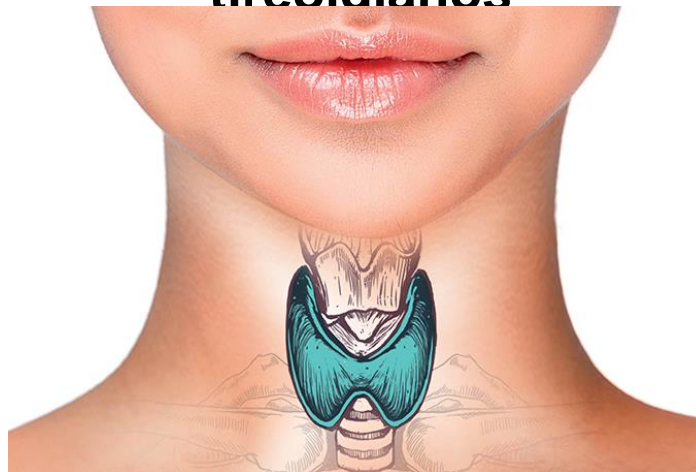
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HIPOTIREOIDISMO

Regressão dos capilares em torno dos folículos tireoidianos



Manejo?
Reposição hormonal
oral

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TKIs - TOXICIDADES

PROTEINÚRIA

The Causes of Proteinuria in Patients Receiving Anti-VEGF Therapy

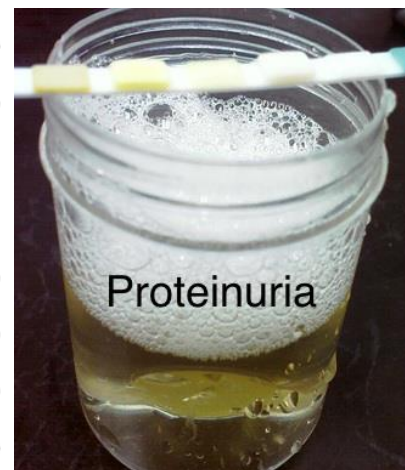
The slit diaphragm dysfunction

loss of endothelial fenestrations in the glomeruli
endothelial cells cytoplasm swelling
podocyte damage
decreased expression of nephrin

The narrowing or occlusion of capillary lumina by basement membrane

Acute interstitial nephritis

Acute tubular necrosis



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TKIs - TOXICIDADES

DIARREIA E SÍNDROME MÃO-PÉ



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Obrigado

felipe.gomes@nob-ba.com.br

