MADRID 2014 ESMO congress

Beyond tumour heterogeneity:
New pathways in kidney cancer

New Drugs and New Targets in RCC

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Disclosure slide

- Research-related funding:

Astellas, AZ, BMS, Eisai, GSK, Janssen, Lilly, Merck, Millenium, Nanobiotix, Novartis, OncoMed, Pfizer, PharmaMar, PsiOxus, Roche/Genentech, Sanofi, Spectrum

- Consultation fee/honoraria:

Astellas, Nanobiotix, Novartis.

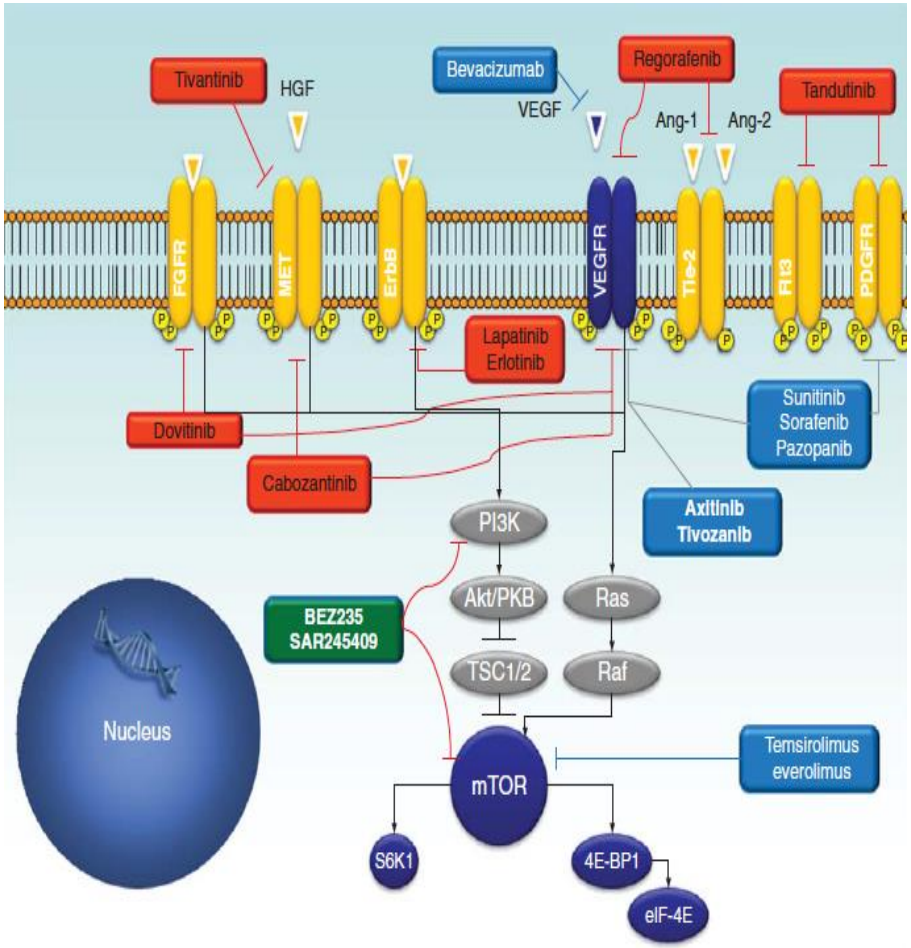
Unmet Needs for Novel Agents in mRCC

- Approved treatments are not curative; median overall survival remains suboptimal and patients ultimately progress
- Drug resistance is a major challenge for both VEGF-targeted therapies and mTOR inhibitors
- Off-target effects can occur with VEGF-targeted therapies and account for some clinically relevant toxicities

Therapeutic agents that target multiple/alternative pathways involved in RCC are currently under investigation

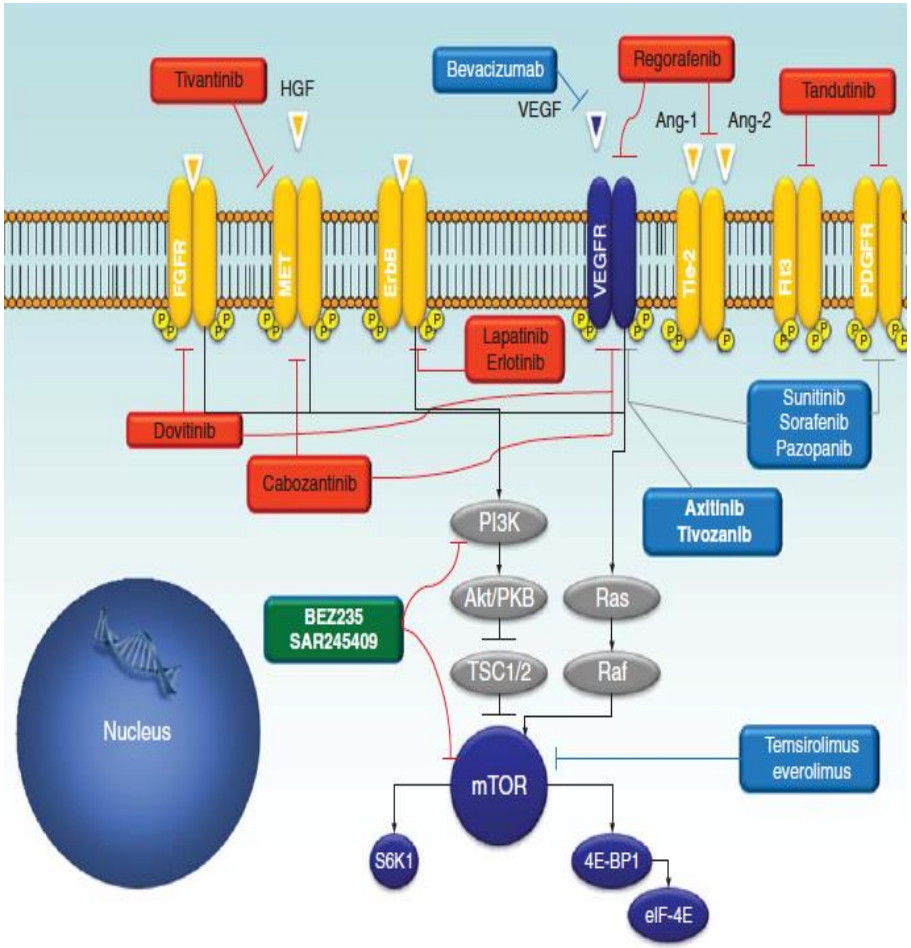
1. Hanahan D, Weinberg RA. *Cell.* 2011;144:646-74.
2. Dancey J. *Nat Rev Clin Oncol.* 2010;7:209-19.

Unmet Needs for Novel Agents in mRCC



- More selective VERGr-TKIs
  (Less toxicity)
  - Tivozanib
- Different targets
  (More activity)
  - cMET (cabozantinib, foretinib)
  - Tie-2 (regorafenib)
  - ALK1/ENG inh
  - PI3K/Akt/mTOR inh

Agenda *(non-immunotherapeutic agents)*

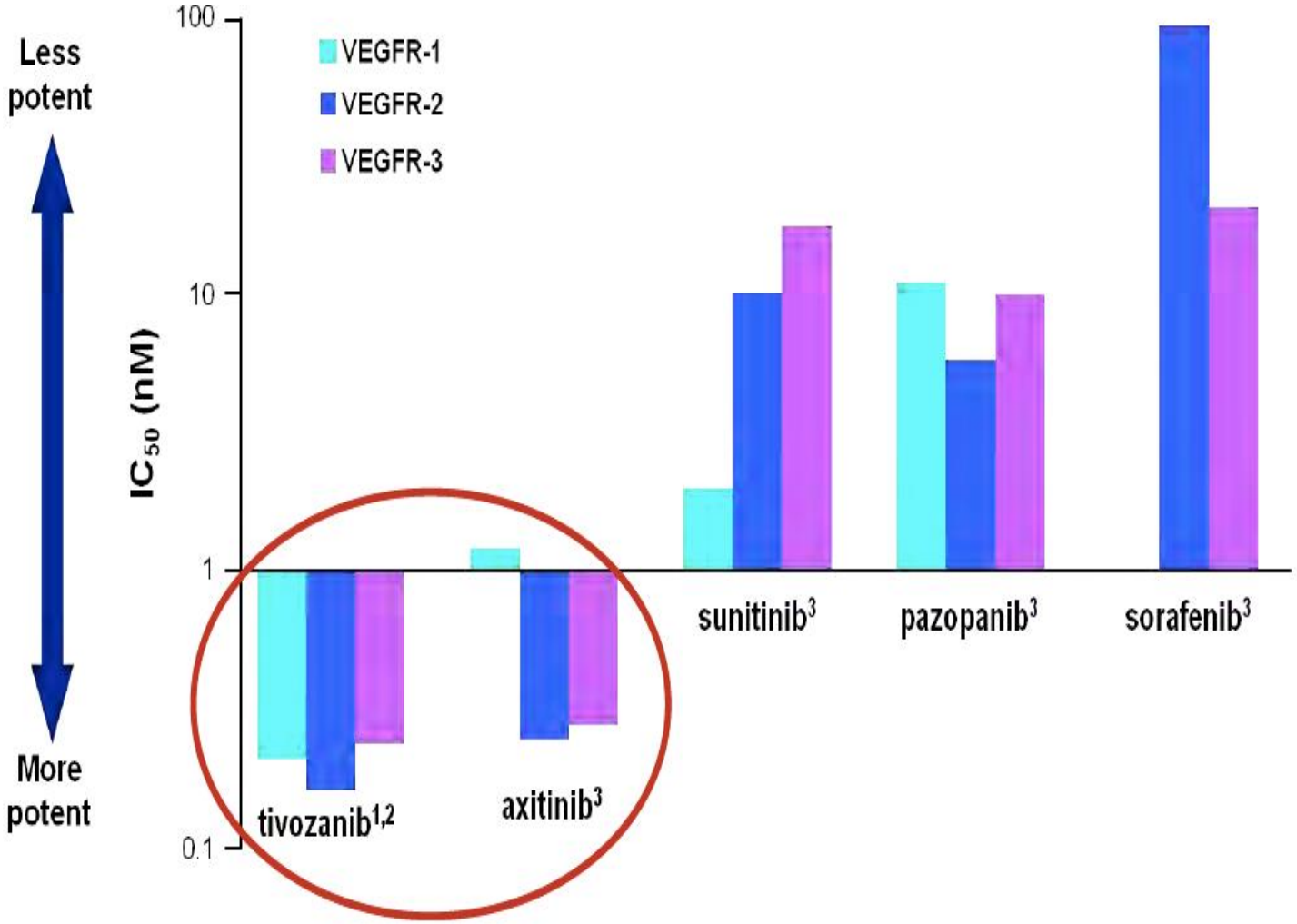


1. **Novel pure antiangiogenics**
   - Tivozanib (VEGFr inh paradigm)
   - Cabozantinib
   - Foretinib
   - Regorafenib
   - Angiopoietin inh
   - ALK1/ENG inh

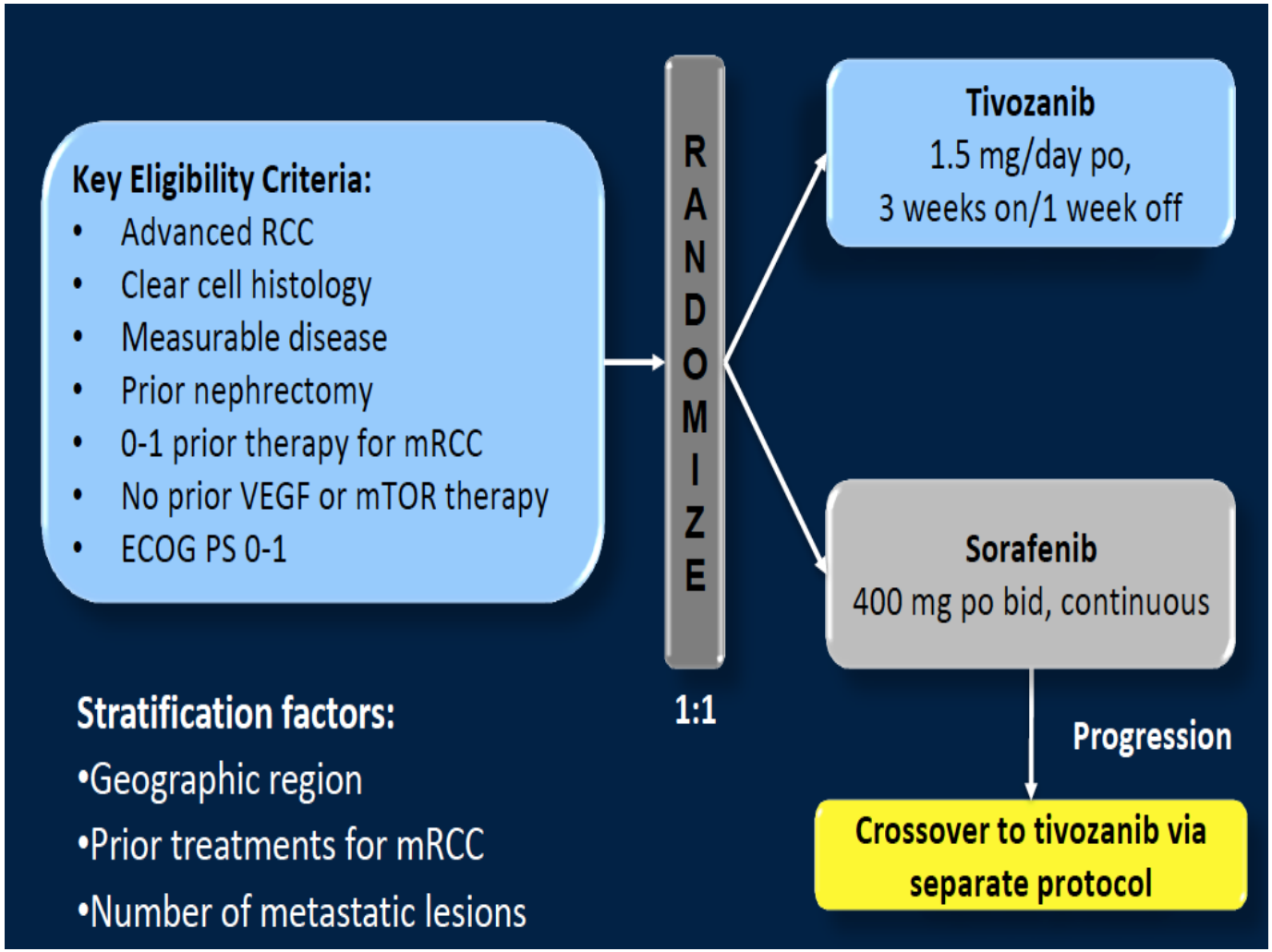
2. **Novel PI3K/Akt/mTOR inh**
   - panPI3K/mTOR inh

1. Novel Antiangiogenics

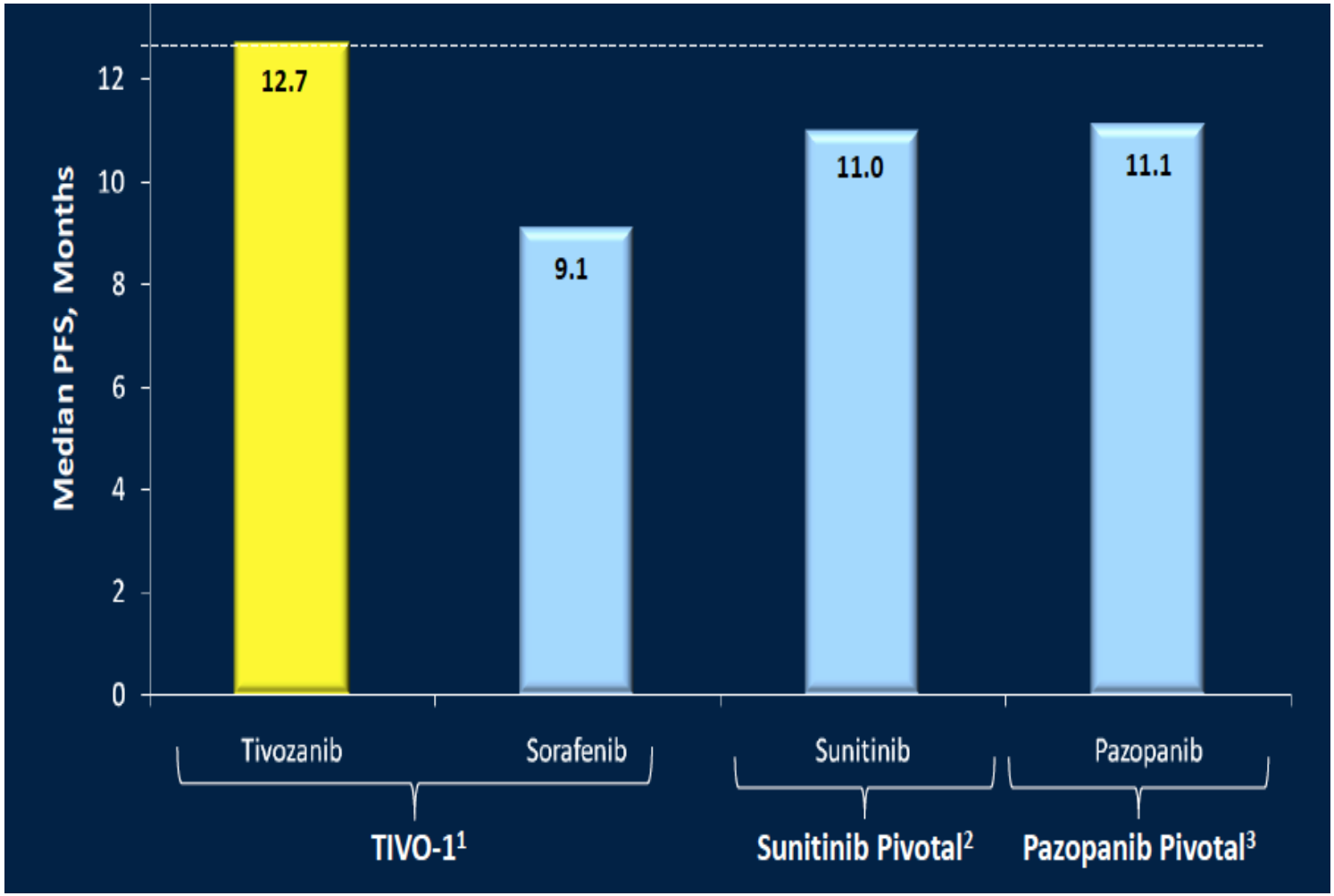
- **Tivozanib's paradigm** (VEGFR inh)
- Cabozantinib (c-MET, VEGFR inh)
- Foretinib (c-MET, VEGFR, Tie-2 inh)
- Regorafenib (VEGFR, PDGFR, FGFR, Tie-2 inh)
- Angiopoietin inhibitors (Trebananib, CVX060)
- ALK1/ENG inhibitors


Less potent
More potent
100
10
1
0.1
IC50 (nM)
VEGFR-1
VEGFR-2
VEGFR-3
tivozanib1,2
axitinib3
sunitinib3
pazopanib3
sorafenib3

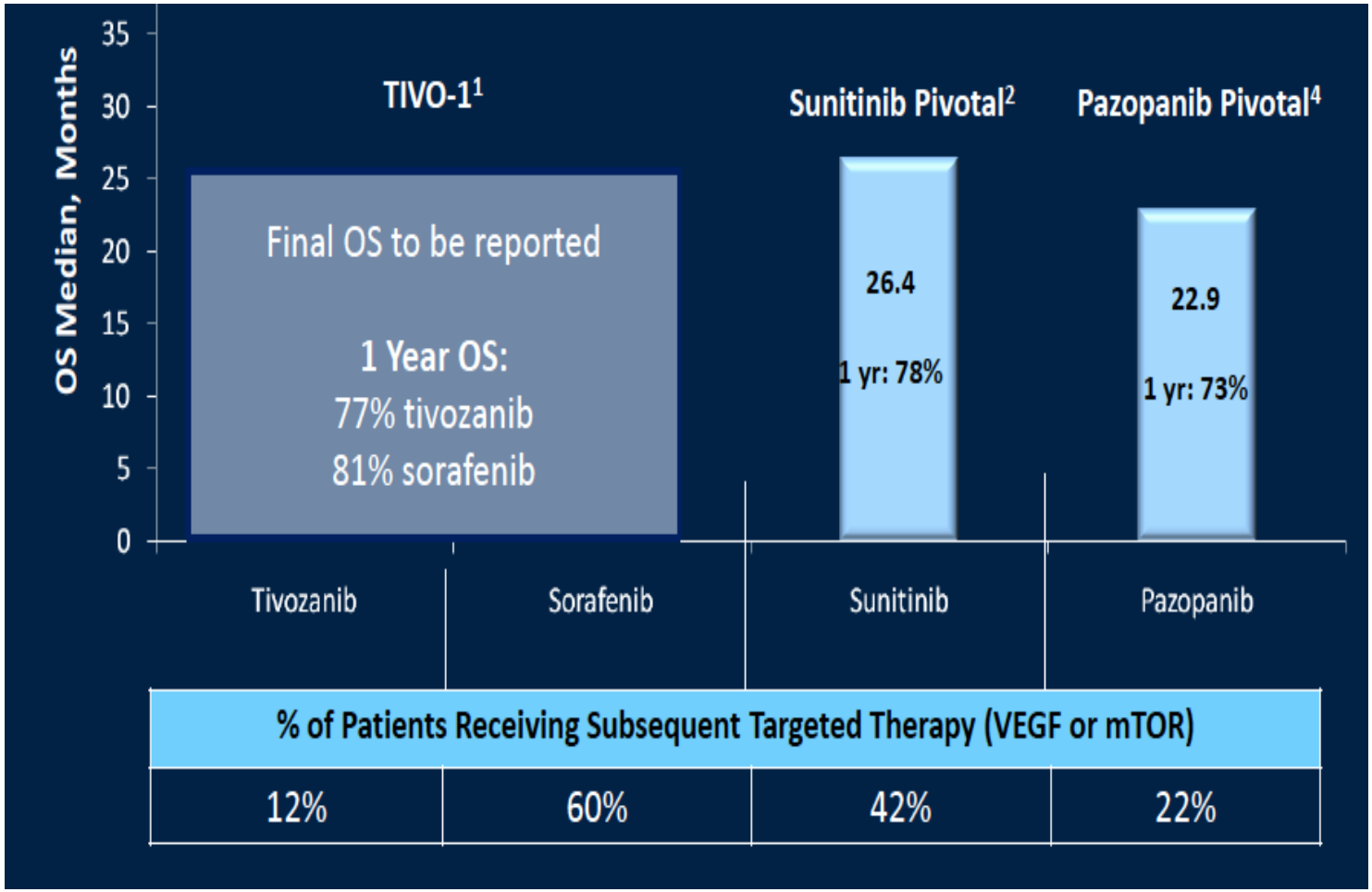
Tivo-1


Key Eligibility Criteria:
• Advanced RCC
• Clear cell histology
• Measurable disease
• Prior nephrectomy
• 0-1 prior therapy for mRCC
• No prior VEGF or mTOR therapy
• ECOG PS 0-1
RANDOMIZE
1:1
Tivozanib
1.5 mg/day po,
3 weeks on/1 week off
Sorafenib
400 mg po bid, continuous
Progression
Crossover to tivozanib via separate protocol
Stratification factors:
•Geographic region
•Prior treatments for mRCC
•Number of metastatic lesions

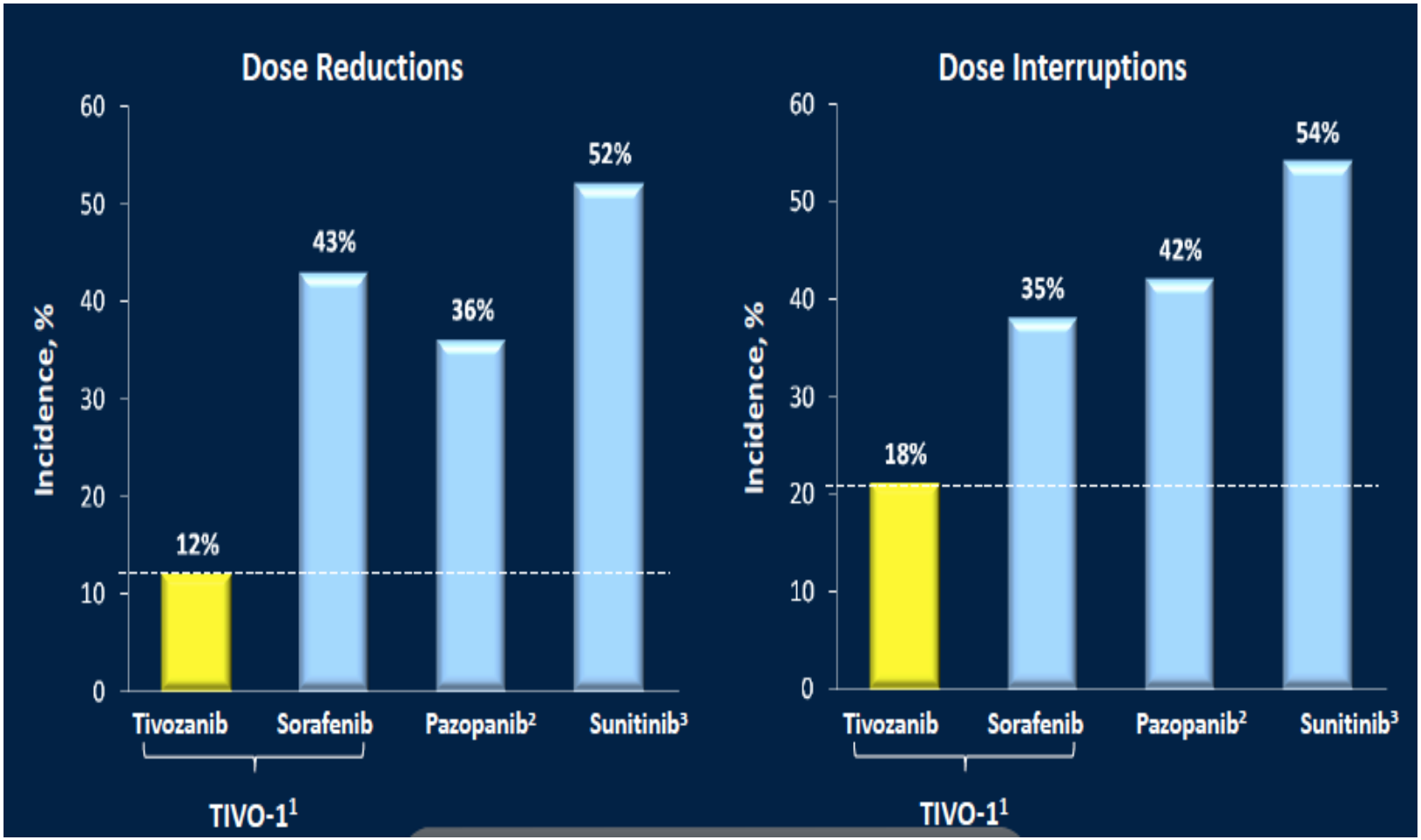
First-line VEGFr-TKIs: PFS



First-line VEGFr-TKIs: 1st year OS



First-line VEGFr-TKIs: toxicity

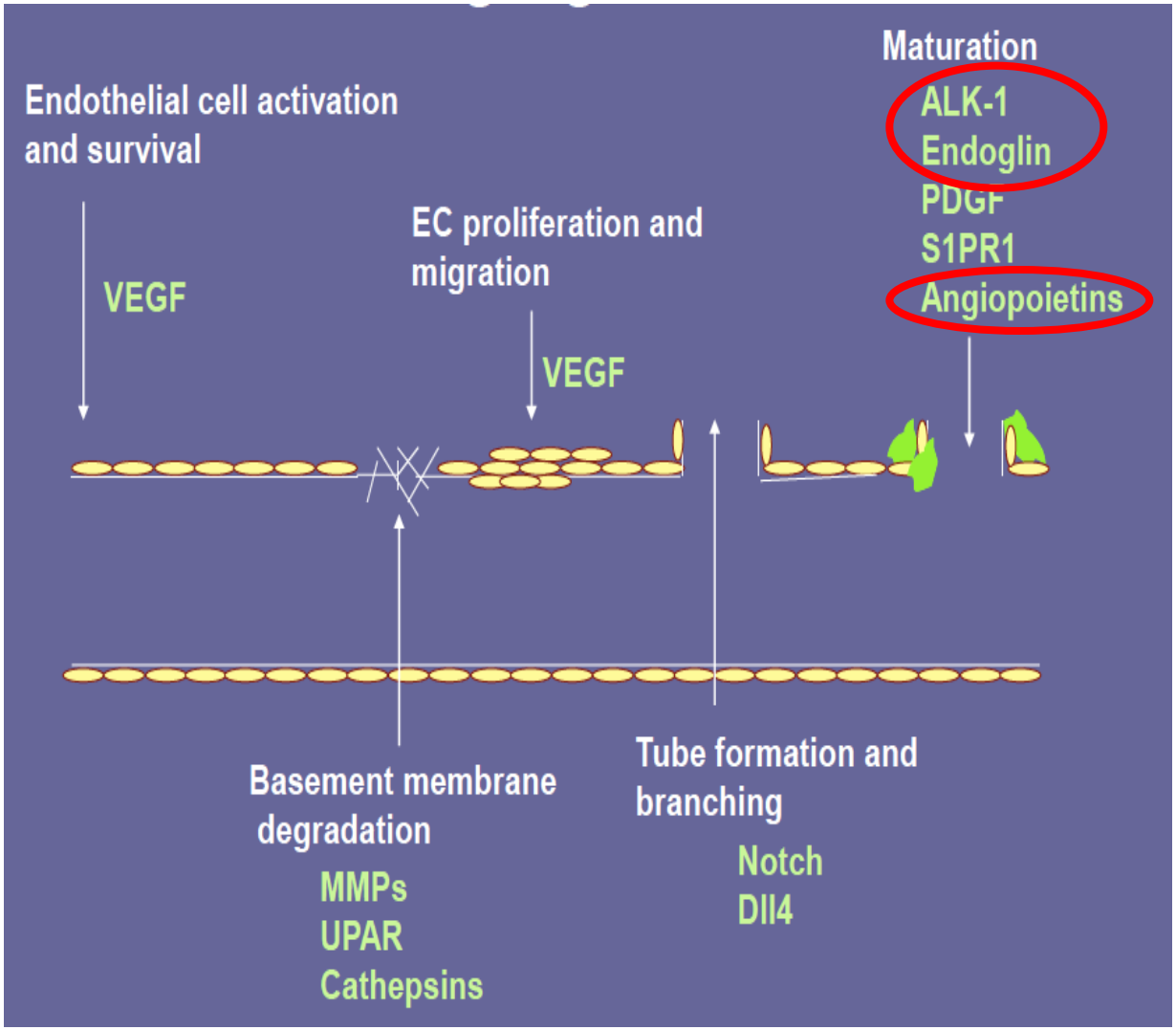


Some "me too" VEGFr-TKIs in Develop

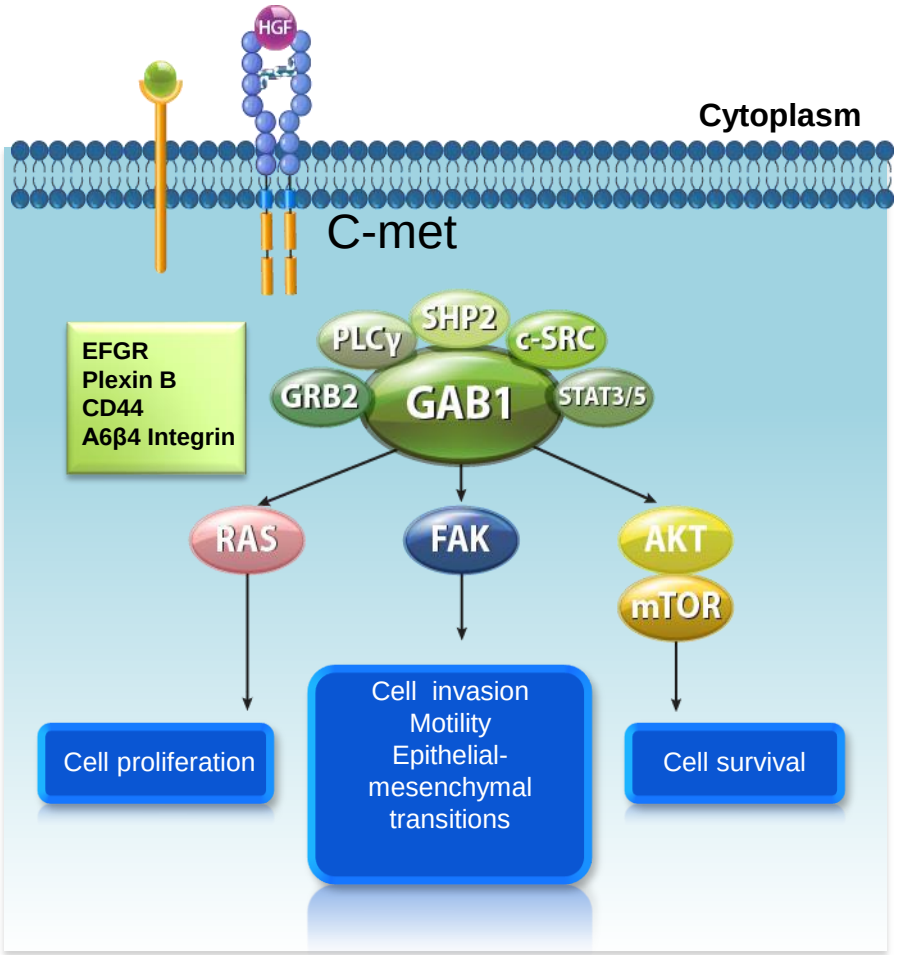
Drug	MOA	Description	Efficacy
Nintedanib[1] (BIBF 1120)	Multi-kinase inhibitor (VEGFr-1 to 3, FGFr-1 to 3 and PDGFr-α and β tyrosine kinases)[1]	Phase II study in untreated patients, vs sunitinib	Ongoing [NCT01024920]
Linifanib[2] (ABT-869)	Inhibitor of VEGF and PDGF receptor TKIs[2]	Phase II study in sunitinib-refractory patients completed	mPFS: 5.4 mo mOS: 14.5 mo
Cediranib[3]	Inhibitor of VEGFr-1, -2 and -3	Phase II study of pts with no prior VEGF inhibitor, vs placebo	mPFS: Cediranib: 12.1 mo Placebo: 2.8 mo

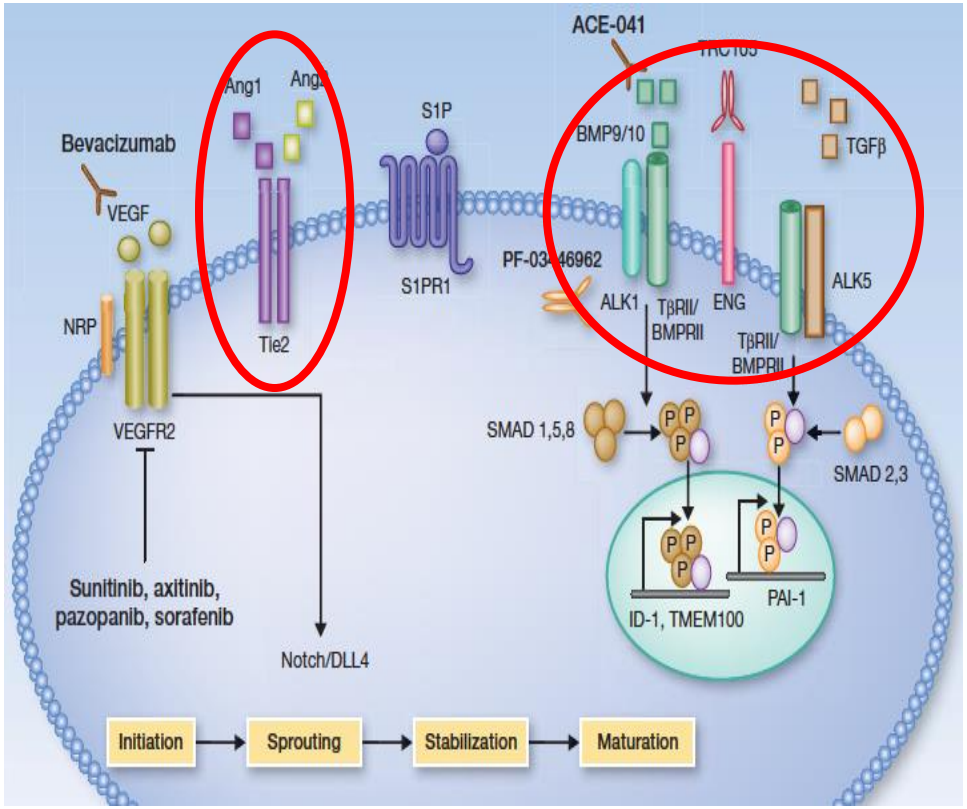
1. Mross K et al. *Clin Cancer Res.* 2010;16:311-9.
2. Tannir NM et al. *Eur J Cancer.* 2011;47:2706-14.
3. Mulders P et al. *Eur J Cancer.* 2012;48:527-37.

Novel antiangiogenic agents



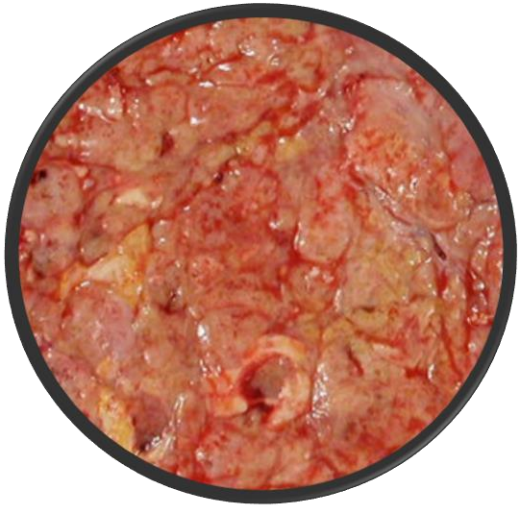
Novel antiangiogenic agents





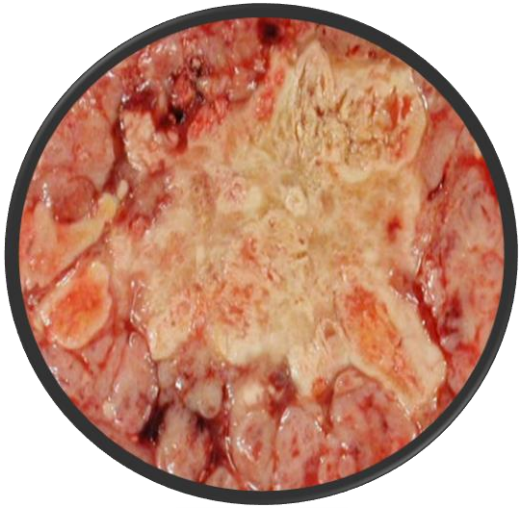
Clinical Challenge for New Antiangiogenics

Genuine hypoxia



Vascular embolization
Angiogenesis inhibitors

Second run of hypoxia



Primary 'angiogenic' switch

Cancer cell proliferation

VEGFR/PDGFR
mTOR

Second 'angiogenic' switch

Cancer cell migration

FGF/FGFR
SDF-1/CXCR4

HGF/MET
TGFβ/ ALK1R,ENG

1. Novel Antiangiogenics

- Tivozanib's paradigm (VEGFR inh)
- **Cabozantinib** (c-MET, VEGFR inh)
- Foretinib (c-MET, VEGFR, Tie-2 inh)
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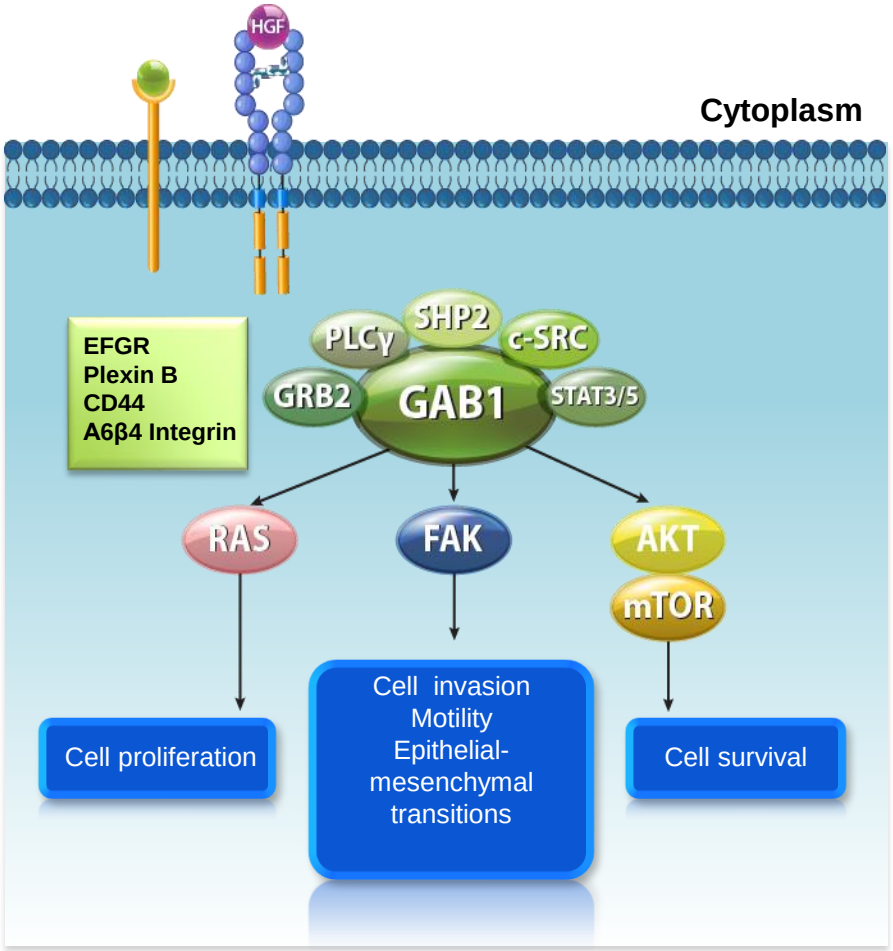
Evasive resistance to VEGF-targeted therapies may occur via MET



- c-MET is a RTK that, after binding its ligand HGF, activates signalling pathways involved in cell proliferation, motility, migration and invasion[1,2]
- c-MET signalling is activated by tumour hypoxia and may be important in resistance to VEGF-targeted agents in cancer therapy[3]
- **Cabozantinib** and **Foretinib** inhibit MET and VEGFr-2[3]

1. Aftab DT et al. *Clin Transl Oncol.* 2011;13:703-9.
2. Organ SL. *Ther Adv Med Oncol.* 2011;3:S7-19.
3. Eder JP et al. *Clin Cancer Res.* 2009;15:2207-14.

Cabozantinib: Anti-tumour Activity in mRCC

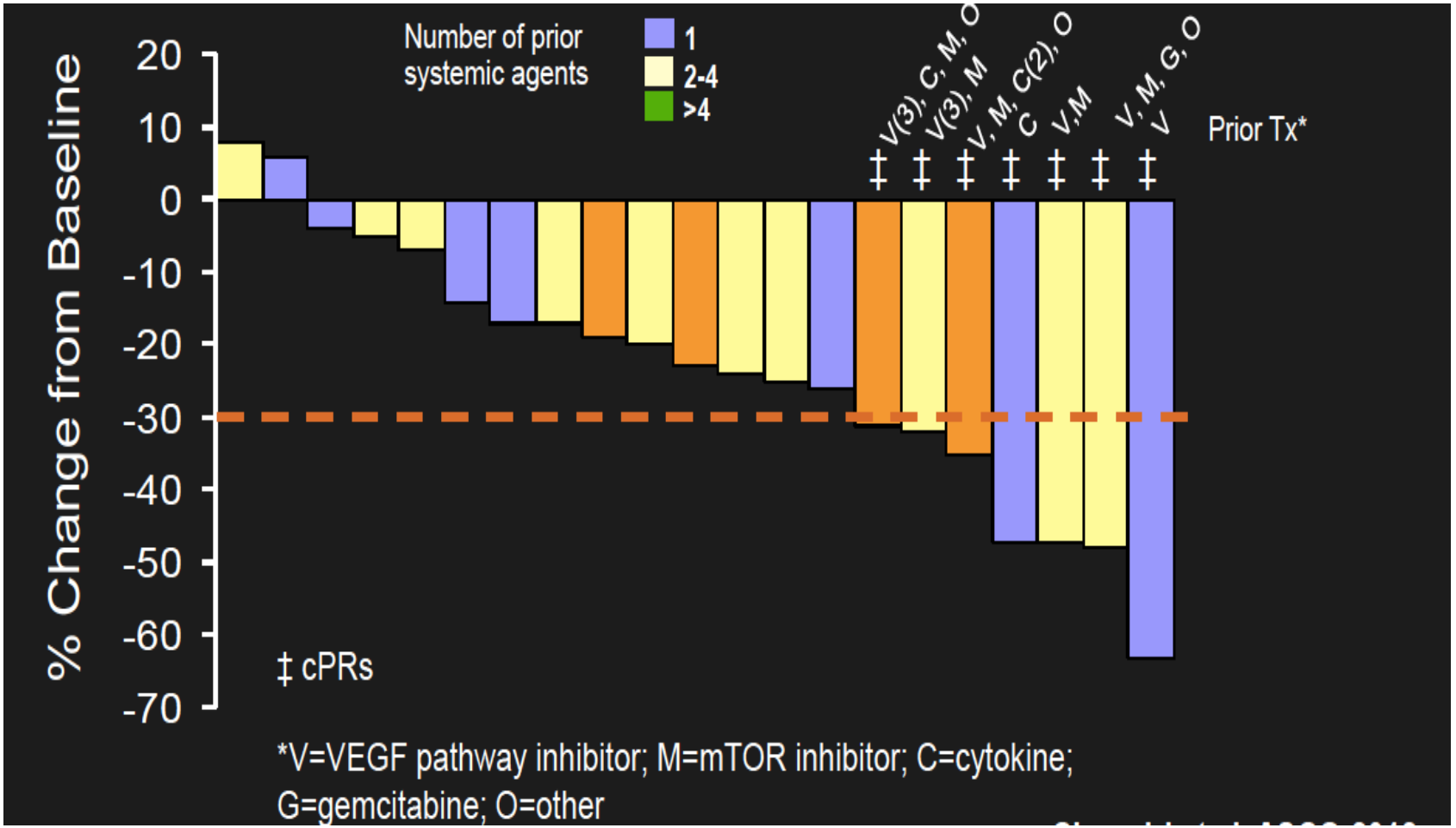
- Anti-tumour activity of cabozantinib was evaluated in a Phase I drug-drug interaction study in 25 patients with heavily-pretreated mRCC
  - Patients with PD following standard therapies received cabozantinib (140 mg) and rosiglitazone (4 mg)

Outcome	
Disease control rate (PR + SD) at 4 months	**72%**
% of tumour regression (range, reduction in measurements)	**–4% to –63%**
Median PFS (95% CI)	**14.7 month (7.3 to NR; 8 events)**

AEs ≥ Grade 3 severity: hypophosphatemia (36%), hyponatremia (20%), and fatigue (16%)

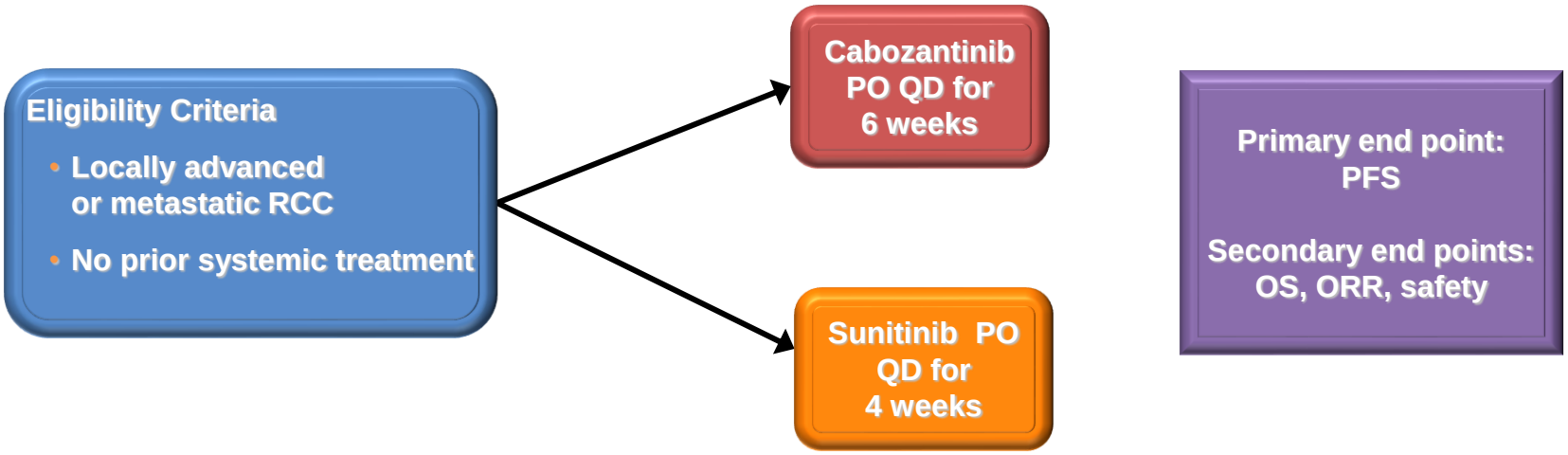
Chouieri TK et al. *J Clin Oncol.* 2012;30: abstract 4504.

Cabozantinib: Anti-tumour Activity in mRCC



Chouieri TK et al. *J Clin Oncol.* 2012;30: abstract 4504.

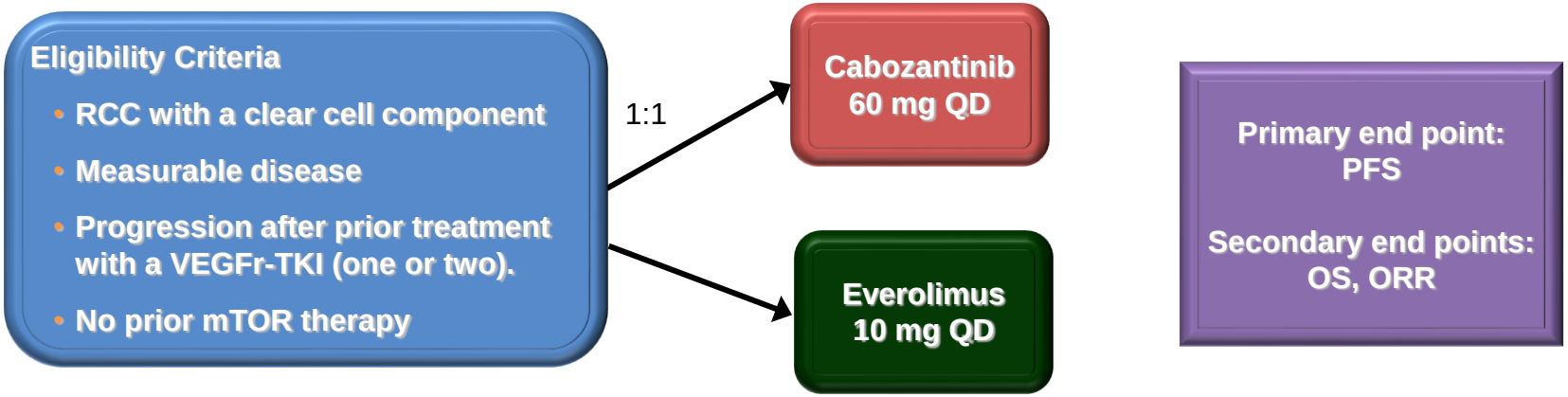
ALLIANCE/CALGB Phase II Study of First-line Cabozantinib vs Sunitinib in Patients with mRCC



- Cabozantinib 60 mg (Label dose for thyroid medullary cancer: 140 mg)

Target enrolment: 150 patients
Study completion date: 2013.

METEOR Study: Phase III study of Cabozantinib vs. Everolimus



- Cabozantinib 60 mg (Label dose for thyroid medullary cancer: 140 mg)

Target enrolment: 650 patients
Estimated study completion date: 2015.

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Ph2 in papillary RCC: ORR and toxicity

Foretinib inhibit cMET and VEGFr2 potently; also, Tie2

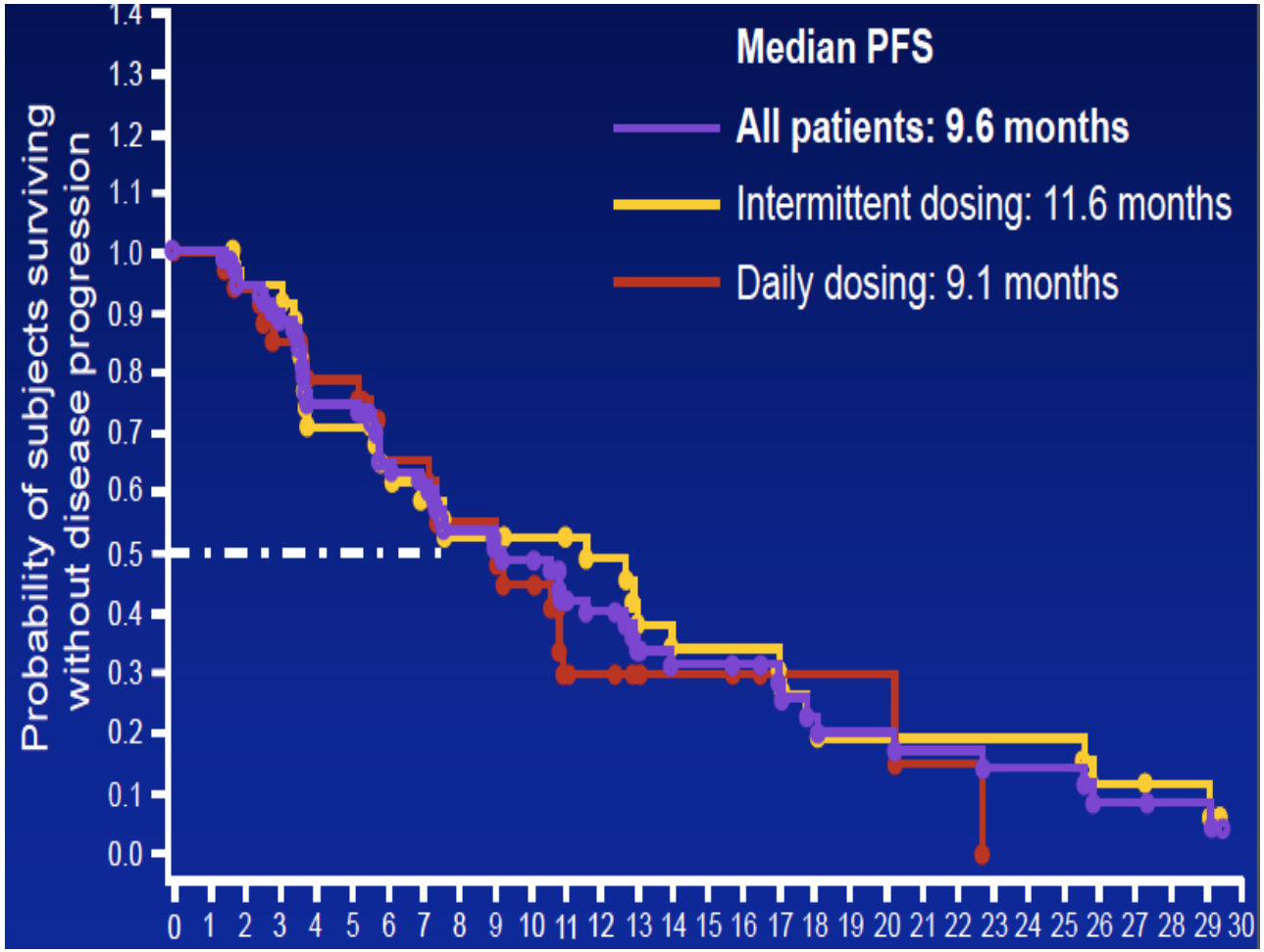
	Intermittent dosing (n=37)	Daily dosing (n=37)	TOTAL (N=74)
Overall Response Rate n (%)	5 (13.5)	5 (13.5)	10 (13.5)

- Duration of response: 18.5 months
- Disease stabilization rate (ORR + Stable Disease): 88%

- Fatigue, G-I tox, hypertension; pulmonary emboli

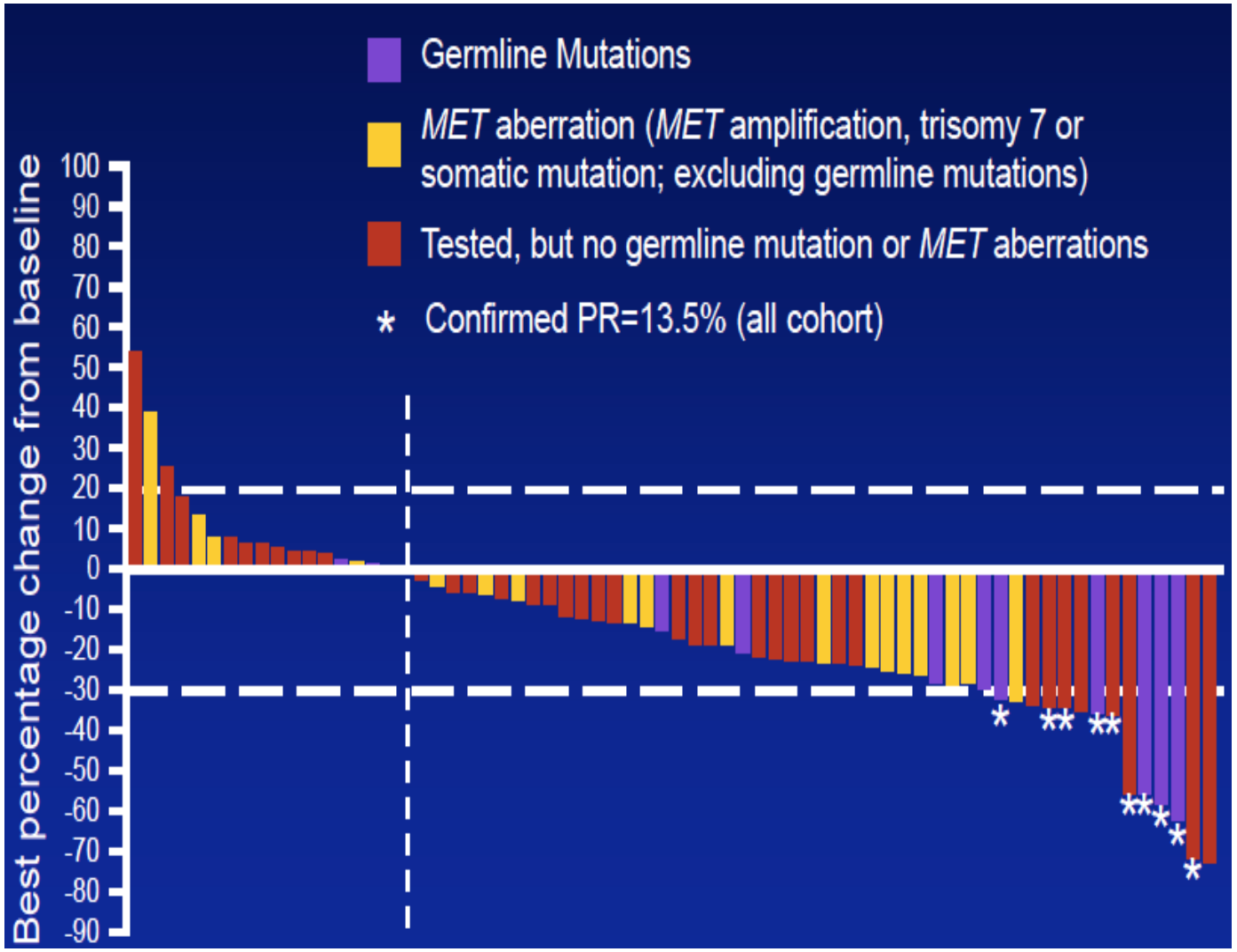
Choueiri, JCO 2012.

Ph2 in papillary RCC: PFS



Choueiri, JCO 2012.

Ph2 in papillary RCC: tumour shrinkage



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- ALK1/ENG inhibitors

Regorafenib for patients with previously untreated metastatic or unresectable renal-cell carcinoma: a single-group phase 2 trial

Tim Eisen, Heikki Joensuu, Paul D Nathan, Peter G Harper, Marek Z Wojtukiewicz, Steve Nicholson, Amit Bahl, Piotr Tomczak, Seppo Pyrhonen, Kate Fife, Petri Bono, Jane Boxall, Andrea Wagner, Michael Jeffers, Tiffany Lin, David I Quinn

- First line therapy with **regorafenib** (inhibitor of VEGFR, PDGFR, FGFR, *TIE2*)
- Regorafenib 160 mg/day (3 week on, 1 week off)
- Primary endpoint: ORR
- N = 49 patients

Eisen, Lancet 2012.

Ph2 of regorafenib in RCC: ORR

	Patients (n [%])	90% CI (%)
Objective response	19 (39·6%)	27·7–52·5
Complete response	0 (0·0%)	0·0–4·7
Partial response	19 (39·6%)	27·7–52·5
Stable disease	20 (41·7%)	29·6–54·6
Disease progression	5 (10·4%)	4·2–20·7
Could not be assessed*	4 (8·3%)	2·9–18·1

Eisen, Lancet 2012.

Ph2 of regorafenib in RCC: toxicity

	Grade 3 or 4	All grades
Any event	35 (71%)	48 (98%)
Hand and foot skin reaction	16 (33%)	35 (71%)
Fatigue	4 (8%)	26 (53%)
Hypertension	3 (6%)	24 (49%)
Diarrhoea	5 (10%)	22 (45%)
Alopecia	0 (0%)	22 (45%)
Mucositis (functional or symptomatic) in the mouth	1 (2%)	21 (43%)
Rash or desquamation	3 (6%)	19 (39%)
Voice changes	0 (0%)	17 (35%)
Anorexia	3 (6%)	14 (29%)
Nausea	0 (0%)	13 (27%)
Constipation	0 (0%)	12 (24%)
Vomiting	0 (0%)	11 (22%)
Renal failure	5 (10%)	5 (10%)

- Two grade 4 cardiac ischemic events
- Two toxic deaths (hemoptisis, cardiac arrest)

Eisen, Lancet 2012.

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- **Angiopoietin inhibitors** (Trebananib, CVX060)
- ALK1/ENG inhibitors

Trebananib

- The angiopoietins, Ang-1 and Ang-2, are ligands for Tie-1 and Tie-2, which are endothelial receptors (blood-vessel maturation, integrity and stability)
- Trebananib (AMG-386) is an anti-angiopoietin peptibody (peptide-Fc fusion protein) that can disrupt the Ang/Tie-2 axis
- Phase II study of sunitinib plus sequential cohorts of trebananib at either 10 mg/kg or 15 mg/kg:
  - PFS of 13.9 months and more than 16.0 months for the two cohorts, respectively.
  - The ORRs were 58% and 59%, respectively,
  - Virtually all side effects were attributable to sunitinib.
- Disappointing results with sorafenib plus trabananib (?)

Atkins, JCO 2012

CVX-050/PF-04856884

- CVX-050 is a humanized monoclonal antibody fused to two Ang-2 binding peptides

- Phase Ib study of CVX-050 plus axitinib in pretreated RCC
  - N = 18 pts
  - Most common related AEs: anorexia in 10 pts (56%), diarrhea 8 (44%), fatigue 8 (44%), nausea 7 (39%), hypertension 6 (33%) and vomiting 6 (33%).
  - Treatment-related thromboembolic events (TEEs) were observed: PE in 2 pts (11%), and cerebrovascular accident (CVA), presumed bowel ischemia, and possible cardiac chest pain in 1 pt (6%) each.
  - Three partial responses

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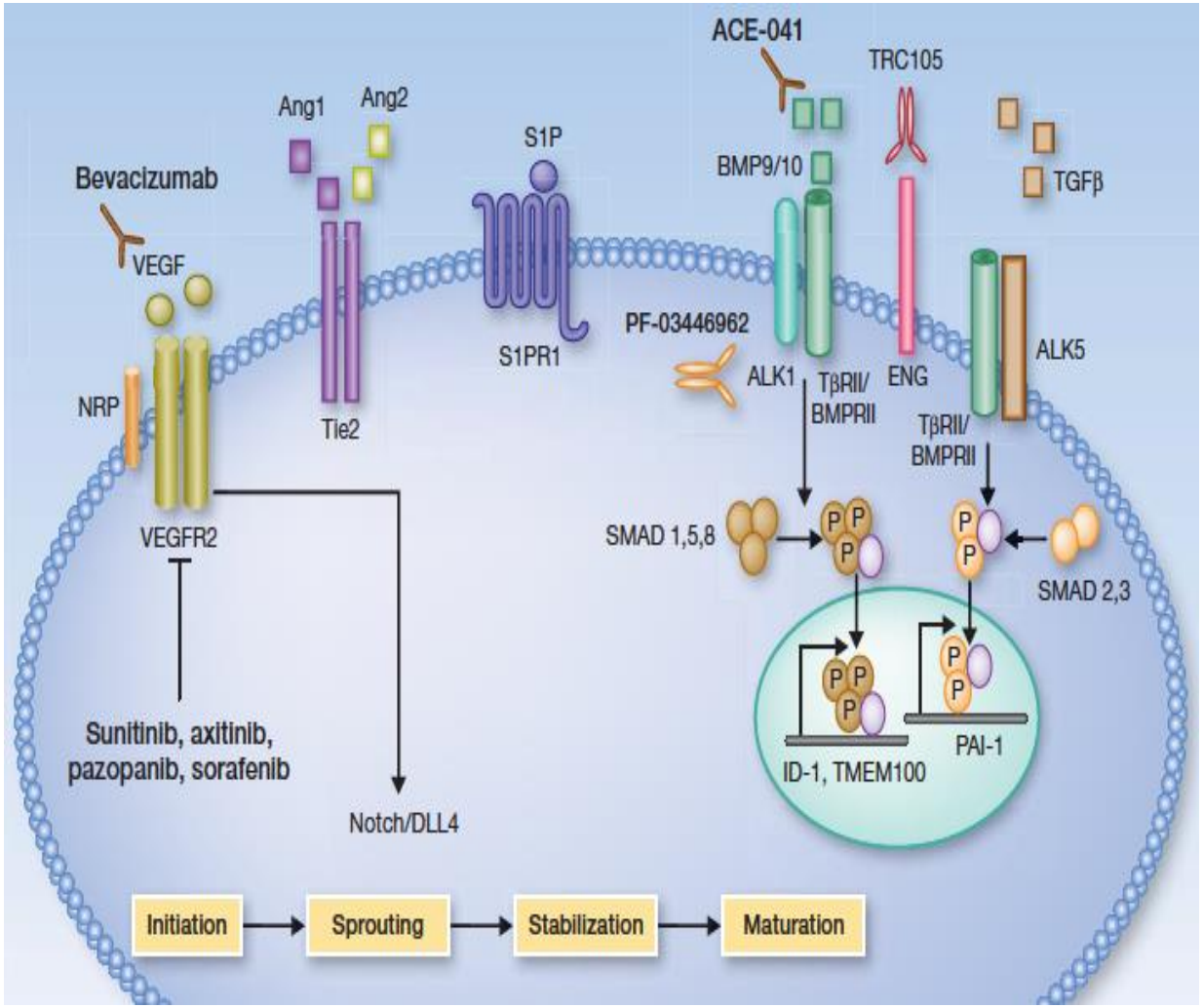
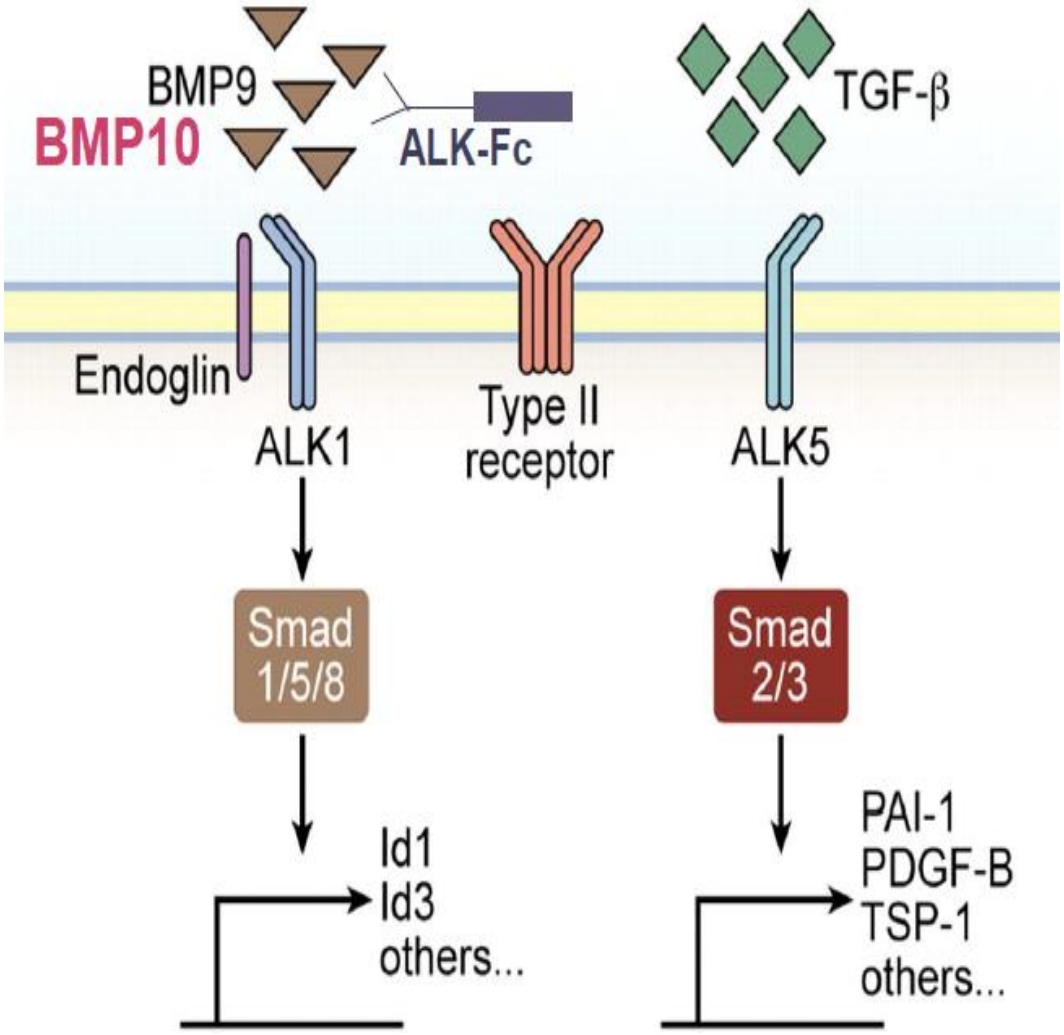
- **ALK1/ENG inhibitors**

Activin Like Kinase (ALK-1) and Endoglin (ENG) Receptors



- Type 1 TGFbR superfamily member
- Expressed on activated Endothelial Cells
- ALK1R loss leads to Hereditary Telangiectasia Syndrome

ALK-1 and ENG receptors Inhibitors in the Clinic

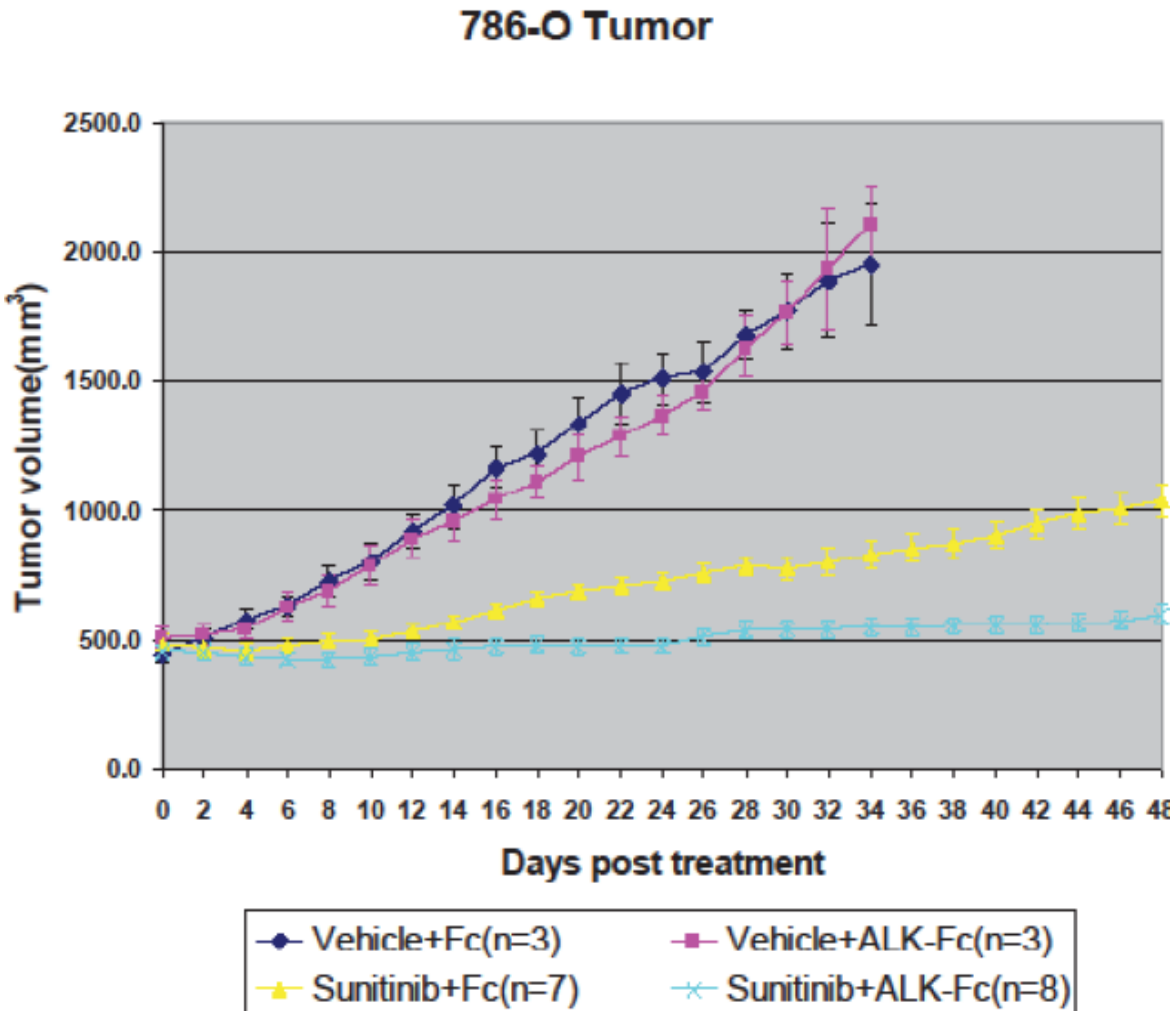


- **ALK-1-Fc** (Genentech) and hALK-1-Fc fusion protein (ACE-041, **delantercept**) binds to and neutralized activity of BMP9 and 10
- MoAb against ALK-1 Receptor (**PF 3446962**)
- MoAB against ENG Receptor (**TRC 105**)

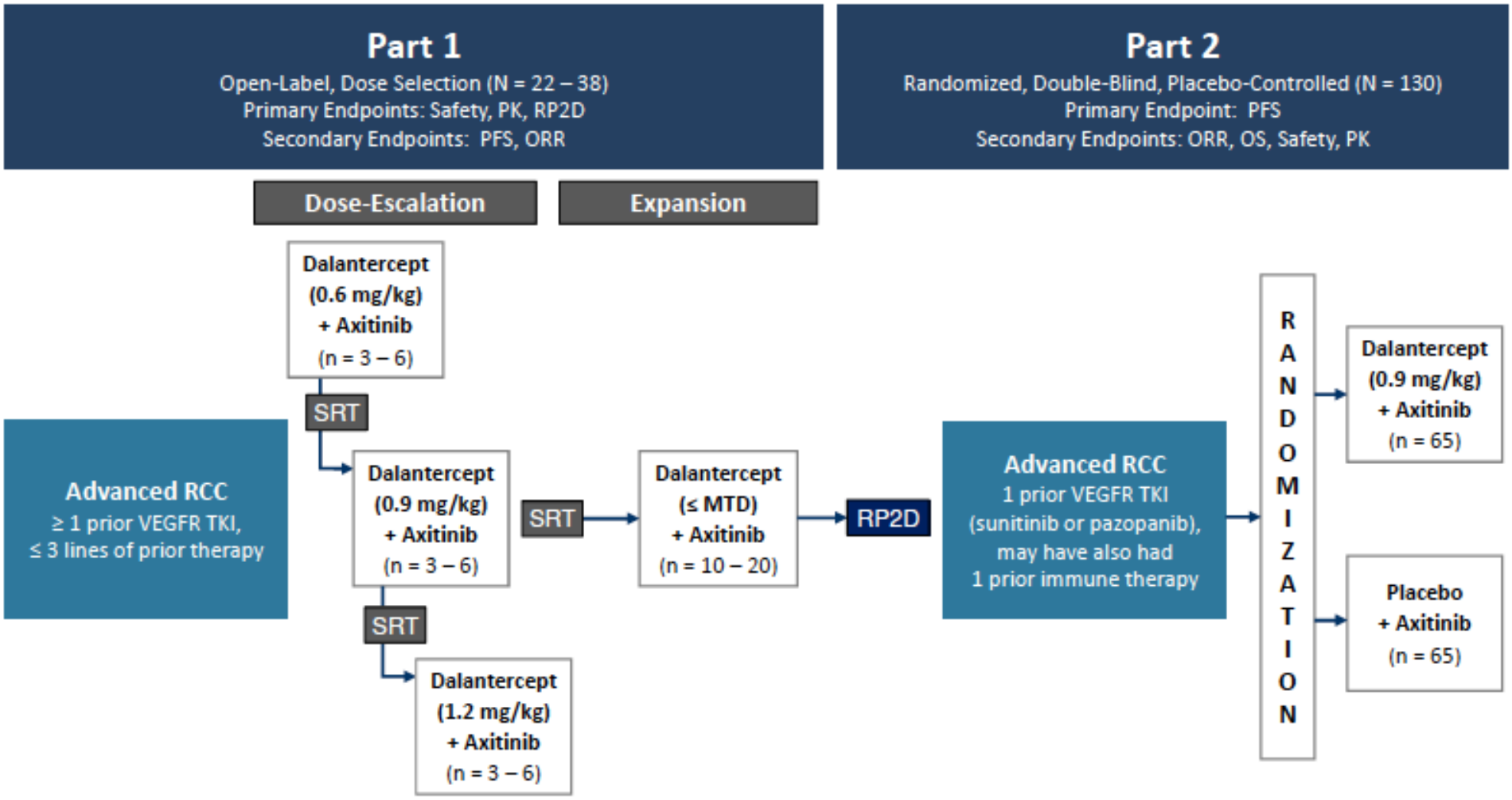
All of them exhibit good tolerance and antiangiogenic activity

- Ph1-2, active ACE041 and TRC105 in RCC

Synergistic activity of sunitinib and ALK-Fc, in vivo



Dalantercept + Axitinib



Atkins et al, ASCO 2014

Dalantercept + Axitinib (phase 1 part results)

Objective Response Rate Analyses RECIST 1.1*				
Endpoint	**0.6 mg/kg** (N = 4)	**0.9 mg/kg** (N = 4)	**1.2 mg/kg** (N = 12)	**Overall** (N = 20)
Partial Response, n (%)	2 (50.0)	1 (25.0)	2 (16.7)	5 (25.0)
Stable Disease, n (%)	0	3 (75.0)	7 (58.3)	10 (50.0)
Disease Control Rate ≥ 6 cycles, n (%)	2 (50.0)	2(50.0)	7 (58.3)	11 (55.0)
Progressive Disease, n (%)	2 (50.0)	0	3 (25.0)	5 (25.0)

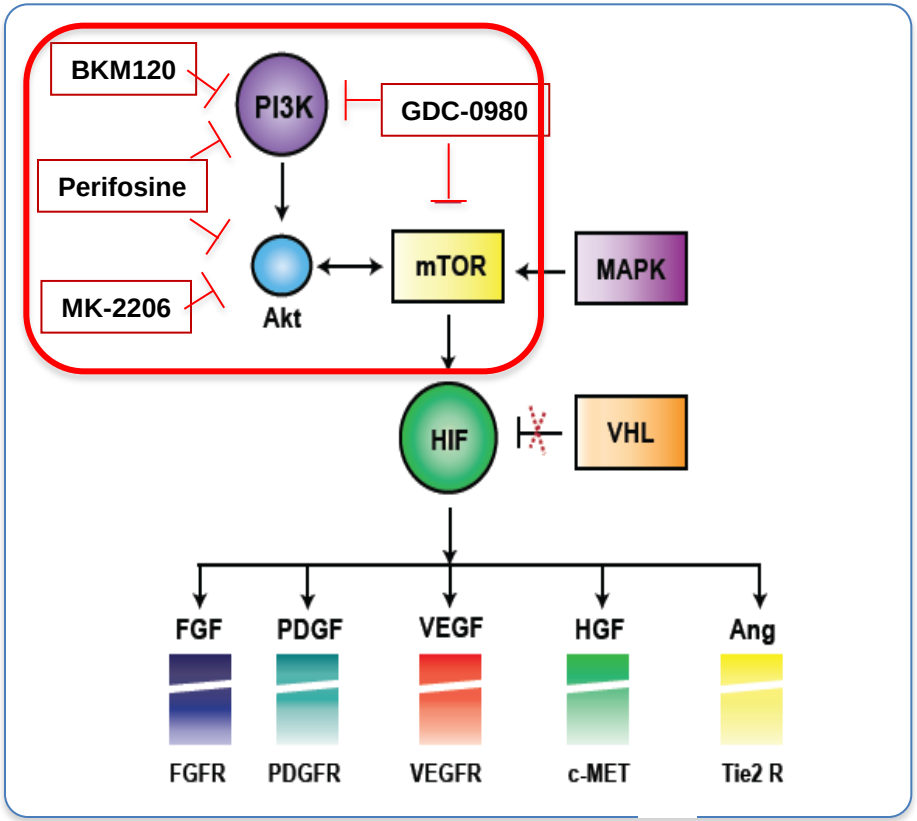
Common toxicities of axitinib plus peripheral edema (improved with decreased dose of daltantercept)

Atkins et al, ASCO 2014

2. Novel PI3K/Akt/mTOR Inhibitors

- There may be a limit to what can be expected with agents which primarily only target tumor endothelium
- PI3K/Akt/mTOR has been shown to be constitutively activated in approximately half of RCC and degree of activation correlated with worse clinical outcome
- Potential improvement upon rapalogues
  - Better inhibition of mTOR
  - Inhibitors of PI3K or Akt
  - Dual inhibitors of PI3K/mTOR

Novel PI3K/Akt/mTOR Inhibitors



- Novel non-allosteric kinase inhibitors are small molecules that block the ATP binding sites of specific kinases in the PI3K/mTOR pathway

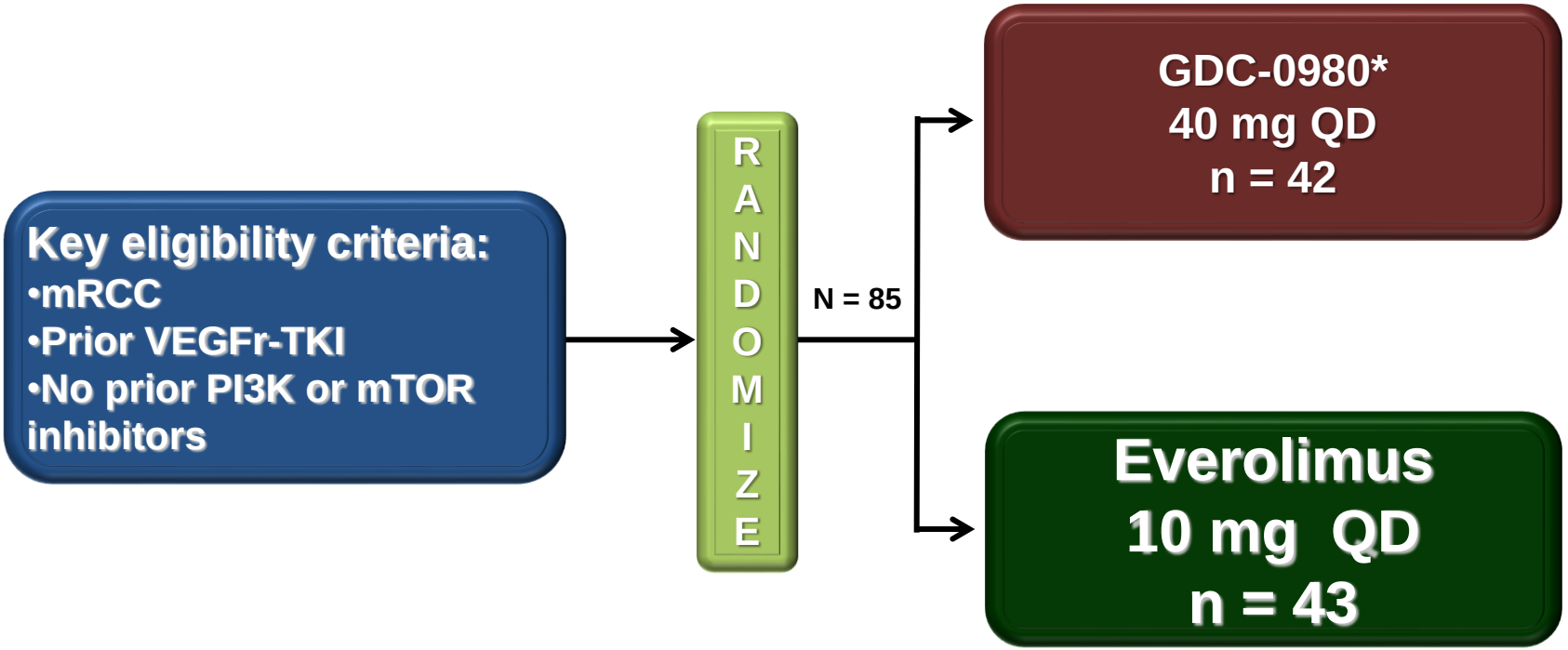
Adapted from Cowey CL, Hutson TE. *Clin Adv Hematol Oncol.* 2010;8:357-64.

Novel PI3K/Akt/mTOR inhibitors

Drug	MOA	Trial Status
AZD-8055[1]	Specific inhibitor of mTOR kinase, inhibits mTORC1 and mTORC2	Phase I/II open-label study, completed; results not reported (NCT00731263)
Buparlisib (BKM-120) BYL719	Selectively inhibits PI3K in an ATP-competitive fashion	Phase I study, completed
MK-2206[6]	Allosteric Akt-1/Akt-2 inhibitor	Phase II study in VEGFr-TKI-refractory patients, vs everolimus, recruitment suspended
GDC-0980 BEZ-235	Dual PI3K and mTOR kinase inhibitor	Demonstrated anti-tumour activity in phase I· Now, Ph2
Perifosine[5]	PI3K/Akt pathway inhibitor[5]	Phase II study in VEGFr-TKI-refractory patients; mPFS, 14.2 wk[5]

1. Chresta C et al. *Cancer Res.* 2010;70:288-98.
2. Maira S-M et al. *Mol Can Ther.* 2012;11:317-28.
3. Wallin J et al. *Mol Cancer Ther.* 2011;10:2426-36.
4. Wagner AJ et al. Presented at ASCO Annual Meeting; 3–7 June 2011; abstract 3020.
5. Cho DC et al. *Cancer*. 2012;118:6055-62.
5. Jonasch E et al. *J Clin Oncol.* 2013;31: abstract 4517.

ROVER study



Primary end point: PFS (investigator)
Secondary end points: safety, OS, ORR, Duration of Response, PL

QD, once daily.

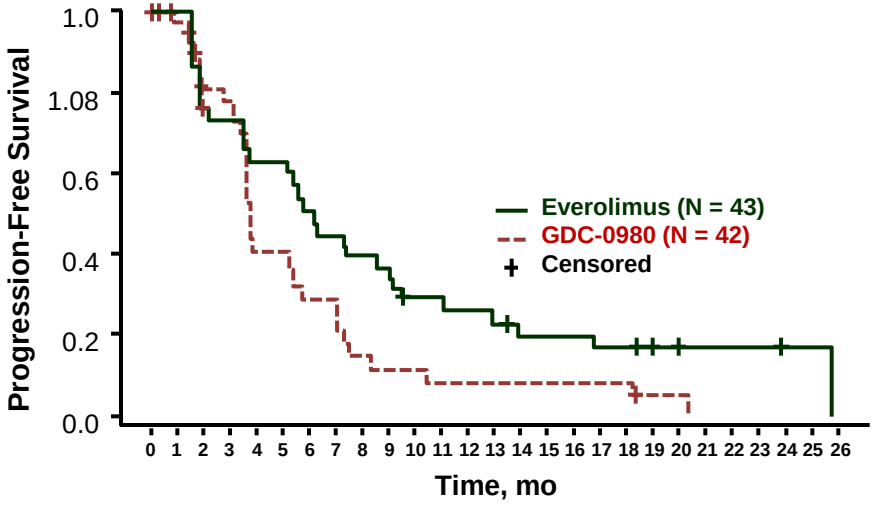
Powles T et al. ASCO Symposium; May 30-June 3, 2014, Chicago, IL, USA. abstract 4525.

*GDC-0980; pan-PI3K/mTOR (TORC1/2) inhibitor

ROVER study: PFS and OS

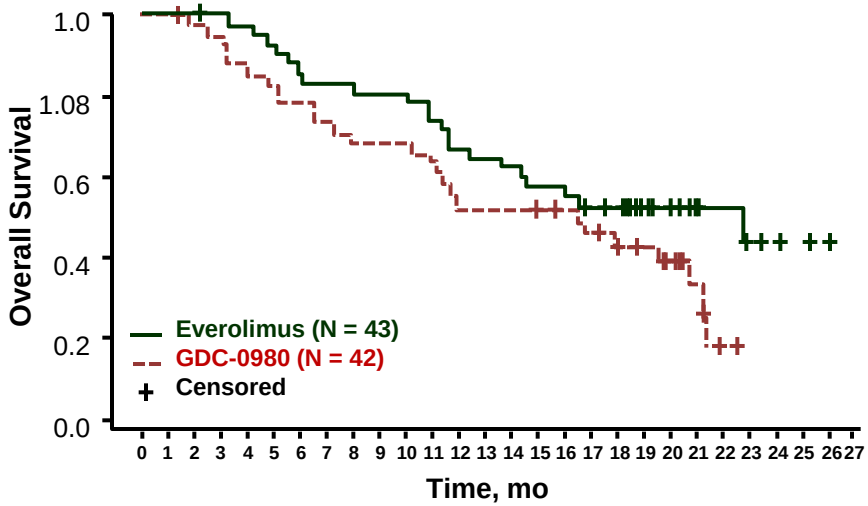
Progression-Free Survival

	GDC-0980	Everolimus
Median time, mo	3.7	6.1
95% CI for median	(3.5–5.4)	(3.7–9.0)
Hazard Ratio	2.12	
(95% CI)	(1.23–3.63)	
Log-rank *P*	< .01	



Overall Survival

	GDC-0980	Everolimus
Median time, mo	16.5	22.8
95% CI for median	(10.8–21.3)	(12.4–NE)
Hazard Ratio	1.77	
(95% CI)	(0.97–3.24)	
Log-rank *P*	0.06	



Powles T et al. ASCO Symposium; May 30-June 3, 2014, Chicago, IL, USA. abstract 4525.

Other potential targets

- *IL8* and *Human Double Minute 2* (MDM2 inhibitors), for acquired resistance to VEGF pathway inhibitors
- *HIF-2 alpha*
  - The most relevant HIF in the development and progression of RCC
  - Inhibition of HIF-2 alpha is sufficient for suppression of tumor growth in VHL-defective RCC cell lines
  - HIF-1 alpha may function as a tumor suppressor in VHL-null RCC
- *Neurofibromin 2 (Merlin)* and its *Hippo-Yap pathway*
  - 33% of VHL wild-type ccRCC have inactivating mutations of NF2
  - Knockout of *NF2* in mouse kidney epithelium has been shown to lead to the development of invasive RCC

Potentially relevant in RCC… but no clinical data, yet

Conclusions

- VEGFR inh and mTOR inh are still the back bone of RCC treatment, but they are possibly already at their best plateau as single agents
- Understanding and overcoming resistance is a major challenge
- New targets are arising, and promising novel drugs are being tested
  - Novel pure antiangiogenics: cMET, Tie2, ALK1/ENG, angiopoieting inh
  - Novel PI3K/Akt/mTOR inh
- cMET/VEGFR2 inh, cabozantinib, is the most advanced one between the novel drugs (excluding T-cell modulators)