Alternating VEGF and mTOR Pathway. CON (was assigned, not chosen)

EORTC-GU Group

9:05	Alternating VEGF and mTOR Pathways PRO – Thomas Hutson. D.O., Pharm.D. CON – Joaquim Bellmunt, M.D.

Joaquim Bellmunt

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5th European International Kidney Cancer Symposium. London 07-08 May 2010

What is the optimal sequence: Is a different mode of action necessary ?

Can patients refractory to a targeted agent derive benefit from another targeted agent?

What and when is the optimal time to use mTOR inhibitors in the treatment sequence?

TKI → TKI is preferred than TKI → mTOR where is the evidence? My arguments

1. **In phase III everolimus was compared against placebo not against a switch to another TKI[1]**
2. **The PFS obtained with TKIs after sunitinib and/or sorafenib is similar to that obtained for everolimus after sunitinib and/or sorafenib[3–10]**
3. **Fewer data (or lower level of evidence) doesn´t mean a lack of efficacy**
4. **Different TKIs have different target profiles so cross-resistance is <u>not</u> inevitable[2]**
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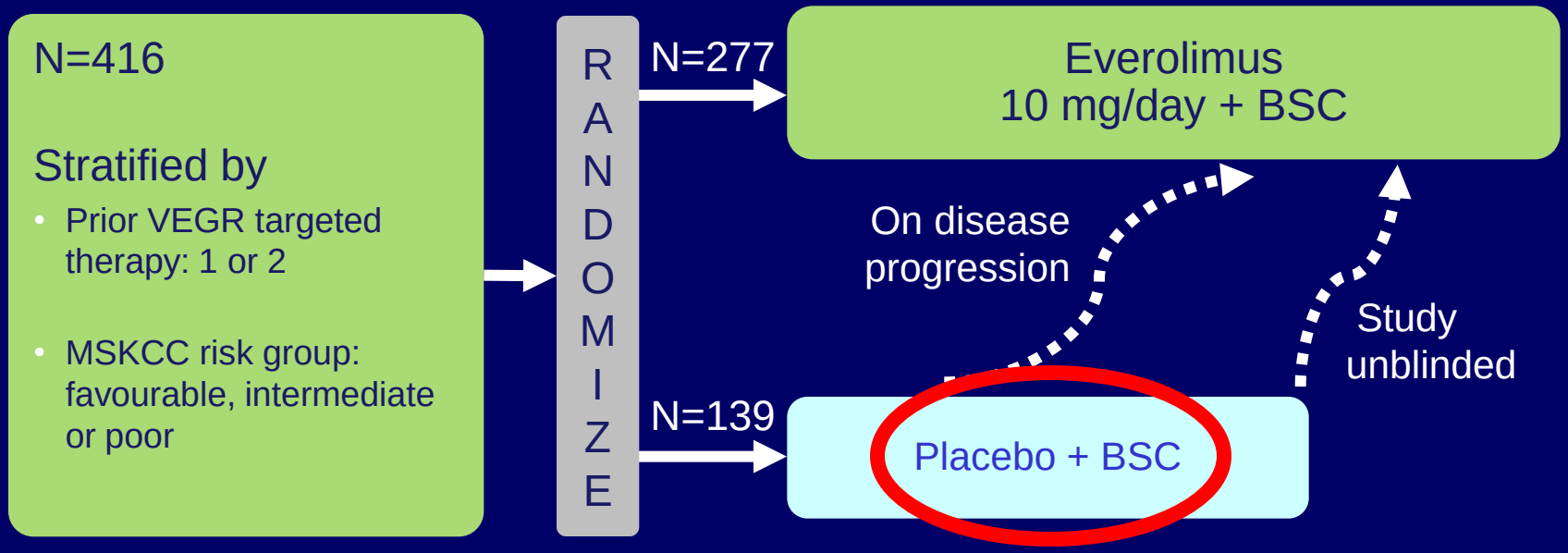
RECORD 1 phase III: everolimus vs placebo



- No direct comparison between everolimus and TKIs in TKI refractory patients
- At the time this trial was designed was a reasonable approach

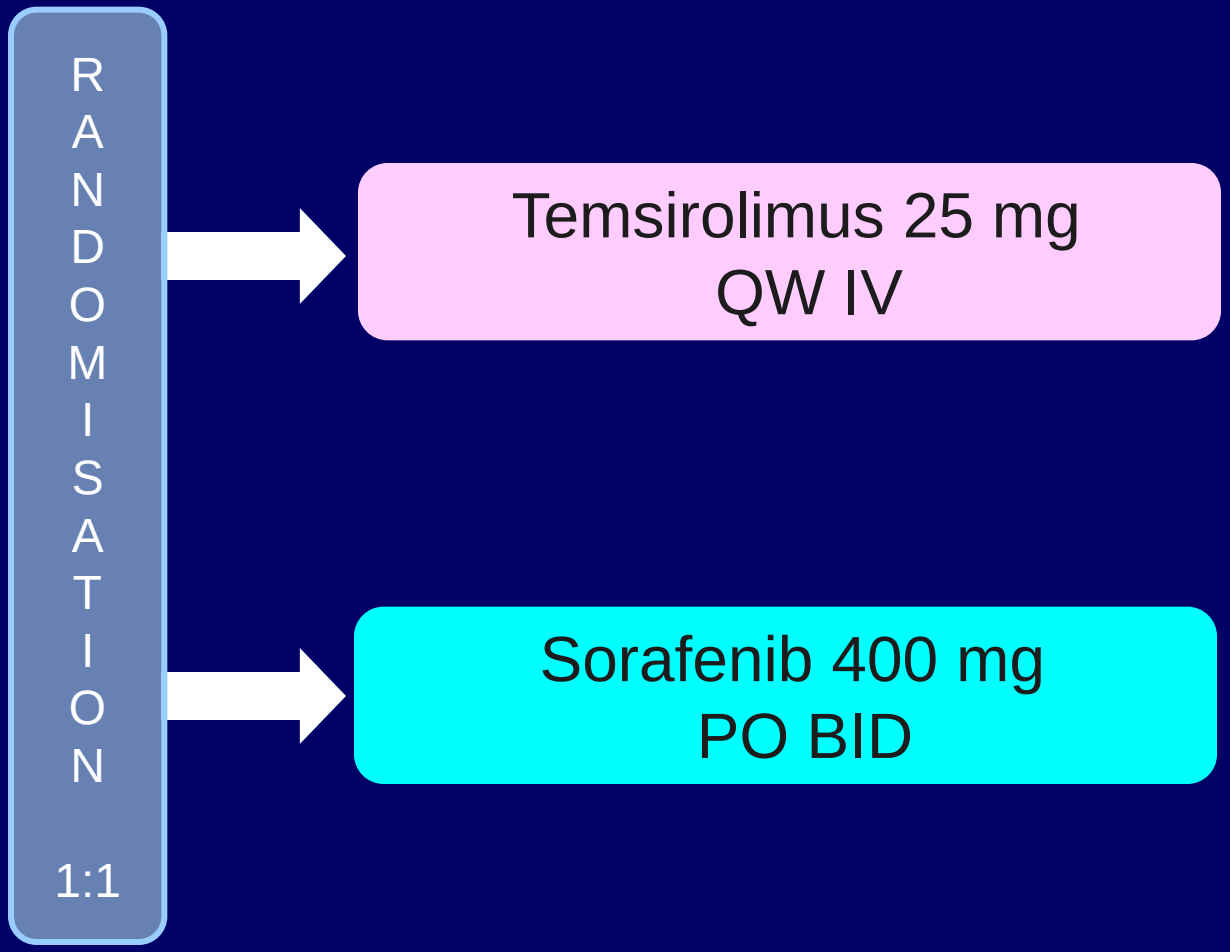
TKI, tyrosine kinase ihhibitor

Motzer et al. Lancet 2008:372:449–56

INTORSECT: Temsirolimus vs Sorafenib Second-Line in Patients who Failed First-Line Sunitinib (N=480)

Eligibility
mRCC
At least 2 weeks since prior Rx with sunitinib
At least 1 measurable lesion

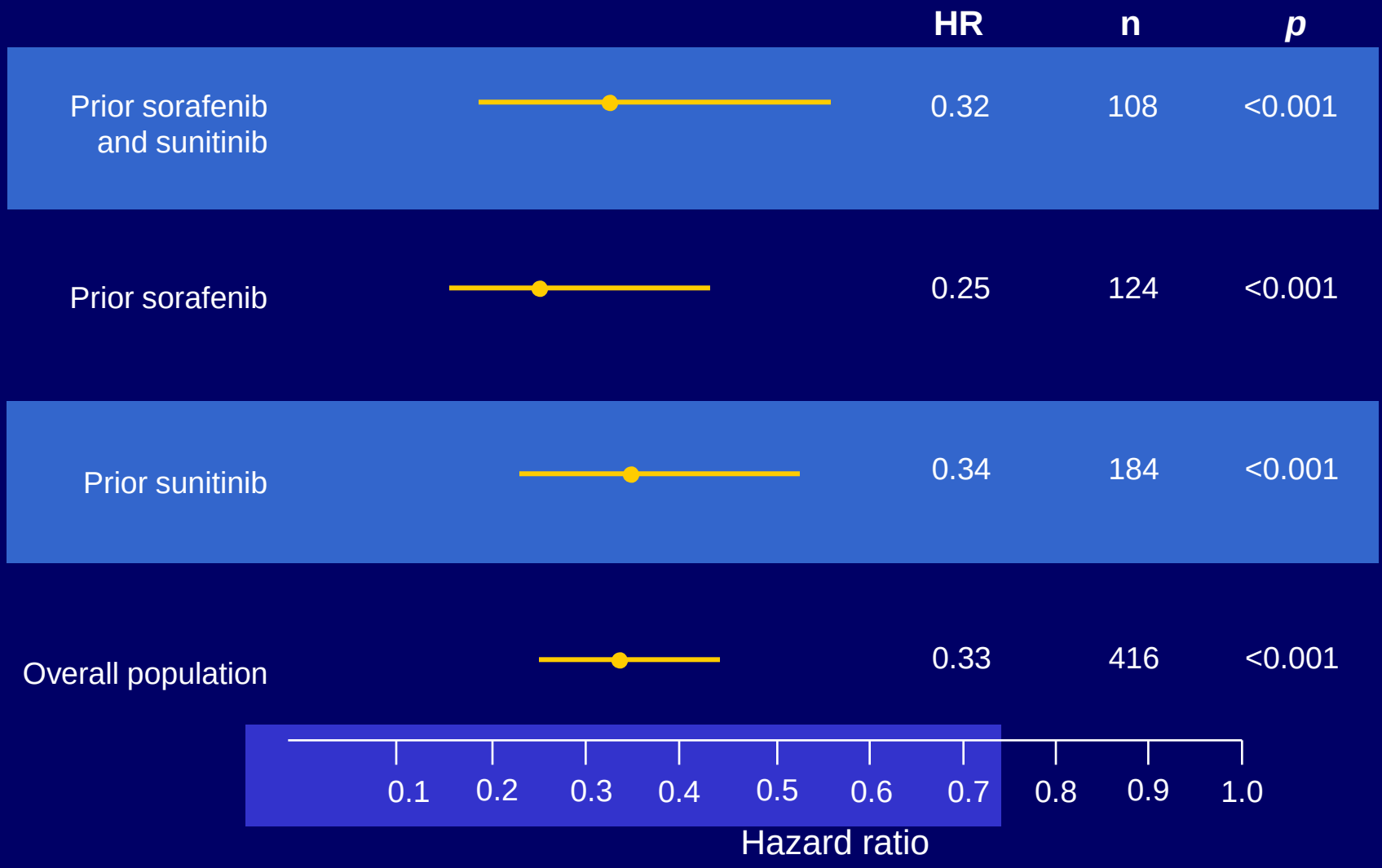
Stratification
Nephrectomy status, duration of response to sunitinib, MSKCC risk group and RCC histology



Primary endpoints: PFS, safety and efficacy
Secondary endpoints: RR, OS, SD at 12, 24, and 36 weeks, DR, best tumour shrinkage

Temsirolimus is not approved for second-line use in mRCC

Everolimus is as effective after two TKIs as after one TKI: PFS hazard ratio



RECORD 1: PFS maintained after multiple lines of treatment. No need to immediate switch

	Median PFS (months)	
	Everolimus	Placebo
Overall population (N=416)	4.90	1.87
Prior sorafenib treatment (n=124)	5.88	2.83
Prior sunitinib treatment (n=184)	3.88	1.84
Prior sorafenib and sunitinib (n=108)	4.01	1.84
Prior bevacizumab (+ sorafenib or sunitinib or both) (n=38)	5.75	1.77

Escudier B et al. ESMO 2008; abstr 720

PFS with TKI-TKI is comparable with PFS TKI-mTOR

Failing TKI	Subsequent treatment	PFS (months)
Sunitinib	Sorafenib[1-5]	2.8–8.9
	Everolimus[8]	3.9
Sorafenib	Sunitinib[1-7]	5.0–12.9
	Everolimus[8]	5.9
	Axitinib[9]	7.8–9.1
Sunitinib and sorafenib	Axitinib[9]	7.1
	Everolimus[8]	4.0

1. Porta C, et al. EAU 2009 abstr 252. 2. Tamaskar I, et al. J Urol 2008;179:81-6
3. Merseburger AS, et al. Expert rev. Anticancer Ther. 2009; 9:1428–34. 4. Dudek AZ, et al. Cancer 2009;115:61-7
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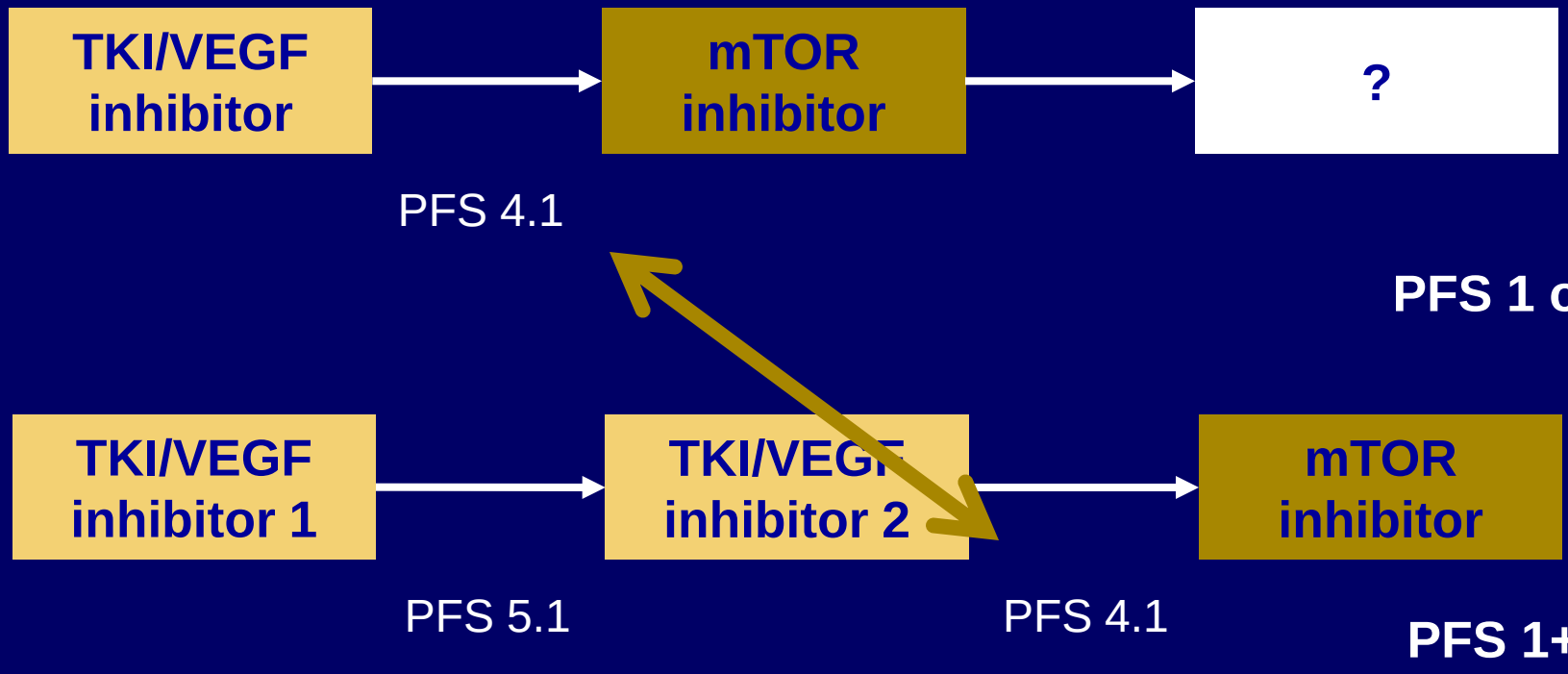
7. Eichelberg C, EAU 2009; abstr 251. 8. Escudier B, et al. ESMO 2008;abstr 72O
9. Rini BI, et al. J Clin Oncol 2009;27:4462–8

What is the optimal sequence: Are we adding additional PFS ?



1. Kay et al EAU 2009; abstr 257. 2. Tamaskar I, et al. J Urol 2008;179:81–6. 3. Richter S, et al. Onkologie 2008;31:234, abstr V684
4. Mancuso AP, et al. J Clin Oncol 2009;27:abstr e16027. 5. Drabkin HA, et al. J Clin Oncol 2007;25:abstr 5041
6. Sepulveda J, et al. ASCO 2008;26:abstr 16100. 7. Zimmermann K, et al. Oncol 2009;76:350–354. 8. Shepard DR, et al. ASCO 2008, abstr 5123
9. Choueiri TK, et al. ESMO 2008; abstr 593. 10. Eichelberg C, EAU 2009; abstr 251. 11. Dudek AZ, et al. Cancer 2009; 115:61–7
12. Di Lorenzo G, et al. J Clin Oncol 2009;27:4469-74. 13. Beck J, et al. ECCO 2007, abstr 4506. 14. Sablin MP, et al. ASCO 2007, abstr 5038
15. Porta C, et al. manuscript in preparation. 16. Escudier B, et al. ESMO 2008; abstr 720

What is the optimal sequence: Is a different mode of action necessary?

Phase III data[1]

Limited data on patients refractory to mTOR inhibitors

Evidence suggests no cross-resistance between TKIs[2–15]

Phase III data

Everolimus is as effective after two TKIs as after one TKI[16]

1. Kay et al EAU 2009; abstr 257. 2. Tamaskar I, et al. J Urol 2008;179:81–6. 3. Richter S, et al. Onkologie 2008;31:234, abstr V684
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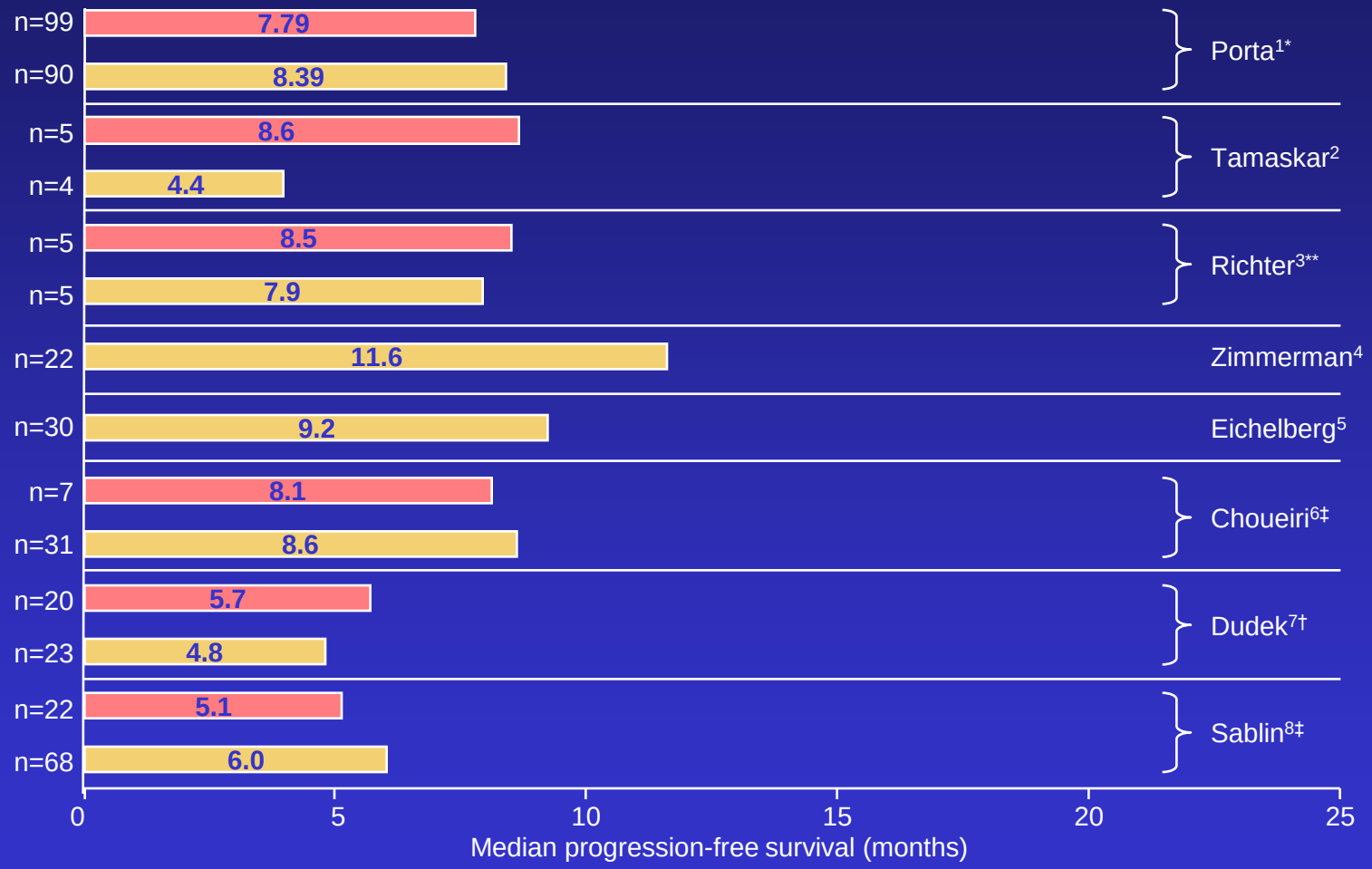
*Sequential therapy has been investigated in >600 patients with advanced RCC**

	Number of patients	
	Sunitinib → sorafenib	**Sorafenib → sunitinib**
Tamaskar (retrospective)	5	4
Richter (retrospective)	5	5
Mancuso (phase II)	13	–
Sepulveda (prospective)	20	–
Zimmermann (retrospective)	–	22
Shepard (phase II)	24	–
Choueiri (retrospective)	7	31
Eichelberg (retrospective)	–	44
Dudek (retrospective)	20	29
Di Lorenzo (phase II)	52	–
EU-ARCCS (expanded access)	69	–
Sablin (retrospective)	22	68
Porta (retrospective)	99	90
Total	**336**	**293**
	610	

*Data from phase II, expanded-access and retrospective studies

Paglino C and Porta C. Oncol Rev 2010;4:1–3

Sequential therapy with sorafenib and sunitinib: retrospective studies



* Unpublished data

** Mean PFS

† Median duration of stable disease

‡ Treatment duration

1. Porta C, et al. manuscript in preparation . 2. Tamaskar I, et al. J Urol 2008;179:81-6. 3. Richter S, DGHO 2009;abstr V684
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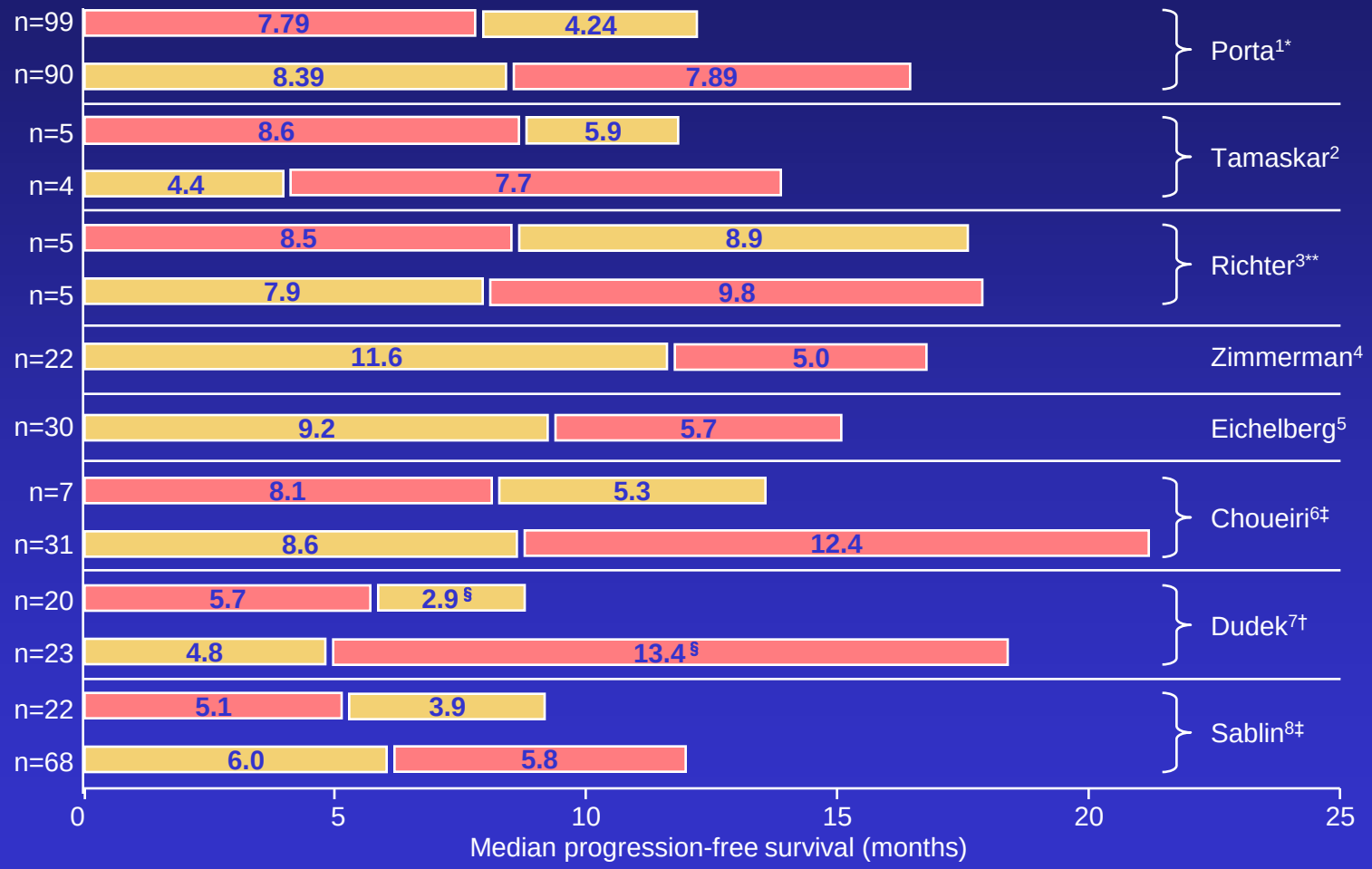

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§ Calculated by subtracting first median from overall median

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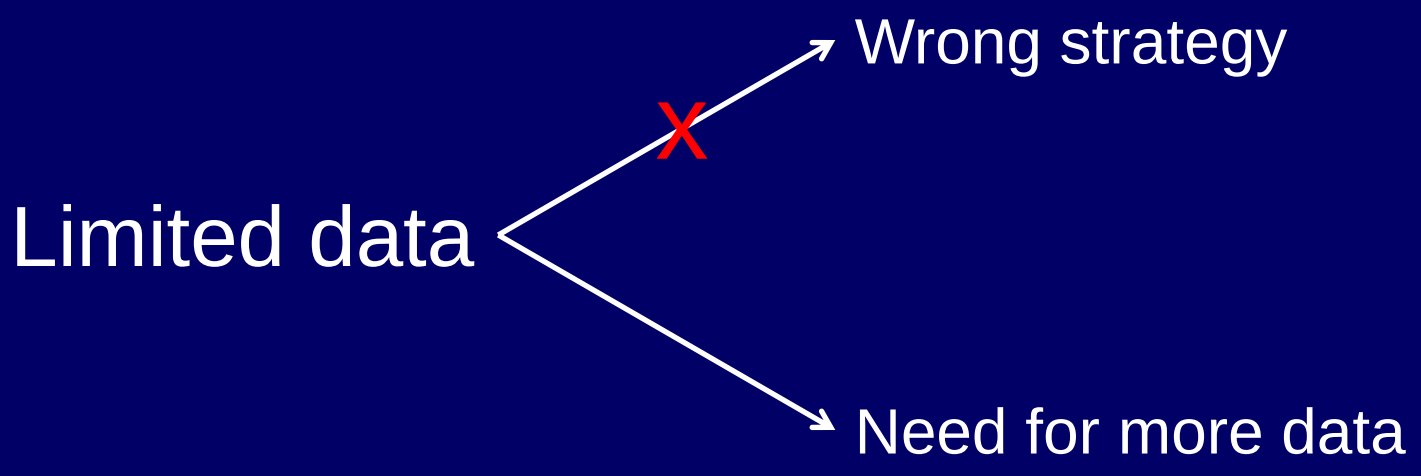
TKI → TKI: studies are mostly retrospective



Ongoing Clinical Trials in mRCC: Sequential Therapies

Trial	Enrollment	Treatment arms
AXIS: Phase III study comparing axitinib vs sorafenib as second-line therapy[1]	693	Axitinib Sorafenib
Phase III study comparing temsirolimus vs sorafenib in sunitinib-refractory patients[2]	440	Temsirolimus Sorafenib
TIVO-1: Phase III study comparing tivozanib (AV-951) vs sorafenib as first-line and second-line therapy[3]	500	Tivozanib Sorafenib
SWITCH: Phase III study comparing sequential treatment with sunitinib vs sorafenib as second-line therapy[4]	540	Sunitinib Sorafenib
RECORD-3: Phase II study comparing sunitinib vs everolimus as first-line and second-line therapy[5]	390	Sunitinib Everolimus

[1]NCT00678392; [2]NCT00474786; [3]NCT01030783; [4]NCT00732914; [5]NCT00903175

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TKI targets are at least in part different. Differences in mode of action.

Target	IC_{50} (nM)*			
	Sunitinib[1,2]	Sorafenib[1,3,4]	Pazopanib[1,5]	Axitinib[1]
VEGFR-1	2	–	10	1.2
VEGFR-2	10	90	30	0.25
VEGFR-3	17	20	47	0.29
PDGFR-β	8	57	84	1.7
EGFR	880	58	–	–
c-KIT	10	68	74	1.6
FGF-1R	880	580	14	230
FLT-3	14	58	–	–
Raf-1	–	6	–	–
CSF-1R	100	–	–	–

*IC_{50} represents the concentration of a drug that is required to achieve 50% inhibition of the enzyme in a biochemical assay

TKI=tyrosine kinase inhibitor

1. Schmidinger M and Bellmunt J. Cancer Treat Rev 2010; Feb 15 [Epub ahead of print]
2. EU SmPC Sutent® October 2009. **3.** Wilhelm SM, et al. Cancer Res 2004;64:7099–109
4. EU SmPC Nexavar® November 2009. **5.** Kumar R, et al. Mol Cancer Ther 2007;6:2012–21

Differences in mode of action between TKIs

Sunitinib targets[1]	Sorafenib targets[2]	Pazopanib targets[3]	Axitinib targets[4]
PDGFR-β	PDGFR-β	PDGFR-β	PDGFR-β
c-KIT	c-KIT	c-KIT	c-KIT
FLT-3	FLT-3		
RET	RET		
VEGFR-2, -3	VEGFR-2, -3	VEGFR-2, -3	VEGFR-2, -3
VEGFR-1	c-RAF, b-RAF	VEGFR-1	VEGFR-1
PDGFR-α		PDGFR-α	PDGFR-α
CSF-1R			

1. Roskoski R. Biochem Biophys Res Commun 2007; 356:323–8. 2. Wilhelm SM, et al Cancer research 2004; 64: 7099–109
3. Sternberg et al. ASCO 2009; abstr 5051. 4. Sonpavde G, et al. Expert Opin Investig Drugs 2008; 17:741–8

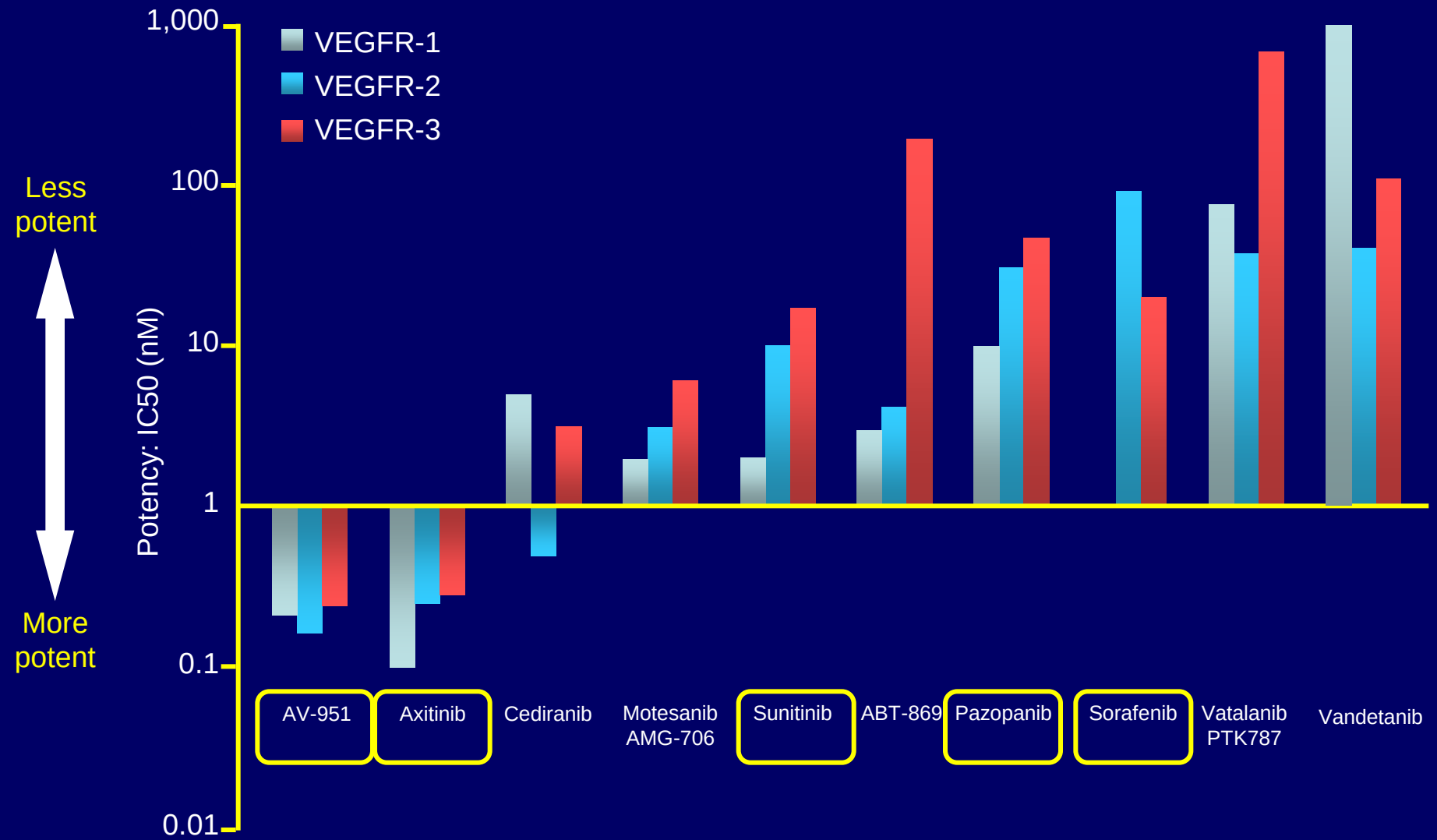
Comparative ANTI-PDGFR Activity for Selected TKIs

IC50 nM

TKI	PDGFR-β
Sorafenib	80
Sunitinib	8
Pazopanib	84
Axitinib	1.6
Vatalanib	580
AV-951	1.7

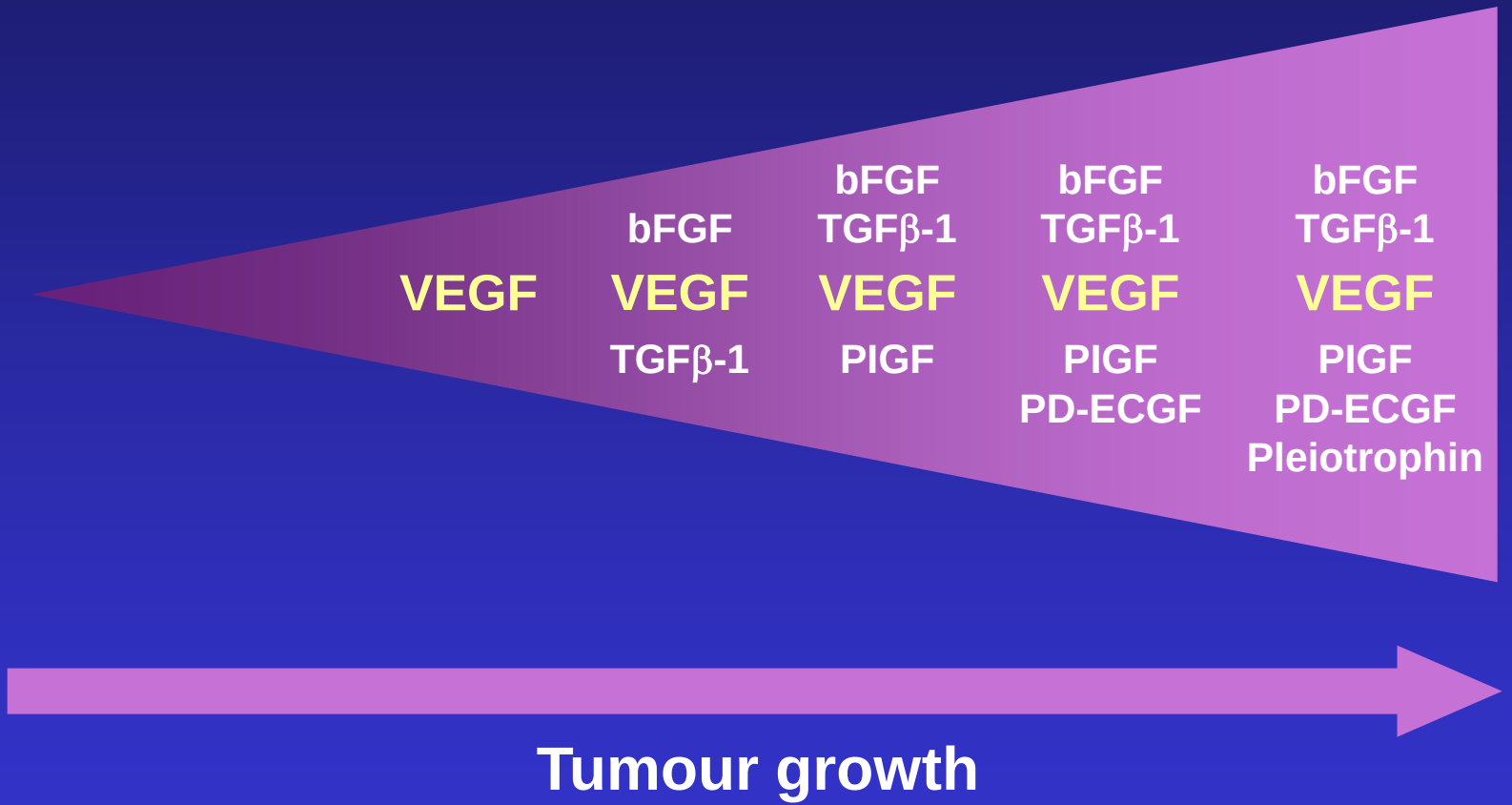
Adapted from Chow LQM, Eckhardt SG. *J Clin Oncol.* 2007;25:884–896.

Relative Potencies of VEGFR TKIs



Chow LQM, Eckhardt SG. *J Clin Oncol*. 2007;25:884-896. Eskens FALM, et al. Proceedings of the 99th Annual Meeting of the American Association for Cancer Research. 2008. Abstract LB-201.

Tumour growth factor expression may support using anti-VEGF therapy throughout treatment.....



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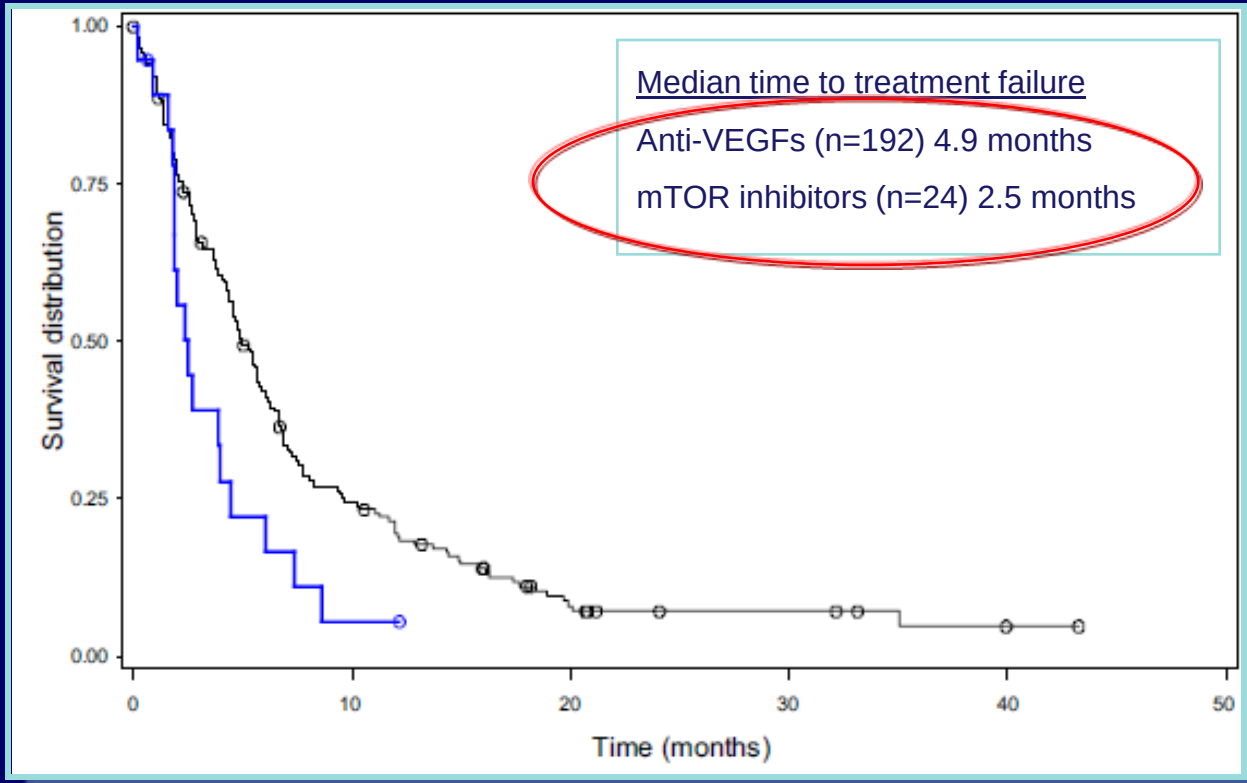
10. Escudier B, et al. ESMO 2008;abstr 72O. 11. Vickers MM, et al. Urol 2010; doi:10.1016/j.urology.2009.12.031

Anti-VEGFs prolonged time to treatment failure compared with mTORs following anti-VEGF failure

Retrospective study of patients with mRCC who received 2nd-line therapy after 1st-line VEGF-targeted therapy

216 patients across 7 cancer centres



Anti-VEGFs:
- sorafenib (n=80)
- sunitinib (n=93)
- bevacizumab (n=11)

mTORs:
- temsirolimus (n=21)
- everolimus (n=3)

Vickers MM, et al. Urol 2010; doi:10.1016/j.urology.2009.12.031

Integrating response and tolerability
A customized approach?

- Does response to a second agent depend on the response to the first?

- In patients with poor tolerability on a first TKI would a switch to mTORs be more acceptable than a switch to another TKI?

Optimal sequence may depend on response to first treatment

Sablin et al. 2009. So → Su vs Su → So

- Response to second tx not dependent on response to first tx

Table 4. *SU efficacy in SO-SU group*

	No. SO	No. SU (%)			
		PR	SD	PD	Not Evaluated
PR	11	2 (18)	7 (64)	2 (18)	—
SD	45	6 (13)	24 (53)	11 (25)	4 (9)
PD	10	2 (20)	3 (30)	4 (40)	1 (10)
Not evaluated	2	—	1	—	1

Dudek et al. 2009. So → Su vs Su → So

Longer PFS on second tx:

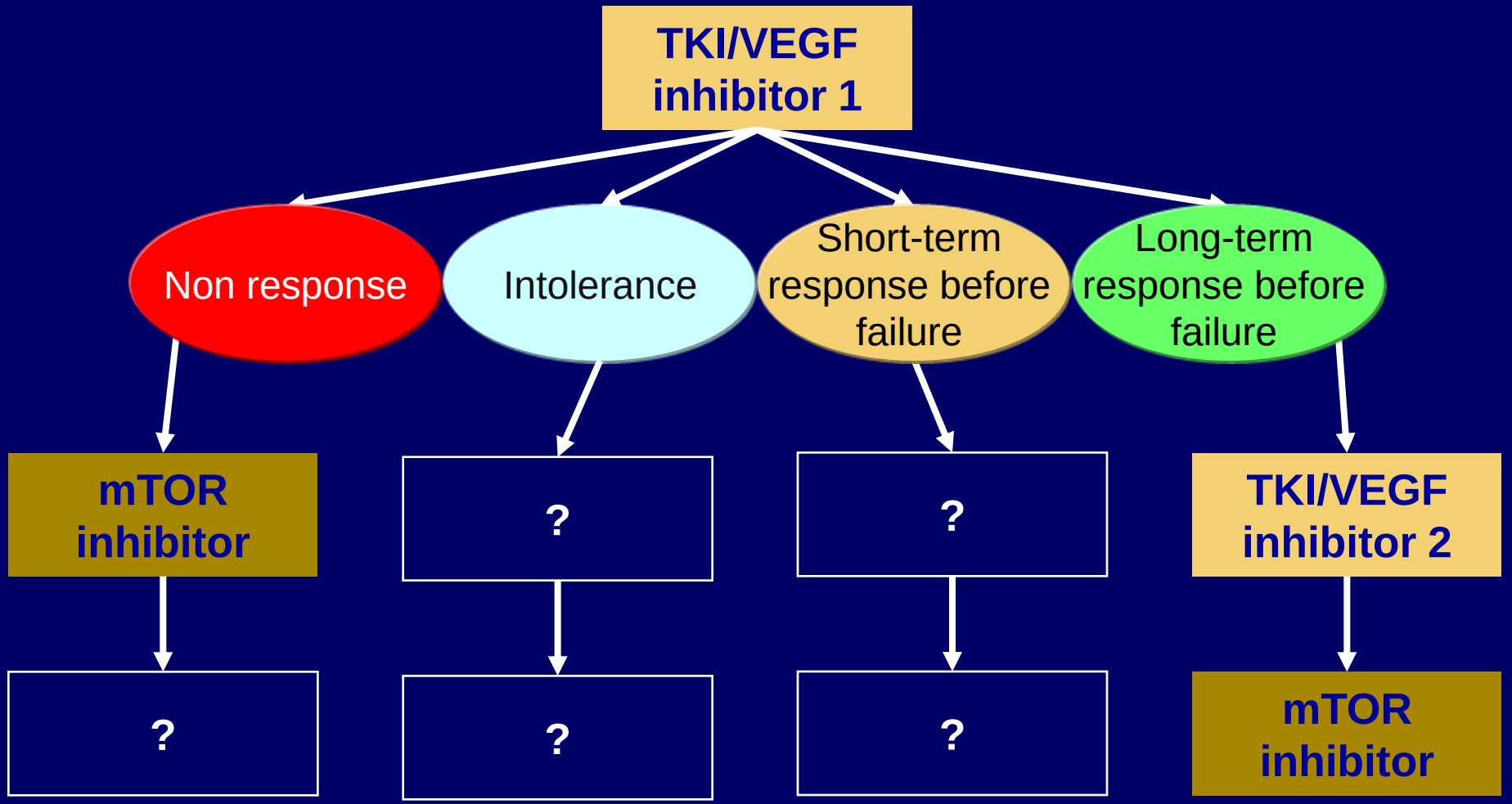
- in patients switching for PD compared with those switching for AEs
- in patients with PR on first tx compared to those with PD

The median time to progression after the second treatment was 46.9 weeks for those switching to the other agent because of toxicity of first-line therapy and 67.0 weeks for those switching because of disease progression ($P = .495$).

Variable	Category	No.	Median TTP, wk	*P*
Best response for first treatment	PR + SD	34	74.6	.019
	PD + AE	15	40.6	

1. Sablin MP, et al. J Urol 2009;182:29-34. 2. Dudek AZ, et al. Cancer 2009; 115:61–7

Optimal sequence may depend on response to first treatment: A clinically customized approach



My “CON” position

- I need to support customized sequential use of TKIs in mRCC in patients …
- Need for more well stratified and prospectively designed clinical trials Integrating clinical prediction (prior RR, PFS, toxicity), molecular markers and methods of imaging to understand the next steps for sequential therapy !!!!!
- Present level 1 evidence might be incomplete… But, we need to follow Science before further improvement is evident

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