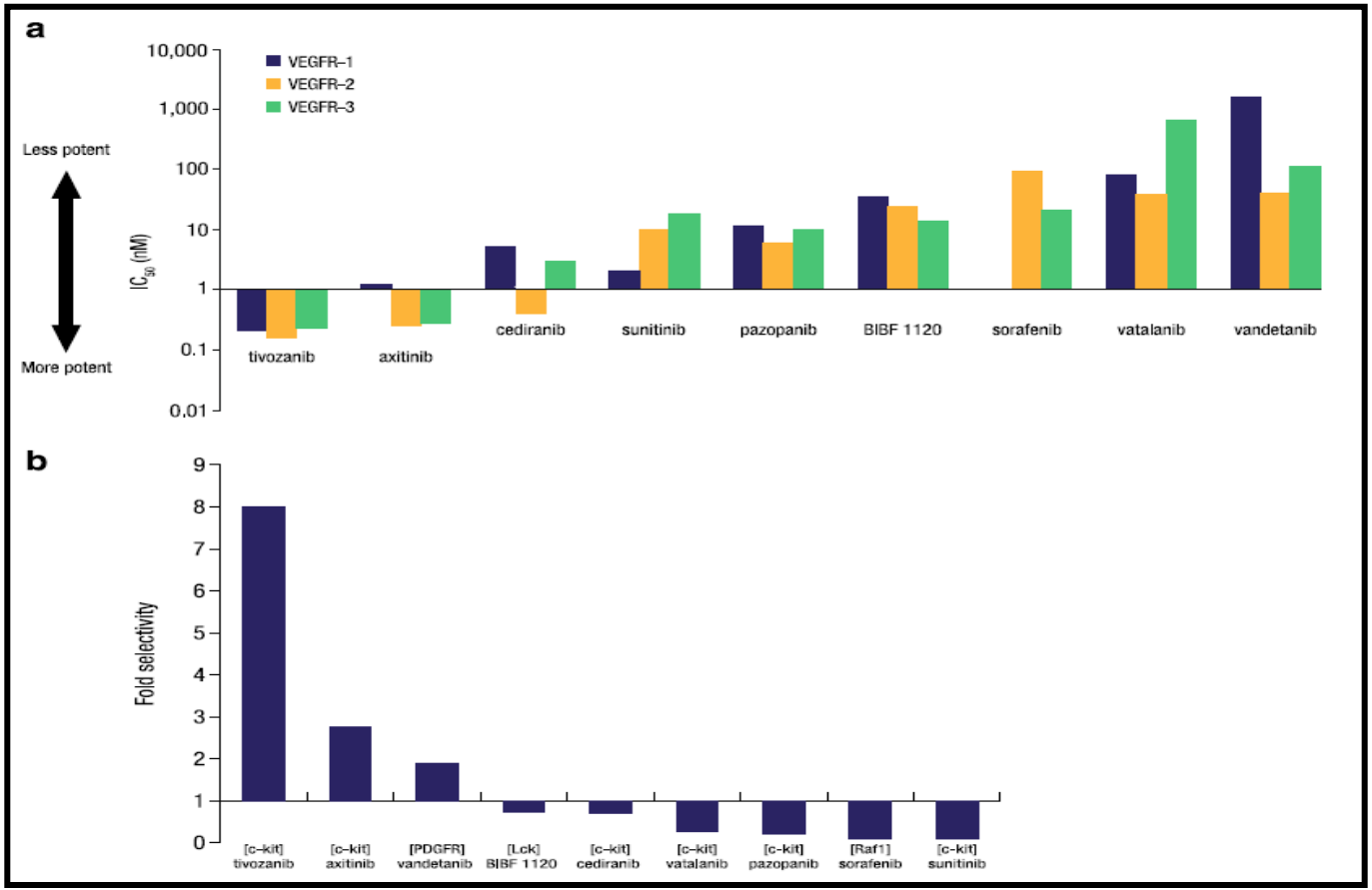
The Royal Marsden NHS
NHS Foundation Trust

The Cytokine Era is Over: What Should We Do About Sorafenib?

James Larkin FRCP PhD
London UK

TKI affinities for VEGFRs



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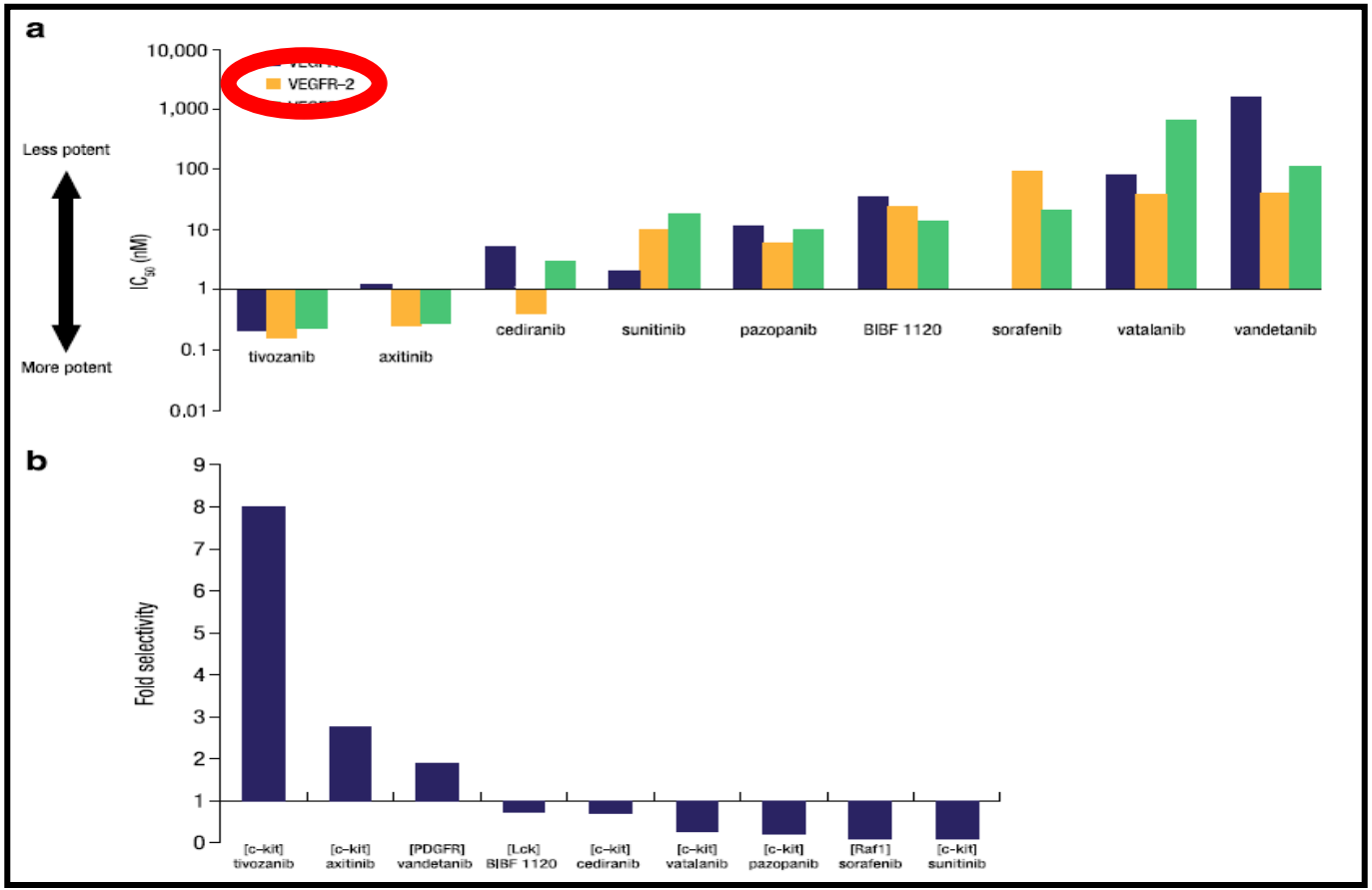

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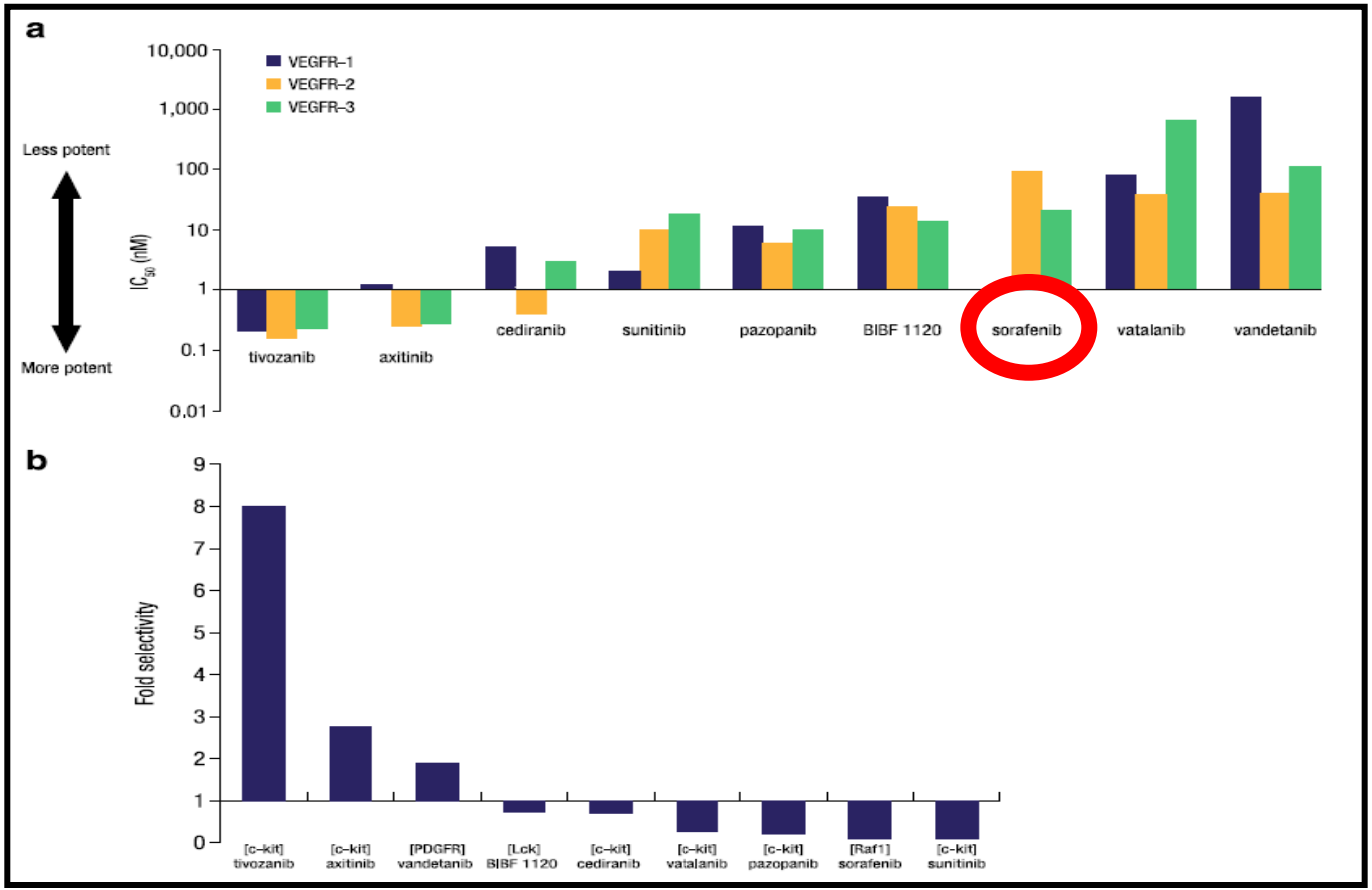

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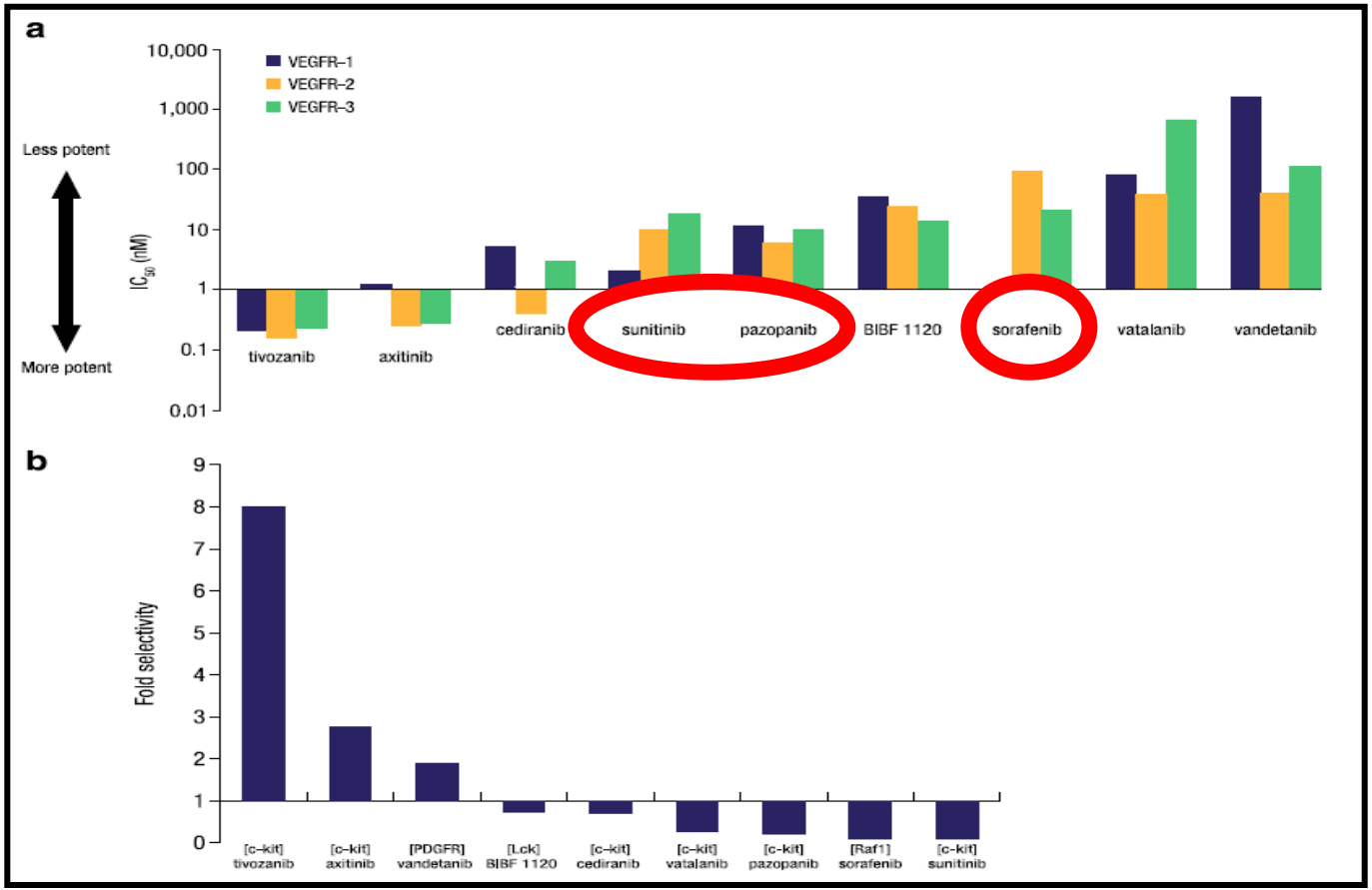

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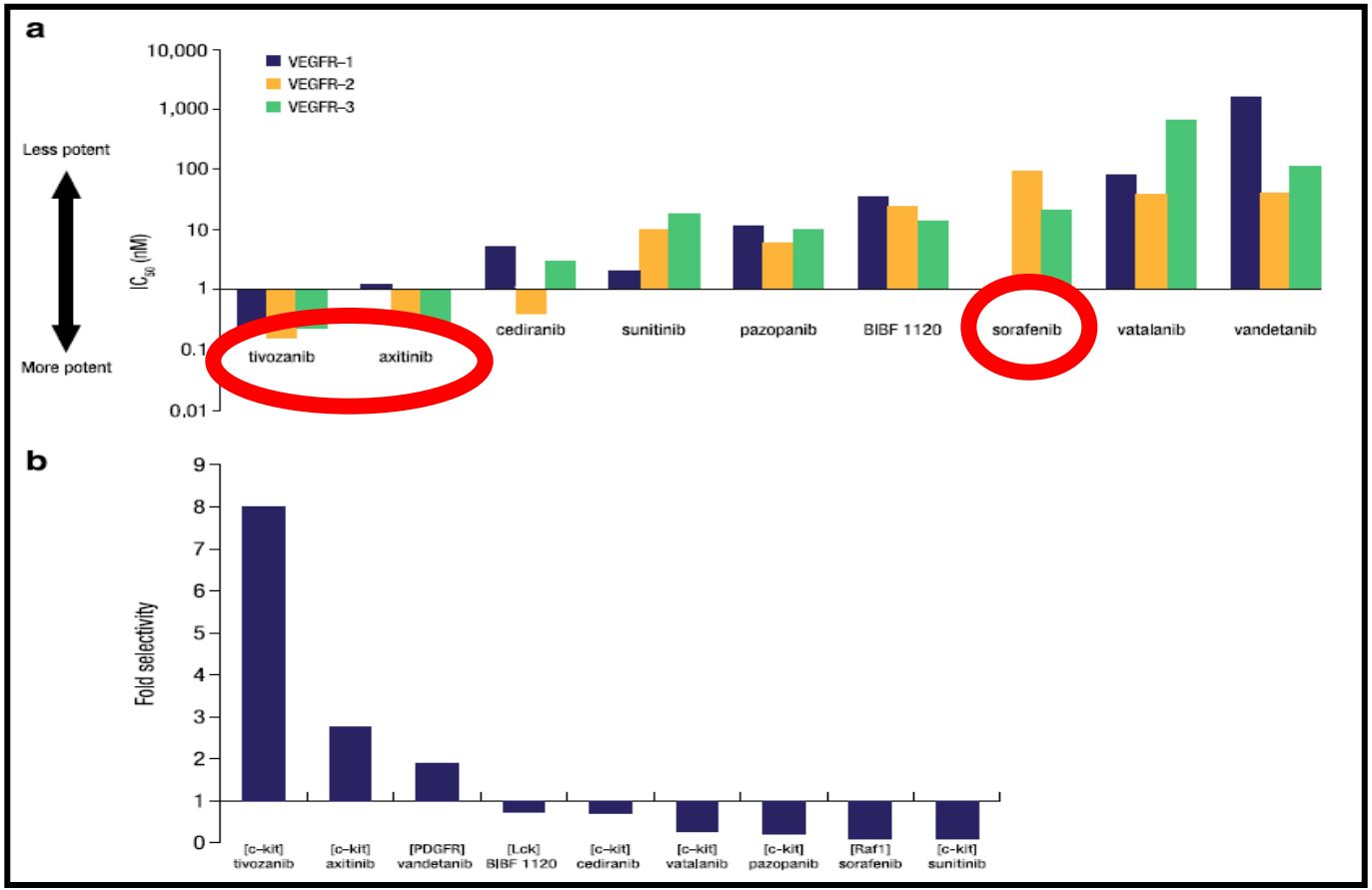

TKI affinities for VEGFRs

	IC_{50} (nM)*			
Target	**Sorafenib[1]**	**Pazopanib[2]**	**Sunitinib[3]**	**Axitinib[3]**
VEGFR-1	**–**	**10**	**2**	**1.2**
VEGFR-2	**90**	**30**	**10**	**0.25**
VEGFR-3	**20**	**47**	**17**	**0.29**
PDGFR-β	**57**	**84**	**8**	**1.7**
EGFR	**>10,000**	**>20,000**	**880**	**–**
c-KIT	**68**	**74**	**10**	**1.6**
FGFR1	**580**	**140**	**880**	**230**
Flt-3	**58**	**>20,000**	**14**	**–**
CRAF	**6**	**–**	**–**	**–**
CSF-1R	**–**	**146**	**100**	**–**

*IC_{50} concentration of drug required to achieve 50% inhibition of the enzyme

1. Wilhelm et al. Cancer Res 2004
2. Kumar et al. Mol Cancer Ther 2007
3.Schmidinger & Bellmunt Cancer Treat Rev 2010

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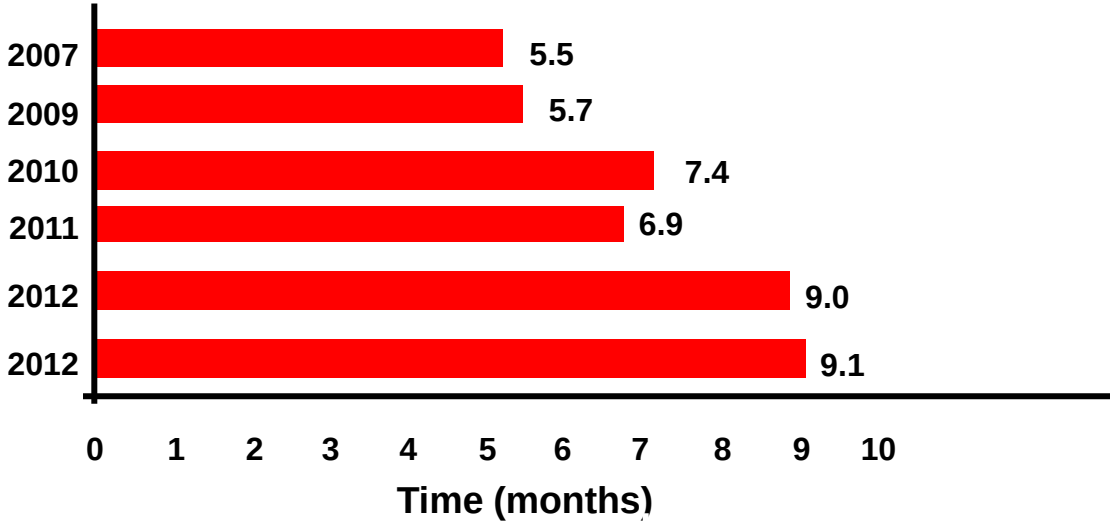
Increased Median PFS in RCTs in Renal Cell Carcinoma 1st line 2007 – 2012



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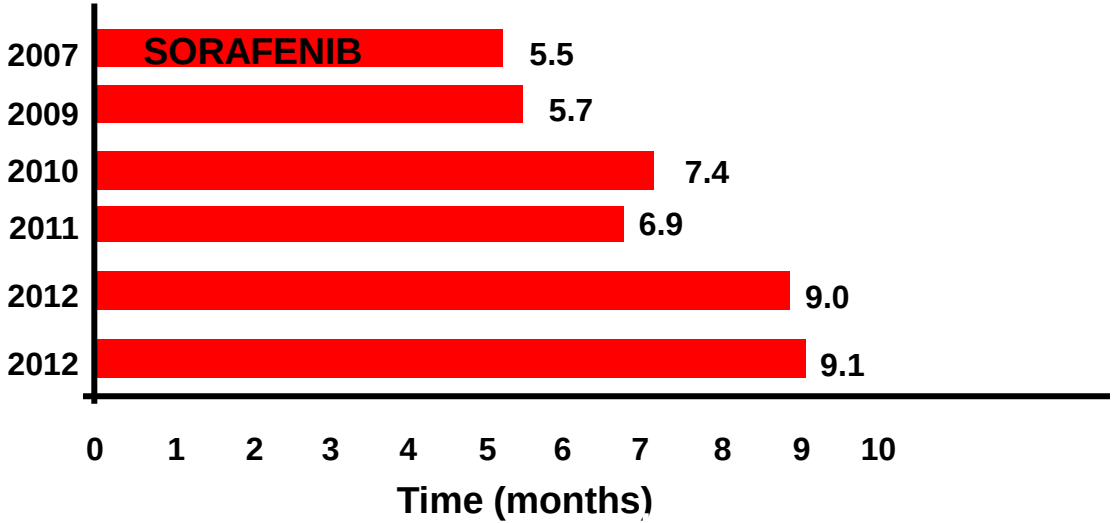

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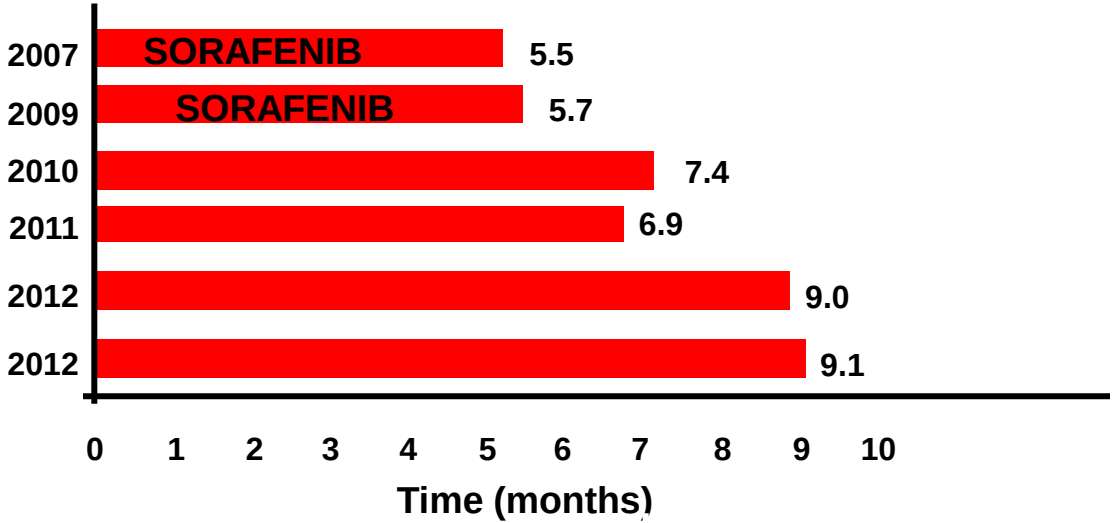

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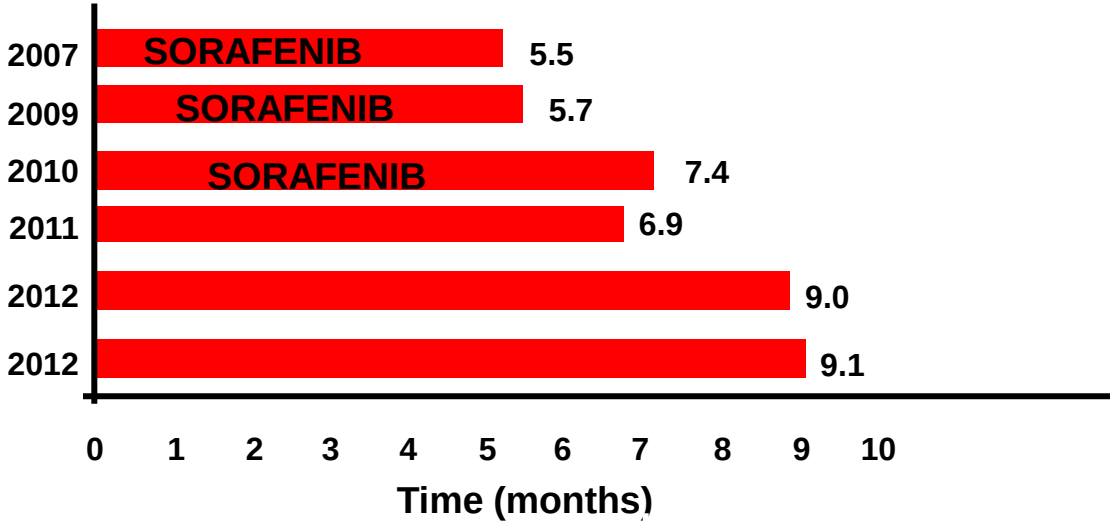

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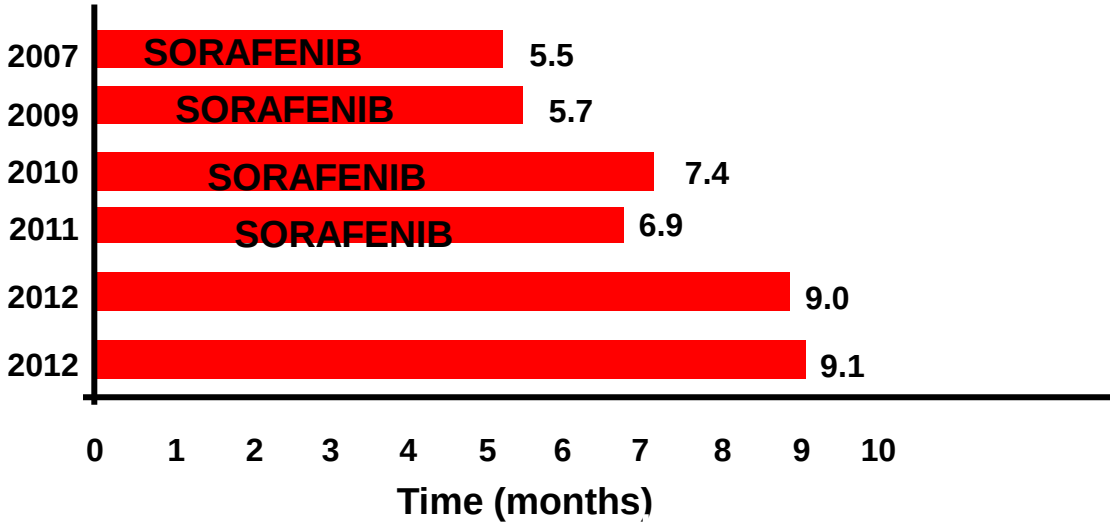

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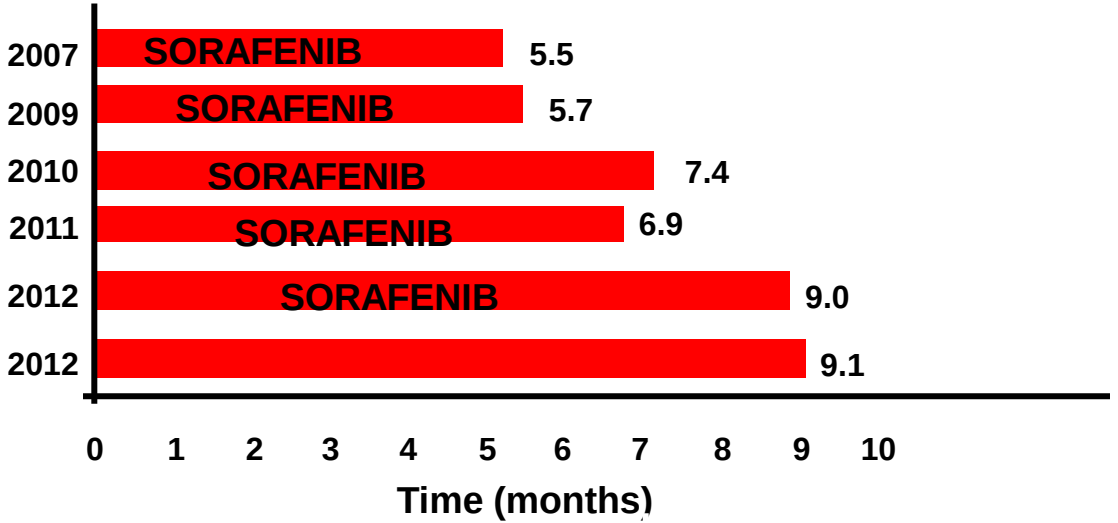

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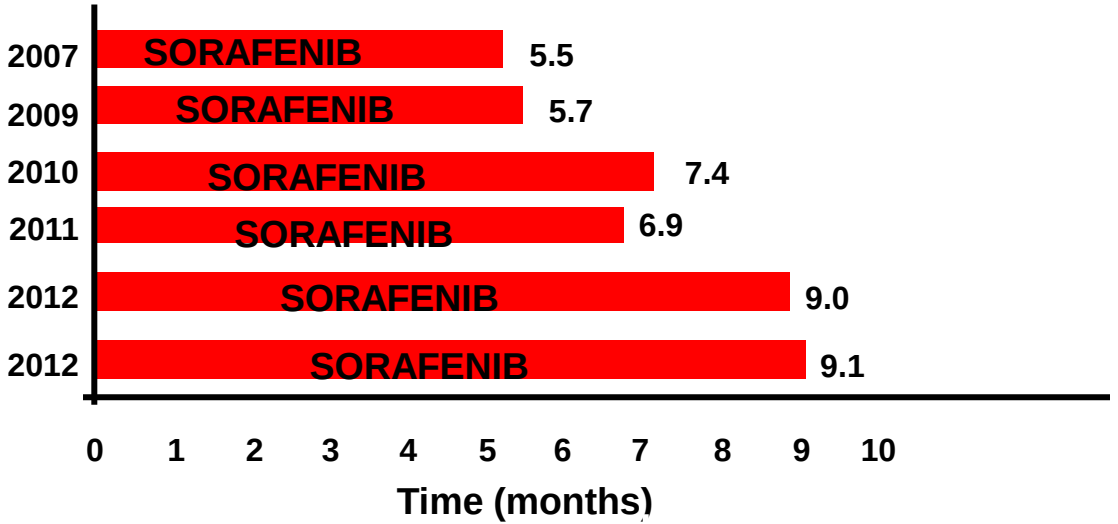

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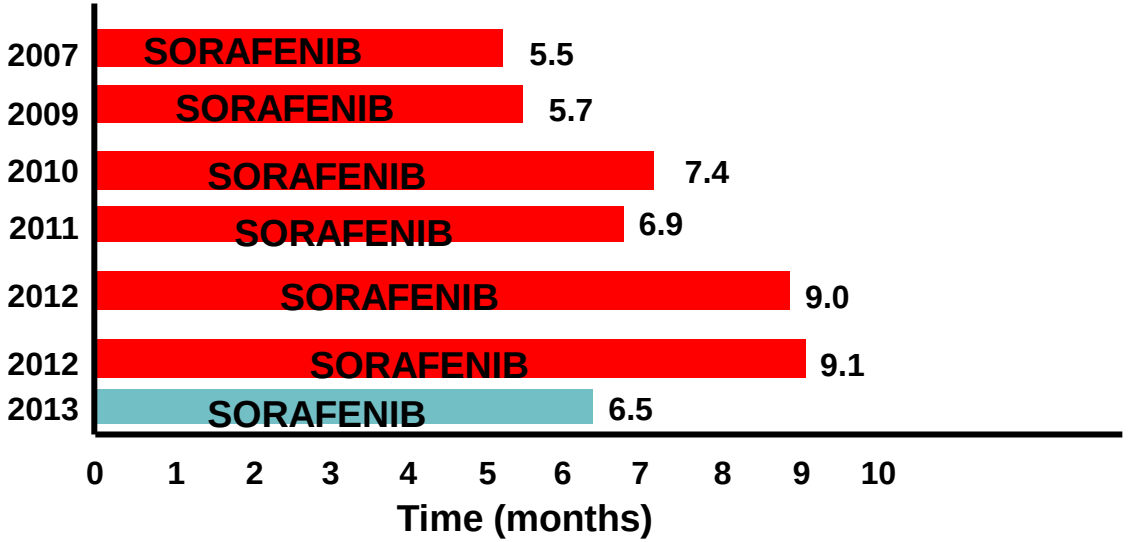

Sorafenib Median PFS in RCTs in Renal Cell Carcinoma 1st line 2007 – 2013

Author	Comparator	Year	n	PFS median
Escudier	Placebo	2007	451 77 cytokine naive	5.5
Escudier	IFN	2009	97	5.7
Jonasch	Sor + IFN	2010	40	7.4
Procopio	Sor + IL-2	2011	62	6.9
Rini	Sor + AMG386	2012	51	9.0
Motzer	Tivozanib	2012	257 181 treatment naive	9.1
Hutson	Axitinib	2013	96	6.5

Escudier NEJM 2007, JCO 2009, Jonasch Cancer 2010, Procopio BJC 2011, Rini Cancer 2012, Motzer ASCO 2012, Hutson GU ASCO 2013

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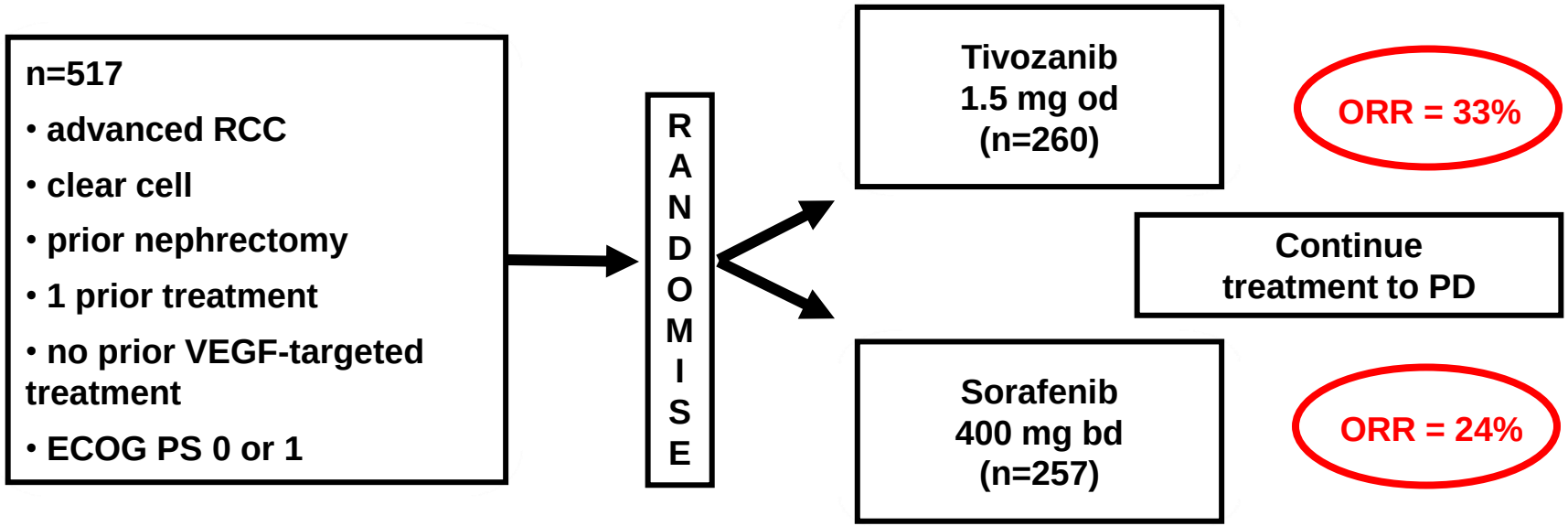
Why is Sorafenib Efficacy Improving?

- TARGET was predominantly post cytokine
- 2007-2012 most randomised trials small so vulnerable to random noise
- Side effect management / confidence / scan interpretation amongst physicians improved over time so patients staying on treatment longer
- Illustrates that physician familiarity with an drug is important for efficacy and toxicity management?

However, randomised trials show that other VEGFR TKIs have greater efficacy and better tolerability than sorafenib...

What about 1st line?

TIVO-1: Advanced clear cell mRCC Tivozanib vs Sorafenib



Primary endpoint: PFS

Motzer ASCO 2012

TIVO-1: Advanced clear cell mRCC
Tivozanib vs Sorafenib

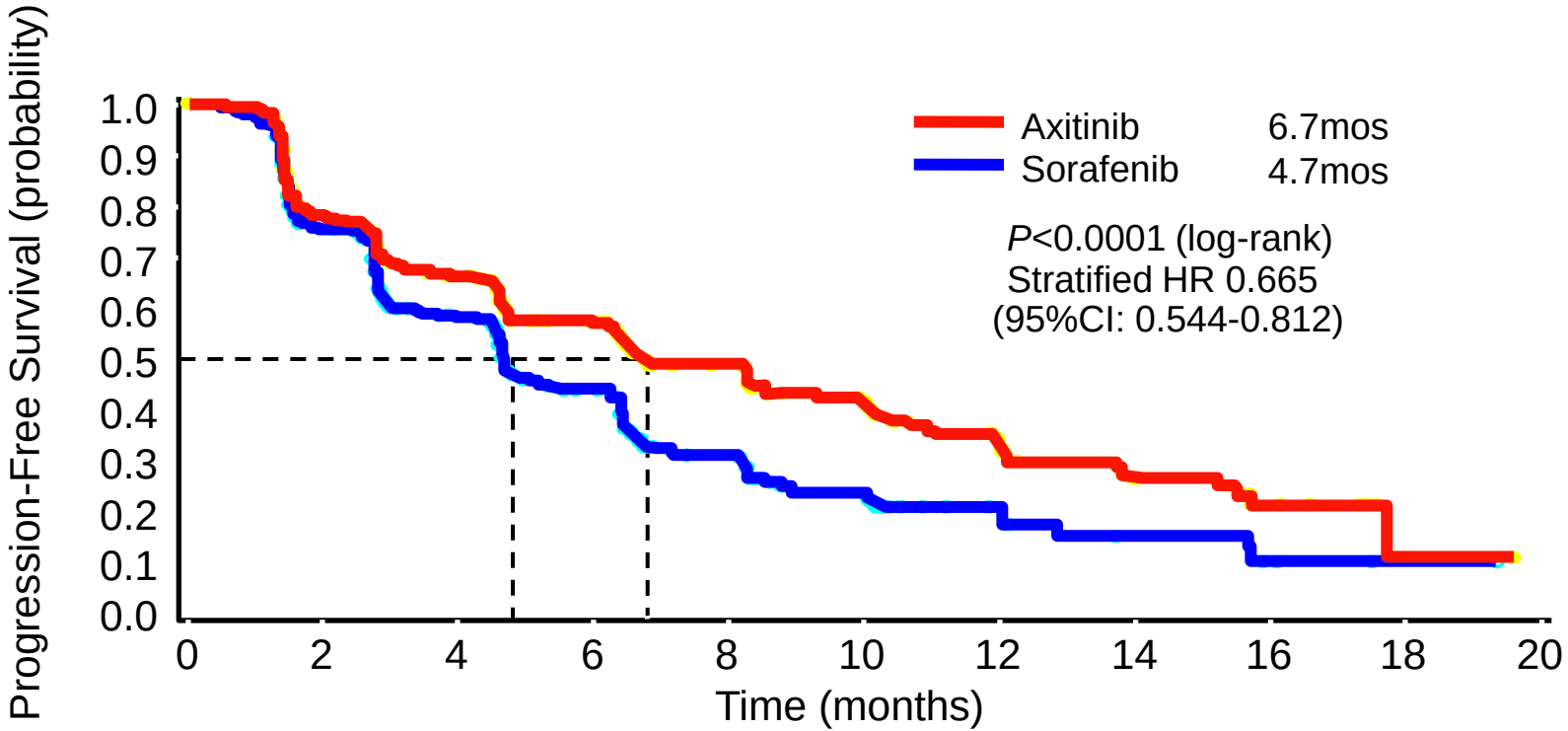
Overall, median PFS

Treatment naïve pts, median PFS

Motzer ASCO 2012

What about 2nd line?

AXIS: 2nd line Axitinib vs Sorafenib
PFS median, independent review



Rini Lancet 2011

What about the Elderly?

- A specific literature exists
- (because drug has been around longer than others)
- Clearly can be well tolerated and safe
- In my opinion, if sorafenib causes less cardiac toxicity than e.g. axitinib, then it is because it is a less potent VEGFR TKI

Procopio BJC 2013 Eisen JNCI 2008

Conclusions

- Sorafenib is active in RCC but ‘cleaner’ anti-VEGF drugs have greater efficacy
- I don’t see many clinical scenarios in which sorafenib would be preferred to other VEGFR TKIs (assuming access to approved therapies)
- Physicians should become familiar with and use a small number of agents well; for VEGFR TKIs I suggest that this is sunitinib/pazopanib 1st line and axitinib 2nd line

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- Could 25% less average efficacy be justified by 25% less cost? Could this catch on?

Thank you