Sequence or Combination and If Yes, Which ?

INTORACT, INTORSECT and RECORD-2

abstracts LBA21_R, 783O and LBA22_PR

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Disclosures:

- Member of Global and/or Canadian Advisory Boards for Pfizer, Novartis, GlaxoSmithKline, for Renal Cell Carcinoma
- Meeting and travel support by Pfizer, Novartis, GlaxoSmithKline
- Was an investigator on the INTORSECT study

Abstracts to Discuss

- LBA21_PR: Randomized phase IIIb trial of temsirolimus and bevacizumab versus interferon and bevacizumab in metastatic renal cell carcinoma: Results from INTORACT
- 783O: Randomized phase II study of first-line everolimus (EVE) + bevacizumab (BEV) versus interferon alfa-2a (IFN)+BEV in patients (pts) with metastatic renal cell carcinoma (mRCC): RECORD-2
- LBA22_PR: Temsirolimus vs sorafenib as second line therapy in metastatic renal cell carcinoma: Results from the INTORSECT trial.

RCC Treatment Algorithm: 2012

Treatment Status	Patient Status	Therapy (Level 1 evidence)	Other Options (≥ Level 2)
First Line	Good or intermediate risk	Sunitinib Bevacizumab + IFN Pazopanib	High-dose IL-2 (Sorafenib) Observation Clinical Trial
	Poor risk	Temsirolimus	Sunitinib Pazopanib Clinical trial
Second Line	Failed cytokines	Sorafenib Pazopanib Axitinib	Sunitinib Bevacizumab Clinical Trial
	Failed VEGFR inhibitor	Everolimus Axitinib	TKI's Temsirolimus Clinical Trial
	Failed mTOR inhibitor	?	

Treatment of Metastatic RCC
Open Questions

- What is the best sequence of agents
  - TKI-mTOR-?
  - TKI-TKI-mTOR ?.....
- What is the best second line therapy
- Are combinations superior to sequential therapy
- Can we identify clinically relevant biomarkers
- …….

First-line Treatment of good/intermediate mRCC

Study	ORR, %	Median PFS, mo*	Median OS, mo*
Sunitinib vs IFN-α[1]	47 vs. 12	11 vs. 5 *P* < 0.001	26.4 vs 21.8 *P* = 0.051
Bevacizumab + IFN-α vs IFN-α[2]	31 vs. 13	10.2 vs. 5.4 *P* = 0.0001	23.3 vs. 21.3 *P* = 0.91
Bevacizumab + IFN-α vs IFN-α[3]	25.5 vs. 13.1	8.5 vs. 5.2 *P* = 0.0001	18.3 vs. 17.4 *P* = 0.097
Pazopanib vs placebo[6]	32 vs. 4	9.2 vs. 4.2 *P* = 0.0001	22.9 vs. 20.5 *P* = 0.224
Tivozanib vs sorafenib[5]	33 vs 23	11.9 vs. 9.1 *P* < 0.042	Not Reported

*Intent to treat analysis

Can combination regimens exceed these results ?

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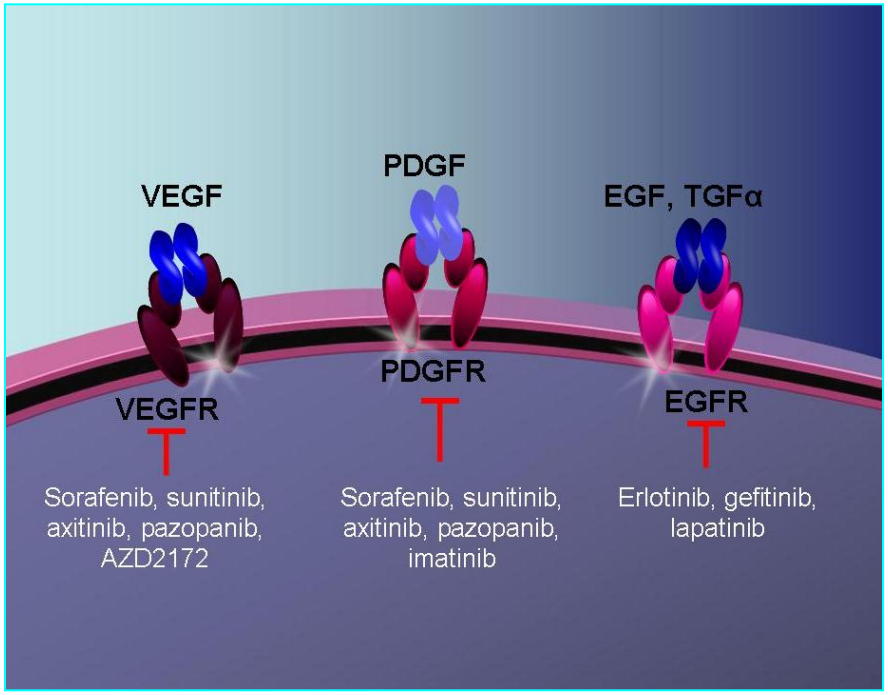
1. Motzer RJ et al. *J Clin Oncol*. 2009; 2. Escudier B et al. *Lancet*. 2007. 3. Rini B et al. *J Clin Oncol*. 2008;
4. Escudier B et al. *J Clin Oncol*. 2009; 5. Hudes G et al. *N Engl J Med*. 2007. 6. Sternberg C et al. *J Clin Oncol*. 2010;

Combinations of Targeted Agents

- Rationale:
  - Combination of 2 active agents may lead to increased activity
  - Potential for additive or synergistic effect
  - Delay or avoid development of resistance
- What are we looking for
  - Substantial increase in CR rate (prerequisite for cure)
  - Significantly better PFS (must be better than the sequence)
  - Longer overall survival
  - Tolerable toxicity profile
  - .....

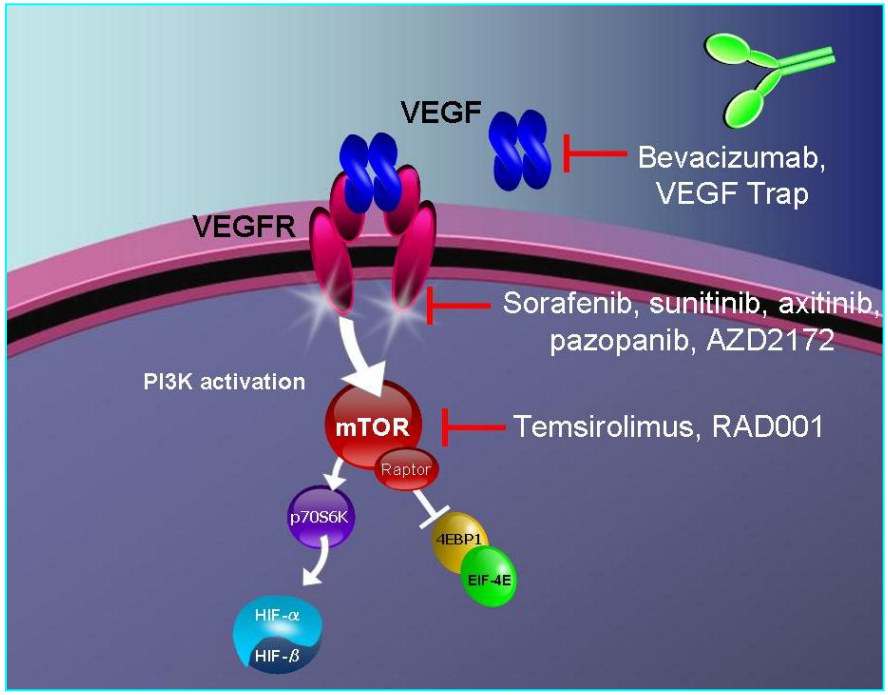
Combination of targeted Agents: Horizontal versus Vertical Blockade

Horizontal Blockade



Multiple different signaling pathways are targeted

Vertical Blockade



A single signaling pathway e.g. VEGF is targeted in ≥ levels

Adapted from: Sosman JA, Puzanov I, Atkins M. *Clin Cancer Res 2007*

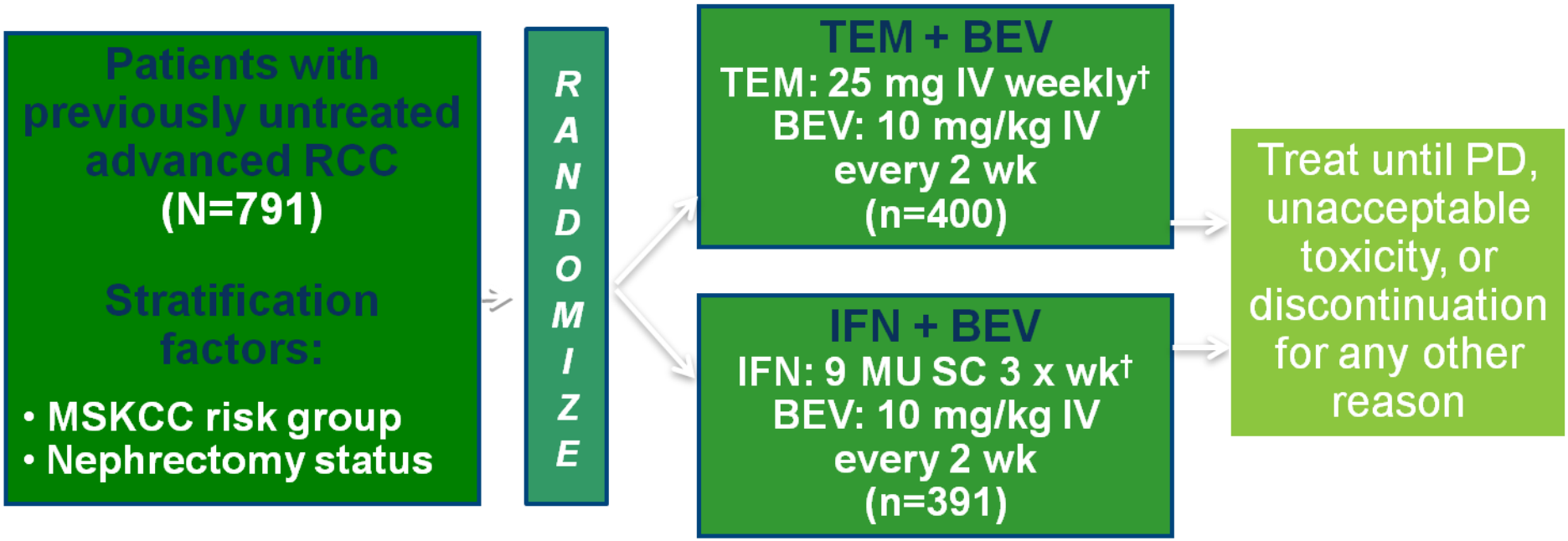
Rational Combinations of Targeted Therapies

- **TKI + bevacizumab:**
  - Su[Too Toxic]ab
  - Sorafenib + bevacizumab
- **TKI + mTOR**
  - Te[Too Toxic]nib
  - Everolimus + sorafenib
- **mTOR + bevacizumab**

Feasible, confirmed in the current larger studies

Feldman *et al. J Clin Oncol* 2008; Cooney et al. *J Clin Oncol* 2008; Sosman *et al. J Clin Oncol* 2008; Fischer P *et al. J Clin Oncol* 2008; Rosenberg *et al. J Clin Oncol* 2008; Whorf RC *et al. J Clin Oncol* 2008; Merchan et al J Clin Oncol 2011.

INTORACT (LBA21_PR) Study Design



Key eligibility criteria:

- Age ≥ 18 years with confirmation of advanced clear-cell RCC
- ≥ 1 measurable lesion per RECIST criteria
- No prior systemic treatment for RCC
- KPS ≥ 70%

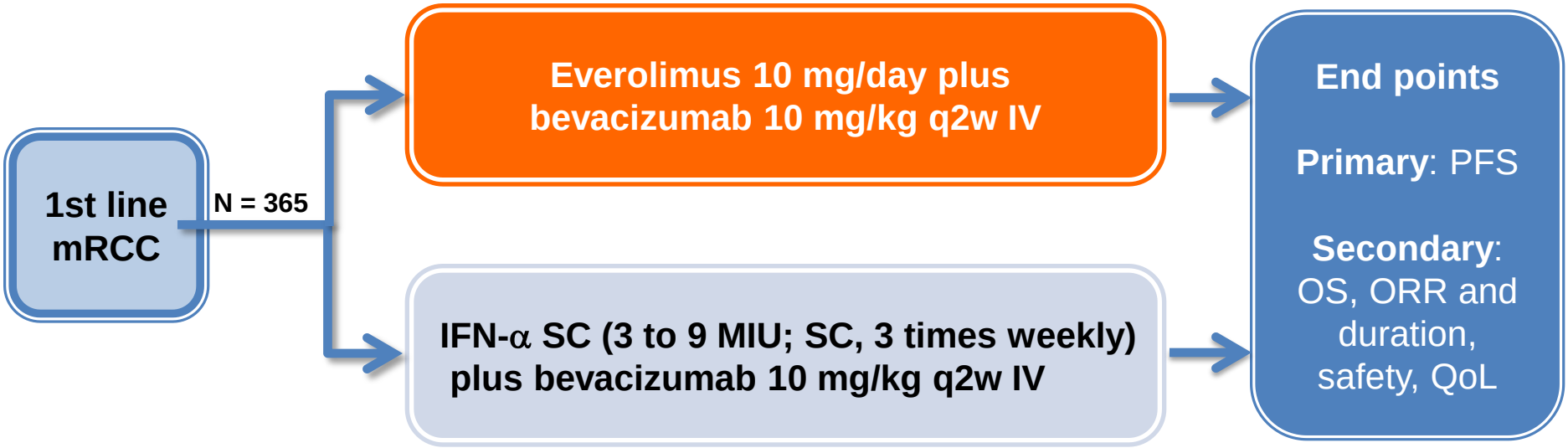
Key exclusion criteria:

- Prior systemic treatment for mRCC, including prior therapy with VEGF or mTOR inhibitor

Rini B et al : abstract LBA21_PR, ESMO 2012

RECORD-2 (abstr. 783O): Study Design

Randomized, open-label, phase II study



Key eligibility criteria:

- Age ≥ 18 years with confirmation of advanced metastatic clear-cell RCC
- ≥ 1 measurable lesion per RECIST criteria
- Prior nephrectomy
- KPS ≥ 70%

Key exclusion criteria:

- Prior systemic treatment for mRCC, including prior therapy with VEGF or mTOR inhibitor

INTORACT and RECORD-2

- Design
  - Well designed and conducted randomized phase III and II, respectively
- Choice of comparator
  - Bevacizumab / Interferon is an accepted first-line option albeit not as frequently used in clinical practice as sunitinib or pazopanib
- Objective -Were the trials looking for too big of a difference ?
  - Both trials were looking for an approximately 30% improvement in PFS
  - At least what we would expect from combining 2 active agents
- Both studies accrued rapidly

First-line Treatment of good/intermediate mRCC

Study	ORR, %	Median PFS, mo	Median OS, mo
Sunitinib vs IFN-α[1]	47 vs. 12	11 vs. 5 *P < 0.001*	26.4 vs 21.8 *P = 0.051*
Bevacizumab + IFN-α vs IFN-α[2]	31 vs. 13	10.2 vs. 5.4 *P = 0.0001*	23.3 vs. 21.3 *P = 0.91*
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Pazopanib vs placebo[4]	32 vs. 4	9.2 vs. 4.2 *P < 0.0001*	22.9 vs. 20.5 *P = 0.224*
BEV/TEM vs BEV/IFN[5]	28 vs. 28	9.1 vs. 9.3 *p=0.759*	25.8 vs. 25.5 *p=0.638*
BEV/EVER vs BEV/IFN[6]	27 vs. 28	9.2 vs. 10 *p=0.485*	NA vs. 26

No difference to existing first line options

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1. Motzer RJ et al. *J Clin Oncol.* 2009; 2. Escudier B et al. *Lancet.* 2007. 3. Rini B et al. *J Clin Oncol.* 2008; 4. Sternberg C et al. *J Clin Oncol.* 2010; 5. Rini et al ESMO 2012; 6. Ravaud et al ESMO 2012

Patient Characteristics of Current First-line Trials

Study	MSKCC G / I	PS	Clear cell	Prior nephrectomy
Sunitinib vs IFN-α[1]	> 90 %	0-1	✔	91 % vs. 89 %
Bevacizumab + IFN-α vs IFN-α[2]	> 90 %	KPS ≥ 70 %	✔	✔
Bevacizumab + IFN-α vs IFN-α[3]	> 90 %	KPS ≥ 70 %	✔	85 % vs. 85 %
Pazopanib vs placebo[4]	> 90 %	0-1	✔	89 % vs. 88 %
BEV/TEM vs BEV/IFN[5]	> 90 %	KPS ≥ 70 %	✔	85 % vs. 86 %
BEV/EVER vs BEV/IFN[6]	> 90 %	KPS ≥ 70 %	✔	✔

No difference to existing first line options

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1. Motzer RJ et al. *J Clin Oncol.* 2009; 2. Escudier B et al. *Lancet.* 2007. 3. Rini B et al. *J Clin Oncol.* 2008; 4. Sternberg C et al. *J Clin Oncol.* 2010; 5. Rini et al ESMO 2012; 6. Ravaud et al ESMO 2012

Rationale for Bevacizumab / Temsirolimus combination

- Phase I study: N = 12, all ECOG 0–1
- Prior therapy: n = 7, cytokines in 6/7
- RR: NO CR PR=7 (60 %) SD = 3 (25 %)
- PFS: n/a

Combination feasible with both agents given at full dose

High response rate → further testing recommended

Merchan ASCO 2007

Rationale for Everolimus/Bevacizumab combination

Phase II study: N = 30 untreated patients in preliminary report
N = 50 untreated patients in final report

Median PFS: 12 months in ASCO 2008 presentation
(9 months in abstract)
9.1 months in the final report (JCO 2010)

RR: NO CR PR=23 % SD = 53 %

Combination feasible with both agents given at full dose

Very active ("12 months PFS") → further testing recommended

Whorf et al ASCO 2008; Hainsworth et al JCO 2010

Rationale for RECORD-2 and INTORACT

BUT

- Small trials
- No CR
- PR rate comparable to historical data e.g. sunitinib
- PFS not available/comparable to historical data e.g. sunitinib
- I am not aware of any preclinical additive/synergistic effect

↓

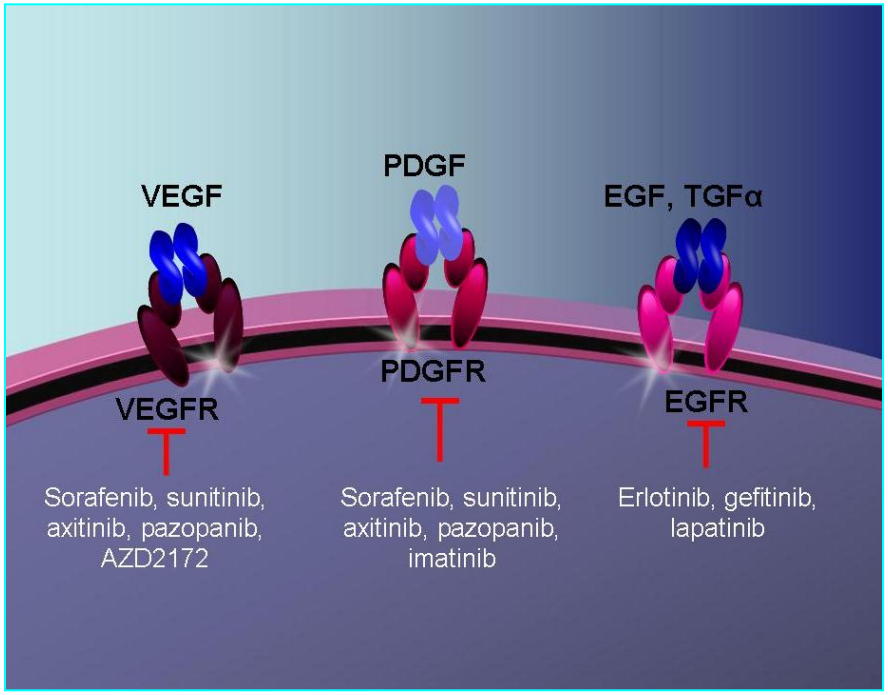
Rationale strong enough for further development ?

↓ Temsirolimus / Bevacizumab
Randomized phase III trial

↓ Everolimus / Bevacizumab
Randomized phase II trial

Combination of targeted Agents: Horizontal versus Vertical Blockade

Horizontal Blockade



Multiple signaling pathways downstream of HIF-α are targeted

Vertical Blockade

A single signaling pathway e.g. VEGF is targeted in ≥ levels

Adapted from: Sosman JA, Puzanov I, Atkins M. *Clin Cancer Res 2007*

Future Combinations of Targeted Agents

- Sound pre-clinical rationale (synergy/additive)
- Convincing efficacy in phase II
- Acceptable toxicity profile
- Phase III trial design should include a sequence as comparator
- Combine agents with different mechanism of action
  - e.g TKI plus antibody against other target
  - e.g. Immunotherapy with TKI

RCC Treatment Algorithm: 2012

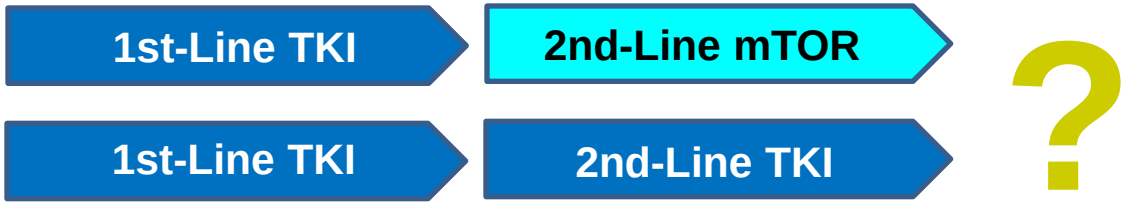
Treatment Status	Patient Status	Therapy (Level 1 evidence)	Other Options (≥ Level 2)
First Line	Good or intermediate risk	Sunitinib Bevacizumab + IFN Pazopanib	High-dose IL-2 (Sorafenib) Observation Clinical Trial
	Poor risk	Temsirolimus	Sunitinib Pazopanib Clinical trial
Second Line	Failed cytokines	Sorafenib Pazopanib Axitinib	Sunitinib Bevacizumab Clinical Trial
	Failed VEGFR inhibitor	Everolimus Axitinib	TKI's Temsirolimus Clinical Trial
	Failed mTOR inhibitor	?	

Choice of Second-Line Therapy

- Individual physician knowledge of data
- Distinct safety profiles of different agents
- Experience with drugs
- Availability of and access to various drugs
- Patient-specific issues such as co-morbidities, toxicities experienced on first-line therapy

Does Sequence Matter?

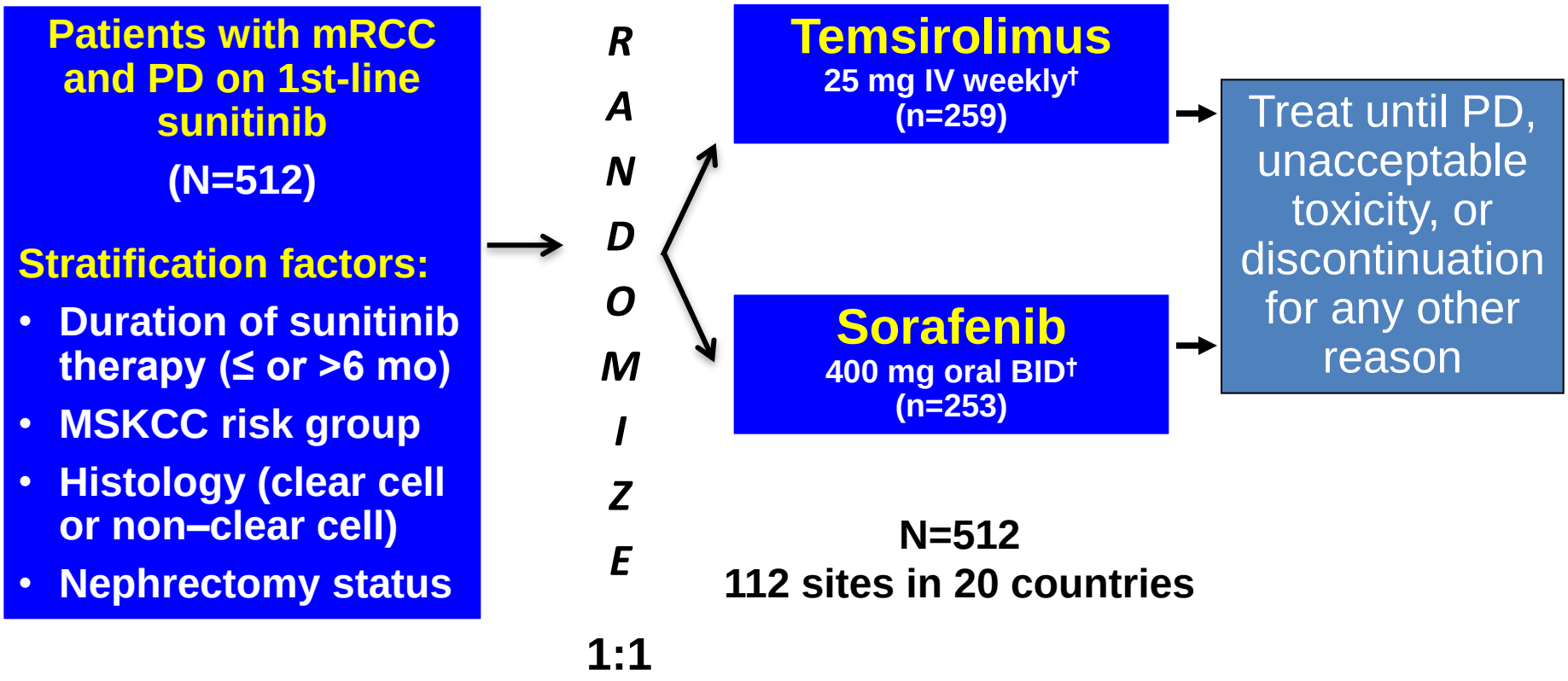
(in the Absence of Predictive Markers)



Sequences of Targeted Therapies	mPFS 1st drug, mo (95% CI)	mPFS 2nd drug, mo (95% CI)
Any VEGF to any mTOR (n = 277)	7.8 (6.5–9.1)	3.4 (2.9–4.5)
Sunitinib to temsirolimus (n = 115)	7.2 (5.7–9.3)	3.2 (2.6–5.0)
Sunitinib to everolimus (n = 130)	8.6 (6.6–10.7)	3.7 (2.8–5.3)
Any VEGF to any VEGF (n = 541)	7.5 (6.9–8.0)	4.0 (3.7–4.6)
Sunitinib to sorafenib (n = 257)	7.6 (6.5–8.2)	3.6 (2.9–4.1)
Sorafenib to sunitinib (n = 152)	7.3 (6.2–8.5)	5.2 (4.2–6.8)

Heng et al. *J Clin Oncol*. 2012;30(suppl5):Abstr 387.

INTORSECT (LBA22_PR) Study Design



First patient randomized: September 25, 2007; last patient randomized: January 31, 2012.
Data cutoff: May 4, 2012. At present, 2 patients are on study.

Hutson T. et al abstract LBA22_PR, ESMO 2012.

INTORSECT

- Design
  - Well designed and conducted randomized phase III study
  - "cleanest" study thus far with regards to prior therapy, included sunitinib pretreated patients only
- Choice of comparator
  - Sorafenib was an acceptable second-line option at the time of study development
- Objective –Was the trial looking for too big of a difference ?
  - Trial was looking for a 33% improvement in PFS
- Study accrued rapidly

Results of Current second-line Trials

Study	ORR, %	Median PFS, mo
Temsirolimus vs. sorafenib[1]	8 % vs. 8 %	4.3 vs. 3.9 p> 0.05
Everolimus vs placebo[2]	1.8 % vs. 0 %	4.6 vs. 1.8* p< 0.05
Axitinib vs. sorafenib[3]	19 % vs. 9 %	4.8 vs. 3.4 p< 0.05

*Sunitinib pretreated patients only

No statistically significant nor clinically meaningful benefit for temsirolimus over sorafenib

1. Hutson T. et al abstract LBA22_PR ESMO 2012; 2. Motzer RJ et al. *Cancer 2010*; 3. Rini B. Lancet 2011;

Patient Characteristics of Current second-line Trials

Study	MSKCC G / I	PS	Clear cell	Prior anti VEGF
Everolimus vs placebo[1]	> 85 %	KPS ≥ 70 %	✔	Sunitinib and/or sorafenib
Axitinib vs. sorafenib[2]	65% vs. 64%	ECOG 0-1	✔	sunitinib
Temsirolimus vs. sorafenib[6]	> 85 %	ECOG 0-1	83 % vs. 82 %	sunitinib

No substantial difference to existing second-line options

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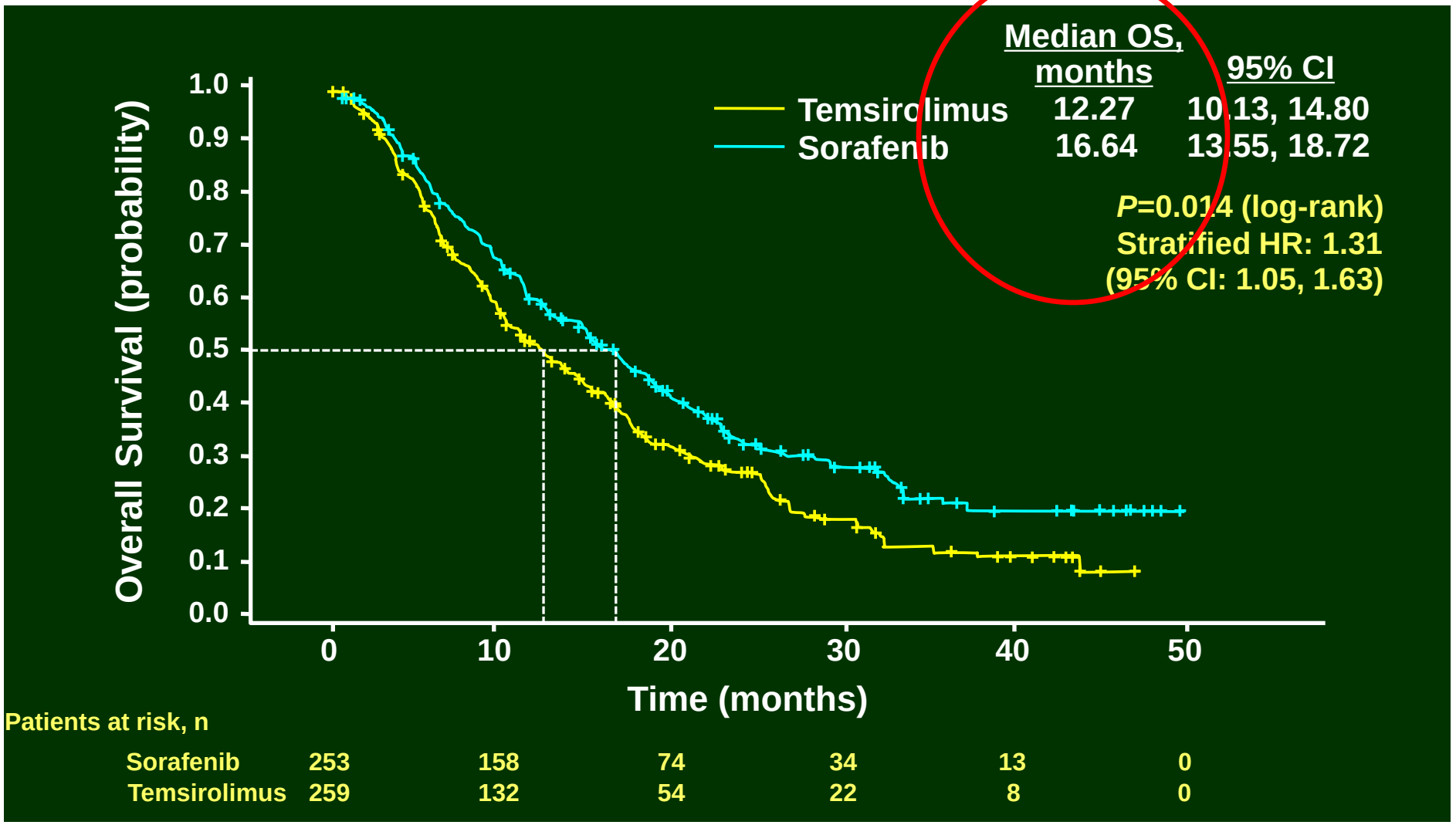
1. Motzer RJ et al. *J Clin Oncol.* 2009; 2. Rini B. Lancet 2011; 3. Ravaud et al ESMO 2012

INTORSECT: Overall Survival



Results of Current second-line Trials

Study	ORR, %	Median PFS, mo	Median OS, mo
Temsirolimus vs. sorafenib[1]	8 % vs. 8 %	4.3 vs. 3.9	12.3 vs. 16.6
Everolimus vs placebo[2]	1.8 % vs. 0 %	4.6 vs. 1.8*	14.8 vs. 14.4
Axitinib vs. sorafenib[3]	19 % vs. 9 %	4.8 vs. 3.4	15.2 vs. 16.5

*Sunitinib pretreated patients only

Numerically longest OS rates have been reported with second line TKI in particular sorafenib

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1. Hutson T. et al abstract LBA22_PR ESMO 2012; 2. Motzer RJ et al. *Cancer 2010*; 3. Motzer R. et al abstract 793PD ESMO 2012;

INTORSECT: Overall Survival

- **True effect ?**
- **False positive ? (secondary endpoint)**
- **Difference in tumor biology and behavior ?**
  - More rapid progression/tumor growth in one group ?
  - RCC is a molecularly very heterogenous tumor and patients with similar clinical presentation can have very different molecular profiles

Stewart G et al Nat Rev Urol 2011

- **Dose delivery ?**
  - Discontinuation due to AEs TEM 17% vs. SOR 14%

INTORSECT: Overall Survival

- **Subsequent therapies ?**
  - few patients had third line therapy and vast majority crossed over to the other drug

- Is previous VEGF therapy altering the biology of the disease
  - protein expression in mRCC is heterogenous and expression of key proteins appear to vary with sunitinib therapy

Stewart G. et al GU ASCO 2012

The significant survival difference remains to be conclusively explained

PFS as a Surrogate for OS in Metastatic RCC

- Several retrospective studies have demonstrated a correlation between PFS and OS
- The vast majority of patients included into these studies were first-line patients
- PFS has become an acceptable standard endpoint for first-line studies

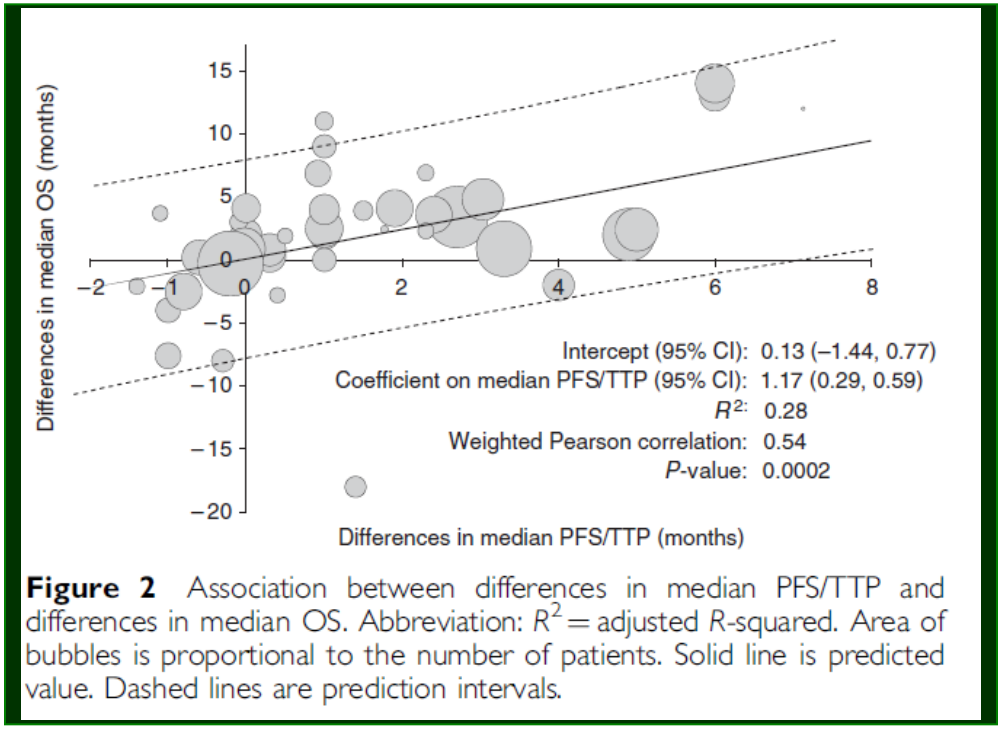

Figure 2 Association between differences in median PFS/TTP and differences in median OS. Abbreviation: R^2 = adjusted R-squared. Area of bubbles is proportional to the number of patients. Solid line is predicted value. Dashed lines are prediction intervals.

Hotte S et al Curr Oncol 2011; Heng D et al Cancer 2011; Delea et al Br J Cancer 2012

Is PFS a good surrogate for OS in metastatic RCC ?

Trial / Agent	PFS	OS
Temsirolimus vs. Sorafenib	4.28 months vs 3.91 months	12.27 months vs 16.64 months
Axitinib* vs. Sorafenib	4.8 months vs 3.4 months	15.2 months vs 16.5 months

*sunitinib pretreated pts only

Concept of PFS as surrogate for OS is challenged in second line therapy

Needs to be examined

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Hutson T et al ESMO 2012
Motzer R et al ESMO 2012

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Conclusions (1)

- Combinations of targeted agents in metastatic RCC remain investigational
- "Vertical blockade" with combinations of currently available agents is either too toxic or lacks additive / synergistic effects
- "Horizontal blockade" may become feasible with the large number of agents in development
- Combinations with immunotherapy (e.g. PD-1 inhibitors) are under investigation

Conclusions (2)

- Sequential therapy remains the standard of care
- Current second line options include everolimus and axitinib
- Optimal sequence remains to be defined
- There appears to be an uncoupling of the relationship between PFS and OS in the second line setting
  - Implications for trial design in the future
- Biomarkers are urgently needed to allow a more rational selection of therapy and allow for patient enrichment in clinical trials

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	Failed VEGFR inhibitor	Everolimus Axitinib	TKI's Temsirolimus Clinical Trial
	Failed mTOR inhibitor	?	