



SEQUENCING TARGETED THERAPIES AND BEST OPTIONS FOR 2ND LINE TREATMENT IN MRCC

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STANDARD OF CARE IN 1st-line MRCC

Prognostic risk group	First-line	Second-line
Good	Sunitinib ^{1,2} Bevacizumab + IFN- α ² IL-2 based treatment (in selected patients)	Sorafenib
Intermediate	Sunitinib ¹ Bevacizumab + IFN- α	
Poor	Temsirolimus ^{1,2} (option sunitinib or sorafenib)	

¹Ljungberg B, et al. *Eur Urol* 2007;51:1502–1510

²NCCN clinical practice guidelines in oncology: Kidney Cancer. 2008

SEQUENCING TARGETED THERAPIES

PHASE II STUDIES
OR
RETROSPECTIVE STUDIES

Sorafenib ⇔ Sunitinib

Sunitinib ⇔ Sorafenib

- **90 patients with RCC from 4 sites in France**
- **In the last 3 years, patients received sequential treatment**
 - **Sorafenib followed by sunitinib (So-Su; n=68) or**
 - **Sunitinib followed by sorafenib (Su-So; n=22)**

Sorafenib ⇒ Sunitinib

Efficacy of sorafenib (N = 66)		Sunitinib			
		PR, n (%)	SD, n (%)	PD, n (%)	NE, n (%)
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)
NE	2	—	1 (50)	—	1 (50)

PR = Partial response; SD = Stable disease; PD = Progressive disease; NE = Not evaluable.

Sunitinib ⇒ Sorafenib

Efficacy of sunitinib (N = 22)		Sorafenib		
		PR, n (%)	SD, n (%)	PD, n (%)
PR	5	1 (20)	2 (40)	2 (40)
SD	12	1 (8)	7 (58)	4 (34)
PD	5	0	3 (60)	2 (40)

PR = Partial response; SD = Stable disease; PD = Progressive disease.

Sunitinib ⇨ Sorafenib

- 23 patients progressing under sunitinib
- Sorafenib : 800 mg/d continuously
- 20/23 patients were evaluable
- Efficacy
 - PR: 2 (9%) patients
 - Minor response: 2 (9%) patients
 - SD: 10 patients

Bevacizumab ⇒ Sunitinib

- **61 patients with metastatic RCC^{1,2}**
- **1st line bevacizumab-based therapy**
- **Sunitinib: 50 mg/day for 4/6 weeks**
 - **PR: 14 (23%) patients; SD: 36 (59%) patients²**
 - **Duration of PR: 41 weeks**

PR = Partial response; SD = Stable disease

Sorafenib or Sorafenib and Sunitinib ⇒ Axitinib

Patients with mRCC refractory to:

Group 1. Sunitinib and sorafenib (n=14)

Group 2. Cytokine and sorafenib (n=29)

Group 3. Sorafenib alone (n=15)



Axitinib*:

5 mg orally bid (starting); titrated to 7 mg BID, then to 10 mg bid

Sorafenib or Sorafenib and Sunitinib ⇒ Axitinib

- **ORR**

- Group 1 (sunitinib and sorafenib resistant): 7%
- Group 2 (cytokines and sorafenib): 28%
- Group 3 (sorafenib alone): 27%

- **PFS (median follow-up of 10.3 months)**

- Group 1 (sunitinib and sorafenib resistant): 7.1 mo
- Group 2 (cytokines and sorafenib): 9 mo
- Group 3 (sorafenib alone): 7.7 mo

SEQUENCING TARGETED THERAPIES WITH ANTI ANGIOGENIC THERAPY IN CONCLUSION

- No cross-resistance
- Importance of PR ~ related to 1st line
- No data of 2nd line following INF α and bevacizumab
- No change in toxic profile compared to 1st line
 - But similar side effects may recur
- No prospective data on predictive information of 1st line on results in 2nd line

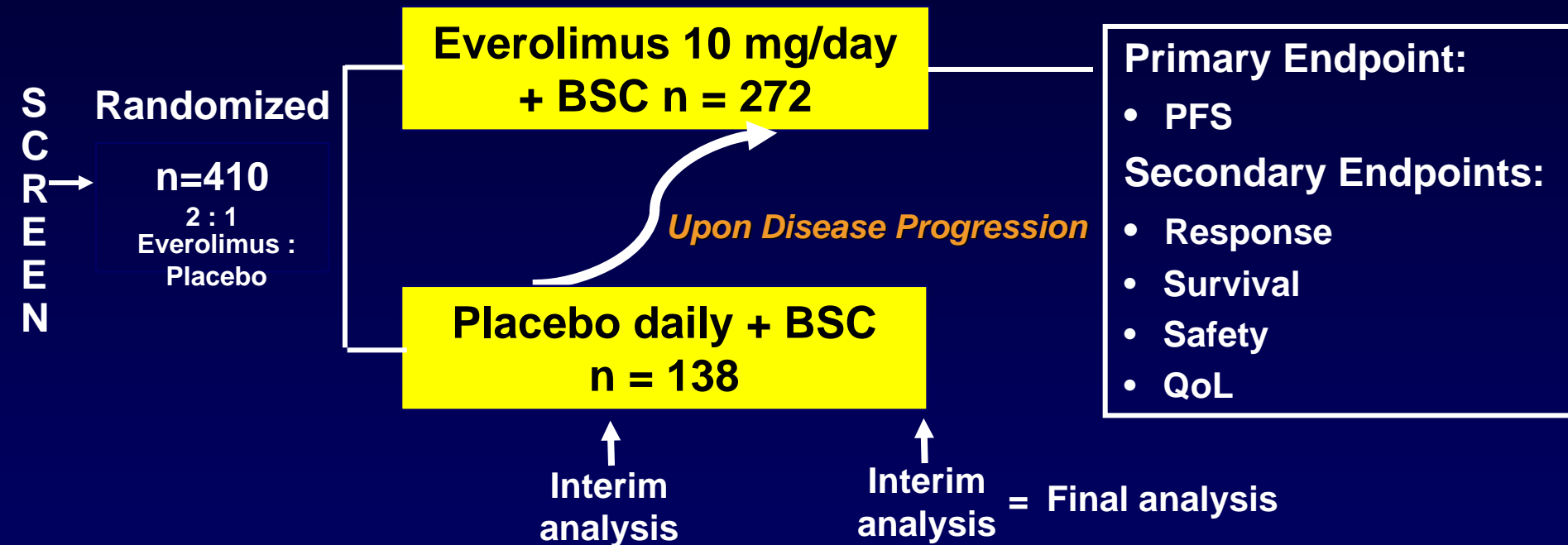
STANDARD OF CARE IN 2nd line MRCC

Prognostic risk group	First-line	Second-line
Good	Sunitinib Bevacizumab + IFN-α IL-2 based treatment (in selected patients) (Option : sorafenib)	Option : sorafenib Option : sunitinib Sorafenib (Option : sunitinib)
Intermediate	Sunitinib Bevacizumab + IFN-α (Option : sorafenib)	Option : sorafenib Option : sunitinib (Option : sunitinib)
Poor	Temsirolimus (Option sunitinib or sorafenib)	

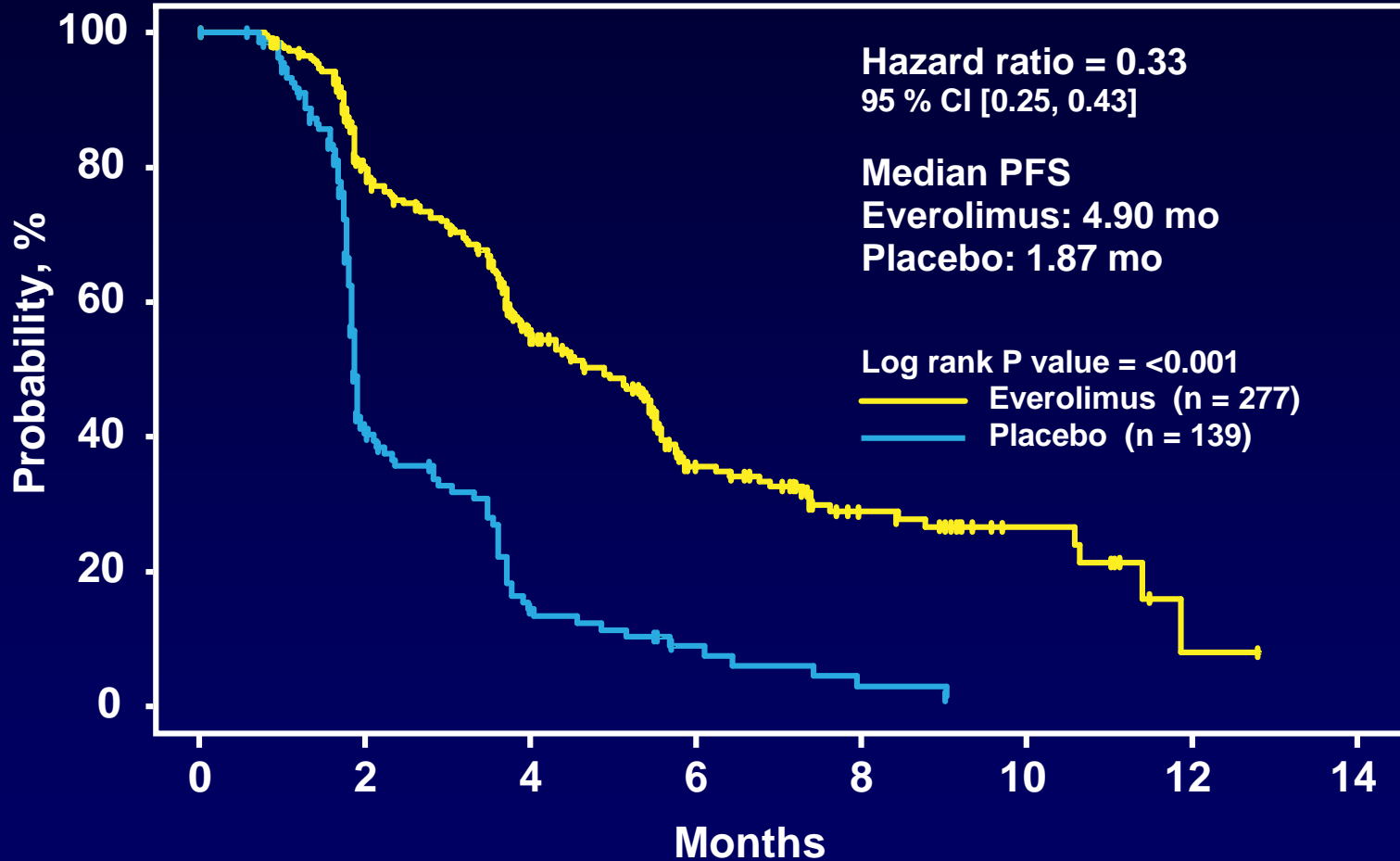
SEQUENCING TARGETED THERAPIES

PHASE III

EVEROLIMUS FOR PROGRESSION AFTER VEGFR-TKI



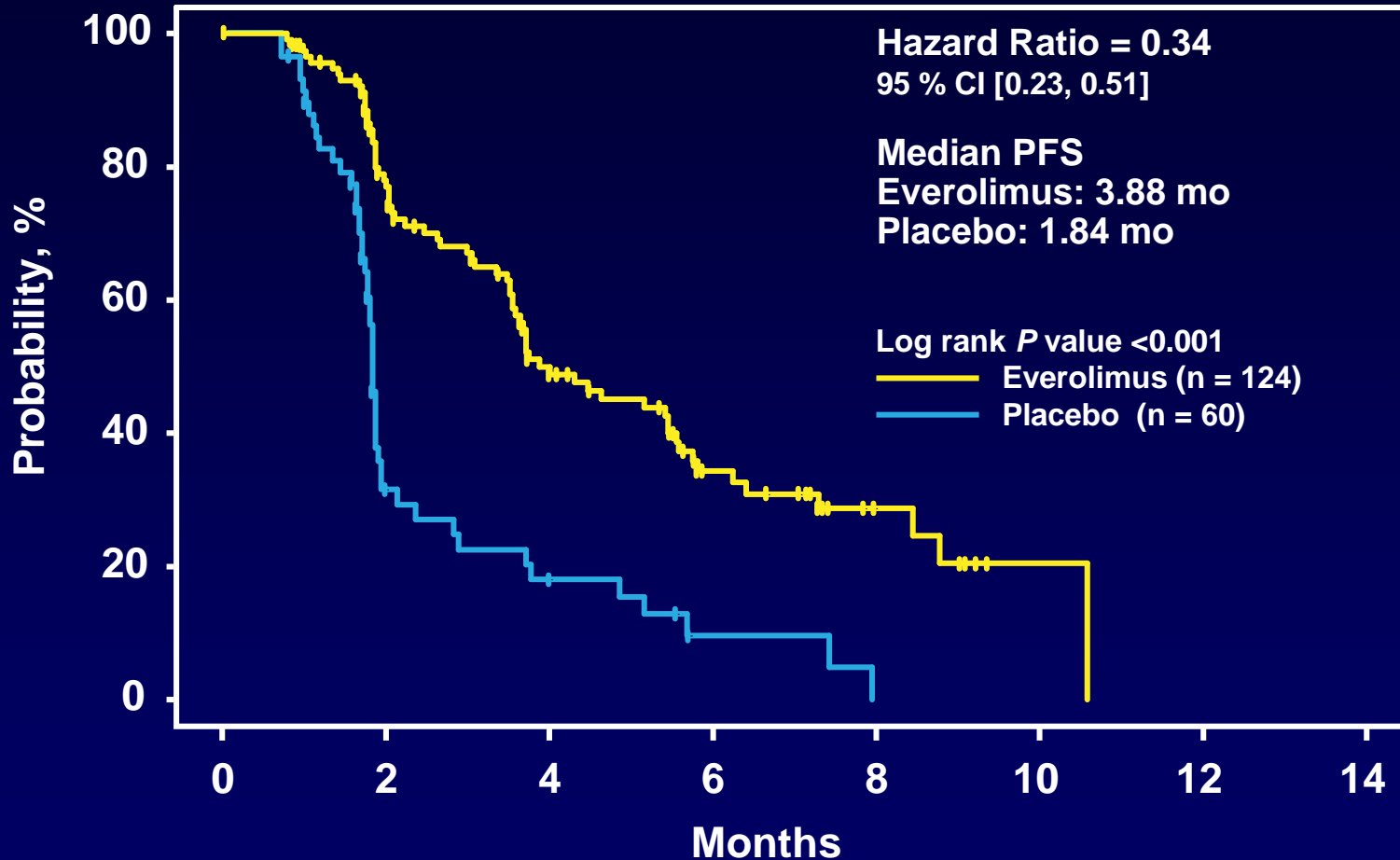
Progression-Free Survival by Treatment Central Radiology Review



Patients at risk

Everolimus	277	192	115	51	26	10	1	0
Placebo	139	47	15	6	2	0	0	0

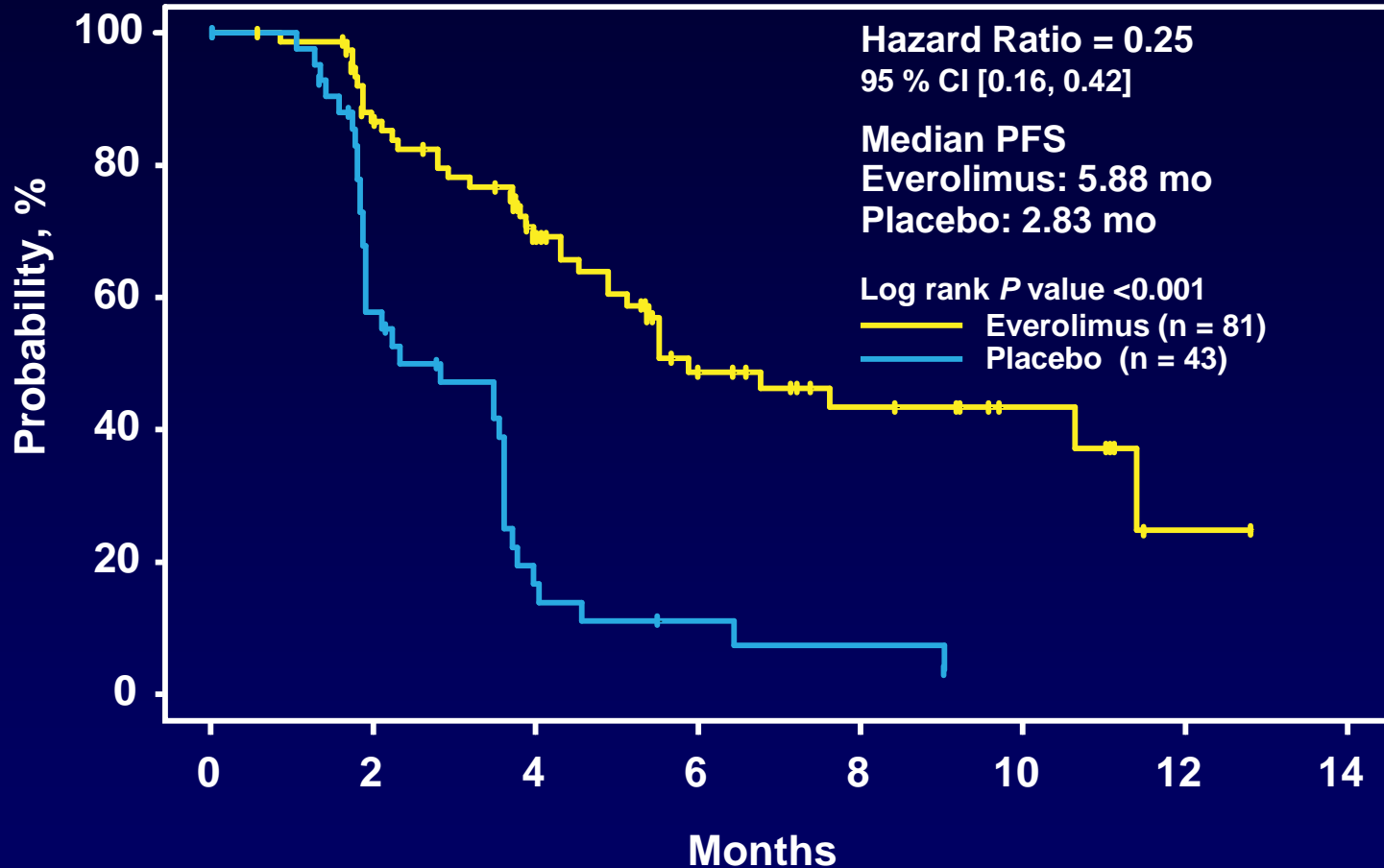
Progression-Free Survival by Treatment After Sunitinib



Patients at risk

	0	2	4	6	8	10	12	14
Everolimus	124	80	44	20	7	1	0	0
Placebo	60	15	8	2	0	0	0	0

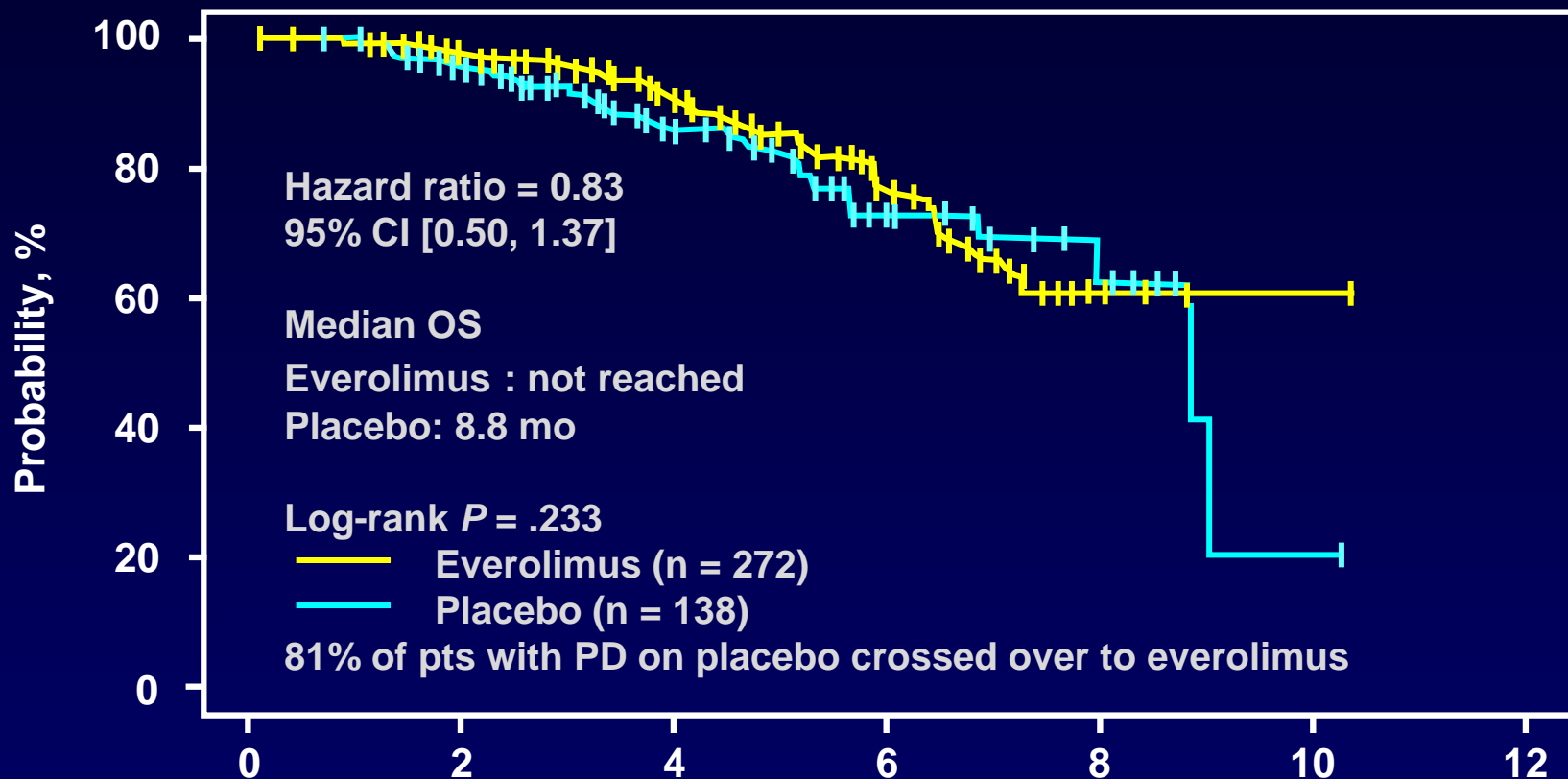
Progression-Free Survival by Treatment After Sorafenib



Patients at risk

Everolimus	81	63	43	23	15	7	1	0
Placebo	43	23	6	3	2	0	0	0

Overall Survival by Treatment

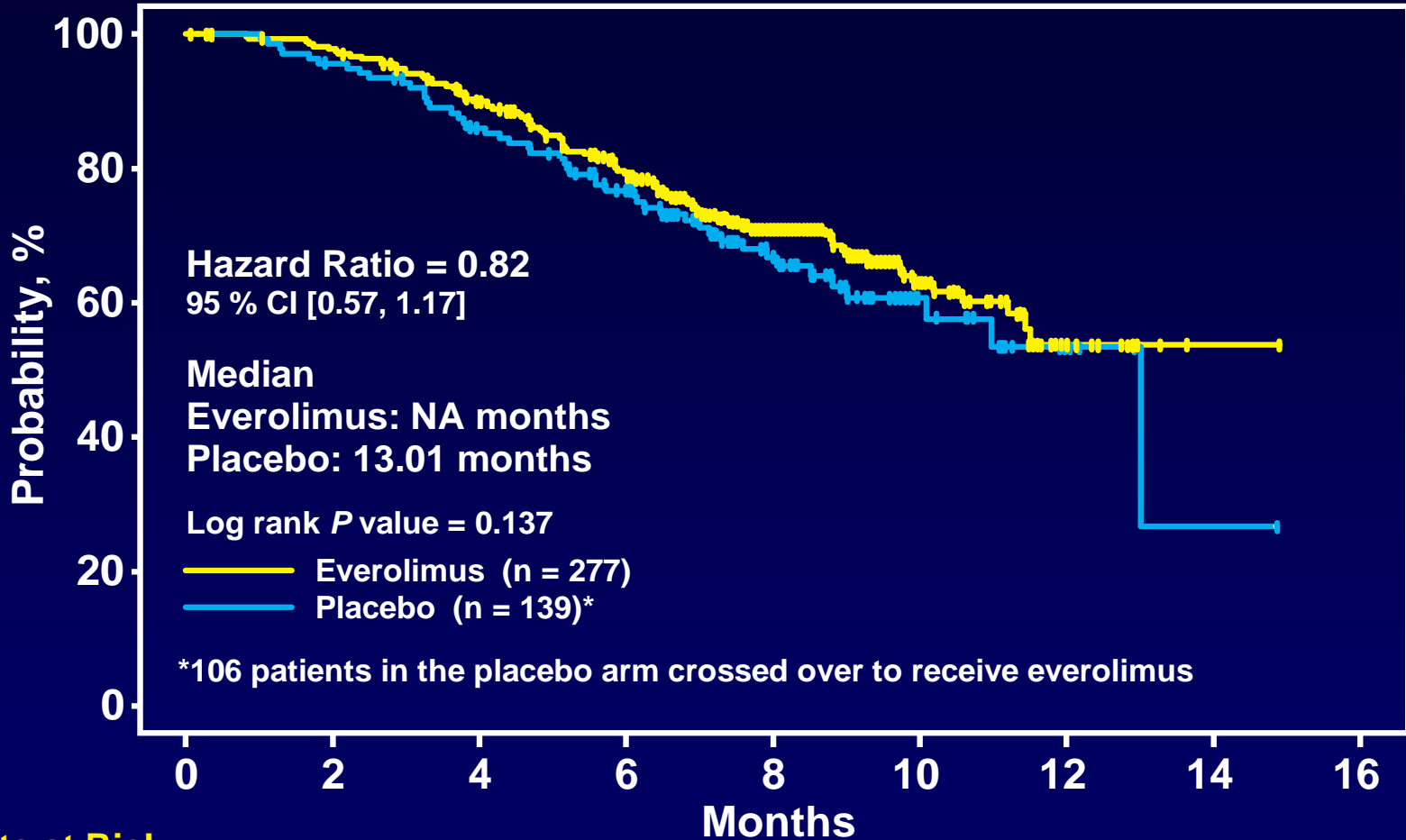


Patients at risk, n

Everolimus	272	229	126	61	9	1	0
Placebo	138	111	62	25	9	1	0

PD = Progressive disease.

Overall Survival by Treatment



Patients at Risk

	0	2	4	6	8	10	12	14	16
Everolimus	277	267	236	191	108	52	11	1	0
Placebo	139	131	114	91	53	19	6	1	0

SEQUENCING TARGETED THERAPIES IN CONCLUSION

- Significant gain of mTOR inhibitor with everolimus, when progression after sunitinib and/or sorafenib
- Questions about the better sequence and arguments to do so
 - mTOR inhibitor after one or both VEGFR TKI ?
 - Efficacy on the 1st VEGFR TKI to recommend a 2nd line with anti angiogenic therapy or with mTOR inhibitor ?

STANDARD OF CARE IN 2nd-line MRCC

Prognostic risk group	First-line	Second-line
Good	<p>Sunitinib^{1,2}</p> <p>Bevacizumab + IFN-α² IL-2 based treatment (in selected patients)</p>	<p>Everolimus</p> <p>Option : sorafenib</p> <p>Option : sunitinib</p> <p>Sorafenib</p> <p>Option : sunitinib</p>
Intermediate	<p>Sunitinib¹</p> <p>Bevacizumab + IFN-α</p>	<p>Everolimus</p> <p>Option : sorafenib</p> <p>Option : sunitinib</p>
Poor	<p>Temsirolimus^{1,2} (option sunitinib or sorafenib)</p>	<p>?</p>

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²NCCN clinical practice guidelines in oncology: Kidney Cancer. 2008

TAKE HOME MESSAGE

- 2nd line is available after progression under 1st line with VEGFR TKI
- No cross resistance between VEGFR TKI
- Positive phase III trial in favor of an mTOR inhibitor: Everolimus after VEGFR TKI
- No available data on 2nd line after mTOR inhibitor

CONCLUSION

- 2nd line is available in MRCC patients
- Everolimus (phase III data based) or VEGFR TKI (phase II data based)
 - With many questions: Best sequence,..
- Probably the major challenge in coming years
- Place for clinical trials :
 - i.e.: mTOR inhibitor vs. VEGFR TKI