

Case #7—Sequencing Systemic Therapy for Metastatic Renal Cell Carcinoma: Does One Algorithm Fit All?

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Clinical Case (1)

- **68-year-old woman**
- **Diagnosis of clear cell renal carcinoma 18 months ago**
- **Radical nephrectomy**
- **10 months later : para-aortic lymph nodes and both lungs metastases**
- **Sunitinib : PR for 7 months**
- **Currently**
 - shortness of breath with exertion
 - nonproductive cough
 - mild/moderate low back pain.

Clinical Case (2)

- **CT SCAN CHEST AND ABD:**
 - PD in lung and retroperitoneal lymph nodes
 - Largest pulmonary nodule: 3.8 cm
- **BONE SCAN: L4-5 and the right ischium**
- **LABS:**
 - WBC $4.0 \times 10^9/L$, platelets $140 \times 10^9/L$, Hgb 11.0 g/dL.
 - Creatinine, calcium, and alkaline phosphatase: normal limits
- **MEDICAL HISTORY: Hypertension on atenolol**
- **ECOG PS: 1**

Question 1

Which second-line systemic therapy would you choose?

- Everolimus
- Sorafenib
- Temsirolimus
- Pazopanib
- Clinical trial participation (AXIS trial—axitinib vs sorafenib)
- Bevacizumab + IFN alpha

Second-Line Options for RCC Treatment (Clear Cell Carcinoma)

Population	Standard	Option
<u>Post cytokine</u>	Sorafenib	Bevacizumab
		Sunitinib
<u>Post VEGFR TKI</u>	Everolimus	Pazopanib
		Sunitinib
		Clinical trial

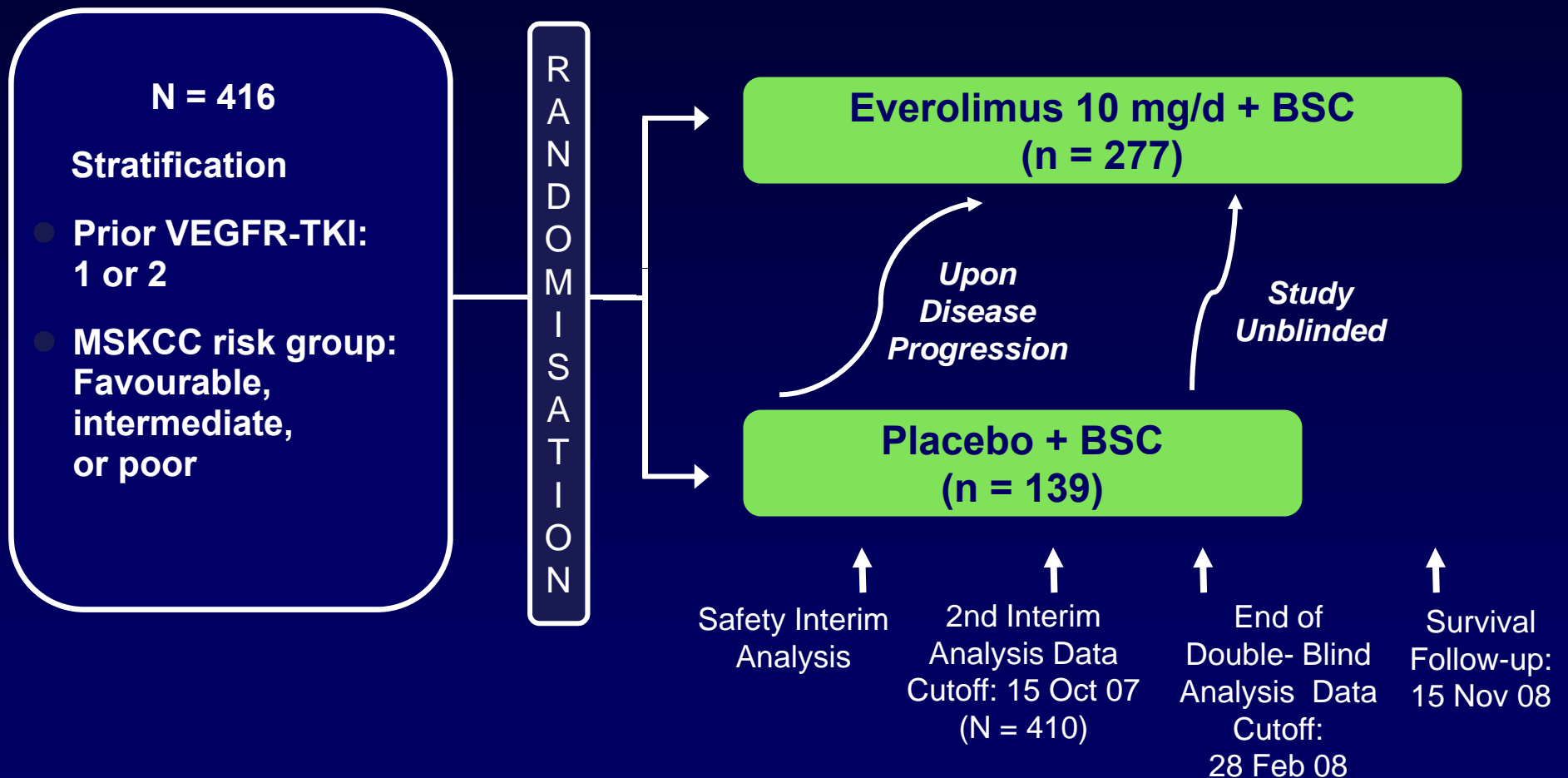
Escudier B, et al. *Ann Oncol*. 2009;20(Suppl 4):81-82.

de Reijke TM, et al. *Eur J Cancer*. 2009;45(5):765-773.

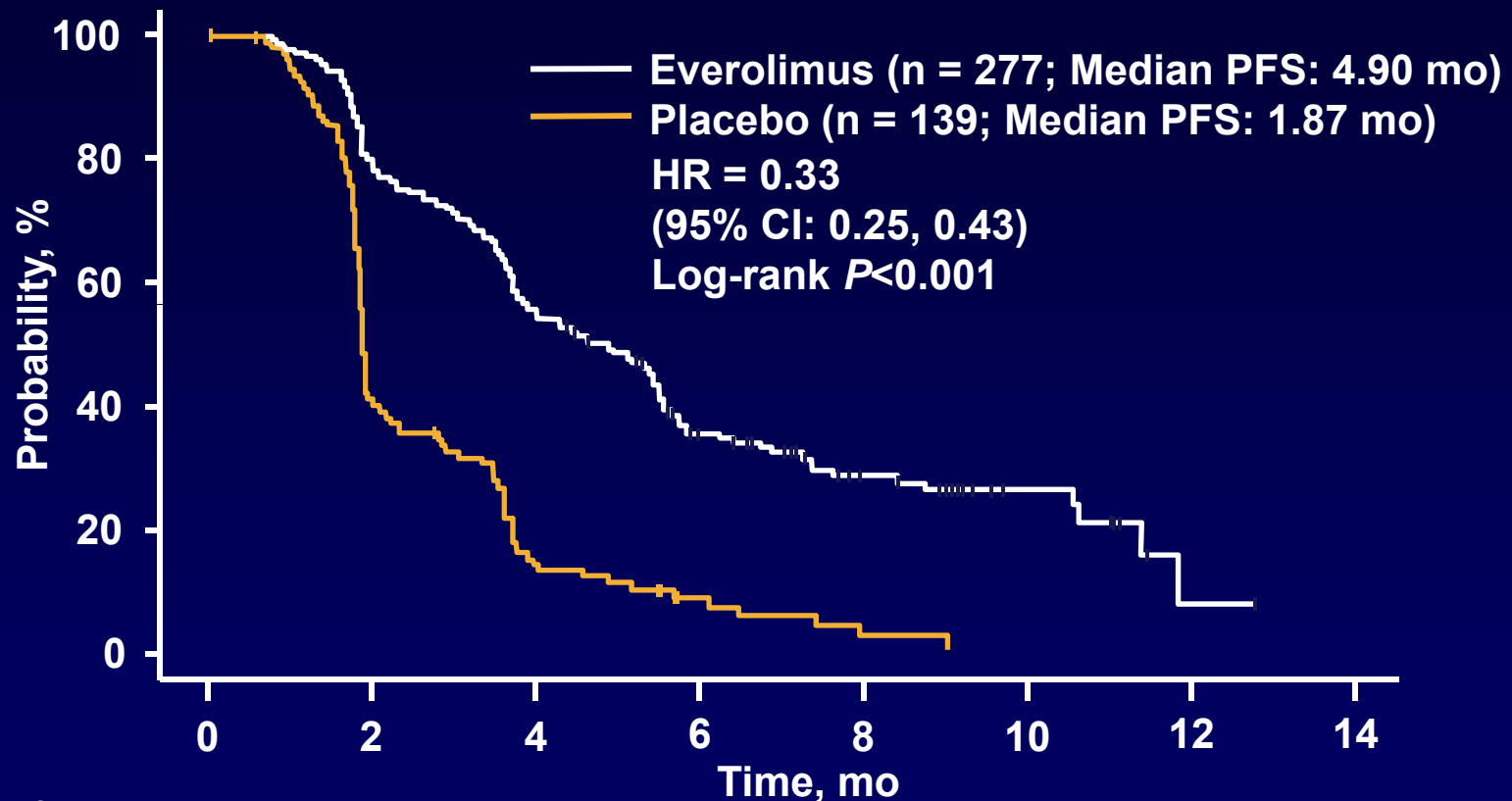
Ljungberg B, et al. *Guidelines on Renal Cell Carcinoma* [online]. 2009. Available online at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/RCC.pdf. Accessed October 4, 2010.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Renal cell carcinoma. Available online at: http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf. Accessed October 4, 2010.

Sequential TKI → mTOR Therapy: RECORD-1 Study Design and Conduct



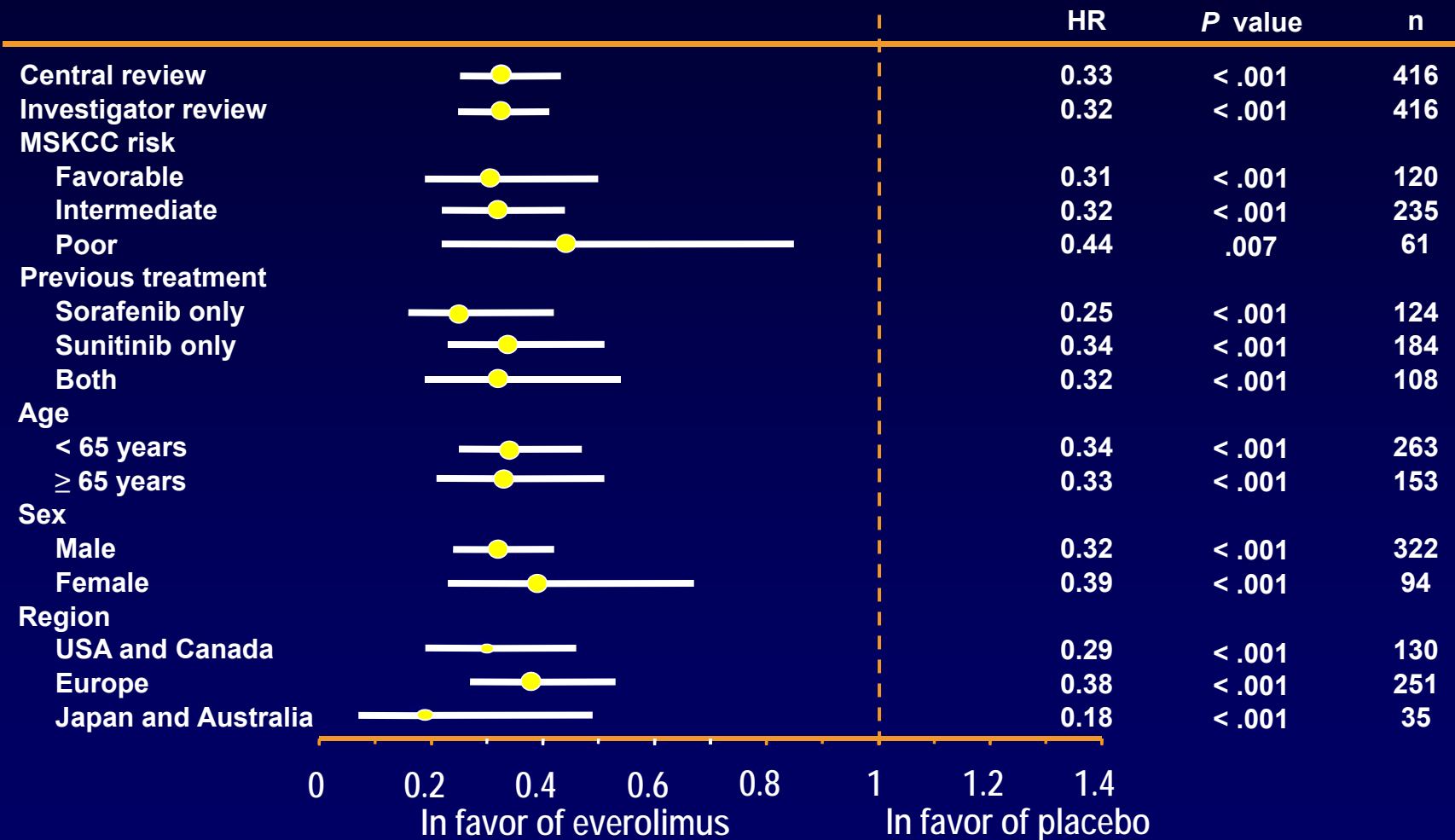
Sequential TKI → mTOR Therapy: RECORD-1 PFS by Treatment



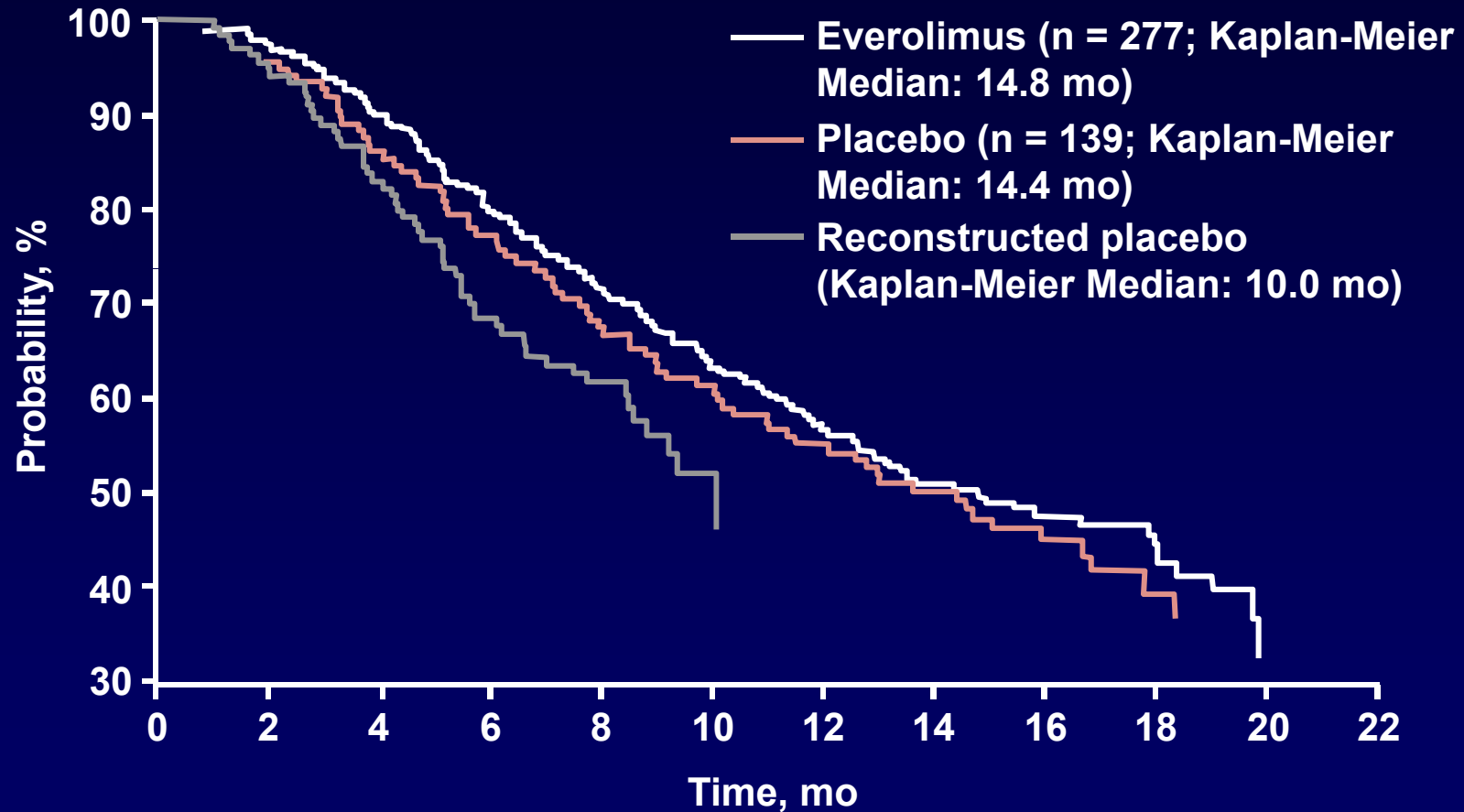
No. of Patients at Risk

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

RECORD-1 Study: PFS Benefit to All Patient Subgroups



Sequential TKI → mTOR Therapy: RECORD-1 OS With Exploratory RPSFT Analysis



RPSFT = Rank-Preserving Structural Failure Time

Can Patients Be Resensitized Through Changing Mechanism of Action?

Case of patient treated with sunitinib → everolimus → sunitinib

- 60-year-old man
 - Nephrectomy for T2, Nx, M1, clear cell RCC; intermediate risk
 - Lung and mediastinal lymph nodes
- Stable disease for 5 months on everolimus after progression on sunitinib
 - Followed by progression and appearance of new brain and bone lesions
 - Ineligible for clinical trial because of brain metastases
- Treated again with sunitinib
 - Partial response (RECIST) on the lung, mediastinal lymph nodes, and 1 brain metastasis after 2 cycles and for 1 year
 - Toxicity profile was similar to previous experience (asthenia, mucositis, and arterial hypertension), but hand–foot syndrome symptoms were decreased

Can Patients Be Resensitized Through Changing Mechanism of Action?

Retrospective analysis of antiangiogenic therapy after progression with everolimus

- 39 patients with mRCC received everolimus after progression on a TKI
- Of these patients, 15 received further treatment after progression on everolimus (14 evaluable)
 - TKIs: 5 treated with sunitinib, 7 with sorafenib, 2 with both agents
 - Other agents: 2 treated with bevacizumab, 1 with investigational
- 86% achieved disease control (PR or SD)

	Post Everolimus (N = 14)
PR, n (%)	3 (21)
SD >3 mo, n (%)	9 (64)
PR or SD, n (%)	12 (86)
Median PFS, mo	5.1

Retrospective TKI → TKI (Sablin, Dudek)

- Retrospective review of patients treated with a VEGFR-TKI after progressing on another VEGFR-TKI

Sequence	Sablin, et al. 2009			Dudek, et al. 2009		
	No. of Patients	ORR*	SD	No. of Patients	ORR*	SD
Sorafenib → sunitinib	68	15%	51%	29	21%	38%

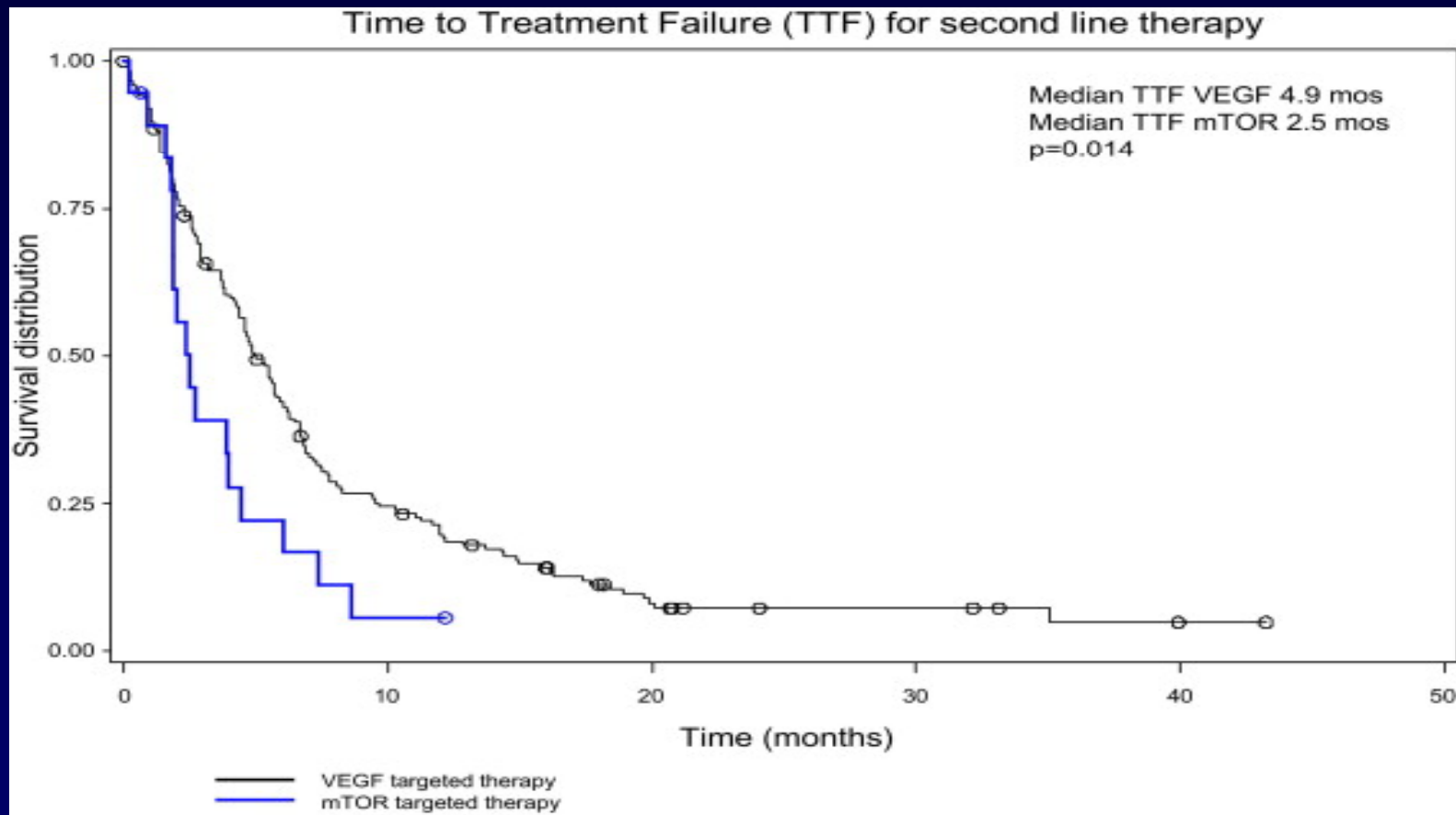
No correlation between efficacy in 1st-line and efficacy in 2nd-line, but

Best response to 1 ST -line	Pts	TTP (w)
PR+SD	34	74.6
PD+AE	15	40.6

Retrospective TKI → TKI or mTOR Inhibitors (Vickers)

645 patients 1st-line

2nd-line 192 TKI (Su: 93; So: 80; Bev: 11; Ax: 8) / 24 mTOR I (Tem: 21; Ev: 3)



Vickers MM, et al. *Urology*. 2010;76(2):430-434.

Prospective TKI → TKI Analysis (Di Lorenzo)

Phase II study of sorafenib in sunitinib-refractory patients

- **Primary endpoint**
 - **ORR: 9.6% (95% CI: 5–17)**
 - Endpoint for positive study: 15% ORR
- **Secondary endpoints**
 - Median TTP was 4 months (range, 2–10)
 - Median OS was 8 months (range, 4–16)

	Cycle 1	Cycle 2
PR, n	0	5
SD, n	40	5
PD, n	12	42

- **Response to sunitinib did NOT predict for response to sorafenib**

Which Second-Line Systemic Therapy Would You Choose?

- **Everolimus (Level 1)**
- **Sorafenib (Level 2/3)**
- **Temsirolimus?**
- **Pazopanib (No data)**
- **Clinical trial participation (AXIS trial—axitinib vs. sorafenib)?**
- **Bevacizumab + IFN alpha (No data)**

Waiting for Results

- **Phase III, 2nd-line**
- **Post sunitinib: temsirolimus vs sorafenib**
- **Post VEGF TKI or mAb: axitinib vs sorafenib**
- **No phase III vs everolimus**

Which Second-Line Systemic Therapy In This Clinical Case

- 1st-line
 - Started with more efficient: sunitinib
 - Yes PR but \leq PFS in pivotal study
 - Impact of angiogenesis? ~ 6 months
- Proposal
 - **Everolimus (Level 1)**
 - > Sorafenib
 - Or clinical trial

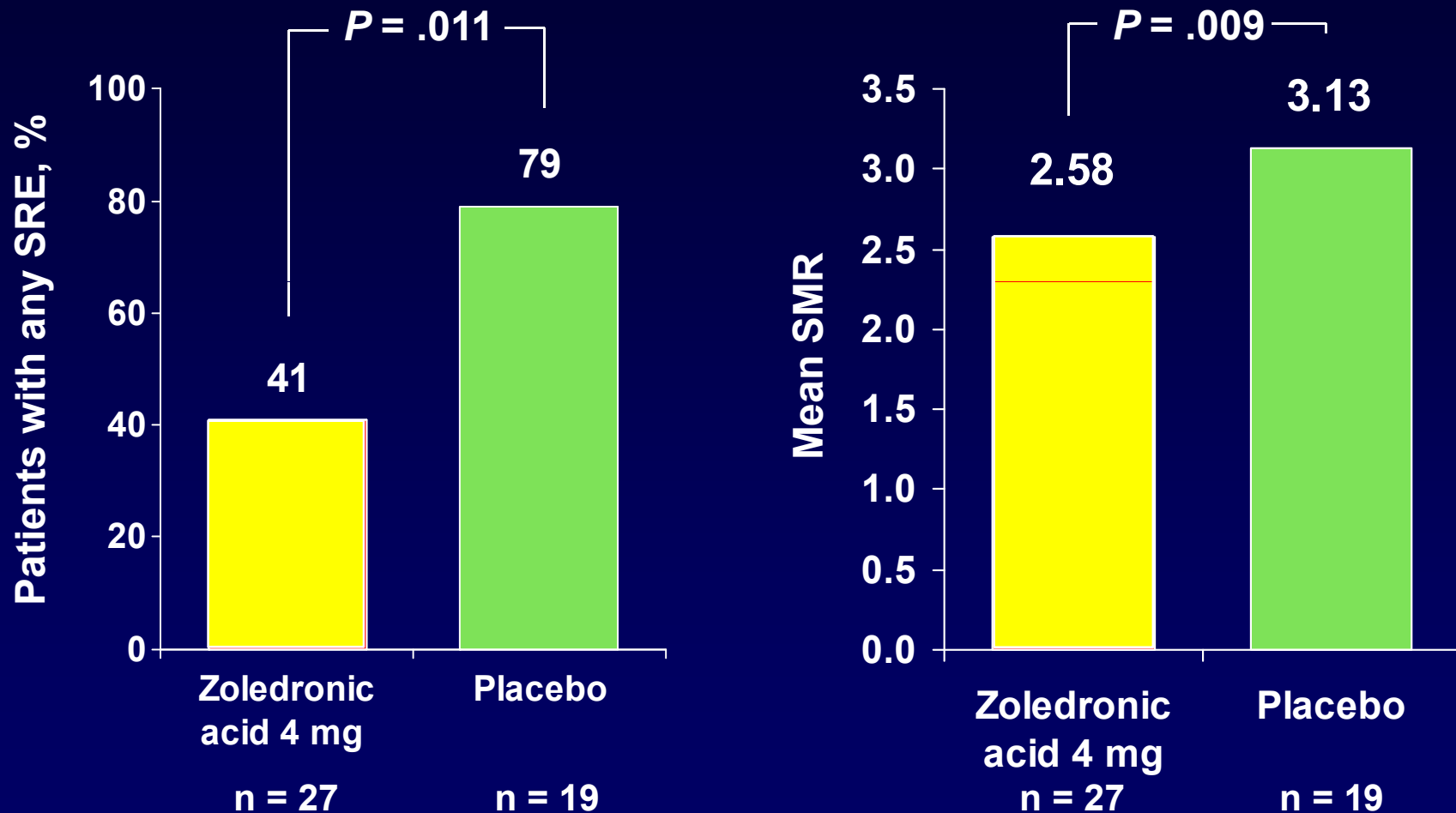
Question 2

Which best describes your approach to bone-targeted therapy for this patient's symptomatic bone metastases?

- **Begin zoledronic acid now**
- **Begin an oral bisphosphonate now**
- **Recommend a clinical trial of denosumab now**
- **Irradiate painful areas of bone metastasis and defer bone-targeted therapy until bone metastases are more widespread**
- **I generally do not recommend bone targeted therapy for bone metastases from renal cell carcinoma**

RCC Subset—Exploratory Analysis

ZOL Reduced Percent of Patients With Any SRE and SMR

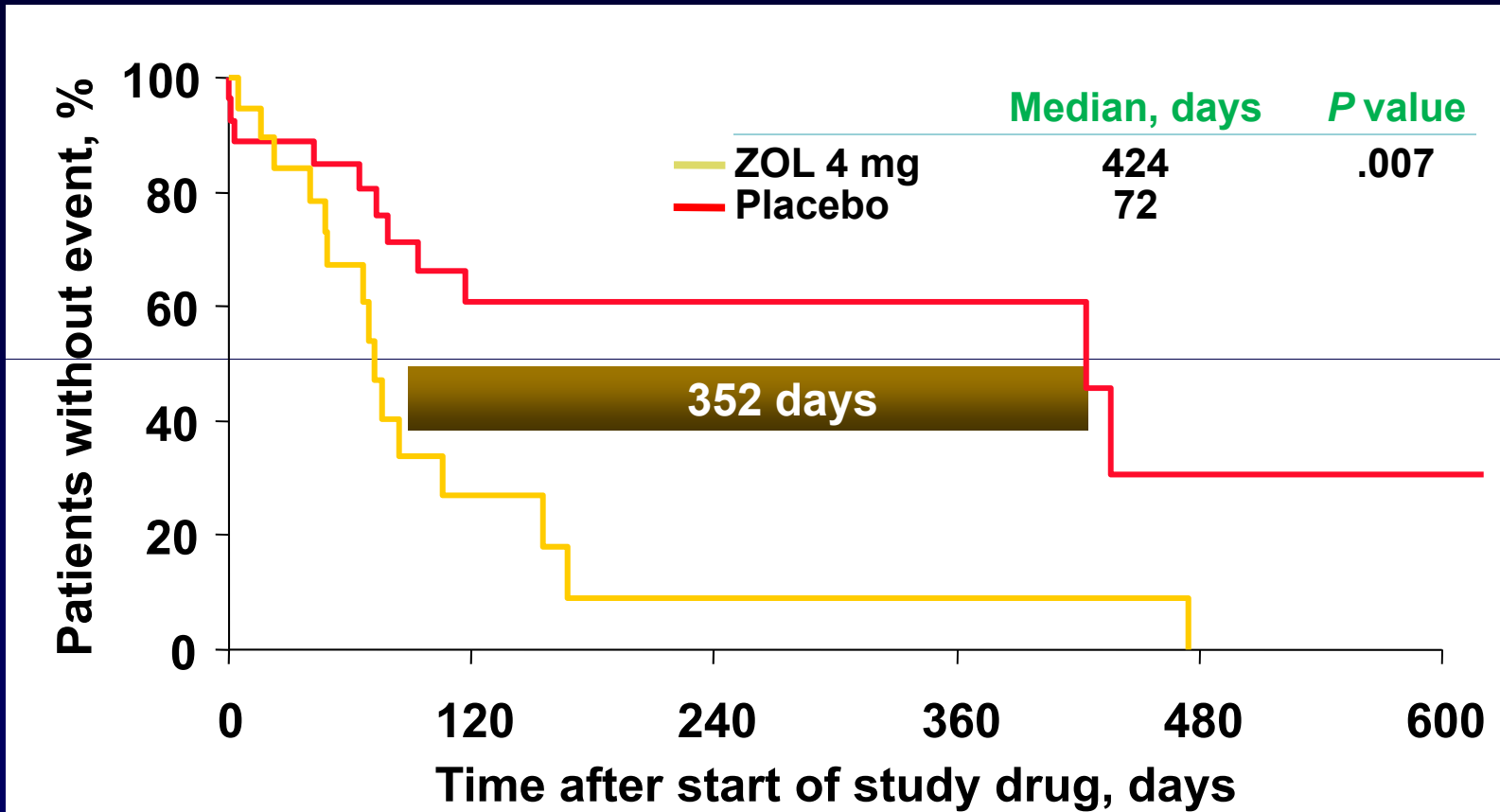


RCC, renal cell carcinoma; ZOL, zoledronic acid; SRE, skeletal-related event; SMR, skeletal morbidity rate, in events per year.

Data from Saad F, et al. *BJU Int.* 2005;96(7):964-969.

RCC Subset—Exploratory Analysis

ZOL Significantly Delayed the Time to First SRE

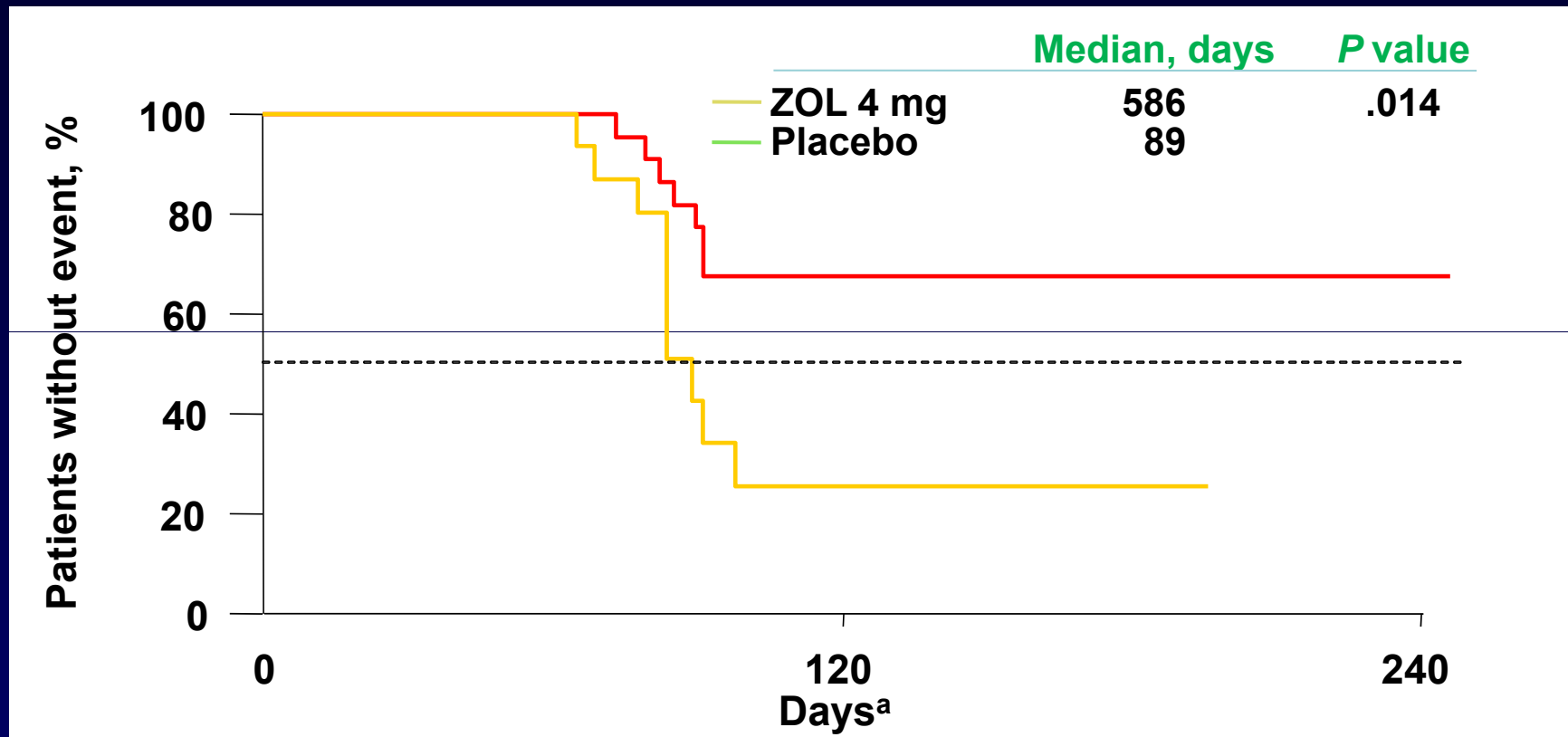


ZOL 4 mg	27	12	7	4	2	1
Placebo	19	4	1	1	0	0

RCC, renal cell carcinoma; ZOL, zoledronic acid; SRE, skeletal-related event.

Adapted from Saad F, et al. *BJU Int.* 2005;96(7):964-969.

Zoledronic Acid Increases Time to Bone Lesion Progression in Patients With RCC (n = 46)



ZOL 4 mg	27	13	7
Placebo	19	3	0

- Median time to first bone lesion was > 1 year (not seen in prostate cancer)

^a After start of study drug.

Adapted from Saad F, et al. *BJU Int.* 2005;96(7):964-969. Lipton A, et al. Presented at: What Is New in Bisphosphonates? Seventh Workshop on Bisphosphonates—From the Laboratory to the Patient; March 24-26, 2004; Davos, Switzerland. Poster 28.

Oral Bisphosphonates in RCC

- **NO SPECIFIC DATA**

Denosumab in RCC

- No data
- Denosumab > zoledronic acid in breast carcinoma and HRPC
- So far interesting approach to test
- Ok for inclusion in trials

Bone Radiotherapy and RCC

Characteristics	No. of evaluable patients	Pain improved, no. (%)	Significant pain improvement, no. (%)	Complete response, pain score = 0, no. (%)	Median duration of response, mos
Global pain score	20	5 (25)	3 (15)	2 (10)	1
Site specific	23	19 (83)	11 (48)	3 (13)	3
LASA	24	15 (63)	8 (33)	2 (8)	3
EORTC	23	14 (61)	8 (35)	2 (9)	3

Which Best Describes Your Approach to Bone-Targeted Therapy for This Patient's Symptomatic Bone Metastases?

What is the situation?

- PD but not an “emergency” situation
- Pain mild/moderate. Medical treatment ?
- Expected “tumor shrinkage” for everolimus and/or sorafenib : < 10%
- RTE and everolimus not recommended
- RTE and sorafenib ok

Which Best Describes Your Approach to Bone-Targeted Therapy for This Patient's Symptomatic Bone Metastases?

If pain not controlled easily by medical treatment

- **First radiotherapy**
- **Then second-line treatment**
- **Considering 3 bone sites / painful: bisphosphonates**

If pain controlled easily by medical treatment

- **Second-line treatment**
- **Pain medically controlled: discuss bisphosphonates**
- **Keep radiotherapy**

Clinical Case (3)

- **Everolimus (10 mg PO/day) is begun**
- **After 6 weeks of therapy, the patient complains of worsening of respiratory symptoms (shortness of breath and cough)**
- **She is afebrile and CXR shows a small left pleural effusion**

Question 3

**Which of the following
is the most likely explanation?**

- **Disease progression involving lungs with malignant pleural effusion**
- **Opportunistic infection**
- **Noninfectious pneumonitis secondary to everolimus**
- **Congestive heart failure**

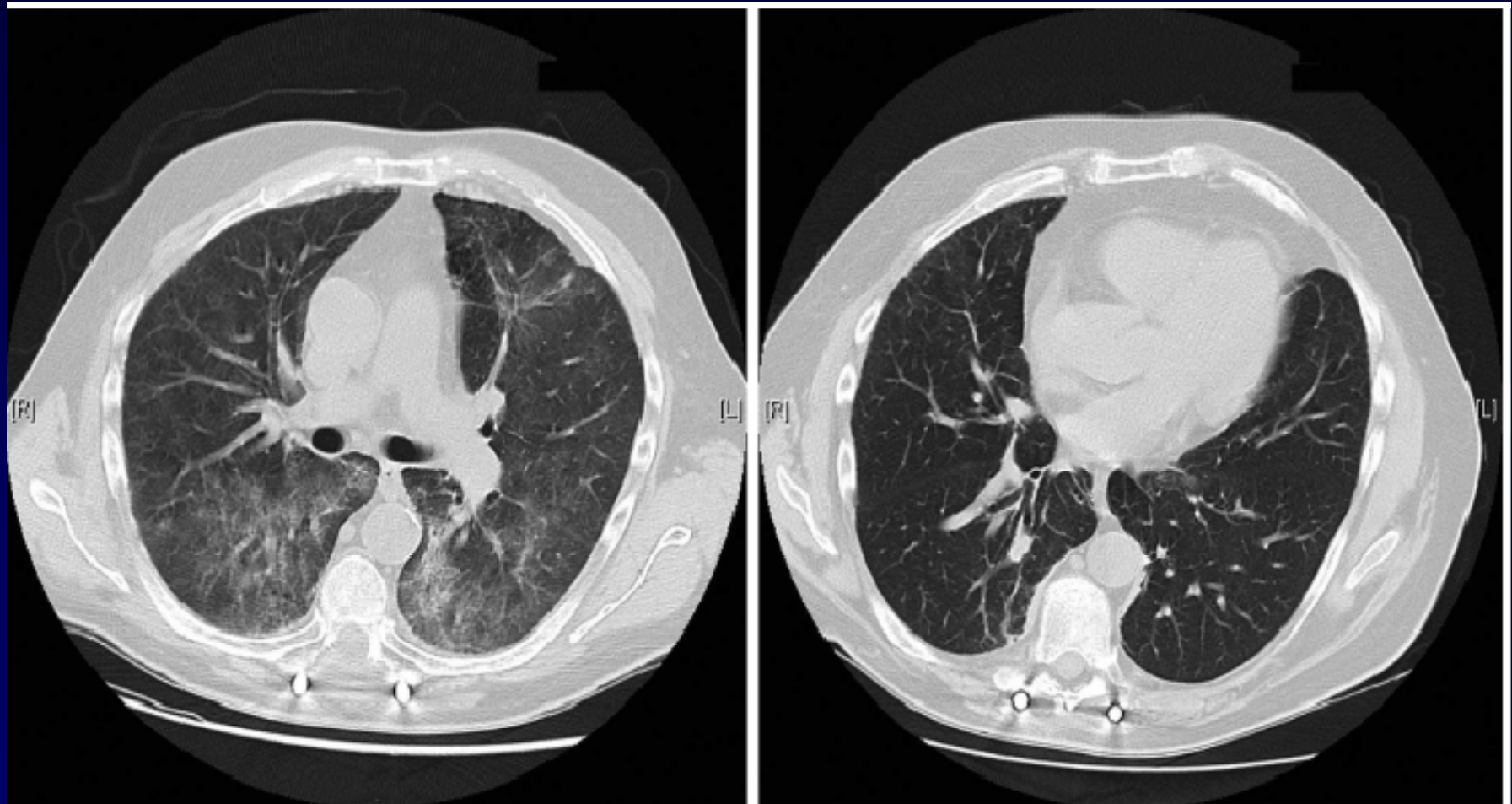
Non-Infectious Pneumonitis With mTOR Inhibitors

	All Grades, %	Grade 3/4, %
Everolimus (n = 274)	14	4
Temsirolimus (n = 208)	29*	NR

Motzer RJ, et al. *Cancer*. 2010;116(18):4256-4265.

Torisel® (temsirolimus) [prescribing information]. Philadelphia, Pennsylvania: Wyeth Pharmaceuticals Inc; 2008.

Non-Infectious Pneumonitis



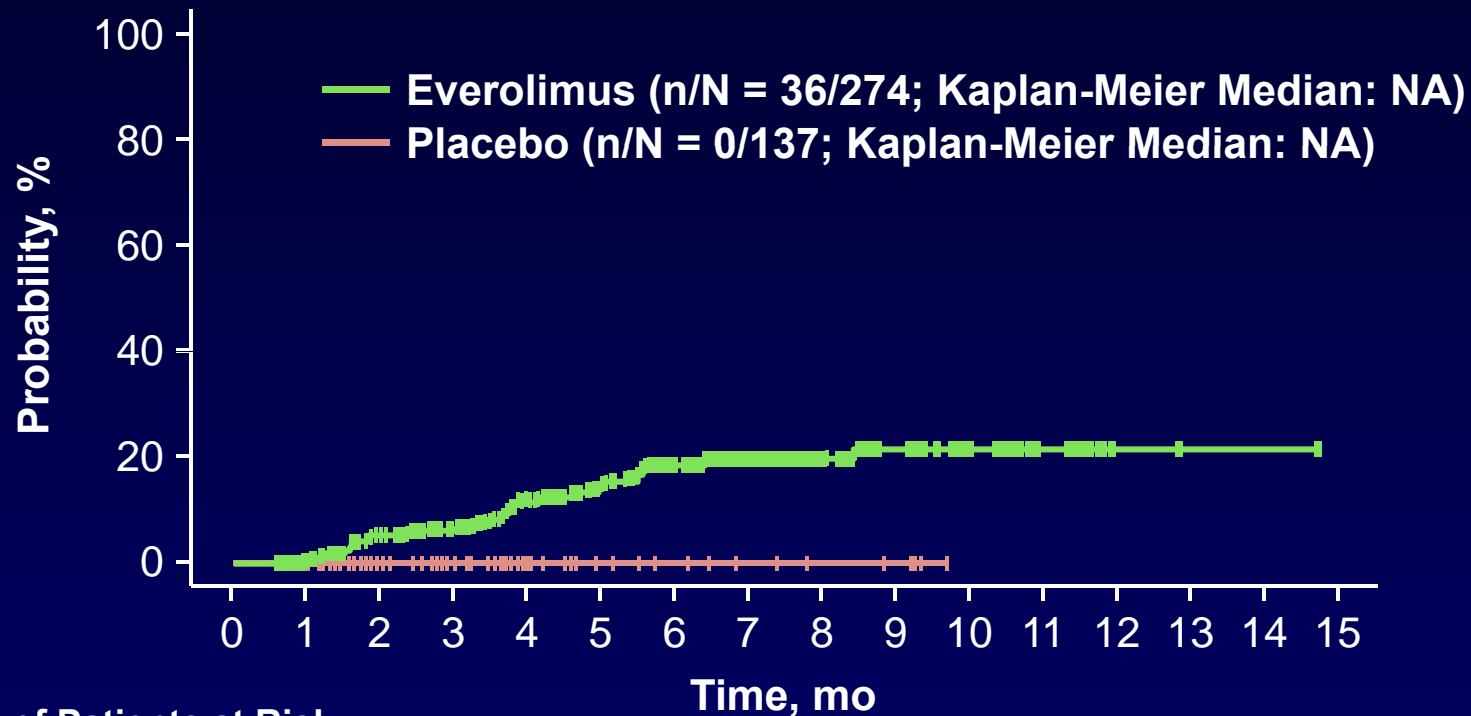
White DA, et al. *Am J Respir Crit Care Med.* 2010;182(3):396-403.

Non-Infectious Pneumonitis



White DA, et al. *Am J Respir Crit Care Med.* 2010;182(3):396-403.

Non-Infectious Pneumonitis With mTOR Inhibitors: Time to Diagnosis in Record-1



No. of Patients at Risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Everolimus	274	257	213	176	140	117	90	72	46	32	20	10	2	1	1	0
Placebo	137	124	69	51	28	20	13	8	5	4	0	0	0	0	0	0

- In temsirolimus-treated patients who developed interstitial lung disease, onset occurred within first 8 weeks of treatment for 60% (31/52)

Non-Infectious Pneumonitis With mTOR Inhibitors: Clinical Management Strategy*

Grade	Symptoms	Management	Dose Modification
1	Asymptomatic	<ul style="list-style-type: none"> • No specific therapy 	<ul style="list-style-type: none"> • No change
2	Symptomatic, not interfering with ADL	Depending on severity of Symptoms: <ul style="list-style-type: none"> • consider consulting a pulmonologist • consider diagnostics to exclude infectious causes • consider steroids 	<ul style="list-style-type: none"> • Decrease dose until grade ≤ 1 and restart at initial dose • Hold dose if symptoms are troublesome • If no recovery to grade ≤ 1 within 3 wks, discontinue
3	Symptomatic, interfering with ADL, O ₂ indicated	<ul style="list-style-type: none"> • Consult a pulmonologist • Consider diagnostics to exclude infectious causes • consider antibiotics/steroids based on clinical evidence 	<ul style="list-style-type: none"> • Hold dose until recovery to grade 1 • Restart dose within 3 wks at reduced dose[†] if evidence of clinical benefit
4	Life-threatening, ventilatory support indicated		<ul style="list-style-type: none"> • Discontinue

*Based on the Novartis Patient Management on Everolimus Advisory Board (20 April 2009). [†]5 mg daily.
ADL = activities of daily living.

Cancer Therapy Evaluation Program. *Common Terminology Criteria for Adverse Events, v3.0*. Bethesda, MD: National Cancer Institute, US National Institutes of Health; August 9, 2006. Available at: http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf. Accessed October 12, 2010.
White DA, et al. *Am J Respir Crit Care Med*. 2010;182(3):396-403. Novartis data on file.