Randomized, Open Label, Phase III Trial of Pazopanib versus Sunitinib in First-line Treatment of Patients with Metastatic Renal Cell Carcinoma (mRCC): Results of the COMPARZ Trial

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Disclosures

Dr. Motzer has served as an advisor for Pfizer, Inc. and as a study investigator for GlaxoSmithKline, Pfizer Inc, Astellas, AVEO Oncology, Novartis, Bristol-Meyers Squib and Eisai

Research Funding

- This study was sponsored by GlaxoSmithKline

Pazopanib vs Sunitinib in Metastatic RCC

- Pazopanib and sunitinib are oral multi-kinase angiogenesis inhibitors that each showed progression-free survival (PFS) benefit for mRCC patients in phase III trials[1]
- Indirect comparison analysis of pazopanib versus sunitinib revealed[2]:
  - Comparable PFS
  - Differentiated safety profile for certain AEs
    - Lower incidence including fatigue, hand-foot syndrome, stomatitis with pazopanib
    - Lower incidence for liver function test abnormalities with sunitinib
- The phase III COMPARZ trial VEG108844 (NCT00720941) was designed to provide a direct comparison of the efficacy, safety, and tolerability for pazopanib and sunitinib

1. Motzer R, *et al.* New England Journal of Medicine 2007;356:115
   Sternberg *C, et al.* Journal of Clinical Oncology 2009;29:475
2. McCann L, *et al.* ASCO Genitourinary Cancers Symposium 2010 Abstract #413

Study Objectives

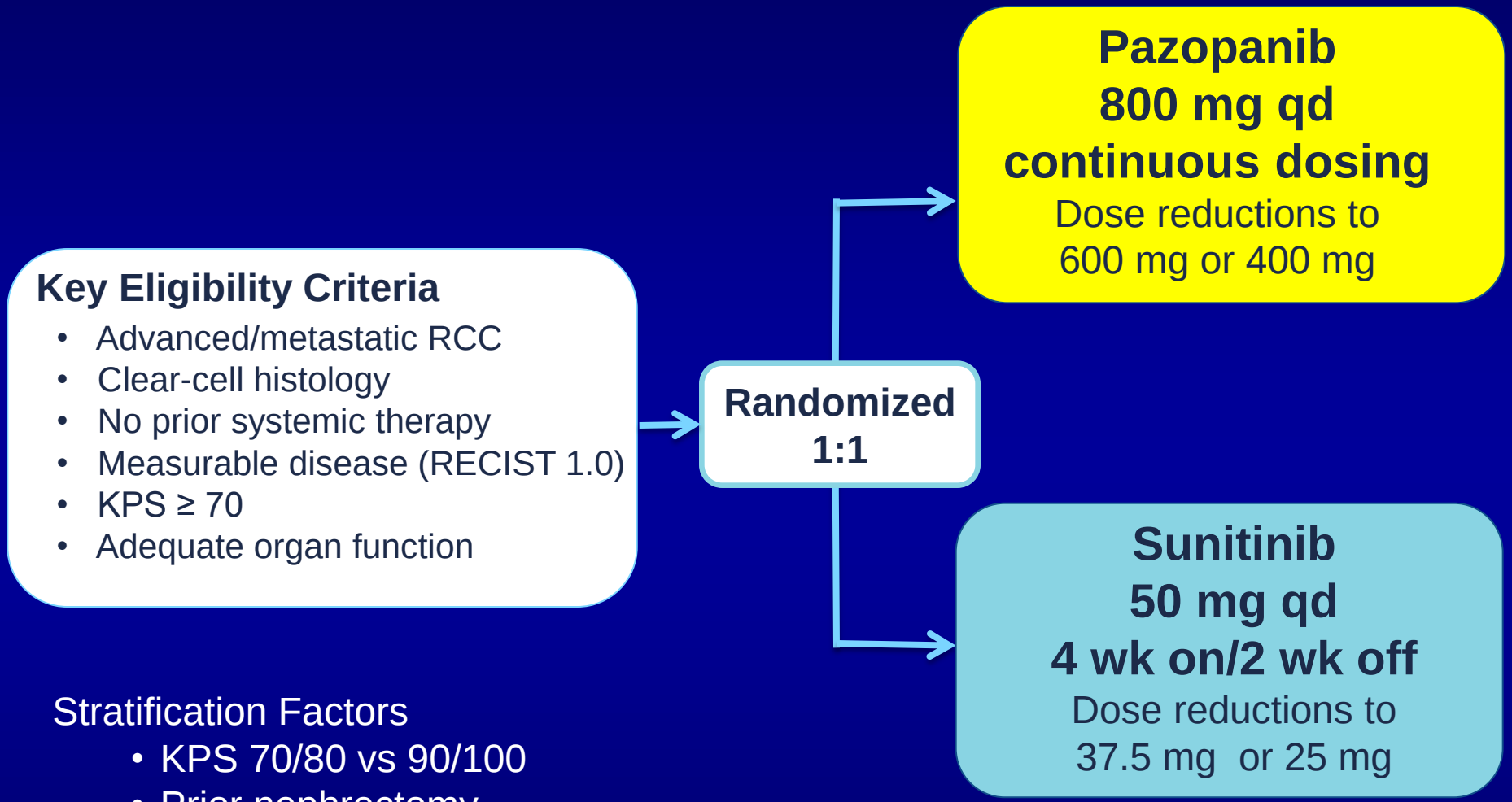
Primary

- To evaluate and compare PFS in patients treated with pazopanib to those treated with sunitinib as initial systemic therapy

Secondary

- Overall survival (OS)
- Objective response rate (ORR)
- Safety
- Patient-reported outcomes

Study Design



Stratification Factors

- KPS 70/80 vs 90/100
- Prior nephrectomy
- Baseline LDH >1.5 vs ≤1.5 × ULN

Study Assessments

- Disease assessments weeks 6, 12, 18, 24 and then every 12 weeks
- Other assessments - 6 week cycles
  - Safety
    - Baseline, Day 28 & Day 42 of every cycle through cycle 9, Day 42 of every cycle from cycle 10
  - Patient-reported outcomes
    - Baseline (except for CTSQ), Day 28 every cycle
    - Measures:
      - » FACIT-Fatigue
      - » Functional Kidney Symptom Index (FKSI-19)
      - » Cancer Therapy Satisfaction Questionnaire (CTSQ)
      - » Supplementary Quality of Life Questionnaire (SQLQ)

Statistical Analysis Plan

- PFS non-inferiority demonstrated if upper bound of 95% CI for HR<1.25
  - Cox proportional hazard analysis adjusted for stratification factors
  - By independent review
- 631 PFS events needed for 80% power
- Planned enrollment of 1100 patients

Baseline Characteristics

	Pazopanib (n = 557)	Sunitinib (n = 553)
Median age (range), years	61 (18-88)	62 (23-86)
Gender, % male	71	75
Prior nephrectomy, %*	82	84
Karnofsky Performance Status, %*		
90/100	75	76
70/80	25	24
Lactate dehydrogenase, %*		
≤1.5 × ULN	93	95
Number of organs involved, %		
1 or 2	58	56
≥ 3	42	44

*Stratification factor

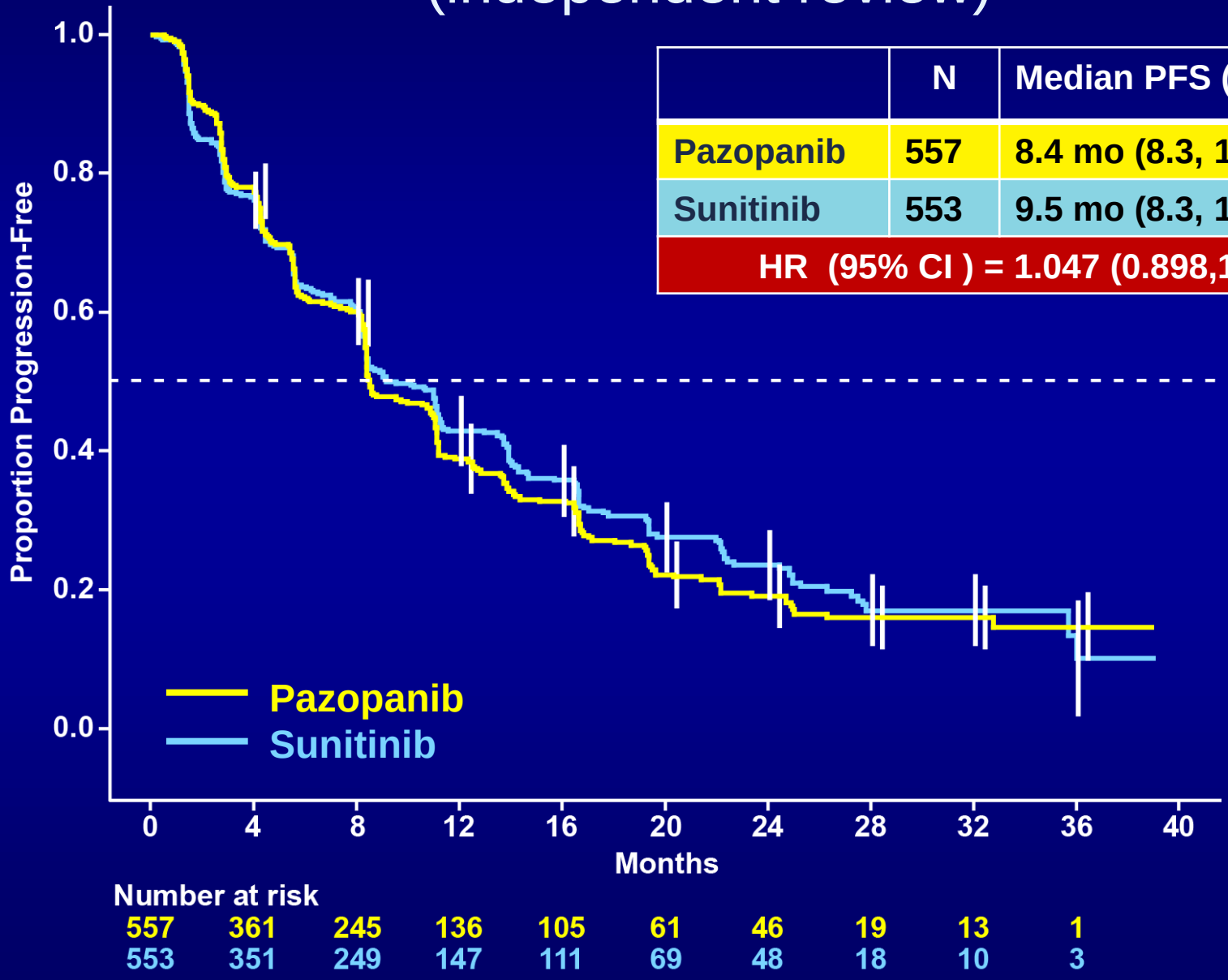
Baseline Characteristics

	Pazopanib (n = 557)	Sunitinib (n = 553)
MSKCC risk category[1], %		
Favorable	27	27
Intermediate	58	59
Poor	12	9
Unknown	3	4
Most common metastatic sites, %		
Lung	76	77
Lymph node	40	45
Bone	20	15
Liver	15	20

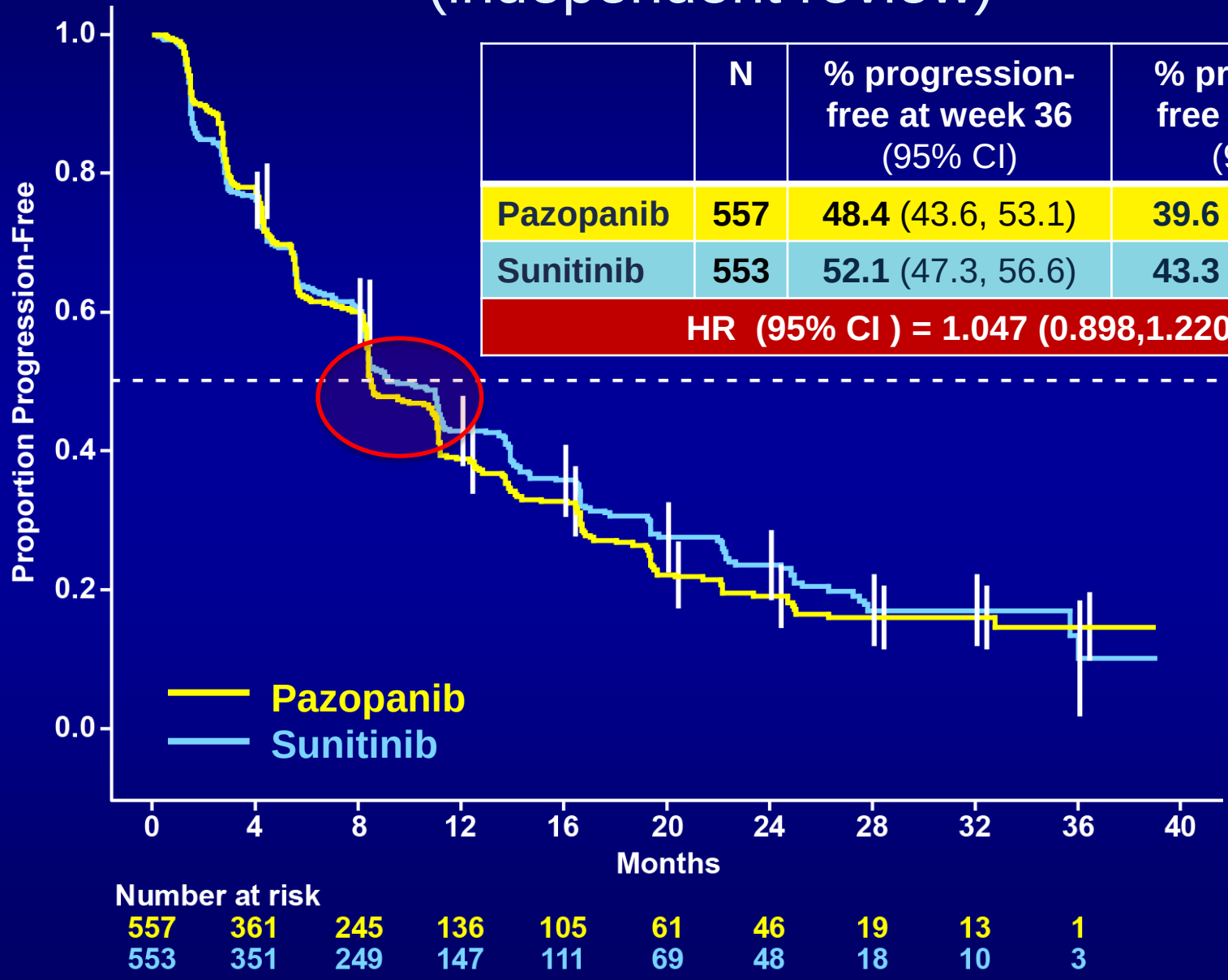
1. Motzer R, *et al.* Journal of Clinical Oncology 2002 20:2376

Primary Endpoint: Progression-free Survival (independent review)

	N	Median PFS (95% CI)
Pazopanib	557	8.4 mo (8.3, 10.9)
Sunitinib	553	9.5 mo (8.3, 11.1)
HR (95% CI) = 1.047 (0.898,1.220)		

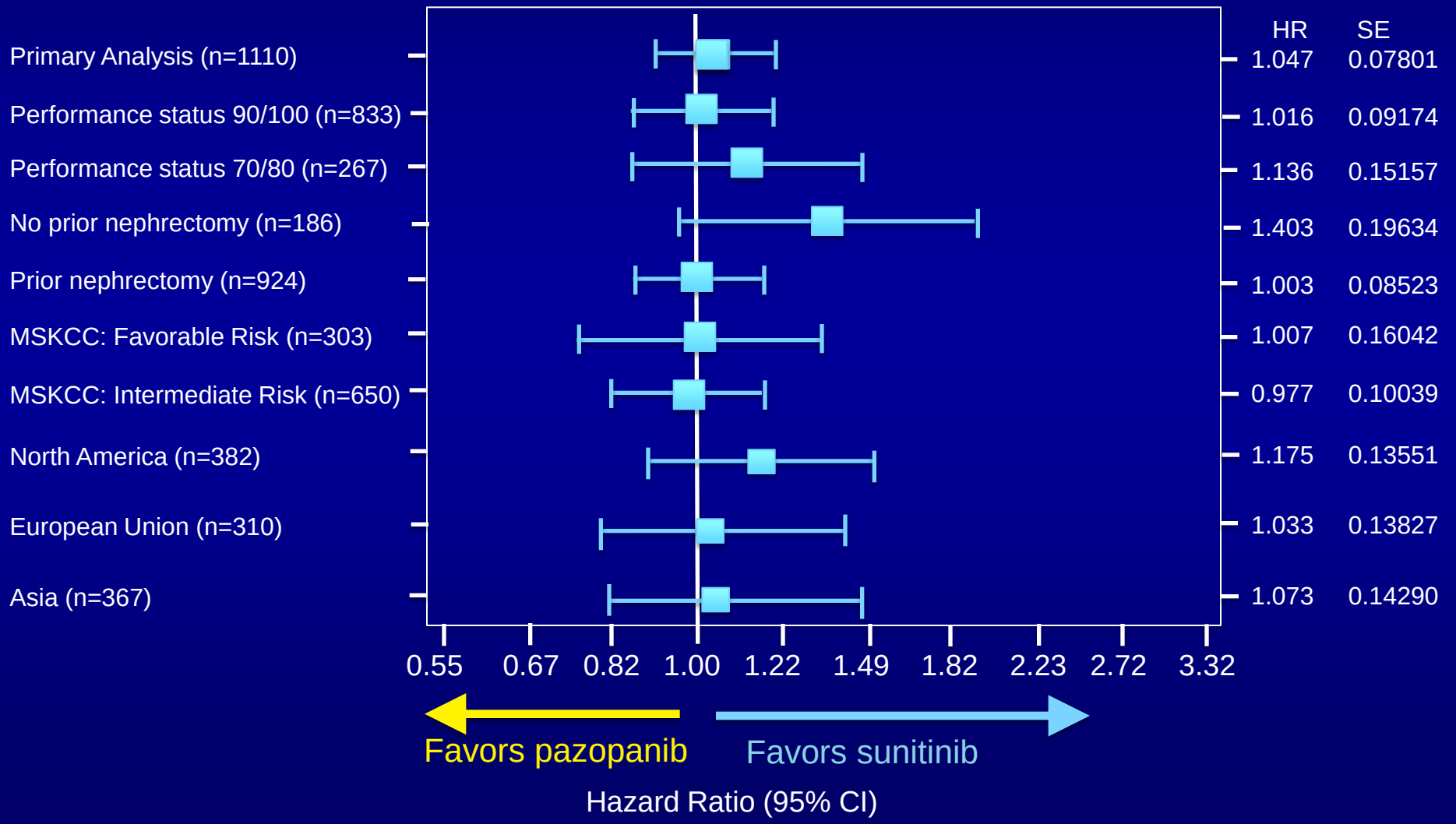


Primary Endpoint: Progression-free Survival (independent review)



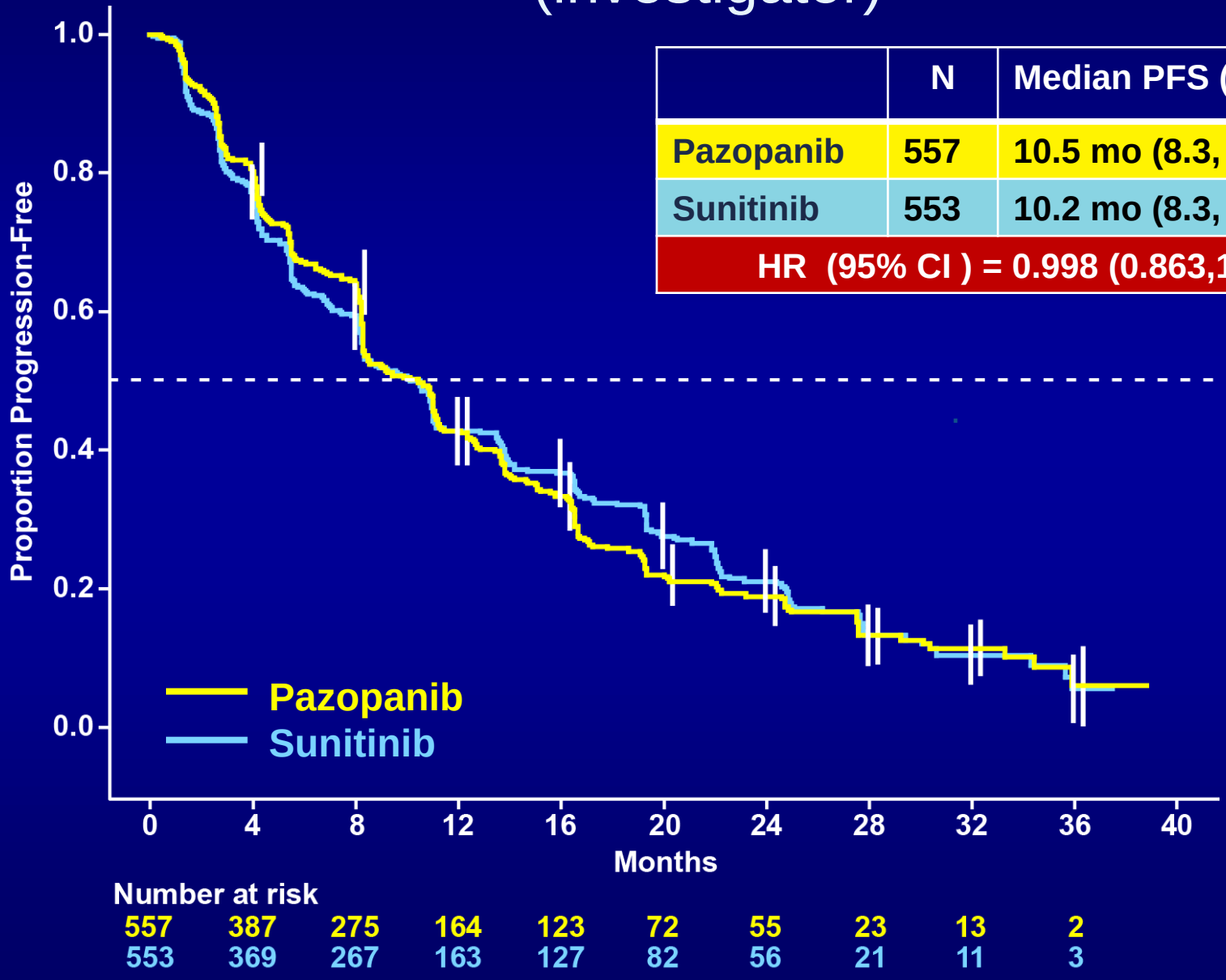
	N	% progression-free at week 36 (95% CI)	% progression-free at week 48 (95% CI)
Pazopanib	**557**	**48.4** (43.6, 53.1)	**39.6** (34.9, 44.3)
Sunitinib	**553**	**52.1** (47.3, 56.6)	**43.3** (38.5, 48.0)
HR (95% CI) = 1.047 (0.898,1.220)			

Subgroup Analyses of PFS (independent review)



Primary Endpoint: Progression-free Survival (investigator)

	N	Median PFS (95% CI)
Pazopanib	557	10.5 mo (8.3, 11.1)
Sunitinib	553	10.2 mo (8.3, 11.1)
HR (95% CI) = 0.998 (0.863,1.154)		

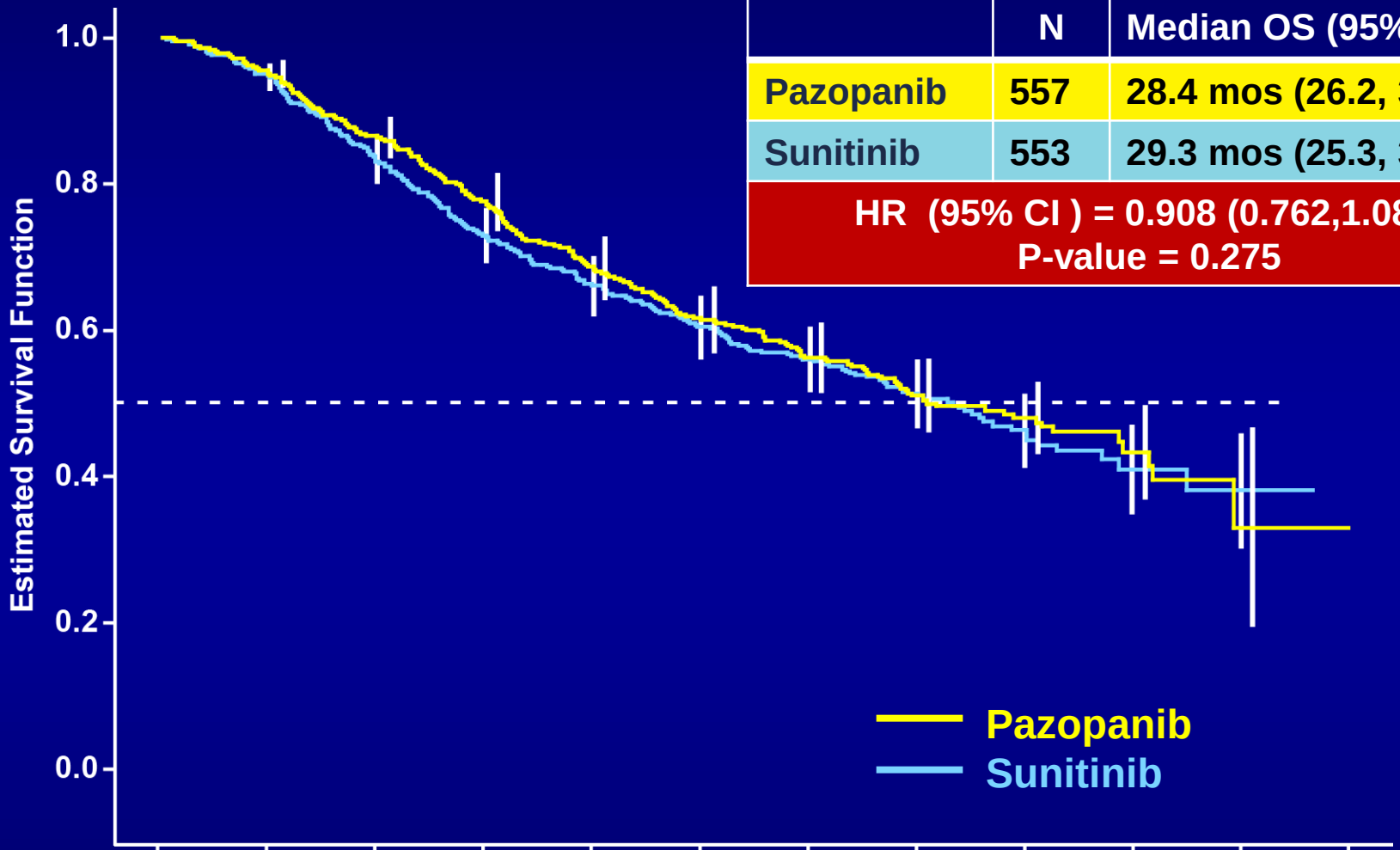


Best Response by RECIST 1.0 (independent review)

	Pazopanib (n = 557)	Sunitinib (n = 553)
Best overall response, %		
Complete response (CR)	<1	<1
Partial response (PR)	31	24
Stable disease	39	44
Progressive disease	17	19
Not evaluable	13	12
Objective Response Rate (CR +PR), %	31	25
95% CI	26.9, 34.5	21.2, 28.4
P value	**0.032**	

Interim Analysis of Overall Survival

	N	Median OS (95% CI)
Pazopanib	557	28.4 mos (26.2, 35.6)
Sunitinib	553	29.3 mos (25.3, 32.5)
HR (95% CI) = 0.908 (0.762,1.082) P-value = 0.275		



Number at risk

557	521	458	384	327	274	223	142	82	28	3
553	501	431	354	313	269	225	148	69	28	3

Treatment Duration and Dose Adjustments

	Pazopanib (n = 554)	Sunitinib (n = 548)
Median duration of treatment (months, range)	8.0 (0–40)	7.6 (0–38)
Dose reductions, %	44	51
Discontinuations due to AEs[1], %	24	19

1. Most common reason: pazopanib arm (liver event, 6%); sunitinib arm (cytopenia, 3%)

Laboratory Abnormalities

	Pazopanib (n = 554) %		Sunitinib (n = 548) %	
Chemistry labs (≥35%)	All Grs	Gr3/4	All Grs	Gr 3/4
ALT	60	15/2	43	4/<1
AST	61	11/1	60	3/0
Hypoalbuminemia	33	<1/0	42	2/0
Bilirubin	36	3/<1	27	2/<1
Creatinine	32	<1/0	46	<1<1
Hyperglycemia	54	5/0	57	4/<1
Hyponatremia	35	7/<1	32	7/<1
Hypophosphatemia	36	4/0	52	8/<1
Hematology labs				
Leukopenia	43	1/0	78	6/0
Neutropenia	37	4/<1	68	19/1
Thrombocytopenia	41	3/<1	78	18/4
Lymphopenia	38	5/0	55	14/<1
Anemia	31	1/<1	60	6/1

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AST	61	60
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Lymphopenia	38	55
Anemia	31	60

Yellow highlight: Risk greater for pazopanib and 95% CI for relative risk does not cross 1

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Neutropenia	**37**	**68**
Thrombocytopenia	**41**	**78**
Lymphopenia	**38**	**55**
Anemia	**31**	**60**

Blue highlight: Risk greater for sunitinib and 95% CI for relative risk does not cross 1

Most Common Adverse Events (treatment-emergent)

	Pazopanib (n = 554) %		Sunitinib (n = 548) %	
Adverse Event [a]	**All Grs**	**Gr 3/4**	**All Grs**	**Gr 3/4**
Any event [b]	>99	59/15	>99	57/17
Diarrhea	63	9/0	57	7/<1
Fatigue	55	10/<1	63	17/<1
Hypertension	46	15/<1	41	15/<1
Nausea	45	2/0	46	2/0
Decreased appetite	37	1/0	37	3/0
ALT increased	31	10/2	18	2/<1
Hair color changes	30	0/0	10	<1/0
Hand-foot syndrome	29	6/0	50	11/<1
Taste Alteration	26	<1/0	36	0/0
Thrombocytopenia	10	2/<1	34	12/4

[a] AE ≥30% in either arm

[b] 2% of patients in pazopanib arm and 3% of patients in sunitinib arm had grade 5 adverse events.

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Hair color changes	**30**	**10**
Hand-foot syndrome	29	50
Taste alteration	26	36
Thrombocytopenia	10	34

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ALT increased	31	18
Hair color changes	30	10
Hand-foot syndrome	**29**	**50**
Taste alteration	**26**	**36**
Thrombocytopenia	**10**	**34**

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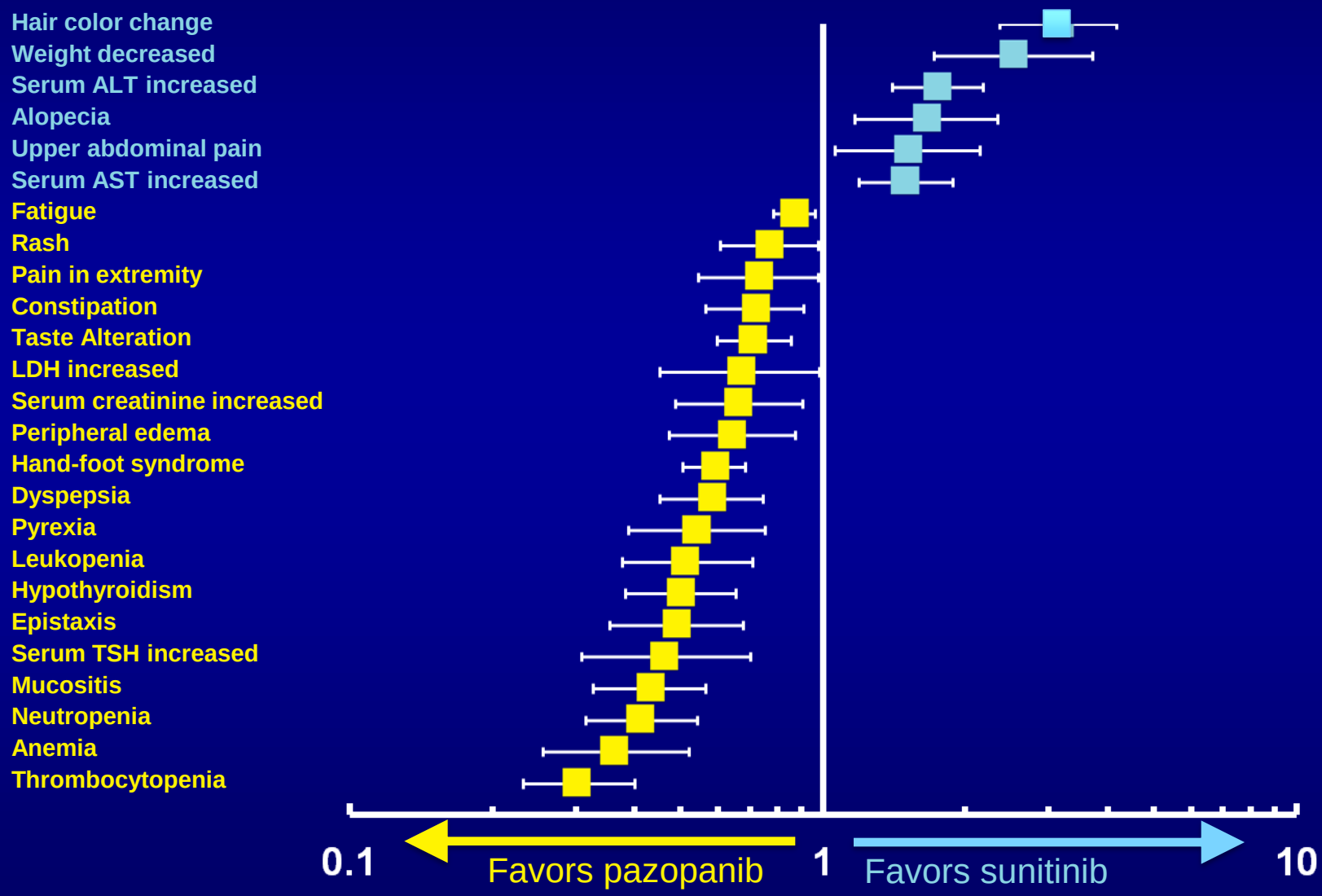
Blue Highlight: Risk greater for sunitinib and 95% CI for relative risk does not cross 1

Relative Risk in Adverse Events

AE occurrence ≥10% in either arm; 95% CI for RR does not cross 1



Quality of Life Results (first 6 months[1])

Instrument	Domain Description	Treatment difference : mean change from baseline [2]	P -value
FACIT-F	Fatigue/Total score	**2.32**	**<0.001**
FKSI-19	Kidney Symptom Index/Total score	**1.41**	**0.018**
	Physical	**0.78**	**0.027**
	Emotional	0.05	0.409
	Treatment Side Effects	**0.31**	**0.033**
	Functional Well Being	**0.31**	0.098
Cancer Treatment Satisfaction Questionnaire (CTSQ)	Expectations of Therapy	**1.41**	0.284
	Feelings about Side Effects	**8.50**	**<0.001**
	Satisfaction with Therapy	**3.21**	**<0.001**
Supplementary Quality of Life Questionnaire (SQLQ)	Worst mouth/throat soreness	**0.505**	**<0.0001**
	Worst foot soreness	**0.204**	**0.0016**
	Worst hand soreness	**0.267**	**0.0008**
	Limitations due to mouth/throat soreness	**0.94**	**<0.001**
	Limitations due to foot soreness	**0.65**	**0.014**

[1]Pre-specified analysis. HRQoL changes in mean scores over time were analyzed with a repeated measures analysis of covariance (ANCOVA).

[2]**Yellow Font**: favors pazopanib. Blue Font: favors sunitinib. P-value <0.05 is statistically significant

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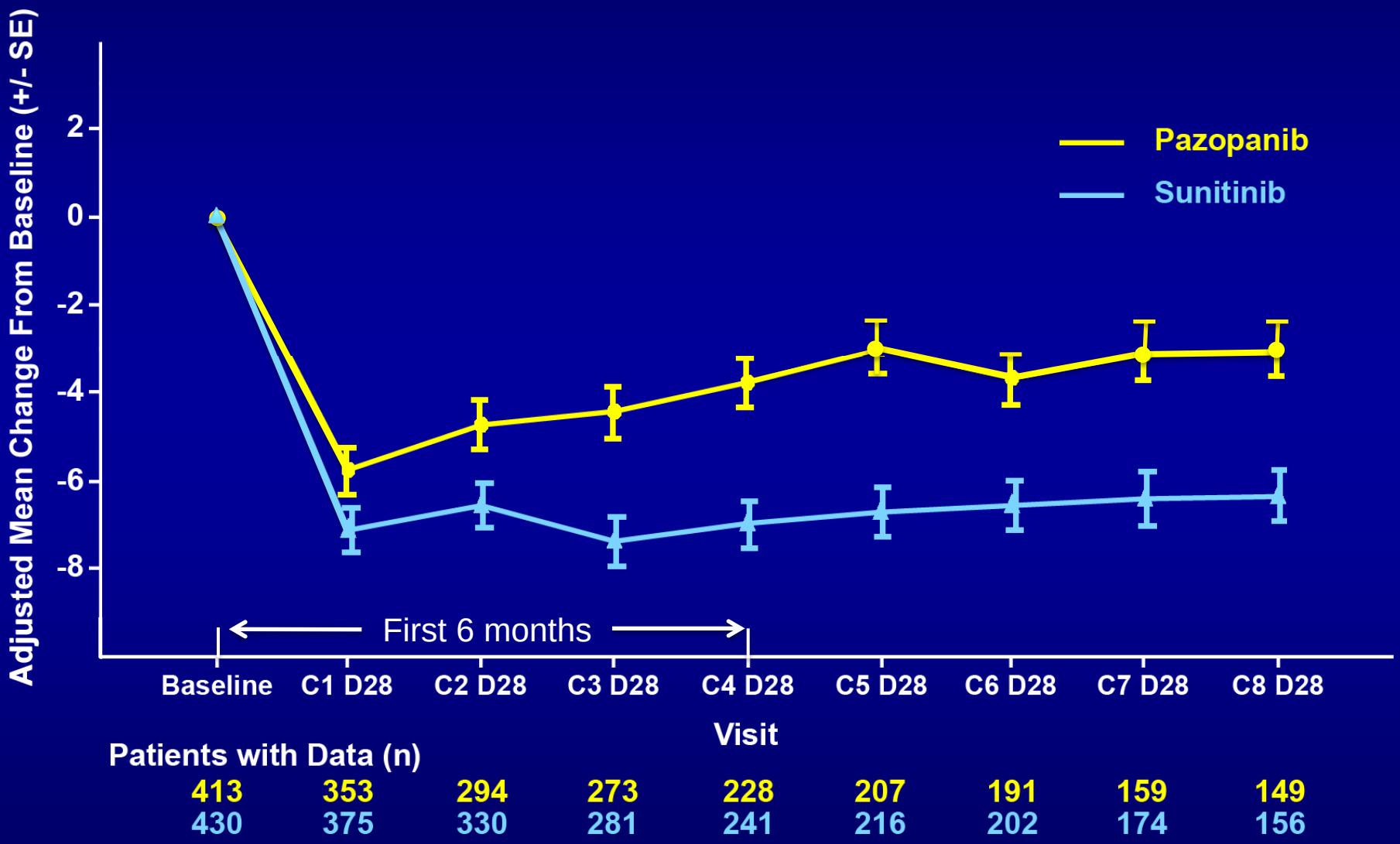
Quality of Life Result: FACIT-Fatigue



Quality of Life Results: PISCES[1]

Randomized double-blind, placebo-controlled, cross-over study in patients with metastatic renal cell carcinoma

Instrument	Timing	Domain Description	Treatment difference[2,3]	P value
FACIT- F	Every 2 weeks	Fatigue/Total score	**2.5**	**0.002**
Supplementary Quality of Life Questionnaire	Every 2 weeks	Worst mouth/throat soreness	**0.38**	**<0.001**
		Worst foot soreness	**0.08**	**0.026**
		Worst hand soreness	**0.16**	**0.005**
		Limitations due to mouth/throat soreness	**0.60**	**<0.001**
		Limitations due to foot soreness	**0.58**	**0.003**

1. Escudier BJ, *et al*.. J Clin Oncol 30, 2012 (suppl; abstr CRA4502)
2. Cella D, *et al*. ESMO Congress 2012 poster 792PD

3. Yellow Font: favors pazopanib

P-value <0.05 is statistically significant

Conclusions

- This phase III trial demonstrates non-inferiority of pazopanib compared to sunitinib for progression-free survival
- Pazopanib efficacy is further supported by similar response rates and overall survival
- The differentiated safety profile of pazopanib includes:
  - Lower incidence of hand-foot syndrome, fatigue, and mucositis
  - Higher incidence of liver function test abnormalities
- Quality of life assessment favors pazopanib over sunitinib

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Many Thanks to the Patients and Investigators