

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

Robert Motzer¹, T. E. Hutson², James Reeves³, Robert Hawkins⁴, Jun Guo⁵, Paul Nathan⁶, Michael Staehler⁷, Paul de Souza⁸, Jaime R. Merchan⁹, Kate Fife¹⁰, Jie Jin¹¹, Robert Jones¹², Hirotugu Uemura¹³, Ugo De Giorgi¹⁴, Ulrika Harmenberg¹⁵, Jinwan Wang¹⁶, David Cella¹⁷, Lauren McCann¹⁸, Keith Deen¹⁸, and Toni K. Choueiri¹⁹

¹Memorial Sloan Kettering Cancer Center, NY, NY, USA; ²Baylor Sammons Cancer Center/Texas Oncology, Dallas, TX, USA; ³Florida Cancer Specialists, Fort Myers, FL, USA; ⁴University of Manchester and The Christie Hospital, NHS Foundation Trust, Manchester, United Kingdom; ⁵Renal Cancer and Melanoma Unit, Peking University Cancer Hospital, Beijing, China; ⁶Mount Vernon Hospital, Middlesex, United Kingdom; ⁷Department of Urology, Interdisciplinary Centre on Renal Tumors, University of Munich, Munich, Germany; ⁸University of Western Sydney School of Medicine, MMRG, CRG, Sydney, Australia; ⁹University of Miami, Sylvester Cancer Center, Miami, FL, USA; ¹⁰Oncology Centre, Addenbrooke's Hospital, Cambridge, United Kingdom; ¹¹Peking University First Hospital, Beijing, China; ¹²Institute of Cancer Sciences University of Glasgow, Glasgow, United Kingdom; ¹³Department of Urology, Kinki University Faculty of Medicine, Osaka, Japan; ¹⁴IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola, Italy; ¹⁵Department of Oncology, Radiumhemmet Karolinska University Hospital, Stockholm, Sweden; ¹⁶Cancer Hospital, CAMS & PUMC, Beijing, China; ¹⁷Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; ¹⁸GlaxoSmithKline, Inc., Collegeville, PA, USA; ¹⁹Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

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 trials¹
- Indirect comparison analysis of pazopanib versus sunitinib revealed²:
 - 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

Key Eligibility Criteria

- Advanced/metastatic RCC
- Clear-cell histology
- No prior systemic therapy
- Measurable disease (RECIST 1.0)
- KPS ≥ 70
- Adequate organ function

**Randomized
1:1**

**Pazopanib
800 mg qd
continuous dosing**

Dose reductions to
600 mg or 400 mg

**Sunitinib
50 mg qd
4 wk on/2 wk off**

Dose reductions to
37.5 mg or 25 mg

Stratification Factors

- KPS 70/80 vs 90/100
- Prior nephrectomy
- Baseline LDH >1.5 vs $\leq 1.5 \times$ 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, %* | | |
| $\leq 1.5 \times \text{ULN}$ | 93 | 95 |
| Number of organs involved, % | | |
| 1 or 2 | 58 | 56 |
| ≥ 3 | 42 | 44 |

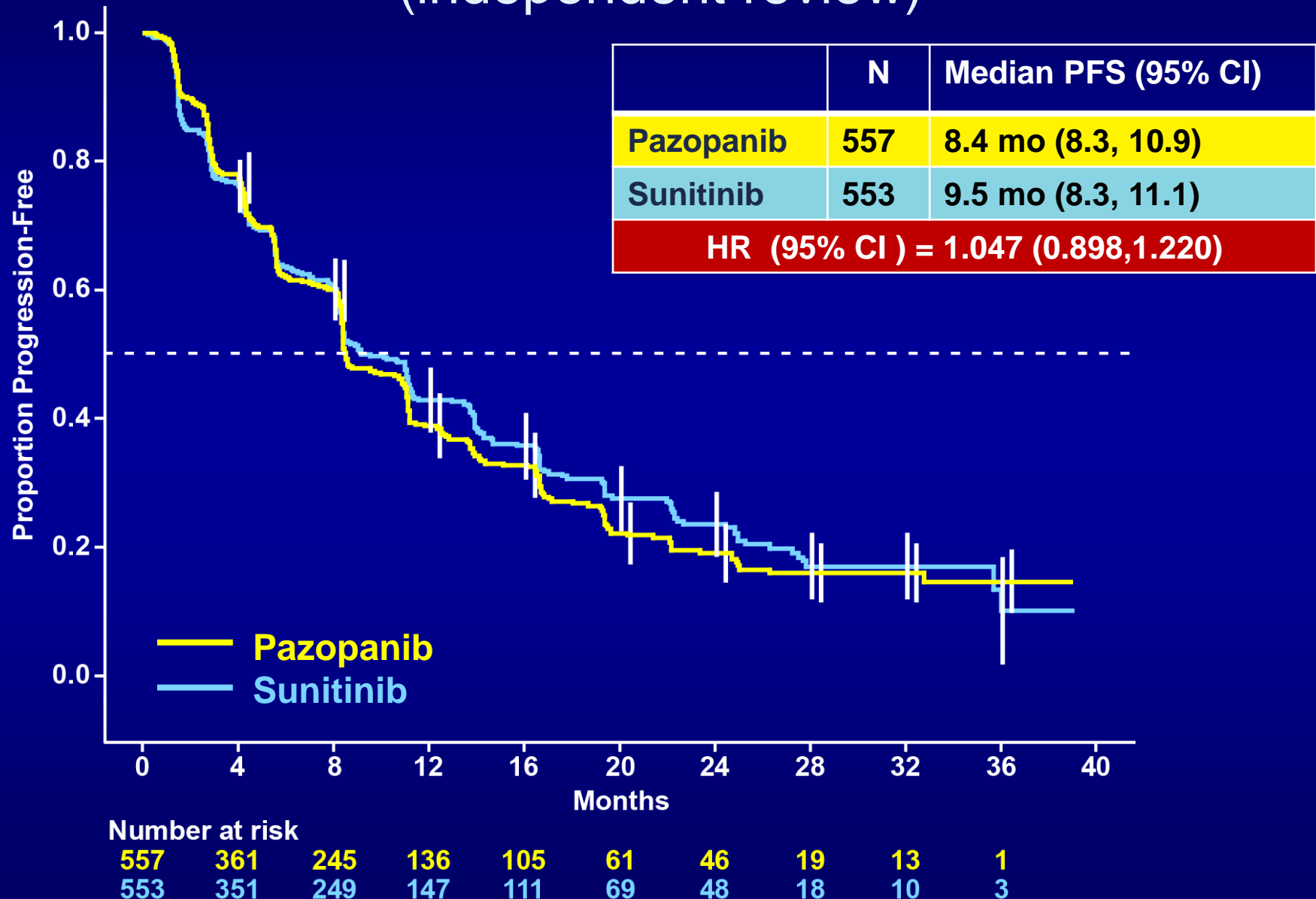
*Stratification factor

Baseline Characteristics

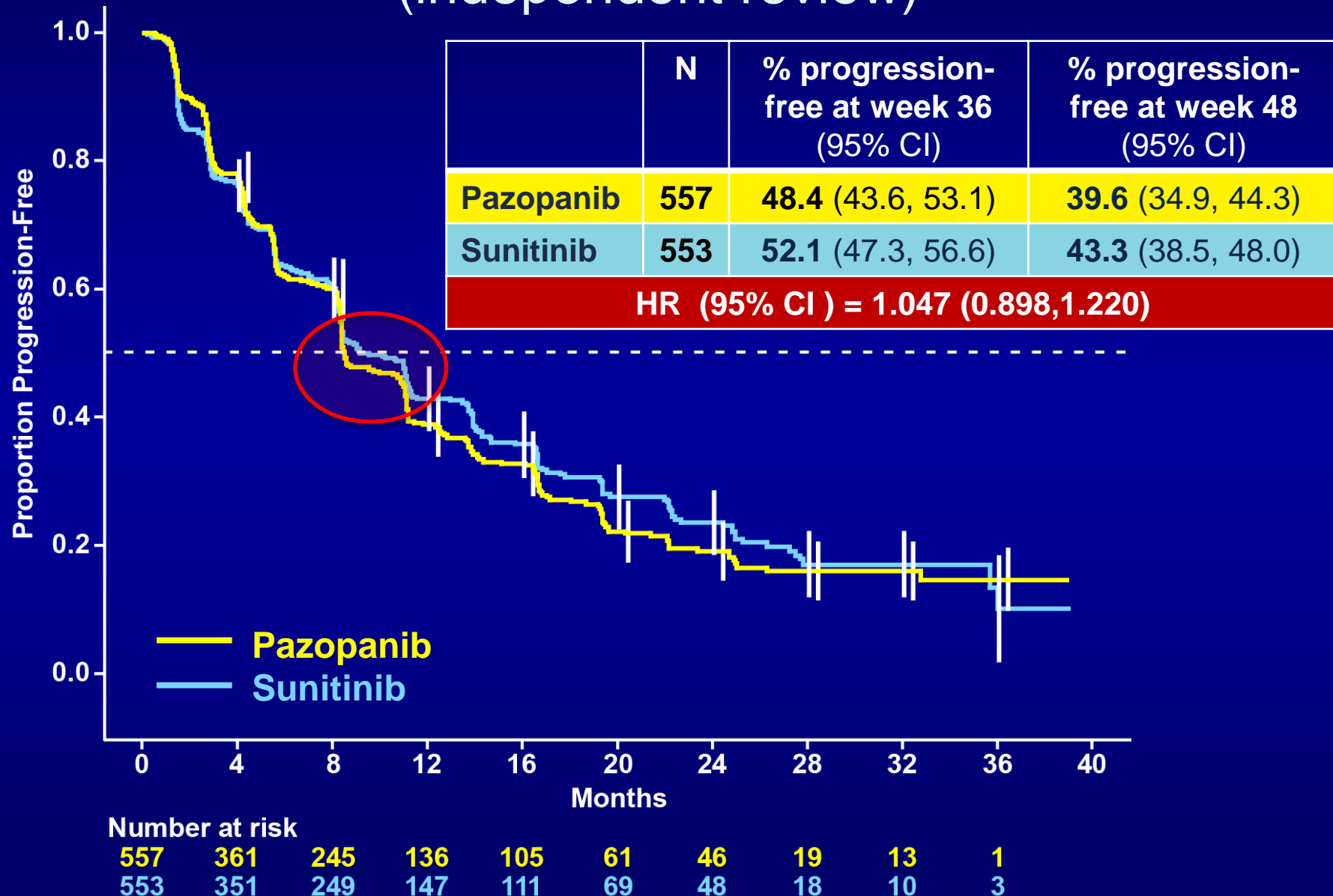
| | Pazopanib (n = 557) | Sunitinib (n = 553) |
|--------------------------------------|------------------------|------------------------|
| MSKCC risk category ¹ , % | | |
| Favorable | 27 | 27 |
| Intermediate | 58 | 59 |
| Poor | 12 | 9 |
| Unknown | 3 | 4 |
| Most common metastatic sites, % | | |
| 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

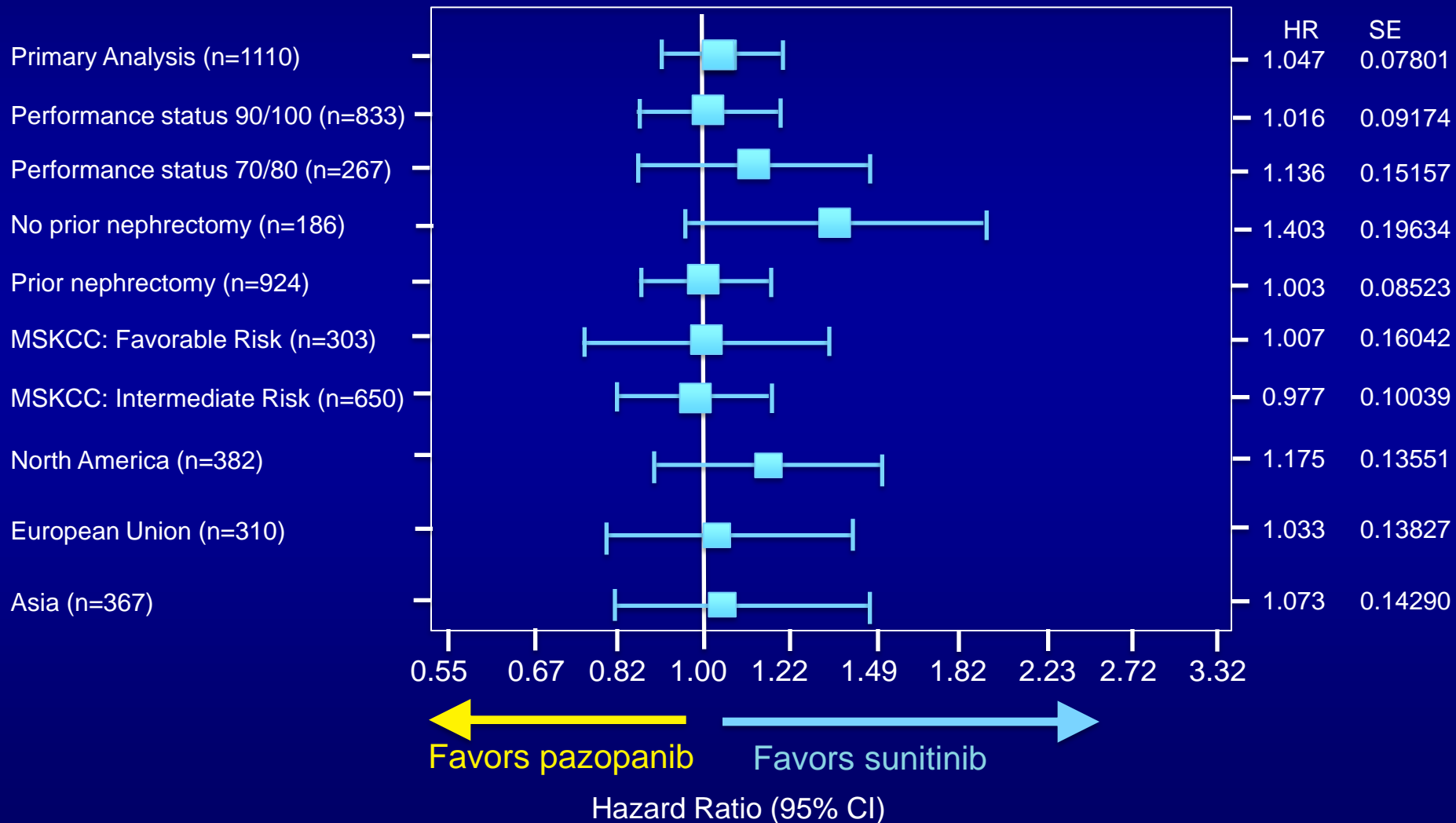
Primary Endpoint: Progression-free Survival (independent review)



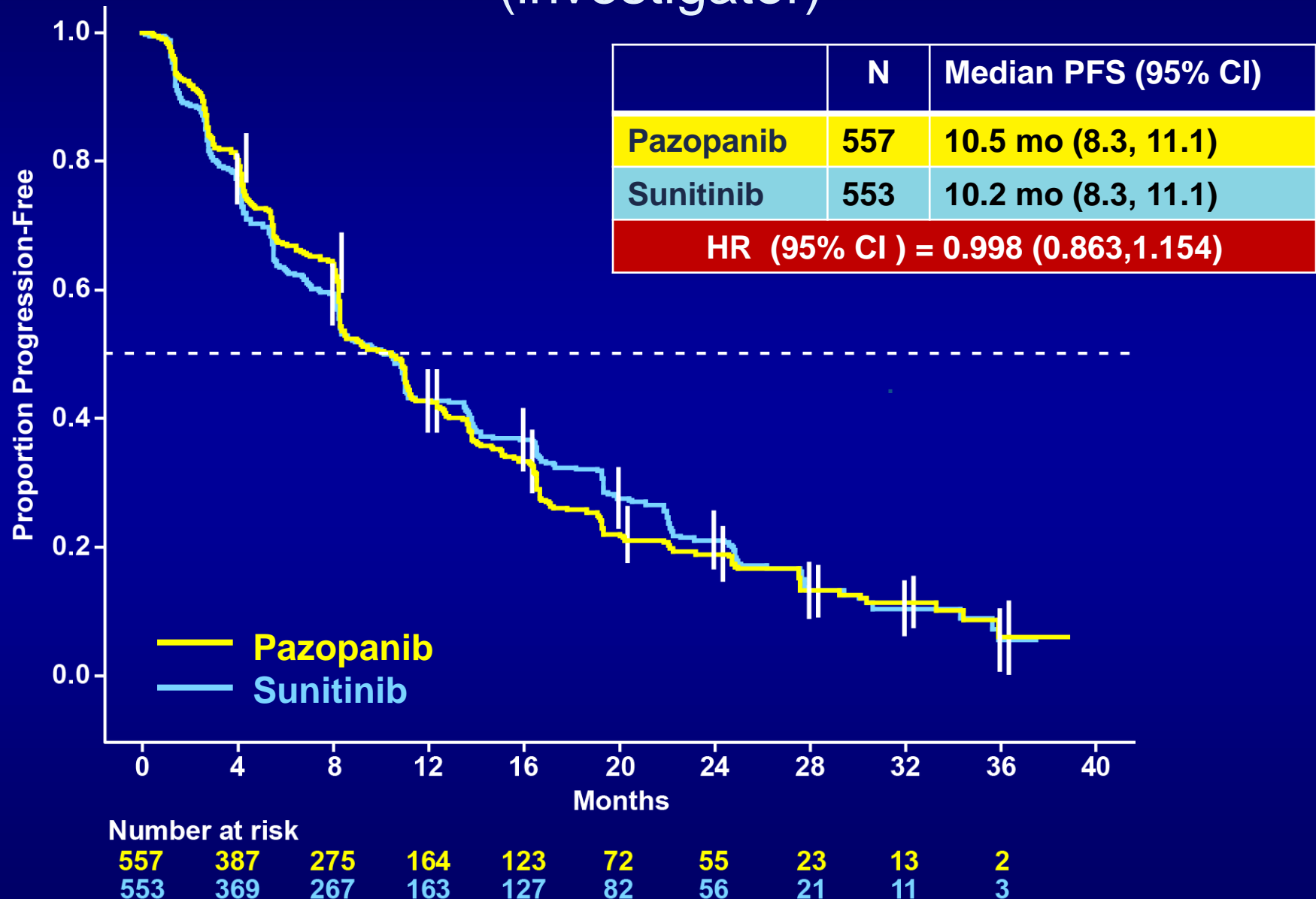
Primary Endpoint: Progression-free Survival (independent review)



Subgroup Analyses of PFS (independent review)



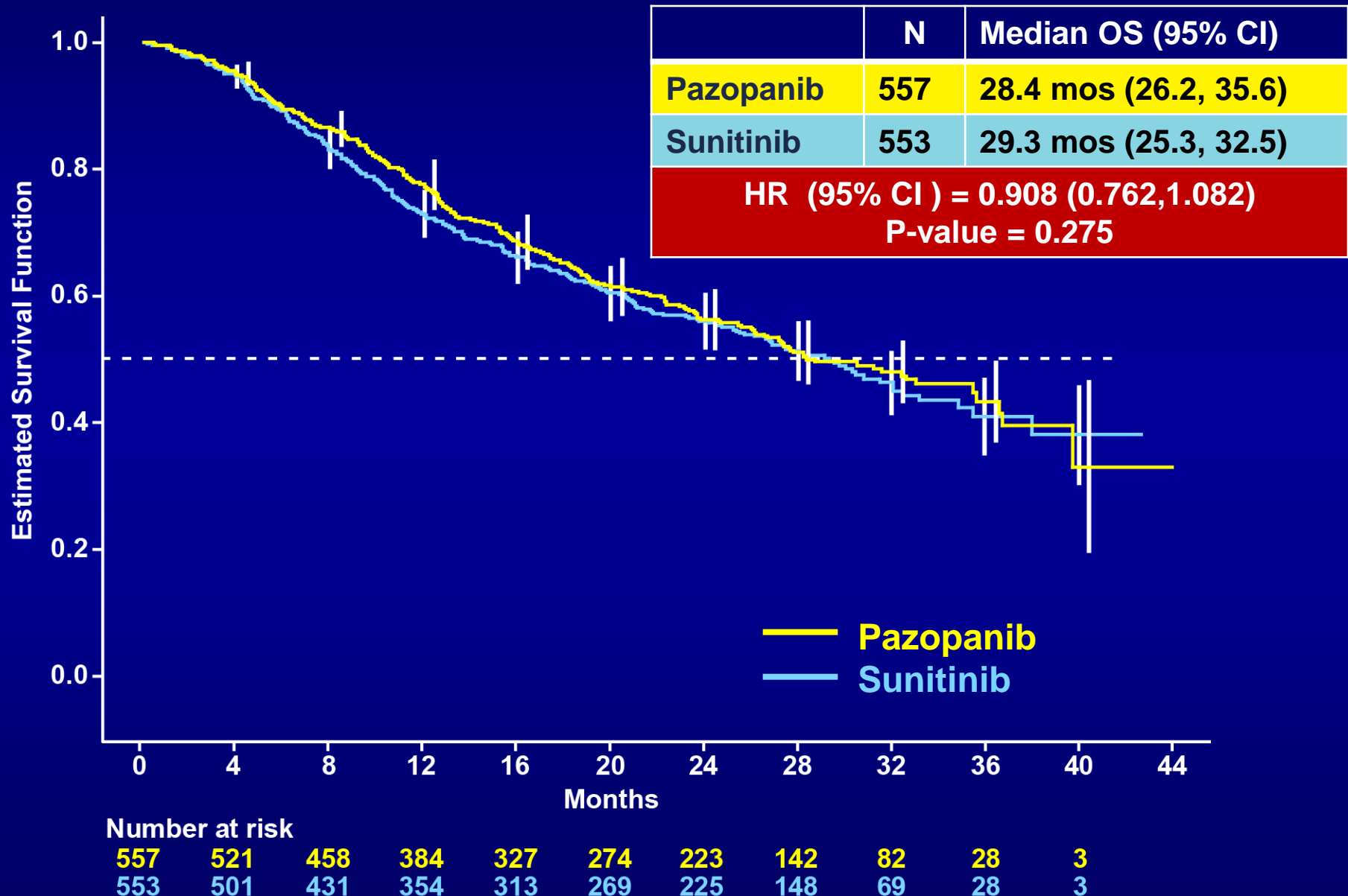
Primary Endpoint: Progression-free Survival (investigator)



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



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 |

Laboratory Abnormalities

| | Pazopanib (n = 554), % | Sunitinib (n = 548), % |
|-----------------------|---------------------------|---------------------------|
| Chemistry labs (≥35%) | All Grades | All Grades |
| ALT | 60 | 43 |
| AST | 61 | 60 |
| Hypoalbuminemia | 33 | 42 |
| Bilirubin | 36 | 27 |
| Creatinine | 32 | 46 |
| Hyperglycemia | 54 | 57 |
| Hyponatremia | 35 | 32 |
| Hypophosphatemia | 36 | 52 |
| Hematology labs | | |
| Leukopenia | 43 | 78 |
| Neutropenia | 37 | 68 |
| Thrombocytopenia | 41 | 78 |
| Lymphopenia | 38 | 55 |
| Anemia | 31 | 60 |

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

Laboratory Abnormalities

| | Pazopanib (n = 554), % | Sunitinib (n = 548),% |
|-----------------------|---------------------------|--------------------------|
| Chemistry labs (≥35%) | All Grades | All Grades |
| ALT | 60 | 43 |
| AST | 61 | 60 |
| Hypoalbuminemia | 33 | 42 |
| Bilirubin | 36 | 27 |
| Creatinine | 32 | 46 |
| Hyperglycemia | 54 | 57 |
| Hyponatremia | 35 | 32 |
| Hypophosphatemia | 36 | 52 |
| Hematology labs | | |
| Leukopenia | 43 | 78 |
| 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.

Most Common Adverse Events (treatment-emergent)

| | Pazopanib (n = 554) % | Sunitinib (n = 548) % |
|----------------------------|--------------------------|--------------------------|
| Adverse Event ¹ | All Grades | All Grades |
| Any event ² | >99 | >99 |
| Diarrhea | 63 | 57 |
| Fatigue | 55 | 63 |
| Hypertension | 46 | 41 |
| Nausea | 45 | 46 |
| Decreased appetite | 37 | 37 |
| ALT increased | 31 | 18 |
| Hair color changes | 30 | 10 |
| Hand-foot syndrome | 29 | 50 |
| Taste alteration | 26 | 36 |
| Thrombocytopenia | 10 | 34 |

¹ AE ≥30% in either arm

² 2% of patients in pazopanib arm and 3% of patients in sunitinib arm had grade 5 adverse events

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

Most Common Adverse Events (treatment-emergent)

| | Pazopanib (n = 554) % | Sunitinib (n = 548) % |
|----------------------------|--------------------------|--------------------------|
| Adverse Event ¹ | All Grades | All Grades |
| Any event ² | >99 | >99 |
| Diarrhea | 63 | 57 |
| Fatigue | 55 | 63 |
| Hypertension | 46 | 41 |
| Nausea | 45 | 46 |
| Decreased appetite | 37 | 37 |
| ALT increased | 31 | 18 |
| Hair color changes | 30 | 10 |
| Hand-foot syndrome | 29 | 50 |
| Taste alteration | 26 | 36 |
| Thrombocytopenia | 10 | 34 |

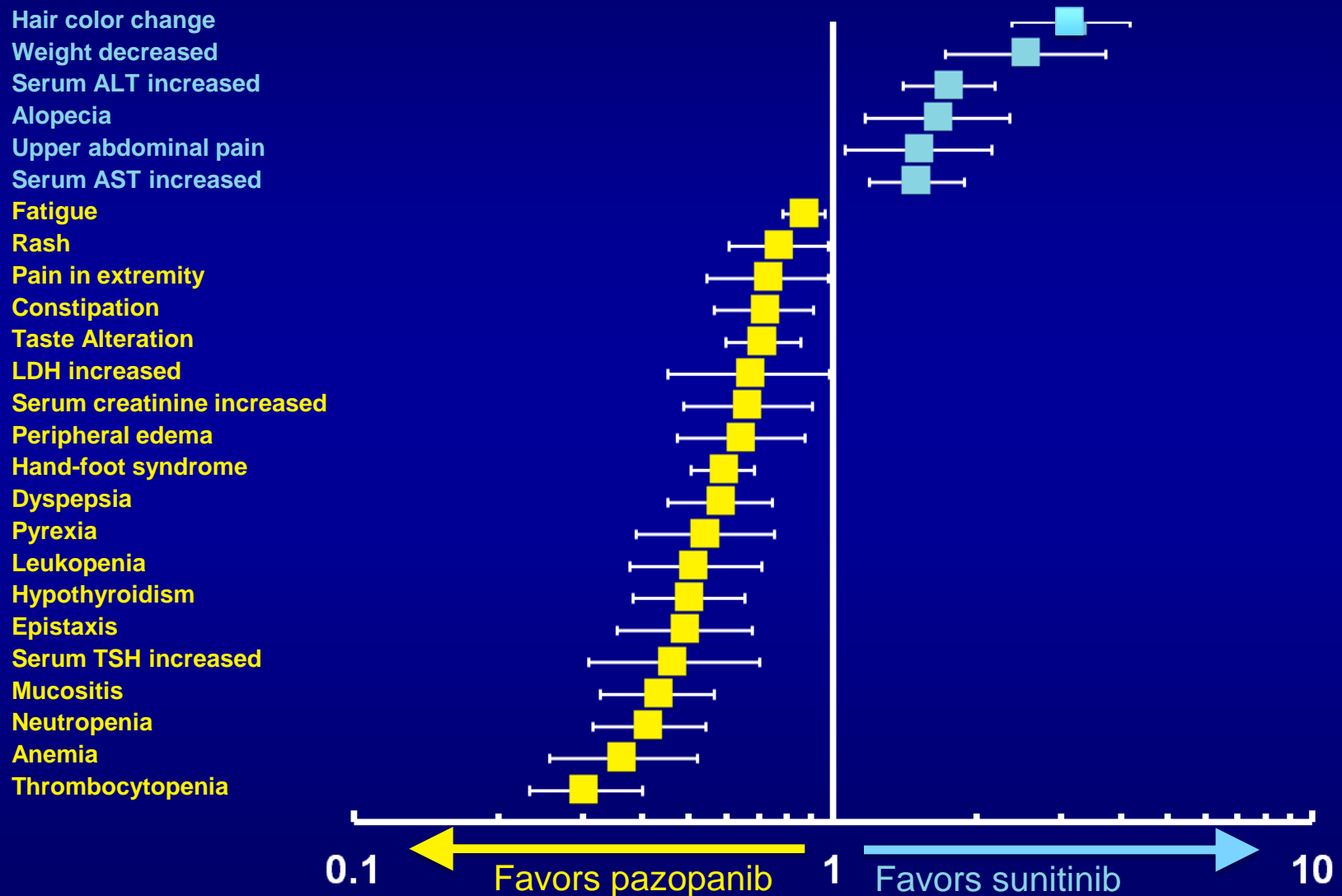
¹ AE ≥30% in either arm

² 2% of patients in pazopanib arm and 3% of patients in sunitinib arm had grade 5 adverse events

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

Relative Risk in Adverse Events

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



Quality of Life Results (first 6 months¹)

| 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 |

¹Pre-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

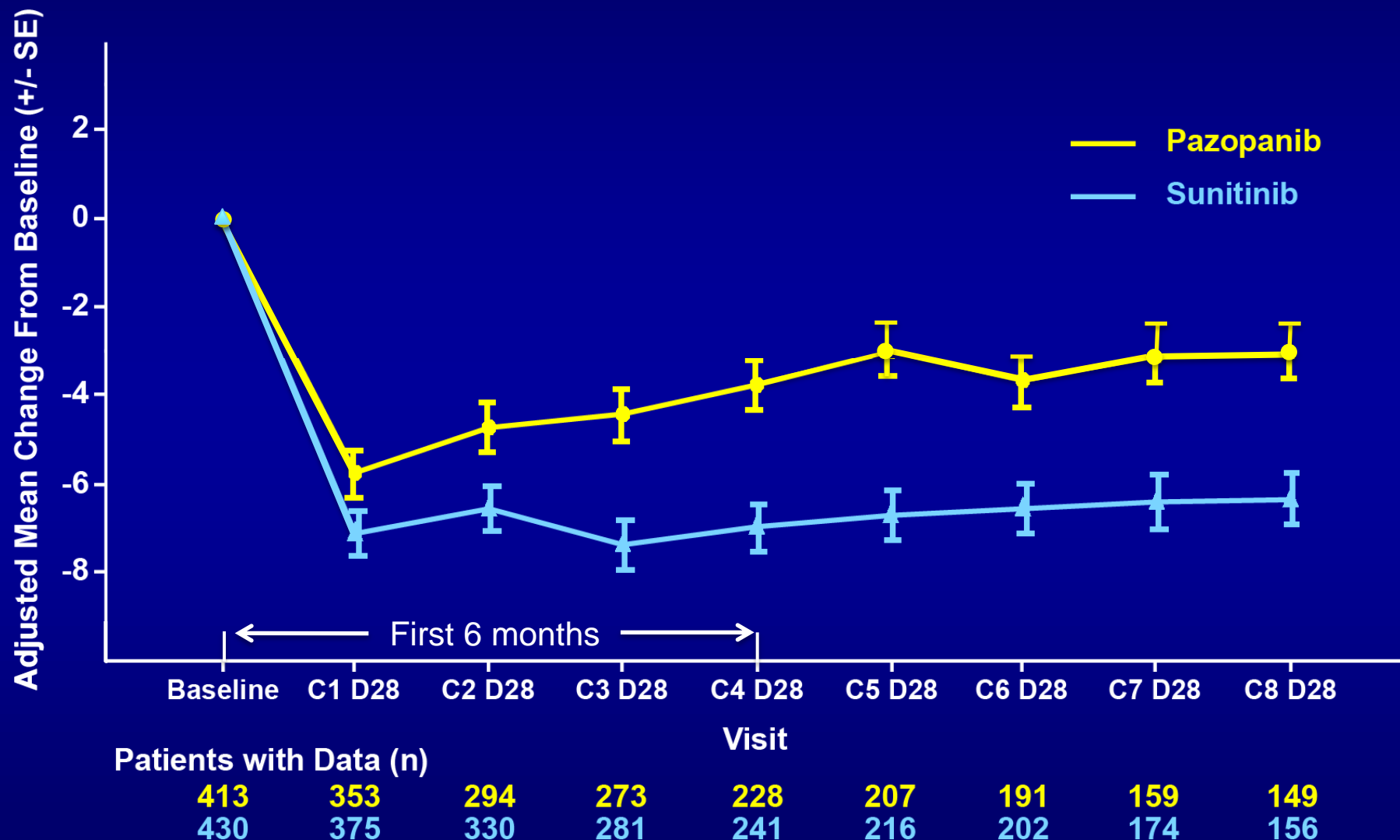
Quality of Life Results (first 6 months¹)

| 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 |

¹Pre-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

Quality of Life Result: FACIT-Fatigue



Quality of Life Results: PISCES¹

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

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

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

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

North America

| | |
|----------------------|--------------------|
| Robert Alter | Jennifer Knox |
| Thomas Anderson | Stacey Knox |
| Edward Arrowsmith | Michael Kosmo |
| Hazem Assi | Steven Kuross |
| Venkatadri Beeki | Primo Lara |
| William Berry | Theodore Logan |
| John Caton | Mary MacKenzie |
| Laurie Chen | Yvonne Manalo |
| Toni Choueiri | Jaime Merchan |
| Joseph Clark | Wilson Miller |
| Allen Cohn | Robert Motzer |
| Edward Crane | David Nanus |
| Christopher Croot | Craig Nichols |
| Brendan Curti | Scott North |
| Piotr Czaykowski | Thomas Olencki |
| Nancy Dawson | Richard Orłowski |
| Asad Dean | Joseph Pasquazzo |
| Harry Drabkin | Kelly Pendergrass |
| Arkadiusz Dudek | Daniel Petrylak |
| William Edenfield | Elizabeth Plimack |
| Peter Eisenberg | Martin Reaume |
| Marc Ernstoff | James Reeves |
| Louis Fehrenbacher | Donald Richards |
| Mark Fleming | Paul Richards |
| John Fruehauf | Dean Ruether |
| Vijaya Gadiyaram | Hanna Sanoff |
| Peter Graze | John Sarantopoulos |
| Andrew Greenspan | Subhash Sharma |
| John Hainsworth | John Showel |
| James Hampton | Guru Sonpavde |
| Beth Hellerstedt | Denis Soulieres |
| Charles Henderson | Isaac Tatur |
| David Hoffman | John Thompson |
| Sebastien Hotte | John Thropay |
| Thomas Hutson | Ulka Vaishampayan |
| George Keogh | Nicholas Vogelzang |
| James Khatcheressian | Pawel Zalewski |
| Goetz Kloecker | David Zenk |
| Mark Knapp | |
| James Knost | |

Europe

| | |
|----------------------------|-------------------------|
| Peter Albers | Anna Laurell |
| Dino Amadori | Maurizio Leoni |
| Amit Bahl | Olaf Loosveld |
| Laurens Beereport | Giovanni Lo Re |
| Sergio Bracarda | Pilar López Criado |
| Oscar Breathnach | Guillermo Lopez Vivanco |
| Janet Brown | John McCaffrey |
| Giacomo Carteni | Ray McDermott |
| Daniel Castellano Gauna | Begoña Mellado |
| David Chao | Paul Nathan |
| Simon Chowdhury | Franco Nolè |
| Magdalena Cwikiel | Poulam Patel |
| Linda Evans | Jose Luis Perez Gracia |
| Kate Fife | Franciscus Peters |
| Albert Font Pous | Emilio Portin |
| Thomas Gauler | Johanneke Portielje |
| Jose Luis Gonzalez Larriba | Thomas Powles |
| Richard Griffiths | Detlef Rohde |
| John Haanen | Karl Rohmann |
| Ulrika Harmerberg | Jordi Rubio |
| Stefan Hauser | Robert Rudolph |
| Robert Hawkins | Jan Schleicher |
| Axel Hegele | Stefan Siemer |
| Axel Heidenreich | Michael Staehler |
| Jacobus van der Hoeven | Cora Sternberg |
| Juergen Jacob | Michael Truss |
| Robert Jones | Emile E. Voest |
| Maccon Keane | John Wagstaff |
| Michael Koenigsmann | Steffen Weikert |
| James Larkin | Manfred Wirth |

Asia Pacific

| | |
|-----------------------|---------------------|
| Arun Azad | Norio Nonomura |
| Antonino Bonaventura | Louise Nott |
| Wen-Cheng Chang | Wataru Obara |
| Yen-Hwa Chang | Yen-Chuan Ou |
| Po-Hui Chiang | Mototsugu Oya |
| Jinsoo Chung | Shukui Qin |
| Ian Davis | Xiubao Ren |
| Paul De Souza | Sun Young Rha |
| Hiroyuki Fujimoto | Nobuo Shinohara |
| David Goldstein | Christopher Steer |
| Jun Guo | Shunji Takahashi |
| Howard Gurney | Tatsuya Takayama |
| Katsuyoshi Hashine | Kazunari Tanabe |
| Shigeo Horie | Katsunori Tatsugami |
| Lisa Horvath | Yoshihiko Tomita |
| Yiran Huang | Taiji Tsukamoto |
| Jie Jin | Hirotsugu Uemura |
| Tomomi Kamba | Jinwan Wang |
| Ganessan Kichenadasse | Hsi-Chin Wu |
| Yasuyuki Kobayashi | Liping Xie |
| Jae-Lyun Lee | Masahiro Yao |
| Hyo-Jin Lee | Dingwei Ye |
| Winston Liauw | Xu Zhang |
| Ho Yeong Lim | Fangjian Zhou |
| Chia-Chi Lin | |
| Jun Miyazaki | |

Many Thanks to the Patients and Investigators