5 Minute JournalClub

Pazopanib in Patients with Treatment-Naïve or Cytokine-Pretreated Advanced RCC

For more visit ResearchToPractice.com/R5MJC

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

Advances in the biologic understanding of renal cell cancer and the emergence of clinical trial data with targeted therapeutic agents have resulted in the availability of novel treatment strategies for this challenging disease. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these rapidly evolving data sets. To bridge the gap between research and patient care, this CME activity will deliver a serial review of recent key presentations and publications and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with renal cell cancer.

LEARNING OBJECTIVE

- Critically evaluate the efficacy and side-effect profile of oral pazopanib 800 mg/day continuous dosing monotherapy for patients with advanced clear cell renal carcinoma who are treatment naïve or have received prior cytokine therapy.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentation, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Thomas E Hutson, DO, PharmD
Director, GU Oncology Program
Texas Oncology, PA
Charles A Sammons Cancer Center
Baylor University Medical Center
Co-Chair, GU Research
US Oncology
Dallas, Texas

Advisory Committee: Bayer Pharmaceuticals Corporation, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Consulting Agreements: Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Paid Research: GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Speakers Bureau: Bayer Pharmaceuticals Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth.

Robert J Motzer, MD
Genitourinary Medical Oncologist
New York, New York

Advisory Committee: Novartis Pharmaceuticals Corporation; Paid Research: Novartis Pharmaceuticals Corporation, Pfizer Inc, Wyeth; Speakers Bureau: Bayer Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc.

David I Quinn, MBBS, PhD
Medical Director, Norris Cancer Hospital and Clinics
Leader, Developmental Therapeutics
Head, GU Cancer Section
Division of Cancer Medicine and Blood Diseases
USC/Norris Comprehensive Cancer Center
Los Angeles, California

Advisory Committee: Bayer Pharmaceuticals Corporation, Genentech BioOncology, GPC Biotech, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Pfizer Inc, Sanofi-Aventis, Wyeth; Speakers Bureau: Bayer Pharmaceuticals Corporation, Lilly USA LLC, Millennium Pharmaceuticals Inc, Onyx Pharmaceuticals Inc, Pfizer Inc, Sanofi-Aventis, Wyeth.

EDITOR — Neil Love: Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Centocor Ortho Biotech Services LLC, Cephalon Inc, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, GlaxoSmithKline, ImClone Systems Incorporated, Lilly USA LLC, Merck and Company Inc, Millennium Pharmaceuticals Inc, Monogram Biosciences, Novartis Pharmaceuticals Corporation, OSI Oncology, Roche Laboratories Inc, Sanofi-Aventis and Wyeth.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.

This program is supported by an educational grant from GlaxoSmithKline.

Cosponsored by Research To Practice and City of Hope.

Last review date: November 2009
Expiration date: November 2010

Nobody seems to care much anymore about the ancient backbone of medical oncology, cytotoxic chemotherapy, and in the past decade, so-called biologic agents — mainly antibodies, TKIs and other small molecules — have dominated a clinical trials infrastructure that is being led by industry while publicly funded research sputters along.

However, with the many benefits offered by biologics come a panoply of new toxicity issues that challenge clinicians in ways never before imagined. Nowhere is this dynamic more evident than in renal cell cancer in which six new agents have been approved in the past four years.

In this issue of 5MJC, we examine three recent reports that attempt to better define tolerability considerations surrounding the most utilized class of new RCC drugs, the VEGF TKIs. We begin with a **report by Escudier et al** of a Phase II study of continuous daily dosing of sunitinib at 37.5 mg, with findings that look generally similar to the 50-mg four week on, two week off regimen that has become the most commonly used first-line therapy in this disease. Despite this intriguing new data set, no one will stick his or her neck out one way or the other in predicting the results of the hopefully soon to be reported EFFECT trial comparing these two regimens as front-line therapy in a head-to-head Phase II randomized study.

At our recent **renal cell cancer investigator think tank** [login required], Eric Jonasch and others suggested the possibility of yet another sunitinib regimen: 50 mg a day, two weeks on, one week off. The undercurrent to all of these efforts is the belief — variably embraced by RCC investigators — that treatment benefit may in some way be correlated with TKI "dose under the curve." How any of these regimens compares to the recently FDA approved bevacizumab/interferon combination or to bev alone is currently unknown.

Speaking of FDA approval, we also include **two new data sets** on the most recently green-lighted renal cell agent, another TKI, pazopanib, which again, by indirect comparison seems similar to sunitinib. However, Tom Hutson, also on our think tank program, predicts that an upcoming Phase III trial comparing these two complicated TKIs in the first-line setting will demonstrate essentially equivalent efficacy but different side-effect profiles, with pazopanib perhaps better tolerated but bringing with it a significant risk of hepatic dysfunction, usually reversible transaminitis.

The traditional oncology focus on challenging complications of chemotherapy including neutropenic infections, nausea and vomiting has now shifted to an array of new toxicity issues with these novel biologic agents. Our ability to prevent or ameliorate these — either with new dosing and administration schedules or with second- or third-generation agents with different pharmacologic profiles — is important now and could be life-saving in the future, if and when we see imatinib/CML-like magic with these or other similar agents or combinations.

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates each of the two educational activities, comprised of a slide set and accompanying commentary, for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

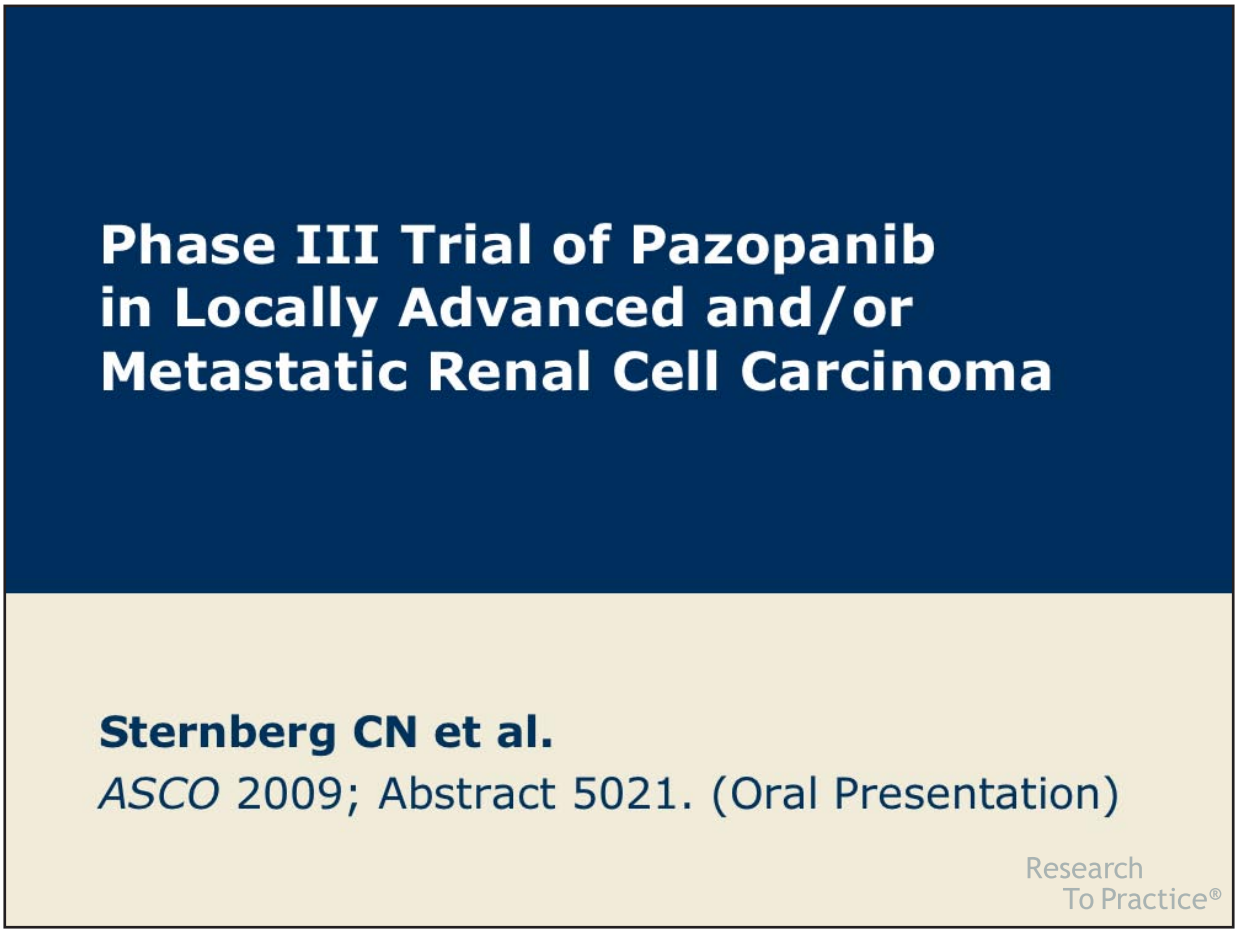
Pazopanib in Patients with Treatment-Naïve or Cytokine-Pretreated Advanced RCC

Presentations discussed in this issue:

Sternberg CN et al. **A randomized, double-blind phase III study of pazopanib in treatment-naïve and cytokine-pretreated patients with advanced renal cell carcinoma (RCC).** ASCO 2009;**Abstract 5021**.

Hawkins RE et al. **An open-label extension study to evaluate safety and efficacy of pazopanib in patients with advanced renal cell carcinoma (RCC).** ASCO 2009;**Abstract 5110**.

Slides from the ASCO presentations and transcribed comments from a related "Think Tank" (June 10, 2009) featuring Thomas E Hutson, DO, PharmD, Robert J Motzer, MD and David I Quinn, MBBS, PhD

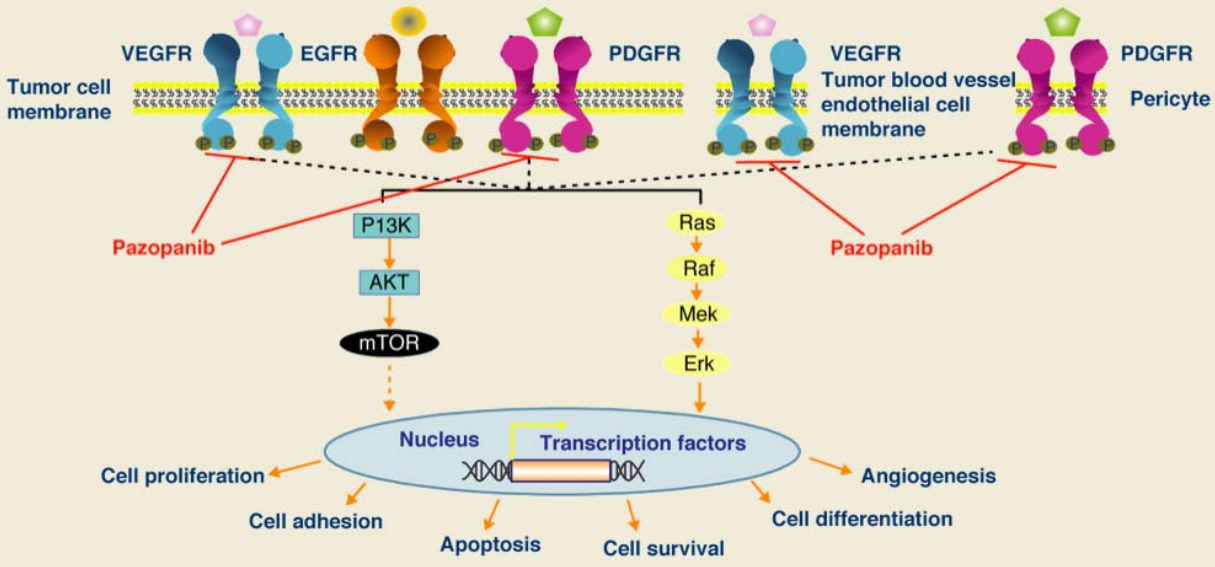


Introduction

- Pazopanib, an oral angiogenesis inhibitor, has high affinity for PDGFR and VEGFR 1, 2 and 3 and also targets C-kit
- Clinical efficacy of pazopanib demonstrated in a Phase II trial in patients with advanced renal cell carcinoma (RCC) (ASCO 2008;Abstract 5046)
  - ORR, 34.7%
  - PFS, 11.9 mos vs 6.2 mos (placebo)
- Current study objectives:
  - Evaluate the efficacy and safety of single-agent pazopanib in treatment-naïve and cytokine-pretreated patients with locally-advanced or metastatic clear-cell RCC

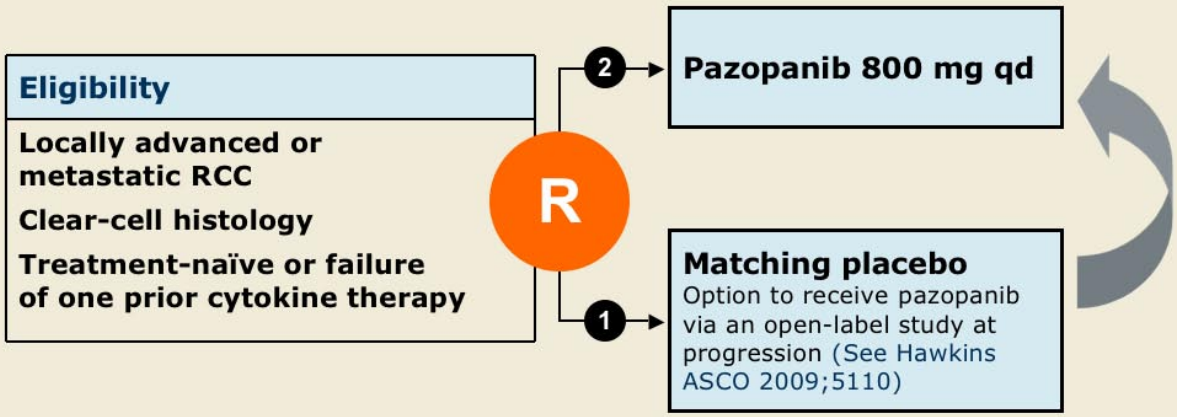
Source: Sternberg CN et al. *ASCO* 2009; Abstract 5021.

Pazopanib: Mechanisms of Action



Source: Reprinted with permission. Sonpavde G et al. Expert Opin Investig Drugs 2008;17(2):253-261.

Phase III Randomized, Placebo-Controlled Pivotal Trial (VEG105192)



Source: Sternberg CN et al. *ASCO* 2009; Abstract 5021.

Research To Practice®

Overall Efficacy Results

	Pazopanib (n = 290)	Placebo (n = 145)	Hazard ratio
Median progression-free survival (PFS) Treatment-naïve (n = 233) Cytokine-pretreated (n = 202)	9.2 mos 11.1 mos 7.4 mos	4.2 mos 2.8 mos 4.2 mos	0.46[1] 0.40[1] 0.54[2]
Median overall survival (OS)	21.1 mos	18.7 mos*	0.73[3]
Overall response rate (ORR, CR + PR) Treatment-naïve Cytokine-pretreated Duration of response (DoR)	30% 32% 29% 59 wks	3% 4% 3% —	— — — —

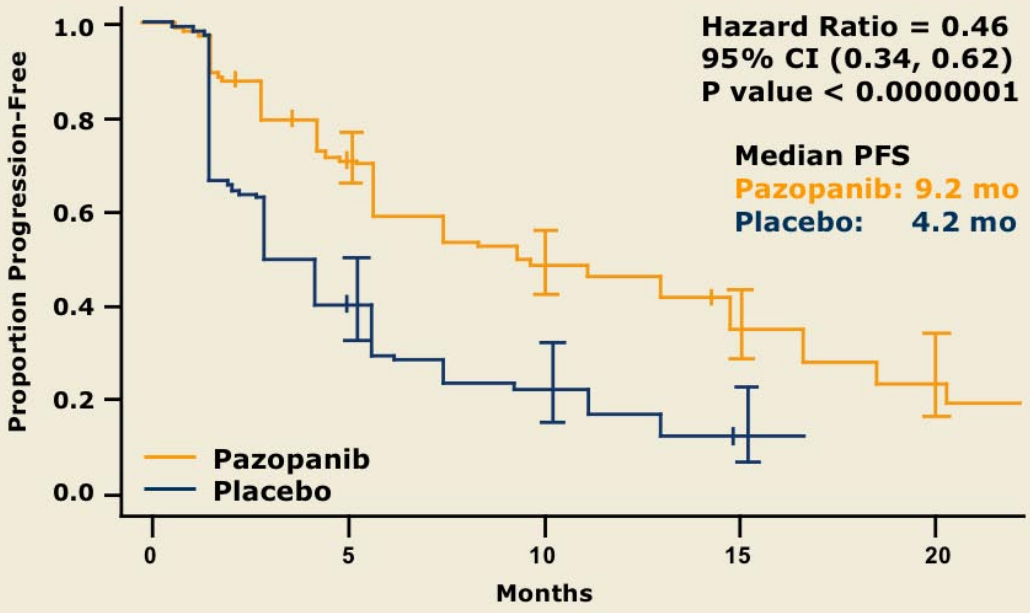
[1]$p < 0.0000001$, [2]$p < 0.001$, [3]$p < 0.02$

*48% of patients received pazopanib after disease progression

Source: Sternberg CN et al. *ASCO* 2009; Abstract 5021.

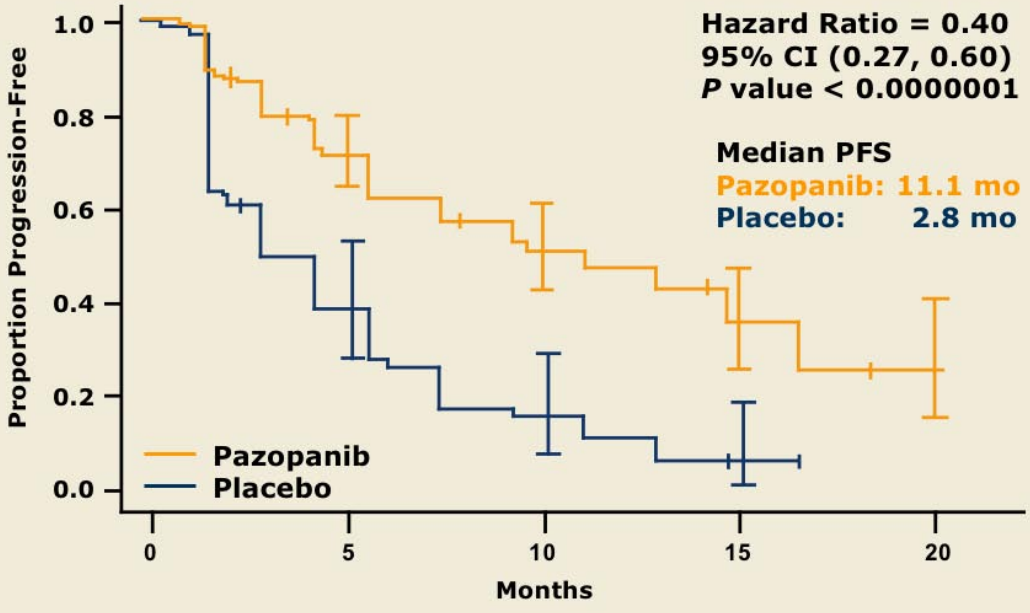
Research To Practice®

PFS in the Overall Study Population



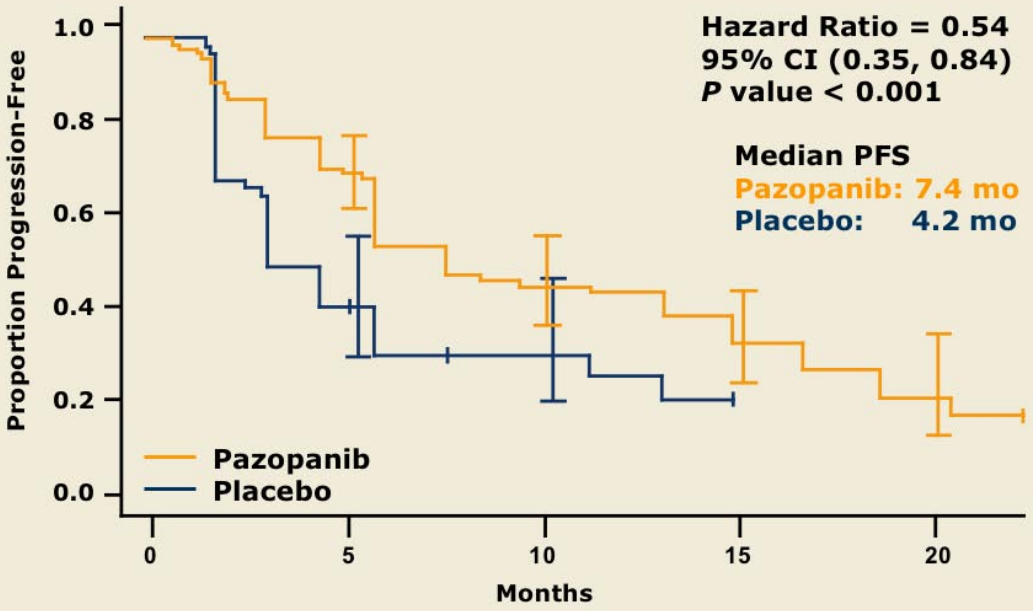
Source: Reprinted with permission. Sternberg CN et al. *ASCO* 2009; Abstract 5021.

PFS in the Treatment-Naïve Subpopulation



Source: Reprinted with permission. Sternberg CN et al. *ASCO* 2009; Abstract 5021.

PFS in the Cytokine-Pretreated Subpopulation



Source: Reprinted with permission. Sternberg CN et al. *ASCO* 2009; Abstract 5021.

Select Adverse Events and Laboratory Abnormalities

Adverse Event	Pazopanib (n = 290), %		Placebo (n = 145), %	
	All grades	G 3/4	All grades	G 3/4
Any event*	92	40	74	20
Diarrhea	52	3	9	< 1
Hypertension	40	4	10	<1
Fatigue	19	2	8	2
Nausea/vomiting	47	2	17	2
Laboratory abnormalities				
ALT	53	12	22	1
AST	53	7	19	<1
Hyperglycemia	41	<1	33	1
Hyperbilirubnemia	36	3	10	1
Lymphopenia	31	4	24	1
Anemia	22	2	31	1

*4% in pazopanib arm and 3% in placebo arm had grade 5 events

Source: Sternberg CN et al. *ASCO* 2009; Abstract 5021.

Results: Selected Adverse Class Effects of Multi-Targeted TKIs

All Grades	Pazopanib (n = 290)	Placebo (n = 145)
Proteinuria	9%	0%
Hypothyroidism	7%	0%
Hand-foot syndrome	6%	<1%
Mucositis/stomatitis	4% / 4%	<1% / 0%
Arterial thromboembolism (≥ Grade 3)	3% (2%)	0%

Source: Sternberg CN et al. *ASCO* 2009; Abstract 5021.

Research To Practice®

Summary and Conclusions

- Oral pazopanib monotherapy (vs placebo) is active in patients with locally-advanced or metastatic, clear-cell RCC
  - Treatment-naïve: PFS = 11.1 mos vs 2.8 mos (HR = 0.40)
    ORR = 32% vs 4%
  - Cytokine-pretreated: PFS = 7.4 mos vs 4.2 mos (HR = 0.54)
    ORR = 29% vs 3%
- Interim OS data are not yet mature (HR = 0.73, p = 0.02)
- Low rate (<10% all grade) of proteinuria, hypothyroidism, hand-foot syndrome, mucositis/stomatitis, arterial thromboembolism
- Liver function test abnormalities (all grade): ALT = 53%, AST = 53%
- These data indicate a favorable risk/benefit profile for pazopanib in treatment-naïve and cytokine-pretreated advanced RCC

Source: Sternberg CN et al. *ASCO* 2009; Abstract 5021.

Research To Practice®

An Open-Label Extension Study to Evaluate Safety and Efficacy of Pazopanib in Patients with Advanced Renal Cell Carcinoma (RCC)

Hawkins RE et al.

ASCO 2009; Abstract 5110. (Poster)

Research To Practice®

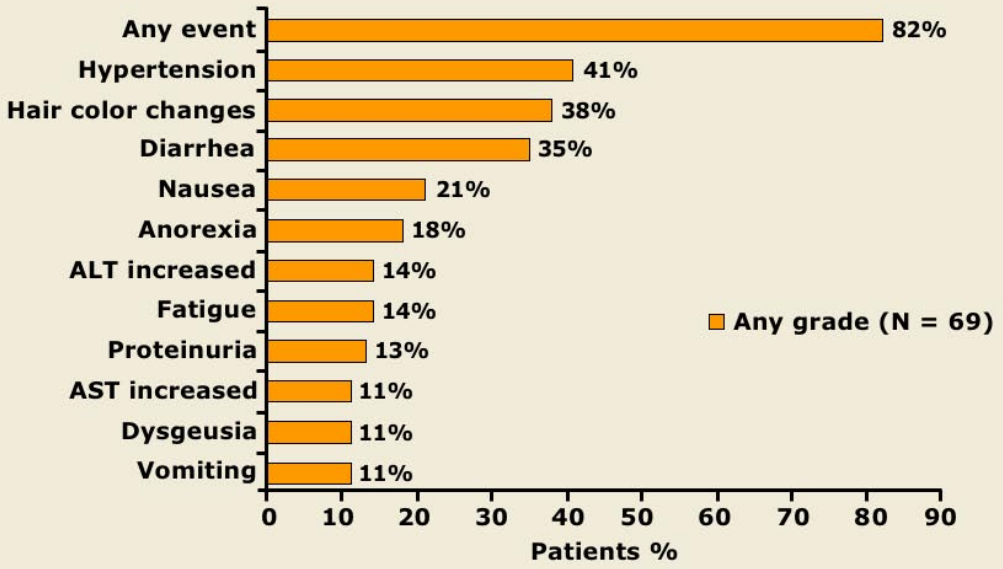
Introduction

- VEG105192 (N = 435) is a double-blind, placebo-controlled, phase III study comparing pazopanib 800 mg/day vs placebo in treatment-naïve or cytokine-pretreated patients with advanced/metastatic RCC (See Sternberg ASCO 2009;5021)
  - PFS = 9.2 mos vs 4.2 mos, HR = 0.46, $p < 0.0000001$
  - OS = 21.1 mos vs 18.7 mos, HR = 0.73, $p = 0.02$
  - Low rate (<10% all grade) of proteinuria, hypothyroidism, hand-foot syndrome, mucositis/stomatitis, arterial thromboembolism
- **Current study objectives:**
  - Evaluate safety and efficacy of pazopanib 800 mg/day continuous dosing for eligible patients who progressed on placebo in the pivotal trial (VEG105192) until progression, death or unacceptable toxicity

Source: Hawkins RE et al. *ASCO* 2009; Abstract 5110.

Research To Practice®

Treatment-Related Adverse Events in > 10% of Patients



Source: Hawkins RE et al. *ASCO* 2009; Abstract 5110.

Research To Practice®

Results: Efficacy

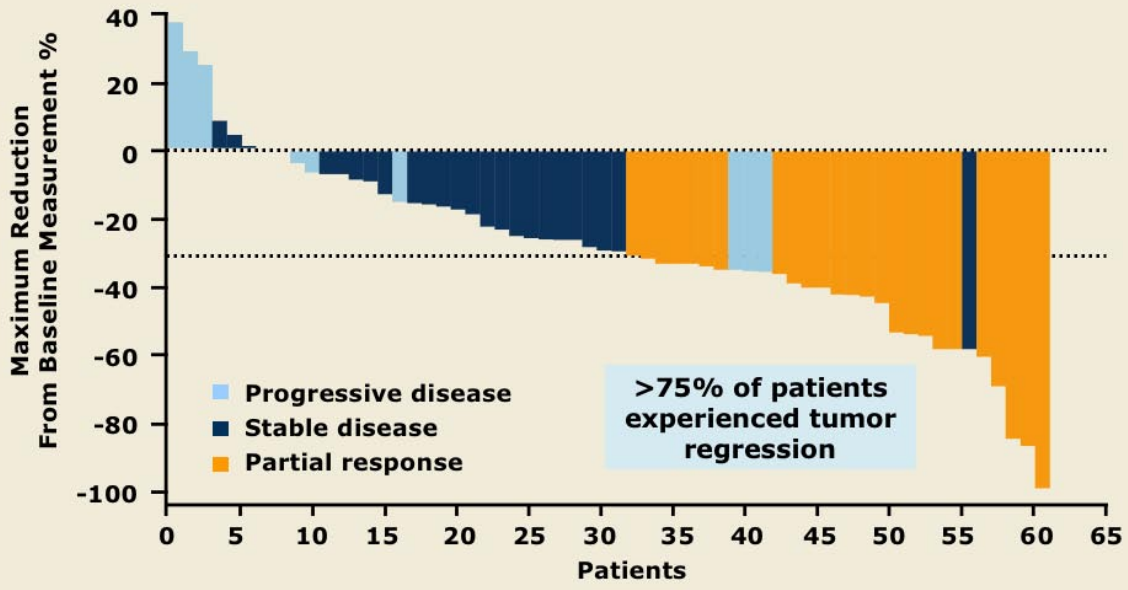
	800 mg qd (N = 71)
Overall response rate (CR + PR)	32.4%
Complete response (CR)	0%
Partial response (PR)	32.4%
Stable disease (SD)*	35.2%
Progressive disease (PD)	14.1%
Unknown	18.3%
Median progression-free survival (PFS)	8.3 mos

*A confirmed response of SD required that the SD assessment occur no earlier than 12 weeks after the screening scans

Source: Hawkins RE et al. *ASCO* 2009; Abstract 5110.

Research To Practice®

Maximum Decrease of Tumor Diameter from Baseline (Investigator-Assessed)



Source: With permission from Hawkins RE et al. *ASCO* 2009; Abstract 5110.

Research To Practice®

Summary and Conclusions

- Overall, pazopanib was relatively well tolerated
  - Most AEs or laboratory abnormalities were low grade and manageable
- The tumor response and PFS supports the clinical efficacy of pazopanib observed in the pivotal phase III study for treating patients with advanced RCC who were either treatment-naïve or cytokine-pretreated
  - ORR = 32.4%
  - Median PFS = 8.3 mos
- These findings support the continued evaluation of pazopanib in advanced RCC
  - A phase III study (N=876) comparing pazopanib with sunitinib in treatment-naïve patients with advanced RCC is ongoing (COMPARZ, NCT00720941)

Source: Hawkins RE et al. *ASCO* 2009; Abstract 5110.

Research To Practice®

NEIL LOVE, MD: Tom, we've been talking about dose intensity with VEGF tyrosine kinase inhibitors, particularly sunitinib, and a related issue is whether other less toxic agents can be identified that might allow for longer-term treatment and maybe greater efficacy. What's your take on this ASCO paper on pazopanib, and what are your global thoughts at this point on side effects, particularly compared to sunitinib?

THOMAS E HUTSON, DO, PHARMD: Clinical trial data such as this report suggest that the long-term toxicities that make the use of sunitinib difficult for patients — fatigue, diarrhea, mucositis, hand-foot syndrome — appear to be significantly less with pazopanib. My general anecdotal experience also is that pazopanib may be more tolerable than sunitinib with long-term use. The side-effect profile is certainly different with pazopanib in that you see some liver transaminase elevations and also hypertension and skin hypopigmentation. I treated an African-American patient who developed vitiligo-like areas on the face with the medication.

DR LOVE: What about efficacy compared to sunitinib?

DR HUTSON: Clearly, definitive data will come out of the randomized trial evaluating both, but based on what we know today, one would say that pazopanib is in the same ballpark of efficacy as sunitinib, based on progression-free survival and response rate.

DR LOVE: Bob, what's your take on this?

ROBERT J MOTZER, MD: We really need the Phase III comparison, but pazopanib is a highly active compound, as seen in this ASCO report. The one toxicity that needs to be addressed is the hepatic toxicity, but otherwise, the frequencies of other toxicities that have been problematic with sunitinib, including fatigue and hand-foot syndrome, were reported with less frequency.

DAVID I QUINN, MBBS, PHD: Based on this study and other data, I think pazopanib will be a viable alternative for patients in the first-line metastatic setting and also with disease progression after a cytokine. Our view is that pazopanib is probably better tolerated than sunitinib in terms of fatigue, but I want to see Phase III data to validate that. We may see a little more hypertension than with sunitinib, which is a bit of an issue to manage in some patients. But, I think it's a player in the arena. When we look at the current options for advanced renal cell carcinoma, it's immunotherapy/cytokines, VEGF inhibition and mTOR inhibition — it's a matter of how to optimally deliver these. I think having another agent available is a good thing because there's more choice.

Dr Hutson is Director of the GU Oncology Program at Texas Oncology-Baylor Charles A Sammons Cancer Center and Co-Chair of US Oncology GU Research in Dallas, Texas.

Dr Motzer is Genitourinary Medical Oncologist in New York, New York.

Dr Quinn is Medical Director of Norris Cancer Hospital and Clinics, Leader of Developmental Therapeutics and Head of the GU Cancer Section in the Division of Cancer Medicine and Blood Diseases at USC/Norris Comprehensive Cancer Center in Los Angeles, California.