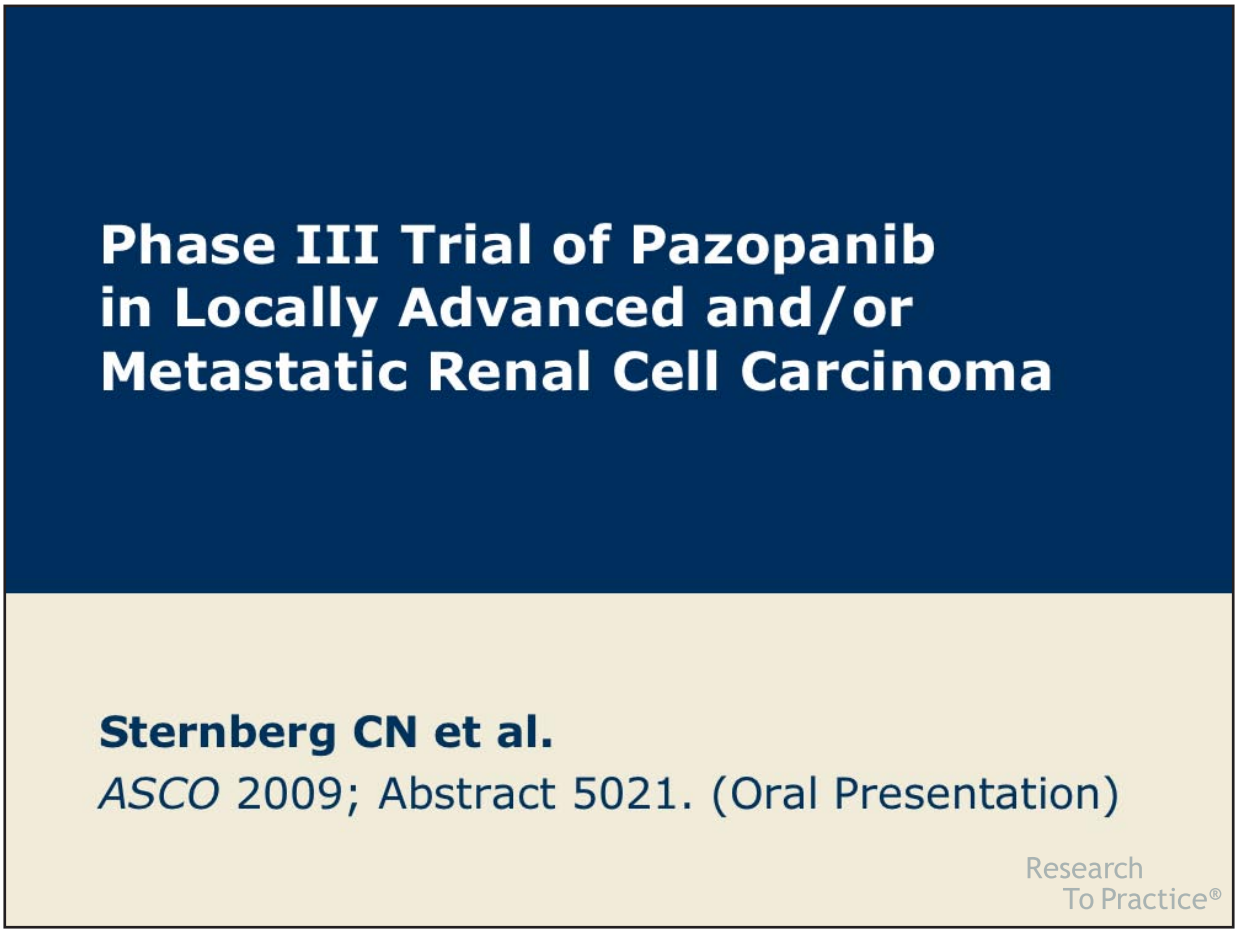
Pazopanib in Patients with Treatment-Naïve or Cytokine-Pretreated Advanced RCC

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

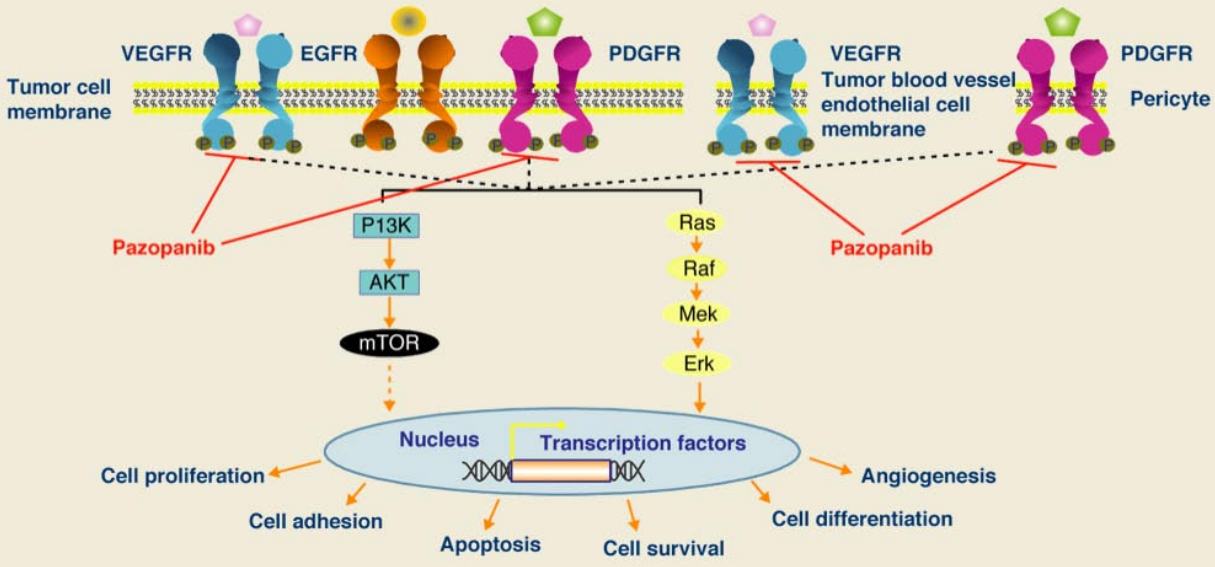


Introduction

- 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

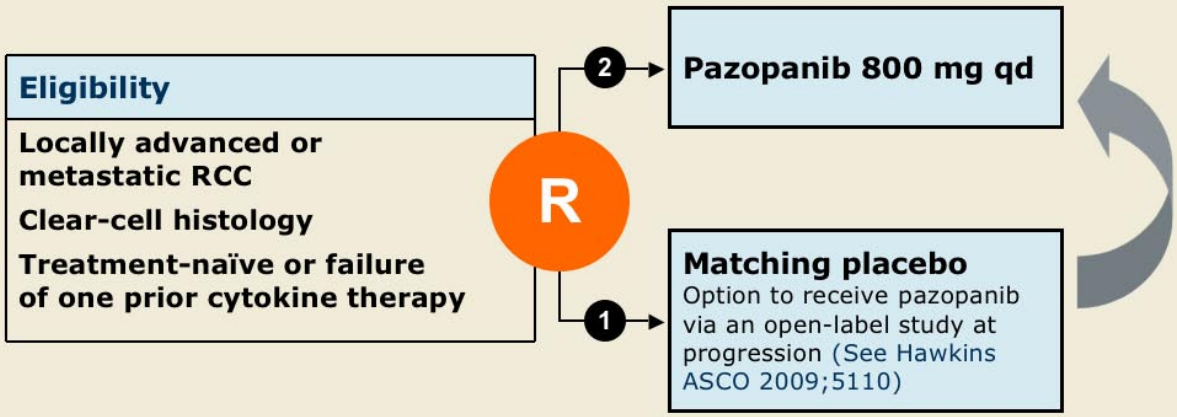
Source: Sternberg CN et al. *ASCO* 2009; Abstract 5021.

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.

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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.

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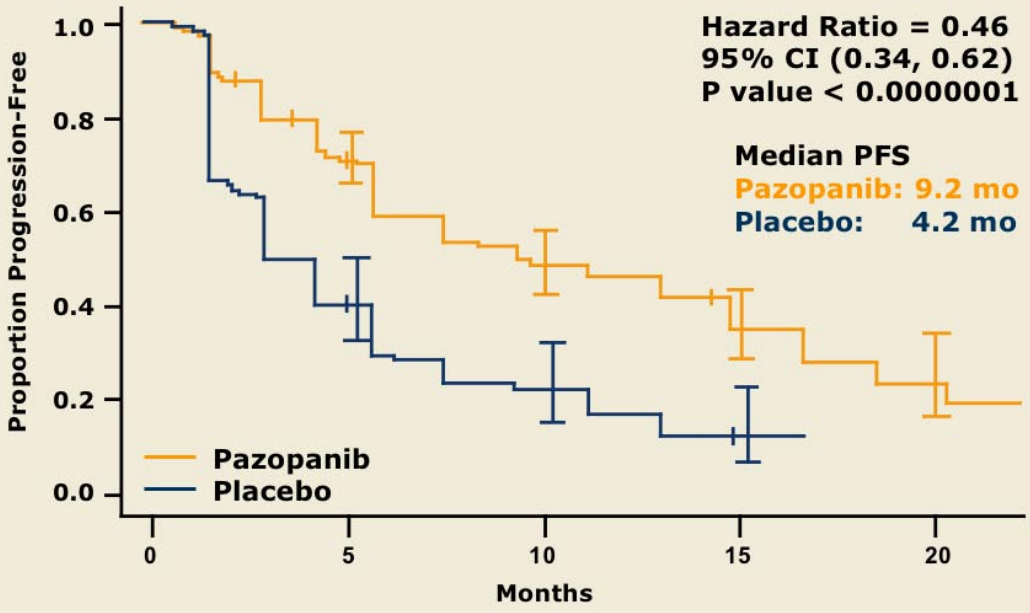
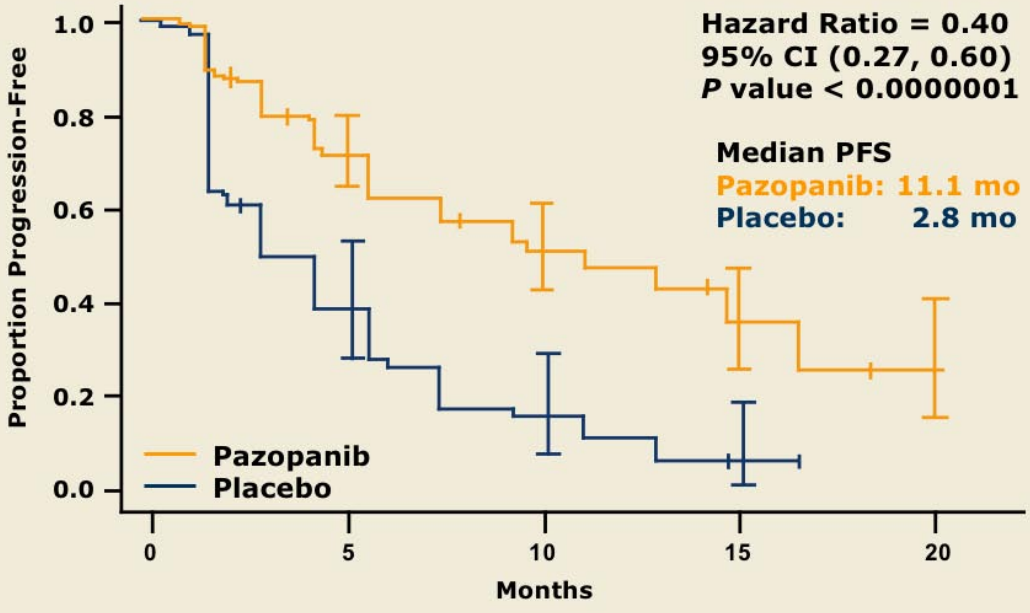
PFS in the Overall Study Population



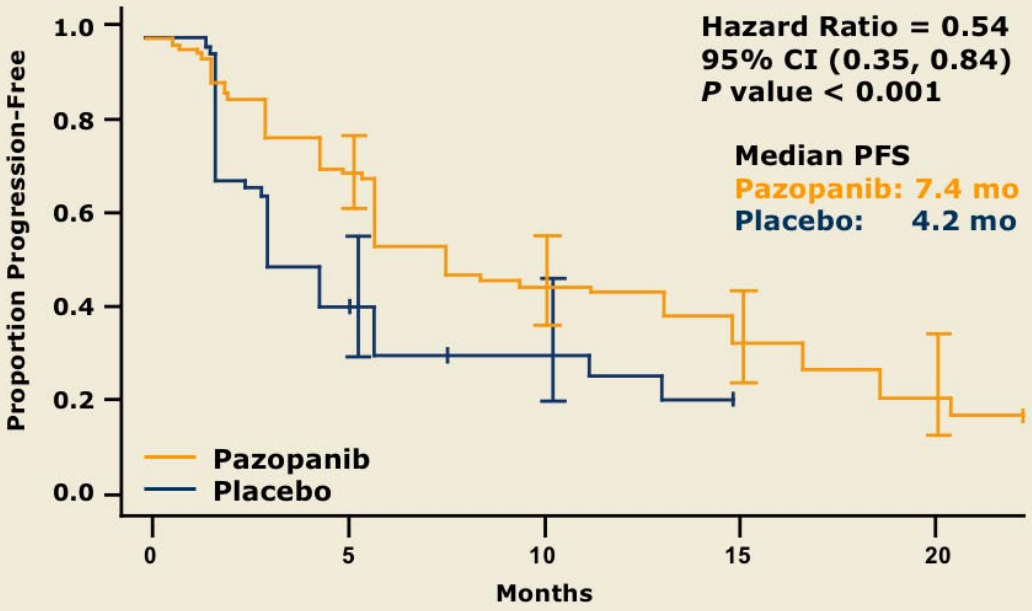
Source: Reprinted with permission. Sternberg CN et al. *ASCO* 2009; Abstract 5021.

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.

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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.

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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)

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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.

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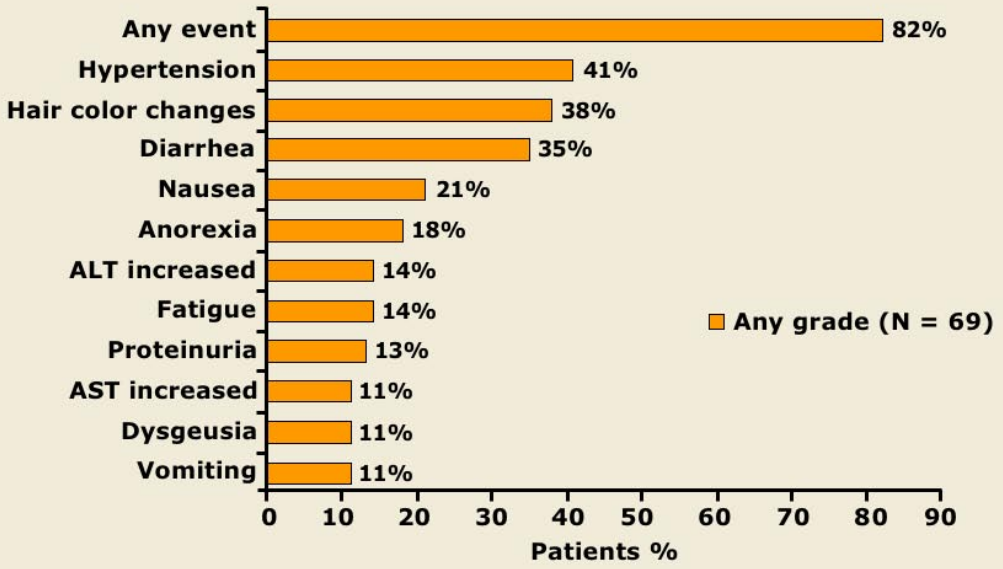
Treatment-Related Adverse Events in > 10% of Patients



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

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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.

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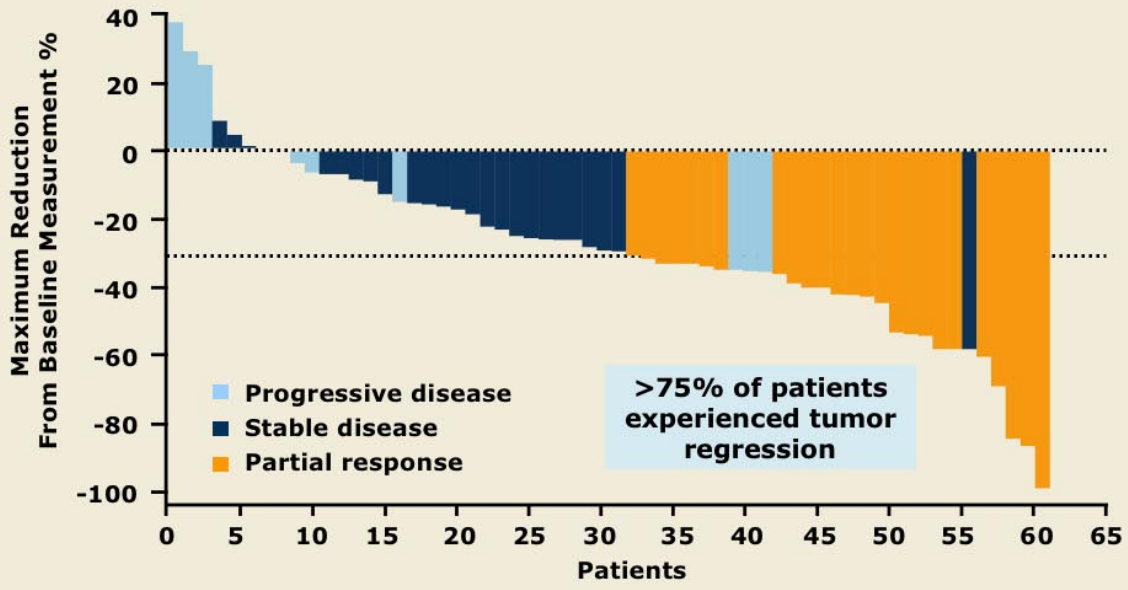
Maximum Decrease of Tumor Diameter from Baseline (Investigator-Assessed)



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

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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.

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