

## Oncology Highlights: ASCO 2009 Genitourinary Cancers

*Abstracts: 5011, 5018, LBA5019, 5020,  
5021, 5047, 5048, 5049*

Andrea Harzstark, M.D.  
Assistant Professor of Clinical Medicine  
Helen Diller Family Comprehensive Cancer  
Center  
Department of Medicine  
University of California, San Francisco

Slides courtesy of Charles Ryan, M.D.

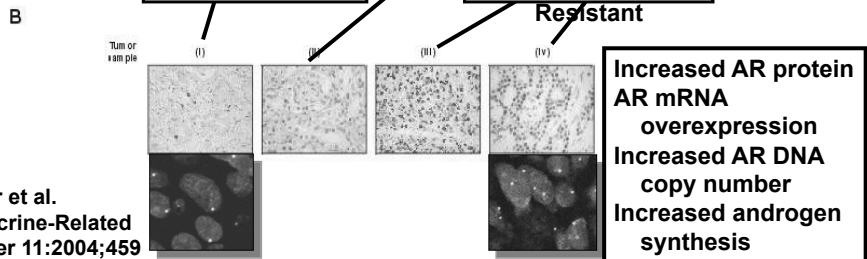
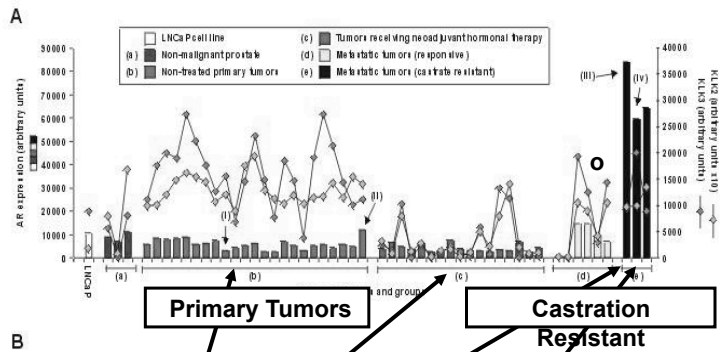
<b>Number</b>	<b>Disease</b>	<b>Author</b>	<b>Topic</b>
5011	Prostate Ca	Scher	MDV3100 – Novel Anti-Androgen
5018	Bladder Ca	Hahn	Gem/Cis/Bev in metastatic Urothelial Ca
LBA5019	Kidney Ca	Rini	IFN/Bev vs IFN – OS analysis
5020	Kidney Ca	Escudier	IFN/Bev vs IFN – Final results
5021	Kidney Ca	Sternberg	Pazopanib in metastatic RCC
5047	Prostate Ca	REID	Abiraterone in Docetaxel refractory PC
5048	Prostate Ca	Danila	Abiraterone in Docetaxel refractory PC
5049	Prostate Ca	Fleisher	CTC in Abiraterone treated patients

# Antitumor Activity of MDV3100 in a Phase 1-2 Study of Castration-Resistant Prostate Cancer

H. I. Scher, T. Beer, C. Higano, M. Taplin, E. Efstathiou, A. Anand, D. Hung, M. Hirmand, M. Fleisher, C. Sawyers

Memorial Sloan-Kettering Cancer Center, New York, NY; Oregon Health and Science University, Portland, OR; University of Washington, Seattle, WA; Dana Farber Cancer Institute, Boston, MA; M.D. Anderson Cancer Center, Houston, TX; Medivation, San Francisco, CA; and the Prostate Cancer Clinical Trials Consortium

## Androgen Receptor Overexpression is Frequent in Castration Resistant Tumors and is a Target for Therapy



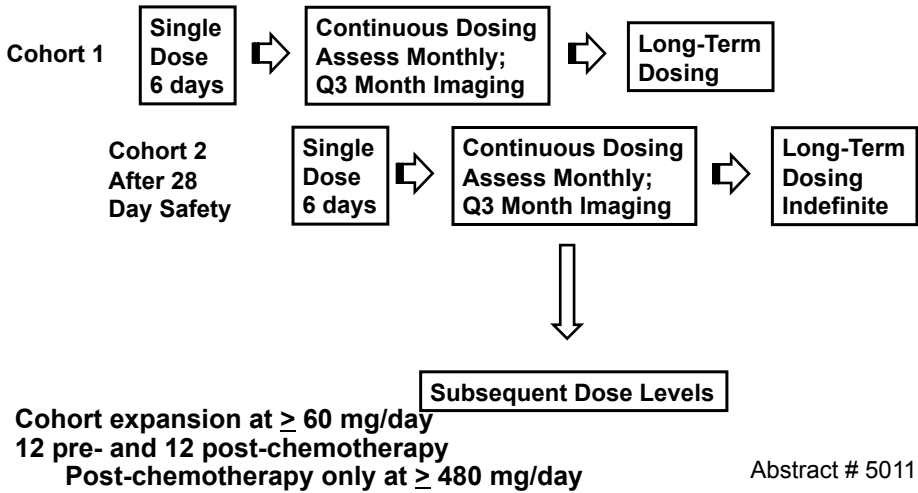
Scher et al. Endocrine-Related Cancer 11:2004;459

# MDV3100

## A Second-Generation Antiandrogen

1. Engineered for activity in prostate cancer cells that overexpress the androgen receptor (AR).
2. Binds the AR more potently than bicalutamide.
3. Unlike bicalutamide, MDV3100 inhibits nuclear translocation of the AR and its binding to DNA.
4. Induces apoptosis in prostate cancer cells.

### Trial Design



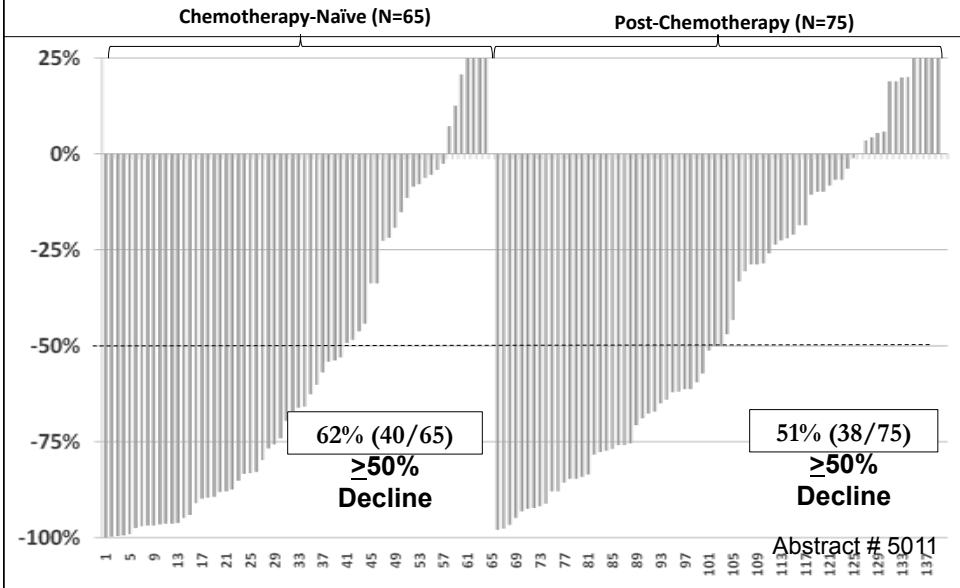
**MDV3100 Was Generally Well-Tolerated**  
Possibly Related Grade 2/3 Adverse Events in 2 Patients

Adverse Event	All Doses (N = 140)		≤240 mg/day (N = 60)	
	G2	G3	G2	G3
Fatigue	29 (21%)	12 (9%)	8 (13%)	3 (5%)
Nausea	11 ( 8%)	-	2 ( 3%)	-
Anorexia	4 ( 3%)	-	-	-
Seizure	-	3 (2%)	-	-

1. Only one subject discontinued treatment due to fatigue which coincided with disease progression
2. There were 2 witnessed seizures (1 each at 600 and 360 mg/day) and a possible unwitnessed seizure (at 480 mg/day).
  - Both patients with witnessed seizures were taking concomitant medications that can cause seizure
3. MTD determined to be 240 mg/day; patients at higher doses were lowered to 240 mg/day

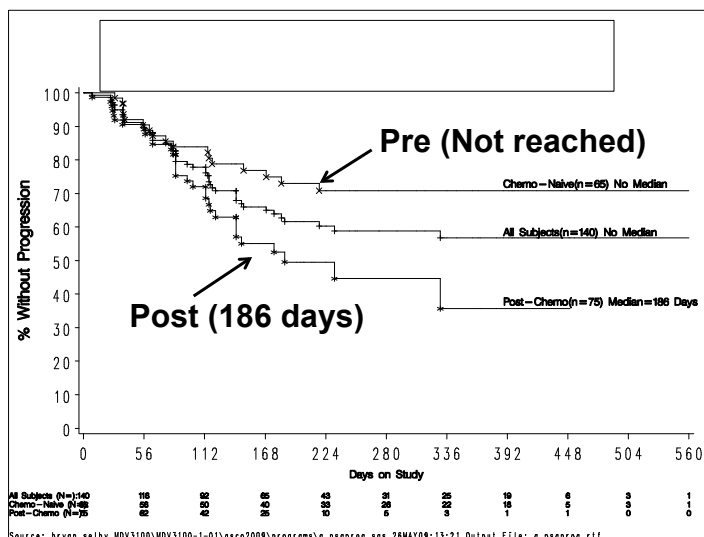
Abstract # 5011

**Waterfall Plot of Best Percent PSA  
Change from Baseline**



Abstract # 5011

## Time to PSA Progression For Pre- and Post-Chemotherapy Treated Patients



## Summary and Conclusions

- MDV3100 is a second-generation antiandrogen engineered for activity in cells that overexpress AR, unique from bicalutamide.
- The drug is active in CRPC both **before** and **after** chemotherapy as shown by:
  - declines in PSA, imaging, CTC conversion rates, and PET
- MDV3100 is generally well-tolerated
- A **Phase 3** placebo-controlled survival trial in post-docetaxel CRPC patients is beginning this year

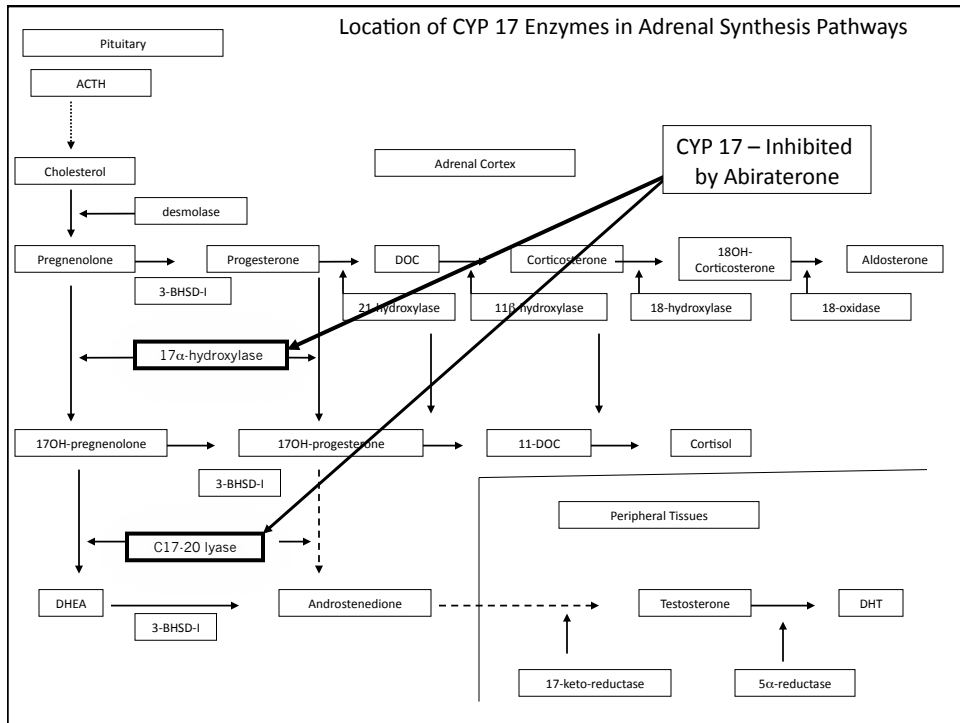
Dose selected to be 240 mg/day based upon:

- Significant anti-tumor effects plateau at this dose
- Few side effects
- Benefit:risk ratio

Abstract # 5011

# Abiraterone

Abstracts 5047,5048,5049



## Phase 2 multicenter study of abiraterone acetate plus prednisone therapy in docetaxel treated CRPC patients: Impact of prior ketoconazole.

Danila D<sup>1</sup>, de Bono J<sup>2</sup>, Ryan C<sup>3</sup>, Denmeade S<sup>4</sup>, Smith M<sup>5</sup>, Taplin ME<sup>6</sup>, Bubley G<sup>7</sup>, Molina A<sup>8</sup>, Haqq C<sup>8</sup>, Scher H<sup>9</sup>

<sup>1</sup>Department of Medicine, Joan and Sanford E. Weill College of Medicine of Cornell University, New York, New York; <sup>2</sup>Cancer Research UK Centre for Cancer Therapeutics, Institute of Cancer Research, Royal Marsden Hospital, UK; <sup>3</sup>University of California-San Francisco Comprehensive Cancer Center, San Francisco CA; <sup>4</sup>Chemical Therapeutics Program, The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD; <sup>5</sup>Division of Hematology-Oncology Massachusetts General Hospital, Boston, MA; <sup>6</sup>Dana-Farber Cancer Institute, Harvard Medical School, Boston MA; <sup>7</sup>Beth Israel Deaconess Medical Center, Boston, MA; <sup>8</sup>Department of Clinical Research and Development, Cougar Biotechnology, Los Angeles, CA; <sup>9</sup>Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY.

Abstract No: 5048

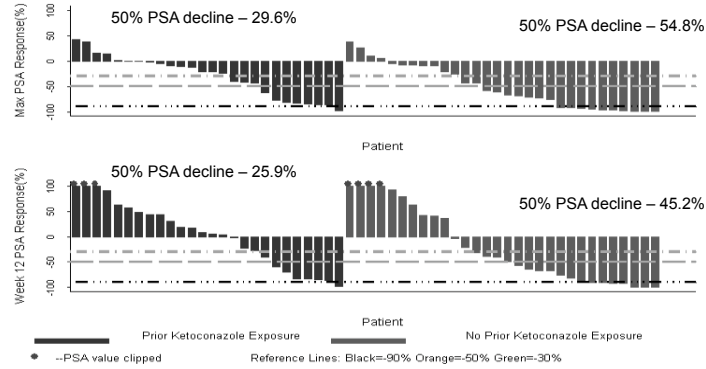
## COU 004 – Abiraterone + Prednisone: Baseline Patient Characteristics

(N=58)

<b>Age (Median)</b>	69.5 years (range 44-86)
<b>ECOG Performance Status</b>	<b>n (%)</b>
ECOG 0	24 (41.1)
ECOG 1	31 (53.4)
ECOG 2	2 ( 3.4)
Unknown	1 ( 1.7)
<b>Prior Hormonal Therapies:</b>	<b>n (%)</b>
LHRH Agonists	57 (98.3) <sup>1</sup>
Antiandrogens	53 (91.4)
Estrogens	9 (15.5)
Diethylstilbestrol	8 (13.8)
Other estrogens	1 ( 1.7)
Steroids	21 (36.2)
Dexamethasone	5 ( 8.6)
Other Steroids	20 (34.5)
Ketoconazole	27 (46.6)
Orchiectomy	3 ( 5.2)

Abstract No: 5048

### Change in PSA with Treatment (N=58)



In this study, the comparison between the decline in PSA >50% in keto-naïve patients vs. keto exposed patients was not statistically significant (p=0.07).

**Abstract No: 5048**

### Circulating tumor cells (CTC) in patients with metastatic castration-resistant prostate cancer (CRPC) receiving abiraterone acetate (AA) after failure of docetaxel-based chemotherapy.

M. Fleisher, D. C. Danila, M. Leversha, D. Rathkopf, S. Slovin, A. Anand, M. Koscuizka, C. Haqq, H. I. Scher

**Abstract No: 5049**

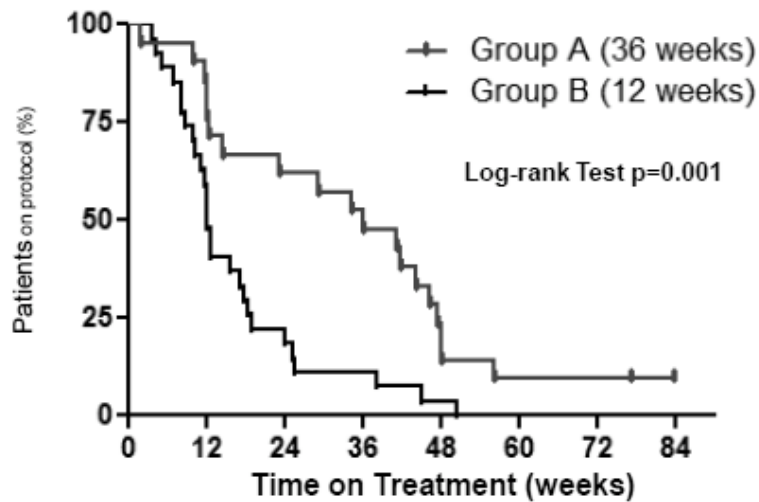
## Investigators monitored changes in CTC number with therapy in patients treated with abiraterone therapy

Pts #(48pts total)	Baseline CTC	Post Therapy CTC	PSA decline>50%	Time on protocol
11 (23%)	> 5 CTC	< 5 CTC	9	Group A
11 (23%)	< 5 CTC	< 5 CTC	4	
24 (50%)	> 5 CTC	> 5 CTC	4	Group B
2 (4%)	< 5 CTC	> 5 CTC	1	

Among pts with baseline CTC > 5, the CTC decline to <5 was associated with a decline in PSA by >50% (p< 0.001).

Changes in CTC with treatment may represent valuable intermediary endpoints for clinical benefit.

**Abstract No: 5049**



Group A = < 5 post therapy CTCs  
Group B = >5 post therapy CTCs

## Bladder Cancer

**A multicenter phase II study of cisplatin (C), gemcitabine (G), and bevacizumab (B) as first-line therapy for metastatic urothelial carcinoma (UC): Hoosier Oncology Group GU04-75**

**Abstract #5018**

N. M. Hahn<sup>1</sup>, W. M. Stadler<sup>2</sup>, R. T. Zon<sup>3</sup>,  
D. Waterhouse<sup>4</sup>, J. Picus<sup>5</sup>, S. Nattam<sup>6</sup>, C.  
S. Johnson<sup>7</sup>, S. M. Perkins<sup>7</sup>, M. J.  
Waddell<sup>1</sup>, C. J. Sweeney<sup>1,8</sup>

<sup>1</sup>Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, <sup>2</sup>University of Chicago Cancer Research Center, Chicago, IL, <sup>3</sup>Northern Indiana Cancer Research Consortium, South Bend, IN, <sup>4</sup>Oncology and Hematology Care Inc., Cincinnati, OH, <sup>5</sup>Washington University School of Medicine Siteman Cancer Center at Barnes-Jewish Hospital, St. Louis, MO, <sup>6</sup>Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, <sup>7</sup>Indiana University School of Medicine, Division of Biostatistics, <sup>8</sup>University of Adelaide, Adelaide, Australia

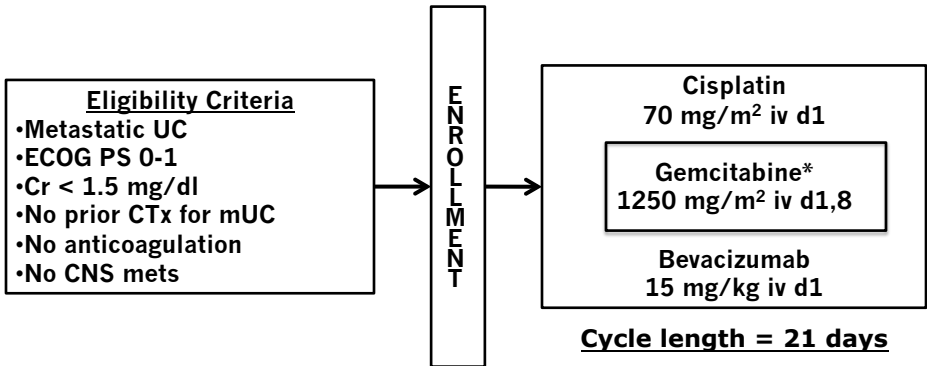
# Statistical Design

- Primary Endpoint
    - Progression Free Survival (PFS)
  - Secondary Endpoints
    - Response Rates
    - Toxicity
    - Overall Survival (OS)
- $(H_0)$  PFS = 7.5 months<sup>1</sup>
  - $(H_1)$  PFS = 11.25 months
  - $\alpha=0.10, \beta=0.14$
  - Sample size = 40
  - 10% dropout rate expected
  - Final sample size = 45

<sup>1</sup>Von der Maase H, et al, JCO 2000;17:3068-77

Abstract #5018

# Gem/Cis/Bev -Study Schema



- Maximum of 8 cycles of Cisplatin and Gemcitabine
- Maximum 1 year of Bevacizumab therapy
- \*Gemcitabine reduced to 1000 mg/m<sup>2</sup> iv d1,8 after first 17 patients due to 7 DVT/PE events

Abstract #5018

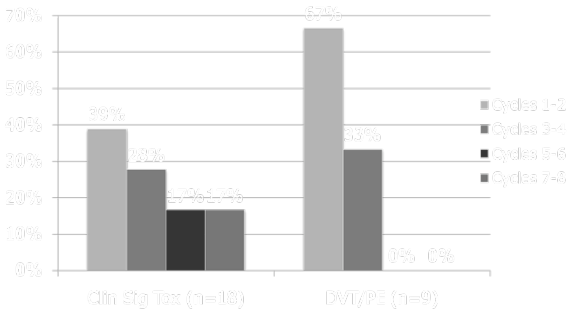
# Non-Hematologic Toxicity

	Gem 1250 (n=18)	Gem 1000 (n=25)	Total (n=43)
	Gr 3-4 %	Gr 3-5 %	Gr 3-5 %
<b>DVT/PE</b>	<b>39</b>	<b>8</b>	<b>21</b>
<b>HTN</b>	<b>6</b>	<b>4</b>	<b>5</b>
<b>Proteinuria</b>	<b>6</b>	<b>0</b>	<b>2</b>
<b>Hemorrhage</b>	<b>0</b>	<b>12*</b>	<b>7*</b>

\*One treatment related death due to cerebral hemorrhage was observed

Abstract #5018

# Toxicity and Conclusions



- Bevacizumab adds significant toxicity
- The PFS of 8.2 months did not meet the designed primary endpoint
- The OS of 19.1 months is beyond that expected from cisplatin plus gemcitabine alone

Abstract #5018

## Renal Cell Carcinoma

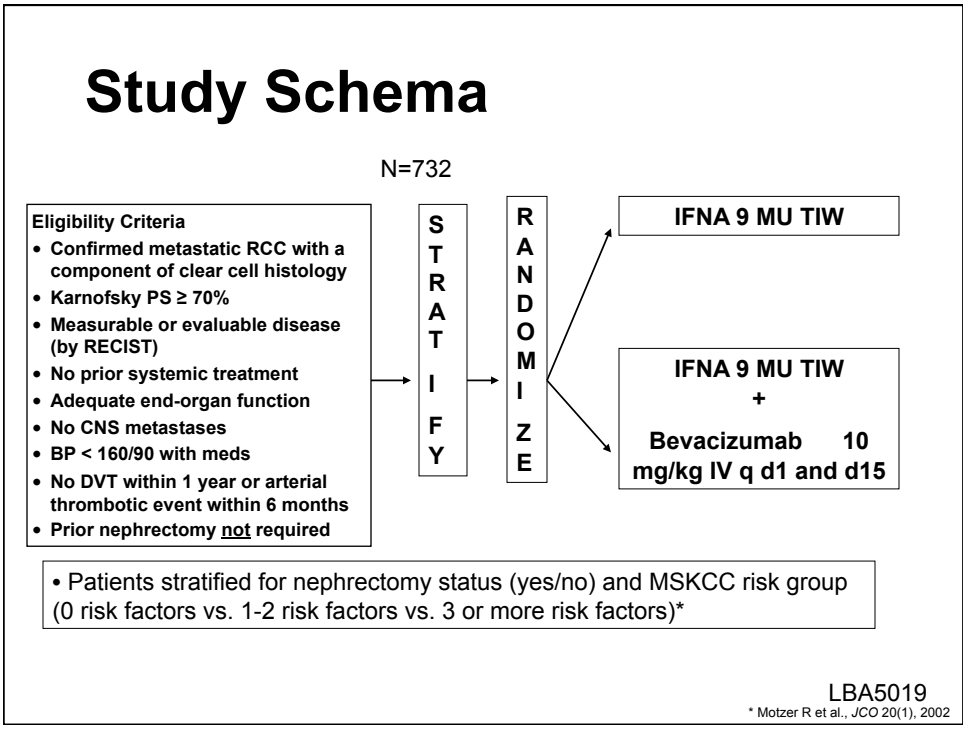
### **Bevacizumab plus Interferon-alpha versus Interferon-alpha Monotherapy in Patients with Metastatic Renal Cell Carcinoma: Results of Overall Survival for CALGB 90206**

Brian I. Rini<sup>1</sup>, Susan Halabi<sup>2,3</sup>, Jonathan E. Rosenberg<sup>4</sup>, Walter M. Stadler<sup>5</sup>, Daniel A. Vaena<sup>6</sup>, James N. Atkins<sup>7</sup>, Joel Picus<sup>8</sup>, Piotr Czaykowski<sup>9</sup>, Janice Dutcher<sup>10</sup> and Eric J. Small<sup>4</sup>

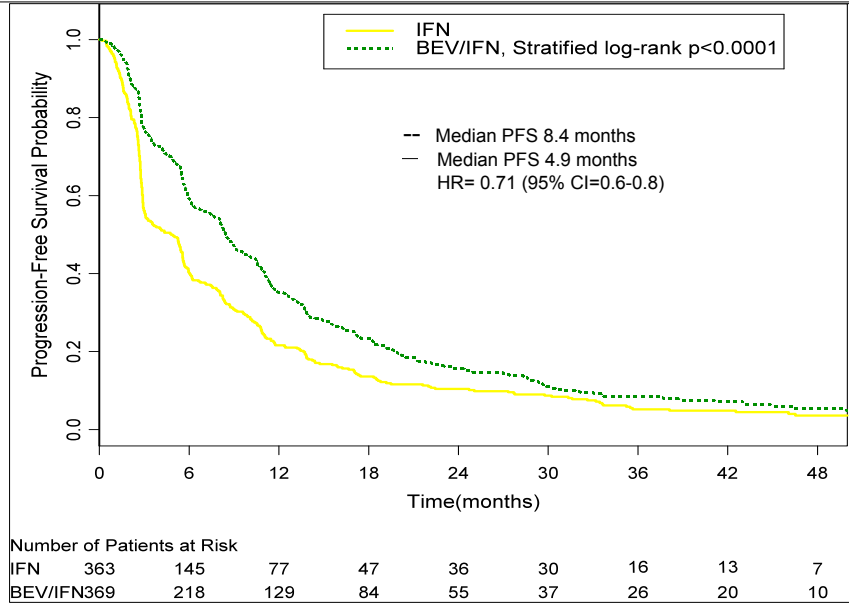
Bevacizumab FDA approved for use in combination with interferon alpha for metastatic RCC 8/3/09

LBA5019

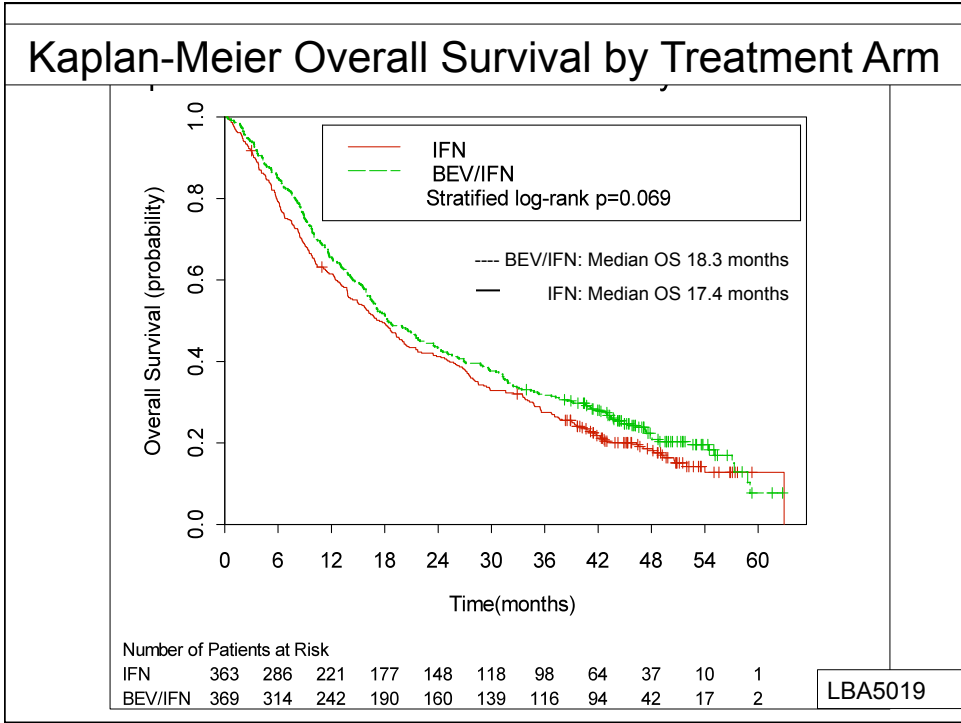
# Study Schema



## Kaplan-Meier Progression-Free Survival by Treatment Arm



LBA5019



### Second-line Therapy Received in Patients who Discontinued Protocol Therapy for Any Reason Other Than Death

	Bevacizumab + IFN (n=351)	IFN monotherapy (n=350)
Percentage of patients receiving <u>any</u> second-line therapy	54%	62%
VEGF-targeted therapy	37%	46%
Bevacizumab	6%	14%
Chemotherapy	18%	14%
Investigational therapy	11%	18%
Cytokines	13%	14%

\* Fifty-six percent of patients overall received at least one subsequent systemic therapy

LBA5019

## Median OS (months) according to treatment arm and subsequent therapy

	Bevacizumab + Interferon	Interferon	Total (unstratified log-rank p comparing arms)	Stratified HR
Received 2 <sup>nd</sup> -line therapy (n=408)	31.4	26.8	28.2 (p=0.079)	0.80 (p=0.055)
Did not receive 2 <sup>nd</sup> -line therapy (n=324)	13.1	9.1	10.2 (p=0.059)	0.82 (p=0.108)
<b>Total</b>	18.3	17.4	18.1 (p=0.097)	0.86 (p=0.069)

LBA5019

## Objective Response

	Bev + IFN (n=325)	IFN (n=314)
Overall Response rate	25.5% [95% CI = 20.9-30.6]	13.1% [95% CI = 9.5-17.3]
CR	3.7%	1.9%
PR	23.4%	12.7%
p < 0.0001		
Duration of response	11.9 months [95% CI = 8.3 – 14.8]	9.7 months [95% CI = 7.6 – 19.8]
p = 0.362		

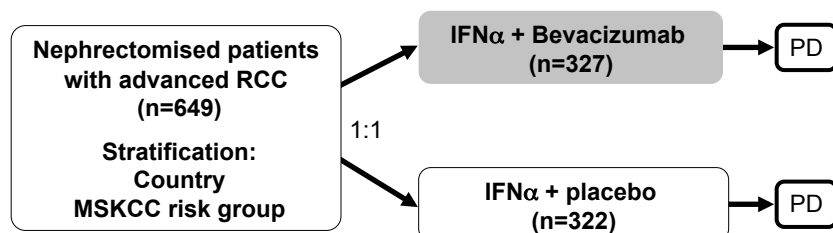
Note: patients with measurable disease only

## Final results of the phase III, randomised, double-blind AVOREN trial of first-line bevacizumab + interferon- $\alpha$ 2a in metastatic renal cell carcinoma

Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S,  
Ravaud A, Golding S, Jethwa S on behalf of the AVOREN  
investigators

Abstract # 5020

### AVOREN study design



- Endpoints
  - primary:\* OS
  - secondary: PFS, TTP, TTF, RR, safety
- Treatment
  - bevacizumab/placebo 10mg/kg i.v. q2w
  - IFN 9MIU s.c. t.i.w. (maximum 52 weeks)

Abstract # 5020  
\*PFS is the primary endpoint for regulatory approval in the USA  
Escudier, et al. Lancet 2007

## Summary of published AVOREN data

- Final analysis of PFS performed at the time of the interim analysis
  - significant increase from 5.4 to 10.2 months when bevacizumab is combined with IFN (HR=0.63; p=0.0001)<sup>1</sup>
  - good safety profile
- By reducing the IFN dose for safety issues
  - PFS benefit is maintained<sup>2</sup>
  - decreased incidence of grade 3/4 events<sup>2</sup>

Abstract # 5020

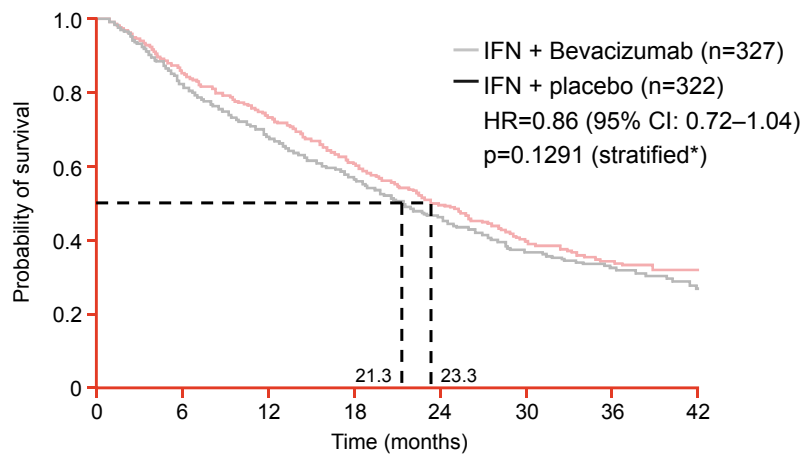
1. Escudier, et al. Lancet 2007; 2. Melichar, et al. Ann Oncol 2008

## Objectives

- Final analysis of OS
- Clinical cut-off September 2008
- Median follow-up: 22 months
- Statistical considerations
  - required 445 events from 649 randomised patients
  - 80% power to detect an improvement in OS from 13 to 17 months
  - corresponding to an HR of 0.76 at a two-sided overall significance level of 0.05

Abstract # 5020

## Final OS



Abstract # 5020

\*Stratified by Motzer score and region

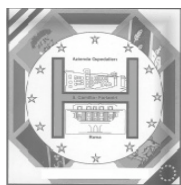
## OS by post-protocol therapies

	IFN + Bevacizumab vs IFN + placebo (n)	Median OS		HR (95% CI)
		IFN + Bevacizumab (months)	IFN + placebo (months)	
Subsequent TKI*‡	113 vs 120	<b>38.6</b>	<b>33.6</b>	0.80 (0.56–1.13)
Subsequent sunitinib	83 vs 92	<b>43.6</b>	<b>39.7</b>	0.88 (0.58–1.35)
Subsequent sorafenib	60 vs 50	<b>38.6</b>	<b>30.7</b>	0.73 (0.44–1.20)

\*Subsequent therapy defined as any post-protocol therapy, any line (before or after PD)

‡TKIs include sunitinib, sorafenib, pazopanib, erlotinib, blinded sorafenib, blinded sunitinib and unspecified protein TKI

Abstract # 5020



## Phase III Trial of Pazopanib in Locally Advanced and/or Metastatic Renal Cell Carcinoma

Cora N. Sternberg,<sup>1</sup> Cezary Szczylik,<sup>2</sup> Eun S. Lee,<sup>3</sup>  
 Pamela Salman,<sup>4</sup> Jozef Mardiak,<sup>5</sup> Ian D. Davis,<sup>6</sup>  
 Lini Pandite,<sup>7</sup> Mei Chen,<sup>8</sup> Lauren McCann,<sup>8</sup>  
 Robert E. Hawkins<sup>9</sup>

<sup>1</sup>San Camillo and Forlanini Hospitals, Rome, Italy; <sup>2</sup>Military Institute of Medicine, Warsaw, Poland; <sup>3</sup>National Cancer Center, Gyeonggi-do, Korea; <sup>4</sup>Fundación Arturo López Pérez, Santiago, Chile; <sup>5</sup>National Oncological Institute, Klenová, Bratislava, Slovakia; <sup>6</sup>Austin Hospital, Melbourne, Australia; <sup>7</sup>GlaxoSmithKline, Inc., Research Triangle Park, NC, USA; <sup>8</sup>GlaxoSmithKline, Inc., Collegeville, PA, USA; <sup>9</sup>University of Manchester and Christie Hospital NHS Foundation Trust, Manchester, UK **Abstract No:** 5021

## Pazopanib

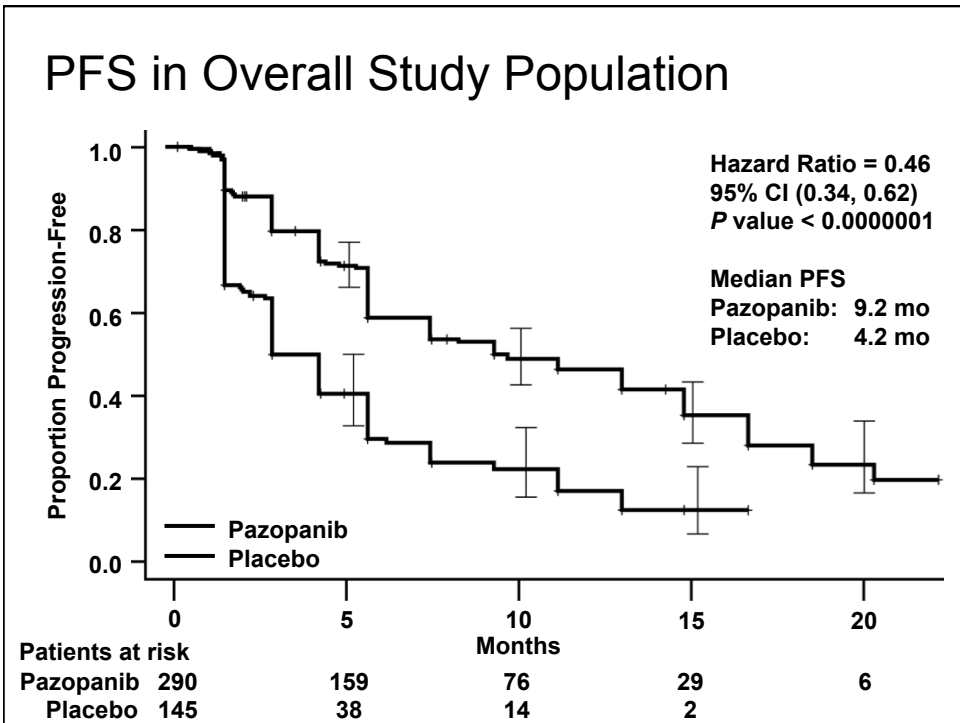
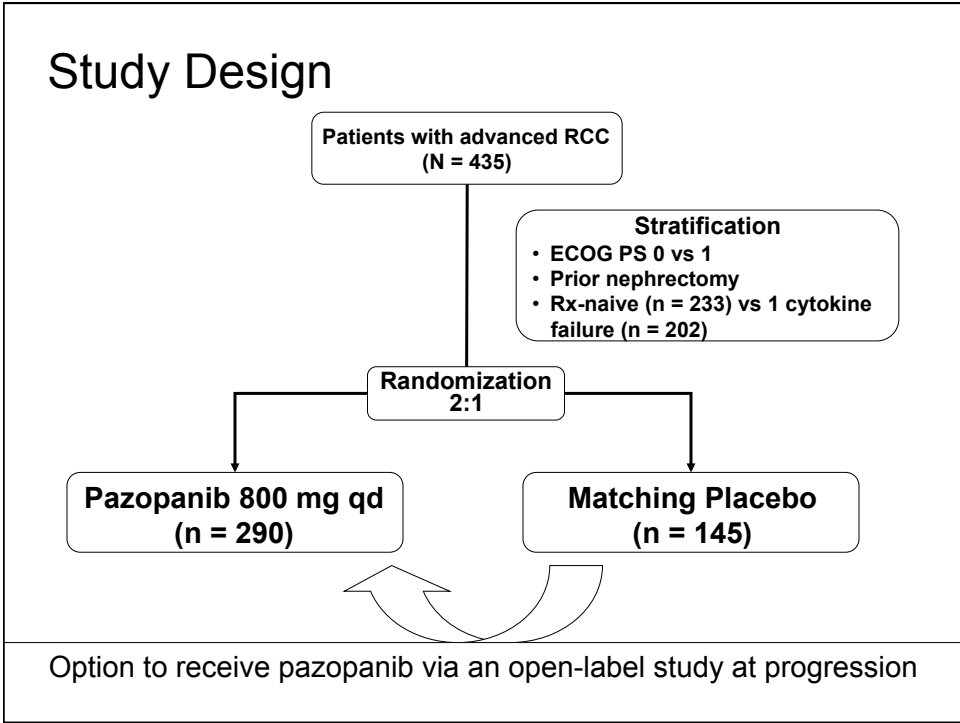
- An oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit
- Clinical efficacy demonstrated in advanced RCC in a Phase II study<sup>1</sup>

### Kinase affinity profile

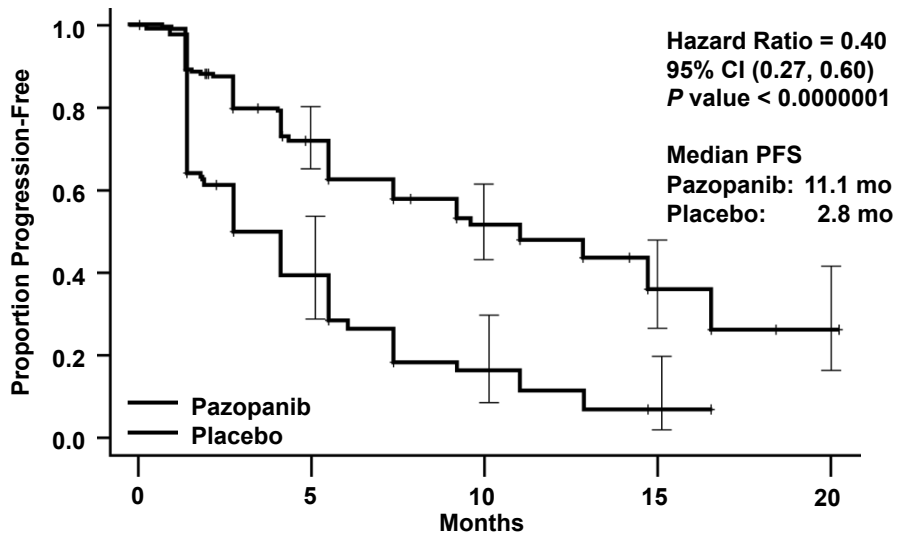
	$K_i^{app}$ (nM)
VEGFR-1	15
VEGFR-2	8
VEGFR-3	10
PDGFR- $\alpha$	30
PDGFR- $\beta$	14
c-Kit	2.4

**Abstract No:** 5021

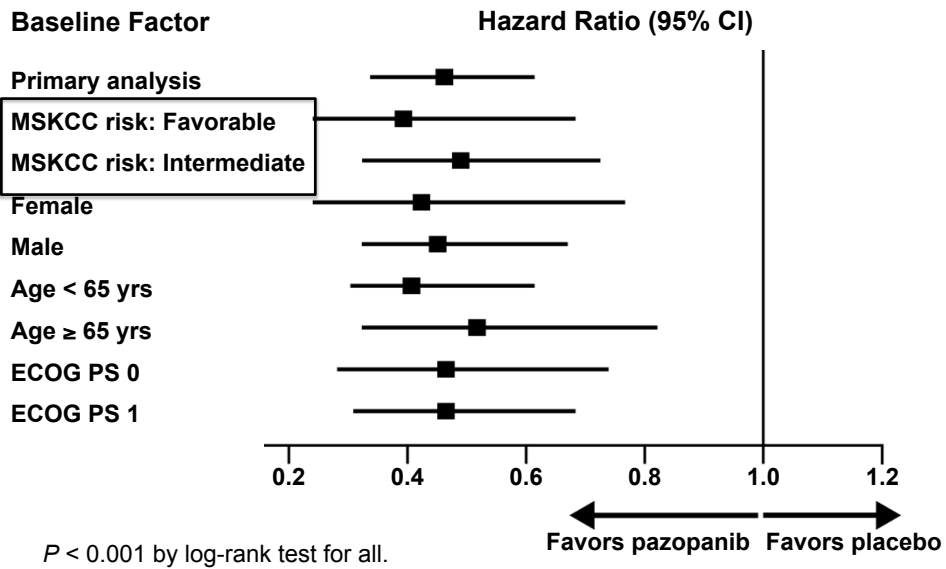
1. Hutson TE, et al. *J Clin Oncol*. 2007;25(suppl):18S:5031.

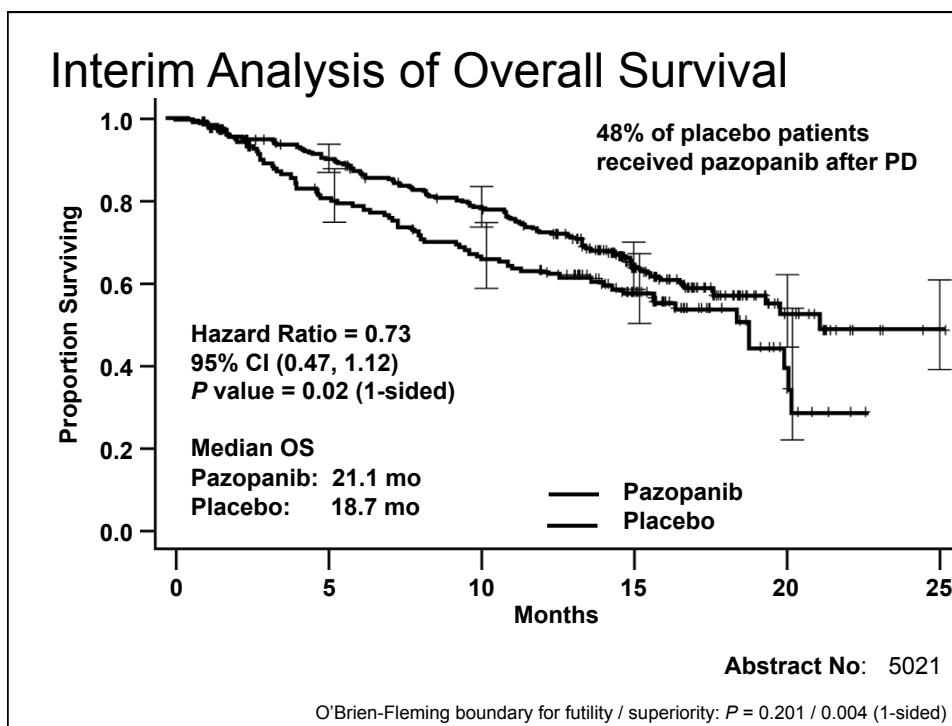


### PFS in Treatment-Naive Subpopulation



### Subgroup Analysis of PFS





### Most Common Adverse Events ( $\geq 10\%$ )

Adverse Event	Pazopanib (n = 290) %			Placebo (n = 145) %		
	All Grs	Gr 3	Gr 4	All Grs	Gr 3	Gr 4
Any event <sup>a</sup>	92	33	7	74	14	6
Diarrhea	52	3	< 1	9	< 1	0
Hypertension	40	4	0	10	< 1	0
Hair color changes	38	< 1	0	3	0	0
Nausea	26	< 1	0	9	0	0
Anorexia	22	2	0	10	< 1	0
Vomiting	21	2	< 1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Hemorrhage <sup>b</sup>	13	1	< 1	5	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

<sup>a</sup> 4% of patients in pazopanib arm and 3% of patients in placebo arm had grade 5 adverse events.

<sup>b</sup> Included hemorrhage from all sites; 1% patients in pazopanib arm had grade 5 events.

**Median exposure: pazopanib 7.4 (0 - 23) vs placebo 3.8 (0 - 22) months**

## Pazopanib Summary

- Significant improvement in PFS and RR compared with placebo in treatment-naïve and cytokine-pretreated patients
- Significant improvement in PFS was observed in all subgroups
- The safety profile was acceptable
- Interim OS data are not yet mature
- FDA decision expected November 2009
  
- *Probably the last placebo arm study in TKI naïve patient population*

**Thank you**