

ASCO 2009

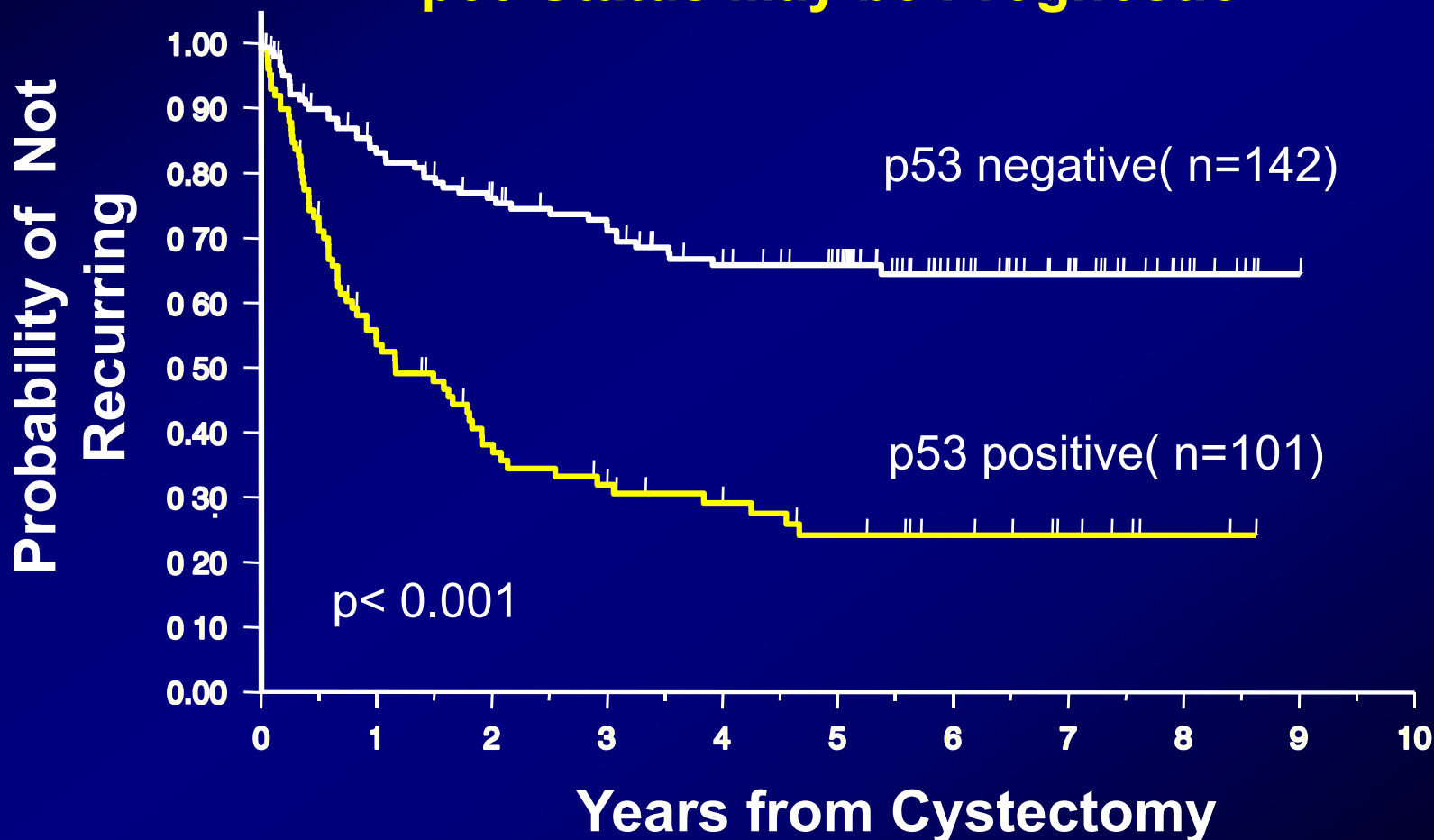
GU Malignancies:
Bladder, Renal, Prostate
Dean Bajorin, MD, FACP

Bladder Cancer Themes

1. Can p53 select patients more likely to benefit from adjuvant chemotherapy? (Abstract 5017)
2. New drugs targeting the VEGF axis. Does bevacizumab added to gemcitabine + carboplatin result in better response and survival? (Abstract 5018)
3. What is the true risk of vascular thrombotic events (VTE) in urothelial cancer? (Abstract 5074)

Abstract 5017. Stadler et al. SWOG Phase III Trial of p53 Targeted Adjuvant Therapy for Patients with Organ- Confined Node-Negative Urothelial Bladder

p53 Status May be Prognostic



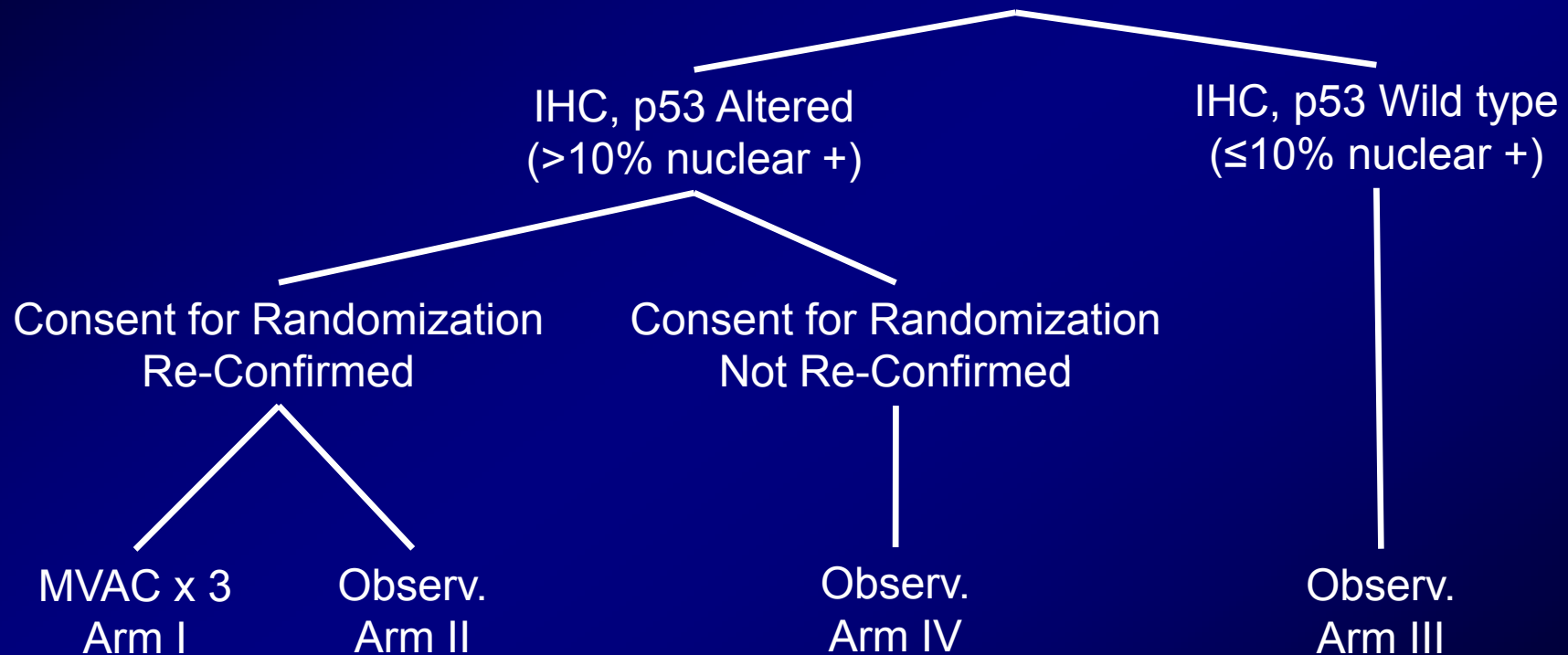
p53 Status May be Predictive of Chemotherapy Benefit

- USC randomized trial of adjuvant chemotherapy versus observation
 - Improved time to recurrence (TTR)
 - No improvement in overall survival (OS)
- Retrospective assessment of p53 status and outcome (chemo vs. observation)

<i>p53 Status</i>	<i>TTR relative risk</i>	<i>OS relative risk</i>
<i>Wild type</i>	<i>1.1 (p = 0.89)</i>	<i>1.0 (p = 1.00)</i>
<i>Mutant</i>	<i>3.0 (p = 0.006)</i>	<i>2.6 (p = 0.005)</i>

STUDY DESIGN

Radical Cystectomy (P1, P2a, P2b, NO, MO)
Registration - Consent to p53 Analysis and
Randomized Trial



Specific Aims

- Compare survival patients with tumors with mutant p53 treated with M-VAC to those who are observed.
- Compare survival patients with mutant p53 tumors who are observed to patients wild-type p53 who are also observed.

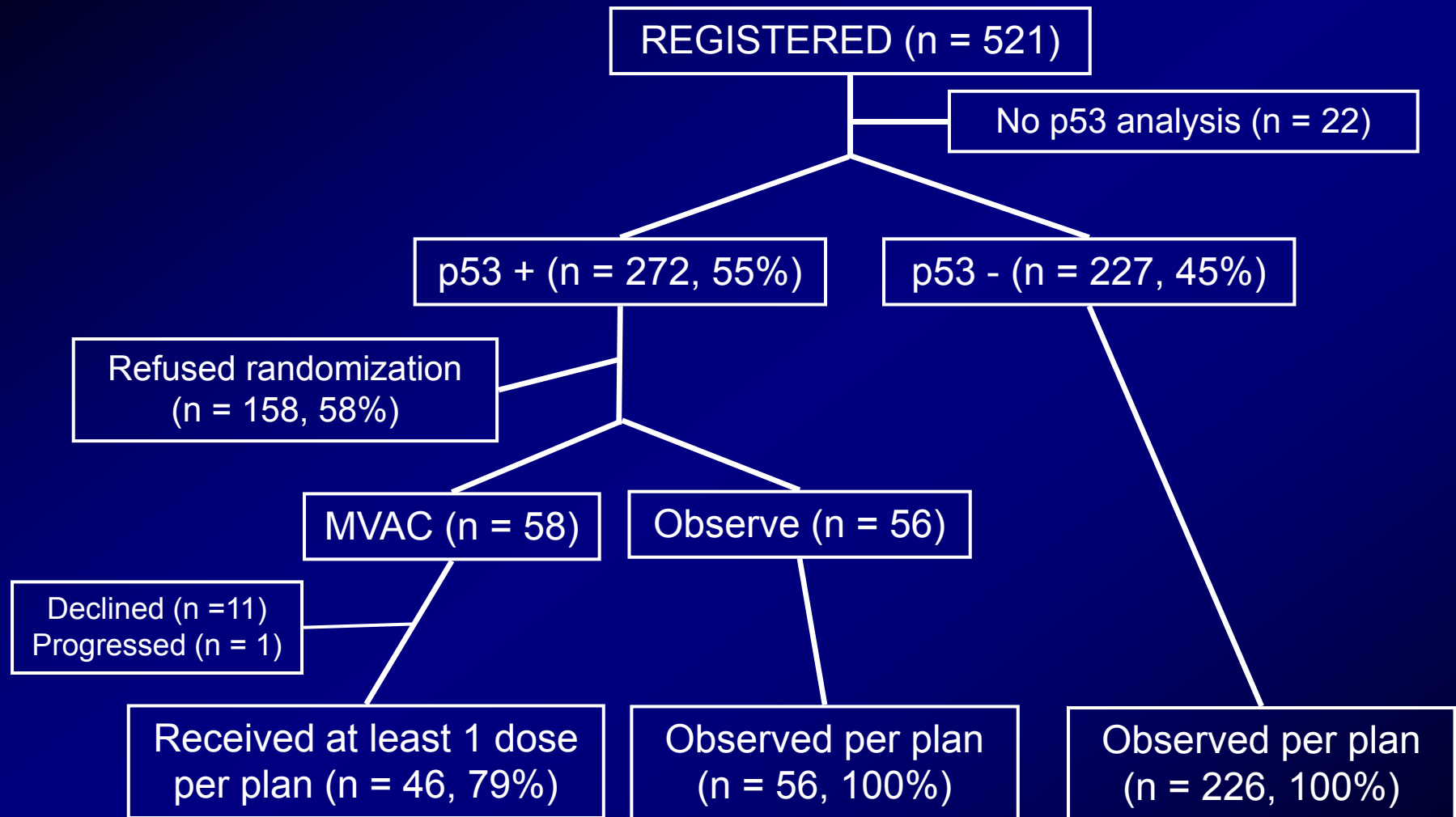
Eligibility Criteria

- P1 – P2 on radical cystectomy + bilateral PLND
- No previous RT or systemic chemotherapy
- ECOG 0 – 1
- Creatinine \leq 1.8 mg/dl; LFT's \leq 2x ULN
- No metastatic disease (CT if < 15 PLN removed)

Statistical Design

- Sample Size Calculations:
 - Detect absolute recurrence rate improvement of 20% at three yrs (N=190)
 - 50% to 70%: TTR HR = 0.52
 - 60% to 80%: TTR HR = 0.44
 - $\alpha=0.05$ (1-sided); power $(1-\beta) = 0.86 - 0.90$
- Planned Interim Analysis: 100 pts
- The DSMB reviewed the first 110 randomized pts and recommended study closure based on a futility analysis suggesting that the probability of detecting a significant difference in TTR in the randomized population would be highly unlikely.

STUDY CONDUCT



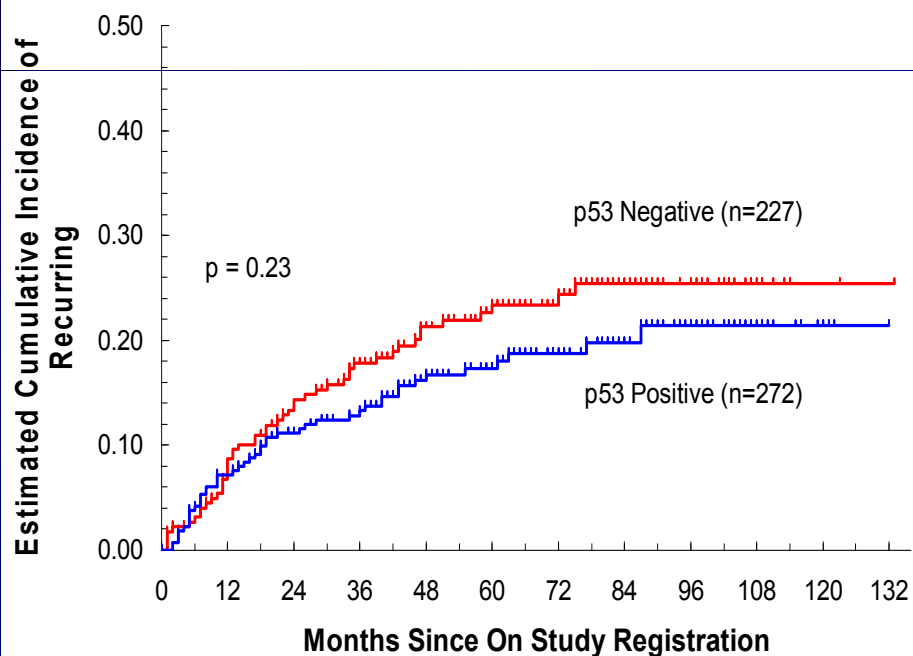
Baseline Characteristics

Factors	p53 Status		p-value
	p53 Negative	p53 Positive	
Total patients	227 (45%)	272 (55%)	
Lymph nodes removed			0.14
<15	68 (30%)	98 (36%)	
≥15	159 (70%)	173 (64%)	
Missing	0	1	
Lymphovascular Invasion			0.97
No	117 (52%)	142 (52%)	
Yes	46 (20%)	56 (21%)	
Missing	64 (28%)	74 (27%)	
p21 Status			<0.001
Absent	35 (16%)	110 (41%)	
Present	190 (84%)	160 (59%)	
Missing	2	2	

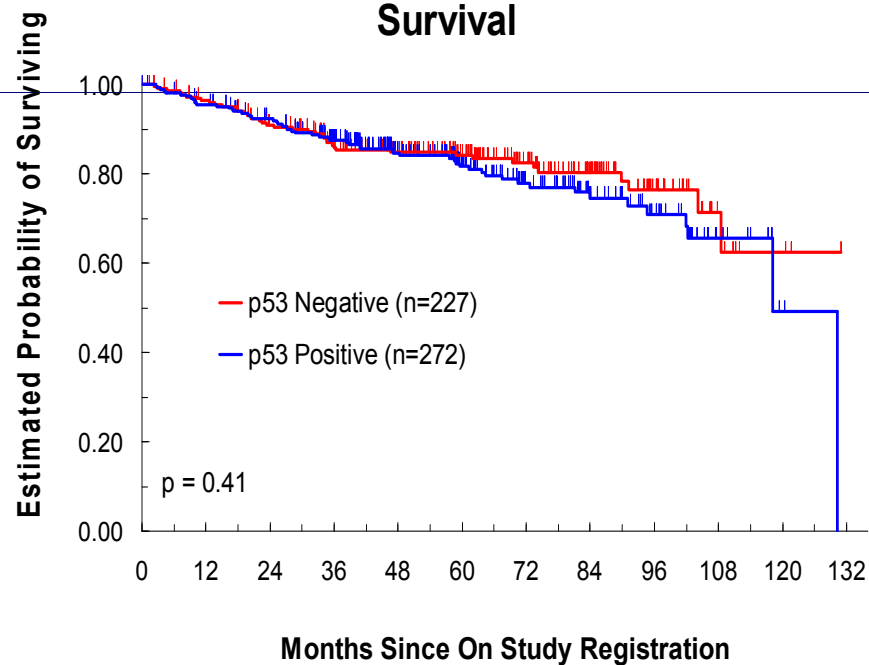
Factors	p53 Status		p-value
	p53 Negative	p53 Positive	
Total patients	227 (45%)	272 (55%)	
Age at Registration			0.59
<65	127 (56%)	159 (58%)	
≥65	100 (44%)	113 (42%)	
Gender			0.43
Female	49 (22%)	50 (18%)	
Male	178 (78%)	222 (82%)	
Race			0.24
Caucasian	203 (89%)	251 (92%)	
Black	13 (6%)	9 (3%)	
Asian	6 (3%)	3 (1%)	
Hispanic	3 (1%)	8 (3%)	
Other	2 (1%)	1 (1%)	
Stage			0.64
P1	87 (38%)	98 (36%)	

Association of p53 status with Recurrence and Survival

Association of p53 Status with Recurrence



Association of p53 Status with Overall Survival

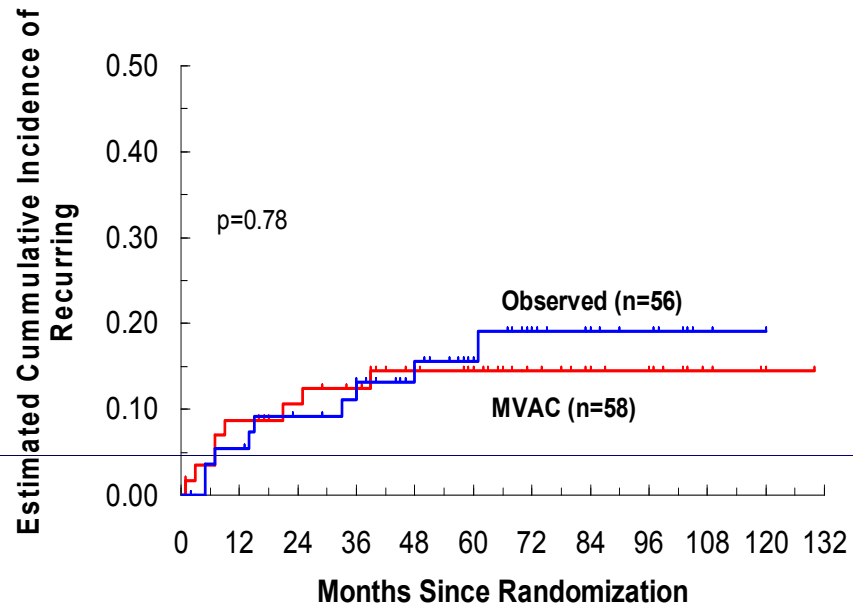


Randomized Pt Characteristics

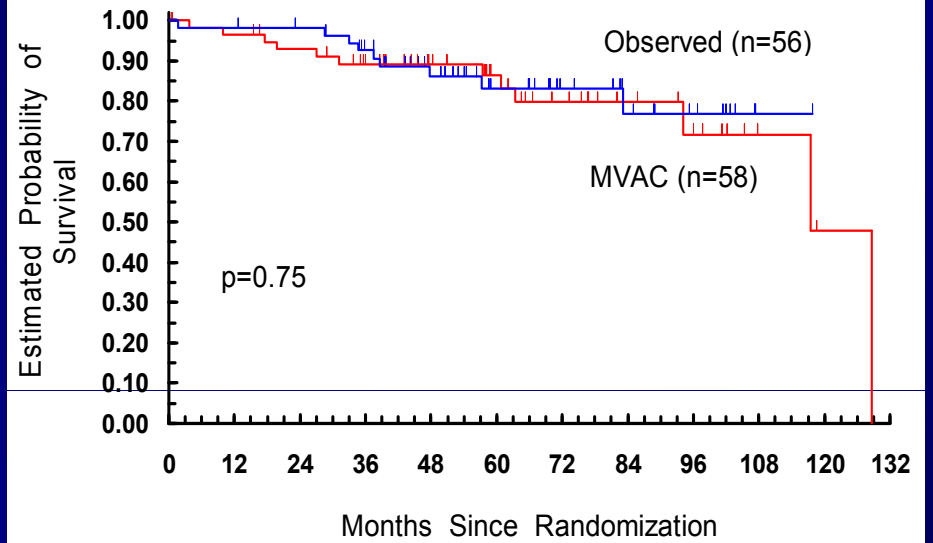
Factors	Treatment Arm		p-value
	MVAC	Observation	
Total patients	58 (51%)	56 (49%)	
Age at Registration			0.32
<65	37 (64%)	41 (73%)	
>65	21 (36%)	15 (27%)	
Gender			0.60
Female	7 (12%)	9 (16%)	
Male	51 (88%)	47 (84%)	
Stage			0.43
P1	21 (36%)	16 (29%)	
P2	37 (64%)	40 (71%)	
Grade			1.00
1 or 2	2 (3%)	1 (2%)	
3 or 4	56 (97%)	55 (98%)	

Factors	Treatment Arm		p-value
	MVAC	Observation	
Total patients	58 (51%)	56 (49%)	
Lymph nodes removed			0.24
<15	20 (34%)	14 (25%)	
≥15	37 (64%)	42 (75%)	
Missing	1 (2%)	0	
Lymphovascular invasion			0.38
No	33 (57%)	25 (45%)	
Yes	13 (22%)	14 (25%)	
Missing	12 (21%)	17 (30%)	
Bladder CIS			0.52
No	16 (27%)	12 (21%)	
Yes	34 (59%)	32 (57%)	
Missing	8 (14%)	12 (21%)	
p21			0.85
Absent	24 (41%)	22 (39%)	
Present	34 (59%)	34 (61%)	

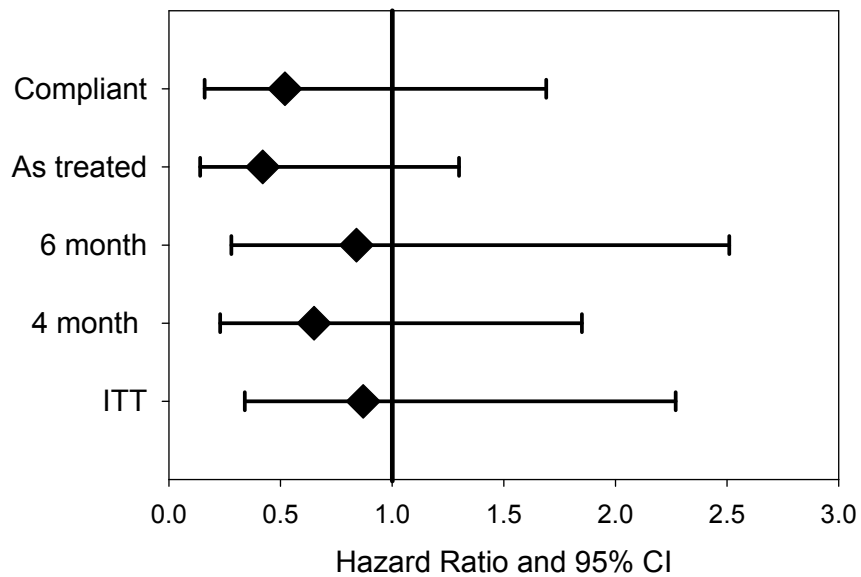
Recurrence: MVAC (Arm 1) vs. Observation (Arm 2)



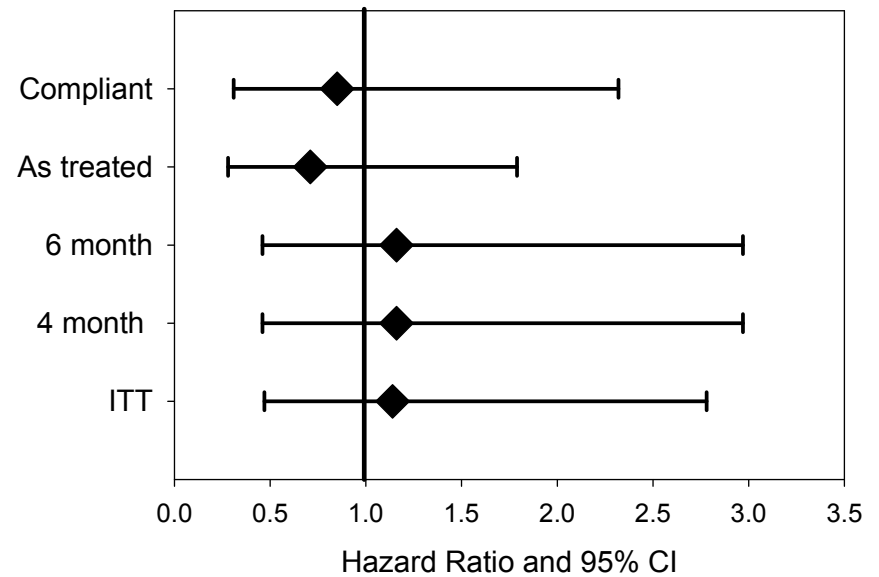
Overall Survival: MVAC vs. Observation (Arm 2)



TIME TO RECURRENCE



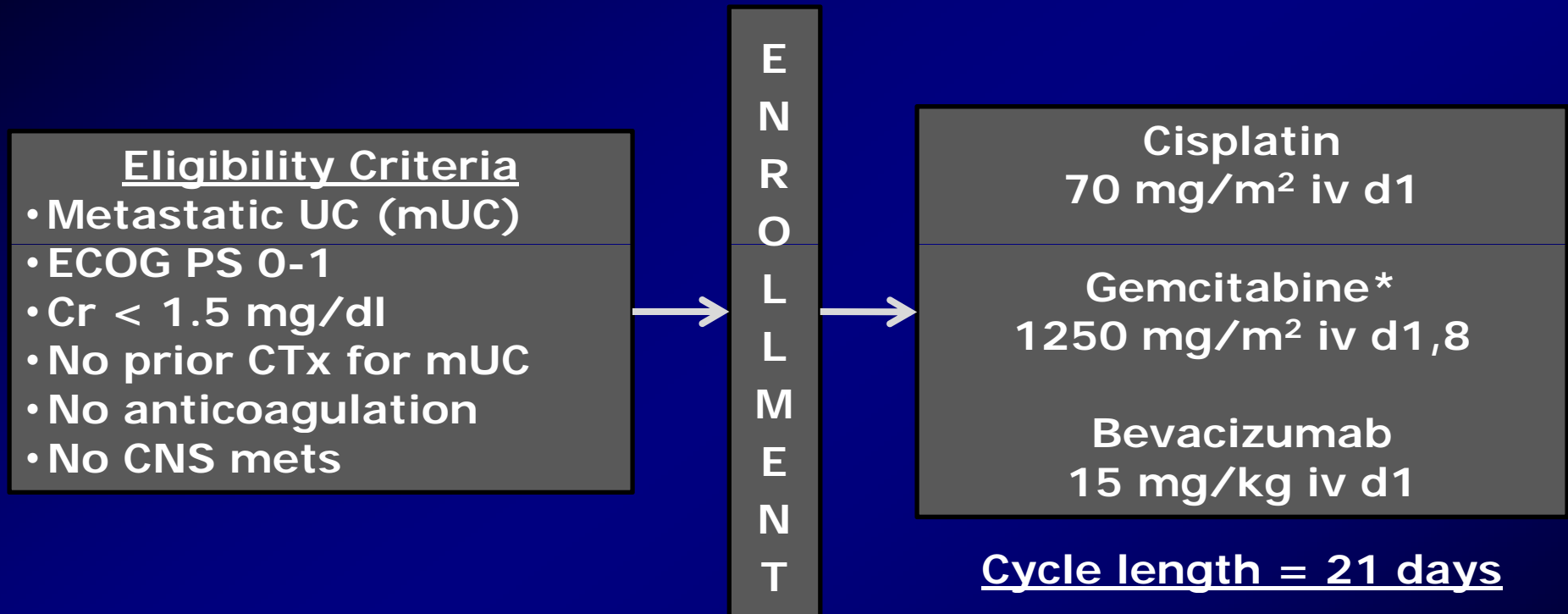
OVERALL SURVIVAL



Conclusions

- prognostic value of p53 not confirmed
 - ? Secondary to stage migration, IHC, underpowered
- Predictive value of p53 not confirmed
 - ? Secondary to underpowered trial
- Need for biomarker validation confirmed
 - Analytic validity, clinical qualification purposes
- Large randomized bladder cancer trials can be performed
 - source for additional exploratory biomarkers

Abstract 5018 Hahn et al for the Hoosier Oncology Group Phase II study of Gemcitabine, Cisplatin and Bevacizumab in Patients with Metastatic Urothelial Cancer



- Maximum of 8 cycles of Cisplatin and Gemcitabine
- Maximum 1 year of Bevacizumab therapy
- *Gemcitabine reduced to 1000 mg/m² iv d1,8 after first 17 patients due to 7 DVT/PE events

Trial Design and Patient Demographics

Primary Endpoint: Progression Free Survival (PFS)

Secondary Endpoints: Response, Toxicity, Survival

(H_0) PFS = 7.5 months vs (H_1) PFS = 11.25 months

Sample size of 40, 10% dropout rate = Final of 45

Median Age	66	(41-78)
Male	33	77%
ECOG PS 0	26	60%
Prior Cystectomy	13	30%
Visceral Mets	22	51%
PS 1 and Visceral mets	10	23%

Therapy Administration

- Median chemotherapy cycles – 6 (2-8)
- 30% patients entered Bevacizumab maintenance portion
- 60% patients required dose modifications
 - 42% discontinued therapy due to toxicity
 - 21% discontinued Bevacizumab due DVT/PE

Toxicity (1)

Gem 1250
(n=18)

Gem 1000
(n=25)

Total
(n=43)

Gr 3-4 %

Gr 3-4 %

Gr 3-4 %

Anemia

11

12

12

Platelets

17

8

12

Neutropenia

33

36

35

Febrile Neutropenia

0

4

2

DVT/PE

39

8

21

HTN

6

4

5

Proteinuria

6

0

2

Hemorrhage

0

12*

7*

Toxicity (2)

Gem 1250
(n=18)

Gem 1000
(n=25)

Total
(n=43)

Gr 3-4 %

Gr 3-5 %

Gr 3-5 %

Vascular

0

4*

2*

Renal Failure

0

4

2

Cardiac

6

8*

7*

%

90% CI

**Clinically Significant
Toxicity (All patients)**

42

29 - 56

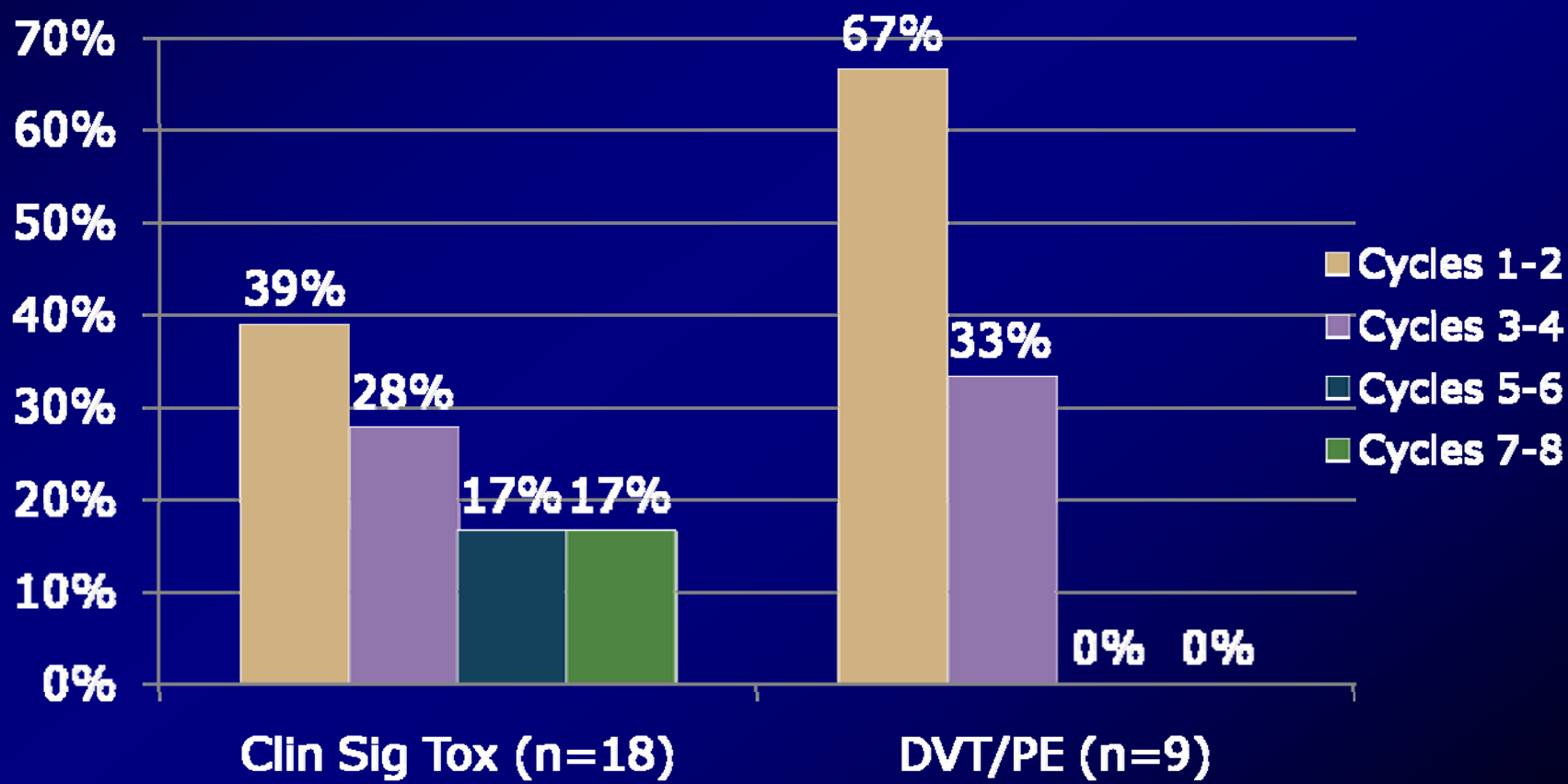
DVT/PE (Gem 1000)

8

1 - 23

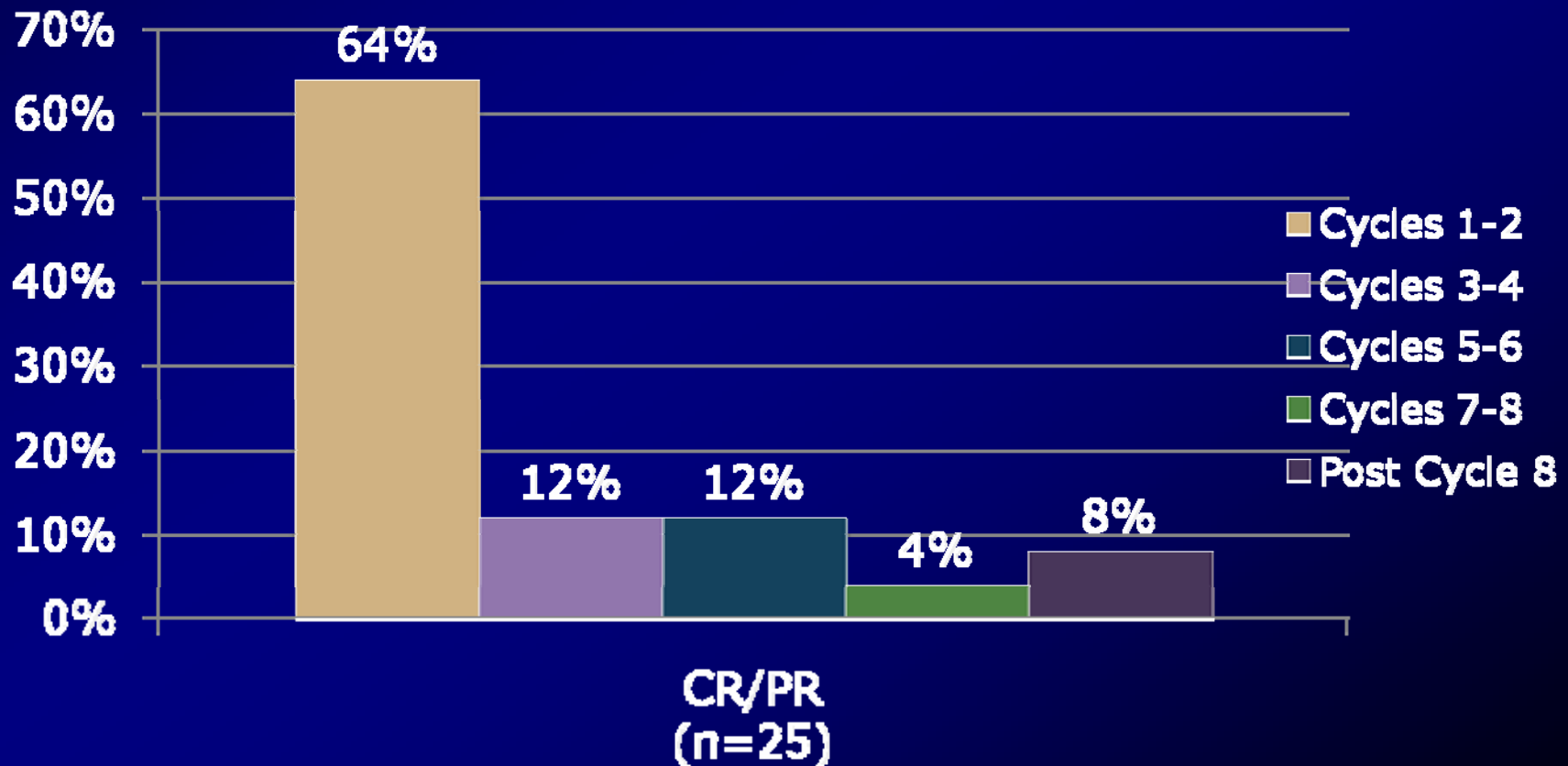
*One aortic dissection and one sudden cardiac death

Toxicity Timing

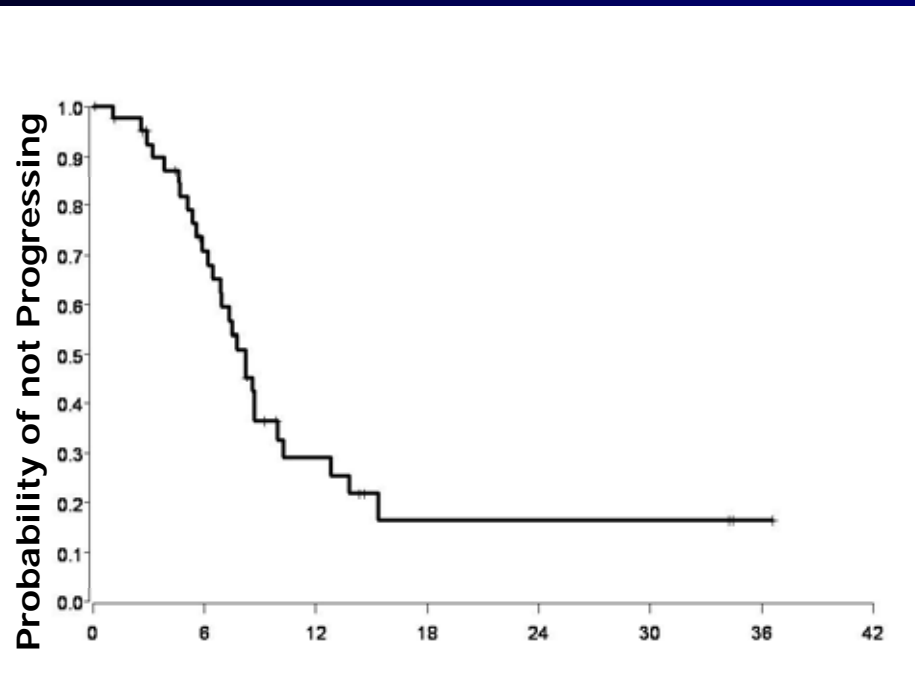


Tumor Responses and Timing

	N=43	% (95% CI)
Complete Response*	6	14 (5-28)
Partial Response	19	44 (29-60)



Progression-Free Survival

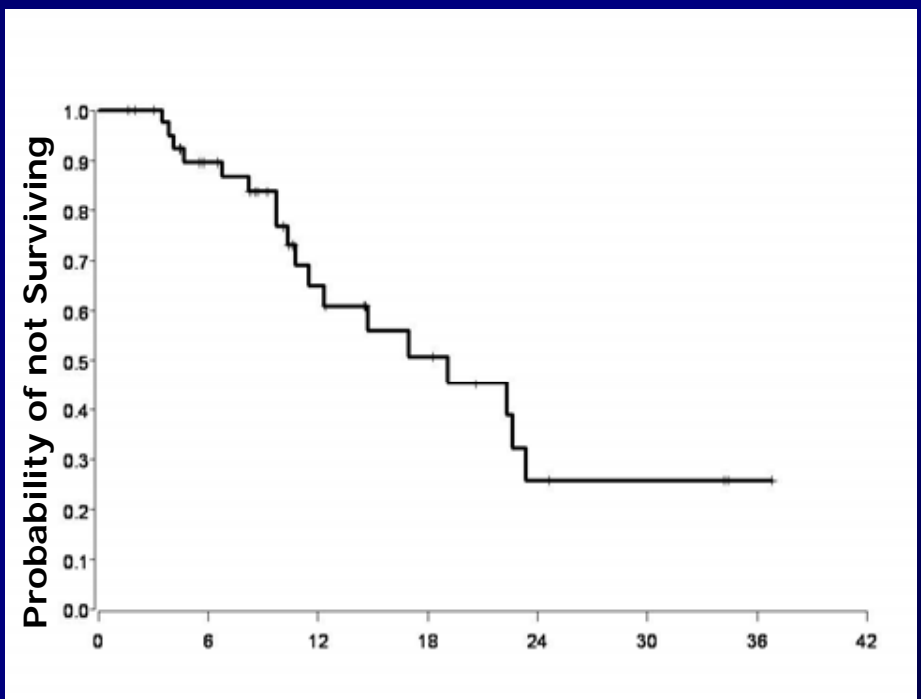


Median PFS = 8.2 m (95% CI 6.5 – 10.0)

Median follow-up = 14.6 m (Range 2-37)

12-month PFS = 29%

Overall Survival



Median OS = 19.1 m (95% 11.5 – 23.4)

Median follow-up = 14.6 m (2-37)

12-month OS = 65%

Conclusions

- Bevacizumab is associated with significant toxicity in metastatic urothelial carcinoma patients
- 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
- A randomized trial is indicated

Abstract 5074 Apolo et al. VTE in TCC patients treated with carboplatin Therapy

- Patients with advanced TCC on an MSKCC protocol of gemcitabine, carboplatin, and bevacizumab from 6/2006 to 9/2008 were evaluated for VTE.
- A contemporary control group of TCC patients receiving carboplatin plus gemcitabine alone during the same time period was retrospectively studied for VTE
- Patients with simultaneous PE and DVT were considered to have one VTE.

Methodology

Study Population*

Bevacizumab 10 mg/m² given 2 weeks prior to any chemotherapy

Then,

Bevacizumab (15mg/kg on day 1)

Carboplatin (AUC 4.5 on day 1)

Gemcitabine (1000 mg/m² on days 1,8)

Contemporary Controls*

Gemcitabine (1000 mg/m² on days 1,8)

Carboplatin (AUC 4-5 on day 1)

*Therapy was planned for 6 cycles of treatment recycled at 3 week intervals. Patients analyzed for this study had at least 3 cycles of chemotherapy.

Patient Demographics n=88

	Gemcitabine Carboplatin n=63	Gemcitabine Carboplatin Bevacizumab n=25
Karnofsky Performance Status		
≥ 70 %	55 (87%)	25 (100%)
< 70 %	2 (3%)	0
Not documented	6 (10%)	0
Carboplatin		
AUC 5	34 (54%)	0
AUC 4.5	6 (10%)	25 (100%)
AUC ≤ 4	23 (37%)	0
Prior pelvic surgery		
Yes	23 (37%)	12 (48%)
No	40 (63%)	13 (52%)
Presence of mass near pelvic vessels		
Yes	23 (37%)	9 (36%)
No	40 (63%)	16 (64%)

Vascular Thromboembolic Events

	Gemcitabine Carboplatin n=63	Gemcitabine Carboplatin Bevacizumab n=25
Deep venous thrombosis	4 (6%)	1 (4%)
Pulmonary embolus	4 (6%)	2 (8%)
Deep venous thrombosis + Pulmonary embolus	2 (3%)	1 (4%)
Arterial thrombosis and embolus	0	0
Cerebrovascular accident	0	0
Myocardial infarction	1 (2%)	0
Total Events	11 (17%) (95% CI 9-29%)	4 (16%) (95% CI 5-36%)
All pts (n=88)	15 (17% ; 95% CI 11-26%)	

Symptomatic vs. Incidental VTE

	Gemcitabine Carboplatin n=11	Gemcitabine Carboplatin Bevacizumab n=4
Symptomatic	7 (64%)	2 (50%)
Incidental	4 (36%)	2 (50%)

TCC “Take-Home” Points from ASCO 2009

- There is no role for p53 (by IHC) in advanced TCC
- Adding bevacizumab to GC has no impact on response but may increase survival prompting a phase III trial.
- Higher dose of Gemcitabine or adding bevacizumab to GC may increase VTE.
- The VTE incidence in UC is high, similar to colon cancer and much greater than NSCLC and breast cancer
- Carboplatin therapy and Cisplatin therapy both have a high rate of VTE.

Renal Cancer Themes

Interferon plus bevacizumab (abstracts 5019 and 5020)

Pazopanib in treatment-naïve and cytokine-treated patients (5021).



Risk Groups for Advanced RCC

Risk Groups	No. of Factors	2-Yr Survival %
Favorable	0	45
Intermediate	1-2	17
High	≥ 3	3

- **Pretreatment features associated with shorter survival**
 - Low Karnofsky performance status (< 80%)
 - High lactate dehydrogenase level (> 1.5 x ULN)
 - Hemoglobin level < LLN
 - High corrected serum calcium
 - Absence of nephrectomy (DFI < 1 year)

Abstract 5019 Rini et al. Bevacizumab plus Interferon-alpha versus Interferon-alpha Monotherapy in Metastatic Renal Cell Carcinoma: Results of Overall Survival for CALGB 90206

Eligibility Criteria

- Confirmed metastatic RCC with a component of clear cell histology
- Karnofsky PS \geq 70%
- Measurable or evaluable disease (by RECIST)
- No prior systemic treatment
- Adequate end-organ function
- No CNS metastases
- BP < 160/90 with meds
- No DVT within 1 year or arterial thrombotic event within 6 months
- Prior nephrectomy not required

S
T
R
A
T
I
F
Y

R
A
N
D
O
M
I
Z
E

IFNA 9 MU TIW

IFNA 9 MU TIW
+

Bevacizumab
10 mg/kg IV
q d1 and d15

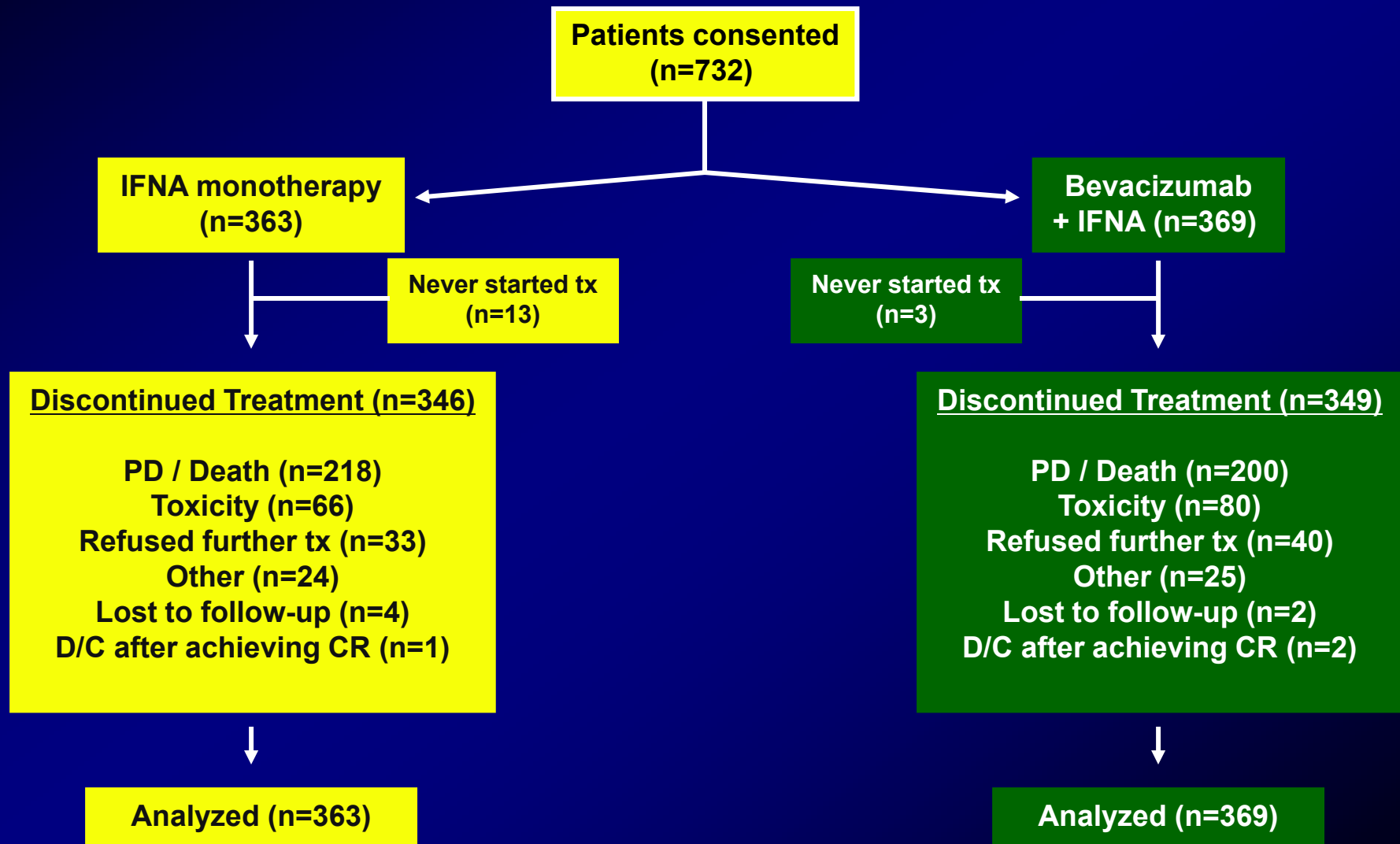
- Patients stratified for nephrectomy status (yes/no) and MSKCC risk group (0 risk factors vs. 1-2 risk factors vs. 3 or more risk factors)*

• Primary endpoint is overall survival

Statistical Methods

- The primary endpoint was OS, defined as the time from randomization to death due to any cause
- The trial was designed with 86% power to detect a hazard ratio (HR) of 0.76 (assumed median OS improvement 13 to 17 months), assuming a two-sided type I error of 0.05
- The primary analysis was an intent-to-treat approach using the stratified log-rank statistic, and the present analysis was based on the target number of 588 deaths
- Secondary endpoints: Progression-free survival (PFS), objective response rate (RECIST criteria), safety

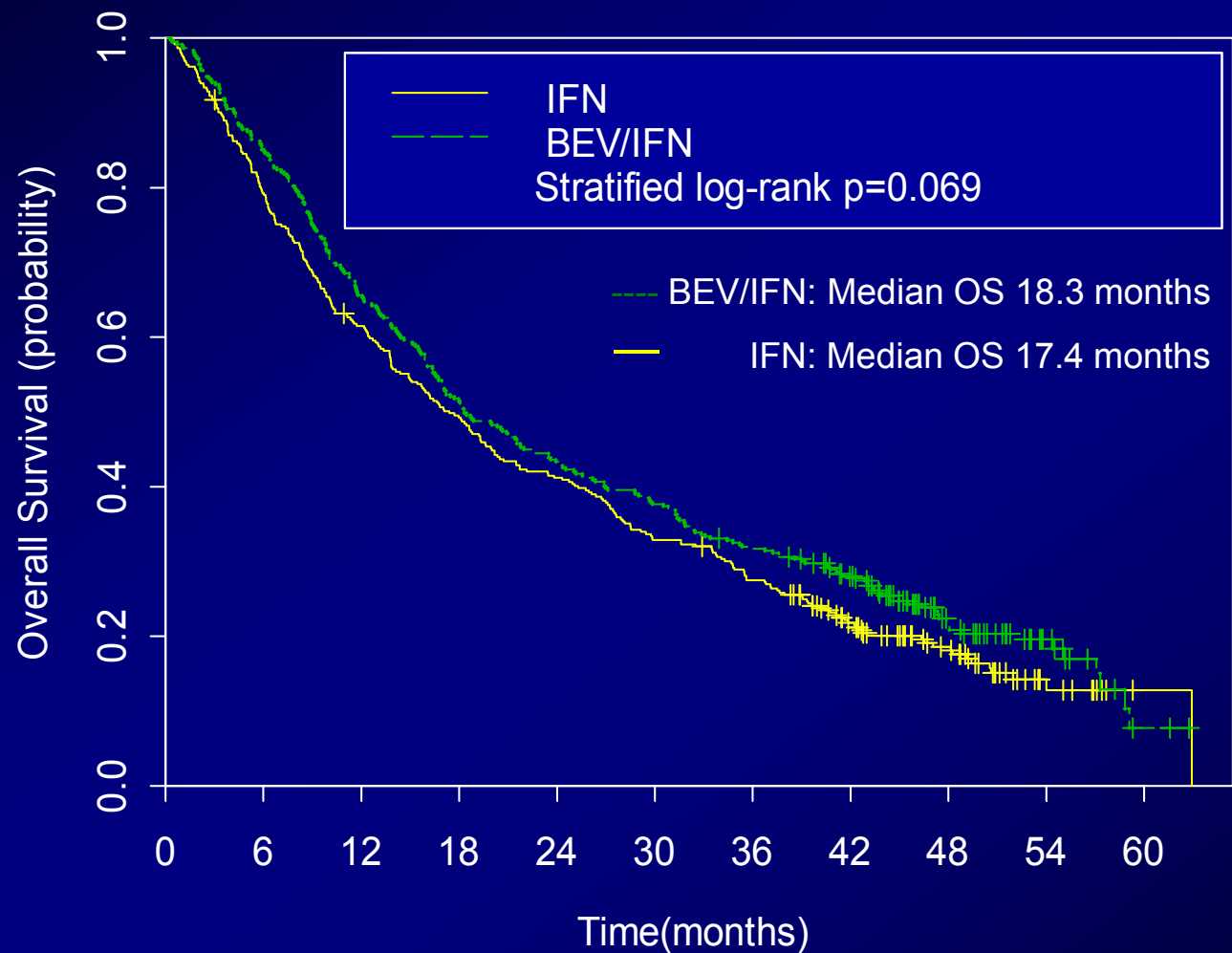
Patient Disposition



Baseline Demographics and Clinical Characteristics (n=732)

	Bevacizumab plus IFN (n=369)	IFN monotherapy (n=363)
Sex – no. (%)		
Male	269 (73%)	239 (66%)
Female	100 (27%)	124 (34%)
Median Age, years (inter-quartile range)	61 (56-70)	62 (55-70)
ECOG performance status – no. (%)		
0	230 (62%)	227 (62%)
1	132 (36%)	133 (37%)
2	7 (2%)	3 (1%)
Previous nephrectomy – no. (%)	312 (85%)	308 (85%)
Previous radiation therapy – no. (%)	35 (9%)	38 (10%)
Common Sites of Metastases		
Lung	252 (68%)	254 (70%)
Lymph node	130 (35%)	129 (36%)
Bone	104 (28%)	109 (30%)
Liver	74 (20%)	73 (20%)
Number of adverse risk factors		
0 (favorable)	97 (26%)	95 (26%)
1-2 (intermediate)	234 (64%)	231 (64%)
≥ 3 (poor)	38 (10%)	37 (10%)

Kaplan-Meier Overall Survival by Treatment Arm



Number of Patients at Risk

IFN	363	286	221	177	148	118	98	64	37	10	1
BEV/IFN	369	314	242	190	160	139	116	94	42	17	2

Overall Survival by MSKCC Risk Status*

Risk Group	%	Median OS (months)		
		BEV/IFN	IFN	HR
Favorable (0 risk factors)	26	32.5	33.5	0.89
			(p = 0.524)	
Intermediate (1-2 risk factors)	64	17.7	16.1	0.87
			(p = 0.174)	
Poor (≥ 3 risk factors)	10	6.6	5.7	0.76
			(p = 0.25)	

* Motzer R et al., JCO 20(1), 2002

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

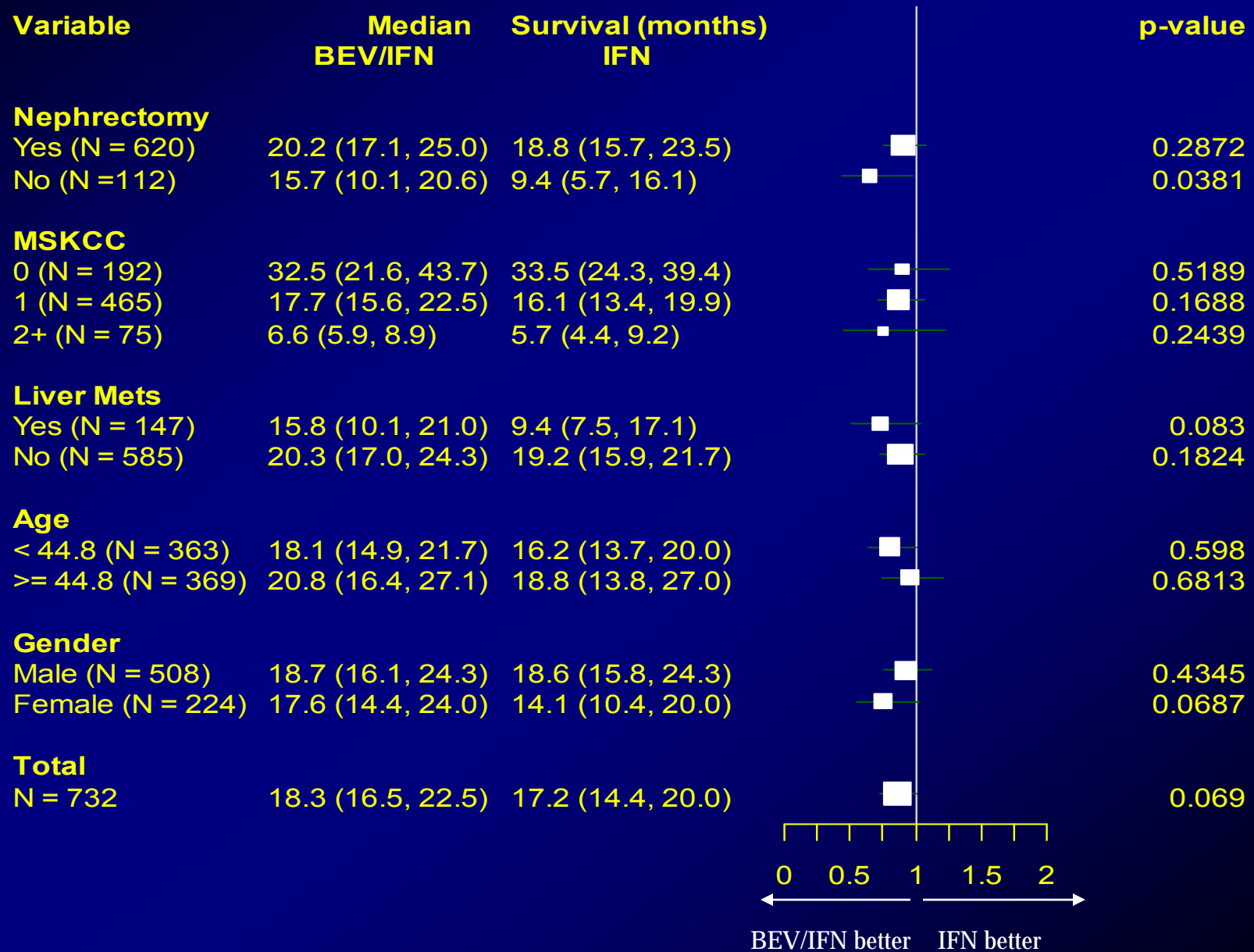
	Bevacizumab + IFN (n=351)	IFN monotherapy (n=350)
Percentage of patients receiving <u>any</u> second-line therapy	54%	62%
VEGF-targeted therapy	37%	46%
Bevacizumab	6%	14%
Chemotherapy	18%	14%
Investigational therapy	11%	18%
Cytokines	13%	14%

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

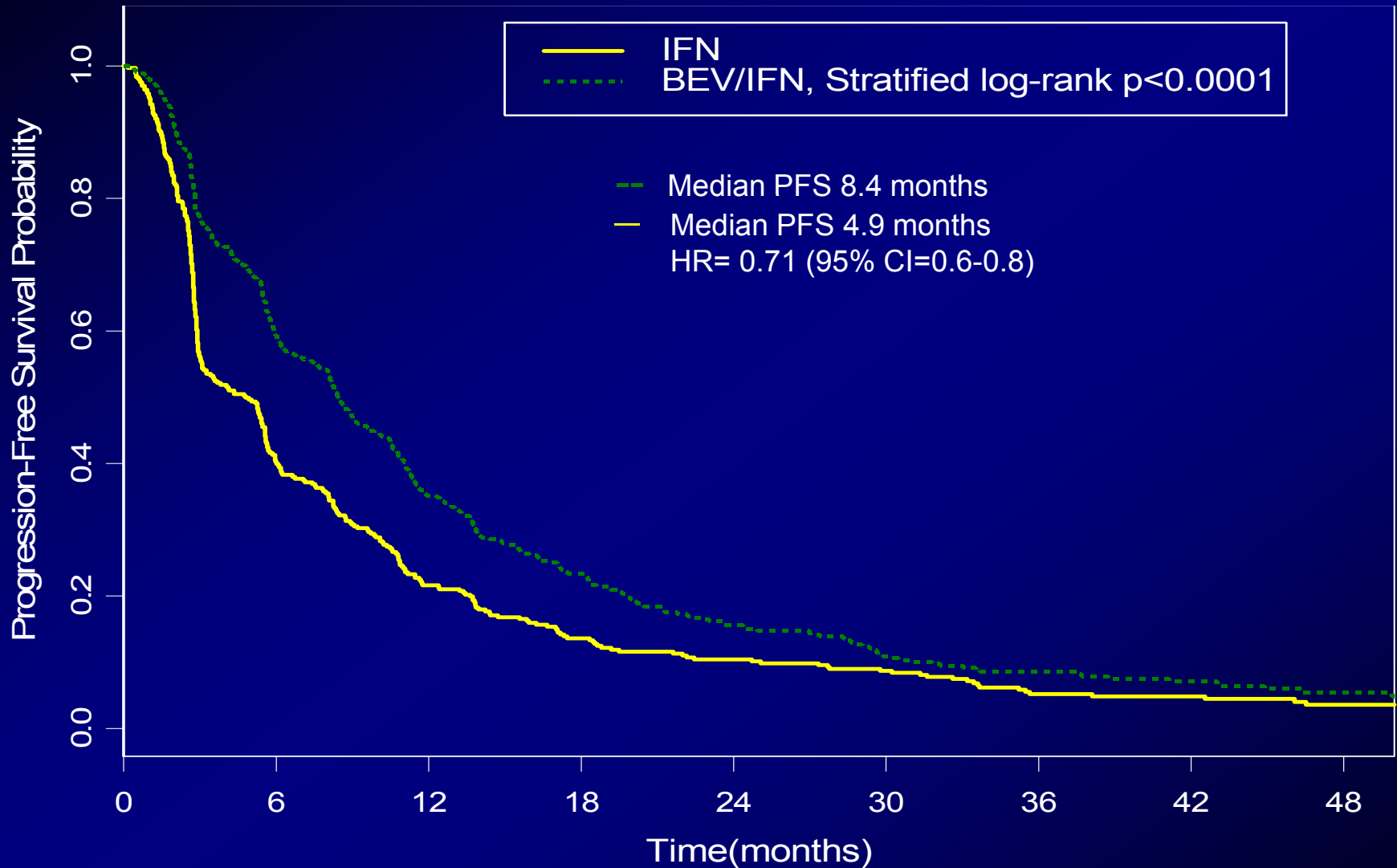
Median OS (months) according to treatment arm and subsequent therapy

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

Forest Plot of Overall Survival in Select Subgroups



Kaplan-Meier Progression-Free Survival by Treatment Arm



Number of Patients at Risk

	0	6	12	18	24	30	36	42	48
IFN	363	145	77	47	36	30	16	13	7
BEV/IFN	369	218	129	84	55	37	26	20	10

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

Frequency of selected grade 3 or 4 AEs

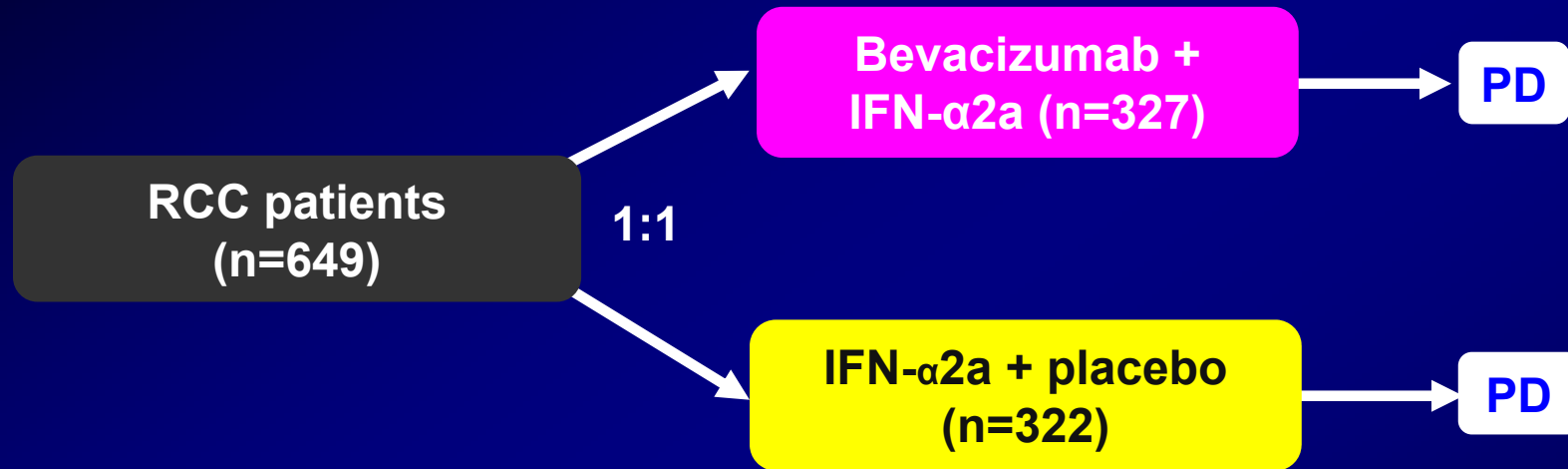
Adverse event	Bevacizumab + IFN (n=366)	IFN (n=352)
Any grade 3/4 adverse event	79%	61%
Fatigue/asthenia/malaise	37%	30%
Anorexia	17%	8%
Proteinuria	15%	<1%
Hypertension	11%	0%
Hemorrhage	2%	<1%
Venous thromboembolism	2%	1%
Gastrointestinal perforation	<1%	0%
Arterial ischemia	1%	0%

Conclusions

- Overall survival is greater in patients receiving bevacizumab plus interferon compared to interferon alone, but does not meet pre-defined criteria for significance
- The most robust OS is achieved in patients with favorable underlying disease biology who are able to receive subsequent therapy
- Bevacizumab and IFN results in a greater progression-free survival and objective response rate versus IFNA alone.
- Toxicity is greater in the combination therapy arm, including more fatigue, anorexia, hypertension and proteinuria

Abstract 5020 Escudier et al

Plenary Presentation of IFN +/- bevacizumab



- Bevacizumab/placebo 10mg/kg i.v. q2w until progression
- IFN- α 2a 9MIU s.c. three times/week (maximum of 52 weeks) (dose reduction allowed)
- Multinational ex-US study: 101 study sites in 18 countries
- Stratification factors: country and Motzer score

PD = progression of disease; i.v. = intravenous; s.c. = subcutaneous

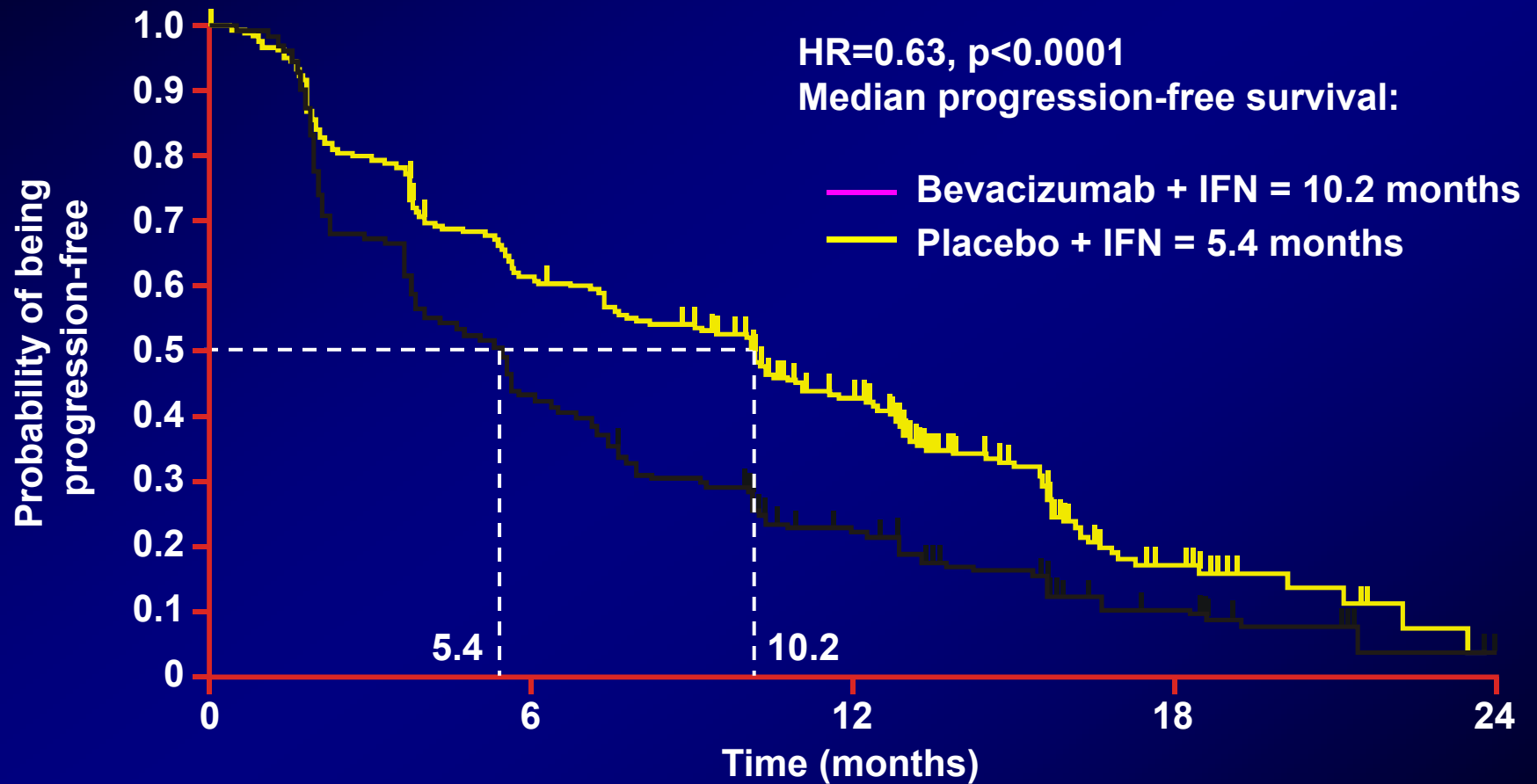
P.I. Bernard Escudier

Tumor response (investigator assessed)

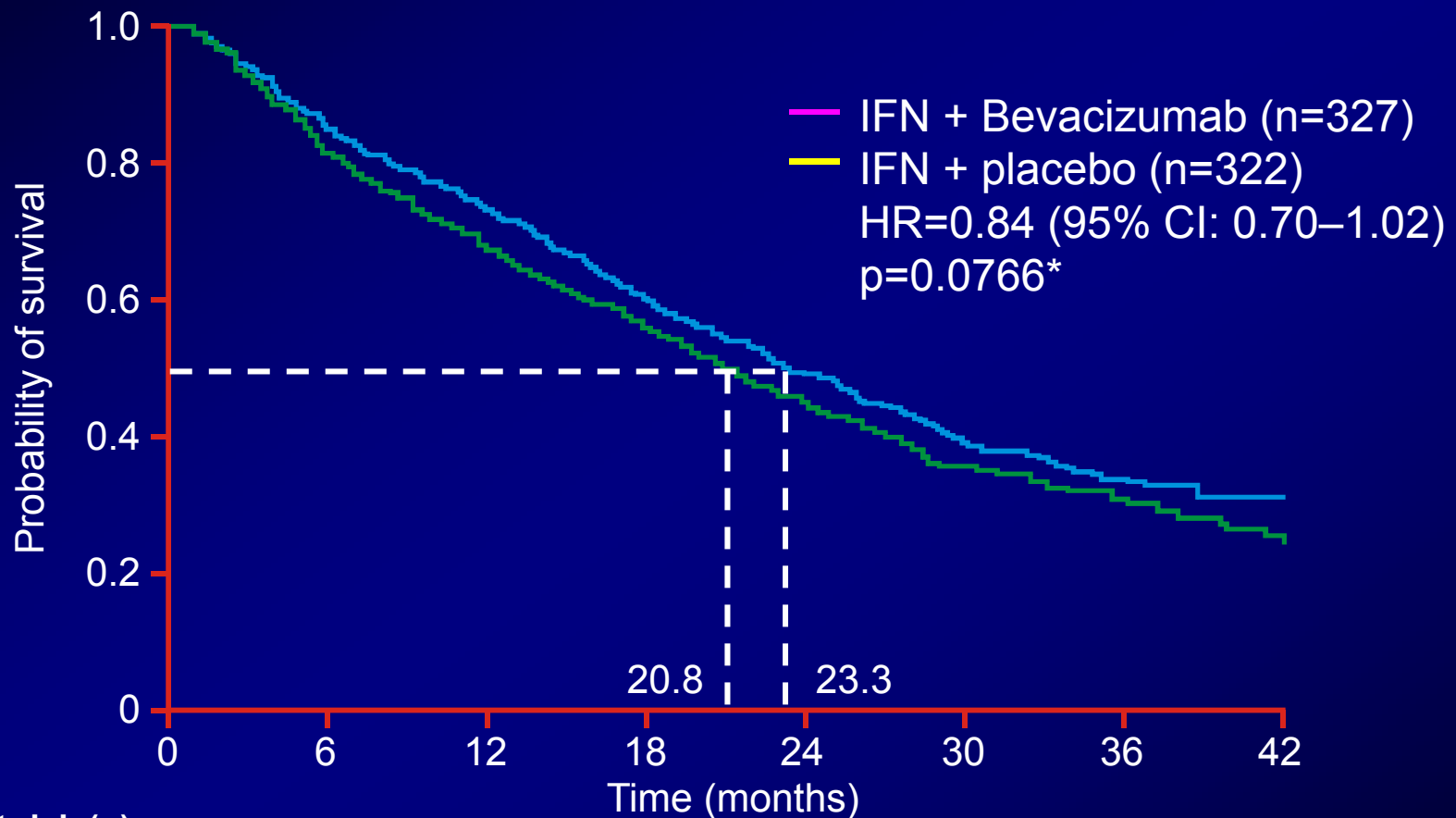
Response	IFN + placebo (n=289)	Bevacizumab + IFN (n=306)
Overall response rate (%)*	13	31
Complete response	2	1
Partial response	11	30
		p<0.0001
Median duration of response (months)	11	13
Median duration of stable disease (months)	7	10

*Patients with measurable disease only

Progression-free survival (investigator assessed)



Survival: Censoring crossover patients



Patients at risk (n)

Bevacizumab + IFN	327	278	237	194	157	124	84	27
IFN + placebo	322	262	216	173	131	101	69	19

*Stratified by Motzer score and region

Summary of subsequent medical therapies

Treatment, n (%)	IFN + Bevacizumab (n=327)	IFN + placebo (n=322)
Total patients with ≥1 treatment	180 (55)	202 (63)
VEGF inhibitors		
Sunitinib	83 (25)	92 (29)
Sorafenib	60 (18)	50 (16)
Bevacizumab	10 (3)	12 (4)
Other*	7 (2)	6 (2)
mTOR inhibitors [‡]		
	14 (4)	6 (2)
Cytokines		
	32 (10)	52 (16)
Chemotherapy [§]		
	28 (9)	47 (15)

*Protein TKI, pazopanib, erlotinib, blinded sorafenib, blinded sunitinib, angiogenesis inhibitors NOS, VEGF inhibitor NOS

[‡]Temsirolimus, everolimus (RAD001)

[§]Antimetabolites, vinca alkaloids and antineoplastic agents

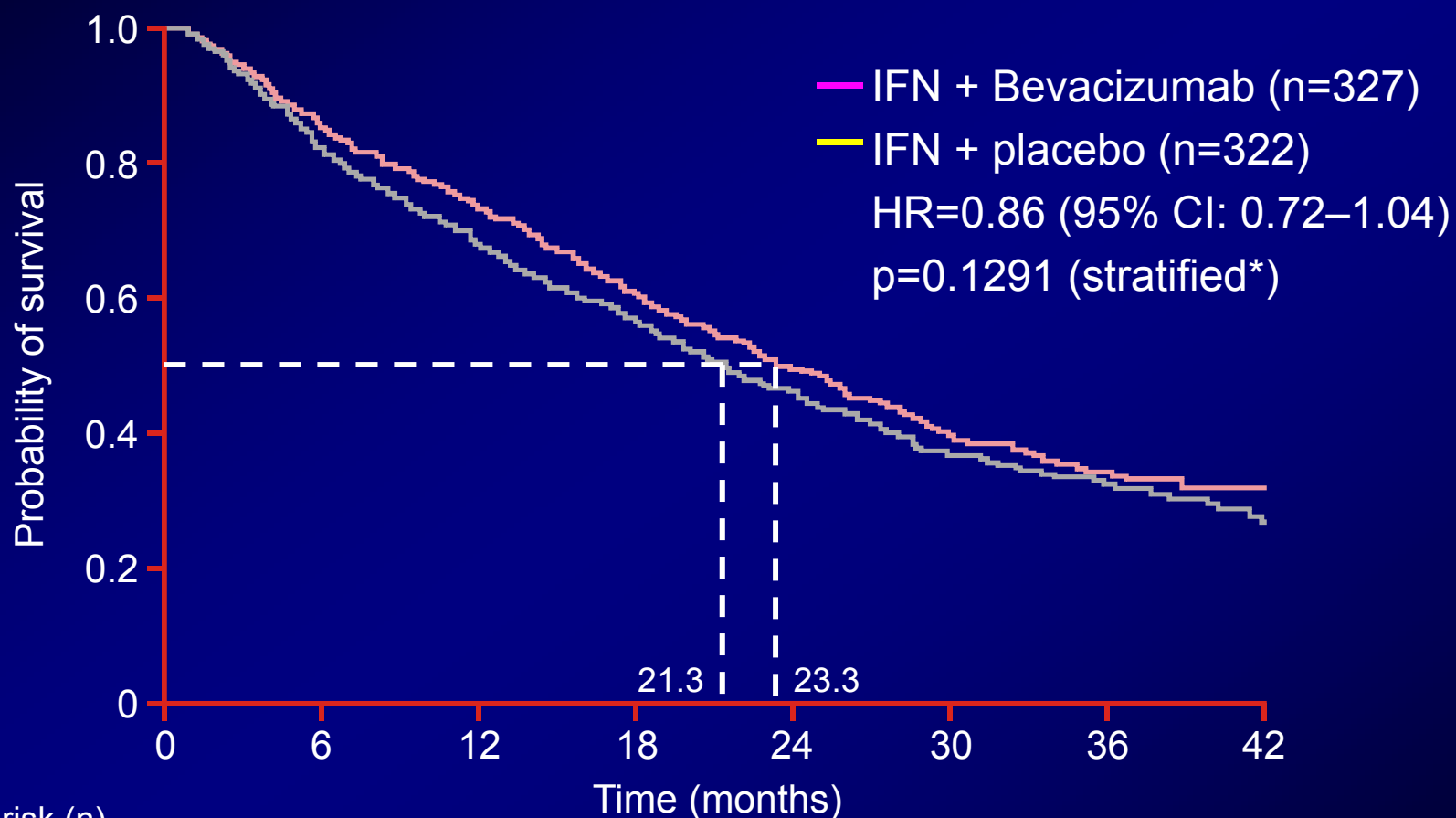
OS by post-protocol therapies

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

Final OS



Patients at risk (n)

	0	6	12	18	21.3	23.3	24	30	36	42
IFN + Bevacizumab	327	278	237	194	157	124	84	27		
IFN + placebo	322	262	216	177	141	113	78	22		

*Stratified by Motzer score and region

Final OS: unstratified and stratified analyses

	Cox regression		p value	
	HR	95% CI	Log-rank	Wilcoxon
Unstratified	0.91	0.76–1.10	0.3360	0.2046
Stratified*	0.86	0.72–1.04	0.1291	0.0969

*Stratified by Motzer score and region

Multiple Cox regression analysis for OS

- A multiple Cox regression model controls for several predetermined baseline prognostic factors that influence survival independent of treatment
- Variables included in the analysis
 - gender, age, Motzer score, location of metastases (lung, bone, liver), body weight loss, number of sites, baseline SLD, region, baseline VEGF, and some lab values (albumin, creatinine, alkaline phosphatase, WBC count, platelets)
- Adjustment for these factors resulted in an improved treatment effect
 - HR=0.78 (95% CI: 0.63–0.96); p=0.0219

Conclusions

- The addition of bevacizumab to IFN results in a trend for improved survival and significant improvement in progression-free survival and tumor response
- Survival benefit is confounded by post-protocol bevacizumab (crossovers) and subsequent TKI treatment.
- The treatment effect is significant when controlled for other factors.

Abstract 5021. Sternberg et al. Phase III Trial of Pazopanib in Locally Advanced and/or Metastatic Renal Cell Carcinoma

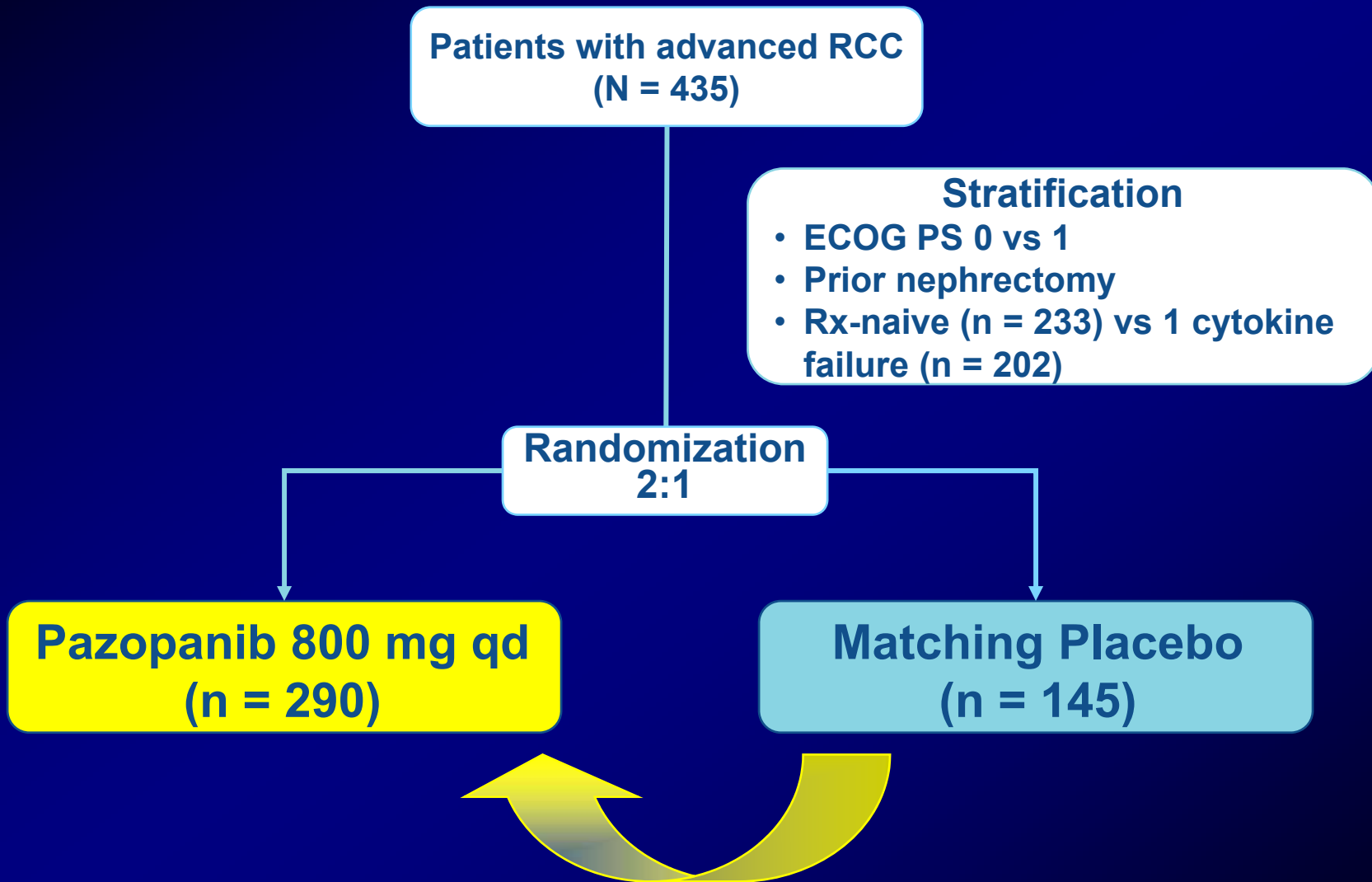
- An oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit
- Clinical efficacy demonstrated in advanced RCC in a Phase II study¹

Kinase affinity profile

	K_i^{app} (nM)
VEGFR-1	15
VEGFR-2	8
VEGFR-3	10
PDGFR- α	30
PDGFR- β	14
c-Kit	2.4

Study Design: 80 Sites in 22 countries

Enrolled: Apr 06 - Apr 07



Option to receive pazopanib via an open-label study at progression

Patient Eligibility

- Locally advanced and/or metastatic RCC
- Clear-cell histology
- Treatment-naive or failure of 1 prior cytokine therapy
- Measurable disease by RECIST
- ECOG PS 0 or 1
- Adequate organ function
- Age \geq 18 years

Endpoints and Analysis Plan

Primary:

- Progression-free survival (PFS)
 - > 90% power to detect 80% improvement in median PFS
 - Adequately powered in the treatment-naive, cytokine-pretreated subpopulations

Secondary:

- Overall survival (OS)
 - 90% power to detect a 50% improvement in median OS
- Overall response rate (ORR), duration of response, safety, health-related quality of life (HRQoL)

Analysis Plan:

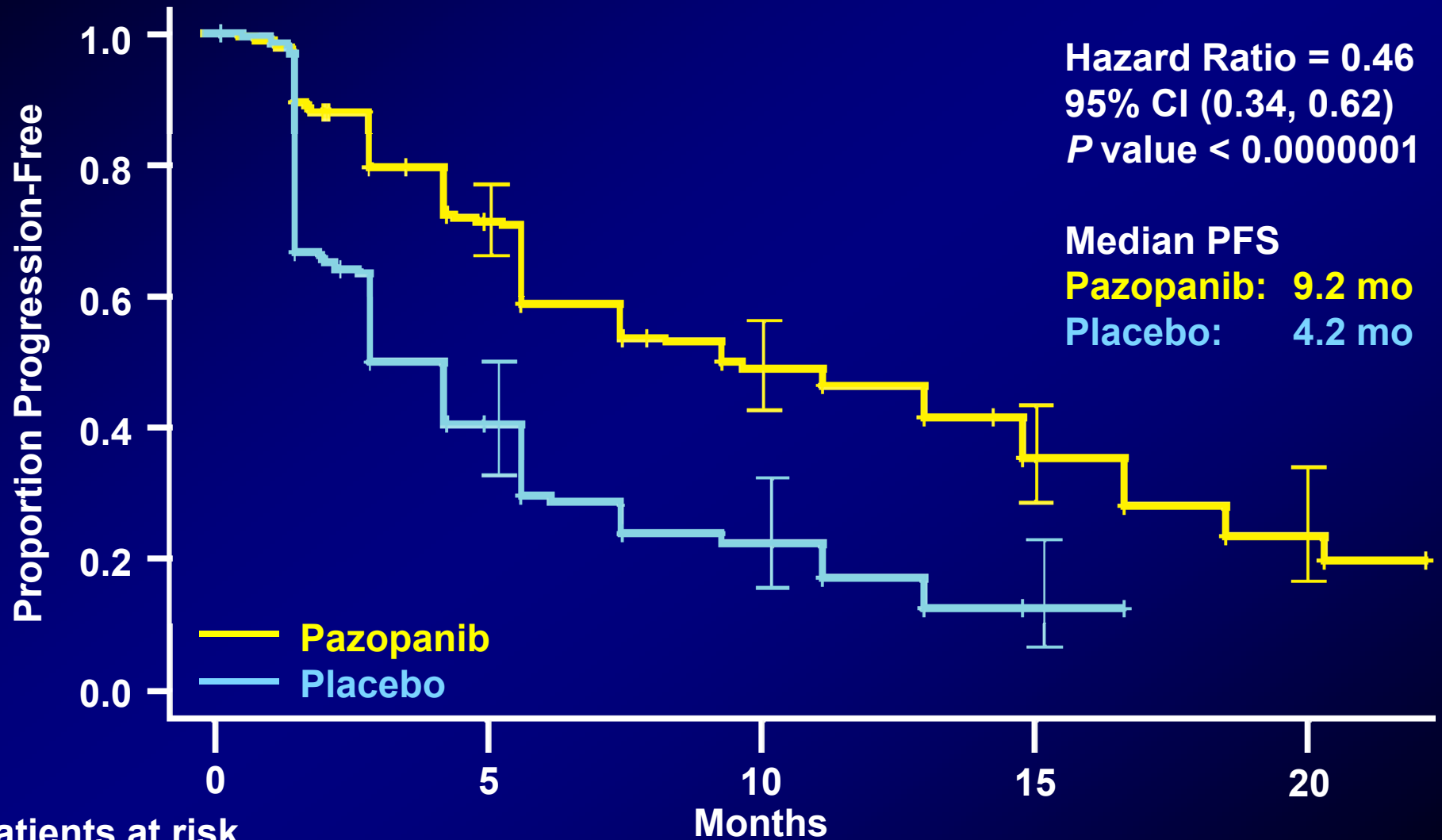
- One single analysis for PFS, one planned interim analysis for OS (at the time of PFS analysis)
 - Clinical cutoff: May 23, 2008

PFS and ORR results presented here are based on independent review.

Demographic and Baseline Disease Characteristics

	Pazopanib (n = 290)	Placebo (n = 145)
Median age (range), yrs	59.0 (28 – 85)	60.0 (25 – 81)
Gender, % male	68	75
Metastatic sites, %		
Lung	74	73
Lymph node	54	59
Bone	28	26
Liver	26	22
Number of organs involved, %		
1 & 2	45	48
≥ 3	55	52
ECOG PS 0 / 1, %	42 / 58	41 / 59
MSKCC risk category, %		
Favorable	39	39
Intermediate	55	53
Poor / Unknown	3 / 3	3 / 4

PFS in Overall Study Population



Patients at risk

Pazopanib 290
Placebo 145

159
38

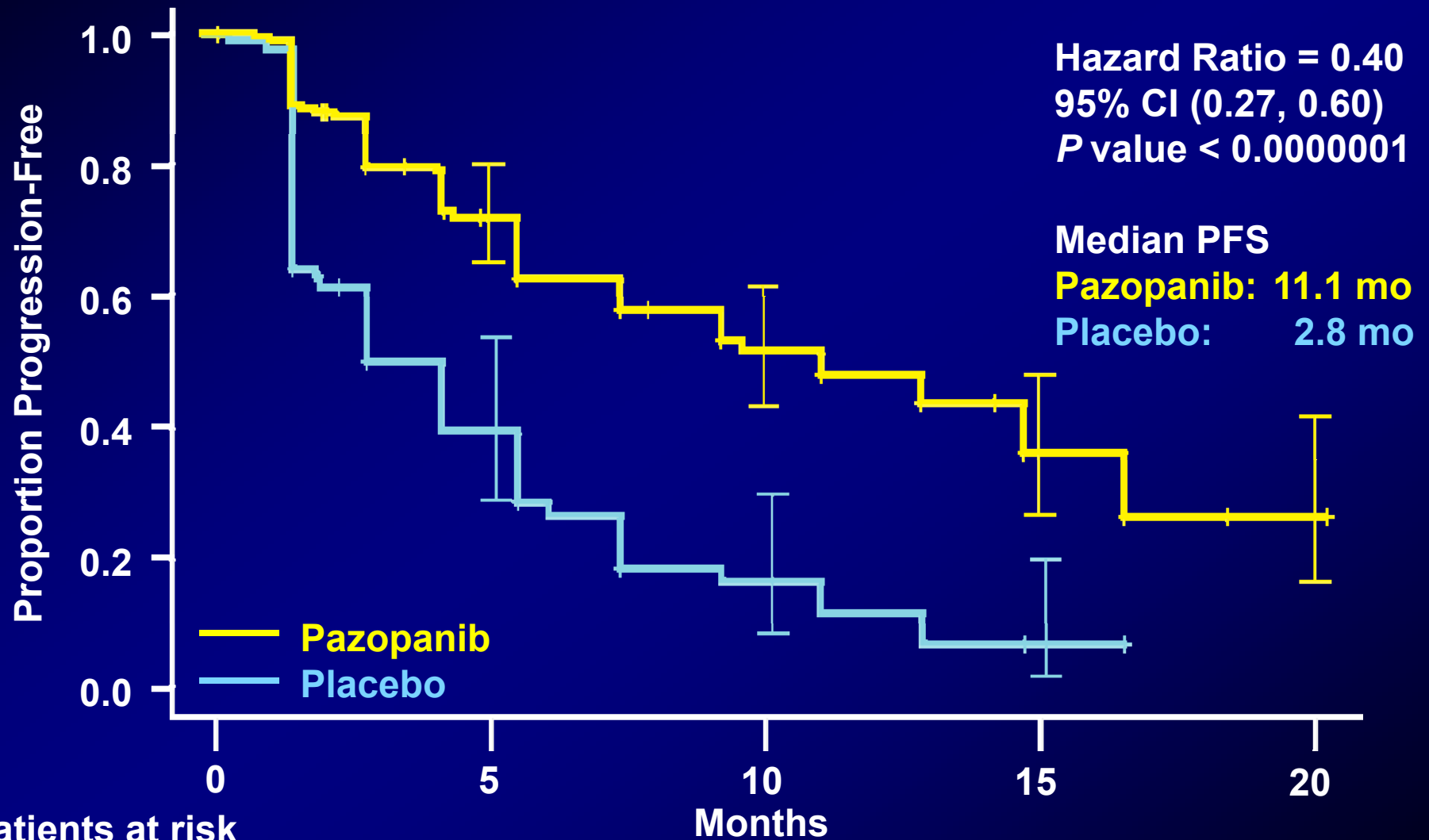
Months

76
14

29
2

6

PFS in Treatment-Naive Subpopulation



Patients at risk

Pazopanib 155
Placebo 78

34
22

10

39
7

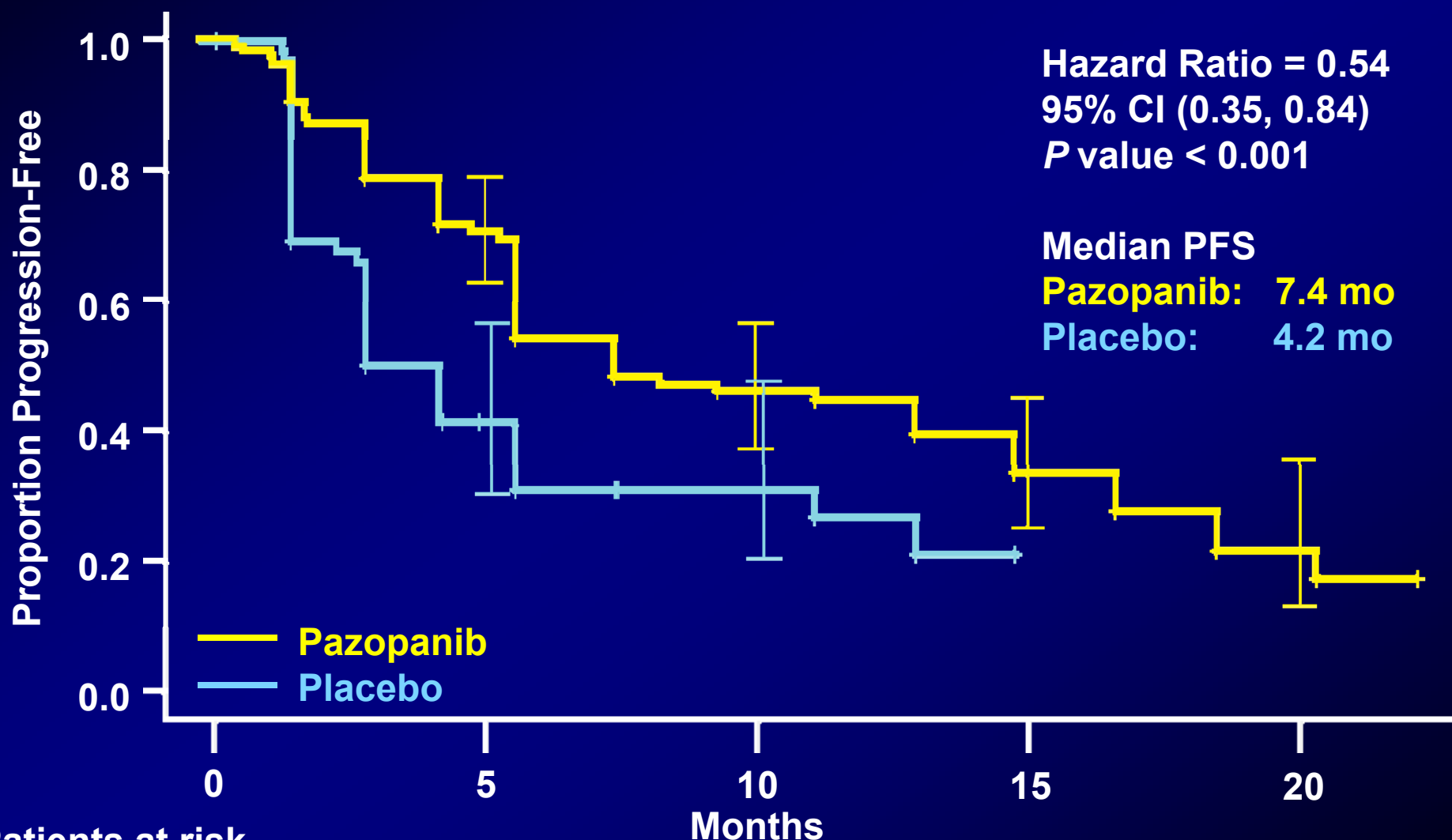
15

11
2

20

1

PFS in Cytokine-Pretreated Subpopulation



Patients at risk

Pazopanib 135

Placebo 67

75

16

37

7

18

5

Subgroup Analysis of PFS

Baseline Factor

Hazard Ratio (95% CI)

Primary analysis

MSKCC risk: Favorable

MSKCC risk: Intermediate

Female

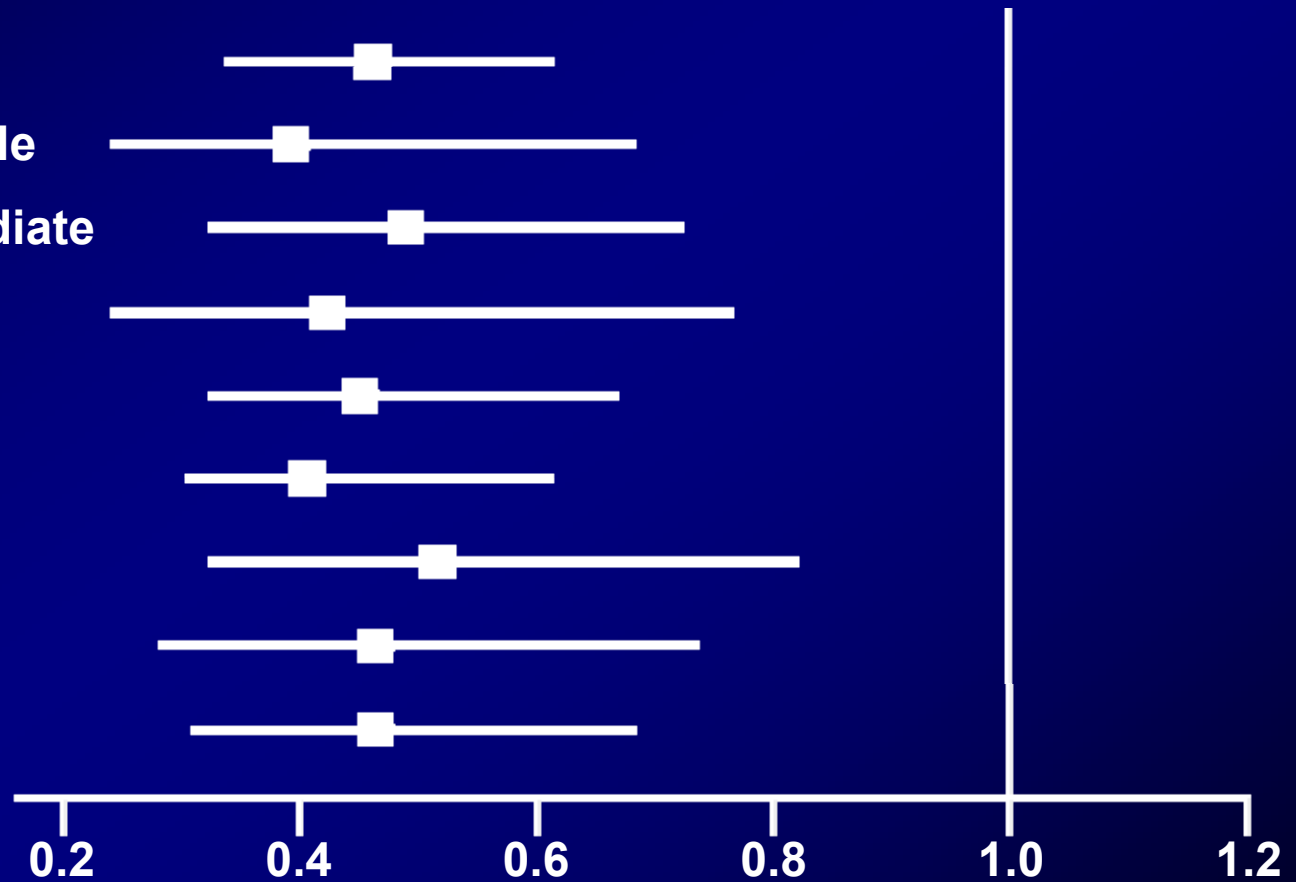
Male

Age < 65 yrs

Age ≥ 65 yrs

ECOG PS 0

ECOG PS 1



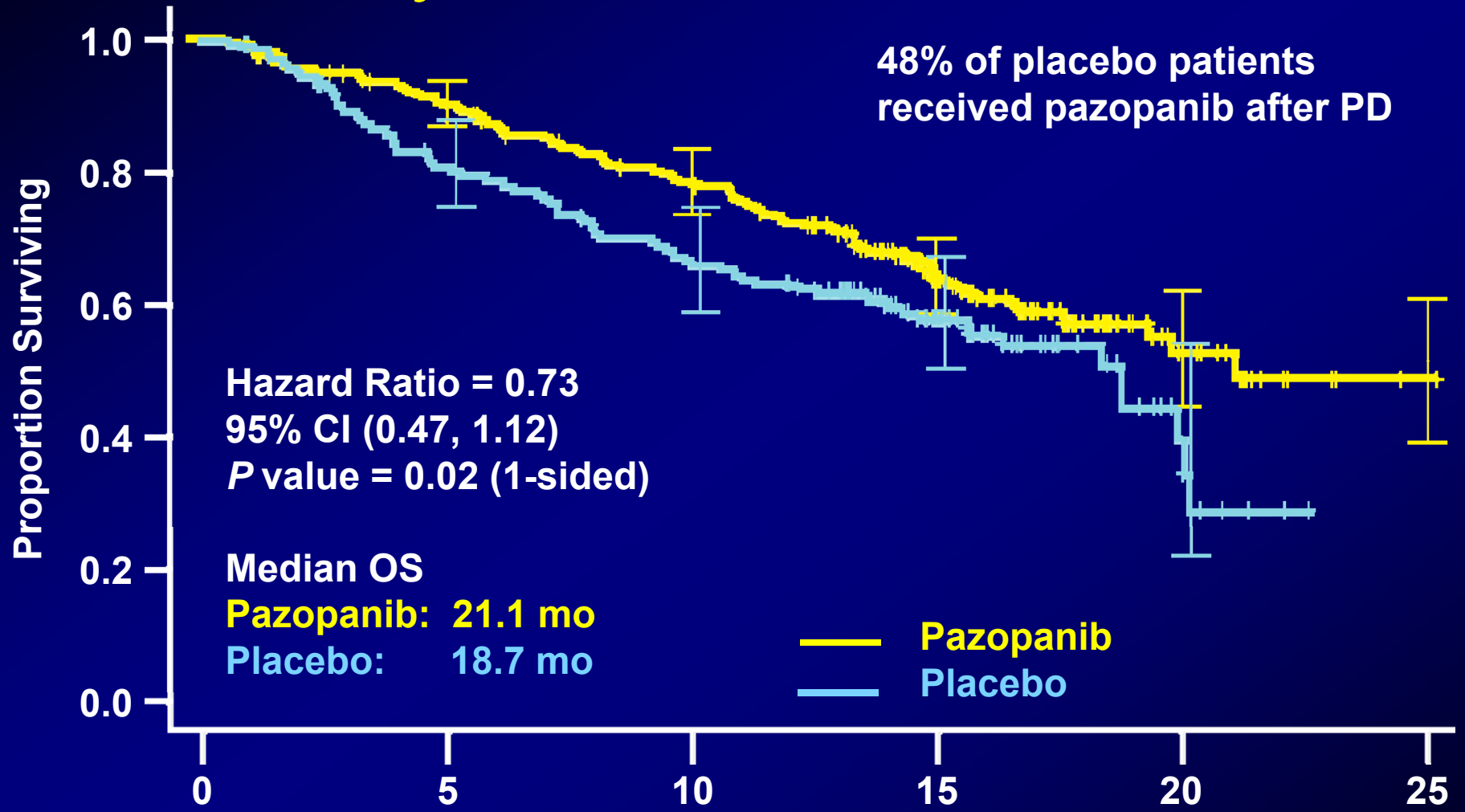
← Favours pazopanib Favours placebo →

$P < 0.001$ by log-rank test for all.

Tumor Response

	Pazopanib (n = 290)	Placebo (n = 145)
ORR (CR + PR), %		
Overall population	30	3
Treatment-naive	32	4
Cytokine-pretreated	29	3
Duration of response, weeks	59	—

Interim Analysis of Overall Survival



Patients at risk

Months	0	5	10	15	20	25
Pazopanib	290	254	214	115	20	1
Placebo	145	115	93	52	6	

O'Brien-Fleming boundary for futility / superiority: $P = 0.201 / 0.004$ (1-sided)

Selected Toxicities Seen with TKI's*

Adverse Event	Pazopanib (n = 290)	Placebo (n = 145)
	All Grades, %	All Grades, %
Proteinuria	9	0
Hypothyroidism	7	0
Hand-foot syndrome	6	(< 1)
Mucositis / Stomatitis	4 / 4	< 1 / 0
Arterial thromboembolic	3	0
Hypertension	40	10
Diarrhea	52	9
Emesis	21	8
Fatigue	19	8

*No change seen in RQoL indices: 1. EORTC-QLQ-C30; 2. EQ-5D Index; 3. EQ-5D-VAS

Pazopanib in RCC

- Pazopanib showed significant improvement in PFS compared to placebo.
- Pazopanib's safety profile was acceptable
- Interim OS data not yet mature

The spectrum and potency of VEGF-R inhibitors is not identical

	VEGF R1	VEGF R2	VEGF R3	PDGFR α	PDGFR β	KIT	FLT3	RET
Sorafenib	NA	90	100	50-60	80	68	46	100-150
Sunitinib	10	4	10	5-10	10	13	1-10	100-200
Pazopanib	10	30	47	71	84	72	>1000	>1000
Axitinib	1.2	0.2	0.3	5	1.6	1.7	>1000	>1000
AV-951	0.21	0.16	0.24		1.7	1.6		
BAY 73-4506	16	5	46	NR	74	7	440	1
ABT-869		3	3	35	31	48	13	

* Inhibitory concentrations (kinase IC50 in nanomoles) for relevant targets

VEGF-R Inhibitors in VEGF-targeted Therapy-Naïve RCC Patients

Treatment	Objective Response	% Pts with Tumor Burden Reduction	PFS
Sunitinib	30 - 45%	~ 70-75%	11 months (treatment-naïve) 8.4 months (cytokine-refractory)
Sorafenib	2% - 10%	~ 70-75%	5.5 - 5.7 months
Pazopanib <small>(Sternberg, ASCO 2009)</small>	30%	~ 70-75%	9.2 months
Axitinib	47%	~ 70-75%	15.7 months (cytokine-refractory)
AV-951	24%	83%	8.9 – 11.8 months
BAY 73-4506	27%	84%	NR

RCC “Take-Home” Points from ASCO 2009

- Bevacizumab plus interferon improves PFS and RR compared with interferon alone.
- Bevacizumab plus interferon has a trend for improved survival compared with interferon alone
- Pazopanib improves PFS and RR compared with placebo in both treatment-naïve and cytokine-treated patients
- The safety profile for pazopanib was acceptable
- Pazopanib interim survival are not yet mature

Prostate Cancer Themes

Adjuvant deprivation therapy after prostatectomy for high-risk prostate cancer (5009, Glode et al)

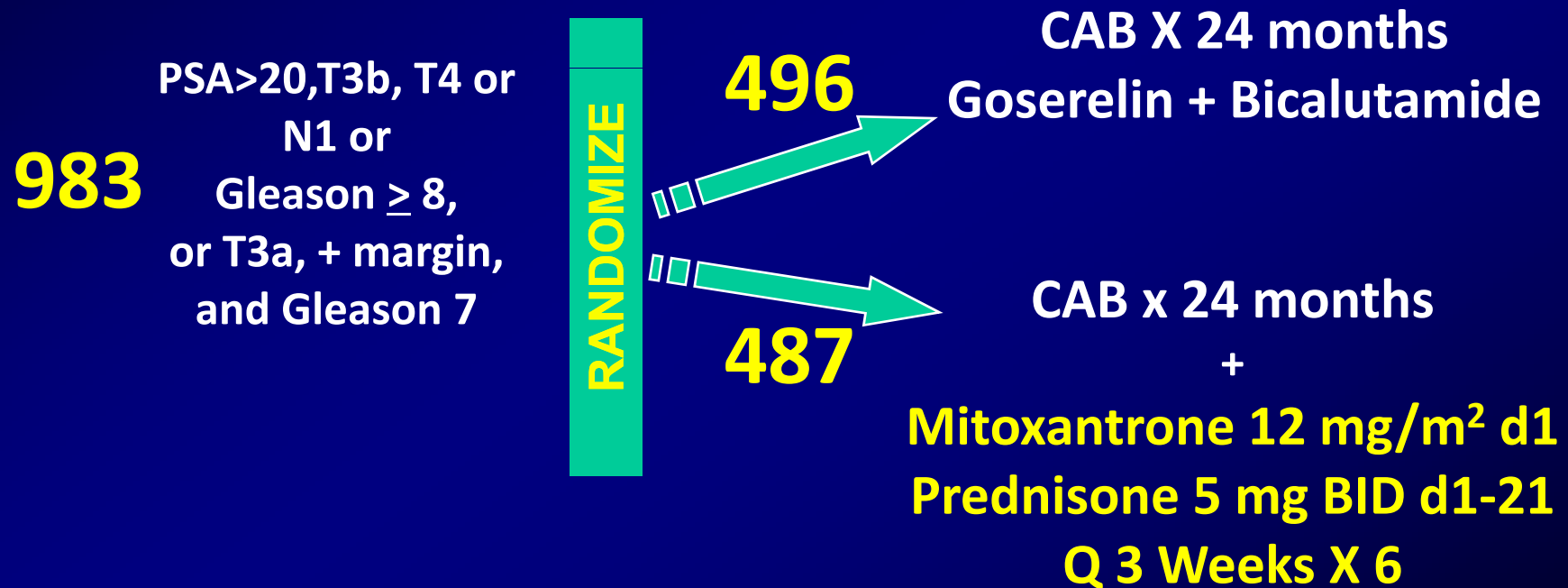
New Drugs for Prostate Cancer:

MDV3100 (5011, Scher et al)

Abiraterone Acetate (5047, Reid & 5048, Danila et al)

Circulating Tumor Cells (5049, Fleisher et al)

Abstract 5009 Glode et al. SWOG 9921: Prolonged Event Free Survival in High Risk Prostate Cancer (PC) Patients Receiving Adjuvant Androgen Deprivation

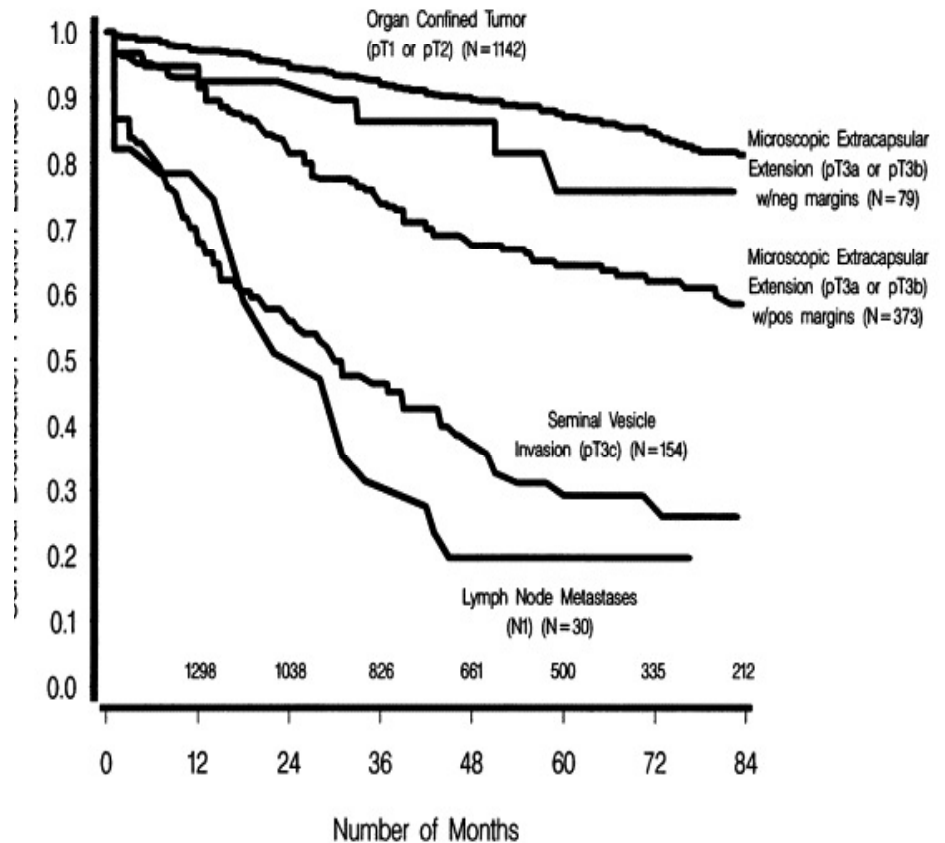
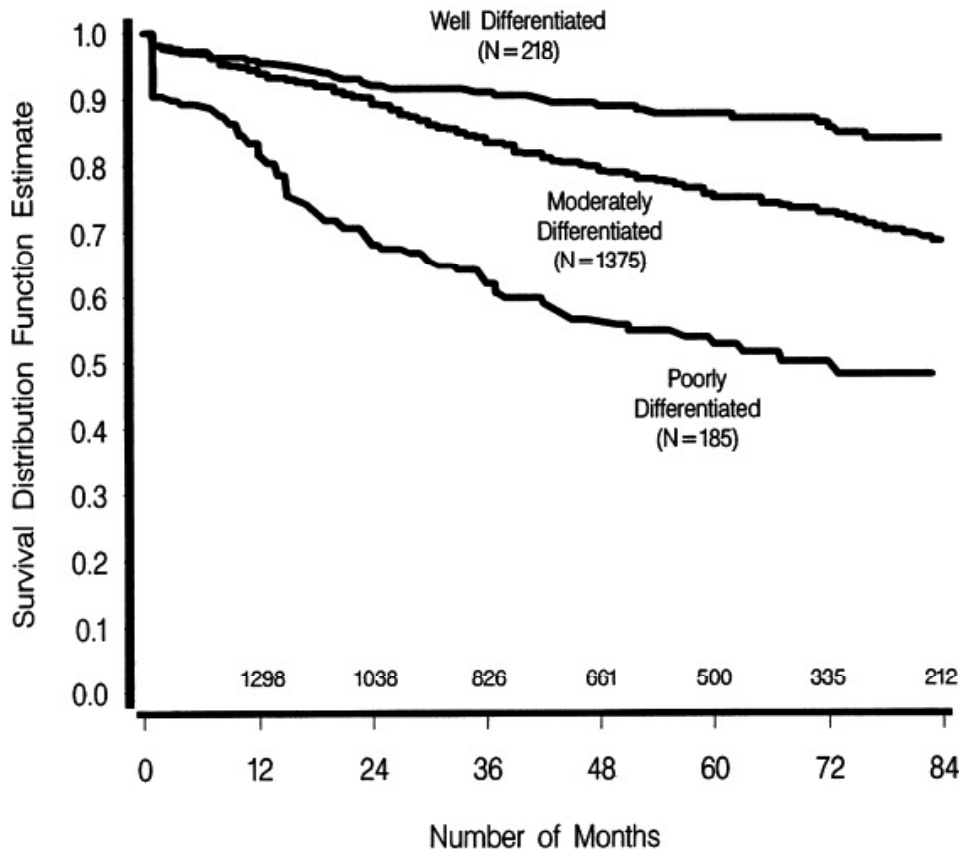


Statistics: 680 eligible patients/arm (1360 overall) has 0.92 power to detect a 30% increase in median survival; one-sided test at $p=0.05$.

Rationale for Protocol

- Immediate androgen blockade improves survival in node positive disease (Mayo Clinic study)
- Androgen blockade improves survival in advanced local disease treated with radiation therapy (Granfors, Bolla, Pilepich, D'Amico studies)
- Adjuvant chemotherapy improves survival in other epithelial malignancies
- Mitoxantrone standard of care in 1997 when this study was conceived. (Canadian Palliation trial (JCO 14:1756) and CALGB 9182 (JCO 17:2506))

Progression Free Survival Prediction circa 1998



**Catalona, W. et. al., J Urology
160:2428, December 1998**

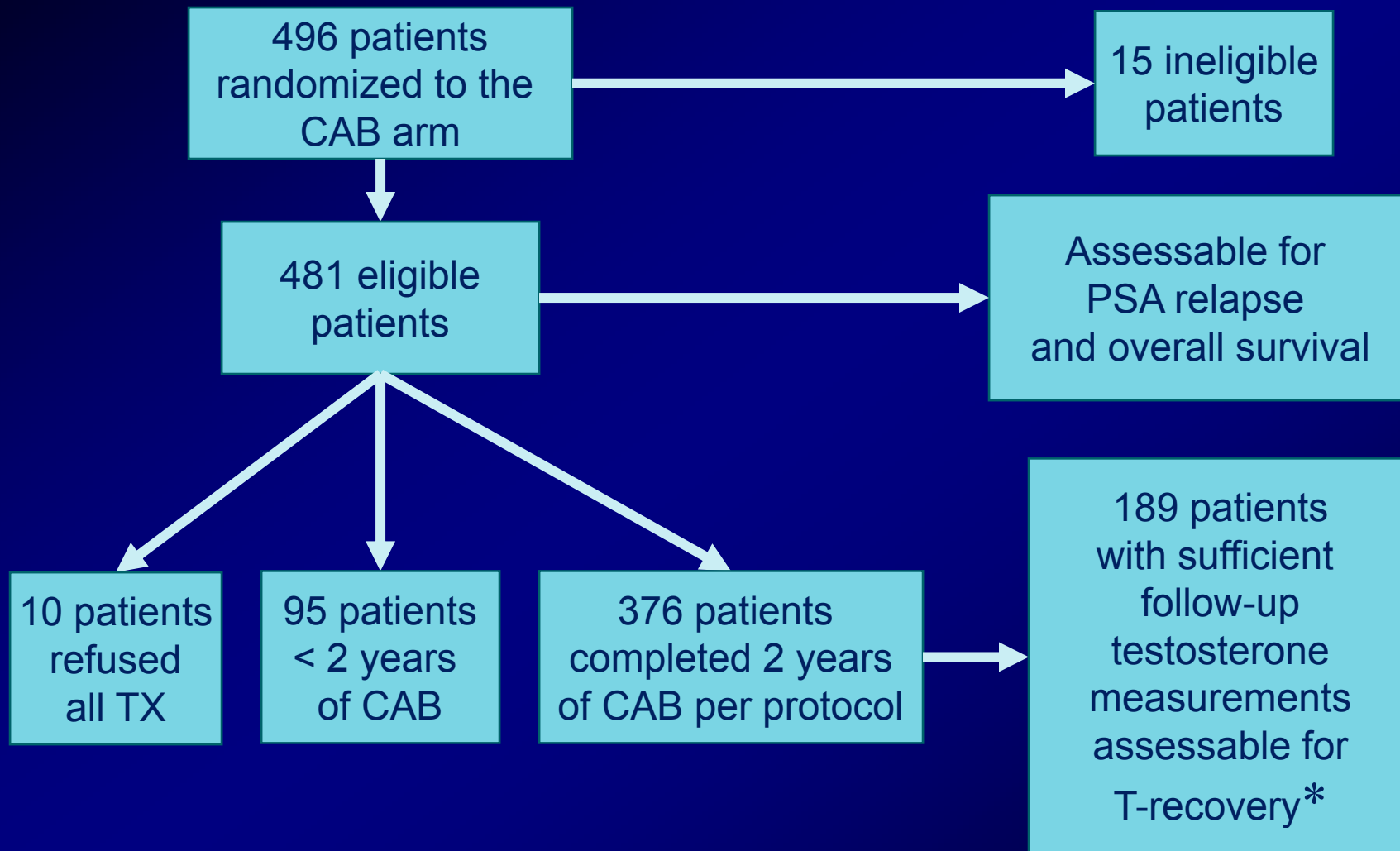
SWOG 9921

- Intergroup Participants: CALGB, ECOG
- Eligibility
 - Prostatectomy \leq 120 days prior to registration and one or more of the following:
 - Path Gleason sum \geq 8
 - pT3b (seminal vesicle) or pT4 or N1
 - Path Gleason's sum 7 and positive margin
 - Preop PSA $>$ 15ng/ml, or biopsy Gleason $>$ 7, or PSA $>$ 10ng/ml with biopsy Gleason $>$ 6

SWOG-9921 Timeline

- Study opened 10/1999.
- 1/2007, DSMC recommended closure to accrual and cessation of chemotherapy due to 3 cases of AML in the chemotherapy arm. Long-term follow-up was continued in both arms.
 - 2 additional cases of AML reported as of May, 2009 (5/487), 0 in the CAB only arm
- In 10/2008, the DSMC granted permission to report:
 - Survival and PSA relapse rates in the CAB arm.
 - Testosterone recovery across both arms.

Results in CAB Arm



* 187 patients from the chemotherapy arm were also included in the testosterone recovery analysis.

Analysis of Outcomes

	Sample Size N	5-Year PSA Relapse-free Estimate (95% CI)	5-Year Overall Survival Estimate (95% CI)
All Eligible Patients Randomized to CAB Arm of S9921	481	92.5% (89.5,95.6)	95.1% (92.6,97.7)

Analysis by Risk Groups

Risk Group	Sample Size N	5-Year PSA Relapse-free Estimate (95% CI)	5-Year Survival Estimate (95% CI)
Low (+margin or ECE and Gl 7)	124	98.5% (95.6,1.00)	94.8% (89.1,100)
Intermediate SV invasion or Gl ≥ 8	275	91.6% (87.5,96.0)	96.5% (93.9,99.3)
High (+ nodes)	77	87.5% (78.8,97.1)	90.3% (82.2,99.3)

Overall Survival Comparisons in D1 High Risk RRP Patients Treated with Adjuvant ADT

Study	N	5-yr Survival	Reference
Mayo Clinic	292	90%	Cancer 70:311, 1992
ECOG 3886	32	90%	Lancet Oncol 7:472, 2006
Univ. Essen	77	75-90%	BJU International 97:985, 2006
Columbia Univ.	24*	94%	Urology 70:723, 2007
USC	239	70-96%	J Urology 172:2252, 2004
THIS STUDY	77	90.3%	

* Not all patients received adjuvant ADT

Testosterone (T) Recovery ($\geq 50\text{ng/ml}$)

- Per protocol, T measured every 6 month intervals
- Patients included in analysis: ≥ 1 T measurement within the first 12 months after completing CAB.

Median T Recovery Time* (95% CI)	6 Month* Overall T Recovery (95% CI)	12 Month* Overall T Recovery (95% CI)	18 Month* Overall T Recovery (95% CI)
9.5 Months (8.7, 10.5)	27.8% (5.6, 71.4)	75.3% (50.8, 90.0)	89.5% (69.8, 96.9)

* Recovery time measured from completion of CAB.

Conclusions

- S9921 shows better than predicted DF-survival in high risk patients who received 2 years of CAB, comparable to contemporary studies
 - Potential causes: stage migration, patient selection, lead time bias, effects of CAB itself.
- 75% of patients have testosterone recovery to above castrate level within one year of stopping CAB
- Much longer follow-up required to assess mitoxantrone's impact on survival.
- Better definitions of high risk disease are needed for future trials (biomarkers, systems pathology)

Abstract 5011 Scher et al. Antitumor Activity of MDV3100 in a Phase 1-2 Study of Castration-Resistant Prostate Cancer (Prostate Cancer Clinical Trials Consortium)

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.

MDV3100 Phase 1-2 Multicenter Trial

Endpoints

1. Determine safety , pharmacokinetics (PK)
2. Assess antitumor activity by PSA response, RECIST, bone
3. Explore markers: Circulating tumor cells; PET with FDG - 18-fluorodeoxyglucose, FDHT 18-fluorodihydrotestosterone

Inclusion Criteria

1. No more than 2 prior chemotherapy regimens, at least one of which contained docetaxel
2. Castrate Resistant, serum testosterone level <50 ng/dL
3. Progressive disease defined as one or more of: 1) 3 rising PSA levels; screening PSA ≥ 2 ng/mL; 2) RECIST; > 2 new lesions on bone scan

Dose Expansions Allowed Rapid Enrollment of 140 Patients Across Dose Levels

Dose (mg/day)	Pre- Chemotherapy	Post- Chemotherapy	Total
30	3	-	3
60	15	12	27
150	15	13	28
240	17	12	29
360	15	13	28
480	-	22	22
600	-	3	3
<i>TOTAL</i>	<i>65</i>	<i>75</i>	<i>140</i>

MDV3100 Was Generally Well-Tolerated

Possibly Related Grade 2/3 Adverse Events in >2 Patients

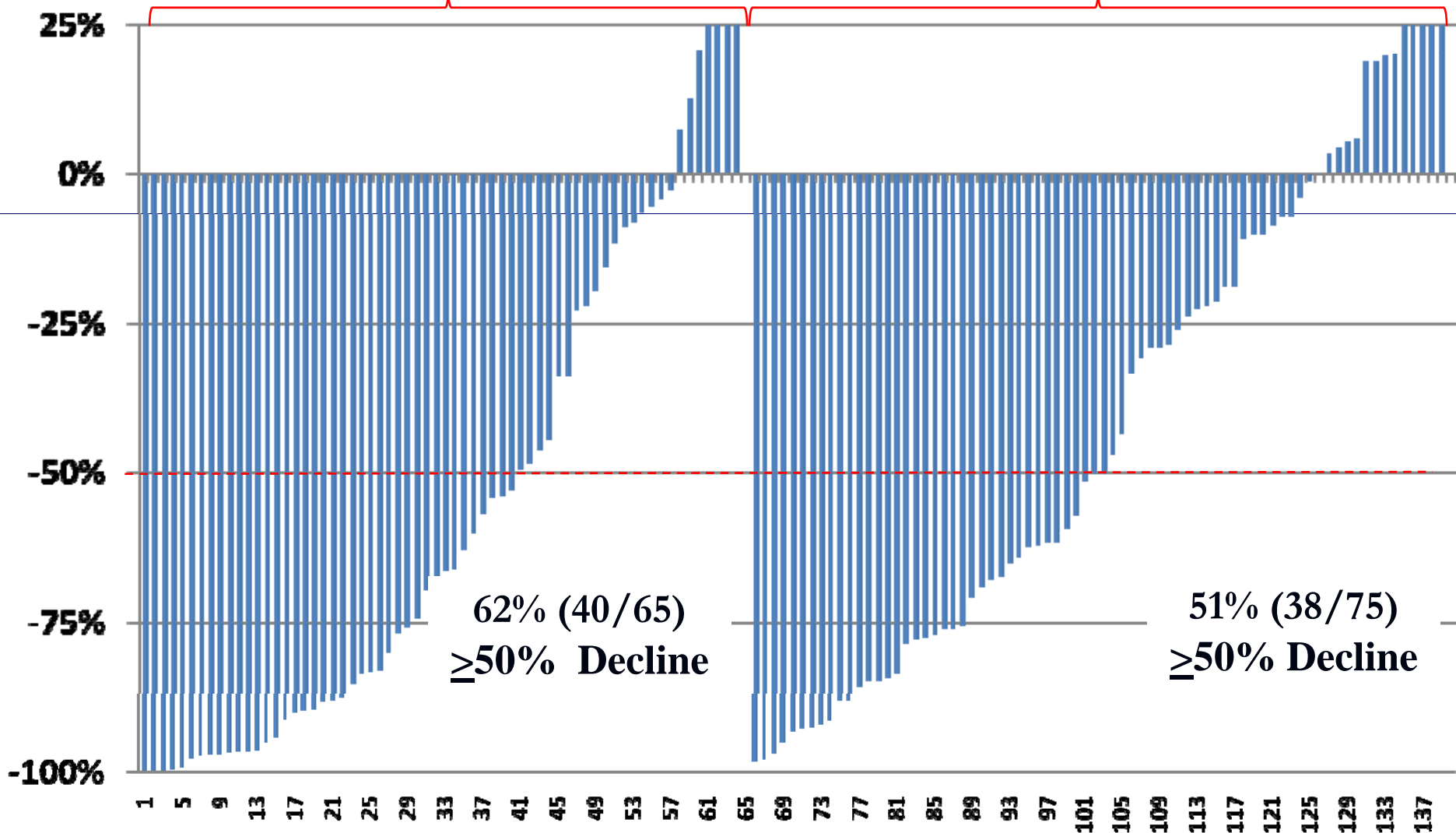
Adverse Event	All Doses (N = 140)		240 mg/day (N = 60)	
	G2	G3	G2	G3
Fatigue	29 (21%)	12 (9%)	8 (13%)	3 (5%)
Nausea	11 (8%)	—	2 (3%)	—
Anorexia	4 (3%)	—	—	—
Seizure	—	3 (2%)	—	—

1. Only one subject discontinued treatment due to fatigue which coincided with disease progression
2. Two witnessed seizures (one each at 600 and 360 mg/day) and a possible unwitnessed seizure (at 480 mg/day) were reported
 - 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

Waterfall Plot of Best Percent PSA Change from Baseline

Chemotherapy-Naïve (N=65)

Post-Chemotherapy (N=75)

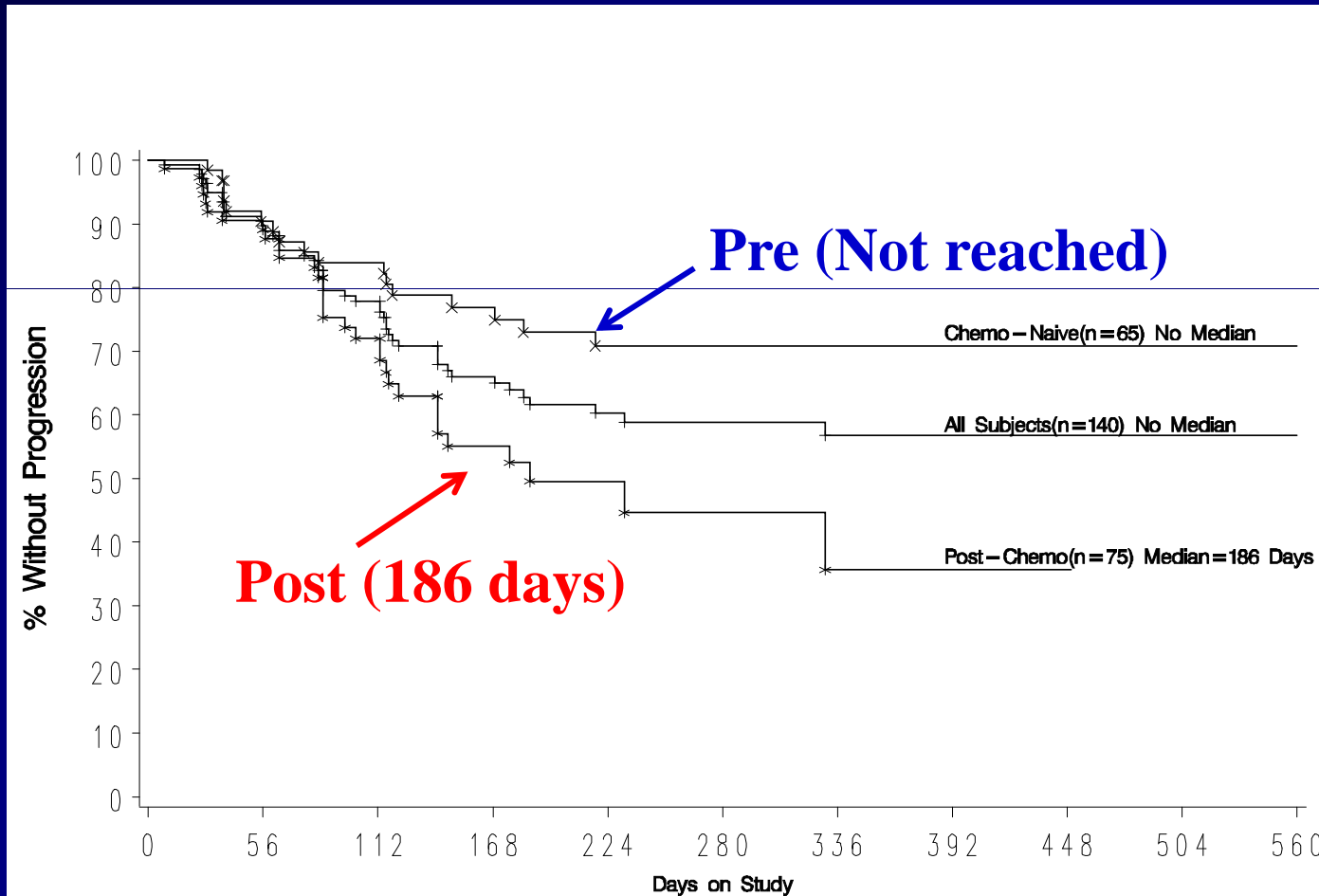


Radiographic Changes in Soft Tissue (N=59) and in Bone (N=109)

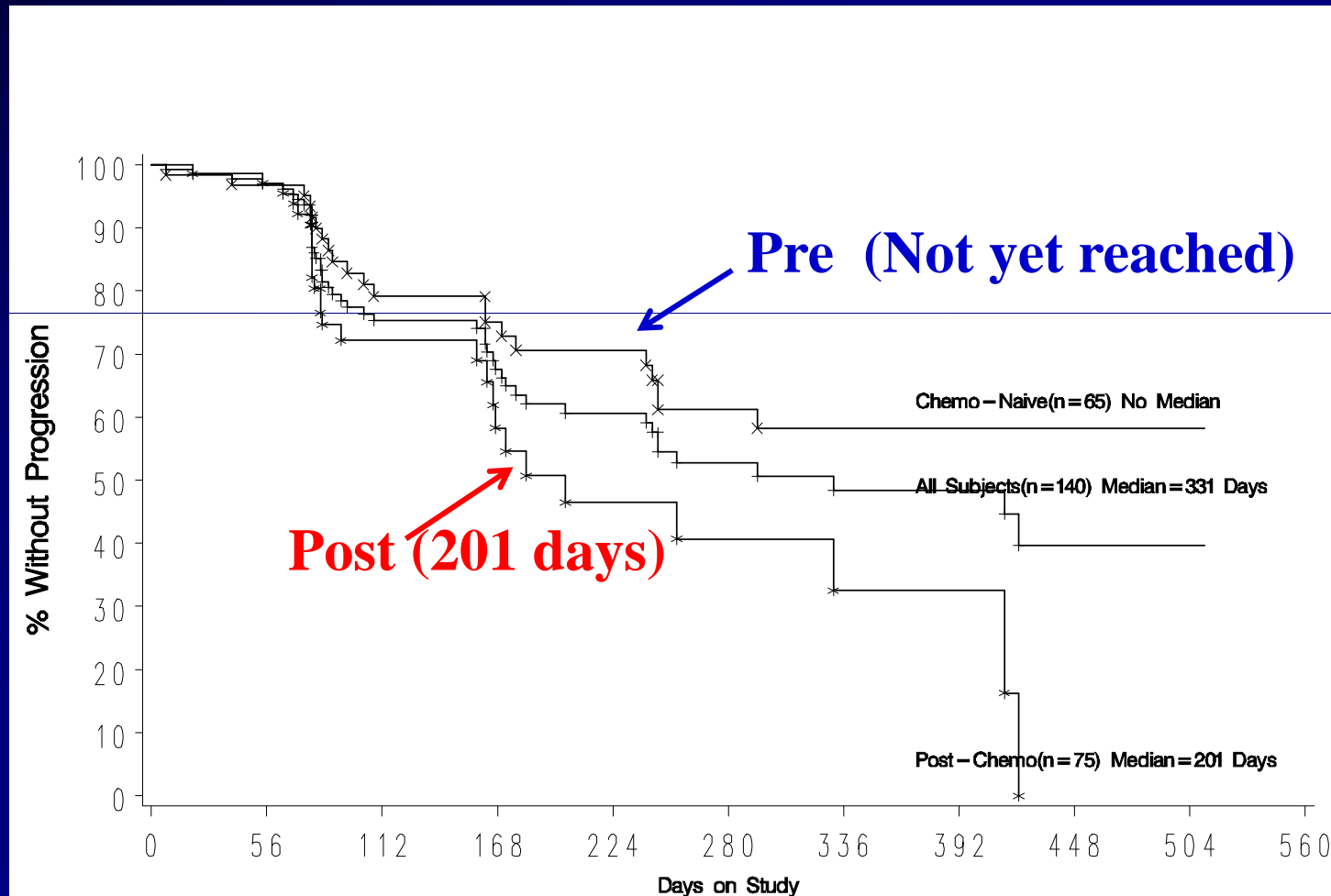
	Chemotherapy-Naïve Patients (N=65)	Post-Chemotherapy Patients (N=75)
<u>Soft Tissue* (Best Response)</u>	N=25	N=34
Partial Response	36% (9/25)	12% (4/34)
Stable Disease	44% (11/25)	53% (18/34)
<u>Bone Scan (Week 12)</u>	N=41	N=68
Stable Disease	63% (26/41)	51% (35/68)

*59 patients with evaluable soft tissue disease as defined by PCWG2 consensus
 . J Clin Oncol 2008.

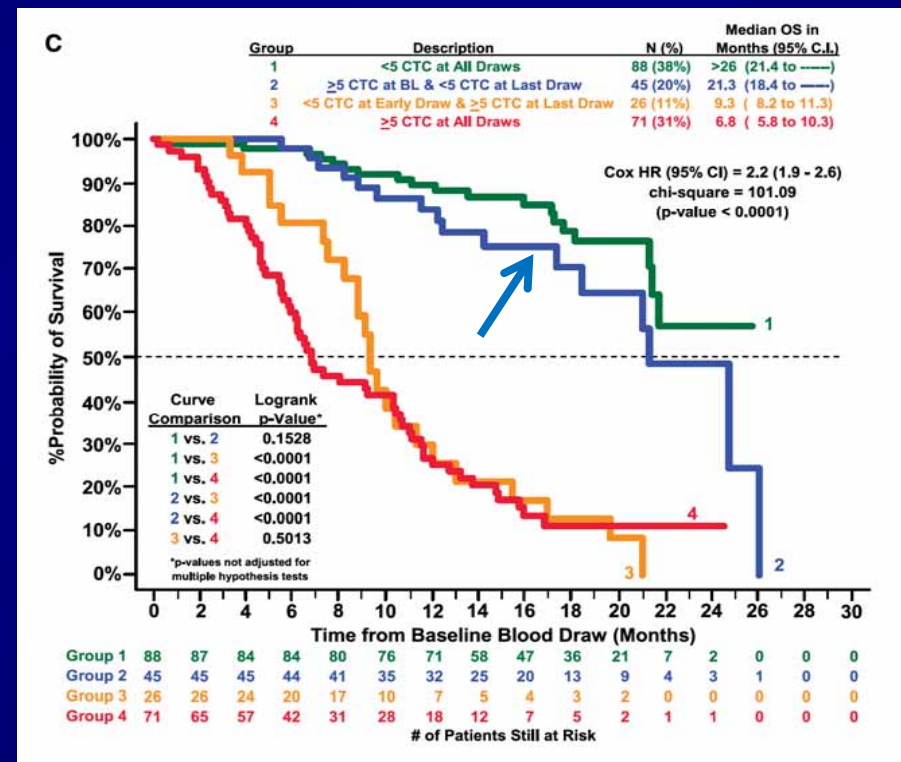
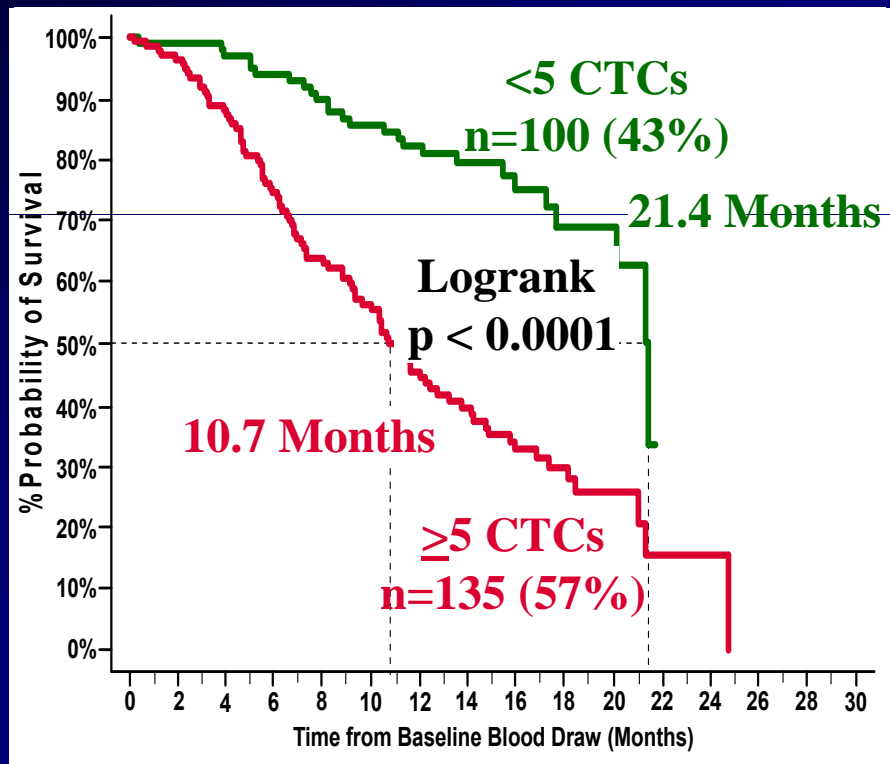
Time to PSA Progression For Pre- and Post-Chemotherapy Treated Patients



Time to Radiographic Progression in Pre- and Post-Chemotherapy Treated Patients



Circulating Tumor Cell Number is Prognostic and Treatment Predictive: Conversion From Unfavorable (≥ 5) to Favorable (< 5) Suggests Treatment Benefit



De Bono, Scher, Montgomery et al. Clin Cancer Res (2008)

Pre- and Post-Treatment CTC Number (N=128/140)

*12 patients with no baseline and/or follow-up CTC count

	Total (N=128/140)	Pre-Chemotherapy (N=60/65)	Post-Chemotherapy (N=68/75)
Favorable to Favorable	91% (70/77)	91% (40/44)	91% (30/33)
Favorable to Unfavorable	9% (7/77)	9% (4/44)	9% (3/33)
Unfavorable to Favorable	49% (25/51)	75% (12/16)	37% (13/35)
Unfavorable to Unfavorable	51% (26/51)	25% (4/16)	63% (22/35)

Favorable < 5 CTCs/7.5 ml

Unfavorable ≥ 5 CTCs/7.5 ml

Conclusions

MDV 3100 is active both before and after chemotherapy

MDV3100 is generally well-tolerated

Dose selected to be 240 mg/day based upon:

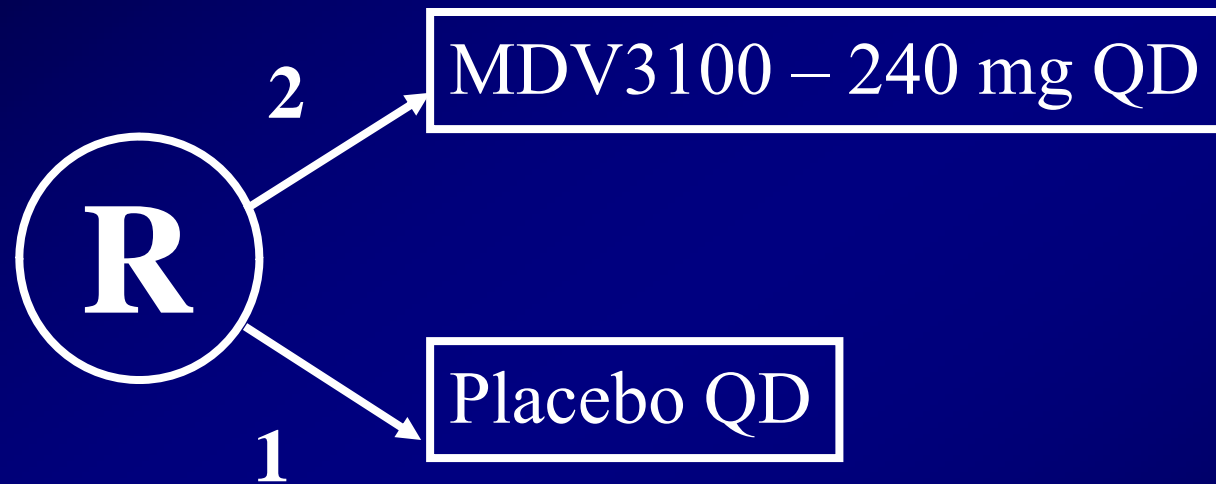
- Significant anti-tumor effects plateau at this dose

- Few side effects

- Benefit:risk ratio

A Phase 3 placebo-controlled survival trial in post-docetaxel CRPC patients is beginning this year

Phase 3 Registration Trial of MDV3100 in Post-Chemotherapy CRPC Patients



Primary Endpoint:	25% survival increase (12 to 15 months)
Sample size:	~1170 (780 and 390)
Statistics:	85% Power; $p=0.05$, two-sided
Biomarkers:	CTC enumeration and profiling with outcome

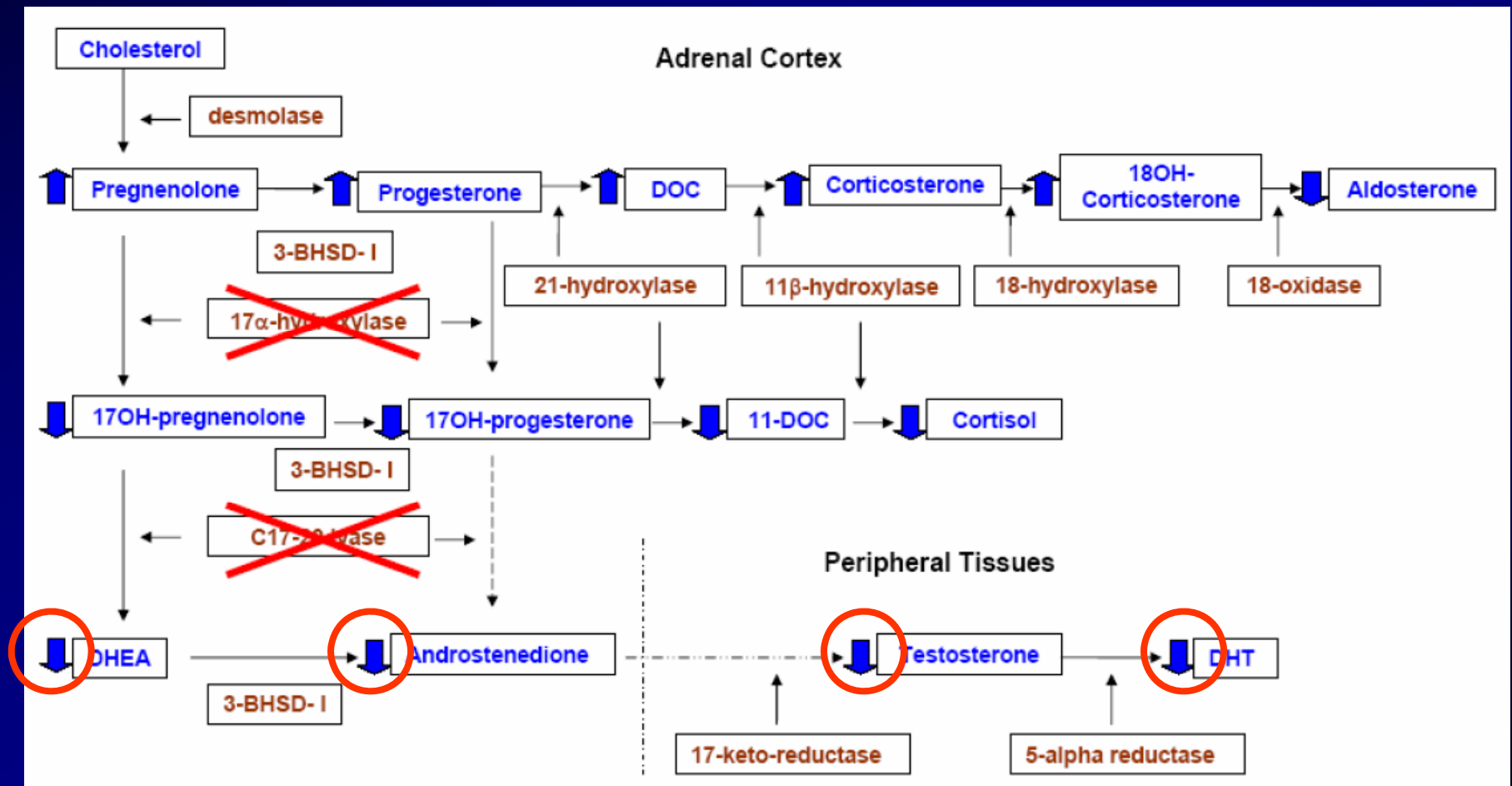
Abstract 5047 Reid et al. A multicenter phase 2 study of abiraterone acetate (AA) demonstrates anti-tumor activity in docetaxel pre-treated castration-resistant prostate cancer (CRPC) patients (pts)

Patient Eligibility

Castrated male patients with androgen independent metastatic prostate cancer

- Documented PSA Progression per PSA Working Group consensus criteria
- ECOG PS of ≤ 2
- Prior Chemotherapy with paclitaxel or docetaxel

Abiraterone acetate (AA) specifically and irreversibly inhibits CYP17, a key enzyme in androgen biosynthesis, blocking two important enzymatic activities in the synthesis of testosterone



Patient Characteristics (N=47)

	Baseline Value
Age (Median)	67.0 years (range 48-87)
ECOG Performance Status	n (%)
ECOG 0	16 (34.0)
ECOG 1	27 (57.4)
ECOG 2	4 (8.5)
Prior Hormonal Therapies:	n (%)
LHRH Agonists	47 (100.0)
Antiandrogens	46 (97.9)
Estrogens	17 (36.2)
Diethylstilbestrol	17 (36.2)
Other estrogens	3 (6.4)
Steroids	27 (57.4)
Dexamethasone	17 (36.2)
Other Steroids	17 (36.2)
Ketoconazole	8 (17.0)
Orchiectomy	0

Study Treatment

- Daily Abiraterone Acetate at a dose of 1000 mg/day
- Concurrent low-dose glucocorticoid, cycled at 28 days
- Patients evaluated for response by PSAWG criteria
- Serum hormone levels were evaluated in all patients

Duration on Study Drug (N=47)

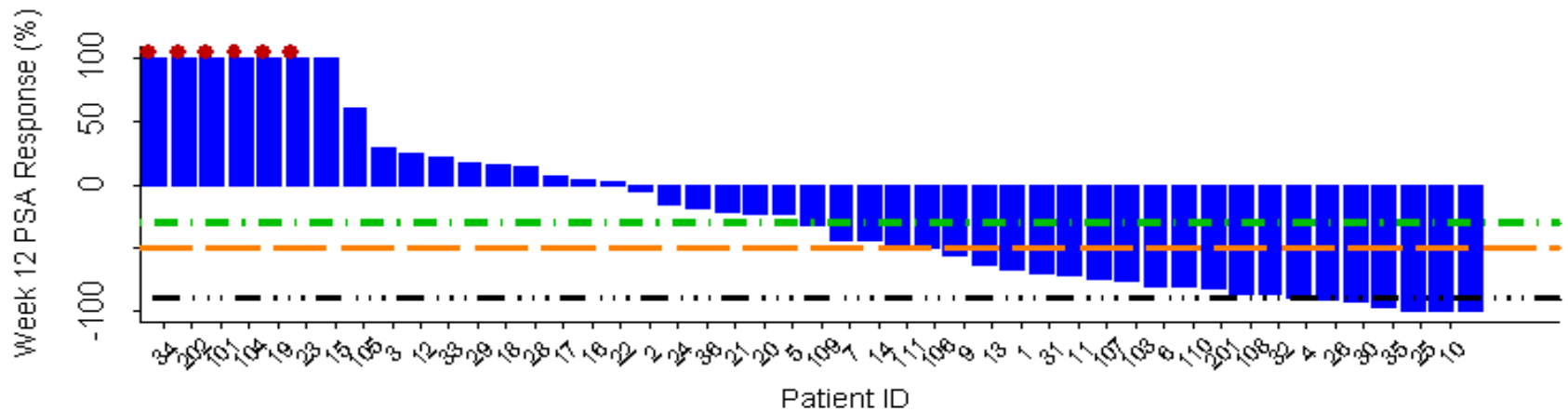
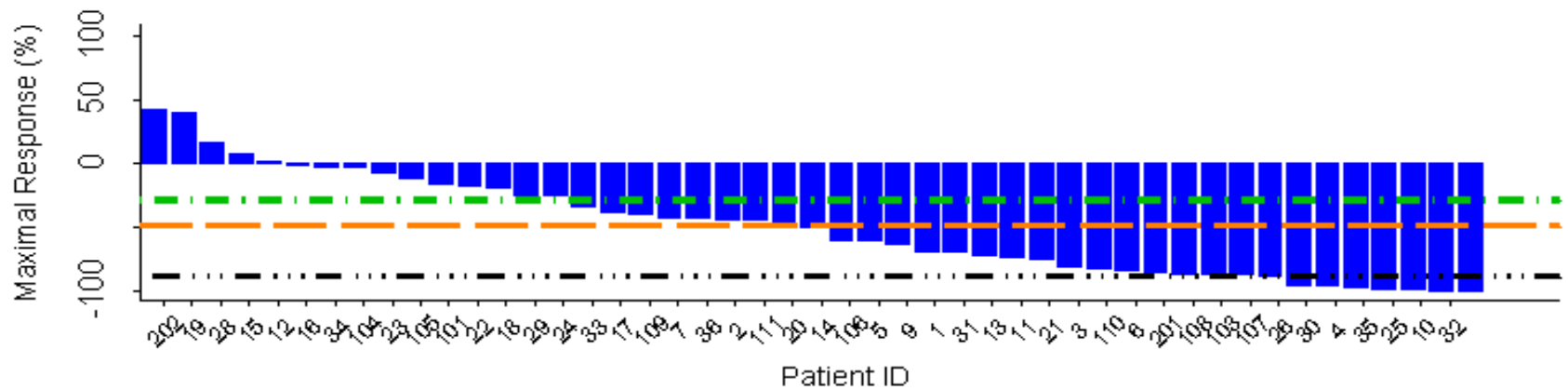
Duration Category	n (%)
0 - ≤12 Weeks	12 (25.5)
13 - ≤ 24 Weeks	16 (34.0)
25 - ≤ 36 Weeks	4 (8.5)
37 - ≤ 48 Weeks	14 (29.8)
> 48 Weeks	1 (2.1)

Abiraterone Acetate (AA) in docetaxel pre-treated castration-resistant prostate cancer patients

All Grade 3/4 Toxicity by NCI CTC Grade

Toxicity (Experienced by ≥ 2 patients)	Grade (N = 47)	
	3 n (%)	4 ² n (%)
Anemia	2 (4.3)	-
Lymphopenia	2 (4.3)	-
Nausea	3 (6.4)	-
Emesis	3 (6.4)	-
Fatigue	4 (8.5)	-
Femur Fracture	2 (4.3)	-
Anorexia	2 (4.3)	-
Groin Pain	2 (4.3)	-
Renal Failure	2 (4.3)	-

Maximal and Week 12 PSA Responses



● --PSA value clipped

Reference Lines: Black=-90% Orange=-50% Green=-30%

Abiraterone Acetate (AA) in docetaxel pre-treated castration-resistant prostate cancer patients

Best Tumor Response (N=47)

Response	n (%)
PR	7 (14.9)
SD	24 (51.1)
PD	5 (10.6)
Unknown	11 (23.4)

Total Week 12 PSA Response (N=47)

Response	n (%)
PSA Decline $\geq 30\%$	24 (51.1)
PSA Decline $\geq 50\%$	19 (40.4)
PSA Decline $\geq 90\%$	6 (12.8)

Best Post-Baseline ECOG Status

(N=47)

	Post-Baseline		
Baseline	ECOG 0	ECOG 1	ECOG 2
ECOG 0	15	1	0
ECOG 1	10	17	0
ECOG 2	0	1	3
Total	25 (53.1%)	19 (40.4%)	3 (6.3%)

Conclusion

- Abiraterone acetate was well-tolerated
- Sustained PSA declines seen
- Improvement in ECOG and RECIST responses
- A Phase 3 trial assessing the efficacy and safety of AA and prednisone in CRPC pts who have failed docetaxel chemotherapy is being conducted

Abstract 5048 Danila et al. Phase 2 multicenter study of abiraterone acetate plus prednisone therapy in docetaxel treated CRPC patients: Impact of prior ketoconazole.

Methods

CRPC with PSA progression on docetaxel chemotherapy

Abiraterone acetate orally at 1000 mg daily for 28 day cycles

Prednisone orally 5 mg twice daily in 28 day cycles

Patients required to have normal organ function, ECOG PS of ≤ 2 .

Primary objective:

PSA decline of $\geq 50\%$ according to PSAWG criteria (PSA response).

Time to PSA Progression was calculated for pts with PSA decline $\geq 50\%$ from baseline until PSA increased 50% above the nadir and more than 5ng/mL; or PSA progression calculated when PSA increased by 25% from baseline.

Baseline Patient Characteristics

(N=58)

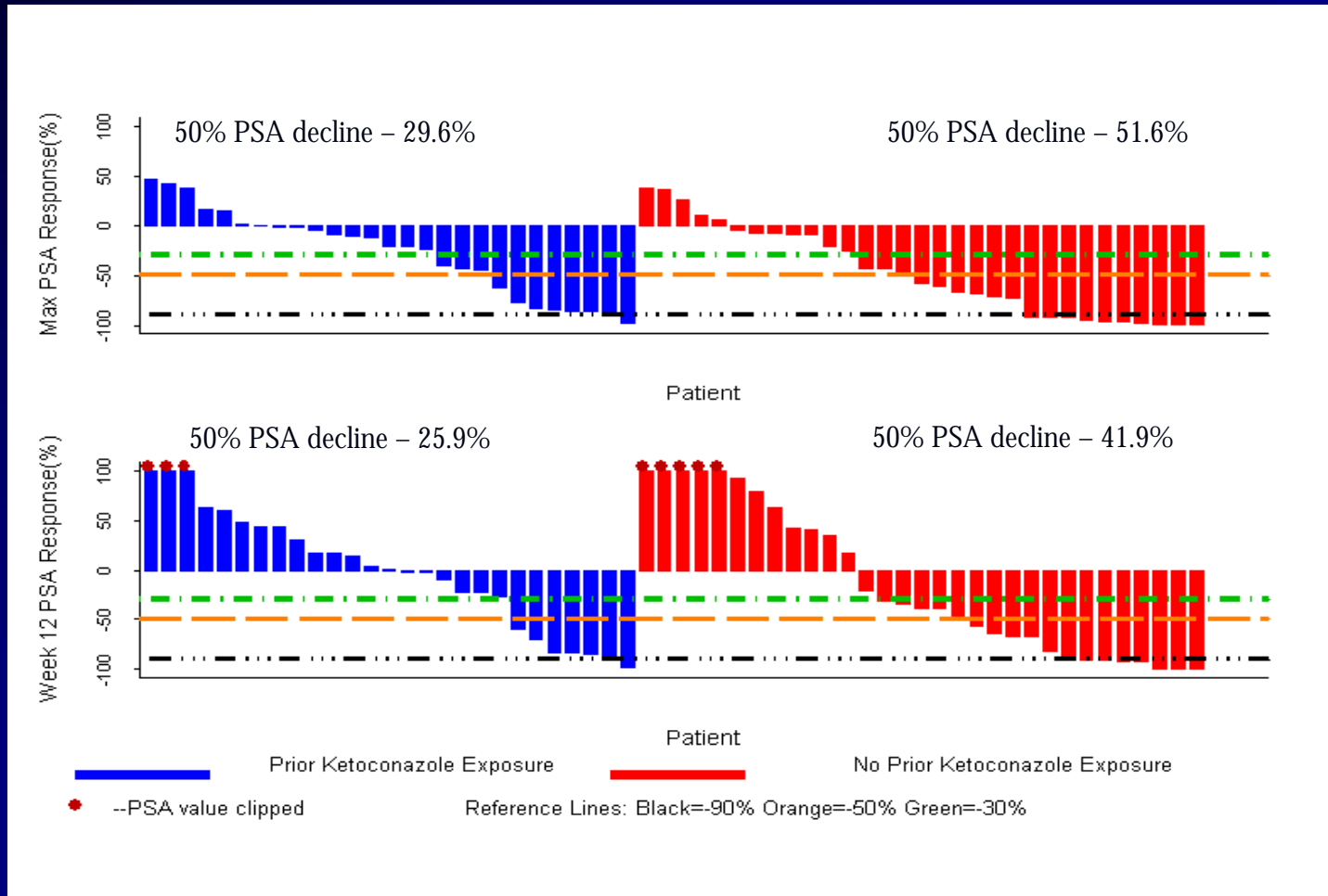
Age (Median)	69.5 years (range 44-86)
Metastases	n (%)
Visceral (with or without bone/soft tissue)	13/58 (22.4)
Bone only	11/58 (19.0)
Soft tissue only	8/58 (13.8)
Bone and soft tissue only	26/58 (44.8)
Prior Hormonal Therapies:	n (%)
LHRH Agonists	57 (98.3)
Antiandrogens	53 (91.4)
Estrogens	9 (15.5)
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)

Duration on Study Drug

(N=58)

Duration Category	n (%)
0 - <12 Weeks	20 (34.5)
12 - <24 Weeks	16 (27.6)
24 - <36 Weeks	6 (10.3)
36 - <48 Weeks	8 (13.8)
≥ 48 Weeks	8 (13.8)

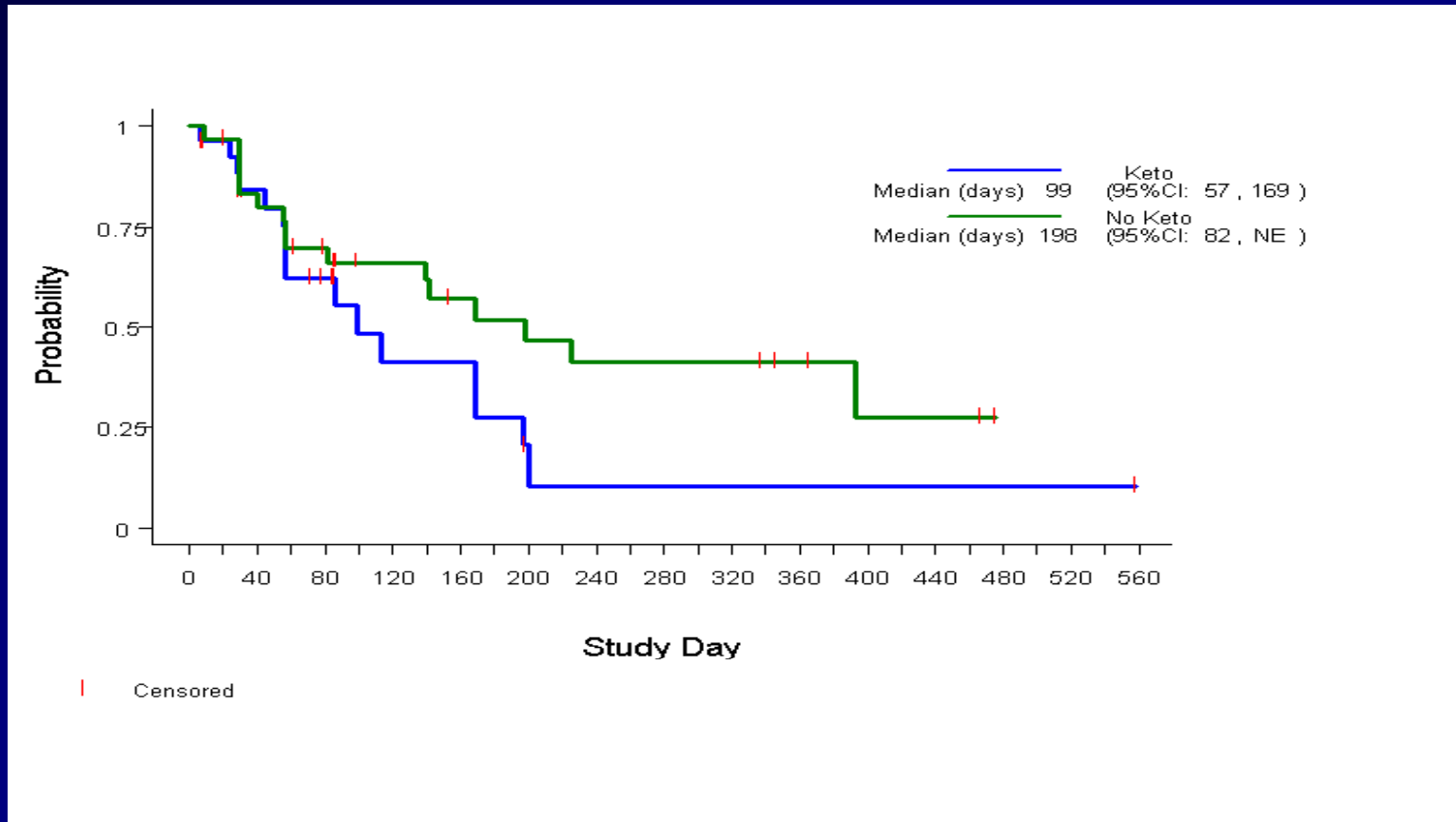
Change in PSA with Treatment (N=58)



* No data on PSA changes in one patient in each group

Time to PSA Progression

(N=58)



Tumor Radiologic Assessment

Tumor Response by CT (Target Lesions)	Number (%) of Patients (n=18)
PR	3 (16.7)
SD	11 (61.1)
PD	4 (22.2)

Tumor Response by Bone	Number (%) of Patients (n=28)
SD	27 (96.4)
PD	1 (3.6)

Grade 3/4 Toxicity by NCI CTCAE ¹ Grade (N=58)

Toxicity by Preferred Term (experienced by ≥ 2 patients)	Grade	
	3 n (%)	4 n (%)
Lymphopenia	4 (6.9)	-
Back Pain	2 (3.4)	-
Pain in Extremity	3 (5.2)	-
Spinal Cord Compression	-	2 (3.4)
Renal Failure	2 (3.4)	-
Dyspnea	2 (3.4)	-

Best Post-Baseline ECOG Results (N=58)

Baseline	Post-Baseline ¹ (n=57)		
	ECOG 0	ECOG 1	ECOG 2
ECOG 0	22	2	0
ECOG 1	14	15	2
ECOG 2	1	1	0
Total	37 (64.9%)	18 (31.6%)	2 (3.5%)

Conclusion

The combination of abiraterone acetate and low dose prednisone is well tolerated.

There is anti-tumor activity in heavily pre-treated patients.

The decline in PSA $>50\%$ in keto-naïve patients vs. keto exposed patients was not statistically different ($p=0.11$).

Improved or stable ECOG PS scores were frequently seen.

Phase III trial in patients previously-treated with docetaxel is ongoing.

Abstract 5049 Fleisher et al. Circulating tumor cells in patients with metastatic castration resistant prostate cancer receiving abiraterone acetate after failure of docetaxel-based chemotherapy

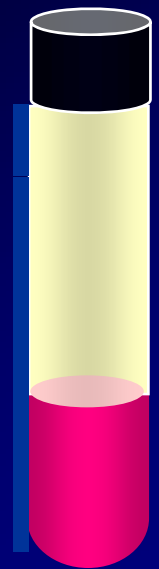
Objectives (N=48)

Aim #1. To study the association of CTC counts, at baseline and after treatment, with outcome after Abiraterone Acetate.

Aim #2. To study androgen receptor gene amplification by FISH in CTC.

Aim #3. To evaluate intermediary endpoints for clinical benefit.

CTC are Counted Using CellTracks

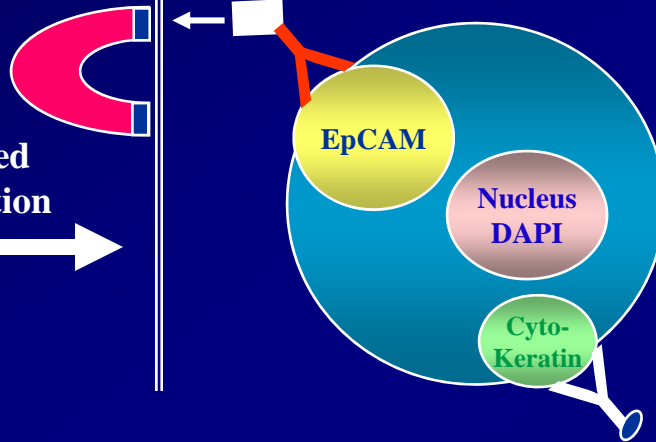


Low Speed
Centrifugation

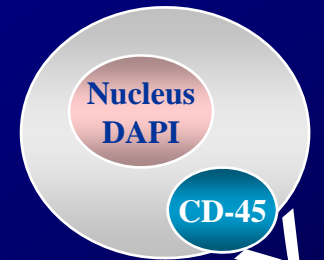
Stable 72 hrs

**SAMPLE
PREPARATION**

α -EpCAM Ferromagnetic
Conjugated MAB



α -CK-6, 8, 18-PE



α -CD-45-APC

**AUTOMATED IMMUNO-
MAGNETIC SELECTION, IF
STAINING CK, CD45, DAPI**



**DIGITAL IMAGE
ANALYSIS**

Veridex LLC

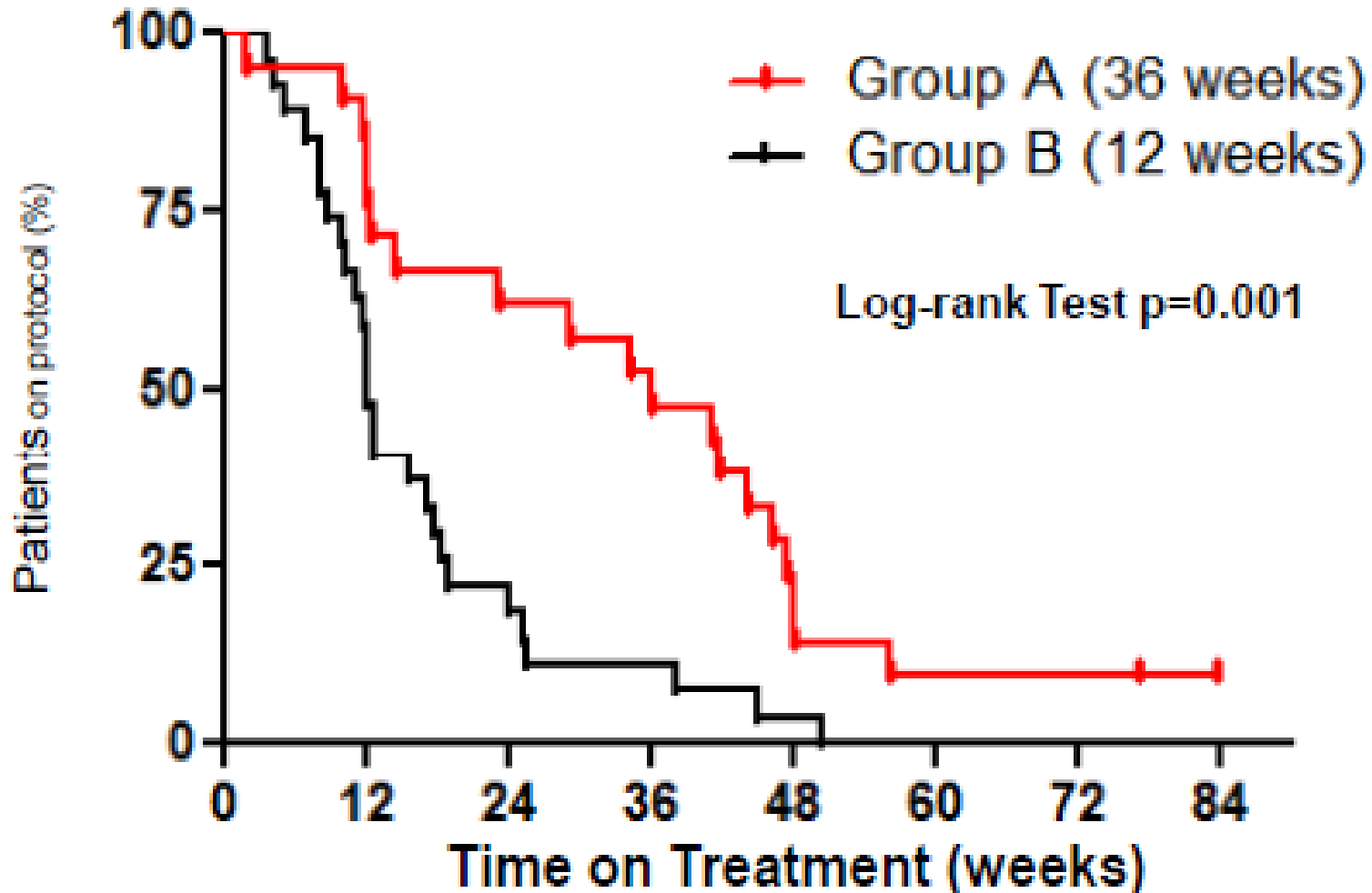
CTC Frequency at Baseline

CTC range	0 – 4	5 – 9	10 – 19	20 – 49	≥ 50	Total
Patient #	13	6	8	10	11	48

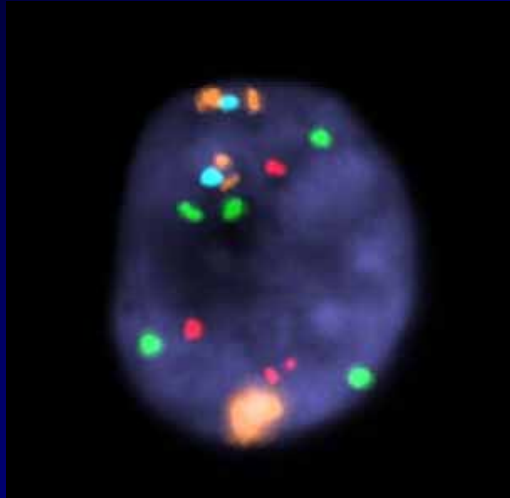
Lowering CTC Correlates with PSA decline $\geq 50\%$

Baseline CTC	Post Rx CTC	Pts # (% of 48 pts total)	PSA decline $\geq 50\%$	Time on treatment
Unfavorable	Favorable	11 (23%)	9 (82%)	Group A
Favorable	Favorable	11 (23%)	4 (36%)	
Unfavorable	Unfavorable	24 (50%)	4 (17%)	Group B
Favorable	Unfavorable	2 (4%)	1 (50%)	

Lowering CTC with Rx Correlates with Longer Time on Treatment



AR Alterations in CTC by FISH



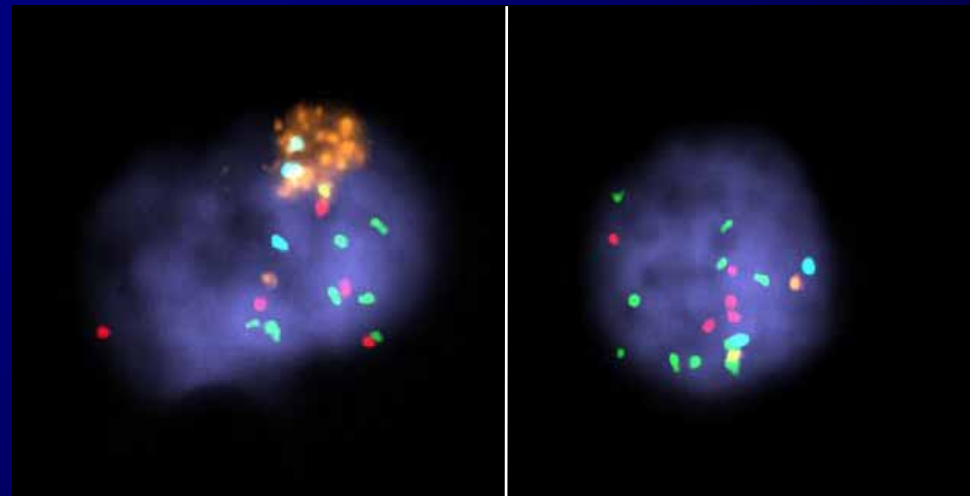
AR in orange

X centromere in aqua

MYC in green

8p (NAT2) in red

Heterogeneity of FISH patterns in CTC from one patient: AR amplification in some cells, and not in others, all with high copy gain for *MYC* and gain 8p



AR FISH Analysis in CTC

	AR Amplified	AR Copy Number Gain	No Abnormal AR Copy	Failed
Patients # (%) n=28	13 (46%)	8 (29%)	5 (18%)	2 (7%)
PSA decline ≥ 50%	5/13 (38%)	2/8 (25%)	4/5 (80%)	

Conclusions

- **Changes in CTC with treatment may represent valuable intermediary endpoints for clinical benefit.**
- **A change from baseline CTC ≥ 5 to <5 with treatment was associated with a significant decline in PSA by $\geq 50\%$.**
- **Molecular profiling of CTC by FISH can be a valuable, noninvasive surrogate for routine tumor profiling.**
- **CTC have the potential to guide therapy selection based on predicting clinically relevant outcomes.**

Prostate Cancer “Take-Home” Points

- MDV 3100 active in CRPC.
- Abiraterone active in CRPC.
- Phase III trials for both trials.
- CTC's and PSA dynamics both predictive of favorable outcomes to therapy.
- CTC technology evolving to more than a prognostic value based on count.