Phase II Study Design In Oncology Drug Development

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Disclosures

I have no relevant disclosures to make for this talk

Learning Objectives

- To define the role of a phase II study in oncology drug development
- To describe the statistical parameters that provide the framework and sample size for a phase II study
- To classify the types of phase II studies used in oncology drug development
- To describe the role(s) of randomization in phase II study design and conduct

Phase II Study

The phase II study has a pivotal role in drug development since the major decision to proceed with further testing is usually based on phase II results

Phase II Study Screens for Efficacy

Primary goal

- Identify and characterize the preliminary clinical efficacy of a new agent/ combination of agents/ schedule of administration

Secondary goals

- Characterize adverse event profile
- Understand mechanism of action
- Further define target population for administration of agent

Phase II Designs

- Multiple designs available
- Variations based on specific stage of development of the therapeutic intervention and how the results will inform continued drug development
- Defining characteristics
  - Endpoints: primary and secondary
  - Single or two stage design
  - Single arm or multiple arm design (randomized)
  - Statistical considerations: Type I and II error rates; H0 and HA (null and target drug activity rates); HR

Principles of Phase II Study Design

In general:

Smaller
- Response rate (H_A)
- α value
- β value

Larger
Sample size

Principles of Phase II Study Design

- Limit the number of patients exposed to a truly inactive drug
- Allow identification of a truly active drug
  - i.e. limit the risk of a false negative result

A Non Exhaustive Overview of Phase II Designs

Standard Single Arm Phase II Study

- Comparison is “fixed” constant
- Binary endpoint (clinical response vs. no response)
- Example
  - $\alpha = 0.10$
  - $B = 0.10$
  - H_0: $p=0.20$ (null response rate)
  - H_A: $p=0.40$ (target response rate)
- Based on design parameters sample size (N)=36
- Conclude effective if 11 or more responses (i.e. observed response rate of ≥0.31)

But we want to limit the exposure of patients to an inactive drug

Examples of Two-Stage Designs

- Gehan two-stage design (1961)
  - It is a two-stage design for estimating the response rate but providing for early termination if the drug shows insufficient antitumor activity
  - The design is most commonly used with a first stage of 14 patients. If no responses are observed, the trial is terminated
- Fleming two-stage design (1982)
  - Fleming's design is a two-stage design that may allow for early termination with an "accept the drug" conclusion
- Simon two stage design (1989)
  - Preserves the type 1 and II error rates and allows an early look; defines minimum and maximum number of patients enrolled under design characteristics

Table C.1 Minimax Designs for $p_1 - p_0 = 0.15$

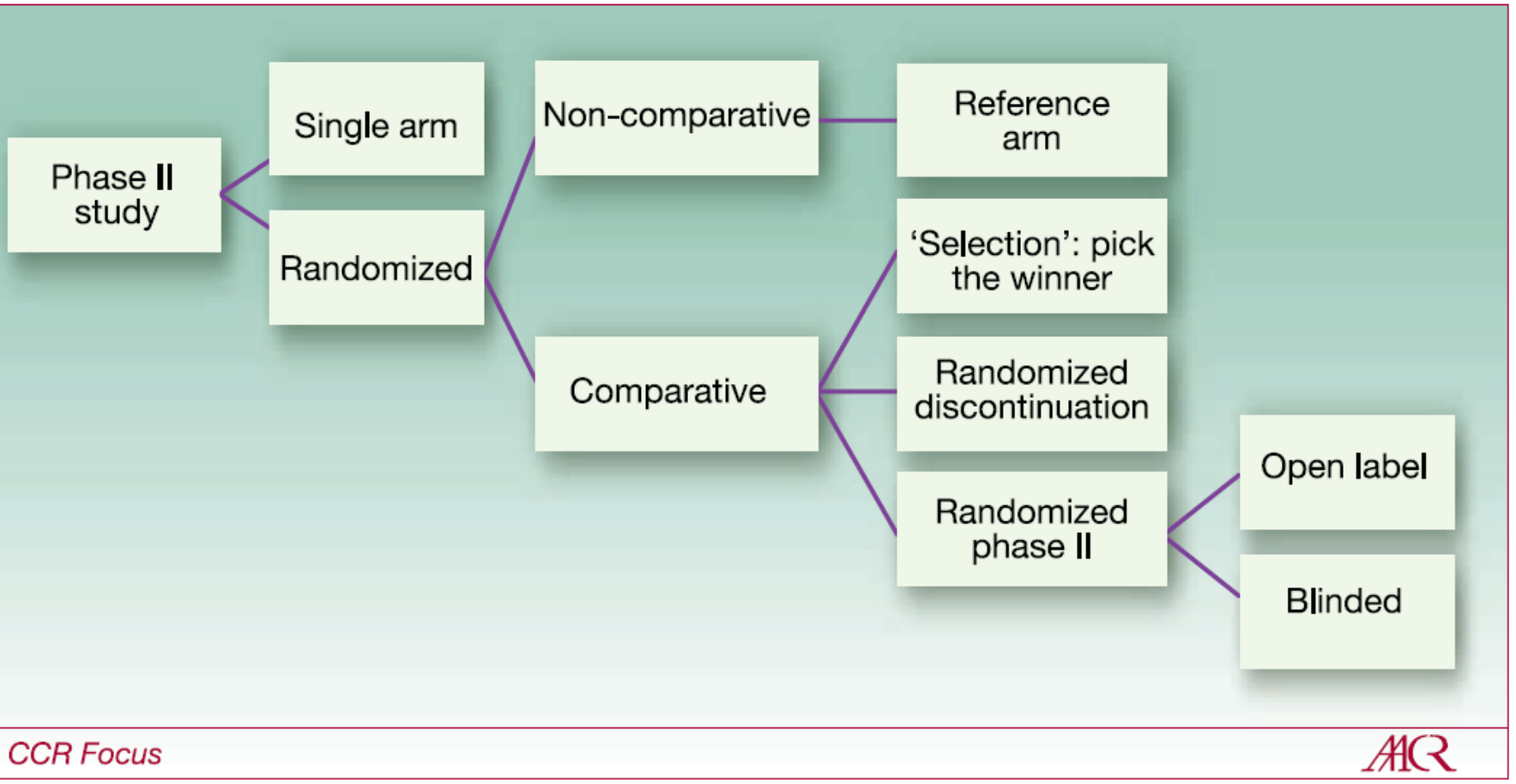
p_0	p_1	α	β	$\leqslant r_1/n_1$	$\leqslant r/n$	EN(p_0)	EN(p_1)	α'	β'	PET(p_0)	PET(p_1)
0.05	0.20	0.10	0.10	0/18	3/32	26.29	24.76	0.072	0.099	0.408	0.517
		0.05	0.20	0/13	3/27	19.77	22.69	0.042	0.199	0.516	0.308
		0.05	0.10	1/29	4/38	32.74	31.44	0.039	0.100	0.584	0.729
		0.05	0.05	1/32	5/50	40.56	38.36	0.037	0.050	0.525	0.647
0.10	0.25	0.10	0.10	2/27	6/40	33.51	32.85	0.098	0.100	0.499	0.550
		0.05	0.20	2/22	7/40	28.82	36.00	0.040	0.197	0.621	0.222
		0.05	0.10	3/31	9/55	40.01	48.77	0.042	0.099	0.624	0.260
		0.05	0.05	4/41	11/70	52.34	60.40	0.042	0.049	0.609	0.331
0.20	0.35	0.10	0.10	6/33	15/58	45.48	55.37	0.099	0.100	0.501	0.105
		0.05	0.20	6/31	15/53	40.43	51.05	0.050	0.198	0.571	0.089
		0.05	0.10	8/42	21/77	58.42	75.79	0.044	0.100	0.531	0.034
		0.05	0.05	15/68	25/95	75.43	85.71	0.050	0.049	0.725	0.344
0.30	0.45	0.10	0.10	16/50	25/69	55.99	64.45	0.100	0.098	0.685	0.239
		0.05	0.20	16/46	25/65	49.63	61.51	0.050	0.197	0.809	0.184
		0.05	0.10	27/77	33/88	78.45	80.83	0.050	0.099	0.868	0.652
		0.05	0.05	19/65	42/114	89.14	113.64	0.046	0.050	0.507	0.007

Can we improve the efficiency of the phase II trial design?

Multiple Arm (Randomized) Phase II Design

- Randomization increasingly used to enhance efficiency of phase II study
- Randomization is a *process* and further details are needed to understand the goals and design of the study

Types of Phase II Studies

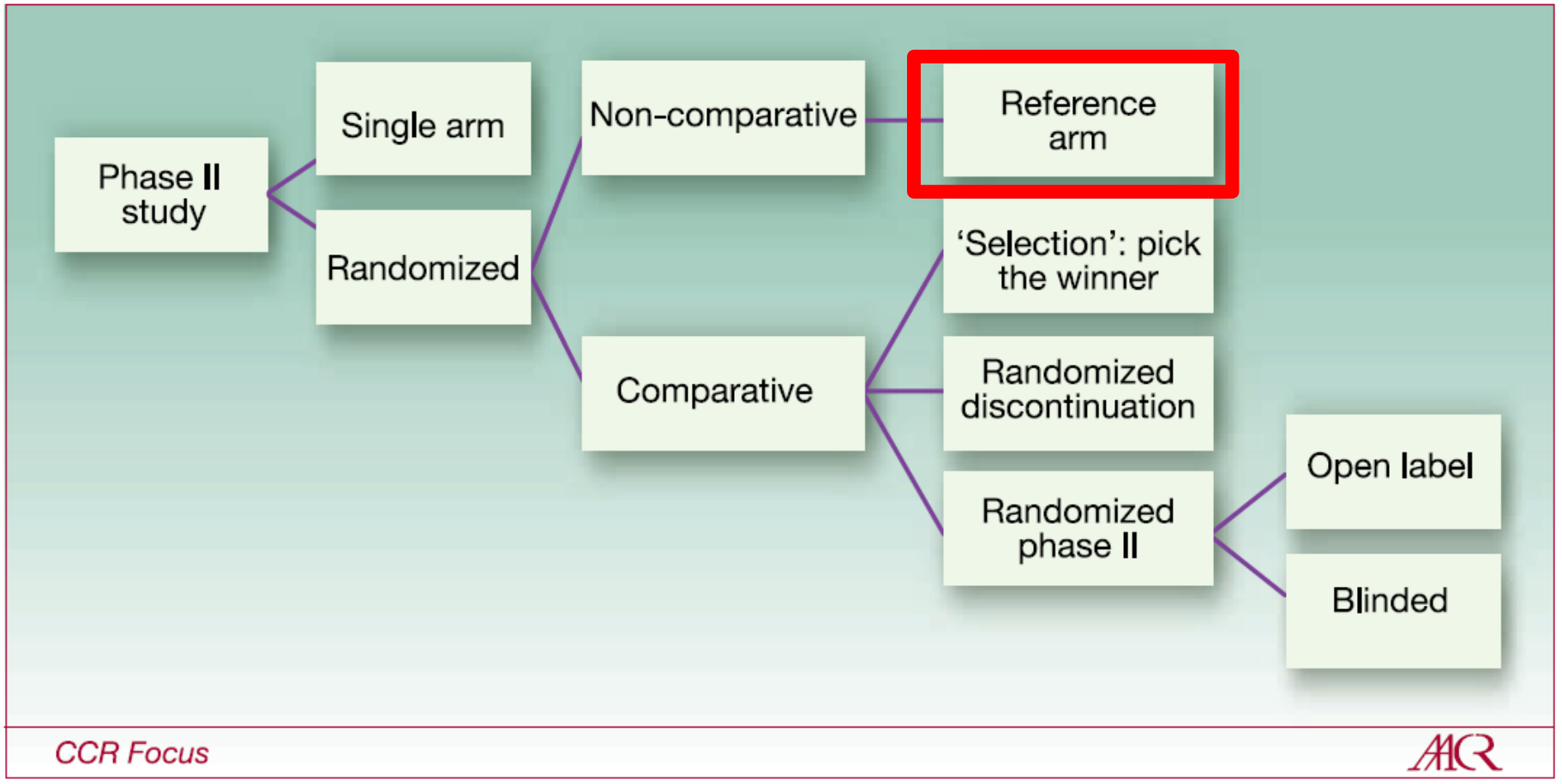


Clin Cancer Res; 16(6) March 15, 2010

Randomized Phase II Study Design: Examples from the NCIC CTG Casebook (and others!)

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

Types of Phase II Studies



Clin Cancer Res; 16(6) March 15, 2010

Docetaxel and Prednisone With or Without OGX-011 in Patients With Metastatic Castration-Resistant Prostate Cancer

NCIC CTG IND.165

CHI ET AL, J CLIN ONCOL 2010

NCIC CTG
NCIC GEC

Rationale

Castration Resistant Prostate Cancer (CRPC)

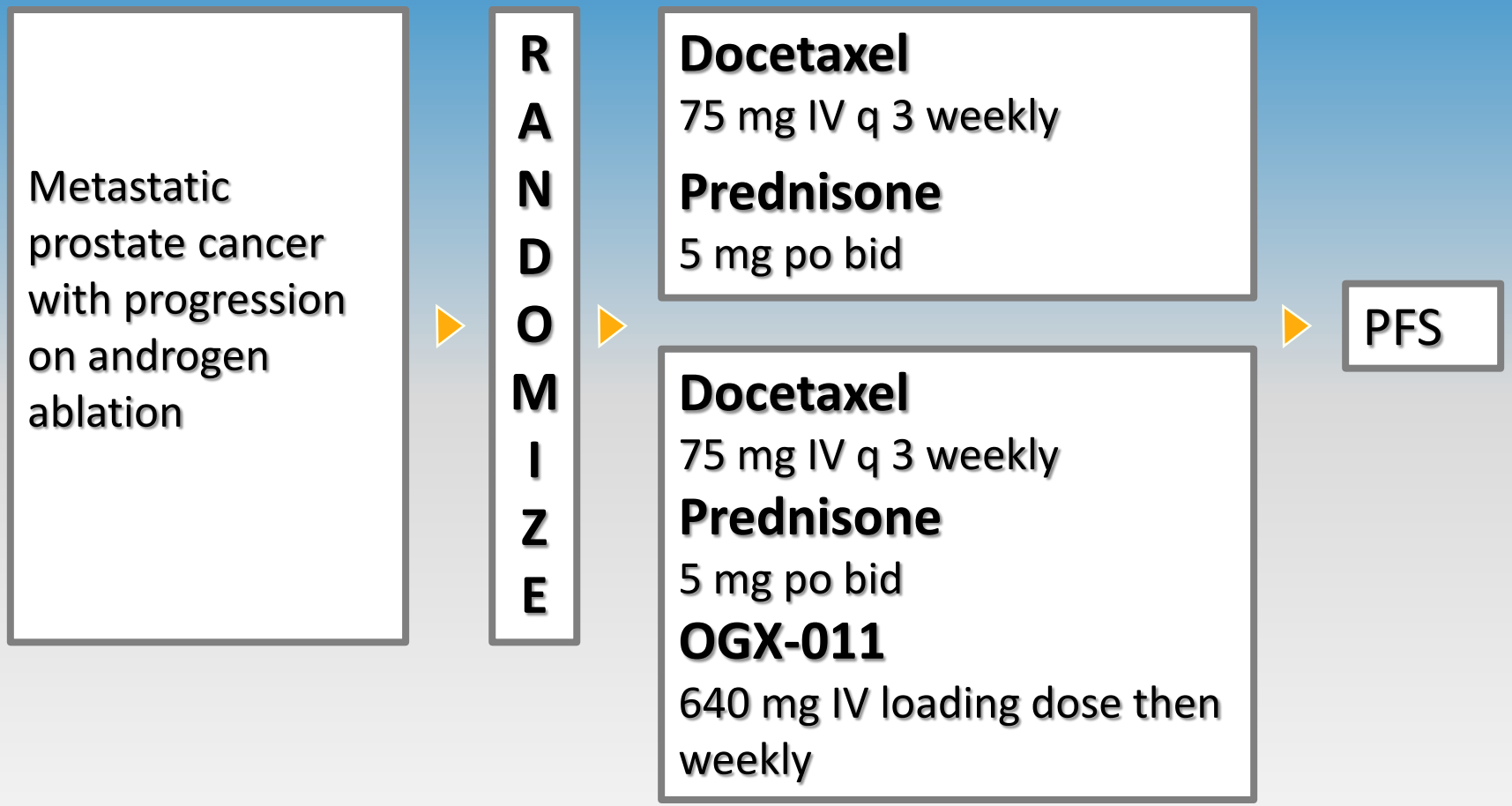
- Characterized by disease progression despite castrate state
- Highly lethal despite chemotherapy sensitivity to docetaxel regimens
- Clusterin is a cell survival protein which is induced by therapeutic stressors and is expressed in CRPC

OGX-011 in CRPC

OGX-011

- Second generation antisense molecule that is complimentary to clusterin mRNA translation initiation site
- Biologically effective dose 640 mg tested prior to prostatectomy
  - Well tolerated
  - > 90% inhibition of clusterin
  - Increased apoptosis
- Phase I study demonstrated safety with docetaxel

NCIC CTG IND.165



N= 40 per arm

NCIC CTG IND.165 Endpoints

Primary

- Proportion of patients with PSA decline $\geq$ 50% from baseline

Secondary

- Response Rate (RR)
- Progression Free Survival (PFS)
- Overall Survival (OS)
- Changes in serum clusterin

NCIC CTG IND.165
Statistical Parameters

Docetaxel + Prednisone + Clusterin arm

- H0 < 40% HA >60%,
- Type 1 error = 10% (1 sided); power = 90%
- 20 or more PSA responses in 40 enrolled patients

Docetaxel + Prednisone arm

- Estimate the true response rate of docetaxel + prednisone at an accuracy of the half length of the 90% CI will be less than 13% when the observed PSA response rate is 40%

NCIC CTG IND.165 Study Design

Open label, randomized, non-comparative phase II study

NCIC CTG IND.165 Patient Demographics

Table 1. Baseline Patient Demographics and Clinical Characteristics (all randomly assigned patients, N = 82)

Demographic or Clinical Characteristic	No. of Patients	
	Arm A: OGX-011 + Docetaxel (n = 41)	Arm B: Docetaxel (n = 41)
Age, years		
Median	69	69
Range	54-84	49-87
ECOG PS		
0	21	20
1	20	21
Measurable disease		
No	14	17
Yes	27	24
Bone/nodal metastases only		
Yes	27	24
No	13	17
PSA, ng/mL		
≤ 100	20	20
> 100	21	21
Median	110.0	110.0
Range	5.6-1,723.4	7.9-1,968.6
Lactate dehydrogenase, U/L		
≤ ULN	24	28
> ULN	17	13
Median	193.0	186.0
Range	120.0-981.0	131.0-741.0
Alkaline phosphatase, U/L		
≤ ULN	24	22
> ULN	17	19
Median	135.0	134.0
Range	54.0-880.0	47.0-1,988.0
Hemoglobin, g/L		
< 100	2	0
≥ 100	39	41
Median	128.0	128.0
Range	96.0-152.0	102.0-158.0
Gleason score at diagnosis		
≤ 7	14	18
8-9	26	22
Unknown	1	1
Progression at random assignment		
Objective	5	9
PSA	35	32
Unknown	1	0
Predicted 24-month survival rate*		
Median, %	25.6	19.6
95% CI	20.4 to 31.0	19.0 to 29.4

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen; ULN, upper limit of normal.
*Predicted 24-month survival calculated by nomogram from Halabi et al.[26]

NCIC CTG IND.165 Adverse Events

Table 2. Commonly Reported Adverse Events

Adverse Event	Arm A: OGX-011 + Docetaxel (n = 40)			Arm B: Docetaxel (n = 41)		
	No. of Patients			No. of Patients		
	Grade 1-2	Grade 3-4	Total %	Grade 1-2	Grade 3-4	Total %
Low hemoglobin	39	0	98	35	3	93
Leukopenia	21	18	98	10	22	78
Neutropenia	8	29	93	7	26	80
Lymphopenia	15	21	90	20	9	71
Fatigue	36	4	100	30	9	95
Neuropathy (sensory)	26	2	70	18	3	51
Rigors/chills	20	4	60	2	1	7
Diarrhea	23	1	60	20	2	54
Fever	20	0	50	7	0	17
Nausea	17	1	45	20	4	59
Myalgia	16	0	40	12	1	32
Thrombocytopenia	11	1	30	8	0	20
Elevated creatinine (normal baseline)*	8	0	23	2	0	5
Vomiting	6	0	15	13	1	34
Febrile neutropenia	0	4	10	0	5	12
Dehydration	4	0	10	3	3	15
Hypotension	3	0	8	1	2	7
Thrombosis	0	3	8	0	2	5
CNS ischemia	0	0	0	0	1	2

*Thirty-five patients had normal baseline on arm A, and 38 patients had normal baseline on arm B.

NCIC CTG
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NCIC CTG IND.165 PSA Response

Confirmed PSA decline ≥ 50%

- Docetaxel+ Prednisone + OGX 011:
  - 58% (90% CI 43.3-70.8)
- Docetaxel + Prednisone:
  - 54% (90% CI 39.8-67.1)

NCIC CTG IND.165 PSA Response

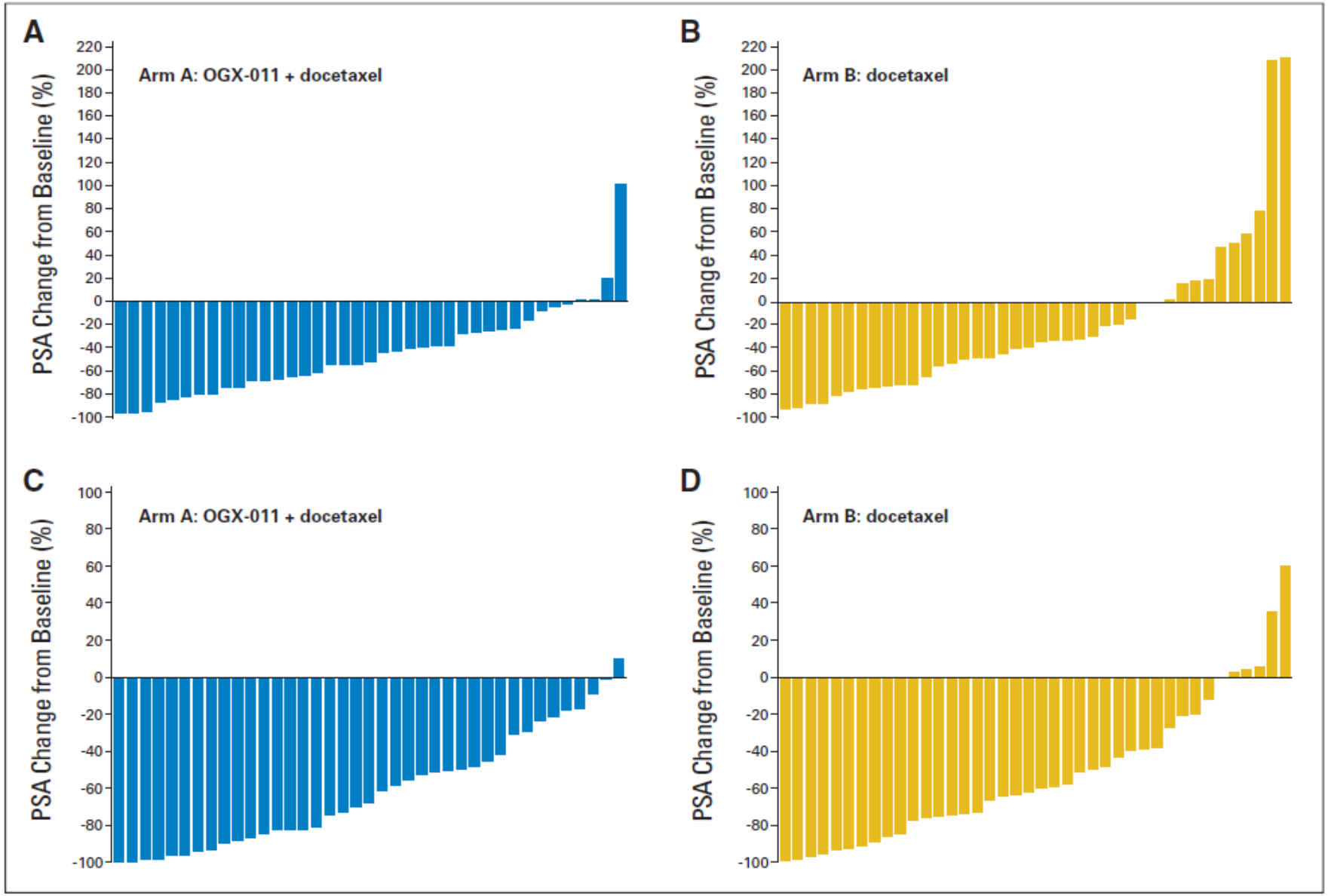


Fig 3. Waterfall plots of greatest percent decline in prostate-specific antigen (PSA) from baseline at (A and B) 12 weeks or (C and D) any time.

NCIC CTG IND.165 OS

OS median follow up 35 months

- Docetaxel+ Prednisone + OGX 011:
  - Median 23.8 months (95% CI 16.2-not reached)
- Docetaxel + Prednisone:
  - Median 16.9 months (95% CI 12.8-25.8)

NCIC CTG IND.165 Other Endpoints

RR

- Docetaxel+ Prednisone + OGX 011:
  - 19% (95% CI 6.6-39.4)
- Docetaxel + Prednisone:
  - 25% (95% CI 9.8-46.7)

PFS

- Docetaxel+ Prednisone + OGX 011:
  - Median 7.3 months (95% CI 5.3-8.8)
- Docetaxel + Prednisone:
  - Median 6.1 months (95% CI 3.7-8.7)

NCIC CTG IND.165 Correlative Studies

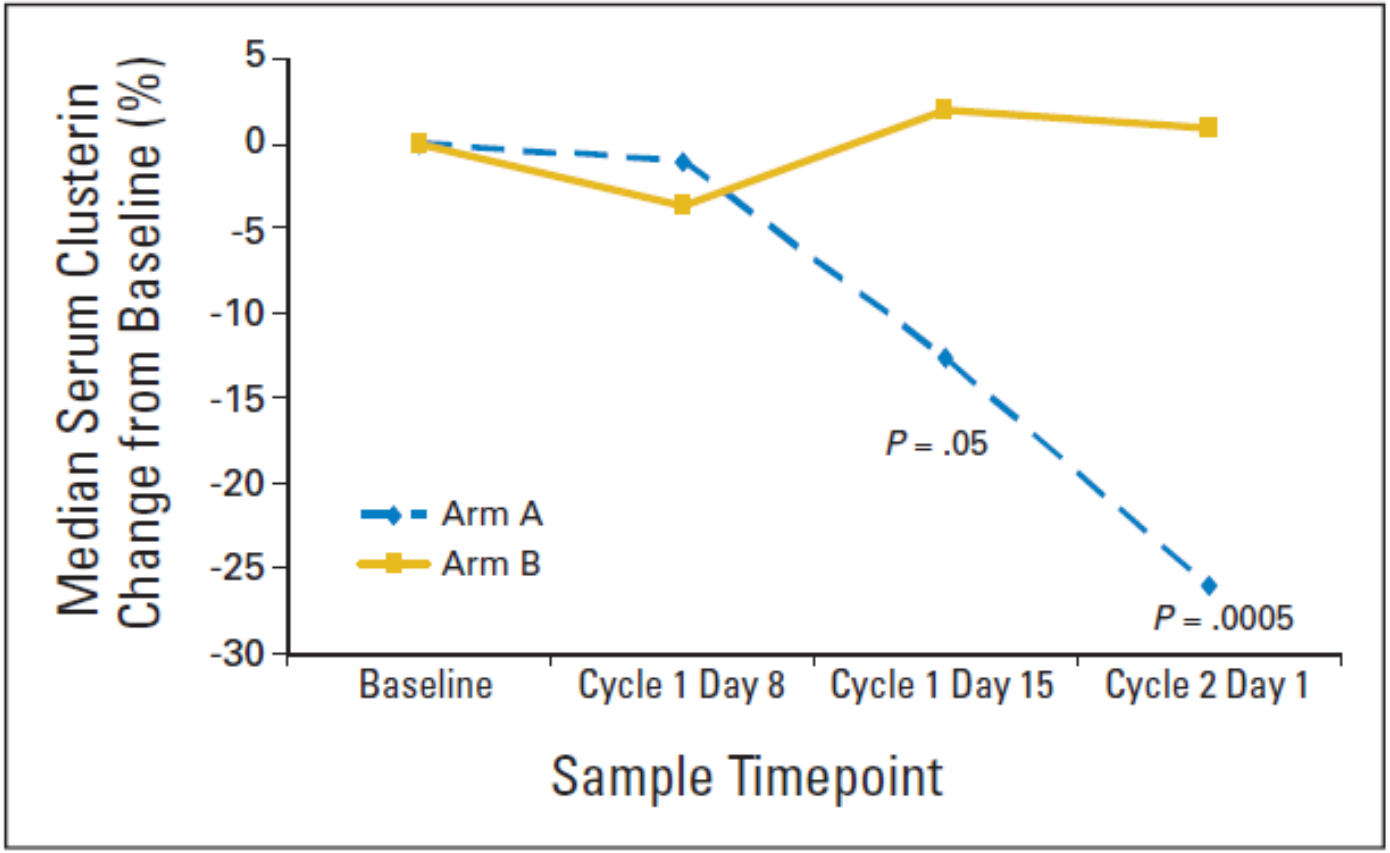


Fig 2. Median percent change in serum clusterin levels from baseline.

NCIC CTG IND.165: Exploratory Analyses

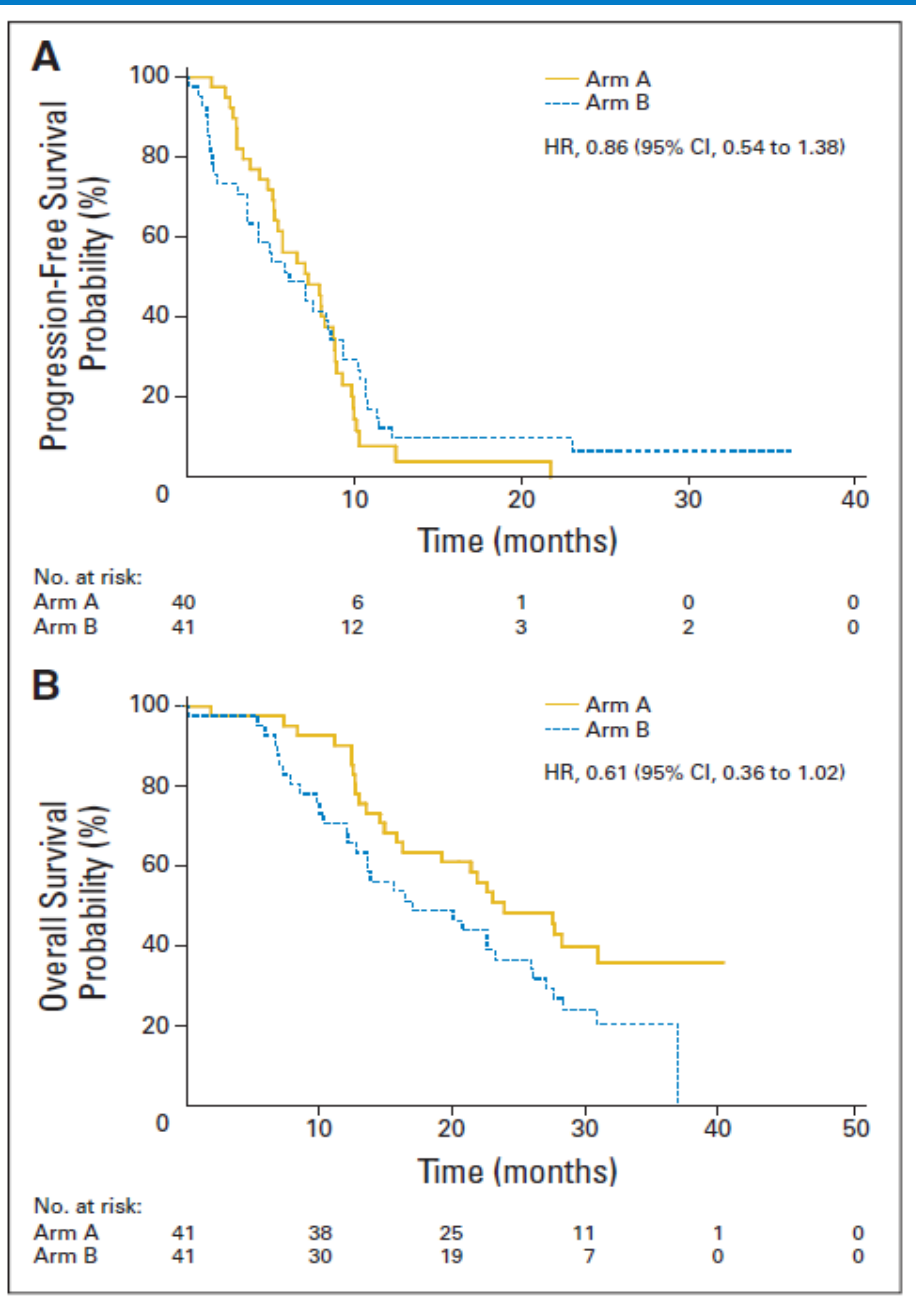


Fig 4. (A) Progression-free survival of patients on arm A (OGX-011 and docetaxel) and arm B (docetaxel). (B) Overall survival of all patients assigned to arm A and arm B.

NCIC CTG IND. 165 Conclusions

Docetaxel/ prednisone plus OGX 011

- Was well tolerated
- Predefined protocol criteria for further study met but similar rates of PSA decline and RR in both arms
- Evidence of biological effect with decreases in serum clusterin
- Trends in PFS and OS are of clinical interest
- Exploratory analyses of OS strongly suggest clinical benefit (HR 0.50 95%CI 0.29-0.87)

Efficacy not confirmed in Phase III clinical trial launched by company

OGX 011 Phase III Results

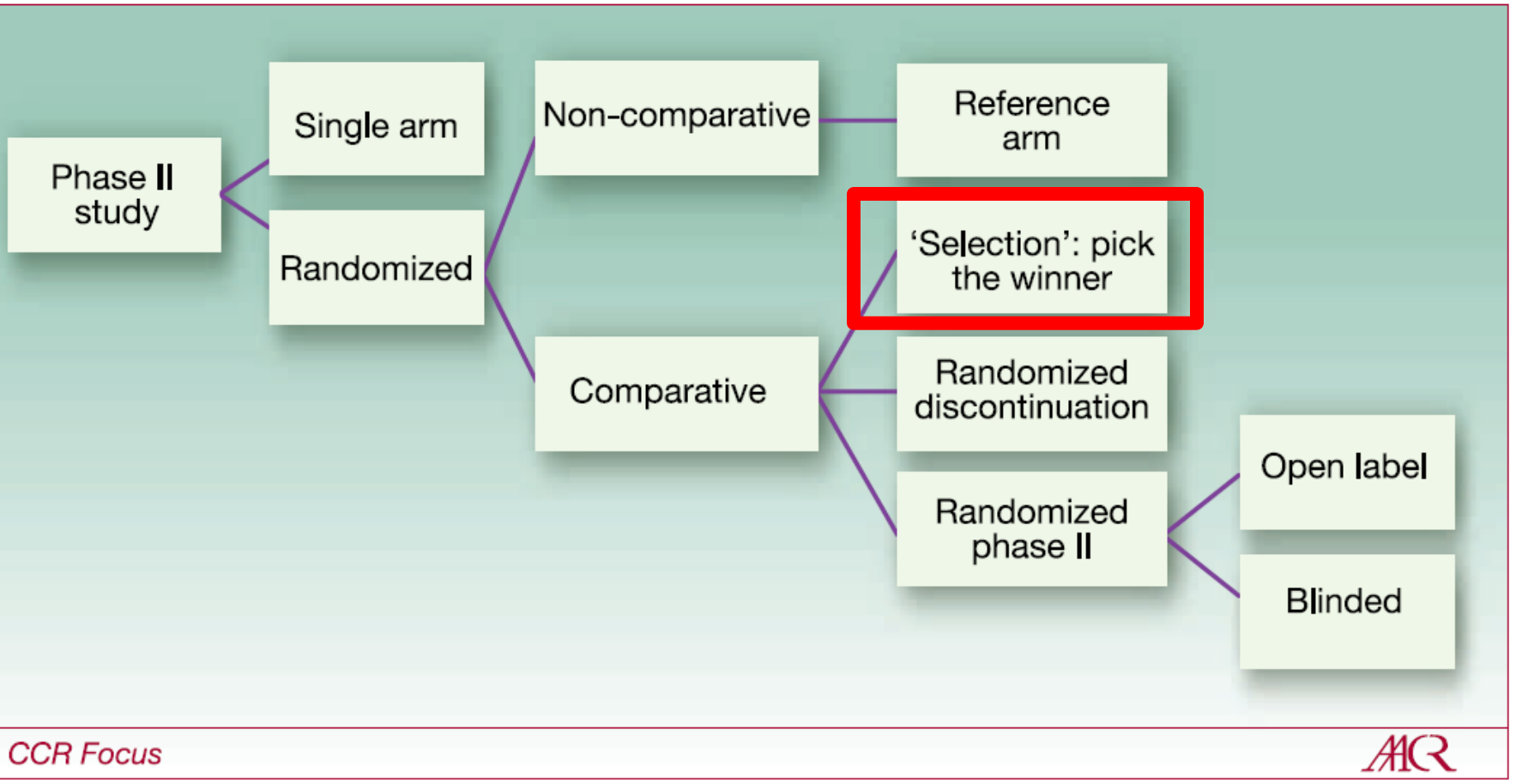
April 28, 2014

OncoGenex Announces Top-Line Survival Results of Phase 3 SYNERGY Trial Evaluating Custirsen for Metastatic Castrate-Resistant Prostate Cancer

BOTHELL, Wash. and VANCOUVER, British Columbia, April 28, 2014 /PRNewswire/ -- OncoGenex Pharmaceuticals, Inc. **(NASDAQ: OGXI)** today announced results from the Phase 3 SYNERGY trial. Top-line survival results indicate that the addition of custirsen to standard first-line docetaxel/prednisone therapy did not meet the primary endpoint of a statistically significant improvement in overall survival in men with metastatic castrate-resistant prostate cancer (CRPC), compared to docetaxel/prednisone alone (median survival 23.4 months vs 22.2 months, respectively; hazard ratio 0.93 and one-sided p value 0.207). The adverse events observed were similar to custirsen's known adverse event profile.

"The results of SYNERGY are unexpected, particularly given the wealth of scientific evidence supporting the targeting of clusterin to combat treatment resistance in first-line prostate cancer," said Scott Cormack, President and CEO of OncoGenex. "A thorough analysis of the data is underway to understand the potential factors that may have contributed to the results. Importantly, we remain strong in our belief that targeting mechanisms of treatment resistance is a critical path forward in the fight against cancer and we continue to actively pursue this approach through the two ongoing Phase 3 trials of custirsen and the seven Phase 2 trials of apatorsen in four tumor types. We would like to thank the men who participated in the SYNERGY trial and the friends and families who supported them."

Types of Phase II Studies



Clin Cancer Res; 16(6) March 15, 2010

EVEROLIMUS
in Breast Cancer

NCIC CTG IND.163

ELLARD ET AL J CLIN ONCOL 2009

Rationale

Breast Cancer

- Common, incurable in the advanced disease setting
- mTOR (mammalian target of rapamycin)
  - Involved in cell replication
  - Mediates the critical PI3K/AKT pathway which is active in breast cancer
  - Other functions: mediates VEGF, PDGF and TGF
  - Preclinical inhibitor of mTOR inhibits proliferation
  - Other mTOR inhibitors active against solid tumours (temsirolimus renal cell carcinoma)

Everolimus in Breast Cancer

Everolimus

- Orally bioavailable
- Pharmacokinetic and pharmacodynamic modelling based on preclinical and clinical findings supported exploration of a weekly and daily schedule of administration

NCIC CTG IND.163

Recurrent/ metastatic breast cancer

Strat factors:
- Visceral metastases
- Prior chemo regimens

RANDOMIZE

Everolimus
10 mg po daily
for 28 days q4 weeks

Everolimus
70 mg po once weekly
(day 1, 8, 15, 22)
q4 weeks

RR and early progression*

N < 30 each arm

*Multinomial stopping rule

NCIC CTG IND.163 Objectives

Primary

- To evaluate in parallel fashion in each arm:
  - Anti tumour efficacy based on RR and early PD

Secondary

- To evaluate in parallel fashion in each arm:
  - Adverse event, time to progression and response duration
  - To correlate RR with molecular markers of mTOR activity
  - To correlate RR with molecular markers of mTOR activity in fresh tumour samples (consenting patients)

NCIC CTG IND.163
Statistical Parameters

No formal comparison between the two arms

- H0 response = 0.05 H0 early progression = 0.60
- HA response =0.20 HA early progression =0.40

First stage, enter 15 patients each arm

- If 0 responses AND 10 or more early progressions, stop entry into that arm.
- If 1 or more responses OR < 10 early progressions, continue that arm and enter 15 more patients.

NCIC CTG IND.163
Statistical Parameters

After 30 patients total per arm

- If 4 or more responses OR if 13 or fewer early progressions, accept drug as worth further study

Corresponds to type 1 error = 10% power = 93%

NCIC CTG IND.163 Study Design

Open label, randomized, selection (with no formal comparison) phase II study

NCIC CTG IND.163 Patient Demographics

Table 1. Patient Demographics and Clinical Characteristics

Patient Demographics and Clinical Characteristics	No. of Patients		
	Daily Schedule (n = 33)	Weekly Schedule (n = 16)	All Patients (N = 49)
Age, years			
Median	61	59	61
Range	33-77	36-77	33-77
ECOG status			
0	20	6	26
1	13	10	23
Prior therapy			
Chemotherapy	28	13	41
Hormone therapy	26	12	38
Immunotherapy	3	0	3
Radiotherapy	31	12	43
Other	2	0	2
No. of prior chemotherapy regimens			
0	5	3	8
1	17	5	22
2	11	8	19
Histology			
Ductal	25	13	38
Lobular	5	1	6
Inflammatory	2	2	4
Other	1	0	1
Estrogen receptor status			
Positive	22	7	29
Negative	8	8	16
Unknown	3	1	4
Progesterone receptor status			
Positive	6	3	9
Negative	14	6	20
Unknown	13	7	20
HER2 status			
Positive	5	1	6
Negative	27	13	40
Unknown	1	2	3
Sites of metastasis			
Liver	16	9	25
Lung	10	8	18
Bone	19	6	25
Nodes	23	9	32

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

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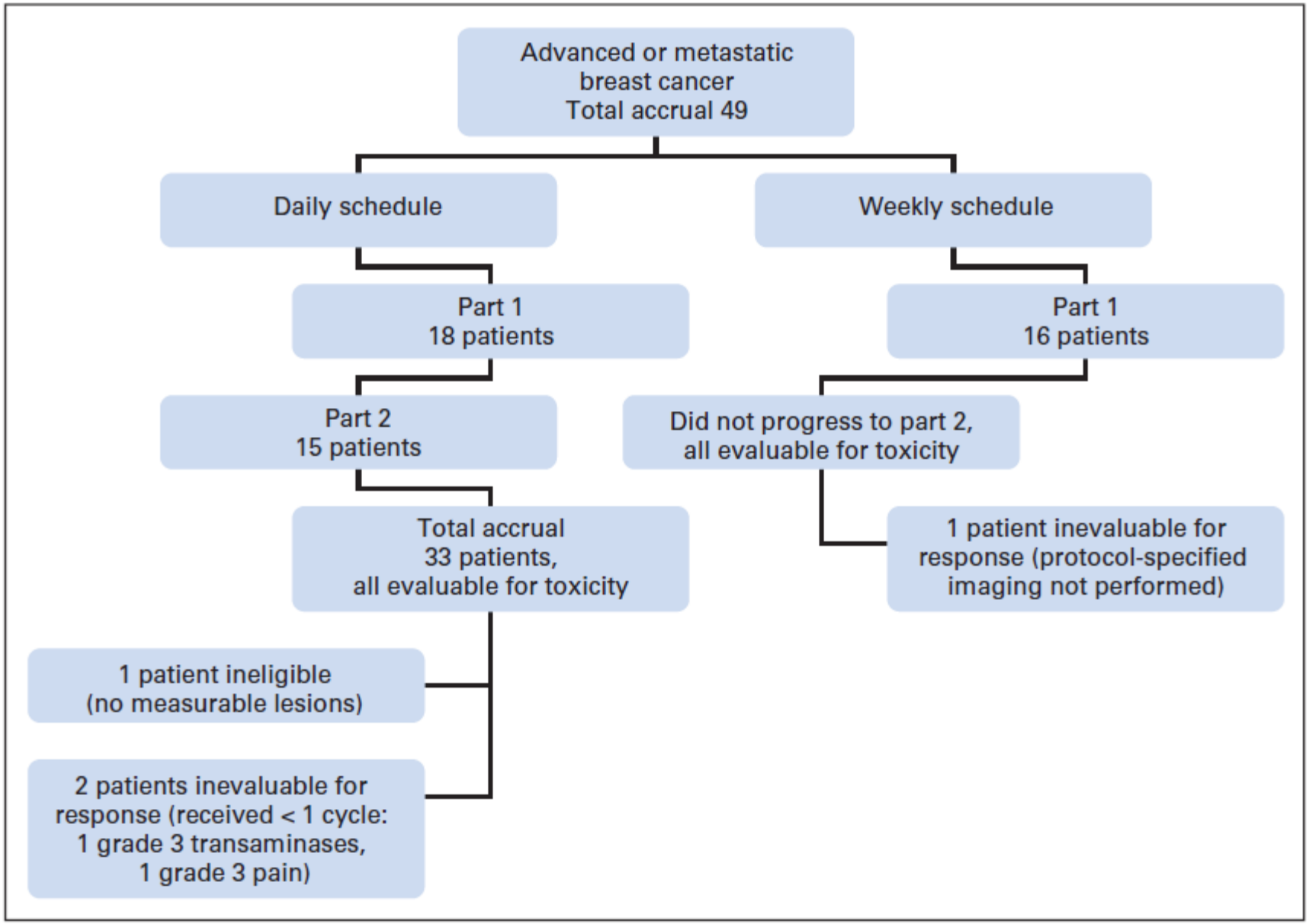
NCIC CTG IND.163 Patient Flow



NCIC CTG IND.163 Adverse Events

Table 2. Adverse Events Considered Possibly, Probably, or Definitely Related to Everolimus

Adverse Event	No. of Patients			
	Daily Schedule (n = 33)		Weekly Schedule (n = 16)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Fatigue	21	5	12	5
Rash	20	0	9	0
Anorexia	14	1	6	0
Constipation	7	0	4	0
Diarrhea	13	1	5	0
Mucositis	13	0	4	0
Nausea	15	0	6	0
Vomiting	4	0	5	0
Bleeding	7	0	1	0
Infection	11	2	2	1
Edema	1	0	1	0
Headache	12	1	7	0
Cough	14	1	5	1
Dyspnea	10	2	2	1
Pneumonitis	14	3	3	0
Granulocytopenia	22	4	8	1
Lymphopenia	21	4	8	1
Anemia	22	1	6	0
Thrombocytopenia	20	0	7	0
Creatinine increase	5	0	2	0
Alkaline phosphatase	10	0	4	0
AST	23	1	8	1
Bilirubin	1	0	0	0
Hyperglycemia	17	0	10	2
Hypercholesterolemia	27	0	13	0
Hypertriglyceridemia	14	0	8	0

NOTE. Adverse events were graded according to Common Terminology Criteria of Adverse Events (version 3).

NCIC CTG IND.163 Response Rate

Table 4. Response

Response Category	No. of Patients		
	Daily Schedule (n = 33)	Weekly Schedule (n = 16)	All Patients (N = 49)
Complete response	1	0	1
Partial response	3	0	3
Stable disease ≥ 6 months	3	2	5
Stable disease < 6 months	12	2	14
Progressive disease	11	11	22
Inevaluable	3	1	4

NCIC CTG IND.163 Correlative Studies

Table 5. Response by Staining (daily schedule only)

Staining Status	No. of Patients				
	CR	PR	SD ≥ 6 Months	SD < 6 Months	PD
PTEN					
None	0	0	0	2	0
Positive	1	3	2	9	10
Unknown	0	0	1	1	1
pAKT					
Positive	0	1	1	7	7
Negative	1	2	1	4	3
Unknown	0	0	1	1	1
CA9					
Positive	0	0	0	1	1
Negative	1	3	2	10	9
Unknown	0	0	1	1	1
ER positive/HER2 positive	0	0	0	1	1
ER positive/HER2 negative	1	2	3	6	7
ER positive/HER2 unknown	0	1	0	0	0
ER negative/HER2 positive	0	0	0	2	1
ER negative/HER2 negative	0	0	0	3	2

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CA9, carbonic anhydrase 9; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

NCIC CTG IND. 163 Conclusions

- Daily dosing of everolimus in minimally pretreated breast cancer patients is active based on predefined study criteria
- Data support further testing
- Unable to demonstrate any statistical association between response and biomarkers
- Efficacy demonstrated using PFS outcome measure in phase III study

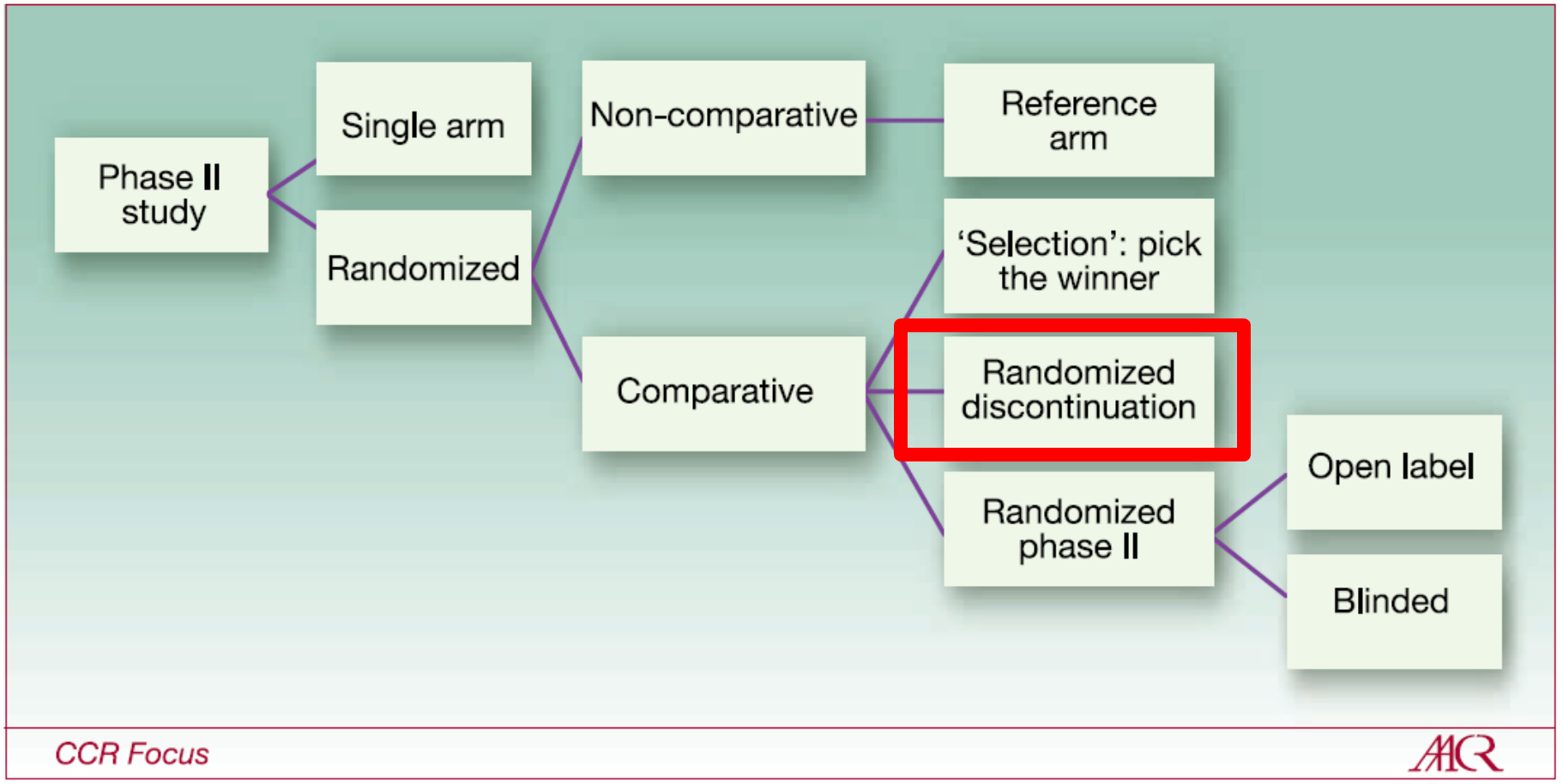
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

Types of Phase II Studies



Clin Cancer Res; 16(6) March 15, 2010

SORAFENIB
in Renal Cell Carcinoma

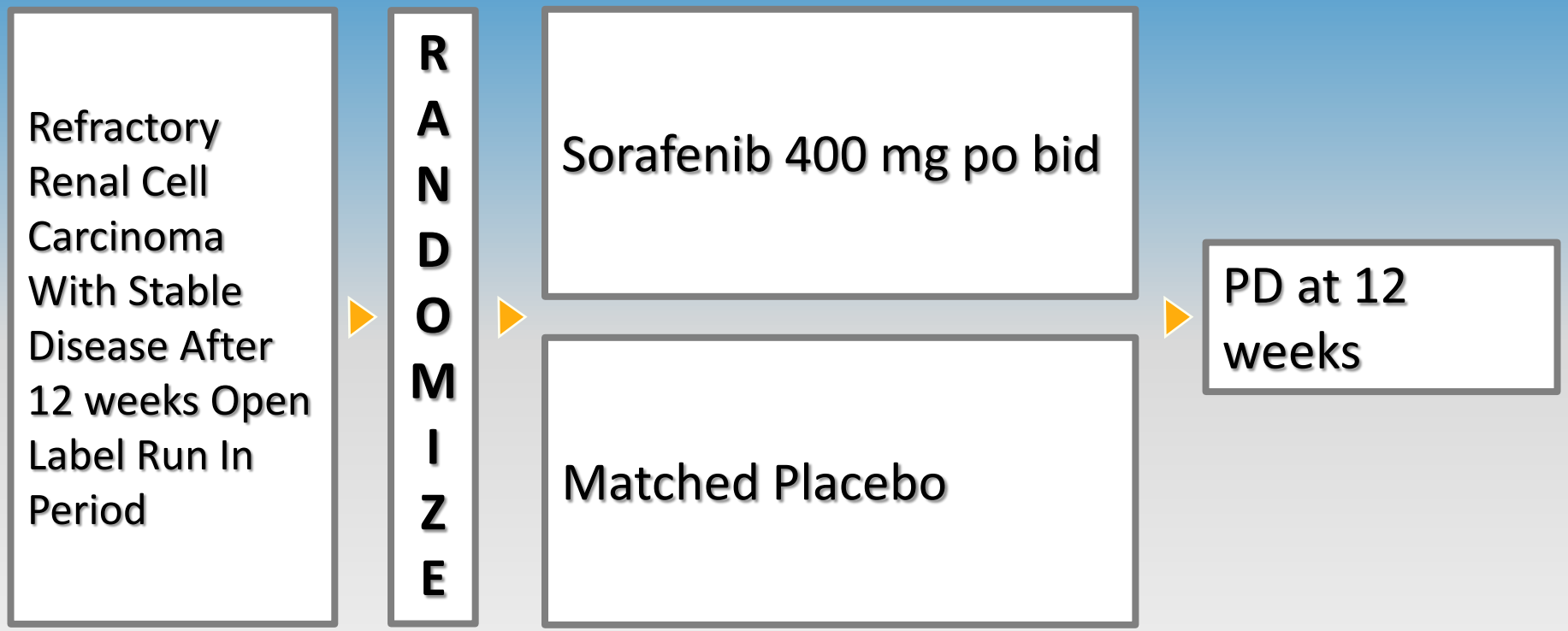
RATAIN ET AL J CLIN ONCOL 2006

Sorafenib

Sorafenib (BAY 43-9006)

- Developed as an inhibitor of Raf-1, a member of the Raf/MEK/ERK signaling
- Active against B-Raf, vascular endothelial growth factor receptor–2, platelet-derived growth factor receptor, Fms-like tyrosine kinase-3 (Flt-3), and stem-cell growth factor (c-KIT)
- Preclinical data suggested inhibition of tumour growth rather than shrinkage
- Phase I studies demonstrated 400 mg po bid daily dose well tolerated

Sorafenib in Renal Cell Carcinoma



N = 100

Sorafenib in Renal Cell Carcinoma

Primary

- Progression Free Status (12 weeks)

Secondary

- PFS at 12 weeks
- Overall PFS
- Response Rate
- Safety

Sorafenib in Renal Cell Carcinoma Statistical Parameters

Enroll 50 patients per arm

- 81% to detect a drug effect that corresponded to a reduction in the progression rate from 90% to 70%, 12 weeks after randomization
- Primary comparison between two treatment groups used a Cochran–Mantel-Haenszel test stratified by baseline ECOG score; 95% CIs were computed using binomial distribution
- PFS after randomization was summarized by the Kaplan-Meier method, and was compared between treatment groups using a log-rank test

Sorafenib in Renal Cell Carcinoma

Placebo controlled, comparative, randomized discontinuation study

Sorafenib in Renal Cell Carcinoma Patient Demographics

Table 1. Baseline Characteristics for All Treated Patients (n = 202)

Characteristic	All Patients (N = 202)		Patients by Random Assignment: Placebo Group (n = 33)		Patients by Random Assignment: Sorafenib Group (n = 32)	
	No.	%	No.	%	No.	%
Sex						
Male	149	74	21	64	26	81
Female	53	26	12	36	6	19
Age, years						
Median	58		60		58	
Range	23-83		23-74		32-76	
ECOG PS						
0	110	54	18	55	18	56
1	92	46	15	45	14	44
TNM stage						
I	21	10	3	9	2	6
II	49	24	6	18	11	34
III	49	24	8	24	9	28
IV	68	34	15	45	8	25
Missing	15	7	1	3	2	6
Histologic subtype						
Clear cell	152	75	25	76	27	84
Papillary	15	7	3	9	0	0
Other	11	5	2	6	1	3
Missing	24	12	3	9	4	13
MSKCC risk category*						
Low	69	34	14	42	13	41
Intermediate	121	60	15	45	18	56
High	6	3	3	9	0	0
Missing	6	3	1	3	1	3
No. of organ sites of disease						
1	32	16	4	12	8	25
2	77	38	15	45	7	22
≥ 3	93	46	14	42	17	53
Sites of disease†						
Lung	154	76	23	70	28	88
Lymph node	86	43	16	48	14	44
Kidney	70	35	15	45	12	38
Liver	52	26	10	30	5	16
Duration of disease						
No. of patients	198		33		31	
No. of years	2.6		2.8		3.3	
Range	0-21.9		0-11.7		0-21.2	
Prior therapy						
Systemic anticancer therapy	170	84	29	88	29	91
IL-2 or interferon	154	76	28	85	26	81
Non-diagnostic surgery	202	100	33	100	32	100
Radiotherapy	68	34	11	33	9	28
Nephrectomy	179	89	29	88	29	91

Abbreviatons: ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan-Kettering Cancer Center (New York, NY); IL, interleukin.
*MSKCC risk category was assessed using four of the five original risk factors[29] as follows: low Karnofsky performance status (< 80%); low serum hemoglobin (< lower limit of normal); high corrected serum calcium (> 10 mg/dL); and absence of prior nephrectomy. High lactate dehydrogenase was omitted as a risk factor for the present study because lactate dehydrogenase measurements were not collected prospectively for all patients, and a more recent publication excluded high lactate dehydrogenase as an independent risk factor for survival.[30] Risk categories were defined as: high risk, ≥ 3 risk factors; intermediate risk, 1-2 risk factors; low risk, no risk factors.
†Target or non-target lesions for > 20% of all 202 patients.

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Sorafenib in Renal Cell Carcinoma

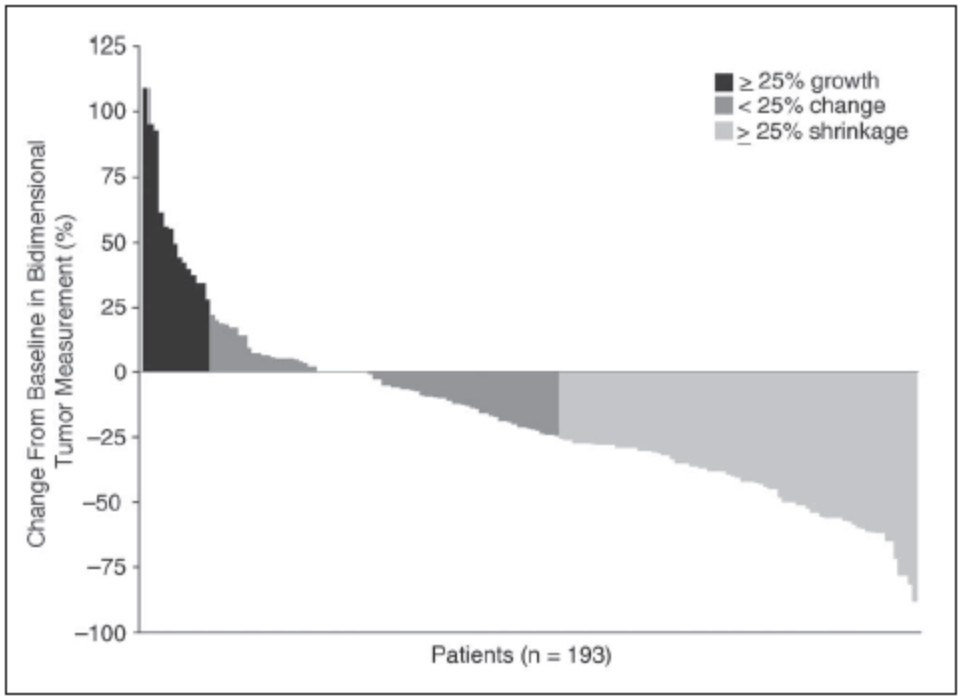

Fig 1. Changes from baseline in investigator-assessed, bidimensional radiographic measurements at 12 weeks for patients with renal cell carcinoma. These measurements were unconfirmed, and therefore do not represent confirmed responses according to modified WHO criteria. Mean change at 12 weeks was −18% (standard deviation, 33%).

Efficacy Primary Endpoint

Progression Free at 12 weeks post randomization
50% (sorafenib) versus 18% (placebo) (p=.0077)

Sorafenib in Renal Cell Carcinoma PFS

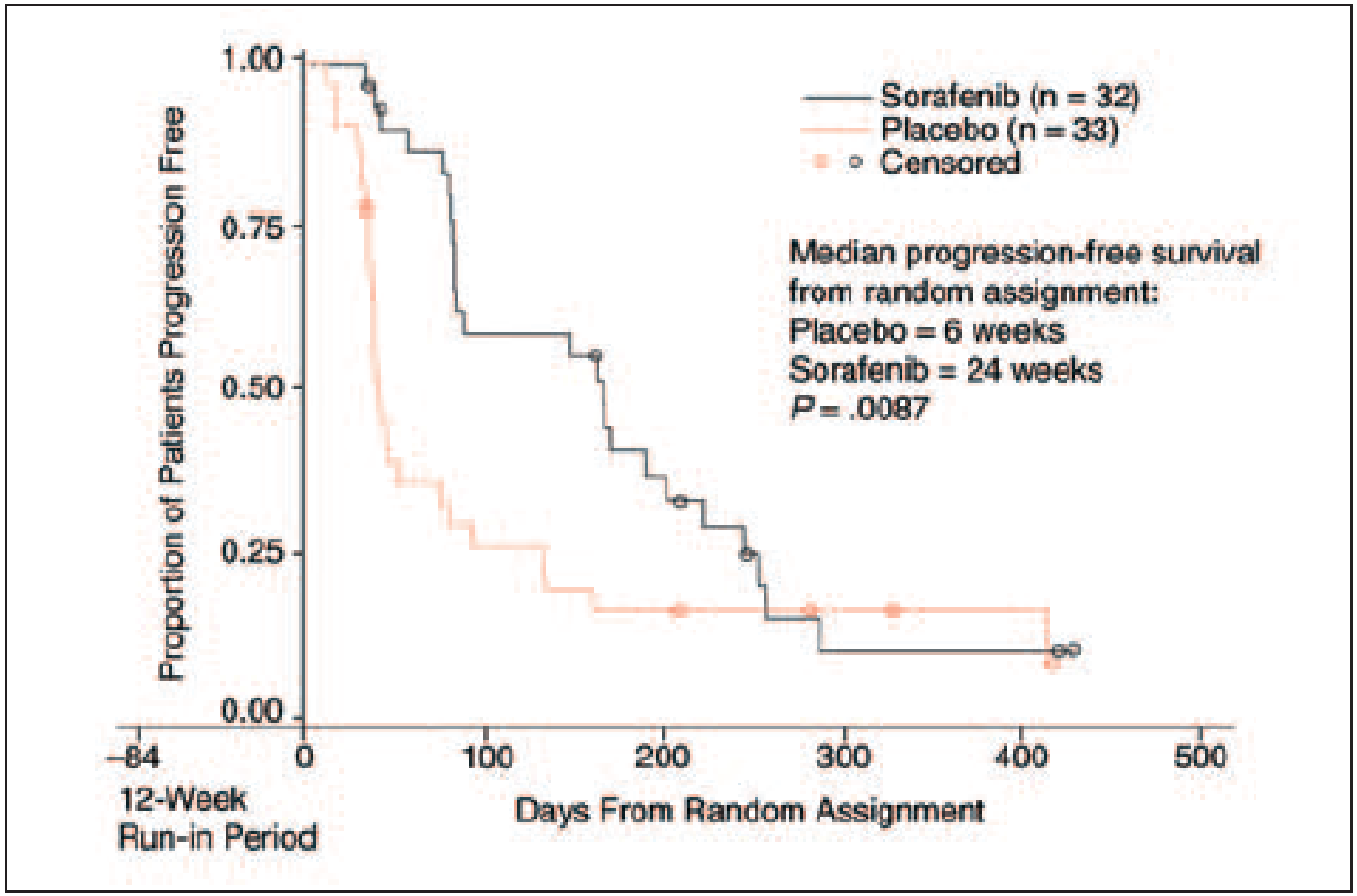

Fig 2. Kaplan-Meier plot of investigator-assessed progression-free survival from week 12 randomization for patients randomized to placebo (n = 33) or to sorafenib (n = 32).

Sorafenib in Renal Cell Carcinoma Safety

- No deaths
- Majority of treatment emergent adverse events were grade 1/ 2
- Most common: fatigue (73%), rash-desquamation (66%), hand-foot skin reaction (62%), pain (58%), diarrhea (58%).
- Most common grade 3/ 4 adverse event: hypertension (31%)

Sorafenib in Renal Cell Carcinoma Conclusions

- Significant disease stabilizing activity
- Tolerable
- Efficacy in renal cell carcinoma confirmed in randomized phase III study using PFS endpoint (FDA approval)

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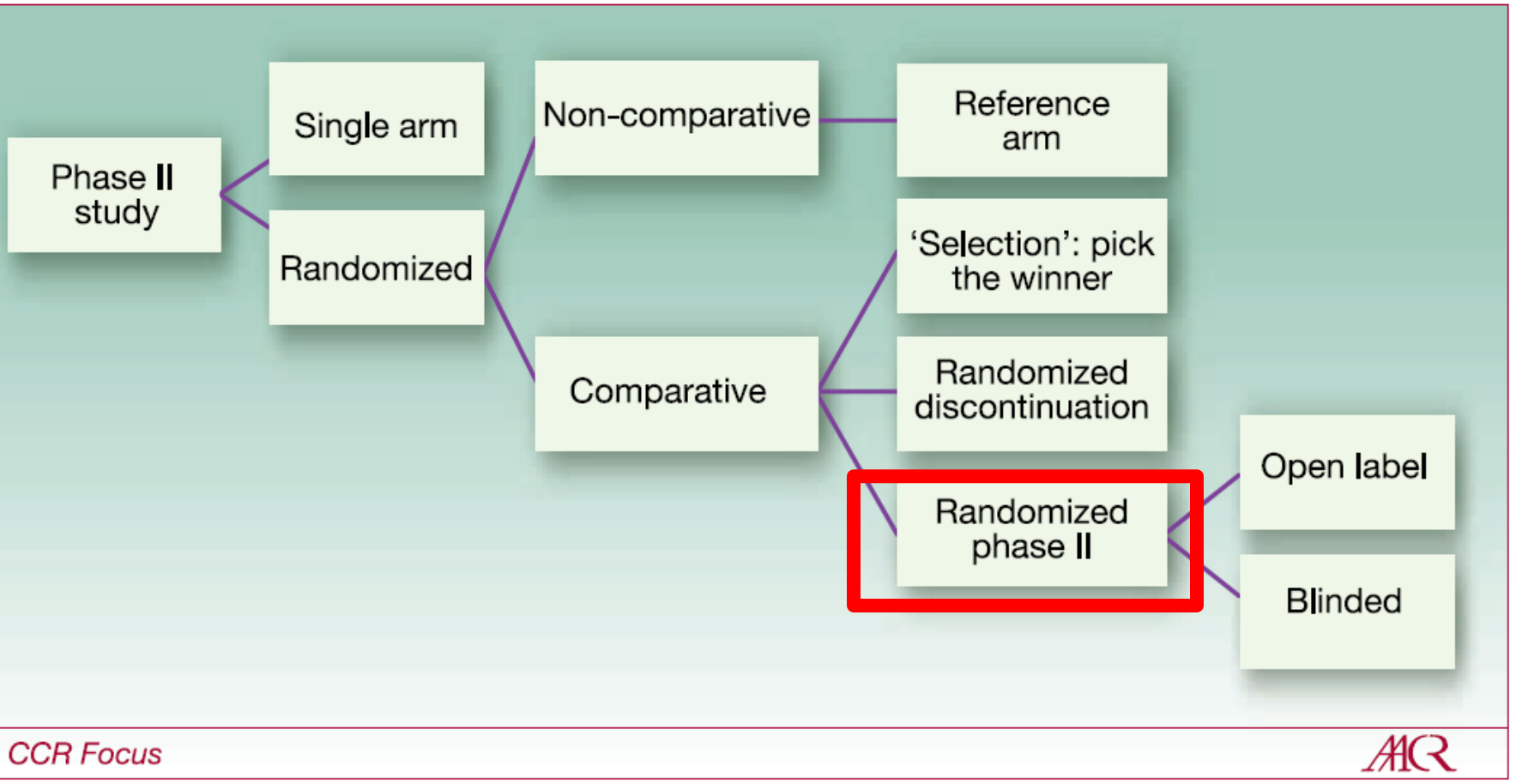
ORIGINAL REPORT

Sorafenib for Treatment of Renal Cell Carcinoma: Final Efficacy and Safety Results of the Phase III Treatment Approaches in Renal Cancer Global Evaluation Trial

Bernard Escudier, Tim Eisen, Walter M. Stadler, Cezary Szczylik, Stéphane Oudard, Michael Staehler, Sylvie Negrier, Christine Chevreau, Apurva A. Desai, Frédéric Rolland, Tomasz Demkow, Thomas E. Hutson, Martin Gore, Sibyl Anderson, Gloria Hofilena, Minghua Shan, Carol Pena, Chetan Lathia, and Ronald M. Bukowski

Types of Phase II Studies



Clin Cancer Res; 16(6) March 15, 2010

VANDETANIB
in Small Cell Lung Cancer

NCIC CTG BR.20

ARNOLD ET AL, J CLIN ONCOL 2007

Rationale

Small Cell Lung Cancer (SCLC)

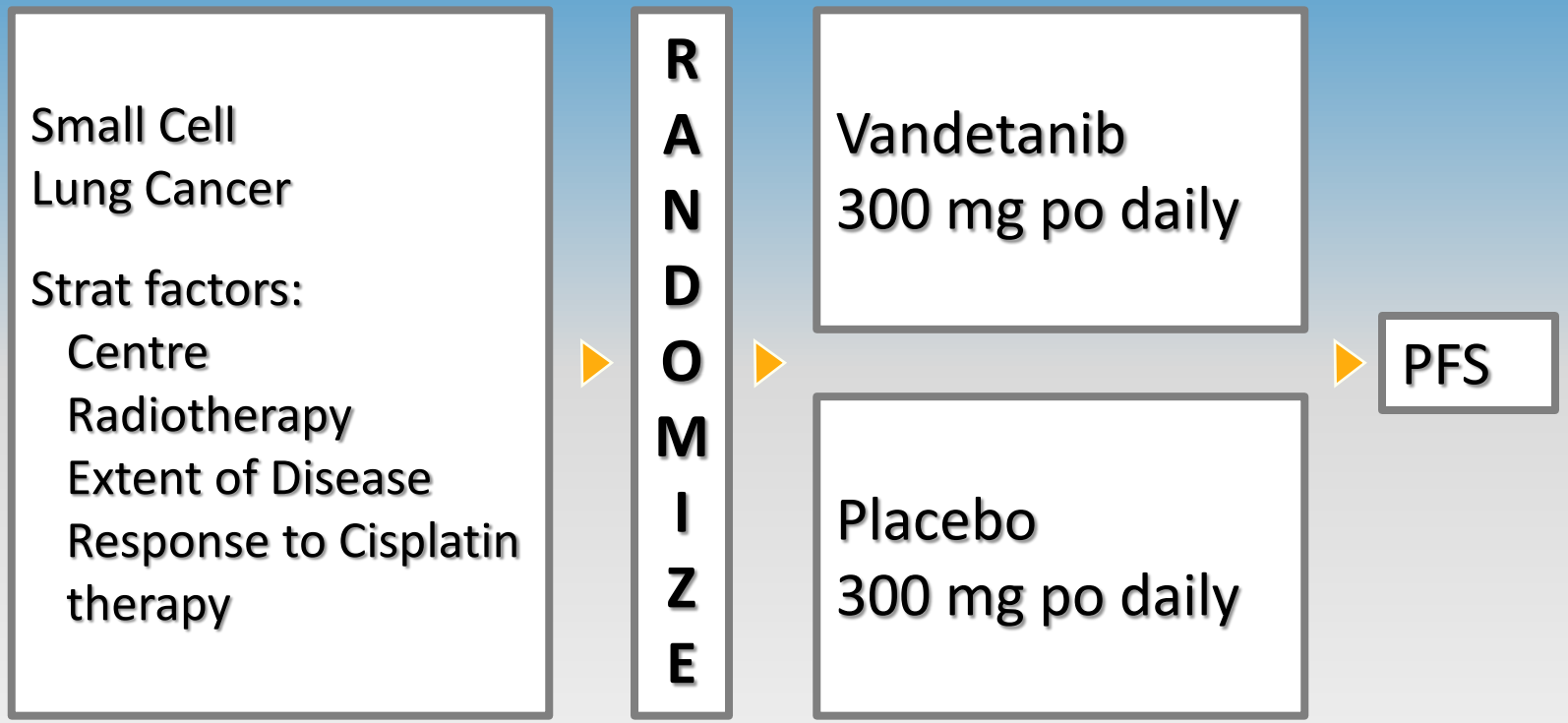
- Highly lethal despite chemotherapy sensitivity
- Failure of other treatment strategies including dose intensification, bone marrow transplant, maintenance chemotherapy
- Angiogenesis may be important and targetable: VEGF, MMP3-11-14, FGF shown to be negative prognostic factors

Vandetanib in Small Cell Lung Cancer

Vandetanib

- Orally bioavailable inhibitor of VEGF receptor 2 and to a lesser extent, EGFR
- Recommended phase II dose (RPTD): 300 mg po daily

NCIC CTG BR.20



N=120 eligible

NCIC CTG BR.20 Objectives

To compare the arms for:

Primary Endpoint

- Progression Free Survival (PFS)

Secondary Endpoints

- Overall Survival (OS)
- Response Rate (RR)
- Toxicity and tolerability
- QOL

NCIC CTG BR.20 Objectives

To assess

- Prognostic significance of VEGF(R) and microvessel density in tumour with outcomes

To compile a biobank

NCIC CTG BR.20
Statistical Parameters

- Target HR: 1.625 (2.5 month increase in median PFS)
- α = 10% (1 sided); power = 80%
- N=120, accrual in 12 months; follow up for 5 months to observe 77 events
- Modified (due to slow accrual) to N=100 to observe 77 events

NCIC CTG BR.20 Study Design

Double blind, randomized, placebo controlled, comparative phase II study

NCIC CTG BR.20 Patient Demographics

Table 1. Patient Characteristics

Characteristic	Vandetanib (n = 53)		Placebo (n = 54)		Total (N = 107)	
	No.	%	No.	%	No.	%
Sex						
Female	26	49.1	23	42.6	49	45.8
Male	27	50.9	31	57.4	58	54.2
ECOG PS						
0	11	20.8	20	37.0	31	29.0
1	37	69.8	29	53.7	66	61.7
2	5	9.4	5	9.3	10	9.3
Race/ethnicity						
Asian			2	3.7	2	1.9
Black	1	1.9			1	0.9
White	52	98.1	51	94.4	103	96.3
Other			1	1.9	1	0.9
Age, years						
Median	56.9		62.4		58.5	
< 60	34	64.2	22	40.7	56	52.3
≥ 60	19	35.8	32	59.3	51	47.7
Thoracic radiotherapy						
Late	3	5.7	8	14.8	11	10.3
Early	24	45.3	19	35.2	43	40.2
None	26	49.1	27	50.0	53	49.5
Extent of disease						
Extensive	30	56.6	31	57.4	61	57.0
Limited	23	43.4	23	42.6	46	43.0
Response to prior therapy						
CR	4	7.5	8	14.8	12	11.2
PR	49	92.5	46	85.2	95	88.8
Prior radiotherapy	35	66.0	36	66.7	71	66.4
Disease sites						
Bone	11	20.8	10	18.5	21	19.6
Brain	1	1.9	3	5.6	4	3.7
Liver	13	24.5	7	13.0	20	18.7
Lung	33	62.3	38	70.4	71	66.4

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response.

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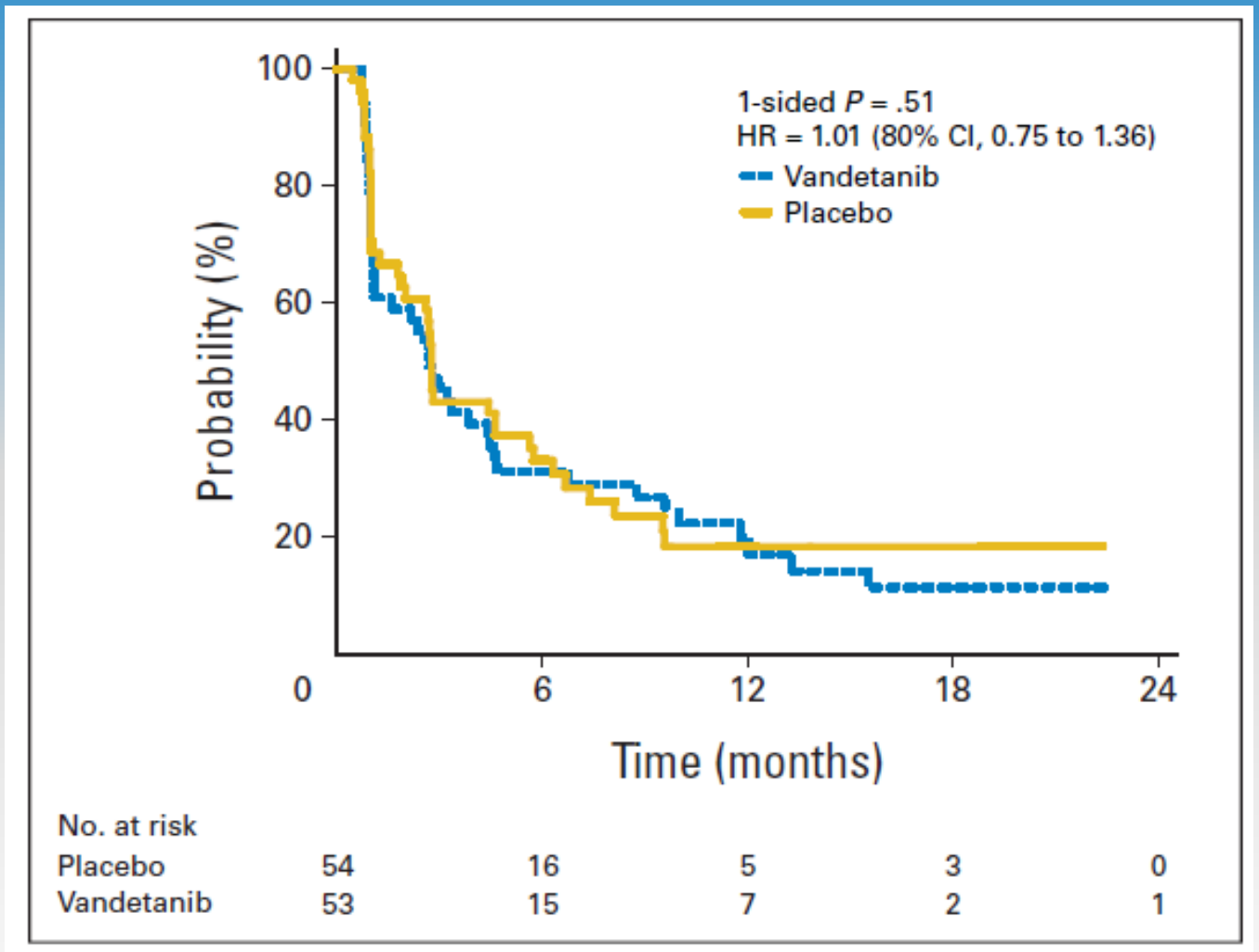
NCIC CTG BR.20 Adverse Events

Table 2. Reported Adverse Events Irrespective of Causality

Adverse Event	%			
	Vandetanib (n = 52)		Placebo (n = 53)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Neutropenia	23	6	17	6
Alkaline phosphatase	38	4	26	0
Bilirubin	7	4	2	0
ALT	48	10	15	4
Hypertension	21	2	9	2
Prolonged QT_C	15	0	0	0
Fatigue	79	14	85	9
Diarrhea	79	17	40	2
Nausea	56	2	55	0
Hemoptysis	4	0	8	0
Pneumonitis	4	2	8	0
Rash	71	4	49	4

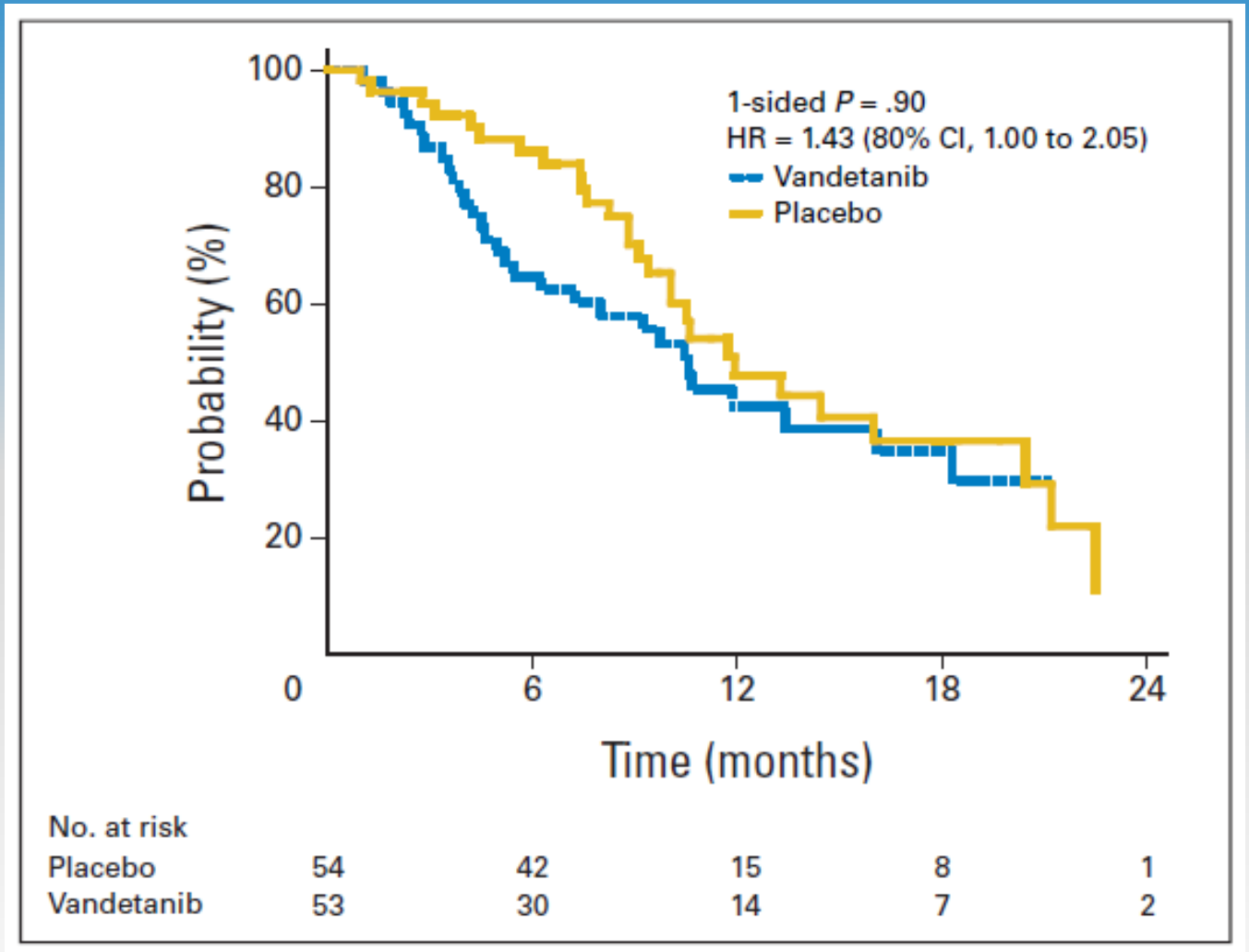
Abbreviation: QT_C, corrected QT interval.

NCIC CTG BR.20 PFS



Progression Free Survival Hazard Ratio (HR)

NCIC CTG BR.20 OS



NCIC CTG
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Overall Survival Hazard Ratio (HR)

NCIC CTG BR.20 Conclusion

The study failed to show a benefit for adjuvant or maintenance vandetanib

ASCO Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

ELLIS ET AL, J CLIN ONCOL 2014

ASCO Perspective

- It is necessary to observe extremely strong signals in phase II studies
  - If we expect clinically meaningful outcomes to be achieved in subsequent phase III studies
- Sometimes results from phase II trials are more optimistic than warranted
- It is even possible that phase III studies will not be necessary if results from well-conducted phase II trials demonstrate exceptional activity that clearly benefits patients

ASCO Recommendations

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point: Improvement Over Current OS That Would Be Clinically Meaningful (months)	Primary End Point: Target HRs	Secondary End Point: Improvement in 1-Year Survival Rate (%)*	Secondary End Point: Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Current → target.

ASCO Recommendations

- The goals established will likely require biomarker enrichment strategies to achieve them
- Validated biomarkers are not currently available to select patients for treatment with specific drugs
- We expect that over time, such biomarkers will be identified and that the goals set forth by these working groups will be achievable

Conclusions

- Phase II studies play a pivotal role in drug development
- The primary goal is to identify new therapies or therapeutic strategies for further testing
- Multiple designs are available and selection should inform current and future drug development
- A randomized phase II study should not be considered a substitute for a properly designed phase III study