Canadian Cancer Trials Group

Phase II Study Design In Oncology Drug Development

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Disclosures

Pfizer

Celgene

Hecht Foundation

CBCF

CIHR

AstraZeneca

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

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

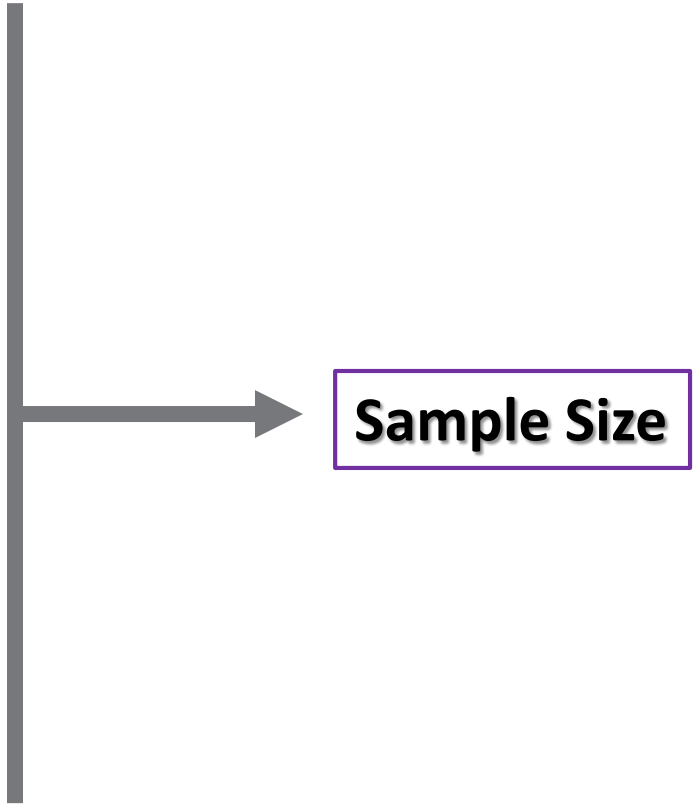
- Characterize adverse event profile
- Understand mechanism of action
- Further define target population for administration of agent

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 (clinical and scientific gaps in knowledge)
- Defining characteristics
  - Endpoints: primary and secondary
  - Single or two stage design
  - Single arm or multiple arm design
  - Statistical considerations: Type I (α) and II (β) error rates; H0 and HA (null and target drug activity rates), HR (hazard ratio)

Statistical Parameters Driving Clinical Trials

- α:
  - Type I error,
  - Probability of a **false-positive** result.
- β:
  - Type II error,
  - Probability of a false-negative results.
- δ:
  - Targeted difference or,
  - Targeted effect 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

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Standard Single Arm Phase II Study

- Comparison is “fixed” constant – historical control
- Binary endpoint (e.g. clinical response vs. no response)
- Requirements
  - α = Type I error
  - β = Type II error
  - H0: null response rate **– uninteresting**
  - HA: target response rate – **interesting**
- Based on design parameters sample size= N
- Conclude treatment effective if prespecified number of responses is demonstrated

Two stage design will limit exposure to inactive drugs

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 due to efficacy or inefficacy
- **Simon two stage design (1989)**
  - Preserves the type I (α) and II (B) error rates and allows an early look; minimizes the expected or the maximum sample size under the null hypothesis of drug inefficacy
- **Other designs…**

Sunitinib in relapsed or refractory diffuse large B-cell lymphoma: a clinical and pharmacodynamic phase II multicenter study of the NCIC Clinical Trials Group

NCIC CTG IND.182

BUCKSTEIN ET AL., LEUK LYMPHOMA 2011

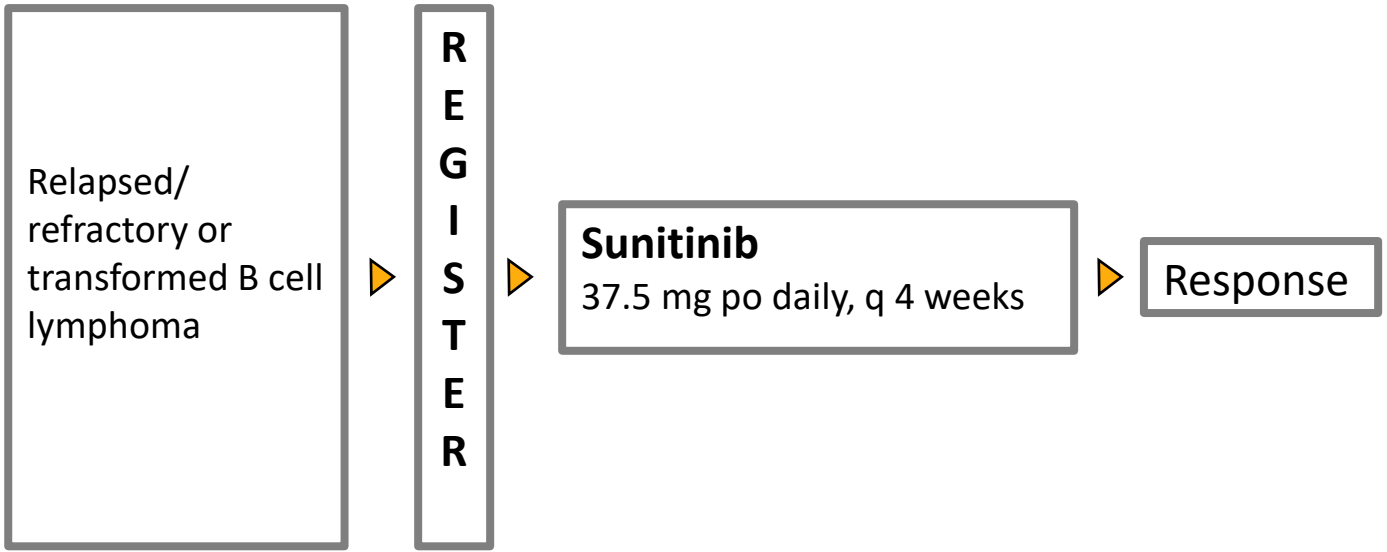
Canadian Cancer Trials Group

Rationale

Relapsed or refractory diffuse large B cell lymphoma

- 25-30% cured with salvage chemotherapy and bone marrow transplant
- VEGF pathway is important – implicated in progression
- Sunitinib is an orally bioavailable inhibitor affecting receptor tyrosine kinases involved in tumor proliferation and angiogenesis (VEGFR-1, -2, -3, and PDGFR-a and –b)

NCIC CTG IND.182



NCIC CTG IND.182 Endpoints

Primary

- Objective response using standard criteria for non-Hodgkin lymphoma

Secondary

- Toxicity
- Progression Free Survival (PFS)
- Anti-angiogenic activity: circulating and apoptotic endothelial cells and precursors

NCIC CTG IND.182
Statistical Parameters

- H0 =5% HA =20%
- Type 1 (α) error = 0.12 ; power (1- β) = 89%
- Two stage:
  - Ist stage: enroll 15 patients – continue if at least one response
  - 2nd stage: additional 10 patients
- Sunitinib worthy of further study if at least 3 responses in 25 patients

NCIC CTG IND.182 Results

Response Rate

- First stage: 17 eligible patients, 15 evaluable for response
  - No responses seen – study stopped
- No convincing pharmacodynamic evidence of antiangiogenic activity (CEC and CEP biomarker analysis)

NCIC CTG IND.182 Conclusions

Sunitinib

- Inactive in patients with relapsed or refractory diffuse large B cell lymphomas

Single Arm Phase II Study Design Limitation

- Challenging due to choice of historic control for estimation of H0
- Biases in patient selection, earlier detection of disease states, differences in disease outcome assessment, improvements in supportive care may contribute to estimate of activity - independent of drug effect

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

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

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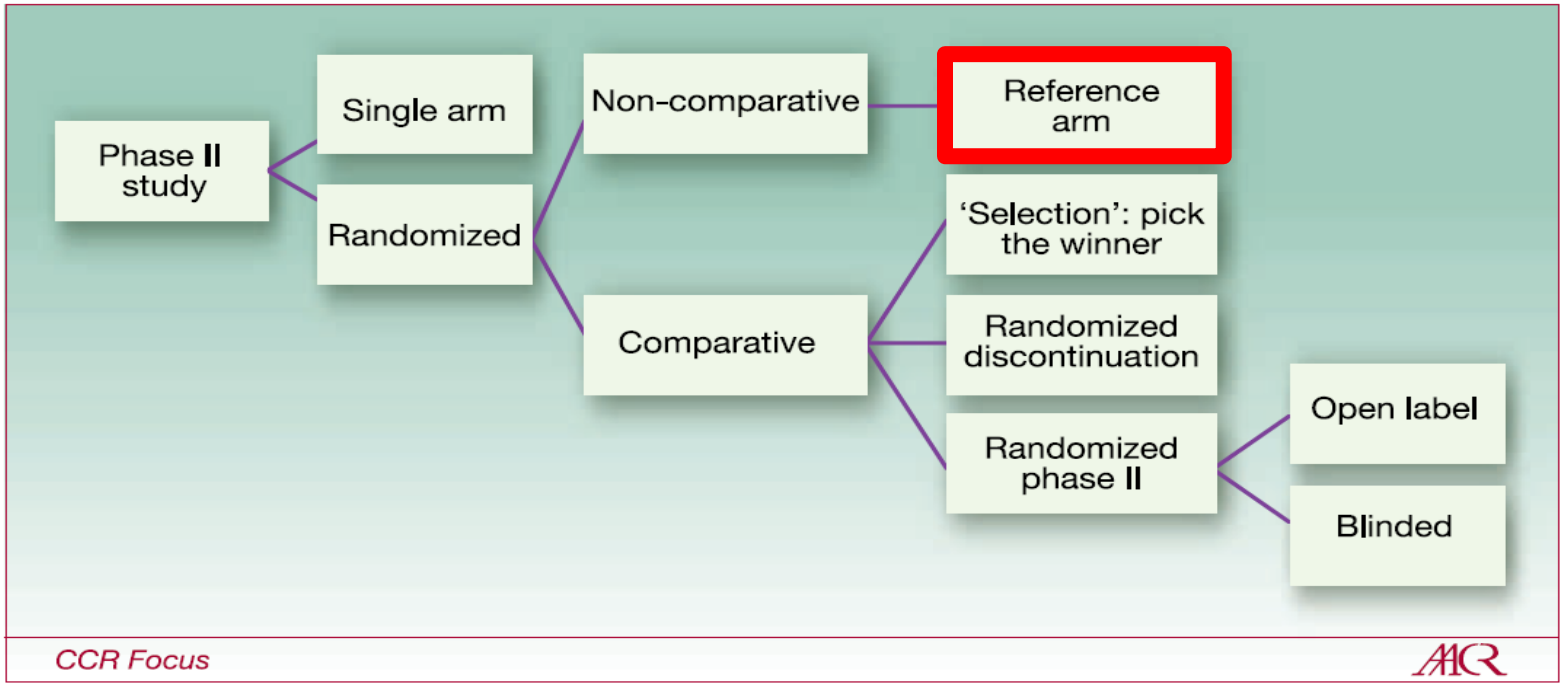
Classification of Phase II Studies



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

Canadian Cancer Trials Group

Rationale

Castration Resistant Prostate Cancer (CRPC)

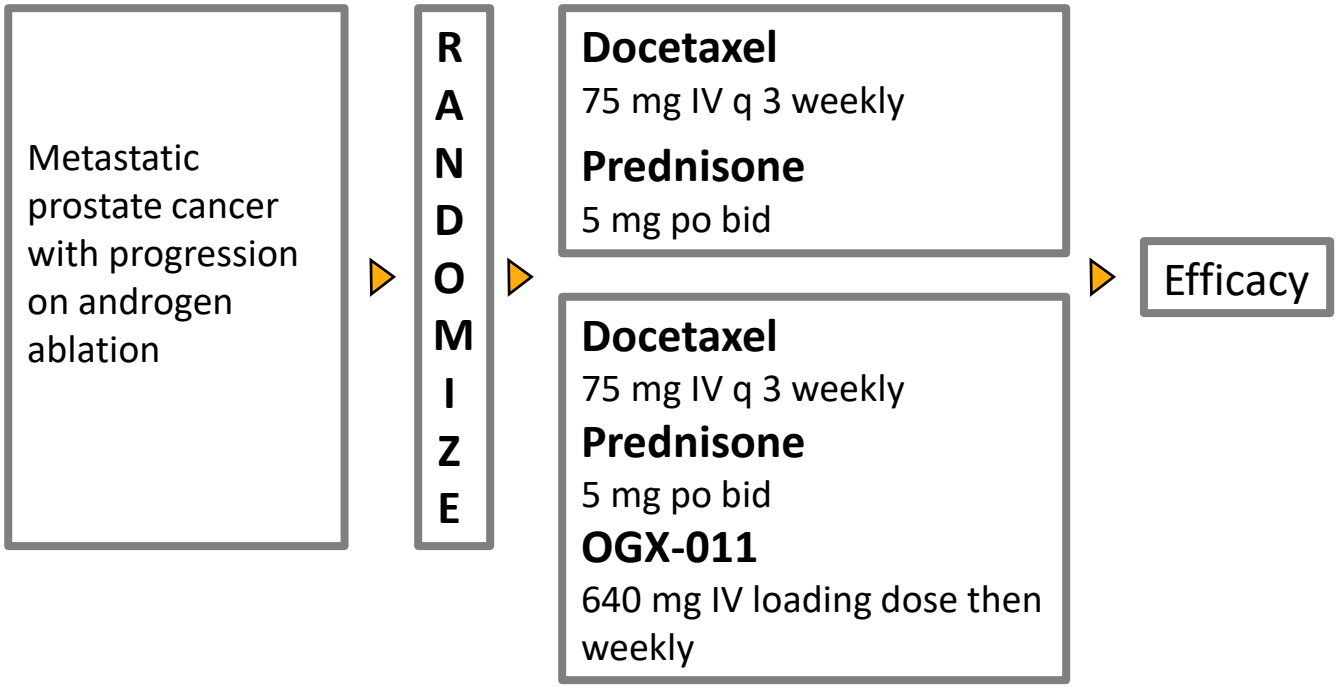
- Characterized by disease progression despite castrate state
- Highly lethal despite chemotherapy sensitivity to docetaxel regimens
- Clusterin is a cell survival protein which is induced by therapeutic stressors and is expressed in CRPC

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

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NCIC CTG IND.165 Endpoints

Primary

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

Secondary

- Response Rate (RR)
- Toxicity
- 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

NCIC CTG IND.165 Study Design

Randomized, non-comparative (with reference arm) phase II study

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IND.165 Patient Flow

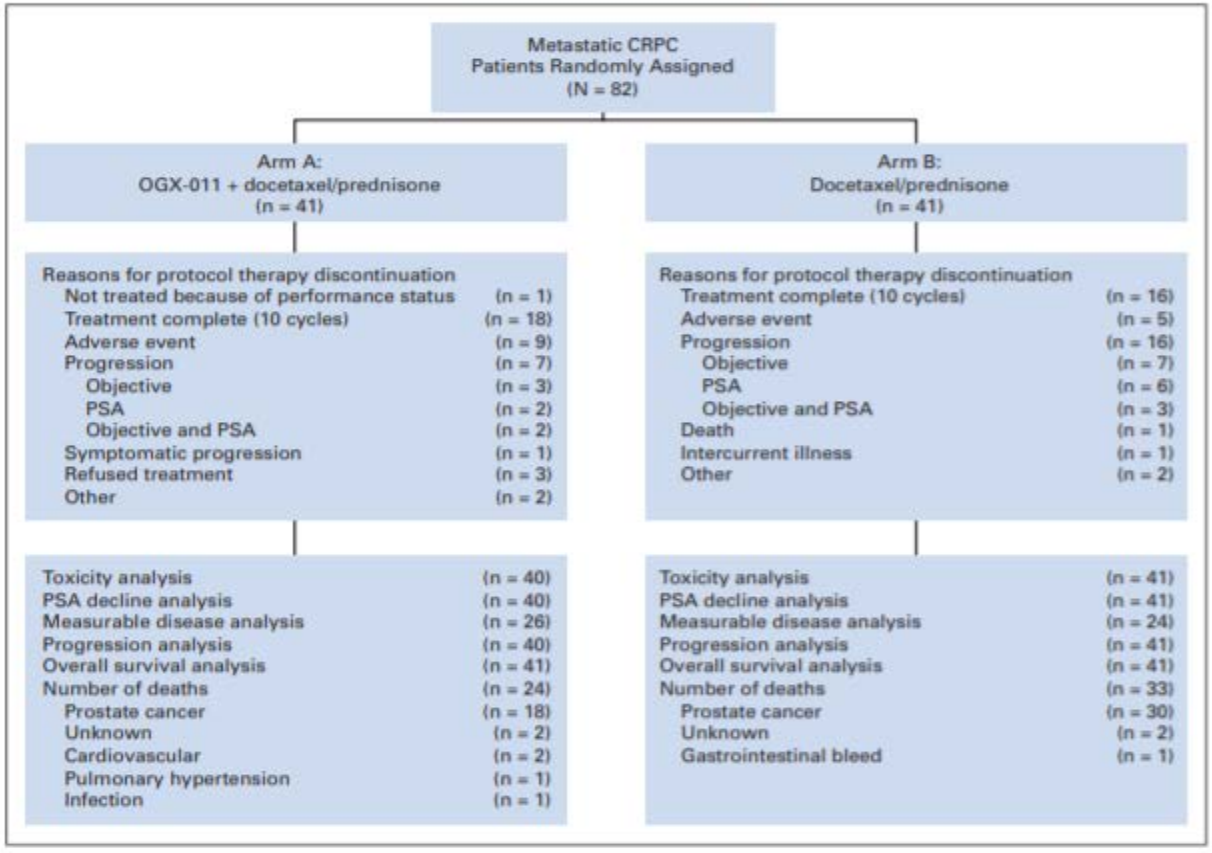

Fig 1. CONSORT diagram. CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen.

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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 Endpoints

Secondary Endpoint	Docetaxel + Prednisone + OGX 011	Docetaxel + Prednisone
RR (95% CI)	19% (95% CI 6.6-39.4)	25% (95% CI 9.8-46.7)
Median PFS (95% CI)	7.3 months (95% CI 5.3-8.8)	6.1 months (95% CI 3.7-8.7)
Overall Survival (95% CI)	Median 23.8 months (95% CI 16.2-not reached)	16.9 months (95% CI 12.8-25.8)

NCIC CTG IND.165: Exploratory Analyses

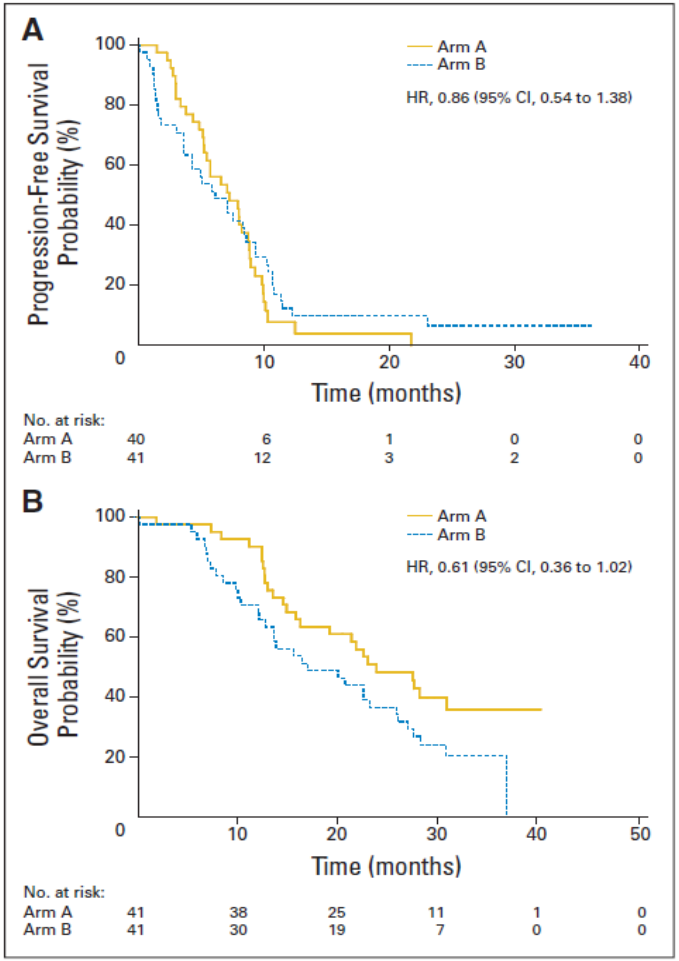

Fig 4. (A) Progression-free survival of patients on arm A (OGX-011 and docetaxel) and arm B (docetaxel). (B) Overall survival of all patients assigned to arm A and arm B.

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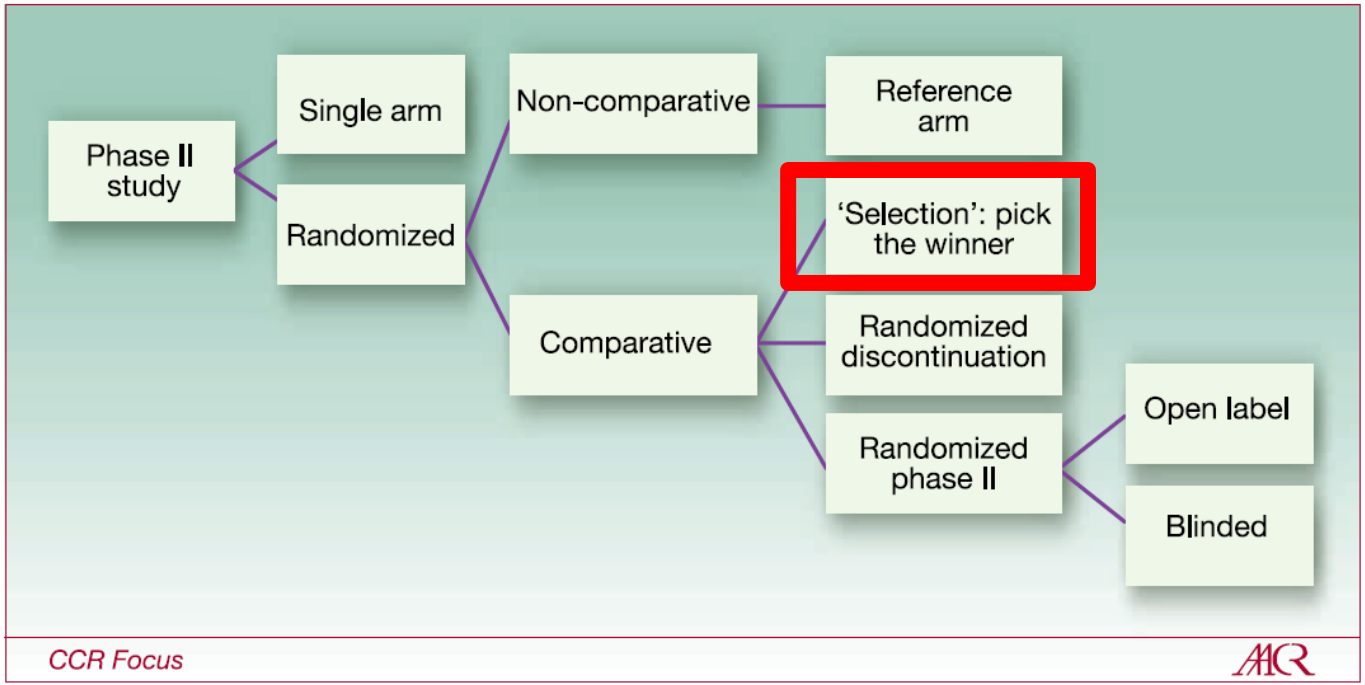
NCIC CTG IND.165 Conclusions

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 trials launched by company (first and second line studies in CRPC)

Classification 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

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Rationale

Breast Cancer

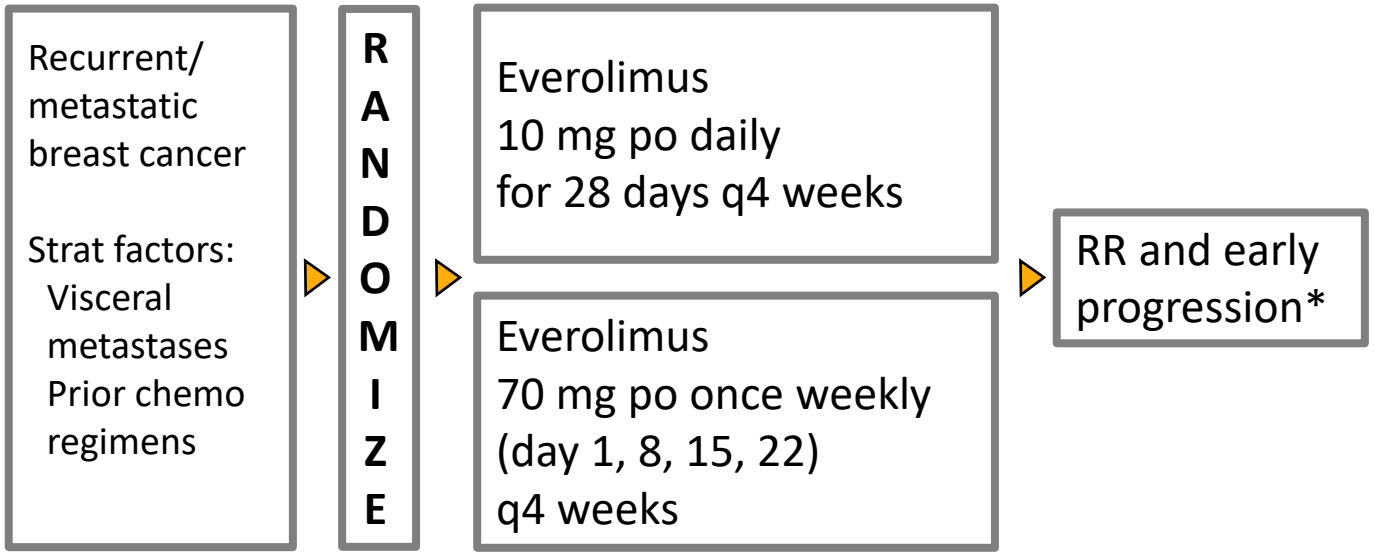
- Common, incurable in the advanced disease setting
- mTOR (mammalian target of rapamycin)
- Involved in cell replication
- Mediates the critical PI3K/AKT pathway which is active in breast cancer
- Other functions: mediates VEGF, PDGF and TGF
- Preclinical inhibitor of mTOR inhibits proliferation
- Other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

Everolimus in Breast Cancer

Everolimus

- Orally bioavailable
- Uncertainty about optimal dosing schedule: weekly versus daily

NCIC CTG IND.163



N ≤ 30 each arm

* Zee B, et al. J Biopharm Stat 1999

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

Randomized, comparative, selection (pick the winner) phase II study

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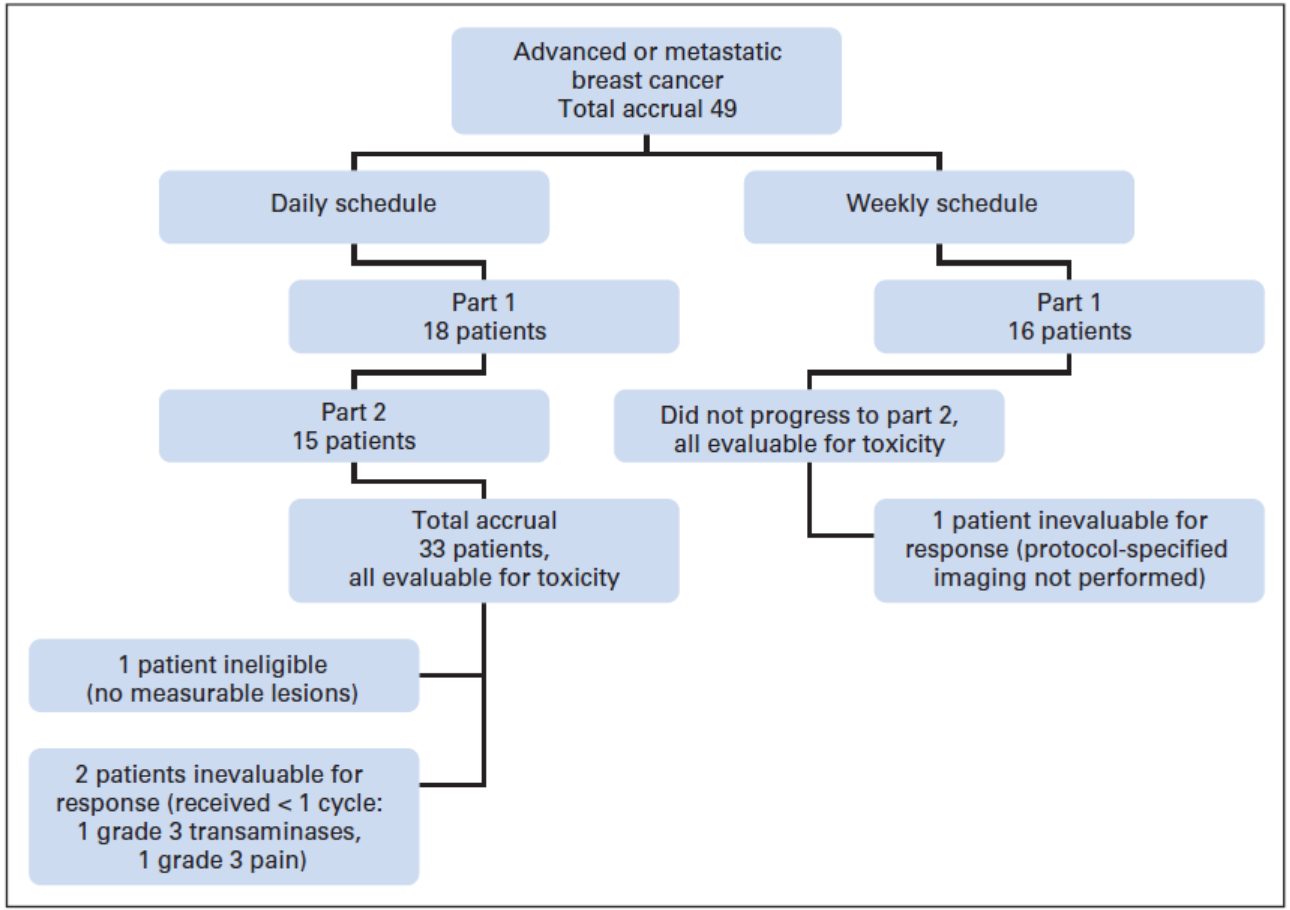
NCIC CTG IND.163 Patient Flow



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NCIC CTG IND.163 Response Rate

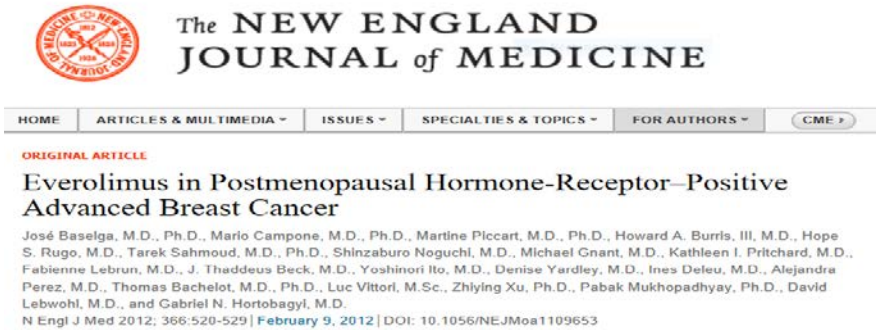
Table 4. Response

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

Daily Schedule: 4 responses (12%; 95% CI, 3.4% to 28.2%)
Weekly Schedule: 0 responses; 11 early progressions end of stage 1

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 in phase III study



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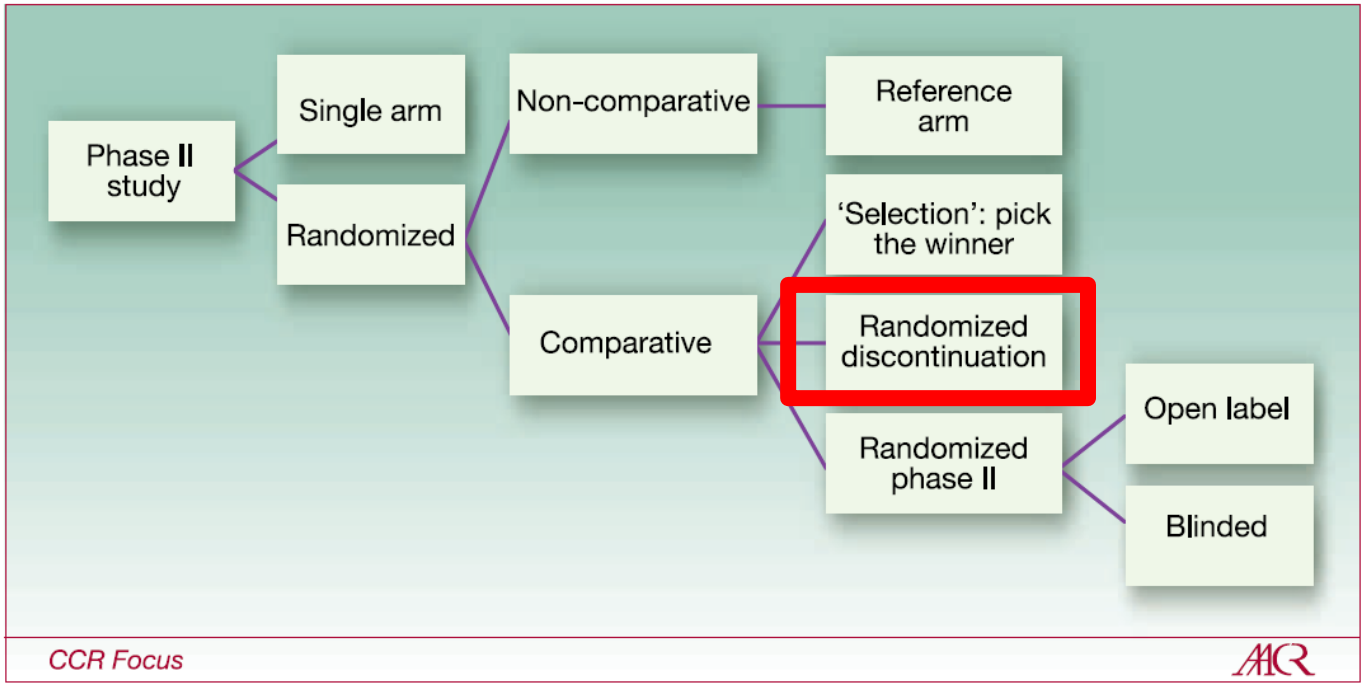
Classification of Phase II Studies



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

SORAFENIB
in Renal Cell Carcinoma

RATAIN ET AL J CLIN ONCOL 2006

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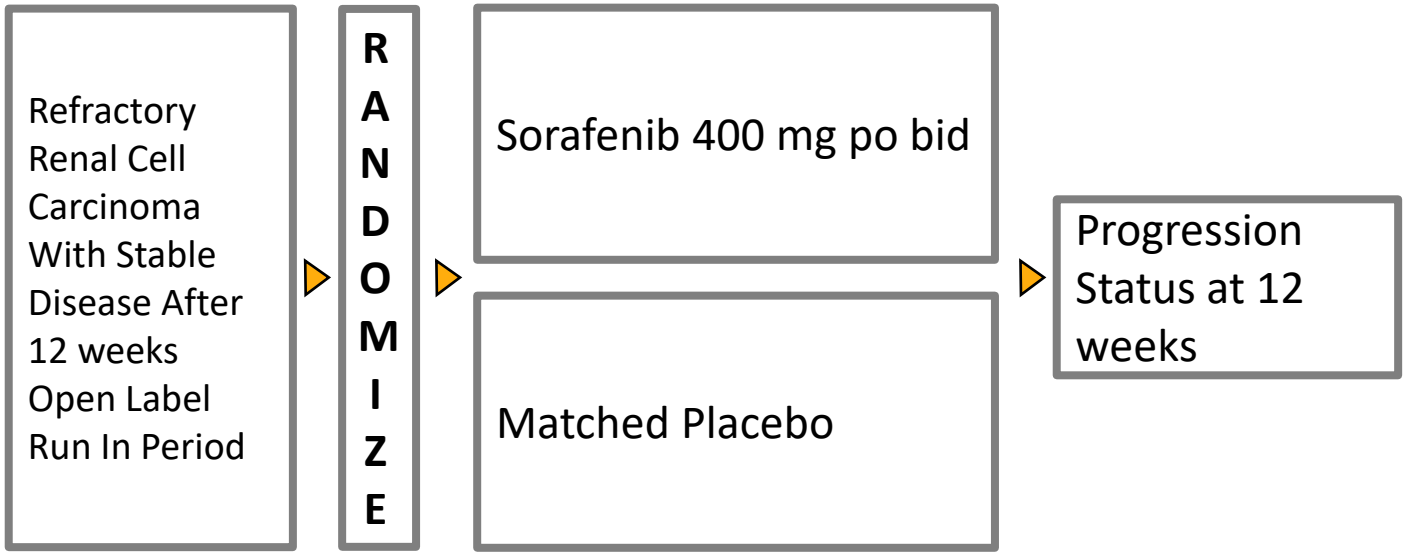
Sorafenib

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 (randomized patients)
- Overall PFS
- Response Rate
- Safety

Sorafenib in Renal Cell Carcinoma
Statistical Parameters

Enroll 50 patients per arm

- 81% power 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

Comparative, randomized phase II discontinuation study

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Sorafenib in Renal Cell Carcinoma: Run in Period

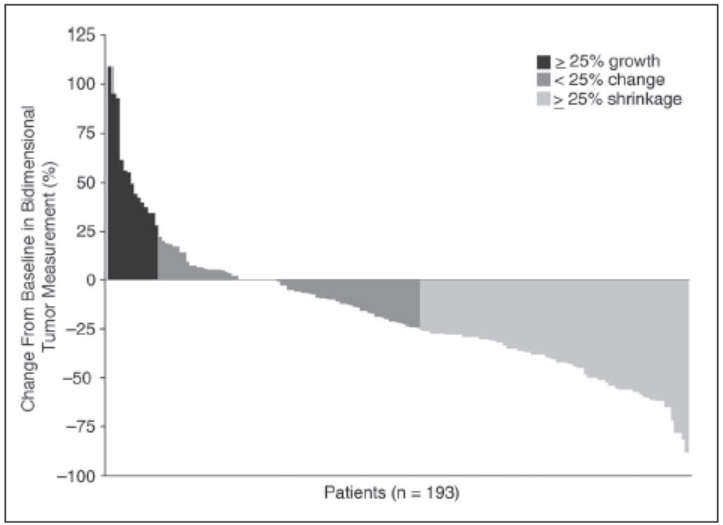

Fig 1. Changes from baseline in investigator-assessed, bidimensional radiographic measurements at 12 weeks for patients with renal cell carcinoma. These measurements were unconfirmed, and therefore do not represent confirmed responses according to modified WHO criteria. Mean change at 12 weeks was −18%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

34% had 'stable' tumour measurements at 12 weeks

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Sorafenib in Renal Cell Carcinoma Efficacy

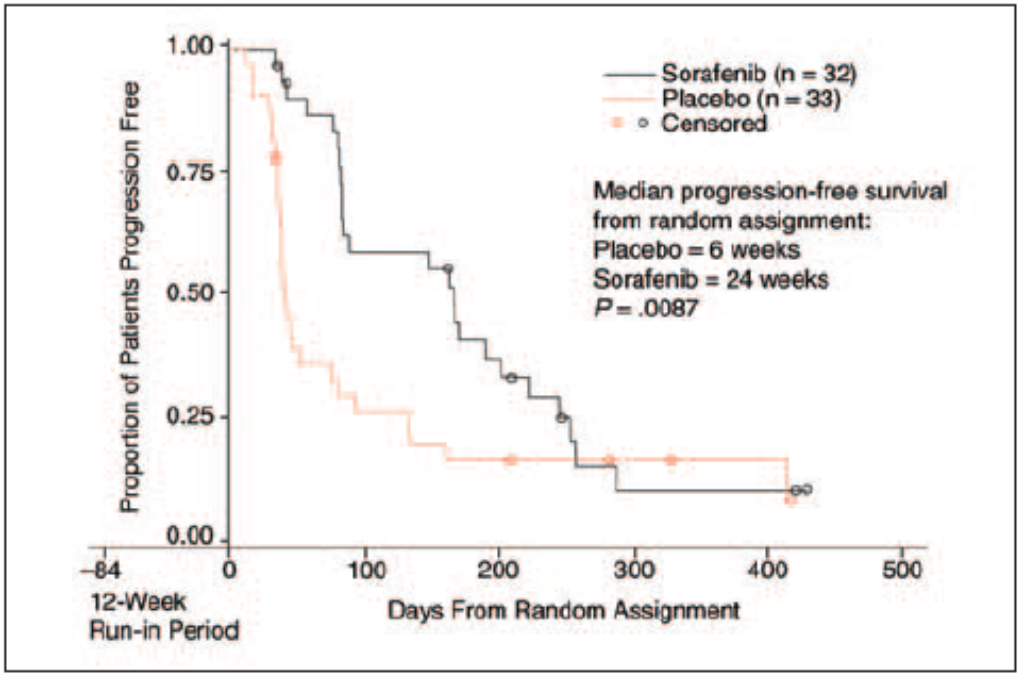

Fig 2. Kaplan-Meier plot of investigator-assessed progression-free survival from week 12 randomization for patients randomized to placebo (n = 33) or to sorafenib (n = 32).

12 week progression free:

Sorafenib 50%
Placebo 18%

P=0.0077

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Sorafenib in Renal Cell Carcinoma Conclusions

- Significant disease stabilizing activity
- Tolerable
- Efficacy demonstrated in phase III study

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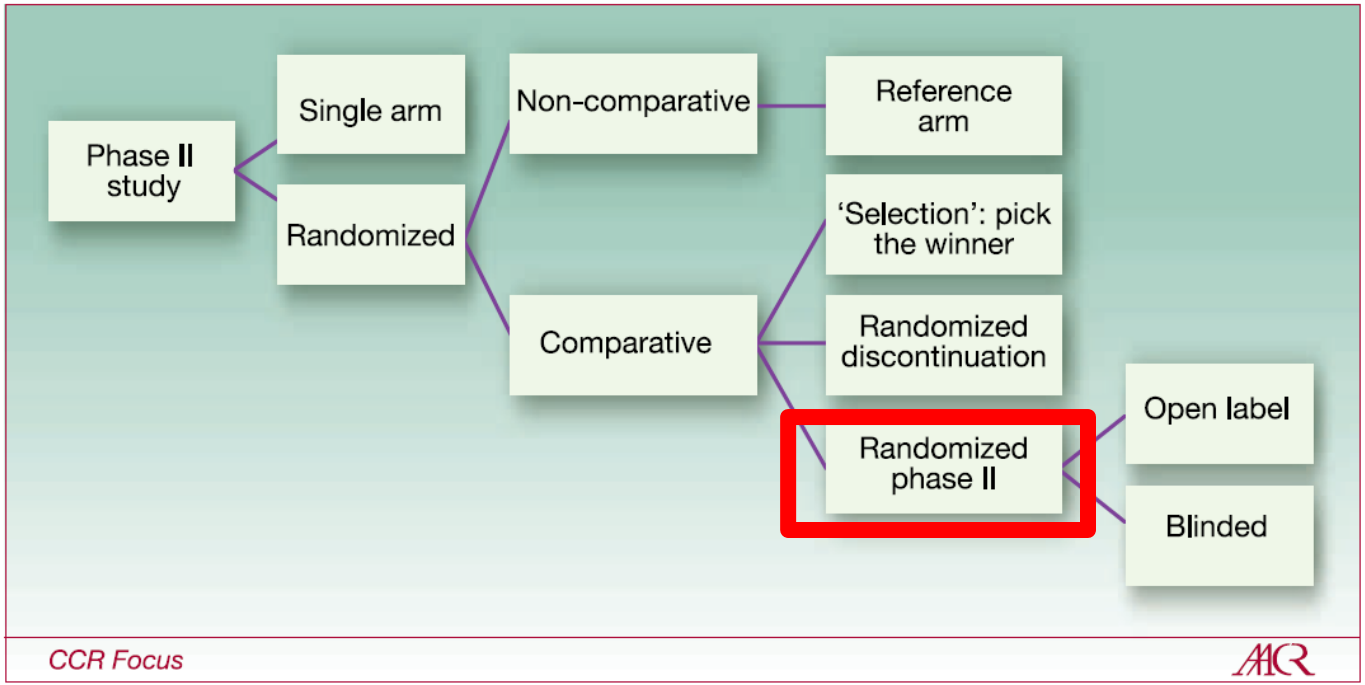
JOURNAL OF CLINICAL ONCOLOGY

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

Classification of Phase II Studies



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

Pelareorep (Reolysin) and Docetaxel in Metastatic Castration Resistant Prostate Cancer

CCTG IND.209

EIGL ET AL, ONCOTARGET 2018

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Rationale

Castration Resistant Prostate Cancer

- Second leading cause of cancer death in men
- Docetaxel effective but has modest benefit

Palareorep

- Preferentially infect and exhibit cytotoxic effects in human cancer cells
- May potentiate anti tumour immune responses
- Preclinical data demonstrated activity against prostate cancer cell lines and xenografts
- Synergism with taxanes
- Phase I trial in combination with docetaxel showed activity and tolerability

IND.209 Statistical Parameters

40 patients treated by pelareorep plus docetaxel and prednisone:

- 92% power H0 12 week LPD rate < 30% vs HA 12 week LPD rate > 50%
- 0.11 significance level

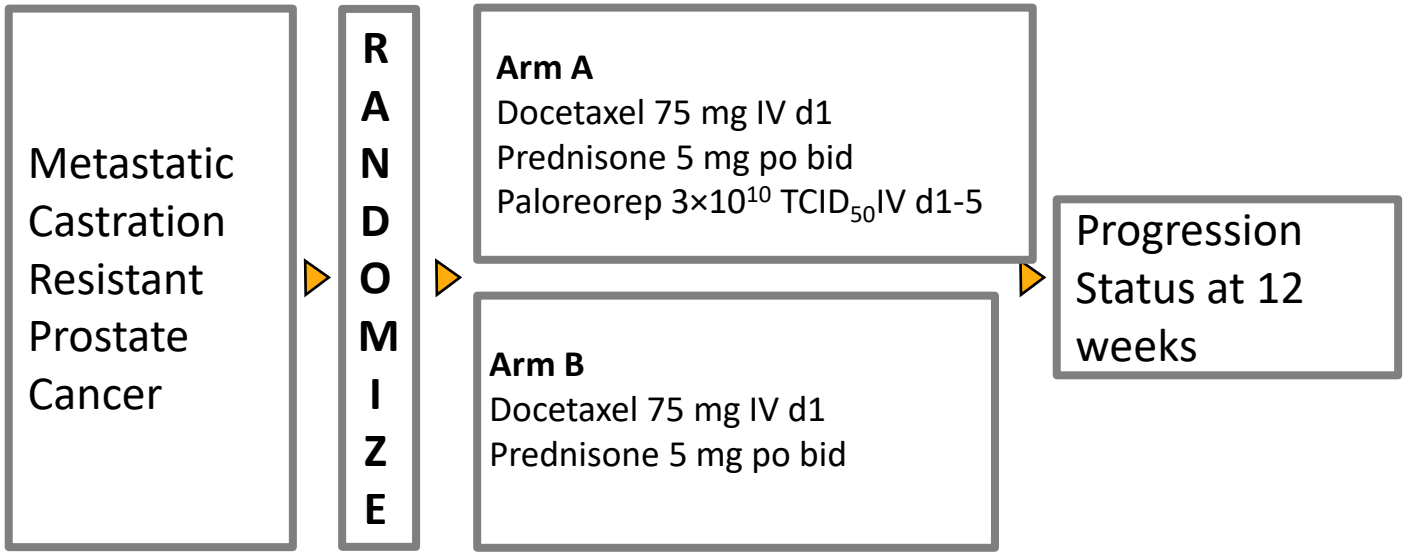
With a total sample size of 80

- 58% power to detect a difference between arms in 12-week LPD rate from 30 to 50% with two-sided alpha 0.1
- 90% power to detect difference between arms in 12 week LPD rate from 20 to 50% with two-sided alpha 0.1

IND.209 Study Design

Comparative, randomized, phase II study

IND.209



N = 80

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IND.209 Endpoints

Primary

- Lack of Progressive Disease (LPD) at 12 weeks

Secondary

- Objective Response Rate
- PSA change rate
- Overall Survival
- CTC counts
- Prognostic/predictive biomarkers

IND.209 Patient Flow

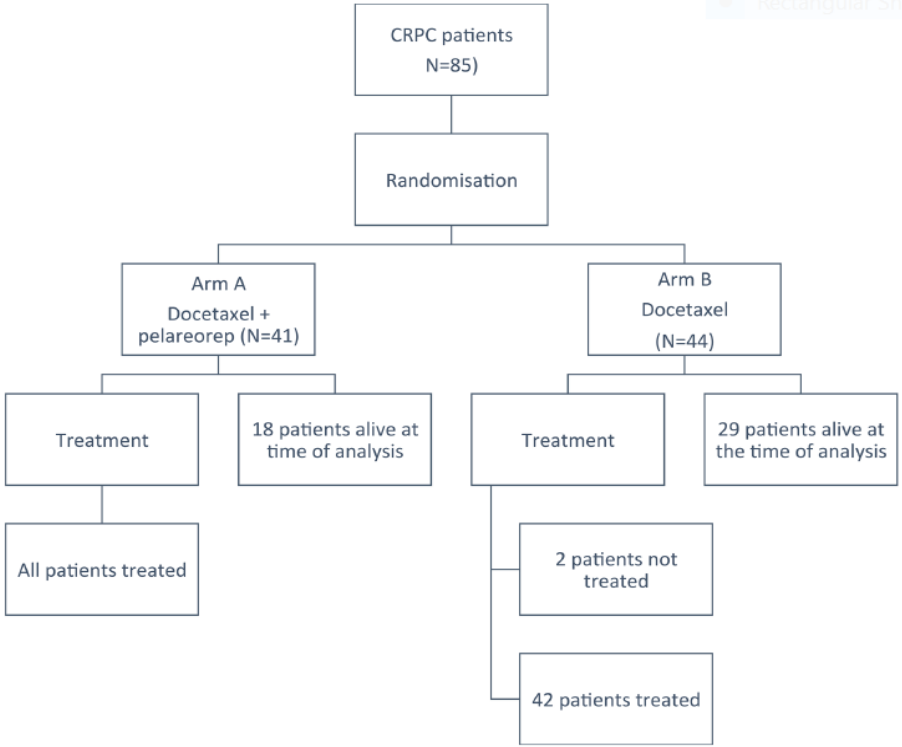

Figure 1: CONSORT diagram outlining subject disposition.

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IND.209 Study Results

- 12-week LPD rate was 61% (Arm A experimental) and 52.4% (Arm B control) p=0.51
- Response rates: 26.7% (Arm A) and 40% (Arm B); adjusted OR 0.53; 95% CI 0.12 to 2.38, p=0.41
- Overall survival: HR 1.83 (95%CI 0.96-3.52, p=0.06) (no benefit)

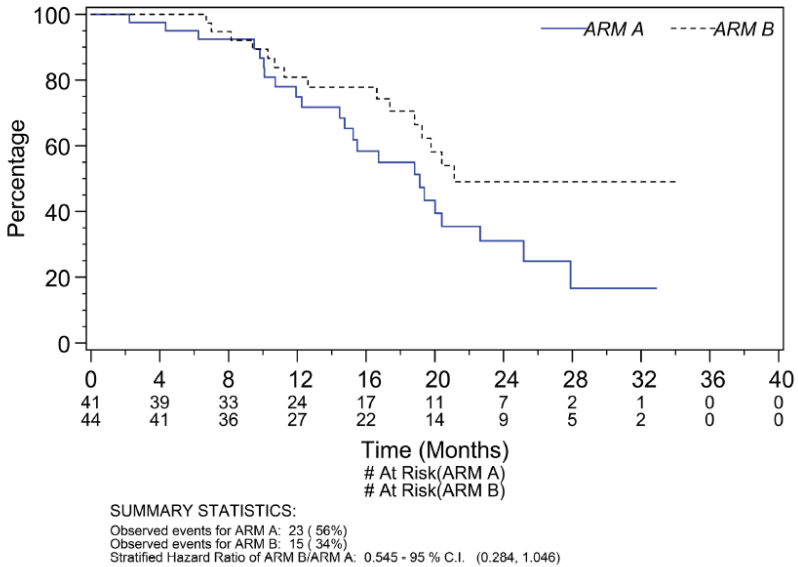

Figure 2: Overall survival.

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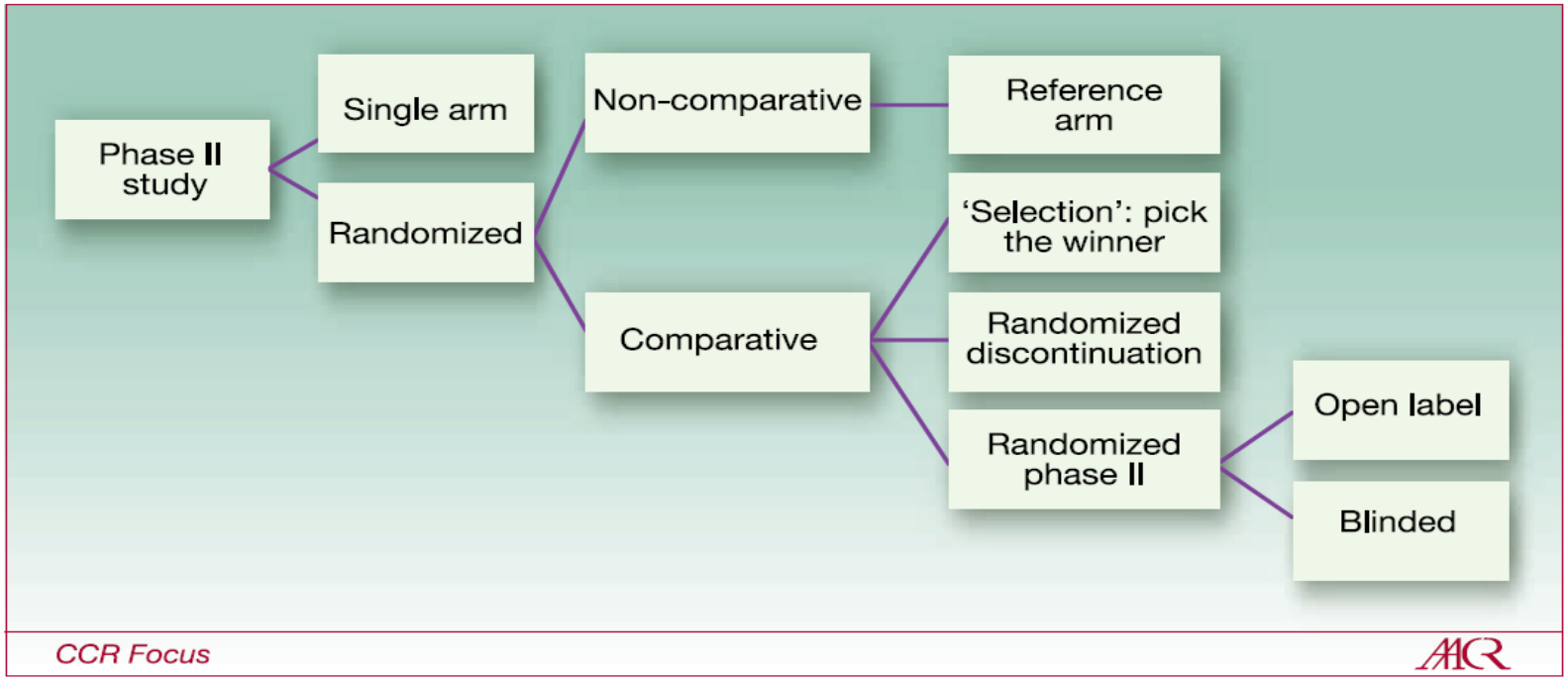
IND.209 Conclusion

- Combination of pelareorep with docetaxel was tolerable with comparable LPD in both arms but response and survival were inferior and so this combination does not merit further study

Learning Objectives

- √ To define the role of a phase II study in oncology drug development
  - Screen for efficacy; characterize safety profile, mechanism of action, identify target population for administration
- √ To describe the statistical parameters that provide the framework and sample size for a phase II study
  - Type I and II error rates; H0 and HA (null and target drug activity rates); HR (hazard ratio)
- √ To classify the types of phase II studies used in oncology drug development

Classification of Phase II Studies



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

Conclusions

- Phase II studies play a pivotal role in drug development
- Multiple designs are available, each with specific objectives that will inform the research agenda and subsequent clinical trials
- *It must be emphasized that a randomized phase II study should almost never be taken as definitive evidence for the superior efficacy of an experimental agent or regimen (Rubinstein L et al 2009)*

Thank You

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