Phase II Design Workshop
New Investigator Clinical Trials Course
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Disclosures

W Parulekar and D Tu

- No disclosures relevant to this workshop

Objectives of Workshop

- To review the types of phase II designs used in drug development in oncology
- To define the statistical parameters of different phase II study designs
- To discuss the advantages and disadvantages of different phase II design strategies using an example of drug evaluation in breast cancer

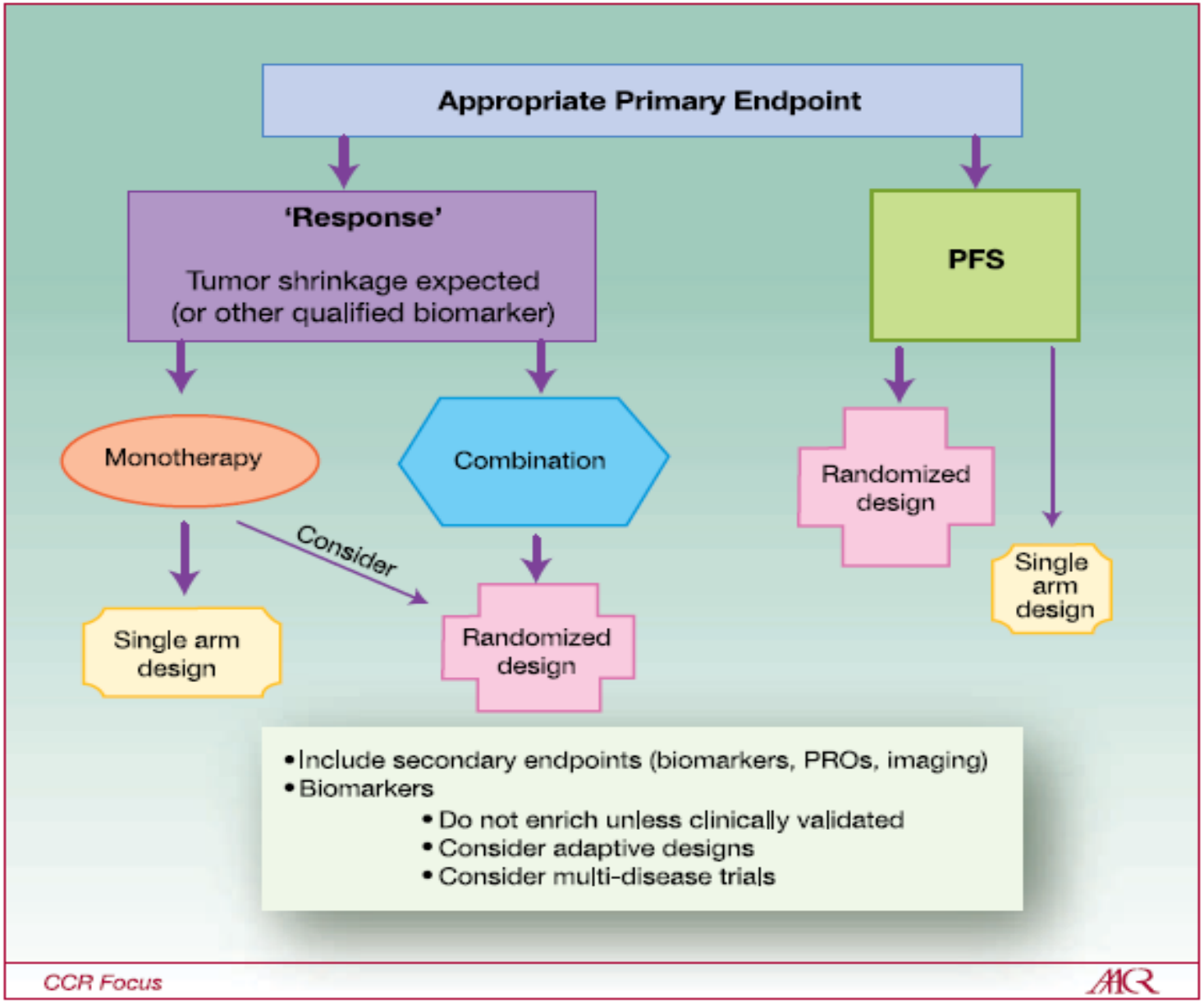
Phase II Study

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



Seymour et al. Clin Cancer Res. 2010; 16:1764-1769

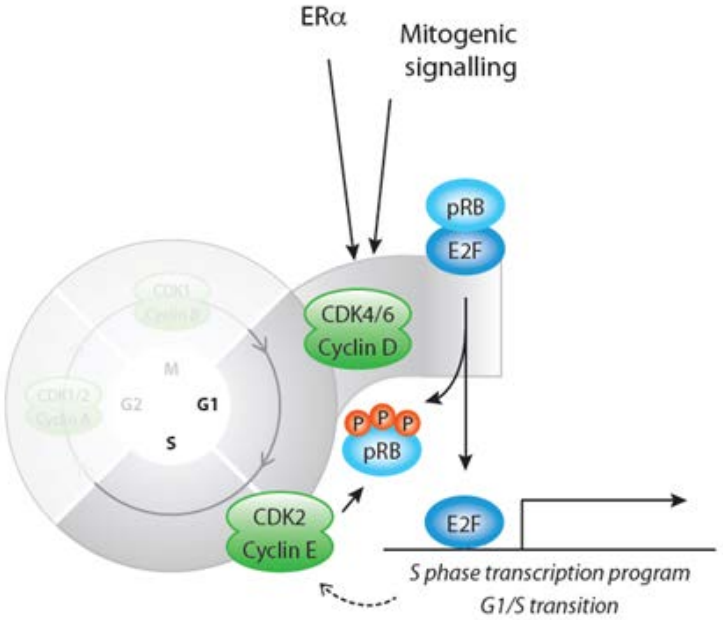
Example

Receptor positive breast cancer

- Common and treatable with endocrine therapy (tamoxifen or aromatase inhibitors)
- Endocrine resistance and death occurs in approximately 25% of patients
- Targeting estrogen independent pathways may improve outcome

CDK 4/6

- Cell cycle progression pathways may be important to target since this may be altered in malignant cells – specifically CDK 4, 6 and cyclin D



Courtesy of Pfizer, 2015

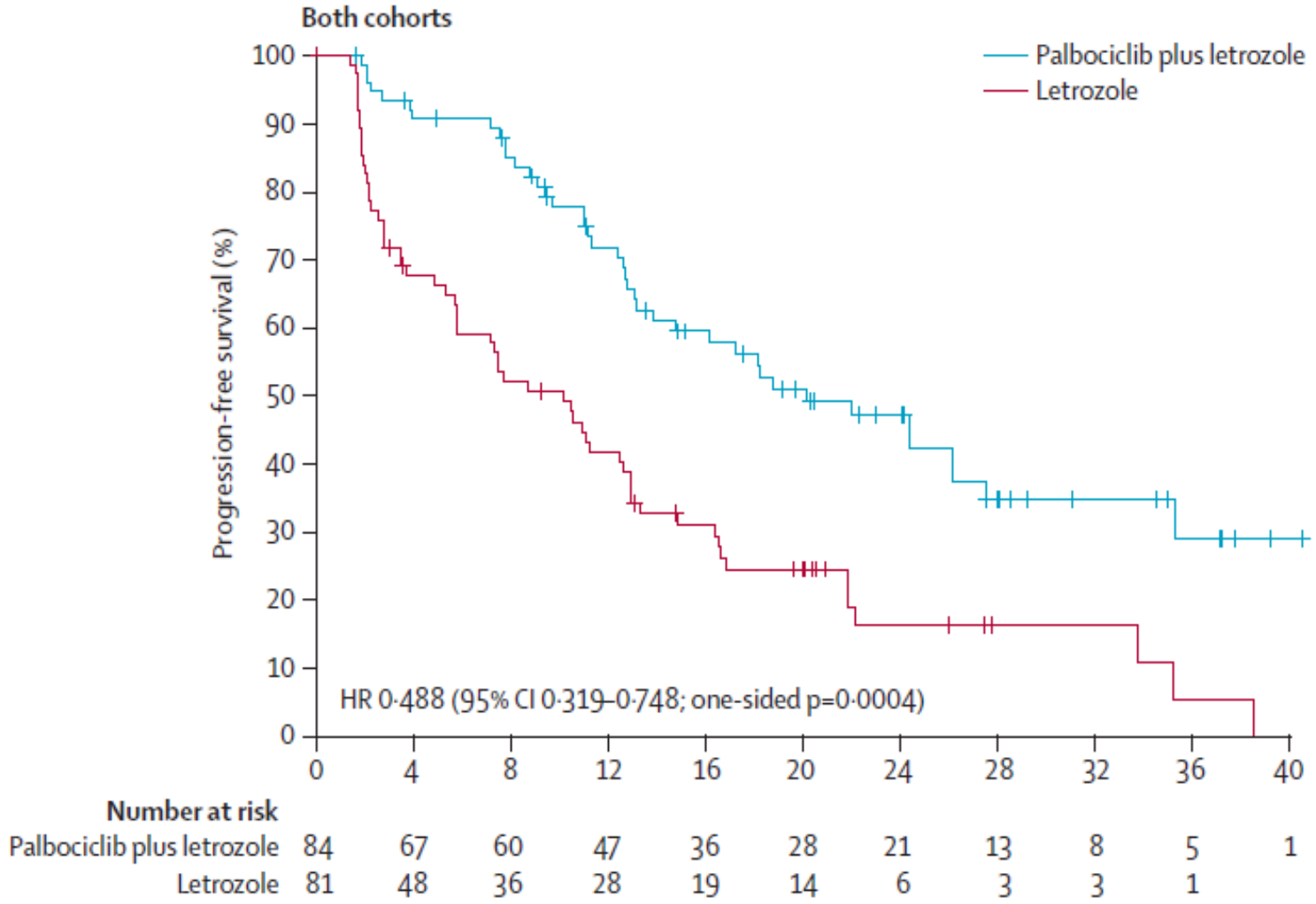
Palbociclib

- Orally active, CDK 4,6 inhibitor results in cell cycle arrest due to inhibition of RB phosphorylation
- Schedule of administration: 125 mg po daily 3 out of 4 weeks
- Accelerated FDA approved for use in first line metastatic setting in combination with letrozole therapy http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf
- Dose limiting toxicity: uncomplicated grade 3/4 neutropenia
- Actual and modelled data - improved therapeutic index possible using daily, continuous dosing at a lower, biologically active dose level

Relevant Clinical Studies

Study Name	Design	Setting	Intervention	Current Status
Paloma 1	Randomized Phase II	Advanced first line; ER+ HER2-	Letrozole +/- Palbociclib	HR: 0.488 p=0.0004; median PFS 20.2 vs 10.2 mo (IA) (Finn et al Lancet Oncol 2015)
Paloma 2	Randomized Phase III	Advanced first line; ER+ HER2-	Letrozole +/- Palbociclib	Ongoing
Paloma 3	Randomized Phase III	Advanced second line; ER+ HER2-	Fulvestrant +/- Palbociclib	HR 0.422 (P<0.000001), median PFS 9.2 vs 3.8 mo (IA) (Turner et al NEJM 2015)
PALLAS	Randomized Phase III	Adjuvant; Hormone receptor +, HER2-	Endocrine therapy +/- 2 years of palbociclib	Pending activation in NCIC CTG

First Line with Letrozole (Paloma 1)
Primary Endpoint: PFS (ITT Population)



Study Hypothesis

Administration of a biologically active, lower dose of palbociclib (100 mg) on a daily, continuous basis may result in greater systemic exposure, activity and tolerability compared to the FDA approved dose of 125 mg po daily for 3 out of 4 weeks

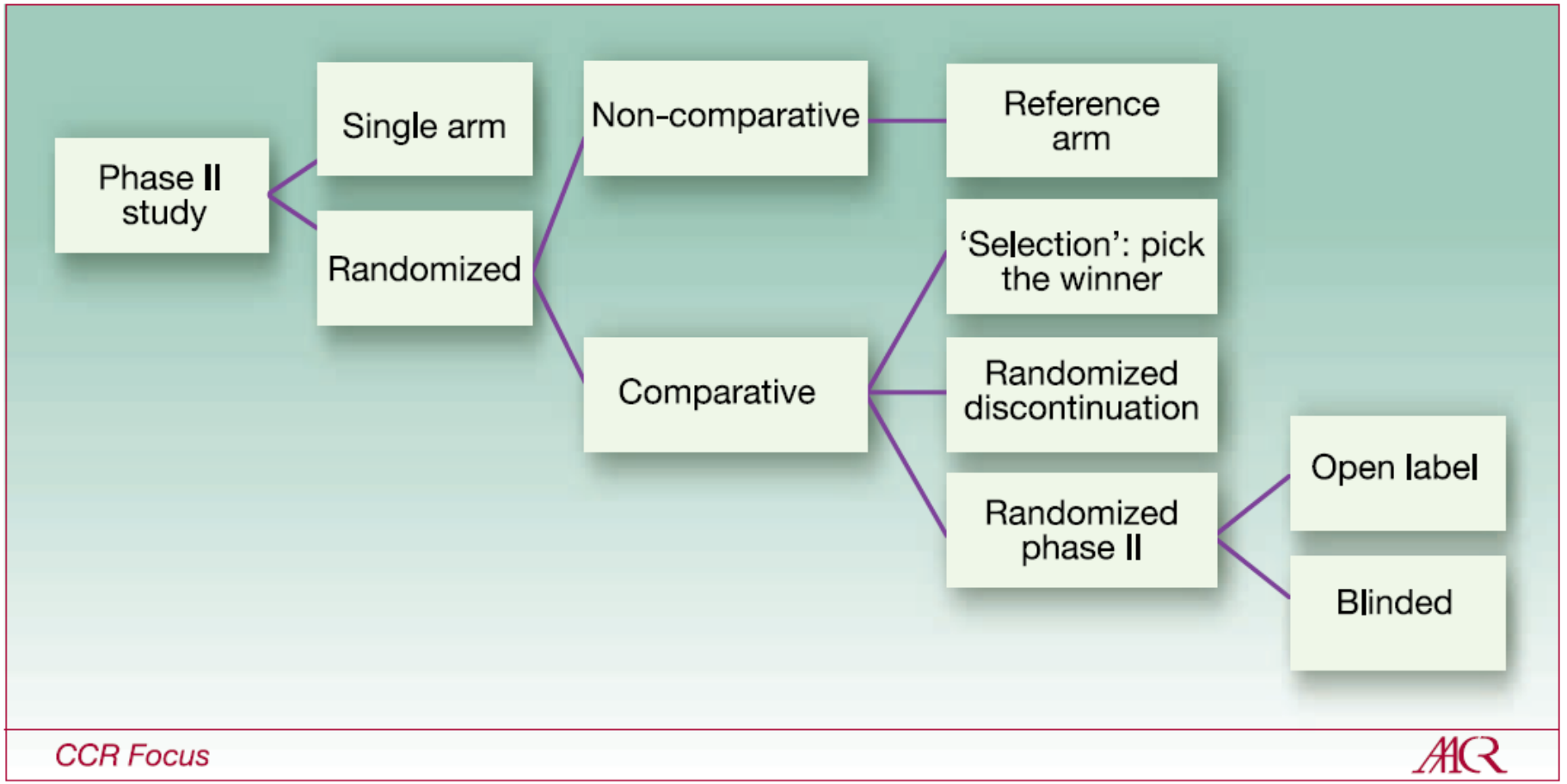
What design elements will you include in your study based on the current literature?

Response

Phase II study including safety, efficacy and pharmacokinetic assessments appropriate study design to meet the objectives

Which phase II study design?

Types of Phase II Studies



Seymour et al. Clin Cancer Res. 2010; 16:1764-1769

Single Arm Phase II

Specify trial design elements

- Primary outcome measure
- Secondary outcome measure
- Type I and type II error rates

Limitations of design?

Single Arm Phase II:

- Specify trial design elements
  - Primary outcome measure: PD rate at 12 months
  - Secondary outcome measure
    - Adverse events, safety, QOL, PK and correlative studies
- Statistical elements: e.g.
  - H0: 50% (first line) HA = $\leq$ 30%(first line)
  - H0: 90% (first line) HA = $\leq$ 70%(first line)
  - α=0.10 β=0.10

Single Arm Phase II

Rejected

- Issues of bias
- Lack of standard dosing arm weakens interpretation and credibility of results

Randomized Phase II: Non-comparative reference arm

- Specify trial design elements
  - Primary outcome measure: PD rate at 12 months
  - Secondary outcome measure
    - Adverse events, safety, QOL, PK and correlative studies
- Statistical elements:
  - H_0 H_A
  - Type I and II error rates

Randomized Phase II: Non-comparative reference arm

H_0 (PD %)	H_A (PD %)	α	β	Sample size both arms 1:1 randomization
First Line				
≥ 50	≤ 30	0.1	0.1	100
≥ 45	≤ 30	0.1	0.1	180
≥ 40	≤ 30	0.1	0.1	400
Second Line				
≥ 90	≤ 70	0.1	0.1	66
≥ 85	≤ 70	0.1	0.1	130
≥ 80	≤ 70	0.1	0.1	160

Randomized Phase II: Non-comparative reference arm

Pros

- Sample size smaller compared to formal comparison
- Greater confidence in experimental arm results when concurrent control results available

Cons

- Not clinically compelling – comparison of new dose and schedule to FDA approved regimen of greater interest

Randomized Phase II: Selection Design

Rejected

- We were not ranking new treatments or regimens for continued development

Randomized Phase II: Formal Comparison

Specify trial design elements

- Primary outcome measure
- Secondary outcome measure
- Type I and type II error rates

Limitations of design?

Randomized Phase II: Formal Comparison

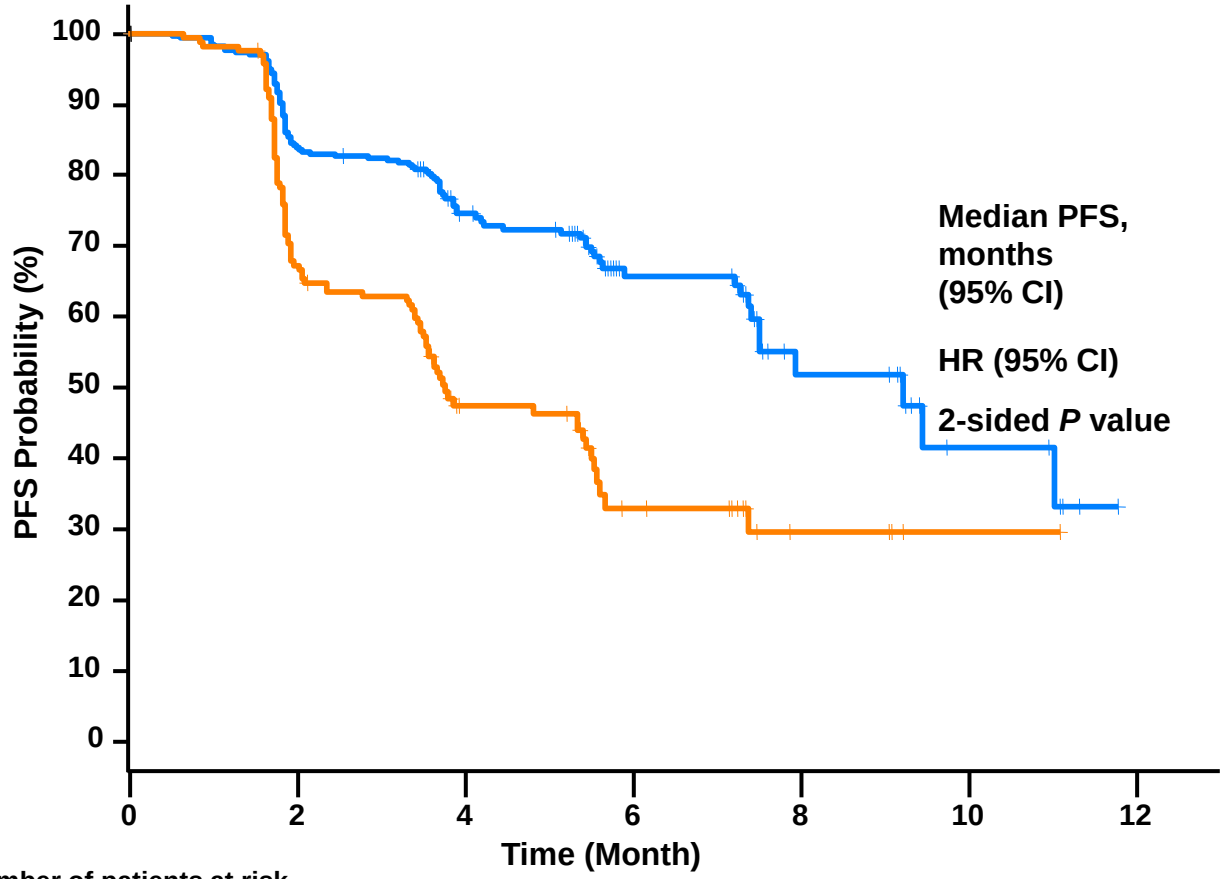
Specify trial design elements

- Primary outcome measure: PFS
- Secondary outcome measure
  - Adverse events, safety, QOL, PK and correlative studies

Statistical elements

- Hazard Ratio (HR), Type I and II error rates

Second Line with Fulvestrant (Paloma 3)
Primary Endpoint: PFS (ITT Population)



	Palbociclib + Fulvestrant n=347	Placebo + Fulvestrant n=174
Median PFS, months (95% CI)	9.2 (7.5, NE)	3.8 (3.5, 5.5)
HR (95% CI)	0.422 (0.318, 0.560)	
2-sided *P* value	<0.000001	

Number of patients at risk

PAL+FUL	347	279	132	59	16	6
PCB+FUL	174	109	42	16	6	1

ASCO 2015
LBA 502

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.

Randomized Phase II: Formal Comparison

- PFS: Randomization to progression or death
- Second line setting chosen – relevant and enable timely completion of study; limit sample size to 180 based on 2 year study timeline
- HR: 0.66 (median PFS: increased 10 to 15 months)
- $\alpha = 0.1$ one sided $\beta=0.2$
- Number of events: 104
- Sample size = 180; 1 year accrual and 1 year follow-up

Randomized Phase II: Formal Comparison

Pros

- Formal comparison using standardized criteria; suitable sample size for secondary outcome measures

Cons

- What target HR should be used? Optimism versus realism given that the only difference between the arms is scheduling

Modified Design

The sample size is based on estimating the hazard ratio (HR) of two arms (experimental vs. control) within a 90% confidence interval (CI). For a 1:1 randomization with 1 year accrual and one-year additional follow-up. If we observe approximately 58 PFS events in each arm, the upper bound of the 90% CI will be 1.36 times the estimated HR and the lower bound will be 0.74 times the estimated HR. Assuming a median PFS of approximately 10 months for both treatment arms, and duration of accrual and follow-up both at 1 year, and a dropout rate of 10%, the study would need to enroll approximately 90 subjects in each arm. If the upper bound of (the 90% CI is < 1, then we can conclude that the experimental Arm is superior to control arm, which will be the case if the observed hazard ratio is 0.736 or lower.

(Motzer et al, J Clin Oncol 2012; 30:1371-1377.)

Summary

Phase II Classification	Pros and Cons	Final Decision
Single arm	**Pros:** Small sample size; standardized outcomes measures **Cons:** Biased results; lack of Standard dose arm	Rejected
Randomized Phase II, non comparative with reference arm	**Pros**: Smaller sample size than a formal comparison; greater confidence in interpretation of experimental arm activity with concurrent control; standardized outcomes measures **Cons**: Formal comparison to the approved schedule more compelling for clinicians	Rejected
Comparative (HR); PFS primary outcome measure, standard Type I and II Error Rates	**Pros:** Prospective plans for formal comparison; informative, standardized outcome measures **Cons:** ambitious HR – unrealistic?; resources	Rejected
Comparative (HR) ; PFS primary outcome measure; precision around HR estimates	**Pros:** Prospective formal comparison; standardized outcome measures **Cons:** Limited use of methodology in literature	Accepted

Conclusions

- Phase II studies play a pivotal role in drug development
- The primary goal is to select promising new drugs/ strategies for further evaluation
- Multiple designs are available and selection should inform current and future drug development

Useful References

Seymour et al. Clin Cancer Res. 2010; 16:1764-1769

El-Maraghi et al. J Clin Oncol 2008:26:1346-1354

Rubinstein et al. J Clin Oncol 2005;23: 7199-7206

Lee et al. J Clin Oncol 2005;23: 4450-4457