Possibilities and risks associated with directly moving from Phase I to Phase III: Adaptive designs and Co

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Case example: Kadcyla (trastuzumab-emtasine, T-DM1)

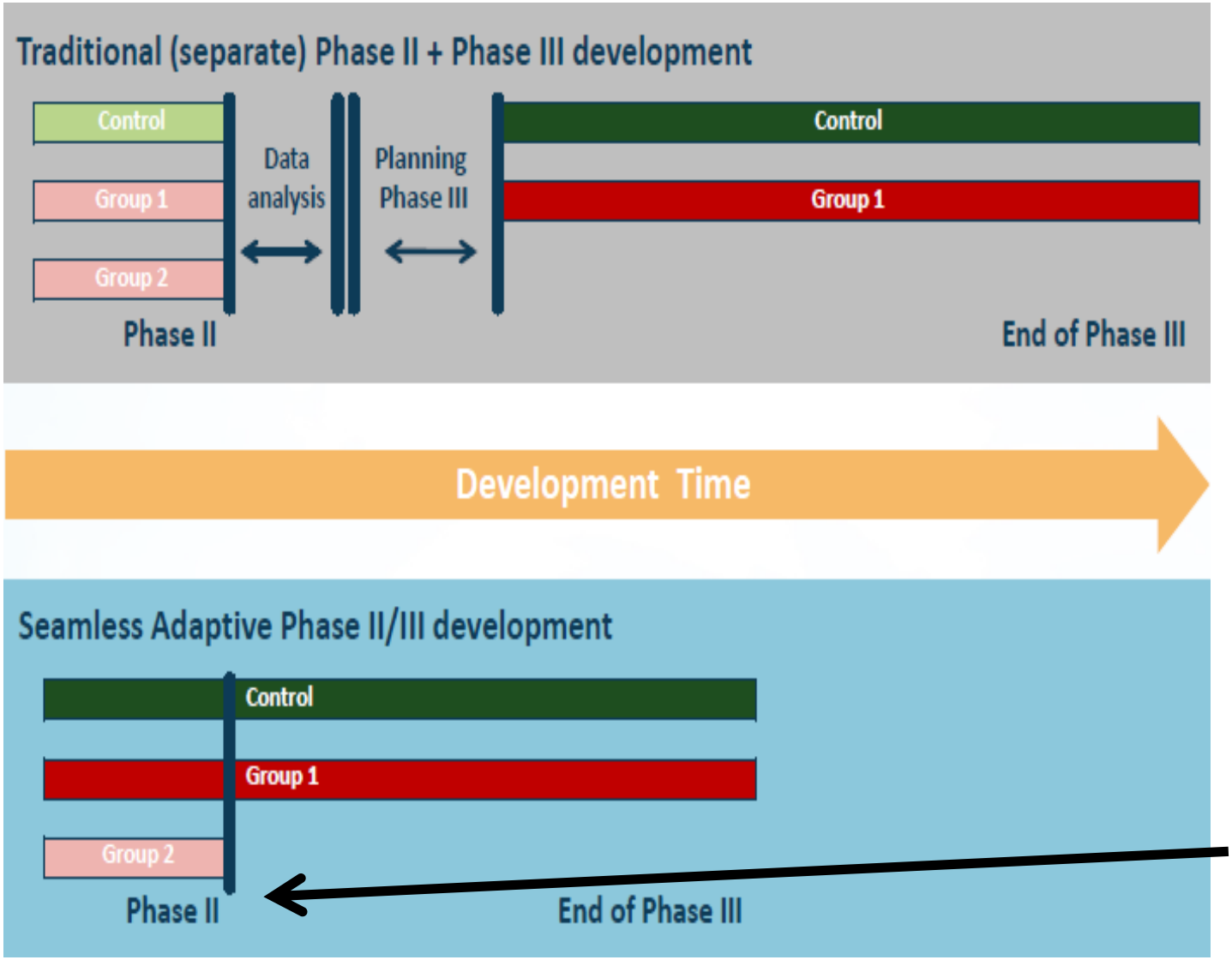
- **“Phase I” data:**
  - A wealth of data of Kadcyla from breast cancer and other solid tumors
  - A lot of data from Herceptin in gastric
  - No Phase I data specifically collected for Kadcyla in gastric cancer
- **Challenges:** Observed a lower exposure of monoclonal antibodies in gastric cancer patients as compared to other solid tumors
- **“Solution”:** Adaptive seamless design with dose selection

Adaptive Designs: EMA

- CHMP Reflection paper: “Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design” (Oct 2007)

- A study design is called “adaptive” if statistical methodology allows the modification of a **design element** (e.g. sample size, randomization ratio, number of treatment arms) at an interim analysis with **full control of the type 1 error.**

Traditional Development and Seamless Adaptive Phase II/III



GATSBY Study Design

Pros	Cons
Savings in time and cost (including no white space between Phase 2 and 3)	Operational more challenging and complex compared to separate Phase II followed by Phase III development
Full Type I error control of study design and statistical procedure	Non-selected group to continue with the pre-planned treatment
Ability to use/contribute stage 1 patients for confirmatory portion of study	**Complex simulations needed to understand design operating characteristics including type I error, power and any bias in estimates**
Dose selection performed by iDMC with Sponsor remaining fully blinded	**iDMC dose selection as somewhat «black box» outside of Sponsor control**
Potential to implement futility interim analysis	Potentially more upfront resources needed

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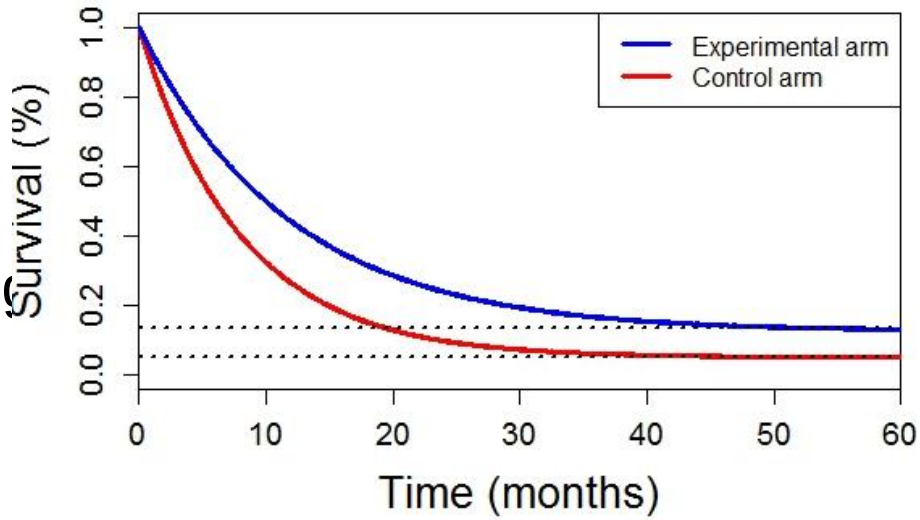
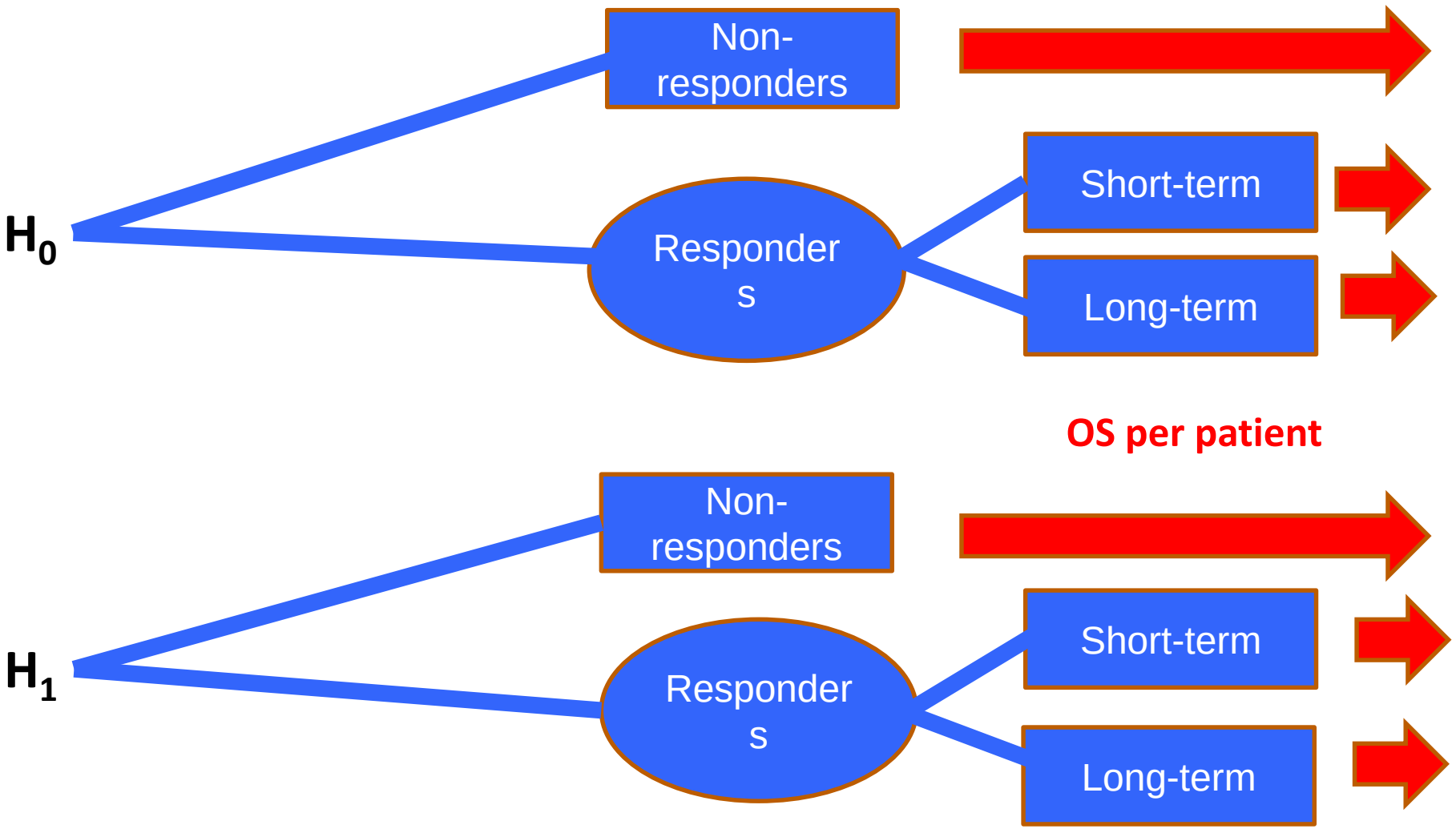
Case example: Drug in AML

- **Phase I data:**
  - Motivating complete response rate for AML
  - CR allows in about 40-50% a transplant (~"cure")
- **Challenges:**
  - Even improved CR rates would still be low (10-20%), hence remaining uncertainty if this drives an OS benefit



- **"Solution":** Phase III design with interim analysis for futility based on intermediate clinical endpoints

Mechanistic model for AML: Link CR with long-term efficacy *(3-component cure rate model)*

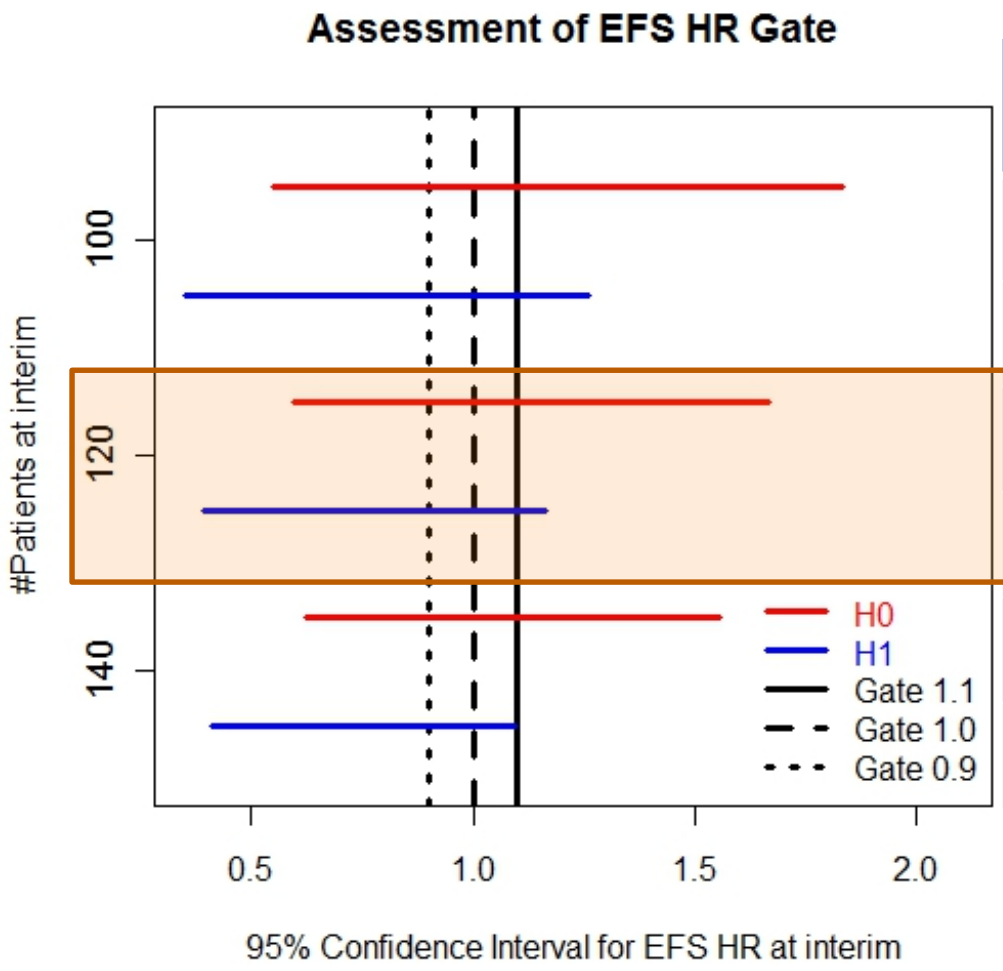


Interim analysis

- **Option 1: CR / EFS:**
  - \+ Get quicker interim decision
  - \- Interim based on surrogate endpoint → association between CR to OS unclear. EFS additional mitigates this uncertainty.

- **Option 2: OS as interim endpoint**
  - \+ Directly accounts for safety aspect of early deaths
  - \+ Entire setup much simpler: less assumptions need to be made.
  - \- Timelines much longer, in particualr if median OS >> median EFS.

Assessment EFS Futility



#Pts at interim	Model	Gate 1.1	Gate 1.0	Gate 0.9
100	H0	36%	51%	66%
100	H1	6%	10%	19%
120	H0	34%	50%	67%
120	H1	5%	8%	14%
140	H0	32%	49%	68%
140	H1	3%	6%	12%

- P(correctly stopping under H0)

- P(wrong stopping under H1)

Disclaimer: *Data generated from real example by superimposing noise*

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AML: VALOR trial

Zoran Antonijevic , JSM 2015

- Vosaroxin & cytarabine vs Placebo & cytarabine
- **Existing (limited) data:** Single arm small Phase II
- Assume 5/7 month median for Control/Treatment (HR=0.71) Require 375 events in 450 subjects (19 month duration)
- But estimate of median is subject to uncertainty What if 5/6.5 month median on Control/Treatment (HR=0.77)?
- HR=0.77 is still clinically meaningful
- More events needed, larger sample size

“Solution”: Adaptive design with sample size adjustment at interim

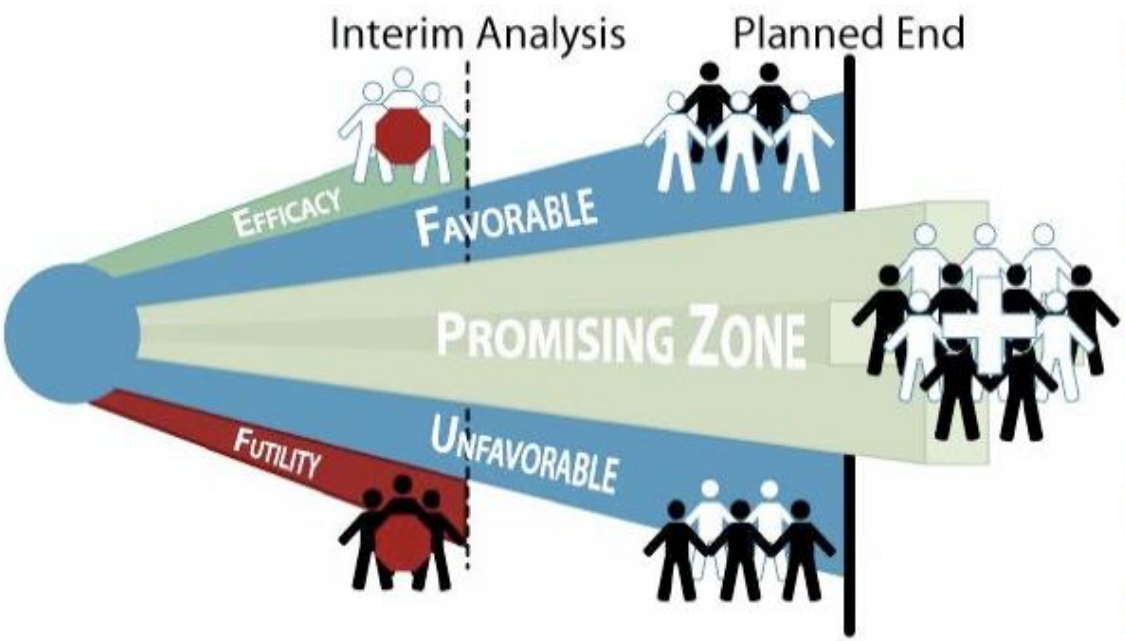
Design elements

	Base Case:	Alternative Case:
Power	90% power to detect a 40% survival difference (5 vs. 7 mo.)	90% power to detect a 30% survival difference (5 vs. 6.5 mo.)
Hazard ratio and α	0.71 and 0.05 (2-sided)	0.77 and 0.05 (2-sided)
Resources needed	375 OS events from 450 evaluable patients	562 OS events from 675 evaluable patients
Enrollment	24 months with 6 months follow-up	30 months with 6 months follow-up

iDMC decisions (guidance based on conditional power at interim with 187 events (50% information fraction))

- Continue the trial to 375 events in 450 patients
- Adjust sample size to 562 events in 675 patients
- Stop early for overwhelming efficacy or futility

Decision at interim based on conditional power



Efficacy zone (OBF)
One-sided p=0.0015

Favorable zone
(CP ≥ 0.9).

Promising zone
(0.3 ≤ CP < 0.9);

Unfavorable zone
(0.1 <CP < 0.3);

Futility zone
(CP ≤ 0.X)

Conditional power: Probability of success (statistical significance) at the end of the trial given the current data trend at the interim analysis

Results

Results interim analysis

- Interim was conducted at 173 events, rather than 187 as planned
- HR was 0.76
- Conditional Power was 82%, in the **promising zone**, so sample size was increased as pre-specified

Results final analysis

- **Unstratified results: HR = 0.87 (95% CI 0.73-1.02), p=0.061**
- Stratified results: HR = 0.83, p=0.024
- Medians: 7.5 months on Vos vs. 6.1 months on Placebo

Conclusions

- We have reviewed three potential cases to deal with limited information based on early phase data
- Suggests that there is **not one-fits-all approach**, but that approach need to be tailored
- This implies it takes some time to work up the scenarios and thus such approach shall be considered early in development to allow sufficient time to develop approach

Doing now what patients need next