Bayesian dual endpoint decision making in Combination studies

David Dejardin and Daniel Sabanés Bové

F. Hoffmann-La Roche, Basel

BBS Conference
Basel - 2016

Outline

Early stage combination trials

Purpose of early stage single agent (SA) trials:

- Establish the dose (Dose escalation part)
- Provide early signs of efficacy (expansion)
  Gating to continue / stop development

Not different in combination

Single endpoint Bayesian Gating

- **Gating on ORR**
- Decision criteria based on **Posterior probability**:

$$\text{GO}: \quad P[p > \theta_u | \text{data}] > 0.8$$
$$\text{no GO}: \quad P[p < \theta_l | \text{data}] > 0.8$$

  - p = probability of response (Endpoint of interest)
  - θ_u = upper target, θ_l = low target
  - 0.8 = confidence level

- $P[p > \theta_u | \text{data}]$ computed from beta$(r + a, n - r + b)$
  n = number of subjects in extension, r = number of PR/CR
- Prior (a, b) chosen as non-informative

CR = Complete response, PR= partial response, CR+PR= OR

Expansion in combinations

Assessment of efficacy in early stage combination trials

- Issues:
  - Incremental benefit compared to partner drug
    - Difficulty to detect in small advanced population
  - Combination of mechanisms of action (MoA)
    - CIT with no effect on ORR
    - Long term benefit combined with short term efficacy in partner
  - Proof of Concept studies (PoC)
    - Minimal signs of efficacy constitute proof of MoA

$\Rightarrow$ Need for more granularity in assessing efficacy
$\Rightarrow$ Look at combination of endpoints

Issues common to single agent (SA) trials, More complex for combination

CIT = Cancer Immuno-therapy

Dual endpoint gating

Exemples of gating on 2 efficacy endpoints

- DoR $\nearrow$, ORR $\rightarrow$

  CIT example

- DCR $\nearrow$, ORR > 0

  PoC or severe indication example

DoR = Duration of Response, DCR = Disease control rate

ORR and DCR

Decision criteria: **Joint posterior probability**

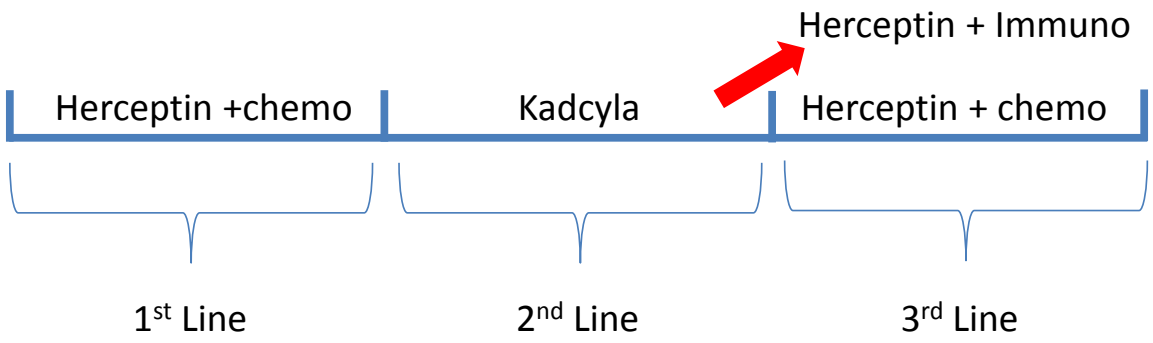
$$P[\, p > \theta_u^{ORR} \text{ and/or } p + s > \theta_u^{DCR} \mid \text{data} \,] > 0.8$$

- p = probability of response
- $p + s$ = probability of disease control
  (s = probability of stable disease)
- 2 thresholds $\theta_u^{ORR}, \theta_u^{DCR}$ (also for no go decision)
- Dependence between p and $s \Rightarrow$ Multinomial distribution
- Vague conjugate prior = Dirichlet$(1/c, 1/c, 1/c)$ with c small

Example 1: ORR and DCR

Goal of example

Illustrate Design of study and gating criteria



- Indication: **3rd line HER2+ breast cancer** after failure of HER2 therapies
- Experimental therapy: CIT (no direct cytotoxic effect) in combination with HER2 therapy
- Purpose of study: Clinical proof of mechanism

Example 1: ORR and DCR

- Expected efficacy with CIT:

  Continuation of HER2 therapy
  CIT
  $\Rightarrow$ **no CR/PR expected**

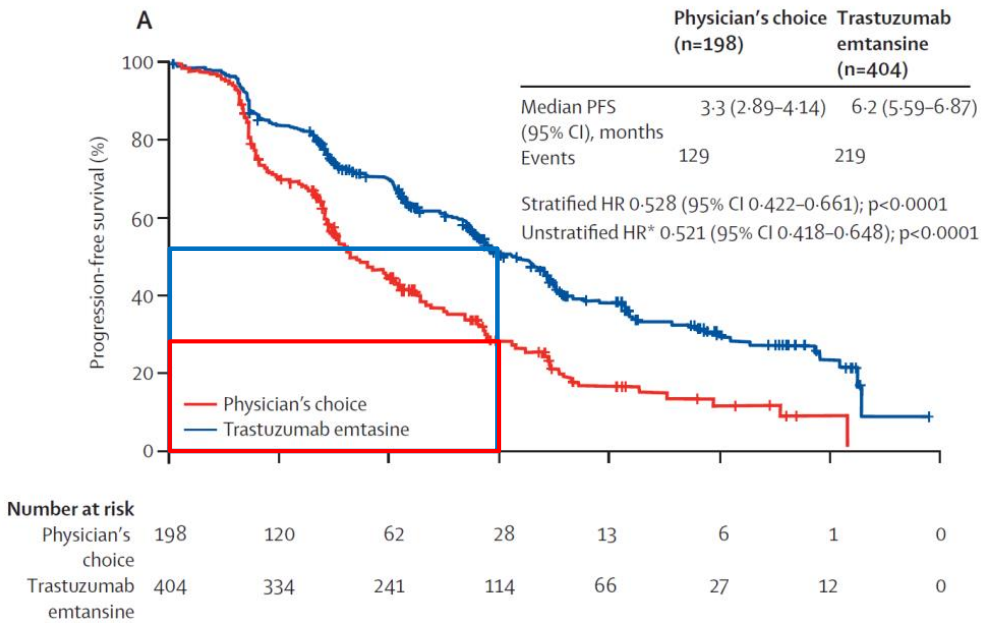
- Effect expected on slowing down progression (=DCR)
- Triple combo with chemo $\Rightarrow$ dilution of effect

- **Why dual endpoint?**
  - Main decision making on DCR
  - If CR/PR observed $\Rightarrow$ strong evidence of MoA

Example 1: ORR and DCR

How do we set target θ_u^{DCR} and θ_u^{ORR}?

- ORR $>$ 10% (no CR/PR expected)
- DCR @ 6mths: Reference = Th3resa trial

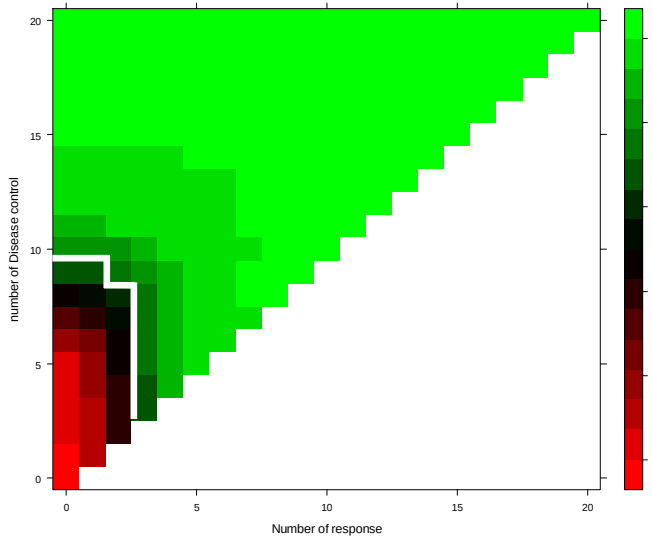


- HER2+chemo
  $\Rightarrow$ DCR @ 6mths $<$ 30%
  DCR @ 6mths = CR/PR/SD maintained for 6 mths
- Kadcyla curve not applicable (subjects get Kadcyla in 2L)

Example 1: ORR and DCR

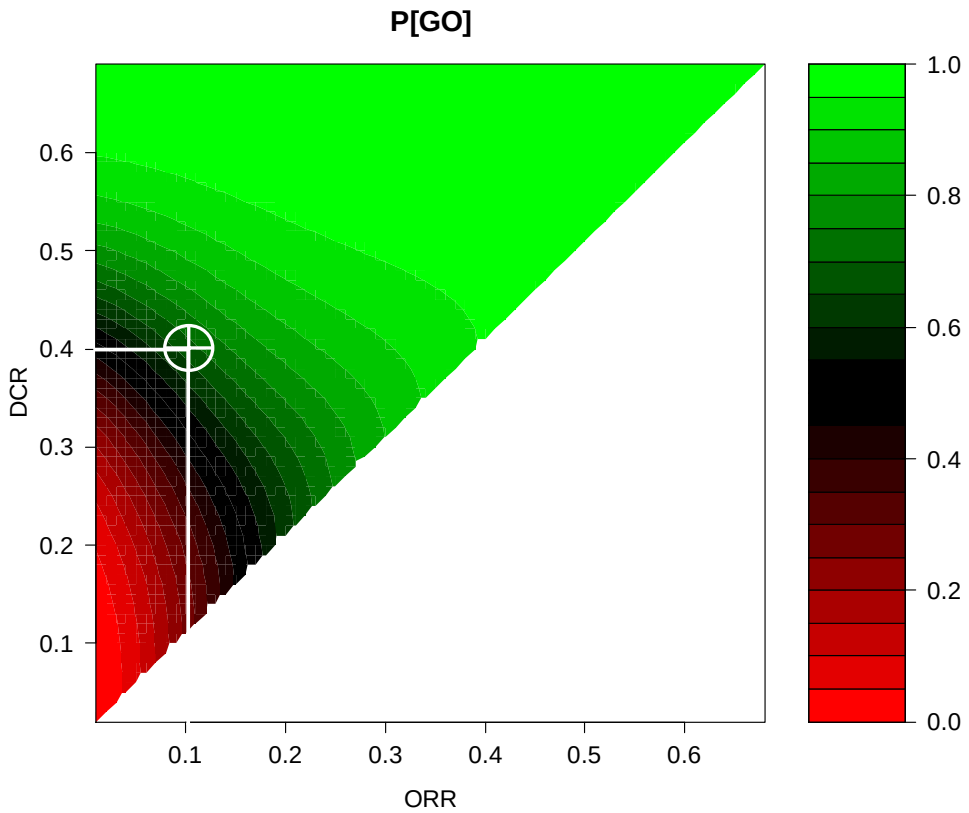
Resulting target: DCR @ 6 mths $>$ 40% or ORR $>$ 10%

- 10% improvement on DCR @ 6 mths over HER2+chemo
- **OR** to capture strong evidence on ORR
- Target using a fixed proportion here: No data in this exact population
- Example: n= 20
- Resulting gate for GO decision:
  DC $\geq$ 10 or
  OR $\geq$ 3 or
  (DC $\geq$ 9 and OR $\geq$ 2)



Example 1: ORR and DCR

- Operating characteristics



- "or" condition ORR and DCR $\Rightarrow$ improved probability for GO
- Same can be done for NO GO decision

ORR and DoR

Decision criteria: Joint posterior probability

$$P[p > \theta_u^{ORR} \text{ and/or } m > \theta_u^{DoR} | \text{data}] > 0.8$$

- d = duration of response with **median** m
- $d|$ data $\sim$ Weibull(λ, k) or other distribution
- $p|$ data $\sim$ beta$(r + a, n - r + b)$
- Working independence assumed
  - p may influence d
  - Complex multi-state models to assess association
  - Small sample sizes in ph1 to check validity of assumptions

ORR and DoR

Weibull model and prior

- Survival function;

$$S(d) = \exp(-\lambda t^k)$$

- Priors
  - $\lambda \perp\!\!\!\perp k$
  - No conjugate $\Rightarrow$ various possible choice (flat)
  - Here $\lambda \sim$ Gamma(0.0001,0.0001) and $k \sim$ Gamma(1,0.0001)
  - Fit can be checked using KM curve / MLE
- Log-normal model also used with flat prior

ORR and DoR: Median or Hazard Ratio (HR)?

HR used for time-to-event models

- Small sample sizes imply parametric model
- HR $\Rightarrow$ **restriction on parameters**
  - Weibull: Shape parameter k common
  - Degree of freedom assuming proportional hazard = 3 instead of 4
- Allows the use of different models for target definition
- Less relevant when target is fixed ($\Leftrightarrow$ data-based target)

Example 2: ORR and DoR

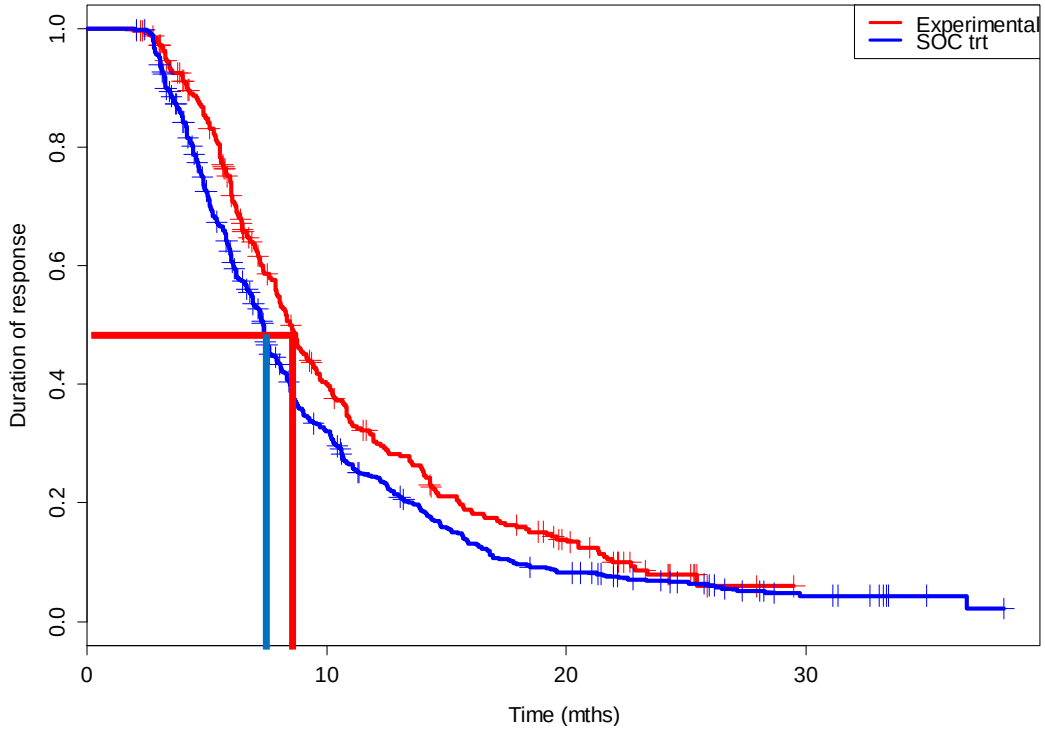
Goal of example

Illustrate benefit of dual endpoint gating criteria

- Indication: 1L metastatic CRC
- Experimental therapy: VGEF inhibitor + SoC
- Data: Large phase 3
- Question: **Compare single ORR criteria vs dual endpoint gating**
- Method: Simulate phase 1 extension by sampling from phase 3 data

Example 2: ORR and DoR

Efficacy in Phase 3 study:



Endpoint	SoC	SoC+Exp.
ORR	47%	49%
DoR	7.4 mths	8.5 mths

Example 2: ORR and DoR

- **Ignoring MoA** :
  - Classical way: **Gating on ORR only**
  - Meaningful Target: **55%** (8% improvement on SoC = 47%)
- **Accounting for MoA** :
  - Probability to respond not increased, but PFS prolonged
  - At least ORR $> 47\%$ $\Rightarrow$ No detrimental effect on ORR
  - **AND** DoR > 8.5 mths (1 mth improvement on SoC)
    $\Rightarrow$ Benefit in terms of DoR

Example 2: ORR and DoR

- Assessment of P[GO] using gate:
  - Sampling n=20 subjects from ph 3 (=simulated ph 1 extension)
  - Frequency of GO decision
- **Results**

Criteria	P[GO]
Improvement on ORR	26%
Improvement on DoR with same ORR	46%

- Gating on ORR only = Too high bar
- Gating on DoR only $\Rightarrow$ Risk of lower ORR
- Dual endpoint gating better uses information on MoA

Target definition

How do we set targets $\theta_u, \theta_l, \theta_u^{DCR}$

- Depends on Goal
  eg: PoC or informing ph 2
- Depends SoC data
  - SoC widely studied $\Rightarrow$ Data available
  - Late stage $\Rightarrow$ No SoC, experimental / off-label use
    $\Rightarrow$ **NO** Data available
- Options:
  - Compared to fixed target (improvement over SoC, partner level)
  - Variable target (historical data, increased variability)

Target definition

- **Fixed target:**
  - Good idea of SoC and clinically relevant improvement
    Clinically relevant improvement needs to be linked to Phase 2/3 endpoint
  - No good data on SoC $\Rightarrow$ Conservative target (high relevant bar)
- **Random target**
  - Defined using Literature / existing studies
  - Accounts for variability of measure
  - DoR impacted by population $\Rightarrow$ Data-based target allows subject matching

Discussion

Benefits

- Goal of early trial = Learning about the drug
  $\Rightarrow$ Dual endpoint gating provides better granularity, more flexibility
- Ideally: Target based on "regulatory endpoints"
  $\Rightarrow$ Alternative endpoints gating allows closer relationship

Limitations:

- Small sample size :
  Is it enough to identify good drugs or stop bad drugs?
- Choice of target crucial
  Use of historical data relevant (bias, drift)?
- Do we need granularity?
  Only very efficacious treatments are of interest

Thank you!