Futility analysis considerations for a phase II trial with short term non-inferiority and long term superiority co-primary endpoints

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Futility analyses

• Stop if, based on the current data, we are unlikely to observe a significant result at the end of the trial

• Improve efficiency

• Reduce number of patients recruited

• Reduce number treated with ineffective regimens
MUK five trial design

Co-primary endpoints:

Proportion of patients achieving ≥VGPR 24-weeks post initial randomisation
- KCD vs. VCD
- Non-inferiority

Progression-free survival
- Maint vs. no maint
- Superiority
Sample size

- Initial randomisation
  - N=300

- VCD
  - N=100
  - No maintenance
    - N=100

- KCD
  - N=200
  - Maintenance randomisation
    - N=140 (min)

  - Maintenance with Krypolis
    - N=70 (min)

  - No maintenance
    - N=70 (min)

- VCD: ≥VGPR rate of 35%
- KCD: ≥VGPR rate of 45%
  - (10% improvement)
- NI margin of 5%
- 1:2 randomisation
- α=0.05 (1 sided), power=80%
Sample size

- VCD: ≥VGPR rate of 35%
- KCD: ≥VGPR rate of 45% (10% improvement)
- NI margin of 5%
- 1:2 randomisation
- α=0.05 (1 sided), power=80%

- PFS measured from maintain randomisation
- No maint: median PFS 12m
- HR=0.67 (increase 6m in median PFS)
- α=0.2 (2 sided), power=80%
MUK five futility analysis considerations

• Analysis methods based on short term co-primary endpoint

  Proportion of patients achieving $\geq$VGPR
  24-weeks post initial randomisation

• After 50% of patients (150) have reached the time-point

Options considered:

• Conditional power

• Conditional power only if treatment difference $\leq$10% 
  (Difference of 10% anticipated / powered)

• No futility analysis, with the option of an inferiority analysis 
  (As safety is a key driver)
Conditional power

The power to show non-inferiority at the final analysis (under different assumptions on the remaining patients) given the current data.

Perform simulations to estimate the number of ≥VGPRs at the final analysis under different scenarios:

• Generate data to represent remaining patients
• Combine simulated patients with current 150 patients and calculate treatment difference and confidence interval

Repeat & combine results to find conditional power:

➢ Percentage of simulations that have demonstrated non-inferiority
Conditional power – simulation scenarios

NO TREATMENT DIFFERENCE
• ≥VGPR rate of 35% with both KCD and VCD

AS POWERED FOR
• 10% difference: ≥VGPR rate of 45% with KCD and 35% with VCD

OPTIMISTIC (‘best case’ scenario)
• Calculate 95% CI of difference seen in first 150 patients
• Use upper limit for difference to simulate under, assuming ≥VGPR rate for VCD as seen in first 150 patients
Conditional power – simulation scenarios

OPTIMISTIC – Example

• Calculate 95% CI of difference seen in first 150 patients
  VCD: 36% (18/50 patients) ≥VGPR
  KCD: 50% (50/100 patients) ≥VGPR
  Difference: 50-36=14%, with 95% CI (-2.5%, 30.5%)

• Use upper limit for difference to simulate under, assuming ≥VGPR rate for VCD as seen in first 150 patients
  Assumptions for simulations of remaining patients:
  VCD: 36% as observed
  KCD: 36+30.5=66.5% using upper limit of 95% CI
Choosing a method

- Choice depends on how the two co-primary endpoints interact
- Maintenance question still relevant if KCD not non-inferior
  - No futility analysis to be performed
- Not relevant if KCD inferior
  - Inferiority interim analysis to be performed

Reminder: not non-inferior ≠ inferior
Conclusions

• Conditional power provides a useful way to consider futility analyses for non-inferiority endpoints

• With co-primary endpoints, the use of a futility analysis requires more thought

• Depends on the interaction of the endpoints

• With a short-term and long-term endpoint combination, the relevance of the long-term endpoint needs to be considered