

Targeted Phase I Oncology Trial

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1. Objective

Develop a modeling approach to explore the operating characteristics of a Bayesian Phase I oncology trial design that enriches enrollment with patients bearing a mutation that favors response.

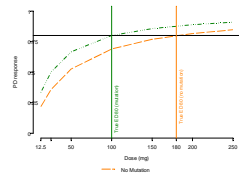
2. Model/Assumptions

A clinical trial is considered where patients are assigned to doses in order to efficiently infer the Maximum Tolerated Dose using a Bayesian methodology. It is assumed that each patient also provides an efficacy response. A simulation analysis is conducted to explore the operating characteristics of a go/no-go decision rule based on evaluating tolerability and efficacy concurrently while enriching the study population with better responders. Patients with a gene mutation are assumed to respond better to the new oncological agent.

There are 4 major inputs to the simulation,

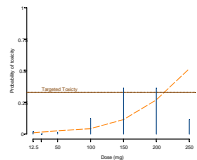
- Mutation frequency (MF)
- Maximal recruitment rate
- Dose-efficacy model
- Dose-toxicity model
- Other assumptions:

An example of hypothetical dose-efficacy model: Emax model



- The efficacy end point could be: (1) Fraction of patients with major cytogenetic/hematologic response (0=none, 1=all), (2) Average fractional shrinkage of tumor size (0=none, 1=total)
- Shrinkage efficacy varies from 0 (worst) to 1 (best)
- Assume Emax model with $E_{max}=1$
- Precision of efficacy measurements $CV=0.1$ (high precision), 0.2, 0.5, 0.8 (low precision)

An example of hypothetical dose-toxicity model



Typical categories of probability of dose-limiting toxicity DLT at dose=d, $p(d)$,

- Under-dosing : $p(d) \in (0, 0.2]$
- Targeted toxicity : $p(d) \in (0.2, 0.35]$
- Excessive toxicity : $p(d) \in (0.35, 0.6]$
- Unacceptable toxicity : $p(d) \in (0.6, 1]$

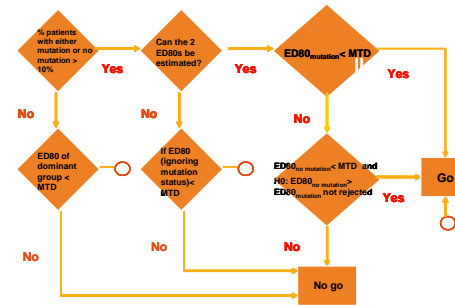
Criteria for MTD:

Select the dose that maximizes the probability of toxicity, p , at targeted toxicity, i.e. $P(0.2 < p(d) < 0.35)$ while controlling the excessive (<25%) and unacceptable toxicity (< 5%).

References:

[1] Beat Neuenschwander, Michael Branson, Thomas Gasponer. A Bayesian approach to phase I cancer trials. Novartis Biometrics Technical Report. 2006

GO criteria



•GO if

- Estimated ED80 of the patients with mutation < MTD
- OR-
- Estimated ED80 of the patients without mutation < MTD and large uncertainty in the estimate of ED80 of patients with mutation (see decision tree for specifics)

- If one of the genotype groups is > 90% of the patient population, then only the ED80 for that group will be estimated.
- If the 2 ED80s are not separately estimable due to the variability of the efficacy measurements, only one pooled ED80 estimate will be estimated.

3. Results/Discussions

Fig 3.1

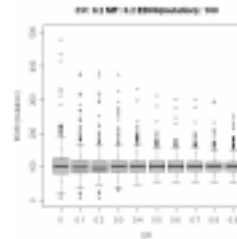


Fig 3.2

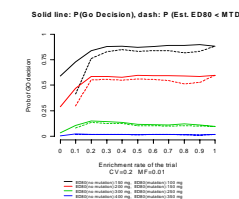
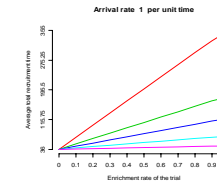


Fig 3.3



• Results show that increasing ER typically will improve the efficacy inference and the accuracy of the Go decision; however, the incremental benefit of increasing ER is diminishing and the diminishing rate depends on precision of the measurements of efficacy/safety end points and mutation prevalence. Refer to Fig. 3.1- 3.2

• The average total recruitment time increases with ER, and the lower the MF the higher the rate that recruitment time increases with respect to ER, which is illustrated in Fig. 3.3

4. Conclusion

The simulation model developed provides guidance in decision-making to go for targeted Phase I oncology trial in terms cost and time saving, accuracy and precision of parameter estimates and accuracy in predicting development success.

