

Title: Targeted Phase I Oncology Trial

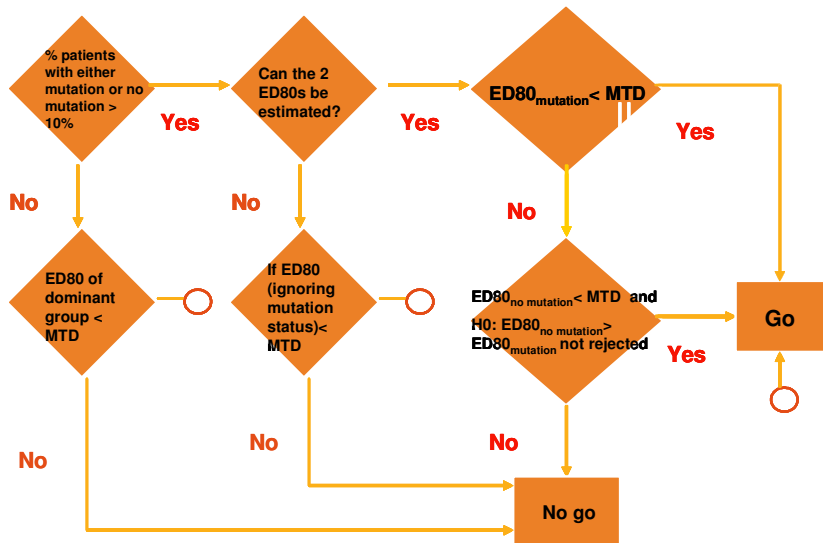
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Objective: Explore the operating characteristics of a Bayesian Phase I oncology trial design that enriches enrollment with patients bearing a mutation that favors response.

Methods: A clinical trial is considered where patients are assigned to doses in order to efficiently infer the Maximum Tolerated Dose using a Bayesian methodology [1]. 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. A trial with such enrichment and efficacy assessment is called a targeted trial. Patients with a gene mutation are assumed to respond better to the new oncological agent. There are 4 major inputs to the simulation, namely, mutation frequency (MF), maximal recruitment rate (ER), dose-efficacy model, and dose-toxicity model. Dose-efficacy is described by an Emax model with ED80 being the minimum effective dose; dose-toxicity is described by a two-parameter logistic regression model. The recruitment of patients is assumed to follow a Poisson process, and without loss of generality the mean is assumed to be 1 per unit time. There are 3 main decision components: maximum tolerated dose (MTD) criterion, enrichment rate, and Go/no-go decision criterion. The MTD criterion is to select a dose that maximizes the posterior probability of the targeted toxicity rate, while controlling posterior probabilities of excessive and unacceptable toxicity. The enrichment rate varies from 0 to 1 with 0: patients mutation are enrolled according to their prevalence in the population and 1: only patients with mutations are enrolled. The Go/no-go criterion is illustrated in Fig. 1.

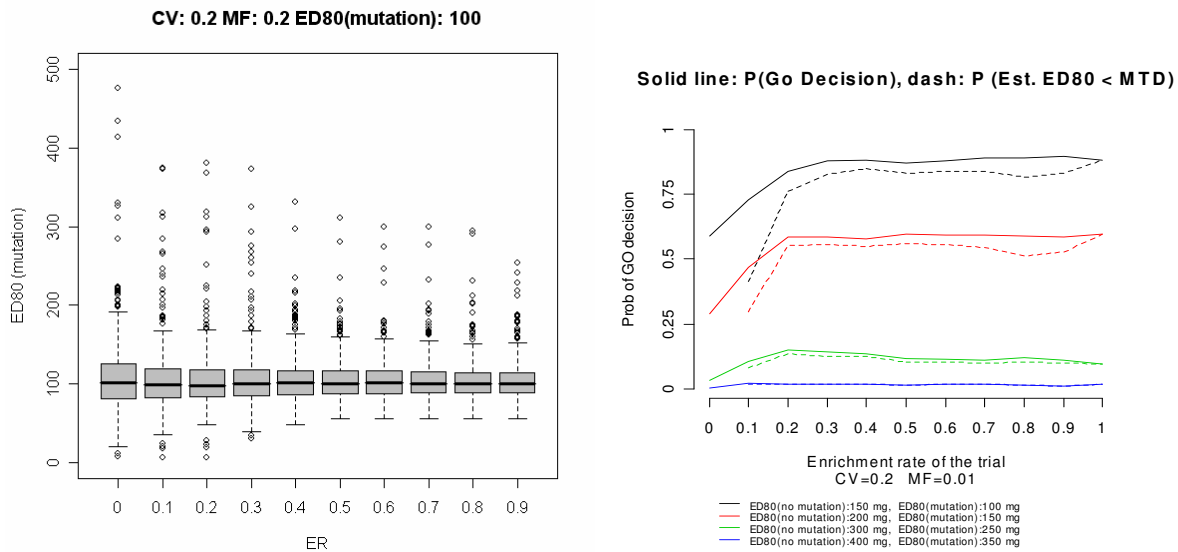
Fig. 1



Several simulation scenarios are considered, i.e., varying the MF in the population, the coefficient of variation (CV) of efficacy measurements, and the true ED80s for both patients with mutation and no mutation. The impact of such a targeted trial on the duration of the trial, the precision of the estimated minimum effective dose, and the go/no-go decision are investigated by varying the ER.

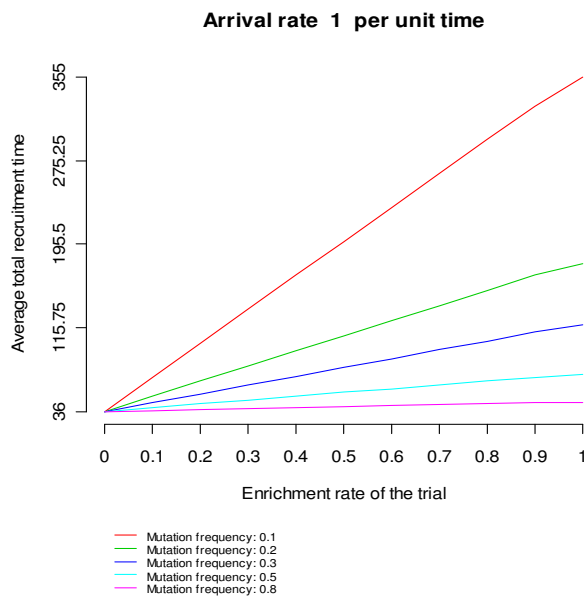
Results: Results show that increasing ER typically will improve the efficacy inference and the accuracy of the Go decision; however, the incremental benefit of increasing ER is diminishing and the diminishing rate depends on precision of the measurements of efficacy/safety end points and mutation prevalence. Refer to Fig. 2 for details.

Fig 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.

Fig. 3



Conclusions: 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. The next step is incorporate the predictability of a biomarker of responder/nonresponder into the model.

References:

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