PubPredict and its Applications: Prediction of Progression Free Survival/Overall Survival Leveraging Publications and Early Efficacy Data

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INTRODUCTION

This project develops a toolset modeling the disease course of refractory and relapsed multiple myeloma with a continuous Markov chain (CMC) model. Based on the modeling, subject-level data of disease course/survival outcomes could be simulated with aggregate-level efficacy statistics as input. Simulated subject-level data is shown to have good approximation of reported external studies.

Motivation:

- In Oncology/Hematology clinical trials, we usually have observations of early efficacies in terms of response rate, depth, timing and duration. However, the follow-up may not be long enough to support the prediction of progression-free survival (PFS) or overall survival (OS), which are usually the primary endpoints for phase 3 studies.
- We tackle the question of establishing a quantitative link between early efficacy outcomes and typical efficacy endpoints in phase 3 trials. Without loss of generalizability, we use R/RMM as disease model.

METHODS

Continuous Time Markov Process

- Transition intensity governs the next stage of transition, and the time of the change.
- The transition intensity for each pair of transition, r and s for example:

$$q_{rs}(t, z(t)) = \lim_{\delta t \to 0} P\left(S(t+\delta t) = s | S(t) = r\right)/\delta t$$

where t is the current time, and z(t) are the covariates at t.

- $q_{rs}(t, z(t))$ is independent of any history of states previously visited, or the time stayed there. It is a function constant over periods of time as defined
- Transition intensity matrix Q:

$$\begin{bmatrix} q_{11} = -\sum_{s \neq 1} q_{1s} & q_{12} & \dots & q_{1n} \\ q_{21} & q_{22} = -\sum_{s \neq 2} q_{2s} & \dots & q_{2n} \\ \vdots & \vdots & \ddots & \dots \\ \dots & \dots & \dots & q_{nn} \end{bmatrix}$$

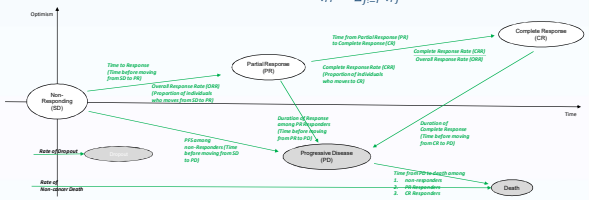
Transition probability $p_{rs}(t)$:

$$p_{rs}(t) = P(S(t_0 + t) = s | S(t_0) = r)$$

Transition probability matrix P(t):

$$P(t) = Exp(tQ) = \sum_{n=0}^{\infty} \frac{t^n}{n!} Q^n$$

- Transition intensity matrix Q – useful properties:
  - Time waiting on state r before any move are exponentially distributed: $\Pr(T_r \geq t) = \exp(q_{rr}t)$
  - Time waiting on state r before moving to each individual state s also exponentially distributed;
  - Once moved (from r), the probability of being on s: $-\frac{q_{rs}}{q_{rr}} = \frac{q_{rs}}{\sum_{j \neq r} q_{rj}}$



Model Setting for R/RMM

- Everyone starts with a stable disease of R/RMM (SD);
- With an effective therapy, a proportion of subjects respond, i.e. transit from SD to partial response (PR), who later deepens to complete response (CR);
- The deeper the response a subject achieves, the less likely for him/her to progress/death;
- Same chances of dropout apply to everyone, no matter of the response status (non-informative).
- Observation ends at dropout/death (these two are terminal states).

Parameterize Algorithm

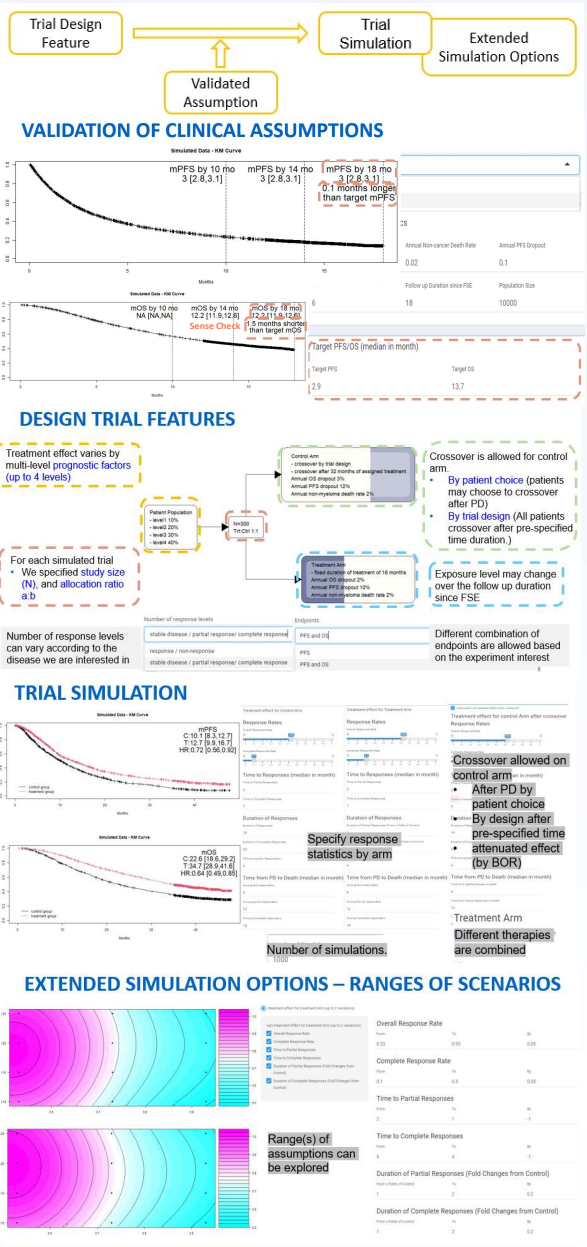
Input Parameters:

- Overall Response Rate (oORR); Complete Response Rate (sCRR)
- Median Time from SD to Progression (PFS.SD); Time to Responses(TtR), Time to Complete Response(TtCR); Duration of Responses among responders (mDoR);
- Median Time from Progression to Death among non-responders, partial responders, complete responders (TPDtDth.SD, TPDtDth.ncr, TPDtDth.cr);
- Dropout (amnldpt.pd, amnldpt.os), non-cancer death (amnldth).

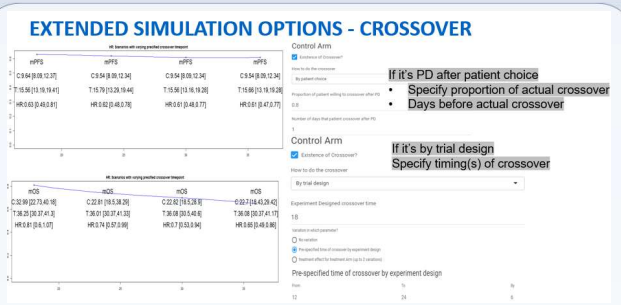
From-To	SD	Sustained SD	PR	Sustained PR	CR	PD.SD	PD.NCR	PD.CR	Dropout PD	Dropout OS	Death
SD	$\sum_{r \neq 1} q_{1r}$	$-\frac{1-oORR}{mTtR} - oORR$	$\frac{oORR}{mTtR}$								
Sustained SD		$\sum_{r \neq 2} q_{2r}$				$\frac{ln2}{mPFS.SD - mTtR}$			$\frac{ln2}{amnldpt.pd}$		$lmd.dth$
PR			$\sum_{r \neq 3} q_{3r}$	$\frac{sCRR/oORR}{mTPDtCR}$	$\frac{1-sCRR/oORR}{mTPDtCR}$						
Sustained PR				$-\sum_{r \neq 4} q_{4r}$			$\frac{ln2}{mDoR \cdot ncr - (mTtCR - mTtR)}$				
CR					$-\sum_{r \neq 5} q_{5r}$			$\frac{ln2}{mDoCR}$			
PD.SD						$-\sum_{r \neq 6} q_{6r}$					$lmd.dth + \frac{ln2}{mTPDtDth.SD}$
PD.NCR							$-\sum_{r \neq 7} q_{7r}$				$lmd.dth + \frac{ln2}{mTPDtDth.ncr}$
PD.CR								$-\sum_{r \neq 8} q_{8r}$			$lmd.dth + \frac{ln2}{mTPDtDth.cr}$

$$lmd.dth = \frac{ln2}{amnldth}$$
$$lmd.dpt.pd = \frac{ln2}{amnldpt.pd}$$
$$lmd.dpt.os = \frac{ln2}{amnldpt.os}$$

PubPredict R shiny Tool

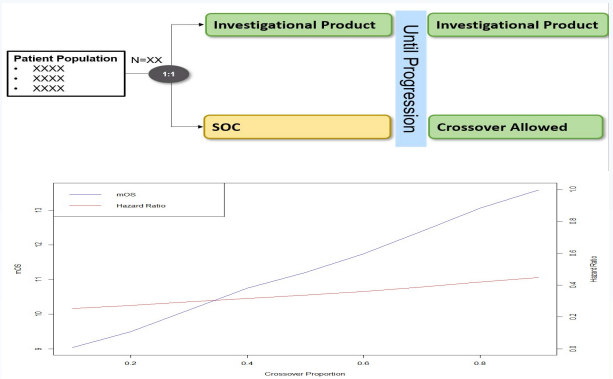


EXTENDED SIMULATION OPTIONS - CROSSOVER



Application

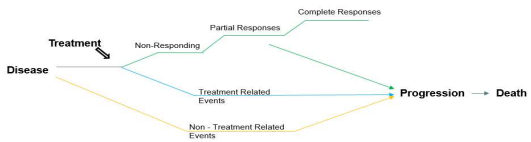
Treatment effects accounting for crossover could be modeled with varying assumptions about response rates, median durations of responses.



Future Directions

Informative censoring could be accommodated.
Time-dependent transition intensities could be explored.
The surrogacy strength of response endpoints (such as response rate, durations) could be simulated and evaluated.

Surrogate endpoint: "A response variable for which a test of the null hypothesis of no relationship to the treatment group under comparison is also a valid test of corresponding null hypothesis based on the true endpoint." Prentice's (1989)



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