Simulation setup

Simulation was conducted under the following settings

1. Markov model where transition rate from state *i* to *j* at time *t*, denoted by $\alpha_{ij}(t)$, ($i = 1, 2$ *and* $j = 2, 3$), only depends on the patient status at time *t*

   1.1 homogeneous time: α_{ij} is constant over time

   1.2 non-homogeneous time: α_{ij} changes over time
2. Semi-Markov model: transition rate depends on the patient's history prior to transition.

The manuscript included simulation results under the homogeneous time Markov model. Results from the non-homogeneous Markov and the semi-Markov models were similar to those of homogeneous Markov model, hence, were not included.

In this supplement, we provide additional simulation parameters. Eight combinations of treatment effect on multi-state transitions and the effect of complete remission on subsequent survival were considered in the simulation study.

- Four settings of possible treatment effects on the multi-state transitions (Figure 1S) were investigated. The subscript C and T below refer to the control and treatment group, respectively):

  i) $\alpha_{ijC} = \alpha_{ijT}\ \forall\ i, j$, (no treatment effects)

  ii) $\alpha_{12C} < \alpha_{12T}$, all other α_{ij}'s equal between groups, (treatment induces early remission)

  iii) $\alpha_{23C} > \alpha_{23T}$, all other α_{ij}'s equal between groups (treatment prolongs life after remission)

iv) $\alpha_{23C} > \alpha_{23T}$ and $\alpha_{13C} > \alpha_{13T}$, all other α_{ij}'s equal between groups (treatment prolongs life both with and without remission)

- For each of the four settings above, two scenarios of remission effect on subsequent survival were evaluated:

  a) $\alpha_{12} > \alpha_{13} = \alpha_{23}$ (remission occurs faster than death and achieving a remission has no effect on the risk of death)

  b) $\alpha_{12} > \alpha_{13} = \alpha_{23}/1.3$ (remission occurs faster than death and achieving a remission lowers the risk of death)

  Note that the effect of remission on mortality was evaluated using the Cox model treating remission as a time-dependent covariate.

Parameters used in the simulation were based on data from CALGB 10603 trial. Specifically,

- The baseline hazard for $\alpha_{13}, \alpha_{23}$was set to 0.1.
- We set α_{12} to four times the baseline for α_{13}, α_{23} (0.1 prior to multiplication by the relevant hazard ratios (HR)). This α_{12} was chosen so that on average, 80 % of the patients would achieve complete remission.
- A difference (corresponding to the inequalities in the scenarios above) was defined as a hazard ratio of 1.3.
- The maximum time for the restricted means is set to 48.
- Sample size was 250 people per group (500 total).
- Censoring times were independent of failure times and set to follow an exponential distribution (20% censoring at the end of study).

- 1000 simulations were run per scenario.

Figure 1S shows the plots of probability-in-state for the eight simulated scenarios. Each panel represents a treatment effect scenario corresponding to scenarios i) – iv) listed above. Each panel includes the curves representing the effect of remission on subsequent survival corresponding to scenarios a) and b) listed above.

Figure 1S. Probability-in-state curves of the eight simulated scenarios