

# Appendix 1. Formulas and Algorithms of the CTMC Model

## 1. Basic definitions of CTMC

A continuous-time Markov chain (CTMC) model is defined over a set of clinical states  $S = \{1, \dots, n\}$ . The process is governed by a generator matrix  $Q = (q_{ij})$ , where each element  $q_{ij}$  represents the instantaneous transition rate from state  $i$  to state  $j$ . The diagonal satisfies  $q_{ii} = -\sum_{\{j \neq i\}} q_{ij}$ .

The forward Kolmogorov equations describe the evolution of transition probabilities:

$$dP(t)/dt = P(t)Q, \text{ with initial condition } P(0) = I.$$

## 2. Transition probabilities

Transition probabilities over an interval of length  $t$  are obtained through the matrix exponential:

$$P(t) = \exp(tQ).$$

Example: the 3-month transition matrix is computed as  $P(3) = \exp(3Q)$ .

## 3. Cohort distribution

Let  $p(0)$  be the initial vector of patient distribution across states after cCRT. The cohort evolution over time is obtained as:

$$p(t) = p(0) P(t).$$

## 4. Survival

Overall survival (OS) is calculated as the probability of not having reached the absorbing death state:

$$OS(t) = 1 - p_{\text{death}}(t).$$

Progression-free survival (PFS) is calculated as the probability of not being in progression or death:

$$\text{PFS}(t) = 1 - p_{\text{progression}}(t) - p_{\text{death}}(t).$$

## 5. Expected time in states

The fundamental matrix is defined as  $N = (-Q_{TT})^{-1}$ , where  $Q_{TT}$  corresponds to the transient states. The expected mean time in each state is obtained from the row sums of  $N$ :

$$E[T_i] = \sum_j N_{ij}.$$

## 6. Piecewise calibration

Model calibration is performed in segments to capture the temporal heterogeneity of immunotherapy. The employed intervals are 0–12, 12–24, and 24–60 months. In each interval, transition rates are optimized through nonlinear least squares, fitting model OS and PFS to published PACIFIC landmarks.

To represent heterogeneity, specific multipliers are applied to the elements of the base  $Q$  matrix in each time segment.

## 7. Sensitivity analysis

Additional sensitivity analyses were explored:

- i) Recalibration with explicit restriction on OS at 60 months.
- ii) Inclusion of a cure-like state to model durable responders.
- iii) Use of flexible hazards (Royston–Parmar) as an alternative approach.