Use of Generalised F Parameterization in Long-Term Extrapolation for Adjuvant Cancer Therapies

MSR95

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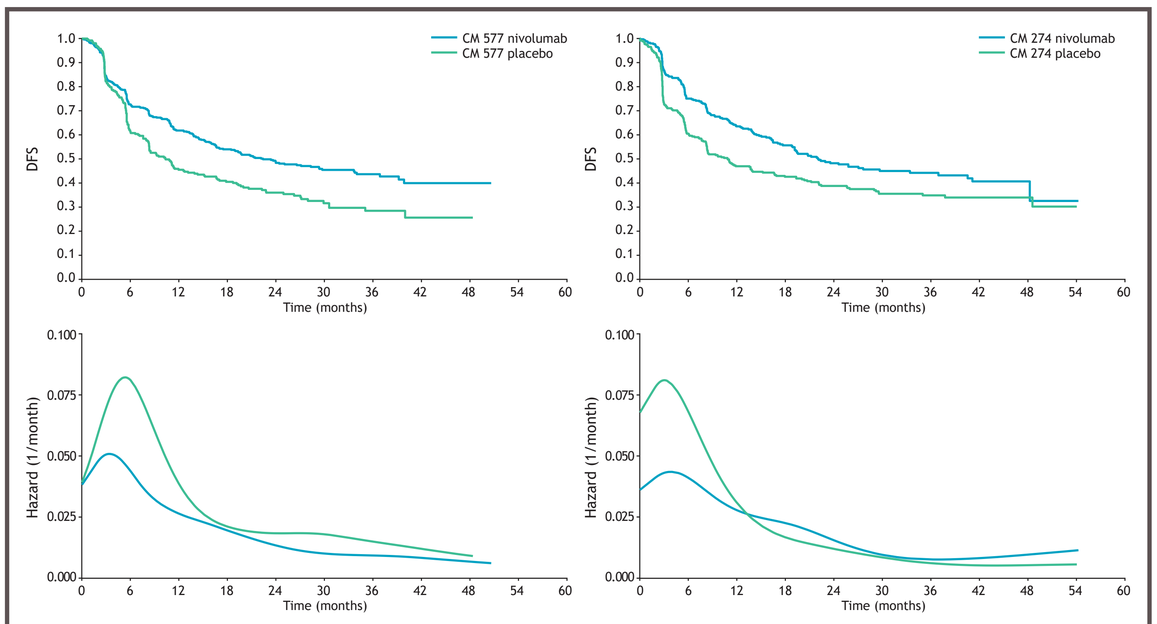
Introduction

- Urothelial and oesophageal cancers pose significant health burden in the UK, with approximately 10,292 and 9,272 newly diagnosed cases each year, respectively[1,2]
- Patients diagnosed with early-stage cancer may be able to receive potentially curative surgery
- Outcomes may be improved by the introduction of adjuvant immunotherapies such as the PD-1 inhibitor nivolumab, which improved disease-free survival (DFS) vs placebo in patients with resected oesophageal or gastroesophageal junction cancer (CheckMate 577) and in patients with muscle-invasive urothelial carcinoma who had undergone radical surgery (CheckMate 274)
- Kaplan-Meier data for DFS from CheckMate 577 and CheckMate 274 (overall intention-to-treat population) demonstrate a distinct hazard profile (**Figure 1**), including a high rate of relapse or death in the initial period following surgery. For patients who remain disease-free, there is an extended period with a low rate of relapse and mortality comparable to the general population
- To accommodate this hazard profile, flexible survival modelling approaches are required to provide good fits to observed data while predicting plausible long-term outcomes
- The simple distributions nominated in the NICE Decision Support Unit Technical Support Document 14 include exponential, Weibull, Gompertz, log-logistic, lognormal, gamma and generalised gamma, as shown in **Figure 2**. The generalised F distribution contains these distribution families, so that it is a highly flexible model and can represent a large range of hazard profiles (some examples in **Figure 3**)

Figure 1. DFS Kaplan-Meier and hazard profile during CheckMate 577 and CheckMate 274



CM 577: 18-02-2021 DBL; CM 274: 01-02-2021 DBL. Survival by Kaplan-Meier estimator, hazards by Poisson B-spline estimator.
CM: CheckMate; DBL: database lock; DFS: disease-free survival.

Figure 2. Nesting of distributions within the generalised F parameter space

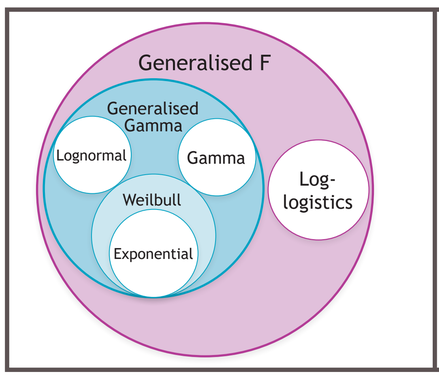
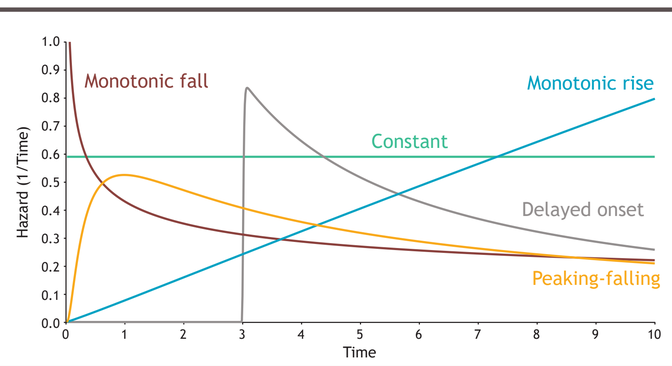


Figure 3. Example hazard profiles within the generalised F parameter space



Objectives

- This research highlights key challenges associated with the GenF distribution and describes potential solutions, using data from CheckMate 577 and CheckMate 274

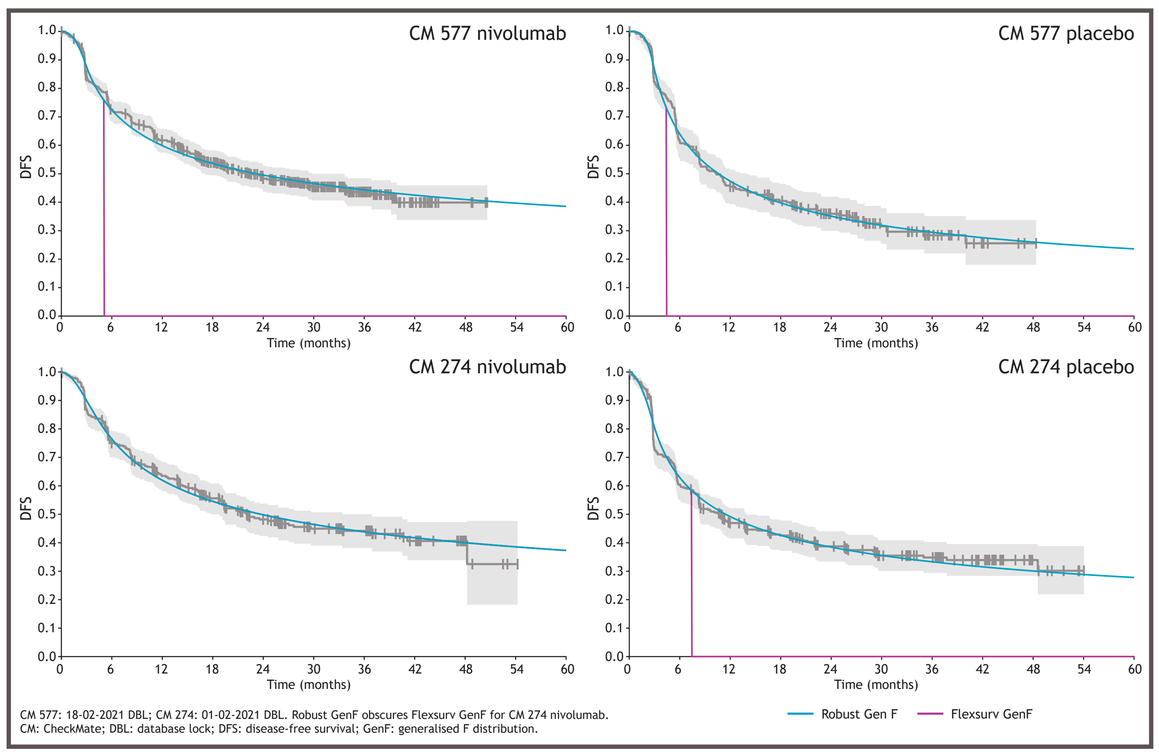
Methods

- GenF extrapolations were derived using patient-level data describing DFS during the CheckMate 577 and CheckMate 274 studies
- CheckMate 577 is an ongoing Phase III trial evaluating nivolumab vs placebo in patients with resected (R0) Stage II or III oesophageal or gastro-oesophageal junction cancer who had received neoadjuvant chemoradiotherapy and had residual pathological disease (minimum follow-up 14.0 months).[3,4] CheckMate 274 is an ongoing Phase III trial comparing nivolumab vs placebo in patients with muscle-invasive urothelial carcinoma who had undergone radical surgery (minimum follow-up 11.0 months)[5,6]
- The GenF parameterisations were initially implemented using the approach described by Prentice (1975)[7] as implemented by the R package flexsurv[8]
- The resulting GenF parameterisations (hereafter described as Flexsurv GenF) were evaluated to describe the implementation challenges
- An alternative evaluation of the GenF distribution was derived (described as robust GenF), and the impact of implementation was assessed

Generalised F distribution: challenges

- Extrapolation of DFS using the Flexsurv GenF function provides an invalid prediction, visualised as a sharp truncation of the survival extrapolation (**Figure 4**). This invalid prediction is a result of error in the evaluation of the GenF probability function in Flexsurv. The exponential of ω (e^{ω}) can result in values that exceed the maximum of the highest representable number in a standard computer (numeric overflow)
  - Numeric overflow is more likely where there is a longer time to the first Kaplan-Meier event in survival data followed by a period of maximal hazard, as in the "Delayed onset" hazard profile shown in **Figure 3**
  - This is of particular relevance in modelling of adjuvant cancer therapies, as there is more likely to be a delay to first event due to treatment initiation criteria and period assessment
  - As a result of the numeric overflow, the survival function drops to 0, visible as an abrupt vertical drop in the survival curve (**Figure 4**)
  - The numeric overflow error impacts the search for the true maximum likelihood parameters and may also impact the parameter uncertainty matrix used for probabilistic sensitivity analysis (PSA)
  - Even if model fitting is not impacted by this issue, extrapolation predictions from the fitted models can be impacted by this numeric overflow error
  - Sampled parameter combinations for PSA may move the time at which overflow occurs within the time horizon, resulting in some PSA draws giving unusually low mean survivals

Figure 4. Predictions from models fitted to CheckMate 577 and CheckMate 274 DFS



CM 577: 18-02-2021 DBL; CM 274: 01-02-2021 DBL. Robust GenF obscures Flexsurv GenF for CM 274 nivolumab.
CM: CheckMate; DBL: database lock; DFS: disease-free survival; GenF: generalised F distribution.

An alternative evaluation of the Generalised F distribution

- An alternative approach was sought to evaluate GenF under conditions where evaluation of e^{ω} will cause numeric overflow (**Equation 1**)
- Use of the robust GenF parameterisation for CheckMate 577 and CheckMate 274 is outlined in **Figure 4**
  - For 3 of 4 models, overflow occurs in Flexsurv GenF within trial follow-up. For nivolumab from CheckMate 274, the Flexsurv and Robust GenF extrapolations completely overlap, demonstrating the validity of the alternative approach
  - Fitting of these models failed unless using the robust implementation described in Equation 1
  - The robust GenF implementation does not affect evaluation prior to overflow

Equation 1. Derivation and definition of an alternative evaluation of the generalised F distribution

Flexsurv GenF density function

$$f(x) = \frac{\delta \left(\frac{s_1}{s_2}\right)^{s_1} e^{s_1 \omega}}{\sigma x \left(1 + \frac{s_1 e^{\omega}}{s_2}\right)^{(s_1+s_2)} B(s_1, s_2)}$$

where: $B(z_1, z_2)$ is the Euler beta function

$$\delta = \sqrt{q^2 + 2p}$$
$$\omega = (\ln(x) - \mu)\delta/\sigma$$
$$s_1 = 2(q^2 + 2p + q\delta)^{-1}$$
$$s_2 = 2(q^2 + 2p - q\delta)^{-1}$$

Defining ω_{crit} as the minimum value of ω at which overflow occurs, for a fixed parameter set then x_{crit} may be defined as that survival time resulting in ω_{crit}. Defining a constant:

$$A \stackrel{\text{def}}{=} \frac{\frac{\delta}{\sigma}\left(\frac{s_1}{s_2}\right)^{s_1}}{B(s_1, s_2)}$$

The log density function is described as:

$$\ln\left(f(x)\right) = \ln A + \omega s_1 - \ln x - (s_1 + s_2)\ln\left(1 + \frac{s_1}{s_2} e^{\omega}\right)$$

As the ω_{crit} is approached, so

$$1 + \frac{s_1}{s_2} e^{\omega} \approx \frac{s_1}{s_2} e^{\omega} \quad \text{assuming} \quad \frac{s_1}{s_2} \gg e^{-\omega}$$

Thus, for high ω, the log density function can be approximated without the exponential term:

$$\ln\left(f(x)\right) \approx \ln A + \omega s_1 - \ln x - (s_1 + s_2)(\ln s_1 - \ln s_2 + \omega)$$

This approximation is invalid at low ω, and so a composite density function is defined where the original evaluation is performed below the critical ω and the approximation occurs at values greater than or equal to the critical ω. Considering the cumulative probability distribution, the density approximation may be integrated trivially.

Defining:

$$C \stackrel{\text{def}}{=} \exp\left(\frac{\mu s_2 \delta}{\sigma} - (s_1 + s_2)\ln\left(\frac{s_1}{s_2}\right)\right)$$

then

$$\int_a^b f(x)dx \approx \left[\frac{ACx^{-\frac{s_2\delta}{\sigma}}}{-\frac{s_2\delta}{\sigma}}\right]_a^b$$

Where $a \geq x_{crit}$. Integrating into the super-critical region therefore proceeds in sequence, using the existing algorithm implemented by flexsurv up to the critical value, and the approximation thereafter, in order to define the cumulative probability over the extended parameter space.

Conclusions

- The generalised F distribution is a highly flexible distribution that can support estimation of DFS in the adjuvant setting
- Evaluation of the generalised F distribution using prevalent algorithms can result in numerical challenges. This study provides solutions to the most common problems
- Although not mandatory for all assessment bodies, including in the UK, the generalised F distribution should be considered, particularly for adjuvant cancer therapies where survival data may be highly immature and require flexible approaches to extrapolation as a natural extension to the recommended distributions for survival modelling that can represent delayed onset hazards without arbitrary cut-point selection, as in piecewise models

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Disclosures

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