Supplementary Materials

Supplementary Methods

Statistical methods

Survival analysis

To accomplish the two study objectives, four variants of the survival Cox model for repeated events were fitted.

The general formulation of the hazard function for a repeated event survival analysis is as follows:

$$\lambda_{i\,k}(t;\mathbf{z}_{i\,k}(t)) = \lambda_{0k}(t)\,\alpha_i \exp\left(\boldsymbol{\beta}'\mathbf{z}_{i\,k}(t)\right)$$

where $\lambda_{0k}(t)$ is the ordered event-specific baseline hazard for the k^{th} event (k=1, 2 PDs). α_i is the frailty for patient *i* assumed as a Gamma (1, θ) distributed random variable. Parameter θ represents patient heterogeneity, by which the higher the θ, the greater the heterogeneity. The covariate effect is modeled by the term $\exp\left(\boldsymbol{\beta}'\mathbf{z}_{i\,k}(t)\right)$. $\mathbf{z}_{ik}(t)$ denotes the covariate vector for the i^{th} subject and the k^{th} event and includes treatment with B, potential confounders (possibly time-dependent) and an interaction term for the differential effect of B between first-line and second-line treatment. Since the study design entailed a treatment crossover, B was specified as a time-dependent covariate in the statistical analysis.

Model *a)* derives from assuming the common baseline $\lambda_0(t)$ for all recurrent events. Models *a)* and *b)* do not include the interaction term for the differential effect of B. Models *a), b),* and *c)* fix the frailty term α_i at 1 for all patients. Not all randomized patients experienced PD, and, more importantly, not all patients experiencing the first PD were eligible to receive the second-line treatment as planned in the study protocol.

Calculation of IPCW

The IPCW method aims to reconstruct the complete population, properly weighting the available observations. Therefore, all patient clinical histories post-first PD are, after weighting, representative of the starting population as though the selective withdrawal had never occurred. The weighting formula is as follows:

$$w_{ij} = \prod_{h=0}^{j} \frac{1}{P(A_{ih} = a_{ih} \mid C_{ih} = c_{ih})}$$

where j denotes the number of discrete time intervals defined by time-varying covariate for each i^{th} patient. A_{ih} indicates the selective withdrawal at the second-line treatment for patient i at time point t_{ih}, C_{ih} variables (time-fixed: age at entry, gender, CT regimen, KRAS mutational status, center, study arm, ECOG PS, tumor localization, LDH-Lactate dehydrogenase; and time-varying: surgery and toxicity) measured right before each time point t_{ih} for patient i. The equation is a product over all time points $\{t_{ih}\}$ from randomization to discrete time point t_{ij}, for each patient i. Weights are then stabilized using the observed time-fixed covariates and the covariates used for the stratified randomization (age at entry, gender, KRAS mutational status, and center).

In practice we fit a Cox model for time to second-line treatment (A_{ih} indicator for the selective withdrawal at the second-line treatment) which estimates the probability of selective withdrawal. This model includes all the C_{ih} variables measured right before each time point t_{ih} for patient i. The IPCW is then the inverse of this probability. To gain in robustness the IPCW is stabilized, *i.e.* calculated as the ratio between the probabilities of selected withdrawals predicted by the Cox model with only the observed time-fixed covariates (age at entry, gender, CT regimen, KRAS mutational

46 status, center, study arm, ECOG PS, tumor localization, LDH-Lactate dehydrogenase);
47 and, in the denominator, the probabilities of selected withdrawals predicted by the Cox
48 model with time-fixed and time-varying covariates.