Bayesian optimality of testing procedures for survival data

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Abstract

Most statistical tests for treatment effects used in randomized clinical trials with survival outcomes are based on the proportional hazards assumption, which often fails in practice. Data from early exploratory studies may provide evidence of non-proportional hazards which can guide the choice of alternative tests in the design of practice-changing confirmatory trials. We study a test to detect treatment effects in a late-stage trial which accounts for the deviations from proportional hazards suggested by early-stage data. Conditional on early-stage data, among all tests which control the frequentist Type I error rate at a fixed $\alpha$ level, our testing procedure maximizes the Bayesian prediction of the finite-sample power. Hence, the proposed test provides a useful benchmark for other tests commonly used in presence of non-proportional hazards, for example weighted log-rank tests. We illustrate the approach in a simulations based on data from a published cancer immunotherapy phase III trial.

1 Introduction

Researchers often use data generated by exploratory clinical studies to specify the protocol of randomized confirmatory phase III trials. Data predictive of the confirmatory trial outcomes, including early estimates of treatment effects, are used to choose the primary endpoints (Gómez et al., 2014), the sample size (Lindley, 1997), the target populations (Lee & Wason, 2018), and other aspects of the study design (Brody, 2016). Still, in most cases prior information is not used to specify in the protocol, as mandated by regulatory agencies, which hypothesis testing procedure will be used in the final analyses to provide evidence of treatment effects. Agencies such as the U.S. Food and Drug Administration require the control of Type I and II errors at acceptable, pre-specified rates (US Food and Drug Administration, 1998).

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In Phase III trials, standard tests, such as Mantel’s log-rank, are often selected even for studies where prior data suggests their underlying assumptions will be violated (Royston & Parmar, 2013; Alexander et al., 2018). For survival endpoints, methods related to the log-rank test are prevalent. Asymptotically, this is the most powerful test with a proportional hazards alternative (Fleming & Harrington, 2011). However, the proportional hazards assumption is often violated in practice, contributing to false-negative findings (Royston & Parmar, 2013), invalidating sample size calculations (Barthel et al., 2006), and affecting interim analyses (van Houwelingen et al., 2005).

Data from early-stage studies can inform about deviations from the assumption of proportional hazards, suggesting the use of alternative methods (Royston & Parmar, 2013). Several extensions and alternatives are available to replace Mantel’s test, such as weighted (Fleming & Harrington, 2011) or adaptive log-rank tests (Yang & Prentice, 2010), and restricted mean survival tests (Royston & Parmar, 2013). Several of these procedures identify the most powerful test against specific alternatives, which may or may not be representative of available estimates from early stage analyses. Moreover, their optimality typically holds in a large-sample sense (e.g. in the local limit for weighted log-rank tests; Fleming & Harrington 2011).

We develop a statistical test to detect treatments effects in late-stage trials, accounting for deviations from the proportional hazards assumption indicated by early-phase studies (e.g. phase II trials). The proposed test does not belong to the weighted log-rank family or other common classes of tests. Starting from decision theory principles (Robert, 2007), we derive it as the solution to the following constrained decision problem (Ventz & Trippa, 2015): conditional on early-stage data, the test maximizes the predicted finite-sample power among all tests which control the frequentist Type I error rate of the late-stage study at a fixed $\alpha$ level. More precisely, the test maximizes the Bayesian predictive probability that the null hypothesis will be correctly rejected at the end of the confirmatory trial. The test therefore provides a useful benchmark for other procedures applicable in presence of non-proportional hazards.

As a motivating example we consider the analysis of a randomized trial with delayed treatment effects on survival outcomes. This is a characteristic which occurs when the treatment requires an induction period before it starts to exert therapeutic effects. When treatment effects are delayed, the hazard functions are not proportional and they separate across arms only later during follow-up (Fine, 2007). Initially overlapping survival curves (c.f. Figure 1a) are well documented in trials of cancer immunotherapies (Chen, 2013; Alexander et al., 2018). They can also be observed in other settings, such as in studies of breast cancer (Mehta et al., 2012) and melanoma (Robert et al., 2015) chemotherapies.

2 Example

We consider data on the survival times of the 361 patients with head and neck carcinomas that participated in CheckMate 141 study (Ferris et al., 2016), a Phase III trial that randomized patients to receive nivolumab, a novel cancer immunotherapy, or standard of care (SOC) in a 2:1 ratio. We reconstructed the individual-
Figure 1: Panel a, reconstructed Kaplan-Meier curves from the CheckMate 141 trial and posterior estimates obtained from the piecewise exponential model (Section 6). Panel b, Monte Carlo estimates of the rejection probability of selected tests (Section 7.1). Panel c, results of the robustness analysis (Section 7.2). Legend: permutation, maximum-BEP test of Section 5 based on the piecewise exponential model (highlighted in red); adaptive, adaptive log-rank test of Yang & Prentice (2010); mantel, classical Mantel’s log-rank test; $G^{0,1}$, Fleming-Harrington weighted log-rank test; lagged, lagged-log rank that ignores the first 10% of observed follow-up times (Zucker & Lakatos, 1990), RMST, test of the difference in restricted mean survival times (Huang & Kuan, 2018).

3 Planning a late-stage trial

We plan a late-stage randomized trial with a survival end-point and a sample size of $n$ patients. This will generate data $x = (t, d, a)$ to test if the treatment has positive effects on the primary outcome. Here, $t = (t_1, \ldots, t_n)$ are the observed follow-up times, $d = (d_1, \ldots, d_n)$ are the corresponding censoring indicators ($d_i = 1$ if $t_i$ is censored, while $d_i = 0$ if an event was observed), and $a = (a_1, \ldots, a_n)$ are the study arm level data of this trial from Figure 1a of Ferris et al. (2016) by means of the DigitizeIt (TM) software (version 2.2) and the data extraction method of Guyot et al. (2012). Figure 1a shows the resulting Kaplan-Meier curves, which compare survival probabilities between the two study arms. These do not clearly separate in the initial 3-4 months of follow-up, a signal of delays in the treatment effects.
indicators \((a_i = 0\) or \(a_i = 1\) if the \(i\)-th patient is randomized to the control or treatment arm\). Patients are assigned to arms with a fixed randomization probability. We assume that censoring times are non-informative in the sense of [Heitjan & Rubin (1991)] and independent of treatment assignment.

For design purposes, we specify a model for the distribution that will generate the data \(x\). This is described by a density \(p_\theta(x)\) that depends on a parameters vector \(\theta \in \Theta\). Here \(\theta\) may be infinite-dimensional if the model is semi- or non-parametric. Typically, \(p_\theta(x)\) will have the form

\[
p_\theta(x) = \prod_{i=1}^{n} r_{i}^{a_i} (1-r)^{1-a_i} h_{a_i}(t_i; \theta)^{1-d_i} S_{a_i}(t_i; \theta) g_i(t_i)^{d_i} G_i(t_i)^{1-d_i}, \tag{1}
\]

where: \(r \in (0,1)\) is the probability of assignment to arm \(a = 1\), \(h_{a}(t; \theta) > 0\) is the hazard function of arm \(a = 0,1\) (for example, in the exponential model, \(h(t; \theta) = \theta_\tau\), \(\theta = (\theta_0, \theta_1) \in \Theta = (0, +\infty)^2\)); \(S_{a}(t; \theta) = \exp \left( -\int_{0}^{t} h_{a}(s; \theta) ds \right)\) is the corresponding survival function; finally, \(g_i(t)\) and \(G_i(t)\) are the density and (left-continuous) censoring function of the \(i\)-th patient. Here, the censoring mechanism is taken as known, a common assumption when planning new experiments ([Chow et al. 2007]). We will later discuss that this assumption is not used in the development of the proposed testing procedure.

We consider the non-parametric null hypothesis \(H_0:\ P \in P_0\), where \(P\) is the true data-generating distribution of \(x\) (i.e. \(P(A)\) is the probability that \(x \in A\)) and \(P_0\) is the class of all distributions which are invariant with respect to permutations of the treatment arm assignments. Hence, \(P \in P_0\) if its likelihood function \(p(x)\) is such that \(p(t, d, a) = p(t, d, a')\) for all \(a'\) obtained by permuting the elements of \(a\).

The alternative hypothesis is instead defined using model (1) as \(H_1:\ P\) has density \(p_\theta(x)\) for some \(\theta \in \Theta_1\), where \(\Theta_1\) is a subset of \(\Theta\). For example, \(\Theta_1\) may include all \(\theta\) such that \(h_0(t; \theta) \neq h_1(t; \theta)\), or such that the median of \(S_1(t; \theta)\) is greater than that of \(S_0(t; \theta)\), or such that the restricted mean survival in arm \(a = 1\) is greater than in arm \(a = 0\) ([Royston & Parmar 2013]).

According to this definition of the null hypothesis, regardless of whether the model \(p_\theta(x)\) is correct or not, when treatment has no effect the treatment assignments \(a_1, \ldots, a_n\) provide no information about the follow-up times \(t\) and censoring indicators \(d\). Hence, the distribution of the data does not change if these are arbitrarily permuted (c.f. [Fisher 1935; Dawid 1988; Good 2006; Pesarin & Salmaso 2010]).

This definition covers distributions in which the observations \((t_1, d_1, a_1), \ldots, (t_n, d_n, a_n)\) from individual patients cannot be considered independent and identically distributed. For example, this may happen when recruiters selectively enroll patients in the trial based on interim analyses or results from other studies published during the enrollment period, or when treatment effects are confounded by trends in latent covariates, amendments of inclusion-exclusion criteria, and improvements in adjuvant therapies ([Tamm & Hilgers 2014]). In such cases, if treatment has no effects we may still expect \(p(x)\) to remain invariant if the treatment arm indicators are permuted.

It is now necessary to choose which \(\alpha\)-level test \(\varphi(x)\) should be used in the late-stage trial. A (randomized) test of \(H_0\) is a function \(\varphi(x) \in [0, 1]\) such that if data \(x\) is observed, then \(H_0\) is rejected with probability \(\varphi(x)\) ([Lehmann & Romano 2006]). A test is non-randomized if it can only attain the values 0 and 1 (only non-
randomized tests are used in practice, but here we also consider randomized tests because of their analytic advantages). The expected value $E_P[\varphi(x)] = \int_{X_0} \varphi(x) dP(x)$ is equal to the probability of rejecting $H_0$ with data generated from the distribution $P$. If $\alpha \in (0, 1)$ and $E_P[\varphi(x)] \leq \alpha$ for all $P \in \mathcal{P}_0$, then $\varphi(x)$ is said to have level $\alpha$.

4 Bayesian expected power

Different $\alpha$-level tests are usually compared with respect to their power functions $\pi_\varphi(\theta) = \int \varphi(x)p_\theta(x)dx$ or its asymptotic approximations. If $\varphi_1(x)$ and $\varphi_2(x)$ are two $\alpha$-level tests for $H_0$ versus the simple alternative $H_1 : \theta = \theta_1$, for some fixed $\theta_1 \in \Theta_1$, then $\varphi_1(x)$ is preferred to $\varphi_2(x)$ if $\pi_{\varphi_1}(\theta_1) \geq \pi_{\varphi_2}(\theta_1)$. Such comparisons are difficult for composite alternative hypotheses. In fact, uniformly most powerful $\alpha$-level tests, i.e. tests achieving the maximum power across all alternative models $\theta_1 \in \Theta_1$, do not necessarily exist (Lehmann & Romano 2006).

To address this problem, some authors proposed to compare tests with respect to their average power. Specifically, the average power of a test $\varphi(x)$ is $\int_{\Theta_1} \pi_\varphi(\theta)p(\theta)d\theta$, where $p(\theta)$ is a distribution weighting each value of $\theta \in \Theta$ based on pre-experimental information (Spiegelhalter & Freedman 1986; O’Hagan et al. 2005). With this metric, two tests are always comparable. Additionally, $\alpha$-level tests maximizing the average power always exist, although these may be randomized (Chen et al. 2007).

To allow data $x_e = (t_e, d_e, a_e)$ from an early-stage trial to inform comparisons between tests, we consider a data-dependent prior $p(\theta|x_e)$. Several approaches have been proposed to incorporate historical data in a prior distribution, including power priors (Ibrahim et al. 2015), meta-analytic priors (Schmid et al. 2016), and commensurate priors (Hobbs et al. 2011). For simplicity, we define $p(\theta|x_e)$ as the posterior distribution $p(\theta|x_e) \propto L(\theta; x_e)p(\theta)$, where, letting $n_e$ be the early-stage trial sample size,

$$L(\theta; x_e) = \prod_{i=1}^{n_e} h_{a_{e,i}}(t_{e,i}; \theta)^{1-d_{e,i}} S_{a_{e,i}}(t_{e,i}; \theta),$$

while $p(\theta)$ is a prior distribution on $\Theta$ whose choice depend on the specific application context. In doing so, we implicitly assume identical treatment effects and survival distributions in the early- and late-stage trials.

Extending the average power approach, the Bayesian expected power (BEP) of $\varphi(x)$ is defined as

$$BEP_{\varphi} = \int_{\Theta_1} \pi_\varphi(\theta)p(\theta|x_e)d\theta,$$

a concept first introduced by Brown et al. (1987) and “rediscovered” by several authors (Liu 2018). It is simple to observe that $BEP_{\varphi} = \Pr(\varphi(x) \text{ rejects } H_0 \text{ and } \theta \in \Theta_1|x_e)$, the probability, conditional on the early-stage data, that $\varphi(x)$ will correctly reject $H_0$ at end of the late-stage trial. This is often called the probability of success of the trial (Liu 2018).

From the point of view of decision theory (Robert 2007), the BEP is the expected value of the utility function $u(\theta, \varphi, x) = I\{\theta \in \Theta_1\} \varphi(x)$ if $H_2$ holds, then the utility increases with the probability $\varphi(x)$ of
rej ecting $H_0$). Indeed,

$$\text{BEP}_\varphi = \int \int u(\theta, \varphi, x)p_\theta(x)p(\theta|x_c)dxd\theta.$$  \hfill (4)

The problem of choosing which test to apply in the late-stage trial can thus be stated as a constrained maximization problem ([Ventz & Trippa 2015]: among $\alpha$-level tests we optimize the BEP.

5 Tests maximizing the expected power

We identify an $\alpha$-level test with maximum Bayesian expected power. Explicit expressions have been obtained for the case where the set $\mathcal{P}_0$ which defines the null hypothesis ($H_0 : P \in \mathcal{P}_0$) is finite ([Chen 2013]. Instead, our choice of $H_0$ includes all distributions that are invariant with respect to permutations of treatment assignment $a_1, \ldots, a_n$. We show that the max-BEP test is a permutation test. This is obtained by computing or approximating the distribution of real-valued test statistic $T(x)$ across all permutations of the treatment assignments, while the values of the follow-up times $t$ and censoring indicators $d$ are kept fixed at the observed values.

To be more formal, for each permutation $\sigma$ of $(1, \ldots, n)$, we denote with $a_\sigma = (a_{\sigma(1)}, \ldots, a_{\sigma(n)})$ the vector obtained by re-ordering the elements of $a = (a_1, \ldots, a_n)$ according to $\sigma$. Moreover, if $T(x)$ is any real-valued statistics, for each $x = (t, d, a)$ we let $T^{(1)}(x) \leq \cdots \leq T^{(n!)}(x)$ be the ordered values of $T(t, d, a_\sigma)$ as $\sigma$ varies across all $n!$ permutations.

The $\alpha$-level permutation test $\varphi(x)$ of $H_0$ based on the test statistic $T(x)$ can now be defined as follows. First, let $k_\alpha = n! - \lfloor \alpha n! \rfloor$, so that, for each $x$, $T^{(k_\alpha)}(x)$ is the $(1-\alpha)$-level quantile of $T^{(j)}(x)$ for $j = 1, \ldots, n!$. Second, let

$$M^+(x) = \sum_{j=1}^{n!} I\{T^{(j)}(x) > T^{(k_\alpha)}(x)\} \quad \text{and} \quad M^0(x) = \sum_{j=1}^{n!} I\{T^{(j)}(x) = T^{(k_\alpha)}(x)\},$$

be the number of $T^{(j)}(x)$’s greater or equal to $T^{(k_\alpha)}(x)$, respectively. Then, the permutation test $\varphi(x)$ is defined by letting $\varphi(x) = 1$ when $T(x) > T^{(k_\alpha)}(x)$, $\varphi(x) = 0$ when $T(x) < T^{(k_\alpha)}(x)$, and $\varphi(x) = (\alpha n! - M^+(x))/M^0(x) < 1$ when $T(x) = T^{(k_\alpha)}(x)$. This satisfies the equality $E_P[\varphi(x)] = \alpha$ for all $P \in \mathcal{P}_0$ ([Lehmann & Romano 2006, Theorem 15.2.1]).

\textbf{Proposition 5.1.} Let $\varphi(x)$ be the $\alpha$-level permutation test of $H_0 : P \in \mathcal{P}_0$ based on the test statistic $T(x) = q(x)$, where $q(x)$ is the density of $Q \notin \mathcal{P}_0$, $Q(A) = \int_A q(x)d\mu(x)$ for every measurable $A$, and $\mu$ is invariant with respect to permutations $\sigma$ assignments $a_1, \ldots, a_n$. If $\varphi'(x)$ is another $\alpha$-level test of $H_0$, then

$$E_Q[\varphi'(x)] \leq E_Q[\varphi(x)],$$

i.e. $\varphi(x)$ has higher power under the alternative $H_1 : P = Q$.

\textbf{Proof.} Let $\mathcal{P}_\mu \subseteq \mathcal{P}_0$ be the set of all distributions dominated by $\mu$ that are invariant with respect to permutations of treatment assignment (a non-empty set, since it includes $q(t, d, a) = \sum_\sigma q(t, d, a_\sigma)/n!$). By Theorem 2 of [Lehmann et al. 1949], for every test $\varphi'(x)$ such that $E_P[\varphi'(x)] \leq \alpha$ for all $P \in \mathcal{P}_\mu$, $\varphi(x)$ guarantees $E_Q[\varphi'(x)] \leq E_Q[\varphi(x)]$. Now, if $\varphi'(x)$ is an $\alpha$-level test of $H_0$, then $E_P[\varphi'(x)] \leq \alpha$ for all $P \in \mathcal{P}_\mu$ and therefore $E_Q[\varphi'(x)] \leq E_Q[\varphi(x)]$. \hfill $\square$
To proceed, let \( P(H_1|x_e) = \int_{\Theta_1} p(\theta|x_e) d\theta > 0 \) be the prior probability of the alternative hypothesis \( H_1 \). Also, 
\[
q(x) = \int_{\Theta_1} p_0(x) \frac{p(\theta|x_e)}{P(H_1|x_e)} d\theta
\]  
(5)
is the density of the predictive distribution of \( x \) conditional on \( \theta \in \Theta_1 \) based on the early-stage data \( x_e \), and \( Q(A) = \int_A q(x) d\mu(x) \). Here, we assume that all densities \( p_0(x) \) are taken with respect to the same dominating measure \( \mu \).

**Proposition 5.2.** For any test \( \varphi(x) \) of \( H_0 \) we have \( \text{BEP}_\varphi = E_Q[\varphi(x)] \), the power of \( \varphi(x) \) against the simple alternative \( H_1 : P = Q \). Consequently, a test \( \varphi(x) \) maximizes the BEP among all \( \alpha \)-level tests if and only if it maximizes the power \( E_Q[\varphi(x)] \) among all \( \alpha \)-level tests.

**Proof.** By Fubini’s theorem, the BEP of a test \( \varphi(x) \) can be written as 
\[
\text{BEP}_\varphi = \int_{\Theta_1} \pi_\varphi(\theta)p(\theta|x_e)d\theta = \int_{\Theta_1} \left[ \int \varphi(x)p_0(x) d\mu(x) \right] p(\theta|x_e) d\theta \\
= \int \varphi(x) \left[ \int_{\Theta_1} p_0(x) p(\theta|x_e) d\theta \right] d\mu(x) = \int \varphi(x) q(x) d\mu(x) \cdot P(H_1|x_e) \\
= E_Q[\varphi(x)] \cdot P(H_1|x_e).
\]

\( \square \)

Without loss of generality, to derive a maximum-BEP test we assume that \( \mu \) is invariant with respect to permutations of the treatment assignments.

Using Propositions 5.1 and 5.2 we can now prove that it is possible to construct a maximum-BEP test which depends on the data \( x \) only through the marginal likelihood
\[
m(x) = \int_{\Theta_1} L(\theta|x) p(\theta|x_e) d\theta.
\]  
(6)
Since \( m(x) \) does not depend on the censoring distribution functions \( G_i(t) \) which appear in Equation 1, the censoring mechanism is irrelevant to identify the optimal test. Note, however, that the censoring mechanism still determines the BEP.

**Proposition 5.3.** Given the early-stage data \( x_e \), the \( \alpha \)-level permutation test based on the marginal likelihood \( T(x) = m(x) \) maximizes the BEP among all \( \alpha \)-level tests of \( H_0 \).

**Proof.** By Proposition 5.1, the \( \alpha \)-level permutation test \( \varphi'(x) \) based on the test statistic \( T'(x) = q(x) \) maximizes the power \( E_Q[\varphi(x)] \) among all \( \alpha \)-level tests of \( H_0 \). By Proposition 5.2, \( \varphi'(x) \) has maximum BEP among all \( \alpha \)-level tests of \( H_0 \). It now suffices to show that \( \varphi'(x) = \varphi(x) \) for all \( x \) such that \( q(x) > 0 \), where \( \varphi(x) \) is the \( \alpha \)-level permutation test based on \( T(x) = m(x) \). To do so, note that, by Equation 1 if \( q(x) > 0 \), then \( m(x) > 0 \) as well, and the ratio \( q(x)/m(x) \) is invariant with respect to permutations of the treatment arm assignments. Indeed, censoring times and treatment assignments are independent. The thesis now follows because \( q(t,d,a_\sigma) \propto m(t,d,a_\sigma) \) for all permutations \( \sigma \).

\( \square \)
Since randomized tests are not used in applications, we will consider the non-randomized version \( \varphi'(x) = I\{m(x) > m(k_x)\} \) of the test \( \varphi(x) \) from Theorem 5.3. Since \( \varphi'(x) \leq \varphi(x) \), \( \varphi'(x) \) is \( \alpha \)-level for \( H_0 \), although it may not achieve the maximum BEP. Nevertheless, \( \varphi'(x) \) still provide a useful benchmark for other tests of \( H_0 \), as its BEP is close to optimal for large \( n \). In fact, in the Appendix, Proposition 10.1 we show that, under mild conditions, \( 0 \leq BEP_\varphi - BEP_{\varphi'} \leq f(\alpha, r, n) \), where the bound is a known function such that \( f(\alpha, r, n) \to 0 \) as \( n \to +\infty \) for all fixed levels \( \alpha \) and randomization probabilities \( r \). In such cases, a moderate size \( n \) is sufficient to obtain a good approximation.

The non-randomized test \( \varphi'(x) \) coincides with the non-randomized procedure which rejects \( H_0 \) whenever when the permutation p-value \( \text{ppv}(x) = \sum \{m(t, d, a_\pi) \geq m(t, d, a)\} / n! \), is less or equal than \( \alpha \) (Lehmann & Romano 2006, Section 15.2.1). Although \( n! \) will typically be too large to compute the \( \text{ppv}(x) \) exactly, the benchmark test can be implemented by a conditional Monte Carlo approximation. Accordingly, given data \( x \), a large random sample of permutations \( \pi_1, \ldots, \pi_B \) (\( B = 10^3 \), say) is used to estimate the \( \text{ppv}(x) \) as \( \hat{\text{ppv}}(x) = \sum_{i=1}^{B} I\{m(t, d, a_\pi) \geq m(t, d, a)\} / B \). The hypothesis \( H_0 \) is then rejected if \( \hat{\text{ppv}}(x) \leq \alpha \) (Pesarin & Salmaso 2010, Section 1.9.3).

6 The piecewise exponential model

To implement our maximum-BEP test, we use a piecewise exponential model (Benichou & Gall 1990). The hazard function \( h_\alpha(t; \theta) \) is constant over a fixed partition \( \tau_0 = 0 < \tau_1 < \cdots < \tau_k < +\infty = \tau_{k+1} \) of the time axis. In particular, \( h_\alpha(t; \theta) = \theta_{a,j} \) if \( t \in \tau_{j-1}, \tau_j \) with \( j = 1, \ldots, k + 1 \), \( t \in \mathbb{R}_+ \), arms \( a = 0, 1 \), and \( \theta = (\theta_{0,1}, \ldots, \theta_{0,k+1}, \theta_{1,1}, \ldots, \theta_{1,k+1}) \in \Theta = (0, +\infty)^{2(k+1)} \).

The likelihood function of the piecewise exponential model depends on a simple set of sufficient statistics. Given data \( x = (t, d, a) \), let \( s_{a,j} = \sum_{i=1}^{n} \max(0, \min(\tau_j - \tau_{j-1}, t_i - \tau_{j-1}))I\{a_i = a\} \) be the total time at risk spent in the interval \( [\tau_j, \tau_{j+1}] \) by patients in arm \( a \). Additionally, let \( y_{a,j} = \sum_{i=1}^{n} d_iI\{a_i = a, \tau_{j-1} \leq t_i < \tau_j\} \) be the number of events observed during \( [\tau_{j-1}, \tau_j] \) in arm \( a \). Then, the likelihood is

\[
L(\theta; x) = \prod_{a=0}^{k+1} \prod_{j=1}^{k+1} \theta_{a,j}^{y_{a,j}} \exp(-\theta_{a,j}s_{a,j}).
\]

For convenience, we use a conjugate prior \( p(\theta) \). This is obtained by letting all \( \theta_{a,j} \) be independent and distributed as a gamma random variable with shape parameter \( u_{a,j} \) and rate parameter \( v_{a,j} \). With this choice, the distribution \( p(\theta|x_e) \) presents independent \( \theta_{a,j} \) components which are gamma distributed with shape parameter \( u_{a,j} + y_{c,a,j} \) and rate parameter \( v_{a,j} + s_{c,a,j} \), where the \( y_{c,a,j} \) and \( s_{c,a,j} \) are the sufficient statistics of \( x_e \). The marginal likelihood \( m(x) \) needed to implement the maximum-BEP test can thus be obtained explicitly from Equation 6

\[
m(x) = \prod_{a=0}^{k+1} \prod_{j=1}^{k+1} \left( \frac{v_{a,j} + s_{c,a,j}}{v_{a,j} + s_{c,a,j} + s_{a,j}} \right)^{u_{a,j} + y_{c,a,j} + y_{a,j}} \frac{\Gamma(u_{a,j} + y_{c,a,j} + y_{a,j})}{\Gamma(u_{a,j} + y_{c,a,j})}.
\]

where \( \Gamma(z) \) is the gamma function.
As an example, Figure 1a shows the posterior means of the survival probabilities in the nivolumab or SOC arm of CheckMate 141 obtained from the piecewise exponential model. For all $j = 1, \ldots, k = 4$, we conveniently defined $\tau_j$ to be the $j$-th quintile of the distribution of follow-up times in the SOC arm. In different words, the prior model is chosen by peaking at the early stage trial. Additionally, we specify gamma priors on the $\theta_{a,j}$ with $u_{a,j} = v_{a,j} = 10^{-3}$ for all $a$ and $j$. The posterior estimates (Figure 1a) reflect the delayed separation in the Kaplan-Meier curves, as the estimated survival probabilities diverge only after 4 months of follow-up.

7 Application: trials with delayed treatment effects

7.1 Simulation study

As an illustration, we use CheckMate 141 data to simulate a large number of phase II and III trials with delayed treatment effects. In these simulations, we compare different tests with respect to their probability of rejecting the hypothesis of no treatment effects at the end of the phase III trial. We consider Mantel’s log-rank test and several others which account for delayed treatment effects: i) a lagged log-rank test that ignores the first 10% of observed follow-up times (Zucker & Lakatos, 1990); ii) the Fleming-Harrington $G^{0.1}$ test, which gives more weight to late events (Fine, 2007); iii) the adaptive log-rank of Yang & Prentice (2010), which weights events according to a preliminary estimate of the hazard functions; and iv) a test of the difference in Restricted Mean Survival Times (RMSTs) across study arms (Huang & Kuan, 2018). We also implement the maximum-BEP test (using the conditional Monte Carlo approach of Section 5) based on phase II data. For all tests, we consider $\alpha = 0.05$ and a two-sided alternative hypothesis.

To simulate a trial of size $n$, we first sample with replacement $n$ patients from the CheckMate 141 data. Then, depending on patient’s membership arms, we generate the corresponding survival times from the Kaplan-Meier curves of Figure 1a. Assuming a maximum follow-up of 15 months, we generate patient’s censoring times by sampling independently from the empirical censoring distribution (Efron, 1981).

Using this approach, we iterate the following steps 10,000 times: i) we simulate a phase II trial of approximately half the size of CheckMate 141 ($n_e = 180$); ii) using the simulated phase II data $x_e$, we determine the marginal likelihood $m(x)$ for the piecewise exponential model (Equation 7); we fix the $\tau_j$s at the quintiles of the follow-up times in the SOC arm from $x_e$ and specify the same gamma prior ($u_{a,j} = v_{a,j} = 10^{-3}$) for the parameters $\theta_{a,j}$ as in Section 6; iii) we simulate a subsequent phase III study, generating a phase III dataset $x$ with sample size $n = 361$; iv) we apply the test to data $x$ and record the corresponding accept-reject decision. The proportion of rejections across iterations is the Monte Carlo estimate of a test’s rejection probability.

Figure 1b reports the estimated rejection probabilities for each testing procedure. The maximum-BEP permutation test based on phase II data has the highest probability of rejecting the null hypothesis (approximately 0.90). The $G^{0.1}$ test and the lagged log-rank test have both estimated rejection probabilities of
approximately 0.87. The adaptive log-rank and RMST tests have lower rejection probabilities, 0.77 and 0.66 respectively. Mantel’s log-rank test has the worst performance, with an estimated rejection probability of 0.60, a third less than the one achieved by our test and the nominal 90% power in the sample size calculations of CheckMate 141 \cite{Ferris, 2016}. This finding is consistent with previous studies, which highlighted how the log-rank test may suffer a severe loss of power when treatment effects are delayed \cite{Fine, 2007, Chen, 2013, Alexander, 2018}.

### 7.2 Robustness analysis

We consider 3 additional simulation scenarios in which the outcome distributions in phase II and III are not identical. In all scenarios, the distribution of the phase II data $x_e$ is the same as in Section 7.1 while the distribution of the phase III data $x$ is different. In Scenario 1, the dataset $x$ is generated from the predictive distribution $q(x)$ (see Equation 5): a value $\theta'$ is first sampled from $p(\theta|x_e)$, then $x$ is generated from the distribution $p_{\theta'}(x)$. Here we assume $r = 2/3$ as in CheckMate 141 and that censoring can only occur after 15 months of follow-up. Proposition 5.2 indicates that, in this scenario, our permutation test has the highest expected power. Scenarios 2 and 3 instead represent two settings in which our test may suffer from a loss of power. In Scenario 2, $x$ is generated by a different piecewise exponential model than the one used to construct the benchmark test. The phase III delay in treatment effects is shorter than expected from phase II data. Specifically, $x$ is generated by a model with only one cut-point, fixed at $\tau_1 = 2$ months, whose parameters are set equal to the maximum likelihood estimates obtained from CheckMate 141 data. Scenario 3 is similar, but the cut-point is fixed at $\tau_1 = 8$ months to represent longer phase III delays than those expected from phase II data.

Figure 1c shows the results of the robustness analysis. As expected, in Scenario 1 our permutation test has a much higher rejection probability than all other tests (0.98). Instead, its performance is sub-optimal in Scenario 2 and 3. Although in Scenario 3 our permutation test may be considered comparable with the others (rejection probability equal to 0.29), in Scenario 2 it has the lowest rejection probability (0.84, compared to 0.90 for the Mantel’s log-rank). These findings support the intuition that the power of the maximum-BEP test depends on how well it is possible to predict the phase III data on the basis of prior information. If the phase II and III trial populations are markedly different, then a test specified using phase II data may perform poorly in the phase III study.

### 8 Generalization to stratified designs

Treatment effects are often expected to vary across patients’ groups defined, for example, by gender or biomarkers. In such cases one can stratify patients with respect to covariates measured before randomization. We focus on the primary goal of testing whether the experimental treatment has no effects across all strata or if it is effective at least in some of the strata (alternative hypothesis), for example in one or multiple
subgroups defined by a relevant biomarker (Freidlin et al., 2010).

The approach that we discussed can be easily generalized to this setting. For simplicity, we consider the case where each patient \(i = 1, \ldots, n\) is categorized by a binary covariate \(z_i = 0, 1\), presence (\(z_i = 1\)) or absence (\(z_i = 0\)) of a specific marker. Data \(x\) thus becomes \(x = (t, d, a, z)\), where \(z = (z_1, \ldots, z_n) \in \{0, 1\}^n\). Similar to the previous paragraphs we assume that censoring is non-informative and independent of treatment assignments conditionally on \(z_1, \ldots, z_n\) (Heitjan & Rubin, 1991).

To illustrate, we specify a piecewise-exponential model \(h_a(t; \theta, z)\) for the hazard function in arm \(a = 0, 1\) for patients with marker level \(z = 0, 1\) (Freidlin et al., 2010):

\[
h_a(t; \theta, z) = \theta_{a,z,j} \text{ for all } t \in [\tau_{j-1}, \tau_j).
\]

The prior remains nearly identical to the previous sections. In particular, the marginal likelihood \(m(t, d, a, z)\), similar to Equation 6, has a closed form expression.

We specify the null hypothesis \(H_0 : P \in \mathcal{P}_0\), where \(\mathcal{P}_0\) is the class of all distributions which are invariant with respect to permutations of the treatment assignment \(a\) within the two \(z\) groups. More precisely, \(P \in \mathcal{P}_0\) if and only if \(p\), the density of \(P\), satisfy \(p(t, d, a, z) = p(t, d, a_\sigma, z)\) for all permutations \(\sigma\) of \((1, \ldots, n)\) such that \(z_{\sigma(i)} = z_i\) for all \(i = 1, \ldots, n\).

With a simple modification, Proposition 5.3 still holds with this new definition of the null hypothesis. Previously, the maximum-BEP permutation test computed the distribution of \(m(x)\) under \(H_0\) by considering all permutations of the treatment arm indicators \(a_1, \ldots, a_n\). In the stratified case, only permutations \(\sigma\) of \((1, \ldots, n)\) such that \(z_{\sigma(i)} = z_i\) for all \(i = 1, \ldots, n\) are considered. If \(\Sigma(z)\) is the set of all such \(\sigma\), then the permutation p-value associated to the maximum-BEP test is given by

\[
ppv(x) = \frac{\sum_{\sigma \in \Sigma(z)} I\{m(t, d, a_\sigma, z) \geq m(t, d, a, z)\}}{|\Sigma(z)|},
\]

where \(|\Sigma(z)| = (\sum_{i=1}^n z_i)!/(n - \sum_{i=1}^n z_i)!\).

To provide an example, we simulate 10,000 phase II \((n_c = 180)\) and phase III \((n = 361)\) trials from CheckMate 141 data in a similar way as in Section 7.1. Differently than in Section 7.1, in every trial 50\% of patients express \((z_i = 1)\) a biomarker predictive of treatment effects (Patel & Kurzrock, 2015). The survival time of a patient in arm \(a = 0\) or with marker \(z = 0\) is generated from the SOC Kaplan-Meier curve in Figure 1a. Instead, the survival time of a patient in arm \(a = 1\) with marker \(z = 1\) is generated from the nivolumab Kaplan-Meier curve in Figure 1a. Censoring times are generated as in Section 7.1.

In each simulated phase III trial, we tested \(H_0\) in three ways: i) we carried out a test based on the stratified Cox proportional hazards model (a common approach in this setting; c.f. Mehrotra et al., 2012); ii) we performed separate log-rank test in the two marker strata and combined the results using the Bonferroni correction (another common approach; c.f. Freidlin et al., 2014); iii) we implemented our maximum-BEP test using the simulated phase II data. Respectively, the estimated rejection probabilities are 0·18 for the stratified Cox model, 0·26 for the Bonferroni-based test, and 0·49 for our permutation test. These results confirm a substantial benefit in the use of prior data to optimize hypothesis testing.
9 Discussion

Data from previous studies should be routinely used to design of late-stage clinical trials. This is especially relevant when standard assumptions, such as the proportional hazards assumption, might not hold. Our approach allows to specify a test for final analyses that accounts for the deviations from proportional hazards suggested by prior data and satisfies the requirements of regulatory agencies (Ventz & Trippa 2015). The test maximizes a decision-theoretic criteria leveraging on prior data and it is of $\alpha$-level for an interpretable null hypothesis.

To implement our permutation test, it is necessary to compute the marginal likelihood of the late-stage data. This may be complicated for non-conjugate models. However, many computational methods are available to approximate it (Friel & Wyse 2012; Pajor et al. 2017).

Although we derived our test assuming a single early-stage dataset, the use of multiple sources of prior data may provide better outcome predictions for late-stage trials. Our approach can incorporate multiple prior datasets using power priors (Ibrahim et al. 2000) or hierarchical models (Spiegelhalter et al. 2004). Our simulations, based on data from the CheckMate 141 trial, confirm that weighted log-rank tests can outperform other tests in presence of delayed treatment effects. However, these tests depend on a set of tuning parameters, such as the duration of the lag time for lagged log-rank tests or the $\rho$ and $\delta$ coefficients of the $G^{\rho,\delta}$ Fleming-Harrington family, which may be hard to tune. Instead, our approach directly translates early-stage data into a test procedure for the late-stage trial.

Robustness analyses highlight how the performance of our approach is dependent on the consistency of outcome data and the similarity of enrolled populations between phase II and phase III trials. Ensuring the transportability of results to subsequent trials remains a major concern in the design of exploratory clinical trials (Wang et al. 2006).

10 Appendix

Denote with $\Pi(x)$ the set of all $\left(\sum_{i=1}^{n} a_i \right)$ distinct datasets obtained from $x = (t, d, a)$ by permuting the elements of $a$ in all possible ways. Here, we will assume that when $q(x) > 0$ the inequality $m(x_1) \neq m(x_2)$ holds for all $x_1, x_2 \in \Pi(x)$ such that $x_1 \neq x_2$.

Proposition 10.1. Let $\varphi(x)$ be the $\alpha$-level permutation test of Proposition 5.3 and $\varphi'(x)$ its non-randomized version. Then

$$0 \leq \text{BEP}_\varphi - \text{BEP}_{\varphi'} \leq f(\alpha, r, n) = \frac{(1 - r)^n}{\alpha} \sum_{s=0}^{n} \left( \frac{r}{1-r} \right)^s$$

Proof. By Proposition 5.2, $0 \leq \text{BEP}_\varphi - \text{BEP}_{\varphi'} = E_Q[\varphi(x) - \varphi'(x)] \leq Q(E)$, where $E$ is the set of all $x$ such that $m(x) = m^{(k_0)}(x)$. Proceeding as in Section 5.9 of (Lehmann & Romano 2006),

$$Q(E) = \int \sum_\sigma I\left\{m(t, d, a_\sigma) = m^{(k_0)}(x)\right\} q(t, d, a_\sigma) dQ(x),$$
where both sums extend over all \( n! \) permutations \( \sigma \) of \((1, \ldots, n)\). If \( q(x) > 0 \), then

\[
\sum_{\sigma} I\{m(t, d, a) = m^{(k_\alpha)}(x)\} q(t, d, a) \leq \sum_{\sigma} I\{m(t, d, a) = m^{(k_\alpha)}(x)\} m(t, d, a) = \sum_{\sigma} I\{m(t, d, a) \geq m^{(k_\alpha)}(x)\} m^{(k_\alpha)}(x)
\]

This concludes the proof. \(\square\)

In general, the approximation provided by Proposition 10.1 will be fairly accurate. For example, if \( \alpha = 0.05 \) and \( r = 1/2 \), the difference \( f(\alpha, r, n) \) between \( \text{BEP}_\varphi \) and \( \text{BEP}_{\varphi'} \) is \( 2^{-n}(n+1)/\alpha < 10^{-3} \) for all \( n \geq 15 \). For \( r \neq 1/2 \) it is \( f(\alpha, r, n) = [(1-r)^{n+1} - r^{n+1}]/\alpha(1-2r) \); for \( r = 2/3 \), the value considered in Section 7, \( f(\alpha, r, n) < 10^{-3} \) for all \( n \geq 25 \).

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Supplementary material

Data and code to replicate the results of Sections 7, 8 is available at https://github.com/andreaarfe/.

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