Estimation of Survival for All Treated Patients in the Randomized Discontinuation Trial Design

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Society for Clinical Trials, May 2011

Outline

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Randomized Discontinuation Trial (RDT) Design

Motivation:

- In phase II oncology clinical trials the primary endpoint has traditionally been objective response, defined as a 30% or greater reduction in tumor size.

- Although this endpoint is appropriate when the experimental agent is *cytotoxic* in nature, it is not suitable for *cytostatic* drugs.

- Another important issue in the era of molecularly targeted therapy is the belief that only a subset of the patient population (those expressing the target) are likely to benefit.

- The RDT design offers a means to "self-select" for a cohort most likely to benefit from a given treatment and to evaluate its disease-stabilizing activity in a controlled manner.

The RDT is an enrichment design:

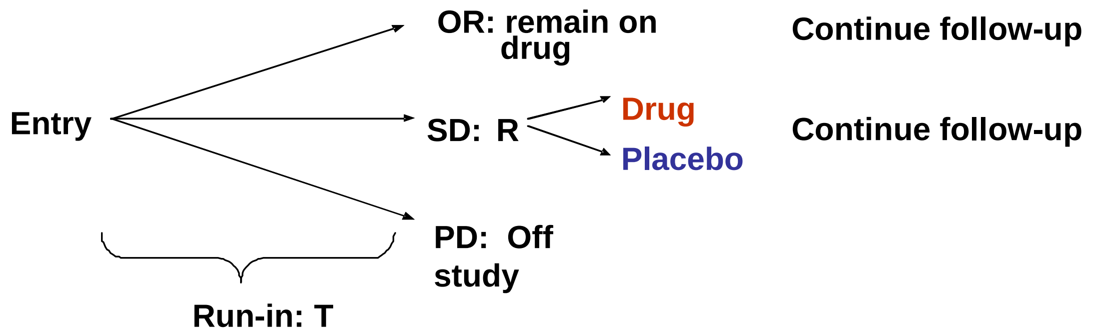


Figure 1. Randomized discontinuation trial design.

The main analysis compares outcomes—for example, progression-free survival—between the two randomized arms measured from the point of randomization.

Comments:

- Efficiency of the RDT design depends on the degree to which enrichment is achieved.

- It must be assumed that there is no carryover effect from the run-in period in those patients randomized to placebo.

- One aspect of the RDT that differs from usual enrichment-type designs is that patients with an objective response are not randomized, but remain on therapy for ethical reasons.

- Evaluations of the RDT compared to other designs can be found in Capra (*Cont Clin Trials*, 2004), Freidlin and Simon (*J Clin Oncol*, 2005), and Fu et al (*J Clin Oncol*, 2009).

Secondary Objective

Estimation of progression-free survival (PFS) for all drug-treated patients, measured from the time of entry into the trial.

-- Useful for historical comparisons and for phase III trial design.

-- Requires combining information from the run-in and post run-in periods.

For $t \leq T$, PFS can be estimated in the usual way.

For $t > T$,

$$\hat{S}(t) = \hat{p}_{OR} * \hat{S}_{OR}(t-T) + \hat{p}_{SD} * \hat{S}_{SD}(t-T)$$

Mean and variance of $\hat{S}(t)$?

Let

X_1 = number of objective responders (OR) during the run-in period

X_2 = number of patients with disease progression (PD)

n_{SD} = number of patients with stable disease (SD)—*fixed by design*

(X_1, X_2) has a negative multinomial distribution with parameters $n_{SD}, m_1, \text{and } m_2,$

$$E(X_i) = m_i$$

$$V(X_i) = \frac{m_i(m_i + n_{SD})}{n_{SD}}$$

$$Cov(X_1, X_2) = \frac{m_1 m_2}{n_{SD}}$$

$$\hat{p}_{OR} = X_1 / (n-1) \qquad \hat{p}_{SD} = (n_{SD} - 1)/(n-1),$$

where $n = X_1 + X_2 + n_{SD}$

$$V(\hat{p}_{OR}) = \frac{X_1(n - X_1)}{n^2(n-1)}$$

$$V(\hat{p}_{SD}) = \frac{n_{SD}(n - n_{SD})}{n^2(n-1)}$$

$$Cov(\hat{p}_{OR}, \hat{p}_{SD}) \cong \frac{-X_1 \cdot n_{SD}}{n^3}$$

$$\hat{S}(t) = \hat{p}_{OR} * \hat{S}_{OR}(t-T) + \hat{p}_{SD} * \hat{S}_{SD}(t-T)$$

Mean and variance can be derived by first conditioning on (X_1, X_2) :

Mean:

$$E[\hat{S}(t)] = E[E(\hat{S}(t) \mid X_1, X_2)]$$

$$= E[\hat{p}_{OR} S_{OR}(t-T) + \hat{p}_{SD} S_{SD}(t-T)]$$

$$= p_{OR} S_{OR}(t-T) + p_{SD} S_{SD}(t-T)$$

$$= S(t)$$

Variance:

$$V[\hat{S}(t)] = E\,[V(\hat{S}(t) \mid X_1, X_2)] + V[E(\hat{S}(t) \mid X_1, X_2)]$$

$$= E\left\{\hat{p}_{OR}^2 V[\hat{S}_{OR}(t-T)] + \hat{p}_{SD}^2 V[\hat{S}_{SD}(t-T)]\right\} + V\left\{\hat{p}_{OR} S_{OR}(t-T) + \hat{p}_{SD} S_{SD}(t-T)\right\}$$

$$= V(\hat{S}_{OR}(t-T))[V(\hat{p}_{OR}) + p_{OR}^2] + V(\hat{S}_{SD}(t-T))[V(\hat{p}_{SD}) + p_{SD}^2] + (S_{OR}(t-T))^2 V(\hat{p}_{OR})$$

$$+ (S_{SD}(t-T))^2 V\left(\hat{p}_{SD}\right) + 2S_{OR}(t-T)S_{SD}(t-T)Cov(\hat{p}_{OR}, \hat{p}_{SD})$$

An estimate of the variance can be obtained by replacing $S_{OR}(t-T)$, $S_{SD}(t-T)$ by their Kaplan-Meier estimators and using Greenwood's formula for $V(\hat{S}_{OR}(t-T))$, $V(\hat{S}_{SD}(t-T))$.

Simulation Study

Phase II trial in which patients are accrued over an interval [0, a] and follow-up is continued for an additional time period f.

Outcomes (OR, SD, PD) during the run-in period, T, were drawn randomly until $n_{SD}'s$ occur.

For patients with outcomes of OR or SD the subsequent time to disease progression/death was drawn from one of two Weibull distributions:

$$S_{OR}(u) = \exp\left(-(\lambda_1 u)^{p_1}\right)$$

$$S_{SD}(u) = \exp\left(-(\lambda_2 u)^{p_2}\right)$$

An additional random censoring mechanism with rate parameter λ_c was also incorporated to allow for losses to follow-up post randomization.

Table 1. Simulation Results

Scenario: $p_{OR} = 0.15, p_{SD} = 0.60, \lambda_1 = 0.003, p_1 = 1.7, \lambda_2 = 0.009, p_2 = 1.2, \lambda_c = 0.0005$

R=10,000 replications.

n_{SD}	Mean n	t	$S(t)$	Mean $\hat{S}(t)$	Empirical Std Dev	Mean $\sqrt{V(\hat{S}(t))}$	Coverage Rates (%) Un	Log	CLL	Logit
100	**166.7**	**18**	**.5852**	**.5848**	**.0465**	**.0465**	**94.6**	**95.0**	**94.9**	**95.1**
		24	**.4298**	**.4296**	**.0490**	**.0490**	**94.6**	**94.8**	**95.2**	**95.1**
		30	**.3114**	**.3113**	**.0457**	**.0459**	**94.5**	**95.0**	**95.0**	**95.1**
		36	**.2259**	**.2261**	**.0409**	**.0409**	**94.1**	**95.2**	**94.8**	**95.3**
		42	**.1652**	**.1655**[1]	**.0368**	**.0359**	**93.6**	**94.9**	**94.7**	**95.1**
		48	**.1221**	**.1229**[2]	**.0326**	**.0322**	**94.2**	**95.8**	**95.9**	**96.3**

[1]R=9987, [2]R=9754

Example

Phase II Placebo-Controlled Randomized Discontinuation Trial of Sorafenib in Patients with Metastatic Renal Cell Carcinoma

Ratain et al, *J Clin Oncol (*2006)

N=202 patients enrolled

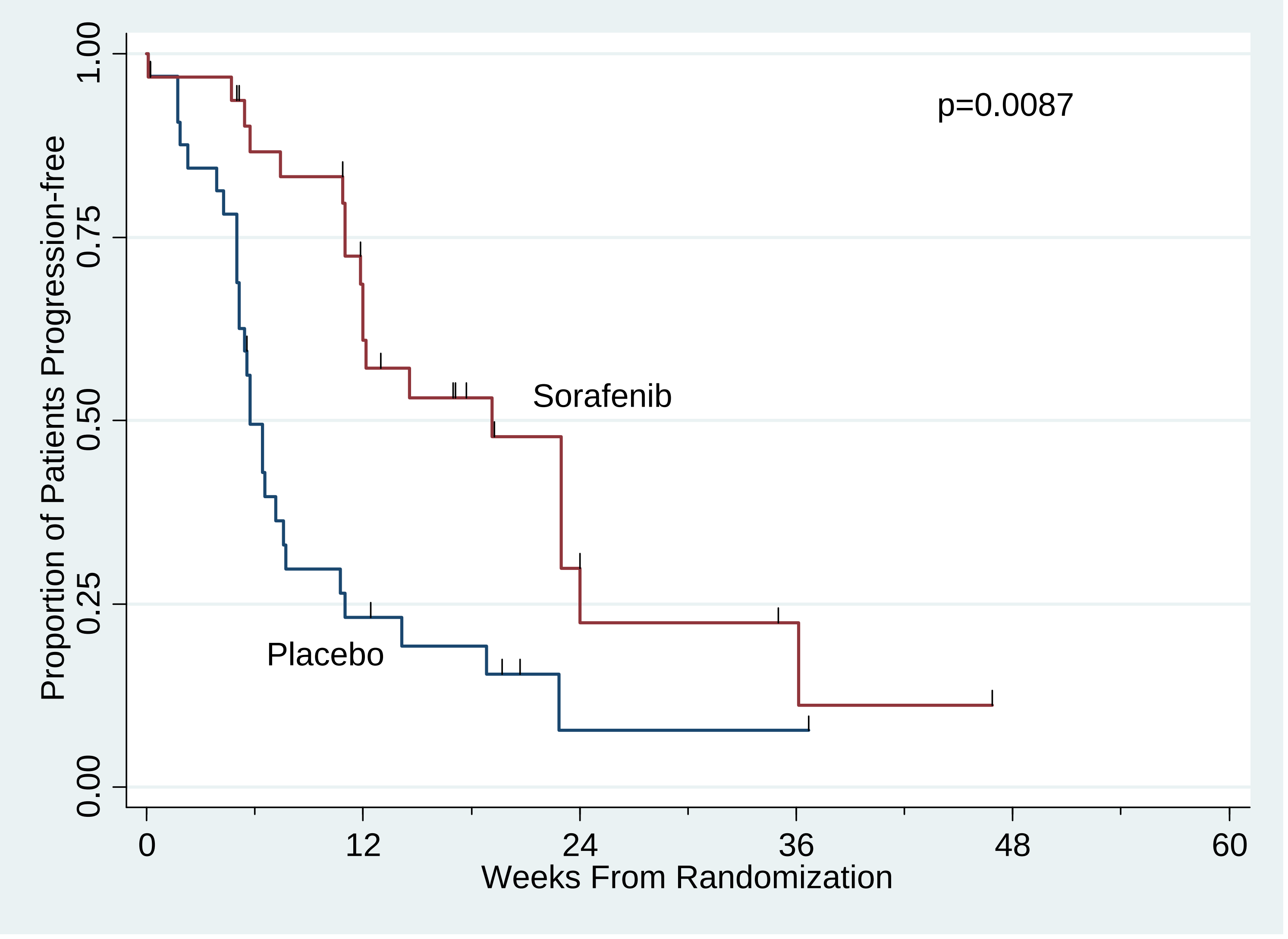
T=12 wks: 58 PD or discontinued treatment

73 OR (25% regression)

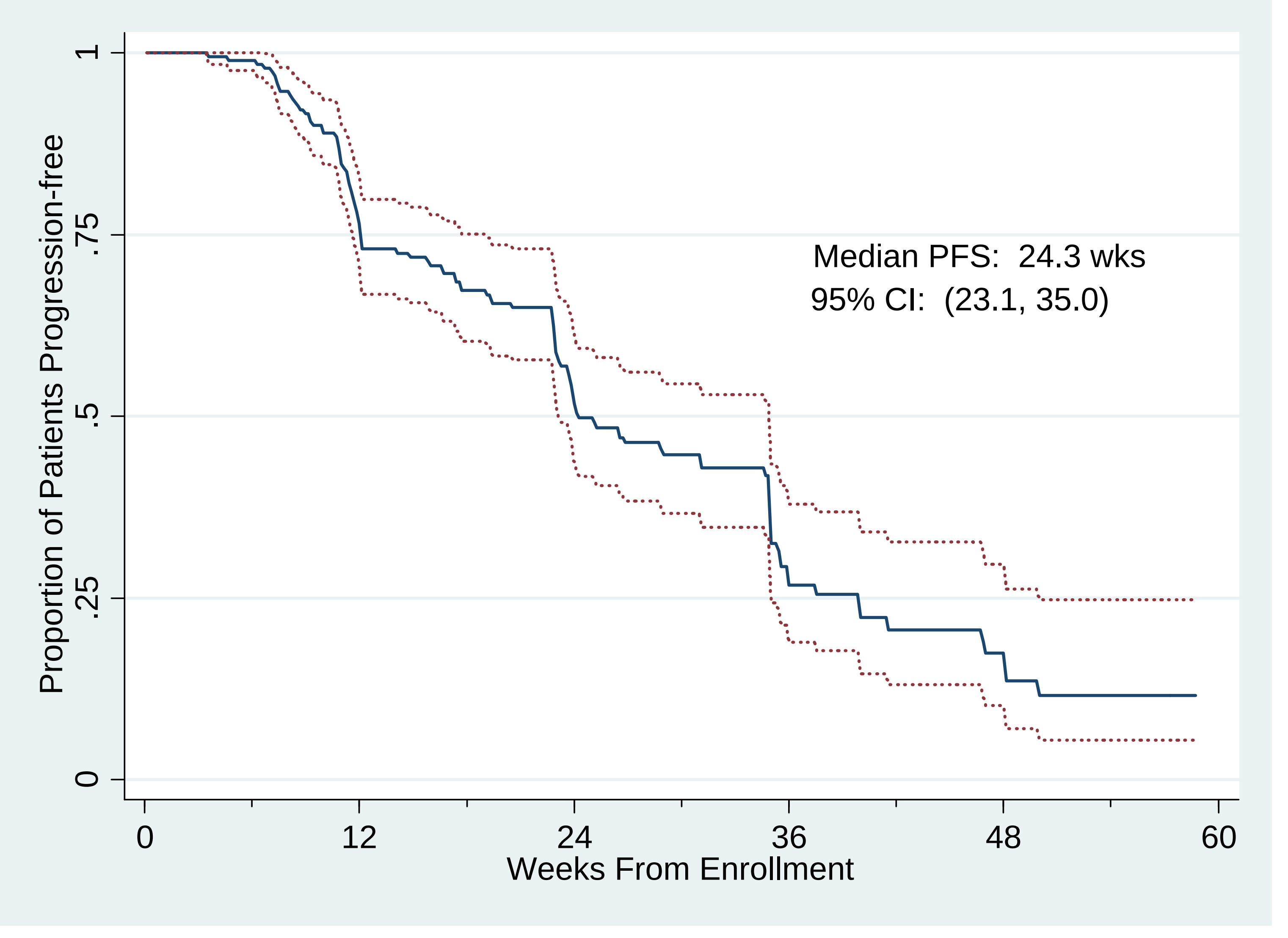
6 Continued on sorafenib despite SD, PD

65 SD R:
- Sorafenib (n=32)
- Placebo (n=35)

PFS in sorafenib and placebo arms, measured from time of randomization



Estimated PFS for sorafenib, measured from the date of entry into the trial



Summary

• The primary focus of the RDT is on the randomized comparison.

• Following this analysis, interest may turn to estimating progression-free survival in the population of all treated patients measured from the time of initial entry into the trial.

• This estimate, together with historical control data, would be useful in planning a follow-on phase III trial in an all-comers trial.

• Such an estimate and its precision can be obtained by piecing together information from the two phases of the RDT trial.

Thank You!