The use of Bayesian designs for trials in rare cancers: application to the LINES trial

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Background

Phase II trial of Linsitinib in patients with relapsed and/or refractory Ewing's Sarcoma

Ewing's Sarcoma

- Prevalence: Two patients per million per year
- Population: Childhood cancer, with average age 15 at diagnosis
- Five year overall survival rate: 60%

Relapsed/refractory setting

- Prevalence: 0.6 patients per million per year
- Five year overall survival rate: less than 10%

Linsitinib

- One of a number of IGF inhibitors to be tested in Ewing's patients
- Dual inhibitor blocking the IGF-1 and IGF-1R cell level pathways
- Extensive phase I testing performed in a general cancer setting
- Failed Phase II and III trials in a number of more common cancers

Main Problem

- Very rare setting (target recruitment is 30 patients per year)
- Known toxicity profile is not Ewing's sarcoma specific

Trial design constraints

- Aim to recruit around 40 patients in 18 months
- Single arm trial
- Two co-primary endpoints; response and toxicity
- Frequent interim analyses
- $p_0^R = 0.2, p_1^R = 0.35, p_0^T = 0.3, p_1^T = 0.1$

Possible Designs

- Frequentist Bryant and Day two stage design
- Bayesian posterior probability design
- Bayesian posterior predictive design
- Bayesian decision theory design
- Hybrid designs

Bryant and Day's two stage design (Bryant and Day 1995)

This is an extension of Simon's two stage design to incorporate two endpoints.
Using alpha=0.1 and power=0.8 the designs are:

Design	Sample size at analysis
Single stage	44
Bryant and Day (optimal)	20, 50
Bryant and Day (minmax)	24, 41

Bayesian approach

$$\text{Prior} * \text{Data} \propto \text{Posterior}$$

- Both endpoints are Binomial
- Uses the conjugate Beta prior
- Chosen a non-informative Beta prior, Beta(1,1)

Posterior probability

Probabilistic summary of the posterior distribution

$$\mathbb{P}(R > p_0^R | \text{data}, \text{prior})$$
$$\mathbb{P}(R < p_1^R | \text{data}, \text{prior})$$

Bayesian sample size (Whitehead et al. 2008)

Whitehead et al. proposed imposing the following restrictions on the posterior probability of the trial

Efficacy: $\mathbb{P}(R > p_0^R | X = x_n - 1) > \eta$

Futility: $\mathbb{P}(R < p_1^R | X = x_n) > \zeta$

The smallest Bayesian sample size is the smallest n such that there exists x_n which satisfies the above inequalities

Frequentist sample size

Minimise n such that there exists x_n satisfying:

$$\mathbb{P}(X \geq x_n | R = p_1^R) > \text{power}$$
$$\mathbb{P}(X \geq x_n | R = p_0^R) < \alpha$$

Bayesian sample size

Minimise n such that there exists x_n satisfying:

$$\mathbb{P}(R < p_1^R | X = x_n) > \zeta$$
$$\mathbb{P}(R > p_0^R | X = x_n - 1) > \eta$$

Initial design

After the first 10 patients and for every cohort of five:

- If $\mathbb{P}(T > 0.3 | \text{prior}, \text{data}) > 0.8$, then recommend stopping for toxicity.
- If $\mathbb{P}(R < 0.2 | \text{prior}, \text{data}) > 0.8$, then recommend stopping for futility.

After the first 20 patients and for every cohort of five:

- If $\mathbb{P}(R > 0.35 | \text{prior}, \text{data}) > 0.9$, then recommend stopping for efficacy.

After closing the trial with 40 patients:

- If $\mathbb{P}(R > 0.35 | \text{prior}, \text{data}) > 0.5$, then recommend further research.

Initial design

Stopping rules	T=0.3 R=0.2	T=0.1 R=0.2	T=0.3 R=0.35	T=0.1 R=0.35
Probability of concluding efficacy	0.012	0.020	0.339	0.559
Probability of stopping early	0.598	0.309	0.555	0.236
Expected number of patients recruited	25.6	32.8	27.7	35.9

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Modified design

After the first 10 patients and for every cohort of five:

- If $\mathbb{P}(T > 0.1 | \text{prior}, \text{data}) > 0.95$, then recommend stopping for toxicity.
- If $\mathbb{P}(R < 0.35 | \text{prior}, \text{data}) > 0.95$, then recommend stopping for futility.

After the first 20 patients and for every cohort of five:

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After closing the trial with 40 patients:

- If $\mathbb{P}(R > 0.2 | \text{prior}, \text{data}) > 0.9$, then recommend further research.

Modified design

Stopping rules	T=0.3 R=0.2	T=0.1 R=0.2	T=0.3 R=0.35	T=0.1 R=0.35
Probability of concluding efficacy	0.018	0.121	0.115	0.717
Probability of stopping early	0.994	0.854	0.995	0.895
Expected number of patients recruited	13.1	22.1	13.6	23.0

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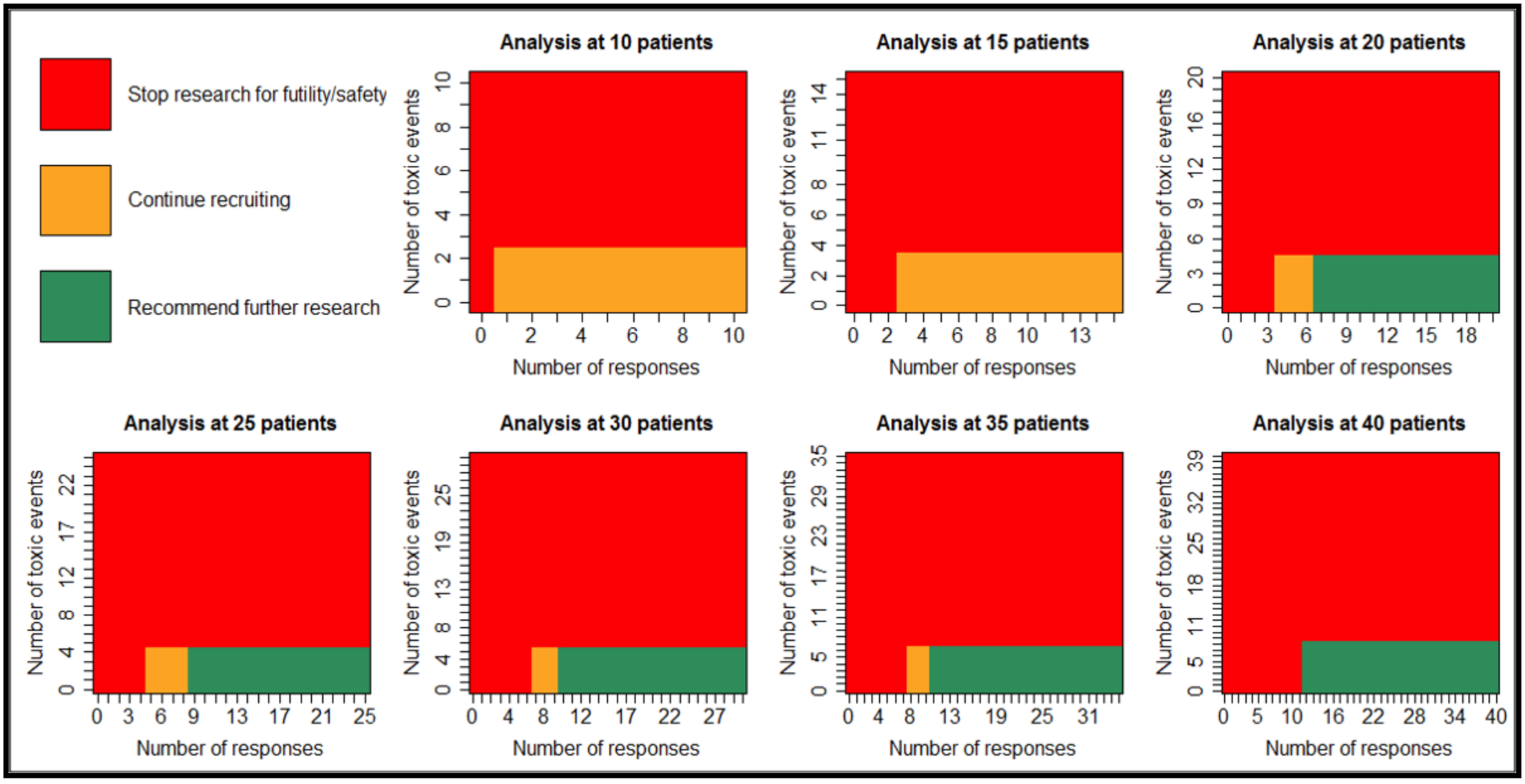
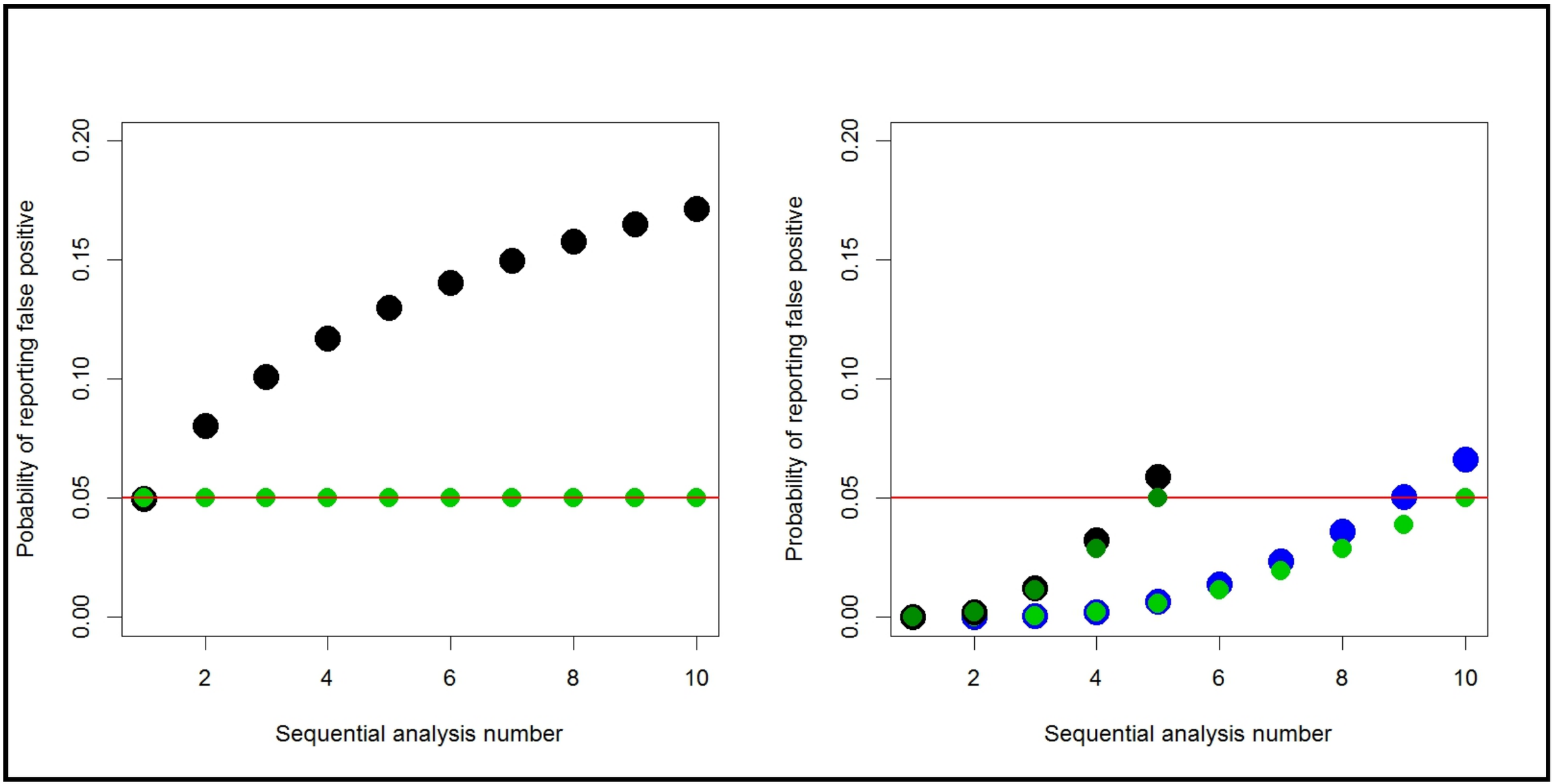

Stop research for futility/safety
Continue recruiting
Recommend further research
Analysis at 10 patients
Analysis at 15 patients
Analysis at 20 patients
Analysis at 25 patients
Analysis at 30 patients
Analysis at 35 patients
Analysis at 40 patients
Number of toxic events
Number of responses

Hybrid Posterior Probability Approach

Proposal

Adjust the levels of the posterior probabilities (η and ζ) using a Lan-DeMets (1995) style alpha spending function

Motivation for alpha spending



Hybrid Posterior Probability Approach

$$t = \frac{\text{Current information}}{\text{Total information}} = \frac{n_{current}}{n_{maximum}}$$

O'Brien-Fleming (1979) alpha spending function: $f(t, \alpha) = 2 - 2\Phi\left(\frac{\alpha/2)}{\sqrt{t}}\right)$

$$\eta^R_{\alpha^R}(t) = 1 - f(t, \alpha^R)$$
$$\zeta^R_{\alpha^R}(t) = 1 - f(t, \alpha^R)$$

Design	Sample size at each analysis	Frequentist properties			
		Type I error	Type II error	Expected sample size H0	Expected sample size H1
Single stage	44	0.1526	0.1161	44	44
Unadjusted	11, 17, 24, 30, 37, 44	0.1864	0.3393	16.39	15.63
Partial adjustment	11, 17, 24, 30, 37, 44	0.1296	0.2926	22.57	25.58
Lan-DeMets adjustment	11, 17, 24, 30, 37, 44	0.1432	0.1996	30.21	30.43
Unadjusted	Continuous	0.171	0.5489	6.86	6.55
Partial adjustment	Continuous	0.0982	0.4702	14.52	17.41
Lan-DeMets adjustment	Continuous	0.1413	0.2199	26.16	25.49

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Why is the trial Bayesian

- No prior information so no added value
- Any future trial after LINES would include the data from LINES in the prior

Potential further research

1. No literature on frequentist Lan-DeMets for multiple endpoints
2. Combining the endpoints in the Bayesian posterior probability based approach

R package

All the sample size programs are available from CRAN in the EurosarcBayes package.

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