

Benefit - Risk Analysis for Oncology Clinical Trials (PP14)



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Background

The conventional analysis of safety and efficacy of clinical trials provide information on risks and benefits in isolation. In the opinion of the authors, this hampers a comprehensive assessment of benefit - risk and leads to underestimate or overestimate the treatment benefit for patients with varying risks (Figure 1). Our focus is on oncology trials where risk-benefit assessment is further complicated by co-morbidities and co-medications.

Regulatory authorities evaluate the risks and benefits of any new drug therapy during the new drug-approval process, quantitative benefit - risk (B-R) assessment is not typically performed, nor is it presented in a consistent and integrated framework when it is used (Guo *et al.*, 2010).

This poster presents how a risk incorporated efficacy model will be used to identify patient categories that have got a net benefit or harm from the treatment. The methodologies presented can be applied on both time to event and binary outcomes that are commonly found in oncology trials.

Classification of patients based on benefit - risk from the therapy

Risk	Benefit	
	Low	High
Low	Low risk, low benefit	Low risk, high benefit
High	High risk, low benefit	High risk, high benefit

Figure 1

1 Identify the common risks

Identify common oncology risks up front for a study to be used for analysis.

Risk of cancer treatment depends on different factors such as patient's demography, medical history, chosen therapy, co-morbidities and co-medications etc.

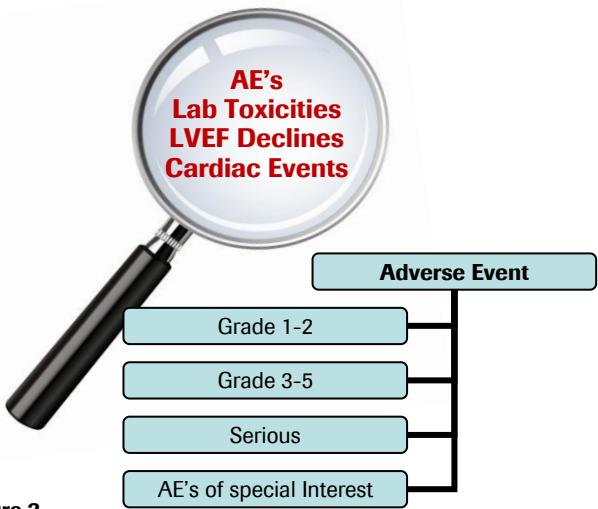


Figure 2

Each risk can be broken down into sub-categories depending on type of risk (Figure 2).

2 Create a Risk Index Scoring System



Figure 3
Identified risks will be ranked and scored (Figure 3) based on the clinical and regulatory judgment. The score is directly proportional to the severity of the risk.

Safety Risk	Index Score
No Adverse Event	0
Adverse Event (Grade 1-2)	1
Adverse Event (Grade 3-5)	5
Lab Toxicity Grade 3-5	15
Serious Adverse Event	20
LVEF Decline of between 10% - 15% from baseline with an absolute value of less than 50%	20
LVEF Decline of more than 15% from baseline with an absolute value of less than 50%	30
Serious Cardiac Adverse Event	30

Table 1

The perceived risk in most cases is a cumulative effect of the above factors (Table 1). The cumulative score will enable us to categorise patients as either High/Low risk.

3 Risk Classification

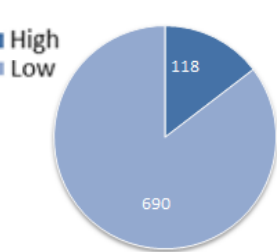


Figure 4

A cut-off value is determined up front based on the Index Scoring System. Any value above this cut-off, patient assigned High risk, conversely Low risk if below.

In the current example (Figure 4), 25th percentile was used as the cut off.

4 Combining Risk categories with Benefits

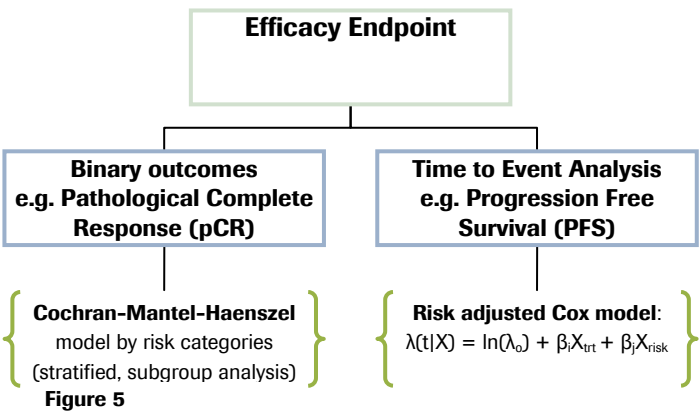


Figure 5

5 B-R analysis using Time to Event Endpoint

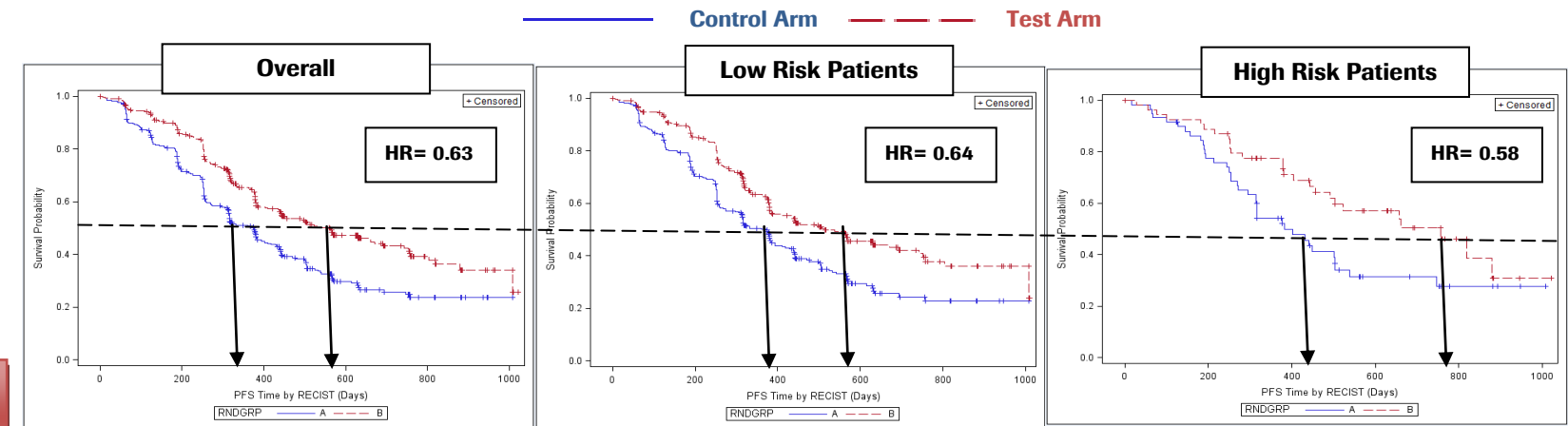


Figure 6a

Figure 6b

Figure 6c

6 Patient Classification based on B-R Analysis

Test Arm	Risk	Benefit*	
		Low	High
Low	N	183	164
	Risk %	52.7%	47.3%
	Benefit %	91%	81.6%
High	N	18	37
	Risk %	32.7%	67.3%
	Benefit %	9%	18.4%

Table 2a

* Benefit is measured as PFS beyond median PFS of the control arm (376 Days)

Control Arm	Risk	Benefit*	
		Low	High
Low	N	216	127
	Risk %	63%	37%
	Benefit %	84.7%	84.1%
High	N	39	24
	Risk %	61.9%	38.1%
	Benefit %	15.3%	15.9%

Table 2b

7 Results

The Kaplan-Meier (K-M) plots (Figure 6) shows the benefit measured as median PFS time between test arm and control. The risk adjusted Cox model (Figure 5), shows there is a discernable difference between the low and high risk groups in terms of Hazard Ratio (shown in Figure 6). Low risk patients have relatively low benefits while high risk patients have relatively higher benefits in terms of HR.

A PFS advantage for the test arm (HR=0.63) has been demonstrated for the overall study population (Figure 6a). The majority of the patients (690/808) showed low risks and the benefit was comparable to the overall population (Figure 6b). when the benefit is weighed against the risks, the high risk subgroup showed a substantially greater benefit (HR=0.58, n=118/808) striking a balance between risks and benefits (Figure 6c).

Only 18% of the patients in the Test Arm, whose PFS is beyond the median PFS of the Control Arm (High Benefit) had a High Risk while patients with Low Benefit in terms of PFS duration only 9% were exposed to High Risks (Table 2a).

Acknowledgements

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SUMMARY

- Integrated analysis of benefit (efficacy) and risk (safety) of cancer drugs is challenging due to complexities in the disease biology and associated treatment.
- The risk and benefit indices depends on the disease setting and the drug tested and need to be pre-specified in the Statistical Analysis Plan.
- Clinical and regulatory input is vital to ensure relevant safety and efficacy parameters are included in the risk and benefit indices and they are independent of each other.
- The proposed B-R analysis provides useful information in an efficient manner to the stakeholders of the test drug to make more informed decisions compared to information provided by isolated safety and efficacy summaries.