PREDICT: a new East© module for Predicting the Future Course of a Trial

Cyrus Mehta

25 July 2014

Role of PREDICT within East

1. PREDICT is primarily a tool for use during interim monitoring although it can also be used at design time if preliminary data are available
2. It predicts the future course of the trial by utilizing current data as the basis for simulating future trials
3. It consists of two tools: PIPs and EnEv
    1. PIPs creates an intuitive graphical display of possible future outcomes and helps DMCs to make decisions regarding early termination for futility or efficacy
    2. EnEv utilizes site-level data on enrollment and patient level data on outcomes to produce accurate forecasts of future enrollment and event rates

PIPs: Predictive Interval Plots

- PIPs are a series of repeated confidence intervals generated by simulating the future course of the trial conditional on the current data
  - The intervals are sorted and stacked to provide an intuitive graphical display that facilitates early termination decisions
  - PIPs focus on **estimation** rather than **hypothesis testing,** thereby introducing clinical relevance into the decision making process

References:

(1) Li L, Evans SR, Uno H, Wei LJ. *Statistics in Biopharmaceutical Research,* 2009, Vol 1, No 4.

(2) Evans SR, Li L, Wei LJ. *DIA Journal*, 2007, vol 41.

EnEv: Enrollment and Event Forecasting

- EnEv provides a unified framework for simulating patient and event arrivals over time
  - Patient arrivals are modelled at the site level as independent Poisson processes
  - Event arrivals are modelled at the patient level under the assumption of exponential survival, taking inputs from the patient arrivals model
  - As new data arrive, the Poisson and exponential survival model parameters are updated by Bayesian methods

References:

(1) Anisimov V, Fedorov V. *Statistics in Medicine*, 2007, Vol 26.

(2) Torgovitsky R. *Cytel Internal Technical Report* for Serono Reflex 27025 Study, 2009.

Outline of this Presentation

- Motivation for PREDICT
  - differentiation from other tools in East
- Two examples of use of PIPs
  - Example 1: early termination for futility
  - Example 2: early termination for futility
- One Example of use of EnEv
  - Use of initial enrollment plan at design stage
  - Use of updated enrollment plan and patient-level data at interim monitoring stage

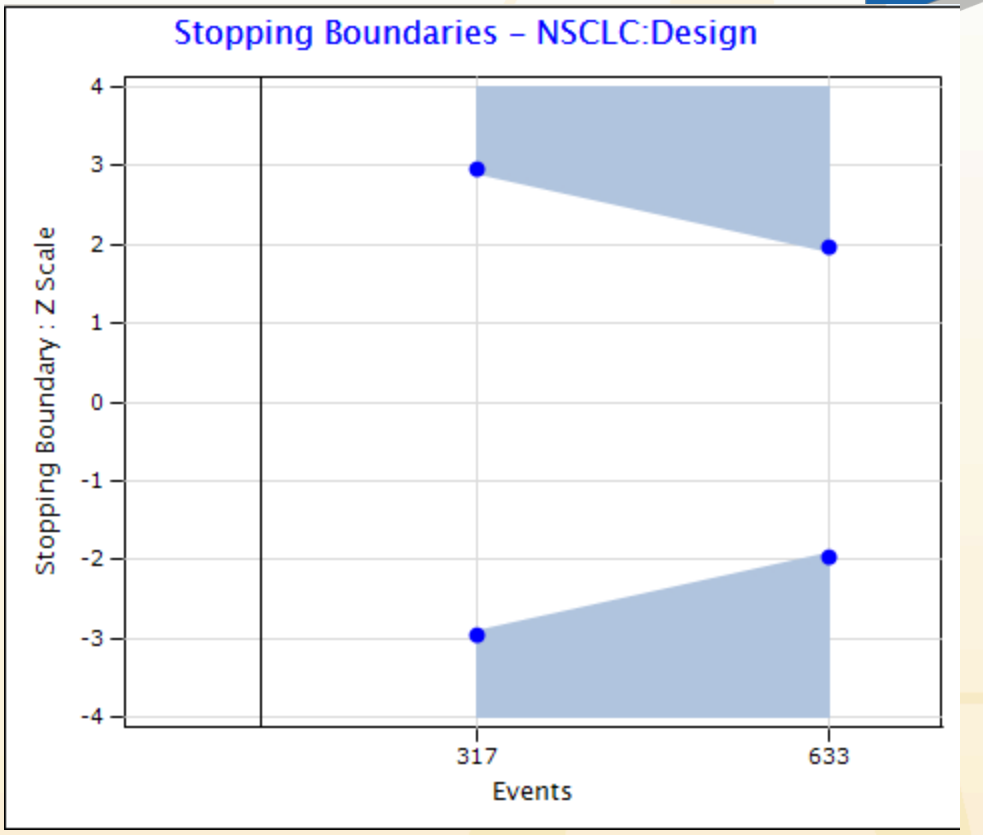
1. Use of PIPs for Futility Stopping

Design of a Non Small Cell Lung Cancer Clinical Trial

Design Parameter	Value
Primary Endpoint	OS
α	0.05
Power	80%
One Interim Analysis	O'Brien-Fleming spending fn
Median (Control Arm)	10 months
Median (Experimental Arm)	12.5 months
Hazard Ratio	0.8
Sample Size	888
Events	633
Plan to enroll for 18 months and follow for 12 more months	

Design Summary

	NSCLC:Design
Mnemonic	SU-2S-LRSD
Test Parameters	
Design Type	Superiority
No. of Looks	2
Test Type	2-Sided
Specified α	0.05
Power	0.8
Model Parameters	
Allocation Ratio (nt/nc)	1
Hazard Ratio (Alt.)	0.8
Var (Log HR)	Null
Boundary Parameters	
Spacing of Looks	Equal
Efficacy Boundary	LD (OF)
Accrual & Dropout Parameters	
Subjects are Followed	Until End of Study
No. of Accrual Periods	1
No. of Dropout Pieces	0
Sample Size	
Maximum	888
Expected Under H0	888
Expected Under H1	879
Events	
Maximum	633
Expected Under H0	632
Expected Under H1	581
Study Duration	
Maximum	30
Expected Under H0	27.9
Expected Under H1	27.8
Accrual Duration	
Maximum	18
Expected Under H0	18
Expected Under H1	17.8



This design has no futility boundary

Interim Analysis after 258 Events

TrtmntID	SRVMON	ArrivalTime	Status	Censor
2	1.4	0.033333333	1	1
2	1.4	0.066666667	1	1
2	13.2	0.066666667	1	1
2	3.3	0.2	1	1
2	5.3	0.533333333	-1	0
1	4	0.866666667	1	1

Summary of Observed Data:

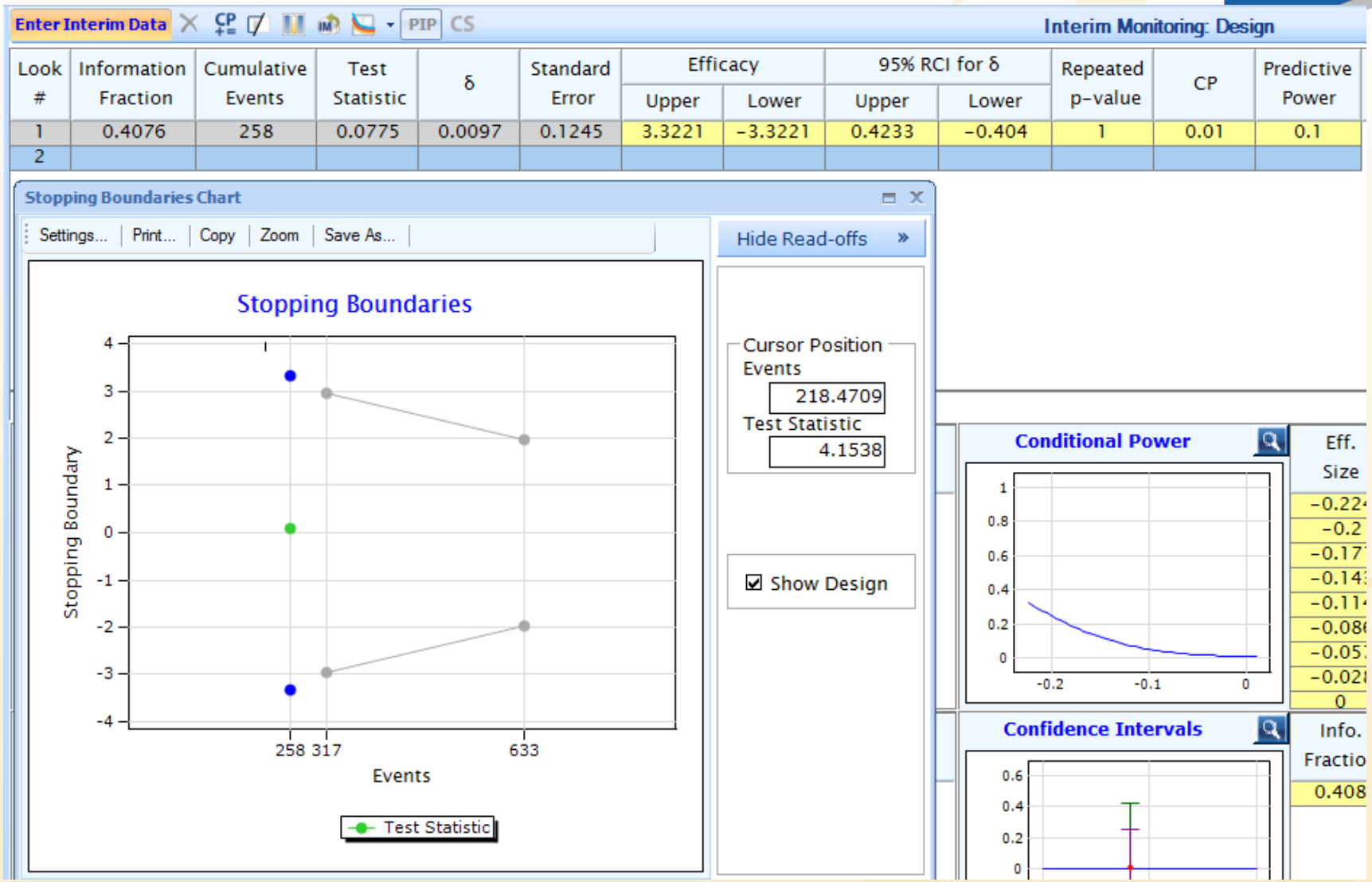
Treatment ID	No.of Subjects	Events		Censored	
		Count	%	Count	%
1	395	126	31.899	269	68.101
2	403	132	32.754	271	67.246
Total	798	258	32.331	540	67.669

Parameter Estimates:

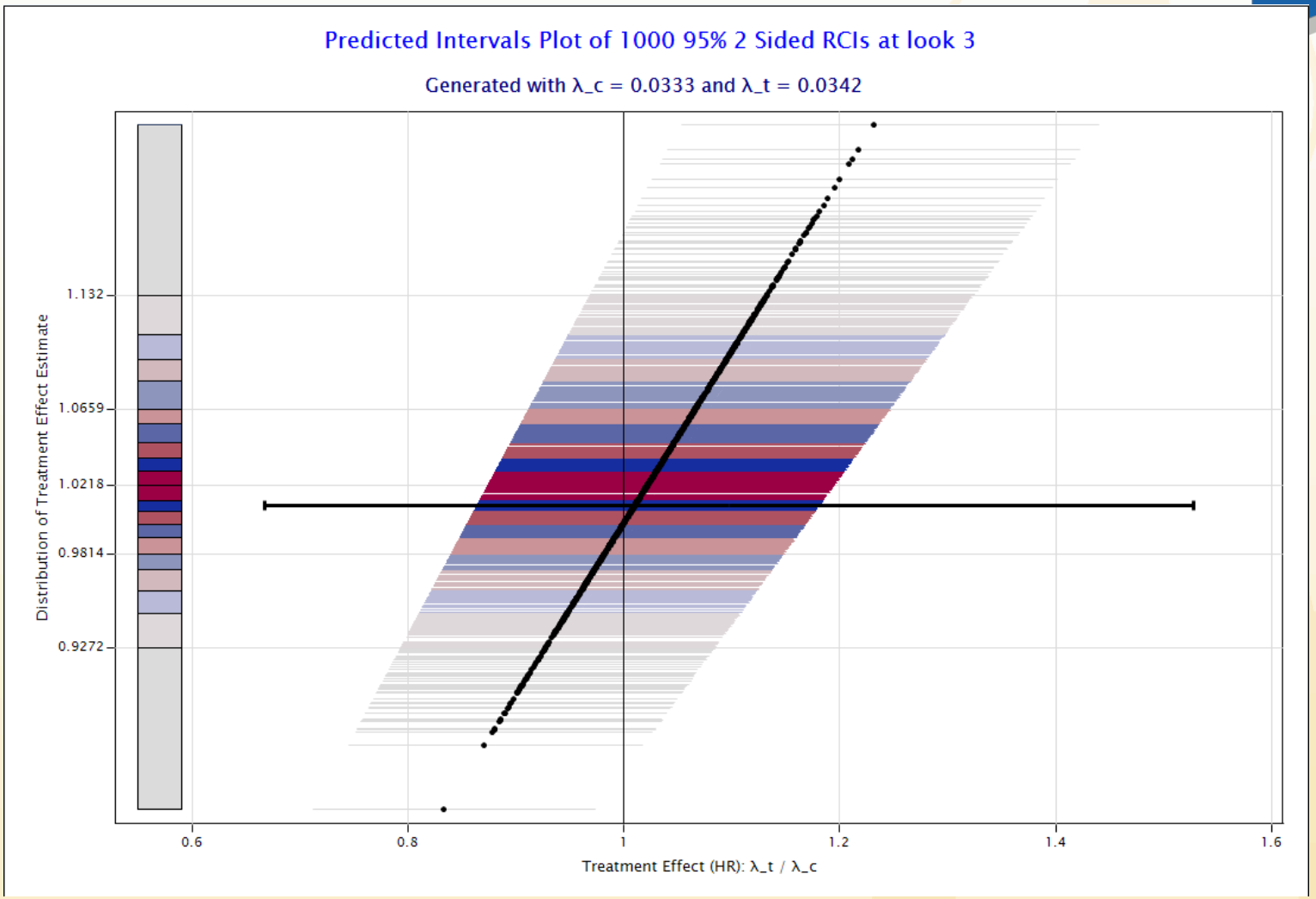
Hazard Ratio (HR)	95% Confidence Interval(2-Sided)	
	Lower Limit	Upper Limit
1.01	0.791	1.289

Interim analysis occurred ahead of schedule due to rapid enrollment

Should we stop for futility?

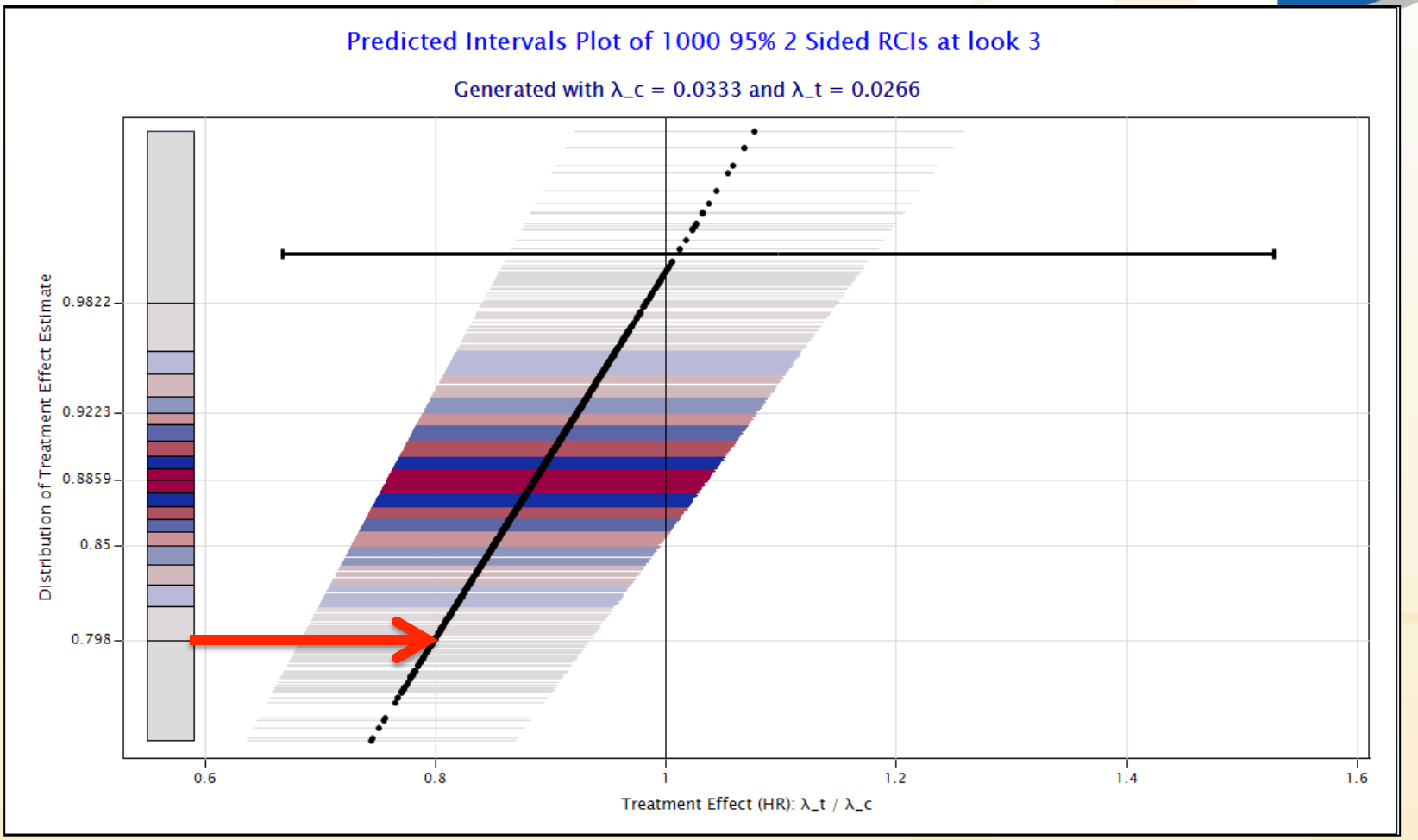


PIP at 258 events under HR=1.01



Only 1 out of 1000 simulations had their upper confidence bound below HR=1

PIP at 258 Events under HR=0.8



Even if the true HR=0.8, the chance of success is only 29%. Moreover only 5% of future simulations show a point estimate for HR that is smaller than 0.798.

The trial was terminated for futility

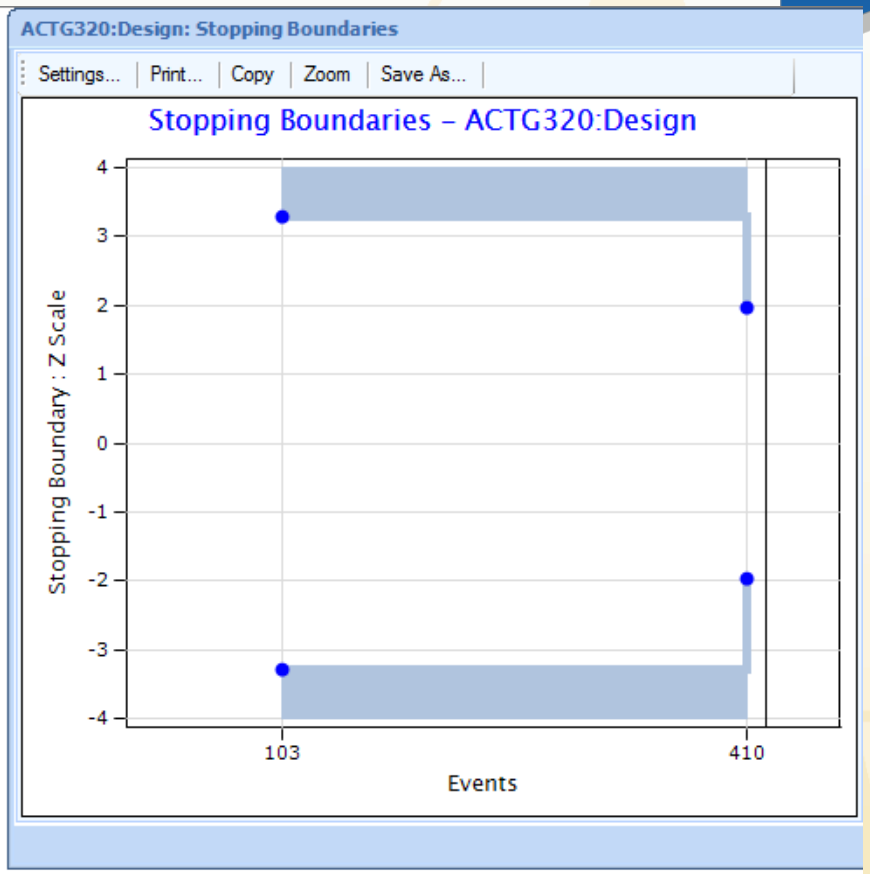
Use of PIPs for Efficacy Stopping

ACTG A320: AZT+Epivir vs AZT+Epivir+Crixivan

Design Parameter	Value
Primary Endpoint	Time to AIDS or Death
a	0.05
Power	93%
1 interim look at 25% information	Haybittle-Peto; p=0.001
Event Free Survival (Control)	67% at 18 months
Event Free Survival (Experimental)	75.25% at 18 months
Hazard Ratio	0.71
Sample Size	1750
Events	410
Plan to enroll for 36 weeks and follow for 48 more weeks	

Design Summary

	ACTG320:Design
Mnemonic	SU-2S-LRSD
Test Parameters	
Design Type	Superiority
No. of Looks	2
Test Type	2-Sided
Specified α	0.05
Power	0.93
Model Parameters	
Allocation Ratio (nt/nc)	1
Hazard Ratio (Alt.)	0.71
Var (Log HR)	Null
Boundary Parameters	
Spacing of Looks	Unequal
Efficacy Boundary	HP
Accrual & Dropout Parameters	
Subjects are Followed	Until End of Study
No. of Accrual Periods	1
No. of Dropout Pieces	0
Sample Size	
Maximum	1750
Expected Under H0	1750
Expected Under H1	1741
Events	
Maximum	410
Expected Under H0	410
Expected Under H1	392
Study Duration	
Maximum	84
Expected Under H0	74.2
Expected Under H1	80.9
Accrual Duration	
Maximum	36
Expected Under H0	36
Expected Under H1	35.8



Interim Analysis after 96 Events

patientnumb	TreatmentID	ArrivalTime	Status	Censor	WeeksOnStu
90905	0	1	0	0	55.1428571
90907	1	1	0	0	55.1428571
90181	0	3	0	0	54.8571429
90908	0	3	1	1	16.2857143
90909	1	3	0	0	54.8571429
211915	1	10	0	0	53.8571429
111321	0	11	0	0	53.7142857
121123	0	11	0	0	53.7142857
90910	1	12	1	1	2.57142857

Summary of Observed Data:

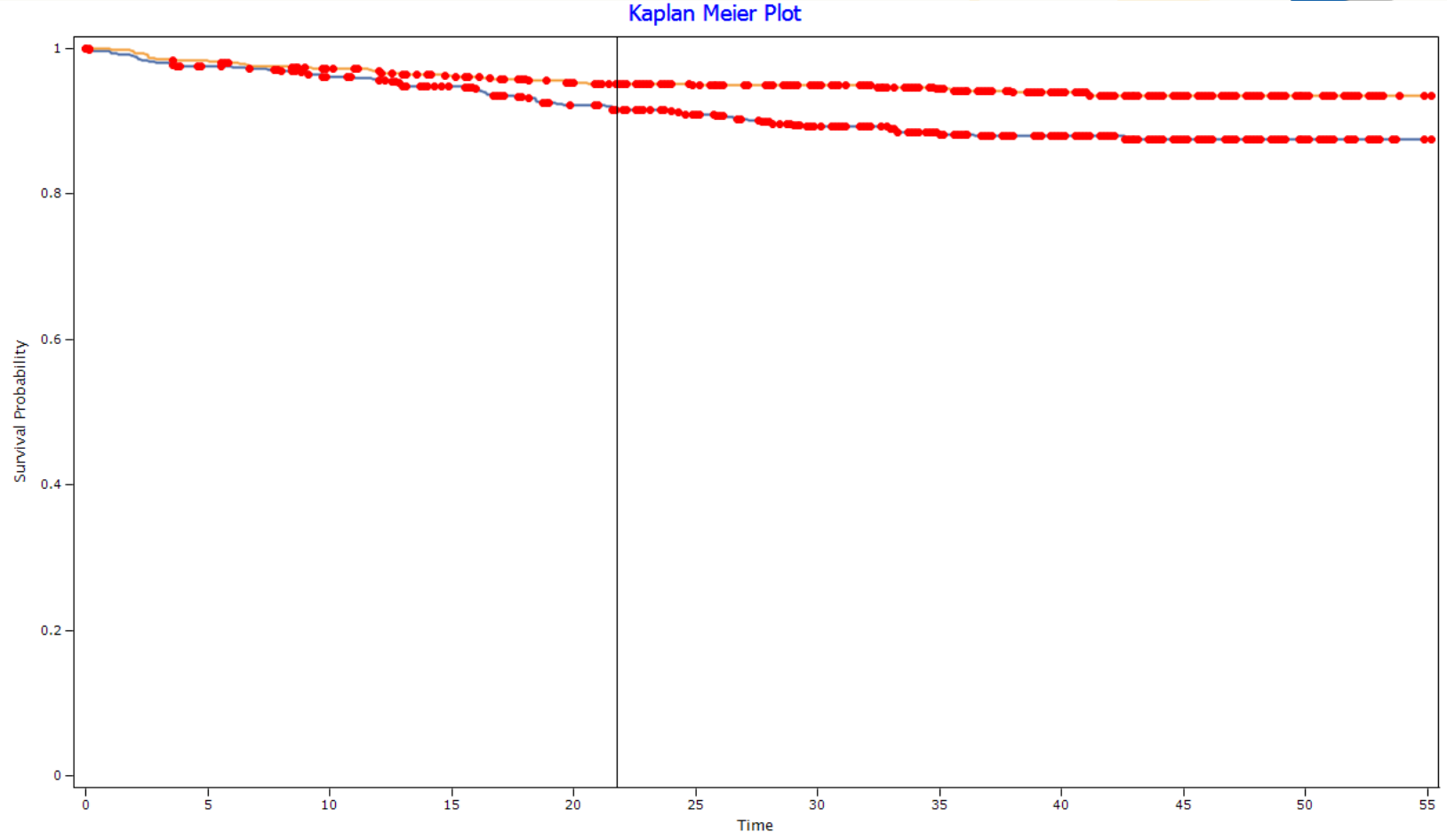
Treatment ID	No.of Subjects	Events		Censored	
		Count	%	Count	%
0	578	63	10.9	515	89.1
1	578	33	5.71	545	94.29
Total	1156	96	8.3	1060	91.7

Parameter Estimates:

Hazard Ratio (HR)	95% Confidence Interval(2-Sided)	
	Lower Limit	Upper Limit
0.5052	0.33	0.77

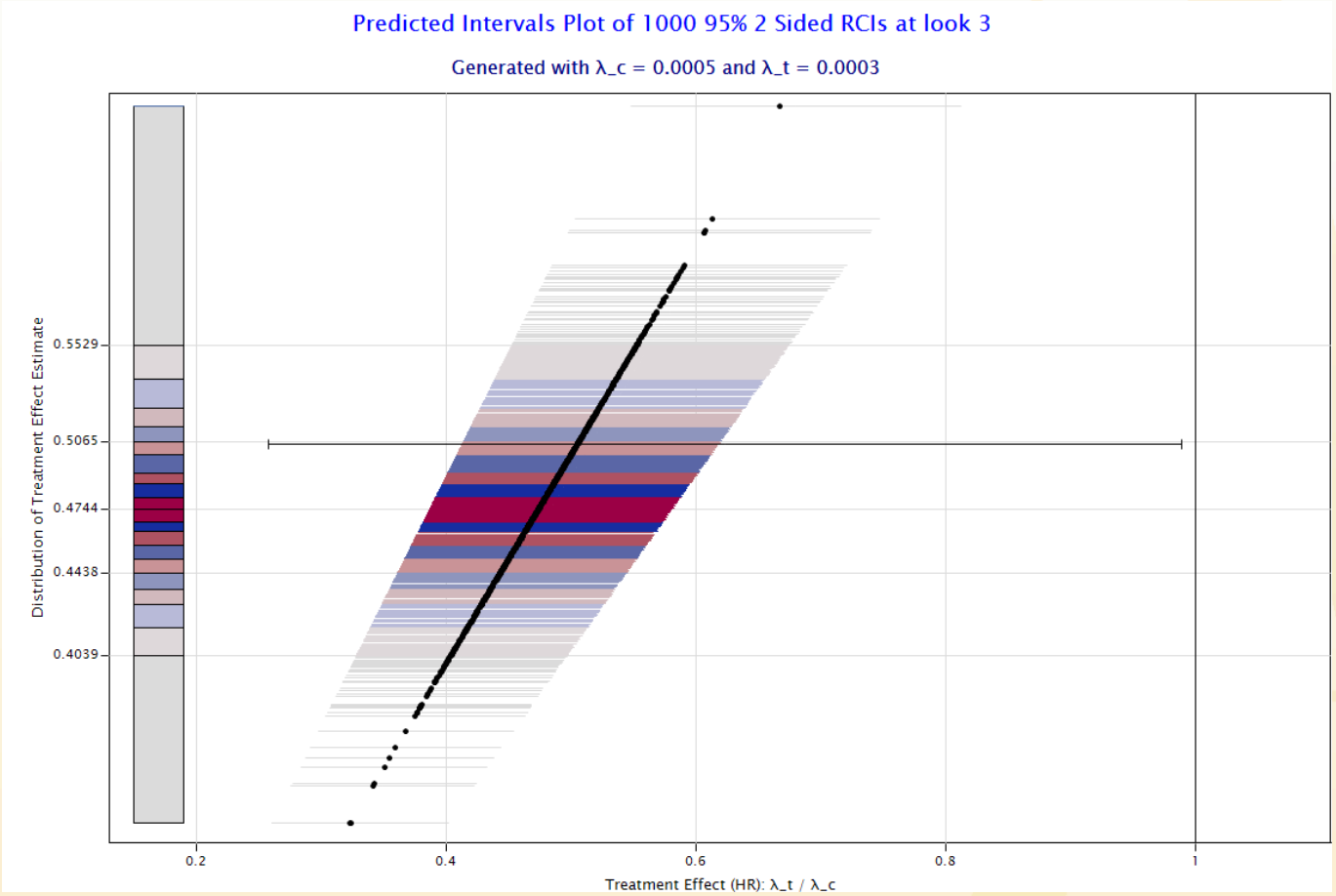
At this interim look the p-value was 0.0008. Thus the HP boundary was **barely** crossed

Kaplan-Meier Plot of Data



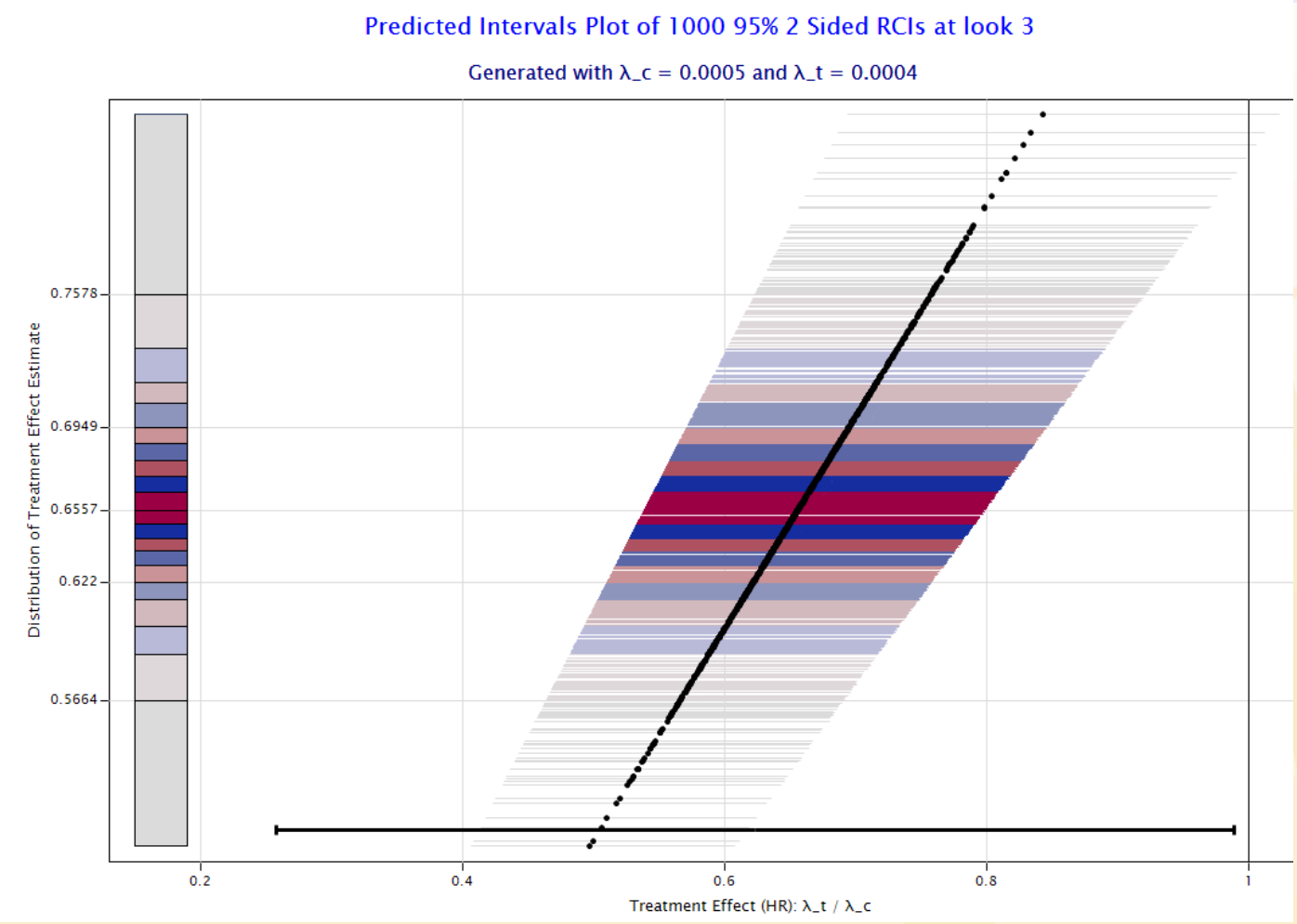
Can the trial be terminated with these early results based on just 25% of the information?

PIP with the Observed Data (HR= 0.5052)



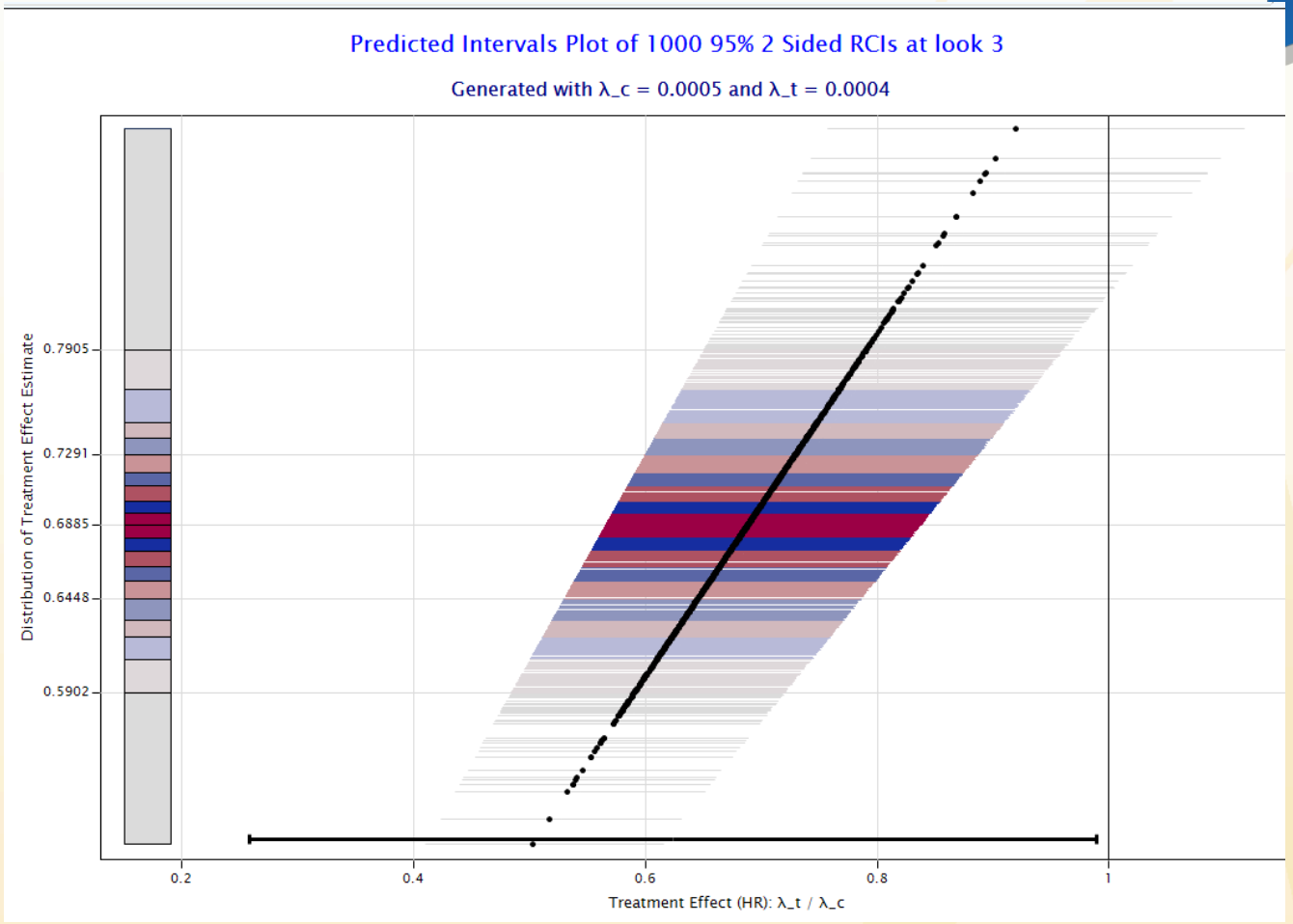
Although the observed upper bound was barely below HR=1, the future intervals are much narrower and 100% of their upper bounds are below HR=1

PIP with Design Specified HR=0.71



Only 3/1000 future simulations had upper bounds exceeding HR=1
Also 95% of point estimates were less than 0.76; still clinically meaningful

Sensitivity Analysis: PIP with HR=0.75



Even if we assume HR=0.75 (on the borderline of clinical significance), only 112/1000 future intervals fail to be below HR=1. **Thus DMC recommended trial termination.**

3. Enrollment and Event Forecasting

Design Parameters for the OncoX Clinical Trial

Design Parameter	Value
Primary Endpoint	OS
α	0.025 (one sided)
Power	90%
One Interim Analysis	$\gamma(-5)$ efficacy and futility boundaries
Median (Control Arm)	5 months
Median (Experimental Arm)	7 months
Hazard Ratio	0.71
Sample Size	460
Events	374
Plan to enroll for 24 months and follow for 6 more months	

Design Details

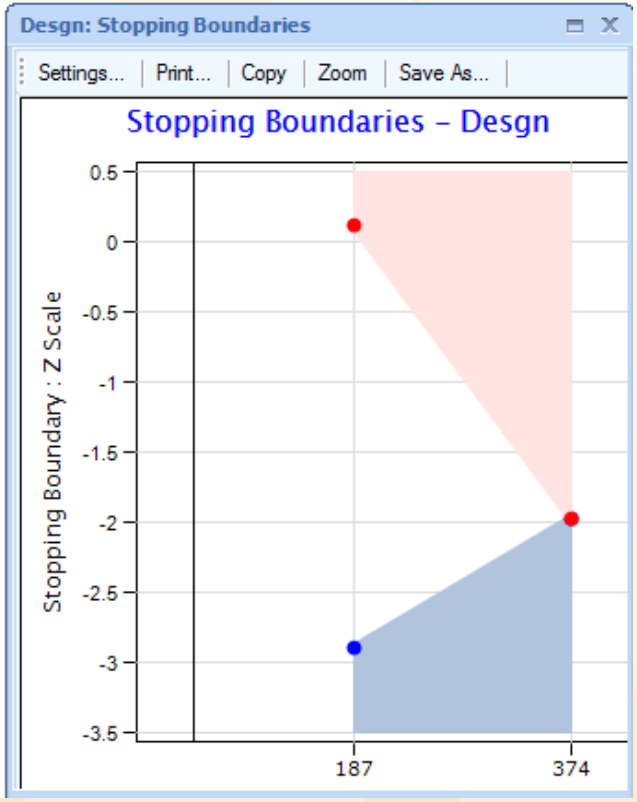
Test Parameters	
Design ID	Desgn
Design Type	Superiority
Number of Looks	2
Test Type	1-Sided
Specified α	0.025
Attained α	0.025
Power	0.909
Model Parameters	
HR = λ_t/λ_c	
Under H0	1
Under H1	0.71
Ratio of Medians:	1.408
Var (Log HR)	Null
Allocation Ratio (n_t/n_c)	1
Boundary Parameters	
Spacing of Looks	Equal
Efficacy Boundary	Gm (-5)
Futility Boundary	Gm (-5) (NB)
Accrual/Dropout Parameters	
Accrual Duration	24
Max Study Duration	30

Sample Size Information

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum	230	230	460
Expected H1	211.017	211.017	422.034
Expected H0	196.727	196.727	393.454
Events (s)			
Maximum	196	178	374
Expected H1	177.843	155.859	318.467
Expected H0	147.891	147.891	289.176
Dropouts (d)			
Maximum	4	7	11
Expected H1	3.703	5.812	9.515
Expected H0	3.639	4.093	7.732
Maximum Information (I):93.5			

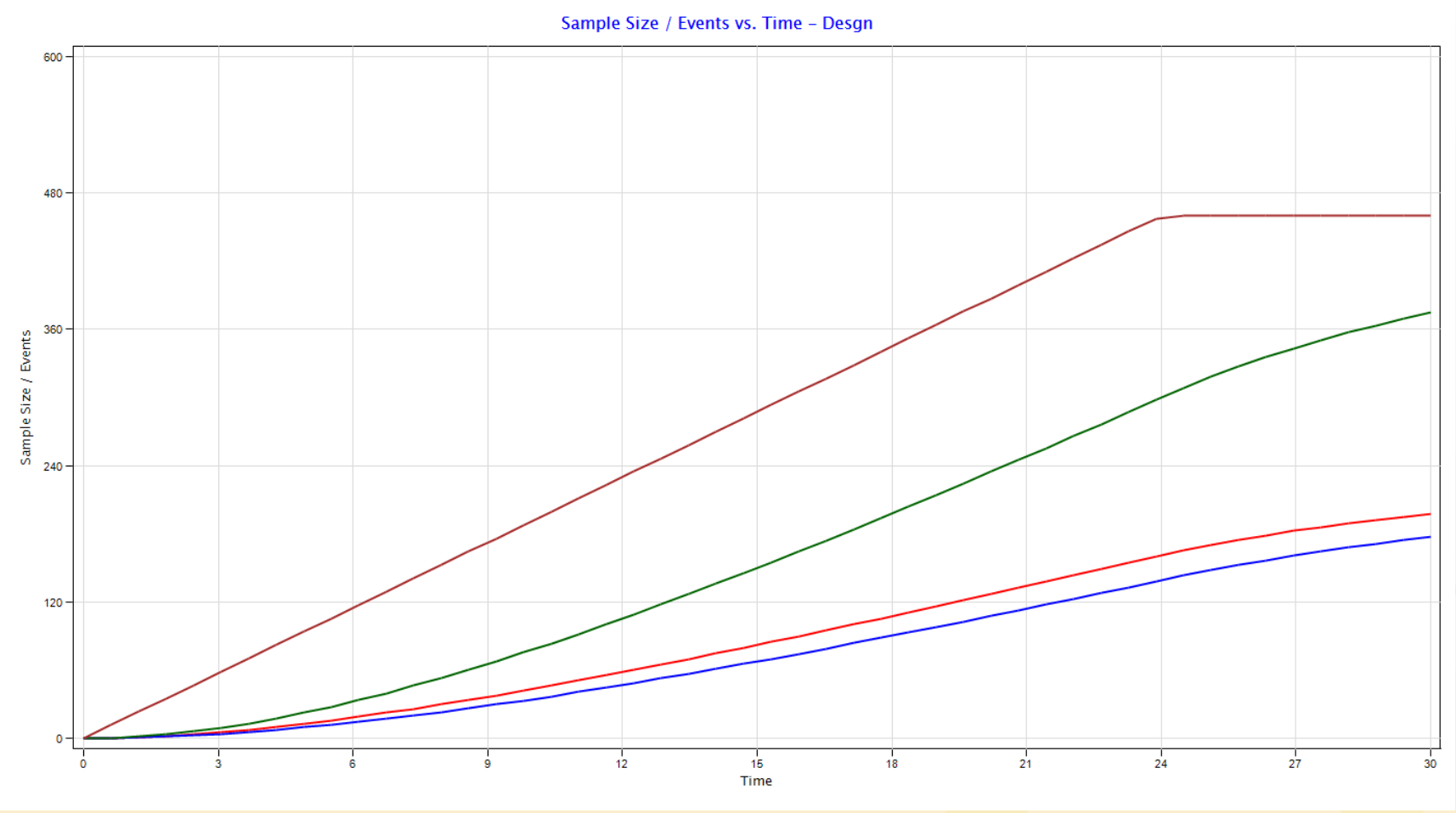
Accrual and Study Duration

	Accrual Duration	Study Duration
Maximum	24	29.934
Expected H1	22.019	26.191



This design will enroll 460 patients and wait for the arrival of 374 events

The e-Chart (ignores site level data)



Assumes constant enrollment for 24 months and 6 more months for follow-up

Initial Enrollment Plan

country, sites, earliest start, latest end, patient/site/month, cap

Country	Nsites	SIP_Start	SIP_End	EnrolRate	EnrolCap
Austria	4	3	6	0.3835	64
Belgium	6	5	6	0.3185	72
CZ	3	4	6	0.247	36
France	9	4	5	0.4485	168
Germany	10	4	5	0.3965	164
Hungary	4	6	8	0.1755	28
ITALY	7	5	7	0.2665	73
Poland	4	4	5	0.481	65
Spain	7	4	6	0.1755	47
UK	8	4	6	0.2795	92
Australia	11	4	6	0.299	181
NewZealand	4	5	6	0.2535	55
Canada	5	6	7	0.234	64
US	39	0	11	0.2535	544

Enter the Enrollment Plan in East

Sample Size: 460

Subjects are followed: Until End of Study

Accrual Model: Poisson

(•) Sites By Regions ( ) Sites

Import Enrollment Plan...

Number of Regions: 14

Piecewise Dropout Information

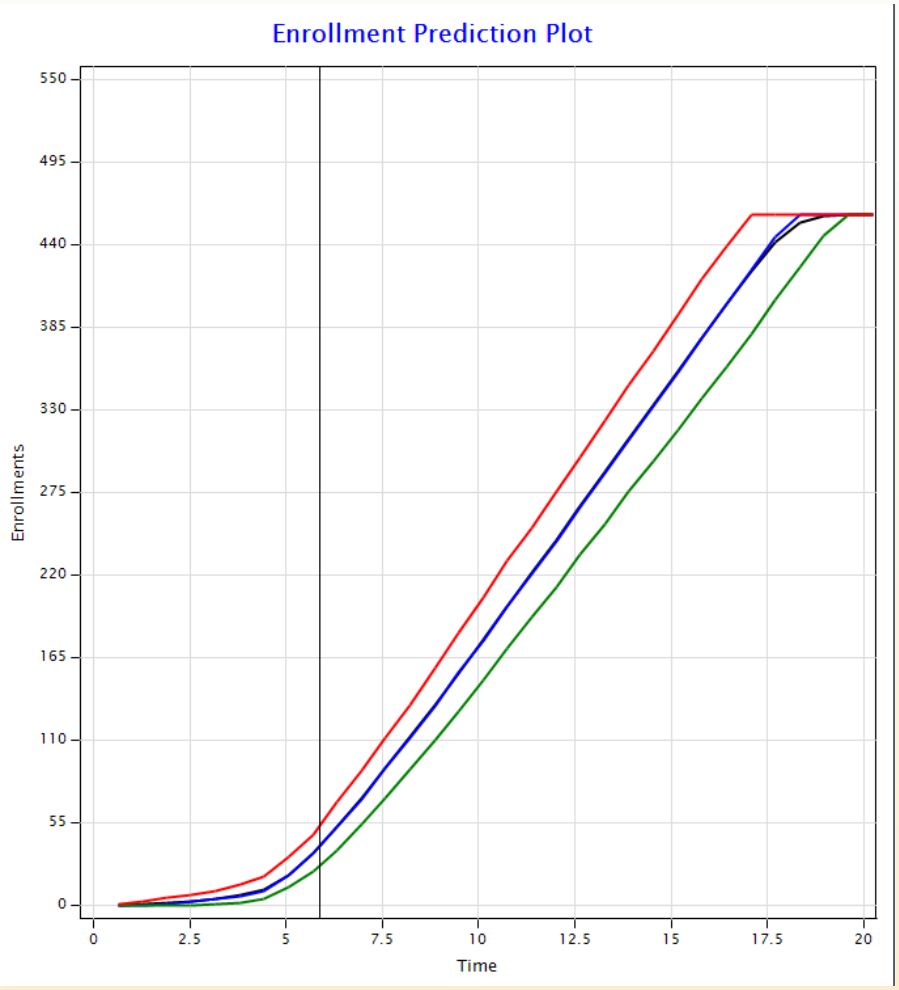
# of Pieces: 1 Input Method: Prob. of Dropout

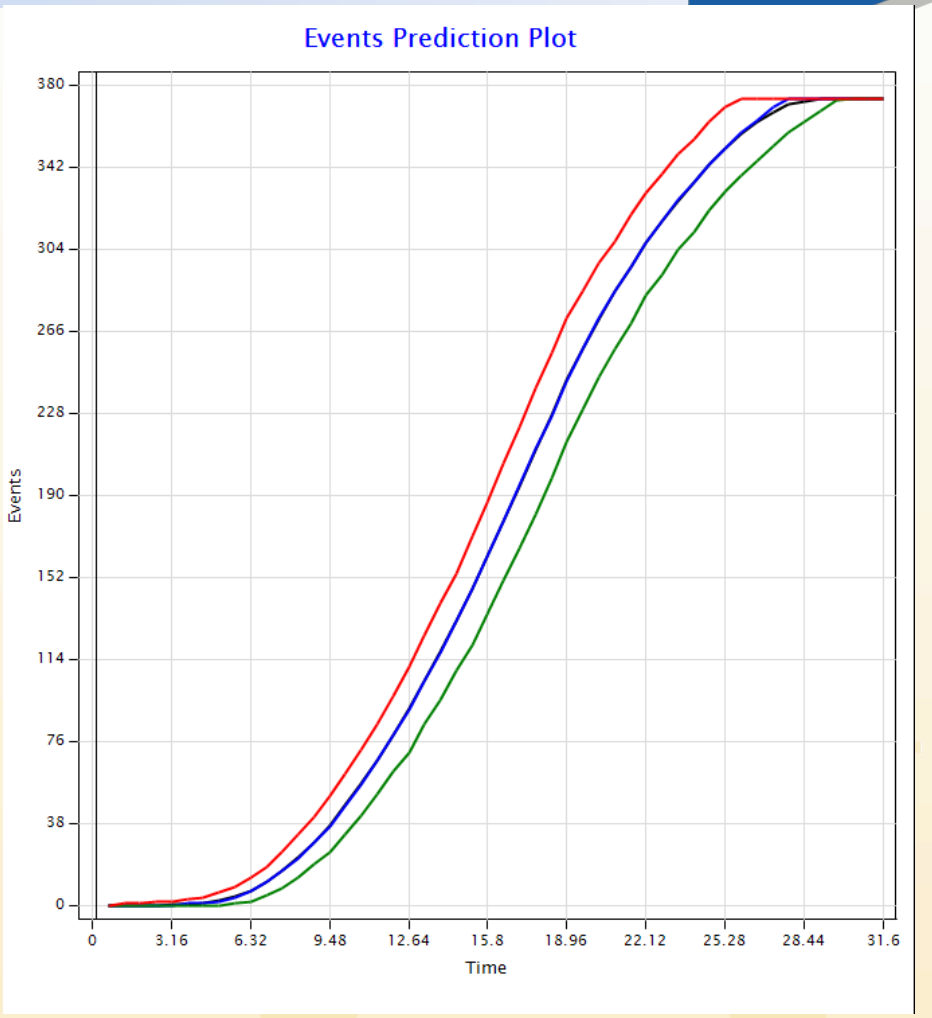
Period #	By Time	Prob. of Dropout (Control)	Prob. of Dropout (Treatment)
1	12.000	0.04	0.04

Note: Period 1 hazard rates apply after time 12.

Region ID	No. of Sites	Site Initiation Period		Accrual Rate /Site	Enrollment Cap
		Start	End		
Austria	4	3	6	0.384	64
Belgium	6	5	6	0.319	72
CZ	3	4	6	0.247	36
France	9	4	5	0.449	168
Germany	10	4	5	0.397	164
Hungary	4	6	8	0.176	28
ITALY	7	5	7	0.267	73

Enrollment and Event Output





Predicting: enrollment duration (17 to 19.5 mths); study duration (26 to 30 mths)

Data at the Interim Analysis (187 events)

InterimSubjectData.cydx

Country	Site_Id	ArrivalTime	TimeOnStudy	Status	Trtmt	Censor
United_States	103	0.493421053	20.2302632	0	0	0
United_States	103	1.08552632	8.32236842	1	1	1
United_States	108	1.5131579	6.74342105	1	0	1
United_States	108	1.64473684	3.75	1	1	1

Hazard Ratio Estimate

Parameter Estimates:

Hazard Ratio (HR)	95% Confidence Interval(2-Sided)	
	Lower Limit	Upper Limit
0.743	0.556	0.994

Enter into Interim Monitoring Worksheet

IM Interim Monitoring:OncoX:Desgn:Interim Monitoring

Edit Interim Data | PIP | CS | Interim Monitoring: Desgn

Look #	Information Fraction	Cumulative Events	Test Statistic	δ	Standard Error	Efficacy	Futility	88.421% RCI for δ	
								Upper	Lower
1	0.5	187	-2.031	-0.297	0.146	-2.895	0.121	0.126	-0.657
2									

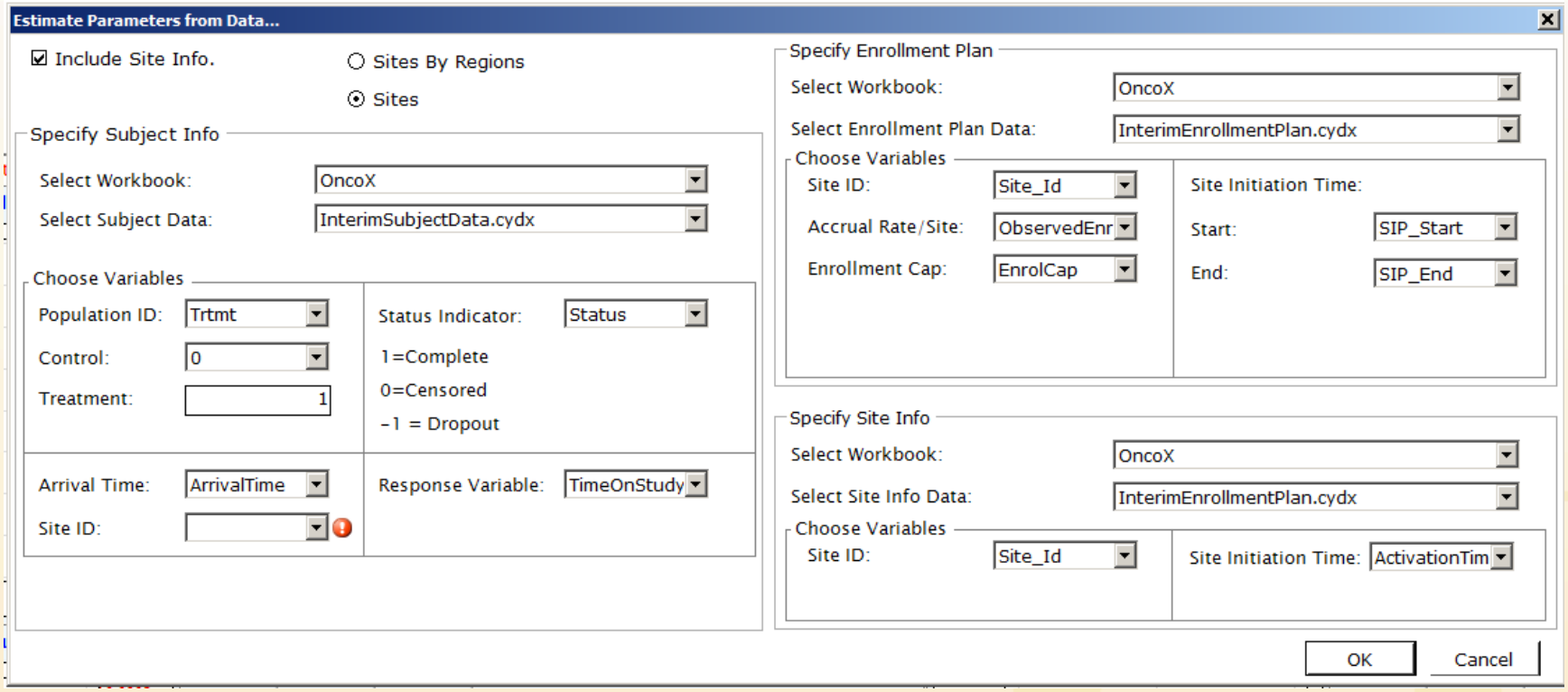
Updated Enrollment Plan

InterimEnrollmentPlan.cydx

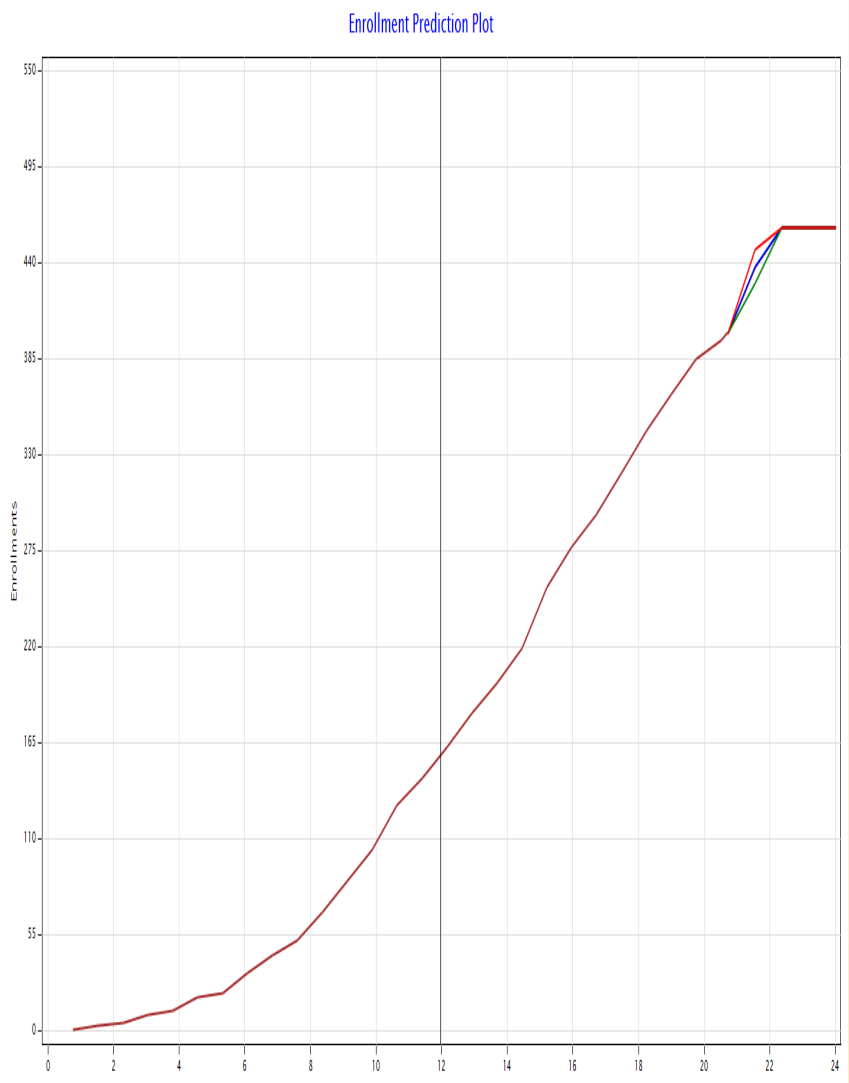
Country: 1 Value: Australia

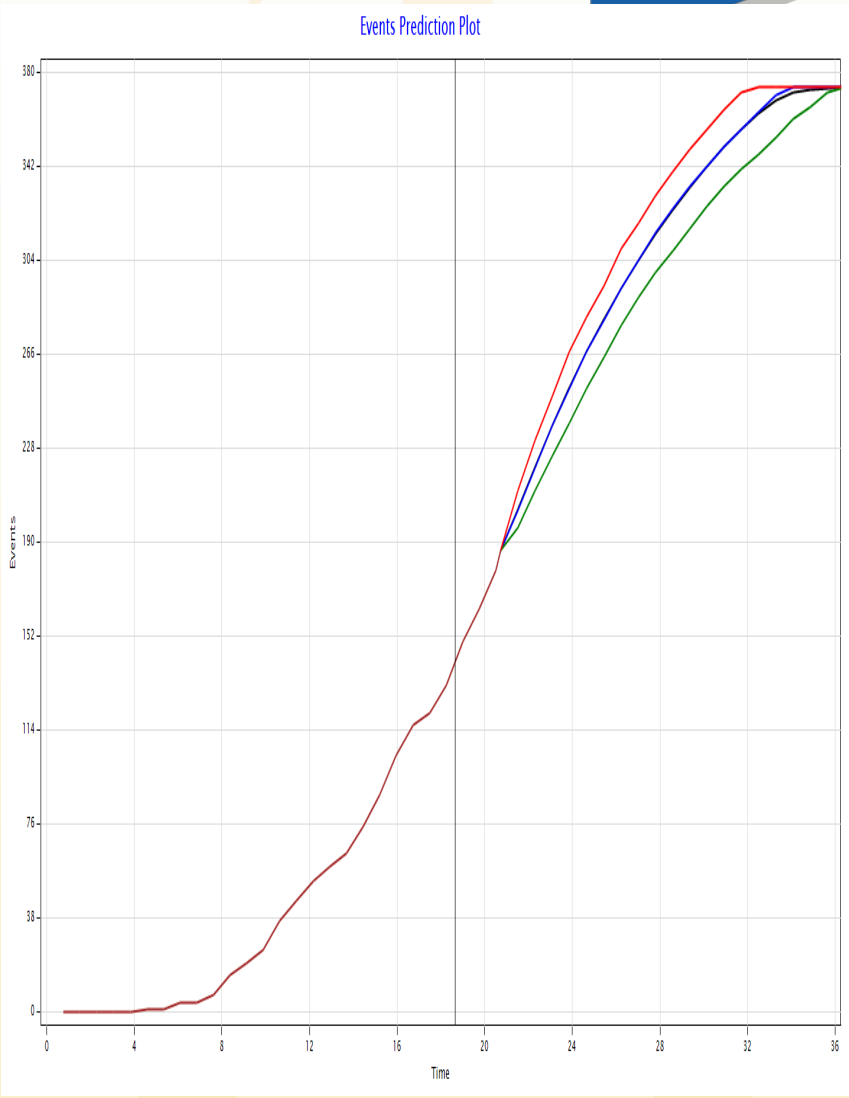
	Country	Site_Id	EnrolCap	ActivationTim	ObservedEnr
1	Australia	601	7	7.66447368	0.153148615
2	Australia	602	27	4.86842105	0.126141079
3	Australia	603	45	8.42105263	0.32513369
4	Australia	604	9	4.17763158	0.181312127
5	Australia	605	7	5.2631579	0.064680851
6	Australia	606	30	6.57894737	0.353488372
7	Australia	607	10	8.05921053	0.473766234
8	Australia	608	9	10.0657895	0.562962963
9	Australia	609	12	19.375	4.44878049
10	Australia	610	16	8.68421053	0.249180328
11	Australia	611	9	7.66447368	0.229722922
12	Austria	401	8	13.7171053	0.142723005
13	Austria	402	24	13.125	0.131601732
14	Austria	403	20	8.91447368	0.169359331
15	Austria	404	12	7.96052632	0.156701031
16	Belgium	301	12	6.57894737	0.63627907
17	Belgium	302	6	7.26973684	0.074327628

Conditional Simulation Entries



Enrollment and Event Output





At month 21, future simulated trials place study duration between 33 and 36 months

Concluding Remarks

- First attempt to use the actual patient-level data at interim monitoring stage for forecasting the future
  - PIPs – future chance of a successful outcome
  - EnEv – future enrollment and event forecasts
- Future Directions:
  - More general models for patient arrival, and survival
  - Integration with Adaptive SSR in East
  - Distribution of p-values and other statistics in PIPs
  - More additions based on user inputs