Precision Medicine for Treatment of Cancer - Methods and Analyses from the Xalkori Experience for ALK-positive NSCLC

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Cytel Seminar on Adaptive Statistical Designs, San Diego - June 19, 2014

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A 2 (Unequal)-Part Presentation

- On the opportunities and challenges associated with the rapid development of Xalkori
- On the use of East for design/monitoring of Phase 3 trials

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Opportunities and Challenges Associated with Development of Xalkori

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Acknowledgement

- Yiyun Tang, Bo Huang and Anna Polli for significant contributions to data analysis and interpretation

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Outline

- Background
- Highlights of Xalkori Data
  - From single arm studies
    - Statistical Considerations for Data Interpretation and Approaches to Address
  - From a randomized trial
- Summary

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Background: Xalkori

- Generic Name: Crizotinib (PF-02341066)
- Class: Small-molecule, ATP-competitive inhibitor of ALK & c-MET/HGFR tyrosine kinases
- Dosing Regimen: 250 mg orally BID continuously
- Indication:
  - For treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ALK-positive as detected by an FDA-approved test (USPI, 05/2014)
- First treatment for advanced NSCLC developed based on knowledge of the underlying genetic drivers of the disease to identify patients most likely to benefit from treatment
- Approved in 5 years from first-in-human based on 2 single arm studies

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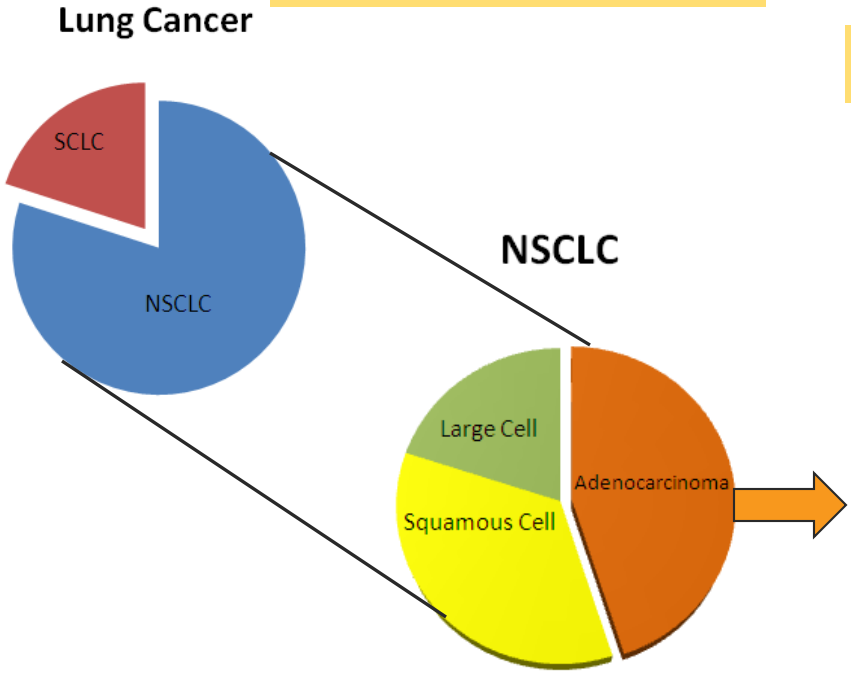
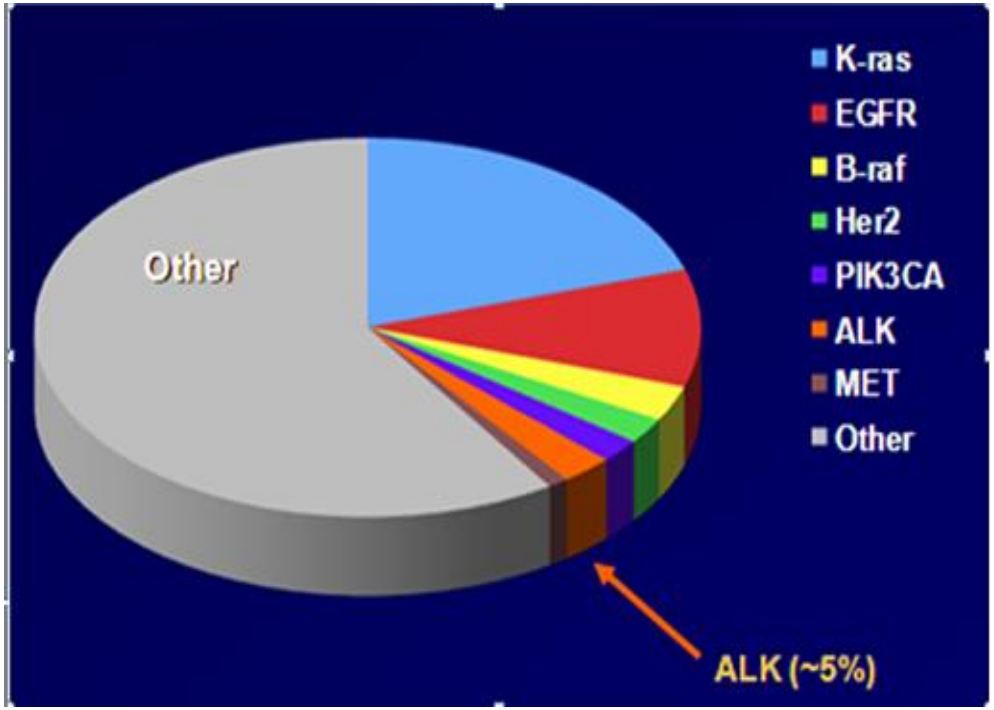
Lung Cancer: from Histology to Biomarker Based Treatment in the Molecular Era

Before: One Disease



Today: Potential Oncogenic Drivers in NSCLC



ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; Her2 = human epidermal growth factor receptor 2; PIK3CA = phosphoinositide-3-kinase, catalytic, alpha polypeptide

Massachusetts General Hospital, data on file. [AT Shaw, personal communication]

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Developing Targeted Therapies - Opportunities & Challenges

- Smaller trials to detect larger treatment differences have greater chance for success

Before: Treat large numbers of patients unselected for relevant genetic events

New Model: Treat (targeted therapies) small numbers of pts all with relevant genetic events

2011 ASCO Blueprint

- Even these smaller trials could be “too large” and challenging to conduct as molecular subsets get smaller

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Typical Endpoints in Oncology

- Objective Response Rate (ORR)
  - % of “responders” relative to population evaluable for response
- Progression-Free Survival (PFS)
  - Time from 1st dose to tumor progression or death
- Overall Survival (OS)
  - Time from 1st dose to death

Note: definitions provided for single arm trials

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Clinical Development in ALK-Positive Advanced NSCLC

Protocol (A808)	Setting	Trial Design	Primary Endpoints
1001 (Phase 1)	All Lines Solid Tumors ALK + NSCLC	Xalkori, Single-Arm, OL	Safety, PK, ORR
1005 (Phase 2)	≥2nd-Line ALK + NSCLC	Xalkori, Single-Arm, OL	ORR, Safety
1007 (confirmatory Phase 3)	2nd-Line ALK + NSCLC	Xalkori vs. (Pemetrexed or Docetaxel), Randomized, OL	PFS
1014 (confirmatory Phase 3)	1st-Line ALK + NSCLC	Xalkori vs. (Pemtrexed/Carboplatin or Pemetrexed/Cisplatin), Randomized, OL	PFS

NSCLC = Non-small cell lung cancer; OL= Open Label; PK=Pharmacokinetic; ORR= Objective Response Rate; PFS= Progression Free Survival

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HIGHLIGHTS OF SINGLE-ARM XALKORI DATA

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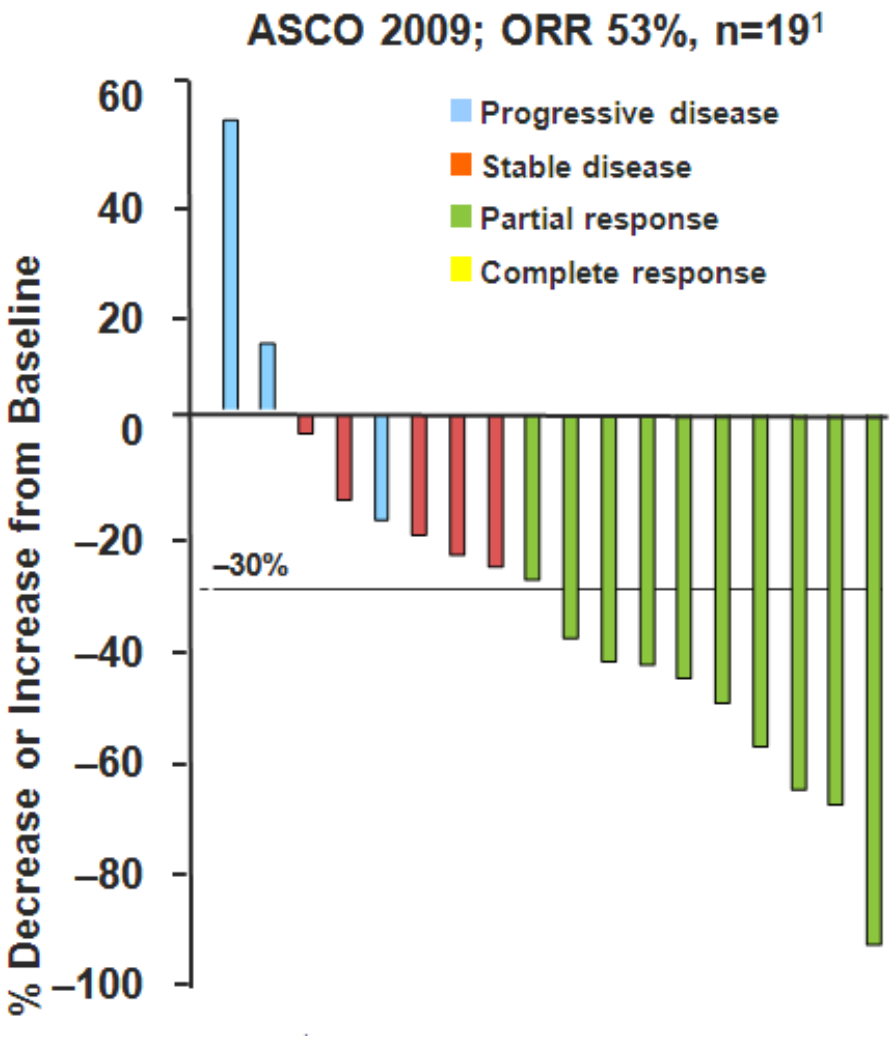
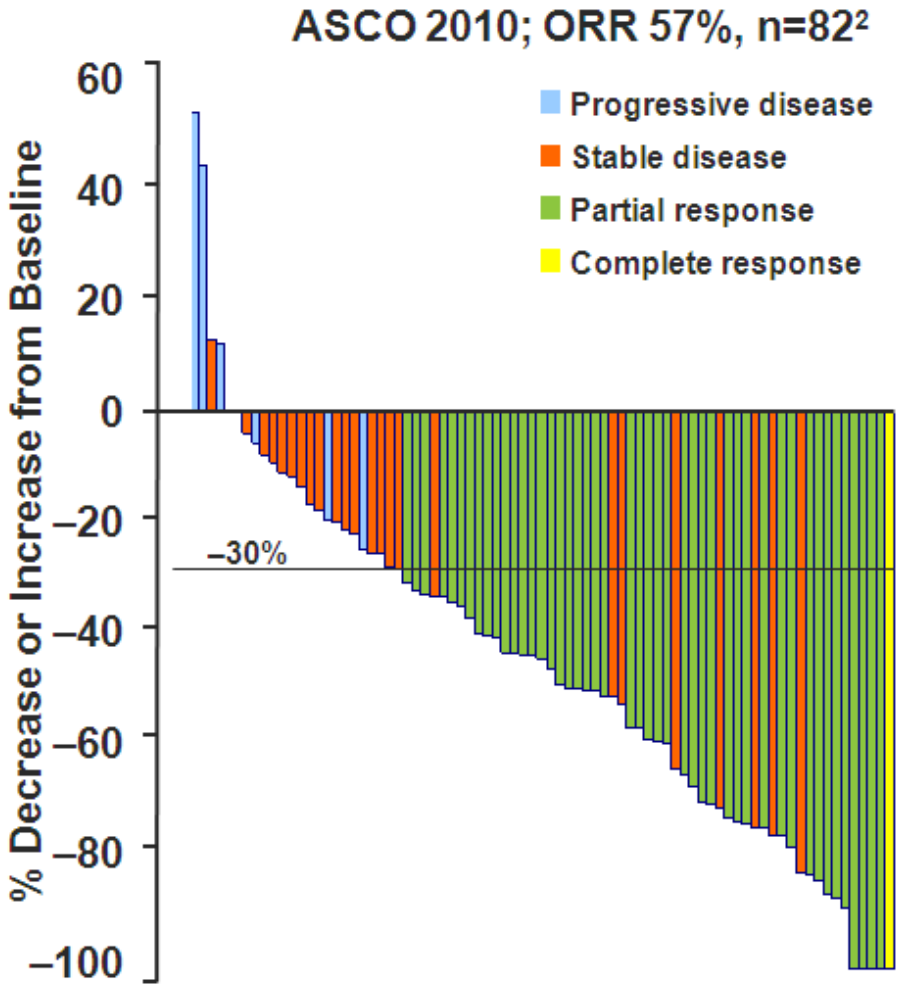
ALK-Positive NSCLC Signs of Anti-Tumor Activity Over Time Study 1001





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Robust and Durable Anti-Tumor Activity

	Study 1001 N=119*	Study 1005 N=136*
Best overall response		
Complete response	**2**	**1**
Partial response	**69**	**67**
ORR	**61% (95% CI: 52%, 70%)**	**50% (95% CI: 42%, 59%)**
Duration of response Median (range) weeks**	**48.1 weeks (4.1+, 76.6+)**	**41.9 (6.1+, 42.1+)**

USPI 08/2011

Assessed by the investigators
**Three patients were not evaluable for response in Study 1001 and 1 patient was not evaluable for response in Study 1005*
*** Preliminary estimates using the Kaplan-Meier method*

- *Impressive ORR even when compared to chemotherapeutic agents approved for 1st line treatment of metastatic NSCLC (ORR: 15-35%)*

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STATISTICAL CONSIDERATIONS FOR DATA INTERPRETATION AND APPROACHES TO ADDRESS

Statistical Considerations

- Efficacy data not based on “typical” endpoints for regulatory approval:
  - ORR
  - Duration of Response
    - Time from first response to disease progression or death
- Single arm data
- No historical data available in the population of interest

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Question 1

- Are characteristics of ALK+ patients (e.g. younger, never/former smoker, adenocarcinoma histology) contributing to observed anti-tumor data?

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Xalkori Efficacy in Context of Historical Data

- Comparisons against unselected patients' data are confounded as ALK+ NSCLC patients have distinct characteristics

- Use data from control* arm of 3 adequate and well controlled Pfizer-sponsored advanced NSCLC studies
  - Covariate-matched analyses for ORR/PFS/OS with resampling to compare Xalkori with matched data from control arms
  - Covariate-adjusted analyses to retrospectively predict efficacy of ALK+ NSCLC patients as if they were treated with one of the control agents:
    - Logistic regression model for ORR
    - Covariate-adjusted expected PFS/OS curves with Cox-PH regression model

** Control arms included: 1st Line Carboplatin/Paclitaxel or Gemcitabine/Cisplatin and ≥ 2nd Line Erlotinib*

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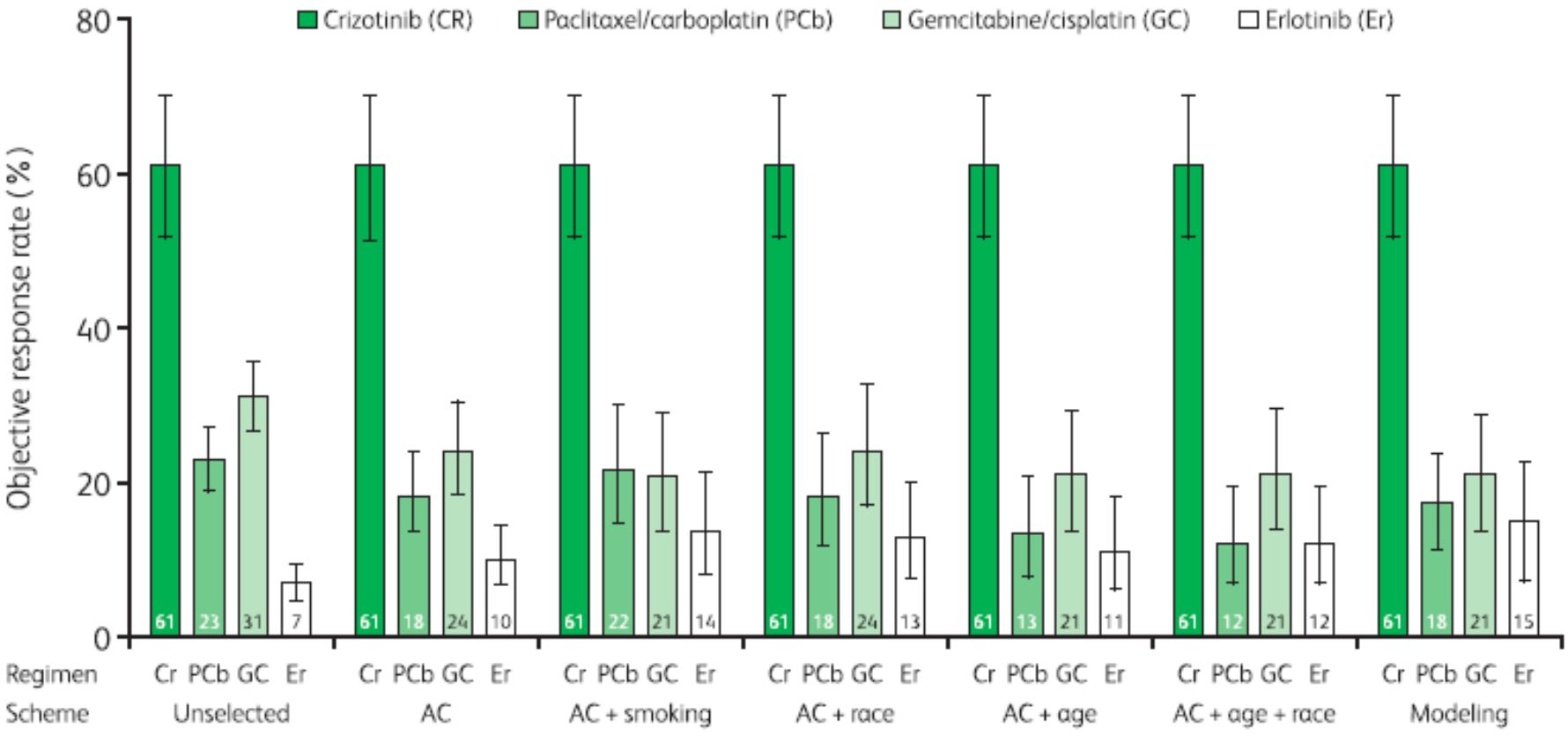
Tang Y, Poster at WCLC 2011; Abstract 1349

ORR by Treatment and Matching Schema Covariate-Matched and Adjusted Analyses, Study 1001



Error bars: 95% exact CI for unselected and AC schemes; average of 95% exact CI from bootstrap samples for AC + smoking, AC + race, AC + age, AC + age + race schemes; estimated 95% CI based on delta method in covariate-adjusted modeling analysis.

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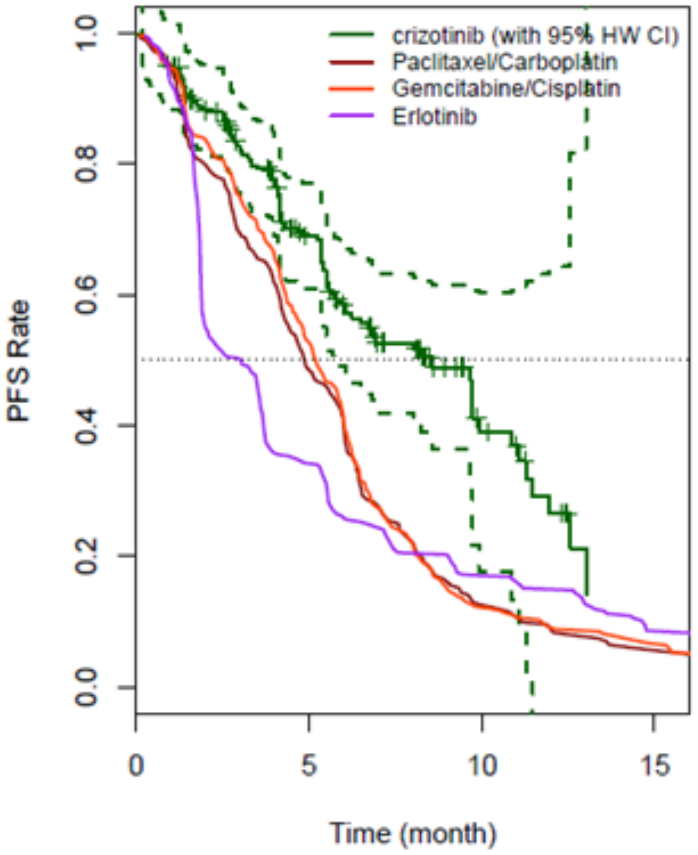
Tang Y, Poster at WCLC 2011; Abstract 1349

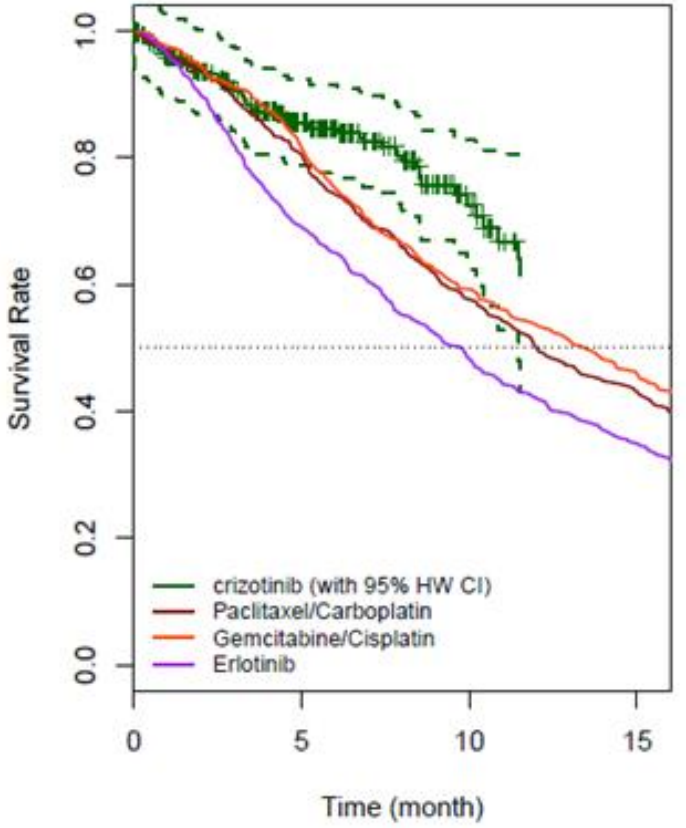
Observed and Expected PFS and OS
Direct Adjustment Method

Xalkori in Study 1005* (N=439) and 3 Control Regimens

PFS



OS



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** As of June 2011*

Summary of Historical Control Analyses

- Using data from ALK+ advanced NSCLC patients in Studies 1001 and 1005, and from unselected advanced NSCLC patients treated with 3 control regimens in ≥1st-line treatment setting, Xalkori was associated with:
  - Higher ORR than that of covariate-matched and covariate-adjusted controls
  - Hazard Ratios against covariate-adjusted controls for PFS and OS between 0.37 and 0.77

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Question 2

- Investigate hypotheses from small (8-19 patients), retrospective reports suggesting that pemetrexed as a single-agent or in combination with chemotherapy may be effective in ALK+ NSCLC (Altavilla et al, 2010; Camidge et al, 2011; Lee et al, 2011)
  - Evaluate Xalkori vs. pemetrexed/docetaxel (chemotherapy choice in randomized Phase 3 Study1007)

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Xalkori vs. Pemetrexed (P) or Docetaxel (D) in ALK+ NSCLC Study 1005

- Within and between-patient time to tumor progression (TTP) and PFS analyses
  - 117 pts who received prior, 2nd line single P/D, were analyzed for Xalkori outcome (within) or compared with 62 patients who received 2nd line Xalkori (between)

PFS	P or D (N=117)	Xalkori (N=117)	Xalkori (N=62)
Median (mo) (95% CI)	3.5 (2.8, 5.3)	5.7 (5.3, 12.0)	NR (9.7, NR)
HR (Xalkori:P/D)		Within	Between
Unadjusted [95% CI]		0.63 (0.44, 0.90)	0.31 (0.16, 0.62)
Adjusted* [95% CI]		0.59 (0.41, 0.85)	0.37 (0.19, 0.74)

** Adjusted for age and ECOG performance status in a backward selected model for "Within" and "Between", respectively*

As of June 2011

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HIGHLIGHTS OF XALKORI DATA FROM 2ND LINE RANDOMIZED PHASE 3 STUDY

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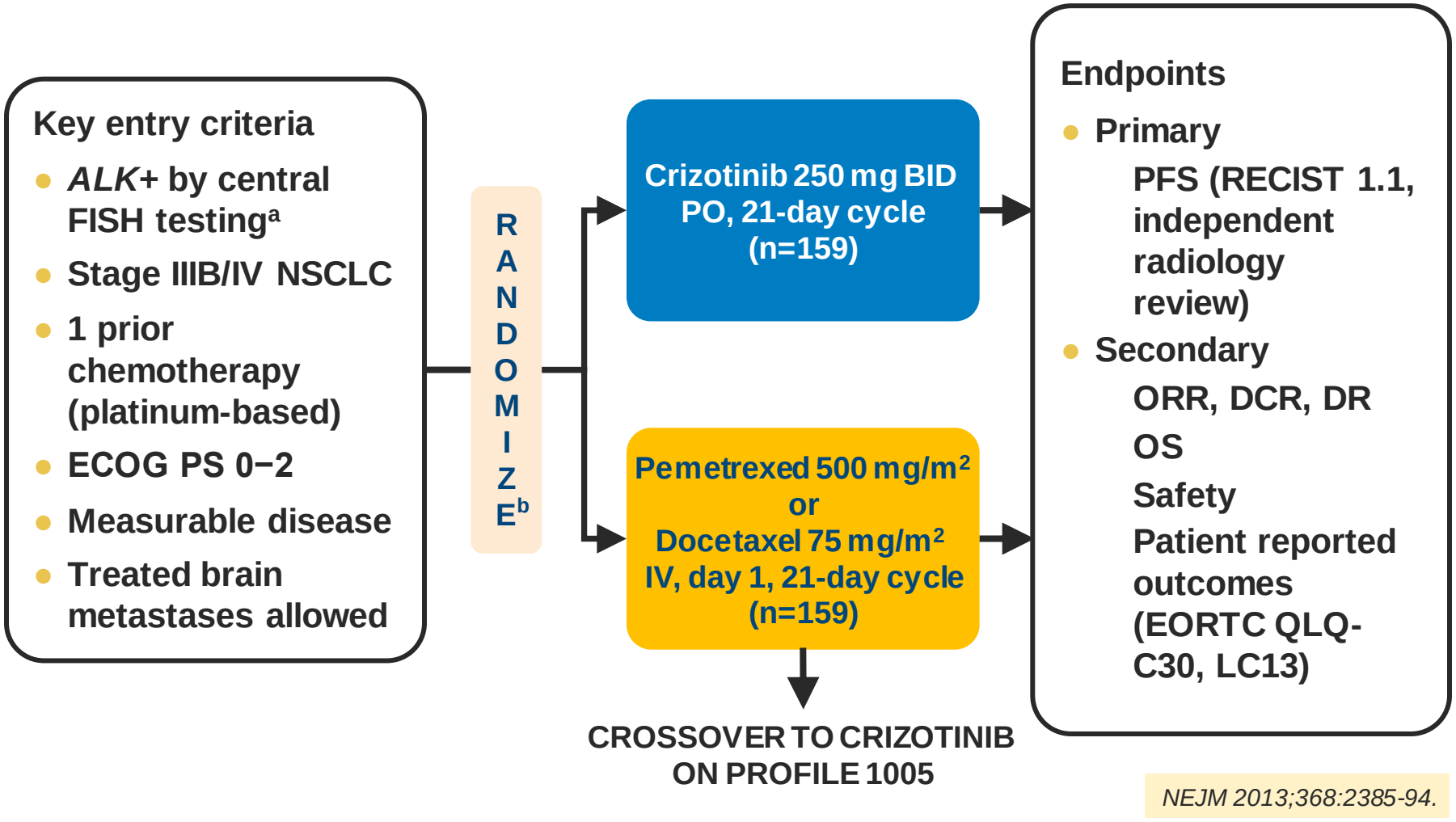
Study Design



NEJM 2013;368:2385-94.

[a] *ALK* status determined using standard *ALK* break-apart FISH assay
[b] Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

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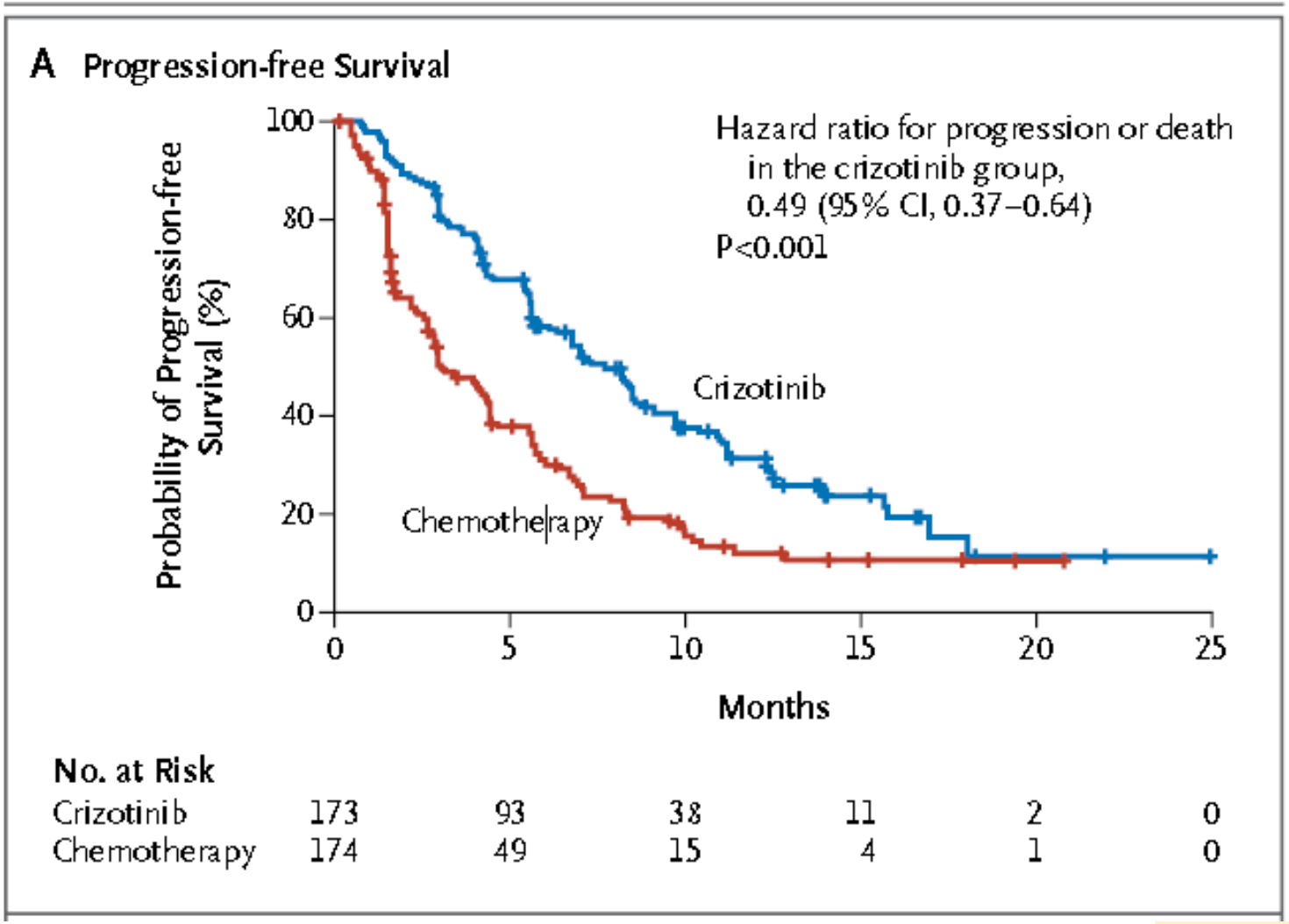
PFS by Independent Radiologic Review (ITT Population)



NEJM 2013;368:2385-94.

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Summary

- In the absence of randomized data, innovative statistical approaches were used to quantify clinical benefit with Xalkori in a quasi-randomized manner
  - Results from the randomized trial "validate" outcomes of retrospective analyses

- *Present:* While single arm trials may be accepted for accelerated approval of drugs for rare conditions, randomized Phase 3 trials likely required as post-marketing requirement

- *Future:* Single arm trials may be sufficient for full approval of precision medicine agents for rare tumors.

Example for Using East to Design/Monitor a Phase 3 trial

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Outline

Examples for using East (v. 6.2) for a Phase 3 Study:

- Trial Design
- Event monitoring

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Example for using East (v. 6.2) for a Phase 3 Study Trial Design

Assumptions for the 2nd Line Phase 3 Study (1007)

- 56% improvement in PFS (Hazard Ratio=0.64)
  - e.g. median PFS 7.0 months vs 4.5 months
- Alpha =0.025 (1-sided)
- Power = 90%
- Non-uniform accrual

NEJM 2013;368:2385-94.

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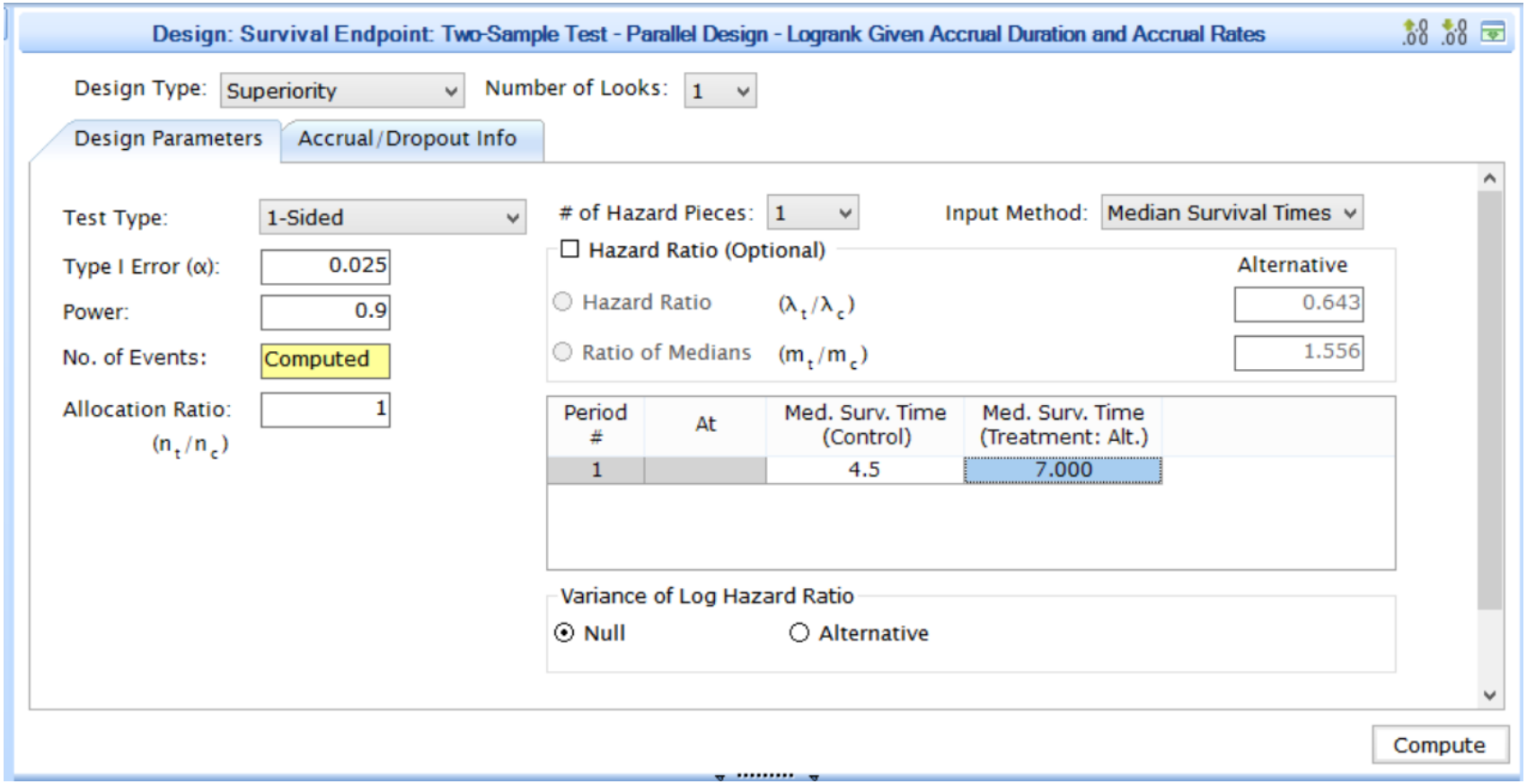
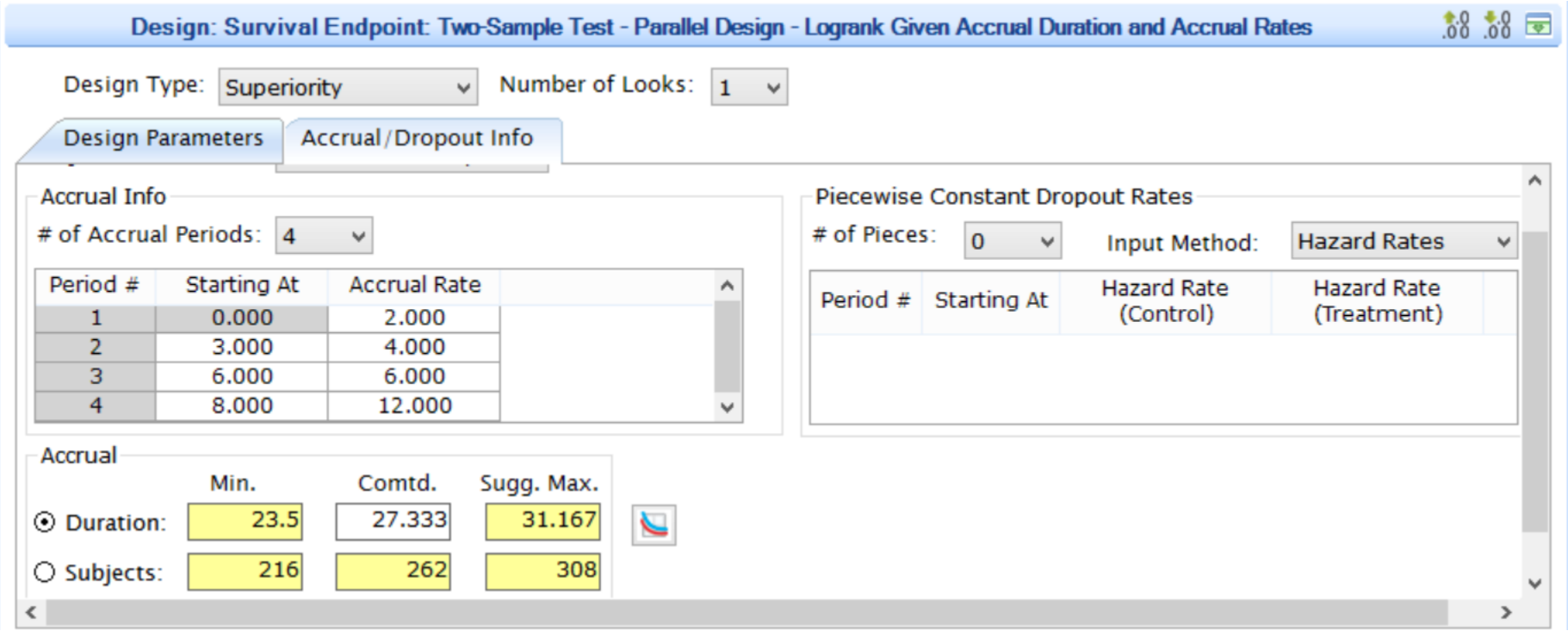
Using East for Event and Sample Size Calculation

- Select "Two-Sample Survival Endpoint Given Accrual Duration & Rates"
- Enter the "Design Parameters" as noted on previous slide



Using East for Event and Sample Size Calculation (2)

- Enter “Accrual/Dropout Info”



Note: Accrual Rate is an example not based on actual assumptions

East Output Summary

Output Summary

	Des3
Mnemonic	SU-2S-LRAR
Test Parameters	
Design Type	Superiority
No. of Looks	1
Test Type	1-Sided
Specified α	0.025
Power	0.9
Model Parameters	
Hazard Ratio (Alt.)	0.643
Var (Log HR)	Null
Allocation Ratio (nt/nc)	1
Accrual & Dropout Parameters	
Accrual Rate	Multiple
Subjects are Followed	Until End of Study
No. of Accrual Periods	4
No. of Dropout Pieces	0
Sample Size	
Maximum	262
Expected Under H0	262
Expected Under H1	262
Events	
Maximum	216
Expected Under H0	216
Expected Under H1	216

Actual Planned Sample Size:

- *217 Events*
- *318 Patients*

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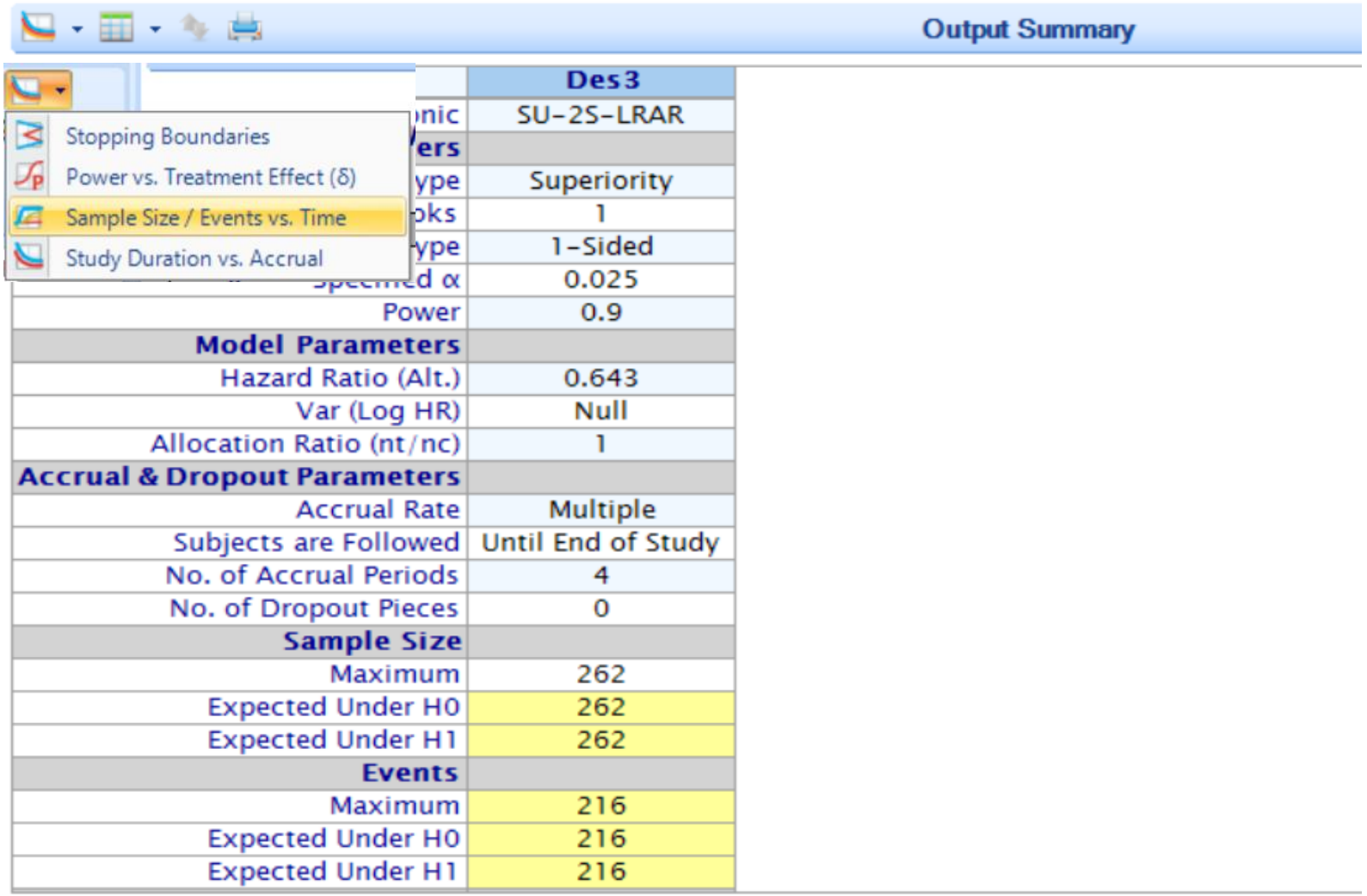
Example for using East (v. 6.2) for a Phase 3 Event Monitoring

At Design and During Study Plot Sample Size/Events vs Time to Determine Event Occurrence



	Des3
nic	SU-2S-LRAR
ers	
ype	Superiority
oks	1
ype	1-Sided
d α	0.025
Power	0.9
Model Parameters	
Hazard Ratio (Alt.)	0.643
Var (Log HR)	Null
Allocation Ratio (nt/nc)	1
Accrual & Dropout Parameters	
Accrual Rate	Multiple
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Sample Size	
Maximum	262
Expected Under H0	262
Expected Under H1	262
Events	
Maximum	216
Expected Under H0	216
Expected Under H1	216

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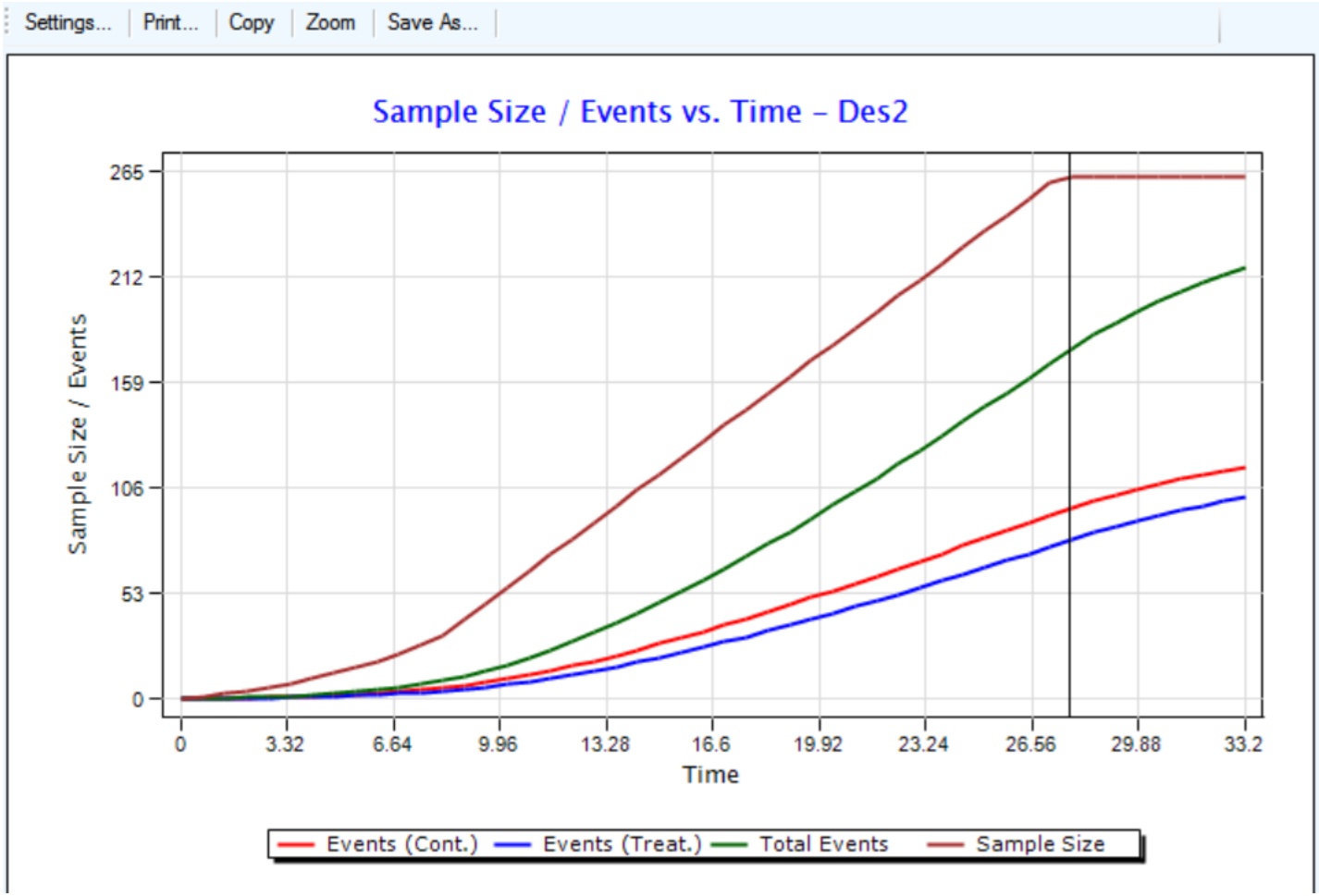
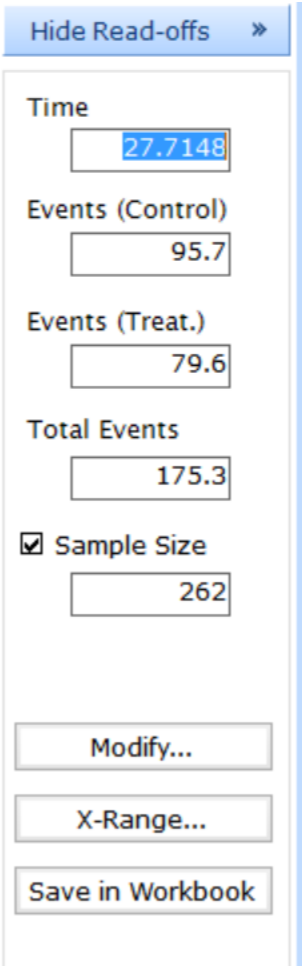
Sample Size/Events vs Time At Design





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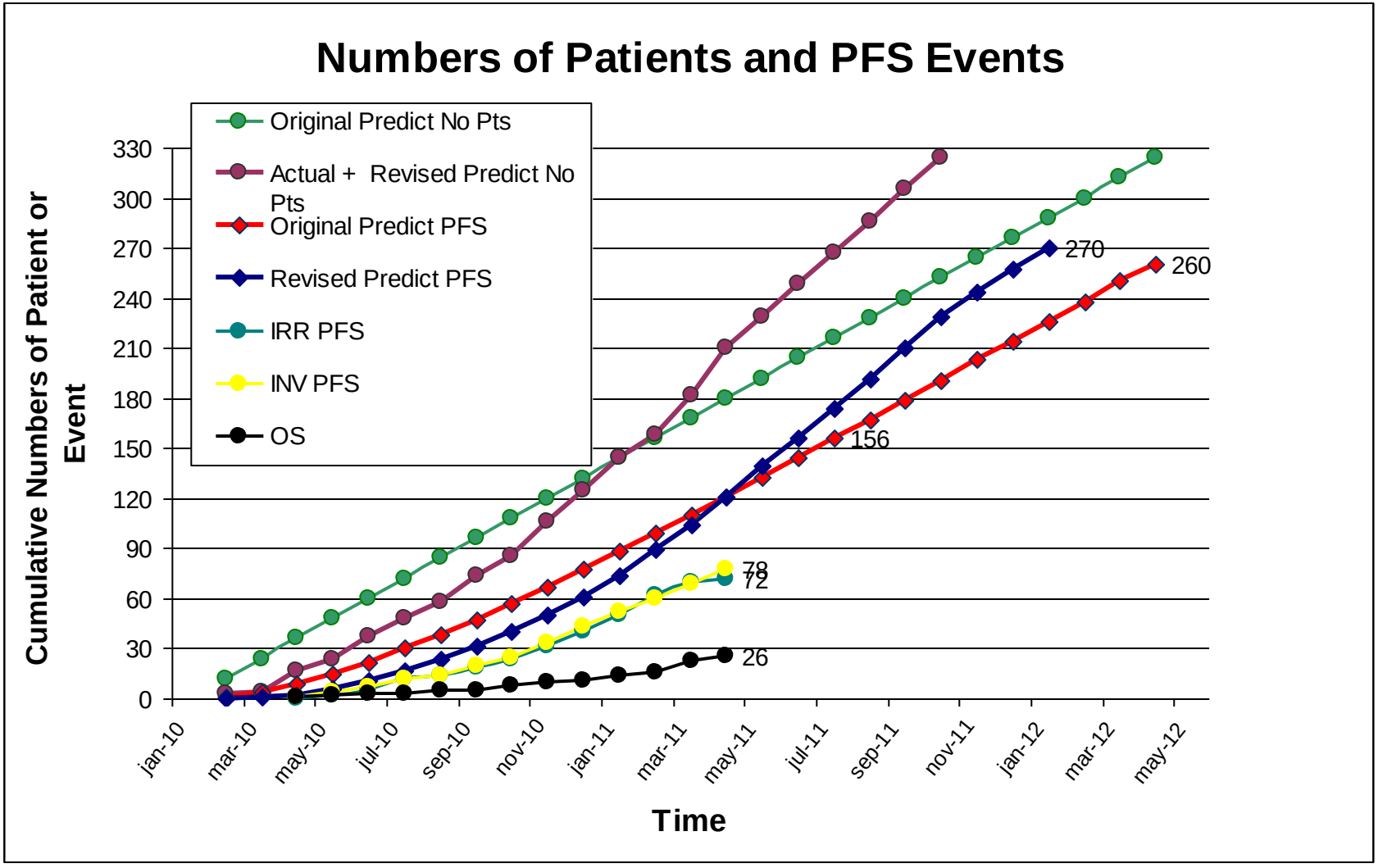
Enrollment and Event Tracking During Study



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IRR = Independent Radiology Review
INV = Investigator
PFS = Progression Free Survival

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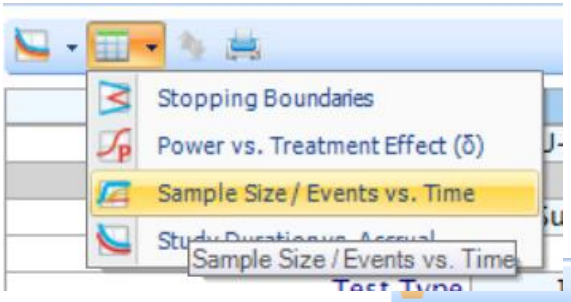
Using EAST for Event Prediction

Under “Show Table” Select “Sample Size/Events vs Time” then “Save as Case Data”



Total Sample Size / Events vs. Time

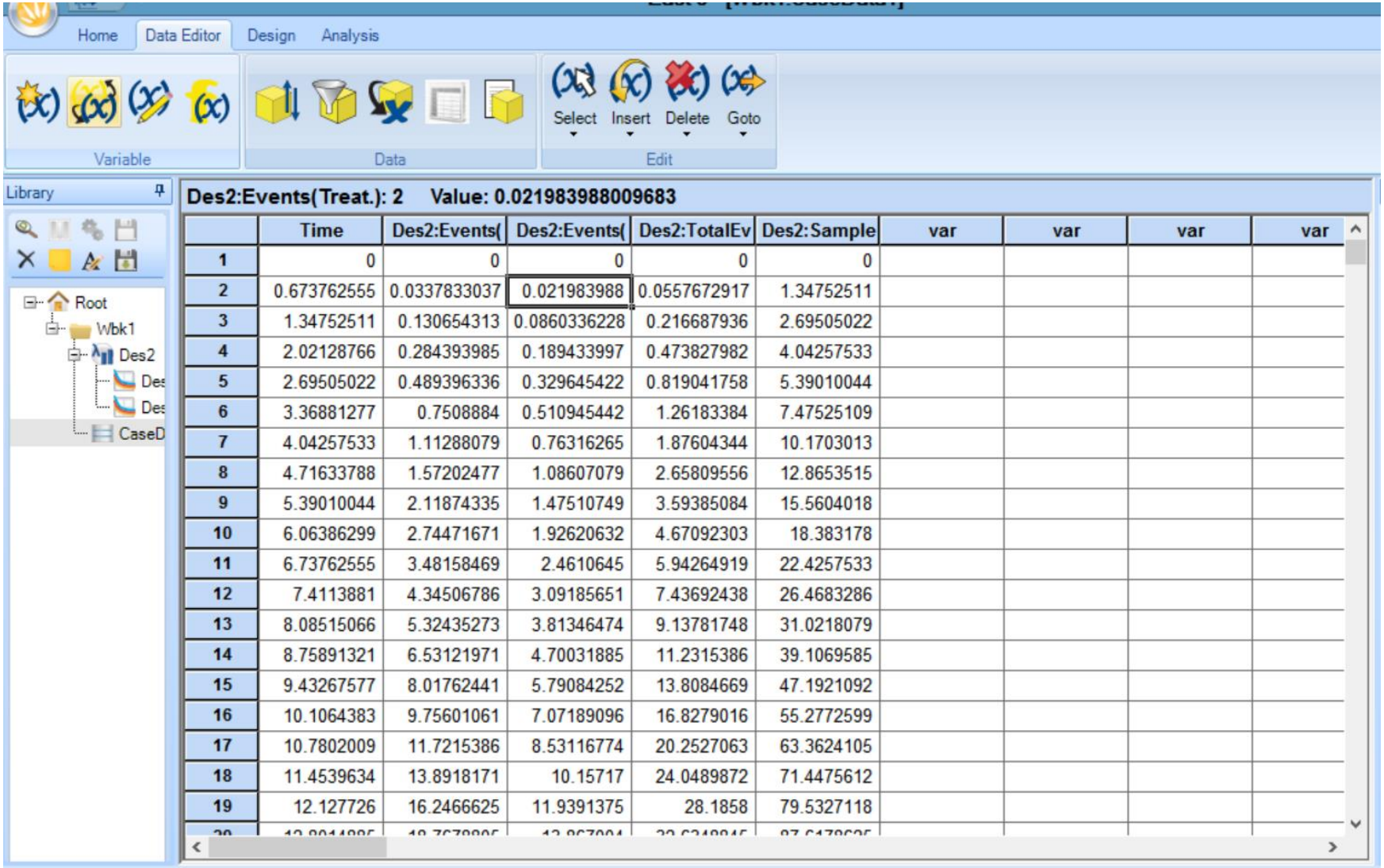
Range for Time

From	To	Step Size	
0	33.014	0.674	Tabulate

Time	Des2:Events (Cont.)	Des2:Events (Treat.)	Des2:Total Events	Des2:Sample Size
0	0	0	0	0
0.674	0.034	0.022	0.056	1.348
1.348	0.131	0.086	0.217	2.695
2.021	0.284	0.189	0.474	4.043
2.695	0.489	0.33	0.819	5.39
3.369	0.751	0.511	1.262	7.475
4.043	1.113	0.763	1.876	10.17
4.716	1.572	1.086	2.658	12.865
5.39	2.119	1.475	3.594	15.56
6.064	2.745	1.926	4.671	18.383
6.738	3.482	2.461	5.943	22.426
7.411	4.345	3.092	7.437	26.468
8.085	5.324	3.813	9.138	31.022
8.759	6.531	4.7	11.232	39.107
9.433	8.018	5.791	13.808	47.192
10.106	9.756	7.072	16.828	55.277
10.78	11.722	8.531	20.253	63.362
11.454	13.892	10.157	24.049	71.448

Save as Case Data

Export Data in Excel and Plot



Des2:Events(Treat.): 2 Value: 0.021983988009683

	Time	Des2:Events(	Des2:Events(	Des2:TotalEv	Des2:Sample	var	var	var	var
1	0	0	0	0	0				
2	0.673762555	0.0337833037	0.021983988	0.0557672917	1.34752511				
3	1.34752511	0.130654313	0.0860336228	0.216687936	2.69505022				
4	2.02128766	0.284393985	0.189433997	0.473827982	4.04257533				
5	2.69505022	0.489396336	0.329645422	0.819041758	5.39010044				
6	3.36881277	0.7508884	0.510945442	1.26183384	7.47525109				
7	4.04257533	1.11288079	0.76316265	1.87604344	10.1703013				
8	4.71633788	1.57202477	1.08607079	2.65809556	12.8653515				
9	5.39010044	2.11874335	1.47510749	3.59385084	15.5604018				
10	6.06386299	2.74471671	1.92620632	4.67092303	18.383178				
11	6.73762555	3.48158469	2.4610645	5.94264919	22.4257533				
12	7.4113881	4.34506786	3.09185651	7.43692438	26.4683286				
13	8.08515066	5.32435273	3.81346474	9.13781748	31.0218079				
14	8.75891321	6.53121971	4.70031885	11.2315386	39.1069585				
15	9.43267577	8.01762441	5.79084252	13.8084669	47.1921092				
16	10.1064383	9.75601061	7.07189096	16.8279016	55.2772599				
17	10.7802009	11.7215386	8.53116774	20.2527063	63.3624105				
18	11.4539634	13.8918171	10.15717	24.0489872	71.4475612				
19	12.127726	16.2466625	11.9391375	28.1858	79.5327118				

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East: A Very Versatile and Useful Tool for Trial Design and Monitoring

At Design Stage Offers:

- Sample size calculations for group sequential design based on design assumptions and accrual information
- A variety of options for spending function boundaries (including user defined) for both efficacy and futility
- Ability to perform simulations to evaluate design operating characteristics under different assumptions and stopping boundaries to select most appropriate for study

Note: this is NOT a comprehensive list!

East: A Very Versatile and Useful Tool for Trial Design and Monitoring (2)

During Study Conduct Offers:

- Event monitoring based on actual accrual and different assumptions for treatment effect
- Calculate alpha at interim and final look based on information fraction to preserve overall Type I error

Note: this is NOT a comprehensive list!

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Q& A

THANK YOU!

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