Cytel

Simulation-based optimization of adaptive designs

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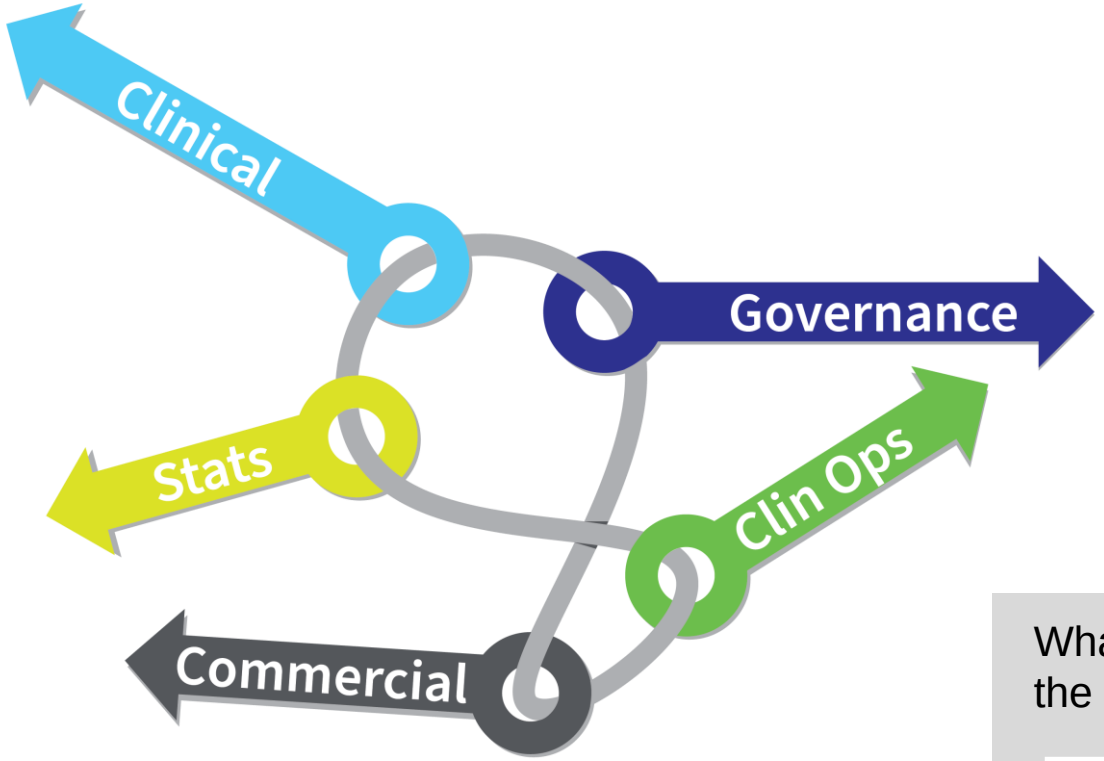
Agenda

- Motivation
- What is success in a clinical trial?
- What if priorities change?
- A case study
- Questions

How Do I Plan the Right Clinical Trial?

- What is the right patient population to treat?
- Is my medicine safe and effective?
- How many patients per arm do we need?
- Can I make a clear decision from the data?
- Will my endpoint be reimbursed?
- What is my benefit-risk profile?
- Is my asset better than the competition?
- How can we go faster?



What clinical trial design will get the right answers?

How can we accomplish these goals quickly and economically?

Need to first define success

- Team input:
  - Endpoints
  - Power
  - Budget
  - Design
  - Decision Criteria
  - **Priorities**

Calculating Probability of Success (for example in EAST)

Clinical Study Description and Fixed Design Requirements

Phase III multicenter, randomized, placebo-controlled, parallel-arm clinical trial to evaluate the efficacy of Treatment versus Control in an acute Myeloid Leukemia study

Endpoint: Median OS

- Control median OS: 8 months
- Treatment effect: HR = 0.7
- Enrollment rate: 20 patients/month
- Sample Size: 451, Events: 331
- Power: 90%
- One-sided alpha: 2.5%

Design Operating Characteristics

Design: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Accrual Rates

Test Parameters	
Design ID	fixed0.7-20subjs
Design Type	Superiority
Number of Looks	1
Test Type	1-Sided
Specified α	0.025
Power	0.90053
Model Parameters	
HR = λ_t/λ_c	
Under H0	1
Under H1	0.7
Med. Surv. Time Control (m_c)	8
Med. Surv. Time Treatment (m_t)	11.429
Var (Log HR)	Null
Allocation Ratio (n_t/n_c)	1
Accrual / Dropouts Parameters	
Accrual Rate	20
Dropout	No

Variable Follow-Up Design: All subjects are followed until failure, drop out or end of study.

Sample sizes and events have been rounded.

Sample Size Information

Sample Size (n)	451
Treatment (n_t)	226
Control (n_c)	225
Events (s)	331
Treatment (s_t)	153
Control (s_c)	178
Information (I)	82.75

Accrual and Study Duration

Accrual Duration	22.55
Max. Study Duration	31.145

Critical Points

Critical Point	-1.96

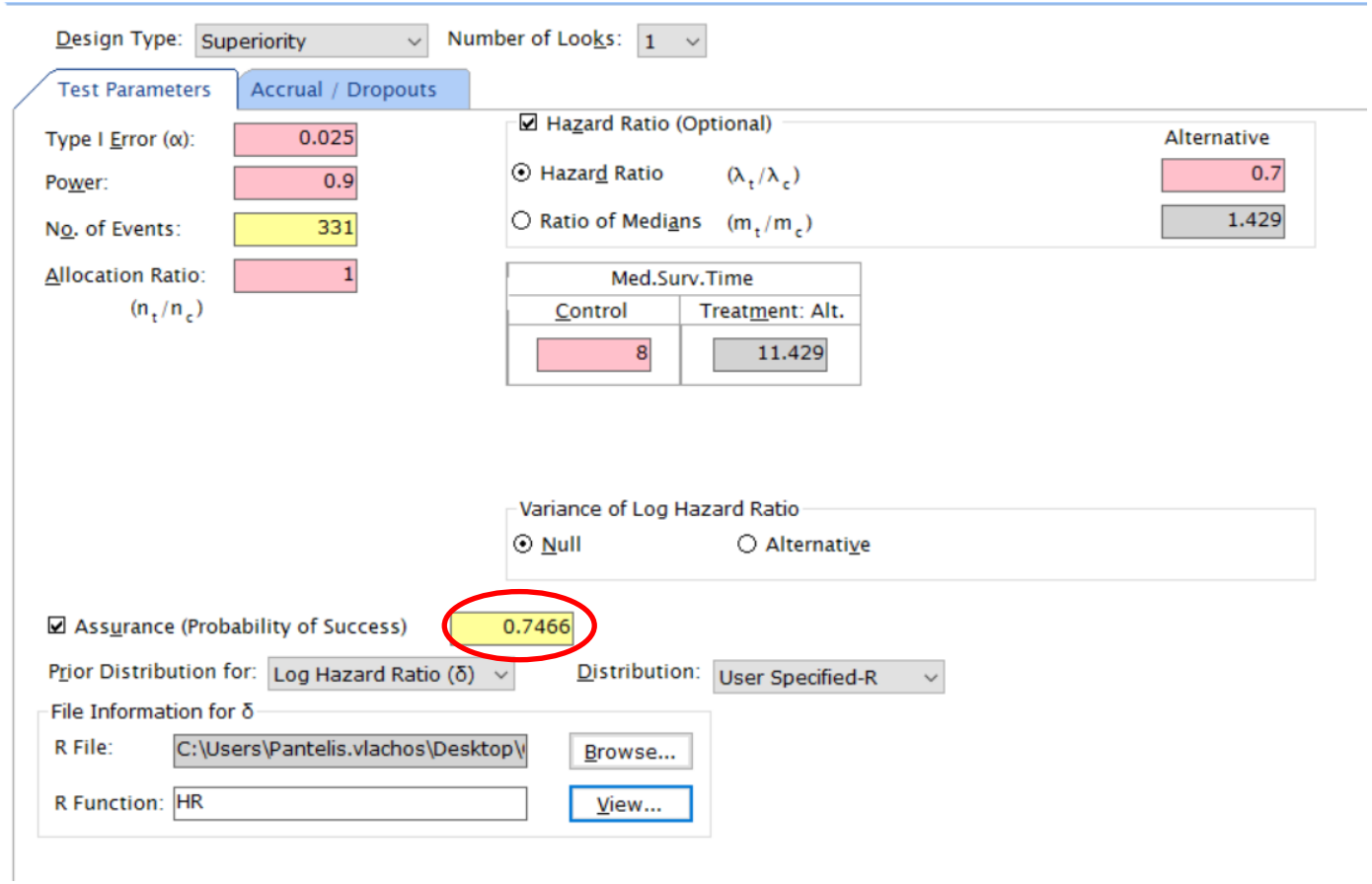
Adding uncertainly in Treatment effect

HR	Pr(HR)
0.60	10%
0.65	15%
0.70	30%
0.75	20%
0.80	15%
1.0	10%

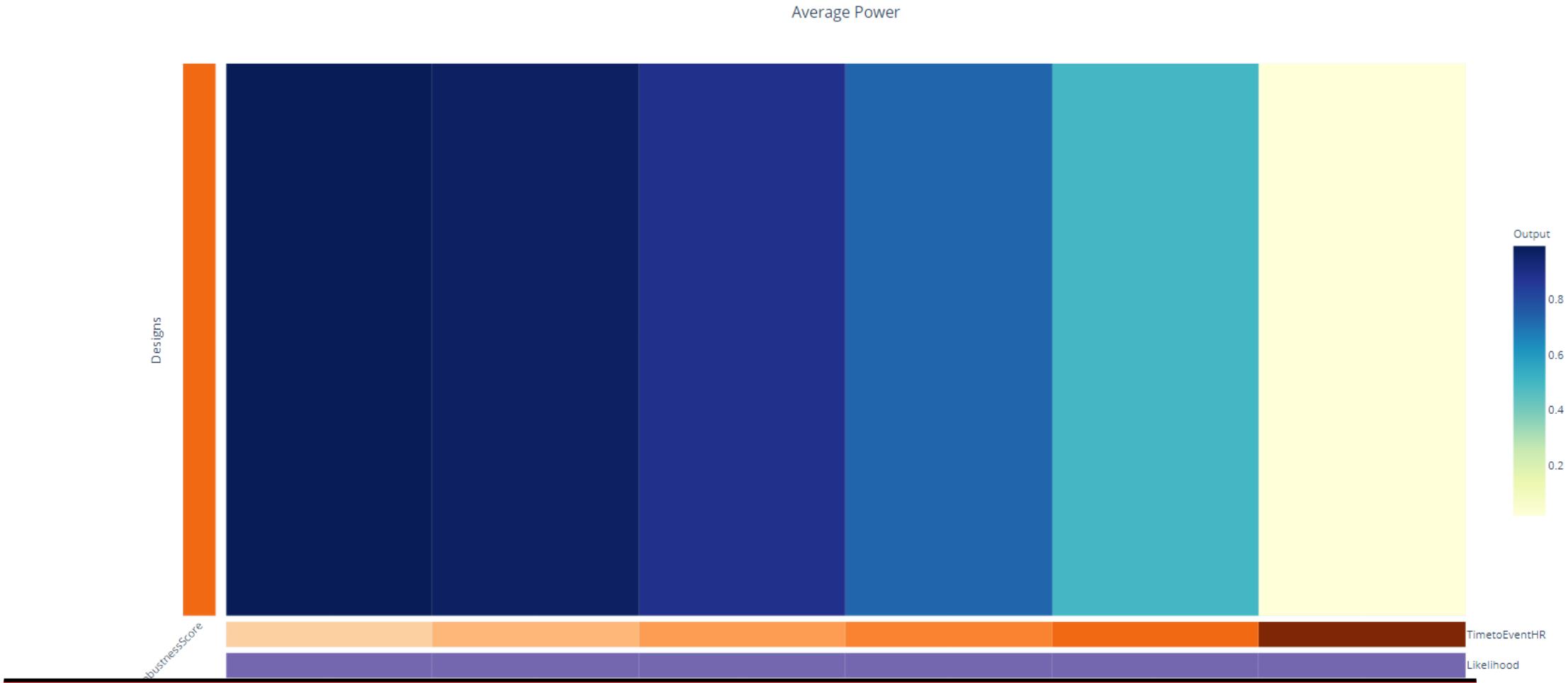
Question: What is the study probability of success if we are only partially certain about the true HR being 0.7

Assurance Calculation

- $PoS = \sum_x P(reject\ H_0 | HR = x) P(HR = x)$
- In EAST:

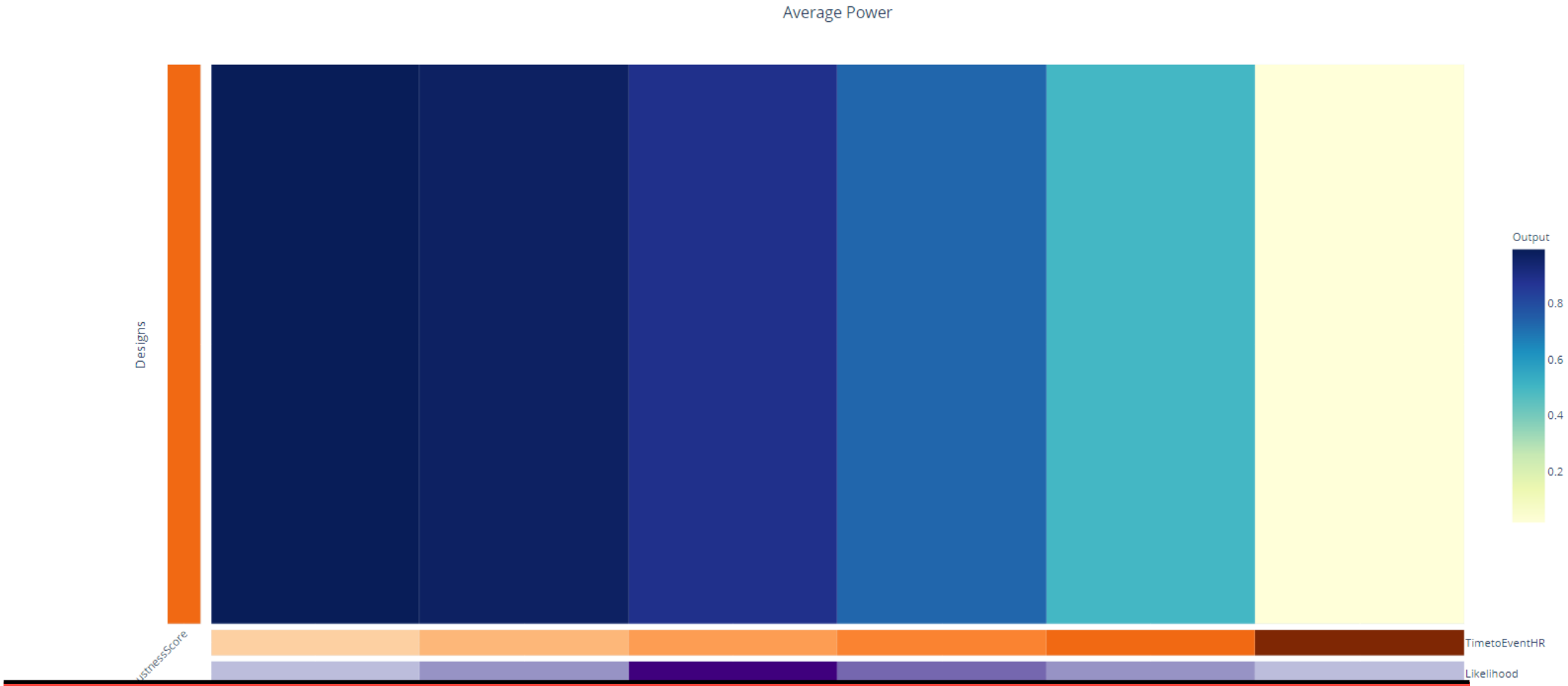


An Alternative display – flat prior on HR – assurance = 0.68



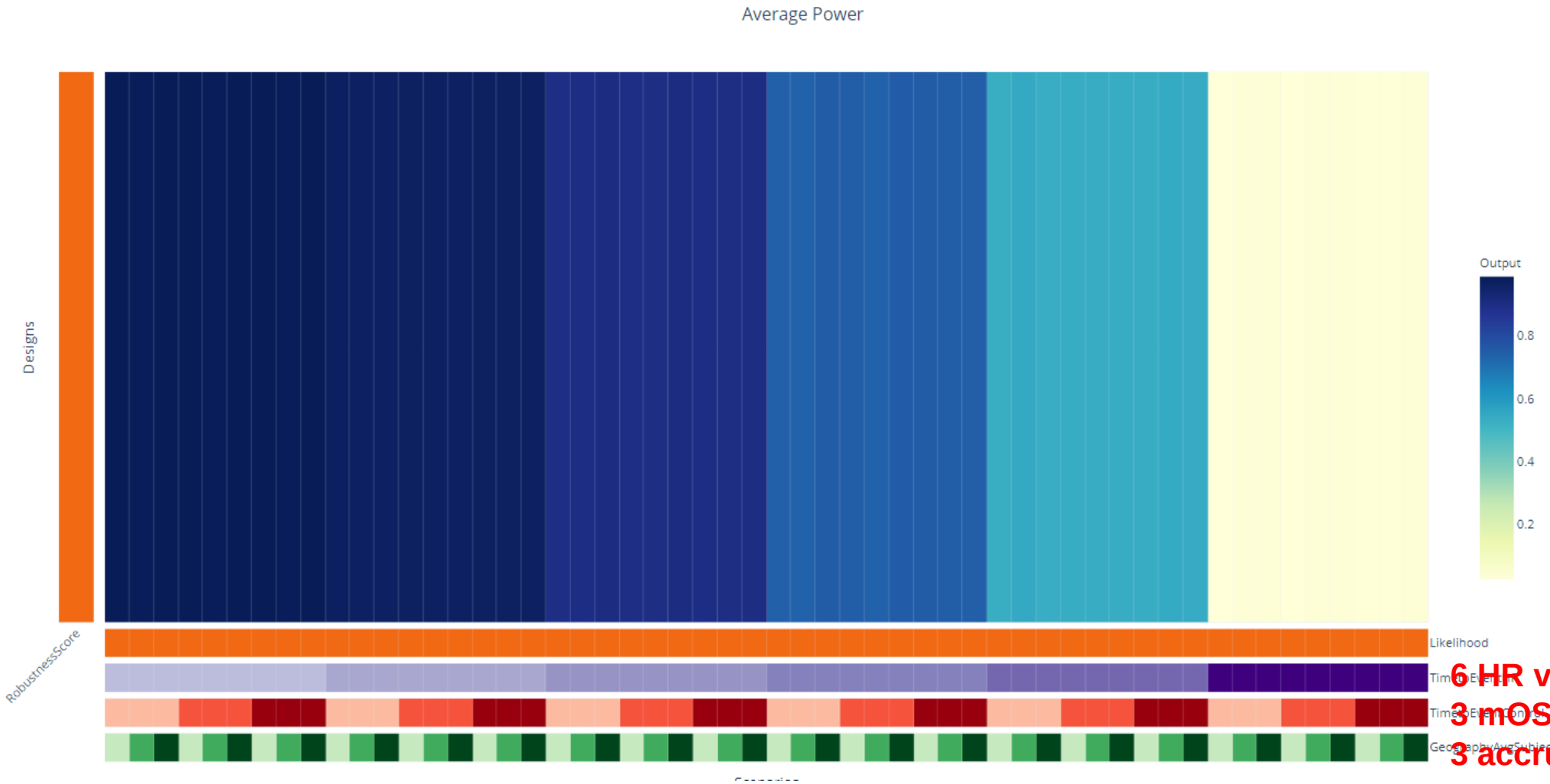
HR	0.6	0.65	0.7	0.75	0.8	1.0
P(HR)	1/6	1/6	1/6	1/6	1/6	1/6

Prior used in EAST example – assurance = 0.74



HR	0.6	0.65	0.7	0.75	0.8	1.0
P(HR)	10%	15%	30%	20%	15%	10%

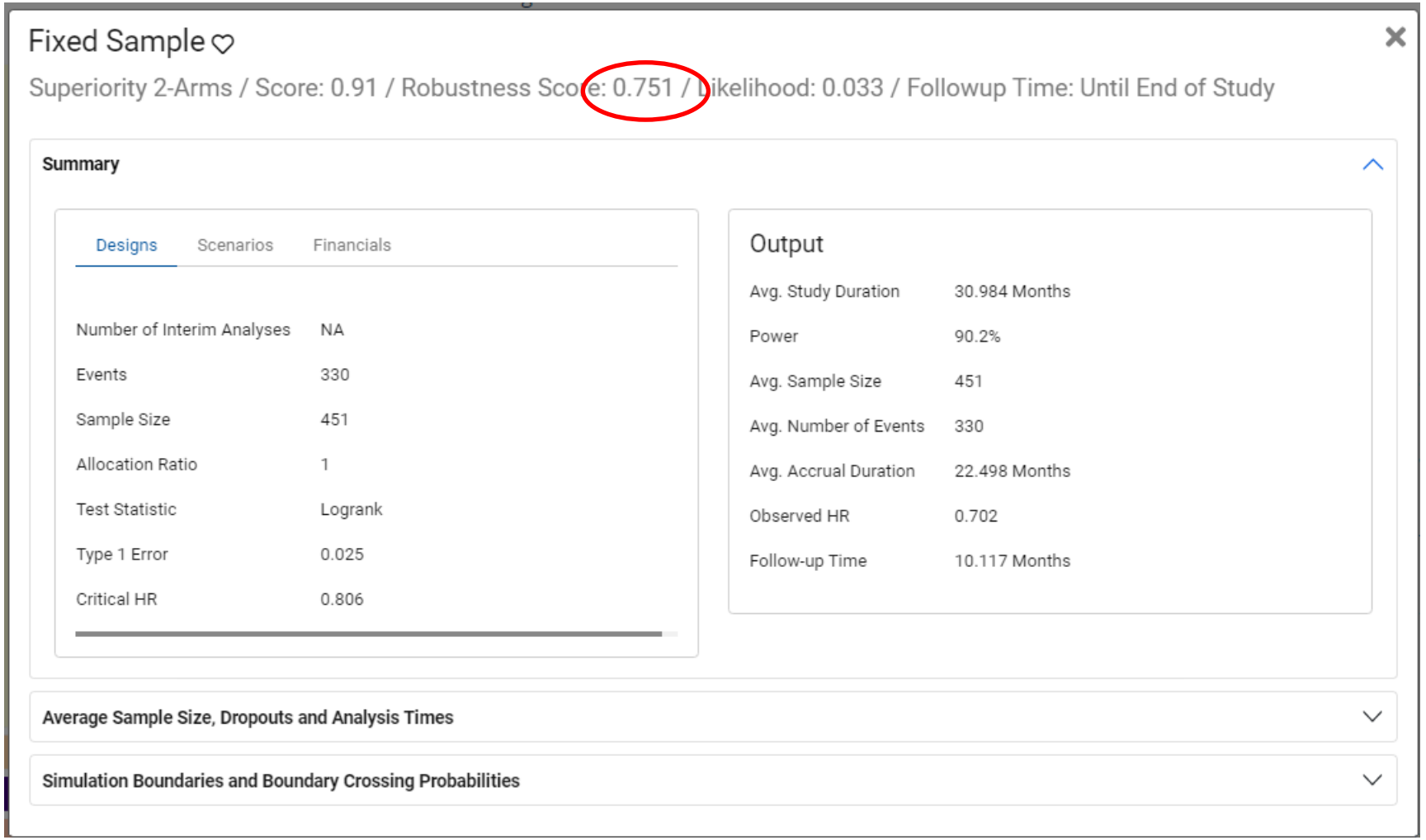
What if we are also uncertain about control mOS and Accrual Equal prior weights (1/54) – Flat prior – PoS = 0.69



6 HR values
3 mOS values
3 accrual rates

54 scenarios

Assuming informative prior HR and flat prior for Ctrl mOS, Accruals – PoS = 0.75



Expanding from Fixed to Adaptive Designs

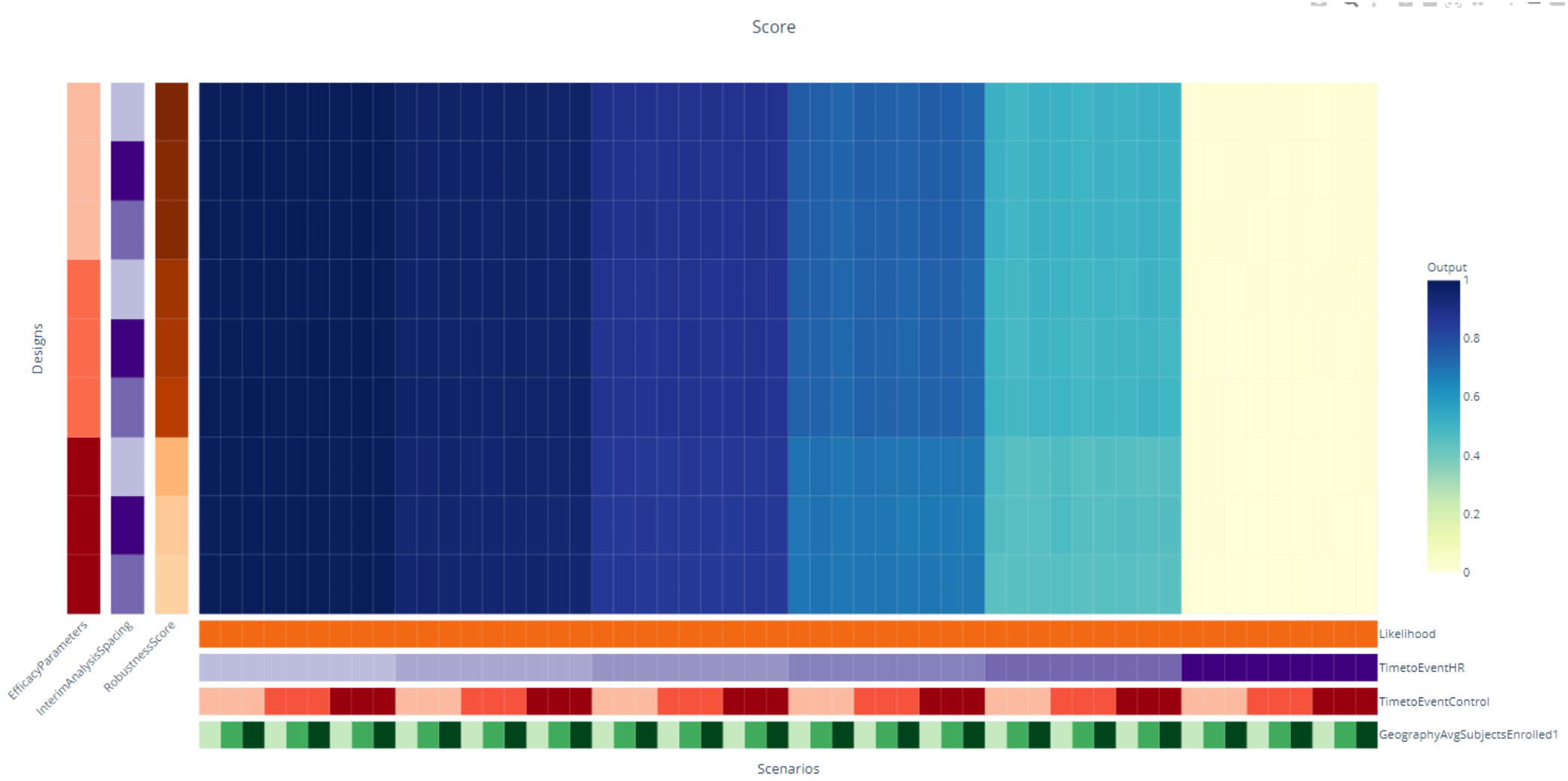
Clinical Study Description and Fixed Design Requirements

Phase III multicenter, randomized, placebo-controlled, parallel-arm clinical trial to evaluate the efficacy of Treatment versus Control in an acute Myeloid Leukemia study

Endpoint: Median OS

- Control median OS: 8 months
- Treatment effect: HR = 0.7
- Enrollment rate: 20 patients/month
- 1 Interim Analysis for Efficacy at either **40%, 50% or 60%** IF
- Alpha-spending according to Gamma rule **(-4,-2,1)**
- Sample Size: 451, Events: 331
- Power: 90%
- One-sided alpha: 2.5%

Using flat prior on unknowns (HR, Ctrl mOS, Accrual) we now have 1 PoS calculation for each possible design



Probability of Success of each design, flat priors

Fixed		GSD								
	IF	40			50			60		
	gamma	-4	-2	1	-4	-2	1	-4	-2	1
68.3%	Probability of Success	68.8%	68.3%	66.3%	68.7%	68.1%	65.9%	68.7%	68.2%	66.0%

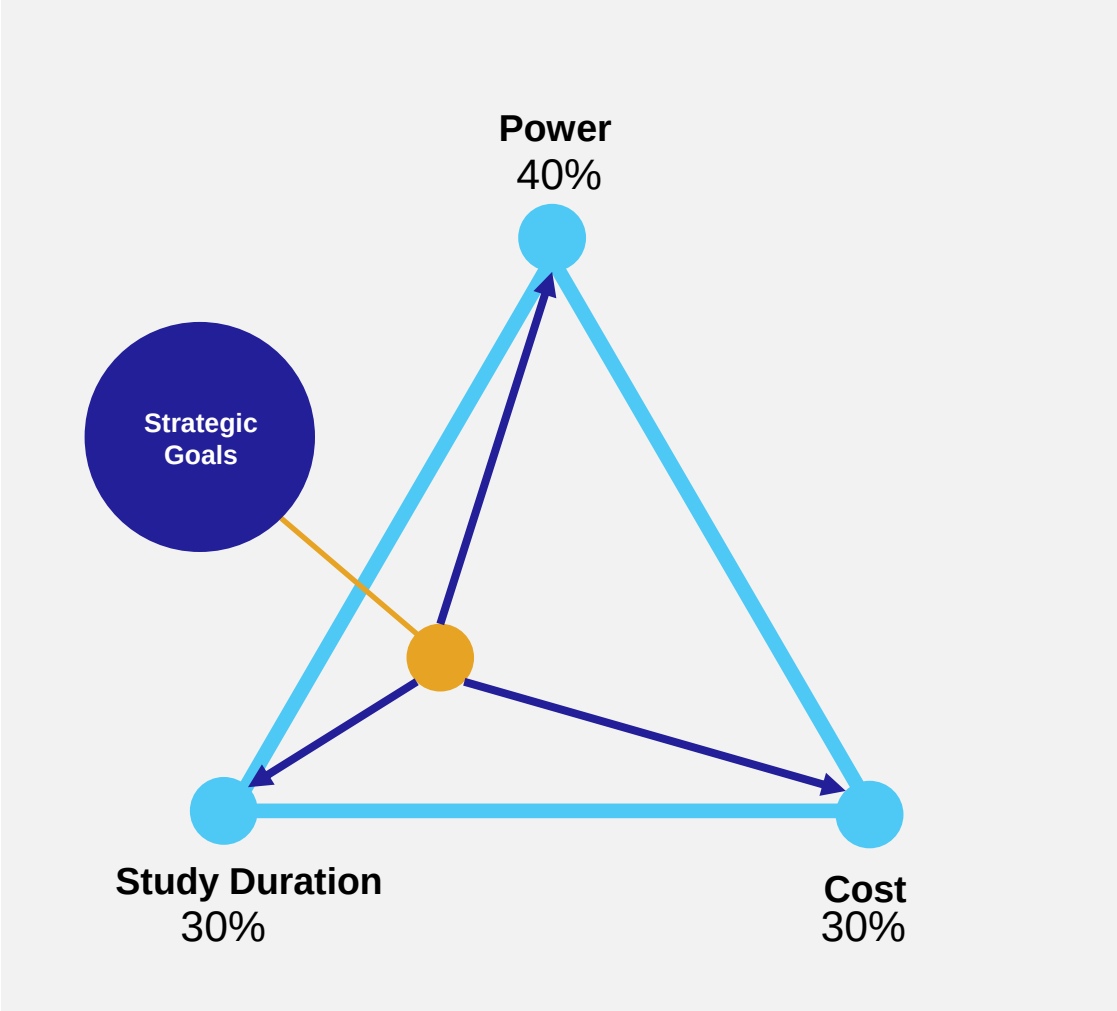
Probability of Success of each design, informative prior for HR, flat prior for Ctrl mOS and Accrual

Fixed		GSD								
	IF	40			50			60		
	gamma	-4	-2	1	-4	-2	1	-4	-2	1
68.3 %	Probability of Success (equal weights)	68.8%	68.3%	66.3%	68.7%	68.1%	65.9%	68.7%	68.2%	66.0%
73.5 %	Probability of Success (unequal weights)	73.9%	73.4%	71.1%	73.8%	73.2%	70.7%	73.9%	73.2%	70.8%

Recap

- We started with $PoS = \sum_x P(reject\ H_0 | HR = x) P(HR = x)$
- We defined a scenario as $\{HR = x, mOS_C = y, r_{acc}$= z} and
- arrived at $\boldsymbol{PoS = \sum_x P(reject\ H_0 | Scenario = s) P(Scenario = s)}$

What if our priorities extend beyond maximizing PoS?



Models can be scored on performance criteria that reflect strategic goals

The score is a weighted function of performance criteria

$$w_P\,(Power - P_{min}) / (P_{max} - P_{min}) + w_T\,(T_{max} - Time) / (T_{max} - T_{min}) + w_C\,(C_{max} - Cost) / (C_{max} - C_{min})$$

Selecting general design-agnostic criteria enable broad strategic comparisons

Scoring is meant to surface areas of interest in the design map that merit further exploration

Robustness score of each design, informative prior for HR, flat prior for Ctrl mOS and Accrual

Fixed		GSD								
	IF	40			50			60		
	gamma	-4	-2	1	-4	-2	1	-4	-2	1
Robustness (equal weights)		44.9%	49.1%	54.2%	45.9%	48.9%	51.7%	44.8%	46.3%	47.5%
Robustness (unequal weights)		46.1%	50.6%	56.1%	47.5%	50.8%	54.0%	46.8%	48.6%	49.9%

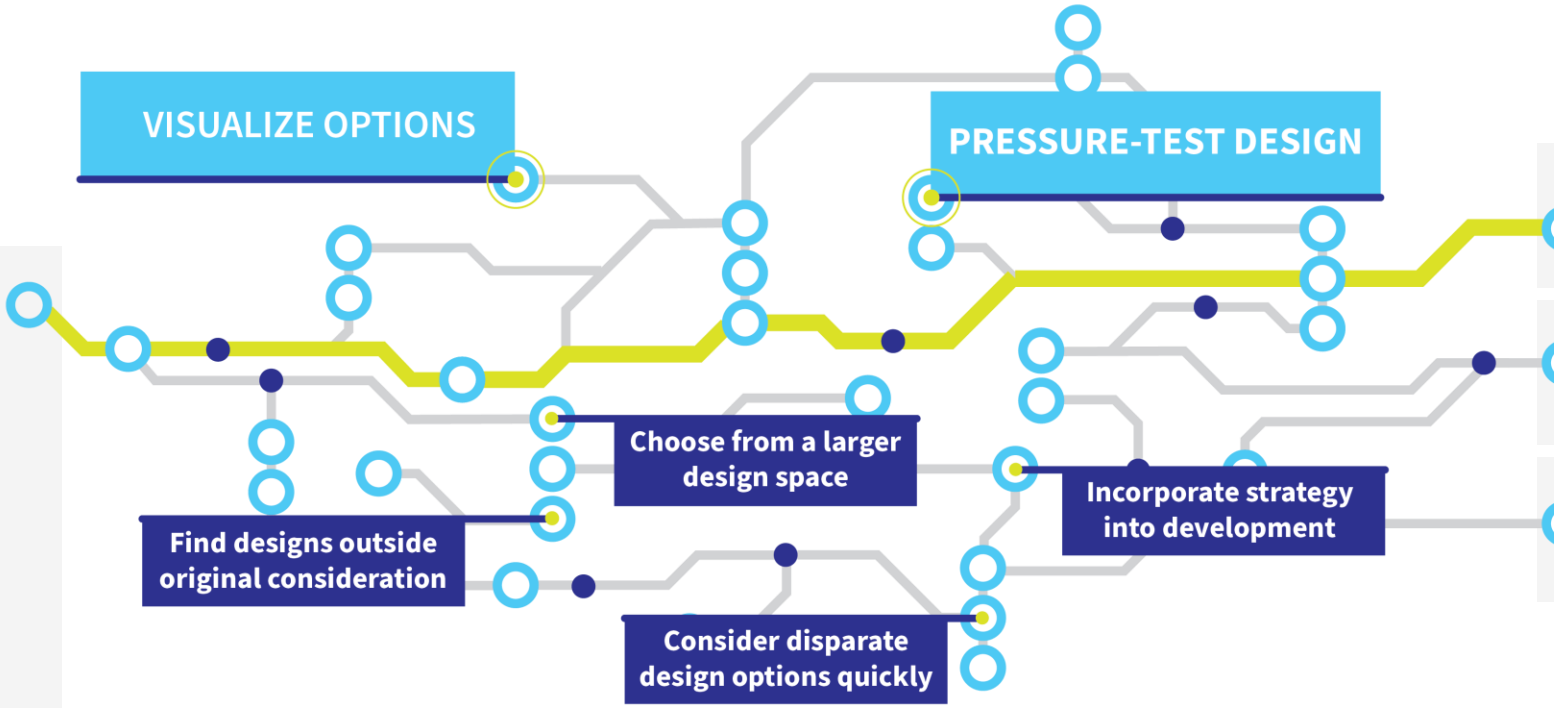
Score = 40%*Power + 30%*Duration + 30%*Sample Size

Find the Right Path for Your Study

TRIAL DESIGN SIMPLIFIED AND SCALED

Define Success

Team input:
Endpoints
Power
Budget
Design
Decision Criteria
Priorities



Better Trial

Faster Trial

Lower Cost Trial

ACCELERATE TO VALUE

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A case study in Multiple Myeloma

Multiple Myeloma Ph 3 Study

Reference Design	Inputs
Planned Sample Size	800
Planned Number of Events	227
Allocation Ratio	1:1
Targeted Treatment Effect (HR)	0.65
Control Median Survival Time	20 months
Type-1 error (1-sided)	0.025
Target Power	85%
Number of Interim Analyses	1
Timing of Interim Analysis	70%
Efficacy Stopping Rule	LD-OBF
Futility Stopping Rule	LD-OBF

Primary Outcome:

Progression Free Survival

Optimization Aim:

Maintain adequate power while minimizing time to market

Questions of interest:

- What is an optimal design that accounts for uncertainty on patient recruitment?
- How will treatment effect variations impact the trial?
- What study design would most optimize cost/sample size?

Cytel Simulation Plan Template

Design Options
Type 1 error: 1 sided 0.025
Allocation Ratios: 1:1
Number of subjects: 700:800:20
Number of events (if TTE): 130,162, 182, 210, 227, 263
Statistical Design: GSD, GSD with SSR
Number of interim analyses: 1IA
Timing of interim analyses: 65%, 70%, 75%
Efficacy Stopping Rules/Alpha Spending Function: OBF
Futility Stopping Rules/Beta Spending Function: OBF, none
Promising Zone (if applicable): min = 0.3, max = 0.8, 0.9
Target Conditional Power (if applicable): 90%, 99%
Max Number of Subjects/Events (if applicable): 1.2, 1.3, 1.4

Population Scenarios
True underlying control response rates: 20m PFS (vary?)
True underlying treatment effects: 0.60, 0.65, 0.67
Dropout rate: 0

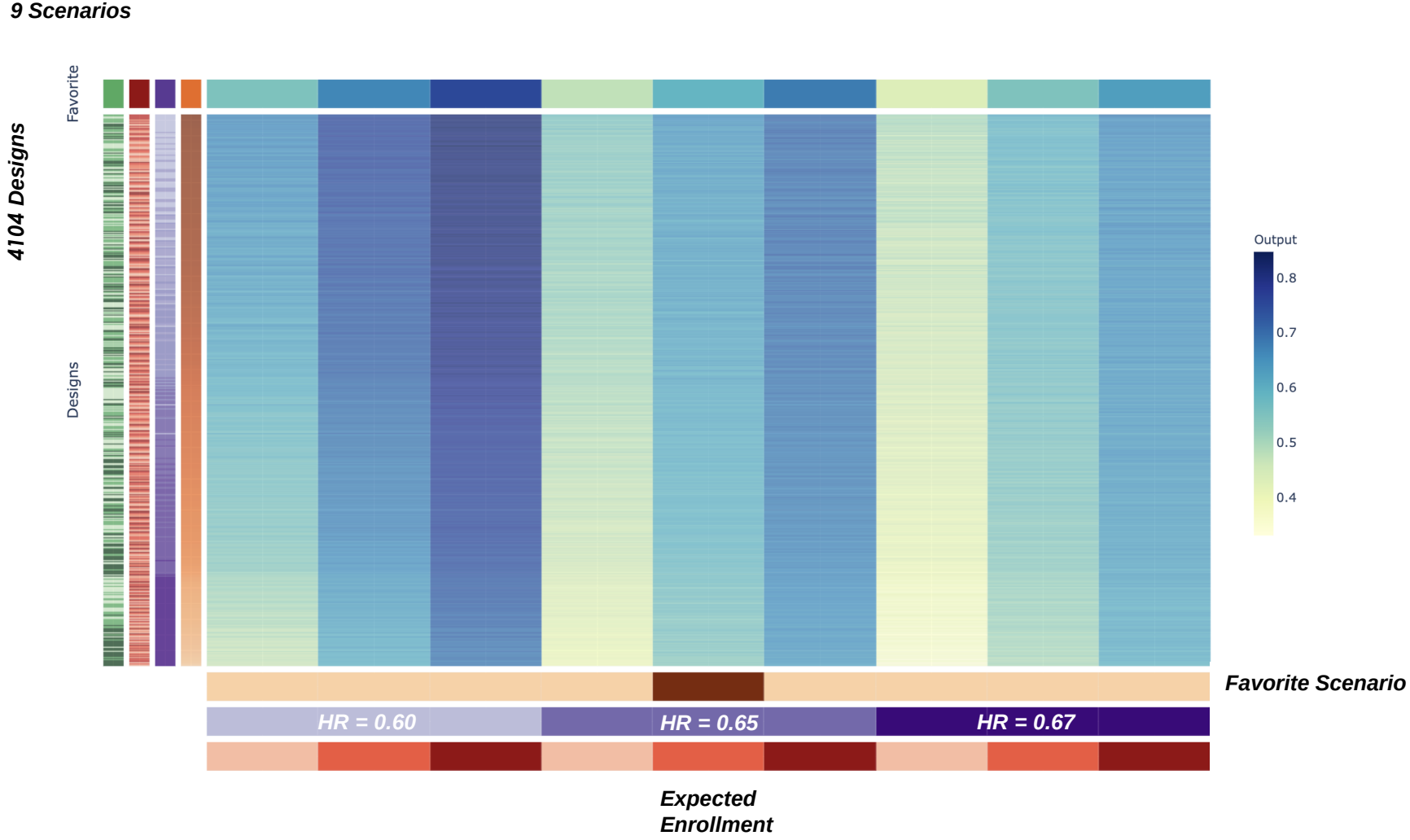
Enrollment Patterns
Enrollment Rates: (Number of periods, starting at time, average enrollment rate) 20pts/mo, 25pts/mo, 30pts/mo

Average Cost per Patient
$100,000

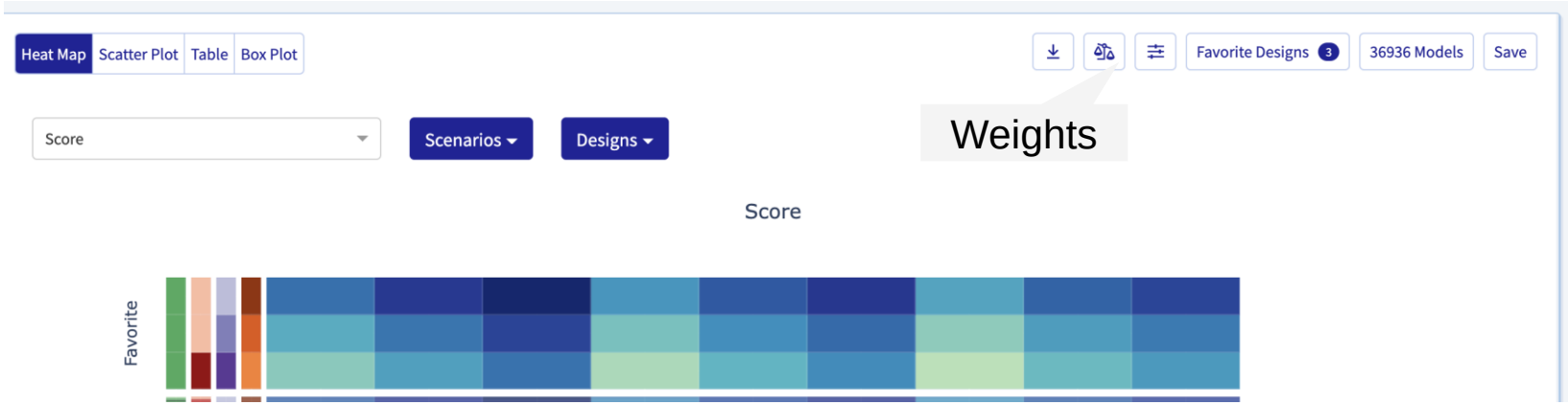
Total number of design options in combination with scenarios (i.e., Models) =
4,104 designs x 9 scenarios = 36,936 models

Multiple Myeloma Study

~37 Million Simulated Trials



Update weights on score and scenarios



Weights

Scoring | Response | Enrollment

Weights must add up to 100%.

	Weight (%)	Threshold
Maximize Probability of Winning	0	0.85
Minimize Sample Size	10	
Minimize Study Duration	90	

Apply | Cancel | Reset All

Weights

Scoring | Response | Enrollment

Weights must add up to 100%.

Set	Weight (%)
Response Set 1	100

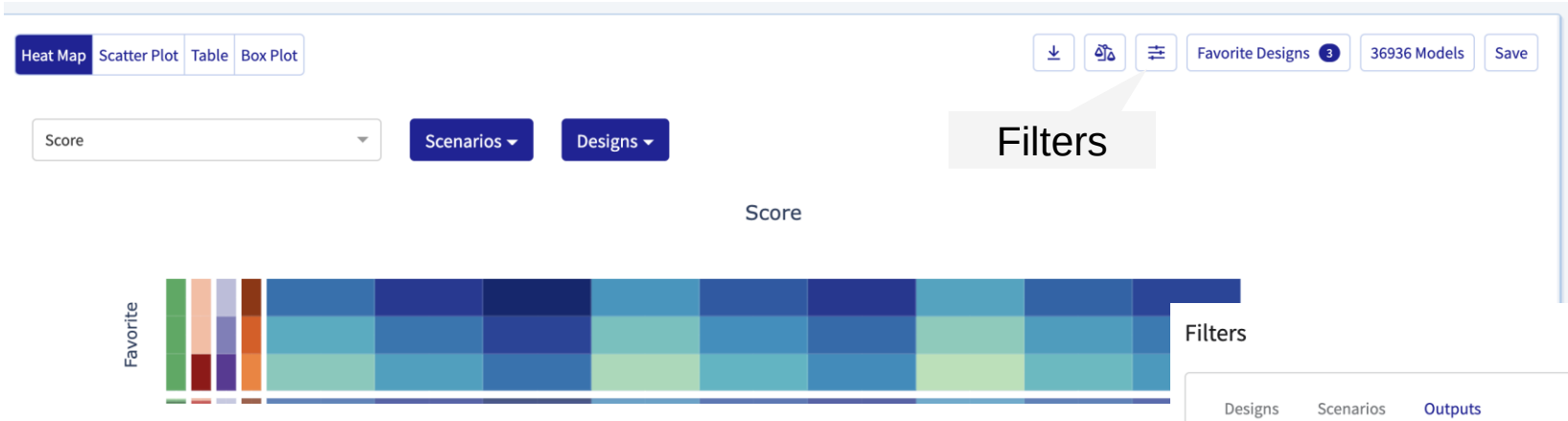
Probability Dropout Control	Weight (%)
0	100

Probability Dropout Treatment	Weight (%)
0	100

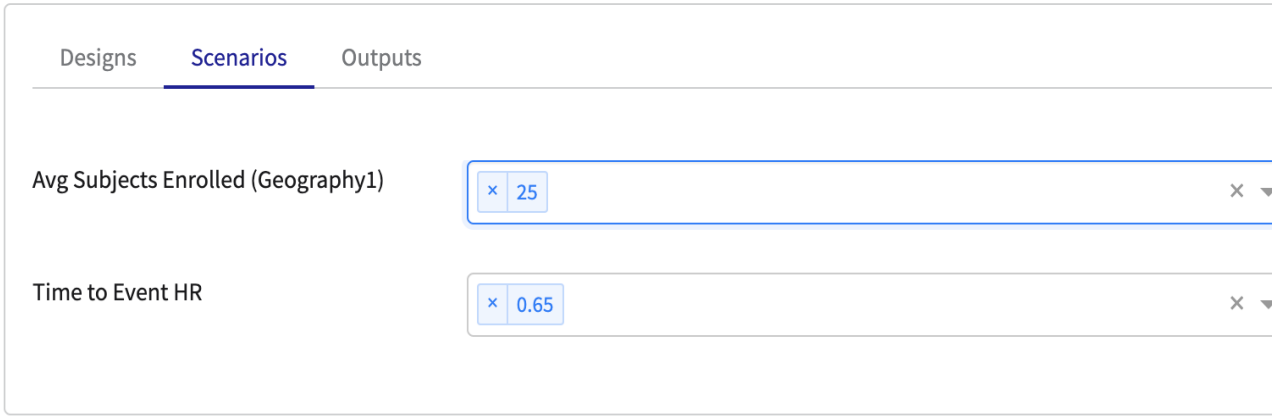
Time to Event Control	Weight (%)
20	100

Time to Event HR	Weight (%)
0.6	33.33
0.65	33.33
0.67	33.33

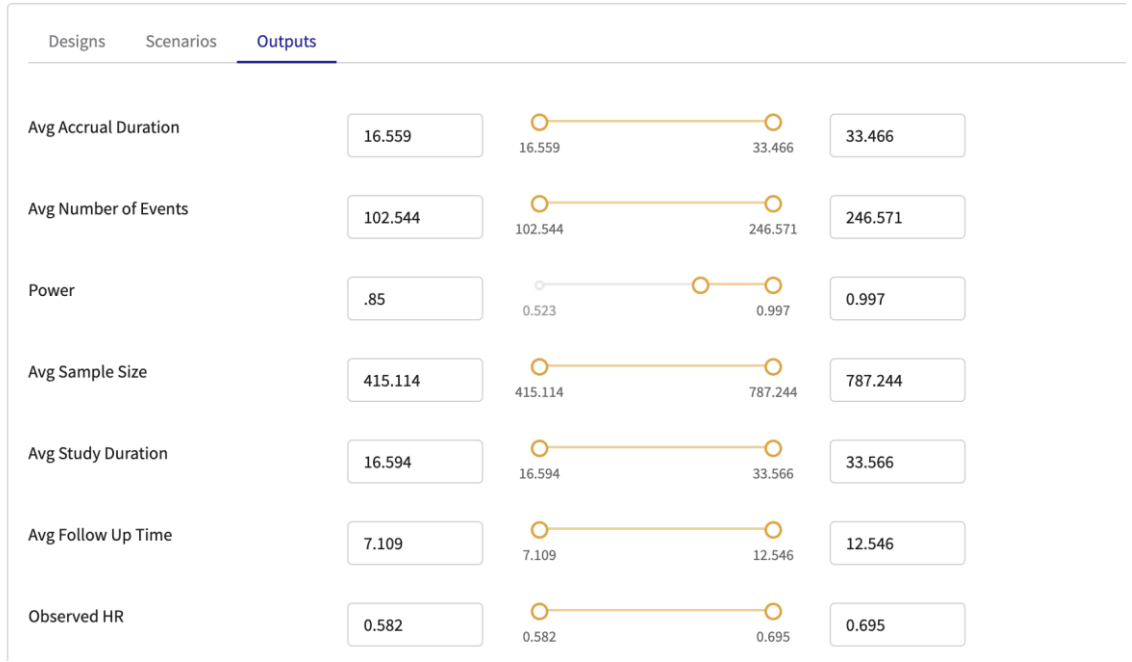
Filter on Scenarios/Designs/Outputs of Interest



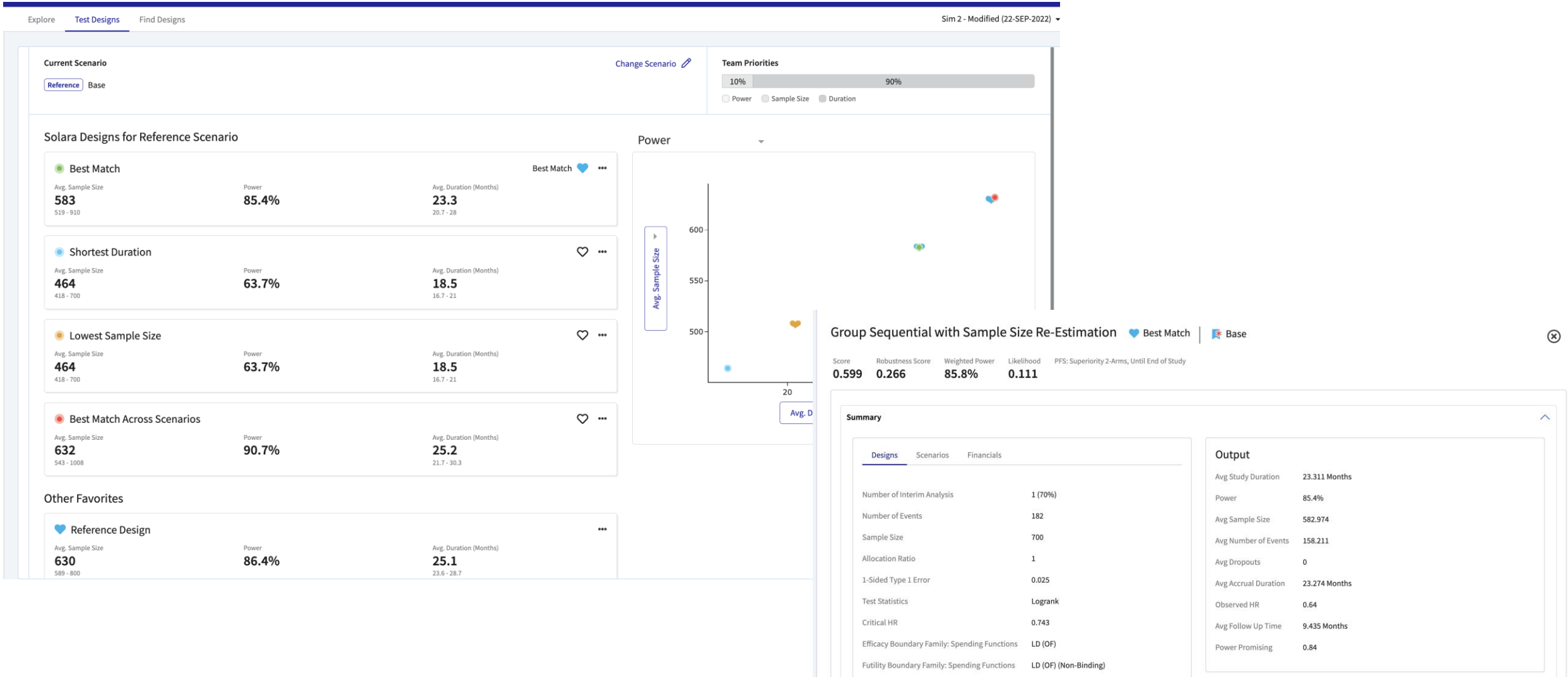
Filters



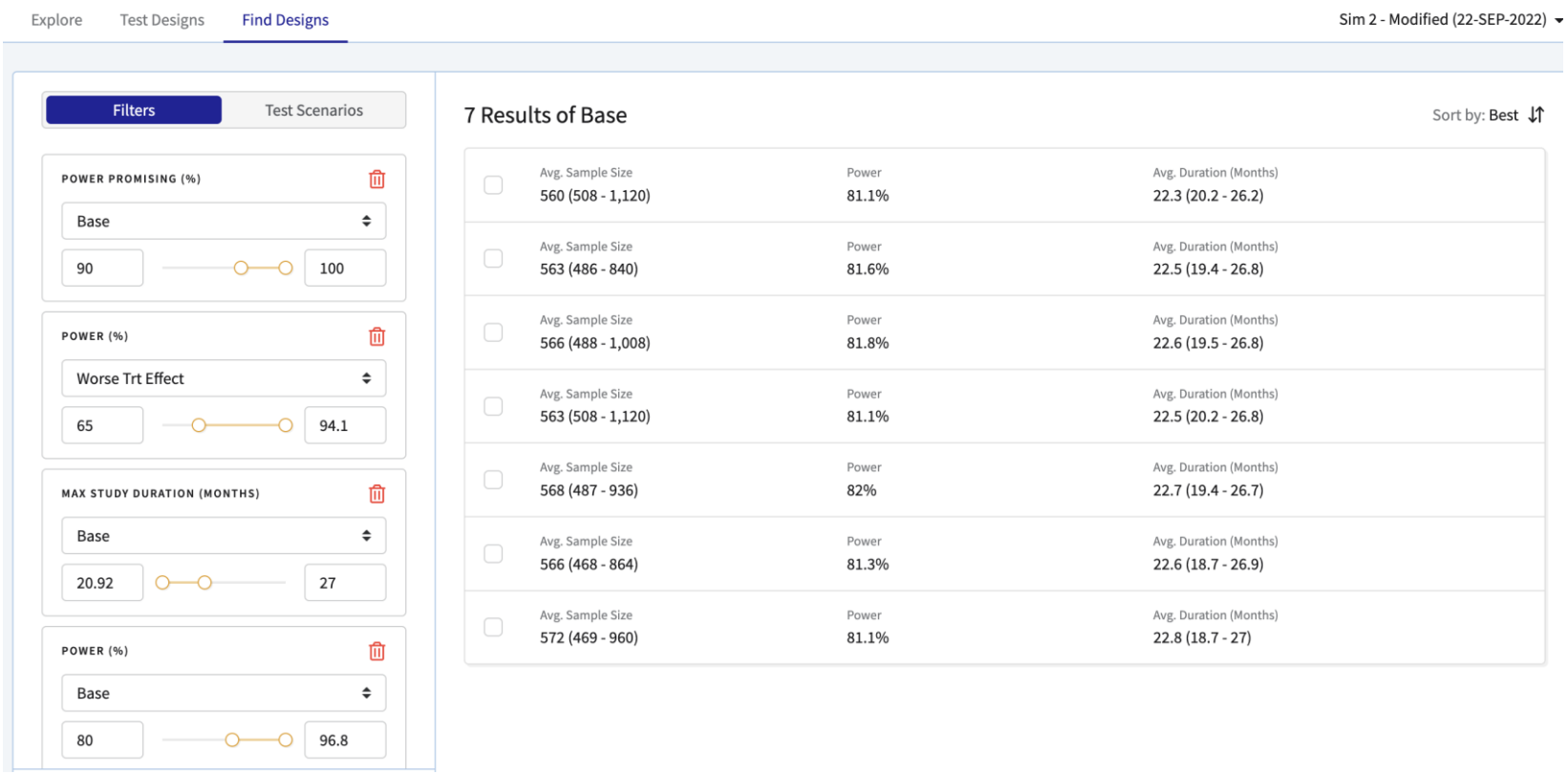
Filters



Test Designs



Find Designs

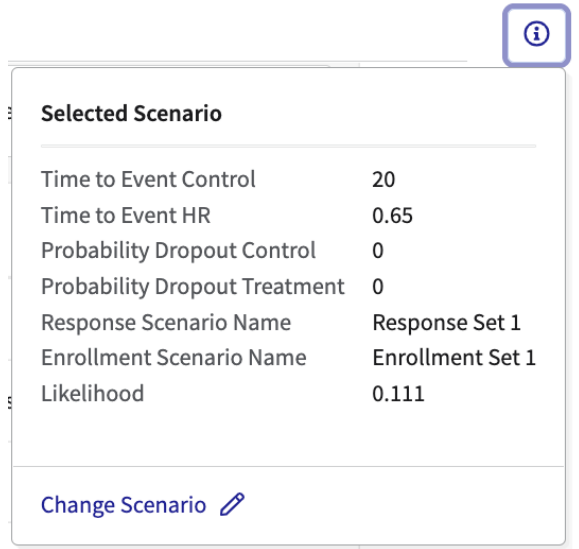


Favorited Designs

Favorite Designs

Summary

Only Show Differences	Best Match	Shortest Duration SSR	Reference Design
Outputs			
Score	0.599	0	0.489
Avg Study Duration	23.311 Months	20.226 Months	25.149 Months
Power	85.4%	72.2%	86.4%
Avg Sample Size	582.974	506.533	629.05
Avg Number of Events	158.211	123.539	180.012
Avg Accrual Duration	23.274 Months	20.186 Months	25.11 Months
Observed HR	0.64	0.652	0.651
Avg Follow Up Time	9.435 Months	8.39 Months	10.036 Months
Power Promising	0.84	0.873	NA
Study Design			
Statistical Design	Group Sequential with Sample Size Re-Estimation	Group Sequential with Sample Size Re-Estimation	Group Sequential
Robustness Score	0.266	0.088	0.319
Weighted Probability of Winning	85.8%	73.8%	88.1%



View favorited designs under different scenarios

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Solara™

First In Class Digital Development Platform for Simulation Guided Clinical Trial Design

Your team's input

- Study endpoints, budget, ranges for sample size / enrollment / treatment effect, design options (e.g. fixed or adaptive)
- Team priorities (speed/cost/power)

East — Proprietary statistical design algorithms

- Trusted and validated for over 30 years
- Industry standard platform used by the FDA

Massive cloud compute power

- Parallel processing for near real-time design space generation

=

What it does:

- Based on team inputs, calculates study datasets for different designs and scenarios of interest
- Monte Carlo simulations scaled and applied across 1000s of permutations
- Helps teams visualize their options and select the best fit for their needs
- ***Routinely finds better designs than the manual process***

Thank you.

Cytel