An R Shiny App to design and analyse basket trials in Oncology

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24 May 2019, BAYES2019, Lyon, France

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Outline

- R Shiny App BHM Basket
  - support for design & analysis of basket trials in Oncology
- Basket trials in Oncology
- Bayesian Hierarchical Model
- Go/No-Go Decision Making

- Example: Basket trial with 7 cohorts and interim futility analysis

Basket trials in Oncology

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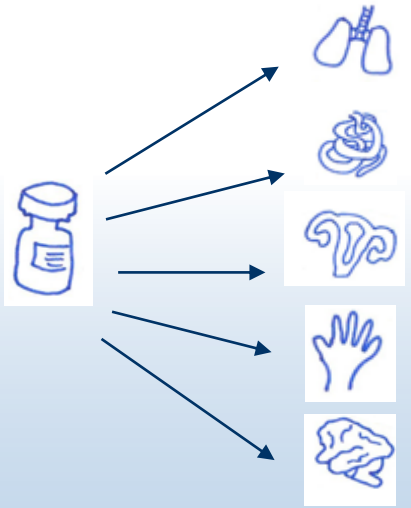
Basket Design

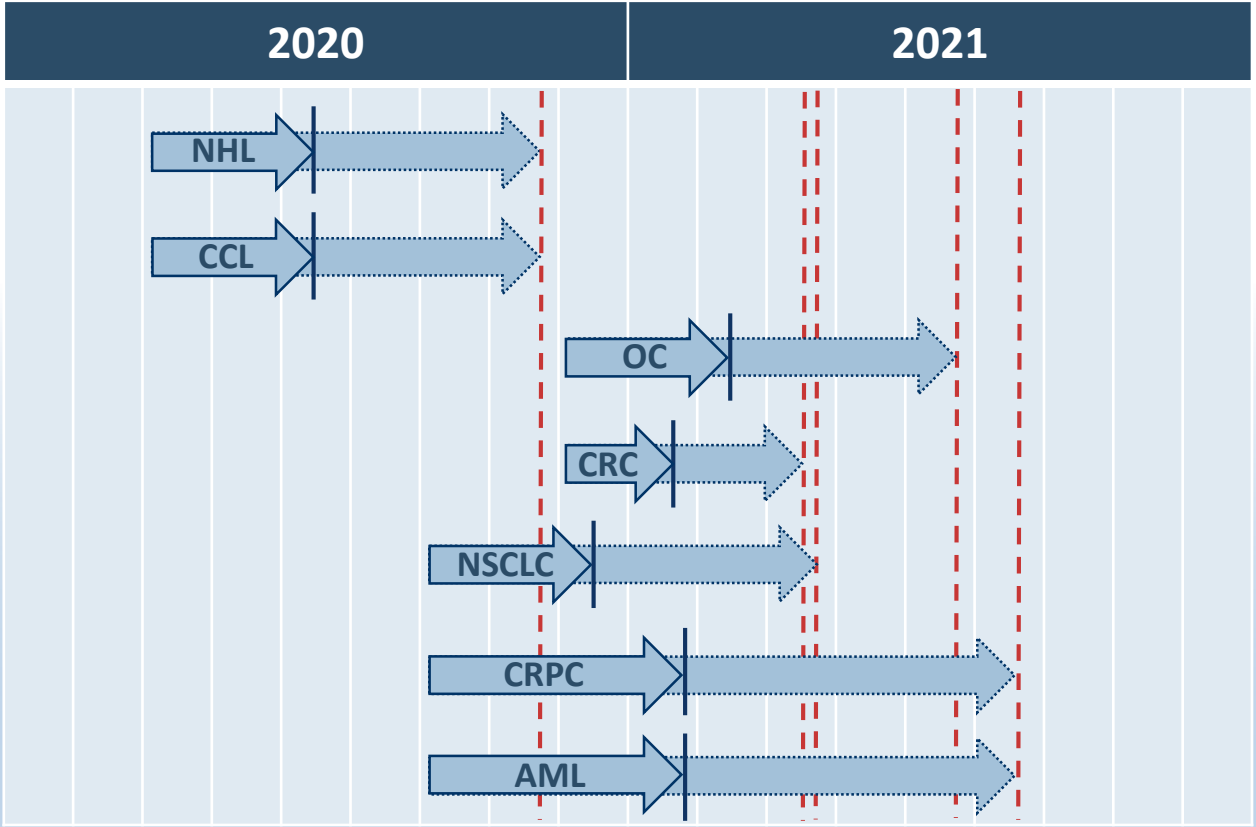
- Basket trial*
  - One experimental treatment
  - (Patients with similar genomic features)
  - Different disease types

- Questions
  - Does the treatment work sufficiently?
  - Can we identify cohorts with a promising effect?



* Renfro and Sargent 2016

Example



Futility Analysis
Recruitment stop if r < c

Final Analysis
Go/No-Go decision
based on BHM

Bayesian Hierarchical Model

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Basket Designs - Analysis Approaches

Stratification — Pooling

- Assumes independent cohorts
- Low precision

- Assumes the same underlying response rate in all cohorts
- Potentially large bias

Bayesian hierarchical model (BHM)

- Assumes exchangeability between cohorts
- Parameter of inter-cohort variation is considered to be random, determines extent of borrowing

BHM adjusting for target rate (Berry et al. 2013)

- Random cohort effect in terms of log-odds of response rate
- Likelihood

$$r_i | p_j \sim Bin(p_j, n_j)$$

$$\theta_j = log\left(\frac{p_j}{1-p_j}\right) - log\left(\frac{\tilde{p}_j}{1-\tilde{p}_j}\right)$$

Exchangeability of log-odds after adjusting for target rates

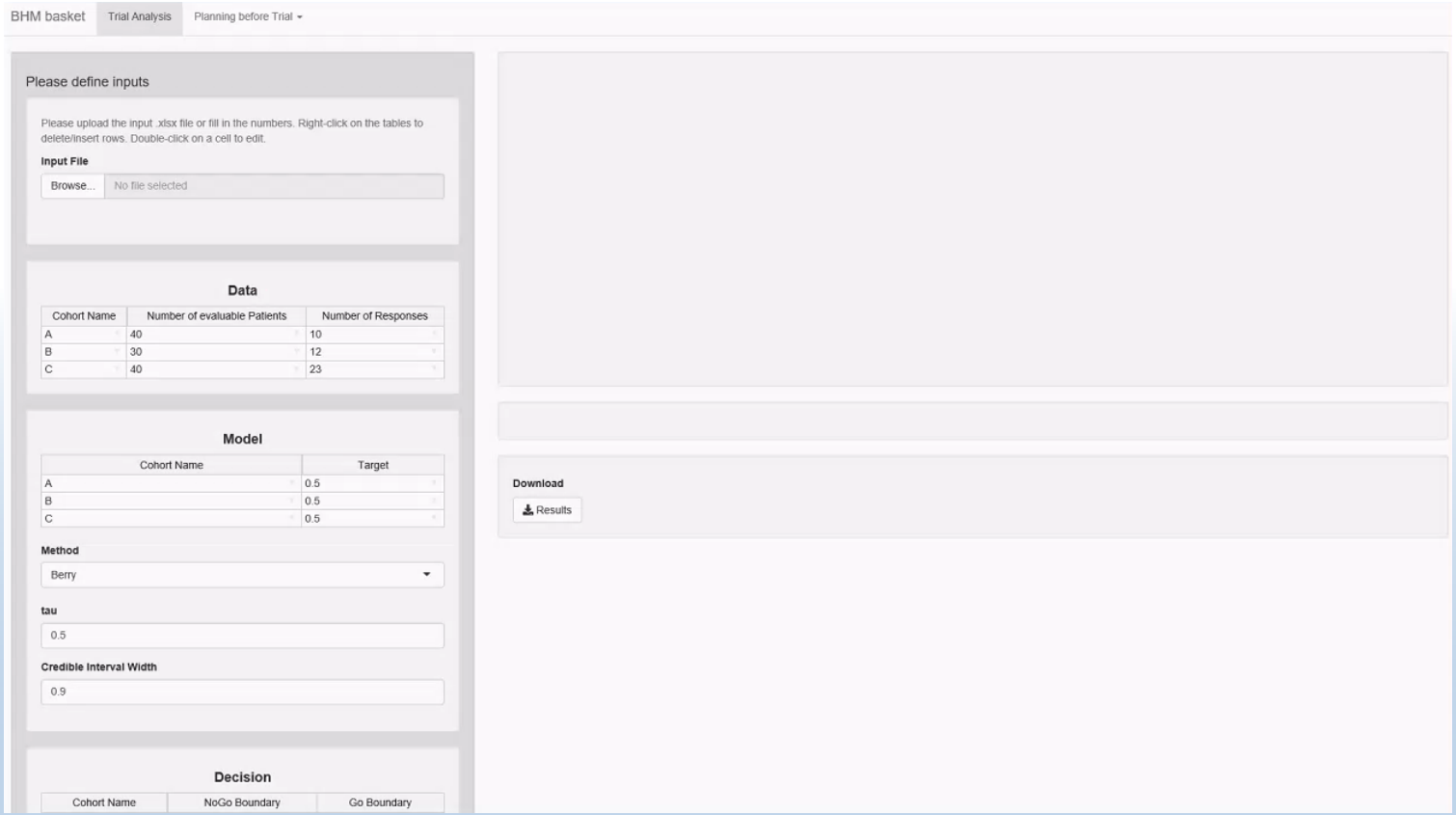
- Prior

$$\theta_j | \mu, \tau \sim N(\mu, \tau^2)$$
$$\mu \sim N(m_\mu, v_\mu)$$
$$\tau \sim HN(s_\tau)$$

Informative prior on inter-cohort variability (Neuenschwander et al. 2015)

- Implementation: R interface to JAGS, R2JAGS package

Implementation – Trial Analysis



Implementation – Trial Analysis

Result Table

Cohort Name	Number of evaluable Patients	Number of Responses	Observed Response Rate	Adjusted Response Rate	5% Quantile	95% Quantile	NoGo Boundary	Go Boundary	Decision
NHL	25	6	0.2400	0.3203	0.1910	0.4455	0.10	0.30	go
CLL	25	10	0.4000	0.3949	0.2791	0.5216	0.10	0.30	go
OC	25	6	0.2400	0.3207	0.1920	0.4458	0.10	0.30	go
CRC	30	20	0.6667	0.5460	0.3919	0.6982	0.10	0.30	go
NSCLC	25	8	0.3200	0.3599	0.2360	0.4815	0.10	0.30	go
CRPC	25	8	0.3200	0.2919	0.1929	0.4194	0.10	0.20	go
AML	25	8	0.3200	0.2928	0.1950	0.4163	0.10	0.20	go

Go/No-Go decision making

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Go/No-Go Decision Making

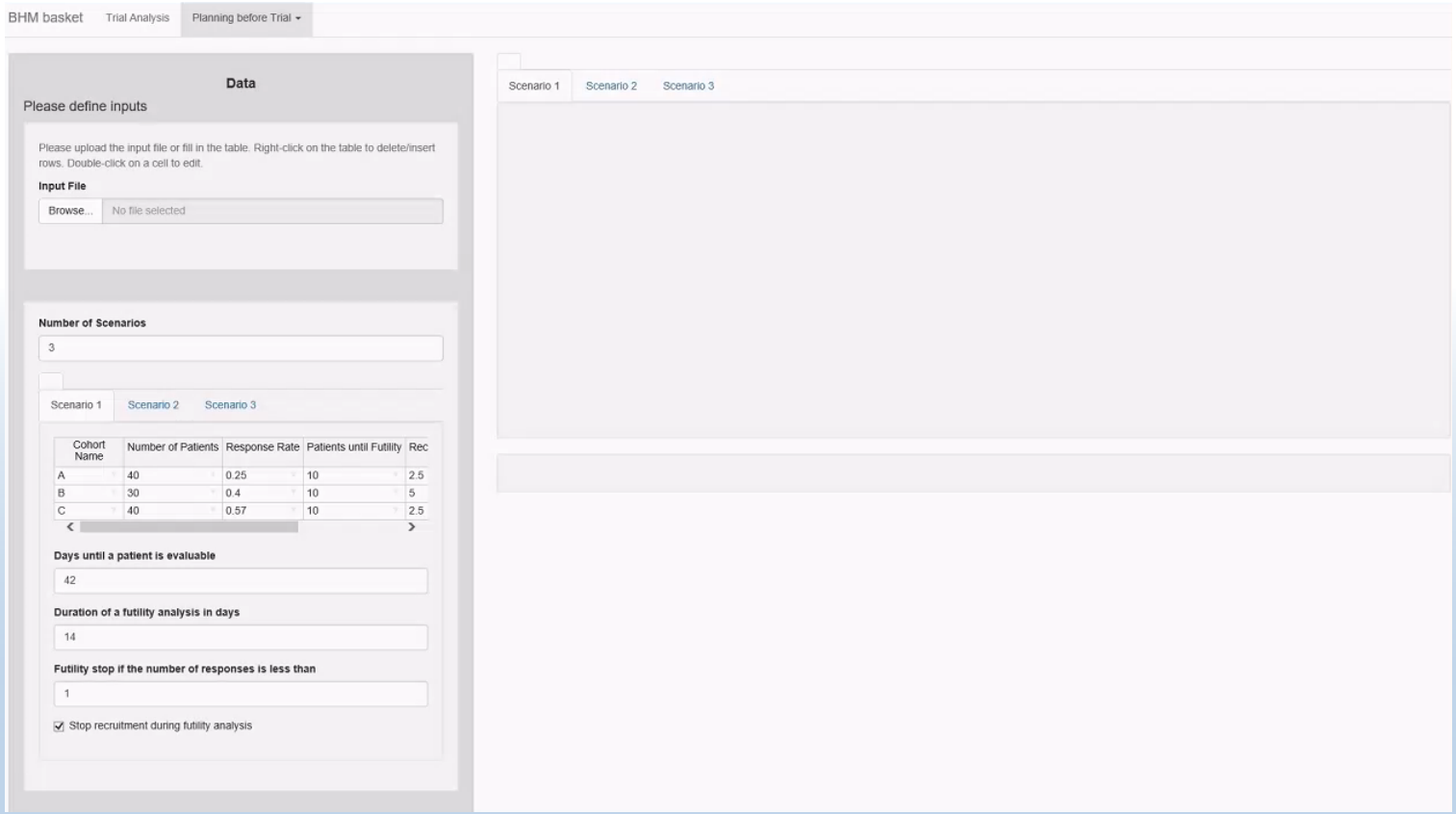
- Quantitative decision making to increase efficiency of drug development (Lalonde et al. 2007)
- Statistical Go/No-Go criteria are predefined, quantifiable criteria to allow for decision making given the observed results in the trial
- Three outcome decision

Δ Treatment effect

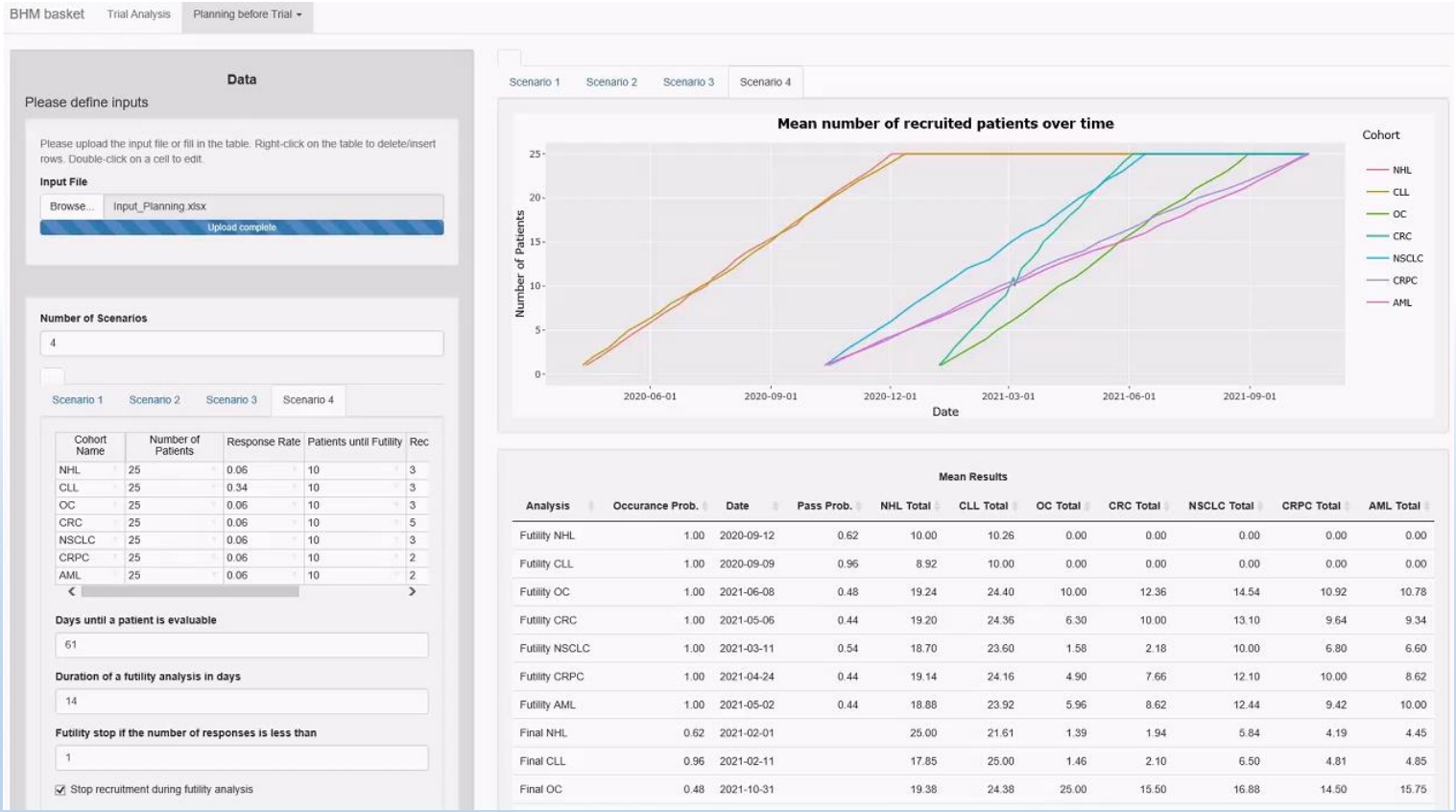
Go/No-Go Decision Making

- Aggregate by-cohort Go/No-Go decisions to arrive at overall decision
  - E.g. overall Go if at least one cohort meets go
  - E.g. overall No-Go if all cohorts are no-go
- Calculate probability of making correct/false decisions under various scenarios
- Calculate average sample size, trial duration and time to overall decision
- Adjust design parameters to arrive at desirable operating characteristics

Implementation – Planning before Trial: Data



Implementation – Planning before Trial: Model



Mean Results

Analysis	Occurance Prob.	Date	Pass Prob.	NHL Total	CLL Total	OC Total	CRC Total	NSCLC Total	CRPC Total	AML Total
Futility NHL	1.00	2020-09-12	0.62	10.00	10.26	0.00	0.00	0.00	0.00	0.00
Futility CLL	1.00	2020-09-09	0.96	8.92	10.00	0.00	0.00	0.00	0.00	0.00
Futility OC	1.00	2021-06-08	0.48	19.24	24.40	10.00	12.36	14.54	10.92	10.78
Futility CRC	1.00	2021-05-06	0.44	19.20	24.36	6.30	10.00	13.10	9.64	9.34
Futility NSCLC	1.00	2021-03-11	0.54	18.70	23.60	1.58	2.18	10.00	6.80	6.60
Futility CRPC	1.00	2021-04-24	0.44	19.14	24.16	4.90	7.66	12.10	10.00	8.62
Futility AML	1.00	2021-05-02	0.44	18.88	23.92	5.96	8.62	12.44	9.42	10.00
Final NHL	0.62	2021-02-01		25.00	21.61	1.39	1.94	5.84	4.19	4.45
Final CLL	0.96	2021-02-11		17.85	25.00	1.46	2.10	6.50	4.81	4.85
Final OC	0.48	2021-10-31		19.38	24.38	25.00	15.50	16.88	14.50	15.75

Implementation – Planning before Trial: Decision

BHM basket | Trial Analysis | Planning before Trial

Model

Please define inputs

Cohort Name	Target
NHL	0.34
CLL	0.34
OC	0.34
CRC	0.34
NSCLC	0.34
CRPC	0.23
AML	0.23

Method: Berry

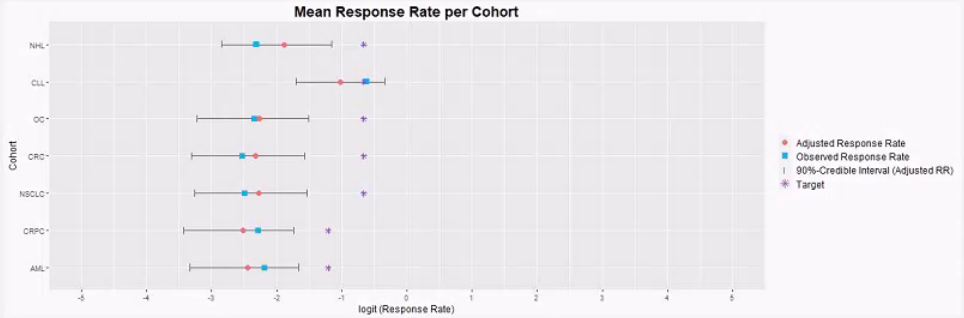
tau: 0.5

Credible Interval Width: 0.9

Seed: 21

▶ Run

Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4



☑ Logit scale

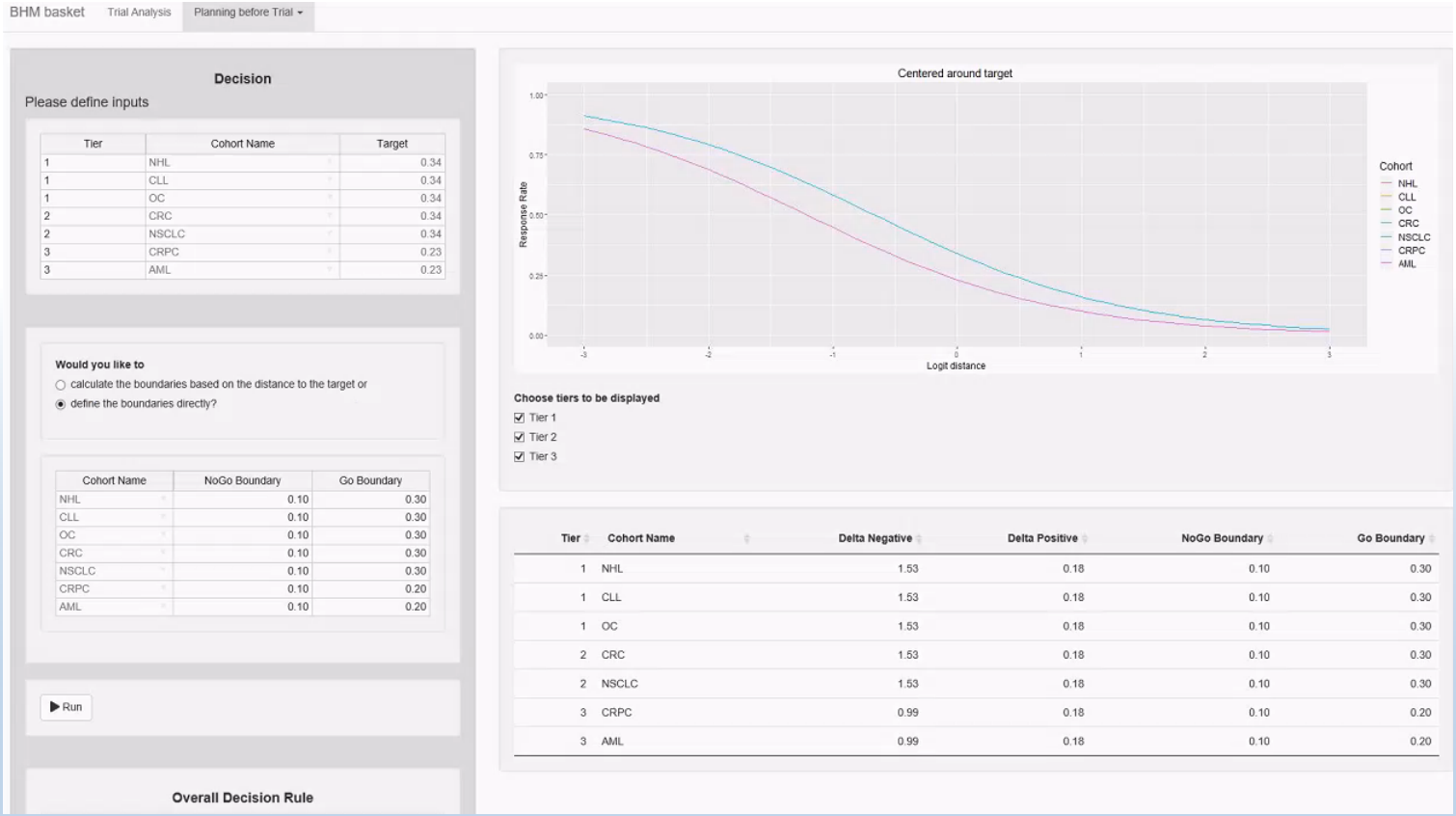
futile cohorts are excluded

Mean Results

Cohort Name	Observed Response Rate	Observed Response Rate (futile cohorts included)	Adjusted Response Rate	5% Quantile	95% Quantile
NHL	0.0903	0.0560	0.1315	0.0552	0.2392
CLL	0.3517	0.3376	0.2656	0.1544	0.4159
OC	0.0883	0.0424	0.0939	0.0382	0.1821
CRC	0.0745	0.0328	0.0893	0.0355	0.1717
NSCLC	0.0770	0.0416	0.0933	0.0372	0.1782
CRPC	0.0927	0.0408	0.0745	0.0315	0.1501
AML	0.1018	0.0448	0.0798	0.0345	0.1595

futile cohorts are excluded

Implementation – Planning before Trial: Operating Characteristics



Implementation – Planning before Trial: Operating Characteristics

Decision Probabilities

Scenarios (true response rate)	adj. RR < 10% for NHL, CLL, OC, CRC, NSCLC, CRPC, AML	adj. RR ≥ 10% - ≤ 30 % for NHL, CLL, OC, CRC, NSCLC, adj. RR ≥ 10% - ≤ 20 % for CRPC, AML	adj. RR > 30% for NHL, CLL, OC, CRC, NSCLC, adj. RR > 20% for CRPC, AML
NHL, CLL, OC, CRC, NSCLC, CRPC, AML	NoGo	Consider	Go
34%, 34%, 34%, 34%, 34%, 23%, 23%	0% (2%, 4%, 0%, 2%, 0%, 6%, 10%)	10% (28%, 18%, 26%, 24%, 16%, 20%, 14%)	90% (70%, 78%, 74%, 74%, 84%, 74%, 76%)
6%, 6%, 6%, 6%, 6%, 6%, 6%	72% (84%, 82%, 98%, 96%, 92%, 100%, 100%)	28% (16%, 18%, 2%, 4%, 8%, 0%, 0%)	0% (0%, 0%, 0%, 0%, 0%, 0%, 0%)
6%, 6%, 6%, 34%, 34%, 23%, 23%	26% (62%, 64%, 58%, 2%, 0%, 10%, 10%)	74% (38%, 36%, 42%, 62%, 54%, 48%, 46%)	0% (0%, 0%, 0%, 36%, 46%, 42%, 44%)
6%, 34%, 6%, 6%, 6%, 6%, 6%	4% (52%, 6%, 78%, 88%, 74%, 96%, 92%)	58% (48%, 56%, 22%, 12%, 26%, 4%, 8%)	38% (0%, 38%, 0%, 0%, 0%, 0%, 0%)

Overall NoGo if the number of NoGo cohorts within tier 1 is at least 3.

Overall Go if the number of Go cohorts within tier 1 is at least 1.

Number of simulations: 50

Which decision probabilities would you like to display?

- ☑ Overall
- ☑ NHL
- ☑ CLL
- ☑ OC
- ☑ CRC
- ☑ NSCLC
- ☑ CRPC
- ☑ AML

☑ Show Overall Decision Rule

☑ Show Cohortwise Decision Rule

☑ Show Scenario Details

Implementation – Planning before Trial: Operating Characteristics

Mean Sample Size and Duration

	Total	NHL Total	CLL Total	OC Total	CRC Total	NSCLC Total	CRPC Total	AML Total	Date
Scenario 1 - Decisive Analysis	84.02	24.48	22.44	5.46	6.10	9.90	7.86	7.78	04/03/2021
Scenario 1 - Last Analysis	171.40	24.70	24.40	25.00	24.70	25.00	24.10	23.50	02/11/2022
Scenario 2 - Decisive Analysis	120.70	19.30	16.30	17.20	16.60	18.10	16.60	16.60	12/02/2021
Scenario 2 - Last Analysis	120.70	19.30	16.30	17.20	16.60	18.10	16.60	16.60	12/02/2021
Scenario 3 - Decisive Analysis	135.28	19.30	16.30	14.24	24.14	23.76	19.86	17.68	10/17/2021
Scenario 3 - Last Analysis	150.10	19.30	16.30	17.20	24.70	25.00	24.10	23.50	01/29/2022
Scenario 4 - Decisive Analysis	100.28	18.36	24.40	10.66	10.42	13.48	11.28	11.68	07/28/2021
Scenario 4 - Last Analysis	128.80	19.30	24.40	17.20	16.60	18.10	16.60	16.60	11/26/2021

Summary

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Summary

- BHM Basket app supports design & analysis of basket trials
- Analysis of response rate in cohorts using BHM of Berry et al. 2013
- Provides operating characteristics under flexible scenarios
  - Recruitment start, rate
  - Cohort size
  - Model parameters
  - Assumed response rates
  - Futility analysis
  - Decision rule

References

Berry SM, Broglio KR, Groshen S, and Berry DA (2013): Bayesian hierarchical modeling of patient subpopulations: efficient designs of phase II oncology clinical trials. Clinical Trials, 10(5), 720-734.

Chang W, Cheng J, Allaire JJ, Xie Y, and McPherson J (2018): shiny: Web Application Framework for R. R package version 1.2.0. https://CRAN.R-project.org/package=shiny.

Lalonde RL, Kowalski KG, Hutmacher MM, Ewy W, Nichols DJ, Milligan PA, Corrigan BW, Lockwood PA, Marshall SA, LJ Benincosa, et al. (2007): Model-based drug development. Clinical Pharmacology & Therapeutics, 82(1), 21-32.

Neuenschwander B, Wandel S, Roychoudhury S, and Bailey S (2015): Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceutical Statistics, 15, 123-134.

Renfro LA and Mandrekar SJ (2017): Definitions and Statistical Properties of Master Protocols for Personalized Medicine in Oncology. Journal of Biopharmaceutical Statistics 28(2), 217-228.

Questions?

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Back-up

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Implementation – Trial Analysis

Input File

Browse... Input_TrialAnalysis.xlsx

Upload complete

Data

Cohort Name	Number of evaluable Patients	Number of Responses
NHL	25	6
CLL	25	10
OC	25	6
CRC	25	10
NSCLC	25	8
CRPC	25	8
AML	25	8

Model

Cohort Name	Target
NHL	0.34
CLL	0.34
OC	0.34
CRC	0.34
NSCLC	0.34
CRPC	0.23
AML	0.23

Method

Berry

tau

0.5

Credible Interval Width

0.9

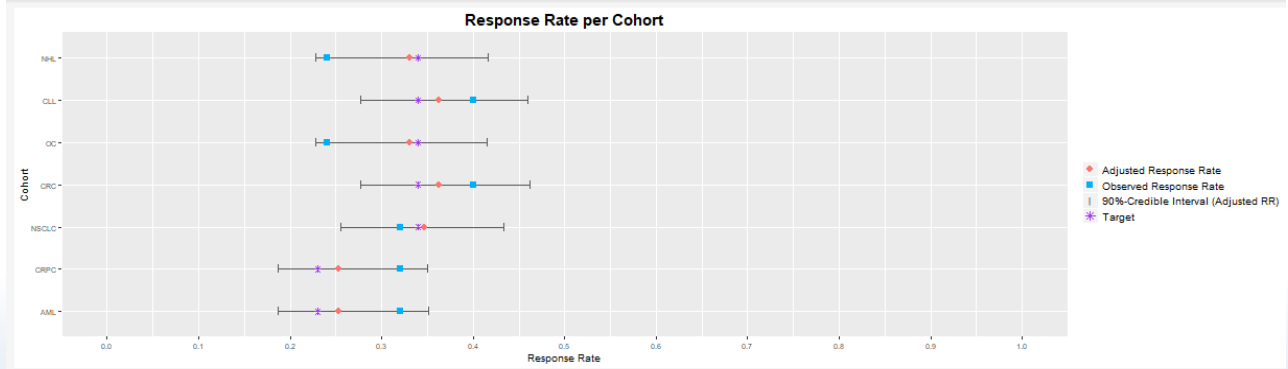
Decision

Cohort Name	NoGo Boundary	Go Boundary
NHL	0.1	0.3
CLL	0.1	0.3
OC	0.1	0.3
CRC	0.1	0.3
NSCLC	0.1	0.3
CRPC	0.1	0.2
AML	0.1	0.2

Seed

21

▶ Run



☐ Logit scale

Result Table

Cohort Name	Number of evaluable Patients	Number of Responses	Observed Response Rate	Adjusted Response Rate	5% Quantile	95% Quantile	NoGo Boundary	Go Boundary	Decision
NHL	25	6	0.2400	0.3312	0.2279	0.4161	0.10	0.30	go
CLL	25	10	0.4000	0.3621	0.2765	0.4600	0.10	0.30	go
OC	25	6	0.2400	0.3309	0.2284	0.4153	0.10	0.30	go
CRC	25	10	0.4000	0.3624	0.2770	0.4619	0.10	0.30	go
NSCLC	25	8	0.3200	0.3464	0.2556	0.4330	0.10	0.30	go
CRPC	25	8	0.3200	0.2534	0.1862	0.3504	0.10	0.20	go
AML	25	8	0.3200	0.2527	0.1863	0.3513	0.10	0.20	go

Download

Results

Implementation – Trial Analysis

Result Table

Cohort Name	Number of evaluable Patients	Number of Responses	Observed Response Rate	Adjusted Response Rate	5% Quantile	95% Quantile	NoGo Boundary	Go Boundary	Decision
NHL	25	6	0.2400	0.3203	0.1910	0.4455	0.10	0.30	go
CLL	25	10	0.4000	0.3949	0.2791	0.5216	0.10	0.30	go
OC	25	6	0.2400	0.3207	0.1920	0.4458	0.10	0.30	go
CRC	30	20	0.6667	0.5460	0.3919	0.6982	0.10	0.30	go
NSCLC	25	8	0.3200	0.3599	0.2360	0.4815	0.10	0.30	go
CRPC	25	8	0.3200	0.2919	0.1929	0.4194	0.10	0.20	go
AML	25	8	0.3200	0.2928	0.1950	0.4163	0.10	0.20	go

Implementation – Planning before Trial: Data

Input File

Browse... Input_Planning.xlsx

Upload complete

Number of Scenarios

4

Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4

Cohort Name	Number of Patients	Response Rate	Patients until Futility	Recruitment Rate/Month	S
NHL	25	0.34	10	3	202
CLL	25	0.34	10	3	202
OC	25	0.34	10	3	202
CRC	25	0.34	10	5	202
NSCLC	25	0.34	10	3	202
CRPC	25	0.23	10	2	202
AML	25	0.23	10	2	202

Days until a patient is evaluable

61

Duration of a futility analysis in days

14

Futility stop if the number of responses is less than

1

☑ Stop recruitment during futility analysis

Seed

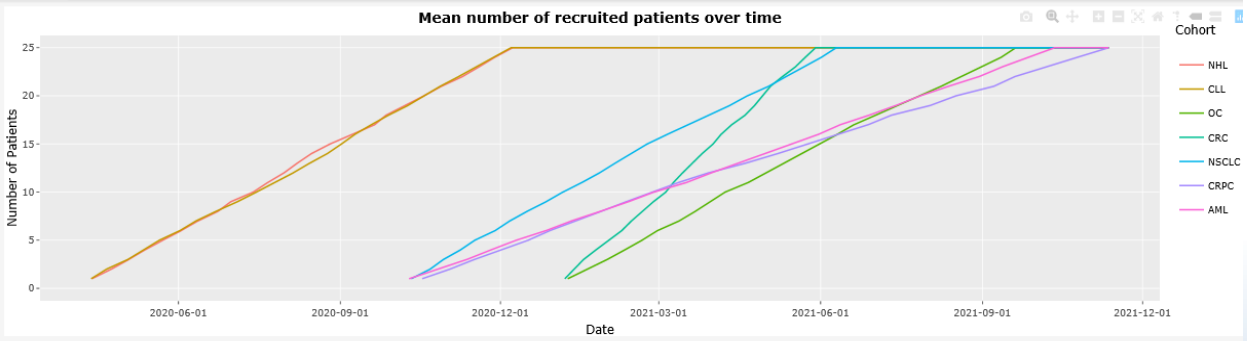
21

Number of Simulations per Scenario

1000

▶ Run

Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4



Mean Results

Analysis	Occurance Prob.	Date	Pass Prob.	NHL Total	CLL Total	OC Total	CRC Total	NSCLC Total	CRPC Total	AML Total
Futility NHL	1.00	2020-09-12	0.98	10.00	9.76	0.00	0.00	0.00	0.00	0.00
Futility CLL	1.00	2020-09-14	0.96	10.12	10.00	0.00	0.00	0.00	0.00	0.00
Futility OC	1.00	2021-06-08	1.00	24.64	24.40	10.00	15.60	18.32	11.92	12.30
Futility CRC	1.00	2021-05-05	0.98	24.52	24.36	6.46	10.00	15.84	9.88	10.58
Futility NSCLC	1.00	2021-03-07	1.00	23.88	23.36	1.42	1.78	10.00	6.44	6.62
Futility CRPC	1.00	2021-04-27	0.94	24.12	24.08	5.42	8.90	14.38	10.00	9.58
Futility AML	1.00	2021-04-28	0.90	24.18	23.90	5.94	8.88	14.66	9.40	10.00
Final NHL	0.98	2021-02-07		25.00	21.82	1.45	2.12	6.96	4.78	5.14
Final CLL	0.96	2021-02-06		22.38	25.00	1.13	1.50	7.06	4.35	4.79
Final OC	1.00	2021-11-20		24.70	24.40	25.00	24.70	24.84	20.34	20.50
Final CRC	0.98	2021-07-29		24.69	24.39	14.65	25.00	22.43	14.51	14.94

Implementation – Planning before Trial: Model

Model

Please define inputs

Cohort Name	Target
NHL	0.34
CLL	0.34
OC	0.34
CRC	0.34
NSCLC	0.34
CRPC	0.23
AML	0.23

Method

Berry

tau

0.5

Credible Interval Width

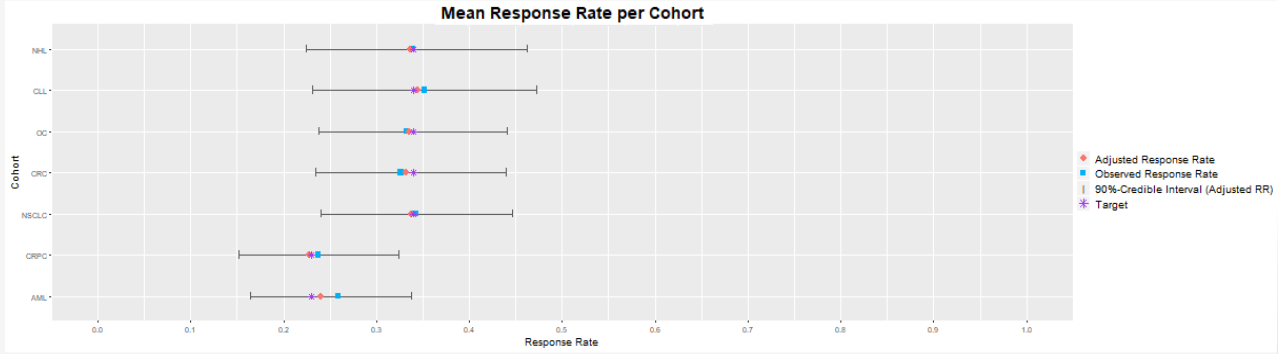
0.9

Seed

21

▶ Run

Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4



☐ Logit scale

Mean Results

Cohort Name	Observed Response Rate	Observed Response Rate (futile cohorts included)	Adjusted Response Rate	5% Quantile	95% Quantile
NHL	0.3388	0.3320	0.3363	0.2242	0.4624
CLL	0.3517	0.3376	0.3445	0.2314	0.4722
OC	0.3328	0.3328	0.3356	0.2381	0.4406
CRC	0.3265	0.3200	0.3317	0.2344	0.4393
NSCLC	0.3424	0.3424	0.3381	0.2400	0.4465
CRPC	0.2374	0.2232	0.2280	0.1518	0.3238
AML	0.2587	0.2328	0.2400	0.1643	0.3377

futile cohorts are excluded

Implementation – Planning before Trial: Decision

Decision

Please define inputs

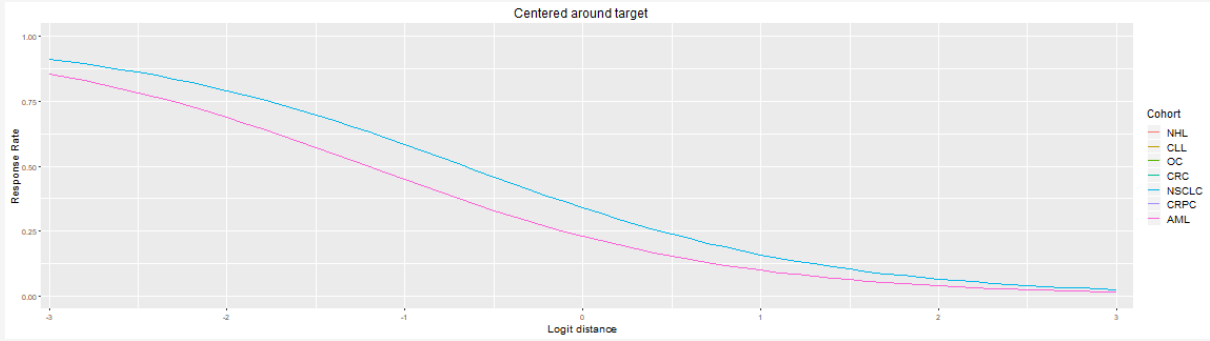
Tier	Cohort Name	Target
1	NHL	0.34
1	CLL	0.34
1	OC	0.34
2	CRC	0.34
2	NSCLC	0.34
3	CRPC	0.23
3	AML	0.23

Would you like to

- ○ calculate the boundaries based on the distance to the target or
- ◉ define the boundaries directly?

Cohort Name	NoGo Boundary	Go Boundary
NHL	0.10	0.30
CLL	0.10	0.30
OC	0.10	0.30
CRC	0.10	0.30
NSCLC	0.10	0.30
CRPC	0.10	0.20
AML	0.10	0.20

▶ Run

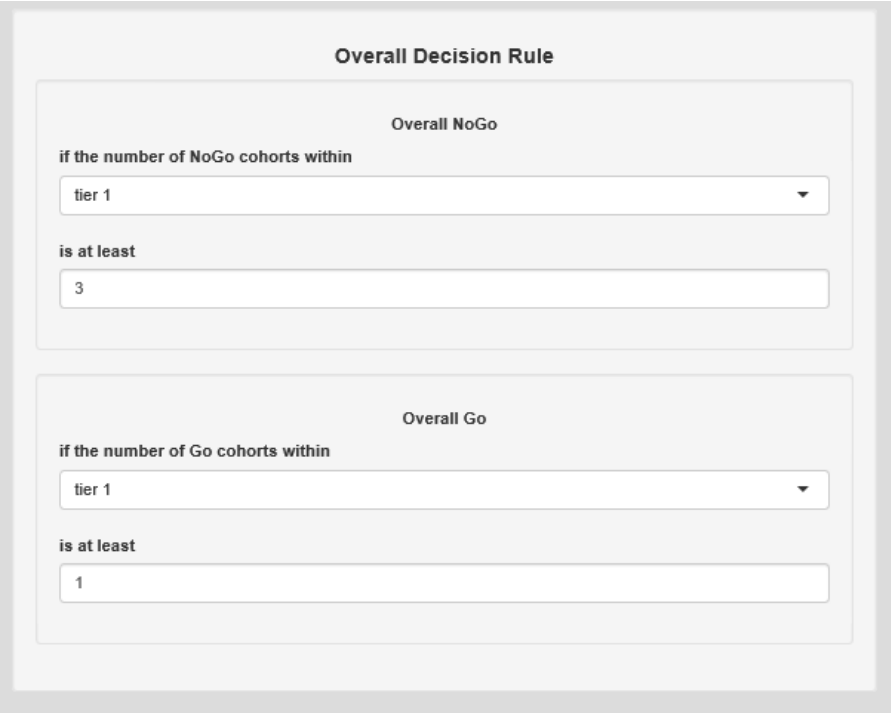


Choose tiers to be displayed

- ☑ Tier 1
- ☑ Tier 2
- ☑ Tier 3

Tier	Cohort Name	Delta Negative	Delta Positive	NoGo Boundary	Go Boundary
1	NHL	1.53	0.18	0.10	0.30
1	CLL	1.53	0.18	0.10	0.30
1	OC	1.53	0.18	0.10	0.30
2	CRC	1.53	0.18	0.10	0.30
2	NSCLC	1.53	0.18	0.10	0.30
3	CRPC	0.99	0.18	0.10	0.20
3	AML	0.99	0.18	0.10	0.20

Implementation – Planning before Trial: Decision



Implementation – Planning before Trial: Operating Characteristics

Decision Probabilities

Scenarios (true response rate)	adj. RR < 10% for NHL, CLL, OC, CRC, NSCLC, CRPC, AML	adj. RR ≥ 10% - ≤ 30 % for NHL, CLL, OC, CRC, NSCLC, adj. RR ≥ 10% - ≤ 20 % for CRPC, AML	adj. RR > 30% for NHL, CLL, OC, CRC, NSCLC, adj. RR > 20% for CRPC, AML
NHL, CLL, OC, CRC, NSCLC, CRPC, AML	NoGo	Consider	Go
34%, 34%, 34%, 34%, 34%, 23%, 23%	0% (2%, 4%, 0%, 2%, 0%, 6%, 10%)	10% (28%, 18%, 26%, 24%, 16%, 20%, 14%)	90% (70%, 78%, 74%, 74%, 84%, 74%, 76%)
6%, 6%, 6%, 6%, 6%, 6%, 6%	72% (84%, 82%, 98%, 96%, 92%, 100%, 100%)	28% (16%, 18%, 2%, 4%, 8%, 0%, 0%)	0% (0%, 0%, 0%, 0%, 0%, 0%, 0%)
6%, 6%, 6%, 34%, 34%, 23%, 23%	26% (62%, 64%, 58%, 2%, 0%, 10%, 10%)	74% (38%, 36%, 42%, 62%, 54%, 48%, 46%)	0% (0%, 0%, 0%, 36%, 46%, 42%, 44%)
6%, 34%, 6%, 6%, 6%, 6%, 6%	4% (52%, 6%, 78%, 88%, 74%, 96%, 92%)	58% (48%, 56%, 22%, 12%, 26%, 4%, 8%)	38% (0%, 38%, 0%, 0%, 0%, 0%, 0%)

Overall NoGo if the number of NoGo cohorts within tier 1 is at least 3.

Overall Go if the number of Go cohorts within tier 1 is at least 1.

Number of simulations: 50

Which decision probabilities would you like to display?

- ☑ Overall
- ☑ NHL
- ☑ CLL
- ☑ OC
- ☑ CRC
- ☑ NSCLC
- ☑ CRPC
- ☑ AML

☑ Show Overall Decision Rule

☑ Show Cohortwise Decision Rule

☑ Show Scenario Details

Implementation – Planning before Trial: Operating Characteristics

Mean Sample Size and Duration

	Total	NHL Total	CLL Total	OC Total	CRC Total	NSCLC Total	CRPC Total	AML Total	Date
Scenario 1 - Decisive Analysis	84.02	24.48	22.44	5.46	6.10	9.90	7.86	7.78	04/03/2021
Scenario 1 - Last Analysis	171.40	24.70	24.40	25.00	24.70	25.00	24.10	23.50	02/11/2022
Scenario 2 - Decisive Analysis	120.70	19.30	16.30	17.20	16.60	18.10	16.60	16.60	12/02/2021
Scenario 2 - Last Analysis	120.70	19.30	16.30	17.20	16.60	18.10	16.60	16.60	12/02/2021
Scenario 3 - Decisive Analysis	135.28	19.30	16.30	14.24	24.14	23.76	19.86	17.68	10/17/2021
Scenario 3 - Last Analysis	150.10	19.30	16.30	17.20	24.70	25.00	24.10	23.50	01/29/2022
Scenario 4 - Decisive Analysis	100.28	18.36	24.40	10.66	10.42	13.48	11.28	11.68	07/28/2021
Scenario 4 - Last Analysis	128.80	19.30	24.40	17.20	16.60	18.10	16.60	16.60	11/26/2021