External Control Designs & Case Study of a Phase 3 Study Design with Hybrid Control in 1L DLBCL

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Why innovative design was needed for our case

Unmet medical need in certain subgroup of DLBCL patients

- Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL) worldwide, with 25,000 newly diagnosed patients in the United States (US) annually
- Standard of care for 1L DLBCL patients established over 20 years ago: it is well characterized and well understood
- Patients in certain subgroup of DLBCL have a poorer prognosis and consequently a high unmet medical need

"Borrowing" patients from the control arm of another study helps us

- Having fewer 'new' patients treated with a control regimen that is well established and that we know well
- **Shorten our study**
- Conducting more efficient trials by sharing control data between trials

Study designs using external controls

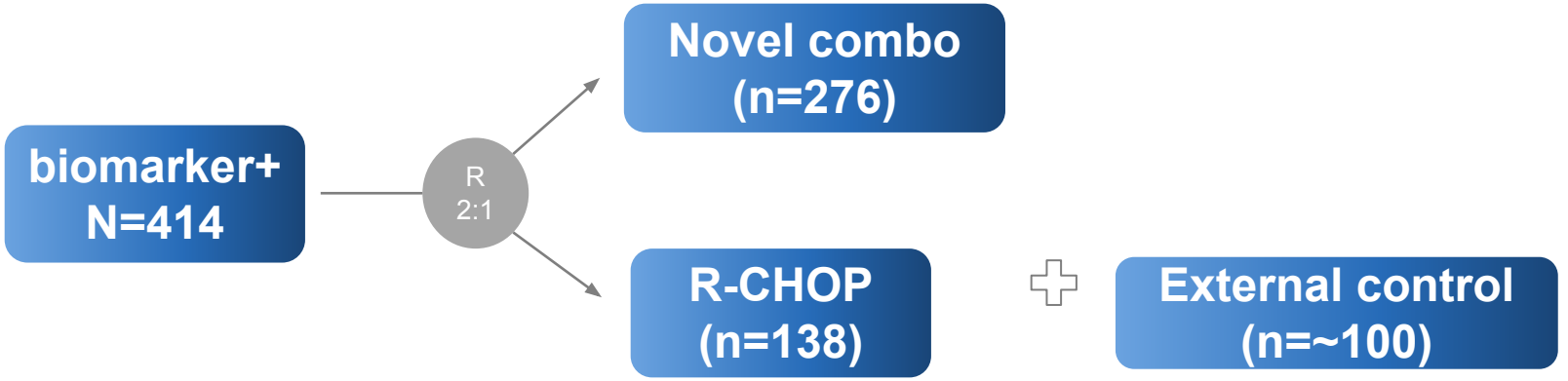
- **Single arm trials**
  - Control always external; measured baseline variables can be balanced to trial population via propensity score or other matching techniques
  - External control can be RWD, other clinical trials, EHRs or a combination
  - Can lead to increased false positive rate or reduced power
  - Extensive pre-planning work required
  - No «fallback» for comparison/interpretation if external control is not used, due to lack of internal control
- **Hybrid designs can look like a great alternative**
  - Small randomized control plus external control; use of external control often data driven (dynamic borrowing, adaptive designs)
  - Results interpretable even if external control data is not used, due to small randomized control arm («fallback»), but comparison is underpowered
  - Still leads to alpha inflation. Addressing this diminishes advantages of external control data
  - Extensive pre-planning work required

Novel designs – Making it happen

Typical design	vs.	Hybrid Bayesian dynamic borrowing
- Decide on parameters - Fixed scenario	**<Front-loading>**	- Extensive simulations - Many scenarios (~20+ for each FDA meeting)
	Implications	- Plan early - Allocate time/resources
	Solutions	- CRAN R Software available: ***psborrow**** - Roche statistics method group and method experts - Learnings from CID program
	Methods R&D	- FDA U01 grant (ongoing work)

*psborrow: Bayesian Dynamic Borrowing with Propensity Score https://cran.r-project.org/web/packages/psborrow/index.html

Proposed Phase 3 Study Design in 1L DLBCL



Primary Endpoint:

- **PFS Investigator Assessed**

Key Secondary Endpoints

- **OS**, based on randomized patients & matched external control

- Analysis of primary endpoint (PFS) based on the randomized patients, designed to provide 80% power at the 5% significance level to detect a target HR of 0.6, one IA at 80% of events
- External control patients to be selected from a contemporary, ongoing internal clinical trial
- External control arm intended to support early OS analysis at the time of the primary PFS analysis
- Randomized study with external control arm using matched external controls through Bayesian dynamic borrowing

Final Analysis Flow Diagram

Roche

Control comparability evaluation

- Apply inclusion/exclusion criteria
- Flag baseline factors with significant difference between internal and external trials

Propensity score matching

- Match patient population between internal and external trials using propensity score matching (PSM)
- Enhance covariates balance by filtering out unmatched patients

Bayesian dynamic borrowing

A method to:

- Automatically downweight external control data based on internal/external control agreement
- Provide inference of treatment effect with hybrid control (i.e. OS analysis)

Sensitivity analysis follows main analysis

* In the rare case of missing data, those data for prognostic factors will be accounted for by using nearest neighbor (NN) imputation under a missing at random (MAR) assumption

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Doing now what patients need next