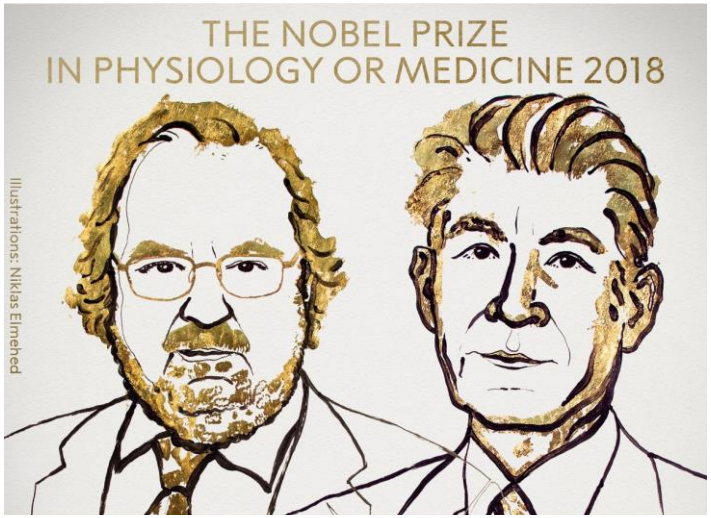
Penalty-Free Statistical Design Options for Late Development of Oncology Immunotherapies

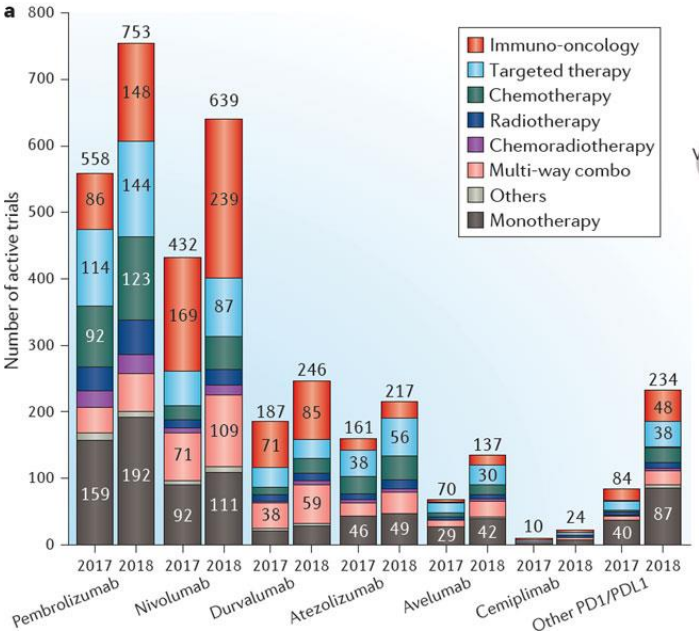
Cong Chen, PhD
Executive Director and Head of Early Oncology Statistics, BARDS
Merck & Co., Inc., Kenilworth, NJ, USA

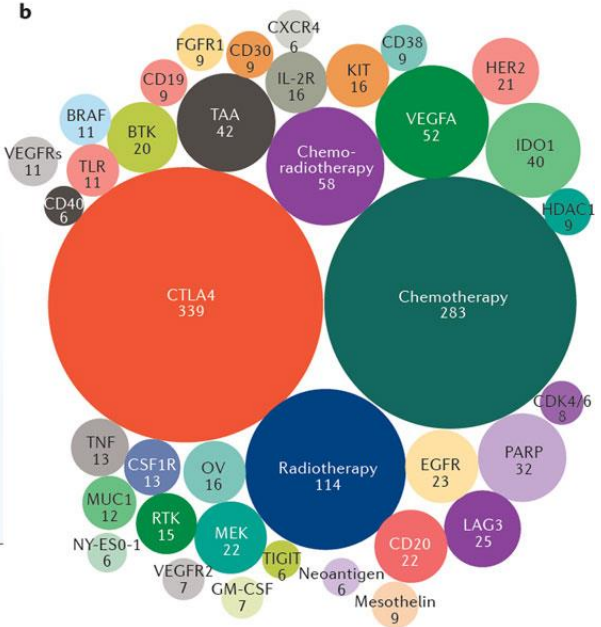
NISS-Merck Virtual Meet-Up, Jan 22, 2019

MERCK

Landscape of IO Development





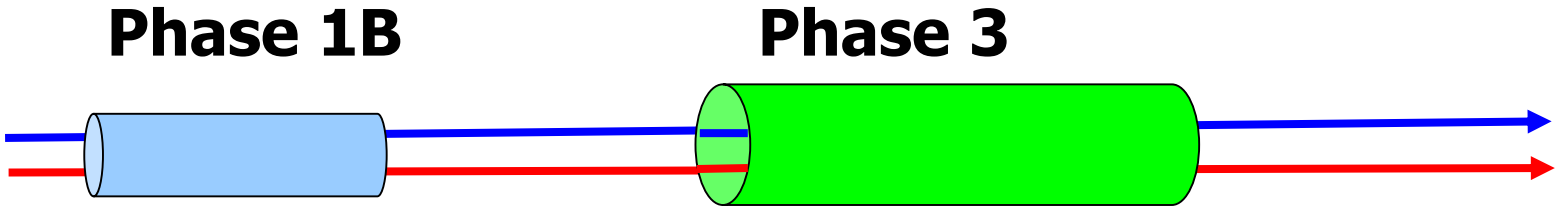


MERCK

Adaptive 2-in-1 Design for Seamless Phase 2/3

Status Quo for Early-to-Late Transition

- A typical program tests a new drug combination with an approved IO in Phase 1, and intends to go directly to Phase 3 once encouraging signal is observed



MERCK

Keytruda+Axitinib in 1L RCC

- Both Keytruda and axitinib were known to have monotherapy activity in RCC prior to combination study
- Phase 1B: 38/52 (**73%**; 95% CI 59·0-84·4) patients achieved an objective response (vs **31%** for sunitinib)
  - The median progression-free survival was estimated as 21 months (vs 11 months for sunitinib)
- KN-426 (Oct 18, 2018)

Merck (MRK) Reports Significant Improved OS & PFS Data from Pivotal Phase 3 KEYNOTE-426 Trial Investigating KEYTRUDA (pembrolizumab) in Combination with Pfizer's (PFE) Inlyta (axitinib)

STREETINSIDER.COM

MERCK

Epacadostat (IDO1) in Melanoma

- The most advanced new MOA right after PD-1/PD-L1
- ECHO-202: Phase 1/2 in combo with pembrolizumab
  - ORR=**56%*** (100 mg) vs ~**37%** for pembrolizumab alone based on historical data
- ECHO-301

BIOTECH

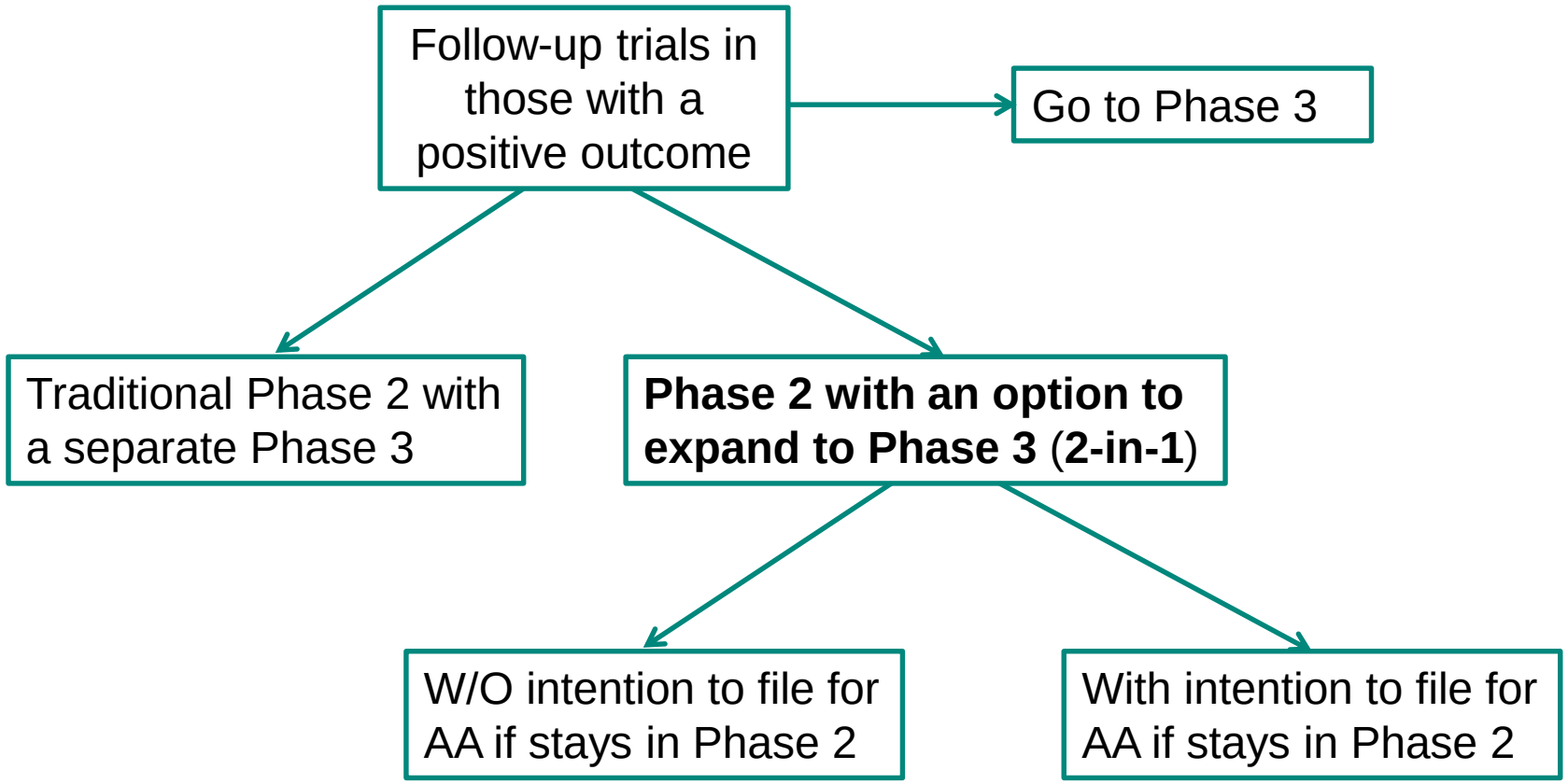
Incyte's cancer drug fails trial, marking major blow for immunotherapy combination treatment

By ADAM FEUERSTEIN @adamfeuerstein / APRIL 6, 2018

*Presentation #1214O , ESMO Annual Meeting 2017

MERCK

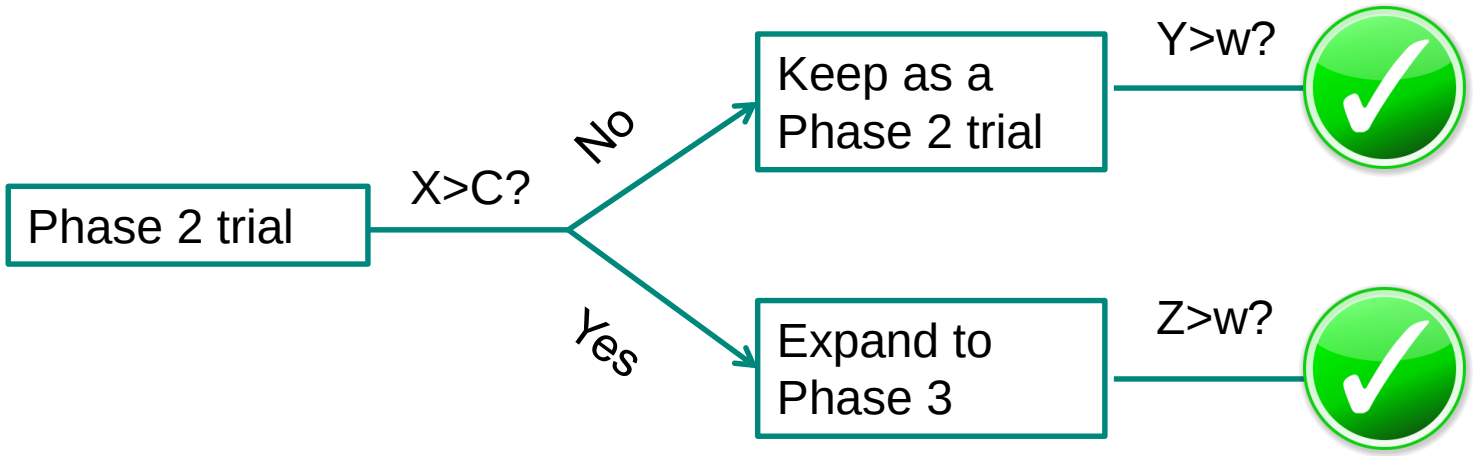
Options Post Phase 1B Efficacy Screening



Chen C, Anderson K, Mehrotra DV, Rubin EH and Tse A. A 2-in-1 adaptive Phase 2/3 design for expedited drug development. *Contemporary Clinical Trials* 2018; 64:238-242.

MERCK

A Generic 2-in-1 Design



- The three standardized test statistics X, Y and Z can be based upon different endpoints
- No penalty if Phase 2 endpoint is used for expansion decision (a sufficient but not necessary condition)
  - i.e.,w=1.96 to keep alpha controlled at 2.5% (1-sided)

MERCK

Key Questions Before You Consider 2-in-1

- Realistically, should you consider a randomized Phase 2 instead of a straight Phase 3 based on Phase 1 data?
- Is the program ready for a registration enabling study?
  - Any mid-trial change is subject to heavy scrutiny
- Is logistics worked out to enable seamless transition?

MERCK

An Example

- A small Phase 1 trial of a combination therapy with SOC has demonstrated exciting ORR in 1st line gastric cancer
  - More patients are being added but uncertainty of treatment effect remains due to single-arm
- A seamless Phase 2/3 trial based on 2-in-1 design with Phase 2 oversized for AA is considered
- Expansion decision targets one month ahead of Phase 2 accrual completion to ensure seamless expansion

MERCK

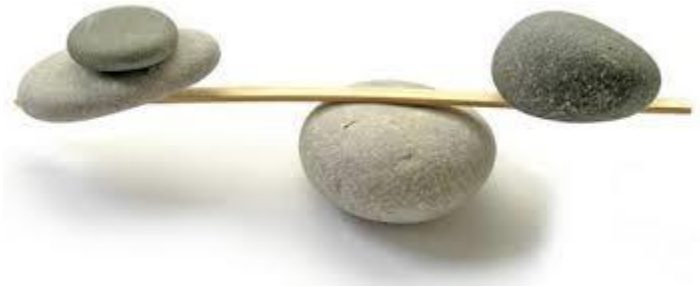
Design Details

- Phase 2 (in case of no expansion)
  - With 240 patients, it has 88% power for detecting an ORR increase of **20%** at 2.5% (one-sided) alpha level
  - Stop the trial early in case of no ORR improvement
  - P-value<0.025 for ORR leads to filing for AA (a Phase 3 trial may still be considered otherwise)
- Phase 3 (in case of expansion)
  - With 460 OS events (600 patients in total), it has 90% power for detecting a hazard ratio (HR) of **0.74** at 2.5% (one-sided) alpha level
  - P-value<0.025 for OS leads to filing for FA

MERCK

A Cost-effective Expansion Bar

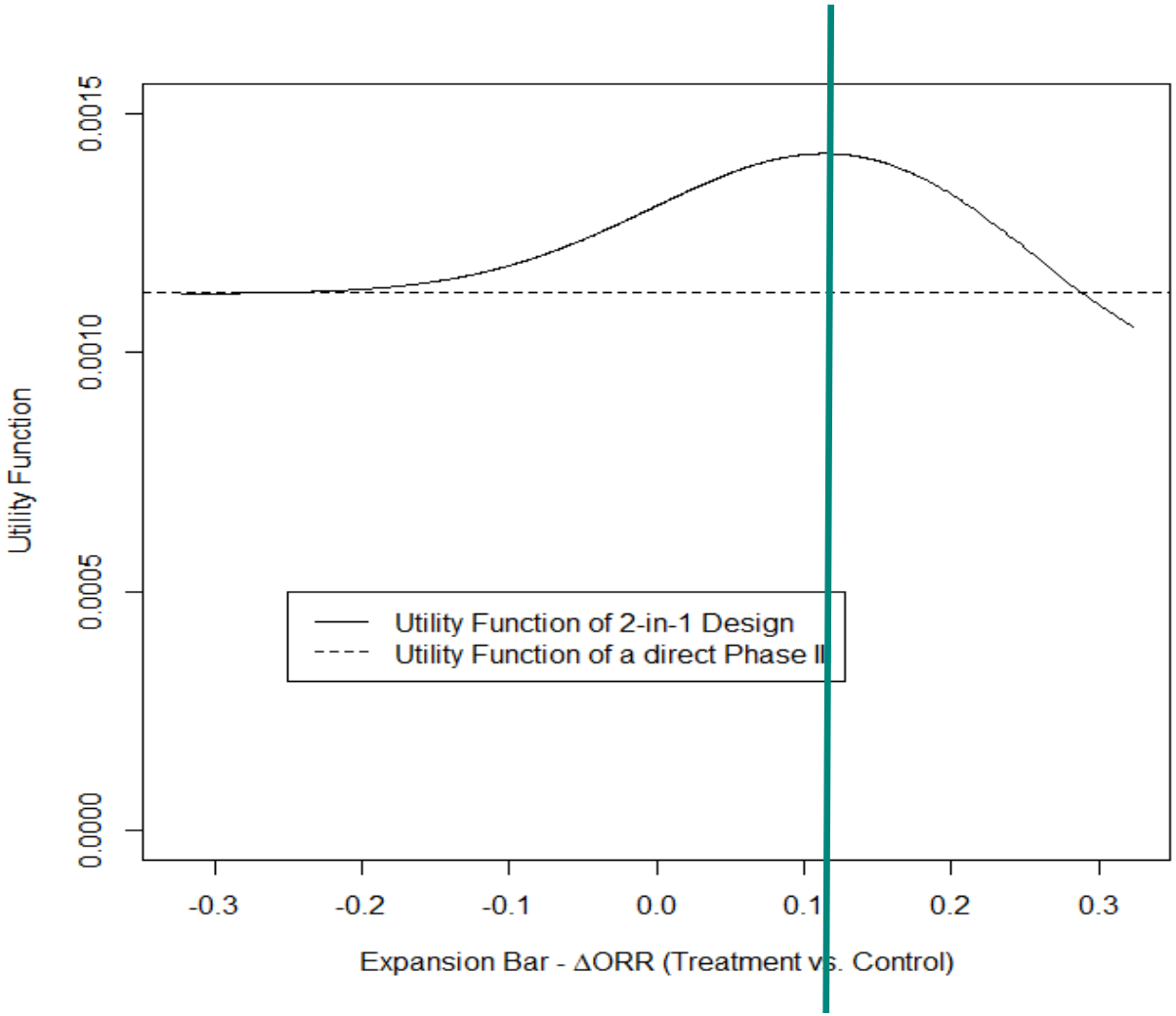
- **Type I error is controlled for any expansion bar**
- A benefit-cost ratio analysis
  - Benefit: value adjusted probability of a positive trial
    - A positive Phase 2 worth 1/3 of a positive Phase 3
  - Cost: expected overall sample size for the study
    - 240+prob(expansion under null or alternative)*360
  - Test drug assumed to have 50% chance of being active



Sun LZ, Li W, Chen C, and Zhao J. Advanced Utilization of Intermediate Endpoints for Making Optimized Cost-Effective Decisions in Seamless Phase II/III Oncology Trials. Under review for publication.

MERCK

BCR Changes with the Expansion Bar



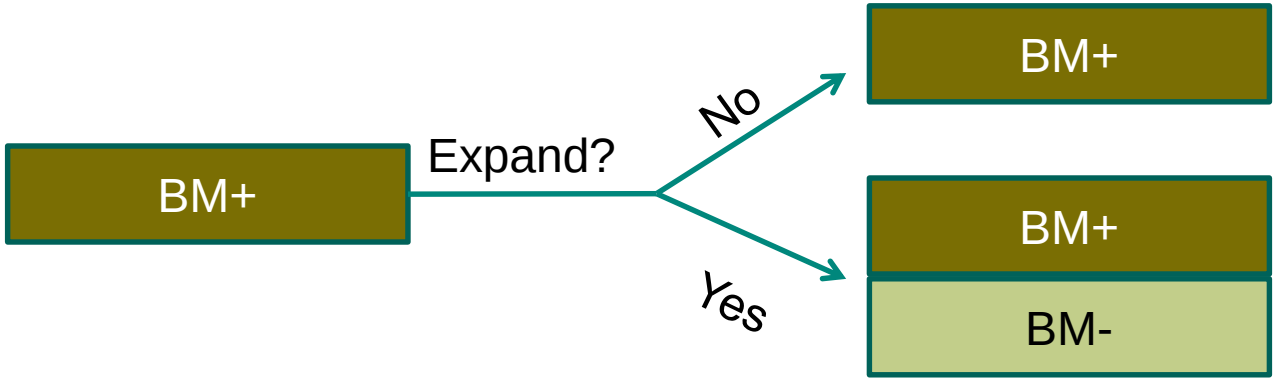
Sensitivity to Input Variables

Prior distribution of treatment effect for OS		Relative value of a positive Phase 2 vs. a positive Phase 3	Approximate optimal expansion bar in ΔORR
P(HR = 0.74)	P(HR = 1)		
1/3	2/3	1:3	12%
		1:5	10%
1/2	**1/2**	**1:3**	**11%**
		1:5	9%
2/3	1/3	1:3	10%
		1:5	8%

Phase 3 Designs With Biomarker Consideration

Expansion of Biomarker+ Patients to All-comers

- *Scenario*: an investigational new drug showed **similar** ORR overall to SOC based on historical data but **higher** ORR in a BM+ population
- *Design*: initiate a biomarker enriched study with an option to expand to **all-comers** if data more promising than expected, suggesting broader activity

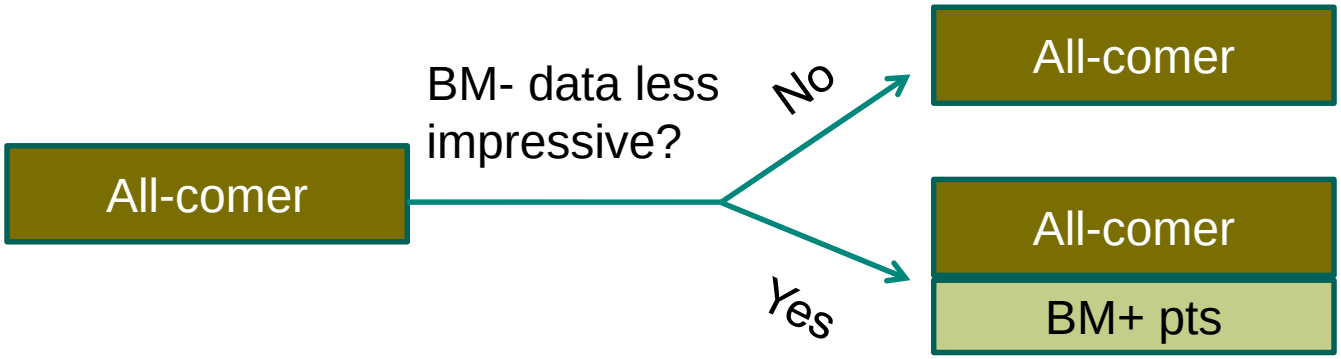


Chen C, Li X, Li W, Beckman RA. Adaptive Expansion of Biomarker Populations in Phase 3 Clinical Trials. *Contemporary Clinical Trials* 2018;71:181-185.

MERCK

Adaptive Expansion of Biomarker+ Population

- *Scenario*: an investigational new drug **improved** ORR over SOC in **both** BM+ and BM- populations but likely more active in BM+ population
- *Design*: initiate an all-comer study with an option to increase number of BM+ patients in case data is less promising in BM- population, suggesting need to hedge



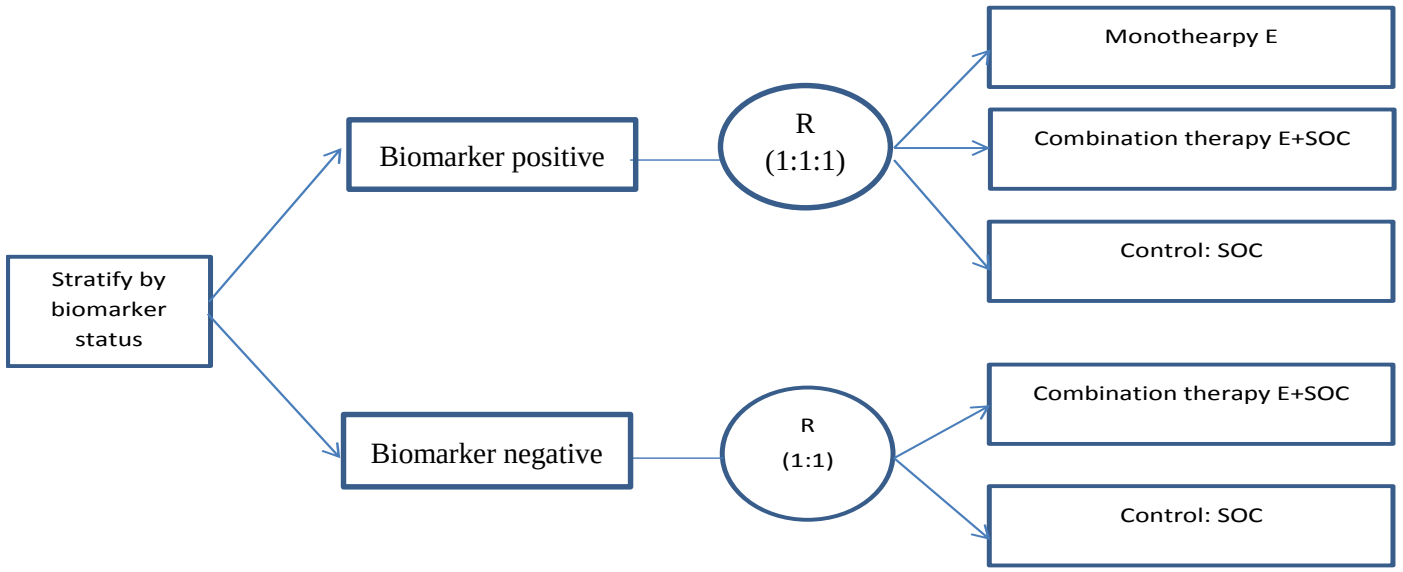
Chen C, Li X, Li W, Beckman RA. Adaptive Expansion of Biomarker Populations in Phase 3 Clinical Trials. *Contemporary Clinical Trials* 2018;71:181-185.

MERCK

Sharing BM+ patients in SOC Arm

- *Scenario*: interested in testing the monotherapy of an investigational new drug vs SOC in a BM+ population and the combination therapy vs SOC in all-comers
- *Design*: a single trial (vs two in conventional approach) that reduces exposure of BM+ patients to SOC

Figure 1 Study Design



Sun L, Chen C. Testing of Monotherapy and Combination Therapy in One Trial with Biomarker Consideration, draft.

MERCK

Discussion

- Additional features (e.g., futility analysis, group sequential design, co-primary endpoints) can be included, and more research is warranted
- A great era for statisticians to not only develop new analysis and design methods but also to get involved in strategic decisions

MERCK

MERCK

A 2-in-1 Design for Phase 2/3 Adaptation

- A randomized Phase 2 trial is started with a pre-specified criterion for expansion to Phase 3
  - All patients including those used for the expansion decision will be included in the Phase 3 final analysis
- The trial is considered positive if Phase 2 (w/o expansion) **or** Phase 3 (w/ expansion) is positive