Statistical considerations for development of novel combination designs for Immuno-oncology development

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Outline

Background

Challenges in development of 2NMEs

Design strategies

Sample size considerations

Analysis considerations

Summary

Background

- Increasing use of PD-(L)1 inhibitors as monotherapies in early line settings (adjuvant, 1st, 2nd line metastatic settings) in several oncology settings such as NSCLC and melanoma

- However, benefit has been approved ONLY in a subset of patients due to primary resistance developed by patients

- Hence, there is a need for development of novel NMEs as combination with approved PD-(L)1 or another novel NME as backbone to overcome the resistance

- Patients likely to benefit with such novel therapies are those who failed PD(L)1 as monotherapy

- Treatment options to consider to overcome the resistance include
  - re-exposure to failed PD-(L)1 in combination with already approved therapy or another NME
  - PD-(L)1 or Immunotherapy NME in combination with already approved therapy or another NME
  - 2 or more NMEs

*NME= New molecular entity; 2-NME Combinations – Combinations of drugs which have not been previously approved as single/combination agents

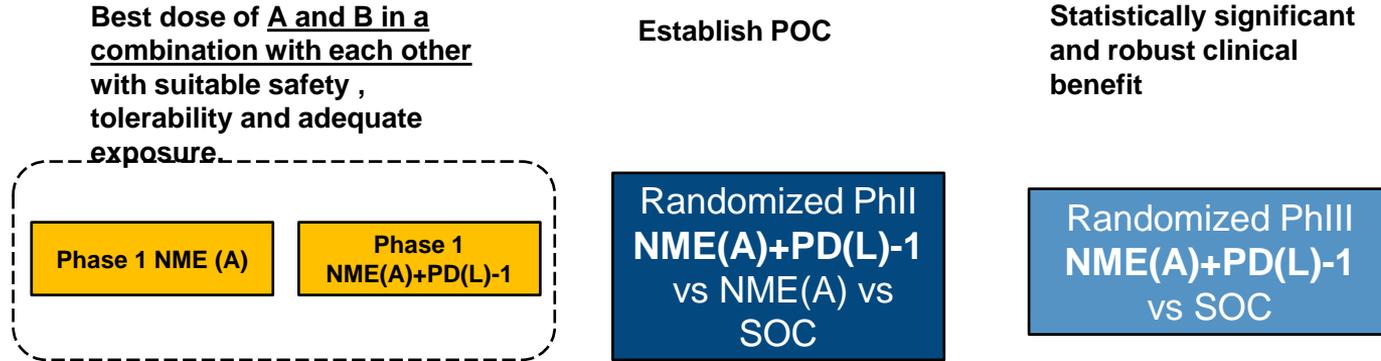NOVARTIS | Reimagining Medicine

Factors to consider for combination therapies

- Re-exposure to PD(L)-1 or new PD(L)-1 class of drugs
    - Refractory status of patients
    - Length of Prior PD(L)-1 treatment and washout period following prior exposure
    - Primary resistance to a PD(L)-1 : will it apply to all PD(L)-1 class of drugs?

- Target 2 or more NME combination
    - Tumor Proliferation is considered to be driven by multiple signaling pathways
    - Combining targeted regimens towards individual receptors gives better chances of multiple shots at the tumor proliferation factors, shutting down the whole pathway

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Challenges in 2 or more NME development

- Limited safety from NMEs

- Over-reliance on pre-clinical models

- Establishing dose for the 2NME combination arm based on safety only

- Lack of Phase II trial data on NMEs

- Complex Phase III study design resulting in more patients exposed to ineffective NMEs in case of lack of efficacy
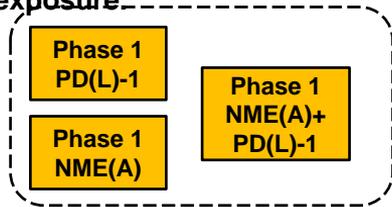
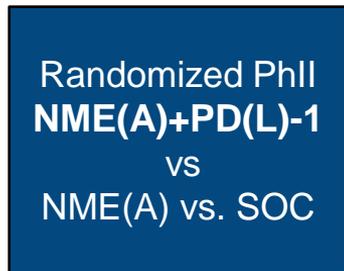# Design strategy for re-exposure to PD(L)-1 in combination with NME

Best dose of <u>A and B in a combination with each other</u> with suitable safety , tolerability and adequate exposure.

Establish POC

Statistically significant and robust clinical benefit

> Phase 1 NME (A)
>
> Phase 1 NME(A)+PD(L)-1

Randomized PhII
NME(A)+PD(L)-1
vs NME(A) vs SOC

Randomized PhIII
NME(A)+PD(L)-1
vs SOC

- Synthetic Lethality

  - Individual **NME(A) and PD(L)-1** ineffective or minimally active, but exhibit high potent activity in combination.
  - **NME(A)+PD(L)-1 vs SOC acceptable in such scenarios.**

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Design strategy for re-exposure to PD(L)-1 in combination with NME

Statistically significant and robust clinical benefit

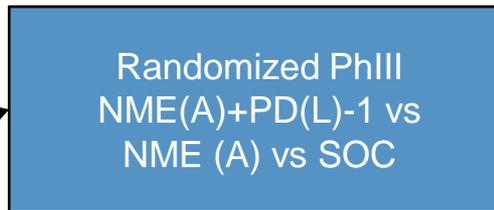**Best dose of <u>A and B in a combination with each other</u> with suitable safety , tolerability and adequate exposure**

Establish POC

Phase 1 PD(L)-1

Phase 1 NME(A)+ PD(L)-1

Phase 1 NME(A)

Randomized PhII
NME(A)+PD(L)-1
vs
NME(A) vs. SOC

Uni-enhancement

Randomized PhIII
NME(A)+PD(L)-1 vs
NME (A) vs SOC

Synthetic Lethality

Randomized PhIII
NME(A)+PD(L)-1
vs SOC

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Combining 2 or more NME targeted or novel IO therapies

Statistically significant and robust clinical benefit

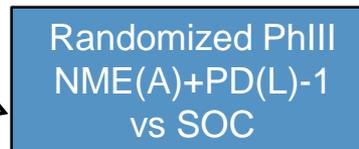**Best dose of <u>A and B in a combination with each other</u> with suitable safety , tolerability and adequate exposure**

Phase 1 NME(A)

Phase 1 NME(AB)
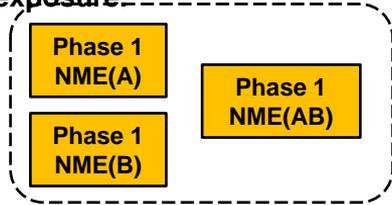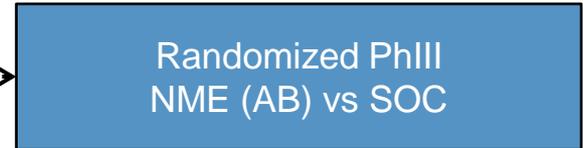
Phase 1 NME(B)

Establish POC

Randomized PhII
NME(AB) vs
NME(A) vs
NME(B) vs
SOC

Uni-enhancement

Randomized PhIII
NME (AB) vs NME (A)/ NME(B) vs SOC

Synthetic Lethality

Randomized PhIII
NME (AB) vs SOC

Co-enhancement

Randomized PhIII
NME (AB) vs NME (A) vs NME (B) vs SOC

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Co-enhancement Design Testing Strategy

Graphical Gatekeeping for multiple endpoint scenarios
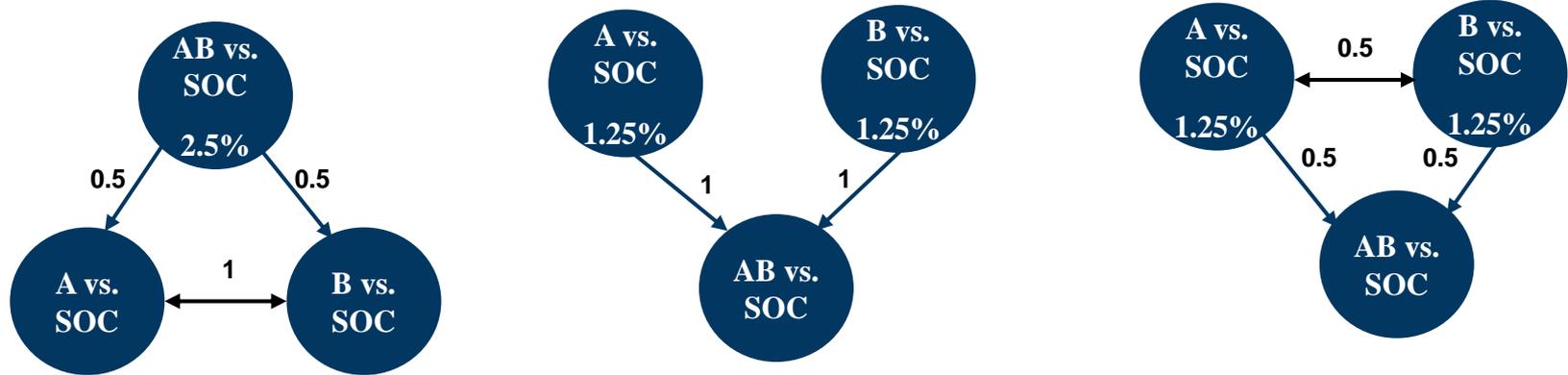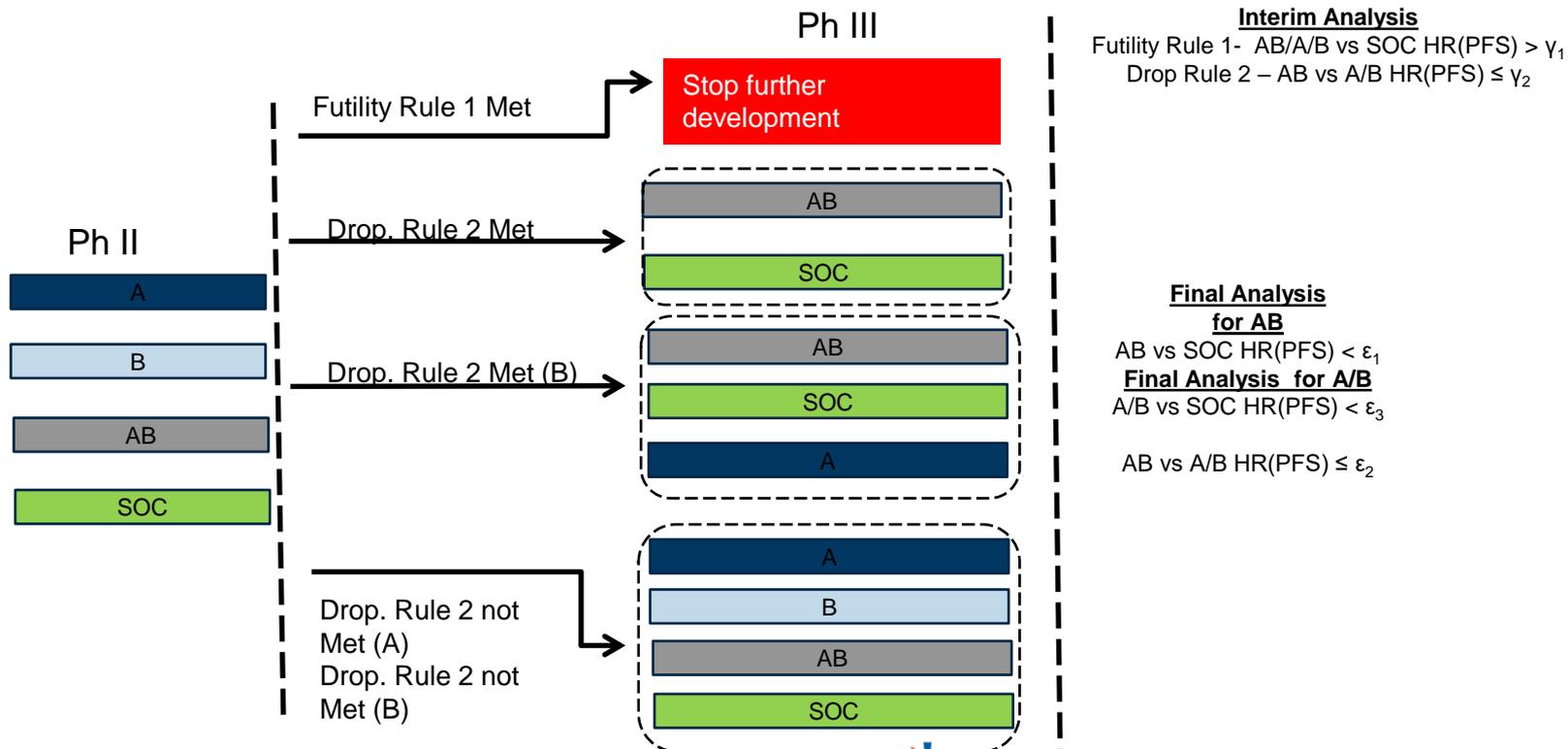

- Graphical Gatekeeping procedures can provide multiple pathways to success and can be designed to give more power to 2NME tests

- Does AB vs A/B need to be tested sequentially if AB vs SOC is statistically significant or can it be a descriptive assessment?

- Under Intersection Union principle overall Type 1 error is controlled
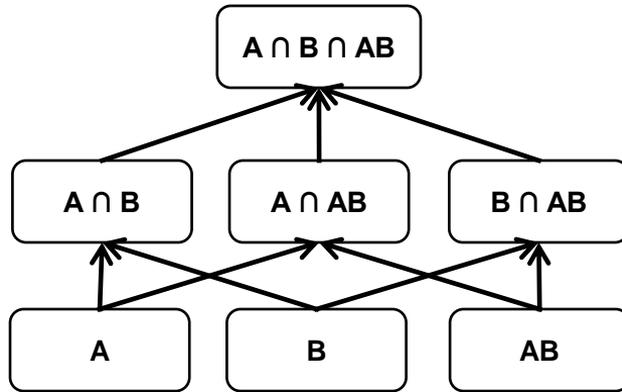
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Adaptive seamless Phase II/III design

- Allows expansion of the Phase II to Phase III via adaptive dropping of individual NME arms

- Involves testing of hypotheses of multiple arms over multiple stages

- Type-I error rate inflation can arise due to :
  - Multiple testing of hypotheses at the interim and final analysis
  - Final testing based on data from multiple stages of trial

- Design adaptations need to be taken into account in the overall hypothesis testing to ensure adequate control of the FWER

- Methodologies such as combination tests and conditional error functions are generally preferred to combine data from multiple stages

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Adaptive 4-Arm Phase II/III

Ph III

Futility Rule 1 Met → Stop further development

Interim Analysis
Futility Rule 1- AB/A/B vs SOC HR(PFS) > γ_1
Drop Rule 2 – AB vs A/B HR(PFS) ≤ γ_2

Ph II

| A |
| B |
| AB |
| SOC |

Drop. Rule 2 Met →

| AB |
| SOC |

Drop. Rule 2 Met (B) →

| AB |
| SOC |
| A |

Drop. Rule 2 not Met (A)
Drop. Rule 2 not Met (B)

| A |
| B |
| AB |
| SOC |

Final Analysis for AB
AB vs SOC HR(PFS) < ε_1
Final Analysis for A/B
A/B vs SOC HR(PFS) < ε_3

AB vs A/B HR(PFS) ≤ ε_2

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Closed Testing Framework

H^0_{AB} can be seen as a IU Hypothesis :
- $H^0_{AB\text{-}SOC}$ U $H^0_{AB\text{-}A}$ U $H^0_{AB\text{-}B}$

1NME Hypotheses :
$H^0_{A\text{-}SOC}$ and $H^0_{B\text{-}SOC}$

- As per close testing principle , to reject an hypothesis(H^0) all intersections containing H^0 must be rejected.

- For eg : To reject H^0_A : H^0_A, $H^0_{A\cap B}$, $H^0_{A\cap AB}$ and $H^0_{A\cap B\cap AB}$ must be rejected.

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Adaptation via p-value combination tests

	Stage 1	Stage 2
H^0_{AB}	Z^1_{AB}	Z^2_{AB}
H^0_A	Z^1_A	Z^2_A
H^0_B	Z^1_B	Z^2_B
$H^0_{A \cap B}$	$Z^1_{A \cap B}$	$Z^2_{A \cap B}$
$H^0_{A \cap AB}$	$Z^1_{A \cap AB}$	$Z^2_{A \cap AB}$
$H^0_{B \cap AB}$	$Z^1_{B \cap AB}$	$Z^2_{B \cap AB}$
$H^0_{A \cap B \cap AB}$	$Z^1_{A \cap B \cap AB}$	$Z^2_{A \cap B \cap AB}$

Based on data at Interim Analysis
$$Z^1 = \frac{S_1}{\sqrt{I_1}}$$

Between interim and Final :
$$Z^2 = \frac{S_2 - S_1}{\sqrt{I_2 - I_1}}$$

S_1 and $S_2 - S_1$ are assumed to be independent.

Independent p-values from 2 stages combined: inverse normal method:

$$C(p1, p2) = w1 \phi^{-1}(1 - p1) + w2 \phi^{-1}(1 - p2)$$

Pre-specified fixed weights based on information fraction:

$$w1 = (n1/N)^{1/2} \; ; \; w2 = (n2/N)^{1/2}, w1^2 + w2^2 = 1$$

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Sample size considerations

- In trials involving multiple hypotheses from multiple arms, sample size calculations need to take into account the power considerations for all the hypotheses
  - Powering the study for the weakest alternative may be a very conservative approach and may imply over powering the remaining hypotheses

- A graphical testing procedure is recommended for allocation of the alpha for each hypothesis under a closed testing framework
  - Final structure of the graphical procedure should reflect the priority of success of each comparison based on the therapeutic landscape

- For time to event trials, follow up required for each comparison may substantially differ due to the difference in events required to adequately power each comparison leading to delays in trial read-out

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Analysis considerations under delayed effect

- Delayed effects observed due to non-proportional hazards in PD(L)-1 NME combination studies
  - Length of delayed effect likely to impact power and treatment effect
  - Adequate follow-up beyond delayed effect time point critical to ensure sufficient power

- Futility and efficacy interim decisions may not be very predictive of the final outcome
  - Will planning for certain proportion of events beyond the time of delayed effect be an option?

- Under non-proportional hazards, log rank and hazard ratio from proportional hazards model may be debatable
  - Alternative approach such as weighted log-rank test, marginal average hazard ratio can be considered

- Follow-up in each arm may be quite different in order to ensure adequate number of events for each comparison
  - Interim treatment adaptation decision rules based on predictive probability is preferred in such scenarios

Summary

- 2 or more NME Co-development likely to be more important with increasing targeted and immunotherapy combinations in oncology

- NME designs involving re-exposure to PD(L)-1 needs to factor in length of prior PD(L1)-1 treatment, refractory status and primary resistance

- A graphical gatekeeping testing strategy is efficient to test multiple hypotheses in NME designs under a closed testing framework

- Delayed effect resulting from immunotherapies likely to impact analysis timing/methods

- Adaptive designs such as dropping ineffective arm at interim analysis can be an efficient approach to handle 2NME development

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