Adaptive Enrichment Design to Address Emerging Uncertainty Regarding Optimal Target Population - Case Study

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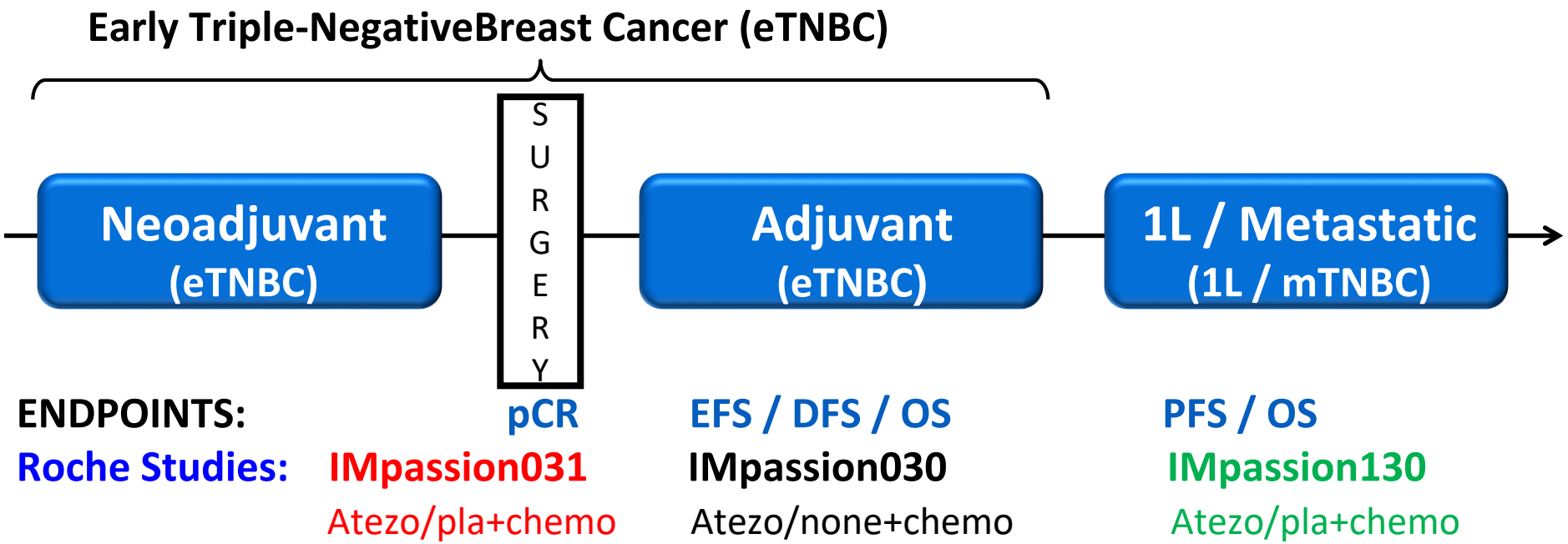
Background

Triple Negative Breast Cancer (TNBC): high unmet medical need

- Absence of ER, PR and HER-2 gene ⇒ reduced or voided benefit from drug targeting these biomarkers
- Poor outcome: rapid progression, short time to relapse[a]



pCR: pathological complete response; EFS: event-free survival; DFS: disease-free survival; OS: overall survival; PFS: progression-free survival. [a] Dent et al. 2007

[a] https://www.esmo.org/Press-Office/Press-Releases/IMpassion130-atezolizumab-nab-pac-triple-negative-breast-cancer-Schmid

Background

Population	PFS-HR[a]
ITT	0.80 (0.69, 0.92)
PD-L1+ *Formal testing*	0.62 (0.49, 0.78)

Original neoadjuvant TNBC Design

- Pathological complete response (pCR): binary endpoint
- All-comer: no pre-specified formal testing for PD-L1+

Background

Emerging Goals for neoadjuvant TNBC study

- Current AC design MIGHT not lead to ITT label even with positive read-out AND
- Efficacy in PDL1+ not formally tested

⇒ Optimize chance of success and timeline for timely patient's access & Minimize exposing patients to futile treatment

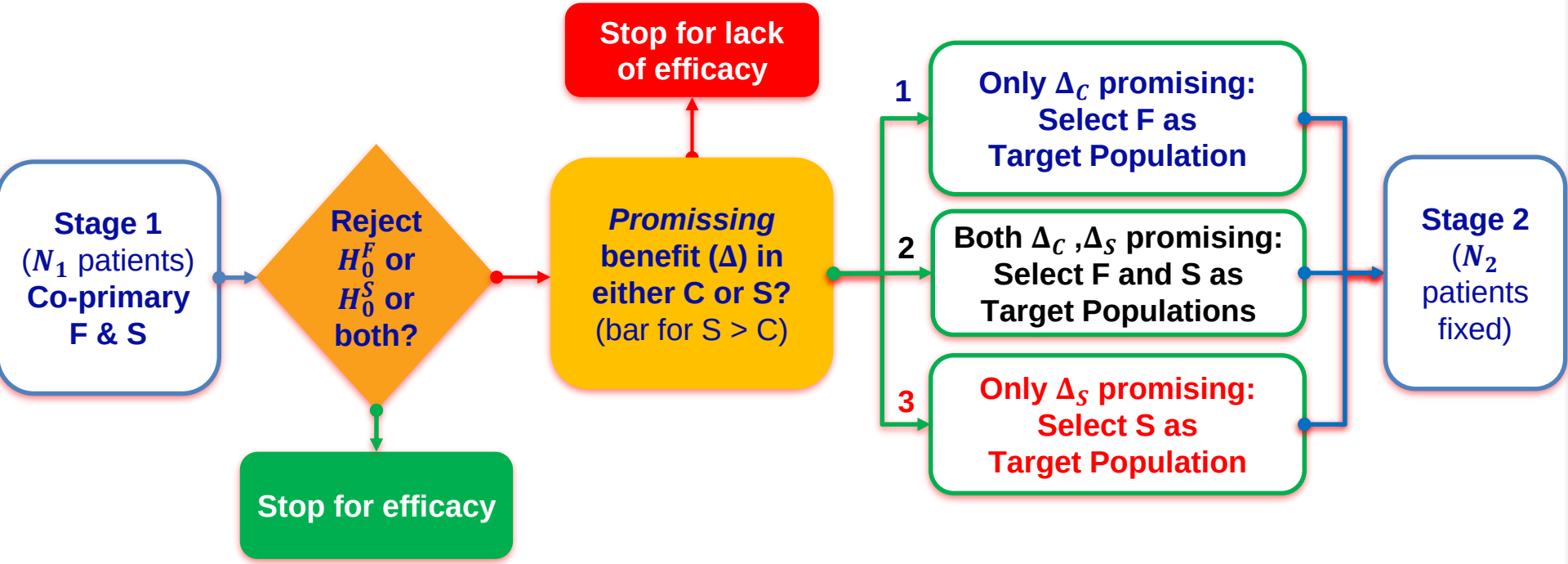
Challenges in extrapolating from 1L to neo-adj. TNBC

- PD-L1 predictive value: inconsistency across treatment lines observed in other indications
- Different entpoints: PFS vs pCR

⇒ Fixed (re)design options at high risk of misspecification

Neo-adjuvant Trial - Adaptive Design

***F** = ITT population, **S** = PDL1+ subpopulation, **C** = PDL1- subpopulation*



Analysis at end of Stage 1 conducted by independent statisticians and reviewed by iDMC, following above prespecified algorithm.

Type-I Error - Sources of Inflation

- Stage 2 and final target population driven by stage 1 outcomes
  - No direct pooling of data BUT: $p_2^h \perp p_1^h$ under H_0^h[a]
  - p-value combination (inverse weighted normal approach)[b]

$$p_{1,2}^h = 1 - \Phi\left\{w_1 \times \Phi^{-1}\left(1 - p_1^h\right) + w_2 \times \Phi^{-1}\left(1 - p_2^h\right)\right\}$$[c]

- Early look at data for efficacy claim at stage 1: α_1, α_2 specified via

$$\left(Z_1^h, Z_{1,2}^h\right) \sim N\left(\mu = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \Sigma = \begin{pmatrix} 1 & w_1 \\ w_1 & 1 \end{pmatrix}\right) \text{ under } H_0^h$$

- Multiplicity in target populations: **F** and **S**
  - Sime's closed test procedure[d]: exploit **positivity** in correlation between **F** and **S**

[a] $h \in \{F, S, F \cap S\}$. [b] Wassmer & Brannath 2016. [c] E.g. $w_1^2 = \frac{N_1}{N_1+N_2}$, $w_2^2 = \frac{N_2}{N_1+N_2}$. [d] $p^{F \cap S} = \min\{2 \times \min(p^F, p^S), \max(p^F, p^S)\}$

Fine-tuning Criteria for Adaptive Design

- Frequency of making "correct" IA decision across key scenarios.

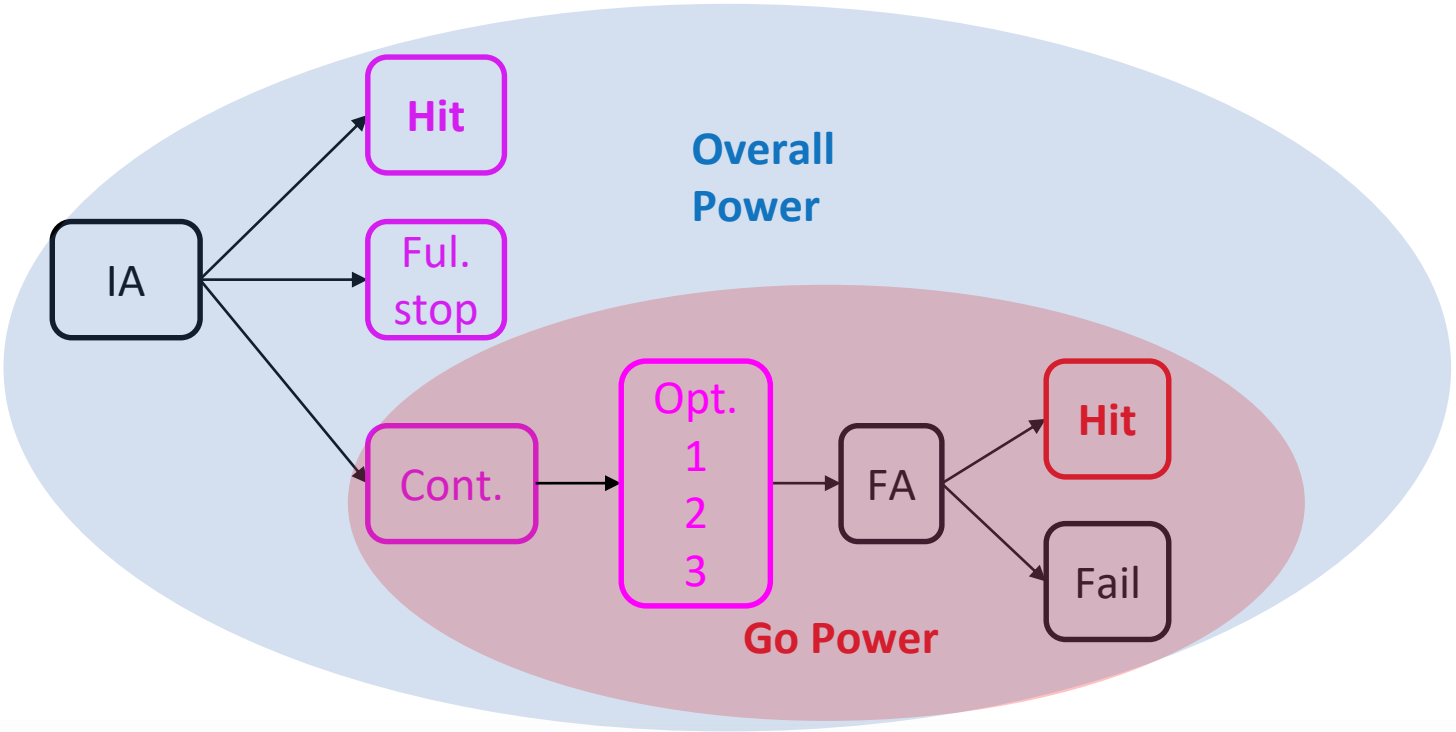
E.g. Frequency of Decision at IA - Threshold: Δ_S=0.14, Δ_C=0.11

(Results for illustration only)

Subgroup S credential	Δ_S	Δ_C	Stop		Continue & Target Population		
			Efficacy	Futility	S only	F only	F &S
Very Strong	0.20	0.04	0.34	0.16	0.38	0.05	0.07
Dismal	0.00	0.00	0.013	0.74	0.11	0.13	0.01

Fine-tuning Criteria for Adaptive Design

- Frequency of making “correct” IA decision across key scenarios.
- Overall power: more relevant if decision made at trial onset or when investment at stage 1 matters.
- Go (conditional) power i.e. Prob. of Success conditional on GO: more relevant if not concerned by wasting stage 1 investment



Why NOT Conditional Power as Decision Criteria?

- At IA „precise“ estimate for each hypothesis not easy due to rejection of their intersection $\boldsymbol{H_0^{F\cap S}}$ as gate keeper.
  - For Sime: $p^{F\cap S} = \min\{2 \times \min(p^F, p^S), \max(p^F, p^S)\}$

  $\Rightarrow$ reject $\boldsymbol{H_0^{F\cap S}}$ at α-level iff **at least one p-value** $\leq \boldsymbol{0.5 \times \alpha}$
  OR **both p-values** $\leq \boldsymbol{\alpha}$

- Not straight-forward for clinician to give input
- $\Rightarrow$ More complex decision tree & simulation needed for optimal thresholds e.g. TAPPAS trial*

- Might be warranted for sample size re-estimation

* An adaptive population enrichment phase III trial of TRC105 and pazopanib versus pazopanib alone in patients with advanced angiosarcoma (TAPPAS trial)

Minimum Detectable Difference

- MDD = min. observed difference $(\hat{\Delta})$ to reject H_0 at α
  - i.e. solution to $\hat{\Delta}_{MDD}/SE(\hat{\Delta}_{MDD}) = \mathrm{Z}_{\alpha}$ (one-sided)
  - Binary outcome: $SE(\hat{\Delta})$ depends on both $\hat{p}_{con}, \hat{p}_{trt}$

  $\Rightarrow$ fix $\hat{p}_{con}$, solve for $\hat{p}_{trt}$

- Rejection of H_0^F (resp. H_0^S) depends on both p-values through rejection of $H_0^{F \cap S}$ in closed test procedure $\Rightarrow$ E.g. at Stage 1

Significance level for $\widehat{\Delta}_{MDD}^{F}$	$\boldsymbol{H_0^S}$ not rejected at α_1	$\boldsymbol{H_0^S}$ rejected at α_1
	$\alpha_1/2$ (higher MDD)	α_1

- Different choice for target populations at stage 2 $\Rightarrow$ various sets of MDDs

Operational and Regulatory Challenges

- Stage 1 enrollment already concluded before amendment → need to minimize accrual gap if stage 2 initiated
  - Timely protocol / SAP / iDMC amendment and gain alignment from iDMC / Regulators
  - Keep sites motivated during enrollment break

- Acceptance by Regulators
  - FDA: minimal questions and swift approval
  - EMA: all statistical details mandated in protocol NOT SAP*

* Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design

CONCLUSION

- Adaptive design = „rescue strategy“ for ad-hoc mid-trial adaptation if original design is challenged
  - Update trial based on its own data → mimimize mispecification risk
  - Established and straight forward theory (at least for binary endpoint) to maintain study‘s integrity

- Operational and regulatory challenges expected
  - Cross-functional discussions: stats, science, ops and reg …
  - Sponsor & iDMC / Regulators interactions

- Prospective design of an adaptive enrichment trial would be preferable in general.

Reference

- Gernot Wassmer and Werner Brannath. *Group Sequential and Confirmatory Adaptive Designs in Clinical Trials*.
- Mehta, et al. *An adaptive population enrichment phase III trial of TRC105 and pazopanib versus pazopanib alone in patients with advanced angiosarcoma (TAPPAS trial)*
- Dent R, Trudeau M, Pritchard KI, et al. *Triple-negative breast cancer: clinical features and patterns of recurrence*.
- https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-methodological-issues-confirmatory-clinical-trials-planned-adaptive-design_en.pdf