Personalised-medicine driven innovations in clinical trials

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Introduction

Innovative Clinical Trial Methods help us to have…

… GREATER patient centricity, Personalized therapy and care, INCREASED diversity, REDUCED cycle times

Patient centric

clinical trials are designed with patient input and use patient centric approaches

Patient diversity

improve clinical trial design and operation to increase patient diversity

Efficient development

reduce in development time without compromising quality of scientific evidence

Personalized approaches is paving the way to next generation medicine

(Precision medicine: an approach to medicine that integrates an individual's characteristics for early disease diagnosis, prognosis, optimal choice of treatment, accurate disease risk estimation, and targeted prevention)

Types of innovative methods

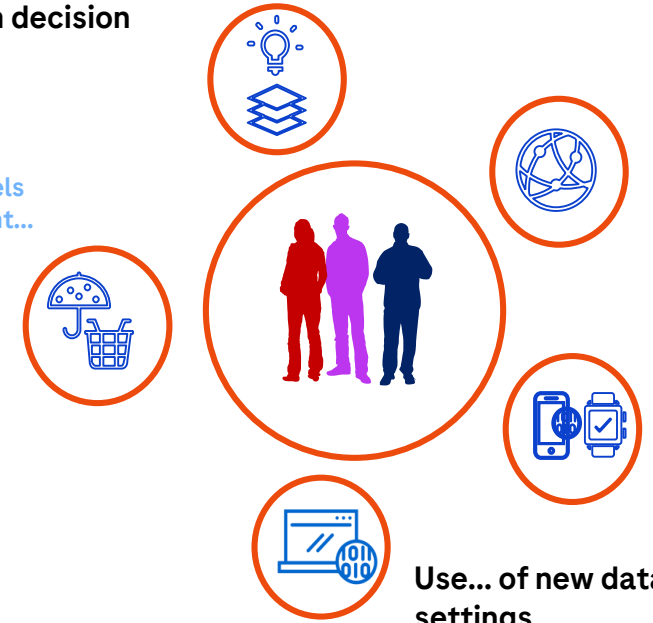
...and the importance of Precision medicine solutions development and applications

Use of innovative statistical analysis and interim decision making

- Adaptive trial design
- Dynamic borrowing
- Digital twins
- Risk prediction models
- Covariate adjustment...

Design more personalised and efficient trials

- Master protocols incl. complex diagnostics
- Platform trials
- Umbrella/basket trials



How we conduct trials to increase patient centricity

- Patient diversity
- Safety monitoring
- Patients Screening
- Decentralized trials
- Patients-meaningful Endpoints

Use... new data types.... in trial settings

- Digital health Tech. Tools
- Molecular endpoints
- Imaging endpoints

Use... of new data sources.... in trial settings

- Historical controls
- RWD
- Model-informed Drug Development (MIDD)

(Enrichment) Adaptive trials –Concepts, examples and considerations

Adaptive design - definitions

A study is called adaptive if statistical methodology allows the modification of a design element [...] at an interim analysis with full control of the type I error.

2007 EMA reflection paper on adaptive designs

Committee for proprietary medicinal products (2007)

Clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.

2019 FDA guidance on adaptive designs

U.S. Food and Drug Administration (2019)

Advantages of Adaptive trial design (over fixed CT)

- Statistical efficiency:
  - Increased power.
  - or Same power with smaller sample size or shorter time.
- More ethical: Stop trial early if unlikely to demonstrate effectiveness.
- Generalizability and improved understanding of drug effects:
  - Possibility to answer broader questions.
- Added flexibility.
  - Re-assess hypothesis at intermediate decision point(s)

Adaptive (and group sequential) Trials

ADAPTIVE DESIGN TYPE	BENEFITS
Group sequential design	Stopping trials early for futility or efficacy, patients don't continue to receive an ineffective treatment
Adaptive dose-finding	Better understanding of treatment doses to improve probability treatment is successful in phase 3
Adaptive enrichment design	Targeting patients most likely to benefit from the treatment, reducing variability to treatment
Seamless P2/3 design	Faster decision making and progressing promising treatments quicker for patients
Sample size re-estimation	Checking assumptions still hold and trial retains sufficient power to assess trial objectives
Adaptive randomization	Patients randomized to treatments which are more likely to be effective, may result with reduced sample size

Two settings of Adaptive Trial designs

Exploratory / Early clinical development trials:

- Goal (of the adaptation): Flexible! The primary goal is estimation of promising drugs effects for internal decision-making.
- Signal seeking, less rigid I error protection
- (Data typically not blinded)
- Continuously looking into data to update estimates.
- Can be included in Master protocols…
- Examples of adaptations: dose-finding, drug combinations selections, biomarker-selected populations, biomarker cut-off selection….

Confirmatory (Phase III):

- Goal: maintain integrity and validity
- Use data of same trial to decide on pre-planned adaptations.
- Protect type I error, although we look into the data multiple times.
- Review by a Independent data monitoring committee (iDMC) at interim steps blinded to sponsors

IMpassion031 (NCT03197935)

Phase III trial in early triple negative breast cancer (TNBC) in neo-adjuvant setting

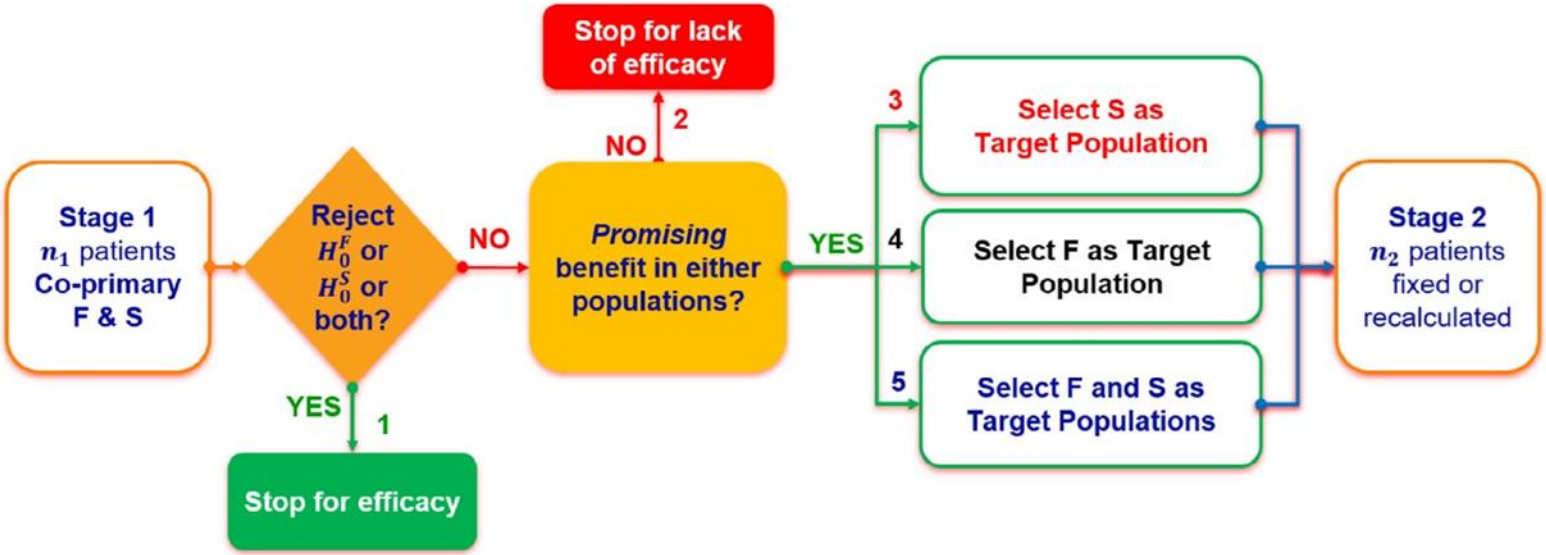
- **Primary objective: Investigate Atezolizumab (PD-L1 inhibitor) and Chemotherapy Compared With Placebo and Chemotherapy**
- **Primary endpoint: pathological complete response (pCR).**
- **Original design: Non-adaptive 2-arm Randomized Clinical Trial**

- **Prior to unblinding (N=205): External data hinting PD-L1 could be predictive of treatment effect in neo-adjuvant TNBC**
  - **Efficacy in PD-L1+ patients could not be formally tested, potentially limiting the label**

- **Adoption of an adaptive trial design**
  - **Optimize chance of success and timeline for timely patient's access & Minimize exposing patients to futile treatment**

Mittendorf et al. 2020

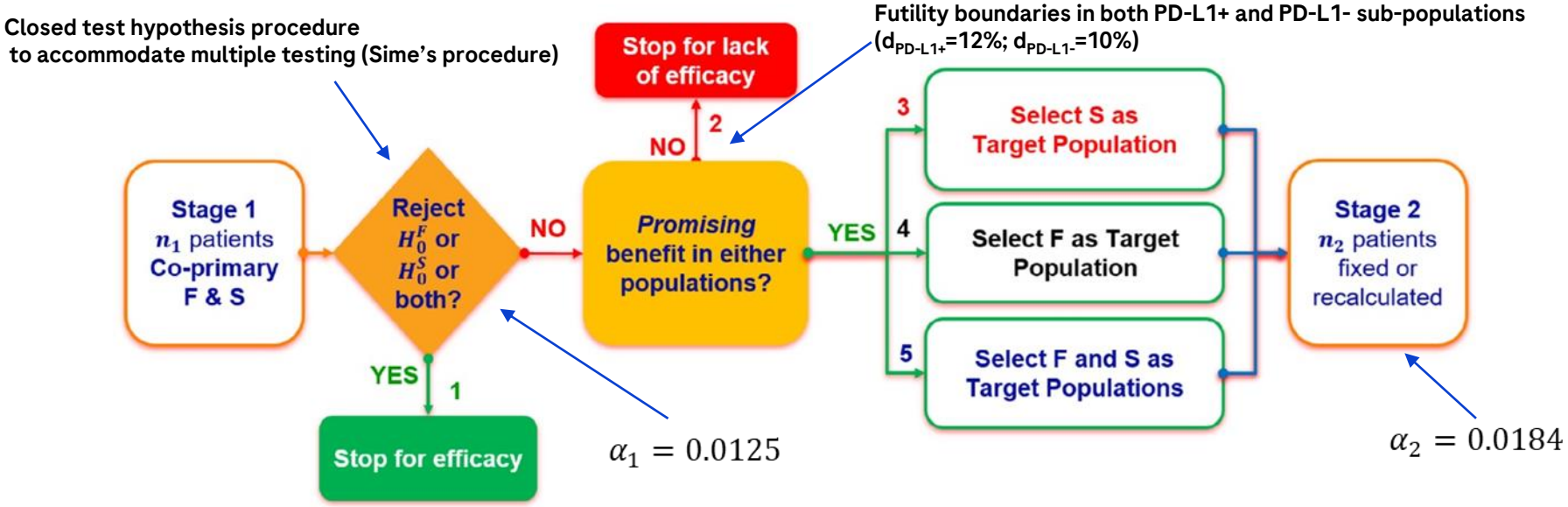
IMpassion031 Enrichment Adaptive Design (AED)



S (Sub-population): PD-L1+ population; F (Full): "All-comers" population

Nguyen Duc et al. (2021)

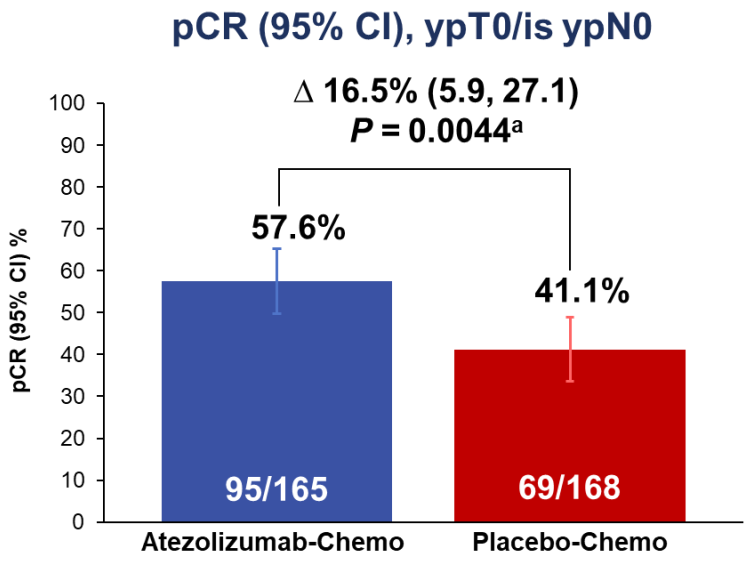
IMpassion031 enrichment Adaptive Design (AED)



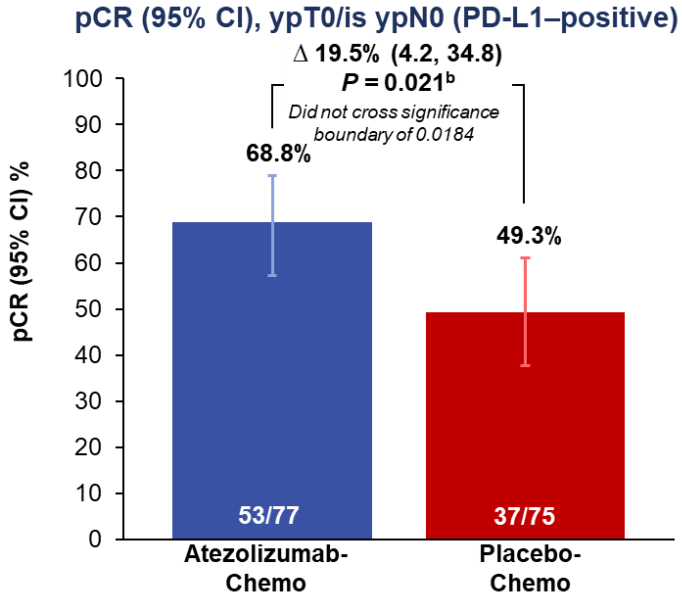
One-side hypothesis testing: Ho: $\pi_{trt}-\pi_{SoC}\leq 0$; **Ha:** $\pi_{trt}-\pi_{SoC}>0$
α_1 and α_2 defined for stage 1 and 2 to protect overall type I error (α=0.025), using adaptive p-values combination procedures
Final test combining stage 1 and stage 2 p-values (≠ from Data pooling)
n_1=205, n_2=128 ; n_2 computed by simulations

Analysis at end of Stage 1 conducted by independent statisticians and reviewed by iDMC, following above pre-specified decision algorithm.

Impassion 031 results



ALL ITT Population (F, N=333)



PD-L1-positive Population (S, N=152)

[a] One-sided significance boundary *P* = 0.0184 (accounting for the adaptive enrichment design). *P* = 0.0085 for the intersection hypothesis of pCR in the ITT and PD-L1–positive population. [b] One-sided significance boundary *P* = 0.0184 (accounting for the adaptive enrichment design).

Learnings & Concerns associated with confirmatory Adaptive trial designs

- Type I error Control ➔ Stat methodology & simulations

- Bias in estimation of treatment effects…when adaptation is not properly accounted for
  ➔ Make use of simulations or existing analytical methods

- Trial planning and pre-specification

" Although statistical methodology has been developed to allow for these types of adaptive designs, these methods should **never be used to replace the careful planning for the statistical design** of a clinical trial. Before starting the trial, an efficient design must be **detailed in the protocol**. Adaptive design methodology then provides a valuable tool for reasonable design changes."

PhRMA, Dragalin (2006)

- Trial conduct and integrity
  - Knowledge of accumulating data can affect conduct of trial

  ➔ Limit access to interim results on treatment effect to individuals independent of trial conduct (iDMC)

Precision medicine as a tool for patients’ safety monitoring (Patient centricity)

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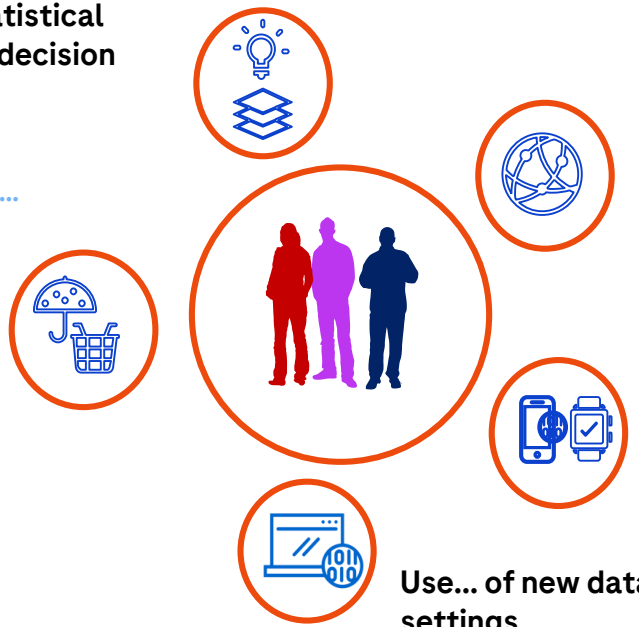

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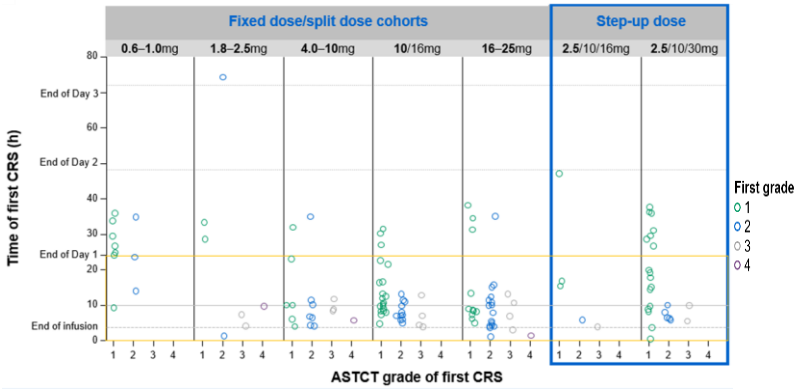
Background

- Glofitamab is a T-cell engaging bispecific antibody targeting CD20 and CD3 with a novel 2:1 format[1]
- Cytokine release syndrome (CRS) observed with glofitamab is typically grade 1–2 severity* with most occurrences confined to the first cycle of therapy[2,3], dose-dependent
- Prediction of an individual patient's CRS risk is not currently possible[4] ; Risk prediction potential Intended use as informing the type of clinical monitoring (overnight hospitalization or outpatient) for patients receiving the first glofitamab dose (2.5 mg), based on calculated risk of Grade 2 or higher CRS.



Data from Phase I (NCT03075696) were used to develop a model to predict occurrence of Grade ≥2 CRS after the first glofitamab dose

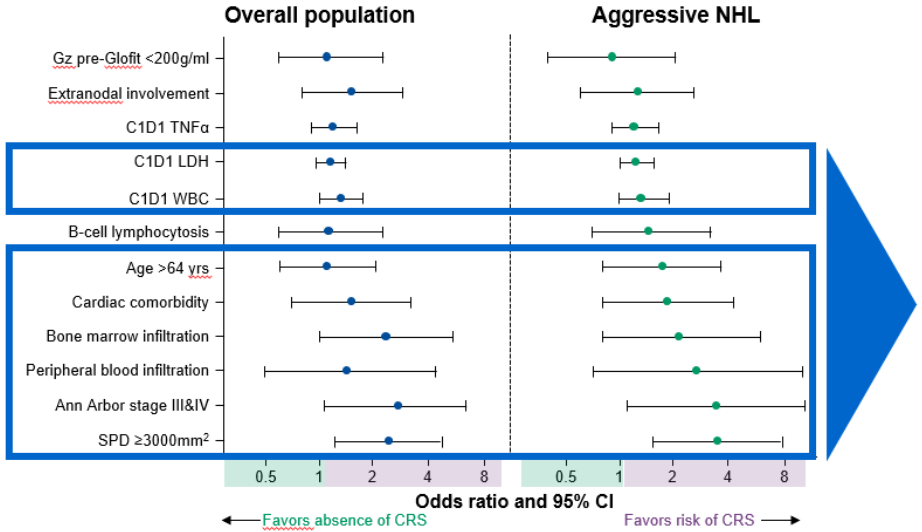
*Per ASTCT (American Society for Transplantation and Cellular Therapy) criteria.

1. Bacac M, et al. Clin Cancer Res 2018;24:4785–97; 2. Yan Z, et al. Front Immunol 2021;12:611366;
3. Hutchings M, et al. J Clin Oncol 2021;39:1959–70; 4. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625-638.

Risk score model: most valuable factors for CRS prediction

- Glofitamab dose and eight factors were selected for inclusion in the CRS Grade ≥2 model
- CRS risk score is a weighted combination of the baseline values of risk factors

Training cohort (fixed, split dose 2.5/10/16mg, N=196) results adjusted for the initial glofitamab dose

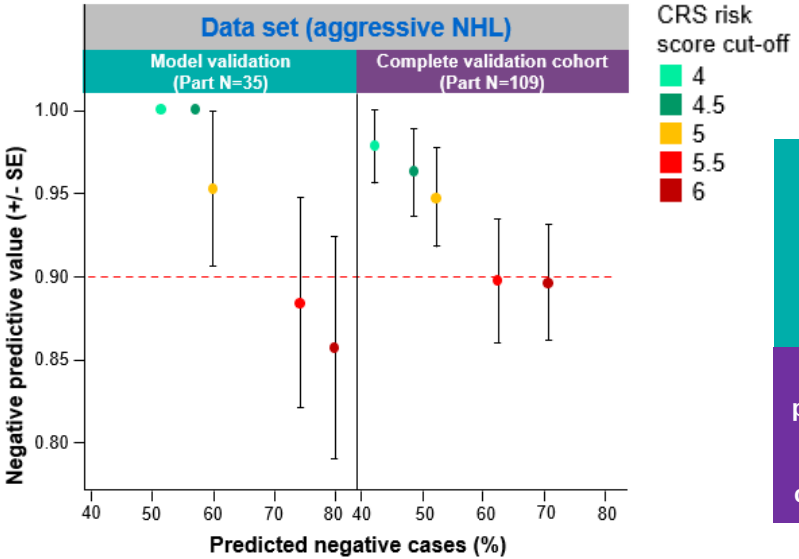


Parameter and cut-off	Weight
Ann Arbor Stage III or IV	2
SPD ≥3000mm²	2
Bone marrow infiltration	1
Atypical cells in PB	1
Age >64 yrs	1
LDH >280U/l	0.5
WBC >4.5*10⁹ cells/l	0.5
Cardiac comorbidity	0.5

CRS risk score = weighted sum of (Weight * Parameter value at baseline), [0, 8.5].

From Krishna V. Komanduri et al. *Poster Presentation at the 63rd ASH Annual Meeting*

Identification of optimal cut-off and final performance: CRS risk score for identification of patients at low risk of Grade ≥2 CRS*



	Low-risk cut-off	Low-risk fraction	Observed incidence of Grade ≥2 CRS (1-NPV)	High-risk fraction	Observed incidence of Grade ≥2 CRS (PPV)
Cut-off identification in the model validation cohort (N=35)	**<4.0**	51%	0%	49%	41%
	<5.0	60%	5%	40%	43%
	<6.0	80%	14%	20%	43%
Final performance in the complete validation cohort (N=109)	**<5.0**	52%	5%	48%	30%

In the final validation a low risk group (CRS risk score <5.0) was identified to be 52% of the test cohort, with patients having only a 5% chance (NPV=0.95, SE=0.03) of experiencing Grade ≥2 CRS

*Data are shown for aggressive NHL cases excluding mantle cell lymphoma histologies. Predicted negative cases = % of patients predicted to have no Grade ≥2 CRS.
NPV, negative predictive value; PPV, positive predictive value; SE, standard error

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Conclusions

Conclusions and key messages

- Precision medicine is a key driver for innovative clinical trials design and clinical development
- Allows personalised, more flexible and efficient trials
  - “tool box” which goes beyond adaptive trial designs (platform trials, basket/umbrella…)
- For confirmatory adaptive designs trials, be mindful of the complexity and purpose of the envisioned adaptation
  - Vet design scenarios carefully
  - Care in the number of stages and decisions, and the unnecessary complexity of the design
- Precision medicine has more impact on clinical development than trial designs!

Doing now what patients need next