

A Tailored In Silico approach for a Given Population and Indication can Effectively inform other Contexts of Use

As demonstrated by Extending an ADC in Silico Trial from Breast Cancer to Gastric Cancer in humans.

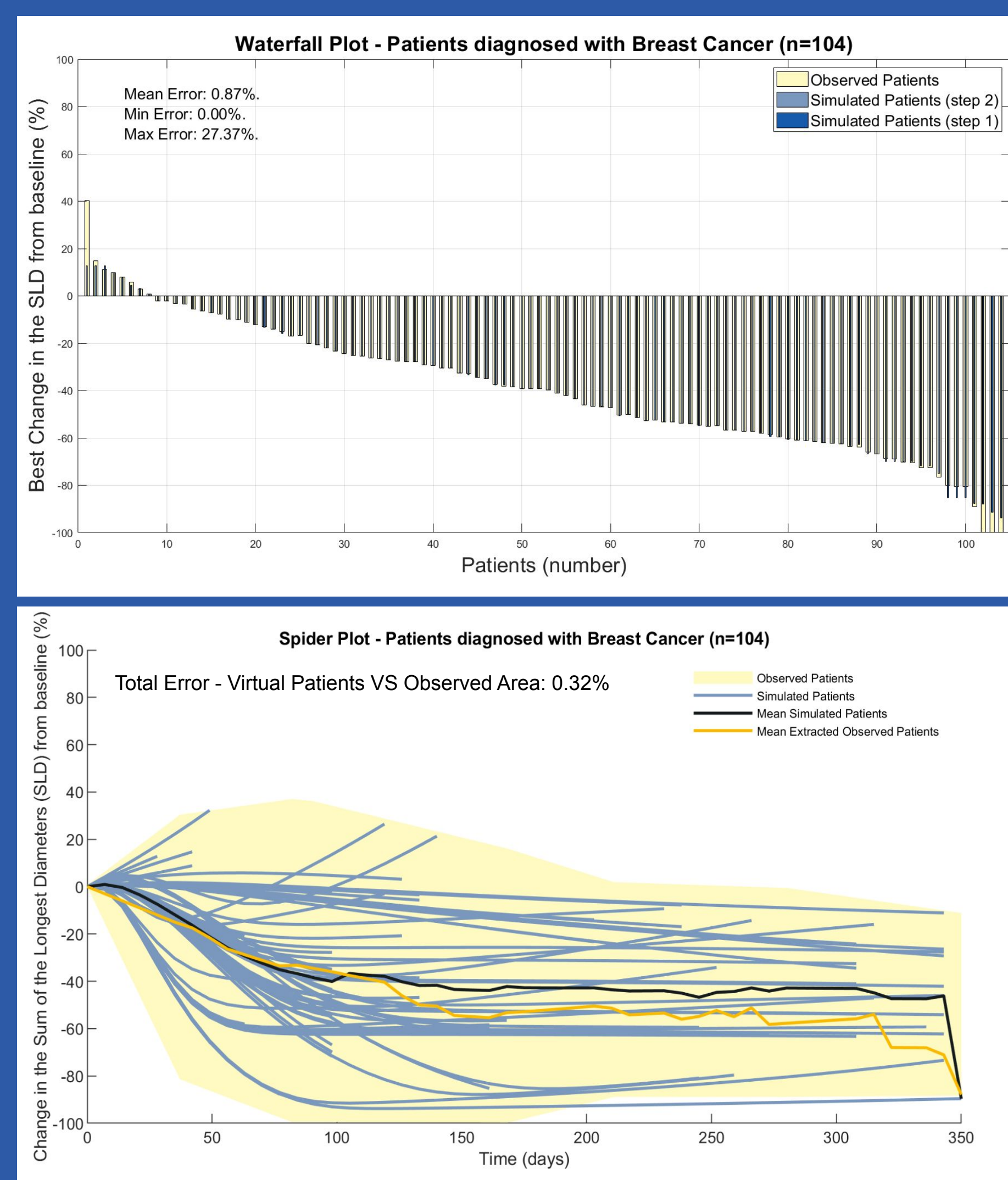


Figure 1. Observed [1] versus Simulated best change from baseline at a population level for a cohort of patients harboring breast cancer under 6.4mpk T-DXd (n=104)

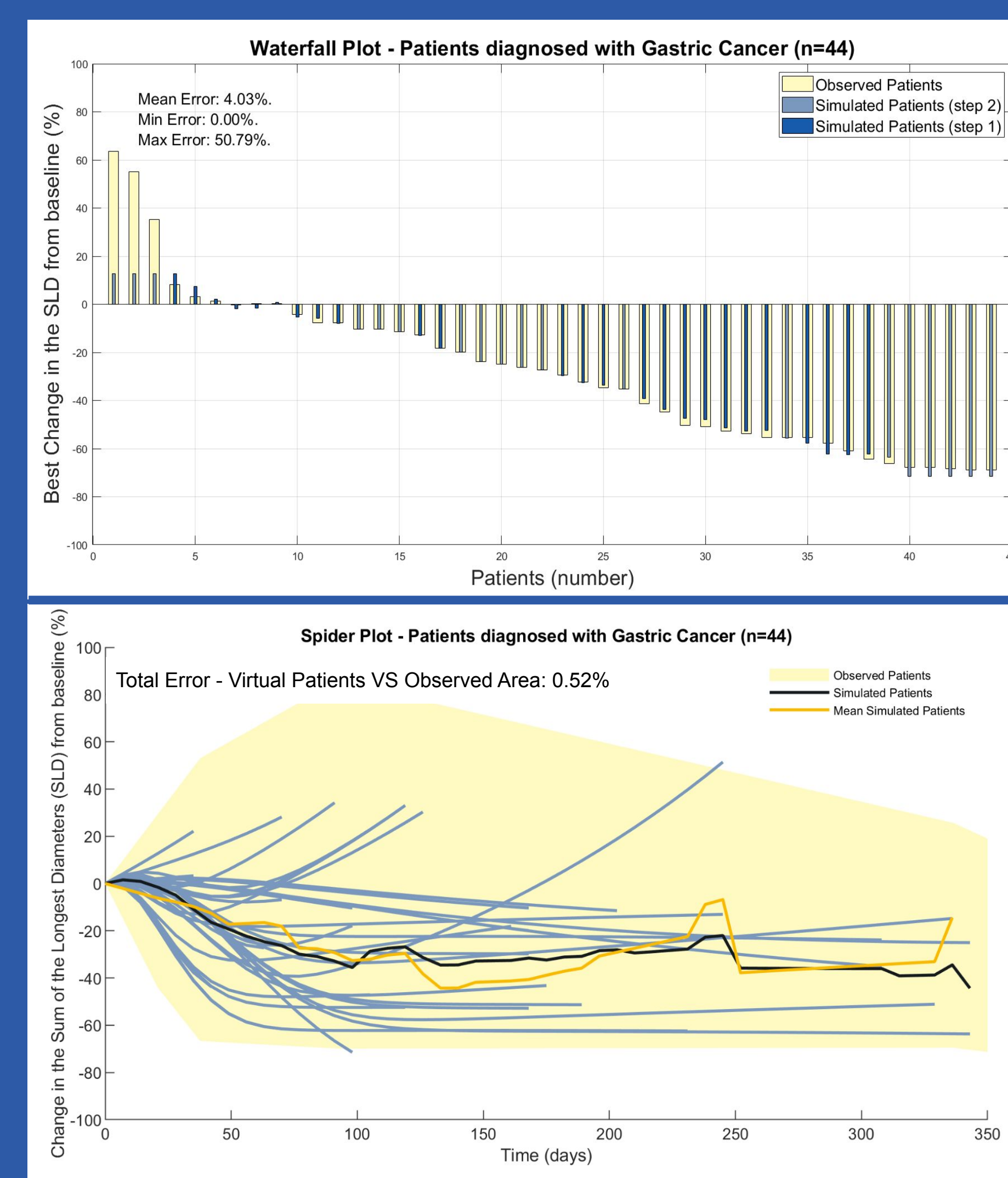
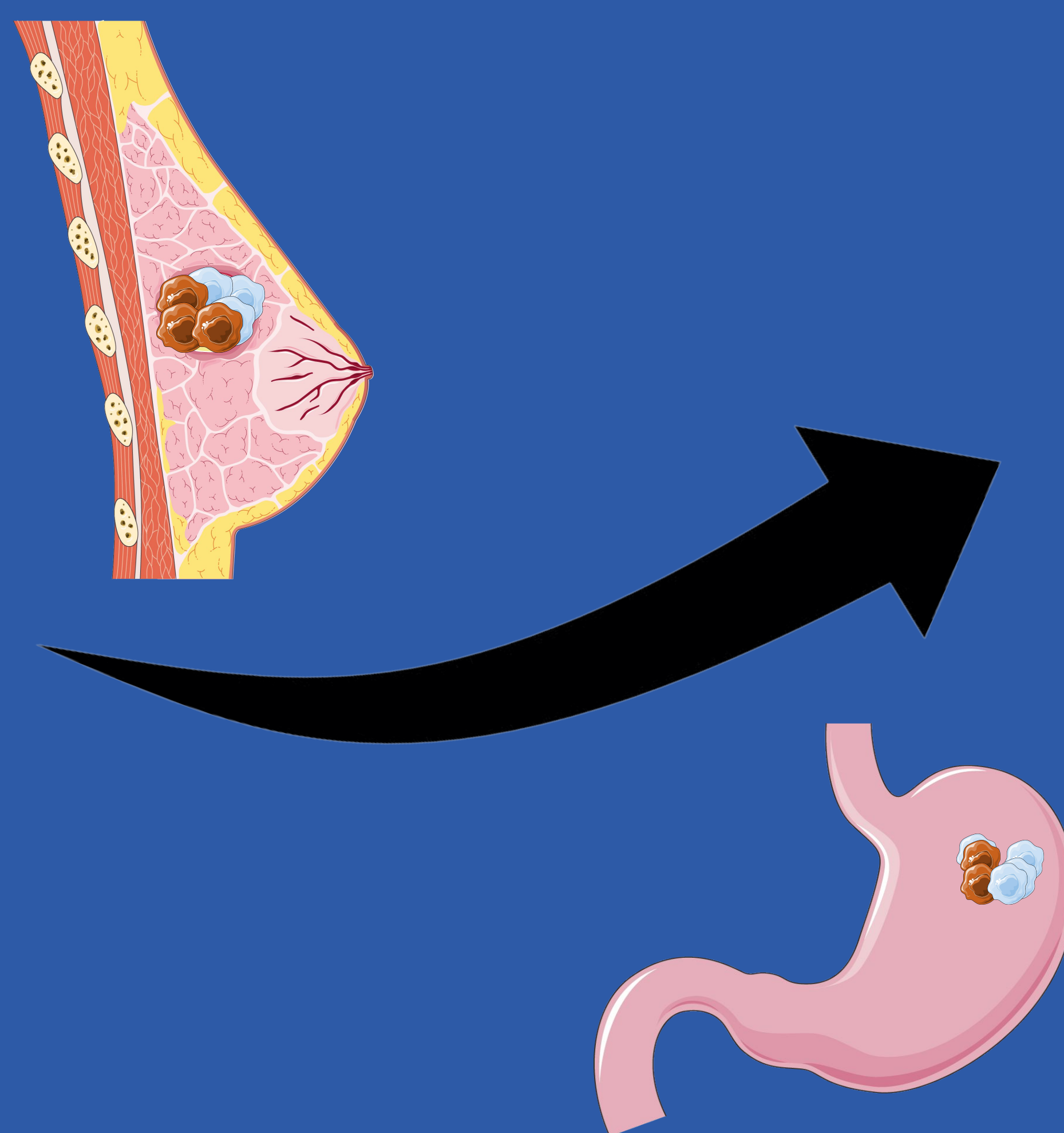


Figure 2. Observed [1] versus Simulated best change from baseline at a population level for a cohort of patients harboring gastric cancer under 6.4mpk T-DXd (n=44)

Context: Why Have We Done This Study

- Antibody-drug conjugate (ADC) represents a significant advancement in oncology therapeutics. It offers targeted delivery of cytotoxic drugs to tumor cells.
- To make informed decisions, it is crucial to grasp the attributes and mechanisms of ADCs ranging from drug pharmacokinetics (PK) and tumor growth inhibition dynamics to the properties of payloads, linkers, and the bystander effect.
- This understanding can be limited by the specific context of use e.g. the population or indication

- Gap:** How to establish the translational process required to apply specific insights from the studies focusing on ADC therapy across clinical indications and later predict the efficacy in patients.
- Short-term Goal:** Develop and implement one robust and reliable protocol that transforms an in silico approach tailored for breast cancer, leveraging multi-level data involving Trastuzumab deruxtecan (T-DXd) and the associated expression of human epidermal growth factor receptor 2 (Her2), into predictive in silico results for dose-exposure response in gastric cancer.
- Long-term Goal:** Establish an ADC platform in order to address this indication expansion.

Material & Methods: How In Silico Helped ?

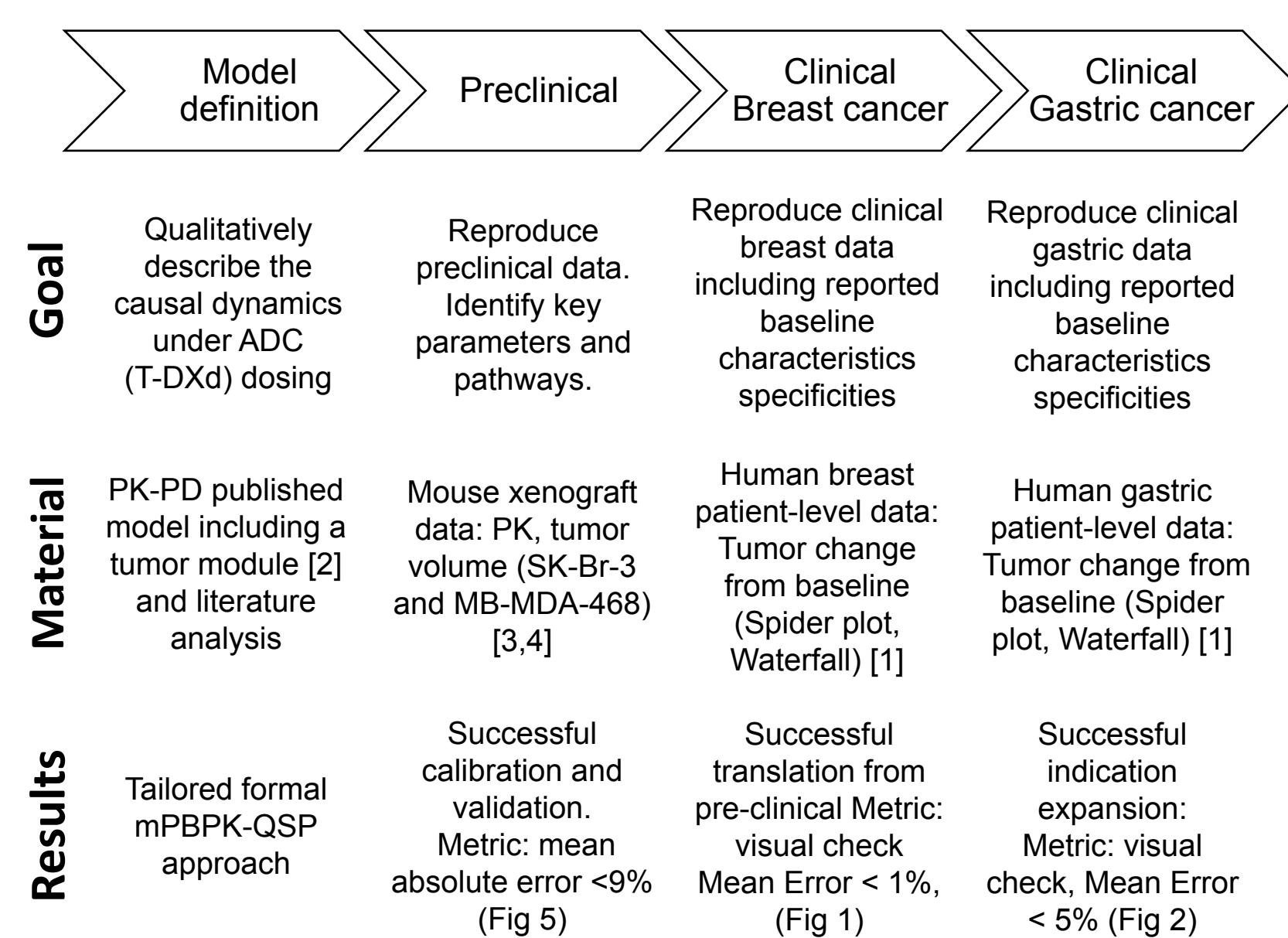
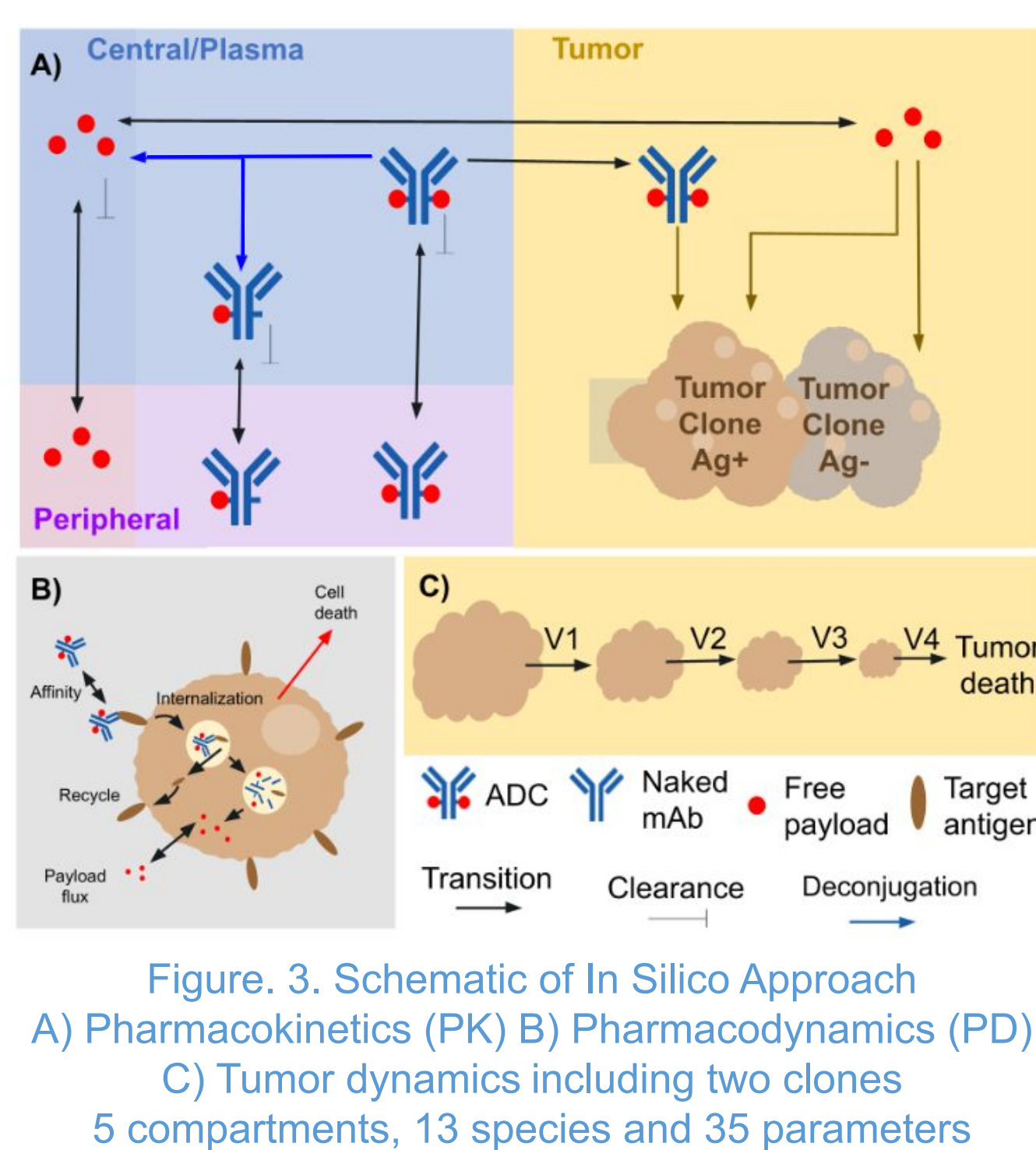


Figure 4. Overview of the strategy: goal, material and results.

Results: At The End, Does This Work ? → YES !

Breast Cancer Context of Use

- Characterization of the pharmacokinetics (PK) of payload and ADC in plasma and tumor tissues.
- Portrayal of the responses witnessed in xenograft mice post-ADC administration (Fig. 5).
- Description of the response in terms of tumor size change from baseline for T-DXd (Fig. 1).

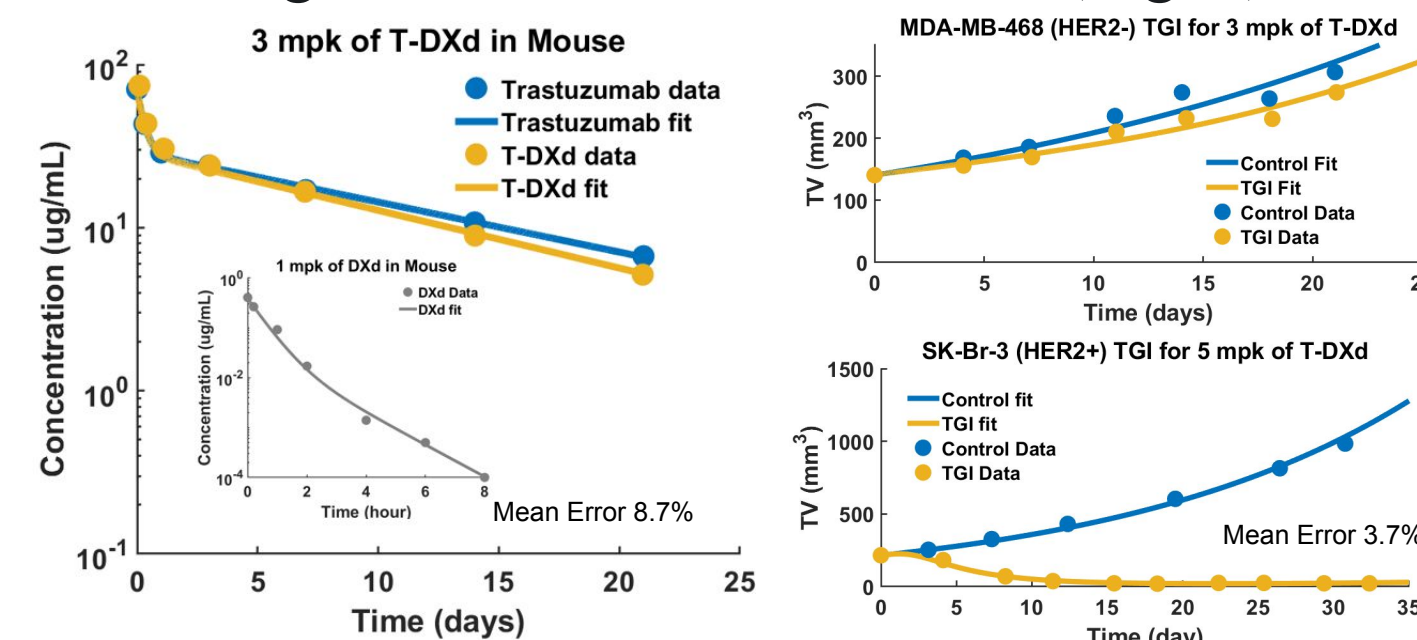


Figure 5. Mice calibration - Observed VS Simulated. (A) PK [3] (B) PD - MDA-MB-468 - 3mpk SK-BR-3 5mpk and Controls. [4]

Gastric Cancer Context of Use

- Prediction of T-DXd efficacy, which align closely with available clinical trial data (tumor size change from baseline) (Fig. 2).
- Evaluation of the key dynamics and associated parameters distribution (Fig. 6).

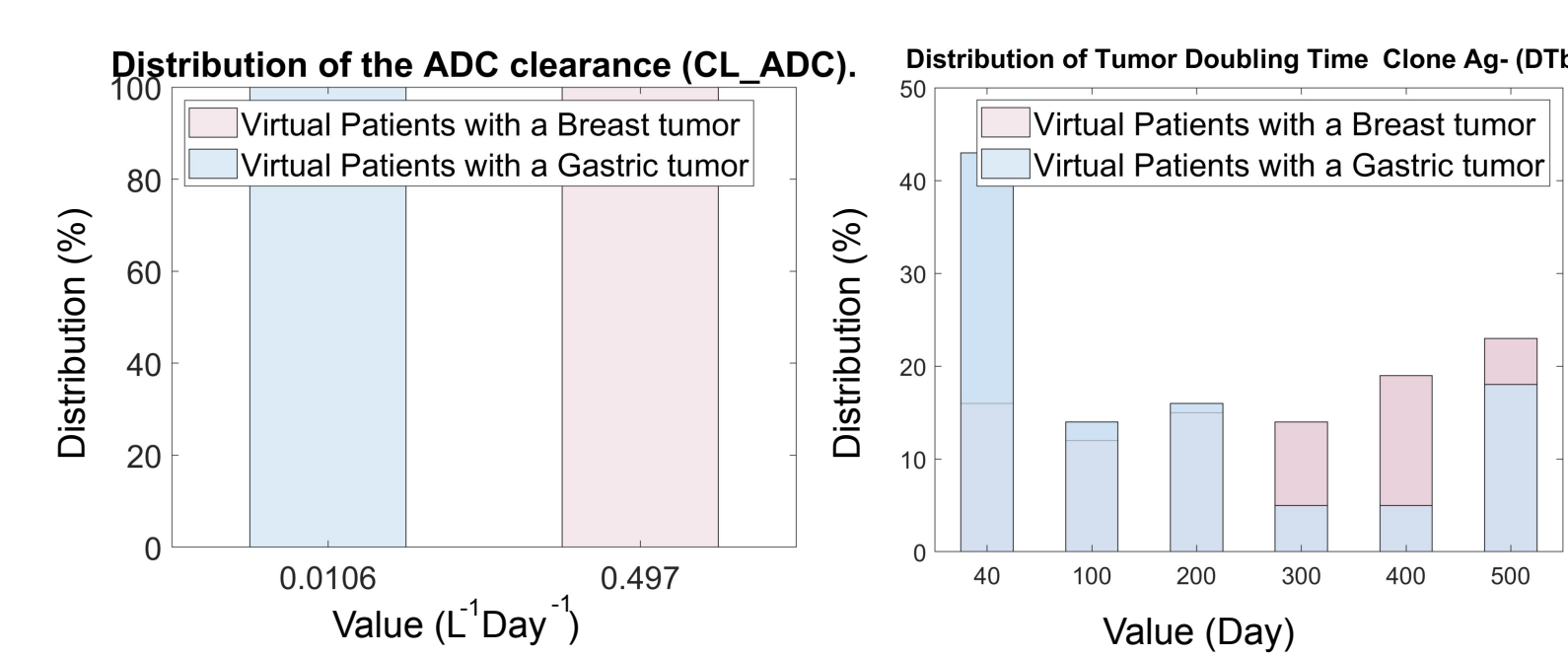


Figure 6. Example of parameters distribution between indications A) Model intrinsic parameter B) Patient specific parameter

How This Could Be Of Interest To You (even if ADC is not your focus)

- Predictive drug outcome modeling:** Integrate diverse data sources with granular contextual knowledge to predict clinical-stage drug outcomes (e.g. spider charts, waterfall plots, ORR)
- Strategic optimization:** Enhance the selection of appropriate patient populations and the expansion of indications or therapies (e.g. payload selection, half-lives improvement)
- PBPK/QSP framework development:** Built a comprehensive framework applicable across multiple stages of drug development, including: analysis of approved drugs, identification of drug characteristics, variability analysis

REFERENCES

- [1] Daiichi-Sankyo Presentation - ASCO, 2018
[2] Singh et al. (2020) [3] Okamoto2020 [4] Ogitan2016
Servier Medical Art was used to create some parts of the figures.
Detailed references and supplementary data available upon request.



- Selection, tailoring and implementation** of a published model [2].
Addition of modules on the systemic distribution and the tumor clone (different drug sensitivity).
It captured drug disposition at cellular level, antigen expression, drug-antigen interaction, internalization, intracellular payload disposition, drug distribution, tumor growth inhibition (TGI) and bystander killing by the drug.
- Calibration** of the homogenous model using different xenograft data (preclinical models, Fig 5.) [3,4]
- Clinical translation and calibration** to breast cancer patients under the approved ADC T-DXd (Fig 1)[1]
Identification of the parameters distribution and correlations in breast cancer.
Two clones based on antigen expression. Calibration of the tumor doubling time, tumor killing rates and tumor clone ratio.
- Reparameterization from breast to gastric cancer** by identifying and updating key parameters.
Based on a sensitivity evaluation and a literature investigation: tumor initial volume, antigen expression, ADC clearance (Fig 6.)
- Qualitative and quantitative indication expansion** of the model in human gastric cancer [1] (Fig 2.)