605 COMPUTATIONAL PATHOLOGY-BASED DIGITAL TWINS ENABLE THE DISCOVERY OF PREDICTIVE BIOMARKERS FOR PRECISION IMMUNO-ONCOLOGY

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Background Exploratory data from single-arm PhI/II clinical trials provide a unique opportunity for predictive biomarker discovery, but have the limitation to estimate the prognostic value in absence of a control arm. This poses a significant risk to subsequent biomarker-driven PhIII trials. A Digital Twin is the computational description a real patient based on their clinical data,[1] including baseline histopathology imaging. In this work, we demonstrate the generation of a virtual randomized PhIII clinical trial (vPhIII) via Digital Twins and their application for predictive biomarker discovery.

Methods Eligible baseline tissue samples of NSCLC patients enrolled in the PhI/II trial 'CP1108' (NCT01693562) and in the randomized PhIII trial 'MYSTIC' (NCT02453282)[4 5] were considered for computational pathology analysis. Relying on Quantitative Continuous Scoring for PD-L1 (PD-L1 QCS), the PD-L1 protein expression was digitally quantified and multidimensional whole slide image (WSI) features for PD-L1 expression were obtained.[2 3]

For each PhI/II patient, its Digital Twin is generated by identifying the most similar matching patient in the PhIII control arm using Euclidean distance and Delaunay triangulation of dimensionality-reduced patient features. This group of Digital Twins comprises the actual observed overall survival (OS) information from the respective study, and therefore could serve as vPhIII. Each PD-L1 QCS feature is evaluated for its median OS time (mOS) benefit in the QCS-positive vPhIII sub-group. The feature providing longest mOS benefit is selected and evaluated for its predictive value validated in the real PhIII cohort.

Results N=121 Digital Twins were generated as vPhIII cohort (figure 1a), while average mOS benefit analysis for each feature indicated that the 20% quantile of PD-L1 tumor cell expression provides optimal stratification (figure 1b). The mOS comparison of the real PhIII (figure 2a) with the vPhIII (figure 2b) showed the OS benefit from durvalumab treatment has been underestimated by the Digital Twins model. Although the selected QCS feature did not indicate significant treatment benefit in the vPhIII (figure 3a), a retrospective analysis of MYSTIC hints towards beneficial patient stratification (figure 3b).

Conclusions Digital Twins based on imaging data are a promising approach to generate virtual randomized and biomarker stratified PhIII trials based on single-arm PhI/II and historic Standard-of-Care data. This proof-of-concept study demonstrates technical feasibility of this innovative methodology. Although further validation is required, the Digital Twin approach may open new ways towards maximizing the success probability of drug development programs, and faster implementation of Precision Oncology in clinical routine.

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Trial Registration NCT01693562, NCT02453282

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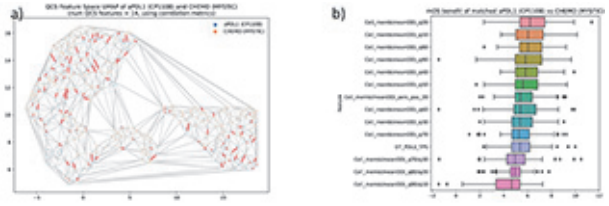
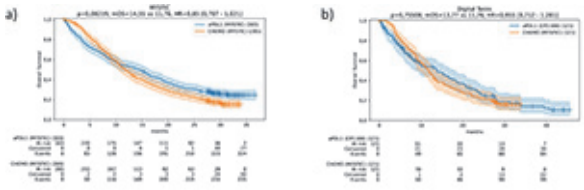
Ethics Approval Clinical studies NCT01693562 and NCT02453282, from which data in this report were obtained, were carried out in accordance with the Declaration of Helsinki and GoodClinical Practice guidelines. The study protocols, amendments, and participant informed consent documents were approved by the appropriate institutional review boards.



Abstract 605 Figure 1 (A) Delaunay triangulated UMAP dimensionality reduction plot of the PD-L1 QCS feature space used to identify the Digital Twins based on anti-PD-L1 (durvalumab) treated CP1108 patients (blue dots) and MYSTIC control arm (orange dots). Each Twin pair is connected by a red line. (B) Ranking of PD-L1 QCS features by average mOS survival benefit in the vPhIII cohort. The mOS benefits had been calculated using 100 Monte-Carlo runs on a 80% subset of the vPhIII cohort. DT_PDL1_TPS represents the predictive performance of human pathologist PD-L1 tumor proportion score. PD-L1 QCS membrane expression quantiles for each patient's WSI have been considered in the range from 10% (q10) to 90% (q90)



Abstract 605 Figure 2 Kaplan Meier analysis of (A) the Ph III MYSTIC study patients (N=303+285) considered in this proof-of-concept work, and (B) vPhIII study Digital Twins (N=121+121) generated by matching considered CP1108 patients with MYSTIC control arm (labelled as CHEMO) patients, using their actually observed OS time and event information

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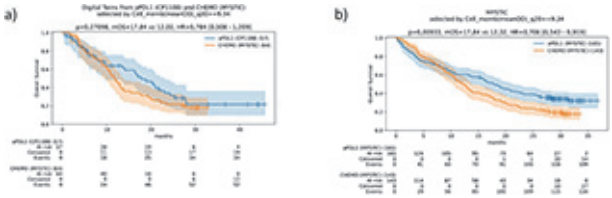

Abstract 605 Figure 3 Kaplan Meier analysis of PD-L1 QCS-positive patients in the (A) vPhIII and (B) real PhIII MYSTIC cohort. 'PD-L1 QCS-positive' is defined by the condition that the 20% quantile of PD-L1 membrane protien expression on all tumor cells of a patient's WSI is larger than 9.34 (on a scale from 0 to 255)

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