Panomics validation of time to next treatment (TNT) as a surrogate outcome measure in 4729 cancer patients

Background
In an era increasingly focused on the value of medicine, attempts are being made to improve the cost-effectiveness of many aspects of medical management (1-2). One potential solution is precision medicine, which uses predictive biomarkers to guide treatment selection to improve outcomes by reducing the use of drugs that are likely to be of little benefit (3).

The measurement of clinical outcomes in real-world precision medicine-associated datasets faces a significant obstacle. Validation requires either prospective hypothesis generation or regulatory and institutional approval. The use of this parameter is predicated on the concept that change of treatment usually occurs in response to a real change in patient status.

The aim of this study was to assess (a) the impact of panomic (multiparametric genomic and proteomic) testing in the prediction of outcome of systemic therapy in advanced cancer, and (b) to define the utility of TNT as a surrogate endpoint for survival in patients stratified based on this predictive capability.

Methods
Panomic profiling was performed in patients with advanced solid tumors who were referred to Caris Life Sciences for molecular profiling as part of their clinical care. A variety of established technology platforms were used, including:

- Immunohistochemistry (IHC)
- Fluorescent in situ hybridization (FISH)/CISH
- Fluorescence in situ hybridization
- Fragment analysis (FA)
- Polymerase chain reaction
- Next-generation sequencing (NGS)
- Mass spectrometry
- Whole-genome sequencing
- Quantitative reverse transcription PCR

Testing was performed under accreditation from CLIA, CAP and ISO 15189:2012. Patients were retrospectively classified as Matched (M) or Unmatched (U) depending on whether they received treatments in line with the predictions of their molecular profiling results. Patients in the unmatched group were more heavily treated after collection in 952 patients from the Caris Registry database. The effect size of a single line of TNT is smaller than the OS effect.

Overall survival is the sum of multiple TNT events, thus choosing a matched therapy over an unmatched one may affect survival at later time points. This is consistent with the previous result, showing that individual lines of matched therapy are better than unmatched and that multiple matches result in a significant increase in OS.

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Results
Figure 1 – Cohort definitions for monotherapies (a) and dual combinations (b) based on predictive association with biomarker results

Table 1 - Registry demographics

Figure 2 – Distribution of tumor type for the Registry cohort (a,b) and the IntrinsiQ cohort (c,d)

Figure 3 – Average number of drugs given per patient in each cohort. Patients in the unmatched group were more heavily treated after profiling, suggesting ineffective therapies were chosen.

Figure 4 – Overall Survival based on treatments administered after tissue collection; an improved OS (HR of 0.69 (CI: (0.56,0.84), p <0.001)) was observed between M (n= 505) and U (n=447), with a median increase of more than 1 year (M = 1069 days and U = 686 days).

Figure 5 – TNT after collection with match status based on the first line of therapy received after collection in 952 patients from the Caris Registry database. The effect size of a single line of TNT is smaller than the OS effect.

Figure 6 – TNT after collection with match status based on the first line of therapy received after collection in 4,729 patients from IntrinsiQ. This is consistent with the previous result, showing that individual lines of matched therapy are better than unmatched and that multiple matches result in a significant increase in OS.

Conclusions
- Our initial data suggest that greater knowledge of predictive biomarkers and their implementation in patient selection may improve clinical outcomes.
- We present a novel framework that integrates molecular profiling and clinical treatment and patient outcome data over a large scale volume to evaluate the utility of panomic testing.
- While the changes in TNT in the Matched and Unmatched cohorts are modest, they are statistically significant and reflect the changes seen in overall survival. Overall survival is the sum of multiple TNT events, thus choosing a matched therapy multiple times has an additive effect resulting in increased survival, explaining why the effect size of a single line of TNT is smaller than the OS effect.

- TNT is an attractive endpoint because it reflects the actual clinical decision process, where a change of treatment is the sine qua non and theoretically may represent a more clinically relevant endpoint than the end of a progression free interval.
- To our knowledge, this is the first large clinical series that has shown a clinically relevant and statistically significant increase in OS in association with broadly based panomic profiling used for the prediction of treatment response.

References