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

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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 hyper-segmentation in studies of niche populations or retrospective analysis of large numbers of patients from clinical practice.

Time-to-next treatment (TNT) is an established endpoint, mostly applied in hematological malignancies, that has recently been used in prostate cancer, breast cancer and colorectal cancer (4-6). 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 (multiplatform 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 upon 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 or chromatic *in situ* hybridization (FISH/CISH)
- Fragment analysis (FA)
- Pyrosequencing and next-generation sequencing (NGS)

Testing was performed under accreditation from CLIA, CAP and ISO 15189:2012

Patients were enrolled into an IRB-approved, multi-center, database designed to collect data on the outcomes of patients under a registry protocol (NCT02678754).

Data were collected at baseline (just after profiling) and every 9 months, up to 63 months or until patient death.

1180 cases of solid tumor malignancy referred for testing between 2009 and 2015 were enrolled in the Registry, providing minimum follow up of 9 months. Additionally, data from 3,702 patients who underwent panomic tumour profiling were obtained from IntrinsiQ Specialty Solutions.

Patients were retrospectively classified as Matched (M) or Unmatched (U) depending on whether they received treatments in line with the predictions of their molecular profile. The definition of M and U was applied based on the first treatment administered after collection of the panomic analysis sample for the creation of TNT data, and for all treatments received for correlation with overall survival data.

Results

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

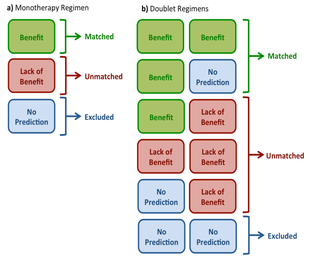


Table 1 - Registry demographics

	Matched (n=505)	Unmatched (n=447)	P-value
Sex			0.254
Female	392(77.6%)	332(74.3%)	
Male	113(22.4%)	115(25.7%)	
Age			0.997
0-40	33(6.5%)	31(6.9%)	
40-50	75(14.9%)	68(15.2%)	
50-60	139(27.5%)	125(28%)	
60-70	145(28.7%)	126(28.2%)	
70-100	113(22.4%)	97(21.7%)	
Race			0.436
American Indian	2(0.4%)	2(0.4%)	
Asian	28(5.5%)	15(3.4%)	
Black	36(7.1%)	39(8.7%)	
Other/Unknown	12(2.4%)	8(1.8%)	
White	427(84.6%)	383(85.7%)	
Grade			0.744
Grade 1 / Well differentiated	27(5.3%)	20(4.5%)	
Grade 2 / Moderately differentiated	147(29.1%)	116(26%)	
Grade 3/ Poorly differentiated	244(48.3%)	232(51.9%)	
Grade 4/ Undifferentiated	20(4%)	18(4%)	
High Grade	20(4%)	4(0.9%)	
Unknown	65(12.9%)	57(12.8%)	

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

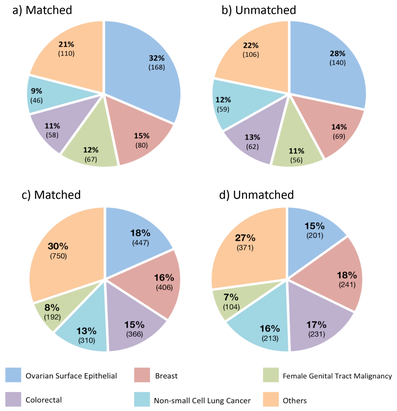


Figure 3 – Average number of drugs given per patient in each cohort. Patients in the unmatched group were more heavily treated after profiling, suggesting ineffective therapies were chosen.

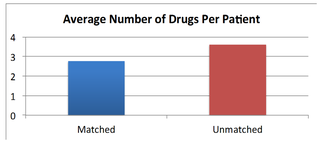


Figure 4 – Overall Survival based on treatments administered after tissue collection; an improved OS (HR of 0.69 (CI: (0.56,0.84),p <0.001)) was observed between M (n= 505) and U (n=447), with a median increase of more than 1 year (M = 1069 days and U = 686 days)

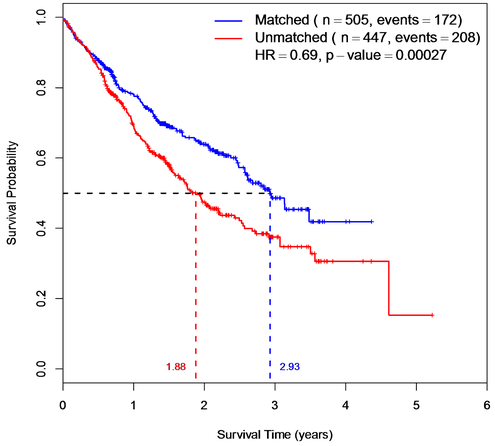


Figure 5 – TNT after collection with match status based on the first line of therapy received after collection in 952 patients from the Caris Registry database. The effect size of TNT reflects the contribution of a single line of therapy to the larger effect observed in OS.

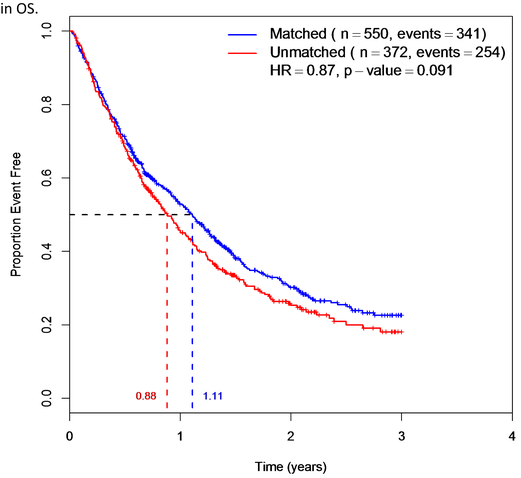
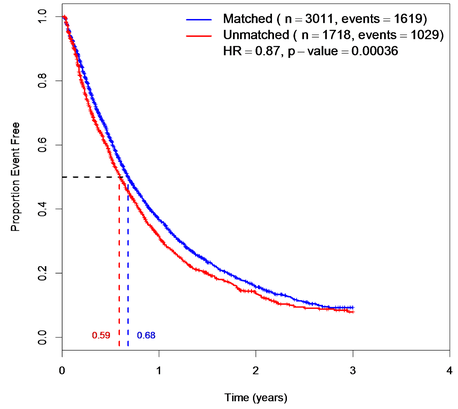


Figure 6 – TNT after collection with match status based on the first line of therapy received after collection in 4,729 patients from IntrinsiQ. This is consistent with the previous result, showing that individual lines of matched therapy are better than unmatched and that multiple matches result in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



Conclusions

- Our initial data suggest that greater knowledge of predictive biomarkers and their implementation into treatment selection may improve clinical outcomes.
- We present a novel framework that integrates molecular profiling and clinical treatment and patient outcome data over a large case 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 biologically 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

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