Implementing functional precision oncology in real-world patients |

The translation of extensive *in vitro* data into personalized treatment by combining genetical and functional assays

1242P

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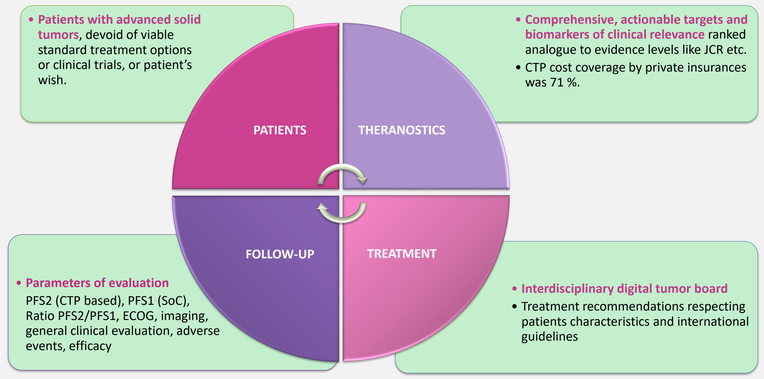
BACKGROUND |

Predictive and prognostic biomarkers for personalising cancer therapy are now widely used, but their application is still far from standard of care (SoC). Concentrating exclusively on genetic alterations within recent basket trials has revealed limited clinical effectiveness. Comprehensive tumor profiling (CTP) emerges as a potential instrument to enhance treatment efficacy revealing additional actionable targets to combine appropriate therapies.

REAL WORLD IMPLEMENTATION OF CTP |

- **Patients with advanced solid tumors**, devoid of viable standard treatment options or clinical trials, or patient's wish.

- **Comprehensive, actionable targets and biomarkers of clinical relevance** ranked analogue to evidence levels like JCR etc.
- CTP cost coverage by private insurances was 71 %.



- **Parameters of evaluation**
  PFS2 (CTP based), PFS1 (SoC), Ratio PFS2/PFS1, ECOG, imaging, general clinical evaluation, adverse events, efficacy

- **Interdisciplinary digital tumor board**
- Treatment recommendations respecting patients characteristics and international guidelines

PATIENT POPULATION |

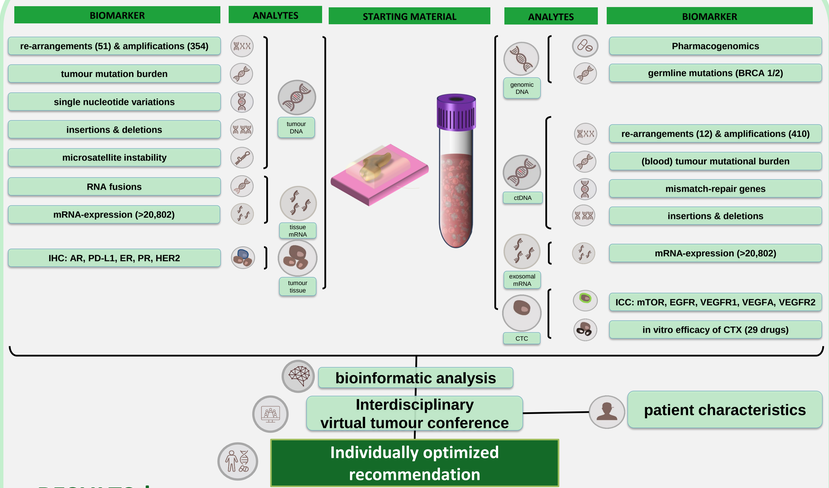
Patients	**42**
Age	**Mean (SD) 64,3 (13,3)**
Sex	**Female 66.7 %; male 33.3%**
Smoker	**Yes 14.3% (6); No 85.7% (36)**
ECOG PFS1	**Mean 0.52**
ECOG PFS2	**Mean 0.60**
Previous Therapies	**Median 2.0**

TUMOR ENTITIES |

	Ovarian	Mamma	Lung	Prostate	Pancreas	CRC	Stomach	Renal	Others
TOTAL (42 patients)	1	18	4	4	4	2	1	2	6

METHODS |

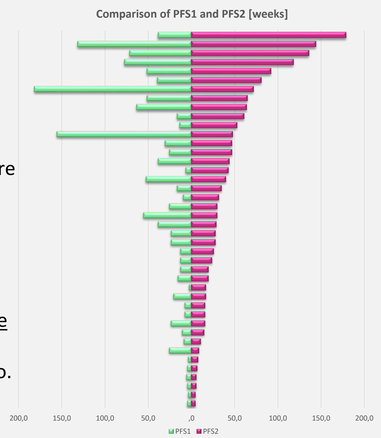
Tissue and/or peripheral blood samples were employed for CTP (exacta®). Next generation sequencing was applied to sequence tumor DNA, 411 genes for ctDNA and 511 genes for tissue derived tumor DNA. Exosomes or tissue was used for the extraction of 20.800 mRNAs. CTCs were harvested from PBMCs by treatment with a proprietary differentially cytotoxic medium up to 100h. The medium induces cell death in non-malignant cells while conferring survival privilege on apoptosis-resistant cells of tumorigenic origin.Viable cells were treated *in vitro* with FDA-approved anti-cancer drugs for 24 h after which apoptotic cell death events were determined. Immunohistochemistry and Immunocytochemistry were performed on tissue/CTC. Pharmacogenomics were used for relevant medications.



RESULTS |

- **Treatments**
  12 % of patients received CTX
  24 % received targeted therapy,
  64 % received combination of CTX & targeted therapy

- **80 % improved** or did not run worse under PFS2 compared to PFS1 under standard of care
- **28 % doubling of PFS2** (in 21% patients PFS2 not reached yet); 57% reached a ratio of at least 1.25
- **Median ratio (PFS2/1) 1,31 (95% CI 0,8-2,1)**



	Median [weeks]
PFS1	**22.5 (95% CI 13-39)**
PFS2	**29.5 (95% CI 24-53)**
PFS2/PFS1	**1.31 (95% CI 0,8-2,1)**

Influencing factors of ratio based on multivariate analysis (cox regression)

- **higher ratio:** isolated bone metastases, total No. of suppressor genes (p=0.003)
- **lower ratio:** ECOG PFS2 (p=0.0001), but ECOG didn´t change significantly, total no. of oncogenes, TP53 (p=0.005), higher grading (p=0.016)

Probability for PFS longer than at least 6 months:

PFS1 50 % - PFS2 62 %

Treatment response

The assessment of Objective Response Rate (ORR) followed RECIST criteria. Utilizing theranostics not only prolonged therapeutic effects but also improved the initial patient response rate. Specifically, the ORR was 64% for the Standard of Care (SOC) group, while it reached 86% in the CTP group. No grade 4 adverse events were observed (CTC).

Therapy modality	Patients	Median PFS2 [weeks]	Median PFS2/1
Targeted + Chemo	27	29 (95% CI 17-40)	1,25 (95% CI 0,8-1,8)
Targeted	10	50 (95% CI 26-92)	1,9 (0,7-3,7)
Chemo	5	15 (95% CI 5-28)	1,09 (95% CI 1-1,2)

DISCUSSION |

The use of Comprehensive Tumor Profiling (CTP) with an expanding scope of analysis has led to the identification of more addressable targets. For instance, we retrospectively identified the not-yet-characterized ERBB2 mutation V697L, which has been described as a gain-of-function mutation with significant clinical impact. However, in our observation, the number of targeted oncogenes did not show a significant correlation with Progression-Free Survival 2 (PFS2) or the PFS ratio.

An important issue is the transferability of results to other cancer types. For example, we observed responses to PARP inhibitors in breast and prostate cancers with deleterious BRCA1 mutations. Similarly, BRAF V600E in melanoma responded well to Vemurafenib as a monotherapy, whereas in CRC, the addition of an EGFR antibody and MEK-inhibitor to Vemurafenib was necessary for efficacy[1].

In principle, tumor progression is driven by complex interactions of genomic, transcriptomic, and proteomic alterations, along with microenvironmental factors and immune system dysfunction, leading to interpatient heterogeneity. Gene alterations do not always correlate with gene expression. In this particular clinical scenario, we administered treatment to a breast cancer patient harboring a PIK3CA E545K mutation, with the expectation of benefiting from mTOR/PIK3CA inhibition. Unfortunately, our analysis revealed that the patient did not manifest an upregulation of mTOR-associated genes at the RNA level. This observation provides a potential explanation for the lack of therapeutic efficacy in this case

Co-alterations play a critical role in determining the choice of targeted therapy. For example, a patient with breast cancer harboring an STK11 Y131* loss-of-function and TP53 R290fs mutation may exhibit PIK3CA-mTOR activation, also predicting a response to antiangiogenic therapy in addition[2,3,4]. This is mediated by mRNA pathways increasing the signaling of VEGFA and HIFalpha. Amplification of FGFR1 and FGFR2 may hyperactivate PIK3CA-mTOR, leading to resistance to PIK3CA inhibitors and endocrine treatments while retaining efficacy to mTOR inhibition[5]. The combination of Everolimus, Bevacizumab, and Capecitabine was successful.

Addressing the challenge of inter- and intratumoral heterogeneity, as well as resistance factors, requires innovative approaches like Antibody-Drug-Conjugates. In one case, a young patient with breast cancer, histologically confirmed to have different subpopulations with varying ERBB2 status, received Trastuzumab-Deruxtecan in the 9th line, resulting in a partial response over 8 months.

Targeted therapy emerged in our real world observation as the most effective treatment modality. We bypassed matching scores as described in highly cited publications, because using multiple targeted therapies within public healthcare system face pharmacoeconomical restrictions. Therefore we extracted maximum information from CTP focusing on cost-effective patient therapies. In our study we reached a median PFS2 (50 weeks) applying only targeted therapy and a ratio (1,9) comparable or even better than other clinical trials.

CONCLUSION |

These encouraging results based on a relatively small patient population under real world conditions can only point the direction of precision oncology. This approach has led to successes across entities (RESILIENT/I-PREDICT/ trial) [6,7]. Integration of modern techniques for diagnostics, prognostics, therapy recommendations based on interdisciplinary expertise as well as documentation must be continuously developed and integrated into the real world.

Our goal has to be not to apply multiple expensive therapies, but tailored treatments acknowledging pharmacoeconomics as well as high clinical efficacy.

References |

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