BIOBANK RESEARCH PROJECT OF THE INFINITY REGISTRY

GENETIC ALTERATIONS WITH POTENTIAL IMPACT ON PD-(L)1 TARGETED TREATMENT IN VARIOUS CANCER ENTITIES

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BACKGROUND

The multicenter precision medicine registry INFINITY investigates biomarker-driven treatment and management of patients with advanced malignancies not eligible for standard therapy options within routine clinical care in Germany. Besides collecting data on patient and disease characteristics as well as clinical outcome, INFINITY also sets up a decentral tissue sample biobank **(Fig. 1)**. The biobank provides the opportunity to perform central pathological analyses using validated test methods and to correlate the results with the clinical database.

PD-(L)1 antibodies are frequently used in different tumor types and several biomarkers have been proposed to identify patients most likely to benefit. However, there is still a great need to further understand mechanisms of resistance to these immunotherapies.

This research project was designed to analyze the genomic tumor profile of patients with clinical benefit from PD-(L)1 antibody treatment compared to those without.

METHODS

Patients who received PD-(L)1 antibodies (monotherapy) were identified from the INFINITY clinical database and the virtual biobank and were assigned to two cohorts for which a case-control design (clinical benefit versus no clinical benefit) based on predefined criteria was used: clinical benefit was defined as treatment duration >182 days and no clinical benefit was defined as treatment duration 22-63 days. Samples were requested from local pathologies and shipped to the central pathological institute (Institute of Pathology and Medical Genetics, University Hospital Basel) **(Fig. 2)**. Next generation sequencing (NGS) was performed at the central pathological institute using the OncomineTM Comprehensive Assay Plus panel, Ion 550TM Chips and Ion 550TM Chef Reagents (Thermo Fisher). Data preparation and annotation of the sequencing results was performed by Molecular Health GmbH using the MH VCF Adapter Suite software version 2.1.0 and MH Guide software version 5.3.0, respectively. R statistics version 4.0.5 was used for data analysis.

RESULTS

Sample selection was performed in 07/2021. Samples of 384 patients were assessed for eligibility resulting in 50 samples from 26 patients with clinical benefit and 24 patients without clinical benefit **(Fig. 3)**. Those 50 samples were located at 31 local pathologies. Upon shipment request, 25 samples were sent to the central pathology. Following sample preparation, quality checks and NGS, NGS data from 19 samples were available for interpretation in the full analysis set (FAS).

Patient characteristics are shown in **Table 1.** Patients with clinical benefit (N=11) were older (median 69.1 vs. 57.1 years), had a longer time from initial diagnosis to treatment start with PD-(L)1 antibody (median 39.9 vs. 32.5 months), and less prior therapy lines, compared to patients without clinical benefit (N=8). Best overall response to PD-(L)1 antibody therapy is shown in **Table 2**. Patients who benefit from PD-(L)1 blockade most often achieved SD (45.5%) or PR (27.3%), while best overall response for patients without clinical benefit was mainly PD (62.5%).

Fig. 4 shows interpreted NGS data depicted as oncoplot, sorted by clinical benefit status. There were no clear differences in both groups regarding tumor mutational burden (TMB), microsatellite status or any other molecular alteration. Interestingly, three genes were identified with alterations occurring in at least 5 patients and exclusively in the sub-group of patients with clinical benefit from PD-(L)1 antibody therapy: KEAP1, PIK3CA and MRE11.

DISCUSSION

With this research project we successfully collected tumor samples from local pathologies for central data analysis. 50% of requested samples were provided, 38% were ultimately included in the final analysis.

Although sample numbers were too small to detect clinically meaningful differences of the tumor profiles of patients who benefited from PD-(L)1 antibody therapy or not, three abundant genetic alterations were identified that occurred exclusively in the sub-group of patients with clinical benefit from PD-(L)1 antibody therapy and, thus, might be genetic alterations of interest for further studies.

In general, the results clearly show that such multidisciplinary projects combining comprehensive clinical and genomic real-world data are feasible. The INFINITY registry provides a real-world dataset to address data gaps and generate new hypotheses on clinical questions that are otherwise difficult to investigate in prospective studies.

Table 1: Patient characteristics at time of start of PD-(L)1 antibody therapy.

Characteristics	Patients with clinical benefit (N = 11)	Patients without clinical benefit (N = 8)
Sex		
Female	5 (45.5%)	3 (37.5%)
Male	6 (54.5%)	5 (62.5%)
Age at start of PD-(L)1 antibody therapy		
Median, years (min–max)	69.1 (55.3-82.7)	57.1 (31.3-83.3)
<70	6 (54.5%)	7 (87.5%)
≥70	5 (45.5%)	1 (12.5%)
ECOG Performance Status		
0-1	10 (90.9%)	5 (62.5%)
2	1 (9.1%)	2 (25.0%)
3-4	0	1 (12.5%)
Missing	0	0
Time since initial diagnosis to start of PD-(L)1 antibody therapy		
Median, months (min–max)	39.9 (8.5-72.8)	32.5 (9.5-94.9)
Number of prior palliative therapy lines		
0	1 (9.1%)	1 (12.5%)
1	6 (54.5%)	1 (12.5%)
2	2 (18.2%)	1 (12.5%)
3	2 (18.2%)	3 (37.5%)
4	0	0
≥5	0	2 (25.0%)
Tumor entity		
Biliary cancer	0	1 (12.5%)
Cervix carcinoma	1 (9.1%)	0
Colorectal cancer	1 (9.1%)	2 (25.0%)
CUP	1 (9.1%)	1 (12.5%)
Esophageal cancer	0	2 (25.0%)
Gastric cancer (incl. junction tumors)	0	1 (12.5%)
Head and neck cancer	1 (9.1%)	0
Penile cancer	2 (18.2%)	0
(Pleura)Mesothelioma	1 (9.1%)	0
Soft tissue sarcoma	1 (9.1%)	0
Uterine/Endometrial cancer	3 (27.2%)	0
Vulva carcinoma	0	1 (12.5%)

Figure 1: Decentral biobank of the INFINITY precision medicine registry.

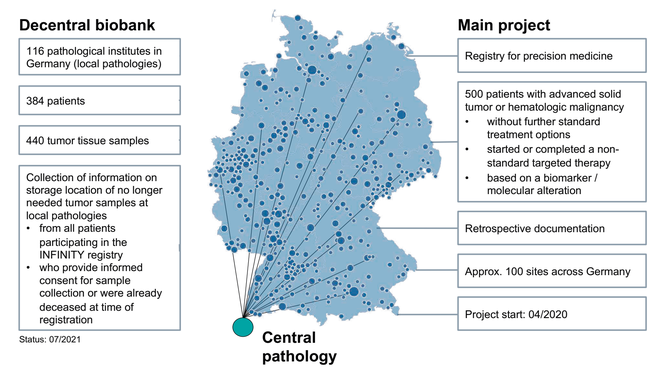


Figure 2: Logistics and distribution of tasks of the multidisciplinary research project.

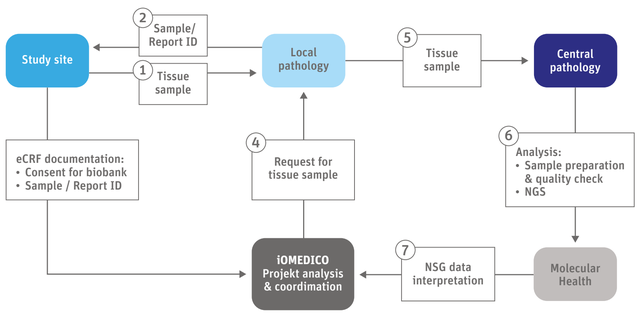


Figure 3: CONSORT diagram.

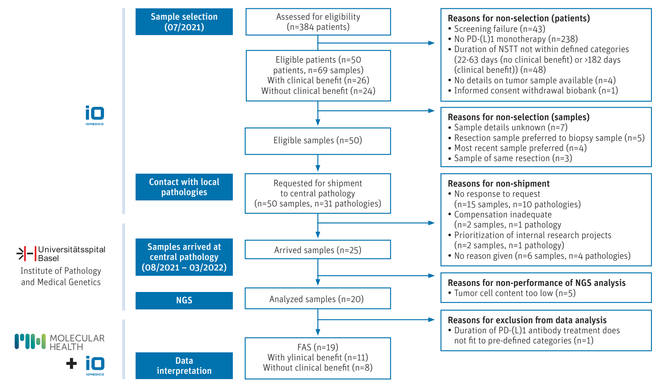
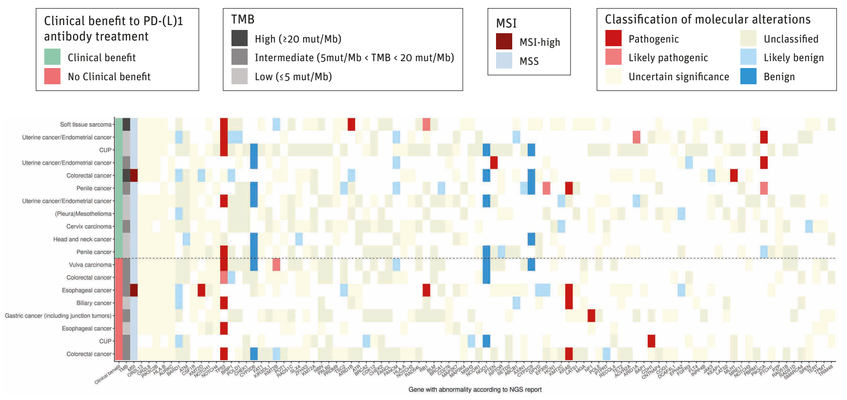


Table 2: Best overall response to PD-(L)1 antibody therapy.

	Patients with clinical benefit (N = 11)	Patients without clinical benefit (N = 8)
Best overall response in first NSTT		
Complete response (CR)	1 (9.1%)	0
Partial response (PR)	3 (27.2%)	0
Stable disease (SD)	5 (45.5%)	0
Progressive disease (PD)	2 (18.2%)	5 (62.5%)
Not evaluable	0	1 (12.5%)
Missing	0	2 (25.0%)

Figure 4: Oncoplot.



Abbreviations:
CR: Complete response; CUP: Cancer of unknown primary; ECOG: European Cooperative Oncology group; FAS: Full analysis set; Max: Maximum; Min: Minimum; MSI: Microsatellite instable; MSS: Microsatellite stable; N: Number; NGS: Next generation sequencing; NSTT: Non-standard targeted therapy; PD: Progressive disease; PD-(L)1: Programmed cell death-(ligand) 1; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TMB: Tumor mutational burden

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Conflicts of interest:
The registry INFINITY is supported by Roche Pharma AG and Bristol-Myers Squibb GmbH & Co.KGaA.

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