GENETIC TUMOR PROFILE OF PATIENTS WITH OR WITHOUT CLINICAL BENEFIT FROM PD-(L)1 ANTIBODY TREATMENT IN VARIOUS CANCER ENTITIES

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 de-identifiable tissue sample biobank comprising information on storage location of no longer needed tumor samples from all patients who participate in INFINITY and provide informed consent for sample collection or who were already deceased at time of registration. The biobank provides the opportunity to perform central pathological analyses using validated test methods and to correlate the results with the clinical database (Fig. 1).

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 a 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 pathologic institute (Institute of Pathology and Medical Genetics, University Hospital Basel). Next generation sequencing (NGS) was performed at the central pathologic institute using the Oncomet Comprehensive Assay Plus panel, Ion S5TM Chips and Ion S5TM Chef Reagents (Thermo Fisher). Data preparation and annotation of the sequencing results was performed by Molecular Health GmbH using the MH VIF Adapter Suite software version 2.10 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. 2). 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 39 samples were available for interpretation in the full analysis set (FAS).

Patient characteristics are shown in Table 1. Patients with clinical benefit (n=26) 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. 39.5 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 with benefit from PD-L1 blockade most often achieved SD (45.5%) or PR (27.3%), while overall response for patients without clinical benefit was mainly PD (62.5%).

Fig. 3 shows interpreted NGS data depicted as Oncplot, 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 MRE21.