Real-world data of off-label drug use in patients with actionable genomic alterations on next-generation sequencing

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Summary
Introduction We analyzed the outcomes of patients with advanced cancers in our institution treated with off-label drugs targeting actionable genomic alteration based on next-generation sequencing who did not qualify for clinical trials. Purposes Our study endpoint was objective tumor response or stable disease at 16 weeks or later after treatment initiation. Methods Sixteen patients were included, 8 treated with immune checkpoint inhibitors targeting PD-L1 expression or TP53 mutations and 8 with other drugs. Tumors were analyzed based on PD-L1 expression, TP53 mutation, MSI, TMB, MMR status, and other targetable alterations. Results Of the 16 patients in the intention-to-treat group, no patients had an objective response after 16 weeks. Eleven patients met the primary study endpoint with stable disease, 8 in the immune checkpoint inhibitors group and 3 in the non-immune checkpoint inhibitors group. Using the log-rank test, the p-value for the difference between groups was 0.008. Conclusions In this study with off-label drugs, immune checkpoint inhibitors targeting TP53 mutations or PD-L1 expression were superior to the other drugs. This suggests the possibility of off-label use of anti-cancer drugs based on next-generation sequencing to be beneficial for advanced cancer patients without other therapeutic options.

Keywords Off-label drug use · Next-generation sequencing · TP53 · PD-L1 · Immune checkpoint inhibitors · Cancer drugs

Introduction

When standard treatment for advanced malignancies fails, and clinical trial enrollment is not an option, many oncologists consider drugs that target actionable genomic alterations. This study addressed the cases in our institution in which drugs were used in situations not currently approved by the United States Federal Drug Administration (FDA), also known as off-label use. Information is scarce in the literature, and it is unclear if this practice is beneficial to patients.

The American Society of Clinical Oncology’s (ASCO’s) Targeted Agent and Profile Utilization Registry (TAPUR) study is a prospective non-randomized clinical trial that is being conducted involving the off-label use of 19 drugs [1]. Our study, in comparison, is retrospective and observational, addressing a variety of off-label drugs used in our institution when clinical trials were not available. We used similar study endpoints and definitions.

Pembrolizumab, a humanized monoclonal immunoglobulin G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities, was the most often drug used off-label. It is approved by the FDA for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden–high (TMB-H) [≥ 10 mutations/megabase (mut/MB)] solid tumors and Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (MMRd) cancers that have progressed following prior treatment and who have no satisfactory alternative treatment options. It is also approved for many other malignancies when specific criteria for PD-L1 companion diagnostics by immunohistochemistry are met.

Our objective was to analyze the outcomes of patients treated with off-label drugs for various solid tumors based on Next-Generation Sequencing (NGS) at our institution.
Methods

We searched our databases from Jan 1, 2020, to Jun 30, 2021, for patients with advanced cancers who underwent comprehensive genomic profiling. Patients enrolled in clinical trials during the entire period or that had no treatment change after NGS within the period of screening were automatically excluded. Inclusion criteria were patients no longer responding to standard anti-cancer treatment or for whom no acceptable standard treatment or clinical trial was available and that elected to receive targeted treatment with off-label drugs for actionable genomic alterations. We also asked oncologists in our cancer center if they had patients that met these parameters. The data was analyzed on Nov 29, 2021, after all patients completed 16 weeks since starting treatment.

Caris-Molecular Intelligence (Irving, TX, USA) and Guardant360 (Redwood City, CA, USA) were the platforms used for NGS analysis. Considering that pembrolizumab was the most common drug used, we investigated if it would consistently reach our study endpoint in tumors with PD-L1 expression or TP53 mutations when TMB was less than 10 mut/MB, MSI-H was not detected or Microsatellite Stable (MSS), and MMRp. Objective tumor response or stable disease at 16 weeks (112 days) or later (SD16+) after treatment initiation were the primary study endpoints based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Radiologic assessment of response to therapy was performed with every imaging study obtained during treatment. We also assessed patients for treatment-related high grade and serious adverse events (SAE), progression-free survival (PFS), and overall survival (OS) within our timeline. PFS was defined as the time from the first treatment dose to radiographic or clinical progression or death from any cause. OS was defined as the time from the first dose of treatment to death from any cause. High grade and serious adverse events were considered when related to the drug and grade 3 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Progression-free survival and overall survival were evaluated using the Kaplan–Meier method. All analyses and plots were done utilizing IBM SPSS version 26, and a p-value < 0.05 was considered significant.

Results

Off-label drug use based on NGS was rare in our institution when applying our strict criteria. A total of 130 profiled patients were manually screened for eligibility and 16 patients were included in the study (12.3%). The remainder of patients (87.7%) received standard of care therapy, were enrolled in clinical trials, or died before treatment initiation. The median age was 64 years (range 20–84 years), 68.75% were males, and 31.25% were females. 18.75% of patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2, 68.75% of 1, and 12.5% of 0. Most patients had stage IV cancer, 12 of 14 (85.71%), 2 had cancers that did not have a staging system established but were considered advanced by the oncologist. Most patients were pre-treated with at least 2 prior systemic therapies, 12 of 16 (75%). All tumors were MMRp and MSS or MSI-H was not detected. TMB was less than 10 (low) in 14 of 16 (87.5%) patients. TP53 mutations were found in 62.5% of tumors and PD-L1 expression in 43.75%. Detailed demographic and clinical characteristics are listed in Table 1.

Pembrolizumab was the most common drug used, 7 of 16 (43.75%) cases. Other targeted therapies included: nivolumab, alpelisib, ado-trastuzumab emtansine, trastuzumab plus pertuzumab, everolimus, trametinib, olaparib.

| Table 1 Baseline patient characteristics |
| --- |
| **Age at diagnosis, median (range), y** | 64 years (20–84) |
| **Total patients** | |
| Male | 11 (68.75%) |
| Female | 5 (31.25%) |
| **Race** | |
| White | 13 (81.25%) |
| Black | 3 (18.75%) |
| **Ethnicity** | |
| Hispanic or Latino | 10 (62.5%) |
| Non-Hispanic or non-Latino | 6 (37.5%) |
| **ECOG Performance Status** | |
| 0 | 2 (12.5%) |
| 1 | 11 (68.75%) |
| 2 | 3 (18.75%) |
| **Number of prior systemic therapies** | |
| 0 | 2 (12.5%) |
| 1 | 2 (12.5%) |
| 2 | 5 (31.25%) |
| ≥ 3 | 7 (43.7%) |
| **High grade and serious adverse events** | 1 (6.25%) |
| **PD-L1 expression** | 7 (43.75%) |
| **TP53 mutation** | 10 (62.5%) |
| **PD-L1 + TP53** | 4 (25%) |
| **MSI-H not detected/ MSS** | 16 (100%) |
| **MMRp** | 16 (100%) |
| **TMB** | |
| Low (0–10 mut/MB) | 14 (87.5%) |
| High (≥ 10 mut/MB) | 2 (12.5%) |
| Age | ECOG | Cancer | Stage | Off-label therapy | Mechanism of action | Target | MSI-H | MMRd | TMB (mut/mb) | TPS3 mutation | PD-L1 expression | PFS, days | OS, days | Response in 16 weeks | Previous therapies |
|-----|------|--------|-------|-------------------|-------------------|-------|------|------|-------------|---------------|-----------------|----------|----------|---------------------|------------------|
| 71  | 1    | Anaplastic carcinoma of the thyroid | IV    | Pembrolizumab     | PD-1 pathway blocker | TP53 mutation | no    | no    | low          | TP53 R248Q     | no              | 375+     | 375+    | SD                  | 2                |
| 46  | 0    | Thymic carcinoma               | IV    | Pembrolizumab     | PD-1 pathway blocker | PD-L1 expression | no    | no    | 5            | no             | 70%             | 136+     | 136+    | SD                  | 3                |
| 65  | 1    | Follicular Thyroid Carcinoma  | IV    | Pembrolizumab     | PD-1 pathway blocker | TP53 mutation and PD-L1 expression | no    | no    | 1            | TP53 E271V/ K132N | 80%            | 480+     | 480+    | SD                  | 2                |
| 67  | 1    | Parotid gland carcinoma       | IV    | Alpelisib         | PI3K inhibitor      | PIK3CA H1074R (12.3%) | no    | no    | 20           | no             | 53              | 220+     | PD      | 4                   |                  |
| 53  | 2    | Adenocarcinoma of the lung   | IV    | Ato-ristuzumab emtansine | HER2 suppression | HER-2 | no    | no    | 1            | no             | no              | 63       | 256     | PD                  | 3                |
| 44  | 0    | Adrenal Cortical Carcinoma   | IV    | Trametinib       | MEK inhibitor       | NF-1 exon 21 p.L828 | no    | no    | 3            | TP53 Exon 6 p.N210I | no              | 219      | 307+    | SD                  | 0                |
| 84  | 1    | Papillary Thyroid Carcinoma  | IV    | Pembrolizumab     | PD-1 pathway blocker | TP53 mutation | no    | no    | 1.94         | no             | 265+           | 265+     | 265+    | SD                  | 1                |
| 57  | 1    | Squamous Cell Carcinoma of the Lung | III   | Everolimus     | mTOR inhibitor | NFE2L2 p.D27Y | no    | no    | 7            | TP53 p.1253del   | no              | 151      | 353+    | SD                  | 4                |
| 77  | 2    | Squamous Cell Carcinoma of unknown primary site | III   | Pembrolizumab     | PD-1 pathway blocker | TP53 mutation and PD-L1 expression | no    | no    | 4            | TP53 R282G, C238Y | CPS:30          | 224      | 361+    | SD                  | 0                |
| 20  | 1    | Parotid Adenocarcinoma       | III   | Olaparib         | PARP1/2 inhibitor | ARID1A A165fs | no    | no    | low          | no             | no              | 96       | 267     | PD                  | 3                |
| 79  | 1    | Adenocarcinoma of the lung   | IV    | Everolimus       | mTOR inhibitor     | STK11 E199 | no    | no    | 7 mut/mb    | no             | no              | 84       | 233     | PD                  | 4                |
| 76  | 1    | Anaplastic carcinoma of the thyroid | IV    | Pembrolizumab     | PD-1 pathway blocker | TP53 mutation and PD-L1 expression | no    | no    | 8 mut/mb    | TP53 A138_ Q144del | 5%             | 133      | 256+    | SD                  | 2                |
talazoparib. Detailed drug use and indications are listed in Table 2.

Of the 16 patients in the intention-to-treat group, no patients had an objective response. Eleven (69.75%) patients met the primary study endpoint of PFS of at least 16 weeks or 112 days. All 8 patients who received off-label immune checkpoint inhibitors (ICI) to target PD-L1 or TP53 mutations had SD16++. The other drugs that met the primary endpoint were trastuzumab plus pertuzumab, everolimus, and trametinib. In the non-immune checkpoint inhibitors (non-ICI) group, only 3 of 8 (37.5%) met the study’s primary endpoints. There was a significant difference between ICI and non-ICI-treated patients ($p = 0.008$, Fig. 1). A single grade 3 adverse event of diarrhea was reported due to the use of alpelisib, leading to treatment discontinuation. In a per-protocol analysis excluding alpelisib, the difference was also significant ($p = 0.014$, Fig. 2).

**Discussion**

A study at MD Anderson at Cooper showed that out of 305 consecutive NGS assays, only 6 patients started off-label therapies (2%) based on the assay result, and they had a poor prognosis [2]. However, in our study the off-label use of ICIs, when targeting PD-L1 expression or TP53 mutations, consistently met our primary endpoint of stable disease at 16 weeks or later. This finding is consistent with previous studies that demonstrated that PD-L1 and TP53 mutations predict response to ICIs [3–9].

A phase 1, non-randomized clinical trial involving 475 patients with 20 types of cancers demonstrated that patients with advanced solid tumors expressing PD-L1 had a higher response rate to pembrolizumab independently of TMB [3]. In addition, a phase 3 randomized, open-label clinical trial with 305 patients with locally advanced or metastatic non-small lung cancer showed that pembrolizumab monotherapy was superior to chemotherapy in adult patients with a PD-L1 TPS of 50% or greater [4], and another clinical trial with 1274 participants concluded superiority with a PD-L1 TPS of 1% or more [5]. These and other studies led to the FDA approval of pembrolizumab for non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma, gastric cancer, esophageal cancer, cervical cancer, and triple-negative breast cancer with specific PD-L1 expression thresholds. A study with 72 patients with advanced NSCLC patients treated with programmed death-1 blockers showed higher overall survival in the TP53 mutated group than in the non-mutated group [6]. Other studies with TP53 mutated tumors showed mixed results to immune checkpoint inhibitors and likely different responses of the various TP53 mutations [7–9].

To characterize off-label use of pembrolizumab we excluded tumors with MSI-H, MMRd, or TMB $\geq 10$ mut/
MB. The most compelling data for the FDA-approved pembrolizumab use in these cases were established in KEYNOTE-158. This phase 2 clinical trial enrolled 1595 patients [10] with 27 different tumor types. Patients received pembrolizumab 200 mg IV every three weeks for 35 cycles (approximately 2 years) or until documented disease progression, unacceptable toxicity, intercurrent illness preventing treatment administration, or patient/investigator decision. Two hundred twenty-three patients with MSI-H/MMRd were evaluated with a median follow-up of 13.4 months. The objective response rate (ORR) in this group was 34.3% and 86.9% had a response duration of 12 months or longer. Complete response was achieved in 9.9% of patients and partial response in 24.5% [11]. Eight hundred five patients were evaluable for TMB, 13% had a TMB $\geq 10$ mut/MB and 87% a TMB $< 10$ mut/MB. The ORR was 29% for TMB-high tumors versus 6% for TMB-low with a median follow-up of 31.7 months [12].

To our knowledge, no studies have simultaneously analyzed PD-L1 expression, TP53 mutation, MSI, TMB, and MMR status across various tumors with real-world data of off-label use of ICIs versus non-ICIs. We also addressed tumors not commonly present in these analyses: papillary thyroid carcinoma, follicular thyroid carcinoma, anaplastic thyroid carcinoma, extramammary Paget’s disease of the scrotum, and squamous cell carcinoma of an unknown primary site. Despite the small sample size, the difference between groups was significant suggesting that ICIs may be beneficial in patients with PD-L1 expression or TP53 mutation in the setting of MSS or MSI-H not detected, TMB $< 10$ mut/MB, and MMRp tumors. This suggests the possibility that off-label use of certain cancer drugs based on NGS may be beneficial for patients without other options of treatment.

This study has limitations. Our sample size was small since we were not conducting a clinical trial but analyzing cases retrospectively of real-world off-label drug use in a single academic institution. Typically, patients who underwent NGS with advanced cancers for whom no acceptable standard treatment was thought to be available, and clinical trial enrollment was not considered an option by the provider, were referred to one of our oncologists, a specialist in precision oncology, indicating that oncologists, in general, are not comfortable prescribing off-label therapies. Treatment was delayed or not feasible for some patients due to challenges with health insurance approval of off-label therapies. Furthermore, our institution is a
Fig. 2 Kaplan–Meier curve showing the percentage of patients who met SD16+ in the off-label immune checkpoint inhibitors group and in the off-label non-immune checkpoint inhibitors group in a per-protocol analysis. Using the log-rank test, the p-value for the difference between groups was 0.014.

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Data availability We conducted an observational retrospective study. The datasets generated and analyzed were gathered from the EPIC database of the Mays Cancer Center, University of Texas Health MD Anderson Cancer Center and are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Ethics approval The institutional review board of the University of Texas Health San Antonio approved this study.

Informed consent For this type of study, formal consent is not required.
Consent to participate Not applicable.

Consent for publication Not applicable.

Research involving human participants and/or animals This research involves human participants. This study was performed in line with the principles of the Declaration of Helsinki. The institutional review board of the University of Texas Health San Antonio approved this study.

Conflict of interests The authors declare no conflict of interest.

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