Real-World Data of Off-Label Drug Use in Patients with Actionable Genomic Alterations on Next-Generation Sequencing

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Research Article

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Abstract

We analyzed the outcomes of patients in our institution treated with off-label drugs targeting actionable genomic alteration based on next-generation sequencing when clinical trials were not available. Our study endpoint was objective tumor response or stable disease at 16 weeks or later after treatment initiation. Sixteen patients were included in this study, 8 were treated with immune checkpoint inhibitors targeting PD-L1 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. 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. 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.

1. 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 Microsatellite Stable (MSS), and 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 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) in our institution.

2. Methods

We searched our databases from Jan 1, 2020, to Jun 30, 2021, for patients who underwent comprehensive genomic profiling. Inclusion criteria were patients no longer responding to standard anti-cancer treatment or for whom no acceptable standard treatment 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, when 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 Next Generation Sequencing (NGS) analysis. Since 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 inferior to 10 mut/Mb, MSI-H was not detected or MSS, and MMR was proficient. 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. 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.

3. Results

Off-label drug use based on NGS was rare in our institution when applying our strict criteria. Typically, patients who underwent NGS with advanced cancers for whom no acceptable standard treatment was available, and clinical trial enrollment was not an option, were referred to one of our oncologists, a specialist in precision oncology. Sixteen patients were included in the study. 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 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 drugs, 12 of 16 (75%). All tumors were MMR proficient and MSI-H was not detected or MSS. 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 37.5%. Detailed demographic and clinical characteristics are listed in Table 1.

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 patients with 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*	3 (18.75%)
MSI-H not detected	16 (100%)
MMR proficient	16 (100%)
TMB	
Low (0-10 mut/mb)	14 (87.5%)
High (≥10 mut/mb)	2 (12.5%)

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, trematinib, olaparib, talazoparib. Detailed drug use and indications are listed in Table 2.

Table 2
– Off-Label drug use, disease profile, and survival. The "+" sign indicates that the patient continued on treatment (PFS) or was alive (OS) after 16

Age	ECOG PS	Cancer	Stage	Off-label therapy	Mechanism of action	Gene targeted	MSI-H	MMRd	TMB (mut/mb)	*TP53* mutation	PD-L1 expressio
71	1	Anaplastic carcinoma of the thyroid	IV	Pembrolizumab	PD-1 pathway blocker	*TP53* mutation	no	no	low	*TP53 R248Q*	no
46	0	Thymic carcinoma	IV	Pembrolizumab	PD-1 pathway blocker	PD-L1 expression	no	no	5	no	70%
65	1	Follicular Thyroid Carcinoma	IV	Pembrolizumab	PD-1 pathway blocker	*TP53* mutation and PD-L1 expression	no	no	1	*TP53 E271V/K132N*	80%
67	1	Parotid gland carcinoma	IV	Alpelisib	PI3K inhibitor	*PIK3CA H1074R* (12.3%)	no	no	20	*TP53 E271V/K132N, K139N, R175H*	no
53	2	Adenocarcinoma of the lung	IV	Ado-trastuzumab emtansine	*HER2* suppression	HER-2	no	no	1	no	no
44	0	Adrenal Cortical Carcinoma	IV	Trametinib	MEK inhibitor	*NF-1* Exon 21 *p.L828*	no	no	3	*TP53* Exon 6 *p.N210fs*	no
84	1	Papillary Thyroid Carcinoma	IV	Pembrolizumab	PD-1 pathway blocker	*TP53* mutation	no	no	1.94	*TP53 G244C/G245I, N131I, M237V*	no
57	1	Squamous Cell Carcinoma of the Lung	III	Everolimus	mTOR inhibitor	*NFE2L2 p.D27Y*	no	no	7	*TP53 p.I255del*	no
77	2	Squamous Cell Carcinoma of unknown primary site		Pembrolizumab	PD-1 pathway blocker	*TP53* mutation and PD-L1 expression	no	no	4	*TP53 R282G, C238Y*	CPS:30
20	1	Parotid Adenocarcinoma	III	Olaparib	PARP1/2 inhibitor	*ARID1A A165fs*	no	no	low	no	no
79	1	Adenocarcinoma of the lung	IV	Everolimus	mTOR inhibitor	*STK11 E199*	no	no	7 mut/mb	no	no
76	1	Anaplastic carcinoma of the thyroid	IV	Pembrolizumab	PD-1 pathway blocker	*TP53* mutationand PD-L1 expression	no	no	8 mut/mb	*TP53 A138_Q144del*	5%
64	1	Squamous cell carcinoma of the tonsil	IV	Talazoparib	PARP1/2 inhibitor	*CHEK2 E239*	no	no	4 mut/mb	*TP53 S127F/R273H*	CPS:20
79	1	Extramammary Paget's disease of the penis and scrotum		Pembrolizumab	PD-1 pathway blocker	PD-L1 expression	no	no	7 mut/mb	no	CPS:20
42	1	Rectal cancer	IV	Trastuzumab plus Pertuzumab	*HER2* suppression	*ERBB2* high(+++)	no	no	13.4 mut/mb	*TP53 Y205D/R213fs*	no
62	2	Gallbladder adenocarcinoma	IV	Nivolumab	PD-1 pathway blocker	PD-L1 expression	no	no	8 mut/mb	no	15%

Of the 16 patients in the intention-to-treat group, no patients had an objective response after 16 weeks. 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 ($p = 0.008$). A single grade 3 adverse event of diarrhea was reported due to the use of alpelisib. In a per-protocol analysis excluding alpelisib, the difference was also significant ($p = 0.014$).

4. 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.

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 NSCLC, HNSCC, gastric cancer, esophageal cancer, cervical cancer, and triple-negative breast cancer with different 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, 8, 9].

To characterize off-label use of pembrolizumab we excluded tumors with MSI-H/MSS, MMRd, or TMB ≥10 mut/mb. The most compelling data for its use in these cases was established in KEYNOTE-158. This phase 2 clinical trial enrolled 1595 patients [10] with 27 different tumor types with a median follow-up of 13.4 months. Patients received pembrolizumab 200 mg IV every three weeks. 233 patients were evaluable for MSI-H/MMRd. The objective response rate (ORR) was 34.3% and 86.9% had a response duration of 12 months or longer [11]. 805 patients were evaluable for TMB, 105 had a TMB ≥10 mut/mb. The ORR was 29% for TMB high patients versus 6% for TMB low [12].

To our knowledge, no studies have simultaneously analyzed PD-L1 expression, *TP53* mutation, MSI, TMB, and MMR status across various tumors with the use of off-label ICIs versus non-ICIs. We also addressed tumors not commonly present on these analyses: papillary, follicular, anaplastic thyroid carcinomas, 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 MMR proficient tumors not currently FDA approved. 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. Mutations that are not currently detected by NGS or not completely understood may have played a role in response to ICIs in the different types of cancer analyzed. For example, a recent study at the MD Anderson Cancer Center with data from over 10,000 tumors included in the Cancer Genome Atlas showed that TMB does not predict response to ICIs equally in different types of cancers [13]. This means that current evidence is insufficient to validate the threshold of 10 mut/Mb and the optimal limit might be higher or lower for different tumor types. Besides, the threshold for PD-L1 expression likely varies among tumors and different *TP53* mutations determine a different response to ICIs. Further studies are needed to validate the use of off-label drugs based on NGS, ICIs in tumors with PD-L1 expression or *TP53* mutations, and their interrelationship with other predictors of tumor response.

Declarations

Ethics declarations

Ethics approval

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.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability

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

Code availability

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Authors` contributions

Gabriel Roman Souza and Daruka Mahadevan contributed to the study conception and design. Material preparation and analysis were performed by Gabriel Roman Souza. Data collection was performed by all authors. The first draft of the manuscript was written by Gabriel Roman Souza and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgment

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Compliance with ethical standards

Disclosure of potential conflicts of interest

The authors declare no conflict of interest.

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.

Informed consent

For this type of study, formal consent is not required.

References

1. Mangat PK, Halabi S, Bruinooge SS, Garrett-Mayer E, Alva A, Janeway KA, Stella PJ, Voest E, Yost KJ, Perlmutter J, Pinto N, Kim ES, Schilsky RL (2018) Rationale and Design of the Targeted Agent and Profiling Utilization Registry (TAPUR) Study. JCO Precis Oncol 2018. 10.1200/PO.18.00122
2. Davis W, Makar G, Mehta P, Zhu GG, Somer R, Morrison J, Kubicek GJ Next-Generation Sequencing in 305 Consecutive Patients: Clinical Outcomes and Management Changes.J Oncol Pract. 2019Dec; 15(12):e1028-e1034. doi: 10.1200/JOP.19.00269
3. Ott PA, Bang YJ, Piha-Paul SA, Razak ARA, Bennouna J, Soria JC, Rugo HS, Cohen RB, O'Neil BH, Mehnert JM, Lopez J, Doi T, van Brummelen EMJ, Cristescu R, Yang P, Emancipator K, Stein K, Ayers M, Joe AK, Lunceford JK (2019) T-Cell-Inflamed Gene-Expression Profile, Programmed Death Ligand 1 Expression, and Tumor Mutational Burden Predict Efficacy in Patients Treated With Pembrolizumab Across 20 Cancers: KEYNOTE-028. J Clin Oncol. Feb 1;37(4):318-327. doi: 10.1200/JCO.2018.78.2276
4. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR (2016 Nov) KEYNOTE-024 Investigators. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 10;375((19):1823–1833. doi: 10.1056/NEJMoa1606774
5. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G Jr, Srimuninnimit V, Laktionov KK, Bondarenko I, Kubota K, Lubiniecki GM, Zhang J, Kush D, Lopes G ; KEYNOTE-042 Investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial.Lancet. 2019 May4;393(10183):1819–1830. doi: 10.1016/S0140-6736(18)32409-7
6. Assoun S, Theou-Anton N, Nguenang M, Cazes A, Danel C, Abbar B, Pluvy J, Gounant V, Khalil A, Namour C, Brosseau S, Zalcman G (2019 Jun) Association of *TP53* mutations with response and longer survival under immune checkpoint inhibitors in advanced non-small-cell lung cancer. Lung Cancer 132:65–71. doi: 10.1016/j.lungcan.2019.04.005
7. Frost N, Kollmeier J, Vollbrecht C, Grah C, Matthes B, Pultermann D, von Laffert M, Lüders H, Olive E, Raspe M, Mairinger T, Ochsenreither S, Blum T, Hummel M, Suttorp N, Witzenrath M, Grohé C KRASG12C/ *TP53* co-mutations identify long-term responders to first line palliative treatment with pembrolizumab monotherapy in PD-L1 high (≥50%) lung adenocarcinoma.Transl Lung Cancer Res. 2021Feb; 10(2):737–752. doi: 10.21037/tlcr-20-958. PMID: 33718018; PMCID: PMC7947421.
8. Lyu Q, Lin A, Cao M, Xu A, Luo P, Zhang J Alterations in *TP53* Are a Potential Biomarker of Bladder Cancer Patients Who Benefit From Immune Checkpoint Inhibition.Cancer Control. 2020 Jan-Dec; 27(1):1073274820976665. doi: 10.1177/1073274820976665
9. Sun H, Liu SY, Zhou JY, Xu JT, Zhang HK, Yan HH, Huan JJ, Dai PP, Xu CR, Su J, Guan YF, Yi X, Yu RS, Zhong WZ, Wu YL (2020 Oct) Specific *TP53* subtype as biomarker for immune checkpoint inhibitors in lung adenocarcinoma. EBioMedicine. 60:102990.. doi: 10.1016/j.ebiom.2020.102990
10. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US) (2000) Feb 29 -. Identifier NCT02628067, Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158); 2015 Dec 9 [cited 2021 Dec 1]; [about 4 screens]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02628067
11. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopez-Martin J, Bang YJ, Frommer RS, Shah M, Ghori R, Joe AK, Pruitt SK, Diaz LA Jr (2020) Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. Jan 1;38(1):1-10. doi: 10.1200/JCO.19.02105
12. Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH Jr, Italiano A, Kao S, Piha-Paul SA, Delord JP, McWilliams RR, Fabrizio DA, Aurora-Garg D, Xu L, Jin F, Norwood K, Bang YJ (2020 Oct) Association of tumour mutational burden with

outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 21(10):1353–1365. doi: 10.1016/S1470-2045(20)30445-9

13. McGrail DJ, Pilié PG, Rashid NU, Voorwerk L, Slagter M, Kok M, Jonasch E, Khasraw M, Heimberger AB, Lim B, Ueno NT, Litton JK, Ferrarotto R, Chang JT, Moulder SL, Lin SY (2021 May) High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types. Ann Oncol 32(5):661–672. doi: 10.1016/j.annonc.2021.02.006

Figures

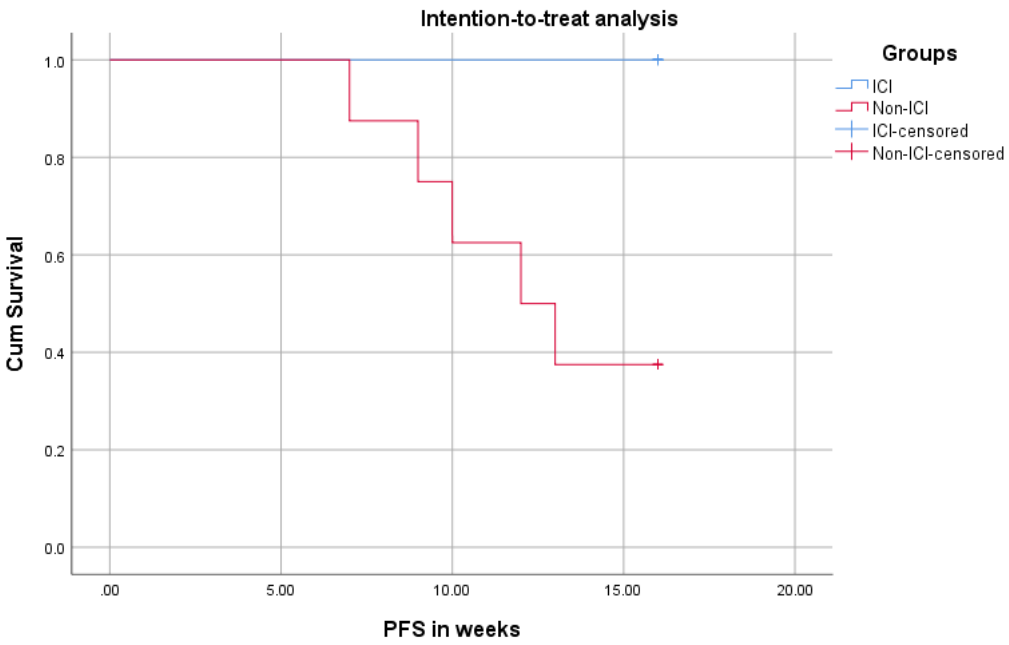

Figure 1

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 an intention-to-treat analysis. Using the log-rank test, the p-value for the difference between groups was 0.008.

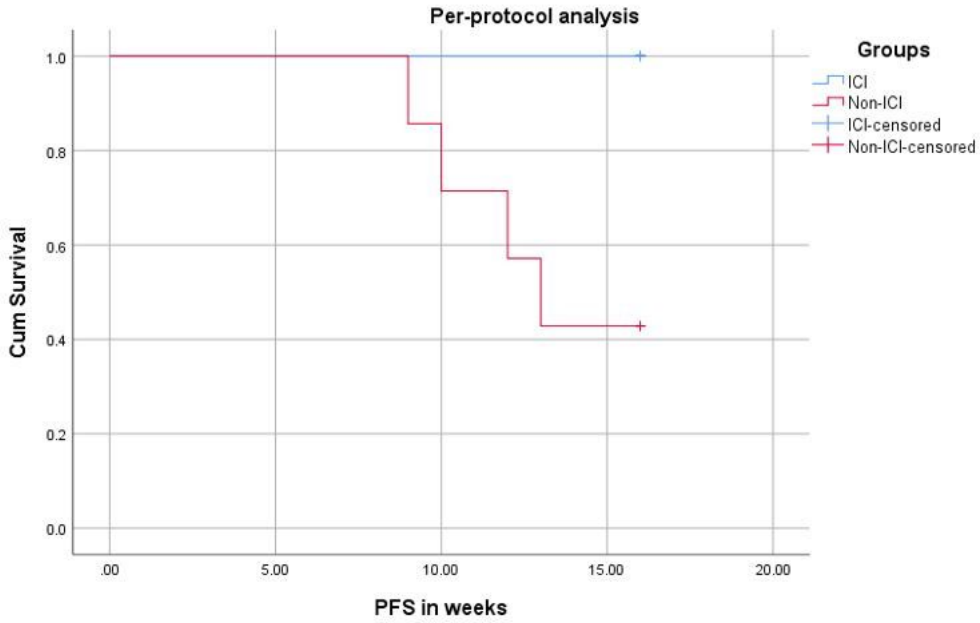

Figure 2

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.