Treatment Rechallenge With Checkpoint Inhibition in Patients With Mismatch Repair–Deficient Pancreatic Cancer After Planned Treatment Interruption

Vaia Florou, MD[1]; Christopher Nevala-Plagemann, MD[1]; Kristin E. Barber, FNP-BC, MSN, AOCNP[1]; Jenna N. Mastroianni, RN[1]; Courtney C. Cavalieri, Pharm D, BCOP[1]; and Ignacio Garrido-Laguna, MD, PhD[1]

INTRODUCTION

The exponential use of immunotherapy agents in metastatic malignancies with traditionally poor survival outcomes has generated new challenges for physicians. One of the major hurdles in clinical practice is to determine the minimum duration of therapy that will have clinical benefit for patients and will result in stable disease (SD) to sustain long-term responses. The decision regarding when to stop therapy is not easy, and most physicians discontinue therapy after 12 to 24 months, according to data from melanoma and lung cancer trials.[1,2] Clinical trials are actively being planned to help understand when it is safe to stop immunotherapy.[3] The optimal duration of therapy has not yet been defined, but there is another question: Do checkpoint inhibitors (CPIs) remain a viable treatment option upon disease progression after a planned treatment interruption? Evidence is accumulating on balancing the risks and benefits when CPIs are re-administered after immune-related adverse events (AEs) develop,[4,5] and on the lack of efficacy when rechallenging after disease progression with the same or a different CPI.[6-8] In contrast, there are limited data on the safety and efficacy of re-administering immunotherapy after planned treatment interruption.

The literature is scarce, but there seems to be efficacy when re-introducing immunotherapy after discontinuing it for reasons other than progressive disease (PD) or development of immune-related AEs (Table 1). Lipson et al[9] reported that a patient with melanoma was successfully rechallenged with immunotherapy after discontinuing intermittent dosing with CPIs in the first-in-human phase I study of the anti-programmed cell death protein 1 (anti-PD-1) antibody BMS-936558. That patient received intermittent therapy for approximately 15 months and achieved a partial response (PR), which was maintained during 16 months of therapy. When PD occurred, retreatment was pursued. The patient again achieved a PR, which was maintained for another 16 months during therapy.[9] Bernard-Tessier et al[10] have published the largest study on this subject to date; eight patients with solid tumors treated with CPIs after a median duration of therapy of 12 months in phase I trials were retreated with the same CPI. Among the eight patients, two (25%) achieved PR, and six (75%) achieved SD. One patient with triple-negative breast cancer and 1 with uveal melanoma achieved PRs after retreatment, but their disease eventually progressed.[10] Robert et al[11] reported the long-term follow-up of patients with melanoma from the KEYNOTE-001 (ClinicalTrials.gov identifier: NCT01295827) study, who had a complete response (CR) and either continued CPI therapy or discontinued therapy and underwent surveillance. In all, 67 of 91 patients eligible for rechallenge chose to discontinue therapy after a median treatment duration of 23 months and 7 months after CR; four of 67 patients had disease progression, and three were retreated with pembrolizumab. Two of these patients had disease progression after 4 and 9 months, and one was still receiving therapy after 15 months when that article was published.[11] More recently, Betof et al[12] reported the long-term outcomes of patients with melanoma treated with CPIs, and 78 patients who were retreated with CPIs were included. The median time between discontinuation of initial treatment and retreatment was 6.3 months; only 16 of 78 patients responded to retreatment with either single-agent anti-PD-1 therapy or with combination therapy with anti-CTLA4.

In 2017, the US Food and Drug Administration approved pembrolizumab for any solid tumor with mismatch repair deficiency (dMMR) after PD with previous treatments. This approval was based on cumulative data across five clinical trials with a total of 149 patients who showed high overall response rates to pembrolizumab.[13] Only 8 patients with pancreatic ductal adenocarcinoma (PDAC) were included in those initial clinical trials [14] and another 22 patients were described in the more recent KEYNOTE-158 (ClinicalTrials.gov identifier: NCT02628067) trial.[15] Despite advances in other solid malignancies,

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TABLE 1. Published Studies on Immunotherapy Rechallenge After a Planned Treatment Interruption

First Author	Initial CPI Duration (months)	Time-Free Treatment (months)	Best Response 1	PFS1 (months)	Best Response 2	Outcome	PFS2 (months)
Bernard-Tessier[10]							
Non–small-cell lung cancer	10.6	10	PR	19.9	SD	Ongoing	NA
Urothelial carcinoma	10.4	19.5	PR	28.5	PR	Ongoing	NA
Uveal melanoma	10.6	12.4	SD	21.3	SD	PD	5.1
Breast cancer	12	11.1	PR	22.9	SD	PD	6.6
Melanoma	10.4	39.7	PR	49	PR	PR	NA
Colorectal cancer	12	5.1	PR	15.8	SD	Off protocol	NA
Urothelial carcinoma	12	6.5	PR	15.8	SD	Ongoing	NA
Colorectal cancer	12	12.6	CR	17.8	SD	Ongoing	NA
Robert[11]							
Melanoma (3 patients)	23 (median)	NA	CR	15.1 (median)	NA	PD	4
						PD	9
						Ongoing	NA
Lipson[9]							
Melanoma	15	16	PR	31	PR	Ongoing	NA
This study							
Pancreatic cancer	17	10	PR	30	PR	Ongoing	> 10[a]
Pancreatic cancer	22	16	PR	38	PR	Ongoing	> 7[a]

Abbreviations: CPI checkpoint inhibitor, CR, complete response; NA, not available; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]Treatment is ongoing.

metastatic pancreatic cancer still has a dismal prognosis with a 5-year overall survival of less than 10%.[16] The prevalence of dMMR in pancreatic cancer is 0% to 1.3%.[17,18] Not surprisingly, CPIs alone have limited efficacy in PDAC.[19]

Here we report the experience at our center with two patients who had dMMR PDAC, treated with immunotherapy and then rechallenged upon PD after a planned treatment holiday. Both patients signed an informed consent stating they have read this article, and they give their permission to publish all the information and images included herein.

CASE PRESENTATION

The first patient is a 69-year-old man who was diagnosed with pancreatic cancer in 2015. He had locally advanced unresectable disease and was treated initially with nab-paclitaxel plus gemcitabine. He completed six cycles of therapy with a reduced dose because of toxicity before PD eventually developed. He was hospitalized several times because of duodenal invasion of the pancreatic mass leading to obstruction, but he recovered and restarted treatment 3 months later with oxaliplatin, leucovorin, and fluorouracil (FOLFOX) and pembrolizumab based on high microsatellite instability findings on genetic sequencing of his tumor (Table 2). FOLFOX was added to pembrolizumab because of rapid clinical disease progression. However, after one cycle, he developed a perforated gastric ulcer that required exploratory laparotomy, and FOLFOX was permanently discontinued. Two months after starting immunotherapy, his tumor had radiographic PR, and carbohydrate antigen 19-9 (Ca 19-9) decreased from 5,503 to 17 U/mL. The radiographic response (PR) plateaued after 13 cycles of pembrolizumab and after Ca 19-9 normalized. He had SD for 17 months, at which point treatment was discontinued. He had periodic imaging for 10 months, at which time he was found to have progression of para-aortic lymphadenopathy. Subsequent biopsy confirmed metastatic PDAC. Interestingly, his tumor markers did not increase at that time (Fig 1A). In light of his previous good response, pembrolizumab was restarted. A computed tomography (CT) scan at 2 months after retreatment showed a PR (Fig 1A), and at 6 months, CT scans showed a sustained radiographic response. He did not develop any grade 3 to 4 immune-related AEs at any point. He still receives CPIs with continuing response approximately 10 months later.

The second patient is a 64-year-old woman with Lynch syndrome who was diagnosed with metastatic dMMR pancreatic cancer in 2016. She received nab-paclitaxel plus gemcitabine for one cycle before she presented for a second opinion at our center. She then enrolled in a clinical trial (ClinicalTrils.gov identifier: NCT02268825)

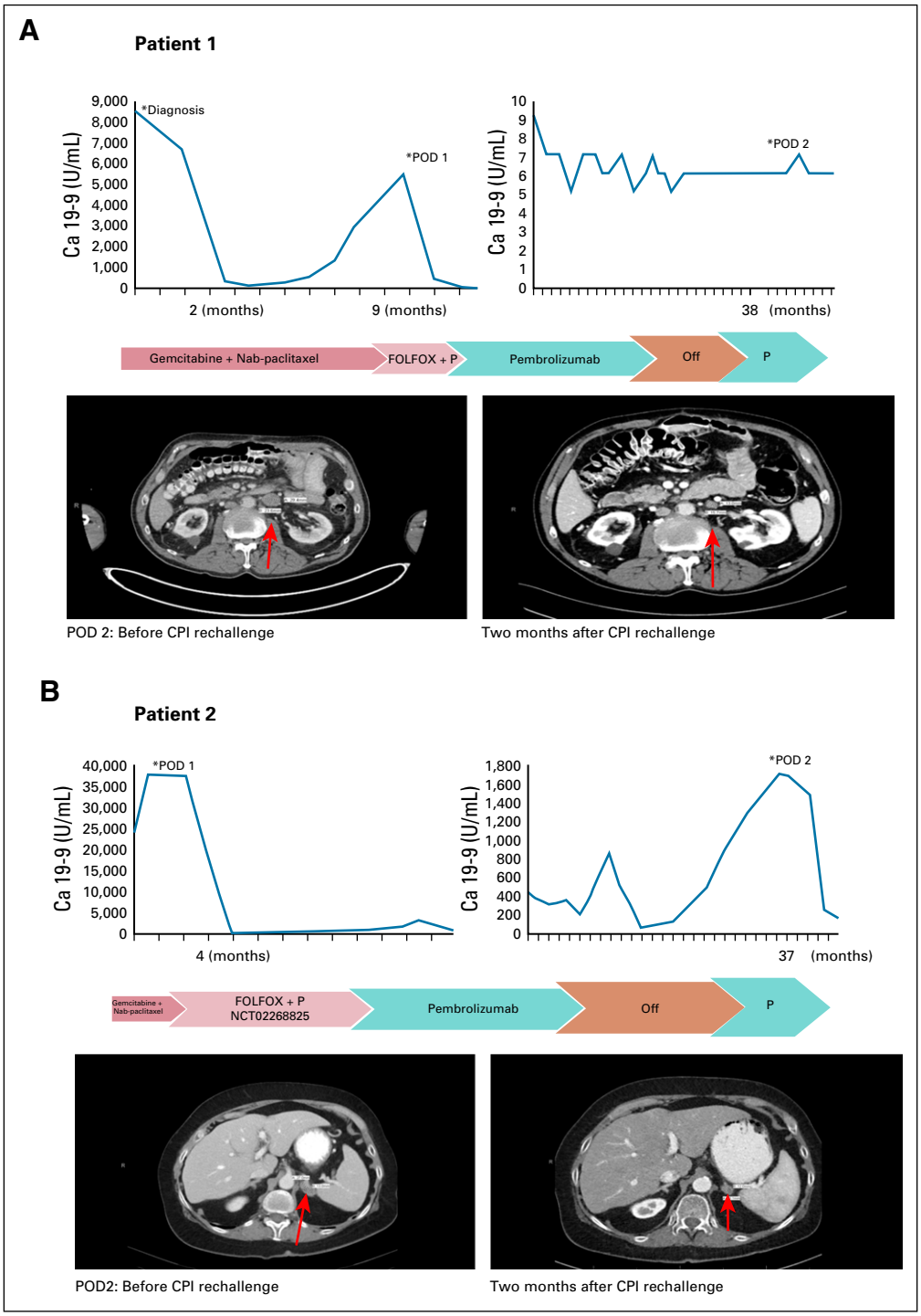

FIG 1. Tumor marker trend, treatment timeline, and imaging for (A) patient 1 and (B) patient 2 at the time of immunotherapy rechallenge. Arrows indicate the sites of disease progression (para-aortic lymphadenopathy for patient 1 and left adrenal metastasis for patient 2). Ca 19-9, carbohydrate antigen 19-9; CPI, checkpoint inhibitor; FOLFOX, oxaliplatin, leucovorin, and fluorouracil; P, pembrolizumab; POD, progression of disease.

that used FOLFOX plus pembrolizumab. CT scans at 3 months showed response in the primary tumor in the body and tail of the pancreas as well as liver metastases. Baseline Ca 19-9 was 37,576 U/mL, and it improved to 279 U/mL. Oxaliplatin was discontinued after cycle 7 because of persistent neuropathy, and fluorouracil plus pembrolizumab were continued for five cycles. At that time, a protocol amendment mandated the addition of celecoxib to the treatment. Our patient was receiving therapeutic anticoagulation for extensive deep vein thrombosis. Because

TABLE 2. Tumor and Germline Genomic Findings

Patient	Germline Testing[a]	MSI Status	Tumor Genomic Findings
1	Negative	MSI-H	*ERBB2* R678Q, *KRAS* G13D, *MSH2* W117, *PIK3CA* T1025A, *RNF43* G659fs*41, *TP53* G154S/P219S-subclonal/P301fs*44, *ARID1A* A339fs*24/K2033fs*9, *ASXL1* G654fs*58/S1095fs*11, *ATR* F1134fs*, *BCOR* Q11074fs*8, *BCORL1* P1681fs*20, *CREBBP* G1335*/R1664C-subclonal, *CTCF* R326, *CTNNB1* K335fs*10, *DNMT3A* E423, *EP300* N1532fs*9, *FLCN* H429fs*39, *KDM6A* R1279, *MLL2* A459fs*23/P2354fs*30, *RAD50* K722fs*14, *SMAD4* H132N, *SPEN* L2806fs*3, *TET2* K1439fs*9
2	Positive, del exons 1-2 in *MSH2*	NA	NA

Abbreviations: del, deletions; MSI, microsatellite instability; MSI-H, microsatellite instability high; NA, not available.

[a]Evaluated genes: *APC*, *ATM*, *BRCA1*, *BRCA2*, *CDDKN2A*, *CHEK2*, *EPCAM* (deletion/duplication only), *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *STK11*, *TP53*.

adding celecoxib would significantly increase her bleeding risk, she was taken off protocol to continue single-agent pembrolizumab under an expanded access program. She continued to receive pembrolizumab for 22 months before treatment was discontinued. At that time, she had a few subcentimeter hypodensities in the liver and a CR in the pancreatic tumor with only some soft tissue stranding around the celiac artery. After 16 months, she experienced PD with increasing Ca 19-9 levels as well as a new left adrenal gland lesion (Fig 1B). Biopsy of the lesion revealed metastatic adenocarcinoma consistent with pancreatic primary. Pembrolizumab was re-initiated. She attained radiographic PR to therapy, as well as improvement in Ca 19-9 levels (Fig 1B). She did not develop any grade 3 to 4 immune-related AEs.

DISCUSSION

Following the success of pembrolizumab in dMMR cancers, numerous CPIs have been approved for a variety of indications.[1,20,21] CPIs have a favorable toxicity profile compared with cytotoxics; however, some patients may develop life-threatening immune-related toxicities.[22]

There is a paucity of literature that addresses the optimal duration of therapy. Unlike cytotoxic chemotherapy, PD-1/programmed death-ligand 1 (PD-L1) inhibitors disrupt tumor immune evasion by restoring the T-cell function.[23] The first long-term survival data from patients treated with CPIs are now becoming available, and recent evidence shows that some patients with metastatic disease attain durable responses to CPIs with survival rates of more than 5 years.[24] These data suggest that in certain patients, alterations to the tumor immune microenvironment and host adaptive antitumor immunity may be irreversible and long-lasting. The ideal duration of therapy required to achieve this effect has not been established, nor have any tumor or host biomarkers been established to identify these patients. Although PD-L1 expression by the infiltrating immune cells may be predictive of some responses at initial therapy or at re-induction of that therapy,[9] it has not been described in all patients and it certainly varied across different histologies. Unfortunately, we could not obtain PD-L1 expression levels in our patients because of the limited tissue in biopsy samples. Clinically, the interval between treatment discontinuation and rechallenge could have predictive value. Although it was not seen in all cases described in the literature (Table 1), most patients who responded to CPIs a second time had long intervals of $>$ 10 months. This is consistent with our patients and could be an explanation for the low responses in the recent melanoma study[12] (the interval was only 6.3 months). However, in that study,[12] patients with PD on first treatment were also included. Finally, one thing that was consistent across the literature was that the quality of initial response (CR, PR, or SD) does not necessarily predict the patients who will benefit from CPI rechallenge.

To our knowledge, this is the first report of patients with dMMR pancreatic cancer who attained a response to treatment rechallenge with CPIs after a treatment holiday. This adds to the growing literature that shows the benefit of this approach. Although the response rates seem lower on re-induction, rechallenging with CPIs may be safe and to some degree efficacious.

AFFILIATION

[1]Department of Internal Medicine, Division of Oncology, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT

CORRESPONDING AUTHOR

Vaia Florou, MD, Department of Internal Medicine, Division of Oncology, Huntsman Cancer Institute, University of Utah School of Medicine, 2000 Circle of Hope, Salt Lake City, UT 84112; e-mail: vaia.florou@hci.utah.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Vaia Florou, Ignacio Garrido-Laguna
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Provision of study materials or patients: Ignacio Garrido-Laguna
Collection and assembly of data: Vaia Florou, Kristin E. Barber, Jenna N. Mastroianni, Courtney C. Cavalieri, Ignacio Garrido-Laguna
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Kristin E. Barber
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Courtney C. Cavalieri
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