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Research Article

Phase Ib/II Study of Lacnotuzumab in Combination with Spartalizumab in Patients with Advanced Malignancies

Jibran Ahmed,[1] Bettzy Stephen,[1] Yali Yang,[1] Evan Kwiatkowski,[1] Chinenye Lynette Ejezie,[1] Shubham Pant[1]

[1]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Address correspondence to Shubham Pant (SPant@mdanderson.org).

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ABSTRACT

Introduction: Blocking the colony-stimulating factor 1 (CSF-1) signal on tumor-associated macrophages can lead to an upregulation of checkpoint molecules, such as programmed cell death ligand 1 (PD-L1), thus causing resistance to this blockade. Combining spartalizumab (PDR001), a high-affinity, ligand-blocking, humanized anti–PD-1 immunoglobulin G4 antibody, with lacnotuzumab (MCS110), a high-affinity, humanized monoclonal antibody directed against human CSF-1 can potentially overcome this resistance. **Methods:** This was a multicenter, phase Ib/II trial using a combination of spartalizumab with lacnotuzumab in patients with advanced cancers, including anti–PD-1/PD-L1 treatment-resistant melanoma, and anti–PD-1/PD-L1 treatment-naïve triple-negative breast cancer, pancreatic cancer, and endometrial cancer (ClinicalTrials.gov identifier: NCT02807844). The primary objective of dose escalation phase Ib was to assess safety, tolerability, and recommended phase II dose. The primary objective of the phase II expansion study was to assess the combination's antitumor activity, including objective response rate and clinical benefit rate. **Results:** A total of eight patients (five in phase Ib and three in phase II) were evaluable for adverse events (AEs) at our study site. All eight patients experienced at least grade 1 AE. The most common treatment-related AEs were increased serum aspartate aminotransferase (38%), fatigue (38%), anemia (25%), increased alkaline phosphatase (25%), hyperbilirubinemia (25%), hypocalcemia (25%), and hypoalbuminemia (25%). Most of these AEs were grade 1 or 2. None of the patients experienced grade 4 AEs and no drug-related fatal AEs were reported among the eight patients treated in the study. One (13%) patient had stable disease (SD) (captured as unknown by the study sponsor because the evaluation criteria set per protocol was not met) and three (38%) patients had progressive disease. Four (50%) patients developed clinical disease progression based on investigator evaluation. One patient with pancreatic cancer achieved immune-related SD for 26 months while on the study treatments. **Conclusion:** The study completed phase Ib dose escalation and phase II. However, gating criteria for efficacy were not met for expansion beyond 80 patients in phase II and the sponsor did not continue development of the combination of spartalizumab and lacnotuzumab for oncology indications. The potential signal of activity in pancreatic cancer should be further explored.

Keywords: Lacnotuzumab, spartalizumab, pancreatic cancer, melanoma, endometrial cancer

INTRODUCTION

Immune checkpoint inhibitors are a revolutionary modality of cancer treatment.[1]

Unfortunately, resistance mechanisms can develop, limiting the efficacy of this approach, and therefore, there is a need for therapies that target the resistance mechanisms.[2] Tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) are among the most abundant immune cells in the tumor microenvironment and are known to mediate therapeutic resistance in cancer.[3,4] Thus, immune escape mediated by TAMs and MDSCs can limit the clinical benefit of immune checkpoint blockade.[5–7] There is also an association between circulating MDSCs and intrinsic resistance to programmed cell death protein 1 (PD-1) inhibition in patients with melanoma.[7,8] In addition, preclinical studies show that single-agent blockade of colony-stimulating factor 1/colony-stimulating factor 1 receptor (CSF-1/CSF-1R) or programmed cell death ligand 1 (PD-L1) has limited efficacy by restraining tumor growth, but the combined blockade of CSF-1R and PD-1 potently elicits tumor regressions.[9]

CSF-1 binds to its receptor CSF-1R, resulting in the proliferation and differentiation of myeloid cells into TAMs and MDSCs, which in turn suppress T cells directly through PD-L1 or indirectly through secretion of the immunosuppressive interleukin (IL)-10[4,10,11] (Fig. 1). Preclinical and clinical studies demonstrate that the blockade of CSF-1 or CSF-1R activates the immune system by limiting tumor infiltration by TAMs and MDSCs or altering macrophage polarization, resulting in significantly enhanced antigen presentation and an increase in CD8+ T cells.[7,12–15] However, inhibition of CSF-1 signaling upregulates checkpoint molecules, including PD-L1 and cytotoxic T-lymphocyte protein 4 (CTLA-4), thereby limiting beneficial therapeutic effects.[9] Tumor cells exploit immune checkpoint pathways to inhibit T-cell proliferation and avoid detection by the immune system.[16]

Anti–PD-1 therapies have demonstrated antitumor activity in multiple solid tumors, such as melanoma, non–small-cell lung cancer, colon cancer, and renal cell carcinoma,[17] and have improved survival in patients with metastatic melanoma, advanced renal cell carcinoma, and advanced non–small-cell lung cancer compared with traditional chemotherapeutic agents.[18]

Spartalizumab (PDR001), a high-affinity, ligand-blocking, humanized anti–PD-1 immunoglobulin G4 antibody, blocks the binding of PD-L1 and PD-L2 to PD-1 (Fig. 1). Lacnotuzumab (MCS110) is a high-affinity, humanized monoclonal antibody directed against human CSF-1 and it blocks the interaction of CSF-1 with CSF-1R on TAMs. Preclinical

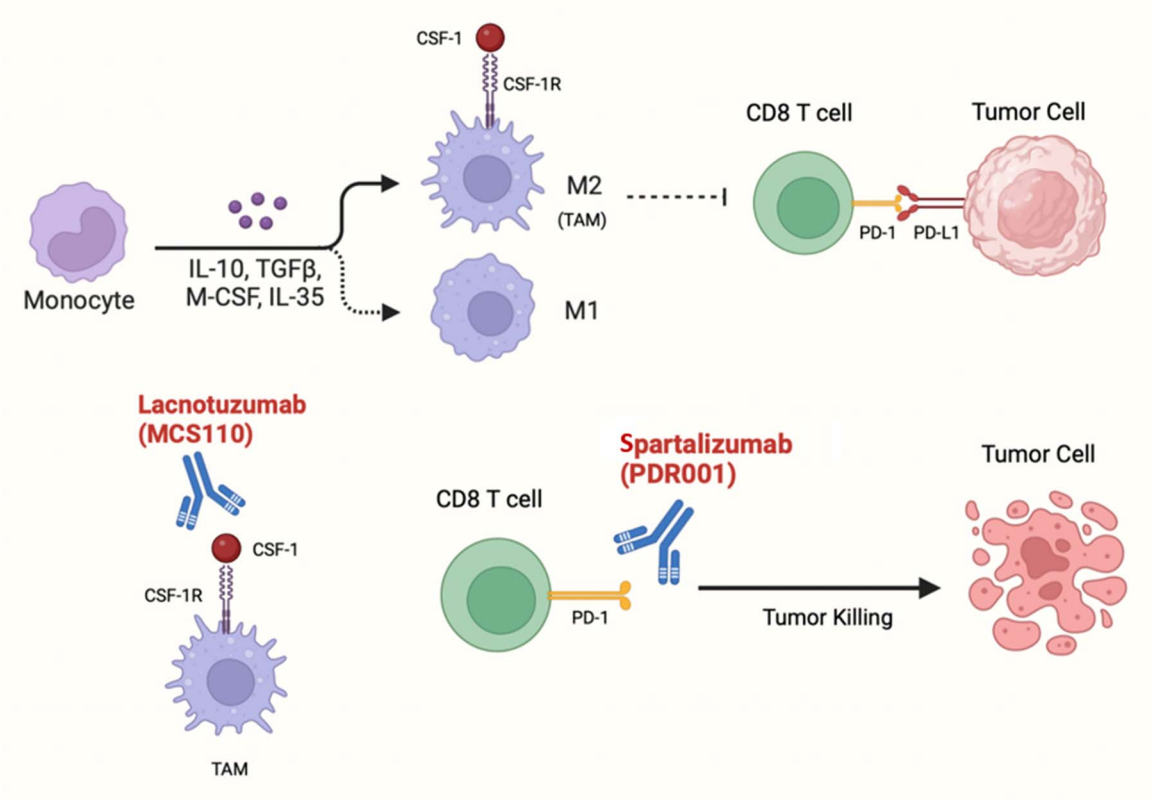

Figure 1. Mechanism of action of spartalizumab (PDR001) and lacnotuzumab (MCS110).

CD8, cluster of differentiation 8; CSF-1, colony-stimulating factor 1; CSF-1R, colony-stimulating factor 1 receptor; IL-10, interleukin 10; IL-35, interleukin 35; M-CSF, macrophage colony-stimulating factor; M, macrophage; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TAM, tumor-associated macrophage; TGFb, transforming growth factor b. This figure was created with BioRender.com.

and clinical studies using spartalizumab showed efficacy and a favorable safety profile.[19] In addition, in vitro preclinical studies have demonstrated the ability of lacnotuzumab to neutralize the activity of CSF-1.[20]

This study aimed to combine lacnotuzumab and spartalizumab to produce TAM depletion, enhanced T-cell activation, and synergistic antitumor activity in the clinical setting.

In a previously published abstract from this same study (ClinicalTrials.gov identifier: NCT02807844), including all patients enrolled in the dose escalation part, patients received increasing doses of lacnotuzumab plus spartalizumab to assess the safety, tolerability, and recommended phase II dose (RP2D).[21] This cohort of patients did not represent the complete trial population. The most common (≥30%) all-grade adverse events (AEs) included increased aspartate aminotransferase (32%), nausea (32%), vomiting (32%), asthenia (30%), and fatigue (30%); the most common (≥10%) grade ≥ 3 AEs were increased aspartate aminotransferase (12%), asthenia (10%), and hyponatremia (10%). One patient had a partial response (PR) and nine had stable disease (SD) (19%). The disease control rate (immune-related PR or immune-related SD) was 27% (13/48). Lacnotuzumab with spartalizumab was well tolerated overall and showed preliminary antitumor activity, notably in the pancreatic cancer cohort. The RP2D was determined to be 300 mg for spartalizumab and 7.5 mg/kg for lacnotuzumab. Here, we present our institutional experience with eight eligible patients enrolled on this trial, five in phase Ib and three in phase II of the study.

The primary objective of the phase Ib part of the study was to characterize the safety and tolerability and to determine the RP2D of lacnotuzumab plus spartalizumab combination. The secondary objectives of phase Ib included estimation of the preliminary antitumor activity. The primary objective of the phase II part of this study was to estimate the antitumor activity of the combination treatment of lacnotuzumab with spartalizumab in each expansion group.

METHODS

Ethics, Institutional Review Board, and Consent

The protocol was approved by the institutional review board at the University of Texas MD Anderson Cancer Center. This clinical study was designed and reported in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Harmonized Tripartite Guidelines for Good Clinical Practice, applicable local regulations (including European Directive 2001/20/EC and U.S. Code of Federal Regulations Title 21), and the ethical principles laid down in the Declaration of Helsinki. Eligible patients enrolled at MD Anderson Cancer Center were included in the study after providing written informed consent approved by the institutional review board at MD Anderson Cancer Center.

Patient Selection

Eligible patients had advanced solid tumors and measurable disease according to response criteria, had received standard-of-care treatment (with no more than three prior lines of treatment), and had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. Patients had adequate laboratory results for complete blood counts, chemistry, and liver and renal functions. Patients with active central nervous system metastases were excluded from the study. Additional inclusion and exclusion criteria are provided in Supplementary Table S1, available online.

Study Design

This was a multicenter, open-label, phase Ib/II study starting with a phase Ib dose escalation portion followed by a phase II part (ClinicalTrials.gov identifier: NCT02807844). Patients were enrolled between December 29, 2016, and October 11, 2018. During the phase Ib part of the study, patients were treated with increasing doses of lacnotuzumab and spartalizumab every 3 weeks until a recommended phase II dose was determined for this treatment combination. The dose escalation decision was guided by a Bayesian logistic regression model with overdose control (EWOC) principle based on dose-limiting toxicity data in the context of available safety. The Bayesian design was used to decide dosage and to estimate the objective response rate (ORR) or clinical benefit rate (CBR). A meta-analytic-predictive approach was used to derive the prior distribution for the single-agent model parameters required by the Bayesian approach.

The phase Ib part of the study included adult patients with advanced or metastatic melanoma, endometrial, pancreatic, and triple-negative breast cancers, who had progressed despite standard therapy or were intolerant of standard therapy, or for whom no standard therapy existed. The phase II part included patients with advanced or metastatic triple-negative breast cancer (TNBC), endometrial cancer, melanoma (groups 1, 3, and 4, respectively), and pancreatic cancer (group 2). The combined treatment was evaluated in disease indications where single-agent PD-1/PD-L1 inhibition did not result in clinically meaningful responses (anti–PD-1/PD-L1 treatment-resistant melanoma) and where the therapeutic resistance may be mediated by TAMs (anti–PD-1/PD-L1 treatment-naïve, pancreatic cancer, and endometrial cancer).

Endpoints, Safety Assessment, and Response Assessment

The primary endpoint of the phase Ib part of the study was assessment of AEs and incidence of dose-limiting toxicity. The secondary endpoints of part Ib of the study included objective response, clinical benefit, disease control, duration of response, and progression-free survival

(PFS), per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and immune-related response criteria (irRC). The primary endpoint of phase II of this study was objective response by RECIST v1.1 for patients in all cohorts except pancreatic cancer and clinical benefit by RECIST v1.1 for the pancreatic cancer patient cohort. Secondary endpoints of phase II part of the study included objective response by irRC and clinical benefit, disease control, duration of response, and PFS by irRC and RECIST v1.1.

The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) was used for grading AEs at every visit.

Response to treatment was assessed every two cycles by clinical evaluation, tumor markers, and imaging per RECIST v1.1 or irRC. Study treatment was discontinued for AEs or progressive disease per irRC.

Treatment Plan

For phase Ib, the six combination dose levels are presented in Supplementary Table S2, available online. RP2D was established before the maximum tolerated dose was reached. For phase II, spartalizumab was given at a dose of 300 mg and lacnotuzumab at 7.5 mg/kg. Both antibodies were administered via intravenous infusion every 3 weeks. Patients continued the study until their disease progressed or until they experienced toxicities that warranted leaving the study or for withdrawing consent.

Statistical Analysis

ORR was defined as the proportion of patients with complete response (CR) or PR by investigator assessment as defined by RECIST v1.1 or irRC. CBR was defined as the proportion of patients with a best overall response of CR or PR (with at least two assessments 4 weeks apart) or with SD $>$ 4 months based on local investigator assessment, as defined by RECIST v1.1 or irRC. We describe the results in these eight patients using descriptive analysis and measures of central tendency as tabulated.

RESULTS

A total of eight patients were screened for the clinical trial at our center; five patients were enrolled in phase Ib, and three patients were enrolled in phase II. The median age of the patients was 59 years (range 32–80 years). In total, 63% (five of eight) of patients had pancreatic cancer and 88% (seven of eight) of patients had received $\geq$ 2 lines of prior treatments. Additional patient characteristics are provided in Table 1.

Of the eight patients treated on the study, one (13%) patient had SD (captured as unknown by study sponsor as evaluation criteria set per protocol was not met) and three (38%) patients had PD per RECIST v1.1. Four (50%) patients did not meet the protocol defined response criteria and based on investigator evaluation these patients developed clinical disease progression. Among these four patients, one patient withdrew consent due to toxicity after being on the study for 1.4 months.

Noteworthy, among them is the antitumor activity observed in a patient with poorly differentiated pancreatic large cell carcinoma, who had progressed on six lines of prior therapy. This patient had irSD for 26 months on the study. A corresponding trend in serum CA19–9 is presented for this patient in Supplementary Figure S1, available online.

AEs and their grades (CTCAE v4.03) are presented in Tables 2 and 3. Although all the patients had treatment-emergent AEs, only four of eight (50%) patients experienced at least one AE related to treatment. The most common treatment-related AEs were increased serum aspartate aminotransferase (38%), fatigue (38%), anemia (25%), increased alkaline phosphatase (25%), hyperbilirubinemia (25%), hypocalcemia (25%), and hypoalbuminemia (25%). There were no grade 4 AEs or treatment-related deaths. One patient developed bilateral central serous chorioretinopathy (grade 3) and was taken off treatment because of withdrawal of consent.

The results of molecular alterations, PD-L1, and microsatellite instability (MSI) status are shown in the Supplementary Table S3, available online.

DISCUSSION

A total of eight patients were enrolled at MD Anderson Cancer Center on this phase Ib/II study. Although

Table 1. Patient characteristics ($N = 8$)

Baseline Characteristics	*n*	%
Age, years		
Median	59	
Range	32–80	
Sex		
Male	5	62.5
Female	3	37.5
Race		
White	6	75
Black	0	0
Hispanic or Latino	1	12.5
Asian	0	0
Other	1	12.5
ECOG status		
0	1	12.5
1	7	87.5
Histology		
Pancreatic	5	62.5
Endometrial	2	25
Melanoma	1	12.5
No. of prior lines of treatment		
0	0	0
1	1	12.5
$\geq$ 2	7	87.5
Site of metastases		
1	1	12.5
$\geq$ 2	7	87.5

ECOG, Eastern Cooperative Oncology Group performance scale.

Table 2. Treatment-emergent adverse events ($N = 8$)

Events, *n* (%)	Any Grade	Grade 1 or 2	Grade 3	Grade 4
AST increase*	5 (63)	4 (50)	1 (13)	0 (0)
Anemia*	4 (50)	3 (38)	1 (13)	0 (0)
Fatigue*	4 (50)	3 (38)	1 (13)	0 (0)
Increase serum creatinine kinase*	4 (50)	4 (50)	0 (0)	0 (0)
Hypoalbuminemia*	3 (38)	3 (38)	0 (0)	0 (0)
Hyperuricemia	3 (38)	3 (38)	0 (0)	0 (0)
Abdominal distention	3 (38)	3 (38)	0 (0)	0 (0)
Hyponatremia	3 (38)	1 (13)	2 (25)	0 (0)
Constipation*	3 (38)	2 (25)	1 (13)	0 (0)
Alkaline phosphatase*	2 (25)	2 (25)	0 (0)	0 (0)
ALT increase*	2 (25)	2 (25)	0 (0)	0 (0)
Lower extremity edema	2 (25)	2 (25)	0 (0)	0 (0)
Abdominal pain	2 (25)	0 (0)	2 (25)	0 (0)
Increased serum creatinine*	2 (25)	2 (25)	0 (0)	0 (0)
Diarrhea	2 (25)	2 (25)	0 (0)	0 (0)
Hyperglycemia	2 (25)	2 (25)	0 (0)	0 (0)
Hypophosphatemia*	2 (25)	1 (13)	1 (13)	0 (0)
Increased serum TSH	2 (25)	2 (25)	0 (0)	0 (0)
Hypocalcemia*	2 (25)	2 (25)	0 (0)	0 (0)
Hyperbilirubinemia*	2 (25)	2 (25)	0 (0)	0 (0)
Nausea	2 (25)	1 (13)	1 (13)	0 (0)
Vomiting	2 (25)	1 (13)	1 (13)	0 (0)
Chills*	1 (13)	1 (13)	0 (0)	0 (0)
Myalgias	1 (13)	1 (13)	0 (0)	0 (0)
Visual disturbance	1 (13)	0 (0)	1 (13)	0 (0)
Hypomagnesemia	1 (13)	1 (13)	0 0)	0 (0)
Hypokalemia	1 (13)	1 (13)	0 (0)	0 (0)
Hyperkalemia	1 (13)	1 (13)	0 (0)	0 (0)
Increased INR	1 (13)	1 (13)	0 (0)	0 (0)
Increased APTT	1 (13)	1 (13)	0 (0)	0 (0)
Hypertension	1 (13)	1 (13)	0 (0)	0 (0)
Tumor-associated pain	1 (13)	1 (13)	0 (0)	0 (0)
Decreased appetite	1 (13)	1 (13)	0 (0)	0 (0)
Anorexia	1 (13)	1 (13)	0 (0)	0 (0)
Leukocytosis	1 (13)	1 (13)	0 (0)	0 (0)
Decreased lymphocyte count	1 (13)	0 (0)	1 (13)	0 (0)
Thrombocytopenia	1 (13)	1 (13)	0 (0)	0 (0)
Melena	1 (13)	1 (13)	0 (0)	0 (0)
Rectal bleeding	1 (13)	0 (0)	1 (13)	0 (0)
Non-cardiac chest pain*	1 (13)	1 (13)	0 (0)	0 (0)
Hypothyroidism	1 (13)	1 (13)	0 (0)	0 (0)
Ascites	1 (13)	0 (0)	1 (13)	0 (0)
Dry skin (xerosis)	1 (13)	1 (13)	0 (0)	0 (0)
Heartburn	1 (13)	0 (0)	1 (13)	0 (0)
Dyspepsia	1 (13)	1 (13)	0 (0)	0 (0)
Fistula	1 (13)	0 (0)	1 (13)	0 (0)
Back pain	1 (13)	1 (13)	0 (0)	0 (0)
Skin ulcer	1 (13)	1 (13)	0 (0)	0 (0)
Dehydration	1 (13)	1 (13)	0 (0)	0 (0)
Tachycardia	1 (13)	1 (13)	0 (0)	0 (0)
Periorbital swelling	1 (13)	1 (13)	0 (0)	0 (0)
Dyspnea	1 (13)	1 (13)	0 (0)	0 (0)
Peripheral sensory neuropathy	1 (13)	1 13)	0 (0)	0 (0)
Pulmonary embolism	1 (13)	1 (13)	0 (0)	0 (0)
Upper respiratory tract infection	1 (13)	1 (13)	0 (0)	0 (0)
Rib fracture	1 (13)	1 (13)	0 (0)	0 (0)
Large intestinal obstruction	1 (13)	0 (0)	1 (13)	0 (0)
Anxiety	1 (13)	1 (13)	0 (0)	0 (0)
Sleep disturbances	1 (13)	1 (13)	0 (0)	0 (0)

*Treatment-related adverse events.
ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; INR, international normalized ratio; TSH, thyroid-stimulating hormone.

Table 3. Treatment-related adverse events ($N = 8$)

Events, *n* (%)	Any Grade	Grade 1 or 2	Grade 3	Grade 4
AST increase	3 (38)	2 (25)	1 (13)	0 (0)
Fatigue	3 (38)	3 (38)	0 (0)	0 (0)
Anemia	2 (25)	2 (25)	0 (0)	0 (0)
Alkaline phosphatase	2 (25)	2 (25)	0 (0)	0 (0)
Hyperbilirubinemia	2 (25)	2 (25)	0 (0)	0 (0)
Hypocalcemia	2 (25)	2 (25)	0 (0)	0 (0)
Hypoalbuminemia	2 (25)	2 (25)	0 (0)	0 (0)
Increase serum creatinine kinase	1 (13)	1 (13)	0 (0)	0 (0)
Constipation	1 (13)	1 (13)	0 (0)	0 (0)
ALT increase	1 (13)	1 (13)	0 (0)	0 (0)
Increased serum creatinine	1 (13)	1 (13)	0 (0)	0 (0)
Hypophosphatemia	1 (13)	0 (0)	1 (13)	0 (0)
Chills	1 (13)	1 (13)	0 (0)	0 (0)
Non-cardiac chest pain	1 (13)	1 (13)	0 (0)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

the study completed phase Ib dose escalation and phase II, however, gating criteria for efficacy were not met for expansion beyond a total of 80 patients in phase II and the sponsor did not continue development of the combination of spartalizumab and lacnotuzumab for oncology indications. As the study did not meet the criteria for further expansion, which precluded evaluation of other efficacy measures, antitumor activity in patients with pancreatic cancer requires further investigation. The treatment combination was overall safe and most of the AEs were grade 1 or 2.

Of the eight patients enrolled at MD Anderson Cancer Center, five patients had pancreatic cancer. Of the remaining three patients, two had endometrial carcinoma and one patient had melanoma. All except one patient with endometrial carcinoma had undergone extensive previous treatment (two or more lines of prior treatment). In particular, one patient with pancreatic cancer had SD for 26 months on the study, which indicates some level of activity with lacnotuzumab plus spartalizumab. In a similar trial with cabiralizumab (another CSF-1 inhibitor) plus nivolumab (another PD-1 inhibitor), PR was noted in four patients with pancreatic cancer treated with these drugs,[22] indicating that the role of CSF-1 inhibitors in combination with PD-1 inhibitor in pancreatic cancer can be further explored. Patients treated with ICIs have shown instances of prolonged stable disease, indicative of durable responses that may also be associated with improved survival.[23] This also warrants the identification of possible biomarkers predicting these responses. Although our site did not include patients with TNBC, the multicenter phase Ib trial included several patients with TNBC. In a recent phase II study, which evaluated the efficacy of lacnotuzumab when added to gemcitabine plus carboplatin in patients with TNBC, the triplet showed similar antitumor activity to that of the chemotherapy (gemcitabine plus carboplatin) alone and reported poor tolerability.[24]

Data on PD-L1 and MSI status were not available for all the patients; however, limited molecular information was available for these patients. Both patients with endometrial cancer had a *TP53* mutation and a coexistent mutation involving the phosphoinositide 3-kinase (PI3K) pathway and had early PD with the treatment combination. Prior studies have reported that concomitant mutations in TP53 gene and PI3K pathway are associated with early progression signifying poor prognosis.[25,26]

Pharmacodynamic effects of the combination on on-target peripheral and tumor-immune microenvironment were presented in a prior study.[27] This previously published flow cytometry analysis demonstrated a decrease in the level of circulating CSF-1 in plasma, and the gene expression profiling of paired biopsy specimens by RNA sequencing showed downregulation of macrophage-associated genes. The data also showed upregulation of T-cell gene signatures. Despite successful target engagement and promising pharmacokinetic profile, the antitumor activity of this combination has been limited.

Several CSF-1/CSF-1R inhibitors have been studied in combination with immunotherapy in clinical trials. Table 4 provides a summary of these trials. These studies include phase I or II clinical trials of CSF-1/CSF-1R monoclonal antibodies or small molecule inhibitors in combination with anti–PD-1/PD-L1 or CD-40 agonistic monoclonal antibodies. Although a few trials are ongoing, the reported data on other trials show either modest or no ORRs, or high rates of grade ≥ 3 toxicities, particularly liver toxicity, and some trials were terminated early due to lack of efficacy despite manageable safety profiles. However, as the other trials complete accrual, more data will be available. The combination of spartalizumab with lacnotuzumab has also been investigated in a biomarker study in gastric cancer (ClinicalTrials.gov Identifier: NCT03694977). The role of CSF-1/CSF-1R inhibition has also been explored in diffuse-type tenosynovial giant cell tumor/pigmented villonodular synovitis in various studies, including those involving the use of lacnotuzumab, reporting a PR of 42% to 100% with the use of CSF-1/CSF-1R small molecule inhibitors or monoclonal antibodies.[28–31] In another study in patients with pigmented villonodular synovitis treated with single-agent pexidartinib (a selective CSF1-R kinase inhibitor), PR was reported in 64% and SD in 36% of patients.[30]

Primary and acquired resistance mechanisms of CSF-1/CSF-1R blockade have been proposed in animal studies, such as those involving the tumor microenvironment and cancer-associated fibroblasts.[32,33] These resistance mechanisms also need further elaboration for future therapeutic options.

Our study is limited by data from a single site, small sample size, and early termination of treatment due to disease progression or drug toxicity. The exploratory analysis of the pharmacodynamic effects of this combination could not be performed in these eight patients because of a small sample size. Nevertheless, our results could inform

Table 4. Results from ongoing and completed trials targeting CSF-1R with combination immunotherapy[34–41]

NCT Identifier	Investigational Drug	Target/Class of Drug	Combination ICI	Clinical Phase	Cancer Types	Comments
NCT02713529[34]	AMG820	CSF-1R/mAb	Pembrolizumab (anti–PD-1 mAb)	1b/2	Pancreatic, colorectal, NSCLC	irPR in 3%, irSD in 34%, grade ≥ 3 AEs in 87.9% of patients The study did not exhibit antitumor activity for further evaluation
NCT02323191[35]	Emactuzumab (RO5509554)	CSF-1R/mAb	Atezolizumab (anti–PD-L1 mAb)	1b	Melanoma, urothelial bladder cancer, NSCLC	ORR 5.6%-12.5%; Grade ≥ 3 AEs in 11.3%
NCT02760797[36]	Emactuzumab (RO5509554)	CSF-1R/mAb	Selicrelumab (RO7009789, agonistic CD-40 mAb)	1b	Advanced solid tumors	SD in 40.5%; Grade 3 or 4 AEs in 62.2%
NCT02554812[37]	PD 0360324	M-CSF/mAb	Avelumab (anti–PD-L1 mAb)	1/2	Advanced solid tumors	Ongoing
NCT03238027[38]	Axatilimab (SNDX-6352)	CSF-1R/mAb	+/− Durvalumab (anti–PD-L1 mAb)	1b	Advanced solid tumors	Completed; Grade ≥ 3 TRAE in 33%; Efficacy data pending
NCT02526017	Cabiralizumab (FPA008)	CSF-1R/mAb	Nivolumab (anti–PD-1 mAb)	1a/1b	Advanced solid tumors	Completed; 6-month DCR 13%, ORR 10%; Grade 3–5 AEs in 43%
NCT02718911[39]	LY3022855	CSF-1R/mAb	Durvalumab (anti–PD-L1 mAb) Tremelimumab (anti–CTLA4 mAb)	1a/1b	Advanced solid tumors	DCR 33%, CR 1.4%, and PR 2.8%
NCT03694977	Lacnotuzumab (MCS110)	Anti–CSF-1 mAb	Spartalizumab (PDR001) (anti–PD-1 mAb)	2	Gastric cancer	unknown
NCT02452424	Pexidartinib (PLX3397)	CSF-1R, cKIT, FLT3/small molecule inhibitor	Pembrolizumab (anti–PD-1 mAb)	1/2	Melanoma, NSCLC, GIST, head and neck squamous cell cancer, ovarian cancer	Terminated early insufficient evidence of clinical efficacy
NCT02777710[40]	Pexidartinib (PLX3397)	CSF-1R, cKIT, FLT3/small molecule inhibitor	Durvalumab (anti–PD-L1 mAb)	1	Pancreatic, colorectal cancer	Completed, clinical benefit rate at 2 months (SD only) was 21%
NCT02829723	Sotuletinib (BLZ945)	CSF-1R/small molecule inhibitor	PDR001 (anti–PD-1 mAb)	1/2	Advanced solid tumors	Terminated; Grade ≥ 3 TRAE in 25%; SD in 45% (unpublished data)
NCT02880371[41]	ARRY-382	CSF-1R/small molecule inhibitor	Pembrolizumab (anti–PD-1 mAb)	1/2	Advanced solid tumors	Terminated (study halted prematurely due to insufficient evidence of clinical efficacy)

AEs, adverse events; CD-40, cluster of differentiation 40; CR, complete response; CSF-1R, colony-stimulating factor 1 receptor; CTLA4, cytotoxic T-lymphocyte associated protein 4; DCR, disease control rate; GIST, gastrointestinal stromal tumor; irPR, immune-related partial response; irSD, immune-related standard disease; M-CSF, macrophage colony-stimulating factor; mAb, monoclonal antibody; NSCLC, non–small-cell lung cancer; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease; TRAE, treatment-related adverse events.

future studies of drugs targeting the CSF-1/CSF-1R pathway in patients with advanced cancer.

CONCLUSION

In conclusion, despite promising preclinical data on response, the current study did not translate those data into objective clinical responses. However, further studies are needed to explore subgroups of patients who could potentially benefit from this combination. Although we know this drug does not have robust clinical activities, we only have data from MD Anderson Cancer Center and not from other sites.

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Data Availability

The data generated in this study are available upon request from the corresponding author.

Supplemental Material

Supplemental materials are available online with the article.

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