Molecular Cancer Therapeutics

Phase I Dose-Escalation Study of Anti–CTLA-4 Antibody Ipilimumab and Lenalidomide in Patients with Advanced Cancers

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Abstract

Preclinical data suggest that combining a checkpoint inhibition with immunomodulatory derivative can increase anticancer response. We designed a dose-escalation study using a 3 + 3 design to determine the safety, maximum tolerated dose (MTD) or recommended phase II dose (R2PD) and dose-limiting toxicities (DLT) of the anti–CTLA-4 antibody ipilimumab (1.5–3 mg/kg intravenously every 28 days × 4) and lenalidomide (10–25 mg orally daily for 21 of 28 days until disease progression or unacceptable toxicity) in advanced cancers. Total of 36 patients (Hodgkin lymphoma, 7; melanoma, 5; leiomyosarcoma, 4; renal cancer, 3; thyroid cancer, 3; other cancers, 14; median of 3 prior therapies) were enrolled. The MTD has not been reached and ipilimumab 3 mg/kg and lenalidomide 25 mg have been declared as R2PD. DLT were grade (G) 3 rash (3 patients) and G3 pancreatitis (1 patient). G3/4 drug-related toxicities other than DLT were G3 anemia (5 patients), G3 thromboembolism (2 patients), G3 thrombocytopenia, G3 rash, G3 hypopituitarism, G3 pneumonitis, G3 transaminitis, and G4 hypopituitarism (all in 1 patient). Eight patients had tumor shrinkage per immune-related response criteria (−79% to −2%) including a PR (−79% for 7.2+ months) in a refractory Hodgkin lymphoma. Using comprehensive genomic profiling, a total mutation burden (mutations/Mb) was evaluated in 17 patients, with one of the patients achieving a PR demonstrated intermediate mutation burden. In conclusion, combination of ipilimumab and lenalidomide is well tolerated and demonstrated preliminary signals of activity in patients with refractory Hodgkin lymphoma and other advanced cancers. *Mol Cancer Ther; 17(3); 671–6. ©2017 AACR.*

Introduction

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) functions as an immune checkpoint, negatively regulating the duration and intensity of the immune response (1). Blocking this checkpoint allows the immune response to persist and increase the immune system's ability to detect and destroy cancer cells. Ipilimumab is a monoclonal antibody that binds to CTLA-4, which activates T-cell–driven anticancer immune response by virtue of blocking the interaction between CTLA-4 and its ligands, CD80/CD86. Ipilimumab is approved by the FDA for treatment of metastatic melanoma (1).

Lenalidomide, a 4-amino-glutamyl analogue derivate of thalidomide, is a so-called immunomodulatory derivative (IMiD), which affects both cellular and humoral immunity and also has antiangiogenic and other antitumor properties, is approved by FDA for treatment of multiple myeloma (2). In multiple myeloma models, immunomodulatory effects of lenalidomide do not only target the multiple myeloma cells directly, but also induce anticancer activity of immune effector cells. However, lenalidomide does not alter myeloid-derived suppressor cell (MDSC)-mediated tumor growth and immune suppression (3–5). Furthermore, *in vitro* experiments in multiple myeloma cells demonstrated that immune response from the checkpoint blockade can be enhanced by lenalidomide with decrease in MDSC-mediated cell growth, which provides framework for clinical evaluation of combination therapy (6). Therefore, we designed a phase I clinical study with ipilimumab and lenalidomide to determine the maximum tolerated dose (MTD) or recommended phase II dose (RP2D), safety, and early signals of clinical activity in patients with advanced cancers.

Materials and Methods

This study was a nonrandomized, dose-escalation phase I clinical trial of ipilimumab and lenalidomide (NCT01750983) performed at The University of Texas MD Anderson Cancer Center (MD Anderson). The primary objective was to determine the MTD or recommended phase II dose (R2PD) and dose-limiting toxicities (DLT) of ipilimumab in combination with lenalidomide in patients with advanced cancer who have progressed on standard

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therapy. Secondary objectives were to assess preliminary signals of antitumor efficacy. The protocol was approved by the Institutional Review Board (IRB). All patients provided written informed consent prior to enrolling on a study.

We enrolled patients aged 18 years and older with advanced or metastatic malignancy with no available standard therapy referred to the Clinical Center for Targeted Therapy at MD Anderson between May 2013 and April 2016. Patient selection was further narrowed to those who met all the eligibility criteria. All patients were 3 or more weeks beyond treatment with cytotoxic chemotherapy, therapeutic radiation, and major surgery. Patients who received palliative radiation immediately before or requiring it during treatment were allowed provided that radiation was not delivered to the only site of disease being treated under the protocol. For those who received biologic/targeted therapy as their last treatment, a washout period of 3 weeks or 5 half-lives (whichever was shorter) was required. Other inclusion criteria included an Eastern Cooperative Oncology Group performance status (ECOG) of 0, 1, or 2; adequate organ and bone marrow function, as defined by an absolute neutrophil count of greater or equal to 1,000/mL, a platelet count greater or equal to 50,000/mL, a creatinine clearance of greater or equal to 60 mL/minute by Cockcroft-Gault calculation, a total bilirubin of less than or equal to 2 times the institutional upper limit of normal, and an alanine aminotransferase level of less than or equal to 5 times the upper limit of normal. Due to the teratogenic nature of lenalidomide, it was required that females use 2 effective contraceptive methods during therapy and at least 4 weeks after completing therapy and for males to use of a latex condom during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy. In addition, a weekly pregnancy test was performed for the first 8 weeks and at the start of a cycle thereafter in all female patients. Patients were excluded if they had a history of organ transplant, autoimmune disease including inflammatory bowel disease, severe motor or sensory neuropathy, angioedema, and those with uncontrolled intercurrent illness, including, but not limited to, uncontrolled infection, uncontrolled asthma, need for hemodialysis or ventilator support.

Patients were enrolled to 5 dose levels using the standard "3 + 3" dose-escalation design (Table 1). The starting doses were 1.5 mg/kg of ipilimumab and 10 mg of lenalidomide and were escalated to 3.0 mg/kg of ipilimumab and 25 mg of lenalidomide. Ipilimumab was given intravenously on day 1 of a 28-day cycle for 4 doses. Lenalidomide was given orally days 1 through 21 of a 28-day cycle until disease progression. Patients were monitored closely for the first 8 weeks with weekly visits consisting of labs and clinical exam for to assess tolerability. Patients who had DLT or completed at least 80% of cycle 1 were evaluable for DLT analysis. MTD was defined as the highest dose at which no more than 33% of patients developed a DLT. DLTs were defined as any clinically grade 3 or 4 nonhematologic toxicity as defined in the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.0), expected and believed to be related to the study medications (except nausea and vomiting, electrolyte imbalances responsive to appropriate regimens or alopecia), any grade 4 hematologic toxicity lasting at least 3 weeks or longer (as defined by the NCI-CTCAE v4.0) or associated with bleeding and/or sepsis, any grade 4 nausea or vomiting lasting more than 5 days despite maximum antinausea regimens, any other grade 3 nonhematologic toxicity including symptoms/signs of vascular leak or cytokine release syndrome, and any severe life-threating complication or abnormality not defined in the NCI-CTCAE v4.0 that is attributable to the therapy observed during the first cycle (28 days) of therapy. If an individual experienced a new clinically significant toxicity grade 3 or greater, treatment was held until recovery to baseline levels or grade 1 or less and the drug to which the toxicity was attributed per physician was reduced by up to 50%. If it was unclear which drug was responsible for the toxicity, then both drugs were reduced by up to 50%.

Scans were performed prior to enrolling patient on treatment and every 2 cycles thereafter. Response to therapy was assessed according to the immune-related response criteria (irRC; ref. 7). The response according to irRC is derived from time-point response assessments based on tumor burden and is divided into 4 categories, immune-related complete response (irCR), immune-related partial response (irPR), immune-related stable disease (irSD), and immune-related progressive disease (irPD). Of the responses irCR constitutes disappearance of all lesions without appearance of any new lesions whereas irPR means tumor burden has decreased by more than or equal to 50% relative to baseline and irPD means tumor burden has increased by more than or equal to 25% relative to nadir. Any response not meeting criteria for irCR or irPR in the absence of irPD is considered irSD.

Comprehensive genomic profiling was performed on DNA extracted from archival FFPE tumor samples from patients with available tissue using the Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists (CAP)-accredited, New York State (NYS)-approved Foundation One (DNA-seq) or the FoundationOne Heme (DNA/RNA-seq) assay. It had a mean coverage depth of 663x for DNA (up to 405 cancer-related genes) and ~3M on-target unique pairs for RNA (265 genes included). All classes of alterations [e.g., base substitution, short insertion, or deletion (indel), focal gene amplification, homozygous deletion, and selected rearrangements] were detected. At least 50 ng of DNA per specimen was isolated and sequenced to high, uniform coverage (average median depth of 734× with 99% of bases covered >100×), as described previously (8). Genomic alterations were determined for each patient sample. To maximize mutation detection sensitivity in heterogeneous

Table 1. Dose-escalation and dose-limiting toxicities

Dose level	Ipilimumab IV q 28 days x 4	Lenalidomide PO daily x 21 q 28 days until disease progression	Number of patients (patients evaluable for DLT)	DLT event
1	1.5 mg/kg	10 mg	4 (3)	
2	1.5 mg/kg	15 mg	11 (8)	G3 rash, G3 pancreatitis
3	3 mg/kg	15 mg	8 (6)	G3 rash
4	3 mg/kg	20 mg	5 (4)	
5	3 mg/kg	25 mg	8 (7)	G3 rash

specimens, we validated the test to detect base substitutions at a ≥5% mutant allele frequency (MAF) with ≥99% sensitivity and indels at a ≥10% MAF with ≥98% sensitivity, with a false discovery rate of <1% (8).Total mutational burden was defined as the number of somatic coding base substitutions and indel alterations minus known driver alterations per megabase (Mb) of genome examined adjusted for the tumor content. A TMB of ≥20 mutations/Mb was considered high; 6–19 mutations/Mb intermediate; and ≤ 5 mutations/Mb low.

Results

Patient characteristics

From May 2013 to May 2016, a total of 71 patients were screened. Of those, 36 met eligibility criteria, were financially cleared by insurance, and received at least one dose of treatment (Fig. 1). The 36 patients' clinical characteristics are shown in Table 2. Most patients treated were female ($n = 24$, 67%), white ($n = 22$, 61%), median age of 56 years (range, 19–75). The most frequently treated tumor types were Hodgkins lymphoma ($n = 7$, 19%), melanoma ($n = 5$, 14%), and leiomyosarcoma ($n = 4$, 11%). The median number of prior therapies was 3 (range, 0–9). A total of 3 (8%) patients received prior ipilimumab and 1 (3%) prior lenalidomide (Table 2).

Table 2. Patients characteristics ($N = 36$)

Patient characteristics	Number
Median age, years (range)	56 (19–75)
Gender, *N* (%)	
Male	12 (33)
Female	24 (67)
Ethnicity, *N* (%)	
White	22 (61)
African-American	5 (14)
Hispanic	4 (11)
Other	5 (14)
ECOG performance status, *N* (%)	
0	6 (17)
1	27 (75)
2	3 (8)
Prior therapies	
Median prior therapies, *N* (range)	3 (0–9)
<5 therapies, *N* (%)	25 (69)
≥ 5 therapies, *N* (%)	11 (31)
Prior ipilimumab, *N* (%)	3 (8)
Prior lenalidomide, *N* (%)	1 (3)
Prior allogenic stem cell transplant (%)	4 (11)
Diagnosis, *N* (%)	
Melanoma	5 (14)
Thyroid cancer	3 (8)
Adrenocortical cancer	2 (6)
Adenoid cystic cancer	2 (6)
Leiomyosarcoma	4 (11)
Hodgkin Lymphoma	7 (19)
Renal cancer	3 (8)
Other (cervical, colorectal, peritoneal, ovarian, triple-negative breast, squamous cell head and neck, chondrosarcoma, osteosarcoma, carcinosarcoma, and teratoma)	10 (28)

Toxicity

All 36 patients were evaluable for toxicity and 28 (78%) were evaluable for DLTs (patients had to complete 80% of planned dosing in cycle 1 or had a DLT). The MTD has not been reached and dose level 5 of intravenous ipilimumab 3 mg/kg on day 1 and oral lenalidomide 25 mg on days 1 through 21 of a 28-day cycle was determined to be the RP2D. Further dose escalation was not pursued because lenalidomide was given in the FDA-approved dose for monotherapy and ipilimumab was also given in the FDA-approved dose except for being given every 4 weeks instead of 3 weeks. DLTs included grade 3 erythematous rash (3 patients) and grade 3 pancreatitis (1 patient; Table 1). Overall, treatment related grade 3 or 4 toxicities included grade 3 rash (4 patients), grade 3 hypopituitarism (1 patient), grade 4 hypopituitarism (1 patient), grade 3 pancreatitis (1 patient), grade 3 pneumonitis (1 patient), grade 3 deep vein thrombosis (1 patient), grade 3 pulmonary embolism (1 patient), grade 3 anemia (5 patients), grade 3 thrombocytopenia (1 patient) and grade 3 transaminitis (1 patient; Table 3). In addition, we observed the following treatment related significant grade 2 toxicities: rash (2 patients), hypopituitarism (1 patient), pneumonitis (1 patient), and deep vein thrombosis (3 patients; Table 3). Although small numbers precluded formal statistical analysis the incidence of deep vein thrombosis/pulmonary embolism was between 7% and 20% (overall incidence 3/36, 8%) in patients on prophylactic low molecular heparin (1/5, 20%), prophylactic anti-aggregation therapy (2/16, 13%) and in patients on no prophylaxis (1/15, 7%).

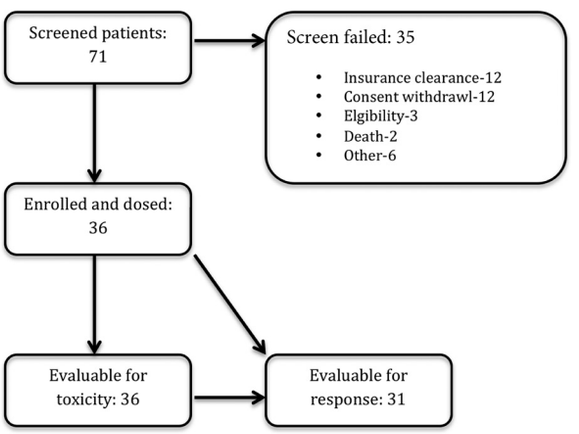

Figure 1.
Enrollment of patients with advanced cancer to the dose-escalation study with ipilimumab and lenalidomide.

Nine patients (25%) had dose interruption due to treatment-related adverse events (rash, $n = 5$) and 5 patients (14%) were dose reduced (lenalidomide) for treatment-related adverse events (rash, $n = 4$). Of interest of 7 patients with Hodgkin lymphoma, 4 had a history of allogeneic transplant without clinically relevant symptoms of graft versus host disease (GVHD). None of these 4 patients experienced any autoimmune side effects or reactivation of GVHD. In addition, a patient with anaplastic thyroid cancer and HIV infection on highly active retroviral therapy did not have any significant adverse events.

Efficacy

Of 36 patients, 33 (92%) had at least one restaging imaging (Fig. 2). Four patients did not have restaging scans because of DLT leading to treatment discontinuation ($n = 1$), clinical progression ($n = 2$), or death ($n = 1$). The best response per irRC was 1 (3%) PR in a patient with refractory Hodgkin lymphoma (prior therapies included ABVD, ICE with panobinostat, brentuximab, and

Table 3. Treatment-related toxicities (mild grade 1 toxicities are not depicted).

Toxicity	Grade 2	Grade 3	Grade 4
Anemia	1 (3)	5 (14)	0
Thrombocytopenia	0	1 (3)	0
Rash[a]	2 (6)	4 (11)	0
Hypopituitarism[b]	1 (3)	1 (3)	1 (3)
Pancreatitis	0	1 (3)	0
Pneumonitis	1 (3)	1 (3)	0
Deep vein thrombosis	3 (8)	1 (3)	0
Pulmonary embolism	0	1 (3)	0
Transaminitis	0	1 (3)	0

[a]Grade 1 rash was observed in 8 patients.
[b]Grade 1 hypopituitarism in 1 patient.

autologous stem cell transplant), which has lasted for 7.2+ months. In addition, 7 patients experienced tumor shrinkage less than a PR: Hodgkin lymphoma −44%, melanoma −33%, Hodgkin lymphoma −27%, teratoma −15%, thyroid carcinoma −14%, thyroid carcinoma −5%, and Hodgkin lymphoma −2% (Fig. 2). Total of 16 (44%) patients had SD, which lasted for at least 4 months in 6 (17%) of them (Hodgkin lymphoma, 4.6 months; teratoma, 28.5+ months; Hodgkin lymphoma, 5.5 months; melanoma, 4.0 months; ovarian cancer, 5.8 months; and leiomyosarcoma, 5 months, Fig. 2). At the time of analysis, 5 patients continued on therapy and 31 patients were discontinued because of disease progression ($n = 29$) or toxicity ($n = 2$).

Comprehensive genomic profiling

Among the 36 patients treated on protocol, 17 patients with diverse cancers (leiomyosarcoma, $n = 4$; renal cancer, $n = 3$; thyroid cancer, $n = 2$; other cancers, $n = 6$) available archival tissue had comprehensive genomic profiling to detect selected somatic molecular alterations and total mutation burden (TMB, mutations/Mb) using targeted next-generation sequencing Foundation One panel (Foundation Medicine) and results along with treatment outcomes are depicted in Table 4. A total of 13 patients had low TMB (≤5 mutations/Mb), 2 patients (including one with a PR) had intermediate TMB (6–19 mutations/Mb), 1 high TMB (≥20 mutations/Mb) and 1 patient had no result (Table 4). Small numbers precluded analysis of association between TMB and treatment outcomes.

Discussion

Our study demonstrated that the combination of 3 mg/kg of ipilimumab and 25 mg of lenalidomide was well tolerated in patients with advanced metastatic malignancies. The DLTs encountered include grade 3 skin rash ($n = 3$) and grade 3 pancreatitis ($n = 1$). Skin rash was the most frequent grade 3 treatment-related toxicity (11%). The rash presented as maculopapular in nature and generally appeared the second week of treatment on the trunk and extremities. In comparison, a phase III

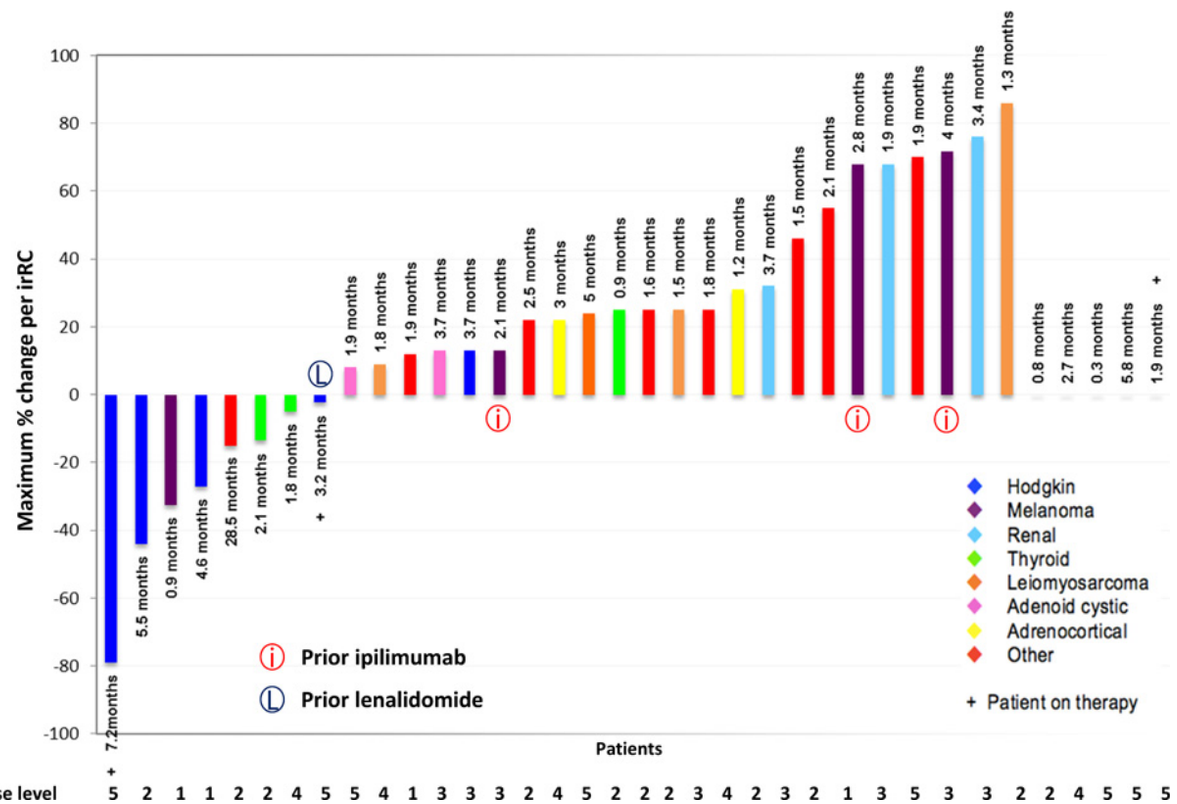

Figure 2.
Waterfall plots shows the best change in size of target lesions assessed using the immune-related response criteria (irRC). Of 36 patients (33 had at least one restaging scan and 31 had measurable disease), there was one partial response (PR) and 7 regressions less than PR. In addition, total of 16 patients had stable disease lasting for 4 months or longer. Time to treatment failure is depicted below or above bars indicating the change in target lesion (+ indicates ongoing therapy). Patients without measurable disease or restaging scan are depicted on the right of the axis.

Table 4. Comprehensive genomic profiling of archival tumor tissue for common genomic alterations and total mutation burden and outcomes

ID	Cancer type	Molecular alterations	Total mutation burden in mutation/Mb	irRC response %	Time to treatment failure in months
5	Anaplastic thyroid carcinoma	NF1 I1845fs*13, VHL E52*, CDKN2A/B loss	5	25	0.9
6	Hurthle cell thyroid carcinoma	DAXX C629fs*16, RB1 D68fs*37, TP53 R175H	3	−14	2.1
7	Immature teratoma	No abnormality	3	−15	28.5+
9	SCCHN	No abnormality	Not done	25	1.6
10	Leiomyosarcoma	PTEN loss, TP53 217V_218VinsVPYERPE	≤1	86	1.3
11	Renal cell carcinoma	BAP1 splice site 375+2T>C, PBRM1 F786fs*5	3	32	3.7
12	Chondrosarcoma	NOTCH2 C1400*, SETD2 K1486fs*3	≤1	22	2.5
13	Leiomyosarcoma	EGFR CNV, AURKB CNV eq, C17orf39 CNV eq, RB1 loss, TP53 loss	7	25	1.5
16	Uterine carcinosarcoma	TP53 K132R	5	25	1.8
19	Renal medullary carcinoma	SMARCB1 splice site 603_628+26del52, SETD2 G1690fs*15, SPTA1 splice site 2996+2T>A	5	76	3.4
20	Melanoma[a]	NF1 loss, GNAQ Q209P, NRAS Q61H sub, ATR splice site 4267_4267-1GG>AA, CKN2A/B, RB1 E50*, ARID2 R274*, ARID2 F1237fs*6, BCOR R810*	81	13	2.1
22	Renal cell carcinoma	MYC CNV, SF3B1 D781G	≤1	68	1.9
26	Adrenocortical carcinoma	No abnormality	5	31	1.2
27	Adrenocortical carcinoma	ERBB3 CNV EQ, FGFR4 CNV EQ, MAP2K2 CNV EQ, CCNE1 CNV	4	22	3.0
28	Leiomyosarcoma	TP53 C135Y, KDM6A Q679fs*12, RB1 loss, ATRX E492*	5	99	1.8
30	Hodgkin lymphoma	IGH-SOCS1 rearrangement	10	−79	7.2+
32	Leiomyosarcoma	RB1 L337fs*12, TP53 G266R	4	24	5.0

[a]Patient received prior ipilimumab.

study in which melanoma patients were treated with single-agent ipilimumab and a combination of ipilimumab with gp100 demonstrated the incidence of grade 3 skin rash to be 0.8% and 1.3%, respectively (1). The notably higher percentage can be attributed to rash being a feature of adding lenalidomide, which as a monotherapy is associated with grade 3 or 4 rash in up to 10% of patients (9). Pancreatitis was seen in a single subject (3%) and presented within 2 days of initial dose of ipilimumab. This was a rare occurrence as immune-related pancreatitis is seen in less than 1.5% patient receiving anti–CTLA-4 antibody treatment (10). This patient was taken off treatment within 10 days of first dose due to elevated amylase and lipase levels accompanied by fever (11, 12). We observed 2 episodes of grade 3 or 4 hypopituitarism among 36 patients treated (6%), which is somewhat higher than incidence of 1.5% observed with single-agent ipilimumab in the registration phase III study in melanoma (1). It remains unclear whether this was pure coincidence or related to the study combination or tumor types enrolled. Of interest, we did not observe any propensity to immune-mediated side effects or reactivation of GVHD in patients with a history of allogeneic stem cell transplant, which was consistent with anecdotal data published in the literature (13). Finally, only 2 patients were taken off therapy because of toxicity while remaining 29 patients discontinued the study due to disease progression.

Using bidimensional irRC, we observed one PR (−79%) in a patient with refractory Hodgkin lymphoma, which continues to be maintained for 7.2+ months. Tumor shrinkage less than PR was observed in additional 7 patients of whom 3 had refractory Hodgkin lymphoma. This is not unexpected because immunotherapy with PD1 antibodies demonstrated activity in refractory Hodgkin lymphoma (14, 15). In addition, there were 6 patients with SD for ≥4 months (4–28.5+ months). Our findings are consistent with published data suggesting that objective responses are infrequent; however, some patients can achieve durable disease control (1, 16, 17).

Our study has several limitations. First, we experienced unusually high number of screen failures ($n = 35$), most of them being related to problems with insurance clearance or consent withdrawal during the screening period. Second, our safety profile was better than anticipated and we finished all preplanned 5 dose levels without reaching an MTD; however, because we did not perform pharmacokinetic analysis it cannot be ruled out that ipilimumab and lenalidomide might negatively affect each other's exposure. Third, despite observing signals of activity in several patients heterogeneity of tumor types enrolled precludes any definitive conclusion and did not identify predictive factors for efficacy despite performing analysis of total mutation burden in subset of patients. Fourth, the study was designed in 2012

shortly before the first phase I study with anti-PD1 antibody nivolumab was published (18). PD1 antibodies demonstrated improved efficacy and better safety profile than ipilimumab and, therefore, might be better candidates for clinical testing of rational combinations (19, 20). Currently, the combination of ipilimumab and lenalidomide is being tested in post stem cell transplant setting in patients with advanced leukemia and lymphoma (NCT01919619).

Disclosure of Potential Conflicts of Interest

V. Subbiah reports receiving other commercial research support from Novartis, Bayer, LOXO, Nanocarrier, Abbvie, Pharmamar, Blueprint Medicines, and Genentech. D.S. Hong reports receiving a commercial research grant from Adaptimmune, Abbvie, Infinity, Kite, Kyowa, Lilly, LOXO, Mirati, Merck, Medimmune, Molecular Template, Novartis, Amgen, Pfizer, Takeda, AstraZeneca, Bayer, BMS, Daiichi-Sanko, Eisai, Genentech, and Ignyta, reports receiving other commercial research support from LOXO and MiRNA, has ownership interest (including patents) in Molecular Match and OncoResponse, and is a consultant/advisory board member for Baxter, Bayer, Guidepoint Global and Janssen. F. Janku reports receiving a commercial research grant from Novartis, BioMed Valley Discoveries, and Foundation Medicine and is a consultant/advisory board member for Foundation Medicine. No potential conflicts of interest were disclosed by the other authors.

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