A Phase 1b/2 Study of the Bruton Tyrosine Kinase Inhibitor Ibrutinib and the PD-L1 Inhibitor Durvalumab in Patients with Pretreated Solid Tumors

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Keywords

Ibrutinib · Durvalumab · Phase 1b/2 · Pancreatic cancer · Breast cancer · Non-small cell lung cancer

Abstract

Background: Ibrutinib, a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, is approved in the United States for the treatment of various B-cell malignancies. Preclinical data suggest synergistic antitumor activity of ibrutinib with programmed death-ligand 1 (PD-L1) inhibitors in solid tumors. This study evaluated ibrutinib plus durvalumab, a PD-L1-tar-

geting antibody, in patients with relapsed/refractory solid tumors. **Methods:** This open-label, multicenter, phase 1b/2 study enrolled previously treated patients with stage III/IV pancreatic adenocarcinoma, breast cancer, or non-small cell lung cancer (NSCLC). Phase 1b determined the recommended phase 2 dose (RP2D). In phase 2, patients were treated at the RP2D to evaluate the safety and antitumor activity of ibrutinib plus durvalumab. **Results:** The RP2D was identified as ibrutinib 560 mg p.o. daily and durvalumab 10 mg/kg i.v.

Trial registration: ClinicalTrials.gov, NCT02401048; registered on March 27, 2015.

every 2 weeks, with 122 patients treated at the RP2D. Median age was 61 years, and the majority of patients (94%) had stage IV disease. Overall response rates (complete or partial responses) were 2% for pancreatic cancer, 3% for breast cancer, and 0% for NSCLC. Median progression-free survival was 1.7, 1.7, and 2.0 months in the pancreatic cancer, breast cancer, and NSCLC cohorts, respectively. Median overall survival was 4.2, 4.2, and 7.9 months in the pancreatic cancer, breast cancer, and NSCLC cohorts, respectively. The safety profiles observed across tumor types were consistent with the known safety profiles for ibrutinib and durvalumab. Grade ≥ 3 adverse events in $\geq 5\%$ of all patients were hyponatremia (10%), dyspnea (7%), maculopapular rash (7%), pneumonia (7%), anemia (6%), and diarrhea (6%). **Conclusions:** The combination of ibrutinib 560 mg daily and durvalumab 10 mg/kg every 2 weeks had an acceptable safety profile. The antitumor activity of the ibrutinib-durvalumab combination was limited in our study population.

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Introduction

Ibrutinib, a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase (BTK), is indicated in the United States for the treatment of various B-cell malignancies and for the treatment of chronic graft-versus-host disease following the failure of one or more lines of systemic therapy [1]. Ibrutinib inhibits BTK activity by binding a cysteine residue (Cys⁴⁸¹) near the adenosine triphosphate-binding pocket of BTK [2]. Sequence analyses show that 10 kinases in the human genome, including the epidermal growth factor receptor (EGFR), human EGFR 2 (HER2/neu), human EGFR 4 (HER4/ErbB4), interleukin-2-inducible T-cell kinase (ITK), and Janus kinase 3, also have a cysteine residue at an analogous position [3]. Potential inhibition of these known oncogenic drivers by ibrutinib is part of the rationale to investigate its therapeutic role in solid tumors.

Consistent with these *in silico* findings, preclinical data show that ibrutinib inhibits EGFR, HER2, and human EGFR 3 in breast cancer cell lines [4] and both EGFR (L858R) and EGFR (T790M) in lung cancer cells [5]. Further, patient data show that ibrutinib inhibits ITK [6]. The inhibition of ITK, in particular, suggests that ibrutinib may also enhance the antitumor immune response given that ITK plays a key role in mediating the balance between Th1/Th2 T cells [6]. Recent preclinical data have shown that the combination of an antibody targeting programmed death-ligand 1 (PD-L1) and ibrutinib sup-

presses tumor growth in mouse models of lymphoma and in preclinical models of triple-negative breast cancer (TNBC) and colon cancer [7]. The enhanced therapeutic activity of PD-L1 blockade by ibrutinib was accompanied by enhanced antitumor T-cell immune responses [7]. Further, the disruption of BTK signaling itself may confer potential benefit by modifying the microenvironment of solid tumors that may improve their sensitivity to other drugs. For example, in pancreatic adenocarcinoma, BTK has been shown to play a role in mast cell degranulation [8] and to suppress B-cell and macrophage-mediated T-cell suppression [9].

Taken together, these data present a viable rationale to explore the safety, tolerability, and preliminary activity of combining ibrutinib with a PD-L1 inhibitor in patients with advanced solid tumors. Accordingly, we conducted a phase 1b/2 clinical study to explore the combination of ibrutinib and durvalumab, an anti-PD-L1 checkpoint immunotherapy, in previously treated patients with advanced pancreatic, breast, or lung cancers.

Materials and Methods

Study Design

This was a prospective, multicenter, open-label, phase 1b/2 study to determine the recommended phase 2 dose (RP2D) of ibrutinib plus durvalumab and to evaluate its safety and preliminary activity in patients with stage III/IV relapsed/refractory solid tumors.

The phase 1b component followed a 6 + 3 dose de-escalation design to evaluate dose-limiting toxicities (DLTs) and determine the RP2D. The DLT observation period included cycle 1 and laboratory assessments on day 1 of cycle 2. If DLTs occurred in 1 or fewer of 6 patients or 2 or fewer of 9 patients during the first 28 days, the dose level was considered safe to proceed with and was defined as the RP2D. The assessment of DLT followed the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) [10]. A DLT was defined as any grade ≥ 3 nonhematologic or grade 4 hematologic adverse event (AE) possibly related to either ibrutinib and/or durvalumab occurring during the DLT observation period.

For the phase 1b dose de-escalation portion of the study, the starting target dose was the approved monotherapy dose of each drug: ibrutinib 560 mg once daily p.o. plus durvalumab 10 mg/kg i.v. every 2 weeks. If this dose was not deemed safe and tolerable, sequential dose de-escalation to the following regimens were prespecified: ibrutinib 420 mg once daily p.o. plus durvalumab 10 mg/kg i.v. every 2 weeks; ibrutinib 560 mg once daily p.o. plus durvalumab 3 mg/kg i.v. every 2 weeks; and ibrutinib 420 mg once daily p.o. plus durvalumab 3 mg/kg i.v. every 2 weeks. Each treatment cycle was 28 days.

Following the determination of the RP2D, additional patients were enrolled and treated in phase 2 to further evaluate the efficacy of the regimen.

Patients

All patients were required to be aged ≥ 18 years; to have adequate renal, hematologic, and hepatic function; and to have an Eastern Cooperative Oncology Group performance status of 0 or 1. Eligible patients for the phase 1b component were required to have pathologic/radiologic confirmation of stage III/IV pancreatic adenocarcinoma, breast cancer (TNBC or HER2-positive by fluorescence in situ hybridization), or non-small cell lung cancer (NSCLC; adenocarcinoma or squamous cell carcinoma), with ≥ 1 disease lesions on computed tomography/magnetic resonance imaging scan that was measurable per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines. The phase 2 component also enrolled 3 cohorts of patients with stage III/IV disease who had pancreatic adenocarcinoma (total $n = 44$), breast cancer (TNBC and HER2-positive breast cancer at an approximate 2:1 ratio, total $n = 43$), or NSCLC (adenocarcinoma and squamous cell carcinoma at an approximate 2:1 ratio, total $n = 43$). For phase 2, provision of a fresh or archival tumor biopsy (formalin fixed and paraffin embedded within 3 months of study entry) was required for patients with breast cancer or NSCLC. For patients with pancreatic adenocarcinoma, a fresh biopsy was not mandatory, but the study limited the number of patients with pancreatic cancer and no baseline tumor sample to no more than 10 patients. Patients with pancreatic adenocarcinoma or NSCLC must have failed at ≥ 1 appropriate systemic first-line treatment regimen. Patients with EGFR-positive NSCLC must have received an EGFR inhibitor, and patients with anaplastic lymphoma kinase-positive NSCLC must have received an anaplastic lymphoma kinase inhibitor. Patients with breast cancer must have had ≥ 2 prior appropriate systemic regimens. Patients who had central nervous system involvement; patients who had received prior treatment with BTK inhibitors, immune checkpoint-targeted immunotherapy, or any anticancer treatment within 21 days of study day 1; or patients who had a mean corrected QT interval of ≥ 470 ms were excluded.

All patients were required to provide written informed consent for participation in this study as approved by the Institutional Review Board/Research Ethics Board/Independent Ethics Committee before any study-specific screening procedures were performed. Patients were also required to grant permission to use protected health information per the Health Insurance Portability and Accountability Act. In addition, patients were required to consent to and sign all approved amendments per the site guidelines during the course of the study. This study is registered at ClinicalTrials.gov (No. NCT02401048).

Study Objectives

The primary objective of phase 1b was to determine the RP2D and the preliminary safety and tolerability of ibrutinib plus durvalumab in patients with relapsed/refractory solid tumors. Secondary objectives in phase 1b included evaluation of overall response rate, disease control rate (defined as complete response, partial response, or stable disease) at week 20 (cycle 5), duration of response, and the pharmacokinetics and pharmacodynamics of the combination regimen.

The primary objective of phase 2 was to determine the overall response rate (complete response plus partial response) of the combination regimen. Secondary objectives in phase 2 included evaluation of disease control rate at week 20, duration of response, progression-free survival, overall survival, safety and tolerability,

and the pharmacokinetics and pharmacodynamics of the combination regimen.

Exploratory objectives included evaluation of immune cell subsets, chemokine/cytokine levels, non-BTK-related pharmacodynamics, and genes/proteins associated with sensitivity/resistance to ibrutinib or durvalumab.

Assessments and Analyses

AEs were graded based on CTCAE version 4.03 [10]. All AEs were documented from the time of signed consent until 30 days following the last dose for ibrutinib and/or 90 days after the last dose for durvalumab. Treatment-emergent AEs (TEAEs) were AEs meeting any of the following criteria: event was not present prior to the treatment-emergent period and occurred during the treatment-emergent period, onset date was missing and the end date was during the treatment-emergent period; event was considered related to study treatment by the investigator regardless of the start date of the event; or the event was present prior to the treatment-emergent period but worsened in severity during the treatment-emergent period, or was subsequently considered related to study treatment by the investigator. Tumor response and disease progression were based on tumor response assessment per the investigator using RECIST 1.1 guidelines for all 3 tumor types [11]. Tumor assessments were conducted at baseline, at the end of cycle 2, and every 3 cycles thereafter. Confirmatory scans for complete or partial responses were obtained ≥ 4 weeks after the initial documentation of a response. In the case of stable disease, tumor measurements must have met the criteria for stable disease at least once after study entry at a minimum interval of 6 weeks from study day 1.

Survival outcomes and duration of response were summarized using Kaplan-Meier estimates [12].

The following pharmacokinetic parameters were determined after the first or steady-state dose: peak concentration ($C_{\max}$), trough concentration (C_{trough}), time to peak concentration ($T_{\max}$), and area under the curve (AUC), as the data allowed. Accumulation to steady state (SS) was assessed as the ratios of $C_{\max,ss}$: $C_{\max}$ and $C_{\text{trough},ss}$: C_{trough} .

Pharmacodynamic assays for ibrutinib included occupancy assays for BTK in peripheral blood mononuclear cells that were performed as described previously [13].

Tumor biopsies were evaluated for PD-L1 expression using the Dako PD-L1 IHC 22C3 pharmDx kit (Cancer Genetics, Inc., Rutherford, NJ, USA). Tumors with $\geq 50\%$ of cells positive for PD-L1 were classified as PD-L1 high.

Statistical Considerations and Analysis of the Patient Cohorts

Patients enrolled and treated with the RP2D in phase 1b went on to continue treatment in phase 2. The safety population included all patients who had received ≥ 1 dose of study treatment ($N = 122$). The study was not powered for comparisons between treatment arms.

Results

Determination of RP2D

The initial dosing cohort in phase 1b tested the highest approved monotherapy dose of ibrutinib (560 mg once daily p.o.) and durvalumab (10 mg/kg i.v. every 2 weeks)

Table 1. Patient demographic and clinical characteristics at baseline

Characteristic	Pancreatic cancer (n = 49)	Breast cancer (n = 45)	NSCLC (n = 28)	Total (N = 122)
Age				
Median age, years (range)	61 (34–84)	55 (31–77)	65.5 (44–84)	60.5 (31–84)
Patients ≥65 years, n (%)	20 (41)	7 (16)	17 (61)	44 (36)
Female sex, n (%)	17 (35)	45 (100)	13 (46)	75 (61)
ECOG performance status, n (%)				
0	19 (39)	17 (38)	8 (29)	44 (36)
1	30 (61)	28 (62)	20 (71)	78 (64)
Cancer stage, n (%)				
III	1 (2)	3 (7)	3 (11)	7 (6)
IV	48 (98)	42 (93)	25 (89)	115 (94)
PD-L1 (programmed death ligand 1) expression, n (%) ^a				
High	0	0	5 (18)	5 (4)
Low/negative	42 (86)	36 (80)	16 (57)	94 (77)
Missing/not evaluated	7 (14)	9 (20)	7 (25)	23 (19)
Histology, n (%)				
Pancreatic adenocarcinoma	49 (100)	0	0	49 (40)
HER2-positive breast cancer	0	17 (38)	0	17 (14)
Triple-negative breast cancer	0	28 (62)	0	28 (23)
NSCLC (adenocarcinoma)	0	0	18 (64)	18 (15)
NSCLC (squamous cell carcinoma)	0	0	10 (36)	10 (8)
Median time (range), months				
From diagnosis	15 (5–99)	40 (4–169)	29 (6–69)	23 (4–169)
From disease progression following last therapy	1 (0.4–5)	1 (0.2–10)	1 (0.1–13)	1 (0.1–13)
History of prior therapies				
Median number of prior radiation/cancer therapies (range)	3 (1–20)	6 (2–19)	3 (1–11)	4 (1–20)
Radiation therapy, n (%)	12 (24)	37 (82)	19 (68)	68 (56)
Surgery or procedures, n (%)	38 (78)	41 (91)	20 (71)	99 (81)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; high PD-L1, ≥50% tumor cell membrane staining; low/negative PD-L1, <50% tumor cell membrane staining.

^a All available tumor samples were tested retrospectively for PD-L1 protein expression using the Dako PD-L1 IHC 22C3 pharmDx kit (Cancer Genetics, Inc., Rutherford, NJ, USA).

[1, 14]. Of the 7 patients who enrolled in the initial dosing cohort, 6 were evaluable for DLTs. Among these 6 patients, 1 patient experienced DLTs of grade 3 maculopapular rash and grade 3 rhabdomyolysis. The observation of DLTs in no more than 1 of 6 evaluable patients fulfilled the protocol-specified criteria for the RP2D for the combination. Accordingly, dose de-escalation was not needed, and all patients enrolled subsequently were treated at this dose. All patients enrolled in phase 1b were followed for response evaluation and overall survival.

Patients, Disposition, and Treatment Exposure

The study enrolled a total of 124 patients, including 50 patients with pancreatic adenocarcinoma, 45 patients with breast cancer, and 29 patients with NSCLC. One patient each with pancreatic adenocarcinoma and NSCLC,

respectively, did not receive study treatment and was excluded from these analyses. The overall study population was predominantly white (85%), was mostly female (61%), and had stage IV/metastatic disease at baseline (94%; Table 1). Progressive disease was the most common best response to prior therapy (44%) and the most common reason for discontinuation of prior therapy (75%). Patients had undergone a median of 3 prior lines of therapy.

By the time of data cutoff, all 122 patients had discontinued the study, and the most common reason for study discontinuation was death (68%; Table 2). The overall median time on ibrutinib treatment was 1.8 months: 1.8 months in the pancreatic adenocarcinoma cohort, 1.4 months in the breast cancer cohort, and 2.6 months in the NSCLC cohort. The overall median time on durvalumab

Table 2. Treatment and patient disposition

	Pancreatic cancer (<i>n</i> = 49)	Breast cancer (<i>n</i> = 45)	NSCLC (<i>n</i> = 28)	Total (<i>N</i> = 122)
Median duration of ibrutinib treatment, months (range) ^a	2.1 (0.2–15.0)	1.4 (0.3–27.6)	2.6 (0.2–23.4)	2 (0.2–27.6)
Patients with dose reduction of ibrutinib due to an AE, <i>n</i> (%)	4 (8)	4 (9)	3 (10)	11 (9)
Primary reason for discontinuing ibrutinib, <i>n</i> (%)				
PD	38 (76)	34 (76)	20 (69)	92 (74)
Death ^b	3 (6)	0	4 (14)	7 (6)
Clinical deterioration	4 (8)	2 (4)	0	6 (5)
Patient decision	0	4 (9)	0	4 (3)
Investigator decision	1 (2)	0	0	1 (1)
Study termination by sponsor	0	1 (2)	0	1 (1)
Median duration of durvalumab treatment, months (range)	1.7 (0–9.3)	1.3 (0–11.7)	2.6 (0–11.6)	1.4 (0–11.7)
Patients with durvalumab interruption due to an AE, <i>n</i> (%)	11 (22)	11 (24)	10 (36)	32 (26)
Patients completed durvalumab treatment, <i>n</i> (%)	0	1 (2)	3 (10)	4 (3)
Primary reason for discontinuing durvalumab, <i>n</i> (%)				
PD	36 (72)	34 (76)	19 (66)	89 (72)
Death ^c	3 (6)	0	3 (10)	6 (5)
Clinical deterioration	4 (8)	2 (4)	0	6 (5)
Patient decision	0	4 (9)	0	4 (3)
Investigator decision	1 (2)	0	0	1 (1)
Primary reason for study discontinuation, <i>n</i> (%)				
Death	34 (68)	33 (73)	17 (59)	84 (68)
Patient decision	8 (16)	6 (13)	0	14 (11)
Study termination	1 (2)	4 (9)	9 (31)	14 (11)
Lost to follow-up	1 (2)	1 (2)	0	2 (2)
Other	6 (12)	1 (2)	3 (10)	10 (8)

AE, adverse event; NSCLC, non–small cell lung cancer; PD, progressive disease.

^a Among treated patients. ^b Three patients died of PD (pancreatic cancer: *n* = 2; NSCLC: *n* = 1), 2 died of worsening disease not meeting the PD criteria (pancreatic cancer: *n* = 1; NSCLC: *n* = 1), and 2 died from AEs (NSCLC: *n* = 2). ^c Three patients died of PD (pancreatic cancer: *n* = 2; NSCLC: *n* = 1), 2 died of worsening disease not meeting the PD criteria (pancreatic cancer: *n* = 1; NSCLC: *n* = 1), and 1 died from AEs (NSCLC: *n* = 1).

treatment was 1.4 months: 1.4 months in the pancreatic adenocarcinoma cohort, 1.3 months in the breast cancer cohort, and 2.6 months in the NSCLC cohort. The most common reason for the discontinuation of either ibrutinib or durvalumab treatment was progressive disease (74 and 72%, respectively).

Safety

Across all tumor types, the most common TEAEs ($\geq 20\%$ of patients) were fatigue (43%), nausea (28%), decreased appetite (26%), hypomagnesemia (23%), anemia (21%), peripheral edema (21%), diarrhea (21%), and dyspnea (21%). There were no clinically meaningful differences in the safety profile across tumor types except for those that could be attributed to tumor type, tumor location, and prior therapies. The most common grade 3 or higher TEAEs ($\geq 5\%$ of patients) were hyponatremia

(10%), dyspnea (7%), maculopapular rash (7%), pneumonia (7%), anemia (6%), and diarrhea (6%; Table 3). Seventy-seven patients (63%) had serious AEs. The most common serious AE ($\geq 5\%$ of patients) was pneumonia (7%). Grade ≥ 3 immune-related TEAEs were reported in 11 patients (9%); the most frequently reported event was maculopapular rash (3%). Eleven patients (9%) had fatal AEs; this included 2 patients with pancreatic adenocarcinoma, 5 patients with breast cancer, and 4 patients with NSCLC. The most common system organ class resulting in death was infections and infestations in 8 patients (7%). Of these, 1 case of sepsis was reported as drug related by the investigator.

Efficacy

In the overall study population (*N* = 122), 2 patients had confirmed response. This included 1 of 43 patients

Fig. 1. Waterfall plot showing maximum percentage change in tumor size relative to baseline in individual patients' target lesions by tumor type (pancreatic adenocarcinoma, breast cancer, and non-small cell lung cancer, NSCLC). SPD, sum of the product of the diameters of the target lesions (mm²).

Table 3. Summary of treatment-emergent adverse events (TEAEs) in patients with pancreatic cancer (adenocarcinoma), breast cancer, and non-small cell lung cancer (NSCLC)

	Pancreatic cancer (n = 49)	Breast cancer (n = 45)	NSCLC (n = 28)	Total (N = 122)
Any grade TEAE	49 (100)	45 (100)	28 (100)	122 (100)
Any grade ≥3 TEAE	38 (78)	35 (78)	21 (75)	94 (77)
Grade ≥3 TEAEs in ≥2% of total patients				
Worsening of pancreatic carcinoma	14 (29)	0	0	14 (11)
Hyponatremia	5 (10)	5 (11)	2 (7)	12 (10)
Dyspnea	1 (2)	7 (16)	1 (4)	9 (7)
Maculopapular rash	0	3 (7)	5 (18)	8 (7)
Pneumonia	0	3 (7)	5 (18)	8 (7)
Anemia	3 (6)	3 (7)	1 (4)	7 (6)
Diarrhea	4 (8)	0	3 (11)	7 (6)
Worsening of breast cancer	0	6 (13)	0	6 (5)
Dehydration	3 (6)	1 (2)	2 (7)	6 (5)
Pyrexia	2 (4)	3 (7)	1 (4)	6 (5)
Pleural effusion	1 (2)	3 (7)	1 (4)	5 (4)
Pulmonary embolism	1 (2)	3 (7)	1 (4)	5 (4)
Vomiting	3 (6)	1 (2)	1 (4)	5 (4)
Abdominal pain	3 (6)	0	1 (4)	4 (3)
Hypokalemia	1 (2)	0	3 (11)	4 (3)

with pancreatic adenocarcinoma who had a partial response and 1 of 38 patients with breast cancer who had a complete response to treatment. The patient with pancreatic cancer was a 71-year-old male with unknown PD-L1

status who had received 5 chemotherapy-based treatments; the duration of response was 10.4 months. The patient with breast cancer was a 66-year-old female with unknown PD-L1 status who had received 2 chemothera-

Fig. 2. Kaplan-Meier estimates of survival by tumor type. **a** Progression-free survival defined as the duration of time from the first dose date of study treatment (ibrutinib or durvalumab) to the first documentation of disease progression or the date of death due to any cause, whichever occurs first. **b** Overall survival defined as the duration of time from the first dose date of study treatment (ibrutinib or durvalumab) to the date of death due to any cause. NSCLC, non-small cell lung cancer.

py-based treatments; the duration of response was 23.0 months. No patients in the NSCLC cohort had an objective response to ibrutinib plus durvalumab. Across all patients enrolled, in addition to the 2 responders, 6 additional patients achieved disease control at cycle 5; all 6

patients were from the NSCLC cohort, and had a response of stable disease (Fig. 1). Among these patients, only 1 patient with NSCLC had prior anti-PD-L1 therapy. Median progression-free survival was 1.8 months in the overall study population (95% CI: 1.7–1.8 months),

Table 4. Bruton's tyrosine kinase occupancy in peripheral blood lymphocytes (means $\pm$ standard error)

Cycle 1, day 1, hour 4	88.2% ($\pm 2.2\%$)
Cycle 1, day 2, pre-dose	85.9% ($\pm 2.4\%$)
Cycle 1, day 15, pre-dose	88.0% ($\pm 2.3\%$)
Cycle 1, day 15, hour 4	86.1% ($\pm 3.7\%$)
Cycle 2, day 1, pre-dose	84.4% ($\pm 3.2\%$)
Cycle 3, day 1, pre-dose	87.8% ($\pm 4.2\%$)
Cycle 4, day 1, pre-dose	90.9% ($\pm 3.9\%$)

1.7 months (95% CI: 1.6–1.8 months) for the pancreatic adenocarcinoma cohort, 1.7 months for the breast cancer cohort (95% CI: 1.5–1.8 months), and 2.0 months (95% CI: 1.7–4.0 months) for the NSCLC cohort (Fig. 2a).

Median overall survival was 6.0 months in the overall study population (95% CI: 3.9–6.9 months), 4.2 months (95% CI: 2.6–6.4 months) for the pancreatic adenocarcinoma cohort, 4.2 months (95% CI: 3.4–7.4 months) for the breast cancer cohort, and 7.9 months (95% CI: 5.4–17.6 months) for the NSCLC cohort (Fig. 2b).

Pharmacokinetics and Pharmacodynamics

Ibrutinib was rapidly absorbed after oral administration, with a median $T_{\max}$ of approximately 2 h. Mean steady-state ibrutinib $C_{\max}$ following once-daily dosing of 560 mg ibrutinib among patients with pancreatic, breast, and lung cancers were 258, 208, and 157 ng/mL, respectively. The corresponding exposures (AUC from time 0 to 24 h after dosing [$AUC_{0-24\text{ h}}$]) to mean steady-state ibrutinib were 2,727, 1,887, and 2,037 ng $\times$ h/mL, respectively. The estimated terminal half-life of both ibrutinib and its metabolite, PCI-45227, were similar (approximately 5–7 h). The mean accumulation ratios based on $AUC_{0-24\text{ h}}$ were 1.89 for ibrutinib and 1.34 for PCI-45227 after repeated daily dosing of ibrutinib in patients with pancreatic, breast, and lung cancers.

Following the initiation of ibrutinib dosing, the mean steady-state BTK occupancy ranged from 84 to 91% with a standard error $\leq 4\%$ (Table 4). Results from exploratory assays on ITK occupancy were not reported because the precision and dynamic range of the assay could not be established. Results of an exploratory analysis of EGFR occupancy were inconclusive.

PD-L1 Expression and Tumor Response

None of the patient tumor samples from the breast and pancreatic cancer cohorts qualified as PD-L1 high ($\geq 50\%$ of cells positive for PD-L1). In the NSCLC cohort, 5 of 24

patients had tumors that were PD-L1 high at baseline. Four of these patients had stable disease, and 1 had progressive disease as their best response to study treatment. Among the patients with low-PD-L1 or PD-L1-negative tumors evaluable for response, 6 of 36 patients with pancreatic cancer, 5 of 30 with breast cancer, and 5 of 13 with NSCLC had stable disease as their best response.

Discussion

This open-label phase 1b/2 study showed that the combination of 560 mg ibrutinib daily and 10 mg/kg durvalumab every 2 weeks was safe in patients with advanced solid tumors. This dose combination was, therefore, used as the RP2D in phase 2. Ongoing data reviews indicated that the combination of ibrutinib and durvalumab did not show meaningful activity in any of the tumor types studied, and, therefore, recruitment was stopped due to lack of efficacy.

The underlying rationale for the study of this combination regimen was based on preclinical findings of potential synergy between ibrutinib and durvalumab to inhibit tumor progression at multiple levels by upregulating the antitumor immune response, inhibiting both treatment resistance modulated by the tumor microenvironment and the activity of oncogenic driver kinases [4–8, 15]. However, this combination showed limited antitumor activity in patients with pancreatic, breast, or lung cancers, as evaluated in the current study.

The available pharmacokinetic data for ibrutinib do not suggest that this was because of a lack of bioavailability or subtherapeutic levels of ibrutinib given that the relevant parameters assessed in this study were comparable to previously established findings with ibrutinib monotherapy [1]. Further, the relatively modest interpatient variability observed in the pharmacokinetics of immunomodulatory monoclonal antibodies that target immune checkpoint pathways similarly rules out the possibility that the durvalumab levels achieved in this study were suboptimal [16]. Unfortunately, the results from exploratory assays on ITK occupancy were unavailable because the precision and dynamic range of the assay could not be established, and an exploratory analysis of EGFR occupancy was inconclusive. Therefore, we could not conclude whether there was clear target engagement with the combination.

The majority of patients enrolled in this study (94%) had stage IV disease at study entry and had failed a median of 3 prior lines of therapy. Molecular characteristics

that may contribute to response to immunotherapy, including tumor mutation burden and microsatellite instability [17], were not assessed in this study population; therefore, it is not clear if patient selection was optimal. Moreover, patients whose tumors were driven by a known oncogenic kinase must have received a therapeutic agent targeting that kinase and must have subsequently progressed or discontinued that treatment. Thus, many of the patients likely had tumors that underwent clonal expansion of a kinase inhibitor-resistant phenotype that would have eliminated, in part, oncogenic drivers potentially responsive to ibrutinib. In addition, the majority of the tumors evaluated had low PD-L1 expression, which is known to be a negative prognostic factor for outcomes to treatment with checkpoint inhibitors [18]. Taken together, these data indicate that combination treatment with ibrutinib and durvalumab is not a feasible option in this patient population.

Overall, the limited antitumor activity observed suggests that immune synergy between ibrutinib and durvalumab was not achieved in this heavily pretreated patient population. However, some questions remain given the low PD-L1 positivity of the tumor tissue from the patients enrolled in this study. Combined treatment with an inhibitor of oncogenic driver kinase(s) and an immune checkpoint therapy in an earlier line of treatment remains a potential option for future clinical research.

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Statement of Ethics

All patients were required to confirm their willingness to participate in this study as approved by the Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC) at each participating study site before any study-specific screening procedures were performed. Patients were also required to grant permission to use protected health information per the Health Insurance Portability and Accountability Act. In addition, patients were required to consent to and sign all approved amendments per the site IRB/REB/IEC guidelines during the course of the study.

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Author Contributions

D.H. and I.D. designed the study. D.H., D.R., M.V., J.J.L., J.C., A.B., T.J.G., P.M., J.B., M.G., A.M., H.W., and E.B. contributed to collecting the data. All authors had full access to the data, were involved in data interpretation, and vouch for accuracy of the data. All authors reviewed and revised the manuscript, provided final approval, and made the decision to submit the manuscript for publication. Medical writing support was provided by a professional medical writer and funded by the sponsor.

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