BMJ Oncology

First-in-human phase 1 study of the arginase inhibitor INCB001158 alone or combined with pembrolizumab in patients with advanced or metastatic solid tumours

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To cite: Naing A, Papadopoulos KP, Pishvaian MJ, *et al*. First-in-human phase 1 study of the arginase inhibitor INCB001158 alone or combined with pembrolizumab in patients with advanced or metastatic solid tumours. *BMJ Oncology* 2024;**3**:e000249. doi:10.1136/bmjonc-2023-000249

Received 07 November 2023
Accepted 03 April 2024

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ABSTRACT

Objective The arginase inhibitor INCB001158 was evaluated for safety (primary endpoint) in locally advanced or metastatic solid tumours; pharmacokinetics, pharmacodynamics and efficacy were also assessed.

Methods and analysis In this non-randomised, open-label, three-part phase 1 study, INCB001158 was orally administered two times per day as monotherapy or in combination with intravenous pembrolizumab 200 mg every 3 weeks. Dose expansion was conducted in tumour-type cohorts (with or without prior anti–PD-1/PD-L1 (programmed death protein 1/programmed death ligand 1) therapy).

Results A total of 107 patients received INCB001158 50–150 mg two times per day as monotherapy, and 153 patients, including 6 with moderate renal impairment, received INCB001158 50–100 mg two times per day combined with pembrolizumab. INCB001158 exposure was similar between groups (median, 56 days (monotherapy); 84 days (combination)). 49 patients (45.8%) on monotherapy and 76 (51.7%) on combination therapy experienced grade ≥3 treatment-emergent adverse events (AEs). The most common INCB001158-related AEs were fatigue (n=10/107 (9.3%)) and nausea (n=10/107 (9.3%)) with monotherapy and diarrhoea (n=24/147 (16.3%)) and fatigue (n=22/147 (15.0%)) with combination therapy. The highest response rate was seen in the anti–PD-1/PD-L1–naive combination therapy group with head/neck squamous cell carcinoma (overall response rate, 19.2%; 4/26 partial responses, 1/26 complete response). Consistent with arginase inhibition activity, plasma arginine dose-dependently increased. Arginase 1 expression in the tumour microenvironment did not correlate with response.

Conclusions INCB001158 was generally well tolerated. Response rates did not exceed background for given tumour types despite demonstrable pharmacodynamic activity. Overall, the limited antitumour activity of arginase inhibition observed suggests that the role of arginine depletion in cancer is multifaceted.

Trial registration number NCT02903914.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Arginase inhibitors have been shown to reverse immunosuppression in preclinical models and in vitro, though they carry the risk of disrupting urea cycle function in the liver.

WHAT THIS STUDY ADDS

⇒ INCB001158, a novel arginase 1/2 inhibitor, was generally well tolerated in adults with advanced or metastatic solid tumours, including those with moderate renal impairment. However, its antitumour efficacy was low.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study raises further questions on the role of arginine depletion in cancer and which patient populations may benefit from arginase inhibition.

INTRODUCTION

The introduction of therapies targeting immune checkpoint proteins, including programmed death protein 1 (PD-1)/programmed death ligand 1 (PD-L1), has transformed treatment for cancer.[1 2] However, many patients experience primary resistance to immune checkpoint inhibition or develop acquired resistance after initial response.[2 3] Combination therapies that target multiple immune evasion pathways within the tumour microenvironment (TME) may help overcome immune checkpoint inhibitor resistance and improve response and survival.

Arginase, an enzyme that hydrolyses arginine to ornithine and urea, is expressed by myeloid-derived suppressor cells (MDSCs), natural killer cells and neutrophils in the

tumour milieu and is found in the plasma from patients with various cancers.[4–6] MDSCs and the arginase they express are linked with inferior clinical outcomes.[3] MDSCs are highly prevalent in patients with cancer and correlate with distant metastasis; they have also been implicated in resistance to anti–PD-1 therapy, with higher levels of tumour-infiltrating MDSCs observed in patient-derived organoids from non-responders versus responders to anti–PD-1 therapy.[7 8] Arginase expression has been associated with poor prognosis in some tumours, including colorectal cancer (CRC) and squamous cell carcinoma of the head and neck (SCCHN).[9 10]

Arginase contributes to the immunosuppressive TME via arginine depletion, which impairs function and proliferation of effector T cells and natural killer cells.[11 12] Conversely, arginase knockout in macrophages diminished tumour growth,[13] and arginine supplementation or arginase inhibition improves antitumour T-cell responses and potentiates the effects of immunotherapy in murine tumour models.[14–17]

Given the immunosuppressive effect of arginase, arginase pharmacological inhibition can be a compelling strategy for cancer immunotherapy.[18] Because arginase participates in the urea cycle to dispose of toxic ammonia, a potential toxicity of concern for arginase inhibitors is disruption of the urea cycle in the liver and subsequent hyperammonaemia.[19] Detection of high orotic acid levels in urine is a sensitive indication of urea cycle disruption: when arginase fails its role in the urea cycle, a metabolic diversion into the pyrimidine synthesis pathway results in buildup of the pyrimidine precursor orotic acid.[20]

INCB001158 is an orally bioavailable small-molecule inhibitor of both arginase isoforms (Arg1/Arg2).[6] INCB001158 reversed T-cell immunosuppression in vitro and reduced tumour growth in multiple syngeneic mouse models.[6] Furthermore, INCB001158 in combination with an anti–PD-L1 antibody resulted in greater preclinical tumour inhibition than either agent alone, providing rationale for clinical evaluation of arginase inhibition combined with immune checkpoint therapy.[6]

Here, we describe the safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of INCB001158 alone or combined with pembrolizumab in patients with advanced or metastatic solid tumours (NCT02903914).

METHODS

Study design

This was a three-part, open-label, non-randomised, phase 1 study (figure 1). In Part 1a, a standard 3+3 dose-escalation design was used to evaluate INCB001158 monotherapy. INCB001158 two times per day was tested in 8 dose levels from 50 mg to 1000 mg. Part 1a also evaluated the food effects of INCB001158 in fed state (cycle 2 day 8) versus fasted state (cycle 1 day 15). In Part 1b, INCB001158 doses that had already been demonstrated to be safe as monotherapy were tested in combination with pembrolizumab in a standard 3+3 dose-escalation design. In Part 1c (USA only), INCB001158 plus pembrolizumab was evaluated in patients with moderate renal impairment (creatinine clearance (CrCl) 30–49 mL/min). The 50 mg two times per day dose was predicted to achieve safe INCB001158 plasma levels in patients with moderately impaired renal function based on PK modelling because area under the concentration–time curve/minimum observed plasma concentration (AUC/C_{min}) values associated with this dose were predicted to fall within the range corresponding to the established recommended phase 2 dose (RP2D) of 100 mg two times per day. Part 2 consisted of INCB001158 monotherapy dose-expansion cohorts, including non-small cell lung cancer (NSCLC; 2a); CRC (2b); or SCCHN, gastric cancer, gastric/gastro-oesophageal junction (GOJ) cancer, renal cell carcinoma, urothelial carcinoma (UC) or melanoma (all 2c). Part 2d (USA only) was a one-way crossover PK study that compared capsule versus tablet formulations of INCB001158. In Part 3, INCB001158 plus pembrolizumab was evaluated at RP2D in patients with NSCLC (3a), melanoma (3b), UC (3c) or microsatellite instability-high CRC (3d) who had progressive or stable disease on anti–PD-1/PD-L1 therapy, or those with anti–PD-1/PD-L1–naive microsatellite stable (MSS) CRC (3e), GOJ cancer (3f), SCCHN (3g) or mesothelioma (3h; figure 1). Tumour types in Parts 2 and 3 were selected based on a higher likelihood of arginase-1–expressing MDSCs or neutrophils being present in the TME.[8 21 22] All NSCLC tumours were *EGFR/ALK*-mutation negative because of a better chance of response to anti–PD-1/PD-L1 therapy.[23]

Patients

The study enrolled patients aged ≥18 years with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function per protocol-defined laboratory values and resolution of treatment-related toxicities from previous cancer therapies.

Additional key eligibility criteria for Parts 1a/2 included histologically or cytologically proven diagnosis of locally advanced or metastatic solid tumours that progressed on standard therapy (see the Study design section and figure 1 for specific requirements for tumour types). For Part 1b, patients with histologically or cytologically proven diagnosis of the tumour types evaluated in Part 3 dose expansion were included. Part 3 comprised patients with unresectable or metastatic tumour types (see the Study design section and figure 1) who progressed on standard therapy. The same criteria for any Part 3 cohort plus CrCl 30–49 mL/min applied to the Part 1c cohort. Exclusion criteria are listed in online supplemental table S1.

Treatment

INCB001158 was administered as an oral tablet or capsule (25 or 100 mg per tablet/capsule) two times per day. In the monotherapy cohorts (Parts 1a/2), INCB001158

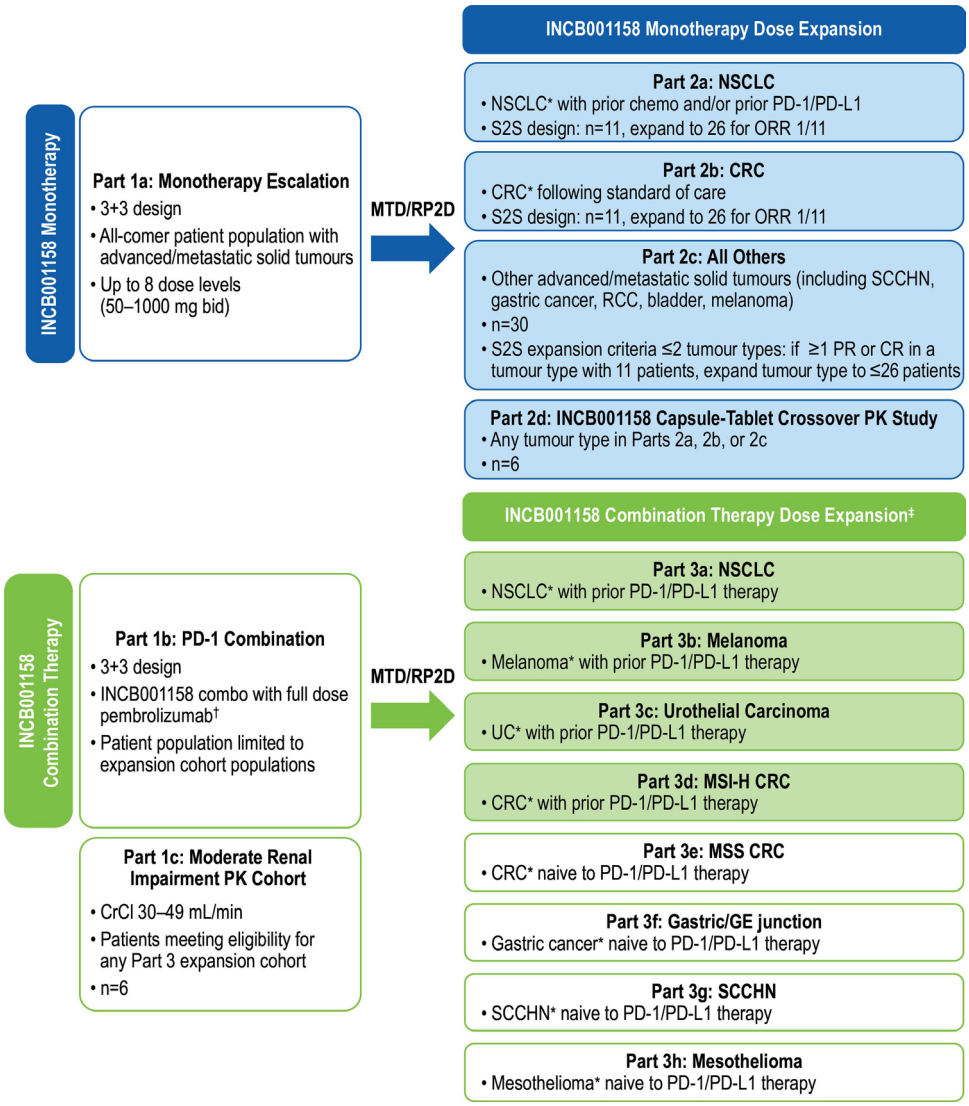

Figure 1 Study design. *Advanced or metastatic cancer. †Full dose pembrolizumab is 200 mg intravenously every 3 weeks. ‡Shaded boxes in combination therapy dose expansion indicate add-on to prior PD-1/PD-L1 therapy with progression or stable disease more than 6 months on pembrolizumab. bid, two times per day; CR, complete response; CRC, colorectal cancer; CrCl, creatinine clearance; GE, gastro-oesophageal; MSI-H, microsatellite instability high; MSS, microsatellite stable; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1; PK, pharmacokinetics; PR, partial response; RCC, renal cell carcinoma; RP2D, recommended phase 2 dose; S2S, Simon 2-stage; SCCHN, squamous cell carcinoma of the head and neck; UC, urothelial carcinoma.

was administered on days 1–28 of each 28-day cycle. In the pembrolizumab combination therapy cohorts (Parts 1b/1c/3), INCB001158 was administered on days 1–21 of each 21-day cycle. Pembrolizumab was administered as a 200 mg intravenous infusion for 30 min on day 1 of each 21-day treatment cycle.

Endpoints and assessments

The primary endpoint was safety, assessed by adverse events (AEs) and changes in laboratory values, vital signs and physical examinations. Common Terminology Criteria for Adverse Events version 4.03, which identifies malignant neoplasm progression as an AE, was used to identify and classify toxicities. Dose-limiting toxicity (DLT) was defined as follows: grade 3–4 non-haematological toxicities meeting certain criteria regarding AE resolution; neutropenia/anaemia/thrombocytopenia meeting certain time/cell count thresholds, or any other grade 3–4 haematological toxicity; clear evidence of urea cycle inhibition (eg, high orotic acid values); AUC_{0-12h} maximum exposure thresholds >100 µg.h/mL; inability to receive ≥75% of INCB001158 and/or 2 doses of pembrolizumab during the DLT evaluation period; any AE deemed treatment-limiting per principal investigator/medical monitor judgement.

Secondary endpoints were the selection of the INCB001158 RP2Ds (monotherapy or combination therapy) based on evaluation of AEs, PK, PD and clinical activity; objective response rate (ORR), best overall response (BOR), duration of response (DOR) and progression-free survival (PFS) per RECIST v1.1

(confirmed responses unless stated otherwise); maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), AUC, terminal-phase disposition half-life ($t_{1/2}$), apparent oral dose clearance and apparent oral dose volume of distribution. PK plasma samples were collected before and after dose distribution on cycle 1 days 1 and 15 for all patients except those in Part 1a and Part 1c, who had additional PK sampling on cycle 1 day 1 at 0.5, 1, 2, 4, 6, 8 and 12 hours after the dose. INCB001158 PD activity was determined by measuring plasma arginine concentration using liquid chromatography with tandem mass spectrometry (Arup Labs, Salt Lake City, Utah, USA). Translational analyses included plasma proteomic analysis (multiplex proximity extension assay, Olink Proteomics, Watertown, Massachusetts, USA); $CD8^+$ T-cell infiltration into tumours (immunohistochemistry; SP16 antibody clone to detect CD8) in paired pretreatment and on-treatment (cycle 2 day 1) tumour biopsy samples; tumour tissue mRNA profiling (next-generation sequencing–based HTG EdgeSeq Precision Immuno-Oncology Panel; HTG Molecular Diagnostics, Tucson, Arizona, USA). The HTG EdgeSeq panel profiled 1392 genes; to focus on genes indicating an inflamed TME, a composite tumour inflammation score was derived using mean mRNA expression data from the following 14 genes: TIGIT, CD27, PDCD1LG2, LAG3, CD274, CD276, CXCR6, CMKLR1, CCL5, PSMB10, CXCL9, HLA-DQA1, STAT1 and HLA-E.[24]

Statistical analyses

The full analysis set comprised all patients who received ≥1 dose of INCB001158 or pembrolizumab and was used to evaluate demographics, baseline characteristics, disposition and PFS. The PK- and PD-evaluable populations comprised all patients who received ≥1 dose of INCB001158 and had ≥1 postbaseline PK or PD sample. The safety-evaluable population was defined as patients who received ≥1 dose of INCB001158 or pembrolizumab. To be evaluable for DLTs, patients were required to receive ≥75% of the planned INCB001158 doses and both cycle 1 pembrolizumab doses (Parts 1b/3); patients who received <75% of planned treatment for any reason other than a DLT (ie, drug-related AEs) were considered non-evaluable for DLTs and replaced. The response-evaluable population (BOR/ORR, DOR) comprised all patients who received ≥1 dose of INCB001158 or pembrolizumab, completed ≥1 baseline scan and had ≥1 postbaseline tumour scan or had discontinued treatment for any reason except unrelated toxicity or death, or withdrawal of consent. Patients enrolled in the expansion cohorts who did not meet response-evaluable requirements were considered non-evaluable for response and replaced.

Sample size for dose-escalation cohorts was determined based on the goal of determining an INCB001158 dose for which the DLT rate was <33%. For the expansion cohorts in Parts 2 and 3, a Simon 2-stage (S2S) design was used; the null hypothesis was that the response rate was equal to the background ORR for each tumour type (online supplemental table S2).

Data were analysed with SAS (V.9 or later; SAS Institute, Cary, North Carolina, USA) and summarised using descriptive statistics (mean, SD, median and range for continuous variables; numbers and patient percentages for categorical values). Time-to-event variables were summarised by Kaplan-Meier plots, medians and ranges.

Patient and public involvement

The design, conduct, reporting, or dissemination plans were not coproduced with either patients or the public.

RESULTS

Patients

As of the data cut-off on 12 February 2021, 107 patients received INCB001158 monotherapy in Parts 1a/2 and 147 patients in Parts 1b/3, plus 6 additional patients in Part 1c (moderate renal impairment) received INCB001158 plus pembrolizumab combination therapy. In the time since the last data cut, all patients in the study had discontinued treatment without change to the conclusions.

In Parts 1a/2, patients (n=107) received INCB001158 monotherapy 50 mg (n=8), 75 mg (n=7), 100 mg (n=85) or 150 mg two times per day (n=7) (online supplemental figure S1A). All patients discontinued INCB001158 monotherapy; the majority discontinued for progressive disease (69.2%), symptomatic deterioration (10.3%), withdrawal by patient (10.3%) and AEs (6.5%). The median (range) age was 64.0 (39–87) years, 54 patients (50.5%) were female, and 88 (82.2%) were white/Caucasian (online supplemental table S3). The most common tumour types were CRC (34.6%), NSCLC (14.0%) and melanoma (12.1%); median (range) time since diagnosis was 3.4 (0.6–29.2) years, and most patients (72.9%) had a baseline ECOG performance status of 1. In this heavily pretreated group, all but 1 patient received prior systemic therapy; 37.4% received 2 prior therapies and 52.3% received ≥3 prior treatments.

In INCB001158 plus pembrolizumab combination Parts 1b/3, patients (n=147) received INCB001158 50 mg (n=10), 75 mg (n=14) and 100 mg (n=123) two times per day. Most patients received the 100 mg two times per day dose level (n=123/147; online supplemental figure S1B), and 141 patients (95.9%) had discontinued INCB001158 treatment, most commonly due to progressive disease (72.8%), symptomatic deterioration (9.5%) and AEs (7.5%). All patients who discontinued INCB001158 also discontinued pembrolizumab. The median (range) age was 62.0 (32–92) years, 95 patients (64.6%) were male, and 131 (89.1%) were white/Caucasian (online supplemental table S3). The most common tumour types were CRC (34.7%), SCCHN (18.4%; 8/35 were positive for human papillomavirus) and NSCLC (11.6%); median (range) time since diagnosis was 2.3 (0.2–20.9) years, and 62.6% of patients had a baseline ECOG performance status of 1. All patients received prior systemic anticancer

therapy; 44.9% received 2 prior therapies, and 39.5% received ≥3 prior therapies.

Among the six patients with moderate renal impairment (Part 1c) who received INCB001158 plus pembrolizumab, five (83.3%) discontinued INCB001158 (progressive disease, 66.7%; AEs, 16.7%). The median (range) age was 76.0 (62–82) years, and the most common diagnoses were SCCHN and UC (n=2 each; online supplemental table S3). Median (range) time since diagnosis was 2.6 (1.1–11.1) years, one-half of patients had a baseline ECOG performance status of 1, and all received either 2 (n=2) or ≥3 (n=4) prior systemic therapies.

Selection of RP2D

The 100 mg two times per day dose versus the 150 mg two times per day dose was selected as the INCB001158 RP2D in both monotherapy and in combination with pembrolizumab based on safety, tolerability, PK, PD and least-pronounced orotic acid elevations in Part 1a.

Safety

The median (range) duration of INCB001158 monotherapy (Parts 1a/2) exposure was 56.0 (7–476) days, and the average daily dose was 198.2 (92.9–300.0) mg/d. Most treatment-emergent AEs (TEAEs) (54.2%) were grade 1/2 in severity (table 1). Serious TEAEs occurred in 36 patients (33.6%); abdominal pain (5.6%), malignant neoplasm progression (4.7%), back pain, cellulitis and small-intestinal obstruction (2.8% each) were the only serious TEAEs reported in >2 patients. One DLT was reported with INCB001158 150 mg two times per day (treatment-related grade 2 malaise). INCB001158-related TEAEs were most commonly fatigue and nausea (9.3% each; online supplemental table S4). Only one patient had a serious INCB001158-related TEAE (grade 3 adrenal haemorrhage that recovered/resolved). TEAEs led to INCB001158 dose interruptions and discontinuations in 33 (30.8%) and 8 (7.5%) patients, respectively; no TEAE led to dose reduction. One patient (0.9%) experienced an immune-related TEAE of colitis (table 1), which led to INCB001158 discontinuation. 10 patients (9.3%) had fatal TEAEs, none of which were considered related to INCB001158; only malignant neoplasm progression (n=5) was reported in >1 patient.

For patients who received combination therapy in Parts 1b/3, the median (range) duration of INCB001158 exposure was 84.0 (7–933) days, and the average daily dose was 197.6 (71.4–200.0) mg/d. Grade ≥3 TEAEs occurred in 76 patients (51.7%; table 1). Serious TEAEs occurred in 56 patients (38.1%), most commonly malignant neoplasm progression (12.9%) and fatigue, nausea or vomiting (3.4% each). One patient in the INCB001158 75 mg two times per day combination group reported a DLT of grade 3 pneumonitis that led to treatment discontinuation. INCB001158-related TEAEs were most commonly diarrhoea (16.3%) and fatigue (15.0%; online supplemental table S4). TEAEs led to INCB001158 dose interruptions, reductions and discontinuations in 59 (40.1%), 4 (2.7%) and 12 (8.2%) patients, respectively. 24 patients (16.3%) had fatal TEAEs, none of which were INCB001158-related and 19 were malignant neoplasm progression. The safety profile for INCB001158 50 mg two times per day combined with pembrolizumab in Part 1c (moderate renal impairment) did not indicate any clinically meaningful difference from that for INCB001158 100 mg two times per day combination therapy in patients with normal renal function (data on file).

Urea cycle inhibition was monitored via orotic acid levels. In the INCB001158 monotherapy cohort, four patients had urinary orotic acid levels >10× the upper limit of normal; all were asymptomatic without significant changes from baseline in plasma ammonia or blood urea nitrogen; those with subsequent orotic acid levels measured showed results returned to normal. No patients receiving INCB001158 plus pembrolizumab combination exhibited excessive urea cycle inhibition.

Antitumour activity

No patient in the monotherapy cohort had an objective response during dose escalation (Part 1a; n=25), and five patients (20.0%) had BOR of stable disease. During dose expansion with INCB001158 100 mg two times per day (Part 2; n=73), one patient with well-differentiated urothelial cancer (1.4%) had a confirmed partial response (table 2). The median (95% CI) PFS was 1.8 (1.8–1.9) months in the dose-escalation cohort (Part 1a) and 1.9 (1.8–2.1) months in the dose-expansion cohorts (Part 2). Cohort 2b (CRC) included one patient with MSS-CRC positive for *NRAS* and *ARAF* mutations who had tumour reduction of ≥30% from baseline (online supplemental figure S2) and an unconfirmed response, making it the only monotherapy cohort to meet the S2S design criteria to expand to Stage 2; however, there were no additional responders at the end of Stage 2.

In combination therapy dose escalation (Part 1b; n=33), two patients (6.1%) had confirmed objective responses (partial response; n=1 each in MSS-CRC (50 mg two times per day) and melanoma (75 mg two times per day)). For patients receiving INCB001158 100 mg two times per day during dose expansion (Parts 1c and 3; n=118), ORR was 10.2% (95% CI, 5.4 to 17.1), including two complete responses (CR; 1.7%) in gastric and SCCHN tumours (n=1 each; table 2). Cohorts 3g (SCCHN; n=6) and 3e (MSS-CRC; n=4; online supplemental figure S3) each included >3 patients with ≥30% tumour reduction. The highest response rate during dose expansion was observed among the 26 patients with SCCHN and no prior anti–PD-1/PD-L1 therapy (ORR, 19.2%; CR, 3.8%; online supplemental table S5). Cohorts 3e and 3g (MSS-CRC and SCCHN, respectively) met the S2S design criteria to expand to Stage 2; however, at the end of Stage 2, the response rates were below the threshold for rejecting the null hypothesis. The median (95% CI) PFS rates were 2.1 (2.0 to 2.3) months for Cohort 3e and 4.4 (2.1 to 6.2) months for Cohort 3g (table 2).

Pharmacokinetics

Administered as monotherapy (Parts 1a/2), INCB001158 was absorbed with a median t_{max} of 3.9 hours after both single-dose (cycle 1 day 1) and multiple-

Table 1 Most common any-grade, grade ≥3 and irTEAEs in patients receiving INCB001158 therapy†‡§

	INCB001158 monotherapy					INCB001158+pembrolizumab combination therapy*			
	Parts 1a and 2					Parts 1b and 3			
TEAE	50 mg two times per day (n=8)	75 mg two times per day (n=7)	100 mg two times per day (n=85)	150 mg two times per day (n=7)	Total (N=107)	50 mg two times per day (n=10)	75 mg two times per day (n=14)	100 mg two times per day (n=123)	Total (N=147)
Any TEAE,† n (%)	7 (87.5)	7 (100.0)	81 (95.3)	7 (100.0)	102 (95.3)	10 (100.0)	13 (92.9)	123 (100.0)	146 (99.3)
Fatigue	1 (12.5)	3 (42.9)	23 (27.1)	3 (42.9)	30 (28.0)	5 (50.0)	3 (21.4)	33 (26.8)	41 (27.9)
Nausea	2 (25.0)	3 (42.9)	18 (21.2)	1 (14.3)	24 (22.4)	3 (30.0)	0	27 (22.0)	30 (20.4)
Constipation	2 (25.0)	1 (14.3)	18 (21.2)	2 (28.6)	23 (21.5)	0	1 (7.1)	30 (24.4)	31 (21.1)
Decreased appetite	0	2 (28.6)	17 (20.0)	2 (28.6)	21 (19.6)	3 (30.0)	2 (14.3)	25 (20.3)	30 (20.4)
Abdominal pain	2 (25.0)	0	15 (17.6)	1 (14.3)	18 (16.8)	2 (20.0)	0	7 (5.7)	9 (6.1)
Anaemia	3 (37.5)	3 (42.9)	11 (12.9)	0	17 (15.9)	1 (10.0)	1 (7.1)	23 (18.7)	25 (17.0)
Oedema peripheral	2 (25.0)	0	13 (15.3)	1 (14.3)	16 (15.0)	1 (10.0)	3 (21.4)	9 (7.3)	13 (8.8)
Vomiting	2 (25.0)	3 (42.9)	9 (10.6)	0	14 (13.1)	2 (20.0)	0	23 (18.7)	25 (17.0)
AST increased	1 (12.5)	0	8 (9.4)	1 (14.3)	10 (9.3)	1 (10.0)	3 (21.4)	23 (18.7)	27 (18.4)
Hypoalbuminaemia	0	0	6 (7.1)	1 (14.3)	7 (6.5)	0	2 (14.3)	22 (17.9)	24 (16.3)
Hyponatraemia	0	1 (14.3)	5 (5.9)	1 (14.3)	7 (6.5)	0	4 (28.6)	28 (22.8)	32 (21.8)
Diarrhoea	0	0	5 (5.9)	1 (14.3)	6 (5.6)	4 (40.0)	2 (14.3)	33 (26.8)	39 (26.5)
ALT increased	0	0	4 (4.7)	1 (14.3)	5 (4.7)	1 (10.0)	2 (14.3)	21 (17.1)	24 (16.3)
Any grade ≥3 TEAE,‡ n (%)	6 (75.0)	2 (28.6)	40 (47.1)	1 (14.3)	49 (45.8)	5 (50.0)	6 (42.9)	65 (52.8)	76 (51.7)
Abdominal pain	1 (12.5)	0	5 (5.9)	0	6 (5.6)	0	0	4 (3.3)	4 (2.7)
Anaemia	1 (12.5)	1 (14.3)	4 (4.7)	0	6 (5.6)	0	0	4 (3.3)	4 (2.7)
Fatigue	0	0	6 (7.1)	0	6 (5.6)	1 (10.0)	0	7 (5.7)	8 (5.4)
Malignant neoplasm progression	0	0	5 (5.9)	0	5 (4.7)	0	3 (21.4)	16 (13.0)	19 (12.9)
Hyponatraemia	0	0	2 (2.4)	1 (14.3)	3 (2.8)	0	3 (21.4)	8 (6.5)	11 (7.5)
Any irTEAE,§ n (%)	0	0	1 (1.2)	0	1 (0.9)	0	2 (14.3)	21 (17.1)	23 (15.6)
Colitis	0	0	1 (1.2)¶	0	1 (0.9)	0	0	5 (4.1)	5 (3.4)
Diarrhoea	–	–	–	–	–	0	0	7 (5.7)	7 (4.8)
Pneumonitis	–	–	–	–	–	0	1 (7.1)	4 (3.3)	5 (3.4)
Rash maculopapular	–	–	–	–	–	0	0	3 (2.4)	3 (2.0)
Hypothyroidism	–	–	–	–	–	0	0	2 (1.6)	2 (1.4)

Continued

Table 1 Continued

TEAE	INCB001158 monotherapy						INCB001158+pembrolizumab combination therapy*			
	Parts 1a and 2						Parts 1b and 3			
	50 mg two times per day (n=8)	75 mg two times per day (n=7)	100 mg two times per day (n=85)	150 mg two times per day (n=7)	Total (N=107)		50 mg two times per day (n=10)	75 mg two times per day (n=14)	100 mg two times per day (n=123)	Total (N=147)
Fever	–	–	–	–	–		0	0	2 (1.6)	2 (1.4)
Rash	–	–	–	–	–		0	0	2 (1.6)	2 (1.4)

*Dose levels listed are for INCB001158; pembrolizumab 200 mg every 3 weeks was administered intravenously.
†TEAEs occurring in ≥15% of total patients in monotherapy or combination therapy cohorts are shown.
‡Grade ≥3 TEAEs occurring in >5% of total patients in monotherapy or combination therapy are shown.
§All irTEAEs are shown for monotherapy cohort; for combination therapy cohort, 17/23 patients experienced irTEAEs that were determined as related to INCB001158 treatment, including 5/7 patients experiencing diarrhoea, 2/5 patients experiencing colitis, 3/5 patients experiencing pneumonitis, 3/3 patients experiencing rash maculopapular, 0/2 patients experiencing hypothyroidism, 2/2 patients experiencing fever and 2/2 patients experiencing rash.
¶This irTEAE was determined to be related to INCB001158 treatment.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; irTEAE, immune-related treatment-emergent adverse event; TEAE, treatment-emergent adverse event.

dose (cycle 1 day 15, fasted conditions) administration; elimination after multiple doses was monophasic (geometric mean $t_{1/2}$ of 5.9 hours (range, 5.2–6.8 hours); online supplemental figure S4 and table 3). INCB001158 plasma exposure (C_{max}, AUC) increased approximately dose proportionally after multiple oral administrations. Steady state was achieved at <1 week of therapy, as observed from predose PK samples (cycle 1 days 1, 8, 15, 22; cycles 2–4).

When combined with pembrolizumab, INCB001158 plasma exposures were similar to those of monotherapy: from cycle 1 day 8 to cycle 4 day 1, the geometric mean predose concentrations of INCB001158 on any given clinic visit ranged from 571 ng/mL to 893 ng/mL for monotherapy and 561 to 794 ng/mL for combination therapy.

In the six patients with moderate renal impairment, the absorption of INCB001158 after the first cycle 1 day 1 dose (reduced 50 mg dose combined with pembrolizumab) was prolonged compared with patients with normal renal function (median t_{max} of 5.9 vs 3.9 hours, respectively). C_{max} and $AUC_{0–8h}$ of INCB001158 after multiple-dose 50 mg two times per day were in the range of those after multiple-dose 100 mg two times per day in patients with normal renal function.

Pharmacodynamics and translational analyses

Plasma arginine levels increased with both monotherapy and combination therapy from baseline to cycle 1 day 15 across all doses (figure 2), consistent with the mechanism of action of INCB001158. Mean on-treatment arginine concentrations appeared to increase with dose, but mean cycle 1 day 15 arginine concentrations were similar across doses (online supplemental figure S5).

Treatment-induced gene expression changes were used to further evaluate PD activity. Plasma protein expression was measured from blood samples (cycle 1 day 1 (baseline), cycle 1 day 15 and cycle 2 day 1). Tumorous mRNA expression was profiled from tumour samples (≤3 months preceding cycle 1 day 1 (before treatment), <1 week of cycle 2 day 1 (on treatment)). Minimal changes were observed after INCB001158 monotherapy: only nine plasma proteins were differentially expressed (false discovery rate p<0.05; fold change >1.2), and no differential mRNA expression was observed (online supplemental tables S6,S7). After pembrolizumab combination treatment, differentially expressed plasma proteins (n=52) and mRNAs (n=10) included CXCL9 and other interferon-regulated gene products, consistent with observed gene expression changes in other anti–PD-1 studies (online supplemental tables S6,S7). Tumour mRNA expression was unaffected by INCB001158 monotherapy per the composite tumour inflammation score (see the Methods section; data on file).

Rates of PFS were unchanged when stratified by plasma arginine levels (low or high at cycle 1 day 15) or PD-L1 expression status, consistent with universally low tumour proportion scores (online supplemental table S8). T-cell

Table 2 Efficacy outcomes

Efficacy outcome	INCB001158 monotherapy		INCB001158+pembrolizumab								
	Dose escalation (Part 1a—total)	Dose expansion (Part 2—total)	Dose escalation (Part 1b—total)	Dose expansion (Part 3)*							
				Cohort 3a	Cohort 3b	Cohort 3c	Cohort 3d	Cohort 3e	Cohort 3f	Cohort 3g	Cohort 3h
Objective response, evaluable n	25	73	33	12	12	12	5	27	13	26	11
BOR, n (%)											
CR	0	0	0	0	0	0	0	0	1 (7.7)	1 (3.8)	0
PR	0	1 (1.4)†	2 (6.1)	1 (8.3)	0	2 (16.7)	0	2 (7.4)	0	4 (15.4)	1 (9.1)
SD	5 (20.0)	22 (30.1)	8 (24.2)	6 (50.0)	6 (50.0)	2 (16.7)	4 (80.0)	5 (18.5)	2 (15.4)	12 (46.2)	7 (63.6)
PD	19 (76.0)	37 (50.7)	21 (63.6)	4 (33.3)	5 (41.7)	7 (58.3)	1 (20.0)	17 (63.0)	9 (69.2)	8 (30.8)	2 (18.2)
NE	1 (4.0)	3 (4.1)	–	1 (8.3)	0	0	0	3 (11.1)	0	1 (3.8)	0
Missing	–	10 (13.7)	2 (6.1)	0	1 (8.3)	1 (8.3)	0	0	1 (7.7)	0	1 (9.1)
ORR, n (%) (95% CI)	0 (0 to 13.7)	1 (1.4) (0 to 7.4)	2 (6.1) (0.7 to 20.2)	1 (8.3) (0.2 to 38.5)	0 (0 to 26.5)	2 (16.7) (2.1 to 48.4)	0 (0 to 52.2)	2 (7.4) (0.9 to 24.3)	1 (7.7) (0.2 to 36.0)	5 (19.2) (6.6 to 39.4)	1 (9.1) (0.2 to 41.3)
PFS, evaluable n	30	77	34	12	12	13	5	27	13	26	11
Events, n (%)	21 (70.0)	58 (75.3)	29 (85.3)	8 (66.7)	10 (83.3)	8 (61.5)	3 (60.0)	22 (81.5)	11 (84.6)	21 (80.8)	8 (72.7)
Median (95% CI), mo	1.8 (1.8 to 1.9)	1.9 (1.8 to 2.1)	2.1 (2.0 to 2.4)	3.9 (1.9 to 15.3)	4.3 (2.0 to 9.0)	2.1 (0.8 to NE)	6.1 (1.6 to NE)	2.1 (2.0 to 2.3)	2.1 (0.8 to 4.7)	4.4 (2.1 to 6.2)	10.2 (1.5 to 10.6)

*Part 1c efficacy was summarised together with Part 3 in the combination therapy dose-expansion table according to the tumour types.
†This patient had well-differentiated urothelial cancer with negative PD-L1 status and mutations in *NRAS*, *PIK3CA*, *RAF1*, *CCNE1*, *ERBB2 (HER2)*, *TERT*, *STK11* and *RB1*.
BOR, best overall response; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 3 INCB001158 plasma PK parameters (Part 1a—monotherapy)

Parameter	INCB001158 50 mg two times per day	INCB001158 75 mg two times per day	INCB001158 100 mg two times per day	INCB001158 150 mg two times per day	Total
Cycle 1 day 1,* n evaluable	8	7	8	7	30
C_{max}, ng/mL	795±259	1350±379	1480±491	2080±632	–
t_{max}, hours	3.9 (2.0–4.1)	2.0 (2.0–6.2)	4.0 (2.1–6.1)	6.0 (3.8–6.0)	3.9 (2.0–6.2)
AUC_{0-t}, h·ng/mL	8100±3250	13 800±4860	15 000±5080	22 700±8420	–
$AUC_{0-\infty}$, h·ng/mL	8860±3810	14 900±5860	17 100±6440	25 700±9320	–
$t_{1/2}$, hours	5.5±1.4	5.3±1.0	5.7±0.7	5.7±0.9	5.6±1.0
CL/F, L/h	6240±1670	5620±1820	6710±2820	6430±1920	6260±2050
V_z/F, L	47 600±13 500	40 800±8090	53 500±16 100	52 000±15 500	48 600±13 900
Cycle 1 day 15,† n evaluable	6	7	7	6	26
C_{max}, ng/mL	1020±293	1940±544	2050±532	3490±1050	–
t_{max}, hours	2.0 (1.9–4.0)	4.1 (2.0–6.1)	4.0 (2.1–5.9)	2.0 (1.9–4.2)	3.9 (1.9–6.1)
AUC_{0-t}, h·ng/mL	8120±1950	15 800±5440	17 200±6040	29 300±10 100	–
AUC_{0-tau}, h·ng/mL	8480±2100	17 500±6350‡	19 000±5520‡	31 000±10 700	–
$t_{1/2}$, hours	5.7±1.1	5.3±1.2‡	6.0±2.2‡	7.0±1.7	6.1±1.6§
CL/F, L/h	6240±1700	4760±1780‡	5700±2050‡	5230±1400	5530±1660§
V_z/F, L	50 500±15 400	36 700±16 400‡	45 100±4280‡	51 500±15 100	47 000±14 200§

All data are presented as mean±SD, except for t_{max}, which is presented as median (range).
*Values shown are after single escalating doses.
†Values shown are after multiple escalating doses.
‡n=4.
§n=20.
$AUC_{0-\infty}$, area under the concentration–time curve extrapolated to time of infinity; AUC_{0-t}, area under the concentration–time curve from time 0 to the last measurable concentration; AUC_{0-tau}, area under the concentration–time curve over the dosing interval; CL/F, apparent oral dose clearance; C_{max}, maximum concentration; PK, pharmacokinetics; $t_{1/2}$, terminal-phase disposition half-life; t_{max}, time to C_{max}; V_z/F, apparent oral dose volume of distribution.

tumour infiltration (immunohistochemistry of $CD8^+$ T cells in pretreatment and on-treatment biopsies) remained unchanged with INCB001158 monotherapy but increased with pembrolizumab combination therapy, which was consistent with previous anti–PD-1 studies (online supplemental figure S6A). T-cell infiltration was evaluated separately for CRC versus non-CRC biopsy samples because CRC represented by far the largest number of available samples (44/93); overall, relatively fewer $CD8^+$ T cells were observed in CRC versus non-CRC samples. The only significant change in T-cell infiltration was an increase after combination therapy in non-CRC samples, although in CRC samples, there was a trend towards decrease with monotherapy and a trend toward increase with combination therapy (online supplemental figure S6B,C).

Arg1 expression in the TME (immunohistochemistry; EPR6672 antibody) was generally low, and the number of Arg1-positive cells was unrelated to BOR (online supplemental figure S7). Furthermore, there was no correlation between TME Arg1 expression and plasma arginine concentration (online supplemental figure S8).

DISCUSSION

In this three-part, phase 1, dose-escalation/dose-expansion study of INCB001158 alone or combined with pembrolizumab, INCB001158 100 mg two times per day was the RP2D for both monotherapy and combination therapy.

INCB001158 was generally well tolerated in both monotherapy and combination therapy. Approximately half of the patients in the safety-evaluable population (monotherapy, n=43; combination therapy, n=89) experienced INCB001158-related TEAEs. Two patients experienced DLTs: 1 protocol-defined DLT of grade 2 malaise (monotherapy) and 1 case of grade 3 pneumonitis leading to treatment discontinuation (combination therapy; 75 mg two times per day INCB001158). At the highest dose level tested, 150 mg two times per day, there was an apparent increase in orotic acid levels, although no symptomatic nor clinically significant urea cycle inhibition was observed. No maximum tolerated dose was reached, and there was no apparent dose-dependent trend in safety results.

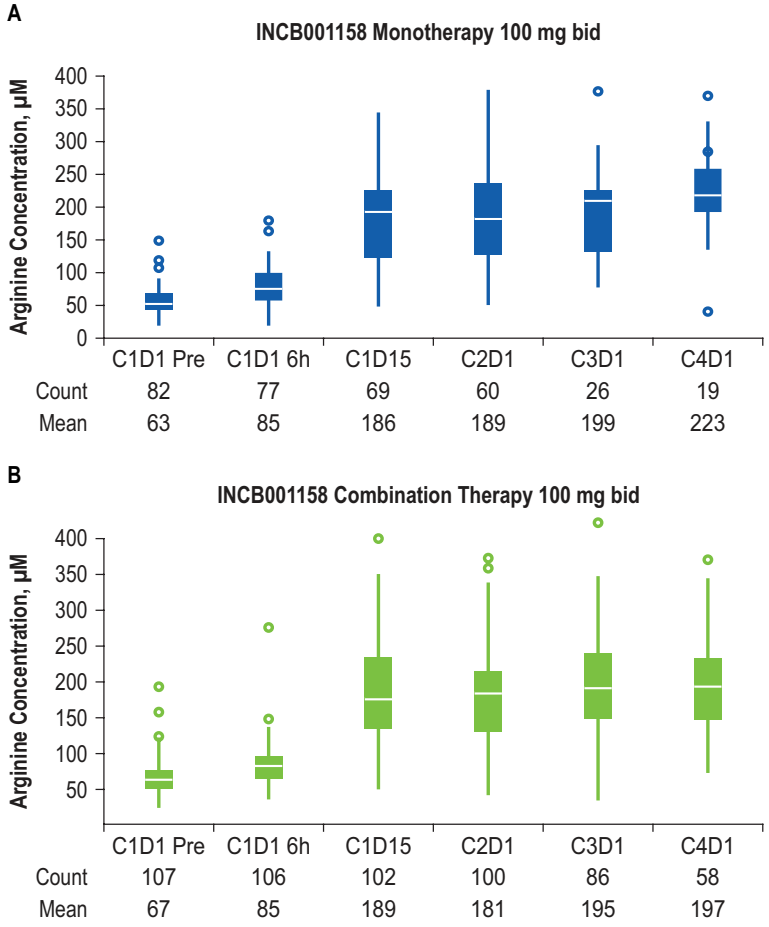

Figure 2 Plasma arginine levels by visit for 100 mg two times per day INCB001158 monotherapy and pembrolizumab combination therapy groups. Monotherapy (A) or combination therapy (B) groups were pooled and the 100 mg two times per day dose (recommended phase 2 dose) is shown. Boxplot lines indicate median plasma arginine levels in µM. bid, two times per day; C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; C2D1, cycle 2 day 1; C3D1, cycle 3 day 1; C4D1, cycle 4 day 1.

Four anti–PD-1/PD-L1–naive and four anti–PD-1/PD-L1–experienced cohorts were chosen for INCB001158 plus pembrolizumab combination therapy (figure 1). The anti–PD-1/PD-L1–experienced cohorts were reasoned to more confidently enable attribution of clinical activity (eg, objective responses) to INCB001158 given disease progression or prolonged stability in response to prior anti–PD-1 monotherapy. The anti–PD-1/PD-L1–naive cohorts were chosen to (1) identify activity in patient populations known to be unresponsive to anti–PD-1 therapy (eg, MSS-CRC) and (2) identify activity of an INCB001158/pembrolizumab combination that could be missed in pembrolizumab-refractory patients. In anti–PD-1/PD-L1–experienced cohorts, efficacy was not above background; in anti–PD-1/PD-L1–naive cohorts, efficacy was not clearly greater than had been previously observed for pembrolizumab monotherapy.[25–29] ORRs among patients with anti–PD-1/PD-L1–naive SCCHN or MSS-CRC receiving combination therapy met the criteria to open Stage 2 (20% or 2%, respectively; online supplemental table S2); therefore, limited efficacy was initially observed. However, the ORRs of the completed two stages ultimately did not meet the criteria to reject the null hypothesis.

INCB001158 reached peak plasma concentration at approximately 2–4 hours postdose after multiple administrations, and plasma exposure increased dose proportionally from 50 mg to 150 mg two times per day. Plasma exposures of INCB001158 were similar after both monotherapy and combination therapy with pembrolizumab.

Consistent with the activity of an arginase inhibitor, PD activity was confirmed by an increase in plasma arginine levels. Despite reaching the PD target, translational data support the limited efficacy observed: there was no clear indication of INCB001158 effect on tumour inflammation or T-cell infiltration into the tumour. Data from sequential tissue biopsies were used to evaluate changes in the TME, rather than liquid biopsy data. Although liquid biopsies are easier, less invasive and able to be done more frequently than tissue biopsies, liquid biopsy technology is most advanced for analysis of treatment response, not the effects of treatment on spatial distribution of intratumoural immune cells.[30 31] The lack of correlation between Arg1 TME expression and better INCB001158 response raises questions about the complexity of cell types in the TME and their corresponding Arg1 expression. The lack of correlation between plasma arginine and tumour Arg1 levels indicates that measurement of circulating arginine

in the plasma may not be an adequate surrogate for understanding arginine expression in the TME.

This is the first comprehensive report of arginase inhibition for the treatment of advanced tumours in a clinical trial setting. INCB001158 is potent, selective and reversible and had single-agent pharmacodynamic activity and efficacy in tumour-bearing mice.[6] These first-in-human findings, with pharmacodynamic increase of plasma arginine but limited observable antitumour efficacy, demonstrate the complex role of amino acid metabolism in cancer biology and immunosuppression within the TME. The limitations of this study include the lack of comparator groups, such as a pembrolizumab monotherapy cohort. Additionally, the patient population was unselected, with the majority having an unknown PD-L1 status.

CONCLUSIONS

The arginase inhibitor INCB001158 alone or combined with anti–PD-1 therapy was generally well tolerated. Despite INCB001158 PD activity indicated by a dose-dependent increase in plasma arginine, no gene expression changes nor enhanced immune activation in the TME could be attributed to INCB001158 action. Limited antitumour activity was observed with INCB001158 monotherapy, and its addition to pembrolizumab did not appear to improve efficacy. Overall, findings from this study suggest that the role of arginine depletion in cancer is multifaceted, and clinical benefit derived from arginase inhibition may be limited.

Acknowledgements Writing assistance was provided by Jane Kovalevich, PhD, and Tina Lynch, PhD, employees of ICON (Blue Bell, Pennsylvania, USA).

Contributors Study design: AN, EK, TB, SG, HK, LC, MS and XC. Acquisition of data: AN, KPP, MJP, OR, GJH, EG, OS and SG. Statistical lead: LC. Data analysis: AN, MJP, HK, LC, MS and XC. Data interpretation: AN, KPP, MJP, OR, GJH, EG, OS, SG, HK, LC, MS, XC, EK and TB. Writing, review and/or revision of the manuscript: AN, KPP, MJP, OR, GJH, EG, OS, SG, HK, LC, MS, XC, EK and TB. AN is the guarantor.

Funding This study was jointly funded by Incyte Corporation (Wilmington, Delaware, USA), Calithera Biosciences (South San Francisco, California, USA) and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA.

Competing interests AN serves on advisory boards or receives consulting fees from CTI, Deka Biosciences, Janssen Biotech, NGM Bio, PsiOxus Therapeutics, Immune-Onc Therapeutics, STCube Pharmaceuticals, OncoSec KEYNOTE-695, Genome & Company, CytomX Therapeutics, Nouscom, Merck Sharp & Dohme Corp, Servier, Lynx Health, AbbVie, PsiOxus; receives research funding from NCI, EMD Serono, MedImmune, Healios Onc. Nutrition, Atterocor/Millendo, Amplimmune, ARMO BioSciences, Karyopharm Therapeutics, Incyte, Novartis, Regeneron, Merck, Bristol-Myers Squibb, Pfizer, CytomX Therapeutics, Neon Therapeutics, Calithera Biosciences, TopAlliance Biosciences, Eli Lilly, Kymab, PsiOxus, Arcus Biosciences, NeoImmuneTech, Immune-Onc Therapeutics, Surface Oncology, Monopteros Therapeutics, BioNTech SE, Seven & Eight Biopharma and SOTIO Biotech AG; receives travel and accommodation expenses from ARMO BioSciences, NeoImmuneTech, NGM Biopharmaceuticals; receives honoraria for speaking engagements from AKH Inc, The Lynx Group, Society for Immunotherapy of Cancer (SITC), Korean Society of Medical Oncology (KSMO), Scripps Cancer Care Symposium, ASCO Direct Oncology Highlights, European Society for Medical Oncology (ESMO), CME Outfitters; has a spouse with research funding, consultant/advisory board, or ad hoc consultancy speaker disclosures from: The Texas Medical Center Digestive Diseases Center, Jeffery Modell Foundation, Immune Deficiency Foundation, Baxalta US Inc, Chao Physician-Scientist Foundation; Takeda, Pharming Healthcare Inc and Horizon Therapeutics USA, Inc.; Alfaisal University. MJP serves on ad hoc advisory boards for Astra Zeneca, Merck, Pfizer, Novartis, Ideaya, Seattle Genetics, Merus; and serves on steering committees for Astellas, Trisalus, Pionyr; has ownership or stock in Perthera, Tumor Board Tuesdays, TRICC; and has institutional funding from Seattle Genetics, Tesaro, Arcus Bio, Ideaya, Repare Tx, Novartis, Pfizer, Merck, Tizonia, Biomed Valley Discovories, Amgen, RenovoRx, Boehringer Ingelheim, Hutchinson Medipharma, Takeda, Exelexis, Caris, Incyte, Ipsen, Natera, Bayer, BMS, Eisai, Foundation Medicine, Taiho. GJH receives institutional research support from Actuate, Bicara, BMS, Exicure, Gateway for Cancer Research, Genentech, GSK, ImmunityBio, KSQ, Kura Oncology, Regeneron,Repertoire, Sanofi Genzyme and Secura Bio; serves in a consulting/advisory role for Bicara, Boxer Capital, BMS, Coherus, Exicure, KSQ, Kura Oncology, Merck, Naveris, Nextech, Regeneron, Sanofi Genzyme and SIRPant. SG, HK, LC, MS and XC are employees and shareholders of Incyte Corporation. KPP, OR, EG, EK and TB have no disclosures to declare.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements. The protocol and all amendments were reviewed and approved by the University of Texas MD Anderson Cancer Center Institutional Review Board of the coordinating principal investigator, Dr Aung Naing (7007 Bertner Avenue, Unit 1637; Chair, Dr Aman Buzdar), as well as the institutional review boards of each study site. All patients provided informed consent before initiation of treatment.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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