Clinical Cancer Research

Phase I Study of the Indoleamine 2,3-Dioxygenase 1 (IDO1) Inhibitor Navoximod (GDC-0919) Administered with PD-L1 Inhibitor (Atezolizumab) in Advanced Solid Tumors

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Abstract

Purpose: IDO1 induces immune suppression in T cells through L-tryptophan (Trp) depletion and kynurenine (Kyn) accumulation in the local tumor microenvironment, suppressing effector T cells and hyperactivating regulatory T cells (Treg). Navoximod is an investigational small-molecule inhibitor of IDO1. This phase I study evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of navoximod in combination with atezolizumab, a PD-L1 inhibitor, in patients with advanced cancer.

Patients and Methods: The study consisted of a 3 + 3 dose-escalation stage ($n = 66$) and a tumor-specific expansion stage ($n = 92$). Navoximod was given orally every 12 hours continuously for 21 consecutive days of each cycle with the exception of cycle 1, where navoximod administration started on day −1 to characterize pharmacokinetics. Atezolizumab was administered by intravenous infusion 1,200 mg every 3 weeks on day 1 of each cycle.

Results: Patients ($n = 157$) received navoximod at 6 dose levels (50–1,000 mg) in combination with atezolizumab. The maximum administered dose was 1,000 mg twice daily; the MTD was not reached. Navoximod demonstrated a linear pharmacokinetic profile, and plasma Kyn generally decreased with increasing doses of navoximod. The most common treatment-related AEs were fatigue (22%), rash (22%), and chromaturia (20%). Activity was observed at all dose levels in various tumor types (melanoma, pancreatic, prostate, ovarian, head and neck squamous cell carcinoma, cervical, neural sheath, non–small cell lung cancer, triple-negative breast cancer, renal cell carcinoma, urothelial bladder cancer): 6 (9%) dose-escalation patients achieved partial response, and 10 (11%) expansion patients achieved partial response or complete response.

Conclusions: The combination of navoximod and atezolizumab demonstrated acceptable safety, tolerability, and pharmacokinetics for patients with advanced cancer. Although activity was observed, there was no clear evidence of benefit from adding navoximod to atezolizumab.

Introduction

Indoleamine 2,3-dioxygenase 1 (IDO1) is a cytosolic enzyme that catalyzes the rate-limiting step of L-tryptophan (Trp) metabolism to kynurenine (Kyn; ref. 1). The main role of IDO1 is the regulation of acquired local and peripheral immune tolerance in normal and pathologic scenarios (2). In cancer, IDO1 induces

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Translational Relevance

Preclinical evidence suggests that combining navoximod, an IDO1 inhibitor, with anti–PD-L1 may improve the clinical activity of immune checkpoint blockade due to IDO's role in immune suppression. This phase I trial is the first study in which the combination of navoximod with atezolizumab was administered to patients with advanced cancer. The combination safety profile appeared tolerable at the navoximod doses administered, which resulted in dose-dependent decreases in plasma kynurenine (Kyn) consistent with systemic modulation of IDO1. However, similar to recent data from other trials combining IDO pathway inhibition with PD-L1/PD-1 inhibition (e.g., ECHO-301), the clinical activity observed did not provide compelling evidence of improvement over single-agent therapy.

immune suppression in T cells through at least two distinct mechanisms. Trp depletion in the local tumor microenvironment activates a starvation response in T cells that impairs their function. In addition, accumulation of Kyn, an endogenous ligand for the aryl hydrocarbon receptor, acts to suppress effector T cells and hyperactivate regulatory T cells (Treg). Together, these effects lead to decreased inflammation and immune responsiveness toward tumors (3, 4).

Increased expression of IDO1 in a variety of human tumors is observed and often associated with worse clinical outcome (5). Mechanistically, inhibition of IDO1 alone is expected to modulate the microenvironment to potentiate the action of immune effectors, but is not expected to kill tumor cells directly, nor initiate a *de novo* antitumor immune response (1). In the clinic, IDO1 inhibition alone has little anticancer effect in a majority of patients (6, 7). However, early-phase studies demonstrating encouraging response rates and durability of responses suggested that the addition of IDO1 inhibitors to programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibition may enhance the efficacy of checkpoint blockade alone (8–11).

Navoximod (GDC-0919; previously NLG919) is an investigational small-molecule inhibitor of IDO1 with a potency of 75–90 nmol/L for IDO1 in cell-based assays (12). In preclinical models, combination treatment of navoximod with anti–PD-L1 more effectively activates intratumoral $CD8^+$ T cells and inhibits tumor growth compared with either single agent alone (13). The open-label phase Ia clinical study of navoximod in 22 patients with solid tumors demonstrated that navoximod was generally well-tolerated, and as expected had limited clinical activity, as a single agent (14). The PD-L1 checkpoint inhibitor, atezolizumab, has been approved in the United States and European Union as a single agent for the treatment of non–small cell lung cancer (NSCLC) and urothelial bladder cancer (UBC). In this phase I study, we examined the combination of navoximod with atezolizumab for the first time as treatment for patients with advanced cancer.

Patients and Methods

Study design

This phase Ib study was an open-label, multicenter, dose-escalation and -expansion study of navoximod in combination with atezolizumab in adult patients with locally advanced or metastatic solid tumors (Supplementary Fig. S1). The primary objectives of the study were to evaluate the safety and tolerability of navoximod and atezolizumab when administered in combination; secondary and exploratory objectives included assessments of immunogenicity, pharmacokinetics, pharmacodynamics, and preliminary signs of antitumor activity.

The dose-escalation stage of the study used a standard 3 + 3 design to evaluate escalating doses of navoximod (50–1,000 mg) with a fixed dose of atezolizumab (1,200 mg), both provided by Genentech, Inc. Navoximod was administered orally every 12 hours (twice daily) continuously for 21 consecutive days of each cycle (days 1–21) with the exception of cycle 1, where navoximod administration started on day −1 to characterize pharmacokinetics. The twice-daily dosing frequency was selected to maximize exposures given the approximately 11-hour half-life of navoximod and was also supported by single-agent safety data (14). Atezolizumab was administered by intravenous infusion every 3 weeks (q3w) on day 1 of each cycle. The dose-limiting toxicity (DLT) assessment window was 22 days (days −1 to 21 of cycle 1) with DLTs defined as any of the following treatment-related toxicities: grade ≥3 nonhematologic, nonhepatic toxicity, severe hematologic toxicity (grade ≥4 neutropenia, grade ≥3 febrile neutropenia, grade ≥4 anemia, grade ≥4 thrombocytopenia, or grade 3 thrombocytopenia associated with clinically significant bleeding); severe hepatic toxicity [grade ≥3 elevation of ALT, AST, or serum total bilirubin; concurrent elevation of ALT or AST >3 × the upper limit of normal (ULN) and total bilirubin 2 × ULN].

If 1 of 3 patients experienced a DLT within the first cycle, 3 additional patients were enrolled at that dose level. If a DLT was observed in ≥ 2 patients at any dose level, escalation ceased and the previous dose was declared the MTD. To acquire additional safety and pharmacodynamic data to more fully inform the dose selection for the expansion stage of the study, additional "backfill" patients were enrolled at dose levels that did not exceed the MTD, but were not included in the DLT-evaluable population.

In the expansion stage, select indications were evaluated (Supplementary Fig. S1). Patients enrolled in the expansion cohorts were given 600 mg or 1,000 mg orally twice daily of navoximod in combination with 1,200 mg i.v. q3w of atezolizumab.

Treatment beyond radiographic progression per RECIST v1.1 was permitted in the absence of evidence of unequivocal progression of disease, decline in Eastern Cooperative Oncology Group (ECOG) performance status, or tumor progression at critical anatomic sites in patients who provided written informed consent. No intrapatient dose escalation was permitted.

Institutional review board approvals for the study protocol, amendments, and informed consent documents were obtained prior to study initiation. Study procedures were conducted in accordance with the Declaration of Helsinki. The ClinicalTrials.gov identifier for the phase Ib study (GO29779) is NCT02471846.

Patient eligibility

Eligible patients were ≥18 years old with histologically documented, incurable, locally advanced, or metastatic solid tumors, had ECOG performance status of 0–1, adequate hematologic and end organ function, and measurable disease per RECIST v1.1. Patients with risk of autoimmune disease or history of infection with HIV, hepatitis B, or hepatitis or C were excluded. Also excluded were patients who received prior treatment with T-cell

costimulatory receptor agonist antibodies or IDO/TDO inhibitors; or concomitant immunosuppressive medication, concomitant acetaminophen at doses ≥1,000 mg per day, or drugs associated with Torsades de Pointes, which could not be safely discontinued.

Patients enrolled in the dose-escalation stage of the study were allowed prior treatment with PD-1, PD-L1, CTLA4, or other checkpoint inhibitors, provided these were discontinued before study start. Patients in the expansion stage of the study were not allowed prior treatment with checkpoint inhibitors except for patients enrolled in the relapsed NSCLC cohort, which specifically required patients to have achieved best response of complete response (CR)/partial response (PR) or stable disease (SD) on most recent therapy with PD-1/PD-L1 inhibitors. All patients enrolled in the expansion stage were required to provide tumor tissue that was evaluable for PD-L1 expression, and enrollment was managed to ensure that fewer than 25% of the patients were PD-L1 negative.

Safety assessments

The safety population included all patients who received at least one dose of navoximod or atezolizumab. Safety assessments included physical examination, vital sign measurements, clinical laboratory testing, triplicate 12-lead electrocardiogram, and monitoring and recording of adverse events (AE) including serious and nonserious AEs of special interest. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The AE reporting period extended for 60 days after the last dose of navoximod and/or atezolizumab or prior to the initiation of a new systemic anticancer treatment whichever occurred first. An internal monitoring committee reviewed the cumulative safety profile at regular intervals following the start of the expansion stage.

Pharmacokinetic assessments

Blood samples were collected for navoximod pharmacokinetic evaluation before and up to 8 hours after single and multiple twice-daily doses of navoximod. Plasma concentrations of navoximod were determined using a validated LC/MS-MS method with a lower limit of quantitation of 1 ng/mL, and pharmacokinetic parameters were estimated using noncompartmental analysis (Phoenix WinNonlin 6.4; Cetara).

Evaluation of tumor response

CT or MRI studies were obtained at screening, and at approximately every 6 weeks for 24 weeks, and every 12 weeks thereafter until disease progression or loss of clinical benefit. Objective response was determined by the investigators according to RECIST v1.1.

Biomarker assessments

Blood was collected to monitor changes in plasma Kyn levels as a peripheral biomarker of IDO1 activity at the same timepoints as pharmacokinetic assessments. Validated LC/MS-MS assays were used to measure the concentration of Kyn in plasma samples, with a lower limit of quantitation of 25 ng/mL (15). Samples were analyzed at Covance Laboratories.

IDO1 and PD-L1 were evaluated in formalin-fixed and paraffin-embedded tumor samples using mAb clones SP260 (Spring Bioscience) for IDO1 and SP142 (Spring Bioscience) for PD-L1 in validated IHC assays. IDO1 and PD-L1 expression was evaluated both on tumor cells (proportion of positive cells estimated as the percentage of total tumor cells) and tumor-infiltrating immune cells (percentage of positive tumor-infiltrating immune cells occupying the tumor), with positivity defined as ≥1%, as described previously for PD-L1 (16). CD8 IHC using mAb clone SP16 (Epitomics) was also performed as described previously (16).

Statistical analyses

In this study, no formal statistical hypotheses were tested, and all analyses were descriptive and exploratory. Design considerations were not made with regard to explicit power and type I error, but rather to obtain preliminary safety, activity, pharmacokinetics, and pharmacodynamics information. All patients who received ≥ 1 dose of navoximod or atezolizumab were included in the safety and activity analyses.

Results

Patient characteristics

From July 2015 to July 2017, 158 patients were enrolled from 18 sites in the United States, Spain, France, and South Korea. Patient demographics and baseline characteristics are summarized in Table 1. The patient population in the dose-escalation

Table 1. Patient baseline and disease characteristics (intent-to-treat population)

Variable	Dose escalation ($n = 66$)[a]	Dose expansion ($n = 92$)	All patients ($N = 158$)
Age (y), median (range)	61 (31–80)	59 (33–78)	59 (31–80)
Sex			
Female	43 (65%)	48 (52%)	91 (58%)
Male	23 (35%)	44 (48%)	67 (42%)
ECOG performance status			
0	33 (51%)	25 (28%)	58 (37%)
1	32 (49%)	65 (72%)	97 (63%)
Race			
Black or African American	2 (3%)	1 (1%)	3 (2%)
White	60 (91%)	51 (55%)	111 (70%)
Asian	2 (3%)	36 (39%)	38 (24%)
Unknown	2 (3%)	4 (4%)	6 (4%)
Most common tumor types			
Lung (NSCLC)	1 (2%)	42 (46%)	43 (27%)
Breast[b]	13 (20%)	12 (13%)	25 (16%)
Ovary	8 (12%)	7 (8%)	15 (10%)
Bladder	3 (5%)	7 (8%)	10 (6%)
Kidney	2 (3%)	7 (8%)	9 (6%)
Endometrial	5 (8%)	2 (2%)	7 (5%)
Cervical	4 (6%)	2 (2%)	6 (4%)
Gastric	2 (3%)	4 (4%)	6 (4%)
Head and neck	3 (5%)	3 (3%)	6 (4%)
Colon	4 (6%)	0 (0%)	4 (3%)
GE junction	3 (5%)	1 (1%)	4 (3%)
Melanoma	2 (3%)	2 (2%)	4 (3%)
No. prior systemic therapies, median (range)	3.0 (1.0–11.0)	3.0 (1.0–17.0)	3.0 (1.0–17.0)
Patients with prior immunotherapy	5 (8%)	17 (19%)	22 (14%)

Abbreviations: GE, gastroesophageal; y, year.

[a]Includes backfill patients;

[b]Triple-negative breast cancer ($n = 17$), estrogen receptor (ER)$^+$/progesterone receptor (PR)$^+$/human epidermal growth factor receptor 2 (HER2)$^-$ ($n = 4$), PR$^+$/ER$^-$/HER2$^-$ ($n = 1$), ER$^+$/ HER2$^-$/PR unknown ($n = 1$), ER/PR/HER2 status unknown ($n = 2$).

Table 2. Treatment-related all-grade AEs in ≥5% of patients receiving 1,200 mg atezolizumab in combination with navoximod (safety population; A). Treatment-related grade ≥3 AEs in ≥2 patients receiving 1,200 mg atezolizumab in combination with navoximod (safety population; B)

A.

	Navoximod 50 mg ($n = 6$)	Navoximod 100 mg ($n = 7$)	Navoximod 200 mg ($n = 12$)	Navoximod 400 mg ($n = 6$)	Navoximod 600 mg ($n = 80$)	Navoximod 1,000 mg ($n = 46$)	All patients ($N = 157$)
Any treatment-related AE	5 (83%)	5 (71%)	9 (75%)	4 (67%)	64 (80%)	31 (67%)	118 (75%)
Fatigue	3 (50%)	3 (43%)	2 (17%)	3 (50%)	13 (16%)	11 (24%)	35 (22%)
Rash[a]	1 (17%)	1 (14%)	1 (8%)	1 (17%)	20 (25%)	11 (24%)	35 (22%)
Chromaturia	-	-	2 (17%)	-	19 (24%)	11 (24%)	32 (20%)
Decreased appetite	1 (17%)	1 (14%)	2 (17%)	1 (17%)	12 (15%)	2 (4%)	19 (12%)
Nausea	1 (17%)	3 (43%)	-	1 (17%)	9 (11%)	5 (11%)	19 (12%)
Vomiting	1 (17%)	2 (29%)	1 (8%)	-	8 (10%)	1 (2%)	13 (8%)
Asthenia	-	-	-	-	8 (10%)	4 (9%)	12 (8%)
AST increased	1 (17%)	-	3 (25%)	-	6 (8%)	1 (2%)	11 (7%)
Diarrhea	1 (17%)	-	1 (8%)	1 (17%)	6 (8%)	1 (2%)	10 (6%)
Anemia	-	1 (14%)	2 (17%)	-	4 (5%)	2 (4%)	9 (6%)
Pyrexia	1 (17%)	-	2 (17%)	1 (17%)	1 (1%)	4 (9%)	9 (6%)
Hypothyroidism	-	-	1 (8%)	1 (17%)	4 (5 %)	1 (2%)	7 (5%)
Infusion-related reaction	-	-	1 (8%)	1 (17%)	1 (1%)	4 (9%)	7 (5%)

B.

	Navoximod 50 mg ($n = 6$)	Navoximod 100 mg ($n = 7$)	Navoximod 200 mg ($n = 12$)	Navoximod 400 mg ($n = 6$)	Navoximod 600 mg ($n = 80$)	Navoximod 1,000 mg ($n = 46$)	All patients ($N = 157$)
Any treatment-related grade ≥3 AE	-	1 (14%)	3 (25%)	1 (17%)	17 (21%)	13 (28%)	35 (22%)
Rash[a]	-	-	1 (8%)	-	4 (5%)	9 (20%)	14 (9%)
Fatigue	-	-	-	1 (17%)	1 (1%)	1 (2%)	3 (2%)
Anemia	-	-	-	-	-	2 (4%)	2 (1%)
Hepatitis[b]	-	-	1 (8%)	-	2 (3%)	-	3 (2%)
Hyperlipasaemia	-	-	-	-	2 (3%)	-	2 (1%)
Pneumonitis	-	-	-	-	2 (3%)	-	2 (1%)
Thrombocytopenia	-	-	-	-	-	2 (4%)	2 (1%)

Abbreviation: AST, aspartate aminotransferase.

[a]Rash includes preferred terms of rash, rash maculo-papular, rash erythematous, rash macular, and rash generalized.

[b]Includes preferred terms of autoimmune hepatitis and hepatitis.

stage was heterogeneous, including over 15 different indications. Patients with an ECOG status of 1 comprised 49% and 72% of the dose-escalation and dose-expansion populations, respectively. Both the dose-escalation and -expansion stage patients were heavily pretreated.

As of November 2017, 151 (96%) patients discontinued from navoximod treatment and 139 (88%) patients discontinued from atezolizumab treatment, primarily due to disease progression (78% and 93%, respectively). Patients were on navoximod and atezolizumab treatment for a median of 51 days (range 1–713) and 56 days (range 1–693), respectively.

Safety and tolerability

Navoximod given in combination with atezolizumab was generally well-tolerated. The MTD of navoximod in combination with atezolizumab was not identified. There was a single DLT of grade 3 sepsis syndrome at the 200 mg dose level considered to be related to both study drugs.

There was no clear relationship between dose and either incidence or severity of AEs. The most common AEs regardless of causality occurring in >20% of patients were fatigue, nausea, decreased appetite, constipation, and chromaturia. Most treatment-related (Table 2A) AEs were grade 1 or 2, with the most common being fatigue, rash, and chromaturia. Grade ≥3 treatment-related AEs (Table 2B) were experienced by 35 patients (22%), with the most common being rash (14 patients, 9%). Overall, treatment-related serious AEs were reported in 15 patients (10%). Fourteen patients (9%) discontinued navoximod treatment due to AEs, and 4 patients (2.5%) discontinued atezolizumab due to AEs. The 4 patients that discontinued atezolizumab due to AEs also discontinued navoximod due to AEs. The AEs leading to treatment discontinuation that were considered related to study treatment were rash, hypersensitivity, pneumonitis, affect lability, anxiety, autoimmune hepatitis, and encephalitis.

One death was attributed to study treatment, occurring in a patient with metastatic prostate cancer and a history of partial vocal cord paralysis. Twenty-three days after treatment discontinuation, the patient experienced grade 4 pneumonitis that improved, yet was subsequently followed by grade 5 respiratory failure. Confounders included possible aspiration.

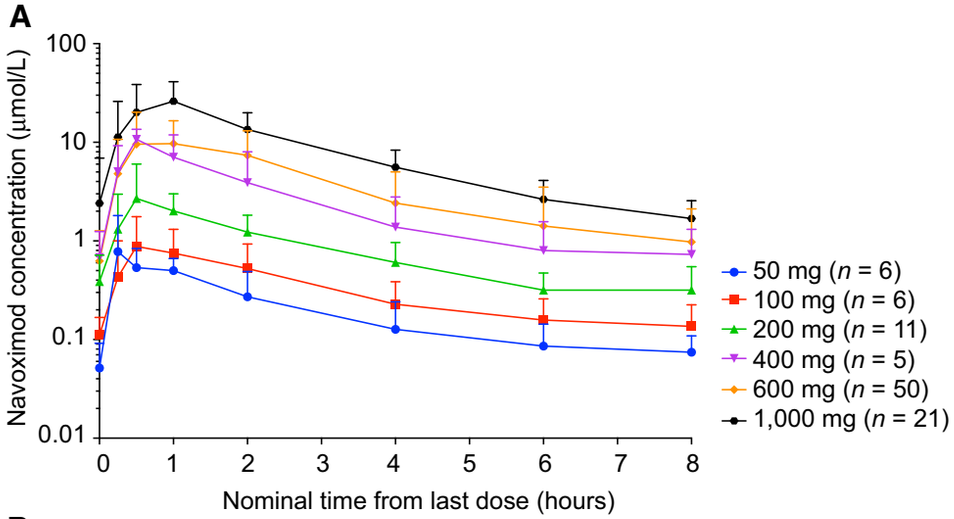
Pharmacokinetics

Navoximod pharmacokinetic evaluations were conducted following the administration of single and multiple oral doses (50−1,000 mg twice daily; Fig. 1). Navoximod was rapidly absorbed [median T_{max} approximately 1 hour (range: 0.25–4 hours)] and demonstrated dose-proportional and linear pharmacokinetics at the evaluated dose levels. The pharmacokinetics of navoximod when given in combination with atezolizumab was consistent with single-agent pharmacokinetic observations (14). Atezolizumab pharmacokinetics in combination with navoximod was consistent with single-agent observations (data not shown).

Antitumor activity

In the dose-escalation stage, 6 of 66 (9%) patients (melanoma, pancreatic, prostate, ovarian, head and neck squamous

A



B

Parameter	Navoximod 50 mg (*n* = 5)	Navoximod 100 mg (*n* = 7)	Navoximod 200 mg (*n* = 12)	Navoximod 400 mg (*n* = 6)	Navoximod 600 mg (*n* = 59)	Navoximod 1,000 mg (*n* = 35)
C_{max} (µmol/L)						
SD	0.620 (52.7)	1.68 (75.7)	2.80 (82.7)	7.70 (75.4)	11.4 (67.4)	23.4 (64.8)
MD	0.915 (61.5)	0.861 (97.9)	2.52 (72.1)	10.4 (26.7)	11.3 (98.4)	27.0 (71.5)
C_{min} (µmol/L)						
MD	0.0412 (85.0)	0.0986 (63.2)	0.167 (493)	0.419 (198)	0.238 (1110)	1.03 (599)
T_{max} (hour)[a]						
SD	1.0 (0.50-1.0)	0.50 (0.25-2.0)	0.75 (0.25-2.0)	0.75 (0.50-1.0)	1.0 (0.25-2.0)	1.0 (0.25-4.0)
MD	0.38 (0.25-2.0)	1.0 (0.25-6.0)	0.50 (0.25-1.0)	0.50 (0.50-1.0)	1.0 (0-2.0)	1.0 (0.50-4.0)
AUC_{0-8} (µmol/L*hour)						
SD	1.34 (20.9)	2.82 (45.9)	5.00 (58.2)	12.5 (47.5)	21.7 (56.8)	45.7 (46.1)
MD	1.54 (35.4)	2.30 (60.6)	6.11 (45.4)	17.5 (69.8)	26.4 (63.4)	58.0 (49.7)

Figure 1.
A, Navoximod plasma concentration–time profile following multiple twice-daily doses. **B,** Single-dose (SD) and multiple dose (MD) pharmacokinetic parameters of navoximod. AUC_{0-8}, area under the curve, measured from 0–8 hours post-navoximod dose; C_{max}, maximum observed concentration; C_{min}, minimum observed concentration; T_{max}, time of maximum observed concentration. Geometric mean (geometric CV%) results are presented unless otherwise indicated. [a]Median (minimum, maximum) results are presented for T_{max}.

cell carcinoma, and cervical cancer) achieved a PR, and 11 (17%) patients achieved a best overall response of SD. The response rate was slightly higher in patients with PD-L1 expressing (4/30, 13%) versus PD-L1–negative tumors (2/29, 7%; Fig. 2). At data cutoff, 5 patients (with melanoma, pancreatic, cervical, prostate, ovarian cancer) remain active and have exceeded 1 year of study treatment.

In the expansion stage where all patients were PD-L1/PD-1 treatment naïve, with the exception of those enrolled in the NSCLC relapsed cohort, there were 10 responders (Table 3). Of the 3 renal cell carcinoma (RCC) responders, 2 patients had received at least 3 different prior lines of therapies in the metastatic setting before entering this study. Of the 3 UBC responders, 1 patient had received at least 3 different prior lines of therapies in the metastatic setting before entering this study.

Pharmacodynamic biomarkers

Consistent with expected systemic modulation of IDO1, navoximod dosing decreased plasma Kyn relative to cycle 1 day 1 predose levels. The mean change from the predose baseline was decreased at all postdose timepoints beyond 1 hour for patients receiving at least 200 mg navoximod dose (Fig. 3A). Similar maximal decreases in Kyn were observed after multiple days of navoximod dosing (Fig. 3B). No statistically significant differences in the level of Kyn suppression were observed between responders versus nonresponders (Supplementary Fig. S2).

An evaluation of selected biomarkers was carried out in serial tumor biopsies from dose-escalation and dose-expansion patients that consented to pretreatment and on-treatment biopsies (Fig. 3C). There was upregulation of IDO1 expression in tumor cells after treatment with the combination of navoximod and atezolizumab, although this did not appear to be dose-dependent. An increase in PD-L1 expression in tumor cells was also observed. In the context of 95% confidence intervals (CI), no significant upregulation of IDO1 and a subtle upregulation of PD-L1 in immune cells was observed. No significant intratumoral increase in CD8 or tumor infiltrating leukocytes (TIL) was observed.

Discussion

This phase Ib study in advanced solid tumors explored the safety, tolerability, pharmacokinetics, and pharmacodynamics of navoximod in combination with atezolizumab. Overall, the combination of atezolizumab and navoximod was generally well-tolerated at the doses explored in this study. No MTD was defined and no apparent dose–response relationship for immune-related adverse events was noted over the dose range explored. The potentially immune-mediated clinically significant adverse events reported (e.g., hepatitis, pneumonitis, sepsis syndrome) are consistent with the well-established safety profile of atezolizumab and other PD-1/PD-L1 inhibitors.

Rash was observed overall in around 20% of patients and was reported at all doses. It was predominantly grade 1–2 in severity, and although rash was the most commonly occurring treatment-related grade 3 AE, only 6 (4%) patients discontinued treatment due to rash, and thus rash was generally manageable. Rash has

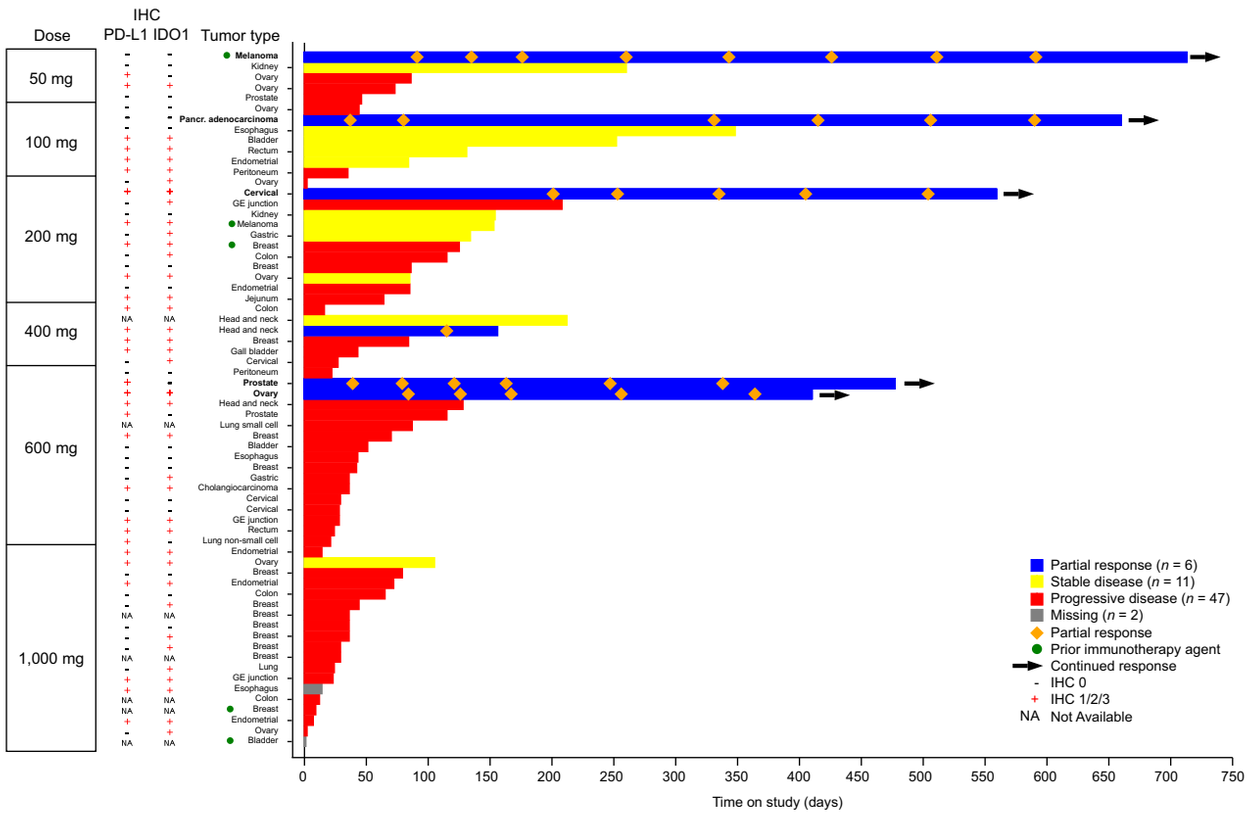


Figure 2.

Time on study treatment and PD-L1 and IDO1 expression for dose-escalation patients. BOR for PD-L1–positive patients ($n = 30$): PR = 4 patients (13%), SD = 6 patients (20%), PD = 19 patients (63%); BOR for PD-L1–negative patients ($n = 29$): PR = 2 patients (7%), SD = 4 patients (14%), PD = 23 patients (79%); BOR for all patients ($n = 66$) regardless of PD-L1 status: PR = 6 patients (9%), SD = 11 patients (17%), PD = 47 patients (71%). Two patients were not evaluable for response because they discontinued treatment prior to reaching first restaging. BOR, best overall response; GE, gastroesophageal; Pancr., pancreatic.

been reported with other IDO inhibitors (8) and may be a class effect of these agents or possibly a combination effect with contributions from both drugs.

Hepatic AEs had been reported in a single-agent study of navoximod (14), and thus inclusion of acetaminophen restrictions (<1,000 mg/day on study) were placed for enrolled patients due to the potential risk of elevated liver function tests. However, no apparent dose-related trend was noted in this study. Hepatic AEs were commonly confounded by the presence of malignant hepatic infiltration.

The observation of pink colored urine (chromaturia) without associated clinical sequelae in up to 20% of patients remains unexplained despite screening for navoximod metabolites that may be chromogenic, or pathologic causes such as hematuria or porphyrins. Chromaturia was documented at greater frequency at higher doses of navoximod and in Asian patients, although

Table 3. Efficacy and PD-L1 IHC in expansion patients. IHC1/2/3 = staining of ≥1% immune cells or tumor cells

	NSCLC (CIT naïve)	NSCLC (relapsed)	TNBC (CIT naïve)	RCC (CIT naïve)	UBC (CIT naïve)	Biopsy A (CIT naïve)	Biopsy B (CIT naïve)	All patients
ORR in all patients	$n = 26$	$n = 16$	$n = 11$	$n = 7$	$n = 8$	$n = 11$	$n = 12$	$n = 91$
Responders (%)	2 (8%)	0 (0%)	1 (9%)	3 (43%)	3 (38%)	0 (0%)	1 (8%)	10 (11%)
ORR in PD-L1 IHC 1/2/3 patients	$n = 14$	$n = 11$	$n = 8$	$n = 7$	$n = 6$	$n = 6$	$n = 8$	$n = 60$
Responders (%)	2 (14%)	0 (0%)	1 (12%)	3 (43%)	2 (33%)	0 (0%)	1 (12%)	9 (15%)
ORR in PD-L1 0 patients	$n = 11$	$n = 4$	$n = 3$	$n = 0$	$n = 0$	$n = 5$	$n = 4$	$n = 27$
Responders (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ORR in IDO1 IHC 1/2/3 patients	$n = 17$	$n = 14$	$n = 8$	$n = 7$	$n = 6$	$n = 8$	$n = 8$	$n = 68$
Responders (%)	2 (12%)	0 (0%)	1 (12%)	3 (43%)	2 (33%)	0 (0%)	1 (12%)	9 (13%)
ORR in IDO1 0 patients	$n = 8$	$n = 1$	$n = 3$	$n = 0$	$n = 0$	$n = 3$	$n = 4$	$n = 19$
Responders (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

NOTE: Of the 91 patients, 2 patients discontinued treatment prior to first restaging.

Abbreviations: CIT, cancer immunotherapy; ORR, overall response rate; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

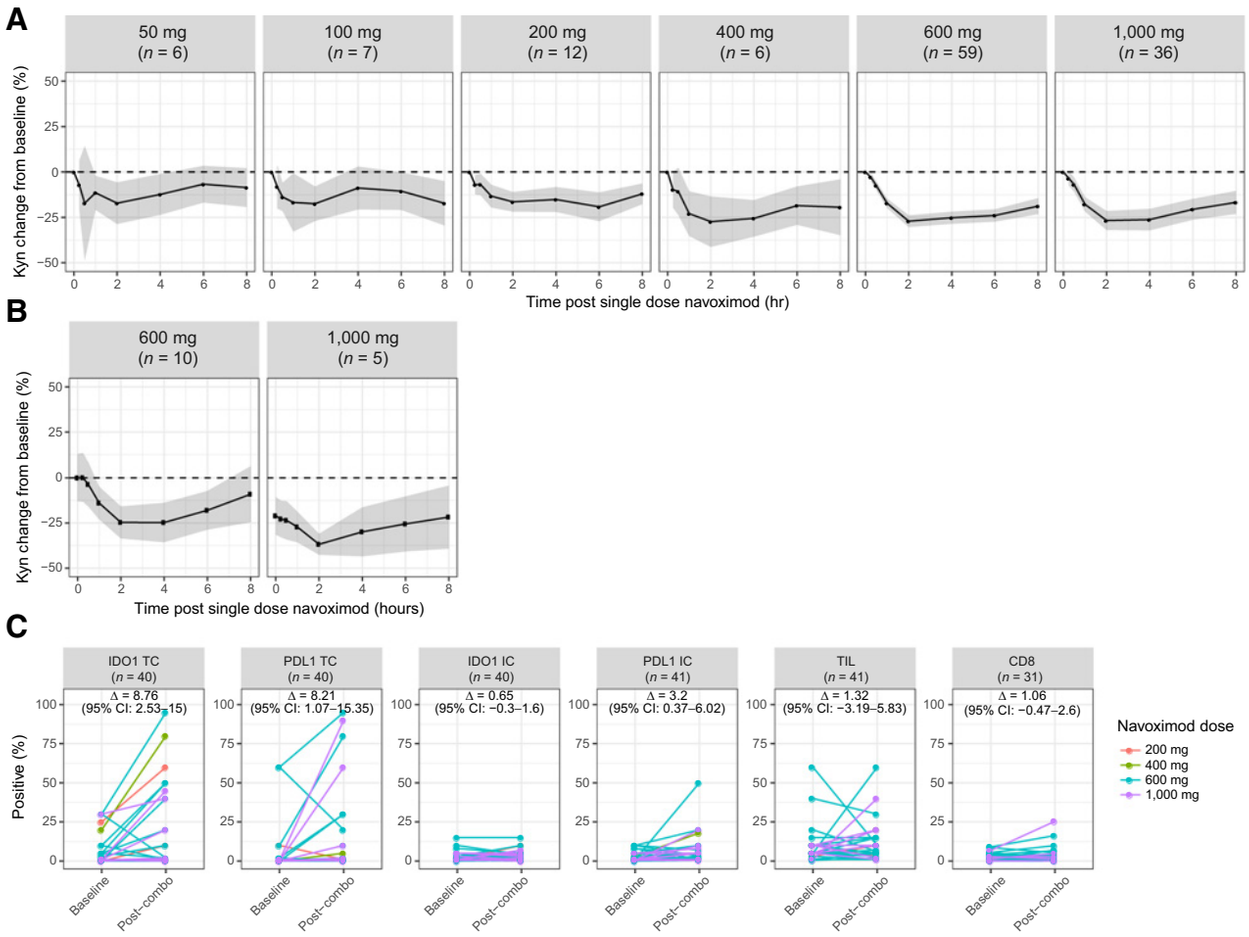


Figure 3.

A, Mean change in plasma Kyn at cycle 1, day 1, following a single oral dose of navoximod relative to day 1 predose levels. Ribbons represent 95% CIs and dashed horizontal lines represent no change from baseline. hr, hours. **B,** Mean change in plasma Kyn at cycle 1, day 8, following a single oral dose of navoximod relative to day 1 predose levels. **C,** Serial tumor biopsy evaluation of IDO1, PD-L1, TIL, and CD8. Mean changes in percentage of positivity and 95% CIs are indicated in each case. IC, immune cells; TC, tumor cells.

reporter bias may have affected this data as awareness was low in initial cohorts at low doses that were conducted only in the United States. This finding has not been reported with other IDO inhibitors.

Pharmacokinetic analyses revealed that at the evaluated dose levels, navoximod demonstrated a dose-proportional and linear pharmacokinetic profile. On average, plasma Kyn depletion was found to display kinetics consistent with the half-life of navoximod, and was generally deeper and more sustained at higher doses of the drug, with a maximum modulation of peripheral Kyn of approximately 25%. Time-matched pharmacokinetic and pharmacodynamic data from all clinical studies with navoximod indicated that steady-state trough concentrations of navoximod are predicted to exceed the IC_{50} for modulation of plasma Kyn in approximately 75% of the patient population dosed at 600 mg twice daily and approximately 90% of the patient population dosed at 1,000 mg twice daily (data not shown; ref. 17). In addition, this analysis indicated that doses above 1,000 mg twice daily were unlikely to result in a meaningful increase in the percentage of patients projected to have steady-state trough concentrations of navoximod greater than the IC_{50} for modulation of plasma Kyn. Coupled with 200 mg tablets being the highest dose strength available for the study, this analysis led to doses above 1,000 mg twice daily not being evaluated in the dose-escalation phase, and both 600 mg and 1,000 mg twice daily dose levels being evaluated in the expansion cohorts.

In serial tumor biopsies, the vast majority of which were obtained from patients dosed at 600 mg and 1,000 mg twice daily navoximod, upregulation of tumor cell IDO1 and PD-L1 expression was observed. Notably, an increase in tumor IDO1 expression was also observed in a neoadjuvant ovarian cancer study following treatment with the IDO1 inhibitor epacadostat (18). A similarly pronounced upregulation of IDO1 and PD-L1 in immune cells was not observed in this phase Ib study. The observation that neither TILs nor CD8 increased posttreatment indicates that the induction of IDO1 and PD-L1 in tumor cells is more likely due to increased IFNγ production in the tumor microenvironment, rather than to increased immune cell infiltration. While our plasma pharmacokinetic/

pharmacodynamic analyses guided selection of 1,000 mg twice daily as the highest evaluated dose in this study, the extent and duration of IDO1 inhibition in the tumor microenvironment required to elicit the desired tumor-killing immune effect is not known. The observed upregulation of tumor IDO1 following treatment with the combination of navoximod and atezolizumab does suggests the possibility that tumor Kyn pharmacodynamics may not mirror plasma Kyn pharmacodynamics in human subjects, and a lack of increased CD8 positivity in tumors following treatment with the combination may indicate that IDO1 inhibition in tumors was insufficient in our study.

Activity was observed at all dose levels evaluated in this study, but is challenging to interpret in the setting of combination with atezolizumab, which has established single-agent activity in tumor types selected for dose expansion. Although interpretation is limited by small numbers and the single-arm design, the overall response rates in the cancer immunotherapy (CIT)–naïve indication-specific cohorts ($n = 75$), regardless of PD-L1 or IDO1 expression status, are not meaningfully distinct from that expected for atezolizumab alone. For example, in patients with CIT-naïve NSCLC previously treated with platinum doublet chemotherapy, the objective response rate (ORR) with the combination of navoximod and atezolizumab observed in this study ($n = 26$ patients) was 8% compared with the ORR of 15% observed with atezolizumab monotherapy in the phase III OAK study (19). In light of the limited evidence of clinical activity, the sponsor stopped enrollment in the study after only 92 out of the originally planned 240 patients were enrolled in the expansion stage, and discontinued development of navoximod as a combination partner to atezolizumab.

Subsequent to the analysis of this phase Ib study, the primary results of the randomized double-blinded phase III ECHO-301 study evaluating epacadostat in combination with pembrolizumab compared with pembrolizumab monotherapy in patients with melanoma have been reported. Despite encouraging phase Ib results across multiple tumor types supporting this combination, the addition of epacadostat to pembrolizumab was not associated with greater clinical benefit—OS HR 1.13, median progression-free survival of 4.7 vs. 4.9 months (HR 1.0), and ORR of 34% vs. 32% (20)—and the trial was halted. Moreover, two phase III clinical trials testing combinations of nivolumab with BMS-986205, a small molecule that inhibits IDO via a distinct mode of binding than epacadostat and navoximod with greater *in vitro* potency (21), were also halted recently (NCT03417037 and NCT03386838), presumably in response to the negative ECHO-301 results. These results illustrate the challenge of interpreting preliminary findings in small, highly selected phase Ib expansion cohorts and advancing to pivotal trials without randomized phase II data, as well as the value of rigorous integrated analyses of safety, pharmacokinetics, pharmacodynamics, and efficacy data to make development decisions.

To date, proof of concept for adding IDO inhibition to anti–PD-1/PD-L1 to improve clinical benefit in unselected patients has not been achieved. Nevertheless, further interrogation of this pathway may be warranted. Concurrent inhibition of both IDO and TDO2 may be required to relieve Kyn-mediated immunosuppression in the TME and drive clinical efficacy, as TDO2 catalyzes the same reaction as IDO, resulting in the production of Kyn. Further development in this space may thus benefit from dual inhibitors of IDO1 and TDO2.

Disclosure of Potential Conflicts of Interest

P.M. LoRusso is a consultant/advisory board member for Agios, Alexion, Pfizer, Ariad, Cybrexa, Agenus, SOTIO, Takeda, Five Prime, Tyme, CytomX, Genentech, Roche/Genentech, and Genmab. Y.-J. Bang is a consultant/advisory board member for AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serono, Bristol-Myers Squibb, Eli Lilly, and BeiGene. M.D. Hellmann reports receiving commercial research grants from Bristol-Myers Squibb; is listed as a co-inventor on a patent filed by MSK related to the use of tumor mutation burden to predict response to immunotherapy, which has received licensing fees from PGDx; is a consultant/advisory board member for Merck, Bristol-Myers Squibb, AstraZeneca, Genentech/Roche, Janssen, Nektar, Syndax, Mirati, and Shattuck Labs. A. Marabelle reports receiving commercial research grants from Bristol-Myers Squibb, MSD, and Merus; reports receiving speakers bureau honoraria from Bristol-Myers Squibb, Roche, Merck Serono, MSD, AstraZeneca, Symphogen, and EISAI; holds ownership interest (including patents) in PEGASCY SAS; is a consultant/advisory board member for AstraZeneca/MedImmune, Roche, Pfizer, MSD, Sanofi, Pierre Fabre, Servier, Molecular Partners, Lytix, Sotio, Cerenis, EISAI, Innate Pharma, and Symphogen; and reports receiving other remuneration from *European Journal of Cancer*. F.S. Hodi reports receiving commercial research grants from Bristol-Myers Squibb and Novartis to his institution; is listed as an inventor on a patent filed by his institution regarding MICA-related disorders; holds ownership interest (including patents) in Apricity; and is a consultant/advisory board member for Bristol-Myers Squibb, Merck, EMD Serono, Novartis, Celldex, Amgen, Genentech, Incyte, Bayer, Aduro, Partners Therapeutics, Sanofi, Pfizer, Pionyr, 7 Hills Pharma, Verastem, Torque, Compass Therapeutics, Takeda, and Surface. L.A. Emens is an employee of FDA and SITC; reports receiving commercial research grants from Genentech/Roche, Merck, Corvus, AstraZeneca, EMD Serono, Aduro Biotech, and Maxcyte; holds ownership interest (including patents) in Aduro Biotech and Molecuvax; and is a consultant/advisory board member for Genentech/Roche, Syndax, Replimune, Macrogenics, MedImmune, AstraZeneca, Bristol-Myers Squibb, Amgen, AbbVie, Bayer, Gritstone, Molecuvax, Novartis, Peregrine, Celgene, Vaccinex, and eTheRNA. F. Barlesi is a consultant/advisory board member for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly Oncology, F. Hoffman-La Roche Ltd., Novartis, Merck, MSD, Pierre Fabre, Pfizer, and Takeda. O. Hamid reports receiving speakers bureau honoraria from Amgen, Bristol-Myers Squibb, Genentech, Novartis, Array, and Sanofi, and is a consultant/advisory board member for Amgen, Novartis, Roche, Bristol-Myers Squibb, and Merck. E. Calvo is an uncompensated employee of Foundation INTHEOS; reports receiving other commercial research support from AstraZeneca, Novartis, BeiGene, and START; reports receiving speakers bureau honoraria from Novartis; holds ownership interest (including patents) in START, Oncoart Associated, and International Cancer Consultants; and is a consultant/advisory board member for AstraZeneca, Guidepoint, Novartis, Roche/Genentech, EUSA Pharma, PsiOxus, GLG, Janssen, Seattle Genetics, AbbVie, Celgene, Pfizer, Servier, Amcure, and Nanobiotix. D. McDermott is a consultant/advisory board member for Genentech. H. Soliman is a consultant/advisory board member for Eli Lilly, Pfizer, Novartis, AstraZeneca, Celgene, and PUMA. I. Rhee holds ownership interest (including patents) in Roche. K. Morrissey holds ownership interest (including patents) in Roche. R. Morley holds ownership interest (including patents) in Roche/Genentech. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The authors take full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the article for publication, and the writing of the article.

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References

1. Munn DH, Mellor AL. IDO in the tumor microenvironment: inflammation, counter-regulation, and tolerance. Trends Immunol 2016;37:193–207.
2. Uyttenhove C, Pilotte L, Théate I, Stroobant V, Colau D, Parmentier N, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med 2003;9: 1269–74.
3. Desvignes L, Ernst JD. Interferon-gamma-responsive non hematopoietic cells regulate the immune response to *Mycobacterium tuberculosis*. Immunity 2009;31:974–85
4. Favre D, Mold J, Hunt PW, Kanwar B, Loke P, Seu L, et al. Tryptophan catabolism by indoleamine 2,3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease. Sci Transl Med 2010;2:32ra6.
5. Brochez L, Chevolet I, Kruse V. The Rationale of indoleamine 2,3-dioxygenase inhibition for cancer therapy. Eur J Cancer 2017;76:167–82.
6. Li F, Zhang R, Li S, Liu J. IDO1: an important immunotherapy target in cancer treatment. Int Immunopharmacol 2017;47:70–7.
7. Prendergast GC, Mondal A, Dey S, Laury-Kleintop LD, Muller AJ. Inflammatory reprogramming with IDO1 inhibitors: turning immunologically unresponsive cold tumors hot. Trends in Cancer 2017;4:38–58.
8. Gangadhar TC, Schneider BJ, Bauer TM, Wasser JS, Spira AI, Patel SP, et al. Efficacy and safety of epacadostat plus pembrolizumab treatment of NSCLC: preliminary phase I/II results of ECHO-202/KEYNOTE-037. J Clin Oncol 35, 2017 (suppl; abstr 9014).
9. Lara P, Bauer TM, Hamid O, Smith DC, Gajewski T, Gangadhar TC, et al. Epacadostat plus pembrolizumab in patients with advanced RCC: preliminary phase I/II results from ECHO-202/KEYNOTE-037. J Clin Oncol 35, 2017 (suppl; abstr 4515).
10. Perez RP, Riese MJ, Lewis KD, Saleh MN, Daud A, Berlin J, et al. Epacadostat plus nivolumab in patients with advanced solid tumors: preliminary phase I/II results of ECHO-204. J Clin Oncol 35, 2017 (suppl; abstr 3003).
11. Smith DC, Gajewski T, Hamid O, Wasser JS, Olszanski AJ, Patel SP, et al. Epacadostat plus pembrolizumab in patients with advanced urothelial carcinoma: preliminary phase I/II results of ECHO-202/KEYNOTE-037. J Clin Oncol 35, 2017 (suppl; abstr 4503).
12. Mautino MR, Link CJ, Vahanian NN, Adams JT, Van Allen C, Sharma MD, et al. Synergistic antitumor effects of combinatorial immune checkpoint inhibition with anti-PD-1/PD-L antibodies and the IDO pathway inhibitors NLG-919 and indoximod in the context of active immunotherapy [abstract]. In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5–9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract nr 5023.
13. Spahn J, Peng J, Lorenzana E, Kan D, Hunsaker T, Segal E, et al. Improved anti-tumor immunity and efficacy upon combination of the IDO1 inhibitor GDC-0919 with anti-PD-l1 blockade versus anti-PD-l1 alone in preclinical tumor models. J Immunother Cancer 2015;3(Suppl 2):P303.
14. Nayak-Kapoor A, Hao Z, Sadek R, Dobbins R, Marshall L, Vahanian NN, et al. Phase Ia study of the indoleamine 2,3-dioxygenase 1 (IDO) inhibitor navoximod (GDC-0919) in patients with recurrent advanced solid tumors. J Immunother Cancer 2018;6:61.
15. Miller D, Tan L, Dorshorst D, Morrissey K, Mahrus S, Milankowski D, et al. A validated surrogate analyte LC-MS/MS assay for quantitation of endogenous kynurenine and tryptophan in human plasma. Bioanalysis 2018;10: 1307–17.
16. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563–7.
17. Burris H, Gordon MS, Hellmann MD, LoRusso P, Emens LA, Hodi FS, et al. A phase Ib dose escalation study of combined inhibition of IDO1 (GDC-0919) and PD-L1 (atezolizumab) in patients with locally advanced or metastatic solid tumors. J Clin Oncol 35, 2017 (suppl; abstr 105).
18. Odunsi K. IDO inhibition: inhibiting the inhibitors in ovarian cancers. ASCO-SITC clinical immune-oncology symposium. ASCO-SITC Clinical Immuno-Oncology Symposium; 2018 Jan 27; San Francisco, CA.
19. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255–65.
20. Long GV, Dummer R, Hamid O, Gajewski T, Caglevic C, Dalle S. Epacadostat plus pembrolizumab versus pembrolizumab alone in patients with unresectable or metastatic melanoma: results of the phase 3 ECHO-301/KEYNOTE-252 study. J Clin Oncol 36, 2018 (suppl; abstr 108).
21. Siu LL, Gelmon K, Chu Q, Pachynski R, Alese O, Basciano P, et al. BMS-986205, an optimized indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor, is well tolerated with potent pharmacodynamic (PD) activity, alone and in combination with nivolumab (nivo) in advanced cancers in a phase 1/2a trial [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1–5; Washington, DC. Philadelphia (PA): AACR; 2017. Abstract nr CT116.