Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

Phase I/IIa Trial of BMS-986148, an Anti-mesothelin Antibody–drug Conjugate, Alone or in Combination with Nivolumab in Patients with Advanced Solid Tumors

Sylvie Rottey[1], Jeffrey Clarke[2], Kyaw Aung[3], Jean-Pascal Machiels[4], Ben Markman[5], Kimberley M. Heinhuis[6], Michael Millward[7], Martijn Lolkema[8], Sandip Pravin Patel[9], Paul de Souza[10], Matteo Duca[11], Giuseppe Curigliano[12], Armando Santoro[13], Takafumi Koyama[14], Michelle Brown[15], Heather Vezina[15], Chunsheng He[15], and Quincy Siu-Chung Chu[16]

ABSTRACT

Purpose: To assess the safety and tolerability of BMS-986148, a mesothelin-directed antibody–drug conjugate (ADC) ± nivolumab, in patients with selected tumors.

Patients and Methods: In an international phase I/IIa study [NCT02341625 (CA008-002)], patients received BMS-986148 monotherapy (0.1–1.6 mg/kg intravenously (i.v.) every 3 weeks or 0.4 or 0.6 mg/kg i.v. once weekly; $n = 96$) or BMS-986148 0.8 mg/kg + nivolumab 360 mg i.v. every 3 weeks ($n = 30$). The primary endpoint was safety and tolerability.

Results: In CA008-002, the most common (≥ 10%) treatment-related adverse events (TRAEs) included increased aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Grade 3/4 TRAEs occurred in 42 patients (49%) receiving BMS-986148 every 3 weeks monotherapy, three (25%) receiving BMS-986148 once-weekly monotherapy, and 10 (33%) receiving BMS-986148 + nivolumab every 3 weeks. Overall, 17 of 126 patients (13%) discontinued because of a TRAE. The MTD of BMS-986148 was 1.2 mg/kg i.v. every 3 weeks. The safety profile of BMS-986148 + nivolumab was similar to that of BMS-986148 monotherapy (0.8 mg/kg). Active ADC exposures increased in a dose-proportional manner with both dosing regimens (every 3 weeks and once weekly). Preliminary clinical activity was observed with BMS-986148 ± nivolumab. No association between mesothelin expression and response was detected.

Conclusions: BMS-986148 ± nivolumab demonstrated a clinically manageable safety profile and preliminary evidence of clinical activity, supporting additional studies combining directed cytotoxic therapies with checkpoint inhibitors as potential multimodal therapeutic strategies in patients with advanced solid tumors.

Introduction

Mesothelin is a glycosylphosphatidylinositol-anchored cell surface protein potentially involved in adhesion (1, 2). Although mesothelin expression is restricted in normal tissues to mesothelial cells of the pleura, including the pericardium, peritoneum, cornea, and conjunctiva (1, 3), mesothelin overexpression occurs in approximately 30% of all cancers (4). Particular tumors, including ovarian, pancreatic, gastric, and non–small cell lung cancers (NSCLCs) and mesothelioma, demonstrate high levels of mesothelin overexpression (1, 5). Increased mesothelin expression has also been correlated with poor overall survival in patients with lung and breast cancers (5–7), possibly because aberrant mesothelin expression in cancers plays an important role in promoting implantation and metastasis (4, 8).

Several mesothelin-directed antibody–drug conjugates (ADCs) are under clinical development (9–11). ADC therapies target a particular molecule (e.g., mesothelin) to selectively deliver a potent cytotoxic compound to antigen-expressing cells, thereby reducing systemic toxicity and improving the therapeutic index of chemotherapeutic agents (12, 13). At least nine ADCs have been approved by the FDA for the treatment of hematologic and solid tumors, demonstrating that ADCs are a feasible anticancer approach (14–22). BMS-986148 is a mesothelin-directed ADC that contains a fully human IgG1 anti-mesothelin mAb conjugated to tubulysin [a cytotoxic compound that disrupts microtubule assembly, leading to impaired proliferation and subsequent apoptosis (23)] via a valine-citrulline linker (24). BMS-986148 has an average drug-to-antibody ratio of 3 (data on file).

Combining checkpoint inhibition, such as anti-programmed death (PD)-1, with directed cytotoxic therapies like mesothelin-directed ADCs could promote immunogenic cell death and T-cell activation and enhance antitumor response in selected solid tumors (25). PD-1 expression can inhibit T-cell activation and expansion of previously activated cells; therefore, blockade of the PD-1 pathway by nivolumab (anti–PD-1) can restore and enhance antitumor T-cell function

[1]Ghent University Hospital, Ghent, Belgium. [2]Duke University Medical Center, Durham, North Carolina. [3]Princess Margaret Cancer Center, Toronto, Ontario, Canada. [4]Cliniques Universitaires Saint-Luc, Brussels, Belgium. [5]Monash Health and Monash University, Melbourne, Victoria, Australia. [6]The Netherlands Cancer Institute, Amsterdam, the Netherlands. [7]Linear Clinical Research and the University of Western Australia, Perth, Western Australia, Australia. [8]Erasmus MC Cancer Center, Rotterdam, the Netherlands. [9]University of California San Diego Moores Cancer Center, La Jolla, California. [10]Western Sydney University School of Medicine, Liverpool, New South Wales, Australia. [11]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy. [12]Istituto Europeo di Oncologia, IRCCS, University of Milano, Milan, Italy. [13]Humanitas University, IRCCS Humanitas Research Hospital, Rozzano-Milan, Italy. [14]National Cancer Center Hospital, Tokyo, Japan. [15]Bristol Myers Squibb, Princeton, New Jersey. [16]Cross Cancer Center Institute, Edmonton, Alberta, Canada.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Quincy Siu-Chung Chu, Department of Medical Oncology, Cross Cancer Institute, University of Alberta, 11560 University Ave, Edmonton, AB T6G 1Z2, Canada. Phone: 780-577-8082; Fax: 780-432-8888; E-mail: quincy.chu@albertahealthservices.ca

Clin Cancer Res 2022;28:95–105

doi: 10.1158/1078-0432.CCR-21-1181

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

Translational Relevance

Mesothelin is a glycosylphosphatidylinositol-anchored cell-surface glycoprotein potentially involved in adhesion and metastasis. Although mesothelin is overexpressed in approximately 30% of cancers, including mesothelioma, ovarian, pancreatic, gastric, and non–small cell lung tumors, its expression is restricted in normal tissues. Hence, selectively targeting mesothelin-expressing cells with antibody-based therapies could potentially increase efficacy and minimize systemic toxicity to extend treatment options for patients with mesothelin-expressing tumors. BMS-986148 is a mesothelin-directed antibody–drug conjugate targeting mesothelin-expressing cells for cytotoxic payload delivery. Preclinical studies demonstrated combining BMS-986148 with the anti-programmed death-1 mAb nivolumab could enhance antitumor effects. The clinical studies presented here (NCT02341625 and NCT02884726) demonstrate that BMS-986148 ± nivolumab has a manageable safety profile in patients with selected advanced solid tumors, with durable responses seen in a subset of patients. These findings support continuing evaluation of mesothelin as a therapeutic target in advanced cancers.

and increase cytokine production, leading to improved clinical outcomes in advanced cancers (26, 27). Tubulin-binding ADCs using divergent chemistries but similar payloads as BMS-986148 (9, 11) have been shown to increase counts of tumor-infiltrating lymphocytes, including CD4- and CD8-positive cells (28). On the basis of the mechanisms of action for BMS-986148 and nivolumab, this combination could potentially enhance antitumor effects by simultaneously disrupting microtubules to induce apoptosis in mesothelin-positive cancer cells, increasing tumor-infiltrating lymphocyte influx, and reducing the immunosuppressive effects of the tumor microenvironment (23, 27, 29, 30). Therefore, BMS-986148 and nivolumab may have complementary mechanisms of action and could potentially provide a multimodal approach to extend clinical benefits observed with single-agent immuno-oncology therapies.

We present results from a global, phase I/IIa trial assessing safety, tolerability, and preliminary efficacy of BMS-986148 ± nivolumab in patients with mesothelin-expressing tumors (CA008-002, NCT02341625). Supporting results from a phase I, open-label study in Japanese patients with selected advanced tumors ($n = 7$) treated with BMS-986148 0.8 mg/kg i.v. monotherapy every 3 weeks (CA008-008, NCT02884726) are described in the Supplementary Data.

Patients and Methods

Study design and treatment

CA008-002 is an open-label phase I/IIa trial investigating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of BMS-986148 alone or in combination with nivolumab in patients with advanced (metastatic, recurrent, refractory, and/or unresectable) solid tumors with selected histologies [pleural or peritoneal mesothelioma (except sarcomatoid mesothelioma), ovarian cancer (except mucinous carcinoma), pancreatic cancer, gastric cancer, or NSCLC (adenocarcinoma only)]. These indications were chosen based on the prevalence of mesothelin positivity in solid tumors (5). This study is being conducted at 17 sites in Australia, Belgium, Canada, Italy, the Netherlands, the United Kingdom, and the United States. This multicohort study comprises dose-escalation, dose-exploration, and dose-expansion phases that evaluate BMS-986148 alone or in combination with nivolumab.

In the dose-escalation phase, patients with the previously mentioned histologies received BMS-986148 0.1, 0.2, 0.4, 0.8, 1.2, or 1.6 mg/kg i.v. every 3 weeks (part 1A); 0.4 or 0.6 mg/kg i.v. once weekly for 3 weeks followed by 1 week off (part 1B); or 0.8 mg/kg i.v. every 3 weeks + nivolumab 360 mg i.v. every 3 weeks (part 3A). During the dose-expansion phase, patients with mesothelioma, NSCLC, pancreatic, ovarian, or gastric cancer and tumor mesothelin expression as assessed by a central laboratory (Mosaic Laboratories) received BMS-986148 1.2 mg/kg i.v. every 3 weeks (part 2) or BMS-986148 0.8 mg/kg i.v. every 3 weeks + nivolumab 360 mg i.v. every 3 weeks (part 3B).

Patient eligibility

Eligible patients were ≥ 18 years old and had histologically confirmed selected advanced solid tumors, ≥ 1 lesion of measurable disease per RECIST v1.1 (or modified RECIST for malignant pleural mesothelioma), and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients must have progressed on or been intolerant of ≥ 1 standard treatment regimen; prior anticancer treatments (e.g., chemotherapy, radiotherapy, hormonal therapy, immunotherapy) were permitted. Patients with NSCLC must have received prior immunotherapy, if available. In the dose-expansion phase, patients were required to have an H-score (31) of ≥ 100 for tumor-cell mesothelin expression, as described below.

Key exclusion criteria included active metastases in the central nervous system or, if the central nervous system was the only site of disease, prior exposure to BMS-986148 or other mesothelin-directed mAbs or ADCs, prior malignancy (except nonmelanoma skin cancers and *in situ* cancers), a history of uncontrolled or significant cardiovascular disease, or chronic hepatitis.

All patients signed consent forms for study entry and tumor biopsies. The protocol, amendments, and patient informed consent forms were reviewed and approved by an Institutional Review Board or independent ethics committee before study initiation. The study was conducted in compliance with the protocol and in accordance with International Conference on Harmonization E6 Guidelines for Good Clinical Practice. Compliance with this standard assures that the rights, safety, and well-being of the enrolled patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible (32).

Study objectives and assessments

The primary objectives were to determine the safety, tolerability, dose-limiting toxicities (DLTs), MTD, and recommended phase II dose of BMS-986148 alone or in combination with nivolumab in patients with selected advanced solid tumors. Adverse events (AEs) were assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAEs) version 4.03 during treatment and for ≥ 100 days after the last dose of study treatment. DLTs were determined based on the incidence, intensity, and duration of treatment-related AEs (TRAEs) reported during the first cycle of study therapy for patients in the dose-escalation phase (21 days for parts 1A and 3A, and 28 days for part 1B). Doses were selected using a modified Fibonacci dose-escalation design, whereas enrollment in dose escalation and MTD determination used a modified toxicity probability interval (mTPI) design. Key secondary objectives include pharmacokinetics, pharmacodynamics, and preliminary antitumor activity. Assessment of tumor response was observed through CT and/or MRI at baseline, every 2 cycles (6 weeks for treatments every 3 weeks, 8 weeks for treatments once weekly; ± 1 week) during the treatment

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

phase, followed by every 12 weeks during the response follow-up phases by RECIST v1.1 (or modified RECIST for malignant pleural mesothelioma). Partial response (PR) or complete response (CR) was confirmed by consecutive assessment ≥ 4 weeks later. Patients receiving BMS-986148 + nivolumab who experienced investigator-assessed clinical benefit, tolerance of study drug, or stable performance status were permitted to continue treatment beyond initial RECIST v1.1–defined progressive disease, as assessed by the investigator as long as treatment beyond progression would not delay an imminent intervention to prevent serious complications of disease progression. Patients were to provide additional written informed consent prior to receiving continued combination study treatment.

Serum samples for pharmacokinetic assessments were collected from all patients receiving BMS-986148 ± nivolumab. Plasma samples were collected at specified timepoints to evaluate concentrations of conjugated and unconjugated tubulysin. Pharmacokinetic parameters included maximum concentration and AUC determined from serum and plasma concentration versus time data.

Mesothelin expression

Because BMS-986148 exploits mesothelin-directed targeting of the cytotoxic payload, distribution of baseline tumor-cell levels of mesothelin expression at the plasma membrane was assessed by IHC on formalin-fixed, paraffin-embedded (FFPE) tumor samples, as described below.

IHC samples from patients in the dose-escalation phases (parts 1A, 1B, and 3A) were analyzed retrospectively using archived tumor samples. IHC samples from patients in the dose-expansion phases (parts 2 and 3B) were assessed prospectively during the screening period to select patients with tumor mesothelin expression with H-score ≥ 100 for inclusion in that part of the study. This H-score cutoff was based on the distribution of plasma membrane mesothelin expression observed in commercially obtained tumor samples from patients with the selected tumor types (data on file).

Histology and IHC staining and evaluation of mesothelin in FFPE human NSCLC tissues was performed by Mosaic Laboratories. FFPE blocks were sectioned at 4 to 5 μm onto positive charged glass slides (Leica), dried, baked, deparaffinized, and rehydrated. Antibodies used were mesothelin mouse monoclonal (clone 5B2) antibody (Leica) and mouse IgG1 isotype control antibody (Abcam) and stored at −20°C.

For antigen retrieval, tissue sections were pretreated for 10 minutes at 110°C using Envision FLEX TRS High pH 9.0 (Dako), cooled at room temperature for 15 minutes followed by a rinse in distilled water. Endogenous peroxide was blocked using Dual Endogenous Enzyme Blocking Reagent (catalog No. S2003, Dako). After incubation in Serum-Free Protein Block (catalog No. X0909, Dako) for 20 minutes, the primary antibody (Mesothelin, Leica) was applied, and the tissue sections were incubated for 1 hour. After removal of the antibody solution, the tissue sections were incubated with Post Primary Block (Novolink HRP Polymer Detection Kit, catalog No. RE7150-CE, Leica) for 30 minutes, incubated in Polymer (Novolink HRP Polymer Detection Kit, catalog No. RE7150-CE, Leica) for 30 minutes, followed by diaminobenzidine chromogen (Novolink HRP Polymer Detection Kit, catalog No. RE7150-CE, Leica) for 5 minutes, and counterstained with hematoxylin (Dako), blued in ammonia water, dehydrated through graded alcohols, cleared in xylene, and coverslipped.

Staining intensity and percentage of tumor cells staining within the membrane and cytoplasm were scored separately. The mesothelin (mouse clone 5B2) assay was evaluated on a semiquantitative scale, and the percentage of cancer cells staining at each of the following four levels was recorded: 0 (unstained), 1+ (weak staining), 2+ (moderate staining), and 3+ (strong staining). An H-score was calculated on the basis of the summation of the product of percentage of cells stained at each intensity using the following equation: (3 × % cells staining at 3+) + (2 × % cells staining at 2+) + (1 × % cells staining at 1+). Cytoplasmic globules were also scored on the basis of staining frequency and average staining intensity. The staining pattern was also recorded as the following: (i) primarily apical; (ii) primarily circumferential/basolateral; or (iii) mixed.

Statistical considerations

In the monotherapy dose-escalation parts of study CA008-002 (parts 1A and 1B), approximately 30 and 24 evaluable patients, respectively, were expected to be treated, depending on the observed DLT rate and guided by an mTPI, with a target DLT rate of 27% (25%–29%) based on Bayesian modeling and posterior inference. Between two and 13 DLT-evaluable patients were to be enrolled to a given monotherapy cohort in part 1A. In the combination dose-escalation part (part 3A), approximately 12 evaluable patients were expected to be treated across two dose levels, with the sample size per dose level guided by an mTPI design, with target DLT rate of 29% (28%–31%). Intrapatient dose escalation of BMS-986148 was not allowed.

During the expansion phase of the study, 25 to 26 patients in the population of interest (e.g., high H-score or 3+ staining populations) were expected to be treated in each tumor cohort. These numbers were based on achieving reasonable precision of the objective response rate (ORR) using a Simon two-stage design.

Efficacy results were evaluated by tumor type, dose, and regimen for monotherapy and combination cohorts. Individual best overall response, duration of response (DOR), and progression-free survival (PFS) were evaluated using RECIST v1.1 (or modified RECIST for malignant pleural mesothelioma). The duration of response and PFS were estimated by Kaplan–Meier methodology.

All patients who received ≥ 1 dose of study drug were evaluated for safety parameters. All recorded AEs were listed and tabulated by system organ class, preferred term, and treatment and evaluated according to NCI CTCAE v4.03. Safety assessments were based on medical review of AE reports and the results of vital-sign measurements.

Data sharing statement

BMS' policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research.html.

Results

Patients

Between May 2015 and April 2019, 126 patients with selected advanced tumors predicted to express high levels of mesothelin were treated with BMS-986148 monotherapy or in combination with nivolumab. In the dose-escalation and dose-expansion parts of the study combined, 96 patients received BMS-986148 monotherapy (every 3 weeks, $n = 84$; once weekly, $n = 12$), and 30 received BMS-986148 + nivolumab. Baseline characteristics and demographics of patients in CA008-002 were consistent across treatment cohorts (**Table 1**). Median mesothelin expression by H-score in the plasma membrane was 195 in patients with mesothelioma and 192 in patients with ovarian cancer (**Fig. 1**).

Across all CA008-002 cohorts, the median age ranged from 62.5 to 63.5 years, and 53% of patients were male. Most patients had received

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

Table 1. Baseline characteristics in CA008-002.[a]

	BMS-986148 monotherapy every 3 weeks (*n* = 84)	BMS-986148 monotherapy once weekly[b] (*n* = 12)	BMS-986148 + nivolumab every 3 weeks (*n* = 30)	Total (*N* = 126)
Median age (range), years	62.5 (30–81)	63.5 (54–78)	62.5 (46–84)	63.0 (30–84)
Sex, *n* (%)				
Male	42 (50)	7 (58)	18 (60)	67 (53)
Female	42 (50)	5 (42)	12 (40)	59 (47)
Ethnicity, *n* (%)				
White	75 (89)	11 (92)	30 (100)	116 (92)
Other	9 (11)	1 (8)	0	10 (8)
ECOG PS, %				
0	28 (33)	5 (42)	13 (43)	46 (37)
1	56 (67)	7 (58)	17 (57)	80 (63)
No. of prior systemic therapies, *n* (%)				
1	25 (30)	4 (33)	12 (40)	41 (33)
2	17 (20)	4 (33)	7 (23)	28 (22)
3	13 (15)	4 (33)	5 (17)	22 (17)
≥ 4	26 (31)	0	4 (13)	30 (24)
Tumor, *n* (%)				
Mesothelioma	42 (50)	2 (17)	16 (53)	60 (48)
Ovarian cancer	26 (31)	1 (8)	2 (7)	29 (23)
Pancreatic cancer	9 (11)	9 (75)	9 (30)	27 (21)
Gastric cancer	3 (4)	0	1 (3)	4 (3)
NSCLC	4 (5)	0	2 (7)	6 (5)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer.
[a]Data include escalation and expansion cohorts.
[b]Once weekly for 3 weeks followed by 1 week off.

prior systemic therapy; 41% of patients had received ≥ 3 prior therapies. The most common tumor types were mesothelioma and ovarian cancer. At the time of database lock (April 1, 2019), the mean duration of BMS-986148 treatment was 15.3 weeks (range, 2.4–115.4 weeks).

The main reason for treatment discontinuation was disease progression (BMS-986148 monotherapy every-3-weeks cohort, 67%; BMS-986148 monotherapy once-weekly cohort, 75%; combination cohort, 67%; Supplementary Table S1). Dose reductions and treatment discontinuations were observed more frequently in the 1.2 mg/kg every 3 weeks monotherapy group (19/59, 32%) versus the 0.8 mg/kg every 3 weeks monotherapy group (1/8, 13%). Overall, 13% of treated patients discontinued treatment due to TRAEs, 32% had ≥ 1 dose delay for an AE, 7% had ≥ 1 dose

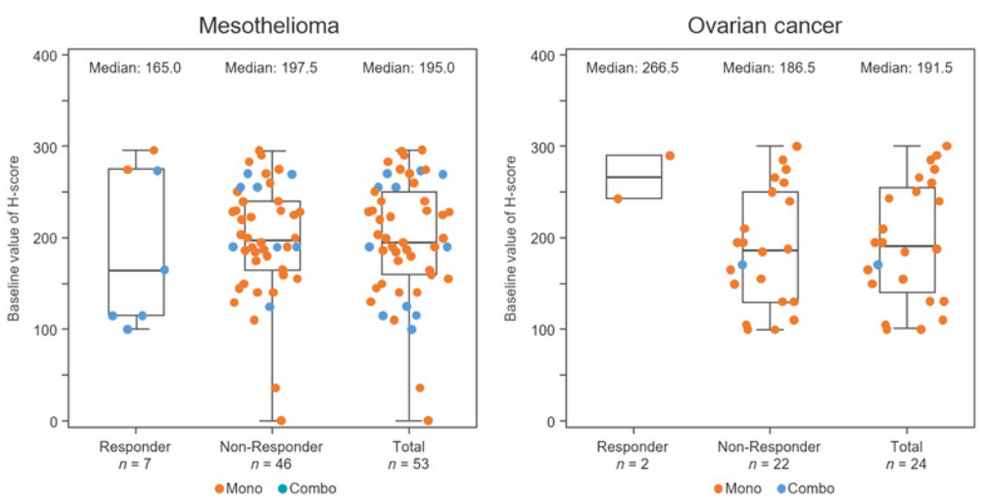

Figure 1.
Association between mesothelin expression level at the plasma membrane and response to BMS-986148 in mesothelioma and ovarian cancer. Response was evaluated using RECIST 1.1 or modified RECIST for malignant pleural mesothelioma; these data include all patients enrolled across dose levels and treatment cohorts in study CA008-002.

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

omission, 6% had ≥ 1 infusion interruption, and 3% had ≥ 1 infusion rate reduction (Supplementary Table S1). Mean (SD) dose intensity per patient was 0.35 (0.11) mg/kg/week in the BMS-986148 monotherapy every-3-weeks cohort, 0.35 (0.09) mg/kg/week in the BMS-986148 monotherapy once-weekly cohort, and 0.23 (0.05) mg/kg/week in the combination cohort.

Monotherapy dose escalation and expansion

In part 1A (dose escalation), six dose levels of BMS-986148 every 3 weeks (21-day cycle) were evaluated in 33 patients as follows: 0.1 mg/kg ($n = 2$), 0.2 mg/kg ($n = 2$), 0.4 mg/kg ($n = 3$), 0.8 mg/kg ($n = 8$), 1.2 mg/kg ($n = 8$), and 1.6 mg/kg ($n = 10$). In part 1B (dose escalation), 12 patients were administered BMS-986148 0.4 mg/kg ($n = 8$) or 0.6 mg/kg ($n = 4$) in a 28-day cycle once weekly for 3 weeks with 1 week off. Part 2 (dose expansion) comprised 51 patients who had ovarian cancer ($n = 22$), mesothelioma ($n = 25$), or NSCLC ($n = 4$) and were treated with BMS-986148 1.2 mg/kg every 3 weeks.

Combination therapy dose escalation and expansion

In part 3A (dose escalation) and part 3B (dose expansion), patients received BMS-986148 0.8 mg/kg + nivolumab 360 mg every 3 weeks. Part 3A comprised 11 patients who had mesothelioma ($n = 3$), ovarian cancer ($n = 2$), NSCLC ($n = 2$), pancreatic cancer ($n = 3$), or gastric cancer ($n = 1$). Part 3B included patients with mesothelioma ($n = 13$) or pancreatic cancer ($n = 6$).

Safety

For the purpose of guiding dose escalation, the DLT assessment period occurred in the dose-escalation parts of the study (parts 1A, 1B, and 3A) during the first cycle of treatment. All patients treated in dose escalation were DLT evaluable. In part 1A, BMS-986148 was administered every 3 weeks in a 21-day cycle. Five of the 10 patients treated at the 1.6 mg/kg dose level every 3 weeks reported DLTs, including four patients with grade 3 elevations of serum transaminases lasting > 5 days and one patient with grade 3 pleuritic pain. In part 1B, in which BMS-986148 was administered once weekly for 3 weeks with 1 week off at 0.4 mg/kg ($n = 8$) or 0.6 mg/kg ($n = 4$), 1 DLT was observed in the 0.4 mg/kg group, and 2 DLTs were observed in the 0.6 mg/kg group; the dose level of 0.6 mg/kg once weekly was considered above the MTD. The 1.2 mg/kg every 3 weeks dose level was determined to be the MTD and the recommended dose for the part 2 monotherapy expansion. In part 3A, 1 DLT was observed among the 11 patients treated with BMS-986148 0.8 mg/kg + nivolumab 360 mg every 3 weeks (Supplementary Table S2), and this dose was used for the combination expansion cohort. All DLTs resolved to grade 1 or baseline levels upon treatment interruption or discontinuation.

The majority of patients experienced TRAEs: 86%, 92%, and 90% of patients in the BMS-986148 monotherapy every 3 weeks, BMS-986148 monotherapy once weekly, and combination cohorts, respectively. The majority of TRAEs were grade 1 or 2. Among the most common TRAEs with BMS-986148 treatment were increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and blood alkaline phosphatase (ALP) levels (**Table 2**). Safety in the BMS-986148 combination with nivolumab cohort was comparable to that in the BMS-986148 monotherapy cohort at the same dose level (0.8 mg/kg), suggesting no additive toxicity profile with the combination (Supplementary Table S3).

Hepatic TRAEs occurred across all treatment cohorts in CA008-002. Three patients experienced grade 4 treatment-related liver abnormality events, including gamma-glutamyltransferase (GGT) increased, ALT increased, and jaundice. Higher doses of BMS-986148 were associated with an increased frequency of hepatic TRAEs and abnormal liver function tests (LFT; **Table 3**; Supplementary Table S3). Similar to the experience in the dose-escalation cohort, the majority of grade ≥ 3 hepatic TRAEs in the dose-expansion cohort resolved with dose interruption, dose reduction, or treatment discontinuation. Overall, the safety experience was similar across the BMS-986148 monotherapy once-weekly and every-3-week cohorts and in combination with nivolumab.

Serious TRAEs were reported in 15 patients (18%) in the BMS-986148 monotherapy every-3-weeks cohort, two patients (17%) in the BMS-986148 monotherapy once-weekly cohort, and seven patients

Table 2. TRAEs with BMS-986148 ± nivolumab (CA008-002).

	BMS-986148 monotherapy every 3 weeks[a,b] ($n = 84$)		BMS-986148 monotherapy once weekly[b,c] ($n = 12$)		BMS-986148 + nivolumab every 3 weeks ($n = 30$)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAE, *n* (%)	72 (86)	42 (49)	11 (92)	3 (25)	27 (90)	10 (33)
TRAEs in ≥ 10% of all patients, *n* (%)						
AST increased	41 (49)	20 (24)	4 (33)	1 (8)	9 (30)	1 (3)
ALT increased	39 (46)	17 (20)	5 (42)	2 (17)	8 (27)	1 (3)
Fatigue	34 (40)	6 (7)	5 (42)	0	8 (27)	0
Nausea	27 (32)	0	2 (17)	0	7 (23)	0
Decreased appetite	22 (26)	1 (1)	2 (17)	0	4 (13)	0
Blood ALP increased	20 (24)	5 (6)	1 (8)	0	2 (7)	0
Vomiting	15 (18)	0	0	0	2 (7)	0
Diarrhea	14 (17)	2 (2)	2 (17)	0	2 (7)	0
Abdominal pain	11 (13)	1 (1)	2 (17)	0	2 (7)	0
Dyspnea	10 (12)	2 (2)	2 (17)	0	0	0
Pleuritic pain	9 (11)	2 (4)	2 (17)	1 (8)	3 (10)	1 (3)
Dysgeusia	6 (7)	0	3 (25)	0	3 (10)	0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Data sorted by monotherapy every 3 weeks any grade column.
[b]All dose levels combined.
[c]Once weekly for 3 weeks followed by 1 week off.

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

Table 3. Hepatic TRAEs with BMS-986148 ± nivolumab (CA008-002).

	BMS-986148 monotherapy every 3 weeks										BMS-986148 monotherapy once weekly						BMS-986148 + nivolumab every 3 weeks	
	0.1–0.4 mg/kg ($n = 7$)[a]		0.8 mg/kg ($n = 8$)[a]		1.2 mg/kg ($n = 59$)[b]		1.6 mg/kg ($n = 10$)[a]		Total ($n = 84$)[b]		0.4 mg/kg ($n = 8$)[a]		0.6 mg/kg ($n = 4$)[a]		Total ($n = 12$)		0.8 mg/kg ($n = 30$)[b]	
n (%)	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Any TRAE	4 (57)	0	6 (75)	1 (13)	52 (88)	32 (54)	10 (100)	9 (90)	72 (86)	42 (49)	7 (88)	1 (13)	4 (100)	2 (50)	11 (92)	3 (25)	27 (90)	10 (33)
Hepatic TRAEs																		
LFT results increased	0	0	0	0	0	0	1 (10)	0	1 (1)	0	0	0	0	0	0	0	1 (3)	0
AST increased	0	0	3 (38)	0	33 (56)	16 (27)	5 (50)	4 (40)	41 (49)	20 (24)	2 (25)	0	2 (50)	1 (25)	4 (33)	1 (8)	9 (30)	1 (3)
ALT increased	0	0	2 (25)	0	32 (54)	15 (25)	5 (50)	2 (20)	39 (46)	17 (20)	3 (38)	0	2 (50)	2 (50)	5 (42)	2 (17)	8 (27)	1 (3)
Blood ALP increased	0	0	0	0	15 (25)	3 (5)	5 (50)	2 (20)	20 (24)	5 (6)	1 (13)	0	0	0	1 (8)	0	2 (7)	0
Blood bilirubin increased	0	0	1 (13)	0	5 (8)	2 (3)	2 (20)	1 (10)	8 (10)	3 (4)	1 (13)	0	1 (25)	0	2 (17)	0	2 (7)	1 (3)
GGT increased	0	0	0	0	2 (3)	2 (3)	1 (10)	0	3 (4)	2 (2)	0	0	0	0	0	0	0	0
Jaundice	0	0	0	0	1 (2)	1 (2)	0	0	1 (1)	1 (1)	0	0	0	0	0	0	0	0
Hepatitis[c]	0	0	0	0	2 (3)	2 (3)	0	0	2 (2)	1 (1)	0	0	0	0	0	0	2 (7)	2 (7)
Drug-induced liver injury	0	0	1 (13)	0	2 (3)	2 (3)	1 (10)	1 (10)	4 (5)	3 (4)	0	0	0	0	0	0	1 (3)	1 (3)
Hepatic TRAEs leading to discontinuation[d]	0	0	1 (13)	0	5 (8)	4 (7)	1 (10)	1 (10)	7 (8)	5 (6)	0	0	0	0	0	0	3 (10)	3 (10)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; Gr, grade; LFT, liver function test; TRAE, treatment-related adverse event.
[a]Includes dose-escalation cohorts.
[b]Includes dose-escalation and dose-expansion cohorts.
[c]Including immune-mediated hepatitis.
[d]Hepatic disorders included ascites, AST increased, ALT increased, drug-induced liver injury I, transaminases increased, and immune-mediated hepatitis.

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

Table 4. Geometric mean (CV%) [*n*] of active ADC exposures with BMS-986148 ± nivolumab (CA008-002).

		BMS-986148 monotherapy every 3 weeks				BMS-986148 + nivolumab every 3 weeks	BMS-986148 monotherapy once weekly	
	Cycle[a]	0.4 mg/kg	0.8 mg/kg	1.2 mg/kg	1.6 mg/kg	0.8 mg/kg	0.4 mg/kg	0.6 mg/kg
C_{max}, μg/mL (CV%) [*n*]	1	2.6 (76.1) [3]	15.8 (46.6) [8]	27.6 (21.6) [56]	40.0 (26.3) [10]	16.8 (26.3) [28]	8.8 (20.3) [8]	13.6 (31.0) [4]
	4	—	16.1 (72.2) [3]	25.3 (24.6) [15]	24.7 (10.5) [3]	16 (15.3) [7]	6.74 (20.4) [2]	—
AUC_{τ}, μg·hour/mL (CV%) [*n*]	1	372 [1]	1093 (67.5) [8]	2304 (37.5) [54]	3238 (36.7) [10]	1320 (40.8) [27]	5.66 (30.1) [8]	1028 (33.4) [3]
	4	—	1283 (104) [3]	2377 (47.6) [14]	1851 (20.6) [3]	1671 (26.2) [6]	680 [1]	—

Abbreviations: ADC, antibody–drug conjugate; AUC_{τ}, area under the curve over the dosing interval; C_{max}, maximum concentration; CV, coefficient of variation.
[a]Cycle 1 is predose through 504 hours postdose.

(23%) in the combination cohort. Grade ≥ 3 serious TRAEs included abdominal pain, anemia, diarrhea, drug-induced liver injury, hepatitis, jaundice, noncardiac chest pain, pericarditis, pleurisy, pneumonitis, pericardial effusion, pleuritic pain, and transaminases increased. Most of the serious TRAEs resolved with dose delay or reduction of BMS-986148 (Supplementary Table S4). Death due to disease progression occurred in 61% of patients in the BMS-986148 monotherapy every-3-weeks cohort, 92% of patients in the BMS-986148 monotherapy once-weekly cohort, and 60% of patients in the combination cohort. One treatment-related death due to pneumonitis occurred in a patient with ovarian cancer and no pre-existing pulmonary disease in the BMS-986148 monotherapy every-3-weeks cohort (1.2 mg/kg) on study day 130. The patient had dyspnea for approximately 1 week before being hospitalized on study day 123, approximately 4 months after initiating treatment. CT scans showed bilateral reticular infiltrate, with no evidence of cardiac pathology or definite evidence of infection. The investigator assessed that the pneumonitis was unlikely related to progressive disease infiltrating the lung. Death on study day 130 was therefore attributed to treatment-related pneumonitis.

Reported ophthalmic AEs, a potential class effect of ADCs, were mostly mild and manageable with topical treatments when indicated. Depending on the type of event, these treatments varied from standard saline solution eye drops (e.g., for dry eyes) to dexamethasone eye drops (e.g., for microcystic epitheliopathy), to cataract surgery. Two patients in the BMS-986148 monotherapy every-3-weeks cohort (1.2 mg/kg) experienced grade 3 ophthalmic AEs: 1 patient exhibited grade 3 keratopathy and grade 3 reduced visual acuity, neither of which were reported as resolved, and one patient had grade 3 cataracts (both eyes) that resolved following dose delay and surgery.

Pharmacokinetics

Total antibody and active ADC exposures increased in a dose-proportional manner when administered every 3 weeks or once weekly (**Table 4**). Active ADC accumulation was not detected after multiple doses of BMS-986148 (0.4–1.6 mg/kg). Clearance of the total antibody and the active ADC appeared linear across doses and dosing regimens. The volumes of distribution for the total antibody and the active ADC were similar to that of total human serum volume, approximately 2 to 3 L. Unconjugated tubulysin concentrations were measurable beginning at 0.4 mg/kg and appeared as early as 24 hours after the end of the BMS-986148 infusion, consistent with formation-rate limited kinetics. Unconjugated tubulysin concentrations increased with dose in the dose-ranging BMS-986148 monotherapy cohorts and were generally low (0.11–0.93 ng/mL) and sustained over the dosing interval. Unconjugated tubulysin concentrations for BMS-986148 at 0.8 mg/kg given in combination with nivolumab were similar to those in the monotherapy cohort and ranged from 0.10 to 0.49 ng/mL.

Clinical activity

Preliminary clinical activity following treatment with BMS-986148 monotherapy or in combination with nivolumab in CA008-002 was observed in 10 of 126 patients across the escalation and expansion cohorts (**Table 5**). Of 51 patients who received BMS-986148 monotherapy in the dose-expansion cohort, three (6%) had a confirmed PR [one with mesothelioma (DOR, 10.35 months) and two with ovarian cancer (DOR, 19.91 and 3.02 months)]. In addition, six of 30 patients (20%) treated with BMS-986148 in combination with nivolumab had a confirmed PR [four with pleural mesothelioma (DOR, 5.09, 8.97, 9.69, and 10.47 months); one with nonpleural mesothelioma (DOR, 5.29 months); and one with pancreatic cancer (DOR, 4.96 months)] (Supplementary Fig. S1A). Two patient cases (one patient with mesothelioma; one patient with ovarian cancer) are described in Supplementary Fig. S2.

The disease-control rate [DCR; defined as CR, PR, or stable disease (SD)] was 56% and 59% in patients with mesothelioma and ovarian cancer, respectively, in the BMS-986148 monotherapy expansion cohorts; patients with mesothelioma treated with the combination had a DCR of 85%. The percentage changes in tumor burden in patients with mesothelioma (Supplementary Fig. S1B) and ovarian cancer (Supplementary Fig. S1C) are shown in the Supplementary Data.

The distribution of baseline median H-score (mesothelin expression) at the tumor cell membrane was evaluated by tumor type and response. Preliminary analysis revealed no significant association between mesothelin expression level and response to BMS-986148 ± nivolumab in patients with mesothelioma or ovarian carcinoma (**Fig. 1**).

Discussion

On the basis of the preclinical safety profile, the potential primary normal tissues that could be affected by BMS-986168 were eye, serosal, gastrointestinal, liver, lymphoid, and bone marrow tissues. Overall, the most common TRAEs were nausea, fatigue, decreased appetite, increased AST/ALT/ALP levels, diarrhea, vomiting, dyspnea, abdominal pain, and pleuritic pain. One case of pneumonitis related to treatment was observed in a patient with ovarian cancer with para-aortic lymph node involvement (treated with BMS-986148 monotherapy 1.2 mg/kg i.v. every 3 weeks) who died. This was the first case of pneumonitis related to BMS-986148 and is not explainable by any of the known mechanisms of action of BMS-986148. The final diagnosis was drug-related pneumonitis in a patient with no obvious clinical risk factors.

Overall, in CA008-002, the safety profile of BMS-986148 was manageable, with the most common TRAEs being low grade and the

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

Table 5. Best overall response with BMS-986148 ± nivolumab (CA008-002).

	BMS-986148 monotherapy				BMS-986148 + nivolumab	
	All escalation ($n = 45$)	All expansion ($n = 51$)	Mesothelioma expansion ($n = 25$)	Ovarian expansion ($n = 22$)	All ($n = 30$)[a]	Mesothelioma ($n = 13$)[b]
ORR, *n* (%)	1 (2)[c]	3 (6)[d]	1 (4)	2 (9)	6 (20)	3 (23)[e]
[95% CI]	[1–12]	[1–16]	[0–20]	[1–29]	[8–39]	[5–54]
Best overall response, *n* (%)						
CR	0	0	0	0	0	0
PR	1 (2)	3 (6)	1 (4)	2 (9)	6 (20)	3 (23)
SD	10 (22)	25 (49)	13 (52)	11 (50)	14 (47)	8 (62)
PD	28 (62)	16 (31)	7 (28)	7 (32)	6 (20)	1 (8)
Not evaluable	6 (13)	0	0	0	0	0
Not reported	0	7 (14)	4 (16)	2 (9)	4 (13)	1 (8)
DCR, *n* (%)[f]	11 (24)	28 (55)	14 (56)	13 (59)	20 (67)	11 (85)
PFS, median, mo (range) [95% CI][g]	NA[h]	2.8 (0.0, 26.5+) [1.5–4.2]	3.8 (0.0+, 26.5+) [1.4–9.5]	2.8 (0.0+, 24.0+) [1.3–4.2]	NA[h]	6.5 (0.6, 19.4+) [2.6–12.1]

Abbreviations: +, censored; CR, complete response; DCR, disease control rate; NA, not available; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]Includes patients from dose-escalation and dose-expansion cohorts.

[b]Includes only patients from the expansion cohort. An additional three patients with mesothelioma were treated in the escalation cohort, with two reporting confirmed PRs lasting 9.69 and 10.41 months.

[c]One patient with mesothelioma assigned to 0.8 mg/kg every 3 weeks had a confirmed PR lasting 10.22 months.

[d]Of four patients with NSCLC treated with monotherapy, none had a best overall response of CR or PR.

[e]The mean ORR was 31% with the combination in the escalation and expansion cohorts with mesothelioma ($n = 16$).

[f]DCR was defined as CR, PR, or SD.

[g]By Kaplan-Meier method.

[h]Aggregate escalation PFS data are unavailable because of the confounding variables of different dose levels in different tumor types.

majority of serious TRAEs resolving with dose delay or reduction. The frequency and intensity of TRAEs increased with higher doses of BMS-986148. Upon data review of the safety and pharmacokinetic profiles from the every 3 weeks and once-weekly dose-escalation cohorts and to align with the nivolumab dosing schedule, the BMS-986148 1.2 mg/kg every 3 weeks dose level was determined to be the MTD and the recommended phase II dose for monotherapy dose expansion. The clinical experience with BMS-986148 monotherapy in Japanese patients treated in CA008-008 (see Supplementary Tables S5 and S6) was consistent with the findings from the larger international CA008-002 study; no new safety signals were observed with BMS-986148 monotherapy in these patients.

BMS-986148 in combination with nivolumab demonstrated a similar safety profile to that of BMS-986148 monotherapy at the same dose level (0.8 mg/kg). Preliminary evidence of clinically meaningful antitumor activity with durable responses was observed in a limited number of patients with mesothelioma and ovarian cancer treated with BMS-986148 ± nivolumab, with possibly greater response rates observed with the combination than with monotherapy.

Hepatic TRAEs were among the most common and dose limiting TRAEs observed with BMS-986148 monotherapy as well as in combination with nivolumab. The observation of LFT abnormalities following treatment with BMS-986148 was consistent with the known adverse event profile of the cytotoxic payload, tubulysin, an antimitotic agent targeting tubulin (33–35). Furthermore, preclinical studies of both tubulysin and BMS-986148 detected increased serum AST and/or ALT levels with skeletal muscle cell degeneration and single-cell necrosis of hepatocytes (data on file). Most hepatic TRAEs were grades 1 to 3; however, three patients enrolled in CA008-002 experienced grade 4 hepatic events. The frequency of LFT-related TRAEs and DLTs increased with higher doses of BMS-986148, with the majority resolving with dose delay, reduction, or discontinuation. A possible antigen-independent mechanism was hypothesized, whereby the payload inhibits microtubule polymerization in Kupffer cells, macrophages, epithelial cells, and endothelial cells, resulting in hepatic injury (23, 36, 37). Further investigation is needed to uncover why off-target hepatotoxicity occurs in a subset of patients treated with BMS-986148.

Patients with an abnormal hepatic laboratory panel (ALT, AST, total bilirubin, and ALP) who met potential drug-induced liver injury criteria were candidates for study drug discontinuation. In addition, depending on the grade and duration of the LFT increase, treatment with BMS-986148 was delayed, dose reduced, or discontinued. In addition, hepatic TRAEs were evaluated and managed per approved toxicity management algorithms when BMS-986168 was administered in combination with nivolumab, with dose reductions of BMS-986168 permitted (38).

As a class, ADCs are often associated with ophthalmic AEs, perhaps because of the robust blood supply, rapidly dividing cell populations, and abundant and variable receptors present in the eye (39). Corneal changes, such as microcystic epithelial alterations and keratopathy leading to blurred vision, have been documented with ADC treatments (40). Ophthalmic AEs were reported in < 10% of patients treated with BMS-986148 in CA008-002, and the majority were low grade, suggesting that targeting mesothelin or using tubulysin as a payload may result in less ophthalmic toxicity than with other ADC molecules. Indeed, these types of events have most often been reported in patients treated with ADCs containing maytansinoid DM4 or monomethyl auristatin-F, with blurred vision and keratopathy observed in 40% and 30% of patients, respectively (40). Treatment with anetumab, a mesothelin-directed ADC under clinical development with a maytansinoid tubulin inhibitor DM4 and hindered disulfide linker (9), has

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

been associated with TRAEs requiring dose reduction in approximately half of patients, including keratitis (21%), blurred vision (11%), and peripheral neuropathy (13%; ref. 41). LFT increases were reported in 30% of patients at the MTD of anetumab (9, 41). Among the most common toxicities observed with DMOT4039A, another mesothelin-directed ADC composed of a monomethyl auristatin E with a valine citrulline linker, were peripheral neuropathy (29%) and gastrointestinal toxicities (11). Thus, the cytotoxic payload incorporated in the ADC may contribute to the frequency and nature of treatment-related AEs, and the differences observed in the safety profiles across these mesothelin-directed ADCs could be due to the cytotoxic payloads or divergent conjugation chemistries (11, 40, 42).

Preclinical studies with BMS-986148 suggested the potential for antigen-dependent ophthalmic toxicity, whereby the ADC molecule might bind to mesothelin on corneal and conjunctival epithelial cells, resulting in necrosis and inflammation (data on file). On the basis of these observations, proactive monitoring and mitigation strategies for ophthalmic AEs were carried out, which may have enabled earlier detection and management, resulting in a less clinically significant profile.

Assessment and mitigation strategies for possible ophthalmic AEs included an 8-point examination at baseline (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination, and fundoscopy) and focused examinations (visual acuity, slit lamp, others as indicated) at predose cycle 2, every other cycle thereafter, and end of treatment. For symptoms of ocular toxicity at any time during treatment with BMS-986148, dose interruption and potential dose reduction or discontinuation were recommended followed by prompt management with an ophthalmologist. However, the toxicity observed in this study was not as prominent as that reported in other studies (40, 41). Further assessment is needed to determine how specifically targeting mesothelin affects the safety profile of BMS-986148 or other mesothelin-directed ADCs.

Mesothelin is a promising target for anticancer therapies because it is differentially expressed in a subset of normal tissues (1), with overexpression occurring in particular tumors (4). On the basis of this differential expression, patients with tumors that have higher levels of mesothelin expression could be more likely to respond to mesothelin-directed ADCs. Preclinical studies of BMS-986148 detected an association between mesothelin expression and response (data on file) similar to preclinical findings for anetumab (9). Phase I studies of anetumab monotherapy (41) and DMOT4039A monotherapy also detected antitumor responses (11). Although most responding patients in these studies had evidence of mesothelin expression, no significant correlation could be established, consistent with the results from CA008-002 (11, 41).

In CA008-002, mesothelin expression was assessed retrospectively in the escalation phase and prospectively for patient selection in the expansion phase, which was limited to patients with tumors expressing mesothelin. However, because patient numbers and responses were limited, our preliminary analyses were not able to assess whether mesothelin expression levels at the plasma membrane were associated with response. Therefore, analyses in a larger patient population are required to determine whether the level of mesothelin expression at the plasma membrane, in the cytoplasm, or in patient serum is correlated with response to BMS-986148 and whether this information could be applied to help prospectively identify patients who may respond to BMS-986148 treatment.

In patients with malignant pleural mesothelioma, median overall survival has been reported as 16 months and, for patients with extensive disease, as only 5 months with standard-of-care chemotherapy, surgery, and radiation (43, 44). Therefore, extending treatment options for patients with mesothelioma is critical because poor response outcomes occur with standard medical treatment or surgery alone (45). Preliminary clinical activity was detected in a subset of patients with tumors treated with BMS-986148 monotherapy or in combination with nivolumab, particularly in patients with mesothelioma treated with the combination. One limitation of CA008-002 is the absence of a comparator arm to enable increased understanding of the contribution of BMS-986148 to the combinatorial clinical activity with nivolumab. Studies in patients with mesothelioma treated with nivolumab monotherapy have reported response rates of 22%, 26%, and 29% (46–48). Furthermore, we observed a median PFS of 6.5 months in patients with mesothelioma treated with BMS-986148 in combination with nivolumab, which is longer than the 2.5-month (46) to 2.6-month (47) median PFS observed with anti–PD-1 monotherapy but similar to the 6.1-month mPFS reported by Okada and colleagues (48). Therefore, additional data are required to understand the contribution of components to this multimodal approach combining an anti-mesothelin ADC and an anti–PD-1 checkpoint inhibitor, but it could represent a novel treatment strategy for patients with metastatic or refractory solid tumors, including mesothelioma, who have experienced limited increases in overall survival despite recent therapeutic advances (5, 49).

Together, these results showed that BMS-986148 monotherapy ± nivolumab exhibited a clinically manageable safety profile in patients with advanced tumors. Promising durable antitumor activity was also observed in some patients with selected tumors. However, additional optimization may be needed to increase the therapeutic index of BMS-986148. Further exploration of patients with extended duration of response to mesothelin-directed ADCs could potentially identify biomarkers to help further identify patients most likely to benefit from this therapeutic approach. These preliminary data support additional studies to assess combinations of directed cytotoxic therapies with immune checkpoint therapies to generate multimodal treatments for patients with advanced solid tumors.

Authors' Disclosures

S. Rottey reports other support from Pfizer, Ipsen, and Bayer, and grants and other support from Roche outside the submitted work. J. Clarke reports grants from Bristol Myers Squibb during the conduct of the study; grants from Bristol Myers Squibb, Spectrum, Adaptimmune, Bayer, Medpacto, AbbVie, Moderna, GlaxoSmithKline, Array, Grid Therapeutics, and Cellular Biomedical Group (CBMG); grants and personal fees from Genentech, AstraZeneca, and Merck; and personal fees from Pfizer, NGM Pharmaceuticals, and G1 Therapeutics outside the submitted work. J.-P. Machiels reports other support from Pfizer, Roche, AstraZeneca, Bayer, Innate, Merck Serono, Boerhinger, Janssen, Bristol Myers Squibb, Novartis, Incyte, Cue Biopharma, ALX Oncology, iTEOS, eTheRNA, NEKTAR, Amgen, MSD, and Psioxus during the conduct of the study. B. Markman reports personal fees from Amgen, Merck, and Bristol Myers Squibb outside the submitted work. M. Millward reports other support from Bristol Myers Squibb during the conduct of the study; personal fees from Merck Sharp & Dohme, Takeda, Roche, Pfizer, and Novartis; and personal fees and other support from Bristol Myers Squibb and AstraZeneca outside the submitted work. M. Lolkema reports grants and personal fees from Astellas, Sanofi, Janssen, and MSD; personal fees from Incyte, Amgen, Bayer, Servier, Roche, Pfizer, AstraZeneca, Novartis, and Julius Clinical outside the submitted work. S.P. Patel reports other support from Bristol Myers Squibb during the conduct of the study; other support from Amgen, AstraZeneca/MedImmune, Bristol Myers Squibb, Certis, Eli Lilly, Fate Therapeutics, Genentech, Genocea, Illumina, Iovance, Merck, Pfizer, Roche/Genetech, Rakuten, and Tempus outside the submitted work. P. de Souza reports personal fees from Eisai outside the submitted work. G. Curigliano reports personal fees from Roche, Pfizer, AstraZeneca, Lilly, Novartis, Daichii Sankyo, Sanofi,

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

Bristol Myers Squibb, Ellipsis, Gilead, and Seagen outside the submitted work. A. Santoro reports other support from AbbVie, Amgen, Arqule, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Eisai, Gilead, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sandoz, Sanofi, Servier, and Takeda during the conduct of the study. T. Koyama reports other support from Sysmex and Chugai outside the submitted work. H. Vezina reports other support from Bristol Myers Squibb outside the submitted work. C. He reports other support from Bristol Myers Squibb outside the submitted work. Q.S.-C. Chu reports personal fees from AbbVie, Amgen, Astellas, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, and Takeda; grants and personal fees from AstraZeneca; grants from Exactis; personal fees and other support from Merck KGaA outside the submitted work. M. Brown is an employee and stock owner of Bristol Myers Squibb. H. Vezina is an employee and stock owner of Bristol Myers Squibb. C. He is an employee and stock owner of Bristol Myers Squibb. No disclosures were reported by the other authors.

Authors' Contributions

S. Rottey: Conceptualization, investigation, methodology, project administration, writing–review and editing. **J. Clarke:** Conceptualization, investigation, methodology, writing–review and editing. **K. Aung:** Investigation, writing–review and editing. **J.-P. Machiels:** Investigation, writing–review and editing. **B. Markman:** Investigation, writing–review and editing. **K.M. Heinhuis:** Investigation, writing–review and editing. **M. Millward:** Investigation, writing–review and editing. **M. Lolkema:** Investigation, writing–review and editing. **S.P. Patel:** Investigation, writing–review and editing. **P. de Souza:** Investigation, writing–review and editing. **M. Duca:** Investigation, writing–review and editing. **G. Curigliano:** Investigation, writing–review and editing. **A. Santoro:** Investigation, writing–review and editing. **T. Koyama:** Investigation, writing–review and editing. **M. Brown:** Conceptualization, data curation, formal analysis, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing. **H. Vezina:** Conceptualization, data curation, formal analysis, validation, methodology, writing–review and editing. **C. He:** Conceptualization, data curation, formal analysis, validation, writing–review and editing. **Q.S.-C. Chu:** Conceptualization, investigation, methodology, writing–review and editing.

Acknowledgments

We thank the patients and their families who made this study possible and the clinical study teams who participated in this study. We thank Filippo De Braud (University of Milan; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy) for his contributions to the study. This study was supported by Bristol Myers Squibb (Princeton, NJ) and ONO Pharmaceutical Company Ltd. (Osaka, Japan). This study was funded by Bristol Myers Squibb. All authors contributed to and approved the work presented here; writing and editorial assistance was provided by Brittany L. Phillips, PhD, and Alex L. Loeb, PhD, CMPP, of Chrysalis Medical Communications, Inc. (Hamilton, NJ) and funded by Bristol Myers Squibb.

This study is financially supportted by Bristol Myers Squibb.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 8, 2021; revised July 7, 2021; accepted October 4, 2021; published first October 6, 2021.

References

1. Pastan I, Hassan R. Discovery of mesothelin and exploiting it as a target for immunotherapy. Cancer Res 2014;74:2907–12.
2. Rump A, Morikawa Y, Tanaka M, Minami S, Umesaki N, Takeuchi M, et al. Binding of ovarian cancer antigen CA125/MUC16 to mesothelin mediates cell adhesion. J Biol Chem 2004;279:9190–8.
3. Jirsova K, Neuwirth A, Kalasova S, Vesela V, Merjava S. Mesothelial proteins are expressed in the human cornea. Exp Eye Res 2010;91:623–9.
4. O'Hara M, Stashwick C, Haas AR, Tanyi JL. Mesothelin as a target for chimeric antigen receptor-modified T cells as anticancer therapy. Immunotherapy 2016;8:449–60.
5. Hassan R, Thomas A, Alewine C, Le DT, Jaffee EM, Pastan I. Mesothelin immunotherapy for cancer: ready for prime time? J Clin Oncol 2016;34:4171–9.
6. Kachala SS, Bograd AJ, Villena-Vargas J, Suzuki K, Servais EL, Kadota K, et al. Mesothelin overexpression is a marker of tumor aggressiveness and is associated with reduced recurrence-free and overall survival in early-stage lung adenocarcinoma. Clin Cancer Res 2014;20:1020–8.
7. Tozbikian G, Brogi E, Kadota K, Catalano J, Akram M, Patil S, et al. Mesothelin expression in triple negative breast carcinomas correlates significantly with basal-like phenotype, distant metastases and decreased survival. PLoS One 2014;9:e114900.
8. Servais EL, Colovos C, Rodriguez L, Bograd AJ, Nitadori J, Sima C, et al. Mesothelin overexpression promotes mesothelioma cell invasion and MMP-9 secretion in an orthotopic mouse model and in epithelioid pleural mesothelioma patients. Clin Cancer Res 2012;18:2478–89.
9. Zhao XY, Subramanyam B, Sarapa N, Golfier S, Dinter H. Novel antibody therapeutics targeting mesothelin in solid tumors. Clin Cancer Drugs 2016;3:76–86.
10. Golfier S, Kopitz C, Kahnert A, Heisler I, Schatz CA, Stelte-Ludwig B, et al. Anetumab ravtansine: a novel mesothelin-targeting antibody-drug conjugate cures tumors with heterogeneous target expression favored by bystander effect. Mol Cancer Ther 2014;13:1537–48.
11. Weekes CD, Lamberts LE, Borad MJ, Voortman J, McWilliams RR, Diamond JR, et al. Phase I study of DMOT4039A, an antibody-drug conjugate targeting mesothelin, in patients with unresectable pancreatic or platinum-resistant ovarian cancer. Mol Cancer Ther 2016;15:439–47.
12. Lambert JM, Morris CQ. Antibody-drug conjugates (ADCs) for personalized treatment of solid tumors: a review. Adv Ther 2017;34:1015–35.
13. Hedrich WD, Fandy TE, Ashour HM, Wang H, Hassan HE. Antibody-drug conjugates: pharmacokinetic/pharmacodynamic modeling, preclinical characterization, clinical studies, and lessons learned. Clin Pharmacokinet 2018;57:687–703.
14. Amiri-Kordestani L, Blumenthal GM, Xu QC, Zhang L, Tang SW, Ha L, et al. FDA approval: ado-trastuzumab emtansine for the treatment of patients with HER2-positive metastatic breast cancer. Clin Cancer Res 2014;20:4436–41.
15. de Claro RA, McGinn K, Kwitkowski V, Bullock J, Khandelwal A, Habtemariam B, et al. U.S. Food and Drug Administration approval summary: brentuximab vedotin for the treatment of relapsed Hodgkin lymphoma or relapsed systemic anaplastic large-cell lymphoma. Clin Cancer Res 2012;18:5845–9.
16. U.S. Food and Drug Administration. FDA approves gemtuzumab ozogamicin for CD33-positive AML in pediatric patients; 2017. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-gemtuzumab-ozogamicin-cd33-positive-aml-pediatric-patients.
17. U.S. Food and Drug Administration. FDA approves inotuzumab ozogamicin for relapsed or refractory B-cell precursor ALL; 2017. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inotuzumab-ozogamicin-relapsed-or-refractory-b-cell-precursor-all#:~:text=On%20Aug.,acute%20lymphoblastic%20leukemia%20(ALL).
18. U.S. Food and Drug Administration. FDA approves polatuzumab vedotin-piiq for diffuse large B-cell lymphoma; 2019. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-polatuzumab-vedotin-piiq-diffuse-large-b-cell-lymphoma.
19. U.S. Food and Drug Administration. FDA grants accelerated approval to enfortumab vedotin-ejfv for metastatic urothelial cancer; 2019. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-enfortumab-vedotin-ejfv-metastatic-urothelial-cancer.
20. U.S. Food and Drug Administration. FDA approves fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive breast cancer; 2019. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-option-patients-her2-positive-breast-cancer-who-have-progressed-available.
21. U.S. Food and Drug Administration. FDA grants accelerated approval to sacituzumab govitecan-hziy for metastatic triple negative breast cancer; 2020. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer.
22. U.S. Food and Drug Administration. FDA granted accelerated approval to belantamab mafodotin-blmf for multiple myeloma; 2020. Available

from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-granted-accelerated-approval-belantamab-mafodotin-blmf-multiple-myeloma.
23. Khalil MW, Sasse F, Lunsdorf H, Elnakady YA, Reichenbach H. Mechanism of action of tubulysin, an antimitotic peptide from myxobacteria. ChemBioChem 2006;7:678–83.
24. Clarke J, Chu S-C, Siu LL, Jean-Pascal M, Markman B, Heinhuis K, et al. BMS-986148, an anti-mesothelin antibody-drug conjugate (ADC), alone or in combination with nivolumab demonstrates clinical activity in patients with select advanced solid tumors (Abstract B057). Mol Cancer Ther 2019;18(suppl 12).
25. Harris SJ, Brown J, Lopez J, Yap TA. Immuno-oncology combinations: raising the tail of the survival curve. Cancer Biol Med 2016;13:171–93.
26. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167–75.
27. Choueiri TK, Fishman MN, Escudier B, McDermott DF, Drake CG, Kluger H, et al. Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma. Clin Cancer Res 2016;22:5461–71.
28. Muller P, Martin K, Theurich S, Schreiner J, Savic S, Terszowski G, et al. Microtubule-depolymerizing agents used in antibody-drug conjugates induce antitumor immunity by stimulation of dendritic cells. Cancer Immunol Res 2014;2:741–55.
29. Santarpia M, Karachaliou N. Tumor immune microenvironment characterization and response to anti-PD-1 therapy. Cancer Biol Med 2015;12:74–8.
30. Weber JS, Ramakrishnan R, Laino A, Berglund AE, Woods D. Association of changes in T regulatory cells (Treg) during nivolumab treatment with melanoma outcome (Abstract 3031). J Clin Oncol 2017;35(suppl 15).
31. Radu OM, Foxwell T, Cieply K, Navina S, Dacic S, Nason KS, et al. HER2 amplification in gastroesophageal adenocarcinoma: correlation of two antibodies using gastric cancer scoring criteria, H score, and digital image analysis with fluorescence in situ hybridization. Am J Clin Pathol 2012;137:583–94.
32. U.S. Department of Health and Human Services Food and Drug Administration. E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1): Guidance for Industry; 2018. Available from: https://www.fda.gov/files/drugs/published/E6%28R2%29-Good-Clinical-Practice–Integrated-Addendum-to-ICH-E6%28R1%29.pdf.
33. Smolinski MP, Bu Y, Clements J, Gelman IH, Hegab T, Cutler DL, et al. Discovery of novel dual mechanism of action Src signaling and tubulin polymerization inhibitors (KX2-391 and KX2-361). J Med Chem 2018;61:4704–19.
34. Rischin D, Bibby DC, Chong G, Kremmidiotis G, Leske AF, Matthews CA, et al. Clinical, pharmacodynamic, and pharmacokinetic evaluation of BNC105P: a phase I trial of a novel vascular disrupting agent and inhibitor of cancer cell proliferation. Clin Cancer Res 2011;17:5152–60.
35. Fanale D, Bronte G, Passiglia F, Calo V, Castiglia M, Di Piazza F, et al. Stabilizing versus destabilizing the microtubules: a double-edge sword for an effective cancer treatment option? Anal Cell Pathol 2015;2015:690916.
36. Leamon CP, Reddy JA, Vetzel M, Dorton R, Westrick E, Parker N, et al. Folate targeting enables durable and specific antitumor responses from a therapeutically null tubulysin B analogue. Cancer Res 2008;68:9839–44.
37. Staben LR, Yu SF, Chen J, Yan G, Xu Z, Del Rosario G, et al. Stabilizing a tubulysin antibody-drug conjugate to enable activity against multidrug-resistant tumors. ACS Med Chem Lett 2017;8:1037–41.
38. Grover S, Rahma OE, Hashemi N, Lim RM. Gastrointestinal and hepatic toxicities of checkpoint inhibitors: algorithms for management. American Society of Clinical Oncology Educational Book. 2018. Available from: https://ascopubs.org/doi/abs/10.1200/EDBK_100013.
39. Eaton JS, Miller PE, Mannis MJ, Murphy CJ. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. J Ocul Pharmacol Ther 2015;31:589–604.
40. Matulonis UA, Birrer MJ, O'Malley DM, Moore KN, Konner J, Gilbert L, et al. Evaluation of prophylactic corticosteroid eye drop use in the management of corneal abnormalities induced by the antibody-drug conjugate mirvetuximab soravtansine. Clin Cancer Res 2019;25:1727–36.
41. Hassan R, Blumenschein GR Jr, Moore KN, Santin AD, Kindler HL, Nemunaitis JJ, et al. First-in-human, multicenter, phase i dose-escalation and expansion study of anti-mesothelin antibody-drug conjugate anetumab ravtansine in advanced or metastatic solid tumors. J Clin Oncol 2020;38:1824–35.
42. Donaghy H. Effects of antibody, drug and linker on the preclinical and clinical toxicities of antibody-drug conjugates. MAbs 2016;8:659–71.
43. PDQ Adult Treatment Editorial Board. Malignant Mesothelioma Treatment (Adult) (PDQ®) Health Professional Version; PDQ Cancer Information Summaries [Internet]. National Cancer Institute (US). 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK65983/.
44. Sugarbaker DJ, Strauss GM, Lynch TJ, Richards W, Mentzer SJ, Lee TH, et al. Node status has prognostic significance in the multimodality therapy of diffuse, malignant mesothelioma. J Clin Oncol 1993;11:1172–8.
45. Blyth KG, Murphy DJ. Progress and challenges in mesothelioma: from bench to bedside. Respir Med 2018;134:31–41.
46. Popat S, Curioni-Fontecedro A, Polydoropoulou V, Shah R, O'Brien M, Pope A, et al. A multicentre randomized phase III trial comparing pembrolizumab (P) vs single agent chemotherapy (CT) for advanced pre-treated malignant pleural mesothelioma (MPM) – results from the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. Ann Oncol 2019;31:1734–45.
47. Quispel-Janssen J, van der Noort V, de Vries JF, Zimmerman M, Lalezari F, Thunnissen E, et al. Programmed death 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma. J Thorac Oncol 2018;13:1569–76.
48. Okada M, Kijima T, Aoe K, Kato T, Fujimoto N, Nakagawa K, et al. Clinical efficacy and safety of nivolumab: results of a multicenter, open-label, single-arm, Japanese phase II study in malignant pleural mesothelioma (MERIT). Clin Cancer Res 2019;25:5485–92.
49. Gray SG, Mutti L. Immunotherapy for mesothelioma: a critical review of current clinical trials and future perspectives. Transl Lung Cancer Res 2020;9:S100–S19.

Published OnlineFirst October 6, 2021; DOI: 10.1158/1078-0432.CCR-21-1181

Clinical Cancer Research

Phase I/IIa Trial of BMS-986148, an Anti-mesothelin Antibody–drug Conjugate, Alone or in Combination with Nivolumab in Patients with Advanced Solid Tumors

Sylvie Rottey, Jeffrey Clarke, Kyaw Aung, et al.

Clin Cancer Res 2022;28:95-105. Published OnlineFirst October 6, 2021.