Background BMS-986218 is a nonfucosylated human IgG1 anti-cytotoxic T-lymphocyte antigen (CTLA)-4 monoclonal antibody with optimized CD16 FcγR binding that enhances T-cell priming and mitigates T-regulatory cell-mediated suppression in the tumor microenvironment. In preclinical models, BMS-986218 increased the proportion of antigen-specific CD8+ effector T cells vs ipilimumab in peripheral blood. We present safety, efficacy, and pharmacodynamic data from the dose-escalation part of the first-in-human study of BMS-986218 ± nivolumab in patients with advanced solid tumors (NCT03110107).

Methods Patients with advanced solid tumors, disease progression on ≥2 lines of therapy (≥1 line for patients with melanoma), and Eastern Cooperative Oncology Group performance status 0–1 were included. Patients received BMS-986218 as monotherapy (2–200 mg Q4W or 20–50 mg Q2W) or as combination therapy (BMS-986218 20–70 mg Q4W plus nivolumab 480 mg Q4W). The primary endpoint was safety and tolerability. Secondary endpoints included preliminary efficacy and characterization of BMS-986218 ± nivolumab pharmacokinetics and immunogenicity.

Results In total, 155 patients were treated on dose escalation; 107 with monotherapy and 48 with combination (table 1). Any-grade and grade 3/4 treatment-related adverse events (TRAEs) were reported in 58% and 18% of monotherapy patients, respectively. The most common grade 3/4 TRAE was diarrhea (5%). Any-grade and grade 3/4 TRAEs were reported in 60% and 27% of combination patients, respectively. The most common grade 3/4 TRAE was colitis (6%) and increased amylase (6%). TRAEs leading to treatment discontinuation were reported in 11% of monotherapy patients and 13% of combination patients. A grade 5 TRAE of pneumonitis was reported in the monotherapy group at the 7-mg Q4W dose level. Partial responses with durations of 1.9–10.3 months were observed with monotherapy and combination therapy in patients with microsatellite-stable colorectal, pancreatic, gastric, and breast cancer. Analysis of peripheral cytokine levels (interferon-γ, CXCL9, and CXCL10) showed increases with increasing BMS-986218 dose in the monotherapy and combination groups (figure 1). Additional preclinical and clinical results will be presented.

Conclusions BMS-986218 demonstrated a tolerable safety profile and preliminary antitumor activity as monotherapy and in combination with nivolumab across various tumor types, including tumors with high unmet need or that are traditionally immune checkpoint inhibitor-insensitive. These results support further investigation of nonfucosylated anti-CTLA-4 therapies. The dose expansion part of the BMS-986218 ± nivolumab study and a phase 1/2 study evaluating anti-CTLA-4 nonfucosylated probody (BMS-986288; NCT03994601 ± nivolumab) are ongoing.

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Trial Registration Clinicaltrials.gov NCT03110107

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Ethics Approval The trial protocol was approved by the institutional review boards or independent ethics committees of each study site and was conducted according to Good Clinical Practice guidelines, per the International Conference on Harmonisation. Patients provided written informed consent based on the principles of the Declaration of Helsinki.
Abstract 592 Figure 1  Change in peripheral interferon-γ, CXCL9, and CXCL10 levels by BMS 986218 dose in the monotherapy and combination groups.