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ONLINE ONLY SUPPLEMENTARY MATERIAL

Eligibility criteria

Inclusion criteria

- Signed informed consent form
- Male or female patients aged ≥18 years at the time of informed consent
- Pathologically documented, definitively diagnosed, advanced colorectal cancer (CRC), pancreatic cancer, or non-small-cell lung cancer (NSCLC) refractory to standard treatment, or the patient had been intolerant to or refused standard treatment. The select tumor types were required to meet the following criteria:
  - Part 1 and group 1: advanced mismatch repair-proficient CRC patients naïve to anti-programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1)/colony-stimulating factor 1 (CSF1)/CSF1 receptor (CSF1R) therapies
  - Part 1 and group 2: advanced pancreatic cancer patients with good performance status (defined as Eastern Cooperative Oncology Group (ECOG) performance status 0–1, good pain management, and adequate nutritional intake) naïve to anti-PD-1/PD-L1/CSF1/CSF1R therapies
  - Part 1 and group 3: advanced NSCLC patients with low (<50%) tumor PD-L1 expression naïve to anti-PD-1/PD-L1/CSF1/CSF1R therapies
  - Part 1 and group 4: NSCLC patients with low (<50%) tumor PD-L1 expression, naïve to anti-CSF1/CSF1R therapies, and who had not

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responded to (disease progression or stable disease >6 months) or had relapsed during monotherapy with anti-PD-1/PD-L1 therapies

  - Part 1 and group 5: NSCLC patients with high (≥50%) tumor PD-L1 expression who were anti-CSF1/CSF1R naïve and had not responded to (disease progression or stable disease >6 months) or had relapsed during monotherapy with anti-PD-1/PD-L1 therapies

- Patients were required to have radiographically and/or clinically measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Index lesions could not be chosen from a previously irradiated field unless there had been radiographic tumor progression in that lesion prior to enrollment
- ECOG performance status of 0 to 1
- Adequate organ function, defined as follows:
  - Hematological: absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, hemoglobin ≥9 g/dL (without need for hematopoietic growth factor or transfusion support)
  - Renal: serum creatinine ≤1.5 x upper limit of normal (ULN), or 24-hour creatinine clearance ≥60 mL/min for patient with creatinine levels >1.5 x ULN
  - Hepatic: serum bilirubin ≤1.5 x ULN or direct bilirubin ≤ULN for a patient with total bilirubin level >1.5 x ULN; aspartate aminotransferase (AST) ≤2.5 x ULN or ≤5 x ULN for patient with liver metastases; alanine aminotransferase (ALT) ≤2.5 x ULN or ≤5 x ULN for patient with liver metastases

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  - Coagulation: international normalization ratio (INR) or prothrombin time (PT) ≤1.5 x ULN, unless the patient is receiving anticoagulant therapy, in which case PT and partial thromboplastin time (PTT)/activated PTT (aPTT) must be within therapeutic range of intended use of anticoagulants; PTT or aPTT ≤1.5 x ULN unless the patient is receiving anticoagulant therapy as long as PT and PTT/aPTT is within therapeutic range of intended use of anticoagulants

- Patients with NSCLC: Available information regarding recently (within 3 months prior to day 1 and no systemic therapy given since the biopsy) evaluated PD-L1 tumor expression status or willing to provide fresh tumor biopsy to determine eligibility. NSCLC patients who failed to respond to or relapsed during previous anti-PD-1/PD-L1 therapy could be enrolled based on previously established PD-L1 tumor expression, if discussed and agreed by Amgen
- Patients with CRC: Availability of a recent (within 3 months prior to day 1 and no systemic therapy given since the biopsy) and biomarker evaluable tumor tissue sample at baseline
- Patients with pancreatic cancer: Availability of a recent (within 3 months prior to day 1 and no systemic therapy given since the biopsy) and biomarker evaluable tumor tissue sample at baseline, whenever feasible

Exclusion criteria

- Known active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases could participate provided they were stable (without evidence of progression by imaging for at

least 4 weeks prior to the first study dose and neurologic symptoms returned to baseline), had no evidence of new or progressing brain lesions, and were not using steroids >10 mg prednisone equivalent for at least 7 days prior to trial treatment. This exception did not include carcinomatous meningitis, which was excluded regardless of clinical stability

- History of other malignancy within the past 2 years with the following exceptions:
  - Malignancy treated with curative intent and with no known active disease present, had not received chemotherapy for ≤2 years before enrollment, and felt to be at low risk for recurrence by the treating physician
  - Adequately treated nonmelanoma skin cancer, cervical carcinoma in situ, superficial or in situ carcinoma of the bladder, or breast ductal carcinoma in situ, without evidence of disease at the time of enrollment
  - Prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of enrollment
- History of interstitial lung disease, (noninfectious) pneumonitis that required steroids, or current pneumonitis
- History or evidence of other active autoimmune diseases that required prolonged systemic treatment in the past 2 years (ie, with use of disease-modifying agents, such as corticosteroids or immunosuppressive drugs)
- Evidence of clinically significant immunosuppression, such as the following:
  - Organ transplant or prior stem cell transplantation
  - Any severe congenital or acquired cellular and/or humoral immune deficiency

  - Other signs or symptoms of clinical immune system suppression or diagnosis of immunodeficiency
  - Concurrent opportunistic infection

- Receipt of systemic immunosuppressive therapy (>2 weeks) within 7 days prior to the first dose of study treatment, including oral steroid doses >10 mg/day of prednisone or equivalent, except for management of adverse events during the course of the study. Patients that required intermittent use of bronchodilators or local steroid injection were not to be excluded from the study
- Receipt of systemic immunostimulatory agents within 6 weeks or 5 half-lives, whichever is shorter, prior to first dose of study treatment (except anti–PD-1/PD-L1 treatment if recruited into group 4 or group 5)
- Evidence of active infection within 2 weeks prior to first dose of study treatment
- Prior chemotherapy, radiotherapy, biological cancer therapy, or major surgery within 28 days prior to enrollment
- Currently participating or had participated in a study (treatment period only) of an investigational agent or used an investigational device within 28 days of enrollment
- Adverse event due to cancer therapy administered more than 28 days prior to enrollment that had not recovered to Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or better. Note: Patients with grade ≤2 neuropathy and alopecia were an exception to this criterion and may have qualified for the study
- Expected to require other cancer therapy while on study
- Other investigational procedures

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- Positive for human immunodeficiency virus (HIV)
- Positive for hepatitis B/C
- Received live vaccine within 28 days prior to enrollment
- Men of reproductive potential and women of childbearing potential who were unwilling to practice a highly effective method(s) of birth control while on study through 4 months after receiving the last dose of study drug
- Women who were lactating/breastfeeding or who planned to breastfeed while on study through 4 months after receiving the last dose of study drug
- Women with a positive pregnancy test
- Women planning to become pregnant while on study through 4 months after receiving the last dose of study drug
- Known sensitivity to any of the products or components to be administered during dosing
- Patient likely to be unable to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the patient's and investigator's knowledge
- History or evidence of psychiatric, substance abuse, or any other clinically significant disorder, condition, or disease (except for those outlined above) that, in the opinion of the investigator or sponsor physician, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion

Definition of dose-limiting toxicity

Dose-limiting toxicities were defined as grade 4 nonhematologic toxicity; grade ≥3 pneumonitis; grade 3 nonhematologic toxicity for >7 days; grade ≥3 nonhematologic

laboratory value requiring medical intervention, hospitalization, or if considered clinically important and persisting for >1 week; grade 3 or 4 febrile neutropenia; grade ≥3 thrombocytopenia with bleeding, grade ≥4 thrombocytopenia lasting >48 hours, or thrombocytopenia requiring intervention; delay in cycle 2 treatment for >2 weeks due to study drug–related toxicity (unless clearly attributable to pembrolizumab only and delay is due to tapering of steroids); any other toxicity leading to permanent discontinuation of AMG 820 or pembrolizumab; and any patient meeting the criteria for a Hy's Law case.

Hepatotoxicity stopping and rechallenge rules

AMG 820 and pembrolizumab were discontinued permanently and the patient followed for possible drug-induced liver injury (DILI), if all of the criteria below were met:

- Total bilirubin ≥2 x ULN following baseline total bilirubin <ULN or INR >1.5
- Increased AST or ALT from <ULN at baseline to ≥3 x ULN
- No other cause for the combination of the above laboratory abnormalities was immediately apparent; important alternative causes for elevated AST/ALT and/or total bilirubin values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis
  - Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
  - Exposure to hepatotoxic agents/drugs or hepatotoxins

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- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-1 antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease, including steatohepatitis
- Nonhepatic causes (eg, rhabdomyolosis, hemolysis)

For patients who did not meet the criteria for permanent discontinuation of study drugs and had no underlying liver disease, study drugs could be withheld for:

- Elevation of either AST or ALT from any baseline value to:
  - >8 x ULN at any time
  - >5 x ULN but <8 x ULN for ≥2 weeks
  - >5 x ULN but <8 x ULN and unable to adhere to enhanced monitoring schedule
  - >3 x ULN with clinical signs or symptoms that are consistent with hepatitis
- Or total bilirubin level >3 x ULN at any time
- Or alkaline phosphatase >8 x ULN at any time

Rechallenge was considered if an alternative cause for impaired liver tests and/or elevated total bilirubin is discovered and the laboratory abnormalities resolve to normal

or baseline. If signs or symptoms recurred with rechallenge, study drugs were permanently discontinued.

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Supplementary Table 1. Sample size considerations for phase 2

	Naïve to Anti–PD-1/PD-L1/CSF1/CSF1R Treatment			Refractory/Relapsed on Anti–PD-1/PD-L1 and Naïve to Anti–CSF1/CSF1R Treatment	
	Group 1 CRC MMR Proficient	Group 2 Pancreatic Cancer	Group 3 NSCLC PD-L1 Low	Group 4 NSCLC PD-L1 Low	Group 5 NSCLC PD-L1 High
Planned sample size	18–43	10–29	19–55	10–29	10–29
Anticipated ORR of AMG 820 + pembrolizumab	≥25%	≥20%	≥30%	≥20%	≥20%
Guideline for stopping enrollment due to futility[a]	OR in ≤2 of initial 18 patients	OR in 0 of initial 10 patients	OR in ≤3 of initial 19 patients	OR in 0 of initial 10 patients	OR in 0 of initial 10 patients

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[a]When patients completed ≥6 months of treatment or earlier if the study achieved the recommended number of responders. Futility stopping rules per protocol were guidelines and did not require mandatory stopping. In addition, enrollment could continue while the initial cohort of patients was followed and assessed for objective response.

Abbreviations: CRC, colorectal cancer; CSF, colony-stimulating factor 1; CSF1R, colony-stimulating factor 1 receptor; MMR, mismatch repair; NSCLC, non-small-cell lung cancer; OR, objective response; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PD-L1 high, cells expressing high levels of PD-L1; PD-L1 low, cells expressing low levels of PD-L1.

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Supplementary Table 2. Treatment-related adverse events of clinical interest

System Organ Class Preferred Term	1,100 mg AMG 820 + 200 mg Pembrolizumab N=98	1,400 mg AMG 820 + 200 mg Pembrolizumab N=18
Number of patients reporting treatment-related adverse events of clinical interest, n (%)	66 (67.3)	12 (66.7)
Endocrine disorders	7 (7.1)	0 (0.0)
Hyperthyroidism	2 (2.0)	0 (0.0)
Hypothyroidism	6 (6.1)	0 (0.0)
Eye disorders	0 (0.0)	2 (11.1)
Uveitis	0 (0.0)	2 (11.1)
Gastrointestinal disorders	2 (2.0)	1 (5.6)
Autoimmune pancreatitis	0 (0.0)	1 (5.6)

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Colitis	2 (2.0)	0 (0.0)
Hepatobiliary disorders	6 (6.1)	1 (5.6)
Autoimmune hepatitis	1 (1.0)	1 (5.6)
Hepatitis	4 (4.1)	0 (0.0)
Immune-mediated hepatitis	1 (1.0)	0 (0.0)
Investigations	61 (62.2)	11 (61.1)
Amylase abnormal	1 (1.0)	0 (0.0)
Amylase increased	18 (18.4)	5 (27.8)
Lipase abnormal	1 (1.0)	0 (0.0)
Lipase increased	18 (18.4)	3 (16.7)
Pancreatic enzymes increased	1 (1.0)	0 (0.0)
Alanine aminotransferase	1 (1.0)	1 (5.6)
Alanine aminotransferase increased	19 (19.4)	4 (22.2)
Aspartate aminotransferase abnormal	0 (0.0)	1 (5.6)

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Aspartate aminotransferase increased	51 (52.0)	10 (55.6)
Blood bilirubin increased	2 (2.0)	0 (0.0)
Gamma-glutamyltransferase increased	2 (2.0)	0 (0.0)
Hepatic enzyme increased	1 (1.0)	1 (5.6)
Liver function test abnormal	0 (0.0)	1 (5.6)
Liver function test increased	1 (1.0)	0 (0.0)
Transaminases increased	5 (5.1)	0 (0.0)
Renal and urinary disorders	2 (2.0)	1 (5.6)
Nephritis	1 (1.0)	0 (0.0)
Nephrotic syndrome	0 (0.0)	1 (5.6)
Acute kidney injury	1 (1.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	5 (5.1)	1 (5.6)

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Pneumonitis	5 (5.1)	1 (5.6)
Skin and subcutaneous tissue disorders	4 (4.1)	0 (0.0)
Dermatomyositis	1 (1.0)	0 (0.0)
Psoriasis	2 (2.0)	0 (0.0)
Erythema nodosum	1 (1.0)	0 (0.0)

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Supplementary Table 3. PD-L1 expression and levels of immune infiltrate in paired tumor biopsies

		% PD-L1		% CD4		% CD8		% CD68		% CD163	
Patient	Response	Screening	EOS	Screening	EOS	Screening	EOS	Screening	EOS	Screening	EOS
1	irPD	0	5	15	30	5	10	10	10	15	15
2	irPD	2	35	30	20	15	25	10	20	35	30
3	irPR	0	5	30	30	15	40	30	35	30	50
4	irPR	0	NA[a]	15	NA[a]	25	NA[a]	25	NA[a]	25	NA[a]
5	irPR	10	NA[a]	2	NA[a]	1	NA[a]	3	NA[a]	20	NA[a]

[a]No tumor cells remaining in biopsy.

Abbreviations: EOS, end of study; irPD, immune-related progressive disease; irPR, immune-related partial response; NA, not available; PD-L1, programmed cell death-ligand 1.

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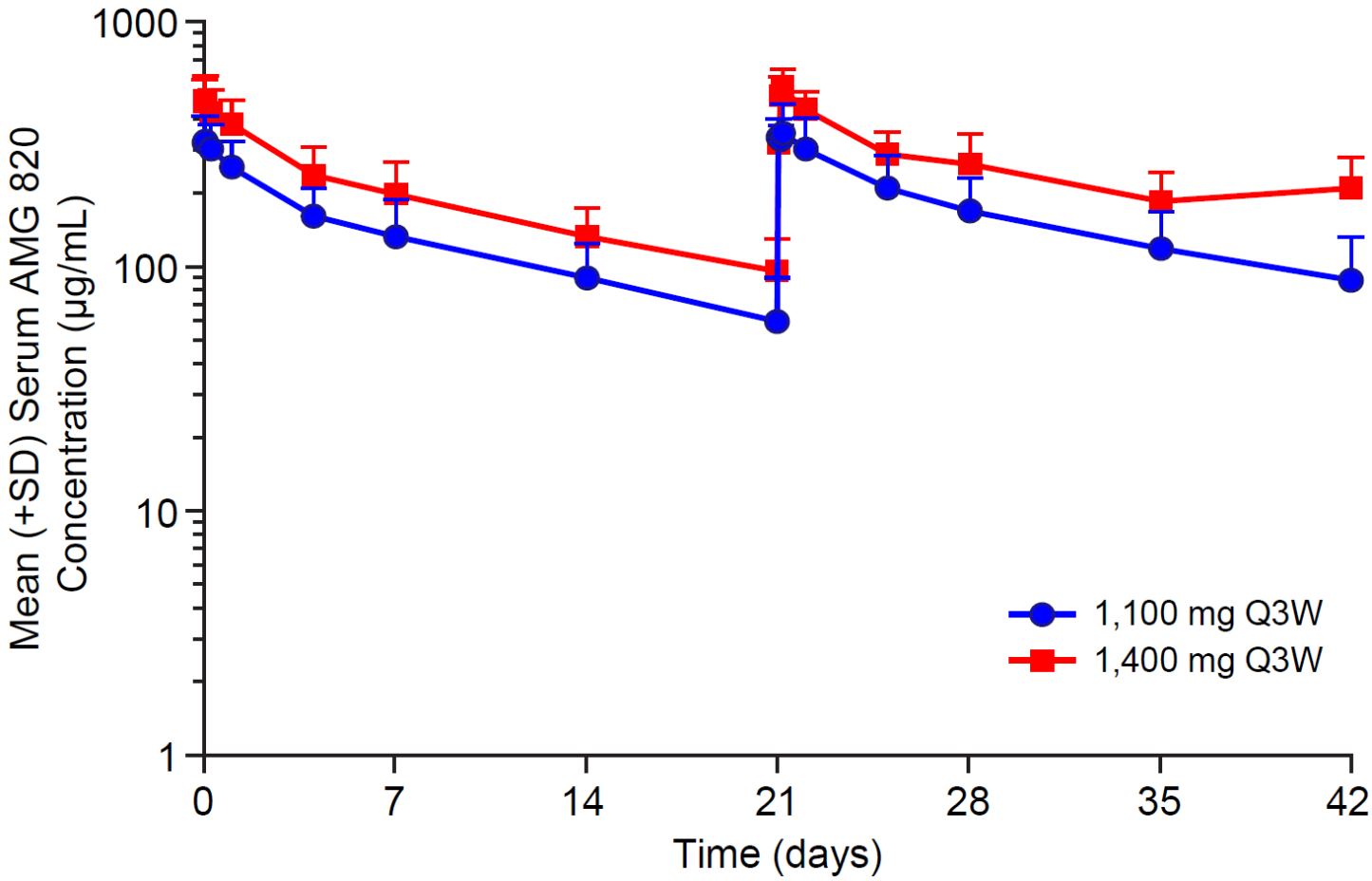
Supplementary Figure 1



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Mean (+SD) cycle 1 and cycle 2 serum AMG 820 concentration-time profiles.

Concentration-time profiles are shown by dose group following Q3W intravenous infusion of 1,100 mg and 1,400 mg AMG 820 to patients with select advanced solid tumors. Abbreviations: Q3W, every 3 weeks; SD, standard deviation.