Original article

Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma

Dana B. Cardin,[1,2] Jill Gilbert,[1,2] Jennifer G. Whisenant,[1,2] Gregory D. Ayers,[3] Florencia Jalikis,[4] Kimberly B. Dahlman,[1,2] Jamye F. O'Neal,[1] Frank Revetta,[4] Chanjuan Shi,[5] Jordan Berlin[1,2]

Abstract

Phase II study explored efficacy of the PD-L1 antibody avelumab in small bowel adenocarcinomas (SBAs). Two patients (2/7; 29%) experienced partial responses and disease-control rate was 71%. Despite the observed benefit, accrual was slower than expected and the study was closed early due to feasibility. Disease rarity and off-label use of immunotherapy were likely drivers of insufficient accrual.

Introduction: Small bowel adenocarcinomas (SBAs) are rare and frequently treated like large intestinal adenocarcinomas. However, SBAs have a very different microenvironment and could respond differently to the same therapies. Our previous data suggested that SBAs might benefit from targeting the PD-1/PD-L1 axis based on PD-L1 staining in almost 50% of SBA tissue samples tested. Thus, we designed a phase 2 study to explore safety and efficacy of avelumab in SBA. **Patients and Methods:** Patients with advanced or metastatic disease were enrolled; ampullary tumors were considered part of the duodenum and allowed. Prior PD-1/PD-L1 inhibition was not allowed. Avelumab (10 mg/kg) was given every 2 weeks, and imaging was performed every 8 weeks. Primary endpoint was response rate. **Results:** Eight patients (n = 5, small intestine; n = 3, ampullary) were enrolled, with a majority (88%) being male and a median age of 61 years. Of 7 efficacy-evaluable patients, 2 (29%) experienced partial responses; stable disease occurred in 3 additional patients (71%). Median progression-free survival was 3.35 months. Most frequent, related toxicities were anemia, fatigue, and infusion-related reaction (25% each), mostly grade ≤2; grade 3 hypokalemia and hyponatremia occurred in one patient, and another reported grade 4 diabetic ketoacidosis. **Conclusions:** Despite the observed benefit, accrual was slower than expected and the study was closed early due to feasibility. A general clinic observation was that patients were receiving immunotherapy off-label as the availability of these agents increased. Off-label availability and disease rarity were likely drivers of insufficient accrual.

Clinical Colorectal Cancer, Vol. 000, No.xxx, 1–8
Keywords: Immune checkpoint inhibition, Immunotherapy, PD-L1, Rare tumor, Small intestine

Introduction

Although the small intestine makes up about 75% of the length of the digestive tract and 90% of its mucosal surface area, cancer of the small intestine is rare, representing only 5% of all gastrointestinal cancers.[1] Despite being rare, small intestine cancers are on the rise, with age-adjusted rates for new cases increased on average 2.2% each year over 2008-2017.[2] Small bowel adenocarcinoma (SBA) represents approximately one-third of all small intestinal cancers, and it is estimated that approximately 11,390 new cases would be diagnosed in the United States in 2021.[3] Due to the rarity of the disease, few prospective studies have been conducted in SBAs and guidelines such as the National Comprehensive Cancer Network Guidelines recommend treating like large intestinal adenocarcinomas. However, small intestinal cancers have a very different microenvironment and, most likely, will respond differently to the same therapies. Additionally, given the non-specificity of symptoms at presentation, a majority of patients are diagnosed with advanced disease, where 5-year survival drops from 65% at stage I to 4% for stage IV.[4] Moreover, patients initially treated with primary tumor resection will experience recurrent disease at a median time to recurrence of 1.3 years with a majority having distant metastases.[5]

No approved therapies exist as large-scale phase III studies are problematic due to the rarity of the disease. However, systemic chemotherapy is regarded as the standard treatment option for

Abbreviations: CIs, confidence intervals; CPS, combined positive score; SBA, small bowel adenocarcinoma.

[1]Vanderbilt-Ingram Cancer Center, Nashville, TN
[2]Department of Medicine (Hematology & Oncology), Vanderbilt University Medical Center; Nashville, TN
[3]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN
[4]Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN
[5]Department of Surgical Pathology, Duke University Health System, Durham, NC

Submitted: Jan 13, 2022; Accepted: Mar 17, 2022; Epub: xxx

Address for correspondence: Dana B. Cardin, MD, Vanderbilt-Ingram Cancer Center, 2220 Pierce Avenue, 777 PRB, Nashville, TN 37232
E-mail contact: dana.cardin@vumc.org

1533-0028/$ - see front matter
https://doi.org/10.1016/j.clcc.2022.03.003

Please cite this article as: Dana B. Cardin et al, Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.03.003

patients with metastatic or recurrent disease despite the lack of prospective, randomized trials evaluating the role of palliative chemotherapy. A combined analysis of several retrospective studies observed a median overall survival of 13 months for patients receiving systemic chemotherapy, versus four months for patients treated with best-supportive care alone.[6] Therefore, exploring novel treatment strategies is vital to improve outcomes for patients with SBA.

We previously published data suggesting that inhibition of programmed death-ligand 1 (PD-L1) might be an attractive treatment option in SBA.[7] Analysis of PD-L1 and PD-1 expression on archived tissue samples demonstrated PD-L1 expression in 18 of the 42 cases (46%) that was mainly localized to the macrophages around the tumor invasive front and in some of the tumor cells adjacent to the macrophages. All tumor samples with PD-L1 expression also had PD-1 expressing tumor infiltrating lymphocytes (TILs), PD-1 positive lymphocytes, and lymphoid aggregates surrounding the tumor. These data were consistent with a previous study that also reported robust PD-L1 staining in 50% of SBAs.[8] Based on these data, we designed this study to evaluate safety and efficacy of avelumab in patients with SBA. Avelumab is a fully human IgG1 antibody that binds with high affinity (0.7 nM) to PD-L1 and blocks the interaction between PD-L1 and its receptor PD-1. Avelumab is approved as monotherapy for patients with metastatic Merkel Cell carcinoma[9,10] and locally advanced or metastatic urothelial carcinoma,[11,12] and in combination with axitinib for first-line treatment of renal cell carcinoma.[13] Immunohistochemistry (IHC) staining using archival tissue was performed to determine the association between microsatellite instability (MSI) status and PD-L1 expression with tumor response.

Materials and Methods

Study Design

We conducted a phase II clinical trial at an academic medical center (clinicaltrials.gov identifier: NCT03000179). Study was approved by the Institutional Review Board, and written informed consent was obtained for all patients. This was a non-randomized, open-label, single arm study conducted in patients with advanced or metastatic SBA. The primary objective was to evaluate response rate (RR). Secondary objectives included evaluation of disease-control rate (DCR), progression-free survival (PFS), overall survival (OS), toxicity, and correlative analysis of PD-L1 staining and microsatellite instability (MSI) status.

Eligibility Criteria

Eligible patients had histologically confirmed SBA that was advanced or metastatic. Ampullary tumors were considered a part of the duodenum and included. Other inclusion criterial were: at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria[14], ≥18 years of age, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ (hematologic, renal, and hepatic) function, and ventricular ejection fraction (≥55%). Patients who received adjuvant or neoadjuvant therapy were also eligible if they had progressed within 6 months of completing therapy and had not received a metastatic regimen, or if they progressed >6 months after completing therapy and have received 1 or 2 lines of therapy for metastatic disease. Patients were excluded if they had prior anti-PD-1/PD-L1 therapy. Additional inclusion and exclusion criteria are listed in the Appendix.

Study Treatment

All patients were treated with 10 mg/kg avelumab administered as 1-hour intravenous infusion every 2 weeks in 14-day treatment cycles until disease progression, unacceptable toxicity, or patient withdrawal. Dose reductions were not allowed, however, treatment delays of up to 4 weeks were allowed for the management of treatment-related toxicities.

Study Assessments

Patient demographics and medical history were recorded at baseline. Adverse events (AEs) were assessed at baseline and bi-weekly during treatment, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Imaging was performed every 8 weeks, and tumor responses were categorized per RECIST v1.1.

Statistical Analysis

Considering the published data[15,16] regarding the responses to standard-of-care chemotherapy at the time this study was designed, we proposed that observing the same or better outcomes with avelumab monotherapy would warrant further therapeutic study in patients with advanced or metastatic SBA. Assuming, a one-sided type I error rate of 5% (one-sample binomial test), 25 patients provided 80% power to reject the null hypothesis of 5% if the true RR of this regimen was 21% or greater. This regimen was considered sufficiently active to warrant further study in more definitive trials if four or more patients among 25 treated experienced an objective response.

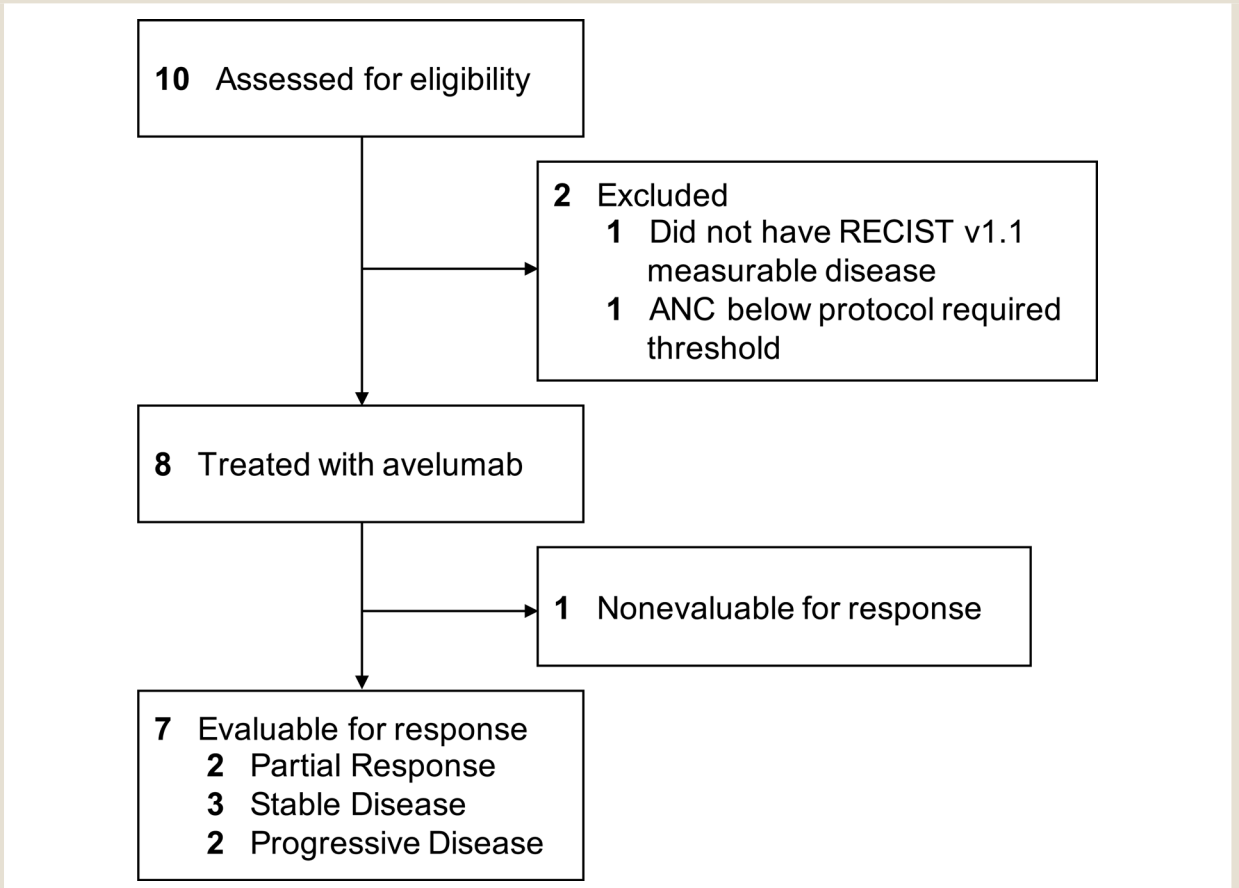
Demographic, baseline patient characteristics, and study outcomes were summarized numerically. Categorical variables, (eg, adverse events) were reported as frequencies and 95% confidence intervals (CIs) were reported. The distributions of PFS and OS were estimated using the Kaplan-Meier (product-limit) method with standard errors based on Greenwood's formula.

Immunohistochemistry

Formalin-fixed paraffin embedded tissue sections were stained with PD-L1 (1:200 dilution) (Cell Signaling #13684). For those patients with unknown clinical MSI status, tissue sections were stained with MLH1 (1:500 dilution) (BD Bioscience #554073, MSH2 (1:250 dilution) (Oncogene Research #NA27T-10UG) antibodies, MSH6 (1:200 dilution) (Abcam #ab92471), or PMS2 (1:100 dilution) (Abcam #ab110638), or for 60 minutes at room temperature. Prior to staining, antigen retrieval was performed in citrate buffer (pH 6.0) for PD-L1, MSH3, PMS2, and MLH1 at 105°C for 15 minutes or in EDTA (pH 9.0) at 97°C for 15 minutes for MSH6. Detection was performed using the Dako Envision + System HRP Labeled Polymer (Dako) with DAB. For PD-L1 expression, combined positive scores (CPS) were calculated by dividing the total number of PD-L1–positive cells (including tumor cells and immune cells) by the total number of viable tumor cells in the entire tumor area. A CPS score of 1% or higher was

Please cite this article as: Dana B. Cardin et al, Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.03.003

Figure 1 CONSORT diagram depicting the number of patients that were consented, received study therapy, and evaluable for response. This figure also depicts the number of samples that were analyzed with the correlative analysis, as well as the subsequent results. ANC, absolute neutrophil count.



considered positive. Loss of nuclear expression of one or more of the four mismatch repair proteins was considered evidence of an MSI-H phenotype.

Results

Patient Characteristics and Treatment

Between March 2017 and August 2019, 10 patients were consented and 8 patients were enrolled (Figure 1). Demographics and baseline disease characteristics are summarized in Table 1. The median age was 61 years (50-67), and 88% were male. Five patients (63%) had disease in the small intestine, while 3 patients (37%) had ampullary tumors. Seven patients had received at least 1 prior therapy that contained 5-FU and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). Unfortunately, due to slow enrollment, the study was closed early and did not enroll the planned 25 patients.

Efficacy

In the efficacy-evaluable patients (n = 7), 2 had a partial response for a RR of 29% (95% CIs: 8%-64%). Three additional patients had stable disease for a DCR of 71% (95% CIs: 36%-92%). One patient was not evaluable for response as they experienced clinical progression prior to the first post-baseline imaging assessment. The median PFS (Figure 2, solid line) and OS (Figure 2, dashed line) was 3.35 months (95% CIs: 2.99-Not Applicable [NA]) and 6.37 months (95% CIs: 3.75-NA), respectively.

In the patients achieving at least stable disease, the median duration of disease control was 4.1 months. One patient with MSI-H small intestinal disease was on treatment and responding for 18.8 months; although this patient didn't meet the criteria for RECIST-defined progression, the treating physician felt the primary tumor was showing slow progression and decided to switch patient to a different therapy. This long responder was also treatment naïve for metastatic disease. This patient is still alive as of the data cutoff date (January 29, 2021; 25.3 months since treatment initiation). The best change in the sum of lesions sizes from baseline is presented in Figure 3. The median percent change was −1.6% (−77.1% to 34.5%). Four patients experienced some tumor regression, with one of these patients having an ampullary tumor.

Safety

Seven of the 8 patients (88%) experienced at least one drug-related AE, most frequent (all grades) was anemia (25%), fatigue

Please cite this article as: Dana B. Cardin et al, Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.03.003

Figure 2 Kaplan-Meier estimates of progression-free survival (solid line) and overall survival (dashed line). The median progression-free survival was 3.35 months (95% confidence interval, 2.99 to Not Applicable). The median overall survival was 6.37 months (95% confidence interval, 3.75 to Not Applicable).

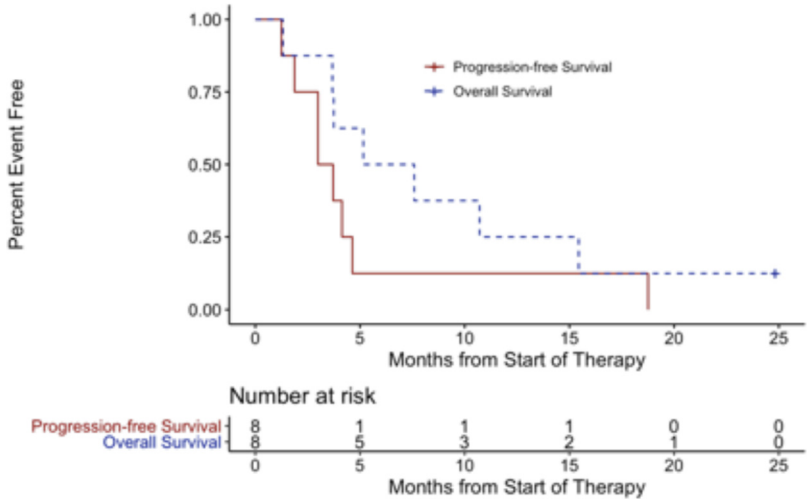
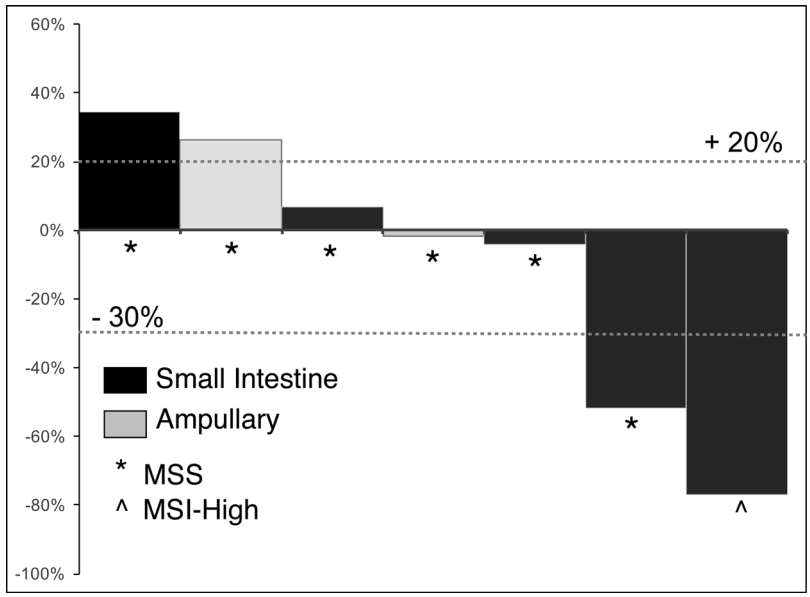


Figure 3 Best percentage change from baseline in sum of target lesions is presented for each patient that was evaluable for response. Dashed lines are RECIST v1.1 criteria for partial response and progression disease. Two responses were observed in small intestinal tumors, one with high microsatellite instability (MSI-High); the other responder was microsatellite stable (MSS). Three additional patients had disease control, one of which had an ampullary tumor.



(25%), and infusion-related reaction (25%). All treatment-related AEs are listed in Table 2, with the highest grade recorded per patient. One patient experienced two Grade 3 events of hypokalemia and hyponatremia and another patient reported Grade 4 diabetic ketoacidosis, which were all attributed to avelumab. No patient withdrew from the study due to toxicity.

Please cite this article as: Dana B. Cardin et al, Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.03.003

Table 1 Baseline Patient Characteristics (n = 8)

Gender – No. (%)	
Male	7 (88)
Female	1 (12)
Median age – No. (interquartile range)	61 (54-66)
Race and ethnicity – No. (%)	
White	8 (100)
Non-Hispanic or Latino	5 (63)
Ethnicity not reported / unknown	3 (37)
Site of disease – No. (%)	
Small intestine	5 (63)
Ampullary	3 (37)
Number of prior therapies – No. (%)	
0	1 (12.5)
1	6 (75)
2	1 (12.5)
PS (ECOG) – No. (%)	
0	3 (37)
1	5 (63)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Table 2 Highlighted Treatment-Related Adverse Events[a]

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4[b]
Anemia	2	0	0	0
Fatigue	1	1	0	0
Infusion related reaction	0	2	0	0
Alanine aminotransferase increased	1	0	0	0
Alkaline phosphatase increased	1	0	0	0
Anorexia	0	1	0	0
Blood bilirubin increased	1	0	0	0
Diarrhea	1	0	0	0
Diabetic ketoacidosis	0	0	0	1
Back pain	1	0	0	0
Diverticulitis per upper GI series	0	1	0	0
Hypokalemia	0	0	1	0
Hyponatremia	0	0	1	0
Nausea	0	1	0	0
Rash maculo-papular	1	0	0	0
Urticaria	1	0	0	0

[a] Highest grade per patient listed.
[b] No treatment-related Grade 5 events.

MSI and PD-L1 Status

MSI and PD-L1 status as a function of response is listed in Table 3. Seven of the 8 patient tumors (87.5%) were microsatellite stable (MSS) and one of the 8 patient tumors (12.5%) was MSI-high due to a MLH1 mutation (c.676C>T; assessed clinically). The MSI-High patient had a durable response. Four of the 8 tumors (50%) were considered PD-L1 positive with CPS of ≥1%. The remaining 4 tumors were PD-L1 negative (Figure 4).

Table 3 Microsatellite Status and PD-L1 CPS in SBA Samples

Patient #	Microsatellite Status	PD-L1 CPS (%)	Tumor Response
01-101	MSS[a]	0	PR
01-102	MSS	0	SD
01-103	MSS	1	SD
01-104	MSS	20	PD
01-105	MSS[a]	0	NE
01-106	MSS[a]	1	SD
01-107	MSS	0	PD
01-108	MSI-High	5	PR

PD-L1: programmed death-ligand 1; SBA: small bowel adenocarcinoma; CPS: combined positive score; MSS: microsatellite stable; MSI-High: microsatellite instability high; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable.
[a] Microsatellite Status from clinical pathology report.

Discussion

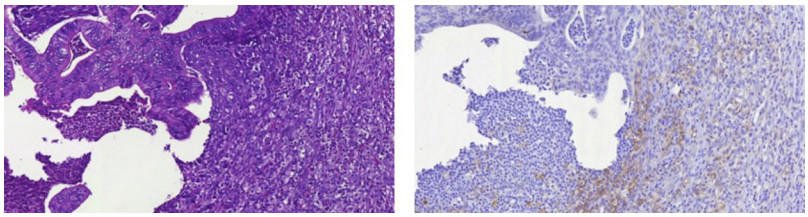
Immune checkpoint inhibitors, specifically agents that target the PD-1/PD-L1, have revolutionized anticancer therapy and improved clinical outcomes of multiple tumor types during the past decade.[17-23] Recently, pembrolizumab and nivolumab were approved for patients with colorectal cancer whose tumors are DNA mismatch repair deficient and MSI-H.[24,25] Small intestinal cancers are often treated similarly to colorectal cancers, yet no approved therapies exist for these patients as large phase II/III trials are logistically challenging due to the rarity of the disease. Our preliminary data,[7] along with a study from another group,[8] demonstrated that approximately 50% of small intestinal tumors overexpressed PD-L1 and also had PD-1 expressing TILs. Based on these data, we hypothesized that small intestinal cancers may benefit from the PD-1/PD-L1 inhibitors. Thus, we designed this pilot study to evaluate safety and efficacy of the PD-L1 agent avelumab.

Avelumab was generally well tolerated in this study. Most treatment-related adverse events were Grade ≤2. One patient experienced two Grade 3 events of hypokalemia and hyponatremia and another patient reported Grade 4 diabetic ketoacidosis that were attributed to avelumab, all of which are rare but known side effects to immune checkpoint inhibitors.[26-32] The primary endpoint of this study was RR, with a target response of >21% across 25 patients. Among the seven efficacy-evaluable patients enrolled to the study, the RR and DCR were 29% (2/7) and 71% (5/7), respectively. Similar to our previous study, 50% of our cohort was PD-L1 positive; albeit a small cohort, PD-L1 positivity did not appear to correlate with response (Table 3).

One of the responding patients was MSI-H with Lynch syndrome, both of which result in genetic hypermutability especially in genes that govern DNA mismatch repair.[33] MSI is a known biomarker for PD-1 blockade and mismatch repair deficiency has been shown to predict response to these agents.[33,34] Le et al.[34] performed a study investigating pembrolizumab in patients with mismatch-repair deficient non-colorectal cancers (NCT01876511); of the five patients with SBA, the RR was 80%, with 2 complete responses and 2 partial responses. Keynote-158 (NCT02628067) evaluated pembrolizumab in patients with MSI-H or mismatch-

Please cite this article as: Dana B. Cardin et al, Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.03.003

Figure 4 PD-L1 positivity in SBA. (A) H&E-stained slide showing invasive moderately differentiated adenocarcinoma with dense peritumoral inflammatory cells. (B) Peritumoral inflammatory cells including histiocytes and lymphocytes showing positive PD-L1 expression with only rare tumor cells expressing PD-L1. Both sections are from patient tumor 01-104. PD-L1: programmed death-ligand 1; SBA: small bowel adenocarcinoma



repair deficient noncolorectal cancers, including small intestinal, and reported a 42% (8/19) RR.[35] Our data along with evidence from these trials support the hypothesis that MSI-H or mismatch-repair deficient SBA may respond to PD-1/PD-L1 inhibitors. Conversely, the other responder in our trial was MSS with negative PD-L1 staining, suggesting another underlying mechanism was driving their tumor response.

Although this study demonstrated promising clinical activity with avelumab in this patient population that is without standard therapies, enrollment was closed early due to slow patient accrual. Low enrollment was in part due to the rarity of the disease; however, during the course of the study, it was noted that patients were able to receive immune checkpoint inhibitors off-label. This study was designed in 2016 and nivolumab received approval for metastatic colorectal cancer with two specific genetic features in 2017. The eligibility criteria of our study excluded patients with prior immune checkpoint therapy, and we felt that amending this criterion would alter the hypothesis and overall study design without improving the potential clinical benefit. At the end of 2019, it was decided to close the study.

To the best of our knowledge, this was the first study designed specifically to evaluate safety and efficacy of PD-L1 inhibitors in SBA. However, shortly after our pilot single-center study opened, the Academic and Community Cancer Research United (ACCRU) consortium opened a multicenter study of pembrolizumab (NCT02949219). This study took 2 years to enroll 41 participants across eight centers, thereby highlighting the rarity of the disease. The primary endpoint of that study was confirmed RR; out of 40 efficacy-evaluable patients, the RR was 8.0% (95% CI: 2.0%-20%).[36] The PFS and OS were 2.8 months (95% CI: 2.7-5.1) and 6.9 months (95% CI: 5.1, Not Reached), respectively. MSI status was available for 55% (n = 22) of the patients; of the 18 MSS patients, one confirmed partial response was observed and the disease-control rate was 50%. Both MSI-H patients achieved a partial response and were alive without progression at the time of the publication. Similar to our results, the high number of patients with MSS contributed to the low RR observed in the study. Therefore, our data, as well as data from others,[34-36] suggest that a companion biomarker, such as MSI-H or DNA mismatch repair deficiency, should be tested in future clinical trials of PD-1/PD-L1 inhibitors in patients with small intestinal cancer. These data also further suggest that a better understanding of risks and benefits of off-label drug use is imperative.

Conclusions

This study demonstrated that avelumab was safe for patients with small intestinal cancers and demonstrated clinical benefit for most patients, including 2 partial responses. However, patient enrollment was slow due to the rarity of the disease and the general observation that some patients were able to receive checkpoint inhibitors off-label. Thus, enrollment was closed early. Nonetheless, avelumab could be an attractive treatment option for patients with advanced SBA, especially in patients with MSI-H tumors.

Clinical Practice Points

- Due to the rarity of SBA, few prospective clinical studies have been conducted leading guidelines (eg, National Comprehensive Cancer Network) to recommend treating similar to large intestinal adenocarcinomas.
- Based on our previous data (PMID:28821192) and another study (DOI:10.1200/jco.2015.33.15_suppl.3619) that demonstrated 50% of SBAs had robust PD-L1 staining, we designed a phase II study to explore safety and efficacy of avelumab.
- Most frequent toxicities were anemia, fatigue, and infusion-related reaction; mostly grade <2. One patient experienced grade 3 hypokalemia and hyponatremia and another patient reported grade 4 diabetic ketoacidosis, all of which are known side effects of immunotherapy.
- RR was 29% (2/7) and disease-control rate was 71% (5/7). Half of the tumors were PD-L1 positive yet PD-L1 positivity did not appear to correlate with response.
- One of the responding patients was MSI-High with Lynch syndrome, both of which result in genetic hypermutability.
- Despite the observed benefit, this study was closed early due to futility. Disease rarity and off-label use of immunotherapy were likely drivers of low accrual in this single-center study.
- A cooperative group (ACCRU) conducted a multicenter study exploring pembrolizumab in SBA, and reported an 8% (3/40) RR and conclusion that the high number of MSS patients contributed to the low RR (PMID:33883178).

Please cite this article as: Dana B. Cardin et al, Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.03.003

- The ACCRU study combined with our study provide evidence that a companion biomarker, such as MSI-H or DNA mismatch repair deficiency, be tested in future clinical trials of PD-1/PD-L1 inhibitors in patients with SBA.

Disclosure

JB is an advisory board member of Insmed, Bayer, Mirati, Ipsen, QED, Oxford Biotherapeutics DSMB: Novocure, Pancreatic Cancer Action Network, Karyopharm, and his institution has received research funding from I-Mab, Dragonfly, Astellas, Atreca, AbbVie, Pfizer, Karyopharm, Boston biomedical, PsiOxus, EMD Serono, BMS. The other authors do not have any relevant conflicts to disclose.

CRediT authorship contribution statement

Dana B. Cardin: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Supervision, Project administration, Funding acquisition. **Jill Gilbert:** Investigation, Resources, Writing – review & editing. **Jennifer G. Whisenant:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization, Funding acquisition. **Gregory D. Ayers:** Methodology, Formal analysis, Visualization, Writing – review & editing. **Florencia Jalikis:** Investigation, Formal analysis, Writing – review & editing. **Kimberly B. Dahlman:** Methodology, Visualization, Resources, Writing – original draft. **Jamye F. O'Neal:** Investigation, Resources, Writing – review & editing. **Frank Revetta:** Investigation, Resources, Writing – review & editing. **Chanjuan Shi:** Investigation, Formal analysis, Writing – review & editing. **Jordan Berlin:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Supervision, Funding acquisition.

Acknowledgments

The authors would like to thank the patients and their families for participating in this research study. Merck and Pfizer reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

Funding: This research was financially supported by Merck (CrossRef Funder ID: 10.13039/100004755), as part of an alliance between Merck and Pfizer. We would also like to the National Institutes of Health / National Cancer Institute and the Vanderbilt-Ingram Cancer Center Support Grant (P30 CA068485).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2022.03.003.

References

1. Neugut AI, Jacobson JS, Suh S, Mukherjee R, Arber N. The epidemiology of cancer of the small bowel. *Cancer Epidemiol Biomarkers Prev*. 1998;7:243–251.
2. National Cancer Institute. Surveillance, Epidemiology, and end results program. cancer stat facts: small intestine cancer. https://seer.cancer.gov/statfacts/html/smint.html; Accessed February 15 2021.
3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71:7–33. doi:10.3322/caac.21654.
4. Reynolds I, Healy P, McNamara DA. Malignant tumours of the small intestine. *Surgeon*. 2014;12:263–270. doi:10.1016/j.surge.2014.02.003.
5. Bakaeen FG, Murr MM, Sarr MG, et al. What prognostic factors are important in duodenal adenocarcinoma? *Arch Surg*. 2000;135:635–641 discussion 641-2.
6. Raghav K, Overman MJ. Small bowel adenocarcinomas–existing evidence and evolving paradigms. *Nat Rev Clin Oncol*. 2013;10:534–544. doi:10.1038/nrclinonc.2013.132.
7. Thota R, Gonzalez RS, Berlin J, Cardin DB, Shi C. Could the PD-1 pathway be a potential target for treating small intestinal adenocarcinoma? *Am J Clin Pathol*. 2017;148:208–214. doi:10.1093/AJCP/AQX070.
8. Pederson K, Smyrk TC, Harrington S. e: Programmed death-ligand 1 (PD-L1) expression in small bowel adenocarcinomas (SBA). *J Clin Oncol*. 2015;33 suppl; abstr 3619. doi:10.1200/jco.2015.33.15_suppl.3619.
9. Kaufman HL, Russell JS, Hamid O, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after >/=1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. *J Immunother Cancer*. 2018;6:7. doi:10.1186/s40425-017-0310-x.
10. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:1374–1385. doi:10.1016/S1470-2045(16)30364-3.
11. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2020;383:1218–1230. doi:10.1056/NEJMoa2002788.
12. Apolo AB, Ellerton JA, Infante JR, et al. Avelumab as second-line therapy for metastatic, platinum-treated urothelial carcinoma in the phase Ib JAVELIN solid tumor study: 2-year updated efficacy and safety analysis. *J Immunother Cancer*. 2020;8. doi:10.1136/jitc-2020-001246.
13. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1103–1115. doi:10.1056/NEJMoa1816047.
14. Schwartz LH, Litiere S, de Vries E, et al. RECIST 1.1-Update and clarification: from the RECIST committee. *Eur J Cancer*. 2016;62:132–137. doi:10.1016/j.ejca.2016.03.081.
15. Mizushima T, Tamagawa H, Mishima H, et al. The effects of chemotherapy on primary small bowel cancer: a retrospective multicenter observational study in Japan. *Mol Clin Oncol*. 2013;1:820–824. doi:10.3892/mco.2013.150.
16. Aparicio T, Zaanan A, Svrcek M, et al. Small bowel adenocarcinoma: epidemiology, risk factors, diagnosis and treatment. *Dig Liver Dis*. 2014;46:97–104. doi:10.1016/j.dld.2013.04.013.
17. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med.*. 2017;377:1824–1835. doi:10.1056/NEJMoa1709030.
18. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833. doi:10.1056/NEJMoa1606774.
19. Cortes J, Cescon DW, Rugo HS, et al. Investigators K-: Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet*. 2020;396:1817–1828. doi:10.1016/S0140-6736(20)32531-9.
20. Fuchs CS, Doi T, Jang RW, et al. safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol*. 2018;4. doi:10.1001/jamaoncol.2018.0013.
21. Ferris RL, Blumenschein Jr G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375:1856–1867. doi:10.1056/NEJMoa1602252.
22. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389:2492–2502. doi:10.1016/S0140-6736(17)31046-2.
23. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379:2108–2121. doi:10.1056/NEJMoa1809615.
24. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383:2207–2218. doi:10.1056/NEJMoa2017699.
25. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18:1182–1191. doi:10.1016/S1470-2045(17)30422-9.
26. Wanchoo R, Karam S, Uppal NN, et al. Adverse renal effects of immune checkpoint inhibitors: a narrative review. *Am J Nephrol*. 2017;45:160–169. doi:10.1159/000455014.
27. Herrmann SM, Alexander MP, Romero MF, Zand L. Renal tubular acidosis and immune checkpoint inhibitor therapy: an immune-related adverse event of PD-1 inhibitor–a report of 3 cases. *Kidney Med*. 2020;2:657–662. doi:10.1016/j.xkme.2020.05.015.
28. Girotra M, Hansen A, Farooki A, et al. The Current Understanding of the endocrine effects from immune checkpoint inhibitors and recommendations for management. *JNCI Cancer Spectr*. 2018;2 pky021. doi:10.1093/jncics/pky021.

Please cite this article as: Dana B. Cardin et al, Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.03.003

29. Takeno A, Yamamoto M, Morita M, et al. Late-onset isolated adrenocorticotropic hormone deficiency caused by nivolumab: a case report. *BMC Endocr Disord*. 2019;19:25. doi:10.1186/s12902-019-0335-x.
30. Trainer H, Hulse P, Higham CE, Trainer P, Lorigan P. Hyponatraemia secondary to nivolumab-induced primary adrenal failure. *Endocrinol Diabetes Metab Case Rep*.. 2016;2016. doi:10.1530/EDM-16-0108.
31. Hong AR, Yoon JH, Kim HK, Kang HC. Immune Checkpoint inhibitor-induced diabetic ketoacidosis: a report of four cases and literature review. *Front Endocrinol (Lausanne)*. 2020;11:14. doi:10.3389/fendo.2020.00014.
32. Yun K, Daniels G, Gold K, McCowen K, Patel SP. Rapid onset type 1 diabetes with anti-PD-1 directed therapy. *Oncotarget*. 2020;11:2740–2746. doi:10.18632/oncotarget.27665.
33. Dudley JC, Lin MT, Le DT, Eshleman JR. Microsatellite instability as a biomarker for PD-1 blockade. *Clin Cancer Res*. 2016;22:813–820. doi:10.1158/1078-0432.CCR-15-1678.
34. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357:409–413. doi:10.1126/science.aan6733.
35. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38:1–10. doi:10.1200/JCO.19.02105.
36. Pederson K, Foster N, Overman MJ, et al. ZEBRA: an ACCRU/IRCI multicenter phase 2 study of pembrolizumab in patients with advanced small bowel adenocarcinoma (SBA). *Ann Oncol*. 2019;30:IV128.

Please cite this article as: Dana B. Cardin et al, Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.03.003