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Clinical Trial Results

Avelumab in Patients With Metastatic Colorectal Cancer

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Abstract

Background: Metastatic colorectal cancer (mCRC) is incurable, and median overall survival is less than 2½ years. Although monoclonal antibodies that block PD-1/PD-L1 interactions are active in microsatellite unstable/mismatch repair deficient tumors, a growing dataset shows that most patients with microsatellite stable/mismatch repair proficient tumors will not benefit from the blockade of PD-1/PD-L1 interactions. Here we present results from patients with mCRC (n = 22) treated with the anti-PD-L1 monoclonal antibody avelumab.

Methods: Patients received treatment on a phase I, open-label, dose-escalation trial via a consecutive parallel-group expansion in colorectal cancer. Patients aged 18 years and older with mCRC measurable by RECIST v1.1 who had received at least 1 line of systemic therapy for metastatic disease enrolled. Patients with prior immune checkpoint inhibitor treatment were excluded. Patients received avelumab 10 mg/kg intravenously every 2 weeks. The primary endpoint was the objective response rate.

Results: Twenty-two participants received treatment from July 2013 to August 2014. There were no objective responses and median progression-free survival was 2.1 months (95% CI: 1.4-5.5 months). There were 5 grade 3 treatment-related adverse events: GGT elevation (n = 2), PRESS (n = 1), lymphopenia (n = 1), and asymptomatic amylase/lipase elevation (n = 1).

Conclusion: As demonstrated with other anti-PD-1/PD-L1 monoclonal antibodies, avelumab is not active in unselected patients with mCRC (ClinicalTrials.gov Identifier: NCT01772004).

Key words: colon cancer; avelumab; immune checkpoint inhibitors; clinical trials; immunotherapy.

Lessons Learned

- As observed in trials testing other immune checkpoint inhibitors, avelumab does not produce objective responses in unselected patients with metastatic colorectal cancer (mCRC).
- In mCRC, the safety profile of avelumab was consistent with the known safety profile of anti-PD-1/PD-L1 antibodies.
- Identification of therapeutic combinations that sufficiently empower the immune system in mCRC remains an unmet goal.

Discussion

Despite the promising activity in other tumor types, multiple clinical studies have shown that immune checkpoint inhibitor (ICI) monoclonal antibodies are not active in unselected patients with mCRC,[1-5] the vast majority of which have microsatellite stable (MSS)/mismatch repair proficient (pMMR) tumors. Prior to the publication of these reports, avelumab (a fully human, IgG1 monoclonal antibody) was also tested in unselected patients with mCRC in an expansion cohort of the JAVELIN Solid Tumor open-label, phase I trial.

Twenty-two patients enrolled between July 15, 2013 and August 18, 2014 (Table 1) and received avelumab 10 μc kg^{-1} intravenously every 2 weeks. Restaging imaging occurred every 8 weeks. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events Version 4.0. All patients previously received

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systemic therapy containing oxaliplatin/fluoropyrimidine and/or irinotecan/fluoropyrimidine and, if indicated, epidermal growth factor receptor (EGFR)-targeted therapy and bevacizumab. Seven patients had confirmed pMMR or MSS disease. The remaining 15 patients did not have tissue available for MMR or microsatelliate instability (MSI) analysis (Table 2).

Avelumab had a safety profile consistent with other anti-PD-1/PD-L1 monoclonal antibodies. Four patients (21%) experienced grade 3 treatment-related adverse events including 3 patients who discontinued treatment. Two patients discontinued treatment after experiencing hepatotoxicity which included grade 3 GGT elevation. One patient discontinued treatment after experiencing grade 3 PRESS. One patient experienced both asymptomatic, grade 3 lymphopenia and asymptomatic, and grade 3 amylase/lipase elevation.

There were no objective responses. Of 19 evaluable patients, 10 had stable disease (SD; 53%) and 9 had progressive disease (PD; 47%) as best overall response. Median progression-free survival (PFS) was 2.1 months (95% CI: 1.4-5.5 months).

In conclusion, mCRC remains an incurable disease. Most patients have intact mismatch repair status, and effective treatment options are limited following progression on first- and second-line chemotherapy-based regimens combined with bevacizumab or EGFR-targeted therapy. The results of this study add to a growing dataset demonstrating that therapeutic blockade of PD-1/PD-L1 interactions is not sufficient to facilitate significant immune-mediated antitumor activity in this population. Identification of therapeutic combinations that sufficiently empower the immune system in mCRC remains an unmet goal.

Table 1. Patient demographic characteristics (n = 22)

Characteristic	No. (%)
Median age, years	50
Range	29-70
Sex	
Female	8 (36)
Male	14 (64)
Median number of prior treatments	3
Range	1-5
Eastern Cooperative Oncology Group (ECOG)	
0	9 (41)
1	12 (55)
2	1 (4)
3	0
4	0
Liver metastases at baseline	
Yes	16 (73)
No	6 (27)
KRAS status	
Wild type	9 (41)
Mutated	7 (32)
BRAF	
Wild type	2 (9)
Mutated	1(5)
Unknown	19 (86)
MSI status	
MSS	7 (32)
MSI-H	0 (0)
Unknown	15 (68)
Sidedness	
Left	14 (64)
Right	8 (36)

Table 2. Treatment-related adverse events (n = 22)

Adverse event	Number (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Akathisia	1 (5)	0	0	0
Alkaline phosphatase increases	1 (5)	1 (5)	0	0
Allergic rhinitis	1 (5)	0	0	0
ALT increased	2 (9)	1 (5)	0	0
AST increased	1 (5)	0	0	0
Arthralgia	0	1 (5)	0	0
Chills	1 (5)	0	0	0
Diarrhea	1 (5)	1 (5)	0	0
Elevated amylase and/or lipase	0	0	1 (5)	0
Fatigue	7 (32)	0	0	0
Fever	3 (14)	0	0	0
Flu-like symptoms	2 (9)	0	0	0
Gamma glutamyl transferase increased	0	0	2 (9)	0
Headache	1 (5)	0	0	0
Hypothyroidism	1 (5)	0	0	0
Hyperglycemia	1 (5)	0	0	0
Infusion reaction	1 (5)	6 (27)	0	0
Lymphopenia	2 (9)	0	1 (5)	0
Myalgia	0	1 (5)	0	0
Nausea	3 (14)	0	0	0
Night sweats	1 (5)	0	0	0
PRESS	0	0	1 (5)	0
Rash-maculopapular	0	1 (5)	0	0
Rigors	1 (5)	0	0	0
Site administration erythema	1 (5)	0	0	0
Vomiting	1 (5)	0	0	0
Weight loss	0	1 (5)	0	0

Author disclosures and references available online.

Trial Information	
Disease	Metastatic colon cancer
Stage of disease/treatment	IV
Prior therapy	One line of systemic therapy
Type of study	Phase I, open-label, dose-escalation trial via a consecutive parallel-group expansion in colorectal cancer
Primary endpoint	Objective response rate
Secondary endpoints	Progression-free survival

Drug Information	
Generic/working name	Avelumab
Company name	EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA
Drug type	Monolonal antibody
Drug class	Anti-PD-L1 monoclonal antibody
Dose	10
Unit	mg kg^{-1}
Route	IV
Schedule of administration	Every 2 weeks

Patient Characteristics	
Number of patients, male	8
Number of patients, female	14
Stage	IV
Age: Median (range)	50 (29-70) years
Number of prior systemic therapies: median (range)	3
Performance status: ECOG	0: 9 1: 12 2: 1 3: 0 4: 0
Cancer types or histologic subtypes	Colon adenocarcinoma, 22; MSS/pMMR, 8; MSS/MSI unknown, 14

Primary Assessment Method	
Title	10 mg kg^{-1} dose level
Number of patients enrolled	22
Number of patients evaluable for toxicity	22
Number of patients evaluated for efficacy	19
Evaluation method	RECIST 1.1
Response assessment, complete response	0 (0%)
Response assessment, partial response	0 (0%)
Response assessment, SD	10 (45.5%)
Response assessment, PD	9 (41%)
Response assessment, not evaluable	3 (15.5%)
Median duration assessments	2.1 months (95% CI: 1.4-5.5 months)

Assessment, Analysis, and Discussion

As the third most common malignancy in the world with an estimated 32 000 patients diagnosed annually in the US alone,[6] identification of an effective immunotherapy for mCRC would fill a substantial void. Apart from the approximately 5%-8% of patients with mCRC with mismatch repair-deficient/microsatellite instability high (dMMR/MSI-H) disease who can derive benefit from ICIs, the available standard of care 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX)-based chemotherapy plus the antivascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab as first-line therapy for mCRC is associated with a median PFS of approximately 10 months and a median overall survival (OS) of only 25-29 months.[7,8] While patients with RAS wild-type disease originating from the left side of the colon also benefit from EGFR-targeted therapy, effective treatment options for mCRC following progression on second-line chemotherapy are limited for patients with disease lacking a therapeutic target. Two salvage agents, trifluridine/tipiracil (also known as TAS-102) and regorafenib, are FDA-approved as monotherapy but generally do not result in objective tumor responses for most patients. Approvals were based on modest survival benefits: a 1.8-month OS improvement (hazard ratio [HR] 0.68; 95% CI: 0.58-0.81; $P < .001$) for TAS-102[9] and

a 1.4-month OS improvement (HR 0·77; 95% CI: 0·64-0·94; one-sided P = .0052) for regorafenib.[10] Avelumab, a fully human IgG1 anti-PD-L1 monoclonal antibody that currently has several FDA-approved oncologic indications,[11-14] was one of several ICIs in development tested in patients with mCRC following the arrival of ICIs to the clinic more than a decade ago. Reports of deep and durable responses in patients with advanced melanoma and the FDA approvals that ensued naturally generated great hope and enthusiasm for trialing in diseases such as mCRC that lack effective treatments following chemotherapy.

The inactivity of ICIs in mCRC was not yet established when this expansion cohort of the JAVELIN Solid Tumor phase I trial began enrollment in 2013. However, at the time of this publication, several published reports, first from all-comer phase I trials and later, from trials dedicated to mCRC, clearly showed that ICIs are active only in patients with mCRC with dMMR/MSI-H mCRC.[1-5,15,16] Additionally, a bifunctional ICI (anti-PD-L1) that also inhibits the immunosuppressive tumor element, transforming growth factor beta, also does not appear to be active in unselected patients with mCRC.[17]

Whether ICI in combination with other agents has a role in unselected patients with mCRC remains an open question. Despite data suggesting that the chemotherapies used for mCRC have favorable immunomodulatory effects,[18-21] results from the phase II AtezoTRIBE study that randomized 218 patients to irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOXIRI) plus bevacizumab versus FOLFOXIRI plus bevacizumab + atezolizumab (anti-PD-L1) for first-line treatment of mCRC do not indicate that there is such a role in this setting. The planned analysis indicated a PFS benefit in the experimental arm that added atezolizumab: 13.1 months (80% CI: 12.5-13.8) in the atezolizumab group and 11.5 months (10.0-12.6) in the control group (HR 0·69; 80% CI: 0.56-0.85; P = .012). However, the trial enrolled patients with dMMR/MSI-H for whom ICIs would be expected to add benefit and included them in the PFS analysis.[22] When excluding those subjects from the PFS analysis, there was no statistically meaningful difference in PFS: 12.9 versus 11.4 months, HR 0.78; 80% CI: 0.62-0.97; P = .071.[23]

In a small, randomized phase II study, the addition of avelumab plus a CEA-targeted vaccine to FOLFOX + bevacizumab also did not indicate a difference in PFS (or overall response rate) in previously untreated patients with mCRC with mismatch repair proficient/microsatellite stable disease, compared to FOLFOX + bevacizumab alone.[24] Correlative analyses identified a post-treatment increase in multifunctional CD4+ and CD8+ T cells specific to cascade antigens MUC1 and brachyury in patients who received the CEA-targeted vaccine plus avelumab that was not seen in patients on the control arm. However, the significance and means by which to therapeutically exploit these T-cell populations are unknown.

Preclinical studies suggest that inhibition of various targets by mutlitargeted tyrosine kinase inhibitors (mTKI) can enhance antitumor immune activity.[25-30] Following those studies, the combination of ICIs plus mTKIs has been explored in multiple clinical trials. Results from a phase Ib study conducted in Japan reported objective responses in 8/24 (33%) patients with mCRC when combining nivolumab with regorafenib (targets VEGF receptors 1-3, TIE2, PDGFR-β, FGFR, KIT, RET, and RAF).[31] Unfortunately, a single-arm, phase II clinical trial conducted in North America observed a response in only 5/70 (7%) patients with mCRC.[32] Another single-arm phase II trial combined pembrolizumab with lenvatinib (targets VEGF receptors 1-3, FGFR1-4, PDGFRα, KIT, and RET). A preliminary report noted objective responses in 7/32 (22%) evaluable patients[33] and results from an ongoing expansion to 100 patients are pending. Durvalumab (anti-PD-L1) plus cabozantinib (targets include MET, AXL, RET, and VEGFR2) also produced encouraging preliminary results in a multisite, single-arm, phase II trial.[34] Of 29 evaluable patients with pMMR/MSS mCRC, 8 (27.6%) experienced objective tumor responses. As it is unclear if the activity seen in the above trials can be reproduced in larger numbers, future studies and subgroup analyses may inform potential biomarkers of clinical benefit.

Testing for mismatch repair, microsatellite instability, and tumor mutational burden (TMB) was not standard at the time that patients were treated on this study. Although the majority of patients with mCRC are pMMR/MSI-H and TMB low, this study is limited in that MMR/MSI is known only in 7/22 patients and TMB is known in none. RAS mutational status was also unknown for most patients.

In conclusion, this study aligns with other trial results demonstrating that with the exception of dMMR/MSI-H mCRC, ICIs are not effective in mCRC.[1-5,15,16] This report adds to this growing dataset and the unmet need for effective therapies in mCRC remains. In such a malignancy where T-cell infiltrate is predictive of outcome,[35] treatment with immunotherapies that increase trafficking to tumor, enhance immune effector cell activity, and/or remove immunosuppressive elements should be explored in future studies.

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Conflict of Interest

The authors indicated no financial relationships.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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