1. ABSTRACT

Title

Canadian Retrospective Observational Study of MVASI in Metastatic Colorectal Cancer

Keywords

MVASI, real world, safety, effectiveness, metastatic colorectal cancer

Rationale and Background

Colorectal cancer (CRC) is the third most common type of cancer and the second most common cause of cancer deaths worldwide.[1] Globally, CRC accounted for 935,173 deaths in 2020, with the highest mortality occurring in Eastern Asia, Central and Eastern Europe, and North America.[1] In 2020, 26,900 Canadians were diagnosed with CRC, representing an average of 73 Canadians diagnosed with the disease each day.[2]

A current option for first-line treatment of metastatic colorectal cancer (mCRC) is bevacizumab together with 5-FU-based combination chemotherapy (i.e., FOLFOX) infusions. MVASI (ABP 215) is a recombinant IgG1 monoclonal antibody (mAB) with an identical amino acid sequence to bevacizumab. Based on evidence from *in vitro* product characterization and clinical studies, MVASI became one of the first therapeutic biosimilars approved through Health Canada's biosimilar regulatory pathway for the treatment of all previously approved bevacizumab indications, including non-squamous non-small cell lung cancer (NSCLC) and mCRC. This was followed by additional approvals for glioblastoma, platinum-sensitive and platinum-resistant recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancers.

Although biosimilars may lead to significant cost savings, acceptance of biosimilar products could be enhanced with safety and effectiveness data in the real world setting. This retrospective chart review aimed to provide safety and effectiveness data for Canadian patients with mCRC treated with MVASI in the real world setting.

Research Question and Objectives

The objectives of this study were as follows:

- **Primary Objective:** To describe the safety of MVASI treatment by assessing the incidence of Events of Interest (EOIs), in first-line mCRC patients in Canada.
- **Secondary Objective:** To describe the effectiveness of MVASI treatment, including Objective Response and Progression Free Survival (PFS), in first-line mCRC patients in Canada.

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- **Exploratory Objective:** To describe the Overall Survival (OS) of patients receiving MVASI treatment as first-line treatment for mCRC in Canada.

Study Design

This study is a retrospective chart review conducted in two waves. Wave 1 and Wave 2 data collection occurred approximately one year and two years after the date of commercial availability of MVASI at participating sites, respectively. Sites involved in Wave 1 and Wave 2 were different. Following their recruitment into the study, Wave 1 and 2 site staff members across Canada reviewed the charts of adult mCRC patients who received MVASI as their first-line biologic treatment.

Setting

The study was conducted at 14 sites including seven academic and seven community-based oncology centres/hospitals in Canada, recruited in two waves. At the time of study start at each centre, site staff identified the charts for all mCRC patients treated with at least 1 dose of MVASI to be screened for the study. If patient charts qualified for enrollment, as per the eligibility criteria, applicable data were collected, including any relevant information available in the chart on the site-specific Chart Review Date (CRD). The data collection period continued for each centre until the centre had reviewed their charts to identify and enter data for eligible patients.

Subjects and Study Size, Including Dropouts

Originally, the study was planned to be conducted at approximately 12 academic and community-based oncology centres/hospitals in Canada. Each wave was anticipated to include approximately six centres. Each Wave 1 centre would have approximately 15 to 20 patient charts meeting the protocol eligibility criteria, for a total of up to approximately 100 patient charts. Similarly, each Wave 2 centre was expected to include approximately 30 to 35 patient charts meeting the protocol eligibility criteria, for a total of up to 200 patient charts. Thus, a total of 300 patient charts were expected to be included from the two waves. However, wave 1 sites encountered recruitment challenges and only 75 eligible patients were identified following the screening of medical records at the six Wave 1 sites. Therefore, 2 more sites than originally planned were recruited in Wave 2 in anticipation of similar challenges. Protocol amendment 2, dated 12-Oct-2021, was implemented to revise the total enrollment target to approximately 225 patients, with 75 and 150 patients expected in Wave 1 and Wave 2, respectively. According to the sample size calculations, the reduced enrollment targets would still allow for detection of the expected number of EOIs.

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This sample size is a convenience sample based on timing of data collection and availability of patient data. Section 9.7 presents additional details on the probability of observing at least one EOI in the planned sample.

Data Source(s) and Methods

This retrospective observational chart review aimed to describe the safety and effectiveness of MVASI therapy in Canadian patients with mCRC. Data collection occurred at the individual centres participating in the study. The data sources were patient medical charts; either paper charts, or electronic medical records, or a combination of both. The standard limitations of chart review studies applied to this study, such as missing or incomplete data.

Statistical Analysis:

1. Primary outcome analysis:
    - The number, percentage and 95% confidence interval (CI) of patients with at least one EOI
2. Secondary outcome analyses:
    - Objective response using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Complete response/Partial response/Stable disease/Progressive disease/Not evaluable/RECIST not assessed), n (%) [95% CI]
    - PFS, calculated as the time from Index Date to date of disease progression
3. Exploratory outcome analysis:
    - Death (yes, no, unknown) at the time of chart review
    - Time from Index Date to death

Results

A total of 395 patients were screened at 14 participating centres across Canada (Alberta [2], Nova Scotia [1], Ontario [5] and Québec [6]). A total of 156 patients failed to meet at least one of the eligibility criteria, resulting in 239 patients being included in the Full Analysis Set (FAS) for final analysis.

Among the 239 patients enrolled in the study, 75 were from Wave 1 and 164 were from Wave 2. Of the enrolled patients, 36/75 (48.0%) of Wave 1 and 98/164 (59.8%) of Wave 2 patients were male. The majority of the patients for whom race data was available were

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Caucasian in both Wave 1 (38/75; 50.7%) and Wave 2 (56/164; 34.1%). Notably, race was unknown for a large percentage of patients in Wave 1 (31/75; 41.3%) and Wave 2 (95/164; 57.9%). The median ages for Wave 1 and Wave 2 patients were 62 years (interquartile range [IQR]: 52, 72) and 67 years (IQR: 58, 73), respectively.

Among patients with available data, most patients had a baseline Eastern Cooperative Oncology Group (ECOG) status of 0 ("Fully active, able to carry on all pre-disease performance without restriction"; 27/62; 43.5% in Wave 1 and 46/109; 42.2% in Wave 2) or 1 ("Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work"; 33/62; 53.2% in Wave 1 and 59/109; 54.1% in Wave 2).

In Wave 1, the median time to the first MVASI administration was 6.0 months (IQR: 3.1, 20.9) from CRC diagnosis and 3.1 months (IQR: 2.1, 4.2) from mCRC diagnosis. For Wave 2 patients, the median time from CRC and mCRC diagnosis to MVASI initiation was 3.8 months (IQR: 2.1, 19.1) and 2.3 months (IQR: 1.6, 3.7), respectively. Among Wave 1 patients, primary tumors were mainly identified in the rectum (18/75; 24.0%), sigmoid (17/75; 22.7%), right not otherwise specified (NOS) (13/75; 17.3%), cecum (12/75; 16.0%), and transverse colon (9/75; 12.0%). In comparison, Wave 2 patients had primary tumors in the rectum (52/164; 31.7%), cecum (44/164; 26.8%), sigmoid (28/164; 17.1%), ascending colon (23/164; 14.0%), and transverse colon (13/164; 7.9%). Primary tumors were associated with a RAS mutation in 42/69 (60.9%) of Wave 1 and 87/141 (61.7%) of Wave 2 patients. BRAF mutation was identified in 14/63 (22.2%) of Wave 1 and 18/135 (13.3%) of Wave 2 patients.

In Wave 1, metastases were present at diagnosis in 43/75 (57.3%) patients and progressive disease was present in 31/75 (41.3%) patients. Likewise, among Wave 2 patients, 94/164 (57.3%) had metastases at diagnosis and 64/164 (39.0%) had progressive disease. Most patients in Wave 1 had 1 (40/75; 53.3%) or 2-3 (35/75; 46.7%) metastatic sites that were primarily located in the liver (48/75; 64.0%) or lung (23/75; 30.7%). Similarly, most Wave 2 patients had 1 (82/164; 50.0%) or 2-3 (76/164; 46.3%) metastatic sites that were primarily located in the liver (113/164; 68.9%) or lung (67/164; 40.9%).

During the treatment period in Wave 1, patients were treated with MVASI for a median duration of 84 days (IQR: 52, 231) and received an average of 8.9 cycles per patient (SD 6.6 cycles per patient, range 1-31 cycles per patient) over their treatment period. In comparison, the median duration of MVASI treatment for Wave 2 patients was 168 days

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(IQR: 77, 336) and the average number of cycles per patient was 12.3 (SD 9.3 cycles per patient, range 1-44 cycles per patient). The longer treatment period for Wave 2 patients was not surprising as the data collection period specified in the protocol design was longer in the second wave of the study.

The most common chemotherapy agent administered with MVASI cycles in both waves of the study was 5-FU-based chemotherapy regimens (632/663; 95.3% in Wave 1 patients and 1,783/1,982; 90.0% in Wave 2 patients).

Of patients in the FAS, 58/75 (77.3%) of the Wave 1 patients and 117/164 (71.3%) of the Wave 2 patients had at least one surgery related to CRC. Of these, the most common type of surgery was primary tumor resection with 50/58 (86.2%) patients in Wave 1 and (96/117, 82%) patients in Wave 2 undergoing the procedure.

Among the patients included in the analysis, at least one EOI was reported for 26/75 (34.7%) of Wave 1 and 70/164 (42.7%) of Wave 2 patients. The most common EOIs were thromboembolic events (11/75; 14.7%), proteinuria (6/75; 8.0%), and hemorrhages (5/75; 6.7%). The most common EOIs in Wave 2 were thromboembolic events (32/164; 19.5%), hypertension (17/164; 10.4%), and proteinuria 12/164 (7.3%).

Data regarding PFS was available for 74/75 (98.7%) of Wave 1 and 164/164 (100.0%) of Wave 2 patients in the FAS. Among the Wave 1 patients, 34/74 (45.9%) had a qualifying PFS event of either progressive disease (27/34; 79.4%) or death (14/34; 41.2%). Of the Wave 2 patients with PFS data, 66/164 (40.2%) had a qualifying PFS event of progressive disease (31/164; 47.0%) or death (46/164; 69.7%). The median PFS time for FAS patients was 9.47 months (95% CI: 6.71, 11.9 months) in Wave 1 and 21.38 months (95% CI: 15.82, not estimable) in Wave 2. Upon assessment of the OS data, 14/75 (18.7%) of Wave 1 and 46/164 (28.0%) of Wave 2 patients died by the end of the chart review period. OS outcomes were unknown for 1/75 (1.3%) and 15/164 (9.1%) of the patients in Wave 1 and Wave 2, respectively.

Discussion

Final analysis results suggest that the mCRC patient population included in the study for this retrospective review of patient charts was generally representative of the Canadian mCRC population treated with first-line bevacizumab or MVASI. Analysis of EOIs and real world effectiveness measures showed that the safety profile of MVASI in our findings are aligned with clinical trial observations of treatment efficacy in mCRC. The shorter median PFS observed in Wave 1 patients relative to Wave 2 may be due to higher proportions of

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comorbidities and smokers at baseline, as well as due to longer time from mCRC diagnosis to MVASI initiation. The median PFS time in Wave 2 was longer than the time reported in other prospective observational studies, potentially due to the sizable percentage of patients in our study with missing outcome data. The real world retrospective nature of these data, warrant cautious interpretation and generalization of the findings.

Marketing Authorization Holder(s)

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