**RESULTS**

Enrollment, follow-up, and site distribution

- A total of 2045 patients receiving BRiTE with regard to targeted BV-associated adverse events for AVF2107g, are shown for comparison.

**Gastrointestinal perforation**

The overall incidence of GIP is 1.7% (as of the March 1, 2006 data cutoff), which is comparable to that observed in recent phase III studies of BV in mCRC.

**Cardiac history:**

- Hypertension requiring medication

**Pregnancy status:**

- Status of pregnancy at start of BV therapy, %

**Incidence of GIP in patient subgroups at potential risk factors**

- The incidence of GIP in each subset of 1960 patients enrolled between February 2004 and June 2005, from 280 study sites in 33 countries, which was collected longitudinally.

- There were 1960 evaluable patients; 5 patients who received BV were considered non-evaluable.

- Median follow-up time was greater than 2.4 months (range 0.1-16.1 months).

**Surgical-pathologic findings in patients with GIP**

- Patients who underwent surgery were considered evaluable for efficacy and safety analysis.

**SUMMARY AND CONCLUSIONS**

- In this large observational study of first-line mCRC patients treated with BV, the safety and efficacy of BV in combination with standard chemotherapy are described.

- The majority of GIPs occurs early, within the first 3 months of BV treatment.

- The overall incidence of GIP was 1.7% (as of the March 1, 2006 data cutoff).

- Patients who received BV were considered evaluable for efficacy and safety analysis.

**REFERENCES**


In this large observational study of first-line mCRC patients treated with BV plus FOLFOX4, it was observed that BV prolongs overall survival and progression-free survival when added to standard chemotherapy in patients with mCRC. Bevacizumab (Avastin®, BV) prolongs overall survival and progression-free survival when added to standard chemotherapy in patients with mCRC. The incidence of GIP in each subset of patients grouped by baseline characteristics is shown in Table 4. The incidence of GIP in each subset of patients grouped by baseline characteristics is shown in Table 4.

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**OBJECTIVES**
- To identify baseline patient and disease characteristics that may be associated with increased risk for developing GIP
- To determine the association between GIP and certain patient characteristics or medical conditions

**METHODS**

**Study design and treatment**
- Observational study including all patients
- Standard chemotherapy: FOLFOX4
- Observation data collected prospectively

**Results**
- The incidence of GIP in each subset of patients grouped by baseline characteristics is shown in Table 4.

**Table 4. Incidence of GIP in Patients With Specific Medical Conditions at Baseline**

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Yes (n = 264)</th>
<th>No (n = 1696)</th>
<th>p-value</th>
</tr>
</thead>
</table>
| **Baseline**
| Age, years | 65-74 | 523 | 1022 | 0.12 |
| Sex | Male | 324 | 1419 | 0.04 |
| **Disease**
| Site(s) of metastatic disease | Primarily local/regional | 60 | 2156 | 0.02 |
| | Intra-abdominal | 52 | 1443 | 0.11 |
| **Patient**
| Race | White | 15 | 204 | 0.02 |

**Conclusions**
- The incidence of GIP in each subset of patients grouped by baseline characteristics is shown in Table 4.

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**REFERENCES**
INTRODUCTION

Bevacizumab (BV), a monoclonal antibody directed against vascular endothelial growth factor (VEGF), improves overall survival and progression-free survival when combined with chemotherapy for metastatic colorectal cancer. BV can increase the risk of serious adverse events (SAEs), including gastrointestinal perforation (GIP), and BV was therefore used in the BRiTE trial (N=411) as an active comparator arm in the pivotal phase III BV trial (AVF2107g) (N=713) that confirmed the overall survival benefit of BV for metastatic colorectal cancer. BV is associated with increased risk of GIP, which is a serious, potentially fatal event associated with increased mortality and morbidity.

METHODS

In this large observational study of metastatic colorectal cancer patients treated with BV as first-line therapy, we evaluated the incidence of GIP and other safety outcomes.

RESULTS

Enrollment, follow-up, and site distribution

• A total of 411 patients were enrolled between February 2004 and June 2005, from 248 study sites in 49 states.
• Median follow-up was 12.9 months at the time of this analysis (March 1, 2006).

Baseline characteristics

• Baseline patient and disease characteristics are shown in Table 2. Baseline patient and disease characteristics for the phase III placebo (AVF2107) are shown for comparison.

Gastrointestinal perforation

• The overall incidence of GIP is 1.7% (as of the March 1, 2006 data cutoff), which is lower than the 3.6% incidence observed in the recent phase III BRiTE trial (Table 3).
• Median time to a GIP event was 2.4 months (range 0.1-16.1 months).

SUMMARY AND CONCLUSIONS

• In this large observational study of first-line BV patients treated with BV as first-line therapy, in which a less selected patient population (BRiTE) was enrolled, a slightly higher incidence of GIP appeared to have a slightly higher incidence of GIP.
• Chronic aspirin or NSAID use, history of peptic ulcer disease, or prior adjuvant chemotherapy for mCRC continued to be associated with increased risk for GIP.
• Prior adjuvant chemotherapy for mCRC was associated with a slightly higher incidence of GIP.

REFERENCES

**RISK FACTORS FOR GASTROINTESTINAL PERFORATIONS IN PATIENTS WITH METASTATIC COLORECTAL CANCER RECEIVING BEVACIZUMAB PLUS CHEMOTHERAPY**

M. Sugrue,1 M. Kozloff,2 J. Hainsworth,3 S. Badarinar,4 A. Cohn,5 P. Flynn,6 R. Steis,7 W. Dong,7 S. Suzuki,7 A. Grothey,8 and the BRITÉ Study Investigators


**Abstract**

Bevacizumab (Avastin®), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has been approved for the treatment of metastatic colorectal cancer (mCRC) due to its overall survival and progression-free survival benefits when combined with chemotherapy.

**Methods**

In this large observational study of first-line mCRC patients treated with fluorouracil (FU) or irinotecan-based chemotherapy in combination with bevacizumab (BV), factors associated with gastrointestinal perforation (GIP) were explored. Baseline patient characteristics, including demographic, clinical, and laboratory data, were collected at study entry. Safety data were collected in an electronic database.

**Results**

Of the 1964 evaluable patients, 1946 received BV. The median study follow-up was 12.9 months. Of these patients, 33 reported a GIP event. The incidence of GIP was 0.7 per 100 patient-years. The most common sites of perforation were the colon and rectum. Patients who received BV in combination with first-line chemotherapy (IFL + BV) had a slightly higher incidence of GIP compared to those who received BV in combination with FOLFOX4 (FOLFOX4 + BV). Additionally, patients who received BV in combination with FOLFOX4 had a significantly lower incidence of GIP compared to patients who received FOLFOX4 alone (FOLFOX4).

**Conclusions**

The incidence of GIP appears to be slightly higher in patients who received BV in combination with IFL compared to those who received BV in combination with FOLFOX4. Further research is needed to understand the underlying mechanisms of GIP in these patients.

**References**

Observational data collected quarterly
• Observational study initiated February 2004
• Data for selected BV-associated events—GIP, postoperative bleeding or wound healing

Characteristics at Baseline

Table 1. Data Collection Schedule

Table 2. AE at Baseline Phase III Study AVF2107g1: Baseline Characteristics

Table 3. Incidence of GIP in BRiTE with Specific Medical History Characteristics at Baseline

Table 4. Incidence of GIP in BRiTE with Medical History Characteristics at Baseline

Table 5. Physician-Identified Surgical-pathologic Findings in Patients with GIP

Figure 1. Kaplan-Meier plot estimate of GIP-free time (right axis). GIP incidence by 9-month increments.

SUMMARY AND CONCLUSIONS

In this large observational study of first-line CRC patients treated with BV + chemotherapy, in which a less-selected population of patients with metastatic colorectal cancer was enrolled, the incidence of GIP was 1.7% at 12 months (range 0.1-16.1 months) with a potential risk of 3.4% at 36 months.

REFERENCES


In this large observational study of first-line mCRC patients treated with BV plus 5-FU/LV, 1.7% of patients receiving BV plus 5-FU/LV experienced gastrointestinal perforation (GIP), which is comparable to that observed in recent phase III studies of BV in metastatic colorectal cancer (mCRC). The median time to GIP was 2.9 months (range 0.1-16.1 months) – Of the 33 reported GIP events, most occurred within the first 3 months of treatment.

-**OBJECTIVES**
- To evaluate the incidence of GIP in a large, real-world population of patients previously untreated for metastatic colorectal cancer receiving BV plus 5-FU/LV chemotherapy.
- To assess the association between patient characteristics and the risk of GIP in patients receiving BV plus 5-FU/LV chemotherapy.

-**METHODS**
- **Study design and treatment**
  - Observational study of patients with metastatic colorectal cancer.
  - Treatment arm: BV plus 5-FU/LV chemotherapy.

- **Eligibility criteria**
  - Metastatic or locally advanced CRC
  - Planned chemotherapy:
    - BV plus 5-FU/LV chemotherapy
  - Signed informed consent

- **Data collection**
  - Specific data collected:
    - Baseline demographics: age, sex, primary tumor site, metastatic site, and history of prior therapies
    - Use of medical co-morbidities (e.g., cardiovascular, diabetes, chronic obstructive pulmonary disease)
    - Use of medications: anticoagulant use, aspirin use
  - Data analyzed:
    - Median follow-up was 12.9 months at the time of this analysis (March 1, 2005, from 248 study sites in 49 states)

- **RESULTS**
  - **Enrollment, follow-up, and site distribution**
    - A total of 1809 patients were enrolled between February 2004 and June 2005, with 2386 study sites in 49 states.
    - The median duration of follow-up was 12.3 months (range 0.1-16.1 months).

- **Clinical follow-up of patients in this community-based registry**
  - Yes (n = 114)
  - No (n = 1695)

- **Conclusions**
  - The incidence of GIP (1.7%) appears similar to that observed in recent phase III studies of BV in metastatic colorectal cancer.
  - The median time to GIP was 2.9 months (range 0.1-16.1 months).

- **SUMMARY AND CONCLUSIONS**
  - In a large observational study of first-line mCRC patients treated with BV plus 5-FU/LV chemotherapy, in which a less selected population of patients compared to phase III trials were enrolled:
  - The incidence of GIP (1.7%) appears similar to that observed in recent phase III studies of BV in metastatic colorectal cancer.
  - The median time to GIP was 2.9 months (range 0.1-16.1 months).
  - The majority of GIP events occur early, within the first 3 months of treatment.

- **REFERENCES**