EFFICACY OF BEVACIZUMAB PLUS CHEMOTHERAPY AS FIRST-LINE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER: UPDATED RESULTS FROM A LARGE OBSERVATIONAL REGISTRY IN THE US (BRiTE)

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INTRODUCTION

• Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has received approval by the US Food and Drug Administration for the first-line treatment of metastatic colorectal cancer (mCRC) in combination with chemotherapy.

• Though the BRiTE observational study evaluated the use of BV in combination with chemotherapy for the treatment of mCRC, the results of the larger pivotal phase III study, AVF21071, were not available at the time of study entry (March 1, 2006).

• The BRiTE observational study included patients who were not part of the AVF21071 study population and did not receive the same chemotherapy regimens as in the pivotal phase III study.

• The BRiTE observational study included patients who were not part of the AVF21071 study population and did not receive the same chemotherapy regimens as in the pivotal phase III study.

• The BRiTE observational study was designed to evaluate the safety and efficacy of BV in a large, less-selected population of patients with mCRC.

RESULTS

Enrollment, follow-up, and site distribution

• Patients (n = 1960) receiving BV in combination with chemotherapy as first-line treatment of mCRC were enrolled from 238 study sites in 45 states between February 2006 and June 2006.

• There were 1978 evaluable patients; 8 patients who never received BV were not considered evaluable.

Baseline characteristics

• Baseline patient and disease characteristics are shown in Table 2.

• Baseline ECOG performance status (PS) was 0 in 88% of patients.

• A higher proportion of patients had 60 years of age (61% vs. 56%).

• A higher proportion of patients had prior adjuvant chemotherapy (39% vs. 27%).

Treatment patterns

• As shown in Figure 1, the 3 chemotherapy regimens that are most commonly combined with BV were FOLFOX (oxaliplatin, infusional 5-FU/leucovorin), FOLFIRI (irinotecan, infusional 5-FU/leucovorin) and IFL (5-FU/LV*,2).

• The distribution of patients by chemotherapy grouping is shown in Figure 2.
# Efficacy of Bevacizumab Plus Chemotherapy as First-Line Treatment of Patients with Metastatic Colorectal Cancer: Updated Results from a Large Observational Registry in the US (BRiTE)

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## INTRODUCTION

Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is a novel agent approved by the US Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer (mCRC) in combination with fluorouracil (5-FU) or a fluoropyrimidine such as leucovorin (LV) or oxaliplatin (FOLFOX).

- BV is one of several antiangiogenic drugs in development for colorectal cancer.
- The BRiTE observational study was initiated at the time of FDA approval of BV for the treatment of mCRC and was designed to evaluate the safety and efficacy of BV in a prospective, nonrandomized, community-based population of patients with mCRC.

## RESULTS

### Enrollment, Follow-up, and Site Distribution

Patients (n = 1960) receiving BV in combination with chemotherapy as first-line treatment of mCRC were enrolled from 308 study sites in 49 states between February 2003 and June 2005.

### Baseline Characteristics

- **Baseline patient characteristics are shown in Table 2.**
- Baseline characteristics are similar across chemotherapy regimens.
- Additionally, baseline characteristics of chemotherapy regimens within the BRiTE observational registry continue to be evaluated as of March 2006.

### Treatment Patterns

As shown in Figure 1, the chemotherapy regimens that are most commonly used in combination with BV are:

- FOLFIRI (irinotecan, infusional 5-FU/leucovorin), and IFL
- FOLFIRI (irinotecan, leucovorin in 5-FU/leucovorin), and IFL
- 5-FU/LV, 5-fluorouracil and leucovorin; FOLFOX, infusional oxaliplatin and 5-FU/LV; FLOX (oxaliplatin, irinotecan, and 5-FU); and IFL

### Survival Outcomes

- The median survival duration was not reached in any chemotherapy regimen.
- The 1-year survival rate was 71% with chemotherapy alone.
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- The 1-year survival rate was 71% with chemotherapy alone.

### Subgroup Analysis

- The median survival duration was not reached in any chemotherapy regimen.
- The 1-year survival rate was 71% with chemotherapy alone.

## Efficacy

- Bevacizumab plus chemotherapy as first-line treatment of mCRC was associated with a significant improvement in overall survival (OS) and progression-free survival (PFS) compared with chemotherapy alone.
- The median PFS estimate for chemotherapy grouping subsets within the BRiTE observational registry continues to be evaluated as of March 2006.

## SUMMARY AND CONCLUSIONS

- In this large, observational study, BV plus chemotherapy was associated with significant improvements in OS and PFS compared with chemotherapy alone.
- The efficacy and safety of BV plus chemotherapy as first-line treatment of mCRC continue to be evaluated as of March 2006.

## REFERENCES

Efficacy of bevacizumab plus chemotherapy as first-line treatment of patients with metastatic colorectal cancer: Updated results from a large observational registry in the US (BRITE)

M. Kozloff1, J. Hainsworth2, S. Badarinath3, A. Cohn4, P. Flynn5, R. Steis6, W. Dong7, S. Suzuki7, S. Sarkar8, M. Sugrue7, A. Grothey8, and the BRiTE Study Investigators

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Introduction

Bevacizumab [BV], a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), extends survival in patients with metastatic colorectal cancer (mCRC) who progress during or after chemotherapy. 

The BRiTE observational study was initiated at the time of FDA approval of BV for first-line treatment of mCRC. 

This observational registry will follow approximately 2000 patients for up to 3 years in order to evaluate the safety and efficacy of BV in a large, less-selected population of patients with mCRC. 

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- A lower proportion of patients had ECOG performance status 0 (43% vs 47%) and a higher proportion of patients was female (56% vs 53%). 

in this large, observational study, age does not appear to be a significant factor in the use of bevacizumab for metastatic colorectal cancer.
# Efficacy of Bevacizumab Plus Chemotherapy as First-Line Treatment of Patients with Metastatic Colorectal Cancer: Updated Results from a Large Observational Registry in the US (BRiTE)

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Village Hospital, Harvey, IL; Saint Barnabas Research Institute/Trenton Oncology Network, Trenton, NJ; Florida Oncology/Cancer Centers, Jacksonville, FL; Rocky Mountain Cancer Centers, Denver, CO; MacNeil Hepatobiliary Oncology, Minneapolis, MN; Alliance Cancer Care, Roanoke, VA; Sentara, Inc., South San Francisco, CA; Mayo Clinic, Rochester, MN

## INTRODUCTION

- Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is approved in the US for the treatment of metastatic colorectal cancer (mCRC) in combination with chemotherapy.
- The BRiTE study, a large, observational study, evaluated the safety and efficacy of BV in combination with first-line chemotherapy in a real-world setting.
- The study included 1960 patients with mCRC from 255 community oncology sites.

## OBJECTIVES

- Evaluate the efficacy and safety of BV in combination with first-line chemotherapy in a real-world setting.
- Assess the impact of patient characteristics on outcomes.

## METHODS

### Study design and setting

- Observational study, initiated in February 2004.
- Eligible patients were adults with mCRC with disease progression on or within 14 days of a first-line chemotherapy regimen at a participating site.
- Data were collected prospectively through the BRiTE registry.

### Patient eligibility criteria

- Metastatic or locally advanced CRC.
- Received BV in combination with first-line chemotherapy.
- Signed informed consent.

### Treatment regimens

- BV was administered at an initial dose of 5 mg/kg followed by 15 mg/kg every 3 weeks.

## RESULTS

### Efficacy

- **Overall response rate (ORR):** 37.7% (95% CI, 34.6–40.8)
- **Overall survival (OS):** Median OS, 14.3 months (95% CI, 13.8–14.8)
- **Progression-free survival (PFS):** Median PFS, 6.4 months (95% CI, 5.3–7.6)

### Baseline characteristics

- **Median age:** 60 years (range, 18–90)
- **ECOG performance status (PS):** 0 or 1 in 93% of patients
- **Status of primary tumor:** Complete resection in 65% of patients
- **Site(s) of metastatic disease:** Liver in 94%, lung in 91%, and peritoneum in 56%

### Subgroup analyses

- **Age:**
  - <65 years: 35% (n = 680)
  - ≥65 years: 65% (n = 1288)
- **ECOG PS:**
  - PS 0 or 1: 93% (n = 1813)
  - PS 2: 7% (n = 147)
- **Treatment regimen:**
  - Irinotecan-containing (n = 755)
  - Oxaliplatin-containing (n = 1226)
  - Neither (n = 477)

### Summary and conclusions

- BV in combination with chemotherapy is well tolerated in a real-world setting.
- The efficacy and safety results from BRiTE are consistent with those observed in randomized trials.

## REFERENCES


## Table 5: Efficacy of bevacizumab (BV) as combination therapy with chemotherapy

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Overall response rate (%)</th>
<th>Median progression-free survival (months)</th>
<th>Median overall survival (months)</th>
<th>Hazard ratio (BV vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV, n = 755</td>
<td>47.6</td>
<td>7.1</td>
<td>14.3</td>
<td>0.70 (0.60–0.82)</td>
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<tr>
<td>Placebo, n = 204</td>
<td>23.3</td>
<td>4.4</td>
<td>12.1</td>
<td>1.00 (Reference)</td>
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</table>

### Table 6: Progression-free survival at different time points

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>BV hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0.59 (0.49–0.73)</td>
</tr>
<tr>
<td>18</td>
<td>0.53 (0.43–0.64)</td>
</tr>
<tr>
<td>24</td>
<td>0.49 (0.40–0.60)</td>
</tr>
</tbody>
</table>

### Figure 3: Kaplan-Meier curve: progression-free survival.

- Baseline characteristics
  - Median age: 60 years
  - ECOG PS: 0 or 1
  - Status of primary tumor: Complete resection
  - Site(s) of metastatic disease: Liver, lung, peritoneum
  - Treatment regimen: Irinotecan-containing, oxaliplatin-containing, neither

### Figure 4: Distribution of patients by chemotherapy grouping and age subsets.

- Median age: 60 years
- ECOG PS: 0 or 1
- Status of primary tumor: Complete resection
- Site(s) of metastatic disease: Liver, lung, peritoneum
- Treatment regimen: Irinotecan-containing, oxaliplatin-containing, neither

### Figure 5: Kaplan-Meier curve: overall survival.

- Baseline characteristics
  - Median age: 60 years
  - ECOG PS: 0 or 1
  - Status of primary tumor: Complete resection
  - Site(s) of metastatic disease: Liver, lung, peritoneum
  - Treatment regimen: Irinotecan-containing, oxaliplatin-containing, neither

### Figure 6: Kaplan-Meier curve: overall survival at different time points.

- Median age: 60 years
- ECOG PS: 0 or 1
- Status of primary tumor: Complete resection
- Site(s) of metastatic disease: Liver, lung, peritoneum
- Treatment regimen: Irinotecan-containing, oxaliplatin-containing, neither

### Figure 7: Kaplan-Meier curve: overall survival at different time points.

- Median age: 60 years
- ECOG PS: 0 or 1
- Status of primary tumor: Complete resection
- Site(s) of metastatic disease: Liver, lung, peritoneum
- Treatment regimen: Irinotecan-containing, oxaliplatin-containing, neither

### Figure 8: Kaplan-Meier curve: overall survival at different time points.

- Median age: 60 years
- ECOG PS: 0 or 1
- Status of primary tumor: Complete resection
- Site(s) of metastatic disease: Liver, lung, peritoneum
- Treatment regimen: Irinotecan-containing, oxaliplatin-containing, neither

### Figure 9: Kaplan-Meier curve: overall survival at different time points.

- Median age: 60 years
- ECOG PS: 0 or 1
- Status of primary tumor: Complete resection
- Site(s) of metastatic disease: Liver, lung, peritoneum
- Treatment regimen: Irinotecan-containing, oxaliplatin-containing, neither

### Figure 10: Kaplan-Meier curve: overall survival at different time points.

- Median age: 60 years
- ECOG PS: 0 or 1
- Status of primary tumor: Complete resection
- Site(s) of metastatic disease: Liver, lung, peritoneum
- Treatment regimen: Irinotecan-containing, oxaliplatin-containing, neither
Efficacy of Bevacizumab Plus Chemotherapy as First-Line Treatment of Patients with Metastatic Colorectal Cancer: Updated Results from a Large Observational Registry in the US (BRiTE)

M. Kozloff, J. Hainsworth, S. Basdaranth, A. Coit, P. Flynn, B. Steis, W. Dong, S. Suzuki, S. Sarkar, M. Sugrue, A. Grothey, and the BRiTE Study Investigators

Introduction

Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has been approved by the US Food and Drug Administration for the treatment of colorectal cancer. BV-based chemotherapy regimens are palliatively effective in patients with metastatic colorectal cancer (mCRC)

The BRiTE observational study initiated at the time of BV approval in 2004 in order to evaluate the safety and efficacy of BV in combination with first-line chemotherapy in a routine community setting

The current analysis evaluates the updated data from this observational study cohort

Methods

Study design and analysis

Observational study initiated February 2004

Chemotherapy regimen, BV dose, and BV schedule were chosen at the discretion of the treating physician

Analytical approach

Analyses were performed according to the chemotherapy regimen, BV dose, and BV schedule

Statistical considerations

PFS was measured from the date of first treatment to the first occurrence of disease progression, death as a result of any cause, or last observation of patients who were censored at the last data cut-off (December 1, 2006)

Results

Enrollment, follow-up, and site distribution

There were 1960 evaluable patients; 8 patients who never received BV were not accounted for in these groupings

Table 1 shows the distribution of patients by chemotherapy grouping and age subsets

Table 2 shows the distribution of patients by chemotherapy grouping and type of adjuvant therapy

Chemotherapy regimens utilized

Chemotherapy regimens utilized in combination with BV were FOLFOX (oxaliplatin, infusional 5-FU/leucovorin), AVF2107 (irinotecan, 5-FU, and leucovorin [IFL]+BV) (Table 3)

The median OS is not yet estimable (95% CI, 9.9–10.9)

Table 3 shows the Kaplan-Meier estimates of survival at 6, 9, and 12 months

Discussion

This is the largest US-based observational study of patients with previously untreated metastatic colorectal cancer receiving BV-based chemotherapy

Conclusions

The updated findings from the BRiTE registry are favorable to historical results for median PFS compared to the pivotal phase III trial AVF2107, the estimated median PFS

The overall survival benefit of chemotherapy regimens plus BV is consistent with the results observed in AVF2107

In this large, observational study, age does not appear to be a significant prognostic factor for PFS in patients with previously untreated metastatic colorectal cancer receiving BV-based chemotherapy

References

1. Ingalls Hospital, Harvey, IL, and the University of Chicago, Chicago, IL; 2. Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; 3. Worldwide Oncology Network, Jacksonville, FL; 4. Rocky Mountain Cancer Centers, Denver, CO; 5. Market Access Hospital, Minneapolis, MN; 6. Atlanta Cancer Care, Roswell, GA; 7. Genentech, Inc., South San Francisco, CA; 8. Mayo Clinic, Rochester, MN

Table 1: Distribution of patients by chemotherapy grouping and age subsets

Table 2: Kaplan-Meier estimates of survival at 6, 9, and 12 months

Table 3: Chemotherapy regimens utilized

Table 6: Efficacy of chemotherapy regimens plus BV

Table 7: Progression-free survival, chemotherapy and age groupings

Table 8: Median overall survival, chemotherapy and age groupings

Table 9: Percentages of patients with disease progression

Table 10: Full bibliography
INTRODUCTION

Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has been approved by the FDA for the treatment of metastatic colorectal cancer (mCRC). BV combined with chemotherapy regimens offers patients with previously untreated mCRC a potential survival advantage.

The BRiTE observational study evaluated at the time of BV approval in the US at the time of initial presentation of patients with mCRC. The primary endpoint was overall survival (OS). The study enrolled 2,125 patients from 298 sites in 40 states between February 2004 and June 2005.

OBSERVATIONAL DESIGN

The BRiTE registry is a descriptive, observational study of patients with previously untreated mCRC who were treated with BV plus chemotherapy regimens. A prospective, observational study evaluated at the time of BV approval in the US at the time of initial presentation of patients with mCRC.

OBJECTIVES

The objectives of the study were to:

- Evaluate the clinical efficacy and overall survival of BV in combination with chemotherapy regimens.
- Evaluate the safety and tolerability of BV combined with chemotherapy regimens.
- Compare the safety and tolerability of BV combined with chemotherapy regimens with historical controls.
- Evaluate the impact of BV on quality of life.

METHODS

Study design and population

- Observation started January 2004.
- Chemotherapy regimens, BV dose, and old schedule were chosen at the physician’s discretion.
- Data were collected quarterly.
- Response assessment, including method and frequency, was determined by the principal investigator.

Statistical considerations

- PFS was measured from the date of first treatment to the first occurrence of investigator-assessed disease progression or death. The remaining patients were censored at the data cutoff date (March 1, 2006).

RESULTS

Enrollment, follow-up, and site distribution

- There were 1226 contributing events (earlier of disease progression or death) from 570 patients, 29.1% of enrollment.

Treatment patterns

- As shown in Figure 1, the 3 chemotherapy regimens that are most commonly combined with BV are FOLFOX (oxaliplatin, infusional 5-FU/leucovorin), FOLFIRI (irinotecan, 5-FU/bolus leucovorin), and IFL (irinotecan, 5-FU, and LV).

- The distribution of patients by chemotherapy group is shown in Figure 2.

- Subgroup analysis: FOLFOX plus BV and IFL plus BV are 10% and 12% of chemotherapy group patients, respectively.

- As shown in Figure 3, the Kaplan-Meier curve for PFS in the eligible patient population is 10.2 months (95% CI, 9.9–10.9) for FOLFOX plus BV, 9.9 months (95% CI, 9.6–10.3) for IFL plus BV, and 8.8 months (95% CI, 8.3–9.3) for IFL plus placebo.

- The median PFS observed in AVF21076 (which used the median PFS observed in a central lab) was 9.5 months (95% CI, 8.9–10.1).

- As shown in Table 6, median PFS for patients with metastatic colorectal cancer receiving BV-based chemotherapy is comparable to historical results for median PFS observed in AVF21076.

- Statistically significant improvements in median OS for patients treated with BV in combination with chemotherapy regimens were observed in AVF21076 compared with historical results. Median OS was 12.4 months for patients treated with BV in combination with chemotherapy regimens in AVF21076 compared with 10.3 months for historical controls.

- As shown in Table 6, median OS for patients with metastatic colorectal cancer receiving BV-based chemotherapy is comparable to historical results for median OS observed in AVF21076.

SUMMARY AND CONCLUSIONS

- The BRiTE registry provides evidence of chemotherapy group survival benefits.
- The median OS observed with BV-based chemotherapy group regimens within the BRiTE registry is comparable to the median OS observed in AVF21076.

- In this large, observational study, age does not appear to be a significant factor in determining response to BV-based chemotherapy group regimens.

REFERENCES

