**LANDMARKS**

Report from the ASCO GI Cancers Symposium

**Colorectal Cancer**

**AVEX AND TRIBE TRIAL RESULTS**

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**TRIAL SUMMARY:** Bevacizumab benefits elderly patients in first study of underrepresented group


Most patients diagnosed with metastatic colorectal cancer (mCRC) are elderly, yet this age group is generally underrepresented in clinical trials. AVEX (Avastin in the Elderly with Xeloda), an open-label phase III trial, evaluated the efficacy and safety of capecitabine (Cape) ± bevacizumab (Bev) in elderly patients with previously untreated mCRC.

Patients ≥70 years with mCRC for whom single-agent chemotherapy was deemed appropriate were randomized 1:1 to receive first-line Cape (1000 mg/m² twice a day on days 1–14) alone or in combination with Bev (7.5 mg/kg) every 3 weeks. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR) and safety. The study was powered to show a difference in PFS, but not OS, between treatment arms. PFS and OS estimates were calculated using Kaplan-Meier methods.

A total of 280 pts across 10 countries were randomized to Cape + Bev (n=140) and Cape alone (n=140). Median age at enrollment was 76 years (range 70–87), and 91.1% of patients had an ECOG (Eastern Cooperative Oncology Group) performance status of 0–1. Baseline patient and disease characteristics were well balanced between arms. Bev + Cape was associated with significantly prolonged PFS compared with Cape alone (median 9.1 vs 5.1 months; hazard ratio [HR] 0.53; 95% confidence interval [CI] 0.41–0.69; p<0.001). ORR was also significantly improved in the Bev + Cape arm (19.3% vs 10.0%; p=0.042). OS was longer in patients treated with Bev + Cape vs Cape alone, although this difference was not statistically significant (median 20.7 vs 16.8 months; HR 0.79; 95% CI, 0.57–1.09; p=0.182). Grade ≥3 adverse events occurred in 59.0% vs 44.1% of patients in the Bev + Cape and Cape arms, respectively. Treatment was generally well tolerated and the safety profile consistent with previously reported data for Bev + Cape.

This is the first randomized study to prospectively evaluate Bev specifically in elderly patients with mCRC. Based on the efficacy and safety results, the authors concluded that Bev + Cape might be an optimal treatment approach to improve outcomes in elderly patients.

**COMMENTARY:** The median age of diagnosis of colorectal cancer (CRC) is 71 years, and 40% of cases diagnosed are in those ≥75 years. Due to usual selection criteria, this group of patients is often underrepresented in clinical trials. In treating older patients, the choice of chemotherapy is often based on the aim of providing an easier and less toxic regimen with drugs such as oral capecitabine monotherapy, an approach often preferred by this group of patients. The main concern in this strategy relates to the potentially reduced efficacy of this monotherapy when compared to complex and more toxic combination chemotherapy. The AVEX trial is important as it has demonstrated that the implementation of the combination of capecitabine with bevacizumab, a generally well-tolerated drug easily administered through intravenous injection in less than 30 minutes, addresses this important objective, offering simpler chemotherapy while enhancing efficacy, with a significant improvement in PFS.

In addition, this trial has important overall implications in the delivery of care in metastatic CRC in the general population, for example using the OPTIMOX approach that introduces intermittent simpler chemotherapy delivery with decreased toxicity and the administration of bevacizumab beyond progression may improve overall efficacy and tolerability in the management of mCRC.

**IN BRIEF**

**Already known**
- The majority of patients diagnosed with metastatic colorectal cancer (mCRC) are elderly, but this patient group is underrepresented in clinical trials.
- Oral capecitabine monotherapy may have reduced efficacy compared to some complex and more toxic combination chemotherapy regimens.

**What this study showed**
- The combination of capecitabine with bevacizumab significantly improved progression-free survival and overall response rate compared with capecitabine alone in elderly patients with previously untreated mCRC. Overall survival was longer with the combination, and treatment was well tolerated.

**Next steps**
- New approaches such as intermittent simpler chemotherapy delivery with decreased toxicity and the administration of bevacizumab beyond progression may improve overall efficacy and tolerability in the management of mCRC.
TRIAL SUMMARY: First-line FOLFOXIRI plus bevacizumab provides benefits in unresectable mCRC

First-line folinic acid (leucovorin [LV]), 5-fluorouracil (5-FU), oxaliplatin and irinotecan (FOLFOXIRI) demonstrated superior activity and efficacy compared to LV, 5-FU and irinotecan (FOLFIRI). Moreover, the outcome is improved by the addition of Bev to first-line doublets. A phase II study of FOLFOXIRI/Bev showed promising activity and manageable toxicities. The present trial compared FOLFOXIRI/Bev to FOLFIRI/Bev as first-line treatment in unresectable mCRC.

Eligibility criteria included: measurable and unresectable mCRC; age 18–75 years; and no prior chemotherapy for advanced disease. Patients were randomized to either FOLFIRI/Bev (Bev 5 mg/kg, irinotecan 180 mg/m², l-LV 200 mg/m², 5-FU bolus 400 mg/m², 5-FU infusion 2400 mg/m² over 48 hours every 2 weeks, arm A) or FOLFOXIRI/Bev (Bev 5 mg/kg, irinotecan 165 mg/m², oxaliplatin 85 mg/m², l-LV 200 mg/m², 5-FU infusion 3200 mg/m² over 48 hours every 2 weeks, arm B). Treatment was planned for a maximum of 12 cycles followed by maintenance with Bev and 5-FU until progression. The primary endpoint was progression-free survival (PFS).

Between July 2008 and May 2011, 508 patients were randomized among 35 Italian centres. Patient characteristics were (for arm A/arm B, respectively): median age 60/61 years; ECOG performance status 1–2 11%/10%; synchronous metastases 81%/79%; and multiple sites of disease 74%/70%. At median followup of 20.9 months, 391 patients have progressed. The study met its primary endpoint: FOLFOXIRI/Bev significantly increased PFS (median 9.5 vs 11.9 months, HR 0.72; 95% CI, 0.59–0.87; p=0.001). Response rate was also significantly increased (53% vs 64%; p=0.015). Main per-patient toxicities were (arm A/arm B): grade 3–4 diarrhoea 10%/18%; grade 3–4 vomiting 3%/4%; grade 3–4 stomatitis 4%/8%; grade 3–4 peripheral neurotoxicity 0%/5%; grade 3–4 neutropenia 20%/49%; febrile neutropenia 6%/8%; hypertension 2%/5%; thromboembolic events 7%/7%; bleeding 1%/1%. Deaths within 60 days occurred in 3% (arm A) and 4% (arm B) of patients.

The study concluded that FOLFOXIRI/bev significantly increases PFS and response rate compared to FOLFIRI/bev, with expected rates of chemotherapy- and bev-related toxicities.

COMMENTARY: Progress in drug development in metastatic CRC in the last decade has led to an increase in median overall survival (OS) exceeding 2.5 years. Data have also demonstrated improved survival in patients exposed to all available drugs. This has led to an interest in triple combination chemotherapy, with evidence of further improved efficacy in terms of response rates and OS. The present study has demonstrated further significant benefit when bevacizumab is combined with triple combinations. This will likely also prove very effective in downsizing metastatic disease, leading to curative resections and further increase in overall cure rates. There is no doubt that this progress heralds a new era, with triple combinations bringing a significant increase in OS and curability of metastatic CRC.

Disclosure: Dr. Maroun is a member of the advisory board and has delivered presentations for Roche.

Already known
• First-line folinic acid (leucovorin [LV]), 5-fluorouracil (5-FU), oxaliplatin and irinotecan (FOLFOXIRI) demonstrated superior activity and efficacy compared to LV, 5-FU and irinotecan (FOLFIRI).
• A phase II study of FOLFOXIRI plus bevacizumab showed promising activity and manageable toxicities.

What this study showed
• In this phase III trial, first-line treatment with FOLFOXIRI/bevacizumab in unresectable mCRC significantly increased progression-free survival and response rate compared to FOLFIRI/bevacizumab, with expected rates of toxicity.

Next steps
• Further research will confirm the benefits of bevacizumab added to triple chemotherapy combinations in increasing overall cure rates in metastatic CRC.