Bevacizumab plus chemotherapy continued beyond first progression in patients with metastatic colorectal cancer previously treated with bevacizumab plus chemotherapy: ML18147 study KRAS subgroup findings†

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Background: ML18147 evaluated continued bevacizumab with second-line chemotherapy for patients with metastatic colorectal cancer (mCRC) progressing after the standard first-line bevacizumab-containing therapy.

Patients and methods: Evaluating outcomes according to tumor Kirsten rat sarcoma virus oncogene (KRAS) status was an exploratory analysis. KRAS data were collected from local laboratories (using their established methods) and/or from a central laboratory (mutation-specific Scorpion amplification-refractory mutation system). No adjustment was made for multiplicity; analyses were not powered to detect statistically significant differences.

Results: Of 820 patients, 616 (75%) had unambiguous KRAS data; 316 (51%) had KRAS wild-type tumors and 300 (49%) had mutant KRAS tumors. The median progression-free survival (PFS) was 6.4 months for bevacizumab plus chemotherapy and 4.5 months for chemotherapy (P < 0.0001; HR = 0.61; 95% confidence interval (CI): 0.49–0.77) for wild-type KRAS and 5.5 and 4.1 months, respectively (P = 0.0027; HR = 0.70; 95% CI: 0.56–0.89) for mutant KRAS. The median overall survival (OS) was 15.4 and 11.1 months, respectively (P = 0.0052; HR = 0.69; 95% CI: 0.53–0.90) for wild-type KRAS and 10.4 versus 10.0 months, respectively (P = 0.4969; OS, P = 0.92; 95% CI: 0.71–1.18) for mutant KRAS. In both analyses, no treatment interaction by KRAS status was observed (PFS, P = 0.4436; OS, P = 0.1266).

Conclusions: Bevacizumab beyond first progression represents an option for patients with mCRC treated with bevacizumab plus standard first-line chemotherapy, independent of KRAS status.

Key words: Bevacizumab, chemotherapy, colorectal cancer, KRAS mutation status

introduction

Randomized clinical studies have shown that the combination of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab with fluoropyrimidine-based chemotherapy is an effective treatment of patients with metastatic colorectal cancer (mCRC), and such combinations are now a standard treatment in the first-line [1–3] and bevacizumab-naïve second-line settings [4]. The ML18147 study [5] and early results from the BEBYP study [6] indicate that continued VEGF inhibition with bevacizumab plus standard second-line chemotherapy (switched over from the first-line regimen) beyond first disease progression significantly prolongs overall survival (OS) [5] and progression-free survival (PFS) [5, 6] in patients with mCRC.

Subgroup analyses have demonstrated that the efficacy of bevacizumab in ML18147 is independent of a range of baseline demographics, pretreatment factors, and clinical factors [7–9]. Several biomarkers have been investigated as a potential means...
of selecting/predicting patients most likely to respond to targeted therapy or to exclude those unlikely to respond [10]. Kirsten rat sarcoma virus oncogene (KRAS) mutations in tumor tissue are present in ∼40% of patients with mCRC [11, 12]. Studies have shown that epidermal growth factor receptor (EGFR) inhibitors are potentially only effective in patients with wild-type KRAS tumors and mostly have no benefit in those whose tumors carry KRAS mutations [13–15]. However, the prognostic value of KRAS has not yet been completely elucidated in second-line treatment [16].

Existing data suggest that the efficacy of first-line bevacizumab does not depend on tumor KRAS mutation status [17–19]. However, the effect of KRAS status on response to post-progression bevacizumab in bevacizumab-pretreated patients has not been investigated. The present exploratory analysis of outcomes according to KRAS status in the ML18147 study was therefore undertaken.

patients and methods

study design

This was a prospective, multicenter, intergroup, randomized, open-label, phase III study (ML18147; clinicaltrials.gov identifier NCT00700102). The study design has been described in detail elsewhere [5] and in brief in the supplementary material, available at *Annals of Oncology* online.

biomarker study

Exploratory end points in ML18147 included analysis of tumor KRAS and B-type Raf kinase (BRAF) mutational status. Biomarker analyses were implemented with version 5 of the study protocol on 1 December 2008, when 233 patients had been enrolled, and became mandatory thereafter. Patients already enrolled, and able to consent were asked to provide written informed consent for biomarker sample collection whenever possible. In order not to negatively affect recruitment, tumor samples were not strictly required for enrollment. Results from local laboratories (using the methods established therein) and from a central laboratory were collected in the case report form (CRF) and used for the analysis.

Archival tumor tissue samples were collected at baseline and again if tumor surgery occurred during enrollment. When tumor tissue was provided, KRAS mutational status was determined by a central laboratory (HistoGeneX, Antwerp, Belgium). All assays were carried out blinded to the study end point. Paraffin or partial blocks containing formalin-fixed tumor tissue were preferred; core biopsy from the tumor block or ≥20 freshly cut slides of formalin-fixed paraffin-embedded tumor were also permitted.

KRAS status was determined using mutation-specific Scorpion ARMS (amplification-refractory mutation system; Qiagen, Hilden, Germany). If no tumor tissue was available for central KRAS analysis, results from local laboratories were retrieved and noted in the CRF whenever feasible. CRF tumor tissue was available for central KRAS analysis, results from local laboratories (amplification-refractory mutation system; Qiagen, Hilden, Germany).

statistical analysis

The statistical design of ML18147 has been described elsewhere [5]. Exploratory PFS and OS analyses by KRAS status were conducted in the KRAS biomarker population, which included all patients with a documented, consistent KRAS status assessment. Patients were excluded from efficacy analyses if KRAS results from local and central laboratories were available but differed. Safety and subsequent anticancer treatment analyses were based on patients with a KRAS status assessment who received ≥1 dose of study drug.

PFS and OS curves by KRAS status were estimated using the Kaplan–Meier method; differences were assessed using unstratified log-rank tests. An unstratified Cox regression model was used to estimate hazard ratios (HRs). Mutation status analyses were exploratory and were intended to examine the consistency of treatment-effect point estimates, i.e. that HRs were on the same side of 1 for both wild-type and mutant KRAS groups. A likelihood ratio test was used to assess interactions between treatment effect and KRAS status. The interaction test was considered negative if $P > 0.05$, indicating a lack of evidence that treatment outcome differed by KRAS mutational status.

KRAS analysis was one component of the ML18147 biomarker program; results were not adjusted for multiple testing. The study was not powered to examine differences within biomarker subpopulations. *Post hoc* OS analyses were conducted using the Cox regression model adjusting for treatment and KRAS status as a single covariate (univariate) or in combination with possibly associated baseline prognostic factors (multivariate): patient population (AIO 0504, ML18147), first-line PFS (≤9 months, >9 months), first-line therapy (irinotecan-based, oxaliplatin-based), time from last dose of bevacizumab (≤42 days, >42 days), Eastern Cooperative Oncology Group performance status (0, >1), age at randomization (<65 years, ≥65 years), sex (male, female), liver metastasis only (yes, no), and number of organs with metastases (≤1, >1). No selection process was employed in the multiple Cox regression analysis. Patients with missing prognostic factors were excluded from these analyses.

result

patient population

Overall, 820 patients were randomized between 1 February 2006 and 9 June 2010 (data cut-off 31 May 2011). The median follow-up was 9.6 months (range 0–45.5 months) for patients who received chemotherapy alone and 11.1 months (range 0.3–44.0 months) for bevacizumab plus chemotherapy. At the time of the primary analysis, 655 of the 819 patients in the intention-to-treat (ITT) population had died and 780 had disease progression.

KRAS data were available for 623 patients, including 221 patients for whom tumor material was submitted to the central laboratory. KRAS data from seven patients were excluded because local and central laboratory testing gave conflicting results. The KRAS biomarker population therefore comprised 616 patients (75% of the ITT population; supplementary Figure S1, available at *Annals of Oncology* online), 300 (49%) of whom had KRAS mutations. The distribution of patients with mutant KRAS tumors was balanced (chemotherapy alone 45%; bevacizumab plus chemotherapy 52%). Baseline demographic and clinical characteristics of the KRAS population were generally well balanced (Table 1) and comparable with those of the ITT population [5].

efficacy

ML18147 met its primary end point [5]. Similar results were observed for the KRAS population (supplementary Figure S2, available at *Annals of Oncology* online); the median OS was 11.9 months for bevacizumab plus chemotherapy and 10.6 months for chemotherapy alone [HR = 0.82; 95% confidence interval (CI): 0.68–0.98; $P = 0.0264$]; the median
PFS was 5.9 versus 4.3 months, respectively (HR = 0.66; 95% CI: 0.56–0.78; P < 0.0001).

Addition of bevacizumab to second-line chemotherapy significantly prolonged PFS versus chemotherapy alone in patients with KRAS wild-type tumors and KRAS mutant tumors (Figure 1A; Table 2). In patients with KRAS wild-type tumors, OS was prolonged with bevacizumab plus chemotherapy versus chemotherapy alone (Figure 1B). In patients with mutant KRAS tumors, OS was similar for both groups. Post hoc univariate and multivariate analyses of OS also showed a treatment benefit for bevacizumab (supplementary Tables S1 and S2, available at Annals of Oncology online). The interaction test by KRAS status, which examined whether the effect of treatment varied with mutant or wild-type KRAS, showed that bevacizumab benefit was independent of tumor mutation status (test of treatment by KRAS status interaction).
Based on data from patients who received chemotherapy only, a clear prognostic effect of KRAS status could not be determined (OS: HR = 1.23, 95% CI 0.95–1.59, \( P = 0.1166 \); PFS: HR = 1.12, 95% CI 0.89–1.41, \( P = 0.3421 \)).

Response rates were low in both treatment groups (Table 2). Disease-control rates were numerically higher in bevacizumab-treated patients in both KRAS groups.

After completing study treatment, 434 patients from the KRAS biomarker population received other therapies, including 84 patients with further bevacizumab and 241 with anti-EGFR antibodies (supplementary Table S3, available at Annals of Oncology online). The proportion of patients receiving subsequent anti-EGFR therapy was substantially higher in patients with wild-type KRAS tumors compared with those with mutant KRAS tumors (69% versus 8%, respectively).

BRAF status was determined for 207 patients (25% of the ITT population; 34% of the KRAS biomarker population); 14 patients had a BRAF mutation, 6 in the bevacizumab plus chemotherapy group and 8 in the chemotherapy-alone group. Given the small number of patients with mutant BRAF (7%), treatment group comparisons were not deemed meaningful.

**tolerability**

The adverse-event profile of continued bevacizumab plus standard chemotherapy was generally comparable in patients with wild-type and mutant KRAS tumors (Table 3).

**discussion**

ML18147 is the first randomized phase III study to demonstrate that OS and PFS are significantly prolonged with continued bevacizumab plus standard chemotherapy compared with chemotherapy alone as second-line treatment of patients with mCRC who progressed after a standard first-line bevacizumab-containing regimen [5].
KRAS status data, either from local laboratories or from a central laboratory, were available for 75% of the ITT population in ML18147; demographics of the biomarker and ITT populations were comparable. Overall, 49% of patients in this study had KRAS-mutant tumors. This is somewhat higher than observed in first-line mCRC studies, e.g. AGIGT MAX (29%).

Table 2. Clinical outcomes in patients receiving chemotherapy with or without bevacizumab after disease progression following first-line bevacizumab-based therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>KRAS wild type Chemotherapy (n = 165)</th>
<th>Bevacizumab + chemotherapy (n = 151)</th>
<th>KRAS mutant Chemotherapy (n = 136)</th>
<th>Bevacizumab + chemotherapy (n = 164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, months</td>
<td>4.5</td>
<td>6.4</td>
<td>4.1</td>
<td>5.5</td>
</tr>
<tr>
<td>OS from randomization, months</td>
<td>11.1</td>
<td>15.4</td>
<td>10.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Type of response, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>n = 164</td>
<td>n = 151</td>
<td>n = 134</td>
<td>n = 164</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>91 (56)</td>
<td>99 (66)</td>
<td>71 (53)</td>
<td>108 (66)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>49 (30)</td>
<td>27 (18)</td>
<td>47 (35)</td>
<td>37 (23)</td>
</tr>
<tr>
<td>Missing&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15 (9)</td>
<td>12 (8)</td>
<td>12 (9)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Response rate, %</td>
<td>5</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Disease control rate, %</td>
<td>61</td>
<td>74</td>
<td>56</td>
<td>70</td>
</tr>
</tbody>
</table>

<sup>a</sup>Unstratified P-value.
<sup>b</sup>Includes patients who were ‘not evaluable’ or had ‘no tumor assessment’ following baseline visit.

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table 3. Overview of adverse events in the KRAS population

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>KRAS wild type Chemotherapy (n = 166)</th>
<th>Bevacizumab + chemotherapy (n = 148)</th>
<th>KRAS mutant Chemotherapy (n = 135)</th>
<th>Bevacizumab + chemotherapy (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>164 (99)</td>
<td>148 (100)</td>
<td>133 (99)</td>
<td>156 (96)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>57 (34)</td>
<td>42 (28)</td>
<td>40 (30)</td>
<td>46 (28)</td>
</tr>
<tr>
<td>Grade 3–5 adverse events</td>
<td>101 (61)</td>
<td>89 (60)</td>
<td>69 (51)</td>
<td>103 (64)</td>
</tr>
<tr>
<td>Grade 5 adverse events</td>
<td>2 (1)</td>
<td>4 (3)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Discontinued any treatment due to adverse events</td>
<td>15 (9)</td>
<td>25 (17)</td>
<td>8 (6)</td>
<td>20 (12)</td>
</tr>
<tr>
<td>Discontinued any chemotherapy due to adverse events</td>
<td>15 (9)</td>
<td>22 (15)</td>
<td>8 (6)</td>
<td>16 (10)</td>
</tr>
<tr>
<td>All deaths</td>
<td>128 (77)</td>
<td>102 (69)</td>
<td>112 (83)</td>
<td>126 (78)</td>
</tr>
<tr>
<td>Death not due to progressive disease</td>
<td>8 (5)</td>
<td>6 (4)</td>
<td>3 (2)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Any adverse event of special interest with bevacizumab</td>
<td>39 (23)</td>
<td>64 (43)</td>
<td>31 (23)</td>
<td>64 (40)</td>
</tr>
<tr>
<td>Grade 3–5 adverse events of special interest with bevacizumab</td>
<td>11 (7)</td>
<td>17 (11)</td>
<td>7 (5)</td>
<td>20 (12)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>1 (&lt;1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
<td>2 (1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Bleeding/hemorrhage</td>
<td>1 (&lt;1)</td>
<td>4 (3)</td>
<td>0</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Abscesses/fistulas</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
<td>0</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Venous thromboembolic event</td>
<td>6 (4)</td>
<td>6 (4)</td>
<td>4 (3)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Arterial thromboembolic event</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Wound-healing complications</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>
AVG2107 (34%), CRYSTAL (37%), and PRIME (40%) [14, 15, 18, 19] but similar to rates in later-line studies [13, 16]. This is likely related to the emergence of data regarding the lack of efficacy of EGFR inhibitors in patients with mutant KRAS tumors during enrollment; and hence, such patients were preferentially enrolled into the present study. Too few patients had BRAF mutations for any correlative analyses to be carried out.

As in the primary analysis in the ITT population, bevacizumab-treated patients in the KRAS population had statistically significant prolongation of PFS and OS versus chemotherapy alone. Patients with wild-type and mutant KRAS tumors achieved a significant PFS benefit from bevacizumab, as reported previously [18, 19]. Patients with wild-type KRAS tumors had significantly prolonged OS as a result of bevacizumab treatment, although there was no statistically significant difference in treatment benefit by KRAS status. The interaction test by KRAS status was negative for both PFS and OS (P > 0.05) and post hoc univariate and multivariate OS analyses showed a benefit of treatment with bevacizumab after adjustment for KRAS status as a single covariate or in combination with prespecified prognostic variables. It is important to note that ML18147 was not powered to detect differences in treatment group within the KRAS subgroups, which may explain the absence of statistically significant differences in OS between treatments.

OS data in bevacizumab-treated patients with KRAS-mutant tumors may have been influenced by subsequent therapies administered after completion of the study, although treatment distribution was balanced in the study. Patient KRAS mutational status is a key factor in the selection of third- and further-line treatment. More treatment options are available for patients with wild-type KRAS tumors, as reflected by the fact that a substantial proportion of those received subsequent EGFR inhibitors; this might have contributed to the long OS observed in patients with KRAS wild-type tumors.

Results from AVF2107 and AGIGT MAX [18, 19] are in line with the present study and suggest that bevacizumab efficacy does not depend on KRAS status. PFS data from the smaller BEBYP study also showed that the PFS benefit derived from bevacizumab treatment, the only reported end point of the BEBYP trial to date, was independent of KRAS status [6]. OS data from BEBYP are immature but may provide further insight into the effect of KRAS status on bevacizumab efficacy in the second-line treatment of patients with mCRC.

Based on the evaluation of the chemotherapy-only group, a clear prognostic effect of KRAS mutational status could not be determined. The prognostic value of KRAS status continues to be controversial, with the present study providing no additional significant information supporting a definitive conclusion.

Exploratory subgroup analysis of the ML18147 biomarker population provides no indication of a different safety profile for patients with KRAS wild-type versus mutant tumors. These findings are consistent with results of AVF2107, in which the incidence of bevacizumab-associated adverse events and grade 3/4 adverse events did not depend on tumor KRAS status [18].

Some limitations of the present study should be considered. This was an exploratory analysis and the study was not powered to detect between-group differences. KRAS results were obtained from different laboratories potentially using different testing methods, so variations in assay protocols and performance cannot be ruled out. The central laboratory analyzed KRAS codons 12 and 13, and while it is likely that local laboratories also analyzed KRAS codons 12 and 13, the full scope of local analyses is unknown. The technology used for the analyses, including micro- and macro-dissection of samples to enrich tumor tissue and avoid dilution of the tumor signal by normal tissue genetic information, is also likely to have differed between the various laboratories.

In conclusion, this analysis of KRAS status in the ML18147 study population did not reveal any apparent effect of tumor KRAS mutational status on the efficacy of second-line bevacizumab in patients progressing following first-line bevacizumab plus standard chemotherapy. Bevacizumab plus chemotherapy represents an effective treatment option for patients with mCRC who were treated with bevacizumab plus standard chemotherapy in the first line, independent of their KRAS mutation status.

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References


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A retrospective study of ampullary adenocarcinomas: overall survival and responsiveness to fluoropyrimidine-based chemotherapy†

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Background: Whether carcinomas of the ampulla of Vater should be classified with biliary tract tumors and treated in a similar manner remains unknown. We sought to compare the outcomes of similarly staged periampullary adenocarcinomas (AAs) and analyze the chemotherapy responsiveness of AAs.

Patients and methods: A total of 905 patients with resected periampullary adenocarcinomas were identified from a prospective surgical registry from 1988 to 2010. A second cohort of 64 metastatic AA patients from 1992 to 2009 who received either front-line fluoropyrimidine-based or gemcitabine-based chemotherapy was also identified.

Results: Overall survival (OS) for AAs was similar to survival with duodenal adenocarcinomas, but was significantly different from both extrahepatic biliary and pancreatic adenocarcinomas (P < 0.001 for each comparison). In multivariate analysis, AAs had a significantly improved OS in comparison with extrahepatic adenocarcinomas (HR = 1.97, P = 0.006). Fluoropyrimidine-based as opposed to gemcitabine-based chemotherapy for metastatic AAs resulted in a significant improvement in time to progression (P = 0.001) but only a trend toward benefit for OS (P = 0.07) in multivariate analysis.

Conclusions: Differences in the natural history of ampullary and extrahepatic biliary adenocarcinomas exist. Analyses of metastatic ampullary adenocarcinomas suggest that fluoropyrimidine-based chemotherapy may represent a more appropriate front-line chemotherapy approach.

Key words: ampullary adenocarcinomas, chemotherapy, fluoropyrimidine, gemcitabine, periampullary

introduction

Until recently, carcinoma of the ampulla of Vater has been classified by the World Health Organization of Tumors as a cancer of the extrahepatic biliary tract. However, as distinct epithelia coalesce within the ampulla (duodenal, pancreatic, and biliary) the exact epithelium origin for these tumors is unknown, and in the most recent fourth edition of the World Health Organization of Tumors, ampullary carcinomas are discussed separately from other periampullary carcinomas. Given this uncertainty, the optimal chemotherapy regimen for ampullary adenocarcinomas (AAs) remains undefined.

Single institution series have suggested improved outcomes for AAs in comparison to extrahepatic cholangiocarcinomas [1]. Though no single study has compared stage stratified outcomes for AAs versus extra hepatic cholangiocarcinomas, a comparison of two separate studies evaluating the SEER database suggests superior 5-year relative survival (RS) for AAs compared with extrahepatic biliary adenocarcinomas when stratified by disease stage: localized, 45% versus 34%; and regional, 31% versus 18%, respectively [2, 3].

In contrast to extrahepatic biliary adenocarcinomas, AAs demonstrate differing histological subtypes: intestinal, pancreaticobiliary, or mixed [4]. These histological subtypes...