# 2. S064 Synopsis

# Clinical Study Report Synopsis: Study H6Q-MC-S064

| | |
|---|---|
| **Title of Study: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study of Enzastaurin with 5-FU/LV plus Bevacizumab as Maintenance Regimen Following First-Line Therapy for Metastatic Colorectal Cancer** | |
| **Number of Investigators:** This multicenter study included 26 principal investigators. | |
| **Study Centers:** This study was conducted at 26 study centers in 5 countries. | |
| **Publication(s) Based on the Study:** None at this time. | |
| **Length of Study:**<br>Date of first patient randomized: 07 March 2008<br>Data cutoff for this report: Data from visits that took place on or before 27 January 2010 are included in this report. | **Phase of Development:** 2 |

**Objectives:**

**Primary:** To compare Arm A versus Arm B in terms of progression-free survival (PFS) measured from the time of randomization after completing 6 cycles of first-line therapy for metastatic colorectal cancer (CRC):

- Arm A: 5-fluorouracil/leucovorin (5-FU/LV) plus bevacizumab in combination with enzastaurin
- Arm B: 5-FU/LV plus bevacizumab in combination with placebo.

**Secondary:**

To compare the following between treatment arms:

- Overall survival (OS) from the time of randomization
- OS and PFS from the start of first-line therapy

To assess the safety and adverse event (AE) profile in both treatment arms using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; Version 3.0, 2006).

**Study Design:** This was a multicenter, double-blind, two-arm, randomized, Phase 2 study in patients who had received 6 cycles with folinic acid, 5-FU, and oxaliplatin (FOLFOX) or folinic acid, 5-FU, and irinotecan (FOLFIRI), plus bevacizumab, for metastatic CRC in the first-line setting. Patients were randomly assigned to receive maintenance therapy on one of the two arms: enzastaurin plus 5-FU/LV and bevacizumab (Arm A) or placebo plus 5 FU/LV and bevacizumab (Arm B) in a 1:1 fashion. Randomization was stratified for the following prognostic factors at baseline using the blocked randomization method:

- prior adjuvant therapy (no versus yes) and
- response to first-line treatment (complete response [CR] or partial response [PR] versus stable disease).

Treatment continued until occurrence of disease progression or any other reason cited in the protocol. One cycle equaled 2 weeks. Disease assessment was made every 6 weeks (that is, after every 3 cycles of treatment) using a modified version of Response Evaluation Criteria in Solid Tumors (RECIST; Therasse et al. 2000). Calculation of PFS for maintenance therapy began when the patient was randomized to either of the study treatment arms. Safety was assessed at every cycle through the evaluation of laboratory and nonlaboratory AEs using the CTCAE (Version 3.0; 2006).

An interim analysis was conducted to assess the safety parameters of 5-FU/LV plus bevacizumab with or without enzastaurin after a total of 15 patients had been randomized and completed at least 1 cycle of study treatment. The interim analysis was reviewed by an assessment committee without stopping enrollment. The final analysis occurred after approximately 50 events of clinical progression, objective progression, or death occurred. Clinical progression was defined as global deterioration of health status requiring discontinuation of treatment without objective evidence of progression.

**Number of Patients**:

Planned: 150; 75 patients in each treatment arm

Randomized: 58 Arm A, 59 Arm B (the number of patients randomized is less than planned due to Amendment A)

As of 27 January 2010 (data included in this report are from visits up to 27 January 2010):

Treated (at least 1 dose): 57 Arm A, 58 Arm B

Number of patients still on study treatment: 16 Arm A, 19 Arm B

Number of patients who discontinued study treatment: 41 Arm A, 39 Arm B

Number of patients still in follow-up: 23 Arm A, 27 Arm B

As of the date of this report, there are no patients on enzastaurin treatment. At the time of this report, there are several patients continuing on the base regimen without enzastaurin/placebo.

**Diagnosis and Main Criteria for Inclusion:** Patients were at least 18 years of age with histologic diagnosis of locally advanced or metastatic CRC (adenocarcinoma, mucinous adenocarcinoma, signet ring, and undifferentiated, but not neuroendocrine carcinoma) that was not amenable to curative therapy, with Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and had adequate organ function (as defined in the protocol). Prior radiotherapy must have been completed 30 days before beginning first-line therapy, and no more than 4 weeks may have passed between the end of first-line therapy (that is, Day 14 of Cycle 6) and randomization.

**Study Drug, Dose, and Mode of Administration:**

Arm A (experimental arm):

- enzastaurin 1125 mg/day given orally three times daily as three 125-mg tablets on Day 1 of Cycle 1 (loading dose) and 500 mg/day given orally two times daily as two 125-mg tablets for subsequent doses.
- 5-FU/LV plus bevacizumab every 2 weeks: LV 400-mg/m$^2$ intravenous (IV) infusion first, then a 5-FU 400-mg/m$^2$ bolus followed by a 2400-mg/m$^2$ IV infusion over 46 hours, and bevacizumab 5-mg/kg IV infusion.

**Reference Therapy, Dose, and Mode of Administration:**

Arm B (control arm):

- placebo, given orally three times daily as three tablets on Day 1 of Cycle 1 and given orally two times daily as two tablets for subsequent doses with 5-FU/LV plus bevacizumab every 2 weeks.
- 5-FU/LV plus bevacizumab every 2 weeks: LV 400-mg/m$^2$ IV infusion first, then a 5-FU 400-mg/m$^2$ bolus followed by a 2400-mg/m$^2$ IV infusion over 46 hours, and bevacizumab 5-mg/kg IV infusion.

**Duration of Treatment:**

Patients could continue treatment until disease progression or until they required discontinuation from study treatment, up to a maximum of 1 year of study treatment unless an extension was granted by the Sponsor.

**Variables:**

Efficacy: The primary efficacy measure for this trial was PFS from the time of randomization, and the secondary efficacy measures for this trial included OS from randomization, and OS and PFS from start of first-line therapy.

Safety: Vital signs, electrocardiograms, clinical laboratory assessments, CTCAE ratings, and AEs were monitored throughout the study.

**Statistical Evaluation Methods:**

Sample Size: The primary objective of the study was to compare Arm A with Arm B in terms of PFS measured from time of randomization after 6 cycles of first-line therapy for metastatic CRC. The purpose of this comparison was not to rigorously demonstrate superiority of Arm A over Arm B (the goal of a Phase 3 study with a statistical comparison at the type I error of 0.05), but to determine if there was a signal or trend pointing toward improvement in PFS with the addition of enzastaurin to 5-FU/LV plus bevacizumab. In this less rigorous comparison, determination of the signal or trend can be based on a larger statistical type I error so that an adequately powered comparison can still be carried out with a limited sample size. This study set the type I error rate at a one-sided level of 0.20. A one-sided test is appropriate since we intended to test only whether the enzastaurin arm was superior to the control arm.

Prior to Amendment A to the protocol, the planned study sample size was 150 patients randomized in a 1:1 ratio (75 patients in each arm; obtained using the formula by Freedman [1982]). However, given recent results of other proof-of-concept Phase 2 trials of enzastaurin, a decision was made to perform an earlier evaluation of the primary endpoint to assess the role of additional studies in CRC. Therefore, the study design was changed to perform a final analysis after approximately 50 events (clinical progression, objective progression, or death) occurred. At that point, enrollment was suspended and the study treatment assignment was unblinded. Patients were permitted to continue therapy. Safety and efficacy assessments were performed at the discretion of the investigator according to local practice standards. Additionally, the PFS primary endpoint was changed to include patients with clinical progression in addition to objective progression or death.

Based on literature, the median duration of PFS (from randomization to progression or death due to any cause) with 5 FU/LV plus bevacizumab was estimated to be 5.5 months. Because randomization of this study occurs after first-line therapy, the estimation for median PFS above does not include the period of approximately 3 months taken to administer the 6 cycles of first-line therapy. This study was powered to detect a 36% improvement in PFS by showing a median PFS of 7.5 months with enzastaurin plus 5-FU/LV and bevacizumab. Based on a log-rank test, assuming that the true PFS hazard ratio (HR) of Arm A to Arm B is 0.73, the study had 60% power to achieve statistical significance at a one-sided level of 0.20.

**Statistical Evaluation Methods (continued):**

Efficacy: The primary analysis was the comparison of PFS between the 2 treatment arms using the log-rank test at the one-sided significance level of 0.20. In addition, Kaplan-Meier analyses were performed on the observed distribution of PFS (Kaplan and Meier 1958). Quartiles, survival rates at appropriate time points, and corresponding 95% confidence intervals (CIs) were calculated. The Cox regression model (Cox 1972) was also be used to estimate treatment group differences adjusted for selected prognostic factors (such as those used for stratification). Secondary efficacy endpoints include assessment of OS from randomization and OS and PFS from start of first-line therapy, and were analyzed in the same manner.

As a sensitivity analysis, PFS was also analyzed by censoring for postdiscontinuation systemic therapy use. In this case, the following two criteria were used for censoring:

(1) for patients not known to have died as of the data cutoff date and who did not have clinical or objective progressive disease, PFS was censored at the date of the last progression-free disease assessment

(2) for patients who received subsequent systemic anticancer therapy (after discontinuation from the study treatment) prior to disease progression or death, PFS was censored at the date of the last progression-free disease assessment prior to initiation of postdiscontinuation systemic anticancer therapy.

Safety:

Enzastaurin, LV, 5-FU, and bevacizumab mean daily doses were summarized by treatment arm using descriptive statistics at each tumor assessment visit and over the entire study.

Adverse events that occurred during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality, were summarized by treatment arm. Summaries were done by CTCAE (Version 3.0; NCI 2003) group, CTCAE preferred term, and Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred terms and CTCAE grade.

Summaries similar to the above were done by study treatment relationship: not related, at least possibly related. Deaths, serious adverse events (SAEs), and discontinuations due to AEs that occurred during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality, were summarized. Frequency counts (and percentages) were done by CTCAE group, CTCAE preferred term, and MedDRA SOC and preferred terms and CTCAE grade. Listings of all AEs, regardless of when they occurred, were done. The incidences of selected AEs from the 2 treatment arms were compared using the Fisher exact test at one-sided significance level of 0.20.

**Summary:**

Protocol Violations:

There were no protocol violations during the study that excluded any patient from receiving study treatment (Table S064.1) The majority of major protocol violations included protocol inclusion/exclusion criteria (20 [34.5%] patients in Arm A and 19 [32.2%] patients in Arm B), incorrect dosing (18 [31.0%] patients in Arm A and 17 [28.8%] patients in Arm B), and incorrect dosing modification of 5-FU/LV (14 [24.1%] patients in Arm A and 12 [20.3%] patients in Arm B). Overall, 37 (31.6%) patients had study-specific violations: enzastaurin or placebo noncompliance (9 [15.5%] patients in Arm A and 5 [8.5%] patients in Arm B, respectively, and study treatment continued despite progression (14 [24.1%] patients in Arm A and 12 [20.3%] patients in Arm B).

Patient Disposition, Baseline Demographics, and Characteristics:

One hundred twenty-three patients entered the study. One hundred seventeen patients were enrolled and treated; 58 were randomized to Arm A and 59 were randomized to Arm B. Of the 123 entered patients, 6 were screen failures (2 did not meet entry criteria, 2 were not enrolled due to patient decision, and 2 were not enrolled due to investigator decision).

Overall, 82 (70.1%) patients discontinued study treatment (42 [72.4%] in Arm A and 40 [67.8%] in Arm B). The majority of patients discontinued due to progressive disease. Table S064.1 provides reasons for discontinuation for all patients who entered the study.

Table S064.2 and Table S064.3 provide demographic and baseline stratification factors and baseline disease characteristics, respectively, for the intent-to-treat (ITT) population.

**Table S064.1. Summary of Reasons for Discontinuation from Study (All Entered Patients)**

| Reason for Discontinuation, n (%) | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=58) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=59) | All (N=117) |
|---|---|---|---|
| Adverse event | 6 (14.3) | 2 (5.0) | 8 (9.8) |
| Death | 1 (2.4) | 0 | 1 (1.2) |
| Lost to follow up | 0 | 0 | 0 |
| Entry criteria not met | 0 | 2 (5.0) | 2 (2.4) |
| Protocol violation | 0 | 0 | 0 |
| Subject decision | 7 (16.7) | 9 (22.5) | 16 (19.5) |
| Investigator decision | 1 (2.4) | 2 (5.0) | 3 (3.7) |
| Sponsor decision | 1 (2.4) | 1 (2.5) | 2 (2.4) |
| Progressive disease | 26 (61.9) | 24 (60.0) | 50 (61.0) |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; N = total population size; n = number of patients.
Source: t_discon.rft.

**Table S064.2. Demographic and Baseline Stratification Factors (Intent-to-Treat Population)**

| | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=58) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=59) | All (N=117) |
|---|---|---|---|
| Age (years) | | | |
| Mean (SD) | 62.55 (10.90) | 62.49 (9.48) | 62.52 (10.16) |
| Median | 63.25 | 64.53 | 64.24 |
| Range | 34.2 – 82.0 | 32.9 – 81.9 | 32.9 – 82.0 |
| Sex, n (%) | | | |
| Female | 21 (36.2) | 21 (35.6) | 42 (35.9) |
| Male | 37 (63.8) | 38 (64.4) | 75 (64.1) |
| Race, n (%) | | | |
| Caucasian | 55 (94.8) | 54 (91.5) | 109 (93.2) |
| African | 1 (1.7) | 2 (3.4) | 3 (2.6) |
| Hispanic | 2 (3.4) | 3 (5.1) | 5 (4.3) |
| Prior Adjuvant Therapy, n (%) | | | |
| Yes | 11 (19.0) | 9 (15.3) | 20 (17.1) |
| No | 47 (81.0) | 50 (84.7) | 97 (82.9) |
| Response to First-line Treatment, n (%) | | | |
| Complete or Partial Response | 32 (55.2) | 34 (57.6) | 66 (56.4) |
| Stable Disease | 26 (44.8) | 25 (42.4) | 51 (43.6) |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; N = total population size; n = number of patients; SD = standard deviation.
Sources: t_demo.rtf and t_strata.rtf.

**Table S064.3. Baseline Disease Characteristics (Intent-to-Treat Population)**

| | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) | All |
|---|---|---|---|
| ECOG Performance Status[a], n (%) | N=58 | N=59 | N=117 |
| 0 | 42 (72.4) | 45 (76.3) | 87 (74.4) |
| 1 | 16 (27.6) | 13 (22.0) | 29 (24.8) |
| 2 | 0 | 1 (1.7) | 1 (0.9) |
| Initial Pathological Diagnosis, n (%) | N=58 | N=59 | N=116 |
| Adenocarcinoma, Mucinous, NOS | 3 (5.2) | 4 (6.9) | 7 (6.0) |
| Adenocarcinoma, Colon | 55 (94.8) | 54 (93.1) | 109 (94.0) |
| Primary Tumor, n (%) | N=58 | N=57 | N=115 |
| TX | 10 (17.2) | 8 (14.0) | 18 (15.7) |
| T0 | 0 | 1 (1.8) | 1 (0.9) |
| Tis | 0 | 0 | 0 |
| T1 | 1 (1.7) | 3 (5.3) | 4 (3.5) |
| T2 | 2 (3.4) | 3 (5.3) | 5 (4.3) |
| T3 | 36 (62.1) | 32 (56.1) | 68 (59.1) |
| T4 | 9 (15.5) | 10 (17.5) | 19 (16.5) |
| Regional Lymph Node, n (%) | N=58 | N=57 | N=115 |
| NX | 9 (15.5) | 10 (17.5) | 19 (16.5) |
| N0 | 12 (20.7) | 13 (22.8) | 25 (21.7) |
| N1 | 14 (24.1) | 11 (19.3) | 25 (21.7) |
| N2 | 22 (37.9) | 22 (38.6) | 44 (38.3) |
| N3 | 1 (1.7) | 1 (1.8) | 2 (1.7) |

(continued)

**Table S064.3. Baseline Disease Characteristics (Intent-to-Treat Population) (concluded)**

| | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) | All |
|---|---|---|---|
| Distant Metastasis, n (%) | N=58 | N=58 | N=116 |
| MX | 5 (8.6) | 3 (5.2) | 8 (6.9) |
| M0 | 6 (10.3) | 2 (3.4) | 8 (6.9) |
| M1 | 47 (81.0) | 53 (91.4) | 100 (86.2) |
| Stage of Disease at Study Entry, n (%) | N=53 | N=54 | N=107 |
| I | 0 | 0 | 0 |
| IIa | 0 | 1 (1.9) | 1 (0.9) |
| IIb | 0 | 0 | 0 |
| IIIa | 0 | 0 | 0 |
| IIIb | 4 (7.5) | 0 | 4 (3.7) |
| IIIc | 2 (3.8) | 1 (1.9) | 3 (2.8) |
| IV | 47 (88.7) | 52 (96.3) | 99 (92.5) |
| Basis for Pathological Diagnosis, n (%) | N=58 | N=58 | N=116 |
| Histopathological | 55 (94.8) | 58 (100) | 113 (97.4) |
| Cytopathological | 3 (5.2) | 0 | 3 (2.6) |
| Time from Initial Diagnosis to Enrollment (days) | N=58 | N=58 | N=116 |
| Mean (SD) | 312.9 (447.97) | 328.2 (438.75) | 320.6 (441.52) |
| Median | 140.5 | 144.0 | 142.5 |
| Range | 94 – 2194 | 98 – 2354 | 94 – 2354 |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; ECOG = Eastern Cooperative Oncology Group; N = total population size; n = number of patients; NOS = not otherwise specified; SD = standard deviation.

[a] ECOG Performance Status: 0=Fully active and asymptomatic; 1=Ambulatory with symptoms; 2=In bed <50% of the time.

Source: t_bslchar.rtf.

Drug Exposures

Table S064.4 and Table S064.5 provide summaries of drug exposure and dose intensity, respectively. Of note, the median number of cycles received was 9 in Arm A and 10 in Arm B. Patient [redacted] from Arm A and Patient [redacted] from Arm B were randomized but did not receive treatment. Patient [redacted] was discontinued due to Sponsor decision and Patient [redacted] was discontinued due to the patient's decision.

Enzastaurin doses were not reduced or omitted for laboratory hematologic toxicity that was attributable to 5-FU/LV or bevacizumab therapy, with the exception of elevated liver transaminases and febrile neutropenia. Any unusual or unexpected AEs that occurred, which were above and beyond the expected safety profile of 5-FU/LV-plus-bevacizumab-combination therapy, and which differed from those described for 5-FU/LV or bevacizumab therapy, were to result in omitting the administration of enzastaurin until the event resolved. In the enzastaurin treatment arm (Arm A), there were 2 (3.5%) patients with enzastaurin dose reductions and 18 (31.6%) patients with enzastaurin dose omissions.

Overall, 93 (80.9%) patients had at least one cycle delay (42 [73.7%] in Arm A and 51 [87.9%] in Arm B). The majority of cycle delays were due to a scheduling conflict (32 patients [76.2%] in Arm A and 50 patients [98.0%] in Arm B). Cycle delays due to an AE occurred in 15 patients (35.7%) in Arm A and 14 patients (27.5%) in Arm B. The most common AE leading to cycle delay was palmar-plantar erythrodysaesthesia syndrome (2 patients [13.3%] in Arm A and 3 patients [21.4%] in Arm B).

Two (3.5%) patients in Arm A (diarrhea, nausea, and vomiting) and 2 (3.4%) patients in Arm B (diarrhea and dizziness) had at least one enzastaurin dose reduction due to an AE.

Eighteen (31.6%) patients in Arm A and 15 (25.9%) patients in Arm B had at least one enzastaurin dose omission due to an AE. Adverse events resulting in a dose omission that occurred in more than one patient in either treatment arm included diarrhea (2 patients in Arm A and 2 patients in Arm B), dizziness (2 patients in Arm A), mucosal inflammation (2 patients in Arm A), fatigue (2 patients in Arm A), and vomiting (2 patients in Arm A and 3 patients in Arm B).

**Table S064.4. Summary of Drug Exposure (Randomized and Treated Patients)**

| | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=57) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=58) | All (N=115) |
|---|---|---|---|
| Mean number of cycles (SD) | 10.8 (8.30) | 12.9 (8.17) | 11.9 (8.27) |
| Median | 9.0 | 10.0 | 10.0 |
| Range | 1 – 36 | 2 – 37 | 1 – 37 |
| Total number of cycles received | 614 | 750 | 1364 |
| Patients completed ≥1 cycle, n (%) | 57 (100) | 58 (100) | 115 (100) |
| Patients completed ≥10 cycles, n (%) | 27 (47.4) | 33 (56.9) | 60 (52.2) |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; N = total population size; n = number of patients; SD = standard deviation.

Source: t_cycles.rtf.

**Table S064.5. Dose Intensity (Randomized and Treated Patients)**

| Treatment Arm | Number of Patients (n) | Planned Mean Daily Dose[a] | Actual Mean Daily Dose (SD)[a] | Mean Relative Dose Intensity[b] (%, SD) |
|---|---|---|---|---|
| **Enzastaurin/Placebo** | | | | |
| Arm A | 57 | 500 | 468.2 (346.86) | 93.6 (69.37) |
| Arm B | 58 | 500 | 462.6 (92.89) | 92.5 (18.58) |
| Total | 115 | 500 | 465.4 (251.84) | 93.1 (50.37) |
| **Leucovorin** | | | | |
| Arm A | 57 | 200 | 171.4 (40.88) | 85.7 (20.44) |
| Arm B | 58 | 200 | 162.1 (44.27) | 81.0 (22.14) |
| Total | 115 | 200 | 166.7 (42.70) | 83.4 (21.35) |
| **5-Fluorouracil Bolus** | | | | |
| Arm A | 57 | 200 | 183.5 (22.22) | 91.7 (11.11) |
| Arm B | 58 | 200 | 176.5 (25.98) | 88.2 (12.99) |
| Total | 115 | 200 | 179.9 (24.34) | 90.0 (12.17) |
| **5-Fluorouracil Infusion** | | | | |
| Arm A | 57 | 1200 | 1080.2 (140.80) | 90.0 (11.73) |
| Arm B | 58 | 1200 | 1068.6 (108.37) | 89.1 (9.03) |
| Total | 115 | 1200 | 1074.3 (125.08) | 89.5 (10.42) |
| **Bevacizumab** | | | | |
| Arm A | 57 | 3 | 2.36 (0.205) | 94.3 (8.21) |
| Arm B | 58 | 3 | 2.26 (0.227) | 90.6 (9.09) |
| Total | 115 | 3 | 2.31 (0.221) | 92.4 (8.83) |

Abbreviation: n = number of patients; SD = standard deviation.

Arm A: 5-fluorouracil/leucovorin plus bevacizumab in combination with enzastaurin.

Arm B: 5- fluorouracil/leucovorin plus bevacizumab in combination with placebo.

[a] Enzastaurin mean dose is mg/day, leucovorin mean dose is mg/m$^2$/week, 5-fluorouracil dose is mg/m$^2$/week, and bevacizumab dose is mg/kg/week.

[b] Dose intensity = (actual mean daily dose/planned mean daily dose)*100.

Source: t_dosint.rtf.

Efficacy:

***Primary Objective***

Table S064.6 summarizes results of the analysis of the primary objective of the study: PFS from randomization. Median PFS was 5.8 months in Arm A compared with 8.1 months in Arm B (HR=1.35, 95% CI: 0.84, 2.16; protocol-specified one-sided test, p=0.896).

Figure S064.1 represents a graphical display of the PFS analysis.

**Table S064.6. Summary of Progression-free Survival from Randomization (Intent-to-Treat Population)**

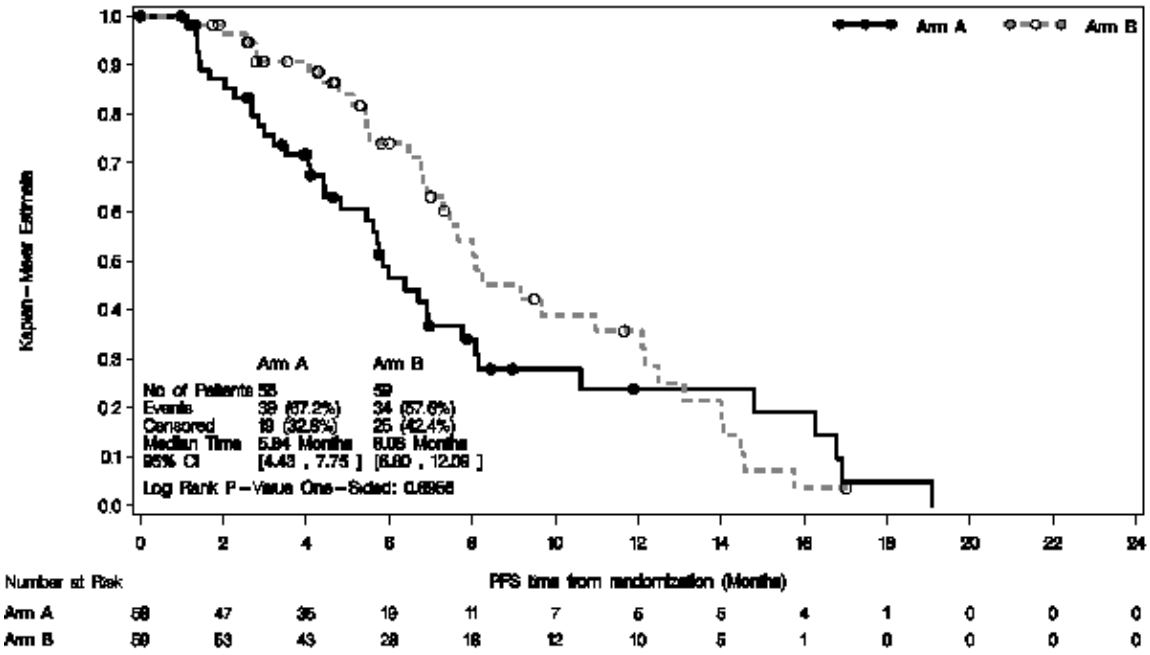
| | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=58) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=59) | p-Values |
|---|---|---|---|
| Kaplan-Meier estimate of PFS (months) from randomization | | | |
| Patients with events, n (%) | 39 (67.2) | 34 (57.6) | |
| Patients censored, n (%) | 19 (32.8) | 25 (42.4) | |
| Median (95% CI) | 5.8 (4.4, 7.8) | 8.1 (6.8, 12.1) | |
| Range | 0 – 19.1 | 0 – 17.0 | |
| Treatment effect HR (95% CI) | 1.35 (0.84, 2.16) | | 0.8956[a]<br>0.2088[b] |
| Probability (95% CI) that PFS is at least | | | |
| 6 months | 46.4 (31.7, 60.0) | 74.0 (58.5, 84.5) | |
| Patients at risk | 19 | 28 | 0.005 |
| 9 months | 27.9 (15.1, 42.1) | 45.1 (28.8, 60.2) | |
| Patients at risk | 7 | 15 | 0.111 |
| 12 months | 23.9 (11.6, 38.6) | 35.7 (20.4, 51.2) | |
| Patients at risk | 5 | 10 | 0.275 |
| 18 months | 4.8 (0.4, 19.1) | -- | |
| Patients at risk | 1 | 0 | -- |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; CI = confidence interval; HR = hazard rate; N = total population size; n = number of patients; PFS = progression-free survival.

[a] Log-rank p-value one-sided.

[b] Log-rank p-value two-sided.

Source: t_sum_pfst.rtf.




Abbreviations: CI = confidence interval; No = number; PFS = progression-free survival.
Arm A: 5- fluorouracil/leucovorin plus bevacizumab in combination with enzastaurin.
Arm B: 5- fluorouracil/leucovorin plus bevacizumab in combination with placebo.

**Figure S064.1. Kaplan-Meier distribution of progression-free survival from randomization by treatment group (intent-to-treat population).**

*Subgroup Analyses of Primary Objective*

Table S064.7 summarizes the Cox regression analysis of PFS from randomization. Table S064.8, Table S064.9, and Table S064.10 summarize PFS subgroup analyses of prior adjuvant therapy, response to first-line therapy, and prior FOLFOX/FOLFIRI use, respectively.

**Table S064.7. Cox Regression Analysis of Progression-free Survival from Randomization (Intent-to-Treat Population)**

| Covariates | N for Alternate Level | N for Reference Level | Hazard Ratio (95% CI) | p-Value[a] |
|---|---|---|---|---|
| Treatment (Arm A vs. Arm B [reference]) | 58 | 59 | 1.43 (0.89, 23.0) | 0.1403 |
| Prior adjuvant therapy (yes vs. no [reference]) | 20 | 97 | 1.42 (0.74, 2.71) | 0.2934 |
| Response to first-line therapy (CR or PR vs. Stable Disease [reference]) | 66 | 51 | 0.70 (0.43, 1.15) | 0.1560 |

Abbreviations: CI = confidence interval; CR = complete response; N = total population size; n = number of patients.

Arm A: 5- fluorouracil/leucovorin plus bevacizumab in combination with enzastaurin.

Arm B: 5- fluorouracil/leucovorin plus bevacizumab in combination with placebo.

[a] P-value is based on the Wald's test.

Source: t_cox_pfst.rtf.

**Table S064.8. Summary of Progression-free Survival from Randomization – Subgroup Analysis of Prior Adjuvant Therapy (Intent-to-Treat Population)**

| | Prior Adjuvant Therapy: Yes | | | Prior Adjuvant Therapy: No | | |
|---|---|---|---|---|---|---|
| | Arm A (N=11) | Arm B (N=9) | p-Values | Arm A (N=47) | Arm B (N=50) | p-Values |
| Kaplan-Meier estimate of PFS (months) from randomization | | | | | | |
| Patients with events, n (%) | 8 (72.7) | 5 (55.6) | | 31 (66.0) | 29 (58.0) | |
| Patients censored, n (%) | 3 (27.3) | 4 (44.4) | | 16 (34.0) | 21 (42.0) | |
| Median (95% CI) | 4.1 (2.0, 5.8) | 9.7 (1.1, 14.0) | | 6.7 (4.8, 8.1) | 8.1 (6.9, 12.1) | |
| Range | 1.4 – 7.9 | 1.1 – 14.0 | | 0 – 19.1 | 0 – 17.0 | |
| Treatment effect HR (95% CI) | 4.33 (1.08, 17.30) | | 0.9867[a]<br>0.0266[b] | 1.16 (0.69, 1.95) | | 0.7136[a]<br>0.5727[b] |
| Probability (95% CI) that PFS is at least | | | | | | |
| 6 months | 12.5 (0.7, 41.9) | 88.9 (43.3, 98.4) | | 54.3 (37.3, 68.5) | 71.3 (53.9, 83.1) | |
| Patients at risk | 1 | 5 | 0.000 | 18 | 23 | 0.122 |
| 9 months | -- | 53.3 (12.5, 82.7) | | 31.9 (17.1, 47.8) | 43.4 (25.7, 59.8) | |
| Patients at risk | 0 | 3 | -- | 7 | 12 | 0.344 |
| 12 months | -- | 35.6 (5.0, 69.9) | | 27.3 (13.1, 43.7) | 35.8 (19.2, 52.7) | |
| Patients at risk | 0 | 1 | -- | 5 | 9 | 0.484 |
| 18 months | -- | -- | | 5.5 (0.4, 21.5) | -- | |
| Patients at risk | 0 | 0 | -- | 1 | 0 | -- |

Abbreviations: CI = confidence interval; HR = hazard rate; N = total population size; n = number of patients; PFS = progression-free survival.

Arm A: 5- fluorouracil/leucovorin plus bevacizumab in combination with enzastaurin.

Arm B: 5- fluorouracil/leucovorin plus bevacizumab in combination with placebo.

[a] Log-rank p-value one-sided.

[b] Log-rank p-value two-sided.

Source: t_sum_systemic.rtf.

**Table S064.9. Summary of Progression-free Survival from Randomization – Subgroup Analysis of Response to First-line Therapy (Intent-to-Treat Population)**

| | Response to First-line Therapy: CR or PR | | | Response to First-line Therapy: Stable Disease | | |
|---|---|---|---|---|---|---|
| | Arm A (N=32) | Arm B (N=34) | p-Values | Arm A (N=26) | Arm B (N=25) | p-Values |
| Kaplan-Meier estimate of PFS (months) from randomization | | | | | | |
| Patients with events, n (%) | 18 (56.3) | 15 (44.1) | | 21 (80.8) | 19 (76.0) | |
| Patients censored, n (%) | 14 943.8) | 19 (55.9) | | 5 (19.2) | 6 (24.0) | |
| Median (95% CI) | 6.9 (5.7, 16.3) | 9.2 (6.9, 12.5) | | 4.8 (3.2, 6.0) | 7.7 (5.5, 12.2) | |
| Range | 0 – 19.1 | 0 – 17.0 | | 1.3 – 16.9 | 1.3 – 15.8 | |
| Treatment effect HR (95% CI) | 1.19 (0.59, 2.41) | | 0.6907[a]<br>0.6186[b] | 1.62 (0.85, 3.09) | | 0.9326[a]<br>0.1347[b] |
| Probability (95% CI) that PFS is at least | | | | | | |
| 6 months | 63.3 (40.6, 79.4) | 76.1 (53.5, 88.8) | | 30.8 (14.0, 49.4) | 72.8 (49.0, 86.8) | |
| Patients at risk | 12 | 13 | 0.338 | 7 | 15 | 0.002 |
| 9 months | 36.9 (17.1, 57.0) | 55.0 (28.8, 75.0) | | 17.6 (4.2, 38.7) | 38.8 (18.8, 58.5) | |
| Patients at risk | 5 | 7 | 0.270 | 2 | 8 | 0.136 |
| 12 months | 29.6 (11.1, 50.9) | 39.3 (15.6, 62.4) | | 17.6 (4.2, 38.7) | 33.3 (14.5, 53.4) | |
| Patients at risk | 3 | 5 | 0.564 | 2 | 5 | 0.266 |
| 18 months | 9.9 (0.7, 33.7) | -- | | -- | -- | |
| Patients at risk | 1 | 0 | -- | 0 | 0 | -- |

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard rate; N = total population size; n = number of patients; PFS = progression-free survival; PR = partial response.

Arm A: 5- fluorouracil/leucovorin plus bevacizumab in combination with enzastaurin.

Arm B: 5- fluorouracil/leucovorin plus bevacizumab in combination with placebo.

[a] Log-rank p-value one-sided.

[b] Log-rank p-value two-sided.

Source: t_sum_pritpyor.rtf.

**Table S064.10. Summary of Progression-free Survival from Randomization – Subgroup Analysis of Prior FOLFOX/FOLFIRI Use (Intent-to-Treat Population)**

| | Prior Use of FOLFOX | | | Prior Use of FOLFIRI | | |
|---|---|---|---|---|---|---|
| | Arm A (N=38) | Arm B (N=36) | p-Values | Arm A (N=20) | Arm B (N=23) | p-Values |
| Kaplan-Meier estimate of PFS (months) from randomization | | | | | | |
| Patients with events, n (%) | 22 (57.9) | 19 (52.8) | | 17 (85.0) | 15 (65.2) | |
| Patients censored, n (%) | 16 (42.1) | 17 (47.2) | | 3 (15.0) | 8 (34.8) | |
| Median (95% CI) | 6.0 (4.4, 6.9) | 7.3 (5.5, 11.0) | | 5.6 (2.7, 10.6) | 9.7 (6.8, 14.0) | |
| Range | 0 – 19.1 | 0 – 17.0 | | 1.3 – 16.8 | 1.1 – 15.8 | |
| Treatment effect HR (95% CI) | 1.24 (0.66, 2.31) | | 0.7521[a]<br>0.4958[b] | 1.35 (0.65, 2.81) | | 0.7930[a]<br>0.4141[b] |
| Probability (95% CI) that PFS is at least | | | | | | |
| 6 months | 46.3 (26.14, 64.0) | 64.7 (42.1, 80.4) | | 45.0 (23.1, 64.7) | 85.3 (60.8, 95.0) | |
| Patients at risk | 10 | 12 | 0.188 | 9 | 16 | 0.003 |
| 9 months | 23.1 (8.7, 41.6) | 29.4 (11.2, 50.5) | | 31.5 (11.9, 53.4) | 62.2 (36.1, 80.1) | |
| Patients at risk | 3 | 5 | 0.650 | 4 | 10 | 0.057 |
| 12 months | 23.1 (8.7, 41.6) | 23.5 (7.6, 44.4) | | 23.6 (6.7, 46.2) | 49.0 (24.1, 69.9) | |
| Patients at risk | 2 | 4 | 0.975 | 3 | 6 | 0.123 |
| 18 months | 11.6 (1.1, 35.4) | -- | | -- | -- | |
| Patients at risk | 1 | 0 | -- | 0 | 0 | -- |

Abbreviations: CI = confidence interval; CR = complete response; FOLFIRI = folinic acid, 5-fluorouracil, and irinotecan treatment; FOLFOX = folinic acid, 5-fluorouracil, and oxaliplatin treatment; HR = hazard rate; N = total population size; n = number of patients; PFS = progression-free survival; PR = partial response.

Arm A: 5- fluorouracil/leucovorin plus bevacizumab in combination with enzastaurin.

Arm B: 5- fluorouracil/leucovorin plus bevacizumab in combination with placebo.

[a] Log-rank p-value one-sided.

[b] Log-rank p-value two-sided.

Source: t_sum_pritpy.rtf.

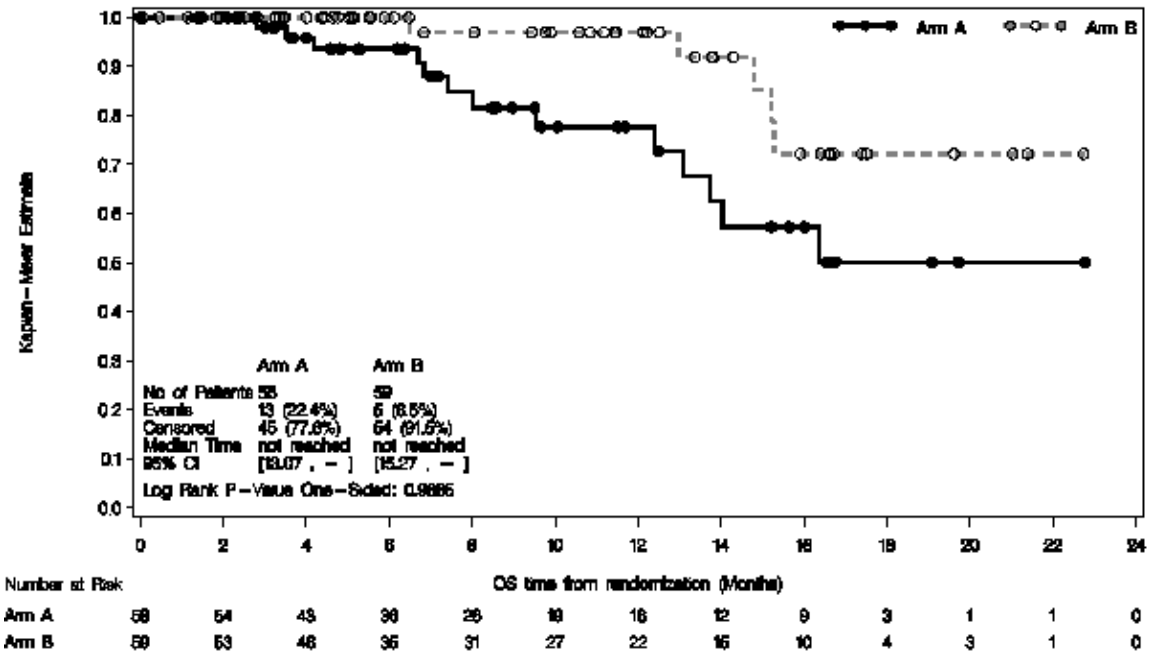
***Secondary Objectives***

Secondary objectives of the study included OS from the time of randomization and from start of first-line therapy, PFS from start of first-line therapy, as well as a sensitivity analysis of PFS. Figure S064.2 represents a graphical display of the OS analysis.

Table S064.11 summarizes results of OS from randomization. Median OS was not calculable (41 patients in Arm A and 39 patients in Arm B had discontinued study treatment as of the data cutoff date). The HR for OS was 3.03 with 95% CI: 1.08, 8.51; one-sided, p=0.987. The censoring rates were 77.6% and 91.5% for Arm A and Arm B, respectively.

Median PFS from start of first-line therapy was 8.9 months in Arm A and 11.3 months in Arm B (HR=1.39, 95% CI: 0.86, 2.23; one-sided, p=0.913).

The sensitivity analysis of PFS (patients who received postdiscontinuation anticancer therapy were not censored back) was also performed and showed no difference with the primary PFS analysis. For PFS from randomization, the median PFS was 5.7 months in Arm A compared with a median of 8.2 months for Arm B (HR=1.53, 95% CI: 0.94, 2.51; one-sided, p=0.957). For PFS from start of first-line therapy, the median PFS was 8.9 months in Arm A compared with a median of 12.0 months for Arm B (HR=1.57, 95% CI: 0.95, 2.59; one-sided, p=0.963).




Abbreviations: CI = confidence interval; No = number; PFS = progression-free survival.

Arm A: 5- fluorouracil/leucovorin plus bevacizumab in combination with enzastaurin.

Arm B: 5- fluorouracil/leucovorin plus bevacizumab in combination with placebo.

**Figure S064.2. Kaplan-Meier distribution of overall survival from randomization by treatment group (intent-to-treat population).**

**Table S064.11. Summary of Overall Survival from Randomization (Intent-to-Treat Population)**

| | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=58) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=59) | p-Values |
|---|---|---|---|
| Kaplan-Meier estimate of OS (months) from randomization | | | |
| Patients with events, n (%) | 13 (22.4) | 5 ( 8.5) | |
| Patients censored, n (%) | 45 (77.6) | 54 (91.5) | |
| Median (95% CI) | -- (13.1, -) | -- (15.3, -) | |
| Range | 0 – 22.8 | 0.1 – 22.7 | |
| Treatment effect HR (95% CI) | 3.03 (1.08, 8.51) | | 0.9865[a]<br>0.0270[b] |
| Probability (95% CI) that OS is at least | | | |
| 6 months | 93.6 ( 81.4, 97.9) | 100.0 (100.0,100.0) | |
| Patients at risk | 36 | 35 | -- |
| 9 months | 81.6 ( 64.6, 90.9) | 97.0 ( 80.4, 99.6) | |
| Patients at risk | 22 | 30 | 0.030 |
| 12 months | 77.7 ( 59.5, 88.4) | 97.0 ( 80.4, 99.6) | |
| Patients at risk | 16 | 22 | 0.014 |
| 18 months | 50.1 ( 27.1, 69.3) | 72.2 ( 44.2, 87.8) | |
| Patients at risk | 3 | 4 | 0.160 |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; CI = confidence interval; HR = hazard ratio; N = total population size; n = number of patients; OS = overall survival.

[a] Log-rank p-value one-sided.

[b] Log-rank p-value two-sided.

Source: t_sum_ost.rtf.

Safety:

Table S064.12 summarizes treatment-emergent adverse events (TEAEs). Of the 115 randomized and treated patients, 108 (93.9%) patients experienced at least one TEAE and 97 (84.3%) experienced at least one TEAE considered to be possibly related to study treatment (51 [89.5%] in Arm A and 46 [79.3%] in Arm B). Treatment-related AEs in Arm A were considered related to 5-FU/LV, bevacizumab, or enzastaurin; TEAEs in Arm B were considered related to 5-FU/LV or bevacizumab. Fifty-five (47.8%) patients experienced at least one treatment-emergent Grade 3/4 AE; 39 (33.9%) had events that were considered to be possibly related to study treatment (21 [36.8%] in Arm A and 18 [31.0%] in Arm B. Twenty-six (22.6%) patients experienced at least one treatment-emergent SAE; 15 (13.0%) patients had events that were considered possibly drug related (11 [19.3%] in Arm A and 4 [6.9%] in Arm B).

Table S064.13 summarizes TEAEs experienced by ≥10% of patients, regardless of causality. The most common TEAEs during the study (regardless of causality) were fatigue (40.9% overall; 42.1% in Arm A and 39.7% in Arm B), diarrhea (37.4% overall; 36.8% in Arm A and 37.9% in Arm B), and nausea (26.1% overall; 26.3% in Arm A and 25.9% in Arm B).

Table S064.14 summarizes TEAEs possibly related to study treatment experienced by ≥10% of patients. The most common TEAEs possibly related to study treatment were fatigue (36.5% overall; 36.8% in Arm A and 36.2% in Arm B), diarrhea (27.8% overall; 28.1% in Arm A and 27.6% in Arm B), and nausea (24.3% overall; 24.6% in Arm A and 24.1% in Arm B).

Table S064.15 summarizes laboratory and nonlaboratory Grade 3 and 4 AEs possibly related to study treatment occurring in more than one patient. More patients developed thrombosis or embolism (including pulmonary embolism) on Arm A (5 [8.8%] patients experienced Grade 3, and 5 [8.8%] patients experienced Grade 4 thrombosis/thrombus/embolism) compared with Arm B (no Grade 3 and 1 [1.7%] patient experienced Grade 4 thrombosis/thrombus/embolism).

Table S064.16 summarizes treatment-emergent SAEs regardless of causality, and Table S064.17 summarizes treatment-emergent SAEs possibly related to study treatment. The most common possibly related treatment-emergent SAEs occurring during the study were pulmonary embolism (4 [7.0%] patients in Arm A), diarrhea (3 [3.5%] patients in Arm A), and stomatitis (2 [3.5%] patients in Arm A); none of which occurred in Arm B.

Table S064.18 summarizes discontinuations due to SAEs and AEs, all of which were related to study treatment. Three patients in Arm A discontinued due to SAEs: 2 patients discontinued due to diarrhea (Patients [redacted] and [redacted]) and one patient due to a pulmonary embolism (Patient [redacted]). One patient in Arm B discontinued due to an SAE of atrial fibrillation (Patient [redacted]). Three patients in Arm A discontinued due to AEs: nausea in one patient (Patient [redacted]) and fatigue in two patients (Patients [redacted] and [redacted]). One patient in Arm B discontinued due to an AE of skin chapped (Patient [redacted]).

Three patients, all in Arm A, received transfusions while on study: 2 patients received packed red blood cells (RBCs) and 1 patient received leukoreduced packed RBCs. Twenty-five patients were hospitalized at least once while on study: 13 in Arm A (7 hospitalizations due to non-drug-related AEs and 7 due to drug-related AEs) and 12 in Arm B (9 hospitalizations due to non-drug-related AEs and 3 due to drug-related AEs).

There were 2 deaths during the study; both patients were in Arm A (Table S064.19). One was due to progressive disease (Patient [redacted]) and one was due to an SAE (see narrative provided in Section 4: arrhythmia, Patient [redacted], during cycle 15). For Patient [redacted], the investigator corrected the reason for discontinuation from "subject decision" to "investigator decision" after the data were locked and extracted. No new data transfer occurred after this correction. The patient discontinued on [redacted]. The investigator noted " intolerance to drug" and "overall deterioration" as rationale for his decision.

Patient narratives for all patients who died on study and within 30 days after date of discontinuation, and who discontinued due to nonserious or SAEs are provided in Section 4 below.

**Table S064.12. Overall Summary of Treatment-Emergent Adverse Events (Randomized and Treated Patients)**

| Parameters, n (%) | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=57) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=58) | All (N=115) |
|---|---|---|---|
| Patients with at least 1 TEAE | 55 (96.5) | 53 (91.4) | 108 (93.9) |
| Possibly related to study treatment | 51 (89.5) | 46 (79.3) | 97 (84.3) |
| Patients with at least 1 Grade 3/4 TEAE | 28(49.1) | 27 (46.6) | 55 (47.8) |
| Possibly related to study treatment | 21 (36.8) | 18 (31.0) | 39 (33.9) |
| Patients who had at least 1 Serious TEAE | 15 (26.3) | 11 (19.0) | 26 (22.6) |
| Possibly related to study treatment | 11 (19.3) | 4 (6.9) | 15 (13.0) |
| Patients who discontinued due to AE | 6 (10.5) | 2 (3.4) | 8 (7.0) |
| Possibly related to study treatment | 6 (10.5) | 2 (3.4) | 8 (7.0) |
| Patients who discontinued due to SAE | 3 (5.3) | 1 (1.7) | 4 (3.5) |
| Possibly related to study treatment | 3 (5.3) | 1 (1.7) | 4 (3.5) |
| Patients who died on therapy | 1 (1.8) | 0 | 1 (0.9) |
| Possibly related to study treatment | 1 (1.8) | 0 | 1 (0.9) |
| Patients who died within 30 days of study treatment discontinuation | 1 (1.8) | 0 | 1 (0.9) |
| Possibly related to study treatment | 0 | 0 | 0 |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; AE = adverse event; CRF = case report form; N = total population size; n = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Source: t_aevover.rtf.

**Table S064.13. Treatment-Emergent Adverse Events Regardless of Causality by System Organ Class Occurring in at least 10% of Patients in Either Treatment Arm (Randomized and Treated Patients)**

| System Organ Class<br>Preferred Term, n (%) | Arm A<br>(Enzastaurin+<br>5-FU/LV+Bevacizumab)<br>(N=57) | Arm B<br>(Placebo+<br>5-FU/LV+Bevacizumab)<br>(N=58) | All<br><br><br>(N=115) |
|---|---|---|---|
| Patients with at least one event | 52 (91.2 | 45 (77.6) | 97 (84.3) |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | 11 (19.3) | 8 (13.8) | 19 (16.5) |
| Neutropenia | 10 (17.5) | 7 (12.1) | 17 (14.8) |
| Anemia | 7 (12.3) | 5 (8.6) | 12 (10.4) |
| Gastrointestinal disorders | | | |
| Diarrhea | 21 (36.8) | 22 (37.9) | 43 (37.4) |
| Nausea | 15 (26.3) | 15 (25.9) | 30 (26.1) |
| Constipation | 13 (22.8) | 5 (8.6) | 18 (15.7) |
| Vomiting | 8 (14.0) | 10 (17.2) | 18 (15.7) |
| Abdominal pain | 10 (17.5) | 5 (8.6) | 15 (13.0) |
| Stomatitis | 7 (12.3) | 4 (6.9) | 11 (9.6) |
| Flatulence | 6 (10.5) | 3 (5.2) | 9 (7.8) |
| General fatigue and administration site conditions | | | |
| Fatigue | 24 (42.1) | 23 (39.7) | 47 (40.9) |
| Mucosal inflammation | 10 (17.5) | 9 (15.5) | 19 (16.5) |
| Pyrexia | 6 (10.5) | 8 (13.8) | 14 (12.2) |
| Investigations | | | |
| ALT increased | 5 (8.8) | 7 (12.1) | 12 (10.4) |
| AST increased | 4 (7.0) | 6 (10.3) | 10 (8.7) |
| Hemoglobin decreased | 6 (10.5) | 2 (3.4) | 8 (7.0) |
| Urine color abnormal | 7 (12.3) | 0 | 7 (6.1) |
| Metabolism and nutritional disorders | | | |
| Decreased appetite | 9 (15.8) | 7 (12.1) | 16 (13.9) |

(continued)

**Table S064.13. Treatment-Emergent Adverse Events Regardless of Causality by System Organ Class Occurring in at least 10% of Patients in Either Treatment Arm (Randomized and Treated Patients) (concluded)**

| System Organ Class<br>Preferred Term, n (%) | Arm A<br>(Enzastaurin+<br>5-FU/LV+Bevacizumab)<br>(N=57) | Arm B<br>(Placebo+<br>5-FU/LV+Bevacizumab)<br>(N=58) | All<br><br><br>(N=115) |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | 7 (12.3) | 5 (8.6) | 12 (10.4) |
| Back pain | 3 (5.3) | 6 (10.3) | 9 (7.8) |
| Nervous system disorders | | | |
| Headache | 10 (17.5) | 8 (13.8) | 18 (15.7) |
| Peripheral sensory neuropathy | 6 (10.5) | 8 (13.8) | 14 (12.2) |
| Dizziness | 6 (10.5) | 6 (10.3) | 12 (10.4) |
| Renal and urinary disorders | | | |
| Proteinuria | 6 (10.5) | 4 (6.9) | 10 (8.7) |
| Respiratory, thoracic, and mediastinal disorders | | | |
| Epistaxis | 16 (28.1) | 13 (22.4) | 29 (25.2) |
| Cough | 13 (22.8) | 11 (19.0) | 24 (20.9) |
| Dyspnea | 7 (12.3) | 5 (8.6) | 12 (10.4) |
| Rhinorrhea | 2 (3.5) | 6 (10.3) | 8 (7.0) |
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysesthesia syndrome | 9 (15.8) | 14 (24.1) | 23 (20.0) |
| Rash | 8 (14.0) | 5 (8.6) | 13 (11.3) |
| Dry skin | 6 (10.5) | 4 (6.9) | 10 (8.7) |
| Vascular disorders | | | |
| Hypertension | 7 (12.3) | 13 (22.4) | 20 (17.4) |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = total population size; n = number of patients.

Source: t_aev10.rtf.

**Table S064.14. Treatment-Emergent Adverse Events Possibly Related to Study Drug by System Organ Class Occurring in at least 10% of Patients in Either Treatment Arm (Randomized and Treated Patients)**

| System Organ Class<br>Preferred Term, n (%) | Arm A<br>(Enzastaurin+<br>5-FU/LV+Bevacizumab)<br>(N=57) | Arm B<br>(Placebo+<br>5-FU/LV+Bevacizumab)<br>(N=58) | All<br><br><br>(N=115) |
|---|---|---|---|
| Patients with at least one event | 46 (80.7) | 40 (69.0) | 86 (74.8) |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | 11 (19.3) | 7 (12.1) | 18 (15.7) |
| Neutropenia | 9 (15.8) | 7 (12.1) | 16 (13.9) |
| Anemia | 7 (12.3) | 3 (5.2) | 10 (8.7) |
| Gastrointestinal disorders | | | |
| Diarrhea | 16 (28.1) | 16 (27.6) | 32 (27.8) |
| Nausea | 14 (24.6) | 14 (24.1) | 28 (24.3) |
| Vomiting | 6 (10.5) | 8 (13.8) | 14 (12.2) |
| General fatigue and administration site conditions | | | |
| Fatigue | 21 (36.8) | 21 (36.2) | 42 (36.5) |
| Mucosal inflammation | 9 (15.8) | 8 (13.8) | 17 (14.8) |
| Investigations | | | |
| ALT increased | 3 (5.3) | 6 (10.3) | 9 (7.8) |
| Urine color abnormal | 7 (12.3) | 0 | 7 (6.1) |
| Nervous system disorders | | | |
| Headache | 7 (12.3) | 6 (10.3) | 13 (11.3) |
| Peripheral sensory neuropathy | 3 (5.3) | 7 (12.1) | 10 (8.7) |
| Respiratory, thoracic, and mediastinal disorders | | | |
| Epistaxis | 14 (24.6) | 11 (19.0) | 25 (21.7) |

(continued)

**Table S064.14. Treatment-Emergent Adverse Events Possibly Related to Study Drug by System Organ Class Occurring in at least 10% of Patients in Either Treatment Arm (Randomized and Treated Patients) (concluded)**

| System Organ Class<br>Preferred Term, n (%) | Arm A<br>(Enzastaurin+<br>5-FU/LV+Bevacizumab)<br>(N=57) | Arm B<br>(Placebo+<br>5-FU/LV+Bevacizumab)<br>(N=58) | All<br>(N=115) |
|---|---|---|---|
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysesthesia syndrome | 8 (14.0) | 13 (22.4) | 21 (18.3) |
| Vascular disorders | | | |
| Hypertension | 6 (10.5) | 13 (20.7) | 18 (15.7) |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; ALT = alanine aminotransferase; N = total population size; n = number of patients.
Source: t_aev10rel.rtf.

**Table S064.15. Summary of Maximum CTCAE Grade 3 or 4 Possibly Related to Study Drug Occurring in More Than 1 Patient in Either Treatment Arm (Laboratory and Nonlaboratory, Randomized, and Treated Patients)**

| CTCAE Term, n (%) | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=57) | | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=58) | | All (N=115) | |
|---|---|---|---|---|---|---|
| | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| **Laboratory** | | | | | | |
| Patients with at least one event | 3 (5.3) | 3 (5.3) | 3 (5.2) | 1 (1.7) | 6 (5.2) | 4 (3.5) |
| Neutrophils/Granulocytes (ANC/AGC) | 1 (1.8) | 3 (5.3) | 1 (1.7) | 1 (1.7) | 2 (1.7) | 4 (3.5) |
| Hemoglobin | 2 (3.5) | 0 | 0 | 0 | 2 (1.7) | 0 |
| **Nonlaboratory** | | | | | | |
| Patients with at least one event | 18 (31.6) | 7 (12.3) | 24 (41.4) | 1 (1.7) | 42 (36.5) | 8 (7.0) |
| Thrombosis/thrombus/embolism | 5 (8.8) | 5 (8.8) | 0 | 1 (1.7) | 5 (4.3) | 6 (5.2) |
| Rash: hand-foot skin reaction | 4 (7.0) | 0 | 5 (8.6) | 0 | 9 (7.8) | 0 |
| Fatigue (asthenia, lethargy, malaise) | 4 (7.0) | 0 | 3 (5.2) | 0 | 7 (6.1) | 0 |
| Hypertension | 2 (3.5) | 0 | 2 (3.4) | 0 | 4 (3.5) | 0 |
| Diarrhea | 1 (1.8) | 1 (1.8) | 2 (3.4) | 0 | 3 (2.6) | 1 (0.9) |
| Anorexia | 2 (3.5) | 0 | 1 (1.7) | 0 | 3 (2.6) | 0 |
| Cataract | 3 (5.3) | 0 | 0 | 0 | 3 (2.6) | 0 |
| Dizziness | 2 (3.5) | 0 | 1 (1.7) | 0 | 3 (2.6) | 0 |
| Mucositis/stomatitis (clinical exam) – oral cavity | 2 (3.5) | 0 | 1 (1.7) | 0 | 3 (2.6) | 0 |
| Nausea | 1 (1.8) | 0 | 2 (3.4) | 0 | 3 (2.6) | 0 |
| Pain gastrointestinal – abdomen NOS | 1 (1.8) | 0 | 2 (3.4) | 0 | 3 (2.6) | 0 |
| Vomiting | 1 (1.8) | 0 | 2 (3.4) | 0 | 3 (2.6) | 0 |
| Neuropathy: sensory | 1 (1.8) | 1 (1.8) | 1 (1.7) | 0 | 2 (1.7) | 1 (0.9) |
| Dehydration | 2 (3.5) | 0 | 0 | 0 | 2 (1.7) | 0 |
| Gastrointestinal, other | 2 (3.5) | 0 | 0 | 0 | 2 (1.7) | 0 |

(continued)

**Table S064.15. Summary of Maximum CTCAE Grade 3 or 4 Possibly Related to Study Drug Occurring in More Than 1 Patient in Either Treatment Arm (Laboratory and Nonlaboratory, Randomized, and Treated Patients (concluded)**

| CTCAE Term, n (%) | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=57) | | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=58) | | All (N=115) | |
|---|---|---|---|---|---|---|
| | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| **Nonlaboratory (continued)** | | | | | | |
| Infection with normal ANC/Grade 1/2 neutrophils – catheter-related | 0 | 0 | 2 (3.4) | 0 | 2 (1.7) | 0 |
| Mucositis/stomatitis (functional/symptomatic) – oral cavity | 2 (3.5) | 0 | 0 | 0 | 2 (1.7) | 0 |
| Weight gain | 0 | 0 | 2 (3.4) | 0 | 2 (1.7) | 0 |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; AGC = absolute granulocyte count; ANC = absolute neutrophil count; CTCAE = common terminology criteria for adverse events;N = total population size; n = number of patients; NOS = not otherwise specified.

Sources: t_labaerel.rtf and t_nonlabae.rtf.

**Table S064.16. Treatment-Emergent Serious Adverse Events Regardless of Causality (Randomized and Treated Patients)**

| System Organ Class<br>Preferred Term, n (%) | Arm A<br>(Enzastaurin+<br>5-FU/LV+Bevacizumab)<br>(N=57) | Arm B<br>(Placebo+<br>5-FU/LV+Bevacizumab)<br>(N=58) | All<br>(N=115) |
|---|---|---|---|
| Patients with at least one event | 15 (26.3) | 11 (19.0) | 26 (22.6) |
| Blood and lymphatic system disorders | | | |
| Anemia | 1 (1.8) | 0 | 1 (0.9) |
| Febrile neutropenia | 1 (1.8) | 0 | 1 (0.9) |
| Thrombocytopenia | 1 (1.8) | 0 | 1 (0.9) |
| Cardiac disorders | | | |
| Arrhythmia | 1 (1.8) | 0 | 1 (0.9) |
| Atrial fibrillation | 0 | 1 (1.7) | 1 (0.9) |
| Gastrointestinal disorders | | | |
| Diarrhea | 3 (5.3) | 0 | 3 (2.6) |
| Stomatitis | 2 (3.5) | 0 | 2 (1.7) |
| Abdominal hernia | 1 (1.8) | 0 | 1 (0.9) |
| Abdominal pain lower | 0 | 1 (1.7) | 1 (0.9) |
| Colonic obstruction | 1 (1.8) | 0 | 1 (0.9) |
| Ileus | 0 | 1 (1.7) | 1 (0.9) |
| Subileus | 0 | 1 (1.7) | 1 (0.9) |
| Vomiting | 1 (1.8) | 0 | 1 (0.9) |
| General fatigue and administration site conditions | | | |
| Mucosal inflammation | 1 (1.8) | 0 | 1 (0.9) |
| Pyrexia | 0 | 1 (1.7) | 1 (0.9) |
| Hepatobiliary disorders | | | |
| Cholecystitis | 0 | 1 (1.7) | 1 (0.9) |

(continued)

**Table S064.16. Treatment-Emergent Serious Adverse Events Regardless of Causality (Randomized and Treated Patients) (continued)**

| System Organ Class<br>Preferred Term, n (%) | Arm A<br>(Enzastaurin+<br>5-FU/LV+Bevacizumab)<br>(N=57) | Arm B<br>(Placebo+<br>5-FU/LV+Bevacizumab)<br>(N=58) | All<br>(N=115) |
|---|---|---|---|
| Infections and infestations | | | |
| Catheter-related infection | 0 | 1 (1.7) | 1 (0.9) |
| Device-related infection | 0 | 1 (1.7) | 1 (0.9) |
| Pneumonia | 0 | 1 (1.7) | 1 (0.9) |
| Staphylococcal bacteremia | 0 | 1 (1.7) | 1 (0.9) |
| Injury, poisoning, and procedural complications | | | |
| Stent malapposition | 1 (1.8) | 0 | 1 (0.9) |
| Investigations | | | |
| ALT increased | 0 | 1 (1.7) | 1 (0.9) |
| AST increased | 0 | 1 (1.7) | 1 (0.9) |
| Blood alkaline phosphatase increased | 0 | 1 (1.7) | 1 (0.9) |
| Metabolism and nutritional disorders | | | |
| Dehydration | 1 (1.8) | 0 | 1 (0.9) |
| Hypertriglyceridemia | 1 (1.8) | 0 | 1 (0.9) |
| Musculoskeletal and connective tissue disorders | | | |
| Joint range of motion decreased | 1 (1.8) | 0 | 1 (0.9) |
| Nervous system disorders | | | |
| Intercranial venous sinus thrombosis | 1 (1.8) | 0 | 1 (0.9) |
| Syncope | 0 | 1 (1.7) | 1 (0.9) |
| Respiratory, thoracic, and mediastinal disorders | | | |
| Pulmonary embolism | 4 (7.0) | 0 | 4 (3.5) |
| Dyspnea | 1 (1.8) | 0 | 1 (0.9) |
| Epistaxis | 1 (1.8) | 0 | 1 (0.9) |
| Oropharyngeal pain | 0 | 1 (1.7) | 1 (0.9) |

(continued)

**Table S064.16. Treatment-Emergent Serious Adverse Events Regardless of Causality (Randomized and Treated Patients) (concluded)**

| System Organ Class<br>Preferred Term, n (%) | Arm A<br>(Enzastaurin+<br>5-FU/LV+Bevacizumab)<br>(N=57) | Arm B<br>(Placebo+<br>5-FU/LV+Bevacizumab)<br>(N=58) | All<br>(N=115) |
|---|---|---|---|
| Vascular disorders | | | |
| Hypertensive emergency | 0 | 1 (1.7) | 1 (0.9) |
| Subclavian vein thrombosis | 0 | 1 (1.7) | 1 (0.9) |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = total population size; n = number of patients.
Source: t_aevser.rtf.

**Table S064.17. Treatment-Emergent Serious Adverse Events Possibly Related to Study Drug (Randomized and Treated Patients)**

| System Organ Class<br>Preferred Term, n (%) | Arm A<br>(Enzastaurin+<br>5-FU/LV+Bevacizumab)<br>(N=57) | Arm B<br>(Placebo+<br>5-FU/LV+Bevacizumab)<br>(N=58) | All<br><br><br>(N=115) |
|---|---|---|---|
| Patients with at least one event | 11 (19.3) | 4 (6.9) | 15 (13.0) |
| Blood and lymphatic system disorders | | | |
| Anemia | 1 (1.8) | 0 | 1 (0.9) |
| Febrile neutropenia | 1 (1.8) | 0 | 1 (0.9) |
| Thrombocytopenia | 1 (1.8) | 0 | 1 (0.9) |
| Cardiac disorders | | | |
| Arrhythmia | 1 (1.8) | 0 | 1 (0.9) |
| Atrial fibrillation | 0 | 1 (1.7) | 1 (0.9) |
| Gastrointestinal disorders | | | |
| Diarrhea | 3 (5.3) | 0 | 3 (2.6) |
| Stomatitis | 2 (3.5) | 0 | 2 (1.7) |
| Vomiting | 1 (1.8) | 0 | 1 (0.9) |
| General fatigue and administration site conditions | | | |
| Mucosal inflammation | 1 (1.8) | 0 | 1 (0.9) |
| Pyrexia | 0 | 1 (1.7) | 1 (0.9) |
| Infections and infestations | | | |
| Staphylococcal bacteremia | 0 | 1 (1.7) | 1 (0.9) |
| Investigations | | | |
| ALT increased | 0 | 1 (1.7) | 1 (0.9) |
| AST increased | 0 | 1 (1.7) | 1 (0.9) |
| Metabolism and nutritional disorders | | | |
| Dehydration | 1 (1.8) | 0 | 1 (0.9) |
| Hypertriglyceridemia | 1 (1.8) | 0 | 1 (0.9) |
| Nervous system disorders | | | |
| Intercranial venous sinus thrombosis | 1 (1.8) | 0 | 1 (0.9) |

(continued)

**Table S064.17. Treatment-Emergent Serious Adverse Events Possibly Related to Study Drug (Randomized and Treated Patients) (concluded)**

| System Organ Class<br>Preferred Term, n (%) | Arm A<br>(Enzastaurin+<br>5-FU/LV+Bevacizumab)<br>(N=57) | Arm B<br>(Placebo+<br>5-FU/LV+Bevacizumab)<br>(N=58) | All<br>(N=115) |
|---|---|---|---|
| Respiratory, thoracic, and mediastinal disorders | | | |
| Pulmonary embolism | 4 (7.0) | 0 | 4 (3.5) |
| Dyspnea | 1 (1.8) | 0 | 1 (0.9) |
| Epistaxis | 1 (1.8) | 0 | 1 (0.9) |
| Vascular disorders | | | |
| Hypertensive emergency | 0 | 1 (1.7) | 1 (0.9) |
| Subclavian vein thrombosis | 0 | 1 (1.7) | 1 (0.9) |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = total population size; n = number of patients.

Source: t_aevserrel.rtf.

**Table S064.18. Summary of Discontinuations Due to Serious Adverse Events and Adverse Events (Randomized and Treated Patients)**

| | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=57) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=58) | All (N=115) |
|---|---|---|---|
| Discontinuations due to SAEs, n (%) | 3 (5.3) | 1 (1.7) | 4 (3.5) |
| Atrial fibrillation | 0 | 1 (1.7) | 1 (0.9) |
| Diarrhea | 2 (3.5) | 0 | 2 (1.7) |
| Pulmonary embolism | 1 (1.8) | 0 | 1 (0.9) |
| Discontinuation due to AEs, n (%) | 3 (5.3) | 1 (1.7) | 4 (3.5) |
| Nausea | 1 (1.8) | 0 | 1 (0.9) |
| Fatigue | 2 (3.5) | 0 | 2 (1.7) |
| Skin chapped | 0 | 1 (1.7) | 1 (0.9) |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; AE = adverse event; N = total population size; n = number of patients; SAE = serious adverse event.
Source: t_discsae.rtf and t_discae.rtf.

**Table S064.19. Summary of Deaths on Study Drug Therapy or Within 30 Days of Study Drug Discontinuation (Randomized and Treated Patients)**

| | Arm A (Enzastaurin+ 5-FU/LV+Bevacizumab) (N=57) | Arm B (Placebo+ 5-FU/LV+Bevacizumab) (N=58) | All (N=115) |
|---|---|---|---|
| Deaths, n (%) | 2 (3.5) | 0 | 2 (1.7) |
| Study disease | 1 (1.8) | 0 | 1 (0.9) |
| Study drug toxicity | | | |
| Arrhythmia | 1 (1.8) | 0 | 1 (0.9) |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; N = total population size; n = number of patients.
Source: t_death.rtf.

**Conclusions:**

- Most AEs occurring during treatment with 5-FU/LV plus bevacizumab and either enzastaurin (Arm A) or placebo (Arm B) were Grade 1 or 2.
    - The most common TEAEs possibly related to study treatment were fatigue (36.5% overall; 36.8% in Arm A and 36.2% in Arm B), diarrhea (27.8% overall; 28.1% in Arm A and 27.6% in Arm B), and nausea (24.3% overall; 24.6% in Arm A and 24.1% in Arm B).
    - The most common possibly related treatment-emergent SAEs occurring during the study were pulmonary embolism (4 [7.0%] patients in Arm A), diarrhea (3 [3.5%] patients in Arm A), and stomatitis (2 [3.5%] patients in Arm A); none of which occurred in Arm B.
    - More patients developed thrombosis or embolism (including pulmonary embolism) on Arm A (17.5% Grade 3-4) compared to Arm B (1.7% Grade 3-4). It is not clear whether this was related to an anti-angiogenic effect, some other effect of study treatment, or because patients tended to develop progressive disease earlier on Arm A.
    - Three patients in Arm A discontinued due to SAEs: 2 patients discontinued due to diarrhea and one patient due to a pulmonary embolism. One patient in Arm B discontinued due to an SAE of atrial fibrillation. Three patients in Arm A discontinued due to AEs: one patient due to nausea and two patients due to fatigue. One patient in Arm B discontinued due to an AE of skin chapped.
    - There were 2 deaths during the study or within 30 days of discontinuation; both patients were in Arm A. One was due to progressive disease and one was due to an SAE (arrhythmia).

- Median PFS was 5.8 months in the enzastaurin group (Arm A) compared with 8.1 months in the placebo group (Arm B) (HR=1.35, 95% CI: 0.84, 2.16; one-sided, p=0.896); the enzastaurin arm failed to demonstrate an advantage in the primary endpoint, PFS.
    - The enzastaurin combination arm (Arm A) failed to demonstrate a PFS advantage and the data suggest an unfavorable outcome for the experimental Arm A. This result is sufficient to recommend no further development of the experimental arm according to the prespecified statistical test (one-sided type I error rate of 0.20).
- Median OS was not calculable (41 patients in Arm A and 39 patients in Arm B had discontinued study treatment as of the data cutoff date). The censoring rates were 77.6% and 91.5% for Arm A and Arm B, respectively. Based on the current database, the high rate of censoring precludes the interpretation of OS results. Estimates of survival are premature and should be regarded with caution due to this high rate of censoring.

- Thirty-five patients (16 in Arm A and 19 in Arm B) remained on treatment as of 27 January 2010; additional data from these patients are not expected to alter the efficacy findings.

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