Capecitabine/irinotecan or capecitabine/oxaliplatin in combination with bevacizumab is effective and safe as first-line therapy for metastatic colorectal cancer: a randomized phase II study of the AIO colorectal study group


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Background: This randomized phase II trial investigated the efficacy and safety of capecitabine/oxaliplatin (CapOx) plus bevacizumab and dose-modified capecitabine/irinotecan (mCapIri) plus bevacizumab as first-line therapy in patients with metastatic colorectal cancer (mCRC).

Patients and methods: Patients received bevacizumab 7.5 mg/kg with oxaliplatin 130 mg/m²/day 1 plus capecitabine 1000 mg/m² bid/days 1–14 or with irinotecan 200 mg/m²/day 1 plus capecitabine 800 mg/m² bid/days 1–14 both every 21 days. The primary end point was 6 months progression-free survival (PFS).

Results: A total of 255 patients were enrolled. The intent-to-treat population comprised 247 patients (CapOx–bevacizumab: n = 127; mCapIri–bevacizumab: n = 120). The six-month PFS rates were 76% (95% CI, 69%–84%) and 84% (95% CI, 77%–90%). Median PFS and OS were 10.4 months (95% CI, 9.0–12.0) and 24.4 months (95% CI, 19.3–30.7) with CapOx–bevacizumab, and 12.1 months (95% CI, 10.8–13.2) and 25.5 months (95% CI, 21.0–31.0) with mCapIri–bevacizumab. Grade 3/4 diarrhea as predominant toxic effect occurred in 22% of patients with CapOx–bevacizumab and in 16% with mCapIri–bevacizumab.

Conclusions: Both, CapOx–bevacizumab and mCapIri–bevacizumab, show promising activity and an excellent toxic effect profile. Efficacy is in the range of other bevacizumab-containing combination regimen although lower doses of irinotecan and capecitabine were selected for mCapIri.

Key words: bevacizumab, CAPIRI, CAPOX, KRAS, metastatic colorectal cancer

Introduction

Randomized clinical studies have shown that bevacizumab (Avastin®) improves progression-free survival (PFS) in patients with previously untreated metastatic colorectal cancer (mCRC) when added to either irinotecan-based [1] or oxaliplatin-based [2] chemotherapy regimens. Capecitabine (Xeloda®) is an oral fluoropyrimidine with established single-agent efficacy in the first-line treatment of mCRC [3] and as adjuvant therapy for stage III colon cancer [4]. More recently, capecitabine in combination with oxaliplatin (CapOx) has demonstrated similar efficacy versus various 5-fluorouracil/folinic acid (FU/FA)/oxaliplatin regimens as first-line therapy for mCRC [5, 6]. However, identifying a capecitabine/irinotecan (CapIri) regimen with an acceptable tolerability profile has proved more difficult. Although CapIri was used successfully in one large phase III study [7], concerns about gastrointestinal toxic effect were raised in two others [8, 9]. Subsequently, some modifications of the CapIri regimen were explored [10].
This randomized phase II trial was conducted to investigate the efficacy and safety of both CapOx plus bevacizumab and dose-modified mCapIri plus bevacizumab, as first-line therapy in patients with mCRC. Given past concerns about toxic effect associated with the CapIri regimen and the findings of our preceding trial [10], we chose lower doses of capecitabine and irinotecan than have been used previously.

patients and methods

study design

This open-label, multicenter, randomized phase II study was carried out according to the Declaration of Helsinki and Good Clinical Practice Guidelines. The protocol was approved by the ethics committee at each participating site. Written informed consent was obtained from all patients before study participation.

patient population

Patients aged ≥18 years with inoperable, histologically confirmed, advanced colorectal cancer and a measurable lesion, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) [11], were enrolled. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and a life expectancy >3 months. No prior systemic immunotherapy or chemotherapy for advanced colorectal cancer was allowed. (Neo)adjuvant chemotherapy or radiochemotherapy had to be completed >6 months before randomization.

Patients were required to have adequate hematologic, hepatic, and renal function. Other exclusion criteria included: disease progression within 6 months of completing adjuvant therapy; known central nervous system metastases; clinically significant cardiovascular disease; use of anticoagulants; serious non-healing wound or ulcer; thrombosis or severe bleeding within 6 months of study admission; continuous aspirin (>325 mg/day) or regular use of non-steroidal anti-inflammatory agents; proteinuria.

treatment plan

Patients were randomly assigned to treatment using a centralized system. Randomization was stratified according to ECOG performance status, number of metastases, leukocyte count, alkaline phosphatase level, and Köhne score [12].

Bevacizumab 7.5 mg/kg was administered as a 30- to 90-min intravenous infusion on day 1. This was followed by either a 2-h intravenous infusion of oxaliplatin 130 mg/m² on day 1 and oral capecitabine 1000 mg/m² twice daily on days 1–14 (CapOx) or a 30 to 90-min intravenous infusion of irinotecan 200 mg/m² on day 1 and capecitabine 800 mg/m² twice daily on days 1–14 (mCapIri) of a 21-day cycle. Treatment was continued until disease progression, unacceptable toxicity, deterioration of ECOG performance status to >2, or withdrawal of patient consent. Patients whose metastases became resectable and who underwent surgical resection/ablation were also withdrawn from further treatment.

Dose modifications for treatment-related toxic effect were carried out according to the study protocol. If severe drug-related toxic effects, such as oxaliplatin-induced neurotoxicity with functional impairment occurred, the latter agents were discontinued and treatment continued with the remaining components of the assigned regimen. Patients were withdrawn from the study if treatment was interrupted for >3 weeks or non-hematologic toxicity grade 4 (except nausea/vomiting).

assessments

Medical history, physical examination, electrocardiogram (ECG), routine blood analysis, ECOG performance status and creatinine clearance were evaluated within 7 days of starting study treatment. During treatment, physical examination and biochemistry analyses were repeated before every treatment cycle and blood counts were carried out weekly. At the end of therapy, routine blood analysis, ECG, and an assessment of vital signs, ECOG performance status, and body weight were carried out.

Tumor assessments using computed tomography or magnetic resonance imaging were carried out within 28 days before study treatment, and were repeated every 9 weeks thereafter and at treatment end. The same target lesions and scanning techniques were used at each assessment, according to RECIST guidelines version 1.0 [11], to define treatment responses. Confirmation of response was carried out during the next staging procedure. After completion of study treatment, patients were followed up every 3 months until death.

Patients were evaluated for adverse events before each treatment cycle until treatment end. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

KRAS mutation analysis

For KRAS mutation status, formalin-fixed paraffin-embedded tumor tissue (FFPE-TT) from most patients was collected after obtaining informed consent or status was reported by investigators. Samples were macro dissected and DNA was extracted using the QIAamp DNA Mini kit (Qiagen, Hilden, Germany). Real-Time PCR amplification for the seven most common KRAS mutations in codons 12 and 13 was carried out using commercially available kits (DxS Ltd., Manchester, UK). Tumor samples with known KRAS mutations served as controls.

statistical analysis

The primary study end point was the PFS rate at 6 months, assessed by investigators, of each treatment arm. A 6-month PFS rate of ≤60% was considered indicative of inadequate activity, whereas a rate of ≥75% was considered sufficiently effective for further studies. The planned sample size was 240 patients (i.e. 120 patients/arm), which had 85% power at a 5% α-level to reject the null hypothesis of a 6-month PFS rate of ≤60% if the true rate was ≥75% (one-stage Fleming design).

Secondary study end points were: overall survival (OS); PFS; toxic effects; secondary resection of liver/lung metastases. PFS was defined as the time from study randomization until disease progression or death. OS was defined as the time from study randomization until death.

All analyses of efficacy were based on the intent-to-treat (ITT) patient population (defined as eligible and assessable patients who underwent randomization). The safety population was defined as all patients receiving ≥1 dose of study drug.

A descriptive analysis of all parameters (mean, median, 95% confidence intervals [CIs]) was carried out. Time-to-event data were analyzed by the Kaplan–Meier method and compared using the log-rank test.

results

patient population

Between 27 July 2005 and 25 October 2006, 255 patients were enrolled at 53 sites in Germany, and randomized to CapOx–bevacizumab (Arm A; n = 127) or mCapIri–bevacizumab (Arm B; n = 128). Eight patients in Arm B were considered ineligible (n = 4) or did not receive study treatment (n = 4; Figure 1). The
ITT and safety populations therefore comprised a total of 247 patients (Arm A, $n = 127$; Arm B, $n = 120$). Baseline demographic and clinical characteristics were well balanced between the treatment arms (Table 1).

Reasons for discontinuing study treatment are presented in supplementary Table S1, available at Annals of Oncology online. The majority of patients discontinued treatment without tumor progression (Arm A, 62%; Arm B, 67%). Patients in Arm A stopped treatment more frequently because of toxic effect (37%), whereas ‘other reasons’, mainly patient choice (e.g. the wish for a break after a long treatment duration, 39%), were more common in Arm B.

treatment exposure
The mean duration of treatment ($\pm$standard deviation) for the ITT population was 6.8 ($\pm$5.4) months in Arm A and 7.9 ($\pm$5.5) months in Arm B (total: 7.4 $\pm$ 5.5 months). The mean number of treatment cycles/patient was 9.4 ($\pm$7.0) and 10.7 ($\pm$7.1), respectively.

Treatment delays were required for 81 patients (64%) in Arm A and 78 patients (65%) in Arm B, and dose reductions were required in 78 (61%) and 54 patients (45%), respectively. The doses of oxaliplatin and irinotecan were to be reduced in 79 cycles (7%), and 22 cycles (2%), for capecitabine in 184 cycles (7%), and bevacizumab in 31 cycles (1%). The most common reasons for treatment delays were laboratory abnormalities (40%/44% of cycles in Arm A/Arm B, mainly hematologic) and patient/physician request (34%/31%). Reasons for dose reductions included laboratory abnormalities (82%/76% of cycles in Arm A/Arm B) and patient/physician request (17%/21%).

efficacy
The cut-off date for the final analysis was 31 August 2011. The mean duration of follow-up for the study population was 26.6 months. The PFS rates after 6 months, as primary study end point, were 76% ($n = 97$; 95% CI, 69%–84%) in Arm A and 84% ($n = 100$; 95% CI, 77%–90%) in Arm B (Table 2). The median PFS was 10.4 months (95% CI, 9.0–12.0 months) and 12.1 months (95% 10.8–13.2 months), respectively [hazard ratio 0.93; 95% CI, 0.82–1.07; $P = 0.30$; Figure 2A]. The median OS were 24.4 months (95% CI, 19.3–30.7 months) and 25.5 months (95% CI, 21.0–31.0) [hazard ratio 0.90; 95% CI, 0.68–1.19; $P = 0.45$; Figure 2B], respectively.

Regarding second and further lines of therapy, information was available on 228 (92.3%) of all patients, of whom 73.2% received any second-line treatment (Arm A 70.0%/Arm B 76.6%). While 85.6% of these patients received the other chemotherapeutic drug (irinotecan after oxaliplatin 89%, vice versa 82.3%), bevacizumab was continued beyond progression in 36.5% of patients, largely within a randomized, controlled, Phase III trial (ML18147) addressing this. Anti-EGFR treatment was given in 46.7% of patients irrespective of KRAS status (Arm A 50%/Arm B 40%). In $\sim$20% of patients, first-line treatment was reintroduced after a temporary treatment discontinuation.

Best overall objective responses, as assessed by the investigators, were similar in both treatment arms (53%; 56%). In Arm A, complete responses were documented in 6 (5%), partial responses in 61 (48%), and stable disease in 36 patients (28%). In Arm B, complete responses were documented in 7 (6%), partial responses in 60 (50%), and stable disease in 34 patients (28%).
Five patients in Arm A (4%) and nine patients in Arm B (8%) underwent resection or ablation of metastases for an overall secondary resection rate of 5% (Table 2).

For analysis of KRAS mutation status, FFPE-TT from 215 patients (87% of ITT) were available (KRAS population). In 141 patients (65.6% of KRAS population), no KRAS mutation was detectable (KRAS wild-type; WT) while in 74 patients (34.4% of KRAS population) a mutation in codon 12 or 13 was found (KRAS mutated; MT). Forty-four (60% of MT) patients showed a G12D mutation, eight (11% of MT) a G12S or G12V mutation and seven patients a G13D mutation (9.5% of MT). Other G12X mutations were found in eight patients (11% of MT). There was a non-significant difference in OS between WT and MT patients (median 27.7 months in WT and 21.7 months in MT, P = 0.81; Figure 2C) both treatment arms combined. However, in this unplanned retrospective analysis, a substantially worse OS in MT patients receiving CapOx–bevacizumab compared with mCapIri–bevacizumab was seen (OS MT CapOx–bevacizumab versus mCapIri–bevacizumab: 18.8 versus 28.7 months; P = 0.03, Figure 2E) whereas OS was not different between the two treatment arms in WT patients (median 28.1 months and 25.5 months; P = 1.0, Figure 2D).

PFS was not different between WT and MT patients in the KRAS population (median 11.7 months and 11.5 months, HR 1.0; P = 1) or between treatment arms in WT (median 10.4 months and 12.1 months, HR 0.88, P = 0.49) and MT patients (median 9.5 months and 12.6 months, HR 0.82, P = 0.43).

### safety

The most frequently reported toxic effects were diarrhea and sensory neuropathy (Table 3), the latter documented only in arm A (grade 3, 24%; grade 4, <1%). Grade 3/4 diarrhea was more common in arm A (22% versus 16%). Grade 3 hand–foot syndrome was observed in 16 patients (13%) in arm A and 9 patients (8%) in arm B. Arm B was associated with more grade 3/4 neutropenia (10%, versus 2%), whereas arm A was associated with more grade 3 thrombocytopenia (6%, versus 0%). Febrile neutropenia was documented in 1 patient (<1%) in arm B. Adverse events of special interest for bevacizumab occurred as anticipated (Table 3). No wound healing complications were documented, whereas one gastrointestinal fistula was observed (arm A).

Toxicity-related treatment discontinuation was more common in arm A (37% versus 14%), but more serious adverse events lead to treatment withdrawal in the arm B (11% versus 5%). The primary reasons for treatment-related discontinuation were neuropathy (n = 11), diarrhea (n = 6), and hematologic toxic effect (n = 4).

The 60-day all-cause mortality rates were 3.1% and 0%. The total 60-day mortality rate was 1.6%.

### Table 1. Baseline Patient Characteristics (Intent-To-Treat Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CapOx–bevacizumab (N = 127)</th>
<th>mCapIri–bevacizumab (N = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84</td>
<td>66</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
<td>34</td>
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<tr>
<td>Age, years (Range)</td>
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<td>ECOG performance status</td>
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<td>0</td>
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<td>52</td>
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<tr>
<td>1</td>
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<td>45</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<tr>
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<td></td>
</tr>
<tr>
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<td>76</td>
<td>60</td>
</tr>
<tr>
<td>Rectum</td>
<td>51</td>
<td>40</td>
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<td>Adjuvant therapy</td>
<td></td>
<td></td>
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<tr>
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<td>77</td>
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<tr>
<td>Yes</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>&lt;1</td>
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<tr>
<td>Leukocyte count, cells/μL&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>&lt;8.0</td>
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<td>57</td>
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<tr>
<td>≥8.0</td>
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<tr>
<td>Alkaline phosphatase, U/L&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>&lt;300</td>
<td>106</td>
<td>85</td>
</tr>
<tr>
<td>≥300</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>

<sup>a</sup>CapOx-bevacizumab, n = 126; mCapIri-bevacizumab, n = 119.
<sup>b</sup>CapOx-bevacizumab, n = 124; mCapIri-bevacizumab, n = 120.

mCapIri, modified capecitabine and irinotecan; CapOx, capecitabine and oxaliplatin; ECOG, Eastern Cooperative Oncology Group.

### Table 2. Efficacy analysis (ITT population)

<table>
<thead>
<tr>
<th>End point</th>
<th>CapOx–bevacizumab (N = 127)</th>
<th>mCapIri–bevacizumab (N = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Primary end point</td>
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<tr>
<td>PFS rate after 6 months</td>
<td>97</td>
<td>76</td>
</tr>
<tr>
<td>95% CI, %</td>
<td>69–84</td>
<td></td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>Median overall survival, months (95% CI)</td>
<td>24.4</td>
<td></td>
</tr>
<tr>
<td>Resection/ablation of liver/lung metastases</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

mCapIri, modified capecitabine and irinotecan; CapOx, capecitabine and oxaliplatin; CI, confidence interval; PFS, progression-free survival.
discussion

This study demonstrates that both regimens, CapOx–bevacizumab and mCapIri–bevacizumab, are equally active first-line regimens for the treatment of patients with mCRC given the limitations of this formal non-comparative analysis within this trial. The 6-month PFS rate for both regimens exceeded 75%, a cut-off value defined prospectively as being indicative of promising activity. These findings were further supported by the reported mature OS data with long follow-up.

The key finding in this study was the favorable activity and tolerability profile of the mCapIri–bevacizumab regimen being reported for the first time in abstract form and now confirmed by finalized data. Previously, most CapIri regimens used higher doses of capecitabine (1000 mg/m² twice daily on days 1–14), and irinotecan, (250 mg/m² on day 1 every 3 weeks), based on phase I recommendations [13, 14]. While an acceptable toxic effect profile was documented in the CAIRO trial [7], excessive gastrointestinal toxic effect was reported in the BICC-C [8] and EORTC 40015 trials [9]. Subsequently, our own findings suggested that modulations of the CapIri regimen may be feasible [10]. Consecutively, we decided to reduce the doses of capecitabine (from 1000 to 800 mg/m² twice daily) and irinotecan (from 250 to 200 mg/m²) and, for the first time, showed good tolerability without any apparent loss of efficacy compared with ‘regular dose’ CapOx [15]. The mature long-

![Figure 2](https://academic.oup.com/annonc/article-abstract/24/6/1580/180163)

Figure 2. (A) PFS by treatment, (B) OS by treatment, (C) OS by KRAS status, both treatment arms combined, and (D) OS by treatment/subgroup: KRAS wild type (E) OS by treatment/subgroup: KRAS mutant.
Several other studies have recently confirmed the observation that toxic effects with capecitabine are observed compared with irinotecan; CapOx, capecitabine and oxaliplatin; GI, gastrointestinal.

Events of special interest to bevacizumab

We documented a median overall survival of 24.4 months with CapOx–bevacizumab and 25.5 months with mCapIri–bevacizumab, which are similar to those data reported recently for CapIri–bevacizumab (23 months) [25] and oxaliplatin bevacizumab-based regimens (median 21.3 to 24.5 months) [2, 18, 23, 24]. We excluded patients with early disease progression after adjuvant therapy, a patient group with a poor prognosis [26] which may have contributed to the favorable result. However, most likely those OS data also reflect the improved treatment options, i.e. secondary resection, targeted agents, available to patients with mCRC.

Our study analyzed KRAS mutational status in close to 90% of patients and in our retrospective analysis we found a difference in survival between CapOx–bevacizumab and CapIri–bevacizumab in KRAS MT patients, while no difference in survival was found in KRAS WT patients. Although not well understood, this is in line with previous reports that have pointed to a lower overall response rate and/or OS of oxaliplatin or any chemotherapy containing regimens in patients with KRAS mutations [18, 27, 28] while survival under irinotecan-based regimens was comparable in WT and MT patients [18, 29]. Other studies did not detect shorter survival times in KRAS WT patients compared with WT when treated with oxaliplatin [23, 30]. Although our analysis was un-predefined and retrospective in nature and subgroups within the treatment arms were small, the effect is interesting considering that modified doses...
of capecitabine and irinotecan were used in the mCapIri protocol.

A very recent report from the SEER database suggests that the survival benefit through bevacizumab may be superior when combined with irinotecan versus oxaliplatin but the authors also state that there is little data from randomized studies comparing irinotecan–bevacizumab and oxaliplatin–bevacizumab protocols [31]. Certainly, the purpose of our trial was not to perform a formal statistical comparison of CapOx–bevacizumab and mCapIri–bevacizumab, but to assess their potential for phase III testing which should be considered when interpreting these results. However, our data including the analysis in KRAS WT and MT patients suggest that KRAS MT patients may gain more benefit from irinotecan-containing protocols than oxaliplatin protocols.

A limitation of our study seemed that eight patients, all of whom were in the mCapIri–bevacizumab arm, had to be excluded from the efficacy evaluation. However, an analysis of OS including all randomized patients \((n = 255)\) revealed comparable median survival times (data not shown).

In conclusion, bevacizumab can safely be added to either CapOx or dose-reduced CapIri, defining two highly active first-line regimens for patients with mCRC. However, the fact that treatment discontinuation for reasons other than disease progression occurred in most patients supports the aim of present trials of these combinations which address the optimal method of treatment de-escalation or discontinuation for each regimen or its constituents.

**funding**

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**disclosure**

WS: honoraria and advisory board member: Roche, Merck Serono, Astra Zeneca, Amgen. AR-S: honoraria from Amgen, Roche, Pfizer, Sanofi-Aventis; advisory board member: Amgen, Roche, Pfizer; studies sponsored by: Roche, Sanofi-Aventis. DA: conducting research supported by speaker’s bureau: Roche, Amgen, Sanofi-Aventis. AT: honoraria from Amgen, Roche, Pfizer, Sanofi-Aventis. Studies sponsored by: Roche, Sanofi-Aventis. MP: honoraria from Merck Serono, Amgen; stock ownership: Novartis, Fresenius, Glaxo, Bayer (here no direct coi); research financing: Roche; education grant and travel support: Roche, Amgen, Sanofi Aventis, Chugai, Celgene, Merck. UG: honoraria and advisory board: Roche and Sanofi-Aventis. JS: honoraria from Roche. All remaining authors have declared no conflicts of interest.

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18. Hoch JR, Mitchell E, Chidac T et al. A randomized phase IIIb trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy
A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213

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Background: Rituximab-hyper-CVAD alternating with rituximab-high-dose methotrexate and cytarabine is a commonly utilized regimen in the United States for mantle cell lymphoma (MCL) based on phase II single institutional data. To confirm the clinical efficacy of this regimen and determine its feasibility in a multicenter study that includes both academic and community-based practices, a phase II study of this regimen was conducted by SWOG.

Patients and methods: Forty-nine patients with advanced stage, previously untreated MCL were eligible. The median age was 57.4 years (35–69.8 years).

Results: Nineteen patients (39%) did not complete the full scheduled course of treatment due to toxicity. There was one treatment-related death and two cases of secondary myelodysplastic syndrome (MDS). There were 10 episodes of grade 3 febrile neutropenia, 19 episodes of grade 3 and 1 episode of grade 4 infection. With a median follow-up of 4.8 years, the median progression-free survival was 4.8 years (5.5 years for those ≤65 years) and the median overall survival (OS) was 6.8 years.

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