Table 1

	Japanese PMS (n = 2696)	First-BEAT (n = 1295)
Hypertension	0.4%	0.5%
Hemorrhage	1.3%	0.8%
Proteinuria	0.1%	–
GI perforation	0.9%	0.7%
Thromboembolism		
Arterial	0.3%	0.6%
Venous	1.3%	1.0%
Wound healing complications	0.4%	0.3%

Onset status by patient background was investigated; however, no new safety signals were detected.
Conclusion: There has been no other large scale, well managed post-marketing safety monitoring data available in Asian countries to date with angiogenesis inhibitor BV for CRC indication. No new ADRs were observed, and no new safety signals were detected, either. Reported number of events was in line with previous clinical experience of First-BEAT international observational study. The data from this surveillance suggest that Avastin is a generally well-tolerated treatment option in Japanese patients.

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Phase I/II study of weekly intermittent capecitabine with bevacizumab and oxaliplatin on an every-2-week schedule for patients with untreated advanced colorectal cancer (CRC) final results

R.K. Ramanathan[1], R. Sehgal[1], K.K. Rajasenan[1], T.L. Crandall[1], E.P. Balaban[1], R.A. Pinkerton[1], P. Kane[1], D.M. Potter[1], B.C. Lembersky[1]. *[1]University of Pittsburgh Cancer Institute, Clinical Trials, Pittsburgh, USA*

Background: Capecitabine and Oxaliplatin (CapOx) with bevacizumab (Bev) is a standard regimen for advanced CRC utilizing Cap on a d 1−14 schedule every 3 wks. Intermittent wkly Cap (3,500 mg/m^2, d 1−7) with Ox (85 mg/m^2) every 2 wks may have advantages compared to the standard CapOx regimen in untreated advanced CRC with superior response and progression free survival (PFS) in a European study (JCO 21, 1307; 2003).
Material and Methods: This phase I/II trial was designed to evaluate weekly intermittent Cap with Ox/Bev in US pts with CRC. The primary endpoint was to detect a 50% improvement in median PFS from 8 to 12 months. Study required 40 patients, with 81% power (1-sided level 0.1 log-rank test). Cap was initially administered at the dose of 2500 mg/m^2 in two divided doses on d 1−7 (n = 11) and was increased to 3000 mg/m^2 dose (n = 29), based on tolerability of the lower dose. The dose of Ox was 85 mg/m^2 and Bev 5 mg/kg. Cycles were repeated every 2 wks. Preliminary results was reported previously (A4061, ASCO 2008).
Results: Patient characteristics: Total accrued 40, with 39 evaluable. Male (n = 25, 40%); ECOG performance status 0 (n = 24), 1 (n = 14); median age 62 (range 38−80 years). Median cycles administered 8 (range 1−25). Dose reduction was required in 21 pts (54%). Pertinent Grade 3/4 toxicities were: Hand Foot syndrome in 10%, diarrhea 18% and peripheral neuropathy in 10% of pts. Bowel perforation in 1 pt (3%) and one death due to a cerebral hemorrhage (3%). Response rate was 36% with one complete response. Downstaging of disease permitted subsequent metastectomy in 10 pts (28%) with R0 resections in 6 pts. PFS is 8.7 mo (5.8−10.7 mo, 95% CI). Median Overall survival is 17 mo. (10.4−24.2 mo, 95% CI). Four of 6 pts with R0 resections are alive with follow up of 12.4 to 42.4 mo.
Conclusions: The first US experience of this regimen shows it to be well tolerated, and Cap (3000 mg/m^2, d 1−7) in combination with Ox and Bev therapy every 2 wks can be safely administered. The incidence of subsequent metastectomy, a marker of activity, is encouraging, and there were no significant surgical complications. The PFS of 8.7 mo is in the range of recently reported studies of CapOX/Bev. (NO16966 study, JCO 12; 2013–2019; 2008.). A phase III trial (n = 430) of this regimen compared to the standard CapOx/Bev regimen has completed accrual in the US.
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Comorbidities in patients with metastatic colorectal cancer (mCRC)

A.Z. Fu[1], Z. Zhao[2], P.F. Wang[2], B. Barber[2], G.G. Liu[3]. *[1]Cleveland Clinic, Quantitative Health Sciences, Cleveland, USA; [2]Amgen Inc., Global Health Economics, Thousand Oaks, USA; [3]Peking University, Health Economics and Management Institute, Beijing, China*

Background: Patients with mCRC often have other medical ailments. These comorbidities may impact treatment decisions, prognoses, and quality of care. This study was conducted to describe the prevalence of comorbidities in the newly diagnosed mCRC population.
Material and Methods: This was a retrospective cohort study using a large claims database from a US national, commercially-insured population. Patients aged ⩾18 with newly diagnosed mCRC between 1/2004 and 6/2008 were selected using the ICD-9 diagnosis codes (CRC: 153.x [excluding 153.5], 154.0, 154.1, 154.8; distant metastasis: 196.0, 196.1, 196.3, 196.5, 197.x (excluding 197.5), 198, 199.0). The index date was defined as the date of the initial mCRC diagnosis. One-year continuous medical and drug benefit coverage prior to the index date was required for the selected cohort. Medical diagnoses and medication treatments were examined. All comorbidities were estimated during 1 year prior to the index date except for traumatic conditions (e.g., major surgery, bone fracture and open wound) which were assessed for 30 days prior to the index date.
Results: Based on the selection criteria, 12,648 patients were included with mean (±standard deviation) age of 66.3 (±13.0) years, 54% male, and 70% with colon primary. Distribution of metastases included liver (40%), lung (14%), bone (6%), and brain (3%). The most prevalent comorbidity was cardiovascular disease (CVD) (62% of patients) including hypertension (41%), coronary artery disease (17%), congestive heart failure (7%), dysrhythmias (14%), arterial thromboembolism including ischemic heart disease (18.6%), and venous thromboembolism (6%). Over 10% of patients had a major surgery, bone fracture, or open wound 30 days prior to mCRC diagnosis; 31% had a history of bleeding; and nearly 12% of patients were treated with anticoagulant and 6% with antiplatelet agents. Additionally, 19% of patients had diabetes, 8% had renal failure or insufficiency, and 5% had skin disorders. Fifty-two percent of patients ⩾65 years old had a significantly higher CVD prevalence (73%; $p < 0.001$).
Conclusions: Comorbid medical conditions are common in patients with mCRC. CVD is the most prevalent comorbidity and affects approximately 3/4 of patients over age 65. It is important to assess comorbidities in all patients with mCRC since their presence may impact treatment decision making.

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KRAS and BRAF mutational analyses in a phase II trial of first-line FOLFOXIRI plus bevacizumab (BV) in metastatic colorectal cancer (mCRC) patients (pts)

L. Salvatore[1], F. Loupakis[1], G. Fontanini[2], C. Cremolini[1], I. Stasi[3], A. Fabbri[4], A. Ciarlo[5], C. Granetto[6], F. Basolo[2], A. Falcone[7]. *[1]U. O. Oncologia Medica 2 Universitaria, Azienda Ospedaliera-Universitaria Pisana Istituto Toscano Tumori, Pisa, Italy; [2]U.O Anatomia Patologica Sperimentale Universitaria, Azienda Ospedaliera-Universitaria Pisana, Pisa, Italy; [3]U. O. Oncologia Medica, Azienda USL 6 Istituto Toscano Tumori, Livorno, Italy; [4]Dipartimento di Medicina Sperimentale e Patologia Oncologia Medica, Università La Sapienza, Roma, Italy; [5]U.O. Oncologia Medica, Ospedale Misericordia e Dolce, Prato, Italy; [6]U.O. Oncologia Medica, Ospedale S. Croce e Carle, Cuneo, Italy; [7]Dipartimento di Oncologia dei Trapianti e delle Nuove Tecnologie in Medicina, Università di Pisa, Pisa, Italy*

Introduction: *KRAS* codon 12 and 13 mutations have recently acquired a strategic importance for the therapeutic algorithm of mCRC pts, since their presence determines resistance to anti-EGFR antibodies. *BRAF* V600E mutation seems to play a similar role. Moreover, a negative prognostic effect of *KRAS* and *BRAF* mutations has been observed in mCRC pts receiving first-line chemotherapy +/− biologics. On the other hand, benefit from BV seems independent from *BRAF*/*KRAS* alterations.
Materials and Methods: Fifty-seven previously untreated mCRC pts were enrolled in a multicenter phase II single-arm study of FOLFOXIRI+BV. DNA was extracted from formalin-fixed paraffin-embedded samples of primary tumour after microdissection. Mutational analyses of *KRAS* codons 12−13 and *BRAF* codon 600 were conducted by means of PCR and direct sequencing.
Results: Analyses were successfully performed in 54 cases. *KRAS* and *BRAF* were mutated (mut) in 21 (39%) and 10 (18.5%) cases, respectively. One sample beared both *KRAS* and *BRAF* mutations. Examined mutations were not associated with response (RR: 27/33, 82% in *KRAS* wild-type (wt) pts vs 15/21, 71% in *KRAS* mut, p = 0.371; 33/44, 75% in *BRAF* wt pts vs 9/10, 90% in *BRAF* mut, p = 0.426). *KRAS* mutated pts had a PFS similar to that obtained by *KRAS* wt pts, (median PFS 13.1 vs 12.2 months; HR = 1.27, p = 0.474). Similar results were obtained for *BRAF*. Combined analysis showed that *KRAS* and/or *BRAF* mut pts had a PFS comparable to that of wt pts (13.1 vs 12.0 months; HR = 1.26, p = 0.456). OS data are still immature.
Conclusions: The outcome of mCRC pts treated with first-line FOLFOXIRI+BV does not differ on the basis of *KRAS* and/or *BRAF* status. Therefore it could be suggested that the triplet combination may counterbalance the negative prognostic impact of such mutations. These preliminary data need confirmation in larger prospective studies.