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TIE2-expressing Myeloid Cells Are Predictive Markers for Bevacizumab in Metastatic Colorectal Cancer

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Background: The purpose of this study was to investigate the potential of TIE2-expressing myeloid cells (TEMs) as surrogate markers of clinical outcome in metastatic colorectal cancer patients to identify responders to first-line bevacizumab in combination with chemotherapy.
Methods: Whole blood samples were analyzed prior to initiation of treatment and on days 4 and 14. TEMs were then isolated and enumerated using flow cytometry. The proportions of TEMs (TIE2-positive, CD11b-positive, CD45-positive and VEGFR2-negative fractions) were calculated as percentages of the total number of mononuclear cells after evaluation of at least 50,000 cellular events.
Results: From July 2007 to September 2009, 51 patients with measurable metastatic colorectal cancer to first-line bevacizumab in combination with FOLFOX were enrolled onto a prospective study. Pts characteristics were as follows: median age: 58 years (range 27−72), PS 0/1: 51/0, Colon/Rectum: 27/24, metastatic site (liver+/−: 30/21, lung+/−: 25/26, bone+/−: 2/49, peritoneum+/−: 10/41, lymph node+/−: 20/31, local+/−: 3/48), best response rates were 70.6% (CR/PR/SD/PD: 2/34/10/5). Patients with $\geqslant$6% levels of TEMs at the baseline had the shorter median progression-free survival (PFS) (6.6 months; 95% CI, 5.9−7.4), than the median PFS of <6% levels of TEMs (15.2 months; 95% CI, 10.2–20.2) ($p < 0.001$). Patients with $\geqslant$6% proportion of TEMs at the baseline had the shorter median overall survival (OS), than the median OS of <6% proportion of TEMs ($p < 0.001$). In univariate analysis, liver metastasis, lung metastasis, and TEMs at the baseline predicted PFS, and lung metastasis and TEMs at the baseline predicted OS. In order to evaluate the independent predictive effect of chemotherapy, multivariate Cox regression analysis was carried out. TEMs at the baseline were the strongest predictor.
Conclusion Levels of TEMs at the baseline were correlated with the prognosis of bevacizumab combination chemotherapy, suggesting that this surrogate marker might play a core role in the selection of candidates for bevacizumab treatment.

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Study 20050203/PRIME − Effect of Post-Progression Anti-Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibody (mAb) Therapy in Patients With Wild-Type (WT) KRas Metastatic Colorectal Cancer (mCRC)

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Background: Panitumumab (pmab), a fully human anti-EGFR mAb, is approved for the treatment of chemorefractory WT *KRAS* mCRC in Europe. Results from the randomized, multi-center 20050203 study with FOLFOX4 +/− pmab for 1st-line therapy demonstrated pmab significantly improved progression-free survival in patients with WT *KRAS* mCRC. A strong trend toward improved overall survival (OS) in the pmab + FOLFOX4 vs FOLFOX4 arm was also observed. Post-progression EGFR mAb use in the control arm may have attenuated the OS results. This analysis, based on data for the primary efficacy results, evaluates the impact of subsequent anti-EGFR mAb therapy on OS in patients with WT *KRAS* mCRC.
Methods: The effect of pmab to OS adjusting for the use of subsequent anti-EGFR mAb therapies was estimated using 3 popular statistical methods for WT *KRAS* patients. Branson & Whitehead estimates the effect of randomized treatment as if no patients in the FOLFOX4 arm received subsequent anti-EGFR mAb therapy. The rank preserving structural failure time model identifies the survival differences that would have been observed had all patients stayed on protocol treatment. Law's method considers patients who received post-progression therapy as having a different underlying prognosis than those who did not.
Results: The median OS for the pmab + FOLFOX4 vs FOLFOX4 arm was 23.9 vs 19.7 months (HR = 0.83; 95% CI, 0.67 to 1.02; P = 0.072). 18% of patients in a median time to use of 10.8 months received subsequent anti-EGFR mAb therapy in the FOLFOX4 arm. Improved OS was consistently observed by three OS sensitivity models compared with the primary OS analysis when accounting for subsequent anti-EGFR mAb use. Results are shown in the table.
Conclusions: Patients receiving FOLFOX4 alone had earlier and more frequent post-progression treatment with anti-EGFR mAb therapy compared with those receiving pmab + FOLFOX4. OS sensitivity analyses by three separate methods suggest that OS in patients with WT *KRAS* mCRC may have been attenuated by subsequent anti-EGFR mAb therapy.

	WT *KRAS*		
	Pmab+FOLFOX4	FOLFOX4 alone	HR (95% CI)
Study 20050203 (primary results)	n = 325	n = 331	
Median OS, mos (95% CI)	23.9 (20.3–28.3)	19.7 (17.6–22.6)	0.83 (0.67–1.02)
Post-progression anti-EGFR mAb therapy, n (%)	26 (8.0)	59 (17.8)	
Median time to subsequent anti-EGFR mAb therapy use, mos	17.9	10.8	
OS sensitivity analysis			
Branson-Whitehead[a]			0.80 (0.63–1.01)
Rank preserving structural failure time model[b]			0.76 (0.59–0.97)
Law's method[c]			0.52 (0.40–0.67)

[a]Branson and Whitehead, 2002; [b]Robins and Tsiatis, 1992; [c]Law and Kaldor, 1996.
mos = months; CI = confidence interval.

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Phase II Study of Panitumumab With Irinotecan for Patients With KRas Wild-type Metastatic Colorectal Cancer (MCRC) Refractory to Standard Chemotherapy − a GERCor Study

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Background: Panitumumab alone in third-line chemotherapy increased Objective Response Rate (ORR) from 0 to 17% [95% CI 11%-25%] and prolonged Progression-free survival (PFS) versus best supportive care in patients (pts) with chemorefractory *KRAS* wild-type (WT) MCRC (Amado et al, J Clin Oncol 2008). This trial (NCT00655499) was evaluating the combination of panitumumab and irinotecan in the same population.
Material and Methods: Main inclusion criteria were: pts with *KRAS* WT MCRC refractory to standard FOLFOX or XELOX ± bevacizumab **and** irinotecan alone or FOLFIRI or CAPIRI ± bevacizumab, PS 0−2, age 18−80 years, bilirubin level $\leqslant$1.5xULN, no prior therapy with EGFR inhibitors. *KRAS* status was assessed in each center for inclusion and a central assessment was done for confirmation after inclusion (allelic discrimination on tumour DNA). Pts received panitumumab (day 1: 6 mg/kg) and irinotecan (day 1: 180 mg/m^2) Q2W until disease progression or unacceptable toxicity. Tumour evaluation was performed every 2 months (RECIST 1.0). The primary endpoint was ORR, with an anticipated rate of 30% and an expected 95% CI between 18.2% and 41.8%.
Results: Sixty-nine pts were included in 12 centers. Four pts were not eligible (2 received EGFR inhibitor, 1 did not receive irinotecan, and 1 received concomitant bevacizumab) and 4 had KRAS mutation at central assessment (4/64:6%). The ORR (n = 61) was 32.8% [95% CI 21.2–44.4] (CR: N = 3, PR: N = 17); 22 (36.1%) pts had stable disease, 18 (29.5%) pts had a progressive disease, and 1 (1.6%) was not evaluable (unacceptable skin toxicity). After a median follow-up of 16.8 months, median PFS and median OS were 6.0 months [95% CI 4.6−7.9] and 14.5 months [95% CI 6.8–18.2], respectively. Three (4.9%) pts stopped treatment for limiting toxicity without toxic death. Most frequent grade 3/4 toxicities were: folliculitis 19.6%, diarrhea 14.7%, and neutropenia 13.1%. There were no infusion reactions. To date, WT KRAS/mBRAF pts (N = 5 among 48 pts analyzed for BRAF) had disease progression at first evaluation. The ancillary study evaluating mutation for BRAF, NRAS and KRAS 61 is ongoing and will be presented.
Conclusions: This trial reached its primary endpoint with an ORR of 32.8%. These results suggest that the combination of panitumumab and irinotecan in third-line chemotherapy should be preferred to panitumumab monotherapy in pts with *KRAS* WT MCRC refractory to standard chemotherapy. Analysis of other tumoral mutations that KRAS, can help to better define the population to treat with this combination.