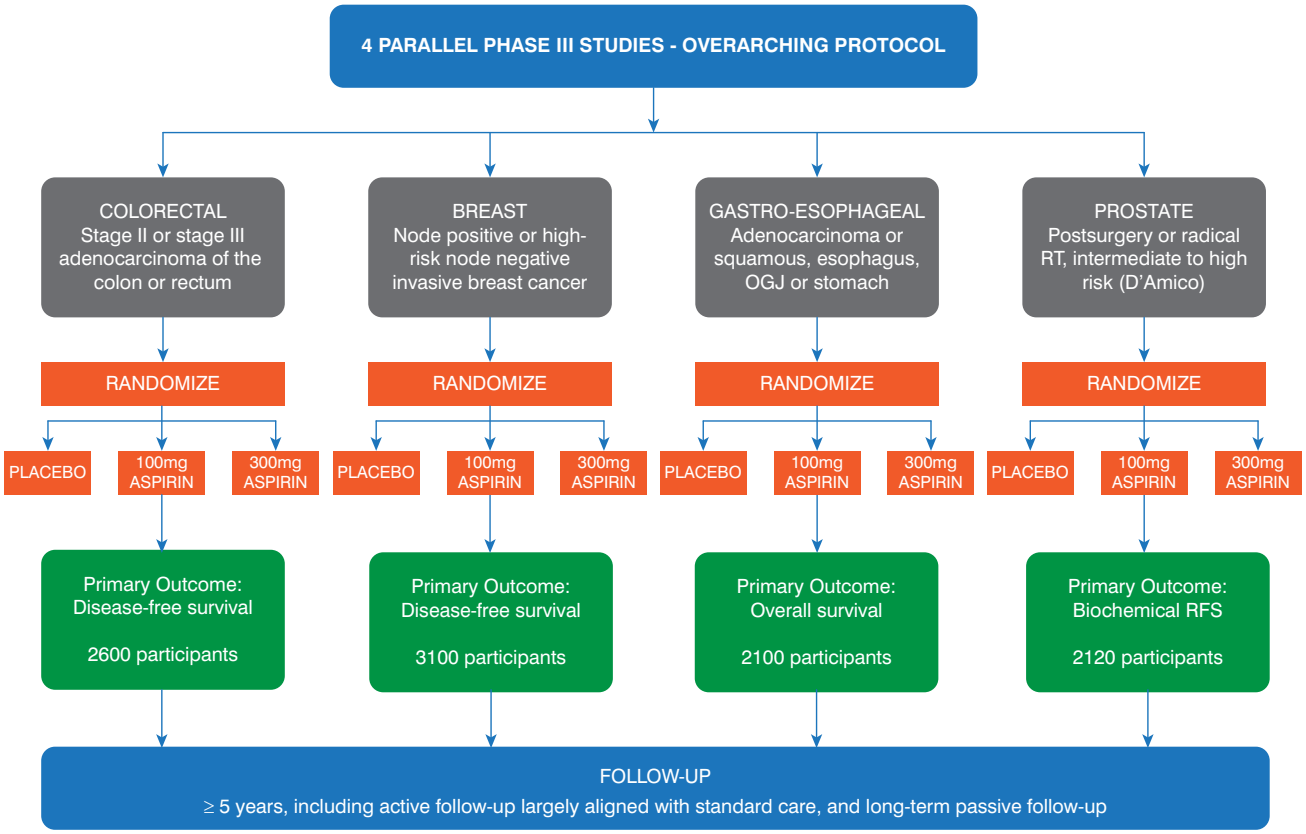
Figure 1. Add-Aspirin Study Plan



OGJ=esophagogastric junction; RFS=relapse-free survival; RT=radiation therapy

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New Analysis of CRYSTAL Results Supports Patient Selection According to *RAS* Mutation Status to Maximize Benefit From CET Therapy

Written by Toni Rizzo

The randomized Phase 3 Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer trial [CRYSTAL; Van Cutsem E et al. *N Engl J Med* 2009] investigated the efficacy and safety of cetuximab combined with a simplified regimen of leucovorin–5-flourouracil–irinotecan (FOLFIRI) for the initial treatment of metastatic colorectal cancer. The study found that cetuximab (CET) added to FOLFIRI improved progression-free survival (PFS), overall survival (OS), and response in patients with *KRAS* 12/13 (exon 2) wild-type disease [Van Cutsem E et al. *N Engl J Med* 2009; Van Cutsem E et al. *J Clin Oncol* 2011]. Patients with *KRAS* exon 2 mutations did not benefit from treatment.

The aim of this analysis of the CRYSTAL study [*Ann Oncol* 2014 (abstr O-0020); Ciardello F et al. *J Clin Oncol* 2014 (abstr 3506)], presented by Eric Van Cutsem, MD, Department of Clinical Digestive Oncology, Leuven Cancer Institute, UZ Leuven, Leuven, Belgium, was to assess the efficacy of CET added to FOLFIRI in patients who had metastatic colorectal cancer with new *RAS* mutations.

KRAS exon 2 wild-type tumor samples from CRYSTAL study patients were screened for 26 new *RAS* mutations in 4 additional *KRAS* codons (exons 3 and 4) and 6 *NRAS* codons (exons 2, 3, and 4) using a technique based on polymerase chain reaction (PCR) amplification of single target DNA molecules. Flow cytometry and fluorescent probes were used to identify wild-type and mutant sequences. The ratio of mutant to wild-type *RAS* DNA

Table 1. CRYSTAL Trial Outcomes of Cetuximab Added to FOLFIRI

	RAS Wild-Type (All Loci)		New *RAS* Mutations		*RAS* Mutations (Any Locus)	
Outcomes	**FOLFIRI + Cetuximab**	**FOLFIRI**	**FOLFIRI + Cetuximab**	**FOLFIRI**	**FOLFIRI + Cetuximab**	**FOLFIRI**
Response rate, %	66.3	38.6	34.4	35.5	31.7	36.0
OR (95% CI; p value)	3.11 (2.03 to 4.78; < .0002)		1.02 (0.33 to 3.15; .97)		0.85 (0.58 to 1.25; .40)	
Median PFS, months	11.4	8.4	7.2	6.9	7.4	7.5
HR (95% CI; p value)	0.56 (0.41 to 0.76; .0002)		0.81 (0.39 to 1.67; .56)		1.10 (0.85 to 1.42; .47)	
Median OS, months	28.4	20.2	18.2	20.7	16.4	17.7
HR (95% CI; p value)	0.69 (0.54 to 0.88; .0024)		1.22 (0.69 to 2.16; .50)		1.05 (0.86 to 1.28; .64)	

OR=odds ratio; PFS=progression-free survival; OS=overall survival.
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molecules in the original tumor DNA sample was determined for patients in whom mutations were identified. A 5% cutoff was selected for the analysis. Treatment outcomes were evaluated according to whether the patients had *RAS* wild-type, new *RAS* mutations, or *RAS* mutations (*KRAS* exon 2 or new *RAS*).

Mutation status was evaluated in 430 of 666 patients (65%) with *KRAS* exon 2 wild-type tumors. Using the 5% cutoff, new *RAS* mutations were identified in 63 of the 430 patients (15%). Comparison of outcomes with mutation status showed that patients with *RAS* wild-type (all loci) tumors treated with CET plus FOLFIRI versus FOLFIRI alone had significantly better response rates (66.3% vs 38.6%; odds ratio, 3.11; 95% CI, 2.03 to 4.78; p < .0001), median PFS (11.4 vs 8.4 months; HR, 0.56; 95% CI, 0.41 to 0.76; p = .0002), and median OS (28.4 vs 20.2 months; HR, 0.69; 95% CI, 0.54 to 0.88; p = .0024). The subgroup with new *RAS* mutations and those with *RAS* mutations at any locus derived no benefit from the addition of CET to FOLFIRI with respect to response rate, PFS, and OS (Table 1).

Analysis of treatment outcomes in subgroups with new *RAS* mutations defined according to a range of sensitivity cutoffs from 20% to .1% supported the use of 5% as a clinically appropriate cutoff point for defining a subgroup of patients most likely to benefit from the addition of CET to FOLFIRI.

Dr. Van Cutsem concluded that in the first-line treatment of metastatic colorectal cancer, patients with *RAS* wild-type tumors derived a marked benefit throughout all efficacy end points with the addition of CET to FOLFIRI. Patients with *RAS* tumor mutations did not benefit from treatment with CET. These results support patient selection according to *RAS* mutation status to maximize benefit from CET therapy.

MM-398 Plus 5-FU and LV Extend OS and PFS in mPAC

Written by Emma Hitt Nichols, PhD

The addition of MM-398 to 5-flurouracil (5-FU) and leucovorin (LV) extended overall survival (OS) and progression-free survival (PFS) in patients with metastatic pancreatic adenocarcinoma (mPAC) who had previously received gemcitabine-based treatment when compared with 5-FU plus LV alone. Andrea Wang-Gillam, MD, PhD, Washington University School of Medicine in St Louis, St Louis, Missouri, USA, presented data from the Study of MM-398 With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer [NAPOLI 1; Von Hoff D et al. *Ann Oncol*. 2014 (abstr O-0003)].

A novel formulation, MM-398 is irinotecan that is encapsulated with a long-circulating nanoliposome. In a Phase 2 trial, MM-398 demonstrated clinical activity in patients with mPAC who had received gemcitabine-based treatment. The purpose of the NAPOLI 1 trial was to further evaluate the safety and efficacy of MM-398 in patients with mPAC.