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.
Reproduced from Ciardello F et al. *J Clin Oncol* 2014 (abstr 3506).

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.

In the open-label Phase 3 NAPOLI 1 trial, 417 patients with mPAC who had received gemcitabine-based therapy were randomly assigned in a 1:1:1 fashion to receive MM-398 monotherapy, 5-FU plus LV (control arm), or MM-398 plus 5-FU and LV. The primary end point was OS, which was compared with that of the control arm. In the study, 398 patients received treatment. Baseline characteristics were similar among all arms, with head of pancreas and liver metastases present in 61% and 68% of patients, respectively.

Treatment with MM-398 plus 5-FU and LV resulted in significant improvements in OS, PFS, time-to-treatment failure, and overall response rate. In patients who received MM-398 plus 5-FU and LV, median OS was 6.1 months (95% CI, 4.8 to 8.9), compared with 4.2 months (95% CI, 3.3 to 5.3) in patients who received 5-FU and LV alone (HR, 0.67; $p = .012$). Patients who received MM-398 plus 5-FU and LV experienced a median PFS of 3.1 months (95% CI, 2.7 to 4.2), compared with 1.5 months (95% CI, 1.4 to 1.8) for those in the control arm (HR, 0.56; $p < .001$). MM-398 monotherapy did not improve any parameters when compared with the control arm.

Grade 3/4 adverse events occurred more frequently in the arm receiving MM-398 plus 5-FU and LV and included a decrease in neutrophil count, as well as fatigue, diarrhea, and vomiting. Other adverse events included febrile neutropenia and sepsis.

In conclusion, Dr Wang-Gillam indicated that, in her opinion, the data from the NAPOLI 1 trial suggest that the addition of MM-398 to 5-FU and LV in patients with mPAC results in a substantial improvement in OS and PFS when compared with 5-FU plus LV alone.

MPACT Trial: SPARC Not Predictive or Prognostic in Pancreatic Cancer

Written by Emma Hitt Nichols, PhD

Secreted protein acidic and rich in cysteine (SPARC) protein expression levels were not associated with overall survival (OS) or progression-free survival (PFS) in patients with metastatic pancreatic cancer from the Phase 3 Study of ABI-007 (Albumin-Bound Paclitaxel) plus Gemcitabine Versus Gemcitabine in Metastatic Adenocarcinoma of the Pancreas trial [MPACT; Hidalgo M et al. *Ann Oncol* 2014 (abstr O-0003)]. Manuel Hidalgo, MD, PhD, Centro Nacional de Investigaciones Oncológicas, Madrid, Spain, presented data from a subanalysis of the MPACT trial.

Previous studies have suggested that increased expression of SPARC is correlated with decreased OS in patients with resectable pancreatic cancer [Infante JR et al. *J Clin Oncol* 2007]. In addition, a Phase 1/2 trial demonstrated that lower levels of SPARC were significantly associated with prolonged OS ($p = .043$) [Von Hoff DD et al. *J Clin Oncol* 2011]. The purpose of this subanalysis of the MPACT trial was to further evaluate the relationship between SPARC and metastatic pancreatic cancer outcomes.

For this analysis, stromal fibroblasts and tumor epithelia harvested from predominantly metastatic lesion were assessed for SPARC levels using immunohistochemistry (IHC) with an anti-SPARC monoclonal antibody that was scored by 2 blinded pathologists [Hidalgo M et al. *Ann Oncol* 2014 (abstr O-0003)]. Stromal SPARC levels were considered high if ≥ 50% of fibroblasts stained positive. Tumor SPARC was measured assessing the histoscore, a well-established method for scoring protein expression in tissue that has heterogeneous staining in cell membranes, cytoplasm, and cell nuclei. Tumor SPARC was considered high if the histoscore was ≥ 100 and negative if the histoscore was 0. Enzyme-linked immunosorbent assay was used to evaluate SPARC levels in plasma collected at baseline and every 8 weeks in the MPACT trial. The IHC assay demonstrated 86% concordance between the Phase 1/2 and MPACT trials, and stromal SPARC was evaluable in 30% of patients from the MPACT trial.

Stromal SPARC expression was high in 71 out of 256 samples and was not associated with OS (HR, 1.019; $p = .903$). In addition, tumor epithelial SPARC, which was low or negative in most samples, was also not associated with OS. Evaluable in 40% of patients, plasma SPARC levels were not significantly different between baseline and time points, and they were not associated with OS. PFS was not associated with SPARC expression levels in any of the samples.

In conclusion, Prof. Hidalgo indicated that, in his opinion, the data from this analysis of the MPACT trial suggest that SPARC expression was not prognostic for OS and was not predictive of treatment response in patients with metastatic pancreatic cancer. Therefore, SPARC analysis requires further study and is not yet recommended to be used for treatment decisions in this patient population.