Table 2. Tumor Response Rates in REACH

	Ramucirumab, n = 283	Placebo, n = 282	*P* Value
Objective response (CR + PR), n (%)	20 (7.1)	2 (0.7)	< .0001
Disease control rate (CR + PR + SD), n (%)	159 (56.2)	129 (45.7)	.0110
CR, n (%)	1 (0.4)	0	
PR, n (%)	19 (6.7)	2 (0.7)	
SD, n (%)	139 (49.1)	127 (45.0)	
PD, n (%)	97 (34.3)	129 (45.7)	
Not evaluable, n (%)	27 (9.5)	24 (8.5)	

CR, complete response; PD, progressive disease; PR, partial response; REACH, the Ramucirumab Second-Line Treatment in Patients With Hepatocellular Carcinoma After First-Line Therapy With Sorafenib study; SD, stable disease.

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The objective response rates were 7.1% in the RAM arm and 0.7% in the PBO arm ($P < .0001$), and the disease control rates were 56.2% and 45.7% ($P = .0110$), respectively (Table 2).

Two hundred and fifty patients had a baseline AFP level ≥ 400 ng/mL. In a prespecified analysis of OS in this subgroup, the OS HR in the RAM group compared with PBO was 0.674 ($P = .0059$), with a median OS of 7.8 months in the RAM group vs 4.2 months in the PBO group.

Dr Zhu concluded that although REACH did not demonstrate a significant improvement in OS with RAM in the intent-to-treat population, an elevated baseline AFP may select a population likely to benefit. Further investigation of RAM is warranted based on the REACH results and the unmet need in this disease.

Phase 3 Trial to Compare Postoperative Chemotherapy With Observation in Stage I or II Endometrial Cancer

Written by Maria Vinall

Patients with stage I or II endometrial cancer are generally treated with surgery. Despite radical surgery, however, patients with medium- or high-risk stage I and II endometrial cancers are still at significant risk of local and distant progression. Adjuvant radiotherapy has not been shown to improve survival, and adjuvant chemotherapy alone has shown greater survival benefit in patients with more advanced disease [Creutzberg CL et al. Curr Oncol Rep. 2011]. The current phase 3 study [NCT01244789] is preparing to evaluate whether survival can be improved in intermediate- and high-risk early-stage patients by offering postoperative chemotherapy instead of postoperative observation alone (standard strategy).

Frederic Amant, MD, EORTC and University of Leuven, Leuven, Belgium, presented the design of the study, which will evaluate this premise in patients with medium- or high-risk node-negative stage I or II endometrial cancer. Eligible patients must have a diagnosis of stage I grade 3, stage II, or stage I or II type 2 endometrioid adenocarcinoma and have undergone hysterectomy and bilateral salpingo- oophorectomy and pelvic lymphadenectomy (LNE; minimum, 12 pelvic nodes; para-aortic LNE optional). All patients are required to be World Health Organization performance status 0 to 2.

Eligible patients will be stratified by histology (endometrioid vs nonendometrioid), stage (1a vs 1b vs 2 disease), para-aortic (≥ 10) and pelvic (≥ 20) LNE versus lesser LNE, and brachytherapy (planned yes/no); they will then be randomized (1:1) to postoperative adjuvant paclitaxel (175 mg/m^2) and carboplatin (AUC5) every 3 weeks for a total of 6 courses or postoperative follow-up without any further treatment. Adjuvant brachytherapy is permitted in both arms; external beam radiotherapy is not allowed. All patients will be followed for a minimum of 3 years.

The primary study end point is overall survival. Secondary end points include disease-specific survival, progression-free survival, toxicity, quality of life based on patient-reported outcomes (EORTC QLQ-C30 and QLQ-EN24—quality-of-life questionnaires for cancer and endometrial cancer), as well as the rates of isolated

pelvic relapse (central and/or pelvic wall), isolated distant relapse, and mix of local and distant relapse. This trial is powered to detect a survival difference of 12%, from 74% to 86% in the endometrioid subgroup for the preplanned subgroup analyses; all other subgroup analyses are exploratory.

Additional translational research objectives include an evaluation of the prognostic and predictive values of tumor biomarkers for clinical outcome, stage, grade of disease, and presence of certain toxicities to chemotherapy. Objectives also include assessment of protein expression and prognostic or predictive markers (eg, EGFR, KRAS, BRAF, NRAS, PIK3CA, PTEN, TP53, and FBXW7) for use in characterizing patients for potential future individual treatment strategies.

This international trial is now enrolling new sites. As of the date of presentation, 44 patients had been randomized to treatment, with a total expected enrollment of 678 patients.

SOR as Adjuvant Therapy After Resection for Pancreatic Cancer Does Not Improve DFS

Written by Wayne Kuznar

Adding sorafenib (SOR) to gemcitabine (GEM) as adjuvant therapy for patients after R1 resection for pancreatic cancer does not improve disease-free survival (DFS) or overall survival (OS) compared with GEM alone. Marianne Sinn, Charité-Universitätsmedizin, Berlin, Germany, presented results from the phase 2b CONKO-006 study.

Even after successful surgery intended as curative, up to 90% of patients with pancreatic cancer suffer a relapse. Adjuvant chemotherapy with GEM can improve DFS and OS, and more importantly, the rate of cure [Oettle H et al. *JAMA*. 2013]. In the CONKO-001 study [ISRCTN34802808], which compared 6 months of postoperative GEM with observation only, 5-year survival was improved from 10.4% to 20.7% with the addition of GEM. R1-resected patients seem to benefit just as well from adjuvant treatment, she said, but because the benefits were discovered in subgroup analysis in CONKO-001, evidence for the benefit remains limited.

On the basis of these results, the multicenter German CONKO-006 trial was designed to investigate the utility of prolonged postoperative therapy with 12 months of the combination of GEM and SOR in patients after R1 resection. The study included 122 patients with R1 resection of pancreatic adenocarcinoma who were randomized in a double-blind fashion to 48 weeks of either GEM 1000 mg/m^2 IV on days 1, 8, and 15, and repeated on day 29, plus continuous SOR 200 mg PO BID, or GEM plus placebo (PBO), for a planned 12 cycles. The definition of R1 resection margin was standardized and documented in the study protocol, including multicolor margin staining and axial slicing and an obligatory analysis of the retroperitoneal resection margin.

SOR was chosen as an adjuvant add-on because it interrupts tumor proliferation by inhibiting Raf kinases and the Raf/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase pathway, said Prof Sinn, and because of its tumor-specific angiogenesis through inhibition of the vascular endothelial growth factor receptor, epidermal growth factor receptor, and platelet-derived growth factor receptor [Siu LL et al. *Clin Cancer Res*. 2006].

Patient characteristics were well balanced between the SOR + GEM and the GEM + PBO groups, including median age (63 years for both), tumor stage T3 and + T4 (97% for both), and the percentage of patients with positive nodes (86% for SOR; 85% for GEM).

Toxicities and side effects, although not severe, were similar to those observed in other studies of GEM and SOR, and included diarrhea, skin reactions in the hands and feet, hypertension, tiredness and fatigue, hematology (leukocytopenia, neutropenia, and thrombocytopenia), and elevated gamma glutamyl transferase.

There was no relevant difference in median treatment duration (26.6 weeks in the SOR + GEM arm vs 25.1 weeks in the GEM + PBO arm). Thirty-three percent of patients in the SOR + GEM arm and 22% in the GEM + PBO arm completed the planned 12 cycles. Thirty-five percent of patients in the SOR + GEM arm and 46% in the GEM + PBO arm discontinued treatment due to disease recurrence.

The primary end point of median DFS from surgery was not significantly different at 9.6 vs 10.7 months in the SOR + GEM and the GEM + PBO arms, respectively ($P = .89$). Median DFS from randomization was 8.7 vs 9.5 months in the 2 groups, respectively. The relapse rate after 18 months was 50% with SOR + GEM and 49% with GEM + PBO. The secondary end point of OS was also not significantly different between the 2 groups. Median OS from surgery was 18.2 months in the SOR + GEM arm and 17.1 months in the GEM + PBO arm ($P = .94$). Median OS from randomization was 17.6 and 15.6 months, respectively, and 1-year survival was 68% and 70%, respectively.

The study data confirm that R1-resected patients must still be considered a high-risk cohort, concluded Prof Sinn.