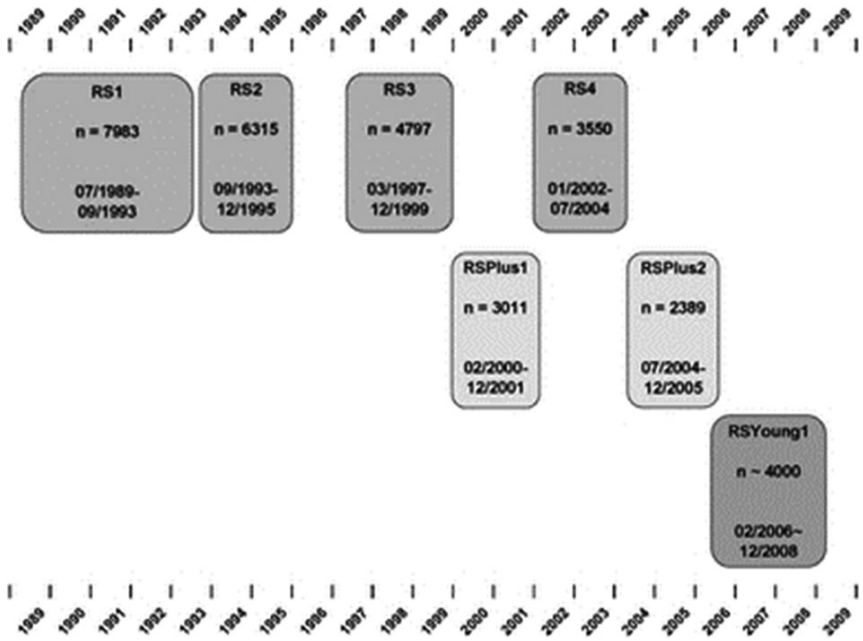
Figure 1. The Rotterdam Study



RS=Rotterdam Study; RS1=baseline examination of original cohort; RS2, RS3, and RS4=reexaminations of the original cohort; RSPlus1=extension of the cohort with individuals in the study district who became age 55 years since the start of the study or those age 55 years or older who migrated into the study district; RSPlus2=reexamination of the extension cohort; RSYoung1=baseline examination of all individuals age 45 years or older living in the study district who had not been examined.

Hofman A et al. The Rotterdam Study: objectives and design update. *Eur J Epidemiol*. 2007; 22: 819–829. With permission from Springer Publishing Company.

linear relationship was observed between SFAs intake and CRC (HR, 0.97; 95% CI, 0.95 to 0.995) among participants with high fiber intake. An increased risk of CRC in participants with low serum cholesterol was associated with a higher PUFAs intake (p *interaction* = .01 for n-3 PUFA and fiber intake; p *interaction* = .05 for n-6 PUFAs and serum cholesterol).

Although data from this study suggest that dietary fat intake interacts with dietary fiber and blood lipids to increase the risk of CRC, further investigation is required to determine how other dietary and nondietary factors affect this risk.

RAINBOW Study Shows Significant Benefits in OS and PFS in Western Patients With Gastric Cancer

Written by Muriel Cunningham

The Study of Paclitaxel With or Without Ramucirumab (IMC-1211B) in Metastatic Gastric Adenocarcinoma [RAINBOW; NCT01170663] is an international double-blind Phase 3 study of patients with metastatic gastric or gastroesophageal junction adenocarcinoma. Eligible patients were those with disease progression within 4 months after receiving first-line platinum- and fluoropyrimidine-based combination chemotherapy, ECOG Performance Status ≤ 1, and adequate organ function. Patients were randomized to treatment with paclitaxel (PTX), 80 mg/m^2, on Days 1, 8, and 15 of a 4-week cycle, combined with either the human immunoglobulin 1 vascular endothelial growth factor receptor 2 targeted antibody ramucirumab (RAM), 8 mg/kg, given intravenously Q2W, or placebo. Randomization was stratified by region, the time to progression after the initial dose of first-line therapy (< 6 vs ≥ 6 months), and whether or not the disease was measurable. Hansjochen Wilke, MD, Kliniken Essen-Mitte, Essen, Germany, presented the results from the planned region 1 subgroup analysis [Wilke H et al. *Ann Oncol*. 2014 (abstr O-0006)]. Region 1 consisted of Europe, Israel, the United States, and Australia; region 2 included Argentina, Brazil, Chile, and Mexico; and Japan, South Korea, Hong Kong, Singapore, and Taiwan made up region 3.

After randomization, patients received treatment and were monitored until disease progression, toxicity

requiring study drug discontinuation, protocol noncompliance, or withdrawal of consent. Overall survival (OS) was the primary end point. Progression-free survival (PFS), objective response rate (ORR), time to progression (TTP), and safety were the secondary end points. A stratified log-rank test was used to compare OS and PFS between treatment groups. The ORR was calculated with a Cochran-Mantel-Haenszel test.

A total of 665 patients were randomized worldwide from December 2010 to September 2012 [Wilke H et al. *Ann Oncol.* 2014 (abstr O-0006); *J Clin Oncol.* 2014 (abstr LBA7)]. Of these, 398 were from region 1: 198 in the RAM + PTX group and 200 receiving PTX alone. The baseline characteristics of the patients were considered well balanced between the 2 treatment groups. The median OS was 8.57 months for patients in the RAM + PTX group and 5.91 months for patients receiving PTX alone (HR, 0.726; 95% CI, 0.580 to 0.909; p = .0050). Median PFS was 4.24 months for RAM + PTX versus 2.83 months for PTX alone (HR, 0.631; 95% CI, 0.506 to 0.786; p < .0001). The median TTP was 5.36 months for the RAM + PTX group, compared with 3.15 months for PTX alone (p = .0002). The ORR was 26.8% for patients receiving RAM + PTX and 13.0% in the PTX arm (p = .0004). The significant benefits observed in the Western population were consistent with those observed in the overall intent-to-treat population.

The adverse event profile of the region 1 subgroup was also considered similar to that of the overall patient population. Adverse events grade 3 or higher that occurred in >5% of patients receiving RAM + PTX were neutropenia (32.1% [RAM + PTX] vs 14.7% [PTX]), hypertension (17.9% vs 2.0%), leukopenia (9.7% vs 4.1%), fatigue (10.2% vs 5.1%), asthenia (7.7% vs 2.0%), anemia (6.6% vs 6.1%), abdominal pain (6.6% vs 4.6%), and general physical health deterioration (5.6% in both treatment arms).

These results demonstrate that in the Western population, just as in the overall study population, the combination of RAM and PTX resulted in better survival parameters at the expense of significantly increased risk for neutropenia.

No Benefit to Adding Oxaliplatin to Capecitabine in Locally Advanced Rectal Adenocarcinoma

Written by Lynne Lederman

Treatment options for locally advanced rectal cancer include chemotherapy, surgery, and radiation therapy. It is not known if adding oxaliplatin to capecitabine would increase the efficacy of chemotherapy for patients with locally advanced rectal cancer. Hans-Joachim Schmoll, MD, PhD, Martin Luther University Halle-Wittenberg, Halle, Germany, reported the disease-free survival (DFS) results from the interim analysis of Chemotherapy and Radiation Therapy Before Surgery Followed by Capecitabine With or Without Oxaliplatin in Treating Patients With Locally Advanced Rectal Cancer [PETACC-6; NCT00766155].

PETACC-6 is a randomized, Phase 3 trial to determine if the addition of oxaliplatin to preoperative oral fluoropyrimidine-based chemoradiation (CRT) followed by postoperative adjuvant fluoropyrimidine-based chemotherapy (CT) improves DFS in patients with locally advanced rectal adenocarcinoma [Schmoll HJ et al. *Ann Oncol* 2014 (abstr O-0017)]. PETACC-6 enrolled 1094 patients with rectal adenocarcinoma within 12 cm from the anal verge that was T3 or T4 and/or node-positive, nonmetastatic, and either resectable at the time of enrollment or expected to become resectable. Patients were randomly assigned 1:1 to receive 5 weeks of preoperative CRT with capecitabine, followed by 6 cycles of adjuvant CT with capecitabine (arm 1) or capecitabine plus oxaliplatin (arm 2) before and after surgery.

DFS was defined as the time from random assignment to the first event of loco-regional failure, distant failure, the appearance of a secondary cancer, or death. Unresectable tumors or distant metastases that were discovered at surgery were deemed failures at the time of surgery. To detect an increase in 3-year DFS with 80% power from 65% with capecitabine alone to 72% with capecitabine plus oxaliplatin (HR, .763) using a 2-sided alpha of 5%, 440 events were required; an interim analysis for early efficacy required 200 events.

Of the 547 patients in each arm, 543 in arm 1 and 528 in arm 2 began preoperative treatment (3 patients in arm 2 did not receive oxaliplatin); of these patients, 420 (77.3%) in arm 1 and 381 (72.6%) in arm 2 began postoperative chemotherapy per protocol. In arm 2, 45 patients (11.8%) did not receive postoperative oxaliplatin. Reasons for treatment discontinuation included progressive disease (3.9% in arm 1 vs 3.8% in arm 2), toxicity (7.7% vs 16.5%), complications of surgery (8.7% vs 9.1%), and patient refusal (5.9% vs 10.8%).

At the planned interim analysis, with a median follow-up of 31 months, there were 124 DFS events in arm 1 and 121 DFS events in arm 2 (adjusted HR, 1.036; 95% CI, 0.806 to 1.331; p = .781). The 3-year DFS in arm 1 was 74.5% (95% CI, 70.1% to 78.3%), which was higher than anticipated. The 3-year DFS in arm 2 was 73.9% (95% CI, 69.5% to 77.8%). The conditional power for the HR of 0.763 was only 7%. With 245 DFS events at 31 months of