

Progress in Personalized Therapy: *KRAS* Status Predicts Response to First-line Cetuximab for Metastatic Colorectal Cancer

Advancing the use of targeted agents for treating cancer has been linked with determining molecular markers that may predict response to therapy. At Sunday's Plenary Session, Eric Van Cutsem, MD, PhD, of the University Hospital Gasthuisberg at Leuven, Belgium, and colleagues revealed that patients who had colorectal tumors that expressed normal *KRAS*, a molecule involved in several physiologic pathways, showed better clinical responses when a cetuximab-based regimen is used as first-line therapy (Abstract 2).

At ASCO's 2007 Annual Meeting, Dr. Van Cutsem reported data from the phase III Cetuximab Combined with Irinotecan in First-line Therapy for Metastatic Colorectal Cancer (CRYSTAL) study,

which showed that patients with metastatic colorectal cancer (mCRC) had significantly better clinical responses when cetuximab was added to first-line FOLFIRI — a regimen of fluorouracil, leucovorin and irinotecan.

For the current study, Dr. Van Cutsem used available archival tumor samples from 540 of the 1,198 patients and reported that when clinical responses were re-evaluated based on whether tumors showed normal or mutant *KRAS* expression, progression-free survival and overall objective responses were better for patients with tumors that expressed normal *KRAS*.

Tumor samples were tested for the presence of mutations in codon 12/13 of *KRAS*, a commonly seen mutation. *KRAS* mutation was detected in 192 samples. The 36% frequency was similar to the *KRAS* mutational frequency observed in other studies. Of 348 tumor samples that expressed normal *KRAS*, Dr. Van Cutsem showed that when clinical responses were re-evaluated, 1-year progression-free survival rates were 25% and 43% for patients with normal *KRAS* tumors receiving FOLFIRI and the combination of cetuximab plus FOLFIRI, respectively. Median progression-free survival also improved for patients receiving cetuximab and FOLFIRI in the presence of normal *KRAS* tumors (8.7 vs. 9.9 months; hazard ratio: 0.68; $p = 0.017$). Overall the increase in the objective response rate was highly significant for patients who received cetuximab in combination with FOLFIRI (59.3% vs. 43.2% for patients receiving FOLFIRI alone; $p = 0.0025$).

When clinical responses were re-evaluated for the 192 patients whose tumors harbored the *KRAS* mutation, overall responses and progression-free survival were similar whether patients received FOLFIRI or FOLFIRI plus cetuximab.

See *KRAS*, Page 9A

INSIDE THIS SECTION

Cancer Prevention

Lung Cancer Screening Remains Controversial Despite Two New Studies..... 12A

Central Nervous System Tumors

Initial Treatment with Radiotherapy or Chemotherapy Provides Equivalent Progression-free Survival for Anaplastic Glioma..... 6A

Genitourinary (Prostate & Testes) Cancer

Thalidomide Offers Benefit in PSA-recurrent Localized Prostate Cancer..... 12A

Plenary Sessions

Progress in Genetic Analysis of Breast and Ovarian Cancers Offers New Opportunities for Intervention..... 4A

International Trial Establishes Role of Cetuximab for Advanced EGFR-expressing NSCLC..... 4A

Single Injection of Carboplatin Reported to be an Option for the Treatment of Stage I Seminoma..... 6A

Special Award Lectures

Pediatric Oncology Award Recipient Highlights Ongoing Challenges in Pediatric Brain Cancer..... 8A

Dr. Patricia A. Ganz Receives 2008 ASCO/American Cancer Society Award..... 10A

Special Sessions

ASCO/ECCO Session Sheds Light on the Therapeutic Oncology Vaccines..... 15A

Tumor Biology

Erythropoietin Receptor mRNA is Associated with Poor Local-regional Progression-free Survival for Unresected Head and Neck Cancers..... 14A

General Meeting Information

InBrief..... 2A

Late-breaking Abstracts..... 11A

CETUXIMAB + CHEMOTHERAPY IN *KRAS* WILD-TYPE: DATA CONSISTENCY

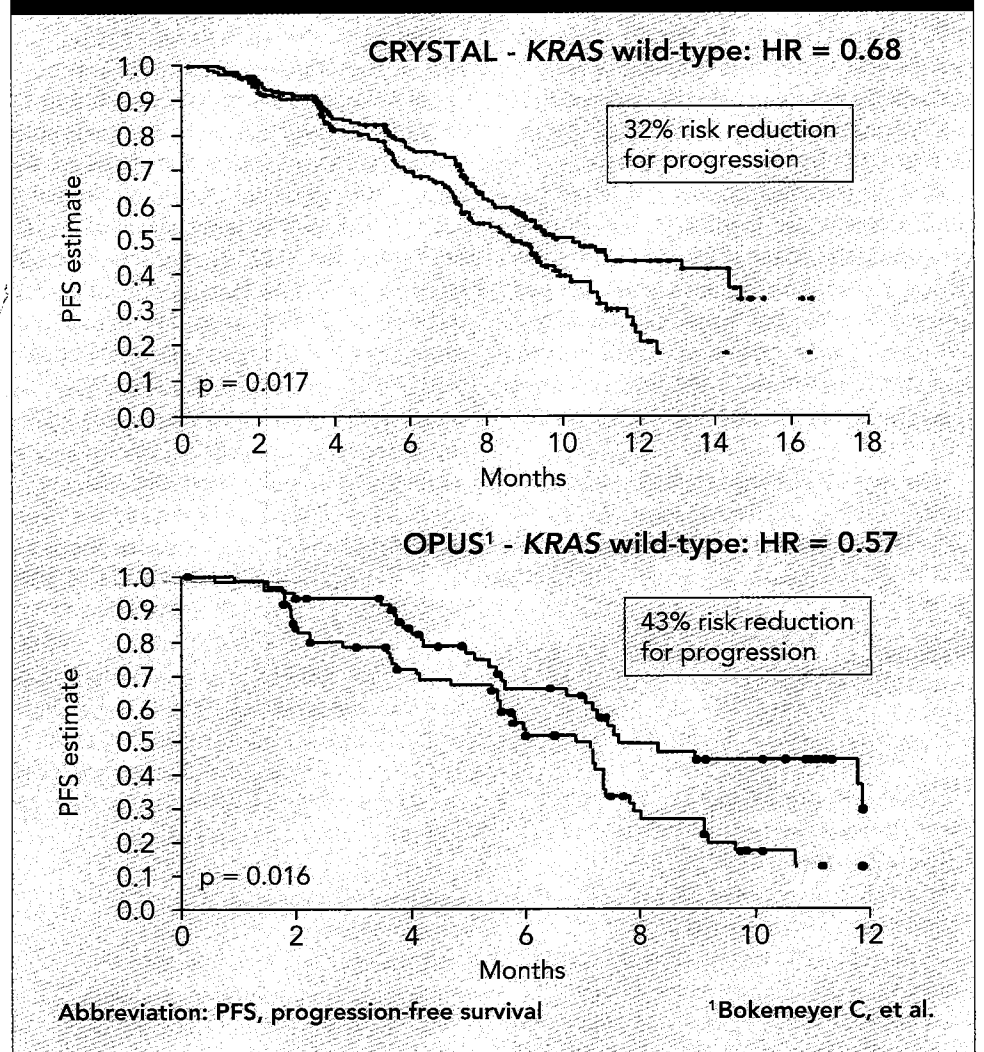


Figure 1. Progression-free survival curves from the CRYSTAL and OPUS studies for patients with normal *KRAS* status.

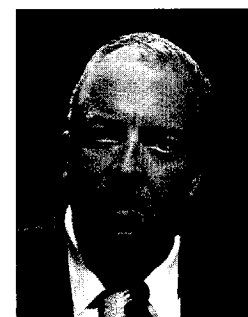
Zoledronic Acid Added to Endocrine Therapy Improves Outcome for Premenopausal Patients with Early Breast Cancer

Zoledronic acid has been found to increase disease-free survival by 36% and relapse-free survival by 35% for premenopausal patients who received adjuvant endocrine therapy for early breast cancer (Abstract LBA4). Michael Gnant, MD, of the Medical University of Vienna, Austria, presented the data on behalf of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) during Sunday's Plenary Session.

Adjuvant endocrine therapy with ovarian suppression is used as an effective alternative to standard cytotoxic chemotherapy for premenopausal patients with endocrine-responsive breast cancer. ABCSG-12 is the first study to compare endocrine suppression with goserelin plus tamoxifen to goserelin plus an aromatase inhibitor (anastrozole).

Adjuvant bisphosphonate therapy (zoledronic acid) was included in two of the four treatment arms both to mitigate the marked bone loss

associated with complete ovarian suppression and to explore whether the antitumor effects demonstrated previously in preclinical and clinical settings might translate into a longer time to disease recurrence and improved survival.



Michael Gnant, MD

The study was a randomized, open-label, phase III, modified 2x2, four-arm trial of oral tamoxifen and goserelin with or without zoledronic acid compared with oral anastrozole and goserelin with or without zoledronic acid for 3 years.

The primary endpoint of this trial was disease-free survival for the 903 patients who received

anastrozole compared with the 900 patients who received tamoxifen. Secondary endpoints included overall survival and the effect of the treatments on local-regional relapse. The effect of treatment on bone metastasis-free survival was considered to be an exploratory endpoint.

At a median follow-up of 60 months, overall 5-year disease-free survival was 94% and overall survival was 98.2%. No difference in disease-free survival was detected among patients who received tamoxifen and those patients who received anastrozole. There was no advantage in relapse-free or overall survival rates for anastrozole over tamoxifen.

In the analysis of zoledronic acid, the bisphosphonate improved the primary endpoint of disease-free survival (hazard ratio [HR] = 0.643,

See *Zoledronic Acid*, Page 2A

