**Cetuximab (Erbitux)**
**Presenter:** Eric Van Cutsem, MD, University Hospital Gasthuisberg, Leuven, The Netherlands

The epidermal growth factor receptor (EGFR) is expressed by most colorectal cancers. Cetuximab (Erbitux, Bristol-Myers Squibb) is an immunoglobulin (IgG1) monoclonal antibody that specifically targets EGFR with high affinity. Dr. Van Cutsem presented results of the CRYSTAL trial (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer). This is the first phase 3 study to assess the combination of cetuximab plus FOLFIRI as a first-line therapy for colorectal cancer. FOLFIRI consists of 5-fluorouracil (5-FU), leucovorin, 5-fluorouracil (5-FU), and irinotecan (Camptosar, Pfizer).

CRYSTAL included 1,217 patients (mean age, 61 years) with histologically confirmed unresectable metastatic colorectal cancer with EGFR expression in either the primary tumor or in metastases. Patients were chemotherapy-naive or had stopped prior therapy, excluding irinotecan, at least six months previously. They were randomly assigned to receive cetuximab plus FOLFIRI or FOLFIRI alone. The trial’s primary endpoint was progression-free survival. Reporting efficacy results, Dr. Van Cutsem said that CRYSTAL met its primary endpoint. For the cetuximab/FOLFIRI arm, progression-free survival was 8.9 months; for the FOLFIRI-alone arm, the rate was 8 months (15% reduction, hazard ratio [HR], 0.851; 95% confidence interval, 0.769-0.940; P = 0.0022). At one year, progression-free survival rates were 34% with cetuximab/FOLFIRI and 23% for FOLFIRI alone.

The overall response rate was higher for the combination arm (46.9%) than with the FOLFIRI-alone arm (38.7%), and the disease control rate was similar for both groups (about 85%). Significantly more cetuximab/FOLFIRI patients (6%) were able to have surgery with curative intent, compared with the FOLFIRI-alone group (2.5%). More patients receiving the combination (4.3%) had no residual tumor after resection, compared with 1.5% receiving FOLFIRI alone. More patients with metastases only to the liver had no residual tumor (9.8% receiving cetuximab/FOLFIRI vs. 4.5% receiving only FOLFIRI).

Treatment discontinuation rates were slightly higher with FOLFIRI alone (10.5%) than with the combination (81 patients). Grade 3 and 4 adverse events, however, occurred more often with cetuximab/FOLFIRI (78%) than with FOLFIRI alone (59.5%). Rates of neutropenia (26.7% with the combination vs. 23.3% with FOLFIRI only) and of febrile neutropenia (2.7% with the combination vs. 2.2%) were generally similar.

Skin reactions were higher with the cetuximab/FOLFIRI regimen (18.7%) than with FOLFIRI (0.2%), and these rates strongly correlated with efficacy. None of the patients had grade 4 lesions, and there were no cetuximab-related deaths.

Dr. Van Cutsem concluded that the CRYSTAL trial met its primary objective of demonstrating that adding cetuximab to FOLFIRI increased progression-free survival.

**Dasatinib (Sprycel)**
**Presenter:** Neil P. Shah, MD, University of California School of Medicine, San Francisco

The tyrosine kinase inhibitor (TKI) dasatinib (Sprycel, Bristol-Myers Squibb) is approved for the second-line treatment of chronic myeloid leukemia (CML) that is resistant to imatinib mesylate (Gleevec, Novartis). Most TKIs have long half-lives, resulting in continuous target inhibition, according to Dr. Shah. Because dasatinib has a short half-life (3 to 5 hours, compared with 18 to 60 hours with other TKIs), twice-daily dosing (70 mg) was chosen to provide more consistent target inhibition in phase 2 studies of dasatinib. The adverse event of pleural effusions, however, was more common with twice-daily dosing in early studies, whereas the major cytogenetic response rate with once-daily dosing was equivalent to that for patients who were treated twice a day.

To determine whether transient (once-daily) target inhibition allowed for equivalent efficacy and improved toxicity, compared with more continuous inhibition, Dr. Shah and his colleagues evaluated 662 patients with chronic-phase CML. Enrolled participants were randomly assigned to receive dasatinib at 100 mg or 140 mg once daily or twice daily.

The median duration of treatment was 11.5 months. Complete hematological response, major cytogenetic response, and complete cytogenetic response rates were similar for all treatment groups (Table 1). Progression-free survival was significantly longer with a dose of 100 mg once daily, compared with 70 mg twice daily (16 patients with disease progression vs. 30 patients with disease progression, respectively; P = 0.032).

Grade 3 and 4 nonhematological side effects were generally similar for all groups. For hematological grade 3 and 4 events, thrombocytopenia was significantly less common with dasa-

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tinib 100 mg once daily.

Pleural effusions of any grade were less frequent with 100 mg (10 patients vs. 16 to 20 for other dose groups). Dose interruptions and reductions were significantly fewer in the patients receiving dasatinib 100 mg once daily, although more dose escalations were required (18 patients, vs. 8 to 16 in groups receiving the other doses).

Compared with patients receiving currently used dosing of 70 mg twice daily, significantly fewer patients receiving 100 mg once daily discontinued treatment because of toxicity ($P = 0.012$).

Dr. Shah determined that dasatinib 100 mg once daily was the optimal dose schedule for chronic-phase CML.

Pemetrexed (Alimta) and Gemcitabine (Gemzar) plus Platinum

**Presenter:** Born H. Gronberg, MD, St. Olavs Hospital, Trondheim, Norway

In stage IIIB/IV non–small-cell lung cancer (NSCLC), the combination of pemetrexed (Alimta, Eli Lilly) plus carboplatin (Paraplatin, Bristol-Myers Squibb) as a first-line chemotherapy produced significantly less toxicity than the combination of gemcitabine (Gemzar, Eli Lilly) plus carboplatin. In addition, patients receiving the pemetrexed/carboplatin (Pem/Carbo) regimen needed fewer transfusions than those receiving the gemcitabine/carboplatin (Gem/Carbo) combination.

This finding emerged from a clinical trial among 537 patients with NSCLC conducted by Dr. Gronberg. Noting that platinum-based doublets are considered standard treatment in these patients, he said that the rationale for the trial was that phase 2 trials had suggested that pemetrexed plus a platinum agent might be equally effective as standard doublets but with a more favorable toxicity profile.

He explained: “Pemetrexed is easy to administer and might provide a better quality of life to this population with poor performance status and significant comorbidity.”

Patients (median age 65 years, 57.5% male) were randomly assigned to receive four three-week cycles of either (1) pemetrexed 500 mg/m² plus carboplatin (with an area-under-the curve [AUC] concentration of 5) (Pem/Carbo) or (2) gemcitabine 1,000 mg/m² plus carboplatin (with an AUC concentration of 5) (Gem/Carbo).

Both patient groups received vitamin supplementation. Patients who were 75 years of age and older received 75% of the dose.

Among grade 3 and 4 toxicities, leukopenia (22%/44%, respectively), granulocytopenia (38%/48%), and thrombocytopenia (24%/54%) were all significantly higher with Gem/Carbo. The need for blood transfusions and platelet transfusions (28%/42%) was significantly lower with Pem/Carbo (3%/9%).

Median overall survival was similar for the two groups: 7.3 months with Pem/Carbo and 7.0 months with Gem/Carbo.

Dr. Gronberg suggested, “While there were no differences in overall survival, patients receiving Pem/Carbo experienced significantly less toxicity.”

### Table 1 Dasatinib and Chronic Myeloid Leukemia: Hematological and Cytogenetic Responses

<table>
<thead>
<tr>
<th>Dose/Response</th>
<th>100 mg Once Daily (%)</th>
<th>50 mg Twice Daily (%)</th>
<th>140 mg Once Daily (%)</th>
<th>70 mg Twice Daily (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematological response</td>
<td>92</td>
<td>93</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Major cytogenetic response</td>
<td>64</td>
<td>58</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td>Complete cytogenetic response</td>
<td>46</td>
<td>46</td>
<td>47</td>
<td>50</td>
</tr>
</tbody>
</table>

### Enzastaurin

**Presenter:** Gerold Bepler, MD, PhD, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

Both protein kinase-C (PKC) and P13k (phosphatidylinositol 3-kinase)/AKT are overexpressed and overactive in lung cancer tissues and cell lines. Enzastaurin is an oral serine/threonine kinase inhibitor that targets the PKC and P13/AKT pathways, inducing tumor apoptosis. It also inhibits tumor cell proliferation and suppresses tumor-induced angiogenesis.

Dr. Bepler presented a phase 2 study among patients with NSCLC whose disease had progressed after one or two previous therapies.

Patients (n = 55) received oral enzastaurin 500 mg once daily for a planned maximum duration of six cycles of 28 days each. The participants had received at least one prior regimen, at least one of which was platinum-based.

The mean age of the patients was 63 years, 55% were men, and 78% had stage IV disease. Most patients (62%) completed between two and six enzastaurin cycles. The primary study objective was to estimate progression-free survival at six months.

At a six-month interim analysis, the median progression-free survival time was 1.8 months, and the rate of progression-free survival was 13%. Best overall response assessment among 48 patients continuing therapy showed stable disease in 19 patients (34%) and progressive disease in 29 patients (53%). The median overall survival time was 1.8 months, and the rate of 12-month overall survival was 44%. No objective tumor responses were observed.

Enzastaurin was well tolerated. Fatigue was the most common drug-related toxicity, reported at rates of 14.5% for grade 1 toxicities, 12.7% for grade 2, and 3.6% for grade 3. Fatigue was observed in patients whose disease progressed but not in patients whose disease had stabilized. Five patients died of non–drug-related causes during the study. Two of the deaths were attributed to disease progression.

“Long-term disease stabilization in three patients who had progressed after one or two prior therapies suggests enzastaurin may have activity in NSCLC,” Dr. Bepler said.

Although the rate of disease stabilization was modest, one patient was treated for 20 months before disease progression, and six patients were treated for longer than six months.

He summarized as follows: “This is an oral drug [associated] with only minor fatigue. With molecular markers, perhaps PKC via immunohistochemistry, we may be able to select those patients more likely to respond.”

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Meeting Highlights: ASCO

Denileukin Diftitox (Ontak)

**Presenter:** H. Miles Prince, MD, Peter MacCallum Cancer Institute, Melbourne, Australia

Patients with cutaneous T-cell lymphoma (CTCL) experienced durable major responses with good tolerability when they were treated with denileukin diftitox (Ontak, Seragen/ Ligand), according to results of a phase 3 clinical trial. A recombinant DNA-derived cytotoxic protein, denileukin diftitox (Dd) was approved by the Food and Drug Administration (FDA) for patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the interleukin-2 (IL-2) receptor.

Professor Prince reported that Dd was evaluated at two dose levels: 9 mcg/kg per day or 18 mcg/kg per day. Both doses were given as a 30-minute infusion over five days of a 21-day cycle to 144 patients who had biopsy-confirmed CTCL (stage IA–III) with 20% or more CD25-positive T cells. The primary endpoint was the overall response rate (RR).

For placebo patients, the overall RR was 15.9% (7/44); for patients receiving Dd 9 mcg/kg per day, the rate was 37.8%; and for those receiving 18 mcg/kg per day, it was 49.1%, compared with placebo (P = 0.029 and P = 0.0015, respectively).

Progressive disease was reported in 52.3% of the placebo patients, in 26.7% of those receiving Dd 9 mcg/kg per day, and in 16.4% of the patients treated with 18 mcg/kg per day.

For secondary endpoints of progression-free survival and time to treatment failure, the pattern of dose response favoring the higher Dd dose persisted. The duration of response and the time to the first response, however, favored the 9-mcg/kg dose. Both Dd doses were significantly superior to placebo for all of these parameters.

Although adverse events were reported at similar rates for placebo (90.9%) and Dd (97.0%), discontinuations of treatment attributable to adverse events were more frequent in the Dd groups (20%) than in the placebo group (9.0%), as were serious adverse events (36% with Dd vs. 22.7% with placebo). Dr. Prince emphasized, however, that serious adverse events decreased over time in both Dd groups, reaching levels similar to those of the placebo group.

He explained that mild-to-moderate vascular leak syndrome, characterized by fever, edema, and reduced albumin levels, dropped off sharply after the second cycle of therapy.

“Importantly, we didn’t use dexamethasone in this trial. But in day-to-day practice, we do give steroids, which increases response rates and reduces side effects.”

He concluded: “The key thing is that we demonstrated major responses that are durable with a very good toxicity profile. Denileukin diftitox represents a way of avoiding the side effects of chemotherapy.”

Capecitabine (Xeloda)

**Presenter:** George W. Sledge, MD, Indiana University Cancer Center, Indianapolis, Indiana

The Xeloda in Combination with Avastin as First-Line Treatment for HER2-Negative Metastatic Breast Cancer (XCAL-IBr) trial examined capecitabine (Xeloda, Roche), an oral prodrug of 5-FU, plus bevacizumab (Avastin, Roche) as a first-line treatment for metastatic breast cancer. The combination was more active in women with estrogen receptor–positive (ER-positive) tumors, Dr. Sledge reported.

Patients with HER2-negative metastatic breast cancer received first-line therapy with capecitabine 1,000 mg/m² twice daily for 14 days with seven days off plus bevacizumab 15 mg/kg IV in three-week cycles. Patients whose disease progressed went on to second-line treatment consisting of bevacizumab plus paclitaxel (Taxol, Bristol-Myers Squibb) or vinorelbine (Navelbine tartrate, GlaxoSmithKline) on four-week cycles. The primary study endpoint was time to progression.

Among 106 women (mean age, 56.8 years), hormonal status was ER-positive in 57 patients (54%) and ER-negative in 49 (46%); 62 subjects (58%) were postmenopausal. Forty-eight patients (45%) had lung metastases; 56 (53%) had a primary liver tumor, and 60 (57%) had a primary lung tumor. Enrolled patients had not received any previous chemotherapy, except for that given in the neoadjuvant (16%) or adjuvant (65%) setting at least six months before their entry into the trial.

At a median follow-up of 12.9 months, the median time to progression was 5.7 months; median overall survival had not yet been reached, but it was beyond 16 months.

The overall response rate, consisting of complete and partial responses, was 38%. Dr. Sledge said that although the trial met its primary endpoint, he found the results “somewhat disappointing,” compared with an earlier trial. (The initial assumption had been that the time to progression would be 5.6 months.) This finding spurred an exploratory analysis of the impact of hormone receptor status (Table 2).

As an unplanned analysis, Dr. Sledge indicated, the finding can be used only to generate a hypothesis; however, he suggested that the combination of capecitabine and bevacizumab would be more active in ER-positive patients.

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**Table 2: Efficacy of Capecitabine plus Bevacizumab According to Hormonal Status of Patients with Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th></th>
<th>Total No. of Patients</th>
<th>ER-Negative Status*</th>
<th>ER-Positive Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 106)</td>
<td>(n = 49)</td>
<td>(n = 57)</td>
</tr>
<tr>
<td>Median time to disease progress (months)</td>
<td>5.7 months</td>
<td>4.0 months</td>
<td>8.9 months</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>16.0+ months</td>
<td>7.5 months</td>
<td>16.6+ months</td>
</tr>
<tr>
<td>Overall response rate (complete responses + partial responses)</td>
<td>38%</td>
<td>27%</td>
<td>47%</td>
</tr>
</tbody>
</table>

* ER-positive versus ER-negative status (P < 0.0001).