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DRUG DEVELOPMENT IN ONCOLOGY

## THE EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) PATHWAY IN CANCER

### PART IV — DEVELOPMENTAL INDICATIONS OF COMMERCIALLY AVAILABLE ERBB PATHWAY INHIBITORS



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# THE EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) PATHWAY IN CANCER

## PART IV — DEVELOPMENTAL INDICATIONS OF COMMERCIALLY AVAILABLE ERBB PATHWAY INHIBITORS

This article is Part IV of a 5-part series elucidating the role of the EGFr/ErbB pathway in cancer and its treatment. This issue assesses the clinical status of commercially available EGFr inhibitors in developmental indications. Part I (V8, #11/12; March 28, 2007) of this series addressed ErbB receptors and ligands, downstream signaling in EGFr pathways, clinical laboratory detection methodologies, and products for diagnostic, prognostic, and theragnostic applications. Part II (V9, #1/2; May 31, 2007) addressed the relationship of aberrant ErbB receptor expression and mutations within specific cancer indications and provided an overview of therapeutic approaches. Part III (V9, #3/4; September 15, 2007) reviewed the clinical performances and roles of approved, commercially available ErbB inhibitors, assessed worldwide trends in pricing, reimbursement, and treatment costs, and provided current global market estimates and near-term market projections. Part V, the last of the series, will describe and analyze the many novel drugs in development targeting the EGFr pathway and provide a competitive outlook and longer term market forecasts.



## DEVELOPMENTAL INDICATIONS OF APPROVED ERBB/EGFR INHIBITORS

Marketed EGFr inhibitors are in development for new indications either closely related to approved cancer indications or for different malignancies. A clinical trial in an indication for which an approval has already been obtained usually tests the approved compound in a new drug combination or treatment regimen. Such trials are often undertaken to establish efficacy of the drug in an earlier line of therapy, test less toxic drug combinations, or demonstrate some other therapeutic advantage that will enable new regulatory claims. The goal is to expand the drug's labeling for the treatment of a particular malignancy. Such trials may provide head-to-head comparisons against established therapeutic regimens, evaluate the roles of biomarkers, gather safety data, etc. Clinical trials for the (exact) approved indication may also continue well after approval has been granted and the drug has been launched. These trials provide phase IV data and are sometimes required during the drug's initial approval process. One of the most important goals of additional trials within a broad cancer indication is to gain approval for drug treatment in earlier disease stages, ideally, in adjuvant/neoadjuvant settings. Of course, marketed EGFr inhibitors are also in development for new indications unrelated to those that are currently approved.

At present, most clinical trials of approved ErbB-pathway inhibitors are in combination with cytotoxics. In essence, the cytotoxic component serves to kill most actively proliferating cancer cells, while the ErbB-targeted agent blocks signals that promote the creation and survival of new cancer cells. Combinations of targeted agents without a cytotoxic component are also under investigation to eliminate the toxicities of cytotoxic chemotherapies and to more effectively target the complex biology of cancer. Use of combination strategies acting simultaneously at different points in the ErbB and other signal transduction pathways may significantly enhance the anticancer efficacy of targeted agents. Trials are underway with combinations of approved targeted agents and combinations of approved and novel targeted drugs in development that address relevant pathways.

This issue addresses developmental indications of approved ErbB inhibitors as monotherapies and in combinations with approved cancer therapeutics. Novel ErbB inhibitors and combinations of approved ErbB inhibitors with novel cytotoxics and/or other targeted therapies are the topics of the next (and last) issue in this series.

The seven approved ErbB inhibitors addressed in this issue are trastuzumab (Herceptin; Genentech), lapatinib (Tykerb; GlaxoSmithKline), erlotinib (Tarceva; OSI Pharmaceuticals), cetuximab (Erbitux; ImClone Systems), gefitinib (Iressa; AstraZeneca), panitumumab (Vectibix; Amgen), and nimotuzumab (Centre of Molecular Immunology). Approval status of these agents has been discussed in detail in FO, V9#3/4.

### BREAST CANCER

In recent years it has been concluded that breast cancer is not one disease, but many different forms of cancer, all of which originate in the breast. As such, different strategies are under evaluation for the different manifestations of breast cancer including the use of ErbB inhibitors.

Breast cancer is the major indication for ErbB-pathway inhibitors. Currently the largest global market in this group of drugs is accounted by the HEr2 inhibitor trastuzumab, and this sector may also support the widespread use of another HEr2 inhibitor, lapatinib. Breast cancer, however, has not yet been a promising indication for ErbB inhibitors that do not target HEr2. Nevertheless, nearly all commercialized ErbB inhibitors are under investigation in breast cancer, but R&D intensity varies according to the sponsor's estimated likelihood that a particular agent will eventually play a role in this indication.

Currently, trastuzumab is the dominant ErbB inhibitor addressing HEr2-positive (HEr2+) breast cancer, from early disease in the adjuvant setting to advanced or metastatic disease. As might be expected, trastuzumab, in combination with other agents, comprises the largest ongoing clinical development program in breast cancer. This widespread effort is based on the drug's validated activity in HEr2+ advanced or metastatic breast cancer, dictating its use in trials enrolling any HEr2+ patients.

Trastuzumab is under investigation in combination with an extensive array of cytotoxics that have shown activity in various types and stages of breast cancer, with other approved targeted agents, and with novel developmental drugs.

Lapatinib, recently approved for the treatment of advanced or metastatic breast cancer in combination with capecitabine (Xeloda; Roche), is attempting to catch up. Its dual targeting capability, involving both HEr2 and EGFr, seems unlikely to provide a great advantage in breast cancer because EGFr inhibitors have not been effective in the treatment of breast cancer, alone or in combination with cytotoxics. However, several trials are currently underway testing the combination of trastuzumab and lapatinib. This approach is based on preclinical findings that EGFr activation is associated with resistance to trastuzumab in breast cancer cell lines and the observation of synergistic action between EGFr tyrosine kinase inhibitors and trastuzumab in HEr2+ cell lines that co-express EGFr. In addition to the possibility of combating trastuzumab resistance, the combination of a monoclonal antibody (MAb) and a small molecule tyrosine kinase inhibitor (TKI), acting on different mechanisms of the same target, may be more effective than the dual targeting capabilities of lapatinib, alone.

Currently, there are no predictors of response to EGFr inhibitors in patients with breast cancer. Of the EGFr inhibitors under investigation in breast cancer, erlotinib is undergoing the most extensive clinical development program. Panitumumab is not currently in clinical trials in breast cancer. However, in a preclinical experiment, panitumumab, in combination with an antibody against IL-8, inhibited tumor cell proliferation and tumor development and also prevented metastasis of human breast cancer MDA-231 cells in a SCID mouse model (Salcedo R, etal, Clin Cancer Res, Aug 2002;8(8):2655-65). A few trials with cetuximab in breast cancer have been completed or are ongoing, mostly in patients with HEr2 non-overexpressing tumors. Gefitinib also does not appear to have a role in the treatment of breast cancer.

## Advanced or Metastatic Breast Cancer

In the USA, approximately 10% of patients newly diagnosed with breast cancer have locally advanced and/or metastatic disease. Between 20% and 85% of patients diagnosed with early breast cancer will develop recurrent and/or metastatic disease, depending upon the initial stage at diagnosis, tumor biology, and treatment strategy. Each year, approximately 60,000 women are treatment candidates for metastatic (Stage IV) breast cancer, either newly diagnosed or with progressive disease who may have already been treated with multiple regimens.

Among the ErbB-pathway inhibitors, both trastuzumab and lapatinib have been approved for the treatment of metastatic breast cancer expressing HEr2 (see FO, V9#3/4). However, unlike the broad indication for trastuzumab, the March 2007 FDA approval of lapatinib was for a very narrow indication. Lapatinib was approved in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HEr2 and who have been previously treated with chemotherapy, including an anthracycline, a taxane, and trastuzumab.

***Trastuzumab*** is used globally for the treatment of advanced or metastatic HEr2+ breast cancer. Despite its success, only about half of patients with metastatic disease who are selected for trastuzumab treatment by current diagnostic technologies, respond to the drug. The current clinical development strategy in patients treated with trastuzumab is to enhance effectiveness while reducing side effects. There are two approaches that may accomplish this, better patient selection or more effective combination regimens to combat resistance. Although resistance to trastuzumab may, in the long term, be reversed by combinations with novel targeted agents, in the short term, improved patient selection might eliminate treatment of patients unlikely to benefit from this approach. Various projects are ongoing to fine-tune the selection of patients most likely to benefit from treatment with trastuzumab.

Many large, late stage trials are testing trastuzumab in combination with various cytotoxics in order to expand treatment options in breast cancer and, possibly, identify combinations with higher efficacies than that of trastuzumab in combination with taxanes. Although, overall, positive results have been reported, efficacies have been approximately equal to those of approved regimens. No significantly more efficacious regimens have yet been identified. More than 128 trials have been initiated with trastuzumab in advanced or metastatic breast cancer; approximately 66 (24 randomized) are currently active.



Use of trastuzumab is a validated treatment approach in patients with HEr2+ breast cancer and is added to all regimens treating patients with HEr2+ advanced or metastatic breast cancer. One of the most effective treatment approach in advanced or metastatic breast cancer is represented by taxane-based regimens. With longer follow-up, the benefit of adding concurrent trastuzumab to paclitaxel after doxorubicin/cyclophosphamide has become clearly evident; the hazard of disease recurrence decreased by 52% [hazard ratio (HR)=0.48] and hazard of death was reduced by 35% (HR=0.65, p=0.0007), equivalent to an improvement in overall survival (OS) of 54%. Hazard of disease recurrence is increased in patients with greater numbers of positive nodes, estrogen receptor (Er)-negative tumors, and larger tumors. With an increase in the median follow-up of 11 months and 225 additional events, substantial improvement of outcomes with the addition of trastuzumab to chemotherapy is still evident. Improvement persists despite some degree of crossover occurring after the initial results were reported. Life-threatening cardiac events, most commonly congestive heart failure (CHF), were observed 3% to 4% of patients,

more often in the trastuzumab group. Other adverse events (AE) reported include dyspnea and interstitial pneumonitis at a rate of <1.0% (Perez EA, etal, ASCO07, Abs. 512).

Trastuzumab has also been approved for use in combination with docetaxel (Taxotere; sanofi-aventis). This combination, with or without carboplatin, was investigated in a randomized phase III clinical trial (protocol ID: UCLA-0109024; BCIRG-007; ROCHE-UCLA-0109024; GENENTECH-UCLA-0109024; NCI-G02-2116; NCT00047255), as first line therapy in patients with metastatic breast cancer with HEr2 amplification by FISH. A total of 263 patients were randomized and administered chemotherapy every 3 weeks for 8 cycles with weekly trastuzumab (2 mg/kg; loading dose of 4 mg/kg), followed by trastuzumab (6 mg/kg) every 3 weeks, until disease progression. Patients were stratified by center and prior neoadjuvant taxane chemotherapy. The primary endpoint was time-to-progression (TTP). Secondary endpoints included OS, response rate, duration of response, clinical benefit, and safety.

A total of 131 patients were treated in each arm. According to the initial efficacy analysis, conducted at 204 events, there were no significant differences between the doublet or triplet arms regarding median TTP (11.1 versus 10.4 months, p=0.57), ORR (73% in both arms), duration of response (10.7 versus 9.4 months), or clinical benefit (67% in both arms). At 39 months median follow-up, median OS was 36.40 months in the trastuzumab and docetaxel arm and 36.57 months in the plus carboplatin arm. More patients treated with the triple combination were treated with the maximum number of chemotherapy cycles, and fewer discontinued treatment because of nonhematologic toxicity. The most common Grade 3/4 toxicities were neutropenic infection (16.8% for the doublet arm versus 9.2% for the triplet arm), thrombocytopenia (2% versus 15%), asthenia (5% versus 12%), anemia (5% versus 11%), and diarrhea (2% versus 10%); 2 (1.5%) patients died of sepsis in the triplet arm. Absolute left ventricular ejection fraction (LVEF) declines of >15 % was observed in 5.5% of patients in the doublet arm versus 6.7% in the triplet arm; 1 patient (0.8%) experienced symptomatic CHF in the doublet arm. Both regimens were highly effective in treating women with HEr2+ metastatic breast cancer. Both treatment arms demonstrated high response rates; median TTP was >10 months, and median OS was >36 months. Cardiac toxicity was not a significant problem with either treatment (Pegram M, etal, ASCO07, Abs. LBA1008).

Trastuzumab appears to complement the effects of many chemotherapeutic agents that are active in metastatic HEr2+ breast cancer, even in heavily pretreated patients. From May 2001 to June 2006, 70 patients (Er+=57%, Pgr+=40%, visceral disease=49/70, and metastases in two or more sites=41/70), treated with trastuzumab, were included in a retrospective analysis undertaken to evaluate safety and activity of trastuzumab-containing regimens in patients with HEr2+ metastatic breast cancer. Trastuzumab was administered as a single agent in 12 patients and in combination in 58 patients (vinorelbine=48%, docetaxel=29%, and paclitaxel=23%). Previous treatments for metastastic disease were hormone therapy in 11 (16%) patients and one or more lines of chemotherapy in 25 (36%) patients. In first line settings, the response rate was 41%, SD was 47%, and TTP was 8 months (range=1-44). In second line settings, the response rate was 23%, SD was 62%, and TTP was 9 months (range=3-23). Beyond second line, RR was 22%, SD was 78%, and TTP was 9 months (range=4-19). OS was 19.2 months (range=3-62 months). Median cumulative trastuzumab dose was 5,286 mg (range=464-17,940 mg). Trastuzumab was well tolerated. Median LVEF was 62% at baseline and 59% at the end of treatment. Relevant AE were only 1 asymptomatic LVEF decrease to 40% from 60% at baseline requiring treatment discontinuation; 6 reversible asymptomatic LVEF declines of 10% to 15%; 2 reversible tachycardia cases; one case of Grade 3 hyperbilirubin; and 2 transient increases in transaminases. According to these results, trastuzumab-containing therapies in metastatic breast cancer are safe and remarkably active, even in heavily pretreated women with HEr2-overexpressing metastatic cancer. Patients benefit from continued trastuzumab therapy, as shown by the maintenance of TTP even beyond second line treatment (Adamo B, etal, ASCOBC07, Abs. 175).

Single agent trastuzumab may also be an option as first line therapy of patients with newly diagnosed HEr2+ metastatic breast cancer. The goal of this approach is to bypass standard chemotherapy in cases of responsive disease. A phase II clinical trial evaluated responses to first line induction therapy with trastuzumab in patients with HEr2 + metastatic breast cancer and subsequent responses to weekly paclitaxel and carboplatin. Concurrent trastuzumab with chemotherapy was conditional on induction responses to single agent trastuzumab. A loading dose of 8 mg/kg followed by weekly trastuzumab (4 mg/kg) was administered to 61 patients with metastatic breast cancer overexpressing HEr2 (2+ or 3+). After 8 weeks of induction, trastuzumab was discontinued in 20 patients with progressive disease who were then treated with weekly paclitaxel (70 mg/m$^2$) and carboplatin (AUC=2) for 6 cycles every 8 weeks. Responders in the induction phase were treated with 8 additional weeks of trastuzumab before beginning weekly paclitaxel and carboplatin concurrently with weekly trastuzumab (2 mg/kg). Among 58 patients evaluable for response, 31 had been previously treated in the adjuvant setting (doxorubicin=22), and 34 were Er+. HEr2 expression was 3+ in 41 patients and 2 + in 20. At the initial 8-week trastuzumab evaluation, 38 (66%) patients were progression-free, representing 1 CR and 11 PR for a response rate of 22%. Disease progressed in only 2 patients in this group during the additional 8 weeks of trastuzumab. The 20 HEr2 + patients who progressed on induction trastuzumab retained chemosensitivity to weekly paclitaxel and carboplatin with

a 61% RR. A 76% ORR was noted among responders of induction trastuzumab continuing to weekly trastuzumab concurrently with paclitaxel and carboplatin. TTP in patients with 3+ versus 2+ tumors with the 3-drug combination was 17.1 months versus 11.4 months (overall 14.5 months). In this trial, chemosensitivity to paclitaxel and carboplatin was maintained despite a 16-week induction treatment with single agent trastuzumab (Yardley A, etal, ASCO02, Abs. 127).

Considerable research is underway to improve the assessment of HEr2 status as it relates to breast cancer and its treatment. Currently, the dominant testing technologies (i.e., FISH and IHC), classify patients with breast cancer as either HEr2+ or HEr2-, providing the basis for patient selection. At best, these technologies provide a semi-quantitative analysis, which is not an accurate or precise view of HEr2 biology in breast cancer. These current selection technologies probably constitute a first generation approach. Many studies are ongoing to identify additional markers that might interfere with the optimal performance of HEr2 inhibitors.

Monogram Biosciences (South San Francisco, CA) has developed HERmark, a proprietary diagnostic that quantifies HEr2 expression and HEr2:HEr2 dimerization in patients with breast cancer. It is the company's first product based on its VeraTag technology, a proximity-based assay technology platform for quantification of proteins and functional protein complexes. The College of Pathologists (CAP) confirmed that the HERmark assays have been approved for routine patient testing in Monogram's CLIA-certified clinical reference laboratory.

Results from 3 reported studies provide the basis for Monogram's ongoing work in metastatic breast cancer. In December 2007, Monogram presented results at the San Antonio Breast Cancer Symposium (SABCS) describing the use of the HERmark Assay for the identification of patients with metastatic breast cancer who are most likely to respond to Herceptin. In 3 cohorts of Herceptin-treated patients with metastatic breast cancer who were identified as HEr2+ by conventional assays, preliminary data suggest that HERmark may identify patients who are likely to respond to Herceptin with greater precision than currently available tests. The HERmark Assay might enable stratification of patients according to the degree of clinical benefit achievable with Herceptin. HERmark analysis was performed on tissue samples from patients with metastatic breast cancer who were selected by IHC testing and treated with Herceptin. Current testing methods identified all patients as appropriate for Herceptin treatment, while the HERmark Assay distinguished separate sub-populations of patients with different clinical outcomes.

Patients with higher levels of expression had significantly better clinical outcomes. The objective response rate of patients with higher HEr2 expression levels (i.e., in the upper half of the distribution of the study cohort) was 59% compared to 18% for those with lower levels (i.e., in the lower half of the distribution). According to additional analysis, median TTP was 12.8 months in patients with higher HEr2 expression values, compared to only 4 months among those in the lower half of the distribution. This result was statistically significant (p=0.01). Finally, multivariate Cox proportional hazards models identified HEr2 expression (HR=0.16, p<0.001) and HEr2:HEr2 dimer levels (HR=0.32, p<0.001), as measured by HERmark, as statistically significant predictors of TTP.

In June 2007, at the American Society of Clinical Oncology (ASCO) meeting, Monogram reported results of HERmark studies in two patient cohorts. In one of these studies, in patients stringently selected by FISH testing, the HERmark assay measured a gradient of HEr2 expression and HEr2 homodimer levels that significantly correlated with TTP and OS of patients treated with Herceptin. The second cohort was selected by IHC in a clinic-based setting. Upon repeat testing, there was a response gradient among patients with IHC-confirmed HEr2+ disease; patients with higher levels of HEr2 expression and HEr2 homodimer levels, measured by HERmark, lived longer than those with lower levels.

***Lapatinib*** is under an intensive evaluation in metastatic breast cancer. Of the approximately 60 trials initiated with this agent in breast cancer, 31 have been in metastatic disease, and 18 are currently active.

Positive results from the phase III clinical trial (protocol ID: GSK-EGF100151, UCLA-0403074-01; NCT00078572) that served as the basis for lapatinib's approval in the treatment of metastatic breast cancer, prompted GlaxoSmithKline to open a global Lapatinib Expanded Access Program (LEAP, or EAP) in June 2006. The goal is to provide pre-approval access to lapatinib in combination with capecitabine to patients with the same clinical characteristics as those who benefited from the combination regimen tested in EGF100151. The trial will enroll 3,400 patients. LEAP was designed to provide access to lapatinib and capecitabine in a phase IV clinical trial (protocol ID: EGF103659; NCT00338247) rather than in a single patient IND/named patient format. Unlike EGF100151, LEAP allows enrollment of patients without measurable disease, with ECOG PS 2, and with brain metastases. At the data cut-off date of April 27, 2007, 1,500 patients (North America=780, EU-564, ROW=156) had been enrolled at 321 centers. Sites in the USA were closed to further enrollment in March 2007, one week after regulatory approval of lapatinibby the FDA, and sites in Switzerland, where the drug was recently approved, will close soon.

In LEAP, all patients are evaluated for safety throughout the trial, but reporting of safety data is limited to serious AE (SAE). To date, there have been 423 SAE reported in 265 patients; 41% of these are considered related to trial treatment. The investigator determined that only 1 (abnormal hepatic function) of 18 deaths linked to SAE was related to the trial drugs. Another patient, for whom

the investigator did not report the relationship, died of acute renal failure/acidosis. Other (non-fatal) SAE included decreased LVEF (n=6; completely recovered=5, lost to follow-up=1) and pneumonitis/lung infiltration (n=4). The most frequently reported SAE was diarrhea (n=47). No new safety signals were identified based on these data. The reported SAE are consistent with the known safety profile of lapatinib and capecitabine. Overall, 172 patients withdrew from the program, mostly because of progressive disease (63%). To date, no additional safety issues have been identified in early safety data from LEAP. LEAP represents an important example of closing the gap between the time when positive results are reported from phase III trials of a new oncology agent and the time when patients have access.

A multicenter (n=139), international, randomized, double blind, phase III clinical trial (protocol ID: EGF30001; NCT00075270; NCT00085046) was conducted to compare the safety and efficacy of lapatinib plus paclitaxel to paclitaxel alone as first line treatment in patients with incurable advanced (Stage IIIb/c) or metastatic (Stage IV) breast cancer at first diagnosis or relapse, untested or negative for HEr2. Between January 2004 and July 2005, 579 patients from 24 countries were stratified by metastatic site and randomized (lapatinib/paclitaxel= 293 and placebo=286) to 1 of 2 treatment arms. In arm 1, patients are administered IV paclitaxel (175 mg/m$^2$) every 21 days on day 1, and oral lapatinib (1500 mg) once daily on days 1-21. In arm 2, patients are administered paclitaxel IV on day 1 and oral placebo once daily on days 1-21. In both arms, courses repeat every 21 days. Primary endpoint was TTP; secondary endpoints included AE, ORR, PFS, clinical benefit response, relapse-free survival, and OS. Tumor tissue was obtained from the most recent biopsy of 451 (78%) patients and centrally analyzed in blinded fashion for biomarker patterns.



Of 579 patients who were included in the analysis, 87% presented with Stage IV breast cancer; 55% had prior adjuvant chemotherapy or anti-hormonal therapy, and none had previous trastuzumab therapy. At the time of analysis, 561 (97%) patients progressed or otherwise withdrew. Most common AE were alopecia (58%), neurological events (55%, Grade 3=8%), diarrhea (42%, Grade 3=9%), nausea (32%), and rash (32%, Grade 3=2%). SAE in the lapatinib/paclitaxel group included neutropenia (n=22), febrile neutropenia (n=10), diarrhea (n=24), and asymptomatic LVEF decrease (n=5). In the placebo/paclitaxel group, fewer patients experienced neutropenia (n=14), febrile neutropenia (n=3), and diarrhea (n=2). Neutropenia and thrombocytopenia AE related to treatment were 18% in the lapatinib/paclitaxel group and <1% in the placebo/paclitaxel group. LVEF decrease of 20% relative to baseline and below lower limits of normal was reported 15 times. A total of 12% of AE led to treatment withdrawal. CNS relapse was reported in 11 patients (2%). Response rate (CR + PR) was 35.1% in the lapatinib/paclitaxel group and 25.3% in the placebo/paclitaxel group (p=0.008). Clinical benefit rate (CR + PR + SD ≥6 months) was 40.5% in the lapatinib/paclitaxel group and 31.9% in the placebo/paclitaxel group (p=0.025). Median duration of response values for the lapatinib/paclitaxel and placebo/paclitaxel groups were 6.5 and 6.2 months, respectively. Median TTP was 25 weeks and median ORR was 30%.

Because enrollment was predominantly from countries with limited HEr2 testing capability, a subgroup of patients was expected to be HEr2+. Biomarker evaluations showed that, in the lapatinib group, 19% of tumor tissue samples were HEr2+, 74% were HEr2-negative, and 7% were inconclusive. In the placebo group, 15% were HEr2+, 77% were HEr2-negative, and 8% were inconclusive. Median duration of response after treatment with lapatinib/paclitaxel was higher in patients with HEr2+ tumors (7.4 months) than in patients with HEr2-negative tumors (6.2 months). Median duration of response after treatment with paclitaxel only was higher in patients with HEr2-negative tumors (8.5 months) than in patients with HEr2+ tumors (5.5 months). Median TTP after lapatinib/paclitaxel treatment was higher in patients with HEr2+ tumors (8.1 months) than in those with HEr2-negative tumors (5.8 months). TTP after paclitaxel treatment alone was similar in patients with HEr2+ and HEr2- tumors. For HEr2+ tumors, a median OS of 24 months for patients treated with lapatinib/paclitaxel versus 19 months for those treated with paclitaxel only (HR=0.64), was not statistically significant. For HEr2-negative tumors, there was no substantial difference in OS between the 2 arms. There was no significant difference in TTP, event-free survival, and OS between the lapatinib/paclitaxel and placebo/paclitaxel groups in patients with HEr2-/untested advanced breast cancer. The predefined central analysis of HEr2+ tumors shows that paclitaxel/lapatinib has a statistically significant superiority over paclitaxel alone in ORR, clinical benefit response, TTP, and event-free survival (Di Leo A, etal, ASCO07, Abs. 1011).

***Erlotinib*** has been and continues to be under evaluation on a limited scale in metastatic breast cancer. A phase II clinical trial was conducted to assess the benefit of adding erlotinib to docetaxel as first line treatment in chemotherapy-naïve patients with recurrent or metastatic breast cancer. IV docetaxel (35 mg/m$^2$) was infused weekly for 3 weeks every 4 weeks, and erlotinib (150 mg) was administered daily without interruption. Erlotinib was to be continued in 4-week cycles after maximum tumor response or disease stabilization following a minimum of 6 cycles of the combined regimen. The median number of cycles of the combined regimen, delivered to 31 of 40 enrolled patients between December 2002 and September 2005, was 4 (range=1-9) and of erlotinib, following chemotherapy, was also 4 (range=1-29). The first 26 patients were treated with the planned docetaxel dose of 35 mg/m$^2$. However, because of nonhematologic toxicity, the dose was subsequently lowered to 30 mg/m$^2$; 11/31

(36%) patients were not evaluable because of toxicity. Hematologic Grade 3 or 4 toxicity was seen in 45% of cases. Principal nonhematologic Grade 3/4 toxicities included nausea, diarrhea, and constitutional symptoms seen in 30% of patients. Also, 4/9 patients (1 each) treated with erlotinib subsequent to the combination regimen experienced hematologic, hepatic, constitutional, and eye Grade 3 toxicity. Best clinical response in the 20 evaluable patients included 11 PR (55%), while disease stabilized in 7 (35%), and progressed in 2 (10%). OS (n=31) was 71% at 12 months, 42% at 24 months with median OS of 23 months. This combination therapy showed promising activity with a favorable response compared to other trials and was associated with moderate-to-severe hematologic and nonhematologic toxicities. Randomized trials are warranted to further investigate the efficacy of this combination compared to single agent docetaxel (Kaur H, etal, ASCO06, Abs. 10623).

A phase II clinical trial (protocol ID: NCCTG-N0234, CDR0000298778) of erlotinib in combination with gemcitabine (Gemzar; Lilly) as a first or second line therapy in patients with metastatic breast cancer was performed in the USA to determine the tolerability and efficacy of this regimen. Patients were administered erlotinib (150 mg) PO daily in combination with gemcitabine (1000 mg/m$^2$) on days 1 and 8 of 21-day cycles. A total of 59 patients (prior adjuvant chemotherapy=68%, prior anthracycline=81%, prior taxane=78%, prior anthracycline and taxane=61%; no previous chemotherapy for MBC=44%, 1 previous chemotherapy for MBC=56%) were enrolled. Median number of cycles administered was 4 per patient (range=1-17). Severe (Grade 3/4) hematologic AE included neutropenia (35%), thrombocytopenia (9%), and anemia (7%). Severe (Grade 3/4) nonhematologic AE included fatigue (14%), dyspnea (12%), diarrhea (9%), rash (7%), and infection (4%). Trial treatment is still underway in 10 patients. Reasons for discontinuing treatment included disease progression (76%), patient refusal (14%), AE (4%), new primary (2%), and symptomatic deterioration (4%). Among 59 evaluable patients, there were 8 objective responses, corresponding to an ORR of 14%. Median length of response was 4.6 months. At last follow-up, 12 patients were alive without progression and 28 were alive with progression (median length of follow-up=4.3 months, maximum follow-up=12 months), and 19 died. Median PFS was 2.8 months. The 6-month survival rate was 75%. These results indicate that, although the combination of erlotinib and gemcitabine is well tolerated, it has lower than expected activity as first or second line therapy in metastatic breast cancer compared to historical controls of gemcitabine-based combination treatment (Graham D, etal, ASCO05, Abs. 644).

A phase II clinical trial (protocol ID: MSKCC-02119; NCI-5761; NCT00054132) of erlotinib, in combination with bevacizumab, was initiated in the USA, in January 2003, to determine the safety, response rate, TTP, and efficacy of this regimen in patients with metastatic breast cancer, refractory to 1 or 2 prior regimens. Patients were administered oral erlotinib (50 mg/day) daily and IV bevacizumab (15 mg/kg) every 3 weeks. According to an interim analysis based on 13 patients, 38 cycles of therapy were delivered with a median of 2 cycles/patient (range=2-9). Among 9 patients evaluable for response, there was 1 (11%) confirmed PR, and disease stabilized in 2 (22%) at 9 weeks and progressed in 5 (56%); 1 (11%) patient was removed from the trial following 1 treatment cycle because of an allergic drug reaction. Grade 4 toxicities included 1 case of pulmonary embolism (8%) and 1 case of neutropenia (8%). Additional toxicities potentially related to erlotinib and/or bevacizumab, included Grade 2 rash (46%), Grade 2 diarrhea (23%), Grade 3 hypertension (15%), and Grade 3 nausea/vomiting (8%). These results indicate that the combination of bevacizumab and erlotinib is active in patients with metastatic breast cancer (Dickler M, etal, ASCO04, Abs. 2001).

***Cetuximab***, is also under investigation in metastatic breast cancer, in combination with various cytotoxic regimens. Preliminary results of a randomized phase II clinical trial (protocol ID: CA225200; NCT00248287) of weekly irinotecan plus carboplatin with or without cetuximab in patients with metastatic breast cancer is ongoing at 59 sites in the USA, under PI Joyce A. O'Shaughnessy, MD, of US Oncology (Houston, TX). The trial's primary endpoint is objective response rates associated with this combination regimen; secondary objectives are progression-free survival (PFS), OS, and safety. A total of 163 patients with measurable disease were randomly assigned to either arm 1 treatment with irinotecan (90 mg/m$^2$) followed by carboplatin (AUC=2) on days 1 and 8 of each 21-day cycle, or arm 2 treatment as in arm 1 with the addition of IV cetuximab (400 mg/m$^2$ for the first dose and 250 mg/m$^2$ weekly thereafter). Patients with progressive disease in arm 1 could cross over to single agent cetuximab (arm 1b). Enrollment has been completed. According to a preliminary report on 103 patients (prior adjuvant chemotherapy=76 and 1 prior chemotherapy for metastatic disease=33) treated for >4 months, 49 and 54 were enrolled in arms 1 and 2, respectively. Among 36 patients in arm 1 currently evaluable for response, the objective response rate was 19% compared to 39% among 31 patients evaluable for response in arm 2. Grade 3/4 toxicities (arm 1/arm 2) were fatigue (6%/18.5%), diarrhea (18%/50%), vomiting (12%/17%), neutropenia (50%/91%), and thrombocytopenia (12%/20%). This preliminary assessment suggests that the addition of cetuximab to an irinotecan plus carboplatin regimen may improve antitumor activity but is associated with greater toxicity (O'Shaughnessy J, etal, SABCS07, Abs. 308).

***Gefitinib*** does not appear to have a key role in the treatment of metastatic breast cancer and continues to be hampered by serious toxicity. Gefitinib failed as monotherapy in the second line setting in a phase II clinical trial, conducted by the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG), in patients with advanced

breast cancer (Francis P, etal, SABCS05, Abs. 4080). A similar result was reported from a multicenter, randomized, double blind, parallel group phase II clinical trial (protocol ID: D7913C00148; 1839IL/0148; NCT00247481) that evaluated gefitinib or placebo in combination with docetaxel, as first line treatment in patients with metastatic breast cancer. In this trial, conducted in France between September 2002 and October 2005, there appeared to be no benefit of adding gefitinib to docetaxel (Tubiana-Hulin M, etal, SABS07, Abs. 1081).

A randomized, blinded, placebo-controlled, phase II clinical trial, conducted at Rikshospitalet-Radiumhospitalet Medical Center (Oslo, Norway), evaluated the effect and toxicity of a combination of docetaxel with or without daily gefitinib (250 mg) in patients with pretreated metastatic breast cancer. Docetaxel (35 mg/m$^2$) was administered as 6 weekly IV doses of to all patients, followed by one week of rest. Evaluation of tumor response according to RECIST was performed before continuing on a new treatment cycle. Patients included in the trial were taxane naive, but previous treatment with endocrine or anthracycline-based therapy was allowed. Initially, the trial was to enroll 66 patients with 33 to be treated with gefitinib. However, the trial was closed early because of the relative large proportion of patients experiencing treatment-related toxicity. Among 11 of 18 treated patients with progressive disease, 6 were treated with gefitinib and 5 with placebo. Among these 18 patients, 7 (gefitinib=3, placebo=4) were removed from the trial because of toxicity. SAE were reported in 6 patients treated with gefitinib, but in only 2 patients in the placebo group. The majority of SAE were related to fluid loss caused by reduced oral fluid intake and/or diarrhea. Administration of gefitinib in addition to conventional chemotherapy did not appear to influence the feasibility of such combination treatment in general. However, some patients experienced toxicity that may have been exaggerated by the addition of a TKI, which was reflected in the larger number of patients with SAE in the gefitinib group (Engebraaten O, etal, SABCS06, Abs. 1093).



### Triple Receptor Negative Breast Cancer

Triple negative breast cancer (Er-, Pgr- and HEr2-) is a subtype of invasive breast cancer that does not express estrogen receptor (Er), progesterone receptor (Er), and HEr2. It is very similar to the basal-like subtype that expresses low levels of Er, Pgr, and HEr2 as defined by gene expression profiling. Triple negative breast cancer accounts for approximately 15% of all breast cancer cases. Depending on the stage of diagnosis, it can be extremely aggressive and is more likely to recur and metastasize than other types of breast cancer. Although triple receptor negative breast cancer typically responds to initial chemotherapy, it is associated with shorter OS. It occurs most often in African American and younger women. Because it is a recently recognized form of breast cancer, very little is known about the pathology of triple receptor negative breast cancer.

In the neoadjuvant setting, triple negative expression status among patients with breast cancer constitutes an independent unfavorable prognostic factor with regard to OS, unless pathologic CR (pCR) occurs after chemotherapy. Among 1,143 patients treated at M. D. Anderson Cancer Center (Houston, TX) in neoadjuvant trials, 827 (72%) were treated with a taxane, either as a single agent (n=60), or in combination with an anthracycline (n=767). The remaining were treated with anthracycline-only chemotherapy. Overall, 258 (23%) tumors were triple negative. There were 63/257 (25%) pCR in patients with triple negative tumors, compared to 99/888 (11%) in patients with non triple negative tumors (p=.0082). Triple negative status correlated significantly with high nuclear grade (p<.0001), but there was no significant correlation with any established clinicopathologic parameter. However, 5-year OS was 66% in the triple negative group, compared to 83% in the non-triple negative control group (p<.0001). In multivariate analyses, triple negative status (HR=2.0, p<.0001), increased tumor size (HR=1.5, p<.0001), positive nodal status (HR=1.4, p=.0002), and high nuclear grade (HR=1.7, p=.0089) were significantly associated with decreased 5-year OS. Achievement of pCR was a stronger predictor of survival than triple negative status (C. Liedtke, etal, ASCO07, Abs. 10519).

Although HEr2 inhibitors do not have a role in its treatment, investigators report that triple negative breast cancer cells overexpress EGFr. However, these cells are not as sensitive to EGFr inhibition as HEr2+ cells are to HEr2 inhibition, but EGFr inhibition may enhance response to chemotherapy in triple negative breast cancer (Corkery B, etal, ASCO07, Abs. 14071).

Investigators at the University of British Columbia, Vancouver Hospital, and British Columbia Cancer Agency (Vancouver, Canada) conducted a study to identify an IHC profile for breast basal-like tumors. A series of such tumors was collected and tested for protein patterns characteristic of this subtype. A panel of 21 basal-like tumors was obtained using gene expression profiles. These tumors were typically IHC negative for Er and HEr2 but positive for basal cytokeratins, EGFr, and/or c-Kit. Using breast carcinoma tissue microarrays representing 930 patients with 17.4-year mean follow-up, basal cytokeratin expression was associated with low disease-specific survival. EGFr expression was observed in 54% of cases positive for basal cytokeratins, compared to 11% of negative cases, and was associated with poor survival independent of nodal status and size. c-Kit expression was more common in basal-like breast cancer than in other breast tumors but did not influence prognosis. A panel of four antibodies (Er, EGFr, HEr2, and cytokeratin 5/6) accurately and with high specificity identified basal-like tumors using standard available clinical tools. Many basal-like tumors express EGFr and may be treatable with EGFr inhibitors (Nielsen TO, etal, Clin Cancer Res, 15 Aug 2004;10(16):5367-74).

In the phase II clinical trial (protocol ID: NCCTG-N0234; NCT00059852) of gemcitabine plus erlotinib described

above, tissue and serum were obtained for translational studies of Er, Pgr, HEr2, and proteins related to the EGFr pathway. Markers were evaluated centrally, blinded to patient outcome. Among the 57/59 eligible patients with complete data, 20/57 had triple negative disease. A PR rate of 25% and clinical benefit rate (PR + SD >6 months) of 25% was observed in patients with triple negative disease, compared to a PR rate of 14% (p=0.30) and clinical benefit rate 22% (p=0.75) in others. However, median PFS of 72 days, versus 98 days (p=0.13), and OS of 227 days, versus 738 days (p<0.001), were shorter in patients with triple negative disease. This treatment approach produced inferior results in patients with triple negative breast cancer (Thome S, etal, ASCO07, Abs. 1071).

A phase II clinical trial with gefitinib was designed to assess the efficacy and safety of once daily, single agent gefitinib (500 mg) in two separate parallel groups of patients with advanced breast cancer and hormone-resistant disease, which was defined as hormone receptor-positive disease progressing after both tamoxifen and an aromatase inhibitor, or hormone receptor-negative breast cancer. The trial was to enroll in each group 45 patients previously treated with only one chemotherapy regimen for advanced disease. The primary endpoint in each patient group was clinical benefit rate, defined as CR + PR + SD at 24 weeks. Tumor samples from primary or relapsed disease were tested for EGFr expression to assess the potential correlation with disease control by gefitinib. Among 66 patients who enrolled in the trial, disease stabilized in 1/40 (2.5%) patients with acquired hormone resistance treated for 28 weeks. Among 25 patients with hormone receptor-negative disease, disease stabilized in 2 (8%) patients treated for 24 and 40 weeks, respectively. The patient treated for 24 weeks discontinued gefitinib treatment because of skin rash. At this gefitinib dose, 85% patients experienced skin rash (>Grade 1=43%). There were no CR or PR in either group, and disease progressed in most patients at the first assessment at 8 weeks. Because of the absence of responses and low clinical benefit rate, the trial was closed to further enrollment. Although previous preliminary reports (Robertson JF, etal, ASCO03, Abs. 23, and Baselga J, etal, ASCO03, Abs. 24) suggested activity of gefitinib in advanced breast cancer, in this trial, gefitinib did not produce any responses and was associated with a low clinical benefit rate in these patients with advanced breast cancer who were not heavily pretreated (Francis P, etal, SABCS05, Abs. 4080).

Cetuximab, in combination with cisplatin, is under investigation in a randomized phase II clinical trial (protocol ID: EMR 200027-051; NCT00463788) in the treatment of triple receptor negative metastatic breast cancer refractory to one previous chemotherapy regimen. The trial, dubbed BALI-1, to enroll 180 patients, was initiated in May 2007 in Europe and Israel. The primary objective is determination of overall response, defined as having a best overall confirmed CR or PR during the trial. Secondary outcome measures include time-to-response, PFS, and OS. A similar randomized phase II clinical trial (protocol ID: 06-0220; LCCC 0403; NCT00492375), underway in the USA, is investigating cetuximab with or without carboplatin in this indication.

Investigators at Hadassah Ein Kerem (Jerusalem, Israel) are conducting a small phase I/II clinical trial (protocol ID: cpblb1-HMO-CTIL; NCT00353717), combining cetuximab and paclitaxel, to assess the tolerability and response rate of this regimen and conduct pathologic analysis to assess the correlation of response with EGFr expression.

A multicenter, randomized phase II clinical trial (protocol ID: TBCRC 001; 2006-0183; NCT00420329) of cetuximab with carboplatin in patients with triple negative metastatic breast cancer was initiated in December 2006 by the Translational Breast Cancer Research Consortium (TBCRC). The goal is to assess OS with single agent cetuximab (arm 1) and in combination with carboplatin (arm 2). Eligible patients had measurable disease and were pretreated with ≤3 chemotherapy regimens, but had no prior treatment with platinum-based regimens or an EGFr inhibitor. Recruitment in arm 1 was closed in March 2007, according to pre-specified response criteria. Patients randomized to arm 1 were treated with cetuximab alone (400 mg/m$^2$, then 250 mg/m$^2$ weekly); carboplatin (AUC=2) weekly for 3 of 4 weeks was added upon disease progression. Patients in arm 2 were treated with cetuximab plus carboplatin throughout. The primary endpoint is objective response (CR+PR). Among 21 evaluable patients in arm 1, 86% had been previously treated with (neo)adjuvant chemotherapy, usually anthracycline/taxane-based, and 62% had also been treated with at least 1 regimen for metastatic disease. Single agent cetuximab was well tolerated. Grade 3 drug-related AE were rash (n=4), fatigue (n=1), cellulitis (n=1), back pain (n=1), irregular menses (n=1), and elevated LFT (n=1). There was 1 case of Grade 4 anaphylaxis. There was 1 PR (4%) that lasted >40 weeks. Disease stabilized in 4 (19%) and progressed in 16 (76%). Disease progressed quickly in most patients. It progressed at 4 weeks into therapy in 5 (24%) patients and by 8 weeks in 10 (48%).

After progression, carboplatin was added to cetuximab in 19 patients, of whom 14 are currently evaluable. There are 4 (28%) unconfirmed PR and 4 (28%) SD. Molecular subtyping of 10 tumors from the overall trial confirmed basal-cell cancer in 9 patients (claudin subtype=1). Treatment with cetuximab alone was well tolerated but resulted in a low response rate and, therefore, failed the criteria for ongoing evaluation. Arm 2 was completed in mid-2007. Translational studies confirming molecular subtype, identifying biologic effects of EGFr inhibition and platinum, evaluating circulating tumor cells (CTC), and studying the BRCA1 pathway are ongoing (Carey LA, etal, SABCS07, Abs. 307).

In a nonrandonized phase II clinical trial (protocol ID: OSI3875s; 10864; NCT00491816), initiated in July 2007, in the USA, the efficacy of erlotinib, in combination with

docetaxel and carboplatin, is under evaluation for the treatment of patients with Stage II or Stage III, triple negative breast cancer in the neoadjuvant setting. The primary objective of this trial is to determine whether the combination of chemotherapy and erlotinib will eliminate microscopic disease at the time of surgery in >20% of enrolled patients. After completing chemotherapy, all patients will be treated with maintenance erlotinib for 12 months.

The EGFr inhibitors may face competition in the triple negative breast cancer indication by approved therapeutics targeting other relevant pathways, such as the angiogenesis inhibitors, bevacizumab and sunitinib (Sutent; Pfizer), both of which are in clinical trials for this indication.

### Breast Cancer Metastasized to the Brain

Treatment for brain metastases is an area of significant unmet medical need because breast cancer is the second most common type of cancer to metastasize to the brain. One third of women with HEr2 overexpressing metastatic breast cancer develop CNS metastases (Bendell JC, etal, Cancer 2003;97:2972-2977). Overall disease prognosis is poor once brain metastasis occurs. The average 1-year survival after such a diagnosis is estimated at about 20%.

***Trastuzumab*** may be effective in preventing and/or treating breast cancer metastasized to the brain. Data indicate that HEr2+ breast cancer confers an increased risk of brain metastases. Although several studies have evaluated brain metastases in trastuzumab-treated patients, data regarding brain metastases in trastuzumab-naïve HEr2+ patients had not been reported until ASCO07. This trial addressed the critical issues of time to central nervous system (CNS) metastasis, death, and death subsequent to brain metastasis in relation to trastuzumab treatment. The retrospective study evaluated 750 patients diagnosed with HEr2+ metastatic breast cancer between June 1977 and January 2006. The control group consisted of patients with HEr2+ metastatic breast cancer treated at a single institution before trastuzumab was available.



Of the 750 patients in the trial, 689 were treated with trastuzumab during the follow-up period, while the remaining 61 patients were not treated with trastuzumab. Median follow-up was 32 months. A total of 251 patients developed CNS metastases. Adjustments were made for other known prognostic variables, including age, Er and Pgr status, pathologic stage, and site of initial metastasis. A 2.84 times greater risk of CNS metastases ($p<0.0001$) was observed in trastuzumab-treated patients compared to those who were not treated with trastuzumab. Time-to-death following CNS metastasis did not differ significantly between trastuzumab-treated and untreated patients. It was concluded that, in a large trial, patients with HEr2+ metastatic breast cancer treated with trastuzumab were at significantly increased risk of developing CNS metastases compared to those who were not treated with trastuzumab. Investigation into biologic mechanisms that explain this difference are needed (Pinder MC, etal, ASCO07, Abs. 1018).

Another retrospective study examined the course of disease as a function of HEr2 status in 50 consecutive patients with primary breast cancer who developed brain metastases. Many factors were evaluated, including HEr2 and Er/Pgr status, tumor stage, nodal stage, use of whole brain radiotherapy (WBRT) as initial management of CNS disease, initial number of metastases, hormonal therapy, use of trastuzumab, and Karnofsky Performance Status (KPS). A total of 54% of patients were HEr2+, while only 15% were Er+; only one HEr2+ patient was not treated with trastuzumab. A total of 72% of patients were node positive, tumor (T) stage was T1=24%, T2=36%, T3=8%, and T4=16%, and only 5 had metastases at the time of diagnosis. Adjuvant chemotherapy was administered to 90% of the sampled patients, and 94% underwent radiation to the primary site; 66% had ≤3 initial brain metastases, and 38% underwent WBRT as part of the initial CNS management. Median follow-up was 55 weeks. There were 2 independent OS predictors from the time of initial diagnosis of CNS disease, HEr2 positivity ($p=0.007$) and ≤3 initial brain metastases ($p=0.003$). For HEr2+ patients, MST was 65 weeks, compared to 33 weeks for HEr2- patients. Actuarial 1-year survival was 87% for HEr2+ patients and 44% for HEr2- patients. This group concluded that, although HEr2+ patients appear to be at a greater risk of developing brain metastases, OS from time of initial diagnosis of brain metastasis appears to be longer in this cohort, which may be a function of improved extracranial control provided by trastuzumab in patients with HEr2+ disease (Sawrie SM, etal, ASCO07, Abs. 1016).

According to another retrospective study, CNS metastasis not only did not adversely effect OS, but patients who developed CNS metastases lived longer than patients without CNS metastases, possibly because of more aggressive management of CNS metastases or lack of extracranial progression. A total of 100 patients with HEr2+ metastatic breast cancer who were treated with trastuzumab with or without chemotherapy, between January 2000 and January 2005, were selected for the presence (n=50) or absence (n=50) of CNS metastases. In the 50 patients with CNS metastasis, the most common site was the cerebellum (82%). These patients experienced symptoms related to increased intracranial pressure, primarily caused by disease-related cerebral edema (73%). There was no statistically significant difference between the two groups in OS from the time of initial diagnosis of breast cancer. Of interest, patients with CNS metastases lived longer (61.3 months) than those without CNS metastases (47.1 months). Survival time after disease progression or recurrence was significantly longer (36.8 months versus 22.0 months; $p=0.02$) in patients with CNS metastases (Verma S, etal, ASCO07, Abs. 1017).

***Lapatinib*** inhibited brain colonization in animal models of dual EGFr and Her2 overexpressing breast cancer cells (Palmieri D, etal, SABCS07, Abs. 210). Lapatinib is currently under investigation in a multicenter (n=46), international, randomized, open label, uncontrolled phase II clinical trial (protocol ID: 107671; EGF107671; NCT00437073), in combination with topotecan or capecitabine, in the treatment of recurrent brain metastases in HEr2+ breast cancer following cranial radiotherapy. The trial, initiated in February 2007, will enroll 110 patients with HEr2+ breast cancer with progressing brain lesion(s), despite prior treatment with WBRT and/or stereotactic radiosurgery and prior treatment with trastuzumab, either alone or in combination with chemotherapy.

A multicenter (n=99), international, nonrandomized, open label, phase II clinical trial (protocol ID: EGF105084, NCT00263588) of PO lapatinib (750 mg), administered twice daily in patients (n=241) with HEr2+ breast cancer with brain metastases following trastuzumab-based systemic therapy and cranial radiotherapy, was initiated in December 2005 under lead investigator Nancy U. Lin, MD, at Dana-Farber Cancer Institute (Boston, MA). Radiographic evidence of progressive brain metastases with at least 1 measurable brain lesion was required. Primary endpoint was CNS response, defined as 50% volumetric reduction of CNS lesions in the absence of new lesions, reduced need for increased dose of steroids, and no progressive neurological signs/symptoms, or progressive extra-CNS disease. CNS disease progression was defined as either 40% volumetric increase from nadir, increase in steroid requirements, or progression of neurological signs/symptoms.

A total of 241 patients, 210 with current non-CNS disease and 31 with undetectable non-CNS disease were enrolled in this trial from December 2005 to November 2006. Preliminary data is available from the first 104 patients who have undergone independent radiology review. There were 19 PR, defined by ≥50% volumetric reduction in brain lesions, with no progression of tumor outside the brain, no increase in steroid requirements, or worsening of neurologic symptoms. A ≥20% volumetric reduction in brain lesions was observed in 46 patients. Median PFS was 15.1 weeks. Disease stabilized in 102 patients for at least 8 weeks, based on composite response criteria, and progressed in 22% of patients within the first 6 months of lapatinib treatment. Most common AE were Grade 3/4 diarrhea (13%), Grade 3/4 skin rash (3%), Grade 3 nausea (3%), Grade 3 vomiting (4%), Grade 3 fatigue (3%), and Grade 3 anorexia (1%). The trial was later amended to allow patients with disease progression in the brain and/or non-CNS progression to be treated with the combination of daily lapatinib (1250 mg) and capecitabine (2000 mg/m$^2$/day). Among 40 patients treated with this combination, a ≥50% volume reduction in brain metastasis was observed in 8, and a ≥20% volume reduction in 16 patients. This trial confirms the single agent activity of lapatinib in patients with recurrent brain metastases from HEr2+ breast cancer (Lin NU, etal, ASCO07, Abs. 1012).

According to more mature results from this extension arm of this phase II clinical trial, the combination of lapatinib and capecitabine shrank tumors that had spread to the brain and had progressed on lapatinib monotherapy in patients with HEr2+ breast cancer. Specifically, a 50% volumetric reduction in measurable brain metastases was observed in 20% of patients treated with lapatinib plus capecitabine. Overall, a volumetric decrease ≥20% was seen in 37% of patients. According to preliminary results of the extension arm of the initial 49 patients enrolled and treated as of March 2007, volume reduction in brain metastases of at least a 20% was observed in 18 patients (37%), without disease progression outside of the brain, increase in steroid requirements, or worsening of neurologic signs or symptoms. Median reduction in brain metastases was 4.8 cm. Among these 18 patients, a volume reduction in brain metastases of least 50% was noted in 10 (20%), with a median reduction in brain metastases of 7.1 cm. As of September 2007, 3 patients remained on the original trial with lapatinib monotherapy and 8/51 patients remained on treatment in the extension arm of lapatinib plus capecitabine. Among the 51 patients enrolled in the extension arm, there were 10 (20%) PR, and disease stabilized in 20 (39%) and progressed in 15 (29%). The status of 6 (12%) patients was unknown at the time of this report (Lin NU, etal, SABCS07, Abs. 6076).



## Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is highly aggressive, spreads rapidly, often requires full mastectomies, and is associated with a worse outlook than other types of breast cancer. The average lifespan after diagnosis is about 3 years. IBC is a rare form of breast cancer, representing 1% to 2% of all diagnosed cases. Standard treatment is a combination of anthracyclines and taxanes for 24 weeks, which results in a clinical response rate of about 60% to 75%, but OS is lower than other forms of breast cancer. Overexpression of HEr2 in IBC occurs in about 50% of cases, which is nearly twice as frequent as the 25% to 30% incidence in breast cancer overall, and is associated with a worse prognosis.

Both trastuzumab and lapatinib have been clinically investigated and shown promise in treating IBC. Positive results regarding the use of trastuzumab in the neoadjuvant setting in this indication are described in the section on neoadjuvant chemotherapy in early breast cancer.

***Lapatinib*** monotherapy has been clinically tested in specifically in patients with IBC. A phase II trial concluded that lapatinib monotherapy is active in women with IBC who have been heavily pretreated. This nonrandomized, open label, phase II trial (protocol ID: EGF103009, NCT00105950) of lapatinib in patients with relapsed or refractory IBC was initiated in March 2005 at multiple

locations (n=8) in the USA and Canada, to determine safety and efficacy of daily lapatinib (1500 mg), permitted to continue as long as the patient was benefiting from the treatment. Patients with relapsed/refractory IBC, based on clinical criteria, were assigned after analysis of a fresh tumor biopsy, to cohort A for HEr2 overexpressors or cohort B for EGFr and/or HEr2 non-overexpressors. Clinical response was documented on day 56 and in the case of CR or PR, confirmed on day 84 and every 8 weeks thereafter. Tumor expression of HEr2, p-HEr2, EGFr, p-ErbB3, IGF-Ir, PTEN, Er/Pgr, E-cadherin, β-catenin, and Rho B/C was analyzed by quantitative IHC from a fresh, pretreatment biopsies.

Among 34 enrolled patients, clinical response data were available from 22, of which 17 had biopsies analyzed and assigned to cohorts A (n=11) or B (n=6). Among 11 evaluable patients, there were 8 (72%) responses (CR+PR) to lapatinib in cohort A, documented by RECIST, skin disease, or both. There were no responders in cohort B. In all responders tumors overexpressed HEr2 and increased p-HEr2 (2+/3+), co-expressed IGF-Ir, and expressed activated p-ErbB3. PTEN status did not affect response to lapatinib. Toxicity was generally Grade 1/2 skin and gastrointestinal (GI); 1 case of Grade 3 cardiotoxicity necessitated withdrawal from the trial. HEr2 overexpression, but not EGFr expression alone, predicted for sensitivity to lapatinib in IBC. High HEr2, p-HEr2, and IGF-Ir co-expression predicted clinical response to lapatinib monotherapy in patients with relapsed/refractory IBC, illustrating the importance of selecting patients based on biology, rather than histology alone, in order to maximize the clinical efficacy of ErbB kinase inhibitors in treating breast cancer (Spector NL, etal, ASCO06, Abs. 502). According to more mature results, among 57 patients assigned to either cohort A or cohort B, 15/24 (62%) patients in cohort A responded to lapatinib. Tumors of all responders overexpressed HEr2 and all also demonstrated increased pHEr2 (2+/3+), coexpression of IGF-Ir, and expression of activated p-ErbB3. Treatment with lapatinib was well tolerated. Grade 1/2 toxicity represented 90% of all AE; 57 events were GI related, and 23 were skin rashes. Only 10 events were Grade 3/4, including diarrhea, anorexia, headache, anemia, and thrombocytopenia.

In another trial, lapatinib monotherapy and lapatinib in combination with paclitaxel were significantly active in women with newly diagnosed IBC. Patients were divided into 2 cohorts on the basis of biomarker analysis (HEr2+=30 and HEr2-=5). PO lapatinib (1500 mg) was administered once daily for 2 weeks and then combined with once weekly paclitaxel (80 mg/m$^2$) for an additional 12 weeks. Lapatinib was more effective in the 30 patients with HEr2-overexpressing tumors. During the first 2 weeks of lapatinib monotherapy, there were 10 (30%) clinical responses. After combination therapy, there were 3 (10%) CR, and 20 (67%) PR, for a clinical response rate of 77%. Disease stabilized in another 3 (10%) patients, and response was not established in the remaining 4 patients. In operated patients, a pathologic CR, defined as no evidence of residual invasive tumor, including no residual tumor in the axillary lymph nodes, was observed in 3/18 (17%) patients. There were 4 PR, and disease progressed in 1 patient during therapy in the HEr2- cohort. Side effects of lapatinib were predictable and manageable. The most common were diarrhea and skin rash. Diarrhea was reported by nearly all patients, Grade 1/2 in 12 (34%) and >Grade 3 in 21 (60%) patients. Skin rash was Grade 1/2 in 20 (57%) patients and >Grade 3 in 3 (9%). Treatment with this regimen of lapatinib and paclitaxel lasted only 14 weeks, which is 10 weeks shorter than the usual period. The overall clinical response rate of 80% is somewhat higher than that reported (60-75%) for standard chemotherapy. The 30% response rate after 2 weeks of monotherapy provides proof of principle that lapatinib monotherapy is effective in IBC (Cristofanilli M, etal, SABC06, Abs. 1).

***Trastuzumab*** was very effective, and well tolerated with acceptable cardiac safety in a subpopulation of patients with IBS treated with this drug in combination with chemotherapy in the neoadjuvant setting. According to updated data from the NOAH clinical trial (see below), among 228 evaluable patients with HEr2+ breast cancer, 61 were diagnosed with IBC. There were 14 patients with IBC among the 99 evaluable patients with HEr2-negative breast cancer. A total of 31 patients with HEr2+ IBC were treated with trastuzumab in addition to chemotherapy. In this group, trastuzumab plus chemotherapy led to a CR in nearly 3 times as many patients with IBC compared to chemotherapy alone (55% versus 19%, p=0.004). The combination treatment led to complete disappearance of tumors from both the breast and the lymph nodes (total pathological CR) in 48% of patients, compared to 13% in the chemotherapy alone group (p=0.002). Data is not yet mature (Baselga J, etal, ECCO07, Abs. 2030).

### Adjuvant/Neoadjuvant/Early-Stage Treatment

Adjuvant or neoadjuvant use of agents to treat major common malignancies is the holy grail of drug development because it applies to large populations with early stage disease. In the USA alone, most of the approximately 200,000 new cases of breast cancer diagnosed each year are candidates for adjuvant treatment. Also, clinical response to neoadjuvant chemotherapy is a validated surrogate marker for improved survival. The neoadjuvant setting offers a unique opportunity to identify biologic correlates of response and resistance because it provides access to biopsies of resected primary tumors and early assessment of response to therapy, which is not possible in the adjuvant setting. However, because CR following neoadjuvant chemotherapy is achieved in only one third of patients with HEr2- tumors (the CR rate doubles in those with HEr2+ tumors) there is a need for more effective regimens and better predictors of outcome. At present, among ErbB-pathway inhibitors, only trastuzumab has been approved for this indication in breast cancer. Lapatinib is

under investigation in this indication, based on the validated HEr2 target.

***Trastuzumab*** is the first targeted agent to be approved for the adjuvant treatment of Her2+ breast cancer. Because of the validated role of HEr2 in all stages of breast cancer, trastuzumab is currently included in most combination therapy trials in early stage HEr2+ breast cancer.

According to updated results from the joint efficacy analysis of two phase III clinical trials (NCT00005970 and NCT00004067) of trastuzumab in patients with surgically removed HEr2+ breast cancer (see FO, V9#3/4), among 3,969 women enrolled, there have been 619 events (trastuzumab=222, non-trastuzumab=397) and 258 deaths. First events were recurrence (n=511), contralateral breast disease (n=18), other second primary tumors (n=48), and death without recurrence or second primary tumors (n=42). Median follow-up is 2.9 years for the 3,711 patients who are still alive. At 4 years follow-up, DFS rate and OS rate were 85.9% and 92.6%, respectively, in the trastuzumab group, and 73.1% and 89.4%, respectively, in the non-trastuzumab group. Hazard ratio for adjuvant chemotherapy (trastuzumab/non-trastuzumab) was 0.49 ($p<0.0001$) for DFS and 0.63 ($p=0.0004$) for OS. For years 1 to 4, rates of a first event per 1,000 women/year were 26.7, 52.9, 49.6, and 23.2 for the trastuzumab group, and 42.3, 102.3, 107.6 and 61.5 for the non-trastuzumab group (Perez EA, ASCO07, Abs 512).

A randomized, phase III clinical trial (protocol ID: UCLA-0102006; AVENTIS-TAX-GMA-302; BCIRG-006; UAB-0106; UAB-F010326012; NCI-G01-197; NCT00021255) compared adjuvant standard doxorubicin/cyclophosphamide for 4 cycles followed by docetaxel (AC-T) for 4 cycles, or 2 trastuzumab-containing regimens, doxorubicin/cyclophosphamide followed by docetaxel with trastuzumab for 1 year (AC-TH), or docetaxel plus carboplatin for 6 cycles with trastuzumab for 1 year (TCH), in 3,222 patients with node-positive or high risk node-negative HEr2+ early breast cancer. According to results from the second planned interim analysis of this trial at a median follow-up of 36 months, both AC-TH and TCH significantly improved DFS and OS, compared to controls. The relative reduction in risk of relapse was 39% ($p<0.0001$) for AC-TH and 33% ($p=0.0003$) for TCH. Congestive heart failure occurred in 0.4% of patients in the AC-T and TCH arms, compared to 1.9% of patients treated with AC-TH. The global safety profile was acceptable in all 3 arms and more favorable in TCH than AC-TH (Robert NJ, etal, on behalf of the BCIRG 006 Investigators, ASCO07, Abs.19647).

A multicenter (n=84), randomized, phase III clinical trial (protocol ID: INCA-PHARE; INCA-RECF0146; EUDRACT-2006-000070-67; NCT00381901) was initiated in September 2006 in France, to compare adjuvant trastuzumab, administered for 6 months versus 12 months, in women with nonmetastatic, resectable breast cancer. The primary objective is DFS. Secondary objectives are incidence of cardiotoxicity, comparison of cardiotoxicity and DFS in patients treated with concurrent trastuzumab and chemotherapy versus sequential administration, and correlation of these parameters with HEr2 polymorphism. Patients are randomized to one of two treatment arms. Patients in arm 1 continue treatment with IV trastuzumab for 12 months and those in arm 2 for 6 months in the absence of disease progression or unacceptable toxicity. Patients who have already completed 6 months of trastuzumab at randomization do not undergo further trastuzumab therapy. Some patients undergo blood collection for HEr2 polymorphism analysis. After completion of therapy, patients are followed periodically for approximately 5 years. The trial will enroll 7,000 patients. Study Chair is Xavier Pivot, MD, Centre Hospitalier Regional (CHR)-Hopital Jean Minjoz (Besancon, France).

NOAH (NeOAdjuvant Herceptin) is an international, randomized phase III clinical trial conducted in Italy, Germany, Spain, and Russia, to determine the antitumor activity and safety of neoadjuvant trastuzumab, in combination with chemotherapy, in 228 patients with centrally confirmed HEr2+ (IHC 3+ or FISH+) locally advanced breast cancer. Patients were treated with 3 cycles of doxorubicin (60 mg/m$^2$), and paclitaxel (50 mg/m$^2$) every 3 weeks, 4 cycles of paclitaxel (175 mg/m$^2$) every 3 weeks, and 3 cycles of CMF consisting of cyclophosphamide (600 mg/m$^2$), methotrexate (40 mg/m$^2$), and 5-FU (600 mg/m$^2$) every 4 weeks on days 1 and 8, with (n=115) or without (n=113) concomitant trastuzumab at an 8 mg/kg loading dose then 6 mg/kg every 3 weeks for 1 year, before surgery. Patients with HEr2- negative disease (IHC 0/1+; n=99) were treated with chemotherapy in parallel. The primary endpoint was event-free survival. Secondary endpoints were ORR, pCR rate, and safety. Baseline characteristics were well balanced for randomized patients (median tumor size=5.5 cm). IBC was present in 40% of HEr2+ and 14% of HEr2- tumors. Baseline LVEF was similar in all 3 groups.

Adding trastuzumab to chemotherapy in patients with HEr2+ tumors improved ORR, which was 81% in the trastuzumab group versus 73% in non-trastuzumab group ($p=0.18$). It also significantly increased the pCR rate (43% versus 23%; $p=0.002$), including eradication of tumor from lymph nodes (38% versus 20%; $p=0.003$). This response pattern was also observed in patients with IBC. For the trastuzumab and non-trastuzumab groups, CR was 60% and 51.3%, PR was 20.9% and 22.1%, SD was 0.9% and 5.3%, and progressive disease was 4.3% and 6.25%, respectively. ORR (66%) and pCR rate (17%) for patients with HEr2-negative disease were similar to patient responses in the HEr2+ group not treated with trastuzumab. The most common serious AE was febrile neutropenia (8% with trastuzumab, 4% without trastuzumab). Absolute LVEF decreases of 10% were observed in 11% of patients treated with trastuzumab, and 1 patient experienced a cardiac event with LVEF <45%. One patient with HEr2-negative

disease died after surgery because of pulmonary embolism. Neoadjuvant trastuzumab plus this chemotherapy regimen significantly improved the pCR rate of locally advanced breast cancer compared to chemotherapy alone. Treatment was well tolerated with acceptable cardiac safety (Gianni L, etal, ASCO07, Abs. 532).

In the first half of 2008, Genentech plans to initiate a clinical trial in HEr2-overexpressing ductal carcinoma in situ (DCIS) to investigate trastuzumab as treatment for patients with Stage 0 disease who have undergone a mastectomy or lumpectomy. This trial is part of the company's strategy to move trastuzumab into earlier stage disease indications and eliminate the need for chemotherapy.

Monogram Biosciences initiated a study in which HERmark assays are performed on tissue samples from up to 1,600 patients with breast cancer treated with trastuzumab in the adjuvant setting. In September 2007, Monogram licensed technology from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation, which provides the company access to tissue samples from breast cancer patients treated with trastuzumab in a phase III clinical trial (protocol ID: NSABP-B-31; NCT00004067). Monogram will pay annual license fees to NSABP and additional royalties in the case of successful development and commercialization of certain products resulting from the licensed rights. The goal of the trial is to clinically validate the ability of HERmark to predict clinical outcome in newly diagnosed trastuzumab-treated patients with operable breast cancer on a first course of adjuvant chemotherapy.



***Lapatinib*** is under investigation in the adjuvant/neoadjuvant setting. In December 2006, GlaxoSmithKline and Massachusetts General Hospital Cancer Center initiated TEACH (Tykerb Evaluation After CHemotherapy), a multicenter (n=533), international, randomized, double blind, placebo-controlled phase III clinical trial (protocol ID: EGF105485; NCT00374322) of adjuvant lapatinib in women with early stage HEr2-overexpressing breast cancer with either positive or negative node involvement. The goal is to determine whether adjuvant treatment with lapatinib will improve DFS in this setting.

The trial is designed to compare the efficacy and safety of lapatinib versus placebo in women who had been treated for early stage, HEr2+ breast cancer and have no clinical or radiographic evidence of disease. Participants must have completed primary adjuvant chemotherapy prior to trial entry but must not have been treated with trastuzumab. Patients are randomized to either lapatinib (1500 mg) or matching placebo, administered orally once daily. Patients continue treatment for a maximum of 12 months or until disease recurrence, development of a second primary cancer, withdrawal from the trial because of unacceptable toxicity, or consent withdrawal. All women will be followed until death or trial closure. The trial's primary efficacy endpoint for analysis is DFS. Secondary endpoints include overall survival; recurrence-free intervals (local, regional, distant, contralateral breast, and central nervous system); rate of CNS recurrence; toxicity; health-related quality of life (QoL); biomarkers; and optional pharmacogenetics.

The TEACH trial was proposed by Study Chair Paul Goss, MD, Director of Breast Cancer Research, Massachusetts General Hospital Cancer Center. The protocol was established through the collaboration of members on the TEACH Steering Committee. Approximately 3,000 women will be enrolled. The opportunity for lapatinib as adjuvant treatment of early breast cancer relies on the fact that, although trastuzumab is becoming part of standard adjuvant therapy together with chemotherapy, many thousands of women with early stage HEr2+ breast cancer have already been treated with adjuvant therapy without trastuzumab. Although these patients remain at elevated risk of relapse, there is no data to support initiating additional trastuzumab treatment in patients who were not treated with trastuzumab within seven weeks of completing adjuvant therapy. Furthermore, trastuzumab is not licensed for use in all countries.

A phase II clinical trial (protocol ID: NU-05B2; GSK-NU-05B2; NU-1434-009; NCT00331630) was initiated in May 2006 at Robert H. Lurie Comprehensive Cancer Center at Northwestern University (Chicago, IL), under PI Virginia G. Kaklamani, MD, to determine the clinical response rate of nanoparticle albumin-bound paclitaxel (Abraxane; Abraxis Oncology) combined with lapatinib in treatment-naive patients with Stage I/III breast cancer in the neoadjuvant setting. Secondary objectives are to determine the pCR rate, correlate proliferation (Ki67), apoptosis (cleaved caspase-3), and angiogenesis markers, measured before and after treatment; conduct other correlative studies, including the status of EGFr, HEr2, matrix metalloproteinases (MMP), and transforming growth factor β (TGFβ) before and after treatment; and determine the toxicity of this regimen.

A total of 30 patients are assigned to 1 of 2 treatment groups. In group 1, the first 10 patients are treated with IV Abraxane over 30 minutes on day 1 and oral lapatinib once daily on days 1-21, every 21 days for 4 courses in the absence of disease progression or unacceptable toxicity. In group 2, the next 20 patients are treated with Abraxane and lapatinib, at a higher dose, as in group 1. Treatment repeats every 21 days for 4 courses in the absence of disease progression or unacceptable toxicity. Patients undergo blood collection and tumor biopsies periodically for correlative biomarker studies.

A randomized, open label, uncontrolled, single group assignment, phase I/II clinical trial (protocol ID: INST 0514C; NCT00455039) with single agent lapatinib, was initiated in July 2005 at the University of New Mexico (Albuquerque, NM), under PI Melanie Royce, MD, in women with advanced (Stage III) or metastatic (Stage IV) HEr2+ breast cancer in the neoadjuvant setting, to assess biologic correlates of response and resistance.

***Erlotinib*** is also under investigation in the treatment of early breast cancer. Investigators at Vanderbilt-Ingram Cancer Center (Nashville, TN) report that a short course of erlotinib reduces cell proliferation and active MAP kinase and S6 in untreated operable breast cancer. A trial of neoadjuvant erlotinib was designed to determine the cellular activity of the drug against breast tumors and determine whether the molecular profile was suggestive of EGFr dependence. Newly diagnosed patients with operable breast cancer were treated with erlotinib (150 mg/day) for 7-10 days until 24 hours prior to surgery, at which time a blood sample was collected to measure erlotinib plasma levels. Changes in apoptosis and cell proliferation, measured at the initial biopsy and the post-treatment surgical specimen, were used to assess drug-mediated cellular activity *in vivo*. Surrogate markers of response were sought using IHC for both total and phosphorylated EGFr, HEr2, Akt, MAPK, and S6. Erlotinib was well tolerated in the 33 patients treated in the trial, causing no delays in surgery; 2 patients discontinued treatment because of Grade 2 skin rash, which was reversible after drug discontinuation. Overall, 5 tumors were positive for total EGFr by IHC, but p-EGFr was negative in all cases. Ki67 changed significantly in response to therapy (p=0.004), decreasing by >75% in 8/26 tumors with treatment; p-MAPK and p-S6 also changed significantly (p=0.002 and p=0.001, respectively). There was a significant correlation between changes in Ki67 and p-S6 but not between Ki67 and p-MAPK. No apoptosis induction or significant changes in nuclear localization and/or total levels of p-Akt were observed (Guix M, etal, SABCS06, Abs. 6090).

A clinical trial (protocol ID: WSU-2006-138; NCT00503841) to investigate erlotinib treatment in 44 women undergoing surgery for Er-negative and Pgr-negative (may be positive or negative for HEr2) Stage I/III disease is in the planning stage at the Barbara Ann Karmanos Cancer Institute (Detroit, MI), under PI Elaina M. Gartner, MD. The primary objective is to estimate the effect of erlotinib on expression of interleukin (IL)-1α in patients with Er-negative, EGFr-positive, and IL-1α-positive breast cancer. Secondary objectives are to estimate the effect of erlotinib on the expression of nuclear NFκB and amphiregulin (AR) and on the rates of IL-1α, nuclear NFκB, and androgen receptor (Ar) expression in these patients; follow their clinical course; and assess the toxicity of a 15-day regimen of daily oral administration of erlotinib.

***Gefitinib***, in combination with chemotherapy, does not appear to have a role in the treatment of breast cancer in the neoadjuvant setting. A randomized placebo-controlled phase II clinical trial (protocol ID: 1839IL/0712; NCT00239343) was conducted in Europe (Denmark, Norway, Sweden) to determine whether the addition of gefitinib to preoperative chemotherapy would increase the pCR rate. In this trial, 144 patients with operable breast cancer, tumor diameter of >2.0 cm and Er-negative tumors, were assigned to 4 cycles of epirubicin (90 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$), with or without gefitinib (250 mg daily). After surgery, patients in both arms were treated with adjuvant epirubicin and cyclophosphamide or docetaxel. The primary objective was pCR (no invasive residual) at surgery. Secondary endpoints were CR and overall ORR assessed by palpation, mammography, and ultrasonography, which prevailed in case of disagreement. Median age, tumor size, and nodal status were comparable at baseline in the two groups. A pCR was noted in 8 of 71 (11%) patients assigned to the gefitinib arm and in 8 of 73 (11%) patients assigned to placebo arm (p=0.95). There were 50 CR in both the gefitinib group (70%) and the placebo group (68%); 9 patients discontinued treatment following an AE in the gefitinib arm, compared to 2 patients in the placebo arm. Adding gefitinib to preoperative chemotherapy in patients with operable, Er-negative breast cancer did not provide any significant benefit in this setting (Ejlertsen B, etal, SABCS07, Abs. 5056).

## Approved ErbB Pathway Inhibitors in Combination with Hormonal Therapy

There appears to be a link between Er-positive breast cancer cells with acquired hormone resistance and EGFr signaling, which is not seen with the parental hormone-sensitive cells. Also, breast cancer cells show an inverse correlation between Er and EGFr; Er-negative breast tumors are more likely to express EGFr.

Trastuzumab has been approved in combination with hormonal therapy (see FO, V9 #3/4). Approximately 45% to 50% of HEr2+ breast tumors are also Er+, and evidence of crosstalk between HEr2 and Er signaling pathways in breast cancer suggests that combining treatments that target these different pathways may provide better outcomes than either agent alone. Nearly all ErbB-pathway inhibitors are under investigation in combination with hormonal modulators (see Exhibit 1). According to the French National Epidemiological Study (ESTHER)3 approximately 61% of breast cancer tumors are Er+, and a significant number (14%) are both Er+ and HEr2+. Er+/HEr2+ breast cancer is a distinct subgroup with a relatively poor prognosis because of HEr2 positivity.

Trastuzumab, in combination with anastrozole (Arimidex; AstraZeneca) in the first line treatment of women with Er+ and/or Pgr+, HEr2+ metastatic breast cancer, doubled PFS and significantly improved the clinical benefit rate, TTP, and ORR compared to treatment with anastrozole alone. OS was longer in the trastuzumab plus anastrozole arm despite crossover of more than half of the patients in the anastrozole arm to trastuzumab upon progressive disease (Mackey JR, etal, SABCS06, Abs. 3).

Similar results were obtained with the combination of letrozole (Femara; Novartis) and trastuzumab. A phase II clinical trial enrolled 33 postmenopausal women with Er+ and/or Pgr+ and HEr2+ advanced breast cancer to be treated with letrozole (2.5 mg), administered daily, and trastuzumab (2 mg/kg), administered weekly, until disease progression or unacceptable toxicity. Among 31 evaluable patients, the majority (82%) had been treated with tamoxifen; 82% had HEr2 FISH+ and/or IHC 3+ tumors. There

**Exhibit 1**
**Combination Trials of ErbB Inhibitors and Hormone Modulators in Breast Cancer**

| Protocol ID | Treatment | Patients | Phase/Indication | Status |
|---|---|---|---|---|
| **Trastuzumab** | | | | |
| NCT00171847 | Letrozole | 370 | Phase IV ❑ metastatic, postmenopausal, HEr2+ and hormone receptor-positive (Er+ and/or Pgr+) breast cancer | Ongoing |
| NCT00134680 | Letrozole | 33 | Phase II ❑ advanced, postmenopausal, HEr2+ and hormone receptor-positive (Er+ and/or Pgr+) breast cancer | Completed |
| NCT00405938 | Anastrozole or fulvestrant with bevacizumab and trastuzumab | 80 | Phase II ❑ metastatic, postmenopausal, hormone receptor-positive (Er+ and/or Pgr+) breast cancer, first line | Ongoing |
| NCT00138125 | Fulvestrant | 120 (40 per treatment arm) | Phase II (randomized) ❑ metastatic, postmenopausal, hormone receptor-positive (Er+ and/or Pgr+) breast cancer, first line | Ongoing |
| **Lapatinib** | | | | |
| NCT00073528 | Letrozole | 760 (380 per treatment arm) | Phase III (randomized) ❑ advanced (Stage IIIb) or metastatic (Stage IV), postmenopausal, hormone-receptor positive breast cancer | Closed |
| NCT00499681 | Letrozole | 36 | Phase II (randomized) ❑ early stage (Stage I/II) or locally advanced (Stage III), postmenopausal breast cancer, neoadjuvant | Closed |
| NCT00422903 | Letrozole | 91 | Phase II (randomized) ❑ early stage hormone-positive (Er+ and/or Pgr+) and HEr2-negative breast cancer, neoadjuvant | Ongoing |
| NCT00390455 | Fulvestrant | 324 | Phase III (randomized) ❑ postmenopausal, advanced (Stage III) or metastatic (Stage IV) breast cancer, second line | Ongoing |
| NCT00424164 | Tamoxifen | 20 | Phase I ❑ advanced or metastatic breast cancer | Ongoing |
| **Erlotinib** | | | | |
| NCT00179296 | Letrozole | 150 | Phase II ❑ locally advanced or metastatic, postmenopausal, hormone receptor-positive (Er-positive and/or Pgr-positive) breast cancer, second line | Ongoing |
| NCT00570258 | Fulvestrant | 130 | Phase II (randomized) ❑ hormone receptor-positive metastatic breast cancer refractory to first line hormonal therapy | Ongoing |



were 8 responders (1 CR and 7 PR) for an ORR of 26%; the clinical benefit rate was 52%. Median TTP was 5.8 months, and median duration of response was 20.6+ months. Excluding IHC 2+, FISH- tumors, the OR was 24%, the clinical benefit rate was 44%, TTP was 5.5 months, and the duration of response was 17+ months. The combination was well tolerated, with only two events requiring termination of trial medication. Combined trastuzumab and letrozole treatment in patients with HEr2+ and Er+ advanced breast cancer produced durable responses consistently lasting for at least 1 year in 25% of patients. While these data are promising for a subgroup, trastuzumab plus

letrozole was inactive in 50% of patients. This finding demonstrates that Er+ HEr2+ advanced breast cancer is heterogeneous, and additional agents may be required for optimal management (Marcom PK, etal, Breast Cancer Res Treat, Mar 2007;102(1):43-9).

A phase IV clinical trial (protocol ID: CFEM345C2403; NCT00171847) is ongoing in Europe with a combination of letrozole and trastuzumab. Goals are to determine TTP, which is assessed by clinical palpation and radiologic imaging every 3 months, ORR/clinical benefit rate, time-to-treatment failure, duration of response/clinical benefit during treatment, and OS during follow-up.

A randomized, double blind, placebo-controlled, phase III clinical trial (protocol ID: GSK-EGF30008, UCLA-0311034-01, NCT00073528) is underway to assess letrozole, with or without lapatinib, in the treatment of postmenopausal women with Stage IIIb/IV breast cancer. Patients are stratified according to site of disease (soft tissue/visceral versus bone only) and prior adjuvant antiestrogen therapy (<6 months from discontinuation, ≥6 months from discontinuation, or no prior antiestrogen therapy). In arm 1, patients are treated with lapatinib (1500 mg/day) and letrozole (2.5 mg/day), while those in arm 2 are treated with placebo and letrozole once daily. Treatment in both arms continues in the absence of disease progression or unacceptable toxicity. QoL is assessed at baseline, every 12 weeks during therapy, and upon discontinuation of therapy. The primary endpoint is TTP (6-month PFS). Secondary endpoints include overall response rate, clinical benefit, time-to-response, duration of response, 6-month PFS, OS, toxicities, QoL, biomarkers, and proteomic analysis/genetic variants. This multicenter (USA=87, ROW=164) trial began in November 2003 with an enrollment goal of 1,280, and has since been closed.

In September 2006, the Cancer and Leukemia Group initiated a multicenter (n=281), open label, randomized, double blind, placebo-controlled phase III clinical trial (protocol ID: CALGB-40302; NCT00390455) of fulvestrant (Faslodex; AstraZeneca), with or without lapatinib in the second line treatment of postmenopausal women with Stage III/IV breast cancer that is hormone receptor-positive and expresses HEr2. The primary outcome measure is PFS. Secondary outcome measures include toxicity, ORR as defined by RECIST (for patients with measurable disease), duration of tumor response, OS, and QoL. According to the protocol, patients are stratified according to prior tamoxifen therapy (yes or no) and bone disease only (yes or no). Patients are randomized to one of two treatment arms. In arm 1, patients are treated with oral lapatinib once daily on days 1-28 and fulvestrant intramuscularly (IM) on days 1 and 15 of course 1 and on day 1 of each subsequent course. In arm 2, patients are treated with oral placebo once daily on days 1-28 and fulvestrant as in arm I. In both arms, treatment repeats every 28 days in the absence of disease progression or unacceptable toxicity. QoL is assessed at baseline and then on day 1 of every 2 courses of treatment (i.e., day 1 of courses 3, 5, 7, etc.). After completion of treatment, patients are followed every 6 months for 2 years and then annually for 3 years. A total of 324 patients will be accrued for this trial in the USA.

Gefitinib has also been evaluated in clinical trials in combination with letrozole, anastrozole, fulvestrant, and tamoxifen; all these trials have been closed.

A randomized phase II clinical trial (protocol ID: D7917C00225; 1839IL/0225; NCT00229697) of gefitinib or placebo in combination with tamoxifen in two patient populations with hormone receptor-positive metastatic breast cancer, was initiated in October 2003, in the USA, Canada, and Europe. Stratum 1 (S1) enrolled patients with newly diagnosed metastatic breast cancer or who had completed adjuvant tamoxifen 1 year before trial entry. Patients in stratum 2 (S2) had developed metastatic breast cancer during/after adjuvant aromatase inhibitor (AI) or had failed first line aromatase treatment. The primary response variables and criteria for potential further evaluation of gefitinib were PFS with 5% improvement in survival time in S1, and clinical benefit rate, defined as CR+PR+SD, with 5% improvement. Patients in both strata were randomized to either tamoxifen (20 mg/day), in combination with either gefitinib (250 mg/day) or placebo. The trial recruited 290 patients (S1=206, S2=84) from 54 centers in 12 countries. HEr2 was overexpressed in 43 of 289 (15%) patients.



In S1, the PFS HR of gefitinib to placebo was 0.84 (p=0.31); median PFS was 10.9 versus 8.8 months. The clinical benefit rate was 50.5% (53/105) with the combination, compared to 45.5% (46/101) with placebo. Objective response rates were 12.4% (13/105) and 14.9% (15/101), respectively. In S2, the clinical benefit rate was 29.2% (14/48) with gefitinib and 31.4% (11/35) with placebo (p=0.52), and there were no objective responses. In S2 for PFS, the HR for gefitinib to placebo was 1.16 (p=0.58). Median PFS was 5.7 months with gefitinib versus 7.0 months with placebo. Patients treated with tamoxifen plus gefitinib experienced a higher incidence (26% versus 15%) of SAE, Grade 3/4 AE (41% versus 15%), and withdrawals because of AE (16% versus 4%), compared to the placebo arm. There were 4 deaths in the combination arm; a fatal pulmonary embolus was considered related to tamoxifen in the placebo arm. In S1, the numerical advantage in PFS for patients treated with the combination met the predefined criterion for further evaluation of the tamoxifen/gefitinib combination. These results are consistent with the concept that the ErbB-pathway may play a role in acquired resistance to tamoxifen in some patients, and blockade may yield longer disease control. In S2 the numerical disadvantage in the clinical benefit rate for patients treated with the combination, compared to controls, emphasizes differences in patient populations in the two strata, which are presumed to be related to previous breast cancer

therapy. Safety results showed no unexpected findings for either arm (Osborne K, etal, SABCS07, Abs. 2067).

### Approved ErbB Pathway Inhibitors in Combination with Other Approved ErbB Inhibitors

Overexpression of HEr2 is frequently associated with expression of EGFr, and EGFr expression influences response to HEr2 inhibition. Overexpression of EGFr in tumors that also overexpress HEr2 is associated with a worse outcome. Furthermore, elevated levels of EGFr have been detected in breast cancer cell lines that are resistant to trastuzumab. These findings suggest that the combination of the two targeted approaches may offer clinically meaningful advantages.

In a preclinical trial, investigators at Dublin City University, and St. Vincent's University Hospital (Dublin, Ireland), evaluated the benefit of combining dual inhibition of EGFr and HEr2 with chemotherapy in HEr2-overexpressing breast cancer cell lines. Combinations of trastuzumab, gefitinib, or lapatinib were tested in two HEr2 and EGFr-positive breast cancer cell lines, SKBR3 and BT474. Dual targeting with trastuzumab and gefitinib was synergistic in SKBR3 cells and additive in BT474 cells. Combined treatment with trastuzumab and lapatinib was synergistic in both SKBR3 cells and BT474 cells. Dual targeting with gefitinib and lapatinib was additive in SKBR3 cells but antagonistic in BT474 cells. Trastuzumab alone and gefitinib alone did not induce significant apoptosis in SKBR3 cells, whereas lapatinib induced significant apoptosis. Combined treatment with trastuzumab and lapatinib further enhanced apoptosis induction. Combined treatment with trastuzumab and gefitinib induced apoptosis comparable to lapatinib alone. Pretreatment with combinations of EGFr and HEr2 inhibitors, followed by the addition of cytotoxic chemotherapy, enhanced the cytotoxicity of the chemotherapy drugs. These results suggest that dual targeting of EGFr and HEr2, by combining trastuzumab with EGFr/HEr2 tyrosine kinase inhibitors, may improve response to treatment in patients with HEr2-overexpressing tumors that also express EGFr (O'Donovan N, etal, SABCS06, Abs. 2073).

Quantitative profiling of ErbB family receptor dimerization interactions may help decipher trastuzumab resistance mechanisms and optimize therapeutic approaches for breast cancer. In order to investigate EGFr mediation of breast cancer disease progression and resistance to trastuzumab, HEK293 and BT474 cell lines were transfected with a panel of wild type (wt) EGFr and mutants, EGFr (L747-A750), EGFr (L858R), EGFr (K745M), EGFr (L747-A750)/T790M, EGFr (L858R)/T790M, and EGFrvIII, which were created by site-directed mutagenesis. Cells were stimulated with growth factors in the absence or presence of various combinations of trastuzumab and erlotinib. Proximity-based, multiplexed electrophoretic tag (eTag) assays were used to detect and quantify HEr1, HEr2, and HEr3 expression and phosphorylation levels and HEr1:HEr1, HEr1:HEr2, HEr1:HEr3, HEr2:HEr2, and HEr2:HEr3 dimers. High levels of wt EGFr and mutants were expressed in both HEK 293 and BT474 cell lines. In comparison to wt EGFr, an increased sensitivity to EGFr inhibition by erlotinib was observed in EGFr (L747-A750), and EGFr (L858R) mutants. In contrast, EGFr (L747-A750)/T790M, and EGFr (L858R)/T790M mutants were resistant in both HEK293 and BT474 cells. High levels of constitutive HEr2 phosphorylation were observed in the BT474 cells, which were not changed significantly in the presence of coexpressed wt EGFr and mutant receptors. HEr2 phosphorylation was reduced slightly in the presence of erlotinib. In BT474 cells, TGF-mediated decreases in HEr2 phosphorylation were enhanced in the presence of trastuzumab. Furthermore, trastuzumab mediated an increase in HEr2 homodimerization with concomitant increase in HEr2 phosphorylation. Increasing levels of EGFr:HEr2 heterodimerization were detected in BT474 cells coexpressing EGFr. The pattern of HEr2 phosphorylation and dimerization in HEr2-overexpressing cells with coexpressed EGFr mutant receptor was modulated in the presence of trastuzumab and erlotinib (Dua R, etal, SABCS07, Abs. 4108).

Trastuzumab is under investigation in several clinical trials in combination with various EGFr inhibitors in advanced breast cancer. In one clinical trial (protocol ID: ECOG-1100; NCT00024154), patients with HEr2+ metastatic breast cancer, treated with 0 to 2 prior chemotherapy regimens for metastatic disease, an LVEF of 50%, and no prior trastuzumab therapy, were treated with trastuzumab (2 mg/kg/week) and gefitinib (250-500 mg/day) until disease progression, unacceptable toxicity, or withdrawal of consent. A 3+3 design was used to determine MTD in the phase I portion of the trial. In phase II, patients were stratified according to prior chemotherapy exposure (group 1=none; group 2=1-2 prior regimens). The primary endpoint was an increase in the proportion of PFS in group 1 from 50% to 65% at 6 months and from 50% to 70% at 3 months in group 2. Most of the 36 eligible patients enrolled in phase II had visceral organ involvement. Among those enrolled in group 1, there was 1 CR, 1 PR, and disease stabilized in 7 for >24 weeks. Median TTP was 2.9 months. There were no responses in group 2, and median TTP was 2.5 months. The toxicity profile of trastuzumab in combination with gefitinib (250 mg/day) was acceptable. However, interim analysis found that TTP did not meet predetermined endpoints required for trial continuation. Further use of this combination is not supported, and these results have implications for other trials using concurrent trastuzumab and EGFr TKI regimens (Moulder SL, etal, ASCO07, Abs. 1033).

A randomized, double blind, placebo-controlled, phase III clinical trial (protocol ID: EGF104383; NCT00272987) is comparing the activity of paclitaxel, trastuzumab, and lapatinib to paclitaxel, trastuzumab, and placebo as first line treatment of chemotherapy-naive patients with HEr2+ metastatic breast cancer. Patients are treated with IV paclitaxel (80 mg/m$^2$), weekly, for 3 weeks of a 4-week cycle, IV

trastuzumab (4 mg/kg loading dose and 2 mg/kg thereafter), weekly, and PO lapatinib (1000 mg), daily, or with paclitaxel, trastuzumab and placebo. Primary outcome is TTP. Secondary outcomes are ORR, clinical benefit, time-to-response, duration of response, PFS and OS, QoL, incidence of brain metastasis, tolerability, incidence of fatigue, and biomarkers. The trial will first enroll an open label safety cohort of 20 patients to assess tolerability of the triplet combination. Total planned accrual is 70 patients.

An international, multicenter (n=165), randomized, open label, phase III clinical trial (protocol ID: EGF104900; NCT00320385) is underway to compare the safety and efficacy of the combination of lapatinib plus trastuzumab to lapatinib monotherapy in patients with metastatic breast cancer with progressive disease on trastuzumab-containing regimens. Primary outcome is PFS. Secondary outcomes are OS, ORR, clinical benefit, time-to-response, duration of response, and QoL. Total planned enrollment is 270; this trial is closed to recruitment.

A phase I/II clinical trial (protocol ID: CHNMC-03049, ZENECA-1839US/0274, ZENECA-IRUSIRES0012; NCT00086957) was initiated in January 2004 to evaluate gefitinib in combination with trastuzumab and docetaxel as second line treatment in patients with HEr2 overexpressing metastatic breast cancer.

### Approved ErbB Pathway Inhibitors in Combination with Other Approved Targeted Agents

Targeting the ErbB pathway for the treatment of breast cancer has resulted in significant clinical benefits but does not constitute a definitive approach, even in tumors proven to overexpress ErbB targets. For example, metastatic disease progresses within 1 year of treatment in the majority of patients with HEr2-overexpression, despite initial response to trastuzumab. Also, no clear benefit of EGFr inhibitor treatment in EGFr-overexpressing breast cancer has been established.

The complexity of the ErbB signaling pathway provides the rationale for combining ErbB-pathway inhibitors with other targeted agents in the treatment of breast cancer. Many such combinations are currently under investigation in clinical trials. Combinations of approved ErbB pathway inhibitors with novel, developmental agents, such as cytotoxics and targeted drugs, and the rationale for these strategies will be discussed in FO V9#7/8, along with detailed profiles of novel ErbB pathway inhibitors.

***Bevacizumab*** (Avastin; Genentech), an inhibitor of vascular endothelial growth factor (VEGF), was approved in Europe in March 2007 for first line treatment of women with metastatic breast cancer in combination with paclitaxel. The approval is based on results from the pivotal phase III clinical trial (protocol ID: ECOG-2100, CANNCIC-E2100, NCCTG-E2100, NSABP-E2100), in which median PFS of patients treated with bevacizumab plus paclitaxel was 11.3 months, compared to 5.8 months in those treated with paclitaxel alone. The secondary endpoint of overall survival was longer in the bevacizumab-containing arm, as indicated by an HR of 0.87. This improvement, however, did not reach statistical significance (p=0.14). Overall, there was a 52% risk reduction (HR=0.48) of disease progression or death associated with the addition of bevacizumab to paclitaxel, based on an independent, blinded review of patient scans. Bevacizumab in combination with paclitaxel was generally well tolerated in patients with locally recurrent or metastatic breast cancer at the recommended dose of 10 mg/kg every two weeks.

In December 2007, however, the FDA Oncologic Drugs Advisory Committee (ODAC) voted 5 to 4 that data in the sBLA, submitted in August 2007, were not sufficient to establish a favorable risk/benefit analysis for the use of bevacizumab, in combination with paclitaxel, for this indication. The absence of a clear OS benefit was one of the reasons for not recommending approval. The sBLA was based on results from the same phase III clinical trial that provided the basis for the European approval. The FDA, which is not bound by the recommendations of its advisory committees, is expected to make a decision on this sBLA by February 23, 2008.

Bevacizumab is under investigation in combination with trastuzumab, either alone or in conjunction with cytotoxic agents, in the treatment of early stage and/or metastatic breast cancer (Exhibit 2). A phase II clinical trial (protocol ID: EGF103890; NCT00444535) is also ongoing to evaluate lapatinib, in combination with bevacizumab, in patients with HEr2+, inoperable, locally advanced (Stage IIIb/IIIc with a T4 lesion), or metastatic (Stage IV) breast cancer.



***Everolimus*** (Certican; Novartis), a once daily oral inhibitor of the mammalian target of rapamycin (mTOR) pathway, has demonstrated broad clinical activity in multiple tumors. It is under investigation in two phase I/II clinical trials in combination with trastuzumab and in a phase I clinical trial in combination with lapatinib, or erlotinib, or trastuzumab, or cetuximab in various solid tumors, including breast cancer.

## LUNG CANCER

According to the World Health Organization (WHO), lung cancer is the most common cancer worldwide, with 1.2 million new cases diagnosed annually. Lung cancer kills more than 3,000 people per day worldwide (Kamangar F, etal, J Clin Oncol 2006;24(14):2137-50). Non-small cell lung cancer (nsclc), a difficult to treat malignancy, accounts for 80% of all lung cancer cases. Most newly diagnosed cases of nsclc represent locally advanced or metastatic disease. Patients diagnosed with nsclc typically have a life expectancy of only 8 to 10 months (Schiller JH, etal, NEJM 2002;346:92-8, and Sandler A, etal, NEJM 2006:355; 2542-50).

**Exhibit 2**
**Ongoing Clinical Trials in Breast Cancer Combining Bevacizumab and Trastuzumab**

| Protocol ID | Combination Treatment | Patients (#) | Phase/Indication |
|---|---|---|---|
| NCT00364611 | Docetaxel | 100 | Phase II ❑ metastatic breast cancer, first line |
| NCT00095706 | | 50 | Phase I/II ❑ HEr2 overexpressing, metastatic or relapsed breast cancer |
| NCT00428922 | Docetaxel | 39 | Phase II ❑ HEr2 overexpressing, metastatic breast cancer, first line |
| NCT00392392 | Carboplatin and nab-paclitaxel (Abraxane) | 30 | Phase II ❑ Stage I/III adenocarcinoma of the breast or inflammatory breast cancer, HEr2 overexpressing, neoadjuvant |
| NCT00464646 | Epirubicin, cyclophosphamide and docetaxel | 105 | Phase II ❑ locally advanced (Stage III), HEr2 overexpressing, breast cancer, adjuvant or neoadjuvant |
| NCT00365365 | Docetaxel | 225 | Phase II (randomized) ❑ node-positive breast cancer, adjuvant |
| NCT00520975 | Carboplatin and paclitaxel | 489 | Phase III (randomized) ❑ HEr2 overexpressing metastatic breast cancer, first line |
| NCT00391092 | Docetaxel | 100-500 | Phase III (randomized) ❑ HEr2 overexpressing metastatic breast cancer, first line |



Approximately 171,000 patients are newly diagnosed with nsclc in the USA each year. Although radiotherapy and surgery are curative options for very early disease, about 60% to 70% of all diagnosed patients, between 100,000 and 120,000 patients in the USA, are treated with first line drug therapy, and half of them, between 50,000 and 60,000, are treated with second line therapy. Almost 25% of newly diagnosed patients present with advanced (Stage IIIa/b) or metastatic (Stage IV) disease.

The three main types of nsclc include:

- adenocarcinoma, the primary form of lung cancer, begins in cells that line the alveoli (alveolar epithelial cells) and produce mucus
- squamous cell carcinoma, also referred to as epidermoid carcinoma, develops from squamous cells that line the airways of the lungs; it is the second most common type of nsclc, accounting for 29% of all cases
- large cell carcinoma involves several types of large cells

In October 2007, Rosetta Genomics (North Brunswick, NJ and Rehovot, Israel) successfully completed the prevalidation phase for a diagnostic test that uses a single microRNA to differentiate squamous from non-squamous lung cancer with high sensitivity and specificity. Launch of this test is expected in 2008.

Lung cancer represents a unique opportunity for ErbB inhibitor therapeutics. Approved indications of ErbB-pathway inhibitors for this indication are described in FO V9#1/2. Both gefitinib and erlotinib have been approved as second line treatment in advanced nsclc. However, gefinitib is applicable only to a narrow indication. Erlotinib is one of several recommended second line treatment options for advanced disease and the recommended third line treatment for advanced disease. Currently, no ErbB pathway inhibitors are approved as single agents or in combination with standard regimens for the first line treatment of advanced or metastatic lung cancer or in the adjuvant or neoadjuvant settings as first line treatment for early disease. However, promising results emerging from recently completed clinical trials may result in new approvals and wider clinical use.

## Advanced or Metastatic NSCLC

Advanced or metastatic nsclc, usually classified as Stage IIIb and Stage IV disease, represents a major opportunity for ErbB-pathway inhibitors, and many trials combining these inhibitors with one or more cytotoxics and/or other targeted therapies are ongoing. The outlook for individual agents may depend on results from clinical trials that are based on specific classifications or manifestations of nsclc, including:

- nsclc subtype (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, etc.)
- male versus female
- presence of tumor markers
- smoker, nonsmoker, never smoker

***Erlotinib*** has been and continues to be more aggressively evaluated in lung cancer than any other drug of its class. New regimens with erlotinib are in development to potentially define expanded role(s) in nsclc. However, to

date, erlotinib has disappointed as a first line treatment in nsclc. Although it demonstrated significant activity as a single agent in second and third line therapy, two large randomized phase III clinical trials failed to demonstrate survival benefit of the combination of erlotinib plus chemotherapy, compared to chemotherapy alone, as first line therapy for advanced nsclc. The negative findings of these two trials, TRIBUTE (USA) and TALENT (Europe), provoked follow-up subset analyses in attempts to identify biomarkers for patient selection and new clinical trials of erlotinib, combined with various approved cytotoxics and/or targeted agents, in first line treatment of advanced nsclc.

TALENT was a placebo-controlled phase III clinical trial in patients with previously untreated advanced (Stage III or IV) nsclc. Patients were administered erlotinib (150 mg/day) or placebo, combined with up to six 21-day cycles of chemotherapy, consisting of gemcitabine (1,250 mg/m$^2$) on days 1 and 8 and cisplatin (80 mg/m$^2$) on day 1. Chemotherapy was administered for a maximum of 6 cycles, after which patients continued on trial drug until disease progression. Treatment with trial drug beyond disease progression was permitted. The primary endpoint was duration of survival with secondary efficacy endpoints of TTP, RR, duration of response (using RECIST), PK and pharmacodynamics, and QoL. The status of EGFr and HEr2 expression was also assessed. TALENT enrolled 1,172 patients at 164 sites worldwide. There were no statistically significant differences in OS, TTP, or QoL (time to symptomatic progression). The toxicity profile of erlotinib combined with gemcitabine was not significantly inferior to gemcitabine alone, with the exception of increased incidence of Grade 3/4 diarrhea (<1% placebo versus 6% erlotinib) and Grade 3/4 skin rash (<1% placebo versus 10% erlotinib). In this trial, erlotinib in combination with gemcitabine did not improve survival or other treatment outcomes in patients with advanced nsclc (Gatzemeier U, etal, ASCO04, Abs. 7010).

TRIBUTE was a prospective, placebo-controlled clinical trial (protocol ID: OSI2298g; MSKCC-01122, NCT00047736) that randomized patients with previously untreated advanced (Stage IIIb/IV) nsclc to erlotinib (150 mg/day) or placebo with a course of 6 cycles of carboplatin plus paclitaxel, followed by maintenance erlotinib monotherapy for those responding to the combination regimen. The primary endpoint was OS. Secondary endpoints included TTP, ORR, duration of response, and time-to-symptomatic progression. Sample size of 1,050 was based on an 80% power to detect a 25% benefit in OS. Among a total of 1,059 patients (erlotinib=526 and placebo=533) treated, there were no differences in median OS, ORR, or TTP in patients treated with erlotinib with chemotherapy compared to chemotherapy alone. Placebo and erlotinib were equivalent in terms of overall AE and SAE, excepting rash and diarrhea (erlotinib=47.7%, placebo=43.2%). There was an imbalance in SAE attributed as leading to death (erlotinib=53; placebo=27), but only 5 of the 80 fatalities were partially related to the trial drug by the reporting investigators. In this trial, erlotinib combined with carboplatin and paclitaxel chemotherapy did not confer a survival advantage over carboplatin and paclitaxel alone in patients with previously untreated advanced nsclc (Herbst RS, etal, ASCO04, Abs. 7011).

In subgroup analyses of the pivotal second line phase III clinical trial (protocol ID: CAN-NCIC-BR21, BR.21; NCT00036647) of erlotinib in patients with relapsed nsclc in which erlotinib significantly increased MST (HR=0.71, p<0.0001), OS was prolonged (HR=0.44, p=0.008) in patients who were positive for increased EGFr copy number by FISH. In a similar subgroup analysis of TRIBUTE, in which FISH was performed on all available tissue samples, FISH+ samples had a high level of polysomy or gene amplification. According to FISH analysis of samples from 245 patients (erlotinib=121; placebo=124 placebo), outcomes in patients treated with placebo from this subgroup were better than those in the overall population, suggesting that this subgroup may not be representative. Among the 100 patients (41%) who were FISH+, there were 33 cases of amplification and 67 of high polysomy. OS in FISH+ patients treated with erlotinib and chemotherapy and those treated with chemotherapy alone was similar. However, RR was lower in the erlotinib combination arm compared to the chemotherapy alone arm, but TTP was longer (marginally significant; HR=0.59). The TTP benefit appeared after approximately 6 months, during the maintenance part of the trial. The researchers concluded that, in this retrospective analysis, FISH+ did not predict survival benefit in TRIBUTE. The lower RR in the erlotinib combination arm in this group, taken together with the improved TTP during maintenance therapy, suggests that a nonconcurrent combination approach (chemotherapy followed by erlotinib in sequence) warrants further investigation (Hirsch FR, etal, ASCO07, Abs. 7570).

The negative results of TRIBUTE and TALENT are typical of those obtained with the combination of targeted agents with standard cytotoxic chemotherapy in the treatment of unselected patients with advanced nsclc. Most of these trials have yielded disappointing results. Although the reasons for these failures are not fully understood, the lack of patient selection is clearly a contributing factor. Results of preclinical studies and clinical trials indicate antagonism between EGFr TKI and cytotoxic chemotherapy in tumor cells with wt EGFr. In stark contrast, massive apoptosis in tumor cells harboring somatic mutations in EGFr was observed upon exposure to EGFr TKI. This finding suggests that cell kill in tumor cells with particular EGFr mutations should be enhanced with the combination of cytotoxic chemotherapy and EGFr TKI, similar to that observed with the combination of chemotherapy and trastuzumab in breast cancer. However, other studies suggest that sequential treatment with cytotoxic chemotherapy and EGFr inhibitors would be more effective and less toxic.

A randomized phase II clinical trial (protocol ID: JHOC-J0432; JHOC-WIRB-20041142; NCT00287989) was undertaken in the USA, to determine whether administration of pulsed erlotinib before or after chemotherapy would improve the response rate in patients with advanced nsclc. Chemotherapy-naïve patients with Stage IIIb or IV nsclc, who were former or current smokers were treated with carboplatin (AUC=6) and paclitaxel (200 mg/m$^2$) and randomly assigned to one of three arms, erlotinib (150 mg) on days 1 and 2, and chemotherapy on day 3; erlotinib (1500 mg) on days 1 and 2 and chemotherapy on day 3; or chemotherapy on day 1 and erlotinib (1500 mg) on days 2 and 3. Up to six 21-day cycles of treatment were administered. Primary endpoint was ORR (CR+PR). The trial's objective was to 'pick the winner' based on comparison to the chemotherapy alone arm of TRIBUTE (RR 19%), with a desirable RR of 50%. A total of 87 patients were randomized to the 3 arms. Most common Grade 3/4 toxicities were neutropenia (39%), fatigue (15%), and anemia (12%). Grade 3/4 rash or diarrhea were uncommon. In pretreatment with erlotinib, overall RR (CR+PR) was 18% (5/28) with a dose of 150 mg and 35% (9/26) with a dose of 1500 mg. In post-treatment erlotinib at a dose of 1500 mg, the overall RR was 24% (6/25). For all patients treated with erlotinib, the overall RR was 25% (20/79). In this trial, treatment with erlotinib before or after administration of carboplatin and paclitaxel failed to improve response rates compared to TRIBUTE. The benefit of pulsatile administration of erlotinib that was predicted by preclinical models was not evident in this clinical trial (Riely GJ, etal, ASCO07, Abs. 7619).

After the TALENT trial failed to show a survival benefit for erlotinib and chemotherapy in first line treatment of nsclc, an analysis of the relationship of biomarkers and treatment-related benefit was undertaken. Biomarkers were analyzed by IHC and FISH and sequencing was performed in tumor tissue collected from 500 patients. Survival, response, and TTP were correlated with biomarker data in retrospective subset analyses, which included EGFr and Kras mutation analysis (293 formalin-fixed tissue samples), PCR amplification and sequencing for EGFr exons 18-21, 23, and Kras exons 2 and 3, IHC analysis of such biomarkers as EGFr, EGF, EGFrvIII, HEr2, TGFa, and pAKT, and FISH assays for EGFr, HEr2 and AKT. According to complete sequencing data for 191 (EGFr) and 163 (Kras) samples, most of the EGFr mutations were found in adenocarcinoma samples. EGFr mutations were confirmed in 15 samples, and 24 mutations were confirmed for Kras. Correlations of response rates to mutation status were not statistically significant. Gene amplification by FISH of EGFr, HEr2, and AKT was only observed in single samples. Expression rates by IHC for all assessed biomarkers were mainly low, except for EGFr and pAKT (57% showed pAKT 3+ staining). It was concluded that, although predictive biomarkers and their patterns may eventually inform tailored therapy in nsclc, identification remains in an early phase. In this study no single marker that consistently predicted tumor sensitivity or resistance to erlotinib was identified. Tissue collection and analysis is recommended for future trials with erlotinib (Gatzemeier U, etal, ASCO05, Abs. 7028).

Early subset analysis of TRIBUTE identified prolonged survival in never smokers. Monotherapy trials of EGFr TKI (Shah NT, etal, ASCO03, Abs. 2524; Miller VA, etal, ASCO03, Abs. 2491) had suggested that never smokers and patients with bronchioloalveolar cell carcinoma (BAC) are more likely to benefit from these agents. Although erlotinib in combination with chemotherapy did not confer an OS advantage over chemotherapy alone in TRIBUTE, the addition of erlotinib to chemotherapy significantly prolonged survival in never smokers. This observation is consistent with results of prior trials of EGFr TKI and warrants confirmation in a randomized trial (Miller, VA, etal, ASCO04, Abs. 7061).

More than 6,500 patients have been enrolled and treated in the single arm, international phase IV clinical trial (TRUST), which provides access to erlotinib to patients with Stage IIIb/IV nsclc refractory to 1 or 2 regimens, and in patients who are unsuitable for chemotherapy. PO Erlotinib (150 mg/day) is administered until progression or unacceptable toxicity. Patients are assessed for response, PFS, OS, and safety. Where possible, tumor tissue samples are collected from German centers for IHC testing for EGFr and pMAPK, FISH testing for EGFr gene copy number, and DNA sequencing for EGFr and Kras gene mutations. Biomarker results are assessed for correlations with treatment benefit. In November 2006, biomarker data were available from 287 of 393 German patients with median age of 65 years; male/female ratio of 59%/41%; Caucasian/Asian/no data (99%/1%/<1%); non-smoker/former or current smoker (25%/75%); and adenocarcinoma/squamous cell carcinoma/BAC/large cell/other/no data (57%/33%/3%/2%/1%/4%). Second line treatment with erlotinib was administered in 40% of patients. Among 230 patients with response data, the CR+PR rate was 7.4%, and median PFS was 11.0 weeks. According to preliminary analyses, the 223/278 patients with tumors with EGFr IHC+ staining experienced longer OS (HR=0.75; p=0.1) and PFS (HR=0.71; p=0.03) compared to those with EGFr IHC-. OS (HR=0.53; p=0.02) and PFS (HR=0.38; p=0.0001) were significantly prolonged in patients who were EGFr FISH+ (28/133), compared to those who were FISH-. OS (HR=1.5; p=0.18) and PFS (HR=1.6; p=0.08) were shorter in patients with Kras mutations (17/107), compared to those with wt Kras. pMAPK+ status (29/108) was also associated with shorter OS (HR=2.6; p<0.0001) and PFS (HR=1.6; p=0.0007). Because TRUST is a single arm trial, conclusions regarding the prognostic or predictive significance of these biomarkers cannot be made. However, based on this trial, patients with nsclc, treated with erlotinib, whose tumors are EGFr IHC+, EGFr FISH+ or pMAPK- may have better outcomes than those with EGFr IHC-, EGFr FISH-, or pMAPK+ tumors (Schneider C, etal, ASCO07, Abs. 7674).

In two ongoing post-marketing trials with erlotinib, EGFr status is determined prior to randomization in order to assess its prognostic value in nsclc. SATURN, a randomized phase III clinical trial (protocol ID: BO18192, NCT00556712), will enroll 500 patients and evaluate erlotinib maintenance therapy compared to placebo. In TITAN, erlotinib will be compared to pemetrexed (Alimta; Lilly) or docetaxel in the second line setting.

The efficacy of erlotinib as first line monotherapy in previously untreated patients with advanced nsclc was investigated in two single agent phase II clinical trials. In one of these trials (protocol ID: 02308; NCT00137800), erlotinib was evaluated in chemotherapy-naïve elderly (>70 years) patients (n=76) with nsclc. An objective response was observed in 8/66 (12%) evaluable patients, and disease stabilized in 32 (48%); 12/14 patients with stable disease did not harbor an EGFr mutation. Erlotinib was well tolerated. As expected, rash (75%) and diarrhea (61%) were the most frequently observed side effects. Major AE were Grade 3/4 rash in 9% and diarrhea in 1% of patients; 3 patients experienced interstitial pneumonitis. Discontinuation of trial treatment because of toxicity was required in 9 patients, and there was 1 treatment-related death caused by pneumonitis. Overall MST was an impressive 11 months. MST for patients with stable disease was 12 months (Jackman D, etal, ASCO05, Abs. 7148).

In the other first line monotherapy, phase II trial in patients (n=53) with nsclc, the objective response rate was 22.7 % with 1 CR, 11 PR, and 16 (32%) cases of SD. Tumor responses were observed in both males and females and across various histologic subtypes, including squamous cell carcinoma. In this trial, chemotherapy-naive patients with Stage IIIb/IV nsclc were treated with daily oral erlotinib (150 mg) until disease progression or unacceptable toxicity. Tumor response was assessed every 6 weeks, and samples were analyzed for potential molecular markers of treatment response and survival. The primary endpoint was the proportion of patients without disease progression after 6 weeks of treatment. The overall rate of nonprogression at 6 weeks was 52.8% (28 of 53 patients). Responses were observed across many patient clinical characteristics. The median duration of tumor response was 333 days, MST was 391 days, and median TTP was 84 days. Erlotinib was well tolerated. The main treatment-related AE were mild-to-moderate rash and diarrhea. According to biologic studies based on histologic material from 29 patients, tumors from 4 of the 5 responders and from 1 patient with SD harbored a classic EGFr mutation. Among those with progressive disease, abnormal EGFr point mutations were detected in 2 patients (one with T790M mutation), and Kras mutations were detected in 10 nonresponders. Erlotinib shows significant antitumor activity in the first line treatment of advanced nsclc and may be a viable alternative to chemotherapy. Patient selection cannot easily be based on clinical or biologic variables (Giaccone G, etal, Clin Cancer Res, 15 Oct 2006;12(20 Pt 1):6049-55; comment in 5919-20).

The single agent activity reported in the first line monotherapy setting from these two trials is promising and appears to be similar to the activity observed when erlotinib was combined with cytotoxic chemotherapy. However, toxicity in the monotherapy trials was lower than that observed in the combination trials. Larger studies are warranted to confirm the efficacy of erlotinib as front line therapy for advanced nsclc, especially in enriched patient populations based on both clinical and molecular characteristics. The results of these two trials also suggest evidence of clinical benefit with erlotinib as monotherapy even in patients without EGFr mutations (Johnson DH, Clin Cancer Res, 2006;12:4451s-4457s). Positive results from these trials stand in stark contrast to those from TRIBUTE and TALENT, which found no clinical benefit when erlotinib was administered concurrently with doublet platinum-based chemotherapy, carboplatin and paclitaxel, or gemcitabine and cisplatin.

As of March 2007, a multicenter, nonrandomized, open label, phase II clinical trial (protocol ID: ML 20539; NCT00452075) was to be conducted in Europe to investigate erlotinib and predictive markers as first line treatment of patients with inoperable, locally advanced, recurrent or metastatic (Stage IIIb or Stage IV) nsclc medically unsuitable for chemotherapy. Primary outcomes are CR, PR, and SD at 8 weeks. Secondary outcomes are safety and correlation of EGFr expression rate and FISH predictive for response. This trial will be conducted in 2 phases. Phase 1 will accrue 10 patients; if <1 response is observed, the trial will stop, and if >1 response is observed, accrual will continue for up to 29 patients, until sufficient activity (disease control rate) is observed in at least 5 patients. The principal investigator (PI) for this trial is Pappot Helle, MD, at the Department of Oncology, Rigshospitalet (Copenhagen, Denmark).

A multicenter (n=9), dose-escalation, 2-stage, phase I clinical trial (protocol ID: OSI-774-107; NCT00294736) was initiated in November 2005 to define MTD of erlotinib and evaluate its PK in current smokers with nsclc, when erlotinib is dosed at MTD versus 150 mg/day. In part 1 of the trial, sequential cohorts of patients currently smoking 10 cigarettes/day for 1 year and no prior treatment with an EGFr inhibitor were treated with escalating doses of erlotinib for 14 days until DLT in 2/6 patients. In part 2, after the MTD of erlotinib was identified, patients were randomized to MTD or 150 mg/day, with PK assessed at day 14. Patients were allowed erlotinib treatment beyond day 14 until progressive disease or toxicity. This trial was completed in July 2007.

A total of 22 patients (median age=61 years) were enrolled. Dose levels included 200 mg/day (n=3, with 3 MTD-evaluable patients), 250 mg/day (n=6, 3 MTD-evaluable), 300 mg/day (n=8, 6 MTD-evaluable), and 350 mg/day (n=5, 5 MTD-evaluable). Histology types included

adenocarcinoma (n=9), squamous cancer (n=6), and other (n=7). All 22 patients had been previously treated with chemotherapy and 14 with prior radiotherapy. Median number of cigarettes smoked was 18 per day (range=10-40) and median duration of smoking was 42 (range 10-54).

There were no major hematologic toxicities. DLT was observed in 1/6 MTD-evaluable patients at 300 mg/day and in 2/5 patients at 350 mg/day, in the form of Grade 3 acneiform dermatitis and Grade 3 fatigue/decreased performance status. Treatment was well tolerated. Common Grade 1/2 toxicities were skin toxicity (59%), diarrhea (55%), and 14% each nausea, vomiting, and metabolic or eye disorders. MTD of erlotinib in patients with nsclc who continue to smoke was 300 mg/day. A total of 20 patients were entered into an extended treatment phase after completion of the initial 14 days of erlotinib treatment. The only Grade 3/4 AE in this treatment phase was a Grade 3 rash at the 350 mg/day dose level. Part 2 of the trial aims to compare the steady state PK of erlotinib at 300 versus 150 mg/day and is ongoing. The potential benefits of a higher dose of erlotinib in current smokers may warrant further evaluation (Hughes AN, etal, ASCO07, Abs. 3597).

Because of previously reported SAE with TKI treatment in nsclc, particularly interstitial lung disease (ILD), the incidence of ILD leading to death in TRIBUTE was studied retrospectively. ILD is a rare but serious complication of EGFr TKI therapy that is fatal in about 1/3 of cases. Little is known about the incidence, severity, or risk factors for ILD, the difference in risk between gefitinib and erlotinib, or whether concurrent chemotherapy increases this risk. ILD is, reportedly, more common in Asian patients treated with gefitinib. In TRIBUTE, fatal serious AE were blindly reviewed by an independent panel, which included a medical oncologist, radiologist, and pulmonologist. A total of 41 (3.9%) fatal respiratory AE met criteria and were assigned to 1 of 4 potential attributions, including progressive nsclc, concurrent illness, toxicities not related to the trial drug, or ILD. Panel members made independent assignations, after which each case was discussed jointly and consensus was reached by vote, if necessary.

Fatalities were reported in 80/1,059 (7.6%) patients; 53/526 (10.1%) had been treated with erlotinib, and 27/533 (5.1%) had been treated with placebo (p=0.002). Consensus assignation for the 41 respiratory AE were nsclc=18 (44%), concurrent illness=15 (37%), toxicities not related to the trial drug=5 (12%), and ILD=3 (7%). Although no statistical differences in assignation by arm were observed, all 3/523 (0.6%) ILD cases occurred in the erlotinib arm. According to the researchers, this trial is the only independent blinded assessment of respiratory SAE and ILD related to an EGFr TKI (erlotinib) plus chemotherapy. Fatal ILD occurred in 0.6% of patients treated with the combination. Applying the approximation that 1/3 of EGFr TKI-induced ILD cases are fatal suggests that the overall incidence in this arm was probably about 1.5%-2%, which may be higher than previous reports of EGFR TKI alone in the non-Japanese population. More trials designed to better define the underlying pathophysiology and risk factors for ILD are needed (Gandara DR, etal, ASCO06, Abs. 7071).

Erlotinib is also under investigation in various clinical trials in combination with radiotherapy, or radiosurgery, either as monotherapy, or in combination with temozolomide (Temodar; Schering-Plough) in patients with brain metastases secondary to nsclc. A randomized phase III clinical trial (protocol ID: RTOG-0320; NCT00096265) was initiated in October 2004 in the USA to evaluate whole brain radiation therapy (WBRT and stereotactic radiosurgery, with or without temozolomide or erlotinib, in 381 patients with brain metastases secondary to nsclc.

The combination of bevacizumab (15 mg/kg) every 3 weeks and daily erlotinib (150 mg) was evaluated in a phase I/II clinical trial in patients with platinum-resistant nsclc. Initially, 12 patients were treated in a dose-escalation portion to determine the safety of the combination. The trial enrolled 6 patients in the phase I portion, and 28 additional patients in the phase II portion. Disease control rate, defined as CR+PR+SD, was 85%, and ORR was 20%. After this exploratory trial, two active phase III clinical trials, ATLAS and the BeTa, were initiated to determinate the activity of the combination of bevacizumab and erlotinib. The trials will compare erlotinib, with or without bevacizumab, as first line (ATLAS) or second line (BeTa) therapy (Herbst RS, etal, J Clin Oncol 2005; 23(11):2544–2555).

The overall limited response rate to EGFr TKI in nsclc and the mechanisms mediating drug resistance are poorly understood. According to a recent report, insulin-like growth factor-I receptor (IGF-Ir) activation interferes with the antitumor activity of erlotinib. In nsclc cells, treatment with erlotinib increased levels of the EGFr/IGF-Ir heterodimer localized on the cell membrane, activated IGF-Ir and its downstream signaling mediators, and stimulated mTOR-mediated *de novo* protein synthesis of EGFr and survivin. In these cells, *in vitro* and *in vivo* studies showed that inhibition of IGF-Ir activation, suppression of mTOR-mediated protein synthesis, or knockdown of survivin expression abolished resistance to erlotinib and induced apoptosis. These findings suggest that enhanced synthesis of survivin protein, which is mediated by the IGF-Ir/EGFr heterodimer, counteracts the antitumor action of erlotinib. This mechanism suggests that agents targeting IGF-Ir should be integrated into EGFr TKI treatment regimens in patients with nsclc (Morgillo F, etal, Cancer Research, 2006;66(20):10100-10111).

***Cetuximab***, may improve survival in advanced nsclc. In September 2007, it was reported that cetuximab, in combination with platinum-based chemotherapy (vinorelbine plus cisplatin), met its primary endpoint of increasing OS, compared to chemotherapy alone, in a phase III clinical trial (protocol ID: EMR 62202-046; NCT00148798), in chemotherapy-naive patients with advanced nsclc. No data

were provided to indicate how long responding patients lived, and no other results were provided. Baseline and safety information from the first 370 patients in this trial, which is known as First Line Treatment for Patients with Epidermal growth factor inhibitor (EGFr)-eXpressing advanced nsclc (FLEX), were reported at the 2006 ASCO annual meeting. Patients with EGFr-expressing advanced Stage IIIb nsclc with documented malignant pleural effusion or metastatic Stage IV nsclc were randomized 1:1 either to group A, and treated with cetuximab at a 400 mg/m$^2$ initial dose and then with 250 mg/m$^2$ weekly, cisplatin (80 mg/m$^2$) on day 1, vinorelbine (30 mg/m$^2$) on day 1 and 8, or to group B for treatment with cisplatin and vinorelbine as in group A for a maximum of 6 3-weekly cycles. Cetuximab was administered until progression or unacceptable toxicity. Primary endpoint is OS. Secondary endpoints are PFS, response rate, disease control rate, safety, QoL, and PK. Total enrollment of 1,100 was planned to show an increase of MST of 25% with 90% power. Since November 2004, 1,037 patients had been randomized, 689 were under treatment, and 348 had discontinued treatment. Of the first 370 patients (analyzed by the Data Safety Monitoring Board), 91% of patients have metastatic (Stage IV) nsclc (adenocarcinoma=52 and squamous cell carcinoma=30%), 29% are never smokers, and 17% are Asian. The 10 most frequent AE were nausea, neutropenia, vomiting, anorexia, fatigue, constipation, anemia, febrile neutropenia, rash, and diarrhea (Von Pawel J, ASCO06, Abs. 7109).

Aggressive evaluation of cetuximab is underway in combination with various cytotoxic agents that are active in nsclc, including carboplatin or cisplatin, paclitaxel or docetaxel, gemcitabine, pemetrexed, bevacizumab, and others. An 800-patient, multicenter (n=112), randomized phase III clinical trial (protocol ID: CP02-0452; NCT00095199) was initiated in October 2004, in the USA and Canada, to compare docetaxel or pemetrexed with or without cetuximab in patients with recurrent or progressive nsclc after platinum-based therapy.

***Gefitinib*** was originally investigated in unselected populations with nsclc, and results were inconsistent. Impressive activity, along with considerable toxicity, was reported in early phase II trials of gefitinib plus combination chemotherapy. Large, randomized, phase II trials (IDEAL 1 and 2), however, reported only modest activity of gefitinib in nsclc; and phase III trials (INTACT 1 and 2), failed to demonstrate any benefit in adding gefitinib to chemotherapy (Vokes EE, and Chu E, Oncology (Williston Park) 2006;20(5 Suppl 2):15-25). The regulatory history of gefitinib in nsclc is discussed in detail in FO, V9#3/4.

Updated data is available from the randomized, multicenter (n=176) phase III clinical trial (protocol ID: SWOG-S0023; CTSU; CAN-NCIC-BR.15; NCCTG-S0023; NCT00020709) of gefitinib versus placebo maintenance after definitive chemoradiation, followed by docetaxel, in patients with locally advanced Stage III nsclc. Median PFS for the gefitinib arm (n=118) was 8 months, compared to 12 months for the placebo arm (n=125). With a current median follow up of 27 months, median OS for the gefitinib arm was 23 months and 35 months for the placebo arm (p=0.013). A total of 47 patients from the gefitinib arm and 71 patients from the placebo arm were alive at the time of this report. Among 71 gefitinib-treated patients who died, 61 died of cancer, 2 of toxicity, and 1 of other causes. Of the 54 placebo-treated patients who died, 43 died of cancer and 3 of other causes. Overall OS for the 571 eligible patients was 19 months. Grade 3/4 toxicities in the gefitinib arm (n=107) were rash (7%), diarrhea (6%) and neutropenia (<1%). No Grade 3/4 toxicities were observed in the placebo arm. Patients were treated with the SWOG 9504 core regimen comprising cisplatin (50 mg/m$^2$) on days 1 and 8, etoposide (50 mg/m$^2$) on days 1-5, every 28 days for 2 cycles with concurrent thoracic radiation (1.8-2 Gy fractions/day) for a total dose 61 Gy, followed by 3 cycles of docetaxel (75 mg/m$^2$). Patients without progressive disease were randomized to gefitinib (250 mg/day) or placebo until progressive disease, intolerable toxicity or 5 years. Maintenance gefitinib was safe and well tolerated in this unselected population, but produced inferior survival compared to placebo. Decreased survival was caused by cancer, not gefitinib toxicity (Kelly K, etal, ASCO07, Abs. 7513). This updated data conforms to earlier reports in which the investigators concluded that, taken together with the negative ISEL trial findings, this trial casts doubt on a role for gefitinib therapy in nsclc, particularly in unselected populations.



The Cancer and Leukemia Group B (CLGB) sponsored a multicenter (n=10), open label, phase II clinical trial (protocol ID: CALGB-30106; NCT00040794) to determine the efficacy of combining chemoradiotherapy and gefitinib in patients (n=64) with Stage III nsclc. Primary outcome measures were tolerability, ORR, failure-free survival, and OS. Planned accrual was 18-144 patients (9-72 patients per stratum). Patients were assigned to stratum 1 (weight loss ≥5%) or stratum 2 (weight loss <5%). Patients in both strata were treated with induction chemotherapy comprising paclitaxel (200 mg/m$^2$) and IV carboplatin (AUC=6), every 3 weeks for 2 cycles, plus daily oral gefitinib (250 mg). After induction, patients in stratum 1 were treated with daily oral gefitinib (250 mg/day) and daily concurrent radiotherapy (200 cGy for 33 fractions, total dose=6600 cGy), 5 days each week, and IV paclitaxel (50 mg/m$^2$) followed by carboplatin (AUC=2) weekly for 7 weeks. Patients in stratum 2 were treated with only gefitinib and radiotherapy as in stratum 1. Maintenance gefitinib was initiated after all toxicities were ≤Grade 2. Gefitinib was removed from induction therapy on May 2004, after considering results from the phase III SWOG-S0023 clinical trial that showed no benefit in adding gefitinib to paclitaxel and carboplatin.

Among 64 enrolled patients, 59 were evaluable (stratum 1=20, stratum 2=39; Stage IIIa=51%, Stage IIIb=49%). Tumor types included adenocarcinoma (30%), squamous

cell carcinoma (45%), and others (25%). There was no clear increase in acute, high grade, in-field toxicities compared to chemoradiotherapy alone. In stratum 1, PR was observed in 29% of patients treated with induction chemotherapy (RR=29%), and CR in 5% and PR in 45% of those with full treatment (RR=50%). In stratum 2, PR was seen in 13% of patients undergoing induction chemotherapy (RR=13%) and CR in 5% and PR in 76% of those under full treatment (RR=81%). Stratum 1 poor risk median failure-free survival was 11.5 months, 1-year survival was 60%, and median OS was 19.0 months. Stratum 2 good risk median failure-free survival was 9.2 months, 1-year survival was 47%, and median OS was 12.0 months. The small sample size in this clinical trial prevented planned data analysis. Survival of good risk patients in stratum 2 (chemoradiotherapy and gefitinib) was disappointing, while survival of poor risk patients in stratum 1 (radiotherapy and gefitinib) is promising and warrants further investigation (Ready N, etal, ASCO06, Abs. 7046).

A randomized, open label, multicenter (n=50) phase III clinical trial (protocol ID: D791AL00001; V-15-32; NCT00252707) was conducted in Japan to compare the OS of gefitinib (250 mg/day) to docetaxel (60 mg/m$^2$), every 3 weeks, in patients (n=489) with Stage IIIb/IV or recurrent nsclc refractory to 1 or 2 chemotherapy regimens. Primary outcome measure was OS. Secondary outcomes were PFS, time-to-treatment failure, QoL, objective tumor response, disease control rate, and AE. The confidence interval (CI) of the hazard ratio (HR; gefitinib/docetaxel), derived from an unadjusted Cox proportional hazard model, was used to assess non-inferiority of OS. Non-inferiority in OS was not achieved (HR=1.12) according to predefined criterion (upper CI limit for HR<1.25). However, no significant difference in OS (p=0.330) or PFS (p=0.335) was apparent between treatments. Post trial, 36% of gefitinib-treated patients were administered subsequent docetaxel, and 40% had no other therapy apart from gefitinib. A total of 53% of docetaxel-treated patients were treated with subsequent gefitinib, and 26% were administered no other therapy apart from docetaxel. Gefitinib, compared to docetaxel, significantly improved ORR (22.5% versus 12.8%; p=0.009), time-to-treatment failure (HR=0.63; p<0.001), and QoL. Grade 3/4 AE occurred in 40.6% of patients in the gefitinib arm and 81.6% in the docetaxel arm. Incidence of ILD was 5.7% (n=14) and 2.9% (n=7), respectively; 4 deaths were attributed to AE in the gefitinib arm (3 possibly from treatment-related ILD) and 1 from pneumonia (not considered treatment-related), and none occurred in the docetaxel arm. Secondary endpoints were largely unaffected by subsequent therapy, suggesting evidence of clinical efficacy of gefitinib in these patients (Niho S, etal, ASCO07, LBA7509).

Selection of patients with nsclc who are most likely to respond to gefitinib is based on the presence of somatic EGFr mutations, which correlate with increased response and survival. The first trial with gefitinib, referred to as iTARGET (Trial to Assess the Response to Gefitinib in EGFr-mutated nsclc Tumors), was a prospective, multicenter (n=11) phase II clinical trial, conducted to assess response to gefitinib as first line treatment in patients (n=98) with nsclc harboring EGFr mutations. Patients were eligible if they were chemotherapy-naïve, diagnosed with Stage IIIb with pleural effusion or metastatic (Stage IV) nsclc with measurable disease, and had ≥1 characteristics associated with mutations (female gender, adenocarcinoma histology, non-smoking history, East Asian descent). Patients underwent direct DNA sequencing of tumor tissue EGFr exons 18-24. Mutation-positive patients were treated with gefitinib (250 mg/day) until progressive disease or unacceptable toxicity. Primary outcome was RR by RECIST.

Tumor samples from 98 patients (adenocarcinoma=89; female=69; non-smoking=37; East Asian=2) were sequenced, and EGFr mutations were detected in 34 patients. Observed mutations were exon 19 deletions (n=18), L858R (n=9), exon 20 insertions (n=3), T790M/L858R (n=2), G719A (n=1), and L861Q (n=1). Among the 34 patients with EGFr mutation, 20 were female, 31 had adenocarcinoma, 19 were non-smokers, and 2 were East Asian. A total of 31 were treated with gefitinib. The best predictor of EGFr mutation was non-smoking history. Reasons for non-treatment were patient preference (exon 19 deletion=1) and mutation associated with gefitinib-resistance (T790M/L858R=1; exon 20 insertion=1). AE were mainly Grade 1/2 rash (n=20), diarrhea (n=18), and Grade 3 ILD (n=1) after 2 weeks of treatment. Among the 31 treated patients, there was 1 CR, and 16 PR, and disease stabilized in 12 and progressed in 2. ORR was 55%, 78% in patients with L858R and 59% in patients with deletion 19. Median PFS was 11.4 months, and median OS was 20.8 months. FISH status was assessed in 29/31 treated patients and correlated with therapy outcomes. FISH+ status was present in 22% of assessed cases, including high polysomy (n=19) and gene amplification (n=3). RR was 50% in patients with FISH+ tumors and 43% in FISH- tumors. There was no significant difference in TTP between the 2 FISH status groups. Presence of a demonstrated resistance mechanism at screening suggests the use of an alternative to first generation EGFr TKI therapy. The researchers concluded that first line gefitinib therapy in patients with EGFr mutation-positive nsclc is feasible in a multicenter trial, well tolerated, and yields a substantial RR and PFS. This strategy should be compared to standard chemotherapy in a genotype-directed randomized trial (Sequist LV, etal, ASCO07, Abs. 7504).

A large Asian phase III clinical trial (protocol ID: D791AC00007; NCT00322452), referred to as IPASS (Iressa Pan Asian Study), was initiated in March 2006 to compare gefitinib in combination with carboplatin and paclitaxel as first line treatment of selected patients with nsclc. Inclusion criteria include locally advanced Stage IIIb disease not amenable to local therapy or metastatic (Stage IV) adenocarcinoma in never smokers or light ex-smokers (ceased smoking at least 15 years before day 1 of

trial treatment and have a total of ≤10 pack-years of smoking history). The primary outcome measure is PFS. Secondary measures include OS, ORR, and safety and tolerability. Enrollment goal is 1,220 patients. This trial has been closed to enrollment; final results are expected in July 2009.

A non-randomized, open label, uncontrolled, phase II clinical trial (protocol ID: D7913L00056; NCT00344773), conducted in Korea, is investigating gefitinib as first line treatment in patients with recurrent pulmonary adenocarcinoma with EGFr mutations. The primary outcome measure is ORR based on RECIST. Secondary outcome measures include PFS, OS, safety, and laboratory parameters. EGFr mutational analysis is performed on histologic biopsies. A total of 145 patients were to be enrolled in this trial, which has been closed to enrollment.

A multicenter (n=77) prospective randomized, double blind, placebo-controlled phase III clinical trial (protocol ID: CAN-NCIC-BR19; ECOG-CAN-NCIC-BR19; SWOG-CAN-NCIC-BR19; CTSU; NCT00049543) was initiated in September 2002, in the USA, Canada, and Peru to compare gefitinib to placebo in the treatment of patients with completely resected primary Stage Ib, Stage II, or Stage IIIa nsclc, to determine whether gefitinib is effective in delaying nsclc recurrence. The primary outcome measure is OS. Secondary outcome measures and goals include DFS, toxicity, determination of the prognostic significance of EGFr expression and phosphorylation, and the establishment of a comprehensive tumor bank linked to a clinical database for further study of molecular markers in patients treated with these regimens. A total of 1,242 patients were to be accrued in this trial, which is closed to enrollment.

***Nimotuzumab*** increased the radiosensitivity of human nsclc cell lines both *in vitro* and *in vivo*, supporting previous clinical observations of the effect of nimotuzumab with radiation in other malignancies. Positive preliminary results from a phase I/II trial (protocol ID: YMB1000-010; NCT00369447) of nimotuzumab in combination with radiation in patients with Stage IIb, III, or IV nsclc unsuitable for radical chemoradiotherapy, were presented in September 2007 at the 12th World Conference on Lung Cancer in Seoul, Korea. Preliminary data from the first two cohorts of the phase I part of the phase I/II trial indicated that clinical benefit (PR or SD) was observed in all 13 patients to date. In the trial, conducted at 3 centers in Canada by the National Cancer Institute of Canada (NCIC), the OS of patients with advanced nsclc with SD as best response to treatment was similar to that in patients with PR. According to YM BioSciences (Mississauga, Ontario, Canada), the reported absence of side effects, particularly of severe rash, makes nimotuzumab therapeutically attractive in this setting.

The phase I component is evaluating the safety and feasibility of administering nimotuzumab at 3 dose levels (100 mg, 200 mg, and 400 mg weekly) with palliative radiation (30 Gy in 10 fractions). An optimal effective dose will be selected for the randomized phase II component of the trial, in which OS is the primary endpoint. Among the 6 patients enrolled in the first cohort (100 mg), there were 4 PR and 2 SD. Median OS was 41.5 weeks; all patients ultimately progressed. Neither of 2 reported SAE were attributable to nimotuzumab. There was no Grade 3/4 rash or diarrhea in this cohort. Among 7 patients enrolled in the second cohort (200 mg), there were 2 PR and 5 SD. Median OS of this group has not yet been reached but currently exceeds 25 weeks. Grade 3/4 rash and diarrhea were also absent in this cohort. Enrollment of the third cohort (400 mg) is ongoing, and completion of accrual is anticipated by the end of 2007. YM BioSciences is conducting the trial in Canada, and Kuhnil Pharmaceutical is conducting a parallel trial in Korea using the same protocol. The interim report from the phase I trial in Korean patients is anticipated early in 2008.

### Bronchoalveolar Carcinoma (BAC)

Bronchioloalveolar carcinoma (BAC) is a subtype of adenocarcinoma of the lung with unique pathologic, clinical, and molecular characteristics. Until recently, BAC was considered a rare form of nsclc. While pure BAC tumors occur in about 3%-5% of patients with nsclc, there is evidence that as many as 20% to 25% of all cases of nsclc diagnosed each year in the USA have features consistent with BAC. BAC subtypes are of particular interest because their incidence is increasing, particularly in younger, women who have never smoked. EGFr inhibitors have demonstrated response rates of 20%-30% in patients with advanced BAC, but have been hampered by the lack of established methods for patient selection.



In the first International Association for the Study of Lung Cancer (IASLC)/ASCO consensus conference, investigators reviewed trials performed specifically in BAC and trials in nsclc that included patients with BAC. They concluded that future clinical trials should be designed specifically for patients with BAC. Although most of the trial participants have been men with a history of smoking cigarettes, proportionally, more are women and never smokers. Although patients with BAC are routinely treated with drugs and regimens appropriate for patients with all subtypes of adenocarcinoma of the lung, 4 trials have been performed specifically in this disease. The panel also concluded that there is insufficient evidence to confirm or refute the assertion that BAC sensitivity to chemotherapy is different from that of other lung cancer histologic types (Kris MG, etal, J Thorac Oncol, Nov 2006;1(9 Suppl):S32-6).

Based on preclinical and clinical data suggesting relevance of EGFr in BAC, a multicenter (n=98), international, phase II clinical trial (protocol ID: SWOG-S0126; NCT00029003) was initiated in December 2001, in the USA, with gefitinib treatment in both previously untreated and treated patients with selected Stage IIIb (with malignant effusions) or Stage IV BAC. The trial's objectives were to determine 1-year survival, PFS, and OS, the frequency

and severity of toxic effects, the response rate in patients with measurable disease, and the correlation of EGFr and EGFrvIII overexpression with clinical outcome in patients treated with gefitinib. Patients are stratified according to prior systemic treatment for BAC (yes versus no). The previously untreated stratum closed to accrual as of February 2003. According to the protocol, patients are treated with oral gefitinib once daily. Treatment continues in the absence of disease progression or unacceptable toxicity. Patients are followed every 6 months for 2 years and then annually thereafter. Howard L. West, MD, of the Swedish Cancer Institute at Swedish Medical Center (Seattle, WA), is Study Chair.

A total of 136 eligible and assessable patients (untreated=101, previously treated=35) were treated with gefitinib (500 mg) daily until progression or prohibitive toxicity. Response rate, based on RECIST, was 17%, with 6% CR among 69 previously untreated patients with measurable disease, and 9% with no CR among 22 pretreated patients. Median survival was 13 months for both chemonaïve and previously treated patients. OS at 3 years was 23%. Toxicity consisted mainly of rash and diarrhea; 2% of patients died of presumed ILD. Exploratory subset analyses revealed improved survival among women (p=0.031), patients developing a rash (p=0.003), never smokers (p=0.061), and patients with a PS of 0 or 1 (p=0.015). Gefitinib is an active agent in advanced stage BAC with specific patient subsets demonstrating significantly improved clinical outcomes (West HL, etal, JCO, 20 Apr 2006;24(12):1807-13).



Increased EGFr gene copy number by FISH has been strongly associated with increased sensitivity to gefitinib in patients with BAC in this trial. EGFr copy number by FISH was assessed and correlated with treatment response and survival. Tumor tissue from 81 patients with advanced stage BAC treated with gefitinib was classified into two categories, FISH+ (high polysomy/gene amplification) and FISH- (disomy, trisomy, and low polysomy). A total of 55 patients with measurable disease were evaluated for response. Among 19 FISH+ patients, 12 (63%) experienced disease control (response or SD) versus 14/36 (39%) patients in the FISH- group (p=0.099). A total of 81 patients were evaluable for survival. MST of the FISH- patients was 8 months. Although MST for the FISH+ group had not yet been reached at the time of this report, it is approaching 18 months, for an HR=2.02 (p=0.042). Median PFS for FISH- patients was 4 months (range=2-5 months), compared to 9 months (range=3-20 months) in the FISH+ group, for an HR=1.67 (p=0.072). EGFr copy number by FISH remained a significant predictive factor after accounting for smoking status, sex, histology, and performance status. This trial found a strong association between increased EGFr gene copy number detected by FISH and sensitivity for gefitinib treatment in patients with advanced stage BAC. These results suggest that EGFr gene copy number detection by FISH can be used to select patients with BAC for treatment with EGFr inhibitors (Hirsch FR, etal, ASCO05, Abs. 7030).

### Early Stage, Nonmetastatic NSCLC

Early stage, nonmetastatic, nsclc, in the adjuvant, neoadjuvant or locally advanced (nonmetastatic) setting, represents another promising indication for EGFr inhibitors. The standard treatment for Stage Ia nsclc (i.e., surgery followed by observation) proves inadequate for 25% of patients in whom disease recurs and eventually results in death. Therefore, adjuvant chemotherapy may provide a means of reclaiming these patients.

Erlotinib is under evaluation in early nsclc. A nonrandomized, open label, phase II clinical trial (protocol ID: OSI TAR 728; NCT00385996) was initiated in October 2006 at Weill Medical College of Cornell University, under the direction of Nasser K Altorki, MD, to assess the efficacy of erlotinib in patients with Stage I/II nsclc. Primary outcome is RR. Secondary outcomes are TTP and DFS, assessed every 3 months for the first 6 months and then yearly for 2 years, and safety. Approximately 30 patients are to be treated with erlotinib (150 mg/day) for 3 weeks followed by surgical resection at week 4. High resolution CT scans for tumor response assessment are obtained at baseline and after 3 weeks of treatment. Postoperative chemotherapy is administered at the discretion of the treating physician. Patients are followed for recurrence and survival for 2 years.

In September 2006, OSI Pharmaceuticals initiated a multicenter (n=223), international, placebo-controlled, phase III clinical trial (protocol ID: OSI-774-302; NCT00373425), referred to as RADIANT, to enroll approximately 945 patients with surgically removed EGFr-positive (confirmed by IHC or FISH) Stage Ib/IIIa nsclc who have completed up to 4 cycles of standard adjuvant platinum-based chemotherapy or are chemotherapy naive. The trial's primary objective is to evaluate the effectiveness of adjuvant therapy with erlotinib in prolonging DFS. Secondary objectives are the comparison of OS between trial arms, safety evaluation of adjuvant erlotinib therapy, and exploration of the prognostic value of EGFr-related biomarkers that may be associated with clinical outcomes. Patients are randomized 2:1 to either erlotinib (150 mg) or placebo, once daily, for 2 years. This trial will evaluate the potential benefit of treating patients with erlotinib as a targeted adjuvant therapy after surgery, while gaining a better understanding of how testing for EGFr in tumor tissue may help identify patients who are likely to derive the most significant benefit from erlotinib therapy. This approach is highly relevant in patients with early stages of lung cancer, when tumor tissues are more likely to be available for testing, and disease may be curable. OSI received a Special Protocol Assessment (SPA) from the FDA for this trial.

A multicenter, phase II clinical trial (protocol ID: ECOG-E4503; NCT00087269) of neoadjuvant erlotinib in patients with early stage (Stage Ia/IIIa), operable nsclc was initiated in the USA to determine the response rate, safety,

and tolerability of this treatment. Patients are administered oral erlotinib once daily on days 1-14, or on days 1-21 in the absence of unacceptable toxicity. Patients then undergo surgical resection on the last day of trial drug administration (day 14 or day 21). Patients may be administered chemotherapy and/or radiotherapy after surgical resection at the discretion of the primary physician. Patients are followed for 5 years. A total of 55 to 110 patients were to be accrued for this trial. Steven M. Keller, MD, Montefiore Medical Center (Bronx, NY), is Protocol Chair. Patient recruitment for this trial began in December 2004 and was closed as of April 2007.

## COLORECTAL CANCER

Each year approximately 154,000 Americans are diagnosed with colorectal cancer (CRC), and 57,000 die of the disease. More than 370,000 Europeans develop CRC every year, accounting for 13% of the total cancer burden and approximately 200,000 deaths (Parkin DM, etal, CA Cancer J Clin 2005; 55: 72-108).

### Advanced or Metastatic Colorectal Cancer

In the USA, approximately 25% of newly diagnosed patients present with metastatic disease, and 5-year survival rates in metastatic CRC are as low as 5% (Argiris A, etal, Cancer 2004;101:2222-2229).

***Cetuximab*** is evolving into a key therapeutic for advanced CRC, an indication that represents a major area of expansion for this drug. Cetuximab is widely approved as a monotherapy in patients with EGFr-expressing metastatic CRC who are intolerant to irinotecan-based therapy and, in combination with irinotecan, in patients with disease refractory to irinotecan-based chemotherapy. These indications were FDA approved based on objective response rates. In October 2007, the FDA approved new labeling for a monotherapy indication as third line treatment of EGFr-expressing metastatic CRC in patients with EGFr-expressing disease after failure of both irinotecan and oxaliplatin (Eloxatin; sanofi-aventis)-based regimens. The label now includes OS data. With this new labeling, cetuximab became the only approved biologic therapy to demonstrate improved OS as a single agent in patients with metastatic CRC.

Approval of the sBLA was based on prolonged OS from a large, randomized, multicenter, phase III trial comparing cetuximab plus best supportive care (BSC) to BSC alone in 572 patients with EGFr-expressing metastatic CRC after failure of irinotecan and oxaliplatin-based regimens. BSC included all approved palliative therapies designed to alleviate pain and treat other effects caused by metastatic CRC in this patient population. Heather-Jane Au, MD, from the National Cancer Institute of Canada (NCIC; Kingston, ON, Canada) presented results from the randomized, phase III clinical trial (protocol ID: NCIC CTG CO.17) conducted by the NCIC Clinical Trials Group (NCIC CTG) and the Australasian Gastro-Intestinal Trials Group (AGITG), in patients with metastatic CRC who failed, or were intolerant to all the recommended therapies. EGFr expression was confirmed by IHC. Patients were randomized 1:1 and treated either with cetuximab in combination with BSC (n=287), or BSC alone (n=285). Patients were monitored for disease progression and the development of unacceptable toxicity. Primary endpoint was OS. Secondary endpoints were PFS, ORR, safety, QoL, and cost-effective analysis/cost-utility analysis. The cetuximab regimen was 400 mg/m$^2$ for week 1, followed by 250 mg/m$^2$, once weekly for every subsequent week.

MST in patients treated with cetuximab in combination with BSC was 6.1 months, compared to 4.6 months (HR=0.77; p=0.0046) in those treated with BSC alone. The investigators concluded that, in this trial, cetuximab significantly prolonged OS compared to BSC, which represents the first time that a single-agent biologic targeted therapy has shown a survival benefit in CRC. The safety profile of cetuximab monotherapy is acceptable and consistent with the reported incidence from previous monotherapy trials. According to health-related QoL data analysis, the NCIC CTG CO.17 trial also met its primary QoL endpoint, demonstrating higher physical function and global health scores at 8 and 16 weeks in the cetuximab group, compared to BSC alone. Patients treated with cetuximab experienced significantly less deterioration in health related QoL and a longer time period before deterioration occurred. NCIC CTG CO.17 researchers concluded that cetuximab offers survival and health related quality of life benefits for patients with advanced CRC (Au H, etal, ASCO07, Abs. 4002).



Cetuximab is also under investigation, in combination with validated cytotoxic chemotherapy regimens, as first or second line treatment for metastatic CRC. According to results from the nearly 1,300-patient European Prospective Investigation of Cancer (EPIC) trial, which compared irinotecan plus cetuximab to irinotecan alone as second line therapy following oxaliplatin-based therapy, EPIC failed to meet its primary endpoint of increased OS. However, statistically significant improvements in PFS and RR in the cetuximab arm were reported, along with better preservation of health-related QoL, represented by less deterioration in symptom scores (pain, nausea, insomnia) and global health status scores. EPIC was a multinational, multicenter (USA=215 and ROW=35), phase III clinical trial (protocol ID: CA225006; NCT00063141), which investigated the impact of cetuximab on survival of patients with pretreated EGFr-expressing metastatic CRC. Patients were randomized to either cetuximab (400 mg/m$^2$ priming dose followed by 250 mg/m$^2$ weekly) and irinotecan (350 mg/m$^2$) every 3 weeks, or irinotecan alone. OS was the primary endpoint; QoL was one of the secondary endpoints.

OS was comparable between the cetuximab plus irinotecan (n=648) and irinotecan alone (n=650) arms. Some researchers speculate that the failure of the cetuximab arm to extend survival may have been influenced by subsequent therapy; 46% of patients in the irinotecan

alone arm were treated with cetuximab (89% in combination with irinotecan). Cetuximab plus irinotecan was superior to irinotecan alone n PFS (HR=0.69, p<0.0001) and RR (16.4 versus 4.2%, p<0.0001). Consistently higher scores in QoL were observed in patients in the cetuximab plus irinotecan arm on 10 of the 15 scales used, compared to patients in the irinotecan arm, and improvement in some measures, such as global health status (p=0.047), pain (p<0.0001), and nausea (p<0.0001), reached statistical significance (Eng C, etal, ASCO07, Abs. 4003).

Compared to the irinotecan alone arm, the response rate (CR+PR) was higher in the cetuximab plus irinotecan arm, 16.4% (1.4% + 15%) versus 4.2% (0.2% + 4%; p<0.0001). The disease control rate (CR+PR+SD) at 61.4% versus 45.8% (p<0.0001) was also superior. Median PFS in the combination therapy arm was 4 months, compared to 2.6 months in the irinotecan therapy alone arm (p=<0.0001). Median OS values were not significantly different at 10.71 months for the combination arm and 9.99 months for the irinotecan alone arm (p=0.7115).

Grade 3/4 AE were higher in the cetuximab plus irinotecan arm, occurring in 71.6% of patients, versus in 56.8%. AE included diarrhea, nausea, abdominal pain, fatigue, and vomiting. A comparison of QoL changes from baseline between treatment arms favored the combination therapy arm. Similarly, symptoms such as fatigue, nausea and vomiting, pain, diarrhea, and insomnia were more effectively managed in the combination therapy arm. The combination of cetuximab plus irinotecan resulted in better QoL despite increased toxicity (diarrhea, fatigue), compared to irinotecan monotherapy. This trial is the first in which the addition of a biologic agent to a cytotoxic treatment platform provides better QoL than the cytotoxic regimen alone. QoL considerations have become more important because survival time of patients with metastatic CRC has increased from 10 to 20 months during the last 10 years.

A multicenter, randomized phase III clinical trial (protocol ID: CALGB-SWOG-S0600, ECOG-SWOG-S0600, CAN-NCIC-SWOG-S0600, NCCTG-SWOG-S0600; NCT00499369) of irinotecan and cetuximab, with or without bevacizumab, was initiated in June 2007 in the USA and Canada, under Study Chair Philip J. Gold, MD, of the Swedish Cancer Institute, to assess this combination in patients with metastatic CRC that progressed during first line therapy with bevacizumab and FOLFOX, or OPTIMOX or XELOX. Primary outcome measure is OS. Secondary outcome measures include PFS, ORR, and tolerability and safety profile. Approximately 1,260 patients are to enroll in this trial estimated to be completed in January 2010. Patients are stratified by performance status (0 versus 1 or 2), discontinuation of oxaliplatin during first line therapy (yes or no), planned concurrent chemotherapy (FOLFIRI versus single agent irinotecan), and time from last dose of bevacizumab (14-42 days versus = 43 days). Patients are treated with single agent irinotecan IV over 90 minutes on day 1, repeated every 21 days in the absence of disease progression or unacceptable toxicity, or FOLFIRI (irinotecan IV over 90 minutes and leucovorin calcium IV over 2 hours on day 1 and 5-FU IV continuously over 46-48 hours on days 1 and 2). Treatment repeats every 14 days in the absence of disease progression or unacceptable toxicity. Patients are randomized to 1 of 3 treatment arms. In arm 1, patients are treated as outlined above and with cetuximab IV over 1-2 hours on day 1. Courses repeat every 14-21 days, depending upon the chemotherapy regimen, in the absence of disease progression or unacceptable toxicity. In arm 2, patients are treated as in arm I with the addition of bevacizumab IV over 30 minutes on day 1. Courses repeat every 14-21 days, depending upon chemotherapy regimen, in the absence of disease progression or unacceptable toxicity. In arm 3, patients are treated as in arm II except that a higher dose of bevacizumab is used. After completion of treatment, patients are followed every 6 months for up to 3 years.

Results were reported from a major phase III clinical trial (protocol ID: EMR 62202-013; NCT00154102) with cetuximab, dubbed CRYSTAL (Cetuximab combined with iRinotecan in first line therapY for metaSTatic colorectAL cancer). The CRYSTAL trial investigated the effectiveness of cetuximab in combination with standard FOLFIRI, compared to FOLFIRI alone in the first line treatment of patients with EGFr-expressing metastatic CRC. In January 2007, ImClone Systems and Bristol-Myers Squibb reported that this trial met the primary endpoint of increasing median duration of PFS over FOLFIRI alone, in patients with previously untreated metastatic CRC. Patients were randomized 1:1 to either cetuximab (400 mg/m$^2$ initial dose then 250 mg/m$^2$/week) plus FOLFIRI comprising irinotecan (180 mg/m$^2$), folinic acid (400 mg/m$^2$), bolus 5-FU (400 mg/m$^2$), and 5-FU infusion (2,400 mg/m$^2$) over 46 hours, every 2 weeks (group A) or FOLFIRI alone (group B). The primary endpoint was PFS; secondary endpoints were OS, RR, disease control rate, and safety. A total of 633 events were required to statistically.

There was also a significant 3-fold difference in numbers of patients with initially inoperable disease who were operated with a chance of cure, favoring the cetuximab/chemotherapy combination (4.3% versus 1.5%; p=0.0034). No residual tumor was detected after resection of metastases. For the approximately 20% of patients with metastases confined to the liver, the addition of cetuximab increased the rate at which resection became possible (9.8% versus 4.5%). Outcomes were more favorable in patients with metastases exclusively in the liver, compared to the rest of the population. In this group, median PFS was 9.2 months when treated with FOLFIRI alone and 11.4 months with the addition of cetuximab (HR 0.637; p=0.023). There was a correlation between rash and PFS. Median PFS of the 18% of patients with Grade 3 rash was 11.3 months, compared to 9.54 months for those with Grade 2 rash, and 5.4 months for those with Grade 0 or 1 rash (Van Cutsem E, etal, ASCO07, Abs. 4000).

According to Dr. Hans-Joachim Schmoll of Martin Luther University (Halle, Germany), CRYSTAL shows that the benefit of targeting EGFr with cetuximab, which had been observed in the salvage setting of metastatic CRC, is now proven for first line use also. CRYSTAL also confirms the findings of a smaller phase II trial (protocol ID: CALGB 80203; NCT00077233), which randomized 224 patients to first line FOLFOX, with or without cetuximab. In this trial, a significant difference in response rates of 52% versus 38% favored the combination (p=0.029). The curves of the cetuximab arms of both trials showed an identical slope, with no separation from the control curves for PFS in the early weeks of treatment. However, a wide separation emerges later in each trial.

The definitive chemotherapy regimen to be used in conjunction with cetuximab should be determined by the ongoing US Intergroup phase III clinical trial (CALGB-C80405; SWOG-C80405; NCT00265850), which was initiated in November 2005. Patients with inoperable locally advanced or metastatic disease, not previously treated with either bevacizumab or cetuximab, are treated with combination chemotherapy (physicians' choice of either FOLFIRI or FOLFOX) and then randomized to 1 of 3 treatments, bevacizumab, cetuximab, or both. To date, 641 patients have been randomized of a total of about 2,300 planned. This trial, the results of which are many years away, should help determine the relative benefit of chemotherapy plus either targeted agent or their combination, in prolonging survival of patients with advanced CRC.

A potentially important role for determination of Kras mutations is also emerging for the prediction of response to cetuximab. Kras has been implicated in cell-growth regulation and oncogenesis. Mutated Kras is constantly activated irrespective of the status of EGF, and signaling continues despite anti-EGFr therapy. Mutated Kras is detected in approximately 40% of cases of metastatic CRC. Kras mutations were identified in 39.5% of 85 Italian patients who were treated with cetuximab for metastatic CRC. Unlike earlier reports, the presence of Kras mutations in this trial did not preclude the possibility of an objective response to cetuximab-based therapy, although the RR was much lower (6%) in patients with Kras mutations than in those without Kras mutations (32%). EGFr overexpression by FISH correlated with response, but not survival. HEr2 overexpression was rare (4.9% by FISH) and had no impact on clinical outcomes. These findings suggest that particular molecular profile(s) may predict response to cetuximab. They also conform to the understanding of cetuximab as a signal transduction inhibitor upstream of ras and suggest other potential points of therapeutic intervention (Finocchiaro G, etal, ASCO07, Abs. 4021).

***Panitumumab*** is approved in the USA for the treatment of patients with EGFr-expressing metastatic CRC after disease progression on, or following fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy regimens. In December 2007, the European Commission (EC) granted conditional marketing authorization for panitumumab as monotherapy for the treatment of patients with EGFr-expressing metastatic CRC with wt (non-mutated) Kras genes after failure of fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy regimens. The approval is based on a positive benefit/risk assessment in patients with few treatment options. As part of the CHMP review, clinical data were provided supporting the utility of Kras mutation status as a biomarker for clinical outcome. Biomarker data were generated from a prospectively defined analysis of the randomized, controlled phase III clinical trial (protocol ID: 20020408, NCT00113763) that investigated the effect of Kras status (non-mutated versus mutated) in patients with metastatic CRC treated with panitumumab. The analysis demonstrated that the effect of panitumumab on PFS was confined exclusively to the approximately 60% of patients whose tumors harbored wt Kras. There was no clinical benefit in patients with tumors carrying Kras mutations, regardless of endpoint.

In March 2007, Amgen discontinued treatment in the phase IIIb Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) clinical trial (protocol ID: 20040249; NCT00115765), which was investigating the drug as first line treatment of patients with metastatic CRC. In one arm, patients were treated with oxaliplatin or irinotecan-based chemotherapy and bevacizumab, with panitumumab. In the second (control) arm, treatment was every 2 weeks with oxaliplatin or irinotecan-based chemotherapy and bevacizumab, without panitumumab. Discontinuation was based on a preliminary review of data from a pre-planned interim efficacy analysis scheduled after the first 231 events (death or disease progression). This analysis revealed a statistically significant difference in PFS in favor of the control arm. An unplanned analysis of OS also demonstrated a statistically significant difference favoring the control arm. An increased incidence of Grade 3 SAE of diarrhea, dehydration and infections was observed in panitumumab-treated patients. In addition, an increased incidence of pulmonary embolism was observed in patients treated with panitumumab compared to those who were not (4% and 2%, respectively). There was 1 (<1%) fatality from pulmonary embolism of a patient treated with panitumumab.

The rationale for the PACCE trial was based on the similar mechanisms of action of panitumumab and cetuximab. It was thought that panitumumab would be as effective as cetuximab when administered in combination with chemotherapy. The rationale for combining bevacizumab with panitumumab was based on preclinical data suggesting that combined use of these antibodies would lead to an increased response rate, compared to either antibody alone.

Clinical trials are now underway to compare the addition of panitumumab to established regimens used for second line and first line treatment of metastatic CRC. A multicenter (n=188) randomized, open label, active control, phase III clinical trial (protocol ID: 20050181;

NCT00339183) was initiated in May 2006, to evaluate panitumumab plus FOLFIRI, compared to FOLFIRI alone, as second line therapy for metastatic CRC. Primary outcome measures are OS and PFS. Secondary outcome measures are ORR, TTP, and duration of response. A total of 1,100 patients will be enrolled at 57 centers in Europe and Australia.

A multicenter (n=78), open label, single arm, phase II clinical trial (protocol ID: 20060277; NCT00411450), dubbed PRECEPT, was initiated in December 2006 to evaluate the combination of panitumumab with FOLFIRI as second line treatment in patients with metastatic CRC refractory to first line treatment with FOLFOX and bevacizumab. Primary outcome is the effect of Kras mutation status (wt versus mutant) in tumor tissue on efficacy endpoints. The secondary objective is to evaluate the safety profile in terms of incidence of AE and significant laboratory changes. A total of 150 patients will be enrolled in the USA.

A multicenter (n=106), open label, randomized, 2-arm, phase II, clinical trial (protocol ID: 20060141; NCT00418938), dubbed SPIRITT, was initiated in November 2006 in the USA. SPIRITT will enroll approximately 200 patients with metastatic CRC refractory to first line fluoropyrimidine and oxaliplatin-based chemotherapy with at least 4 doses of bevacizumab. Failure is defined either as toxicity-based or because of progressive disease. Patients are randomized 1:1 either to a once-every-two-weeks FOLFIRI regimen plus panitumumab (6 mg/kg) or the same FOLFIRI regimen plus bevacizumab (either 5 mg/kg or 10 mg/kg, depending on physician choice and institutional standard of care). Primary outcome measures include ORR (CR+PR) at weeks 17 and 25 and best response (CR versus PR versus SD versus progressive disease) anytime during treatment. Secondary outcome measures include median PFS at weeks 17 and 25, disease control response (CR, PR, or SD), duration of response, and safety.



A randomized, multicenter (n=116), phase III trial (protocol ID: 20050203; NCT00364013), dubbed PRIME, was initiated in July 2006 to determine the safety and efficacy of panitumumab in combination with FOLFOX, compared to FOLFOX alone as first line therapy in patients with metastatic CRC. The trial's primary outcome measure is PFS. Secondary outcome measures include OS, ORR, duration of response, TTP, and safety and tolerability. A total of 900 patients will be enrolled at sites in Europe, Canada, and Australia. The expected completion is March 2010.

A multicenter (n=26), open label, non-randomized, single arm, phase II trial (protocol ID: 20060314; EUDRACT# 2006-006739-36; NCT00508404) was initiated in April 2007 in Europe to evaluate the efficacy of the addition of panitumumab to FOLFIRI as first line therapy in metastatic CRC. ORR over the duration of the trial is the primary outcome measure. Secondary outcome measures are PFS, disease control rate, duration of response, time to response, TTP, duration of SD, time-to-treatment failure, and safety. A total of 150 patients will be enrolled at centers in Europe (Austria, France, Germany, Sweden).

The usefulness of EGFr positivity by IHC to identify patients with metastatic CRC who may respond to panitumumab remains obscure and is under study. Panitumumab has antitumor activity in patients with low or undetectable EGFr tumor membrane levels, measured by IHC. A multicenter, single arm, phase II clinical trial (protocol ID: 20030250; NCT00089635) enrolled patients with documented disease progression during or after treatment with a fluoropyrimidine and adequate doses of irinotecan and oxaliplatin, within 6 months after the most recent chemotherapy regimen; 2-3 prior regimens; and low (1%-9%) or negative (<1%) by EGFr tumor membrane staining by IHC. Patients were treated with panitumumab (6mg/kg) every two weeks until progressive disease or intolerability. Tumor assessments were performed every 8 weeks until progressive disease or discontinuation. Endpoints were ORR through week 16, overall ORR, response duration, PFS, and safety. Overall ORR in the <1% EGFr expression and 1%-9% EGFr expression (positivity) groups was the same (Mitchell EP, etal, ASCO07, Abs. 4082).

***Nimotuzumab*** is under evaluation as second line treatment in advanced CRC. Enrollment of the first 5 patients of the initial 50-patient cohort of a phase II trial (protocol ID: YMB 1000-015; NCT00493857) of nimotuzumab in patients with CRC refractory to irinotecan-containing regimens, was initiated in July 2007. Patients are treated with nimotuzumab in combination with irinotecan. Primary endpoints are RR and safety. This single arm trial will enroll approximately 100 patients in about 14 sites in Canada. Two 50-patient cohorts will be enrolled consecutively. Patients in the first cohort are treated with one of the conventional dosing schedules of irinotecan, along with weekly dosing of nimotuzumab. Patients in the second cohort will be treated with irinotecan, along with nimotuzumab administered every two weeks. The trial's PI is Dr. Amil Shah, of the BC Cancer Agency (Vancouver, Canada). It is anticipated that data will be available within 12 months.

## Colorectal Cancer Metastasized to the Liver

Liver metastases are common in advanced CRC. Advances in liver resection have spurred the evaluation of novel chemotherapeutic approaches in the neoadjuvant and adjuvant setting specifically targeting liver metastasis.

As reported above, the CRYSTAL trial found a significant, 3-fold difference in numbers of patients with initially inoperable liver metastases who were operated with a chance of cure, which favored the cetuximab/chemotherapy combination (4.3% versus 1.5%; p=0.0034). This finding indicates that cetuximab may have a significant role in the treatment of patients with liver metastases attributable to CRC.

A multicenter, randomized, open label, phase III clinical trial (protocol ID: USCTU-4351; USCTU-EPOC; EUDRACT-2006-003121-82; ISRCTN22944367; EU-20732; NCT00482222) was initiated in February 2007 in Europe (UK), under PI Tamas Hickish, MD, Royal Bournemouth Hospital, and John N. Primrose, MD, Southampton General Hospital. The trial is designed to compare oxaliplatin and fluoropyrimidine-based chemotherapy, with or without cetuximab, before and after surgery in patients with operable metachronous or synchronous liver metastases form CRC, who had not been previously treated with chemotherapy for metastatic disease. The primary outcome measure is PFS. Secondary outcome measures include RR before surgery as assessed by RECIST, pathologic resection status, OS, safety and toxicity, QoL, and cost effectiveness. Approximately 340 patients are to enroll in this trial; 2014 is the estimated completion date.

A multicenter, open label, randomized, phase II clinical trial (protocol ID: EORTC-40051; EUDRACT-2005-002825-29; NCT00438737) of neoadjuvant and adjuvant cetuximab and FOLFOX, with or without bevacizumab, was initiated in January 2007 in Europe, under PI Bernard Nordlinger, MD, Hopital Ambroise Pare (Boulogne, France). The goal is to evaluate the side effects and effectiveness of these regimens in treating patients with potentially totally respectable, metachronous or synchronous liver metastases from previously resected CRC. The trial is expected to enroll 100 patients stratified according to participating center and planned degree of liver resection, i.e., major (3 segments) or minor (<3 segments). Randomization is to 1 of 2 treatment arms. In arm 1, patients are treated with FOLFOX beginning on day 1 and with IV cetuximab over 1 to 2 hours on days 1 and 8. Treatment repeats every 14 days for 6 courses in the absence of disease progression or unacceptable toxicity. Between 3 to 5 weeks after completion of this regimen, patients undergo liver resection. Beginning between 4 to 8 weeks after surgery, patients are treated with another 6 courses of FOLFOX and cetuximab, as in neoadjuvant therapy. In arm 2, patients are treated as in arm 1, with the addition of IV bevacizumab over 30-90 minutes on day 1. Treatment repeats every 14 days for 6 courses in the absence of disease progression or unacceptable toxicity, except that bevacizumab is not administered during course 6. Between 3 to 5 weeks after completion of FOLFOX, cetuximab, and bevacizumab, patients undergo liver resection. Beginning between 4 to 8 weeks after surgery, patients are treated with another 6 courses of FOLFOX, cetuximab, and bevacizumab, as in neoadjuvant therapy. After completion of treatment, patients are followed every 3 months for 2 years and then every 6 months for at least 3 years.

A multicenter, open label, randomized, phase II clinical trial (protocol ID: CELIM; NCT00153998), was initiated in November 2004 in Europe (Austria and Germany), under PI Gunnar Folprecht, MD, University Hospital "Carl Gustav Carus" (Dresden, Germany), and Claus-Henning Köhne, MD, Klinikum Oldenburg, in Germany. This trial will compare the combination of cetuximab and FOLFOX with the combination of cetuximab and FOLFIRI in the neoadjuvant treatment of patients with inoperable liver metastases from CRC. Primary outcome measure is tumor response per RECIST in the intention-to-treat population. Secondary outcome measures are rate of R0 liver resection, PFS, DFS after resection, OS, safety, and molecular predictive markers for response and toxicity. A total of 135 are to enroll in this trial based on pretreatment evaluation including abdominal CT scans to be reviewed by 3 reference surgeons. In case of inoperable disease, CT or ultrasound-guided biopsy of one of the liver metastases is performed, unless biopsy material is available from prior biopsy of one of the liver metastases. Formalin-fixed, paraffin embedded metastatic tissue is sent to a reference laboratory for IHC analysis of EGFr expression. All patients are treated for 4 months (8 cycles) with either regimen. Resection is performed between 4 and 6 weeks after the last chemotherapy dose. If resection is not possible after chemotherapy, chemotherapy is continued until tumor progression (maximal duration of treatment 2 years); patients are evaluated for a potential resection every 2 months. After resection, postoperative treatment is planned for 3 months (6 cycles). Treatment starts between 4 and 8 weeks after the operation.



### Adjuvant/Neoadjuvant Treatment for Early Stage Colorectal Cancer

Curative surgical intervention is common in a large proportion of newly diagnosed cases of CRC and, as such, represents a unique commercial opportunity for EGFr inhibitors in the adjuvant/neoadjuvant setting. Current adjuvant chemotherapy for operable CRC includes combinations of such cytotoxics as 5-FU, capecitabine, or oxaliplatin.

A multicenter (n=8), open label, randomized, controlled, phase III clinical trial (protocol ID: EU-20547; EUDRACT-2005-003463-23; MERCK-FFCD-PETACC-8; NCT00265811) was initiated in France in November 2005, sponsored by the Federation Francophone de Cancerologie Digestive and chaired by Julien Taieb, MD, CHU Pitie-Salpetriere (Paris, France). The goal is to evaluate adjuvant chemotherapy (FOLFOX-4) with cetuximab, compared to FOLFOX-4 alone, in the treatment of patients with completely resected (R0) Stage III colon cancer. Primary outcome measure is DFS. Secondary outcome measures include 3-year DFS, OS, 5-year OS, treatment compliance, identification of prognostic factors, safety, and markers predictive of relapse and/or treatment efficacy. Estimated enrollment is 2,000. The trial is scheduled for completion in December 2014. According to the protocol, patients are stratified according to obstruction/perforation status (no obstruction/no perforation versus obstruction and/or perforation), N stage (N1 versus N2), and T stage (T1-T3 versus T4). Randomization

is to 1 of 2 treatment arms. In arm 1, patients are treated with oxaliplatin over 2 hours on day 1 and leucovorin over 2 hours and 5-FU continuously over 22 hours on days 1 and 2. In arm 2, patients are treated with chemotherapy as in arm 1 plus cetuximab IV over 1-2 hours on days 1 and 8. In both arms, treatment repeats every 14 days for up to 12 courses in the absence of disease progression or unacceptable toxicity. After completion of treatment, patients are followed periodically for approximately 5 years. A similar phase III clinical trial (protocol ID: NCCTG-N0147; ECOG-N0147; NCT00079274), expected to enroll 2,648 patients, was initiated at 703 sites in North America in February 2004.

## OTHER MALIGNANCIES

### Head and Neck Cancer

Head and neck cancer is the sixth most common malignancy, worldwide, affecting about 500,000 people each year and causing nearly 250,000 deaths. According to the American Cancer Society (ACS), 81,550 Americans will be diagnosed with head and neck cancer in 2007, which includes cancer of the tongue, the rest of the mouth, salivary glands and inside the throat, voice box, eye and orbit, thyroid gland, and lymph nodes of the upper neck. Furthermore, it is estimated that more than 12,900 Americans will have died from this disease in 2007. Head and neck cancer most often affects people over the age of 50, and men are twice as likely as women to be diagnosed with head and neck cancer In the USA, the 5-year survival rate for invasive oral cavity and pharyngeal cancer has remained unchanged at 53% since 1976.



***Cetuximab*** has been approved in combination with radiation therapy for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) and as monotherapy in patients with recurrent or metastatic SCCHN refractory to platinum-based therapy. Despite approved indications, incorporation of cetuximab into clinical practice in SCCHN has been problematic because data comparing first line cetuximab plus radiation therapy to standard chemoradiotherapy has not been available nor has it been available for the combination of cetuximab with chemoradiotherapy. Clinical trials are currently underway to provide this data and further elucidate the role of cetuximab in SCCHN, among them several randomized clinical trials evaluating the addition of cetuximab to various chemoradiotherapy regimens.

In a large, multicenter (n=70), phase III clinical trial (protocol ID: EMR 62202-002; NCT00122460), dubbed EXTREME, cetuximab provided significant benefits as a first line therapy in metastatic SCCHN. This trial was initiated in December 2004 to assess the efficacy and safety of cetuximab in combination with standard chemotherapy commonly used in recurrent or metastatic SCCHN. The main inclusion criterion was Stage III/IV recurrent and/or metastatic SCCHN, not suitable for local therapy. Patients were randomized to two groups. Patients in group A were treated with cetuximab (initial dose 400 mg/m$^2$ then 250 mg/m$^2$ weekly) plus a maximum of six 3 weekly cycles of IV cisplatin (100 mg/m$^2$) on day 1, or carboplatin (AUC=5) on day 1, and 5-FU (1000 mg/m$^2$) as a daily continuous infusion for the first 4 days of each cycle. Patients in group B were treated with the same cytotoxic regimen as in group A, but without cetuximab. Cetuximab treatment continued until progression or unacceptable toxicity. The primary endpoint was OS. Secondary endpoints included PFS, RR, disease control rate, safety, and QoL.

A total of 442 patients were recruited within a year across 35 European sites and randomized into group A (n=222) or group B (n=220). The most frequent primary tumor site was pharynx (47%), followed by larynx (25%). As specified by protocol, survival analysis was conducted after 340 events. MST was 7.4 months in the chemotherapy alone arm compared to 10.1 months for the chemotherapy plus cetuximab arm (p=0.036), which is among the longest ever reported in a phase III trial in these patients. The cetuximab arm reduced risk of dying by >20% (HR 0.79; p=0.0362). Overall, the addition of cetuximab to standard chemotherapy resulted in a clinically meaningful survival benefit (Vermorken J, etal, ASCO07, Abs. 6091). According to Professor Vermorken, MST of >7 months has not been exceeded in 25 years with any other systemic therapy in this setting. Because these patients have extremely severe disease and very poor prognosis, extending survival by 2.7 months from the standard 6 or 7 months represents a breakthrough. This finding should change clinical practice.

In this trial, the 1-year survival rate was 39% in the cetuximab plus chemotherapy arm compared to 31% in the chemotherapy-alone arm. Few differences in side effects were observed between the two trial arms, except for a higher incidence of skin reactions with cetuximab. According to Marshall Posner of the Dana-Farber Cancer Institute, EXTREME is a trial of major importance with an impressive 35% increase in MST. It could never be replicated because, in the future, patients who progress on standard chemotherapy alone would have to be permitted to crossover to cetuximab. Survival may have been extended further if patients whose disease progressed while on cetuximab continued treatment. Further research is needed to investigate cetuximab with other promising chemotherapy combinations. At present, it is reasonable for every patient to expect access to palliative treatment with an anti-EGFr therapy at some point for recurrent disease.

In January 2007, final results were reported from a multinational, randomized, active control, phase III clinical trial (protocol ID: UAB-9901; IMCL-CP02-9815; NCI-G99-1657; NCT00004227) initiated in May 2000. This trial compared radiotherapy alone with radiotherapy plus cetuximab in locoregionally advanced SCCHN. Patients were randomly assigned to treatment with high dose radiotherapy (n=213) or high dose radiotherapy plus weekly cetuximab (n=211). Primary endpoint was duration

of control of locoregional disease. Secondary endpoints were OS, PFS, ORR, and safety. Median duration of locoregional control was 24.4 in the cetuximab arm versus 14.9 months in the control arm. At a 54-month follow-up, ORR was 49.0% in the combined therapy arm, compared to 29.3% with radiotherapy alone (HR for death=0.74). Radiotherapy plus cetuximab significantly prolonged PFS (HR for disease progression or death=0.70). With the exception of acneiform rash and infusion reactions, duration of the normal tissue toxicities was comparable between the 2 arms. The incidence of Grade 3+ toxic effects, including mucositis or dysphasia, did not differ significantly between the two groups. For all treated patients, the median duration of any mucositis or dysphagia was 3 months. Among those with mucositis, 28% experienced this toxicity for 3 months that was accompanied by dysphagia in 31.5%; <10% suffered these toxicities for >15 weeks. These findings were similar for the two treatment arms. Researchers concluded that treatment of locoregionally advanced SCCHN with concomitant high dose radiotherapy plus cetuximab improves locoregional control and reduces mortality without increasing the common toxic effects associated with radiotherapy (Bonner JA, etal, NEJM, 9 Feb 2006;354(6):567-78).

***Panitumumab*** is also under investigation in combination with chemoradiotherapy. According to preliminary results of a phase I/II trial in head and neck cancer, panitumumab may be added to chemoradiotherapy without magnifying the expected toxicities of the treatment (Wirth LJ, etal, ASCO07, Abs. 6083).

SPECTRUM, the largest ongoing clinical trial of panitumumab in head and neck cancer is SPECTRUM, a multicenter (n=106) randomized, open label, phase III trial (protocol ID: 2005025; NCT00460265) in patients with recurrent or metastatic head and neck cancer. The purpose of this European trial is to determine the safety and efficacy of panitumumab in combination with chemotherapy, compared to chemotherapy alone, as first line therapy for metastatic and/or recurrent SCCHN. The primary outcome measure is OS. Secondary outcome measures are PFS, ORR, duration of response, TTP, safety, time-to-response, and patient-reported outcomes. Potential biomarker development is an exploratory objective. The trial, initiated in June 2007, will enroll 650 patients.

PRISM (Panitumumab Regimen In Second line Monotherapy of head and neck cancer) is a multicenter (n=26), open label, non-randomized, phase II clinical trial (protocol ID: 20062088; NCT00446446) of panitumumab monotherapy for second line treatment of metastatic or recurrent SCCHN. This trial was initiated in the USA in May 2007 and will enroll approximately 50 patients in North America. Primary outcome is ORR. Secondary outcomes are time-to-response, duration of response, rate of disease control, TTP, PFS, OS, and safety.

A multicenter (n=68), randomized, open label, controlled, phase II clinical trial (protocol ID: 20050236; NCT00454779), dubbed PARTNER (Panitumumab Added to Regimen for Treatment of head and Neck cancer Evaluation of Response) was initiated in January 2007 in the USA. This trial will evaluate docetaxel and cisplatin chemotherapy, with or without panitumumab, as first line treatment of patients with metastatic or recurrent SCCHN and panitumumab monotherapy as crossover second line treatment in patients with refractory disease. Primary outcome measure is PFS. Secondary outcome measures include estimations of ORR, rate of disease control, duration of response, time-to-response, and OS, and assessment of the safety of panitumumab when added to combination chemotherapy. Estimated enrollment is 150 patients.

A multicenter (n=10), randomized, phase II trial (protocol ID: 20062080; NCT00500760) was initiated in September 2007 in the USA, Canada, and Europe (Finland) to determine whether adding panitumumab to chemoradiation in patients with inoperable, locally advanced SCCHN improves the efficacy of chemoradiation, without adding unmanageable toxicity. The primary outcome measure is locoregional control rate at 2 years. Secondary outcome measures include PFS, OS, duration of local regional control, CR rate by 6 months, ORR by 6 months, safety, QoL, and exploratory investigation of potential biomarkers. Anticipated total enrollment is 150 patients.



***Erlotinib*** is undergoing aggressive evaluation in head and neck cancer. An ongoing clinical trial is testing the combination of cisplatin, docetaxel, and erlotinib in patients with advanced SCCHN with no prior EGFr inhibitor therapy, who may have been treated with prior induction, concomitant or adjuvant chemotherapy, but not for recurrent/metastatic disease. Nasopharynx and sinus sites are excluded. Treatment consists of docetaxel (75 mg/m$^2$) and cisplatin (75 mg/m$^2$) IV every 3 weeks and erlotinib (150 mg) by mouth, daily. All drugs are started on day 1. Patients are treated with growth factor support. At the time of this report, 50 patients had been accrued, 47 available for analysis, and 43 evaluable for efficacy. There were 4 CR, 25 PR, and 12 SD, for an ORR of 67% and disease control rate of 95%. After follow-up of 19 months, median OS was 11 months (range=8.61-22.5), and PFS was 6.01 months (range=4.37-8.25). There were 6 cases of Grade 3/4 febrile neutropenia, 4 of Grade 3/4 dehydration, 3 of Grade 3 diarrhea, and 2 of 3/4 GI bleeding. The most common Grade 1/2 toxicities were diarrhea, nausea, and rash. The combination of cisplatin, docetaxel, and erlotinib was well tolerated and with very encouraging activity in recurrent/metastatic SCCHN. Tissue collection and analysis are underway for correlative markers, including the downstream EGFr pathway markers, p-AKT, MEK, and Kras (Kim ES, etal, ASCO07, Abs. 6013).

Erlotinib has been investigated in several phase I/II clinical trials in combination with chemoradiotherapy and other approved ErbB inhibitors, or other targeted agents,

including bevacizumab. A multicenter (n=14) phase I/II clinical trial (protocol ID: UCCRC-11956A; NCI-5701; UCCRC-NCI-5701; NCT00055913) was initiated in May 2003, under PI Ezra Cohen, MD, at that University of Chicago. This trial includes a dose-escalation phase I trial, followed by a randomized phase II trial of bevacizumab in combination with erlotinib in patients with recurrent or metastatic SCCHN, refractory to surgery or radiotherapy. Trial objectives are determination of MTD and DLT, ORR, and SD/absence of early progression in patients treated with this combination. In phase I, patients were treated with escalating doses of 5, 10, or 15 mg/kg of IV bevacizumab over 30-90 minutes on day 1 and oral erlotinib on days 1-21. Courses repeated every 21 days in the absence of disease progression or unacceptable toxicity. Cohorts of 3 to 6 patients were treated with escalating doses of bevacizumab until MTD was determined.

In phase II, the first course was 28 days in length, and all subsequent courses were 21 days long. In the first course, patients were randomized to 1 of 2 treatment arms. In arm 1, patients were treated with IV bevacizumab (15 mg/kg) over 30 to 90 minutes on day 14 and oral erlotinib (150 mg) on days 1-28. In arm 2, patients were treated with IV bevacizumab over 30 to 90 minutes on day 1 and oral erlotinib on days 1-28. In all subsequent courses, all patients were treated with bevacizumab as in arm 2 and oral erlotinib on days 1-21. Courses repeat every 21 days in the absence of disease progression or unacceptable toxicity. A total of 7 patients were enrolled in the phase I portion of this trial, and 45 patients (arm 1=22, arm 2=23) were treated in the phase II portion. In phase I, disease stabilized in 6 patients. In phase II, there were 2 (4%) CR, 5 (10%) PR, and disease stabilized in 26 (54%) and progressed in 15 (31%) patients (Vokes EE, etal, ASCO07, Abs. 5504).

A multicenter (n=26), randomized, open label, phase III clinical trial (protocol ID: ML20294; NCT00412217) was initiated in November 2006 in Europe (Spain) to evaluate maintenance treatment with erlotinib (150 mg) following concurrent chemoradiotherapy or radiotherapy alone in patients with high risk totally resected SCCHN. The primary outcome measure is PFS. Secondary outcome measures include OS and safety. Patients are randomized to either PO erlotinib daily or standard of care and treated until disease progression. Target enrollment is 100-500 patients.

A multicenter, open label, randomized phase II clinical trial (protocol ID: UWCC-6106; UWCC-05-9278-H/B; GENENTECH-OSI3602s; FHCRC-6106; NCT00410826) was initiated in June 2006 by the Seattle Cancer Care Alliance, under PI Renato G. Martins, MD, MPH, to evaluate cisplatin and radiotherapy, with or without erlotinib, in treatment-naïve patients with Stage III/IV SCCHN. Primary outcome measure is CR rate, measured by pathologic and radiologic methods. Secondary outcome measures are DFS, OS, QoL, and safety. This trial will also determine whether symptomatic improvement observed in the first week of erlotinib treatment alone is a predictor of CR and long term disease control. Patients are stratified according to nodal involvement (N0/N1 versus N2/N3), participating center, and performance status (0 or 1 versus 2), and randomized to 1 of 2 treatment arms. In arm 1, patients are treated with cisplatin IV on days 1, 22, and 43 and undergo conformal or intensity-modulated radiotherapy once daily, 5 days a week, on days 1-47, and oral erlotinib on days -7 to 47. In arm 2, patients are treated with chemoradiotherapy as in arm 1, without erlotinib. Within 10-14 weeks after completion of chemoradiotherapy, patients with N2 or N3 disease at baseline undergo neck dissection. QoL is assessed at baseline, periodically during treatment, 30 days after completion of treatment, and then every 6 months thereafter. After completion of treatment, patients are followed periodically for 5 years. The trial, to enroll 204 patients, is to be completed in June 2009.

A multicenter (n=5), open label, randomized, phase II clinical trial (protocol ID: 06-111; NCT00392665) was initiated in October 2006 in the USA, under PI Lori Wirth, MD, at Dana-Farber Cancer Institute (Boston, MA). The goal is to evaluate the efficacy of erlotinib plus bevacizumab (arm A) or erlotinib plus sulindac (arm B) in patients with incurable, inoperable, recurrent and/or refractory metastatic SCCHN. The primary outcome measure is PFS. Secondary outcome measures are ORR, duration of OS and ORR, and safety. In arm A, IV bevacizumab is administered on day one of each 3-week cycle and PO erlotinib is administered once daily. In arm B, treatment consists of once daily erlotinib in combination with twice daily sulindac. Participants may stay in the trial as long as they benefit without developing excessive side effects or progressive disease. After treatment is discontinued, patients are followed closely for 30 days and then every 1 to 2 months. The trial is scheduled to enroll 82 patients and complete in October 2009.

A multicenter, randomized, double blind, placebo-controlled, parallel assignment, phase III clinical trial (protocol ID: 2003-0824; NCT00402779), dubbed EPOC (Erlotinib Prevention of Oral Cancer) was initiated in November 2006 at M. D. Anderson Cancer Center, under PI Vassiliki Papadimitrakopoulou, MD. The primary outcome measure is to determine whether erlotinib can reduce the incidence of oral cancer in the high risk setting of oral leukoplakia with loss of heterozygosity (LOH). Two cohorts of patients with oral intraepithelial neoplasia (IEN) with no oral cancer history are included, those with LOH at 3p14 and/or 9p21 and a history of curatively treated oral cancer and those with the same LOH, plus at one other chromosomal region. Secondary outcome measures are assessment of the size, number, and appearance of oral IEN and correlation with cancer risk. A panel of molecular markers for correlation with oral cancer development in patients with IEN will also be evaluated. Erlotinib (19 mg) or placebo is administered continuously for 1 year.

The trial period is 4.5 years. Interim analyses will be conducted at the end of year 2.5 and year 3.5, and the final analysis will be performed at the end of year 4.5. The trial is scheduled to enroll 150 participants and complete in November 2010.

***Gefitinib*** is under evaluation in a limited clinical program in head and neck cancer. A randomized phase III clinical trial (protocol ID: ECOG-E1302; NCT00088907) is ongoing to evaluate docetaxel in combination with gefitinib, compared to docetaxel alone, in the treatment of patients with metastatic or locally recurrent head and neck cancer.

Because gefitinib has demonstrated evidence of antitumor activity in patients with SCCHN in phase I and II trials, a multicenter (n=110), randomized, partially blinded, parallel group, comparative, phase III clinical trial (protocol ID: 1839IL/0704; EudraCT no.2004-002662-38; NCT00206219), dubbed IMEX (IRESSA versus MEthotreXate) was initiated in November 2003 in Europe, Asia, and Canada to evaluate gefitinib versus methotrexate in patients with recurrent SCCHN. Patients with histologically confirmed recurrent SCCHN were randomized (1:1:1) to gefitinib (250 mg/day or 500 mg/day), or methotrexate (40 mg/m$^2$) weekly, with the option to escalate methotrexate to a maximum of 60 mg/m$^2$ in the absence of unacceptable toxicity. Gefitinib doses were blinded. The primary endpoint was OS. Secondary endpoints were ORR, safety and tolerability, symptom improvement, and QoL. Exploratory endpoints included EGFr gene copy number measured by FISH.

A total of 486 patients were treated. Neither gefitinib 250 mg/day nor 500 mg/day improved OS compared to methotrexate. The methotrexate group demonstrated a numerical advantage that did not reach statistical significance. Median OS in the 3 groups was 5.6 months (gefitinib 250 mg/day), 6.0 months (gefitinib 500 mg/day), and 6.7 months (methotrexate). ORR was 2.7% (gefitinib 250 mg/day), 7.6% (gefitinib 500 mg/day), and 3.9% (methotrexate), with no statistically significant difference between either of the gefitinib arms and methotrexate. AE were consistent with those previously observed for gefitinib and methotrexate, with the exception of tumor hemorrhage, which was observed in 8.9% (14/158) with gefitinib 250 mg/day, 11.4% (19/166) with gefitinib 500 mg/day, and 1.9% (3/159) with methotrexate. Neither gefitinib 250 mg/day nor 500 mg/day demonstrated improvement in OS compared to methotrexate. AE profiles were generally consistent with those previously observed for each agent, with the exception of tumor hemorrhage observed with gefitinib (Simon J, etal, AACR07, Abs. 3522).

***Lapatinib*** is under evaluation in a multicenter (n=147), international, randomized, double blind, placebo-controlled, parallel assignment, phase III clinical trial (protocol ID: EGF102988; NCT00424255) in high risk SCCHN following surgery. The trial, initiated in February 2007, is comparing the efficacy of adjuvant daily PO lapatinib (1500 mg) to placebo. In this trial, lapatinib is administered within 4-7 weeks post-operatively in combination with radiotherapy and cisplatin for 7 weeks, followed by maintenance with lapatinib or placebo for 1 year. The trial will enroll 680 patients to determine whether lapatinib is effective in reducing disease recurrence, measured by DFS. Secondary endpoints are OS, disease-specific survival, time-to-recurrence, safety, and QoL. Eligibility includes Stage II/IVa SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx, with no evidence of gross residual disease, and with at least one high risk pathologic factor, such as extracapsular extension of nodal disease (<5 mm) or an involved resection margin (<1 mm).

This phase III trial is based on results from an open label, dose-escalation, phase I clinical trial of lapatinib (range=500-1500 mg) plus chemoradiation in 31 patients with head and neck cancer. This trial identified lapatinib (1500 mg once daily) as the optimal dose regimen in combination with chemotherapy and radiotherapy. The response rate to this combination regimen was 89%. Most common side effects were mouth ulcers (87%), radiation skin injury (65%), nausea (61%), swallowing difficulties (52%), and vomiting (52%).

## Pancreatic Cancer

Pancreatic cancer is one of the deadliest malignancies. According to WHO, more than 216,000 people worldwide are diagnosed each year with pancreatic cancer. Approximately 84,000 of these diagnoses originate in North America, Europe, and Japan. In the USA, 37,170 new cases and 33,370 deaths are expected in 2007. Most pancreatic tumors originate in exocrine duct cells or the acinar cells that produce digestive enzymes. These tumors, referred to as pancreatic ductal adenocarcinoma (PDAC), account for nearly 95% of all cases of pancreatic cancer. Most patients with pancreatic cancer are in the advanced stages of the disease at the time of diagnosis.

Surgery and chemotherapy, the primary treatment options, of limited benefit. One EGFr inhibitor, erlotinib, is approved in the USA and Europe, among other regions, as first line treatment, in combination with gemcitabine, for locally advanced or metastatic pancreatic cancer.

***Erlotinib*** approval was based on a randomized phase III clinical trial that was the first, since the introduction of gemcitabine in 1996, to demonstrate a statistically significantly survival benefit in advanced pancreatic cancer. The survival benefit is very modest (median OS of the combination is 6.24 months, compared to 5.91 months for gemcitabine alone), however, and this combination has not become the standard of care (Moore MJ, etal, J Clin Oncol, 2007;25(15):1960-6).

An open label phase II clinical trial (protocol ID: OSI-Tar-725; NCT00497224) of erlotinib monotherapy in patients with metastatic or locally advanced, inoperable pancreatic cancer previously treated with up to one line of gemcitabine-based chemotherapy was initiated in

November 2006 in Canada. The PI is Malcolm Moore, MD, of Princess Margaret Hospital (Toronto, Canada). The feasibility of dose escalation of erlotinib and the drug's activity will also be evaluated in patients who do not develop a rash. Clinical outcome will be correlated to EGFr status based on IHC and gene amplification and Kras mutations from archival tumor tissue. The presence of erlotinib-induced rash was associated with improved survival in phase II and III trials in diverse tumor types and is associated with higher steady state concentrations of erlotinib. Part of the rationale for this trial is based on the most efficacious use of erlotinib in nsclc. The optimal efficacy of erlotinib in nsclc is not in combination with first line cytotoxic chemotherapy for advanced disease, but as a single agent after cytoxic chemotherapy. Preclinical and clinical data suggest that erlotinib will have activity as a single agent in advanced pancreatic cancer. Enrollment will total 35 patients.

***Nimotuzumab***, is under investigation in a multicenter (n=8), randomized, placebo-controlled, phase IIb/IIIa clinical trial (protocol ID: OSAG101-PCS07; NCT00561990) in chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer. This trial was initiated in September 2007 in Europe (Germany) under PI Dirk Strumberg, MD, at Marienhospital Herne. Patients are treated with either gemcitabine plus nimotuzumab or gemcitabine plus placebo. Primary endpoints are TTP and OS. QoL and RR are among the secondary endpoints. This trial is expected to recruit 188 patients. The protocol for this trial parallels a protocol already in place for a trial in nsclc underway in Canada and Korea.



## Primary Brain Cancer

Primary brain cancer, such as glioma, is a target for treatment with EGFr inhibitors because EGFr amplification and overexpression frequently occurs in malignant glioma and is associated with poor prognosis. Approximately 40,000 cases of malignant glioma are diagnosed each year in the USA, Europe, and Japan. Approximately 65% of these cases are operable.

The Academic Hospital Vrije Universiteit Brussel (Brussels, Belgium) sponsored a stratified phase II clinical trial to investigate the antitumor activity of cetuximab in patients (n=22) with recurrent glioblastoma multiforme (GBM) following surgery, radiotherapy, and chemotherapy. The primary endpoint was OR. Secondary endpoints were safety and toxicity, 6-month and median PFS, and median OS. Adult patients were allocated to 2 parallel treatment strata according to EGFr gene amplification status determined by FISH. According to a Simon 2-phase phase II design, 1 response in 13 patients/stratum was required to continue patient recruitment and complete the second stage of recruitment. Cetuximab was administered at 400 mg/m$^2$ as a 2-hour infusion on day 1 and 250 mg/m$^2$ as a 1-hour infusion on day 8 and for all subsequent weekly doses.

Between May 2005 and May 2006, 22 patients were enrolled (no EGFr amplification=14; EGFr amplification=8; under investigation=2). A total of 7 patients are on treatment, 5 are on follow-up, 10 have died from progressive disease, and 1 patient withdrew consent before treatment initiation. Treatment-related toxicity included Grade 1 dermatitis (47.4%), Grade 2 dermatitis (31.6%), Grade 1/2 folliculitis (36.8%/36.8%), and Grade 1 pruritus (21.1%). SAE consisted of increased headache, infectious leg cellulitis, diminished consciousness, intratumoral hemorrhage associated with tumor regression, and deep venous leg thrombosis. All SAE were single occurrences, reversible, and non fatal. Among 19 patients evaluable for response, there were 2 PR, one with EGFr amplification and the other without. Disease stabilized in 2 patients, both with EGFr amplification and progressed in 15 (EGFr amplification=4; no EGFr amplification=11). Overall disease control rate was 21%. Median TTP was 9 weeks, and median OS was 13 weeks. Cetuximab can be safely administered to pretreated patients with recurrent GBM. No correlation was established between EGFr and/or PTEN gene copy numbers and cetuximab response (Sadones J, etal, ASCO06, Abs. 1558).

Nimotuzumab is currently in development in primary brain cancer. In August 2007, Oncoscience (Wedel, Germany) was cleared to conduct a multicenter, randomized phase III clinical trial with nimotuzumab as first line treatment of GBM in Europe. Nimotuzumab is being compared to the current standard of care, which is radiotherapy with concomitant and adjuvant temozolomide. The primary endpoint is PFS. RR and symptom control are among the secondary endpoints. The trial is expected to recruit 150 patients. This trial is based on positive findings from a phase II clinical trial of 29 adults with newly diagnosed high grade glioma, including both anaplastic astrocytoma and GBM, who were treated with surgery, external beam radiotherapy, and nimotuzumab. Treatment was well tolerated. MST is 17.5 months for the patients with GBM and has not yet been reached for the patients with anaplastic astrocytoma.

Diffuse intrinsic pontine glioma (DIPG), an orphan drug indication, is a particular target of nimotuzumab. In August 2007, YM Biosciences obtained permission to import nimotuzumab into the USA for use in clinical trials in DIPG. Also in August 2007, the FDA approved initiation of a multicenter (n=8), single arm, monotherapy, phase II clinical trial of nimotuzumab in inoperable, recurrent, pediatric DIPG. Participating sites in the USA include members of the Pediatric Oncology Experimental Therapeutics International Consortium (POETIC). In June 2007, YM BioSciences also received a no objection letter from Health Canada to initiate a similar trial under PI Eric Bouffet, MD, Sylvain Baruchel, MD, and Ute Bartelsy, MD, at the Hospital for Sick Children (Toronto, Canada). The primary endpoint is ORR, with a target of 15%.

The design of a phase III trial of nimotuzumab was based on a phase II trial conducted in Germany in refractory and relapsed high grade glioma, including GBM, anaplastic astrocytoma, and DIPG, in children and adolescents. Treatment consisted of weekly IV nimotuzumab (150 mg/m$^2$) for 6 weeks, and in SD cases, consolidation therapy of 4 infusions in 3 weeks. Updated, positive results were presented in 2007 from the multicenter (n=4), phase II clinical trial of nimotuzumab in pediatric patients (n=47) with refractory/relapsed high grade glioma. Between June 2004 and April 2006, 45 of 47 enrolled patients (median age=11 years) were evaluable for response. Diagnoses included GBM (n=13), anaplastic astrocytoma (n=12), and DIPG (n=22). First line therapies were surgery (n=12), radiotherapy (n=47), and chemotherapy (n=44).

According to an MRI at week 8 (per RECIST), there were 2 PR, and disease stabilized in 14 and progressed in 29 patients. SD/PR was assessed as the largest diameter of the index lesion changed by -50% to +16% (median=-11%). PR/SD was observed in 2/13 patients with GBM, 2/11 with anaplastic astrocytoma, and 8/21 with DIPG. Among 12 patients who continued with consolidation therapy, there were 4 PR, and disease stabilized in 2 and progressed in 6 at week 21. A total of 44 patients died from disease progression. Median OS was 4.4 months and significantly better for responders (median=10 months) than for non-responders (median=4.0 months). Grade 1/2 AE included fever (n=2), gastroenteritis (n=1), hypokalemia (n=2), paresthesia (n=1), fatigue (n=3), bronchitis (n=1), exanthema (n=1), and vomiting (n=3). There were no SAE related to the trial medication. SAE related to tumor progression included dizziness, disorientation, visual hallucination, restlessness, seizures, ataxia, vomiting, and somnolence. No side effects resulted from consolidation therapy. The repeated application of nimotuzumab is well tolerated and safe. Nimotuzumab has cytotoxic efficacy in heavily pretreated relapsed high grade glioma, especially in DIPG (Bode U, etal, ASCO07, Abs. 2006).

In this phase II clinical trial, a clinical benefit after 8 weeks of induction treatment, including 1 PR and 7 SD, was observed in 8/21 (35%) of children with recurrent DIPG, which represents a significant outcome in these end-stage patients. These 8 patients continued on maintenance therapy, and at week 21, there were 3 PR and 1 SD. There are no reports of OR in this patient population.

In August 2007, the 40th and final patient was enrolled in a multicenter (n=11) phase III clinical trial (protocol ID: OSAG101-BSC05; NCT00561691) combining nimotuzumab with radiation in the treatment of pediatric DIPG. The trial, conducted in Europe (Germany, Italy, Russia) under PI Udo Bode, MD, of the University of Bonn, in Germany, has a primary endpoint of PFS. OS is a secondary endpoint.

Nimotuzumab, linked to DTPA and labeled with Y-90, has also been evaluated as locoregional radioimmunotherapy, delivered by direct administration of the drug into the postoperative cavity through an indwelling catheter. ORR was 28.5% in 102 patients with GBM (Riva P, etal, ASCO03, Abs. 446).

### Primary Liver Cancer

Hepatocellular cancer (HCC) is one of the world's most common malignancies. Worldwide, more than 600,000 new cases are diagnosed each year; about 30,000 cases are diagnosed in Europe, and approximately 15,000 cases in the USA. Current therapies provide limited benefit, and the mortality rate of HCC is high.

An open label, phase II clinical trial was conducted at the Hannover Medical School in Germany to test the activity of cetuximab in patients with inoperable advanced or metastatic HCC. Prior regional or systemic therapy was permitted. The primary endpoint was PFS at 24 weeks of treatment. Secondary endpoints included OS, ORR, tolerability, and identification of surrogate markers. Tumor biopsies were performed prior to treatment, after 4 weeks, and at time of progression. Specimens were analyzed for genetic instability and cell-cycle regulation. Cetuximab was administered at 400 mg/m$^2$ IV on week 1 and at 240 mg/m$^2$ weekly thereafter until progressive disease.

A total of 32 patients were enrolled, of which 27 were evaluable for tumor response. Disease stabilized in 12 (44.4%) patients for at least 8 weeks of treatment; 15 (55.6%) did not respond to cetuximab. Median TTP for all patients was 8.0 weeks. The median TTP was 22.5 weeks (range=11-48 weeks) among those with SD lasting more than 8 weeks, compared to a median TTP of 6.0 weeks (3-8) in patients with progressive disease. No treatment-related SAE were noted. Preliminary evaluation of surrogate markers showed no correlation with cytogenetic abnormalities based on FISH analyses of chromosomes 1 and 8. Furthermore, only 5 of 21 tumor specimens were positive for EGFr expression without gene amplification, evaluated by FISH. Serial tumor specimens from 5 responding and 7 non-responding patients were available for determination of changes in p27 and p21 expression. These two markers were upregulated simultaneously in 60% (3/5) of responding patients and detectable in only 1/7 (14%) patients who failed treatment. In this trial, cytogenetic aberrations of chromosomes 1 and 8 failed to predict response to cetuximab. In a subgroup of patients with SD >8 weeks, induction of p21 and p27 were associated with prolonged TTP (>20 weeks). Further evaluation of p21 and p27 as early molecular markers of tumor response is warranted to identify patients who are most likely to benefit from anti-EGFr therapies (Gruenwald V, etal, ASCO07, Abs. 4598).

A multicenter (n=3), non-randomized, open label, phase II clinical trial (protocol ID: 04-347; NCT00142428) was initiated in the USA in January 2005 to determine the therapeutic potential of cetuximab in patients (n=30) with inoperable, refractory or metastatic HCC. The trial's PI is Andrew X. Zhu, MD, at Massachusetts General Hospital. Primary endpoint is PFS. Secondary endpoints include

response rate, duration of response, OS, and AE. Initial dose of cetuximab is 400 mg/m$^2$ IV administered over 120 minutes, followed by weekly infusions at 250 mg/m$^2$ IV over 60 minutes. Each cycle is defined as 6 consecutive weekly treatments. The 30 patients enrolled in this trial were treated with a median number of 1 cycle per patient. Disease stabilized in 5 patients and progressed in 16 following 1 cycle of treatment, with only 1 patient remaining on the trial. Median PFS and OS were 41 days and 157 days, respectively. Treatment was generally well tolerated with no treatment-related deaths. Grade 1/2 toxicities included rash (83%), fatigue (47%), hypomagnesemia (27%), nausea (20%), anemia (13%), diarrhea (13%), anorexia (13%), and elevation of SGOT/SGPT (10%). Grade 3 SGOT, hypomagnesemia, and fever without neutropenia occurred in 1 patient (3%) each. In this phase II clinical trial, cetuximab was not active in HCC (Zhu AX, etal, ASCO06, Abs. 14096).

### Gastric Cancer

Stomach cancer, one of the leading causes of cancer-related deaths worldwide, is associated with poor prognosis and a 5-year survival rate of only 20%. It is particularly common in Asia. The annual worldwide incidence of adenocarcinoma of the stomach and gastroesophageal junction is approximately 800,000 cases. Approximately 21,260 of these cases occur in the USA, 50,000 in Western Europe, 110,000 in Japan, and 58,000 in Korea. The median survival for patients with advanced gastric cancer from the time of diagnosis is approximately 7 to 8 months. The principal treatment for gastric cancer is surgery, which may be combined with chemotherapy in Stage III/IV disease.



The reported incidence of HEr2 positivity in gastric cancer ranges from 6%-35%. A randomized, open label, phase III clinical trial (protocol ID: BO18255), referred to as ToGA, was initiated in Europe in September 2005. The goal was to evaluate fluoropyrimidine and cisplatin chemotherapy, with or without trastuzumab, on PFS in patients with HEr2+ advanced gastric cancer. A specific HEr2 test process was established for this trial based on IHC and FISH and a scoring system specific for gastric cancer (Hofmann M, etal, ASCOGI06, Abs. 24). Among 1,024 tumor samples assayed, 243 were HEr2+ positive, and 781 were HEr2-, for an overall HEr2-positivity rate of 23.7%. HEr2 positivity differed significantly by histologic subtype, such as intestinal (36%), diffuse (7%) and mixed (23%) disease. HEr2 positivity also varied according to tumor site and was 36% (8/22) for gastroesophageal junction tumors and 21% (60/291) for gastric tumors. Sample numbers were very small, and these results must be interpreted with caution. The HEr2-positivity rate was similar in specimens obtained by biopsy (168/689; 24%) or surgery (71/322; 22%). Overall, the HEr2-positivity rate in advanced gastric cancer was found, in a large sample, to be as high as it is in breast cancer at approximately 24% (León-Chong J, etal, ASCO07, Abs. 15057). Another group had previously reported a 13.5% HEr2 overexpression/amplification rate in advanced gastric or gastroesophageal junction cancer.

A phase II clinical trial of trastuzumab and cisplatin was initiated in chemotherapy-naïve patients with histopathologically confirmed inoperable locally advanced or metastatic gastric adenocarcinoma with HEr2 overexpression/amplification. Prior adjuvant radiotherapy and/or chemotherapy were permitted. IHC was performed using Dako's (Glostrup, Denmark) HercepTest, and followed by FISH when IHC=2. HEr2 expression was ruled negative if IHC=2 but FISH was negative. Trastuzumab (8 mg/kg loading dose) on day 1 in first cycle and 6 mg/kg (maintenance doses), and cisplatin (75 mg/m$^2$) on day 1, were administered every 21 days until progression, unacceptable toxicity or withdrawal of informed consent. Of the 21 patients included to date, 17 were evaluable. Histologic subtypes were intestinal (50%), diffuse (25%), and unknown (25%); 56% had gastric and 44% gastroesophageal junction cancer. A total of 16 patients had metastases (liver=59%, lymph nodes=47%, peritoneum=23%, lung=17%, and other=24%); 5 patients had undergone surgery; and 2 had adjuvant chemotherapy. A median (range=1-14) of 2 cycles was delivered. There were 1 CR and 5 PR for a 35% overall response, and disease stabilized in 3 (17%), for a 52% disease control. Disease progressed in 4 patients, and it was too early to evaluate another 4 patients. There was no Grade 4 toxicity. Main Grade 3 AE included asthenia (n=3), nausea/vomiting (n=3), diarrhea (n=2), anorexia (n=2), and neutropenia (n=1). The combination of trastuzumab and cisplatin was well tolerated with promising activity in advanced gastric cancer (Cortés-Funes H, etal, ASCO07, Abs. 4613).

### Esophageal Cancer

Although relatively rare in most of the developed world, esophageal cancer reaches epidemic proportion in countries such as Iran, China, India, and Japan. In 2007, there were approximately 15,560 cases diagnosed in the USA, and 13,000 deaths. The two major types of esophageal cancer are squamous cell carcinoma and adenocarcinoma. The incidence of adenocarcinoma has steadily risen in the USA and now accounts for nearly 50% of esophageal cancer. Squamous cell carcinoma accounts for most cases of esophageal cancer diagnosed elsewhere.

Several clinical trials with neoadjuvant chemoradiation have resulted in pCR rates of 20-30% in esophageal cancer, presumably by enabling R0 resections and reducing early local and distal metastases. Based on a retrospective analysis of a phase II trial, a high CR rate was observed in patients with esophageal carcinoma undergoing neoadjuvant combination treatment with docetaxel and cisplatin, with or without cetuximab. However, the addition of cetuximab resulted in no observed difference in response. A phase III clinical trial was suggested (Fillos TJ, etal, ASCO07, Abs. 15093).

Cetuximab is being evaluated in a multicenter, randomized, phase II/III clinical trial (protocol ID: WCTU-

SCOPE-1; EU-20739; EUDRACT-2006-002241-37; ISCRTN47718479; CTA-17853/0202/001-0001; NCT00509561) of cisplatin plus capecitabine, with or without cetuximab, as first line treatment of patients with nonmetastatic localized (T1-4, N0-1) esophageal cancer that was initiated in Europe in May 2007. This trial is sponsored by the Wales Cancer Trials Unit, under Study Chair Tom Crosby, MD, at Velindre NHS Trust (Cardiff, UK). Primary outcome measures are treatment failure rate at 24 weeks and OS. Secondary outcome measures include feasibility, toxicity, QoL, and health economics. Patients are randomized to 1 of 2 treatment arms. In arm 1, patients are treated with IV cisplatin over 2 hours on days 1, 22, 43, and 64 and oral capecitabine twice daily on days 1-84. Beginning in week 7, patients also undergo radiotherapy 5 days a week for 5 weeks (weeks 7-11). Treatment continues in the absence of disease progression or unacceptable toxicity. In arm 2, patients are treated as in arm 1 with the addition of cetuximab IV over 1-2 hours on day 1 in weeks 1-12. Treatment continues in the absence of disease progression or unacceptable toxicity. QoL and health economics are assessed at baseline, during treatment, and at pre-specified time points during follow-up. After completion of treatment, patients are followed every 3 months for 1 year, every 4 months for 1 year, and then annually for a minimum of 5 years. Estimated enrollment is 420 patients.

### Ovarian Cancer

Each year more than 182,000 patients are newly diagnosed with ovarian cancer, worldwide. In the USA, approximately 22,000 new cases of ovarian cancer and about 15,000 deaths were expected in 2007. About half of all ovarian tumors occur in postmenopausal women. Because ovarian cancer is frequently asymptomatic in the early stages, it is often not diagnosed until it progresses to Stage III or IV, when 5-year survival rates decline to 10-20%. Virtually all newly diagnosed patients undergo surgery, which is typically followed by radiation and chemotherapy; about half do not respond to treatment because of resistance to platinum-based drugs.

Variable rates of HEr2 protein overexpression and gene amplification have been reported in advanced ovarian cancer. Treatment with trastuzumab, as single agent, resulted in a 7% response rate in heavily pretreated patients with 3+ and 2+ HEr2 immunostaining (Bookman MA, J Clin Oncol, 15 May 2003;21(10 Suppl):149s-167s).

A more recent phase II clinical trial (protocol ID TCHERCEPTIN1; NCT00189579), was conducted in Europe (France) by the Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) to test the combination of trastuzumab with paclitaxel and carboplatin in patients with resistant advanced ovarian cancer and HEr2 gene amplification. In this trial, HEr2 status was screened in 321 patients (first line=243 and relapsing=78) by IHC, and confirmed by FISH. Of the 321 patients tested, 22 (6.7%) were HEr2+, but only 7 (32%) met the trial's eligibility criteria, including measurable lesions (n=4) or elevated CA 125 levels and non-measurable lesions (n=3). There were 3 CR (6, 7+, and 24+ months) and disease stabilized in 2 patients for 3 months. Toxicity was moderate, with 1 patient each experiencing febrile neutropenia, Grade 3 infection, Grade 2 neurotoxicity, and decrease of LVEF after 23 cycles of trastuzumab. Although HEr2 overexpression and amplification was low in advanced ovarian cancer (6.7 %), there were 3 CR among 7 patients with resistant disease when trastuzumab was added to conventional chemotherapy (Guastalla JP, etal, ASCO07, Abs. 5559).

A multicenter phase II clinical trial (protocol ID: MCCRC-RC0661; MCCRC-RC0661-LAPTOP-OC; MCCRC-06-002426; NCT00436644) was initiated in March 2007 in the USA to test lapatinib in combination with weekly topotecan in the treatment of platinum-refractory or resistant ovarian or primary peritoneal carcinoma. The trial is underway at several Mayo Clinic locations under Study Chair Paul Haluska, MD, PhD. Primary outcome measure is response rate (CR or PR). Secondary outcome measures are TTP; duration of CR or PR; OS; toxicity; expression of EGFr, HEr2, hypoxia-induced factor 1 α (HIF-1α), CD31, breast cancer resistance protein, and topoisomerase I, measured by IHC; and determination of the feasibility of monitoring circulating tumor cells with specific biologic markers to determine or follow response in these patients. Estimated enrollment is 39 patients. Patients are treated with oral lapatinib once daily on days 1-28 and topotecan IV over 30 minutes on days 1, 8, and 15. Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity. Blood samples are collected at baseline and on day 8 of course 1 (immediately after the topotecan infusion) and evaluated for pharmacologic studies. After the completion of treatment, patients are followed periodically for 2 years.



A multicenter (n=92), international, randomized, phase III clinical trial (protocol ID: EORTC-55041; EUDRACT-2004-004333-34; NCT00263822) is comparing erlotinib to observation in patients with no evidence of disease progression after first line, platinum-based chemotherapy for high risk ovarian epithelial, primary peritoneal, or fallopian tube cancer. This trial was initiated in September 2005, under Study Chair Antonio Jimeno, MD, Hospital Universitario 12 de Octubre (Madrid, Spain). Primary outcome measure is PFS. Secondary outcome measures include OS, AE profile, QoL, and cutaneous toxicity. Estimated enrollment is 830 patients. Patients are stratified according to disease stage (Stage I/II versus Stage III/IV), participating center, age (=65 versus >65), response to first line therapy (no evidence of disease/CR versus PR versus SD), and type of first line therapy (platinum-based versus platinum/taxane combination versus platinum-based triplet). Patients are randomized to 1 of 2 treatment arms. In arm 1, patients are treated with oral erlotinib once daily for up to 2 years in the absence of disease progression or unacceptable toxicity. In arm 2, patients undergo observation as per standard of care. QoL is assessed at

baseline and then every 3 months for up to 2 years. After completion of treatment, patients are followed periodically.

A multicenter (n=3) randomized phase II clinical trial (protocol ID: 07-039; NCT00520013) is evaluating bevacizumab, with or without erlotinib, as first line consolidation chemotherapy after carboplatin, paclitaxel and bevacizumab induction therapy in patients with newly diagnosed Stage III or IV ovarian, fallopian tube and primary peritoneal cancer and papillary serous mullerian tumors. This trial was initiated in the USA, under PI Susana Campos, MD, MPH, at Dana-Farber Cancer Institute, in August 2007. Primary outcome measures are PFS at 3 years and toxicity of the two consolidation regimens. Secondary outcome measure is response to induction therapy. Estimated enrollment is 60 patients. Trial completion is estimated in August 2010. According to the protocol, patients are treated with paclitaxel IV on day 1 and carboplatin IV on day 1 of each 21-day cycle for 6 cycles and IV bevacizumab for cycles 2-6. Subsequently, patients are randomized into one of two groups. In Group 1, patients are treated with bevacizumab administered every 3 weeks for 1 year. In Group 2, patients are treated with bevacizumab and daily PO erlotinib for 1 year. This second part occurs about one month after second look surgery in patients free of cancer by CT or MRI to determine if there is residual disease not detected by imaging. The operation, if recommended, will occur about one month after the 6th cycle of treatment.



## Bladder Cancer

Each year approximately 321,000 people, worldwide, are newly diagnosed with transitional cell carcinoma (TCC) of the bladder. Most, about 233,000 cases, are non-muscle invasive (superficial) disease; 70% of these are considered high grade tumors. In the USA and the European Union, approximately 178,000 people each year are newly diagnosed with superficial bladder cancer; 96,000 are high risk cases. In the USA, more than 100,000 cases of new (approximately 67,000) or recurrent superficial bladder cancer occur each year. Approximately 111,000 people are diagnosed with bladder cancer each year in the 25 EU countries, and 37,000 die from this disease. Muscle-invasive disease is present in approximately 25% of all new patients at the time of diagnosis. Of the remaining 75% who initially present with superficial disease, 10%-15% progress to invasive cancer.

Despite initial successful treatment, bladder cancer is a lifelong disease. More than half of patients with advanced bladder cancer experience recurrences. The prevalence of superficial bladder cancer is second to skin cancer, with an estimated 500,000 to 600,000 'walking worried' individuals in the USA and 1 million in Europe who are undergoing surveillance for recurrent bladder cancer. Bladder cancer has traditionally been treated by transurethral resection (TUR) and intravesical Bacillus Calmette-Guerin (BCG). However, about 30% of high risk cases are refractory to standard therapy with BCG. Options for patients with bladder cancer who fail BCG are limited. Historically, cystectomy has been the standard of care in this setting. Intravesical delivery of chemotherapeutic agents has demonstrated limited efficacy.

Overexpression of HEr2 protein has been detected in 27%-80% of urothelial carcinoma in various studies and correlated with early tumor recurrence and invasiveness. In nonrandomized trials, HEr2 was overexpressed in almost 25% of patients with bladder cancer and 50 to 60% of them responded to the combination of trastuzumab with standard chemotherapy. A prospective, randomized, phase II clinical trial, underway in Europe, was designed to compare treatment of chemotherapy-naïve patients with HEr2+ metastatic bladder cancer with trastuzumab plus standard chemotherapy (gemcitabine and platinum) to standard chemotherapy alone. The primary endpoint is PFS. Total sample size is estimated at 126 patients, of which 37 were accrued at 11 centers between February 2004 and December 2006. Interim safety analysis found no significant differences between the treatment arms with regard to all grade toxicities. Grade 3/4 leukopenia (53%), granulocytopenia (53%), anemia (33%), and thrombocytopenia (60%) were observed in the trastuzumab plus standard chemotherapy arm. Grade 1/2 diarrhea was slightly more frequent in the trastuzumab arm. Asymptomatic LVEF reduction occurred in one patient in each arm. The researchers concluded that the combination of trastuzumab with standard chemotherapy for bladder cancer was safe. No significant differences in serious adverse events were observed, including cardiac toxicities (Beuzeboc P, etal, ASCO07, Abs. 15565).

## Mesothelioma

Each year, inoperable malignant mesothelioma, an asbestos-related cancer, afflicts approximately 10,000 people worldwide, including 4,000 in the USA.

A multicenter, phase II clinical trial (protocol ID: SWOG-S0218; NCT00039182) was initiated in the USA in May 2002 to assess the 1-year survival rate of chemotherapy-naive patients with inoperable malignant pleural mesothelioma treated with erlotinib. The PI was Linda Garland, MD. This trial was reported closed in April 2003. Although malignant pleural mesothelioma (MPM) expresses high levels of EGFr, and preclinical studies have identified antitumor activity of EGFr tyrosine kinase inhibitors (TKI) in MPM, single-agent erlotinib was not effective. In this trial, previously untreated patients with MPM were treated with erlotinib (150 mg/day) on days 1 through 28 of each 28-day dosing cycle. Courses were repeated every 28 days in the absence of disease progression or unacceptable toxicity. Patients were followed every 6 months for 2 years and then annually for 1 year. Archived patient tumors were analyzed for expression (by IHC) of EGFr, phospho-EGFr, HEr2, phospho-extracellular signal-regulated kinase (ERK), and phosphatase and tensin homolog (PTEN) and also for phosphorylation of members of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway.

Among the 63 treated patients, EGFr was overexpressed in 75% of tumors. High expression levels were also found for phospho-ERK (82%), phospho-Akt (84%), phospho-mTOR (74%), and phospho-forkhead (74%). HEr2 was rarely expressed, and loss of PTEN was rare. In 33 patients with measurable disease, there were no objective responses, 4 patients were not evaluable, and disease stabilized in 14 (42%) and progressed in 15 (45%). Toxicities were mainly constitutional (51%), dermatologic (82%), and GI (52%). There was one death on trial, related to dyspnea. Overall MST was 10 months; 1-year survival rate was 43%; and median PFS was 2 months. Activation of the ERK and PI3K/Akt downstream pathways are possible resistance mechanisms to EGFr TKI. The activated PI3K/Akt pathway is a potential therapeutic target for MPM (Garland LL, etal, J Clin Oncol, 10 Jun 2007 Jun 10;25(17):2406-13).

## MARKET UPDATE

The global market of commercialized ErbB-pathway inhibitors continued its fast paced growth in 2007. Global sales were nearly $5 billion in the first 9 months of 2007; USA sales were nearly $2 billion and overseas sales were slightly over $3.0 billion (Exhibit 3).

The market success of these agents has spurred intense competition for market share within their approved indications and a broad clinical development program evaluating these drugs in all major cancer indications, mostly in combinations with standard cytotoxic regimens, but also in combination with each other, and in combination with other approved and/or novel targeted anticancer agents.

The upcoming last FUTURE ONCOLOGY issue (V9#7/8) in this series will present a review of ongoing evaluations of the approved ErbB-pathway inhibitors in combination with novel drugs addressing different pathways that have been identified as playing a role in the modulation of the ErbB pathway in cancer. These approaches are attempting to combat the emergence of early and late resistance hampering the effectiveness of currently approved drugs. In addition V9#7/8 will profile over 50 novel agents, in various stages of development, targeting the ErbB pathway, and several immunotherapy approaches.

This last issue of this series will also include a short analysis of this sector and a forecast of its outlook.

**Exhibit 3**
**Global Sales of ErbB-pathway Targeted Agents in the First Nine Months of 2007**

| Developer | Drug Designation | USA Sales ($000) | ROW Sales ($000) | Total Sales ($000) | Change (%) |
|---|---|---|---|---|---|
| Genentech ❑ Roche | Herceptin ❑ Trastuzumab | 960.0 | 2,017.3 | 2,977.3 | 26.0 |
| ImClone Systems ❑ Merck KgaA, Bristol-Myers Squibb | Erbitux ❑ Cetuximab | 506.5 | 470.2 | 976.7 | 17.6 |
| OSI Pharmaceuticals ❑ Genentech, Roche | Tarceva ❑ Erlotinib | 305.0 | 336.7 | 641.7 | 90.0 |
| AstraZeneca | Iressa ❑ Gefitinib | — | 168.0 | 168.0 | -3.0 |
| Amgen | Vectibix ❑ Panitumumab | 137.0 | — | 137.0 | NA |
| GlaxoSmithKline | Tykerb ❑ Lapatinib | 48.0 | 16.0 | 64.0 | NA |
| Total | | $1,956.5 | $3,008.2 | $4,964.7 | |

*Note: Small discrepancies are the result of currency translations*
*Source: NEW MEDICINE's Oncology KnowledgeBASE (nm\|OK), December 2007*



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