FUTURE ONCOLOGY
TECHNOLOGY, PRODUCTS, MARKETS AND SERVICE OPPORTUNITIES
A NEW MEDICINE PUBLICATION SEPTEMBER 15, 2007 VOLUME 9, NUMBER 3/4

STATE-OF-THE-ART IN THE TREATMENT OF CANCER

THE EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) PATHWAY IN CANCER

PART III – COMMERCIALLY AVAILABLE EGFR INHIBITORS

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One of the most exciting developments in cancer research in recent years has been the clinical validation of first generation molecularly targeted drugs that inhibit pathogenic tyrosine kinases. The epidermal growth factor (EGF) receptor (EGFr) pathway was the first cancer-related signaling pathway to be successfully targeted with specific agents at the molecular level. The clinical validation, regulatory approval, launch, and commercial success of first generation EGFr inhibitors represented a critical milestone in efforts to treat cancer by molecular targeting. First generation EGFr inhibitors are based on extracellular, monoclonal antibody (MAb) mechanisms of action and intracellular, small molecule tyrosine kinase inhibitors (TKI) approaches. Both have been firmly established as effective therapeutic options in clinical practice throughout the world.

In fact, enough experience has been acquired since the mid-2002 approval of gefitinib (Iressa; AstraZeneca), that it can serve as an example of both the opportunities and pitfalls that EGFr family inhibitors face as they enter uncharted waters regarding effectiveness, toxicities, and market competitiveness. The clinical roles of these agents are only now being defined, and no final chapters have

been written, even for gefitinib, which is currently finding great clinical market success outside the USA and undergoing testing in many new clinical trials, which is in line with the views of many oncologists who believe that indiscriminant patient selection undermined its effectiveness data.

Although the benefits of treatment of appropriately selected patients with first generation TKI have been clinically validated, they remain marginal in most indications. Drug developers are now focusing their clinical development efforts on identification of the tumor subtypes that will be most responsive to these agents, within both approved and new indications. On the horizon, new drug R&D is focused on compounds with greater effectiveness than first generation TKI and the ability to circumvent acquired resistance, which is problematic and limits efficacy of first generation compounds (Baselga J, Science, 2006;312(5777):1175-8).

This article is Part III of a 5-part series elucidating the role of the EGFr/ErbB pathway in cancer and its treatment. This issue reviews the clinical performances and roles of approved, commercially available ErbB inhibitors. Worldwide trends in pricing, reimbursement, treatment costs, current global markets, and near-term market projections are also assessed. Part I (V8, #11/12; March 28, 2007) of this series addressed ErbB receptors and ligands, downstream signaling in EGFr pathways, and 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 IV, which will appear in the next issue of FUTURE ONCOLOGY, will assess the performances of commercially available EGFr inhibitors in new indications under clinical development and provide long-term market forecasts. Part V, the last of the series, will describe and analyze the many novel drugs in development targeting the EGFr pathway.

PROFILES OF APPROVED ERBB/EGFR INHIBITORS

Since the introduction of Iressa in Japan in 2002, EGFr pathway inhibitor development has evolved rapidly. At present, 7 different agents with various mechanisms of action have entered the market (Exhibit 1) in the USA and/or abroad. Four of these, cetuximab, panitumumab, nimotuzumab, and trastuzumab, are monoclonal antibodies (MAb) and 3, gefitinib, erlotinib, and lapatinib, are small molecule drugs. Among these inhibitors of the EGFr/ErbB pathway, 5 block EGFr, one blocks HEr2 and one blocks both EGFr and HEr2. Mechanisms of MAb and small molecule TKI targeting of ErbB receptors were reviewed in the previous issue of FUTURE ONCOLOGY (V9#1/2:1965-1980).

Although the association of HEr2 overexpression with (a subtype of) breast cancer and the therapeutic benefit of trastuzumab as a targeted agent for this breast cancer subtype are not in dispute, the case for targeting EGFr remains much less convincing. Early reports of EGFr overexpression by nearly every solid tumor proved to be exaggerated, and the problems caused by qualitative methodologies for detection of EGFr overexpression and inter-observer variability have only recently been addressed albeit not uniformly among cancer researchers. Pathogenic downstream activation of the EGFr pathway also poses a challenge for EGFr inhibitors. 'Downstream' refers to events occurring after ligand binding to the extracellular portion of EGFr and receptor dimerization and also after the first major intracellular event of tyrosine kinase activation. Many downstream proteins, including K-ras, Raf, ERK, MAP kinase, Akt, and others, mediate signal transduction in the EGFr pathway; and deregulation of one or more of these mediators may induce activation (or inactivation) of the pathway. Such downstream activation has direct implications for the effectiveness of EGFr inhibitors. A pathway activated at a point downstream of EGFr would be unlikely to respond to EGFr inhibitors. A greatly reduced response might be observed as a consequence of inhibition of related pathways.

There are also indications of important differences between the activities of MAb and small molecule TKI. In general, small molecule drugs have demonstrated higher failure rates than large molecules, such as MAb. Large molecules are more selective for their targets than small molecule TKI. Also, small molecule TKI may cause side effects because of activities at non-cancer cell receptors. MAb may have another therapeutic advantage over small molecules because of an additional mechanism of action, antibody-dependent cellular cytotoxicity (ADCC), by which immune effector cells are induced to kill tumor cells. It has also been suggested that, because the two classes of EGFr inhibitors target different points in the pathway and display different performance profiles in the clinic, combination therapy using both may prove to be more effective than either used as a single agent. So-called 'total EGFr blockade,' using both types of inhibitors, is currently in early stage clinical trials designed to test the principle.

The profiles of the 7 commercially-available EGFr inhibitors below focus on mechanisms, clinical trials directly leading to regulatory approvals, and selected clinical and commercial considerations that were and are critical to regulatory approval and current clinical use. The trials (leading to approval) cited for each agent are addressed in detail in the Approved Indications section below.

Gefitinib (Iressa; AstraZeneca)

Gefitinib/ZD1839 (Iressa; AstraZeneca), an orally available low molecular weight quinazolone, is a selective and reversible ATP-competitive inhibitor of EGFr tyrosine kinase activity. Gefitinib is cytostatic towards a range of human cancer cell lines that express functional EGFr and

inhibits tumor cell proliferation via upregulation of p27. In addition, the efficacy of cytotoxic agents is enhanced in xenografted tumors following co-administration of Iressa. Additive and synergistic effects have also been observed with radiation.

Gefinitib was the first EGFr TKI to be approved worldwide. It was approved in Japan in 2002 and the USA in 2003 for the treatment of advanced non-small cell lung cancer (nsclc), based on the results of a randomized phase II clinical trial. Unfortunately, in December 2004, according to an initial analysis of the primary endpoint of the phase III Iressa Survival Evaluation in Lung cancer (ISEL) trial, the drug failed to significantly prolong survival in the overall population, compared to placebo. However, subsets of patients, such as never smokers, Asians, and in some cases those with adenocarcinoma or bronchioloalveolar cancer (BAC), derived statistically significant survival benefit with gefitinib over placebo.

Subsequently, mutations in the tyrosine kinase-binding domain of the EGFr were identified and found to predict for efficacy of gefitinib (for a description of these mutations, see V9#1/2:1960). These mutations are located near the catalytically active site of the receptor kinase, the binding site for gefitinib. In *in vitro* studies, mutant receptors signal at a higher level in response to EGF and do not turn off, conferring a growth advantage to tumor cells but, at the same time, making them much more susceptible to TKI, such as gefitinib. The prevalence of these mutations, which is approximately 10-13% in patients with nsclc in the USA, was greater in patient subsets benefiting in the ISEL trial. Based on recent trials, objective responses are seen in about 60-85% of the patients with EGFr mutations treated with single agent EGFr TKI. It is likely that tumors with EGFr mutations are critically dependent on the activated EGFr pathway for sustenance and proliferation, thereby accounting for the enhanced efficacy with EGFr blockade. Other predictive markers in addition to the EGFr mutations are the subject of much investigation. The three studies listed below highlight critical findings related to increased gefitinib activity in patients with nsclc and EGFr mutations.

Somatic mutations were identified in the tyrosine kinase domain of the EGFr gene in 8/9 nine patients with gefitinib-responsive lung cancer, compared to none of 7 non-responders ($p<0.001$). Mutations were either small, in-frame deletions, or amino acid substitutions clustered around the ATP-binding pocket of the tyrosine kinase domain. Similar mutations were detected in tumors from 2/25 (8%) patients with primary nsclc not exposed to gefitinib. All mutations were heterozygous, and identical mutations were observed in multiple patients, suggesting an additive specific gain of function. *In vitro*, EGFr mutants demonstrated enhanced tyrosine kinase activity in response to EGF and increased sensitivity to inhibition by gefitinib (Lynch TJ, etal, NEJM, 20 May 2004; 350(21):2129-2139).

Mutations were more frequent in adenocarcinoma [15/70 (21%)] than in other types of nsclc [1/49 (2%)], more frequent in women [9/45 (20%)] than in men [7/74 (9%)], and more frequent in patients from Japan [15/58 (26%)] compared to patients from the USA [1/61 (2%)]. In adenocarcinoma, a higher proportion of patients were diagnosed with EGFr mutations in Japan [14/41 (32%) than in the USA [1/29 (3%]. The highest fraction of EGFr mutations was observed in Japanese women with adenocarcinoma [8/14 (57%)]. Notably, patient characteristics that correlate with the presence of EGFr mutations also correlate with clinical response to gefitinib treatment. Gefitinib may be particularly effective for treating lung cancer with somatic EGFr mutations, and prospective clinical trials of EGFr inhibition in patients with EGFr mutations might reveal increased patient survival (Paez JG, etal, Science, 4 Jun 2004; 304(5676):1497-1500). L858R-mutant EGFr is particularly sensitive to inhibition by gefitinib, compared to wild type (wt) EGFr. When mutation status and response to gefitinib were determined in 4 lung adenocarcinoma and bronchioloalveolar carcinoma (BAC) cell lines, an extraordinary drug sensitivity was observed in the H3255 cell line, originally derived from a malignant pleural effusion from a Caucasian female nonsmoker with lung adenocarcinoma (Gorre ME, etal, Science 2001;293:876).

After the release of the ISEL trial findings, Iressa was all but removed from the USA market for the nsclc indication. Then, in January 2005, AstraZeneca withdrew the European Marketing Authorization Application (MAA) that had been submitted to the European Medicines Agency (EMEA) for the use of Iressa in nsclc. Although these regulatory developments were devastating news for the developers of Iressa, the nsclc outcome with gefitinib was hailed as a major breakthrough by cancer experts and as a victory for molecular medicine. First, the drug was dramatically effective against a cancer target, thus proving that inhibition of tyrosine kinases has a definite role in the treatment of cancer. Secondly, the gefitinib experience showed that it may be possible to screen patients for a specific target in order to initiate treatment early for a maximum effect, while preventing unnecessary exposure to toxicities of therapies in patients who are unlikely to respond.

Gefitinib remains a viable treatment option in nsclc outside the USA and Europe, primarily in Japan and other Asian countries, and is under investigation in numerous clinical trials for a variety of indications.

Cetuximab (Erbitux; ImClone Systems)

Cetuximab is a chimerized IgG1 MAb directed against the ligand-binding site in the extracellular domain of EGFr. Development of cetuximab was first reported in 1983 (Sato JD, etal, Mol Biol Med, Dec 1983;1(5):511-29, and Kawamoto T, etal, PNAS USA, Mar 1983;80(5):1337-41) by John Mendelsohn's group at M. D. Anderson Cancer Center

(Houston, TX). C225 is the human:murine chimeric version of murine MAb 225. Patients treated in phase I trials with the murine version of 225 developed human anti-mouse antibody (HAMA) reactions, which led to the development of the chimeric version of MAb 225, known as C225/cetuximab. Cetuximab exhibited improved receptor binding and antitumor activity in human tumor xenografts; and many of the animals treated with C225 were tumor free at the end of the treatment protocol. The dissociation constant of C225 was found to be about 5-fold lower than murine 225, suggesting that the increased capacity of C225 to compete with ligand for binding to EGFr was responsible for its increased *in vivo* antitumor effect (Goldstein NI, etal, Clin Cancer Res, 1995;1:1311-1318).

In April 1993, the University of California San Diego granted ImClone an exclusive worldwide license to a USA patent covering MAb that bind to EGFr. Also, in June 1994, Aventis Pharmaceuticals granted ImClone an exclusive worldwide license to pending patent applications covering the use of anti-EGFr MAb in combination with specific chemotherapeutic regimens.

In vitro and *in vivo* animal studies show that binding of Erbitux to EGFr blocks phosphorylation and activation of receptor-associated kinases, causing inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF) production. *In vitro* studies show that Erbitux also mediates antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. Although EGFr levels and mutations do not appear to correlate with response to cetuximab in colorectal cancer, gene amplification resulting in an increased number of gene copies of EGFr, may be predictive. Data suggest that combined treatment with the MAb EGFr inhibitor, cetuximab, and an EGFr TKI may increase the potency of EGFr signaling inhibition, and may improve the therapeutic ratio for anti-EGFr-targeted therapies. Data also demonstrate that cetuximab binds to and internalizes EGFrvIII, suggesting that cetuximab may also be a candidate for the treatment of tumors that express EGFrvIII.

2004

Cetuximab's long history includes clinical, regulatory, and commercial ups and downs. Initially, in 1998, ImClone reached an agreement with Merck KGaA for marketing rights of cetuximab outside of North America (excluding Japan). Then, in September 2001, ImClone struck a lucrative, $1 billion-potential deal with Bristol-Myers Squibb (BMS) for the USA, Canada, and Japan. This agreement appeared to have been premature for BMS when, in 2002, the FDA refused to accept ImClone's Biologics License Application (BLA) for colorectal cancer based on a phase II clinical trial of cetuximab, despite promising results; and ImClone still had not obtained approval anywhere in the world. The agreement between the companies was subsequently revised in March 2002, reducing the total remaining payments to $700 million from $800 million. Under the new agreement, BMS paid ImClone $140 million in the first quarter of 2002, and agreed to pay ImClone $60 million in March 2003 and an aggregate of $500 million upon the achievement of certain milestones. Also BMS agreed to pay ImClone a distribution fee based on a flat rate of 39% of product revenues in North America.

In December 2003, the Swiss Agency for Therapeutic Products (Swissmedic) approved the use of Erbitux, in combination with irinotecan, for the treatment of patients with colorectal cancer refractory to standard chemotherapy treatment with irinotecan. This (combination) approval was the first for Erbitux anywhere in the world. The Swiss approval was based on the multicenter (n=57), phase III BOND (Bowel Oncology with Cetuximab Antibody) clinical trial (protocol ID: CA225006; NCT00063141). Merck immediately began shipment of Erbitux in Switzerland.

USA approval followed soon after, in February 2004, when FDA approved Erbitux for use in combination with irinotecan in the treatment of patients with EGFr-expressing, metastatic colorectal cancer refractory to irinotecan-based chemotherapy, and also for use as a single agent in patients with EGFr-expressing, metastatic colorectal cancer who are intolerant to irinotecan-based chemotherapy. Like the Swiss approval, the USA approval was based on results from the BOND trial. It was noted at the time that the effectiveness of Erbitux is based on objective response rates. At this time, no data were available that demonstrated an improvement in disease-related symptoms or increased survival in patients treated with Erbitux.

Subsequently, a supplemental (sBLA) was filed with the FDA, which was accepted for filing and review by the agency in June 2007, seeking to include evidence of improved overall survival in the product labeling for Erbitux in the third line treatment of patients with metastatic colorectal cancer. The sBLA was granted priority review with a likely action date in early October 2007. If the sBLA is approved, Erbitux would be the only biologic therapy to demonstrate overall survival as a single agent in patients with metastatic colorectal cancer. The sBLA, which is based on results from a large, randomized, multicenter, phase III clinical trial (protocol ID: CDR0000353486; CAN-NCIC-CO17; AGITG-CAN-NCIC-CO17; BMS-CA225-025; IMCL-CAN-NCIC-CO17; NCT00079066), seeks to update the monotherapy indication to include patients with EGFr-expressing metastatic colorectal cancer whose disease has progressed following treatment, or who were not candidates to be treated with, irinotecan or oxaliplatin-based chemotherapy. The sBLA also seeks to include data on overall survival relative to best supportive care (BSC) considered to be all approved palliative therapies designed to alleviate pain and treat other effects caused by advanced colorectal cancer in this patient population.

In June 2004, ImClone Systems was granted marketing approval by the European Commission (EC) for Erbitux for this indication, in combination with irinotecan and as a single agent, and regulatory approval has since been obtained in more than 53 countries.

Exhibit 1
Approved and Commercialized Inhibitors of the ErbB Pathway

Developer ❑ Affiliate(s)	Generic Name ❑ Brand Name ❑ Other Designantion	Target(s)	Description	Administration Route
Amgen ❑ Japan Tobacco	Panitumumab ❑ Vectibix ❑ ABX-EGF (formerly clone E7.6.3)	EGFr ❑ Extracellular	Fully human IgG2 MAb	IV
AstraZeneca	Gefitinib ❑ Iressa ❑ ZD1839, ZD-1839	EGFr ❑ Intracellular (RTK)	4-anilinoquinazoline small molecule	PO
Centre of Molecular Immunology/CIMAB ❑ YM Biosciences, Oncoscience, Kuhnil Pharmaceutical, Biocon Biopharmaceuticals, Biotech Pharmaceuticals, Innogene Kalbiotech, Daiichi Sankyo	Nimotuzumab ❑ TheraCIM HR3, TheraCIM h-R3, TheraCIM hR3 (USA), Theraloc (Europe), CIMAher (Latin America) ❑ YM-1001, OSAG101, h-R3	EGFr ❑ Extracellular	Humanized MAb	IV
Genentech ❑ Roche, U Pennsylvania, PDL BioPharma, Chugai	Trastuzumab ❑ Herceptin ❑ rhuMAb HER2	HEr2 ❑ Extracellular	Recombinant DNA-derived humanized IgG1κ MAb (4D5)	IV
GlaxoSmithKline (GSK)	Lapatinib ditosylate ❑ Tykerb (USA, EU), Tyverb ❑ 572016, GW572016, GW 572016, GSK 572016	EGFr and HEr2 ❑ Intracellular (RTK)	4- anilinoquinazoline small molecule	PO
ImClone Systems ❑ U California San Diego, sanofi aventis, Merck KGaA, Bristol-Myers Squibb, Genentech, Centocor	Cetuximab ❑ Erbitux ❑ IMC-C225	EGFr ❑ Extracellular	Chimeric IgG1 MAb	IV
OSI Pharmaceuticals (OSIP) ❑ Genentech, Roche	Erlotinib ❑ Tarceva ❑ CP 358774, OSI-774, R1415, NSC 718781	EGFr ❑ Intracellular (RTK)	4-anilinoquinazoline small molecule	PO, IV

2005

In January 2005, ImClone signed license agreements with Genentech and Centocor for rights to patents relating to antibody technology and use of antibodies targeting EGFr, related to Erbitux and IMC-11F8.

In December 2005, Switzerland was again the first country to approve Erbitux, this time for head and neck cancer. Swissmedic approved Erbitux, in combination with radiation, for the treatment of patients with previously untreated, advanced squamous cell carcinoma of the head and neck, based on results from the phase III trial (UAB-9901; NCI-G99-1657; IMCL-CP02-9815; IMCL-9815; NCT00004227), which included 424 patients with advanced squamous cell carcinoma of the oropharynx, larynx, or hypopharynx that had spread through the head and neck region. Patients were randomized to either radiation plus weekly Erbitux therapy (n=211), or radiation alone (n=213), for 6 to 7 weeks. This trial was the basis of a supplemental BLA (sBLA) approved by the FDA in March 2006, and an MAA approved in Europe in April 2006.

This trial demonstrated unquestionable improvement in locoregional control, progression-free survival (PFS), and overall survival (OS) among patients treated with cetuximab plus radiotherapy, compared to radiotherapy alone, without increasing incidence of severe mucositis. However, the trial did not compare the combination of cetuximab plus radiotherapy to the current standard of care, platinum-based chemoradiotherapy. Furthermore, radiotherapy was not administered uniformly to all patients. Because of these shortcomings of the trial, the role of cetuximab in the treatment of advanced head and neck cancer lacks definitive findings, despite the approvals of the indication.

In July 2006, ImClone and Merck KGaA amended their 1998 development and license agreement. ImClone consented to Merck's sublicense of intellectual property rights relating to an anti-EGFr antibody to Takeda. Merck and Takeda signed an alliance in September 2005 for development and commercialization of matuzumab (EMD72000),

a humanized EGFr-targeting MAb. Merck paid ImClone a total of €7.5 million and increased its fixed royalty to 9.5% for all sales of Erbitux outside the USA and Canada. Freedom to operate was also promoted for the development and commercialization of matuzumab, outside the USA and Canada, and for ImClone's IMC-11F8, a fully human EGFr-targeted IgG1 MAb, within the USA and Canada. ImClone and its partner Bristol-Myers Squibb continue to hold exclusive licenses to key patents covering certain uses of EGFr-targeted MAb in the USA and Canada.

In February 2007, ImClone Systems and Bristol-Myers Squibb submitted an application to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for the use of Erbitux in treating patients with advanced colorectal cancer. Erbitux is the first IgG1 MAb that inhibits the EGFr to be submitted for marketing authorization in Japan. The Japanese submission was based on results from studies conducted in Europe and Japan, which confirm the activity of Erbitux in patients with metastatic colorectal cancer. The Japanese filing is a result of a development collaboration between ImClone Systems, Bristol-Myers Squibb, and Merck KGaA.

In July 2007, ImClone and BMS also amended their co-development and co-promotion agreement for Erbitux in North America and agreed to expand investment in the ongoing clinical development plan by up to several hundred million dollars. Development costs, up to a threshold value, are to be paid by BMS. Costs in excess of the threshold are to be shared by the companies according to a predetermined ratio. Funding is to be used to add phase II and phase III clinical trials to further explore the activity of Erbitux in a wide variety of applications, including brain, breast, bladder, gastric, lung, pancreatic, and prostate cancer. The goal is to use the results of these trials to support new registrational opportunities for Erbitux. In April 2006, ImClone Systems received the final $250 million milestone payment under this agreement, triggered by FDA's approval of Erbitux (cetuximab) for use in the treatment of squamous cell carcinoma of the head and neck on March 1, 2006. This was the final payment under the commercial agreement. Total milestone payments received under the agreement were $900 million.

In September 2007, Repligen (Waltham, MA) reached a settlement in the lawsuit against ImClone for infringement of USPTO-issued patent # 4,663,281 based on ImClone's manufacture and sale of Erbitux. The settlement provides for ImClone to make a payment of $65 million to co-plaintiffs Repligen and the Massachusetts Institute of Technology (MIT; Cambridge, MA) and will result in net proceeds to Repligen of approximately $40 million after payment of obligations to MIT and legal expenses. The settlement agreement serves as the basis for Repligen and MIT to dismiss the lawsuit against ImClone and Repligen has granted ImClone a non-exclusive sublicense to certain patent rights.

Erbitux is manufactured by ImClone Systems for territories served by BMS and by Merck KgaA for its territories. In 2004, ImClone received FDA approval to manufacture Erbitux at its BB36 facility, which has a capacity of 30,000 liters. Subsequently, in the fourth quarter of 2005, the company completed BB50, a 250,000 square-foot plant that more than doubled the production volume capacity for the drug. BB50 was approved by the FDA, and Erbitux production began there in June 2006. The BB50 facility contains three distinct suites, with a total future production volume capacity of up to 110,000 liters. In January 2007, Merck KGaA announced plans to consolidate its production of Erbitux in Corsier-sur-Vevey, Switzerland.

In a far-reaching development program announced in July 2007, ImClone and BMS described plans to evaluate Erbitux in phase II and III clinical trials in many different indications in order to expand the market for this drug.

Erlotinib (Tarceva; OSI Pharmaceuticals)

Like gefitinib, erlotinib is a low molecular weight oral quinazoline that reversibly inhibits EGFr kinase. In preclinical studies, OSI-774 treatment led to the accumulation of p21, caused G1 block, inhibited cell proliferation, induced apoptosis in cells, and downregulated molecular effectors of invasion. The drug is active in xenografted human tumors, both as a single agent and in combination with cisplatin.

Erlotinib was originally developed by OSI Pharmaceuticals (Melville, NY) in collaboration with Pfizer. In April 1986, the companies entered into a 15-year collaborative research agreement for erlotinib. The first 5 years focused primarily on understanding the molecular biology of oncogenes. Eventually, the collaboration was expanded to focus on discovery and development of cancer therapeutics, culminating in an April 1996 agreement under which Pfizer was granted an exclusive, worldwide license to make, use, and sell the therapeutic products resulting from this collaboration in exchange for royalty payments. In September 2000, however, in order to meet FTC requirements for its merger with Warner-Lambert, Pfizer transferred the IND dossier and all development and marketing rights for erlotinib to OSI. Under terms of this agreement, OSI obtained a royalty-free license to all rights for the further development and commercialization of erlotinib.

OSI quickly found new development partners for erlotinib. In January 2001, OSI, Genentech, and Roche entered into concurrent agreements for the global codevelopment and commercialization of erlotinib, and the drug's development program took off. Tarceva has since been widely approved for the treatment of advanced nsclc and pancreatic cancer. Notably, no regulatory jurisdiction, including the USA, Switzerland, or Canada, requires EGFr testing in order to initiate treatment of patients treated with Tarceva.

In November 2004, FDA approved Tarceva for the treatment of patients with locally advanced or metastatic nsclc after failure of at least one prior chemotherapy regimen. Approval was based on data from a pivotal phase III

2006

clinical trial (protocol ID: CAN-NCIC-BR21, BR.21; NCT00036647) that compared Tarceva to placebo for the treatment of patients with advanced nsclc, following failure of first or second line chemotherapy (Shepherd F, etal, N Engl J Med, 14 Jul 2005;353(2):123-32). Tarceva is the only drug in the EGFr class to demonstrate, in a phase III clinical trial, as monotherapy, an increase in survival in patients with advanced nsclc. In the USA, Tarceva was launched within 2 business days after its approval.

Subsequently, in March 2005, Swissmedic approved Tarceva for this indication. In July 2005, Health Canada approved Tarceva or the treatment of patients with locally advanced or metastatic nsclc following failure of first or second line chemotherapy and whose EGFr expression status is positive or unknown. In September 2005, Roche received approval from the EC to market Tarceva in the European Union (EU) for this indication. In none of these jurisdictions, drug labels require testing for EGFr status.

In April 2006, an NDA was submitted to the Japanese Ministry of Health, Labour and Welfare (MHLW) by Chugai Pharmaceutical, a Japanese affiliate to Roche, for the use of Tarceva for the treatment of advanced or recurrent nsclc. The filing is based on results of a phase II clinical trial that confirmed the safety and efficacy of Tarceva in Japanese patients, along with the data from the nsclc trial BR.21.

In November 2005, the FDA approved Tarceva in combination with gemcitabine chemotherapy for the treatment of advanced pancreatic cancer in chemotherapy-naive patients. Tarceva is the first drug to have shown a significant improvement in OS in a phase III clinical trial when added to gemcitabine chemotherapy in first line treatment of pancreatic cancer. Tarceva is also the first new potential therapy in nine years to have shown, in a randomized clinical trial, a statistically significant improvement in survival of patients with advanced pancreatic cancer, and is the first EGFr inhibitor to be approved in the treatment of pancreatic cancer.

In January 2007, the EC granted marketing authorization for Tarceva, in combination with gemcitabine, as first line therapy for metastatic pancreatic cancer. Six months earlier, in July 2006, Roche had received a negative opinion from the European Committee for Medicinal Products for Human Use (CHMP), regarding approval of Tarceva for this indication. However, Roche requested a re-examination of the data supporting the filing, and the MAA was granted.

Lapatinib (Tykerb; GlaxoSmithKline)

Lapatinib ditosylate (Tykerb), developed by GlaxoSmithKline (GSK), is an orally available selective dual inhibitor of receptor tyrosine kinases (RTK) EGFr and HEr2. Lapatinib is bound to an inactive-like conformation of EGFr that is very different from the active-like structure bound by erlotinib. Lapatinib has a very slow off-rate from the purified intracellular domains of EGFr and ErbB2, compared to erlotinib and gefitinib. Treatment of tumor cells with these inhibitors downregulates receptor tyrosine phosphorylation; and the slow off-rate of lapatinib correlates with prolonged downregulation. The differences in the off-rates of these drugs and the ability of lapatinib to inhibit ErbB2 can be explained by the enzyme-inhibitor structures (Wood ER, etal, Cancer Res, 15 Sep 2004; 6652-6659).

Lapatinib reversibly inhibits the tyrosine kinase components of both ErbB1 and ErbB2 receptors. Inhibition of both the PI3K/AKT kinase and the Erk1/2 MAP kinase pathways contribute to the induction of apoptosis by lapatinib. In cell lines, combining lapatinib with selected antiestrogens prevents a shift in the dependence of cell survival from ErbB2 to the estrogen receptor and may be a strategy for reducing resistance to lapatinib (Xia W, etal, ASCO06, Abs. 2075). Clinical trials are underway to investigate the genetic basis for patients who may be predisposed to AE associated with lapatinib (Zaks TZ, etal, ASCO06, Abs. 3029).

In March 2007, the FDA approved lapatinib, in combination with capecitabine (Xeloda; Roche), 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. Tykerb represents the first targeted, once daily oral treatment option for this patient population.

Also in March 2007, GlaxoSmithKline submitted an NDA in Japan for approval of lapatinib both as monotherapy and in combination with Xeloda, for patients with advanced or metastatic HEr2-positive breast cancer previously treated with chemotherapy, including an anthracycline, a taxane, and trastuzumab.

In October 2006, GlaxoSmithKline filed an MAA with the EMEA for approval to market Tykerb in combination with capecitabine, for the treatment of advanced or metastatic HEr2-positive breast cancer refractory to prior therapy, including trastuzumab. Data included in the filing is the same as that filed with the FDA. Marketing applications for lapatinib have also been submitted in many other countries, including Switzerland, Canada, Brazil, Australia, and South Korea.

Approval in all jurisdictions is based on a pivotal phase III clinical trial (protocol ID: GSK-EGF100151, UCLA-0403074-01; NCT00078572) that enrolled 399 women with advanced or metastatic HEr2-positive breast cancer whose disease had progressed following treatment with trastuzumab and other cancer therapies. Median TTP, assessed by independent reviewers, was 27.1 weeks for the combination of Tykerb plus capecitabine versus 18.6 weeks for capecitabine as a single agent. The hazard ratio of 0.57 (p=0.00013) represents a 43% reduction in the risk of progression for patients treated with the combination. Differences between treatment groups based on unblinded investigator assessments were smaller, but were clinically and statistically significant. Because of these results, the

trial was closed early, in April 2006. Findings are based on data from 321 women.

Panitumumab (Vectibix; Amgen)

Panitumumab is a fully human IgG2 MAb targeting EGFr. This construct (ABX-EGF) was developed by Cell Genesys using the XenoMouse technology platform originally developed by Xenotech. Xenotech was an equally owned limited partnership formed in 1991 by Cell Genesys and JT America, Japan Tobacco's (JT) USA subsidiary. Subsequently, in 1996 Cell Genesys assigned its interest in Xenotech to its subsidiary Abgenix. Then, in December 1999, Abgenix became the sole owner of the XenoMouse technology platform by acquiring all of JT America's interest in Xenotech. Abgenix paid $47 million to JT America for its 50% interest and $10 million as compensation to JT to relinquish certain option and license rights to which it was entitled.

In July 2000, Abgenix and Immunex entered into a joint development and commercialization agreement for ABX-EGF. Immunex's rights to the ABX-EGF collaboration were then inherited by Amgen, when it acquired Immunex in July 2002. As the development of panitumumab progressed, Amgen also acquired Abgenix, in April 2006, to become the sole owner of this drug.

Panitumumab, a fully human high affinity IgG2 monoclonal antibody (MAb) specific to human EGFr with a molecular weight of 147 kDa, was generated using XenoMouse technology. Panitumumab is produced in genetically engineered mammalian CHO cells.

Panitumumab binds specifically to EGFr with high affinity, preventing its activation and intracellular EGFr signaling. It blocks binding of both EGF and TGF-alpha to various EGFr expressing human carcinoma cell lines, abolishing EGF-dependent tumor cell activation and proliferation, including EGFr tyrosine phosphorylation. Upon binding to EGFr on tumor cells, panitumumab is internalized but not degraded, suggesting that it may be recycled to the cell surface. In *in vitro* studies, panitumumab also inhibits spontaneous production of angiogenic factors, such as VEGF and interleukin 8 (IL-8) by tumor cells. Although IgG1 antibodies (e.g., cetuximab) have been shown to activate the complement pathway and mediate ADCC, induction of ADCC by IgG2 isotype antibodies such as panitumumab has not yet been demonstrated.

In September 2006, after priority review, the FDA approved Vectibix (panitumumab). Vectibix is the first entirely human MAb approved for the third line treatment of patients with EGFr-expressing metastatic colorectal cancer after disease progression on, or following trteatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy regimens. FDA approval of Vectibix was based on a PFS endpoint, achieved in a phase III clinical trial (protocol ID: 20020408, NCT00113763) that compared treatment with Vectibix to best supportive care (BSC) in a heavily pretreated population with EGFr-expressing colorectal cancer. Vectibix is the first anti-EGFr MAb shown to significantly improve PFS in patients with metastatic colorectal cancer. Currently, no data is available indicating improvement in disease-related symptoms or increased survival with Vectibix.

In May 2007, Amgen received notice from the EMEA that the European CHMP adopted a negative opinion regarding its MAA for Vectibix in patients with metastatic colorectal cancer refractory to previous chemotherapy. In accordance with European regulations, Amgen requested a re-examination of the CHMP opinion through the appeal procedure and, in September 2007, Vectibix received a positive opinion from the CHMP recommending conditional marketing authorization in the European Union for use in patients with refractory metastatic colorectal cancer with non-mutated K-ras. This decision is based on a positive benefit/risk assessment of clinical data supporting use of K-ras mutation status as a biomarker for clinical outcome. These data were evaluated in combination with the overall clinical benefit observed in the pivotal trial (protocol ID: 20020408, NCT00113763) and safety data. K-ras plays an important role in cell growth regulation and oncogenesis. Mutated K-ras is constantly activated irrespective of the status of EGF, and signaling continues despite anti-EGFr therapy. Mutant K-ras is detected in approximately 40% of cases of metastatic colorectal cancer.

In March 2007, Amgen discontinued treatment with Vectibix in the PACCE trial because of lack of effectiveness and high toxicity. PACCE was a multicenter, randomized, open label, controlled, phase IIIb clinical trial (protocol ID: 20040249, NCT00115765) of chemotherapy and bevacizumab, with and without panitumumab, which was initiated in April 2005 to evaluate the addition of Vectibix to standard chemotherapy and bevacizumab (Avastin; Genentech) in the first line treatment of metastatic colorectal cancer. The option of adding Vectibix was subsequently discontinued.

Various efforts are underway to develop tests to predict the effectiveness of Vectibix therapy. Scientists from Amgen used breast, colon, lung, and pancreatic xenograft models to identify genes whose expression profiles could be used to predict responsiveness to panitumumab monotherapy. Panitumumab was administered twice per week at doses of 20, 100, 200, and 500 µg/mouse; response was defined as a 40% reduction of tumor volume, compared to control. Untreated xenograft samples were arrayed on the Affymetrix human U133A gene chip. Panitumumab treatment of 300 mm^3 established xenografts resulted in 8 responsive models, including nsclc lines with EGFr kinase domain mutations, and 12 non-responsive models. A supervised multivariate classification technique was used to identify gene sets that could predict responsiveness to panitumumab, independent of the known connection to the EGFr pathway. The gene set could predict treatment outcome in a leave-one-out validation. Panitumumab can inhibit the growth of breast,

colon, lung and pancreatic tumor xenografts. Tissue type had more influence on the clustering of models than responsiveness (or lack of responsiveness) to panitumumab. Using a supervised analysis, gene sets, regardless of their known association to EGFr signaling, can be generated from microarray data that can predict response in xenograft models. This approach may be helpful in selecting genes that could stratify patients responsive to panitumumab therapy (Boedighiemer M, etal, AACR05, Abs. 1).

Nimotuzumab (Theraloc; Centre of Molecular Immunology)

Nimotuzumab, a humanized MAb directed against EGFr, prevents EGF and TGFα binding to EGFr, resulting, potentially, in direct inhibition of cell growth and/or, possibly, ADCC. Nimotuzumab was developed in Cuba by the Centre of Molecular Immunology (CIM; Havana, Cuba).

YM BioSciences obtained the license for nimotuzumab from CIMAB (Havana, Cuba), representing CIM. CIMYM, a subsidiary of YM BioSciences, is developing the product and holds licenses in Europe, North America, and the Pacific Rim countries, excluding India and China. In November 2003, YM BioSciences signed a development and licensing agreement for the European market to Oncoscience (Wedel, Germany). In November 2005, YM BioSciences licensed nimotuzumab to Innogene Kalbiotech (Singapore) for Singapore, Taiwan, Thailand, Indonesia, Malaysia, Philippines, and South Africa, and other emerging markets, and in June 2005, licensed the drug to Kuhnil Pharmaceuticals (Seoul, South Korea) that is funding clinical development in South Korea. In July 2006, YM BioSciences licensed nimotuzumab development and marketing rights in Japan to Daiichi Sankyo (Tokyo, Japan).

CMAB licensed rights to nimotuzumab in the People's Republic of China to Biotech Pharmaceuticals (Beijing, Japan), and to Biocon Biopharmaceuticals, a joint venture between Biocon (Bangalore, India) and CIMAB for the Indian subcontinent.

Nimotuzumab is approved in China, India, and some South American countries, for the treatment of head and neck cancer and, specifically, for nasopharyngeal cancer, which is a major health problem in Asia. The drug was approved in China in 2005. Also, in July 2006, India's Drug Controller General granted marketing approval to nimotuzumab for the treatment of head and neck cancer.

In September 2006, the Office of Foreign Assets Control (OFAC) of the Treasury Department approved a license that allows YM BioSciences' wholly owned USA subsidiary to import nimotuzumab into the USA for the purpose of clinical trials in pediatric patients with pontine glioma, an orphan drug indication.

Nimotuzumab is manufactured in a continuous process using a stirred tank perfusion bioreactor. A 500-litre capacity reactor, approved by regulators in Canada, is expected to be expanded to a 1,000 litre scale of continuous fermentation in 2007.

Trastuzumab (Herceptin; Genentech)

Trastuzumab is a recombinant DNA-derived humanized IgG1κ MAb (4D5) targeting the extracellular domain of the HEr2 protein. Herceptin was approved in 1998 as a first line treatment, in combination with paclitaxel, for HEr2-positive metastatic breast cancer (Slamon DJ, etal, NEJM, 2001;344:783-792). At that time, the approval of Herceptin was hailed as a major step in the treatment of a particularly aggressive form of metastatic breast cancer. In addition to its effectiveness in the approved indication, the mechanism of action of trastuzumab conformed to the relatively new concept of targeted drug therapy, which linked the presence of a tumor marker with an agent designed to modify its cancer-related behavior. Herceptin is marketed by Genentech in the USA and Roche in the rest of the world.

Trastuzumab is based on MAb technology licensed by Genentech from the University of Pennsylvania (Philadelphia, PA), where it was developed in the laboratories of Jeffrey A. Drebin, MD, PhD, and Mark I. Greene, MD, PhD. Beginning in the early 1980s, these investigators collaborated with the laboratory of Robert Weinberg, PhD, at MIT, to develop a MAb against HEr2 (Drebin JA, etal, Cell, 1985;41:697-706, and Drebin JA, etal, Oncogene, 1988;2:273-277). Trastuzumab was later humanized using technology licensed from Protein Design Labs, now known as PDL BioPharma (Freemont, CA).

Although the exact cytotoxic mechanism of trastuzumab is not clearly understood, the agent specifically inhibits the proliferation of and is cytotoxic to tumor cells that overexpress HEr2 protein. Trastuzumab binds HEr2 at two antigen-specific sites and may decrease EGFr pathway signaling by preventing HEr2 dimerization, increasing receptor endocytosis and destruction, immune activation, reducing shedding of the extracellular domain (i.e., reducing formation of ligand-independent p95), or other mechanisms. Trastuzumab is a mediator of ADCC. Although the mechanism of ADCC is not clearly understood in this case, strong evidence suggests that trastuzumab binding to HEr2 mediates ADCC via Fc-competent immune effector cells such as natural killer (NK) cells and monocytes.

In July 1998, Roche obtained exclusive marketing rights for Herceptin outside of the USA. Under terms of the agreement Roche paid a substantial upfront fee, as well as cash milestones tied to product development activities. Roche also agreed to contribute equally with Genentech to global development costs and to make royalty payments on product sales. Herceptin is marketed in Japan, by Chugai, a Roche business unit.

Herceptin was approved in the USA in September 1998 for the treatment of metastatic breast cancer expressing HEr2, either as first line therapy in combination with paclitaxel, or as a single agent for second or third line therapy.

It was later approved in Canada, Europe, and Japan and is currently registered in more than 77 countries. In January 2005, the EC approved the combination of Herceptin and docetaxel for treatment of patients with metastatic breast cancer overexpressing HEr2. In May 2007, the EC approved the combination of Herceptin plus an aromatase inhibitor for the treatment of postmenopausal patients with HEr2- and hormone receptor-positive metastatic breast cancer. The last approval was based on data from the international phase III TAnDEM clinical trial, which showed that the addition of Herceptin to hormonal therapy doubled the median PFS, from 2.4 months to 4.8 months (Kaufman B, ESMO06 Abs. LBA2).

The finding that Herceptin is effective in reducing the risk of relapse/metastases in the adjuvant setting in patients with early breast cancer was a major breakthrough for this agent. Based on compelling data from phase III clinical trials, Herceptin was approved as an adjuvant treatment in HEr2-postive early breast cancer in 2002 in New Zealand and Australia. At the same time, several countries had developed clinical guidelines and committed funding to allow eligible patients faster access, prior to licensing specifically for this indication.

In May 2006, the EC approved Herceptin for patients with early stage HEr2-positive breast cancer following surgery and standard chemotherapy. This approval was granted within less than 3 months of Roche's MAA submission in February. Approval was based on results from the international HERceptin Adjuvant (HERA) trial, in which Herceptin treatment, after standard chemotherapy, significantly (by 46%) reduced the risk of cancer recurrence, compared to chemotherapy alone (Piccart-Gebhart M, etal, NEJM, 20 Oct 2005;353:16). Similarly benefits were observed in three other major trials, including NCCTG N9831 (USA), NSABP B-31 (USA), BCIRG 006 (international). In a major coup for Genentech/Roche, in August 2006, the National Institute for Health and Clinical Excellence (NICE; UK) recommended that Herceptin treatment be reimbursed for women with early stage HEr2-positive breast cancer. In November 2006, after a slight delay, FDA also approved Genentech's BLA for the adjuvant indication, based on results from the four trials above. At present, adjuvant treatment of early stage HEr2-positivebreast cancer with Herceptin is considered to be medically sound and economically justified, despite the high cost of the drug.

Although the selection of patients for treatment with Herceptin is rationally guided by biopsied tumor levels of overexpression of HEr2, investigators are looking for additional biomarkers that may guide treatment (as they are with other targeted agents).

Serum-based biomarkers have great clinical appeal because of the relative ease of biopsy (by venipuncture) of blood. In one study, a meta-analysis of 7 clinical trials of first line trastuzumab therapy (with or without chemotherapy) was undertaken to determine whether a change in serum HEr2/neu correlates with clinical outcome. Serum HEr2/neu change was defined as a decrease of >20% at the follow-up visit. Data was obtained from 307 patients (hormone receptor-positive, n=156; hormone receptor-negative, n=133; unknown hormone receptor status, n=18). Patients with >20% serum HEr2/neu change (n=191) and those with </=20% serum HEr2/neu change (n=116) were followed for a median of 30 days. OS data was based on 236 patients. Median decrease in serum HEr2 levels for all patients was 31.0%. Compared to patients with <20% decrease in HEr2 levels, those with >20% decrease experienced a higher ORR ($p<0.001$), longer duration of response ($p=0.008$), longer TTP ($p<0.001$), and longer median OS ($p=0.018$). Results were similar regardless of the timing of the second serum draw (<30 days versus >30 days) after the start of trastuzumab treatment. Patients with ≤20% decrease in serum HEr2 levels experienced less benefit from trastuzumab therapy, and additional HEr2-targeted therapies should be considered in those patients (Ali SM, etal, ASCO06, Abs. 500).

APPROVED CLINICAL INDICATIONS

EGFr pathway inhibitors are approved and launched in at least one major market for five key cancer indications, including metastatic colorectal cancer; early stage and metastatic breast cancer; advanced lung cancer; advanced head and neck cancer; and advanced pancreatic cancer (Exhibit 2).

Breast Cancer

Breast cancer is the most common malignancy in American women and second leading cause of cancer deaths in women. According to the American Cancer Society (ACS), in 2007, an estimated 178,000 women will be diagnosed with breast cancer in the USA, and approximately 40,000 will die from the disease. Worldwide, more than 1 million women are diagnosed with breast cancer every year. Metastatic breast cancer is the leading cause of cancer deaths in women globally, causing more than 400,000 deaths annually. Among metastatic breast cancer, HEr2-positive disease, which affects approximately 20% to 30% of women with breast cancer (Harries M and Smith I, Endocr Relat Cancer 2002;9:75-85), demands immediate and special attention because HEr2-positive tumors are fast growing and are particularly likely to relapse.

Two targeted therapies are approved for HEr2-positive metastatic breast cancer, trastuzumab and lapatinib. Trastuzumab is also approved for early-stage HEr2-positive disease, in the adjuvant setting, in combination with a taxane.

Despite the benefits of trastuzumab in various settings, many patients do not respond to treatment and, in others, tumors develop resistance to the drug. Efforts are being directed at indentifying biomarkers that determine patients' response to this drug.

Metastatic breast cancer expressing HEr2 may be treated with trastuzumab or lapatinib, albeit at different stages of the disease and for different indications.

Exhibit 2
Approved Cancer Indications of ErbB-pathway Inhibitors

Indication	Agent	Type	Approvals		
			USA	Europe	ROW
Metastatic colorectal cancer					
Second line, monotherapy	Cetuximab	MAb	x	x	x
Second line, combination chemotherapy	Cetuximab	MAb	x	x	x
Third line, monotherapy	Cetuximab	MAb	x	x	x
Third line, combination chemotherapy	Cetuximab	MAb			
Third line, monotherapy	Panitumumab	MAb	x		
Metastatic breast cancer					
First line, combination chemotherapy	Trastuzumab	MAb	x	x	x
Second or third line, monotherapy	Trastuzumab	MAb	x	x	x
Third line, combination chemotherapy	Lapatinib	TKI			
Advanced lung cancer					
Second or third line, monotherapy	Gefitinib	TKI			x
Second line, monotherapy	Erlotinib	TKI	x	x	x
Advanced head and neck cancer					
First line, combination with radiation therapy	Cetuximab	MAb			
Second line, monotherapy	Cetuximab	MAb	x		
First line combination with radiation therapy	Nimotuzumab	MAb			x
Advanced pancreatic cancer					
First line, combination	Erlotinib	TKI	x	x	x

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When it was approved in the USA in September 1998 for metastatic breast cancer, Herceptin became the first ErbB-targeted drug to be approved for any indication anywhere in the world. The USA approval was based on a randomized clinical trial that investigated the combination of Hereptin with standard chemotherapy. According to final results from this pivotal phase III trial involving 469 women, those treated weekly with Herceptin and standard cycles of chemotherapy (anthracycline and cyclophosphamide, or paclitaxel) as a first line therapy experienced a 24% increase in median OS, an addition of almost 5 months (25.1 months versus 20.3 months), compared to chemotherapy alone. Increased efficacy was observed in both chemotherapy subgroups to which Herceptin was added. The combination of Herceptin and chemotherapy compared to chemotherapy alone improved the overall response rate from 32% to 50%, increased TTP from 4.6 to 7.4 months, and increased median duration of response from 6.1 to 9.1 months (Slamon DJ, etal, 15 Mar 2001;344(11):783-792).

Subsequently, in January 2005, the EC approved the use of docetaxel (Taxotere; sanofi-aventis), in combination with Herceptin, for the treatment of patients with metastatic breast cancer whose tumors overexpress the HEr2 gene. The approval was based on results from an international randomized phase III clinical trial (protocol ID: M77001). This trial demonstrated a superior efficacy of the docetaxel-trastuzumab regimen, with significant improvement in OS and other efficacy endpoints, including objective response rate, TTP, and MST (Extra JM, etal, ECCO03, Abs. 672; Extra JM, etal, ASCO05, Abs. 555; Marty M, etal, J Clin Oncol, 1 Jul 2005;23(19):4265-74). The trial randomized 186 patients (docetaxel=94, docetaxel/ trastuzumab=92). At the latest analysis, at a median follow-up of 45.1 months in the docetaxel arm and 54 in the combination arm, 48 (25%) patients were still alive; 3 patients in the combination arm were still being treated with trastuzumab. The superior survival benefit with the combination regimen was maintained (31.3 versus 22.7 months). However, because the majority (57%) of patients randomized to docetaxel subsequently crossed over and were treated with trastuzumab, the survival difference was no longer significant (p=0.0876). At this juncture, 42 patients in the combination arm and 28 in the docetaxel

arm survived >3 years, 20 patients in the combination arm and 10 in the docetaxel arm survived >4 years, 9 patients in the combination arm and 4 in the docetaxel arm survived >4.5 years, and 1 patient in the docetaxel arm survived >5 years. Among those surviving over 3 years, 79% in the docetaxel arm had crossed over to trastuzumab. Therefore, the combination of docetaxel with trastuzumab is superior to docetaxel alone as first line treatment for HEr2-positive metastatic breast cancer provided a substantial long term survival benefit, with 22% of patients on the combination regimen surviving >4 years (Marty M, etal, SABCS06, Abs. 2067).

In May 2007, the EC approved trastuzumab in combination with an aromatase inhibitor for the treatment of postmenopausal patients with HEr2+ and hormone receptor-positive metastatic breast cancer. The approval was based on data from the international phase III TAnDEM clinical trial, which showed that the addition of Herceptin to hormonal therapy doubled the median PFS, from 2.4 months to 4.8 months (Kaufman B, ESMO06, Abs. LBA2).

TAnDEM is the first randomized trial to show that the specific subset of patients with both HEr2- and hormone receptor-positive disease are at increased risk of relapse, which makes the positive results achieved with Herceptin even more meaningful. TAnDEM, conducted by Roche, is a randomized phase III clinical trial (protocol ID: BO16216; NCT00112450; NCT00022672), which compared Herceptin in combination with the aromatase inhibitor anastrozole (Arimidex; AstraZeneca) to anastrozole alone as first line therapy (or second line hormonal therapy) in postmenopausal women with metastatic HEr2+ and hormone receptor-positive, i.e., estrogen receptor (Er)-positive and/or progesterone receptor (Pgr)-positive breast cancer.

Enrollment began in January 2001 with 208 patients randomized at 77 centers in 22 countries. Median PFS, the primary endpoint of the trial, was 4.8 months for patients treated with the combination, compared to 2.4 months for patients treated with hormonal therapy alone (p=0.0016). Patients in the combination arm also responded significantly better to treatment; overall response rate was 20.3% versus 6.8% (p=0.018), and there was a positive trend in median OS (28.5 months versus 23.9 months; p=0.325), despite the fact that, in the hormonal therapy alone arm, more than half of the patients (58/104) crossed over upon disease progression to be treated with Herceptin during the trial, and an additional 15 of 104 patients were treated with Herceptin at a later time point. Overall safety data in both arms of the trial were acceptable, given the known safety profile of each of the drugs in the advanced breast cancer setting. Patients in this trial are being followed for side effects (Mackey JR, etal, SABCS06, Abs. 3).

The Esther Study Group investigated the incidence of HEr2 and Er/Pgr overexpression in patients with newly diagnosed metastatic breast cancer and compared patient characteristics and outcomes of HEr2-positive and HEr2-negative disease. From June 2000 to November 2001, 96 centers in France participated in a prospective epidemiologic study including 741 consecutive patients with newly diagnosed metastatic breast cancer. HEr2 and hormonal receptor overexpression was assessed by IHC. Among 699 evaluable patients, 67% were postmenopausal, 29.6% were HEr2 3+, 61.4% were Er+, and 66.6% either Er+ or Pgr+. Notably, 22.4% of Er+ and 21.3% of Pgr+ tumors were also HEr2 3+, and 23% of Er+ and Pgr+ tumors showed IHC 3+ staining for HEr2. HEr2 overexpression was more frequent in invasive ductal carcinoma than in invasive lobular carcinoma (32.1% versus 16.5%; p=0.0033), and was associated with a shorter time to relapse (p=0.0294). HEr2 overexpression was not associated with either tumor grade or nodal involvement. These findings confirm that initial HEr2 overexpression at presentation is frequent in metastatic breast cancer (close to 30% as assessed by IHC 3+ staining) and is associated with a shorter time to relapse than HEr2-negative disease. Importantly, nearly a quarter (22.4%) of Er+ tumors in metastatic breast cancer were also HEr2+. This significant group of patients could possibly benefit from the addition of trastuzumab to their treatment (Penault-Llorca F, etal, ASCO05, Abs. 764).

Lapatinib, in combination with capecitabine (Xeloda), was approved by the FDA in March 2007 for the treatment of advanced or metastatic breast cancer, overexpressing HEr2, in patients previously treated with chemotherapy, including an anthracycline, a taxane, and trastuzumab. Data submitted were obtained from a planned interim analysis of an international, multicenter, open label, phase III clinical trial (protocol ID: GSK-EGF100151, UCLA-0403074-01; NCT00078572; NCT00086814) in women with advanced or metastatic breast cancer, with documented HEr2 overexpression, and whose disease progressed following treatment with Herceptin and other cancer therapies. A total of 324 women were randomized to treatment with capecitabine with or without lapatinib. The trial was stopped in April 2006 because it had met its primary endpoint of increased TTP and exceeded predetermined stopping criteria.

This phase III clinical trial was initiated in June 2004 at locations in the USA (n=43), Europe, and South America. Goals included determination of median TTP, overall response, clinical benefit, time to response, duration of response, 6-month PFS, OS, toxicity, and QoL for the two regimens. The primary endpoint was detection of a 50% increase in TTP in the combination arm, compared to the capecitabine alone arm. Patients were stratified according to disease stage (Stage IIIb versus IV) and site (visceral versus nonvisceral). Enrolled women had advanced or metastatic breast cancer with documented HEr2 overexpression, that had progressed after treatment with trastuzumab and other cancer therapies. In one arm, patients were treated with oral capecitabine (2000 mg/m^2/day) on days 1 to 14, and oral lapatinib (1250 mg) once daily, on days 1-21, not at the same time of day as capecitabine administration. In the other arm, patients

were treated with capecitabine (2500 mg/m²/day), alone, on days 1 to 14. In both arms, courses repeated every 21 days in the absence of disease progression or unacceptable toxicity.

According to the trial protocol, the interim analysis was reviewed by an Independent Data Monitoring Committee (IDMC). Of the 392 patients enrolled in the trial, 321 were included in the analysis, 160 in the combination arm, and 161 in the monotherapy arm. Results of the interim analysis indicated that the trial exceeded its primary endpoint and the trial was halted in April 2006. All women enrolled in the trial at the time it was halted continued to be followed and those treated with capecitabine alone were offered the option of switching to the combination therapy of capecitabine and lapatinib.

Treatment with the combination of lapatinib and capecitabine nearly doubled TTP compared to the capecitabine monotherapy arm. Median PFS was 36.9 weeks in the combination arm, compared to 17.9 weeks in the capecitabine arm (HR=0.48, p=0.000045). Adverse events (AE) leading to discontinuation were similar in the combination arm (14%) and capecitabine monotherapy arm (11%), as were overall AE. Diarrhea was more common in the combination arm (58%) than in the capecitabine arm (39%). Hand-foot syndrome occurred in 43% of patients in the combination arm, versus 34% in the capecitabine arm. Rash was experienced by 30% of patients in the combination arm (Grade 3 rash in <1%), and 18% in the capecitabine arm (Grade 3 in 3%). An asymptomatic relative decrease of 20% in LVEF occurred in 2.5% of patients in the combination arm and in <1% of patients in the capecitabine alone arm; all patients recovered normal LVEF. Additional analysis trial suggested that Tykerb may also play a role in decreasing the occurrence of brain metastases. In the interim analysis, only 4 patients experienced CNS relapse in the lapatinib plus capecitabine arm, compared to 11 in the capecitabine alone arm (Cameron D, etal, SABCS06, Abs. 2).

GlaxoSmithKline is using advanced technologies, including pharmacogenetics, to better define patient populations that may respond to lapatinib. Identification of response-predictive biomarkers would enable selection of patients for treatment based on an individual's specific tumor biology, rather than by histology alone. A recent molecular profile study found that the mTOR effector, p70 S6 kinase 1 (S6K1), was a useful biomarker for the biologic effects of Tykerb in HEr2-overexpressing breast cancer cells. The purpose of this study was to determine molecular profiles of the effects of trastuzumab and lapatinib on intracellular oncogenic kinase signaling.

The researchers simultaneously analyzed the activation status of all 3 major families of mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinases (ERK1/2), c-Jun N-terminal kinases (JNK 1–3), and different p38 isoforms. They also studied other intracellular kinases, including AKT, GSK-3, RSK1/2, MSK1/2, HSP27 and p70 S6 kinase 1 (p70S6K1). Drug effects were studied in paired control and HEr2-transfected breast cancer cells (MCF-7 and MCF-7/Her2–18 clone, respectively), using the recently developed human phospho-MAPK array, Proteome Profiler, a semi-quantitative protein array technology that allows parallel screening of the relative levels of phosphorylation of multiple intracellular kinases. Treatment with either trastuzumab or lapatinib identically affected the HEr2-regulated activation status of the MAPK, ERK1/2, JNK 1–3, and p38, and of the serine/threonine kinases, AKT, GSK-3, RSK1/2, MSK1/2, and HSP27. A notable difference was detected in deactivation of p70S6K1 in the breast cancer cells. Trastuzumab failed to deactivate p70S6K1, while Tykerb greatly inhibited HEr2-enhanced p70S6K1 activation, to levels even lower than those seen in control cells. [Control cells constitutively exhibit high levels of phospho-p70S6K1 because of a natural genomic amplification of the p70S6K1 gene on chromosome 17q23.]

Elevated p70S6K1 levels have been associated with resistance to trastuzumab in both metastatic cancer that overexpresses HEr2 and/or expresses HEr1. Elevated p70S6K1 levels have also been associated with clinical response to lapatinib. This study suggests that the serine-threonine kinase, p70S6K1, a marker for mTOR activity in regulating protein translation, should be considered a specific biomarker for the biological effects of lapatinib in HEr2-overexpressing breast cancer (Vazquez-Martin A, etal, EORTC-NCI-AACR06, Abs. 554).

Adjuvant treatment with Herceptin in resected non-metastatic breast cancer represents a novel indication for inhibitors of the ErbB pathway. Herceptin was evaluated in the adjuvant setting in early breast cancer in women with high risk disease in combination with the standard treatment approaches of surgery, chemotherapy and, in some cases, radiotherapy. Results from four large trials (Exhibit 3), involving over 12,000 patients from around the globe, provided consistent evidence that Herceptin reduces the risk of cancer coming back by about 50%, providing the best chance of long term survival to women with an aggressive form of early stage breast cancer.

Results with Herceptin in the adjuvant setting in breast cancer were hailed as 'stunning.' According to these trials, trastuzumab reduces the 3-year risk of recurrence by about one-half, with a similar benefit observed across all trials, despite differences in patient populations, chemotherapy regimens, and the sequence of treatment.

At a 2-year follow-up, according to interim results from the combined analysis of the NSABP B-31 and NCCTG N9831 trials, mortality was reduced by 33% in patients treated with trastuzumab, and there was a trend toward an OS benefit in both the HERA and BCIRG trials. Results were also positive in the FinHer trial. Further follow-up of the major adjuvant trials will clarify the survival benefit for women treated with trastuzumab and the optimal duration of treatment (i.e., 1 or 2 years). Overall, results from clini-

cal trials are sufficiently compelling to consider 1 year of adjuvant trastuzumab treatment for women with HEr-2-positive early breast cancer based on the risk:benefit ratio demonstrated in these trials (Baselga J, etal, Oncologist 2006;11(Suppl 1):4-12).

Adjuvant chemotherapy with HEr2 inhibition is currently undergoing review in terms of optimal length of treatment, sequence of drug therapy, long term survival, short term and long term toxicity effects, and its application in the real world outside the clinical trial setting.

Regarding survival, follow-up indicates that the addition of trastuzumab reduced the absolute risk of death by 1.8% over 2 years, implying that one extra woman will be alive for every 55 treated. However, 12.5% of women randomized to trastuzumab died or relapsed over an average of 2 years.

In terms of toxicities, investigators report that symptoms of heart disease in the adjuvant trials, experienced in 3% to 4% of women, improved immediately with appropriate intervention. It should be noted here that the trials excluded women with known heart disease. Therefore, it is likely that the majority of cases of cardiotoxicity were *de novo*, the direct cause of the adjuvant regimen incorporating Herceptin. In the HERA trial, women with HEr2+ disease, completing an anthracycline-containing regimen as first line adjuvant treatment were ineligible for trastuzumab treatment because of cardiac abnormalities caused by anthracyclines, squarely placing trastuzumab as the source of cardiotoxicity. Also, length of treatment may play a role in this area as, in the FinHer trial, a shorter treatment interval, prevented all such toxicity. In the HERA trial, the conclusion is that trastuzumab will raise the absolute risk of symptomatic congestive heart failure (CHF) by 2% at 2 years from 0.4% from 1 year, and by 5% if subclinical toxicity is included. For symptomatic CHF, it is estimated that one in 51 women (95% CI 37.2–80.1) will be affected, while all cardiotoxicity, including subclinical effects, will impact one in 20 women (95% CI 16.0–25.7).

The claim that adjuvant trastuzumab cardiotoxity is fully reversible is also in dispute, as is the long term effect of these drugs. Unfortunately, large crossover from the control arm to treatment with Herceptin in the pivotal phase III trials has made comparisons to assess the long term cardiac effects of Herceptin impossible. Generally, however, in the short term, the benefits of event-free and overall survival at 2 years, trump the low incidence and seemingly reversible cases of cardiotoxicity.

Protocols of the four pivotal trials differed in minor and major ways. In two of the trials, conducted primarily in the USA, Herceptin was dosed in combination with paclitaxel, which followed a doxorubicin plus cyclophosphamide regimen, while in the HERA trial, conducted primarily off shore, treatment with Herceptin was initiated after completion of adjuvant chemotherapy. Also, all of these 3 trials required treatment with Herceptin lasting at least one year, and HERA also investigated a 2-year treatment period. Another trial (FinHer) in the adjuvant setting, conducted in Finland, used a different chemotherapy combination regimen, and required only a 9-week treatment period with Herceptin (Joensuu H, etal, NEJM, 23 Feb 2006;354:809-820).

According to results from the international HERceptin Adjuvant (HERA) clinical trial (protocol ID: CDR0000256320; BIG-01-01; EU-20216; ROCHE-B016348E; ROCHE-B016348C; EORTC-10011; CAN-NCIC-MA24; IBCSG-28-02; NCT00045032), Herceptin treatment after standard chemotherapy significantly reduced the risk of cancer recurrence by 46% compared to chemotherapy alone (Piccart-Gebhart M, etal, NEJM, 20 Oct 2005;353(16):1659-72). HERA, conducted by Roche and the Breast International Group (BIG), is one of the largest adjuvant trials ever undertaken in patients with breast cancer. Enrollment began in December 2001, and nearly 5,100 HEr2-positive patients were enrolled at 480 sites in 39 countries before the trial was closed at the end of March 2005. HERA evaluated Herceptin every 3 weeks for 12 months or 24 months, after standard adjuvant systemic chemotherapy and radiotherapy (if applicable) in women with early stage HEr2-positive breast cancer. HERA allowed for the use of a wide range of chemotherapy regimens, and patients with either lymph node-positive and lymph node-negative breast cancer were eligible. According to the interim analysis, the trial met its primary efficacy endpoint, showing a statistically significant improvement in disease-free survival (DFS) in the 12-month arm, in patients treated with Herceptin; the risk of cancer recurrence was reduced by 46% compared to chemotherapy alone. The interim analysis compared Herceptin versus observation and did not compare 12 months versus 24 months treatment duration.

Overall survival was a secondary endpoint of the HERA trial. The drug's effect on overall survival in the HERA trial was evaluated in 1703 women who had been randomized for treatment with trastuzumab for 1 year, and 1698 women from the control group, with median follow-up of 23.5 months (range=0-48 months). Analyses were based on an intent-to-treat basis. Among enrolled women, 97 (5.7%) randomized to observation alone and 58 (3.4%) randomized to 1 year of treatment with trastuzumab were lost to follow-up. Also, 172 women stopped trastuzumab prematurely, and 59 deaths were reported in the trastuzumab, and 90 in the control groups. The unadjusted hazard ratio (HR) for the risk of death with trastuzumab, compared with observation alone was 0.66 (95% CI 0.47-0.91; p=0.0115). There were 218 DFS events reported with trastuzumab compared with 321 in the control group. The unadjusted HR for the risk of an event with trastuzumab compared with observation alone was 0.64 (0.54-0.76;

Exhibit 3
Completed Trials of Adjuvant Trastuzumab in the Treatment of Early Breast Cancer

Trial Description	Protocol ID ❑ Trial Acronym	Trial Status	Indication ❑ Enrollment	Reference	Results
Randomized trial of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab	NSABP-B-31, NCT00004067	Phase III (begin 3/00, closed 4/05) USA, Canada	Women with node-positive breast cancer overexpressing HEr2 ❑ 2,085 patients	Romond EH, etal, NEJM, 20 Oct 2005; 353(16): 1673-84).	At 3 years, the absolute difference in DFS between the trastuzumab and control arms was 12%; trastuzumab therapy was associated with a 33% reduction in the risk of death (p=0.015).
Randomized trial of doxorubicin plus cyclophosphamide followed by paclitaxel with or without trastuzumab	NCCTG-N9831; CALGB-49909; ECOG-N9831; SWOG-N9831; GUMC-00224; CAN-NCIC-MA.28; NCT00005970	Phase III (begin 6/00, closed 4/05) USA, Canada, Peru, South Africa	Women with high risk (node-positive or node-negative) breast cancer overexpressing HEr2 ❑ 3,406 patients	Romond EH, etal, NEJM, 20 Oct 2005; 353(16): 1673-84).	
Randomized 3-arm comparison of 1 year and 2 years treatment with trastuzumab versus no trastuzumab	BIG-01-01; EU-20216; ROCHE-B016348E; ROCHE-B016348C; EORTC-10011; CAN-NCIC-MA24; IBCSG-28-02; NCT00045032 ❑ Herceptin Adjuvant (HERA)	Phase III (begin 12/01, closed 3/05) Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Europe (Austria, Belgium, Croatia, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Russia, Spain), Guatemala, Hong Kong, Israel, Japan, Korea, Singapore, South Africa, Sweden, Switzerland, UK) Thailand	Women with HEr2-positive primary breast cancer, and positive or negative nodes who completed adjuvant chemotherapy ❑ 5,100	Piccart-Gebhart M, etal, NEJM, 20 Oct 2005; 353(16): 1659-72, and Smith I, etal, Lancet, 6 Jan 2007;369 (9555):29-36	At a median follow-up of 2 years, the unadjusted HR for the risk of death with trastuzumab, compared with observation alone was 0.66 (0.47-0.91; p=0.0115), and the unadjusted HR for the risk of an event with trastuzumab compared with observation alone was 0.64 (0.54-0.76; p<0.0001).
Adjuvant docetaxel or vinorelbine with without trastuzumab for breast cancer	ISRCTN76560 285 ❑ FinHer	Phase III (begin 10/00, closed 9/03) Europe (Finland)	Women with high risk (node-positive or node-negative) breast cancer overexpressing HEr2 ❑ 235	Joensuu H, etal, NEJM, 23 Feb 2006; 354(8):809-820).	The 3-year recurrence-free survival rate was 89% for those treated with trastuzumab compared to 78% for untreated patients; HR for recurrence or death is 0.42 (0.21-0.83; p=0.01).

Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), August 2007

p<0.0001). A 2-year follow-up of trastuzumab after adjuvant chemotherapy in HEr2-positive breast cancer indicates that 1 year of treatment with trastuzumab after adjuvant chemotherapy has a significant overall survival benefit after a median follow-up of 2 years. The emergence of this benefit after only 2 years reinforces the importance of trastuzumab in the treatment of women with HEr2-positive early breast cancer (Smith I, etal, Lancet, 6 Jan 2007;369(9555):29-36).

Two large randomized phase III clinical trials were also undertaken in the USA to assess the role of Herceptin in the adjuvant setting. These trials were conducted under a CRADA between Genentech and NCI. Genentech provided trastuzumab and partial funding support, but did not participate in the design of the trials or data collection. Both trials were stopped early after committees monitoring interim results determined that trastuzumab plus chemotherapy was clearly superior to chemotherapy alone and should be made available to all participants.

One of these trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP) phase III clinical trial (protocol ID: CDR0000067269; NSABP-B-31; NCT00004067, initiated in February 2000, compared doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 21 days for 4 cycles, followed by paclitaxel (175 mg/m^2) every 3 weeks for 4 cycles (group 1), to the same regimen with the addition of trastuzumab, beginning with a loading dose (4 mg/kg) administered with the first dose of paclitaxel, and followed by weekly doses of 2 mg/kg for 51 weeks (group 2). Beginning on May 16, 2003, paclitaxel (80 mg/m^2) could also be administered weekly for 12 weeks at the investigator's discretion.

Another trial, the North Central Cancer Treatment Group (NCCTG) phase III clinical trial (protocol ID: CDR0000067953; NCCTG-N9831; CALGB-49909; ECOG-N9831; SWOG-N9831; GUMC-00224; CAN-NCIC-MA.28; NCT00005970), initiated in May 2000, compared three regimens, doxorubicin and cyclophosphamide as in group 1 of trial NSABP-B-31, followed by weekly paclitaxel (80 mg/m^2) (group A); the same regimen of trastuzumab as NSABP-B-31, following paclitaxel (group B); and the same regimen as group 2 of NSABP-B-31 (group C). In NSABP-B-31, treatment assignments were balanced according to nodal status, planned hormonal therapy, type of surgery (lumpectomy versus mastectomy), intended radiotherapy, and institution. Trial N9831 employed a dynamic allocation procedure that balanced the marginal distributions of nodal status and hormone-receptor status between groups.

Enrollment in these trials required a pathologic diagnosis of adenocarcinoma of the breast demonstrated by IHC staining for HEr2 protein of 3+ intensity or HEr2 gene amplification by FISH. Initially, eligible patients in both trials were required to have histologically proven, node-positive disease. However, as of May 2, 2003, patients with high risk node-negative disease became eligible for trial N9831. High risk node-negative disease was defined as a tumor of >2 cm in diameter and positive for Er or Pgr, or a tumor >1 cm in diameter and negative for both Er and Pgr. Other requirements were adequate hematopoietic, hepatic, and renal function and a LVEF that met or exceeded the lower limit of normal. Patients with clinical or radiologic evidence of metastatic disease were excluded. Complete resection of the primary tumor and axillary node dissection were required.

At the time of the final analysis, of the 2,043 patients enrolled in trial NSABP-B-31 as of February 15, 2005, 1,736 had at least one follow-up evaluation. By November 1, 2004, 1,633 patients had been enrolled in groups A and C of trial N9831, 1,615 of whom had follow-up data submitted by March 15, 2005. Except for 191 patients with node-negative breast cancer who were enrolled in trial N9831, the groups from each trial were similar.

In April 2005, the independent data-monitoring committees of each trial recommended closing enrollment and releasing the results from both trials. Because group 2 in trial NSABP-B-31, group C in trial N9831, and the control groups of these trials were identical, except for differences in the scheduling of paclitaxel treatment and some aspects of hormonal therapy and radiotherapy, the NCI and FDA approved a joint-analysis plan developed by the NSABP and NCCTG. The joint analysis combines data from group 1 and group A (referred to as the control group) for comparison with group 2 and group C (referred to as the trastuzumab group). Group B of trial N9831 was excluded because the protocol required trastuzumab administration after completion of chemotherapy, rather than concurrently. The plan required an initial interim analysis after 355 events. Before the data were locked, 2,043 patients (of a planned total of 2,700) were enrolled in trial NSABP-B-31 and 1,633 patients (of a total of 2,000 for the comparison of group A with group C) were enrolled in trial N9831.

By March 15, 2005, 394 events (recurrence, second primary cancer, or death before recurrence) had been reported, triggering the first scheduled interim analysis. Of these, 133 were in the trastuzumab group, and 261 were in the control group (HR=0.48; p<0.0001). This result crossed the early stopping boundary. The absolute difference in DFS between the trastuzumab group and the control group was 12% at 3 years. Trastuzumab therapy was associated with a 33% reduction in the risk of death (p=0.015). The 3-year cumulative incidence of class III or IV congestive heart failure or death from cardiac causes in the trastuzumab group was 4.1% in trial NSABP-B-31 and 2.9% in trial N9831. Trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide was found to improve outcomes of women with surgically removed HEr2-positive breast cancer (Romond EH, etal, NEJM, 20 Oct 2005;353(16):1673-1684).

The FinHer trial, conducted in Finland, under PI Heikki Joensuu, MD, Helsinki University Central Hospital, compared docetaxel with vinorelbine for the adjuvant treatment of early breast cancer. Women with tumors that

overexpressed HEr2 were also assigned to concomitant treatment with trastuzumab or no such treatment. The purpose of the trial was to compare tolerability, safety and efficacy of single agent vinorelbine and single agent docetaxel as adjuvant treatments of early breast cancer with moderate to high risk for cancer recurrence, and of trastuzumab administered concomitantly with vinorelbine or docetaxel in this setting. The trial's primary objective was recurrence-free survival. Secondary outcome measures were survival, safety, QoL, and cardiac ejection fraction.

According to the protocol, patients are treated with weekly vinorelbine (25 mg/m^2) for 8 weeks followed by cyclophosphamide, epirubicin and 5-fluorouracil (CEF) for 3 weeks versus thrice weekly docetaxel (100 mg/m^2) for three weeks followed by CEF for 3 weeks. Whenever tumor is HEr2-positive, a second randomization is undertaken between weekly trastuzumab (2 mg/kg) concomitantly with vinorelbine/docetaxel versus no trastuzumab. Nine trastuzumab infusions were administered at one-week intervals; the first infusion (4 mg/kg) was administered on day 1 of the first docetaxel or vinorelbine cycle; subsequent doses (2 mg/kg) were administered over periods of 30 minutes. Trastuzumab was infused before docetaxel or vinorelbine. No trastuzumab was administered during CEF administration.

Patients were <66 years-of-age, with nonmetastatic disease with confirmed Pgr and HEr2 status (by IHC and FISH), and with estimated risk of breast cancer recurrence of >25% within the first 5 years from diagnosis. Eligible patients had either at least one positive axillary node (regardless of the primary tumor size or its hormone-receptor status) or a node-negative breast-cancer mass at least 20 mm in diameter and a negative test for Pgr (usually defined as staining of <10% of the cancer cells). The staging workup included isotope bone scanning; chest radiography or computed tomography (CT); and CT or ultrasonography of the upper abdomen.

A total of 1010 women were treated with 3 cycles of docetaxel or vinorelbine, followed by 3 cycles of 5-FU, epirubicin, and cyclophosphamide. The 232 women whose tumors had an amplified HEr2 gene were further assigned to 9 weekly trastuzumab infusions, or no trastuzumab. Recurrence-free survival at three years was better (HR=0.58; 95% CI, 0.40 to 0.85; p=0.005) with docetaxel (91%) than with vinorelbine (86%), but overall survival did not differ between the groups. Within the subgroup of patients with HEr2-positive disease, the 3-year survival of those treated with trastuzumab was better (89%) than for those who were not treated with trastuzumab (78%) yielding an HR for recurrence or death of 0.42 (95% CI, 0.21 to 0.83; p=0.01). Docetaxel was associated with more adverse effects than vinorelbine. Trastuzumab was not associated with decreased left ventricular ejection fraction or cardiac failure. In this trial, adjuvant treatment with docetaxel, as compared with vinorelbine, improved recurrence-free survival in women with early breast cancer. A short course of trastuzumab administered concomitantly with docetaxel or vinorelbine is effective in women with breast cancer with an amplified HEr2 gene (Joensuu H, etal, NEJM, 23 Feb 2006;354(8):809-820). In this trial, at a median follow-up of 3 years, the effect on event-free survival was in the range of that reported with the administration of trastuzumab for a year after adjuvant chemotherapy.

Colorectal Cancer

Colorectal cancer is the third most common cancer in both men and women, and the second leading cause of cancer-related deaths in Western Europe and the USA after lung cancer. The overall 5-year survival of patients with colorectal cancer is approximately 50%. In the USA, approximately 154,000 people will be diagnosed with cancer of the colon or rectum in 2007; 50% of these patients will have metastatic disease at the time of diagnosis. Worldwide, colorectal cancer is the fourth most commonly diagnosed malignancy, with an estimated annual incidence of 1,023,000 and 529,000 deaths.

Standard cytotoxic chemotherapy for advanced colorectal cancer results in median survival time (MST) of around 20 months, which may prove an upper limit for such an approach. Longer survival outcomes therefore depend on the newer targeted approaches, including EGFr inhibitors. The rationale for investigating EGFr inhibitors in colorectal cancer is based on the observation that EGFr is expressed in up to 77.7 % of cases of colorectal cancer.

The first EGFr inhibitor to enter the market in colorectal cancer was cetuximab, which was approved for second and subsequent lines of treatment in patients with advanced colorectal cancer whose disease progressed while on irinotecan. To date, panitumumab has not been approved for combined use with chemotherapy and is indicated only after disease progression in patients who already treated with oxaliplatin, irinotecan, and a fluoropyrimidine.

In metastatic colorectal cancer, both cetuximab and panitumumab are indicated after failure of first line or second line and beyond chemotherapy, unlike bevacizumab, which has been approved in the first line setting in combination with FOLFOX. Bevacizumab is also indicated for second line treatment in combination with chemotherapy regimens that involve such drugs as oxaliplatin, irinotecan, and/or fluoropyrimidines.

Cetuximab was first evaluated in the USA as second line therapy in a multicenter phase II clinical trial (protocol ID: MSKCC-01034, NCI-G01-1970, IMCL-CP02-0141) in patients with metastatic colorectal cancer with progressive disease on or after treatment with irinotecan. IV cetuximab was administered over 1-2 hours weekly for 6 weeks. Treatment was repeated in the absence of disease progression or unacceptable toxicity. Patients were followed at 4 weeks and every 3 months thereafter. The PI was Leonard Bruce Saltz, of Memorial Sloan-Kettering

Cancer Center. This trial was conducted between April 17, 2001 and July 12, 2001 and completed in October 2001. A total of 57 patients with metastatic colorectal cancer expressing EGFr were enrolled. Enrolled patients were selected among 140 patients screened for EGFr expression. At least a 1+ expression of EGFr was detected in 105 (75%). Treating physicians determined that in 61 of 105 patients who met all other eligibility criteria, there was radiologic evidence of failure on irinotecan or an irinotecan-containing regimen; 4 patients who experienced clinical deterioration before initiation of cetuximab therapy were excluded. Among the 57 enrolled patients, 47 (82%) were treated within 3 months of their last irinotecan dose, 7 (12%) within 3 to 6 months, and 3 (5%) were treated more than 6 months after their last irinotecan dose. Median duration of trial treatment was 6.4 weeks (range=1 to 67 weeks). Nearly all cetuximab doses administered were at the full planned loading dose of 400 mg/m^2 and subsequent weekly doses of 250 mg/m^2. All planned doses of cetuximab were administered to 36 (63%) patients during the trial, while 18 (32%) missed either one or two planned doses of cetuximab, and 1 patient missed more than 2 of the planned doses of cetuximab. Two (3.5%) patients were administered only the test dose of cetuximab. All patients in the trial were considered evaluable for efficacy.

Among the 57 treated, there were 6 (10.5%) partial responses (PR) based on investigator assessments and minor responses or disease stabilization in 20 (35%) additional patients, lasting for at least 12 weeks from the date of initiation of cetuximab treatment. The independent response assessment committee concurred with five of the six investigator-adjudicated responses (major response rate of 8.8%; 95% CI, 3% to 19%) reclassifying one investigator-adjudicated major response as a minor response. Response did not appear to be correlated with the degree of EGFr expression. Among 16 patients who had been treated with only one prior regimen, only one patient (as determined by both the investigators and the independent review committee) experienced a PR, for a response rate of 6.3%, indicating that the response rate was neither superior or different in patients treated with more than one prior regimen. Median TTP was 1.4 months, with a median duration of response of 4.2 months in the 5 responders. MST from the initiation of trial protocol therapy for the 57 treated patients was 6.4 months (Saltz LB, etal, JCO, 1 Apr 2004;22(7):1201-1208). Despite these results the FDA did not accept this trial for the BLA filing because it did not incorporate a comparative arm.

Cetuximab was approved later on the basis of a randomized 2-arm phase II clinical trial conducted by Merck KGaA in Europe. This trial, referred to as BOND (Bowel Oncology with Cetuximab Antibody), evaluated Erbitux as a single agent and in combination with irinotecan in 329 patients with EGFr-expressing metastatic colorectal cancer refractory to irinotecan-based chemotherapy. Erbitux administered in combination with irinotecan (n=218) resulted in an objective response rate of 22.9%, median duration of response of 5.7 months, and median TTP of 4.1 months. Erbitux single agent treatment (n=111) resulted in a 10.8% objective response rate, median duration of response of 4.2 months, and median TTP of 1.5 months. In this trial, Erbitux, administered in combination with irinotecan chemotherapy, benefited >50% of patients. Erbitux treatment decreased tumor size by >50% in 23% of patients and halted tumor growth in an additional 33% (Cunningham D, etal, NEJM, 22 Jul 2004;351(4):337-45).

In order to obtain information on overall survival, a randomized, open label, multicenter, phase III clinical trial (protocol ID: CAN-NCIC-CO17, AGITG-CAN-NCIC-CO17, BMS-CA225-025, IMCL-CAN-NCIC-CO17; NCT00079066) of cetuximab with best supportive care (BSC) compared to BSC alone in patients with pretreated metastatic EGFr+ colorectal cancer was initiated in August 2003, at multiple locations in Australia and Canada, to determine OS, as its primary endpoint, and TTP, objective response rate, QoL and toxicity as secondary endpoints. Patients were randomized to 1 of 2 treatment arms. In arm I, patients were managed by BSC, defined as measures designed to provide palliation of symptoms and improve QoL as much as possible. In arm II, patients were administered BSC as in arm I in combination with cetuximab. In both arms, treatment continued in the absence of disease progression or unacceptable toxicity. QoL was assessed at baseline, and then at 4, 8, 16, and 24 weeks (or until deterioration to ECOG PS 4 or hospitalization for end-of-life care). Patients were followed every 4 weeks. Derek Jonker, MD, of the NCIC Clinical Trials Group (NCIC CTG) and Chris Karapetis, of the Australasian Gastro-Intestinal Trials Group (AGITG) were Protocol Chairs. This trial was closed to recruitment in August 2005.

In November 2006, this trial met its primary efficacy endpoint showing a statistically significant improvement in overall survival. These are the first data of an anticancer therapy to demonstrate overall survival in this setting. From November 2003 to August 2005, the trial enrolled 572 patients with EGFr detectable tumors by IHC, who had been pretreated an anti-thymidylate synthase inhibitor, such as 5-FU or capecitabine, and to have failed both irinotecan and oxaliplatin-based regimens unless these drugs were contraindicated. Patients were randomized to either cetuximab plus BSC (n=287) or BSC alone (n=285). Final analysis was performed when 456 deaths were observed. Tumor assessments were completed every 8 weeks until progression. Grade 3 toxicities more frequent in the cetuximab arm included rash/desquamation (12% versus 0%), infection without neutropenia (13% versus 5%), confusion (6% versus 2%), other pain (15% versus 7%), and hypomagnesemia (6% versus 0%). Grade 3 anemia was more common in the BSC alone arm (4% versus 11%). The median survival was 6.1 and 4.6 months in the cetuximab and control arms, respectively, with a HR of 0.77 (95% CI, 0.64 to 0.92; p=0.005). Treatment with cetuximab resulted in a significant improvement in the risk

of disease progression with a HR for TTP of 0.68 (95% CI, 0.57 to 0.80; p<0.0001). Overall survival and TTP benefits were robust to adjustment in multiple variable Cox proportional hazards models. There were 19 (6.6%) objective responses (CR+PR) with cetuximab and none with BSC alone. Cetuximab is the first biologic targeted therapy that as a single agent has demonstrated improvement in both survival and TTP in patients with chemotherapy-refractory mestatic colorectal cancer (Jonker D, etal, AACR07).

Although increased EGFr expression has been reported to correlate with more aggressive disease, an increase in metastases, and advanced tumor stage, measurement of EGFr expression as a method for identifying patients with colorectal cancer most likely to respond to treatment remains controversial. It is also notable that overall response rates for patients treated with cetuximab, either as a monotherapy or in combination with irinotecan, are only 10.8% and 22.9% respectively (Frieze DA and McCune JS, Ann Pharmacother 2006;40(2):241–50). Investigators at Merrimack Pharmaceuticals (Cambridge, MA) developed a data-driven mechanistic model of the ErbB signal transduction network comprising ErbB1 (EGFr/HEr1), ErbB2 (HEr2), ErbB3, ErbB4, and multiple EGF-like ligands. The model was developed based on signaling data from a cancer cell line (A431) using pErbB1, pErbB2, pAKT, and pERK as readouts. This model can be used to predict dynamic pERK and pAKT signaling behavior and responses to EGFr inhibitors in several other cell lines. Based on simulation data, a decision tree was constructed for identifying patients most likely to respond to cetuximab based on protein expression profiles (Schoeberl B, etal, EORTC-NCI-AACR06, Abstract 650).

The lack of correlation between EGFr protein overexpression measured by IHC, or EGFr mutations with response to cetuximab in colorectal cancer has been frustrating to both oncologists and drug developers. Recent findings suggest that gene amplification, which results in an increased number of gene copies for EGFr as measured by FISH, may be predictive. In one study, investigators at Bristol-Myers Squibb sought to identify predictive markers of response for development into molecular diagnostics to enhance the effectiveness of cetuximab therapy in colorectal cancer. Preclinical investigation, using transcriptional profiles of 164 primary tumors and 21 sensitive and resistant cell lines, identified a list of genes that may predict response. A phase II clinical trial of cetuximab monotherapy was conducted in patients with metastatic colorectal cancer to examine whether these markers could be validated in a clinical setting. RNA was isolated from pretreatment core biopsies and profiled on Affymetrix gene chips. DNA isolated from pretreatment core biopsies was used for both EGFr gene copy number and mutation analysis. An interim statistical analysis of transcriptional profiling data was performed to determine whether the markers are differentially expressed between patients who derive clinical benefit, described as PR or SD, and those with progressive disease. Pathway analysis tools were used to identify biologic relationships between the predictive markers identified. Several candidates distinguished between responders and non-responsders with high accuracy. The top candidate sensitivity markers identified from this analysis are key players in the EGFr signaling pathway. Their strikingly higher expression levels in responders suggest that tumors addicted to the EGFr pathway respond to cetuximab. Approximately 20 top response prediction markers were found to be associated with the EGFr network. They may be used either singly or in combination for patient selection to enhance the effectiveness of cetuximab therapy. Extension of this analysis is underway to include a larger set of patients from this trial (Khambata Ford S, etal, AACR06, Abs. 4032).

A phase I clinical trial in patients with EGFr-expressing metastatic colorectal cancer compared the safety, PK, and pharmacodynamics of the standard weekly cetuximab dosing schedule (400 mg/m^2 initial dose and 250 mg/m^2 weekly) to a more convenient every 2 weeks schedule of 400, 500, 600, or 700 mg/m^2 dose. Dose levels were escalated if no DLT was observed. Both groups were treated with cetuximab alone for 6 weeks, followed by the FOLFIRI (irinotecan/folinic acid/5-FU) regimen. Among 29 patients treated, 9 were in the weekly group and 20 (400 mg/m^2=10, 500 mg/m^2=20) were in the every two weeks regimen group. No DLT has been observed to date. PK data are predictable and comparable between both regimens, and no differences were noted in EGFr inhibition between the two. Cetuximab at 400 and 500 mg/m^2 every 2 weeks may be an alternative and convenient schedule of administration. MTD of this new regimen has not yet been reached and dose escalation is ongoing (Tabernero J, etal, ASCO06, Abs. 3085).

The initial dose of cetuximab is administered with premedication with H1 antagonist diphenhydramine (50 mg, IV). However, most early clinical trials with cetuximab permitted investigator discretion in use of premedication after the initial dose of cetuximab. Investigators at Memorial Sloan-Kettering Cancer Center (MSKCC; NY, NY) examined records of patients treated with cetuximab from February 2004 through February 2005, outside of a clinical trial, in order to establish the degree of premedication use. Records of adverse events were also reviewed, and any moderate or severe/life-threatening reactions were evaluated for presence or absence of concurrent premedication. As per MSKCC guidelines, all patients were treated with 50 mg of diphenhydramine prior to the initial loading dose of cetuximab, and 25 mg of diphenhydramine prior to the second dose. A total of 115 patients were administered one or more doses of cetuximab without premedication, resulting in 746 doses of cetuxmab administered without diphenhydramine premedication. No severe or life-threatening reactions to cetuximab occurred during these doses. Therefore, omission of diphenhydramine premedication after the initial two doses of cetuximab is MSKCC's current practice, which appears not to alter the safety profile of cetuximab. Considering the side effects

of diphenhydramine, routine long tern use of antihistamine premedication with cetuximab administration does not appear to be warranted (Timoney J, etal, ASCO06, Abs. 13521).

Panitumumab was approved by FDA in September 2006, as monotherapy, based on results from a phase III clinical trial that was completed in 2005. This international, multicenter, randomized controlled phase III clinical trial (protocol ID: 20020408, NCT00113763) compared panitumumab plus BSC to BSC alone in patients with refractory metastatic colorectal cancer (CRC). It was conducted by the Panitumumab Study Team, under PI Marc Peeters, MD, PhD, of the University Hospital Gasthuisberg (Leuven, Belgium). A ≥1% tumor-cell membrane staining for EGFr by IHC was required for eligibility for this trial. Enrolled patients had failed chemotherapy for metastatic disease, including treatment with a fluoropyrimidine, irinotecan, and/or oxaliplatin. Patients were randomized 1:1 to either panitumumab (6 mg/kg), every 2 weeks plus BSC or BSC alone (excluding antineoplastic therapy). Tumor responses per modified RECIST were conducted by blinded central review and assessed at weeks 8, 12, 16, 24, 32, 40, 48, and every 12 weeks thereafter until progression. Responses were confirmed at 4 weeks after criteria were first met. The primary objective was to assess whether panitumumab plus BSC improved PFS versus BSC alone. Secondary objectives included best objective response rate and safety. A total of 463 patients were randomized, 231 (50%) to panitumumab plus BSC and 232 (50%) to BSC alone. All but 1 of the patients were treated with at least 2 prior chemotherapy regimens (37% were treated with 3); 67% had colon cancer, and 33% had rectal cancer. Median follow-up was 19 weeks. A significant improvement in PFS favoring panitumumab was observed ($p<0.0001$). Relative progression rate was 46% lower in patients treated with panitumumab compared to those on BSC alone (HR=0.54). By the first scheduled assessmenat week 8, more patients (49%) were alive without progression in the panitumumab group compared to the BSC group (30%). This difference continued through week 32. After 6 months (week 24), approximately four times as many panitumumab-treated patients (18%) were alive without progressive disease versus 5% with BSC alone. At week 32, twice as many panitumumab-treated patients (10%) were alive and progression-free compared to 4% with BSC alone.

Generally, panitumumab was well tolerated. Per protocol, administration of panitumumab did not require premedication or a loading dose, and the incidence of infusion reactions (of any severity) was low (1%). As expected, more patients (90%) in the panitumumab group had skin-related toxicities versus the BSC group (9%). Fatigue (24% versus 15%), abdominal pain (23% versus 17%), nausea (22% versus 15%), and diarrhea (21% versus 11%) were also higher in the panitumumab group. There were no Grade 3/4 infusion related reactions; 1 patient discontinued panitumumab because of a Grade 2 hypersensitivity reaction. Hypomagnesemia was observed in 38% of panitumumab-treated patients (Grade 3/4=3%). No *de novo* human anti-human antibody (HAHA) or anti-panitumumab antibody formation was observed. In patients with anti-panitumumab antibodies, there was no impact on efficacy, safety, or PK. Panitumumab at 6 mg/kg every two weeks improved PFS and was well tolerated in patients with metastatic colorectal cancer who failed standard chemotherapy (Peeters M, eatl, AACR06, Abs. CP-1).

Mean PFS was 96 days with panitumumab versus 60 days for BSC (HR=0.540). Approximately 75% of patients (n=174) in the BSC group entered a crossover arm to be treated with panitumumab after disease progression. Panitumumab treatment showed a clinical benefit in patients crossing over from the BSC arm, despite disease progression. There was a 9% PR rate, 1 CR, and disease stabilized in 32% of patients. An interim analysis of OS between the two groups was similar. The rate (75%) and timing (median=7.0 weeks) of crossover from the BSC alone arm to panitumumab, and the antitumor activity observed after crossover, likely confounded the ability to demonstrate a treatment effect on OS (HR=0.93). Panitumumab improved PFS and response rate regardless of the measured level or intensity of EGFr staining. Improvements in PFS and disease control occurred regardless of age, sex, primary tumor location (colon versus rectum), or performance status.

Lung Cancer

Lung cancer is a leading cause of cancer deaths worldwide. Lung cancer is classified by histopathology into small cell lung cancer (sclc;~20%) and non-small cell lung cancer (nsclc; ~80%); nsclc is further subdivided into adenocarcinoma, which includes bronchioloalveolar cancer (BAC) and squamous and large cell cancer. Treatment of advanced, inoperable lung cancer remains woefully inadequate; nsclc kills over 3,000 people daily worldwide (Kamangar F, etal, J Clin Oncol 2006;24(14):2137-50). This malignancy is usually diagnosed at an advanced stage; patients diagnosed with the disease 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).

Standard platinum-based doublets produce objective response rates of 15% to 40% and median survivals of 8 to 10 months as first line regimens. Two ErbB pathway inhibitors, gefitinib and erlotinib, both of which are small molecule TKI, have been approved as monotherapies for the second line treatment of advanced nsclc. Treatment of advanced nsclc with these EGFr TKI results in similar response rates and survival times as that using docetaxel and pemetrexed, another approved second line regimen.

Gefinitib, the first EGFr inhibitor to be commercialized in the USA and elsewhere for the treatment of cancer, was approved for the treatment of refractory or recurrent, inoperable nsclc in the second line setting. Despite accept-

able response rates, treatment with gefitinib, in combination with best supportive care (BSC), failed to increase OS, according to a placebo-controlled phase III clinical trial (ISEL) conducted outside the USA in patients with advanced nsclc who had been treated with 1 or 2 previous chemotherapy regimens. Although there was a statistically significant enhancement in tumor response rate and an extension of time-to-treatment failure, these positive results did not translate into a statistically significant survival benefit. The ISEL trial, the largest performed at the time in a population with refractory advanced nsclc, was designed to determine OS, time to treatment failure, overall response rare (ORR), QoL, and treatment tolerability. Patients were randomized (2:1) to gefitinib (250 mg/day) with BSC or placebo and BSC. A total of 1692 patients from 210 centers in 28 countries were randomized to gefitinib (n=1129) or placebo (n=563). At 7.2 months median follow-up, MST of gefitinib was 5.6 months, compared to 5.1 months for placebo in the overall population (HR=0.89) and 6.3 months for gefitinib, compared to 5.4 months for placebo in patients with adenocarcinoma (n=812; HR=0.84).

Preplanned subgroup analyses indicated statistically different survival outcomes in patients of Asian origin compared to non-Asians, and in smokers, compared to never smokers. Among patients of Asian origin, gefitinib-treated patients survived longer (9.5 months) than placebo-treated patients (5.5 months), for a HR of 0.66. Among never smokers, gefitinib-treated patients survived longer (8.9 months) than placebo-treated patients (6.1 months), for a HR of 0.67. Compared with placebo, gefitinib significantly improved TTP (3.0 compared to 2.6 months; HR=0.82) and ORR (8.0% compared to 1.3%). Gefitinib was well tolerated, with a safety profile consistent with previously reported trials of gefitinib (250 mg) monotherapy. Although there was a small difference between gefitinib and placebo in the ISEL trial in terms of survival, it did not reach statistical significance in the overall population or in patients with adenocarcinoma. Preplanned subgroup analyses indicated survival benefits in patients of Asian origin and never smokers (Thatcher N, etal, AACR05, Abs. LB-6).

The negative results of the ISEL trial raised several questions about the utility of gefitinib in nsclc and the differences between gefitinib and erlotinib. Preclinical data have suggested that the approved dose of gefitinib (250 mg/day) may not achieve sufficient plasma concentrations to inhibit wt EGFr, though mutant EGFr is inhibited. Gefitinib was not administered at its maximally tolerated dose (700-1000 mg/day) in these trials. However, under the current status of this drug, it may prove difficult to clinically evaluate higher doses in the nsclc indication.

In a worldwide Expanded Access Program (EAP), gefitinib was made available to >37,000 patients who did not respond to standard treatment or were ineligible for or refused chemotherapy. Among 1,671 consecutive patients enrolled at 11 sites in the USA arm of EAP, 198 with advanced nsclc had not been previously treated with chemotherapy. These patients were treated with gefitinib (250 mg/day) until treatment failure or emergence of toxicity. Treated lasted for a mean of 4.7 months. The most common adverse events were diarrhea (31.3%) and rash (31.3%). In terms of response, the CR rate was 0.7%, the PR rate was 5.6%, and disease stabilization occurred in 40.6%. MST was 6 months, and estimated 1-year survival was 29.7%. The majority of these patients were not subsequently treated with chemotherapy (Govindan R, etal, Lung Cancer, Sep 2006;53(3):331-7).

Investigators analyzed ISEL tumor biopsy samples to examine relationships between biomarkers and clinical outcome after gefitinib treatment in this placebo-controlled setting. Biomarkers included EGFr gene copy number by FISH (n=370), EGFr (n=379) and phosphorylated Akt (p-Akt) protein expression (n=382) by IHC, and mutations in EGFr (n=215), K-ras (n=152), and BRAF (n=118). High EGFr gene copy number was a predictor of a gefitinib-related effect on survival (high copy number HR=0.61; low copy number HR=1.16). EGFr protein expression was also related to either positive (HR=0.77) or negative (HR=1.57) clinical outcome. Response rates were higher (37.5%) in patients with EGFr mutations compared to those without such mutations (2.6%); there were insufficient data for survival analysis. No relationship was observed between p-Akt protein expression and survival outcome, and the limited amount of data collected for K-ras and BRAF mutations prevented any meaningful evaluation of clinical outcomes in relation to these mutations. Therefore, EGFr gene copy number was found to be a predictor of clinical benefit from gefitinib in ISEL. The researchers noted that additional studies are warranted to assess these biomarkers fully for the identification of patients most likely to benefit from gefitinib treatment (Hirsch FR, etal, JCO, 1 Nov 2006; 24 (31):5034-5042).

Despite the disappointing results in non-Asian populations, gefitinib is widely used in Asia for the nsclc indication, based on positive results from clinical trials. A phase II clinical trial was conducted at Tohoku University (Sendai, Japan) between June 2004 and October 2005, to investigate the efficacy and feasibility of gefitinib for the treatment of chemotherapy-naïve patients with advanced nsclc harboring EGFr mutations. EGFr gene status was examined by obtaining tumor samples from these patients, then sequencing the DNA of EGFr exons 18 to 23. Patients harboring EGFr mutations were treated with gefitinib (250 mg/day) as a single agent. Among 75 patients examined for EGFr status, 25 (33%) harbored EGFr mutations. EGFr mutations were significantly frequent in females ($p<0.01$) and never or light smokers ($p<0.001$). Among 16 patients with EGFr mutations enrolled in the trial, the overall response rate was 75%, disease control rate was 88%, and median PFS was 9.7 months. No life-threatening toxicity was observed. The researchers concluded that a random-

ized trial comparing gefitinib to standard chemotherapy is warranted to assess the proper timing of gefitinib in the treatment of patients with tumors harboring EGFr mutations (Inoue A, etal, JCO, 20 Jul 2006;24(21):3340-3346).

In order to evaluate the predictive values of somatic mutations in the EGFr tyrosine kinase domain and EGFr gene amplifications associated with gefitinib sensitivity in patients with nsclc, investigators at the National Cancer Center Institute (Tokyo, Japan) studied consecutive patients with nsclc who relapsed after surgery and were subsequently treated with gefitinib. Surgical specimens were analyzed in 66 patients treated with gefitinib (250 mg/day) between July 2002 and May 2004. Direct sequencing of exons 18-24 of EGFr was performed to detect mutations, and quantitative real-time PCR was performed to analyze the EGFr gene copy number using DNA extracted from laser-captured tumor cells. All patients were Japanese, female/male (26/40); adenocarcinoma/other (62/4); never/former/current smoker (31/12/23); prior chemotherapy yes/no (29/37). Among all 66 patients, somatic mutations were detected in 39 (59%); 20 patients had deletions in exon 19, 17 had point mutations (L858R) in exon 21, 2 had point mutations (G719S or G719C) in exon 18, and 4 had minor secondary mutations in exons 18 or 20. EGFr mutations were seen in 69%/53% of the female/male patients, 68%/83%/35% of never/former/current smokers, 73%/50% of patients with adencarcinoma with/without predominant papillary growth, and 72%/27% of adencarcinoma patients with/without BAC features. EGFr gene amplification (=3/cell) was observed more frequently (56%) in patients with EGFr mutations than in those with wt EGFr (26%), and high level amplification (=6/cell) was observed only in patients with EGFr mutations (33% versus 0%). CR/PR/SD/progressive disease were observed in 2/29/4/1 patients with EGFr mutations and in 0/3/5/14 patients with wt EGFr, respectively. In patients with EGFr mutations, the response rate was higher (84% versus 11%), median time-to-progression (TTP) was longer (12.6 versus 1.7 months), and OS was longer with 1-year OS of 80% versus 47%. Other factors, including the EGFr gene copy number, were not independent predictors of clinical outcomes. EGFr mutations are frequently detected in Japanese patients with nsclc and strongly predict gefitinib sensitivity (Takano T, etal, ASCO05, Abs. 7032).

Interestingly, investigators in Taiwan report different treatment responses in a case of lung adenocarcinoma coexpressing mutant EGFr in the primary lung mass and a wt gene in metastatic bone lesions, indicating that at least two strains of tumor cells may present in a single patient (Chou W-C, etal, Japanese J Clin Onc 2006;36(8):523-526).

In September 2007, Aureon Laboratories (Yonkers, NY) completed an initial study with AstraZeneca using predictive pathology to identify patients with nsclc that may benefit from treatment with Iressa. The project integrated a patient's clinical data with tumor biomarker profiles and image analysis features using on-slide technologies and machine learning approaches developed at Aureon. Aureon Laboratories confirmed that specific clinical features appear to be associated with overall survival and has identified several protein biomarkers, which appear important in predicting prognosis. Aureon's Systems Pathology platform includes computer based image analysis of tumor tissue samples and tissue-based, quantitative biomarker assessment coupled with sophisticated mathematical tools to develop models of response and outcome prediction. Aureon's Systems Pathology technology is the foundation for the Prostate Px test. This approach is particularly applicable to targeted therapies to pre-classify patients for response to a specific drug prior to actual drug use, leading to more effective, personalized treatment and shorter, more focused clinical trials.

Erlotinib was first approved in the USA in 2004 in nsclc based on results from a pivotal phase III trial (protocol ID: CAN-NCIC-BR21, CAN-NCIC-BR.21; NCT00036647), which demonstrated improved survival in patients with advanced nsclc. The global trial, performed by the NCIC-CTG based at Queen's University, in collaboration with OSI Pharmaceuticals, involved 86 sites in 17 countries. Patients with Stage IIIb or IV nsclc were eligible if they had been previously treated with 1 or 2 chemotherapy regimens. Patients were stratified according to center, performance status, response to prior chemotherapy, number of prior regimens, and prior platinum-based therapy. They were randomly assigned in a 2:1 ratio for treatment with oral erlotinib (150 mg/day), or placebo. A total of 731 patients were enrolled, of which 49% had been previously treated with 2 chemotherapy regimens; 93% had been administered a platinum-based chemotherapy. A decrease of 30% in the risk of death (HR=0.70) was observed in patients treated with erlotinib, compared to those treated with placebo, and an MST of 6.7 months compared to 4.7 months, for a 42.5% improvement. Additionally, 31% of erlotinib-treated patients were alive at 1 year, compared to 22% in the placebo arm. ORR was 8.9% in the erlotinib arm and <1% in the placebo group, median duration of the response was 7.9 months and 3.7 months, respectively, and PFS was 2.2 months and 1.8 months (hazard ratio=0.61), respectively. Discontinuation of erlotinib was required in 5% of patients because of toxicity. In addition to being the first non-cytotoxic treatment to improve survival in advanced lung cancer, erlotinib extended survival across most subsets of patient populations in this trial. In addition to achieving this primary endpoint, erlotinib also met all secondary endpoints of the trial, which included time to symptom deterioration, PFS, and response rate (Shepherd F, etal, N Engl J Med, 14 Jul 2005;353(2):123-32).

An analysis of molecular and clinical markers in tumor samples from a subset of patients in this trial was undertaken to ascertain correlations between EGFr status and

response rate and survival. Analysis of 177 samples of patients treated with erlotinib for mutations in the EGFr gene confirmed previous observations that the tumor response rate was higher in the subset of patients with mutations; however, when survival was assessed, there was no apparent difference in survival benefit between patients with wt or mutated EGFr in their tumors (wt EGFr HR=0.73; mutated EGFr HR=0.77), compared to a statistically significant improvement in survival (HR=0.73) reported for the overall patient population. In univariate analyses, survival was longer in the erlotinib group than in the placebo group when EGFr was expressed (HR EGFr+=0.68, HR EGFr-=0.93) or a high number of copies of EGFr were detected (HR=0.44), compared to low numbers (HR=0.85). In multivariate analyses, adenocarcinoma, never having smoked, and expression of EGFr were associated with objective response. The HR for patients whose tumors were determined to be wt was 0.73, compared to 0.77 for patients whose tumors expressed mutated EGFr. In multivariate analysis, survival after treatment with erlotinib was not influenced by the status of EGFr expression, number of EGFr copies, or EGFr mutation. Investigators concluded that among patients with nsclc who were treated with erlotinib, the presence of an EGFr mutation may increase responsiveness, but is not indicative of a survival benefit (Tsao MS, etal, N Engl J Med, 14 Jul 2005;353(2):133-44).

QoL was one of this trial's secondary endpoints that assessed time to deterioration of cough, dyspnea, and pain. Mean changes from baseline in QoL domains and symptoms and proportions of patients improving/deteriorating were also compared between the arms. Both arms had comparable baseline QoL. In the primary symptom analysis, 451 patients were evaluated for cough, 522 for dyspnea, and 527 for pain. A clinically and statistically significant longer time to deterioration of tumor-related symptoms was observed in patients treated with erlotinib, 4.9 versus 3.68 months for cough (p=0.04), 4.7 versus 2.89 months for dyspnea (p=0.01), and 2.79 versus 1.91 months for pain (p=0.02). These findings were confirmed by analysis of the proportion of patients with >10 point improvement in these symptoms (44%, 34%, and 30% respectively, all significantly different from placebo). Differences in QoL domains were also seen in physical function, which was improved in 31% of patients treated with erlotinib, compared to 19% on placebo (p=0.01), and 35% versus 26% in global QoL (p<0.01). Analysis of change over time revealed a general trend towards improvement in most symptoms and QoL domains in erlotinib arm (with the exception of diarrhea), but deterioration in the placebo arm. Therefore, erlotinib was found to improve survival, tumor-related symptoms, and some aspects of QoL in previously treated patients with nsclc (Bezjak A, etal, ASCO05, Abs: 7018).

In a special meeting during the September 2007 meeting of the International Association for the Study of Lung Cancer (IASLC) in Seoul, South Korea, sponsored by Genentech, Roche and OSI Pharmaceuticals, oncologists reported that erlotinib is a viable candidate across the board for second line treatment of nsclc. Although erlotinib may be more effective in certain patient groups, nearly all patient groups appear to gain survival time with the drug in nsclc. For instance, although women had more than twice as high a response rate as men and adenocarcinoma was more than three times as likely to respond as other histologic types of nsclc, response rate was not a good indicator of benefit by itself. OS reflected an identical 20% reduction in risk in men and women (p=0.01 and p=0.03, respectively), and treatment with erlotinib equally benefited patients with either adenocarcinoma or squamous-cell carcinoma (p=0.008 and p=0.0007, respectively). In the NCIC-CTG trial, patients with tumors with high EGFr expression did not survive significantly longer than those with low expression (p=0.12). At this point, no biomarkers or patient characteristic can be reliably used to predict clinical benefit, precluding selection of patients on the basis of the current data in clinical practice.

In the same vein, although a greater response rate with erlotinib was seen in Asian compared to non-Asian patients (18.9% versus 7.5%), treatment with the drug yielded a significant overall survival benefit for non-Asians (HR=0.8). Also, as reported in the in the NCIC-CTG trial, although smokers (current and ex) did not gain a significant overall survival advantage with erlotinib (HR=0.9, p=0.14), it could be that these patients need to be treated with higher erlotinib doses. According to PK evaluations in a separate trial in healthy volunteers, drug exposure in smokers was at most 65.2% compared to nonsmokers at the same dose. It is possible that cigarette smoke induces liver enzymes that are responsible for metabolism of erlotinib. Dose escalation trials are currently ongoing to investigate this premise.

Head and Neck Cancer

According to the American Cancer Society (ACS), in 2007, 81,550 Americans will be diagnosed with head and neck cancer, which includes cancer of the tongue, the rest of the mouth, the salivary glands and inside the throat, the voice box, eye and orbit, thyroid, and the lymph nodes in the upper neck. It is estimated that, in 2007, more than 12,900 Americans will die from this disease. Head and neck cancer most often affects people over the age of 50, and men are twice as likely to be diagnosed as women. The most common risk factors are tobacco and excessive alcohol use.

Squamous cell cancer of the head and neck (SCCHN), the most common form of cancer of the head and neck is the sixth most common cancer worldwide, with 600,000 people diagnosed with SCCHN annually; 40,000 are diagnosed in the USA and 100,800 in Europe. Approximately 65% of all patients are diagnosed with advanced disease.

Head and neck cancer involving the oropharynx, hypopharynx, larynx, and oral cavity is very difficult to treat. Because of the key functions of these structures

(e.g., swallowing, eating, speaking, and breathing), surgery is often not an option. The recommended treatment is chemoradiotherapy, which is often associated with severe toxicity. Nevertheless, currently practiced chemoradiotherapy increased the 3-year survival in inoperable head and neck cancer from <20% with radiotherapy alone to 35-50%; more aggressive chemoradiotherapy approaches result in 70% survival rates.

The role of EGFr expression in SCCHN remains obscure. Although EGFr is a validated target in SCCHN, predictive markers of response to EGFr small molecule TKI have not been conclusively identified. Researchers are seeking to identify biomarkers to increase the understanding ot the role of EGFr-targetd drugs in the treatment of head and neck cancer.

A molecular analysis of the EGFr pathway in SCCHN undertaken by investigators at Okayama University and Wakayama Medical University, in Japan, employed PCR and direct sequencing to detect the mutation status of the hot spot regions of EGFr (exons 19, 20, 21) and K-ras (codons 12, 13, 61). The same tumor samples were also analyzed for mutations in the TK domain of ErbB2 (exons 18, 19, 20, 21, 22, 23) and B-Raf (exons 11 and 15). No mutations in EGFr or ErbB2 were present in 79 samples of SCCHN used in the study; and mutations were not detected in the downstream effectors of K-ras and B-Raf. Although these genes are overexpressed in SCCHN, mutations are not common and may not play a significant role for the activation of the EGFr pathway in Japanese patients with SCCHN. Unlike lung cancer, in which EGFr mutation is linked to an increased response to TKI, the response of SCCHN overexpressing both EGFr and ErbB2 to TKI has been limited in clinical trials. The lack of mutations in the TK domain of EGFr and ErbB2 may explain this phenomenon (Gunduz M, etal, AACR07, Abs. 5241).

Investigators at Vanderbilt University (Nashville, TN), Thomas Jefferson University (Philadelphia, PA), and Constella Health Sciences (Durham, NC) correlated an activated EGFr signature with the presence of increased EGFr gene copy number in SCCHN. This research group previously showed that 58% of SCCHN exhibits increased EGFr gene copy number by FISH and that positive FISH status is associated with worse survival. This study assessed the relationship between EGFr gene copy number and EGFr-dependent signaling pathways by comparing transcriptional signatures between HaCaT cells overexpressing EGFr and SCCHN tumors with known EGFr gene copy numbers. 'Activated EGFr signature' was defined as differential expression of genes between EGF-stimulated and un-stimulated HaCaT cells. This signature was used in the evaluation of gene expression data from 44 SCCHN tumors and 6 normal mucosal epithelia, which were clustered and correlated with EGFr FISH status. Co-regulated pathways affected by EGF stimulation were also determined. The activated EGFr signature contained 203 unique genes and was established by selecting genes with >4-fold changes upon EGF stimulation of HaCaT cells. The activated EGFr signature co-segregated with EGFr FISH positivity ($p<0.0001$) in 33 tumors with known FISH status. Six signaling targets expressed at higher levels upon EGF stimulation were identified, including Myc, VEGF, NFκB1, NRG1, SMARKA4, and TGFα. Downregulation of CDKN1B and CEPB4 were also consistently observed. High levels of Myc, VEGF, and NFκB1 expression were previously identified in patients with high risk SCCHN with poor prognosis. High expression of the EGFr ligand, TGFα, is also associated with poor prognosis in SCCHN and with gefitinib resistance in nsclc. This group concluded that preliminary data suggest that increased gene copy number in SCCHN is associated with EGFr activation and that activated EGFr signature provides additional therapeutic targets, such as co-regulated pathways and specific downstream genes useful in refining optimal combination therapies with currently available EGFr inhibitors (Chung CH, AACR07, Abs. 5031).

Cetuximab was approved by the FDA for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) in combination with radiation therapy, and also as a single agent for recurrent or metastatic SCCHN after failure of prior platinum-based chemotherapy, based on a pivotal, international, randomized phase III trial (protocol ID: UAB-9901; NCI-G99-1657; IMCL-CP02-9815; IMCL-9815; NCT00004227), of 424 patients with locally or regionally advanced squamous cell carcinoma of the oropharynx, hypopharynx, or larynx with no prior therapy that compared the addition of Erbitux to radiation therapy (n=211) to radiation therapy alone (n=213). This clinical trial was one of the largest trials ever conducted in patients with SCCHN. Pretreatment assessment for evidence of EGFr expression was not required in patients with SCCHN.

Treatment with Erbitux, in combination with radiation therapy, provided clinically significant improvement in survival and locoregional control. The addition of Erbitux resulted in a 9.5-month improvement in median duration of locoregional control (24.4 months versus 14.9 months; HR=0.68). Erbitux was dosed weekly, starting one week before radiation and continuing for the duration of radiation therapy. The median number of Erbitux doses administered in the trial was 8 (range=1-11). Results also showed a 19.7-month improvement in median survival (49.0 months versus 29.3 months; HR=0.74).

Another pivotal trial was a single arm, multicenter, phase II trial designed to assess the effects of Erbitux as a single agent for this indication. The trial analyzed 103 patients with recurrent or metastatic SCCHN not suitable for further local therapy, who had failed platinum-based chemotherapy. Erbitux was administered until disease progression or unacceptable toxicity. Median number of doses was 11 (range=1-45). The clinically meaningful objective response rate was 13%, and median duration of response was 5.8 months (range=1.2-5.8 months). In this trial, the absolute and relative improvements in the 3-year

rate of survival were 10% and 22%, respectively. Furthermore, improvements were reported in locoregional control, PFS, and overall survival (Bonner JA, etal, NEJM, 2006 Feb 9;354(6):567-78).

Incorporating cetuximab plus radiotherapy in clinical practice has been problematic because this regimen has not been compared to cisplatin-based chemoradiotherapy. Clinical evaluation of platinum-based chemoradiotherapy shows greater improvement than that obtained with cetuximab and, therefore, chemoradiotherapy with cisplatin remains the standard of care. Patients who cannot tolerate platinum-based chemotherapy could benefit from the addition of cetuximab to radiotherapy. Also, the benefit from adding cetuximab to radiotherapy may be specific to particular sites of head and neck cancer and/or to the type of radiotherapy administered. Cetuximab did not improve survival of patients with hypopharyngeal or laryngeal cancer, and the addition of cetuximab had no effect on distant metastases. The benefits of additing cetuximab to radiotherapy, in terms of a survival and locoregional control, were mostly confined to patients with oropharyngeal cancer, which was the diagnosis in more than half the enrolled patients. However, these patients also fare better with cisplatin-based chemoradiotherapy.

In a European phase III clinical trial in which platinum-based chemoradiotherapy was compared with radiotherapy alone, the absolute and relative improvements in the rate of survival at 3 years in patients with oropharyngeal cancer were 70% and 20%, respectively. These rates dropped to 30% and 5% at 5 years. In another phase III clinical trial, treatment of patients with very advanced hypopharyngeal and oropharyngeal cancer with platinum-based chemotherapy plus hyperfractionated radiotherapy was not associated with a significant improvement in survival. A subgroup analysis of data from that trial showed that patients with oropharyngeal cancer had a significant gain in survival from chemoradiotherapy. Long-term absolute improvement has yet to be determined. (Posner MR, Wirth LJ, N Engl J Med 2006 Feb 9; 354(6):634-6).

In terms of the radiotherapy used, cetuximab appeared to be effective only when added to hyperfractionated radiotherapy. However, although treatment of the oropharynx and hypopharynx with hyperfractionated radiotherapy is effective, it is associated with a high rate (25%) of esophageal stenosis (Staar S, etal, Int J Radiat Oncol Biol Phys 2001;50:1161-1171; erratum, Int J Radiat Oncol Biol Phys 2001;51:569).

In the last analysis, trials of platinum-based chemoradiotherapy have shown greater improvement in patients with inoperable SCCHN than cetuximab plus radiotherapy. Randomized phase III clinical trials underway should definitely establish whether cetuximab plus radiotherapy is a better therapy than platinum-based chemoradiotherapy and whether cetuximab can be added to platinum-based chemoradiotherapy (Posner MR, etal, NEJM, 9 Feb 2006;354(6):634-636). The cetuximab plus radiotherapy trial left many questions unanswered. The trial was not sufficiently powered to detect treatment-related differences within subgroups, such as patients who treated with once-daily radiotherapy, compared to those treated with a concomitant radiation-boost technique, or patients with laryngeal or hypopharyngeal cancer. The numbers of patients in these subgroups were too small for definitive conclusions to be drawn. The trial was sufficiently powered to examine only outcomes in the overall population.

Nimotuzumab is approved abroad in Asia and other world regions for the treatment of advanced head and neck cancer and specifically, nasopharyngeal cancer.

A trial was conducted in China to evaluate the short-term and long-term efficacy and toxicity of nomotuzumab, in combination with radiotherapy, in patients with newly diagnosed locoregionally advanced (Stage III-Ivb) nasopharyngeal carcinoma (NPC) with moderate or strong EGFr expression. Patients were randomized into a radiotherapy alone group or a radiotherapy plus nimotuzumab group.. Similar type dose and technique of radiotherapy was administered in both groups. The combination group was also treated with weekly IV nimotuzumab (100 mg) concurrently with radiotherapy. A total of 35 patients were enrolled, 17 in radiotherapy alone group and 18 in combination group. During treatment, only 1 patient withdrew from the combination group. CR rates at the end of treatment, and 5 and 17 weeks after treatment, were significantly higher in combination group than in radiotherapy alone group, reported as 72.2% versus 35.3%, 83.3% versus 41.2%, and 83.3% versus 47.1%, respectively ($p<0.05$). Median follow-up time was 31.9 months (range=4.2-40.7 months). There were no significant differences in 3-year locoregional control, distant metastasis-free survival, and overall survival rates between the 2 groups. In terms of toxicities, except for 1 patient who suffered from Grade 2 vomiting, no patient developed other adverse events in the combination group, and there were no significant differences in radiotherapy-related adverse events between the two groups. Therefore, although nimotuzumab enhances the response of patients with advanced NPC when combined with radiotherapy, it does appear to improve long term patient outcome compared to treatment with radiotherapy alone (Wu RR, etal, Ai Zheng, Aug 2007; 26(8):874-9).

Pancreatic cancer

In 2007, in the USA, approximately 33,700 people will be diagnosed with cancer of the pancreas. Pancreatic cancer accounts for about 6% of all cancer deaths, or about 32,000 deaths per year. The current 5-year survival rate is about 5%. The number of deaths from this disease highlights the importance of seeking better therapies for pancreatic cancer through clinical trials testing novel drugs. During the past 30 years, little has changed both in the incidence of pancreatic cancer and the mortality associated eith this disease.

Tarceva, in combination with gemcitabine, was the first EGFr inhibitor approved by FDA for the treatment of pancreatic cancer. Approval was based on a randomized phase III clinical trial (protocol ID: CAN-NCIC-PA3, OSI-CAN-NCIC-PA3; NCT00026338) that met a primary endpoint of improving survival. This international multicenter (n=>200), double blind, placebo-controlled phase III trial evaluated Tarceva in patients with unresectable, locally advanced or metastatic pancreatic cancer. The trial randomized 569 patients to either gemcitabine plus concurrent Tarceva or gemcitabine plus placebo. A total of 521 patients were randomized to 100 mg/day of Tarceva or placebo, and 48 were randomized to 150 mg/day of Tarceva or placebo. The Onocologic Drugs Advisory Committee (ODAC) review focused on the 100 mg/day cohort. A statistically significant (23%) improvement in OS (HR=0.81), also referred to as a 19% reduction in the risk of death, was observed in patients treated with gemcitabine plus Tarceva (100 mg/day), compared to the gemcitabine plus placebo group. After one year, 23% of patients treated with Tarceva plus gemcitabine were alive, compared to 17% of patients treated with gemcitabine plus placebo. A statistically significant improvement in PFS (HR=0.77) was also observed. Although no difference in tumor response was observed (8.6% in patients the Tarceva group versus 7.9% in the placebo arm), the disease control rate (CR+PR+SD) was significantly improved (59% in the Tarceva plus gemcitabine arm versus 49% in the gemcitabine plus placebo arm).

Rash and diarrhea were the principal Tarceva-related side effects and generally characterized as mild-to-moderate. Safety findings were consistent with previous studies of Tarceva in both monotherapy and combination settings. Rash was reported in 69% of patients treated with Tarceva plus gemcitabine and 30% of those treated with gemcitabine plus placebo; diarrhea was reported in 48% and 36%, respectively; 2% of the patients discontinued Tarceva because of rash and 2% discontinued because of diarrhea. Possible interstitial lung disease (ILD) was experienced in 2.3% in the Tarceva plus gemcitabine arm, compared to 0.4% in the gemcitabine plus placebo arm. The incidence of serious ILD-like events in the Tarceva and gemcitabine arm was higher than the 0.8% incidence reported for both the Tarceva monotherapy and placebo arms in the pivotal study of Tarceva in advanced nsclc. The incidence of possible ILD from all clinical trials with Tarceva is 0.7%.

TOXICITIES

Despite early expectations that targeted therapies will be associated with negligible toxicity, treatment with all approved inhibitors of the ErbB pathway results in some moderate toxic side effects and some serious adverse events.

Skin rash

Skin rash of any grade, specifically an acneiform rash of the face and upper body, occurs in approximately 75% of patients treated with EGFr inhibitors. Patients with severe rash often require dose reduction or interruption, which may compromise effectiveness of treatment, or even treatment cessation. Soon after the first introductions of EGFr inhibitors, oncologists began to observe and report anecdotal evidence of a relationship between the occurrence of rash and positive clinical outcome. Recent clinical trials support this notion and suggest a correlation between skin rash development and severity and treatment outcome. In most trials, skin rash appears to be dose-related and, to some degree, a surrogate marker of efficacy. The clinical usefulness of skin as a surrogate marker of efficacy and predictor of treatment response is not clear. The occurrence skin toxicity, alone, does not predict a positive response and is not a necessary condition for optimal outcome.

Several trials of dosing, the occurrence and severity of skin rash, and optimal response are currently ongoing. One trial of patients treated with erlotinib described response and survival outcomes in those who developed rash and those who did not. This trial was based on retrospective analysis of data from a multicenter (n=101), open label, nonrandomized, phase II clinical trial in Spain (TargeT) of oral erlotinib (150 mg/day) in patients with confirmed Stage IIIb/IV nsclc. Data were available for 1255 patients (active/former smoker=82%, adenocarcinoma histology=51%); baseline characteristics were similar in patients with and without rash. Administration of erlotinib as first, second, and third line treatment were 26%, 39%, and 35%, respectively. Of 698 evaluable patients, ORR was 12.6%, with 51% controlled disease rate. Skin rash of any grade was observed in 73.4%, with observed responses in 14.3%. ORR in patients with no rash was 8.1% (p=0.03). Controlled disease rate was significantly higher in patients with rash (56.6%) than in those without rash (35.48%; p<0.0001). Median TTP in patients with rash was 3.8 months, compared to 2.3 months in those with no rash (p<0.001). OS was 6.5 months in patients with rash, versus 2.3 months in those with no rash (p<0.001). TTP was significantly longer longer (4.2 months; p<0.001) and OS (7.9 months) in patients who developed Grade 2 rash. Therefore, there may be a correlation between skin rash development and severity and treatment outcome and skin rash appears to be a surrogate marker of efficacy. Prospective studies are underway to investigate the association between higher doses of erlotinib, skin rash, and optimal response. Data from the retrospective analysis indicate that skin toxicity is neither a sufficient nor necessary condition for an optimal outcome (Cobo M, etal, ASCO07, Abs. 7602).

The association between severity of skin toxicity and panitumumab efficacy was investigated in 5 clinical trials, 4 phase II clinical trials and 1 phase III clinical trial, in patients (n=640) with metastatic colorectal cancer. Toxicity was examined in patients with progressive disease on or after treatment with 5-fluorouracil, oxaliplatin, and/or irinotecan. Patients were administered panitumum-

ab 6 mg/kg every 2 weeks or 2.5 mg/kg weekly until progressive disease or intolerability. Participating sites included Vanderbilt University Medical Center (Nashville, TN), University Hospital Gasthuisberg (Leuven, Belgium), Ghent University Hospital (Ghent, Belgium), UCLA School of Medicine (Los Angeles, CA), and Fox Chase Cancer Center (Philadelphia, PA). Tumors were assessed using modified WHO or RECIST criteria (blinded central review in 4/5 studies). Endpoints included ORR, PFS, and OS. Only patients with 2 infusions (exposure of over 2 weeks for weekly dosing or over 4 weeks for dosing every 2 weeks) were analyzed to help correct for lead-time bias. Out of 640 patients, 612 were included in the analysis set. Median duration of PFS was 8.4 weeks, median OS was 6.9 months, and ORR was 9.0%. Most skin toxicities were erythema (54%, Grade 3/4=4%), pruritus (53%, Grade 3/4=2%), dermatitis acneiform (52%, Grade 3/4=5%), and rash (39%, Grade 3/4=2%). OR was observed in 3.3% of patients with Grade 0-1 skin toxicity (n=240) and in 47% of those with Grade 2-4 skin toxicity (n=372; odds ratio=4.2, p=0.0003). Median PFS in patients with Grade 0-1 and Grade 2-4 skin toxicity was 8.0 and 13.1 weeks, respectively. Median OS in patients with Grade 0-1 and Grade 2-4 skin toxicity was 4.5 and 8.5 months, respectively (HR=0.47, p<0.0001). Severity of skin rash was correlated with increased efficacy of panitumumab in terms of ORR, PFS, and OS (Berlin J, etal, ASCO07, Abs. 4134).

One company points to the absence of skin rash as an advantage of its EGFr inhibitor. According to YM Bioscience, as of July 2006, no cases of skin rash were observed with nimotuzumab in trials underway in India. The company reported that the absence of this side effect could prove to be a key differentiator for nimotuzumab in the marketplace.

The treatment of EGFr inhibitor-induced skin rash may represent a significant unmet clinical need. Hana Biosciences (South San Francisco, CA) acquired exclusive rights to develop and commercialize menadione, a preclinical product candidate for the prevention and treatment of skin rash associated with EGFr inhibitors. Menadione, a small molecule phosphatase inhibitor, is an activator of EGFr signaling. In laboratory studies, menadione (Vit K3) reversed EGFr inhibition caused by cetuximab and erlotinib (Perez-Soler R, etal, ASCO06, Abs. 3036). *In vivo* study results suggest that topically applied menadione may restore EGFr signaling in the skin of patients treated systemically with EGFr inhibitors. Hana expects to complete formulation of menadione and file an Investigational New Drug (IND) application by the end of 2007. The company estimates that, each year, more than 50,000 patients are affected by EGFr inhibitor-associated rash. At present, there is no specifically targeted treatment for this rash.

Cardiotoxicity

Cardiotoxicity, specifically ventricular dysfunction and cardiac failure, has been reported for both MAb-based and small molecule TKI inhibitors of HEr2 and EGFr. However, very few prospective studies have examined cardiotoxicities using predetermined cardiac endpoints, including left ventricular function. As a result, cardiac toxicity associated with these agents is not well understood. [Case report studies are problematic in cancer patients, who may exhibit typical CHF symptoms (e.g., dyspnea, fatigue, edema) as side effects of anticancer therapies rather than left ventricular dysfunction.] However, based on significant current clinical experience, trastuzumab may be classified as having known cardiotoxicity, whereas lapatinib, cetuximab, erlotinib, gefitinib, and panitumumab may be classified as having low cardiotoxicity (Force T, etal, Nature Rev Cancer, 2007(May);7: epub). Little has been published about nimotuzumab in the medical literature. It is clear that an EGFr inhibitor drug class effect is not the cause of cardiotoxicity, and that cardiotoxicities of these drugs must be assessed individually. At the same time, it is clear that cardiotoxicity is uncommon in drugs that inhibit EGFr and more common in drugs that target HEr2.

Cardiotoxicity caused by trastuzumab is a major adverse effect of the drug. It was initially reported in 2001, in what was the first report of cardiotoxicity caused by a targeted agent (Slamon, *ibid*). In August 2005, an FDA advisory was issued to physicians regarding a significant increase in cardiotoxicity in patients treated with trastuzumab for HEr2-positive breast cancer. The advisory was based on preliminary safety data from trial NSABP B-31.

According to results from this trial, the 3-year cumulative incidence of CHF and cardiac death was 4.1% among women treated with Herceptin and chemotherapy, compared to 0.8% in women treated with chemotherapy alone. This trial was designed to characterize trastuzumab-associated cardiotoxicity and to determine whether changes observed in serial cardiac monitoring during treatment could identify early cardiac toxicity and predict risk. In patients with adequate cardiac function, 30.5% required at least one dose delay because of asymptomatic decrease in LVEF or cardiac symptoms. Trastuzumab was discontinued in 18.6% of patients before the completion of 1 year of treatment because of asymptomatic decrease in LVEF (14.3%) or symptomatic cardiac dysfunction/other cardiac toxicity (4.3%). Furthermore, an increase in the 3-year cumulative incidence of New York Heart Association Class III and IV CHF was observed in trastuzumab patients, along with 4.1% mortality. The combination of anthracycline and cyclophosphamide (AC) plus trastuzumab was associated with the highest incidence (27%) and severity of cardiac dysfunction, compared to 8% for AC alone. Incidence of cardiac dysfunction in patients treated with the combination of trastuzumab and paclitaxel was 13%, compared to 1% for paclitaxel alone. Patient age and LVEF following chemotherapy with doxorubicin and cyclophosphamide were determined to be likely predictors of risk for symptomatic cardiac dysfunction. It was recommended

that patients treated with trastuzumab be monitored for deteriorating cardiac function.

According to updated 5-year cardiac dysfunction data involving patients (all with normal post-AC LVEF) who began post-AC treatment, 10 of 872 (1.3%) control patients subsequently had confirmed cardiac events (CHF=9 and cardiac death=1), compared to 35 of 932 (3.9%) trastuzumab-treated patients (CHF=35 and no cardiac death). The difference in cumulative incidence at 5 years was 2.7%. Risk factors for CHF were age >50 (5.2-5.3%), requirement for hypertension medication (7.7%), and post AC-LVEF values of 50-54% (13.0%). It was concluded that the administration of trastuzumab with paclitaxel after AC increases incidence of CHF and that risk factors for increased risk of cardiotoxicity should be carefully considered when discussing benefits and risks of this therapy (Rastogi P, etal, ASCO07, Abs. LBA513).

Since issuance of the 2005 trastuzumab advisory regarding cardiotoxicity, efforts have been made to further characterize the risk of cardiotoxicity, understand its pathophysiology, clinically manage this side effect, and determine its role on patient selection for trastuzumab therapy. In 4 subsequent trastuzumab trials, increases of 5-17% in the frequency of asymptomatic decreased LVEF and 1-3% in the incidence of symptomatic CHF were reported. Incidence of cardiotoxicity outside of clinical trials is not known, however, higher rates were observed in at least one sequential patient report (McArthur HL and S Chia, N Engl J Med, 5 Jun 2007;357(1):94-5).

Most patients treated with trastuzumab do not develop cardiac toxicity, which indicates that other factors, such as comorbidities, genetic background, and, possibly, immune system function must influence the risk of developing this problem. It is known that trastuzumab cardiotoxicity is at least partially reversible. Although the pathophysiologic mechanisms of cardiotoxicity remain poorly understood, several mechanisms have been proposed. They include drug interactions with cytotoxic chemotherapeutics, MAb-mediated ADCC, ErbB2 receptor downregulation, and inhibition of ErbB2 signaling in cardiomyocytes (see Force, etal). For example, ErbB2 and its ligands, neuregulin, and ErbB3/ErbB4 are involved in cardiomyocyte survival and growth in the postnatal and adult heart, and HEr2 inhibition may interrupt functioning of the pathway required for the heart's response to stress.

Because lapatinib targets HEr2, a prospective trial to evaluate its cardiotoxicity was undertaken early in its development. The study found a low rate of cardiotoxicity associated with lapatinib treatment. Cardiac safety of lapatinib was prospectively evaluated in 3,127 patients from 18 clinical phase I-III clinical trials. Cardiac risk factors assessed included age, underlying cardiovascular disease, and previous exposure to anthracycline, trastuzumab, or mediastinal/left sided radiation (XRT). Of 3127 patients treated with lapatinib, 41 (1.3%) experienced decreased LVEF. Decreased LVEF occurred within 9 weeks of treatment initiation in 66% of cases, 10-16 weeks in 15%, and 17-24 weeks in 12%. Of the 41 patients with decreased LVEF, 4 were symptomatic (0.1% incidence), most of whom responded promptly to standard CHF therapy. Risk factors for decreased LVEF in patients with breast cancer treated with lapatinib included previous or concomitant medication (86%; trastuzumab, 41%; anthracyclines, 32%); mediastinal/left sided radiation (36%); lapatinib as part of combination therapy (59%); and other significant cardiac history (50%). LVEF recovery was observed in 12 of 22 patients with breast cancer and decreased LVEF. In the remaining 10 patients with breast cancer and decreased LVEF, 2 died with LVEF decrease. No association between Ile655Val polymorphism and decreased LVEF (p=0.479) was observed. The researchers concluded that lapatinib-associated LVEF decrease is rarely symptomatic and generally reversible and non-progressive. Incidence of symptomatic and asymptomatic lapatinib-associated LVEF decrease was 1.3% among 1,674 patients with breast cancer and 1.3% among 1,453 patients with non-breast malignancies treated with lapatinib. The average LVEF decrease was 29% relative to baseline, and average duration was 42 days (Perez EA, etal, ASCO06, Abs. 583).

RESISTANCE

Resistance to EGFr/HEr2 inhibitors may be defined as an initial low response rate (i.e., intrinsic resistance) or a decline or lack of treatment response after initial effectiveness (i.e., acquired resistance); lack of 'sensitivity' to an agent may be used to describe initial treatment failure. Trastuzumab, for the treatment of HEr2-overexpressing breast cancer, demonstrates the highest sensitivity rate of the EGFr inhibitors; 30-40% of treated patients respond. Mechanisms of resistance, including roles of gene mutations and non-mutation related causes of resistance, were reviewed in the last issue (V9#1/2:1981-1982).

Many studies of genes and proteins associated with EGFr inhibitor resistance are underway because specific molecular mechanisms that contribute to intrinsic or acquired resistance have not been well characterized. Many of these involve molecular targets currently under investigation alone or in combination with ErbB pathway inhibitors, and will be discussed in upcoming issues of this series.

Much research into resistance has focused on the small molecule TKI, erlotinib and gefitinib; less is known about the more recently launched lapatinib. In nsclc, although initial responses to gefitinib and erlotinib are dramatic in some patients, progressive disease eventually develops in most initial responders. In some patients, in addition to a primary drug-sensitive EGFr mutation (exon 19 deletion or L858R point mutation), a second site T790M amino acid change (exon 20) is also observed (see resistance review in last issue). This group is establishing tetracycline-inducible mouse models of EGFr-dependent lung adeno-

carcinoma responsive and resistant to erlotinib that should be useful for testing new strategies to overcome acquired resistance (Politi K, Pao W, Zakowski M, Varmus H).

Based on the largest biomarker analysis of patients with colorectal cancer treated with cetuximab, EGFr FISH-positivity was associated with a significant benefit in response and TTP. In addition, K-ras mutation analysis identified a group of patients with the lowest chance to benefit from the therapy; and increased HEr2 gene copy number predicted early escape from cetuximab therapy. The goal of this study was to identify biological predictors for sensitivity/resistance to cetuximab treatment in colorectal cancer, including comparison of biomarker results in primary tumors and corresponding metastases. EGFr (IHC, FISH), HEr2 (FISH), and K-ras (mutation) were analyzed in paraffin embedded tumor blocks from 85 colorectal cancer patients treated with cetuximab. EGFr FISH-positive patients (n=41) showed a significantly higher RR (29.3% versus 6.8%) and TTP (6.6 versus 3.7 months) than EGFr FISH-negative patients (n=44). EGFr expression assessed by IHC was not associated with any clinical endpoint. Increased HEr2 gene copy number was associated with shorter TTP and survival. Compared to patients with wild type K-ras (n=49), K-ras mutation carriers (n=32) exhibited lower RR (6.3% versus 26.5%), shorter TTP (3.7 versus 6.3 months), and shorter survival (8.3 versus 10.8 months). In 22 patients with available primary and metastatic tumor tissue no differences in EGFr FISH, HEr2 FISH, or K-ras results between these sites were observed (Finocchiaro G, etal, ASCO07, Abs. 4021).

A series of newly established EGFr inhibitor-resistant clones, derived from human nsclc and SCCHN cell lines, were subjected to long term exposure to cetuximab or erlotinib, and changes were measured in the phosphorylated and unphosphorylated state of >40 key signaling proteins involved in pathways regulating cell cycle progression, proliferation, apoptosis, adhesion, and migration. Among them, Akt and several MAPK family members, including Erk1/2, Stat1, and JNK, were highly activated in the cetuximab and erlotinib-resistant cells. Proliferation and survival consequences of manipulation of these candidate resistance molecules are being evaluated using specific pharmacological inhibitors or siRNA knockdown approaches. DNA microarray screening studies comparing EGFr inhibitor-resistant subclones to parentals are underway in an effort to identify differentially regulated genes that may contribute to the EGFr inhibitor-resistance phenotype.

The insulin-like growth factor I receptor (IGF-Ir)has been implicated in trastuzumab resistance in breast cancer cells. Levels of HEr2 and IGF-Ir protein were determined in 24 breast cancer cell lines; and the antiproliferative effect of trastuzumab on HEr2 positive breast cancer cell lines was assessed. The effects of IGF-I/IGF-Ir inhibition on proliferation and response to trastuzumab were also investigated. No significant correlation was observed between levels of HEr-2 and response to trastuzumab in 10 HEr2-positive breast cancer cell lines, but IGF-Ir levels correlated with resistance to growth inhibition by trastuzumab. Phosphorylated IGF-Ir was not detected in any of these HEr2 positive cell lines. High levels of phosphorylated IGF-Ir, however, were detected in 3 trastuzumab-conditioned cell lines. The trastuzumab-conditioned cell lines were then treated with IGF binding protein 3 or the IGF-Ir antibody IR3 to block IGF-Ir, but neither treatment significantly inhibited the growth of the cells or enhanced antiproliferative effects of trastuzumab. These results suggest that increased expression and/or activation of IGF-IR may play a role in the response to trastuzumab. Although not demonstrated by this study, the combination of anti-IGF-Ir therapy and trastuzumab may be advantageous over trastuzumab alone. More research is required to determine whether anti-IGF-Ir antibodies or specific IGF-Ir tyrosine kinase inhibitors would be effective in overcoming IGF-Ir-mediated trastuzumab resistance (Browne BC, etal, AACR06, Abs. 1221).

One major finding is the consistent upregulation of ErbB ligand gene clusters. Amphiregulin, HB-EGF, neuregulin-1, and TGF-alpha are expressed at levels of up to >15-fold higher in resistant clones, compared to parental cells. In the cultured media of resistant cells, 3-4 fold increases of TGFα and neuregulin-1 expression have been observed. Studies are ongoing using siRNA to assess the impact of ErbB ligand upregulation on EGFr inhibitor-resistant phenotype. Identification and functional validation of candidate molecules involved in EGFr inhibitor-resistance will, hopefully, facilitate development of clinical strategies for overcoming acquired resistance (Benavente S, etal, AACR06, Abs. 1246).

GLOBAL MARKETS

The global market for ErbB inhibitors has demonstrated phenomenal growth during the last year and a half. In 2006, total worldwide (WW) sales of ErbB inhibitors were $5,160 million, which represented a 71.4% increase over the 2005 total of 3,007.9 million (Exhibit 4). Global revenues reached $3,215 million in the first 6 months of 2007, an increase of 34.2% over the first six months of 2006 (Exhibit 5).

Herceptin

Herceptin accounts for the lion's share of this market, with WW revenues of $3,134 million in 2006, up 81.9% from 2005 levels. Although global sales growth remains strong worldwide, it has slowed considerably during the first 6 months of 2007, when it was estimated at 30%. Most of the growth posted in the first half of 2007 was the result of rapid adoption of Herceptin in markets outside the USA. USA sales of Herceptin were $311 million in 1Q07, up 7% compared to 1Q06, and $329 million in 2Q07, up 3% from $320 million in 2Q06.

Erbitux

Erbitux represents the second largest market segment in the ErbB inhibitor sector, with WW sales of $1,100 million in 2006, up 56.7% from $702.1 million in 2005. Global sales growth of Erbitux slowed considerably during the first 6 months of 2007, when it was estimated at 24.4%. WW sales in the first half of 2007 were $625.3 million. Sales posted by Bristol-Myers Squibb were $322 million in the first half of 2007, up 4% from $310 million in the same period in 2006; USA sales were $318 million, up 3%, and ROW sales were $4 million. ROW sales posted by Merck KGaA were $303.3 million during the first 6 months of 2007 and accounted for nearly all of the overall growth.

Breaking down the Erbitux market further, WW sales were $306.1 million in 1Q07, up 34.3% from $227.9 million in 1Q06. USA sales of Erbitux were $160.1 million in 1Q07, up 16% from $138 million in 1Q06, while ROW sales were $146 million. WW sales of Erbitux were $319.2 million in 2Q07, up 16% from $274.8 million in 2Q06. ROW 2Q07 sales of were $157.2 million, up 53% from $102.5 million in 2Q06. USA in-market net sales of Erbitux in 2Q07 were $162.1 million ($160 million of these sales were in the USA, down 7%, and $2 million were outside the USA), down 6% from $172.4 million in 2Q06. This year-to-year 2Q decline in USA sales is largely attributable to two factors, the approval of Vectibix in 3Q06 and an increase in 2Q06 sales caused by a one-time bolus of sales of approximately $15 million, which was related to pent-up demand for Erbitux after receiving FDA approval in head and neck cancer. Notably, the 2Q07 increase in sales represents a significant milestone, reversing a negative sales trend observed since the introduction of Vectibix.

Tarceva

WW sales of Tarceva were approximately $409 million in 1H07, up 41% over 1H06 levels. WW sales of Tarceva were $198 million in 1Q07, up 48% compared to $133 million in 1Q06. USA sales were $102 million in 1Q07, compared to $93 million in 1Q06; and ROW sales were $96 million, up 140%, compared to the $40 million in 1Q06.

WW sales of Tarceva were $212 million in 2Q07, up 35% over 2Q06 levels. USA sales of $102 million in 2Q07, compared to $103 million in 2Q06, were negatively impacted by approximately $9 million of reserve adjustments because of unusually high product returns of expiring inventory to Genentech. Excluding this adjustment, USA sales of Tarceva were up 7% in 2Q07, compared to 2Q06.

Iressa

WW sales of Iressa were $52 million in 1Q07 and $61 million in 2Q07, compared to $50 million in 1Q06 and $62 million in 2Q06. WW sales of Iressa were $113 million in 1H07, up 1% from $112 million in 1H06. Almost all revenues from Iressa are generated outside the USA. In 1H07, Iressa sales were up 6% in Japan and 40% in China, compared to 1H06.

Vectibix

USA sales of Vectibix were $51 million in 1Q07 and $45 million in 2Q07, for a total of $96 million in 1H07. The decrease in 2Q07 compared to 1Q07 was attributed to customer reaction to unfavorable PACCE study results released late in 1Q07 and a decline in market growth of EGFr-related therapeutics for metastatic colorectal cancer.

Tykerb

WW sales of Tykerb were $8 million in 1Q07; USA sales were $6 million and ROW sales were $2 million. WW sales of Tykerb were $24 million in 2Q07; USA sales were $20 million, and ROW sales were $4 million. WW sales were $32 million in 1H07; USA sales were $26 million and ROW sales were $6 million.

PRICING AND REIMBURSEMENT

High prices of ErbB inhibitors have had little impact on the commercial success of these drugs. However, pricing and reimbursement trends need to be monitored diligently as the mood darkens regarding healthcare costs, in general, and drug costs, in particular. Costs are being scrutinized by governments and private insurance sources looking for better, more cost-effective options.

Rationale for High Prices

Generally, prices of ErbB pathway inhibitors are considered high by any standard. Drug prices vary considerably from country to country and between providers and end users. In the USA, average wholesale prices (AWP) of the drugs vary (Exhibit 6), mostly between MAb-based IV therapies and small molecule oral drugs. AWP had been the only standard measure of drug prices until 2003, when Medicare adopted an average sales price (ASP) measure to combat abuses in AWP reporting by the pharmaceutical sector. Retail prices are based on mark-ups of as high as 30% over AWP. AWP or ASP represent only one factor in determining the per-patient/per-treatment course cost burden of a drug. For cancer drugs, required doses, duration of treatment, and average number of courses administered to patients may vary widely for different indications.

The industry's public explanations for high prices of new cancer drugs appear to have shifted somewhat in recent years. After many years of explaining high prices as necessary to cover the cost of research and development and/or production, industry executives now also increasingly add to their rationale the consideration of a cancer drug's value to the patient. Prices of drugs with no direct alternatives are set at the discretion of their suppliers. At present, cancer drugs with unique activities (but in some cases marginal benefits) and no competitive alternatives successfully command the high prices set by their suppliers. In 2005, Genentech raised the price of Tarceva by about 30%, to $32,000 for one year of treatment, justifying the increase by the fact that the drug worked better than anticipated and is thereby more valuable.

Exhibit 4
Global Sales of ErbB-pathway Targeted Agents in 2005/2006

		USA Sales ($000)			ROW Sales ($000)			Total Sales ($000)		
Developer	**Drug Designation**	**2005**	**2006**	**Change (%)**	**2005**	**2006**	**Change (%)**	**2005**	**2006**	**Change (%)**
Genentech ❑ Roche	Herceptin ❑ Trastuzumab	747.2	1,234.0	65.1	975.1	1,900.0	94.8	1,722.3	3,134.0	81.9
ImClone Systems ❑ Merck KGaA, Bristol-Myers Squibb	Erbitux ❑ Cetuximab	431.1	646.0	49.8	271.0	454.0	67.5	702.1	1,100.0	56.7
OSI Pharmaceuticals ❑ Genentech, Roche	Tarceva ❑ Erlotinib	274.9	402.0	46.2	35.6	248.0		310.6	650.0	109.3
AstraZeneca	Iressa ❑ Gefitinib	65.1	8.3	(87.5)	208.0	228.7	9.9	273.0	237.0	(13.1)
Amgen	Vectibix ❑ Panitumumab		39.0						39.0	
Total		1,518.3	2,329.3	53.4	1,489.7	2,830.7	90.0	3,008.0	5,160.0	71.4

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

Exhibit 5
Global Sales of ErbB-pathway Targeted Agents in the First Half of 2007

Developer	**Drug Designation**	**USA Sales ($000)**	**ROW Sales ($000)**	**Total Sales ($000)**	**Change (%)**
Genentech ❑ Roche	Herceptin ❑ Trastuzumab	640.0	1,300.3	1,940.3	30.0
ImClone Systems ❑ Merck KGaA, Bristol-Myers Squibb	Erbitux ❑ Cetuximab	318.0	307.3	625.3	24.4
OSI Pharmaceuticals ❑ Genentech, Roche	Tarceva ❑ Erlotinib	204.0	205.0	409.0	41.0
AstraZeneca	Iressa ❑ Gefitinib			113.0	2.0
Amgen	Vectibix ❑ Panitumumab	96.0		96.0	
GlaxoSmithKline	Tykerb ❑ Lapatinib	26.0	6.0	32.0	
Total				3,215.60	34.2

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

This first price effect of competition in the ErbB inhibitor market occurred when Amgen introduced Vectibix at a price 20% lower than that of Erbitux. However, Vectibix still costs $4,000 per infusion; and with infusions scheduled for every two weeks, a year's treatment would cost about $100,000, although most patients for whom the drug is indicated would not be expected to survive longer than a few months.

Although developers employ a variety of justifications, the true reasons for high prices and, more to the point, the

market's willingness to bear them, may subconsciously reflect the rather ephemeral nature of these agents, the desperation surrounding a diagnosis of cancer, and the inadequacy of current therapies in treating major malignancies. Despite some claims and press reports, the first generation molecularly targeted drugs are, hopefully, short term, stop gap predecessors to more definitive and efficacious therapies, which are fully expected emerge from the many next generation agents currently in clinical development.

Reimbursement Determines Market Success

One of the key determinants for successful marketing of a high priced drug is reimbursement. Reimbursement is usually linked to the intrinsic value of a drug. Although this linkage is less direct in the USA and some European countries with similar reimbursement systems, it is prevalent in countries with more socialized systems. The strategy of linking reimbursement to intrinsic value has been evident in the market successes of such drugs as Gleevec and Herceptin, which have been convincingly proven to be effective and now command large markets outside the USA. These drugs achieved large sales volumes in very short periods of time because of rapid acceptance by health care systems around the world.

It is more difficult to obtain reimbursement for high priced drugs in some countries than in others. The UK is one of the toughest markets to enter with high priced drugs. For example, in May 2007, the National Institute for Health and Clinical Excellence (NICE) concluded that Erbitux was not cost effective for the treatment of head and neck cancer. Although MST of patients treated with Erbitux was 49 months, compared to 29.3 months for those treated with radiation alone, the committee pointed out that most treatment regimens for this malignancy involve chemoradiotherapy, offering patients an alternative to Erbitux plus radiotherapy. In contrast, in July 2006, the Scottish Medicines Consortium approved Erbitux for use within NHS Scotland for the treatment of patients with head and neck cancer who are not appropriate for or unable to tolerate chemoradiotherapy.

In some cases, NICE has recommended coverage of high priced cancer drugs for reimbursement in the UK. In August 2006, NICE recommended coverage of Herceptin in the adjuvant setting for women with early stage HEr2-positive breast cancer. Of the 35,000 women diagnosed with breast cancer each year in the UK, approximately 20,000 are expected to be suitable for HEr2 testing, of which about 5,000 may benefit from Herceptin. Using this calculation, the drug may save around 1,000 lives per year at an annual cost of about £100 million. Recommendations by NICE are made independently of budgetary considerations. In cases like that of Herceptin, approval could force the National Health Service to cut other health services.

However, NICE might not have considered the HERA schedule to be cost effective if the FinHer trial, which used a fifth of the amount of trastuzumab as in HERA, had been the comparator. However, NICE could not consider the FinHer protocol because the agency could only consider licensed indications and Roche had only sought and obtained marketing authorization for a 1-year schedule. Roche had little to gain filing for approval of a regimen that would reduce the use of trastuzumab significantly. Actually the opposite occurred as HERA investigated a 2-year regimen of trastuzumab.

In an interesting development, high prices of cancer drugs have prompted NICE to consider entering into a 'money-back guarantee' arrangement with Janssen-Cilag, a Johnson and Johnson company, regarding the application of bortezomib (Velcade; Millennium Pharmaceuticals) for the second line treatment of multiple myeloma. According to the proposal, as of June 2007, NICE's independent advisory committee is recommending that all suitable patients be offered treatment. Responding patents (CR or PR) are kept on the drug and funded by the NHS. Patients showing a minimal or no response are to be taken off the drug, with the drug costs refunded by the manufacturer. The draft recommendations follow an evaluation of a refund scheme put forward by the drug's manufacturer. The final decision on whether to put the refund scheme into practice rests with the manufacturer and UK's Department of Health.

In this scheme, all patients who may benefit from the drug are given the chance to be treated. At the same time, the drug's manufacturer assumes the economic burden associated with treatment failure. In addition to the shared responsibility in paying for the treatment, this approach also introduces a rigorous evaluation regarding the success or failure of a treatment in the real world setting. In order to evaluate treatment effectiveness, response to bortezomib is measured using serum M-protein after a maximum of four cycles of treatment, and treatment is continued only in patients with a reduction in serum M-protein ≥50% or more indicating a CR or PR. The manufacturer must rebate the full cost of bortezomib associated with nonresponders, but these patients have the option to continue therapy until they and their clinicians consider it appropriate to stop.

NICE had originally rejected reimbursement for the bortezomib monotherapy indication in multiple myeloma because the cost of treatment, estimated at £3,000 per cycle exceeded NICE thresholds. This novel proposal was put forth after an appeal from the drug's manufacturer this decision was upheld. The Appeal Panel asked the Appraisal Committee to assess, among other things, the benefits of a refund scheme proposed by the drug's manufacturer. NICE expects to issue final guidance (pending any appeals) to the NHS in October 2007.

TREATMENT COSTS

By superficial examination, prices of newly approved anticancer agents appear to be absurdly high. Some are quoted as high as $100,000 per treatment regimen. Although new anticancer drugs are priced much higher than nearly all other new drugs in other therapeutic indications, some unique aspects of anticancer drug treatment contribute to the high prices. Anticancer agents usually target a narrow indication; and the number of potentially treatable patients, based on affected populations in the West, is usually limited. High prices per patient may allow developers to recoup the cost of R&D expenses, which may be as high as those for a drug addressing large markets involving patients with conditions requiring chronic intervention.

Unlike most chronic diseases, most patients with cancer have a narrow treatment window. As a result, developers of anticancer agents do not enjoy the year-to-year expansion of populations as more patients initiate chronic treatment. Also in some cases concerning biologic anticancer agents, manufacturing and quality control may present substantial challenges requiring significant upfront and ongoing investments. On the other side of the ledger, the marketing of oncology drugs costs less than that for most other drug (e.g., the number of practicing oncologists is relatively small, they are relatively sophisticated and willing to try new therapies, etc.), revenues ramp up and grow rapidly after approval, and many new drugs are shielded from competition because of the lack of alternatives. The lack of alternatives is expected to become less true, as more and more new agents addressing the same cancer indications are introduced into the market.

Treatment costs of the commercialized ErbB inhibitors, like those of other newly approved anticancer agents, are very high. Costs per regimen vary and depend on the particular cancer indication and length of treatment, which is determined by the individual patient's response or emergence of serious adverse events. The true cost of treatment is much greater than the price of individual agents because of the prevalent use of combination regimens and multiple sequential therapeutic interventions. In the past it was rare to encounter cases involving more than 2 or 3 separate, distinct treatment attempts involving the same patient. Now, patients may be treated with as many as 7 distinct interventions, most of which may be high-priced combination regimens.

Although targeted therapies for cancer had long been of great scientific and experimental interest, the approval of imatinib mesylate (Gleevec/Glivec; Novartis) for the treatment of hematologic malignancies in adults, brought the field into new clinical and commercial realities. The impressive effectiveness of imatinib resulted in great strides during the last two decades in the treatment of hematologic malignancies in adults (matching past achievements in treating childhood leukemia).

None of the approved EGFr inhibitors approach the effectiveness of imatinib; most of the recently commercialized agents provide incremental benefits that are measured in months of life gained, not years. Clearly, overall survival has been extended as patients are offered multiple treatments in succession (which, to date, the health care system in the USA has been willing to reimburse), and advances in supportive care have mitigated the often-serious side effects of cancer treatment regimens.

Currently, however, the health care system in the USA appears to have reached a crisis mode (again), with virtually all health care costs rising uncontrollably. The very small life-extension benefits achievable with very expensive anticancer treatments are now being scrutinized more closely. Cost-benefit analysis is one of the yardsticks used in assessing the reasonableness of treatment costs. The rising costs of cancer care provide an easy target for critics who rely on cost-benefit analysis. Patients with cancer require costly, highly specialized acute care, which has a high failure rate. Patients with hypertension or diabetes may account for far higher lifetime costs of treatment, but their treatment is associated with much more favorable cost-effectiveness ratios.

Simple cost-benefit ratios often come up short when applied to cancer treatment costs. In a study assessing the cost-effectiveness of adding erlotinib to gemcitabine (Gemzar; Eli Lilly) in advanced pancreatic cancer, investigators concluded that the combination does not approach cost effectiveness at even the highest year-per-life gained parameters. In a recent clinical trial comparing gemcitabine alone with gemcitabine plus erlotinib as first line therapy in 569 randomized patients, a small but statistically significant difference in survival (6.0 versus 6.4 months; p=.028) favored the combination regimen. The impact on survival is small; however, with nearly 33,000 new cases of pancreatic cancer diagnosed each year, the impact of the combined regimen on health care costs is expected to be large. Using the known survival data and costs, investigators analyzed the incremental cost-effectiveness of adding erlotinib to a gemcitabine regimen. Costs for a 6-month course of gemcitabine were developed using Medicare reimbursement from the January 2006 CMS Drug Payment Table and Physician Fee Schedule, assuming no change in infusion reimbursement. Because erlotinib was not approved as a Medicare Part B drug, costs were developed from wholesale and retail sources. Drug dosing and schedules were based on the clinical trial protocol leading to approval. Incremental cost effectiveness of adding erlotinib was calculated. A 6-month course of gemcitabine alone costs $23,493. The addition of erlotinib increases cost by $12,156 wholesale or $16,613 retail. Given an increase of 0.4 months in median survival over gemcitabine alone, the addition of erlotinib costs $364,680 per year of life gained (YLG) wholesale and $498,379 per YLG retail. Even a shorter therapy of 4 and 5 months results in YLG costs of $415,316 and $332,252, respectively.

In order to reach cost effectiveness at the 6-month treatment option at the level of $100,000 per YLG, the retail price of erlotinib would have to be reduced to 20% of the current retail price, to $18.52 per tablet (Grubbs SS, etal, ASCO06, Abs. 6048).

Colorectal Cancer

In the USA, an older standard treatment of 5-FU/leucovorin achieved a MST of approximately 12 months, at a cost of about $4,000 for the drugs alone. FOLFOX, a more recent first line treatment regimen, extends life by another 5-6 months at a cost of $44,000. Both of these first line treatments have been supplanted by a regimen consisting of FOLFOX and bevacizumab, which doubles the MST of the 5-FU/leucovorin regimen (i.e., MST = 2 years), at a cost of >$100,000. The cost-benefit ratio in terms of life years gained is judged to be reasonable in this case.

Erbitux has been on the USA market since early 2004 and is currently approved in most major markets around the world for the second line treatment of metastatic colorectal cancer, refractory to FOLFOX and bevacizumab, mostly in combination irinotecan-based regimens. Erbitux costs about $10,000 per month, resulting in a full treatment cost of about $100,000. Using published reports and aggregate data from NCCTG 9741, investigators at the Fox Chase Cancer Center (Philadelphia, PA), Mayo Clinic (Rochester, MN), and the University of North Carolina at Chapel Hill, developed a Markov model which assumes forward progression through up to three lines of therapy, compared to 5FU/LV alone. Patients who do not die of toxicity transition through supportive care prior to death. Only drug costs and no other direct or indirect costs were included in this analysis. Dose modifications for toxicity are defined as 80% of standard doses.

In the treatment of metastatic colorectal cancer, the most important development has been the increase in MST, from approximately 54.7 weeks with the 5-FU plus leucovorin (5FU/LV) regimen at a cost of $4,000, to approximately 70 weeks with first line FOLFOX regimen at a cost of $44,000, and to approximately 84.4 weeks with a first line FOLFIRI then FOLFOX regimen at $55,000. Adding bevacizumab (Avastin; Genentech) followed by irinotecan to the FOLFOX regimen increases life expectancy to 95.1 weeks, a mere 10.7 weeks advantage at more than double the cost (estimated at $114,000). Use of cetuximab with these regimens as second or third line treatment may add another 10-15 weeks of life at an additional cost of $4,000 to $59,000 (Wong Y, etal, ASCO06, Abs. 3515). For instance, in a first line plus second line setting, a combination of FOLFOX plus bevacizumab, then irinotecan and then cetuximab plus irinotecan costs more than $173,000 and results in an MST of about 117 weeks.

Breast Cancer

Herceptin is considerably more cost effective than other EGFr inhibitors and was rapidly adopted for reimbursement in most developed countries for both metastatic and adjuvant settings. In most cases, cost-effectiveness analyses pointed to a favorable quality-adjusted life years (QALY) measure in both settings. The cost effectiveness of Herceptin is achieved by careful patient selection based on proven pharmacogenomics, which increases survival rates in advanced disease and reduces risk of recurrence of early disease. Effective selection of patients who are most likely to respond to Herceptin also spares those who are unlikely to respond the significant side effects of the treatment and saves significant funds for the health care system.

Worldwide, there is no dispute over the cost-effectiveness of Herceptin in the metastatic breast cancer. An analysis of the treatment costs at a European institution for 40 consecutive patients treated for metastatic breast cancer from 2000 to 2006, concluded that treatment with Herceptin plus chemotherapy was effective and well tolerated and provide a good QoL. Tumors of all patients treated expressed HEr2 (IHC 3+ or FISH+); LVEF was >50%. Metastatic sites were observed in the liver (n=18), lymph nodes (n=10), bone (n=9), skin (n=7), and lung (n=5); 11 cases exhibited multiple (1-3) metastatic sites. All patients were treated with Herceptin at a loading dose of 4 mg/kg and 2 mg/kg weekly thereafter, in combination with weekly paclitaxel (80 mg/m^2; n=26) or weekly vinorelbine (25 mg/m^2; n=14). Endpoints were TTP, duration of response, toxicity (including cardiac events), and OS.

A total of 1,271 courses of weekly Herceptin were administered (average=28 courses per patient, range=8-72). There were 22 CR and PR (CR+PR=55%); 11 CR, 6 PR, 3 SD, and 6 PD, (RR=65.3%) in the Hereceptin plus paclitaxel arm. There were 2 CR, 3 PR, 4 SD, and 5 PD (RR=35.7%) in the Herceptin plus vinorelbine arm. The most responsive (CR+PR) sites were 15 (37.5%) in the liver, 11 (27.5%) in the lung, 8 (20%) in the lymph nodes, and 6 (15%) in the skin. TTP was 7 months (range=2-27 months), and response duration was 6.7 months (range=2-26 months). OS at 5 years was estimated at 26.4 months. Grade 4 hematologic toxicities occurred in 2 patients and Grade 3 in 3; Grade 3 neurologic toxicities were seen in 19 patients. There was no significant cardiologic toxicity, but LVEF was reduced to 40% in 4 patients. Seven patients developed brain metastasis during therapy. No responses were observed in patients with progressive disease who continued Herceptin treatment in combination with cytotoxic chemotherapy. The median cost of treatment with Herceptin per patient was €16,147, with a range of €3,987 to €39,959 (Scola A, etal, ASCO07, Abs. 11517).

Swedish investigators assessed the cost effectiveness of HEr2 testing and treatment with Herceptin in combination with chemotherapy, compared to chemotherapy alone. They used a Markov state transition model to simulate HEr2 testing and subsequent treatment in a hypothetical cohort of 65-year old patients with metastatic breast cancer, based on work by Marty, etal. (Marty, etal, J Clin Oncol, 2005;23(19):4265-4274). Outcomes included lifetime costs, QALY, and cost per QALY gained. Five differ-

Exhibit 6
Estimated Average Prices of Approved ErbB Inhibitors in the USA

Drug	Unit	AWP ($)	Dose	Wholesale cost per Month ($0)
Erbitux	100 mg (50 ml of 2 mg/ml)	576.0	400 mg first dose and 250 weekly (51 weeks)	11,016.0
Tarceva (nsclc)	150 mg tablet	86.6 (introduced at 67.5)	150 mg daily	2,660.0
Tarceva (pancreatic cancer)	100 mg tablet		100 mg daily	
Iressa	250 mg tablet	56.6	250 mg daily	1,700.0
Tykerb	250 mg tablet	23.2	1250 mg daily for 3 weeks every month	2,467.5
Vectibix	100 mg (5 ml of 20 mg/ml)	960.0	6 mg/kg twice monthly	8,294.4
Herceptin	440 mg multidose vial of powder with 20 ml diluent	3,108.2	4 mg/kg loading dose and 2 mg/kg weekly maintenance dose*	4,490.2

** Alternative approaches (not favored in the USA) of adjuvant Herceptin include an 8 mg/kg loading dose and 6 mg/kg maintenance dose administered at 3 weekly intervals, or 9 weekly infusions of a 4 mg/kg loading dose and 2 mg/kg weekly maintenance doses.*

Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), August 2007

ent testing and treatment strategies were evaluated. The cost per QALY gained was estimated at about SEK485,000 (~$70,000) and the cost per life year gained to be about SEK332,000 (~$47,000) for the strategy of IHC testing for all patients, with FISH confirmation of 2+ and 3+, and Herceptin and chemotherapy treatment for FISH-positive patients. For the strategy of FISH testing for all patients, with Herceptin and chemotherapy for FISH-positive patients, the cost per QALY gained was estimated at SEK561,000 (~80,000) and the cost per life-year gained at 384,000 SEK (~55,000).

Results were sensitive to changes in the quality adjustment of life years with metastatic disease, the risk of breast cancer related death, and test characteristics. This analysis found that the present Swedish guidelines of IHC testing for all patients with metastatic breast cancer, with FISH confirmation of 2+ and 3+, followed by Herceptin and chemotherapy treatment for FISH-positive patients is a cost-effective treatment option. However, further research on budget impact of trastuzumab treatment and patient accessibility to trastuzumab treatment is needed (Lidgren M, etal, ASCO07, Abs. 1088).

Based on data from trial BCIRG 001, a 35% risk for relapse at 5 years was used for patients with HEr2-positive metastatic breast cancer treated with conventional adjuvant chemotherapy, and a 50% risk reduction for adding Herceptin, for an absolute benefit of 17.5%. The cost per relapse prevented for a 33% and a 50% reduction in relapse rate would be €152,000 and €63,000, respectively. Assuming a 50% reduction in the rate of relapse (from 35% to 17.5%) the real cost of adjuvant Herceptin per patient treated is not €34,000, but approximately €11,000. The corresponding real costs of trastuzumab for 100 patients would be €3.4 million for a 25% reduction in relapse, €2.6 million for 50% reduction, €2.1 million for 80% reduction, and €1.8 million for 100% reduction. Based on absolute relapse reductions of 7% in BCIRG 001, 5% in CALGB 9344, and 4% in dose-dense CALGB 9741, the costs per prevented relapse were calculated as €148,000 for CALGB 9344, and €126,000 for CALGB 9741. Assuming no retreatment of patients with HEr2+ metastatic breast cancer, adjuvant trastuzumab appears to be a relatively cost-effective means of reducing relapses. Reports of the efficacy of short adjuvant trastuzumab regimens suggest the possibility of even greater cost-effectiveness (Wilson E, etal, ASCO06, Abs. 6081, and O'cearbhaill R, etal, ASCO07, Abs. 6534). Institut Curie (Paris, France) conducted a retrospective review of patients (n=137) treated with Herceptin for HEr2-overexpressing metastatic breast cancer to estimate the cost and determine the financial impact of Herceptin in the adjuvant setting. Objectives were to analyze prescription patterns, survival, and cost data, and determine financial aspects of trastuzumab treatment in the metastatic setting. Inclusion period was from January 1, 2001 to December 31, 2003. Median patient age was 52 years; 85% of patients had 3+ HEr2 and 15% had 2+ HEr2 overexpression. As of December 31, 2004,

40% of patients were still on treatment. All possible Herceptin-based regimens included Herceptin monotherapy, maintenance therapy, and combination therapy with docetaxel, paclitaxel, vinorelbine, capecitabine, or gemcitabine. Health insurance reimbursement for a 150 mg bottle of trastuzumab was 652 francs. MST from first treatment with trastuzumab was 38.5 months. Average cost of the first year treatment was 43,435.58 francs/patient, 36,419.01 francs/ patient for second year treatment, and 37,198.94 francs/patient for third year treatment. Drug costs represent 78% of hospital stay costs and 2.9% of the budget of Institut Curie. Data showed a very high level of expenses of Herceptin for the treatment of patients with metastatic breast cancer (Doz MA, etal, ASCO06, Abs. 663).

The potential pharmacoeconomic impact of adding Xeloda (capecitabine) to a combination of Taxotere and Herceptin in the treatment of metastatic breast cancer became an issue when results from the CHAT trial indicated an advantage of 4.4 months in median TTP, and 2 months in median PFS. Direct medical costs during the trial were estimated from the Italian health system perspective. Actual doses of both regimens were modeled from trial data. Grade 3/4 AE and related medications were analyzed to estimate costs of treating major AE. Other costs, relating to laboratory tests and drug administration, were assumed to be the same in both arms. The total direct medical costs were slightly lower for the Xeloda combination, at €15,250, than for the Taxotere and Herceptin arm, at €15,570; drug costs were €14,370 and €14,690, respectively. The Xeloda arm resulted in more Grade 3/4 nonhematologic AE (77% versus 68%) but less Grade 3/4 neutropenia (54% versus 77%), complicated neutropenia (20% versus 24%), and febrile neutropenia (14% versus 23%). The estimated mean AE costs per patient were similar in both arms. Because it is administered orally, Xeloda did not increase the number and duration of infusion visits or costs. The researchers concluded that this triple combination is a good alternative for the treatment of advanced/metastatic breast cancer (Bonetti A, etal, ASCO07, Abs. 17036).

Despite worldwide acknowledgement of favorable cost-benefit analyses of Herceptin in the metastatic breast cancer setting, the developing world struggles with the high cost of the treatment. A report from Bangladesh illustrates the limited access to Herceptin because of its high cost. From January 2003 to December 2006, among 250 patients with metastatic breast cancer seeking treatment, 96 (38%) were eligible for Hereceptin but only 11 could afford the treatment (Hossain M, etal, ASCO07, Abs. 14139).

Unlike its use in the metastatic setting, the use of Herceptin in the adjuvant setting is still debated. Although the general prevailing view is that it is cost effective, there is less agreement on how Herceptin should be used in combination regimens and regarding duration of treatment. The different recommended schedules may have a dramatic impact on WW revenues of Herceptin in the early stage breast cancer indication. Two aspects of the treatment are controversial, concurrent versus sequential administration of Herceptin and taxane-based chemotherapy, and short (~9 weeks) concurrent combination therapy or long (12 months) concurrent or sequential therapy.

In metastatic breast cancer, data indicate that Herceptin is more effective and provides synergistic benefit when used concurrently with cytotoxic (e.g., taxane) chemotherapy, rather than sequentially as a single agent. There are data supporting the notion that, in early breast cancer, concurrent treatment may also confer greater benefit (e.g., improved DFS) than sequential treatment.

In the USA, the prevailing treatment regimen for HEr2+ breast cancer in the adjuvant setting is 12 months of Herceptin, initiated concurrently with a standard taxane regimen. A recent, high-powered analysis that concluded that trastuzumab is cost effective in the adjuvant setting was based on results from NSABP-B-31and NCCTG N9831. Among other factors (e.g., safety and effectiveness), these trials evaluated the lifetime clinical and economic implications of adjuvant trastuzumab therapy in early HEr2-positive breast cancer. Long term survival and outcomes analysis were projected from 4-year joint analysis data and extrapolated to 20-year and lifetime horizons. Joint analysis compared doxorubicin plus cyclophosphamide with adjuvant paclitaxel (ACP) therapy to doxorubicin plus cyclophosphamide with adjuvant paclitaxel and trastuzumab (ACPT) therapy. A Markov model with 4 health states (adjuvant therapy, DFS, recurrence, death) was used to assess expected costs, life years, and QALY for a 50-year-old woman. Cardiotoxicity was higher with trastuzumab. Actual total trastuzumab doses were used in the analysis, which were lower than the scheduled dose. Incremental costs associated with the addition of trastuzumab to adjuvant therapy were estimated using AWP, Medicare reimbursement rates, and other published data. These costs included testing for HEr2 status, drug and administration costs for trastuzumab, cardiac monitoring, treatment of cardiotoxicity, treatment following recurrence, and end-of-life costs for dying patients. Utility estimates were derived from literature.

Projected life expectancy from the Markov model was 3 years longer for trastuzumab patients (19.4 years versus 16.4 years). Over a 20-year horizon, addition of adjuvant trastuzumab to ACP therapy is estimated to cost an additional $43,913, with an expected gain of 1.28 QALY and a cost/QALY of $34,201. The key drivers of cost-effectiveness are the cost of treatment and improvement in DFS. Adding trastuzumab to standard adjuvant therapy reduces the risk of recurrence and improves OS in patients with early breast cancer. Lifetime projected cost per QALY of adjuvant trastuzumab is $26,417. The model projects a cost-utility ratio that is below that of many other treatments used in patients with cancer (Garrison LP, etal, ASCO06, Abs. 6023).

In other markets throughout the work, similar conclusions have been reached, based on different treatment protocols. In Europe, Herceptin is administered in the adjuvant setting for 12 months after completion of a taxane-based regimen, based on results from the HERA trial in which Herceptin, administered after standard chemotherapy reduced the risk of cancer recurrence at 12 months by 46% compared to chemotherapy alone. This 2-year median follow-up data from HERA shows that the absolute increase in DFS was 6.1%, and that 1.8% more women were still alive compared with the chemotherapy only group. Therefore, one year after completing a 12-month course of Herceptin, recurrence was delayed in 1 in every 16 Herceptin-treated patients, and one extra death was avoided (delayed) for every 55 people treated. It is notable that a 2-year follow-up is relatively short, and whether or not these results translate to longer-term benefits remains to be seen. It should also be noted that the difference between the control group and the Herceptin-treated group was less at 2-year median follow-up than at 1-year median follow-up, which raises legitimate questions about the durability of the responses achieved with Herceptin.

Irish investigators evaluated the cost effectiveness of adjuvant Herceptin by estimating savings gained from the reduced risk of relapse. Herceptin costs approximately €30,000 per patient and reduces the risk of relapse by 33-50%. This risk reduction may decrease the use of high-priced drugs for the treatment of relapsed metastatic disease, thus justifying the use of adjuvant Herceptin in early disesease. Investigators at St. Vincent's University Hospital (Dublin, Ireland) evaluated the real cost of adjuvant trastuzumab in the context of the current use of trastuzumab in metastatic breast cancer and the predicted reduction in the risk of relapse. Retrospective analysis compared the mean cost per patient of adjuvant trastuzumab, trastuzumab for the treatment of metastatic breast cancer, and standard adjuvant chemotherapy. The costs per patient were €34,000 for adjuvant Herceptin, €47,000 for Herceptin in metastatic disease, €8,800 for docetaxel, €7,400 for paclitaxel, and €9,300 for filgrastim. In this hospital, the mean cost per patient with metastatic breast cancer treated with a Herceptin-based combination regimen was €108,000.

Investigators at the University of Tromso, in Norway, evaluated the marginal cost effectiveness of trastuzumab in adjuvant treatment of HEr2+ early breast cancer in a model-based cost effectiveness analysis. In this model, societal costs were calculated according to Norwegian prices as of September 2005 and converted to euro at the rate of €= NOK7.81. Life expectancy data were based on the literature and prolonged according to qualified guess (10% and 20% improved OS). The comparator was the FEC100 regimen alone. The median increased cost per patient treated was calculated at €16,713 to €35,714. The yielding cost per life year saved was between €5,571 and €32,616, depending on survival gain (10% or 20% improvement in OS) and discount rate (0% or 3%) employed. The sensitivity analyses documented survival gain, discount rate, and price of trastuzumab as the major factors influencing the cost-effectiveness ratio. This economic evaluation supports the cost effectiveness of Herceptin in the adjuvant setting in early breast cancer (Norum J and Olsen JA, ASCO06, Abs. 628).

Canadian investigators developed a Markov model to calculate the incremental costs and outcomes of 12 months of adjuvant Herceptin following chemotherapy in a hypothetical cohort of 1,000 women with HEr2+ positive breast cancer over a lifetime. The model consisted of four broad health states, disease-free, local recurrence, distant recurrence, and death. Each survival state was stratified as experienced with or without cardiotoxicity. The baseline rate of recurrence, HR of recurrence, and rate of adverse cardiac events were taken from recent randomized clinical trials. The cost of treatment was based on a previous cost study (Drucker, etal, ASCO 2006). Costs of local and distant cancer recurrence were derived from the literature, with an adjustment for the cost of palliative Herceptin (Potvin et al, ASCO 2005). Utility weights were taken from the literature.

The model took a direct payer perspective, with costs reported in 2006 Canadian dollars (CDN$). Costs and QALY were both discounted by 3% annually. The primary analysis assumed 5 years of benefit with adjuvant Herceptin therapy and an HR=1.0 during the remainder of the horizon. Per 1,000 treated patients, adjuvant Herceptin was associated with a lifetime gain of 1,267 QALY and an incremental cost of CDN$38.8 million. Lifetime cost utility was CDN$30,630 per QALY gained. Adjuvant Herceptin met a CDN$50,000/QALY threshold at year 17. Cost utility results were particularly sensitive to changes in the analysis horizon and assumptions regarding the long-term HR of adjuvant Herceptin. The researchers concluded that lifetime cost utility of adjuvant Herceptin appears reasonable. However, more clinical follow-up is required to clarify the long-term outcomes of adjuvant Herceptin and confirm these cost utility estimates (Skedgel C, etal, ASCO07, Abs. 6574).

In New Zealand, health authorities have adopted a different tactic. The use of Herceptin, in combination with a taxane, is permitted in the adjuvant setting, but limited to 9 weeks of treatment, rather than the recommended 12 months. High priority funding for Herceptin in early HEr2-positive breast cancer was approved based on the Pharmacology and Therapeutics Advisory Committee's (Pharmac) recommendation of the 9-week regimen, which was based on FinHer trial results (with the combination of Herceptin with docetaxel). Results from the FinHer trial were comparable to those obtained in HERA. There was an 11.7% absolute reduction in disease recurrence at 3 years median follow-up, compared to the control group. The FinHer trial reported no severe heart failure, although its size may not have been sufficient to detect such an effect.

The 9-week regimen was effective in reducing relapse, at a lower overall cost, compared to the 12-month regimen evaluated in other trials. According to New Zealand health authorities, the 9-week regimen is the most cost-effective option. In this regimen, Herceptin is administered concurrently with taxane chemotherapy, and a lower dosage is employed, which may be less cardiotoxic (although more data is needed regarding cardiotoxicity). Funding of the 9-week treatment regimen for all of the 350 eligible women in New Zealand, would cost about $6 million. A group of women who sued Pharmac challenging the 9-week treatment reimbursement guideline, lost their High Court bid in August 2007, but other claims are pending.

In Australia, clinicians have a number of approved options for using Herceptin including long (12 months) and short duration (9 weeks) regimens, concurrently with, or after, chemotherapy.

COMPETITIVE ANALYSIS & NEAR TERM MARKET FORECAST

Worldwide markets for EGFr/HEr2 inhibitors are expected to reach $6,576.40 million in 2007 (Exhibit 7). Sales of Herceptin, Erbitux, and Tarceva are expected to grow by 22.5-25% this year, principally because of growth outside the USA. Moderate adoption rates are forecast in 2007 for the newer market entrants, Vectibix and Tykerb, mostly because of the limited indications for both drugs. Longer-term market forecasts and developmental indications for the commercially available EGFr/HEr2 inhibitors will be addressed in Part IV of this series, which will appear in the next issue of FUTURE ONCOLOGY.

The recent approval and launch of Tykerb marked the first direct competition to Herceptin in the targeted therapies for breast cancer market since its USA introduction in 1998. Because these drugs act at different points in the EGFr pathway, Tykerb is a TKI (of both HEr2 and EGFr), while Herceptin works by extracellular receptor blockade, the rationale for using these agents in combination (along with a cytotoxic drug) is compelling. However, the high prices of these drugs, lack of clinical trial results demonstrating efficacy of such an additive approach, and lack of reimbursement status for the combination (which awaits clinical proof of increased efficacy) means that Tykerb and Herceptin will compete for patients with HEr2-positive breast cancer. In the near term (through 2008), Herceptin is expected to remain dominant, with Tykerb therapy used principally in patients with Herceptin-resistant disease.

The limited approval and reimbursement status of Tykerb and oncologists' preferences and financial interests are major factors that will limit early adoption of Tykerb. Approval of Tykerb in the USA as a second line treatment is very limited compared to the broad approval of Herceptin, in the first line and adjuvant setting in the USA, EU, and other countries. Tykerb's limited approval scope is also expected to negatively impact reimbursement. In addition to limiting reimbursement for non-approved indications, managed care organizations are playing an increasing role in monitoring responses of patients to new agents, such as Tykerb, and requesting discontinuation of treatment in non-responders.

The extensive experience of oncologists with Herceptin and their preferences and financial interests are also critical factors that will limit early acceptance of Tykerb. Oncologists are comfortable with Herceptin because of its long history of clinical success and their experience in its administration. Arguments in favor of IV treatment over oral therapy include much more precise dosing and confirmation of compliance, which is a significant problem with oral cancer treatments. Furthermore (and perhaps most compelling), in-office administration of IV therapies is an important source of income for oncology practices, which would be reduced by switchover to Tykerb. In the longer term, proponents of Tykerb believe the drug's dual HEr2/EGFr target activities will prove more efficacious than Herceptin, and that patients treated with Tykerb may be less likely to develop resistance to treatment because of dual targeting. However, as an antibody, the induction of immune effector cells to kill tumor cells via ADCC by Herceptin may provide an efficacy advantage over Tykerb. Such determinations await more clinical data. Side effects such as rash and diarrhea occur with both drugs.

GlaxoSmithKline is aggressively pursuing clinical trials of Tykerb in combination with Herceptin; 14 ongoing clinical trials are investigating the combination of Herceptin and Tykerb, with ten at least partly sponsored by GlaxoSmithKline. Two of these are phase III trials that are currently recruiting; one is a phase III trial that was scheduled to begin enrollment in July 2007. The other trials are phase I, I/II, or II. Demonstration of increased efficacy of the combination could define a role for Tykerb's clinical use. Demonstration of equivalent efficacies of Tykerb alone, Herceptin alone, and the combination of the two might stimulate use of the lower cost option between Tykerb and Herceptin. Head-to-head comparisons might demonstrate superiority of one of these two treatments, providing rationale for its market dominance. Ongoing marketing, based on current data, and future marketing based on comparative clinical trial results will play critical roles. According to some observers, GlaxoSmithKline has traditionally been less than aggressive in its marketing of oncology products.

In 2007, total WW sales of Herceptin are forecast to grow at approximately 30% over 2006 levels, with growth occurring mostly outside the USA, driven by increased uptake for early stage disease and, in the EU, by the newly approved indication of hormone-receptor positive breast cancer, in combination with hormonal therapy. Tykerb is expected to experience a moderate adoption rate, with use in 2007 and early 2008 occurring principally in the approximately 30% of patients with HEr2-positive breast cancer resistant to Herceptin.

Having reversed a decline in sales after the introduction of Vectibix, Erbitux is forecast to grow by 22.5% this year.

Exhibit 7
Forecast of Global Sales of ErbB-pathway Targeted Agents in 2007

Developer	Drug Designation	Total WW Sales ($ 000)	Change (%)
Genentech ❑ Roche	Herceptin ❑ Trastuzumab	3,917.5	25.0
ImClone Systems ❑ Merck KGaA, Bristol-Myers Squibb	Erbitux ❑ Cetuximab	1,347.5	22.5
OSI Pharmaceuticals ❑ Genentech, Roche	Tarceva ❑ Erlotinib	812.5	25.0
AstraZeneca	Iressa ❑ Gefitinib	248.9	5.0
Amgen	Vectibix ❑ Panitumumab	165.0	—
GlaxoSmithKline	Tykerb ❑ Lapatinib	85.0	—
Total		6,576.40	27.4

Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), August 2007

The aggressive pursuit of new indications by ImClone and Bristol-Myers Squibb, including nsclc for which positive results (but no clinical details) were announced by ImClone in September 2007, will be addressed in the next issue of FUTURE ONCOLOGY.

Tarceva sales, for second line use in nsclc and for pancreatic cancer, have been stable in the USA since late 2006, the second full year the drug was on the market in the USA (and first full year in the EU). OSI believes that the stability was a result of increasing competition in the second and third line setting in nsclc and changing reimbursement policies in the USA that no longer favorably reimbursed IV therapies as in the past (i.e., Medicare reform, Part B). The company also believes, however, that "… economic considerations remain an important factor in influencing choice of therapy in favor of Part B drugs especially in situations where the data may be perceived as equivocal. We believe this situation will adjust over time (as pressure on Part B reimbursement increases) and with the emergence of key new data such as that from the SATURN [nsclc] trial."

Having dropped to less than $9 million in 2006 in the USA, Iressa sales are now forecast to grow by 5.0% in 2007, based almost entirely outside the USA, mostly in Asia.

Although Vectibix achieved $39 million in 4Q06, the quarter in which it was launched, and followed in 1Q07 with $51 million, 2Q07 sales declined because PACCE trial results showed that the combination of Vectibix plus Avastin in colorectal cancer caused increased incidences of diarrhea, dehydration, and infections without improving the 12-week response rate. Although these results were not expected to directly affect sales, they cast a shadow over the prospects of this drug as an early stage treatment for colorectal cancer. On a more positive note, however, the September 2007 conditional approval of Vectibix in the EU may contribute to revenues in late 2007 and beyond.

As indications of approved drugs expand, it is becoming increasingly difficult to anticipate the future. It is possible that strict requirements for patient selection, based on confirmed biomarkers, and approvals for narrow indications with use restricted by reimbursement guidelines to prevent physician choices, may do little to reduce prices but have devastating effects on revenue. Perhaps the era of blockbuster drugs in the oncology sector may be coming to an end, not so much because of competition of generics and biosimilars on price but by the shrinking of eligible patient populations who may be candidates for such treatments. If a 'money-back guarantee' approach, discussed above, is widely applied, manufacturers could lose significant revenues if all patients who may benefit from a drug are treated but most fail to respond. Such a scenario could encourage careful and restricted upfront patient selection, saving everyone concerned the rigors of treatment regimens doomed to fail and unnecessary expenses.

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FUTURE ONCOLOGY

PUBLISHED BY **NEW MEDICINE, INC.**

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SUBSCRIPTION INFORMATION:

- FUTURE ONCOLOGY (ISSN 1082-331X) is published as 12 issues (several double issues) per subscription period, with a free index listing companies/institutions and subjects covered.
- A one-volume subscription to the electronic version is US $840 and to a hard copy version, sent first class to U.S. addresses, is US $1040, and sent air mail to foreign addresses, US $1,100.
- Volumes V3, V4, V5, V6, and V7 are $2,400 (U.S.) and $2,460 (outside the U.S.), either electronic or hard copy versions.
- Volumes V6 and V7 are $1,400 (U.S.) and $1,460 (outside the U.S.).
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