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Preface

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The 21st Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium focused on novel molecularly targeted therapies and the impact that they have had on the treatment of malignancies such as non-small cell lung cancer (NSCLC) and chronic myeloid leukemia (CML) as well as their potential use as angiogenesis inhibitors. Entitled "Novel Therapy against Malfunctioning Molecules," the 2006 Symposium attracted physicians and researchers from all over the world to listen to presentations on the current status and future applications of molecularly targeted therapies and to participate in "Meet the Expert" sessions.

Bruce E. Johnson (Dana-Farber Cancer Institute, Boston) opened the symposium with his keynote address "Impact of *EGFR* mutations on treatment of non-small cell lung cancer." In this presentation, Dr. Johnson discussed the association between the presence of somatic mutations in the epidermal growth factor receptor (*EGFR*) gene in NSCLC patients and dramatically improved responses to treatment with the EGFR-tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib compared with in patients with wild-type *EGFR* in their tumors. Furthermore, specific mutations of the *EGFR* have emerged as predictive markers of resistance to EGFR-TKI therapy. Recently, irreversible EGFR inhibitors have been identified that are effective against cell lines with secondary acquired resistance mutations in the *EGFR* and may be beneficial in patients who relapse after treatment with gefitinib and erlotinib.

The title of the first session was "EGFR Tyrosine Kinase Inhibition as a Strategy for Lung Cancer Therapy." Gefitinib and erlotinib compete with ATP at the ATP-binding site in the tyrosine kinase domain of *EGFR* and were therefore proposed to prevent early signaling cascades responsible for events such as proliferation in various cancer cells. However, phase II clinical trials of EGFR-TKIs showed that only a small subset of patients responded to this therapy. William Pao (Memorial Sloan-Kettering Cancer Center, NY) summarized how a variety of molecular and biological approaches have identified somatic mutations in the tyrosine kinase domain of *EGFR* and *KRAS* genes that are responsible for conferring sensitivity and primary and secondary resistance to these agents, and show promise in defining new molecular subsets of lung cancer that have relevance in the clinic.

Yasushi Yatabe (Aichi Cancer Center, Japan) explained in his presentation how unsupervised hierarchical clustering in expression profiling analyses allows

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molecular classification of tumors based on similarity of genome-wide expression patterns. This has led to the division of lung cancers into two distinct branches that unexpectedly do not segregate small cell lung cancer and NSCLC: one branch includes adenocarcinoma alone while the other includes all four histological subtypes. Furthermore, it has been shown that adenocarcinomas in these two branches are associated with different patterns of involvement of *EGFR* mutation and the impact of smoking. Evidence for differential therapeutic response according to expression profiles of tumors may lead to greater understanding of cancer pathogenesis and better clinical strategies for treatment.

In the third presentation of this session, Shinichi Toyooka (Okayama University, Japan) explained how research into the role of *EGFR* gene mutations in tumor responsiveness to gefitinib and erlotinib has led to the development of a sensitive assay for detecting the major *EGFR* mutations and spotlighted differences in the evolution of *EGFR*- and *KRAS*-mediated tumorigenesis.

Session 2, "Results of Recent Clinical Trials," began with a presentation by Kazuhiko Nakagawa (Kinki University School of Medicine, Japan) outlining the clinical development of EGFR-TKIs in Japan. The IDEAL1 Study revealed that whereas objective tumor response rate was similar to that observed in previous studies at around 20%, population subsets including Japanese people, females, nonsmokers, and those with adenocarcinomatous disease, exhibited especially high drug sensitivity to gefitinib. Further investigation of which patients might benefit the most from EGFR-TKIs led to the discovery that *EGFR* mutations conveying enhanced signaling via EGFR also augment binding affinity of this receptor to gefitinib, thereby increasing its clinical antitumor effects. Dr. Nakagawa also described an ongoing phase III study of combined use of gefitinib with conventional anticancer agents in Japanese patients with NSCLC that is expected to evaluate conclusively the usefulness of this therapy in that population.

Kazuto Nishio (National Cancer Center Research Institute, Japan) presented a survey of *EGFR* mutations discovered in tumor types other than adenocarcinoma of the lung including ovarian and colorectal malignancies and discussed the possibility of the application of EGFR-specific TKIs to the treatment of these tumors. Although this approach seems feasible, its success likely depends on the frequency of such mutations. In this respect, ethnic differences in the frequency of somatic mutations have been revealed that may predict not only clinical response but also toxicity profiles in patients taking EGFR-TKIs.

The third session went by the title "Postoperative Adjuvant Therapy for Lung Cancer." In this session, Yukito Ichinose (National Kyushu Cancer Center, Japan) presented the results of a Japanese phase III placebo-controlled clinical trial of bestatin for the adjuvant treatment of resected stage I NSCLC. Bestatin is a potent aminopeptidase inhibitor with immunostimulant and antitumor effects. Thought to inhibit aminopeptidase *N*, bestatin thereby prevents involvement of this aminopeptidase in tumor cell invasion and angiogenesis. In this study, a total of 402 patients who had undergone complete resection of stage I squamous cell carcinoma were randomly assigned to receive bestatin or placebo for 2 years postoperatively. As a result, 5 year survival in the bestatin and placebo groups was 81 and 74%, respectively ($P = 0.033$). No severe adverse events were detected in either group. Hence bestatin was found to be safe and significantly prolonged survival in this patient population.

Session 4 was entitled "Challenges in Hematologic Malignancies." Neil P. Shah (UCSF School of Medicine, San Fransisco) opened the session with a presentation focusing on compounds targeting Bcr-Abl kinase and its mutant forms in CML. Durable hematologic and cytogenetic responses are achievable in the majority of patients with CML in chronic phase that undergo treatment with the Bcr-Abl kinase inhibitor imatinib. However, many patients progress to accelerated or blast phase CML despite continued therapy with imatinib, possibly due to developing Bcr-Abl kinase point mutation or overexpression. On the other hand, two second-generation Bcr-Abl inhibitors, dasatinib and nilotinib, have been shown to inhibit nearly all imatinib-resistant mutant forms tested preclinically and are undergoing clinical trial evaluation.

New agents to overcome resistance to imatinib were also the topic of the presentation made by Shinya Kimura (Kyoto University Hospital, Japan). Dr. Kimura described the development of NS-187, a potent and selective dual Bcr-Abl/Lyn-TKI resulting from chemical modification of imatinib guided by molecular modeling. NS-187 is 25–55 times more potent than imatinib against wild-type Bcr-Abl in vitro. This agent also inhibited the phosphorylation and growth of all Bcr-Abl mutants tested except T315I. NS-187 was additionally shown to inhibit Lyn, which might be involved in imatinib resistance, and does not target Scr kinase, potentially conferring this agent an excellent safety profile. Phase I trials planned in the USA in 2006 will evaluate the safety and efficacy of NS-187 against Philadelphia-positive leukemias.

In his basic lecture, Scott Hammond (University of North Carolina, Chapel Hill) described his studies of

microRNAs (miRNAs), short, noncoding RNAs that posttranscriptionally regulate gene expression. Using microarray technique, Dr. Hammond found that although many miRNAs are downregulated in cancer, several miRNA genes are overexpressed in tumor cell lines and primary tumors. Moreover, tumor cell lines originating from a variety of different tissue sites exhibited similar patterns of expression. Among miRNAs that were highly expressed in cancer cell lines, one cluster encoded in a single primary transcript named chr13ORF25 was commonly noted. This primary transcript was termed OncomiR-1 due to its encoding miRNAs that probably promote cellular events associated with cancer. Studies conducted using transgenic mouse model of Burkitt's lymphoma confirmed that expression of OncomiR-1 in these animals dramatically accelerated the development of lymphoma. Reports of successful miRNA inhibition in the live mouse have raised the possibility of anticancer therapeutics based on miRNA inhibitors.

In the final session entitled "Angiogenesis Inhibition" Yasufumi Sato (Tohoku University, Japan) delivered a presentation on vasohibin. Although blood vessels are normally quiescent tissues in adult humans, they have the capacity to form neo-vessels under certain conditions. For instance, angiogenesis is a key event in various remodeling processes that take place in pathologic conditions such as tumor growth and metastasis. Dr. Sato searched for vascular endothelial growth factor (VEGF)-inducible genes in endothelial cells by cDNA microarray analysis, and found that protein expressed by the human vasohibin gene exhibited antiangiogenic activity in human umbilical vein endothelial cells. Thus vasohibin was proposed as the first endothelium-derived negative feedback regulator of angiogenesis. Vasohibin cDNA transfection into Lewis lung carcinoma (LLC) cells did not alter proliferation of these cells in vitro. LLC cells were then inoculated in mice, and after 8 days it was observed that luminal vessels of tumors were smaller when cells were transfected with vasohibin-producing clones compared with mock-transfectant cells.

We would like to express our gratitude to all the participants in the 21st Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium. We also thank Bristol-Myers Squibb for their continuing generous support for this symposium series.