regated according to the DLBCL subgroup distinction demonstrating that the DLBCL subgroups represent pathogenetically distinct diseases. GCB DLBCL patients have a relatively favorable clinical outcome. However, the DLBCL subgroup distinction did not fully capture the clinical variability of these patients, and therefore clinical data were used to discover individual genes with expression patterns that predicted overall survival. The majority of predictive genes fell into gene expression signatures that reflected the cell of origin, proliferation rate, and the host immune response to the tumor. 17 genes representing these biological features were used to create a multivariate model that divided the patients into quartiles with strikingly distinct 5-year survival rates of 73%, 71%, 34% and 15%. It is critical to improve the cure rates for those DLBCL patients predicted to have a poor response to conventional therapy. Gene expression profiling revealed that ABC DLBCL tumors express genes that are activated by the NF-kB family of transcription factors, and this was not a feature of GCB DLBCLs. ABC DLBCL cell lines had nuclear NF-kB due to constitutive activity of the IkB kinase. Inhibition of the NF-kB pathway was selectively toxic to ABC DLBCL cells, thus defining a new molecular target in the currently refractory subgroup of DLBCLs. Gene expression profiling is also very effective in defining the mechanism of action of oncogenes and tumor suppressors and thus can reveal new targets for therapeutic intervention. Recent results using this approach in the lymphoid malignancies will be presented.

Tuesday 19 November

PLENARY SESSION 1

EGF-receptor targeting – clinical achievements

4

Biology of ErbB/HER receptors

Y. Yarden, *Weizmann Institute of Science, Department of Biological Regulation, Rehovot, Israel*

Cancer arises following stochastic accumulation of several independent mutations in oncogenes and tumor suppressor genes, but inhibition of any single target can potentially reverse the oncogenic process. Unlike conventional therapeutic approaches, targeted therapy is based upon detailed mechanistic understanding of the oncogenic process and its molecular players. Currently, immunotherapies targeting cell surface receptors like HER2/ErbB-2 and the epidermal growth factor receptor (EGFR/ErbB-1) show effectiveness in breast and head and neck cancers, respectively. Likewise, highly specific low molecular weight inhibitors of tyrosine kinases effectively block certain malignancies. The mechanisms underlying these pharmacological strategies will be discussed in the context of a signaling network and the biology of ErbB/HER receptors

5

Update on tyrosine kinase inhibitors

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Over the last few years, an increasing number of small molecules inhibitor of the EGFR TK have entered clinical trials. Though similar in their basic mechanism of action these agents differs with regard to their specificity for members of the EGFR family and the nature of their interaction with the ATP binding pocket of the receptor. Selected examples include ZD1839; OSI-774; EKB-569; CI-1033; GW216 and PKI1-16. In phase I studies these compounds were well tolerated and resulted in dose related diarrhea and cutaneous acneiforme rashes as the most significant toxicities. Pharmacological studies demonstrated adequate oral absorption and the achievement of biologically relevant plasma concentrations. Correlative biological studies showed inhibition of the targeted receptor and related pathways. Subsequent Phase II and III studies explored the efficacy of these agents. Key features of these trials include the use of phase II randomized design to explore the activity and toxicity of different doses and the early launching of randomized phase III studies. In non-comparative trials, objective responses and prolonged stables disease were observed in a substantial number of patients accompanied by improvement of symptoms. Preliminary data from the first large randomized clinical trials with Iressa in NSCLC, however, are negative. A major debate in the disease oriented development of this class is whether or not patients should be selected for disease-oriented studies based on the expression of the receptor. The lack of robust and well standardized methods to assess receptor expression as well as suitable tissues for analysis in most patients led to the predominant conduction of studies in non selected patient populations. While the non-selection of patients appeared appropriate, every effort should be made to collect tumor tissues for retrospective biological studies. In conclusion, a significant number of small molecules inhibitors of the EGFR are currently in clinical development. Although phase II studies showed a substantial number of patients with evidence of antitumor response, the impact of these agents in cancer mortality remains to be determined. Additional clinical and translational studies are needed to fully elucidate the real value of this target and its inhibitors in cancer treatment.

6

Strategies to optimise anti-EGF receptor therapies

J. Baselga, *Vall Hebron University Hospital, Department of Medical Oncology, Barcelona, Spain*

Anti-epidermal growth factor receptor (EGFR) agents including monoclonal antibodies (Mabs) and tyrosine kinase inhibitors have clear, but modest, single-agent antitumor activity in epithelial tumors. A strategy to augment their activity would be to treat tumors that depend on the EGFR pathway. Early data from anti-EGFR Mabs clinical trials have shown that, unlike with anti-erbB2 therapies, higher levels of EGFR expression by immunohistochemistry (IHC) do not predict higher response rates. Therefore, a comprehensive evaluation of EGFR regulating and dependent genes may be required. We are performing pre and post treatment IHC assays to study tumor expression of EGFR ligands and activated EGFR, ERK, PI3K and Akt. The recently reported ability to profile gene expression using fixed paraffin-embedded tissues (FPET) could enable development of new molecular assays to guide selection of patients for anti-EGFR (and other targeted) therapies. We are collaborating with scientists at Genomic Health, Inc. who have developed new validated assays that can quantitate gene expression of up to 400 cancer-related genes from archival tumor blocks. We are exploring in head and neck carcinoma, colon carcinoma, and breast carcinoma the correlation between molecular profiles and other assessments, such as activation of the ERK's by IHC and clinical response to EGFR inhibitor therapy. Archival tumor tissue from 75 patients, including patients treated with anti-EGFR agents, are being assayed for quantitative expression of the HER kinase system, and for more than 160 other genes important in growth, proliferation, signaling, and apoptosis. The following HER kinase system genes are assayed: EGFR, ErbB2, ErbB3, ErbB4, TGFalpha, Amphiregulin, Betacellulin, HB-EGF, MMP9, Erk1, Erk2, STAT1, STAT3, STAT5A, and STAT5B. Initial data on 19 patients with head and neck cancer showed that EGFR and TGFalpha genes were expressed in the tumor tissue in all patients. Of note, there was a large variation in EGFR expression between patients (up to 100-fold) and a smaller variation in TGFalpha expression between patients (up to 15-fold). We will present and discuss the data we have obtained on the correlation between quantitative gene expression and IHC expression. The results from this study will be used to design larger studies required to confirm the clinical utility of these new FPET tumor assays to guide the selection of patients for EGFR-targeted therapy.

7

Epidermal growth factor inhibitors: issues in clinical development

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EGFR is a member of the receptor tyrosine kinase family that includes HER2, HER3, and HER4. When EGFR-related ligands bind the HER receptors, they trigger a network of signaling pathways that may alter cell proliferation, survival, and motility. In cancer cell, hyperactive signaling through EGFR may occur through overproduction of ligands or receptors, or constitutive receptor activation. Such aberrant signaling activates pathways that stimulate many of the properties associated with cancer cells: proliferation, migration, stromal invasion, angiogenesis, and resistance to apoptotic signals. Because of the frequency of abnormalities in EGFR signaling in human cancer and because of the success of agents such as trastuzumab (Herceptin™) for the treatment of breast cancer and imatinib (Gleevec/Glivec™) for chronic myelogenous leukemia and gastrointestinal stromal tumors, which are directed at specific molecular alterations in cancer cell signaling pathways, EGFR is an attractive target for therapeutics development. Strategies to inhibit EGFR signaling include blocking ligand