Scientific Symposium (Mon, 26 Sep, 14:45−16:45)
Joint ESMO-JSMO Scientific Symposium On What Can We Learn From Global Clinical Trials?

326 INVITED

Index: Building a Collaborative Trials Network in India

Abstract not received

327 INVITED

Molecular Based Patient Selection in Global Clinical Trials for Non-Small Cell Lung Cancer

I. Okamoto[1]. [1]*Kinki University School of Medicine, Department of Medical Oncology, Osaka, Japan*

Small-molecule tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR) were the first molecularly targeted agents to become clinically available for the treatment of non-small cell lung cancer (NSCLC). Early clinical trials of EGFR-TKIs with thousands of patients was not biomarker driven, accumulating negative or marginally positive data. However, the discovery of somatic mutations in EGFR and of the association of such mutations with a high response rate to EGFR-TKIs had remodeled our approach for clinical development of EGFR-TKIs. Under the background of high incidence of *EGFR* mutations in Asian NSCLC patients, three Asian landmark phase III trials have now led to the new paradigm of using EGFR-TKIs for first-line treatment of *EGFR*-mutation positive advanced NSCLC.

Another excitement in NSCLC is now *EML4-ALK*, which was discovered by Japanese group led by Prof. Mano. This fusion gene results in dominant oncogenic activity providing very specific therapeutic target. The presence of EML4-ALK in NSCLC is associated with younger onset, never- or light-smoking history and adenocarcinoma with signet cell features, and *EML4-ALK* rearrangement appear to be mutually exclusive of *EGFR* and *KRAS* mutations. The first ALK-targeted therapy tested in the clinic is crizotinib, a small molecule tyrosine kinase inhibitor, which demonstrated marked activity in phase I study for EML4-ALK-positive NSCLC. Although the overall frequency of *EML4-ALK* in the general NSCLC population is pretty low (~5%), the lesson from EGFR-TKIs story led to the design of clinical trial for rapid development of ALK-targeted therapy. There are two ongoing phase III trials comparing crizotinib to standard chemotherapy, and all patients enrolled onto those trials must have advanced NSCLC harboring *ALK* rearrangements as shown by FISH analysis at a central laboratory. Given the rarity of *EML4-ALK* rearrangement in NSCLC, multi-institutional and international collaboration would be essential for conducting these large phase III clinical trials.

The important lessons is that diligent use of molecular targeted agents for molecularly-selected patients could dramatically improve the clinical outcome in advanced NSCLC. The promise of molecular-targeted drugs against these driver gene alterations brings us closer to personalized lung cancer therapy.

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Lessions From Global Clinical Trials for Gastric Cancer − Are They Steps Ahead?

A. Ohtsu[1], T. Doi[1]. [1]*National Cancer Center Hospital East, Gastrointestinal Oncology/Gastroenterology, Kashiwa Chiba, Japan*

There are several disparities in treatment outcomes between Japan and others in the treatment for metastatic gastric cancer (mGC). Overall survival (OS) in the recent several randomized studies as front line treatments in Japan showed longer survival than in the West, while no remarkable differences in progression free survival (PFS) were observed. Longer OS in Japanese trials seems to be caused by longer survival post-progression possibly due to higher rate of receiving second or further line chemotherapy. Recently, two global registration trials (ToGA and AVAGAST) involving Japan have been conducted. Adding trastuzumab to chemotherapy showed significant OS and PFS prolongation in HER2 positive mGC compared with chemotherapy alone, while bevacizumab did not achieve significant OS prolongation despite significant PFS prolongation. There were remarkable regional differences in subset analysis of AVAGAST study: less advantage from bevacizumab were obtained in Asian population than in Europe and pan-American population. These results yield several controversies: whether these differences are caused by differences in biology or medical practice. However, these regional differences were caused not by the differences in bevacizumab arm but by chemotherapy alone arm between the regions. It is evident that establishing biomarker for bevacizumab is mandatory to achieve significant benefit. On the contrary, recent analysis of Japanese subset in ToGA has revealed equivalent hazard ratio for OS and PFS between the two arms to the whole population when adjusted patient background. There are no remarkable differences not only in HER2 biology but in efficacy of trastuzumab between Japanese subset and whole data set.

These two global studies have provided various valuable data in considering regional differences in treatment outcomes. There were remarkable differences in outcomes of subset for non-measurable lesions, which might be caused by less tumour burden in Japanese than others and suggest that it seems desirable to exclude such patients to adjust heterogeneities of gastric cancer in future studies. On-going biology researches in the two global studies analyzed central laboratory with the same methods are providing valuable information for true biological differences between Japanese and other mGC. Further global studies with other targeting agents are underway to achieve further improvement of the outcomes and will clarify true differences in biology and medical practice.

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Industry-Led Global Trials − Do Benefits Outweigh Pitfalls?

Abstract not received

Scientific Symposium (Mon, 26 Sep, 14:45−16:45)
Challenges and Opportunities in the Development of Personalised/Precision Medicine: Perspectives From the Therapeutics and Diagnostics Industries

330 INVITED

The Development of Vemurafenib for BRAF-mutated, Metastatic Melanoma

F. Borellini[1]. [1]*Roche, Global Product Strategy, South San Francisco, USA*

Personalized healthcare, or the delivery of the right care to the right patient at the right time, remains the ultimate goal of the health care professional. In oncology, the tremendous progress in understanding cancer biology at the molecular and genetic level has made it possible to envision cancer treatments tailored to the specific alterations found in a patient's tumour. The development of vemurafenib, a novel, oral agent that selectively targets mutated, oncogenic *BRAF*, and the parallel development of its companion diagnostic for the detection of BRAF V600 mutations in tumour samples highlight both the opportunities and the challenges of personalizing cancer care.

331 INVITED

Strategies, Experiences and Challenges in the Development of Companion Diagnostics

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332 INVITED

Registration-Directed Co-Development of Biomarkers and Therapeutics

R. Buller[1], H. Sakul[1], K. Wilner[2], N. Selaru[3], I. Taylor[4], S. Ho[1], E. Donnelly[5]. [1]*Pfizer Inc., Translational Oncology, San Diego,* [2]*Pfizer Inc., Oncology Clinical Development, San Diego,* [3]*Pfizer Inc., Oncology Clinical Development Biostatistics, San Diego,* [4]*Pfizer Inc., Translational Oncology, Groton,* [5]*Pfizer Inc., Regulatory Strategy Oncology, Groton, USA*

Pharmaceutical development is passing into an era where drug developers are not just talking about precision medicine and patient selection strategies, but actually implementing pivotal trials which are designed around the prospective development of a drug with an associated companion diagnostic (CDx) test. Examples include programs targeting BRAF, EGFR, MEK, MET, and ALK. This overview of CDx/therapeutic agent co-development will highlight some of the critical path issues of the co-development process, drawing upon the ongoing Pfizer experience of crizotinib treatment of patients with ALK-positive NSCLC.

Ideally, CDx development considerations begin well before a drug candidate is selected. Practically, the relevant patient selection biomarker which will eventually be converted into a CDx may not emerge until well into Phase 2 development or even just prior to Phase 3. Key assay performance issues such as reproducibility and portability may need to be supplemented with bridging studies to demonstrate concordance between early assay versions and the clinical use assay for simultaneous regulatory approval of the drug and the CDx.