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

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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.

328 INVITED

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

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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.

329 INVITED

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

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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

Abstract not received

332 INVITED

Registration-Directed Co-Development of Biomarkers and Therapeutics

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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.

Multiple factors beyond the selection of a diagnostic development partner impact the drug, diagnostic co-development process. These include *epidemiological factors*, such as biomarker prevalence and prognostic significance; *operational* factors, such as development of sufficiently broad informed consent design for screening and CDx development purposes, country specific regulations for handling tissue or DNA samples, and recruitment of biomarker negative individuals for treatment with study drug; as well as *technical* factors, such as the types of samples to be analyzed (e.g. surgical resections, cytological specimens, plasma), global differences in tissue handling and interpretation of results obtained from an FDA approved platform. However, the co-development process does not end with approval of the CDx and drug. What happens with existing laboratory developed tests already in the marketplace − but perhaps designed for use in annotative testing rather than patient selection-quality clinical tests?
A significant, non-incremental, treatment benefit of the drug under development can be a powerful driver for regulatory interactions as well as investigator interest and patient enthusiasm. Crizotinib, being developed for the treatment of ALK-positive NSCLC, has provided a tremendous opportunity to put into clinical and regulatory practice the process of simultaneous submission of therapeutic and diagnostic regulatory packages relating CDx performance with clinical efficacy.

Scientific Symposium (Mon, 26 Sep, 14:45−16:45) **Joint ECCO, EASD and EASO Session On Diabetes, Obesity and Cancer**

333 INVITED

Obesity, Diabetes, Treatments for Diabetes and Their Effect on Cancer Incidence and Mortality − an Overview

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The association between type 2 diabetes and some types of cancer is well established and the complexity of this association is receiving increasing recognition. Many factors influence the risk of both diabetes and cancer including age, sex, ethnicity, socioeconomic status, obesity/insulin resistance, diet (including alcohol intake), physical activity levels and smoking history. The presence of diabetes may influence the uptake of cancer screening. Diabetes treatments may influence the risk of cancer independently of their effect on glycaemia and complicate investigation of the association between diabetes and cancer. Both observational and experimental study designs have a place in investigating the association between treatment of diabetes and cancer but both approaches also have limitations. The aim of the presentation is to introduce the complexity involved in attempting to clarify the factors that contribute to the associations between obesity, diabetes, hyperglycaemia, diabetes treatment and cancer.

334 INVITED

Are There Early Common Origins of Obesity, Diabetes and Cancer?

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Obesity, diabetes and cancer do have early origins defined as conditions influencing level of risk later in life. Occurrence of obesity early in life is undoubtedly associated with increased risk of later type 2 diabetes and of various cancers (postmenopausal breast, endometrial, colon, kidney, oespohagus). The associations will be illustrated by results of studies based on linkage between large registers of records from the school health examinations and draft board examinations, carried out since 1936 and 1943, respectively, in the Copenhagen area in Denmark, and providing information about early body sizes at birth, during school ages and in young adulthood, and registers including data on hospitalization, diabetes and cancer. Main questions are at what age these associations are established, and especially what the role the prenatal, the prepubertal and the pubertal period have, and if the associations can be considered as consquences of one causal pathway such as that passing through the metabolic syndrome with different effects. Although the answers to these questions may inform the search for early common targets for preventive actions, there are currently no available applicable unified solution.

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Diabetes and the Cancer Patient Pathway

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A number of epidemiologic studies have identified a positive association between type 2 diabetes and cancer incidence and mortality for a variety of cancers. Meta-analyses also found that pre-existing diabetes was associated with increased risk of postoperative mortality and reduced survival after cancer diagnosis.
There are a variety of pathways by which diabetes might influence the risk of mortality in cancer patients: First, previous studies and meta-analyses noted obese and diabetic women were less likely to receive cancer screening, which may lead to advanced stage at cancer diagnosis. Second, patients with diabetes often have other diabetes-related comorbid conditions that may influence clinical decision-making. Some studies found cancer patients with diabetes were treated less aggressively than those without diabetes. Third, previous clinical studies have observed patients with diabetes had increased risks of cancer recurrence and second cancer. Fourth, some studies suggested when cancer occurs in an adult with diabetes, it can divert attention and resources, leading to inadequate diabetes care and increased risk of diabetic complications. However, the findings were not consistent. Finally, diabetes is a well established risk factor for infection-related mortality and cardiovascular disease death.

336 INVITED

Diabetes, Metformin and Clinical Studies in Cancer

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It is increasingly recognized that patients with diabetes have an increased risk of cancer and poorer cancer-related outcomes. Furthermore, emerging evidence suggests that insulin-modifying therapies used to treat diabetes may influence cancer outcomes. Treatment with insulin and insulin secretagogues has been associated with increased cancer incidence and mortality. Conversely, there is growing evidence that metformin, an insulin sensitizer, may play a beneficial role in cancer, both through insulin-dependent and insulin-independent mechanisms. In animal studies, metformin inhibits tumour growth, decreases tumour burden and even prevents tumour development. Insulin, IGF-I and hyperglycemia are known to be growth promoters and are reduced in diabetic patients taking metformin. Hyperinsulinemia has specifically been shown to be an adverse prognostic factor in breast cancer, and metformin treatment in non-diabetic breast cancer patients reduces circulating insulin levels. Metformin also has direct effects on the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathways, which are involved in cellular proliferation. This effect may also contribute to lower cancer incidence and better cancer outcomes.
Observational studies in humans also suggest a protective effect of metformin on cancer-related outcomes. Several large studies have shown that metformin treatment in diabetic patients is associated with a significant reduction in cancer incidence and mortality, when compared to no metformin or to sulphonylurea treatment. Specific reductions in the incidence of breast, pancreatic, and hepatic cancers have been documented with metformin use, while effects on prostate cancer are inconsistent. Metformin may also affect cancer prognosis. One clinical study reported that metformin treatment in breast cancer patients receiving neoadjuvant chemotherapy was associated with significantly higher pathologic complete response rates.
While the data for metformin and cancer are promising, the interpretation of these findings is difficult due to the observational nature of these studies. It is still unclear to what extent metformin is truly protective or whether the apparent benefit is relative to the potential harmful effects of other, insulin-promoting diabetes treatments. We also do not know whether these benefits will translate into similar effects in non-diabetic patients. There are currently several ongoing randomized controlled trials that will help to resolve these issues. The registered trials are individually studying breast, prostate, pancreatic, and other cancers, and involve both patients with early and advanced stages of disease. Most of the trials are being conducted in non-diabetic patients. The results of these trials will help to elucidate the true impact of metformin on specific cancers and among the non-diabetic population.