that were only involved if necessary were radiation oncologists (7); surgeons (6) and medical oncologists (6) or nurses (5). Besides medical professionals, specialists that were always involved were communication specialists (3); statisticians (2), social science specialists (2) and clinical epidemiologists (2); and health economic specialists (1) and informaticians (1). Disciplines that were involved only if necessary were health economics (9); clinical epidemiology (8) and statistics (8); communication (6) and informatics or library sciences (6); and social sciences (5).
Patient involvement was by participation in the development group (5); review by representatives of patient organizations (5); survey of patients views and preferences (4) and in 38% of guideline development patients were not involved.
Many oncology organisations are involved in the development of guidelines. These guidelines cover the multidisciplinary and interdisciplinary approach of cancer patients. However, the systematic involvement (always involved) of oncology specialities such as medical oncologists, radiation oncologists, surgeons and nurses in guideline development groups is only 38%. Similar percentage are observed for patient involvement. In future, it is important that all cancer disciplines developing guidelines should reach a consensus which disciplines and should contribute to cancer guideline development and how patient organisations can be involved.

Special Session (Sun, 25 Sep, 15:00−16:00)
Novel Targeted Therapies for Metastatic Non-Small Cell Lung Cancer

186 INVITED

ALK Inhibitors in Lung Cancer

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The normal function of the anaplastic lymphoma kinase (ALK) in adult humans is unknown. Oncogenic rearrangements of *ALK*, which place one of several different 5′ fusion partners and their associated promoter region upstream of the 3′ kinase domain of *ALK*, have been described in a number of rare lymphomas and solid tumours. In 2007, a rearrangement of *ALK* resulting in a fusion gene with *EML4* was described in approximately 4% of non-small cell lung cancers (NSCLC). Other, rarer, non-*EML4* fusion partners (*KIF5B* and *TFG*) have also subsequently been described in NSCLC, together potentially accounting for up to 20% of *ALK* gene rearrangements in NSCLC.
Several different methods exist for detecting ALK gene rearrangements − both fluorescence in-situ hybridization (FISH) using break-apart probes and immunohistochemistry (IHC) have the potential to detect rearrangements or aberrant expression (given the low levels of the native protein in most normal tissues), respectively, regardless of the 5′ fusion partner. In contrast, RT-PCR − while potentially offering additional information on the exact fusion partner and site of the relevant gene breakpoints requires the fusion partner to be known. Each technique has its pros and cons and is in a different state of development. FISH is the current gold-standard having been used as the entry criterion for all of the clinical trials of crizotinib (the furthest advanced ALK inhibitor to date).
Crizotinib (PF-02341066) is an orally bioavailable small molecule inhibitor of both ALK and MET. In the phase I trial of crizotinib, following determination of the recommended phase II dose and schedule (250 mg BID po) in an all-comers advanced cancer population, specific patient groups were prescreened for evidence of either ALK or MET activation with efficacy then explored within these different molecularly defined cohorts. Following the discovery of *ALK* rearrangements in NSCLC, an additional ALK positive NSCLC cohort was added to the trial. Although case reports of crizotinib's efficacy have been presented for both an *ALK* rearranged inflammatory myofibroblastic tumour and a *MET* gene amplified NSCLC, most data are available from the *ALK* rearranged NSCLC cohort. The objective response rate to crizotinib in this population is approximately 60% regardless of age, sex, performance status and line of therapy. Responses are often rapid and may be dramatic. The median progression free survival in this population is approximately 10 months. Side-effects are predominantly restricted to the gastro-intestinal and visual systems and are generally mild − although rare severe transaminitis and neutropenia have been reported. Crizotinib was submitted for accelerated approval to the FDA in early 2011. Results are awaited. Mechanisms of resistance to crizotinib include probable pharmacokinetic failure in sanctuary sites (CNS), proven gate-keeper mutations and the potential for the selection of as yet undescribed second-drivers. Multiple other ALK inhibitors and other agents targeting ALK gene rearranged cancers are now entering clinical trials.

187 INVITED

IGF1R Inhibitors

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The insulin-like growth factor (IGF) system plays an important role in a variety of physiologic processes and in diseases such as cancer. Insulin-like growth factor (IGF) signaling is essential for cell survival, proliferation, and development, and plays a key role in tumour progression. The IGF system comprises the ligands IGF-1 and IGF-2, the IGF binding proteins (IGFBPs) 1−6, and the receptors IGF-IR and IGF-2R. IGF-IR is activated by IGF-1 and IGF-2, while IGF-2R binds IGF-2 only. Overexpression of IGF-IR and mutation of IGF-2R have been described in NSCLC. Furthermore, studies have suggested a correlation between high levels of circulating IGF-1/low levels of IGFBP3 and the incidence and severity of NSCLC. IGF-1R expression is higher in squamous cell carcinoma than in other histological subtypes, and seems to confer some adverse prognosis in the adjuvant and advanced disease setting.
Due to the potential relevance of this pathway many research groups and pharmaceutical companies have developed IGF pathway inhibitors: monoclonal antibodies directed to the external domain or tirosine kinase inhibitors. Preclinical experiments showed that these inhibitors exhibited antitumour activity in cultured lines and human xenografts in mice. In addition they showed synergistic or additive effects in combination with chemotherapy or other targeted agents, such EGFR TKIs or mTor inhibitors. Initial clinical trials showed these agents are usually well tolerated as monotherapy or in combination, and hyperglycemia (GH mediated) was descibed as a class effect. Early studies suggested activity in Ewing and some other sarcoma, adrenal carcinomas, breast tumours and lung cancer. Unfortunately, the encouraging results of a phase II trial in NSCLC comparing carboplatin plus paclitaxel with or without figitumumab were not further validated in two randomized phase III trials of the anti IGF-1R in combination with paclitaxel/carboplatin or erlotinib. Preliminary biomarker trial suggested a role for serum IGF-1 (total or free) as a potential predictor of toxicity and efficaccy asociated with the treatment. We believe the available data further support the study of this class of agents in lung cancer, including NSCLC, with a particular focus on biomarker validation and targeted combination (mTor inhibitors, PI3k inhibitors, etc.).

188 INVITED

Novel Molecular Targeted Agents in NSCLC (Beyond EGFR, ALK and IGFR1)

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NSCLC is currently being revisited on the basis of modern molecular portraits that allow the identification of new molecular subtypes.

Molecular alteration	Frequency in adenocarcinoma	Frequency in squamous cell carcinoma	Potential drugs
EGFR mutation	10−40%	2−5%	Gefitinib Erlotinib Afatinib PF-00299804
EML4-ALK translocation	5−7%	Rare	Crizotinib New ALK-inhibitors HSP90 inhibitors
HER2 mutation or amplification	2% 6%	Rare 2%	Trastuzumab Lapatinib PF-00299804 Afatinib
PI3K mutation or amplification	5% <10%	5% <10%	GDC-0941 XL-147 XL-765 PX-866 BEZ-235 BKM120 PF-05212384
MET amplification	<10%	<10%	XL184 ARQ917 MetMab
RAS mutation	10−30%	5%	Sorafenib
RAF mutation	3%	2%	AZD6244; GSK1120212; AS703026; RO4987655
FGFR1 amplification	5%	20%	BJG398 AZD4547 TKI258

Large scale studies have identified frequent mutations mainly in TP53, RB1, CDKN2A, and STK11 tumour suppressors and in EGFR, KRAS and