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

NRAS oncogenes. Many other molecular abnormalities have been reported in other genes such as PI3K, PTEN, AKT1, MDM2, APC, HER2, KDR, MET, CTNNB1, ATM, BRAF, AKT1 and more recently ALK as well as FGFR1. Of note FGFR1 amplification has been reported in up to 20% of squamous cell carcinoma and 5% of adenocarcinomas.
Beyond the now classical oncogene-drivers represented by EGFR mutation and ALK translocation, many other molecular abnormalities could be used for selection of specific therapies such as amplification of HER2 and FGFR1; or activating mutations of HER2, HER3, HER4, FGFR2, KDR. . . Nevertheless the correlations between the presence of such abnormalities and clinical response are still not firmly documented, although some interesting case reports have been reported. The table below provides a summary of specific alterations, their frequencies and their potential corresponding molecular targeted interventions. DNA repair markers are also potential predictors of standard anti-cancer therapies (ERCC1, MSH2, BRCA1, PARP).

Scientific Symposium (Sun, 25 Sep, 14:45−16:45) **Improved Pain Control Through a Collaborative Approach Between Oncology, Pain and Palliative Care Specialists**

189 INVITED

How to Improve Cancer Pain Control Through European Guidelines for Opioid Treatment and Cancer Pain Diagnosis

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The principle for optimal cancer pain control with primary focus on the use of opioids was published as a second edition by WHO in 1996. The analgesic ladder concept, in which the choice of analgesics is determined by the severity of the pain, is the central idea behind the opioid guidelines. Despite the global impact of the WHO guidelines, 50% of cancer patients with pain are not adequately treated. Barriers to optimal pain control may be linked to 1) insufficient knowledge about the pathophysiology of cancer pain, 2) inferior assessment and classification of cancer pain, 3) sub-optimal treatment, and 4) inadequate implementation of evidence-based knowledge into clinical practice. An updated version of the European Association for Palliative Care (EAPC) guidelines were published in 2001. The guidelines have been criticized for the non-systematic approach in the development, and incomplete review of available literature. Therefore a rigorous evidence-based methodology and a wide international development process was initiated, and in 2011 the Evidence-based Guidelines for the use of Opioid Analgesics in the Treatment of Cancer Pain: the 2011 EAPC Recommendations are emerging. The present version of the EAPC guidelines contain substantial novelties, also in content. One relevant change regards the content of recommendation 2, which modifies the original role of oral morphine as a first step-three opioid. This recommendation values the available evidence from studies with other opioids (hydromorphine and oxycodone), but also acknowledges the lack of evidence supporting the description of first choice for any of these drugs.

190 INVITED

Chemotherapy Including Modern Targeted Therapies to Prevent and to Treat Cancer Pain

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Despite decades of research the evidence that palliative chemotherapy prevents or relives cancer pain is very limited. Although it is widely held that tumour shrinkage is generally associated with relief of pain there is a profound paucity of data concerning the analgesic benefits of cytotoxic chemotherapy and biological therapies. Direct evidence of analgesic benefit is restricted to a very small number of trials mainly in pancreatic cancer and prostate cancer. Bone modifying agents such as bishosphonates and denusumab have, overall, shown only limited analgesic effects and there major benefits have been related to the prevention of painful bone related events. This presentation will review existing data and propose that pain related data be collected in amore systematic manner in clinical trials, particularly among patents with advanced cancers.

191 INVITED

What is the Place for an Effect of Surgery to Prevent And/or to Treat Cancer Pain

B. Axelsson[1]. [1]*Mid Sweden University, Department of General Surgery, Östersund, Sweden*

The paradox when considering surgery to prevent/treat cancer pain is of course that surgery itself causes pain. Post-operative pain usually subsides within 1−2 weeks but sometimes can be longlasting which has been emphasized in a review by Perkins and Kehlet. They concluded that long lasting post-operative pain has an incidence of up to 50% or more in studies of breast surgery, thoracotomy, and amputations.
Besides pain, surgery is inevitably connected with other types of morbidity and even mortality. This makes the decision when to make use of surgery indeed challenging. A conscious calculation of pros and cons has to conclude that the advantages dominate. If the realistic goal of care is cure, radical surgery is the main option in many cancer diseases. The meticulous use of skin incisions and tissue friendly dissection techniques that minimizes the risk of nerve injuries are known to decrease the frequency of post-operative neuropathic pain.
In a palliative context performance status, length of survival, chance of effect, risk of complications, time to recovery, and patient's acceptance of the proposed surgical intervention are factors to be included in the decision making process. When estimated survival prognosis is less than a couple of months large surgery is, in principle, contraindicated. Minimal invasive techniques may still be justifiable if the non-surgical treatment alternatives have failed or are likely to have little or no effect.
Stabilizing orthopedic surgery for painful skeletal metastases, stenting, by-passing or venting procedures for mechanical obstructions of bowel, bile or urinary tracts, limb amputation in selected cases of sarcoma or melanoma, neuroablative or neurostimulatory procedures, implantation of neuropharmacologic delivery systems are examples of surgical procedures that can increase pain relief. Meticulous patient selection and timing is of outmost importance to succeed.

192 INVITED

What is the Place and Effect of Radiotherapy and What is the Optimal Schedule for Cancer Pain

P.J. Hoskin[1]. [1]*Mount Vernon Hospital, Cancer Centre, Northwood Middlesex, United Kingdom*

The place for radiotherapy in cancer pain, is any situation where pain can be related to a mass effect or infiltration of a local tumour. The mechanism of pain may be complex and radiotherapy may affect not only the tumour bulk itself, causing extensive cell death but also the release of nociceptive cytokines and nerve conduction. It is therefore active both in visceral, musculoskeletal and neuropathic pain.
Pain relief after radiotherapy is generally good with both high response rates and durable response seen. As an example, metastatic bone pain will respond in 70 to 80% of patients with a durable response for many months often spanning the remaining life expectancy of the patient. Similar response is seen with bone related neuropathic pain, pain from non small cell lung cancer (NSCLC) and from progressive liver metastases.
The optimal schedule for cancer pain in the palliative setting is the lowest amount of radiotherapy which is compatible with effuicacy. As a basic principle if this can be achieved with a single dose of radiation this will be the optimal schedule.
There is good level 1 evidence to support this policy in metastatic bone pain, neuropathic pain, and NSCLC. Short fractionated schedules delivering 5 to 10 treatments may be preferred in some settings, for example in brain metastases, where there may be impending spinal canal compression or pathological fracture from painful bone metastases and in NSCLC patients who have good performance status and limited metastatic disease.
In summary, radiotherapy is the most effective treatment for cancer pain in many settings where the mechanism of pain is due to direct tumour growth with 70% or so of patients having durable response from low dose treatment often requiring a single exposure of radiation.

193 INVITED

A Future Research Agenda to Improve Pain Control Through Collaborative Efforts

D. Büche[1]. [1]*Kantonsspital St. Gallen, Palliativzentrum, St. Gallen, Switzerland*

Many of the cancer patients suffer from pain during their illness. Mostly the analgesia follows the WHO ladder approach. For severe pain we use