The proof of concept of pharmacogenetics, namely that drug response is a heritable trait, is accepted. However, despite emerging evidence, pharmacogenetic testing has not yet found its way to routine patient care. Replication of earlier findings and validation in prospective trials are required to establish clinical value and cost-effectiveness of pharmacogenetic testing in oncology. Moreover, pharmacogenetics will increasingly be used in discovery and development of future anticancer drugs.

Advocacy Session (Tue, 22 Sep, 13:00–14:30)
Cancer in the workplace

134 INVITED

EU Plan for a safer workplace: the Community Strategy on Health and Safety at Work 2007–2012

F.J. Alvarez Hidalgo[1]. [1]*European Commission, Unit "Health Safety and Hygiene at Work", Luxembourg, Luxembourg*

Thanks to the adoption and application in recent decades of a large body of Community laws on the protection of the health and safety of workers at work, it has been possible to improve working conditions in the EU Member States and make considerable process in reducing the incidence of work-related accidents and illnesses.
The most recent data available show that, during the period of the previous Community strategy 2002–2006, the rate of fatal accidents at work fell by 17% while the rate of workplace accidents leading to absences of more than three days fell by 20%.
In spite of the progress achieved, the number of accidents at work and the incidence of occupational illnesses are still too high. This situation takes a heavy human toll in terms of the suffering endured by workers and their families, but also generates considerable economic repercussions which have an impact on business competitiveness and productivity.
It is therefore important to pursue a joint action strategy in this area at national and Community level determining the objectives and priorities which must be targeted in order to achieve the change in attitudes needed if regulatory provisions are to be applied effectively; this strategy should be accompanied by measures to provide information and training as well as technical assistance to SMEs and to promote a healthy working environment.
An ongoing, sustainable and uniform reduction in accidents at work and occupational illnesses continues to be the prime objective of the Community strategy for the period 2007–2012, adopted by the European Commission the 21 February 2007. In the Commission's view, the overall objective during this period should be to reduce the incidence of accidents in the EU by 25%.
In order to achieve this ambitious goal, the following main objectives are contained in the new Community Strategy:
- guarantee the proper implementation of EU legislation;
- support SMEs in the implementation of the legislation in force;
- adapt the legal framework to changes in the workplace and simplify it;
- promote the development and implementation of national strategies;
- encourage changes in the behaviour of workers and encourage their employers to adopt health-focused approaches;
- develop methods for identifying and evaluating new potential risks;
- improve the tracking of progress;
- promote health and safety at international level.

136 INVITED

Working with cancer – how to benefit from staying in employment

P. Litchfield[1]. [1]*BT Group plc, Chief Medical Officer, London, United Kingdom*

The European population is ageing at the same time as working lives are being extended. The early detection of cancers is improving as is the effectiveness of treatment. The consequence of these long term trends is that more people in work are developing cancer and more employees are surviving to continue their careers. Employers therefore need to give greater consideration to cancer as a workplace health issue and how to improve the effectiveness of their policies, procedures and practices in managing people who become ill. The moral case for supporting people who develop cancer to remain in work is underpinned by increasing legislative requirements and the prohibitive costs of medical retirement.
In many societies cancer remains a taboo subject which is rarely spoken about. Consequently knowledge of the effects on people of cancer and its treatment is not well understood by the general population. The great majority of healthcare professionals are poorly informed about the nature of work outside their own industry and are rarely skilled at assessing functional capability. Neither patient nor practitioner may see work as an important outcome measure of cancer treatment although it is now well established that work can have positive health effects and that unemployment is significantly detrimental. Educating the various stakeholders is therefore an essential precursor to improving employment rates of those with cancer.
Overcoming the barriers to remaining in employment during and after treatment for cancer can appear daunting but, in practice, is usually straightforward. The majority of adjustments required are attitudinal and administrative rather than physical and therefore requiring capital expenditure. Recognising the nature of common problems, such as fatigue, allows managers to apply common sense in adjusting work load and time without having to rely overly on professional guidance which introduces delay and expense. Making time to listen and having access to guidance on what (or what not) to say are simple measures that can be applied universally and which make a huge difference. Returning to work can be a stressful time for both patient and manager but realistic planning can diffuse much of the stress and greatly improve the chances of success. After initial rehabilitation most people need few if any adjustments and reminding managers of the effectiveness of modern treatment when they are considering the recruitment or promotion of cancer survivors may be necessary.
The key to staying in employment with cancer is strong partnership working between the individual concerned and their manager. Patients need to be honest and open about their capability and managers need to listen and avoid making assumptions – both need to be realistic. Third parties such as family, treating clinicians and occupational health professionals should ensure that the wants and needs of the cancer sufferer remain paramount, within the constraints of what is practicable, and resist being either overprotective or cavalier with their advice.

Scientific Symposium (Tue, 22 Sep, 14:45–16:45)
Targeted therapy in breast cancer

137 INVITED

Optimising anti-HER2 therapy in early breast cancer

M. Piccart[1], P. Bedard[2], E. de Azambuja[3]. [1]*Institute Jules Bordet – BIG aisbl, Medicine Department, Brussels, Belgium;* [2]*Institute Jules Bordet – BIG aisbl, Medicine, Brussels, Belgium;* [3]*Institute Jules Bordet, Breast, Brussels, Belgium*

Results are now available from six trials randomizing more than 13,000 women with HER-2 positive early breast cancer to trastuzumab versus non-trastuzumab based adjuvant chemotherapy. Aside from the negative PACS 04 trial (528 HER-2 positive patients only), these studies demonstrate remarkably consistent results: the addition of trastuzumab significantly reduces recurrence by approximately 50% and improves overall survival by 30% irrespective of tumour size, nodal status, schedule of administration, and type of chemotherapy. Nevertheless, there remain many unanswered questions regarding optimal adjuvant trastuzumab, such as: i) the relationship between trastuzumab efficacy and markers of HER2 assessment (HER2 protein expression, gene copy number, and chromosome 17 polysomy), topoisomerase II co-amplification, c-MYC and PTEN; ii) the selection of patients for non-anthracycline based chemotherapy; iii) the decision to administer trastuzumab in a sequential or concurrent manner with chemotherapy; iv) the minimal effective duration of trastuzumab and v) the treatment of small (<1 cm) node-negative HER-2 positive tumours. Longer follow-up from the adjuvant trastuzumab trials suggests that trastuzumab-induced cardiac toxicity may be time-limited and reversible with discontinuation of trastuzumab and the introduction of cardiac medications. However, longer follow-up is required to further confirm this hypothesis. Future studies with promising novel anti-HER2 agents, such as the ongoing ALTTO trial with lapatinib, will use cutting edge technologies to prospectively identify biomarkers for rational tailing of anti-HER-2 targeted therapy.

138 INVITED

Anti-HER2 therapy treatment after progression

G. von Minckwitz[1]. [1]*German Breast Group, GBG Forschungs GmbH, Neu-Isenburg, Germany*

Treatment with anti-Her2 agents, especially trastuzumab, has been proven in vitro and clinically to be highly synergistic in combination with various cytotoxic and endocrine agents. Blocking of the down-stream proliferation signal of the HER2 receptor, either by binding of an antibody to the external domain or of an tyrosine-kinase inhibitor to the intracellular ATP binding site of this receptor is considered as the main mechanism of action. Further mechanisms under discussion are the prevention of the cleavage of the

external domain, leading to the more active truncated p95 form of the HER2 receptor or the inhibition of HER2 receptor mediated neo-angiogenesis. Only recently, antibody-dependent cellular cytotoxicity (ADCC) has raised significant interest as it might explain the activity of trastuzumab beyond progression (TBP). By binding via immunoglobulin fragment C receptor (FCGR) the to the HER2 receptor, trastuzumab attracts natural killer cells, which become activated and release substances that perforate the tumor cell and promote tumor cell death in concert with a new cytotoxic or targeted agent. Polymorphisms of the FCGR was found to correlate with different levels of activity of trastuzumab which supports this concept.
The GBG26 trial has demonstrated that TBP works clinically. 156 patients that were progressing during trastuzumab treatment received further chemotherapy with capecitabine alone or together with continuing trastuzumab. A significant increase in response and clinical benefit rate, a significant prolongation of time to progression and a trend towards longer overall survival was observed for those patients continuing trastuzumab. The combination of trastuzumab and capecitabine increased only the rate of anemia, but no other toxicity was more frequent compared to capecitabine alone. This result is supported by various retrospective observational studies. Again treatment beyond progression was superior, sometimes even led to significant differences in overall survival compared to patients continuing TBP. However, there was always uncertainty in these observational studies, why trastuzumab was continued or not.
Further prospective trials are supporting this concept. The EGF 100151 trial investigated lapatinib in a similar setting. 399 patients received capecitabine with or without lapatinib resulting in a significant increase in response rate and progression-free survival. Especially brain metastasis appeared less frequent in the combination treatment. The lapatinib combination was associated with more diarrhea and skin reactions. The EGF104900 study explored treatment with lapatinib with or without trastuzumab in heavily and trastuzumab pretreated patients. Again, TBP achieved a longer progression-free survival. A phase II study (BO17929) reported higher efficacy for the combination of trastuzumab and pertuzumab in trastuzumab pre-treated patients compared to a low clinical activity of pertuzumab alone in a preceding study. Currently a head to head comparison of trastuzumab and lapatinib in combination with capecitabine is planned in trastuzumab pre-treated patients.
In conclusion in vivo data and clinical evidence support the concept of TBP, which represents a paradigm shift in oncology, where usually all treatments are discontinued in the event of tumor progression. A continues blockade of HER2 throughout all stages of breast cancer has therefore to be considered.

139 INVITED

Antiangiogenic drugs – quo vadis?

D. Miles[1]. [1]*Mount Vernon Hospital, Middlesex, United Kingdom*

Angiogenesis has been deemed an attractive target for the potential treatment of cancer for several decades. Following the biological definition and molecular identification of vascular endothelial growth factor (VEGF), agents targeting this ligand and its receptor have been developed and resulted in improvements in progression-free and/or overall survival in several tumour types. Though proof of principle has been demonstrated, the therapeutic effects are moderate.
Efforts to identify predictive markers to improve the therapeutic index and thereby the practical feasibility of this approach, remain a challenge. Levels of receptor, ligand, or polymorhisms of the same have not clearly defined the utility of VEGF targeted therapy and continuing efforts directed at expression arrays and functional imaging are subjects of intensive research.
Angiogenesis is a complex, multi-factorial process and further improvements in efficacy are likely to require agents targeting multiple pathways in addition to VEGF (e.g. Tie – and Tie-2) though consequent increases in toxicity must be anticipated. Vascular disrupting agents and competitive substrate analogues of nitric oxide synthase are also in clinical development.
The VEGF dependence of 'micrometastatic' disease has recently been raised as an issue following presentation of the results of the C08 trial in colorectal cancer. More prolonged suppression of the 'angiogenic switch' may be required to have a significant, long-term effect on the risk of disease recurrence in the adjuvant setting.

140 INVITED

Combinations of endocrine agents and new targeted drugs: where do we stand ?

N. Harbeck[1]. [1]*University of Cologne, Breast Cancer, Koln, Germany*

Endocrine Therapy, the oldest targeted therapy for the treatment of breast cancer, has been available for more than a century by now. Only recently, other targeted options against growth factor receptors or VEGF have become available for routine clinical use. Mostly, these agents have been developed in combination with a chemotherapy backbone. Yet, the majority of breast cancers is endocrine responsive and combinations with endocrine therapy also have the potential of being less toxic than those with chemotherapy. Moreover, preclinical evidence also suggests that resistance to endocrine therapy may be mediated by growth factor receptors such as EGF-R and HER2. Consequently, combinations of endocrine therapy and HER1 or HER2 have so far been best explored regarding their clinical utility.
In a randomized phase II trial, Osborne et al. (SABCS 2007) showed that combined tamoxifen and gefitinib rendered a slightly better median PFS than tamoxifen alone; this finding was later supported by Christofanilli et al. (ASCO 2008) using anastrozole and gefitinib.
In the phase III Tandem trial (Mackey et al SABCS 2006), patients receiving anastrozole and trastuzumab had a significantly increased median PFS compared to those treated by anastrozole alone (4.8 vs. 2.4 months). Yet, the response to aromatase inhibitor (AI) monotherapy was disappointingly low in this HER2 positive population. Evaluating letrozole and lapatinib vs. letrozole alone, Johnston et al (SABCS 2008) showed a significantly increased median PFS (8.2 vs. 3.0 months) for the combination in a randomized phase III first line trial in HER2 positive disease. No significant difference was seen in HER2 negative disease. Again, the PFS rate in the AI alone arm suggests that endocrine therapy alone may not be sufficiently effective in triple positive disease. Data of the ELECTRA first line trial combining letrozole and trastuzumab are expected at the end of 2009. In the annually updated evidence-based AGO guidelines (www.ago-online.de), the combination of AI + trastuzumab and letrozole + lapatinib are considered as therapy options in HER2 positive disease.
Recently, combinations of endocrine therapy with other targeted agents such as the mTOR inhibitor RAD001 have proven to be effective in the neoadjuvant setting (Baselga et al, SABCS 2007). Unfortunately, there is so far no predictive marker indicating patients who will mostly likely benefit from this therapy. An ongoing GEICAM-GBG trial is currently evaluating letrozole + bevacizumab in the first line setting.
Only recently, combinations of endocrine therapy and targeted agents have become available for clinical use in breast cancer. Yet, so far, therapeutic benefits are mostly modest, and it is still unclear which patients will benefit more from combing a targeted therapy with an endocrine backbone and where a chemotherapy backbone would be most appropriate. Nevertheless, further evaluation of such combinations will be most important given the large percentage of endocrine responsive breast cancer and the favourable safety profile of endocrine therapy.

Scientific Symposium (Tue, 22 Sep, 14:45−16:45)
Locally-advanced rectal cancer

141 INVITED

Rectal cancer staging: which method is optimal?

R. Beets-Tan[1]. [1]*University Hospital of Maastricht, Departments of Radiology and Surgery, Maastricht, The Netherlands*

There is a challenging task for radiologists in helping to improve the therapeutic management of rectal cancer patients. With more tailor made treatment strategies for different risk groups and for the good responders after neoadjuvant treatment there is a growing need for an accurate imaging selection tool.
The pretreatment assessment of local tumor spread includes the determination of the depth of tumor growth in the rectal wall, the circumferential resection margin at TME, the depth of tumor invasion in surrounding pelvic structures, and the nodal status. US, CT and MRI are being used for staging of rectal cancer, each one with its own power and weaknesses.
After preoperative chemoradiation often advanced tumors drastically shrink so the debate now is whether less extensive surgery can be done for the responders or whether even surgery can be omitted in the complete responders. This is only an option if imaging after chemoradiation can accurately select the responders from the non responders and the partial responders from the complete responders.
Learning objectives of the lecture:
1. To understand the evidence in imaging of rectal tumors.
2. To understand what is the best imaging method for rectal cancer staging and restaging.
3. To understand future directions in rectal cancer imaging.