in patients with platinum-sensitive recurrent ovarian cancer who received carboplatin, gemcitabine and placebo or the same cytotoxic chemotherapy supplemented with bevacizumab.
Multiple issues remain to be addressed. With respect to bevacizumab it is not clear if the sole benefit is due to effective maintenance or whether there is a benefit in combination remission induction regimens. If maintenance treatment is the key issue, then should we continue the treatment until progression or stop after a defined period, as in ICON7 and GOG218? It is also not clear whether bevacizumab should be continued beyond progression or if the drug is effective in the recurrent disease setting if patients have had previous exposure to VEGF inhibitors.
Multiple VEGF receptor tyrosine kinase inhibitors are being tested in the first and second line treatment setting and data from those trials are eagerly awaited. Meanwhile, new agents, for instance those that target the Angiopoietin systems, are in late phase development. If the latter trials prove positive and are taken in conjunction with recent data concerning PARP inhibitors in serous ovarian cancer, it is likely that within a few years there may be 2–3 effective maintenance agents in ovarian cancer. This will then generate a further question of whether these new agents should be used in combination or sequentially to maintain response in this disease, mandating the validation of predictive biomarkers for each agent.

379 INVITED

Update on Targeted Therapies in Ovarian Cancer (OC)

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In 2011 relevant data have been made available with the two most extensively studied classes of molecular targeted agents, antiangiogenics and, respectively, PARP inhibitors (PARPi). The results recently reported with bevacizumab, given with chemotherapy at the time of tumour recurrence in patients with platinum sensitive/resistant disease, have raised the question of the optimal schedule and timing of treatment with antiangiogenics in the overall management of OC.
The results achieved with the PARP inhibitor olaparib (AZD2281) given as consolidation in patients with platinum sensitive relapsed high grade serous OC, have confirmed the frequency in this population of a dysfunction of the homologous recombination (HR) repair, and have broadened the clinical application of the compound. Meanwhile new PARPi (iniparib, BSI-201) have been tested in OC, and combinations of PARPi (olaparib, iniparib) with chemotherapy have been developed and evaluated for antitumour activity.
Among the most promising new molecular targeted agents are the small molecule inhibitor of the type1 insulin-like growth factor receptor (IGF-1R) and insulin receptor (IR) OSI-906 and the potent dual MET/VEGF inhibitor cabozantinib (XL184). The clinical results so far achieved, even though limited, indicate new promising pathways to be investigated.
Finally, more recent knowledge of the biological effects and of the pharmacokinetic profile of the modulator of gene transcription trabectedin, one of the active "old" drugs in OC, supports a new line of clinical development targetting inflammatory and proangiogenic factors.

Scientific Symposium (Tue, 27 Sep, 09:00–11:00) **PARP Inhibiting Strategies: From Molecular Mechanisms to Rational Clinical**

380 INVITED

Cellular Responses to DNA Damage: Molecular Insights and New Strategies for Cancer Therapy

Abstract not received

381 INVITED

Preclinical Evaluation of PARP Inhibitors in Mouse Models of Human Breast Cancer

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Background: The induction of synthetic lethality by inhibition of poly(ADP-ribose) polymerases (PARPs) is a promising therapeutic strategy for tumours that are deficient in homology-directed DNA repair, such as BRCA1/2-associated breast or ovarian cancers. Using mouse models in which BRCA1/2-deficient mammary tumours develop, we found a high sensitivity of the tumours to the PARP inhibitor olaparib [1,2], which was confirmed in clinical trials [3,4]. Despite this exciting new therapeutic option, these clinical trials also showed the presence of cases with refractory disease.
Material and Methods: To identify mechanisms that counteract the clinical efficacy of olaparib, we used the *K14cre;Brca1*$^{F5-13/F5-13}$*;p53*$^{F2-10/F2-10}$ mouse model in which mammary tumours develop that highly resemble their human counterpart[5]. We also replaced one *Brca1*$^{F5-13}$ allele by alleles that mimic specific BRCA1 founder mutations.
Results: In our models, we identified 3 different factors that may compromise the success of PARP inhibition in BRCA1-associated cancers.

1. We observed that some founder mutations, like BRCA1^{C61G}, contribute to mammary carcinogenesis in a similar fashion as large intragenic *Brca1* deletions, but the resulting tumours are less sensitive to olaparib.
2. Acquired resistance to olaparib in the mouse mammary tumours is frequently mediated by up-regulation of the drug efflux transporter MDR1/P-glycoprotein[1]. Mice bearing *Mdr1*$^{-/-}$*;Brca1*$^{-/-}$*;p53*$^{-/-}$ tumours showed a prolonged response to olaparib, but eventually also acquired drug resistance.
3. In several olaparib-resistant *Mdr1*$^{-/-}$*;Brca1*$^{-/-}$*;p53*$^{-/-}$ tumours we found a loss of 53BP1 expression, suggesting that partial restoration of homology-directed repair may also underlie resistance.

Conclusions: We think that information derived from realistic preclinical models provides useful information to guide new clinical trials and to optimize the selection of patients that may benefit from PARP inhibitors.

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382 INVITED

Combining PARP Inhibitors With DNA Damaging Agents: Clinical Studies

Abstract not received

383 INVITED

Radiosensitization by PARP Inhibition

Abstract not received

Scientific Symposium (Tue, 27 Sep, 09:00–11:00) **Unravelling Ras PI3 Kinases Targets**

384 INVITED

Targeting of PI3K/AKT and MEK Signaling

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Combined targeting of PI3K/AKT/TOR signaling and MEK signaling is an attractive therapeutic strategy, especially for the treatment of RAS driven cancers. Multiple trials are pursuing this strategy with drugs from either the same company's portfolio (eg Genentech; GSK) or with agents derived from two separate company portfolios. Tolerability and safety appears achievable and preliminary evidence of antitumour activity has been reported. This talk will focus especially on a Phase I trial of the allosteric AKT inhibitor MK2206 and the MEK inhibitor, AZD6244. Antitumour activity in RAS mutant and driven non-small cell lung cancer, low grade ovarian cancer and pancreatic cancer has been reported with this combination. Safety findings, PK-PD evaluation and antitumour activity will be reported.

385 INVITED

The Role of BRAF and KRAS in Melanoma Progression

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The small G-protein NRAS is mutated about 20% of human melanomas and BRAF, a protein kinase that is activated downstream of NRAS, is mutated in another 45% of cases. BRAF inhibitors block BRAF mutant melanoma cell proliferation, but they increase the proliferation of cells that express oncogenic NRAS. We have shown that this is because inhibition of BRAF in the presence of oncogenic RAS drives paradoxical activation of CRAF, a closely related protein kinase that then stimulates pathway activation to drive tumorigenesis. Intriguingly, the BRAF inhibitor

vemurafenib induces cutaneous squamous cell carcinomas (cuSCC) in about 25% of melanoma patients. We find that a high proportion of these tumours express oncogenic RAS and we also show that BRAF inhibitors accelerate formation of cuSCC in mice treated with DMBA and TPA. Critically, MEK inhibitors block the induction of cuSCC by BRAF inhibitors and the established tumours regress following treatment with the anti-proliferative drug 5-FU. Our data suggest that BRAF drugs are not tumour promoters *per se*, but rather that accelerate tumour formation from pre-existing, pre-malignant lesions present in the skin of susceptible patients.

386 INVITED

MEK-RAF Inhibitors

Abstract not received

387 INVITED

PI3K Pathway Inhibitors: What Have we Achieved and Future Directions

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Inappropriate PI3K signaling is one of the most frequent occurrences in human cancer and is critical for tumour progression. Several molecular aberrations have been described affecting key components of this pathway, with implications not only for tumorigenesis but also for resistance to other antineoplastic agents. Examples include genetic mutations and amplifications (*PIK3CA, AKT*) and loss of function of negative regulators of the pathway (PTEN). Emerging preclinical research has significantly advanced our understanding of the PI3K pathway and its complex downstream signalling, interactions and importantly, the crosstalk with other pathways. Rapalogs are the first inhibitors of downstream effectors of the PI3K pathway to enter the clinic, although with limited clinical antitumour activity. The cellular response to mTOR complex (mTORC) 1 inhibition, which upregulates AKT via negative-feedback loop in some cell lines, combined with the discovery of the direct involvement of mTORC 2 in the activation of AKT, have led to development of rationally designed drugs targeting key elements of this pathway. These include: (a) pure pan-PI3K inhibitors, targeting all isoforms of PI3K; (b) dual PI3K/ mTOR inhibitors; (c) AKT inhibitors; (d) mTORC 1 and 2 inhibitors; and (d) isoform-specific PI3K inhibitors, including the alpha isoform activated in *PIK3CA* mutants and the delta isoform upregulated in hematologic neoplasms. Frequent toxicities reported in the first-in-human trials included rash, asthenia, diarrhea, nausea, mucositis, transaminase elevation and hyperglycemia. These agents are still in early phases of clinical development, some already entering phase 1b and 2 trials. Clinical benefit with partial responses and prolonged disease stabilization have been reported in multiple tumour types, such as breast, ovarian, endometrial, prostate, lung, mesotheliomas, sarcomas and lymphomas. Importantly, clinical benefit has not been restricted to patients whose tumour harbor PI3K pathway activation. Preliminary reports of the pharmacodynamic effects of PI3K pathway inhibitors have shown reduction of activation of key pathway readouts in the order of 50 to 90% both in tumour and surrogate tissues (such as pAKT, pPRAS40, pS6K and p4EBP1), giving reassurance that a target is being hit. Other biomarkers of pathway inhibition under investigation include increase in plasma C-peptide levels and reduction of glucose avidity on FDG-PET scans. Recognizing that PI3K pathway operates in complex networks in which the outcomes of pharmacologic modulation may be difficult to predict is of paramount importance. Therefore, the next generation of trials with PI3K pathway inhibitors is focusing in combination strategies, including other targeted therapies (such as anti-HER2 agents and MEK inhibitors) and conventional chemotherapy. Results of these studies are eagerly anticipated.

Scientific Symposium (Tue, 27 Sep, 09:00−11:00)
Head and Neck Cancer in the Elderly Patient

388 INVITED

Management of the Elderly Patient in Head and Neck Cancer

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Squamous-cell carcinoma of the head and neck (SCCHN) represents a heterogenous tumour entity that requires multimodality approaches depending on primary tumour location, clinicopathological stage at diagnosis and patient co-morbidities. As average lifespan is improving, an increasing number of SCCHN patients belong to the "elderly" patient population; Given the fact that many of these patients have a history of heavy smoking and/or alcohol consumption, chronic obstructive pulmonary disease and coronary heart disease, the implementation of therapeutic modalities used for fit patients becomes particularly challenging. The fact that patients older than 70 years of age are rarely included in clinical trials in SCCHN further compromises optimal treatment for this patient group. Compared to their younger counterparts, elderly patients are reported to receive less aggressive treatment and are less likely to be treated with curative intent. However, recent data support the position that the physiological, rather than the chronological age of the patient should guide therapeutic decisions: Locoregional control rates and disease-free survival in elderly patients treated with radiotherapy or chemoradiotherapy, either with curative intent or in the palliative setting, are comparable to those seen in younger patients. Moreover, the implementation of new chemotherapeutic agents, such as the taxanes and the use of molecular targeted agents, including monoclonal antibodies against the Epidermal growth factor receptor (EGFR), provide the clinician with a broad spectrum of treatment choices with diverse toxicity profiles. The improvements that have been accomplished in both surgical procedures, including organ preservation strategies, and radiotherapy delivery, including short hypofractionated techniques, offer to the clinician important tools, especially in the treatment of the more "fragile" elderly patients. Therefore, age alone should not be the main criterion for therapeutic planning: A thorough geriatric assessment should be the first and important step for selecting further treatment options; In patients receiving systemic treatment, chemotherapy doses should be modified according to the renal and hepatic function; Alimentation and nutritional status should be constantly evaluated, especially in patients undergoing radiotherapy in the upper aerodigestive tract. Last but not least, emotional well-being should be a priority for these older patients that suffer from substantial co-morbidities and may require psychological and social support.

389 INVITED

Special Considerations in Surgery for Elderly Patients With Head and Neck Cancer

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The elderly population is growing rapidly and a substantial part of the population is over 70 years in age. In parallel with this increase in advanced age, the incidence of cancer and the risk of multisystem failures are also raising. For a long time surgery had been often withheld for elderly patients. This led to inappropriate treatment when surgery was considered as the best option but rejected by principle considering the patient's age. Due to the advances in anesthetic and surgical techniques as well as in pre and postoperative care, surgery has been increasingly used for this growing segment of the population. There are accumulating and converging reports on the safety of surgery in elderly patients. There is a consensus for considering the preoperative general status instead of the chronological age. On the contrary there is no consensus on the definition of the elderly population that is arbitrarily defined as over 65, over 70 or over 80 in the different publications.

As far as head and neck surgery is concerned the situation is significantly more complex. On one hand head and neck surgery generates less post-operative morbidity than thoracic or abdominal surgery and rarely results in major hemodynamic shift. On the other hand elderly patients with head and neck cancer have accumulated multiorgan failures due to the normal ageing process but also due to their lifestyle (tobacco/alcohol, occupational exposures) as well as nutritional and/or pulmonary consequences induced by tumours growing on the upper aerodigestive tract. This situation is also to be considered in the particular sociocultural context of most of head and neck patients. However notwithstanding these considerations, head and neck cancer surgery is more and more proposed in elderly patients with satisfactory postoperative outcome. More recently major head and neck surgery including lengthy procedures with microvascular free tissue transfer has being reported with comparable surgical complications to a younger population of patients. But all these retrospective studies have been carried out on selected population of patients. The major predictive factors for either local or systemic postoperative complications are obviously linked to the preoperative status of the patients.

In conclusion when surgery is selected as a part of the therapeutic programme for an elderly patient the risk-benefit ration must be approached with caution and in the light of the life expectancy. The anesthesiologic and geriatric evaluations must assess the preoperative performance status and physiological reserve in order to determine whether the patient's condition is compatible with surgery and to anticipate possible postoperative complications requiring adapted preoperative care and perioperative monitoring. The psychological profile and cognitive functions must also be evaluated in particular when mutilating surgery (such as total laryngectomy) is indicated.