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