all advanced cases. It is also expected that as a result of identification of oncogenic addition loops, biomarker-based trial enrichment will be the mainstay to progress in this field towards a more personalized approach. Drugs blocking key drivers will be added to backbone therapies in selected populations to maximize the efficacy and cost-benefit of these otherwise expensive interventions.

373 INVITED

Novel Imaging Techniques and Treatment Assessment for Evaluating Benefit From Targeted Agents

V. Vilgrain[1], M. Zappa[1], O. Bruno[1], S. Faivre[2], E. Raymond[2]. [1]*Université Paris, Service d'Imagerie Médicale, Paris, France;* [2]*Université Paris, Service d'Oncologie, Paris, France*

Sorafenib, a tyrosine kinase inhibitor, has shown clinical efficacy in patients with hepatocellular carcinoma (HCC) and is the standard of care for patients with advanced-stage HCC. Nowadays, many targeted therapies are evaluated in HCC either as sole treatment or in combination with other treatments such as tumour ablation, chemo-embolization, and surgical resection. Therefore, there is a need to assess efficacy of targeted therapy in HCC.
RECIST is the reference method to evaluate treatment efficacy in soild tumours but does not seem appropriate in evaluating targeted therapy as objective responses were seen in very few cases in patients treated with sorafenib or sunitinib.
New criteria have been proposed to evaluate treatment efficacy of non surgical treatments in patients with HCC. The most common ones are the Choi criteria, the EASL criteria, and the modified RECIST criteria. All these criteria mainly focus on internal tumour changes such as appearance of necrosis or disappearance of tumour hypervascularity. Many examples will be shown during the lecture.
Another approach is based on functional imaging and especially perfusion-related imaging. Contrast-enhanced ultrasound, CT perfusion and dynamic contrast-enhanced MR imaging have the capability to assess perfusion changes in patients under treatment. Advantages and disadvantages of these modalities will be discussed.
Last, other functional tools that are not routinely used will be presented.

374 INVITED

Local Therapy for HCC

E. Lartigau[1]. [1]*Centre Oscar Lambret, Radiotherapy Department, Lille, France*

The management of hepatic tumours, is becoming an increasingly significant problem. Hepatocellular carcinoma (HCC) (and colorectal cancer (CRC)) are among the five most common causes of cancer deaths worldwide. The incidence of HCC is increasing, linked with hepatitis B and C. An increase in the incidence of cholangiocarcinoma (CC) has also been reported. For several years, surgical resection has been the standard treatment for HCC. Unfortunately, the majority of patients with hepatobiliary tumours or HCC are inoperable, either because of impaired liver function, central location of the tumour, or comorbid illness. For these patients, other techniques have been developed and evaluated such as liver transplantation, systemic chemotherapy, intra-arterial hepatic chemoembolization, immunotherapy, destruction by radiofrequency, cryotherapy, and laser thermotherapy. Currently, the exact indication for each of these different treatment modalities has not been defined, and there is no standard treatment for inoperable hepatic tumours. Radiotherapy, alone or combined with chemotherapy, has become an additional treatment option.
Stereotactic body radiation therapy (SBRT) for liver disease has been reported with encouraging rates of local control and toxicity. Unfortunately, the published series are heterogeneous for the doses used as well as the number of patients treated, and so do not permit reliable univariate or multivariate analyses. A review of different techniques will be presented.

375 INVITED

Liver Transplantation and Resection for HCC

Abstract not received

Scientific Symposium (Tue, 27 Sep, 09:00–11:00)
From Bench to Bedside in Ovarian Cancer

376 INVITED

New Concepts on the Origins of Ovarian Cancer

J. Prat[1]. [1]*Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona Department of Pathology, Barcelona, Spain*

Epithelial ovarian tumours are heterogeneous neoplasms which are classified according to cell type into serous, mucinous, endometrioid, clear cell, transitional, and squamous cell tumours. Parenthetically, none of these cells are found in the normal ovary and the development of different tumour cells has long been attributed to mullerian "neometaplasia" of the ovarian surface epithelium (mesothelium). More importantly, these tumours are further subdivided into benign, borderline (intermediate), and malignant (carcinoma) depending upon the degree of cell proliferation and nuclear atypia, and the presence or absence of stromal invasion.
Malignant epithelial tumours (carcinomas) are the most common ovarian cancers, accounting for 90% of cases, and are the most lethal gynecological malignancies. Currently, based on light microscopy and molecular genetics, ovarian carcinomas are subdivided into at least five main subtypes: high-grade serous carcinomas (70%), endometrioid carcinomas (10%), clear cell carcinomas (10%), mucinous carcinomas (5%), and low-grade serous carcinomas (<5%) (Table). These tumours account for 98% of ovarian carcinomas, can be reproducibly diagnosed, and are inherently different diseases, as indicated by differences in epidemiological and genetic risk factors, precursor lesions, patterns of spread, molecular events during oncogenesis, response to chemotherapy, and outcome.
Recent evidence suggests that what have been traditionally thought to be primary ovarian cancers actually originate in other pelvic organs and involve the ovary secondarily. In fact, it has been proposed that high-grade serous carcinomas arise from precursor epithelial lesions in the distal fimbriated of the fallopian tube, whereas endometrioid and clear cell carcinomas originate from ovarian endometriosis.

Table: Ovarian carcinoma: clinical and molecular features of the 5 most common subtypes

	HGSC	LGSC	MC	EC	CCC
Risk factors	BRCA1/2	?	?	HNPCC*	?
Precursor lesions	Tubal intraepithelial carcinoma	Serous borderline tumour	cystadenoma/ borderline tumour?	Endometriosis	Endometriosis
Pattern of spread	Very early transcoelomic spread	Transcoelomic spread	Usually confined to ovary	Usually confined to pelvis	Usually confined to pelvis
Molecular abnormalities	BRCA, p53	BRAF, KRAS	KRAS, HER2	PTEN	HNF1
Chemosensitivity	High	Intermediate	Low	High	Low
Prognosis	Poor	Intermediate	Favorable	Favorable	Intermediate

*Hereditary non-polyposis colorectal carcinoma.

377 INVITED

Genomics of Ovarian Cancer – Utility as Predictive Biomarkers

Abstract not received

378 INVITED

New Directions in Angiogenesis Therapy

G.C. Jayson[1]. [1]*Christie Hospital/ University of Manchester, Medical Oncology, Manchester, United Kingdom*

Ovarian cancer accounts for thousands of lives each year and new treatments are needed. Although surgery and chemotherapy are effective cytoreductive strategies, maintenance therapy had proved elusive until recent data on anti-angiogenic agents emerged. Two trials, GOG218 and ICON7, have tested the benefit of adding bevacizumab, an anti-Vascular Endothelial Growth Factor (VEGF) antibody to carboplatin and paclitaxel. The trials demonstrated that in patients with bulk residual FIGO stage III/IV disease, progression free survival (PFS) was increased by approximately 6 months in the experimental arms. Overall survival (OS) data for ICON7, presented recently, reported an 8-month OS advantage in high-risk patients on the experimental arm.
GOG218, which incorporated doses of bevacizumab that were twice those used in ICON7, has not yet reported an OS difference, although mature data are not yet available. The reason for the apparent difference in survival between the two trials is unknown but may be due to the more widespread use of VEGF inhibitors in the control arm after progression in GOG218. Evidence to support the hypothesis that bevacizumab is active in recurrent disease emerged in the recently presented OCEANS trial, which demonstrated that bevacizumab improves PFS by 4 months

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)

C. Sessa[1]. [1]*IOSI -San Giovanni Hospital, Department of Medical Oncology, Bellinzona, Switzerland*

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

S. Rottenberg[1], J.E. Jaspers[1], R. Drost[1], P. Bouwman[1], M.J. O'Connor[2], P. Borst[1], J. Jonkers[1]. [1]*Netherlands Cancer Institute- Antoni van Leeuwenhoek Hospital, Molecular Biology, Amsterdam, The Netherlands;* [2]*AstraZeneca, Aldery Park, Macclesfield, United Kingdom*

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

J.S. de Bono[1]. [1]*Royal Marsden Hospital, Drug Development Unit & Institute of Cancer Research, Sutton, United Kingdom*

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

R. Marais[1]. [1]*Institute of Cancer Research, Signal Transduction Team, London, United Kingdom*

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