Ovaries are very sensitive to cytotoxic treatment, especially to radiation and alkylating agents, which are classified as high risk for gonadal dysfunction. The type and dose of chemotherapeutic agent are known to influence the progression to ovarian failure, with alkylating agents increasing the risk of POF by a factor of 9. Cyclophosphamide is the agent most commonly implicated in causing damage to oocytes and granulosa cells in a dose-dependent manner. This follicular destruction generally results in the loss of both endocrine and reproductive functions, depending on the dose and the age of the patient. Indeed, Larsen *et al*. reported a four-fold increased risk of POF in teenagers treated for cancer, rising to 27-fold in women between 21 and 25 years of age.
Several options are currently available to preserve fertility in cancer patients and allow them to conceive when they have overcome their disease: embryo cryopreservation, oocyte cryopreservation and ovarian tissue cryopreservation. The choice of the most suitable strategy depends on different parameters: the type and timing of chemotherapy, the type of cancer, the patient's age and partner status. The only established method of fertility preservation is embryo cryopreservation, according to the Ethics Committee of the American Society for Reproductive Medicine, but this option requires the patient to be of pubertal age, have a partner or use donor sperm, and be able to undergo a cycle of ovarian stimulation, which is not possible when chemotherapy has to be initiated immediately or when stimulation is contraindicated according to the type of cancer. Cryopreservation of oocytes can be performed in single women who are able to undergo a stimulation cycle, although the effectiveness of this technique is still low, with pregnancy and delivery rates ranging from 1 to 5% per frozen oocyte.
Cryopreservation of ovarian tissue is the only option available for prepubertal girls, and for woman who cannot delay the start of chemotherapy. Ovarian tissue can theoretically be frozen using three different approaches: as fragments of ovarian cortex, as entire ovary with its vascular pedicle or as isolated follicles. The indications for cryopreservation of ovarian tissue in case of malignant and non-malignant disease are summarized in a recent review. For patients who need immediate chemotherapy, ovarian tissue cryopreservation is the only possible alternative.
The main aim of this strategy is to reimplant ovarian cortical tissue into the pelvic cavity (orthotopic site) or a heterotopic site like the forearm or abdominal wall once treatment is completed and the patient is disease-free. To date, we have performed 11 reimplantations of cryopreserved ovarian cortex. All of them have recovered their ovarian function.

47 INVITED

Advances in male fertility preservation

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For post-pubertal males diagnosed with cancer (or any other medical condition where the curative treatment has a high risk of causing subsequent infertility) the technology of sperm banking is now well established. This means that if infertility is subsequently present after medical treatment has finished, the male has the option to use his frozen sperm samples, in association with an appropriate Assisted Reproductive Technology (see below), in order to try and father a child at a later date.
It is estimated that many thousands of men each year across Europe will bank their sperm prior to cancer treatment and may keep it in storage for many years. However, audit data suggests that of these relatively few men (10−20%) actually return to use their samples in assisted conception. This may reflect the fact that in a high proportion of men natural fertility is restored following treatment, or that the initial motivations for banking sperm may not have been for reproductive reasons. Alternatively, it may be that access to assisted conception services (e.g. funding) is too difficult or that the treatments involved are too off-putting.
For those men who do use their frozen sperm, the options in assisted conception include relatively simple treatments such as Intra-uterine insemination (IUI). This is where a prepared sample of sperm is inseminated into his partner's uterus at the most fertile part of her cycle. However, this can only be achieved when the post-thaw quality of sperm is very good and where enough sperm were banked initially to allow several attempts at treatment. Where banked sperm is too poor, or the amount of sperm too limited, more complex assisted conception techniques such as in vitro fertilisation (IVF) or Intra-Cytoplasmic Sperm Injection (ICSI) need to be attempted. Successful births have been reported from sperm samples that have been frozen nearly 30 years and there is no evidence that babies born from the use of frozen sperm are any less healthy than their naturally conceived counterparts.
Sadly, for pre-pubertal boys (or any male who is temporarily azoospermic at the time sperm banking is first attempted) there are currently no proven strategies to protect fertility. Although experimental strategies have been attempted, none have been proven and entered mainstream clinical practice.

Scientific Symposium (Mon, 21 Sep, 16:15−18:15)
Genetic aberrations in lung cancer

48 INVITED

The role of biomarkers in selecting the right targeted agent to combine with chemotherapy

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Several genetic biomarkers have been investigated retrospectively and some prospectively to select patients for single agent treatment. The most successful example is the use of EGFR mutations to select patients to treat with EGFR tyrosine kinase inhibitors, in first line treatment of advanced non-small cell lung cancer (NSCLC). However, when it comes to combination of chemotherapy and a targeted agents, the use of biomakers is less intuitive, because of the potentially confounding markers that make tumors more sensitive to chemotherapy and their interaction with the potential targets of targeted agents. Genetic markers of chemotherapy efficacy has also been investigated, but they have so far not been used extensively for selection of treatment outside clinical trials. Furthermore, for targeted agents such as the angiogenesis inhibitors, there is really no good genetic marker that is well established for patient selection, and combination of chemotherapy and angiogenesis inhibitors has been performed empyrically, with variable results.
Probably the use genetic markers of targeted agents activity when they are combined with chemotherapy, should take into consideration the effect of these markers when the targeted agents are given alone. For instance, it is likely that patients with advanced NSCLC who have an EGFR mutation or an Alk translocation will respond better to combinations of EGFR tyrosine kinase inhibitors or Alk inhibitors, also when combined with chemotherapy. However, the effects of combinations in unselected patients have been so far surprising, in that either no additive effect has been shown or even detrimental effects. So, clearly more efforts should be devoted to investigated markers that would identify patients who benefit, also for combined treatments and these markers may somewhat differ from those that are used for single agent selection.

49 INVITED

Molecular mechanisms of lung cancer development – how to use our knowledge of molecular biology in more effective therapies

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Growth factors and their transmembrane receptors contribute to all phases of tumor progression, from the initial phase of clonal expansion, through angiogenesis to metastasis. A relevant example comprises the epidermal growth factor (EGF) and the respective receptor tyrosine kinase, namely ErbB-1/EGFR, which belongs to a prototype signaling module that drives carcinoma development. The extended module includes two autonomous receptor, EGFR and ErbB-4, and two non-autonomous receptors, namely: a ligand-less oncogenic receptor, HER2/ErbB-2, and a kinase-dead receptor (ErbB-3). This signaling module is richly involved in human cancer and already serves as a target for several cancer drugs. Due to inherent complexity and a large amount of experimental data, we propose a systems approach to understanding ErbB signaling. EGF – to – ErbB signaling is envisioned as a bow-tie configured, evolvable network, sharing modularity, redundancy and control circuits with robust biological and engineered systems.
Along with autocrine loops involving one of the seven ligands of EGFR, and overexpression of EGFR due to amplification of the corresponding genomic locus, mutations within the catalytic tyrosine kinase domain are prevalent in lung cancer, whereas deletions in non-catalytic portions of EGFR are frequently diagnosed in brain tumors of glial origin. Concentrating on catalytic site mutants of EGFR, we found that mutant receptors gain oncogenic activity by evading a universal mechanism of receptor inactivation. This mechanism entails recruitment of an ubiquitin ligase, CBL, to the active receptor, thereby enabling ubiquitinylation and sorting for lysosomal degradation. How exactly EGFR mutants evade CBL and ubiquitinylation remains unknown, but potential mechanisms include enhanced heterodimerization with HER2/ErbB-2 or altered interactions with the HSP90 chaperone. The implications of the mode of oncogenesis of EGFR mutants will be discussed in the context of drug interceptors.