nurses entering the workforce at present over half of the EU nursing workforce are over 45 years of age. As these staff approach retirement there needs to be sufficient numbers of younger recruits to replace them or an encouragement to entice staff to stay within the clinical setting.
The introduction of new therapies and improved survival of those diagnosed with cancer creates a longer term health care provision. The current success means that the numbers of people who have faced cancer is increasing by 2% a year requiring different ways of managing the volume of those who require future follow up, surveillance and after care. Oncology has focused on acute episodic care however these new developments require a shift to chronic illness models. Increasing complexity of treatment delivery requires broad skills from the nursing workforce and higher levels of proficiency and competence. Education is therefore fundamental in relation to increasing skills, keeping those nurses once trained and sustaining continuing professional development needs to be a future priority. Progress in recognising specialist cancer nursing across Europe is imperative for sustaining staff numbers and improving health outcomes. The importance of curriculum frameworks and standards across Europe will help in understanding the competence of cancer nurses. Part of this is through effective knowledge sharing through the exchange of good practice. Questions as to whether we can provide a workforce for future cancer care or what skill sets this workforce will require is important for us all. EONS aims to increase the visibility of the issues facing cancer nursing in the future.

Special Session (Thu, 24 Sep, 11:15−12:15)
Mouse models of cancer

336 INVITED

Identification of cancer genes and their collaborative networks by large-scale mutagenesis in tumour prone mice

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Insertional mutagenesis has proven to be a versatile tool to identify genes whose activation or inactivation can confer a selective advantage to cells in vitro or in vivo. The system has been exploited over the last 25 years successfully in the mouse to identify new oncogenes and tumor suppressor genes. With the availability of the complete mouse genome sequence and reliable PCR techniques this approach has become much more powerful. The insertional mutagenesis screen we performed to accelerate lymphomagenesis in mice illustrates this. Infection of newborn mice with replication-competent Moloney Murine Leukemia Virus gives rise to T and B cell lymphomas. The underlying mechanism is proviral activation of proto-oncogenes and inactivation of tumor suppressor genes. Retroviral insertional mutagenesis in over 1000 tumor-predisposed KO and control mice was performed. The largest specific cohort consisted of p53 and p19Arf KO mice. The resulting dataset with over 500 common insertion sites marking known and unknown proto-oncogenes, tumor suppressor genes, and microRNAs, also identified genotype-specific common insertion sites and highly significant co-occurrence of mutations and hits in tumor suppressor genes. The size of the dataset provided new information that could not have been extracted from smaller datasets collected previously, illustrating the “added value” of performing these studies on a large scale in defined genetic backgrounds. The approach is complementary to and can confirm the cancer-causing nature of genes identified by other approaches such as SNP analysis and high throughput sequencing of cancer genomes. Illustrating examples will be presented.

337 INVITED

Targeting DNA-repair deficiency in mouse models for BRCA-associated breast cancer

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Genetically engineered mouse (GEM) models of human cancer not only permit us to gain a detailed insight into the specific genetic changes that drive tumor initiation and progression [1], but also provide the tools to define the underlying mechanisms of drug response and acquired resistance. Once these processes are understood in sufficient detail it may be possible to design combination therapies that give rise to complete remissions, while at the same time eliminating remnant cells that might elicit recurrent disease.

Women carrying germline mutations in BRCA1 or BRCA2 are strongly predisposed to developing basal-like breast cancers, which frequently contain TP53 mutations. To study the role of BRCA1/2 loss-of-function in breast oncogenesis, we have generated conditional mouse models for BRCA1- and BRCA2-associated hereditary breast cancer based on combined inactivation of BRCA1/2 and p53 in epithelial tissues [2,3]. The mammary tumors that arise in our BRCA1 mouse model show strong similarity to BRCA1-associated breast cancer with respect to high tumor grade, expression of basal cell markers and high degree of genomic instability due to loss of homology-directed double-strand break (DSB) repair [3]. This model may therefore be helpful in predicting chemotherapeutic responses of human BRCA1-associated and BRCA1-like tumors. Indeed, preclinical intervention studies with conventional and targeted chemotherapeutics showed a selective sensitivity of BRCA1-deficient mouse mammary tumors towards agents that directly or indirectly cause DSBs, such as platinum drugs [4] or PARP inhibitors [5]. Treatment of tumor-bearing mice with the clinical PARP inhibitor olaparib (AZD2281) inhibited tumor growth without signs of toxicity, resulting in strongly increased survival. However, long-term treatment with olaparib resulted in the development of drug resistance, caused by up-regulation of P-glycoprotein drug efflux pumps. Indeed, acquired resistance could be effectively reversed by co-administration of olaparib and the P-glycoprotein inhibitor tariquidar.
BRCA1-deficient mouse mammary tumors become resistant to all drugs tested, with one exception: platinum-based chemotherapy drugs. Although tumors cannot be eradicated with cisplatin or carboplatin, the tumor recurrences invariably remain sensitive to retreatment with these drugs. These results data suggest that (partial) BRCA1 activity is required for induction of platinum resistance. Indeed, it has been reported that BRCA-associated hereditary ovarian cancers may become resistant to carboplatin by acquiring genetic reversion mutations in BRCA1/2, resulting in re-expression of BRCA1/2 and re-activation of homology-directed DSB repair [6,7]. In the mouse mammary tumors BRCA1 is inactivated by a large deletion in the Brca1 gene that cannot be reversed by any secondary mutation. To model chemotherapy resistance by genetic reversion, we have generated novel BRCA1-deficient mouse mammary tumor models mimicking defined human BRCA1 founder mutations (185-delAG and 5382-insC).

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Special Session (Thu, 24 Sep, 11:15−12:15)
Clinical implications of new discoveries in cancer genetics

338 INVITED

Genetic susceptibility to breast cancer – new developments and clinical application

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Common cancers exhibit familial aggregation, consistent with substantial variation in inherited susceptibility. Over the past 25 years, the underlying genetic basis for this susceptibility has become increasingly understood. Three important classes of genetic loci have been identified: “high-penetrance” genes, such as *BRCA1* and *BRCA2*; “intermediate-penetrance” genes, such as *ATM* and *CHEK2*, in which mutations confer 2−3 fold risks; and “low-penetrance” loci (such as *FGFR2*), in which common polymorphisms confer more moderate risks, typically <1.5 fold. The high-penetrance loci are central in genetic counselling, but most genetic variation is explained by lower risk loci. While most if not all the important high-penetrance loci have been identified, identification of lower penetrance loci through genome-wide association studies is still in its infancy, and more further loci should be identifiable through genome scans and resequencing. Generally, genetic loci combine multiplicatively, consistent with multiple independent pathways.
Recent genome-wide association association studies have identified thirteen genetic loci with common susceptibility alleles. These loci include several plausible candidate genes, including *FGFR2*, *TNRC9*, *MAP3K1*, *LSP1* and *NEK10*, but also “gene deserts”. For the most part, the loci were not previously suspected to be related to carcinogenesis, and point to new disease mechanisms. While the risks conferred by the susceptibility

alleles are low, the combined effects are sufficiently large to be important in risk prediction, targeted screening and prevention.

Special Session (Thu, 24 Sep, 11:15−12:15)
Established and emerging imaging applications

341 INVITED

PET-CT: has sensitivity and specificity improved for staging and response monitoring?

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FDG-PET-CT has established itself as an important cancer staging and therapy monitoring imaging modality in the last decade and has replaced CT in many questions. While FDG-PET mostly adds sensitivity to the combined exam, CT offers mostly specificity. However, not infrequently FDG-PET adds specificity and CT sensitivity. As a result, FDG-PET-CT is a more accurate staging modality than either of its two parts and several publications also demonstrate that it is better than FDG-PET and CT read side by side. The value of PET-tracers other than FDG is much less well elucidated. Some data are available on F-choline-PET-CT in recurrent prostate cancer, in F-DOPA and F-DOTATOC and others for staging and therapy monitoring of neuroendocrine tumors and FLT is considered useful in therapy monitoring.
Outcome studies on diagnostic imaging are difficult to perform because the imaging specialists do not control the ensuing therapy path. Therefore, the best current measure is the impact on management, where the researchers look at the percentage in which adding a PET-CT results in a relevant change in patient management. Many studies on different cancers have appeared which demonstrate that PET-CT results in such changes in 20−50% of the cases. Furthermore, in therapy monitoring a number of studies have appeared which demonstrate that after therapy, patients who show persistent FDG uptake will have a decreased survival when compared to those in which FDG-uptake has either been reduced or has disappeared. These data therefore suggest that PET (-CT) may serve as a surrogate endpoint for the evaluation of therapy in many cancers. FDG-uptake much more strongly correlates with successful therapy than the morphological imaging modalities.
In summary, FDG-PET-CT has considerably improved staging and therapy monitoring in the last few years justifying the worldwide growth of the number of examinations performed.

Special Session (Thu, 24 Sep, 11:15−12:15)
Trial methodology

342 INVITED

The role of randomised trials and surrogate biomarkers in early clinical development

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Phase II trials in cancer patients are essentially a screen to reject treatments having insufficient activity to warrant further study. The primary end-point of phase II trials is often the response rate, i.e. the proportion of patients with measurable lesions in whom a substantial tumour regression is observed. Often phase II trials are uncontrolled, and consist of treating one group of patients with the experimental drug. The major drawbacks of this approach are that the results of these trials may depend more on the patient selection than on the drug's true activity, and that cytostatic agents may control the tumor growth rather than cause it to shrink in the vast majority of patients. The first of these drawbacks can be addressed by randomizing patients between the experimental arm and a control group receiving standard of care. The second drawback can be addressed by using a more statistically sensitive endpoint than the response rate, for instance repeated measurements of the tumor or, if possible, specific biomarkers (e.g. prostate-specific antigen in prostate cancer, functional imaging, etc.) Even though these biomarkers are seldom validated surrogates for long-term clinical endpoints, they may better reflect the anti-tumor activity of new therapies than a mere response rate. The traditional approach to phase II design, which is to demand that the response rate of the new therapy exceed some pre-defined threshold, may then be replaced by a suitably powered statistical comparison of repeated measures of the biomarker between the randomized groups.

343 INVITED

Integration of diagnostic markers into the development process of targeted agents

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New technology and biological knowledge make it increasingly feasible to predict which patients require systemic therapy and which are most or least likely to benefit from a specific treatment. Using genomic classifiers to target treatment can greatly benefit patients, reduce societal medical costs and improve the chance of success in new drug development. There are, however, many challenges in effectively co-developing new drugs with predictive classifiers.
Much of the conventional wisdom about how to develop and utilize predictive biomarker classifiers is flawed. The data used to develop a predictive classifier should be distinct from the data used to test hypotheses about treatment effect in subsets determined by the classifier. Developmental studies are exploratory, but studies on which treatment effectiveness claims are to be based should be definitive studies that test pre-specified hypotheses (33). This presentation will describe phase III clinical trial designs for utilizing biomarker classifiers in new drug development. The presentation will cover randomized enrichment designs (20,21) that utilize predictive biomarkers for selecting patients as well as randomized stratification designs (72−75) that do not restrict eligibility but permit evaluating the treatment overall for all randomized patients as well as for one pre-defined biomarker determined subset of patients. The adaptive signature design of Freidlin and Simon (38) and the adaptive threshold design of Jiang et al. (53) will also be presented. Reprints of the above citations are available at http://brb.nci.nih.gov using the specified citation numbers. Interactive software for designing clinical trials with predictive biomarkers is also available at that website.

Special Session (Thu, 24 Sep, 11:15−12:15)
Sarcomas in adolescents

344 INVITED

Managing sarcomas in teenagers and young adults

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Sarcomas account for 10% of cancers occurring in 15−24 year olds. Within this group there is considerable clinical and biological heterogeneity and incomplete understanding of optimal treatments.
Most clinical research attention has focused on the management of bone sarcomas, particularly osteosarcoma and Ewing's tumours. Several factors have been studied which consistently identify patient groups with differing outcomes. Age at diagnosis appears to affect prognosis in Ewing's tumours but less obviously in localised extremity osteosarcoma. Any underlying biological or treatment delivery variables which may explain these observations have yet to be elucidated. Whether different treatment approaches for bone sarcomas should be adopted for teenagers and young adults (TYA) is unclear and will require systematic prospective evaluation.
Soft tissue sarcomas affect all ages. The numerous histiotypes are not evenly distributed across all age ranges. In the progression from childhood through adolescence to adulthood, rhabdomyosarcoma is replaced as the commonest subtype by the many different subtypes recognised by adult oncologists. There is little guidance about appropriate management of 'adult-type' soft tissue sarcomas occurring in TYA and this group have not been systematically studied. Their representation within clinical trials may be biased towards those with adverse features. There is considerable variation in practice particularly regarding the use of adjuvant chemotherapy. Few studies address whether specific approaches to treatment are appropriate for TYA with soft tissue sarcoma.
In the future, biologists and clinicians familiar with sarcomas affecting TYA and adults need to work together to share understanding and to design rational treatment programmes aimed at improving outcomes for TYA.

345 INVITED

Hot topics in sarcoma of adolescence

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Sarcomas of adolescence encompass malignant bone sarcomas, such as osteosarcoma and Ewing sarcoma, and soft tissues sarcomas, such as rhabdomyosarcoma, synovial sarcoma and Kaposi sarcoma.
The focus of this lecture will be put on difference in outcome between children and adolescents in tumors with similar diagnosis, of which