

non-randomised studies, primarily evaluating safety and immunological responses to treatment. Five studies described grade III/IV flu-like symptoms and gastro-intestinal events in 7–30% of patients. Anti-CA-125 antibodies and CA-125 specific T-lymphocytes were frequently detected, albeit response rates varied between studies. Despite the promising immunological responses in these studies, two randomised placebo controlled trials found equal progression free and/or overall survival rates for patients treated with placebo or CA-125 directed antibody.

Antigen-specific active immunotherapy studies were generally small phase I or II studies primarily investigating safety and immunogenicity of a vaccine. Overall, treatment was well-tolerated, with local inflammatory side effects at the site of immunisation most frequently reported. Anti-tumour immune responses, i.e. tumour-specific antibodies and T-lymphocytes, were induced by most strategies studied. Whether these are also clinically active, still has to be evaluated in large randomised controlled trials.

**Conclusion:** A general observation of this review, which forms a major limitation for reliable conclusions regarding the achievability of immunotherapy as a treatment for ovarian cancer, is the lack of uniformity in trial conduct, clinical and immunological response definitions and trial reporting. An additional concern is the observation that although the majority of studies were phase I or II trials, adverse events were often not or only sparsely mentioned. We strongly advocate the adoption of universally accepted immunological and clinical response definitions, guidelines for adverse events reporting, as well as internationally accepted directives for trial conduct and reporting to ensure that in the future it will be possible to make reliable inferences about the feasibility of immunotherapy as a treatment for ovarian cancer.

## Special Session (Wed, 23 Sep, 13:30–14:30) Cancer stem cells and radiation resistance

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INVITED

### Radioresistance of cancer stem cells

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Recent publications are providing increased support for the role of cancer stem cells (CSC) in different human malignancies. CSC are defined as a subpopulation of tumour cells which have the capacity to self-renew and to generate the heterogeneous lineages of cancer cells within a tumour. CSC were initially isolated from human acute myeloid leukaemia, and were subsequently identified in a number solid cancers. It is postulated that CSC are responsible for recurrences and metastases after anticancer treatment because they escape conventional therapies. This implies that better knowledge of the biological differences between CSC and non-CSC may improve tumour therapy dramatically. To achieve an improved curative effect of radiation therapy only the radiosensitivity of cancer stem cells should matter since these are the cause of local tumour recurrences after complete responses. The isolation of CSC from solid tumours can be done with sorting methods for Hoechst dye excluding side populations (SP) cells and more importantly with CSC-specific cell surface markers. Radiation is one of the main modalities used in the treatment of solid tumours. Our own work tested the hypothesis that cancer cell lines would contain a subpopulation of CSC with lower intrinsic radiation sensitivity compared to the non-CSC in the same culture based on several studies which have demonstrated the relative radioresistance of CSC in brain tumours, and breast cancer. In this study, we used a panel of cell lines from five tumour types to examine the clonogenic survival and  $\gamma$ H2AX foci formation of CSC isolated using the respective markers for the corresponding tumour type. While in some of the cell lines we could confirm a less radiosensitive phenotype the majority of the lines did not. In conclusion we can state that, although we reliably identified CSC in cell lines we could not confirm the radioresistant phenotype in this model in general. This is critical to consider in exploring models essential for assessing the biological advantage of CSC.

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### Cancer stem cells as determinant of tumour radioresistance

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Recent experiments which combined isolation of tumour cell population based on specific surface markers with tumour transplantation assays support that cancer stem cells are a specific subpopulation of all cancer cells. The proportion of cancer stem cells in most tumours appears to be very small compared to the vast majority of cancer cells which are non-tumorigenic. An overview of experimental and clinical data

will be given to explore methodology to measure stem cell biology for radiotherapy and the question which role the number of cancer stem cells, their intrinsic radiosensitivity, and other radiobiological parameters play in tumour radioresistance will be given. Recurrent tumours after radiotherapy originate by definition from at least one surviving cancer stem cell while permanent local tumour control requires inactivation of all cancer stem cells. Local tumour control assays therefore functionally measure survival of the subpopulation of cancer stem cells, and can be considered as a gold standard in this respect. In contrast changes in tumour volume after therapy, i.e. tumour response, are governed by the changes in the mass of tumour cells, i.e. primarily by the non-stem cells. Today the vast majority of preclinical studies in cancer research use volume dependent parameters such as tumour regression or tumour growth delay as experimental endpoints. This carries the substantial risk that new treatments may be optimized for their effect on the bulk of non-stem cancer cells, with no improvement in the curative potential. Experimental data provide evidence for the importance of cancer stem cell number and density for local tumour control and suggest that the response of cancer stem cells and non-tumorigenic cells to radiation and combined treatment may dissociate. The question whether cancer stem cells are intrinsically more radio resistant than non-stem cells can not be answered unequivocally at the present time but is important, particularly for the development of bioassays to predict radioresistance before or during radiotherapy.

## Special Session (Wed, 23 Sep, 13:30–14:30) Imaging in drug development

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INVITED

### Imaging in early drug development-the pharmacology audit trail

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Novel imaging technologies offer unprecedented opportunities to image tumor biology. Rather than merely documenting site, size and morphology of tumors we can now image microvascular function, hypoxia, tumor metabolism and proliferation, and apoptosis. Currently anatomical imaging measurements for measurement of tumor response are used in late phase trials as a surrogate for the clinical endpoint of change in overall survival and in early phase trials as an indicator of anti-tumor activity. However anatomical techniques may be inadequate to determine if a drug is worth taking forward to Phase II for compounds which produce prolongation of stable disease rather than tumor shrinkage and for drugs targeting pathways which may only be driving tumor growth in a subset of tumor types. In these cases, other imaging techniques such as Dynamic Contrast Enhanced MRI (DCE-MRI) to measure changes in tumor microvasculature, <sup>18</sup>Fluoro-Deoxy Glucose PET (FDG-PET) to measure changes in tumor metabolism and glucose transport, and <sup>18</sup>Fluorine-Labeled Thymidine PET (FLT-PET) to measure changes in tumor metabolism, can be used to document the 'pharmacology audit trail'. This 'audit trail' requires demonstration that the drug achieves biologically relevant exposures, that it modulates the target of interest, that this target modulation translates into anti-tumor activity, and support for selection of a dose or dose range, and the dose schedule to take forward into Phase II trials.

Effective use of these imaging tools in early phase development requires some modification of 'traditional' early phase trials design and implementation. Ideally the same techniques planned for early phase clinical trials should be used in pre-clinical models to compare dose response and time course of the imaging endpoint with dose response for anti-tumor efficacy. Use of the above imaging techniques may require expansion of cohorts to ensure an effect of clinical relevance can be measured. This requires a larger investment in Phase I, but would allow a 'proof of confidence' decision, and a No Go if no/limited effects are seen in the tolerable dose range. The more novel techniques are by their nature less standardized, with significant differences in methodology between centers even for such a widespread technique as FDG-PET. There is frequently a lack of data on repeatability between and within patients and sites and over the timepoints of interest. Knowledge of the multi-center repeatability is required to adequately size cohorts for assessment of treatment effect. Image analysis methodology needs validation, with quality control of initial image acquisition. If data are to be shared across multiple sites there is a need for a centralized database, compatible with the different hardware and software at each site. Industry needs to work with academia to develop acceptable standards for these steps. The presentation will discuss updates on repeatability in multi-center trials for dynamic MRI, FDG and FLT-PET, and illustrations of how decision-driving data utilizing these techniques have been obtained in preclinical and clinical experiments for compounds in the BMS pipeline including brivanib, a FGFR and VEGFR2

tyrosine kinase inhibitor and BMS-754807, a small molecule IGFR tyrosine kinase inhibitor.

### Special Session (Wed, 23 Sep, 13:30–14:30) Using evidence-based cancer nursing practice

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Overcoming the barriers to making change in cancer services

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Understanding factors that hamper change in health services is the key to successful evidence implementation, clinical innovation and a thriving health care environment. Following a consideration of the latest evidence around organisational change, a series of case examples will be presented to demonstrate how innovations in practice settings were achieved, despite considerable barriers to their implementation.

### Special Session (Wed, 23 Sep, 13:30–14:30) Sentinel node staging and clinical implications in GI tract

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Any value in colorectal cancer ?

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The single most important parameter of prognosis in patients with localized colon cancer is the presence of nodal metastases at the time of surgical treatment. The 5 year survival rate for node negative patients (stage II) is 70–80% but only 45–50% for those with node positive tumors (stage III). Therefore, it is most important to accurately reflect the status of the regional lymph nodes.

This requires improvement of the surgical methods radicality as well as a more accurate determination of the indications for adjuvant chemotherapy administration.

Sentinel lymph node mapping (SLNM) and retrieval provides representative nodes to facilitate ultrastaging. The potential benefit of in vivo sentinel node biopsy (SNB) is the detection of aberrant changes and the possibility of detailed examination of high risk lymph nodes to improve assessment of lymph node metastases.

Factors of influence are a low number of lymph nodes resected due to inadequate surgical lymphadenectomy and/or inadequate pathological examination and the technique for the localization and definitions of the sentinel node. Ultrastaging by in-depth techniques improves detection of lymph node micrometastases and results in upstaging of 8–20%.

Good results of sentinel node harvesting in colorectal cancers have been shown by large studies. In a multicenter trial that included 500 patients SLNM showed patients' success, accuracy, sensitivity, and negative predictability values of 98%, 96%, 90%, and 93%, respectively [1].

Focused examination for SLNM provides an efficient detection of micrometastases with consequent results for upstaging and relation with patients' outcome. Future perspectives for early colon cancers may be treatment by local resection therapy only with a minimal invasive surgical sentinel node procedure.

#### References

- [1] Saha S, Seghal R, Patel M et al (2006) A multicenter trial of sentinel lymph node mapping in colorectal cancer: prognostic implications for nodal staging and recurrence. *Am J Surg* 191: 305–310

236 INVITED  
Sentinel node staging and clinical implication in GI-tract oesophageal/gastric cancer

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The different techniques of sentinel lymph node staging (radio colloid, inks, fluorescence markers, nano particles) will be discussed regarding clinical feasibility, sensitivity and specificity for upper GI-tract cancer. None of the techniques is ideal and sufficiently effective for oesophageal or gastric cancer. Tumor location, tumor size, tumor type and technical experience of the investigator are the most significant factors for applicability and reliable results. Therefore, the technique of sentinel lymph node mapping

must be tailored according the clinical context and technical aspects. Improved sentinel lymph node navigation and biopsy together with a sophisticated histopathological work up of the sentinel lymph node (including immunohistochemistry) will influence (more and more) to an increasing degree clinical decisions in the future. Examples are the indication for neoadjuvant therapies, limited (minimal access) surgeries or for radical lymph node dissection in upper GI-tract cancer.

### Special Session (Wed, 23 Sep, 13:30–14:30) Defining optimal strategies for HPV vaccination

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Post-vaccination HPV surveillance

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Effective HPV surveillance programs will be an essential component of appropriately implemented HPV vaccination programs. To contribute to improving quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact, WHO has initiated a global HPV LabNet. The LabNet facilitates implementation of standardized, state-of-the-art HPV laboratory methods by introducing international standards and proficiency testing in order to make results comparable across laboratories worldwide. The LabNet is also intended to form the basis for development of a global network for HPV surveillance by using standardized and harmonized laboratory methodologies in order to provide sound data to policy-makers.

Major components of HPV surveillance systems that are currently being explored in pilot projects include:

- surveillance for and HPV typing of condyloma acuminata in designated sentinel STD clinics. As condyloma has a short incubation time, this will be the earliest clinical condition that will reflect where control of the spread of HPV has been achieved.
- surveillance for the prevalence of HPV vaccine types and non-vaccine types in sexually active youth groups. A possible system to do this is anonymised HPV testing concomitantly with the Chlamydia screening programs.
- surveillance for the prevalence of HPV vaccine types and non-vaccine types in organised cervical screening
- assessment of the proportion of HPV-associated neoplasias (CIN, VIN/VaIN, cervical cancer and other HPV-associated cancers) that is attributable to vaccine and non-vaccine types of HPV and whether these proportions change over time.

### Special Session (Wed, 23 Sep, 13:30–14:30) Oncology societies: why?

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Why young scientists within oncology should join ESTRO

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The aim of this talk is to present the many reasons why young scientists in the field of oncology should join ESTRO. The arguments can basically be sorted into two categories, the first relating to who choose radiotherapy (RT) as a speciality, the second to the role and membership advantages of ESTRO as the key European organisation in the field of RT.

Second only to surgical management, RT is the most important treatment modality for cancer in terms of the contribution to patient survival. Today, about 50% of all cancer patients receive RT. The RT profession is an interdisciplinary speciality in its own, embracing the four different disciplines of radiation oncology, biology, physics and technology. Development in each of these disciplines, as well as the successful integration of the achievements, is instrumental for the further improvement of cancer therapy by RT.

ESTRO was founded in 1980, and its membership base has grown steadily ever since, with currently more than 4200 members. Currently, 61% of ESTRO's members are radiation oncologists while 24% are physicists; 22% of the members are residing outside Europe. In addition to becoming part of a large scientific community to broaden your professional network, ESTRO membership gives access to ESTRO's monthly scientific journal, *Radiotherapy and Oncology*, its quarterly membership magazine as well as dedicated members pages on the ESTRO website ([www.estro.org](http://www.estro.org)). Reflecting its membership base, ESTRO activities of both educational and scientific character are aiming at all four disciplines in the field of