a more accurate and comprehensive clinical database and to ensure that any unexpected treatment issues are identified promptly. The EMEA guidelines will permit the use biosimilars for indications for which they have not been formally studied (ie, extrapolation) when proper justification is provided. While the EMEA guidelines are scientifically rigorous and provide a pathway for the approval of biosimilars, they do not fully address some important post-approval issues relevant to physicians, particularly in the oncology setting. These include automatic substitution with biosimilars, labeling so that physicians can make informed decisions, and nonproprietary naming for accurate prescribing and dispensing practices. Currently, the EMEA cannot guarantee the interchangeability of biosimilars with reference products, and because of the potential for differential clinical response it would appear prudent that automatic substitution should not be allowed for any biopharmaceutical – biosimilars or innovator products. Also, the use of biosimilars for indications based on extrapolation of data must be weighed against the possibility for differences in safety and efficacy. Such issues underscore the need for full disclosure in the product labeling of biosimilars so that physicians and patients can make informed decisions regarding product selection. A thorough knowledge of the issues surrounding biosimilars will ensure the appropriate use of biopharmaceuticals.

16 INVITED

Follow-on erythropoietins – Pros and cons

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Background: Erythropoietin biosimilars are not generic equivalents of the innovator product and are likely to be approved in Europe soon.
Material and Methods: This report presents a review of present literature on biosimilar erythropoietins. Literature search included Medline and abstracts from ASCO, ESMO, ASH, EHA and ECCO meetings (2000-2007).
Results: Amino acid sequences of biosimilars of erythropoietin will most likely be similar to that of endogenous erythropoietin, but glycosylation patterns will differ. Differences in glycosylation may have a significant impact on the rate of plasma clearance, on receptor binding, and importantly on biological and on clinical activity. A recent study comparing 11 erythropoietin products from 4 different countries (Korea, Argentina, China, India), revealed significant variations in the distribution of erythropoietin isoforms. Further, in vivo bioactivity ranged from 71% to 226%, with 5 products failing to meet their own specifications.
Due to the differences in carbohydrate moiety and possibly immunogenicity and clinical activity, appropriate labelling of the drugs as unique molecules is mandatory. This is particularly important for identification of eventual late adverse effects during pharmacovigilance studies. Hence, switching or substitution between innovator products and biosimilars should not be enforced automatically, and must be viewed as a change in clinical management. Rigorous pharmacovigilance programs are needed to capture possible side effects and to build a database establishing the clinical use of each product.
On the positive side, biosimilars will increase the usage of drugs and benefit more patients. The introduction of biosimilars will motivate industry to increase its research efforts even further in order to develop new drugs, which will be protected by patent rights for a defined period.
Conclusion: Biosimilars are not identical to the innovator drug, cannot automatically be substituted and need careful pharmacovigilance programs. Their introduction will allow a greater number of patients to actually receive treatment, and will drive industry to further enhance its research efforts.

17 INVITED

G-CSF biosimilars – approval process, substitution and extrapolation

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Two G-CSF products differing with respect to biological characteristics and approved indications are currently available in Europe. Comparative studies have demonstrated differences between these two products with regard to pharmacological properties and clinical outcomes and are not considered interchangeable. According to EMEA guidelines, G-CSF biosimilars have to demonstrate comparability in efficacy and safety to one of the two G-CSF products in the prophylaxis of severe cytotoxic chemotherapy-induced neutropenia. While a two-arm comparability study is recommended for chemotherapy regimens with known frequency and duration of severe neutropenia, a 3-arm study (including placebo arm) is required for other chemotherapy regimens.
Since limited clinical experience will be available at approval of biosimilars, substitution represents a major challenge. Automatic substitution may lead to the administration of multiple products and events would not be able to be linked to a specific product. Furthermore, the identification of biopharmaceutical products might not be possible if multiple products share one International Nonproprietary Name (INN).
Although data extrapolation has a rational basis, the process by which indications for a product were approved should be known. A potential concern with the concept of data extrapolation arises in particular for G-CSF biosimilars, since efficacy and risks may differ in patient populations depending on age, on disease (malignant or non-malignant) and immunosuppression. As an example non-immunosuppressed patients with chronic neutropenia may be more likely to develop antibodies to biopharmaceutical agents than immunosuppressed patients. Especially the use of G-CSF biosimilars for stem cell mobilization from healthy donors in allografting presents an ethical dilemma. Since healthy donors receive no therapeutic benefit from the receipt of CSFs for stem cell mobilization, ethical concerns dictate that drug safety be of paramount concern. Sufficient experience with the biosimilar product and adequate follow up should be required.
In summary, information is the key to mitigating the potential concerns regarding the use of biosimilars. Any change from one product to another should be considered as a change in clinical management. Extrapolation should be avoided for use of biosimilars in healthy stem cell donors as long as sufficient data from stem cell mobilization in patients are available.

Special session (Mon, 24 Sep, 13:30−14:30)
Retroperitoneal sarcoma

18 INVITED

Surgical standards of treatment

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The specific problems of retroperitoneal soft tissue sarcoma relate to the proof of malignancy by biopsy and the heterogeneity of huge tumors with sometimes low grade and high grade compartments. Biopsy needs to prove that lymphoma, extragonadal germ cell tumors and lymph-node metastasis of tumors of the testicles do not hide behind a sarcomatous appearance. The future of defining molecular targets might also offer preoperative targeted therapy with new substances, for example in myxoid or round-cell liposarcoma.
The primary goal of surgery is an R0 resection – adjuvant chemotherapy has not proven to be of value. Thus, planning of the operative treatment must be made not to leave viable tumor tissue behind. At the first stage, an adequate imaging of the whole abdomen starting from the diaphragm down to the lower pelvis is required not to miss an extension of the tumor to the thorax, the lower pelvis, the adductors or paravertebrally. Usually retroperitoneal sarcoma is in close contact to one of the kidneys. If there is any risk that the kidney or the ureter will be involved in the resection, assessment of the function of the contralateral kidney is mandatory.
Concerning resectability the limits of resection are the spine, the neuroforamen, major involvement of the aorta, invasion or extension to the root of the mesentery with major small bowel resection as a consequence, bony structures as the ileo-sacral joint and extraabdominal extension. The retroperitoneal compartment, sarcoma usually originates in, offers a unique possibility for a radical resection. However, this means that tumor removal is a multivisceral resection by principle. Dissection of the aorta or vena cava, resection of the psoas muscle, removal of the internal oblique muscle, as well as keeping the sarcoma covered by large bowel resection and nephrectomy are the crucial steps. Extended resections include removal of parts of the vena cava and graft reconstruction, as well as partial resection of the aorta with graft or patch plasty and finally also autotransplantation of the kidney in case of involvement of the fatty capsule of the kidney only. Resection and reconstruction by diaphragm with a synthetic graft may complete the approach.
It must be born in mind that after removal of a huge retroperitoneal mass the small bowel will move to the former tumor bed and by this way makes postoperative adjuvant radiotherapy inefficient due to the limit of tissue radiation tolerability. Consequently, radiotherapy should be used prior to the operation. In high-grade soft tissue sarcoma, preoperative radio-/chemotherapy could be useful. Recently, in a randomized prospective trial, systemic chemotherapy combined with deep wave hyperthermia has proven effective, not only in the down-staging of tumors, but also in improving survival. This methodology might not be available at any center, but an experienced sarcoma center is required to offer the patient an optimum standard of care. A multistep explanation of the therapeutic

approach to patient and relatives is of importance to allow adequate coping with the disease.

19 INVITED

Is there a rationale for pre or postoperative radiotherapy or chemotherapy?

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Retroperitoneal sarcomas (RPS) still represent a therapeutic challenge. Whereas most specialists agree that the surgery is the primary treatment of choice many RPS are difficult to resect and carry a high level of local relapse and a poor prognosis even following a complete resection. In an attempt to improve the outcome various adjuvant therapies have been administrated. Although their usefulness has been demonstrated, at present there is no clear prospective data indicating that these adjuvant treatments will improve survival. Radiotherapy (RT) is the most cited adjuvant treatment that may impact on local control. However, due to the proximity of critical normal tissues the delivery of therapeutic doses of external beam RT is problematic and could result in unacceptable toxicity. Data indicate that low dose RT is of little benefit and that increasing the dose delays but does not prevent local recurrence in the majority of patients. This therapeutic dilemma is unfortunate and thus better strategies are needed, i.e. intensity-modulated RT, intraoperative placement of tissue expanders to displace the small bowel out of the RT field, intraoperative RT therapy and brachytherapy. Most have applied the RT postoperatively but recently a number of studies have indicated that preoperative RT could be a preferable method of delivering adjuvant external beam RT as it may be better tolerated, permits the RT to be directed more precisely to the tissues at risk and may reduce the risk of tumour implantation at resection. Hopefully the newer diagnostic tools like PET/CT or MR may help giving a more accurate determination of the RT treatment volume and thus allow higher doses and decrease toxicity. Systemic chemotherapy could be an alternative treatment option but its use is controversial and most RPS have shown poor response to the present chemotherapeutic drugs. Despite few data neoadjuvant chemotherapy has been proposed as an adjunct to surgery and RT to improve resectability and to reduce the risk of relapse. With the present knowledge RPS should undergo a complete resection if possible and in individual cases pre or postoperative radiotherapy and/or chemotherapy could be added especially in grade 3 or 4 tumours with microscopically involved resection margins. Obviously there is a critical need for future large multicenter trials of RPS evaluating the optimal use of the various treatment options either alone or in combination and to allow such studies to be performed RPS should be referred to multidisciplinary sarcoma centres.

20 INVITED

Contribution of pathology to decision-making in retroperitoneal sarcoma

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The retroperitoneum is the second most common site of origin of sarcomas; 15% of all primary sarcomas are retroperitoneal. In adults sarcomas in the retroperitoneum are less common than (Non-) Hodgkin Lymphoma, parenchymatous epithelial tumours (renal, adrenal, pancreas) and metastatic disease from a known or unknown primary elsewhere. In the first two decades, nephroblastoma (Wilm's tumour) and neuroblastoma are the more common retroperitoneal tumours. In contrast to the extensive predominance of benign soft tissue lesions elsewhere, in the retroperitoneum mesenchymal lesions are more likely to be malignant. The most prevalent mesenchymal tumours in the retroperitoneum are of lipomatous, myogenic and neural origin. Liposarcomas are the most common sarcomas in the retroperitoneum, especially well differentiated liposarcoma and dedifferentiated liposarcoma. Well differentiated liposarcoma is most common and is regarded a low grade sarcoma that does not metastasize. The recurrence rate is however high due to problematic surgery, bearing the risk (10−20%) of dedifferentiation. Dedifferentiated liposarcoma has the capacity to metastasize, irrespective of the extent of dedifferentiation. Leiomyosarcoma is the second most common sarcoma at this site while its benign counterpart, leiomyoma, is almost non-existing at this site. Retroperitoneal leiomyosarcoma bears a very poor prognosis. Of the neurogenic tumours benign schwannoma is most common. Malignant peripheral nerve sheath tumour is mostly associated with a preexisting neurofibroma, and half of the patients suffer from neurofibromatosis type I. It is a high grade tumour with a very poor prognosis. In addition, non-neoplastic masses such as retroperitoneal fibrosis may occasionally pose a problem in their distinction from sarcoma. Gastro-intestinal stromal cell tumours (GIST) occasionally involve the retroperitoneum either by direct extension from the intra-abdominal gastro-intestinal tract, or origin in the retroperitoneal part of the duodenum. It is important to recognize GIST since targeted adjuvant treatment due to KIT overexpression is available. High grade pleomorphic sarcoma NOS (previously grouped under "Malignant Fibrous Histiocytoma"), lacking any differentiation, constitutes an additional small subset (~7%) of retroperitoneal sarcomas. Histopathological classification of retroperitoneal mesenchymal tumours can be difficult but is aided by immunohistochemistry and molecular diagnostics.

Special session (Mon, 24 Sep, 13:30−14:30)
The management of neck nodes

21 INVITED

Sentinel node biopsy: a diagnostic or therapeutic procedure?

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The presence of cervical node metastasis remains the most significant prognostic indicator in tumours of the upper aero digestive tract. Despite advances in imaging techniques of CT, MRI, PET and ultrasound, the detection of early metastasis and particularly micrometastasis remains a problem and the management of the N0 neck remains controversial.
The principle of sentinel node biopsy is that tumour migrates in an orderly fashion to a first echelon or sentinel node and that the pathological status of this node reflects the status of the whole nodal basin. Sentinel node biopsy (SNB) is now used routinely in malignant melanoma and breast cancer and has proved to be an excellent staging technique.
The first successful SNB in head and neck cancer was performed in 1996 by Alex and Cragg on a patient with supraglottic carcinoma. The Canniesburn Plastic Surgery Unit developed a method for widespread use in head and neck cancer. Based on the technique used in malignant melanoma. This comprised the triple diagnostic technique of preoperative lymphoscintigraphy, intraoperative blue dye injection, and intraoperative gamma probe localisation. Together with other medical centres, mainly in Europe, identification of sentinel nodes was in the region of 90 to 97%. Subsequent research showed the importance of additional pathological examination of the sentinel node in the form of step serial sectioning and immunohistochemistry.
Between 1998 and 2002 patients were recruited into this European multi centre study evaluating the reliability of sentinel node biopsy as a staging tool in patients with clinical T1 or T2 N0 head and neck squamous cell carcinoma. The patients underwent either sentinel node biopsy assisted elective neck dissection or sentinel node biopsy alone with all sentinel node positive patients subsequently undergoing a therapeutic neck dissection. 134 patients met the inclusion criteria for the study and 79 underwent sentinel node biopsy alone while 55 patients underwent sentinel node biopsy and immediate elective neck dissection. The sentinel node was successfully harvested in 125 of the 134 patients, giving an overall identification rate of 93%. Floor of mouth had the lowest identification rate and proved the most problematic. 42 of the 125 clinically node negative patients were upstaged (34%). 32 of these cases were upstaged by routine H&E staining while a further 10 patients required additional pathology in the form of step serial sectioning and immunohistochemistry.
The mean follow up is now 5.5 years. Five patients have subsequently developed disease in the neck and four of these false negative SNB results were in patients with floor of mouth tumours. The overall sensitivity of SNB as a technique for identifying metastasis was 91%
Conclusion: Sentinel node biopsy can be successfully applied to early T1/T2 tumours of the oral cavity and oropharynx and used as a staging tool. Problems remain when applying this technique to tumours in the floor of the mouth. SNB is minimally invasive, cost effective and has a low associated morbidity. It may also identify abnormal drainage patterns allowing the treatment plan to be altered accordingly. Initial results of the long term follow up study demonstrate that this type of nodal biopsy is not harmful to the patient and that neck recurrence is very similar to more extensive selective neck dissection procedures.