best 5 fluorouracil, with expected median overall survival of 6−8 months. Outcomes could not be more different in 2009.
The definition of surgical resection with curative intent is now the ability to preserve 25−30% of disease-free functioning liver with good vascular inflow and outflow (which accounts for 20% of patients with liver only disease). Five and 10 year overall survival after hepatectomy is 50% and 26%. We now have good evidence to show the survival benefit of ablation therapies over chemotherapy alone in non-resectable disease. Modern chemotherapy regimens combined with state-of-the- art biological therapies can achieve median survival in incurable disease approaching 3 years, and perhaps more significantly can render over 40% of patients with non-resectable liver-only disease amenable to surgery with curative intent. Five year survival for all patients with CRCLM now approaches 30%.
Such progress has only been made possible by the adoption of multi-disciplinary team working (MDT). MDTs are now mandatory by law for the treatment of cancer patients in a number of European countries and being increasingly adopted in the others.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
The management of malignant pleural mesothelioma

249 INVITED

Biology of mesothelioma

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Malignant pleural mesothelioma is an aggressive tumor, with a poor prognosis. Its incidence is increasing worldwide as a result of widespread exposure to asbestos, and is predicted to peak in the next 10−20 years. The results of the available therapeutic resources are poor. Surgery and radiotherapy have a limited role in highly selected patients and systemic therapy is the only potential treatment option for the majority of patients. Despite some definite activity of the novel antifolates such as pemetrexed and raltitrexed, only small steps forward were recently made possible. Pemetrexed and raltitrexed are now a recognized standard treatment. However, the results even in combination with platinating agents, are still meager, with an extension of a median survivals by only 3 months and with a median survival of approximately one year.
An improvement of the knowledge of major molecular pathways involved in malignant mesothelioma is needed in order to define proper targets for the systemic treatment of this disease. Malignant mesothelioma cells show an increased or dysregulated growth. The cells produce and respond to many autocrine growth factors, such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), platelet-derived growth factors (PDGF) A and B, transforming growth factor b (TGFb), and angiogenic factors, such as vascular endothelial growth factor (VEGF). The corresponding receptors to these growth factors activate the PI3K−Akt pathway, which has a crucial role in malignant pleural mesothelioma cell survival and contributes to the anti-apoptotic phenotype. Unfortunately, the clinical results of available target therapeutics are still modest. Several compounds are in pre-clinical evaluation, and interesting results are emerging from cell lines studies. Moreover, novel biomarkers are under evaluation as a useful predictive or prognostic tool. The tailor-made treatment derived from the biologic and genetic characterization of tissue will offer better outcomes against malignant pleural mesothelioma in the future.
The principal goals of this presentation are to summarize the current knowledge in terms of major molecular pathways involved in malignant mesothelioma and outline the therapeutic approaches in development.

251 INVITED

Radiotherapy

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Patients with malignant pleural mesothelioma (MPM) often present with advanced symptomatic disease in which thoracic radiotherapy (RT) plays mainly a palliative role. The evidence to support the role of radiotherapy in this disease has mainly been derived from non-randomised data with the exception of the use of prophylactic irradiation to intervention tracts. The impact of radical or palliative thoracic RT on quality of life is not well known. In vitro studies have suggested that MPM is only partially radiosensitive.
Palliative RT: is routinely offered to control symptoms such as thoracic pain and dyspnoea on the basis of small retrospective studies. However there is no randomised data demonstrating the impact of palliative RT on symptom control, quality of life or survival.
Radical RT: there is no evidence to support the use of radical thoracic RT alone in MPM. This treatment modality is generally not offered as a routine treatment as the dose delivered to the disease is limited by the dose given to the adjacent organs at risk.
Post operative RT: the role of surgery for MPM is controversial. The best-documented multimodality approach to MPM is pleuropneumonectomy, followed by chemotherapy and radiotherapy in selected patients with earlier stages of disease. Post operative radical doses to the hemithorax have been reported to be tolerable and seem to decrease the rate of local failure after extrapleural pneumonectomy although no randomised data is available on the impact of postoperative RT compared to surgery alone. Post operative hemithoracic RT without extrapleural pneumonectomy is associated with significant toxicity on the normal lung tissue. Intensity-modulated radiotherapy allows for an increase in dose to the pleural cavity and a reduction in radiation doses to organs at risk. The ESMO 2008 clinical guidelines state that 'Modern radiotherapy techniques allow for delivering high-dose radiotherapy in an attempt to improve local control after EPP'
Prophylactic irradiation to intervention tracts (PIT): according to the current literature patients who undergo chest instrumentation, may develop seeding at the site of intervention, leading to subcutaneous tumour in 10 to 50% of cases. This is believed to be reduced by the common practice of prophylactic irradiation to intervention tracts (PIT). However two of the three published randomised controlled trials do not support the use of PIT but the evidence is contentious as these trials were not adequately powered. Furthermore they did not include patients receiving systemic chemotherapy and did not always collect data on the impact of PIT and track recurrence on quality of life and symptom control. The ESMO 2008 clinical guidelines state that 'Prophylactic radiotherapy to reduce the incidence of port metastases is controversial and not routinely applied'.
In conclusion, in MPM there are unmet needs to develop more effective radiation treatments that can improve quality of life and survival. Patients should be offered inclusion in a clinical trial whenever possible.

252 INVITED

The role of surgery in the management of malignant pleural mesothelioma

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Surgery has a primary role in the diagnosis and staging of malignant pleural mesothelioma (MPM). Therapeutic surgery has a role in symptom control and prolongation of disease-free interval. Radical surgery is intended to remove all macroscopic disease to offer long-term survival as part of multimodality therapy.
Whilst percutaneous biopsy is often used to diagnose MPM thoracoscopy is usually required in early disease. In most cases now medical thoracoscopy is employed but surgical thoracoscopy or open pleural biopsy may be needed in equivocal cases. Staging is as important in MPM as in other cancers particularly as major surgery carries high risk. Mediastinoscopy is the basis of surgical staging and video assisted mediastinoscopy may be combined with video assisted thoracoscopy via the cervical approach to offer diagnosis, staging and pleurodesis at one step.
Symptomatic control of pleural effusion can be achieved by video assisted thoracoscopic surgery (VATS) and talc insufflation. VATS can also be used to perform parietal pleurectomy which controls effusion and retards tumour progression. In cases of entrapped lung VATS may be used to perform visceral pleurectomy to allow lung re-expansion. Dyspnoea cannot be relieved in these cases unless the lung is decorticated.
Complete macroscopic tumour clearance can be attempted in selected patients in order to achieve long-term survival. This is conventionally achieved by extrapleural pneumonectomy (EPP) with en-bloc removal of pleura, lung, pericardium and diaphragm. This operation is associated with high morbidity and an operative mortality of around 5%. There is recently renewed interest in lung-sparing radical surgery or radical pleurectomy/decortication which is best termed total pleurectomy. There is evidence that this approach is equally effective as EPP in more advanced disease and carries lower operative risk and is suitable for a wider population.
Radical surgery alone is not considered optimum treatment and a multi-modality program is preferred. Additional chemotherapy can either be given preoperatively, intraoperatively as intravcavitary therapy or postoperatively. There is debate surrounding all these 3 routes. Additional radical hemithorax irradiation can only be given after EPP and while local disease control can be increased there are potentially toxic side-effects.
As the incidence of MPM increases in Western Europe evidence for these surgical strategies is urgently needed. The paucity of high grade therapeutic evidence is being addressed in anumber of on-going surgical trials. The CRUK sponsored MARS trial has completed its feasibility study of comparing EPP vs no EPP; an EORTC trial assessing the role of post EPP hemithorax irradiation is underway and the MesoVATS trial continues in UK to assess the benefits of VATS pleurectomy/decortication.

The role of surgery in EPP remains controversial. Less invasive methods are available for diagnosis and symptom control. Comparative survival benefits have been recorded from chemotherapy regimes alone.
Mesothelioma surgery can be complex and of high risk and should therefore be concentrated in specialized centres. There remiains a problem with equity of access to specialist skills, however. Well designed clinical trials are the best solution to these problems and the future aspiration of surgical enthusiasts.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
What are the side-effects of therapy in mRCC and how to handle them?

254 INVITED

Tyrosine kinase inhibitors

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The tyrosine kinase inhibitors have a range of side-effects which are only now becoming familiar to oncologists. Many of the toxicities are understated in their severity by use of the CTC. These criteria were developed for use with intermittent chemotherapy and it has become apparent that even grade 2 toxicities may significantly impair the quality of a patient's life. Often toxicities reported in studies are only really noticed if they are grade 3 or worse.
The main toxicities of TKI therapy are fatigue, rash, diarrhoea, hypertension, stomatitis, hypothyroidism and of particular importance in the neo-adjuvant or adjuvant setting, a potential to reduce healing. In addition there are emerging toxicities such as cardiac toxicity, the exact incidence and severity of which is still a matter for debate. Whilst most multi-targeted tyrosine kinase inhibitors exhibit most of the side-effects noted above, each tyrosine kinase inhibitor has its particular profile. For example, stomatitis and fatigue tend to be more marked with sunitinib. Rash tends to be more marked with sorafenib. Liver function disturbances tend to be more marked with pazopanib. Most of the side effects can be handled by patients, such that the large majority of patients are able to stay on treatment. Particular interventions may be useful to minimise the effect of side-effects and these interventions are often best used early in the course of a side-effect's natural history or even as preventative measures. The measures include using children's toothpaste and children's toothbrushes for stomatitis. Avoiding strong spirits or curries also for stomatitis. Diarrhoea may be handled by standard techniques such as loperamide. Hypertension should be rigorously controlled as evidence is accumulating that this reduces the risk of other cardiac toxicities. Standard agents may be used although care should be taken in choosing concomitant medications to use with tyrosine kinase inhibitors. Rash and hand/foot syndrome are often best managed preventatively by keeping the skin moist and supple with the use of emollient creams and occasionally urea-containing creams particularly where there is hyperkeratosis.
These side-effects, their severity and management will be discussed in the session. Mention will also be made of the possible future benefits of more precisely targeted tyrosine kinase inhibitors.

255 INVITED

mTOR inhibitors, bevacizumab

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Therapy of metastatic RCC has changed a lot in the past 3 years with approval of many new targeted agents. Due to the number of approved agents, and to the fact that very few patients (if any) are cured with these agents, side effects have to be taken into account both in terms of helping to choose the best drug to provide in each individual patient and in terms of management. In addition, toxicity should be considered differently when given chronically, since grade 1−2 toxicity is dramatically different when occurring for a few days or permanently.
Among targeted agents used in mRCC, mTOR inhibitors (temsirolimus and everolimus) and bevacizumab are very selective targeted agents, for which side effects are directly linked to the mechanism of efficacy, which might be different from tyrosine kinase inhibitors.

1. mTOR inhibitors mainly produce fatigue, skin rash and stomatitis. However, some less common side effects such as pneumonitis and algodystrophia should be known. Interestingly, most of these side effects are rapidly reversible when the drug is stopped. Metabolic dysregulation is directly due to mTOR inhibition. Usually mild, hyperglycemia, hyperlipemia might require adequate measures
2. bevacizumab has been used in oncology for more than 6 years and toxicity profile is well characterizes. VEGF inhibition induces hypertension, glomerular damages which can induce proteinuria and increased risk of bleeding and thrombosis. In RCC in addition, bevacizumab is given with interferon (IFN), and classical toxicity of IFN might be slightly increased by the addition of bevacizumab. However, specific side effects of bevacizumab appear similar to those observed without IFN, in other tumor types

In conclusion, a better knowledge of the side effects of the available drugs in RCC should help the physician to determine whether the benefit of a drug is large enough to justify its use in an individual patient.

256 INVITED

Do combination and sequential therapies have increased side-effects?

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Since 2005 the panorama of metastatic renal cell carcinoma (mRCC) treatment has radically changed, with four molecularly targeted agents (Sorafenib, Sunitinib, Temsirolimus and Bevacizumab – the latter in combination with Interferon) currently registered and available in European Union Countries, and two more (Everolimus and Pazopanib) presently under evaluation. Despite these dramatic improvements, no individual agent will benefit all mRCC patients, who should still be regarded as incurable; it is therefore mandatory to design rational clinical trials to try to further improve the results obtained so far. Two treatment strategies can be followed: to combine these agents, or to sequence them. Both strategies leave some questions open (do the mechanisms of action matter? does the target matter? in sequencing treatments, does the agent sequence matter? in combining treatments, is a 'horizontal' or a 'vertical' blockade better? and many more), but the issue of the tolerability of combination and sequential therapies appears to be key. Currently, available data are scarce and somehow biased. As for sequential treatments, we can mainly rely on retrospective series, while data relative to the safety of combinations come mainly from phase I trials, even though some of these combinations have already entered phase III development! Sequential therapies appear feasible, with a predictable and manageable adverse events profile and no signs of increased toxicity (except, probably, for fatigue and hypertension). Differently, combination treatments, while possibly providing increased activity, appear to be poorly tolerated, especially at full doses, and to cause even completely new toxicities (e.g. microangiopathic hemolytic anemia for the Sunitinib plus Bevacizumab combination). Furthermore, the choice of the agents to combine and the design of phase I studies proved to be extremely relevant when toxicity profile is taken into account. While waiting for the results of several phase II and III trials currently underway, we can say that the safety profile of combination treatments is somehow worrying (though there are some exceptions), while there is less concern for the safety of sequential treatments. To clarify not only activity but also safety issues, specific and well designed studies are badly needed.

257 INVITED

Cytokines and vaccines

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In mRCC the standard of care in Europe has, until the recent introduction of the targeted agents, been interferon alpha 2a (IFNα-only) based on the results of several randomised trials. In particular, the MRC RE01 study which showed a modest but clinically and statistically significant overall survival advantage for IFNα over MPA.
Interleukin-2 (IL2) when given intravenously at high dose by bolus injection results in response rates of 14−23% (13−15) but more importantly, about 7% of patients obtain a durable complete remission lasting over three years and some of these have been maintained for ten years. However, no randomised trial has ever shown a survival advantage for this treatment over a control group.
The toxicity profile of immunotherapy with IFN and IL2 is related to the aspecific nature of the treatment. In the largest trial in RCC, randomising IFNα versus INF, interleukin 2 (IL2) plus fluorouracil (FU) (IIF) in patients with previously untreated mRCC, no differences in PFS and overall survival exist. The toxicity is however different: during treatment there was significantly more grade 3/4 toxicity associated with IIF compared to IFNα-only (56% versus 38%, $p < 0.001$). Fatigue was significantly worse for IIF patients with 22%, 45% 24% and 2% experiencing grade 1, 2, 3 and 4 fatigue respectively, compared to 34% 39% 17% and <1% in IFNα-only patients. There was no evidence of significant differences between treatment arms in terms of worst quality of life score for tiredness, lack of appetite, shivering or lack of energy. Serious adverse events were reported in 6% and 5% of patients receiving IFNα-only and IIF, respectively.