objective responses is, however, often difficult in locally advanced disease. Lack of adequate quality assurance and control in radio(chemo)therapy trials can have influenced the outcome negatively. Equivalence between two treatments will be seen when the two treatments are equally effective, but also equally ineffective.
Discussion: Design issues can, in an improper way, have had an influence on how we presently treat advanced pancreatic cancer and design future trials.

151 INVITED

Single agent versus combination of drugs in advanced pancreatic cancer

C. Louvet. *Hôpital Saint Antoine, Paris, France*

Since the publication of the Burris study in 1997, gemcitabine (Gem) single agent is the reference treatment of advanced pancreatic cancer. Many attempts to improve the poor results of this reference treatment have been performed during the past 10 years.
Gem administered as a fixed-dose rate (i.e. 10 mg/m^2/mn infusion) is theoretically more efficient as compared to a 30′ infusion. A randomized phase II study showed encouraging results, but the ECOG phase III study failed to demonstrate a significant advantage for Gem FDR over Gem 30′ in terms of survival, even if the survival curves were clearly separated.
Randomized phases III have been performed, based on the same design, which consisted in a comparison between gem single agent versus Gem combined with an other drug (either conventional chemotherapy or biological agents). The great majority of these studies were based on "promising" results observed in a previous phase II, but almost all of them also failed to demonstrate a significant improvement of survival, and none were convicting enough in terms of clinical relevance to justify a consensus on a new standard of care. Several drugs had no activity when combined to Gem (such as pemetrexed, exatecan, marismastat, irinotecan, tifarbinib). A Gem + capecitabine combination showed a survival advantage in preliminary results, but definitive results are pending, and one gem + cap trial and two gem + 5FU trials were found to be negative. Cisplatin or oxaliplatin combined to gem significantly improved response rate and PFS, but failed to significantly improve survival. Addition of erlotinib to Gem significantly improved survival, but the median survival gap was only 15 days. Recent data showed during past ASCO meeting indicated that neither bevacizumab nor cetuximab combined to Gem were able to improve the survival results of Gem single agent. Meta-analysis or pooled-analysis demonstrate that combined treatments are more efficient as compared to gem single agent, but the magnitude of such an advantage remains very low. It seems however to be of interest for selected situations, such as platinum salts in patients with PS 0.
Therefore, to date, Gem single agent should remain the standard treatment at least in clinical trials. In clinical practice, additional options such as gem + erlotinib, gem + capecitabine or gem + platinum salt should also be considered.

152 INVITED

Biological agents in advanced pancreatic cancer

M. Moore. *Princess Margaret Hospital, Medical Oncology, RM5-205, Toronto Ontario, Canada*

Background: The results of combination chemotherapy in advanced pancreatic cancer have been disappointing and it remains one of the most lethal malignancies. Improvements in systemic therapy are more likely to be found with the new 'biological' therapies that target specific features of the malignant genotype and phenotype. Pancreatic cancer is a logical place to test such agents given the range of known molecular changes associated with this disease.
Materials and Methods: We will review the results of randomized trials of targeted therapies that have been conducted and identify some new and promising avenues of investigation.

Table 1. Summary of studies of targeted molecular therapeutics evaluated

Reference	# Pts	Regimens	Survival
Bramhall, 2001	414	Gem vs Marimastat	Gemcitabine superior
Bramhall, 2002	239	Gem vs Gem/Marimastat	No difference
Moore 2003	377	Gem vs BAY12-9566	Gemcitabine superior
van Cutsem 2004	700	Gem vs Gem/Tipifarnib	No difference
Moore, 2005	569	Gem vs Gem/erlotinib	Gemcitabine + erlotinib superior
Phillip 2007	704	Gem vs Gem/Cetuximab	No difference
Kindler 2007	602	Gem vs Gem/Bevacizumab	No difference

Results: Pathways or targets that have been evaluated in phase III trials have included matrix metalloproteinase inhibition, K-ras, angiogenesis, epidermal growth factor receptor. Unfortunately most of these randomized trials of targeted therapy in pancreatic cancer have been negative with the exception of the NCIC trial of gemcitabine plus erlotinib which showed a modest but significant improvement in overall and progression free survival [HR 0.80 and 0.76 respectively].
Conclusions: Future investigations will examine other targets in pancreatic cancer such as src, M-TOR or FAK, explore combinations of targeted therapy. As it is probable that any intervention will only work in subsets of patients It is important that these trials include molecular correlates so that therapy can be individualized.

Symposium (Wed, 26 Sep, 14:45−16:50)
Innovations in prostate cancer – preclinical and clinical

153 INVITED

Biological profiling in prostate cancer

J. Schalken. *University Hospital Nijmegen, Urology Research Laboratory, Nijmegen, The Netherlands*

It is now generally accepted that (prostate) cancer has a diverse molecular basis, resulting in a spectrum of diseases with marked differences in biological behaviour. It is the ultimate challenge to be able to predict the biological behaviour of the cancer, understand its molecular basis in order to tailor the treatment for an individual patient. This concept is often referred to as individualized medicine. The development of molecular tools for life sciences research has revolutionized our understanding of cancer, and we believe the era of molecular medicine has commenced.
Molecular profiling is a rather old concept (identify molecular difference between for instance cancer- and benign tissue) but it is now developed on high throughput technology platforms (genomic- and expression profiling) yielding vast data sets. The algorithms to validate the resulting panels of new targets for diagnosis, prognosis, therapy are pivotal. To this end phenotypical as well as functional studies can be performed. In the past decade several new targets for prostate cancer were validated of which the prostate cancer specifically expressed gene, PCA3, and the unique fusion gene between TMPRSS2 and erg/ETV1/ETV4 have entered the clinical arena.
PCA3 is strongly over expressed in prostate cancer. After initial clinical evaluation using a RUO test (research use only), the marker has been developed on a validated clinical molecular diagnostics platform (APTIMA/DTS400). The test has proven to be very specific hence the first clinical indication for using the test is in determining prostate biopsy strategy. More recently, the PCA3 score, which can be determined non invasively, also appeared to be helpful in discriminating clinically significant from insignificant cancers. Thus evidence for further indications for the PCA3 test can be expected in the near future.
The fusion transcript between the androgen regulated TMPRSS2 gene and the ets related oncogenes erg, ETV1 or ETV4 (abbreviated as 'T2-erg') are uniquely found in ~60% of prostate cancers. Initial studies have shown that the panel of PCA3 and 'T2-erg' is a major step forward in the molecular diagnosis of prostate cancer. Furthermore, the T2-erg test may help in following endocrine therapy in a subset of patients with prostate cancer.
Clearly, these developments haven't resulted in a 'perfect' test panel, yet they mark the introduction of molecular tools in prostate cancer management and biological profiling is proving its clinical utility.

154 INVITED

Image-guided 4D radiotherapy for prostate cancer

J. Lebesque. *The Netherlands Cancer Institute, Radiation Oncology, Amsterdam, The Netherlands*

In the last decade dose-escalation for radiotherapy of prostate cancer has been studied extensively because of unsatisfactory local control and survival results with the past treatment doses. From the results of four phase-III randomized studies, with in total 2207 patients randomized, it became evident that higher radiation doses resulted in significant higher biochemical higher control rates. However, these higher doses also gave rise to higher toxicity rates, especially for gastro-intestinal complications, like rectal bleeding, fecal incontinence and high stool frequency.
Detailed analysis of these complications showed that they all were dependent on the volume of irradiated anorectum. Therefore new irradiation techniques with reduced margins and tighter dose distributions are being introduced in the clinic, thereby reducing the exposed rectum volumes and complication rates.
However, these new techniques might jeopardize the good local control rates, because the risk of geometrical missing the tumor. From two of the

trials, there were indications that high-risk patents with a full rectum in the planning CT scan had less biochemical control compared with patients with a relatively empty rectum. These results indicated that image guidance techniques are of paramount importance in combination with intensity modulated radiotherapy (IMRT).
Several image guidance techniques are currently in clinical use: ultrasound, implanted markers and Cone Beam CT on the treatment machine. The advantages and disadvantages of these techniques will be discussed in detail.

155 INVITED

Laparascopic surgery

T. Piechaud. *France*

Abstract not received.

156 INVITED

Comparison of laparoscopic prostatectomy with open radical prostatectomy for early stage PCA. Is there a real benefit for the patient?

M. Wirth. *Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik fü Urologie, Dresden, Germany*

Open retropubic radical prostatectomy is the standard treatment of localized prostate cancer in men with an adequate life expectancy. It was superior to watchful waiting in clinically diagnosed disease in a randomized trial concerning tumor control and overall mortality. New surgical approaches like conventional laparoscopic and robotic radical prostatectomy have not been investigated in a prospective randomized trial in comparison with open surgery yet. In experienced hands, the results of the different surgical approaches seemed to be comparable. Recent non-randomized comparative studies, however, suggest that conventional laparoscopy has an increased risk of postoperative urinary incontinence. Furthermore, there is a long learning curve in conventional laparoscopy which is associated with an increased risk of positive margins and rectal injuries that may cause fistulas. Until now, there is no conclusive evidence that laparoscopic approach has any clinically meaningful advantages compared with open surgery. Robot-assisted radical prostatectomy is an advancement of laparoscopic surgery. Centers with a high case load report excellent outcome concerning potency and uninary continence as well as tumor control in properly selected patients. The number of centers offering robot-assisted radical prostatectomy is fastly growing despite the currently still very high costs of this procedure. The development in the years to come will show whether robot-assisted radical prostatectomy wil establish a new standard of care of localized prostate cancer.

157 INVITED

Chemotherapy developments in hormone refractory prostate cancer, ongoing trials in early and advanced disease

R. De Wit. *Erasmus University Medical Center, Department of Medical Oncology, Rotterdam, The Netherlands*

In the late 1990s, phase I and II studies using docetaxel demonstrated substantial activity in terms of pain responses and median survival figures of 16−20 months, that warranted the initiation of two randomized phase III studies; TAX 327 and study SWOG 99−16. TAX 327 investigated the regimen of docetaxel 75 mg/m^2 every 3 weeks plus prednisone (10 mg daily), and the weekly regimen of docetaxel 30 mg/m^2 (5 of 6 weeks) plus prednisone, versus mitoxantrone 12 mg/m^2 every 3 weeks plus prednisone. 1,006 patients were randomized. The docetaxel every 3 weeks regimen resulted in significantly superior survival and higher PSA and pain response rates compared with mitoxantrone. The survival was 18.9 vs 16.5 months, the reduction in the HR of death was 0.76 (0.62−0.92). In an updated survival analysis (ASCO prostate 2007) the survival benefit has sustained (19.2 vs 16.3 months, HR 0.87).
SWOG 99−16 was built on the prejuidice that the combination of docetaxel plus estramustine had the greatest therapeutical potential and was the comparator against mitoxantrone plus prednisone. Also in this study the median overall survival was superior in the group receiving the docetaxel regimen, 17.5 vs 15.6 months, HR 0.80 (0.67−0.97). The incorporation of estramustine in the docetaxel regimen, however, was characterized by increased gastrointestinal and cardiovascular toxicity (mostly thromboembolic complications).
These study results have prompted studies to test the use of chemotherapy earlier in the course of the disease, such as the International trial TAX 3501, investigating immediate adjuvant hormonal treatment plus docetaxel vs hormonal treatment alone vs deferred therapy by the same therapeutical options in patients prostate cancer at high risk of relapse after radical prostatectomy. In the setting of androgen independent disease, studies will be aimed to investigate the addition of new active agents to docetaxel. Ongoing and planned randomised studies are employing the addition of high-dose calcitriol, DN-101 (International Industry sponsored trial), the addition of bevacuzimab (CALGB/ECOG/NCIC), astrasentan (SW0G) and the bisphosphonate risedronic acid (Netherlands).
In the setting of 2nd line chemotherapy, the recently completed SPARC trial has identified the oral platinum compound satraplatin as effective therapy. In the SPARC trial, 950 patients failing one line of chemotherapy were randomized to receive satraplatin plus prednisone, or placebo plus prednisone. Satraplatin provided significantly superior PFS and Time To Pain Progression. Results have been presented at ASCO 2007 and will also be available at ECCO 14.

Symposium (Wed, 26 Sep, 14:45−16:50)
Development of early markers of response

158 INVITED

Introductory talk (broad overview multiple approaches)

G.B. Mills. *USA*

Abstract not received.

159 INVITED

Targeting MEK in tumors with BRAF and RAS mutations

D. Solit. *Memorial Sloan-Kettering Cancer Center, Medicine, New York, USA*

Constitutive ERK activation is a common finding in human cancer and is often the result of activating mutations of BRAF and RAS. BRAF missense mutations occur in approximately 8% of human tumors, most frequently in melanoma, papillary thyroid cancer and colon cancer. Mutations in BRAF have been found predominantly in tumors in which RAS is commonly mutated but concurrent mutations of both BRAF and RAS are extremely rare. Though over 40 different kinase domain mutations in BRAF have been identified, a single base-pair substitution in exon 15 at codon 600 (V600E) is found in over 80% of cases. The majority of mutations identified cause constitutive kinase activation with the V600E mutation demonstrating approximately 500-fold greater kinase activity than wild-type BRAF. Supporting its classification as an oncogene, V600E BRAF stimulates ERK signaling, induces proliferation and is capable in model systems of promoting transformation. However, BRAF mutations are common in nevi and colon polyps suggesting that BRAF mutation alone is insufficient for tumorigenesis and additional mutations are required for cancer development. Though such data suggest that BRAF mutation is likely an early initiating event in tumors such as melanoma and colon cancer, preclinical studies suggest that tumors with V600E BRAF mutation remain dependent upon BRAF for proliferation and survival. Given its frequent occurrence in human cancer and the continued requirement for BRAF activity in tumors with BRAF mutation, efforts are underway to develop targeted inhibitors of BRAF and its downstream effectors. The first generation of RAF inhibitors, including sorafenib, were notable for their lack of specificity and potency for RAF and these agents have shown limited efficacy in tumors with a high incidence of BRAF mutation such as melanoma. Novel inhibitors of the pathway with greater selectivity for BRAF and MEK are now in Phase 1 and 2 clinical trials with promising early results. To maximize the likelihood of success with these agents, clinical trials enriched with patients whose tumors possess BRAF and RAS mutations have been proposed.

160 INVITED

Biopsy-driven biomarker development: pharmacodynamic studies in early clinical trials

J. Tabernero, T. Macarulla, J. Capdevila, A. Prat, F.J. Ramos, E. Elez, J. Baselga. *Vall d'Hebron University Hospital, Medical Oncology Department, Barcelona, Spain*

The selection of a therapeutic effective dose with conventional cytotoxic agents has been usually based on the consecution of the maximally tolerated dose. This principle does not apply for targeted agents, where the definition of the optimal biologic dose (OBD) would be preferred instead. The definition of OBD may be established based on pharmacokinetic endpoints or, preferably, by demonstrating the desired effect on the target molecule in normal or tumor host tissues. Normal tissues such as peripheral blood mononuclear cells, skin, mucosa or hair may be good surrogates for evaluating the exposure of a selected drug and kinetics of the target