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

inhibition in a clinical model. However, tumor pharmacodynamic studies may be better to explore the biologic effects of a selected agent than normal surrogate tissues, as tumor cells often respond in a different way to targeted drugs than normal cells. Therefore, the antineoplastic PD effect of a selected compound on the human tumor cells in the human host can only be evaluated when tumor biopsies are obtained before and during treatment. It has been also shown that the acquisition of sequential tumor biopsies before and on-treatment may be instrumental to elucidate mechanism of resistance to these targeted agents, either primary or secondary. We and others support PD studies with tumor biopsies from patients enrolled in clinical trials with new targeted therapies. These studies can not only evaluate the biologic effect of the drug in the tumor, but they may also identify the genomic and proteomic profile of the population with highest chances to benefit from treatment. In this presentation we will review the potential applications of these pharmacodynamic studies and give some examples validating this biomarker development approach.

161 INVITED

Function MRI – dynamic imaging of vascularity and diffusion imaging of cellularity

A.R. Padhani. *UK*

Abstract not received.

162 INVITED

PET scan

E. Aboagye. *UK*

Abstract not received.

Symposium (Wed, 26 Sep, 14:45−16:50)
Receptor signalling targets

163 INVITED

Introduction: The Rap1 signalling network in cell adhesion

J.L. Bos. *UMC Utrecht, Physiological Chemistry, Utrecht, The Netherlands*

Rap1 is molecular switch in a signaling network that regulates the integrity of cell layers, i.e. it stimulates integrin-mediated cell adhesion, inhibits migration, induces polarity and stabilizes cell-cell contacts. The network is activated by variety of different stimuli through a number of different guanine nucleotide exchange factors (GEFs), including the cAMP responsive Epac, the calcium responsive CalDAG-GEF, the PDZ-domain containing PDZ-GEF and C3G. Downstream from Rap1 a number of effectors have been assigned, including RapL and Riam in integrin-mediated cell adhesion, and Tiam and Vav in the control of the actin cytoskeleton. We will report on various aspects of this signaling network, including the differential usage of GEFs in the regulation of cell-cell junctions. Specifically, C3G is involved in the recruitment of E-cadherin to junctions, PDZ-GEF2 is involved in the maturation of junctions and Epac is involved in the regulation of the barrier function.

164 INVITED

mTOR-S6K1 signaling and cell growth control

J. Blenis, X. Ma, M. Holz, C. Richardson, R. Anjum. *Harvard Medical School, Department of Cell Biology, Boston, USA*

Background: Growth factor and oncogene-regulated PI3 kinase- and Ras-activated signaling pathways converge upon the nutrient- and energy-sensing mTOR pathway to modulate cell growth, survival and proliferation. In several human diseases, components of these pathways are often amplified or mutated resulting in inappropriate cell growth. The purpose of our research is to thoroughly define at a molecular and biochemical level how mTOR is regulated and signals, and how when improperly regulated this pathway contributes to carcinogenesis.
Materials and Methods: Multiple approaches including tandem affinity purifications, two-hybrid screens, proteomic screens, biochemical analysis and RNAi-based screens are being used to define this signaling system.
Results: The translation initiation factor eIF3, and the translation preinitiation complex (PIC), serve as scaffolds to promote growth factor- and nutrient-dependent initiation of mTOR-Raptor (mTORC1) signaling and phosphorylation of its two major effectors, the eIF4E binding proteins (4EBPs) and the S6 protein kinases (S6K1/2). Phosphorylation of these effectors results in their release from the PIC and promotes assembly of the translation initiation complex at the 5′ cap of mRNA. Once released from eIF3, S6K1 becomes activated and associates with the exon-junction complex of newly synthesized mRNA. Here the activated enzyme is positioned to phosphorylate targets involved in the pioneer round of translation. Thus, mTORC1 and S6K1 regulate assembly of the translational apparatus needed for pioneer and steady state translation, and connect growth factor signaling, nutrient availability and energy status to the energy consuming process of protein synthesis.
Conclusions: Rapamycin, a specific inhibitor of mTORC1, has emerged as a drug with potential therapeutic efficacy alone or in combination therapy. We are beginning to uncover the molecular basis of how mTORC1 and its effector, S6K1 are activated by multiple growth factor- and oncogene-regulated pathways, which in turn regulate cell growth through translation initiation and mRNA biogenesis. These studies are uncovering a basic mechanistic understanding of processes involved in regulating protein synthesis and are potentially revealing novel points of therapeutic intervention.

165 INVITED

Systems approach to growth factor signaling and to therapeutic intervention

Y. Yarden, I. Amit. *Weizmann Institute of Science, Department of Biological Regulation, Rehovot, Israel*

Growth factors and their transmembrane receptors contribute to all steps of tumor progression, from the initial phase of clonal expansion, through angiogenesis and metastasis. Hence, the information relay system involved in growth factor signaling provides potential sites for signal interception and tumor inhibition. A relevant example comprises the epidermal growth factor (EGF) and the respective receptor tyrosine kinase, namely ErbB-1/EGFR, which belongs to a prototype signaling module that drives carcinoma development. The extended module includes two autonomous receptors, EGFR and ErbB-4, and two non-autonomous receptors, namely: a ligand-less oncogenic receptor, HER2/ErbB-2, and a kinase-dead receptor (ErbB-3). This signaling module is richly involved in human cancer and already serves as a target for several cancer drugs. Due to inherent complexity and a large amount of experimental data, we propose a systems approach to understanding ErbB signaling. EGF-to-ErbB signaling is envisioned as a bow-tie configured, evolvable network, sharing modularity, redundancy and control circuits with robust biological and engineered systems. My presentation will concentrate on system controls, a plethora of negative feedback loops, which include E3 ubiquitin ligases, receptor endocytosis and newly transcribed genes. Because network fragility is an inevitable tradeoff of robustness, systems level understanding is expected to identify therapeutic opportunities for targeting aberrant activation of the network in human pathologies. Specific examples will be discussed with an emphasis on gene expression and the control of metastsis.

166 INVITED

PKB-FoxO

B. Burgering. *University Medical Center Utrecht, Laboratory of Physiological Chemistry and Centre for Biomedical Genetics, Utrecht, The Netherlands*

The class O of Fox transcription factors (FoxO) has recently become a focus of interest, after it was shown that its C. elegans homologue DAF-16 is critical in determining organismal lifespan and stress resistance. In higher organisms FoxO transcription factors have important roles in metabolism, cellular proliferation, stress tolerance and probably also aging. The activity of FoxOs is tightly regulated by post-translational modifications (PTMs), including phosphorylation, acetylation and ubiquitination. We will discuss how these PTMs of Foxo are regulated and what their functional consequences are. Remarkably, the enzymes identified to be responsible for the regulation of these PTMs are often identical between FoxOs and p53, and our recent studies indicate that the interplay between FoxOs and p53 mediated by these PTM modifying enzymes might underlie a ‘trade-off’ between disease and lifespan, the principal hallmark of aging.

167 INVITED

Pre-clinical studies of BRAF signalling in cancer

R. Marais. *Institute of Cancer Research, Signal Transduction Team, London, United Kingdom*

BRAF is a protein kinase that is mutated in 7% of human cancer. Mutations are particularly common (50−70%) in melanoma, but are also reasonably frequent in thyroid, ovarian, colorectal and billiary tract cancers. The mutations activate BRAF by destabilizing an inactive conformation of the kinase domain and allowing the active conformation to prevail. Inhibitors of BRAF are being developed and preclinical studies suggest that inhibitors of HSP90 are also likely to be effective for the treatment of BRAF mutant