Also in families with exact the same mutation differences in pentrance and expression can be observed. In Leiden a large founder population is present showing a specific 19 basepair deletion called P16-Leiden and even these families show variation in nevus phenotypes and the association with pancreatic carcinoma. In part these variations may be explained by the presence or absene of risk modifying genes like genes for skin type, hair color, sun sensitivity etcetera. Also the presence or absence of genes involved in the formation of moles ("nevus genes" are not yet identified) may interact with the final phenotype of the patiënt. We have observed that P16- Leiden negative family members may show increased numbers of AN, indicative of nevus genes segregating in the family apart from the P16- Leiden mutation.
These observations of variable phenotype and uncertain cancer risks (and the very low yield of mutations in 2 case families) has lead to the opinion of the International Melanoma Consortium not to recommend DNA testing to patients and families.
Since the penetrance figures for the P16-Leiden mutation are fairly well known we have decided to start offering DNA testing to these families in a research setting. Non-mutation carriers are kept in the yearly skin screening if they exhibit 5 or more AN. Psychological studies are being carried out to study the impact of knowledge of gene carriers about their increased pancreatic cancer risk, a disorder for which no screening is possible and no preventive messures are known.

148 INVITED

Genetic predisposition in Spain and Latin America

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Introduction: The Genetics of Melanoma network is a non-profit international consortium (GenoMEL) focused in studies of melanoma genetic susceptibility in Europe, Australia, North America and Israel. Nowadays GenoMEL is obtaining samples and data from an even wider geographical and ethnical spread of familial melanoma in Latin America.
Objective: To study the well-known genes for melanoma (MM) susceptibility (CDKN2A/p14arf, CDK4, MC1R) in familial and multiple primary MM in Spain and Latin America.
Material and Methods: Patients with genetic susceptibility for MM (familial and multiple primaries) from Spain and Latin American countries and Sporadic melanoma cases from Spain were included. Genetic studies, clinical fenotyping and specific follow-up of a subgroup of patients are performed.
Results: CDKN2A mutations were identified in 30% of families, 10% of multiple primaries and 1% of sporadic cases. CDKN2A mutations are responsible of MM susceptibility in a substantial percentage of familial MM patients in Latin American countries. Some CDKN2A mutations have a founder effect: G101W or 358delG originated in Mediterranean countries and −34G>T originated in United Kingdom, some of them were detected in Latin American families. Other CDKN2A missense mutations were detected in Mexican families like I49T described in North America and M52T not previously described. One melanoma patient was homozygote for the I49T mutation in Mexico. The nonsense germline E88X CDKN2A mutation was detected in two not related Uruguayan families. MC1R gene modifies the penetrance of CDKN2A in Spanish population. In multiple primaries the risk to be carrier of a CDKN2A mutation increases with number of primaries, early age of onset and presence of familial history of melanoma. In sporadic melanomas, CDKN2A mutations were associated with gender (males), early age of onset and multiple primary melanomas. An specific follow up programme including total body photography, dermoscopy and recently confocal microscopy permits the diagnosis of early melanomas in high risk patients.
Conclusion: Knowledge on the genetic epidemiology and surveillance programmes of melanoma is of great interest and will contribute for an efficient and reliable management of high risk melanoma patients in Spain and Latin American countries.

Symposium (Wed, 26 Sep, 14:45−16:45)
The challenge of treating advanced pancreatic cancer from translational to clinical trials

149 INVITED

Are there rational novel targets for pancreatic cancer therapeutics? Observations from the M.D. Anderson Cancer Center SPORE in Pancreatic Cancer

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The recent failure of two large randomized phase III trials of the targeted monocloncal antibodies bevacizumab and cetuximab and the limited value of erlotinib has emphasized that therapy for advanced pancreatic cancer remains suboptimal. For this disease it now appears that therapeutically targeting individual proteins involved in the growth of pancreatic cancer cells will only lead to minor incremental improvements in patient survival. What should be our collective response to this fact? The pancreatic cancer SPORE at the M. D. Anderson Cancer Center is attempting to exploit aspects of pancreatic cancer molecular biology in order to discover and evaluate new targets for therapeutic development. Three general approaches are being taken: (1) Understanding the molecular biology of transcription factors activated pancreatic cancer and developing means to inhibit them. Thus far, we have analyzed NFκB and Specificity (Sp) proteins. NFκB has been targeted using the natural product curcumin with promising early activity documented in a pilot clinical trial. Sp proteins regulate many downstream proteins critical to cancer development and growth, including vascular endothelial growth factor. Non-steroidal anti-inflammatory agents such as celecoxib and tolfenamic acid promote proteasomal degradation of Sp1, Sp3, and Sp4 and will be assessed in future clinical trials. (2) Pancreatic cancer cells appear to be particularly susceptible to endoplasmic reticular (ER) stress and cellular proteotoxicity. ER stress can be induced in pancreatic cancer cells using the FDA-approved agent bortezomib. The proteotoxicity of bortezomib against pancreatic cancer cells appears to be due to the failure of bortezomib to stimulate the phosphorylation of PERK, leading to hypophosphorylation of eif2a. Despite bortezomib's inhibition of protein degradation through inhibition of the proteosome, eif2a allows protein translation to continue leading to cellular proteotoxicity. Combinations of bortezomib and protein disrupting agents such as SAHA or specific HDAC inhibitors appear particularly effective in stimulating apoptosis in pancreatic cancer cell lines in vitro and in vivo. A clinical trial assessing this therapeutic approach is underway. (3) Finally, new targets for pancreatic cancer are needed. We are therefore using a novel synthetic lethal screen in Drosophila to identify new targets that will then be evaluated and exploited in vertebrate systems. It is our belief that our efforts to develop new treatments for pancreatic cancer need to be closely integrated with the global efforts to understand the molecular biology of this disease and that future strategies should be rationally designed rather than empiric.

150 INVITED

Trial design issues in advanced pancreatic cancer

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Background: Progress has been slow in pancreatic cancer treatment. Although tumour biology is likely most important for this, design issues may contribute.
Methods: Reports of clinical phase II and III trials in major oncology journals during the past 10 years were scrutinized for aspects that could have influenced the treatment results. Some of these aspects will be discussed.
Results: The results of the many phase II trials, particularly in the locally advanced cases, are often more dependant upon patient selection than treatment efficacy. Since the gains in chiefly survival have been limited, the problems with sufficient power were of concerns, although lately several adequately powered phase III trials have been concluded. It could then be discussed whether some of the gains, shown to be statistically significant, are clinically meaningful considering toxicity and costs. It has been discussed whether patients with locally advanced disease only should be included with those with metastatic disease in trials evaluating systemic treatments. In phase II trials, this can heavily biaz the results, but stratification in the phase III trials can overcome the problem. Evaluation of

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

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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

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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

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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

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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