in the development of pancreatic ductal adenocarcinoma (Guerra et al., Cancer Cell, 2007).
We have used the same targeting strategy to generate mice carrying an endogenous H-ras oncogene. As recently reported in humans suffering from Costello syndrome, germ line expression of H-RasV12, unlike that of K-RasV12, is tolerated during embryonic development. Moreover, these mice do not develop overt tumor formation at least for nine months. These observations indicate that H-Ras and K-Ras oncoproteins have significantly different properties in vivo.

107 INVITED

Biological roles of PI 3-kinase isoforms

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The PI 3-kinase pathway has been implicated in a wide variety of physiological responses, and is considered as a therapeutic target amongst other in cancer and inflammation. Mammals have 8 distinct isoforms of PI3K, and global inhibition of all isoforms of PI3K is toxic in vivo. Therapeutic intervention with the PI3K pathway will therefore most likely have to be centered on specific (subsets of) PI3K isoforms. However, identifying the indications that will provide the best opportunity for isoform-selective PI3K inhibitors is the subject of intense debate. Indeed, it has turned to be particularly difficult to gain insight into the physiological roles of PI3K isoforms by classical mouse gene targeting/knock-out approaches. We have pioneered the use of so-called 'kinase knockin' mice in which we have created germline inactivating mutations in the ATP-binding site of PI 3-kinase isoforms. This strategy more faithfully mimics pharmacological inhibitors than the classical knock-out approaches, and has allowed us to uncover isoform-selective roles of several isoforms of PI3K and begin validation of these PI3Ks as therapeutic targets. An overview of these efforts will be presented.

108 INVITED

Preclinical and clinical studies

G.B. Mills. *USA*

Abstract not received.

Symposium (Tue, 25 Sep, 14:45−16:50)
Issues in geriatric oncology

109 INVITED

The right treatment for elderly with cancer is not easy to determine: a research strategy

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Background: Never ending discussions on the right oncological treatment of, especially frail, elderly with cancer; obvious reasons being a limited but often varying, life expectancy, vulnerability, complicating presence of co-morbidity, increasign with age flattening above 80 years and social reasons like being cared for at home, transportation. Quality of life matters a lot when your time is relatively short. Communication problems are large. One could argue that the right treatment hardly exists: there is either over- or undertreatment.
Materials: Data from the population-based Eindhoven Cancer Registry that comprise co-morbidity and SES and various studies on prevalence, effects on stage and treatment policy and outcome; literature on research strategy and a forthcoming special issue on Cancer management in the Elderly of the European Journal of Cancer based on an ESO course in april 2007.
Results: Prevalence of serious co-morbidity is substantial in elderly (less than one third being without overt serious co-morbidity, with sometimes small, sometimes large effects on life expectancy, but necessitating medical and organizational adaptations in care supply. Medical care in the (very) elderly is in fact individualized, as patients become more unique medically and socially, thus hampering traditional clinical research e.g. by means of RCT's. The annual number of specific (with respect to pattern of co-morbidity) older patients per hospital is usually rather small, which points to regional collaboration. Geriatricians with extensive knowledge of oncological treatments are usually scarce.
Conclusions: Prospective (and also retrospective, if suitable) research should be population-based, thus exhibiting the broad spectre of disease and health status. Collaborations of large numbers of hospitals is necessary in order to have adequate numbers in subgroups. When the standard oncological treatment risks to be overtreatment, the study should rather focus on complications, side effects that determine QL. When, more or less deliberately, undertreatment is administered (less lymphnode sampling and/or adjuvant treatment) studies are necessary of recurrence rates and metastasis, and of QL at short and longer term. One could argue to learn more from at short term less risky undertreatment than from (the oncologically right?) overtreatment. Results should be more expressed in numbers needed to treat, stage, etc to avoid one (extra) recurrence, or side effect or complication.
With respect to care development, practical steps should be taken to develop or cut care paths (in the jungle of) the hospital that take account with co-morbidity management and address communication problems.

110 INVITED

Comorbidity assessment and the influence of comorbidity on toxicity and choice of treatment

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One characteristic of ageing is an increased prevalence of comorbidity. In western coutries, 35% of people aged 65−79 reports at least two diseases, this ratio increases up 70% at age 80 and older.
Comorbidity may affect the accuracy of cancer screening or diagnosis. It can also influence both treatment and prognosis of cancer itself. Then, comorbidity requires careful assessment before planning cancer treatment. Various scales are available to measure it, with the capacity for predicting, for instance, the risk for hospitalization or death. Concomitant morbid conditions may be more difficult to treat, adding complexity in terms of competing risks; potentially incompatible therapies; burden or costs of therapies that patient can not tolerate, and synergistic likelihood of adverse outcomes, including disability and death. In many cases, geriatricians should help oncologists to define the hierarchy of patient diseases, including cancer and prioritize those requiring immediate treatments.
On the other hand, a common comorbidity in elderly patients such as diabetes mellitus has been suspected to worsen cancer outcomes. Obesity appears also to affect the prognosis of prostate cancer or breast cancer. Conversely hypothyroidism seems to be associated with a lesser incidence of breast cancer.
Furthermore, multiple concomitant diseases frequently lead to polypharmacy, increasing the likelihood of drug interaction with chemotherapy agents or supportive treatment. In fact, inappropriate medication use is frequent in older people taking at least 5 medications.
The management of elderly cancer patients should take into account not only the impact of cancer treatment on comorbidity and the effect of comorbidity in delivering cancer treatment, but also the impact of comorbidity on the behavior of the cancer in the elderly patients.

111 INVITED

The essentials of geriatric oncology studies: do's and don'ts

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What is a geriatric oncology study? This is not a study of elderly patients defined as aged above 65, but it should be a study that takes into account principles of geriatric assessment. It should ideally include patients representative of all "elderly categories". This means including frail patients, because of age alone or because of biological limitations. Study endpoints may vary, from relapse-free survival to overall survival, as in many settings deth from other causes may become a predominant issue, while patients value relapse-free time. Geriatric oncology studies need also to overcome the perceived "impossibility" that prevails in many settings. Well informed elderly patients and their caregivers will never refuse a well conceived study. There is a need to define standardized geriatric assessment tools to collect information in cancer patients. Once ongoing studies will have provided further information, an effort to coordinate cooperative groups should be done, so that all use a common tool, which will be a means to compare studies. This is similar to the easier but long process which lead to the adoption of performance status as a key element of all studies in oncology. The SIOG (International Society for Geriatric Oncology) Task Force on Geriatric assessment suggested that some of the data analyzed should be: checking whether screening tools correctly identify patients (i.e., too well, too ill); validating inclusion/exclusion categories; developing a scoring algorithm to identify target groups, identifying the best candidates for a specific intervention. b) defining the patient's status: prospective data about the importance of hemoglobin levels, albumin levels, creatinine clearance and drug interactions are needed. Studies should evaluate these determinants prospectively in order to define for which drugs such data are important in the choice of the treatment. c) definition of the disease: