vemurafenib induces cutaneous squamous cell carcinomas (cuSCC) in about 25% of melanoma patients. We find that a high proportion of these tumours express oncogenic RAS and we also show that BRAF inhibitors accelerate formation of cuSCC in mice treated with DMBA and TPA. Critically, MEK inhibitors block the induction of cuSCC by BRAF inhibitors and the established tumours regress following treatment with the anti-proliferative drug 5-FU. Our data suggest that BRAF drugs are not tumour promoters *per se*, but rather that accelerate tumour formation from pre-existing, pre-malignant lesions present in the skin of susceptible patients.

386 INVITED

MEK-RAF Inhibitors

Abstract not received

387 INVITED

PI3K Pathway Inhibitors: What Have we Achieved and Future Directions

J. Tabernero[1], R. Dienstmann[1], A. Cervantes[2], I. Braña[1], M. Alsina[1], J. Rodon[1]. [1]*Vall D'Hebrón University Hospital, Medical Oncology Department, Barcelona, Spain;* [2]*Clinic Hospital, Medical Oncology Department, Valencia, Spain*

Inappropriate PI3K signaling is one of the most frequent occurrences in human cancer and is critical for tumour progression. Several molecular aberrations have been described affecting key components of this pathway, with implications not only for tumorigenesis but also for resistance to other antineoplastic agents. Examples include genetic mutations and amplifications (*PIK3CA, AKT*) and loss of function of negative regulators of the pathway (PTEN). Emerging preclinical research has significantly advanced our understanding of the PI3K pathway and its complex downstream signalling, interactions and importantly, the crosstalk with other pathways. Rapalogs are the first inhibitors of downstream effectors of the PI3K pathway to enter the clinic, although with limited clinical antitumour activity. The cellular response to mTOR complex (mTORC) 1 inhibition, which upregulates AKT via negative-feedback loop in some cell lines, combined with the discovery of the direct involvement of mTORC 2 in the activation of AKT, have led to development of rationally designed drugs targeting key elements of this pathway. These include: (a) pure pan-PI3K inhibitors, targeting all isoforms of PI3K; (b) dual PI3K/ mTOR inhibitors; (c) AKT inhibitors; (d) mTORC 1 and 2 inhibitors; and (d) isoform-specific PI3K inhibitors, including the alpha isoform activated in *PIK3CA* mutants and the delta isoform upregulated in hematologic neoplasms. Frequent toxicities reported in the first-in-human trials included rash, asthenia, diarrhea, nausea, mucositis, transaminase elevation and hyperglycemia. These agents are still in early phases of clinical development, some already entering phase 1b and 2 trials. Clinical benefit with partial responses and prolonged disease stabilization have been reported in multiple tumour types, such as breast, ovarian, endometrial, prostate, lung, mesotheliomas, sarcomas and lymphomas. Importantly, clinical benefit has not been restricted to patients whose tumour harbor PI3K pathway activation. Preliminary reports of the pharmacodynamic effects of PI3K pathway inhibitors have shown reduction of activation of key pathway readouts in the order of 50 to 90% both in tumour and surrogate tissues (such as pAKT, pPRAS40, pS6K and p4EBP1), giving reassurance that a target is being hit. Other biomarkers of pathway inhibition under investigation include increase in plasma C-peptide levels and reduction of glucose avidity on FDG-PET scans. Recognizing that PI3K pathway operates in complex networks in which the outcomes of pharmacologic modulation may be difficult to predict is of paramount importance. Therefore, the next generation of trials with PI3K pathway inhibitors is focusing in combination strategies, including other targeted therapies (such as anti-HER2 agents and MEK inhibitors) and conventional chemotherapy. Results of these studies are eagerly anticipated.

Scientific Symposium (Tue, 27 Sep, 09:00−11:00)
Head and Neck Cancer in the Elderly Patient

388 INVITED

Management of the Elderly Patient in Head and Neck Cancer

I. Moutzios[1], K.N. Syrigos[1]. [1]*Medical School University of Athens, Oncology Unit GPP, Athens, Greece*

Squamous-cell carcinoma of the head and neck (SCCHN) represents a heterogenous tumour entity that requires multimodality approaches depending on primary tumour location, clinicopathological stage at diagnosis and patient co-morbidities. As average lifespan is improving, an increasing number of SCCHN patients belong to the "elderly" patient population; Given the fact that many of these patients have a history of heavy smoking and/or alcohol consumption, chronic obstructive pulmonary disease and coronary heart disease, the implementation of therapeutic modalities used for fit patients becomes particularly challenging. The fact that patients older than 70 years of age are rarely included in clinical trials in SCCHN further compromises optimal treatment for this patient group. Compared to their younger counterparts, elderly patients are reported to receive less aggressive treatment and are less likely to be treated with curative intent. However, recent data support the position that the physiological, rather than the chronological age of the patient should guide therapeutic decisions: Locoregional control rates and disease-free survival in elderly patients treated with radiotherapy or chemoradiotherapy, either with curative intent or in the palliative setting, are comparable to those seen in younger patients. Moreover, the implementation of new chemotherapeutic agents, such as the taxanes and the use of molecular targeted agents, including monoclonal antibodies against the Epidermal growth factor receptor (EGFR), provide the clinician with a broad spectrum of treatment choices with diverse toxicity profiles. The improvements that have been accomplished in both surgical procedures, including organ preservation strategies, and radiotherapy delivery, including short hypofractionated techniques, offer to the clinician important tools, especially in the treatment of the more "fragile" elderly patients. Therefore, age alone should not be the main criterion for therapeutic planning: A thorough geriatric assessment should be the first and important step for selecting further treatment options; In patients receiving systemic treatment, chemotherapy doses should be modified according to the renal and hepatic function; Alimentation and nutritional status should be constantly evaluated, especially in patients undergoing radiotherapy in the upper aerodigestive tract. Last but not least, emotional well-being should be a priority for these older patients that suffer from substantial co-morbidities and may require psychological and social support.

389 INVITED

Special Considerations in Surgery for Elderly Patients With Head and Neck Cancer

J. Lefebvre[1]. [1]*Centre Oscar Lambret, Department of Head and Neck Surgery, Lille, France*

The elderly population is growing rapidly and a substantial part of the population is over 70 years in age. In parallel with this increase in advanced age, the incidence of cancer and the risk of multisystem failures are also raising. For a long time surgery had been often withheld for elderly patients. This led to inappropriate treatment when surgery was considered as the best option but rejected by principle considering the patient's age. Due to the advances in anesthetic and surgical techniques as well as in pre and postoperative care, surgery has been increasingly used for this growing segment of the population. There are accumulating and converging reports on the safety of surgery in elderly patients. There is a consensus for considering the preoperative general status instead of the chronological age. On the contrary there is no consensus on the definition of the elderly population that is arbitrarily defined as over 65, over 70 or over 80 in the different publications.

As far as head and neck surgery is concerned the situation is significantly more complex. On one hand head and neck surgery generates less post-operative morbidity than thoracic or abdominal surgery and rarely results in major hemodynamic shift. On the other hand elderly patients with head and neck cancer have accumulated multiorgan failures due to the normal ageing process but also due to their lifestyle (tobacco/alcohol, occupational exposures) as well as nutritional and/or pulmonary consequences induced by tumours growing on the upper aerodigestive tract. This situation is also to be considered in the particular sociocultural context of most of head and neck patients. However notwithstanding these considerations, head and neck cancer surgery is more and more proposed in elderly patients with satisfactory postoperative outcome. More recently major head and neck surgery including lengthy procedures with microvascular free tissue transfer has being reported with comparable surgical complications to a younger population of patients. But all these retrospective studies have been carried out on selected population of patients. The major predictive factors for either local or systemic postoperative complications are obviously linked to the preoperative status of the patients.

In conclusion when surgery is selected as a part of the therapeutic programme for an elderly patient the risk-benefit ration must be approached with caution and in the light of the life expectancy. The anesthesiologic and geriatric evaluations must assess the preoperative performance status and physiological reserve in order to determine whether the patient's condition is compatible with surgery and to anticipate possible postoperative complications requiring adapted preoperative care and perioperative monitoring. The psychological profile and cognitive functions must also be evaluated in particular when mutilating surgery (such as total laryngectomy) is indicated.