Presidential Sessions

Presidential Session II

Sunday 25 September 2011, 12:20−14:40

G1 Hamilton Fairley Award

New therapeutic avenues in lung cancer based on disturbances in PI3K and RAS pathways

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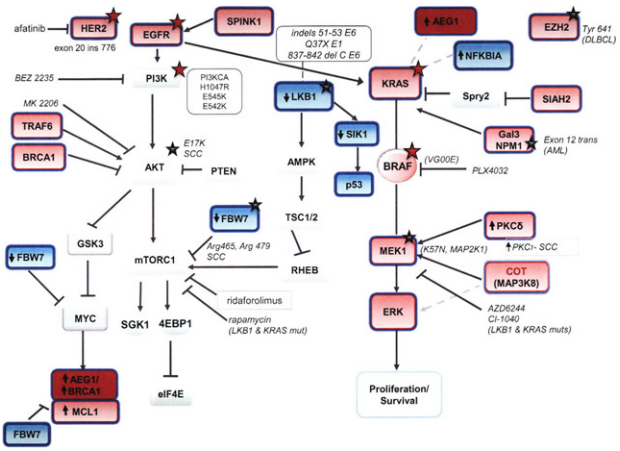
The vast majority of tumors, including lung cancer, have several alterations in the PI3K and RAS pathways, as well as in p53. The new challenge in providing better treatment for patients lies in understanding the relationship between different genetic abnormalities that can serve both as prognostic markers and as the basis for novel therapeutic intervention. For example, we have observed that AEG-1 and BRCA1 mRNA expression significantly influences progression-free survival (PFS), either in metastatic non-small-cell lung cancer (NSCLC) patients with or without EGFR mutations. BRCA1 mRNA expression was also an independent prognostic marker in erlotinib-treated EGFR mutated NSCLC patients, with significant differences in the length of PFS according to BRCA1 levels: median PFS was 27 months in patients with low BRCA1 mRNA expression [1]. Moreover, a significantly better PFS was obtained in those patients who had elevated expression of NFKBIA (a gatekeeper of the EGFR pathway and the inhibitor of NFκB activation) [2].

FBW7 is an important tumor suppressor gene that degrades mTORC1 and the loss of FBW7 could be a potential biomarker for treatment with mTOR pathway inhibitors [3]. FBW7 also inhibits the pro-survival protein MCL1 which is a crucial regulator of apoptosis triggered by antitubulin drugs. It has been suggested that profiling FBW7 and MCL1 status of tumors in terms of protein levels, messenger RNA levels and genetic status could be useful for predicting patient response to antitubulin drugs [4,5]. Intriguingly, in a systematic characterisation of somatic mutations in cancer genomes, a high frequency of FBW7 was observed in squamous cell lung cancer. However, in the report no details of the type of EGFR mutations are given [6]. Hotspot mutations have been described in FBW7 that occur in high frequencies, 30%, in cholangiocarcinomas and also in T-ALL [7]. Therefore, it is of great interest to examine FBW7 status, including mRNA expression.

EZH2, an oncogene which activates NFκB and RAS, was closely correlated with BRCA1 expression in a series of 60 metastatic NSCLC patients, but with no correlation between levels of EZH2 and K-ras mutations. EZH2 mutations (Try641) have been reported in follicular and diffuse large B-cell lymphomas [8].



BRAF mutations have been identified in NSCLC, more frequently in women (9%), and only V600E had prognostic significance in a series of 1000 lung cancers screened (Marchetti et al., in press). In addition, MEK1 mutations have been described at low frequencies [9], which could be susceptible to treatment with selective inhibitors [10]. MAP3K8 (the gene encoding COT) is a MAPK pathway agonist that drives resistance to RAF inhibition in BRAF (V600E) cell lines [11]. Other downstream components that can influence clinical behavior of tumors with K-ras mutations is the recently described model for PKCδ regulation of apoptosis and survival in K-ras dependent NSCLC [12]. Overexpression of PKCδ promotes tumor progression in pancreatic cancer [13].

Therefore, in tumors with K-ras mutations, many genetic modifiers can be relevant in delivering prognostic information and for predicting response to selective inhibitors, including MEK inhibitors [10] or mTOR inhibitors. Interestingly, overexpression of the atypical PKCι confers poor prognosis in early NSCLC and is amplified in squamous cell lung cancer [14]. LKB1/STK11 is also one of the most frequently mutated tumor suppressor genes in NSCLC [15].

References

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Presidential Session III

Monday 26 September 2011, 12:15−14:25

G2 ECCO Clinical Research Award

Adjuvant Systemic Treatment for Women with Breast Cancer: The Future of Clinical Trials

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Adjuvant systemic therapies have been studied for several decades in randomized clinical trials. Historically, prognosis (primarily nodal status) and age (as surrogate for menopausal status) were the main features that defined eligibility of patients for specific trials. Evidence regarding the importance of steroid hormone receptors and HER2 overexpression/amplification for determining appropriate treatments required consideration of these two additional features for study eligibility. Within the past decade the heterogeneity of breast cancer was further highlighted with the recognition of biological subtypes based on gene expression. Recently, intrinsic biological subtype nomenclature was recommended to provide a ‘short-hand’ for specific clinico-pathological classification to be applied in clinical practice and trial design. The following subtypes were defined: “Luminal A”, “Luminal B HER2-negative”, “Luminal B HER2-positive”,

"HER2-positive" and "Triple-negative". The need for specific trials for each of these subtypes is an obvious evolution within the field of adjuvant systemic therapies. While research on HER2-positive disease has progressed rapidly, clinical research on the adjuvant treatment of "Triple-negative" or "Luminal B" breast cancers lack initiatives. Reasons for such limited clinical research include the relatively small size of subpopulations in which niche trials should be performed and the enormous costs involved in conducting and monitoring an adjuvant trial. Nevertheless, results from past trials indicate the need to improve outcomes for several cohorts of breast cancer patients. These include treatment strategies for young women, improved endocrine therapies to reduce the risk of late relapse in endocrine-responsive cohorts, and combined targeted therapy such as novel cytotoxic combinations together with DNA repair inhibitors for patients with triple negative disease.

Presidential Session I
Saturday 24 September 2011, 13:45−15:35
1BA BEST ABSTRACT

A Pivotal Multicenter Trial Evaluating Efficacy and Safety of the Hedgehog Pathway Inhibitor (HPI) Vismodegib in Patients With Advanced Basal Cell Carcinoma (BCC)

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Background: The Hedgehog (Hh) signaling pathway is implicated in pathogenesis of BCC. While most BCCs are mostly surgically managed, rare BCCs can become locally advanced (laBCC) or metastatic (mBCC), leaving no effective therapeutic alternatives. Vismodegib (GDC-0449) is a first-in-class small-molecule inhibitor of Hh signaling. In a phase 1 trial, a 55% response rate was seen in 33 patients (pts) with advanced BCC, and treatment was generally well tolerated (Von Hoff, NEJM 2009), leading to this pivotal trial of vismodegib.
Materials and Methods: This pivotal, multicenter, 2-cohort (laBCC and mBCC) nonrandomized study (NCT00833417; ERIVANCE BCC, SHH4476g; sponsored by Genentech; closed to enrollment). Pts with laBCC had histologically-confirmed BCC that was inoperable or for whom surgery would be significantly disfiguring. Pts with mBCC had histologically-confirmed RECIST-measurable disease. Pts received 150 mg oral vismodegib daily until disease progression. The primary endpoint is overall response rate (ORR) by independent review (IRF), using RECIST for mBCC and a composite endpoint for laBCC including improvements in tumor dimension and ulceration, pathologic clearance of BCC, and RECIST if applicable. Primary hypotheses tested are that ORR is significantly >20% for laBCC and >10% for mBCC. Secondary endpoints include duration of response, response per investigator (INV), and safety.
Results: 104 pts (71 laBCC/33 mBCC) were enrolled at 31 sites in US, Europe and Australia. For laBCC, the IRF ORR was 43% (95% CI 31−56%; $p < 0.0001$) and INV ORR was 60% (95% CI 47−72%). For mBCC, the IRF ORR was 30% (95% CI 16−48%; $p = 0.0011$) and INV ORR was 46% (95% CI 28−62%). Adverse events (AEs) in >30% of pts were muscle spasms, alopecia, taste disturbance, weight loss and fatigue. Serious AEs were reported in 26 pts (25%); 4 patients (4%) experienced serious AEs considered related to vismodegib. Fatal AEs were reported in 7 pts (7%), none considered related to vismodegib. Duration of response, histopathology, and detailed safety will be presented.
Conclusions: This pivotal study confirms the significant clinical benefit of vismodegib in both laBCC and mBCC, as measured by tumor response, and further characterizes the AE profile. These results demonstrate the potential role of vismodegib for the treatment of advanced BCC.

Presidential Session II
Sunday 25 September 2011, 12:20−14:40
2BA BEST ABSTRACT

Synchronous Chemo-radiation Can Reduce Local Recurrence in Early Stage Breast Cancer: Results of the SECRAB Trial (ISRCTN: 84214355) Presented on Behalf of the SECRAB Steering Committee

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Background: The sequencing of chemotherapy (CT) and radiotherapy (RT) after surgery for early breast cancer (EBC) remains controversial. Previous studies using a mitozantrone based regimen have shown that synchronous (Syn) CT-RT does not significantly improve loco-regional recurrence (LLR) and resulted in worse toxicity. SECRAB was designed to determine the optimal sequence of CT and RT in patients having a CMF or anthracycline (A)-CMF regime. The results of a planned analysis looking at local recurrence (LR) are presented.
Materials and Methods: SECRAB was a prospective, randomised multicentre trial comparing sequential (Seq) to Syn RT. RT schedules included 40 Gy/15F over 3 weeks, 45 Gy/20F over 4 weeks and 50 Gy/25F over 5 weeks. Syn RT was administered between cycles 2 and 3 for CMF or 5 and 6 for A-CMF. Seq RT was delivered on CT completion. Key eligibility criteria were completely excised EBC, fit for and requiring adjuvant CT and RT. Between Jul 98 and Mar 04, 2296 women were randomised. LR was defined as a recurrence in the ipsilateral breast or chest wall. Time to LR was calculated as the time from entry until first LR or date of censor.
Results: With a median follow-up of 8.8 years there were 63 and 41 LR in the Seq and Syn arms and 5-year LR rates were 5.1% (95% CI: 3.8%, 6.4%) and 2.8% (95% CI: 1.8%, 3.8%) respectively. There was a significant benefit for Syn RT with a 35% reduction in the risk of LR ($HR_{Syn} = 0.65$, 95% CI: 0.44, 0.96; $p = 0.03$). There was benefit for Syn RT across all treatment (CT regimen, duration of RT, RT boost) and biological subgroups (grade, lymph node status, tumour size, vascular invasion and excision margin). A previous analysis of LRR rates showed no significant difference between Seq and Syn RT ($HR_{Syn} = 0.82$, 95% CI: 0.60, 1.10; $p = 0.19$). Benefit for Syn RT was not seen in patients with regional recurrence, as 80% of these were outside the radiation field. Previously presented results showed an increase in acute skin toxicity in patients treated with Syn treatment however a recent analysis of quality of life data has shown no difference between the two arms.
Conclusions: Syn RT using a CMF or A-CMF regimen has resulted in a significant reduction in LR. The magnitude of benefit is comparable to the effects of chemo-radiation seen in other tumour sites. This is the first study to show this effect in EBC.
Sponsor: University Hospitals Birmingham NHS Foundation Trust

Presidential Session III
Monday 26 September 2011, 12:15−14:25
3BA BEST ABSTRACT

VANTAGE 014: Vorinostat (V) in Patients With Advanced Malignant Pleural Mesothelioma (MPM) who Have Failed Prior Pemetrexed and Either Cisplatin or Carboplatin Therapy: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial

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Background: V is a histone deacetylase inhibitor that alters gene expression and protein activity. Five of 13 previously treated patients with