EML4/ALK and Ras Inhibitors

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This session discussed two targets for therapeutics, one very new, EML4/anaplastic lymphoma kinase (ALK) translocation and the other very old, the ras pathway. The developments in epidermal growth factor receptor (EGFR) inhibition have brought these two areas together as disease characterized by these abnormalities is unresponsive to EGFR inhibition. The recent discovery of the EML4/ALK translocation has identified the underlying biology for another group of patients characterized by never smoking history and provided a new target for therapy. Ras mutations and other abnormalities of this pathway are an old target that has been associated with relative resistance to EGFR tyrosine kinase inhibitors and conventional chemotherapeutics.

SUMMARY OF PRESENTATIONS

EML4-ALK and PF 02341066

Drs. Alice Shaw and Ross Camidge presented updates on EML4/ALK and its inhibitor, PF-02341066 (crizotinib). Perhaps the most important development this year in oncology is the emerging story of the EML4-ALK translocation in non-small cell lung cancer (NSCLC). This translocation was originally discovered as part of a rational search by Soda et al.[1] In this seminal article, Soda et al. described the identification of the translocation, its transforming nature, the potential of specifically targeted agents to inhibit the fusion gene with resulting tumor shrinkage in an animal model, and the demographics of patients who had the gene. These patients were characterized by a nonsmoking history, adenocarcinoma histology, and absence of EGFR mutation.

Shortly after the discovery, the group at Massachusetts General Hospital began to screen never smoking patients who were EGFR negative for the translocation. The technique used was fluorescence in situ hybridization. They identified a number of patients. They confirmed the findings of Soda et al. that the phenotype of the patient with EML4/ALK translocation is a scant or never smoker, relatively young, with an adenocarcinoma histology, and who is relatively unresponsive to chemotherapy or EGFR inhibitors.[2] Recently noted is that the patients seem to have a histologically distinct disease, characterized by a signet ring-type mucinous adenocarcinoma.[3]

A fortuitous development was that PF-02341066, which was already in development as a c-met inhibitor and undergoing evaluation in patients resistant to EGFR tyrosine kinase inhibitors, also demonstrated significant in vitro activity against cell lines with activated ALK with an IC_{50} of 20 nM. During phase I testing, a patient with the translocation had a significant clinical response. The ultimate maximum tolerated dose/recommended phase 2 dose was 250 mg twice daily. The major toxicities identified were ALT elevation and mild (grades 1 and 2) nausea, vomiting, fatigue, and "sight disturbance." Only the ALT elevations were potentially dose limiting.

This phase I trial coupled with the clinical and laboratory data led to rational testing of the agent in a population of patients enriched for the EML4/ALK translocation and reported by Dr. Camidge. Remarkably, there was a response rate of 64% and a clinical benefit rate (stable disease + partial response + complete response) of 95%. Importantly, much of this benefit was sustained with a median duration of 19+ weeks and a progression-free survival that was not reached. This result has led to a phase III trial currently enrolling patients (Figure 1). A phase II trial is also open for patients with the translocation not meeting the eligibility requirements for the phase III study.

Ras Targeting

Abnormalities of the ras pathway (Figure 2) are frequent in NSCLC. Activated k-ras is a common abnormality in NSCLC, particularly in adenocarcinoma. K-*ras* mutations are, for the most part, mutually exclusive with EGFR mutations and EML-4/ALK translocations. Dr. Scaglioni presented a novel approach to targeting this common abnormality. Downstream effectors of ras activation are mTOR and phosphatidylinositol 3-kinase. BEZ235 is a dual inhibitor of phosphatidylinositol 3-kinase and mTOR that is entering investigation.[4] In preclinical models, it has been demonstrated to suppress tumor growth without causing apoptosis.[5]

B-RAF

B-raf mutations are relatively uncommon in NSCLC (2%); however, the advent of an effective agent raises the possibility that effective treatment for these patients may be available in the near future. As discussed by Dr. George Riely, PLX4032 has demonstrated clear evidence of activity in patients with B-raf mutated melanoma with a response rate of 70% (albeit with an n = 27).[6] This agent is currently in an expansion phase at 960 mg/m^2 orally twice daily in B-RAF-mutated melanoma. The toxicities of the agent are primarily cutaneous, with rash (68%) and photosensitivity common, but not usually severe (i.e., grades 1 and 2). Interestingly, a high incidence of cutaneous squamous cell carcinomas has been noted. Other toxicities include nausea, fatigue, and LFT abnormalities. Another potential therapeutic for these patients

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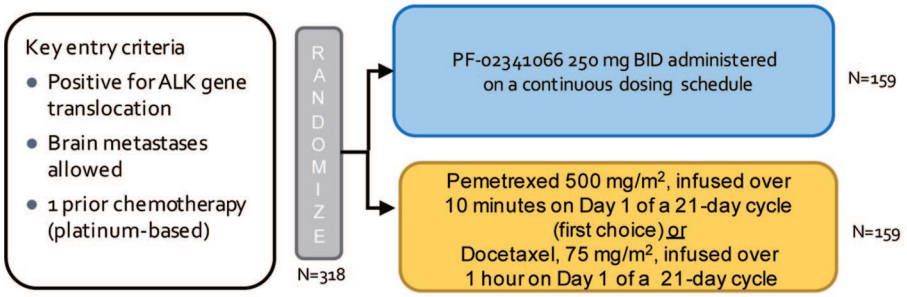
Trial design	Endpoints	Stratification	Study Sites	FSFV
Multicenter, randomized, open-label	Primary: PFS Secondary: ORR, DR, DCR, OS, Safety, QoL, biomarkers	ECOG PS (0/1 vs. 2) Previous EGFR TKI treatment Brain metastases	WW	Ongoing



www.clinicaltrials.gov (NCT00932893)

FIGURE 1. Profile-1007: Phase 3 study of PF-02341066 vs. pemetrexed or docetaxel in patients with non-small cell lung cancer (NSCLC) with a translocation or inversion event involving the ALK gene locus.

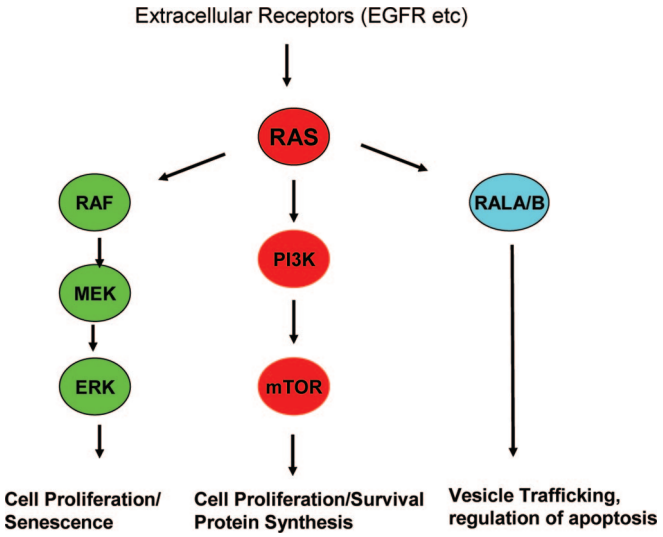


FIGURE 2. Ras pathway.

is an inhibitor of MEK, which is downstream of B-RAF with AZD6244. A trial of this agent is currently in progress.

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