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Authors

Hrustanovic, Gorjan
Bivona, Trevor G

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RAS-MAPK in ALK targeted therapy resistance

Gorjan Hrustanovic^{1,2} and Trever G Bivona^{1,2,*}

¹Department of Medicine; University of California at San Francisco; San Francisco, CA USA; ²Helen Diller Family Comprehensive Cancer Center; University of California at San Francisco; San Francisco, CA USA

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The clinical success of ALK targeted therapy is limited by resistance. To identify rational co-targeting strategies to enhance clinical outcomes, we explored the molecular basis of ALK oncogene dependence in ALK gene rearrangement positive (ALK+) lung adenocarcinoma. We discovered that the RAS-RAF-MEK-ERK pathway is the critical downstream pathway necessary for ALK+ tumor cell survival. Upfront co-targeting of ALK plus MEK enhanced response and forestalled resistance in preclinical ALK+ tumor models, providing rationale for a new approach the treatment of ALK+ patients.

Major advances in the treatment of lung cancer have occurred through the use of molecular targeted therapy acting against certain tumor-promoting genetic alterations present in specific subtypes of the disease.¹ However, targeted therapy resistance is a significant problem. Unraveling the basis of resistance is critical to understand the fundamental processes of aberrant cell signaling in cancer cells and to design therapeutic strategies to suppress resistance and improve patient survival.^{1,2}

We recently investigated the biological basis of resistance to targeted therapies against the anaplastic lymphoma kinase (ALK) in *ALK* gene rearrangement-positive lung adenocarcinoma (ALK+).³ ALK+ disease accounts for ~5–7% cases of lung adenocarcinoma, and this subset of lung cancer patients is treated with ALK inhibitors such as crizotinib and ceritinib (among other agents currently in clinical trials).³ The initial ALK inhibitor response is typically incomplete in these patients, with acquired resistance occurring within 12 months on therapy.⁴ Furthermore, up to 40% of ALK+ patients fail to respond to initial ALK inhibitor treatment, exhibiting innate resistance.⁴

Generally, efforts to thwart resistance have focused on treating acquired resistance after it has emerged.² An alternative approach to enhance initial response and

combat acquired resistance is to use rational upfront polytherapies that target the main oncoprotein (such as oncogenic ALK) and an important downstream effector of that oncoprotein. For example, upfront (but not second-line) inhibition of BRAF^{V600E} plus its main effector, MEK1/2, shows activity superior to RAF or MEK inhibitor monotherapy in BRAF^{V600E}-mutant melanoma patients.^{5,6}

The most appropriate upfront polytherapy strategy is less clear in cancers

with an oncogenic receptor kinase, such as ALK, that engages multiple downstream pathways.⁷ We addressed this knowledge gap in ALK+ lung adenocarcinoma to identify a rational upfront polytherapy strategy to enhance patient survival.⁷ Using models of lung adenocarcinoma harboring the major oncogenic ALK fusion EML4-ALK (echinoderm microtubule associated protein like 4-ALK), we found that the RAS-MAPK pathway, but not other established ALK effectors such

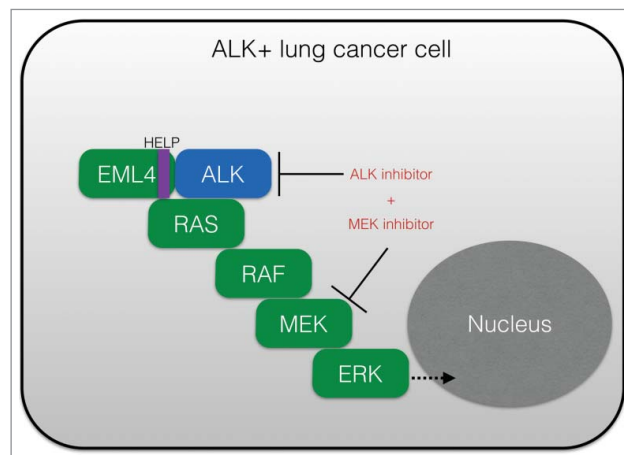


Figure 1. Upfront polytherapy targeting ALK and MEK in ALK+ lung adenocarcinoma. Shown is a schematic of the critical role of RAS-RAF-MEK-ERK (RAS-MAPK) signaling in ALK+ (EML4-ALK positive) tumor cells, and the rational co-targeting strategy to inhibit both ALK and MEK to enhance response. MAPK, mitogen activated protein kinase; ALK, anaplastic lymphoma kinase; HELP, HELP domain in EML4 (echinoderm microtubule associated protein like 4).

*Correspondence to: Trever G Bivona; Email: trever.bivona@ucsf.edu
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as PI-3K (phosphoinositide-3 kinase) or JAK/STAT, is essential for tumor cell survival. EML4-ALK activated RAS-MAPK (mitogen activated protein kinase) signaling via all 3 major RAS GTPase isoforms (H-, N-, K-RAS), acting through the HELP domain of EML4. MAPK pathway reactivation via either *KRAS*^{WT} (wild type) copy number gain or decreased expression of the MAPK phosphatase DUSP6 was sufficient to promote ALK inhibitor resistance *in vitro*. Furthermore, these molecular events were each associated with ALK inhibitor resistance in *ALK+* patients. Dual ALK-MEK inhibition in the upfront setting enhanced both the magnitude and duration of response in *ALK+* lung adenocarcinoma preclinical models, *in vitro* and *in vivo*. Altogether, our findings revealed RAS-MAPK dependence as a hallmark feature of *ALK+* lung adenocarcinoma and indicate that upfront ALK-MEK targeted polytherapy may

suppress or prevent resistance and improve patient outcomes.

The findings in our study prompt new areas for investigation. The data raise the possibility that combining an ALK inhibitor such as crizotinib or ceritinib with a MEK such as trametinib could induce complete tumor response in *ALK+* patients (Fig. 1). This hypothesis warrants testing in clinical trials. Furthermore, *KRAS*^{WT} copy number and DUSP6 downregulation should be further investigated as novel biomarkers of ALK inhibitor response in *ALK+* patients, and potentially other tumor subsets with similar MAPK pathway dependence such as those with oncogenic mutations in *RAS-RAF-MEK-ERK* or *EGFR*.

Moreover, our findings further suggest that the signaling properties of certain oncogenic fusion kinases (here, EML4-ALK) may be regulated by determinants within the fusion partner of the relevant kinase (here, EML4) (Fig. 1). Beyond a

role in promoting dimerization of the kinase, our data indicate that EML4 (specifically its HELP domain) is crucial for proper intracellular localization of EML4-ALK and activation of RAS and downstream RAF-MEK-ERK signaling. Thus, a new layer of regulation of EML4-ALK oncogene function is revealed that could have relevance for the function of other ALK fusion proteins and of additional kinase fusion proteins more generally. The cell biological regulation of EML4-ALK/RAS engagement and signaling, and potentially of other kinase fusion proteins, is an interesting area for future investigation. Coordinated basic and translational studies will further define the role and regulation of RAS-MAPK signaling in *ALK+* cancer cells, and those with other oncogenic fusion kinases, with important implications for improving oncogenic fusion-positive patient outcomes.

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