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Receptor-Associated Kinase Inhibitor and Intracellular Resistance Pathways

Faculty Presenter
Jeffrey Engelman, MD, PhD, Vice President and Global Head of Oncology, Novartis Institutes for BioMedical Research, Cambridge, MA, USA

Scholars' Summaries

*Authored by **Meghan Campo, MD,** Dana-Farber Cancer Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*

In this lecture, Dr. Jeffrey Engelman reviewed the concept of tumor heterogeneity within the context of advanced *EGFR*-mutant lung cancer. Patients with somatic mutations in *EGFR* typically respond well to EGFR tyrosine kinase inhibitors with a median PFS of 1-2 years; however, acquired resistance limits clinical outcomes. Interrogation of acquired resistance biopsies is necessary to develop hypotheses of resistance. On progression biopsies, the original EGFR mutation invariably persists, though it is often accompanied by a new mechanism of resistance such as mutation/amplification of the original mutation, development of bypass tracts, or lineage change.

Implicit to the concept of resistance is the notion of tumor heterogeneity, the observation that different tumor cells can demonstrate distinct morphologic and phenotypic profiles, including cellular morphology, gene expression, proliferation, and metastatic potential. Intra- and inter-tumor heterogeneity poses significant challenges in designing effective treatment strategies. However, research into understanding and characterizing heterogeneity can lead to better therapies.

Dr. Engelman stressed the need for serial biopsies in order to study the evolution of tumor cells during therapy/in response to therapy to better understand the dynamic populations of different clones. We were reminded that assumptions based on prior biopsies (i.e. presence of T790M) may not hold after subsequent therapies, and repeat tissue testing should be considered to guide therapy.

As a clinician, one of the primary points I took away from this lecture is that, instead of thinking about the presence of a mutation as a binomial variable (i.e. either a patient has T790M or does not) we should consider its presence on a dynamic spectrum, one that can evolve and thereby alter treatment strategies.

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*Authored by **Siddhartha Devarakonda, MD,** Barnes-Jewish/Washington University in St. Louis School of Medicine, St. Louis, MO, USA*

Targeted therapy with receptor tyrosine kinase inhibitors (TKIs) has significantly improved outcomes in cancer patients. However, almost all patients treated with TKIs eventually progress. The mechanisms underlying TKI resistance are heterogeneous both at an inter- and intra-patient level. These mechanisms predominantly involve target modification (through a second mutation), activation of bypass signaling pathways (through multiple mechanisms), or histological transformation. TKI resistance can either emerge gradually, when "persister" slow-cycling cells that survive initial therapy acquire resistance conferring alterations *de novo,* or rapidly, when pre-treatment sub-clones containing these alterations are readily selected by therapy. Understanding these mechanisms of resistance and the process by which they evolve could facilitate the development of novel therapeutic approaches.

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*Authored by **Victoria Wang, MD, PhD,** University of California – San Francisco (UCSF) San Francisco, CA, USA*

Dr. Jeffrey Engelman presented a talk on the resistance mechanisms of tyrosine kinase inhibitors, using the EGFR NSCLC as a model. Often resistance mechanisms arise due to acquired mutations that alter drug binding to the targeted kinase. For example, erlotinib cannot bind to EGFR which harbors the T790M mutation. Other resistance mechanisms include bypass track, such as c-MET amplification. Acquiring tissue biopsy upon relapse is critical for identification of resistance mechanisms. Biopsy at the point of maximal response is perhaps even more important, though it remains difficult and is not routinely performed. Advances in non-invasive, liquid biopsies may be helpful in sampling the catalogue of mutations which arise during the course of treatment. Upon prolonged drug treatment with a TKI, tumor cells may alter their cell fates and become less differentiated (as with a transformation to SCLC), with additional mutations in p53 and Rb. Finally, Dr. Engelman presented new data on the evolution of resistant clones. Clinically, low frequency clones with pre-existing mutations appear to be more sensitive to drugs compared with clones harboring mutations which arise during treatment. The latter displays more intrinsic drug resistance, a state that is associated with an increase in EMT and down-regulation of the apoptotic machinery.