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Neoadjuvant oncogene-targeted therapy in early stage non-small cell lung cancer as a strategy to improve clinical outcome and identify early mechanisms of resistance

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Abstract

Evaluations of resistance mechanisms to targeted treatments in non-small cell lung cancer (NSCLC) are necessary for development of improved treatment after progression and to help delay progression. Populations of cells that survive after initial treatment form the basis of resistance via outgrowth of resistant clones or activation of alternative signaling pathways. Here we describe a clinical trial approach in which patients with *EGFR*, *ALK*, *ROS1* and *MET* exon 14 alterations and early stage (IA–IIIA) NSCLC will be treated with induction epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) or crizotinib, a TKI which inhibits anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1) and hepatocyte growth factor receptor (MET). We will evaluate resected tumor samples for pathologic response to induction therapy, overall response rate and disease free survival. Additionally, we will assess patients for early evidence of resistance to targeted therapy in terms of activation of alternative signaling pathways and for identification of resistance clones in remnant cell populations.

Introduction

Incomplete responses to oncogene-targeted treatments in patients with oncogenic driver mutations in non-small cell lung cancer (NSCLC) promote tumor cell therapy resistance, forming a survival niche that fuels subsequent disease progression.[1] Studies of resistance

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mechanisms have focused on evaluation of patients with metastatic disease who have progressed after targeted treatment.[2–6] This has allowed for significant advances in understanding the complex mechanisms of acquired resistance that develop, but has not yet permitted long-term disease control for the majority of patients with metastatic disease. An alternate approach to sequential targeted therapy is upfront combination therapy to potentially improve both the depth and duration of initial response. In order to inform potential combination strategies it will be necessary to understand tumor cell survival mechanisms early in therapy.

Discussion

An approach to studying remnant tumor samples following oncogene-targeted therapy would be the administration of tyrosine kinase inhibitors for a defined period of time prior to surgical resection in oncogene-positive patient populations. Neoadjuvant studies of chemotherapy for patients with early stage, resectable NSCLC (stages IB-IIIA) have been performed previously. A meta-analysis of 15 trials (2385 patients) demonstrated significant but modest improvements in overall survival at 5 years from 40 to 45% (HR 0.87, 95% CI 0.78–0.96, P=0.007), time to distant recurrence at 5 years improved from 60% to 70% (HR 0.69, 95% CI 0.58–0.82; p<0.001) and a recurrence free survival improvement from 30% to 36% at 5 years across all stages (HR 0.85, 95% CI 0.76–0.94, P=0.002).[7] In addition to providing benefit to patients by potentially improving overall survival and reducing the risk of disease recurrence, evaluation of the tumor response to targeted therapy in the neoadjuvant setting provides an excellent opportunity to study residual disease, given that patients undergo definitive surgical resection as a predetermined part of their treatment plan. Tissue-based molecular evaluations of targeted therapy response in neoadjuvant treatment of early stage NSCLC have not been performed.

We are in the process of implementing two clinical trials in which patients with early stage NSCLC with activating mutations in *EGFR* or *ALK*, *ROS1* or *MET* exon 14 are screened and either enrolled in a trial of a neoadjuvant EGFR TKI if their tumors contain activating *EGFR* mutations or to a trial of neoadjuvant crizotinib if their tumors contain *ALK*, *ROS1* or *MET* alterations (Figure 1). The characteristics and clinical relevance of these target genes is described below.

Activating mutations in *EGFR* are known to promote growth and proliferation pathways.[8] Targetable activating mutations are present in 15–20% of unselected patient populations and are typically located in the tyrosine kinase domain.[9,10] Multiple EGFR TKIs have demonstrated dramatic improvements in progression free survival compared with traditional platinum doublet chemotherapy in the first line setting.[11–13] Inevitably all patients who receive EGFR TKIs eventually develop resistance mutations and progression free survival is typically 9–13 months. Resistance can develop de-novo through mutations in tumor DNA, via activation of alternative signaling pathways, or through competitive selection of mutations that are resistant to EGFR TKIs that are already present at low levels in the heterogeneous tumor deposits.[4,5,14,15]

Fusion of echinoderm microtubule-associate protein-like 4 and anaplastic lymphoma kinase generates a fusion gene, *EML4-ALK*, that has tumor transforming potential.[16] In an unselected patient population, *EML4-ALK*, and other *ALK* fusions, have been identified in 1 to 7% of patients with non-small cell lung cancer (NSCLC) depending on the cohort evaluated.[16–20] A similar oncogenic fusion gene involves *ROS1*, a gene initially identified as the homolog of the transforming v-ros sequence from the UR2 avian sarcoma virus which encodes a receptor tyrosine kinase (RTK) with an as yet unidentified cognate ligand.[21]. Rearrangements in this gene have been found in 1–2% of patients with lung cancer.[20,22,23] *ROS1* fusions been identified in brain, cholangiocarcinoma and ovarian cancer, and other cancer types in addition to NSCLC.[24] Finally, *MET* is an RTK whose ligand is the hepatocyte growth factor (HGF). The *MET* proto-oncogene can be mutated or altered in many ways to become an oncogenic driver including through amplification (~5%) or exon 14 skip mutations (~4% of patients).[20,25] Though individually each of these mutations makes up a small percentage of the total NSCLC population, in total, their composite prevalence approaches 10% of an unselected population. Each of these oncogenic drivers can be successfully targeted by crizotinib.[26–28]

In *ALK*-positive NSCLC, frontline treatment with crizotinib demonstrated a progression free survival of 10.9 months compared with 7 months in a platinum doublet and the overall response rate (ORR) was 74% compared with 45%.[29] The disease control rate in this study was 92% with crizotinib and 81% with standard of care chemotherapy. This is important because it demonstrates that the vast majority of patients with an *ALK* rearrangement will respond to neoadjuvant treatment therefore, from a surgical standpoint, the risk of progression while receiving neoadjuvant treatment is very low.

The development of resistance pathways typically does not become clinically evident for many months. In metastatic *ALK* positive NSCLC resistance mechanisms are now being characterized. In one evaluation of resistance mechanisms, four of eleven patients (36%) developed secondary mutations in the tyrosine kinase domain of *ALK*.[3] Interestingly, within this cohort, 2 patients were *ALK* resistant but no mechanisms of resistance were identified. A recent preclinical collaborative effort in *ALK* positive fusion lung cancer models demonstrated that inhibition of the GTPase RAS-mitogen-activated protein kinase pathway in combination with inhibition of *ALK* improved the duration and depth of response compared to single-agent ALK inhibition.[30]

In *ROS1*-positive NSCLC, the response rate to treatment was 72% in the expansion cohort of the phase I study.[31] Additionally, the median progression free survival in this population was 19.2 months, though the upper limit has not yet been reached. Finally, the disease control rate was 90% for this cohort. Resistance to *ROS1* is also in the early stages of characterization, but ROS1 mutations, as well as RAS and KIT bypass signaling have been identified in ROS+ NSCLC patients with resistance to crizotinib.[2,32–34] Additionally, preclinical modeling from a patient derived *ROS1* cell line suggests that some tumors may utilize EGFR activation as a mechanisms of acquired resistance.[35]

Similarly, *MET* is another RTK in which mutations in can result in oncogenic activity, via skipping or other mechanism.[27,36] Multiple case series evaluating the efficacy of MET

inhibitors in these populations are have demonstrated promising results in many with patients, particularly those with exon 14 mutations.[36–41] Resistance mutations have not yet been characterized in this population.

Each of the gene abnormalities listed above not only demonstrates substantial clinical response to EGFR TKIs or crizotinib but also demonstrates that despite initial response, resistance typically develops via multiple different mechanisms. Residual disease from incomplete responses forms the basis for the development of resistance.[42] As noted, resistance mechanisms include not only secondary mutations of target genes or other related pathway genes but also can include target gene amplification and influence of secondary pathways as well as phenotypic switching from epithelial to mensenchymal patterns of growth.[5,25,43] These mechanisms of resistance were initially identified in *EGFR* mutated tumors treated with EGFR TKIs, however, similar mutation mechanisms have now been identified in *ALK* and *ROS1*.[2,3]

Currently the majority of efforts in overcoming resistance have been focused on evaluation and treatment after resistance becomes evident through radiologic disease progression. Notably however, Blakely et. al. utilized a patient-derived mouse xenograft model to demonstrate activation of a survival pathway in a patient with oligometastatic disease who had an incomplete response to frontline treatment with erlotinib. They demonstrated that upfront treatment with combination therapy using erlotinib in combination with NF-κB inhibition can improve treatment response in mouse models. We propose that it is critical to further investigate responses to treatment early in the treatment course in human tumor samples to further characterize early treatment response to EGFR TKIs. The ALCHEMIST trial is a large effort to evaluate the benefit of adjuvant treatment in genotype-selected patients.[44] A neoadjuvant approach to both patient treatment and resistance development is critical to advance our understanding of tumor resistance and will compliment the aims of the ALCHEMIST study by looking in a small subgroup of molecularly identified patients to determine if a neoadjuvant targeted therapy approach can provide information on mechanisms of cancer cell survival and ultimately lead to improvements in clinical outcomes by allowing more complete cancer cell elimination.

Neoadjuvant chemotherapy has demonstrated significant benefit for patients with early stage NSCLC.[7] However, the role of targeted therapies in neoadjuvant therapy has not been well-defined. Importantly however, ongoing studies have demonstrated encouraging results: In a study of 60 non-squamous patients with early stage lung cancer treated with erlotinib for 21 days prior to surgery, patients with EGFR activating mutations 40% (3 of 7) had a pathological response with > 50% tumor necrosis at the time of resection. In patients with wildtype EGFR, only 20% (8 of 35 patients) had > 50% necrosis in their tumors at the time of resection.[45] More recently a small series highlighted the neoadjuvant treatment of two patients with stage IIIA, *ALK*-positive NSCLC with crizotinib prior to resection. Significant reduction in tumor size and FDG avidity on PET scan was observed.[46] While these results suggest that neoadjuvant therapy may be beneficial to patients with activating mutations prior to surgery, a prospective trial in pre-selected lung cancer patients has not been completed nor has molecular analysis of tumor samples of residual disease following oncogene-targeted neo-adjuvant treatment been done.

Conclusions

Evaluation of tumor tissue early in treatment will allow for identification of early adaptive mechanisms of cell survival in the setting of oncogene-targeted therapy. We advocate for induction treatment of early stage NSCLC to allow for both identification of early mechanisms of resistance and to determine whether we can demonstrate similar response rates to metastatic disease and ultimately increase disease free survival. We are leading a series of coordinated novel clinical trials in early stage oncogene-driven (*EGFR* mutant, *ALK* fusion, *MET* exon14 mutant, *ROS1* fusion) lung cancer that aim to move the field forward to understand and pre-empt residual disease and enhance clinical outcomes.

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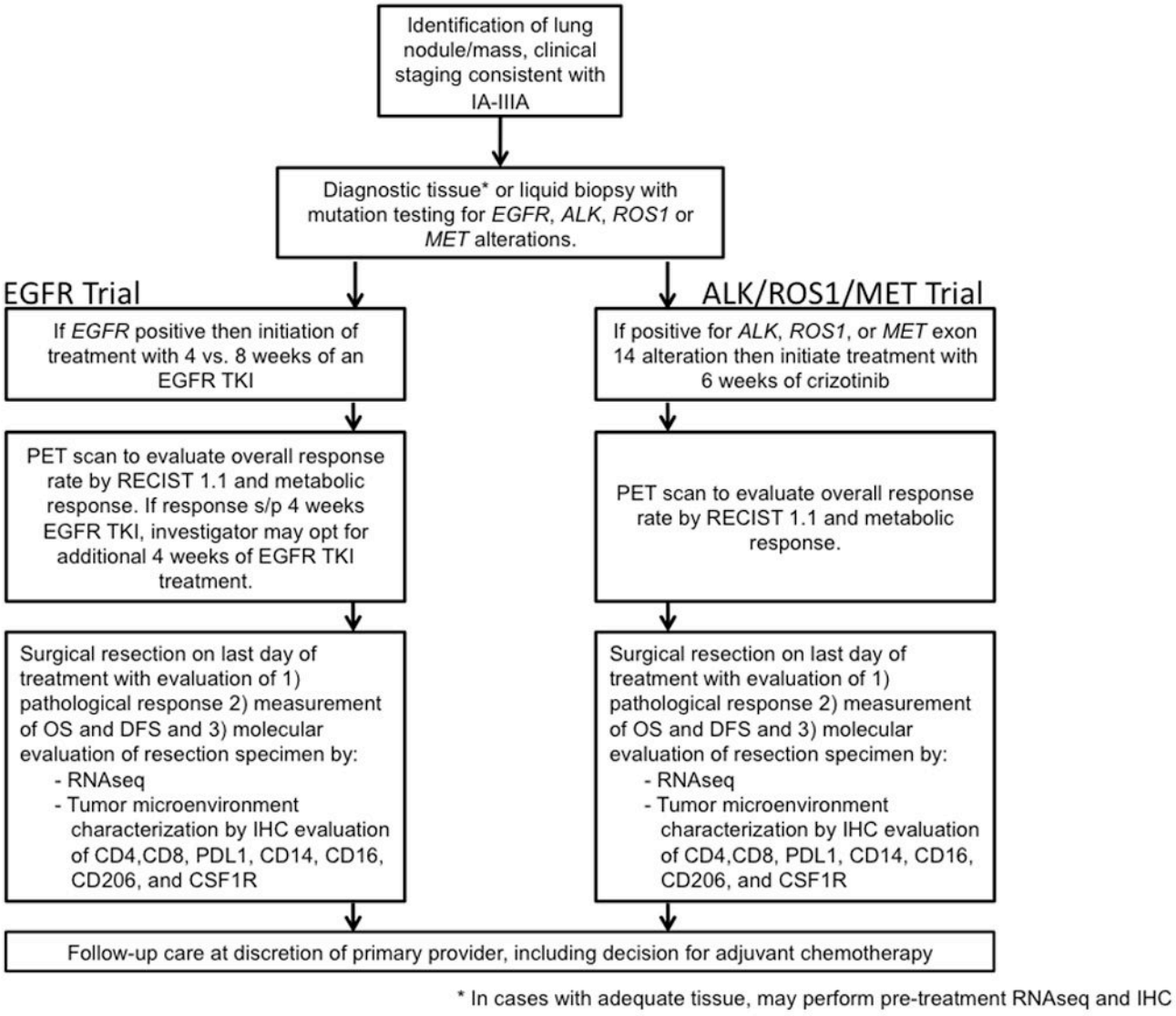

Figure 1.
Consort diagram