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Acquired Resistance to Targeted Therapies Against Oncogene-Driven Non–Small-Cell Lung Cancer: Approach to Subtyping Progressive Disease and Clinical Implications

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Abstract

In the emerging era of targeted therapy for advanced-stage non–small-cell lung cancer, it is becoming increasingly important to anticipate underlying driver oncogene alterations at the time of initial diagnosis and tumor-tissue acquisition, so that patients can be selected in a timely fashion for first-line tyrosine kinase inhibitor (TKI) therapy if their cancers are found to harbor tyrosine-kinase-activating mutations in the epidermal growth factor receptor gene or gain-of-function rearrangements in the anaplastic lymphoma kinase gene. However, despite the clear benefits of TKI therapy over chemotherapy in these settings, the eventual emergence of acquired resistance and progressive disease (PD) is universal. How to best approach oncogene-driven non–small-cell lung cancer at the time of acquired resistance to initial TKI therapy is an increasingly complex question because of variability in mechanisms of resistance, extent of PD, and inter- and inpatient tumor heterogeneity. Here we propose an approach to subtyping PD in the setting of acquired resistance as well as subsequent clinical implications.

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Background

A transition from empiric to targeted and personalized therapy of non–small-cell lung cancer (NSCLC) is well under way, largely as a result of extensive efforts in genomic characterization.¹⁻³ Over the past 10 to 15 years, NSCLC, previously viewed as a single disease, has been “ungrouped,” initially through histologic subtyping and more recently through recognition of multiple clinically and biologically distinct molecular subsets, the magnitudes of which have been demonstrated only through next-generation sequencing of large numbers of cancers.^{3,4} These studies have delineated the complexity of NSCLC at the genomic level, both differentiating it from less complex cancers and pointing out a striking degree of inter- and inpatient tumor heterogeneity. At present, epidermal growth factor receptor (*EGFR*) gene activating mutations and anaplastic lymphoma kinase (*ALK*) fusion genes represent the most actionable

of these oncogene-driven and molecularly defined subsets, based on availability of effective tyrosine kinase inhibitor (TKI) therapy for each.^{5,6} Undoubtedly, others will join this actionable category in the not too distant future as newer targeted therapies become available.⁷

In *EGFR*-mutated NSCLC, randomized clinical trials comparing therapy with *EGFR* TKIs such as gefitinib, erlotinib, or afatinib with chemotherapy have repeatedly demonstrated superior patient outcomes for the TKIs, as measured by response rate and progression-free survival (PFS).⁸⁻¹² More recently, the same has been shown for the *ALK* inhibitor crizotinib.¹³ Although no improvement in overall survival has been demonstrated in these trials, this finding has largely been attributed to crossover from chemotherapy to targeted therapy. Regardless, TKI therapy for cancers harboring *EGFR* activating mutations or *ALK* fusions can be viewed as a positive step toward personalized therapy: selecting the right therapy for the right patient.

Despite the observed clinical benefits, the overall impact of these targeted therapies has been limited by an almost universal development of acquired resistance. Even in these most TKI-sensitive subsets of NSCLC, PD is typically observed within about 10 to 14 months.⁸⁻¹³ Initial studies evaluating therapeutic decision-making at the time of acquired resistance and Response Evaluation Criteria In Solid Tumors (RECIST) PD have tended to lump all patients together,

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regardless of the location or number of PD sites or magnitude of PD. Results from small pilot studies addressing the topic of TKI acquired resistance to TKI in NSCLC could thus be affected by great heterogeneity in patient prognoses, treatment options, and likely outcomes, leading to confusion about the appropriate therapeutic approaches outside of the clinical trial arena. Furthermore, increased understanding of “dynamic signalability” in adaptive resistance mechanisms to targeted therapies adds to the need for an integrated approach.¹⁴ Here we describe an algorithm for subtyping PD that accounts in part for this variability. Further, we hypothesize that “best” management options at the time of PD differ depending on the PD subtype and the mechanism or mechanisms of acquired or adaptive resistance. Lastly, we describe a clinical trial design suitable for addressing the circumvention of acquired resistance to TKI therapy against oncogene-driven NSCLC.

Proposal for PD Subtyping in the Setting of Acquired Resistance to EGFR- or ALK-Directed TKI Therapy

Conceptually, it is obvious that not all NSCLC patients who develop acquired resistance to targeted TKIs are created equal in terms of the extent or sites of PD or rate of PD. Inter- and intra-patient tumor heterogeneity, as well as emerging data on adaptive

resistance mechanisms, all add to the complexity.¹⁴⁻¹⁸ Moreover, treatment options vary widely.¹⁹⁻²² Thus, as depicted in Figure 1, we propose that PD in the setting of acquired resistance to EGFR- or ALK-directed TKI therapy in NSCLC be broadly subtyped into 1) central nervous system (CNS) sanctuary PD, 2) oligo-PD and 3) systemic PD, for clinical considerations as well as clinical trial design. In this categorization scheme, CNS sanctuary PD represents isolated CNS failure, primarily parenchymal brain metastasis, in the absence of systemic PD. We propose excluding leptomeningeal carcinomatosis from the CNS sanctuary category because of the lack of good treatment options for its long-term control. Oligo-PD refers to new sites or regrowth in a limited number of areas. For consistency, we propose a maximum of 4 PD sites for this category. Lastly, systemic PD represents what oncologists generally perceive as PD following chemotherapy, that is, multisite progression, which may include new metastatic sites as well as regrowth in previously responsive sites of disease.

Clinical Implications of PD Subtyping

PD subtyping in the setting of acquired resistance to TKI therapy for EGFR mutation-positive or ALK-positive (ALK⁺) NSCLC provides a rational approach to both clinical trial design

Figure 1 Subtyping Progressive Disease

Abbreviations: CNS = central nervous system; PD = progressive disease.

Figure 2 Approaches to Systemic PD in Oncogene-Driven NSCLC With TKI Acquired Resistance

Abbreviations: *ALK* = anaplastic lymphoma kinase gene; *EGFR* = epidermal growth factor receptor gene; NSCLC = non-small-cell lung cancer; PD = progressive disease; RECIST = Response Evaluation Criteria In Solid Tumors; TKI = tyrosine kinase inhibitor.

and day-to-day patient management. Ensuring homogeneity in patient characteristics and prognostic factors is a hallmark of clinical trial design: comparing “apples to apples,” as discussed below. Just as important, clinical decision-making outside of a clinical trial that takes into account the individual patient situation is in fact another step toward the goal of personalized therapy. For example, in CNS sanctuary PD as defined here, there appears to be a good rationale for a local-regional approach to PD by surgical resection, focused radiotherapy, or whole-brain radiotherapy, and for continuing TKI therapy as long as systemic remission is maintained. In this case, isolated CNS relapse may well represent pharmacodynamic failure due to poor TKI penetrance into the brain, rather than emergence of resistant tumor clones. Indeed, pilot studies employing this approach suggest that PFS can be extended in a clinically meaningful way.¹⁹⁻²²

In the setting of oligo-PD, a similar approach may be possible dependent on the exact location, the number of new or recurrent sites of disease, and the rate of progression. Past studies addressing this topic have included anywhere from 1 to 5 sites as compatible with oligometastasis, with increasing numbers of sites generally associated with worse outcome when treated with local therapy. For example, the report of Salama showed that when stereotactic body radiation therapy was employed in the setting of oligo-metastatic NSCLC, those patients with 1 to 2 sites fared better than those with 3 to 5.²³ Others have defined oligo-PD as 4 or less sites.^{20,21} Although a minority of NSCLC patients with TKI acquired resistance fall within the oligo-PD category, some studies suggest that in *ALK*⁺ cases, this subset may represent up to 1/3 of all patients.²¹ Treating the sites of oligo-PD with stereotactic body radiation therapy or surgical resection where feasible, while continuing the same TKI therapy, may be a reasonable approach as long as systemic remission is otherwise maintained. In 1 such study in *EGFR*-mutated or *ALK*⁺ NSCLC, a substantial number of patients with PD after initial response to TKI therapy were deemed candidates for local

ablative therapy (LAT). In this series, LAT extended the time to further disease progression. In a few cases, LAT was again utilized at the time of subsequent oligo-PD.²¹ Despite these favorable preliminary results, only randomized trials comparing this approach with switch therapy can fully address the standard of care issue for oligo-PD.

When TKI acquired resistance can be categorized as systemic PD, a number of different therapeutic options are possible, as described in Figure 2. Assuming multiple new sites or regrowth in multiple areas, options include 1) switch therapy, 2) continued therapy with the same TKI alone, with the hopes of slowing further PD, or 3)

Figure 3 Randomized Phase II Trial (S1300) in *ALK*-positive NSCLC Progressive After Crizotinib Therapy

Abbreviations: *ALK*⁺ = anaplastic lymphoma kinase positive; CR = complete response; DCR = disease control rate; FISH = fluorescence in situ hybridization; NSCLC = non-small-cell lung cancer; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = standard deviation; TKI = tyrosine kinase inhibitor.

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Figure 4 Clinical Trial Design to Address Circumvention of Acquired Resistance in Oncogene-Driven NSCLC

Abbreviations: NSCLC = non-small-cell lung cancer; TKI = tyrosine kinase inhibitor.

addition of another agent(s) to the same TKI. The classic approach to acquired resistance, option 1, switch therapy, most commonly represents chemotherapy in this setting, with the presumptions that a majority of new growth or regrowth is due to TKI-resistant clones and that the best therapeutic option is an entirely new strategy, such as chemotherapy. With acquired resistance to either EGFR-directed TKIs in EGFR-mutated NSCLC or the ALK-directed TKI crizotinib in ALK⁺ NSCLC, there is good rationale for a switch to chemotherapy in the second-line setting. In the Spanish Lung Cancer Group trial of erlotinib in EGFR-mutated NSCLC, the benefits of erlotinib appeared similar whether the TKI was administered as first-line or second-line therapy following chemotherapy, suggesting that chemotherapy does not significantly alter EGFR TKI sensitivity.²⁴ Moreover, EGFR-mutated NSCLC may be more sensitive to platinum-based chemotherapy than nonmutated cancers, based on deficient DNA repair, as exemplified by low excision repair cross-complementing group 1 (ERCC1) protein levels.²⁵ Similarly, pemetrexed-based therapy seems to be particularly active in ALK⁺ cancers, perhaps because of an interrelationship with ALK signaling or target gene-expression levels for pemetrexed activity.²⁶⁻²⁸

Switch to a second-generation TKI with activity in the acquired resistance setting is an attractive approach and an area of considerable preclinical and clinical research, based on presumed mechanisms of resistance.^{29,30} Somewhat surprisingly, in the setting of acquired resistance to EGFR TKIs, second-generation agents directed against the “gatekeeper” T790M resistance mutation, while typically showing good activity in vitro, have largely failed in the clinic, raising the question of how often T790M actually represents a clinically actionable resistance mechanism.^{30,31} In contrast, preliminary data suggest that ALK-directed, second-generation TKIs are highly active clinically.^{29,32} While much has been made of the rationale for option 2, continuation of the same TKI alone in order to prevent disease flair or slow progression due to residual sensitive tumor clones, in reality this approach is of limited appeal in the setting of systemic PD, especially in a symptomatic patient with treatment alternatives.

Clearly, the way forward is to direct attention toward the mechanisms of acquired resistance and to develop means of overcoming them. To this end, option 3, addition of another agent(s) to the original TKI, offers considerable potential to both address emergent resistant tumor clones and to maintain suppression of

Figure 5 Phase II/III Trial of Afatinib With or Without Cetuximab in EGFR-Mutated NSCLC (S1403)

Abbreviations: EGFR = epidermal growth factor receptor; NSCLC = non-small-cell lung cancer; PDX = patient-derived xenograft; TKI = tyrosine kinase inhibitor.

suppressed but residual sensitive clones.¹⁵ As an example of this approach in ALK⁺ NSCLC with acquired TKI resistance, S1300 is a developing North American Intergroup trial that randomizes patients with acquired crizotinib resistance to either switch therapy (pemetrexed) or continuing crizotinib with the addition of pemetrexed. (Fig. 3). Based on preclinical modeling and clinical data from rebiopsy of ALK⁺ NSCLC at the time of acquired resistance to crizotinib, multiple potential secondary drivers or bypass pathways have been identified.^{18,31} The hypothesis to be explored in S1300 is that differential activity will be observed in individual patients, depending on the mechanism(s) of resistance: ALK-dominant versus ALK-nondominant.¹⁸ Another trial using this approach is IMPRESS, in which patients post-PD on gefitinib are randomized to continued gefitinib plus chemotherapy or chemotherapy alone (NCT01544179).

Prevention or Circumvention of Acquired Resistance in Oncogene-Driven NSCLC

Considering the difficulties in addressing acquired resistance once it is established, an attractive alternative is to design tactics to delay or circumvent resistance before it develops, ie, as part of first-line therapy. As described in Figure 4, a potential clinical trial strategy for circumvention of resistance would be to compare the current approach of targeted monotherapy (such as erlotinib for EGFR-mutated NSCLC or crizotinib for ALK⁺ NSCLC) followed at PD by a second-line agent directed at a known mechanism of resistance to a second-generation TKI in which delay or circumvention of resistance is anticipated, with a multidrug therapy regimen either intercalated or given concurrently. In the latter case, the regimen would introduce either new drug classes or drugs aimed at the most likely mechanisms of resistance to the TKI in question. PFS would be the primary endpoint, with overall survival as a secondary endpoint. If potential antagonism with multidrug therapy is anticipated, the combination could be employed in an intercalated fashion designed to achieve pharmacodynamics separation.^{33,34} An example of the intercalated approach is the recently published FASTACT-2, which combined intermittent dosing of the EGFR TKI erlotinib together with chemotherapy to achieve pharmacodynamic separation.³⁵ Multidrug therapy employing 2 or more targeted agents (a “targeted therapy cocktail”) concurrently is an attractive approach now being investigated in oncogene-driven cancers in a variety of clinical settings. An example is S1403, a developing phase II/III trial combining the second generation EGFR TKI afatinib with the EGFR-directed monoclonal antibody cetuximab in first-line therapy of EGFR-mutated NSCLC (Fig. 5), mimicking a strategy employed successfully against human immunodeficiency virus (HIV) disease.³⁶ With a sample size of 328 patients with EGFR-mutated cancer, S1403 seeks to improve PFS by 30% as a measure of benefit.

Conclusion

In summary, acquired or adaptive resistance to targeted therapies in oncogene-driven NSCLC is an expected and almost universal phenomenon. However, individual cases of acquired resistance are highly variable from both a mechanistic and a clinical standpoint. Therefore, therapeutic approaches to patients in the acquired

resistance setting should be individualized as well. Subgrouping PD into categories such as CNS sanctuary PD, oligo-PD, and systemic PD provides the basis for integrating mechanistic data from tumor rebiopsy into therapeutic decision-making and clinical trial design. Taken together with increased understanding of dynamic tumor cell signaling in adaptive resistance to targeted therapies, development of more-effective drug combinations with greater potential for prolonged long-term survival or even cure seems likely. Lastly, innovative clinical trial designs will be required to address the multifactorial nature of acquired resistance in order to reverse it once established, and even more important, to anticipate the most likely mechanisms and circumvent them.

Disclosure

The authors have stated that they have no conflicts of interest.

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