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A crowded, but still varied, space: brigatinib in anaplastic lymphoma kinase-rearranged non-small cell lung cancer

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Considering that, as recently as 10 years ago, physicians caring for patients with advanced lung cancer had only a handful of conventional cytotoxic agents from which to choose, the field's recent development and competition seem truly remarkable. A prime example of this shifting and crowded landscape is immunotherapy. Since 2015, three different checkpoint inhibitors targeting programmed death 1 (PD-1) or PD-1 ligand (PD-L1) have received U.S. FDA approval, with several others currently in clinical trials. While these drugs may differ by specific target (PD-1 versus PD-L1), antibody species (humanized versus fully human), and IgG subclass (IgG1 versus IgG4), it remains unclear whether there are clinically meaningful differences in efficacy or toxicity between these agents.

The treatment of anaplastic lymphoma kinase (ALK)-positive lung cancer has seen similar developments. Although these cases represent only 3–5% of non-small cell lung cancer (NSCLC), researchers and pharmaceutical companies have devoted intense effort to this disease subset. The field received an initial boost by the rapidity of drug development. Largely because the first-generation ALK inhibitor crizotinib was already under clinical development as a MET inhibitor, the interval between discovery of the ALK target and evidence of a clinically effective drug was a remarkably short 3 years, [1–4] compared to 41 years between the discovery of BCR-ABL and approval of imatinib and 26 years between the discovery of epidermal growth factor receptor (EGFR) and approval of erlotinib.[4] For ALK-positive lung cancer, the pace of development has not slowed. Within 3–5 years, so-called second-generation ALK inhibitors such as ceritinib and alectinib, both of which have clear activity in crizotinib-resistant cases, were available. By contrast, it took more than a decade to develop and approve a late-generation EGFR inhibitor that had meaningful efficacy in erlotinib- and gefitinib-resistant cases.[5]

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This time period also saw increased understanding of the heterogeneous and complex science of crizotinib resistance in ALK-positive lung cancer. Broadly, mechanisms can be characterized as pharmacologic or biologic. Pharmacologic reasons may include patient non-adherence, reduced absorption, drug interactions, and most importantly inadequate blood-brain barrier penetration. Indeed, up to 40% of progression on crizotinib occurs in the central nervous system. [6] Biologic mechanisms include bypass tracks with alternate oncogenes such as *EGFR* and V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) (35% of cases), [7] [8] *ALK* gene copy number gain (20% of cases) [9], and *ALK* resistance mutations (35% of cases). To date, more than a dozen *ALK* resistance mutations have been identified, including gatekeepers analogous to T790M in *EGFR* mutant NSCLC [10] and T315I in chronic myeloid leukemia, which reduce crizotinib binding and enhance ATP affinity. [8, 11–14]. A potential explanation for why this secondary mutational landscape is more complex than that of *EGFR* (which is dominated by exon 20 T790M) is that *EGFR* resistance mutations appear to convey a selective growth disadvantage [8] [15] whereas *ALK* mutations may increase proliferation.[8]

In general, later-generation *ALK* inhibitors demonstrate efficacy in crizotinib-resistant cases through a number of features, including enhanced *ALK* kinase inhibition,[16] [17] better activity against second-site mutated *ALK*, activity against other oncogenic targets, and improved blood-brain barrier penetration.[18] In contrast to the numerous PD-1 and PD-L1 inhibitors, the various *ALK* inhibitors have some clear and clinically meaningful differences, including toxicity. With crizotinib, characteristic adverse effects may include visual changes, peripheral edema, renal dysfunction, and orthostatic hypotension. [19] For ceritinib, diarrhea and transaminitis require dose modification in approximately two-thirds of cases [15] Alectinib causes constipation and creatine phosphokinase elevations.[20]

Continuing this trend, in a recently published phase 1/2 trial, Gettinger and colleagues show that the potent oral *ALK* inhibitor brigatinib has comparable efficacy to other late-generation *ALK* inhibitors but a distinct toxicity profile. [21] In preclinical models, brigatinib has a broader spectrum of activity than certinib and alectinib, including not only *ALK* resistance mutations but also *ROS1* fusions and mutant *EGFR*[22] The trial enrolled a total of 137 patients in a phase 1 dose escalation cohort (N=66) and five disease- and molecularly-defined phase 2 cohorts (N=69). Although multiple molecular diagnostic techniques for diagnosis of *ALK* positivity, including Next Generation sequencing and *ALK* protein expression by immunohistochemistry [23] in addition to fluorescent in situ hybridization (FISH) are now widely accepted, in this trial enrollment into *ALK* cohorts required demonstration of *ALK* gene fusion by FISH. Treatment-related adverse events were predominantly grade 1–2 and included nausea, fatigue, and diarrhea. Grade 3–4 events included increased lipase concentration, hypertension, and most notably pulmonary toxicity, including a 4% rate of fatal events. Radiographically, these cases featured linear or ground glass opacities. In the phase 2 trial, two dosing regimens were initially studied: 90 mg orally daily and 180 mg orally daily. Due to the emergence of pulmonary toxicity within 48 hours of treatment initiation in the 180 mg cohort, the schedule was modified to include a 7-day lead-in of 90 mg daily. Overall, 14% of patients required dose reductions.

Brigatinib demonstrated an efficacy profile expected for contemporary late-generation ALK inhibitors. Among the eight crizotinib-naïve *ALK*-rearranged cases, all responded (median progression-free survival [PFS] not reached). Response rate was 74% for crizotinib-treated cases (median PFS 14.5 months). Intracranial response rate was 50%. Median intracranial PFS was 15.6 months for all assessable patients and 22.3 months for assessable patients with no prior brain radiotherapy. Activity was also noted in ROS1-positive NSCLC, as well as other *ALK*-rearranged malignancies including inflammatory myofibroblastic tumor and neuroendocrine tumor. Despite encouraging preclinical data, only 5% of *EGFR*-mutant NSCLC cases had an objective response.

These results lead to as many questions as they answer. Are second-generation ALK inhibitors best used as initial treatment or following crizotinib failure? It would seem that reserving second-generation ALK inhibitors for post-crizotinib failure would yield the greatest overall period of disease control. However, first-line use of drugs such as ceritinib or alectinib may have greater PFS than the overall combined PFS when they follow crizotinib. [18, 24] Which cases of ALK-positive brain metastases may be treated medically, and which are best approached initially with resection or radiation therapy? In this trial, enrollment of previously untreated brain metastases was limited to those that were neurologically stable and not requiring escalating steroid doses or anticonvulsants. Could brigatinib use be extended to those patients with symptomatic intracranial disease? At what point should disease progression on an ALK inhibitor be addressed with a change in systemic therapy, and when can local treatments be employed to prolong disease control? Small series have demonstrated that surgical resection or stereotactic ablative radiation in cases of oligo-progression, with continuation of the initial systemic targeted therapy, may extend disease control for several months.[25] Such an approach is particularly effective against intracranial progression, presumably because it may represent failure of drug delivery rather than emergence of systemic resistance. Perhaps most relevant to the trial under discussion, which second-generation ALK inhibitor has greatest efficacy? Which has the least toxicity?

While it may difficult to distinguish the clinical efficacy of the various PD-1/PD-L1 inhibitors from one another, it has become clear that there are sufficient distinguishing characteristics among ALK inhibitors that, at least in some cases, their selection may be tailored to individual cases (see Table 1). Importantly, non-ALK activity may differ substantially. Crizotinib and brigatinib have efficacy against ROS1-positive NSCLC, but alectinib does not. Unique among clinically available ALK inhibitors, crizotinib also has activity against NSCLC harboring tyrosine-protein kinase Met (*cMET*) exon 14 mutations. [26]; [27]. Activity also differs across the spectrum of secondary *ALK* resistance mutations. Indeed, some rare cases of molecular resistance to late-generation ALK inhibitors regain sensitivity to crizotinib [28]. Realistically, there are too many mutations and too many drugs for clinicians to remember these associations. Awareness of and access to these data are critical to optimal patient care. Similarly, physicians must thoroughly understand each drug's monitoring requirements and toxicity profile. Crizotinib may cause *hypotension*, while brigatinib may cause *hypertension*. Ceritinib may cause diarrhea, while alectinib may cause constipation. The visual changes associated with crizotinib may be striking. However, they do not impact visual acuity and resolve spontaneously in most cases despite continued drug administration. Oncologists unfamiliar with this clinical pattern may inappropriately

reduce or discontinue dosing. Brigatinib pulmonary toxicity suggests that combinations with immune checkpoint inhibitors be approached with caution.

While the addition of brigatinib strengthens our anti-ALK armamentarium, it represents an incremental rather than revolutionary advance. ALK inhibitors and other molecularly targeted therapies requiring daily administration convey chronic toxicities that may rarely be severe but frequently impact quality of life. And clinical outcomes remain suboptimal. We continue to measure survival in intervals of several months. Particularly given the relatively young age of many ALK-positive patients cancer, in 2017 a diagnosis of advanced ALK-rearranged NSCLC remains tragic, with decades of life lost. Let us hope that forthcoming discoveries can truly change that.

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Table

ALK inhibitors, targets, mutational activity profiles, and toxicities

Drug	Targets	Sensitive ALK mutations	Resistant ALK mutations	Most common grade 1–2 side effects	Most common grade 3–4 side effects	References
Crizotinib	ALK MET ROS1	L1198F	L1151T ins L1152R C1156Y F1174L L1196M L1198F G1202R S1206Y G1269A	Visual changes Orthostatic hypotension, Elevated creatinine, Peripheral edema Nausea Diarrhea Fatigue Constipation		[18][29]
Ceritinib	ALK IGF-R1 InsR ROS1	L1196M G1269A I1171T S1206Y L1152R F1174L V1180L	G1202R F1174C C1156Y	Constipation Abdominal pain Decreased appetite	Diarrhea Vomiting Dehydration Elevated LFTs Low Phosphorous Elevated Lipase Fatigue	[16][18]
Alectinib	ALK LTK GAK	L1196M C1156Y F1174L G1269A S1206Y L1152R I1151T-ins	G1202 V1180L I1171T	Dysgeusia Elevated AST Elevated ALT Elevated bilirubin Elevated creatinine Rash Constipation Fatigue Myalgia Edema Elevated CPK Nausea Photosensitivity	Neutropenia Elevated creatinine Elevated CPK	[20]
Brigatinib	ALK ROS1 EGFR (including T790m) *	G1202R L1196M C1156Y G1202R G1269A S1206Y I1151T-ins F1174C I1171T D1203N E1210K F1245C	L1198F	Nausea Fatigue Headache, Diarrhea Vomiting Edema	Elevated ALT Dyspnea Pneumonia Pulmonary embolism Elevated lipase Hypertension Elevated amylase Fatigue Hyponatremia Hypophosphatemia	[21]

Drug	Targets	Sensitive ALK mutations	Resistant ALK mutations	Most common grade 1–2 side effects	Most common grade 3–4 side effects	References
Entrectinib	NTRK, ROS1, ALK	L1196M C1156Y		Paraesthesia Asthenia Nausea Vomiting Myalgia Arthralgia Dysgeusia Diarrhea	Asthenia Muscle weakness Cognitive impairment	[30]
Lorlatinib	ALK ROS1	L1196M G1202R G1269A	L1198F	Hypercholesterolemia Peripheral edema Peripheral neuropathy	Hypercholesterolemia	[31]

* Preclinical evidence of activity against activating and resistance EGFR mutations but minimal clinical efficacy.

InsR: Insulin receptor.
IGF-R1: Insulin like growth factor.
MET: Proto-oncogene protein c-**MET**
ALK: Anaplastic lymphoma kinase
EGFR: Epidermal growth factor receptor
ROS1: ROS Proto-Oncogene 1
LTK: Leukocyte Receptor Tyrosine Kinase
GAK: Cyclin G-associated kinase
ALT: Alanine transaminase
AST: Aspartate transaminase
LFTs: Liver function tests
CPK: Creatine phosphokinase
NTRK1: Neurotrophic tyrosine kinase 1