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CASE REPORT

Successful and On-going Long-Term Disease Control (>24 Months) with Gilteritinib in an *ALK*+ NSCLC Patient with Brain Metastasis Who Has Progressed on Multiple ALK TKIs. A Case Report and Review of Literature on Gilteritnib

Sai-Hong Ignatius Ou[1,2], Cathleen June Park[1,2], Zhaohui Liao Arter[1,2], Misako Nagasaka[1,2]

[1]Department of Medicine, University of California Irvine School of Medicine, Orange, CA, 92868, USA; [2]Chao Family Comprehensive Cancer Center, Orange, CA, 92868, USA

Correspondence: Sai-Hong Ignatius Ou, University of California Irvine School of Medicine, 200 South Manchester Ave, Suite 400, Orange, CA, 92868, USA, Email ignatiusou@gmail.com

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Background: Despite the approval to date of 3 generations of ALK tyrosine kinase inhibitors (TKIs) and the clinical development of a 4th-generation ALK TKI, neladalkib (NVL-655), patients still eventually progress on sequential treatment of various generations of ALK TKIs. Patients with advanced *ALK*+ NSCLC can survive many years with sequential use of various generations of ALK TKIs but will eventually exhaust all approved available ALK TKIs. Further options for these patients besides clinical trial could include the repurposing of approved multi-targeted TKIs for other oncologic indications. Gilteritinib, a multi-targeted FLT3 (and AXL, ALK, ROS1) TKI, is approved as monotherapy at 120 mg once daily for *FLT3*+ refractory/relapsed acute myelogenous leukemia (AML).

Case Description: Patient is currently an 82-year-old African-American female never-smoker who was diagnosed with stage 4 NSCLC at age 62. Almost 7.5 years after initial diagnosis and after disease progression on multiple chemotherapy regimens, her tumor was found to harbor an *EML4-ALK v1* fusion. Since then, she has been treated with multiple ALK TKIs including crizotinib, alectinib, brigatinib, and lorlatinib sequentially (from age 75 to 80) but requiring dose reduction and interruption of lorlatinib due to neurocognitive toxicity from previous stereotactic brain radiation and resection and eventual discontinuation of lorlatinib. Repeat plasma genotyping after discontinuation of lorlatinib revelaed *EML4-ALK v1* without known off-targeted resistances. With written consent from patient and family, she was started on gilteritinib 80 mg once daily with a quick dose increase to 120 mg and achieved stable disease with rapid clearance of *ALK* fusion from plasma, stability of the CNS metastasis, as well as a decrease in CEA and size of the left upper lesion. Patient is alive today and doing well without CNS effects while on full-dose gilteritinib.

Conclusion: This is the first patient case report with >24 months on-going follow-up demonstrating that gilteritinib could be repurposed as a potent and tolerable ALK inhibitor based on previously reported pre-clinical activity and with potential CNS activity. A Phase 2 trial of gilteritnib in alectinib- or lorlatinib-refractory *ALK*+ NSCLC is being planned (NCT07140016).

Plain Language Summary:

Key findings

Gilteritinib could be repurposed as a potent and tolerable ALK TKI with CNS activity.

What is known and what is new

Preclinically, gilteritinib has been demonstrated to possess potent ALK inhibitory activity with an IC_{50} similar to lorlatin (Figure 1) and can overcome certain acquired *ALK* mutations. Gilteritinib has also demonstrated activity in AML harboring an *RANBP2-ALK* fusion. This case report extends this pre-clinical observation to successfully treating one patient with advanced *ALK*+ NSCLC with progression on all three generations of ALK TKI and not eligible for clinical trial with neladalkib, demonstrating safety of full-dose gilteritinib 120 mg once daily with intracranial activity without CNS adverse events, unlike what this patient experienced with lorlatinib even at a very low dose.

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What is the implication, and what should change now?

Gilteritinib could be repurposed as a potent and tolerable ALK TKI in the refractory/relapsed setting against several single acquired *ALK* resistance mutations (but not *ALK* G1202R gate-keepr mutation) without off-target resistance mechanisms. Given its safety, tolerability, and similar IC_{50} to lorlatinib (IC_{50} = 0.78nM [gilteritinib]; IC_{50} = 1.2nM [lorlatinib]), gilteritinib should be investigated in earlier settings in the treatment of advanced *ALK*+ NSCLC. Currently, there is a Phase 1–2 clinical trial of gilteritinib in *ALK*+ NSCLC ongoing at the University of Michigan (NCT06225427) and Astellas Pharma Inc, which owns gilteritinib, is planning phase 2 trial of gilteritinib in alectinib- and lorlatinib-refractory *ALK*+ NSCLC patients (NCT07140016).

Keywords: gilteritinib, lorlatinib, ALK fusion, non-small cell lung cancer

Introduction

Since the discovery of anaplastic lymphoma kinase (ALK) fusion in non-small cell lung cancer (NSCLC) in 2007,[1,2] there are now 6 ALK TKIs approved in the US (crizotinib, ceritinib, alectinib, brigatinib, ensartinib, lorlatinib) and 8 ALK TKIs (the 6 ALK TKIs approved in US plus iruplialkib and envronalkib) approved in China as of early 2025. *ALK* fusion constitutes about 5% of actionable driver mutations in NSCLC.[3] Sequential use of different generations of ALK TKIs has led to extended survival of patients with advanced *ALK*+ NSCLC[4] but invariably lead to the emergence of compound resistance mutations[5] where currently a fourth-generation ALK TKI, neladalkib (NVL-655) is being developed to overcome these compound mutations (ALKOVE-1, NCT05384626). However, the current developmental pathway for full approval of neladalkib is in the first line metastatic setting with the launch of the Phase 3 ALKAZAR trial (NCT06765109) comparing neladalkib to alectinib. Hence, in the future, many countries may not follow potential accelerated approval indications of neladalkib in the US and may not be able to use neladalkib in the refractory setting to overcome compound ALK resistance mutations. Hence, repurposing of approved TKIs that have wildtype ALK kinase activity is needed, given the rarity of these oncogenic drivers.

Gilteritinib (ASP2215) is a multi-targeted FLT3/AXL inhibitor[6] that was approved as a single agent at 120 mg once daily on November 29, 2018, for the treatment of relapsed/refractory acute myelogenous leukemia (AML) with a *FLT3* mutation based on the ADMIRAL trial.[7] Gilteritinib achieved significant overall survival benefit over chemotherapy in relapsed/refractory AML (9.3 months vs 5.6 months; hazard ratio [HR] = 0.64; 95% confidence interval [CI], 0.49 to 0.83; P<0.001).[7] This remains the only approved indication for gilteritinib to date.

Beginning in 2021, there were emerging preclinical data that gilteritinib could also be a very potent ALK TKI and as equipotent against wildtype *EML4-ALK* fusion as lorlatinib and far much more potent than second-generation ALK TKIs (Figure 1).[8–10] Gilteritinib can overcome many acquired single *ALK* mutations, but it is projected to be ineffective against the solvent-from *ALK* G1202R mutation (IC_{50} = 168 nM).[8] Importantly, however, in preclinical models, gilteritinib can overcome I1171N based and non G1202R compound mutations (ie IC_{50} = 3.2 nM against I1171N/F1174N)[8,9] and has modest activity against G1202R/L1198F compound mutations.[8] Furthermore, gilteritinib has been shown to inhibit *NPM1-ALK* fusion transcript and anaplastic large cell lymphoma cell lines,[11] indicating preclinically that gilteritinib can function as a bonafide ALK TKI.

Case Description

Patient is an 81-year-old life-long never-smoker African-American female. She was diagnosed with stage 4 non-small cell lung cancer at the age of 63, more than 18 years ago and was treated at an outside medical facility for 7.5 years until a second opinion consult at our institution in 2011. A previous *ALK* fluorescence in situ hybridization (FISH) performed in 2007 was reported as negative. Confirming her never-smoking status, at our institution, we performed a fine needle biopsy of a growing liver metastasis followed by next-generation sequencing which detected an *EML4-ALK* variant 1 fusion transcript (Foundation Medicine Inc, Cambridge, MA).

Patient was initially treated with multiple chemotherapy regimens during the 7.5 years prior to the *ALK* positivity diagnosis (Figure 2). After the diagnosis of *ALK* positivity, she received crizotinib x 16 months and started on alectinib upon progression on crizotinib. She received alectinib for 2 years and 4 months before developing brain metastases and

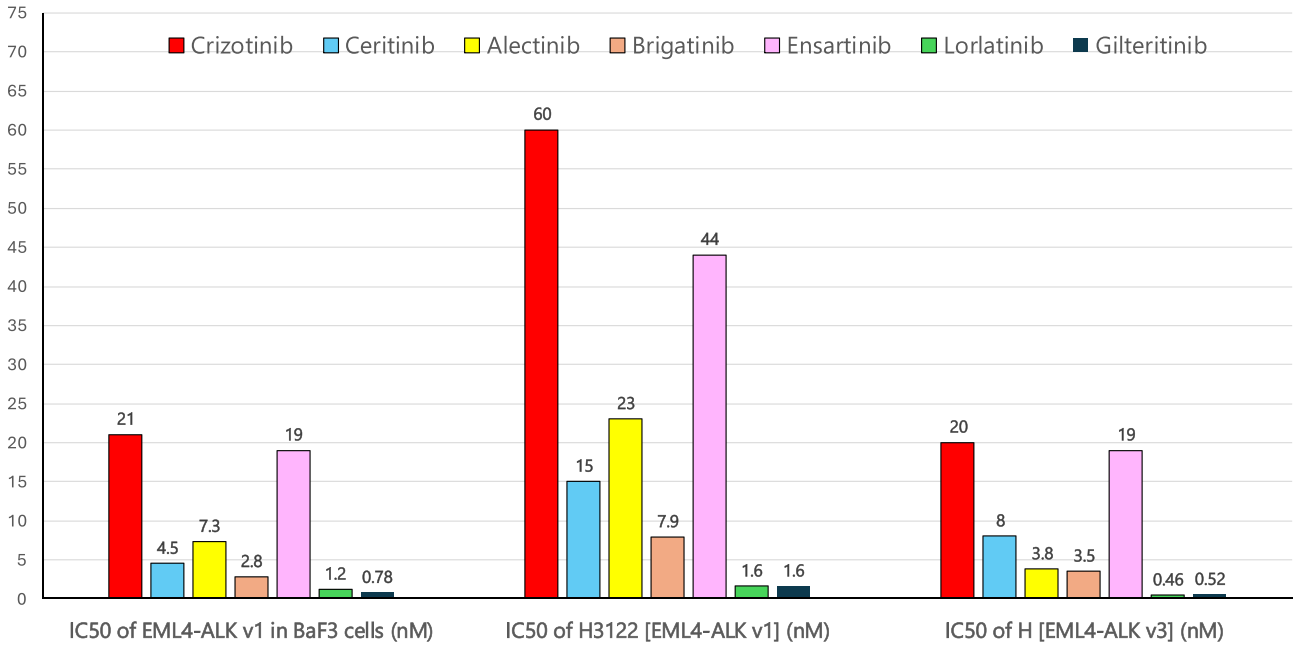

Figure 1 Comparison of reported IC_{50} of various generations of ALK TKIs with various background of EML4-ALK variants. Bar chart graph adopted from data from reference 4.

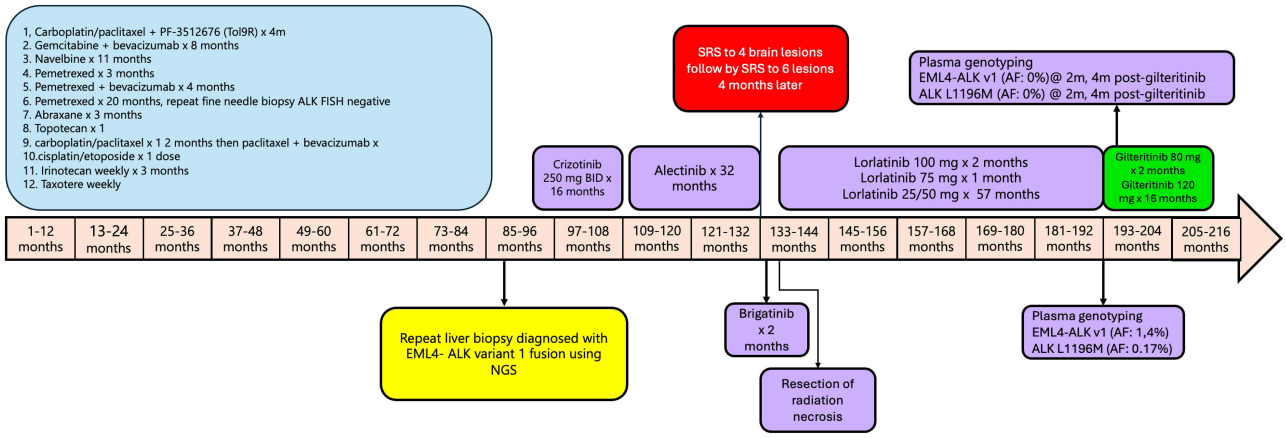

Figure 2 Timeline of the treatment history of patient over a period of 18.5 years.

received stereotactic radiation (SRS) twice over a period of 4 months to 4 and 6 separate lesions, respectively. With the loss of central nervous system (CNS) control, brigatinib was started but patient did not tolerate treatment well with emergent hypertension. Patient was then switched to lorlatinib through an expanded access program. One month after starting lorlatinib at 100 mg once daily, patient developed radiation necrosis requiring resection of the necrotic brain tissue. Lorlatinib was restarted at 75 mg once daily, but patient developed cognitive side effects including forgetfulness and personality changes and lorlatinib dose was eventually reduced to 25 mg once daily three months after starting lorlatinib. Patient continued lorlatinib 25 mg once daily for 36 months, but cognitive side effects again developed with memory loss and inability to perform selfcare. Lorlatinib was subsequently reduced to 25 mg every other day and then eventually held. After 3 months of interruption of lorlatinib, the patient's cognitive status improved to be able to perform activities of daily living and selfcare but could not tolerate resuming lorlatinib 25 mg every other day and thus, lorlatinib was discontinued.

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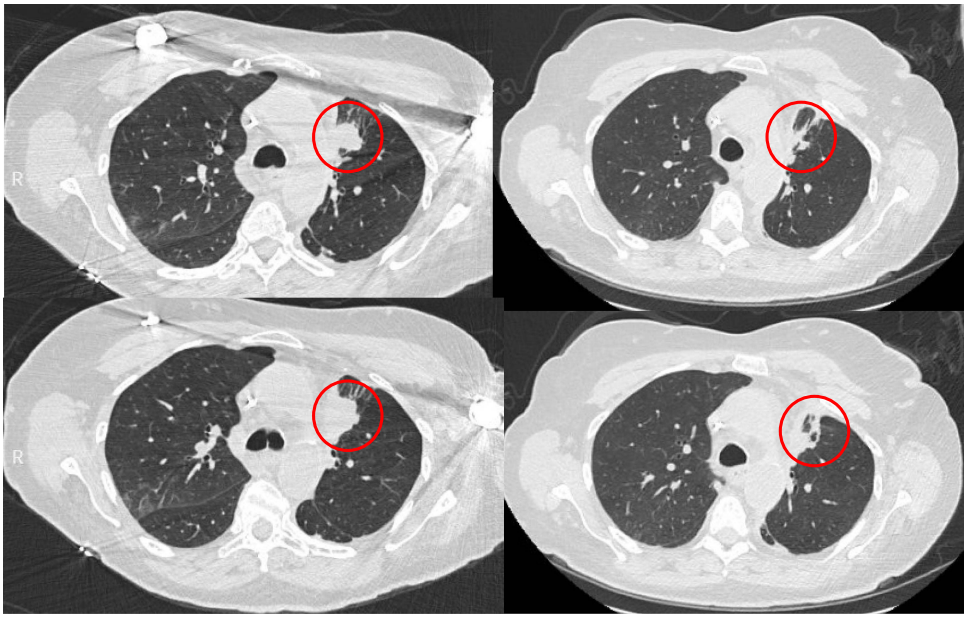

Figure 3 Radiographic response to gilteritinib 120 mg once daily after 3 months of treatment. Decrease in the left upper lobe mass was noted. The red circles denoted the tumor responses to gilteritinib treatment.

Patient's mental status improved after discontinuation of lorlatinib. With patient's improved performance status, the patient and her family desired further treatment. Given the sequalae of CNS effects, the patient was not eligible for participating in a clinical trial with fourth-generation ALK TKI NVL-655 (nedalalkib). We decided to start gilteritinib given its vigorous pre-clinical data of being a very potent ALK TKI and after discussions about the pre-clinical activity of gliteritinib with the patient and her family, full informed consent was obtained from patient and patient's family. Pre-gilteritinib treatment plasma genotyping revealed *EML4-ALK v1* at allele frequency (AF) of 1.4% with an acquired resistant *ALK* mutation of L1196M (AF of 0.7%). Other clinically significant co-mutations included *TP53* G245A (AF of 0.33%), *CHECK2* R117fs*1 (AF of 0.16%), *DNMT3A* R882P (AF of 0.17%). Gilteritinib was started at 80 mg once daily for 2 months and repeat plasma genotyping revealed disappearance of the *EML4-ALK v1* and the *ALK* L1196M mutation. Radiographic imaging 3 months after starting gilteritinib revealed decrease in the left upper lobe mass (Figure 3). Patent tolerated treatment well with no side effects and the dose of gilteritinib was increased to the approved (in AML) full dose of 120 mg once daily and repeated plasma genotyping revealed continual clearance of both the *EML4-ALK v1* and acquired resistance mutation.

Patient continued on gilteritintib and remained well through telemedicine visits, but due to social factors (long travel distance from home to UCI, old age, the long duration of treatment, patient and family preference), surveillance scans were obtained sparingly. Repeat plasma genotyping 18 months after starting gilteritinib revealed continued clearance of *EML4-ALK v1*. Repeat CT scans showed stable disease in the primary tumor and CEA remained low. The CEA level was monitored throughout her treatment at our institution (Figure 4). To date, the patient has not encountered any laboratory abnormalities, including myelosuppression, while on full dose of gilteritinib treatment.

Discussion

We believe our patient case provides the first ever long-term clinical evidence that gilteritinib can be repurposed as a potent and tolerable ALK inhibitor. Granted that patient has survived stage 4 *ALK*+ NSCLC for more than 18 years, her tumor may have an indolent biology although *TP53* mutation, which is a poor prognostic factor,[12] was detected immediately prior to the start of gilteritinib. That being said, our case report has provided objective evidence of tumor shrinkage observed in CT scans. Further supportive evidence includes disappearance of circulating *EML4-ALK v1* fusion for the duration of gilteritinib treatment and decrease in the level of the CEA tumor marker (Figure 4). Furthermore, the clearance of *ALK* L1196M is

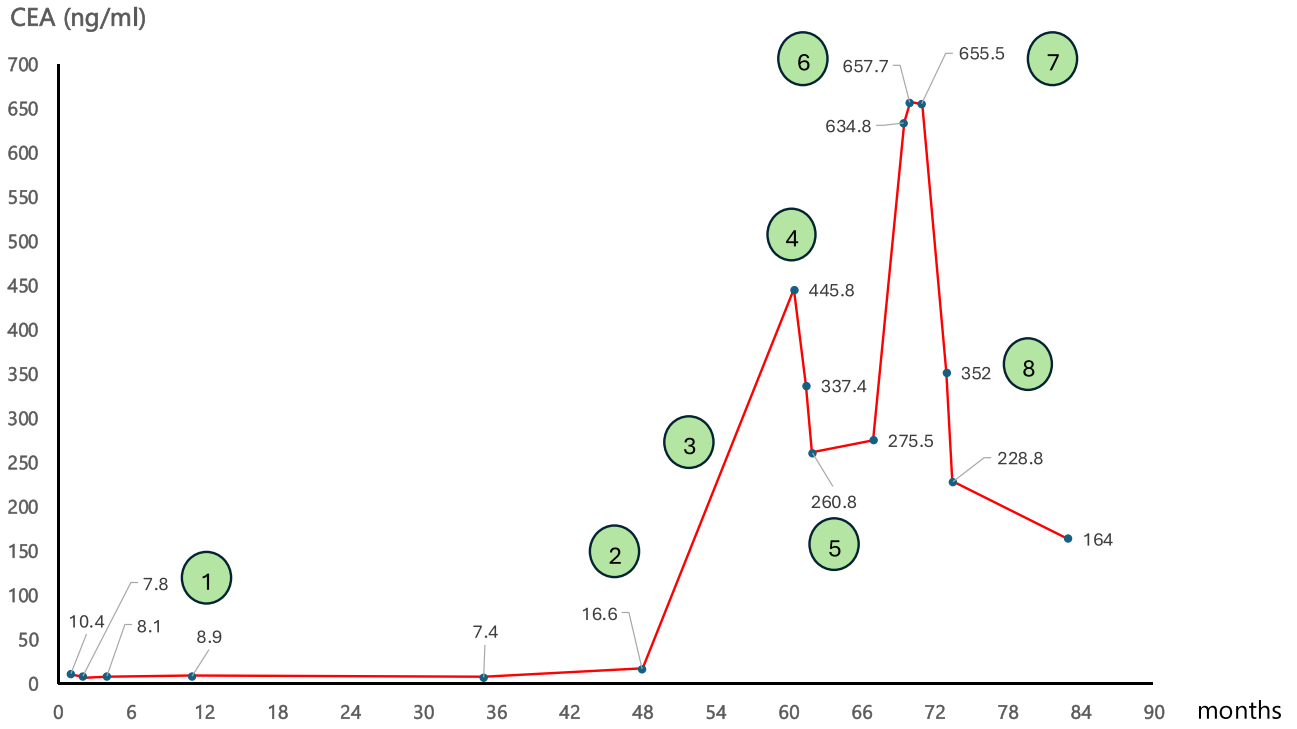

Figure 4 Graph of carcinoembryonic antigen (CEA) during treatment history of patient after *EML4-ALK* fusion was diagnosed at our institution throughout various treatments. Circle 1. Start of alectinib treatment. Circle 2. Start of lorlatinib 100 mg treatment with dose reduction to 75 mg after 1 months of treatment and reduction to 25 mg 3 months later after resection of radiation necrosis. Circle 3. Lorlatinib at 25 mg once daily. Circle 4. Lorlatinib 25 mg every other day to eventual discontinuation. Circle 5. Restarted lorlatinib 25 mg every other day. Circle 6. Permanent discontinuation of lorlatinib. Circle 7. Gilteritinib at 80 mg once daily. Circle 8. Gilteritinib at 120 mg once daily.

consistent with pre-clinical gilteritinib data (IC_{50} = 20 nM against *ALK* L1196M)[6] and reflected in the long survival (>24 months) of our patient with single-agent gilteritinib. Additionally, full-dose gilteritinib 120 mg once daily was well tolerated, and there were no cognitive side effects per patient and patient's family as compared to even the lowest possible dosing of lorlatinib 25 mg every other day. Given patient's history of progressive CNS metastasis, the absence of new neurocognitive symptoms for >24 months further indicates that gilteritinib may have CNS activity as well.

Our patient had experienced all three generations of ALK TKIs with twice stereotactic radiation and brain resection and given her age had significant CNS adverse events to lorlatinib. The cognitive effect exhibited by this patient on even very low-dose lorlatinib is correlated to the presence of brain metastasis (P = 0.008) and previous brain radiation (P = 0.033) as previously reported.[13] Based on the 5-year CROWN data update,[14] lorlatinib should be considered the preferred first-line treatment of advanced *ALK*+ NSCLC.[15,16] Given the excellent activity of lorlatinib against CNS metastasis,[13] a similar situation with our patient with progressive CNS metastasis on sequential ALK TKIs is unlikely to occur if her *ALK*+ NSCLC is diagnozed today with lorlatinib as first-line treatment.

It took a second opinion consult 7.5 years after the initial diagnosis to diagnose this patient as having an *ALK*+ NSCLC, despite the knowledge that patient was a lifelong never-smoker. Patient was initially diagnosed in 2007 during the dawn of a new era of molecular targeted therapies, with the adaptation of regular testing for *EGFR* mutation and the initial development of the diagnostic test for *ALK* fusion with *ALK* FISH which was technically challenging.[17] Indeed, the initial *ALK* FISH of the patient's tumor was read as negative. However, as we now fully appreciate life-long never-smokers with NSCLC of having a prolonged survival and their tumors of almost always harboring an actionable driver mutation, repeated biopsy should be performed using both DNA and RNA next-generation sequencing to identify any actionable driver mutation as the pre-test probablity of an actionable driver mutation is high.

Finally, gilteritinib has been shown to induce a complete morphological response in *RANBP2-ALK* AML.[18] Gilteritinib also has pre-clinical activity as a ROS1 TKI with IC_{50} of 11.1 nM against wildtype CD74-ROS1 but importantly IC_{50} of <1 nM against the *ROS1* (Cβ6) L2086F mutation[19] which confers resistance to all current type I ROS1 TKIs.[11]

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Additionally, pre-clinically gilteritinib is a potent LTK TKI with IC_{50} = 0.3 nM against *CLIP1-LTK* fusion.[20] Thus, our successful case report based on published pre-clinical data on gilteritinib can also serve as supporting evidence for "repurposing" gilteritinb in *ROS1*+ NSCLC patients with a *ROS1* L2018F mutation[21] and even rarer molecular alteration of *LTK*+ NSCLC.[22] Already, Astella Pharma is planning a phase 2 study of gilteritinib in alectinib- or lorlatinib-refractory *ALK*+ NSCLC patients (NCT07140016). However, we need to be aware gilteritinib is not effective against *ALK* G1202R solvent-front mutation, based on pre-clinical data; hence patient selection in alectinib-refractory patients is important not to enroll patients with *ALK* G1202R or with off-target resistance mechanism that gilteritnib is not expected to overcome, such as *MET* amplification, commonly found in certain subgroup of alectinib- or lorlatinib-refractory patients[23] although inhibiting FLT3 and AXL pathway may be able to circumvent resistance driven by *MET* amplification given the extensive cross-talk among human receptor tyrosine kinases.[24] Given the exceedingly long PFS acheivied by lolratinib in the CROWN study, it is a long shot in next decade that gilteritinib can replace lorlatinib as first-line treatment but can be useful in certain clinical situation if the resistance mechanisms are known.

Acknowledgment

We thank our patient and her family for enrolling in several ALK TKI clinical trials and always having close clinic follow ups despite the travel distance and social challenges and placing their trust on the treating clinicians. A signed informed consent for her case history to be published and presented has been obtained (and scanned into our EPIC electronic medical record). Institution approval for this case report is not required since this is case report is not considered research.

Disclosure

Dr Sai-Hong Ignatius Ou reports stock ownership from MB Therapeutics, Blossom Hill Therapeutics, Nuvalent, Nuvation Bio, Lilly; personal fees from Pfizer, during the conduct of the study. Dr Zhaohui Arter is on the advisory board for Catalyst, J & J, Rigel, outside the submitted work. Dr Misako Nagasaka reports personal fees from AstraZeneca, Daiichi Sankyo, Pfizer, Lilly, Genentech, Regeneron, Johnson and Johnson, Mirati/BMS, Takeda; non-financial travel support from AnHeart/Nuvation Bio, outside the submitted work. The authors report no other conflicts of interest in this work.

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