



Overcoming Central β -Sheet #6 (C β 6) *ALK* Mutation (L1256F), *TP53* Mutations and Short Forms of *EML4-ALK* v3/b and v5a/b Splice Variants are the Unmet Need That a Re-Imagined 5th-Generation (5G) *ALK* TKI Must Deliver

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Abstract: Despite the development and approval of seven anaplastic lymphoma kinase (*ALK*) tyrosine kinase inhibitors (TKIs) spanning over three “generations” since the discovery of *ALK* fusion positive (*ALK*+) non-small cell lung cancer (NSCLC), there remains intrinsic and acquired resistances to these approved TKIs. Currently, a fourth-generation (4G) *ALK* TKI, NVL-655, is being developed to attack some of the unmet needs such as compound resistance mutations *in cis*. However, *EML4-ALK* variant 3 and *TP53* mutations are intrinsic genomic alterations that negatively modulate efficacy of *ALK* TKIs. Potentially, in the shifting landscape where lorlatinib should be the first-line *ALK* TKI of choice based on the CROWN trial, the central β -sheet #6 (C β 6) mutation *ALK* L1256F will be the potential acquired resistance mutation to lorlatinib which may be resistant to current *ALK* TKIs. Here we opine on what additional capacities a putative fifth-generation (5G) *ALK* TKI will need to possess if it can be achieved in one single molecule. We propose randomized trial schemas targeting some of the intrinsic resistance mechanisms that will lead to approval of a prototypic fifth-generation (5G) *ALK* TKI and actually be beneficial to *ALK*+ NSCLC patients rather than just design a positive pivotal superiority trial for the sole purpose of drug approval.

Keywords: *EML4-ALK* variant 3a/b, *TP53* mutation, *ALK* TKIs, fifth generation *ALK* TKI, *ALK*+ NSCLC, circulating tumor DNA, next-generation sequencing, C β 6 mutation

Introduction

Since the discovery of anaplastic lymphoma kinase fusions in NSCLC in 2007,^{1,2} tremendous progress has been achieved in the understanding and treatment of advanced *ALK*+ NSCLC. A total of seven *ALK* tyrosine kinase inhibitors (crizotinib, ceritinib, alectinib, brigatinib, ensartinib, lorlatinib, iruplinakib) have been approved for the first-line (1L) treatment of advanced *ALK*+ NSCLC in various regions of the world.³ Iruplinakib was approved on January 9, 2024 in China for the first-line treatment of advanced *ALK*+ NSCLC.

However, on-target and off-target resistance are major challenges to continual successful treatment of *ALK*+ NSCLC from sequential use of *ALK* TKIs.⁴

ALK+ NSCLC patients are generally diagnosed at the peak earning potential of their lives (median age in the early 50s). Already with only 2 generations of *ALK* TKIs available, sequencing of *ALK* TKIs have been shown to prolong overall survival (OS) to 7.5 years.^{5,6} Now with lorlatinib, a third-generation (3G) *ALK* TKI approved for 1L treatment of advanced *ALK*+ NSCLC where its median PFS is still not reached at median follow-up time of 36.7 months⁷ with

potential of the eventual median PFS of > 60 months;³ together with the development of NVL-655, a 4th generation (4G) ALK TKI in clinical development,^{8,9} the OS of patients diagnosed with newly advanced *ALK*+ NSCLC in 2023 should exceed a decade. As many *ALK*+ NSCLC patients have become long-term survivors due to the introduction of successive generations of potential ALK TKIs, we have invariably created huge expectation among these patients to come up with even better treatment at the time of eventual progression, an invisible “TKI treadmill”. Thus anticipating future unmet needs in the treatment of advanced *ALK*+ NSCLC, a fifth-generation (5G) of ALK TKI will need to address some of the intrinsic resistance mechanisms that are becoming evident from all the randomized clinical trials.

Intrinsic Biological Resistance to ALK TKIs in *ALK*+ NSCLC

It is important to note *ALK*+ NSCLC is not a monolithic molecular subgroup of NSCLC.¹⁰ The companion diagnostics approved early in the treatment of advanced *ALK*+ NSCLC are fluorescence-in-situ hybridization (FISH) and immunohistochemistry (IHC), which can only detect the presence of DNA breakpoint or aberrant ALK protein expression, respectively, but none of them can detect the fusion partner. FISH is highly operator dependent and IHC in the past was dependent on the reagents used which can affect the staining intensity.¹¹ Now with an automated Ventana system the results of the IHC are dichotomous (Yes/No) and not by degrees of staining which will likely lead to rare false positive and false negative results.¹²

Indeed, FISH and IHC each potentially has a 10–15% false positive rate when measured against each other when analyzed from pivotal randomized phase 3 trials where PFS was also recorded^{13,14} (Table 1). From retrospective central laboratory analyses, both PROFILE1014 and ALEX phase 3 trials identified about ~15% of the patients enrolled from a single diagnostic test determined by central laboratory who were not positive by an alternative test (FISH followed by IHC [PROFILE1014]¹³ or IHC followed by FISH [ALEX]¹⁴) (Table 1). Indeed, the FISH/IHC “double positive” patients had numerically better (lower) hazard ratio (HR) than the overall trial population in both trials. Importantly, patients whose samples did not test positive by a second test by central laboratory did not benefit from crizotinib in PROFILE1014 or from alectinib in ALEX (Table 2).

With the advent of next-generation sequencing (NGS), we know there are up to > 90 DNA fusion breakpoints in *ALK*+ NSCLC.¹⁵ The vast majority of the ALK fusions in *ALK*+ NSCLC are echinoderm microtubule-associated protein-like 4 (*EML4*)-ALK fusion but there are different breakpoints occurring in the *EML4* gene. The two most common variants (variant 1 and variant 3) accounted for about 75% of the *EML4*-ALK fusion variants. Variant 1 is generated from the

Table 1 Percentage of Double Positive Test (PROFILE1014 and ALEX) from Retrospective Analysis of Central Labs

	PROFILE1014		
	Crizotinib (N)	Chemotherapy (N)	Total (N)
ALK FISH+ (entry criteria)	90	82	172
ALK IHC+	78 (86.7%)	78 (86.7%)	78 (86.7%)
ALK IHC-	63 (76.8%)	63 (76.8%)	63 (76.8%)
ALH indeterminate	141 (82.0%)	141 (82.0%)	141 (82.0%)
	ALEX		
	Crizotinib (N)	Alectinib (N)	Total (N)
ALK IHC+	151	152	303
ALK FISH+	97 (65%)	106 (70%)	203 (67%)
ALK FISH-	18 (12%)	21 (14%)	39 (13%)
ALK FISH Unknown	36 (24%)	25 (16%)	61 (20%)

Table 2 Comparison of Efficacy of Crizotinib (PROFEILE 1014) and Alectinib (ALEX) per Retrospective Analysis of Central Laboratory Analysis by FISH and IHC

	PROFILE1014					
	PROFILE1014 All		PROFILE1014 FISH+/IHC+		PROFILE1014 FISH+/IHC-	
	Crizotinib	Chemo	Crizotinib	Chemo	Crizotinib	Chemo
N	172	171	60	49	6	8
ORR (95% CI)	74% (67–81)	45% (37–63)	86.7% (75.8–93.1)	44.9% (31.9–58.7)	33.3% (9.7–70.0)	37.5% (13.7–69.4)
HR for PFS (95% CI)	0.454 (0.346–0.596)		0.401 (0.252–0.639)		1.74 (0.431–6.789)	
	ALEX					
	ALEX all		ALEX IHC+/FISH+		ALEX IHC+/FISH-	
	Alectinib	Crizotinib	Alectinib	Crizotinib	Alectinib	Crizotinib
N	152	151	106	97	14	11
ORR (95% CI)	83% (76–89)	76% (68–82)	91% (83–95)	81% (72–89)	29% (11–52)	44% (22–69)
Median PFS	NR (17.7 – NR)	11.1m (9.1–13.1)	NR (NR – NR)	12.7m (9.2–14.9)	3.8m (1.9 – NR)	7.4m (2.7 – NR)
HR for PFS (95% CI)	0.47 (0.34–0.65) P < 0.001		0.4 (0.27–0.61) P < 0.0001		1.45 (0.59–3.53) P = 0.41	

fusion of exons 1–13 of *EML4* to exons 20–29 of *ALK* (E13:A20) while variant 3 is generated from fusion of exons 1–6 of *EML4* to exons 20–29 of *ALK* (E6:A20).¹⁰ It has been demonstrated there is differential protein stability¹⁶ with the longer/larger variant 1 with more disorganized helical structure of *EML4* leading to proteasome degradation and hence being more sensitive to *ALK* TKIs than variant 3 which has a shorter more compact structure and less likely to be directed to proteasomes for degradation.¹⁶ Indeed all six (data not available for irupinlakib) approved *ALK* TKIs had lower IC_{50} against *EML4-ALK* v1 than *EML4-ALK* v3.^{3,17} Analysis of circulating tumor DNA (ctDNA) from both first-line (1L)^{18–20} and second-line 2L²¹ randomized phase 3 trials of next-generation *ALK* TKIs (alectinib, brigatinib, lorlatinib) indicated *EML4-ALK* v3 had a shorter PFS than *EML4-ALK* v1 confirming many retrospective analysis.¹⁰

Additionally, *EML4-ALK* v3 has two splice variants generated by differential splicing by inclusion of a cryptic exon (exon *EML4* 6b) of 11 amino acids (*EML4-ALK* v3b).²² Hence commercial sequencing reports using DNA next-generation sequencing (NGS) report both variant 3a and 3b, *EML4-ALK* v3a/b. *EML4-ALK* v3a is more resistant to crizotinib than *EML4-ALK* v3b.²³ Importantly, the ratio of v3a/3b is dynamic and the ratio of the v3a/v3b increased with treatment with crizotinib leading to more of the more resistant *EML4-ALK* v3a to crizotinib.²² Thus, targeting differential splicing of *EML4-ALK* v3a/b could potentially target one unmet need that could not be achieved by current generations of *ALK* TKIs.²³

Furthermore, we now have increasing understanding that *TP53* mutations (*mt*) conferred poorer response to *ALK* TKIs from retrospective analysis,^{16,24} and from the 1L and second-line (2L) randomized trials described above.^{19–21,25} The combination of *EML4-ALK* v3/*TP53mt* had the shortest PFS outcome.^{19–21} This is important since from the CROWN results, lorlatinib is likely to achieve a long median PFS of > 60 months³ but for patients with *EML4-ALK*v3/*TP53mt*, achieved only a median PFS of 20 months when treated with lorlatinib.²⁰

Fourth-Generation (4G) *ALK* TKI in Development and Anticipating Future Unmet Needs

Currently only one fourth-generation (4G), NVL-655, is in clinical development.⁹ NVL-655 is primarily designed to overcome double *ALK* mutations in cis which are generated by sequential use of *ALK* TKIs.²⁶ The available pre-clinical data did not suggest NVL-655 has selective activity against *EML4-ALK*v3 or *TP53* mutations.⁹ Indeed, preliminary efficacy data showed that the ORR was 54% among *ALK*+ NSCLC patients with single or compound *ALK* mutations but only 22% among *ALK*+ NSCLC patients without any known *ALK* mutations.⁹ These early preliminary results indicate

that current 4G ALK TKI as a pure ALK TKI is unlikely to overcome off-target resistances when on-target acquired resistance *ALK* mutations were not detected.

Another less well-known mutation, *ALK* L1256F, located in the central β -sheet number 6 (C β 6), that has been demonstrated pre-clinically to confer resistance to lorlatinib²⁶ and likely NVL-655 but could be overcome by alectinib pre-clinically.²⁶ So far no (C β 6) *ALK* L1256F mutation has been reported from patient cases in the literature. The PFS2 data from the CROWN study indicated there is effective post-lorlatinib treatment although the breakdown of the efficacy (chemotherapy, alectinib, other ALK TKI) is required to identify the most effective treatment.²⁴ Given the adoption of 1L lorlatinib is likely to increase over time especially when the median PFS of lorlatinib from CROWN finally matures, the potential emergence of *ALK* L1256F as the initiating mutation underlying a separate set of compound resistance mutations would create a new category of novel compound *ALK* L1256F resistant mutations creating a new unmet need.

Qualities That a Fifth-Generation (5G) ALK TKI Must Possess to Overcome Unmet Needs

The evolution of the expected or ideal “functional capacities” of successive generations of ALK TKI are depicted in Figure 1. The potential additional capacities of a prototypic 5G ALK TKI are also depicted. As described above, the ability to overcome *TP53* mutations, “reverse” the differential splicing ratio of *EML4-ALK v3a/b*, and to overcome C β 6 mutation will be desirable properties of a 5G ALK TKI. Whether these additional properties can be structurally conferred in one single molecule is unknown. Another approach will be to overcome this evolving unmet need by a multi-targeted TKI or combination therapy approach. Targeting RNA splicing by targeting kinases involved in RNA splicing has been successful in a subset of muscular dystrophy and is being investigated in multiple cancer types.^{23,27}

On-target resistance mutations are one major pathway conferring resistance to current ALK TKIs approved or in clinical trial. There are many off-target resistances that involve histologic transformation or activation of bypass signaling pathways.⁴ Alterations in the *MET* gene especially *MET* amplification, is a common off-target resistance mechanism.²⁸ Combination therapy with a *MET* TKI such as capmatinib or tepotinib has been successfully combined with next generation ALK TKIs.²⁹ While we do not expect 5G ALK TKI to be able to overcome *MET* amplification the ability to combine with *MET* TKIs would still be important.

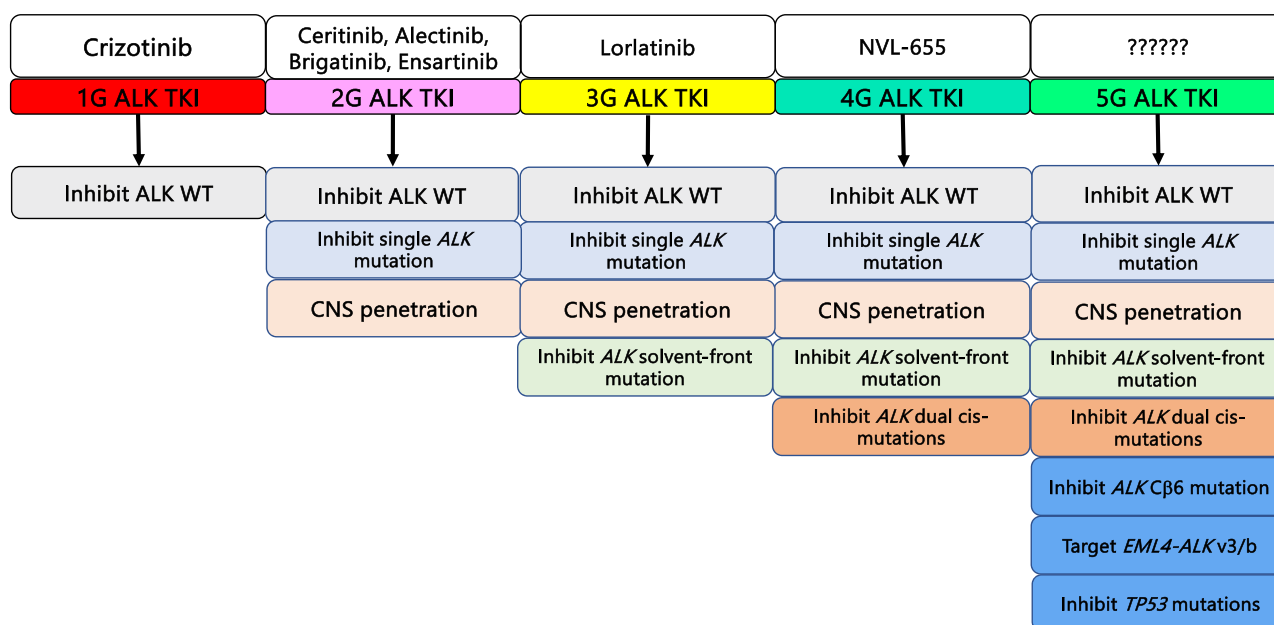
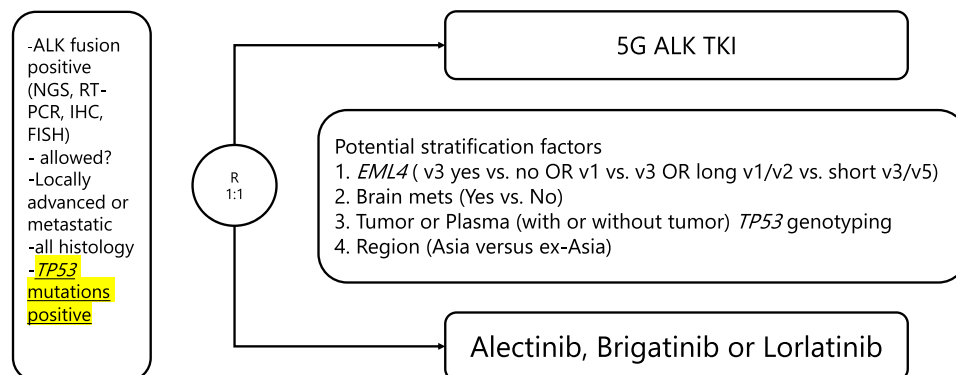


Figure 1 Graphic depiction of the increasing capacities of successive generation of ALK TKI being developed including the anticipated capacities of a prototypic 5th-generation (5G) ALK TKI to overcome anticipated resistances to current approved or investigational ALK TKIs.

If Such 5G ALK TKIs Can Be Designed in the Future, What is the Development Pathway of the Compounds (Molecularly Based Design/Stratification versus Clinical-Base Design/Stratifications)?

We have previously proposed the pivotal phase 3 clinical designs of a 4G ALK TKI in the 1L, 2L, and 3L setting.⁸ We expanded this thought exercise to a prototypic 5G ALK TKI on the assumption that lorlatinib should be the 1L treatment of choice for advanced *ALK*+ NSCLC given the likely eventual mature PFS of lorlatinib from CROWN will be > 60 months and our perspective is to advance the discourse on treatment of advanced *ALK*+ NSCLC for the next decade and beyond by extending beyond the > 60 months PFS 1L lorlatinib will achieve. We proposed two randomized trials molecularly based schemas: one in the 1L setting (Figure 2A) and one in the 2L setting (Figure 2B). Given our projection that the mature PFS of lorlatinib will be > 60 months,³ a pivotal head-to-head 1L against lorlatinib will be seemingly impractical. However, *TP53* mutations have been demonstrated to significantly negatively modulate median PFS treated with alectinib,^{18,25,30} brigatinib,¹⁹ and even with lorlatinib.²⁰ Hence 1L treatment of *TP53*+/*ALK*+ NSCLC patients remained unsatisfactory and an unmet need. Therefore, a frontline trial of a 5G ALK TKI versus alectinib, brigatinib, or lorlatinib among *TP53*+/*ALK*+ NSCLC patients is scientifically sound, and easier to achieve superior outcome for the investigational ALK TKI given the control arm PFS of only 16–20 months. Lastly, *TP53* mutations represent ~40% of advanced *ALK*+ NSCLC patients²⁶ thus maintaining the commercial viability of developing a 5G ALK TKI in the first-line setting.

A Potential Randomized trial design 5G ALK TKI (First Line Molecular Selected Design)



B Potential Randomized trial design 5G ALK TKI (Second Line Molecular stratified Design)

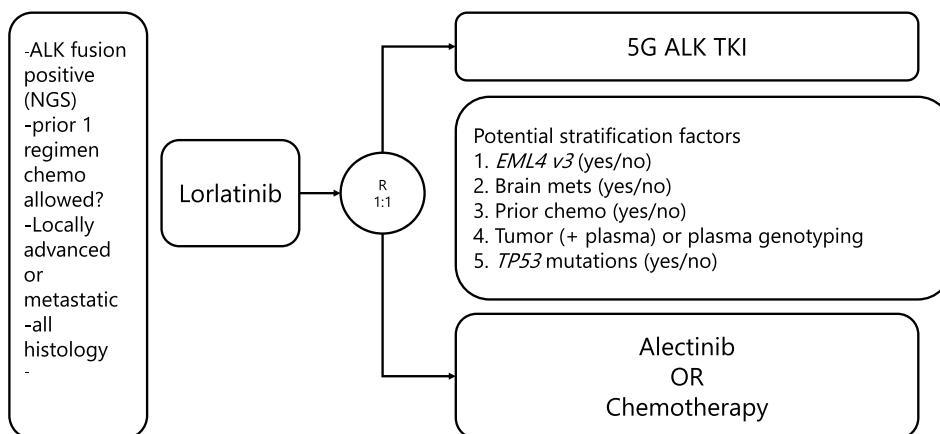


Figure 2 Continued.

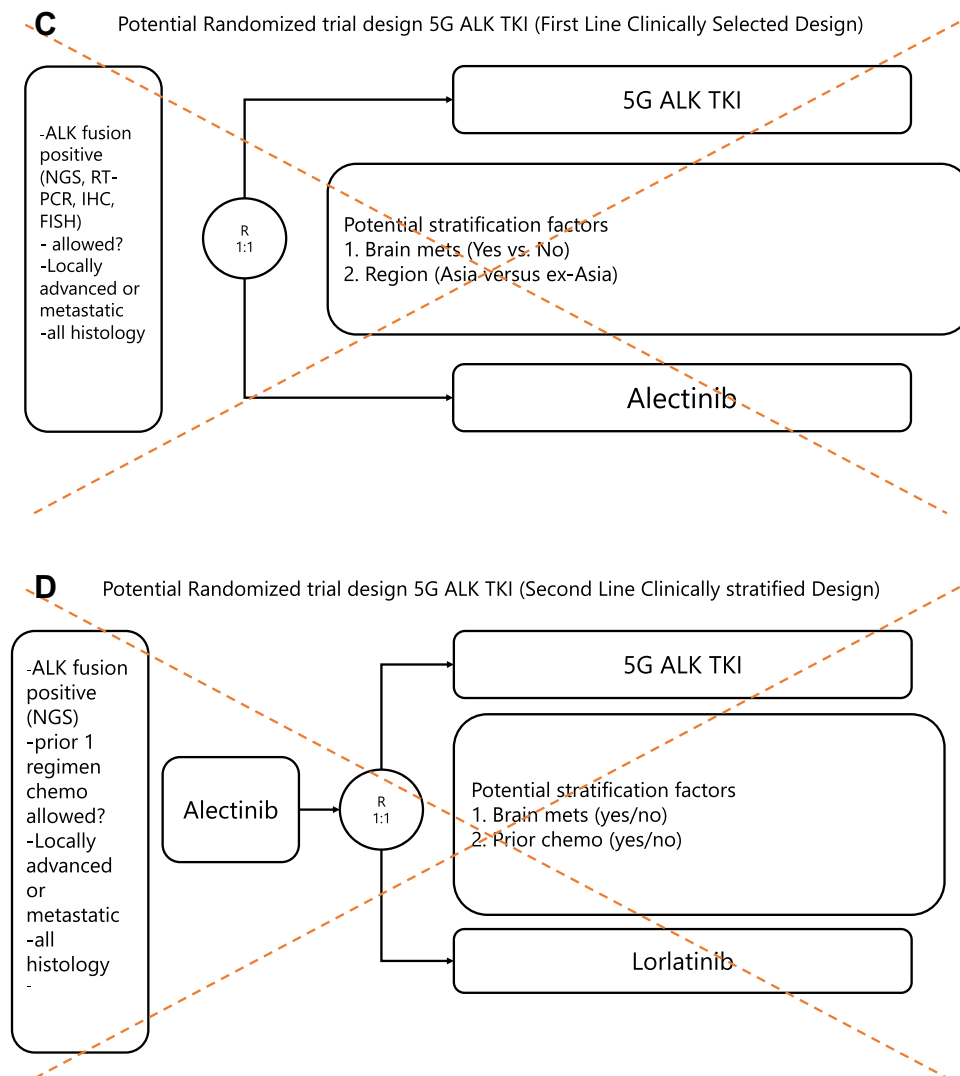


Figure 2 Hypothetical designs of pivotal randomized trials of a hypothetical 5th generation ALK TKI.

Notes: (A) Hypothetical design of a pivotal randomized molecular-selected phase 3 first-line trial of a 5G ALK TKI versus alectinib, brigatinib, or lorlatinib with ALK+ NSCLC patients harboring *TP53* mutations. This design addresses the unmet need of *TP53* mutations and *EML4-ALK* short variants (*v3* and *v5*). Design of this first-line (1L) randomized trial will require the concurrent development of a companion diagnostic test for *TP53* mutations and detection of *EML4-ALK* variants. This trial design is feasible given the median PFS of ALK+ NSCLC patients with *TP53* mutations treated with lorlatinib is about 20 months and about 16-18 months with brigatinib and alectinib. Hence the statistical power is to be superior to ~20 months of PFS. (B) Hypothetical design of a pivotal molecularly stratified randomized phase 3 second-line (2L) trial of a 5G ALK TKI post first-line lorlatinib with ALK+ NSCLC patients. This design built upon using the most potent ALK TKI lorlatinib upfront and not the most popular ALK TKI alectinib upfront. Although no ALK TKI has been approved in the post 1L lorlatinib setting, alectinib can theoretically overcome ALK L1256F mutation. Alternate treatment option for the control arm will be platinum-pemetrexed chemotherapy. (C) Hypothetical design of an unsatisfactory clinically selected design of a pivotal 1L phase 3 trial comparing alectinib with 5G ALK TKI for all comers given PFS which did not address the poor prognostic subset of patients with *TP53* mutations or "short form" of *EML4-ALK* variants (*EML4-ALK v3* or *v5*). Furthermore, the median PFS of alectinib is shorter than the projected PFS achieved by lorlatinib in CROWN. Thus being superior to alectinib does not advance the holistic treatment paradigm for ALK+ NSCLC patients. This trial design is solely a conduit for approval of a 5G ALK but lorlatinib will have proven far superior than alectinib. Thus developing a similar ALK drug without addressing the true unmet need of current ALK+ NSCLC patients is suboptimal. (D) Hypothetical design of an unsatisfactory clinically selected design of a pivotal 2L phase 3 trial comparing with sequencing of alectinib to lorlatinib versus sequencing alectinib to a 5G ALK TKI. While given the median PFS of lorlatinib post-alectinib is about 5.5 months a 5G ALK TKI should be able to win over lorlatinib but even if the median PFS is triple the median PFS of lorlatinib the cumulative median PFS (26 + 16.5) will still be shorter than the projected 1L lorlatinib of > 60 months.

Stratifications for the 1L trial would potentially include *TP53* mutations as determined from tumor versus plasma (with or without tumor). The ability to detect ctDNA such as *TP53* mutations from the plasma is highly correlated to tumor burden.^{20,25,31} Advanced ALK+ NSCLC with undetectable ctDNA (e.g. *TP53* mutations) achieved the best PFS among patients in alectinib-^{25,30} or lorlatinib-treatment group.³¹ Thus, if *TP53* mutation is only detected from tumor genotyping versus plasma genotyping this may have prognostic significance.

Second stratification factor will be *EML4-ALK v3* versus *non-EML4-ALK v3* given the double genotype of *EML4-ALKv3+/TP53mt+* has the worst PFS from CROWN and supported from a real-world study utilizing the Guardant plasma genotyping database.^{20,30} This stratification also allows isolation of the individual group contribution of *TP53* mutations versus the contribution of *EML4-ALK* variants which will also allow enrollment more *ALK+* NSCLC compared with just *TP53+* or *EML4-ALK v3* patients (and potentially expand the indication of 5G *ALK* TKI) as *TP53* mutations are relatively common among high tumor burden advanced *ALK+* NSCLC (~40–45%).²⁰ A broader stratification could be the “long” form of *EML4-ALK (v1 + v2)* vs the short form of *EML4-ALK (v3a/b + v5a/b)*, thus is another option but the placement of *EML4-ALK* variants outside these 4 groups will have to be determined specifically in the protocol.

For the 2L randomized trial molecularly stratified design, we proposed post-lorlatinib where a prototypic 5G *ALK* TKI will be tested against chemotherapy or alectinib. There is no *ALK* TKI approved by the FDA for post 1L lorlatinib progression treatment. The impressive PFS2 reported in CROWN were aggregate of alectinib, other non-alectinib *ALK* TKIs and chemotherapy in equal proportion of patients who received these subsequent treatments.³² Given that C β 6 *ALK F1256F* mutation could be overcome by alectinib,²⁶ either standard platinum-based chemotherapy or alectinib should be acceptable by health authorities with the comparator arm under further analysis from CROWN (Figure 2B). Given the likelihood of PFS with either alectinib or chemotherapy will be short, *ALK+* NSCLC patients regardless of *TP53* mutation status should be enrolled with *TP53* mutations as a stratification factor.

The purpose of this perspective is to propose trial design schemas to actually benefit patients as the indication from the trial design will be the indication strictly followed by the vast majorities of health authorities globally in contrast to the relatively lax reimbursement practice in the US allowing “off-label”, “earlier-line”, or “later line” use.²⁹ We avoid a clinically based design that solely for the purpose of drug approval, but the primary endpoint will not benefit patients or advance the treatment of *ALK+* NSCLC with intrinsic resistance disease. For example, a head-to-head clinically based 1L trial of a prototypic 5G *ALK* TKI against alectinib will not benefit patients since first, lorlatinib will very likely within 2–3 years’ time demonstrate PFS that will likely double the PFS achieved by alectinib in ALEX. And with the adoption of lorlatinib as 1L treatment, the role of a 5G *ALK* lies as second-line treatment post-lorlatinib or ideally as 1L treatment of specific sub-population such as *TP53+* and/or *EML4-v3+ ALK+* NSCLC that is relatively refractory to 1L lorlatinib. Thus, the additive sequencing a 5G *ALK* TKI after alectinib is unlikely to duplicate the PFS achieved by 1L lorlatinib alone. Second and more importantly, the design avoids addressing the *TP53* mutations that led to only ~20 months for 1L lorlatinib (Figure 2C).

A 2L clinically stratified design pitting a 5G *ALK* TKI against lorlatinib post-alectinib again does not address the short 5.5 months PFS achieved by lorlatinib post-alectinib in their phase 1/2 trial that led to the initial approval lorlatinib post alectinib/ceritinib.³³ Furthermore, lorlatinib should be used in 1L setting⁸ and sequencing a prototypic 5G *ALK* TKI is still unlikely to reach a cumulative PFS of > 60 months⁸ (Figure 2D). Approval of a 5G *ALK* TKI in the 2L setting does not benefit *ALK+* NSCLC in most of the regions of the world since a second-line blanket indication may be the ideal situation to use a 5G *ALK* TKI as off-label use beyond the trial indication outside US is prohibited.

Third, CNS metastasis remains a significant comorbidity in advanced *ALK+* NSCLC³⁵ and it is a given that all next-generation *ALK* TKIs should be optimized to have potent CNS activity. Another important factor is if the protocol allows 1 regimen of platinum-based chemotherapy (as not all regions of the world are reimbursing first-line use of next-generation *ALK* TKI). Thus allowing 1 prior chemotherapy regimen will allow more patients to be eligible given some of the genotyping results, especially *TP53* mutation status, may not be available when treatment began. One challenge of the design of these trials will be to satisfy the FDA requirement for development of simultaneous companion diagnostic NGS tests for *TP53* mutation and *EML4-ALK* variants from both tumor tissue and plasma, which may be too expensive a requirement and “a bridge too far” for many small biotech companies.³⁶ Thus, companies that develop a 5G *ALK* TKI must be well capitalized to meet this challenge.

Conditions Necessary for the Successful Deployment of 5G *ALK* TKI

All the above-mentioned resistances and unmet needs since the first-generation *ALK* TKI, crizotinib, require general adoption of NGS. As discussed above, two (FISH and IHC) of the four (tumor and plasma NGS by Foundation Medicine

Inc.) FDA approved companion diagnostic tests for detection of *ALK* fusions cannot identify the actual fusion or the particular *EML4-ALK* variant nor the *TP53* mutations status. We understand that IHC is a fast and cheap method to detect *ALK* fusion especially in resource-constrained regions of the world, but to continue further advancement of the treatment of *ALK*+ NSCLC patients, it is important to go beyond the “tip of the iceberg” by identifying the *ALK* variants and the *TP53* mutation status at the time of diagnosis. As we strive to fully incorporate NGS in our practice of precision medicine, the inevitable need to overcome *TP53* mutations and *EML4-ALK* variant 3 (and 5) from these NGS reports never goes away.³⁴

Disclosure

Dr Sai-Hong Ignatius Ou reports honoraria from AnHeart Therapeutics, BMS, Claris Life Science, Pfizer, JNJ/Janssen, Daiichi Sankyo, Eli Lilly, OncLive, and DAVA Oncology LLP; has received research funding to his institution from Blueprint Medicines, Daiichi Sankyo, ERASCA Therapeutics, Janssen/JNJ, Merus, Mirati Therapeutics, Merck, Nuvalent, Pfizer, Roche, Revolution Medicine, Sanofi, and Takeda; is a scientific advisory board member of AnHeart Therapeutics and Elevation Oncology; having stock ownership in Turning Point Therapeutics, Elevation Oncology, MBrace Therapeutics, BlossomHill Therapeutics, Lilly, Nuvalent, and Theseus Therapeutics, outside the submitted work. Dr. Lee reports no conflicts of interest in this work.

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