

UC Irvine

UC Irvine Previously Published Works

Title

Will the clinical development of 4th-generation “double mutant active” ALK TKIs (TPX-0131 and NVL-655) change the future treatment paradigm of ALK+ NSCLC?

Permalink

<https://escholarship.org/uc/item/7rk5x7pc>

Journal

Translational Oncology, 14(11)

ISSN

1944-7124

Authors

Ou, Sai-Hong Ignatius
Nagasaka, Misako
Brazel, Danielle
[et al.](#)

Publication Date

2021-11-01

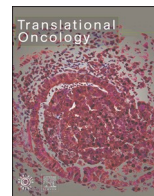
DOI

10.1016/j.tranon.2021.101191

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed



Will the clinical development of 4th-generation “double mutant active” ALK TKIs (TPX-0131 and NVL-655) change the future treatment paradigm of ALK+ NSCLC?

Sai-Hong Ignatius Ou^{a,b,*}, Misako Nagasaka^{a,b,c}, Danielle Brazel^a, Yujie Hou^d, Viola W. Zhu^{a,b}

^a University of California Irvine School of Medicine, 200 South Manchester Avenue, Suite 400, Orange, CA, United States

^b Chao Family Comprehensive Cancer Center, Orange, California, United States

^c St. Marianna University, School of Medicine, Kawasaki, Japan

^d Samuel Curtis Johnson Graduate School of Management, Cornell University, Ithaca, New York, United States

ARTICLE INFO

Keywords

TPX-0131

NVL-655

“Single mutant active”

“Double mutant active”

ALK+ NSCLC

Anaplastic lymphoma kinase tyrosine kinase inhibitors

4th-generation ALK TKI

ABSTRACT

Our current treatment paradigm of advanced anaplastic lymphoma kinase fusion (ALK+) non-small cell lung cancer (NSCLC) classifies the six currently approved ALK tyrosine kinase inhibitors (TKIs) into three generations. The 2nd-generation (2G) and 3rd-generation (3G) ALK TKIs are all “single mutant active” with varying potencies across a wide spectrum of acquired single ALK resistance mutations. There is a vigorous debate among clinicians which is the best upfront ALK TKI is for the first-line (1L) treatment of ALK+ NSCLC and the subsequent sequencing strategies whether it should be based on the presence of specific on-target ALK resistance mutations or not. Regardless, sequential use of “single mutant active” ALK TKIs will eventually lead to double ALK resistance mutations *in cis*. This has led to the creation of fourth generation (4G) “double mutant active” ALK TKIs such as TPX-0131 and NVL-655. We discuss the critical properties 4G ALK TKIs must possess to be clinically successful. We proposed conceptual first-line, second-line, and molecularly-based third-line registrational randomized clinical trials designed for these 4G ALK TKIs. How these 4G ALK TKIs would be used in the future will depend on which line of treatment the clinical trial design(s) is adopted provided the trial is positive. If approved, 4G ALK TKIs may usher in a new treatment paradigm for advanced ALK+ NSCLC that is based on classifying ALK TKIs based on the intrinsic functional capabilities (“single mutant active” versus “double mutant active”) rather than the loosely-defined “generational” (first-, second-, third-, fourth-) classification and avoid the current clinical approaches of seemingly random sequential use of 2G and 3G ALK TKIs.

Introduction

There are currently six globally approved anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) (crizotinib, ceritinib, alectinib, brigatinib, ensartinib, lorlatinib) for the treatment of anaplastic lymphoma kinase fusion-positive (ALK+) non-small cell lung cancer (NSCLC). All six ALK TKIs have been investigated in phase 3 randomized trials conducted globally, regionally, or in specific country against then the current standard of care at the time of the inception of the clinical trials [1].

Crizotinib (PROFILE1014 [2,3], and PROFILE1029 [4]) and ceritinib (ASCEND-4) [5] have demonstrated statistically significant improved median progression-free survival (mPFS) over platinum-based chemotherapy. Alectinib (ALEX [6,7], J-ALEX [8,9], ALESIA [10]), brigatinib

(ALTA-1 L [11,12]), ensartinib (eXalt3) [13], and lorlatinib (CROWN) [14] have demonstrated statistically improved mPFS over crizotinib (Table 1). With the exception of ensartinib, all of the five ALK TKIs have been approved for the first-line (1L) treatment of advanced ALK+ NSCLC in the US and ensartinib should be approved for the 1L treatment of ALK+ NSCLC soon based on the positive eXalt3 trial (Fig. 1).

Current landscape of ALK TKI development and clinical use

The development of 2nd-generation (2G) and 3rd-generation (3G) ALK TKIs became necessary due to two major unmet clinical needs with 1L crizotinib use. We now know there is an unrelentingly high cumulative incidence of central nervous system (CNS) metastases among ALK+ NSCLC patients, which is significantly higher than that in RET+ or

* Corresponding author.

E-mail address: siou@hs.uci.edu (S.-H.I. Ou).

<https://doi.org/10.1016/j.tranon.2021.101191>

Received 2 July 2021; Received in revised form 29 July 2021; Accepted 29 July 2021

1936-5233/© 2021 The Authors.

Published by Elsevier Inc.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

ROS1+ NSCLC patients [15]. Crizotinib has suboptimal CNS activity in terms of controlling, delaying, or preventing CNS progression [5-14,16,17]. Second, crizotinib after all by hindsight, was not a potent ALK TKI [18] and consequently, there are a wide spectrum of acquired ALK mutations reported with the use of crizotinib including the recalcitrant solvent-front ALK mutations albeit the solvent-front mutations constitute a small fraction of the resistance mutations to crizotinib [18,19]. The most common recalcitrant acquired ALK mutation derived from the use of 2G ALK TKIs is the solvent front ALK G1202R mutation [19]. It seems the more potent the 2G ALK TKI, the higher the chance of G1202R emerging as a resistance mutation [20]. Lorlatinib, generally considered a 3G ALK TKI, was designed for high CNS penetration and the ability to inhibit G1202R [18,21,22]. The results from CROWN seem to bear out the pre-clinical data with lorlatinib demonstrating a significantly reduced hazard ratio of 0.28 for progression or death over crizotinib.

The 2G and 3G ALK TKIs address both aforementioned clinical unmet needs to various degrees based on pre-clinical data and randomized phase 3 trials [5-14,16,17]. Thus, 2G or 3G ALK TKIs have mostly supplanted crizotinib as the standard of care of 1L treatment of advanced ALK+ NSCLC [1], though which ALK TKI should be the first ALK TKI to use is debatable [1,23]. Regardless, sequential use of ALK TKIs is the current practice but the debate rages on the correct sequence with lorlatinib often used as the last “salvage” option although lorlatinib has demonstrated the best efficacy data using cross-trial comparison [1,23].

However, it is important to note that both 2G and 3G ALK TKIs are only “single mutant active” ALK TKIs. Hence sequential use of ALK TKIs

can lead to the development of double mutations *in cis* [24-27]. “Cis” mutations occur on the same chromosome allele as opposed to “trans” mutations which occur on different chromosomal alleles. Clinically “trans” double mutations could be inhibited by combination of two different ALK TKIs that target each single mutation on a different allele. On the other hand, “cis” double mutations are not inhibited by current “single-mutant active” ALK TKI as the double mutations are on the same DNA allele resulting in an ALK protein with two concurrent mutations [27]. The frequency of ALK double mutations seemed to increase from 24% among alectinib (regardless of prior ALK TKIs) progressors increase to 48% among lorlatinib progressors al received prior second-generation ALK TKIs [25].

It is important to note in ALK+ NSCLC the ALK kinase domain is wildtype, so the emerging resistance mutations depend largely on the specific structure of a particular TKI utilized. Thus, as expected, the various combinations of double ALK mutations depend on how ALK TKIs are sequenced [26,27]. Importantly, given the solvent front ALK G1202R mutation is the most common subtype to emerge from 2G ALK TKI use, the combination of G1202R-based double mutations is becoming the most clinically important major unmet need in the treatment landscape of ALK+ NSCLC. While there are not many reports on the acquired ALK resistance mutations to 1L lorlatinib, from pre-clinical experiments and the prediction based on *ROS1* L2086F being the known acquired resistance mutation detected in *ROS1*+ NSCLC patients [28,29], one of the main resistance mutations seen in ALK+ NSCLC patients treated with 1L line lorlatinib will likely be ALK L1256F (analogous to

Table 1

List of first-line randomized trials of ALK TKIs in ALK+ NSCLC.

Study	Ethnicity	Sample Size	Median age	Female (%)	Asian (%)	Brain metastases (%)	Intervention arm	Control arm	Topline results mPFS by BIRC	Ref
PROFILE 1014	Multiple	172/171	52/54	60/63	45/47	26/27	Crizotinib 250 mg twice daily	PbCT (pemetrexed 500 mg/m ² + cisplatin 75 mg/m ² or carboplatin AUC=5-6 every 3 weeks (≤6 cycles)	10.9 m/7.0m (HR=0.45; 95% CI: 0.35-0.60; p<0.0001)	2,3
PROFILE 1029	Asian	104/103	48/50	51.9/58.3	100/100	20.2/31.1	Crizotinib 250 mg twice daily	PbCT (pemetrexed 500 mg/m ² + cisplatin 75 mg/m ² or carboplatin AUC=5-6 every 3 weeks (≤6 cycles)	11.1 m/6.8m (HR = 0.402; 95% CI: 0.286-0.565; p < 0.0001)	4
ASCEND-4	Multiple	189/187	55/54	54/61	40/44	31/33	Ceritinib 750 mg once daily	PbCT (pemetrexed 500 mg/m ² + cisplatin 75 mg/m ² or carboplatin AUC=5-6 every 3 weeks (4 cycles) followed by maintenance pemetrexed)	16.6 m/8.1m (HR=0.55; 95% CI: 0.42-0.73; p < 0.0001)	5
ALEX	Multiple	152/151	58/54	55/58	45/46	42/38	Alectinib 600 mg twice daily	Crizotinib 250 mg twice daily	25.7 m/10.4m (HR=0.5; 95% CI: 0.36-0.70; p < 0.0001)	6
ALESIA	Asian	125/62	51/49	49/45	100/100	35/37	Alectinib 600 mg twice daily	Crizotinib 250 mg twice daily	NR/10.7m (HR=0.37; 95% CI: 0.26-0.61; p<0.0001)	10
J-ALEX	Japanese	103/104	61/59.5	60/61	100/100	14/28	Alectinib 300 mg twice daily	Crizotinib 250 mg twice daily	34.1 m/10.2m (HR=0.37; 95% CI: 0.26-0.52; p < 0.0001)	9
ALTA-1L	Multiple	137/138	58/60	50/59	43/36	29/30	Brigatinib 90 mg daily x 7 days then 180 mg once daily	Crizotinib 250 mg twice daily	24.0 m/11.0m (HR=0.49; 95% CI: 0.35-0.68; p < 0.0001)	11
eXalt3	Multiple	143/147	54/53	46/43	54/57	33/39	Ensartinib 225 mg once daily	Crizotinib 250 mg twice daily	25.8 m/12.7m (HR=51; 95% CI: 0.35-0.71; p = 0.0001)	13
CROWN	Multiple	149/147	61/56	56/62	44/44	26/27	Lorlatinib 100 mg once daily	Crizotinib 250 mg twice daily	NR/9.3m (HR=0.28; 95% CI: 0.19-0.40; p < 0.0001)	14

The value on the left of each entry is for interventional arm and on the right is for control arm.

AUC: area under the curve; BIRC: blinded independent review committee; CI: confidence intervals; HR: hazard ratio; m: month; mPFS: median progression-free survival; NR: not reached; NSCLC: non-small cell lung cancer; Ref: reference; TKIs: tyrosine kinase inhibitors.

ROS1 L2086F) [28] From pre-clinical data, it is anticipated that ALK L1256F will be sensitive to alectinib [26].

Optimal sequencing of current next generation “single mutant active” ALK TKIs

Currently, there is no consensus on how best to sequence the “single mutant active” ALK TKIs. Some advocate 2G ALK TKIs in particular alectinib due to prescribers’ familiarity with alectinib together with its perceived favorable side effect profile and “saving” lorlatinib, the only 3G ALK TKI as the “last resort” [23]. Others advocate using cross-trial comparison and use the most potent ALK TKI upfront which generally would be lorlatinib given the side effects of lorlatinib can be expertedly managed [1].

Current unmet need in the treatment landscape of ALK+ NSCLC for on-target resistance

Regardless of the sequencing strategy utilized, this practice invariably leads to development of double ALK mutations which essentially destroys the efficacy even most potent ALK TKIs such as lorlatinib or brigatinib [27]. The mPFS of 1L lorlatinib achieved in CROWN is likely to be > 30 months [1]. The efficacy of lorlatinib as measured by mPFS after two or more lines of “single mutant active” ALK TKIs was between 5.5 months (95% CI: 2.7–9.0) immediately post-one “single mutant active” ALK TKI to 6.9 months (95% CI: 5.4–9.5) post-crizotinib and one to two “single mutant active” ALK TKIs from the phase 2 lorlatinib pivotal trial [30]. The real-world experience of lorlatinib also indicated a decrement of mPFS when lorlatinib was used as a later line of therapy [31]. Similarly, a real world retrospective analysis showed the mPFS of brigatinib post-alectinib was about 4.4 months (95% CI: 1.8–5.6) [32]. A prospective investigation conducted in Japan where brigatinib was used in the post-alectinib setting achieved the mPFS of 7.3 months (95% CI: 3.7–9.3), albeit alectinib was given at half the global recommended dose [33]. Results from a globally conducted study of using brigatinib post-alectinib at 600 mg twice daily and post-ceritinib should be available shortly [34]. These aggregate clinical results indicate that even with the most potent “single mutant active” ALK TKIs, their efficacies

degrades over increasing prior sequential exposure to other ALK TKIs.

4th-generation (4G) “double mutant active” ALK TKIs

To address the unmet need of the emergence of multiple combinations of acquired double ALK mutations, there are currently two 4G ALK TKIs (TPX-0131 [35, 36] and NVL-655 [37]) being developed. Detailed though likely partial pre-clinical data were presented as poster format at the annual meetings of the American Association for Cancer Research (AACR) in 2021. Both TPX-0131 and NVL-655 can inhibit acquired double “compound” ALK mutations in addition to a wide spectrum of single ALK mutations (Table 2 and Table 3).

Clinical properties expected of 4G ALK TKIs for potential role as the 1L treatment of ALK+ NSCLC

Potent wildtype ALK inhibitory activity

The most obvious property any ALK TKI must possess is potent inhibitory activity against the wildtype ALK regardless of the line of treatment envisioned. For TPX-0131, the IC₅₀ by biochemical kinase assay was 1.4 nM. The cellular IC₅₀ in the background of *EML4-ALK* was 0.4 nM compared to 0.8 nM for lorlatinib [35,36].

For NVL-655, the IC₅₀ by biochemical kinase assay was 1.2 nM compared to 2.2 nM for lorlatinib [37]. In Ba/F3 cells transfected with *EML4-ALK* variant 1, the cellular IC₅₀ was 1.6 nM for NVL-655 compared to 4.2 nM for lorlatinib. Thus, both candidate 4G ALK TKIs have prima facie evidence that they have at least similar if not more potent ALK inhibitory activity than lorlatinib.

Inhibition against *EML4-ALK* variant 3

It is important to note that ALK+ NSCLC is not one cancer. Although *EML4-ALK* variants account for about 85% of all ALK fusion variants identified in ALK+ NSCLC [38], there are >90 fusion partners to ALK identified in ALK+ NSCLC [39]. Furthermore, among *EML4-ALK* variants, there are at least >12 *EML4-ALK* variants determined by the fusion breakpoint at *EML4* to ALK, among which *EML4-ALK* variant 1 (v1; E13,

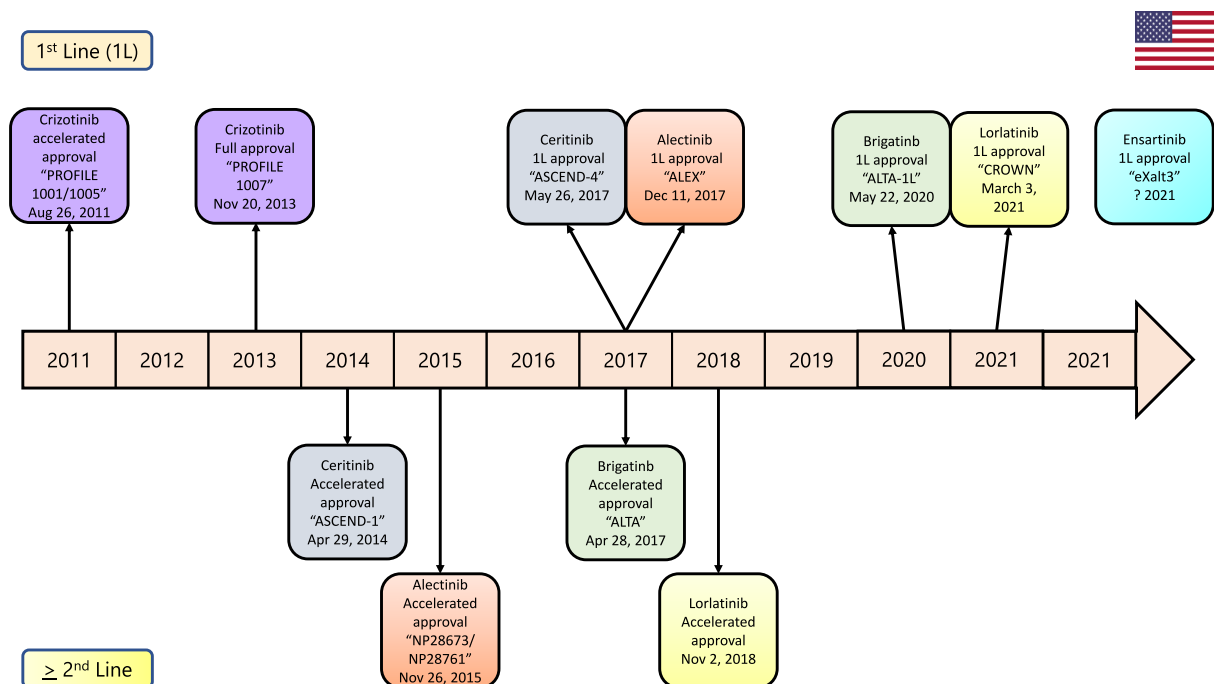


Fig. 1. Schema on the timeline of US FDA approval of ALK TKIs.

Table 2
Published biochemical kinase activity of TPX-0131 and NVL-655.

ALK	IC ₅₀ (nM) TPX-0131*	NUV-655
wt	1.4	1.2
G1202R	0.9	NR
G1202 del	0.5	NR
F1174L	0.7	NR
F1174S	1.2	NR
F1174C	1.8	NR
G1269A	1.6	NR
G1269S	6.6	NR
L1152R	1.1	NR
L1152P	2.9	NR
C1156Y	0.2	NR
I1171N	2.3	NR
V1180L	1.6	NR
L1196M	0.3	NR
L1198F	1.0	NR
S1206R	0.5	NR
R1275Q	0.8	NR
D1203N	4.4	NR
E1210K	0.3	NR
L1198F/G1202R	0.6	NR
L1198F/L1196M	0.2	NR
L1198F/C1156Y	0.2	NR
E1210K/S1206C	0.2	NR
E1210K/D1203N	6.3	NR
T1151I/L1152insT	1.2	NR
G1202R/L1196M	NR	2.5

* Kinase activity determined by Reactive Biology Inc
NR: not reported; wt: wildtype.

Table 3
Published cellular inhibitory activity of TPX-0131 and NVL-655.

ALK	IC ₅₀ (nM)* TPX-0131	NUV-655**
wt	0.4	1.6
G1202R	0.2	NR
G1202del	0.5	NR
L1198F/I1171N	1.6	NR
L1198F/L1196M	< 0.2	NR
L1198F/C1156Y	< 0.2	NR
G1202R/L1198F	< 0.2	2.0 (EML4-ALK v1)
G1202R/C1156Y	0.2	NR
G1202R/L1196M	0.7	7.0 (EML4-ALK v1)
G1202R/1269A	9.9	3.0 (EML4-ALK v1)
G1202R/G1269A/L1198F	0.2	NR
G1202R/G1269A/L1204V	14.9	NR

* IC₅₀ were not side by side comparison. They were reported by the manufacturer of each compound.

** IC₅₀ determined from Ba/F3 cell line
NR: not reported; wt: wildtype.

A20) and variant 3 (v3; E6, A20) are the two major variants, with each variant accounting for 35–40% of all the *EML4-ALK* variants [38]. However partially due to the increased protein stability of *EML4-ALK* v3 relative to *EML4-ALK* v1, there is increased intrinsic resistance to ALK TKI inhibition for *EML4-ALK* v3 regardless of the ALK TKI [40,41]. Therefore, it is important to test the ALK inhibition potency of future ALK TKIs in development against the background of *EML4-ALK* v3. It is unknown whether TPX-0131 or NVL-655 was tested against the *EML4-ALK* v3 background in the cellular inhibition assays.

CNS penetration

One of the hallmarks of next-generation “single mutant active” ALK TKIs is their potent CNS activity given the unrelenting propensity of CNS metastases during the disease course of *ALK+* NSCLC [15]. In a rat model, TPX-0131 has demonstrated penetration to the brain tissue at

approximately 66.1% (2180/3300 ng.h/ml) of plasma concentration. The concentration of TPX-0131 in cerebrospinal fluid (CSF) was 119 ng.h/ml, approximately 3.6% of plasma concentration [36]. Importantly, the ratio of CSF/plasma will have to corrected for unbound TPX-0131 in the plasma while it is generally accepted that TPX-0131 is mostly unbound in the CSF but highly protein-bound in plasma.

Similarly, NVL-655 has demonstrated high unbound brain-to-plasma partition coefficient ($K_{p,uu} = 0.16$ at 1 h) and a high CSF-to-unbound plasma partition coefficient (1.2 at 1 h) after a single oral dose of 10 mg/kg in Wistar Han rats based on orthotopic CNS implant experiments [37]. Thus, both candidate 4G ALK TKIs have demonstrated their ability to penetrate to the CNS in animal models.

Ability to inhibit a wide spectrum of compound mutations primarily “anchored” by ALK G1202R, G1269A, F1174X, and I117N

The main impetus for the development of 4G ALK TKIs is to overcome the on-target compound *ALK* mutations *in cis* which are mostly double mutations arising from sequential use of next-generation “single mutant active” ALK TKIs, especially including *ALK* G1202R-based double mutations. From the publicly disclosed data, it seems both candidate compounds can overcome many double mutations *in vitro* (Table 2 and Table 3). Interestingly, TPX-0131 also provided *in vitro* data showing its ability to overcome triple *ALK* mutations *in cis*. Nevertheless, it is important to note that the spectrum of double mutations is diverse [27]. As a result, it is likely that some double mutations may be resistant to either TPX-0131 or NVL-655.

Potential on-target resistance to 4G ALK TKIs

Resistance to ALK TKIs consists of both on-target and off-target mechanisms. Off-target resistance mechanisms to 4G ALK TKIs will likely involve *MET* amplification which has been reported with the use of next-generation ALK or RET TKIs [42–46]. On-target resistance mechanisms such as single, double, or triple mutations are likely to be the most logical mechanism of resistance and will largely depend on the structures of TPX-0131 and NVL-655. Given cellular IC₅₀ of 189–516 nM, single *ALK* mutation I1171N/S/T will likely confer resistance to TPX-0131 [36]. Potentially double mutation G1202R/G1269A and triple mutation G1202R/G1269A/L1204V mutation may also confer resistance to TPX-0131 with a cellular IC₅₀ of 9.9 nM and 14.9 nM, respectively [36]. There is very limited public information on the broad-spectrum inhibitory activity of NVL-655, but likely some single or double mutations will confer resistance to NVL-655 as we await more public disclosure of the properties of NVL-655 or clinical trial results.

What will be the optimal role for 4G ALK TKIs (1st-, 2nd-, 3rd-line) and the potential corresponding trial design?

First-line (1L) indication

In drug development, one of the main goals is to develop a compound to be the 1L treatment even if the initial development is in the refractory setting. This is especially true about “single mutation active” ALK TKIs as all five of them have completed randomized phase 3 trials in the front-line setting given the requirement to show clinical benefit in a randomized phase 3 trial (Table 1) for full regulatory approval by the US FDA if initial approval is in the refractory setting (Fig. 1).

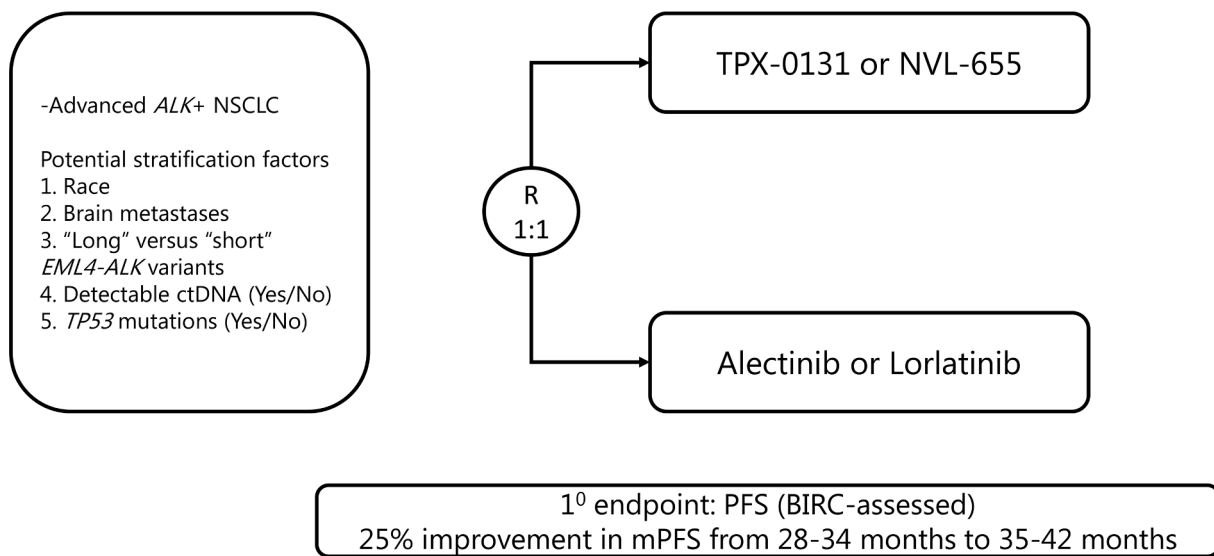
With “single mutant active” ALK TKIs being the standard of care for 1L treatment of advanced *ALK+* NSCLC, TPX-0131 or NVL-655 will have to be compared against an ALK TKI used frequently in the front-line setting such as alectinib or lorlatinib rather than crizotinib. However, given the impressive mPFS achieved by the “single mutant active” ALK TKIs is between 28 and 34 months as determined by blinded independent review committee even an improvement of mPFS of 25% will require the 4G ALK TKIs to achieve a minimum mPFS of 35 to > 40

months (Fig. 2A).

Given the expected small incremental increase of mPFS in the 1L setting, if achievable, a major challenge to launch a front-line trial is the number of patients required will be close to 500–600 (250 to 300 patients per arm) in total, which is double the total numbers of the previous front-line trials. It will require many clinical sites globally and a long accrual period. Furthermore, the sponsors will have to purchase and supply the comparator ALK TKI for likely 28–34 months per patient.

In summary, to run one such phase 3 trial is very costly with no guaranteed success. Nevertheless, if such front-line trial was ever conducted and turned out to be positive, the landscape of 1L and overall treatment of ALK+ NSCLC will change completely which will lead to further questions about subsequent sequencing but indicating further alteration of the natural history of advanced ALK+ NSCLC. Nevertheless, if such 1L trial shows supremacy of the 4G ALK TKI, this will provide insight to the natural history of the ALK+ NSCLC by validating the continual

A Conceptual first-line randomized phase 3 trial design of 4G ALK TKIs



B Conceptual second-line randomized phase 3 trial design of 4G ALK TKIs

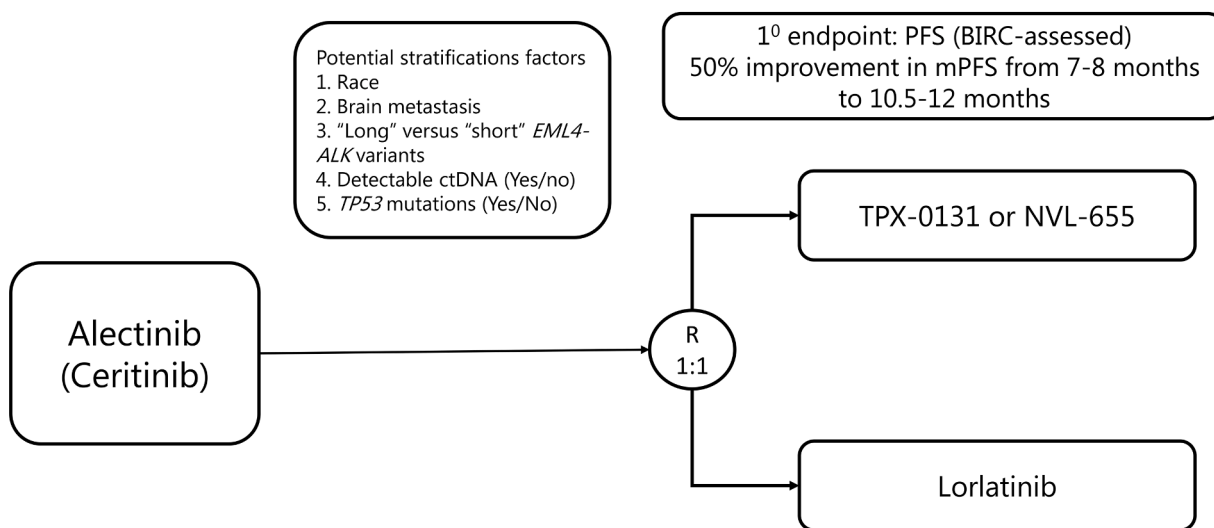


Fig. 2. (A) Conceptual first-line randomized phase 3 trial design of 4 G ALK TKIs. 4G: 4th-generation; BIRC: blinded independent review committee; ctDNA: circulating tumor DNA; mPFS: median progression-free survival. (B) Conceptual second-line randomized phase 3 trial design of 4 G ALK TKIs. Lorlatinib does not have FDA indication immediately post-1 L brigatinib or immediately post-1 L ensartinib. Given alectinib is the most widely used 1 L ALK TKI, the trial is designed for post-1 L alectinib. 1L: first-line; 4G: 4th-generation; BIRC: blinded independent review committee; ctDNA: circulating tumor DNA; mPFS: median progression-free survival. (C) Conceptual third-line randomized phase 3 trial design of 4 G ALK TKIs. 4G: 4th-generation; BIRC: blinded independent review committee; ctDNA: circulating tumor DNA; mPFS: median progression-free survival.

C Conceptual third-line randomized phase 3 trial design of 4G ALK TKIs

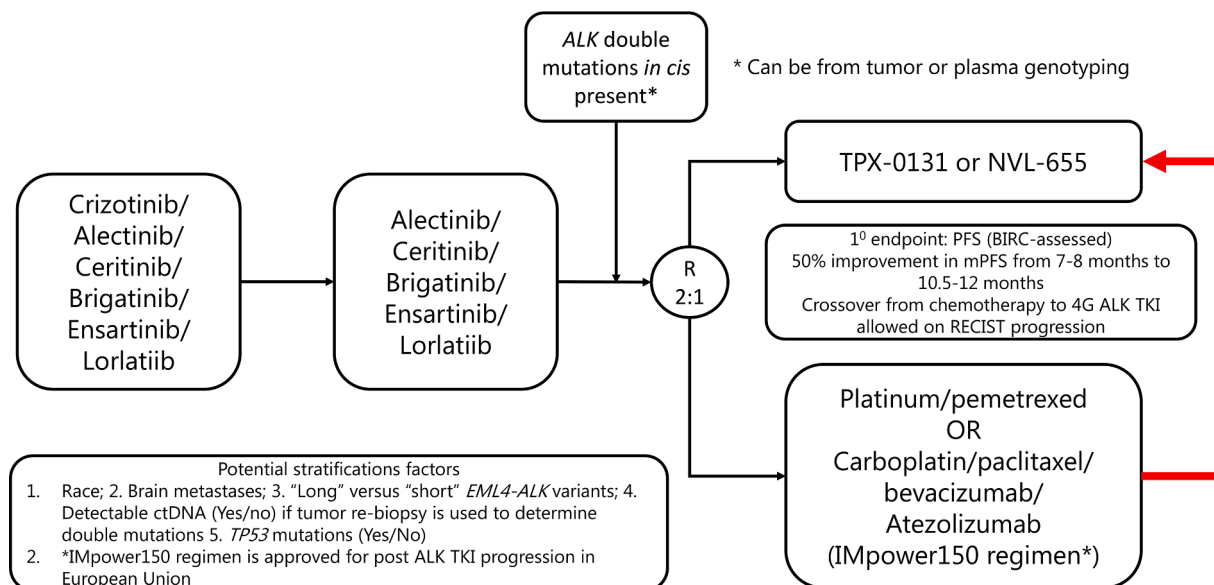


Fig. 2. (continued).

dependency on ALK signaling pathway remains the linchpin oncogenic process of *ALK+* NSCLC.

Second-line (2L) indication

Currently, lorlatinib has the indication for post-alectinib, post-ceritinib, and post-crizotinib and one other ALK TKI in addition to its 1L indication. Given the *in vitro* potency of either TPX-0131 or NVL-655 being similar to (or even slightly better than) lorlatinib, it is not unreasonable to design a 2L post-alectinib (or post-ceritinib unlikely though) phase 3 trial comparing either TPX-0131 or NVL-655 to lorlatinib (the current approved second line use of lorlatinib which is post 1L alectinib or post 1L ceritinib) (Fig. 2B). The mPFS of lorlatinib post-alectinib/post-ceritinib is approximately 5.5 months in the pivotal phase 2 trial [30], so an increase in mPFS of 50% translating to a mPFS of 9–10 months will require a relatively short follow-up period and faster time to read out either efficacy or futility. Furthermore, both TPX-0131 and NVL-655 may have a better side effect profile than lorlatinib [46,47]. NVL-655 does not have TrkB activity with resultant side effects of dizziness, dysgeusia, and truncal neuropathy manifested as tingling [48], thus may be more tolerable than lorlatinib which has TrkB activity although the cognitive side effects profile of lorlatinib are not typical of TrkB inhibition [46,47].

This 2L design scenario is very plausible even for an expected goal of 50%–100% improvement in mPFS from the mPFS achieved by lorlatinib, but ultimately it will depend on the observed efficacy of the dose expansion cohorts of TPX-0131 or NVL-655. This design also does not incorporate a molecularly directed selection so all patients with *ALK+* NSCLC who progress on 1L alectinib or ceritinib will be eligible regardless of their resistance mutations thus allowing an eventual broad indication and wide availability of the 4G ALK TKIs to *ALK+* NSCLC patients. However, this 2L design does not change the treatment paradigm of *ALK+* NSCLC much by replacing a “single mutant active” where there is still a role in this setting with a “double mutant active” ALK TKI.

Molecularly-directed third-line (3L) indication

Given TPX-0131 and NVL-655 are designed to specifically overcome acquired *ALK* double mutations *in cis*, a potential phase 3 design can be

used for this specific indication. Since sequential use of “single mutant active” ALK TKIs that will lead to double resistance mutations as part of the resistance spectrum, our proposed design will allow optimal sequential use of two ALK TKIs including the use of crizotinib as the first ALK TKI. However, eligibility criteria will need to require the presence of *ALK* double mutations as detected by either tumor or plasma genotyping after progression on two prior ALK TKIs and will exclude off-target resistance mechanisms such as *MET* amplification. Whether only a subset of specific *ALK* double mutations is allowed to enroll or any double mutation combinations are allowed will depend on the intrinsic properties of the “double mutant active” ALK TKIs and the phase 2 dose expansion results. As both 4G ALK TKIs will likely inhibit the majority of the acquired double mutations, too narrow of an eligibility criteria may slow enrollment and limit eventual regulatory indications and availability to these 4G ALK TKI to *ALK+* NSCLC patients.

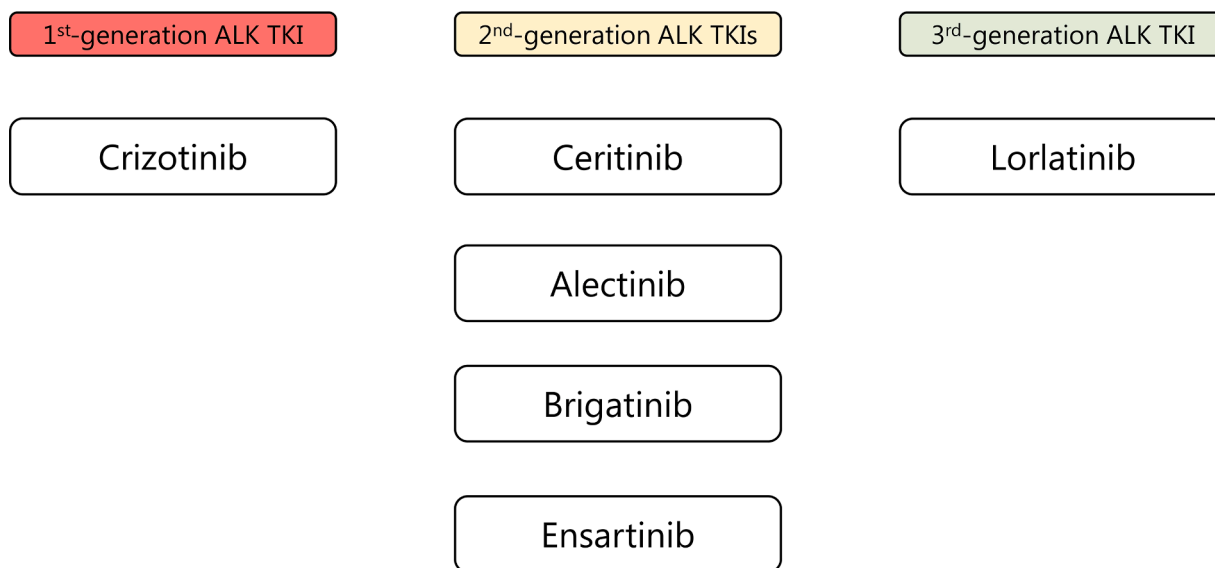
The comparator arm in this trial will likely be platinum-based chemotherapy. Currently the IMpower150 regimen of carboplatin/paclitaxel/bevacizumab/atezolizumab [49] is approved by the European Medical Agency (EMA) for post-ALK TKI progression [50]. In a post-hoc analysis, the 4-drug regimen in IMpower150 demonstrated an improvement in mPFS in either *EGFR+* or *ALK+* NSCLC patients from 6.1 months to 9.7 months (HR = 0.59, 95%CI: 0.34–0.94) [49]. It is important to note that this post-hoc data was driven by mostly *EGFR+* patients (77%) who achieved an improvement of mPFS from 6.9 months (95%CI: 5.7–7.5) to 10.2 months (95%CI: 7.9–15.2) [51]. *ALK+* NSCLC constituted only 23% of the patients analyzed and the mPFS achieved for *ALK+* NSCLC patients had to be shorter than 9.7 months for the 4-drug regimen given *EGFR+* NSCLC patients achieved mPFS of 10.2 months but the aggregate group achieved only 9.7 months of mPFS. Furthermore, this regimen has not been approved by the US FDA for use in *EGFR+* or *ALK+* NSCLC post TKI progression. And no specific and detailed analysis of the efficacy of IMpower150 in *ALK+* NSCLC specific have been reported in contrast to for *EGFR+* NSCLC patients [51,52].

Alternatively, platinum/pemetrexed is the most commonly used chemotherapy and it is another treatment option that could be given for the treatment of *ALK+* NSCLC post-ALK TKI progression. Platinum/pemetrexed treatment should retain significant clinical activity in chemotherapy-naïve *ALK+* NSCLC patients. Assuming platinum/pemetrexed maintains a similar mPFS of 7 to 8 months in chemotherapy-naïve

ALK+ NSCLC as demonstrated in PROFILE1014, PROFILE1029 and ASCEND-4, a desired 50% improvement in mPFS will require TPX-0131 and NVL-655 to achieve a mPFS of 10.5 to 12 months (Fig. 2C). How realistic is the mPFS of 10.5 to 12 months expected of a third sequential ALK TKI will have to be determined again from the initial phase 1–2 expansion cohorts. Given there is continuous cumulative incidence of CNS metastases, whether to continue the previous ALK TKI beyond progression will be controversial but there is currently no prospective

study that has demonstrated superiority of continuing the previous ALK TKI with the addition of chemotherapy to switching to chemotherapy alone [53]. Therefore, the above proposed study design should be feasible, especially if a 2:1 randomization to 4G ALK TKI versus chemotherapy and allowing crossover to 4G ALK TKI from chemotherapy upon progression are permitted. The question on how to synchronize standard of care chemotherapy globally such as IMpower150 though approved by EMA, should not be considered standard of care

A Current “Functional” View of ALK TKIs



B Future “Functional” View of ALK TKIs

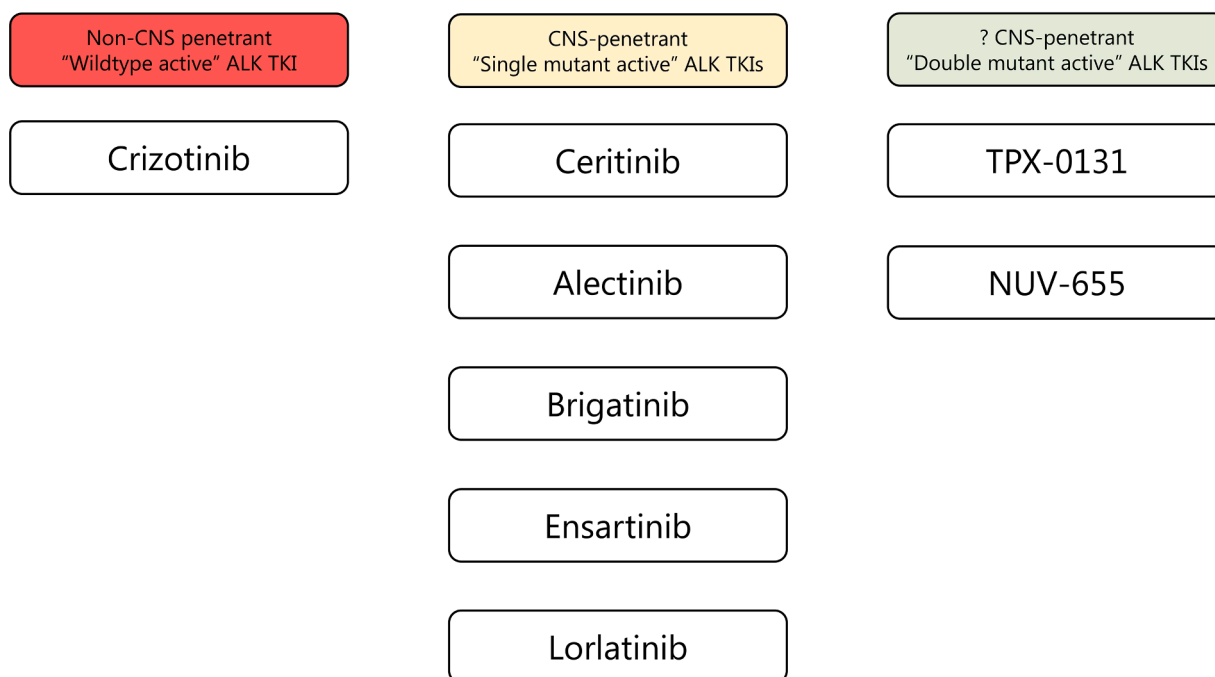


Fig. 3. (A) Current “functional” view of ALK TKIs showing one current concept of classifying ALK TKIs into 1st-generation, 2nd-generation and 3rd-generation ALK TKIs. (B) Future “functional” view of ALK TKIs showing one future concept of classifying ALK TKIs into “wildtype active”, “single mutant active”, and “double mutant active” ALK TKIs with the development of 4th-generation ALK TKIs.

given it is based on a very small subgroup post-hoc analysis with no specific breakout of the survival data for *ALK*+ NSCLC patients has been reported.

Another major challenge to this trial design is the need to develop a companion diagnostic (CDx) to detect these double mutations [54]. While this clinical design is the holy grail of precision oncology treatment, the sponsors of these 4G *ALK* TKIs will have to take into consideration of the cost and time needed to develop CDx, the limited number of eligible patients due to the built-in molecular selection, and the eventual restricted approved label indication for these 4G *ALK* TKIs based on this design. This molecularly driven 3L clinical design may be part of the development plan with. While this 3L trial design will also allow the optimal use of existing approved *ALK* TKIs prior to 4G *ALK* TKIs fulfilling the unmet need promise of these two 4G *ALK* TKIs, it will only extend the treatment paradigm rather than “revolutionizing” the treatment paradigm which is so desperately needed in *ALK*+ NSCLC. This 3L molecular-driven clinical design may be part of the development plan simultaneously conducting either a 1L or 2L design. Only the 1L design though high risk will lead to practice-changing results.

Concluding thoughts

The chances of both “double mutant active” compounds receiving accelerated conditional approval is high for the indication of “progression on two prior *ALK* TKIs” with the requirement of a randomized phase 3 trial demonstrating clinical benefit for full regulatory approval. The aforementioned trial proposals provide a framework for regulatory phase 3 trial designs based on the current clinical practice with the intention for 1L, 2L, and 3L approvals. Depending on early trial data and which trial design (Fig. 2) adopted by the sponsors, these compound could potentially be the new standard of care or reserved as the “break the glass” last resort *ALK* TKI and any indication in between.

Hopefully, adoption of new prognostic factors into the next generation trials such as *EML4-ALK* v1 versus *EML4-ALK* v3 (or long variants versus short variants), presence or absence of detectable *ALK* fusion variants by ctDNA at the study entry, presence or absence of *TP53* mutations [38] will further help us understand the disease process of *ALK*+ NSCLC. Of note, double mutations tend to be more common in *EML4-ALK* v3 or other short variants of *EML4-ALK* [27,38,55], thus stratification based on *EML4-ALK* variants may not be easily performed for the molecularly-directed 3L trial design. How these future pivotal phase 3 trials of 4G *ALK* TKIs are designed will likely affect the treatment landscape of *ALK*+ NSCLC for years to come and affect our biological understanding of this disease entity. We eagerly await to see whether a “double mutant active” *ALK* TKI will be superior to a “single mutant active” *ALK* TKI and if it will change our classification of *ALK* TKIs from a generational perspective (Fig. 3A) to a mechanistic approach (Fig. 3B).

CRedit authorship contribution statement

Sai-Hong Ignatius Ou: Conceptualization, Methodology, Visualization, Investigation, Writing – original draft, Writing – review & editing, Validation, Supervision. **Misako Nagasaka:** Conceptualization, Methodology, Visualization, Investigation, Writing – original draft, Writing – review & editing, Validation. **Danielle Brazel:** Conceptualization, Writing – review & editing, Validation. **Yujie Hou:** Conceptualization, Writing – review & editing, Validation. **Viola W. Zhu:** Conceptualization, Methodology, Visualization, Investigation, Writing – original draft, Writing – review & editing, Validation.

Declaration of Competing Interest

Sai-Hong Ignatius Ou was a member of the scientific advisory board (SAB) of Turning Point Therapeutics until April 2019 and has stock ownership in Turning Point Therapeutics, which is developing TPX-0131; is a member of the SAB of Elevation Oncology and has stock

ownership in Elevation Oncology; has received speaker honoraria from AstraZeneca, Merck, Pfizer, Roche/Genentech, and Takeda/ARIAD; has received advisory fees from AstraZeneca, Pfizer, Roche-Foundation Medicine, Roche/Genentech, Spectrum, Daiichi Sankyo, Jassen/JNJ, and X-covary.; **Misako Nagasaka** serves on the advisory board for AstraZeneca, Caris Life Sciences, Daiichi-Sankyo, Takeda, Novartis, EMD Serono, Janssen, Lilly and Genentech. She is a speaker for Blueprint Medicines, has received study funding from Tempus and has received travel support from An Heart Therapeutics.; **Danielle Brazel** and **Yujie Hou** have nothing to declare; **Viola W. Zhu** is currently an employee of Nuvalent which is developing NVL-655; has received honoraria from AstraZeneca, Blueprint, Roche-Foundation Medicine, Roche/Genentech, Takeda, and Xcovery; and had stock ownership of Turning Point Therapeutics (until May 2020).

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] M. Nagasaka, S.I. Ou, Lorlatinib should be considered as the preferred first-line option in patients with advanced *ALK*-rearranged NSCLC, *J. Thorac. Oncol.* 16 (4) (2021 Apr) 532–536.
- [2] B.J. Solomon, T. Mok, D.W. Kim, et al., First-line crizotinib versus chemotherapy in *ALK*-positive lung cancer, *N. Engl. J. Med.* 371 (23) (2014 Dec 4) 2167–2177.
- [3] B.J. Solomon, D.W. Kim, Y.L. Wu, et al., Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in *ALK*-mutation-positive non-small-cell lung cancer, *J. Clin. Oncol.* 36 (22) (2018 Aug 1) 2251–2258.
- [4] Y.L. Wu, S. Lu, Y. Lu, et al., Results of PROFILE 1029, a Phase III Comparison of First-Line Crizotinib versus chemotherapy in East Asian patients with *ALK*-positive advanced non-small cell lung cancer, *J. Thorac. Oncol.* 13 (10) (2018 Oct) 1539–1548.
- [5] J.C. Soria, D.S.W. Tan, R. Chiari, et al., First-line ceritinib versus platinum-based chemotherapy in advanced *ALK*-rearranged non-small-cell lung cancer (ASCEND-4): a randomized, open-label, phase 3 study, *Lancet* 389 (10072) (2017 Mar 4) 917–929.
- [6] S. Peters, D.R. Camidge, A.T. Shaw, et al., Alectinib versus crizotinib in untreated *ALK*-positive non-small-cell lung cancer, *N. Engl. J. Med.* 377 (9) (2017 Aug 31) 829–838.
- [7] D.R. Camidge, R. Dziadziuszko, S. Peters, et al., Updated efficacy and safety data and impact of the *EML4-ALK* fusion variant on the efficacy of alectinib in untreated *ALK*-positive advanced non-small cell lung cancer in the global phase III ALEX study, *J. Thorac. Oncol.* 14 (7) (2019 Jul) 1233–1243.
- [8] T. Hida, H. Nokihara, M. Kondo, et al., Alectinib versus crizotinib in patients with *ALK*-positive non-small-cell lung cancer (J-ALEX): an open-label, randomized phase 3 trial, *Lancet* 390 (10089) (2017 Jul 1) 29–39.
- [9] K. Nakagawa, T. Hida, H. Nokihara, et al., Final progression-free survival results from the J-ALEX study of alectinib versus crizotinib in *ALK*-positive non-small-cell lung cancer, *Lung Cancer* 139 (2020) 195–199.
- [10] C. Zhou, S.W. Kim, T. Reungwetwattana, et al., Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomized phase 3 study, *Lancet Respir. Med.* 7 (5) (2019 May) 437–446.
- [11] D.R. Camidge, H.R. Kim, M.J. Ahn, et al., Brigatinib versus crizotinib in *ALK*-positive non-small-cell lung cancer, *N. Engl. J. Med.* 379 (21) (2018 Nov 22) 2027–2039.
- [12] D.R. Camidge, H.R. Kim, M.J. Ahn, et al., Brigatinib versus crizotinib in advanced *ALK* inhibitor-I *ALK*-positive non-small cell lung cancer: second interim analysis of the phase III ALTA-1L Trial, *J. Clin. Oncol.* 38 (31) (2020) 3592–3603, 2020 Nov 1.
- [13] G. Selvaggi, H.A. Wakalee, T. Mok, et al., Phase 3 Randomized study of ensartinib vs crizotinib in anaplastic lymphoma kinase (*ALK*)-positive NSCLC patients: eXalt3, *J. Thorac. Oncol.* 15 (2020), 10S: e41–e42.
- [14] A.T. Shaw, T.M. Bauer, F. de Marinis, et al., First-Line Lorlatinib or crizotinib in advanced *ALK*-positive lung cancer, *N. Engl. J. Med.* 383 (21) (2020 Nov 19) 2018–2029.
- [15] A. Drilon, J.J. Lin, T. Filleron, et al., Frequency of brain metastases and multikinase inhibitor outcomes in patients with *RET*-rearranged lung cancers, *J. Thorac. Oncol.* 13 (10) (2018 Oct) 1595–1601.
- [16] S. Gadgeel, S. Peters, T. Mok, et al., Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (*ALK*+) non-small-cell lung cancer: CNS efficacy results from the ALEX study, *Ann. Oncol.* 29 (11) (2018 Nov 1) 2214–2222.
- [17] M. Nishio, K. Nakagawa, T. Mitsudomi, et al., Analysis of central nervous system efficacy in the J-ALEX study of alectinib versus crizotinib in *ALK*-positive non-small-cell lung cancer, *Lung Cancer* 121 (2018) 37–40.

- [18] L. Horn, J.G. Whisenant, H. Wakelee, et al., Monitoring therapeutic response and resistance: analysis of circulating tumor DNA in patients with ALK+ lung cancer, *J. Thorac. Oncol.* 14 (2019) 1901–1911.
- [19] J.F. Gainor, L. Dardaei, S. Yoda, et al., Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer, *Cancer Discov.* 6 (10) (2016 Oct) 1118–1133.
- [20] H. Qiao, C.M. Lovly, Cracking the code of resistance across Multiple Lines of ALK inhibitor therapy in lung cancer, *Cancer Discov.* 6 (10) (2016 Oct) 1084–1086.
- [21] T.W. Johnson, P.F. Richardson, S. Bailey, et al., Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-*h*] [2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations, *J. Med. Chem.* 57 (11) (2014 Jun 12) 4720–4744.
- [22] H.Y. Zou, L. Friboulet, D.P. Kodack, et al., PF-06463922, an ALK/ROS1 inhibitor, overcomes resistance to first and second generation ALK inhibitors in preclinical models, *Cancer Cell* 28 (1) (2015 Jul 13) 70–81.
- [23] D.R. Camidge, Lorlatinib should not be considered as the preferred first-line option in patients with advanced ALK rearranged NSCLC, *J. Thorac. Oncol.* 16 (4) (2021 Apr) 528–531.
- [24] S. Yoda, J.J. Lin, M.S. Lawrence, et al., Sequential ALK inhibitors can select for lorlatinib-resistant compound ALK mutations in ALK-positive lung cancer, *Cancer Discov.* 8 (6) (2018 Jun) 714–729.
- [25] I. Dagono-Jack, M. Rooney, J.J. Lin, et al., Treatment with next-generation ALK inhibitors fuels plasma ALK mutation diversity, *Clin. Cancer Res.* 25 (22) (2019 Nov 15) 6662–6670.
- [26] K. Okada, M. Araki, T. Sakashita, et al., Prediction of ALK mutations mediating ALK-TKIs resistance and drug re-purposing to overcome the resistance, *EBioMedicine* (2019).
- [27] V.W. Zhu, M. Nagasaka, R. Madison, et al., A novel sequentially evolved EML4-ALK v3 G1202R/S1206Y in cis double mutation confers resistance to lorlatinib: a brief report and literature review, *JTO Clin. Res. Rep.* 2 (2020), 100116.
- [28] K.P. Papadopoulos, E. Borazanci, A.T. Shaw, et al., U.S. phase I first-in-human study of taletrectinib (DS-6051b/AB-106), a ROS1/TRK inhibitor, in patients with advanced solid tumors, *Clin. Cancer Res.* 26 (2020) 4785–4794.
- [29] J.J. Lin, N.J. Choudhury, S. Yoda, et al., Spectrum of mechanisms of resistance to crizotinib and lorlatinib in ROS1 fusion-positive lung cancer, *Clin. Cancer Res.* 27 (10) (2021 May 15) 2899–2909.
- [30] B.J. Solomon, B. Besse, T.M. Bauer, et al., Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study, *Lancet Oncol.* 19 (2018) 1654–1667.
- [31] V.W. Zhu, Y.T. Lin, D.W. Kim, et al., An International real-world analysis of the efficacy and safety of lorlatinib through early or expanded access programs in patients with tyrosine kinase inhibitor-refractory ALK-positive or ROS1-positive NSCLC, *J. Thorac. Oncol.* 15 (2020) 1484–1496.
- [32] J.J. Lin, V.W. Zhu, A.J. Schoenfeld, et al., Brigatinib in patients with alectinib-refractory ALK-positive NSCLC, *J. Thorac. Oncol.* 13 (10) (2018 Oct) 1530–1538.
- [33] M. Nishio, T. Yoshida, T. Kumagai, et al., Brigatinib in Japanese patients with ALK-positive NSCLC previously treated with alectinib and other tyrosine kinase inhibitors: outcomes of the phase 2J-ALTA trial, *J. Thorac. Oncol.* 16 (3) (2021 Mar) 452–463.
- [34] E.S. Kim, F. Barlesi, T. Mok, et al., ALTA-2: phase II study of brigatinib in patients with ALK-positive, advanced non-small-cell lung cancer who progressed on alectinib or ceritinib, *Future Oncol.* 17 (14) (2021 May) 1709–1719.
- [35] J.J. Cui, E. Rogers, D. Zhai, et al., TPX-0131: a next generation macrocyclic ALK Inhibitor that overcomes ALK resistant mutations refractory to currently approved ALK inhibitors, in: Proceedings of the Annual Meeting of the American Association for Cancer Research 2020; 2020 Apr 27–28 and Jun 22–24, Philadelphia (PA) 80, AACR; Cancer Res, 2020. Abstract nr 5226.
- [36] B.W. Murray, D. Zhai, W. Deng, et al., TPX-0131, a potent CNS-penetrant, next-generation inhibitor of wild-type ALK and ALK-resistant mutations, *Mol. Cancer Ther.* (2021) online. 10.1158/1535-7163.MCT-21-0221.
- [37] H.E. Pelish, A. Tangpeerachaiikul, N.E. Kohl, et al., NVL-655 is a selective, brain-penetrant ALK inhibitor with antitumor activity against the lorlatinib-resistant G1202R/L1196M compound mutation, *AACR* (2021) (abstract # 1468).
- [38] S.S. Zhang, M. Nagasaka, V.W. Zhu, et al., Going beneath the tip of the iceberg. Identifying and understanding EML4-ALK variants and TP53 mutations to optimize treatment of ALK fusion positive (ALK+) NSCLC. *Lung Cancer* (2021) (in press).
- [39] S.I. Ou, V.W. Zhu, M. Nagasaka, Catalog of 5' fusion partners in ALK+ positive NSCLC Circa 2020, *JTO Clin. Res. Rep.* 1 (2020), 100015.
- [40] J.M. Heuckmann, H. Balke-Want, F. Malchers, et al., Differential protein stability and ALK inhibitor sensitivity of EML4-ALK fusion variants, *Clin. Cancer Res.* 18 (17) (2012 Sep 1) 4682–4690.
- [41] P. Workman, R. van Montfort, EML4-ALK fusions: propelling cancer but creating exploitable chaperone dependence, *Cancer Discov.* 4 (6) (2014 Jun) 642–645.
- [42] I. Dagono-Jack, S. Yoda, J.K. Lennerz, et al., MET Alterations are a recurring and actionable resistance mechanism in ALK-positive lung cancer, *Clin. Cancer Res.* 26 (11) (2020 Jun 1) 2535–2545.
- [43] J.J. Lin, S.V. Liu, C.E. McCoach, et al., Mechanisms of resistance to selective RET tyrosine kinase inhibitors in RET fusion-positive non-small-cell lung cancer, *Ann. Oncol.* 31 (2020) 1725–1733.
- [44] E.Y. Rosen, M.L. Johnson, S.E. Clifford, et al., Overcoming MET-dependent resistance to selective RET inhibition in patients with RET fusion-positive lung cancer by combining selpercatinib with crizotinib, *Clin. Cancer Res.* 27 (2021) 34–42.
- [45] V.W. Zhu, S.S. Zhang, J. Zhang, et al., Acquired tertiary MET resistances (MET D1228N and a novel LSM8-MET fusion) to selpercatinib and capmatinib combination in a *KIF5B-RET+* NSCLC patient who acquired MET amplification as initial resistance to selpercatinib, *J. Thorac. Oncol.* (2021) in press.
- [46] E. Coco, M. Scaltriti, A. Drilon, NTRK fusion-positive cancers and TRK inhibitor therapy, *Nat. Rev. Clin. Oncol.* 15 (12) (2018 Dec) 731–747.
- [47] T.M. Bauer, E. Felip, B.J. Solomon, et al., Clinical management of adverse events associated with lorlatinib, *Oncologist* 24 (8) (2019 Aug) 1103–1110.
- [48] M. Nagasaka, Y. Ge, A. Sukari, et al., A user's guide to lorlatinib, *Crit. Rev. Oncol. Hematol.* 151 (2020 Jul), 102969.
- [49] M.A. Socinski, R.M. Jotte, F. Cappuzzo, et al., Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC, *N. Engl. J. Med.* 378 (24) (2018 Jun 14) 2288–2301.
- [50] https://www.ema.europa.eu/en/documents/overview/tecentriq-epar-medicine-overview_en.pdf (assessed June 11, 2021) 2021.
- [51] M. Reck, R. Jotte, T.S. Mok, et al., IMPower150: an exploratory analysis of efficacy outcomes in patients with EGFR mutations. Presented at: 2019 European Society of Medical Oncology, *Ann. Oncol.* 30 (suppl_2) (2019) ii38–ii68. 10.1093/annonc/mdz063.
- [52] M. Reck, T.S.K. Mok, M. Nishio, et al., Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial, *Lancet Respir. Med.* 7 (5) (2019 May) 387–401.
- [53] J.J. Lin, A.J. Schoenfeld, V.W. Zhu, et al., Efficacy of platinum/pemetrexed combination chemotherapy in ALK-positive NSCLC refractory to second-generation ALK inhibitors, *J. Thorac. Oncol.* 15 (2020) 258–265.
- [54] S.H. Ou, R.A. Soo, A. Kubo, et al., Will the requirement by the US FDA to simultaneously co-develop companion diagnostics (CDx) delay the approval of receptor tyrosine kinase inhibitors for RTK-rearranged (ROS1-, RET-, AXL-, PDGFR-alpha-, NTRK1-) non-small cell lung cancer globally? *Front. Oncol.* 4 (2014 Apr 1) 58.
- [55] J.J. Lin, V.W. Zhu, S. Yoda, et al., Impact of EML4-ALK variant on resistance mechanisms and clinical outcomes in ALK-positive lung cancer, *J. Clin. Oncol.* 36 (12) (2018 Apr 20) 1199–1206.