


# Spotlight on Furmonertinib (Alflutinib, AST2818). The Swiss Army Knife (del19, L858R, T790M, Exon 20 Insertions, “uncommon-G719X, S768I, L861Q”) Among the Third-Generation EGFR TKIs?

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**Abstract:** Osimertinib, a third-generation (3G) epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) is now considered the standard of care for the first-line (1L) treatment of advanced *EGFR*+ NSCLC due to statistically significant improved progression-free survival (PFS) and overall survival (OS) compared with first-generation (1G) treatment from the FLAURA trial. Recently two other 3G EGFR TKIs (aumolertinib and furmonertinib) have been approved in China for treatment of *EGFR* T790M+ NSCLC. Randomized Phase 3 trials of these two 3G EGFR TKIs have also demonstrated PFS over gefitinib respectively. Among these two Chinese home-grown, 3G EGFR TKIs, furmonertinib seems to most closely resemble osimertinib in terms of dosing regimen, efficacy and adverse events profile. In this article, we reviewed the clinical activity and adverse events of furmonertinib at 80 mg daily (approved dose), potential usage of 160 mg daily for CNS metastasis in *EGFR*+ NSCLC, and usage of 160 mg or 240 mg daily in *EGFR* exon20 insertion positive (*EGFR*ex20ins+) NSCLC patients.

**Keywords:** furmonertinib, Alflutinib, third generation EGFR TKI, non-small cell lung cancer, EGFR T790M mutation, exon 20 insertions, uncommon *EGFR* mutations

## Introduction

Historically, epidermal growth factor receptor (*EGFR*+) positive non-small cell lung cancer (NSCLC) has been optimally treated using first-generation (1G) (gefitinib, erlotinib, icotinib) and second-generation (2G) TKIs (afatinib, dacomitinib) based on statistically improved progression-free survival (PFS) over standard platinum-doublet chemotherapy.<sup>1</sup> Invariably resistance develops, most commonly due to acquiring the *EGFR* gatekeeper mutation T790M which alters drug binding and enzymatic activity of the EGFR protein and abolishes the binding of 1G and 2G EGFR TKIs inside the EGFR kinase domain pocket.<sup>2</sup> Additionally, adverse events of 1G and 2G from EGFR TKIs are common and can be severe such as rash, diarrhea, mucositis, and stomatitis that limit the quality of life of patients. Hence, many 3G EGFR TKIs have been developed from multiple global pharmaceutical companies to overcome these resistance mutations<sup>3</sup> but only osimertinib has been successfully approved for second-line (2L) *EGFR* T790M+ NSCLC based on AURA-3 trial<sup>4</sup> and then 1L approved based on improved PFS and OS in FLAURA.<sup>5,6</sup> By September 2019, osimertinib has been approved for 1L treatment of *EGFR*+ NSCLC in over 75 countries and in more than 80 countries for *EGFR* T790M+ NSCLC.<sup>7</sup> More recently, at least seven 3G EGFR TKIs that are structurally similar to osimertinib were being developed from essentially China and Republic of Korea.<sup>8</sup> The Phase 2 safety and clinical efficacy trials of these 3G EGFR TKIs in *EGFR* T790M+ NSCLC patients have been published and summarized.<sup>8</sup> Among these seven 3G EGFR TKIs, furmonertinib and aumolertinib have been approved in

China and lazertinib has been approved in Republic of Korea for treatment of *EGFR* T790M+ NSCLC.<sup>3,7</sup> Additionally, head to head trials of furmonertinib and aumolertinib against 1G *EGFR* TKIs have been published.<sup>8–10</sup>

Furmonertinib (AST2818), previously known as alflutinib, is a novel 3G TKI that received approval in China in March 2021 to treat locally advanced or metastatic *EGFR* T790M+ NSCLC that developed after progression on treatment with 1G *EGFR* TKIs.<sup>10</sup> Much of the Chinese prescribing information is summarized here.<sup>11</sup> To date, clinical trial results have indicated the efficacy and adverse events of furmonertinib are similar to osimertinib.<sup>10</sup> Here, we review the efficacy and adverse events of furmonertinib as a strong competitor of osimertinib in treatment of *EGFR*+ NSCLC.

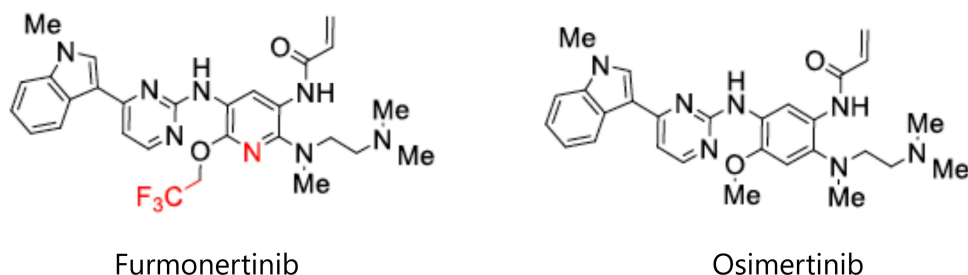
## Furmonertinib Pre-Clinical Data

Furmonertinib (AST2818, Alflutinib) is manufactured by Shanghai Allist Pharmaceuticals Co., Ltd. in Shanghai, China. Furmonertinib is designed with a trifluoro-ethoxypyridine-based modification of osimertinib (Figure 1). Essentially the methyl-group on the methoxy pyridine ring of osimertinib is replaced with three fluorine groups. The adjacent benzene ring is replaced with one nitrogen to form an azabenzene ring. The binding of trifluoroethoxyl in a hydrophobic pocket to an unexplored binding pocket of *EGFR* protein may improve its activity and stability.<sup>11</sup>

While the structure of furmonertinib is published,<sup>12</sup> comprehensive pre-clinical data on the in vitro biochemical kinase, cellular proliferation, and xenograft inhibition potency against various *EGFR* mutations especially against *EGFR* T790M or *EGFR* exon20 insertions (*ex20ins*) has not been published by the manufacturer although there were selectively presented in poster format in the 2022 North America Conference on Lung Cancer held in Chicago, USA from September 23–25, 2022.<sup>13</sup> Neither was any pre-clinical central nervous system (CNS) potency of furmonertinib published. Finally, comparison of pre-clinical activities of furmonertinib to osimertinib has not been published although they have been cited indirectly.<sup>12</sup>

## Furmonertinib Pharmacokinetic (PK) Data

Furmonertinib is metabolized by CYP3A4 to its active metabolite AST5902 in human hepatocytes experiments.<sup>14</sup> Furmonertinib is also a potent inducer of CYP3A4 similar to rifampin in its potency to induce CYP3A4.<sup>14</sup> AST5902 is potentially a CYP3A4 inducer also. Furmonertinib is not an inducer of CYP1A2 or CYP2B6.<sup>14</sup> Hence, the steady state of the furmonertinib may be affected by auto-induction and lead to subtherapeutic levels. Indeed itraconazole, a potent CYP3A4 inhibitor increased the level of furmonertinib in healthy volunteers. At a steady 80 mg once daily dose, the median  $T_{max}$  of furmonertinib on empty stomach is about 3 hours with a half-life of about 40.6 hours.<sup>15</sup> The administration of itraconazole, a potent CYP3A4, increased steady state furmonertinib's  $T_{max}$  to 6 hours and half-life to 70.3 hours.<sup>15</sup> Single dose high-fat food effect study drug absorption indicated the peak concentration of furmonertinib increased by approximately 53%, and the  $AUC_{0-24}$  increased by approximately 32%.<sup>16</sup> However, the peak concentration of its metabolite AST5902 decreased by approximately 20%, and the AUC decreased by approximately 8%.<sup>16</sup> Overall from population PK studies, while auto-induction of CYP3A4 and food effect decreased and increased the level of furmonertinib respectively, the corresponding inverse increase and decrease of level of AST5902 essentially balanced out with the total active ingredients remaining the same.<sup>17</sup>



**Figure 1** Comparison of the structure of furmonertinib and osimertinib.

## Determination of Furmonertinib Phase 2 Dose

The Phase 1 dose escalation of furmonertinib investigated the safety of furmonertinib from 20 mg to 240 mg daily (20 mg, 40 mg, 80 mg, 160 mg, and 240 mg) with dose expansion with 40 mg, 80 mg, 160 mg, 240 mg in *EGFR* T790M + NSCLC patients. Overall, no dose limiting toxicity (DLT) was observed and thus the maximum tolerated dose (MTD) was not determined. The steady concentration  $AUC_{0-24}$  (ng·h/mL) of furmonertinib increased less than proportional with increased dose: about 100% from 40 mg to 80 mg, about 50% increase from 80 mg to 160 mg and about 25% increase from 160 mg to 240 mg. The overall response rate (ORR) in the 40 mg, 80 mg, 160 mg, and 240 mg groups were 83.3% (5/6), 77.8% (35/45), 78.0% (39/50), and 66.7% (10 of 15), respectively. The CNS ORR in the 40 mg, 80 mg, 160 mg, and 240 mg groups were 50.0% (1/2), 100.0% (4/4), 66.7% (6/9), and 50.0% (1/2), respectively. Importantly, the median PFS and duration of response (DOR) were similar among 80 mg, 160 mg, and 240 mg patients and much longer than the 40 mg. In terms of adverse events, grade 1–2 QTc prolongation was observed in eight (6%) patients: two patients at 20 mg, 40 mg, 80 mg and 160 mg respectively. Including QTc prolongation, all other adverse events from furmonertinib are similar in incidence and severity as osimertinib. Thus, 80 mg once daily was selected as the phase 2 dose going forward.

## Furmonertinib Phase II Clinical Data (*EGFR* T790M+ NSCLC)

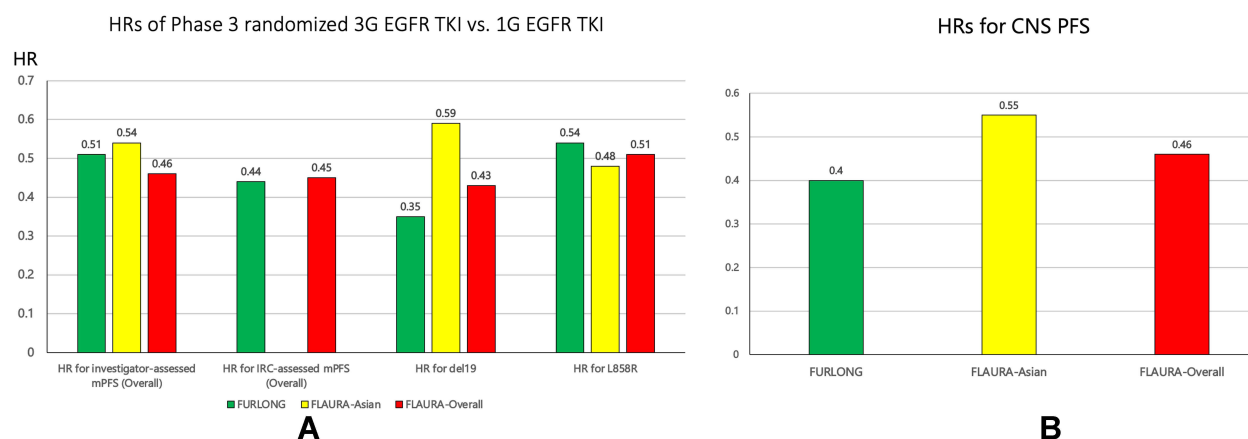
A phase 2b multicenter single arm pivotal study enrolled 220 patients investigated the efficacy and safety of furmonertinib in *EGFR* T790M+ NSCLC patients across 46 hospitals in China after progression on 1G or 2G *EGFR* TKIs. The ORR and PFS for furmonertinib were 74% (95% CI: 68–80%) and 9.6 months (95% CI: 8.2–9.7)<sup>18</sup> compared favorably to ORR of 62% (95% CI: 54–69%) and PFS of 9.7 months from the phase 2 osimertinib AURA17 trial conducted exclusively in China. Interestingly, a higher number of patients in the trial had CNS metastases (48% versus 37% in AURA17).<sup>19</sup> Adverse events profile was also similar between furmonertinib and osimertinib including incidence of QTc prolongation (Table 1). Grade 3 QTc prolongation is defined as > 500 milliseconds. Based on this pivotal trial, furmonertinib received approval in China on March 2021 to treat locally advanced or metastatic *EGFR* T790M+ NSCLC.<sup>3,11</sup>

## FURLONG: Furmonertinib versus 1G *EGFR* (gefitinib) TKI (FURLONG) Phase 3 Trial

Furmonertinib 80 mg once daily was compared with gefitinib 250 mg once daily in a randomized phase 3 trial as 1L treatment of advanced stage activating *EGFR*+ NSCLC across 55 hospitals in mainland China in the FURLONG study. Stratification factors were *EGFR* mutation subtype and presence/absence of CNS metastasis. Like FLAURA, FURLONG was a placebo-controlled, double-blind, double dummy study. Furthermore, unlike FLAURA, FURLONG's primary endpoint is independent review committee (IRC)-assessed PFS. Median PFS in patients receiving furmonertinib was significantly higher at 20.8 months (95% CI: 17.8–23.5) compared with those receiving gefitinib at 11.1 months (95% CI: 9.7–12.5) (HR = 0.44; 95% CI: 0.34–0.58;  $p < 0.0001$ ).<sup>9</sup> These efficacy results compare favorably to the overall FLAURA results and Asian subgroup analysis of FLAURA as assessed by the investigators (osimertinib: 16.5m (95% CI: 13.8–

**Table 1** Comparison of Incidence of QTc Prolongation Between Furmonertinib and Osimertinib

	Furmonertinib			Osimertinib		
	Phase I Dose Expansion (80 mg Once Daily)	Phase 2 (T790M+)	Phase 3 (FURLONG arm)	AURA1 + 2 Dose Expansion	AURA-3 (T790M)	FLAURA (Osimertinib arm)
<b>N</b>	48	220	178	411	279	279
<b>All Grade</b>	4.2%	15.5%	9.0%	5.1%	2.5%	10.0%
<b>Grade 1–2</b>	4.2%	15.5%	5.6%	3.9%	2.5%	7.8%
<b>Grade 3–4</b>	0%	0%	3.4%	1.2%	0%	2.2%



**Figure 2 (A)** Comparison by HR of PFS overall (investigator-assessed, independent review committee [IRC] assessed), PFS of del19 and PFS of L858R patients among FURLONG overall, FLAURA-Asian and FLAURA-overall groups. **(B)** Comparison of HRs of CNS PFS among FURLONG, FLAURA-Asian, FLAURA-overall.

20.7) versus gefitinib/erlotinib: 11.0 months (95% CI: 9.5–12.6) (HR = 0.54; 95% CI 0.41, 0.72;  $p < 0.0001$ ). Given the potential differences in the composition of the patient population, only comparison of IRC-assessed and investigator-assessed hazard ratios were plotted for comparison (Figure 2A).<sup>20</sup> Adverse events among furmonertinib and osimertinib were similar in nature and incidences.

## CNS Efficacy of Furmonertinib (FURLONG)

CNS metastases occur frequently in *EGFR*+ NSCLC patients. Close to 34% (121/357) of the patients enrolled in FURLONG and 36% of the patients enrolled onto FLAURA had baseline metastasis. Thus, the ability for a 3G *EGFR* TKI to penetrate the blood–brain barrier is important to treat the CNS metastasis and also theoretically to delay or even prevent the emergence of CNS metastasis in *EGFR*+ patients who do not have CNS metastasis at the diagnosis. Not surprisingly furmonertinib achieved superior PFS over gefitinib regardless of CNS metastasis.<sup>21</sup> More granular analysis of the FURLONG trial focusing on the CNS PFS also demonstrated superior CNS PFS of furmonertinib over gefitinib with an HR of 0.40. Importantly, the CNS PFS advantage for furmonertinib was similar for del19 or L858R patients<sup>21</sup> and compares favorably to the HR for CNS PFS in the overall FLAURA<sup>22</sup> (Figure 2B). The numerical value of CNS PFS in the furmonertinib arm of FURLONG was similar to the osimertinib arm of FLAURA but given the CNS PFS are constrained by the difference in patient characteristics (sex, age, number of CNS lesions, *EGFR* mutation subtype: del19 versus L858R, smoking status), we are comparing HRs rather than the actual CNS PFS.

It has been demonstrated that osimertinib at 160 mg daily achieved good CNS control including patients with leptomeningeal carcinomatosis (LC). In a multi-center single arm study of osimertinib at 160 mg in the patients with brain metastasis, intracranial ORR and disease control rates were 55.0% and 77.5%, respectively.<sup>23</sup> The median progression-free survival (PFS) was 7.6 months (95% CI: 5.0–16.6); the median overall survival (OS) was 16.9 months (95% CI: 7.9–not reached (NR)). In the LC cohort, intracranial disease control rate was 92.5% and complete response rate was 12.5%. The median OS was 13.3 months (95% CI 9.1–NR); the median PFS was 8.0 months (95% CI: 7.2–NR).<sup>23</sup> Similar retrospective study also revealed similar efficacy of high dose (160 mg) of osimertinib in CNS metastasis and leptomeningeal carcinomatosis.<sup>24</sup> Furmonertinib 160 mg daily is now being investigated in several single institutions study in *EGFR*+ patients with CNS metastasis (iFORCE, NCT05465343; NCT05379803).

## Comparison of Incidence of QTc Prolongation of Furmonertinib and Osimertinib

QTc prolongation is a rare unique adverse event in furmonertinib and osimertinib. The vast majority of QTc prolongation from furmonertinib is grade 1–2 (< 500 ms). (Table 1) provides a comparison of the reported incidence of QTc prolongation.

## Furmonertinib Efficacy in *EGFR* exon20 Insertion (*EGFR*ex20ins+) positive NSCLC

Insertion mutations into the exon 20 of *EGFR* in NSCLC (*EGFR*ex20ins+) constitute a diverse population of activating *EGFR* mutations.<sup>25</sup> While currently there are two US FDA approved drugs, mobocertinib (a 3G *EGFR* TKI) and amivantamab (a bi-specific *EGFR*/MET antibody), nevertheless, the treatment of *EGFR*ex20ins+ NSCLC still require optimization. Case reports and small-scale clinical trials have indicated that osimertinib has demonstrated clinical activity against a certain subset of *EGFR*ex20ins+ NSCLC and mostly at the higher dose of 160 mg rather than 80 mg.<sup>26–28</sup> At 160 mg, the ORR was 27% among 17 *EGFR*ex20ins+ NSCLC patients treated with a median duration of response (DOR) not reached (95% CI: 4.7–NR) and median PFS of 9.6 months (95% CI: 4.1–10.7).<sup>27</sup> At 80 mg of osimertinib, there was no objective response among 12 patients treated from a different study.<sup>28</sup> In comparison among the 114 platinum-pretreated patients, the ORR for mobocertinib in their “pivotal” registration trial was 28% (95% CI: 20–37), median PFS of 7.3 months (95% CI: 5.5–9.2) and median DOR was (95% CI: 7.4–20.3).<sup>29</sup>

Furmonertinib has demonstrated pre-clinical activity against *EGFR*ex20ins+ NSCLC with IC<sub>50</sub> against *EGFR*20ins S768\_D770dup at 11nM, 14nM against A767\_V769dup, and 20nM against N771\_H773dup.<sup>30</sup> Several case reports have reported clinical activity of furmonertinib at 160 mg daily against treatment-refractory *EGFR* ex20ins mutations (one unknown, one *EGFR* P772\_H773insV).<sup>31,32</sup> A small-scale study of the clinical activity of furmonertinib at 160 mg or 240 mg dose against *EGFR*ex20ins (FAVOUR, NCT04858958).<sup>30</sup> Cohort 1 of FAVOUR using 240 mg of furmonertinib has completed with an IRC-assessed ORR of 60% and DRC of 100%. Of note 20% (2/10) had grade 1–2 QTc prolongation (no grade ≤ 3 QTc prolongation) not significantly higher than the incidence when furmonertinib is given at 80 mg daily. There was also 20% grade 1–2 creatinine phosphokinase (CPK) elevation.<sup>30</sup> Hence a large single arm study of furmonertinib 240 mg daily is being planned in China (NCT05466149). Additionally, a phase 1b dose escalation study of furmonertinib in exon20 insertion in *HER2* and *EGFR* in US is ongoing (NCT05364073, FURMO-002) sponsored by the US ArriVent Biopharma who licensed ex-China rights furmonertinib from Allist. The pre-clinical efficacy of furmonertinib against *HER2* was recently presented with Ba/F3 cellular IC<sub>50</sub> against *ERBB2* A775\_G776insYVMA at 118nM and 25nM cellular IC<sub>50</sub> against *ERBB2* V777\_G778insGC.<sup>13</sup>

## Future Development of Furmonertinib

The role of adjuvant osimertinib in resected early-stage *EGFR*+ NSCLC has been well established by ADAURA<sup>33</sup> and approved by the FDA.<sup>34</sup> Similarly, furmonertinib has commenced a similarly designed trial in China. The FORWARD trial enrolled resected stage II–IIIA *EGFR*+ NSCLC patients and randomized them to adjuvant furmonertinib versus placebo (NCT04853342).

Additionally, unlike the role of immune checkpoint inhibitors in driver mutation negative NSCLC, the role of neoadjuvant *EGFR* TKI in early stage resectable and consolidation/maintenance *EGFR* TKI in optimally treated locally advanced *EGFR*+ NSCLC remained to be determined. Clinical trials addressing these roles for *EGFR* TKI are being planned or on-going with furmonertinib: neoadjuvant (chemo + furmonertinib in Stage IIIA–IIIB *EGFR*+ NSCLC; FORESEE, NCT05430802; single agent furmonertinib in stage IIIA–IIIB *EGFR*+ NSCLC, FRONT, NCT04965831).

Finally, afatinib, 2G *EGFR* TKI, is the only *EGFR* TKI approved to treat the three “uncommon” *EGFR* mutations (G719X, S768I, L861Q).<sup>35</sup> Osimertinib has demonstrated clinical activity against these three “uncommon” *EGFR* mutations in a small prospective multi-center trial with an ORR of 50% (18/36; 95% CI: 33–67%) and median PFS was 8.2 months (95% CI: 5.9–10.5).<sup>36</sup> Furmonertinib recently published pre-clinical data against G719S (Ba/F3 cellular IC<sub>50</sub> = 12.4nM), L861Q (Ba/F3 cellular IC<sub>50</sub> = 3.8nM), and S768I (Ba/F3 cellular IC<sub>50</sub> = 21.6nM),<sup>13</sup> thus it is conceivable that furmonertinib should be investigated as an *EGFR* TKI against the three “uncommon” *EGFR* mutations with potentially better tolerability profile.

## Concluding Remarks

Furmonertinib has achieved excellent clinical efficacy and safety profile in both activating *EGFR*+ NSCLC mutations and the acquired *EGFR* T790M mutation. Phase 1 dose escalation trial has indicated furmonertinib has a wide therapeutic window (from 80 mg to 240 mg). In essence, furmonertinib is as efficacious as osimertinib as 1L treatment of advanced

*EGFR*+ NSCLC. In contrast to osimertinib, furmonertinib could theoretically be active against *EGFR*ex20ins albeit at higher dose based on promising data at 240 mg dose. Furthermore, pre-clinical data suggests furmonertinib has potential clinical activity against the three “uncommon *EGFR* mutations. With the potential of lower pricing, furmonertinib can be the one drug that can be used to treat the vast majority of activating *EGFR*+ mutations.

## Disclosure

Dr Sai-Hong Ignatius Ou previously owned stock from Turning Point Therapeutics (prior to August 17, 2022) and Elevation Oncology (prior to September 30, 2022); owns stock and stock options and is a member of the scientific advisory board of BlossomHill Therapeutics; owns stock in MBrace Therapeutics; reports personal fees from Elevation Oncology, Lilly, Pfizer, DAVA Oncology LLP, BeiGene, and JNJ/Janssen, outside the submitted work. The authors report no other conflicts of interest in this work.

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