AFATINIB SEREAL

Scientific Evidence from REAL world beyond clinical trials

AFATINIB forms irreversible covalent bonds with EGFR receptors with high affinity and has flexible dosing for routine practice[1,2,5]

Differences of mechanism of action, potency and specificity between AFATINIB and 1st generation TKIs

	AFATINIB	Gefitinib	Erlotinib
MoA	Irreversible covalent bonding[2]	Reversible[3]	Reversible[4]
IC50 value (nM) for Del19	0.2~2	4.1~306	4.9~14
IC50 value value (nM) for L858R	4	26	16
Dosing	40mg/30mg/20mg[5]	One dose : 250mg[6]	150mg/100mg/25mg[7]

Differences of biochemical properties between Del19 and L858R mutations[8-10]

Hypothesis	Del19	L858R
ERK & AKT Phosphorylation[8]	Inhibition by EGFR-TKI at lower concentration in Del19 cell lines	Inhibition by EGFR-TKI at higher concentration in L858R cell lines
	EGFR-TKI concentration may have different implications for patients with Del19 vs. L858R mutations, and that phosphorylation activity correlates with EGFR-TKI dose and plasma concentration	
Downstream signaling[9]	Activation without dimer formation in Del19 cells	Activation only with dimer formation in L858R mutation cells
	The difference of these active mechanisms is affecting the treatment effect	
Dissociation[10]	1st Gen TKIs have low dissociation constants for Del19 (0.54 and 0.48)	1st Gen TKIs have higher dissociation constants for L858R (0.94 and 0.97)
	Low plasma concentrations of EGFR-TKI in L858R patients resulted in rapid dissociation, may lead to reduced treatment efficacy	

- Preclinical evidence suggests that EGFR mutations are associated with differential sensitivities to EGFR TKIs and IC50 values of AFATINIB were less than 10nM for common EGFR mutations (Del19/L858R) based on in vitro data generated using Ba/F3 cells[1]

Summary of the in vitro sensitivities of Ba/F3 cells expressing each EGFR mutation to various TKI[1]

Category	Mutations	Gefitinib	Erlotinib	AFATINIB	Osimertinib
Del19	delE746_A750	4.8	4.9	**0.9**	1.1
	delE746_S752insV	306	14	**0.2**	
	delL747_A750insP	7.4	13	**1**	
	delL747_P753insS	4.1	5.4	**2**	
	delS752_I759	35	7.9	**0.2**	
L858R		26	16	**4**	9

IC50 values (nM) of **<10=blue, 10–99=light blue, 100–999 =yellow,** respectively. When the exact value was not described in the literature, the approximate number was estimated from each figure.

References

1. Kobayashi Y, et al. *Cancer Sci* 2016;107(9):1179–86.
2. Solca F, et al. *J Pharmacol Exp Ther* 2012;343(2):342–50.
3. Wakeling AE, et *al. Cancer Res* 2002;62(20):5749–54.
4. Hidalgo M, et al. *J Clin Oncol* 2001;19: 3267–79.
5. AFATINIB prescribing information 2019 July.
6. Gefitinib prescribing information 2017 July.
7. Erlotinib prescribing information 2018 June.
8. Okabe T, et al. *Cancer Res* 2007;67(5):2046–53.
9. Cho J, et al. *Cancer Res* 2013;73(22):6770–9.
10. Karaman MW, et al. *Nat Biotechnol* 2008;26(1):127–32.

EGFR : Epidermal Growth Factor Receptor
TKI : Tyrosine Kinase Inhibitor
MoA : Mechanism of Action
IC50 : The half maximal inhibitory concentration

For healthcare professionals only.
Futher prescribing information available: https://www.boehringerone.com/vn/oncology/afatinib/thong-tin-thuoc/thong-tin-ke-toa

Boehringer Ingelheim

Boehringer Ingelheim Vietnam
Floor 14, Mplaza building
39 Lê Duẩn Street, District 1, Hochiminh City, Vietnam
Phone: (+84) (028) 3823 6919

Document Number: PC-VN-101464
Production Date: June 2021