Osimertinib as an emerging therapeutic modality in nonsmall cell lung cancer: Opportunities and challenges in Indian scenario

Sir,

Osimertinib is a third-generation, central nervous system (CNS)-active epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), with selectivity against EGFR sensitizing as well as T790M mutation of EGFR.[1] The mono-anilino-pyrimidine framework, developed by *AstraZeneca*, targets double-mutant (activating mutation + T790M) form of EGFR resistant to first- and second-generation TKIs[2] [Figure 1]. Besides being approved in other countries for the specified indication, on August 9, 2018, it was granted import and marketing permission by the DCGI, to be used in advanced nonsmall cell lung cancer (NSCLC) patients with EGFR exon 19 deletion or exon 21 (L858R) mutations.[3] The commercially available form is distributed under the brand name *Tagrisso*© which is available at the strength of 40 or 80 mg.[3]

Osimertinib binds irreversibly to the EGFR kinase, via the C797 amino acid covalent bond, accounting for its potent, highly selective inhibition.[1] The salient pharmacokinetic properties, including large tissue distribution, slow absorption, and moderate clearance, with favorable pharmacodynamic parameters are in accordance with its surge in therapeutic purposes.[4] It also demonstrated higher penetration into CNS compared to gefitinib, afatinib, or rociletinib in EGFR-mutated mouse brain metastasis model.[4] Osimertinib was found to be 200 times more potent against L858R/T790M than wild-type EGFR *in vitro*.[1] It possesses very low activity against additional kinases, such as ERBB2, ERBB4, ACK1, ALK1, BLK, BBK, MLK1, and MNK2.[1]

Preliminary Phase III Trial (AURA III) indicated improvements in median progression-free survival (PFS) in osimertinib group (10.1 vs. 4.4 months, hazard ratio 0.30, $P < 0.001$), in patients of T790M-mutant advanced NSCLC in comparison with intravenous pemetrexed plus carboplatin or cisplatin for up to six cycles in 2:1 ratio.[2] The median PFS was also significantly higher in patients with CNS metastasis ($n = 144$) in osimertinib group.[2] However, Indian data on osimertinib are limited with one completed trial[5] and two trials on-going recently [Table 1]. Currently, a Phase III, randomized, double-blind multicenter clinical trial is being conducted in India (18 patients out of 200) as a subcenter.[6] The safety profile of osimertinib is also being assessed in an observational Phase IV study.[7]

In many ways, this necessitates the development of an appropriate diagnostic test to identify the mutational status, especially in India where the annual incidence of lung cancer is 6.9% with majority attributed to NSCLC variety (80%–85%).[2] Interestingly, with the varying incidence of T790M mutation in India, a specific strategy adopted by *AstraZeneca* insists upon proper access to

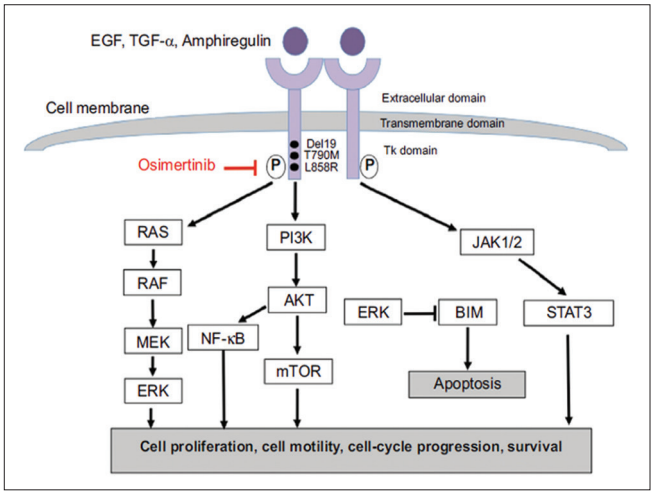

Figure 1: Epidermal growth factor receptor pathway and mechanism of action of osimertinib

Table 1: Recent trials of osimertinib in India

Trials	Status	Methodology	Result
Noronha V *et al*.[5]	Completed	Interventional study; Osimertinib 80mg administered in 13 patients with T790m mutation positive NSCLC with median duration of follow up of 2.5 months	Better clinical response in 75% of patients, 55% having partial radiologic response by revised RECIST 1.1 criteria
(CTRI/2018/10/016042)[6]	Ongoing	Phase III, randomized, double-blind multicentric (India as a sub-centre) study to assess the efficacy & safety of osimertinib as a maintenance therapy in locally advanced EGFR positive NSCLC followed by platinum based chemoradiation therapy (18 patients out of 200)	Progression free survival (PFS) will be assessed
(CTRI/2018/10/015941)[7]	Ongoing	Observational phase IV study in 60 patients with metastatic EGFR T790M positive NSCLC	Number, frequency & proportion of adverse event; serious adverse event (SAE); adverse event of special interest will be assessed

this diagnostic test. These include development of proper infrastructure, enlightening the medical and pathological experts of interest along with standardization of test quality through external quality assurance program.[8]

Despite the impressive development of osimertinib, some pitfalls still persist. Detection of T790M mutation by serum-based circulating cell-free tumor DNA is a complex, costly procedure with high false-negative results.[9] Advancement of diagnostic modalities to address further mechanism of resistance to osimertinib, i.e., C797S mutation in exon 20, needs to be accomplished.[2] Finally, the price of *Tagrisso*© (INR 490,846 [$6998] for 30 tablets) might limit the significant patient pool affording this therapy with an impedance over further development of this molecule in India.[8] A recent study suggested that the reduction of osimertinib price by 20%–25% can be favorable on the basis of cost-effectiveness profile in most of the countries around the globe.[10] However, cost-sharing and risk-sharing approach may not be appropriate. Other measures such as managed entry agreement and compassionate access program can be adopted to ensure timely access to highly effective as well as an expensive drug like osimertinib.[10]

Comments

As a new molecule, osimertinib holds promising esteem in future on account of its effectiveness and safety. A dilemma still persists as the paradigm of lung cancer treatment is shifted toward acquiring novelty in the context of a financial limitation faced in countries like India. Engaging multiple stakeholders may be rational to curb out pressure on the patients, payers, and also drug manufacturers.

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Conflicts of interest

There are no conflicts of interest.

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