EGFR TYROSINE KINASE INHIBITOR USED IN NON-SMALL CELL LUNG CANCER

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ABSTRACT: Lung cancer is a malevolent lung growth characterized by unrestrained cell expansion in tissues of the lung. EGFR is occupied dissimilar fundamental presentation of cancer cells that includes expansion of cells, enlargement, propagation, apoptosis regulation etc. make it a prime objective for lung cancer. EGFR is a tyrosine kinase inhibitor that is proposed in epithelial cells. EGFR inhibitors are drugs that connect to firm parts of EGFR and stop the expansion of cells. Till date, EGFR inhibitors are classified into two categories first one is tyrosine kinase inhibitor and the second one is monoclonal antibodies. Tyrosine kinase inhibitor binds to the area of tyrosine kinase in the epidermal growth factor receptor and hinders the activity of EGFR. Monoclonal antibodies bind to the extracellular components of EGFR prevent it to bind with its own receptor so that stop cell division. This review encompasses complete updates on a generation of epidermal growth factor receptor tyrosine kinase inhibitor used in the treatment of non-small cell lung cancer.

INTRODUCTION: Lung cancer is a very rapidly growing and serious disease worldwide. It is a primary cause of death globally. It is the most commonly diagnosed cancer with an annual death rate being over 1.3 million globally 1. In the year 2017, estimates suggested that, in North America alone, 222,500 new cases of lung cancer and 155,870 deaths occurred 2. Lung cancer is mainly divided into two groups i.e. small cell lung cancer and non-small cell lung cancer. Non-small cell lung cancer constituted about 75-80% of lung cancer and is further divided into three types adenocarcinoma (about 40%), squamous carcinoma (25-20%) and large-cell carcinoma (5-15%). There are numerous treatments for lung cancer which mainly include surgery, chemotherapy and radiotherapy moreover individual or maybe in combination. Among different type of lung cancer, non-small cell lung cancer is a heterogeneous disease which typically harbors numerous “oncogenic driver mutation” occurring at varied frequencies of 2 to 25 3. These derived oncogenic mutations stimulate signaling cascades leading to uncontrolled growth and proliferation 4, 5, 6.

For overcoming this problem novel treatments are discovered which directly target the driver mutation to control the process of cancer was discovered and termed as “Target therapies”. Target therapies are an approach in which we can target the specific tumor cells which are responsible for the cause of disease and increase the survival time of the patient. At present several oncogenic mutation drivers have been accepted in adenocarcinoma including epidermal growth factor receptor (EGFR), anaphylactic lymphomas kinase (ALK),
Kirsten rat sarcoma viral homolog (KRAS), and V-Raf murine sarcoma viral oncogene homolog B (BRAF) 7.

Epidermal growth factor receptor belongs to the HER/erbB family of tyrosine kinase receptor which includes (HER 1, HER 2, HER 3 and HER 4). All the receptor shows a related molecular structure which is composed of an extracellular ligand-binding domain, a short hydrophobic transmembrane region and an intra cytoplasmic tyrosine kinase domain 8. ErbB receptors are activated by growth factors of the EGF family. Six ligands of EGFR are known.

TABLE 1: EGFR LIGANDS AND THEIR RECEPTORS 9,10

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ligands</th>
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<tbody>
<tr>
<td>EGFR</td>
<td>EGF, Transforming growth factor-α (TGF-α), Amphiregulin (AR), Betacellulin (BTC), Heparin-binding EGF-like growth factor (HB-EGF) and Epiregulin (EPR)</td>
</tr>
<tr>
<td>ErbB2</td>
<td>None</td>
</tr>
<tr>
<td>ErbB3</td>
<td>NRG-1and NRG-2</td>
</tr>
<tr>
<td>ErbB4</td>
<td>Betacellulin (BTC), Heparin-binding EGF-like growth factor (HB-EGF) and Epiregulin (EPR), Tomoregulin, NRG-1, NRG-2, NRG-3 and NRG-4</td>
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ErbB2 is a distinctive member of the ErbB family which does not bind with any of the known ligands, therefore it is preferred heterodimeric partner for other EGFR. EGFR plays a serious function in the very important cellular process which includes propagation, discrimination, relocation, endurance and angiogenesis. EFGR activated by receptor overexpression as well as dependent and independent ligand mechanism. EGFR bind to six known receptors including EGFR itself and transforming growth factor α. EGFR controls the growth of cell and proliferation through a transduction signaling pathway. Mutation of this receptor causes uncontrolled cell growth and proliferation.

Homodimerization and heterodimerization with other family members ligand lose its ability to bind with its own specific binding site activate tyrosine kinase. This autophosphorylation of the cytoplasmic domain of the receptor takes place resulting in activation of the downstream signaling pathway. In downstream signaling pathway adaptor molecule not bind with their receptor which increases process likes proliferation, angiogenesis etc. Discrimination of EGFR can lead to a variety of cancer including ovarian, head, neck, breast and lung. EGFR Pathway in non small cell lung cancers is illustrated below.

Mutation, amplification, and overexpression of growth factor receptors such as EGFR, HER-2 and C-MET are most frequent in NSCLC tumors from non-smoker patients. These genetic changes most commonly observed in Asiatic society, and women.

In young and nonsmoker patients EML4/ALK fusion gene is observed. In smoker patient KRAS mutation and signaling pathway observed. In squamous cell carcinoma, PI3K signaling pathway observed.


<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>Disease</th>
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<tbody>
<tr>
<td>EGFR Mutation</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>Cetuximab resistance in colorectal cancer</td>
<td></td>
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<tr>
<td>Anaplastic and follicular thyroid cancer</td>
<td></td>
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<tr>
<td>Lung adenocarcinoma</td>
<td></td>
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<tr>
<td>Inflammatory skin and bowel disease</td>
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<tr>
<td>Gastric and breast cancer</td>
<td></td>
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<tr>
<td>Prostate cancer</td>
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<tr>
<td>Polycystic kidney disease, glomerulonephritis, Diabetic nephropathy</td>
<td>Generation of new oligodendrocytes potential treatment of white matter injury in premature children</td>
</tr>
<tr>
<td>Overexpression of ErbB2</td>
<td></td>
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<tr>
<td>Overexpression of ErbB2 and ErbB3</td>
<td></td>
</tr>
<tr>
<td>Dysregulated EGFR signaling</td>
<td></td>
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<tr>
<td>Overexpression of EGFR</td>
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</table>

In contrast to all EGFR is occupied various essential functioning of tumor cells, for this reason, making it a prime target in lung cancer. The presence of EGFR mutation which includes deletion in exon 19 or L858R substitution in exon 21 (arginine group replaces leucine at codon 858R) has been reported in non-small cell lung cancer. For overcoming this problem EGFR inhibitors are developed. EGFR inhibitors are classified into two categories first one is tyrosine kinase inhibitor and the second one is monoclonal antibodies. Tyrosine kinase inhibitor binds to the area of tyrosine kinase in the epidermal growth factor receptor and hinders the activity of EGFR. Monoclonal antibodies bind to the extracellular components of EGFR prevent it to bind with its own receptor so that stop cell division. EGFR TKI’s plays a very important role in the prevention of lung cancer. Four generations of EGFR inhibitors have been developed for the treatment of non-small cell lung cancer. At present, first-generation EGFR tyrosine kinase inhibitor gefitinib and erlotinib, second-generation afatinib and third-generation osimertinib approved from food and drug administration (FDA) for the treatment of metastatic non-small cell lung cancer.

**First Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors:** First-generation EGFR inhibitors gefitinib and erlotinib are the first-line treatments for non small cell lung cancer with activating EGFR mutations (deletion in exon 19 or L858R substitution in exon 21). Patience shows a good response for these drugs but these drugs develop secondary T790M mutations after one year of treatment. Secondary T790M mutation of EGFR reported in 2005 when the threonine group is replaced with a bulky methionine group in codon 790 in exon 20 of the EGFR gene. T790M located in the ATP binding pocket of the catalytic region and also refer to as a “gate keeper residue”. Replacement of threonine with bulkier group methionine delays the binding of these drugs. A recent study reveals that T 790 M not affect the binding of EGFR and EGFR TKI’s but it increases the binding affinity of ATP and EGFR result in less binding with EGFR TKI’s. For overcoming this problem second-generation EGFR TKI’s inhibitors are developed to treat NSCLC.

**Gefitinib:** Gefitinib is a reversible EGFR TKI’s inhibitor manufactured by AstraZeneca. On July 13 2015, gefitinib approved as a first-line treatment for non-small cell lung cancer.

**Erlotinib:** It also a reversible EGFR TKI’s inhibitor manufactured by Roche. In 2013, Erlotinib was approved by a federal agency (FDA) as a first-line treatment for EGFR mutation in non-small cell lung cancer.
Icotinib: It is a potent small-molecule inhibitor of EGFR tyrosine kinase developed by Zhejiang Bata Pharma Ltd. State food and drug administration of china approved this drug for non small cell lung cancer patients particularly with EGFR mutation 28.

Second Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: Afatinib and Dacomitinib are drugs used as a second-generation EGFR irreversible inhibitor and approved by FDA for treatment of non-small cell lung cancer. Afatinib (BIBW2922) is an irreversible epidermal growth factor receptor tyrosine kinase inhibitor. Due to the presence of acrylamide warhead capable of alkylating cys79. This drug covalently and irreversibly binds a cysteine residue in EGFR to amino acid position 797. By forming covalent and irreversible bond afatinib block EGFR, HER 2 and HER 4 kinase. This enables it to inhibit EGFR kinase activity even in the presence of an EGFR T 790 M mutation. Dacomitinib (PF-00299804) is an irreversible inhibitor of EGFR, HER 2 and HER 4. Second-generation EGFR inhibitors possess a structurally related quinazoline base core scaffold and are identified as an ATP competitive inhibitor of wild type EGFR. These drugs show a good effect on these mutations but show toxic effect over body 29.

Afatinib (Giotrif): Afatinib developed by Boehringer Ingelheim for the oral treatment of cancer. It is an aniline-quinazoline derivative that covalently binds to EGFR, ErbB/HER2 and ErbB 4/HER 4. Covalent binding downregulates ErbB signaling by irreversibly inhibit tyrosine kinase autophosphorylation 30.

Dacomitinib (PF-0299804): Dacomitinib developed by Pfizer is an oral highly selective quinazalone-based irreversible inhibitor of EGFR, HER2 and HER 4. It covalently binds to a cysteine residue in the catalytic domain of the HER receptors. In comparison with first-generation EGFR tyrosine kinase inhibitor, it shows comparable inhibitory activity against the wild type EGFR kinase in-vitro. It is more potent than afatinib against EGFR sensitizing mutations (del19, L858R). It inhibits both wild type and mutant HER 2 kinase 31.

Neratinib (HKI-272): It is an irreversible pan-ErbB inhibitor and shows a positive response in non-small cell lung cancer patients with G719X mutations in EGFR 27.

Pelitinib (EKB-569): Pelitinib used as a potent irreversible epidermal growth factor receptor tyrosine kinase inhibitor and clinical trial are ongoing for the treatment of non-small cell lung cancer 27.

Canertinib (CI-1033): Canertinib is a pyrido-pyrimidine derivative that used a potent kinase inhibitor of erbB receptor family 27.
Third Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: Many third-generation drugs are developed for the treatment of EGFR T790M mutation (Osimertinib, Rociletinib, Olmutinib, ASP-8273, Nazartinib, PF-06747775, Avitinib, HS-10296, and WZ-4002). In these drugs, osimertinib is the only approved drug used for lung cancer.

Osimertinib (AZD9291): Osimertinib is an oral, potent, irreversible EGFR-TKI’S that inhibits both EGFR-TKI’S sensitizing and EGFR T790M resistance mutation while sparing the wild type EGFR tyrosine kinase. It is a mono-anilino-pyrimidine compound developed by AstraZeneca for the treatment of non-small cell lung cancer. In November 2015, osimertinib received approval under the breakthrough program for metastatic epidermal growth factor receptor T 790 M as detected by a USFDA approve test for the treatment of patients with non-small cell lung cancer who has progressed on or after EFGR TKI therapy. On March 30, 2017, osimertinib approved by USFDA for treatment of metastatic EGFR T790M mutation-positive non-small cell lung cancer based on AURA3 study.

Osimertinib metabolized into circulating metabolites AZ5104 and AZ7550. AZ5104 shows greater potency against exon 19 detection T790M mutants (both 8-fold) and wild type (5 fold) and AZ7550 shows comparable potency and selective profile to osimertinib. Osimertinib efficacy compared with first-generation inhibitors (gefitinib or erlotinib) in the flaura study. Flaura is a phase III, double-blind, randomized study to identify the efficacy and safety of osimertinib (80 mg orally once daily) against first-generation EGFR inhibitor (gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily) in patients suffering from metastatic non-small cell lung cancer. Flaura study shows that osimertinib shows higher efficacy as compared to first-generation EGFR TKI’S Inhibitor and used for patients with metastatic on small cell lung cancer with EGFR sensitizing mutation especially with brain metastasis.

Rociletinib (CO-1686): Rociletinib is an orally delivered and irreversible EGFR tyrosine kinase inhibitor that targets the common forms of EGFR including T790M while exhibiting minimal activity towards the wild-type receptor. Oral administration of Rociletinib as single-agent induces tumor regression in EGFR mutated non-small cell lung cancer tumor xenograft and transgenic models. Rociletinib increases resistance time at EGFR by alkylating Cys 797 and thereby preventing toxic effect. Engel J and coworkers confirmed the alkylation of Cys797.

Rociletinib was initially investigated in phase I/II study in TIGER-X trial for a patient who has failed EGFR TKI in first-line setting. Updated pooled analysis report of TIGER-X/TIGER-2 reported a lower response rate of 34% for 625mg b.i.d dose and 28% for 500mg b.i.d dose. In year 2016 analysis report of TIGER-X was confirmed ORR was 45% (95% CI, 31 to 60) and 18 patients with T790M negative disease the confirmed ORR was 17% (95% CI, 4 to 41). Based on this data, FDA voted against the accelerated approval of rociletinib because of lower efficacy and Clovis stopped the clinical development of this drug.

Olmutinib (BI 1482694/HM61713): Olmutinib used as an EGFR mutant specific TKI active against mutant EGFR isoforms including T 790 M. Phase I/II trial HM-EMSI-101 was conducted to recognize the safety, tolerability, pharmacokinetics of olmutinib in Korean patients with EGFR TKI’S pretreated patients. Among 34 patients who take olmutinib more than 650 mg, the ORR was 58.8 %. Phase II suggested the dose of olmutinib was 800 mg/day. Boehringer Ingelheim works together with Hanmi Pharmaceutical to develop olmutinib in ELUXA trial. Due to unpredicted enhance in skin toxicity in trial Boehringer stop the development of olmutinib. Now Hanmi Pharmaceutical manufactured Olmutinib.

Nazartinib (EGF819): Nazartinib is a covalent irreversible mutant selective EGFR inhibitor it inhibits both L 858 R, Del19 (EGFR activating mutation) and T790M (resistance mutation) while sparing wild type EGFR. Results of preclinical studies give the evidence that it shows similar selectivity and wild type sparing property to other third-generation EGFR inhibitors. In phase, I dose ranging from 75 to 350 mg given to patients once daily. On January 29, 2016, 152 patients are treated with this drug in seven cohorts. In 127 patients confirmed ORR was 44% (56/127) with a 91%
control rate of disease. 9.2 months (95% CI 9.0-NE) was the median PFS. The most common side effect included diarrhea (40%), maculopapular rash (39%), pruritus (32%), dry skin (23%), stomatitis (23%) and fatigue (21%) 3rd and 4th-grade adverse effect includes maculopapular rash (14%), anemia (6%) and diarrhea (6%). Phase II trial is ongoing performed with six cohorts. In phase I/II nazartinib concomitantly being investigated in combination with capmatinib (INC28) specific MET inhibitor 40.

Avitinib: It is a pyrrolopyrimidine based moiety act as an irreversible inhibitor of EGFR TKI’s and distinct from other pyrimidine based irreversible inhibitors like osimertinib. It shows activity against EFGF mutation and T790M while sparing wild type 41. Avitinib in the USA used as a second-line therapy in NSCLC patients who have acquired the gatekeeper T790M after using first-generation inhibitors. In China, clinical trials are initiated. Phase I/II investigated for EGFR mutant patients who had progressed on first-line EGFR TKI. In seven cohorts about 136 patients are treated dose ranging from 50 mg to 350 mg bid. Excepted 50 mg bid dose all dose show their response. ORR and DCR were 44% and 84% correspondingly. With 150-300 mg Bid dose observed ORR and DCR were 51% and 89% correspondingly 42. Phase II recommended dose was 300 mg bid. 1st and 2nd observed side effect includes diarrhea (38%) and rash (24%) and 3rd and 4th-grade adverse effect diarrhea (2%) and rash (2%).

PF-06747775: It is a pyrrolopyrimidine based moiety act as an irreversible inhibitor of EGFR T790M. It shows potent activity against four mutant’s exon 19 Del, L858R, and double mutant T790M/L858R and T790M/Del in preclinical trial 43. Phase I study was done with 44 EGFR mutant patients with six dose escalation (25mg - 600 mg) and 2 doses increase cohorts (200 mg and 300 mg). Phase II recommended dose was 200 mg daily. Most common side effect observed with all grade adverse events includes diarrhea (57%), rash (59%) paronychia (52%) and dry skin (25%) 44.

ASP8273: It is an irreversible tyrosine kinase inhibitor inhibits T790M mutation with limited activity against EGFR wild type. Phase I/II investigated for EGFR mutant Japanese patient who had progressed on first-line EGFR TKI, the ORR observed 50% with all patients’ doses with ≥ 100 mg and with patients T790M ORR observed 80%. An observed side effect includes diarrhea (56%), nausea (31%), vomiting (31%) and thrombocytopenia (31%). Less commonly observed side effects are skin rashes (9%) and interstitial lung disease (2%) like events. In AA phase III trial ASP 8273 evaluate against first-generation EGFR TKI in the first-line treatment of EGFR mutant advanced non-small cell lung cancer was later initiated. Due to a lack of clinical efficacy, this trial was discontinued on the recommendation of the Independent Data Monitoring Committee in May 2017 34.

OSIMERTINIB

ROCILETINIB

OLMUTINIB

NAZARTINIB

AVITINIB

PF-06747775
Fourth Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: In first and second-generation EGFR T790M mutation mechanism is a prime cause for resistance. Third-generation EGFR Inhibitors are developed to treat resistance mechanisms like osimertinib has been approved for the treatment of metastatic non-small cell lung cancer. But after ten-month of treatment, this drug shows resistance in the lung cancer patient. To overcome this problem fourth-generation EGFR TKI’S inhibitor is developed which acts on EGFR C797S mutation located on tyrosine kinase domain. The first compound which was discovered for this purpose was EAI001 which acts against L858R/T790M mutation but it shows modest potency against individual L858R and T790M mutant. EAI001 after medicinal chemistry optimization it was found that EAI045 show higher effectiveness and selectivity for L858R/T790M mutation. It is developed as an allosteric non-ATP-competitive inhibitor of mutant EGFR 45.

TABLE 3: EGFR TKI GENERATION FOR METASTATIC EGFR MUTANT NSCLC 24

<table>
<thead>
<tr>
<th>Generation</th>
<th>Drug</th>
<th>Company</th>
<th>EGFR Inhibition</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Generation</td>
<td>Gefitinib</td>
<td>AstraZeneca</td>
<td>Competitive Reversible</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>F. Hoffmann-La Roche</td>
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<tr>
<td>Second Generation</td>
<td>Afatinib</td>
<td>Boehringer Ingelheim</td>
<td>Covalent Irreversible</td>
<td>Approved</td>
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<td></td>
<td>Dacomitinib</td>
<td>Pfizer</td>
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<td></td>
<td>Neratinib</td>
<td>Puma Biotechnology</td>
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<td></td>
<td>EKB-569</td>
<td>Wyeth</td>
<td>Covalent Irreversible</td>
<td>Phase III</td>
</tr>
<tr>
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<td>HKI-272</td>
<td>Wyeth</td>
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<td>Phase II</td>
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<tr>
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<td>CI-1033</td>
<td>Pfizer</td>
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<tr>
<td></td>
<td>ZD6474</td>
<td>AstraZeneca</td>
<td>Reversible</td>
<td>Phase III</td>
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<tr>
<td>Third Generation</td>
<td>Osimertinib</td>
<td>AstraZeneca</td>
<td>Covalent Irreversible</td>
<td>Phase III (Approved)</td>
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<tr>
<td></td>
<td>Rocletinib</td>
<td>Clovis</td>
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<td>Phase II/III (Stopped)</td>
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<tr>
<td></td>
<td>Olmutinib</td>
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<td>ASP8273</td>
<td>Astellas</td>
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<td>Phase III</td>
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<td>Novartis</td>
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<tr>
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<td>Avitinib</td>
<td>Ace Bio</td>
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<tr>
<td></td>
<td>HS-10296</td>
<td>Jiangsu Hansoh</td>
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CONCLUSION: EGFR tyrosine kinase inhibitor plays a very important role in treating non small cell lung cancer. Three classes of EGFR inhibitors are approved by the FDA for the treatment of EGFR mutant non small cell lung cancer.

Afatinib, Erlotinib (first generation), Gefitinib (second generation) and Osimertinib (third-generation) EGFR inhibitors are approved by the FDA for the treatment of EGFR mutant/T790M. Recently, the fourth-generation drug under process which acts as aalosteric non-ATP-competitive inhibitor.

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REFERENCES:


