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Onco News

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From the Desk of Editor

Dear Readers,

Lung cancer is the most common cancer in the world, accounting for more than 1.8 million new cases every year worldwide. Thirteen percent of all cancers found in human beings have primaries in the lung. It kills more patients every year than breast cancer, prostate cancer and colon cancers combined.

More than half of the lung cancer cases are detected at a very late stage. Five year survival rate of these patients is extremely poor. Lung cancer can be broadly classified into small cell (15%) and non-small cell carcinomas (85%). Adenocarcinoma and squamous cell carcinomas together form 90% of non-small cell lung cancers (NSCLC).

Today we should make all efforts to take biopsy (Not simply FNAC) to obtain tissue for various molecular and genomic tests in NSCLC especially (Tissue is an issue). In Non Small Cell Lung Cancers, today we can say it is a chronic disease and its prognosis is not inferior to congestive heart failure.This has become possible with advent of Targeted therapies and recent addition of Immune therapeutics.One such targeted molecule is Afatinib ,which is a second generation EGFR inhibitor drug.

With regards and wish you colorful and joyous Holi ,

Dr Naresh Somani
M.D.,D.M.
Senior Medical Oncologist

Inside This Issue

Afatinib is an irreversible ErbB-family blocker, which blocksEGFR along with HER2, ErbB3 & ErbB4

Introduction :

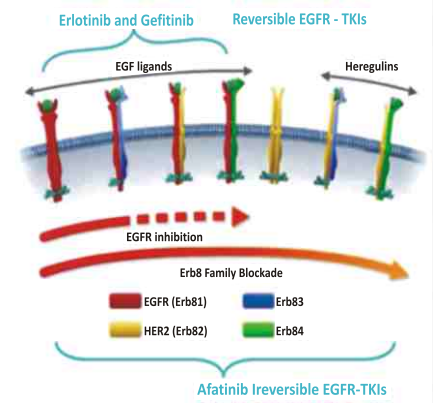
Traditionally, advanced stageNSCLC patients are offered chemotherapy, which are known to cause toxic side effects like bone marrow suppression, neutropenia and hair loss in most patients.

Targeted therapies, by targeting the mutation responsible for making the cell cancerous, can selectively kill only the cancer cells without causing serious side effects. For EGFR Mutation positive patients (whose percentage is 25-35% in India). Afatinib, which is an irreversible Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR - TKI) has significantly improved overall survival in cancer patients while offering them a better quality of life.

Mechanism of Action : Afatinib is an irreversible ErbB-family blocker, which blocks EGFR along with HER2, ErbB3 and ErbB4. It binds irreversibly to the tyrosine binding domain in the intracellular region of these receptors and thereby blocks the downstream signal transduction of the carcinogenic stimulus.

By its irreversible action, it causes sustained inhibition. Hence, Afatinib's effect is seen for a longer duration as compared to reversible inhibitors like Gefitinib. Its pan ErbB family blockade makes it a more potent anticancer drug, as compared to reversible EGFR-TKIs like Erlotinib or Gefitinib.

P.T.O.



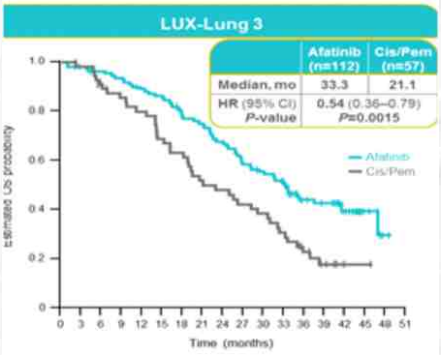
Resistance develops to all anticancer therapies. However clinical studies have shown that resistance to Afatinib is developed at a much later stage as compared to other therapies for the treatment of patients with EGFR mutation positive lung cancer.

Afatinib vs Chemotherapy : Afatinib is the only drug to have demonstrated Overall survival (OS)benefit in EGFR mutation positive lung cancer patients, while the reversible EGFR-TKIs have failed to show any survival benefits as compared to chemotherapy. Afatinib showed a median OS of 33.3 months as compared to only 21.1 months with Cisplatin + Pemetrexed chemotherapy regimens in patients with exon 19 deletion mutation in the LUX-Lung 3 trial, thereby significantly increasing the survival of lung cancer patients by more than 12 months with a better quality of life.

Afatinib is the only drug to have demonstrated Overall survival (OS) benefit in EGFR mutation positive lung cancer patients

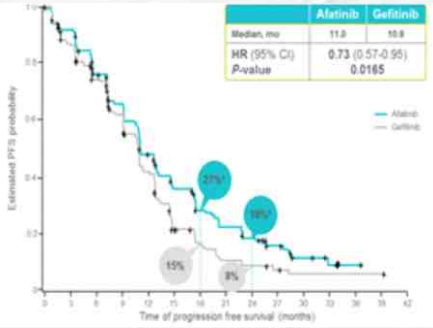
Similar results were seen in LUX-Lung 6 trial, where Afatinib showed a median OS of 31.4 months as compared to only 18.3 months with Cisplatin + Gemcitabine chemotherapy regimens. Afatinib significantly increased the survival of lung cancer patients by 13 months with a better quality of life.

Objective response rate (ORR) and Progression free survival (PFS) were also significantly better with Afatinib than chemotherapy regimens in both LUX-Lung 3 and LUX-Lung 6 clinical trials.



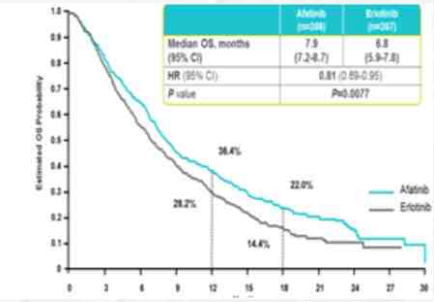
Afatinib vs Gefitinib : Afatinib was compared head to head with Gefitinib in LUX-Lung 7 trial where Afatinib demonstrated a significantly better Progression free survival, Time to treatment failure and objective response rate as compared to Gefitinib, thereby demonstrating a superior efficacy as compared to Gefitinib in the management of EGFR mutation positive NSCLC.

Afatinib was also tolerated well by the patients in LUX-Lung 7, as the discontinuation rates were similar in both the comparator arms. Grade 3 liver enzyme elevation and Interstitial Lung Disease seen with Gefinitib were absent in Afatinib arm. Diarrhea, skin rashes were the most common side effects seen with Afatinib, and were managed easily with dose reduction.



Afatinib vs Erlotinib : Afatinib was compared head to head with Erlotinib in LUX-Lung 8 trial where Afatinib demonstrated a significantly better Overall survival, Progression free survival and Disease Control rate as compared to Erlotinib, thereby demonstrating a superior efficacy as compared to Erlotinib in the management of squamous cell carcinoma of lung in second line setting.

Afatinib demonstrated a manageable safety profile, which was comparable to erlotinib's safety profile. Patient reported outcomes were better in Afatinib arm as compared to Erlotinib in LUX-Lung



Conclusion : Afatinib has significantly improved the outcome in patients with non-small cell lung cancer and has become the TKI of choice in EGFR positive patients.

My Experience of Afatinib in NSCLC : We have treated 50 EGFR mutation positive patients upfront with Afatinib with a response rate of 60% (which includes CR+PR+SD). In two responding patients drug was discontinued due to grade 3 skin toxicities.

Step up to a new level of first-line efficacy

- The first approved **irreversible ErbB Family Blocker**†
- First targeted therapy to show **significant first-line PFS and OS benefit**^ as well as better QoL vs chemotherapy in EGFR M+ NSCLC[1,2,3]
- Superior efficacy vs gefitinib revealed in head-to-head trial in **first-line EGFR M+ NSCLC**[4]

†Indication and usage: Xovoltib (afatinib) is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s)

^Secondary endpoint, primary endpoint was PFS and was met; combined post-hoc analysis of common EGFR mutations (del19/L858R) vs chemotherapy in LUX-Lung 3 and LUX-Lung 6 (LUX-Lung 3 vs pemetrexed/cisplatin and LUX-Lung 6 vs gemcitabine/cisplatin).

1. Yang JC et al. Lancet Oncol 2015;16(2):141-51 2. Sequist LV et al. J Clin Oncol 2013;31(27):3327-3334.
3. Yang JC et al. J Clin Oncol 2013;31(27):3342-3350

*N=345. PFS=progression-free survival; OS=overall survival; QoL= quality of life

For the use of Registered Medical Practitioner or a Hospital or a Laboratory

Abbreviated Prescribing Information of XOVOLTIB

ACTIVE INGREDIENTS: Each film-coated tablet contains 20 mg or 30 mg or 40 mg or 50 mg afatinibas dimaleate. INDICATIONS: Treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth factor Receptor EGFR mutation. **DOSAGE & ADMINISTRATION:** 40 mg/day without food until disease progression oruntil no longer tolerated.Establish EGFR mutation status prior to initiation of therapy. Dose escalation to maximum 50 mg/day to be considered in patients tolerating 40 mg/day in first 3 weeks. For Grade 2 (prolonged or intolerable) or Grade • 3 adverse reactions, interrupt until Grade 0/1. Resume with dose reduction by 10 mg decrements. **SPECIAL POPULATIONS:** *Renal Impairment:* Dose adjustments not necessary in mild or moderate renal impairment. Treatment in severely impaired renal function (< 30 mL/min creatinine clearance) not recommended. *Hepatic Impairment:* Dose adjustments not necessary in mild(Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Treatment in severe (Child Pugh C) hepatic impairment not recommended. Hepatic failure including fatalities reported during treatment in less than 1% of patients. In these patients, confounding factors included pre-existing liver disease and/or comorbidities associated with progression of underlying malignancy. Periodic liver function testing recommended in patients with pre-existing liver disease. Dose interruption if liver function worsens. Discontinue treatment if severe hepatic impairment develops. *Children:* No relevant use in paediatric population. Treatment not recommended. **CONTRAINDICATIONS:** Hypersensitivity to XOVOLTIB or to any excipients. **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE:** *Assessment of EGFR mutation status:* Use well-validated and robust methodology to assess EGFR mutation status. *Diarrhoea:* Diarrhoea within first 2 weeks or severe diarrhoea (Grade 3) within first 6 weeks reported. Proactive management with antidiarrhoeals (e.g. loperamide) important. Interrupt and reduce dose or discontinue if diarrhoea is severe. *Skin related adverse events:* Rash/acne reported. Protective clothing, and use of sun screen advisable for patients exposed to sun. Bullous, blistering, exfoliative skin conditions including Stevens Johnson syndrome reported. Interrupt or discontinue treatment if severe. *Female gender, lower body weight, and underlying renal impairment:* High exposure observed. Close monitoring recommended. *Interstitial Lung Disease (ILD):* ILD or ILD like adverse reactions including fatalities reported. If ILD is diagnosed, discontinue treatment permanently. *Keratitis:* Exercise caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Interrupt or discontinue treatment if ulcerative keratitis is confirmed. If keratitis diagnosed, consider the benefits and risks of continuing treatment. *Left ventricular function:* No studies done in abnormal left ventricular ejection fraction (LVEF) or with significant cardiac history.Consider cardiac monitoring at baseline and during treatment. If ejection fraction is below institution's lower limit of normal interrupt or discontinue treatment. *Lactose:* Contains lactose. Not recommended in patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. **DRUG INTERACTIONS:** Substrate of P-gp and BCRP. Exposure increased by strong P-gp and BCRP inhibitors and decreased by strong P-gp inducers. Administer strong P-gp inhibitors6 or 12 hrs apart from XOVOLTIB. Moderate inhibitor of P-gp and inhibitor of BCRP. May increase the bioavailability of orally administered BCRP substrates.Co-administration of a high-fat meal significantly decreases exposure. **PREGNANCY AND LACTATION:** *Women of childbearing potential:* Avoid becoming pregnant. Use adequate contraceptive methods for at least 1 month after the last dose. *Pregnancy:* No adequate data. Potentially hazardous to foetus. *Lactation:*Excreted in human milk.Advise mothers against breast-feeding. *Fertility:* No studies performed. Adverse effect on human fertility cannot be excluded. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:** Ocular adverse reactions may affect ability to drive or use machines. **UNDESIRABLE EFFECTS:** *Very common > 1 in 10:* Paronychia, decreased appetite, epistaxis, diarrhoea, stomatitis,rash, dermatitis acneiform, pruritus, dry skin, nausea, vomiting. *Common: > 1 in 100 and < 1 in 10:* Cystitis,dehydration, hypokalaemia,dysgeusia, conjunctivitis, dry eye, rhinorrhoea, dyspepsia, cheilitis, alanine aminotransferase increased, aspartate aminotransferase increased, palmar-plantar erythrodysaesthesia syndrome, muscle spasms, renal impairment/renal failure, pyrexia, weight decreased. *Uncommon ≥1 in 1,000 and < 1 in 100:* Keratitis, interstitial lung disease, pancreatitis. **OVERDOSAGE:** Highest dose studied in clinical trials was 160 mg once daily for 3 days and 100 mg once daily for 2 weeks. Dermatological (rash/acne) and gastrointestinal (especially diarrhoea) adverse reactions observed. Overdose in 2 healthy adolescents with 360 mg each of afatinib associated with adverse events of nausea, vomiting, asthenia, dizziness, headache, abdominal pain and elevated amylase (< 1.5 times ULN). *Treatment:* No specific antidote. In cases of suspected overdose, with hold XOVOLTIB and initiate supportive care. Eliminate unabsorbed XOVOLTIB by emesis or gastric lavage. **SHELF LIFE:** 3 years. **STORAGE:** Store in original package in order to protect from moisture and light.

Refer to full prescribing information before use.

API version: XOV/API/IN/2016/01 dated 15 Apr 2016 based on Local pack insert version dated 7th December 2015.

For full prescribing information or any other information , contact Boehringer Ingelheim India Pvt Ltd,
1102, 11th Floor, Hallmark Business Plaza, Guru Nanak Hospital Road,
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- It is a clinical research and academic orgazation for promotion of same in Rajasthan.
- SoMex Academic & Research Committee helps medical fraternity & others in evaluating & designing clinical trials & protocols.
- Somex has conducted more than 30 Clinical Trials with diverse indications Including Phase 1 and 2, 3 and BA/BE Studies.
- Somex also designes and conducts Seminars, CMEs & Medical Conferences. It has conducted more than 40 CMEs in various medical fields.
- Conducts Cancer Awareness & Health Survey programs.

Manuscript Assistance
Manish Kumawat
(Clinical Research Coordinator)
Mobile: +91-8058884708

Contact Person :
Mukesh Sharma
(Operational Head)
Mobile: +91-9414525600

Doctors Compensation & Satisfaction Survey 2016

(A Health Professional Survey)

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-:: For details of Health Survey ::-
http://www.somexresearch.com/health-survey.asp

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SoMex Research & Health Pvt. Ltd., Clinical Research and Academic Organization
277, IInd Floor, Shri Gopal Nagar, 80 Feet Road, Gopalpura Bye Pass, Jaipur-302019

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Dr. Naresh Somani on behalf of SoMex Research & Health Pvt. Ltd., Jaipur
Ph. 0141-2504996, 8104124996, Fax : 2504110 • Email: contact@somexresearch.com • Twitter @DrNSomani