IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Recent advancements in epidermal growth factor receptor (EGFR) inhibitors for the treatment of lung cancer

Deepika Mohil*, Amit Mittal

School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar - Delhi G.T. Road, Phagwara, Punjab (India) - 144411

Abstract:

Lung cancer is one of the top leading causes of deaths among people around the globe and tends to affect millions of individuals worldwide. People who smoke have the greatest risk of lung cancer, though lung cancer can also occur in people who have never smoked. The sundry treatment options available for the treatment of lung cancer includes following ways; Surgery, Chemotherapy, Targeted therapy, and Immunotherapy. Targeted therapy is a treatment that targets the cancer's specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This type of treatment blocks the growth and spread of cancer cells and limits damage to healthy cells. Targeted therapy for NSCLC includes; epidermal growth factor receptor (EGFR) inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, drugs targeting ROS1 genetic changes, drugs targeting NTRK fusion, drugs targeting BRAF V600E mutations, drugs targeting MET exon 14 skipping, drugs targeting RET fusion, and anti-angiogenesis therapy. Among these methods and targets, epidermal growth factor receptor (EGFR) inhibitors are considered to be most reliable and worthy targets for the treatment of lung cancer. The major classes of drugs under this includes: Osimertinib, Erlotinib, Afatinib, Dacomitinib, and Gefitinib.

Keywords: Cancer, lung cancer, targeted therapy, EGFR inhibitors.

INTRODUCTION

Cancer isn't a single disease but is a huge family of diseases which can invade in any part of the body. It is usually characterised by abnormal and uncontrolled growth of cells, moreover sometimes tend to spread in other parts of the body as well, this process is known as metastasis and is the utmost reason for deaths of cancer's patients making cancer as the 2nd most leading cause of mortality across the globe with approximately 10 million deaths in 2020. [1]

The most common types of cancers in males include colorectal, lung, liver, prostate, and stomach cancer. On the other hand, the most prevalent types of cancer in females comprise of breast, thyroid, cervical, lung, and colorectal cancer. [1]

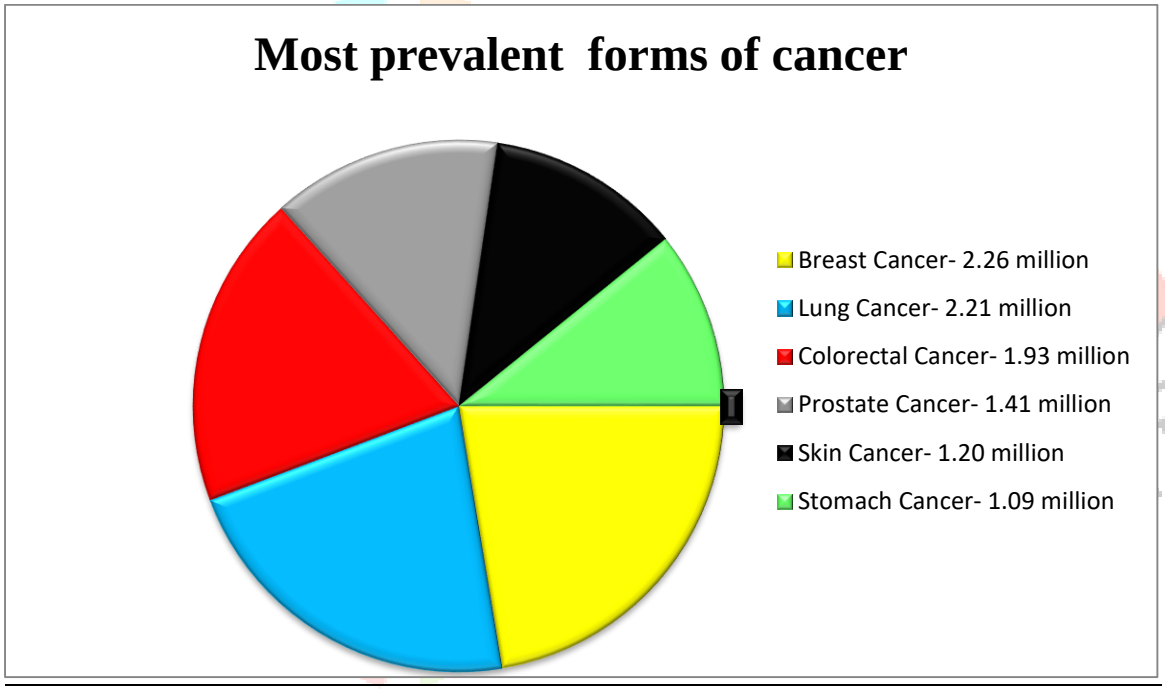


Fig. 1: The above pie chart represents the various types of cancers which were highly prevalent in the year 2020.

Although above are the highly prevalent cancers, undeniably, the cancers causing highest number of deaths per year are camouflaged in these only. Where low and middle income countries comprises of an estimated 70% deaths of cancer's patients. [1]

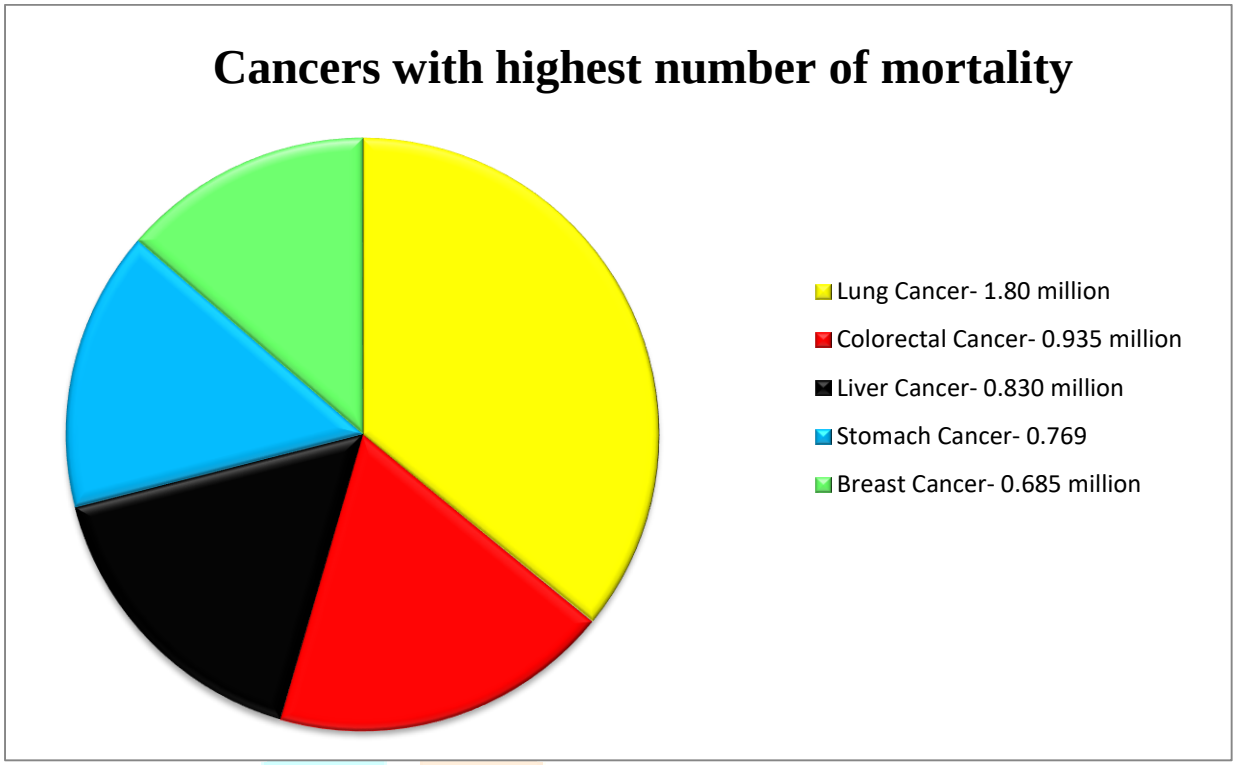


Fig. 2: The above pie chart depicts the mortality data of cancer's patients in the year 2020.

Transformation of normal healthy cells to tumour cells is multi-process succession of pre-cancerous lesion into malignant tumour gives rise to cancer. These alternations comes up as the output of patient's genetic factors interconnection with either or more of the physical, chemical and biological carcinogens. [1]

Physical carcinogens	Chemical carcinogens	Biological carcinogens
• Ultraviolet (UV) radiations • Corpuscular radiations • Electromagnetic radiations • Low and high temperatures • Mechanical traumas • Solid and gel materials	• Arsenic • Aflatoxin • Tobacco smoke • Cadmium • Trichloroethylene • N-methylcarbamate esters • N-Nitrosodimethylamine • O- Aminoazotoluene • Polychlorinated biphenyls • 2-Acetylaminofluorene • 4- Aminobiphenyl	• Oncogenic parasites: Schistosoma Hematobium • Oncogenic bacteria: Helicobacter pyroli bacilli • Oncogenic fungi: Asperigillus falvus

	• 2-Napthylamine	

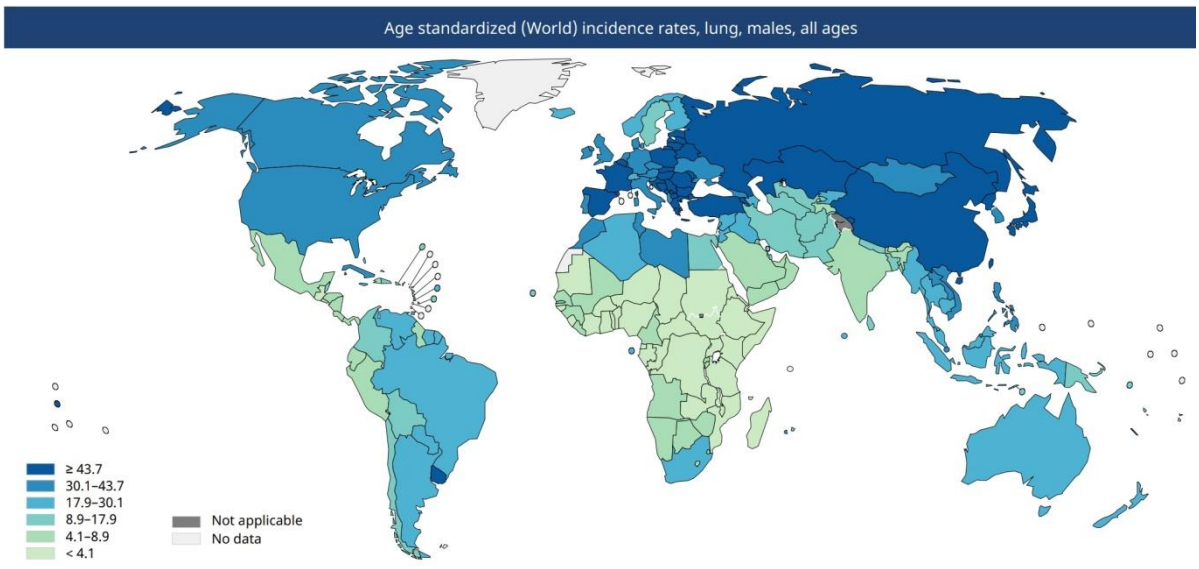
Table 1: This table illustrates the various types of carcinogens. [1, 5]

The risks of cancer's development in the body rises continuously with the increasing age. It is so because with age, the body's overall system of repairing damaged cells decreases and thereby the system becomes weak. [1]

Lung Cancer

Being the 2nd most prevalent form of cancer, lung cancer reports millions of deaths every year in western and eastern countries globally [1, 6, 9]. It has been reported that people who fall in the age category of lesser than 40 years are less likely to develop lung cancer [10]. Smoking has always been pointed out as one of the substantial grounds for causing lung cancer in males and females of certain age groups [7, 13, 14].

There are basically two forms of lung cancer; Non-small cell lung cancer (NSCLC) and small cell lung cancers (SCLC) accounting for almost 85% and 15% of total lung cancer cases, correspondingly. These are the lung malignancies of non- smoking class which are usually categorised into squamous cell, large cell and adenocarcinoma [8, 11, 12, 13]. Among these, adenocarcinoma is most prevalent form of NSCLC and accounts for maximum number of patients i.e. 40% patients of lung cancer [12, 13].



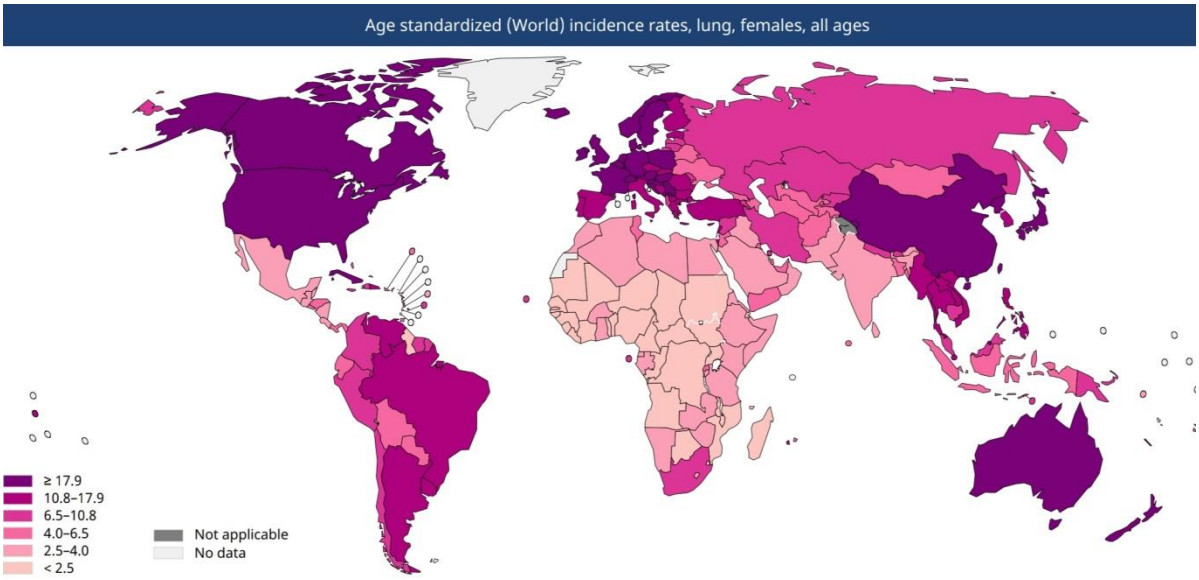


Fig. 3: The above figure represents the lung cancer incidence rates in all ages of males and females, respectively [30].

Diagnostic tests for Lung Cancer

Almost all of the lung cancers are detected after they've started causing some sort of issues to the patient, rest of the cancers can be easily found with screening tests. Considering that the ultimate diagnosis of lung cancer is only done by testing and observing the sample of lung cells in laboratories. The diagnostic tests for lung cancer are basically divided into six different categories with further classifications. [2, 3]

S.no.	Categories of tests	Various techniques for detection
1.	Imaging tests to look for lung cancer	Chest X-ray Computed tomography (CT) scan Magnetic resonance imaging (MRI) scan Positron emission tomography (PET) scan Bone scan
2.	Tests to diagnose lung cancer	Sputum cytology Thoracentesis Needle biopsy Fine needle aspiration (FNA) biopsy

		Core biopsy Transthoracic needle biopsy Bronchoscopy
3.	Tests to find lung cancer spread in the chest	Endobronchial ultrasound Endoscopic esophageal ultrasound Mediastinoscopy and mediastinotomy Thoracoscopy
4.	Lung function tests (LFTs)	There are different types of LFTs, but they all comprises of making the patient breathe in and out through a tube that is connected to a machine that measures airflow.
5.	Lab tests of biopsy and other samples	Molecular tests for gene changes Tests for certain proteins on tumor cells
6.	Blood tests	Complete Blood Count (CBC) Blood chemistry tests

Table 2: The above table represents sundry techniques used for detection of lung cancers. [2,3]

Treatment for NSC Lung Cancer

Sundry treatment options are available for NSCLC. The choice of treatment basically depends on the stage of NSCLC.

S.No.	Treatment	Description
1.	Surgery	Usually preferred for stage-I and II cancers when not contraindicated. Stages of cancer are indicated as per the severity and malignancy of the cancer.
2.	Neoadjuvant Chemotherapy	Beneficial for early treatment of micro-metastases, and down staging of tumour.
3.	Adjuvant Chemotherapy	It is indicated in patients with stage-II and III-A disease after surgical resection has been done.
4.	Immunotherapy	Used for the management of Stage-III NSCLC where surgical resection can't be performed.
5.	Chemotherapy for advanced stages of cancer	It is generally preferred for patients who possess metastatic cancer which requires systemic treatment.
6.	Targeted therapy	It targets the cancer's specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This blocks the growth and spread of cancer cells and limits damage to healthy cells. Targeted therapy for NSCLC includes; • Epidermal growth factor receptor (EGFR) inhibitors, • Anaplastic lymphoma kinase (ALK) inhibitors, • Drugs targeting ROS1 genetic changes, • Drugs targeting NTRK fusion, • Drugs targeting BRAF V600E

		mutations, • Drugs targeting MET exon 14 skipping, • Drugs targeting RET fusion, and anti-angiogenesis therapy.

Table 3: The above table illustrates the various types of treatment options available for treatment of NSCLC. [13, 15, 26, 27, 28, 29]

The Epidermal Growth Factor Receptor (EGFR) Pathway in Non-Small Cell Lung Cancer (NSCLC)

The Epidermal Growth Factor Receptor (EGFR) - ErbB1 is a trans- membrane tyrosine kinase receptor is one of the family members of ErbB receptors, where other members comprises of; ERBB2 (HER2/neu), ERBB3 (HER3), and ERBB4 (HER4). [4, 16, 17]

An extracellular ligand-binding domain, a trans-membrane domain, and a cytoplasmic domain carrying tyrosine auto-phosphorylation sites in the tyrosine kinase zone, are the three main characteristic features of EGFR's structure [18, 19]. EGFR goes through auto-dimerization and dimerization with other members of ErbB receptors family following after the ligand binding. [14, 31]

18-24 exons are clustered around the ATP-binding pocket of the enzyme and encode the EGFR kinase domain. Among these, 18-21 are the exons where most of the mutations take place. Dimerization and ligand binding are important pre-requisites which help in triggering the EGFR signalling with targeted functions [14, 32, 33]. Therefore, these results in EGFR's increased kinase activity, directing the increased potential activation of downstream pro-survival signal pathways that enhances the NSCLC cells' tumour-genesis [20].

Interleukin 6(IL-6)/Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (ERK), and phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR are the three major downstream signalling pathways that are activated by EGFR [16, 17, 20].

Almost 90% of the total EGFR mutations are accounted by two types of mutations i.e. L858R and exon-19 deletion. In addition, T790 mutation is also seen in few of the cases. L858R are point mutations in exon-21 resulting in substitution of arginine in place of leucine at codon- 858. Furthermore, exon-19 deletion is simply the in- frame deletions in exon 19 [21-24].

EGFR-tyrosine kinase inhibitors (TKIs) comprising of gefitinib, erlotinib(1st generation EGFR-TKI), afatinib, dacomitinib(2nd generation EGFR-TKI), and osimertinib(3rd generation EGFR-TKI) have shown potential activity in preventing the EGFR L858R or exon 19 deletion mutations. [4, 21, 22, 23, 24, 25]

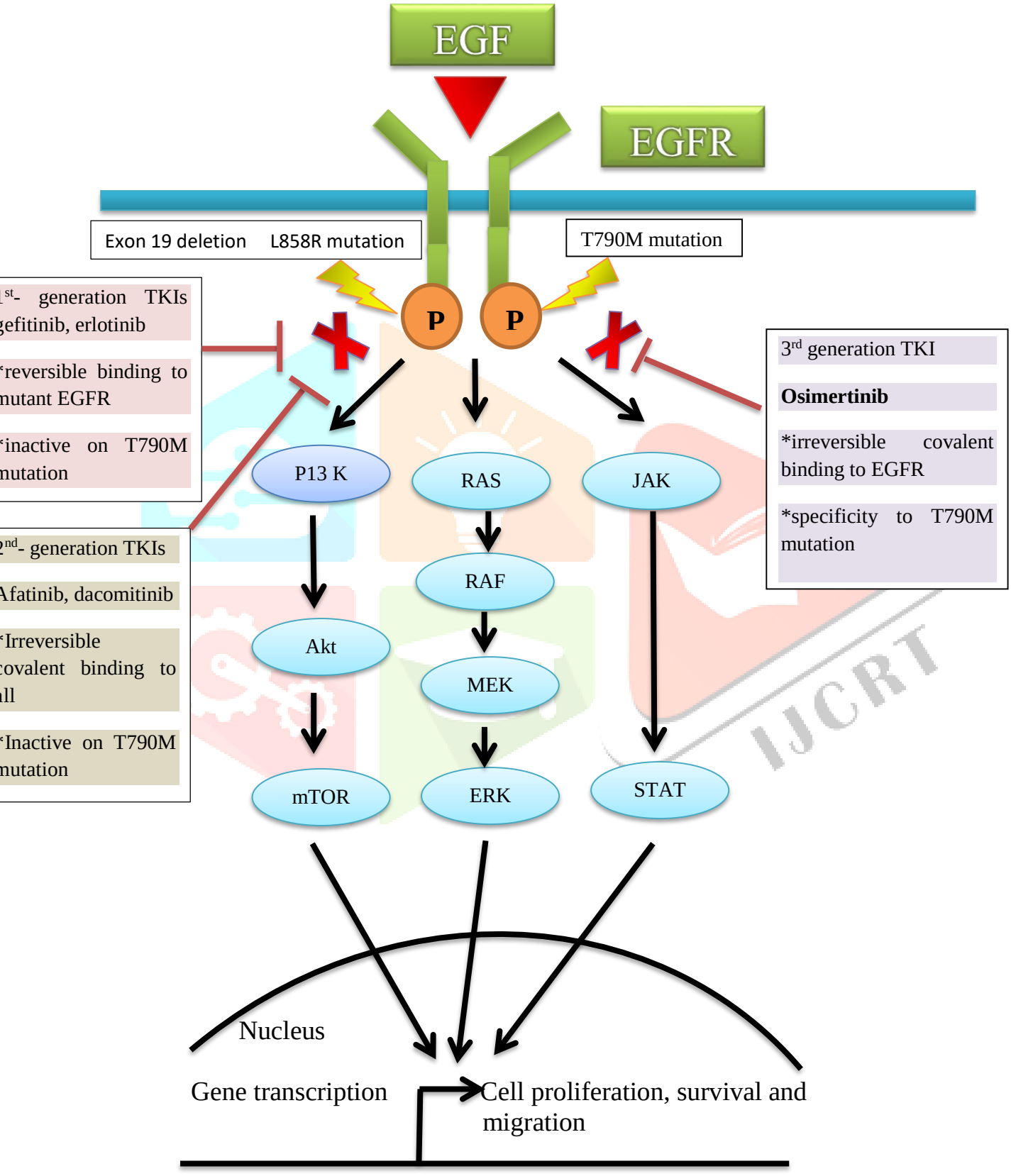


Fig. 4: The above figure represents the Epidermal Growth factor receptor (EGFR) pathway in non- small cell lung cancer. [4]

Targeting EGFR in Lung Cancer

It has been found through several systemic researches that EGFR can be considered as a novel target for the treatment of lung cancer [34]. The considerable approaches used for inhibition of EGFR are: a) Inactivation of intracellular TK signalling, and b) Neutralizing antibodies used against EGFR and its ligands.

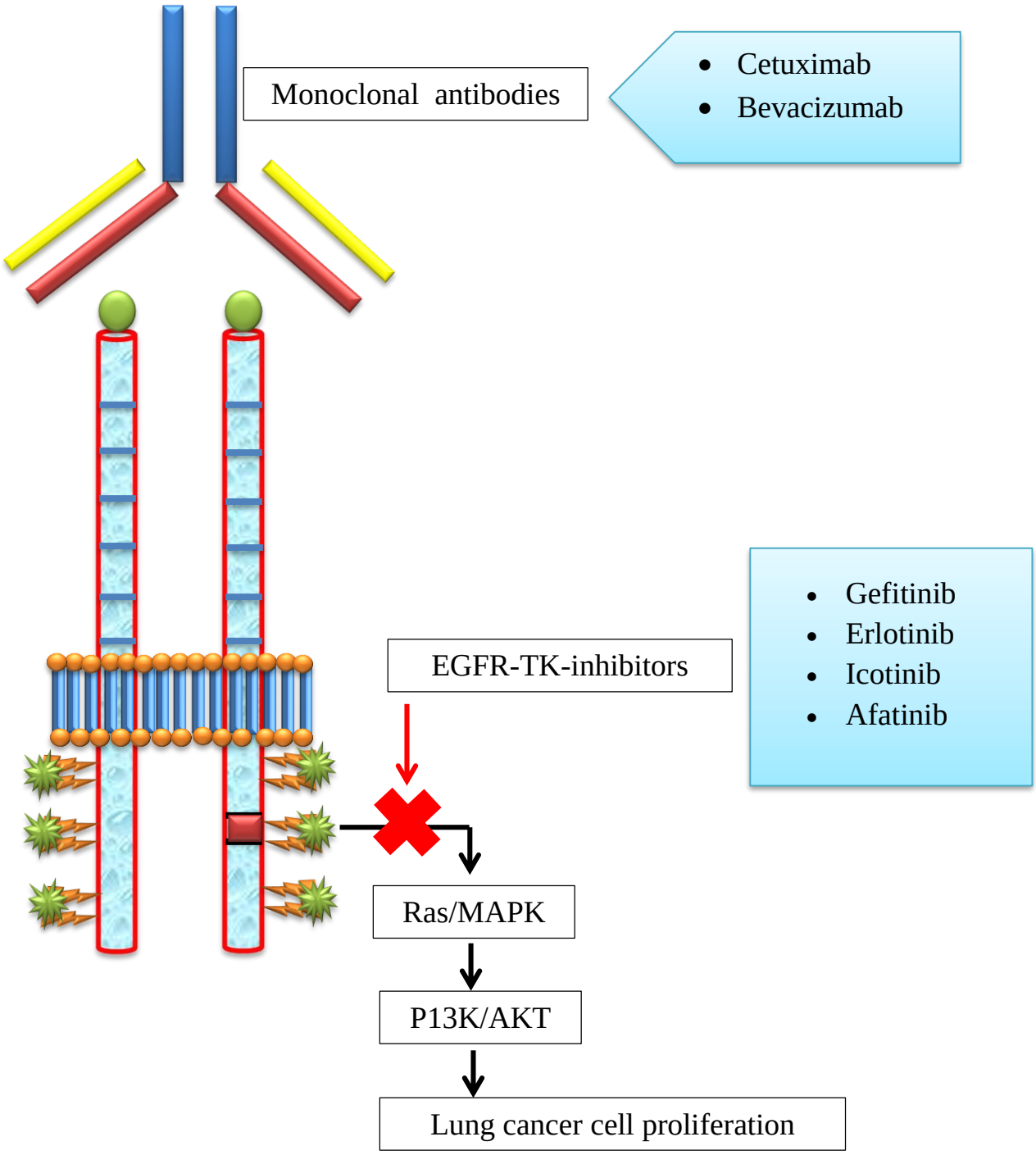
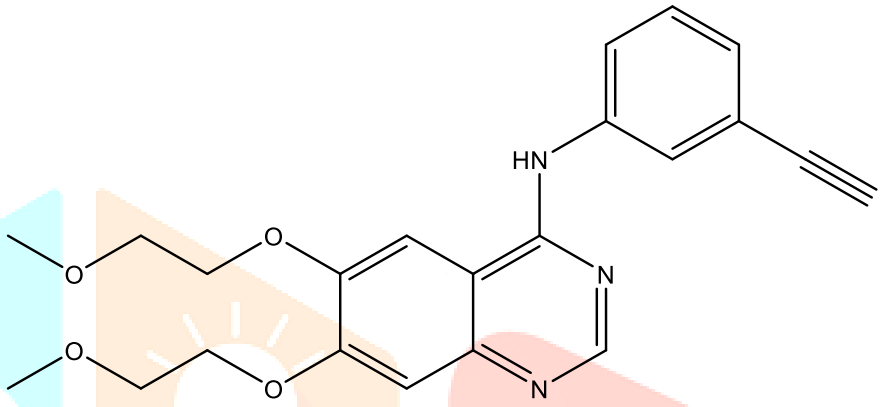
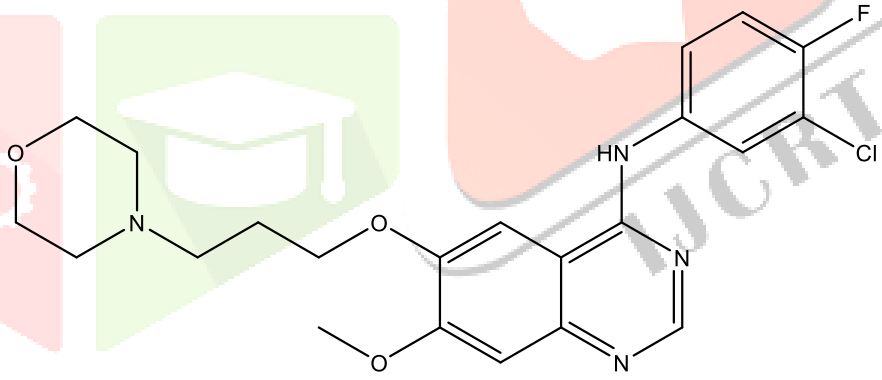


Fig. 5: EGFR-TK-inhibitors inhibiting the EGFR pathway ultimately blocking the lung cancer cells' proliferation [35, 36].

Erlotinib and Gefitinib are the most thoroughly considered EGFR- TK inactivators for Lung Cancer [37, 38]. Whereas, EGFR functioning is blocked by using monoclonal antibodies such as Cetuximab and Bevacizumab [39, 40]. Above are the types of effective EGFR

inhibitors for hindering proliferation of malignant cells of lung cancer, increasing apoptosis, and decreasing the metastasis of lung cancer [39, 41].

EGFR Inhibitors

S.no.	Name	Structure
1.	Erlotinib	
2.	Gefitinib	

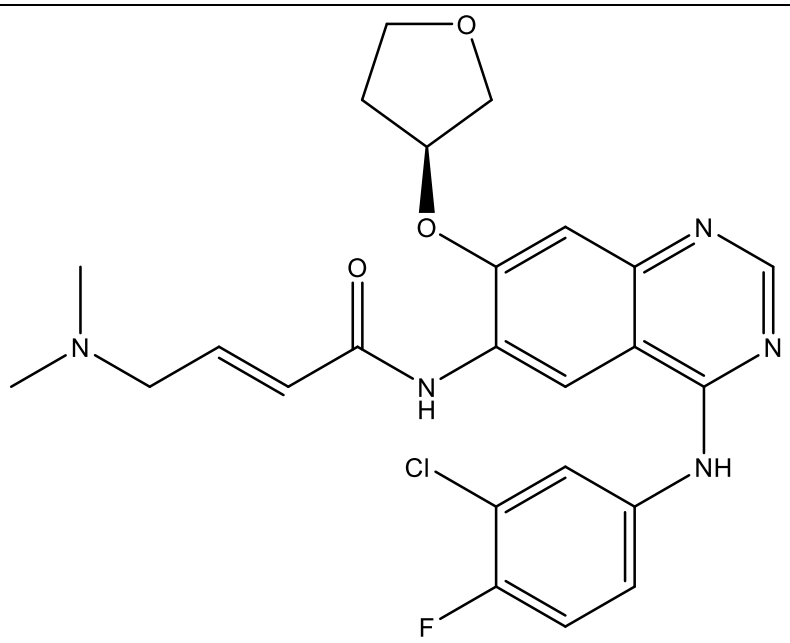
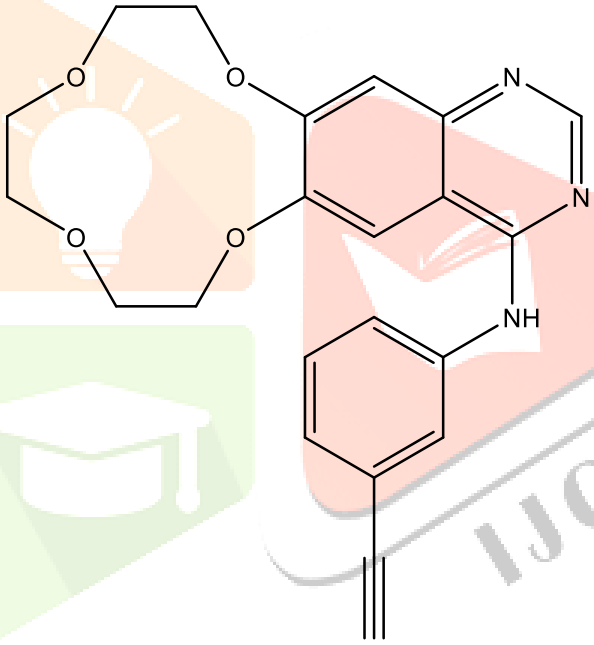
3.	Afatinib	
4.	Icotinib	

Table 4: The above table shows the various EGFR inhibiting drugs available for the treatment of lung cancer. [42, 43, 44, 45]

- **Erlotinib**

Erlotinib principally works through inhibiting the tyrosine phosphorylation by stopping up the intracellular ATP binding site of EGFR [46, 47]. The various extensive adverse side effects related to Erlotinib are, particularly on skin, intestine and eyes. Therefore, over a period of time it's been suggested to go for reduced doses and treatments with fixed time intervals to avoid and manage toxic effects of Erlotinib [48]. The specific roles of erlotinib in treating NSCLC and SCLC in patients were proven by clinical trials. [46]
Survival rates of NSCLC patients were improved using Erlotinib when compared to the single-line chemotherapy [49]. On the other hand, Erlotinib was found to be much effective when used in the second line treatment of old aged NSCLC patients [50, 51]. The two line treatment undoubtedly improved the patients' health by relieving the

symptoms of respiratory uneasiness, cough, chest pain and sundry discomforts [52]. A potential effectiveness in the treatment was shown by Erlotinib when used in combination with permetrexed and docetaxel chemotherapeutics [14, 53]. Nonetheless, Erlotinib was found to be the most effective third line treatment for the patients with declined performance in health improvement [53]. Erlotinib didn't only ameliorate patients' life but also improved lung cancer's palliative symptoms with adequate drug toleration as a third line treatment [54, 55, 56].

- **Gefitinib**

On the basis of the data obtained from the clinical trials, Food and Drug Administration (FDA) countersigned Gefitinib in 2003 as a 3rd line treatment [38]. It was reported that in phase II, as well as in phase III, the drug was effectively able to prevent metastasis, where many different chemotherapies had failed [57]. Surprisingly, in phase III trial, 250 mg/Kg Gefitinib was failed when discussed about the overall survival of 1,700 patients [58]. These reports ultimately made FDA to think over the mandatory use of Gefitinib for the pre- treated patients of cancer [14, 46, 58]. Remarkably, it was found that Gefitinib had very less number of side effects and was adequately tolerated when compared to other drugs of chemotherapies [59].
Certain disadvantages were also seen with the continued use of first line EGFR-TK inhibitors, though Erlotinib and Gefitinib were perfect to be used as second and third line drugs for treatment of Lung cancer [60]. Significant resistance was seen with the use of Erlotinib and Gefitinib [61-63]. Therefore, to avoid such cons, second line drugs (Afatinib) were proposed for better treatment of Lung cancer [60].

- **Afatinib**

Afatinib principally works by binding to 773, 803, and 805 cystine residues of EGFR-TK [64, 65]. It was basically found effective against resistances which were shown in case of Erlotinib and Gefitinib, and in cells with T790M and HER2 mutations within EGFR's gene [64, 66]. Certain side effects such as severe diarrhoea, mouth ulcers, skin rashes, upset stomachs, etc. were reported during the studies of Afatinib [60, 67, 68]. Afatinib, when used in combination with other drugs showed remarkably enhanced progressive survival result, as compared to single drug therapy [67]. Afitinib and cetuximab combination was found to be much effective in place where a co- treatment of Erlotinib or Gefitinib failed when used with tyrosine kinase (TK) monoclonal antibody (Cetuximab) [64]. The reason in the failure of Erlotinib or Gefitinib with Cetuximab lies in the development of T790M mutation in EGFR's genes which can be easily treated using combination of Afatinib and Cetuximab [69]. Nevertheless, Afatinib too possesses the risk to develop resistance in patients with lung cancer [60, 64, 70].

- **Icotinib**

Icotinib has found its use in the treatment of patients who suffered from NSCLC with brain metastasis during the diagnosis and treatment [71]. Other drugs used in Chemotherapies crashed to cross the BBB (Blood Brain Barrier). Moreover, Erlotinib, Gefitinib and Afatinib were only able to reach by the outer cranial lesions [72]. In

addition, it has been reported that Icotinib not only effective for brain metastasis, but also for the sundry EGFR mutations seen in patients [14, 73, 74, 75]. The various side effects seen in patients includes acne, lesions, and diarrhoea, however, all side effects were non-severe and didn't cause any sort of liver damage. Overall, it can be easily stated that Icotinib isn't only potent, but also safer for advanced NSCLC with brain metastasis [76]. There are others drugs too going in different phases of the clinical trial which could be used for the treatment of lung cancer in future if found to be safe and effective.

Conclusion:

With the advancement of time, Cancer has taken up more disastrous and deadly forms. The limited options available for the treatment or cure, has always stood as a thrilling challenge for the physicians as well as for the patients. Despite the growing challenges, Science too has evolved into a lot more and has been able to give potential drug candidates for the treatment of lung cancer. Looking on the potency, efficacy and less number of side effects of the EGFR inhibitors, these drugs have come up forward for the effective treatment of Lung Cancer. Though, owing to the limited options in this category, still many researches and studies need to be carried out in order to achieve the desired level of treatment in patients and hopefully, all the challenges would soon be come across.

Acknowledgement:

With thanks giving to one who is above all (God), this could not be done apart from his grace and mercy being courageous, patient and humble may give up and make someone to stay focused. This review writing isn't easy, it needs hard work, trying to do things as much as a person can and this could not be made possible without God's help he who provides life to us. This manuscript is a welcome and challenging experience for as it took a great deal of hard work and dedication for its successful completion. It's my pleasure to take this opportunity to thank all those who helped me directly or indirectly in preparation of this paper. I am so thankful to my beloved parents who have always been there for me in all ways through their support and care which made me to keep on doing my work. I would also like to thank my friends who took keen interest in the project and helped provide the necessary information that I needed. I am very thankful to my mentor Dr. Amit Mittal for his guidance, encouragement, precious suggestions, crucial help, paying attention to all my problems. I'm grateful to Dr. Monica Gulati, Senior Dean, Lovely School of Applied Medical Sciences, Lovely Professional University, whose continuous supervision helped me to overcome many problems during the project .Acknowledgment cannot be completed without expressing gratitude to our chancellor Mr. Ashok Mittal who provides the facilities, equipment's and faculty who helped to reach my goals.

Data Availability
Not declared.

Conflicts of Interests
Nil

Funding Source
No external funding declared.

References:

1. https://www.who.int/news-room/fact-sheets/detail/cancer [Cited on 1st of April, 2021 at 07:12 am IST].
2. https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/how-diagnosed.html [Cited on 1st of April, 2021 at 12:33 pm IST].
3. https://www.cancer.net/cancer-types/lung-cancer-small-cell/diagnosis [cited on 2nd of April, 2021 at 02:15 pm IST].
4. Hsu P.C., Jablons D.M., Yang C.T., You L. Epidermal Growth Factor Receptor (EGFR) Pathway, Yes-Associated Protein (YAP) and the Regulation of Programmed Death-Ligand 1 (PD-L1) in Non-Small Cell Lung Cancer (NSCLC), Int. J. Mol. Sci. 2019, 20, 3821, 1-19.
5. https://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652007000400004 [Cited on 2nd April, 2021 at 03:50 pm IST].
6. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in europe in 2006. Ann Oncol. 2007;18:581–592.
7. Boyle P. Cancer, cigarette smoking and premature death in europe: a review including the Recommendations of european cancer experts consensus meeting, helsinki, october 1996. Lung Cancer. 1997; 17:1–60.
8. Hodkinson PS, Mackinnon A, Sethi T. Targeting growth factors in lung cancer. Chest. 2008; 133:1209–1216.
9. Sarorius B, Sartorius K. How much incident lung cancer was missed globally in 2012? An ecological country-level study. Geospat Health, 2016; 11(2):396.
10. Kratzke R, Franklin MJ, Lung Cancer epidemiology, In: Schwab M, ed. Encyclopedia of Cancer, Berlin, Germany: Springer; 2011: 2100-2104.
11. Travis Wd, Brambilla E, Nicholson AG, et al. The 2015 Wolrd Health Organisatin classification of lung tumors; impact of genetic, clinical and radiologic advances since the 2004 classification, J Thorac Oncol, 2015; 10(9): 1240-1242.
12. Travis Wd, Brambilla E, Burke AP, Marx A, Nicholson AG, et al. Introduction to the 2015 Wolrd Health Organisatin classification of tumors of the lung, pleura, thymus, and heart, J thorac Oncol, 2015; 10(9):1240-1242.
13. Duma N., Davila R.S., Molina J.R. Non- Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment, Thematic review on Neoplastic hematology and medical oncology, Mayo clinic, 2019;94(8):1623-1640.
14. Liu T.C., Jin X, Wang Y. and Wang K., Role of epidermal growth factor receptor in lung cancer and targeted therapies, Am. J. Cancer Res. 2017; 7(2): 187–202.

15. Hirsch F.R., Scagliotti G.V., Mulshine J.L., Kwon R., Curran W.J., Wu Y.L., Ares L.P., Lung cancer: current therapies and new targeted treatments, 2016, http://dx.doi.org/10.1016/S0140-6736(16)30958-8.
16. Herbst, R.S. Review of epidermal grwth factor receptor biology. Int. j. Radiat. Oncol. Biol. Phys. 2004, 59, 21-26
17. Hynes, N.E.; Lane, H.A. ERBB receptors and cancer: The complexity of targeted inhibitors. Nat. Rev. Cancer 2005, 5, 341- 354.
18. Nicholson, R.I.; Gee, J.M.; Harper, M.E. EGFR and cancer prognosis. Eur. J. Cancer 2011, 37, S9-S15.
19. Hirsch, F.R.; Varnella- Garcia, M,; Bunn, P.A., Jr.; Di Maria, Veve, R., Bremmes, R.M.; Baron, A.E.; Zeng, C.; Franklin, W.A. Epidermal growth factor receptor in non- small- cell lung carcinomas: Correlation between gene copy number and protei expression and impact on prognosis. J. Clin. Oncol. 2003, 21, 3798-3807.
20. Sharma, S.V.; Bell, D.W.; Settleman, J.; Haber, D.A. Epidermal growth factor receptor mutations in lung cancer. Nat. Rev. Cancer 2007, 7, 169-181.
21. Paz-Ares, L.; Soulieres, D.; Moecks, J.; Bara, I.; Mok, T.; Klughammer, B. Pooled analysis of clinical outcome for EGFR TKI- treated patients with EGFR mutation- positive NSCLC. J. Cell. Mol. Med. 2014, 18, 1519- 1539.
22. Taniguchi, Y.; Tamiya, A.; Nakahama, K.; Naoki, Y.; Kanazu, M.; Omachi, N.; Okishio, K.; Kasai, T.; Atagi, S. Impact of metastatic status on the prognosis of EGFR mutation-positive non-small cell lung cancer patients treated with first-generation EGFR-tyrosine kinase inhibitors. Oncol. Lett. 2017, 14, 7589–7596.
23. Hsu,P.C.;Liu,C.Y.;Li,S.H.;Huang,S.H.;Wang,C.L.;Kou,C.H.;Chung,F.T.;Chen,C.H.;Yu,C.T. ;Yang,C.T. Efficacy of platinum based combination chemotherapy in advanced lung adenocarcinoma harbouring sensitive epidermal growth factor receptor (EGFR) mutations with acquired resistance to first-line EGFR tyrosine kinase inhibitor (TKI). Cancer Treat. Commun. 2016, 9, 48–55.
24. Russo, A.; Franchina, T.; Ricciardi, G.; Battaglia, A.; Picciotto, M.; Adamo, V. Heterogeneous Responses to Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors (TKIs) in Patients with Uncommon EGFR Mutations: New Insights and Future Perspectives in this Complex Clinical Scenario. Int. J. Mol. Sci. 2019, 20, 1431.
25. Kobayashi, Y.; Togashi, Y.; Yatabe, Y.; Mizuuchi, H.; Jangchul, P.; Kondo, C.; Shimoji, M.; Sato, K.; Suda, K.; Tomizawa,K.;etal. EGFR Exon18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs. Clin. Cancer Res. 2015, 21, 5305–5313.
26. Ginsberg RJ, Rubinstein LV, Group LCS, Randomized trial of lobectomy versus limited resection for T1 N0 non- small cell lung cancer. Ann Thorac Surg. 1995; 60(3): 615-623.
27. Depierre A, Milleron B, Moro- Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except TIN0), II and IIIa non-small-cell lung cancer. J Clin. Oncol. 2002; 20(1):247-253.
28. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J. Clin. Oncol. 2008; 26(21):3552-3559.
29. Yoon SM, Shaikh T, Hallman M, Therapeutic management operations for stage III non-small cell lung cancer. World J. Clin. Oncol. 2017; 8(1):1-20.
30. https://gco.iarc.fr/today/online-analysis-map?v=2020&mode=population&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_other=1&projection=natural-

earth&color_palette=default&map_scale=quantile&map_nb_colors=5&continent=0&show_ranking=0&rotate=%255B10%252C0%255 [Cited on 2nd April, 2021 at 14:48 pm IST].

31. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2010;141:1117–1134.
32. Carcereny E, Moran T, Capdevila L, Cros S, Vila L, de Los Llanos Gil M, Remon J, Rosell R. The epidermal growth factor receptor (EGRF) in lung cancer. Transl Respir Med. 2015;3:1.
33. Yarden Y. The EGFR family and its ligands in human cancer. Signalling mechanisms and therapeutic opportunities. Eur J Cancer. 2001;37(Suppl 4):S3–8
34. Hodkinson PS, Mackinnon A, Sethi T. Targeting growth factors in lung cancer. Chest. 2008;133:1209–1216
35. Huang SM, Bock JM, Harari PM. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. Cancer Res. 1999;59:1935–1940.
36. Perrotte P, Matsumoto T, Inoue K, Kuniyasu H, Eve BY, Hicklin DJ, Radinsky R, Dinney CP. Anti-epidermal growth factor receptor antibody C225 inhibits angiogenesis in human transitional cell carcinoma growing orthotopically in nude mice. Clin Cancer Res. 1999;5:257–265.
37. Langer CJ. Emerging role of epidermal growth factor receptor inhibition in therapy for advanced malignancy: focus on NSCLC. Int J Radiat Oncol Biol Phys. 2004;58:991–1002.
38. Kris MG, Natale RB, Herbst RS, Lynch TJ Jr, Prager D, Belani CP, Schiller JH, Kelly K, Spiridonidis H, Sandler A, Albain KS, Cella D, Wolf MK, Averbuch SD, Ochs JJ, Kay AC. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA. 2003;290:2149–2158.
39. Marmor MD, Skaria KB, Yarden Y. Signal transduction and oncogenesis by ErbB/HER receptors. Int J Radiat Oncol Biol Phys. 2004;58:903–913
40. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RF 3rd, Gaudreault J, Damico LA, Holmgren E, Kabbinavar F. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J. Clin. Oncol. 2004;22:2184–2191
41. Raben D, Helfrich B, Chan DC, Ciardiello F, Zhao L, Franklin W, Baron AE, Zeng C, Johnson TK, Bunn PA Jr. The effects of cetuximab alone and in combination with radiation and/or chemotherapy in lung cancer. Clin Cancer Res. 2005;11:795–805
42. National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 176870, Erlotinib. Retrieved May 2, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Erlotinib.
43. National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 123631, Gefitinib. Retrieved May 2, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Gefitinib.
44. National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 10184653, Afatinib. Retrieved May 2, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Afatinib.
45. National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 22024915, Icotinib. Retrieved May 2, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Icotinib.

46. Syrigos KN, Saif MW, Karapanagiotou EM, Oikonomopoulos G, De Marinis F. The need for third-line treatment in non-small cell lung cancer: an overview of new options. Anticancer Res. 2011;31:649–659.
47. Perez-Soler R, Chachoua A, Hammond LA, Rowinsky EK, Huberman M, Karp D, Rigas J, Clark GM, Santabarbara P, Bonomi P. Determinants of tumor response and survival with erlotinib in patients with non--small-cell lung cancer. J. Clin. Oncol. 2004;22:3238–3247.
48. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P, Seymour L National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353:123–132
49. Hensing TA, Schell MJ, Lee JH, Socinski MA. Factors associated with the likelihood of receiving second line therapy for advanced non-small cell lung cancer. Lung Cancer. 2005; 47:253–259.
50. Rossi D, Dennetta D, Ugolini M, Catalano V, Alessandroni P, Giordani P, Baldelli AM, Casadei V, Graziano F, Luzi Fedeli S. Activity and safety of erlotinib as second-and third-line treatment in elderly patients with advanced non-small cell lung cancer: a phase II trial. Target Oncol. 2010; 5:231–235.
51. Lyseng-Williamson KA. Erlotinib: a pharmacoeconomic review of its use in advanced non-small cell lung cancer. Pharmacoeconomics. 2010; 28:75–92.
52. Zhu CQ, da Cunha Santos G, Ding K, Sakurada A, Cutz JC, Liu N, Zhang T, Marrano P, Whitehead M, Squire JA, Kamel-Reid S, Seymour L, Shepherd FA, Tsao MS National Cancer Institute of Canada Clinical Trials Group Study BR.21. Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the national cancer institute of canada clinical trials group study BR.21. J. Clin. Oncol. 2006; 24:3831–3837.
53. Ng R, Loreto M, Lee R, Leighl NB. Brief report: retrospective review of efficacy of erlotinib or gefitinib compared to docetaxel as subsequent line therapy in advanced non-small cell lung cancer (NSCLC) following failure of platinum-based chemotherapy. Lung Cancer. 2008; 61:262–265.
54. Dancey J, Shepherd FA, Gralla RJ, Kim YS. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial. Lung Cancer.
55. De Marinis F, Pereira JR, Fossella F, Perry MC, Reck M, Salzberg M, Jassem J, Peterson P, Liepa AM, Moore P, Gralla RJ. Lung cancer symptom scale outcomes in relation to standard efficacy measures: an analysis of the phase III study of pemetrexed versus docetaxel in advanced non-small cell lung cancer. J Thorac Oncol. 2008; 3:30–36.
56. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, Esteban E, Molinier O, Brugger W, Melezinek I, Klingelschmitt G, Klughammer B, Giaccone G SATURN investigators. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010; 11:521–529.
57. Cohen MH, Williams GA, Sridhara R, Chen G, McGuinn WD Jr, Morse D, Abraham S, Rahman A, Liang C, Lostritto R, Baird A, Pazdur R. United states food and drug administration drug approval summary: gefitinib (ZD1839; Iressa) tablets. Clin Cancer Res. 2004; 10:1212–1218.
58. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V, Carroll K. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from

a randomised, placebo-controlled, multicentre study (iressa survival evaluation in lung cancer) Lancet. 2005; 366:1527–1537.

59. Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, Li LY, Watkins CL, Sellers MV, Lowe ES, Sun Y, Liao ML, Osterlind K, Reck M, Armour AA, Shepherd FA, Lippman SM, Douillard JY. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet. 2008; 372:1809–1818.
60. Joshi M, Rizvi SM, Belani CP. Afatinib for the treatment of metastatic non-small cell lung cancer. Cancer Manag Res. 2015; 7:75–82.
61. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009; 361:947–957.
62. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, Nukiwa T North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010; 362:2380–2388.
63. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K, Fukuoka M West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010; 11:121–128.
64. Chen X, Zhu Q, Zhu L, Pei D, Liu Y, Yin Y, Schuler M, Shu Y. Clinical perspective of afatinib in non-small cell lung cancer. Lung Cancer. 2013; 81:155–161.
65. Solca F, Dahl G, Zoephel A, Bader G, Sanderson M, Klein C, Kraemer O, Himmelsbach F, Haaksma E, Adolf GR. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. J Pharmacol Exp Ther. 2012; 343:342–350.
66. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, Padera RF, Shapiro GI, Baum A, Himmelsbach F, Rettig WJ, Meyerson M, Solca F, Greulich H, Wong KK. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008; 27:4702–4711.
67. Yap TA, Popat S. Toward precision medicine with next-generation EGFR inhibitors in non-small-cell lung cancer. Pharmgenomics Pers Med. 2014; 7:285–295.
68. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu CP, O'Byrne K, Feng J, Lu S, Huang Y, Geater SL, Lee KY, Tsai CM, Gorbunova V, Hirsh V, Bennouna J, Orlov S, Mok T, Boyer M, Su WC, Lee KH, Kato T, Massey D, Shahidi M, Zazulina V, Sequist LV. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015; 16:141–151.
69. Ribeiro Gomes J, Cruz MR. Combination of afatinib with cetuximab in patients with EGFR-mutant non-small-cell lung cancer resistant to EGFR inhibitors. Onco Targets Ther. 2015; 8:1137–1142.
70. Kim Y, Ko J, Cui Z, Abolhoda A, Ahn JS, Ou SH, Ahn MJ, Park K. The EGFR T790M mutation in acquired resistance to an irreversible second-generation EGFR inhibitor. Mol Cancer Ther. 2012; 11:784–791.
71. Villano JL, Durbin EB, Normandeau C, Thakkar JP, Moirangthem V, Davis FG. Incidence of brain metastasis at initial presentation of lung cancer. Neuro Oncol. 2015; 17:122–128.

72. Fekrazad MH, Ravindranathan M, Jones DV Jr. Response of intracranial metastases to erlotinib therapy. J. Clin. Oncol. 2007; 25:5024–5026.
73. Eichler AF, Kahle KT, Wang DL, Joshi VA, Willers H, Engelman JA, Lynch TJ, Sequist LV. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. Neuro Oncol. 2010; 12:1193–1199.
74. 99. Porta R, Sanchez-Torres JM, Paz-Ares L, Massuti B, Reguart N, Mayo C, Lianes P, Queralt C, Guillem V, Salinas P, Catot S, Isla D, Pradas A, Gurpide A, de Castro J, Polo E, Puig T, Taron M, Colomer R, Rosell R. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. Eur Respir J. 2011; 37:624–631.
75. Fan Y, Huang Z, Fang L, Miao L, Gong L, Yu H, Yang H, Lei T, Mao W. A phase II study of icotinib and whole-brain radiotherapy in Chinese patients with brain metastases from non-small cell lung cancer. Cancer Chemother Pharmacol. 2015; 76:517–523.
76. Xu J, Liu X, Yang S, Zhang X, Shi Y. Efficacy and safety of icotinib in patients with brain metastases from lung adenocarcinoma. Onco Targets Ther. 2016; 9:2911–2917.