Targeted Therapy in Non-Small Cell Lung Cancer: Review Article

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ABSTRACT
Lung cancer is responsible for the majority of cancer-related deaths in this nation. Based on histological type, the two primary forms of lung cancer are small cell lung cancer (SCLC) (15%) and non-small cell lung cancer (NSCLC) (85%). The genesis of lung cancer is impacted by an assortment of variables, involving cigarette smoking, pollutants in the air, factors related to the environment, workplace cancer-causing agents, nutrition, infections caused by viruses, previous lung disorders, inherited, and immunologic factors. Oftentimes, non-small cell lung cancer does not become apparent until it has advanced. In between 50 and 75% of patients, coughing prevails, subsequent to hemoptysis, chest discomfort, and breathlessness. Laboratory abnormalities or paraneoplastic syndromes are less frequent signs. The most prevalent type of cancer that leads to mortality is lung cancer. Lung cancer occurrence worldwide was estimated at around 1.8 million new cases in 2012, according to the International Agency for Cancer Research (IARC) of the WHO. It is presently being established which therapy is best for persons with lung cancer. Specifically, for those with pulmonary adenocarcinoma, large-cell histology, and non-small-cell lung cancer, it is critical to look for PD-L1 expression levels, EGFR alterations, ALK, and ROS1 translocations. These tests can also be carried out on squamous cell histology patients who have never smoked or smoke seldom. A thorough genomic scan for HER2 insertions, BRAF mutations, MET, TRK, and RET variants could potentially uncover experimental targeted medicines currently undergoing evaluation in human clinical studies in alongside contributing to various other molecular discrepancies.
Keywords: Lung cancer, Mortality, SCLC, Non SCLC, EGFR, Review, Sohag University.

INTRODUCTION

Globally, lungs cancers rank as one of the biggest contributors of cancer-related death. Non-small cell lung cancer (NSCLC) (85%) and lung cancer with small cells (SCLC) (15%) are the two primary forms of lung malignancy according to histopathological type [1].
Biopsy needs to be done for the histological verification of the diagnosis. The stage of NSCLC impacts both the future prospects and available therapies, which is crucial. TNM staging is based on the existence of metastases (M), how much lymph nodes are influenced (N), and the features of the underlying tumor (T). The options for therapy for the stages of NSCLC determine treatment options, but other variables such as the

patient's general well-being and breathing capacity are also crucial. The origin, diagnosis, course of therapy, and new medications employed in it are all going to be examined in this research [2].

Incidence and etiology:

The biggest cause of fatalities from cancer globally is lung cancer. 2012 recorded 1.8 million new instances of lung cancer around the world, according to the International Organization for Research on Cancer (IARC) of the World Health Organisation (WHO). Reality that the United States' 5-year survival rate is still just 18% highlights the high overall ratio of fatalities to prevalence [3].
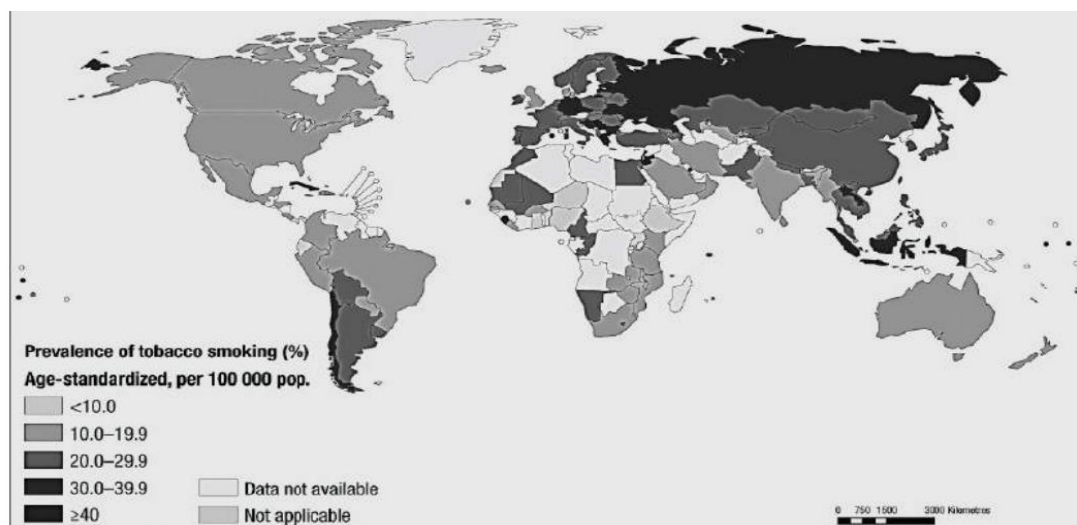
Figure 1: Adult tobacco consumption by nation in 2015, as a percentage; developed based on data from the Worldwide Health Observatory of the World Health Organisation (WHO)[4].

Diagnosis:

Before it has advanced, pulmonary cancer of non-small type couldn't be recognized. In between 50 and 75% of patients, coughing prevails afterwards hemoptysis, chest discomfort, and breathlessness. Laboratory anomalies and paraneoplastic symptoms are further typical symptoms. Histological verification with biopsy is a requirement for confirmation. In compliance with the indications and symptoms, lung cancer patients are grouped into four groups [5].

History and clinical examination:

1. Main tumor-related signs and symptoms: The most prevalent signs are hemoptysis, shortness of breath, and coughing. Furthermore, the tumor may restrict airways, causing stridor, localized rhonchus, atelectasis, pneumonia, and abscess [6].

2. Intrathoracic spread symptoms and signs consist of lung cancer can advance internally by lymphatic spread or direct extension. The chest wall and pleura, vascular systems, intrathoracic organs, and nerves may all be influenced by this spread. Horner's condition, arm weakness, atrophy of the hands' muscles, involvement of the chest wall and pleura, chest pain, pleurisy, and discomfort of breath, the superior vena cava syndrome, tamponade of the heart, and esophageal involvement are the hallmarks of nerve involvement. These manifestations result from vascular structure contribution and hoarse diaphragmatic paralysis [7].

3. Laboratory testing, symptoms, and indications of extra thoracic metastasis: The extra thoracic involvement-related signs and symptoms show up in around one-third of lung cancer patients. The skin, lymph nodes, suprarenal glands, the liver, and the bones frequently get impacted by distant metastases. Bone metastases can be detected by regional bone pain and raised blood calcium and alkaline phosphatase levels.

Radiological imaging in lung cancer:

Indirect and direct outcomes are 2 distinct kinds of radiographic lung cancer findings. Samples of direct findings comprise NSCLC and any concomitant tumor, nodule, or infiltrative lesions. Early-stage bronchioalveolar carcinomas may exhibit lesions that are opaque like ground glass. Nonresponsive pneumonia or atelectasis trapped air on one side, a pleural effusion, and diaphragm palsy are just a few instances of indirect signs. Nodules and masses, two terms applied for describing 3 cm-diameter circular or oval pulmonary masses, correspondingly [8].

With *Positron Emission Tomography*, the whole body and the thorax may be imaged tomographically.

In-lab examinations a full blood count and biochemical evaluations such electrocardiography, alkaline phosphatase, albumin, ALT, AST, GGT, total bilirubin, urea, creatinine, LDH, Na, K, and AST ought to perform [9].

Interventional methods for lung cancer diagnosis:

1. Bronchoscopy: Recent, bronchoscopy is employed for multiple therapeutic applications (brachytherapy, laser therapy, endobronchial stent application, etc.), and additionally for determining the stage and diagnosis of lung cancer. Though it is currently the primary technique to acquire tissue diagnoses for endoscopic lung malignancies, its efficacy is restricted by the location and size of the malignancy [10].

2. Percutaneous transthoracic needle aspiration is an effective and trustworthy way to diagnose thoracic cancers. It is carried out under the supervision of fluoroscopy, ultrasonography, and CT. Its evaluation accuracy is from 80 to 95%; particularly for tumors with a diameter under 3 cm. Interventions relying on computed tomography have a specificity of 96-100% and a sensitivity of 89-92% [11].

3. Pleural fluid analysis: Pleural fluid exists in 50% of instances of cancer of the lungs. Pleural fluid occurs in eight percent to fifteen percent of cancer of the lung's patients. A percentage of pleural fluid is brought on by non-cancerous circumstances, such as pneumonia, mediastinal lymphatic blockage, and post-obstructive atelectasis [9].

Targeted Therapy:

1. Crizotinib: Small-molecule tyrosine kinase inhibitor crizotinib is a first-generation ALK inhibitor. After a phase I study and afterwards phase II and phase III confirmatory procedures, the FDA granted crizotinib a license. Crizotinib and a platinum doublet with pemetrexed have been reported in PROFILE 1014 as the most commonly used therapies for advanced NSCLC with an ALK rearrangement. The PFS, RR, and response duration of crizotinib were superior to those of conventional cytotoxic therapy. Unluckily, whereas second- and next-generation ALK antagonists have been displayed to have greater efficacy intracranially, crizotinib limits CSF penetration [12]

2. Ceritinib: In accordance with the phase III research ASCEND-4, front doublet platinum therapy performed better by ceritinib. Crizotinib-resistant cells are susceptible to the therapies, in particular those with the gatekeeper mutation L1196M, based on preclinical study. People who switched from crizotinib to ceritinib or got single-agent chemotherapy were additionally examined for ASCEND-5 as PFS and RR progressed. Persons with progressing NSCLC (non-small cell lung cancer) who have an ALK rearrangement and who might profit from therapy or are treatment-naive can take advantage of crizotinib [13].

3. Alectinib: Following 2 single-arm clinical trials, the second-generation ALK inhibitor alectinib received FDA clearance in 2015 for therapy of those have metastatic NSCLC that were ALK positive with experienced intolerance to crizotinib [14]. Alectinib is successfully treating either the gatekeeper mutant L1196M or the crizotinib-resistant alterations C1156Y and F1174L.

4. Brigatinib: For those with Stage IV NSCLC who have advanced or grown refractory to crizotinib, there is a second-generation tyrosine kinase antagonist named brgatinib that acts versus active ALK and mutant L1196M [15].

5. Lorlatinib: The FDA designated lorlatinib as a breakthrough drug in 2017. This unique third generation ALK inhibitor has been invented to enhance CNS access and tackle ALK-resistant mutations like G1202R. In its first open-label phase I study involving humans on progressed ALK-positive NSCLC (46% ORR, 9.6 mo. PFS), it displayed promise. Though the exact position for the hierarchy of medications now on the market is unclear, lorlatinib is currently anticipated to be taken by individuals who are refractory to second-generation inhibitors or a number of TKIs. Research is now being done to determine the effectiveness of it in first-line circumstances (NCT03052608) [16].

ROS Proto-oncogene 1 (ROS-1):

The chicken c-ros gene's cellular counterpart, ROS-1, first came to light. This gene is a proto-oncogene for the UR2 sarcoma virus's v-ros transforming sequence [17].

It is a gene that generates a kinase called receptor tyrosine that relates to the insulin receptor family and is remarkably comparable to the leukocyte receptor tyrosine kinase (LTK) and anaplastic lymphoma kinase (ALK) on chromosome 6q22. Yet, it additionally appears in the brain, peripheral nerves, stomach, small gastrointestinal tract, and colon in human adults, the expression of the ROS1 protein seems to be most significant in the kidneys. It doesn't exist in the lungs. In research employing mice as a model, animals lacking the receptor seem to be in excellent shape. There are no known ligands for the receptor [18].

It has been documented that the arising of the combining of FIG and SDC4 along with ROS1 boost IL3 independent proliferation in murine Ba/F3 cells, implying that this expansion may be impeded by small-molecule ROS1 inhibitors. The initially approved therapy for advanced NSCLC with positive ROS1 fusion is crizotinib, which was given permission. In a phase I expansion group, ROS1-positive NSCLC exhibited a 72% rate of responsiveness and a median survival no progression of 19.2 months [19].

Homolog B1 Raf Murine Sarcoma Viruses Oncogene (BRAF):

The first BRAF proto-oncogene mutations emerged in 2002, with an overall cancer mutation incidence of 8% and a lung cancer mutation incidence of 3%. The cytoplasmic B-Raf protein is encoded by the proto-oncogene BRAF. B-Raf encodes a sort of protein triggers and phosphorylates MEK, and MEK then phosphorylates and fires up ERK, which is downstream. Through this signaling route, genes choosing cell survival and proliferation are upregulated [20].

Healthy cells employ extracellular signals like growth stimuli, which access the cell through transmembrane receptors, to trigger this signaling pathway. But because the B-Raf protein is constitutively active in tumor cells that possess the BRAF alteration, regulatory mechanism is missing from those cells. Increased cell survival with proliferation is caused by this, irrespective of external stimuli. In 1-3% of individuals with NSCLC, BRAF mutations are detected [21].

MET Proto-oncogene (MET):

On chromosome 7q31, the MET proto-oncogene came to light in the early 1980s. The transmembrane tyrosine kinase that this enzyme creates interacts with the ligand scatter hormone/hepatocyte growth factor (HGF). The nuclear factor kappa B (NF-kB) pathway, the mitogen-activated protein kinase (MAPK), the signalling transducers and activator of transcription (STATs), and the phosphoinositide-3-kinase (PI3K)/AKT, and downstream signaling are all triggered as an outcome of the downstream signaling, which boosts cell proliferation, restricts apoptosis, and boosts cell motility. The MET pathway typically seems inappropriate in lung cancer. The phosphorylation of proteins (p-MET), overexpression, amplification, rearrangement, and alterations are just a few of the approaches exploited [22].

The curative benefits of tivantinib in patients who acquired obstacles to these EGFR TKIs were not proven in a phase II study containing 45 patients with late-stage locally progressing or metastatic EGFR mutation-positive non-small-cell cancers of the lungs who had advanced on erlotinib or gefitinib; nevertheless, those with high activated MET signaling had a greater likelihood of survival by tivantinib/erlotinib [23].

Rearranging Through Transfection Kinase (RET) and Tropomyosin-Related Kinase (TRK):

1. TRK: The NTRK1, NTRK2, and NTRK3 genes encode three transmembrane proteins referred to as TrkA, TrkB, and TrkC, which are components of the tropomyosin receptor kinase (Trk) receptor family. These receptor tyrosine kinases, which have been detected in human brain tissue, act across the nervous system and activate neurotrophin (NTs).The chromosome 1q21-q22 carries the NTRK1 gene. Mutations in this gene impede the TrkA protein's ability to function, which may end up in congenital anhidrosis and pain sensitivity. Chromosome 9q22.1 encodes the NTRK2 gene, which codes for the TrkB receptor [24]. As the drug entrectinib can pass through the blood-brain barrier, managing cerebral metastases and GBMs with NTRK, ROS1, or ALK triggering gene fusions could profit from its application. All five patients (n=5) in the subgroup of cancer patients with NTRK-rearranged tumors reacted well to entrectinib therapy and had considerable intracranial activity [25]. The multi-kinase

inhibitors altiratinib (DCC-2701) and sitravatinib (MGCD516), which were previously demonstrated to have an inhibitory impact on TrkA and TrkB in vitro, are currently going through phase I trials.

2. RET: A proto-oncogene called RET (rearranged during transfection) may evolve into an oncogene via cytogenetic rearrangement and activating point mutations. RET is located on chromosome 10q in humans. In healthy adult tissues and throughout development, RET expression is lowest. It is principally expressed by urogenital cells and neural crest-derived cells [26]. Overall, RET-rearranged lung adenocarcinomas (LUADs), whose diameters are smaller (3 cm) and display N2 disease (54%), are more prevalent in patients under 60 (73%) and non-smokers (82%). As fusion partners of RET in NSCLC, eight distinct genes have been found out: The more prevalent mutations are KIF5B, CCDC6, NCOA, TRIMM33, CUX1, KIAA1468, KIAA1217, and FRMD4A. Identifying actual fusions may be done with high sensitivity and precision via the reverse transcriptase polymerase chain reaction, also known as (RT-PCR), yet it is unreliable in finding novel fusion partners or isoforms. Several medications presently researched in phase II trials for lung adenocarcinoma with RET positivity [27].

Checkpoint Inhibitors:
A- PD1/PD-L1/2 Inhibitors

1. Nivolumab: The IgG4-blocking antibodies nivolumab affects the PD-1 checkpoint protein and prohibits it from interacting with PDL1/2. Nivolumab was strongly accepted and display no dosage restriction consequences in a preliminary phase I research involving 39 patients who had terminal melanoma with metastases, colon cancer, castrate-resistant cancer of the prostate, renal cell carcinoma, and non-small-cell lung cancer (NSCLC). Anti-tumor act proof emerged during the period of dose expansion and escalation in 6/39 patients up to a level of 10 mg/kg [28].

2. Pembrolizumab: A substitute IgG monoclonal antibody termed pembrolizumab targets the PD1 on PD1 and PD-L1 are hindered from interacting with cancer cells by T cells. It obtained formal authorization from the FDA for the application of malignant cells that are a minimum of 50% PD-L1-expressing and EGFR/ALK wild-type cells in the first-line therapy of NSCLC. In the phase III KEYNOTE024 research, which laid the groundwork for its FDA approval, those with EGFR/ALK wild-type NSCLC and at least 50% PD-L1-expressing tumor cells were contrasted to those getting platinum-based conventional chemotherapy or pembrolizumab monotherapy. PFS (10.3 months vs. 6 months; HR: 0.50; 95% CI: 0.37-0.68; P 0.001) and OS (6-month OS rate of 80.2% vs. 72.4%; HR: 0.60; 95% CI: 0.41-0.89; P = 0.005) both advanced in the pembrolizumab subgroup [26].

3. Atezolizumab: Atezolizumab is an antibody towards PD-L1, the ligand for PD-1, in contrast to nivolumab and pembrolizumab. Atezolizumab boosts antibody-reliant cell-mediated toxicity, interacting with the PD-L1 receptor on cancerous cells helps boost the body's immune system's ability to combat cancer cells. It has been permitted to be administered as an instance of medication in NSCLC patients with cancer that has spread who are EGFR- or ALK-negative and who condition has gotten worse following getting platinum-containing chemotherapy [29]. Overall, until more immune checkpoint blockers are ultimately permitted by the FDA, those with NSCLC in the frontline scenario are going to keep selecting pembrolizumab as their therapy of choice [30].

4. Durvalumab: Stage III NSCLC that is incurable but has not advanced afterwards concomitant platinum-based radiation therapy and chemotherapy has been licensed for the curative administration of durvalumab, a humanized immunoglobulin G1 kappa monoclonal antibody. It prohibits PD-1 and CD80 (B7.1) from attaching to programmed cell death ligand 1 (PD-L1). The PACIFIC trial, an extensive phase III study that randomly allocated patients with inoperable stage III NSCLC who had not advanced further and who had finished a minimum of two courses of platinum-based chemotherapy to receive either the PD-L1 antibody or a placebo, offered the foundation for the PD-L1 antibody's approval [31].

B- CTLA-4 Antagonists
Outstanding accomplishments have been reported among individuals with advanced NSCLC who have never undergone chemotherapy when A medication that inhibits PD-1 (nivolumab) along with a CTLA 4 antagonist (ipilimumab) are given alongside it but ipilimumab might not be as effective without PD-1 inhibition. Ipilimumab with paclitaxel and carboplatin has been contrasted to paclitaxel and carboplatin alone as the initial course of therapy in one phase II randomized control study. The main outcome, progression-free survival, nevertheless failed to substantially vary among the two groups. In the ipilimumab arm, there additionally was no OS improvement [32].

Other Potential Immune Therapy Targets:
1. HER2: The ERBB2 gene, a proto-oncogene situated on chromosome 17q12, codes for the protein molecule referred to as the human epidermal growth factor receptor 2 (Her2). Her2 is a tyrosine kinase receptor that belonging to the EGFR family. It had demonstrated that a multiplex screen and next-generation sequencing may detect Her2 alterations in 1-4% of NSCLC malignancies. In contrast with smokers, these types of tumors are more commonly observed in adenocarcinomas and in women. Exon 20 mistakes phosphorylate Her2, which in turn stimulates downstream pathways as PI3K/AKT/mTOR and RAS/RAF/MEK/ERK [33].

2. Viruses Oncogene Homolog of Kirsten Rat Sarcoma (KRAS): Cell division is mostly controlled

by the KRAS gene, which is identified on chromosome 12p12.1. The four proteins HRAS, KRAS4a, KRAS4b, and NRAS, which offer as mediators of the mitogen-activated protein kinase (MAPK) pathway, are manufactured by this RAS gene family member. The role of these proteins as binary switches that stimulate or disable a number of pathways involved in cancer survival, proliferation, angiogenesis, and differentiation via effector proteins is conducted out by guanosine triphosphatases (GTPases). About to 20 to 30% of all oncogenic traits linked with NSCLC are KRAS mutations, based upon research. Smokers are more likely to have the widespread KRAS mutation, G12C, whereas never smokers seem to possess KRAS transitions [32].

3. Phosphatidylinositol-4,5-Bisphosphate 3-Kinase: NSCLC carcinogenesis and development are facilitated by PI3K/AKT signaling and Catalytic Subunit Alpha (PIK3CA). For PI3K, which boosts cell survival, PIK3CA encodes. AKT is activated farther downstream when it is. Gain-of-function abnormalities in PIK3CA and AKT1, along with modifications in are among the negative regulatory protein PTEN, of system abnormalities that have been recognized in 16% of cases of cancer [34].

4. Ephrin Type-B Receptor 4 (EPHB4): Whereas arterial endothelial cells frequently express Ephrin B2, the receptor's partner ligand, venous endothelial cells frequently express EphB4, the receptor. In epithelial cancers, EphB4 is highly expressed, which has been connected with a poor outcome in a number of cancer subtypes. Due to the obvious of the improved migration, proliferation, and adhesion of cancer cells in response of this, the pathways PI3K/AKT/mTOR, Rho, Ras, Abl, Src, and MAPK are stimulated. In a dose-finding phase IA research, the synthetic drug sEphB4-HSA, which ceased EphB4 from binding with its ligand, had beneficial outcomes. In a phase II clinical study (NCT03049618), the effects of pembrolizumab and sEphB4-HSA in combination are presently being studied [35].

5. Fibroblast Growth Factor Receptor (FGFR): (FGFR) and the path it is a part of are crucial for the progression of the cell cycle, surviving, and multiplication. They possess the capacity to activate the RAS and MAPK signaling cascades. About 3-19% of NSCLC patients had FGFR mutations. Most of these aberrations involve sequence of nucleotide alterations and gene amplifications [31].

CONCLUSION

The most appropriate therapy for cancer of the lungs patients has been determined by screening for EGFR alterations, ALK and ROS1 translocations, PD-L1 expression levels, particularly for individuals with adenocarcinoma of the lungs, Cancer of the lungs that is non-small cell and has large-cell histology. Individuals have squamous cell histology that never or

just occasionally smoke can also undergo such tests. Broad genomic testing to identify genetic variations including BRAF alterations, HER2 insertions, MET, TRK, and RET alterations may also be helpful in locating experimental targeted drugs that are currently under investigation in human studies.

DECLARATIONS

- **Permission to publish:** I vouch for the consent of all writers to submit the work.
- Data and materials are readily available.
- **No competing interests.**
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