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## Review Article

# Target Therapies in Lung Cancer

**A. Bearz, M. Berretta, A. Lleshi, and U. Tirelli**

*Department of Medical Oncology, National Cancer Institute, Via Gallini 2, CRO-IRCCS, 33081 Aviano, Italy*

Correspondence should be addressed to A. Bearz, abearz@cro.it

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Targeting intracellular signaling molecules is an attractive approach for treatment of malignancies. In particular lung cancer has reached a plateau regarding overall survival, and target therapies could offer the possibility to improve patients' outcome beyond cytotoxic activity. The goal for target therapies is to identify agents that target tumor-specific molecules, thus sparing normal tissues; those molecules are called biomarkers, and their identification is recommended because it has a predictive value, for example, provides information on outcome with regard to a specific treatment. The increased specificity should lead to decreased toxicity and better activity. Herein we provide an update of the main target therapies in development or already available for the treatment of nonsmall cell lung cancer.

## 1. Introduction

Nonsmall cell lung cancer (NSCLC) remains a leading cause of death worldwide among patients diagnosed with malignancy [1]. Despite new chemotherapy regimens and new cytotoxic combinations investigated in multiple randomized clinical trials in recent years, no significant improvement in the prognosis of patients with lung cancer was achieved. The five-year survival rate for all patients diagnosed with NSCLC is about 15%, only 5% better than 40 years ago [2]. Significant progress has been made in the recent years in understanding the molecular mechanism of lung cancer. Multiple pathways that are active in NSCLC progression and growth were identified [3]. New therapeutic approaches that target various different aspects of tumor progression and metastasis have been intensively investigated in NSCLC, with benefit/advantage on median overall survival, recently increased to more than one year.

Many drugs that block tumor vascularization (angiogenesis) or interfere with the activity of growth factor receptors and molecular pathways downstream triggered are already used in clinical practice, and more are on study. In this paper we will discuss the basic mechanism of activity and rationale for using those new drugs.

## 2. Tumor Angiogenesis

In 1971, Dr. Judah Folkman put forward the theory that malignant tumors cannot grow beyond a certain size without recruiting their own blood vessels (tumor angiogenesis) through a process that involved production of a soluble growth factor that was secreted by the tumor itself [4]. He also proposed that the local tumor growth and formation of metastases could be prevented by inhibiting the tumor angiogenesis. Among the list of factors that induce tumor angiogenesis, the most important is vascular endothelial growth factor A (VEGF), discovered in 1983 [5]. VEGF is the primary survival factor of vascular endothelial cells, stimulates proliferation, and migration and inhibits apoptosis and modulates their permeability. Those biological functions are mediated upon binding to receptor tyrosine kinases: vascular endothelial growth factor receptors 1, 2, and 3 (VEGFR 1,2,3) [6–9].

Expression of VEGF within tumors is regulated by multiple factors including the level of oxygen within the tumor, growth factors and cytokines produced by the tumor, and mechanism involving oncogene/tumor suppressor inactivation [10]. Hypoxia and Hypoxia-inducible factor (HIF) in the microenvironment are the most important

factors driving angiogenesis, tumor cell proliferation, cell survival and progression, metastatic spread, and apoptosis [11].

There are two major way of blocking the VEGF pathways blocking the activation of extracellular part of VEGF receptor by inhibiting antibodies against VEGF molecule or blocking the activation of tyrosine kinase within the intracellular part of VEGF receptor by tyrosine kinase inhibitors [12, 13].

Bevacizumab is a humanized, monoclonal antibody that binds to VEGF. In 2004 a phase II trial investigated the use of bevacizumab in advanced NSCLC patients [14]. This trial highlighted the most important side effect of bevacizumab, the bleeding events. In particular the majority of patients having tumors with squamous histology and centrally located in close vicinity to major blood vessels had serious pulmonary bleeding. Following this trial, Eastern Cooperative Oncology Group conducted a phase III trial (E4599) comparing paclitaxel and carboplatin chemotherapy alone and the same chemotherapy combined with bevacizumab [15]. After completion of 6 cycles of treatment, patients receiving bevacizumab with chemotherapy continued on bevacizumab as single agent until disease progression or intolerable toxicity occurred. Patients with squamous histology, brain metastases, and central localization were excluded from the study.

The combination of chemotherapy and bevacizumab resulted in the significant improvement in median survival by 2 months when compared with chemotherapy alone group, 12.3 versus 10.3 months, respectively.

The AVAiL trial investigated similar approach as ECOG 4599 study in advanced NSCLC patients, comparing cisplatin and gemcitabine alone versus the same chemotherapy combination with bevacizumab in two different doses [16]. Although the study was powered for overall survival (OS), the primary endpoint was changed from OS to progression-free survival (PFS) during accrual. Median PFS improved upon adding Bevacizumab to chemotherapy both with 7.5 mg/kg dose and 15 mg/kg when compared with chemotherapy alone. However, no survival benefit was observed with adding bevacizumab to standard chemotherapy as shown in ECOG trial. There are multiple different reasons for this different result including insufficient statistical power of the study or the different platinum-based doublet combined with bevacizumab that may matter.

There are ongoing trials with new antiangiogenic molecules as the vascular disrupting agent ASA404, just concluded and press-released to be negative, and oral small-molecule tyrosine kinase inhibitors. Among those TKIs, Vandetanib (ZD6474, AstraZeneca), an inhibitor of VEGFR2/3, RET, and EGFR, has the more advanced development program; in second-line, phase III trial Zodiac [17], Vandetanib showed a slightly improvement of PFS when combined with Docetaxel, 4 and 3.2 months, respectively; there was no statistical difference in the PFS when combined with Pemetrexed in another randomized phase III trial (ZEAL) for second-line treatment [18]. Vandetanib was compared to Erlotinib in a phase III trial for pretreated patients affected by advanced NSCLC, Zest trial [19]. The study did not meet its primary objective of demonstrating PFS prolongation.

In the Zephyr trial Vandetanib was compared to placebo in patients resistant to chemotherapy and EGFR inhibitors; any statistically significant advantage was reported neither for the progression-free survival nor for the overall survival [20]. Many other trials are ongoing with Sunitinib, multityrosine kinase inhibitor of VEGF, Kit, FLT3, PDGFR, and Raf, Sorafenib, inhibitor of PDGFR- $\beta$ , Raf, c-Kit, FLT3, and all VEGFRs, BIBF1120, a potent triple inhibitor of VEGFR 1,2,3, fibroblastic growth factor, and PDGFR, Axitinib, a potent inhibitor of all three VEGFRs [21]. In particular the results of the SUN 1087 trial have been recently reported; in this phase III trial Sunitinib in combination with Erlotinib was compared to Erlotinib in patients with previously treated advanced NSCLC, bringing a statistically significant improvement in PFS but not in OS [22]. NExUS, a phase III, randomized, double-blind, placebo-controlled study evaluated Sorafenib versus placebo in combination with two chemotherapeutic agents, gemcitabine and cisplatin, in treatment-naive nonsmall cell lung cancer patients [23]. No advantage in OS was demonstrated; however, a slight improvement in PFS was shown, although this was not the primary endpoint of the study.

### 3. EGFR Pathway

The Epidermal Growth Factor (EGF) pathway was discovered by Stanley Cohen in the sixties [24]; later in 1980 involvement of its receptor, EGFR, in the tumor genesis was demonstrated. The EGFR pathway can be modulated by monoclonal antibodies that block EGFR (Cetuximab, Panitumumab) or by small molecule tyrosine kinase (TKIs) (Erlotinib, Gefitinib) that interfere with activation of EGFR. The first important trials were designed with TKI Gefitinib, Ideal 1 and 2, two large Phase II trials, demonstrating an antitumoral activity of Gefitinib in the treatment of advanced NSCLC, in particular in adenocarcinoma, females, nonsmokers and Asian population [25, 26]. Although two North American groups reported the importance of EGFR mutations (exon 19 and exon 21 L858R) for prediction of higher response rate and their prevalence in nonsmoker, Asian, female population with adenocarcinoma [27, 28], two large randomized clinical trials, placebo-controlled, phase III were already started, assessing Gefitinib or Erlotinib in second or further line of therapy, respectively, the ISEL and BR.21 trials [29, 30]. Response rate was similar in both trials, 8%; however, only the Erlotinib trial reached a significant impact on overall survival. Later on, clinically or molecularly enriched trials confirmed the role of mutations and as predictive and prognostic positive biomarker. In the IPASS trial, East Asian patients who were never or light smokers were randomized to receive chemotherapy or gefitinib as first-line treatment [31]. Patients who were EGFR mutation positive benefited more from gefitinib, whereas the mutation-negative patients did better with chemotherapy. The same result was obtained from a Korean trial, First Signal, showing the consistence of those results [32].

The West Japan and North East Japan groups conducted parallel trials, where molecularly selected population for

EGFR mutations was randomized to receive chemotherapy of Gefitinib as first-line treatment. Both trials demonstrated the significant superiority in time to progression of the patients receiving Gefitinib [33, 34]. Overall survival did not differ between the two arms, likely for a crossover effect. The same result, for example, no difference in overall survival despite the significant benefit in PFS, was obtained in the IPASS trial [35].

Cetuximab as an antibody to EGFR may work differently from the TKIs. Two phase III trials, FLEX and BMS 099, combined chemotherapy with or without Cetuximab in the treatment of chemo-naïve patients with advanced NSCLC [36]. Patients on the FLEX trial had to be EGFR positive by immunohistochemistry (IHC), and patients who received the Cetuximab had a modest but significant survival benefit. On the BMS 099 trial, there was no patient selection and no survival advantage for the Cetuximab arm [37]; however, the lack of a significant survival advantage could be due to the small sample size of the study.

There are now a number of new-generation EGFR inhibitors. BIB9229 (Afatinib) is an oral irreversible TKI of both EGFR and HER2, and it demonstrates activity in EGFR mutants resistant to Erlotinib, Gefitinib, and Lapatinib. It has demonstrated single agent activity in patients with EGFR mutations (LUX-Lung2) and in EGFR TKIs failures [38].

IMC-11F8 is a fully human IgG1 antibody with an epitope similar to Cetuximab. It is currently being evaluated in clinical trials in colon and lung cancer.

#### 4. KRAS

KRAS mutations are found predominately in the adenocarcinoma histologic subtype of NSCLC (approximately 30%) and less frequently in the squamous cell carcinoma subtype (approximately 5%) [39]. KRAS mutations are associated with a history of tobacco use, and the frequency of KRAS mutations varies among different ethnic groups [40, 41]. The mutant KRAS genes in human cancers encode mutated proteins that harbor single amino acid substitutions, in lung cancer primarily at codons 12 and 13. Mutant KRAS proteins are constitutively activated, leading to stimulus-independent, persistent activation of downstream effectors, in particular, the Raf-MEK-ERK cascade [42, 43]. It has been recently investigated the role of KRAS mutations and EGFR in 1081 patients, and those patients with KRAS mutations had a shorter survival than patients with EGFR mutations or EGFR/KRAS wild type [44]. Although there is a reasonable biologic rationale to support the hypothesis that NSCLC tumors with KRAS mutations are resistant to EGFR-TKIs, the clinical data confirming it have been elusive. This might be a result of the very low prevalence of KRAS and EGFR mutations in NSCLC [45] and the low rate that tumor tissue has been available for KRAS mutational analysis from trials.

#### 5. MET Receptor Tyrosine Kinase

The c-MET (hereafter referred as MET) receptor tyrosine kinase was originally identified as the cellular homologue of

the TPR-MET oncoprotein [46]. MET can be overexpressed in a number of malignancies, sometimes mutated, or sometimes even amplified. MET located on chromosome 7 encodes for a single precursor that is posttranscriptionally modified, forming a transmembrane protein. The ligand for MET has been identified as hepatocyte growth factor (HGF). Ligation of MET receptor to HGF leads to activation of its intrinsic tyrosine kinase. Activating mutations of MET have been reported in a variety of cancers such as lung cancer, melanoma, mesothelioma, and pancreatic cancer; MET can also be amplified in lung cancer.

Several MET inhibitors are currently under evaluation, like ARQ 197 or PF 23411066; promising results of a phase II trial with ARQ 197 associated to chemotherapy were recently presented at the ASCO meeting [47].

#### 6. ALK

A new fusion oncogene, named EML4-ALK, has been described in about 4% of NSCLC patients, mostly in never smokers, young, male, usually not harboring EGFR mutations. The oncogene is due to a translocation within chromosome 2 bringing to a fusion between the N-terminus of the echinoderm microtubule-associated protein-like 4 (EML4) and the intracellular domain of anaplastic kinase (ALK), and its tyrosine kinase activity can be triggered by ALK, MET, and HGF. The activity of EML4-ALK can be abolished by an oral compound, PF 02341066 (Crizotinib, Pfizer) [48]. EML4-ALK can be tested by FISH, the recommended dose is 250 mg twice daily and after the promising results of a phase II trial, a phase III trial is ongoing.

#### 7. Insulin Growth Factor Pathway

The insulin growth factor receptor (IGFR) is involved in essential steps of cancer development such as survival, proliferation and metastases [49]. Predictive factors, that is, predictive biomarkers, are yet not identified, although it has been suggested that pretreatment levels of circulating free IGF1 could help in selecting responsive patients [50].

Several compounds, including monoclonal antibodies and tyrosine kinase inhibitors, are currently under clinical investigation in NSCLC. The major toxicity is hyperglycemia and fatigue, as class effect. The figitumumab (CP-751,871) is the only anti-IGF1R monoclonal antibody whose phase III trial has already finished, and no statistical improvement was demonstrated by adding figitumumab to standard chemotherapy in advanced NSCLC patients [51].

More trials are ongoing with other antibodies with different affinity to IGF1R, like IMC-A12 and MK-0646.

#### 8. Conclusions

Although a platinum doublet remains the standard treatment for advanced NSCLC patients and histology drives the choice of the drugs, biomarkers are useful for prognostic and predictive information. Up to now, the lack of established predictive biomarker to select patients for the antiangiogenic

drugs may be the cause of the modest results observed with VEGFR inhibitors small molecules; the data obtained with bevacizumab are significant only when bevacizumab is combined with taxanes, likely for a synergistic activity; however, the lack of a predictive marker is a big issue for all those drugs.

EGFR mutations are present in 35% of the Asian population and in 15% of the Caucasian population; patients affected by advanced NSCLC with sensitizing mutations in the EGFR gene are highly responsive to EGFR-TKIs with dramatical improvement of their OS, and they should receive those drugs during their treatment. EML4-ALK and EGFR mutations are reported to be mutually exclusive; therefore, EML4-ALK should be checked in patients EGFR negative, for the outstanding results obtained with Crizotinib in the phase II trial, to be confirmed. Other molecular markers and target drugs are advancing rapidly, so the molecular analysis of tumor tissue for molecular characterization is a crucial step in defining the best treatment strategy.

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