

Practical tips and tricks with recently approved molecular targeted agents in non-small-cell lung cancer

Stefan Zimmermann, Solange Peters *

Centre Hospitalier Universitaire Vaudois (CHUV), Oncology Department, Lausanne, Switzerland

The detection of driver mutations in the epidermal growth factor receptor (EGFR), the rearrangement of anaplastic lymphoma kinase (ALK) genes and the subsequent development of targeted therapy have transformed the treatment of lung cancer. In a Caucasian population, as illustrated by the Biomarker France database, these alterations represent 9.4% and 4.0%, respectively, in 10,000 samples of non-small-cell lung cancer (NSCLC) [1]. Of these patients, 56.9% received treatment according to their molecular profile, either with labelled drugs or in a bio-guided trial. Similarly, the Lung Cancer Mutation Consortium, after testing more than 1000 patients with lung adenocarcinoma, found 15% to harbour an EGFR mutation and 8% an ALK rearrangement [2]. An actionable driver alteration was detected in 62% of these tumours. The use of targeted therapies has raised practical questions related to therapy sequences and durations, the role of chemotherapy, the role of combination with chemotherapy, the validity of Response Evaluation Criteria in Solid Tumours (RECIST) criteria, utility of therapeutic rechallenge with the same drugs and several additional issues that arise in the wake of all significant medical progress. This article will address some of these questions and highlight some areas of controversy.

2. Whom and when to test?

The College of American Pathologists recommends testing for EGFR mutations and ALK rearrangements in all patients with lung adenocarcinoma, irrespective of clinical characteristics. In the setting of lung cancer resection specimen availability, EGFR and ALK testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, but is not recommended in lung cancer that lacks any adenocarcinoma component. In the setting of more limited lung cancer specimens (biopsy, cytology) where an adenocarcinoma component cannot be excluded, EGFR and ALK testing may be performed in cases showing squamous- or small-cell

histology, with clinical criteria such as young age and lack of smoking history being useful in selecting the subset for testing. Primary tumours or metastatic lesions are considered equally suitable for testing, and testing of many different areas within a single tumour is not necessary. For patients with multiple, apparently separate, primary lung adenocarcinomas, each tumour should be evaluated. Testing should be ordered at the time of initial diagnosis of advanced-stage disease (stage IV according to the tumour-node-metastasis (TNM) staging system 7th edition) or at the time of recurrence or progression in patients who originally presented with lower-stage disease. Testing for EGFR should be prioritised over other molecular markers, followed by ALK, and only later other molecular markers in lung adenocarcinoma, for which published evidence is insufficient to support the development of testing guidelines at the present time [3].

3. When to start treatment?

First-line EGFR tyrosine kinase (TKI) therapy in patients whose tumour harbours an activating mutation of the EGFR gene has not translated into prolonged overall survival in four randomised trials with mature overall survival (OS) data [4–7], owing to the fact that the vast majority of patients receiving chemotherapy as first-line treatment received EGFR TKI as salvage therapy upon disease progression [4–9].

Why do guidelines advocate use of first-line over chemotherapy [10]? To start with, EGFR mutational status may be altered under first-line chemotherapy, and selection of patients for targeted therapy on the basis of molecular testing on the initial biopsy may be inadequate [11]. Furthermore, in the randomised trials, up to 41% of patients treated with initial chemotherapy did not receive second-line EGFR TKI, mostly because of rapid tumour progression leading to death or reduced performance status, thus excluding these patients from the opportunity to receive the most efficient treatment [5–7]. Quality-of-life data also favour use of EGFR TKI over

* Corresponding author: Tel.: +41 795560192.

E-mail address: Solange.Peters@chuv.ch (S. Peters).

1359-6349/\$ - see front matter Copyright © 2013 ECCO - the European Cancer Organisation. All rights reserved.

<http://dx.doi.org/10.1016/j.ejcsup.2013.07.058>

chemotherapy in first-line treatment. Finally, the high intracranial response rate of EGFR TKIs may defer use of cerebral radiotherapy in patients with central nervous system metastatic disease.

ALK TKIs such as crizotinib are being studied for first-line treatment. Their use is restricted to second and further lines at the present time. OS has not been reported, and is unlikely to be improved as the study design allowed for cross-over to crizotinib in the control arms upon disease progression.

4. Which TKI to choose?

Gefitinib, erlotinib and afatinib have shown significant prolongation of progression-free survival (PFS) in the first-line setting as compared with a platinum doublet. No adequately powered trial has compared these TKIs. Gefitinib and erlotinib are both appropriate as first-line treatment, afatinib being commercially unavailable at the present time with a possible slightly higher gastrointestinal toxicity.

5. When to stop treatment?

All patients on EGFR TKI ultimately develop acquired resistance, which translates into progressive disease as per RECIST criteria. However, only a fraction of tumour clones might carry a resistance mechanism, and interruption of TKI therapy may result in tumour flares. The ASPIRATION trial (NCT01310036) currently compares PFS evaluated by RECIST criteria with PFS until 'progressive disease according to the investigator', defined as symptomatic progression, multiple progression or threat to a major organ. A randomised phase II trial compared chemotherapy plus erlotinib with chemotherapy alone in EGFR TKI-responsive NSCLC that subsequently progresses [12]. No improvement in PFS or OS could be detected, although the number of enrolled patients was low and the trial terminated early. Improvement in RR but not in PFS or OS could be shown in a recent retrospective trial [13]. However, the controversy about continuing EGFR TKI beyond progression is ongoing, with promising retrospective results reported against the switch to chemotherapy [14,15] or by adding local treatment to TKI [16], or combining TKI with chemotherapy [17]. The IMPRESS trial is an ongoing phase III trial expected to clarify the role of TKIs beyond progression. For progression limited to the brain, local therapy to the area of progression may lead to prolonged disease control.

6. What to do upon disease progression?

Despite initial activity of EGFR TKIs, all patients eventually develop acquired resistance. The most common mechanism of resistance is the EGFR T790M secondary mutation, which accounts for 50–60% of cases, and results in increased kinase affinity for adenosine triphosphate [18]. Second-generation EGFR TKIs – such as neratinib, afatinib and dacomitinib – are effective in preclinical gefitinib- and erlotinib-resistant EGFR T790M models, but to date their delivery in EGFR TKI-resistant patients have shown disappointing results in the clinic. Combination of afatinib with cetuximab in EGFR TKI-resistant patients resulted in a 30% response rate and 75%

disease control rate, with significant gastrointestinal toxicity [19]. Other mechanisms of resistance include MET amplification, with no commercially available inhibitor, HER2 amplification potentially amenable to treatment with anti-HER2 monoclonal antibodies or histological transformation to small-cell lung cancer, which requires cytotoxic chemotherapy. Additional potential mechanisms of acquired resistance to EGFR TKIs may develop, including altered EGFR trafficking, amplification or activation of downstream or overlapping pathways and expression of drug-efflux transporters. Standard treatment upon progression on EGFR TKI remains cytotoxic chemotherapy. Later rechallenge with EGFR TKI may result in some modest degree of response (range 4–24%) and a significant disease control rate (range 45–67%) [20–22].

Resistance mechanisms to crizotinib are multiple, and include ALK-dominant mechanisms such as resistance mutations and copy number gain, and ALK non-dominant mechanisms through the outgrowth of clones containing a separate activated oncogene. In contrast to the EGFR setting, where the T790M mutation predominates, the spectrum of ALK resistance mutations is broad. Several distinct second-generation ALK inhibitors which are potentially efficient in preventing/overcoming TKI resistance are under development. A response rate of 80% has been observed during treatment with LDK378 in patients who had experienced disease progression after crizotinib treatment [23]. Similarly to EGFR TKIs, successful later rechallenge with ALK inhibitors has been reported in case reports [24].

7. What toxicity to expect?

Grade 3 or 4 toxicities occur infrequently with EGFR TKIs, with the exception of skin rash, fatigue and diarrhoea (13%, 6% and 5%, respectively in the Caucasian European Randomised Trial of Tarceva versus Chemotherapy (EURTAC) cohort). Grade 1 or 2 toxicities, however, occur in most patients, with rash, fatigue and diarrhoea bothering the majority of patients (67%, 51% and 52%, respectively), and with appetite loss, alopecia, anaemia and arthralgia occurring in a minority of patients (31%, 14%, 11% and 10%, respectively). Rare but potentially fatal interstitial pneumonitis occurs in 1% of patients. Overall, one third of patients require dose reduction or treatment discontinuation because of adverse effects [9]. Topical skin care is mandatory. Systemic antibiotics and anti-diarrhoeal drugs may be necessary to manage higher-grade toxicity.

Frequent toxicities of the ALK inhibitor crizotinib include vision disorders (62%), nausea (53%) and diarrhoea (43%). Patients are less frequently affected by oedema (28%), constipation (27%), fatigue (20%) decreased appetite (19%), dizziness (16%) and dysgeusia (12%). Potentially dose-limiting, increased alanine aminotransferase levels occur in 13% of patients, with less than 5% being of grade 3 or 4. Rapid-onset low testosterone is common in male patients. Renal cysts and pneumonitis have been described, but their frequency is unknown [25,26].

Conflict of interest statement

None declared.

REFERENCES

- [1] Barlesi F, Blons H, Beau-Faller M, et al. Biomarkers (BM) France: results of routine EGFR, HER2, KRAS, BRAF, PI3KCA mutations detection and EML4-ALK gene fusion assessment on the first 10,000 non-small cell lung cancer (NSCLC) patients (pts). *J Clin Oncol* 2013;31:abstr 8000.
- [2] Johnson EB, Kris MG, Berry LD, et al. A multicenter effort to identify driver mutations and employ targeted therapy in patients with lung adenocarcinomas: The Lung Cancer Mutation Consortium (LCMC). *J Clin Oncol* 2013;31:abstr 8019.
- [3] Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013;8:823-59. <http://dx.doi.org/10.1097/JTO.0b013e318290868f>.
- [4] Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent irressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol* 2012;30:1122-8.
- [5] Mitsudomi T, Morita S, Yatabe Y, et al. 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;11:121-8.
- [6] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-57.
- [7] Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735-42.
- [8] Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380-8.
- [9] Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239-46.
- [10] Peters S, Adjei AA, Gridelli C, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23(Suppl. 7):vii56-vii64.
- [11] Bai H, Wang Z, Chen K, et al. Influence of chemotherapy on EGFR mutation status among patients with non-small-cell lung cancer. *J Clin Oncol* 2012;30:3077-83.
- [12] Halmos B, Pennell NA, Otterson GA, et al. Erlotinib beyond progression study: randomized phase II study comparing chemotherapy plus erlotinib with chemotherapy alone in EGFR tyrosine kinase inhibitor (TKI)-responsive, non-small cell lung cancer (NSCLC) that subsequently progresses. *J Clin Oncol* 2013;31:abstr 8114.
- [13] Goldberg SB, Oxnard GR, Digumarthy S, et al. Chemotherapy with erlotinib or chemotherapy alone in advanced NSCLC with acquired resistance to EGFR tyrosine kinase inhibitors (TKI). *J Clin Oncol* 2012;30:abstr 7524.
- [14] Nishie K, Kawaguchi T, Tamiya A, et al. Epidermal growth factor receptor tyrosine kinase inhibitors beyond progressive disease: a retrospective analysis for Japanese patients with activating EGFR mutations. *J Thorac Oncol* 2012;7:1722-7.
- [15] Yang JJ, Chen HJ, Yan HH, et al. Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer. *Lung Cancer* 2013;79:33-9.
- [16] Oxnard GR, Lo P, Jackman DM, et al. Delay of chemotherapy through use of post-progression erlotinib in patients with EGFR-mutant lung cancer. *J Clin Oncol* 2012;30:abstr 7547.
- [17] Faehling M, Eckert R, Kamp T, et al. EGFR-tyrosine kinase inhibitor treatment beyond progression in long-term Caucasian responders to erlotinib in advanced non-small cell lung cancer: a case-control study of overall survival. *Lung Cancer* 2013;80:306-12.
- [18] Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013;19:2240-7.
- [19] Janjigian JJ et al. Activity of afatinib/cetuximab in patients with EGFR mutant NSCLC and acquired resistance to EGFR inhibitors. *Ann Oncol* 2012;23. abstr 12270.
- [20] Tomizawa Y, Fujita Y, Tamura A, et al. Effect of gefitinib rechallenge to initial gefitinib responder with non-small cell lung cancer followed by chemotherapy. *Lung Cancer* 2010;68:269-72.
- [21] Koizumi T, Agatsuma T, Ikegami K, et al. Prospective study of gefitinib readministration after chemotherapy in patients with advanced non-small-cell lung cancer who previously responded to gefitinib. *Clin Lung Cancer* 2012;13:458-63.
- [22] Heon S, Nishino M, Goldberg SB, et al. Response to EGFR tyrosine kinase inhibitor (TKI) retreatment after a drug-free interval in EGFR-mutant advanced non-small cell lung cancer (NSCLC) with acquired resistance. *J Clin Oncol* 2012;30:abstr 7525.
- [23] Shaw AT, Camidge DR, Felip E, et al. Results of a first-in-human phase I study of the ALK inhibitor LDK378 in advanced solid tumours. *Ann Oncol* 2012;23:abstr 4400.
- [24] Browning ET, Weickhardt AJ, Camidge DR. Response to crizotinib rechallenge after initial progression and intervening chemotherapy in ALK lung cancer. *J Thorac Oncol* 2013;8:e21.
- [25] Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363:1693-703.
- [26] Shaw AT, Kim D-W, Nakagawa K, et al. Phase III study of crizotinib versus pemetrexed or docetaxel in patients with advanced ALK-positive NSCLC (PROFILE 1007). *Ann Oncol* 2012;23. abstr LBA1 PR.