***Jamal Gasmi, MD, PhD**, medical director, Medpace, discusses two noteworthy advances in personalised therapy for advanced NSCLC*

A **RELATIVELY NEW** approach, personalised medicine exists to tailor treatment options to a patient's inherent genetic or other personalised makeup, versus a traditional compound mechanism of action approach. This method has yielded some promise in not only treating non-small cell lung cancer (NSCLC) patients, but also in the development of oncology treatments more generally.

Our understanding of biologic and molecular cancer profiles have contributed to the fragmentation of cancer over a variety of oncology subsets. Each subset of cancer is now less common and benefits from a unique treatment approach. Notable success of numerous molecularly targeted agents has dramatically changed the treatment paradigm for several cancer subtypes including NSCLC. Two major advances based on promising compounds and treatments have been achieved in subgroups of NSCLC patients over the last decade.

1. USE OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) AS A PREDICTIVE BIOMARKER AND TYROSINE KINASE INHIBITORS (TKI) AS FOR TREATMENT DECISIONS

Defects in the EGFR pathway have been implicated in NSCLC. In early development, EGFR-TKIs (gefitinib or erlotinib) as single agents in pre-treated NSCLC patients brought some enthusiasm[1]. However, in Phase III trials, no significant advantage has been observed by the addition of TKIs to standard chemotherapy over placebo with standard chemotherapy[2-3]. Further investigations identified a subgroup of patients suitable for EGFR-TKI: female Asian patients who have never smoked with adenocarcinoma subtype. Further analyses have identified that patients with EGFR mutation are most likely to benefit from EGFR-TKI therapy[4-5]. Based on these findings, a large randomised trial has been conducted in Asia comparing gefitinib to standard chemotherapy in first-line treatment of advanced NSCLC. Eligibility criteria required female patients to have an adenocarcinoma subtype and identify as either having never smoked or being a light smoker. Overall progression-free survival (PFS) as the main endpoint favoured gefitinib. Most importantly, in retrospective analysis, patients with EGFR mutation have significantly better PFS with gefitinib, whereas patients with wild type have a better PFS with chemotherapy. This data strongly supported the position of EGFR status as a predictive biomarker, playing a major role in the treatment decision[6].

Subsequent studies using EGFR-activating mutation as the selection process, confirmed that first-line therapy with an EGFR-TKI was better for progression-free survival – although in most of the studies, this did not translate to overall survival[7-8]. The finding is leading to a new treatment paradigm for the management of advanced NSCLC.

2. ANAPLASTIC LYMPHOMA KINASE (ALK) TRANSLOCATION AND ITS INHIBITOR WINS FDA ACCELERATED APPROVAL

This is a success story. Four years after the first report of ALK rearrangement in NSCLC, and based on impressive data of two single arm Phase II trials, the FDA granted accelerated approval to crizotinib, an ALK inhibitor for the treatment of patients with advanced NSCLC who are ALK positive. A large, recently reported Phase III trial comparing crizotinib to chemotherapy in previously treated, ALK positive NSCLC patients confirmed the Phase II outcomes[9-11].

CONCLUSION AND FUTURE DIRECTION

Definite progress has been made in the management of advanced NSCLC. EGFR and ALK status should dictate a personalised approach in the treatment of advanced NSCLC. Other targetable oncogenes have been identified[12], and several clinical trials with targeted agents against these abnormalities are ongoing. The main challenge is to accelerate the pace of innovation in NSCLC biology and treatment. To achieve this goal, cooperative efforts across institutions, industry, regulatory authorities, and payers is crucial to make personalised therapy a reality. **P**

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