Malki and Aziz, Clon Transgen 2015, 4:3
DOI: 10.4172/2168-9849.1000e120

Cloning & Transgenesis
ISSN: 2168-9849

Editorial Open Access

Novel Targeted Therapy for Lung Cancer: Revisited

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Editorial

Lung cancer accounts for about 27% of all cancer deaths and considered as the leading cause of cancer-associated death worldwide. Genotype-driven therapeutics is a standard of care for majority of subgroup of NSCLC patients with admetastatic disease. Recently, targeting NSCLC harboring anaplastic lymphoma kinase (ALK) fusions and ROS1 fusions have produced similar results in terms of overall response rate (ORR). Based on the fact that EGFR and ALK mutations are mutually exclusive, to the patients who carry ALK rearrangements are currently treated with an ALK inhibitor (crizotinib or ceritinib. BRAF targeting Tyrosine Kinase Inhibitors TKIs (dabrafenib, vemurafenib) are approved for BRAF mutated malignant melanoma and currently in phase III trials, the classical V600E mutation are most common and they occur within exons 11 and 15. BRAF V600E mutations are associated with light/never smoker status, while non-V600E mutations are more frequent in former or current smokers and are associated with poorer outcome. Clinical data revealed that BRAF activating mutations may predict sensitivity to inhibition of MEK which is confirmed by clinical response seen with MEK TKIs in BRAF mutated melanoma. Additionally, synergistic activity for the combination of BRAF- and MEK-inhibition has been demonstrated in another preclinical model. Many current trials in BRAF mutated lung adenocarcinoma investigate BRAF-, MEK- and AKT-inhibitors.

BRAF activating mutations are found in 1%-3% of NSCLC. About 50% of these *BRAF* mutations are the V600E mutation that is also seen in melanoma. Unlike *EGFR*, *ALK*, and *ROS1* genetic alterations that are accompanied with light or never smoking status, *BRAF* mutations in NSCLC are often reported in current or former smokers. In a phase II study, 17 patients with *BRAF* V600E-mutant NSCLC received dabrafenib, which had previously shown activity in *BRAF* V600E-mutant melanoma. Other (54%) evaluable patients had PR, with 1 patient having stable disease. Another ongoing phase II study tests dabrafenib vs. dabrafenib and trametinib, an inhibitor of MEK that is downstream of BRAF, in patients with BRAF V600E mutation-positive NSCLC.

In summary, international guidelines recommend investigating of the following seven genes before starting palliative intent therapy for lung cancer: KRAS, EGFR, ALK, ROS1, HER2, BRAF, RET. However, only for EGFR and ALK approved therapies are currently successfully used. With the growing number of genomic drivers and novel molecularly targeted agents in smaller patient subgroups will improve preclinical and clinical research. Additionally, novel approaches in clinical research have to be further investigated as the evaluation of tailored therapies can be highly challenging when the genomic aberrations are uncommon.

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Received August 29, 2015; **Accepted** August 30, 2015; **Published** August 31, 2015

Citation: Malki AM, Aziz HA (2015) Novel Targeted Therapy for Lung Cancer: Revisited. Clon Transgen 4: e120. doi: 10.4172/2168-9849.1000e120