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Targeting oncogenic drivers in lung cancer: celebrating a decade of progress

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In the past decade, remarkable progress was achieved in the field of targeted therapy for patients with advanced non-small cell lung cancer and oncogenic driver mutations. From a clinical point of view, it all began in 2004, when three groups independently discovered the predictive role of activating epidermal growth factor receptor (EGFR) mutations for EGFR tyrosine kinase inhibitors [1–3]. Five years later, the promise of "targeted therapy beats chemotherapy" was fulfilled for the first time in thoracic oncology, when the pivotal IPASS trial demonstrated superior activity of gefitinib compared with first-line chemotherapy in patients with activating EGFR mutations [4]. This was confirmed by a number of follow-on trials with different EGFR inhibitors, including erlotinib and afatinib [5]. In 2007, EML4-ALK fusion in lung cancer was discovered, leading to the rapid clinical development of crizotinib [6]. Again, the pivotal PROFILE trials demonstrated superiority of crizotinib over first- and second-line chemotherapy in patients with ALK rearrangement [7, 8]. Today, clinical research is focused on next generation ALK and EGFR inhibitors with improved activity in the central nervous system and against tumors with secondary resistance mutations [9, 10]. In clinical routine, frontline targeted therapy is considered a new standard-of-care in patients with tumors harboring EGFR or ALK aberrations.

Combined, tumors with EGFR and ALK aberrations make approximately 20 % of all nonsquamous lung cancers in Western populations. Further mutations exist with lower incidence (<3%), for which targeted therapies have been used in analogy to other cancer types. In 2006, response to trastuzumab in a patient with human epidermal growth factor receptor 2- (HER2-) mutated lung cancer was reported [11]. This was exciting because the activity of trastuzumab in previous lung cancer trials had been only modest [12]. In 2013, a European cohort study provided further evidence to support HER2-targeted therapy in patients with HER2-mutated lung cancer [13]. In a phase I trial, neratinib and temsirolimus showed promising activity, and further trials with this combination are ongoing [14]. Recently, we reported successful treatment of a patient with HER2 mutation by ado-trastuzumab emtansine (T-DM1) [15]. A prospective clinical trial with T-DM1 is currently enrolling patients with lung cancer positive for HER2 by immunohistochemistry (NCT02289833). As HER2 expression and mutation are not the same, it will be interesting to see if this trial is using the right selection marker.

In 2012, the first results of a phase I trial with crizotinib in patients with ROS1 rearrangement were reported [16]. Because of the high degree of homology between the kinase domains of ROS1 and ALK, and the potent inhibition of ROS1 kinase by crizotinib, the results were excellent and confirmed in the final report in 2014 [17]. This trial had an immediate impact on clinical practice, as demonstrated by the EUROS1 cohort study [18]. The ongoing EUCROSS trial is expected to produce further relevant data (NCT02183870), while other studies are focusing on acquired resistance and other ROS1 inhibitors to overcome crizotinib resistance [19]. In 2012, we published a patient with BRAF V600E lung cancer responding to vemurafenib [20]. Vemurafenib and dabrafenib are approved for the treatment of patients with advanced melanoma harboring BRAF V600E. Recently, further patients with BRAF V600E lung cancer treated with vemurafenib were reported, and a phase I trial demonstrated good activity of dabrafenib [21–23]. A prospective phase II trial with vemurafenib is planned in France (registration number pending), and a retrospective

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cohort study is ongoing in Europe (EURAF). Of note, half of the BRAF mutations in lung cancer are located outside of codon 600 and may not respond to commercially available RAF inhibitors [24]. RET rearrangement in lung cancer was discovered by two independent groups in 2012 [25, 26]. Preliminary results from an ongoing phase I trial suggested promising activity of cabozantinib [27]. Other reports suggested that vandetanib can also work [28–30]. Final results from the US trial with cabozantinib, and first results from the Japanese trial with vandetanib in patients with RET fusion, are awaited with great interest.

As stated in the 2014 National Comprehensive Cancer Network (NCCN) Guidelines, further druggable targets include MET, DDR2, and the list is growing [31]. Pathologists in many centers are currently implementing multiplex, high-throughput technologies to cope with the workload and provide clinicians with timely results. Quality control, expert knowledge, clinical experience, and interaction between pathologists and clinicians are more important than ever. We believe that patients with druggable mutations should preferentially be treated in accredited centers with clinical trial units and access to new drugs. Patients who are not eligible for clinical trials should be registered in cohort studies, such as the ones mentioned earlier. Even with the best available targeted therapies, metastastic lung cancers with druggable mutations progress early, many have mutations that are difficult to treat (for example KRAS mutations), and most have no druggable targets at all. Therefore, chemotherapy, combined with anti-angiogenic therapy, will remain indispensable in the foreseeable future. Continued research in this area, as well as in the field of immunotherapy, should not be neglected.

Conflicts of interest

Both authors declared no potential conflicts of interest.

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