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Personalized medicine in non-small-cell lung cancer: has it come of age?

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"Even though chemotherapy still remains the backbone for most of our patients, a substantial number of patients receive small molecules with a different mode of action offering them much greater and longer benefit compared with chemotherapy."

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In his editorial on the landmark study of Schiller *et al.* in the *New England Journal of Medicine*, Carney stated that chemotherapy in advanced lung cancer had reached a plateau and that the use of specific biologic targets would offer optimism and hope that mortality from this disease may be reduced [1]. Approximately 10 years later the landscape of non-small-cell lung cancer (NSCLC) has changed significantly and his optimism was confirmed. Even though chemotherapy still remains the backbone for most of our patients, a substantial number of patients receive small molecules with a different mode of action offering them much greater and longer benefit compared with chemotherapy. The identification of mutations in the EGFR in 2004 and the proof that these mutations are associated with an increased sensitivity of the tumor to EGFR tyrosine kinase inhibitors (TKIs) [2] became the first, and so far greatest, step towards personalized therapy in NSCLC. It took some years to prove the first case reports in randomized prospective trials, but today there is no doubt that the presence of an activating EGFR mutation is a strong prognostic and predictive marker in NSCLC. The biology of the mutated tumor is so different from common NSCLC that it should be considered to regard this disease as a new entity of lung cancer. The results of a variety of clinical trials that showed a highly increased efficacy of EGFR-TKI compared with conventional chemotherapy in patients harboring activating EGFR mutations led to routine testing for EGFR mutations in patients with advanced NSCLC. The question of which patients are to be screened and when they should be screened is still under discussion and will show differences in various regions. However, there is a consensus that, in general, screening for EGFR mutations should be offered to patients with non-squamous cell NSCLC.

The second story of success was a completely different one. Crizotinib was initially planned to act mainly as a cMET inhibitor as it became evident that amplification of cMET played a role in lung cancer, especially in acquired resistance towards first-generation EGFR-TKIs. The ATP-competitive inhibition of tyrosine phosphorylation caused by activated ALK was initially regarded as just a side-effect of the compound. Things have changed, nowadays only the minority know about the potential cMET-inhibition of the drug and it is just recently that this important target has been explored using Crizotinib. Soda *et al.* reported the presence of the transforming *EML4–ALK* fusion gene caused by an inversion in chromosome 2p detected in the tissue of five out of 75 NSCLC patients [3]. The *ALK* part of the translocation contains the entire intracellular tyrosine kinase domain of ALK. The fusion partner in ALK translocations mediates dimerization of ALK, which results in constitutive kinase activity. They stated that this transformation might be an attractive target or a useful diagnostic tool. In the Phase I trial of crizotinib, investigators noted a dramatic response in a patient with NSCLC harboring an *EML4–ALK* fusion, in the

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subsequent Phase II part of the study, a further 82 patients harboring the fusion product were included. The results showed an impressive response rate of 57% in a heavily pretreated population [4]. It is of note that the translocation is mutually exclusive; there is no coincidence with activating EGFR mutations, although the same patient population (adenocarcinoma, young age, never-smoker) seems to be affected. To date, we have already learnt a lot more about the EML4–ALK patients: they respond well to chemotherapy, especially treatment with pemetrexed, which shows favorable results compared with wild-type patients. Interestingly, the EML4–ALK-positive tumors show histology with signet ring cells, usually found in gastric cancer. The prognosis itself in non-crizotinib-treated patients does not significantly differ from adenocarcinomas without translocation. The updated survival data of the Phase I/II trial shows results comparable with those achieved in patients with an EGFR mutation treated with EGFR-TKIs. Underlining the velocity of the crizotinib story is the fact that patterns of drug resistance were already published in 2010. In parallel to the resistance patterns in EGFR mutations, there is a mutation (L1196M) affecting the gatekeeper position of the tyrosine kinase leading to resistance against ALK inhibitors. Interesting results were reported in a Phase II trial of the HSP-90 inhibitor ganetespib, where durable responses were only seen in tumors harboring an ALK translocation. It is speculated that the combination of an ALK inhibitor and an HSP-90 inhibitor could work synergistically by prolonging the time to acquired resistance to ALK inhibitors [5]. Furthermore, second-generation ALK inhibitors have shown *in vitro* activity in crizotinib-resistant cell lines. The most challenging problem in this success story is the identification of patients with an ALK translocation due to the low incidence rate of 4% ALK-positive patients. In order to identify a positive patient one has to screen at least 25 patients.

The other side of the coin is the story of multiple compounds thought of as the next new stars on the horizon, ending up in Phase III trials without evidence of any benefit for the patients. What went wrong with all of these compounds being tested in trials with approximately 25,000–30,000 patients? In most of the studies, preselection of patients was either not done, or not done efficiently. In targeted therapy, one of the basics is to identify the target. The next step is to make sure that the target is relevant to the oncogenic driver and the last step is to question whether the new compound can definitely hit the target without producing too many side effects. In particular, various compounds targeting the VEGF-pathway have shown no benefit, with the exception of bevacizumab, but instead of stopping recruiting allcomer patients into clinical trials with these compounds and returning to Phase II with biomarker testing, we still have big Phase III trials active, recruiting unselected patients for targeted therapy. A number of oncogenic driver mutations in genes such as *BRAF*, *HER2*, *AKT1* or *MEK1* have been identified in adenocarcinoma, and there are also data showing an oncogenic quality for FGF amplification in squamous cell NSCLC. Unfortunately, however, most of these mutations are only present in a minority of patients. Therefore, reasonable concepts and trial designs are essential for valid evaluation of new specific targeted agents and the crizotinib story might be used as a blueprint. The problem of testing for all these mutations will be immense in the next few years because it will be expensive, time-consuming and there will not be enough tissue. However, with the fast progress in diagnostics, we believe that satisfying sequencing techniques will be affordable and available in the near future. Furthermore, clinicians are already aware that they have to deliver tissue to get the answers to their questions.

What should be done with all the remaining patients not harboring one of the mutations? In this patient population we have chemotherapy and bevacizumab tailored by histology. Furthermore, we have erlotinib, an EGFR-TKI with moderate activity in EGFR wild-type patients. Maybe we will get cetuximab in patients with a positive EGFR-score. All of these approaches lack the momentum of the targeted therapy story mentioned before, but still we have seen slow progress in treatment options and in prolonging survival of our patients. However as long as the biology of tumors is still too complex to be understood we will only make progress in small steps, or by chance.

Taking these facts together, we are happy and proud to say that personalized therapy has come of age in NSCLC, at least for approximately 15% of the patients in a western population, even higher in the asian population. And this happened in a short period of time in a type of cancer that was forgotten and stigmatized because of the high percentage of smokers and the extremely bad prognosis and poor choices of treatment.

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Whether personalized treatment will be the future for the majority of lung cancer patients, most of them being heavy smokers with multiple mutations, remains unclear. We fear that in at least 50% of our patients we will make no or only minor progress, comparable with the situation in small-cell lung cancer where we have not found any relevant progress in systemic therapy in the last decades. For these types of tumor, tobacco control,

screening tools and improvements in chemotherapy will be more helpful in the coming years. However, the more we learn about lung cancer, the better we might be able to identify multiple activated pathways leading to combination drugs and an even more sophisticated design of our treatment choices.

The last question is of high importance but not a medical one: who will pay for it? In a time of crisis that has shaken many nations, it will be of high importance to run trials that show the cost–effectiveness of new drugs. The outcome of these trials will be mainly influenced by the high selection of the tested patient population, as is the case in the crizotinib trials.

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