Editorial

The *Lung* and Winding Road: Twists and Turns on the Way to Personalized NSCLC Therapy

Lung cancer remains the most common cause of cancer death worldwide and, although its incidence is declining in men in Western countries, due to the steady decrease in tobacco smoking, the trend towards increased cigarette smoking in women and in developing countries allows predicting a novel and epidemiologically different lung cancer epidemics in years to come. Non-small cell lung cancer (NSCLC) represents the vast majority (85%) of tobacco-related and –unrelated lung cancers and, despite recent progresses in screening techniques, it is usually diagnosed at an advanced stage, in which surgery and integrated loco-regional therapies have little chance for cure. Thus, NSCLC prognosis remains poor overall, with 5-year survival figures of 11-16% in Europe and USA, respectively. Such already dismal figures suddenly drop to 4% if one considers only advanced, inoperable patients.

For these reasons, the field of systemic therapy for NSCLC is commonly perceived by non-lung experts and the general public alike as one where little has changed in the past 20 years, with cisplatin-based chemotherapy as the cornerstone of treatment and little progress with the addition of second and third-generation cytotoxic agents as the partners of platinum salts. Despite such common misconception, progress has been made even in the standard chemotherapy treatment of advanced NSCLC and the introduction of novel cytotoxic drugs in routine clinical practice has now proven to provide incremental survival benefit in population-based studies. Thus, as chemotherapy remains the treatment of choice for the vast majority (80% or more) of advanced NSCLC patients, improvement in this area is expected to come from the acquisition of further knowledge of the way by which genetic characteristics in normal and neoplastic cells affect responsiveness to, as well as metabolism of, chemotherapeutic drugs; this, in turn, would allow selecting patients who may benefit from treatments that best match the individual's and tumor's genetic profile, resulting in maximum activity and minimal toxicity. The hot (and highly controversial) issue of pharmacogenetic/pharmacogenomic-driven choice of chemotherapy is discussed in detail by Galvani *et al*. in this issue. In this context, expression and function of DNA repair genes and proteins have been studied in different cancers, including NSCLC, not only as a possible biomarker, but also as a clinically useful target; indeed, pharmacological inactivation of PARP has allowed the identification of synthetic lethality with inactivation of other DNA repair proteins, such as BRCA1, and has shown potential to sensitize tumors to commonly used cytotoxic agents. In this Hot Topic issue, Giaj Levra *et al*. discuss data regarding PARP function in the context of DNA repair pathways, as well as clinical data recently generated with PARP inhibitors in NSCLC.

Most importantly, the past decade has witnessed a major paradigm shift in the classification and treatment of NSCLC and we are only beginning to appreciate its clinical impact. The appreciation of the predictive value of histological subtyping and the recognition that each histological subtype is actually a "universe" of different diseases driven by specific and possibly "druggable" molecular aberrations has led to a shift towards a truly personalized treatment approach for patients with advanced NSCLC. Analysis of the mutational landscape of major NSCLC histological subtypes has now reached an unprecedented level of detail, providing candidate therapeutic targets for personalized therapy, to which cancer cells have become "addicted" in such a way that inhibition of the mutated/aberrant protein would result in cessation of cancer growth, in as much as 50% of NSCLC cases.

The history of the successful development of agents that target the two clinically most relevant "driver mutations" in NSCLC, i.e. epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements, also provide intriguing clues to different strategies that could be employed to rapidly and successfully bring new approaches to personalized NSCLC therapy to the patient bedside. Indeed, discovery and targeting of EGFR activating mutations is a paradigmatic example of an empirical, bedside-to-bench, approach to treatment personalization; as discussed by Wannesson *et al*. in this issue, EGFR tyrosine kinase inhibitors (EGFR-TKI) currently constitute the treatment of choice for EGFR-mutant NSCLC, although the biological (and clinical) outcome of EGFR inhibition in this context can be modulated by several pathways, eventually leading to the emergence of resistant clones. In both EGFR-mutant and EGFR-wild type NSCLC, novel EGFR inhibitors, either endowed with irreversible inhibitory activity towards EGFR itself and other EGFR family members (such as HER-2, discussed by Maione *et al*. in this issue) or simultaneously targeting EGFR and angiogenic receptors of the vascular endothelial growth factor receptor (VEGFR) family (critically discussed by Di Maio *et al*. in this issue), are now being developed for clinical use, albeit not always with the expected success. On the other hand, discovery and clinical targeting of the echinoderm microtubule-associated protein-like 4 (EML4)-ALK rearrangement, discussed in this issue by Cappelletti *et al*. together with c-Met (another emerging target in NSCLC), is a paradigmatic example of an hypothesis-driven, bench-to-bedside, approach to treatment personalization; indeed, identification of the EML4-ALK translocation in a small percentage of NSCLC (first reported in 2007) led to the targeted development of crizotinib, a c-Met inhibitor that also targets other receptor tyrosine kinases such as ALK and ROS1, resulting in the accelerated approval granted from the FDA for ALK-rearranged NSCLC in 2012, only five years after the first report of EML4-ALK translocations in NSCLC.

A considerable number of novel potential targets for intervention and matched developmental drugs are currently emerging, raising hope to rapidly develop new, highly specific and effective, treatments for an increasing number of NSCLC patients. Unfortunately, not all of the genetic/molecular alterations described in NSCLC are endowed with clear-cut 'driver' potential, nor can they be efficiently targeted with available drugs, KRAS mutations being perhaps the best example. Indeed, as discussed by Piva *et al*. in this issue, despite its prevalence and its role as a widespread resistance mechanism, attempts at targeting KRAS directly for therapeutic purposes have failed so far. However, renewed hope for KRAS mutant patients derives from the promising activity of compounds that target downstream RAS effectors in both the MAPK and PI3K pathways (discussed in detail by Ciuffreda *et al*. in this issue). In addition to agents that directly target "driver" molecular alterations in NSCLC cells, drug development has recently focused on agents that can modify the tumor-surrounding microenvironment, such as anti-angiogenic drugs. As critically discussed by Pilotto *et al*. in this issue, in unselected NSCLC populations anti-angiogenic agents have so far provided a minimal, albeit significant, clinical benefit, which is burdened by considerable toxicities. In this context, unfortunately, no validated molecular biomarkers of angiogenesis can reliably predict clinical outcome, sensitivity, early response or resistance to any of the investigated anti-angiogenic therapies.

It affords from the above that, despite successes, in NSCLC significant challenges exist both in identifying new targetable aberrations and characterizing the 'driver potential' of the already known ones; indeed, at least half of NSCLC cases are currently orphan of defined, recurrent genetic/molecular aberrations. However, novel genetic and proteomic approaches are offering the opportunity for matching specific genetic defects and aberrant protein-protein interactions with active pathway-targeted inhibitors; moreover, the isolation and characterization of a cellular pool endowed with stem-like traits, and able to recapitulate the parental disease in animals, is enabling investigators to recreate the individual patient tumor in the laboratory. In this issue, Maugeri Saccà *et al*. discuss how novel technologies and cellular and animal models,

applied to lung cancer research, hold the potential to foster a new wave of biomarker-driven clinical trials. One example of such a novel strategy is the use of micro-RNA (miRNA) profiling. miRNA are small single stranded non-coding RNA molecules, which regulate gene expression at the posttranscriptional level. Growing evidence suggests that miRNAs are expressed aberrantly in many human cancers, including NSCLC, and play a significant role in carcinogenesis and cancer progression. In that respect, there is increasing evidence that miRNA profiling may become an accurate way to differentiate tumor subtypes, determine prognosis and response to therapy in NSCLC, as discussed in detail by Cortinovis *et al*. in this issue.

Although methodological innovations are clearly needed to face new challenges, if we look at the changes occurred in the NSCLC scenario in the recent past and are able to learn from successes and failures alike, a truly 'personalized' approach to NSCLC therapy appears, now more than ever, within our reach.

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