It has been nearly four decades since Stanley Cohen was awarded the 1986 Nobel Prize in Medicine for the discovery of epidermal growth factor and its receptor EGFR. The first EGFR inhibitor, gefitinib, was approved in 2003 by the US FDA for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC) patients as a third-line therapy, after failure of platinum-based and docetaxel chemotherapies. In chemotherapy-naive patients, however, gefitinib failed to prolong survival compared with chemotherapy alone in several large, randomized, placebo-controlled trials.

Retrospective subgroup analyses of those clinical trials have indicated improved survival in patients of Asian ethnicity and non-smokers, who harbored certain somatic mutations around the ATP-binding pocket in the tyrosine kinase domain of the EGFR gene. Subsequently, in a large, randomized, double-blinded trial–IPASS (Iressa Pan-Asia Study), gefitinib was compared with carboplatin plus paclitaxel as a first-line treatment in advanced NSCLC. A pre-planned subgroup analysis showed that progression-free survival (PFS) was significantly longer for gefitinib than doublet chemotherapy in patients carrying specific EGFR mutations (EGFR exon 19 deletions or exon 21 L858R substitution mutations). Gefitinib became the first targeted therapy demonstrating significantly longer PFS than doublet chemotherapy, and was approved as first-line therapy for advanced NSCLC in Europe in 2009, and in the US in 2015 alongside a companion diagnostic test to identify suitable patients harboring the appropriate EGFR mutations.

The idea that cancer therapy can be guided by the tumor’s genetic makeup is an exciting one, and over the past couple of decades, a plethora of oncogenic targets and an armamentarium of drugs have been proposed and tested for various cancer types. For EGFR inhibitors alone, some of which can be serious and even lethal if untreated. Interestingly, it has been observed that patients who experienced more AEs also appeared to have more clinical benefit from their cancer treatments. Whether this is simply due to higher therapeutic dosage, or because of underlying differences in patients’ genetic makeups and immunological phenotypes, remains to be elucidated. Validated biomarker signatures that can predict treatment responses in specific subgroups of patients are still lacking.

We have come a long way since the days EGFR, CTLA-4 and PD-1/PD-L1 were discovered, but there remains much to learn. Tumors are well known for their genetic heterogeneity, and clonal evolution occurs regularly under selective pressure of cancer treatment, which helps tumors to evade immunosurveillance and become treatment-resistant. While this can be a drawback for existing targeted treatments, the emergence of tumor-specific neo-antigens, as a result, presents us with an opportunity to capture those neo-epitopes and turn them into new therapeutic targets. With advances in high-throughput next-generation sequencing, longitudinal whole-exome sequencing of tumor biopsies (or validated surrogates such as circulating tumor DNAs) can help monitor tumor clonal evolution and identify newly arisen tumor-specific antigens. Such information can then be used to design chimeric antigen receptor (CAR) T cells or multi-epitope cancer vaccines, which will be truly specific for that particular tumor in that particular patient at that particular time point. If truncal mutations are spotted and intervened early...
enough, prevention of resistant tumor clones may be preempted, thus improving therapeutic success and duration. In parallel, progress in diagnosti
c and prognostic accuracy and speed, coupled with the use of validated preclinical models to predict clinical responses, can help move us closer to the realization of precision medicine in cancer, whereby treatment can be delivered promptly on an evidence-based, case-by-case basis to cancer patients.

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