It is hard to believe that it has been over two decades since the sequence of the human genome was published in 2001, an incredible feat that enabled cancer biologists to study the cancer genome in new light. Only a few years later in 2004, two distinct groups simultaneously identified the presence of somatic mutations in the tyrosine kinase domain of the EGFR gene in a subset of patients with non-small cell lung cancer (NSCLC) responding to the EGFR tyrosine kinase inhibitor (TKI), gefitinib. These seminal studies were quickly followed by the discovery of other oncogenic drivers in NSCLC, involving mutations, translocations, and amplifications of genes such as *MET*, *KRAS*, *BRAF*, *ALK*, *ROS1*, *RET*, and *HER2*. Targeting these molecular aberrations with TKIs has led to a significant shift toward personalized treatment of lung adenocarcinomas instead of a "one size fits all" approach. Rapid progress in therapeutics has led to second and third generation TKIs and combinatorial approaches to circumvent resistance mechanisms. Examples of the latter include targets that result in resistance to *EGFR* TKIs, including *MET*, *AXL*, and the protein kinase C iota pathways, as well as targeting *SRC* and *PM-1* to overcome resistance in *MET* deregulated NSCLCs. Mutant *KRAS*(*G12C*), previously thought impossible to target with small molecule inhibitors, is now targetable using drugs such as sotorasib and adagrasib. Other approaches for *KRAS* mutant NSCLCs include targeting cytokines that promote growth and metastasis, such as IL-22. The success of small molecule TKIs has led to incorporation of these drugs in earlier stages of resected NSCLC. Advances in liquid biopsy technologies that study circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) will help identify patients who will benefit the most from adjuvant TKIs and detect recurrence earlier than surveillance imaging. Interestingly, many TKIs can cross the blood brain barrier; upfront use of third generation TKIs such as osimertinib has resulted in improved control of intracranial disease. The most common mutations in NSCLC affect *TP53*, especially in current or former smokers; targeting these mutations have not been successful to date, but efforts continue to identify downstream targets.

Therapeutic advances have also been made for those patients without actionable genomic alterations. The discovery of the immune checkpoint programmed death ligand 1 (PD-L1) and its cognate receptor PD-1 on activated T cells has led to an entirely novel class of drugs, immune checkpoint inhibitors (ICIs). These drugs have moved the field significantly in the treatment of all stages of NSCLCs. It is becoming apparent that PD-L1, while not entirely precise as a biomarker of response to ICIs, regardless serves as one way to predict response to ICIs. Next generation sequencing of NSCLCs has identified other biomarkers including tumor mutational burden and somatic mutations that may negatively impact response to ICIs. Apart from these genomic biomarkers, there is a burgeoning field studying a multitude of biomarkers predictive of response to ICIs, including clinical phenotypes such as gender and immune phenotypes of the tumor immune microenvironment. Using newer tools such as machine learning will increasingly allow us to identify patients who would most benefit from targeted therapies and immunotherapies and who might benefit from treatment de-escalation. While PD-L1 is the most studied of immune checkpoints used by NSCLCs to evade the adaptive immune system, other immune targets are also being actively studied; these include TIM-3 on the surface of exhausted CD8+ T cells and VISTA-PD-1H, to name a few. These are exciting times in lung cancer therapeutics.

Targeted Therapies in Lung Cancer provides a well-curated and deeply inspiring compilation of contemporary articles describing the past, present, and future directions of precision oncology for lung cancer, giving the reader a comprehensive understanding of lung cancer therapeutics and a glimpse of what the future might hold. Read on!

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