From the Editor

The landscape for lung cancer therapy has changed dramatically in the last 2 decades with the advent of antiangiogenic, growth factor receptor pathway, and, most recently, immunological targeting. Still a highly lethal disease, lung cancer has entered the realm of treatable cancers, notably with improvements in survival and quality of life.

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Ironically, many postulate that the same factors that cause a majority of lung cancers—namely, carcinogenic products in tobacco—also increase the mutational burden compared with cancer in nonsmokers, making these cases more immunogenic and likely to respond to immunotherapy.

In the review by Drs Jeffrey Zweig and Sukhmani K. Padda, the new concept of first-line treatment with checkpoint inhibition is discussed, covering the latest data, with many more such trials pending. Although it is clear that immunotherapy is effective in this setting, the key questions are which checkpoint inhibitor will emerge as the most effective, what level of PD-L1 expression (or other biomarkers) identifies the most likely patients to benefit, and whether there is a role for combination chemotherapy and immunotherapy. At present, the situation is very fluid, with trials reporting results in rapid succession and the FDA approving drugs for defined situations with equal rapidity.

Non–small cell lung cancer (NSCLC) with druggable genomic alterations, specifically *EGFR* mutations and *ALK* rearrangements, are still treated with the appropriate targeted therapy initially. In this issue's review article, "Frontline Immunotherapy in Non–Small-Cell Lung Cancer: For Which Patients Is Platinum Passé?" the story is laid out as to how pembrolizumab demonstrated first-line efficacy as a single agent compared with standard chemotherapy while nivolumab did not. Are the outcomes due to differences in the drugs themselves or study design? The table included in the review points out the key differences in PD-L1 threshold and the percentage of patients who crossed over to immunotherapy upon progression in the control arm that could explain the divergent results.

What about the combination of chemotherapy and immunotherapy? This has been posited as a potential synergistic interaction, each helping the other be more effective through mechanisms that are not yet clear. However, no differences in survival were seen in cohort G of the phase II Keynote-021 trial, even though in the small subset of 50% PD-L1 expression, an 80% response rate was seen. Also, PD-L1 expression was not required in the Keynote-021 trial, so the improvement in the primary endpoint of overall response, as well as time to progression, led to accelerated FDA approval in all nongenomically altered cases of nonsquamous NSCLC. An ongoing phase III trial of similar design could lead to final approval, with other such trials testing newer biological combinations also in progress.

The dizzying speed continues and, most importantly, is offering wider and better options than would have been imagineable just a few years ago.