Current state of immunotherapy: chipping away at the tip of the iceberg.

Nisha Mohindra*

Division of Hematology/Oncology, School of Medicine, Northwestern University Feinberg, USA

Accepted on 14 September, 2017

Editorial

The advent of immunotherapy has vastly altered the treatment landscape of many malignancies, with lung cancer being one of the biggest benefactors. We now have approved immunotherapy agents for both first- and second-line treatment of metastatic non-small cell lung cancer (NSCLC) as well as promising results from immunotherapy agents in extensive-stage small cell lung cancer (SCLC) [1-6]. Three check point inhibitors—nivolumab and pembrolizumab (monoclonal antibody against programmed death 1 (PD-1)), and atezolizumab (monoclonal antibody against programmed death ligand 1 (PDL-1))—have now demonstrated improved overall survival and a favorable toxicity profile when compared to chemotherapy, leading to their respective Federal Drug Administration (FDA) approvals [2-6].There is now evidence that immunotherapy may also have efficacy in earlier stages of disease. The PACIFIC trial demonstrated a significant improvement in progression-free survival with use of durvalumab (anti-PDL1 monoclonal antibody) as consolidation therapy compared to placebo after definitive chemoradiation for inoperable stage III NSCLC. Mature overall survival data are awaited [7].

Despite these advances, many practical questions regarding immunotherapy remain uncertain. Efforts are ongoing to define immune signatures predictive of treatment response, to determine the appropriate duration of treatment length, to develop strategies for optimal sequencing with other systemic agents, and to develop rational combination therapy. The number of trials focused on immune-oncology is considerable, with greater than 800 interventional trials identified within the United States (www.clinicaltrials.gov) [8]. Simultaneous trials are being run with a potential wealth of information to be produced. However, as we move forward in this field, we will need to understand the implications and nuances of these results and how they will be incorporated into, or even change, our current treatment paradigms. Correlative studies will also be important to understanding why some treatments work in certain patients and others failed to produce expected results. We have seen how similar agents directed at the same targets within the tumor microenvironment can yield differing results. For example, two anti-PD1 antibodies, nivolumab and pembrolizumab, were each compared with platinum-doublet chemotherapy in treatment-naïve metastatic NSCLC patients. Pembrolizumab produced an improvement in progression free survival and overall survival compared to doublet chemotherapy in patients whose tumors had at least 50% PDL1 expression [5]. However, nivolumab failed to produce improved outcomes compared to chemotherapy in patients with tumors harboring greater than 5% PDL1 expression [9]. Tumor selection and PDL1 cut-off may have contributed to these differing results, however the divergence between the two trials was notable and not entirely clear. As we move forward, we will need to ensure that we utilize the successes and limitations of prior trials to better refine biomarkers and design trials that answer clinically relevant questions.

The speed with which immunotherapy trials are being done is notable; however, we may be left with more questions than answers. Furthermore, the complexity and plasticity of the immune system makes accurate replication in the preclinical setting challenging. As we continue to discover newer agents directed at the immune microenvironment, we need to understand how these agents factor into immune regulation, how that regulation changes over time, and how best to define "benefit."

Immune check point inhibitors have improved survival for patients with NSCLC. The long term follow-up from the phase 1 dose-escalation expansion cohort of nivolumab in a heavily pretreated metastatic NSCLC population demonstrated a 5-year OS rate of 16%, notably exceeding that produced historically by chemotherapy [10].While these agents have improved outcomes for a subset of our patients, the majority of patients fail to derive benefit from these agents. The key to moving forward in immune-oncology will be to understand how to best personalize immunotherapy and determine whether more patients can benefit from this broad class of treatment. Further, we will need to determine how toxicity and patient-related outcomes factor into treatment decisions to define clinically meaningful results.

With any iceberg, one must proceed with caution, as the depth and magnitude are often far beneath the surface. Our current understanding of immune-oncology is likely only at the surface; however, with a greater understanding from the breadth of ongoing research, the magnitude and depth of potential from these agents may be vast.

References

1. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627-39.
2. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. . N Engl J Med. 2015;373(2):123-35.
3. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer CheckMate 012 results of an open-label, phase 1, multicohort study. The Lancet Oncol. 2017;18(1):31-41.
4. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results

From the Phase Ib KEYNOTE-028 Study. J Clin Oncol. 2017.

5. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.
6. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-65.
7. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017.
8. www.clinicaltrials.gov. 2017.
9. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017;376(25):2415-26.
10. Brahmer J, Horn L, Jackman D, et al. Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer: Clinical characteristics of long-term survivors. AACR Annual Meeting. 2017.

***Correspondance to**

Nisha Mohindra

Division of Hematology/Oncology, School of Medicine

Northwestern University Feinberg, USA

E-mail: Nisha.Mohindra@nm.org