Immunotherapy for non-small cell lung cancer: are we on the cusp of a new era?

Saiama N Waqar
Department of Medicine, Division of Oncology, Washington University School of Medicine, St. Louis, MO, USA

Daniel Morgensztern
Author for correspondence: Department of Medicine, Division of Oncology, Washington University School of Medicine, St. Louis, MO, USA
Tel.: +1 314 747 7409
Fax: +1 314 362 3895
dmorgen@dom.wustl.edu

In this editorial, we highlight the exciting advances in immunotherapy for the treatment of non-small cell lung cancer, with nivolumab being the first immunotherapeutic agent to be approved by the US FDA for the treatment of squamous lung cancer and several other promising immune checkpoint inhibitors currently being evaluated in clinical trials. The next step is to understand the mechanisms of resistance and develop rational combinations in an attempt to further improve the responses and survival in lung cancer.

Lung cancer is the leading cause of cancer-related mortality in the USA, with 162,460 deaths estimated by the American Cancer Society in 2015 [1]. Non-small cell lung cancer (NSCLC), which accounts for 87% of lung cancer, is most commonly diagnosed at an advanced stage, when it is essentially incurable, with palliative treatment aiming to improve symptoms and survival [2]. Although patients with targetable gene abnormalities such as EGFR mutations [3], ALK [4] and ROS1 fusions [5], usually achieve a significant benefit from targeted therapy, they represent a small percentage of the total NSCLC population. For the remaining patients, the treatment of choice for patients who are fit is a platinum-based doublet, with the addition of the VEGF inhibitor bevacizumab in eligible patients. Even in highly selected patients, the median overall survival is usually below 12 months. The benefit from second-line chemotherapy is substantially smaller, with overall response rate (ORR), median progression-free survival (PFS) and median overall survival being approximately 8%, 3 months and 8 months, respectively [6]. Therefore, there is an urgent need for novel therapies, particularly for the patients without targetable driver mutations.

Lung cancer has been considered poorly immunogenic, with no established benefit from cytokines or vaccines. Nevertheless, the recent development of checkpoint inhibitors provided a promising new approach for immunotherapy in patients with NSCLC. Immune checkpoints are inhibitory pathways that maintain self-tolerance and protect the peripheral tissues by modulating the immune responses [7]. The immune response is initiated by the recognition of antigenic peptides presented by the MHC on the surface of antigen-presenting cells by the T-cell receptor. This first signal is not enough to trigger a T-cell response, which depends on additional signaling. The amplitude and duration of the T-cell response depends on the balance between co-stimulatory and inhibitory signals. Therefore, the T-cell response may be amplified by agonists of co-stimulatory receptors or antagonists of inhibitory signals. The two checkpoint targets that have been studied more extensively in lung cancer are the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed death 1 (PD-1) receptor.

Role of immune checkpoint inhibitors

CTLA-4 is involved in the priming phase of T-cells after interacting with antigen-presenting cells. Following the binding of T-cell receptor to antigen-
presenting MHC, a second signal from the binding of B7.1 (CD80) and B7.2 (CD86) on antigen-presenting cells to CD28 on T-cells leads to activation of the latter and the up-regulation of CTLA-4, which inhibits the T-cell activation through binding to the same B7 receptors, dampening the amplitude of the initial immune response. Ipilimumab is a monoclonal antibody against anti-CTLA-4, which is approved for the treatment of melanoma and currently being tested in lung cancer. In a Phase II study, 204 patients were randomized to carboplatin plus paclitaxel and either placebo or ipilimumab [8]. Ipilimumab was started either with the first cycle of chemotherapy (concurrent arm) or in the third cycle (phased arm). The study met its primary endpoint of improved immune-related PFS for phased ipilimumab versus control arm (5.68 vs 4.63 months, log-rank p = 0.05), but not for concurrent ipilimumab versus control [8]. A Phase III trial is currently comparing chemotherapy alone to chemotherapy plus phased ipilimumab. Tremelimumab is another anti-CTLA-4 antibody currently under investigation.

PD-1 is expressed by T cells after prolonged antigen exposure and results in a negative regulation through binding to the ligands PD-L1 and PD-L2, which are expressed primarily in the peripheral tissue. The major role of PD-1 is to regulate the immune responses and minimize damage to bystander tissue by limiting the activity of T cells at the time of inflammatory response to infections. PD-L1 is commonly up-regulated in tumors, where binding to PD-1 in the T cells represents a mechanism of immune evasion leading to tolerance and tumor progression. Therefore, the blockade of the PD-1/PD-L1 pathway represents a rational target for immunotherapy and several monoclonal antibodies against PD-1 and PD-L1 have been developed.

Among the antibodies against PD-1, nivolumab (BMS-936558) was the first to be investigated. In a Phase I trial, among the 76 patients with NSCLC, 14 patients (18%) achieved partial response and 5 (7%) had stable disease for ≥24 weeks [9]. The PFS rate at 24 weeks was 26%. The outcomes were better in patients treated with 3 mg/kg every 2 weeks, with 6 out of 19 (32%) achieving PR and 41% being 24-week PFS. Drug-related adverse events (AEs) of special interest, defined as those with potential immune-related causes, included pneumonitis, colitis, hepatitis, vitiligo, hypophysitis and thyroiditis. There were three drug-related deaths due to pneumonitis, including two patients with NSCLC. Interim results from a Phase I study evaluating the combination of nivolumab and ipilimumab in patients with previously untreated advanced NSCLC are promising, with a reported ORR of 22% and stable disease seen in 33% of the patients treated [10].

MPDL3280A is a monoclonal antibody against PD-L1. In a Phase I trial, the response rates and 24-week PFS among the 53 patients with NSCLC were 23 and 45%, respectively [11]. Despite the small number of patients in each cohort, the study showed a difference in outcomes according to the intensity of PD-L1 staining in tumor-infiltrating immune cells (p = 0.015) but not in tumor cells (p = 0.920) by immunohistochemistry (IHC). Among the six patients with IHC 3, defined as ≥10% of the cells staining positive, both the ORR and 24-week PFS were 83%, with median PFS not reached. In contrast, among the 20 patients with IHC 0, defined as <1% of the cells being positive, the ORR and 24-week PFS were 20 and 44.7%, respectively. The treatment was well tolerated in the 277 patients with various histologies, with 35 (12.6%) grade 3 or 4 treatment-related AEs.

Pembrolizumab (MK-3475) is another anti-PD-1 monoclonal antibody which was evaluated in 221 patients with previously treated NSCLC [12]. The confirmed ORR was 16% in patients with PD-L1 expressing tumors and 10% for those without PD-L1 expression. Among patients with PD-L1 expressing tumors, the ORR for patients treated with 10 mg/kg every 2 or 3 weeks was 19 and 15%, respectively. The treatment was well tolerated, with most drug-related AEs being grade 1 or 2 in severity. The incidence of grade 3 or 4 AEs was 6% with three cases of pneumonitis. The ORR for patients with no PD-L1 expression, weak PD-L1 expression (1–49% tumor cells) and strong PD-L1 expression (250% of tumor cells) was 7, 15 and 37%, respectively [13]. MEDI-4736 and MSB0010718CE are two additional anti-PD-L1 antibodies currently being evaluated in multiple tumors including NSCLC.

The promising results from Phase II trials with anti-PD-1 and anti-PD-L1 led to the initiation of several randomized trials comparing checkpoint inhibitors to docetaxel. One of the studies, comparing 3 mg/kg of nivolumab given every 2 weeks to docetaxel in patients previously treated for squamous cell lung cancer, showed an improvement of 3.2 months in the nivolumab arm, leading to its approval by the US FDA on March 4, 2015.

Future perspectives

Although monoclonal antibodies against PD-1 or PD-L1 appear to be more effective than the standard chemotherapy with docetaxel, the response rates to a single agent in selected patients is below 20%. Furthermore, PD-L1 expression is still not an ideal predictive biomarker for benefit from therapy. One of the difficulties with PD-L1 is lack of a standardized test, with each pharmaceutical company using a different antibody in the IHC and with unknown concordance among the methods. Despite emerging data suggesting that strong PD-L1 staining may be associated with increased response rates, even patients with negative PD-L1 staining benefit from treatment, with response rates being comparable to second-line docetaxel or pemetrexed and better than standard chemotherapy in the third-line setting or beyond.

Immune checkpoint inhibitors are usually well tolerated with a favorable toxicity profile compared to standard chemotherapy, which can cause cytopenias and neuropathy. Grade 3–4 treatment-related AEs reported with nivolumab include fatigue (4%), pneumonitis (3%) and diarrhea (3%) [14]. Nevertheless, checkpoint inhibition is associated with unique AEs, which may require prompt recognition and treatment, with discontinuation of the offending drug and institution of therapy with corticosteroids and other supportive measures.
With the established benefit from PD-L1/PD-1 blockade in previously treated patients, ongoing studies are also evaluating the role of nivolumab (CheckMate 012) in the first-line setting in combination with platinum-doublet therapy, and in combination with erlotinib (NCT01454102) in EGFR-mutant NSCLC. The PACIFIC study is evaluating the role of MEDI4736 following chemoradiotherapy in patients with stage III disease (NCT02125461), where there is a potential role for increasing the cure rates. Studies in the adjuvant setting are also being planned. To paraphrase Winston Churchill’s Bright Gleam of Victory speech in 1942, this is not the end or even the beginning of the end, but perhaps the end of the beginning. Immunotherapy is the most promising treatment for advanced NSCLC in patients without targetable driver gene abnormalities. The next step is to understand the mechanisms of resistance and develop rational combinations in an attempt to further improve the responses and survival. Potential combinations with PD-1 blockade include anti-CTLA-4, tumor vaccines, indoleamine 2,3-dioxygenase-1 inhibitors, drugs targeting co-stimulatory receptors such as OX40 and inhibitory receptors including TIM3 and LAG-3.

Financial & competing interest disclosure

This publication was supported by the National Cancer Institute of the National Institutes of Health, Grant Number 1K12CA167540 and the Clinical Translational Science Award (CTSA) program of the National Center for Advancing Translational Sciences at the National Institutes of Health, Grant Number UL1RR024992. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Waqar is a K12 Paul Calabresi Career Development Award for Clinical Oncology scholar, and Morgensztern is a consultant for Celgene and is on the speaker’s bureau for Boehringer Ingelheim. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References