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Recent results of immunotherapy and perspectives for advanced NSCLC

Denis L. Jardim^{*1} & Debora de Melo Gagliato¹

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It is estimated that 224,390 new cases of lung cancer will be diagnosed in 2016 in USA, making it the second most incident cancer for all genders, only behind breast cancer. Additionally, lung cancer will be first cause of cancer death in USA during this year, causing 150,080 estimated deaths [1]. Although lung cancer mortality is slowly decreasing over the last years, data indicate of lung cancer diagnosis and treatment is still an unmet need. One of the key challenges is that approximately 70% of lung cancers are diagnosed in advanced stage, for which curative treatment is not possible [2]. The majority (85%) of lung cancers are classified as NSCLC, while the remaining represents small-cell lung cancers, which is associated with a dismal prognosis [3].

The standard treatment for advanced NSCLC over the last decade is chemotherapy, including platinum-based doublets. These regimens are associated with a response rate (RR) of approximately 20%, and median overall survival (OS) under 12 months [4]. For selected patients, after

four to six cycles of platinum-doublets regimens, maintenance therapy either with chemotherapy or EGFR inhibitors is associated with a modest improvement in OS [5]. One of the greatest advances obtained over the last decade for the management of advanced NSCLC is the consolidation of a molecular-based approach. Approximately 70% of NSCLC are non-squamous, and 40% of them may present with a targetable genetic alteration. Tyrosine kinase inhibitors are available for patients whose tumors harbor *EGFR* mutations, *ALK* translocations and, more recently, *ROS1* fusions. A matched targeted therapy is associated with an RR of 60–70%, and disease control that frequently surpasses 12 months [6]. Nonetheless, these therapies are not curative; treatment resistance development is almost a rule. In addition, there are no molecularly oriented therapies approved for advanced lung cancers with squamous cell histology. Second-line options for advanced NSCLC were restricted to docetaxel and pemetrexed.

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KEYWORDS

• biomarkers • immune-related toxicities • immunotherapy • lung cancer

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¹Centro de Oncologia do Paraná – Oncoville, Curitiba, Brazil

^{*}Author for correspondence: Tel.: +55 41 3083 0988; denisjardim@centrodeoncologia.com

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A third component on the fight against advanced NSCLC has been recently added: immunotherapy agents. The immune system is known for its importance as a mechanism against tumor initiation and progression. Lung cancer is considered a high immunogenic tumor, in part due to its elevated mutational load [7]. One of the efforts in the field of lung cancer was the development of cancer vaccines that could boost the host immune system against lung cancer cells. Melanoma antigen A3 (MAGE A3) is an antigen expressed in approximately 35% of patients with NSCLC. Recombinant MAGE A3 vaccine as an adjuvant treatment was tested in a randomized Phase II trial including patients with resected NSCLC [8]. This study suggested a beneficial effect for a genetic selected subgroup, which was not confirmed after a press release confirming that a large Phase III trial (MAGRIT trial) failed to meet its coprimary end points [9]. In fact, no vaccine is currently approved for the treatment of NSCLC.

Tumor cells display important molecular features that are very distinct from normal cells. Therefore, a great variety of tumor-associated antigens could potentially elicit host immune system recognition, with consequent tumor elimination. Immune checkpoint proteins compose the immune system pathway that is critical for maintaining self tolerance, modulating physiological immune responses [10]. Tumor resistance, particularly against specific T cells that target tumor antigens, is dependent on those checkpoints pathways. Antibody therapy directed against these negative immunologic regulators is proving very successful in a variety of malignancies.

CTLA-4, an immune checkpoint activated early in antigen presentation, is translocated to the plasma membrane upon interaction between B7 from the antigen-presenting cell (dendritic cell) and CD28 from the T cell. An antibody anti-CTLA-4 was the first class of immunotherapeutics tested in humans and US FDA approved [11].

Later, PD-1, a negative regulator of T-cell activity upon interaction with its ligands, PD-L1 and PD-L2, was evaluated in clinical practice [12]. Of note, PD-1 response regulates late-tumor response in peripheral tissues by effector T cells. The Phase I multicenter trial that evaluated intravenous administration of anti-PD-1 antibody to a variety of patients with advanced solid malignancies was a landmark trial. This

study consolidated the interaction of PD-1 and PD-L1 as an important target for therapeutic intervention. The anti-PD-1 induced durable tumor regression (objective RR of 6–17%) and stabilization of disease (rates of 12–41% at 24 weeks) in a heavily pretreated cancer cohort of patients [13].

Over the last months, important randomized clinical trials were reported testing monoclonal antibodies against PD-1/PD-L1 as a treatment for advanced NSCLC progressing after platinum-based treatment. The CheckMate 017 was a Phase III trial with 272 advanced squamous-cell NSCLC randomized to receive nivolumab at a dose of 3 mg/kg every 3 weeks or docetaxel as a standard second-line treatment. The study was positive for its primary end point, demonstrating an improvement in median OS with nivolumab (9.2 months) versus docetaxel (6 months; hazard ratio [HR]: 0.59; 95% CI: 0.44–0.79; $p < 0.001$) [14]. Importantly, nivolumab also improved progression-free survival (PFS; HR: 0.62; 95% CI: 0.47–0.81; $p < 0.001$) and RR (20 vs 9%; $p = 0.008$) and had a lower incidence of grade 3 and 4 treatment-related adverse events (AEs; 7 vs 55%). CheckMate 057 was a twin Phase III trial with an identical design, testing nivolumab for nonsquamous advanced NSCLC [15]. Similarly, OS was prolonged in this study (median: 12.2 vs 9.4 months [docetaxel]; HR: 0.73; 95% CI: 0.59–0.89; $p = 0.0015$). RR was higher with nivolumab (19 vs 12%; $p = 0.02$), but PFS was not different (HR: 0.92; 95% CI: 0.77–1.1; $p = 0.39$). Treatment-related AEs of grade 3 and 4 were lower with nivolumab (10 vs 54%). Both CheckMate studies were pivotal trials that led to FDA approval of nivolumab as a second-line therapy for metastatic NSCLC.

Pembrolizumab is another monoclonal antibody blocking PD-1 that was tested in a Phase II/III trial. KEYNOTE-010 was a three-arm trial that randomized 1034 patients with previously treated advanced squamous and nonsquamous NSCLC to received pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks versus docetaxel [16]. In this study, patients were selected based on a positive expression of PD-L1 (at least 1%) on tumor cells. Both pembrolizumab arms achieved a benefit in OS, and the 2 mg/kg dose was selected for accelerated approval by the FDA. Median OS for 2 mg/kg arm was 10.4 months versus 8.5 months for docetaxel (HR: 0.71; 95% CI: 0.58–0.88; $p < 0.0001$). This arm was also associated with higher RR

(18 vs 9%; $p = 0.005$), but did not prolong PFS (HR: 0.88; 95% CI: 0.74–1.05; $p = 0.07$). Incidence of grade 3 and 4 treatment-related AEs also favored pembrolizumab arm (13 vs 35%).

Lastly, POPLAR was the most recent published study. In this randomized Phase II trial, 287 patients with NSCLC were randomized to receive either docetaxel or the experimental agent atezolizumab, a PD-L1 checkpoint inhibitor, at a fixed dose of 1200 mg every 3 weeks [17]. Atezolizumab significantly improved the primary end point of OS compared with docetaxel (median OS: 12.7 vs 9.7 months; HR: 0.73; 95% CI: 0.53–0.99; $p = 0.04$). PFS was similar between arms (HR: 0.94; 95% CI: 0.72–1.23) as well as RR (17 vs 15%). Less treatment-related grade 3 and 4 AEs were also observed on atezolizumab arm (11 vs 39%). At the moment we wrote this article, atezolizumab is not yet FDA-approved for NSCLC.

Although different, these studies present important similarities. The most important one is that they all showed a significant OS benefit against a standard second-line therapy (docetaxel) and endorsed PD-1 and PD-L1 as a new active class of drugs for the treatment of advanced NSCLC. All these agents presented a better safety profile compared with chemotherapy. Most frequent AEs included fatigue, nausea and decreased appetite. Immune-related AEs are important concerns with these agents, but high-grade events rarely exceed 1% for the treated population. One interesting aspect is that, with the exception of CheckMate 017, PFS was not prolonged with checkpoint inhibitors. The recognition of this new response paradigm is of upmost importance for future clinical trials end clinicians. All these studies suggested that only looking to percentage of tumor shrinkage or time to progression will not capture the real benefit of immunotherapy. End points such as duration of response and OS (with a special attention to the tail of Kaplan–Meier curves) highlight a group of patients presenting a profound and long benefit, which was rarely achieved with other classes of therapies. Longer follow-up is needed to endorse that some patients may be even cured in the metastatic setting when treated with PD-1/PD-L1 inhibitors.

Identifying the subgroups of patients that will benefit with these agents is also a challenge, especially due to financial costs implicated with the use of these drugs. The disseminate use of checkpoint inhibitors for unselected NSCLC

patients might not be economically sustainable for most societies and development of biomarkers for treatment selection is a forthcoming need. At this moment, the expression of PD-L1 has been the candidate marker to guide therapy. Nonetheless, the FDA approval of nivolumab regardless of PD-L1 status and pembrolizumab approval for PD-L1-positive patients illustrates the controversy of the subject. There is a lack of standardization of PD-L1 testing demonstrated by these four randomized studies. Of note, tests differed according to biomarker evaluation, either prospectively (KEYNOTE) or retrospectively (CheckMate). Also, the antibody used, and type of cell in which PD-L1 expression was measured varied according to each specific study [18]. Overall, with exception of CheckMate 017, the other three studies consistently showed a trend toward improved benefit with increasing expression of PD-L1. Although it is arguable that even the low- or negative-expression group had an outcome similar to docetaxel when treated with checkpoint inhibitors, with a better safety profile, a cost-effective analysis is needed to better determine the feasibility of incorporating immunotherapy for this subgroup of patients. Alternatively, and perhaps more rational, is to explore different biomarkers that will identify long-term responders, which can possibly include exome analysis [19]. The inclusion of patients with the lower probability of benefit with single-agent checkpoint inhibitor on clinical trials combining different immunotherapies, or immunotherapy with other classes of therapies, is also a way to move forward and may extend the benefits of immunotherapy [20].

There was also a small difference on the schedule of these three checkpoint inhibitors. Nivolumab is administered every 2 weeks, while pembrolizumab and atezolizumab on a 3-weekly schedule. Especially for long-lasting treatment, as expected in some cases with immunotherapy, the less frequent schedule could be an advantage for patients living far from the treating centers. Another open question is the duration of treatment. Pembrolizumab was administered for up to 24 months, while nivolumab and atezolizumab were administered continuously until disease progression or development of toxicities. The observation that some patients continue to respond or do not present progression after treatment discontinuation due to toxicities, suggests that a more rational and optimized treatment should be pursued on clinical trials,

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specially to save costs for the health system and inconveniences for patients.

In conclusion, immunotherapy has landed as a new and valid option of treatment for advanced NSCLC in the form of PD-1 and PD-L1 checkpoint inhibitors. Additional research is urgently needed to address important clinical questions in order to make sure that patients and society will indeed enjoy a long and sustainable benefit.

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