



Editorial

Immunotherapy is Here to Stay: A New Treatment Paradigm in Lung Cancer



La inmunoterapia llega para quedarse: un nuevo paradigma de tratamiento en cáncer de pulmón

 Pedro Rocha^a, Edurne Arriola^{a,b,*}
^a Servei d'Oncologia Mèdica, Hospital del Mar, Barcelona, Spain

^b IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain

The treatment paradigm of lung cancer has dramatically changed in recent years with the introduction of immunotherapy. Immune checkpoints inhibitors (ICIs) are antibodies that target the brakes to the effective immune response mediated by CTLA-4 (cytotoxic T-lymphocyte-associated 4) and PD-1 (programmed death 1)/PD-L1 (programmed death ligand-1), releasing these inhibition points. This mechanism of action enhances T-cell mediated immunity, increasing T cell activation and trafficking to the tumour as well as potentiating the effector functions of the host's immune system.¹

ICIs, particularly the anti-PD-1/PD-L1 have changed the standard treatment for the majority of patients with Non-Small Cell Lung Cancer (NSCLC). In the metastatic setting, patients currently need to be sub-classified upfront into molecularly distinct groups through genomic testing (*EGFR*, *ALK*, *ROS1*) and need to be analyzed for PD-L1 status by immunohistochemistry. In patients with tumour PD-L1 expression $\geq 50\%$ (approximately 33% of all patients) in the first line setting, the anti-PD-1 agent pembrolizumab is superior to chemotherapy with a platinum doublet. In the phase 3 trial (KEYNOTE 024) pembrolizumab demonstrated an improvement of more than four months for median progression free survival (mPFS) and a 40% risk reduction of death compared to chemotherapy.²

Recently combination strategies (with chemotherapy or two ICIs) have shown very interesting results. The KEYNOTE 189 has demonstrated superiority of platinum-pemetrexed plus pembrolizumab in non-squamous NSCLC in all comers (regardless of PD-L1) with a gain of approximately 4 months in mPFS and potentially increased survival (immature data).³ In the metastatic squamous NSCLC setting (regardless of PD-L1 expression), the KEYNOTE 407 trial, which compares carboplatin-paclitaxel or nab-paclitaxel with or without pembrolizumab, demonstrated an increase in ORR (58.4% vs 35.0%) and OS of 4.6 months, both results

favouring the pembrolizumab containing arm.⁴ Moreover, the combination of anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) has been tested against chemotherapy in the CheckMate 227. In this study, patients were stratified according to tumour mutational burden (TMB) that accounts for the number of non-synonymous mutations per megabase in the tumour (mutations/megabase). The combination of ipilimumab plus nivolumab in patients with a TMB ≥ 10 (44.2% of all patients evaluated), achieved a two month increase in mPFS, with a 1-year PFS rate of 42.6% vs 13.2% in the chemotherapy arm, despite the toxicity from the combination which leads to discontinuation of 17.4% compared to 8.9% of patients who received chemotherapy. Importantly, the percentage of patients with response who had an ongoing response after 1 year was 68% with nivolumab plus ipilimumab and 25% with chemotherapy.⁵ The toxicity profile, the availability of tissue and techniques in not all centres to perform TMB could be one of the limitations to the use of this combination. These trials will change the standard treatment in the following months incorporating combination strategies in the first-line setting.

In second-line treatment, after chemotherapy failure, two ICIs (nivolumab, and atezolizumab) have demonstrated superior outcomes in patients when compared to standard chemotherapy with docetaxel regardless of histology or PD-L1 status. Pembrolizumab has shown improved efficacy with the same comparator in patients with PD-L1 $\geq 1\%$. These are currently approved treatments based on the results of CheckMate 017 and CheckMate 057 for nivolumab,^{6,7} KEYNOTE 010 for pembrolizumab⁸ and OAK trial for atezolizumab.⁹ All trials showed a clear benefit in Objective Response Rate (ORR) and Overall Survival (OS) with less toxicity compared to docetaxel. Overall, the results were similar between all trials with an ORR around 20% and median OS between 10 and 13 months. Interestingly, in all trials patients with higher PD-L1 expression showed an increased probability of response, although PD-L1 is not a perfect predictive nor prognostic marker in lung cancer. One of the unique and most important results with immunotherapy is the consistent long-term survival queue observed in all trials. The study with the

* Corresponding author.

 E-mail address: earriola@parcdesalutmar.cat (E. Arriola).

longest follow-up with immunotherapy in lung cancer has reported 16% of patients being alive after 5 years of follow up after stopping treatment (maximum immunotherapy duration of 2 years).¹⁰

In locally advanced unresectable patients, where chemoradiotherapy is standard treatment, immunotherapy with the anti-PD-L1 agent durvalumab has also shown benefit. In the PACIFIC trial, patients with stage III NSCLC who did not present a disease progression after platinum-based chemoradiotherapy were randomized to receive durvalumab or placebo during 1 year. A significant benefit in mPFS, of more than 11 months was demonstrated in the durvalumab arm, and with a median time to death or metastasis of 23.2 months with durvalumab Vs 14.6 months with placebo.¹¹ These results have incorporated immunotherapy with ICIs in the locally advanced and metastatic setting of virtually all patients with lung cancer.

Immunotherapy is now being evaluated in earlier stages. A recent report has evaluated the role of neoadjuvant immunotherapy in early stages (I, II and IIIA) for resectable NSCLC. In this small study patients received two cycles of nivolumab before surgery. Results revealed 45% of cases with major pathological response, with a few adverse events and without delay in planned surgery. If confirmed in larger studies, immunotherapy might represent a new tool in the neoadjuvant setting as well.¹²

ICIs have also been tested in Small-Cell Lung Cancer (SCLC) where systemic treatment has not changed for 30 years. Initial studies tested ipilimumab in combination with chemotherapy in advanced disease and despite the negative results compared with chemotherapy alone, a subgroup of patients presented durable responses and unexpectedly long survival.¹³

In the chemoresistant setting, the CheckMate 032, a phase 2 trial, compared nivolumab Vs nivolumab plus ipilimumab in this setting. Encouraging results with nivolumab but particularly from the combination were obtained in this refractory setting with 10–23% of objective responses, respectively. In a retrospective exploratory analysis, PD-L1 was not a predictive marker for benefit but TMB appeared to select patients who benefited most, particularly from the ipilimumab and nivolumab combination with a OS of 22.0 months.¹⁴ This strategy has now been included in the National Comprehensive Cancer Network guidelines incorporating immunotherapy to the treatment of SCLC.

Although ICIs have already changed the scenario of advanced NSCLC and SCLC, with better outcomes and less toxicity compared to traditional chemotherapy, one of the major challenges that remains is the selection of patients who will benefit from this approach. Another open question is which drug or combination might provide the strongest benefit for each patient. Therefore, although these drugs will be available for most patients, it will be important to identify robust predictive biomarkers of benefit in order to save unnecessary toxicities and financial cost.

Translational research in this field is of utmost importance and has provided hints of potentially relevant biomarkers in addition to PD-L1 expression and TMB, such as tumour lymphocytic infiltrate phenotype, gene signatures, mutation clonality or TCR (T-cell receptor) specificities.¹⁵

The future seems bright for patients with lung cancer who will receive immunotherapy and new approaches with new immunotherapy strategies (vaccines, TILs, CAR-T cells, other checkpoint agonists and antagonists) will certainly achieve promising outcomes for our patients.

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