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# Immune checkpoint inhibitors in lung cancer: the holy grail has not yet been found...

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Lung cancer is rich in molecular complexities and driven by different abnormal molecular pathways. Personalised medicine has begun to bring new hope for the treatment of patients with lung cancer, especially non-small cell lung cancer (NSCLC). The development of molecularly targeted therapy (small molecules and monoclonal antibodies) has significantly improved outcomes in the metastatic setting for patients with NSCLC whose tumours harbour activated oncogenes such as epidermal growth factor receptor (EGFR) and translocated genes like anaplastic lymphoma kinase (ALK). In addition, immune checkpoint inhibitors have also dramatically changed the therapeutic landscape of NSCLC. In particular, monoclonal antibodies targeting the programmed death-1 receptor (PD-1) /PD ligand 1 (PD-L1) pathway have emerged as powerful new therapeutic tools in several clinical trials, and some of them are already approved by the Food and Drug Administration (FDA) and American Medical Association (AMA). Immunotherapy is a novel type of treatment that has been tested in patients with metastatic NSCLC. Two anti-PD-1 drugs (nivolumab and pembrolizumab) and one anti-PD-L1 drug (atezolizumab) have been approved as monotherapy for second-line treatment for NSCLC. Recent trials in first-line treatment of advanced or metastatic NSCLC with nivolumab and pembrolizumab have shown promising and also controversial results. The FDA has approved pembrolizumab as a first-line treatment for patients with NSCLC whose tumours express PD-L1 in more than 50% cells based on Keynote-024 trial.<sup>1</sup> This high PD-L1 presence is only observed on about 30% of patients with NSCLC, limiting the use of the newly approved drug in less than one-third newly diagnosed patients.

The results of nivolumab activity, in Checkmate-26 study, compared with chemotherapy

were disappointing.<sup>2</sup> We are still trying to understand the possible reasons for the disappointing progression-free survival (PFS) data and trying to find out how to improve survival with first-line immunotherapy. Either combination with chemotherapy, immunotherapy or newer investigational agents and a good biomarker may be tried.

Keynote-021 tested if the addition of pembrolizumab to the standard doublet chemotherapy (treatment with two chemotherapy drugs, either pemetrexed + platinum in adenocarcinoma or gemcitabine + platinum in squamous cell lung carcinoma) improved outcomes compared with chemotherapy doublet alone.<sup>3</sup> The results were published in November and showed that the trial had met its primary overall response rate (ORR) endpoint, with 55% ORR in the combination treatment group versus 29% in the chemotherapy-alone group. This trial accrued patients with different levels of PD-L1 expression, and as might have been expected, those with PD-L1 in more than 50% of tumour cells had better responses to pembrolizumab + chemotherapy. Data from the Checkmate-012 trial have many drug combinations, and also combined nivolumab with different chemotherapy regimens in different types of NSCLC. The best response rate (47%) was observed in patients who received a combination of nivolumab with carboplatin and paclitaxel. Overall survival was also significantly improved for patients who received this combination treatment. PD-L1 expression appeared to play no role in treatment responses as per this study.

Several studies related to immunotherapy in NSCLC demonstrated that patients with EGFR mutations responded less to nivolumab and pembrolizumab. TATTON is a multi-arm phase Ib trial investigating osimertinib 80 mg in combination with durvalumab (anti-PD-L1 monoclonal antibody) in EGFR-mutant NSCLC.<sup>4</sup> Part A was a

dose escalation study in patients with advanced NSCLC who had received prior treatment with an EGFR-tyrosine kinase inhibitor (TKI). Part B was a dose expansion trial conducted in patients with advanced disease who were EGFR-TKI treatment-naïve. Part A included 21 patients receiving combination osimertinib plus durvalumab. Partial response (PR) was achieved by 12 patients, 9 of them had confirmed PR. Stable disease (SD) was achieved by other nine patients. In part B, of ten patients with evaluable data, eight patients achieved PR, which was confirmed in seven patients, and SD was observed in two patients. Responses were durable and translated into remarkable long-term survival. Both arms noticed increased incidence of adverse events ranging from 35% to 55%. Immunotherapy with EGFR-TKI combination appeared to have a good rational basis in terms of efficacy, relying on a presumption that a highly active therapy, such as an EGFR TKI in EGFR-mutant NSCLC, will lead to tumour apoptosis and enhanced immune priming, with resultant tumour lymphocytic infiltration and induced upregulation of PD-L1. But as explained by Gainor and colleagues from a limited number of patients with paired tumour specimens collected before and at the time of acquired resistance to TKI, they did not find clear changes in tumor-infiltrating lymphocytes (TILs) or PD-L1 expression.<sup>5</sup> Besides, in the mentioned study of concomitant treatment with osimertinib and durvalumab, there was an increase in treatment-related adverse events especially in terms of pneumonitis; hence, this trial was stopped.

Regarding pharmacoeconomics in NSCLC, immunotherapy has a high economic impact for any health system.<sup>6</sup> It is currently unknown for how long patients need to receive 'checkpoint inhibition therapy' in order to develop and sustain the appropriate immunological response. Pembrolizumab was approved as first-line treatment for patients with metastatic NSCLC with high PD-1 expression on October 24, becoming in 2016 the first immunotherapy drug to be ever approved as monotherapy for NSCLC. This approval has selected a restricted population with EGFR/ALK wild-type and PD-L1 expression more than 50% as biomarker when pembrolizumab is used. How economically feasible is immunotherapy in all patients with high PD-L1 expression in NSCLC outside a clinical trial? Future trials will be necessary to address this question. Simply continuing therapy indefinitely once a response is attained may not be necessary when being treated with novel immunotherapy agents, as opposed to the more traditional chemotherapy drugs that have a short PFS (<6 months).

The FDA previously approved pembrolizumab only in patients whose tumours showed the presence of the PD-L1 protein in more than 1% of their cells, whereas nivolumab was approved regardless of PD-L1 status in second-line settings. Finally, in first-line treatment for patients with metastatic NSCLC, nivolumab failed at its primary endpoint (PFS in patients who expressed 5%

PD-L1 or greater in tumour cells) when compared with pembrolizumab. The probable reasons are, first, the patients selected for participation in these trials were quite different from each other as more non-smokers were involved (11% vs 3%) in Checkmate-26 trial compared with Keynote-024. The second reason could be that the PD-L1 positivity (50% vs 30% in mentioned trails) cut-off values were different. Other reasons could be the variability of antibodies and immunohistochemical procedures for positive criteria, heterogeneity of PD-L1 expression and the dynamic expression of PD-L1 itself. Another aspect to consider is that in both studies, Checkmate-012 and Keynote-001, responses were higher in patients with KRAS mutations,<sup>7</sup> so it is interesting to know that KRAS mutations seem to have increased PD-L1 staining.

The FDA approval of two similar but distinct PD-L1 immunohistochemistry (IHC) tests (22C3 pharmDx and 28-8 pharmDx) acknowledges the potential of PD-L1 as a predictive biomarker and helps physicians decide which checkpoint therapy to prescribe. Unfortunately, not all patients respond to these therapies, and evaluation of biomarkers associated with clinical outcomes is crucial and ongoing.<sup>8</sup> Also, the interpretation of PD-L1 (IHC) testing results can be tricky and challenging. In connection with technical difficulties, we should consider that multiple staining methods and primary antibodies exist, with multiple cut-off when determining test positivity, and to all this preanalytical conditions must be added. This result in a high variability in staining performance and multiple readouts. Moreover, in regard to biological issues, there is controversy over whether to consider tumour cells or immune cells or both, and we should also take into account the dynamic heterogeneity of PD-L1 IHC across the tumour sample. This last issue causes a failure to capture tumour complexity, with all its microenvironment.<sup>9</sup>

In their work Challenges & Perspective of Immunotherapy Biomarkers, Ung and Kockx propose a systematic application of a methodology, the HistoOncoImmune, which harnesses histopathology data of the tumour with its corresponding molecular signatures.<sup>10</sup> The selected biomarkers are rigorously validated and can be implemented across multiple clinical trials of various sizes and geographical locations. This system results in an integration of histopathology and molecular technology and provides investigators and physicians a method to understand the tumour microenvironment activity and its interface with the immune system. It offers a methodology to attain a biomarker profile that predicts response or resistance to immune checkpoint therapy.

In summary, considering the results of these trials, it seems that the place of immunotherapy in first-line treatment will be in combination with chemotherapy. Pembrolizumab has a definitive role in first-line treatment for EGFR/EML-ALK4 wild-type NSCLC with PD-L1 expression more than 50%. The predictive

biomarkers that should be considered during single-agent immunotherapy of NSCLC are PD-L1 expression 50%, smoking, EGFR and ALK status, and KRAS mutation positivity. To establish a clear cut-off value of PD-L1 expression for appropriate immunological response and for new predictive biomarkers, further studies are required. Other important factors to be investigated in future trials are for how long a patient needs to receive ‘checkpoint inhibition therapy’ to address pharmacoeconomics and sustain an appropriate immunological response.

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