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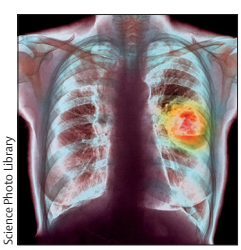
# Immune checkpoint inhibitors: a game changer for metastatic non-small-cell lung cancer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Immune checkpoint inhibitors have become pivotal for the treatment of non-small-cell lung cancer (NSCLC). PD-L1 inhibitors as monotherapy are the standard for second-line therapy (atezolizumab or nivolumab, or pembrolizumab when PD-L1 expression is at least 1%), and even for front-line therapy when PD-L1 expression is at least 50% (pembrolizumab). Front-line administration of standard chemotherapy plus pembrolizumab has been shown to increase survival compared with standard chemotherapy alone, regardless of PD-L1 status and in both squamous and non-squamous histologies.[1,2] Thus, in less than 5 years, immune checkpoint inhibitors have taken centre stage in metastatic disease treatment.

The CheckMate 017 and 057 trials[3,4] benefited from fast-track publication because of the magnitude of the results in favour of nivolumab, which was subsequently approved as a second-line (and beyond) treatment. The analysis by Scott J Antonia and colleagues[5] in *The Lancet Oncology* brings new and very interesting mature data on the long-term results of the four trials assessing second-line nivolumab in NSCLC.[3,4,6,7] The main finding of their pooled analysis is that 4-year overall survival was 14% after second-line and subsequent-line nivolumab therapy was started. Additionally, in the trial with the longest follow-up (CheckMate 003),[6] 6-year overall survival was 15%. Notably, Antonia and colleagues' findings are consistent with the long-term effects of pembrolizumab in the KEYNOTE-001 trial (n=550),[8] in which 5-year overall survival was 16% in previously treated patients (n=449) and 23% in treatment-naive patients (n=101).

Put in perspective with historical data in this setting (5-year survival of <5% in stage 4 disease[9]) and the control groups of the CheckMate trials (4-year overall survival of 5%), these results give hope for a long-term plateau in overall survival of around 15%, which is three-times higher than survival values before the immunotherapy era. These findings are a true game changer for patients diagnosed with metastatic NSCLC.

Objective response at 6 months appeared to be a surrogate marker for predicting overall survival in the pooled analysis of the CheckMate trials: 4-year overall survival was 58% for patients with objective response, compared with 4% for those who had progression. This finding remained consistent when calculating overall survival from inclusion, time of response, or time of progression after best overall response. Furthermore, and similar to the long-term results of KEYNOTE-001,[8] a positive PD-L1 status (PD-L1 expressed in at least 1% of tumour cells in immunohistochemistry) was a prognostic factor, given that 4-year overall survival almost doubled in PD-L1-positive compared with PD-L1-negative patients.

Finally, the study by Antonia and colleagues provides interesting data on late toxicity. Although the majority of treatment-related adverse events

were in the first year, a substantial proportion of them were in the second year and a lower proportion in the third year. However, the exposure-adjusted rate of pneumonitis appeared to be nearly stable (while infrequent) over the first 3 years of exposure. Although the CheckMate trials found few treatment-related adverse events occurring after the third year of exposure, the KEYNOTE-001 study reported that they might still occur, albeit rarely, between years 3 and 5. These results strongly suggest that patients should be monitored for—and their treating physicians should be acutely conscious of—treatment-related adverse events for the entire duration of exposure. However, unlike chemotherapy, there does not appear to be any cumulative toxicity with immunotherapy.

A remaining question is the optimal duration of immune checkpoint inhibitor treatment for patients with objective response. Should treatment be continued until progression or toxicities are seen? Should treatment be stopped in case of a prolonged objective response? Several trials, including IFCT-1701 DICIPLE (NCT03469960), are currently underway to offer answers to these questions.

Now that a combination of chemotherapy and immunotherapy is becoming the standard first-line treatment for all histologies and for all PD-L1 statuses, it is reasonable to expect greatly improved outcomes with an increasing proportion of patients alive 5 years after diagnosis. The horizon might still be far, but it appears that the tide has turned.

*Pierre-Jean Souquet, Sébastien Couraud
Service de Cancérologie Thoracique, Centre Hospitalier Lyon Sud, Institut de Cancérologie des Hospices Civils de Lyon, Lyon 69002, France (P-JS, SC); Intergroupe Francophone de Cancérologie Thoracique, Paris, France (P-JS); and EMR 3738 Ciblage Thérapeutique en oncologie, Faculté de médecine Lyon Sud, Université Lyon, Lyon, France (SC)
pierre-jean.souquet@chu-lyon.fr

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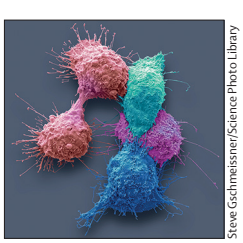
# Chemotherapy-free, but not quite free chemotherapy

Seasoned health-care providers caring for women with epithelial ovarian cancer will not-so-fondly recall the days when upfront clinical trials took several years to complete and consisted of thousands of patients randomly assigned to different combinations or sequences of a handful of cytotoxic drugs with generally disappointing findings.[1] The fact that the vast majority of women will eventually relapse after treatment with primary chemotherapy, and that most of these cases will be recognised at least 6 months after completion of primary chemotherapy, is well established. This platinum-sensitive group of patients generally has a relatively good prognosis following relapse and has traditionally been treated with carboplatin in combination with another cytotoxic drug, such as paclitaxel, gemcitabine, or liposomal pegylated doxorubicin.[2,3] After that, the available options historically consisted of the same short list of cytotoxic drugs, used and reused with diminishing results. Conceptually, this period 15–20 years ago was a much simpler time, with long intervals between the emergence of any practice-changing data. One common phrase circulating at oncology conferences and congresses was that by the time the study had been completed and reported, researchers would have already moved on to more promising options. Yet,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