

Nivolumab in pretreated non-small cell lung cancer: continuing the immunolution

Massimiliano Salati¹, Cinzia Baldessari¹, Bruna Cerbelli², Andrea Botticelli^{3,4}

¹Department of Oncology, University of Modena e Reggio Emilia, Modena Cancer Centre, Modena, Italy; ²Department of Radiological, Oncological and Pathological Sciences, “Sapienza” University of Rome, Rome, Italy; ³Medical Oncology Department, Sant’Andrea Hospital, Rome, Italy; ⁴Department of Clinical and Molecular Medicine, “Sapienza” University of Rome, Rome, Italy

Correspondence to: Massimiliano Salati, MD. Department of Oncology, University of Modena e Reggio Emilia, Modena Cancer Centre, Via del Pozzo 71, 41124 Modena, Italy. Email: maxsalati@live.it.

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Lung cancer is still the leading cause of both cancer-related incidence and mortality worldwide with roughly 1.8 million cases (12.9% of total) and 1.6 million deaths (19.4% of total) annually. Cytotoxic platinum-based doublets have been the backbone of first-line treatment for unselected advanced non-small cell lung cancer (NSCLC) for the last two decades with median overall survival (OS) hardly exceeding 12 months (1). Upon disease progression, the proven efficacy of second-line dated back to 1999 when docetaxel became the standard of care (2). Since then, few therapeutic advances have been made for patients with NSCLC progressing after first-line. Other treatment options have been introduced (pemetrexed for nonsquamous only and erlotinib) that are better tolerated but not superior to docetaxel in head-to-head comparison (3,4). Overall, second-line chemotherapy yielded response rates <10%, median progression-free survival (PFS) of 2 months and median OS of 7–8 months. Newer agents such as the oral angiogenesis inhibitor nintedanib and the anti-VGFR2 ramucirumab both approved in combination with docetaxel, the former by EMA in Europe and the latter by FDA in the US, have resulted in a 1-month absolute survival gain and increased toxicity compared to docetaxel alone.

The efficacy of chemotherapy in NSCLC has clearly plateaued and the addition of targeted drugs to

cytotoxics did not appear to be able to improve historical disappointing outcomes. However, from being quite stagnant for a span of decades, the therapeutic scenario has rapidly evolved in the last few years. The advent of immune checkpoint inhibitors (ICI) has produced a paradigm shift in the fight against cancer. The concept of harnessing the immune system to recognize and attack neoplastic cells though already exploited has finally proved effective in oncology. Unprecedented results in terms of both efficacy and safety have been lately reported by large phase III trials investigating ICI in NSCLC (5-9). On this basis, for NSCLC without oncogenic driver alterations, the anti-PD1 pembrolizumab should be considered a standard first-line treatment in patients with PD-L1 expression $\geq 50\%$ (KEYNOTE-024 trial) and a second-line option in patients with PD-L1 expression $\geq 1\%$ (KEYNOTE-010 trial). Accordingly, the anti-PD1 nivolumab (CheckMate-017 and CheckMate-057 trial) and the anti-PD-L1 atezolizumab in the US (OAK trial) are other approved treatments, regardless PD-L1 status, for previously treated NSCLC.

Despite early evidence of sustained activity of nivolumab from a phase I single-arm study in heavily pretreated patients with a 5-year OS of 16% (10), so far long-term efficacy and safety data for ICI from randomized trials have been lacking in NSCLC. Hence, the results of nivolumab,

the first anti-PD1 inhibitor antibody to be tested, in comparison to conventional chemotherapy have been eagerly anticipated.

Horn and colleagues (11) reported a 2-year follow-up update on nivolumab in previously treated NSCLC by pooling together data from both CheckMate-017 and -057, for squamous and non-squamous NSCLC, respectively. The design of the two trials was quite similar in nature, being two multinational, randomized, phase III trials, comparing nivolumab to docetaxel in stage IIIB/IV NSCLC with disease recurrence or progression on or after one prior platinum-based chemotherapy regimen. In total, 272 patients with squamous and 582 with nonsquamous histology were randomly allocated in a 1:1 fashion to either nivolumab 3 mg/kg every 2 weeks or docetaxel 75 mg/mq every 3 weeks, until disease progression and/or unacceptable toxicity. In the nivolumab arm, upon initial disease progression, continuation of study treatment was permitted if clinically beneficial and well tolerated. The superiority of nivolumab over docetaxel has continued to be maintained over time regardless of histology, with a relative reduction in the risk of death of 28% (HR 0.72; 95% CI, 0.62–0.84). After a minimum follow-up of 24.2 months, 2-year OS with nivolumab versus docetaxel was 23% *vs.* 8% in squamous NSCLC and 29% *vs.* 16% in nonsquamous NSCLC. Also, PFS and overall response rate (ORR) results kept favouring nivolumab for both NSCLC subtypes.

More interestingly, nivolumab responses were long-lasting: 10 out of 27 (37%) responders with squamous and 19 out of 56 (34%) responders with nonsquamous histology had still ongoing responses as of the data cutoff, while no patients in the docetaxel arm demonstrated long term benefit. In addition, median duration of response with nivolumab was 25.5 and 17.2 months in squamous and nonsquamous NSCLC, compared to 8.4 and 5.6 months respectively with docetaxel. In accordance with earlier reports, nivolumab treatment was safe and better tolerated than docetaxel. Treatment-related adverse events were lower in the nivolumab arms (any grade, 68% *vs.* 88%), mainly mild in grade (grade 3–4, 10% *vs.* 55%), and well-managed according to toxicity management guidelines. Moreover, neither new treatment-related deaths nor unexpected events were reported since the primary analyses.

As time goes by, we are getting more and more familiar with the delivery of immunotherapy also in NSCLC akin to other cancer types previously and we are learning how to exploit its potential as well as to face and overcome its limitations.

In both the Checkmate-017 and -057 a substantial subgroup of NSCLC patients achieved a long-term benefit, even though they represent not more than 15–20% of the whole study population. Moreover, a novel group of patients so-called hyperprogressors have been described as patients with an accelerated rate of cancer growth and clinical deterioration on anti-PD-1 treatment. So, which are those most likely to benefit from anti-PD-1 therapy and those who are not and thus potentially amenable to other second-line options (e.g., nintedanib/docetaxel)? One of the greatest challenges for immuno-oncology is to identify biomarkers predictive of response but also of resistance to ICI. To date no reliable predictive factors have been identified in NSCLC, although some clinical parameters have been suggested to have a negative predictive value, i.e., high tumour burden, malignant pleural effusion, poor PS, rapidly progressive disease, brain metastases. However, these factors do not inform about neither patients' immune fitness nor tumour immunological status.

Until now the most extensively investigated biomarker is PD-L1, which is expressed both on tumour and the inflammatory cells. Nonetheless, the determination of PD-L1 displays several issues: firstly PD-L1 is an extremely dynamic marker, secondly they exist different immunohistochemical antibodies and assays in clinical practice resulting in different cut-off points, and lastly lung biopsies may not be representative of the entire tumour. Despite its still controversial role, several studies demonstrated an association between high level of PD-L1 expression on tumour cells and increased response to anti-PD-1/PD-L1 treatment. Another promising biomarker is tumour mutational load, which is well-known to reflect neoantigens burden potentially recognized by the immune system. This has been shown to correlate with better anti-PD-1 response for both pembrolizumab and nivolumab. The same findings were replicated by atezolizumab in the OAK study on peripheral blood. However, mutational load does not take into account neither transcriptomic nor proteomic modifications that depend on other mechanisms such as epigenetic and hence the rationale of the ongoing studies combining anti-PD1-PD-L1 and HDAC inhibitor (ClinicalTrials.gov Identifier: NCT02437136). More interestingly, the co-occurrence of a high tumor mutational burden and PD-L1 expression level of at least 50% has been suggested as predictor of response to nivolumab in NSCLC since in this subset ORR was 75% compared to 16% in that with neither factor (12). Although intriguing, this data must be taken with caution as result of a comparison not powered

for statistical analysis and thus in need of a prospective validation. Moving to a way to overcome anti-PD1/anti-PD-L1 resistance, as already established for chemotherapy, this could be to combine different strategies following the hypothesis that they can enhance each other activity in an additive or synergist fashion by acting complementary. For instance, chemotherapy and radiotherapy are known to induce immunogenic death, TKIs can increase antigenic presentation and modify vascularization thus helping T-cell trafficking, and immunotherapeutic associations can contrast different escape mechanisms used by tumor cells (13). Which could be the best combinatorial approach is currently the subject of intense research.

With nearly one third of responding patients still having an ongoing response to nivolumab at 2 years and others continuing to derive benefit even after study drug discontinuation across both CheckMate-017 and -057, the question of optimal duration of ICI in NSCLC is raising in the researchers' community. Particularly, whether continuous nivolumab exposure is necessary for achieving long-term benefit, also in the light of increasing economic costs. Recent evidence from the ongoing randomized CheckMate-153 trial, has suggested that could be unsafe to stop nivolumab after only 1-year treatment as showed by the inferior 1-year PFS (40% *vs.* 65%, HR 0.42, 95% CI, 0.25–0.71) and a trend towards worse 1-year OS (81% *vs.* 88%) compared to continuous treatment until disease progression (14). These interesting findings warrant further confirmation in properly designed prospective randomized trials.

A further point that remains to be clarified concerns nivolumab role in patients with sensitizing EGFR and ALK alterations. The updated data reported by Horn *et al.* have confirmed previous results showing superimposable outcomes for patients with EGFR-positive disease when treated either nivolumab or docetaxel. Contrarywise, those without EGFR mutation experience improved OS and PFS with nivolumab. Although referring to small numbers, these findings are in line with those of a meta-analysis which demonstrated no OS advantage for the EGFR-mutant subgroup, but a 34% reduction in the risk for death for the EGFR wild-type subgroup (15). A lower mutation load, lack of T-cell infiltration, upregulation of the immunosuppressive molecule CD73 and reduced IFN gamma signature are contributing factors thought to set the stage for an immunotolerant and poorly immunogenic microenvironment in patients harboring EGFR-mutations (16,17). Differences in PD-L1 expression according

to EGFR mutations types may also account for the disappointing response to immune checkpoint blockade seen in this patients' population (18). Still, the brand-new evidence that abnormal gut microbiome composition and antibiotics could negatively affect the outcome of PD-1 blockade in advanced cancer patients, including NSCLC, and how to prevent primary resistance by manipulating gut ecosystem is a captivating research field just in its infancy (19,20). Finally, a plethora of novel immunotherapeutics among other anti-IDO, anti-TIM-3, and anti-LAG3 agents, chimeric antigen receptor T cell therapy, dendritic cell vaccine and viral vector vaccine has lately entered early clinical evaluation in NSCLC, further raising the bar of our expectations. Although until very recently NSCLC treatment has lagged behind that of other cancer types, the introduction of immunotherapy is a major breakthrough potentially able to catch up in the foreseeable future. There is certainly a long way to go but the scenario has never been brighter before for patients with NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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