Editorial

Nivolumab as first line monotherapy for advanced non-small cell lung cancer: could we replace first line chemotherapy with immunotherapy?

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While conventional chemotherapy has been the cornerstone of first line treatment of advanced non-small cell lung cancer (NSCLC) historically, there is a great appeal to the concept of bypassing this potentially toxic and only modestly effective approach with molecularly targeted therapies or immunotherapies that hold the promise of greater efficacy and improved quality of life. Over the past 5-10 years, we have seen novel agents such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors demonstrate striking activity and a generally favorable toxicity profile that have led these agents to be widely adopted as first line therapy ahead of conventional chemotherapy, albeit only in narrowly and molecularly defined subsets. One of the leading aspects of the excitement around immune checkpoint inhibitors such as nivolumab is that they appear to have impressive clinical activity that is not limited to a particular histologic subtype or comparatively small subpopulation, and with a very different and typically milder range of adverse effects than standard chemotherapeutic agents.

Earlier work with nivolumab has demonstrated that this agent can lead to dramatic and durable responses in a minority of patients with advanced NSCLC, as well as some other cancer types (1). This work, however, was in previously treated and sometimes very heavily pre-treated patients, in whom immunotherapy was not competitive with established therapies. While the prolonged responses seen in a minority of patients in this early work suggest the possibility of obviating more toxic and potentially less effective chemotherapy, we have yet to see direct comparisons of the efficacy of nivolumab or other immune checkpoint inhibitors in head to head trials with established chemotherapy standards. Clinical trials that have completed enrollment already directly compared second-line docetaxel to nivolumab in patients with squamous (2) or non-squamous (3) advanced NSCLC, though we don't have results at this time. But to have an immune checkpoint inhibitor displace initial treatment with cytotoxic chemotherapy as the cornerstone of initial therapy for the majority of patients with advanced NSCLC, we would need to see comparable or superior efficacy with the improvement in toxicity profile that these agents promise.

The abstract by Drs. Gettinger and colleagues (4) represents a promising initial effort to assess the potential utility of nivolumab as monotherapy preceding conventional chemotherapy in a relatively broad clinical population that includes patients with either squamous or non-squamous NSCLC, while also seeking to determine whether patients with tumor PD-L1 expression above a 5% threshold using their particular test (DAKO kit, clone 28-8) is associated with significantly greater probability of clinical benefit with nivolumab than PD-L1 negative tumors (4). The study, with a primary endpoint of assessing safety and tolerability of nivolumab as first line therapy, reported at ASCO on the first 20 patients, who split fairly evenly between squamous and adenocarcinoma NSCLC histologies (ten adenocarcinoma, nine squamous, one other); patients with an EGFR mutation or ALK rearrangement were excluded. Patients had been followed a median of 66 weeks.

At the time of study analysis, 15 of the 20 (75%) had

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discontinued therapy, 11 of whom (55%) for disease progression, two (10%) for adverse events (AEs), and one additional patient each (5%) for an unrelated AE or per patient request. Six patients (30%) had an objective response, including two (10%) with a complete response; among these patients, responses were ongoing in four (20%). Another seven patients (35%) demonstrated stable disease as their best response, with progressive disease in the remaining seven patients (35%). There were no clear differences based on tumor histology, with objective responses seen in two of nine (22%) patients with squamous NSCLC, compared with four of 11 (36%) patients with non-squamous NSCLC.

The biomarker of PD-L1 expression was explored in 17 patients, of whom 10 (59%) were designated as PD-L1 positive, of whom five (50%) were responders, and seven (41%) as PD-L1 negative, among whom there were no responders (0%). However, the progression free survival (PFS) at 24-week and 1-year survival were relatively comparable between PD-L1 positive and negative patients (70% *vs*. 57% and 80% *vs*. 71%, respectively).

As has been characteristic of research with immune checkpoint inhibitors thus far, tolerability was overall quite favorable. Specifically, while 17 of 20 patients (85%) experienced at least one treatment-related AE, these were only grade 1 or 2 in 13 of these 17 patients (76%). The two patients who terminated treatment due to serious AEs of elevated transaminases or cardiac failure [1 (5%) each] both recovered after discontinuation of treatment. There were no cases of pneumonitis observed.

What conclusions should be drawn from this early work? A preliminary report on 20 patients cannot overturn the overwhelming preponderance of data on the survival benefit of conventional chemotherapy accumulated over hundreds of trials run over several decades. What this limited report offers is a clear proof of principle that a minority of patients can benefit profoundly from nivolumab, experiencing dramatic and potentially prolonged responses to immunotherapy with good tolerability.

The key issue in interpreting the significance of this research effort is to place it into proper context rather than view it with "irrational exuberance" of envisioning a chemotherapy-free world for most lung cancer patients. At this point, we must recognize that the response rate is very comparable with but not clearly superior to that of standard chemotherapy regimens in the first line setting, and that having 10% of patients discontinue treatment due to prohibitive AEs, with another 10% coming off due to unrelated AEs or clinical judgment does not represent an overwhelming signal of dramatically improved efficacy or tolerability for nivolumab in this setting. While a subset of patients experience marked benefits, tumor histology does not provide predictive guidance about which patients are most likely to benefit. The leading candidate as a predictive biomarker, PD-L1, has no remote consensus for adoption in terms of lab-based technique or threshold for designating patients as positive or negative; accordingly, correlations of outcomes of PD-L1 expression with clinical outcomes of patients treated with various immune checkpoint inhibitors have been most notable for their consistency only in demonstrating a higher response rate in patients considered as PD-L1 expressing, but this marker is neither necessary nor sufficient for observing an objective response or prolonged survival with immune checkpoint inhibitors (5).

Taken together, these data offer a glimpse of a possible future in which nivolumab or another immune checkpoint inhibitor could displace standard chemotherapy as first line therapy for some patients with advanced NSCLC. Before that happens, however, we will need to be able to reliably identify the subset of patients most likely to benefit from immunotherapy and see large-scale trials that directly compare nivolumab or another immune checkpoint inhibitor directly against conventional platinum-based doublet chemotherapy with a prospectively defined improvement in efficacy and/or tolerability.

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