

## Optimal Therapy for Advanced Non-Small Cell Lung Cancer Without Driver Alterations

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There are several pieces of good news regarding outcomes of patients with lung cancer. First, mortality rates are falling, and survival rates are increasing in both men and women (1,2). Second, newer therapies are improving survival while reducing toxicity, which combine for considerable improvement in quality as well as quantity of life. One major improvement in therapy has been the development of immune checkpoint inhibitors (ICIs), which thus far have consisted of monoclonal antibodies that bind to either PD1 or PD-L1 blocking the interactions of these cell surface receptors, which allows for enhanced lymphocyte killing of tumor cells (3-6). The development of multiple ICIs provides more choices for physicians and patients while increasing complexity of treatment decision making.

In this issue of the Journal, Man et al. (7) provide a systematic search of trials of ICIs alone vs chemotherapy in patients with advanced non-small cell lung cancer as either first- or second-line therapy. To simplify the analyses, the authors chose several survival endpoints including 2- and 3-year overall survival (OS) and 1- and 2-year progression free survival (PFS), as well as objective response rates (ORRs). In years past, median survival times were in weeks to months in second-line therapy and about 12 months in first-line therapy. The assessment of both long- and short-term survival and response in this meta-analysis is key because a clinically important minority of patients receiving ICIs experience a long response, often measured in years.

In treatment-naïve patients, benefits with PD-1 blockade over chemotherapy were seen for ORRs in patients expressing PD-L1 of at least 50%, in 2-year OS for PD-L1 of at least 1%, and 3-year OS for unselected patients as well as in 1-year PFS, 2-year PFS in PD-L1 of at least 1% (6). Thus, in the group with the highest PD-L1 expression ( $\geq 50\%$ ), all endpoints favored immunotherapy over chemotherapy. Unfortunately, there were no comparisons of trials with chemotherapy plus immunotherapy compared with immunotherapy alone. As first-line therapy, PD-1 blockade resulted in an ORR of 39.7% (95% confidence interval [CI] = 36.2% to 43.1%) for patients with PD-L1 of at least 50%.

Although Man et al. (7) performed no direct comparison of immunotherapy alone with chemotherapy plus immunotherapy, the ORRs in trials with chemotherapy plus immunotherapy tend to be higher than in trials with immunotherapy alone (8-12). Thus, although this study does not address this issue, it may be that highly symptomatic patients (a minority) in the highest PD-L1 group would do best with combined therapy, whereas the majority receive single-agent ICIs.

In the group with a PDL1 of 1%-49%, the trials evaluated by Man et al. (7) compared immunotherapy with chemotherapy alone again excluding trials with combined chemoimmunotherapy. As their study indicated, 1- and 2-year PFS and 2- and 3-year OS favored immunotherapy over chemotherapy in this group (7). The ORR was 16.6% (95% CI = 13.0% to 20.2%) in patients with PD-L1 of 1%-49%. Subsequent trials not reviewed by Man et al., however, have demonstrated higher ORRs and longer OS benefit for combined chemotherapy and immunotherapy over chemotherapy in this PD-L1 group (8-13).

In the group with no PD-L1 expression, first-line PD-L1 blockade was associated with a lower ORR (8.3%, 95% CI = 0.0% to 17.4%) and lower 2-year OS compared with chemotherapy in the trials analyzed (7). In other trials not analyzed by Man et al. (7), combined chemoimmunotherapy has been associated with a higher ORR and longer OS compared with chemotherapy alone for PD-L1-negative patients (8-13).

In the second-line setting, the authors report that ICIs (pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, and camrelizumab) improve survival outcomes compared with chemotherapy in patients across all PD-L1 subgroups with advanced non-small cell lung cancer (7). This finding is most important in parts of the world where first-line immunotherapy is not available.

The finding that several ICIs alone improved survival over chemotherapy alone in the first-line setting in patients with high PD-L1 has highlighted the importance of determining the PD-L1 score at diagnosis and providing access to one or more of these agents. The similarity of single-agent immunotherapy to chemotherapy in patients with PD-L1 of 1%-49% shown in this

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analysis and the inferiority of single-agent immunotherapy to chemotherapy in patients with PD-L1 of 0% coupled with other trials showing superiority of combined chemoimmunotherapy in these groups suggest that combined chemoimmunotherapy should be standard first-line therapy for patients with PD-L1 of less than 50%. It is important that we now have several choices of ICIs with or without chemotherapy and that patients are appropriately evaluated and treated.

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## Data Availability

Not applicable.

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