time spent in hospital [7–9]. The competence of specialists in an organizational structure of early specialist palliative care should be discussed and clarified. We believe that the palliative care specialist working within oncology needs to be specialized both in oncology and palliative care. The reimbursement system needs to favor the integration of palliative care by economical incentives given to the hospitals. In our country, such an incentive has had major impact on the development of the specialist palliative care [10].

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Funding
None declared.

Disclosure
SK is a stakeholder in Eir Solutions. RH declares no conflict of interest.

More valuable than platinum: first-line pembrolizumab in advanced stage non-small-cell lung cancer

Since the 1980s, platinum-based chemotherapy has been the cornerstone of front-line therapy for advanced stage non-small cell lung cancer (NSCLC). However, the advent of programmed death 1 (PD-1) pathway inhibitors has transformed the management of metastatic NSCLC. In the pivotal randomized, phase III KEYNOTE-024 trial, among NSCLCs with high programmed death-ligand 1 (PD-L1) expression, the PD-1 inhibitor pembrolizumab demonstrated a superior response rate, progression free survival (PFS), and overall survival (OS) compared with platinum doublet chemotherapy [1], leading the U.S. Food and Drug Administration to approve pembrolizumab in October 2016, for the first-line treatment of NSCLCs with a PD-L1 tumor proportion score (TPS) of $\geq 50\%$ [2].

Promising activity for pembrolizumab as initial therapy for NSCLC was first reported in the open-label phase 1b KEYNOTE-001 trial, which included 101 treatment-naïve NSCLC patients [3]. In this issue of the *Annals of Oncology*, Hui et al. [4] report updated results from these 101 patients, now with a median follow-up of almost 2 years. As with the KEYNOTE-010 trial of pembrolizumab versus docetaxel among previously-treated NSCLC patients [5], PD-L1 immunohistochemical (IHC) staining also appears to be a predictive biomarker for response to pembrolizumab in the treatment-naïve setting. For the entire cohort of first-line patients in the KEYNOTE-001 study, the overall objective response rate (ORR) was 26.7%, with a 12-month PFS of 35%, and a median OS of 22.1 months. However, among the subset of patients ($n = 27$) with high PD-L1-expressing tumors (TPS $\geq 50\%$), the ORR was an impressive 51.9%, with a 12-month PFS of 54%, and a 12-month OS of 85%, as compared with an ORR of 17.3% in cases with low PD-L1 expression (TPS 1%–49%) and an ORR of 8.3% in PD-L1 negative cases (TPS <1%). Importantly, pembrolizumab continued to be well-tolerated over time, with only 12 out of the 101 patients (11.9%) experiencing grade 3 or 4 treatment-related adverse events. Furthermore, no treatment-related deaths have been reported to date.

The findings of the KEYNOTE-001 and KEYNOTE-024 trials have already resulted in a paradigm shift in the first-line management of stage IV NSCLC with high PD-L1 expression. However, as the authors discuss, predicting which patients are most likely to respond to PD-1 inhibition continues to be a challenge, and PD-L1 IHC remains an imperfect biomarker for the oncology community. In the first-line NSCLC CheckMate-026 study, nivolumab did not meet the primary endpoint of superior PFS compared with platinum doublet chemotherapy among tumors with a PD-L1 score of $\geq 5\%$, as assessed by the Dako 28-8 PD-L1 antibody for IHC. Perplexingly, among the subset of patients with a PD-L1 score of $\geq 50\%$, nivolumab showed no benefit over chemotherapy [6], even though the 28-8 antibody and the 22C3 PD-L1 antibody used in the KEYNOTE-024 study appear to be highly concordant when compared head-to-head in immunohistochemical assays [7]. Are there meaningful biologic differences between these PD-1 inhibitors or were these apparent inconsistencies between trials due to differences in patient selection or...
interpretation of PD-L1 staining? Among patients in these two studies with a PD-L1 score of ≥50%, whether even higher proportions of PD-L1 positive cells (e.g. TPS of 50–75% vs. 75%–100%) or variations in the intensity of PD-L1 staining (i.e. 1+, 2+, 3+) impact the likelihood, depth, or duration of response to PD-1 inhibition is unknown.

Since only half of patients with a PD-L1 TPS of ≥50% achieved an objective response to pembrolizumab in the KEYNOTE-001 study, are there additional genomic factors that affect a cancer’s sensitivity to PD-1 inhibition? Do differences in total mutational load differentiate pembrolizumab responders from non-responders among cancers with high PD-L1 expression [8]? Are there specific genomic alterations that can potentiate or dampen the efficacy of immune checkpoint inhibitors in this population? For example, mouse and human studies have demonstrated that mutations in genes such as TP53 and STK11/LKB1 can alter the tumor immune microenvironment in lung adenocarcinoma [9,10]. Furthermore, inactivating mutations in JAK1/2 in melanoma are associated with primary and acquired resistance to PD-1 inhibitors [11,12]. Conversely, an activating mutation in JAK3 has been shown to promote PD-L1 expression in NSCLC and was associated with response to PD-L1 inhibition in one patient [13].

In addition to analyzing tumor cell PD-L1 expression and genomics, it will be important to develop robust methods to quantify and phenotype tumor-associated immune cell subsets to better understand how the immune microenvironment modulates the response to immune checkpoint inhibitors in NSCLC. Techniques such as flow cytometry [14], multiplexed immunofluorescence [15], single-cell RNA sequencing [16], and gene expression analysis [17] represent some of the ongoing efforts to more comprehensively profile immune cells within tumors. Given the rapidly growing number of immunomodulatory agents in clinical development, these technologies will hopefully enable the rational selection of combination therapies directed at a cancer’s particular immunophenotype.

Along with discovering additional biomarkers of response to immune checkpoint inhibitors, further studies are necessary to determine which patients are at increased risk for developing serious toxicities from these drugs. Although the frequency of grade 3 and 4 immune-related adverse events was low in KEYNOTE-001, life-threatening side effects can arise at any point throughout the course of treatment with immunotherapy or, in some cases, after treatment has been discontinued. Importantly, our understanding is currently quite limited as to when, how, and why some patients experience potentially devastating toxicities to immunotherapy such as pneumonitis, myocarditis, colitis, or hepatitis, while other patients have virtually no significant side effects. Severe immune-mediated adverse events, although uncommon, can be difficult to manage and typically preclude further treatment with immune checkpoint blockade. It would be useful to determine whether the level of PD-L1 expression in NSCLC also predicts the frequency and severity of treatment-related adverse events, and particularly grade 3 and 4 toxicities. Alternatively, it is possible that the disease response to pembrolizumab is separable from treatment-related adverse events, which may be modulated by other host and tumor factors. Another important question is whether these immune-mediated adverse reactions occur because of activation of tissue-resident immune cells and/or through recruitment of circulating immune cells from the reticuloendothelial system. If circulating immune cells contribute significantly to the immune-mediated side effects of checkpoint blockade, there may be alternative approaches to manage these complications through modulation of immune cell trafficking.

The approach to treatment of stage IV, metastatic NSCLC has changed dramatically since platinum-based chemotherapy regimens were first tested in this disease over 30 years ago. The updated results from KEYNOTE-001 provide clinicians with additional evidence that pembrolizumab is an effective and generally safe therapy that should be offered in the first-line setting to patients with NSCLCs that have ≥50% tumor expression of PD-L1 and lack EGFR mutations or ALK rearrangements. Despite these advances, ongoing research efforts should be aimed at discovering new biomarkers of response and resistance, developing novel immunotherapeutics, improving strategies for choosing combination therapy, and minimizing toxicities from these potentially life-saving treatments.

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Funding
None declared.

Disclosure
MMA received consulting fees from Merck, Bristol-Myers Squibb, and Genetech-Roche. TZ declares no conflicts of interest.

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doi:10.1093/annonc/mdx083
Published online 27 February 2017