Pembrolizumab Increases Historic Survival Rate for Certain People with Advanced Non-Small Cell Lung Cancer

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ASCO Perspective

“These data are similar to what we have seen in other cancers treated with immunotherapy in that there are a population of patients who can live for five years or more. It’s truly remarkable that for more patients than ever before, we no longer have to count survival in months. However, we still have a long way to go to improve outcomes for all advanced NSCLC patients. We look forward to more research helping us determine how to identify these patients,” said ASCO Expert David L. Graham, MD, FACP, FASCO.

CHICAGO – Five-year data from the phase Ib KEYNOTE-001 clinical trial show that pembrolizumab (Keytruda) was safe and effective and substantially increased overall survival for advanced non-small cell lung cancer (aNSCLC). Specifically, 23.2% of people who had not previously been treated with chemotherapy and 15.5% of previously-treated patients were alive after five years, with the greatest benefit observed in patients with higher PD-L1 expression. This represents a marked improvement over 5-year survival rates from the pre-immunotherapy era, which averaged 5.5% for aNSCLC. This is the longest follow-up study to date of people with aNSCLC treated with pembrolizumab, according to the researchers.

The study will be featured in a press briefing today and presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting and is in press with the Journal of Clinical Oncology.
“The uniformly negative outlook that has been associated with a diagnosis of advanced non-small cell lung cancer is certainly no longer appropriate,” said lead study author Edward B. Garon, MD, MS, Associate Professor of Medicine at UCLA, Los Angeles, CA. “The fact that we have patients on this trial that are still alive after 7 years is quite remarkable. We also have evidence that most patients who are doing well after 2 years on pembrolizumab live for 5 years or more.”

Pembrolizumab binds to a protein on the surface of T cells called PD-1. PD-1 binds to ligands including PD-L1, inhibiting an immune response. By blocking PD-1, pembrolizumab activates T cells to attack tumor cells.

Pembrolizumab was first approved by the U.S. Food and Drug Administration for advanced melanoma in September 2014 and in aNSCLC in October 2015. Subsequently, in October 2016, pembrolizumab was approved as a first-line treatment for aNSCLC tumors that do not have \textit{EGFR} or \textit{ALK} gene mutations but that express PD-L1 on 50% or more of their cells.

Most recently, in April of this year, pembrolizumab received an expanded approval for frontline treatment of patients with stage III NSCLC who could not have the tumors surgically removed or irradiated, or aNSCLC with PD-L1 expression levels over 1% and no \textit{EGFR} or \textit{ALK} gene mutations.

\textbf{About the Study}

In 2011, when KEYNOTE-001 began enrollment, immunotherapy treatments were not widely available, so most participants had previously been treated with systemic medicines, or targeted therapies. There were 550 people with aNSCLC in the trial, including 101 patients who had not previously received any treatment and 449 patients who had received prior treatment. All patients received 2 mg/kg of their body weight of pembrolizumab every 3 weeks or 10 mg/kg every two or three weeks. In recent years, however, the protocol was changed to a single dose of 200 mg regardless of body weight every 3 weeks, the typical regimen in clinical practice.

\textbf{Key Findings}

Patients were followed for a median of 60.6 months, or about 5 years. At that point, 18% of
enrollees (100 participants) were still alive. Of those who had not received prior treatment, 23% were still alive after 5 years compared with 15.5% of those previously treated.

Researchers observed that higher levels of PD-L1 expression predicted longest survival. Specifically:

- In previously untreated people, 29.6% with PD-L1 expression of 50% or more were alive after 5 years compared with 15.7% with expression levels below 50%.
- In people who had been previously treated, 25% who had PD-L1 expression levels of 50% or more were alive after 5 years compared with 12.6% with expression levels between 1 to 49%. Only 3.5% of people with expression levels below 1% were alive after 5 years.

Among people receiving pembrolizumab after undergoing previous treatment, 42% had responses that lasted for a median of 16.8 months. For those who received pembrolizumab as initial therapy, 23% had responses that lasted a median of 38.9 months.

Immune-related toxic side effects occurred in 17% of enrollees. The most common side effect was hypothyroidism, where the immune system attacks the body's thyroid glands. The most serious side effect seen was pneumonitis, an inflation of lung tissue, but that was not very common.

**Next Steps**

Dr. Garon noted that the researchers will try refining their understanding of which patients received the most benefit from pembrolizumab as well as identifying impediments that prevent the immune system from destroying tumors so that these mechanisms could also be combatted. The investigators hope to explore possible combination therapies of pembrolizumab with conventional or other immunotherapies.

This study received funding from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

**Study at a Glance**
<table>
<thead>
<tr>
<th>Study Focus</th>
<th>Immunotherapy extending overall survival in people with advanced non-small cell lung cancer expressing PD-L1 of equal or greater than 50%</th>
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<tbody>
<tr>
<td>Trial Type</td>
<td>Phase I clinical trial</td>
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<tr>
<td>Patients on Trial</td>
<td>550</td>
</tr>
<tr>
<td>Treatment Tested</td>
<td>Pembrolizumab</td>
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<tr>
<td>Primary Finding</td>
<td>Pembrolizumab quadrupled pre-immunotherapy era 5-year survival rates for patients when used as initial therapy (23.2% vs. 5.5%). For patients who received prior therapies, pembrolizumab increased survival rates to 15.5%.</td>
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<tr>
<td>Secondary Finding(s)</td>
<td>Across both patient populations studied, 5-year survival rates were highest among those whose tumors had PD-L1 expression of 50% or more vs. 1-49% (as initial therapy arm: 29.6% vs. 15.7%; prior therapy arm: 25% vs. 12.6%)</td>
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