

ペムブロリズマブは非小細胞肺癌がん患者の生存率を上昇させる(Abstract LBA9015)

KEYNOTE-001: 進行非小細胞肺癌がんに対するペムブロリズマブの効果を調査したスタディにおいて、PD-L1の高発現は生存期間が最長であることの予測因子であった

KEYNOTE-001: Higher levels of PD-L1 expression predict longest survival in study of pembrolizumab for advanced non-small cell lung cancer

第Ib相KEYNOTE-001試験の5年間データから、ペムブロリズマブは安全かつ有効であり、進行非小細胞肺癌がん(aNSCLC)の全生存率を大幅に上昇させることが示された。特に、化学療法の前治療歴のない患者の23.2%および化学療法の前治療歴のある患者の15.5%が5年後に生存しており、最も有益性が認められたのはPD-L1の高発現患者であった。これは、aNSCLCの5年生存率が平均5.5%であった免疫療法以前の時代から、著明に改善したことを示している。このスタディ結果は2019 ASCO Annual Meetingで発表され、*Journal of Clinical Oncology*に掲載される。

Full Text

Five-year data from the phase Ib KEYNOTE-001 clinical trial show that pembrolizumab 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 was featured 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.

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.

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.

"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.

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 combated. 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.

"While poor fitness is already known to predict future cardiovascular disease, this is the first study to explore fitness as a marker of future cancer risk prognosis," said lead study author Susan Lakoski, M.D., assistant professor of medicine at the University of Vermont. "This finding makes it clear that patients should be advised that they need to achieve a certain fitness level, and not just be told that they need to exercise. And unlike exercise behavior, which relies on patient self-reporting, fitness can be objectively and accurately measured in a clinical setting."

The study included 17,049 men who had a single cardiovascular fitness assessment as part of a specialized preventive health check-up visit at a mean age of 50 years offered at the Cooper Institute. The fitness test, which is similar to a stress test for heart disease risk, entailed walking on treadmill under a regimen of changing speed and elevation. The men's performance was recorded in established units of fitness called metabolic equivalents or METs. Study participants were divided into five quintiles according to their fitness performance.

Researchers subsequently analyzed Medicare claims data to identify the participants of this study who had developed lung, colorectal, or prostate cancer—the three most common types of cancer among U.S. men. Over a median follow-up period of 20.25 years, 2,332 men were diagnosed with prostate cancer, 276 were diagnosed with colorectal cancer, and 277 were diagnosed with lung cancer. There were 347 deaths due to cancer and 159 men died of cardiovascular disease.

Researchers found that the risk of being diagnosed with lung or colorectal cancer was reduced by 68 and 38 percent, respectively, in men who were the most fit, relative to those who were the least fit. Fitness did not significantly impact prostate cancer risk. In the analysis, data were adjusted for smoking and other factors, such as body mass index and age.

Among the men who developed cancer, those who were more fit at middle age had a lower risk of dying from all the three cancers studied, as well as cardiovascular disease. Even a small improvement in fitness (by 1MET) made a significant difference in survival—reducing the risks of dying from cancer and cardiovascular disease by 14 and 23 percent, respectively.

Another interesting finding was that men who had low fitness had an increased risk of cancer and cardiovascular disease even if they were not obese. This suggests that patients should focus on improving their fitness, regardless of their body weight. Adequate fitness level depends on gender and age. In this study, men who fell in the lowest quintile for fitness achieved less than 13.5 minutes during the treadmill exercise test if they were 40-49 years old, less than 11 minutes if they were 50-59, and less than 7.5 minutes if they were 60 or older.

ASCO Perspective: "This important study establishes cardiorespiratory fitness as an independent and strong predictor of cancer risk and prognosis in men. While more research is needed to determine if similar trends are valid in relation to other cancers and among women, these results indicate that people can reduce their risk of cancer with relatively small lifestyle changes," said ASCO President Sandra M. Swain, M.D., FACP.

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ASCO2019 特集

[News 01]

閉経前進行乳がんにおける生存率の改善

[News 02]

新たに診断された進行胃がんに対する有望な代替手段

[News 03]

レナリドミドは多発性骨髄腫の発症を遅延させる

[News 04]

小児プレジジョン・メディシンの試験は予測を超える

[News 05]

転移性前立腺がんの新たな治療選択

[News 06]

肝転移において低侵襲がん手術は有効である

[News 07]

ペムブロリズマブは非小細胞肺癌がん患者の生存率を上昇させる

[News 08]

オラパリブはBRCA変異を有する膵臓がんの増悪を遅延させる

[News 09]

新たな治療法は進行尿路上皮がんに対し有効である

[News 10]

新しいクラスの薬剤は進行前立腺がん患者において有効である

[News 11]

新たなデータは若年乳がん患者における術後補助療法のガイドとなる

[News 12]

ビタミンDはがん関連死を減少させる

[News 13]

リンパ腫の特定の亜型を有する患者は化学療法を回避することができる可能性がある

[News 14]

乳房部分照射によりQOLが向上する

[News 15]

チェックポイント阻害薬は肺がん再発を減少させるのに有望である

[News 16]

HIV患者に対する免疫療法薬は安全であることが示された