

## 新たに診断された進行胃がんに対する有望な代替手段(Abstract LBA4007)

KEYNOTE-062: ペンブロリズマブは進行胃がんおよび胃食道接合部腺がんに対する化学療法に匹敵する

KEYNOTE-062: Pembrolizumab comparable to chemotherapy for advanced gastroesophageal junction and gastric cancers

PD-L1 陽性、HER2 陰性の進行胃がんおよび胃食道接合部(G/GEJ)がんを有する患者に対し、ペンブロリズマブによる一次治療は標準化学療法に匹敵する生存率をもたらした、と2019 ASCO Annual Meeting で発表された。ランダム化第III相試験 KEYNOTE-062 はまた、PD-L1 高発現腫瘍を有する患者に対し、ペンブロリズマブの全生存率における臨床的に意味のある改善も示した。2年後、ペンブロリズマブを単剤投与された患者の39% (すべてPDL-1 高発現患者)は生存しており、標準化学療法を受けた患者では22% であった。重篤な副作用の発現率は、ペンブロリズマブを単剤投与された患者群で最も低かった。

### Full Text

The KEYNOTE-062 phase III randomized clinical trial achieved its primary endpoint, showing that for patients with PD-L1-positive, HER2-negative, advanced gastric or gastroesophageal junction (G/GEJ) cancer, initial therapy with pembrolizumab resulted in comparable (non-inferior) overall survival as standard chemotherapy. Additionally, pembrolizumab showed clinically meaningful improvement in overall survival among patients with tumors that had high levels of PD-L1 expression. At two years, 39% of patients (all of whom had high PD-L1 levels) that received pembrolizumab alone were alive, compared with 22% of people who received standard chemotherapy. The trial also evaluated combined treatment with pembrolizumab and standard chemotherapy but found this regimen did not improve survival relative to chemotherapy alone.

"This trial shows that front-line pembrolizumab is effective and could provide a new opportunity for people newly diagnosed with advanced gastric or gastroesophageal junction cancers," said lead study author Josep Tabernero, MD, PhD, Head of the Medical Oncology Department at the Vall d'Hebron Barcelona Hospital University Hospital and Institute of Oncology, Barcelona, Spain. "There remains a significant unmet need for treatments for these cancers and our results reinforce the importance of continued research in this field."

The study was featured in a late breaking trial presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.

Gastric cancers are the fifth most frequently diagnosed cancer worldwide. GEJ, a less common cancer, has seen increasing incidence rates during this decade, particularly in Western nations but the reasons for this increase are not entirely clear.

Pembrolizumab was given accelerated approval by the U.S. Food and Drug Administration in September 2017 for patients with recurrent, locally advanced or metastatic, gastric or GEJ cancer with tumors that express PD-L1 with a combined positive score (CPS) of one or more. The CPS is calculated based on the number of PD-L1 positive cells derived from biopsied tissue and the number of viable tumor cells.

The trial enrolled 763 patients with a median age of 62 and 26% had previous gastric surgery to remove a tumor. In total, 69% had gastric cancer and 30% had GEJ cancer, which are typically very similar types of tumors despite their adjacent locations according to Dr. Tabernero. Investigators focused only on HER2-negative cancers, which studies have shown have a higher chance of recurrence after treatment, to limit factors that could affect outcomes.

PD-L1 expression was assessed via CPS. Previous studies of gastric or GEJ cancers have demonstrated that patients with a PD-L1 CPS of one or more may benefit from pembrolizumab, while a PD-L1 CPS of 10 or more indicates a higher likelihood of benefit. In the current trial, all patients had a PD-L1 CPS of one or greater, and 281 (37% of the enrollees) had a score of 10 or more.

The investigators randomly assigned patients, in equal numbers, to receive one of three treatment options as initial therapy: intravenous pembrolizumab, pembrolizumab and chemotherapy, or chemotherapy plus placebo. The patients were followed for a median of 11.3 months.

Treatment with Pembrolizumab Alone: The trial reached its primary endpoint, demonstrating that overall survival for pembrolizumab was non-inferior to standard chemotherapy. A favorable survival outcome was seen among enrolled patients with PD-L1 CPS of 10 or more. Specific findings include:

- Patients with PD-L1 CPS of one or more: Survival was non-inferior to chemotherapy [hazard ratio = 0.91] – median overall survival was 10.6 months for those receiving pembrolizumab compared with 11.1 months for those who received chemotherapy
- Patients with PD-L1 CPS 10 or more: Survival with pembrolizumab was superior to chemotherapy [hazard ratio = 0.69] – median overall survival was 17.4 months for those receiving pembrolizumab compared with 10.8 months for those receiving chemotherapy. After 2 years, 39% of people taking pembrolizumab were alive compared with 22% of those taking chemotherapy.

Overall survival and progression-free survival, regardless of CPS score, for the combination treatment of pembrolizumab and chemotherapy was comparable to that of chemotherapy alone.

The rates of serious side effects were lowest among patients treated with pembrolizumab alone. Grade 3 or higher toxic treatment-related adverse events were found in 17% of people receiving pembrolizumab, 73% of people receiving pembrolizumab and chemotherapy, and 69% receiving only chemotherapy. The most common adverse events were nausea and fatigue. The safety profile of pembrolizumab was consistent with prior experiences of patients who have been treated with it.

"Chemotherapy has been our only option for many years. These results introduce a potential alternative in pembrolizumab that comes with fewer side effects, and importantly, for some it can greatly extend survival. This opens the door to helping patients live longer and better lives," said Richard L. Schilsky, MD, FACP, FSCT, FASCO, Senior Vice President and Chief Medical Officer (CMO) of ASCO.

The investigators are currently analyzing subsets of the data to determine who benefitted the most. Dr. Tabernero noted that better biomarkers than PD-L1 are needed to truly determine who the best responders might be to pembrolizumab alone, as well as in combination with chemotherapy.

The trial enrolled 58% of patients from North America, Europe, and Australia; 25% from Asia; and 17% from other regions of the world. Prior population-based studies have shown that people from Asia usually have better survival rates for gastric and GEJ cancers, have lower amounts of tumor, and slower disease progression. The researchers are currently analyzing the effectiveness of the medicines based on pre-specified geographical regions.

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