Q-TWiST analysis of pembrolizumab combined with chemotherapy as first line treatment of metastatic TNBC that expresses PD-L1

**Background**

- KEYTRUDA® (pembrolizumab) is a humanized monoclonal antibody against programmed death 1 (PD-1) that has durable antitumor activity and manageable safety in triple-negative breast cancer (TNBC).
- Pembrolizumab in combination with chemotherapy showed statistically significant survival benefit in progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone as first-line treatment in patients with locally recurrent and metastatic TNBC (mTNBC) with PD-L1-positive tumors (combined positive score [CPS] ≥ 1) in the KEYNOTE-355 trial.\(^1\) 2
- Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST) analysis compares treatments by evaluating both quantity and quality of survival using a single metric.

**Objectives**

- To complement the previously reported efficacy and safety data from KN355, this study evaluated the overall benefit-risk of pembrolizumab plus chemotherapy compared to chemotherapy using the Q-TWiST analysis.

**Methods**

- **Data Source:** Keynote-355 (KN355): A randomized, controlled, double-blind, global, phase 3 trial in participants with mTNBC, which has not been previously treated with chemotherapy for advanced disease. Patients were randomly assigned in a 2:1 ratio to pembrolizumab + chemotherapy (ne oxal, paclitaxel, or gemcitabine + carboplatin) and placebo + chemotherapy (paclitaxel, or gemcitabine carboplatin).
- **Analysis:** This analysis was based on the data analysis from KN355, with a cutoff date of June 15, 2021, and median follow-up of 44 months.
- **Population:** The population reflected the licensed indication of pembrolizumab in mTNBC+; this analysis focused on an subgroup of the KN355 trial population with PD-L1-positive tumors (combined positive score [CPS] ≥ 1).

**Statistical analysis**

- **Survival time:** Partitioned into 3 health states:
  - Toxicity (TOX): Time from randomization to disease progression with grade 3+ AEs (i.e., PFS minus TOX)
  - Relapse (REL): Time from disease progression to death (i.e., OS minus PFS)
  - Survival curves that correspond to TOX, PFS, and OS were estimated by the Kaplan-Meier (KM) method. The restricted mean duration of each health state was derived from the area under the KM curve.
- **Q-TWiST:** Q-TWiST=UTOX*TOX +UTWiST*T WiST+ UREL*REL
- **The quality health state utility weight:** All grade 3+ events that occurred in the period from randomization to disease progression were summed.
- **TOX:** Time from randomization to disease progression with grade 3+ AEs.
- **PFS:** Time without symptom or toxicity (TWiST): Time from randomization to disease progression without grade 3+ AEs (i.e., PFS minus TOX)
- **OS:** Time without symptom or toxicity (TWiST): Time from randomization to disease progression without grade 3+ AEs (i.e., PFS minus TOX)
- **Q-TWiST analysis:** Differences of mean Q-TWiST between treatment arms were calculated as:
  \[\Delta Q-TWiST = \text{Q-TWiST}_A \text{TOX}_A + \text{Q-TWiST}_A \text{PFS}_A - \text{Q-TWiST}_B \text{TOX}_B - \text{Q-TWiST}_B \text{PFS}_B\]

**Results**

**Duration of health states**

- The drop of the curve at time 0 was due to patients who did not experience any grade 3+ AEs during this time period.
- **The base-case analysis:** The primary analyses were restricted to the median follow-up time (44 months) of the KN355 trial.
- **Secondary analyses:** The benefits continue to accrue over the trial follow-up period.
- **The extended Q-TWiST analysis:** The extended Q-TWiST was 43.0 (95% CI 40.4 to 45.6) months after 52 months, or 20% of mean OS time in this population.

**Conclusions**

- Pembrolizumab plus chemotherapy is associated with statistically significant and clinically meaningful improvement in quality-adjusted survival compared to chemotherapy alone in previously untreated PD-L1-positive mTNBC.
- The benefits continue to accrue over the trial follow-up period.

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**References**


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**Figure 1.** Partitioned survival plots of pembrolizumab plus chemotherapy and chemotherapy alone in KN355. The red, green, and blue curves are KM curves of OS, PFS, and TOX, respectively.

**Figure 2.** Mean Q-TWiST gain of pembrolizumab plus chemotherapy vs chemotherapy alone in previously untreated PD-L1-positive mTNBC in KN355.