KEYNOTE-756: A Randomized, Double-blind, Phase 3 Study of Pembrolizumab or Placebo With Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy for High-Risk, Early-Stage, ER+/HER2− Breast Cancer

BACKGROUND

ER+/HER2− Breast Cancer
- Estrogen receptor–positive (ER+), human epidermal growth factor receptor 2–negative (HER2−) breast cancer accounts for ~60% of breast cancer cases in the United States and is generally associated with a good prognosis.
- A high-risk subpopulation of ER+/HER2− breast cancer is characterized by high tumor grade, resistance to endocrine therapy, and poor prognosis similar to the luminal B molecular subtype.
- For patients with high-risk disease, a positive correlation is observed between pathologic complete response (pCR) and clinical outcomes.

PD-1 Pathway
- Pembrolizumab is a high-affinity, highly selective, humanized monoclonal immunoglobulin G4 antibody that blocks the PD-1 ligands PD-L1 and PD-L2 and blocks the PD-1 ligands PD-L1 and PD-L2.

Breast Cancer
- Breast cancer is characterized by high specific antigen release and clinical outcomes.
- Breast cancer cases in the United States.
- Breast cancer is the most common type of cancer in the United States, with an estimated 2.5% of people being diagnosed with breast cancer each year.
- Breast cancer is a common cancer among women and is the leading cause of cancer deaths among women worldwide.

Patient Eligibility Criteria

Key inclusion criteria
- Age ≥18 years
- Newly diagnosed, pathologically confirmed, high-risk, early-stage ER+/HER2− breast cancer

Key exclusion criteria
- Bilateral invasive breast cancer
- Breast cancer of lobular histology
- History of invasive breast cancer ≤5 years before study start
- Prior treatment for breast cancer
- Prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or with an agent directed at another coinhibitory T-cell receptor
- OS is defined as the time from randomization to the date of death from any cause.
- Patient-reported outcomes (PROs)
- Electronic or paper PRO questionnaires will be completed in the following order:
  - EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D-5L
- Safety
- All adverse events (AEs) will be monitored throughout the study and for 30 days after the cessation of pembrolizumab or placebo in the adjuvant phase and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

STUDY OBJECTIVES

Primary
- pCR rate using the definition of ypT0/Tis ypN0, as assessed by the local pathologist at the time of definitive surgery
- Event-free survival (EFS), as assessed by the investigator

Secondary
- Overall survival (OS) in all patients and in patients with PD-L1–positive (combined positive score [CPS] ≥1) tumors
- pCR rate using the alternative definition of ypT0 ypN0, as assessed by the local pathologist at the time of definitive surgery
- pCR rate using the alternative definition of ypT0/Tis, as assessed by the local pathologist at the time of definitive surgery
- pCR rate using 3 different definitions (ypT0/Tis ypN0, ypT0, and ypT0/Tis) and time of definitive surgery in patients with PD-L1–positive tumors
- EFS in patients with PD-L1–positive tumors
- Safety and tolerability of pembrolizumab + NAC and adjuvant endocrine therapy in all patients
- Health-related quality of life (QOL) using the EORTC QLQ-C30 (30 QLC-C30), the EORTC Breast Cancer-Specific QOL Questionnaire (QLQ-BR23), and the 5-dimensional, 5-level EuroQol (EQ-5D-5L) health status questionnaire

Endpoints and Assessments
- The pCR rate is defined as ypT0/Tis ypN0, absence of residual invasive cancer independent of in situ disease on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes after completion of neoadjuvant systemic therapy per American Joint Committee on Cancer staging criteria (6th edition)
- ypT0/Tis ypN0 as for ypT0/Tis ypN0 but dependent on absence of in situ cancer
- ypT0/Tis: as for ypT0/Tis ypN0 but independent of lymph node involvement
- EFS defined as the time from randomization to:
  - Progression of disease that precludes further systemic treatment
  - Death from any cause

DESIGN

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Figure 1. Pembrolizumab and the PD-1 Pathway

In the ongoing phase 2 study i-SPY 2, pembrolizumab + NAC vs NAC alone improved estimated pCR rates from 13.6% to 24.2% in patients with ER+/HER2− tumors, suggesting that earlier immunotherapy may improve survival.

KEYNOTE-756 (ClinicalTrials.gov identifier, NCT03725694) is a phase 3 study of pembrolizumab (vs placebo) + NAC as neoadjuvant therapy followed by pembrolizumab (vs placebo) + endocrine therapy as adjuvant treatment in patients with high-risk, early-stage ER+/HER2− breast cancer.

Figure 2. Study Design

In the ongoing phase 2 study I-SPY 2, pembrolizumab (vs placebo) + NAC as neoadjuvant therapy followed by pembrolizumab (vs placebo) + endocrine therapy as adjuvant treatment in patients with high-risk, early-stage ER+/HER2− breast cancer.

In the adjuvant phase, patients will receive either pembrolizumab (cohort 1) or placebo (cohort 2) every 3 weeks for 9 cycles, each in combination with investigator’s choice of endocrine therapy (for ≥5 years).

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Figure 3. Countries With Sites Enrolling in KEYNOTE-756 (shown in green)

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Patient-reported outcomes (PROs)
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  - EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D-5L

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