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

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BACKGROUND

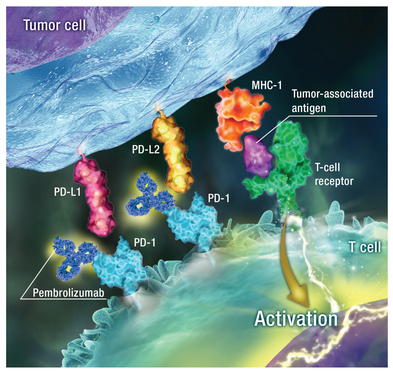
ER+/HER2− Breast Cancer

- 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[1]
- 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[2]
- For patients with high-risk disease, a positive correlation is observed between pathologic complete response (pCR) and clinical outcomes[3]
  - Targeted therapies combined with neoadjuvant chemotherapy (NAC) to improve pCR rates may, therefore, improve survival

Anti–PD-1 Blockade in ER+/HER2− Breast Cancer

- Inhibition of immune checkpoints, such as the programmed cell death receptor 1 (PD-1), may enhance endogenous anticancer immunity when combined with chemotherapy-induced, tumor-specific antigen release[4]
  - PD-1 activation suppresses T-cell–mediated immune responses[5]
- Pembrolizumab is a high-affinity, highly selective, humanized monoclonal immunoglobulin G4κ antibody that blocks the PD-1 ligands PD-L1 and PD-L2 (**Figure 1**)

Figure 1. Pembrolizumab and the PD-1 Pathway



MHC-1, major histocompatibility complex 1; PD-1, programmed cell death receptor 1; PD-L1, PD ligand 1; PD-L2, PD ligand 2.

- In the ongoing phase 2 study I-SPY 2, pembrolizumab + NAC vs NAC alone improved estimated pCR rates from 13.6% to 34.2% in patients with ER+/HER2− tumors,[6] suggesting that earlier immunotherapy may improve survival
- KEYNOTE-756 (ClinicalTrials.gov identifier, NCT03725059) 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

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

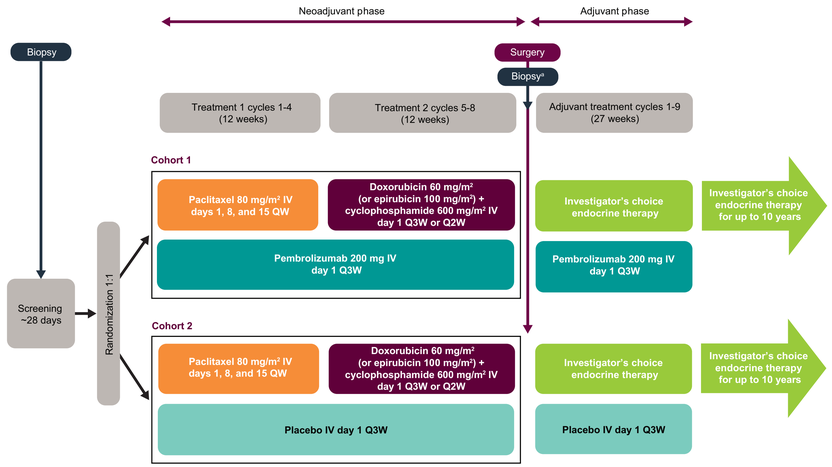
Secondary

- Overall survival (OS) in all patients and in patients with PD-L1–positive (combined positive score [CPS] of ≥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 ypN0, and ypT0/Tis) at the 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 QOL Questionnaire Core 30 (QLQ-C30), the EORTC Breast Cancer–Specific QOL Questionnaire (QLQ-BR23), and the 5-dimension, 5-level EuroQol (EQ-5D-5L) generic health status questionnaire

DESIGN

- KEYNOTE-756 is a randomized, double-blind, placebo-controlled, phase 3 study in approximately 1140 patients with newly diagnosed, previously untreated, high-risk (based on clinicopathologic criteria), early-stage ER+/HER2− breast cancer
- Patients will be treated in a neoadjuvant phase followed by an adjuvant phase (**Figure 2**)

Figure 2. Study Design



IV, intravenously; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks.
[a]Optional biopsy to be used for biomarker studies.

- Treatment regimen in the neoadjuvant phase consists of treatment 1 (paclitaxel) followed by treatment 2 (doxorubicin [epirubicin]/cyclophosphamide)
  - Patients with T1c-T2 cN1-cN2 (tumor size ≥2 cm) or T3-T4 cN0-cN2 grade 3, invasive, ductal ER+/HER2− breast cancer will be randomly assigned 1:1 to 1 of 2 treatment cohorts
  - Patients in cohort 1 will receive pembrolizumab and those in cohort 2 will receive placebo
- As part of local standard of care, all patients will undergo definitive surgery after the last cycle of the neoadjuvant phase regimen
- 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 ≤10 years)
  - Patients will also receive radiation at the discretion of the investigator
- Patients will be stratified by 3 regions. Eastern Europe will be further substratified according to tumor PD-L1 status. All other countries (except China) will be stratified according to nodal status (positive vs negative), tumor PD-L1 status (positive [CPS ≥1] vs negative [CPS <1]), anthracycline dosing schedule (every 3 weeks vs every 2 weeks), and ER status (ER+ ≥10% vs ER+ 1%-9%). China will not be further stratified

Patient Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
• Aged ≥18 years • Newly diagnosed, previously untreated, locally confirmed, high-risk, early-stage ER+/HER2−, nonmetastatic breast cancer[a] – Multifocal tumors (≥2 foci of cancer within the same quadrant; ≥2 cm for at least 1 of the tumors) allowed – Node-negative disease capped at 20% of the total population • Centrally confirmed grade 3, ER+/HER2− breast cancer of ductal histology[b] • ECOG PS of 0 or 1 • Adequate organ function • Provision of a core needle biopsy specimen at screening[c]	• Bilateral invasive breast cancer • Breast cancer of lobular histology • History of invasive malignancy ≤5 years before study start[d] • 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

ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor–positive; HER2−, human epidermal growth factor receptor 2–negative; PD-1, programmed cell death receptor 1; PD-L1, PD ligand 1; PD-L2, PD ligand 2.
[a]Includes either T1c-T2 (tumor size ≥2 cm)/cN1-cN2 or T3-T4/cN0-cN2. [b]Defined by the most recent American Society of Clinical Oncology/College of American Pathologists guidelines. [c]Sample must consist of multiple tumor cores from the primary tumor. [d]Except for adequately treated basal cell or squamous cell skin cancer or in situ ductal or in situ cervical cancer.

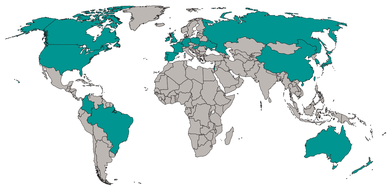
Endpoints and Assessments

- 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 (8th edition)[7]
  - ypT0 ypN0: as for ypT0/Tis ypN0 but dependent on absence of in situ cancer[7]
  - ypT0/Tis: as for ypT0/Tis ypN0 but independent of lymph node involvement[7]
- EFS is defined as the time from randomization to
  - Progression of disease that precludes definitive surgery
  - Local or distant recurrence
  - Second primary malignancy
  - Death from any cause
- OS is defined as the time from date of randomization to the date of death from any cause
- Patient-reported outcomes (PROs)
  - Electronically administered 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[8]
  - Serious AEs will be reported throughout the study until 90 days after the cessation of pembrolizumab or placebo in the adjuvant phase

STATUS

- KEYNOTE-756 is recruiting participants at 227 sites in 22 countries across Asia, Australia, Europe, Israel, New Zealand, North America, and South America (**Figure 3**)

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



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Acknowledgments

Funding for this study was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing and editorial assistance were provided by Rajni Parthasarathy, PhD, and Jenna Lewis, MA, ELS, MedThink SciCom. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Data included in this poster have been previously presented in full at the 36th Annual MBC Conference; March 7-10, 2019; Miami, FL; abstract 747; the ESMO Breast Cancer 2019 Congress; May 2-4, 2019; Berlin, Germany; abstract 121TiP; the ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL; abstract TPS601; the 2019 JSMO Annual Meeting; July 18-20, 2019; Kyoto, Japan; the 5th World Congress on CoBrCa; September 4-6, 2019; San Francisco, CA; the 22nd Annual Meeting of CSCO; September 18-22, 2019; Xiamen, China; and the ESMO Asia Congress; November 22-24, 2019; Singapore; abstract 24TiP.

Author Disclosures

FC has served on an advisory board for or received consultancy fees from Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma GmbH, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Seattle Genetics, and Teva Pharmaceuticals Industries Ltd.

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https://go.aws/2TVbp6a

Presented at the American Society of Breast Surgeons 21st Annual Meeting; April 29-May 3, 2020; Virtual format