KEYLYNK-009: A Phase 2/3, Open-label, Randomized Study of Pembrolizumab + Olaparib vs Pembrolizumab + Chemotherapy After Induction With First-line Pembrolizumab + Chemotherapy in Patients With Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer

Background
- There is an unmet need for tolerable and effective maintenance treatment regimens after induction therapy for patients with metastatic triple-negative breast cancer (TNBC).
- Here we describe the trial design of KEYLYNK-009 (NCT04191135), a randomized, placebo-controlled, adaptive phase 2/3 trial of pembrolizumab in combination with the PARP inhibitor olaparib after induction therapy for treatment of patients with locally recurrent inoperable or metastatic TNBC that has not been previously treated in the metastatic setting.

Study Design
- All enrolled patients will receive 4 to 6 cycles of pembrolizumab + chemotherapy (carboplatin + gemcitabine) as induction therapy.
- Patients who achieve complete or partial response or stable disease with induction therapy will be randomized 1:1 to receive pembrolizumab + olaparib or continue pembrolizumab + chemotherapy (Figure 1).

Toxicities related to induction therapy must be grade ≤1 at randomization (Hb of ≥9.0 mg/dL, grade 2 hyperthyroidism, hypothyroidism, or hyperglycemia; or any grade alopoeisa is acceptable).

This study will enroll ~317 patients in phase 2; if a planned efficacy boundary is met, ~615 additional patients will be enrolled in phase 3.

Endpoints and Assessments
- Primary endpoints:
  - Progression-free survival (PFS) per RECIST v1.1 by blinded independent central review (BICR)
  - Overall survival (OS)
- Secondary endpoints:
  - PFS and OS in patients with BRCA-mutated (BRCAm) tumors
  - Health-related quality of life and time to deterioration using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the breast cancer module (EORTC QLQ-BR23)
  - Visual analog scale using the EuroQol, 5-Dimension, 5-Level Questionnaire in patients with BRCAm tumors
  - Safety and tolerability
- Key exploratory endpoints per RECIST v1.1 by BICR
  - Objective response rate
  - Duration of response
  - Disease control rate
  - Postinduction imaging assessments will be performed every ~6 weeks for the first year and every ~12 weeks thereafter

Status
- Enrollment is ongoing at sites in Canada, Chile, Colombia, France, Hungary, Japan, Poland, Republic of Korea, Spain, Taiwan, Ukraine, the United Kingdom, and the United States (Figure 2).

Figure 1. Study Design

Induction
- Participants:
  - Locally recurrent inoperable or metastatic TNBC not previously treated in the metastatic setting
  - Interval between treatment with curative intent and recurrence ≥6 months
  - Confirmed PD-L1 status

- Carboplatin (AUC 2 on days 1 and 8 of each 21-day cycle) and gemcitabine (1000 mg/m² on days 1 and 8 of each 21-day cycle)
- Pembrolizumab (200 mg Q3W; 4 to 6 cycles)

Randomization is stratified by:
- Response (CR or PR vs SD)
- PD-L1 positive (CPS ≥20) vs PD-L1 negative
- Genomic tumor status (BRCAm vs BRCAwt)

Postinduction
- Olaparib (300 mg twice daily) + pembrolizumab (200 mg Q3W; up to 35 cycles including induction)
- Carboplatin (AUC 2 on days 1 and 8 of each 21-day cycle) and gemcitabine (1000 mg/m² on days 1 and 8 of each 21-day cycle)
- Pembrolizumab (200 mg Q3W; up to 35 cycles including induction)

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Figure 2. Countries With Current and Planned Enrollment Sites for KEYLYNK-009