ASTEFANIA: A phase 3 study of trastuzumab emtansine (T-DM1) plus atezolizumab or placebo as adjuvant therapy in patients with residual invasive breast cancer after neoadjuvant HER2-targeted therapy and chemotherapy

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Background

- Trastuzumab-emtansine (T-DM1) is a human epidermal growth factor receptor 2 (HER2)-targeted antibody–drug conjugate
- In the phase 3 KATHERINE trial, T-DM1 significantly reduced the risk of recurrence of invasive breast cancer or death by 50% compared with trastuzumab ($P<0.001$) in patients with HER2-positive early breast cancer (eBC) with residual invasive disease after pre-operative treatment with a taxane and HER2-targeted therapy, and T-DM1 is now the standard of care in this population[1]
- In KATHERINE, T-DM1 improved the 3-year invasive disease-free survival (IDFS) rate compared with trastuzumab (88.3% vs 77.0%). However, the 3-year IDFS rates were notably lower in patients with inoperable disease or with operable, hormone receptor-negative, node-positive disease (**Table 1**)[2] highlighting a remaining unmet therapeutic need

Table 1. IDFS in patient subgroups from KATHERINE

3-year event-free rate, % (95% CI)	T-DM1	Trastuzumab
All patients	88.3 (85.8–90.7)	77.0 (73.8–80.3)
Inoperable irrespective of hormone receptor and ypN status	76.0 (70.0–82.4)	60.2 (52.7–67.8)
Operable hormone receptor negative with ypN-positive nodes	76.0 (64.5–87.5)	69.5 (56.1–82.9)

- In the randomized, phase 2 KATE2 study, exploratory analyses of a subgroup of patients with HER2-positive and PD-L1-positive locally advanced (LA)/mBC showed that the the addition of the checkpoint inhibitor atezolizumab to T-DM1 resulted in longer median progression-free survival (PFS) (8.5 months vs 4.1 months; HR=0.60, 95% CI 0.32–1.11) and higher 1-year overall survival (OS) rates (1-year OS 94% vs. 88%; HR=0.57, 95% CI 0.23–1.42) compared with the addition of placebo. No clinically meaningful differences in PFS or OS were observed in the intention-to-treat (ITT) population
  - These results add to the available evidence of a predictive value of PD-L1 expression for treatment benefit with checkpoint inhibitors in the advanced breast cancer setting including in triple-negative breast cancer (TNBC)[3–5]
- In the eBC setting, PD-L1 status does not seem to predict benefit with anti-PD-[L]1 agents
  - In IMpassion 031, the pathological complete response rate (pCR) was significantly increased with the addition of atezolizumab versus placebo to neoadjuvant chemotherapy in both the ITT and PD-L1-positive populations of patients with eTNBC[6]
  - In KEYNOTE-522, the pCR rate was greater with the addition of pembrolizumab versus placebo to neoadjuvant chemotherapy in both the PD-L1-positive and PD-L1-negative populations of patients with eTNBC[7]
  - Recent results from the ongoing IMpassion050 study of neoadjuvant atezolizumab versus placebo in combination with pertuzumab, trastuzumab, and chemotherapy in high-risk, HER2-positive eBC are inconclusive[8]
- ASTEFANIA will evaluate the addition of atezolizumab to adjuvant T-DM1 in PD-L1-unselected patients with residual invasive HER2-positive eBC who are at high risk of disease recurrence after neoadjuvant treatment

Study Design

- ASTEFANIA is a phase 3, randomized, double-blind, multicenter, study in patients with centrally-confirmed HER2-positive eBC with residual invasive disease at surgery after neoadjuvant chemotherapy and HER2-directed treatment (**Figure 1**)
  - HER2 positive status is defined as an immunohistochemistry (IHC) score of 3+ or a positive result by in situ hybridization (ratio of ≥2.0 for the number of HER2 gene copies to the number of chromosome 17 copies)
  - Hormone receptor and PD-L1 status are also centrally confirmed
  - PD-L1 status is evaluated by IHC using the Ventana SP142 antibody. Positive status is defined as PD-L1 expression on tumor-infiltrating immune cells (IC) on ≥1% of the tumor area (IC 1/2/3); PD-L1-negative is defined as IC <1% (IC 0)
- Stratification factors:
  - Clinical stage at presentation: stage cT4/any N/M0 or any cT/N2–3/M0 versus stage cT1–3/N0-1/M0
  - Hormone receptor status: estrogen receptor (ER) or progesterone receptor (PgR) positive versus ER and PgR negative or unknown
  - Preoperative HER2-directed therapy: trastuzumab versus trastuzumab plus additional HER2-directed agent(s)
  - PD-L1 status: IC 0 versus IC 1/2/3
- Within 12 weeks of primary surgery, patients are randomized 1:1 to
  - T-DM1 3.6 mg/kg IV every 3 weeks (q3w) plus atezolizumab 1200 mg IV q3w for 14 cycles
  - T-DM1 3.6 mg/kg IV q3w plus placebo (matched to atezolizumab) IV q3w for 14 cycles
- Radiotherapy and/or endocrine therapy are administered per local standards
- Patients will be enrolled at approximately 303 sites worldwide (**Figure 2**)

Figure 1. ASTEFANIA Study Design

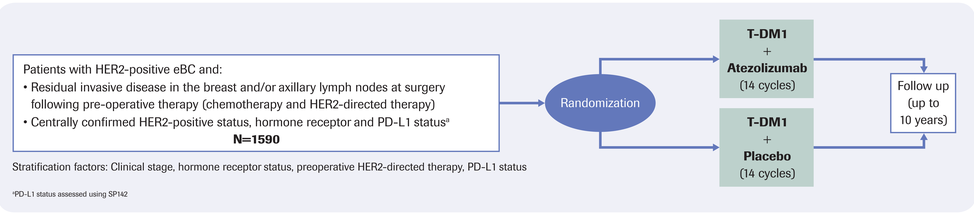
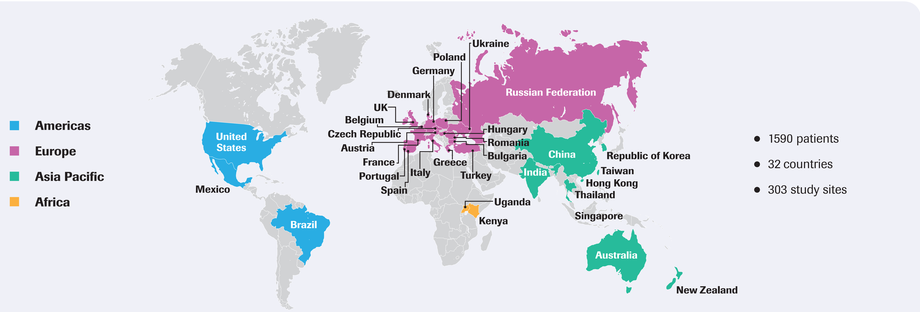


Figure 2. ASTEFANIA Study Sites



Study Objectives

Primary endpoint

- IDFS, defined as time from randomization to the date of the first occurrence of: ipsilateral invasive breast tumor recurrence, ipsilateral locoregional invasive BC recurrence, contralateral invasive BC, distant recurrence, or death from any cause

Secondary endpoints

- IDFS including second primary non-breast invasive cancer
- Disease-free survival including all IDFS events and contralateral or ipsilateral ductal carcinoma (DCIS) or second primary non-breast invasive cancer
- Distant recurrence-free interval
- OS

Other endpoints

- Safety
- Patient-reported outcomes
- Pharmacokinetics
- Immunogenicity

Eligibility Criteria

Key Inclusion Criteria

- Histologically-confirmed invasive breast carcinoma
- Centrally-confirmed HER2-positive disease
- Centrally-confirmed PD-L1 and hormone receptor status
- Clinical stage at presentation: cT4/any N/M0, any cT/N2–3/M0, or cT1–3/N0-1/M0 (patients with cT1mi/T1a/T1b/N0 are not eligible)
- Patients with cT1–3/N0-1 disease at presentation must have pathological evidence of residual invasive carcinoma in axillary lymph node(s) at surgery
- Patients with cT4/any N/M0 or cT1–3/N2–3/M0 disease at presentation must have pathologic evidence of residual invasive carcinoma in the breast and/or axillary lymph node(s) at surgery
- Completion of pre-operative systemic chemotherapy and HER2-directed therapy including ≥9 weeks of taxane and ≥9 weeks of trastuzumab (anthracycline and/or additional HER2-targeted agents are permitted)
- ≤12 weeks between primary surgery and randomisation
- ECOG performance status of 0 or 1
- Screening LVEF ≥50% and no decrease in LVEF by >15 percentage points from pre-chemotherapy LVEF. If no pre-chemotherapy LVEF, screening LVEF ≥55%
- Life expectancy ≥6 months
- Adequate hematological and organ function

Key Exclusion Criteria

- Stage IV breast cancer
- An overall response of disease progression according to the investigator at the conclusion of pre-operative systemic therapy
- Prior treatment with T-DM1, or atezolizumab or other immune checkpoint inhibitors
- History of exposure to various cumulative doses of anthracyclines
- History of other malignancy within 5 years prior to screening
- Current grade ≥2 peripheral neuropathy
- History of idiopathic pulmonary fibrosis, organizing pneumonia, or pneumonitis
- History of or active autoimmune disease or immune deficiency
- Treatment with immunostimulatory or immunosuppressive agents
- Cardiopulmonary dysfunction
- Any known active liver disease

Additional Study Information

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT04873362

EudraCT: 2020-003681-40

Email: global-roche-genentech-trials@gene.com

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