1. ABSTRACT

Title

GARDENIA: A Multi-country Observational Serial Chart Review Study of KANJINTI use in Europe

- **Keywords**

Breast cancer; trastuzumab; KANJINTI; observational study; Europe

- **Rationale and Background**

  KANJINTI was approved in the European Union (EU) in May 2018 as a biosimilar of Herceptin® for treatment of human epidermal growth factor receptor 2 positive (HER2+) early and metastatic breast cancer as well as metastatic gastric cancer. The approval was across all indications after the conduct of one phase 3 trial conducted in a sensitive population with sensitive endpoints, with extrapolation of other indications based upon knowledge of the reference product, the totality of evidence (functional, analytic, preclinical, and clinical) data package, and scientific justification. The phase 3 trial for KANJINTI was conducted in the neo-adjuvant and adjuvant early HER2+ breast cancer setting.

  This observational study provides information on how KANJINTI is adopted for use (including combination use) in routine, daily clinical practice among subjects with breast cancer, including those with metastatic breast cancer.

- **Research Question and Objectives**

  The purpose of this study is to assess how the product is being used in routine clinical practice. The primary objectives are:

  - Describe characteristics of breast cancer subjects receiving Kanjinti, including treatment setting (ie, neo-adjuvant, adjuvant, or metastatic).
  - Describe whether subjects were trastuzumab-treatment naïve or if the subject had switched from a different trastuzumab brand. For subject who had received Herceptin®, which route had been used for administration (IV or SC).
  - Describe use of concurrent therapies given with Kanjinti.
  - Describe reasons for discontinuation of Kanjinti.

- **Study Design**

  This was a single-arm, observational, serial chart review study of adult HER2+ breast cancer subjects treated with KANJINTI. Subjects who had received at least one administration of Kanjinti were considered for enrolment into this study and were followed-up for a minimum of one year after enrolment into study (ie, one year after enrolment of last study subject). The study was planned to finish one year after last subject was enrolled and, consequently, not all subjects were expected to have finished their KANJINTI treatment which was planned and managed independently by participating sites, regardless of study timelines.

- **Setting**

  This study was conducted in cancer treatment centres (including academic, local, and private offices) in selected countries in Europe (France, Greece, Italy, the Netherlands, Poland, Romania, and Spain).

- **Subjects and Study Size, Including Dropouts**

Subjects were eligible for enrolment into study if they had fulfilled the following criteria if they had HER2+ breast cancer (regardless of stage of disease), had received or who were receiving KANJINTI treatment according to the judgment of the physician in routine clinical practice and who were aged 18 years or older at KANJINTI initiation. Subjects were ineligible for study enrolment if they planned participation in an interventional clinical trial, had other cancer types (concurrent to breast cancer), if they had not provided an informed consent (where required per country-specific regulations), and whose medical chart were not available for data abstraction.

A sample size of approximately 500 subjects had been selected for this observational study to permit individual countries (or regions, where applicable) to enrol up to 100 subjects.

- **Data Source and Methods**

  Data were obtained from routine clinical records at least quarterly and transcribed by site staff onto an eCRF to form a longitudinal cohort of subjects for analysis. Since the data collected are those recorded in routine practice, information on KANJINTI administration and adverse events of interest were expected to be reasonably complete, although some missing data were expected. Collection of data was carried out "retrospectively" (ie, data prior to subject enrolment) and "prospectively" (ie, after subject enrolment) via quarterly abstraction of data from subjects' medical charts into the study eCRF. Treatment-emergent adverse events (TEAEs) are analysed in this report and include those safety events starting on or after KANJINTI initiation up to 30 days after last KANJINTI dose.

- **Results**

  A total of 488 KANJINTI-treated subjects were enrolled, sequentially, from 42 participating sites in 7 countries between 28 October 2019 and study close on 13 October 2021. Ninety-nine percent (n=483) of subjects were female, and overall median age of subjects at KANJINTI initiation was 56.0 years. Subjects were almost equally distributed among treatment settings (34.2% [n=167] adjuvant setting; 32.6% [n=159] neo-adjuvant setting; and 33.2% [n=162] metastatic setting) with twice as many new starters (70.5% [n=344] of subjects) as there were switchers (29.5% [n=144]).

  Subjects' oestrogen receptor/progesterone receptor (ER/PR) status at breast cancer diagnosis was available for almost all subjects (97.7%, n=477) with 67.0% (n=327) of subjects being positive. The median elapsed time from breast cancer diagnosis to KANJINTI initiation (available for 458 subjects; 93.9%) was 3.71 months (Q1, Q3: 1.91, 9.07 months), ranging from median 2.99 months (Q1, Q3: 1.45, 4.17 months) among new trastuzumab starters to median 34.73 months (Q1, Q3: 7.36, 65.54 months) among trastuzumab switchers. The overall median elapsed time from KANJINTI initiation to study enrolment was 7.00 months (Q1, Q3: 2.27, 11.93 months), ranging from median 5.44 months among new trastuzumab starters to median of 10.32 months among trastuzumab switchers. The duration of KANJINTI treatments was available for 416 subjects (85.2%), with median duration of 5.65 months (Q1, Q3: 2.60, 11.56 months). The study finished 12 months after last subject was enrolled (allowing for 12 months minimum follow-up for each enrolled subject). At this time point, just over 30% of subjects had completed KANJINTI treatment, 19.5% of subjects were still continuing KANJINTI, and half of subjects (50.0%, n=244) had discontinued KANJINTI. The most frequent reasons for discontinuation included switching to another trastuzumab biosimilar (34.8%, n=85),

switching to Herceptin® (15.6%, n=38), or due to disease progression (11.5%, n=28). Trastuzumab new-starters, when switching after KANJINTI, were more frequently switched to Herceptin® (35.1%) than were those subjects who previously switched (23.9% of whom switched to Herceptin®). Reasons for switching from KANJINTI to another trastuzumab brand were not collected and may have been due to medical or commercial (ie, change in trastuzumab procurement) reasons.

The majority (62.7%; 94 out of 150 subjects) of Stage IV breast cancer subjects had switched from another version of trastuzumab to KANJINTI. Over two-thirds of metastatic subjects were using KANJINTI as first-line therapy, 9.9% were using as second-line, and 7.4% were using as third-line; one subject had previously been treated with subcutaneous trastuzumab.

Among those subjects (n=144) who had switched from a previous trastuzumab, almost half (47.9%, n=69) had switched from intravenous Herceptin®, and 15.3% (n=22) had switched from subcutaneous Herceptin®. Previous trastuzumab brand was unknown for 28.5% (n=41) of switchers, but 5.6% (n=8) of subjects were known to have switched from another biosimilar and 2.8% (n=4) had switched from trastuzumab-emtansine.

Among all subjects, the most frequently used regimens at KANJINTI initiation were combination KANJINTI with pertuzumab and taxane (28.1%, n=137), followed by KANJINTI with paclitaxel (27.9%, n=136), and KANJINTI alone (8.2%, n=40).

Overall, 57.4% (280/488) of subjects were given KANJINTI in the standard dosing schedule, including 80.2% (130/162) of metastatic subjects. Dosing schedule was three times a week for 80.7% (394/488) of subjects, being highest among trastuzumab switchers (91.7%, 132/144) and those in metastatic setting (90.1%, 146/162). Among the 360 subjects for whom initial dosing was reported in milligrams (mg), the median dose was 450 mg (Q1, Q3: 354.5, 567.5 mg). Among the remaining 128 subjects for whom initial dosing was reported in milligram per kilogram (mg/kg), the median dose was 6.0 mg/kg (Q1, Q3: 6.0, 8.0 mg/kg).

Subject status among metastatic subjects at end of study were: 7.4% (n=12) completed KANJINTI treatment; 33.3% (n=54) were still on KANJINTI; 30.2% (n=49) had switched to another trastuzumab; and 29.0% (n=47) had discontinued KANJINTI. Study status for adjuvant subjects at end of study were: 38.3% (n=64) completed KANJINTI treatment; 13.2% (n=22) were continuing KANJINTI; 26.3% (n=44) had switched to another trastuzumab; and 22.2% (n=37) had discontinued KANJINTI. For neo-adjuvant subjects, status at end of study were: 45.9% (n=73) completed KANJINTI; 11.9% (n=19) were continuing KANJINTI; 18.9% (n=30) switched to another trastuzumab; and 23.3% (n=37) had discontinued KANJINTI.

Total of 201 subjects (41.2%) continued onto other non-KANJINTI regimens, with 13.3% (n=65) of subjects continuing onto hormonal therapy, 6.1% (n=30) continuing onto chemotherapy, and 5.9% (n=29) continuing onto subcutaneous Herceptin®.

Almost all subjects (98.6%, n=481) were alive at 30 days after last KANJINTI treatment (seven deaths due to adenocarcinoma [3 subjects], and breast cancer, progression of malignant neoplasm, disease progression, and general physical health deterioration [1 each]), with highest mortality (3.7%, n=6) among metastatic breast cancer subjects. A total of 111 subjects (22.7%) had had a TEAE, ranging from low of 18.6% (n=31) among adjuvant to high of 26.4% (n=42) among neo-adjuvant subjects. Serious TEAEs were reported for 31 subjects (6.4%), with lowest

frequency among adjuvant subjects (4.8%, n=8) and highest among metastatic subjects (9.3%, n=15). Thirty-three subjects (6.8%) had had a treatment-related TEAE during the study, 7 of which were serious (1.4%). These events were more frequent among trastuzumab new starters (8.7%, n=30), than among switchers (2.1%, n=3). By subject treatment setting, these events were most frequent among neo-adjuvant subjects (10.1%, n=16) and lowest for adjuvant subjects (4.2%, n=7).

Overall, 69 (14.1%) subjects had had a TEAE of interest, with 29 subjects (5.9%) having infections, 28 subjects (5.7%) having neutropenia, 14 subjects (2.9%) having pulmonary disorders, 11 (2.3%) having cardiac disorders, and 1 (0.2%) having an administration-site reaction. For the five adverse event categories of interest, treatment-related TEAEs were reported most frequently for neutropenia (2.5% [n=12] of subjects), followed by cardiac dysfunction (1.4%, n=7), pulmonary disorders (0.8%, n=4), and infections (0.2%, n=1); no administration/infusion-related reaction event was reported.

- **Discussion**

  This medical record review study was conducted to assess the 'real-world' utilisation of KANJINTI in Europe. This study represents the most substantial summary of data for biosimilar trastuzumab-treated breast cancer subjects in Europe, with a large number of subjects enrolled equally across the adjuvant, neo-adjuvant, and metastatic setting. Baseline demographic and breast cancer disease data for the adjuvant and neo-adjuvant subjects in GARDENIA are similar to those KANJINTI-treated subjects in the phase 3 LILAC study. One-third of KANJINTI-treated breast cancer subjects were in the metastatic setting and 29.5% of subjects had switched from another trastuzumab product (including 59.3% [96/162] of metastatic subjects). Overall, the safety profile characterised in this study was consistent with the known safety profile of trastuzumab and no new safety signals were detected from the data.

- **Marketing Authorization Holder(s)**
  - Amgen Europe B.V.

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse event
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Oestrogen receptor
EU	European Union

FAS	Full analysis set
HER2	Human epidermal growth factor receptor 2
HER2+	Human epidermal growth factor receptor 2 positive
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multigated acquisition
NA	Not applicable
ORR	Overall response rate
OS	Overall survival
pCR	Pathologic complete response
pPR	Pathological partial response
PFS	Progression-free survival
PR	Progesterone receptor
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDV	Source data verification
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event