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SYNOPSIS

Study Title: A Phase 2 Open-Label, Single Arm Study of Tucatinib in Combination With Trastuzumab and Capecitabine in Participants With Previously Treated Locally Advanced Unresectable or Metastatic HER2+ Breast Carcinoma

Study Number: C4251013 (MK-7119-001)

Regulatory Agency or Public Disclosure Identifier Number: NCT04721977; jRCT2051200152

Study Phase: 2

Name of Study Intervention: Tucatinib

Trade Name: TUKYSA

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Document Version	Report Date
Interim Primary Analysis CSR Version 1.0	09 October 2024
Interim Primary Analysis CSR Amendment (amendment to 09 Oct 2024) Version 2.0	14 January 2025

Number of Study Center(s) and Investigator(s): This study was conducted at 24 sites that enrolled 66 participants in Japan, South Korea, and Taiwan.

Publications: Not applicable

Study Period:

First subject enrolled: 08-Apr-2021

Data cutoff date for primary analysis: 17-Jul-2023

This study was neither discontinued nor interrupted.

Rationale:

This is a single-arm, multicenter, phase 2 study designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and capecitabine in Japanese, South Korean, and Taiwanese participants with unresectable locally advanced or metastatic human epidermal growth factor receptor 2 (HER2)+ breast cancer who had prior treatment with a taxane anticancer agent, trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1).

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Objectives, Endpoints, and Statistical Methods:

Listed below are the objectives, endpoints, and statistical methods that are described in this report.

Objectives	Endpoints	Statistical Methods
Primary		
• Assess the objective response rate (ORR) of tucatinib in combination with trastuzumab and capecitabine by independent central review (ICR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) in the Japanese population	• Confirmed ORR (cORR) by ICR per RECIST v1.1 in the Japanese population	• Point estimate and 2-sided 90% exact confidence interval (CI) by Clopper-Pearson method (Clopper 1934)
Secondary		
• Assess ORR of tucatinib in combination with trastuzumab and capecitabine by ICR per RECIST v1.1 in the all participants population	• cORR by ICR per RECIST v1.1 in the all participants population	• Point estimate and 2-sided 90% exact CI by Clopper-Pearson method
• Assess ORR of tucatinib in combination with trastuzumab and capecitabine by investigator assessment (INV) per RECIST v1.1 in the Japanese population and the all participants population	• cORR by INV per RECIST v1.1 in the Japanese population and the all participants population	• Point estimate and 2-sided 90% exact CI by Clopper-Pearson method
• Assess the duration of response (DOR) of tucatinib in combination with trastuzumab and capecitabine by ICR and INV per RECIST v1.1 in the Japanese population and the all participants population	• DOR by ICR and INV per RECIST v1.1 in the Japanese population and the all participants population	• Kaplan-Meier estimate of median survival time and 90% by log-log transformation (Collette 1994)
• Assess the progression-free survival (PFS) of tucatinib in combination with trastuzumab and capecitabine by ICR and INV per RECIST v1.1 in the Japanese population and the all participants population	• PFS by ICR and INV per RECIST v1.1 in the Japanese population and the all participants population	• Kaplan-Meier estimate of median survival time and 90% by log-log transformation
• Assess the overall survival (OS) of tucatinib in combination with trastuzumab and capecitabine in the Japanese population and the all participants population	• OS in the Japanese population and the all participants population	• Kaplan-Meier estimate of median survival time and 90% by log-log transformation

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Objectives	Endpoints	Statistical Methods
• Assess the safety of tucatinib in combination with trastuzumab and capecitabine in the Japanese population and the all participants population	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and lab abnormalities in the Japanese population and the all participants population • Frequency of dose modifications and treatment discontinuations in the Japanese population and the all participants population • Vital signs and other relevant safety variables in the Japanese population and the all participants population	• AEs, laboratory values, vital signs, and electrocardiogram (ECG) measurements will be listed and summarized with descriptive statistics
Exploratory		
• Evaluate the pharmacokinetics (PK) of tucatinib administered in combination with trastuzumab and capecitabine in the Japanese population, the South Korean population and the all participants population	• Plasma concentrations of tucatinib in the Japanese population, the South Korean population and the all participants population	• Individual (participant) plasma tucatinib concentrations at each sampling time will be listed and summarized with descriptive statistics

Methodology:

This is a single-arm, multicenter, phase 2 study with a safety run-in designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and capecitabine in participants with locally advanced unresectable or metastatic HER2+ breast cancer who had prior treatment with a taxane anticancer agent, trastuzumab, pertuzumab, and T-DM1. This study consists of 3 regional Asian populations defined as Japanese participants enrolled in Japan, South Korean participants enrolled in the Republic of Korea, and Taiwanese participants enrolled in Taiwan. This study is designed to estimate the cORR in the Japanese population and to detect an improvement in the ORR compared with a historical 20% response rate.

Prior to enrollment on the main portion of the trial, a safety run-in was conducted in 4 Japanese participants to assess the safety and tolerability of the standard doses and schedule for the combination of tucatinib, trastuzumab, and capecitabine. The inclusion and exclusion criteria, treatment doses, schedule and study assessments, and safety reporting rules were identical to the main portion of the trial, with the exception of additional study visits and laboratory assessments performed during the first 2 cycles of study intervention. A safety monitoring committee (SMC) consisting of the study clinical director, medical expert, investigators, study statistician, and other study team members evaluated the overall safety of participants enrolled in the safety run-in and found the safety and tolerability acceptable; thus, enrollment into the main portion of the trial was allowed to proceed.

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Treatment was administered in 21-day cycles. Tucatinib 300 mg (150 mg × 2 tablets) was given orally twice daily (PO BID) for a total of 600 mg per day. Trastuzumab was given as a loading dose of 8 mg/kg intravenous followed by 6 mg/kg once every 21 days. Capecitabine was given at 1000 mg/m^2 PO BID on Days 1 to 14 of each cycle. Dose modifications of tucatinib, trastuzumab, and capecitabine were allowed as needed for participant safety. Participants who discontinued capecitabine and/or trastuzumab were allowed to remain on study intervention. Participants who discontinued tucatinib were allowed to remain on study intervention.

While on study intervention, participants were assessed for progression every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose holds or interruptions. After completion of study intervention and after occurrence of disease progression, participants continued to be followed for survival until death, study closure or withdrawal of consent. The safety of participants was monitored by the SMC on an ongoing basis throughout the study.

Note: the terms “subject” and “participant” are used interchangeably in this clinical study report.

Number of Participants (planned and analyzed):

Approximately 55 participants consisting of approximately 42 participants (including 3 to 6 participants in the safety run-in) in the Japanese population, approximately 10 participants in the South Korean population, and approximately 3 participants in the Taiwanese population were planned to be enrolled into this study.

As of the 17-July-2023 data cutoff date for the primary analysis, 104 participants were screened and 66 participants (53 Japanese, 10 South Korean, and 3 Taiwanese participants) were enrolled at 24 sites in 3 countries.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Key Inclusion Criteria

- Histologically confirmed HER2+ breast carcinoma, with HER2+ defined by in situ hybridization (ISH) or immunohistochemistry (IHC) methodology according to the American Society of Clinical Oncology/College of American Pathologists.
    - Tissue blocks or slides must be submitted to confirm HER2 positivity (using IHC, ISH, or fluorescence in situ hybridization [FISH]) by a Sponsor-designated central laboratory
    - Centrally confirmed HER2+ results (either IHC, ISH, or FISH) from a previous study can be used to determine eligibility for this study with approval from the sponsor
- Previous treatment with a taxane anticancer agent, trastuzumab, pertuzumab, and T-DM1, except when the use of taxanes is contraindicated or judged not to be the best treatment at the discretion of the investigator.

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- Radiographically and/or histologically confirmed disease progression on last systemic anticancer treatment for unresectable locally advanced or metastatic HER2+ breast carcinoma.
- Measurable disease as assessed by RECIST v1.1
- Age of majority at time of consent
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
- Life expectancy ≥6 months, in the opinion of the investigator

CNS Inclusion – Based on screening contrast brain magnetic resonance imaging (MRI), participants must have **one** of the following:

- No evidence of brain metastases
- Untreated brain metastases not needing immediate local therapy. For participants with untreated central nervous system (CNS) lesions >2.0 cm on screening contrast brain MRI, discussion with and approval from the sponsor is required prior to enrollment.
- Previously treated brain metastases
    - Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy, provided that there is no clinical indication for immediate re-treatment with local therapy in the opinion of the investigator
    - Participants treated with CNS local therapy for newly identified lesions or previously treated progressing lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if all of the following criteria are met:
        - Time since whole brain radiation therapy is ≥14 days prior to first dose of study intervention, time since stereotactic radiosurgery is ≥7 days prior to first dose of study intervention, or time since surgical resection is ≥28 days
        - Other sites of disease assessable by RECIST v1.1 are present
    - Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

Key Exclusion Criteria

- Prior treatment with:
    - Lapatinib within 12 months of starting study intervention
    - Neratinib, afatinib, or other investigational HER2/epidermal growth factor receptor or HER2 tyrosine kinase inhibitor at any previous time

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- Tucatinib or enrolled on a tucatinib clinical trial and received tucatinib

- Previous treatment with capecitabine (or other fluoropyrimidine [eg, 5-fluorouracil]) for metastatic disease (except in cases where capecitabine was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity). Note: participants who have received capecitabine for adjuvant or neoadjuvant treatment at least 12 months prior to starting study intervention are eligible.
- History of exposure to the following cumulative doses of anthracyclines:
  - Doxorubicin >360 mg/m^2
  - Epirubicin >720 mg/m^2
  - Mitoxantrone >120 mg/m^2
  - Idarubicin >90 mg/m^2
  - Liposomal doxorubicin (eg Doxil, Caelyx, and/or Myocet) >550 mg/m^2
- Treatment with any systemic anticancer therapy (including hormonal therapy), non-CNS radiation, or experimental agent ≤3 weeks of first dose of study intervention or are currently participating in another interventional clinical trial. An exception for the washout of hormonal therapies is gonadotropin releasing hormone agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications
- Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
  - Alopecia and neuropathy, which must have resolved to ≤ Grade 2
  - Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
  - Anemia, which must have resolved to ≤ Grade 2
- Clinically significant cardiopulmonary disease such as:
  - Ventricular arrhythmia requiring therapy
  - Symptomatic hypertension or uncontrolled hypertension as determined by investigator
  - Any history of symptomatic CHF or symptomatic decreases in ejection fraction
  - Severe dyspnea at rest (Common Terminology Criteria for Adverse Events v4.03 Grade 3 or above) due to complications of advanced malignancy
  - Any history of interstitial lung disease or pneumonitis that is Grade 2 or greater
  - Hypoxia requiring supplementary oxygen therapy

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- Positive for Hepatitis B by surface antigen expression, or positive for Hepatitis C infection, or the presence of known chronic liver disease. Participants who have been treated for Hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks. As reactivation of these viruses has not been studied with the combination of tucatinib, trastuzumab, and capecitabine, there is a possible risk of reactivation.
    - Participants who are positive for either antibodies to hepatitis B core or antibodies to hepatitis B surface should be screened using polymerase chain reaction (PCR) measurement of Hepatitis B DNA levels. Participants with Hepatitis B DNA levels by PCR that require nucleoside analogue therapy are not eligible for the trial. The latest local guidelines should be followed regarding the monitoring of Hepatitis B DNA levels by PCR for participants on study treatment.

CNS Exclusion – Based on screening brain MRI, participants must not have any of the following:

- Any untreated brain lesions >2.0 cm in size, unless discussed with the sponsor and approval for enrollment is given
- Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of >2 mg of dexamethasone (or equivalent). However, participants on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) may be eligible with discussion and approval by the sponsor.
- Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to subject (eg, brain stem lesions). Participants who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria.
- Known or suspected leptomeningeal disease as documented by the investigator
- Have poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

Study Interventions, Dose, and Mode of Administration, and Batch Numbers:

Participants in the study received a combination treatment of tucatinib, trastuzumab, and capecitabine according to Table 1. All treatments were given on a 21-day cycle. The manufacturing lot numbers for the investigational product are provided in Table 2.

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Table 1. Study Interventions Administered

Intervention	Intervention Type/Use	Formulation/ Route of Administration	Dose	Frequency	Schedule
Tucatinib	Investigational medicinal product/ Experimental	Tablet/Oral	300 mg (2 x 150 mg)	BID	Daily
Trastuzumab	Approved product	Vial/IV Infusion	Loading dose 8 mg/kg IV, followed by 6 mg/kg IV. A loading dose was not given to participants who received trastuzumab within 4 weeks of Cycle 1 Day 1. These participants received trastuzumab at 6 mg/kg each cycle, including Cycle 1.	Every 21 days	Day 1 of 21-day cycles
Capecitabine	Approved product	Tablet/Oral	1000 mg/m^2	BID	BID for Days 1-14 only of a 21-day cycle

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Table 2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Lot ID	Strength/Potency	Dosage Form
Tucatinib 50 mg tablet	n/a	Merck Lot IDs: T042226 U022730 W016973 W036467 X008363 Y007362	50 mg	Tablet
Tucatinib 150 mg tablet	n/a	Merck Lot IDs: T042233 U022169 W016939 W039295 X018392 X019163	150 mg	Tablet

Duration of Study Intervention:

Study intervention was continued until unacceptable toxicity, disease progression, death, withdrawal of consent, or study closure. In the absence of clear evidence of radiographic disease progression (per RECIST v1.1), development of CNS symptoms, or radiographic changes thought to pose potential immediate risk to the participant, all efforts were made to continue treatment until unequivocal evidence of radiologic progression occurred, as defined in RECIST v1.1.

Summary of Results: (Based on primary analysis data cutoff date of 17-Jul-2023)

Demographic and Other Baseline Characteristics:

The 66 participants in this study were considered to be generally representative of patients with unresectable locally advanced/metastatic HER2+ breast cancer, with and without brain metastases. The median age of participants was 54.0 years (range: 31 to 84) in the Japanese population and 53.0 years (range: 31 to 84) in the all participants population. All 66 (100%) participants were female and Asian. Participants entering the study were ambulatory and able to perform normal activities without assistance as indicated by an ECOG performance status of 0 (84.9% in the Japanese population and 77.3% in the all participants population) and 1 (15.1% in the Japanese population and 22.7% in the all participants population). Participants were heavily pretreated with a median number of prior lines of systemic therapy of 4.0 (range: 2 to 7) in the Japanese population and 3.0 (range: 2 to 7) in the overall study population.

Exposure:

The median duration of tucatinib treatment was 7.6 months (range: 1 to 25) in both the Japanese population and the overall study population. The median relative dose intensity of tucatinib was 92.5% (range: 44 to 100) in the Japanese population and 93.9% (range: 44 to 100) in the overall study population.

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Efficacy Results:

A cORR by ICR of 35.4% (90% CI: 24.0, 48.3) was observed in Japanese participants demonstrating statistical significance against the null hypothesis (cORR ≤20%). A cORR of 40.0% (90% CI: 29.3, 51.4) was observed in the overall study population. Responses were durable, with a median duration of 8.3 months (90% CI: 6.2, 8.5) in the Japanese population and 8.5 months (90% CI: 6.2, 12.4) in the overall study population. The median PFS per ICR was 7.4 months (90% CI: 5.3, 7.6) in the Japanese population and 6.4 months (90% CI: 5.3, 7.5) in the overall study population. The estimated overall survival rate was at 80.2 % (90% CI: 66.7, 88.6) in the Japanese population and 82.5% (90% CI: 71.2, 89.6) in the overall study population at 12 months.

Safety Results:

Tucatinib in combination with trastuzumab and capecitabine was well tolerated in Japanese participants and the overall study population. The types and rates of observed TEAEs were consistent with the established safety profile of tucatinib, except for a higher rate of elevated liver transaminases, which were typically manageable and reversible with dose modifications. Discontinuations due to TEAEs were infrequent (3.0% for both tucatinib and trastuzumab and 9.1% for capecitabine in the all participants population). There were no dose-limiting toxicities in the safety run-in, no TEAEs leading to death, and no new safety risks identified.

Pharmacokinetic Results:

Tucatinib and ONT-993 concentrations in Japanese participants overlapped with the overall study population which included Japanese, South Korean, and Taiwanese participants.

Other Results:

The coronavirus disease 2019 (COVID-19) pandemic did not significantly affect the ability to monitor and manage participant safety during the conduct of the study. Therefore, there was no impact on the integrity and interpretation of results for the study due to the COVID-19 pandemic.

Conclusions:

Overall, the results of this study demonstrated a positive benefit:risk for tucatinib in combination with trastuzumab and capecitabine for Japanese participants and the overall study population with previously treated locally advanced unresectable or metastatic HER2+ breast carcinoma.