10 December 2020
EMA/78409/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tukysa

International non-proprietary name: **tucatinib**

Procedure No. EMEA/H/C/005263/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AE	adverse event
AESI	adverse events of special interest
ASCO	American Society of Clinical Oncology
AUC	area under the concentration-time curve
BID	twice daily
BICR	blinded independent central review
BUN	blood urea nitrogen
CBR	clinical benefit rate
CI	confidence interval
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CSR	clinical study report
DDI	Drug-drug interaction
DFS	disease-free survival
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EOT	end of treatment
ESMO	European Society for Medical Oncology
GCP	good clinical practice
HER2	human epidermal growth factor receptor-2
HR	hazard ratio
HRQOL	health-related quality of life
iPSP	initial Pediatric Study Plan
ITT	intent to treat
LC-MS/MS	liquid chromatography and tandem mass spectrometry
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
ORR	objective response rate
OS	overall survival
Pbo	placebo
PBPK	physiologically based pharmacokinetics
PD	progressive disease
PFS	progression-free survival
$PFS_{BrainMets}$	progression-free survival in subjects with brain metastases
P-gp	P-glycoprotein
PIC	powder in capsule
PK	pharmacokinetics
PO	oral/orally
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PS	performance status
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose

SAE	serious adverse event
SD	stable disease
SSQ	special search query
T-DM1	trastuzumab emtansine
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TQT	QT/corrected QT interval
US	United States
VAS	visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Seagen B.V. submitted on 9 January 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Tukysa, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 December 2018.

The applicant applied for the following indication: Tukysa is indicated in combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 2 prior anti-HER2 treatment regimens.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0036/2018 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance tucatinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did seek Scientific advice from the CHMP.

The applicant obtained CHMP scientific advice in 2017 regarding the non-clinical, clinical, and

chemistry, manufacturing, and controls (CMC) development of tucatinib (EMEA/H/SA/3578/1/2017/SME/I and EMEA/H/SA/3578/1/2017/SME/III).

Quality

Scientific advice pertained to the appropriateness of the starting materials of the synthesis of the active substance, the specifications for the active substance and the finished product, respectively, and the dissolution method for finished product quality control testing.

Non-Clinical

Scientific advice pertained to the suitability of the non-clinical package to support the indication.

Clinical

The scientific advice related to the clinical development of tucatinib included: study design, patient selection and the associated statistical testing plan for the primary end point, choice of the endpoint, safety database.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Blanca Garcia-Ochoa

The appointed co-rapporteur had no prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	9 January 2020
The procedure started on	30 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 April 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	5 May 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 May 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 May 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	22 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 October 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	9 November 2020

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	25 November 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tukysa on	10 December 2020

2. Scientific discussion

2.1. Problem statement

Treatment of patients with HER2+ breast cancer after progression on T-DM1 remains a clinical challenge, and the prognosis of these patients remains poor. There is no single established standard of care (Dieras 2017; Verma 2012) and no approved therapies have demonstrated clinically meaningful improvements in PFS or OS (Blackwell 2012; Geyer 2006; Verma 2012). Preferred regimens include continuation of HER2 targeted therapy with trastuzumab or lapatinib in combination with cytotoxic chemotherapy, such as capecitabine (Cardoso 2018; Giordano 2018; Gradishar 2016). However, the efficacy of these regimens in this setting remains modest, with reported median PFS of 3.3 to 4.9 months (Krop 2014; Rugo 2019) and median OS of 15.8 to 17.2 months (Krop 2017; Rugo 2019). Hence, there is a significant unmet medical need for HER2+ metastatic breast cancer patients, who have progressed despite receiving current standard of care, including 3 prior anti-HER2 agents, and better treatment options for these patients are urgently needed to improve efficacy and tolerability.

2.1.1. Disease or condition

The claimed indication for tucatinib is as follows: Tukysa is indicated in combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 2 prior anti-HER2 treatment regimens.

Hence, patients from the targeted patient population have had at least two prior anti-HER2 treatment containing regimens for locally advanced or metastatic HER2+ breast cancer in the (neo) adjuvant or metastatic setting. Moreover, the inclusion criteria specified that patients should have had received previous treatment with trastuzumab, pertuzumab, and T-DM1, which is standard of care both in the (neo-) adjuvant and the metastatic setting of HER2+ breast cancer.

2.1.2. Epidemiology

Breast cancer is the most common form of cancer in women worldwide (Ferlay 2018), with approximately 2 million patients diagnosed with breast cancer in 2018 and more than 600,000 deaths. Approximately 1% of breast cancer cases occur in men (Siegel 2019). Historically, HER2+ breast cancer tends to be more aggressive and more likely to recur than HER2-negative breast cancer (American Cancer Society 2018; Loibl 2017; Slamon 1987). HER2+ breast cancer also disproportionately affects younger patients, where the proportion of HER2 positivity is higher compared to older patients (Murphy 2019).

Despite advances, locally advanced unresectable or metastatic HER2-positive breast cancer remains an incurable disease, as patients do not have a standard of care option after disease progression on T-DM1, and the prognosis of these patients remains poor. Moreover, no systemic agents are specifically approved for treatment of the patients with HER2+ metastatic breast cancer with brain metastases, who have an even poorer prognosis.

2.1.3. Biologic features

Between 15% and 30% of breast cancers overexpress the HER2 receptor and are classified as HER2+ breast cancer (Cronin 2010; Loibl 2017; Owens 2004; Slamon 1987; Wolff 2014). HER2 is a member of the HER family of receptor tyrosine kinases that also includes epidermal growth factor receptor (EGFR or HER1), HER3, and HER4. HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. In cancer cells, HER2 protein levels can be increased 10 to 100-fold above levels found in normal cells (Kraus 1987; Sliwkowski 1999).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Once HER2+ breast cancer has metastasised, the estimated 5-year overall survival (OS) rate ranges from 15% to 26% (American Cancer Society 2018; National Cancer Institute 2018; National Cancer Institute (NCI)). The introduction of HER2-targeted therapy based on inhibition of HER2 using either antibodies (trastuzumab and pertuzumab), antibody-drug conjugates (ado trastuzumab emtansine [T-DM1]), or small molecule tyrosine kinase inhibitors (TKIs; lapatinib and neratinib) has led to significant and ongoing improvements in disease-free survival (DFS), progression free survival (PFS), and OS in both the adjuvant and metastatic settings (Baselga 2012; Geyer 2006; Slamon 2001; Verma 2012).

2.1.5. Management

First-line treatment for most patients with HER2+ metastatic breast cancer is a combination of trastuzumab plus pertuzumab and chemotherapy. However, within 2 years, the majority of patients treated with this combination will progress (Baselga 2012; Swain 2013). After progression on trastuzumab, pertuzumab, and chemotherapy, standard of care treatment for patients with HER2+ metastatic breast cancer is T-DM1. Although T-DM1 is often given as a second line of metastatic treatment, when patients receive a pertuzumab-based regimen in the neoadjuvant or adjuvant setting and relapse quickly, T-DM1 may also be given as a first-line metastatic agent (Cardoso 2018; Giordano 2018).

Unmet medical need

Treatment of patients after progression on T-DM1 remains a clinical challenge, and the prognosis of these patients remains poor. There is no single established standard of care (Dieras 2017; Verma 2012) and no approved therapies have demonstrated clinically meaningful improvements in PFS or OS (Blackwell 2012; Geyer 2006; Verma 2012). Preferred regimens based on American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN) guidelines for these patients include continuation of HER2 targeted therapy with trastuzumab or lapatinib in combination with cytotoxic chemotherapy, such as capecitabine (Cardoso 2018; Giordano 2018; Gradishar 2016). However, the efficacy of these regimens in this setting remains modest, with reported median PFS of 3.3 to 4.9 months (Krop 2014; Rugo 2019) and median OS of 15.8 to 17.2 months (Krop 2017; Rugo 2019). There remains significant unmet medical need for HER2+ metastatic breast cancer patients who have progressed despite receiving current standard of care, including 3 prior anti-HER2 agents, and better treatment options for these patients are urgently needed to improve efficacy and tolerability.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate-release film-coated tablets for oral administration containing 50 mg and 150 mg of tucatinib as the active substance.

Other ingredients in the tablet core are: copovidone (E1208), crospovidone (E1202), sodium chloride, potassium chloride (E508), sodium hydrogen carbonate (E500), colloidal anhydrous silica (E551), magnesium stearate and microcrystalline cellulose.

Other ingredients in the film coating are: poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b), yellow iron oxide (E172).

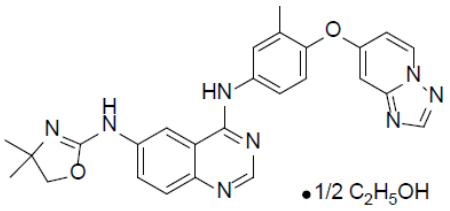
The film-coated tablets are available in oriented polyamide (OPA)/aluminium foil/polyvinyl chloride (PVC) laminate blisters sealed with aluminium foil.

2.2.2. Active Substance

General information

The chemical name of tucatinib is N^6-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-N^4-[3-methyl-4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl]-4,6-quinazolinediamine. Tucatinib is ethanol compounded (2:1). It corresponds to the molecular formula $C_{26}H_{24}N_8O_2$ – ½ C_2H_5OH. Its relative molecular mass is 503.57 and it has the chemical structure shown in Figure 1.

Figure 1. Chemical structure of tucatinib hemiethanolate



The structure of the active substance (AS) was elucidated by a combination of liquid chromatography/mass spectrometry (LC/MS), ^{1}H-, ^{13}C-, ^{15}N- NMR spectrometry, IR spectroscopy, XRD (single crystal and powder crystallography, respectively), thermal gravimetric analysis (TGA, to evaluate molar ratio of solvent) and differential scanning calorimetry (DSC, to further characterise ethanol solvate).

Tucatinib appears as an off-white to yellow, non-hygroscopic crystalline powder. It is practically insoluble in water; in aqueous buffer solutions at pH above 4 it has low solubility (<0.4 mg/ml); below pH 4 the active substance exhibits high solubility (>18.9 mg/ml). The active substance is a weak base with pKas of 2.07, 4.18, and 6.15; its partition coefficient was found to be 5.3.

Tucatinib molecule does not exhibits stereoisomerism.

Polymorphism has been observed for tucatinib. It has been found to exist in many solid-state forms: 4 crystalline anhydrous polymorphs and 25 crystalline pseudopolymorphs have been characterised to

date. Of the 25 pseudopolymorphs, 3 hydrates, 6 classical-type solvates, 1 transient solvate and 3 unique isostructural solvates composing 15 solvates have been identified. Crystalline solvate form (form B) tucatinib hemiethanolate was selected for further development due favourable physico-chemical properties. Tucatinib hemiethanolate (form B) is obtained consistently by the manufacturing process. It has been demonstrated that there is no change in polymorphic form of the active substance during AS storage.

Manufacture, characterisation and process controls

The AS manufacturing sites were stated.

The synthesis of tucatinib hemiethanolate consists in total of six steps.

To the starting materials initially proposed by the applicant, another one was designated upon the request of the CHMP. All SMs have been justified in line with the considerations of ICH Q11 and are acceptable. The SMs are controlled by acceptable specifications. Isolated intermediates in the synthesis are clearly defined and are sufficiently characterised and controlled by appropriate specifications.

Yields of each step and the batch size of active substance have been stated. All solvents, auxiliary materials, catalysts and reagents are sufficiently specified and adequately controlled.
Proven acceptable ranges (PARs) and normal operating ranges (NORs) for material inputs and process/operating parameters were established based on multivariate design of experiments (DOE) and one variable at a time (OVAT) approaches. The resulting PARs, NORs, and target values are listed in all steps of the synthesis. It was confirmed that a design space is not applied for and in line with the PARs definition, only one parameter will be changed at a time keeping the other parameters within their NOR. For each step, a tabulated overview of process parameters covering material inputs and reaction conditions/operating parameters with corresponding PAR and NOR has been presented and criticality of each process parameter was assessed. The synthesis does not have any critical steps. However critical process parameters (CPPs) and non CPP have been identified and were clearly indicated.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The possible impurities from the manufacturing process have been listed and their mutagenic class has been reported. For each step, sufficient details of the fate and purge of impurities in the isolation and purification of the process intermediates and the final active substance have been presented and were updated during the procedure upon the definition of an additional starting material. The potential carry-over of the residual solvents and inorganic impurities used in the manufacturing process used in the manufacturing process has been also adequately discussed. Overall the presented information for all potential impurities, their fate and control, is satisfactory and the control strategy in this regard is considered acceptable.

The process development has been sufficiently described. The same main synthetic route has been used during development. Minor changes during transfer of the process between sites, during scale up and to ensure facility fit have been described sufficiently.

Transferring to the commercial site included minor modifications in step 3, clearer description of step 4 and adjustment of IPCs in same step. An overview of the synthetic processes, sites and use of active substance batches in the finished product studies has been provided. The impact of all modification

throughout the process development has been assessed and concluded either that the product quality is not affected or improved.

The AS is packaged in double low-density polyethylene (LDPE) bags, which are placed in a high-density polyethylene HDPE drum. A satisfactory specification for the LDPE bag is provided. The LDPE complies with the requirements of Regulation (EU) No. 10/2011, Regulation (EC) No. 1935/2004, and with Ph. Eur. 3.1.3 "Polyolefins".

Specification, analytical procedures, reference standards, batch analysis and container closure

The AS specification includes appropriate tests and limits for appearance (visual), identification (HPLC, FT-IR), assay (HPLC), impurities (HPLC, two methods), residual solvents (GC), residue on ignition (Ph. Eur.), palladium (ICP-MS), polymorphic form (XRPD), water content (Ph. Eur.) and microbial enumeration tests (Ph. Eur.).

The limit for any unspecified impurity corresponds to the ICH Q3A identification threshold. The limits proposed for certain specified impurities exceed the ICH Q3A qualification threshold but have been toxicologically qualified and, in addition, were demonstrated as presenting no structural alert for genotoxicity.
The specifications limits for residual solvents have been set according to ICH Q3C, except for ethanol. The limit for ethanol content exceeds ICH Q3C option 1. The ethanol contribution from the hemiethanolate in the AS was theoretically calculated. Ethanol is used in the final step of the manufacturing process to transform tucatinib into the hemiethanolate polymorphic form. As ethanol is a key component of the AS structure, a limit other than the ICH Q3C residual solvent limit is warranted. Using ICH Q3C option 2 (maximum daily dose = 600 mg, PDE 50 mg/day) the concentration limit was calculated. The AS is dissolved during finished product manufacture and it has been demonstrated that ethanol is removed in downstream finished product manufacture. AS batches containing ethanol within the proposed specification limits, result in finished product intermediate (spray-dried dispersion) with ethanol content in a range; which is considered not to impact patient safety and thus the proposed ethanol specification limit in the AS is acceptable.
Risk assessment of elemental impurities in accordance with ICH Q3D has been conducted. Levels of all Class 1 and Class 2A elements are <30% of the PDE, hence no additional controls are deemed necessary. Intentionally added catalyst palladium, was also found below <30% of the PDE but it is controlled in the AS specification.

Batch data were provided for five commercial scale AS batches manufactured at the proposed manufacturing site using the synthetic route proposed for commercial manufacture. Batch data for another ten commercial and pilot scale development batches manufactured at the development manufacturing sites were also provided. All the results comply with the proposed AS specification and demonstrate consistent manufacture and quality of the AS.

Stability

Stability data has been provided for five commercial scale batches manufactured at the proposed manufacturing site. These stability batches were packaged in the proposed container closure system. Stability data were provided for up to 24 months stored at long term conditions (25°C / 60% RH and 30°C / 65% RH) and for up to nine months at accelerated conditions (40°C / 75% RH) according to the ICH guidelines.

Samples were tested for appearance, assay, impurities (specified impurities any unspecified impurity, total impurities), ethanol, water content and polymorphic form. Assay values fluctuated and a tendency to increase in total impurities were observed but both parameters remained within the limits as did all other tested parameters.

Photostability testing was carried out on one commercial scale batch in as per ICH Q1B. No degradation was found in the light-exposed and the controlled samples after the exposure, indicating that AS is not light sensitive.

Stress testing of the AS was performed to evaluate degradation of the AS and the stability indicating capability of the AS HPLC assay and purity method. These studies were conducted using a commercial scale batch placed under a variety of stressed conditions including acidic, basic, oxidative, aqueous, and thermal stress. It was also concluded that the HPLC assay and purity method is stability indicating.

Based on the available stability data, the proposed retest period at the recommended storage temperature is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is an immediate release film-coated tablet presented in two strengths, containing 50 mg and 150 mg of tucatinib respectively. The 50 mg strength tablet is a round, yellow tablet, debossed "TUC" on one side and "50" on the other. The 150 mg strength tablet is an oval-shaped yellow tablet, debossed "TUC" on one side and "150" on the other.

The qualitative composition of Tukysa is presented in section 2.2.1 of this report and in SmPC section 6.1. All excipients used are standard and are commonly used in the pharmaceutical industry. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The two strengths are dose proportional apart from a small difference in the amount of film-coating. The film-coating is non-functional.

The development of the formulation and manufacturing process was conducted following a traditional pharmaceutical development approach that targeted an immediate release oral product. However, principles of enhanced approach as described in ICH Q8 through Q11 such as definition critical quality attributes (CQAs) as well as formulation and process risk assessments have been utilised in formulation and process development, but no design spaces have been claimed.

Tucatinib is a BCS Class 2 compound exhibiting low aqueous solubility and high permeability. Early clinical studies used two different powder in capsule formulations and two different micronised powder in suspension formulations.

The development and selection of the formulation was driven by the early formulations used initially in the clinical development. Different formulations containing tucatinib hemiethanolate were used and compared in clinical studies: powder in capsule, micronised powder in capsule, suspension of micronised active substance, solution of active substance and amorphous tablet formulation, respectively. The observed high inter-subject pharmacokinetic variability and an effect on absorption of tucatinib when administered in the fed state, triggered further development work evaluating enabling formulations of tucatinib. No AS concentrations used in manufacturing process are above the equilibrium solubility limits.

The development of the formulation was described in detail. A discussion of the different solvent systems evaluated, and lots produced from each solvent system were provided. The final solvent

system was selected to minimise residual water and reduce the risk for potential hydrolysis of tucatinib. This solvent system was used throughout clinical development at the commercial manufacturing site and remains unchanged for the proposed commercial process. During manufacture of the intermediate, the AS is converted from tucatinib hemiethanolate (crystalline polymorphic form B) to tucatinib (amorphous form).

In order to ensure the immediate release of drug, the tablet formulation include crospovidone as a disintegrant and multiple disintegrant aids to achieve rapid disintegration to particles or small granules, thereby facilitating rapid dissolution. A dry granulation is employed to improve the flowability, particle size uniformity, and compressibility of the powder blend. The amount of intermediate is adjusted based on its potency with concomitant equivalent adjustments to the weights of sodium chloride, potassium chloride, and sodium bicarbonate.

Two complementary dissolution methods, method 1 and method 2, are used to control the finished product. Dissolution method 1 was included in the initial dossier, while dissolution method 2 was introduced during the procedure following a major objection raised by CHMP concerning the discriminatory power of method 1. The development of both dissolution methods has been sufficiently described and justified. The proposal for the combination of two dissolution methods and their corresponding limits for the control of the finished product has been adequately supported by development data; the approach is acceptable.

Dissolution method 1 has not been demonstrated to be discriminatory with regards to the most critical attributes in the finished product, which are the form of the active substance and the particle size of the intermediate. Since the data presented clearly demonstrates that the dissolution method cannot differentiate between the proposed formulation containing the AS in the amorphous form and a formulation containing 100% crystalline AS, the use of the method to waive any bioequivalence testing in the future is not an option. Based on the dissolution profiles/data presented, the proposed acceptance criteria for dissolution of (method 1) has been justified.

Dissolution method 2 has been demonstrated to be discriminatory with regards to different concentrations of crystalline content, minor composition quantitative changes and hardness of the film-coated tablets. Based on the development data and the test of the pivotal batches and the primary stability batches, the proposed acceptance criterion for dissolution (method 2) has been justified. However, since this acceptance criterion was based on limited batch data and stability data, the CHMP requested, and the applicant has made, the following commitments: 1) to re-evaluate the specification limit for dissolution (method 2) when data from 30 finished product batches and at least 12 months of stability data are available is available post-approval and 2) to submit updated batch analysis data and stability data for the finished product analysed with the complementary dissolution method 2 when data is available post-approval; this approach is accepted (See 3.1.6).

The formulation and manufacturing process of the finished product have remained the same throughout clinical development and remain unchanged for the proposed commercial process. The sites involved in the development and the history of finished product batches produced throughout clinical development including manufacture of the primary stability batches was presented.

A process risk assessment to assess the potential impact of manufacturing process unit operations critical quality attributes (CQAs) has been performed. The process steps feed solution preparation, spray drying and secondary drying and their potential impact on each CQA (assay, related substances, crystallinity, residual solvents, water content and PSD) have been investigated. The proposed PARs have been justified.

For the film-coated tablets, an initial risk assessment was performed to assess the potential impact of manufacturing process unit operations on tucatinib CQAs and a summary was presented. The chosen

CQAs are justified and are all included and controlled in the product specification as discussed later in the report. The unit operations pre-blending, roller compaction, final blending, tablet compression, and film- coating were considered to have a medium overall risk to influence tablet CQAs, and therefore evaluation of the process parameters of these unit operations were evaluated in DOE studies. Based on these investigations PARs for process parameters of each unit operation have been established. The development of the control strategy for tucatinib film-coated tablets has been described in sufficient detail.

Tukysa film-coated tablets are packaged in oPA/ALU/PVC blister sealed with aluminium foil. The suitability of the container closure system was evaluated with respect to safety and compatibility, and with respect to protection from moisture ingress (water vapor transmission rate) and oxygen transmission rates. The proposed container closure system is suitable in order to minimise moisture uptake and the increase in the carbamate (hydrolysis) impurity in the finished product. Satisfactory specifications for the blister were provided. The material complies with Regulation (EC) 1935/2004 on Food Contact Materials, Regulation (EU) No. 10/2011 as amended, Ph. Eur. 3.1.11 and 3.2.2.

Manufacture of the product and process controls

The finished product is manufactured in two sites.

The manufacturing process is divided into the manufacture of the intermediate and the manufacture of the film-coated tablets. The manufacturing process for the intermediate comprises four steps. A flowchart including the applied IPCs was presented. The manufacturing process was described in sufficient detail including conditions/parameters and equipment used. The IPCs have been described including methods and acceptance criteria. The PARs have been set according to the results obtained during pharmaceutical development. No critical process parameters were identified. The release and stability specifications for the intermediate cover relevant parameters for this finished product intermediate and are suitable to control its quality. Sufficient batch analysis data were provided for the intermediate.

The intermediate is packaged in a low-density polyethylene (LDPE) sleeve, cable tied, and placed inside a second LDPE bag with a desiccant bag in between to reduce moisture ingress. The outer bag is then cable tied, placed into an aluminium foil plastic laminated bag, vacuumed down and heat-sealed; it is then placed into a high-density polyethylene (HDPE) drum. The primary container closure system is selected in accordance with the Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03). The LDPE bags in contact with the product comply with Commission Regulation (EU) No. 10/2011 as amended.

The manufacturing process from the intermediate to tucatinib film-coated tablets comprises six steps. A flowchart including the applied IPCs was presented.

A detailed description of the manufacturing process was provided which includes information on equipment and materials used. Based on manufacturing development no critical steps identified. Relevant operating parameters with PARs were tabulated. PAR ranges originating from process development studies have been updated, taking into account process validation results, where appropriate. NORs were introduced as requested which are considered sufficiently narrow. It has been clarified that no design space is claimed. The in-process controls are adequate for this type of manufacturing process and pharmaceutical dosage form.

The packaging material for bulk tucatinib film-coated tablets which is defined as product intermediate was stated. The material complies with Commission Regulation (EU) No. 10/2011 as amended, and Ph. Eur. 3.1.4.

Holding times have been defined and supported by acceptable stability data discussed later in the report. The shelf-life period is calculated from the mixing of the intermediate with remaining excipients in the film-coated tablet; this has been justified as per the Note for guidance on the start of shelf-life of the finished dosage form (EMEA/CVMP/453/01), the Guideline on manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015) and by appropriately designed and conducted stability studies on the intermediate and the respective finished product as discussed below in Stability.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The manufacturing process and dosage form are considered standard, hence validation data for commercial scale has not been presented; this is in line with Guideline on process validation for finished products. In line with the same guideline, detailed process validation schemes for the manufacturing process of the intermediate and the film-coated tablets have been presented. Confirmations have been provided that process validation using the first three production scale batches of the intermediate and the film-coated tablets will be completed prior to commercialisation.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification (FT-IR, HPLC), assay (HPLC), uniformity of dosage units (Ph. Eur.), degradation products (HPLC), dissolution, method 1 and 2 (Ph. Eur., HPLC), water content (Ph. Eur.) and microbial limit tests (Ph. Eur.).

Overall, the specification has been adequately set in accordance with ICH Q6A, Ph. Eur. and based on available comprehensive batch analysis and stability data. The limits for degradation products correspond to ICH Q3B identification threshold, hence they are acceptable. The proposal for the combination of two dissolution methods and their corresponding limits for the control of the finished product has been adequately supported by development data; the approach is acceptable. In relation to this, the CHMP requested, and the applicant has made, two commitments to be addressed post approval, as discussed above. The omission of testing of crystallinity was sufficiently justified since the dissolution method was found capable of differentiating tablets batches spiked with crystalline AS.

A risk assessment for the potential presence of elemental impurities in the finished has been conducted in accordance with ICH Q3D, applying the drug component approach. The relevant discussion has been provided. No elemental impurities were identified to be present at a level of greater than 30% of the PDE limit for oral administration. Based on this, tests for elemental impurities are not included in the finished product specification.

A risk assessment, in line with the guidance documents published on the EMA website, with respect to potential formation of nitrosamine impurities has been presented considering all potential sources along the manufacturing process, including active substance, excipients, water, finished product intermediate manufacture, finished product manufacture, equipment and packaging. The outcome of the risk assessment confirms that there is no risk for nitrosamine impurities formation. The risk assessment is found acceptable and no further confirmatory testing is warranted.

The analytical methods used have been adequately described and validated in accordance with ICH Q2 guideline. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis results were presented for five batches of the 50 mg tablet strength and nine batches of the 150 mg strength; all batches were of commercial scale. Of these batches, three batches per each

strength were manufactured by the proposed manufacturer while the rest are from development sites. All results complied with the specifications in place at the time. The results showed that the finished product meets the proposed specifications and confirm consistency in manufacture.

Stability of the product

Intermediate
The stability of the intermediate has been established based on data from appropriately designed and conducted stability studies. All stability batches were manufactured at the proposed manufacturing site and were packaged in the proposed container closure system. Samples were tested as per the specification of the intermediate and all results were within the specification. Based on this data the intermediate holding time and storage temperature is acceptable.

Film-coated tablets
Stability data from three commercial scale primary stability batches of each strength, stored for up to 12 months under long term conditions (25±2°C / 60±5% RH and 30±2°C / 65±5% RH), for up to 12 months at 5°C/ambient and for up to nine months under accelerated conditions (40±2 ºC / 75±5% RH), according to the ICH guidelines, were provided. These primary stability batches were manufactured at the proposed manufacturing site and were packaged in the proposed container closure system.

Stability samples were tested according to the shelf-life specification tests. Regardless of the storage conditions, results comply with the shelf-life specification limits. Assay was well-within limits; impurities remained low, but with tendency to increase at accelerated conditions for specified impurity (hydrolysis) and total impurities, water content fluctuating but had a tendency to increase. All parameters remained also within the specifications.

Of the primary stability batches, one batch per strength was manufactured using aged intermediate as per the proposed intermediate holding time. There was no difference in the results for the finished product batch containing aged intermediate, compared to other batches. As mentioned above, the finished product shelf life in the SmPC is calculated from the mixing of the intermediate with remaining excipients in the film-coated tablet.

Supportive stability data from the same six primary stability product batches but packaged in HDPE bottles and stored for nine months under the same accelerated conditions were also presented as supportive data since they represent worst case scenario because the level of protection against humidity is lower than that of the blister package. Based on the comparison of the most prominent degradation product in bottles versus blisters at 40°C/75% RH, tablets in blister packaging have the same or better stability profile than tablets stored in bottles. Therefore, the data from batches stored in bottles support the proposed shelf life for product stored in the proposed blister packaging.

One commercial scale batch of each tablet strength has been subjected to photostability testing in accordance with ICH Q1B. The results indicate that the finished product is not sensitive to light.

Forced degradation studies were conducted on tablets from a development batch which were subjected to stress conditions including thermolytic, photolytic, oxidative, and hydrolytic (humidity, acidic, basic) conditions. The stability-indicating nature of the methods has been demonstrated.

Based on the submitted stability data the proposed shelf-life of 24 months without any special storage condition, as stated in SmPC 6.3, is acceptable.

Adventitious agents

None of the materials used in the manufacture of Tukysa film-coated tablets are of animal or human origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The MOs raised during the procedure concerning the starting materials in the active substance synthesis and the suitability of the dissolution method and the corresponding acceptance criteria in the finished product specification have been satisfactorily addressed and the dossier was updated accordingly. The overall control strategy is adequately justified and is acceptable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were two of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to a request to submit additional batch analysis and stability data for the finished product analysed with the complementary dissolution method 2 and the re-evaluation of the specification limit for dissolution method 2. These points are put forward and agreed as recommendations for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to submit updated batch data and stability data for the finished product analysed with the complementary dissolution method 2, when available, via an appropriate post authorisation procedure.

- to re-evaluate the finished product specification limit for dissolution (method 2) once 30 finished product batches have been tested for release and at least 12 months of stability data are available on finished product validation batches, to provide assurance that the appropriate specification is implemented. When available, the updated batch data and stability data and re-evaluation of specification should be submitted via an appropriate post authorisation procedure.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical efficacy and safety of tucatinib were characterised through a battery of pharmacology, pharmacokinetics, and toxicology studies. The potency and selectivity of tucatinib were evaluated in

vitro using biochemical and cellular signalling assays. The anti-tumour activity of tucatinib was evaluated in vitro and in vivo in mouse tumour xenograft models.

The safety pharmacology of tucatinib was evaluated in Good Laboratory Practices (GLP)-compliant studies to examine effects on functions including cardiovascular, gastrointestinal, neurobehavioral and respiratory.

The pharmacokinetics of tucatinib after a single oral or intravenous (IV) dose in mice, rats, and cynomolgus monkeys were investigated. The toxicokinetics (TKs) of tucatinib were evaluated in repeat-dose toxicology studies in rats, rabbits, and cynomolgus monkeys.

The toxicology of tucatinib was evaluated in a series of GLP-compliant studies including: repeat-dose general toxicology studies in the rat and cynomolgus monkey, phototoxicity studies in vitro and in rats, genotoxicity studies including the standard test battery, embryo-fetal toxicity studies in pregnant rats and rabbits.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

Effect of tucatinib on HER2 kinase activity in enzymatic assays (study report TRN-5457)

To determine the potency and selectivity of tucatinib for purified ErbB2 (HER2), ErbB1 (EGFR) and ErbB4 (HER4), biochemical experiments were conducted using purified enzymes. HER3 was not evaluated because it was reported to have minimal kinase activity (Citri et al., 2003). Several approaches were used: for HER2, the kinase assay was performed using the protein kinase domain (amino acids 691-1255) while for EGFR a purified full-length enzyme preparation was used. In both cases, the assays were conducted using 15 μM adenosine triphosphate (ATP) and poly-Glu:Tyr (PGT, 4:1) as a substrate. For HER4, a His6-tagged protein kinase domain was employed (amino acids 706-991) and assays were performed using 7.5 μM ATP with PGT as a substrate. Phosphorylated tyrosine content was determined by ELISA using the phosphotyrosine specific monoclonal antibody (PY20).

The results of these experiments indicated tucatinib was a potent inhibitor of HER2 and was selective for HER2 compared with the ErbB kinase family members EGFR and HER4. Based on Ki calculations, tucatinib demonstrated a 28- to 88-fold increase in potency for HER2 relative to EGFR, and a 92–105-fold increase in potency for HER2 relative to HER4.

Experiments were also conducted to determine the time dependence of tucatinib mediated inhibition of HER2 by monitoring the production of phosphorylated product over time using various concentrations of tucatinib (study report TRN-5457). The results of this analysis were consistent with tucatinib having a slow on rate, and given the low nM potency of HER2 inhibition, the results were also consistent with tucatinib having a very slow off rate. These data were consistent with findings published for the structurally related HER2/EGFR kinase inhibitor lapatinib which was also shown to have a very slow off rate from the kinase domain of HER2 (Wood et al., 2004).

Effect of tucatinib on HER2 kinase activity in BT-474 cells (study report TRN-5480)

The BT-474 cell line was chosen to test the capacity of tucatinib in blocking HER2 phosphorylation as it contains a genomic duplication of the HER2 gene, resulting in high level expression of HER2 protein on the cell surface. The mean IC_{50} value from the aggregate of 16 experiments yielded an IC_{50} value of 9.88 nM.

Effect of tucatinib on EGFR kinase activity in A431 cells (study report TRN-5477)

The cell line A431, an epidermoid carcinoma derived cell line that overexpresses EGFR was employed to determine the capacity of tucatinib in blocking EGFR phosphorylation. Although this cell line expresses high protein levels of EGFR, the expression of HER2 is low. The mean IC_{50} value from the aggregate of 13 experiments yielded an IC_{50} value estimated to be 13,800 nM.

Effect of tucatinib on signal transduction downstream of HER2 kinase (study report TRN-5517)

The assessment was conducted in the HER2+ cell line BT-474. The assays included phosphorylation of HER2, HER3, AKT, ERK1/2 and MEK1 kinases, being all key signal transduction intermediates downstream of HER2. HER2 and HER3 phosphorylation status was determined by measuring total phosphotyrosine levels. For AKT the measurements were focused on the phosphorylation of serine 473 (signaling through PI3 kinase pathway); ERK1/2 were investigated by the phosphorylation status of several members of the kinase pathway

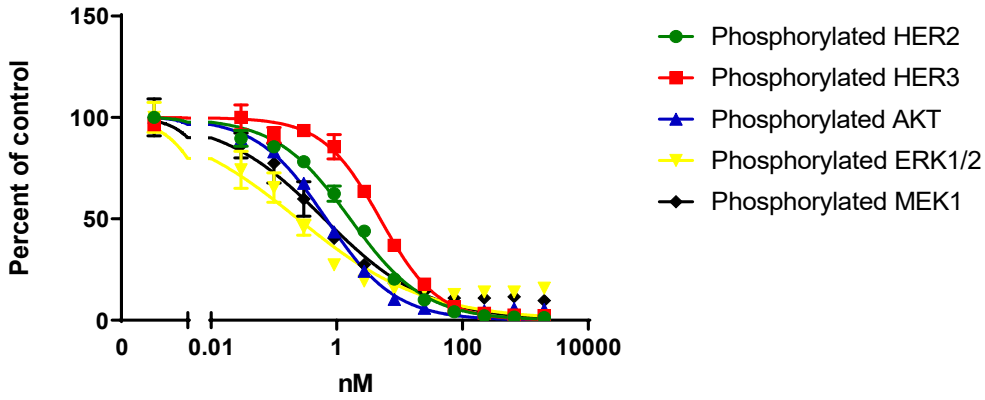
The effect of tucatinib on each of these signaling pathways in BT-474 cells showed that HER2, HER3, ERK1/2, and MEK1 phosphorylation were each inhibited by tucatinib (**Table 1** and **Figure 2**). These data indicate the selective inhibition of HER2 by tucatinib can inhibit signaling initiated by either HER2 homodimers (ERK1/2, MEK1) as well as HER2/HER3 heterodimers (AKT).

Table 1: EC_{50} values for the inhibition of HER2, HER3, AKT, ERK1/2, and MEK1 phosphorylation by tucatinib in BT-474 cells

pHER2EC50 (nM)	pHER3 EC50 (nM)	pAKT EC50 (nM)	pERK1/2 EC50 (nM)	pMEK1 EC50 (nM)
1.63	4.9	0.68	0.24	0.63

EC50 values derived from tucatinib dose response curves in BT-474 cells measuring pHER2 (total tyrosine phosphorylated HER2), pHER3 (total tyrosine phosphorylated HER3) pAKT (phosphorylated serine 473), pERK1/2 (phosphorylated threonine 185/187), pMEK1 (phosphorylated MEK1 serine 222).

Figure 2: Effects of tucatinib administration on the phosphorylation of HER2, HER3, AKT, ERK1/2. and MEK1 (Study TRN-5517)



In addition to the single agent assessment, the activity of tucatinib in combination with 150 µg/ml (1 µM) trastuzumab (a HER2 therapeutic antibody) was also evaluated (Study TRN-5517). Results

obtained in this setting for the combination of trastuzumab and tucatinib, showed enhanced signal transduction inhibition and increased apoptosis of tumoral cells.

Further assessment of the enhanced effect of the combination of trastuzumab and tucatinib was explored in *in vivo* models and will be discussed below.

The applicant studied the relationship between the potency of tucatinib and HER2 protein levels. Several breast carcinoma-derived cell lines, expressing variable levels of HER2 (which were staged in negative, low and high) were employed, and the results showed increased potency of tucatinib on those cell lines presenting higher levels of HER2.

Table 2: EC_{50} values from cell proliferation assays using breast cancer tumour derived cell lines and either tucatinib or T-DM1

Cell Line	HER2 Status	HER2 Expression	Tucatinib Potency (EC_{50} in nM)	T-DM1 Potency (EC_{50} in ng/mL)
HCC-1419	HER2-high	1,515,661	23	704
SK-BR-3	HER2-high	1,384,157	27	13
HCC-1954	HER2-high	1,259,398	50	7
ZR-75-30	HER2-high	1,240,426	156	79
AU-565	HER2-high	1,153,419	33	31
HCC-1569	HER2-high	938,858	249	118
HCC2218	HER2-high	905,340	18	52
BT-474	HER2-high	864,064	33	191
UACC-893	HER2-high	775,719	431	>25,000
UACC-812	HER2-high	722,241	64	37
HCC-202	HER2-high	303,584	282	40
JIMT-1	HER2-low	123,626	15,147	1395
BT-483	HER2-low	82,187	>25,000	>25,000
CAMA-1	HER2-low	57,568	7309	4997
T47D	HER2-low	25,797	4938	>25,000
MCF7 (ATCC)	HER2-low	20,855	10,020	>25,000
MCF7 (NCI)	HER2-low	17,859	>25,000	>25,000
MDA-MB-231	HER2-low	4350	16,482	>25,000
MDA-MB-436	HER2-neg	1702	17,601	23,878
Hs578T	HER2-neg	1663	12,394	11,493
MDA-MB-468	HER2-neg	1[a]	9617	7695
DU4475	HER2-neg	1[a]	8973	>25,000

The results of these experiments demonstrated tucatinib can elicit potent antitumour activity (EC50 values <500 nM) only in breast cancer cell lines expressing ≥300,000 HER2 receptors/cell. The most potent EC50 values for tucatinib (<100 nM) were observed when receptor density on the cell surface approached or surpassed 10^6 ($7x10^5$ to $1.5x10^6$).

Cell proliferation assays were performed using the HER2+ cell line BT-474 and the EGFR amplified cell line A431 to assess how the relative potencies of tucatinib against HER2 or EGFR phosphorylation correlate with effects on cell growth and division . Correlating cytotoxicity in the BT-474 cells was observed (IC50: 15.45 nM). Furthermore, it was demonstrated that tucatinib did not induce cytotoxicity as potently in A431 cells and is thus not an antagonist of EGFR.

In vivo studies

Mouse tumour xenograft models

Either allografted or xenografted tumours, based on HER2 overexpressing cells, were used to study the capacity of tucatinib to inhibit tumour growth in vivo (STUDY TRN 5453; TRN 5458; TRN 5454). While in the allografted HER2-driven tumours both tumour control, measured as tumour growth inhibition, and inhibition of HER2 phosphorylation were observed, no tumour regression was evident at the end of the study.

In xenografted HER2 driven tumours, partial regression was seen in several animals exposed to the highest doses of tucatinib. This effect may be related to the cytotoxic capacity of tucatinib in BT-474 cells used in this model. In the xenograft models, superior antitumor effects were achieved when tucatinib was combined with trastuzumab or docetaxel, setting up the rationale for the combination of these molecules (Study TRN 5452; TRN 5550-3). This is consistent with published data and current clinical practice, showing complementary effects on HER2-driven tumours.

A separate study was conducted with the purpose of demonstrating the effect of tucatinib on HER2 positive brain metastasis (Study TRN 5455). The results showed increased survival of the animals and reduced phosphorylation status of HER2. However, these results deserve additional consideration in light of the observations from the tucatinib distribution assays, which showed limited distribution of tucatinib to brain tissues. Changes on the permeability of tucatinib might be dependent upon different properties of the blood-brain barrier in the tumoral setting. See pharmacokinetics section for further discussion.

Regarding the pharmacodynamic activity of the metabolite ONT-993, it has been studied following the same principles applied to the parent molecule. The first in vitro enzymatic assay was conducted in the absence of tucatinib; in further studies in cells ONT-993 was compared to tucatinib. ONT-993 resulted to be similar to tucatinib in terms of selectivity for HER2, however showed slightly lower potency for HER2 phosphorylation inhibition and cytotoxicity (Study TRN 5457; TRN 5444).

Secondary pharmacodynamic studies

With the purpose of addressing the potential effects of tucatinib and its predominant metabolite (racemic ONT-993) over other kinases, the applicant has conducted two broad kinome assays, studying over 250 kinases on each assay.

Table 3: Results of tucatinib kinome screen showing kinases with inhibition of >75% (25% percent control)

Kinase	Tucatinib concentration (μM)	Percent Control (POC)
EGFR	1	5.2
	10	6.75
EGFR (L858R)	1	24
	10	6.4
EGFR (L861Q)	1	8.45
	10	10.55
EGFR (T790M)	10	11.25
EGFR (T790M, L858R)	10	17.3
ErbB4	1	22.45
	10	5.4

Source: Study TRN-5457

Table 4: Results of tucatinib metabolite kinome screen showing kinases with inhibition of >50% (50% percent control)

Kinase	Tucatinib concentration (μM)	Percent Control (POC)
EGFR (L858R)	1	33.5
EGFR (L861Q)	1	1.5
EGFR (T790M, L858R)	1	46.5
ErbB4	1	35.5

Source: Study TRN-5457

The conditions were adjusted to each particular kinase and much higher concentrations of tucatinib and ONT-993 were employed to assure that any potential effect over a substrate would be seen.

The results showed the preference of both products for ErbB family members including EGFR, ErbB4, and 4 mutant versions of EGFR over other different kinases.

The potential of tucatinib and ONT-993 to interact with other targets besides kinases, including receptors, ion channels, neurotransmitters and peptides has not been investigated. Bibliographical data together with available non-clinical studies and clinical safety data did not indicate any relevant mammalian toxicities related to receptor binding which suggests the absence of off-target effects upon tucatinib administration.

Safety pharmacology programme

A battery of GLP studies was conducted to assess the safety pharmacology of tucatinib. The effects over cardiovascular, respiratory and central nervous system, as well as the effects on the gastrointestinal system were assessed.

Table 5: Safety pharmacology studies

Study Design	Results
hERG Assay	Tucatinib inhibited the hERG channel 0.3% at 0.3 μM, 2.9% at 1 μM, 8.6% at 3 μM, and 42% at 10 μM, respectively, and was not soluble at 30 μM. The calculated IC_{50} was 13.5 μM.
Gastric secretion test in anesthetised rats	No effects at 10 or 30 mg/kg. 100 mg/kg: trend for increased secretion volume and significant increase in secretion acidity 4 hr postdose. NOEL=30 mg/kg.
Charcoal propulsion test in conscious rats	No effect on gut motility at doses up to 100 mg/kg NOEL=100 mg/kg
Irwin profile test in rats	No significant effects. NOEL=100 mg/kg.
Respiratory function in rats	No significant effects. NOAEL=100 mg/kg.
Gastrointestinal tolerance in rats	Gastric irritation was significantly higher at 100 mg/kg than in the vehicle control group.
Cardiovascular study in telemeterised monkeys	No significant effects noted in MABP, HR, or ECG waveforms or in QT and QTc measurements. No effects on body temperature, body weight and food consumption were observed. The only clinical sign was swollen abdomens after the second dose of 30 mg/kg that resolved within 24 hr. NOEL=45 mg/kg BID.

The results indicated substantial gastric irritation and minor changes in gastric secretion upon single, high doses of tucatinib.

Pharmacodynamic drug interactions

The potential concomitant toxicity of tucatinib and trastuzumab was not assessed in non-clinical in vivo models. Concomitant toxicity was studied in the pivotal clinical study HER2CLIMB, and no an increased incidence of adverse cardiac events in the combination treatment arm has been observed (see Clinical safety).

2.3.3. Pharmacokinetics

The pharmacokinetics (ADME) of tucatinib was evaluated in nonclinical species used for pharmacology and safety testing of tucatinib (mouse, rat, rabbit and monkey).

The method developed to measure tucatinib in K2EDTA rat, monkey and rabbit plasma in support of the GLP pivotal toxicological studies has been validated across the concentrations ranging from 1.00-1000 ng/ml. The relative standard deviation (RSD)% of within-run and between-run values is in line with relevant guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). The dilution integrity and long-term stability as well as stability during freeze thaw cycles were assessed and showed that tucatinib is stable for up to 4 freeze-thaw cycles at -70 C in all matrixes and that tucatinib is stable for 403, 426 and 29 days at -70 C in rat, monkey and rabbit plasma, respectively.

Pharmacokinetics (PKs) of *single oral dosing* with tucatinib was investigated in CD-1 mice, adult Sprague-Dawley rats and cynomolgus monkeys.

Table 6: Summary of mean pharmacokinetic parameters (non-compartmental analysis) following a single dose of tucatinib

Species	Route	Dose (mg/kg)	Formulation	CL or CL/F (mL/ min/kg)	Vss or V/F (L/kg)	t1/2 (hr)	AUC24h (µg·h/ mL)	Cmax (µg/ mL)	F (%)
Rat	IV	0.5	IV 1	29.6	1.86	0.725	0.286	0.399	NA
	Oral	10	Solution 3	233	47.1	2.51	1.35	0.236	23.8
		10	Suspension 1	NR	NR	NR	1.23	0.358	21.9
Cynomolgus monkey	IV	1.0	IV 2	105	4.07	0.456	0.171	0.224	NA
	Oral	15	Solution 3	42.6	7.59	1.95	7.35	2.75	>100
		30	Solution 3	61.4	14.9	2.78	9.95	3.09	>100
		45	Solution 3	58.1	18.5	3.62	14.2	3.60	>100

Abbreviations: AUC_{24h}=area under the plasma concentration–time curve from time 0 to 24 hours; C_{max}=maximum observed plasma concentration; CL or CL/F=total body clearance (without or with bioavailability adjusted); F=absolute oral bioavailability; NA=not applicable; NR=not reported; $t_{1/2}$terminal half-life; V_{ss}=volume of distribution at steady state; V/F=volume of distribution over bioavailability

In mice and rats, a greater than dose proportional increase in exposure was observed after single oral dosing. Minimal or no sex differences were observed. Non-linear PK was observed in all three species and t½ was consistent across species.

Table 7: Summary of mean toxicokinetic parameters following multiple dose of tucatinib

Species	Study Number	Dose mg/kg/ dose	Day	C_{max} (µg/mL)	T_{max}[c] (hr)	AUC_{12h} (µg·h/mL)	AUC_{12h}/D (µg·h/mL)/ (mg/kg)	AUC_{24h} (µg·h/mL)
rat	1140-028[a]	10	1	0.686	13[d]	1.18	0.118	3.11
			27	0.745	13[d]	3.15	0.315	6.17
		30	1	4.28	13[d]	8.34	0.278	28.2
			27	5.37	15[d]	29.6	0.988	68.3
		100/60[b]	1	16.5	15[d]	90.7	0.907	208
			27	9.27	4	72.5	1.21	NA
rat	8369684	3	1	0.0279	2	0.107	0.0357	0.331
			88	0.105	2	0.319	0.106	0.637
		10	1	0.250	2	1.34	0.134	4.39
			88	0.864	1	3.70	0.370	8.42
		30	1	2.43	2	14.2	0.474	41.8
			88	6.36	2	41.1	1.37	86.1
cynomolgus monkey	JAY00093	10	1	0.892	1.52	3.01	0.301	NS
			28	1.17	1.41	5.22	0.522	NS
		30	1	2.91	2	14	0.468	NS
			28	4.6	2.33	26.4	0.879	NS
		45	1	4.54	3.03	23.8	0.528	NS
			28	NS	NS	NS	NS	NS
cynomolgus monkey	8369685	2.5	1	0.0339	1	0.103	0.0412	0.183
			91	0.0361	1	0.145	0.0580	0.308
		10	1	0.439	2	1.24	0.124	3.2
			91	0.139	2	0.557	0.0557	2.26
		20	1	1.09	2	4.38	0.219	17.2
			91	1.83	2	9.92	0.496	26.5

Abbreviations: AUC_{0-12h}=area under the plasma concentration–time curve from time 0 to 12 hr; AUC_{0-24h}=area under the plasma concentration–time curve from time 0 to 24 hr; C_{max}=maximum observed plasma concentration; D=dose; NA=not applicable; NS=no samples; T_{max}=time of maximum observed plasma concentration

Formulation for rat studies=0.5% sodium carboxymethylcellulose and 0.1% Poloxamer 188, pH 7; Formulation for cynomolgus monkey studies=0.5% Tween 80 in deionised water, pH 2.6.

d No statistical analysis was conducted in this study due to sparse sampling.

e Rats in the 100 mg/kg/dose group had their doses reduced to 60 mg/kg/dose on Day 8 and thereafter of the study.

f T_{max} values for studies 8369684 and 8369685 are median; for study JAY00093 are mean.

g The T_{max} value was based on data from 0-24 hr post the first dose of the day.

Results in the *repeat dose* PK studies and TK studies as part of the repeat dose toxicity GLP studies generally supported the findings in the single dose studies in mice and rats. Large variations in exposure were observed in monkeys in PK and TK investigations. After single dose administration up to 45 mg/kg a less than dose proportional exposure was observed. In repeat dose administration up to 60 mg/kg/dose for 5 days, mean AUCinf and Cmax values increased in a greater than proportional manner at the 30 to 60 mg/kg doses. In the TK investigations in the repeat-dose toxicological studies,

exposure was linear and dose proportional. Accumulation occurred in the repeat dose PK study in monkeys, however, accumulation was not observed in the TK investigations.

Mean *bioavailability* (F) ranged from 187-302% in monkeys and 34-284 % in rats (however, 21.9-23.8% in rats at 10 mg/kg PO vs. 0.5 mg/kg IV). F was not established in mice. Total body clearance (CL) and volume of distribution (Vss) was consistent in mice and rats, and compared to F, decreased with the increase of the dose. No trend was observed in monkeys.

A similar metabolite rate (MR) was observed in the tested species of 2-5% ONT-993 after single dose and repeat dose. However, in mice, the MR increased to 9.47% in plasma after repeat dosing, whereas the MR in the brain was measured to 21%, which indicated that a larger amount of metabolite was found in brain compared to plasma.

The accumulation of both tucatinib (1.6- to 5-fold) and ONT-993 (3-fold) occurred in all species in the PK investigations, however, no or minimal accumulation occurred in monkeys in the GLP toxicological study. There were no significant gender differences in terms of either Cmax or AUC0-24 in the pivotal studies. Adequate exposure was achieved in plasma via the proposed clinical route with safety margins ranging between 0.03 and 1.0 relative to exposure at the intended clinical dose of 300 mg BID per day.

Distribution studies were conducted using oral administration. Protein binding of tucatinib was similar across nonclinical species and humans and was not associated with drug concentration. Blood-to-plasma ratios for tucatinib in humans suggests that tucatinib resides in the blood and plasma compartments in a similar portion. Tucatinib appears to be a substrate for P-gp transport at low concentrations (<10 µM) and was found to have a high permeability as an active efflux substrate in Caco-2 cells.

In mice, accumulation occurred in the brain with higher concentrations of tucatinib and ONT-993 in the brain tissue than in plasma. Further, tucatinib was shown to preferentially distribute to tumour tissue in the brain of mice. In rats, however, no levels of tucatinib were detected in the brain other than in meninges until 336 h post-dose. The distribution was seen to the excretory organs with the highest levels in liver compared to kidney measurable until 168 h post-dose. There was a clear decrease in radioactivity in all tissues over time with no retention in blood or plasma. After 672 h female and male rats still retained high concentrations of radioactivity in the uveal tract and eyes (33,200 and 7,060 ng eq/ml in females and 28,100 and 3950 ng eq/ml in males, respectively), though the level had decreased significantly (approximately 2-fold) from the highest level. Accumulation in pigmented skin was also observed, however, concentrations were BLQ at 336 h post-dose. It appears that tucatinib has an affinity for pigmented tissue. No toxicological concern was identified regarding accumulation in eye, as repeat dose toxicity studies in monkeys and rats did not reveal any ophthalmic findings, nor was tucatinib considered of phototoxic potential in an in vivo phototoxic investigation.

No data was submitted on placental transfer.

Tucatinib is extensively *metabolised* mainly via oxidative metabolism, where ONT-993 is the main metabolite observed in all species. M4, M5 and M13 is furthermore observed in all species. ONT-993 is a chiral compound, and it was shown that the R-isomer is preferentially formed compared to the S-isomer in both human and cynomolgus monkey, in vitro and in vivo, with observed ratios from 3.2 to 4.85. The in vitro metabolism profile of [14C]-tucatinib was investigated in liver microsomes and hepatocytes from mouse, rat, rabbit, cynomolgus monkey, and human. All metabolites identified in humans in vitro were also observed in the nonclinical species tested. It was shown in vitro that tucatinib is metabolised by multiple CYP enzymes, primarily by CYP2C8, the responsible CYP isoform to form ONT-993, followed by CYP3A4 and CYP3A5, responsible for forming M5 and M9-10. Aldehyde oxidase was also identified as an enzyme involved in the metabolism of tucatinib, potentially to M20.

Unchanged tucatinib was the predominant radioactive component in circulation and *excretion*, followed by oxidative metabolites ONT-993 and M5 as well as hydrolysis metabolite M2 and N-dealkylation metabolite M3 in rats. In rats (30 mg/kg dose oral), the majority of radioactivity was found in faeces (90.9%) with 0.5% recovered in urine. In bile-duct cannulated male rats, bile accounted for 12.3% of the dose while 80.2% was found in the faeces with only 1% recovered in urine. Based on urinary and bile excretion, the absorbed dose was approximately 13.4% in this study. Enterohepatic circulation of tucatinib is observed in rats with minimal effects on PK.

In monkeys, the majority of the orally administered [14C]tucatinib derived radioactivity was excreted as metabolites and, to a lesser extent as unmetabolised tucatinib via faeces. In cynomolgus monkeys, excretion primarily occurred via faeces accounting for 76.6% of the administered dose while excretion via urine accounted for 1.78%. Urinary excretion appeared to be a minor route of elimination for tucatinib and [14C]tucatinib derived radioactivity. In faeces, the sum of identified oxidative/conjugated metabolites were approximately 50%, suggesting that at least 50% of dosed [14C]tucatinib was absorbed.

In humans, tucatinib appeared to undergo extensive metabolism after an oral dose, and with the largest amount of radioactivity identified as tucatinib followed by its metabolites, found predominantly in faeces with lesser amounts found in urine. All metabolites detected in the human plasma samples were observed at exposures less than the 10%. ONT-993 was the most abundant metabolite in human steady state plasma and it accounted for 6.46%. It appears that two human in vivo metabolites (M18 and M28, accounting for 6.07% and 3.86% of the dose in feces) are not observed in nonclinical species. In humans, a mean of 85.8% of the dose was recovered in faeces and 4.09% of the dose was recovered in urine, indicating that excretion in humans is similar to that in rats and monkeys. Tucatinib is well absorbed in humans with >70% absorption based on the sum of faecal metabolites and urine recovery. Excretion into breast milk was not investigated.

Tucatinib is unlikely to induce the activity of CYP3A4 or CYP1A2 in vivo and had insignificant effect on CYP2B6 mRNA expression. Tucatinib is a weak inhibitor of CYP1A2, CYP2B6 and CYP2C19 (IC50 > 25 µM) and a moderate inhibitor of CYP2C9, CYP2D6, CYP2C8, CYP3A4 and UGT1A1 (IC50: 2.4 – 21.1 µM). Further, the Ki for CYP2C9, CYP2C8, CYP3A4 and UGT1A1 is 0.170 – 4.57 µM and the inhibition mechanism was determined as competitive inhibition. Inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2D6 was not metabolism-dependent, however, tucatinib caused metabolism-dependent inactivation of CYP3A. ONT-993 inhibits CYP2D6 (IC50: 7.9 µM) and causes metabolism-dependent inactivation of CYP3A (KI: 1.6 µM). There is low probability of a PK drug interaction for the combination of tucatinib or ONT-993 with capecitabine in vivo. Tucatinib was not a substrate for OAT, OCT or MATE, however, data suggests that tucatinib is a substrate for BCRP and P-gp. In Caco-2 cells and in MDR1 LLC-PK1 cells, it was shown that tucatinib is a P-gp inhibitor. Furthermore, inhibition of OATP1B1, OATP1B3, OCT2, BCRP, BSEP, MATE1 and MATE2-K was shown. ONT-993 is a substrate for BCRP and P-gp as well, and data indicate that ONT-993 may also be a potential substrate for human OATP1B3. ONT-993 was shown to inhibit OCT2, MATE1 and MATE2-K mediated transport.

In the animal toxicity studies, increased serum enzymes, liver weights, and centilobular hypertrophy were found.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies have been submitted. Acute effects are described in the repeat dose toxicity studies.

Repeat dose toxicity

Repeat dose studies were conducted in rats via oral gavage (Study 1140-028; GLP Study 8369684) and in monkeys via naso-gastric (Study JAY00093; GLP study) and oral gavage (Study 8369685; GLP study). Administration via naso-gastric gavage is considered equivalent to administration via oral gavage.

Table 8: Repeat-dose toxicity studies

Study Design	STD10 (rat) or HNSTD (cynomolgus monkeys)
28-day repeat oral dose toxicity study in rats with recovery	>60 mg/kg/day divided BID
90-day repeat oral dose toxicity study in rats with recovery	>60 mg/kg/day divided BID
5-day repeat oral dose toxicity study in cynomolgus monkeys with recovery	120 mg/kg/day divided BID
28-day repeat oral dose toxicity study in cynomolgus monkeys with recovery	20 mg/kg/day divided BID
90-day repeat oral dose toxicity study in cynomolgus monkeys with recovery	40 mg/kg/day divided BID

Mortalities were observed in both rats and monkeys at high doses, i.e. at 120/200mg/kg/day and 90 mg/kg/day for rats and monkeys, corresponding to a safety margin of 12 and 4.5 (Day 1 data), respectively. In rats, the cause of death was interpreted to be the result of gastrointestinal erosion/ulceration for the majority of animals with red discoloration within the GI tract, some with subacute inflammation. Similar effects were observed in monkeys, with clinical signs such as watery faeces and apparent abdominal pain. The effects were however not observed in surviving rats and were generally reversible. In monkeys, faecal abnormalities were observed from 5 mg/kg corresponding to a safety margin of 0.03. Furthermore, decreased food consumption, dehydration, emesis and reduced body weight was observed in both rats at ≥60 mg/kg/day and monkeys at ≥40 mg/kg/day, presumably related to the GI effects, with observations of related changes in clinical chemistry parameters.

Effects on liver was observed in all studies in both rats and monkeys at ≥6 mg/kg/day and ≥20 mg/kg/day, respectively, primarily with increased liver weights and changes in hepatic enzymes levels of ALP and AST as well as changes in cholesterol and total bilirubin. The changes were minimal and reversible and not associated with histological changes in the liver such as necrosis or fibrosis. Treatment-related minimal centrilobular hepatocyte hypertrophy in the 13-week study in female rats at ≥20 mg/kg and swelling and cytoplasmic rarefaction of hepatocytes in the 28-days study in monkeys at 90 mg/kg/day were observed. In monkeys with observed changes of the hepatocytes, only concurrent changes in liver weight and ALP were seen, but not in ALT, AST and/or bilirubin.

In monkeys, changes in red blood cell count with an adaptive regenerative response as well as increases in white blood cell count indicative of an inflammatory response was observed. These changes were not observed in rats and were generally reversible.

In the 28-day study in rats (Study 1140-028) an increased incidence of myofiber degeneration/regeneration of the soleus muscle as well as mononuclear infiltration of the psoas muscle was observed in males receiving 200/120 mg/kg/dose, which was also present in the recovery group. The finding was however not dose-response related and was not observed in the 13-week study in rats nor in monkeys. It was also observed in one male rat in the control group. The finding is not considered of toxicological relevance. Further, increased adrenal gland was observed in the 28-day study in rats. The increase in adrenal gland weight was without microscopic correlates, so it was not

considered of toxicological concern. In the 13-week study in monkeys (Study 8369685), an elevated heart rate was observed at ≥5 mg/kg/day, however, this was not observed during ECG evaluations and did not correlate with other clinical observations, so it was considered incidental. Furthermore, increased kidney weight was observed in the 28-days study in monkeys at ≥60 mg/kg/day (JAY00093). At 90 mg/kg/day, minimal degeneration of tubular epithelium of the medullary rays in the kidney was further observed in 1 male and 2 females, which indicate kidney toxicity at high dose levels corresponding to a safety margin of 4.5 (D1 AUC0-12h data), however, the finding was reversible.

Genotoxicity

Table 9: Genotoxiciy battery

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Gene mutations in bacteria Study AB39LT.503.BTL GLP	Salmonella and E. Coli strains TA98, TA100, TA1535, TA1537, WP2 uvrA	50 – 5000 µg/plate +/- S9	Negative
In vitro mouse lymphoma *Tk* gene mutation assay Study AB39LT.704.BTL GLP	L5178Y mouse lymphoma cells	Initial mutagenesis assay: 10 – 50 µg/mL +/- S9 Extended mutagenesis assay: 0.5-5 µg/mL - S9	Negative
Micronucleus, Chromosomal aberrations *in vivo* Study 0374-1521 GLP	ICR mice, micronuclei in bone marrow	0, 500, 1000 and 2000 mg/kg	Negative

Carcinogenicity

No carcinogenic studies have been conducted (see discussion on non-clinical aspects).

Reproduction Toxicity

No dedicated studies to assess effects of tucatinib on fertility were conducted. However, fertility related findings were observed in the repeat-dose toxicity studies, which have been included in this section.

Two embryo-foetal GLP studies in rats and rabbits have been conducted. No studies investigating pre- and post-natal development were submitted.

Table 10: Reproductive and developmental toxicity

Study type/ Study ID / GLP	**Species; Number Female/ group**	**Route & dose**	**Dosing period**	**Major findings**	**NOAEL (mg/kg/day)**
Female fertility; 28-day and 13-week repeat-dose toxicity study	Sprague Dawley rats; 15 animals/ sex/group	Oral (dosed BID); 28-d: 0, 20, 60, and 200/120 mg/kg/day;	28 days and 13 weeks (4 week recovery)	6 mg/kg: ovaries (↓corpora lutea, corpus luteum cyst and/or increased interstitial cells), uterus (atrophy),	LOAEL: 6 mg/kg:

		13-w: 6, 20, and 60 mg/kg/day		vagina (mucification) <u>60 mg/kg:</u> vaginal epithelial atrophy, ↑weight of uterus/cervix <u>200/120 mg/kg</u>: ovarian follicular atresia	
Male fertility; 13-week repeat-dose toxicity study	Sprague Dawley rats; 15 animals/ sex/group	Oral (dosed BID); 0, 6, 20, and 60 mg/kg/day	13 weeks (4 week recovery)	<u>6 mg/kg:</u> Lobular atrophy of the mammary gland <u>60 mg/kg:</u> ↑weight of prostate gland	LOAEL: 6 mg/kg:
Embryo-fœtal development Study 20160869 GLP	Sprague Dawley Rats; 6 females/group	Oral gavage; 90, 120, and 150 mg/kg /day BID	GD 7-17	Maternal toxicity: ↓Body weight Developmental: ↓fetuses, live foetuses, number of implantations; ↓Fetal body weight; ↓ mean fetal ossification sites; ↑skeletal variations	Dam: No NOAEL (LOAEL: 90 mg/kg/day) Fetus: 90 mg/kg/day
Embryo-fœtal development Study 20144956 GLP	New Zealand White Rabbits; 6 females/group	Orally via stomach tube; 0, 60, 90, 120, and 150 mg/kg/ day BID	GD7-19	Maternal toxicity: ↓Body weight; Developmental: ↑Resorptions, ↓ live foetuses and % males; external and visceral abnormalities, skeletal abnormalities (domed head malformations, severe brain dilation)	Dam: 90 mg/kg/day Fetus: 60 mg/kg/day

In the 28-day repeat-dose toxicity study in rats, an increased incidence of vaginal epithelial atrophy was observed at 60 mg/kg/day (2/12 females) and at 90 mg/kg/day (12/12 females) with increased severity at the higher dose level. No changes were observed in the female recovery group. In the 13-week study in rat, lower uterus/cervix weights were observed in females administered 60 mg/kg/day (reversible), which correlated with microscopic finding of minimal or slight uterine atrophy, with a dose-related increased incidence and severity in females administered ≥6 mg/kg/day. Furthermore, in the ovaries, slightly or moderately decreased corpora lutea was observed in a small number of females administered ≥20 mg/kg/day. Also, slight corpus luteum cyst and/or increased interstitial cells were observed in 2 females administered 60 mg/kg/day. Changes in the ovaries were only partly reversible.

In the 13-week study in rats, minimal to marked lobular atrophy in the mammary gland was observed in males administered ≥6 mg/kg/day corresponding to safety margins of below 1, with a dose-related

increased incidence and severity, which resulted in an appearance similar to that observed for the female mammary gland. The effects were reversible.

No effects on fertility were observed in monkeys and all observations in rats were reversible or partly reversible.

In embryo-foetal developmental studies in rats and rabbits, treatment related developmental variations and malformations were observed. In rats, maternal toxicity was observed at ≥90 mg/kg/day as decreased body weight and body weight gain as well as reduced food consumption. At ≥90 mg/kg/day, decreased the mean number of implantations, total number of foetuses, and mean number of live foetuses, as well as decreased percent of pre- and post-implantation loss and total number of resorptions was observed. At ≥120 mg/kg/day, mean foetal body weights were reduced and a correlating reduction in mean foetal ossification sites resulting in reduced mean number of hindlimb tarsals and phalanges, forelimb phalanges and metatarsals was observed. Tucatinib administration also resulted in an increased incidence of skeletal variations that however lacked a consistent dose-relationship and only a few litters were affected. In rats, developmental effects occurred at maternally toxic doses, where no NOAEL could be established for maternal effects and with a developmental NOAEL of 90 mg/kg/day corresponding to a safety margin of 3.

In rabbits, decreases in food consumption were correlated with reductions in maternal body weight gains and body weight at ≥120 mg/kg/day. At ≥90 mg/kg/day, an increase in the number of late resorptions, total number of resorptions, and percent post-implantation loss was observed as well as a reduction in number of live foetuses and percent male foetuses. At ≥90 mg/kg/day, several external and visceral abnormalities was observed as well as skeletal abnormalities that included domed head malformations, severe brain dilation, incompletely ossified frontals and parietals, and a hole in the parietal region of the skull. In rabbits, foetal toxicity occurred at maternally non-toxic dose levels with a maternal NOAEL of 60 mg/kg, which corresponds to a safety margin of 0.36 based on AUC.

Studies investigating prenatal and postnatal development were not submitted.

Toxicokinetic data

Table 11: Toxicokinetics and interspecies comparison

Animal/Study	**Dose** mg/kg/day	**AUC_{0-12h}** ng*h/ml	**$Cmax_{0-12h}$** ng/ml	**Ratio to Human AUC****	**Ratio to Human C_{max}**
28 day rat*	**20**	**3150**	**1320 F**	**0.6**	**2.1**
			508 M		0.8
	60	29600	7270 F	6.7	11.5
			4780 M		7.6
	120/200	72500	9410 F	13.9	15
			9370 M		15
13 week rat	6	319	105	0.06	0.17
	20	3700	864	0.7	1.4
	60	41100	6360	7.6	10
28 day monkey	**20**	**5220**	**1170**	**1**	**1.9**
	60	26400	4600	5	7.3
	90***	23800	4540	4.5	7.2
13 week monkey	5	145	36.1	0.03	0.06
	20	**557**	**139**	**0.1**	**0.2**
	40	9920	1830	1.9	2.9

NOAEL is highlighted in **bold**
* In the 28 day study in rats, a gender difference > 2-fold was observed at 20 mg/kg/day for Cmax.

** Exposure in humans after 300 mg BID: AUCss = 5234 ng*h/ml, Cmax = 630 ng/ml [Source: Population PK Report].
***Based on D1 data, as D28 was not available due to D14-15 mortalities.

Local Tolerance

Not applicable.

Other toxicity studies

Tucatinib and ONT-993 both show absorption in the UVA region 315-400 nm, which is indicative of a photoreactive potential. Tucatinib and ONT-993 were investigated in the 3T3 Neutral Red Uptake Phototoxicity Test, where both compounds were considered to have a phototoxic potential. Tucatinib and ONT-933 were then tested in vivo in Crl:LE (Long-Evans) pigmented female rats to determine the potential phototoxic effects of tucatinib on the eyes and skin, as distribution studies have shown a potential for tucatinib to accumulate in pigmented tissue. In doses up to 60 mg/kg/day tucatinib, no phototoxic potential was observed for either cutaneous or ocular reactions.

2.3.5. Ecotoxicity/environmental risk assessment

Table 12: Summary of main study results

Substance (INN/Invented Name N6-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-N4-(3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}phenyl)quinazoline-4,6-diamine (tucatinib)			
CAS-number (if available): 937263-43-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log P_{ow}	OECD107	log Pow at pH 1.2 = -3.26 log Pow at pH 5.0 = 2.99 log Pow at pH 7.4 = 3.82 log Pow at pH 9.0 = 3.94	Not PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log Pow at pH 1.2 = -3.26 log Pow at pH 5.0 = 2.99 log Pow at pH 7.4 = 3.82 log Pow at pH 9.0 = 3.94	Not B (< 4.5)
	BCF	<10 L·kg^{-1}	
Persistence	DT50 or ready biodegradability	Total System $DT_{50,\ 12°C}$: 204–308 days Water $DT_{50,\ 12°C}$: 1.1–58.3 days Sediment $DT_{50,\ 12°C}$: 263–667 days	vP
Toxicity	NOEC or CMR	1.0 mg/L	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (e.g. prevalence, literature)	0.749	µg/L	> 0.01 threshold
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc,\ Loam}$ = 6466617 L/kg $K_{oc,\ Sandy\ Loam}$ = 2085081 L/kg $K_{oc,\ Loamy\ Sand}$ = 2153772 L/kg $K_{oc,\ Sludge}$ = 7926 L/kg	Very high binding to sediment

		$K_{oc, Sludge}$ = 23038 L/kg			
Ready Biodegradability Test	OECD 301B	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Total System $DT_{50, 20°C}$: 96.1–145 days Water $DT_{50, 20°C}$: 1.1–27.4 days Sediment $DT_{50, 20°C}$: 124–314 days >10% AR in sediment at or after Day 14 $NER_{test\ end}$ = 26.2–39.0 % Mineralisation = 0.8–1.4 %			Significant shift to sediment observed
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	1.0	mg/L	Green alga, (*Raphidocelis subcapitata*)
Daphnia sp. Reproduction Test	OECD 211	NOEC	2.5	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	1.0	mg/L	Fathead minnow (*Pimephales promelas*)
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEL	1000	mg/L	
Phase IIb Studies					
Aerobic and anaerobic transformation in soil	OECD 307	DT50 DT90	135-436 614-1500	days	*vP in soil*
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	NOEC	1000	mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	120	mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	14-d LC_{50}	>1000	mg/kg	
Collembola, Reproduction Test	ISO 11267	28-d LC_{50} and EC_{50}	1000	mg/kg	*Folsomia candida*
Lumbiculus toxicity	OECD 225	NOEC	220	mg/kg	
Chironomid toxicity	OECD 218	NOEC	72.9	Mg/kg	

2.3.6. Discussion on non-clinical aspects

Pharmacology

Tucatinib is a potent inhibitor of human epidermal growth factor receptor-2 (HER2)-targeted small molecule tyrosine kinase inhibitor.

The potency and selectivity of tucatinib alone were evaluated in vitro using biochemical and cellular signalling assays and the anti-tumour activity of tucatinib was evaluated in vitro and in vivo in mouse tumour allo- and xenograft models. Tucatinib inhibited phosphorylation, cell signaling, and proliferation in vitro, and demonstrated anti-tumour activity alone and in combination with trastuzumab or docetaxel in HER2 amplified tumour xenograft models. Tucatinib demonstrated activity in a mouse

intracranial HER2 amplified tumour xenograft model. However, limited distribution of tucatinib to brain tissues was found in the pharmacokinetics assays (see also further down). It was also shown that combinations with tucatinib and docetaxel or trastuzumab resulted in antitumor activity in terms of improvement in regressions and tumour-free survivors. From a nonclinical point of view, exposure-response relationship and the posology (continuous BID dosing) in patients are justified. In vitro and in vivo proof of concept is considered well established.

Tucatinib was investigated in a kinase assay where binding to other non-target receptors was not detected. A bibliographical review on the potential of tucatinib and ONT-993 to interact with other targets besides kinases, including receptors, ion channels, neurotransmitters and peptides, together with available non-clinical studies conducted with tucatinib, suggest the absence of off-target effects upon tucatinib administration.

In terms of safety pharmacology, tucatinib appeared selective for the intended HER2 tyrosine kinase target, showed low potential for interaction with cardiovascular targets (hERG, Human Embryonic Kidney (HEK293) Cells) and showed no clinically relevant adverse effects in the in vivo CV safety study in monkey. However, the calculated IC_{50} value is higher than the concentrations tested in the assay. Though the potential concomitant toxicity of tucatinib and trastuzumab was not addressed in non-clinical *in vivo* models, concomitant toxicity was, however, studied in the clinical study HER2CLIMB, where an increased incidence of adverse cardiac events in the combination treatment arm did not occur. No indication of impact on respiratory system was revealed in rat, nor in the CNS safety study in rats.

Tucatinib was also tested in a series of gastrointestinal studies to elucidate potential safety issues. In a gastric section study in rats, increase total gastric secretion volume and acidity of gastric secretion was observed, however, the intestinal transit was not affected by tucatinib in a charcoal propulsion test in rats. At high doses, tucatinib was shown to induce a significant increase in number of lesions, length and total score as well as the percentage of animals which developed lesions. Substantial gastric irritation, in line with similar findings observed in the toxicology studies, was detected upon tucatinib administration. The underlying cause for the observed gastrointestinal findings is unknown, however, it appears unlikely that EGFR might play a role in the gastrointestinal toxicity mainly due to the shown selectivity of tucatinib for HER2.

Pharmacokinetics

The pharmacokinetics (ADME) of tucatinib was evaluated in nonclinical species used for pharmacology and safety testing of tucatinib (mouse, rat, rabbit and monkey). The PK after both single and repeat dosing appear well described in rodents. In rats and mice, a nonlinear and greater than dose proportional relationship was observed with signs of accumulation. Large variations in exposure was observed in the monkey, and the applicant was requested to provide further discussions to clarify the trend towards linearity and dose proportionality after single and repeat dosing. The applicant stated that drug-metabolising enzymes or transporters may have played a lesser role for the variability of monkey PK/TK profiles than solubility in the solution-based formulation, which is accepted.

Distribution was evaluated in adult rats, however, in line with ICH S9 distribution in pregnant and nursing rats was not described. Potential accumulation was observed in pigmented tissue, specifically in eye and uveal tract, where tucatinib was still measured in significant amounts after 672 h. However, no relevant effects were observed in repeat-dose toxicity studies or in an in vivo phototoxicity study, so as the finding did not give rise to toxicological concern, the issue was concluded resolved.

When the distribution of tucatinib was addressed in studies involving radiolabelled compound administration, it was evident that the brain distribution of radioactivity was limited in rats and mice with intracerebral tumours. Distribution in brain metastasis could be evaluated for other HER2 tyrosine

kinase inhibitors by using imaging techniques. However, the applicant argued that the penetration of tucatinib in brain metastases might be influenced by several factors and that PET imaging could not be performed with tucatinib mainly due to structural differences in comparison with other TKIs, not allowing synthesizing [^{11}C] tucatinib. The justification was accepted by the CHMP.

It has been suggested that an adaptive response of the liver triggered by the induction of liver enzymes upon tucatinib treatment might be responsible for some findings observed in the repeat-dose toxicity studies (increased liver weights and changes in hepatic enzymes levels of ALP and AST as well as changes in cholesterol and total bilirubin). However, no changes in the enzymatic activity were detected and no increases of CYP1A2, CYP2B6, or CYP3A mRNA levels were seen in PK drug interaction studies. The relationships between the toxic findings and the results of the metabolism assays were discussed by the applicant, who argues that rats are more susceptible than humans towards enzymatic induction and that the results in the rat studies are of limited clinical relevance.

It appears that two human in vivo metabolites (M18 and M28, accounting for 6.07% and 3.86% of the dose in feces) are not observed in nonclinical species. However, according to ICH S9, metabolites only observed in humans does not need to be qualified in nonclinical species. Furthermore, the metabolites are present below 10% and are thus only considered minor metabolites. Taking the indication for advance cancer into consideration, the lack of any characterisation of these two minor metabolites are accepted.

In the DDI studies IC50 values for substrate and transporter assessments have been calculated. According to 'Guideline on the investigation of Drug Interactions', (CPMP/EWP/560/95/Rev. 1 Corr. 2**), the IC50 must only be used if the derivation of Ki is not possible and the in vitro study design should demonstrate linear conditions and a lack of time dependency of inhibition. Using the Cheng-Prusoff equation Ki would be nearly equivalent to the IC50 value and further, pre-incubation of cells with tucatinib was performed to take potential time dependency of inhibition into account. The use of IC50 values are therefore acceptable.

Toxicology

The pharmacological relevance of the toxicological species was discussed by the applicant and taking sequence homology information as well as a justification based on historical use (rat) and higher oral tolerability (monkey) into account, the chosen species were considered acceptable.

The toxicology package presented is in line with the requirements under the relevant guidelines (ICH S9 for an advanced cancer indication) and with due consideration to the proposed posology. No single dose toxicology studies were conducted which is considered acceptable. Repeat-dose toxicology studies in rats and cynomolgus monkeys showed primarily effects on liver presumably as an adaptive response to enzyme induction and GI at safety margins below 1 i.e. at clinically relevant doses leading to weight loss, dehydration and emesis. Similar findings were observed in clinical studies and are included in the SmPC section 4.8.

Kidney toxicity was observed in monkeys at high dose levels, which was however reversible. In clinical trials, an increase in serum creatinine has been observed in patients treated with tucatinib due to inhibition of renal tubular transport of creatinine (see SmPC section 4.8).

Tucatinib is not of genotoxic potential. It was not investigated for carcinogenicity in accordance with ICH S9. Tucatinib was shown to have effects on female fertility in repeat dose toxicology studies, and in embryo-fetal developmental studies in rat and rabbit, tucatinib was teratogenic at clinically relevant dose levels. Studies investigating prenatal and postnatal development were not submitted. This is acceptable according to ICH S9. Additional consideration should be given to toxic observations in the female reproductive organs and male mammary gland and prostate. While no findings were noted in both cynomolgus monkey studies, toxic observations were described in the rat studies. Inherent

differences between species might account for the differential phenotypic reproductive findings. The observations have been included accordingly in the SmPC sections 4.6 and 5.3.

Though tucatinib is distributed and accumulated in the brain and exerts pharmacologically mediated inhibition of HER2 phosphorylation in CNS implanted tumour tissue, no dependence related findings were observed in the repeat-dose studies, and the issue is considered of limited relevance.

A PBT pre-screening was conducted for tucatinib. The experimentally determined LogKow value was below the trigger value of 4.5 according to EMA guidance on ERA (EMEA/CHMP/SWP/4447/00 corr. 2, 01 June 2006) indicating no concern for bioaccumulation. However, the predicted and refined $PEC_{surface\ water}$ values exceed the action limit of 0.01 µg/L according to EMA guidance. Investigations showed that tucatinib is very persistent. Based on the phase I assessment, a phase II tier A assessment is triggered.

GLP compliant OECD tests were carried out according to the EMA guidance and PNEC values for surface water, ground water and microorganisms were derived from the identified NOEC values. The PEC/PNEC ratio remained below the trigger value for all compartments. However, investigations in sewage sludge showed a Kd >3700 L/kg and Koc >10000 L/kg and combined with the property of not readily biodegradable, effects assessments of tucatinib on the terrestrial compartment in a Tier IIB assessment is triggered. Furthermore, logPow at pH 9 was 3.94, thus triggering further investigation of potential bioaccumulation in a fish bioconcentration study. Finally, sediment degradation data showed partitioning to the sediment layer, thus a risk assessment for sediment dwelling organisms is triggered.

In the tier IIB assessment, GLP compliant OECD studies were conducted to investigate fate and effects on the terrestrial compartment according to EMA guidance on ERA. Risk assessments showed that no risk is identified for the terrestrial compartment. However, the study on aerobic soil transformation (OECD 307) showed that tucatinib is very consistent in soil. No risk of bioaccumulation and secondary poisoning was identified based on the bioconcentration study in fish. The studies on Lumbiculus toxicity (OECD 25) and Chironomid toxicity (OECD 218) resulted in an acceptable risk for sediment dwelling species.

2.3.7. Conclusion on the non-clinical aspects

An adequate program of in vitro and in vivo pharmacology was conducted in disease models for tucatinib, supporting the intended clinical use of tucatinib. Nonclinical proof of concept as a HER2-targeted tyrosine kinase inhibitor appear well-established and provided documentation suggesting a lack of off-target binding of tucatinib. Pharmacokinetics of tucatinib is well described in rodents. The toxicological programme of tucatinib was conducted in rats and monkeys, where liver and GI effect were primarily observed. No genotoxic potential was identified, however, tucatinib affects female fertility and showed foetal toxicity at clinically relevant doses. Relevant information is included in the SmPC sections 4.6, 4.8 and 5.3.

Overall the nonclinical part of the dossier is considered approvable. The risks to the environment have been assessed in line with existing guidelines and the outcome of the assessment is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 13: Studies included in the summary of clinical efficacy

Study No.	Phase / Trial type	Design / Control type	Study population	Number of study centers / Locations	Study start / Enrollment status / Total enrollment	Study and control drugs, route and regimen	Key efficacy endpoints
HER2CLIMB (ONT-380-206)	Pivotal	Randomized / Placebo controlled double blind	Subjects with HER2+ locally advanced unresectable or metastatic breast cancer who have progressed and have received prior pertuzumab, trastuzumab, and T-DM1 therapy	155 / United States, Canada, Europe, Australia, Israel	23-Feb-2016 / Closed / 612	300 mg Tucatinib or Placebo (PO), Trastuzumab (IV or SC), and Capecitabine (PO)	• PFS per BICR • OS • PFS per BICR in subjects with brain metastases at baseline • Confirmed ORR per BICR
ONT-380-005	Phase 1b	Open-label / Uncontrolled	Subjects with HER2+ metastatic breast cancer who have progressed and have received prior trastuzumab and T-DM1 therapy for metastatic disease	5 / United States	28-Jan-2014 / Closed / 60	300 mg Tucatinib (PO), Trastuzumab (IV) and Capecitabine (PO)	• ORR per investigator • DOR • PFS per investigator

Study No.	Phase / Trial type	Design / Control type	Study population	Number of study centers / Locations	Study start / Enrollment status / Total enrollment	Study and control drugs, route and regimen	Key efficacy endpoints
ONT-380-004	Phase 1b	Open-label, 3+3 dose-escalation study	Subjects with progressive HER2+ MBC previously treated with trastuzumab and a taxane for metastatic disease. For subjects in CNS disease expansion cohorts, trastuzumab and taxane (together or separately) might have been given at any time prior to study enrollment as part of neoadjuvant therapy, adjuvant therapy, or therapy for metastatic disease	11/ United States, Canada	18-Feb-2014 / Closed / 57	Dose-escalation: 300 mg or 350 mg tucatinib PO BID and T-DM1 3.6 mg/kg IV on Day 1 of each 21-day cycle Expansion: 300 mg tucatinib BID and T-DM1 3.6 mg/kg IV on Day 1 of each 21-day cycle	• ORR • DOR • PFS
ARRAY-380-101	Phase 1	Open-label, dose-escalation study	Subjects with HER2+ advanced solid tumors	4 / United States, Canada	18-Apr-2008 / Closed / 50/	Dose-escalation: 25 to 800 mg tucatinib PO BID, 28-day cycles, capsules (PIC formulation) Expansion: 600 mg PO BID, 28-day cycles, capsules (PIC formulation)	• Best overall response • DOR

Source(s): m5.3.5.1, CSR ONT-380-206; m5.3.3.2, CSR ONT-380-005; m5.3.3.2, CSR ONT-380-004; m5.3.3.2 CSR ARRAY-380-101

2.4.2. Pharmacokinetics

The clinical pharmacology profile of tucatinib was characterised based on the results of 11 clinical studies. Seven of the clinical studies were conducted in healthy subjects and characterised the clinical pharmacology of tucatinib.

Table 14: Tucatinib clinical trials presenting clinical pharmacology data

Study Number	Description	Treatment Regimen	Number of Subjects	Current Study Status
Studies in Subjects with Advanced Cancer/Metastatic Breast Cancer				
Monotherapy Study				
ARRAY-380-101	Phase 1, open-label, multiple dose study to assess the safety, tolerability, and pharmacokinetics of tucatinib given on a daily oral regimen in subjects with advanced cancer.	Dose escalation: 25 to 800 mg PO BID, 28-day cycles, PIC Expansion (at MTD): 600 mg PO BID, 28-day cycles, PIC	Total subjects; N=50 Dose escalation phase; N=33 n=3 each for 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 650 mg BID n=4 for 500 mg and 800 mg BID n=7 for 600 mg BID Dose expansion phase; N=17 n=17 for 600 mg BID	Completed; Final CSR 09 January 2014
Combination Therapy Studies				
ONT-380-005	Phase 1b, open-label study to assess the safety and tolerability of ONT-380 combined with capecitabine and trastuzumab, alone and in combination in HER2+ metastatic breast cancer.	(**Combination 1**: Tucatinib (tablet) 300 mg or 350 mg PO BID of every 21-day cycle and either capecitabine 1000 mg/m^2 PO BID for 14 days of every 21-day cycle; **Combination 2**: trastuzumab 8 mg/kg IV loading dose Day 1 Cycle 1, followed by 6 mg/kgIV Day 1 of all subsequent cycles; or **Combination 3**: capecitabine 1000 mg/m^2 PO BID for 14 days of every 21-day cycle + trastuzumab 8 mg/kg IV loading dose Day 1 Cycle 1, followed by 6 mg/kg IV Day 1 of all subsequent cycles	Total subjects; N=60 Cohort 1A (300 mg Tucatinib BID + Cape) n=7 Cohort 1B (350 mg Tucatinib BID + Cape) n=4 Cohort 2A (300 mg Tucatinib BID + Tras) n=10 Cohort 2B (350 mg Tucatinib BID + Tras) n=4 Cohort 2F (300 mg Tucatinib BID + Tras CNS Expansion) n=8 Cohort 3A (300 mg Tucatinib BID+Cap+Tras) n=22 Cohort 3E (300 mg Tucatinib BID+Cap+Tras CNS Expansion) n=5	Completed; Primary Analysis CSR 30 July 2019

Study Number	Description	Treatment Regimen	Number of Subjects	Current Study Status
HER2CLIMB	Phase 2, randomized, double-blind, controlled study of tucatinib vs. placebo in combination with capecitabine and trastuzumab in patients with pretreated unresectable locally advanced or metastatic HER2+ breast carcinoma.	300 mg tucatinib (tablet) or placebo PO BID every 21-day cycle plus capecitabine 1000 mg/m^2 PO BID for 14 days of every 21-day cycle plus trastuzumab 8 mg/kg IV loading dose Day 1 Cycle 1, followed by 6 mg/kg IV Day 1 of all subsequent cycles.	Total subjects: N=612 Tucatinib: n=410 Placebo: n=202 (2:1 randomization) PK Analysis Set Tucatinib: n=385	Study Ongoing; Primary analysis CSR 07 November 2019
ONT-380-004	Phase 1b, open-label study to assess the safety and tolerability of tucatinib combined with ado-trastuzumab emtansine (trastuzumab emtansine; T-DM1) in patients with HER2+ breast cancer.	Dose escalation: tucatinib (tablet) 300 mg or 350 mg PO BID and T-DM1 3.6 mg/kg IV on Day 1 of each 21-day cycle. Expansion (at MTD): tucatinib (tablet) 300 mg BID and T-DM1 3.6 mg/kg IV on Day 1 of each 21-day cycle.	Total subjects: N=57 Initial cohort (300 mg): n=8 Dose escalation cohort (350 mg): n=7 Expansion cohort: n=23 Expansion cohort with active CNS disease: n=19	Completed: Primary Analysis CSR 08 April 2019
Studies in Subjects Without Cancer				
ARRAY-380-103	Open-label, single-dose, four-period study evaluating the relative bioavailability, potential food effect, and omeprazole drug interaction of oral tucatinib capsules and tablets in healthy subjects.	Single 300 mg PO dose in each of the four treatment periods: Tucatinib capsules (PIC; fasted) tucatinib tablets (fasted) tucatinib fasted (fed) tucatinib tablets (fasted) following omeprazole (40 mg) for 5 days	Total subjects: N=12 Tucatinib capsules fasted: n=12 Tucatinib tablets fasted: n=12 Tucatinib tablets fed: n=11 Omeprazole/tucatinib tablets fasted: n=9	Completed; Final CSR 14 March 2012
ONT-380-008	Phase 1, open-label study of the absorption, metabolism, and excretion of [^{14}C]-tucatinib following a single oral dose in healthy male and female subjects.	Single dose of 300 mg [^{14}C]-tucatinib administered as an oral solution	Total subjects: N=8	Completed; Final CSR 23 January 2019

Study Number	Description	Treatment Regimen	Number of Subjects	Current Study Status
ONT-380-009	Open-label, nonrandomized, single-dose, parallel-group, safety, tolerability, and pharmacokinetic study of tucatinib administered at 300 mg in fasted, hepatically-impaired male and female subjects and fasted matched-control healthy subjects.	Single dose of 300 mg of tucatinib tablet	Total subjects: N=37 Normal hepatic function: n=15 Mild hepatic impairment: n=8 Moderate hepatic impairment: n=8 Severe hepatic impairment: n=6	Completed; Final CSR 05 September 2019
ONT-380-011	Phase 1, randomized, partially double-blind, placebo and positive-controlled study to evaluate the effect of tucatinib on cardiac repolarization in healthy subjects.	Treatment A: tucatinib (tablet) 300 mg for 4 days Treatment B: tucatinib matching placebo for 4 days Treatment C: Single dose of moxifloxain 400 mg	Total subjects: N=53 Sequence ABC: n=9 Sequence CAB: n=8 Sequence BCA: n=9 Sequence CBA: n=9 Sequence ACB: n=9 Sequence BAC: n=9	Completed; Final CSR 11 July 2019
ONT-380-012	Phase 1, open-label, fixed-sequence, 5-part, drug-drug interaction study of tucatinib to evaluate the effects of CYP3A and CYP2C8 inhibition and induction on the pharmacokinetics of tucatinib and to evaluate the effects of tucatinib on the pharmacokinetics of substrates of CYP3A, CYP2C8, CYP2C9, and P-glycoprotein in healthy male and female subjects.	Parts A-C: Single dose of 300 mg tucatinib (tablet) Parts D-E: Tucatinib (tablet) 300 mg BID for 10 or 14 days Part A: itraconazole 200 mg BID Part B: rifampicin 600 mg Part C: gemfibrozil 600 mg BID Part D: Single doses of repaglinide 0.5 mg, tolbutamide 500 mg, midazolam 2 mg Part E: digoxin 0.5 mg	Total subjects: N=116 Part A: n=28 Part B: n=28 Part C: n=28 Part D: n=17 Part E: n=13	Completed; Final CSR 23 August 2019

Study Number	Description	Treatment Regimen	Number of Subjects	Current Study Status
SGNTUC-020	Phase 1, single center, open-label, fixed sequence drug-drug interaction study in healthy subjects evaluating the effects of tucatinib on the PK of a substrate probe of the MATE1/MATE2-K transporters	Tucatinib (tablet) 300 mg BID Metformin 850 mg for oral administration Iohexol, 1500 mg iodine (3235 mg iohexol) for IV administration	Total subjects: N=18	Completed: Final CSR 04 September 2019
SGNTUC-015	Phase 1, open-label, safety, tolerability and pharmacokinetic study of tucatinib (ONT-380) in healthy Japanese and Caucasian subjects	Cohort 1: Tucatinib (tablet) 50 mg BID Days 1 to 13, and QD on Day 14 Cohort 2: Tucatinib (tablet) 150 mg BID Days 1 to 13, and QD on Day 14 Cohort 3: Tucatinib (tablet) 300 mg BID on Days 1 to 13, and QD on Day 14	Total subjects: N=36 Cohort 1: 50 mg: Caucasian, n=6; Japanese, n=6 Cohort 2: 150 mg: Caucasian, n=6; Japanese, n=6 Cohort 3: 300 mg: Caucasian, n=6; Japanese, n=6	Completed: Final CSR 06 Dec 2019

BID = twice daily; CSR = clinical study report; HER2 = human epidermal growth factor receptor-2; IV = intravenous; MATE = multidrug and toxin extrusion; MTD = maximum tolerated dose; PIC = powder-in-capsule; PO = oral; QD = once daily

In addition to the clinical pharmacology studies, several models were developed, including a Population PK model using data from the pivotal phase 3 study HER2CLIMB, a patient factor covariate analysis of HER2CLIMB data, an exposure response analysis of HER2CLIMB data, and a fit-for-purpose and mechanistic physiologically-based pharmacokinetics (PBPK) model using available in vitro and in vivo data.

Absorption

The absorption of tucatinib has been quantified in subjects with and without cancer in single-dose and repeat-dose administration regimens. The Coefficient of variation demonstrates various degrees of inter-subject variation across all studies, mostly moderate to high. The model-predicted Cmax is 630 ng/ml in the target population in a repeat-dose regimen. Tmax is about 2 hours (range 1 to 4 hours; single dose of 300 mg).

The PK variability was high for the PIC (powder in capsule) formulation used in ARRAY-380-101 study. To overcome the variability of the PIC formulation, the tablet formulation was developed. The tablet formulation was evaluated in healthy volunteers in ARRAY-380-103 study. Bioequivalence was not demonstrated for the PK-parameters AUCinf and AUClast as the upper bound of the 90%CI did not fall within the 80-125% no-difference criteria. The tablet formulation had lower inter-subject variability compared to the PIC formulation and has been used in all subsequent additional studies, except a radiolabelled formulation used in ONT-380-008. A10% increase in AUC, was seen for capsules in fasted state when compared to tablets. It is expected that the slight increase in AUC is of minor relevance in healthy subjects, although its impact in cancer patients is unknown.

Concomitant administration with the PPI omeprazole, indicated less than a 15% difference in AUCinf, AUClast and Cmax and findings were not statistically significant when compared to tucatinib administered without omeprazole.

Influence of food

The geometrical mean tucatinib Cmax was about 8% and up to 36 % higher in the fed state compared to the fasted state. The geometrical mean tucatinib Tmax appeared after 4 hours during fed state compared to 1,5 hours in fasted state. The total tucatinib exposure was increased 48% and up to 75 % when tucatinib was administered with food.

Distribution

Vd was 1670 L in healthy volunteers after administration of a single dose. Pop-PK-predicted Vd in subjects with breast cancer at steady state was 730 L.

In vitro assessment demonstrated that 97.1% of tucatinib was bound to plasma proteins in human plasma at 1 µM tucatinib concentration and mean plasma protein binding of ONT-993 was 97.1% at 5 µM tucatinib concentration. Additionally, In vitro blood-to-plasma partitioning of tucatinib in human blood samples suggested that a similar portion tucatinib resides in the blood and plasma compartments.

In ONT-380-008 study (Mass balance study), low association of tucatinib with red blood cells was seen. The geometric mean blood/plasma total radioactivity AUC ratios were 0.557 (based on AUC0-∞) and 0.508 (based on AUC0-t), respectively.

Tucatinib is a substrate of P-gp, which would expect to limit distribution to CNS but reduced number of efflux transporters, acidic interstitial pH and leaky tight junctions enhance tucatinib permeability into the tumour.

Metabolism

Seventeen metabolites of tucatinib has been identified/characterised in humans. From these nine metabolites are unknown and found in very low quantities. Tucatinib and the major metabolite ONT-993 were the most abundant compounds accounting for 79.7% and 9.65% of total plasma radioactivity ($AUC_{0\text{-}24h}$), respectively. According to non-clinical data the predominant circulating metabolite ONT-993 has a potency corrected exposure of less than 10% of tucatinib.

Tucatinib is primarily metabolised by CYP2C8 (75 %) and by a minor degree by CYP3A (10 %). Aldehyde oxidase was determined to comprise approximately 15% of total tucatinib metabolism.

Elimination

Tucatinib is primarily eliminated by metabolism through the hepatobiliary route. Approximately 85.8% of a radio-labelled dose was recovered in faeces (15.9% as unchanged tucatinib), and 4.09% was recovered in urine. The cumulated percentage of tucatinib excreted in urine was less than 1%. Half-lives of tucatinib was 7.13 hours in healthy volunteers and pop-PK predicted T½ was 14.9 hours in the typical breast cancer subject.

In non-clinical studies, tucatinib appeared to be a substrate of P-gp and the influence of this efflux transporter has been investigated using digoxin as probe. The mass balance study suggested that tucatinib is not absorbed and subsequently excreted as unchanged drug in the intestines.

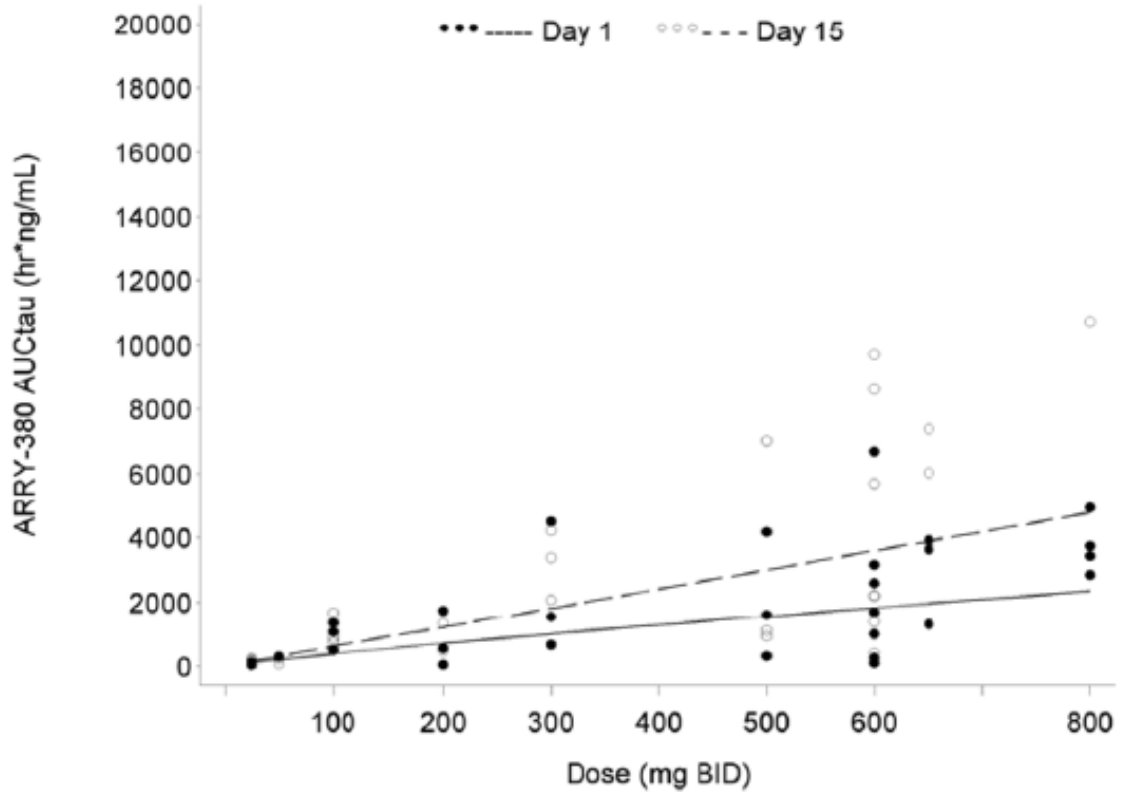
A significant reduction in CL/F (56.3%) was estimated in patients with tablet combination therapy. The greater decrease in CL/F seems to be related to other factors that could not be individually identified.

Dose proportionality

In the dose-escalation study ONT-380-001, the dose range 25 mg BID to 800 mg BID was investigated. The data on dose-proportionality suggested increasing exposure with increasing dose. However, due to dispersion of exposures within each dose- category, broad confidence intervals of 90% CIs for each dose did not lie completely within the range of 0.80 to 1.25.

Geometric mean exposure tended to increase with increasing dose suggesting linearity between tucatinib dose and exposure at therapeutic doses.

Figure 3a: **Evaluation of dose proportionality for tucatinib**



Abbreviations: AUC_{tau} = area under the plasma concentration-time curve for the dosing interval; BID = twice daily; hr = hour(s); mg = milligram(s); mL = milliliter(s); ng = nanogram(s)

Source: ARRAY-380-101 CSR, Figure 4

A dose proportionality assessment demonstrated a linear relationship between exposure metrics (Cmax and AUC) throughout the dose levels evaluated at Day 1 and Day 14. The statistical assessment demonstrated a slope close to the unity, confirming the linear relationship.

Accumulation and time dependencies

In the study ONT-308-004 accumulation of tucatinib was evaluated by comparing plasma concentrations of tucatinib obtained in Cycle 1 and Cycle 2 at doses ranging between 150 and 350 mg tucatinib BID. For the 300 mg dose, a 1.54- and 1.70-fold accumulation was seen for Cmax and AUC0-6, respectively. Similar findings were provided for the 300 mg dose by the pop-PK model, with accumulation of 1.72-fold and 1.52-fold for AUC and Cmax respectively. These accumulation ratios support the proposed dosing regimen of 300 mg tucatinib BID.

Tucatinib trough concentrations were consistent across Cycles 2 to 4 in the study ONT-380-004, thus time-dependency of tucatinib PK is not demonstrated.

Inter-and inter-individual variability

Various degrees of variability in tucatinib and ONT-993 PK parameters have been demonstrated in healthy volunteers and in the target population.

Pharmacokinetics in target population

Three phase 1 studies were conducted in subjects with breast cancer (ONT-380-004, ONT380-005, ARRAY-380-101). These studies were included in a pop-PK analysis along two studies in healthy volunteers (ARRAY-380-103 and ONT-380-012). The Pop-PK analysis provided predicted PK parameters for the target population including Cmax of 630 ng/ml, Cthrough of 257 ng/ml and AUC of 5234 ng*h/ml.

The model predicted an increased tucatinib AUC of 2.29-fold (and up to 4.32-fold) an increased tucatinib Cmax of 1.84-fold (and up to 3.16-fold) in the target population during concomitant treatment with T-DM1 or capecitabine with or without trastuzumab, compared to healthy subjects.

Special populations

Based on pop-PK modelling data race, weight and age were not identified as being predictors of tucatinib PK.

The effect of gender was not evaluated during the covariate analysis on any of the PK parameters because of the lack of male patients in studies ONT-380-004 and ONT-380-005. The non-compartmental comparison of study ONT-380-012 showed higher exposure in females compared to male subjects, with a >20% increase in AUCinf and <20% increase in Cmax. Only two men were included in analysis and the effect of gender could not be established.

No subjects older than 80 years were included and therefore predictions on subjects >80 years are extrapolations.

In SGNTUC-015, no marked differences in AUC between Japanese and Caucasian subjects. No data was collected in children in line with the PDCO decision.

In ONT-380-008, < 5% of the total radioactivity was excreted in urine and cumulated percentage of tucatinib excreted in urine was less than 1%. Additionally, an exploratory pharmacokinetic (PK) analysis using through-samples from the HER2CLIMB study found that mild or moderate impaired renal function did not affect tucatinib Ctrough levels in the target population. No subjects with severe impaired renal function or end-stage renal disease were included in the analysis. Increase serum creatinine levels following repeat dosing of tucatinib has been demonstrated.

In SGNTUC-020 iohexol exposure was unaffected by of tucatinib, demonstrating that GFR is not impacted by repeat dosing of tucatinib. The dose selected of iohexol (5 mL of iohexol IV, 300 mg iodine per mL of solution) appeared slightly low according to SmPC recommendation and dose used in other studies, but the dose was sufficient to capture the intended data.

ONT-380-009 investigated tucatinib exposure in volunteers with different degrees of impaired hepatic function (mild-severe classified by using the Child-Pugh system). Even though less than a two-fold increase in geometrical mean exposure was seen across different stages of impaired hepatic function, up to a 3.7-fold increase in tucatinib Cmax and 3.8-fold increase in AUC was observed in patients with severe hepatic impairment, when compared to Healthy volunteers (Table 15). However, these differences did not reach statistical significance because of the high variability in plasma concentrations.

Table 12: Statistical analyses of plasma concentrations of tucatinib following administration of a single oral dose of tucatinib 300 mg to subjects with normal hepatic function and subjects with mild, moderate, or severe hepatic impairment

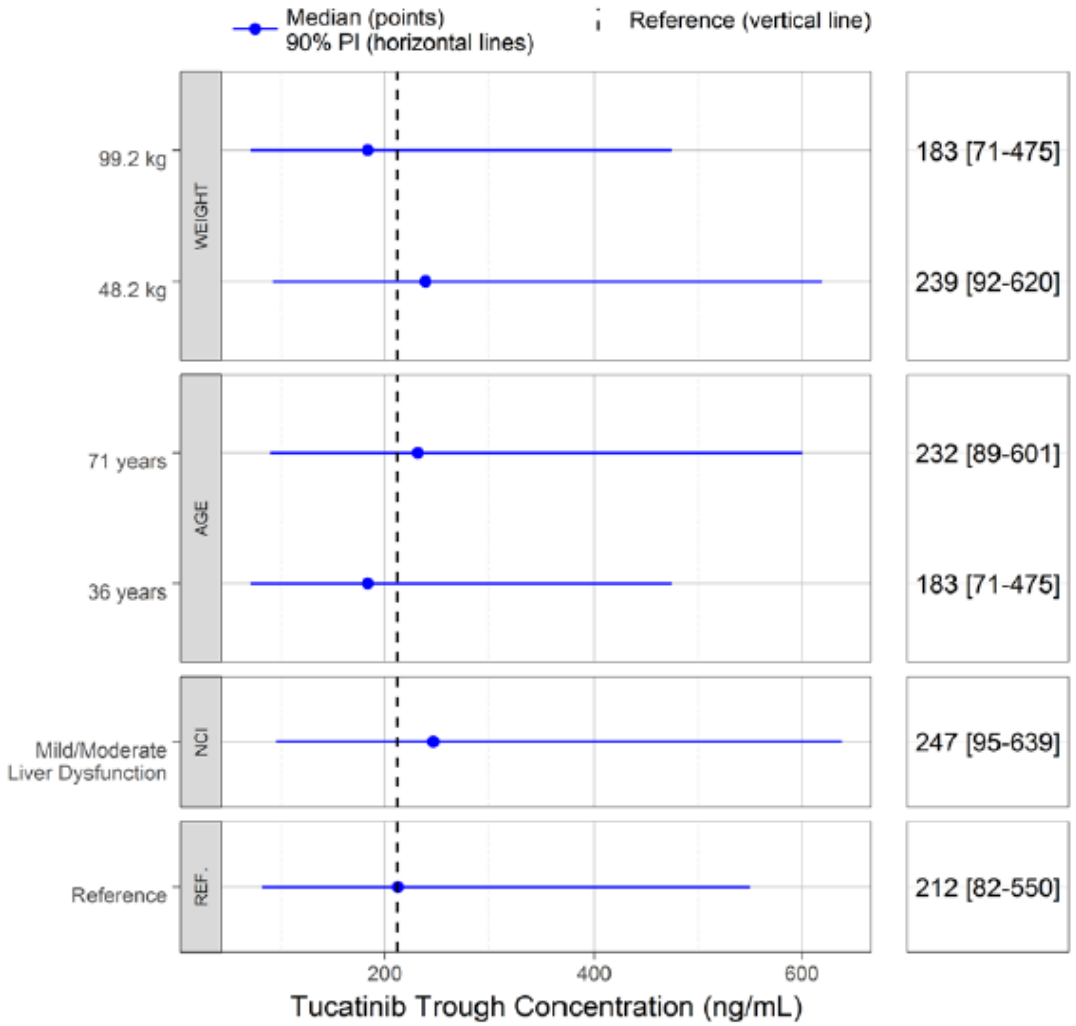
Analyte: Tucatinib

		Test (Mild, Moderate or Severe)		Reference (Normal)			
Parameter	Comparison (Test vs Reference)	n[a]	Geometric Mean[b]	n[a]	Geometric Mean[b]	Geometric Mean Ratio[c](%)	90% Confidence Interval[d](%)
C_{max} (ng/mL)	Mild vs. Normal	8	423	8	407	103.9	(61.6, 175.3)
	Moderate vs. Normal	8	374	8	423	88.5	(42.1, 186.1)
	Severe vs. Normal	6	471	6	401	117.4	(36.6, 376.5)
AUC_{0-t} (h*ng/mL)	Mild vs. Normal	8	2450	8	2500	98.0	(74.3, 129.3)
	Moderate vs. Normal	8	3040	8	2690	113.4	(65.2, 197.2)
	Severe vs. Normal	6	3830	6	2680	143.0	(70.6, 289.9)
$AUC_{0-\infty}$ (h*ng/mL)	Mild vs. Normal	8	2510	8	2540	99.0	(76.3, 128.4)
	Moderate vs. Normal	8	3140	8	2740	114.8	(65.3, 201.8)
	Severe vs. Normal	5	4770	5	2960	161.0	(67.3, 385.3)

[a] n was the number of subjects in each group used in the analysis.
[b] Geometric means calculated by transforming the natural-log means back to the linear scale.
[c] Geometric mean ratio for natural log transformed parameter (expressed as a percent), natural log transformed back to the linear scale.
[d] 90% confidence interval for geometric mean ratio of natural log transformed parameter (expressed as a percent), natural log transformed back to the linear scale.
Source: ONT-380-009 CSR, Table 11

The exploratory pop-PK analysis using through samples from the HER2CLIMB study did not identify impaired hepatic function as a predictor of tucatinib PK, but no subjects with severe impaired hepatic function were included in the analysis (**Figure 3b**).

Figure 3b: **Forest plot of covariate effects on tucatinib trough concentration**



For each covariate scenario, all other covariates were maintained at values for the reference subject (66.7 kg body weight, age 55 years, normal hepatic function). For body weight and age, median (90% PI) C_{trough} values are shown the 5th and 95th percentiles of values in the analysis dataset.
The dashed vertical line represents the typical tucatinib trough concentration following 300 mg BID estimated for a reference subject (212 ng/mL). Numbers in the right-hand panel represent the median [90% prediction interval] of 10,000 simulations incorporating residual error.
NCI = National Cancer Institute; PI = prediction interval; REF. = reference.
Source: Pharmacokinetic Covariate Report, Figure 7

Pharmacokinetic interaction studies / Pharmacokinetics using human biomaterials

Tucatinib and ONT-993 interactions have been investigated *in-vitro*, in-silico and *in-vivo*.

In ONT-380-012 study tucatinib as victim was investigated. Concomitant treatment with tucatinib and itraconazole (a potent CYP3A4 inhibitor) caused approximately a 1.4-fold increase in tucatinib exposure, with a slightly higher exposure to ONT-993. These findings are not considered of clinically relevant magnitude.

Concomitant treatment with tucatinib and rifampicin (a CYP2C8 and CYP3A4 inducer) reduced tucatinib exposure by half and caused up to a 2.5-fold increase in ONT-993 Cmax.

A Pop-PK model of tucatinib was developed to account for the impact of CYP3A4 inducers on the exposures of tucatinib after single or multiple dose regimen of tucatinib. The results suggested that the predicted impact on the exposure of tucatinib of CYP3A4 inducers is negligible when tucatinib is administered in a multiple dose regimen. No clinically significant DDIs are expected when co-administered tucatinib with a moderate inducer of CYP3A4.

Concomitant treatment with tucatinib and gemfibrozil (strong CYP2C8 inhibitor) caused a 3-fold increase in tucatinib exposure and decreased ONT-993 exposure. The effect of moderate CYP2C8 inhibitors was assessed in a Pop-PK model with rosiglitazone as a CYP2C8 substrate in the presence of two virtual moderate CYP2C8 inhibitors using gemfibrozil and its metabolite as a reference. The DDI study simulated with these virtual moderate CYP2C8 inhibitors revealed a 1.98- or 3.08-fold increase in tucatinib AUC (for the inhibitors reproducing the accepted lower and upper, respectively) and less than 2-fold increase in Cmax in both scenarios. These results are in line with those observed in DDI clinical trials and are expected not to be clinically meaningful.

Table 16: Summary of observed tucatinib victim drug-drug interactions

Concomitant Drug (Dose)	Tucatinib Dose	Geometric Mean Ratio (90% CI) of Exposure Measures of Tucatinib Combination/No combination	
		C_{max}	AUC
CYP3A Inhibition Itraconazole (200 mg BID)	300 mg single dose	1.32 (1.23, 1.42)	1.34 (1.26, 1.43)
CYP3A/2C8 Induction Rifampin (600 mg once daily)		0.632 (0.531, 0.753)	0.520 (0.452, 0.597)
CYP2C8 Inhibition Gemfibrozil (600 mg BID)		1.62 (1.47, 1.79)	3.04 (2.66, 3.46)

BID = twice daily; C_{max} = maximum concentration; AUC = area under the curve

Tucatinib as perpetrator was also investigated in ONT-380-012. Tucatinib did not cause clinically relevant PK changes in the CYP2C9 substrate tolbutamide.

Concomitant treatment with tucatinib and repaglinide caused about a 1.7-fold increased exposure to repaglinide. This interaction is not considered of clinically relevant magnitude.

A non-compartmental PK comparison has showed negligible changes in exposure of tolbutamide in the presence of tucatinib.

Tucatinib caused a 5.7-fold increased exposure to CYP3A4 substrate midazolam with a 3-fold increase in Cmax, thereby demonstrating that tucatinib is a strong CYP3A4 inhibitor.

Tucatinib caused about a 1.5-fold increase in digoxin exposure and a 2.4-fold increase in digoxin Cmax. Since digoxin is a narrow-therapeutic interval drug, alterations in PK due to concomitant use of tucatinib may increase the risk of toxicity.

In SGNTUC-020 about a 1.4-fold increased exposure to the MATE1/2-k substrate metformin was seen when co-administered with tucatinib. This interaction is not considered of clinically relevant magnitude.

Table 17: **Summary of observed tucatinib perpetrator drug-drug interactions**

Concomitant Drug (Dose)	Tucatinib Dose	Geometric Mean Ratio (90% CI) of Exposure Measures of Tucatinib Combination/No combination	
		C_{max}	AUC
Repaglinide (CYP2C8) (0.5 mg single dose)	300 mg twice daily	1.69 (1.37, 2.10)	1.69 (1.51, 1.90)
Midazolam (CYP3A) (2 mg single dose)		3.01 (2.63, 3.45)	5.74 (5.05, 6.53)
Digoxin (P-gp) (0.5 mg single dose)		2.35 (1.90, 2.90)	1.46 (1.29, 1.66)
Metformin (MATE1/2-K)[1] (850 mg single dose)		1.08 (0.95, 1.23)	1.39 (1.25, 1.54)

AUC = area under the curve; C_{max} = maximum serum concentration; CYP3A=cyctochrome P450 3A; CYP2C8=cyctochrome P450 2C8; MATE=multidrug and toxin extrusion; P-gp = P-glycoprotein

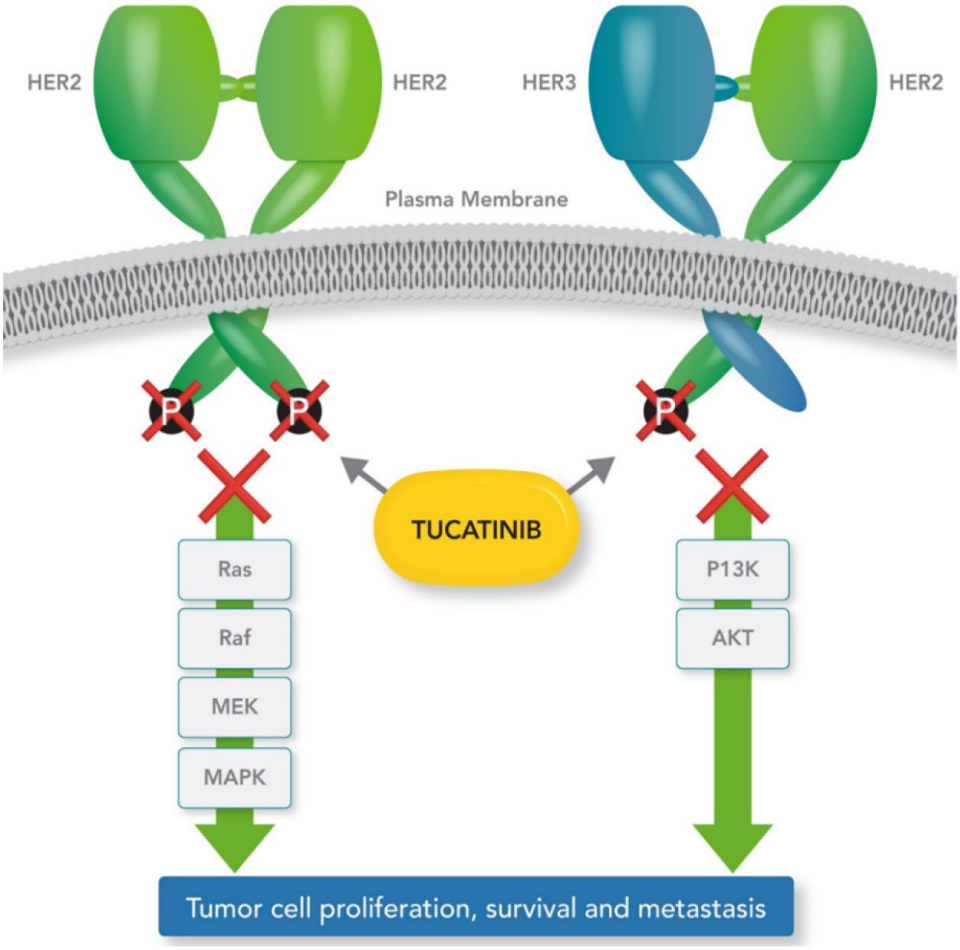
2.4.3. Pharmacodynamics

Mechanism of action and primary pharmacology

Tucatinib is small molecule that belongs to the class of EGFR and HER2 inhibitors. *In-vitro* studies have demonstrated that tucatinib is a potent, human epidermal growth factor-2 (HER2)-specific tyrosine kinase inhibitor that is highly selective towards HER2.

Tucatinib inhibits the intracellular HER2-driven MAP and PI3 kinase signalling pathways (**Figure 4**), thereby inhibiting proliferation, survival and metastasis of the tumour cell. It is not clear whether the mechanism of action imply risk of development of resistance to endocrine-based therapy and thereby lack of efficacy, but preclinical data suggest that resistance to anti-HER2-targeted therapies via upregulation of the ER pathway can be suppressed by the addition of endocrine therapy and in the clinical setting.

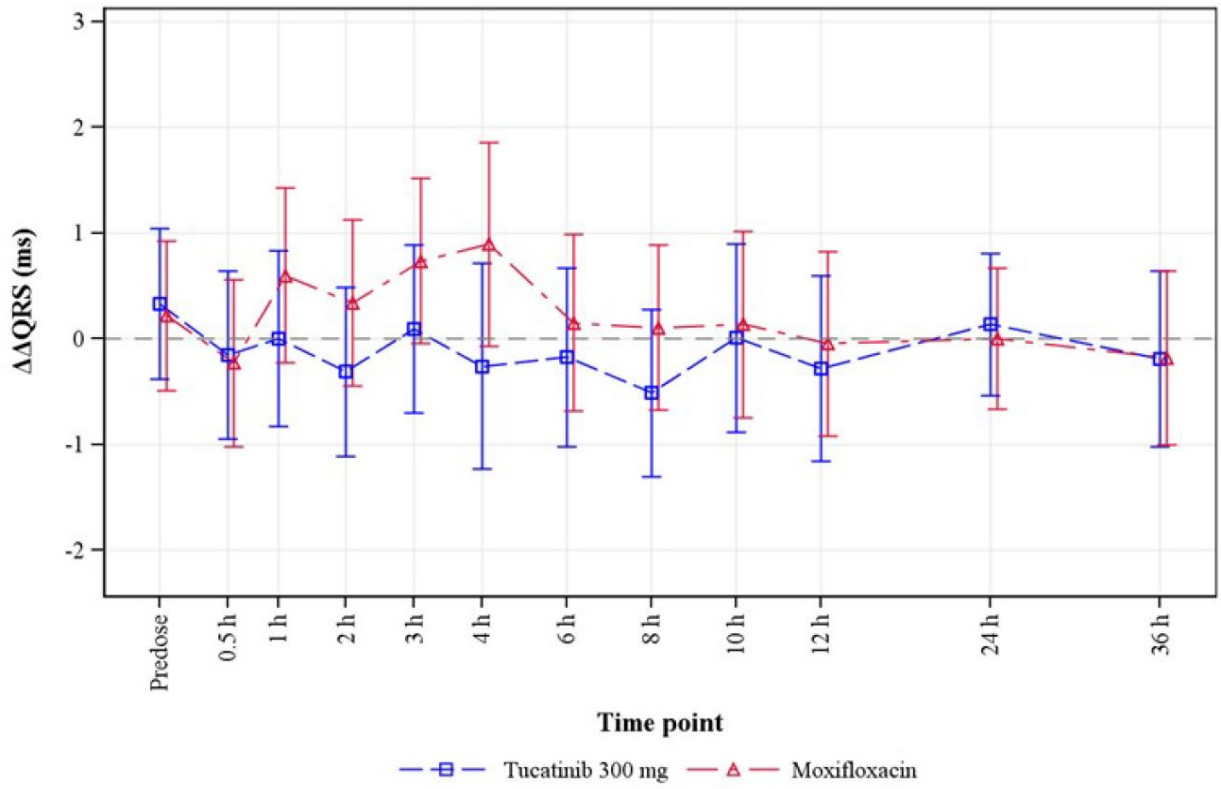
Figure 4: **HER2-driven MAP and PI3 kinase signaling pathways and tucatinib mechanism of action**



Secondary Pharmacology

The effect of tucatinib in human cardiac repolarisation has been investigated in ONT-380-011 conducted in accordance with the ICH E14 guidelines. The study was a cross-over study conducted in healthy volunteers. Subjects received a single dose of 400 mg moxifloxacin on the day of ECG investigation or tucatinib 300 mg BID or placebo for four days prior to ECG investigation during the three study periods. The cardiac repolarisation was investigated by using continuous ECG up to 36 hours postdose. QT intervals were corrected for heart rate by using Fredericia's correction. The analysis was conducted by using a 'by-timepoint' analysis. The moxifloxacin positive control demonstrated sensitivity as the lower bound of the 90% CI of ΔΔQTcF was more than 5 msec 1-24 hours postdose. Tucatinib mean ΔΔQTcF ranged between-2.9 msec at 2 hours postdose to 0.0 msec at 4 hours postdose. The upper bound of the 90% CI of ΔΔQTcF remained below 5 msec at all postdose timepoints. No hysteresis was demonstrated. It was found that the effect of tucatinib 300 mg BID on ECG parameters was similar to that of placebo. Since tucatinib ΔΔQTcF ranged between-2.9 msec and 0.0 msec and the upper bound of the confidence intervals did not exceed 5 msec, no clinically relevant changes in cardiac repolarisation was observed.

Figure 5: **Placebo-corrected Change-from-baseline QRS Interval (ΔΔQRS) Across Timepoints (QT/QTc Population)**



Source: ERT Cardiac Safety Report, Figure 14.2.3.4.

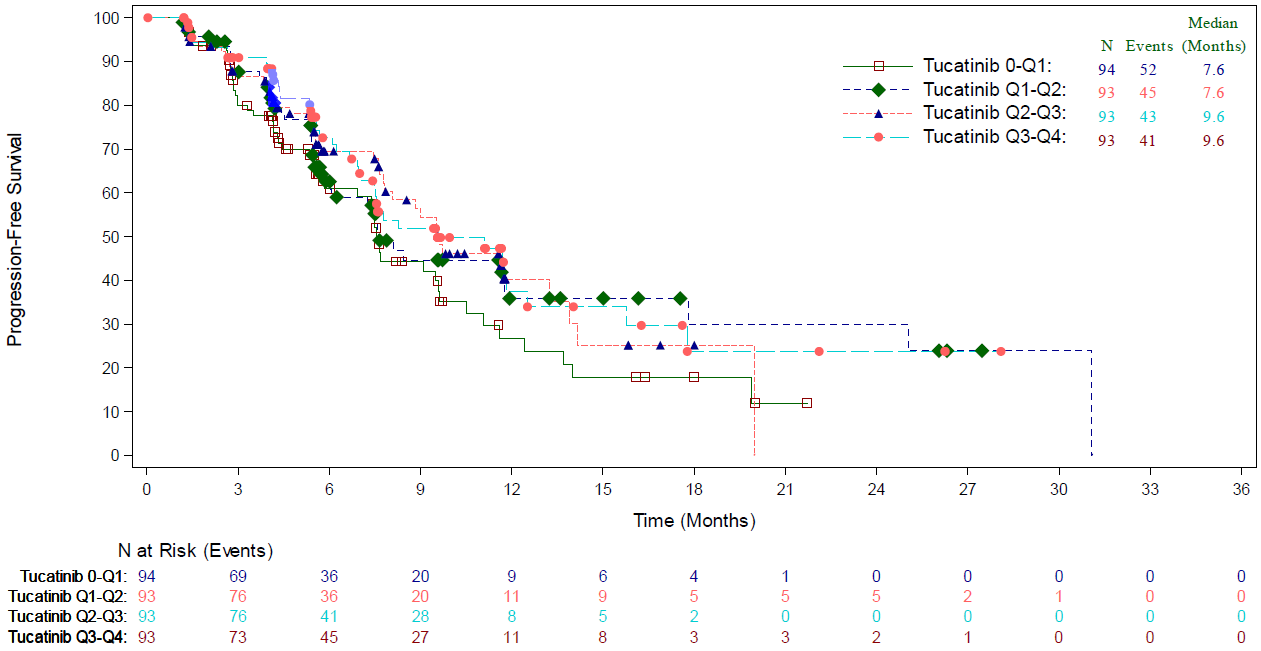
For more information on secondary pharmacology see NC part of this report.

Relationship between plasma concentration and effect

Dose justification

The 300 mg BID dosing regimen, as recommended phase 2 dose, was determined in ONT-380-005 study based on safety findings. The HER2CLIMB data demonstrated that, tucatinib dosed at 300 mg BID in combination with capecitabine and trastuzumab resulted in clinically meaningful prolongation of PFS and OS.

Figure 6: **Kaplan-Meier plots for PFS per BICR by quartiles of average tucatinib trough concentrations (pharmacokinetics analysis population)**



Subjects in Tuc+Cap+Tra arm were categorized into four groups based on the geometric means of their tucatinib predose concentration values on C2D1, C3D1, C4D1, C5D1, and C6D1, using the overall quartiles of the geometric means in Tuc+Cap+Tra arm.
The intervals used for categorization are inclusive all the upper bounds and exclusive of the lower bound, with the exception of 0 - Q1 (inclusive on both sides). Missing concentration values are not included. BLOQ values are imputed as 1/2 BLOQ (0.5 ng/mL) for the calculation of quartiles.
The Q1, Q2 and Q3 values of the geometric means of tucatinib trough concentration in Tuc+Cap+Tra are 53.3 ng/mL, 142.1 ng/mL, and 268.8 ng/mL, respectively.
Source: HER2CLIMB CSR, Figure 11

The incidence of Adverse Events of Special Interest (AESIs) on Cycle 3 Day 1 was low and a large proportion of patients were able to stay at the 300 mg BID dose in the HER2CLIMB study Therefore, the selected dosing-regimen seems reasonable.

Table 18: **Summary of adverse events of interest by quartiles of tucatinib trough (Cycle 3 Day 1) concentration (PK analysis set)**

	Tuc+Cap+Tra (N=385)			
	Tucatinib 0-Q1 (N=66) n (%)	Tucatinib Q1-Q2 (N=65) n (%)	Tucatinib Q2-Q3 (N=66) n (%)	Tucatinib Q3-Q4 (N=65) n (%)
Potential drug-induced liver injury	1 (1.5)	2 (3.1)	0	2 (3.1)
Left ventricular systolic dysfunction leading to a change/discontinuation of study treatment	0	2 (3.1)	2 (3.0)	1 (1.5)
Cerebral Edema	0	0	0	0

Source: HER2CLIMB CSR, Table 14.3.1.6

The safety analysis indicated that drug-induced liver injury, cerebral oedema not attributable to progression of disease, and left ventricular systolic dysfunction leading to dose modification or discontinuation were not associated with tucatinib exposure (Table 22). Tucatinib is considered to have contributed to increased incidences of diarrhoea, PPE, nausea, vomiting, and stomatitis. Those AEs were not associated with increasing tucatinib exposure.

2.4.4. Discussion on clinical pharmacology

The PK of tucatinib has been investigated in a comprehensive development program including studies in healthy subjects and in HER2-positive breast cancer patients. The pharmacology programme comprised 11 clinical pharmacology studies and population PK modelling. Furthermore, data from the phase 3 study was included for some of the analyses.

Validated and cross-validated LC-MS/MS methods were used for quantification of tucatinib and ONT-993 in the development programme. Results were presented using descriptive statistics and data were analysed after log-transformation using linear mixed effect statistical methods and the ratio of mean differences and associated 90% CIs were calculated for evaluation of comparability or effect.

In the popPK model, the residual error model was characterised using a combined error model with a fixed additive and a proportional error term. The applicant conducted requested analysis with an additive residual error using log-transformed data, showing that no significant change was observed when log-transformed observations are considered. Therefore, the use of a combined error model with fixed additive error term and estimated proportional error term seems adequate to characterise the overall performance of tucatinib over time.

A significant change to standard allometric exponents was observed in the popPK model. The covariate-parameter relationship is basically dependent on the available data, which surprisingly leads to assume a different weight effect for the elimination and distribution clearance. The suggestion to include the standard allometric exponents was intended to reduce the number of estimated parameters and increase model stability and parsimony. The applicant performed requested model comparison using estimated and standard allometric exponents which showed a slightly better performance of estimated allometric exponents compared to the use of fixed allometric exponents. The use of estimated allometric exponents has been adequately justified.

The pop-PK model underpredicted the highest concentrations in studies ARRAY-380-103 and ONT-380-012 conducted in healthy male subjects, whereas the model performed acceptably in studies with cancer patients (both males and females). Differences in the absorption phase between healthy subjects (Studies ARRAY-380-103 and ONT-380-012) and cancer patients (Studies ARRAY-380-101, ONT-380-004 and ONT-380-005) were observed, which could demonstrate the lack of capability of the model to capture differences between both sub-groups of individuals. However, the safety of the proposed dosing regimen has been characterised in the cancer population. Reported AE's appear to be manageable and in line with those observed with other tyrosine kinase inhibitors (see also below).

The elimination phase after single dose administration (assuming no steady-state conditions) seemed to be over-estimated (mainly in studies with healthy volunteers), suggesting that an additional peripheral compartment would help to better describe the Cmax region and elimination phase of these studies. The structural part of the population PK model is highly relevant for the estimation of PK endpoints and prospective dose selection in other sub-groups of patients. The contribution of using a 3-compartment model did not statistically or visually change the overall performance of the model. The inclusion of the third distribution compartment into the population PK model was not able to solve the minor discrepancies in the terminal phase of tucatinib's concentrations. This was however considered not crucial for the understanding of the tucatinib's elimination.

No data on absolute bioavailability were provided and concomitant administration with the PPI or food altered the tucatinib exposure, but the differences observed were not of clinically relevant magnitudes. No dose adjustment is required when tucatinib co-administered with PPIs (SmPC section 4.5).

Fasted vs. fed state: The increase in exposure in fed state raised concerns of increased risk of toxicity among subject with high exposure. However, lack of an exposure-safety relationship in the pivotal HER2CLIMB study justifies the administration of tucatinib without regard to food.

Metabolism by CYP2C8 is the major route of tucatinib elimination accounting for 75% of tucatinib metabolism. Since several metabolic pathways are involved in the tucatinib metabolism, variability in tucatinib exposure due to variability in a single pathway is anticipated to be low.

Large variation indicated that PK alterations in some patients might be of clinically relevant magnitude. It was concluded that the large inter-individual variability on Vc/F is related to other covariates that were not evaluated in the model or measured during the study. However, additional concerns have been detected regarding other elements of the population PK model that could explain the large inter-individual variability on Vc/F. Some factors like hepatic function and food effect, affect tucatinib exposure but the model-predicted differences in exposure cannot be fully explained. However, the safety of the proposed dosing regimen has been characterised in the cancer population. Reported AE's appear to be manageable and in line with those observed with other tyrosine kinase inhibitors.

Likewise, a significant reduction in CL/F (56.3%) was estimated in patients with tablet combination therapy. The greater decrease in CL/F also seems to be related to other factors that could not be individually identified.

Large volume of distribution indicates substantial tissue distribution of tucatinib. Tucatinib is a substrate of P-gp, which would expect to limit distribution to CNS, however reduced number of efflux transporters, acidic interstitial pH and leaky tight junctions enhance tucatinib permeability into the tumour.

CYP2C8 is the major route of metabolism accounting for approximately 75%, but no data on genetic polymorphisms have been provided. However, since several metabolic pathways are involved in the tucatinib metabolism, variability in tucatinib exposure due to variability in a single pathway is anticipated to be low. Information that co-administration of tucatinib with strong CYP2C8 inhibitors

such as gemfibrozil should be avoided as this may result in increased risk of tucatinib toxicity is included in the SmPC (section 4.5).

The data on dose-proportionality suggested increasing exposure with increasing dose. A dose proportionality assessment demonstrated a linear relationship between exposure metrics (Cmax and AUC) throughout the dose levels evaluated at Day 1 and Day 14. The statistical assessment demonstrated a slope close to the unity, confirming the linear relationship.

Based on pop-PK modelling data race, weight and age were not identified as being predictors of tucatinib PK. However, only two men were included in analysis and the effect of gender could not be established. Additionally, no subjects older than 80 years were included and therefore predictions on subjects >80 years are extrapolations. Likewise, tucatinib has not been investigated in subjects with severe impaired renal function or End-Stage Renal Disease. This is adequately reflected in the SmPC section 4.2; no dose adjustment is required in patients aged ≥ 65 years.

Increase in serum creatinine has been observed in patients treated with tucatinib, but in SGNTUC-020 iohexol exposure was unaffected by of tucatinib, demonstrating that GFR is not impacted by repeat dosing of tucatinib. No dose adjustment is necessary in mild, moderate, or severe renal impairment (SmPC section 4.2).

Even though less than a two-fold increase in geometrical mean exposure was seen across different stages of impaired hepatic function, up to a 3.7-fold increase in tucatinib Cmax and 3.8-fold increase in AUC was observed in all patients with severe hepatic impairment. These differences did not reach statistical significance because of the high variability. In the proposed SmPC, dose-adjustments are recommended in patients with severe impaired hepatic function, but no dose adjustment is needed in patients with moderate impaired hepatic function as no dose-response relationship between tucatinib exposure and AEs has been established and patients experiencing AEs due to high exposure are manged by dose-adjustment anyway.

Drug-drug interactions has been widely investigated in clinical studies. No interactions of clinically relevant magnitude were seen with itraconazole, tolbutamide, repaglinide or metformin.

The CYP3A/CYP2C8 inducer rifampicin reduced tucatinib exposure by half and according to the proposed SmPC the combinations should be avoided. Moderate CYP3A/CYP2C8 inducers is not expected to have clinically relevant impact on tucatinib exposure. This is adequately reflected in the SmPC section 4.4 and 4.5.

The interaction between repaglinide and tucatinib was not considered of clinically relevant magnitude and no recommendations are needed in the SmPC.

Tucatinib caused a 5.7-fold increase in midazolam exposure and according to the proposed SmPC, concomitant use of tucatinib and sensitive CYP3A substrates should be avoided and if the combination is unavoidable dose-adjustment of the CYP3A4 substrate and increased monitoring is recommended.

Tucatinib is a P-gp inhibitor and caused an increase of 1.5-fold in digoxin exposure. The isolated effect on intestinal P-gp has not been demonstrated. Therefore, a caution for the DDI risk with sensitive intestinal P-gp substrates using dabigatran as an example, have been inserted in the SmPC section 4.4 and 4.5.

Tucatinib is a HER2-specific tyrosine kinase inhibitor indicated for HER2-positive breast cancer. Tucatinib selectively inhibits HER2 which seems to enable inhibition of HER2 while potentially minimising AEs. The relationship between exposure and response was evaluated using HER2CLIMB data. In this study the 300 mg BID dosing regimen was used. Exposure-repose was evaluated by assessing quartiles of mean through concentrations obtained at day 1 of treatment cycle 3. Additionally, Kaplan-Meier analyses of PFS was conducted by assessing quartiles of mean through

concentrations across treatment cycles 2-6. A clear exposure-response relationship could not be established based on the HER2CLIMB data, but the findings indicated that variation in exposure in the 300 mg BID dosing regimen does not affect PFS. The applicant was encouraged to perform a time-to-event analysis to better characterise the exposure-efficacy relationship, however due to limitation of data this was not feasible. This was accepted by the CHMP.

The mechanism of action and primary pharmacology of tucatinib is adequately described. Risk of development of resistance to endocrine-based therapy via upregulation of the ER pathway can be suppressed by the addition of endocrine therapy. Tucatinib is considered to have contributed to increased incidences of diarrhoea, PPE, nausea, vomiting, and stomatitis, but a clear relationship between tucatinib exposure and incidence of these AEs has not been demonstrated.

The rationale behind the clinical dose setting and dosing interval of 300 mg BID tucatinib in combination with capecitabine and trastuzumab seems reasonable when assessing the PK, safety and efficacy findings.

The dosing recommendations and information related to the DDIs have been reflected in the SmPC.

2.4.5. Conclusions on clinical pharmacology

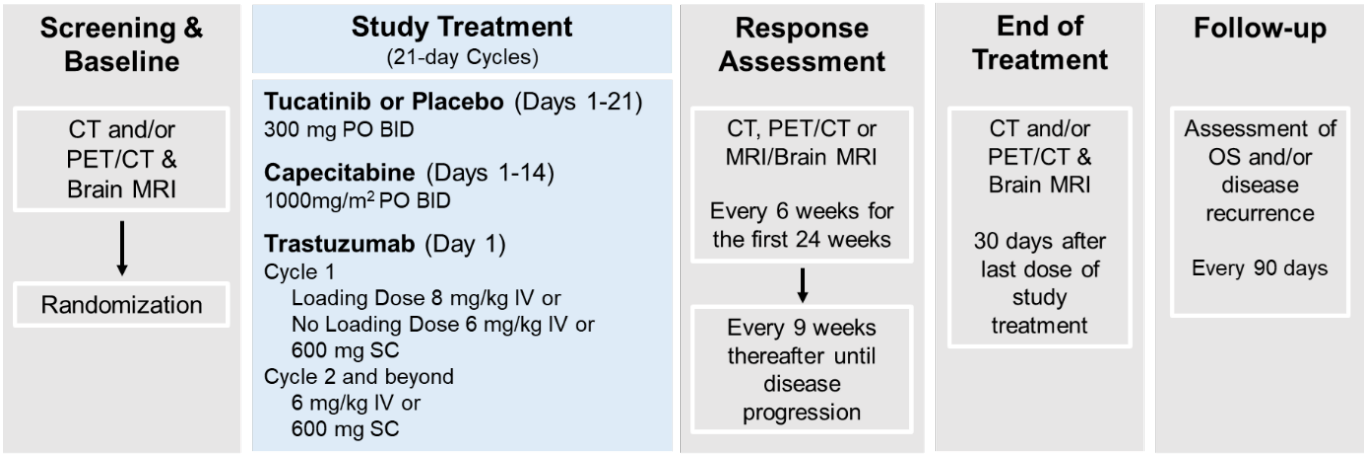
Overall, the PK of tucatinib has been adequately evaluated in a comprehensive clinical pharmacology program.

2.4.6. Dose response study

For more details, please see the clinical pharmacology section.

2.4.7. Main study

Figure 7: Schematic of study design for HER2CLIMB



HER2CLIMB - randomised, double-blind, placebo-controlled, active comparator, global study

Methods

Study Participants

Key inclusion criteria included the following:

- Had histologically confirmed HER2+ breast carcinoma, with HER2+ defined by in situ hybridisation (ISH) or fluorescence in situ hybridisation (FISH) or immunohistochemistry (IHC) methodology
- Had received previous treatment with trastuzumab, pertuzumab, and T-DM1
- Had progression of locally advanced unresectable or MBC after last systemic therapy (as confirmed by investigator), or was intolerant of last systemic therapy
- Had measurable or non-measurable disease assessable by RECIST 1.1
- Was at least 18 years of age at time of consent
- Had Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1 CNS Inclusion – Based on screening contrast brain magnetic resonance imaging (MRI), subjects must have had one of the following:
    - No evidence of brain metastases
    - Untreated brain metastases not needing immediate local therapy. For subjects with untreated CNS lesions >2.0 cm on screening contrast brain MRI, discussion with and approval from the medical monitor was required prior to enrolment
    - Previously treated brain metastases
    - Brain metastases previously treated with local therapy may have been either stable since treatment or may have progressed since prior local CNS therapy, provided that there was no clinical indication for immediate re-treatment with local therapy in the opinion of the investigator
    - Subjects treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may have been eligible to enrol if all of the following criteria were met:
- Time since whole brain radiation therapy was ≥21 days prior to first dose of treatment, time since stereotactic radiosurgery was ≥7 days prior to first dose of treatment, or time since surgical resection was ≥28 days
- Other sites of disease assessable by RECIST 1.1 were present
    - Relevant records of any CNS treatment must have been available to allow for classification of target and non-target lesions

Exclusion criteria

Key exclusion criteria included the following:

- Had previously been treated with:

- lapatinib within 12 months of starting study treatment (except in cases where lapatinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity)
- neratinib, afatinib, or other investigational HER2/ EGFR or HER2 TKI at any time previously

- Had previously been treated with capecitabine (or other fluoropyrimidine [e.g., 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: Subjects who had received capecitabine for adjuvant or neoadjuvant treatment at least 12 months prior to starting study treatment were eligible.

- History of exposure to the following cumulative doses of anthracyclines:
  - Doxorubicin >360 mg/m2
  - Epirubicin >720 mg/m2
  - Mitoxantrone >120 mg/m2
  - Idarubicin >90 mg/m2
  - Liposomal doxorubicin (e.g. Doxil, Caelyx, Myocet) >550 mg/m2
- History of allergic reactions to trastuzumab, capecitabine, or compounds chemically or biologically similar to tucatinib, except for Grade 1 or 2 infusion related reactions to trastuzumab that were successfully managed, or known allergy to one of the excipients in the study drugs
- Had received treatment with any systemic anti-cancer therapy (including hormonal therapy), non-CNS radiation, or experimental agent ≤3 weeks of first dose of study treatment or were currently participating in another interventional clinical trial. An exception for the washout of hormonal therapies was GnRH agonists used for ovarian suppression in premenopausal women, which were permitted concomitant medications
- Had any toxicity related to prior cancer therapies that had not resolved to ≤ Grade 1, with the following exceptions:
  - alopecia and neuropathy, which must have been resolved to ≤ Grade 2; and
  - congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have been resolved completely
  - anaemia, which must have been resolved to ≤ Grade 2
- Had clinically significant cardiopulmonary disease such as:
  - ventricular arrhythmia requiring therapy,
  - uncontrolled hypertension (defined as persistent systolic blood pressure >150 mm Hg and/or diastolic blood pressure >100 mm Hg on antihypertensive medications), or
  - any history of symptomatic CHF
  - severe dyspnoea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy

- hypoxia requiring supplementary oxygen therapy except when oxygen therapy was needed only for obstructive sleep apnea
- presence of ≥ Grade 2 QTc prolongation on screening electrocardiogram (ECG)
- conditions potentially resulting in drug-induced prolongation of the QT interval or torsade de pointes

- Congenital or acquired long QT syndrome
- Family history of sudden death
- History of previous drug induced QT prolongation
- Current use of medications with known and accepted associated risk of QT prolongation

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

- Any untreated brain lesions >2.0 cm in size, unless discussed with medical monitor and approval for enrolment was 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, subjects on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) may have been eligible with discussion and approval by the medical monitor
- 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 oedema may have posed risk to subject (e.g., brain stem lesions). Subjects who underwent local treatment for such lesions identified by screening contrast brain MRI may have still been 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) generalised or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

Treatments

Capecitabine is given at 1000 mg/m2 PO BID for Days 1-14 only of a 21-day cycle. As capecitabine is an oral drug available in fixed doses, the dose administered may not exactly match the calculated dose. Determination of the rounding of capecitabine doses for administration are made according to local institutional practices, with documentation of both the calculated and administered dose.

Trastuzumab is given as a loading dose of 8 mg/kg IV followed by 6 mg/kg q3wk. A loading dose of trastuzumab was not given to subjects who had received trastuzumab within 4 weeks of Cycle 1 Day 1; these subjects received trastuzumab at 6 mg/kg each cycle, including Cycle 1. Trastuzumab may also be given on a weekly basis at 2 mg/kg IV q1wk, but only if the trastuzumab infusion has been delayed and weekly infusions are required to resynchronise the cycle length to 21 days (and after discussion with the medical monitor). Trastuzumab infusion rates are per institutional guidelines. If dosing of trastuzumab is held for >4 weeks, the IV loading dose of 8 mg/kg is given per approved dosing instructions.

Trastuzumab may be administered subcutaneously at 600 mg q3wk. Subcutaneous (SC) trastuzumab does not require a loading dose nor is a weekly schedule available for the SC formulation. Subjects are permitted to transition from IV trastuzumab to SC trastuzumab or from SC to IV trastuzumab.

Tucatinib drug product and placebo are supplied by the study sponsor as yellow round-shaped 50 mg tablets and yellow oval-shaped 150 mg tablets for PO administration. Placebo tablets do not contain the active ingredient but are identical in appearance to active tablets to maintain blinding. Tucatinib was given orally as a 300 mg dose twice daily (BID).

Capecitabine was given as the chemotherapy monotherapy backbone at 1000 mg/m2 PO BID for Days 1-14 only of a 21-day cycle. The study dose is less than what is recommended in the treatment of metastatic breast cancer in the SmPC for capecitabine i.e. 1250 mg/m2 PO BID days 1-14 of a 21-day cycle. The applicant has clarified that the used dose is the approved dose for combination therapy with lapatinib in the US and EU and that similar efficacy has been demonstrated with this dose (1000 mg/m2) versus the single agent approved dose of 1250 mg/m2 PO BID, with less toxicity (Rossi 2007). Moreover, the 1250 mg/m2 PO BID dosing regimen of capecitabine has not been tested in combination with tucatinib.

Objectives

Objectives pertinent to the current report describing the effect of tucatinib versus placebo in combination with trastuzumab and capecitabine are listed below.

Primary Objective

The primary objective is to assess the effect of tucatinib versus placebo in combination with trastuzumab and capecitabine on PFS per RECIST 1.1 based on BICR. Efficacy assessments are performed once every 6 weeks for the first 24 weeks on study, and then once every 9 weeks. Treatment continues until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. Subjects receiving placebo are not permitted to transition to tucatinib treatment. However, subjects with progressive disease (PD) per RECIST 1.1 and isolated progression in the brain may be eligible to continue on the same study treatment arm for clinical benefit after undergoing local therapy to CNS disease, with approval from the medical monitor. These subjects are considered to have PD at time of isolated progression in the brain for the analysis of PFS.

Secondary Objectives

Key Secondary Objectives:

-To assess OS

-To assess PFS in subjects with brain metastases at baseline (PFSBrainMets), defined as subjects with a history of brain metastases, current brain metastases, or equivocal brain lesions at baseline, using RECIST 1.1 based on BICR

-To assess objective response rate (ORR) per RECIST 1.1 based on BICR

Other Secondary Objectives:

-To assess PFS per RECIST 1.1 based on investigator assessment

-To assess objective response rate (ORR) per RECIST 1.1 based on investigator assessment

-To assess the duration of response (DOR) per RECIST 1.1 based on BICR and by the investigator

-To assess the clinical benefit rate (CBR) [stable disease (SD) or non-complete response (CR)/non-progressive disease (PD) for ≥6 months, or best response of CR or partial response (PR)] per RECIST 1.1 based on BICR and by the investigator

-To assess health-related quality of life (HRQoL) and health economics based on subject health status collected using the EQ-5D-5L instrument and health care resources utilised in patient care

Safety Objective

-To assess safety and tolerability

Pharmacokinetic Objective

-To evaluate the pharmacokinetics of tucatinib and metabolite ONT-993 when administered in combination with capecitabine and trastuzumab

The primary objective is to asses PFS by blinded review for a superior efficacy for the tucatinib arm. Key secondary objectives are to assess OS and PFS in the subgroup of patients, who have brain metastases at baseline. Other secondary objectives are to assess PFS, ORR and DOR by investigator, CBR by blinded review and investigator. Lastly, health-related quality of life, safety and tolerability of tucatinib and pharmacokinetics were evaluated.

Outcomes/endpoints

Primary endpoint

PFS

Progression-free survival (PFS) time defined as the time from the date of randomisation to the date of documented disease progression (as determined by BICR assessment using RECIST 1.1) or death from any cause, whichever occurs first.

Key secondary endpoints

PFS_{BM}

Progression-free survival (PFS_{BM}) time in the subgroup of patients with a history of brain metastases or brain metastases at baseline, or with brain lesions of equivocal significance on screening MRI, defined as the time from the date of randomisation to the date of documented disease progression (as determined by BICR assessment) or death from any cause, whichever occurs first.

OS

Overall survival (OS) time defined as the time from the date of randomisation to the date of death from any cause.

Other secondary efficacy endpoints

ORR

Objective response rate (ORR) is defined as achieving a best overall response of complete (CR) or partial response (PR) as determined by BICR and by investigator using RECIST 1.1.

PFS_{INV}

Progression-free survival (PFS_{INV}) time defined as the time from the date of randomisation to the date of documented disease progression (as determined by the investigator using RECIST 1.1) or death from any cause, whichever occurs first.

DOR

Duration of response (DOR) defined as the time from the first objective response (CR or PR) to documented disease progression (PD) (as determined by BICR and by investigator using RECIST 1.1) or death from any cause, whichever occurs first.

CBR

Clinical benefit rate (CBR). Clinical benefit is defined as achieving stable disease (SD) or non-CR/non-PD for ≥ 6 months or a best overall response of complete (CR) or partial response (PR) as determined by BICR and by investigator using RECIST 1.1.

Randomisation and blinding (masking)

The patients were randomised in a 2:1 ratio to tucatinib and placebo arm by a dynamic hierarchical randomisation scheme. The randomisation was stratified by 3 factors, known history of treated or untreated brain metastases (yes/no), ECOG PS (0,1), and region of world (US, Canada, rest of world).

This was a double-blinded trial. Patients, site investigators and personnel, the sponsor (except for designated Clinical Drug Safety (CDS) personnel), and all other individuals involved in the monitoring, data management, and/or conduct of the trial were blinded. Designated CDS personnel may request the treatment assignment of an individual subject in the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR), but will not have access to the overall randomisation scheme.

Unblinded data including deaths, discontinuations, dose reductions, adverse events (serious and non-serious) will be monitored regularly by an independent Data Monitoring Committee (DMC). The independent data coordinating centre preparing this output for the DMC will be unblinded and have access to the overall randomisation scheme.

At the time of the primary analysis for the primary endpoint (PFS), specific sponsor personnel will be unblinded; however, sponsor personnel directly involved in the conduct of the study will remain blinded to individual subject treatment assignments (tucatinib/placebo) until the final analysis for the key secondary endpoint of PFS_{BM}.

At the time of the primary analysis for PFS, part of the personnel will be unblinded, while others involved in the analysis of PFS_{BM} will remain blinded. The applicant has clarified that because the trial met all its prespecified alpha-controlled endpoints, the Sponsor unblinded the trial to allow for cross-over of placebo patients to the tucatinib combination treatment; as such, a blinded team was no longer necessary. The sponsor changed during the conduct of the study, but the integrity of the blinded data was maintained during the transfer of study sponsorship from Cascadian Therapeutics to Seattle Genetics.

Statistical methods

Table 19: Analysis population and re-randomization procedure for efficacy endpoints

Analysis	Population for primary analyses	Use of re-randomization procedure
Primary endpoint: PFS per BICR[a]	ITT-PFS	Yes
Sensitivity analysis for primary endpoint	ITT-PFS	Yes
Subgroup analysis for primary endpoint	ITT-PFS	No
Key secondary endpoints: PFS_{BM}	ITT-$PFS_{BrainMets}$	Yes
Sensitivity analysis for PFS_{BM}	ITT-$PFS_{BrainMets}$	Yes
Subgroup analysis for PFS_{BM}	ITT-$PFS_{BrainMets}$	No
Key secondary endpoints: OS	ITT-OS	Yes
Sensitivity analysis for OS	ITT-OS	Yes
Subgroup analysis for OS	ITT-OS	No
PFS per INV[a]	ITT-PFS	No
PFS_{BM} per INV	ITT-$PFS_{BrainMets}$	No
ORR, CBR and DOR[b]	ITT-OS	No
Exploratory efficacy endpoints	ITT-OS	No

[a] exploratory analyses will also be conducted using ITT-OS analysis set.
[b] exploratory analyses will also be conducted using ITT-PFS analysis set.

Analysis Sets

- Intent-to-Treat (ITT) analysis set will include all randomised subjects. Specifically, the primary analyses for the primary endpoint of PFS per BICR will be conducted using the first 480 randomised subjects in the ITT analysis set (ITT-PFS). Limiting the primary analysis only to the first 480 subjects avoided potential bias from early progression events in the overall population, where many of the subjects would have had a shorter follow-up.

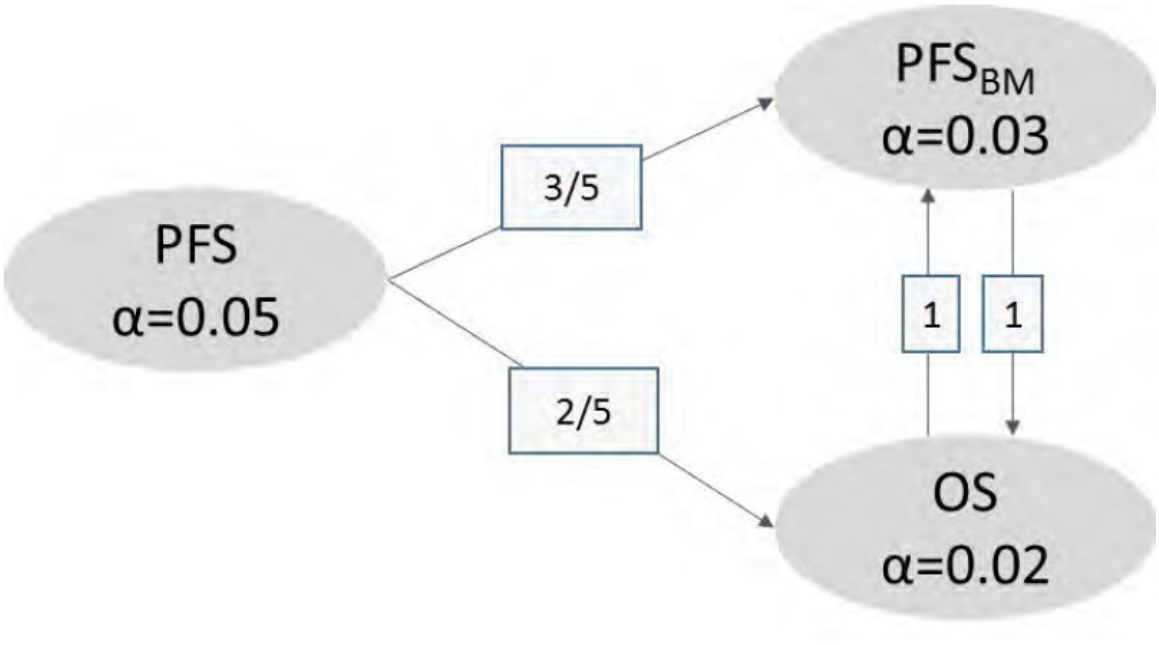
The analyses of the key secondary endpoint OS will be conducted on all the randomised subjects in the ITT analysis set (ITT-OS). The analysis of the key secondary endpoint PFSBM will be conducted using all the randomised subjects in the BM subgroup in the ITT analysis set (ITT- PFSBM).

- The safety analysis set will include all randomised subjects who received at least one dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab).

The ITT analysis set will include all randomised patients. For PFS, only the first 480 randomised patients in the ITT population were included in the primary analysis. The analysis of OS was conducted on all the randomised patients in the ITT. For PFSBM, all the randomised patients in the BM subgroup in the ITT were included in the analysis.

Type I error control

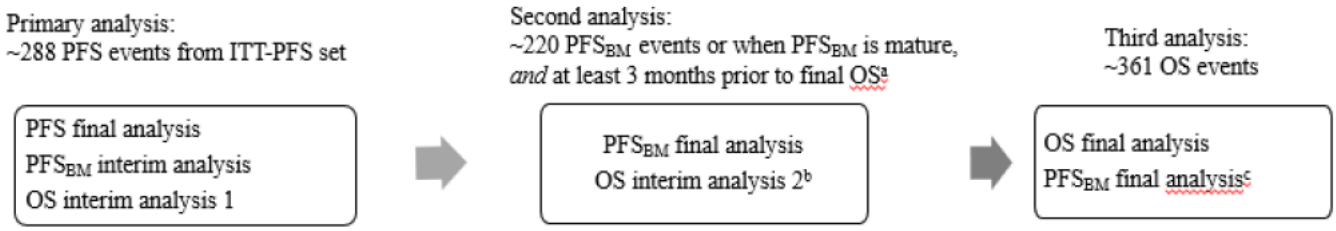
To maintain strong control of the family-wise type I error rate at 0.05, the PFS will be tested at 0.05 level first in the ITT-PFS set, if it is significant, then the key secondary endpoints will be tested using the group sequential Holm variable procedure. One formal interim analysis for superiority is planned for PFS_{BM} and two formal interim analyses for superiority are planned for OS if the primary analysis for PFS is statistically significant. The boundary at interim analysis is determined according to the Lan-DeMets O'Brien- Fleming approximation spending function for two-sided tests.



Type I Error Reallocation Strategy Following Closed Testing Principle

Analyses of the other secondary endpoints will not be subject to formal type I error control. However, if both of the key secondary endpoints (OS and PFS$_{BM}$) are statistically significant, then the ORR by BICR will be formally tested between two treatment arms.

Figure 8: **Timing of Primary and Key Secondary Endpoints Analyses**



[a] If these two conditions are not met, then this analysis will be skipped.
[b] If PFS$_{BM}$ is positive at primary analysis, OS interim analysis 2 will be conducted at 75% OS events (~271)
[c] only if conditions for second analysis timing not met

The primary endpoint PFS was tested at an overall alpha of 0.05. If PFS was significant, the alpha will be split among the key secondary endpoints PFSBM (0.03) and OS (0.02). If one of the key secondary endpoints is statistically significant, the alpha will be transferred to the other endpoint. One interim analysis was planned for PFSBM and 2 IA were planned for OS. A Lan-deMets alpha spending function with an O'Brien-Fleming boundary was implemented to correct for multiple looks. ORR will be formally tested, if the primary and key secondary endpoints are statistically significant.

Primary endpoint

PFS

The two treatment arms will be compared for PFS using a stratified, log-rank test controlling for the randomisation stratification factors. The p-value for this test will be calculated using a re-randomisation-based procedure to reflect the dynamic, hierarchical allocation scheme used for the study randomisation.

For the purpose of describing the treatment effect, the treatment arm hazard ratio and 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the study stratification factors.

Kaplan-Meier curves will be generated by treatment arms. In addition to the primary efficacy analysis (i.e., re-randomisation model analysis), an analysis of PFS time will also be performed using a stratified, log-rank test based on the randomised treatment assignments.

Table 20: Censoring Scheme for Primary Analysis of PFS

Scenario	Progression/Censor Date	Outcome
No post-baseline tumor assessments	Date of randomization	Censored
No documented disease progression or death	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD	Censored
New anti-cancer treatment (systemic, radiation, or surgery) started before PD or death observed	Date of last CR, PR, SD, or non-CR/non-PD on or prior to date of new anti-cancer treatment	Censored
Progressive disease (PD)	Date of PD	Event
Death before first PD assessment	Date of death	Event
Death or progression right after two or more consecutive missed tumor assessments	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD	Censored

Note: CT, PET/CT scans are performed every 6 weeks starting at Cycle 1 Day1 through Week 24 and every 9 weeks starting at Week 24 until documented PD or death.

Sensitivity Analyses for PFS

● Non-proportional hazard: In the case that the proportional hazard assumption is violated, a restricted mean survival time analysis up to 18 months will be performed to compare the mean survival time of the two treatment arms. In addition, the Max-Combo test will be performed to compare the two treatment arms.

● PFS in the ITT-OS Population: PFS per BICR conducted in the ITT-OS population.

If the primary analysis of PFS is significant, the following analyses may be performed for PFS, using the same rerandomisation procedure as for the primary analysis.

● Missing Assessments of Disease Response: To explore the potential impact of missing assessments of disease response on the primary analysis of PFS, two sensitivity analyses will be performed.

(1) Ignoring the missing assessments, i.e., subjects who missed two or more consecutive scheduled assessments before death or PD are considered to have had an event on the date of death or progression.

(2) Imputing the missing assessment, i.e., subjects who missed two or more consecutive scheduled assessments before death or PD are considered to have events at the time of the next scheduled assessment after the last non-missing assessment.

• Stratification: In the case of stratification errors >5% between what is recorded in IRT and eCRF, the hazard ratio and its 95% CI will be estimated using a stratified Cox proportional hazards regression model controlling for the eCRF stratification factors.

• New therapy before PD/death: For subjects who received new anti-cancer therapy before PD or death, two sensitivity analyses will be conducted.

(1) Not to consider any anti-cancer therapies (whether systemic, radiation, or surgery) as a censoring reason.

(2) Not to consider radiation therapies as a censoring reason.

The primary analysis for PFS was using a re-randomisation version of the log-rank test. In addition, a standard log-rank test and a stratified Cox model were also calculated. In the analysis, patients without post-baseline assessments or who started a new anti-cancer therapy before documented PFS-event or without documented PFS event were censored. Patients with death or progression right after two or more consecutive missed tumour assessments were also censored. The applicant also implemented several sensitivity analyses to check the impact of censoring rules and deviation of the proportional hazard assumption.

Key Secondary endpoints

PFS$_{BM}$

This analysis will be performed using the same statistical methods and set of alternative subject randomisations used to evaluate the primary endpoint of overall PFS. The hazard ratio and 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the study stratification factors of ECOG and region.

The sensitivity analyses described for the primary endpoint may be performed, if appropriate.

As an exploratory analysis, the Kaplan Meier curves and summary for PFS in the non-BM subgroup among all randomised subjects will also be presented.

OS

This analysis will be performed using the same statistical methods and set of alternative subject randomisations used to evaluate the primary endpoint PFS.

The hazard ratio and 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the study stratification factors.

The sensitivity analyses for non-proportional hazard and stratification for the primary endpoint may be performed if appropriate.

Table 21: Censoring Scheme for the Primary Analysis of OS

Scenario	Death/Censor Date	Outcome
Not known to have died by data cutoff date	Date last known alive	Censored
Death	Death date	Death

Other Secondary Endpoints

Other secondary endpoints will be analysed using conventional log-rank statistical methods (re-randomisation methods will not be used).

ORR

Comparison of the two treatment arms will be performed using a 2-sided Cochran-Mantel-Haenszel (CMH) test controlling for the study stratification factors. Only response assessments before first documented PD or new anti-cancer therapies will be considered. The proportion of subjects with objective response will be calculated by treatment arm. ORR determined by BICR will be summarised for subjects, who had at least one measurable target lesion at baseline as assessed by BICR among ITT-OS set.

ORR determined by investigator assessment will be summarised for subjects, who had at least one measurable target lesion at baseline as assessed by investigator among ITT-OS set. As exploratory analyses, the same analyses for ORR will also be conducted using ITT-PFS set.

PFS_{INV}

The treatment arm hazard ratio and 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the study stratification factors. Comparison of the two treatment arms will be performed using a stratified log-rank test controlling for the study stratification factors. The nominal p-value from the stratified log-rank test will be provided. Kaplan-Meier estimates of the median (corresponding 95% confidence intervals) will also be computed for each treatment arm.

Subjects who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumour assessment that was a CR, PR, non-CR/non-PD, SD or equivocal progression. Details of the censoring scheme for the analysis of PFS_{INV} are the same as the primary endpoint PFS. The primary analysis of PFS_{INV} will be performed based on ITT-PFS set. PFS_{INV} will also be summarised based on ITT-OS set as an exploratory analysis.

To explore the potential impact of clinical progression on the analysis of PFS, a sensitivity analysis will be performed using the same censoring scheme and methods described for the primary analysis of PFS with the exception that subjects who discontinued any study treatment due to clinical progression will be counted as 'progressed' in the analysis.

PFS_{INV} will also be summarised based on ITT-PFS_{BM} set as exploratory analyses.

In addition, the concordance between BICR and investigator assessed PFS event will be summarised.

CBR

The proportion of subjects with clinical benefit determined by BICR will be calculated by treatment arm. Comparison of the two treatment arms will be performed using a 2-sided CMH test controlling for the study stratification factors. The nominal p-value from the stratified CMH test will be reported. Similar analysis will be performed for CBR determined by investigator assessment. For investigator assessed CBR, the same algorithm for backdating equivocal progression will be applied as in SAP. CBR will be summarised for the ITT-OS set. As exploratory analyses, the same analyses for CBR will also be conducted using ITT-PFS set. Only response assessments before first documented PD or new anti-cancer therapies will be considered. The same derivation of PD date and censoring rules as for primary PFS analysis will apply for duration of SD or non-CR/non-PD.

DOR

Kaplan-Meier estimates of the median (corresponding 95% confidence intervals) will be computed for each treatment arm. The nominal p-value from the stratified log-rank test will be reported. The same derivation of PD date and censoring rules as for primary PFS analysis will apply for DOR. Only those who achieve a confirmed response among the ITT-OS set will be included in the analysis.

The analysis of DOR will be repeated based on BICR assessment and investigator assessment. For DOR per investigator assessment, the same algorithm for backdating equivocal progression will be applied

as in SAP. As exploratory analyses, the same analyses for DOR will also be conducted using ITT-PFS set.

A two-sided CMH-test by the same stratification factors used at randomisation was used to analyse the proportion endpoints (ORR and CBR). PFS-INV and DOR were analysed using a stratified Cox model with the same censoring rules used for PFS. Additional analyses were performed for ORR INV-ORR in ITT-OS, INV-ORR in ITT-PFS and BICR-ORR in ITT-PFS set. Sensitivity analyses to assess the potential impact of clinical progression were performed for PFS_{INV}. Supplementary analysis for DOR were also conducted to assess the robustness of the results (BICR assessment, investigators' assessment and ITT-PFS set).

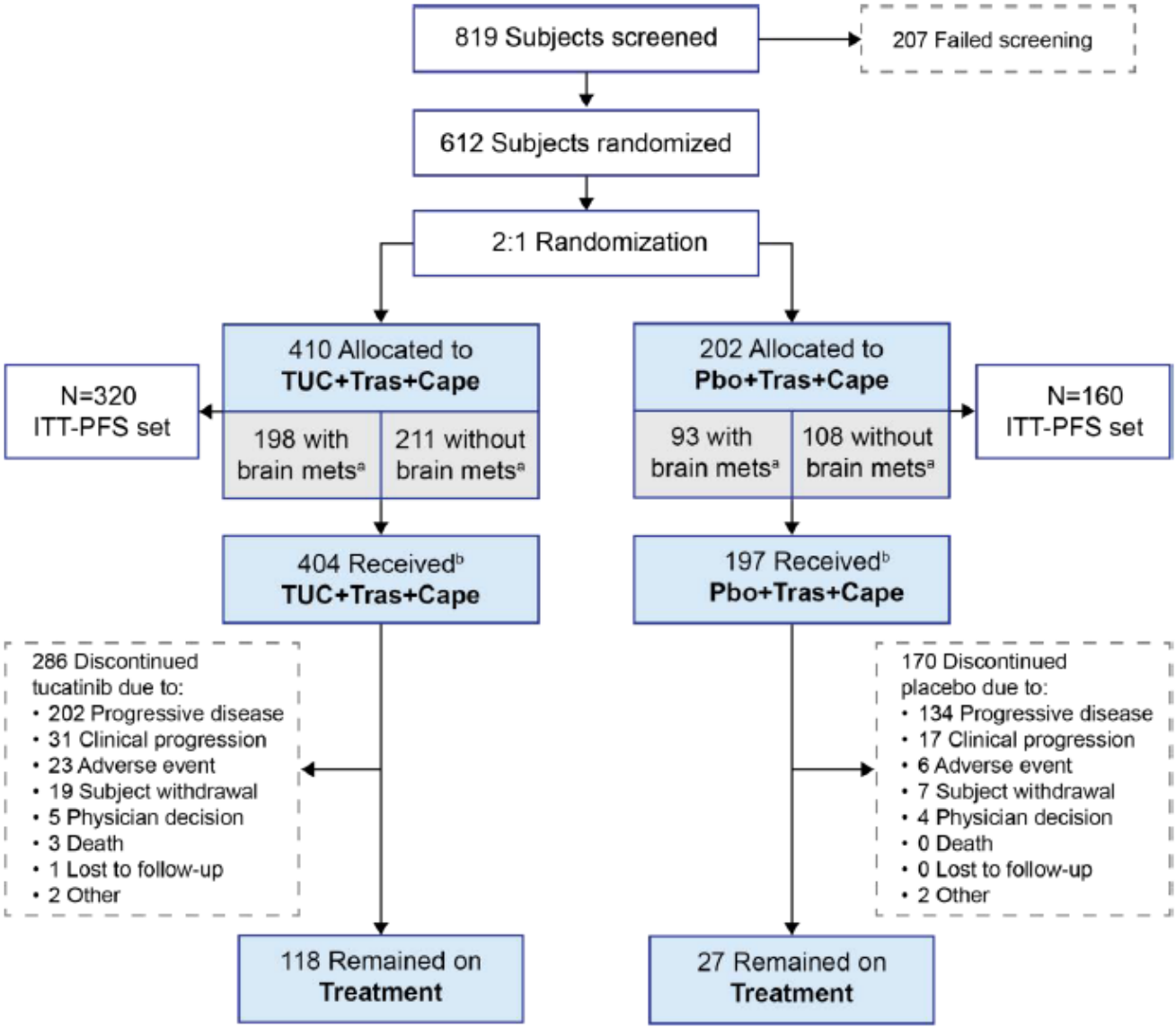
Changes in the Planned Analyses

There were 10 versions of protocol (last version 25 March 2019). The data cut-off date was 04 Sep 2019. The SAP was finalised 7 Aug 2019.

Results

Participant flow

Figure 9: **Summary of subject disposition as of the 04-Sep-2019 data cutoff**



a Based on EDC data. Two randomized subjects did not undergo baseline brain MRI, one randomized to tucatinib arm and one randomized to control arm

b Six subjects randomized to the tucatinib arm and 5 subjects randomized to the control arm did not receive study treatment (see Section 10.1).

Source: Table 14.1.1.3, Table 14.1.1.1, Table 14.1.1.2, Table 14.1.1.5

Conduct of the study

Major amendments to the protocol were done regarding the removal of an interim analyses of PFS, the twice increase in sample size and the change of hierarchical testing of the secondary endpoints. The timing of the primary analysis of PFS was also changed. Most changes were done according to advice from the FDA.

Sample size was initially planned to be 180, but increased to 480 in November 2016 (Protocol v.6) and, then again, up to 600 in November 18 (Protocol V.8).

Baseline data

Table 22: Demographics and baseline disease characteristics of subjects from HER2CLIMB and ONT-380-005 triplet combination cohort

	HER2CLIMB		ONT-380-005
	ITT-OS population Tuc+Cap+Tra (N=410)	ITT-PFS population Tuc+Cap+Tra (N=320)	Tuc+Cap+Tra (N=27)
Age (years)			
Median	55.0	54.0	50
Range	22, 80	27, 80	35, 67
Age category, n (%)			
≤ 65 years	328 (80.0)	252 (78.8)	24 (89)
> 65 years	82 (20.0)	68 (21.3)	3 (11)
ECOG			
0	206 (50.2)	161 (50.3)	17 (63)
1	204 (49.8)	159 (49.7)	10 (37)
Time from diagnosis to randomisation (months)[a]			
Mean (STD)	59.9 (43.0)	59.3 (43.1)	55.75 (43.93)
Median	48.1	46.6	40.38
Min, Max	7.0, 234.8	7.0, 234.8	11.6, 162.1
Disease status at study entry, n (%)			
Unresectable, locally advanced	1 (0.2)	1 (0.3)	12 (44)
Metastatic	409 (99.8)	319 (99.7)	27 (100)
Stage at initial diagnosis, n (%)			
Stage 0-III	264 (64.4)	211 (65.9)	17 (63)
Stage IV	143 (34.9)	108 (33.8)	8 (30)
Unknown/Missing/Not available	3 (0.7)	1 (0.3)	2 (7)
Subjects with history of brain metastases or brain metastases at study entry, n (%)	198 (48.3)	148 (46.3)	11 (41)
Number of prior lines of systemic therapy			
Mean (STD)	4.0 (1.8)	4.1 (1.8)	4.93 (1.82)
Median	4.0	4.0	5.00
Min, Max	2, 14	2, 14	2.0, 9.0

ONT-380-005 - Time from 1st positive biopsy to first study treatment

Source(s): m5.3.5.1, CSR ONT-380-206 Table 14.1.1.6, Table 14.1.1.6a, Table 14.1.2.1, Table 14.1.2.1a, Table 14.1.2.2, Table 14.1.2.2a, Table, 14.1.2.4, Table 14.1.2.4a ; m5.3.3.2, CSR ONT-380-005, Table 14.1.3.1.1, Table 14.1.4.1.1, Table 14.1.5.2

Table 23: Summary of Prior Systemic Therapies ITT - PFS Population

	Tuc+Cap+Tra (N=320)	Pbo+Cap+Tra (N=160)	Total (N=480)
Number of prior lines of systemic therapy			
n	320	160	480
Mean (STD)	4.1 (1.8)	4.0 (2.0)	4.1 (1.8)
Median	4.0	4.0	4.0
Min, Max	2, 14	2, 17	2, 17
Number of prior lines of systemic therapy in the metastatic setting			
n	319	160	479
Mean (STD)	3.1 (1.6)	3.1 (1.7)	3.1 (1.7)
Median	3.0	3.0	3.0
Min, Max	1, 14	1, 13	1, 14
Medication and disease setting, n (%)			
Pertuzumab	320 (100)	159 (99.4)	479 (99.8)
Neoadjuvant/adjuvant only	31 (9.7)	13 (8.1)	44 (9.2)
Metastatic only	277 (86.6)	139 (86.9)	416 (86.7)
Both neoadjuvant/adjuvant and metastatic	12 (3.8)	7 (4.4)	19 (4.0)
(Ado) Trastuzumab emtansine (TDM-1)	320 (100)	160 (100)	480 (100)
Neoadjuvant/adjuvant only	3 (0.9)	2 (1.3)	5 (1.0)
Metastatic only	316 (98.8)	158 (98.8)	474 (98.8)
Both neoadjuvant/adjuvant and metastatic	1 (0.3)	0	1 (0.2)
Trastuzumab	320 (100)	160 (100)	480 (100)
Neoadjuvant/adjuvant only	21 (6.6)	12 (7.5)	33 (6.9)
Metastatic only	180 (56.3)	107 (66.9)	287 (59.8)
Both neoadjuvant/adjuvant and metastatic	119 (37.2)	41 (25.6)	160 (33.3)
Paclitaxel	141 (44.1)	71 (44.4)	212 (44.2)
Neoadjuvant/adjuvant only	28 (8.8)	21 (13.1)	49 (10.2)
Metastatic only	97 (30.3)	47 (29.4)	144 (30.0)
Both neoadjuvant/adjuvant and metastatic	16 (5.0)	3 (1.9)	19 (4.0)
Docetaxel	244 (76.3)	121 (75.6)	365 (76.0)
Neoadjuvant/adjuvant only	71 (22.2)	17 (10.6)	88 (18.3)
Metastatic only	134 (41.9)	81 (50.6)	215 (44.8)
Both neoadjuvant/adjuvant and metastatic	39 (12.2)	23 (14.4)	62 (12.9)

Lapatinib	22 (6.9)	10 (6.3)	32 (6.7)
Neoadjuvant/adjuvant only	4 (1.3)	1 (0.6)	5 (1.0)
Metastatic only	17 (5.3)	8 (5.0)	25 (5.2)
Both neoadjuvant/adjuvant and metastatic	1 (0.3)	1 (0.6)	2 (0.4)
Capecitabine	6 (1.9)	2 (1.3)	8 (1.7)
Neoadjuvant/adjuvant only	1 (0.3)	1 (0.6)	2 (0.4)
Metastatic only	5 (1.6)	1 (0.6)	6 (1.3)
Other	268 (83.8)	132 (82.5)	400 (83.3)
Neoadjuvant/adjuvant only	76 (23.8)	32 (20.0)	108 (22.5)
Metastatic only	104 (32.5)	57 (35.6)	161 (33.5)
Both neoadjuvant/adjuvant and metastatic	88 (27.5)	43 (26.9)	131 (27.3)
Best overall response of the last regimen, n (%)			
CR	5 (1.6)	2 (1.3)	7 (1.5)
PR	51 (15.9)	23 (14.4)	74 (15.4)
SD	108 (33.8)	62 (38.8)	170 (35.4)
PD	109 (34.1)	54 (33.8)	163 (34.0)

	Tuc+Cap+Tra (N=320)	Pbo+Cap+Tra (N=160)	Total (N=480)
Best overall response of the last regimen, n (%) (cont.)			
Unknown	41 (12.8)	17 (10.6)	58 (12.1)
Not available	6 (1.9)	2 (1.3)	8 (1.7)

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-cm-pr-systx.sas Output: t-cm-pr-systx-pitts.rtf (04NOV19:23:47) Data: adsl, adcm

Numbers analysed

A total of 612 patients were randomised 2:1 in the pivotal HER2CLIMB study. Of these, the first 480 patients were analyses for PFS by BIRC (320 on the tucatinib arm and 160 on the control arm). All randomised patients were analysed for OS (410 on the tucatinib arm and 202 on the control arm).

Moreover, all randomised subjects with target and/or non-target parenchymal brain lesions (per RECIST v1.1) at baseline or who have a history of brain metastases, or with brain lesions of equivocal significance on screening magnetic resonance imaging (MRI) based on screening data were analysed for PFS (PFS BrainMets per BICR; N=291; 198 on the tucatinib arm and 93 on the control arm).

Outcomes and estimation

Primary endpoint – PFS by BIRC

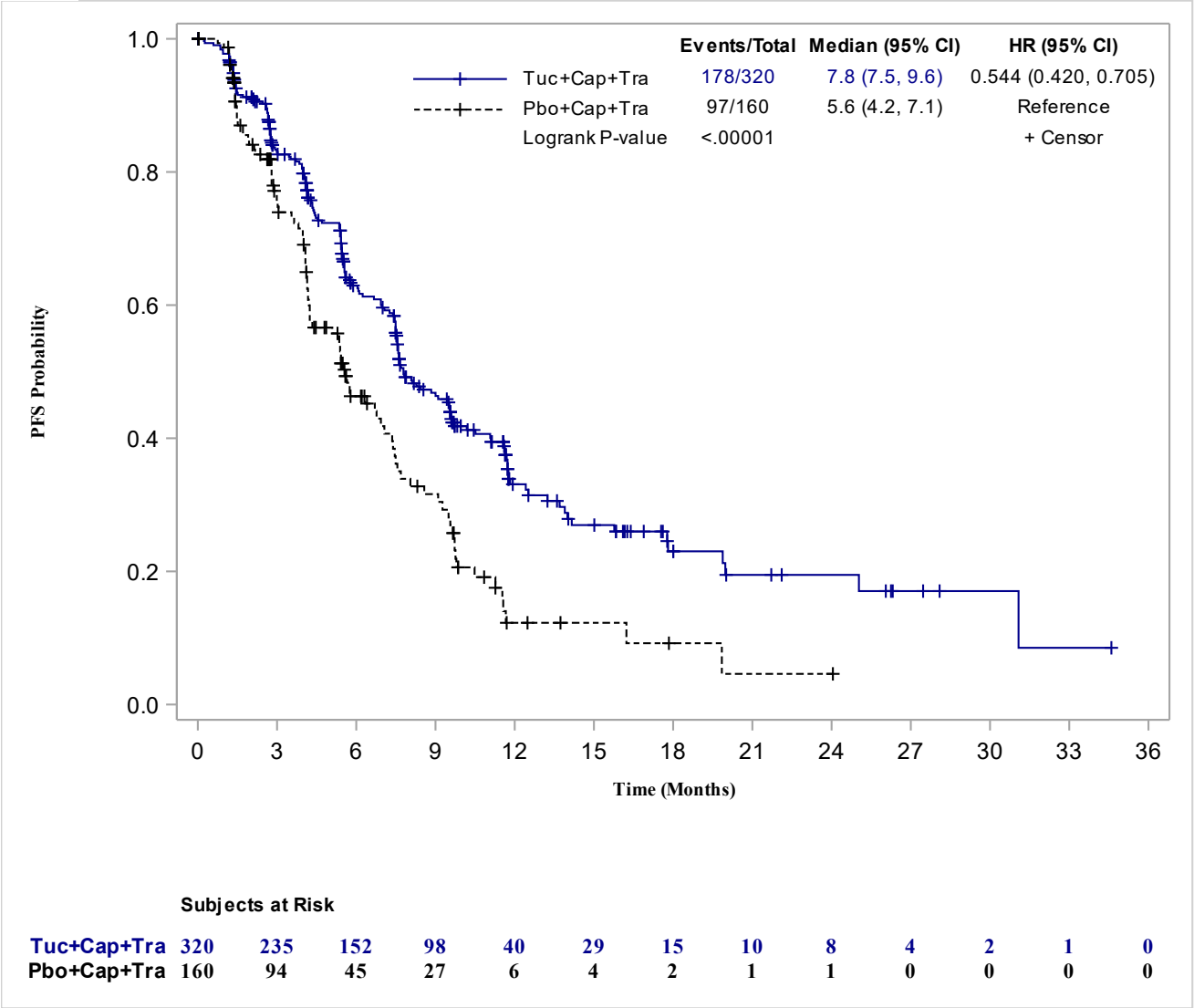
Table 24: Summary of PFS per BICR (ITT-PFS)

	Tuc+Cap+Tra (N=320)	Pbo+Cap+Tra (N=160)
Subjects with progression or death[a], n (%)	178 (55.6)	97 (60.6)
Stratified hazard ratio[b, c] (95% CI)	0.544 (0.420, 0.705)	
Stratified log-rank P-value[c, d]	<0.00001	
Estimated PFS rate[f] at 6 months (95% CI)[e]	62.9% (56.9%, 68.4%)	46.3% (37.2%, 54.9%)
Estimated PFS rate[f] at 12 months (95% CI)[e]	33.1% (26.6%, 39.7%)	12.3% (6.0%, 20.9%)
Median PFS (months) (95% CI)[e]	7.8 (7.5, 9.6)	5.6 (4.2, 7.1)
25th, 75th percentile	4.3, 17.8	3.0, 9.7
Observed min, maxf	0.0+, 34.6+	0.0+, 24.0+

[a] Death without either prior progression or more than two missed assessment visits.
[b] Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra was calculated from the proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
[c] Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomization.
[d] Two-sided p-value based on re-randomization procedure. (Rosenberger and Lachin, 2002).
[e] Calculated using the complementary log-log transformation method (Collett, 1994).
[f] '+' means the observed time was from censored subjects.

Source: Table 14.2.1.1, Table 14.2.1.7

Figure 10: PFS per BICR assessment (ITT-PFS population)



Cap=capecitabine; Pbo=placebo; Tra=trastuzumab; Tuc=tucatinib
Hazard Ratio is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomisation.
Two-sided p-value based on stratified log rank test and rerandomisation procedure (Rosenberger and Lachin, 2002).
Source(s): m5.3.5.1, CSR ONT-380-206, Figure 14.2.1.1.

Table 25: easons for Censoring in Primary Analysis per BICR
ITT - PFS Population

	Tuc+Cap+Tra (N=320) n (%)	Pbo+Cap+Tra (N=160) n (%)
Censored subjects	142 (44.4)	63 (39.4)
Reasons for censoring [a]		
No progression events, still on study	54 (38.0)	9 (14.3)
New anti-cancer treatment (systemic or radiation) started before PD or death observed	75 (52.8)	47 (74.6)
PD or death occurred after two or more consecutive missing scheduled response assessments	6 (4.2)	5 (7.9)
Off study without events	7 (4.9)	2 (3.2)

Page 1 of 1

a Denominator is the number of censored subjects.
Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
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Table 26: Summary of Progression-Free Survival (PFS) per BICR ITT - OS Population

	Tuc+Cap+Tra (N=410)		Pbo+Cap+Tra (N=202)
Subjects with progression or death [a], n (%)	198 (48.3)		112 (55.4)
Stratified Hazard Ratio [b, c] (95% C.I.)		0.535 (0.420, 0.682)	
Stratified Log-rank p-value [c, d]		<.00001	
Median PFS (Months) (95% C.I.) [e]	8.1 (7.6, 9.6)		5.5 (4.3, 6.9)
25th, 75th percentile	4.4, 17.8		3.1, 9.7
Observed min, max [f]	0.0+, 34.6+		0.0+, 24.0+

Page 1 of 1

a. Death without either prior progression or more than two missed assessment visits.
b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
c. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization.
d. Two-sided p-value calculated from stratified log-rank test.
e. Calculated using the complementary log-log transformation method (Collett, 1994).
f. '+' means the observed time is from censored subjects.
Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
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Table 27: Summary of Progression-Free Survival (PFS) per Investigator ITT - OS Population

	Tuc+Cap+Tra (N=410)		Pbo+Cap+Tra (N=202)
Subjects with progression or death [a], n (%)	254 (62.0)		147 (72.8)
Stratified Hazard Ratio [b, c] (95% C.I.)		0.556 (0.451, 0.687)	
Stratified Log-rank p-value [c, d]		<.00001	
Median PFS (Months) (95% C.I.) [e]	7.5 (6.1, 8.0)		4.3 (4.1, 5.6)
25th, 75th percentile	4.1, 13.1		2.7, 8.4
Observed min, max [f]	0.0+, 34.6+		0.0+, 24.0

Page 1 of 1

a. Death without either prior progression or more than two missed assessment visits.
b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
c. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization.
d. Two-sided p-value calculated from stratified log-rank test.
e. Calculated using the complementary log-log transformation method (Collett, 1994).
f. '+' means the observed time is from censored subjects.
Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
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The results of all sensitivity analyses were consistent and supported the primary analysis of PFS per BICR (Table 28).

Table 28: Summary of PFS sensitivity analysis per BICR (ITT-PFS population)

	Nominal stratified log-rank P-value[a, c]	Stratified hazard ratio[b, c] (95% CI)
Sensitivity analysis 1	<0.00001	0.538 (0.418, 0.694)
Sensitivity analysis 2	<0.00001	0.543 (0.422, 0.700)
Sensitivity analysis 3	<0.00001	0.555 (0.435, 0.708)
Sensitivity analysis 4	<0.00001	0.550 (0.426, 0.710)

Sensitivity Analysis 1 (Ignoring Missing Assessments of Disease Response): analysis for PFS time by ignoring the missing assessments in censoring scheme.
Sensitivity Analysis 2 (Imputing Missing Assessments of Disease Response): analysis for PFS time by imputing event time for subjects with missing assessments in censoring scheme.

Sensitivity Analysis 3 (New therapy before PD/death): analysis for PFS time by ignoring all new anti-cancer therapies in censoring scheme.
Sensitivity Analysis 4 (New radiation before PD/death): analysis for PFS time by ignoring all new radiation therapies in censoring scheme.
Two-sided P-value calculated from stratified log-rank test and re-randomisation procedure. (Rosenberger and Lachin, 2002).
Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra.
Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomisation.
Source: m5.3.5.1, CSR ONT-380-206, Table 14.2.1.4

The primary endpoint of PFS by BIRC was statistically significantly improved by 2.2 months in the ITT-PFS population, i.e. from 5.6 months to 7.8 months (HR 0.544 (95%CI: 0.420; 0.705). Data could be considered mature with 55.6% and 60.6% events in the tucatinib versus the placebo-arm, respectively. PFS by BICR conducted in the ITT-OS population was in line with the result from the primary analysis (HR=0.535 (95%CI: 0.420, 0.682), and PFS by INV supports this, see table 14.2.7.5 above.

Many patients were censored for PFS by BIRC in both treatment arms, i.e. 44.4% (n= 142) and 39.4% (n=63), respectively (Table 14.2.1.3). Many of these censored patients switched to new anti-cancer therapy before PD (n=75 and n=47 in each arm, respectively). The main reason for initiation of new anti-cancer therapy was PD per investigator (n=82 of 122 patients i.e. 67%). Another 17 patients (14%) had clinical progression of disease, while 7 patients discontinued due to an AE (6%). 6 patients had radiographic progression, 5 discontinued due to subject decision, and 2 patients stopped due to non-compliance and protocol deviations, respectively. Two pre-specified sensitivity analyses were conducted for subjects who received new anti-cancer therapy before PD or death:

Table 29: Summary of PFS sensitivity analysis per BICR (ITT-PFS)

	Nominal Stratified Log-rank p-value[a, c]	Stratified hazard ratio[b, c] (95% CI)
Sensitivity analysis 1	<0.00001	0.538 (0.418, 0.694)
Sensitivity analysis 2	<0.00001	0.543 (0.422, 0.700)
Sensitivity analysis 3	<0.00001	0.555 (0.435, 0.708)
Sensitivity analysis 4	<0.00001	0.550 (0.426, 0.710)

Sensitivity Analysis 1 (Ignoring Missing Assessments of Disease Response): analysis for PFS time by ignoring the missing assessments in censoring scheme.
Sensitivity Analysis 2 (Imputing Missing Assessments of Disease Response): analysis for PFS time by imputing event time for subjects with missing assessments in censoring scheme.
Sensitivity Analysis 3 (New therapy before PD/death): analysis for PFS time by ignoring all new anti-cancer therapies in censoring scheme.
Sensitivity Analysis 4 (New radiation before PD/death): analysis for PFS time by ignoring all new radiation therapies in censoring scheme.
[a] Two-sided p-value calculated from stratified log-rank test and re-randomization procedure. (Rosenberger and Lachin, 2002).
[b] Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra.
[c] Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomization.
Source: Table 14.2.1.4

Secondary endpoints

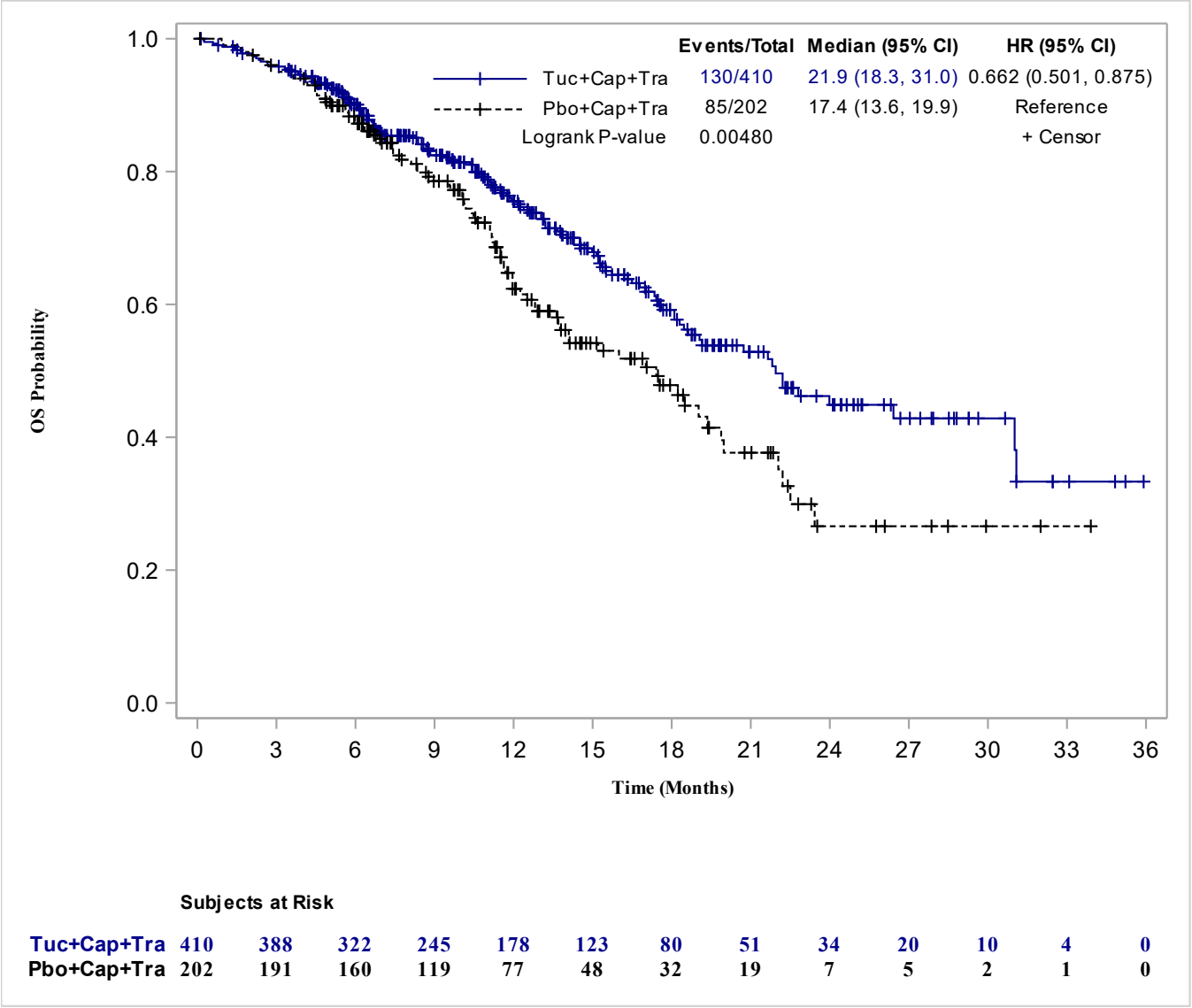
OS

Table 30: Summary of OS (ITT-OS)

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
Number of deaths, n (%)	130 (31.7)	85 (42.1)
Stratified hazard ratio [a, b] (95% C.I.)	0.662 (0.501, 0.875)	
Stratified Log-rank p-value [b, c, d]	0.00480	
Estimated OS rate[e] at 12 months (95% CI)[f]	75.5% (70.4%, 79.9%)	62.4% (54.1%, 69.5%)
Estimated OS rate[e] at 24 months (95% CI)[f]	44.9% (36.6%, 52.8%)	26.6% (15.7%, 38.7%)
Median OS (months) (95% C.I.) [f]	21.9 (18.3, 31.0)	17.4 (13.6, 19.9)
25th, 75th percentile	12.2, -	10.2, -
Observed min, maxg	0.1+, 35.9+	0.1+, 33.9+

a Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra was calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
b Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomization.
c Two-sided p-value based on re-randomization procedure (Rosenberger and Lachin, 2002).
d Statistically significant after adjustment for multiplicity. The threshold for statistical significance is 0.0074.
e As estimated using Kaplan-Meier methods
f Calculated using the complementary log-log transformation method (Collett, 1994).
g '+' means the observed time is from censored subjects.
Source: Table 14.2.3.1, Table 14.2.3.2

Figure 11: **Survival by Treatment Arm (ITT population – all randomised subjects)**



Cap=capecitabine; Tra=trastuzumab; Tuc=tucatinib
Statistically significant after adjustment for multiplicity. The threshold for statistical significance was 0.0074.
Hazard ratio was computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomisation.
Two-sided p-value based on stratified log-rank test and re-randomisation procedure (Rosenberger and Lachin, 2002).
Source: m5.3.5.1, CSR ONT-380-206, Figure 14.2.3.1

PFS in patients with brain metastases

Table 31: Summary of PFS per BICR in subjects with brain metastases (ITT-PFS$_{BrainMets}$)

	Tuc+Cap+Tra (N=198)	Pbo+Cap+Tra (N=93)
Subjects with progression or death[a], n (%)	106 (53.5)	51 (54.8)
Stratified hazard ratio[b, c] (95% CI)[c]	0.483 (0.339, 0.689)	
Stratified log-rank P-value[c, d, e]	<0.00001	
Estimated PFS rate[f] at 6 months (95% CI)[g]	60.4% (52.4%, 67.5%)	33.9% (21.0%, 47.2%)
Estimated PFS rate[f] at 12 months (95% CI)[g]	24.9% (16.5%, 34.3%)	-
Median PFS (months) (95% CI)[g]	7.6 (6.2, 9.5)	5.4 (4.1, 5.7)
25th, 75th percentile	4.2, 11.8	3.0, 7.5
Observed min, max[h]	0.0+, 34.6+	0.0+, 11.6

Brain metastases population is defined as a subset of subjects with a history of brain metastases or presence of brain metastases or brain lesions of equivocal significance on screening MRI.

a Death without either prior progression or more than two missed assessment visits.

b Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra. A hazard ratio <1.0 favored the Tuc+Cap+Tra arm.

c Computed using stratification factors (ECOG PS: 0/1, and Region of world: North America /Rest of World) at randomization.

d Two-sided p-value based on re-randomization procedure (Rosenberger and Lachin, 2002).

e Statistically significant after adjustment for multiplicity. The threshold for statistical significance was 0.0080.

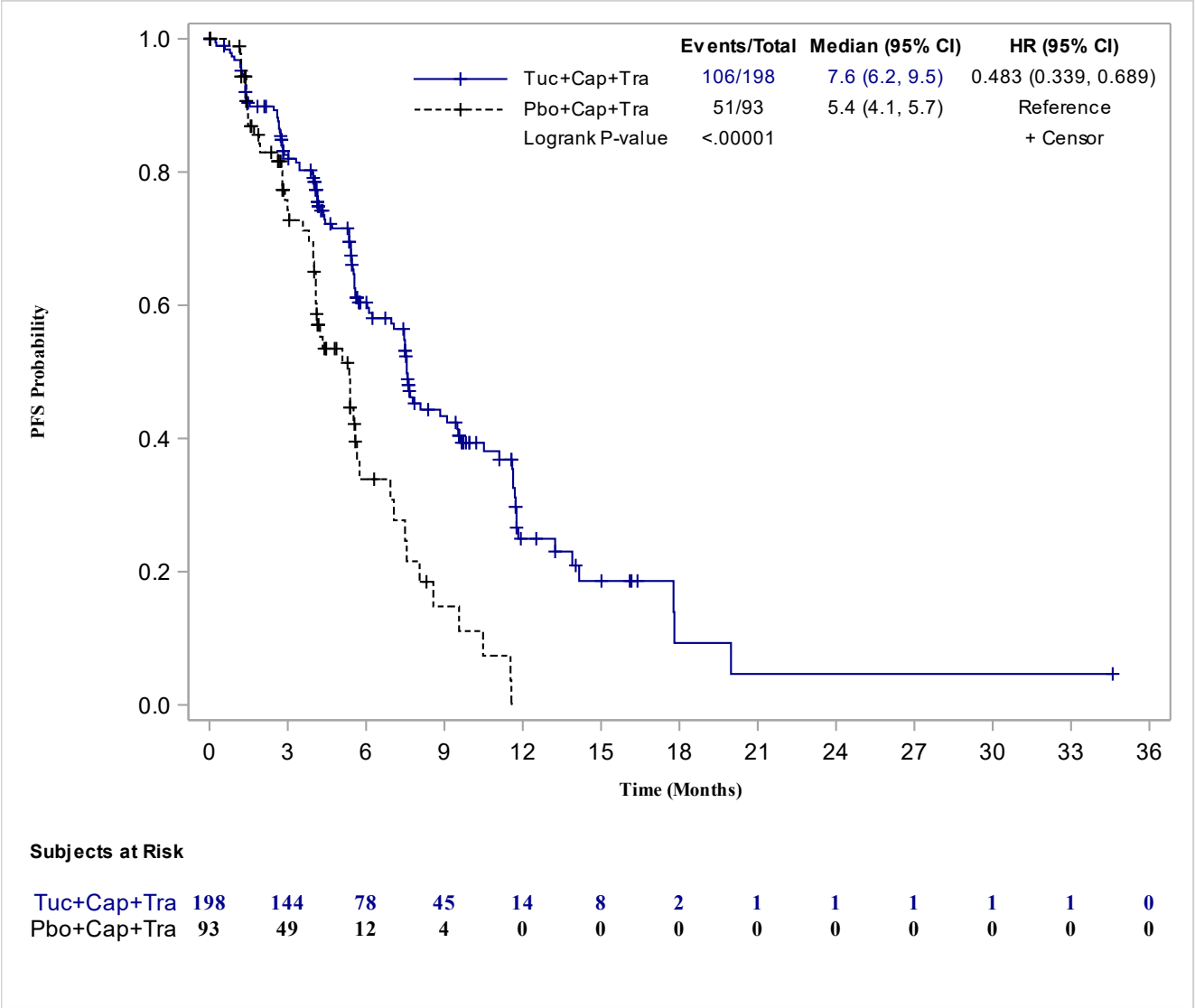
f As estimated using Kaplan-Meier methods

g Calculated using the complementary log-log transformation method (Collett, 1994).

h '+' means the observed time was from censored subjects.

Source: Table 14.2.2.1, Table 14.2.2.2

Figure 12: BICR in the ITT-PFS$_{BrainMets}$ population



Cap=capecitabine; Tra=trastuzumab; Tuc=tucatinib
Statistically significant after adjustment for multiplicity. The threshold for statistical significance was 0.0080.
Brain metastases population was defined as a subset of subjects with a history of brain metastases or presence of brain metastases or brain lesions of equivocal significance on screening MRI.
Hazard ratio was computed from the Cox proportional hazards model using stratification factors (ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomisation.
Two-sided p-value based on stratified log rank test and re-randomisation procedure (Rosenberger and Lachin, 2002).
Source(s): m5.3.5.1, CSR ONT-380-206, Figure 14.2.2.1

Of the 198 patients treated with tucatinib, more than half have had an PFS brain event. These patients, who had a history of brain metastases or presence of brain metastases on MRI, had a statistically significant improvement of PFS from 5.4 months to 7.6 months

The intracranial response rates by BICR and investigator are shown below. The assessment of BIRC vs INV differs both regarding the number of evaluable patients at baseline (48 vs 55 patients in the tucatinib arm) and the fractions of patients with response (35.4% vs 47.3% with tucatinib) and the DOR (8.2 months vs 6.8 months with tucatinib).

Table 32: Summary of intracranial confirmed objective response per BICR in subjects with active brain metastases and measurable brain lesions at baseline

	Tuc+Cap+Tra (N=48)	Pbo+Cap+Tra (N=21)
Best overall response[a], n (%)		
CR	1 (2.1)	0
PR	16 (33.3)	5 (23.8)
SD	25 (52.1)	14 (66.7)
PD	3 (6.3)	2 (9.5)
Not available[b]	3 (6.3)	0
Confirmed ORR (95% CI)[c], %	35.4 (22.2, 50.5)	23.8 (8.2, 47.2)
DOR[d] (95% CI)[e], months	8.2 (4.1, 9.7)	2.8 (2.6, 8.9)

a Confirmed best overall response assessed per RECIST v1.1
b Subjects with no post-baseline response assessments.
c Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934)
d As estimated using Kaplan-Meier methods.
e Calculated using the complementary log-log transformation method (Collett, 1994).

Table 33: Summary of intracranial confirmed objective response per investigator in subjects with active brain metastases and measurable brain lesions at baseline in the HER2CLIMB Study

	Tuc+Cap+Tra (N=55)	Pbo+Cap+Tra (N=20)
Best overall response[a], n (%)		
CR		1 (5.0)
PR	23 (41.8)	3 (15.0)
SD	24 (43.6)	16 (80.0)
PD	2 (3.6)	0
Not available[b]	3 (5.5)	0
Confirmed ORR (95% CI)c, %	47.3 (33.7, 61.2)	20.0 (5.7, 43.7)
Stratified CMH p-value for ORRd	0.03241	
DOR[e] (95% CI)[f], months	6.8 (5.5, 16.4)	3.0 (3.0, 10.3)

a) Confirmed best overall response assessed per RECIST v1.1.

b) Subjects with no post-baseline response assessments.
c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934).
d) Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomisation.
e) As estimated using Kaplan-Meier methods.
f) Calculated using the complementary log-log transformation method (Collett, 1994).

ORR

Table 34: Summary of objective response per BICR assessment (ITT-OS population)

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
Best Overall Response[a], n (%)		
CR	7 (1.7)	2 (1.0)
PR	135 (32.9)	37 (18.3)
SD	155 (37.8)	100 (49.5)
Non-CR/Non-PD	62 (15.1)	26 (12.9)

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
PD	27 (6.6)	25 (12.4)
Not Evaluable (NE)	0	3 (1.5)
Not Available[b]	22 (5.4)	8 (4.0)
Not Applicable[c]	2 (0.5)	1 (0.5)
Subjects with Objective Response of Confirmed CR or PR, n	142	39
Objective response rate (ORR), %	34.6	19.3
95% CI[d] for ORR	(30.0, 39.5)	(14.1, 25.4)
Stratified CMH p-value for ORR[e]	0.00011	

a. Confirmed best overall response assessed per RECIST 1.1.
b. Subjects with no post-baseline response assessments.
c. Subjects with no evidence of disease at baseline per BICR.
d. Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934).
e. Cochran-Mantel-Haenszel test controlling for stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomisation

Table 35: Summary of objective response per investigator assessment (ITT-OS population)

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
Best Overall Response[a], n (%)		
CR	12 (2.9)	4 (2.0)
PR	138 (33.7)	35 (17.3)
SD	151 (36.8)	96 (47.5)
Non-CR/Non-PD	47 (11.5)	21 (10.4)
PD	41 (10.0)	36 (17.8)
Not Evaluable (NE)	0	1 (0.5)
Not Available[b]	21 (5.1)	9 (4.5)
Not Applicable[c]	0	0
Subjects with Objective Response of Confirmed CR or PR, n	150	39
Objective response rate (ORR), %	36.6	19.3
95% CI[d] for ORR	(31.9, 41.5)	(14.1, 25.4)
Stratified CMH p-value for ORR[e]	0.00002	

a. Confirmed best overall response assessed per RECIST 1.1.
b. Subjects with no post-baseline response assessments.
c. Subjects with no evidence of disease at baseline.
d. Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934).
e. Cochran-Mantel-Haenszel test controlling for stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomisation

ORR is now shown for the entire ITT-OS population (n=612). Updated ORR by BIRC with tucatinib was 34.6% (95%CI: 30.0; 39.5) vs 19.3% (95%CI: 14.1;25.4) in the control arm.

ORR per investigator on the tucatinib arm was 36.6% (95%CI: 31.9, 41.5) versus 19.3% (95%CI: 14.1, 25.4) on the control arm (nominal P=0.00002).

DOR

Duration of response was analysed in patients with measurable disease at baseline in the ITT-OS. The median DOR per BICR on the tucatinib arm was 8.3 months (95%CI: 6.2, 9.7) and 6.3 months (95%CI: 5.8, 8.9), on the control arm. The median DOR per investigator was 6.9 months (95%CI: 6.2, 8.3) on the tucatinib arm and 6.9 months (95%CI: 4.2, 8.9) on the control arm.

ORR was presented for the ITT-OS population, but only the patients who had measurable disease are included.

Clinical benefit rate (CBR)

Table 36: Summary of objective response per BICR (ITT-OS population)

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
Best Overall Response[a], n (%)		
CR	7 (1.7)	2 (1.0)
PR	135 (32.9)	37 (18.3)
SD	155 (37.8)	100 (49.5)
Non-CR/Non-PD	62 (15.1)	26 (12.9)
PD	27 (6.6)	25 (12.4)
Not Evaluable (NE)	0	3 (1.5)
Not Available[b]	22 (5.4)	8 (4.0)
Not Applicable[c]	2 (0.5)	1 (0.5)
Subjects with Clinical Benefit (Confirmed CR or PR, or non-CR/non-PD or SD⩾6 months[d]), n	245	77
Clinical Benefit Rate (CBR), %	59.8	38.1
95% CI[e] for CBR	(54.8, 64.5)	(31.4, 45.2)
Stratified CMH p-value for CBR[f]	<.00001	

a. Confirmed best overall response assessed per RECIST 1.1.
b. Subjects with no post-baseline response assessments
c. Subjects with no evidence of disease at baseline.
d. Subjects with BOR=SD or Non-CR/Non-PD are considered having non-CR/non-PD or SD ⩾6 months if there was no progression, or death, or new anti-cancer therapy within 6 months from randomisation.
e. Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934).
f. Cochran-Mantel-Haenszel test controlling for stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomisation

Table 37: Summary of objective response per investigator assessment (ITT-OS population)

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
Best Overall Response [a], n (%)		
CR	12 (2.9)	4 (2.0)
PR	138 (33.7)	35 (17.3)
SD	151 (36.8)	96 (47.5)
Non-CR/Non-PD	47 (11.5)	21 (10.4)
PD	41 (10.0)	36 (17.8)
Not Evaluable (NE)	0	1 (0.5)
Not Available[b]	21 (5.1)	9 (4.5)
Subjects with Clinical Benefit (Confirmed CR or PR, or non-CR/non-PD or SD⩾6 months[c]), n	238	76
Clinical Benefit Rate (CBR), %	58.0	37.6
95% CI[d] for CBR	(53.1, 62.9)	(30.9, 44.7)
Stratified CMH p-value for CBR[e]	<.00001	

a. Confirmed best overall response assessed per RECIST 1.1.
b. Subjects with no post-baseline response assessments
c. Subjects with BOR=SD or Non-CR/Non-PD are considered having non-CR/non-PD or SD ⩾6 months if there was no progression, or death, or new anti-cancer therapy within 6 months from randomisation.
d. Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934).
e. Cochran-Mantel-Haenszel test controlling for stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomisation

Subsequent therapies

Seattle Genetics Protocol ONT-380-206

Table 38: Subsequent Anti-Cancer Systemic Therapies ITT - OS Population

	Tuc+Cap+Tra (N=410) n (%)	Pbo+Cap+Tra (N=202) n (%)	Total (N=612) n (%)
Subjects who have discontinued or never received tucatinib or placebo	292	175	467
Subjects who received one or more subsequent new anti-cancer systemic therapies [a]	202 (69.2)	139 (79.4)	341 (73.0)
Subjects who received one or more subsequent new anti-HER2 regimens [a]	164 (56.2)	119 (68.0)	283 (60.6)
Types of subsequent anti-HER2 agents received [a]			
Antibody	146 (50.0)	100 (57.1)	246 (52.7)
Trastuzumab	141 (48.3)	97 (55.4)	238 (51.0)
Pertuzumab	11 (3.8)	10 (5.7)	21 (4.5)
Margetuximab	5 (1.7)	4 (2.3)	9 (1.9)
ZW25	2 (0.7)	2 (1.1)	4 (0.9)
MCLA-128	0	1 (0.6)	1 (0.2)
Tyrosine kinase inhibitor	49 (16.8)	42 (24.0)	91 (19.5)
Lapatinib	37 (12.7)	32 (18.3)	69 (14.8)
Neratinib	11 (3.8)	11 (6.3)	22 (4.7)
Poziotinib	1 (0.3)	0	1 (0.2)
Pyrotinib	1 (0.3)	0	1 (0.2)

	Tuc+Cap+Tra (N=410) n (%)	Pbo+Cap+Tra (N=202) n (%)	Total (N=612) n (%)
Subjects who received one or more subsequent new anti-HER2 regimens [a] (cont.)			
Antibody drug conjugate	11 (3.8)	15 (8.6)	26 (5.6)
T-DM1	5 (1.7)	5 (2.9)	10 (2.1)
DS-8201A	4 (1.4)	6 (3.4)	10 (2.1)
SYD985	3 (1.0)	3 (1.7)	6 (1.3)
DHES0815A	0	2 (1.1)	2 (0.4)
Subjects who received one or more subsequent new hormonal or CDK inhibitor therapies [a]	30 (10.3)	17 (9.7)	47 (10.1)
Subjects who received one or more subsequent new PD-1/PD-L1 inhibitor therapies [a]	10 (3.4)	3 (1.7)	13 (2.8)
Subsequent systemic anti-cancer treatments ever received, regimen name [b]			
5-Fluorouracil and Cyclophosphamide and Epirubicin	1 (0.5)	1 (0.7)	2 (0.6)
5-Fluorouracil and Cyclophosphamide and Methotrexate	1 (0.5)	0	1 (0.3)
5-Fluorouracil and Trastuzumab	0	1 (0.7)	1 (0.3)
ABBV-368	1 (0.5)	0	1 (0.3)
AZD2014 and AZD8186	1 (0.5)	0	1 (0.3)

Patient-related outcome (PRO)

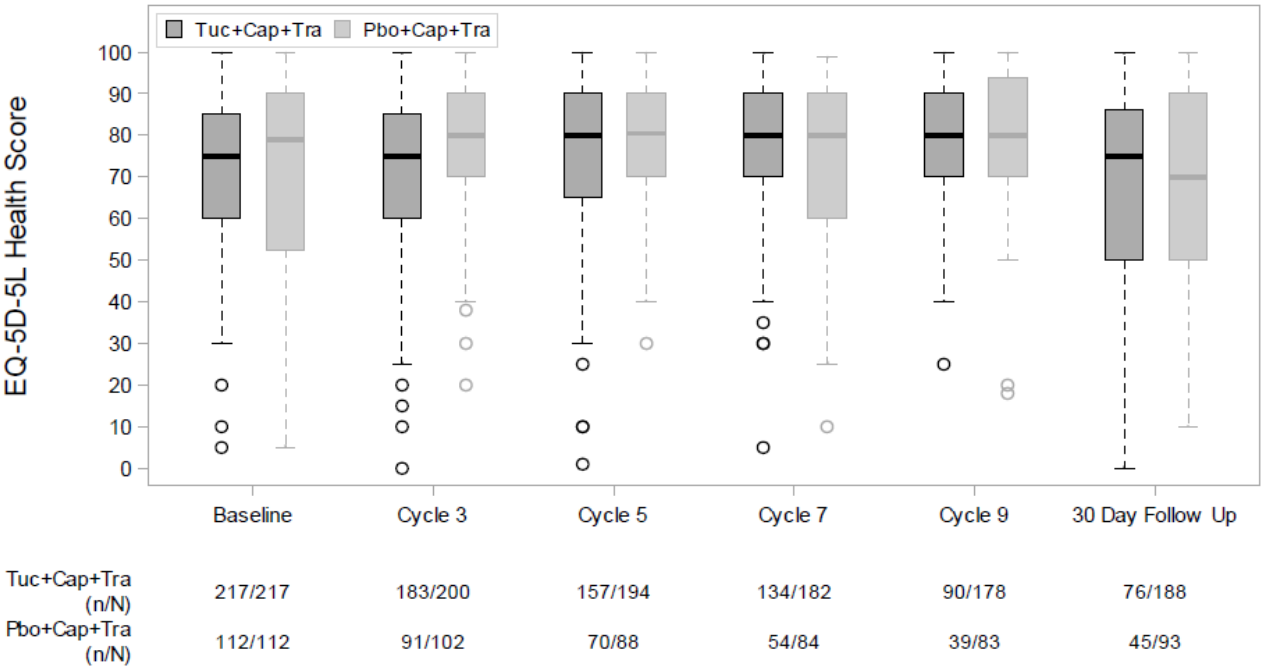
Table 39: Summary of health care resource (safety analysis population)

	Tuc+Cap+Tra (N=404)	Pbo+Cap+Tra (N=197)
Cumulative incidence of hospitalizations per subject year[a]		
n	404	197
Mean (STD)	0.9 (2.7)	1.1 (2.6)
Median	0.0	0.0
Min, max	0.0, 37.5	0.0, 23.1
95% CI for the mean	0.6, 1.1	0.7, 1.4
Total length of stay (days) per subject year[a]		
n	94	51
Mean (STD)	25.0 (31.4)	32.4 (49.9)
Median	12.3	16.1
Min, max	1.4, 178.7	0.9, 263.5
95% CI for the mean	18.5, 31.4	18.4, 46.5
Total number of hospitalizations	143	75
Reason for hospitalization visit, n (%)		
Hospitalization for AE	124 (86.7)	64 (85.3)
Planned hospitalization (other than AE)	10 (7.0)	6 (8.0)
Ambulatory surgery	3 (2.1)	0
Other	6 (4.2)	5 (6.7)
Number of ER visits per subject year[a]		
n	52	29
Mean (STD)	3.1 (2.4)	3.3 (2.6)
Median	2.2	2.7
Min, max	0.3, 10.0	0.9, 11.6
95% CI for the mean	2.4, 3.8	2.3, 4.3

a Subject year was calculated from the first dose date of tucatinib or placebo to the last date of tucatinib or placebo + 37 days for each subject.

Source: Table 14.2.8

Figure 13: **EQ-5D-5L of Health Score**

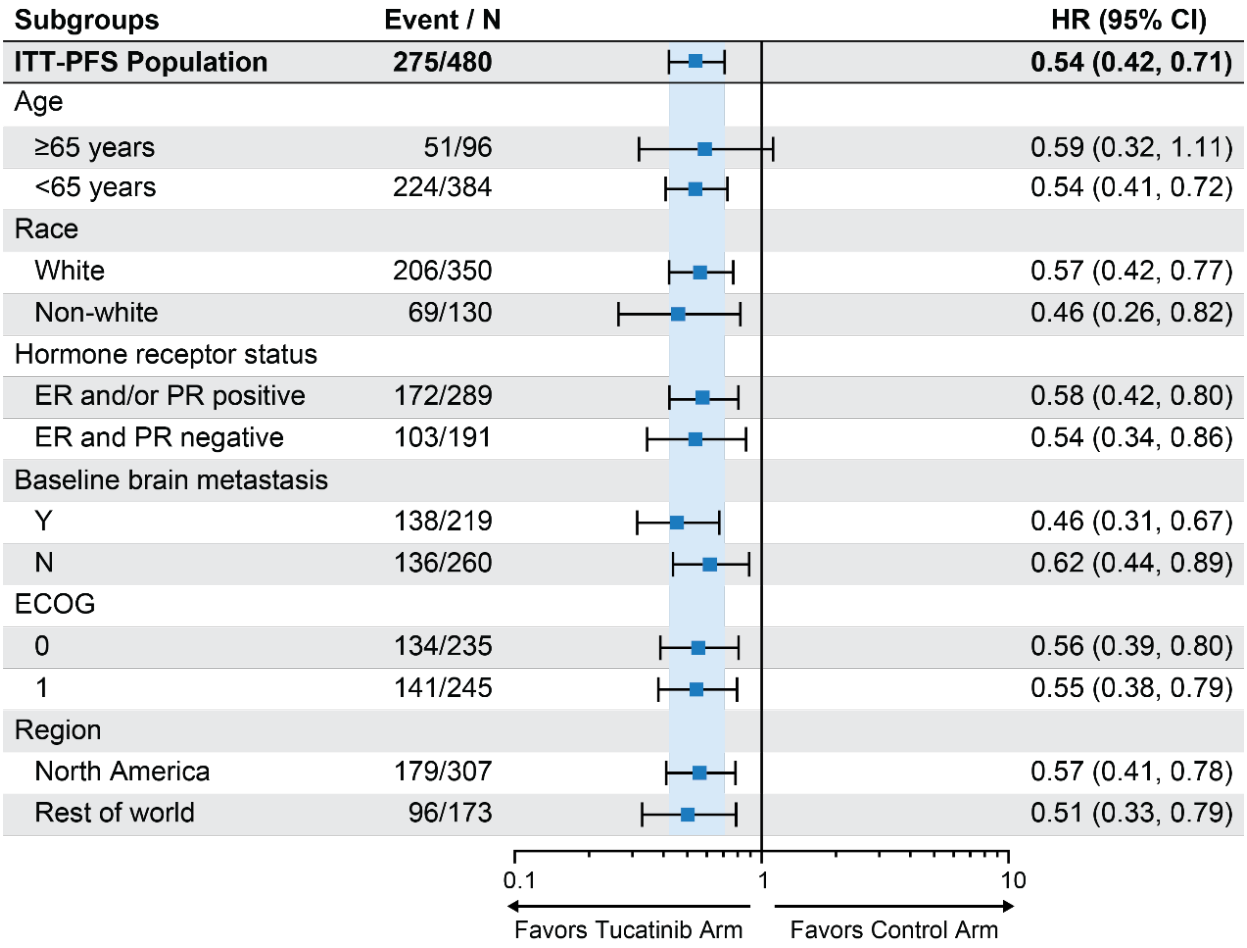


Baseline was defined as most recent non-missing assessment on or before first dose date.
n/N: n is the number of subjects who completed the survey. N is the number of subjects who completed baseline survey and are still on study. Cycles where the number of subjects in each arm remained ≥20% of initial cohort size are presented.
The length of the box represents the interquartile range (the distance between the 25th and 75th percentiles). The horizontal line in the box interior represents the group median. The whiskers extend to the group minimum and maximum values.
Source: Figure 14.2.7.1.6

PRO-data concerning hospitalisations and ER visits show no clinically meaningful differences between the treatment arms. Moreover, HRQoL scales measuring anxiety/depression, mobility, pain/discomfort, self-care, and usual activities were done in a subset of the ITT population (n=330) and did not show any meaningful differences, suggesting that tucatinib treatment do not have a detrimental effect on health-related quality of life.

Ancillary analyses

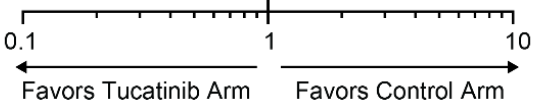
Figure 14: Hazard ratio and 95% CI for PFS per BICR by subgroups (ITT-PFS population)



Hazard ratio was calculated from cox regression model considering stratification factors from randomisation.
'Race Non-White' included subjects with race other than white.
'Hormone receptor status: ER and PR negative' included subjects without positive oestrogen or positive progesterone.
'Baseline brain metastasis: Y' included subjects with a history of brain metastases or presence of brain metastases or brain lesions of equivocal significance on screening MRI per EDC data.
Source(s): m5.3.5.1, CSR ONT-380-206, Figure 14.2.1.2

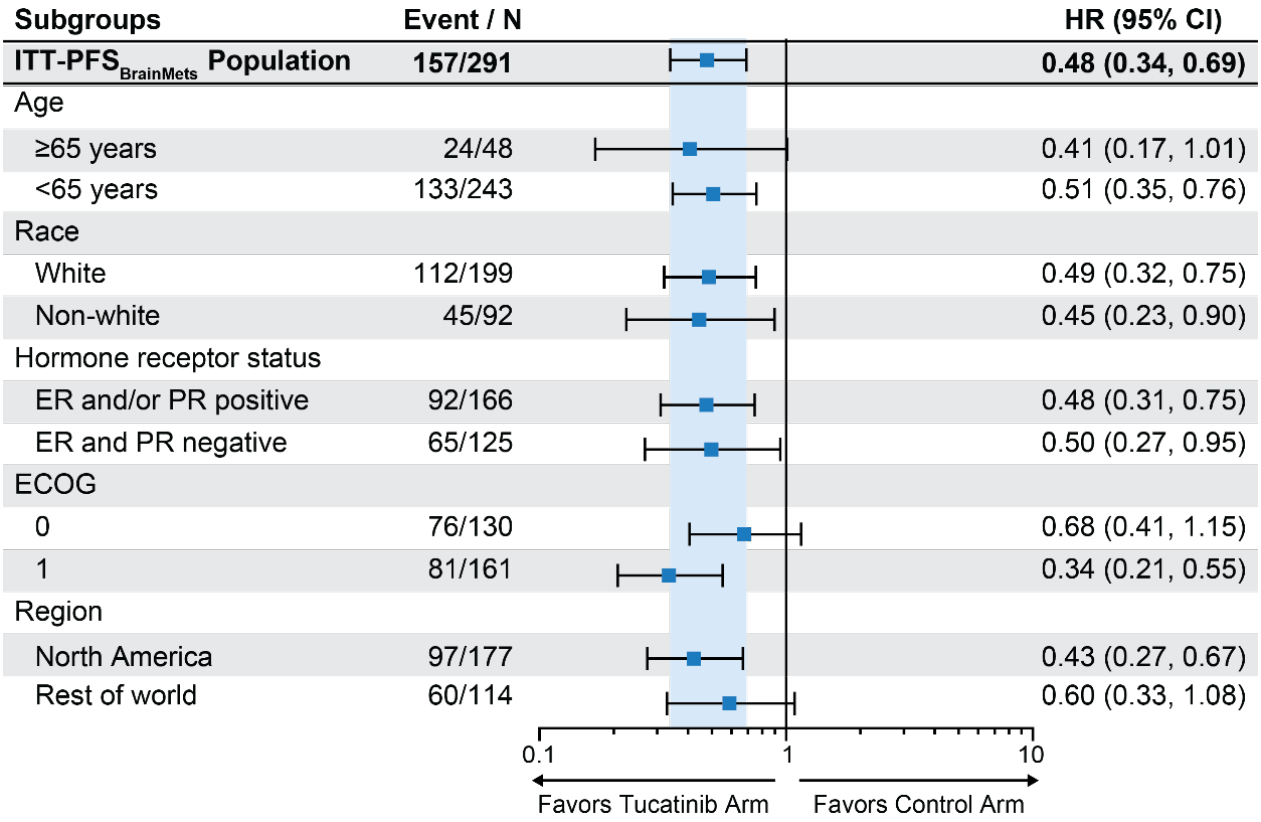
Figure 15: Hazard ratio and 95% CI for OS by subgroups (ITT-OS population)

Subgroups	Event / N	HR (95% CI)
ITT-OS Population	**215/612**	**0.66 (0.50, 0.88)**
Age		
≥65 years	53/116	0.58 (0.32, 1.06)
<65 years	162/496	0.69 (0.50, 0.95)
Race		
White	160/444	0.69 (0.50, 0.96)
Non-white	55/168	0.51 (0.28, 0.93)
Hormone receptor status		
ER and/or PR positive	128/370	0.85 (0.59, 1.23)
ER and PR negative	87/242	0.50 (0.31, 0.80)
Baseline brain metastasis		
Y	114/291	0.58 (0.40, 0.85)
N	101/319	0.72 (0.48, 1.08)
ECOG		
0	81/298	0.51 (0.33, 0.80)
1	134/314	0.84 (0.59, 1.20)
Region		
North America	148/369	0.68 (0.48, 0.95)
Rest of world	67/243	0.63 (0.39, 1.03)



Hazard ratio was calculated from cox regression model considering stratified factors from randomisation.
'Race Non-White' included subjects with race other than white.
'Hormone receptor status: ER and PR negative' included subjects without positive oestrogen or positive progesterone.
'Baseline brain metastasis: Y' included subjects with a history of brain metastases or presence of brain metastases or brain lesions of equivocal significance on screening MRI per EDC data.
Source(s): m5.3.5.1, CSR ONT-380-206, Figure 14.2.3.2

Figure 16: Hazard ratio and 95% CI for PFS per BICR by subgroups (ITT-PFS$_{BrainMets}$)



Hazard Ratio was calculated from cox regression model considering stratification factors from randomisation.
'Race Non-White' included subjects with race other than white.
'Hormone receptor status: ER and PR negative' included subjects without positive oestrogen or positive progesterone
Source: m5.3.5.1, CSR ONT-380-206, Figure 14.2.2.2.

For the primary endpoint, PFS by BIRC, the point estimates are all in favour of tucatinib and only in patients of more than 65 years of age, do the 95%CI overlap with 1.

For the key secondary endpoint OS, all of the point estimates again favour treatment with tucatinib; however, the 95%CI's overlap with 1 in the subgroups who are ≥65 years, HR and/or PR positive, do not have brain metastases, and are ECOG PS 1.

For PFS in the subgroup of patients with brain metastases at baseline, the sample size is smaller than with the two previous subgroup analyses (n=291). In spite of this, all of the point estimates are still in favour of tucatinib and only a few and small overlaps of 1 occur.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial HER2CLIMB

Title: Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pre-treated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma

Study identifier	ONT-380-206 (HER2CLIMB)		
Design	HER2CLIMB is an ongoing, randomised, double-blind, placebo-controlled, active comparator, global study of tucatinib or placebo in combination with trastuzumab and capecitabine in subjects with locally advanced unresectable or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab, and T-DM1 (ado-trastuzumab emtansine or trastuzumab emtansine). Subjects were randomised in a 2:1 ratio to receive tucatinib or placebo in combination with trastuzumab and capecitabine. Randomisation was performed using a dynamic hierarchical randomisation scheme and was stratified by presence or history of treated or untreated brain metastases (yes, no), Eastern Cooperative Oncology Group (ECOG) Performance Status (0, 1), and region of world (US, Canada, Rest of World). Six hundred twelve subjects were randomised.		
	Duration of main phase:		3 years 7 months (February 2016 to September 2019)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypo-thesis	Superiority		
Treatment groups	Tucatinib arm		<u>Treatment</u> Tucatinib 300 mg PO BID for Days 1-21 of a 21-day cycle, capecitabine 1000 mg/m2 PO BID for Days 1-14 only of a 21-day cycle, trastuzumab loading dose 8 mg/kg IV on Day 1, followed by 6 mg/kg on Day 1 of a 21-day cycle. In instances of subcutaneous (SC) trastuzumab use, a fixed dose of 600 mg was administered without a loading dose. <u>Duration</u> All treatments were given on a 21-day cycle. Treatment continued until unacceptable toxicity, disease progression, withdrawal of consent. <u>Number of subjects</u> N = 410
	Control arm		<u>Treatment</u> Placebo PO BID for Days 1-21 of a 21-day cycle, capecitabine 1000 mg/m2 PO BID for Days 1-14 only of a 21-day cycle, trastuzumab loading dose 8 mg/kg IV on Day 1, followed by 6 mg/kg on Day 1 of a 21-day cycle. In instances of SC trastuzumab use, a fixed dose of 600 mg was administered without a loading dose. <u>Duration</u> All treatments were given on a 21-day cycle. Treatment continued until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. <u>Number of subjects</u> N = 202
Endpoints and definitions	Primary endpoint	PFS	Progression free survival (PFS), defined as the time from randomisation to documented disease progression as determined by blinded independent central review (BICR) per RECIST 1.1 or death from any cause, whichever occurs first, in the first 480 patients randomised (N = 320 in the tucatinib arm; N = 160 in the control arm).
	Secondary endpoint	OS	Overall survival in all 612 subjects randomised (N = 410 in the tucatinib arm; N = 202 in the control arm).
	Secondary endpoint	$PFS_{BrainMets}$	PFS in the 291 subjects with brain metastases at baseline (N = 198 in the tucatinib arm; N = 93 in the control arm), defined as subjects with a history of brain metastases, current brain metastases, or equivocal brain lesions at baseline, using RECIST 1.1 based on BICR.
	Secondary endpoint	ORR	Confirmed objective response rate (cORR) per RECIST 1.1 based on BICR in the 511 subjects who had measurable disease by BICR (N = 340 in the tucatinib arm; N = 171 in the control arm).

Data cutoff for primary analysis	04 September 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis of PFS per BICR was conducted using the data cut-off date of 04 September 2019, at which time 275 PFS events (disease progression or death) had occurred in the ITT-PFS population (N = 480). The pre-specified interim analyses for the key secondary endpoints OS and $PFS_{BrainMets}$ per BICR were conducted as a result of the statistically significant PFS analysis. Both key secondary endpoints were statistically significant; therefore, OS and $PFS_{BrainMets}$ analyses are considered final and no more formal statistical testing will be conducted. Additionally, the alpha-controlled secondary endpoint of confirmed ORR by BICR was formally tested between two treatment arms and was also found to be statistically significant in favour of the tucatinib arm.		
Descriptive statistics and estimate variability	**Treatment group**	**Tucatinib+Trastuzumab+Capecitabine (tucatinib arm)**	**Placebo+Trastuzumab+Capecitabine (control arm)**
	Number of subjects	N = 320	N = 160
	Median PFS (months)	7.8	5.6
	95% CI	(7.5, 9.6)	(4.2, 7.1)
	Number of subjects	N = 410	N = 202
	Median OS (months)	21.9	17.4
	95% CI	(18.3, 31.0)	(13.6, 19.9)
	Number of subjects	N = 198	N = 93
	Median $PFS_{BrainMets}$ (months)	7.6	5.4
	95% CI	(6.2, 9.5)	(4.1, 5.7)
	Number of subjects	N = 340	N = 171
	cORR (%)	40.6	22.8
	95% CI	(35.3, 46.0)	(16.7, 29.8)
Effect estimates per comparison	Primary endpoint: PFS	Comparison groups	Tucatinib arm vs control arm
		Hazard Ratio	0.544
		95% CI	(0.420, 0.705)
		P-value	<0.00001
	Secondary endpoint: OS	Comparison groups	Tucatinib arm vs control arm
		Hazard Ratio	0.662
		95% CI	(0.501, 0.875)
		P-value	0.00480
	Secondary endpoint: $PFS_{BrainMets}$	Comparison groups	Tucatinib arm vs control arm
		Hazard Ratio	0.483
		95% CI	(0.339, 0.689)
		P-value	<0.00001

	Secondary endpoint: cORR	Comparison groups	Tucatinib arm vs control arm
		Stratified CMH p-value for ORR	0.00008
Notes			

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Table 40: Number of cancer subjects by age group

	Age <65 years (N=632)	Age 65 to <75 years (N=133)	Age 75 to <85 years (N=14)	Age ⩾85 years (N=0)	Total (N=779)
Controlled studies	496 (78.5)	103 (77.4)	13 (92.9)	0	612 (78.6)
Non-controlled studies	136 (21.5)	30 (22.6)	1 (7.1)	0	167 (21.4)

Note: Only subjects who received or were randomised to receive (i.e., Study ONT-380-206) at least one dose of tucatinib/placebo are included. ONT-380-206 was the only controlled study.

Gender

Of the 5 male subjects, 3 were randomised to the tucatinib arm, of whom 1 had PR and 2 had a best response of SD.

Age

In the HER2CLIMB study, clinical benefit was achieved both among subjects <65 years and those ≥ 65 years in the tucatinib arm (PFS per BICR HR= 0.54 and 0.59, respectively; OS HR=0.69 and 0.58, respectively).

Supportive studies

ONT-380-005 (Phase 1b Study)

Study Design

Study ONT-380-005 evaluated tucatinib in combination with capecitabine alone (Combination 1), trastuzumab alone (Combination 2), and with both trastuzumab and capecitabine (Combination 3; tucatinib triplet combination), in subjects with progressive HER2+ MBC who have received prior treatments with both trastuzumab and T-DM1 for metastatic disease. The primary objective of the study was to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of tucatinib to be given in combination with capecitabine alone, with trastuzumab alone, and with both trastuzumab and capecitabine. The study used a 3+3 design to evaluate escalating dose levels of tucatinib to determine the MTD/RP2D for each combination. Three pre-defined dose cohorts were planned for Combinations 1 and 2, and cohort advancement was based on safety data. If <2 subjects experienced dose-limiting toxicity, in both these combinations then tucatinib would be evaluated for Combination 3. Secondary efficacy objectives included the evaluation of tucatinib and capecitabine

pharmacokinetic (PK) and anti-tumour activity (both systemically and in the brain). The study completed enrolment in December 2015. The DCO date for the primary analysis was 06-Mar-2018.

An additional expansion cohort of subjects with central nervous system (CNS) metastases that were either untreated or progressing after prior radiation therapy was also enrolled.

The doses of trastuzumab and capecitabine in the study were as follows:

- trastuzumab 8 mg/kg IV loading dose Day 1 Cycle 1, followed by 6 mg/kg IV Day 1 of all subsequent cycles.
- capecitabine 1000 mg/m^2 PO BID for 14 days of every 21-day cycle;

Following initiation of study treatment, CT/MRI scans of all areas of known disease were to be obtained at the end of every 2 treatment cycles through Cycle 6, and then at the end of every 3 treatment cycles, until PD, initiation of a new therapy, or withdrawal of consent.

Study Population

A total of 60 subjects were enrolled and treated at 5 study sites in the US. The safety analysis set included all subjects who received at least 1 dose of study treatment (tucatinib, capecitabine, or trastuzumab). Efficacy was analysed in 2 populations of subjects:

- Efficacy analysis set - all subjects from the safety analysis set who had at least 1 identifiable (target and/or nontarget) lesion at baseline and (1) had at least 1 post-baseline disease assessment or (2) if they had no post-baseline disease assessment, discontinued study treatment due to death, clinical or radiologic PD, or an AE.
- Measurable disease set - all subjects from the safety analysis set who had at least 1 measurable target lesion at baseline and (1) had at least 1 post-baseline disease assessment or (2) if they had no post-baseline disease assessment, discontinued study treatment due to death, clinical or radiologic PD, or an AE.

Statistical Analysis

This study was designed to assess the safety, tolerability, and MTD/RP2D of tucatinib given in combination with trastuzumab and/or capecitabine. No formal statistical comparisons between dose cohorts were performed.

Subject Disposition

Twenty-seven of the 60 subjects enrolled were assigned to the tucatinib triplet combination cohort of 300 mg PO BID tucatinib + trastuzumab + capecitabine. The majority of subjects in the tucatinib triplet combination cohort discontinued from the study due to disease progression (19 [70%] subjects), 1 subject (4%) discontinued due to AEs, and 2 subjects (7%) died.

Demographics

All the subjects in the tucatinib triplet combination cohort were female and the median age was 50 years (range, 35 to 67 years). The majority of subjects were white and not Hispanic or Latino. Seventeen subjects (63%) had ECOG PS of 0 and 10 subjects (37%) had an ECOG PS of 1.

Baseline Disease Characteristics

The median time from first positive biopsy for breast cancer to first study treatment was 40.4 months (range, 11.6 to 162.1 months) in the tucatinib triplet combination cohort (Table 45). Eleven subjects (41%) had past or current brain metastases at baseline. The median number of prior lines of systemic therapy was 5 (range, 2 to 9).

Table 41: Study ONT-380-005 baseline disease characteristics – tucatinib triplet combination

	Tuc+Cap+Tra (N=27)
Primary diagnosis	
Time from 1st positive biopsy to first study treatment (months)[a]	
n	24
Median	40.38
Range	11.6 - 162.1
Distant metastases	
Yes	27 (100)
Past or current brain metastases	
Yes	11 (41)
Time from 1st diagnosis of brain metastases to 1st study treatment (months)	
n	8
Median	3.27
Range	0.4 - 28.1
Stage at initial diagnosis	
Stage, n (%)	
I - III	17 (63)
IV	8 (30)
Missing	2 (7)
Metastatic disease at study entry, n (%)	
Visceral disease	
Yes	18 (67)
Number of prior lines of systemic therapy for breast cancer	
Mean (SD)	4.93 (1.82)
Median	5.00
Min, Max	2.0 - 9.0
Number of prior lines of systemic therapy per disease setting, n (%)	
Neoadjuvant	12 (44)
Adjuvant	9 (33)
Metastatic	27 (100)

a First positive biopsy for breast cancer.

Source(s): m5.3.3.2, CSR ONT-380-005, Table 14.1.4.1.1, Table 14.1.5.2

Exposure

The median duration of exposure of tucatinib in the tucatinib triplet combination cohort was 8.5 months (range, 1.4 to 32.9). The median RDI of tucatinib in these 27 subjects was 92.86% (range, 39 to 100).

Efficacy

Objective response rate per Investigator

Of the 27 subjects treated with the tucatinib triplet combination, 23 subjects (85%) had measurable disease. One subject (4%) had a CR and 13 subjects (56.5%) had PRs; ORR was 60.9% (95% CI: 38.5, 80.3) (Table 46). Of the 11 subjects with the baseline history of brain metastases, 9 subjects (81.8%) had measurable disease with an ORR of 55.6% (5/9 subjects; 95% CI: 21.2, 86.3). Of the

16 subjects with no baseline history of brain metastases, 14 subjects (87.5%) had measurable disease and an ORR of 64.3% (9/14 subjects; 95% CI: 35.1, 87.2).

Table 42: Study ONT-380-005 response assessment –measurable disease set

	Tuc+Cap+Tra (N=23)
Best overall response	
CR	1 (4.3)
PR	13 (56.5)
SD	6 (26.1)
PD	3 (13.0)
NE	0 (0)
ORR	
n (%)	14 (60.9)
95% CI[a]	(38.5, 80.3)

a Exact binomial CI

Source(s): m5.3.3.2, CSR ONT-380-005, Table 14.2.1.1.1

Duration of Response

The median DOR of the subjects with measurable disease treated with the tucatinib triplet combination was 11.1 months (95% CI: 2.9, 18.7). The median DOR was 14.9 months (95% CI: 4.9, 21.4) in the subjects with a baseline history of brain metastases and 8.9 months (95% CI: 2.8, 19.4) in the subjects without a baseline history of brain metastases.

PFS per investigator assessment

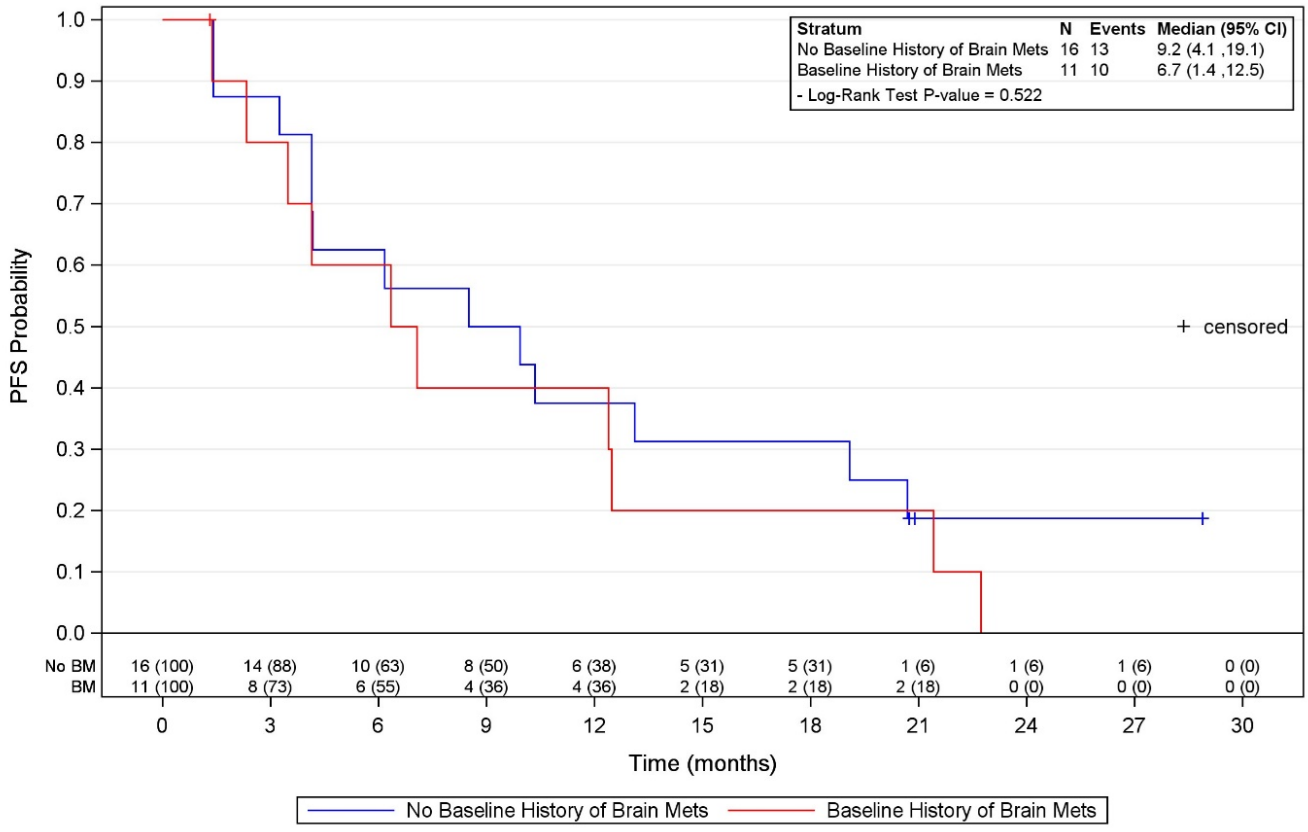
The median PFS per investigator assessment of the 27 subjects who were treated on the tucatinib triplet combination cohort was 7.8 months (95%CI: 4.1, 12.5) (Table 47). The median PFS in the 11 subjects with a baseline history of brain metastases was 6.7 months (95%CI: 1.4, 12.5) and 9.2 months (95%CI: 4.1, 19.1) in the 16 subjects without a history of brain metastases (Figure 9).

Table 43: Study ONT-380-005 progression-free survival per investigator assessment – efficacy analysis set

	Tuc+Cap+Tra (N=27)
Subjects included in analysis, n/N (%)	
Events	23 (85)
Radiographic progression	22 (81)
Clinical progression	0
Death	1 (4)
Censored	4 (15)
PFS time (months)	
Min, Max	1.3, 28.9
25th Percentile (95% CI)	4.1 (1.4, 6.2)
Median (95% CI)	7.8 (4.1, 12.5)
75th Percentile (95% CI)	19.1 (9.9, 22.7)

Note: PFS was defined as the time from 1st dose of study treatment to the date of documented disease progression or death.
Source(s): m5.3.3.2, CSR ONT-380-005, Table 14.2.1.3.1

Figure 17: Progression-free survival by baseline history of brain metastases - Tuc 300 BID + Cap + Tras – safety analysis set



Source(s): m5.3.3.2, CSR ONT-380-005, Figure 3

ONT-380-005 Efficacy Conclusions

The ONT-380-005 study provided the initial evidence of the clinical activity of tucatinib in combination with trastuzumab and capecitabine in HER2+ MBC and supported the initiation of the HER2CLIMB study:

- The ORR in this study for subjects with measurable disease was 60.9% (95%CI: 38.5, 80.3)

    - The ORR in subjects with a baseline history of brain metastases was 55.6% (95%CI: 21.2, 86.3) and 64.3% (95%CI: 35.1, 87.2) in subjects with no baseline history of brain metastases

- The median DOR for subjects with measurable disease treated with the tucatinib triplet combination was 11.1 months (95%CI: 2.9, 18.7). In subjects with a baseline history of brain metastases DOR was 14.9 months (95%CI: 4.9, 21.4) and in subjects without a baseline history of brain metastases DOR was 8.9 months (95%CI: 2.8, 19.4)
- The median PFS per investigator of the subjects treated with the tucatinib triplet combination was 7.8 months (95%CI: 4.1, 12.5)

Supporting Study: ONT-380-004 (Phase 1b)

ONT-380-004 is an ongoing phase 1b, open-label, dose-escalation study in subjects with HER2+ MBC designed to identify the MTD or RP2D of tucatinib in combination with the approved dose of T-DM1 (3.6 mg/kg every 21 days) and to assess the safety and tolerability of the combination. Other objectives included evaluation of tucatinib and T-DM1 PK, anti-tumour activity, and exploration of potential biomarkers.

A total of 57 subjects were enrolled and treated at 11 centres in the US and Canada. In the initial protocol, the starting dose level was 300 mg PO BID using the tablet formulation, 50% of the MTD for the tucatinib powder-in-capsule (PIC) formulation; the protocol was later amended to include the doses of 300, 350, and 400 mg BID. The MTD was determined to be 300 mg BID, which achieved a similar drug exposure as the MTD of the PIC formulation, 600 mg BID. An additional CNS expansion cohort was enrolled and treated at the MTD for subjects with metastases not requiring immediate local treatment which were either untreated or had progressed after prior radiation therapy/surgery.

Fifty subjects were treated at 300 mg BID dose level, including 8 subjects treated in the initial dose-escalation cohort of 300 mg BID, 23 in the MTD expansion cohort, and 19 in the CNS expansion cohort. The median age of subjects enrolled in the 300 mg cohorts was 51 years (range, 30 to 72). All subjects were female, and most were white (74%). Most subjects in the 300 mg cohorts had past or current brain metastases (60%) and nearly all (98%) had distant metastases. As of the DCO date of 31-Jan-2018 for the primary analysis, most subjects had discontinued from the study, the majority of which discontinued due to PD. Six subjects in the 300 mg cohort enrolled in the long-term extension phase of the study.

For the 34 subjects in the measurable disease analysis set treated with tucatinib 300 mg BID + T-DM1, CR was observed in 1 subject (2.9%) and PR in 15 subjects (44.1%). The ORR was 47.1% (95%CI: 29.8, 64.9) with a DOR of 7.0 months (95%CI: 2.8, 19.6). In the 30 subjects with a baseline history of brain metastases treated with tucatinib 300 mg BID + T-DM1, 21 (70%) subjects had measurable disease with an ORR of 47.6% (95%CI: 25.7, 70.2) and a median DOR of 7.0 months (95%CI: 1.5, NE). In the 20 subjects with no baseline history of brain metastases treated with tucatinib 300 mg BID + T-DM1, 13 subjects (65%) had measurable disease with an ORR of 46.2% (95%CI: 19.2, 74.9) and a median DOR of 19.6 months (95%CI: 2.8, NE).

The median PFS for the 48 subjects in the efficacy analysis set who were treated with tucatinib 300 mg BID + T DM1 treatment was 8.2 months (95%CI: 4.8, 10.3). The median PFS for the 29 subjects with a baseline history of brain metastases was 6.7 months (95%CI: 4.8, 10.2), and 8.2 months (95% CI: 3.1, 21.2) for the 19 subjects without a baseline history of brain metastases.

Supporting Study: ARRAY-380-101 (Phase 1)

ARRAY-380-101 is a completed first-in-human, open-label, phase 1 dose-escalation study of tucatinib monotherapy in subjects with advanced HER2+ solid tumours. This study was designed to identify the MTD and to assess the safety, PK and preliminary efficacy of tucatinib using a PIC formulation.

A total of 50 subjects (43 subjects with MBC, 6 subjects with colorectal cancer, and 1 subject with salivary gland cancer) were enrolled onto the study. All subjects had received at least 1 prior systemic anticancer regimen, with an overall median of 5 (range, 1 to 15) prior regimens.

In the dose-escalation phase of the study, 33 subjects were enrolled and received tucatinib at doses ranging from 25 to 800 mg PO administered BID. The dose of 600 mg BID was determined to be the MTD and an additional 17 subjects with MBC were enrolled and treated at the MTD in the dose expansion phase of the study.

Of the 35 efficacy-evaluable subjects with MBC, 5 subjects (14%) achieved a PR, with a median DOR of 12.3 weeks (95%CI: 4.1, 28).

In this study, tucatinib showed single-agent activity with a favourable safety profile in heavily pretreated subjects.

2.4.8. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy assessment of the new active substance tucatinib is primarily based on the pivotal HER2CLIMB study, which is a randomised, double-blind, placebo-controlled, multicentre, phase 2 study conducted in 169 centres over a 3-year period and the study population was predominantly comparable to the European patient population. A total of 612 patients were randomised 2:1 to the tucatinib arm (n=410) and the control arm (n=202).

Major amendments to the protocol were done regarding removal of an interim analyses of PFS, a twice increase in sample size, and change of the hierarchical testing of the secondary endpoints. The timing of the primary analysis of PFS was also changed. However, the applicant has sufficiently justified this**.**

The design of the pivotal HER2CLIMB study is endorsed. Importantly, all patients were screened with MRI of the brain at baseline, allowing monitoring of a treatment effect despite metastases to the brain. The patients were randomised 2:1 between a backbone of capecitabine and trastuzumab plus tucatinib or placebo, which is endorsed, as the chosen backbone therapies are considered a recommendable treatment option in the absence of a SOC in the proposed setting.

The inclusion criteria are endorsed. Especially, it is supported that patients should have had received previous treatment with trastuzumab, pertuzumab, and T-DM1, which is standard of care both in the (neo-) adjuvant and the metastatic setting of HER2+ breast cancer. The inclusion of patients with stable brain metastases are highly endorsed as metastases to the brain is a common clinical problem resulting in high morbidity and mortality in the targeted HER2+ MBC patient population. The patients had to fulfil strict CNS in- and exclusion criteria and for example patients with ongoing use of systemic corticosteroids for control of symptoms of brain metastases at total dose of >2 mg dexamethasone (or equivalent) were excluded, and the in-and exclusion criteria regarding patients with brain metastases are reflected in the SmPC.

The exclusion criteria are also acceptable. Any previous anti-HER2 targeting TKI’s such as lapatinib and neratinib were not allowed, which is acceptable as tucatinib is in the same category of drugs and the efficacy of tucatinib is better assessed and confirmed in a TKI-naïve study population.

The pivotal study included patients from 169 study centres over a period of ~3 years and predominantly from populations that are similar to the European populations. This is an acceptable recruitment time and the study population is overall considered comparable to the European patient population. Trastuzumab was standardly dosed and administered either as iv or sc formulation, which is acceptable. Although trastuzumab is generally favoured over lapatinib, practicing oncologists confronted with such a choice considers whether the patient has brain metastases and the treatment-free interval. Lapatinib, given the low molecular weight, is more efficiently crossing the blood-brain compared to trastuzumab. In the absence of brain metastases, trastuzumab is usually re-challenged given a treatment-free period over six months or, even, a year. With this in mind, an uncertainty remains that at least in a subset of the patient population included in the HER2CLIMB trial a lapatinib-based treatment could have been considered as a better treatment option, but since this is not interfering with isolation of the treatment effect/benefit of Tukysa in the intended patient population, it is not a blocking issue preventing a positive benefit risk conclusion for the product.

The dosing of capecitabine was lower than what is normally recommended for metastatic breast cancer, but since the approved dose of capecitabine for combination with lapatinib was used, this is acceptable. The recommended dose of tucatinib is 300 mg orally twice daily, which seems acceptable from an efficacy point of view.

Baseline demographic and disease characteristics were well balanced between the treatment arms. It is noted that ~45% had brain metastases at baseline and that the patients had a median of 4 previous lines of therapy, most of these in the metastatic setting. This is reflective of or maybe even a more pre-treated study population, than what is required for the targeted patient population encompassed by the applied indication. In spite of 62.7% of the cases were diagnosed at stage III or below, only 33% had received neoadjuvant or adjuvant trastuzumab, and this is hard to understand, because it has been a standard treatment for many years. All patients were incurable at study entry and, as reflected by the applied indication and the inclusion criteria, they should all have received treatment with trastuzumab, pertuzumab and TDM1. In the setting of a clinical trial and testing a new drug substance such as tucatinib, it is acceptable that the included patients were more heavily pre-treated than the targeted patient population, as long as they have received available standard of care, which is the case here. There are no imbalances in the baseline- and disease characteristics that are considered to have had a major impact on the study results.

The primary objective is to assess PFS by blinded review (BIRC). Key secondary objectives are to assess OS and PFS in patients with brain metastases at baseline. Other secondary objectives are to assess PFS, ORR and DOR by investigator as well as the clinical benefit rate (CBR) by blinded review and investigator. Lastly, health-related quality of life, safety and tolerability of tucatinib and pharmacokinetics were evaluated. The primary endpoint of PFS by BIRC is acceptable in the pivotal study, as this was placebo-controlled and randomised in a treatment setting, where prolonged PFS is clinically meaningful and relevant as the primary efficacy endpoint. In this metastatic setting, where many patients have severe disease manifestations such as brain metastases, having OS as key secondary endpoint is clinically relevant and endorsed. PFS in patients with brain metastases at baseline is also considered an important key secondary endpoint, as it is known that the brain may often be the first site of progression in patients with the targeted HER2-positive breast cancer disease. The other secondary endpoints, such as response rate (ORR) and the durability of the responses (DOR), are also considered clinically relevant endpoints. Moreover, the clinical benefit rate (CBR), which is often used in the setting of metastatic breast cancer because it includes a clinically relevant stabilisation of the targeted disease, is also endorsed as a clinically meaningful secondary endpoint.

The blinding procedures described to keep the study masked throughout conduct are generally considered adequate. The use of an independent DMC to assess unblinded data and all endpoints determined by BICR using RECIST 1.1 is endorsed.

The strategy used to keep the overall type I error at 5% is accepted. It is noted that the testing strategy was modified several times during the course of the trial. According to the applicant, the changes were not data driven (see also below).

The use of a re-randomisation test as the primary analysis is endorsed, since this test reflects the randomisation strategy. This test can only provide a p-value and therefore the difference in PFS between the treatment arms is difficult to interpret from a clinical point of view. This drawback was mentioned in the Scientific Advice given by the CHMP (EMA/CHMP/SAWP/367605/2017). The use of a Cox model to contextualise the results is accepted given the difficulties to find an estimate with clinical interpretation using a randomisation test. The censoring rules are not agreed. While administrative censoring is not expected to introduce bias, censoring of patients with missing assessment before progression, lost to follow-up or who switched to other therapies before DP is not considered adequate. Those patients could have a different PFS risk than the patients remaining in the study. However, the applicant presented several sensitivity analyses using the Cox model, where the censoring rules were changed to assess the impact of the censoring rules. This is endorsed. There were 27.8 % (N= 88) and 33.7 % (N=54) of the patients, who were censored due to the above-mentioned reasons in the tucatinib and placebo arms, respectively (Table 14.2.1.3). It is of concern that around one third of the patients left the study before experiencing a PFS event and therefore it is reassuring that the results of the sensitivity analyses are concordant with those presented in the primary analysis.

Both PFS_{BM} and OS were analysed in a similar fashion as PFS, using a randomisation version of the log-rank test and Cox proportional hazards regression model stratified by the randomisation factors to contextualise the results. This is agreed.

Since no censoring rules were specified for PFS_{BM}, it is understood that the same rules implemented for PFS applied here. For OS, patients who did not die at the time of the analysis or are lost to follow-up, were censored at the date they were last known to be alive. As mentioned above, the censoring rules for PFS_{BM} are not agreed either. The applicant performed the same sensitivity analysis as for PFS to PFS_{BM}, which had concordant results with the primary analysis. According to the protocol, patients will be followed up for survival except in case of withdrawal of consent or study closure. The number of patients with missing survival status is low (18 and 5 patients in the Tuc+Cap+Tra and Pbo+Cap+Tra arms, respectively) and this is not expected to impact the presented results.

The statistical methods used for the analyses of the secondary endpoints are overall agreed. The applicant has provided the requested supplementary analysis for ORR using the OS ITT population (n=612): 1) using the total number of patients in the denominator; 2) including only those patients with measurable disease at baseline. It is noted that the ORR remain clinically significantly improved in the tucatinib arm. The tables of ORR by BIRC and INV are shown in the results section.

Small changes regarding descriptive statistics and secondary/exploratory endpoints were done after the finalisation of the SAP. These changes are considered minor and will not affect the primary results.

Twenty-five percent screen failures are acceptable. Most of the randomised patients were treated in the respective treatment arms and it is noted that there were an acceptable number of patient withdrawals and only 1 patient lost to follow-up.

The exclusion of randomised patients from the ITT-PFS dataset is not agreed, since it is not in line with the intention to treat principle. A supplementary analysis of PFS was conducted in the ITT-OS population and the result was similar to that presented for the primary analysis. Therefore, this issue is not further pursued. The definition of the analysis sets for OS and PFSBM is agreed.

The applicant has justified the two protocol changes that led to increasing the sample size, first from 180 to 480 and lastly to 600 patients. A retrospective analysis of the initial 442 subjects (out of the planned 480) that were already enrolled in the trial by the time version 8 of the protocol was

implemented, has been provided that overall shows consistency with the final analysis. These results provide some reassurance though other supplemental analyses (e.g. on the data before and after the implementation of this second sample size amendment) could have proven more informative, i.e. to confirm that the results were not driven by the latter group. The rationales presented are however considered sufficiently convincing and since the applicant states that data integrity was maintained throughout the process, the changes made can be considered acceptable.

Efficacy data and additional analyses

The primary endpoint of PFS by BIRC was statistically significantly improved by 2.2 months in the ITT-PFS population (n=480), i.e. from 5.6 months to 7.8 months (HR 0.544 (95%CI: 0.420; 0.705)). Data could be considered mature with 55.6% and 60.6% events on the tucatinib versus the placebo-arm, respectively. PFS by BICR conducted in the ITT-OS population was in line with the result from the primary analysis (HR=0.535 (95%CI: 0.420, 0.682), and PFS by INV also supports this. The KM curves separate early and keep being significantly separated in the observation time available. Median follow-up time for PFS is ~10 months, and the applicant will provide the final results by the end of Q2 2023, which is acceptable (see also Efficacy conclusion). The observed difference in PFS of 2.2 months is considered clinically relevant for this heavily pre-treated patient population, considering that ~45% of the patients have a poor prognosis due to brain metastases at baseline.

It is agreed that the sensitivity analyses are in line with the primary analysis of PFS by BIRC. The applicant has provided requested additional information/analyses to those available in the original submission. For the primary analysis FDA censoring rules were used. Separate sensitivity analyses considering the four categories of censoring reasons as events have been provided and the results were consistent with the primary analysis. The key secondary endpoint was OS and partly mature data show a statistically significantly improved OS in the ITT population from 17.4 months to 21.9 months with tucatinib, HR 0.662 (95%CI: 0.501; 0.875). The KM curves separate after 7 months and the difference between the curves seem to increase with time in favor of the tucatinib arm. The median OS of ~17 months for the placebo arm with 42.1% events show the dismal prognosis for this patient population and the observed OS difference of 4.5 months is considered clinically relevant in this setting. Median follow-up time for OS is ~14 months and the applicant will also provide the final results by the end of Q2 2023, which is acceptable (see also Efficacy conclusion).

Of the 198 patients with brain metastases at baseline who were treated with tucatinib, more than half have had an PFS brain event, so the PFS BM data are quite mature. These patients had a statistically significant improvement of PFS from 5.4 months to 7.6 months, which is in line with PFS benefit shown for the ITT-PFS population. The difference of 2.2 months, HR 0.483 (95%CI: 0.339; 0.689) is clinically relevant and the KM curves clearly separate after 3 months of treatment and, as observed for PFS by BIRC, the difference seem to increase with time. These data are considered fairly robust, since MRI was done at baseline, and the sample size is adequate for an assessment. The applicant has provided data from 48 patients with measurable brain metastases and the ORR was 35.4% with a median duration of response of 8.2 months, which is clinically relevant for this patient population. Hence, clinically relevant efficacy is also observed with tucatinib in patients with evidence of brain metastases at baseline.

Brain metastases frequently have a clinical impact at a much smaller size than body metastases due to their location within the skull. While target lesions per RECIST v1.1 are limited to those measuring at least 1 cm, lesions can be clinically meaningful at smaller sizes when located in critical areas of the brain. In addition, subjects frequently have multiple small lesions that represent meaningful disease burden, but individually do not meet the criteria to be deemed measurable disease, and cannot be assessed for partial response. This limits the number of subjects with brain metastases assessable for brain-specific activity in the context of a combined body and brain reading paradigm. In addition, brain lesions often

represent a relatively smaller proportion of the overall "Sum of Diameters" compared to visceral lesions which are often larger. This relative size differential may result in a clinical situation where a brain lesion has progressed and requires intervention with radiation, but the overall increase in the size of body plus brain lesions has not met the +20% threshold for radiographic progressive disease per RECIST v1.1. If radiation is given to a target lesion in this clinical setting, the subject would no longer be considered evaluable for response and would be censored from efficacy analyses, to avoid confounding the response analysis with radiation treatment. Importantly, subjects with brain metastases have a more complex history of prior radiation to the brain than those without brain metastases. Subjects can undergo several courses of brain radiotherapy during the course of their disease, which can include focal radiation treatment to different lesions at different times performed at different facilities and/or whole brain radiotherapy. Unlike body radiation which is more typically given to areas which would be considered non-target lesions (e.g. bone, chest wall), brain lesions may be target lesions, but must be either untreated or progressing after prior radiation/surgery to be evaluable as a target. This requires detailed collection and documentation of baseline data and careful selection to ensure target lesions are correctly selected and evaluated.

The CHMP considering these caveats, concluded that the ORR by BIRC is considered the most clinically relevant measure although both the ORR by BIRC and Investigator are presented; hence, the ORR by BIRC of 35.4% (95%CI: 22.2; 50.5) in 48 patients with measurable brain metastases, who had a median duration of response of 8.2 months (95%CI: 4.1; 9.7) is the numbers and results assessed and considered relevant to display in the SmPC. This ORR and DOR are considered clinically relevant in this patient population, where approximately half of the patients have brain metastases at targeted treatment setting. ORR was presented for the ITT-OS population, but only the patients who had measurable disease were included. Therefore, a supplementary analysis for ORR using the entire ITT-OS population (n=612) is provided and results are in line with the primary analysis. Taking this into account, the presented data for patients with measurable disease do show an increased response rate in the tucatinib arm from 22.8% to 40.6% of the patients, which is considered clinically relevant, while the updated ORR by BIRC in the entire population for the tucatinib arm was 34.6% (95%CI: 30.0;39.5). It is acknowledged that some patients with metastatic breast cancer have bone-only disease, which per definition is unmeasurable. Moreover, brain metastases are not always measurable by RECIST criteria, so if the brain is the only site of possible measurable disease, this can also be challenging. However, the clinical benefit rate (CBR) is designed to compensate for this by including cases of stable disease for more than 6 months, better reflecting the overall benefit in treated patients, including those with unmeasurable disease.

The CBR results show a clinically and statistically significant improvement of CBR by BIRC with tucatinib from 38.1% to 59.8% of the patients. A response or a stabilisation for ≥6 months of metastatic, incurable breast cancer in two thirds of the study population, who are heavily pre-treated, is considered a highly clinically relevant improvement. The CBR was analysed in the entire ITT-OS population. As mentioned, the clinical benefit rate (CBR) is considered a clinically relevant endpoint for patients with metastatic breast cancer, who might have unmeasurable disease e.g. due to bone-only disease or unmeasurable brain metastases. The CBR results show a clinically and statistically improvement of CBR by BIRC with tucatinib from 38.1% to 59.8% of the patients, which is similar to the CBR by INV. A response or a stabilisation for ≥6 months of metastatic, incurable breast cancer in two thirds of a study population, who are heavily pre-treated, is considered a highly clinically relevant improvement.

Although the patients in HER2CLIMB were heavily pre-treated, with a median of 4 prior treatment regimens, 73% of the patients had one or more subsequent treatment regimens and 60.6% of the patients had anti-HER2-targeted treatment regimens. Many continued trastuzumab-based treatments and almost 20% received a tyrosine kinase inhibitor, most frequently lapatinib (14.8%) or neratinib

(4.7%). Only 5.6% received an antibody-conjugate, most frequently experimental agents as they should have received TDM1 before entering the pivotal study. In the HR positive subgroup 10.1% received a new anti-hormonal treatment or CDK4/6-inhibitors, while very few (2.8%) were treated with immunotherapy (anti-PD1/PDL1). Overall, the subsequent treatments may affect the overall survival rate; however, as tucatinib shows efficacy despite metastases to the brain, which is often the site of progression for patients with HER2-positive MBC, the improvement of OS should still be sustainable.

PRO-data concerning hospitalisations and ER visits show no clinically meaningful differences between the treatment arms. Moreover, HRQoL scales measuring anxiety/depression, mobility, pain/discomfort, self-care, and usual activities were done in a subset of the ITT population (n=330) and did not show any meaningful differences, suggesting that tucatinib treatment do not have a detrimental effect on health-related quality of life. Data on the HRQoL has been removed from the SmPC, since there are no formal type I error control.

Subgroup analyses of efficacy of tucatinib regarding PFS, OS, and PFS in patients with brain metastases at baseline are consistent across all subgroups, with no clinically meaningful differences observed.

2.4.9. Conclusions on the clinical efficacy

The results from the pivotal HER2CLIMB study show clinically relevant efficacy of the addition of tucatinib to the backbone therapies of capecitabine and trastuzumab regarding PFS, OS and PFS in patients with brain metastases at baseline.

However, the CHMP considers the following measures necessary to address limitations related to efficacy: submission of final PFS and OS data in order to further investigate the efficacy of tucatinib in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2 positive locally advanced or metastatic breast cancer who have received at least 2 prior anti HER2 treatment regimens (Post-Authorisation Efficacy Study in accordance with the European Commission Delegated Regulation (EU) No 357/2015 indent a; See Annex II).

2.5. Clinical safety

Patient exposure

Overall, subjects have been exposed to tucatinib in 4 studies in subjects with cancer, including the pivotal trial HER2CLIMB (ONT-380-206) and 8 studies in subjects without cancer (see table 48).

The applicant presented an integrated analysis with the following safety analysis populations was conducted:

- HER2CLIMB safety analysis population: All randomised subjects who received at least 1 dose of study treatment (tucatinib 300 mg oral dose [PO] twice daily [BID] or placebo plus capecitabine and trastuzumab), with subjects allocated to the treatment group associated with the regimen received (N=601; 404 on the tucatinib arm and 197 on the control arm). In the tucatinib arm, 3 subjects did not receive at least one dose of capecitabine, and one subject did not receive at least one dose of trastuzumab.

The applicant has provided further updated safety data with a DCO of 29 May 2020, resulting in additional 9 months of follow-up. As of the new DCO, 118 of the 404 patients (29.2%) on the tucatinib

arm had received at least 12 months of tucatinib treatment and the median exposure to tucatinib was 7.4 months (range, <0.1 to 43.6), with 54 patients (13.4%) still receiving tucatinib treatment.

- Pooled safety analysis population 1 (Pool 1): Subjects who received tucatinib ≥300 mg PO BID tablet in combination with capecitabine and trastuzumab on Studies HER2CLIMB and ONT-380-005 (N=431)

- Pooled safety analysis population 2 (Pool 2): Subjects who received tucatinib ≥300 mg PO BID tablet in combination with capecitabine alone, trastuzumab alone, or capecitabine and trastuzumab in Studies HER2CLIMB and ONT-380-005 (N=464)

- Monotherapy analysis population: Subjects who received tucatinib ≥600 mg PO BID powder-in-capsule (PIC) on Study ARRAY-380-101 (N=31)

The tucatinib integrated safety population included all subjects who received tucatinib doses at or above the MTD/RP2D (600 mg PO BID PIC or 300 mg PO BID tablet).

Table 44: Overall number of subjects exposed to tucatinib

Study ID	Tucatinib Dose	Diagnosis	Number of Subjects Exposed	Planned Duration	Range of Exposure
Subjects with cancer					
ARRAY-380-101	25 to 800 mg PO BID	Solid tumors	50	Until progression or unacceptable toxicity	<1 to 21.8 months
ONT-380-004	300 mg or 350 mg PO BID	mBC	57	Until progression	<1 to 40.0 months
ONT-380-005	300 mg or 350 mg PO BID	mBC	60	Until progression	<1 to 32.9 months
HER2CLIMB	300 mg PO BID	mBC	404	Until progression	<0.1, 35.1 months
Subjects without cancer					
ARRAY-380-102	300 mg	Healthy	14	Total 4 doses	
ARRAY-380-103	300 mg	Healthy	12	Total 4 doses	
ONT-380-008	300 mg	Healthy	8	Single Dose	
ONT-380-009	300 mg	Healthy/hepatic impaired	37	Single Dose	
ONT-380-011	300 mg	Healthy	51	Total 9 doses	
ONT-380-012	300 mg	Healthy	28	Total 2 doses	
			28	Total 2 doses	
			28	Total 2 doses	
			17	Total 20 doses (10 days BID)	
			13	Total 28 doses (14 days BID)	
SGNTUC-015	300 mg	Healthy	36	Total 27 doses (13 days BID, 1 day QD)	
SGNTUC-020	300 mg	Healthy	18	Total 14 doses (7 days BID)	

Table 45: Summary of Exposure: Duration of Treatment
Tucatinib Integrated Safety Population

	ONT-380-206 Pbo+Cap+Tra (N=197)	ONT-380-206 Tuc+Cap+Tra (N=404)	Tuc+Cap+Tra (Pool 1) (N=431)	Tuc and (Cap and/or Tra) (Pool 2) (N=464)	ARRAY-380-101 Tuc Mono[a] (N=31)
Duration of Tucatinib or Placebo exposure (months)					
n	197	404	431	464	31
Mean (STD)	6.1 (5.0)	9.3 (8.0)	9.5 (8.2)	9.3 (8.1)	3.9 (4.2)
Median	4.4	7.4	7.4	7.0	2.7
Min, Max	<0.1, 26.9	<0.1, 43.6	<0.1, 43.6	<0.1, 43.6	<0.1, 21.8
Duration of Capecitabine exposure (months)					
n	197	401	428	439	NA
Mean (STD)	6.0 (4.9)	8.9 (7.7)	9.1 (7.9)	9.0 (7.8)	NA
Median	4.4	6.3	6.6	6.8	NA
Min, Max	0.3, 27.1	0.3, 43.8	0.3, 43.8	0.3, 43.8	NA
Duration of Trastuzumab exposure (months)					
n	197	403	430	452	NA
Mean (STD)	6.3 (5.0)	9.6 (8.0)	9.7 (8.2)	9.5 (8.2)	NA

Page 1 of 2

Duration of Trastuzumab exposure (months) (cont.)					
Median	4.6	7.6	7.6	7.2	NA
Min, Max	0.7, 27.5	0.7, 44.2	0.7, 44.2	0.7, 44.2	NA

Page 2 of 2

a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ARRAY 380-101: 26NOV2013
Source: O:\Projects\Tucatinib\meta\180daysafetyupdate_1820\v01\outputs\tlfs\pgms\t-ex-dur.sas Output: t10-01-04-ex-dur-iss-safs.rtf (10SEP20:17:22) Data: adsl, adexsum

Adverse events

Table 46: Summary of Treatment-Emergent Adverse Events (Tucatinib Integrated Safety Population)

n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Subjects with any TEAE	191 (97.0)	401 (99.3)	428 (99.3)	461 (99.4)	30 (96.8)
Subjects with Grade ⩾3 TEAE	101 (51.3)	239 (59.2)	257 (59.6)	268 (57.8)	18 (58.1)
Subjects with treatment-emergent SAE	58 (29.4)	118 (29.2)	129 (29.9)	138 (29.7)	11 (35.5)

Subjects with TEAEs leading to death	6 (3.0)	8 (2.0)	8 (1.9)	8 (1.7)	1 (3.2)
Subjects who discontinued any study treatment due to TEAE	20 (10.2)	48 (11.9)	51 (11.8)	51 (11.0)	4 (12.9)
Subjects who discontinued tucatinib/placebo due to TEAE	7 (3.6)	23 (5.7)	25 (5.8)	25 (5.4)	4 (12.9)
Subjects who discontinued capecitabine due to TEAE	19 (9.6)	44 (10.9)	47 (10.9)	47 (10.1)	NA
Subjects who discontinued trastuzumab due to TEAE	6 (3.0)	17 (4.2)	19 (4.4)	19 (4.1)	NA

Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from Studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from Studies HER2CLIMB and ONT-380-005.
Data cutoff: ONT-380-206, 29MAY2020; ONT-380-005, 06MAR2018; ARRAY 380-101, 26NOV2013
Includes subjects from ARRAY-380-101 Study who received PIC (powder-in-capsule) ⩾600 mg PO BID.
Source: Table 10.2.1

Table 47: Treatment-emergent adverse events occurring in ≥10% of subjects in Pool 1 (Tucatinib Integrated Safety Population)

n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Subjects with any event	191 (97.0)	401 (99.3)	428 (99.3)	461 (99.4)	30 (96.8)
Diarrhoea	106 (53.8)	331 (81.9)	351 (81.4)	369 (79.5)	19 (61.3)
Palmar-plantar erythrodysesthesia syndrome	105 (53.3)	262 (64.9)	280 (65.0)	289 (62.3)	0
Nausea	88 (44.7)	241 (59.7)	262 (60.8)	275 (59.3)	17 (54.8)
Fatigue	87 (44.2)	192 (47.5)	204 (47.3)	218 (47.0)	14 (45.2)
Vomiting	51 (25.9)	149 (36.9)	163 (37.8)	172 (37.1)	12 (38.7)
Decreased appetite	41 (20.8)	104 (25.7)	113 (26.2)	116 (25.0)	4 (12.9)
Stomatitis	28 (14.2)	105 (26.0)	108 (25.1)	111 (23.9)	3 (9.7)
Headache	40 (20.3)	94 (23.3)	100 (23.2)	107 (23.1)	4 (12.9)
Aspartate aminotransferase increased	22 (11.2)	89 (22.0)	96 (22.3)	100 (21.6)	5 (16.1)
Alanine aminotransferase increased	13 (6.6)	85 (21.0)	91 (21.1)	95 (20.5)	5 (16.1)
Anaemia	24 (12.2)	86 (21.3)	91 (21.1)	92 (19.8)	2 (6.5)
Blood bilirubin increased	21 (10.7)	80 (19.8)	81 (18.8)	81 (17.5)	0
Hypokalemia	25 (12.7)	67 (16.6)	73 (16.9)	76 (16.4)	2 (6.5)
Constipation	42 (21.3)	66 (16.3)	70 (16.2)	79 (17.0)	5 (16.1)
Abdominal pain	32 (16.2)	66 (16.3)	69 (16.0)	72 (15.5)	2 (6.5)
Arthralgia	12 (6.1)	64 (15.8)	69 (16.0)	74 (15.9)	3 (9.7)
Weight decreased	12 (6.1)	62 (15.3)	68 (15.8)	69 (14.9)	1 (3.2)
Cough	24 (12.2)	62 (15.3)	65 (15.1)	69 (14.9)	6 (19.4)

n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Blood creatinine increased	3 (1.5)	62 (15.3)	63 (14.6)	63 (13.6)	2 (6.5)
Back pain	25 (12.7)	53 (13.1)	57 (13.2)	57 (12.3)	6 (19.4)
Dyspnoea	25 (12.7)	52 (12.9)	57 (13.2)	59 (12.7)	5 (16.1)
Dizziness	27 (13.7)	51 (12.6)	54 (12.5)	63 (13.6)	2 (6.5)
Epistaxis	10 (5.1)	50 (12.4)	52 (12.1)	54 (11.6)	3 (9.7)
Peripheral sensory neuropathy	12 (6.1)	51 (12.6)	51 (11.8)	51 (11.0)	0
Urinary tract infection	16 (8.1)	44 (10.9)	51 (11.8)	54 (11.6)	7 (22.6)
Dyspepsia	19 (9.6)	44 (10.9)	49 (11.4)	52 (11.2)	1 (3.2)
Pain in extremity	17 (8.6)	47 (11.6)	49 (11.4)	52 (11.2)	9 (29.0)
Upper respiratory tract infection	16 (8.1)	42 (10.4)	48 (11.1)	52 (11.2)	4 (12.9)
Oedema peripheral	20 (10.2)	43 (10.6)	46 (10.7)	51 (11.0)	3 (9.7)
Dry skin	18 (9.1)	41 (10.1)	45 (10.4)	47 (10.1)	2 (6.5)
Muscle spasms	6 (3.0)	43 (10.6)	43 (10.0)	48 (10.3)	3 (9.7)

Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from Studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from Studies HER2CLIMB and ONT-380-005.
Data cutoff: ONT-380-206, 29MAY2020; ONT-380-005, 06MAR2018; ARRAY 380-101, 26NOV2013
Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) ⩾600 mg PO BID.
Source: Table 10.2.4

Table 48: Treatment-emergent Grade 3 or higher adverse events occurring in ≥2% of subjects in Pool 1 (Tucatinib Integrated Safety Population)

n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Subjects with any event	101 (51.3)	239 (59.2)	257 (59.6)	268 (57.8)	18 (58.1)
Palmar-plantar erythrodysesthesia syndrome	18 (9.1)	56 (13.9)	59 (13.7)	60 (12.9)	0
Diarrhoea	17 (8.6)	53 (13.1)	56 (13.0)	57 (12.3)	1 (3.2)
Fatigue	8 (4.1)	22 (5.4)	26 (6.0)	27 (5.8)	0
Alanine aminotransferase increased	1 (0.5)	23 (5.7)	25 (5.8)	26 (5.6)	2 (6.5)
Aspartate aminotransferase increased	1 (0.5)	19 (4.7)	21 (4.9)	22 (4.7)	2 (6.5)
Anaemia	5 (2.5)	16 (4.0)	18 (4.2)	18 (3.9)	2 (6.5)
Hypokalemia	10 (5.1)	15 (3.7)	16 (3.7)	16 (3.4)	2 (6.5)
Nausea	7 (3.6)	16 (4.0)	16 (3.7)	17 (3.7)	1 (3.2)
Hypophosphatemia	4 (2.0)	13 (3.2)	14 (3.2)	15 (3.2)	0
Pulmonary embolism	4 (2.0)	13 (3.2)	13 (3.0)	13 (2.8)	0
Vomiting	8 (4.1)	13 (3.2)	13 (3.0)	15 (3.2)	0

Neutropenia	9 (4.6)	11 (2.7)	11 (2.6)	12 (2.6)	0
Pneumonia	1 (0.5)	9 (2.2)	10 (2.3)	11 (2.4)	0
Stomatitis	1 (0.5)	10 (2.5)	10 (2.3)	10 (2.2)	0

Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from Studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from Studies HER2CLIMB and ONT-380-005.
Data cutoff: ONT-380-206, 29MAY2020; ONT-380-005, 06MAR2018; ARRAY 380-101, 26NOV2013
Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) ⩾600 mg PO BID.
Source: Table 10.2.

A detailed assessment of the adverse events of special interest with tucatinib are shown below.

Adverse events of special interest

Diarrhoea

Table 49: Summary of Treatment-Emergent Adverse Events of Vomiting, Nausea, and Diarrhea Tucatinib Integrated Safety Population

	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subject with any TEAE of Diarrhoea, n (%)	106 (53.8)	331 (81.9)	351 (81.4)	369 (79.5)	19 (61.3)
Number of Diarrhoea events	189	789	821	850	23
Number of Diarrhoea events resolved, n (%)	159 (84.1)	638 (80.9)	657 (80.0)	676 (79.5)	19 (82.6)

Page 5 of 6

Time to resolution (days)					
n	159	638	657	676	19
Mean (STD)	19.5 (33.2)	38.1 (68.6)	39.0 (71.1)	38.2 (70.4)	32.2 (62.9)
Median	6.0	8.0	8.0	8.0	4.0
Min, Max	1, 284	1, 548	1, 548	1, 548	1, 229
Number of Diarrhoea events recovering/resolving, n (%)	3 (1.6)	21 (2.7)	21 (2.6)	22 (2.6)	0
Time to onset of first TEAE of Diarrhoea (days)					
n	106	331	351	369	19
Mean (STD)	44.7 (50.6)	26.7 (47.9)	26.2 (46.9)	25.8 (46.6)	42.8 (42.9)
Median	22.0	12.0	12.0	12.0	29.0
Min, Max	1, 265	1, 420	1, 420	1, 420	1, 171

Page 6 of 6

Events of gastrointestinal toxicity are searched from vomiting (PT), nausea (PT) and Diarrhea (PT).
Resolution is defined as event outcome of recovered/resolved, or recovered/resolved with sequelae.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 03/06/2018, ARRAY 380-101: 11/26/2013

Table 50: Summary of Treatment-Emergent Adverse Events of Grade 3 or Higher Vomiting, Nausea, and Diarrhea Tucatinib Integrated Safety Population

	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subject with any TEAE of Diarrhoea, n (%)	17 (8.6)	53 (13.1)	56 (13.0)	57 (12.3)	1 (3.2)
Number of Diarrhoea events	23	62	65	66	1
Number of Diarrhoea events resolved, n (%)	20 (87.0)	51 (82.3)	53 (81.5)	54 (81.8)	1 (100)
Page 5 of 6					
Time to resolution (days)					
n	20	51	53	54	1
Mean (STD)	15.9 (17.6)	34.7 (63.0)	33.8 (62.0)	33.9 (61.4)	1.0 (-)
Median	6.5	9.0	9.0	9.5	1.0
Min, Max	1, 66	1, 287	1, 287	1, 287	1, 1
Number of Diarrhoea events recovering/resolving, n (%)	0	0	0	0	0
Time to onset of first TEAE of Diarrhoea (days)					
n	17	53	56	57	1
Mean (STD)	49.1 (37.7)	78.3 (102.8)	76.2 (100.4)	75.1 (99.8)	56.0 (-)
Median	34.0	36.0	36.5	36.0	56.0
Min, Max	10, 124	4, 487	4, 487	4, 487	56, 56
Page 6 of 6					

Events of gastrointestinal toxicity are searched from vomiting (PT), nausea (PT) and Diarrhea (PT).
Resolution is defined as event outcome of recovered/resolved, or recovered/resolved with sequelae.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 03/06/2018, ARRAY 380-101: 11/26/2013

Even though prophylactic use of antidiarrhoeals was not required per protocol, antidiarrhoeal medication was often used in HER2CLIMB as 77.3% vs 58.5% in the tucatinib vs the placebo arm took this medication in the same cycle while reporting diarrhoea and the median duration of use was 3 days per cycle in both arms.

Table 51: Summary of antidiarrhoeal medications (subjects with diarrhoea who took antidiarrhoeals in HER2CLIMB)

	Tuc+Cap+Tra (N=404)	Pbo+Cap+Tra (N=197)
Subjects who ever report diarrhea during the entire study, n (%)	331 (81.9)	106 (53.8)
Subjects who ever took antidiarrheal during the entire study [a], n (%)	256 (77.3)	62 (58.5)
Total number of cycles where diarrhea reported, n	3402	503
Total number of cycles subject took antidiarrheal [b], n (%)	1639 (48.2)	197 (39.2)
Total number of cycles subject did not take antidiarrheal [b], n (%)	1756 (51.6)	306 (60.8)
Unknown [b], n (%)	7 (0.2)	0
Duration of treatment per cycle (days)		
Unknown	40	14
n	216	48
Mean (STD)	5.0 (4.7)	4.1 (3.6)
Median	3.0	3.0
Q1, Q3	2.0, 6.5	1.7, 5.8
Min, Max	1.0, 21.0	1.0, 21.1

Page 1 of 5

Diarrhea is searched from preferred term of diarrhea, including new or continuing diarrhea event.
Duration of treatment per cycle is calculated as mean of duration of antidiarrheal medication for cycles where subjects reported diarrhea event and antidiarrheal medication.
a Subjects who took antidiarrheal medication and reported diarrhea in the same cycle during study.
b The denominator is the total number of cycles where diarrhea was reported.
Dictionary: MedDRA v23.0
Data Snapshot: 10SEP2020, Data Cutoff Date: 29MAY2020
Source: O:\Projects\Tucatinib\meta\180daysafetyupdate_1820\v01\outputs\tlfs\pgms\t-ae-summ-diarr-cm.sas Output: t14-03-02-03-06-ae-summ-diarr-cm-safs.rtf (10SEP20:17:18) Data: adsl, adae, adex, adcm

The denominator is the total number of subjects who ever took antidiarrhoeal and reported diarrhoea event in the same cycle during the entire study. Dictionary: WHODrug Global September 2018 B2. Data Cutoff Date: 04SEP2019

Nausea and vomiting

Table 52: Summary of Treatment-Emergent Adverse Events of Vomiting, Nausea, and Diarrhea Tucatinib Integrated Safety Population

	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subject with any TEAE of Vomiting, n (%)	51 (25.9)	149 (36.9)	163 (37.8)	172 (37.1)	12 (38.7)
Number of Vomiting events	85	274	295	305	13
Number of Vomiting events resolved, n (%)	79 (92.9)	251 (91.6)	271 (91.9)	279 (91.5)	10 (76.9)

Time to resolution (days)					
n	79	251	271	279	10
Mean (STD)	11.1 (19.5)	15.8 (38.2)	15.3 (37.1)	15.0 (36.6)	5.8 (8.3)
Median	2.0	2.0	2.0	2.0	2.0
Min, Max	1, 101	1, 270	1, 270	1, 270	1, 26
Number of Vomiting events recovering/resolving, n (%)	0	3 (1.1)	3 (1.0)	3 (1.0)	0
Time to onset of first TEAE of Vomiting (days)					
n	51	149	163	172	12
Mean (STD)	60.9 (85.8)	62.2 (130.3)	66.8 (137.0)	66.4 (134.2)	39.0 (39.6)
Median	33.0	21.0	19.0	20.0	27.5
Min, Max	1, 333	1, 1025	1, 1025	1, 1025	1, 121

Subject with any TEAE of Nausea, n (%)	88 (44.7)	241 (59.7)	262 (60.8)	275 (59.3)	17 (54.8)
Number of Nausea events	123	369	395	412	21
Number of Nausea events resolved, n (%)	94 (76.4)	265 (71.8)	281 (71.1)	290 (70.4)	15 (71.4)

Time to resolution (days)					
n	94	265	281	290	15
Mean (STD)	36.6 (53.6)	47.2 (73.3)	51.5 (95.1)	51.0 (93.7)	20.9 (34.4)
Median	11.0	16.0	17.0	18.0	4.0
Min, Max	1, 372	1, 417	1, 961	1, 961	1, 107
Number of Nausea events recovering/resolving, n (%)	3 (2.4)	12 (3.3)	13 (3.3)	14 (3.4)	0
Time to onset of first TEAE of Nausea (days)					
n	88	241	262	275	17
Mean (STD)	39.9 (75.4)	37.1 (84.5)	40.0 (95.1)	41.0 (95.0)	15.7 (15.0)
Median	12.5	9.0	9.0	9.0	13.0
Min, Max	1, 499	1, 599	1, 693	1, 693	1, 63

Events of gastrointestinal toxicity are searched from vomiting (PT), nausea (PT) and Diarrhea (PT).
Resolution is defined as event outcome of recovered/resolved, or recovered/resolved with sequelae.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 03/06/2018, ARRAY 380-101: 11/26/2013

Table 53: Summary of Treatment-Emergent Adverse Events of Grade 3 or Higher Vomiting, Nausea, and Diarrhea Tucatinib Integrated Safety Population

	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subject with any TEAE of Vomiting, n (%)	8 (4.1)	13 (3.2)	13 (3.0)	15 (3.2)	0
Number of Vomiting events	8	17	17	19	0
Number of Vomiting events resolved, n (%)	8 (100)	15 (88.2)	15 (88.2)	17 (89.5)	0

Time to resolution (days)					
n	8	15	15	17	0
Mean (STD)	6.8 (7.1)	4.3 (2.8)	4.3 (2.8)	5.0 (4.5)	- (-)
Median	5.0	3.0	3.0	3.0	-
Min, Max	1, 24	1, 11	1, 11	1, 19	-, -
Number of Vomiting events recovering/resolving, n (%)	0	0	0	0	0
Time to onset of first TEAE of Vomiting (days)					
n	8	13	13	15	0
Mean (STD)	83.6 (179.6)	56.5 (49.5)	56.5 (49.5)	60.8 (48.0)	- (-)
Median	20.0	56.0	56.0	57.0	-
Min, Max	3, 527	3, 191	3, 191	3, 191	-, -

Subject with any TEAE of Nausea, n (%)	7 (3.6)	16 (4.0)	16 (3.7)	17 (3.7)	1 (3.2)
Number of Nausea events	7	19	19	20	1
Number of Nausea events resolved, n (%)	6 (85.7)	15 (78.9)	15 (78.9)	16 (80.0)	1 (100)

Time to resolution (days)					
n	6	15	15	16	1
Mean (STD)	10.3 (8.3)	9.5 (12.6)	9.5 (12.6)	10.1 (12.4)	5.0 (-)
Median	7.5	4.0	4.0	5.0	5.0
Min, Max	3, 24	2, 45	2, 45	2, 45	5, 5
Number of Nausea events recovering/resolving, n (%)	0	0	0	0	0
Time to onset of first TEAE of Nausea (days)					
n	7	16	16	17	1
Mean (STD)	101.3 (191.3)	65.0 (79.8)	65.0 (79.8)	65.1 (77.3)	106.0 (-)
Median	18.0	39.5	39.5	43.0	106.0
Min, Max	2, 527	5, 311	5, 311	5, 311	106, 106

Events of gastrointestinal toxicity are searched from vomiting (PT), nausea (PT) and Diarrhea (PT).
Resolution is defined as event outcome of recovered/resolved, or recovered/resolved with sequelae.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 03/06/2018, ARRAY 380-101: 11/26/2013

Stomatitis

Table 54: 'eatment-Emergent Adverse Events of Stomatitis by Preferred Term Tucatinib Integrated Safety Population

Preferred Term	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subjects with any event	43 (21.8)	139 (34.4)	145 (33.6)	151 (32.5)	5 (16.1)
Stomatitis	28 (14.2)	105 (26.0)	108 (25.1)	111 (23.9)	3 (9.7)
Oropharyngeal pain	9 (4.6)	30 (7.4)	33 (7.7)	35 (7.5)	1 (3.2)
Mouth ulceration	4 (2.0)	11 (2.7)	11 (2.6)	11 (2.4)	1 (3.2)
Oral pain	3 (1.5)	6 (1.5)	7 (1.6)	7 (1.5)	0
Lip ulceration	0	5 (1.2)	5 (1.2)	6 (1.3)	0
Glossodynia	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
Lip blister	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.4)	0
Tongue blistering	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Aphthous ulcer	1 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	1 (3.2)
Oral dysaesthesia	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Tongue ulceration	0	1 (0.2)	1 (0.2)	1 (0.2)	0

Page 1 of 1

Events of stomatitis are searched from special stomatitis search terms.
Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Dictionary: MedDRA v23.0 Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 03/06/2018, ARRAY 380-101: 11/26/2013

Table 55: Treatment-Emergent Grade 3 or Higher Adverse Events of Stomatitis by Preferred Term Tucatinib Integrated Safety Population

Preferred Term	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subjects with any event	1 (0.5)	10 (2.5)	10 (2.3)	10 (2.2)	0
Stomatitis	1 (0.5)	10 (2.5)	10 (2.3)	10 (2.2)	0
Oral pain	0	1 (0.2)	1 (0.2)	1 (0.2)	0

Page 1 of 1

Events of stomatitis are searched from special stomatitis search terms.
Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Dictionary: MedDRA v23.0 Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 03/06/2018, ARRAY 380-101: 11/26/2013

Hepatotoxicity

Table 56: Treatment-Emergent Adverse Events of Hepatotoxicity by Preferred Term Tucatinib Integrated Safety Population

Preferred Term	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subjects with any event	51 (25.9)	179 (44.3)	190 (44.1)	196 (42.2)	5 (16.1)
Aspartate aminotransferase increased	22 (11.2)	89 (22.0)	96 (22.3)	100 (21.6)	5 (16.1)
Alanine aminotransferase increased	13 (6.6)	85 (21.0)	91 (21.1)	95 (20.5)	5 (16.1)
Blood bilirubin increased	21 (10.7)	80 (19.8)	81 (18.8)	81 (17.5)	0
Hyperbilirubinaemia	8 (4.1)	28 (6.9)	30 (7.0)	32 (6.9)	0
Ascites	1 (0.5)	4 (1.0)	5 (1.2)	5 (1.1)	0
Gamma-glutamyltransferase increased	6 (3.0)	5 (1.2)	5 (1.2)	5 (1.1)	0
Hepatocellular injury	1 (0.5)	5 (1.2)	5 (1.2)	5 (1.1)	0
Transaminases increased	1 (0.5)	5 (1.2)	5 (1.2)	5 (1.1)	0
Hepatotoxicity	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0

International normalised ratio increased	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Ocular icterus	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Bilirubin conjugated increased	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Hepatic fibrosis	0	0	1 (0.2)	1 (0.2)	0
Jaundice	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Liver injury	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Portal hypertension	0	0	1 (0.2)	1 (0.2)	0
Varices oesophageal	0	0	1 (0.2)	1 (0.2)	0
Hepatic pain	1 (0.5)	0	0	0	0
Hepatic steatosis	1 (0.5)	0	0	0	0

Liver function test increased	1 (0.5)	0	0	0	0
Oesophageal varices haemorrhage	2 (1.0)	0	0	0	0

Events of hepatotoxity are searched from Drug related hepatic disorders - comprehensive search SMQ (narrow), which includes Cholestasis and jaundice of hepatic origin SMQ, Liver related investigations, signs and symptoms SMQ, Liver related coagulation and bleeding disturbances SMQ and Drug related hepatic disorders - severe events only SMQ.
Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Dictionary: MedDRA v23.0 Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ARRAY 380-101: 26NOV2013
Source: O:\Projects\Tucatinib\meta\180daysafetyupdate_1820\v01\outputs\tlfs\pgms\t-ae-pt.sas Output: t10-03-01-aept-hept-iss-safs.rtf (10SEP20:17:07) Data: adsl, adae

Table 57: Treatment-Emergent Grade 3 or Higher Adverse Events of Hepatotoxicity by Preferred Term Tucatinib Integrated Safety Population

Preferred Term	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subjects with any event	10 (5.1)	42 (10.4)	46 (10.7)	47 (10.1)	3 (9.7)
Alanine aminotransferase increased	1 (0.5)	23 (5.7)	25 (5.8)	26 (5.6)	2 (6.5)
Aspartate aminotransferase increased	1 (0.5)	19 (4.7)	21 (4.9)	22 (4.7)	2 (6.5)
Hyperbilirubinaemia	1 (0.5)	3 (0.7)	5 (1.2)	5 (1.1)	0
Blood bilirubin increased	5 (2.5)	4 (1.0)	4 (0.9)	4 (0.9)	0
Hepatotoxicity	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
Transaminases increased	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Ascites	1 (0.5)	0	1 (0.2)	1 (0.2)	0
Hepatocellular injury	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Gamma-glutamyltransferase increased	1 (0.5)	0	0	0	0

Oesophageal varices haemorrhage	2 (1.0)	0	0	0	0

Events of hepatotoxity are searched from Drug related hepatic disorders - comprehensive search SMQ (narrow), which includes Cholestasis and jaundice of hepatic origin SMQ, Liver related investigations, signs and symptoms SMQ, Liver related coagulation and bleeding disturbances SMQ and Drug related hepatic disorders - severe events only SMQ.
Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Dictionary: MedDRA v23.0 Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ARRAY 380-101: 26NOV2013
Source: O:\Projects\Tucatinib\meta\180daysafetyupdate_1820\v01\outputs\tlfs\pgms\t-ae-pt.sas Output:

Palmar-plantar erythrodysaesthesia

Table 58: Summary of Treatment-Emergent Adverse Events of Palmar-plantar Erythrodysaesthesia Syndrome Tucatinib Integrated Safety Population

	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subject with any TEAE of Palmar-plantar Erythrodysaesthesia Syndrome, n (%)	105 (53.3)	262 (64.9)	280 (65.0)	289 (62.3)	0
Number of Palmar-plantar Erythrodysaesthesia Syndrome events	156	412	435	445	0
Number of Palmar-plantar Erythrodysaesthesia Syndrome events resolved, n (%)	96 (61.5)	243 (59.0)	254 (58.4)	259 (58.2)	0
Time to resolution (days)					
n	95	241	252	257	0
Mean (STD)	83.0 (75.2)	95.3 (101.3)	95.5 (101.5)	94.4 (100.8)	- (-)
Median	63.0	61.0	59.5	57.0	-
Min, Max	1, 356	1, 608	1, 608	1, 608	-, -
Number of Palmar-plantar Erythrodysaesthesia Syndrome events recovering/resolving, n (%)	5 (3.2)	25 (6.1)	25 (5.7)	25 (5.6)	0
Time to onset of first TEAE of Palmar-plantar Erythrodysaesthesia Syndrome (days)					
n	105	262	280	289	0
Mean (STD)	46.8 (40.7)	56.3 (72.8)	54.9 (70.9)	54.3 (70.2)	- (-)
Median	35.0	34.5	33.5	33.0	-
Min, Max	1, 194	1, 648	1, 648	1, 648	-, -

Page 1 of 2

Page 2 of 2

Events of Palmar-plantar Erythrodysaesthesia Syndrome are searched from the preferred term (PT).
Resolution is defined as event outcome of recovered/resolved, or recovered/resolved with sequelae.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 03/06/2018, ARRAY 380-101: 11/26/2013

Table 59: Summary of Treatment-Emergent Adverse Events of Grade 3 or Higher Palmar-plantar Erythrodysaesthesia Syndrome Tucatinib Integrated Safety Population

	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subject with any TEAE of Palmar-plantar Erythrodysaesthesia Syndrome, n (%)	18 (9.1)	56 (13.9)	59 (13.7)	60 (12.9)	0
Number of Palmar-plantar Erythrodysaesthesia Syndrome events	18	64	67	68	0
Number of Palmar-plantar Erythrodysaesthesia Syndrome events resolved, n (%)	13 (72.2)	40 (62.5)	41 (61.2)	41 (60.3)	0

Page 1 of 2

Time to resolution (days)					
n	13	39	40	40	0
Mean (STD)	61.2 (23.6)	78.4 (102.0)	79.8 (101.0)	79.8 (101.0)	- (-)
Median	54.0	43.0	43.0	43.0	-
Min, Max	30, 102	4, 439	4, 439	4, 439	-, -
Number of Palmar-plantar Erythrodysaesthesia Syndrome events recovering/resolving, n (%)	0	5 (7.8)	5 (7.5)	5 (7.4)	0
Time to onset of first TEAE of Palmar-plantar Erythrodysaesthesia Syndrome (days)					
n	18	56	59	60	0
Mean (STD)	88.9 (53.8)	127.1 (128.6)	130.5 (129.6)	128.9 (129.1)	- (-)
Median	71.0	74.5	75.0	74.5	-
Min, Max	32, 192	7, 623	7, 623	7, 623	-, -

Page 2 of 2

Events of Palmar-plantar Erythrodysaesthesia Syndrome are searched from the preferred term (PT).
Resolution is defined as event outcome of recovered/resolved, or recovered/resolved with sequelae.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 03/06/2018, ARRAY 380-101: 11/26/2013

Rash

The overall incidence of rash was higher on the tucatinib arm (21.8% vs. 14.7%), but ≥ grade 3 events were rare (<1%).

The majority of events were resolved and the median time to onset was 42 vs 27 days on the tucatinib arm compared to the control arm, while the median time to resolution was 24 vs 12 days. Rash rarely resulted in tucatinib discontinuation.

The incidence of rash was higher in the tucatinib monotherapy study compared to the tucatinib arm of HER2CLIMB (29.0% vs. 21.8%).

Cardiac Toxicity

The incidence of QT prolongation was similar in the tucatinib and placebo control treatment arms of the HER2CLIMB study (4.7% vs 4.6%) and the incidence of grade ≥3 events was also similar (1.7 vs 1.0%). This is consistent with pool 1 and QT prolongation occurred in <5% across all safety populations. Dose modifications and discontinuations due to this event were rare; however, 1 patient in the tucatinib arm discontinued treatment due to cardiac arrest.

Table 60: Summary of Cardiac Ejection Fraction
Tucatinib Integrated Safety Population

	ONT-380-206 Pbo+Cap+Tra (N=197)	ONT-380-206 Tuc+Cap+Tra (N=404)	Tuc+Cap+Tra (Pool 1) (N=431)	Tuc and (Cap and/or Tra) (Pool 2) (N=464)	ARRAY-380-101 Tuc Mono[a] (N=31)
Baseline value, n (%)					
>=50%	197 (100)	404 (100)	431 (100)	464 (100)	31 (100)
<50%	0	0	0	0	0
Worst post-baseline, n (%)					
<20%	0	0	0	0	0
20-39%	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
40-49%	7 (3.6)	8 (2.0)	8 (1.9)	8 (1.7)	2 (6.5)
>=50%	159 (80.7)	339 (83.9)	362 (84.0)	383 (82.5)	14 (45.2)
No post-baseline	30 (15.2)	54 (13.4)	58 (13.5)	70 (15.1)	15 (48.4)

Page 1 of 3

Change from baseline, n (%)					
n[b]	167	350	373	394	16
No decrease or <10% decrease from baseline	138 (82.6)	289 (82.6)	308 (82.6)	326 (82.7)	15 (93.8)
Decrease 10-<16% from baseline	24 (14.4)	49 (14.0)	52 (13.9)	55 (14.0)	1 (6.3)
Decrease 16-<20% from baseline	4 (2.4)	8 (2.3)	8 (2.1)	8 (2.0)	0
Decrease >=20% from baseline	1 (0.6)	4 (1.1)	5 (1.3)	5 (1.3)	0
Worst post-baseline <50% and decrease >=10% from baseline	8 (4.1)	9 (2.2)	9 (2.1)	9 (1.9)	1 (3.2)

Page 2 of 3

Time to the worst post-baseline value (months)[c]					
n	29	61	65	68	1
Mean (STD)	4.6 (3.3)	7.8 (4.6)	7.8 (4.7)	7.9 (5.4)	5.8 (-)
Median	2.7	5.7	5.7	5.7	5.8
Min, Max	0.1, 13.1	2.1, 19.1	2.1, 19.1	2.0, 30.6	5.8, 5.8
Maximum post baseline grade, n (%)					
Normal	138 (70.1)	287 (71.0)	306 (71.0)	324 (69.8)	14 (45.2)
Grade 2	28 (14.2)	57 (14.1)	60 (13.9)	63 (13.6)	2 (6.5)
Grade 3	1 (0.5)	6 (1.5)	7 (1.6)	7 (1.5)	0
Grade 4	0	0	0	0	0
Not available	30 (15.2)	54 (13.4)	58 (13.5)	70 (15.1)	15 (48.4)

Page 3 of 3

Any modality (ECHO or MUGA) was counted in the summaries regardless of the baseline modality.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
b Number of subjects with baseline and at least one post-baseline value. Percentages in the following rows are based on this number.
c Includes subjects with >=10% cardiac ejection fraction decrease from baseline.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005;
Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ARRAY 380-101: 26NOV2013

The incidence of decreased LVEF was also similar between the treatment arms of HER2CLIMB (Table 10.3.10 in ISS with data cut off 29May 2020) and most patients (~82.5%) had no clinically meaningful change from baseline (Table 10.3.13 in ISS with data cut off 29May 2020). A maximum decrease of 20% or more from baseline was rarely observed (1.1% vs 0.6%). Among patients with a worst post-baseline ejection fraction below 50%, the decrease was 10% or more in 2.2% of patients on the tucatinib arm and 4.1% of patients on the control arm. In patients with a 10% or higher decrease in ejection fraction from baseline, the median time to their worst post-baseline value was 5.7 vs 2.7 months on the tucatinib vs the control-arm.

Cerebral oedema

Overall, 4 cases of cerebral oedema were observed in the HER2CLIMB study

Updated safety data informed of one case of grade 2 cerebral oedema in the tucatinib arm. The grade 2 event was observed 52-year-old woman for 9 days and according to the listing above, no change of dose for any of the study drugs were deemed necessary and resolved/recovered.

Table 61: Cerebral oedema cases (May 29, 2020 data cut-off)

	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Number of Cerebral Edema events recovering/resolving, n (%)	1 (33.3)	0	0	1 (25.0)	0
Time to onset of first TEAE of Cerebral Edema (days)					
n	3	1	2	3	0
Mean (STD)	343.0 (232.0)	102.0 (-)	54.5 (67.2)	96.3 (86.6)	- (-)
Median	341.0	102.0	54.5	102.0	-
Min, Max	112, 576	102, 102	7, 102	7, 180	-, -

	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subject with any TEAE of Cerebral Edema, n (%)	3 (1.5)	1 (0.2)	2 (0.5)	3 (0.6)	0
Number of Cerebral Edema events	3	1	2	4	0
Number of Cerebral Edema events resolved, n (%)	2 (66.7)	1 (100)	2 (100)	3 (75.0)	0
Time to resolution (days)					
n	2	1	2	3	0
Mean (STD)	9.5 (0.7)	9.0 (-)	22.5 (19.1)	16.3 (17.2)	- (-)
Median	9.5	9.0	22.5	9.0	-
Min, Max	9, 10	9, 9	9, 36	4, 36	-, -

Creatinine increase

Increases in serum creatinine, mostly grade 1, were observed in 13.9% of subjects on the tucatinib arm of HER2CLIMB. There were no grade ≥3 events, and acute kidney injury and renal failure TEAEs were infrequent with similar incidence between treatment arms. A mean increase in creatinine levels of approximately 30% was observed within the first cycle of tucatinib treatment; levels remained elevated but stable and returned to baseline upon treatment discontinuation. Most post-baseline values were within the upper limit of normal. BUN values remained stable throughout tucatinib treatment.

Treatment-related AEs

Table 62: Summary of Treatment-Emergent Treatment-Related Adverse Events Tucatinib Integrated Safety Population

	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subjects with any treatment-related TEAE	180 (91.4)	393 (97.3)	420 (97.4)	450 (97.0)	23 (74.2)
Tucatinib/placebo-related TEAE	144 (73.1)	345 (85.4)	365 (84.7)	392 (84.5)	23 (74.2)
Subjects with treatment-related ≥Grade 3 TEAE	60 (30.5)	184 (45.5)	196 (45.5)	200 (43.1)	7 (22.6)
≥Grade 3 Tucatinib/placebo-related TEAE	32 (16.2)	117 (29.0)	122 (28.3)	124 (26.7)	7 (22.6)
Subjects with any treatment-related TE SAE	14 (7.1)	47 (11.6)	50 (11.6)	52 (11.2)	0
Tucatinib/placebo-related TE SAE	12 (6.1)	30 (7.4)	31 (7.2)	33 (7.1)	0

Subjects with treatment-related TEAEs leading to death	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
Tucatinib/placebo-related TEAEs leading to death	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.4)	0
Subjects who discontinued tucatinib/placebo due to treatment-related TEAE	5 (2.5)	17 (4.2)	19 (4.4)	19 (4.1)	0
Due to tucatinib/placebo-related TEAE	5 (2.5)	14 (3.5)	15 (3.5)	15 (3.2)	0

Treatment-related TEAE is defined as TEAEs related to any of the study treatment (tucatinib or placebo, capecitabine, trastuzumab).
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ARRAY 380-101: 26NOV2013

Table 63: Tucatinib/Placebo-Related Treatment-Emergent Adverse Events by Preferred Term Tucatinib Integrated Safety Population

Preferred Term	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subjects with any event	144 (73.1)	345 (85.4)	365 (84.7)	392 (84.5)	23 (74.2)
Diarrhoea	59 (29.9)	224 (55.4)	233 (54.1)	246 (53.0)	8 (25.8)
Nausea	42 (21.3)	164 (40.6)	172 (39.9)	181 (39.0)	10 (32.3)
Fatigue	52 (26.4)	122 (30.2)	127 (29.5)	136 (29.3)	5 (16.1)
Vomiting	22 (11.2)	87 (21.5)	89 (20.6)	94 (20.3)	3 (9.7)
Aspartate aminotransferase increased	13 (6.6)	69 (17.1)	72 (16.7)	75 (16.2)	5 (16.1)
Alanine aminotransferase increased	9 (4.6)	67 (16.6)	71 (16.5)	74 (15.9)	5 (16.1)
Decreased appetite	13 (6.6)	60 (14.9)	62 (14.4)	62 (13.4)	2 (6.5)
Palmar-plantar erythrodysaesthesia syndrome	16 (8.1)	52 (12.9)	54 (12.5)	54 (11.6)	0
Blood bilirubin increased	13 (6.6)	52 (12.9)	52 (12.1)	52 (11.2)	0
Stomatitis	8 (4.1)	36 (8.9)	38 (8.8)	39 (8.4)	0
Anaemia	8 (4.1)	32 (7.9)	34 (7.9)	34 (7.3)	1 (3.2)
Headache	6 (3.0)	30 (7.4)	31 (7.2)	33 (7.1)	2 (6.5)

Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Dictionary: MedDRA v23.0 Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ARRAY 380-101: 26NOV2013

There were more treatment-related events in the tucatinib arm of the HER2CLIMB study (85.4% vs 73.1%). Treatment-related Grade ≥3 events were observed in 45.5% vs 30.5% with tucatinib vs placebo. More patients discontinued tucatinib due to ADRs in the tucatinib arm (4.2% vs 2.5%). Hence, the addition of tucatinib increases the overall treatment-related toxicity, but the level of ADRs is acceptable as this rarely leads to discontinuations.

Adverse drug reactions based on HER2CLIMB safety data

Determination of ADRs was based on HER2CLIMB safety data. A broad review of all grade AEs in the HER2CLIMB study was conducted, using different incidence cut-offs. This review informed the initial selection criteria for the determination of ADRs as follows:

- an incidence of ≥10% in the tucatinib arm regardless of causality, and

- ≥5% higher incidence in the tucatinib arm compared to the control arm.

As a subsequent step, each AE term selected using the above criteria was further evaluated for possible causal association. The AE terms identified using the absolute incidence rate cut-off and the relative frequency between the treatment arms in HER2CLIMB are listed below. A pooled analysis of subjects treated with tucatinib in combination with trastuzumab and capecitabine in the HER2CLIMB and ONT-380-005 studies is also presented below.

The frequency categories of ADRs included in the SmPC were determined from the pooled analysis of results from subjects treated with tucatinib + trastuzumab + capecitabine in the HER2CLIMB and ONT-380-005 studies (n=431).

Table 64: Initial adverse reaction terms based on absolute incidence and relative frequency

	HER2CLIMB						tucatinib + trastuzumab + capecitabine[1] N=431
	tucatinib + trastuzumab + capecitabine N=404			placebo + trastuzumab + capecitabine N=197			
SOC Preferred Term	Any Grade %	Grade 3 %	Grade 4 %	Any Grade %	Grade 3 %	Grade 4 %	Any Grade %
Blood and lymphatic system disorders							
Anemia	20	4	0	12	3	0	20
Gastrointestinal disorders							
Diarrhea	81	12	<1	53	9	0	81
Nausea	58	4	0	44	3	0	60
Vomiting	36	3	0	25	4	0	37
Stomatitis[2]	32	2	0	14	<1	0	32
Investigations							
AST increased	21	4	0	11	<1	0	22
ALT increased	20	5	0	7	<1	0	20
Blood bilirubin increased[3]	19	<1	<1	10	3	0	18
Weight decreased	13	1	0	6	<1	0	14
Metabolism and nutrition disorders							
Decreased appetite	25	<1	0	20	0	0	25
Musculoskeletal and connective tissue disorders							

	HER2CLIMB						tucatinib + trastuzumab + capecitabine[1] N=431
	tucatinib + trastuzumab + capecitabine N=404			placebo + trastuzumab + capecitabine N=197			
SOC Preferred Term	Any Grade %	Grade 3 %	Grade 4 %	Any Grade %	Grade 3 %	Grade 4 %	Any Grade %
Arthralgia	15	<1	0	5	<1	0	15
Nervous System Disorders							
Peripheral sensory neuropathy	12	<1	0	6	<1	0	11
Respiratory, thoracic, and mediastinal disorders							
Epistaxis	12	0	0	5	0	0	11
Skin and subcutaneous tissue disorders							
Palmar-plantar erythrodysesthesia syndrome (PPE)	63	13	0	53	9	0	64
Rash[4]	20	<1	0	15	<1	0	21

Note: Terms in this table reflect AEs reported in ≥10% of subjects in the tucatinib arm of HER2CLIMB, with ≥5% higher incidence in the tucatinib arm versus the control arm.

1 Includes subjects who received tucatinib + trastuzumab + capecitabine in HER2CLIMB and ONT-380-005

2 Stomatitis includes stomatitis, oropharyngeal pain, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysesthesia, tongue ulceration, aphthous ulcer

3 Blood bilirubin increased also includes hyperbilirubinemia

4 Rash includes rash maculo-papular, rash, dermatitis acneiform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema, skin toxicity, and dermatitis

These AE terms were further evaluated for possible causal association with tucatinib using the following criteria: analysis of AEs and relevant laboratory values from HER2CLIMB, with adjustment for time at risk; analysis of AEs and relevant laboratory values in ONT-380-005 (tucatinib ± trastuzumab ± capecitabine) and ARRAY-380-101 (tucatinib monotherapy); the mechanism of action of tucatinib; medical judgement.

Based on this review, anaemia, decreased appetite, peripheral sensory neuropathy, and PPE syndrome were determined not to be causally associated with tucatinib, although each occurred with a higher crude incidence rate in the tucatinib arm of the HER2CLIMB study.

Serious adverse events and deaths

SAEs

Table 65: Treatment-Emergent Serious Adverse Events by Preferred Term Tucatinib Integrated Safety Population

Preferred Term	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subjects with any event	58 (29.4)	118 (29.2)	129 (29.9)	138 (29.7)	11 (35.5)
Diarrhoea	7 (3.6)	17 (4.2)	17 (3.9)	17 (3.7)	1 (3.2)
Vomiting	5 (2.5)	11 (2.7)	11 (2.6)	12 (2.6)	1 (3.2)
Seizure	2 (1.0)	10 (2.5)	10 (2.3)	12 (2.6)	0
Nausea	3 (1.5)	9 (2.2)	9 (2.1)	10 (2.2)	0
Pneumonia	2 (1.0)	8 (2.0)	9 (2.1)	10 (2.2)	0
Ejection fraction decreased	3 (1.5)	6 (1.5)	6 (1.4)	6 (1.3)	0
Dyspnoea	6 (3.0)	5 (1.2)	5 (1.2)	5 (1.1)	1 (3.2)
Abdominal pain	0	4 (1.0)	4 (0.9)	4 (0.9)	0
Dehydration	0	4 (1.0)	4 (0.9)	4 (0.9)	0
Fatigue	2 (1.0)	3 (0.7)	4 (0.9)	4 (0.9)	0
Pleural effusion	6 (3.0)	3 (0.7)	4 (0.9)	5 (1.1)	0
Pulmonary embolism	3 (1.5)	4 (1.0)	4 (0.9)	4 (0.9)	0

Page 1 of 13

Sepsis	1 (0.5)	4 (1.0)	4 (0.9)	4 (0.9)	0
Abdominal pain upper	1 (0.5)	3 (0.7)	3 (0.7)	4 (0.9)	0
Arthralgia	0	3 (0.7)	3 (0.7)	3 (0.6)	0
Cholecystitis	0	3 (0.7)	3 (0.7)	3 (0.6)	0
Gastroenteritis	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
Muscular weakness	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
Brain oedema	2 (1.0)	1 (0.2)	2 (0.5)	3 (0.6)	0
Cancer pain	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.4)	0
Cardiac failure	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.4)	0
Cellulitis	1 (0.5)	1 (0.2)	2 (0.5)	2 (0.4)	1 (3.2)
Confusional state	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.4)	0
Constipation	2 (1.0)	2 (0.5)	2 (0.5)	2 (0.4)	0
Fall	0	2 (0.5)	2 (0.5)	2 (0.4)	0

Page 2 of 13

Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Dictionary: MedDRA v23.0 Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ARRAY 380-101: 26NOV2013

Approximately 29% of the patients in both arms had an SAE in the HER2CLIMB study and the most commonly observed SAEs in the tucatinib vs placebo arm were diarrhoea (4.2% vs 3.6%), vomiting (2.7 vs 2.5%), and nausea (2.2% vs 1.5%).

Deaths

Table 66: Treatment-Emergent Adverse Events Leading to Death by Preferred Term Tucatinib Integrated Safety Population

Preferred Term	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a b] (N=31) n (%)
Subjects with any event	6 (3.0)	8 (2.0)	8 (1.9)	8 (1.7)	1 (3.2)
Sudden death	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Cardiac arrest	1 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0
Cardiac failure	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Dehydration	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Multiple organ dysfunction syndrome	1 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0
Sepsis	1 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0
Septic shock	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Malignant neoplasm progression	0	0	0	0	1 (3.2)
Myocardial infarction	1 (0.5)	0	0	0	0
Respiratory failure	1 (0.5)	0	0	0	0
Systemic inflammatory response syndrome	1 (0.5)	0	0	0	0

Page 1 of 1

Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
b In study ARRAY 380-101, one death due to malignant neoplasm progression was reported as an adverse event.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Dictionary: MedDRA v23.0 Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ARRAY 380-101: 26NOV2013

Overall, 8 patients died from treatment-emergent events in the tucatinib arm (2%) vs 6 patients (3%) in the placebo arm. Detailed narratives have been provided and are assessed as follows:

One patient died of cardiac failure, while receiving tucatinib and trastuzumab, but had discontinued capecitabine due to PPE. Since MUGA scans had been normal throughout her study participation and the initial respiratory failure was caused by grade 3 pleural effusion and cardiac failure, it is likely that the underlying cause of death was disease progression.

One patient died due to sepsis and it was considered related to capecitabine. Especially since the dose of capecitabine used was 1500 mg/m^2/day, which is higher than the dose recommended in the SmPC for capecitabine in combination with tucatinib i.e. 1000 mg/m^2/day.

One patient died due to multiple organ dysfunction, which was induced by severe diarrhoea that is assessed most likely due to the capecitabine treatment. The patient continued a full dose of tucatinib together with capecitabine up until 6 days before her death and it cannot be ruled out that tucatinib could have worsened/and or contributed to the severe diarrhoea due to the temporal plausibility. One patient died due to dehydration, primarily due to severe diarrhoea and this was considered possibly related to tucatinib (and capecitabine). These two subjects, both on the tucatinib arm, who reported Grade 4 events of diarrhoea. One of the 2 subjects died from dehydration, the other from multiple organ dysfunction syndrome. In both subjects, diarrhoea was ongoing at the time of death. Both events were concurrent with a suspected infection. The median time to onset of the first event of

diarrhoea was 12 days on the tucatinib arm; 80.9% of events resolved, with a median time to resolution of 8 days. On the control arm, the median time to onset of the first event of diarrhoea was 22 days; 84.1% of events resolved, with a median time to resolution of 6 days.

One patient died due to cardiac arrest, respiratory failure, and sepsis, which was not considered related to tucatinib.

One patient died due to septic shock, diarrhoea, hypernatremia, Clostridium difficile colitis, white blood cell count decreased, neutropenia, and thrombocytopenia, which was deemed not related to tucatinib but to capecitabine treatment.

One patient died of sudden death, which was considered due to an unknown cause and not related to tucatinib.

One patient died of sudden death, which was considered due to an unknown cause and not related to tucatinib.

In the placebo arm, further six narratives are presented, of which 1 death was deemed related to the blinded study drug, which was placebo + capecitabine + trastuzumab. Updated safety data did not change these results.

Laboratory findings

Seattle Genetics Protocol ONT-380-206

Table 67: atment-Emergent Laboratory Abnormalities
Safety Analysis Set

	Tuc+Cap+Tra (N=404)			Pbo+Cap+Tra (N=197)		
Parameter	G 1-2 n (%)	G ≥ 3 n (%)	G 4 n (%)	G 1-2 n (%)	G ≥ 3 n (%)	G 4 n (%)
Hematology						
Hemoglobin low	216 (53.5)	12 (3.0)	0	92 (46.7)	2 (1.0)	0
Leukocytes low	79 (19.6)	6 (1.5)	1 (0.2)	30 (15.2)	10 (5.1)	0
Neutrophils low	225 (55.7)	7 (1.7)	2 (0.5)	107 (54.3)	11 (5.6)	1 (0.5)
Platelets low	111 (27.5)	1 (0.2)	0	44 (22.3)	2 (1.0)	0
Chemistry						
Alkaline phosphatase high	95 (23.5)	0	0	32 (16.2)	0	0
ALT high	155 (38.4)	30 (7.4)	0	50 (25.4)	1 (0.5)	0
AST high	148 (36.6)	20 (5.0)	0	47 (23.9)	2 (1.0)	0
Blood bilirubin high	186 (46.0)	4 (1.0)	1 (0.2)	52 (26.4)	6 (3.0)	0
Creatinine high	388 (96.0)	0	0	174 (88.3)	0	0
Potassium high	23 (5.7)	1 (0.2)	1 (0.2)	8 (4.1)	1 (0.5)	0
Potassium low	119 (29.5)	24 (5.9)	2 (0.5)	49 (24.9)	9 (4.6)	2 (1.0)

Page 1 of 1

Treatment-emergent laboratory abnormalities are defined as abnormalities that are new or worsened on or after receiving the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab) and up through 30 days after the last dose of study treatment (i.e., last dose of tucatinib/placebo).
Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-lb-abnorm.sas Output: t-lb-abnorm-safs.rtf (04NOV19:23:49) Data: adsl, adlb

Approximately half of the patients in HER2CLIMB had grade 1-2 low haemoglobin (53.5% vs 46.7%). Grade ≥3 events were rarely observed (3% vs 1%). Low leucocytes were observed of low grade in 19.6% vs 15.2%, while low grade low neutrophils were observed in 55.7% vs 54.3%. Low platelets were observed of low grade in 27.5% vs 22.3%, but seldomly observed of ≥ grade 3 events. Increased liver enzymes and bilirubin plus grade ≥3 ALT and AST increase were more frequently observed with tucatinib.

Safety in special populations

Age

Table 68: Treatment-emergent adverse events occurring in subjects <65 and ⩾65 years of age on both treatment arms (HER2CLIMB Safety Analysis Set)

	Age <65 years[a]		Age ⩾65 years	
	HER2CLIMB Tuc+Cap+Tra N=322 n (%)	HER2CLIMB Pbo+Cap+Tra N=164 n (%)	HER2CLIMB Tuc+Cap+Tra N=82 n (%)	HER2CLIMB Pbo+Cap+Tra N=33 n (%)
Subjects with any event	320 (99.4)	159 (97.0)	81 (98.8)	32 (97.0)
Diarrhoea	260 (80.7)	91 (55.5)	71 (86.6)	15 (45.5)
Palmar-plantar erythrodysesthesia syndrome	209 (64.9)	93 (56.7)	53 (64.6)	12 (36.4)
Nausea	190 (59.0)	78 (47.6)	51 (62.2)	10 (30.3)
Fatigue	148 (46.0)	73 (44.5)	44 (53.7)	14 (42.4)
Vomiting	114 (35.4)	43 (26.2)	35 (42.7)	8 (24.2)
Headache	83 (25.8)	38 (23.2)	11 (13.4)	2 (6.1)
Decreased appetite	80 (24.8)	33 (20.1)	24 (29.3)	8 (24.2)
Stomatitis	82 (25.5)	21 (12.8)	23 (28.0)	7 (21.2)
Aspartate aminotransferase increased	65 (20.2)	21 (12.8)	24 (29.3)	1 (3.0)
Anaemia	65 (20.2)	20 (12.2)	21 (25.6)	4 (12.1)
Alanine aminotransferase increased	62 (19.3)	13 (7.9)	23 (28.0)	0
Blood bilirubin increased	61 (18.9)	17 (10.4)	19 (23.2)	4 (12.1)
Arthralgia	58 (18.0)	12 (7.3)	6 (7.3)	0
Constipation	53 (16.5)	36 (22.0)	13 (15.9)	6 (18.2)
Abdominal pain	53 (16.5)	28 (17.1)	13 (15.9)	4 (12.1)
Blood creatinine increased	53 (16.5)	1 (0.6)	9 (11.0)	2 (6.1)
Cough	50 (15.5)	17 (10.4)	12 (14.6)	7 (21.2)
Hypokalemia	49 (15.2)	18 (11.0)	18 (22.0)	7 (21.2)
Weight decreased	48 (14.9)	8 (4.9)	14 (17.1)	4 (12.1)
Back pain	45 (14.0)	19 (11.6)	8 (9.8)	6 (18.2)
Dizziness	44 (13.7)	21 (12.8)	7 (8.5)	6 (18.2)
Pain in extremity	43 (13.4)	15 (9.1)	4 (4.9)	2 (6.1)
Peripheral sensory neuropathy	41 (12.7)	12 (7.3)	10 (12.2)	0
Dyspnoea	39 (12.1)	18 (11.0)	13 (15.9)	7 (21.2)
Dyspepsia	38 (11.8)	16 (9.8)	6 (7.3)	3 (9.1)
Upper respiratory tract infection	36 (11.2)	14 (8.5)	6 (7.3)	2 (6.1)
Muscle spasms	36 (11.2)	5 (3.0)	7 (8.5)	1 (3.0)
Epistaxis	35 (10.9)	7 (4.3)	15 (18.3)	3 (9.1)
Dry skin	34 (10.6)	15 (9.1)	7 (8.5)	3 (9.1)
Insomnia	33 (10.2)	15 (9.1)	6 (7.3)	2 (6.1)

TEAEs occurring with ≥10% incidence among subjects <65 years of age on the tucatinib arm are displayed.
Dictionary: MedDRA v23.0 Data cutoff: 29MAY2020
Source: Table 10.2.15 and Table 10.2.16

Gender

A total of 5 male subjects were enrolled and randomised in the HER2CLIMB study, including 3 subjects on the tucatinib arm and 2 subjects on the control arm. There were no new safety signals identified in male subjects treated with tucatinib in HER2CLIMB. No other male subjects were included in the tucatinib integrated safety population.

Hepatic and Renal Insufficiency

In Study ONT-380-009, a single 300 mg dose of tucatinib was well tolerated in subjects with mild, moderate, or severe hepatic function. In subjects with moderate and severe hepatic impairment, increases in tucatinib exposure were <2-fold compared to subjects with normal hepatic function, and did not meaningfully impact tucatinib exposure. Renal elimination is a minor contributor to tucatinib elimination (4% of radiolabeled dose was recovered in urine in Study ONT-380-008). Renal impairment is predicted to have low impact on tucatinib PK.

Extrinsic Factors

No subgroup analyses were performed by extrinsic factors.

Table 69: Summary of treatment-emergent adverse events by age groups (HER2CLIMB safety analysis set)

	Tuc+Tra+Cap N=404			Pbo+Tra+Cap N=197		
	Age <65 (N=322) n (%)[a]	Age ≥65–74 (N=74) n (%)[a]	Age ≥75–84 (N=8) n (%)[a]	Age <65 (N=164) n (%)[a]	Age ≥65–74 (N=29) n (%)[a]	Age ≥75–84 (N=4) n (%)[a]
Any TEAE	320 (99.4)	73 (98.6)	8 (100)	159 (97.0)	28 (96.6)	4 (100)
Subjects with TE SAE	80 (24.8)	27 (36.5)	1 (12.5)	45 (27.4)	10 (34.5)	3 (75.0)
Fatal[b]	4 (5.0)	4 (14.8)	0	3 (6.7)	3 (30.0)	0
Hospitalization/prolong existing hospitalization[b]	68 (85.0)	26 (96.3)	0	38 (84.4)	9 (90.0)	3 (100)
Life-threatening[b]	5 (6.3)	3 (11.1)	0	1 (2.2)	2 (20.0)	0
Disability/incapacity[b]	5 (6.3)	1 (3.7)	0	1 (2.2)	0	0
Other (medically significant)[b]	0	0	0	1 (2.2)	0	0
AE leading to tucatinib/placebo treatment discontinuation	15 (4.7)	7 (9.5)	0	3 (1.8)	3 (10.3)	0
Psychiatric disorders	64 (19.9)	13 (17.6)	0	31 (18.9)	5 (17.2)	1 (25.0)
Nervous system disorders	163 (50.6)	32 (43.2)	3 (37.5)	74 (45.1)	13 (44.8)	1 (25.0)
Accidents and injuries	50 (15.5)	13 (17.6)	0	19 (11.6)	1 (3.4)	0
Cardiac disorders	16 (5.0)	8 (10.8)	2 (25.0)	12 (7.3)	2 (6.9)	1 (25.0)
Vascular disorders	48 (14.9)	15 (20.3)	1 (12.5)	18 (11.0)	3 (10.3)	0
Cerebrovascular disorders	6 (1.9)	0	0	2 (1.2)	0	0
Infections and infestations	172 (53.4)	35 (47.3)	5 (62.5)	70 (42.7)	11 (37.9)	2 (50.0)
Anticholinergic syndrome	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	66 (20.5)	18 (24.3)	0	29 (17.7)	7 (24.1)	1 (25.0)

Treatment-emergent AEs are defined as events that are new or worsened on or after receiving the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab) and up through 30 days after the last dose of tucatinib/placebo).

a Percentages are calculated based on total number of subjects in each age group of the treatment arm.

b Percentages are calculated based on total number of subjects with any TE SAE in the treatment arm and age group.

Psychiatric disorders, Nervous system disorders, Cardiac disorders, Vascular disorders and Infection and infestations are from corresponding system organ classes. Accidents and injuries is from Accidents and injuries SMQ (narrow).

Cerebrovascular disorders are from Central nervous system haemorrhages and cerebrovascular conditions (SMQ) 3 sub-SMQs (narrow): Conditions associated with central nervous system haemorrhages and cerebrovascular accidents, Haemorrhagic central nervous system vascular conditions, and Ischaemic central nervous system vascular conditions.

Anticholinergic syndrome is from Anticholinergic syndrome SMQ (narrow). Quality of life decreased is from preferred terms of Impaired quality of life and Quality of life decreased.

Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures is from preferred terms of Orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, and any preferred terms that contain fracture.

Dictionary: MedDRA v22.0, Data Cutoff Date: 08NOV2019

Immunological events

Not applicable.

Safety related to drug-drug interactions and other interactions

The potential of tucatinib to be a DDI perpetrator or victim was evaluated in the two clinical DDI studies (ONT-380-012 and SGNTUC-020), a physiologically-based PK analysis (m5 PBPK report), and in non-clinical in vitro and in vivo systems (see clinical pharmacology section).

Discontinuation due to AES

Table 70: Treatment-emergent adverse events resulting in tucatinib/placebo discontinuation in ≥2 subjects in Pool 1 (Tucatinib Integrated Safety Population)

n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2	Tuc Mono[a] ARRAY-380-101 N=31

				Tuc and (Cap and/or Tra) N=464	
Subjects with any event	7 (3.6)	23 (5.7)	25 (5.8)	25 (5.4)	4 (12.9)
Diarrhoea	1 (0.5)	4 (1.0)	5 (1.2)	5 (1.1)	0
Alanine aminotransferase increased	1 (0.5)	4 (1.0)	4 (0.9)	4 (0.9)	0
Aspartate aminotransferase increased	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
Blood bilirubin increased	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
Vomiting	0	3 (0.7)	3 (0.7)	3 (0.6)	0
Nausea	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Respiratory failure	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Sepsis	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.4)	0

Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from Studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from Studies HER2CLIMB and ONT-380-005.
Data cutoff: ONT-380-206, 29MAY2020; ONT-380-005, 06MAR2018; ARRAY 380-101, 26NOV2013
Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) ⩾600 mg PO BID.
Source: Table 10.2.9

Table 71: Treatment-Emergent Adverse Events Resulting in Tucatinib/Placebo Discontinuation by Preferred Term Tucatinib Integrated Safety Population

Preferred Term	ONT-380-206 Pbo+Cap+Tra (N=197) n (%)	ONT-380-206 Tuc+Cap+Tra (N=404) n (%)	Tuc+Cap+Tra (Pool 1) (N=431) n (%)	Tuc and (Cap and/or Tra) (Pool 2) (N=464) n (%)	ARRAY-380-101 Tuc Mono[a] (N=31) n (%)
Subjects with any event	7 (3.6)	23 (5.7)	25 (5.8)	25 (5.4)	4 (12.9)
Diarrhoea	1 (0.5)	4 (1.0)	5 (1.2)	5 (1.1)	0
Alanine aminotransferase increased	1 (0.5)	4 (1.0)	4 (0.9)	4 (0.9)	0
Aspartate aminotransferase increased	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
Blood bilirubin increased	1 (0.5)	3 (0.7)	3 (0.7)	3 (0.6)	0
Vomiting	0	3 (0.7)	3 (0.7)	3 (0.6)	0
Nausea	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Respiratory failure	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Sepsis	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.4)	0
Acute respiratory failure	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Asthenia	0	0	1 (0.2)	1 (0.2)	0
Bone pain	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Cardiac arrest	0	1 (0.2)	1 (0.2)	1 (0.2)	0

Cardiac failure	1 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0
Choking	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Decreased appetite	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Dehydration	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Depressed mood	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Dermatomyositis	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Dizziness	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Ejection fraction decreased	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Fatigue	0	0	1 (0.2)	1 (0.2)	0
Hepatotoxicity	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Hyperbilirubinaemia	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Optic neuropathy	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	1 (0.2)	1 (0.2)	0

Pleural effusion	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Pyogenic granuloma	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Pyrexia	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Rash maculo-papular	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Septic shock	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Urticaria	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Brain oedema	1 (0.5)	0	0	0	0
Hypoaesthesia	0	0	0	0	1 (3.2)
Malignant neoplasm progression	0	0	0	0	2 (6.5)
Multiple organ dysfunction syndrome	1 (0.5)	0	0	0	0
Myelodysplastic syndrome	0	0	0	0	1 (3.2)

Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column.
a Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) >=600 mg PO BID.
Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from study ONT-380-206 and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from study ONT-380-206 and ONT-380-005.
Dictionary: MedDRA v23.0 Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ARRAY 380-101: 26NOV2013

Slightly more patients discontinued tucatinib/placebo on the tucatinib arm (5.7% vs 3.6%). The most common AEs leading to discontinuation were diarrhoea and increased ALT (1% vs 0.5%) followed by AST increased, bilirubin increased and vomiting (0.7% vs 0-0.5%).

A similar fraction of patients discontinued capecitabine on both treatment arms (10.9% vs 9.6%) and the most common AEs leading to discontinuation were PPE (2.7% vs 2%) and diarrhoea (1.7% vs 1%) followed by ALT increased (1% vs 0%), dehydration (0.7% vs. 0), and AST increased (0.5% vs. 0).

More patients discontinued trastuzumab on the tucatinib arm (4.2% vs 3.0%) in HER2CLIMB. The most common AEs leading to trastuzumab discontinuation included: ALT increased (0.7% vs. 0), diarrhoea (0.7% vs. 0.5%), AST increased (0.5% vs. 0), bilirubin increased (0.5% vs. 0.5%), respiratory failure (0.5% vs. 0), and sepsis (0.5% vs. 0.5%).

Table 72: Summary of Capecitabine Dose Holds
Safety Analysis Set

	Tuc+Cap+Tra (N=404)	Pbo+Cap+Tra (N=197)
Total number of dose holds due to AE	635	227
Number of subjects with a dose hold due to AE, n (%)	285 (70.5)	115 (58.4)
Number of dose holds due to AE/subject, n (%)		
1	123 (30.4)	59 (29.9)
2	67 (16.6)	28 (14.2)
>=3	95 (23.5)	28 (14.2)
Dosing after dose hold due to AE, n (%)		
Resumed at same dose	274/635 (43.1)	83/227 (36.6)
Resumed at reduced dose	213/635 (33.5)	75/227 (33.0)
Further hold due to other reason[a]	9/635 (1.4)	4/227 (1.8)
Further hold due to AE[a]	70/635 (11.0)	34/227 (15.0)
No further dosing	69/635 (10.9)	30/227 (13.2)
Not available	0	1/227 (0.4)

a The further hold occurred in the beginning of the next cycle after Day 15-21 of the current cycle where capecitabine administration is not planned per protocol.
b Duration calculated only for subjects who had resumed dosing at the same dose or at a reduced dose following a dose hold.
Data Snapshot: 10SEP2020, Data Cutoff Date: 29MAY2020

More patients in the tucatinib arm resumed capecitabine at the same dose, while a similar fraction (~33%) resumed at reduced dose. Hence, the dosing of the backbone chemotherapy of capecitabine seem not to be compromised by AEs from the addition of tucatinib.

The overall discontinuation rate due to AEs in the tucatinib arm was 11.9% vs 10.2% in the placebo arm, and this is an acceptable rate considering the treatment setting and the heavily pre-treated study population. As both capecitabine and tucatinib treatment often leads diarrhoea and other GI symptoms, it is difficult to disentangle the precise cause of these events. However, it is clear that most toxicity from the study treatment combination stems from tucatinib or capecitabine, but the discontinuation rates are still within an acceptable level with further updated safety data.

Post marketing experience

Not applicable.

2.5.1. Discussion on clinical safety

The safety population consists in patients who received the study treatment combination of tucatinib, capecitabine, and trastuzumab. It comprises 404 patients from the pivotal HER2CLIMB study, and is the main focus for this assessment, as the study is randomised, placebo-controlled and the doses of both capecitabine and tucatinibcorrespond to the ones applied for. Other safety data from pool 1 and 2 (n=431 and n=464, respectively), and the phase 1 data on monotherapy from 31 patients are considered supportive. The size of the safety data available on patients, who have received the study treatment combination is considered acceptable.

The median duration of exposure to tucatinib or placebo for the safety population (n=601) was 7.4 months (range:<0.1-43.6) (data cut-off 29-May-2020). As of the new DCO, 118 of the 404 patients (29.2%) on the tucatinib arm had received at least 12 months of tucatinib treatment and with 54 patients (13.4%) still ongoing on tucatinib treatment, the median exposure is now acceptable and in line with the median PFS on the tucatinib arm (7.8 months).

Most recent updated safety data show that almost all of the patients experienced at least one AE in HER2CLIMB, and ~59.2% experienced a ≥grade 3 AE. A quarter of the patients had an SAE (29.2%); however, only 2% of the patients had an SAE leading to death. The overall discontinuation rate due to AEs was 11.9%, and 5.7% discontinued tucatinib (SmPC section 4.8).

In the HER2CLIMB study, the most frequently reported all-causality clinical AEs were (tucatinib vs placebo-arm): diarrhoea (81.9% vs 53.8%), palmar-plantar erythrodysaesthesia i.e. PPE (64.9% vs 53.3%), nausea (59.7% vs 44.7%), fatigue (47.5% vs 44.2%), vomiting (36.9% vs 25.9%), decreased appetite (25.7% vs 20.8%), stomatitis (26.0% vs 14.2%), and headache (23.3% vs 20.3%). It is noted that these AEs are commonly observed with capecitabine treatment, which is part of the study treatment combination. However, the clinical AEs of diarrhoea, PPE, nausea, vomiting, and stomatitis were less frequently observed in the placebo arm, so tucatinib is considered accountable for these increased incidences.

Updated grade 3 AEs were reported in (tucatinib vs placebo-arm): 59.2% vs 51.3% of the patients and the most common clinical ≥ grade 3 events were PPE (13.9% vs 9.1%), diarrhoea (13.1% vs 8.6%), and fatigue (5.4% vs 4.1%), and it is noted that the both the increment and the incidences are diminished, which is reassuring. Especially, it is noted that the overall high rate of diarrhoea in the tucatinib arm (81.9%) was only a grade ≥3 event in 13.1%, although it is evident that tucatinib is contributing to this high overall rate of diarrhoea. Moreover, the similar rates in both treatment arms of other clinical AEs such as fatigue and headache, and grade ≥3 AEs, such as nausea and vomiting,

are most likely due the toxicity of capecitabine. Headache may also be a symptom associated with a history of brain metastases, which was present at baseline in ~48% of the patients.

Overall, updated safety data with relevant exposure showed a minor increase of AEs and grade 3 AEs, mostly in both treatment arms, which is acceptable and to be expected with longer exposure.

Adverse events of special interest include diarrhoea, nausea, vomiting, hepatotoxicity, PPE, rash, cardiac toxicity, cerebral oedema, and increased creatinine.

Diarrhoea was very commonly observed and the incidence was increased when tucatinib was added to capecitabine and trastuzumab. In HER2CLIMB, diarrhoea occurred sooner (tucatinib vs placebo-arm) with median time to onset 12 vs 22 days, and the event lasted longer i.e. 8 vs 6 days. Grade ≥3 AEs of diarrhoea occurred in 13.1% on the tucatinib arm and 8.6% on the control arm. Even though high-grade events were within an acceptable level and patients who had to permanently discontinue tucatinib/placebo was low (0.5-1%), SAEs were observed in ~4% of the patients and 2 patients died from dehydration and multiple organ dysfunction, respectively, due to ongoing diarrhoea. Similar incidences of diarrhoea were observed in the supporting studies.

If diarrhoea occurs, antidiarrhoeals should be administered as clinically indicated. For Grade ≥3 diarrhoea, treatment with tucatinib should be interrupted, then dose reduced or permanently discontinued (SmPC section 4.4). Diagnostic tests should be performed as clinically indicated to exclude infectious causes of Grade 3 or 4 diarrhoea or diarrhoea of any grade with complicating features (dehydration, fever, neutropenia). Diarrhoea is an identified risk which will be managed by routine risk minimisation. This risk will continue to be monitored through routine pharmacovigilance activities and discussed as a safety concern in PSURs.

Nausea was frequently observed in both treatment arms; however, clearly more frequent in the tucatinib arm (59.7% vs 44.7%). The median time to onset was a bit shorter (9 vs 12.5 days) and the mean time to resolution was longer (47.2 vs 36.6 days) in patients on the tucatinib arm.

Vomiting was also frequently observed in both arms, again more frequent with tucatinib (36.9% vs 25.9%). The time to onset was also shorter (21 vs 33 days) and the mean time to resolution longer 15.8 vs 11.1 days in the active arm. Both AEs are also known with capecitabine. The overall risk of nausea and vomiting is currently acceptable and the predominantly low grade and manageable incidence of these events do not require additional prophylactic measures beyond the dose modification guidance proposed in Section 4.2 of the SmPC.

Stomatitis was also more frequently observed on the tucatinib arm (26.0% vs 14.2%), which is expected, as tucatinib is a TKI that targets HER2. The level of stomatitis observed in HER2CLIMB indicates that the maximum tolerated dose of both capecitabine and tucatinib was probably used.

In HER2CLIMB, increased hepatotoxicity was observed with tucatinib (44.3% vs 25.9%) and this was especially observed for elevated AST, ALT, and bilirubin. More grade ⩾3 events of hepatotoxicity were observed with tucatinib than with placebo (10.4% and 5.1%), however the time to resolution was similar (22.0 vs 23.5 days; median 50.6 vs 50.2).

There was one case that met the laboratory criteria (ALT, AST, bilirubin, ALP) of Hy's law, and this patient recovered following dose modification of both tucatinib and capecitabine. The patient continued treatment for 12 cycles until PD. In a further analysis for any potential drug-induced liver injury, all patients, except the one mentioned with combined elevations of transaminases and bilirubin, had confounding possible alternative aetiologies for these abnormalities.

Overall, increased hepatotoxicity with earlier onset and longer time to resolution was observed with the study treatment combination. However, this was within an acceptable level and could generally be handled with dose-modifications of tucatinib and/or capecitabine. ALT, AST, and bilirubin should be

monitored every three weeks or as clinically indicated. Based on the severity of the adverse reaction, interrupt dose, then dose reduce or permanently discontinue treatment with tucatinib (SmPC section 4.4).

Hepatotoxicity is an identified risk of tucatinib which will be followed up via routine pharmacovigilance through signal detection, adverse reaction reporting, and discussion in PSURs. Beyond adverse reactions reporting and signal detection, a follow-up Hepatic Event Questionnaire is included as a routine pharmacovigilance activity. This is considered acceptable. Additional pharmacovigilance activities and/or risk minimisation measures are not warranted.

As the hepatic safety profile in subjects with chronic liver conditions is unknown, the safety in subjects who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease has been included as a safety concern in the RMP under missing information.

An increased incidence of PPE was observed with tucatinib (64.9% vs 53.3%) and the median time to onset was similar in both arms. More grade ≥3 events were observed with tucatinib (13.9% and 9.1%). However, it is acknowledged that the exposure of capecitabine was longer in the tucatinib arm and this may have affected the incidences of PPE, which is a known adverse event with capecitabine. For this reason, PPE is not considered an ADR or important potential risk for tucatinib.

The incidence of rash was higher in the tucatinib monotherapy study compared to the tucatinib arm of HER2CLIMB (29.0% vs. 21.8%). However, the sample size was small in the monotherapy study (N=31). The TEAEs were primarily Grade 1, with Grade ≥3 events reported in less than 1% of subjects. Overall, rash is a known AE of TKI's such as tucatinib and is considered to be induced by tucatinib. Nevertheless, the event is considered manageable and it is agreed that rash should not be listed as a safety concern.

Cardiac toxicity was expected with tucatinib as it is a HER2- targeted therapy, and this is a class effect with other anti-HER2 therapies. Overall, the incidences of AEs of QT prolongation and decreased LVEF on treatment with tucatinib does not seem to be clinically meaningfully increased.

Although cardiotoxicity was not seen specifically for tucatinib, HER2-directed therapies have the potential to cause cardiotoxicity, especially in the elderly when combined with anthracycline-based chemotherapy regimens. Cardiotoxicity with tucatinib is not considered a potential risk but there is a possibility that this could be seen in subjects with other significantly cardiotoxic chemotherapy agents; therefore, the safety profile in this patient population may be different. The safety in patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin has been included in the list of safety concerns under missing information. The Standard AE Reporting Form was updated to inquire if patients received prior cumulative anthracycline doses equivalent to > 360 mg/m^2 doxorubicin when cardiac events are reported which will allow closer monitoring of cardiotoxicity in patients who have received prior anthracycline doses equivalent to >360 mg/m^2 in the post-marketing setting. The two ongoing studies (Study SGNTUC-016 (HER2CLIMB-02), and Study SGNTUC-017 (MOUNTAINEER)) were included as additional pharmacovigilance activities to further characterise this risk.

Overall, 4 cases of cerebral oedema were observed in the HER2CLIMB study including 1 case observed with capecitabine and tucatinib treatment. In one of the cases, the cerebral oedema observed was most likely due to the underlying disease (brain metastases), prior surgery, and the discontinuation of steroids.

Updated safety data informed of one case of grade 2 cerebral oedema in the tucatinib arm. Since the patient had multiple brain metastases at study entry, had known epilepsy, and the event of cerebral oedema was of low grade and resolved after 9 days, it was not considered to be evidence of a potential risk with tucatinib but assessed as related to the underlying disease.

There were more treatment-related adverse events in the tucatinib arm vs placebo arm of the HER2CLIMB study (85.4% vs 73.1%). Treatment-related Grade ≥3 events were observed in 45.5% vs 30.5% with tucatinib vs placebo arm.

Approximately 29% of the patients in both arms had a serious adverse event (SAE) in the HER2CLIMB study and the most common were diarrhoea (4.2% vs 3.6%), vomiting (2.7% vs 2.5%), and nausea (2.2% vs 1.5%). It is noted that more patient in the placebo arm had dyspnoea, pleural effusion, and headaches, which may be signs of clinical progression. Overall, the rate of SAEs with tucatinib is acceptable considering the treatment setting and targeted patient population.

In the pivotal study, 8 patients died from treatment-emergent adverse events in the tucatinib arm (2%) vs 6 patients (3%) in the placebo arm. After review of the detailed narratives it is agreed with the applicant that two of 8 cases of AEs leading to death can be considered related to tucatinib treatment. In one case the patient died due to multiple organ dysfunction, which was induced by severe diarrhoea that was assessed most likely due to the capecitabine treatment (reported above). The patient continued a full dose of tucatinib together with capecitabine up until 6 days before her death and it cannot be ruled out that tucatinib could have worsened/and or contributed to the severe diarrhoea due to the temporal plausibility. In another case, the patient died due to dehydration primarily due to severe diarrhoea and this was considered possibly related to tucatinib (and capecitabine; reported above). Relevant monitoring is put in place to miminise the risk of diarrhoea. In the placebo arm, 1 death was deemed related to the blinded study drug, which was placebo+capecitabine+trastuzumab.

With regards to laboratory abnormalities, haematological toxicity was overall assessed as most likely due to capecitabine and there is no clear pattern at this time showing that tucatinib contributes very much, if anything, to this type of toxicity. Low grade liver toxicity was also observed but remains to an acceptable level.

The overall discontinuation rate due to AEs in the tucatinib arm was 11.9% vs 10.2% in the placebo arm, and this is an acceptable rate, considering the heavily pre-treated study population. As both capecitabine and tucatinib treatment often leads diarrhoea and other GI toxicity, it is difficult to disentangle which of the drugs that is the main contributor to these events. However, it is noted that slightly more patients discontinued tucatinib/placebo on the tucatinib arm (5.7% vs 3.6%), while a similar fraction of patients discontinued capecitabine on both treatment arms (10.9% vs 9.6).

More patients discontinued tucatinib due to ADRs in the tucatinib arm (4.2% vs 2.5%), while a similar proportion of patients in both arms discontinued either capecitabine or trastuzumab due to ADRs. Hence, the addition of tucatinib increases the overall treatment-related toxicity. Nevertheless, the level of ADRs is so far acceptable as this rarely leads to discontinuations.

Adverse events according to age were presented. In the HER2CLIMB study, 82 patients who received tucatinib were ≥65 years, of whom 8 patients were ≥75 years. For the tucatinib arm, there were slightly more toxicity in patients aged ≥65 years old, most commonly pertaining to diarrhoea, fatigue, nausea and vomiting, decreased appetite, AST/ALT increased, and anaemia. In the placebo arm, the small number of patients ≥65 years, (n=33) makes these patterns hard to interpret. Dose adjustment due to age beforehand is not warranted.

There were no patients ≥85 years enrolled on the study. There were too few patients ≥75 years to assess differences in safety. Therefore, the SmPC reflects tucatinib has not been investigated in patients above the age of 80 years. The incidence of serious adverse reactions was 36.5% in patients ≥ 65 years compared to 24.8% in patients < 65 years. It is noted that there were significantly more fatal events (14.8% vs 5%) and cardiac disorders (10.8% vs 5%) in the population of ≥65-74 years of age. The group of ≥75-84 is too small (n=8) for any conclusions.

Based on findings from animal studies and its mechanism of action, tucatinib may cause harmful effects to the foetus when administered to a pregnant woman (see also discussion on non-clinical aspects and SmPC section 4.6).

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 of the SmPC is a contraindication (see SmPC section 4.3).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Since the numbers of patients exposed to tucatinib longer than 12 months is considered very limited (n=118, 29.2% received at least 12 months of tucatinib treatment as of 29 May 2020), long-term safety is considered a safety concern included as missing information in the RMP. To further characterise the safety of tucatinib in the long term, two ongoing studies (Study SGNTUC-016 (HER2CLIMB-02), and Study SGNTUC-017 (MOUNTAINEER)) have been included as additional pharmacovigilance activities in the RMP.

HER2CLIMB-02 (SGNTUC-016) is an ongoing randomised, double-blind pivotal trial in subjects with metastatic breast cancer. Approximately 230 subjects will be treated with tucatinib in combination with T-DM1. MOUNTAINEER (SGNTUC-017) study is an ongoing single-arm, open-label pivotal trial in subjects with metastatic colorectal cancer. This study consists of 3 cohorts and will enrol approximately 110 subjects. Subjects enrolled in Cohort A or Cohort B will be treated with tucatinib and trastuzumab combination therapy, and subjects enrolled in Cohort C will be treated with tucatinib monotherapy. Data from these cohorts will support further characterisation of tucatinib's long-term safety profile.

2.5.2. Conclusions on the clinical safety

The safety profile of tucatinib is as could be expected with a HER2-targeting TKI. The updated safety data with relevant median exposure did not lead to any major clinically relevant differences of AEs, SAEs and discontinuations and therefore the safety profile of tucatinib in combination with capecitabine and trastuzumab is considered overall acceptable and clinically manageable.

2.6. Risk Management Plan

The Safety Specification (Part II, SI-SVIII) from RMP version 0.3, dated 04-NOV-2020 is assessed below.

2.6.1. Safety Specification

Summary of safety concerns

Table 73: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Diarrhoea Hepatotoxicity
Important potential risks	Embryo-foetal toxicity

Summary of safety concerns	
Missing information	Patients with prior cumulative anthracycline doses equivalent to >360 mg/m2 doxorubicin Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease Long-term safety

Pharmacovigilance plan

Table 74: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
SGNTUC-016: A study of tucatinib vs. placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with advanced or metastatic HER2+ breast cancer (HER2CLIMB-02) Ongoing	To evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting; further assess and characterise important risks and missing information	Diarrhoea, hepatotoxicity, embryo-foetal toxicity, missing information for patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin, long-term safety	Final CSR	Projected Q2 2025
SGNTUC-017: Tucatinib plus Trastuzumab in Subjects with HER2+ Colorectal Cancer (MOUNTAINEER) Ongoing	To evaluate efficacy and safety of tucatinib, administered as monotherapy and in combination with trastuzumab, in subjects with HER2-positive, RAS wild-type, unresectable or metastatic CRC; further assess and characterise important risks and missing information	Diarrhoea, hepatotoxicity, embryo-foetal toxicity, long-term safety	Final CSR	Projected Q4 2022

Risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Table 75: **Description of Routine Risk Minimisation Measures by Safety Concern**	
Safety Concern	**Routine Risk Minimisation Activities:**
Diarrhoea	Routine risk communication: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for diagnostic tests to exclude infectious causes are included in SmPC Section 4.4. Other risk minimisation measures beyond the PI: • None
Hepatotoxicity	Routine risk communication: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for liver function monitoring are included in Section 4.4. Other risk minimisation measures beyond the PI: • None
Embryo-foetal toxicity	Routine risk communication: • SmPC Section 4,4, 4.6, and 5.3 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for verification of pregnancy status in females of childbearing potential prior to initiating treatment with tucatinib is included in SmPC Section 4.6 • Recommendation for males and females of reproductive potential to use contraception during and up to at least 1 week after treatment is included in SmPC Section 4.6 Other risk minimisation measures beyond the PI: • None
Missing Information	
Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None

Table 76: Description of Routine Risk Minimisation Measures by Safety Concern	
Safety Concern	**Routine Risk Minimisation Activities:**
	Other risk minimisation measures beyond the PI: • None
Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	Routine risk communication for hepatotoxicity: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures for hepatotoxicity to address the risk: • Recommendations for liver function monitoring are included in Section 4.4. Other risk minimisation measures beyond the PI: • None
Long term safety	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the PI: • None

Additional risk minimisation measures

NA

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 17 April 2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. New Active Substance

The applicant compared the structure of tucatinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer,

mixture of isomers, complex or derivative of any of them.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tukysa (tucatinib) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It has an obligation to conduct post-authorisation efficacy studies [REG Art 9(4)(cc), Art 10a(1)(b), DIR Art 21a(f), Art 22a(1)(b)];

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for tucatinib is combination therapy with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases at baseline, who have received at least 2 prior anti-HER2 treatment regimens.

3.1.2. Available therapies and unmet medical need

In the targeted patient population, who have received at least 2 prior anti-HER2 treatment regimens, there are no standard of care. Available therapy would typically consist of chemotherapy in monotherapy in combination with trastuzumab, but no single regimen is approved for the applied treatment setting after treatment with trastuzumab, pertuzumab and TDM-1. Moreover, limited efficacy of these used regimens is observed, with reported median PFS of 3.3 to 4.9 months (Krop 2014; Rugo 2019) and a median OS of 15.8 to 17.2 months (Krop 2017; Rugo 2019).

Hence, there is a high unmet medical need for further targeted therapy, and there is also a high unmet medical need for a therapy that are active in the CNS for patients with brain metastases, as there is no systemic treatment approved for this indication, and brain metastases are a major clinical problem in this patient population. The prognosis of HER2+ advanced breast cancer patients, progressed to several HER2-directed agents and with brain metastasis, remains dismal.

3.1.3. Main clinical studies

The pivotal study HER2CLIMB is a randomised, double-blind, placebo-controlled, multicentre, phase 2 study conducted in 169 centres over a 3-year period and the study population was predominantly comparable to the European patient population. A total of 612 patients were randomised 2:1 to the tucatinib arm (n=410) and the control arm (n=202). Moreover, 198 patients with brain metastases at baseline were treated with tucatinib.

3.2. Favourable effects

The primary endpoint of PFS by BIRC was statistically significantly improved by 2.2 months in the ITT-PFS population (n=480), i.e. from 5.6 months to 7.8 months (HR 0.544 (95%CI: 0.420; 0.705). There were 55.6% and 60.6% events on the tucatinib versus the placebo-arm, respectively. The KM curves separate early and keep being separated in the observation time available. Median follow-up time for PFS is ~10 months. PFS by BICR conducted in the ITT-OS population support the result from the primary analysis (HR=0.535; 95%CI: 0.420, 0.682).

The key secondary endpoint of OS showed a statistically significant improvement in the ITT population from 17.4 months to 21.9 months with tucatinib, HR 0.662 (95%CI: 0.501; 0.875). The KM curves separate after 7 months and the difference between the curves seem to increase with time in favor of the tucatinib arm. There were 31.7% and 42.1% events on the tucatinib vs the placebo arm. Median follow-up time for OS is currently ~14 months.

PFS in patients with brain metastases at baseline was statistically significant improved from 5.4 months in the control arm to 7.6 months with tucatinib, which is a difference of 2.2 months, HR 0.483 (95%CI: 0.339; 0.689). The KM curves clearly separate after 3 months of treatment.

ORR in the brain by BIRC in 48 patients with brain metastases at baseline was 35.4% (95%CI: 22.2; 50.5), and the median duration of response was 8.2 months (95%CI: 4.1; 9.7).

ORR by BIRC is now presented for the entire ITT-OS population (n=612) and there was an increased response rate in the tucatinib arm from 19.3% to 34.6% of the patients with measurable disease. The clinical benefit rate (CBR by BIRC) is including patients who had a response or a stabilisation for ≥6 months and this was also statistically significant improved with tucatinib from 38.1% to 59.8% of the patients.

Subgroup analyses of efficacy of tucatinib regarding PFS, OS, and PFS in patients with brain metastases at baseline are consistent across all subgroups, with no clinically meaningful differences observed.

3.3. Uncertainties and limitations about favourable effects

The key secondary endpoint OS was partly mature; the data show a statistically significantly improved OS at a median follow-up time of approximately 14 months. The applicant will provide the final study results post-authorisation by the end of Q2 2023, which is acceptable (see PI and RMP).

3.4. Unfavourable effects

All of the patients experienced at least one AE, and most of these were assessed to be treatment-related. The most commonly observed AEs were (tucatinib vs placebo-arm): diarrhoea (81.9% vs 53.8%), PPE (64.9% vs 53.3%), nausea (59.7% vs 44.7%), fatigue (47.5% vs 44.2%), vomiting (36.9% vs 25.9%), decreased appetite (25.7% vs 20.8%), stomatitis (26% vs 14.2%), and headache (23.3% vs 20.3%).

Grade 3 AEs were reported in (tucatinib vs placebo-arm): 59.2% vs 51.3% of the patients and the most common were PPE (13.9% vs 9.1%), diarrhoea (13.1% vs 8.6%), and fatigue (5.4% vs 4.1%).

Adverse events of special interest include diarrhoea, nausea, vomiting, hepatotoxicity, PPE, rash, cardiac toxicity, cerebral oedema, and increased creatinine. Worth mentioning is the increased risk of diarrhoea (81.9% vs 53.3%) and hepatotoxicity (44.3% vs 25.9%), especially reported as elevated AST, ALT, and bilirubin.

In the pivotal HER2CLIMB study, 8 patients died from treatment-emergent adverse events in the tucatinib arm (2%) vs 6 patients (3%) in the placebo arm. Overall, 2 deaths were possibly related to tucatinib/capecitabine treatment.

Approximately 29% of patients in both arms had a serious adverse event (SAE), most commonly diarrhoea (4.2% vs 3.6%), vomiting (2.7% vs 2.5% and nausea (2.2% vs 1.5%).

The discontinuation rate of any study treatment due to AEs was 11.9% on the tucatinib arm vs 10.2% on the placebo arm. More patients discontinued tucatinib/placebo on the tucatinib arm (5.7% vs 3.6%), while a similar fraction of patients discontinued capecitabine on both treatment arms (10.9% vs 9.6%).

3.5. Uncertainties and limitations about unfavourable effects

There are no major uncertainties or limitations about unfavourable effects.

Since the numbers of patients exposed to tucatinib longer than 12 months is considered very limited (n=83, 20.5%), long-term safety is considered a safety concern included as missing information in the RMP. To further characterise the safety of tucatinib in the long term, two ongoing studies (Study SGNTUC-016 (HER2CLIMB-02), and Study SGNTUC-017 (MOUNTAINEER)) have been included as additional pharmacovigilance activities in the RMP.

HER2CLIMB-02 (SGNTUC-016) is an ongoing randomised, double-blind pivotal trial in subjects with metastatic breast cancer. Approximately 230 subjects will be treated with tucatinib in combination with T-DM1. MOUNTAINEER (SGNTUC-017) study is an ongoing single-arm, open-label pivotal trial in subjects with metastatic colorectal cancer. This study consists of 3 cohorts and will enrol approximately 110 subjects. Subjects enrolled in Cohort A or Cohort B will be treated with tucatinib and trastuzumab combination therapy, and subjects enrolled in Cohort C will be treated with tucatinib monotherapy. Data from these cohorts will support further characterisation of tucatinib's long-term safety profile.

3.6. Effects Table

Table 77: Effects Table for tucatinib in combination with capecitabine and trastuzumab for HER2+advanced breast cancer (data cut-off: 04 September 2019)

Effect	Short Description	Unit	Treatment Tucatinib	Control Placebo	Uncertainties/ Strength of evidence	Ref
Favourable Effects						
PFS by BIRC	Progression-free survival	Months (95%CI)	7.8 (7.5; 9.6)	5.6 (4.2; 7.1)	HR 0.544 P<0.0001	PFS-ITT pop N=480
OS	Overall survival	Months (95%CI)	21.9	17.4	HR 0.662 P=0.0048	OS-ITT=612
PFS BM	PFS	Months (95%CI)	7.6	5.4	HR 0.483 P<0.0001	N=198 who had tucatinib
ORR	Confirmed response rate by BIRC	% (95%CI)	34.6 (30.0; 39.5)	19.3 (14.1; 25.4)		N= 511 with measurable disease
Unfavourable Effects HER2CLIMB safety population; 404 tucatinib arm and 197 placebo arm						
Any AEs		%	99.3	97.0		
Grade ⩾3 AEs		%	59.2	51.3		
SAEs		%	29.2	29.4		
AEs leading to discontinuation		%	11.9	10.2		
AEs leading to death		%	2.0	3.0		
Diarrhoea		%	81.9	53.8		
PPE		%	64.9	53.3		
Nausea		%	59.7	44.7		
Fatigue		%	47.5	44.2		
Vomiting		%	36.9	25.9		

Abbreviations: PFS BM: PFS in patients with brain metastases at baseline; AE: Adverse Event; SAE: Serious Adverse Event; PPE: Palmar-plantar Erythrodysaesthesia.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefit of tucatinib in combination with capecitabine and trastuzumab in the proposed treatment setting after prior exposure to trastuzumab, pertuzumab and TDM-1 is considered clinically meaningful, since the primary endpoint of PFS by BIRC was met and showed a 2.2 months improvement. Moreover, the key secondary endpoint of OS shows clinically meaningful improvement of 4.5 months despite only partly mature data with ~30% events on the tucatinib arm. PFS in patients with brain metastases at baseline was also improved by 2.2 months, so efficacy is considered shown with tucatinib despite metastases to the brain. In addition, efficacy of tucatinib regarding PFS, OS, and PFS in patients with brain metastases at baseline are consistent across all subgroups, with no clinically meaningful differences observed.

Since PFS by BIRC is mature and OS partly mature with no sign of a detrimental effect, it is acceptable that the final PFS and OS data will be provided as a post-authorisation efficacy study (PAES).

The reported adverse events with tucatinib seem to be manageable and mostly pertaining to gastrointestinal toxicity from tucatinib and/or capecitabine. The safety profile did not change significantly with updated safety data and relevant median exposure, therefore the safety of tucatinib in combination with trastuzumab and capecitabine is considered acceptable.

To contextualise, tucatinib is indicated in a setting where there is no standard of care available and currently used treatment regimens show limited efficacy. Moreover, there are currently no approved therapies indicated for HER2+ breast cancer patients with brain metastases. Hence, there is a high unmet medical need for further treatment options for the targeted patient population in the proposed setting.

3.7.2. Balance of benefits and risks

The benefit of tucatinib in combination with capecitabine and trastuzumab is favourable. However, the key secondary endpoint OS was partly mature with data showing a statistically significantly improved OS at a median follow-up time of approximately 14 months. Therefore, the submission of the final OS and PFS results from study HER2CLIMB as a PAES, in accordance with the European Commission Delegated Regulation (EU) No 357/2014 indent a), has been imposed by the CHMP (see Annexes and RMP).

3.7.3. Additional considerations on the benefit-risk balance

The submission of final OS and PFS results from study HER2CLIMB to further investigate the efficacy of tucatinib in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2 positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens has been imposed by the CHMP (in accordance with the European Commission Delegated Regulation (EU) No 357/2014 indent a).

3.8. Conclusions

The overall B/R of tucatinib in combination with capecitabine and trastuzumab is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tukysa is favourable in the following indication:

Tukysa is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2 positive locally advanced or metastatic breast cancer who have received at least 2 prior anti HER2 treatment regimens.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate the efficacy of tucatinib in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2 positive locally advanced or metastatic breast cancer who have received at least 2 prior anti HER2 treatment regimens, the MAH should submit the final analysis for OS and PFS from study HER2CLIMB.	30 June 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tucatinib is a new active substance and has not been authorised previously in the European Union.