Effect of multiple-dose osimertinib on the pharmacokinetics of simvastatin and rosuvastatin

R Donald Harvey[1], Noemi Reguart Aransay[2], Nicolas Isambert[3], Jong-Seok Lee[4], Tobias Arkenau[5], Johan Vansteenkiste[6], Paul A Dickinson[7], Khanh Bui[8], Doris Weilert[9], Karen So[10], Karen Thomas[11], Karthick Vishwanathan[12]

[1]Winship Cancer Institute of Emory University, Atlanta, GA, USA

[2]Department of Medical Oncology, Hospital Clinic Barcelona; Translational Genomics and Targeted Therapeutics in Solid Tumors, IDIBAPS, Barcelona, Spain

[3]Department of Medical Oncology, Centre GF Leclerc, Dijon, France

[4]Seoul National University, Bundang Hospital, Seoul, South Korea

[5]Sarah Cannon Research Institute, London, UK

[6]Respiratory Oncology Unit (Respiratory Diseases), University Hospital KU Leuven, Leuven, Belgium

[7]Seda Pharmaceutical Development Services, Alderley Edge, UK

[8]Quantitative Clinical Pharmacology, AstraZeneca, Waltham, MA, USA

[9]IQVIA, Overland Park, KS, USA

[10]Global Medicines Development / Global Clinical Development, AstraZeneca, Royston, UK

[11]Biostatistics and Informatics, AstraZeneca, Macclesfield, UK

[12]Clinical Pharmacology, Early Clinical Development, AstraZeneca, Waltham, MA, USA

Corresponding author:

Dr Karthick Vishwanathan, PhD, 35 Gatehouse Drive, Waltham, MA 02451, USA. Tel: +1 781 839 4877; Karthick.Vishwanathan@astrazeneca.com

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Summary

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Aim: We report on two phase I, open-label, single-arm studies assessing the effect of osimertinib on simvastatin (CYP3A substrate) and rosuvastatin (breast cancer resistance protein substrate [BCRP] substrate) exposure in patients with advanced epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer who have progressed after treatment with an EGFR tyrosine kinase inhibitor, to determine, upon coadministration, whether osimertinib could affect the exposure of these agents.

Methods: 52 patients in the CYP3A study (pharmacokinetic [PK] analysis, *N* = 49), and 44 patients in the BCRP study were dosed (PK analysis, *N* = 44). In the CYP3A study, patients received single doses of simvastatin 40 mg on Days 1 and 31, and osimertinib 80 mg once daily on Days 3–32. In the BCRP study, single doses of rosuvastatin 20 mg were given on Days 1 and 32, and osimertinib 80 mg once daily on Days 4–34.

Results: Geometric least squares mean (GLSM) ratios (90% confidence intervals) of simvastatin plus osimertinib for area under the plasma concentration-time curve from zero to infinity (AUC) were 91% (77–108): entirely contained within the pre-defined no relevant effect limits, and C_{max} of 77% (63, 94) which was not contained within the limits. GLSM ratios of rosuvastatin plus osimertinib for AUC were 135% (115–157) and C_{max} were 172 (146, 203): outside the no relevant effect limits.

Conclusions: Osimertinib is unlikely to have any clinically relevant interaction with CYP3A substrates and has a weak inhibitory effect on BCRP. No new safety concerns were identified in either study.

What is the current knowledge on the topic?

- Osimertinib is a potent, oral, central nervous system-active, irreversible EGFR-TKI selective for both EGFR-TKI sensitizing (EGFRm) and T790M resistance mutations.
- *In vitro* studies show that osimertinib can inhibit or induce CYP3A/5 enzymes, and inhibit breast cancer resistance protein (BCRP) transporter.

What this study adds to our knowledge

- Osimertinib is unlikely to have any clinically relevant interaction with CYP3A substrates and has a weak inhibitory effect on BCRP substrates.

Introduction

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are the standard first-line treatment for non-small cell lung cancer (NSCLC) patients with TKI sensitising mutations in EGFR (EGFRm) [1-3]. However, the majority of patients who initially respond to EGFR-TKIs ultimately develop resistance, with over 50% of tumours harbouring the EGFR T790M resistance mutation [4-10]. Osimertinib is a potent, oral, central nervous system active, irreversible EGFR-TKI selective for EGFRm and T790M resistance mutations [11-13]. Osimertinib is approved and also recommended for the treatment of patients with metastatic EGFR T790M-positive advanced NSCLC [1,3]. In the phase III AURA3 trial, osimertinib provided a higher objective response rate (71% vs 31%) and significantly longer progression-free survival than platinum-based doublet chemotherapy (median 10.1 vs 4.4 months; hazard ratio [HR] 0.30; 95% confidence interval [CI] 0.23, 0.41; p<0.001) [14].

As part of treatment with osimertinib, it is important to understand potential drug-drug interactions (DDI) due to the risk of comorbidities requiring concomitant therapy in this patient population. *In vitro* studies have shown that osimertinib has potential to be a competitive inhibitor and inducer of CYP3A and that it is a competitive inhibitor of the breast cancer resistance protein (BCRP) transporter [15]. CYP3A is the most important enzyme involved in the metabolism of drugs [16], while BCRP is involved in the elimination of certain widely prescribed medicines with relatively narrow therapeutic margins, including rosuvastatin at the higher dose [17,18]. Comorbidities commonly associated with NSCLC, such as chronic obstructive pulmonary disease or diabetes [19], may need to be treated with concomitant medications that are metabolised through CYP3A or transport-mediated elimination via BCRP. Moreover, statins are a common co-medication in this patient population. Therefore, it is important to understand any potential implications osimertinib could have on the exposure and thereby, the efficacy and safety of these agents when co-administered.

Osimertinib has two active metabolites which circulate at ~10% of the exposure of osimertinib and less than 10% of the total drug related exposure and were not considered for DDI potential.

We report two clinical studies designed to investigate the impact of multiple doses of osimertinib on the pharmacokinetics (PK) of simvastatin and simvastatin acid (a sensitive CYP3A substrate and its metabolite; [NCT02197234]), and rosuvastatin (a substrate for BCRP and a medication likely to be administered concomitantly with osimertinib; [NCT02317016]). The two active metabolites of osimertinib (AZ5104 and AZ7550), which represent approximately 10% each of osimertinib exposure [20], were also monitored, though were not considered likely to contribute to any DDI. 4β-hydroxy-cholesterol (4BHC) concentration ratios were measured in order to understand the overall effect of CYP3A modulation following multiple dose administration of osimertinib. Both studies were conducted in patients with advanced EGFRm NSCLC after disease progression during or after a prior EGFR-TKI. Herein, we report results that show the PK-mediated potential for DDI between these agents.

Methods

Details of in vitro CYP inhibition, transporter inhibition and CYP induction potential of osimertinib are provided in Supplementary information.

Clinical Trial design

Both studies were phase I, open-label, single-arm studies in patients with EGFRm NSCLC with disease progression during or after treatment with an EGFR-TKI. They were conducted in accordance with International Conference on Harmonization–Good Clinical Practice guidance, and protocols were reviewed and approved by an Independent Ethics Committee and Institutional Review Board prior to implementation. Written informed consent was obtained from all participants.

Each study consisted of two parts. Part A was designed to assess the effect of osimertinib on simvastatin and simvastatin acid (CYP3A study) or rosuvastatin (BCRP study) exposure and was split into three segments: Periods 1–3. Part B allowed patients to have continued access to osimertinib after the PK phase (Part A) and provided additional safety data. Only Part A results are described in this report.

In the CYP3A and BCRP studies, patients received a single oral dose of simvastatin 40 mg or rosuvastatin 20 mg, respectively, alone on Day 1 (Period 1) and remained in the clinic for approximately 32 to 34 h, during which time blood samples for PK analysis and safety information were collected. Patients then received osimertinib 80 mg orally once daily for 28 Days (Period 2, Days 3 to 30 in the CYP3A study, and Days 4 to 31 in the BCRP study) and returned to the clinic in weekly intervals for collection of osimertinib and metabolite (AZ5104 and AZ7550) trough levels. In Period 3 on Day 31 of the CYP3A study and Day 32 of the BCRP study, patients received a single oral dose of simvastatin 40 mg, or rosuvastatin 20 mg, in combination with osimertinib 80 mg. In the CYP3A study, this was followed by a final oral dose of osimertinib 80 mg on Day 32, whereas In the BCRP study

this dosing was followed by subsequent daily doses of osimertinib 80 mg on Days 33 and 34. Patients remained in the clinic for approximately 32 to 34 h, during which time blood samples for PK analysis and safety information were collected.

In both studies, patients fasted from at least 2 h before dosing to at least 2 h after dosing on simvastatin and rosuvastatin dosing days. Osimertinib was to be given with 1 h of fasting before to 2 h after dosing.

A sufficient number of patients were enrolled to address the primary PK study objectives, as measured by AUC and C_{max}. The studies were powered based on a within-subject coefficient of variation of 45% for simvastatin and 41% for rosuvastatin, assuming an increase of approximately 20% in the coefficient of variation observed in healthy subjects. No change in exposure for simvastatin and rosuvastatin when given with osimertinib was assumed. It was estimated that 40 and 34 patients would be needed to ensure evaluation for PK analysis in the CYP3A and BCRP studies, respectively. These sample sizes were expected to provide 90% power for the 90% CIs for both AUC and C_{max} ratios to be within 70% to 143%. The relevant no-effect boundary was determined based on the high variability of simvastatin and rosuvastatin. Also, with the exposure response of simvastatin and rosuvastatin, a change of 0.7 to 1.43 fold is unlikely to alter its benefit risk and hence, this margin was used [21].

Participants

Adult patients with a histological or cytological confirmed diagnosis of EGFRm NSCLC, and radiological confirmation of disease progression during previous continuous treatment with an EGFR-TKI, were enrolled. Inclusion criteria included local confirmation that tumours harboured an EGFR mutation known to be associated with EGFR-TKI sensitivity, an Eastern Cooperative Oncology Group performance status 0–1 with no deterioration over the previous 2 weeks, and a life expectancy of ≥12 weeks as estimated at the time of screening.

Exclusion criteria included inadequate bone marrow reserve or organ function and unresolved toxicities from any prior therapy exceeding CTCAE Grade 1. In both studies, patients were required to avoid any food/drugs with known CYP3A inducer/inhibitor effects; if patients were taking CYP3A inhibitors/inducers, a sufficient wash out was required before enrolment. Based on the prescribing information of simvastatin and rosuvastatin, patients treated with concomitant medications likely to cause PK interaction, or another statin, were excluded. The BCRP study was limited to patients of non-Asian ethnicity to avoid BCRP polymorphism [17,22]. Intake of Seville oranges or grapefruits was prohibited in both studies as these act as potent inhibitors of CYP3A [23].

Objectives

The primary objective of both studies was to assess the exposure (AUC and C_{max}) of simvastatin or rosuvastatin when administered as a single dose alone and in combination with osimertinib. Secondary objectives were to assess the PK of simvastatin (and simvastatin acid) and rosuvastatin, respectively, when administered as a single dose alone and in combination with osimertinib, and to assess the PK of osimertinib (and metabolites) when administered in combination with simvastatin and rosuvastatin, respectively. Safety and tolerability of osimertinib alone and in combination with simvastatin and rosuvastatin, respectively, were also evaluated. The potential for osimertinib to induce CYP3A through changes in post-dose to pre-dose ratios for 4BHC concentration was assessed as an exploratory objective.

Statistical methods

The PK analysis set was defined as dosed patients with at least one quantifiable plasma concentration collected post-dose without any important deviations or events that could alter the evaluation of the PK. Important deviations or events included dosing deviations, vomiting following oral dosing, and administration of or changes in concomitant medications thought to affect simvastatin or rosuvastatin PK. With respect to osimertinib, any deviations or events

resulting in osimertinib AUC_{τ} (AUC during the dosing interval) falling below the 10th percentile of exposure of the overall patient population resulted in exclusion of the patients' simvastatin or rosuvastatin PK data from the analyses.

To evaluate the effect of osimertinib on simvastatin, simvastatin acid or rosuvastatin exposure, natural log-transformed AUC (and AUC from zero to the last quantifiable concentration at time "t" [AUC_{0-t}]) and C_{max}, were compared between treatments using a mixed effects analysis of variance, with treatment as a fixed effect and patient as a random effect. The mean differences and the CIs were back transformed to the original scale in order to give estimates of the geometric mean ratios ([osimertinib + simvastatin/rosuvastatin] vs simvastatin/rosuvastatin alone) and the associated 90% CIs. No effect on the PK of simvastatin/rosuvastatin after co-administration of osimertinib was concluded if the 2-sided 90% CIs for the ratios of simvastatin/rosuvastatin AUC (or AUC_{0-t}) and C_{max} were within the range of 70% to 143%. For simvastatin/rosuvastatin and simvastatin acid, analyses of time to maximum concentration (t_{max}) were performed using the Wilcoxon Signed Rank Test. The Hodges-Lehman median estimator of the difference in treatments ([osimertinib + simvastatin/rosuvastatin] – simvastatin/rosuvastatin alone) and 90% CIs are presented.

The safety analysis set included all patients who received at least one dose of osimertinib or either statin. Safety assessments in both studies included AE reporting graded by CTCAE v4.0, physical examination, vital signs, electrocardiogram, ophthalmic examination, clinical chemistry, coagulation, hematology, and urinalysis. For additional information, see the supplementary appendix.

Bioanalysis

Samples for the determination of simvastatin, simvastatin acid, rosuvastatin, 4BHC, and osimertinib and its metabolites (AZ5104 and AZ7550) in plasma were analysed by Covance Laboratories at their sites globally using validated bioanalytical methods. Simvastatin, simvastatin acid, and 4BHC were detected in plasma containing K_2EDTA using high

performance liquid chromatography (HPLC) followed by tandem mass spectrometric (MS/MS) detection. Rosuvastatin was detected in plasma containing lithium heparin using supported-liquid extraction, and analysed using HPLC- MS/MS. Calibration, quality control and clinical study samples (40 µL) were spiked with (^{13}C, $^{2}H_3$) osimertinib as an internal standard, processed by protein precipitation and then simultaneously assayed for osimertinib, AZ5104 and AZ7550 using reversed-phase HPLC with Turbo Ion Spray® MS/MS. Drug-to-internal standard peak area ratios for the standards were used to create a calibration curve using $1/x^2$ weighted least-squares regression analysis. Concentrations of each analyte were quantified by comparing ratios in trial samples with the relevant calibration curve. During validation of all assays, no analytically significant interferences from endogenous matrix components were observed. All methods demonstrated acceptable selectivity with mean normalised matrix factors of 1.00 ± 0.08 observed at the concentrations tested. The lower limit of quantification of the method was 16 nM for osimertinib, 1.65 nM for AZ5104 and AZ7550, 0.04 ng/mL for rosuvastatin, 0.05 ng/mL for simvastatin and simvastatin acid and 4 ng/mL for 4BHC. Accuracy ranged from 93% to 112% and precision from 2.5% to 10.1% for all analytes in both studies.

PK parameters for plasma osimertinib, AZ5104, AZ7550, simvastatin, simvastatin acid and rosuvastatin non-compartmental methods were calculated and summarised with Phoenix® WinNonlin® Version 6.4, (Pharsight Corp., A Certara Company, Princeton, New Jersey, USA). PK and safety summaries, as well as the inferential analyses for simvastatin/rosuvastatin and simvastatin acid, were performed by IQVIA using SAS® Version 9.2 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

In vitro studies

In human liver microsomes, only CYP3A4/5 using nifedipine as the substrate showed inhibition at less than 25 uM (IC50 = 5.1 uM with nifedipine as substrate and >25 uM for midazolam as substrate). Osimertinib is not an inhibitor (IC50 > 30 uM) for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1. No time dependent inhibition was observed for any of the enzymes.

No induction in mRNA or activity was observed for CYP2B6 and up to 16% of positive control for CYP1A2 was observed. A concentration dependent maximal induction of up to 173-fold (89% of positive control) in one lot and 4.9 fold (45% of positive control) in the other two lots in mRNA and activity was observed for CYP3A4/5.

For transporter inhibition, the inhibition values and the potential for interaction are shown in Supplementary Table 1. The results indicate that BCRP inhibition (mostly via intestinal) inhibition is likely. Based on *in vitro* data, osimertinib is not likely to be a clinically relevant inhibitor of Pgp, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 and MATE2K transporters.

Patients

In the CYP3A study, 57 patients were enrolled across 17 centres in Asia, North America and Western Europe. Of these patients, 52 were assigned to and received treatment, of whom 49 were included in the PK analysis set. Of the three patients excluded from PK analyses, two were excluded as their clinical imaging showed excessive hepatic metastases which was significantly reduced after 4 weeks of treatment with osimertinib, which likely confounds the DDI results, and one was excluded due to changes in concomitant medication (a CYP3A4 inducer) dosing during the treatment period. In the BCRP study, 55 patients were enrolled from 13 centers across Western Europe and North America (no Asian patients in the BCRP study). Of these, 44 patients were assigned to and received treatment, all of whom were included in the PK analysis set. Baseline

demographics, disease characteristics and allowed concomitant medications are shown in Table 1.

CYP3A study: simvastatin PK

Geometric mean plasma concentrations of simvastatin are shown in Figure 1. Geometric mean simvastatin concentrations were slightly lower following co-administration of osimertinib over the initial 4 hours while the terminal concentrations appeared to exhibit a similar decline. The simvastatin acid profiles were similar to each other following administration of simvastatin alone and simvastatin with osimertinib throughout the time course. With rosuvastatin, the concentrations were higher for the first 24 hours, following administration of osimertinib and rosuvastatin, compared with rosuvastatin alone. After 24 hours, both rosuvastatin concentrations appeared to exhibit a similar decline. Administration of osimertinib with simvastatin decreased the area under the plasma concentration–time curve from zero to infinity (AUC) for simvastatin by approximately 9%, and the maximum plasma concentration (C_{max}) by approximately 23%, compared with administration of simvastatin alone (Table 2). Table 2 shows that exposure of simvastatin acid relative to simvastatin was similar across treatments, based on arithmetic mean metabolite-to-parent ratios (MR) for AUC and C_{max}. Individual and geometric mean AUCs of simvastatin and simvastatin acid alone, versus in combination with osimertinib are shown in Figure S.1, supplementary appendix.

The geometric least squares mean (GLSM) ratios of evaluable patients receiving simvastatin plus osimertinib to simvastatin alone for AUC and C_{max} are shown in Table 3: the 90% CI of GLSM ratio for AUC was entirely contained within the no relevant effect limits of 70% to 143%, but the reduction seen for C_{max} was not entirely contained within these limits. No effect of osimertinib on AUC or C_{max} of simvastatin acid was observed.

Osimertinib did not affect the time to maximum concentration (t_{max}) or the half-life of simvastatin or simvastatin acid (Table 3). The mean apparent plasma clearance (CL/F) was slightly higher with osimertinib and simvastatin versus simvastatin alone (Table 2).

BCRP study: rosuvastatin PK

Geometric mean rosuvastatin plasma concentration–time profiles are shown by treatment in Figure 1. AUC, AUC_{0-t} and C_{max} of rosuvastatin were higher with osimertinib and rosuvastatin versus rosuvastatin alone (Table 2). Individual and geometric mean AUCs of rosuvastatin alone versus in combination with osimertinib are shown in Figure S.2, supplementary appendix. GLSM ratios of rosuvastatin plus osimertinib to rosuvastatin alone for AUC and C_{max} were 135% (115–157) and 172% (146–203), respectively (Table 3). The 90% CIs of the GLSM ratios for these parameters were not contained within the predefined no relevant effect range of 70% to 143%. Co-administration of osimertinib had no effect on rosuvastatin t_{max} (Table 3). The half-life of rosuvastatin was similar: 19.8 h when given with osimertinib versus 19.5 h with rosuvastatin alone.

CL/F and volume of distribution (Vz/F) were both lower with rosuvastatin plus osimertinib compared with rosuvastatin alone as shown in Table 2.

Osimertinib and metabolites PK

PK parameters for osimertinib and the metabolites AZ5104 and AZ7550 after 29 days of dosing are shown in Table 4. In both studies, visual observations indicated that steady state was attained for osimertinib and its metabolites at the time of Period 3 evaluation of PK interaction. Across the two studies, the metabolite-to-parent ratio for AUC during the dosing interval ($MRAUC_{\tau}$) and MRC_{max} for AZ5104 and AZ7550 were approximately 10% of osimertinib.

4β-hydroxy-cholesterol

Following multiple doses of osimertinib, plasma concentrations of 4BHC increased by approximately 10% relative to baseline (Day 1 pre-dose) in the CYP3A study and approximately 15% in the BCRP study, following 4 weeks of osimertinib dosing. Geometric mean (90% CI) post/pre-dose 4BHC concentration ratios were 1.139 (1.10, 1.22) and 1.087 (1.04, 1.19) on Day 24 and Day 31 in the CYP3A study, and 1.147 (1.08, 1.22) and 1.153 (1.08, 1.23) on Day 25 and Day 32 in the BCRP study.

Safety

Mean (standard deviation) total treatment duration of osimertinib in the CYP3A study was 29.3 (2.93) days, with a median of 30.0 days (range 14 to 35 days). In the BCRP study, mean total treatment duration of osimertinib was 27.4 (3.77) days, with a median of 26.0 days (range 22 to 47 days); mean of 4.2 (1.78) days for Period 3 (osimertinib plus rosuvastatin). The actual treatment duration (excluding dose interruptions) was similar to total treatment duration in both studies.

The number and percentage of patients with an adverse event (AE) in any category during Part A (see Methods) is summarised in Table 5. Across treatment periods, 44 patients (85%) in the CYP3A study and 40 patients (91%) in the BCRP study, experienced AEs. Of the all causality AEs in both studies, the majority were mild or moderate in severity; three (6%) and seven (16%) reported Grade ≥3 AEs in the CYP3A and BCRP studies respectively, none of which were considered related to study treatment. There were no possibly causally related AEs leading to death or discontinuation of osimertinib, simvastatin or rosuvastatin. Two patients died due to disease progression in the BCRP study.

The most common all causality AEs in the CYP3A study they were dry skin (grouped term, 11 patients [21%]), rashes and acnes (grouped term, 10 patients [19%]) and diarrhea (eight patients [15%]). In the BCRP study they were dyspnoea (11 patients [25%]), decreased appetite and diarrhea (nine patients [20%] each). In the CYP3A study there was

one AE of a cardiac event: a non-serious, Grade 1 event of electrocardiogram QT prolonged that was considered possibly causally related to osimertinib by the investigator. There were no cases of interstitial lung disease reported in either study.

More details on patient safety can be found in the Supplementary Appendix.

Discussion

Based on *in vitro* data, osimertinib was shown to have potential to be an inhibitor and inducer of CYP3A and an inhibitor of intestinal BCRP transport. Hence, we evaluated the impact of osimertinib on the PK of simvastatin, a sensitive CYP3A substrate, and rosuvastatin, a BCRP substrate, in patients with EGFRm NSCLC following progression on an EGFR-TKI. For further details of the *in vitro* data see the supplementary appendix. Baseline demographics in both studies were consistent with other osimertinib clinical trials, except with regard to race in the BCRP study [14,24,25].

Simvastatin is particularly sensitive to CYP3A inhibition due to high first-pass metabolism, leading to very low bioavailability [26]. Simvastatin was chosen as the sensitive substrate in the CYP3A, rather than midazolam, as the study was performed in patients who would be at risk of impaired respiratory function if treated with midazolam [27]. Moreover, the common use of simvastatin in the NSCLC patient population, makes the use of simvastatin a more relevant substrate to study the CYP3A interaction potential of osimertinib. In this study, a small decrease in C_{max} of simvastatin and no effect on the AUC of simvastatin, or on the AUC and C_{max} of simvastatin acid (all within the pre-defined limits) when dosed with osimertinib was observed. Although the decrease in C_{max} was not within the pre-defined no relevant effect limits, the changes in C_{max} are unlikely to be of clinical relevance as AUC is considered the PK parameter of interest for efficacy of most compounds. Simvastatin acid, which is also formed predominately via CYP3A in the liver, showed no effect after osimertinib treatment; therefore, no clinically meaningful impact on CYP3A substrate

exposure is expected when co-dosed with osimertinib. This lack of change in the PK of simvastatin and simvastatin acid suggests that there is a lack of effect on CYP3A by osimertinib. As bioavailability of simvastatin is so low (5%), in comparison to other statins that utilise the CYP3A pathway (such as atorvastatin, bioavailability: 12%), it is probable that other statins that use this pathway are less likely to have any clinically meaningful impact when co-dosed with osimertinib [26].

In the BCRP study, rosuvastatin was chosen as the BCRP substrate as it is another statin that is likely to be co-administered with osimertinib. Rosuvastatin is eliminated mostly through an efflux-mediated process in the gut and in the bile (minimal elimination via metabolism). This study showed an effect on the exposure of rosuvastatin after co-administration with osimertinib; AUC of rosuvastatin was increased by approximately 35% and C_{max} by approximately 72%, compared with the administration of rosuvastatin alone; the 90% CIs of AUC and C_{max} were not contained within the predefined range. These changes are likely due to inhibition of BCRP-mediated efflux by osimertinib during the first pass (osimertinib is not an inhibitor of OATP1B1 or OATP1B3 and does not cause any clinically relevant DDI via this pathway) [15,28]. Based on our results, the inhibition of BCRP by osimertinib most likely occurs in the absorption/distribution phase, as opposed to the elimination phase. As BCRP is found in both efflux from the blood to the intestines and efflux from the liver to bile ducts to the intestines,[29] and rosuvastatin is largely eliminated by faeces;[30] it is likely that osimertinib-mediated BCRP inhibition increased rosuvastatin absorption by both blocking efflux into bile, which allowed recirculation into blood, and blocking efflux from blood back to intestines. This leads to a notable extension of time taken for rosuvastatin to be eliminated through efflux into the gut and, thereby, an increased absorption and/or slower elimination due to reduced efflux by the intestinal mucosa. Though Vz/F was lower with rosuvastatin co-administration, compared with rosuvastatin alone, there was no difference in the half-life of rosuvastatin with and without osimertinib, suggesting that any inhibition of the elimination of the circulating rosuvastatin levels by osimertinib (after first

pass) is negligible. The decrease in Vz/F is likely a byproduct of non-compartmental analysis, where because AUC was greater, CL was lower, and thus so too was Vz/F (due to the elimination rate being similar with and without osimertinib); therefore, this result should be interpreted with caution. These small (<2-fold) changes to the PK of rosuvastatin suggest that osimertinib acts as a weak inhibitor of BCRP transporter.

4BHC levels were measured in an exploratory capacity in order to gauge the induction potential of osimertinib on CYP3A. In both studies, an increase in 4BHC levels of 10–15% relative to baseline following 28 days of osimertinib administration was observed. As 4BHC is the product of a CYP3A-catalysed reaction, plasma concentrations of 4BHC are expected to increase when CYP3A induction occurs [31]. However, it is important to note that 4BHC has a half-life of approximately 17 days and the length of dosing in these studies was 4 weeks, compared with a dosing period of around 2 weeks in similar studies [32,33]. Even with a longer dosing duration, this increase was not deemed to be clinically significant and the data reported here suggest a low potential for CYP3A induction.

The exclusion of two patients from the CYP3A study's PK analysis was due to their PK results. Both had higher (~10 fold) simvastatin exposure in Period 1 (simvastatin alone) compared with all other patients dosed in that period and computed tomography scans prior to study entry indicated significant tumour burden in the liver. By week 6 of the study, there were reductions of approximately 50% and 80% in liver metastases from baseline and the patients returned to within normal simvastatin exposure ranges. It is possible that treatment with osimertinib reduced this tumour burden. A limitation of this study was that due to its fixed sequence design, patients could have clinically improved during the intervening period between the two doses of simvastatin and efficacy determination was not an objective in this study. Therefore, liver function could have been slightly different between the doses as occurred with the two patients discussed here.

In the CYP3A study, steady-state exposures observed for osimertinib and its metabolites were similar to those observed in other osimertinib clinical trials [20]. Slightly

higher mean exposures were observed in the BCRP study, but were within the expected exposures of osimertinib across clinical studies; however, overall PK parameter ranges and geometric mean metabolite-to-parent ratios for the metabolites (approximately 10%) were similar to other clinical trials [20]. The higher exposure of osimertinib in the BCRP study may have resulted in increased inhibition of BCRP, potentially presenting an overestimation of the DDI between the two drugs. The numbers of AEs reported here were lower, the majority of AEs were mild or moderate and similar to those reported in the AURA studies [14,25,34]. Overall, in both studies, osimertinib was well tolerated in patients with EGFRm-positive NSCLC whose disease had progressed during treatment with an EGFR-TKI and for whom no new safety concerns were identified.

In conclusion, as osimertinib neither strongly induces nor strongly inhibits CYP3A to a clinically relevant extent, PK-mediated interactions are unlikely and hence, osimertinib can be used concomitantly with CYP3A substrates. Osimertinib had a minor (<2-fold change) inhibitory effect on rosuvastatin exposure; therefore, caution is recommended when using osimertinib with sensitive BCRP substrates with a narrow therapeutic index.

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Conflict of interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: J. Vansteenkiste reports honoraria for AstraZeneca, during the conduct of the study. P. A. Dickinson is a former employee of, and shareholder in; AstraZeneca; his current organisation provides services to AstraZeneca. K. Bui and K. Thomas declare contract work for AstraZeneca. D. Weilert is an employee of IQVIA, Clinical Research Organization, which was contracted to execute the two studies on behalf of AstraZeneca. K. So and K. Vishwanathan are employees of, and shareholders in AstraZeneca. The other authors have nothing to disclose.

Author contributions

P.A.D., R.D.H., N.I., N.R.A., K.S., K.T., J.V., and K.V. wrote the manuscript.

P.A.D., R.D.H., K.S., K.T., K.V., and D.W. designed the research.

T.A., R.D.H., N.I., J.-S.L., N.R.A., J.V., and K.V. performed the research.

T.A., K.B., R.D.H., K.S., K.T., K.V., and D.W. analyzed the data.

K.V. contributed new reagents/analytical tools.

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Figure legend

Figure 1: Geometric mean plasma concentration (ng/mL) vs time by treatment [semi-log scale] (pharmacokinetic analysis set). **A,** simvastatin. **B,** simvastatin acid. **C**, rosuvastatin