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Pharmacokinetic boosting of osimertinib with cobicistat in patients with non-small cell lung cancer: The OSIBOOST trial

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ABSTRACT

Introduction: Exposure to osimertinib, a third generation epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI) for treatment of non-small cell lung cancer (NSCLC) and a sensitizing *EGFR* mutation, can be substantially below average. We evaluated whether plasma levels could be boosted by co-administration of cobicistat, a strong Cytochrome P450 3A-inhibitor.

Methods: This was a pharmacokinetic, proof-of-concept clinical trial (the OSIBOOST trial, NCT03858491). NSCLC-patients with osimertinib were eligible if their steady state osimertinib plasma trough concentration was low (≤195 ng/mL). On day 1, the area under the plasma curve ($AUC_{0\text{-}24,ss}$) of osimertinib and its metabolite (AZ5104) was calculated using a limited sampling strategy (four samples). Cobicistat co-treatment (150 mg, once daily) was started on day 2. Between day 22–26, a second AUC was determined. Cobicistat dose could be escalated if the osimertinib trough concentration was still ≤ 195 ng/mL, in the absence of toxicity. Primary endpoint was the increase in osimertinib exposure, secondary endpoint was toxicity. Cobicistat could be continued during the expanded access phase, with follow-up (2–4 months) of the boosting effect.

Results: The mean baseline osimertinib trough concentration for the eleven enrolled patients was 154 ng/mL. In all patients, cobicistat addition led to an increase in osimertinib exposure. Mean increase in total $AUC_{0\text{-}24ss}$ (AUC osimertinib + AUC AZ5104) was 60%, (range 19%–192%). The boosting effect was consistent over time. No grade ≥ 2 toxicity was observed.

Conclusion: Pharmacokinetic boosting of osimertinib with cobicistat in patients with NSCLC is feasible without increasing toxicity, although the degree of boosting is variable.

1. Introduction

Approximately 10% of Caucasian patients, with adenocarcinoma of the lung, have a sensitizing epidermal growth factor receptor (*EGFR*) mutation [1]. Targeted therapy, especially tyrosine kinase inhibitors (TKIs), have revolutionized the treatment outcome of patients with oncogene addicted non-small cell lung cancer (NSCLC), with unprecedented 5-year overall survival (OS) of 40%–60% [2]. Osimertinib, a third generation EGFR-TKI, recommended at a flat dose of 80 mg once daily (QD), is used in *EGFR* mutation positive NSCLC-patients, both as first line treatment in patients with metastatic disease as well as in the adjuvant setting [3–5].

In clinical practice, therapeutic drug monitoring (TDM) can be used to monitor the exposure to increase efficacy or limit toxicity of treatment. For osimertinib, a correlation has been observed between area under the plasma concentration–time curve ($AUC_{0\text{-}24,ss}$) and the occurrence of rash or diarrhea [6]. However, no relation was observed between systemic exposure and efficacy outcomes, although large

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variation was observed in osimertinib $AUC_{0\text{-}24,ss}$ and the maximal concentration ($C_{max,ss}$) after multiple dosing [6–9].

Although central nervous system (CNS) penetration of osimertinib is good, increasing osimertinib exposure, especially in patients with subaverage blood levels, could theoretically further improve responsiveness of metastases in the CNS, which is a common metastatic site in *EGFR*-mutated NSCLC [10,11]. Increasing the osimertinib exposure can be achieved by doubling the daily dose [9], but this is expensive. Because osimertinib is mainly metabolized by Cytochrome P450 3A (CYP3A), co-administration with a strong CYP3A-inhibitor could potentially be an affordable method to increase osimertinib exposure [12]. Previous research demonstrated that co-administration of osimertinib with itraconazole caused a 24% increase in osimertinib $AUC_{0\text{-}24,ss}$ [13]. However, itraconazole is not the most potent CYP3A-inhibitor available [14,15] and has additional pharmacological properties and therefore off-target effects. Cobicistat is a strong CYP3A inhibitor, lacks off target effects and has previously been studied extensively as booster for antiretroviral therapies [16,17]. Given its highly potent CYP3A inhibiting property and favorable safety profile, cobicistat may be an excellent candidate drug to use as booster in the oncology setting as well. Until now, the experience with cobicistat in the oncology setting is extremely limited [18,19]. Although one study evaluated a similar approach with ritonavir in erlotinib patients [20], the boosting capacity of cobicistat on osimertinib exposure is unknown.

Therefore, in this pharmacokinetic, proof-of-concept study (OSIBOOST trial), we evaluated if, and to what extent, cobicistat could increase osimertinib exposure, and whether the boosting effect was stable over time.

2. Methods

2.1. Patients

Patient eligibility criteria included a) using osimertinib as part of their regular treatment plan, without any signs of progression or if treatment beyond progression was deemed appropriate by the treating physician because of continuing clinical benefit; b) 18 years or older; c) World Health Organization (WHO) performance status (PS) of 2 or lower; d) able and willing to sign informed consent; e) able and willing to undergo whole blood sampling for pharmacokinetic analysis and f) steady state plasma trough concentration ($C_{min,ss}$) of osimertinib $\leq$ 195 ng/mL. The plasma trough concentration of osimertinib was determined previously during routine care before study participation. The threshold $C_{min,ss}$ was selected based on the population mean observed in the two participating centers, which was 224 ng/mL (data not published). Exclusion criteria were: a) concurrent use of a drug that is known to strongly inhibit or induce CYP3A4/CYP3A5 (see appendix A for specific drugs); b) concurrent use of a drug that is metabolized by CYP3A4/CYP3A5 and has a small therapeutic window (see appendix A for specific drugs; c) concurrent use of products that are known to influence CYP3A4/CYP3A5-activity (e.g. grapefruit(juice), St. John's wort); d) impairment of gastrointestinal function that may alter absorption of osimertinib or cobicistat (ulcerative disease, uncontrolled nausea of vomiting, malabsorption syndrome or small bowel resection); e) pregnancy or breast feeding and f) chronic liver disease, with a Child-Pugh score class C.

2.2. Trial design

This was a pharmacokinetic, proof-of-concept study in two comprehensive cancer centers in the Netherlands, Maastricht University Medical Centre (MUMC +) and the Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital (NKI/AVL) (the OSIBOOST trial).

In this study, cobicistat was selected as CYP3A-inhibitor, given its high potency, lack of off-target effects, and based on the wide experience with cobicistat as boosting agent for antiretroviral therapies.

Patients were asked to visit the hospital twice for pharmacokinetic (PK) blood sampling. The second PK visit was scheduled 22–26 days after the first PK visit. Cobicistat use started the day after the first PK visit and continued up to and including the day of the second PK visit. After the second PK day, patients a) could opt to stop cobicistat treatment, b) could continue cobicistat treatment on expanded access basis if substantial boosting was observed and the treating physician approved continuation after shared decision making with the participant or c) were asked to participate in a subsequent part of the study, in which the cobicistat dose was escalated in a stepwise manner to 150 mg, twice daily (BID) or four times a day (QID). Dose escalation of cobicistat was solely performed in patients who still had an osimertinib plasma trough concentration $\leq$ 195 ng/mL on the second PK-visit and if the previous cobicistat dose did not cause additional toxicity. An overview of the design of the study is schematically shown in Fig. B1 in appendix B.

The study was conducted in accordance Good Clinical Practice guidance. The study protocol (NCT03858491 / EudraCT number 2018–004290-28) was reviewed and approved by an independent ethics committee (METC19-013). This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw).

2.3. Procedures

On both PK days, blood samples were collected on pre-specified time points, which were used to plot the plasma concentration–time curve of osimertinib to calculate the $AUC_{0\text{-}24,ss}$. EDTA whole blood samples were collected for pharmacokinetic analysis at four different time points: predose, 0.5–1.5 h post-dose, 2.5–3.5 h post-dose and 7–8 h post-dose, which were similar to the moments used in the phase II and III AURA registration studies of osimertinib. Blood samples drawn for osimertinib measurement were transported and processed immediately, as the stability of osimertinib in blood (plasma) at room temperature is limited [15]. Osimertinib and metabolite AZ5104 concentrations were determined in a pharmaceutical laboratory in the MUMC+, using a previously described and validated assay [21]. In addition, an electrocardiogram was evaluated, as well as hematology, renal and liver function tests (sampled pre-dose).

2.4. Outcomes

The primary outcome was the change in total $AUC_{0\text{-}24,ss}$ for osimertinib and AZ5104. AZ5104 was incorporated in the pharmacokinetic analyses, as it was shown to be potent against mutated *EGFR in vitro* [9]. However, it is complex to estimate the exact contribution of AZ5104 to the *in vivo* antitumor effect. Therefore we pragmatically decided to weigh the $AUC_{0\text{-}24,ss}$ of AZ5104 similar to the $AUC_{0\text{-}24,ss}$ of osimertinib and calculate a total $AUC_{0\text{-}24,ss}$ (osimertinib + AZ5104). The AUC constructed for the first PK day was used as baseline, and change was calculated as: (AUC_{SECOND}–AUC_{FIRST}) / AUC_{FIRST}. Secondary outcomes included information on CYP3A4 and CYP3A5 genotype, adverse events (AEs, registered according to CTCAE v5.0 [22]) and osimertinib plasma trough concentration(s) after study participation (in patients that continued cobicistat) as a surrogate marker of $AUC_{0\text{-}24,ss}$ 2–4 months after study participation to evaluate whether the effect of cobicistat lasted and was consistent with results seen on the second PK day. For CYP3A4 genotype several alleles were evaluated: *1A, *1B, *1G, *6, *8, *11, *13, *16, *17, *18, *20, *22 and *26. Furthermore, for CYP3A5 alleles *1 - *7 were evaluated.

2.5. Pharmacokinetic and statistical analysis

For the $AUC_{0\text{-}24,ss}$ curve we assumed that the concentration of osimertinib 24 h after the intake of osimertinib was similar to the concentration measured immediately pre-dose. The $AUC_{0\text{-}24,ss}$ was estimated using the trapezoidal method [23]. Results are shown in percentages, concentrations or presented descriptively. As this was a

pharmacokinetic, proof-of-concept study, no formal statistical tests were performed.

3. Results

3.1. Patients

In total 11 patients were enrolled, with a mean age of 67.4 years. Four patients were male, and one patient was a current smoker. All patients had WHO PS 0–1. Five patients had exon 19 deletion as primary *EGFR*-mutation, four exon 21 L858R, and two an uncommon *EGFR*-mutation. Furthermore, the T790M mutation was identified in nine patients. One patient was regularly treated in the first line with osimertinib, and ten patients in a later treatment line. Ten patients were treated with 80 mg once daily, while one patient received 160 mg daily, but still had a plasma trough concentration < 195 ng/mL.

3.2. Pharmacokinetic analyses

The mean baseline osimertinib $C_{min,ss}$ was 154 ng/mL, which was measured during steady state for all patients, during the screening phase before study participation. The mean duration between the start of osimertinib and the first plasma trough concentration measurement was 64 days (range: 15–224 days). During the intervention period, all patients experienced an increase in osimertinib + AZ5104 exposure. The mean total $AUC_{0\text{-}24,ss}$ increase was 60% (range 19%–192%), which seemed to be larger in women (73%; range 19%–192%) as compared to men (38%; range 21%–52%), with one patient experiencing a considerably large increase in osimertinib exposure of 192% (see Fig. C4).

The increase in total $AUC_{0\text{-}24,ss}$ was mainly driven by an increase of the osimertinib $AUC_{0\text{-}24,ss}$, as the absolute $AUC_{0\text{-}24,ss}$ of AZ5104 remained similar, while the $AUC_{0\text{-}24,ss}$ of osimertinib increased after co-administration of cobicistat (Fig. 1). Among all patients, no major deviations in treatment compliance were observed, and no interfering CYP3A-treatments were started during the study period.

After co-administration with cobicistat, three patients had osimertinib plasma trough levels that were still below 195 ng/mL. Therefore, the cobicistat dose was escalated to 150 mg BID in these patients. One patient experienced a decrease in osimertinib exposure upon escalation to cobicistat 150 mg, BID, compared to cobicistat 150 mg, QD (+52% [QD] to + 39% [BID]), relative to osimertinib baseline exposure. The other two patients experienced an increase in osimertinib exposure (+21% [QD] to + 27% [BID], and + 35% [QD] to + 55% [BID], respectively, relative to baseline). The dosing frequency of cobicistat was further increased in one patient that experienced a decrease in osimertinib exposure. The exposure of osimertinib further decreased with cobicistat 150 mg, QID (+1%, relative to baseline exposure). In general, trough values ($C_{min,ss}$) of osimertinib correlated well with the total $AUC_{0\text{-}24,ss}$ ($R^2 = 0.926$), which is shown in Fig. D1 in appendix D.

3.3. Pharmacogenetics

Information about CYP3A4/CYP3A5 genotype was available for 7/11 patients. The evaluation of pharmacogenetics was done after study participation (informed consent was obtained in concordance with an approved amendment to the original trial protocol) and some patients were unable to supply an additional blood sample because they were meanwhile treated in another hospital or were lost to follow-up. Six patients carried the CYP3A4*1B/*1B variant, and one patient had the CYP3A4*1B/*1G polymorphism. Therefore, all patients were extensive CYP3A4 metabolizers. Furthermore, all seven patients were CYP3A5 non-expressers (CYP3A5*3/*3 in six patients, and CYP3A5*2/*3 in one patient). Both the extensive CYP3A4 metabolizer phenotype and the CYP3A5 non-expressor phenotype are the most frequently (>85–90%) found phenotypes in Caucasians. For these seven patients, genetic polymorphisms could therefore not explain any variation seen in osimertinib exposure and the total boosting effect of cobicistat.

3.4. Safety

No serious or unexpected AEs were observed. All reported AEs (n = 20) were of grade 1, of which 14 AEs were potentially related to osimertinib (ten = possible, one = probable, three = related) (see Table 1).

3.5. Follow-up after study

In total, nine patients opted to continue cobicistat after the study intervention period, and six patients were willing to give one or two additional blood sample(s) during the expanded access phase. The measured plasma trough concentrations were extrapolated to an AUC, based on the correlation between $C_{min,ss}$ and $AUC_{0\text{-}24,ss}$ seen at the two study PK visits. In five patients, the extrapolated AUC was comparable (mean difference = 21%) to the total $AUC_{0\text{-}24,ss}$ seen on the last study visit. However, in one patient, a considerable increase in the plasma trough concentration, and consequently the extrapolated AUC, was noticed (increase = 376%). This could not be explained by adjustments

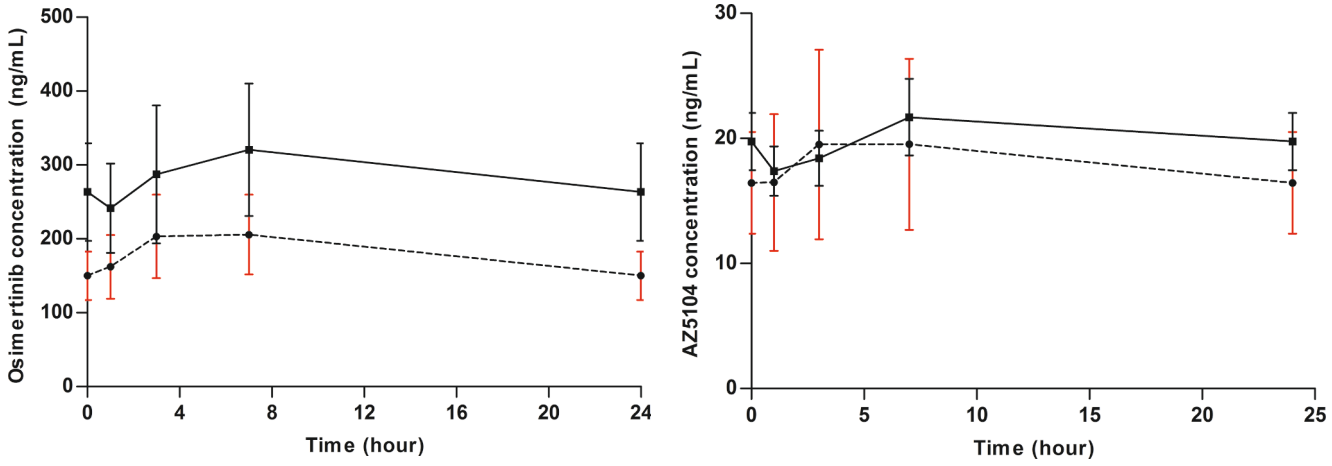

Fig. 1. Mean plasma concentrations (n = 11) for osimertinib and AZ5104 on both PK days. Legend: mean plasma concentration of osimertinib on PK day I (dotted line) and PK day II (solid line), with variation shown in red and black, respectively (left) and mean plasma concentration of AZ5104 on PK day I (solid line) and PK day II (dotted line), with variation shown in red and black, respectively (right). PK day I represents baseline osimertinib exposure during steady state, and PK day II reflects the osimertinib exposure at the end of the intervention period; i.e. osimertinib in the presence of cobicistat addition. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Baseline characteristics and boosting of osimertinib exposure in patients simultaneously treated with cobicistat (150 mg, QD) for osimertinib AUC alone and the total AUC (osimertinib plus AZ5104) during steady state.

Patient	Sex	Primary EGFR-mutation	T790M	Previous EGFR-TKI treatment	Baseline trough concentration (ng/mL)	Boost $AUC_{0\text{-}24,ss}$ - osimertinib	Boost $AUC_{0\text{-}24,ss}$ – total
#1	Female	Exon 19 deletion	Yes	Erlotinib	219	22%	19%
#2	Male	L858R	Yes	Erlotinib	151	21%	21%
#3	Male	Exon 19 deletion	Yes	Erlotinib	134	39%	35%
#4	Female	L858R	No	Erlotinib	118	37%	35%
#5	Male	L858R	Yes	Erlotinib	162	50%	44%
#6	Female	Exon 19 deletion	Yes	Erlotinib Gefitinib	185	50%	46%
#7	Male	Exon 19 deletion	Yes	Erlotinib	107	56%	52%
#8	Female	Other	Yes	–	150	77%	68%
#9	Female	Exon 19 deletion	No	Gefitinib	156	77%	75%
#10	Female	L858R	Yes	Erlotinib	155	77%	76%
#11	Female	Other	Yes	Afatinib	114	215%	192%

Abbreviations: EGFR = epidermal growth factor receptor, TKI = tyrosine kinase inhibitor, ng = nanogram, mL = millilitre, AUC = area-under-the-curve, 0–24, ss = from 0 to 24 h during steady state.

in co-medication or changes in treatment adherence. As no possibly osimertinib-related AEs were reported for this patient it was decided to continue simultaneous treatment with osimertinib and cobicistat.

4. Discussion

In this study, the boosting capacity of cobicistat on osimertinib exposure was evaluated in patients with NSCLC who had a low osimertinib plasma trough concentration, i.e. ≤ 195 ng/mL. In all patients, treatment with cobicistat led to an increase in the total $AUC_{0\text{-}24,ss}$ of osimertinib + AZ5104, without adding significant toxicity. The increase in osimertinib exposure was stable in general, even after long-term continuation of osimertinib plus cobicistat 150 mg QD, in most patients. Furthermore, a large increase in osimertinib exposure in one patient was noticed during the study (+192%) period and in one patient during the follow-up (+376%, after extrapolation of the plasma trough concentration. Potential causes for interpatient differences in osimertinib boosting including CYP3A-genotypes and changes in co-medication were excluded. We were unable to find a plausible explanation for these large increases, and decided to continue treatment as long as the combination treatment was well tolerated. Both patients continued cobicistat addition to osimertinib for at least six months, after study participation, without any safety concerns.

Dose escalation of cobicistat (to 150 mg BID or QID) led to inconsistent results. In two patients the increase of the cobicistat dosage to 150 mg BID let to a further increase in osimertinib exposure, relative to the increase seen with cobicistat 150 mg QD. However, in one patient, cobicistat dose escalation resulted in a decrease in osimertinib exposure, which was even more so when the dose was further escalated to 150 mg QID. Unfortunately, we were unable to identify the cause of this paradoxical effect as changes in adherence and use of co-medication with potential CYP3A influencing effects were ruled out.

In contrast to the extensive number of studies investigating the use of cobicistat in patients with acquired immunodeficiency syndrome (AIDS), the use of cobicistat to boost the exposure to anti-cancer drugs has only been described in two cases [18,19]. A patient with renal cell carcinoma was treated with axitinib and experienced low axitinib plasma trough concentrations. Because solely increasing the dosage of axitinib or combining the therapy with the intake of grapefruit juice did not lead to the desired outcome, cobicistat was used to boost axitinib exposure. Eventually, adequate exposure was achieved when combining axitinib (10 mg, QID), with cobicistat (150 mg, QID). In this case-report, the effect of cobicistat was mainly seen on the maximum axitinib concentration, while the plasma trough concentration of axitinib remained relatively constant [18]. Another study was planned to evaluate the boosting capacity of cobicistat in patients treated with crizotinib. However, due to limited patient accrual, as a consequence of the marketing authorization for alectinib, only one patient was included. In this patient the combination with cobicistat, 150 mg QD, led to an increase in crizotinib exposure of 78%. No information was available about the consistency of the boosting effect of cobicistat, as only one patient was included, and no follow-up crizotinib exposure measurement was performed [19]. Our clinical trial is the first formal clinical trial in which a group of patients with cancer is treated with cobicistat to improve the exposure to an anti-cancer drug, including follow-up trough concentration measurements.

Osimertinib has two active metabolites, AZ5104 and AZ7550. *In vitro* studies demonstrated that AZ5104 may have a slightly higher potency for mutated *EGFRs* as compared to osimertinib, while the potency of AZ7550 is thought to be lower for mutated *EGFRs* compared to osimertinib. As both metabolites are formed to a similar extent (approximately 10% of the $AUC_{0\text{-}24,ss}$ of osimertinib), we decided to incorporate AZ5104 in this analyses, and ignore the minimal contribution of AZ7550 to the total effect [9]. However, it is rather complex to estimate how much osimertinib and its metabolites contribute to the anti-tumor effect *in vivo*. In addition to the potency of the metabolite, other factors could contribute to the antitumor activity, such as body distribution, tumor tissue penetration and protein binding. Lack of this information makes it difficult to make a reliable estimation of the exact effect of AZ5104 *in vivo* compared to the effect of osimertinib itself. Therefore, we arbitrarily allocated similar importance (1:1) to the $AUC_{0\text{-}24,ss}$ of osimertinib and the $AUC_{0\text{-}24,ss}$ of AZ5104, which was shown in Table 2 as total $AUC_{0\text{-}24,ss}$. A different allocation of importance of osimertinib and AZ5104 would have led to slightly different results of the boosting capacity of cobicistat. However, as the effect of cobicistat was mainly seen in the $AUC_{0\text{-}24,ss}$ of osimertinib itself, we believe a different allocation of importance for osimertinib and AZ5104 would not have led to other conclusions.

In this study, cobicistat increased osimertinib exposure in all patients, and in most patients a sufficient effect (plasma trough concentration > 195 ng/mL) was achieved with cobicistat 150 mg QD co-administration. A larger boosting effect was seen in women compared to men. This apparent difference may potentially be explained by the higher CYP3A activity in women in general [24], as a higher CYP3A baseline activity offers an opportunity for a more pronounced inhibitory effect of cobicistat.

Consequently, the osimertinib boosting results of our study could have multiple potential implications for clinical practice. In patients with low osimertinib exposure, cobicistat could be used to increase osimertinib exposure in a cheap and safe manner, as cobicistat has no physiological off-target effects. While the penetration of osimertinib in the CNS is considerably better compared to first- and second-generation EGFR-TKIs [25], the CNS remains a common metastatic and progression site for *EGFR*-mutated NSCLC [5,10]. Therefore, in patients experiencing CNS (oligo-) progression, dose escalation might be considered to increase osimertinib exposure and anti-tumor activity in the CNS

Table 2
Adverse events reported in patients during simultaneous treatment of osimertinib and cobicistat 150 mg, QD.

Patient	AE	Specify	Grade	Relation to osimertinib
#1	Deviating laboratory value	AF, ASAT, LD and monocytes	1	Possible
#1	Rash		1	Probable
#3	Cough		1	Possible
#3	Diarrhea		1	Related
#3	Rhagades		1	Related
#5	Deviating laboratory value	ASAT, gGT and LD	1	Possible
#6	Deviating laboratory value	CK	1	Related
#6	Rhagades		1	Possible
#7	AV-block		1	Possible
#7	Deviating laboratory value	Creatinine, CK and urea	1	Possible
#8	Diarrhea		1	Possible
#8	Deviating laboratory value	AF and potassium	1	Possible
#10	Pain	Headache	1	Possible
#11	Pain	Due to earlier fracture	1	Possible

Abbreviatons: AF = alkaline phosphatase, ASAT = aspartate amino transaminase, AV = atrioventricular, CK = creatinine kinase, gGT = gamma glutamyltransferase, LD = lactate dehydrogenase.
This table shows all adverse events that were related to the osimertinib treatment (possible/probable/related).

[11,26]. As the price of 150 mg cobicistat is approximately 200 times less than doubling the osimertinib dose, the use of cobicistat may be a viable option to increase (cerebral) osimertinib exposure. A more general approach, of boosting osimertinib exposure purely based on the plasma trough concentration, to improve osimertinib effectiveness is less evident, as a definitive exposure–response relation seems absent for osimertinib. Especially boosting in patients with initially high osimertinib exposure may be less ideal, as it could this could lead to a higher level of toxicity (≥259 ng/mL) [27]. However, inhibiting CYP3A-activity could theoretically increase the anti-tumor activity of osimertinib, as intratumoral CYP3A activity would be inhibited, which is increased in NSCLC-patients [28].

Furthermore, in patients with an average or relatively high osimertinib exposure, addition of cobicistat may enable the use of a lower osimertinib dose, while maintaining similar exposure. However, the magnitude of osimertinib boosting in this study may not be representative for all osimertinib users. Given the low osimertinib exposure at baseline, CYP3A4 activity in our study population may be higher compared to patients with relatively high osimertinib exposure. Although other factors are involved, this may implicate that the boosting effect of cobicistat may be less pronounced in patients with average to high osimertinib exposure. Therefore, evaluating the effect of cobicistat in patients with a higher initial osimertinib exposure will be interesting, to further develop a strategy for osimertinib boosting by cobicistat in clinical practice.

However, the variation seen in osimertinib boosting by cobicistat so far makes it challenging to compose a *one-fits-all* approach. A similar variation was seen in a study by Boosman *et al*, which evaluated the boosting capacity of ritonavir on erlotinib exposure [28]. More research is warranted to evaluate whether the boosting method can be fine-tuned using TDM guidance. Future research could therefore also focus on evaluating whether the approach presented in this study could be used for other (expensive) targeted small-molecule inhibitors. Any drug that is predominantly metabolized by CYP3A4/5 and is still under patent could be a viable option and potentially lead to a more tailored treatment in clinical practice with possibly considerable cost-savings.

5. Conclusion

In this study concomitant use of cobicistat successfully increased the osimertinib exposure ($AUC_{0\text{-}24,ss}$, osimertinib + AZ5104). Cobicistat addition was well tolerated and its boosting effect on osimertinib was constant during the follow-up.

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Author contributions

Conceptualization: AV, RG and SC. Methodology: AV, RG and SC. Validation: JG. Formal analysis: AV, JG. Investigation: AV, JG, LH, SD, JI, ES. Data curation: AV, JI. Writing – original draft: AV Writing – review & editing: JG, LH, SD, JI, ES, AD, RG and SC. Visualization: AV. Supervision: LH, RG and SC. Project administration: AV and SC. Funding acquisition: RG and SC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.07.012.

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