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

#318

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Ard van Veelen and Sander Croes both declare no conflict of interest.

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Purpose

To evaluate if, and to what extent cobicistat could increase osimertinib exposure, and whether the boosting effect was stable over time.

Methods

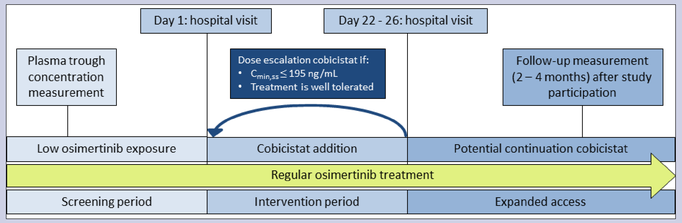

Figure 1: schematic overview of the OSIBOOST trial for patients with low initial osimertinib exposure ($C_{min,ss} \leq 195$ ng/mL).

Inclusion:

- ❖ Osimertinib as regular treatment
- ❖ 18 years or older
- ❖ Performance status ≤ 2
- ❖ $C_{min,ss} \leq 195$ ng/mL

Exclusion:

- ❖ Concurrent use of CYP3A4/CYP3A5 influencing drugs/(food)products or CYP3A4/CYP3A5 metabolised drugs with a small therapeutic window.
- ❖ Impairment of gastrointestinal function.
- ❖ Pregnancy or breast feeding.
- ❖ Chronic liver disease, with a Child-Pugh score class C.

Primary outcome: change in total $AUC_{0\text{-}24,ss}$ for osimertinib and its active metabolite (AZ5104) combined.

Secondary outcomes: safety and the consistency of the boosting by cobicistat.

Results

Eleven patients, with a mean age of 67.4 years, were included and additionally treated with cobicistat, 150 mg once daily. Ten patients were treated with 80 mg osimertinib daily, while one patient received 160 mg osimertinib daily, but still experienced low $C_{min,ss}$. Mean plasma concentration for osimertinib and AZ5104 are shown in figure 2 and individual boosting is shown in figure 3. .

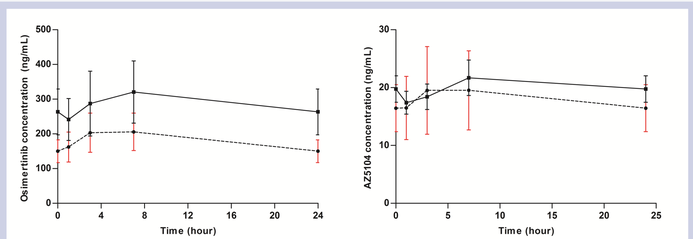

Figure 2: mean plasma concentration of osimertinib on PK day I (dotted line) and PK day II (solid line), with variation shown in red and black, respectively (left) and mean plasma concentration of AZ5104 on PK day I (dotted line) and PK day II (solid line), with variation shown in red and black, respectively (right) . PK day I = only osimertinib, PK day II = osimertinib + cobicistat.

Dose-escalation of cobicistat led to inconsistent results. Boosting increased in two patients, when the cobicistat dosage was escalated to 150 mg twice daily, while boosting decreased in one patient.

Abbreviations: $C_{min,ss}$ = trough concentration during steady state, ng = nanogram, mL = millilitre, CYP = cytochrome P450, $AUC_{0\text{-}24,ss}$ = area-under-the-curve (0 – 24 hours) during steady state, mg = milligram, PK = pharmacokinetic, CTCAE = common terminology criteria for adverse events, v = version.

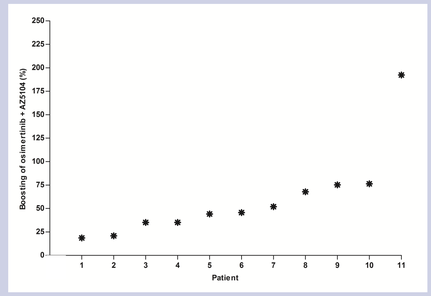

Figure 3: total boosting of osimertinib + AZ5104 with 150 mg cobicistat (daily) per patient.

Pharmacogenetic data was available for seven patients, and no abnormalities were observed (all were extensive CYP3A4 metabolizers, and CYP3A5 non-expressors).

No serious or unexpected adverse events were observed. All potentially related adverse events (n = 14) were scored as grade 1 (CTCAE, v5.0).

The effect of cobicistat was stable during follow-up (up to six months) with a mean difference to the second hospital visit of 21%, with the exception of one patient. This patient experienced a considerable increase in osimertinib exposure (+376%). This increase could not be explained by co-medication or treatment adherence.

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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