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Letter to the Editor

Reply to 'The use of buparlisib as a radiosensitiser: What about toxicity?'

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Dear Editor,

We thank Professor van Dam for his letter and the positive comment that our trial 'nicely suggests that further research aiming to develop PI3K inhibitors as radiosensitisers should be encouraged' [1]. We agree with this statement and feel that it would be ideal to combine ionising radiation with a PI3K inhibitor with the best toxicity profile.

At the inception of our trial, buparlisib and BEZ235 were the only clinical candidate PI3K inhibitors which had been shown to reduce tumour hypoxia in preclinical models [2]. As BEZ235 is recognised to inhibit DNA-PKcs, we anticipated it would be associated with increased radiation-induced toxicity [3]. Therefore, buparlisib was the most suitable PI3K inhibitor available to us.

During our trial, we carefully monitored mood changes using patient self-reported questionnaires for depression (patient health questionnaire (PHQ)-9) and anxiety (generalised anxiety disorder (GAD)-7) at screening, baseline and days 8, 14, 28 and 56 [4]. As we reported in Table 2 [4], treatment-related altered mood was observed in only three (14%) patients (grade 1 for two patients and grade 2 for one patient) and personality change in one (5%) patient (grade 1), not one patient as stated in Professor van Dam's letter [1]. All four of these adverse events (AEs) occurred in patients receiving the highest dose of buparlisib.

We did not observe any buparlisib-related liver dysfunction in our study. In fact, not a single AE relating to elevated alanine aminotransferase, aspartate aminotransferase or bilirubin was reported for any patient.

Overall, we found that combining a two-week course of buparlisib with radiotherapy was associated with acceptable toxicity. This is especially encouraging given that patients with metastatic non–small cell lung cancer (NSCLC) requiring palliative radiotherapy represent a particularly unwell patient group. The short duration of drug treatment required to induce tumour radiosensitisation, as was used in our study, means that more frequent or severe side-effects are less likely to occur. We agree that the toxicity profile of more prolonged buparlisib therapy, as in the NEO-ORB and other studies highlighted by Professor van Dam, has significantly hampered its clinical adoption and that combining radiotherapy with better tolerated PI3K inhibitors would be desirable. However, alternative inhibitors would require preclinical data specifically showing reductions in tumour hypoxia rather than simply demonstrating alterations in intrinsic

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radiosensitivity. Merely altering intrinsic cellular radiosensitivity would also likely increase normal tissue side-effects, whereas reducing tumour hypoxia is likely to induce tumour-specific radiosensitisation.

To our knowledge, buparlisib remains the only PI3K inhibitor to be shown to reduce tumour hypoxia in the clinical setting and to be well tolerated when used specifically as a radiosensitiser for NSCLC.

Conflict of interest statement

The authors declare they have no conflicts of interest.

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