Safety and tumour hypoxia modifying effect of buparlisib with radiotherapy in NSCLC: a phase I dose escalation study

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Background
The Ras/PI3K/Akt pathway plays an important role in determining intrinsic and extrinsic tumour radiosensitivity. Buparlisib (BKM120) is a highly specific pan class-1 PI3K inhibitor. This class of agents has been shown to reduce tumour hypoxia *in vivo,* leading to increased radiation response. We therefore conducted a phase I, 3+3 dose-escalation and expansion clinical trial combining buparlisib with palliative thoracic radiotherapy in NSCLC to determine the safety, DLT and MTD of this combination. Buparlisib's effect on tumour hypoxia was also investigated.

Methods
Patients with advanced stage NSCLC received 2 weeks of oral buparlisib. F-misonidazole (F-MISO) PET scans were used to assess tumour hypoxia prior to starting buparlisib and 1 week into treatment. Palliative thoracic radiotherapy (20Gy in 5 fractions) was delivered during the second week of treatment. Hypoxic tumour volume (HV) was defined as the volume with a tumour-to-blood F-MISO uptake ratio ≥ 1.4.

Results
From June 2013 to August 2017, 21 patients were recruited. 11 patients were registered to the dose escalation phase with 9 evaluable for MTD analysis: 3 in Cohort 1 (50mg OD), 3 in Cohort 2 (80mg OD) and 3 in Cohort 3 (100mg OD). No DLT was reported therefore 100mg OD was declared the MTD and 10 patients received this dose in the expansion phase. Of all patients who received buparlisib (n=21), 1 SAE (Grade 3 hypoalbuminaemia) was possibly related to buparlisib (5%). No SAEs were unexpected. The most common buparlisib-related AEs were Fatigue (8.3%) and nausea (3.3%). 93.9% of all AEs with any relation to buparlisib were ≤ Grade 2. There was no reported radiotherapy associated toxicity. 15 patients were evaluable for tumour hypoxia imaging analysis. Median change in HV in Cohort 1 (n=3), Cohort 2 (n=3) and Cohort 3 combined with the expansion cohort (n=9) was 7%, -18% and -20%, respectively.

Conclusions
This is the first clinical trial of a specific PI3K inhibitor with concurrent radiotherapy in NSCLC. This combination was found to be safe and well-tolerated. This study provides clinical evidence that PI3K inhibition rapidly reduces tumour hypoxia and therefore warrants further trials combining this class of agents with radiotherapy.