46P AB521, a clinical-stage, potent, and selective Hypoxia-Inducible Factor (HIF)-2α inhibitor, for the treatment of renal cell carcinoma

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Background: The transcription factor hypoxia-inducible factor 2α (HIF-2α) is a key oncogenic driver in clear cell renal cell carcinoma (ccRCC). HIF-2α protein levels are tightly regulated post-translationally in an oxygen-dependent manner. Hypoxic conditions or aberrations in the Von-Hippel Lindau (VHL) ubiquitin ligase complex lead to HIF-2α stabilization and transcription of various pro-tumorigenic gene sets. Clinical evidence indicates that inhibition of HIF-2α is an effective strategy to mitigate tumor growth, particularly in ccRCC, a cancer that has a high prevalence of pVHL dysfunction. Herein we present the discovery and characterization of AB521, a potent and selective small molecule HIF-2α inhibitor that exhibits profound antitumor activity in preclinical models.

Methods: The potency of AB521 was evaluated using a suite of biochemical and cell-based assays. Efficacy and pharmacodynamic markers were also evaluated in mice bearing established A498 and 786-O ccRCC xenograft tumors treated with AB521 alone or in combination with cabozantinib.

Results: Biochemical binding assays and protein co-crystal structure elucidation demonstrated that AB521 avidly binds the HIF-2α PAS-B domain lipophilic cavity. AB521 potently inhibited HIF-2α-dependent reporter transcription and VEGF protein secretion in 786-O cells. AB521 selectively inhibited HIF-2α-, but not HIF-1α-, regulated gene expression in Hep3B hepatocellular carcinoma cells. AB521 significantly regressed mouse ccRCC xenograft tumors and decreased on-target pharmacodynamic markers in a dose-dependent manner. Additionally, AB521, in combination with a cabozantinib, showed enhanced anti-tumor activity in the A498 xenograft model relative to either single agent therapy. Finally, AB521 had favorable pharmacokinetics in preclinical species, resulting in a projected pharmacokinetic profile suitable for once-daily dosing in humans, which may result in a higher level of HIF-2α inhibition relative to other clinical candidates in this space.

Conclusions: AB521 is a novel and selective HIF-2α inhibitor with potent anti-tumor activity, and clinical evaluation of this molecule is underway.

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47P Prevalence of mutations in common tumour types in Northern England and utility of Experimental Cancer Medicine Centre (ECMC) CRUK Trial Finder

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Background: Genomic profiling of tumours has expanded rapidly, and is of increasing importance in early phase trial units in matching patients to targeted clinical trials. It is recognised that mutational signatures vary by demographic group, however, regional differences are not yet characterised. This was investigated by comparing relative prevalence of mutations for common cancers presenting to Newcastle ECMC to The Cancer Genome Atlas (TCGA) and comparative utility of trial matching modalities within and outside the UK.

Methods: Detailed clinicogenomic outcome data was obtained for patients with advanced cancer presenting to Newcastle ECMC with profiling completed September 2017 – December 2020. Prevalence of commonly identified mutations in lung, colorectal, breast and prostate cancer was compared to TCGA GDC Data Portal. Experimental Cancer (EC) Trial Finder utility in matching trials was assessed, compared to Molecular Tumour Boards (MTB) and sequencing reports. Statistical analysis was conducted using SPSS Version 27.0. P values <0.05 were considered statistically significant.

Results: Of 311 patients with advanced cancer the most common tumour types were lung (n = 131, 42%), colorectal (n = 44, 14%), breast (n = 36, 12%) and prostate (n = 18, 6%). $\geq$1 genomic finding was identified in the majority (n = 260, 84%). Significant differences in prevalence of mutations compared to TCGA were identified, including a high prevalence of EGFR in lung cancer (P = 0.001); RB1 in lung and breast (P = 0.01, P = 0.0002); and multiple mutations in prostate. EC Trial Finder demonstrated significantly different utility than sequencing reports in identifying trials for mutations identified at $\geq$5% prevalence (P = 0.007).

Conclusions: Regional differences in mutational signatures remain challenging to characterise. Advanced disease stage may account for increased prevalence of specific mutations, notably in the prostate cancer cohort. EC Trial Finder shows utility in finding targeted trials in the regional population. Sequencing reports may over report 'actionable' mutations. Understanding of local prevalence and trial availability could increase the number of patients enrolled onto matched clinical trials.

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48P cERBB-2/HER-2neu overexpression and its prognostic significance in uterine carcinosarcoma

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Background: Uterine carcinosarcomas (CS) represent one of the worst prognostic group within uterine tumors. Her-2 overexpression is associated with a poor prognosis in serous endometrial carcinoma. However, there is not enough data in the literature regarding Her-2 overexpression in uterine CS. Therefore we aimed to determine the Her-2 overexpression rate in uterine CS and evaluate its relation with prognosis and whether Her-2 overexpression is determinant in the life expectancy of these patients.

Methods: Between January 2013 and December 2020, 51 patients with uterine CS have included in this study. Her-2 overexpression was examined by both protein and gene status were evaluated by Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) respectively on paraffin embedded hysterectomy specimens. of 51 CS patients.

Results: Her-2 protein expression in epithelial component was negative in 42 patients (score 0 in 33 cases, score 1(+) in 9 cases), score 2(+) in 7 patients and score 3(+) in 2 patients. None of the patients showed Her-2 protein expression within the sarcomatous component of the tumors. Her-2 gene amplification was negative in both epithelial and sarcomatous tumor areas by FISH method. There was no difference between the Her-2 overexpression negative and positive groups in terms of disease-free survival (DFS) and overall survival (OS) values. Her-2 protein overexpression was significantly higher in tumors of patients diagnosed at 65 years or older (p=0,046).

Conclusions: The literature on Her-2 in uterine carcinosarcomas has quite conflicting results. Our results show that there is no relationship between overexpression of Her-2 and prognosis in uterine carcinosarcoma.

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49P Antitumor effects of cationic dendritic molecules and their complexes with microRNA in glioblastoma stem-like cells

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Background: An important way for anti-tumor drug development is using of molecular targets involved in the regulatory pathways during tumorogenesis. As it was found microRNAs (miRs) are active players in this processes. Manipulations with miR-34a and onco-miR-21 demonstrated their effectiveness as antitumor intervention in glioblastoma (GBM), so stable and efficient nanocarriers should be found. One of the