788TiP ACELARATE: A randomised phase III, open label, clinical study comparing NUC-1031 with gemcitabine in patients with metastatic pancreatic carcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) is predicted to be the second leading cause of cancer-related death by 2030 (Rahib et al, 2014). The overall 5-year survival rate is currently less than 7%. Gemcitabine is used for patients who are not suitable for combination therapy, but the response is poor at less than 10% (Conroy et al, 2011). Gemcitabine efficacy is limited due to intrinsic or acquired resistance mechanisms associated with transport, activation and breakdown. NUC-1031, a phosphoramidate transformation of gemcitabine, is designed to overcome the three key resistance mechanisms responsible for a poor survival prognosis to gemcitabine. In a Phase I study, NUC-1031 was well tolerated and demonstrated anti-tumour activity across a wide range of advanced cancers, including PDAC (Blagden et al, ASCO 2015). This ongoing Phase III study is designed to compare NUC-1031 with gemcitabine as first-line treatment in patients with PDAC who are unsuitable for combination chemotherapy.

Trial design: First-line patients with metastatic PDAC are being randomised to either NUC-1031 (825 mg/m^2) or gemcitabine (1000 mg/m^2) on days 1, 8 and 15 of a 28-day cycle until disease progression. Patients unsuitable for combination chemotherapy with a PS of 0-2 are eligible. Over 125 patients have been randomised across more than 20 centres. To detect a hazard ratio of 0.705 between the two arms, 270 events must be obtained from 328 patients, assuming a median survival of 6 months in the control (gemcitabine) arm. The primary outcome measure is overall survival. Secondary outcome measures include progression free survival, objective response rate, disease control rate, quality of life and safety. Translational research will explore the use of biomarkers for predictive benefit of NUC-1031 over gemcitabine.

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