Final results of ProGem1, the first in-human phase I/II study of NUC-1031 in patients with solid malignancies.

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Background: NUC-1031 is a first-in-class nucleotide analogue utilising phosphoramidate chemistry to enhance anti-cancer efficacy and safety. In preclinical studies NUC-1031 demonstrated potent anti-cancer activity, generating high intracellular levels of the active cytotoxic di-fluoro-deoxycytidine triphosphate (dFdCTP) by overcoming key drug resistance mechanisms associated with nucleoside analogues.

Methods: This study was comprised of 1) dose escalation part: 3–8 patients (pts) per cohort received 5-15 minute IV infusion of NUC-1031 starting at 500mg/m$^2$ once weekly on days 1, 8, 15 in 4 weekly schedule (q4w), or 375mg/m$^2$ twice-weekly on days 1 & 5, 8 & 12, 15 & 19 q4w and 2) expansion part at the recommended Phase II dose (RP2D). Endpoints were (primary) safety and tolerability, (secondary) pharmacokinetics (PK), pharmacodynamics and efficacy. Results: ProGem1 enrolled 68 pts, mean age 56 (20 - 83 yrs), average 2.7 prior lines of chemotherapy (range 1 - 6) with 16 primary cancer types. Dose-
limiting toxicities occurred in 4 pts: G4 thrombocytopenia (2); G3 elevated ALT (2). 25 SAEs were ‘possibly/probably related’ to study drug, and 2 > G2: elevated ALT (4) and lung infection (3). Commonest AEs ≥ G3 ‘possibly/probably related’ were: neutropenia (16), fatigue (13), elevated GGT (10). NUC-1031 was stable, with plasma half-life of 8.3 hours. High intracellular levels of the active anti-cancer agent dFdCTP (Cmax = 475.5 µM/L) were rapidly achieved and maintained for 24 hours. Notable efficacy results were observed: 5 RECIST Partial Responses (10%); 33 Stable Disease (67%) for an ITT disease control rate (DCR) of 56% and on treatment analysis (OTA) DCR of 78%. PRs and SDs were observed in pts refractory/relapsed to prior nucleoside analogue therapy and were durable, mean PFS 6.1 months (range 2 – 20 mths). The RP2D was 825mg/m² given on days 1, 8, 15, q4w. **Conclusions:** NUC-1031 has demonstrated impressive clinical activity with durable DCR (ITT 56%; OTA 78%) in a wide range of patients with advanced and rapidly progressing disease. NUC-1031 is well-tolerated at the RP2D. Phase III clinical studies in ovarian, pancreatic and biliary cancers are planned this year and combination studies are currently recruiting. Clinical trial information: NCT01621854

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