A first in human Phase I/II study of NUC-1031 in patients with advanced gynecological cancers.

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Background: Acquired resistance to chemotherapy hampers patients'survival from many gynecological malignancies. NUC-1031, a first-in-class nucleotide analogue, utilises phosphoramidate chemistry to overcome key drug resistance mechanisms and enhance anti-cancer activity. **Methods:** NUC-1031 was given as a single injection either 1) on days 1,8, & 15 of a 28 day cycle (q4w) in doses ranging from 500mg/m^2 to 1000mg/m^2, or 2) as a twice weekly schedule on days 1 & 5, 8 & 12, 15 & 19 q4w at 375mg/m^2. Primary endpoints were safety and tolerability, and secondary endpoints were pharmacokinetics (PK), pharmacodynamics and efficacy. **Results:** Of 68 patients (pts) enrolled in this study, 18 had primary gynecological cancers: 13 ovary/fallopian tube (comprising high grade serous (HGS) (10), G2 endometrioid (2), mixed clear cell/serous (1)), 3 endometrium (comprising G3 serous (2), MMMT (1)), and 2 cervix (SCC). Pts had a mean age of 59 years (age range 42-78 yrs) and received an average of 3.5 prior chemotherapy regimens. All pts with HGS cancers were platinum resistant with average platinum-free interval 3.7 months (range 0.3 – 6.9 mths). NUC-1031 was well tolerated. In total 9 SAEs were reported in 7 pts. The most common AEs of grade ≥ 3 considered 'possibly/probably related'

to the study agent were: myelosuppression (8); fatigue (6); GGT (3). The PK profiles revealed high and sustained intracellular levels of the active metabolite dFdCTP (AUC of 2.1 nmol/million cells/hr) over 24 hrs. Fourteen of the 18 pts had received at least 2 cycles of NUC-1031 and were evaluable for RECIST assessment of response. Significant disease control rate (DCR) was observed: 2 Partial Responses (14%); 11 Stable Disease (79%) for an ITT DCR of 72% and on treatment analysis (OTA) DCR of 93%. The mean PFS was 7.5 months (range 3 – 15 mths), with 3 pts showing ongoing disease control. **Conclusions:** NUC-1031 showed clear signs of clinical activity in patients with gynecological cancers, OTA DCR 93%. The agent was well tolerated, with durable SD and PR observed, PFS 7.5 months. A Phase Ib study of NUC-1031 in combination with carboplatin is ongoing. Phase III studies are planned in both platinum sensitive and refractory gynecological cancers. Clinical trial information: NCT01621854
