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**59TIP Phase III study of NUC-1031 + cisplatin vs gemcitabine + cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121)**

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**Background:** Biliary tract cancer (BTC) is an aggressive disease with a poor prognosis. Gemcitabine + cisplatin (GemCis) is the accepted global standard of care; however, key cancer resistance mechanisms associated with the transport, activation and breakdown of gemcitabine are known to limit its clinical activity. NUC-1031 is a phosphoramidate transformation of gemcitabine designed to overcome these key resistance mechanisms and generate much higher levels of the active anti-cancer metabolite, dFdCTP, in cells. Promising efficacy has been observed in the phase Ib ABC-08 study of NUC-1031 + cisplatin for first-line treatment of advanced BTC. Of 21 patients (pts) enrolled in 2 dose cohorts (NUC-1031 625 mg/m<sup>2</sup> or 725 mg/m<sup>2</sup> + cisplatin 25 mg/m<sup>2</sup> on Days 1 and 8 of 21-day cycles), 16 were considered to be efficacy evaluable. In this population, 1 pt had a CR and 6 pts had PRs, resulting in an ORR of 44% (7/16). This compares favorably to the 26% ORR reported for GemCis. In addition, 6 pts had SD, resulting in a DCR of 81% (13/16). The combination was well tolerated with no unexpected AEs or DLTs. The recommended dose of NUC-1031 with cisplatin was 725 mg/m<sup>2</sup>. The encouraging efficacy and tolerability profile led to initiation of a global registration study.

**Trial design:** NuTide:121 is a phase III, open-label, randomised study of NUC-1031 + cisplatin vs GemCis for first-line treatment of advanced BTC. Pts ≥18 years with histologically- or cytologically-confirmed BTC (including cholangiocarcinoma,

gallbladder, or ampullary cancer), who have had no prior systemic chemotherapy for locally advanced/metastatic disease, are eligible. A total of 828 pts are being randomised (1:1) to either 725 mg/m<sup>2</sup> NUC-1031 or 1000 mg/m<sup>2</sup> gemcitabine, both with 25 mg/m<sup>2</sup> cisplatin, administered on Days 1 and 8 of 21-day cycles. Primary endpoints are OS and ORR. Secondary endpoints include PFS, safety, PK and pt-reported QoL. In addition to the final analysis, three interim analyses are planned. NuTide:121 is being conducted at approximately 125 sites across North America, Europe and Asia Pacific.

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