NuTide:121 Global Phase III study of NUC-1031 plus cisplatin vs gemcitabine plus cisplatin for first-line treatment of patients with advanced biliary tract cancer

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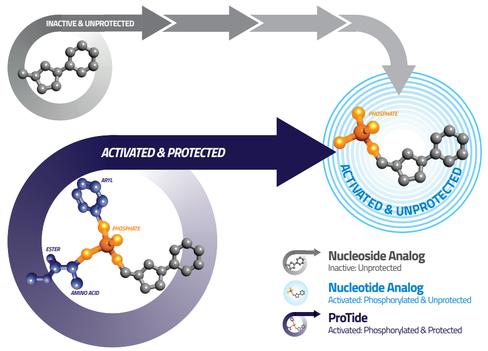
BACKGROUND

- No approved agents exist for the first-line treatment of locally advanced/metastatic biliary tract cancer (BTC)
- Current standard of care remains gemcitabine + cisplatin:
  - Median overall survival (OS) 11.7 months (ABC-02)[1]
- Resistance to chemotherapy is associated with poor survival
- Effective new agents and combinations are required

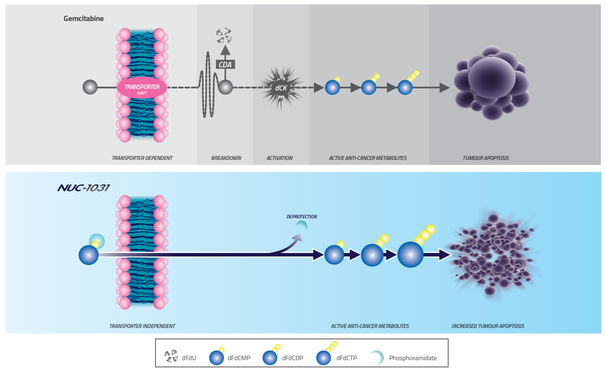
Transforming nucleoside analogs into ProTides



NUC-1031: A ProTide transformation of gemcitabine

- A new class of anti-cancer agents
- Overcomes key gemcitabine resistance mechanisms[2]
  - Cellular uptake independent of nucleoside transporters (hENT1)
  - Activation independent of deoxycytidine kinase (dCK)
  - Protected from breakdown by cytidine deaminase (CDA)
- In comparison to gemcitabine, NUC-1031 has[3]:
  - Greater plasma stability ($t_{1/2}$ 8.3 hours vs 1.5 hours)
  - Increased intracellular levels of active anti-cancer metabolite, dFdCTP (217x)
  - Reduced toxic metabolites

NUC-1031 bypasses the key cancer resistance pathways of gemcitabine



ABC-08 (Phase Ib study NUC-1031 + cisplatin)

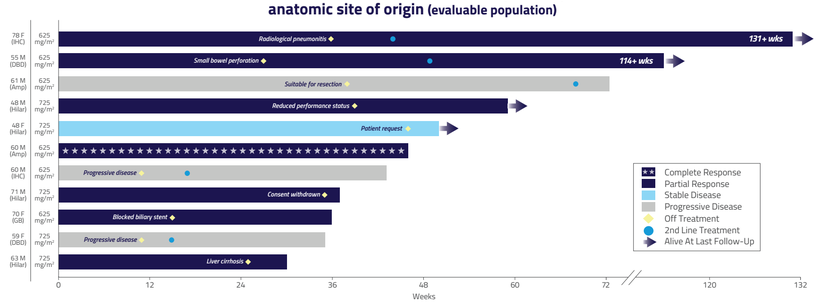
Patient characteristics

- Age ≥18 years, ECOG PS 0 or 1
- Previously untreated histologically or cytologically-confirmed adenocarcinoma of the biliary tract that is locally advanced, unresectable or metastatic
- Intention-to-treat (ITT) population: 14 patients
- Evaluable population: 11 patients completed ≥1 cycle

Safety profile

- NUC-1031 + cisplatin was well-tolerated
- Multiple cycles administered (median 8; range 3.5-14)
- No unexpected adverse events (AEs)
- No dose-limiting toxicities (DLTs)
- Grade 3 AEs included: fatigue (21%), neutropaenia (14%), pyrexia (14%), nausea (7%), and increased liver function enzymes (ALT; 14%, AST; 7%)
- No Grade 4 treatment-related AEs
- No patients discontinued due to NUC-1031-related events

Treatment duration and best overall response by BTC anatomic site of origin (evaluable population)



ABC-08 summary

- NUC-1031 + cisplatin shows encouraging efficacy compared to standard of care
- All BTC subtypes sensitive to NUC-1031 + cisplatin
- Durable responses
- NUC-1031 + cisplatin is well-tolerated over multiple cycles

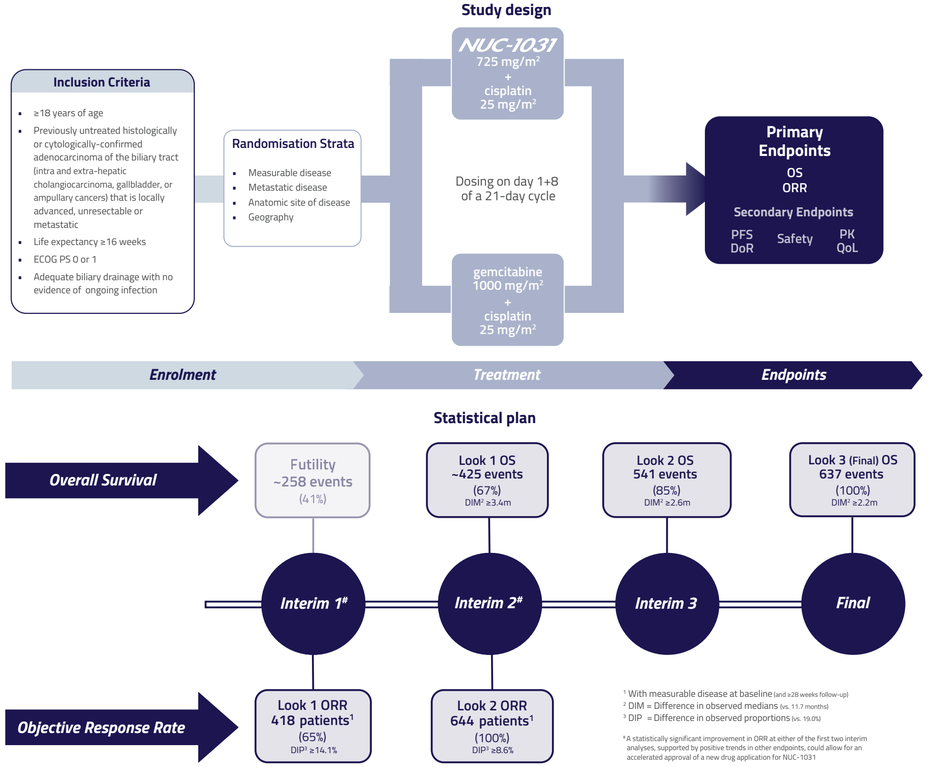
Objective response rates in ABC-08 and ABC-02

	ABC-08 NUC-1031+ cisplatin	ABC-02[1] gemcitabine + cisplatin
Complete Response	**7%** (1/14)	**0.6%** (1/161)
Partial Response	**43%** (6/14)	**25.5%** (41/161)
Objective Response Rate	**50%** (7/14)	**26.1%** (42/161)

Note: Responses unconfirmed in ABC-08 and ABC-02

NuTide:121 (Phase III study of NUC-1031 + cisplatin)

Study design



Statistical plan

[1] With measurable disease at baseline (and ≥28 weeks follow-up)
[2] DIM = Difference in observed medians (vs. 11.7 months)
[3] DIP = Difference in observed proportions (vs. 19.0%)

[#] A statistically significant improvement in ORR at either of the first two interim analyses, supported by positive trends in other endpoints, could allow for an accelerated approval of a new drug application for NUC-1031

NuTide:121 study sites (15 countries ~130 sites)

SUMMARY

- Global Phase III study at ~130 sites across North America, Europe and Asia-Pacific
- NUC-1031 + cisplatin has the potential to improve survival outcomes in patients with BTC
- Further study information: **NuTide121@nucana.com**

REFERENCES: 1. Valle et al. N Engl J Med 2010; 362:1273-1281. 2. Slusarczyk et al. J Med Chem 2014; 57:1531-1542. 3. Blagden et al. Br J Cancer 2018; 119:815-822.

ABBREVIATIONS: BTC: biliary tract cancer OS: overall survival hENT1: human equilibrative nucleoside transporter 1 dCK: deoxycytidine kinase CDA: cytidine deaminase dFdCTP: difluoro-deoxycytidine triphosphate AE: adverse event DLT: dose-limiting toxicity ITT: intention to treat ECOG: eastern cooperative oncology group ORR: objective response rate PS: performance status PK: pharmacokinetics QoL: quality of life $t_{1/2}$: half-life dFdCMP: difluoro-deoxycytidine monophosphate dFdCDP: difluoro-deoxycytidine diphosphate dFdU: difluoro-deoxyuridine PFS: progression free survival DoR: duration of response DIM: difference in observed means DIP: difference in observed proportions