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NUC-1031 in combination with cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121)

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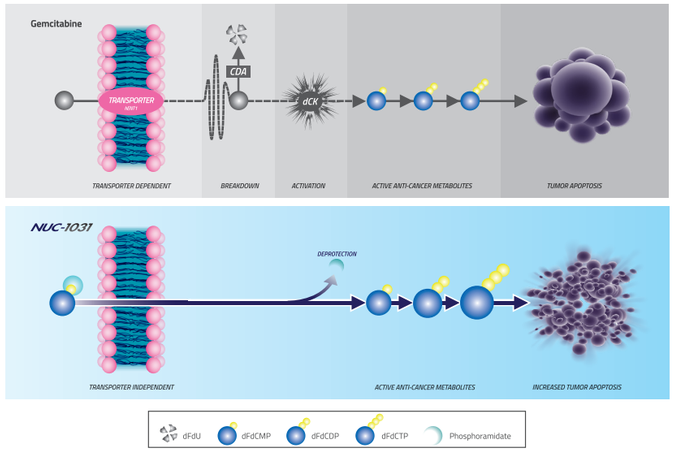
Background

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

NUC-1031 bypasses the key cancer resistance pathways of gemcitabine



NUC-1031: The first anti-cancer ProTide

- A new class of anti-cancer agents
- ProTide transformation of gemcitabine
- 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

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

Patient characteristics

- Age ≥ 18 years, ECOG PS 0 or 1
- 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

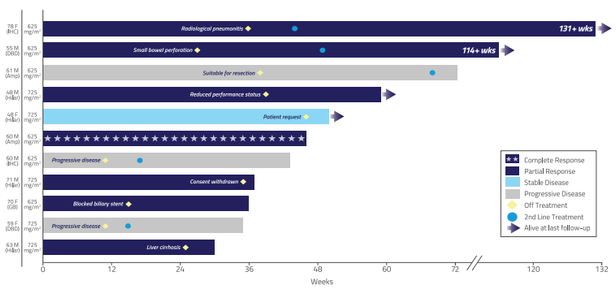
- NUC-1031 + cisplatin was well-tolerated
- Multiple cycles administered (median 8; range 3.5-14)
- No unexpected adverse events (AEs)
- No dose-limiting toxicities (DLTs)
- Grade 3 AEs included: fatigue (21%), neutropenia (14%), pyrexia (14%), nausea (7%), and increased liver function enzymes (ALT;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

Objective Response Rates in ABC-08 and ABC-02

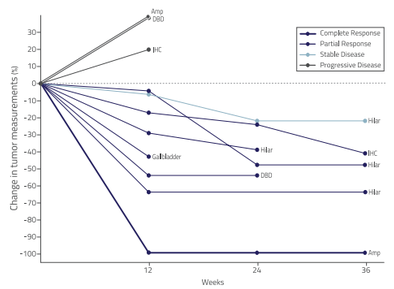
	ABC-08 NUC-1031 + cisplatin	ABC-02[1] gemcitabine + cisplatin
	ITT	Evaluable
Complete Response	**7%** (1/14)	**0.6%** (1/161)
Partial Response	**43%** (6/14)	**25.5%** (41/161)
Objective Response Rate	**50%** (7/14)	**26.1%** (42/161)

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

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

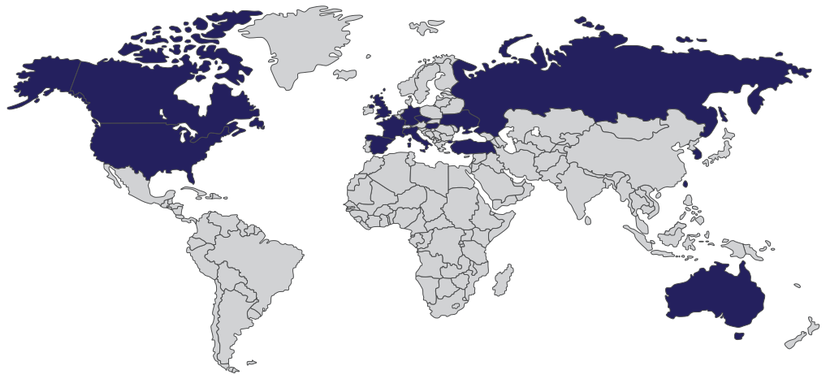


Tumor burden during study treatment (Evaluable population)

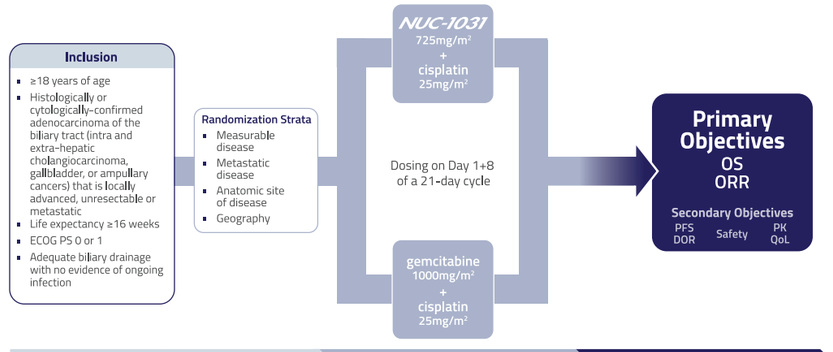


NuTide:121 (Phase 3 study of NUC-1031 + cisplatin)

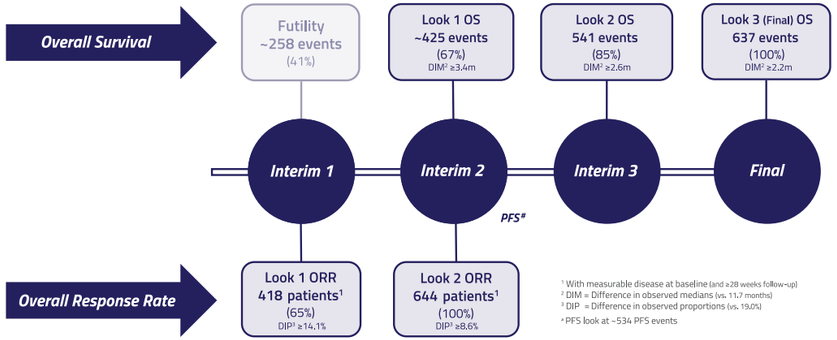
International multi-center study (15 countries ~120 sites)



Study design



Interim and final analysis 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%)
* PFS look at ~534 PFS events

Summary

ABC-08
- 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

NuTide 121
- Global Phase 3 study that will be conducted at ~120 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. Slyusarczyk *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 PFS: progression-free survival PK: pharmacokinetics DOR: duration of response QoL: quality of life

Data current as of 30th Aug 2018. Data cleaning ongoing.