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

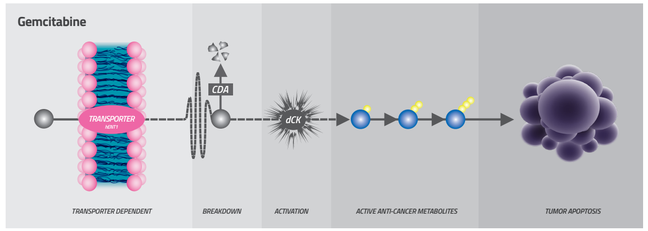
Biliary Tract Cancer (BTC)

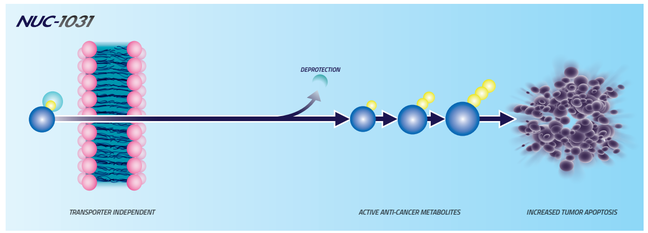
- Aggressive cancer with a poor prognosis
- Heterogenous disease consisting of distinct subgroups
  - Intra and extra-hepatic cholangiocarcinoma, gallbladder, or ampullary
- No approved agents exist for the first-line treatment of advanced BTC
- Current standard of care: gemcitabine + cisplatin
  - Median overall survival (OS) 11.7 months (ABC-02)[1]
- Resistance to chemotherapy is associated with poor survival
- Effective new agents and combinations are required

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





Phase 1b ABC-08 study: NUC-1031 + cisplatin[4]

- Favorable safety profile that was tolerated over multiple cycles
- Encouraging efficacy with activity across all BTC subtypes (44% ORR*)

* Efficacy evaluable patients

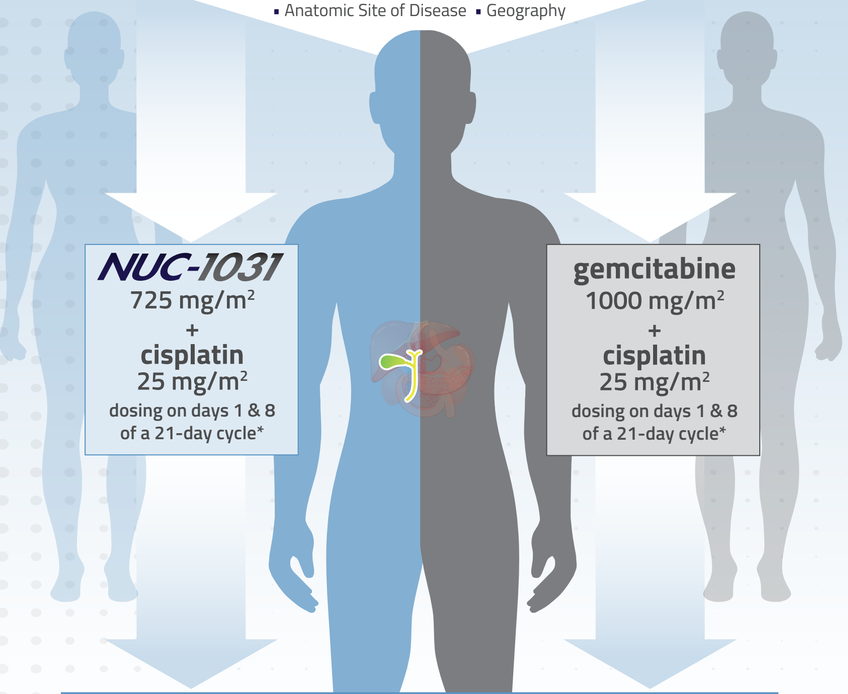
NuTide 121

INCLUSION CRITERIA

- Previously untreated histologically or cytologically-confirmed adenocarcinoma of the biliary tract (intra and extra-hepatic cholangiocarcinoma, gallbladder, or ampullary cancers) that is locally advanced, unresectable or metastatic
- ≥18 years of age
- Life expectancy ≥16 weeks
- ECOG PS 0 or 1
- Adequate biliary drainage with no evidence of ongoing infection

RANDOMIZATION STRATA

- Measurable Disease
- Metastatic Disease
- Anatomic Site of Disease
- Geography



NUC-1031
725 mg/m²
+
cisplatin
25 mg/m²
dosing on days 1 & 8 of a 21-day cycle*

gemcitabine
1000 mg/m²
+
cisplatin
25 mg/m²
dosing on days 1 & 8 of a 21-day cycle*

PRIMARY ENDPOINTS

- Overall Survival
- Objective Response Rate

SECONDARY ENDPOINTS

- PFS
- DoR
- Safety
- PK
- QoL

*until unacceptable toxicity or progressive disease

NuTide:121 (Statistical Plan)

RECRUITMENT → FOLLOW UP → FINAL ANALYSIS

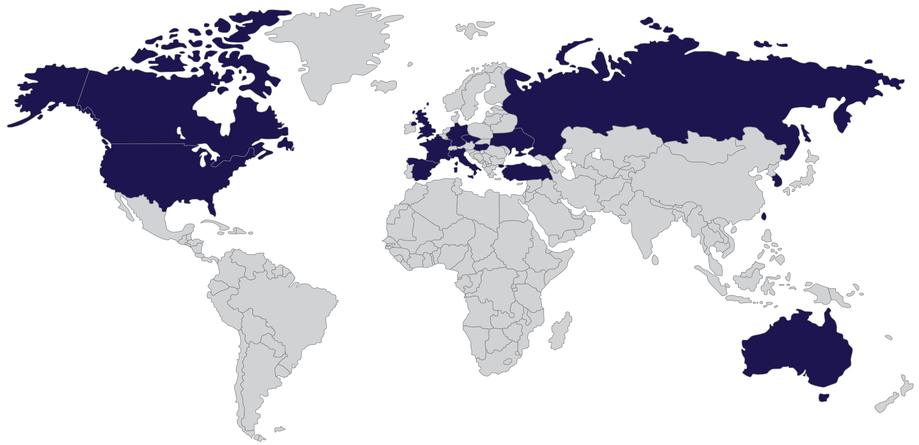
Accelerated Approval
Interim 1 or 2 designed to support

Regular Approval
Interim 2, 3 or 4 designed to support

Interim 1	*Interim 2*	*Interim 3*	*Final*
ORR 418 evaluable patients DIP ≥14%*,#	**ORR** 644 evaluable patients DIP ≥9%*,#		
	OS ~425 events DIM ≥3.4m*	**OS** ~541 events DIM ≥2.6m*	**Final OS** ~637 events DIM ≥2.2m*

* DIP = Difference in observed proportions (vs. an estimated 19.0%) for statistical significance. Measurable disease at baseline and ≥28 weeks follow-up.
* DIM = Difference in observed medians (vs. an estimated 11.7 months) for statistical significance.

NuTide:121 study sites (15 countries: ~126 sites)



SUMMARY

- Global Phase III study at ~126 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. 4. McNamara MG et al. Oncologist 2021; 26(4):669-678.

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

The first author has no conflicts of interest to declare