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A new ProTide, NUC-1031, combined with cisplatin for the first-line treatment of advanced biliary tract cancer (ABC-08)

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Background

- No approved agents exist for the treatment of locally advanced/metastatic biliary tract cancer (BTC)
- Current standard of care (SOC) remains gemcitabine + cisplatin (ABC-02)[1]
- Resistance to chemotherapy reduces patient survival
- Effective new agents and combinations are required

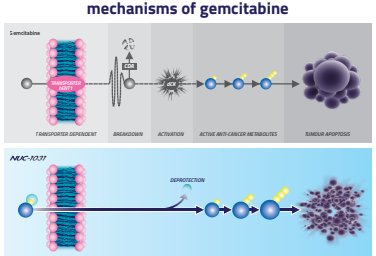
ProTides: NucleoTide Analogs

- A new class of anti-cancer agents
- Transformative phosphoramidate chemistry
- Increase intracellular levels of active anti-cancer metabolites
- Potential for broad clinical utility

NUC-1031: The First Anti-Cancer ProTide

- ProTide transformation of gemcitabine
- Overcomes key gemcitabine resistance mechanisms[2,3]
  - 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:
  - Greater plasma stability
  - Increased intracellular levels of active anti-cancer metabolite, dFdCTP
  - Reduced toxic metabolites

NUC-1031 overcomes the key cancer resistance mechanisms of gemcitabine



Study Design

Primary Objectives

- Safety
- RP2D

Secondary Objectives

- ORR, PFS, OS
- PK

Methods

- Cohort 1: 625 mg/m² NUC-1031 +25 mg/m² cisplatin
- Cohort 2: 725mg/m² NUC-1031 + 25mg/m² cisplatin
- IV infusion on Days 1 and 8 of a 21-day cycle
- Treatment continued until intolerable toxicity or PD

Patient Population

- Aged ≥18 years, ECOG PS 0 or 1
- Non - resectable or recurrent / metastatic histo/cytologically - verified cholangiocarcinoma, gallbladder or ampullary carcinoma
- No prior systemic therapy for BTC

Results

Patient Characteristics

- **Intention-to-treat (ITT) population:** 14 patients: Cohort 1 (n=8); Cohort 2 (n=6)
- **Efficacy Evaluable (EE) population:** 11 patients completed ≥ 1 cycle
- Median age 61 years (range 48-78 years)
- BTC subtypes: hilar (n=5), distal bile duct (n=4), ampullary (n=2), intrahepatic (n=2), and gallbladder (n=1)

Reason for treatment discontinuation	Patients (n)
Treatment delay >21 days	**9***
Blocked biliary stent	2
Biliary drainage	1
Cholangitis	1
Liver cirrhosis	1
Radiological pneumonitis	1
Small bowel perforation	1
Reduced performance status	1
Patient request	1
Other	**1**
Patient suitable for resection	1
Disease progression	**2**
Death	**1#**
Consent withdrawn	**1**
Total patients off study	**14**

** No treatment delays >21 days were drug related.*
\# The patient was scheduled to come off study due to biliary obstruction and pyrexia, which prevented continuation of treatment. The patient died shortly before being discontinued from the study due to complications arising.

Results

Efficacy

Objective Response Rates in ABC-08 and ABC-02

	ABC-08		ABC-02
	Efficacy Evaluable	ITT	ITT
Complete Response	**9%** (1/11)	**7%** (1/14)	**0.6%** (1/161)
Partial Response	**55%** (6/11)	**43%** (6/14)	**25.5%** (41/161)
Objective Response Rate	**64%** (7/11)	**50%** (7/14)	**26.1%** (42/161)

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

- Encouraging anti-tumour activity for NUC-1031 + cisplatin
- Median follow-up 44 weeks (range 16-131 weeks)

Recommended Phase II Dose

- No difference between Cohort 1 and Cohort 2 (safety, efficacy, PK)
- RP2D of NUC-1031 is 625 mg/m² (+ cisplatin 25 mg/m²)
- Expansion cohort ongoing (n=6)

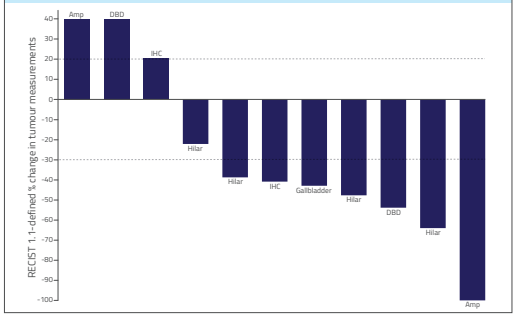
Safety Profile

- NUC-1031 + cisplatin was well tolerated
  - No unexpected adverse events (AEs)
  - Multiple cycles administered (median 8; range 3.5-14)
- 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

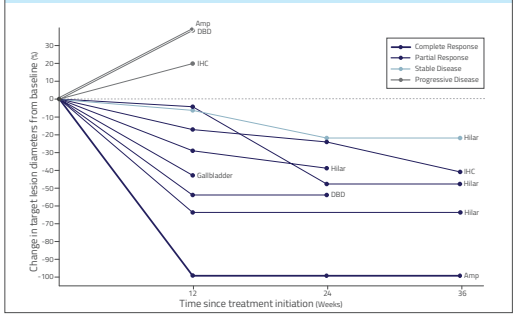
Pharmacokinetics

- NUC-1031 + cisplatin generated stable and high levels of intracellular dFdCTP in patients' peripheral blood mononuclear cells
- Intracellular dFdCTP levels were durable (mean half-life = 22 hours)

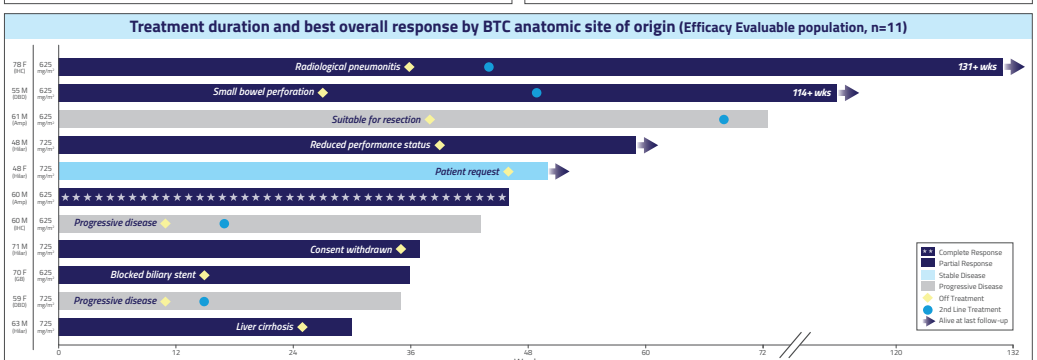
Best response to treatment (Efficacy Evaluable population)



Tumour burden during study treatment (Efficacy Evaluable population)



Treatment duration and best overall response by BTC anatomic site of origin (Efficacy Evaluable population, n=11)



Conclusions

Safety

- NUC-1031 + cisplatin is well-tolerated over multiple cycles
  - No unexpected AEs
  - No DLTs
  - No discontinuations related to NUC-1031

RP2D

- NUC-1031 (625 mg/m²) + cisplatin (25 mg/m²)

Efficacy

- Encouraging ORR compared to SOC
- All subtypes sensitive to NUC-1031 + cisplatin
- Durable tumour shrinkage
- Promising survival outcomes in difficult to treat population

Global Phase III Study Planned

First-line advanced BTC

NUC-1031 (625 mg/m²) + cisplatin (25 mg/m²) vs gemcitabine (1000 mg/m²) + cisplatin (25 mg/m²)

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. Cancer Res* 2016; 76: Suppl abstr 2914.

DBD: Distal Bile Duct **IHC:** intrahepatic Cholangiocarcinoma **Hilar:** Hilar Cholangiocarcinoma **GB:** Gallbladder

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