ABC-08: A phase Ib, multi-centre, open-label study of a first-in-class nucleotide analogue NUC-1031 in combination with cisplatin in patients with locally advanced/metastatic biliary tract cancers

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BACKGROUND

- No agents 'approved' specifically for the treatment of advanced/metastatic biliary tract cancer
- Current standard of care remains gemcitabine + cisplatin (ABC-02)[1]
- No clinical studies since ABC-02 have reported an extension in overall survival
- Resistance to chemotherapy reduces patient survival
- Effective new agents and combinations are required

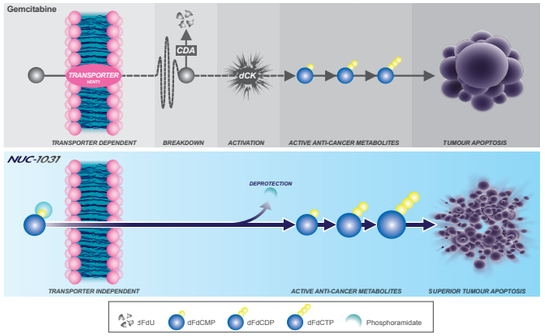
ProTides: NucleoTide Analogues

- A new class of anti-cancer agents
- Designed to overcome key cancer resistance mechanisms
- Transformative phosphoramidate chemistry
- Increase intracellular levels of active anti-cancer metabolite, difluorodeoxycytidine triphosphate (dFdCTP)
- Broad clinical utility

NUC-1031: The First Anti-Cancer ProTide

- NUC-1031 is a first-in-class nucleotide analogue
- A 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)
    - Greater stability
    - Reduction in toxic metabolites

NUC-1031 bypasses the key cancer resistance pathways of gemcitabine



PRO-001: First-in-Human Study

- Highly active as a single agent in relapsed/refractory cancers[4]
  - 78% disease control rate (DCR) in advanced solid tumours
  - 93% DCR in patients with advanced gynaecological cancers
- Well-tolerated
  - No unexpected adverse events (AEs)
  - Manageable myelosuppression and reversible transaminase elevation
- Generated considerably higher intracellular levels of dFdCTP compared with gemcitabine on an equimolar basis[3]
  - 217× greater C_{max}
  - 139× greater AUC

STUDY DESIGN

Objectives

Primary

- Assess safety of NUC-1031 in combination with cisplatin
- Determine the recommended Phase II dose of NUC-1031 in combination with cisplatin

Secondary

- Efficacy
- Progression-free survival
- Response rate
- Overall survival
- Pharmacokinetics (PK)

Methods

- Starting dose of NUC-1031 in Cohort 1 was 625 mg/m^2 administered IV on days 1 and 8 in combination with cisplatin (25 mg/m^2) of a 21-day schedule (Cohort 1; results presented)
- The Cohort 2 dose of NUC-1031 was 725 mg/m^2
- Treatment to continue until intolerable toxicity or progressive disease

Patient Population

- Aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
- Non-resectable or recurrent/metastatic histo-/cytologically verified cholangiocarcinoma, gallbladder or ampullary carcinoma
- No prior systemic therapy

COHORT 1 RESULTS (625 mg/m^2)

Patient Characteristics

- 8 patients (5 males, 3 females)
- Median age 66 years (range 55-78)
- 6 patients received ≥1 cycle

Tumour Sites

Intrahepatic	Hilar	Distal Bile Duct	Ampulla	Gallbladder
2	1	2	2	1

Safety Profile

- NUC-1031+ cisplatin well-tolerated
  - No unexpected AEs reported
  - Multiple cycles administered (median 4; range 0.5-12)
- No Dose Limiting Toxicities (DLTs)
- Grade 3 related treatment-emergent adverse events (TEAEs) included:
  - 2 neutropaenia
  - 2 ALT, 1 AST
  - 1 nausea
  - 1 pyrexia
  - 1 GGT
- No Grade 4 related TEAEs
- 2 patients discontinued early due to non-drug related events: cholangitis and blocked stent

Pharmacokinetics

- Combination with cisplatin generated stable and high levels of intracellular dFdCTP in patient's peripheral blood mononuclear cells
- Intracellular dFdCTP levels were durable (mean $t_{½}$=22 hours)
- PK data are consistent with first-in-human PRO-001 study

Cohort 1 Pharmacokinetic Parameters (n=6)

	NUC-1031 plasma Mean (Min-Max)	dFdCTP intracellular Mean (Min-Max)
$AUC_{0\text{-}4}$ (μg/mL/hr)	206 (54 - 579)	12.41 (8.08 - 21.04)
C_{max} (μg/mL)	130 (29 - 280)	4.26 (2.46 - 6.64)

Efficacy

- Strong efficacy signal for NUC-1031 (625 mg/m^2) in combination with cisplatin (25 mg/m^2)
  - 1 Complete Response (13%), 3 Partial Responses (38%), 1 Stable Disease (SD) (13%)
  - Objective Response Rate = 50%
  - Disease Control Rate = 63%
- The patient with SD had sufficient tumour shrinkage to allow surgical resection

Objective Response Rates in ABC-08 and ABC-02 Studies

	ABC-08	ABC-02[1]
	NUC-1031 + cisplatin 625 mg/m^2 + 25 mg/m^2	gemcitabine + cisplatin 1000 mg/m^2 + 25 mg/m^2
Complete Response	13% (1/8)	0.6% (1/161)
Partial Response	38% (3/8)	25.5% (41/161)
Objective Response Rate	50% (4/8)	26.1% (42/161)

CONCLUSIONS

- ABC-08 Cohort 1 data demonstrated strong efficacy signals
  - Objective Response Rate = 50%
  - Stable Disease = 13%
  - Disease Control Rate = 63%
- Regimen is well-tolerated
  - No unexpected AEs
  - No DLTs
- NUC-1031 is stable in plasma and generates significant intracellular levels of the active anti-cancer metabolite, dFdCTP
- Trial Management Group review of Cohort 1 and 2 data established that the Cohort 1 dose was optimal
- NUC-1031 at 625 mg/m^2 + cisplatin at 25 mg/m^2 is an attractive and effective combination for treatment of patients with advanced/metastatic biliary tract cancer
- A Phase III study comparing NUC-1031 + cisplatin versus gemcitabine + cisplatin as first-line treatment of patients with advanced/metastatic biliary tract cancer is planned

1. Valle *et al. N Engl J Med* 2010; 363:1273-1281 2. Slusarczyk *et al. J Med Chem* 2014; 27:513-542 3. Blagden *et al. Cancer Res* 2016; 76: Suppl abstr CT028 4. Blagden *et al. J Clin Oncol* 2015; 33: Suppl abstr 2514

Data current as of 22nd Nov 2017. Data cleaning ongoing.