Anti-cancer activity in patients with advanced ovarian and biliary tract cancers treated with NUC-1031 and platinum agents

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Background

- Nucleoside analogs and platinum agents remain cornerstone therapies for many solid malignancies
- Resistance to chemotherapy reduces patient survival
- Patients with advanced biliary tract cancer (BTC) or recurrent ovarian cancer (OC) have limited treatment options
- Effective new agents and rational combinations are required

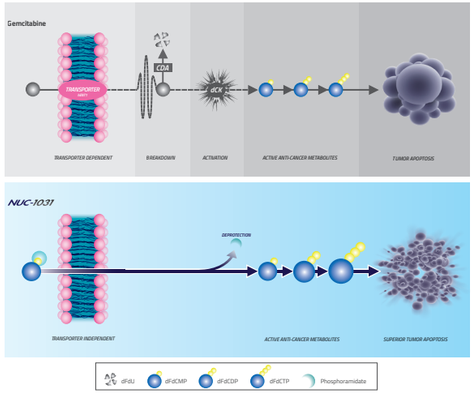
ProTides: NucleoTide Analogs

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

NUC-1031: The First Anti-Cancer ProTide

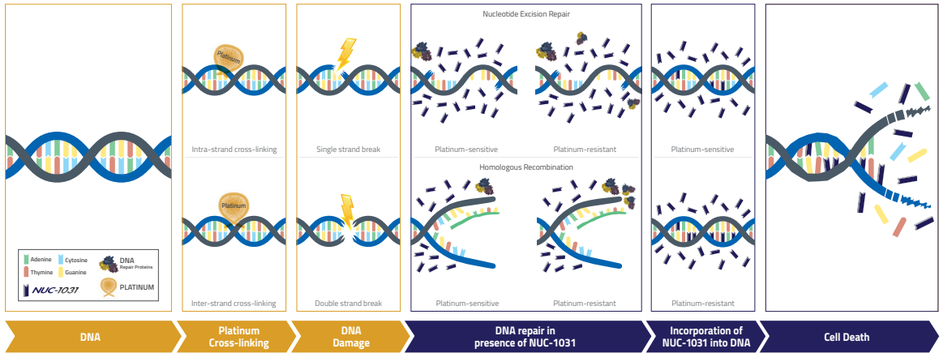
- ProTide transformation of gemcitabine
- Overcomes key gemcitabine resistance mechanisms associated with a poor survival prognosis[1]
  - Cellular uptake independent of nucleoside transporters (hENT1)
  - Activation independent of deoxycytidine kinase (dCK)
  - Protected from breakdown by cytidine deaminase (CDA)
- Increased intracellular generation of the active anti-cancer metabolite, dFdCTP: 217 greater than gemcitabine[2]

NUC-1031 overcomes the key cancer resistance mechanisms of gemcitabine



Potential Mechanism of NUC-1031 + Platinum Synergy

- NUC-1031 and platinum agents induce cancer cell death through a variety of different mechanisms
  - Platinum forms DNA adducts
  - Activates DNA damage response
  - Attempted repair by removal of adducts and synthesis of new DNA strands
  - Anti-cancer metabolite (dFdCTP) incorporated into DNA leading to cell death
- These mechanisms may be complementary in causing irreversible DNA damage
- Hypothesis: Platinum treatment primes or sensitizes cancer cells to further damage with NUC-1031
- This synergy is proposed to exist in both platinum-sensitive and platinum-resistant tumors



Ovarian Cancer: NUC-1031 + Carboplatin (PRO-002 study)[3]

Phase Ib study of NUC-1031 (500-750 mg/m²) + carboplatin (AUC 4 or 5) in 25 patients with recurrent OC who had exhausted all therapeutic options

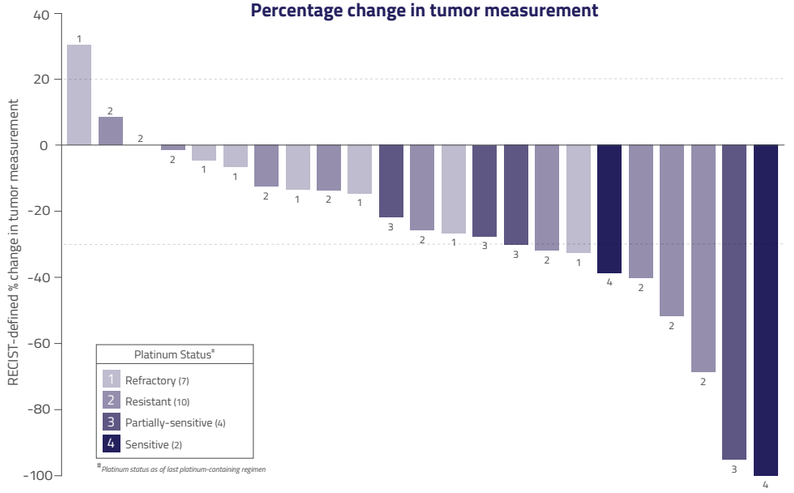
- Heavily pre-treated population (median 3 prior chemotherapy lines; range: 2-6)
- 23 patients evaluable for response (received ≥1 cycle):
  - 7 platinum-refractory
  - 10 platinum-resistant
  - 4 partially platinum-sensitive
  - 2 platinum-sensitive
- High levels of disease control across all platinum status subgroups
- Combination is well-tolerated over multiple cycles

Best overall response

	All evaluable patients (n=23)	Platinum-refractory patients (n=7)	Platinum-resistant patients (n=10)	Platinum-partially sensitive patients (n=4)	Platinum-sensitive patients (n=2)
CR	1 (4%)	0	0	0	1 (50%)
PR	8 (35%)	1 (14%)	4 (40%)	2 (50%)	1 (50%)
ORR	**9 (39%)**	**1 (14%)**	**4 (40%)**	**2 (50%)**	**2 (100%)**
SD	13 (57%)	5 (71%)	6 (60%)	2 (50%)	0
DCR	**22 (96%)**	**6 (86%)**	**10 (100%)**	**4 (100%)**	**2 (100%)**

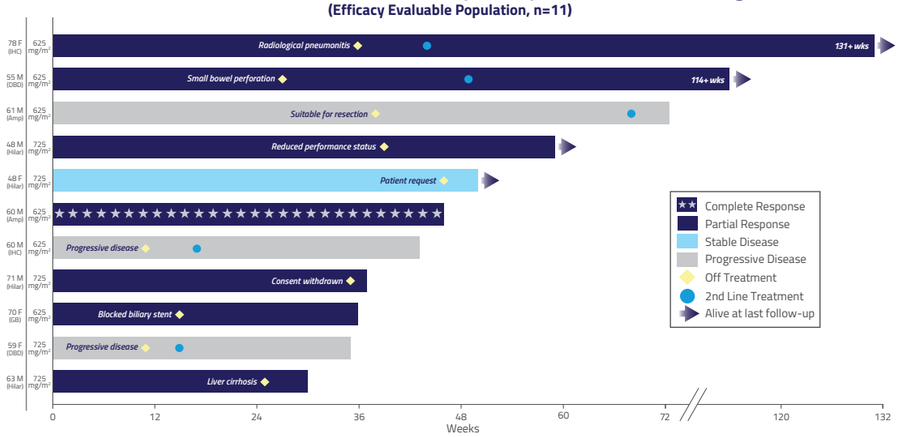
A confirmatory scan was not performed in all responders
Platinum status as of last platinum-containing regimen

Percentage change in tumor measurement



Biliary Tract Cancer: NUC-1031 + Cisplatin (ABC-08 study)[4]

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



Phase Ib study of NUC-1031 (625 or 725 mg/m²) + cisplatin (25 mg/m²) as first-line therapy in patients with advanced BTC

- Intention-to-treat (ITT) population: 14 patients
- Evaluable population: 11 patients (completed ≥1cycle)
- Promising ORR compared to standard of care (gemcitabine + cisplatin)
- Responses achieved in all BTC subtypes
- Durable tumor shrinkage
- Combination is well-tolerated over multiple cycles

Objective response rates

	ABC-08 NUC-1031 + cisplatin	ABC-02[5] 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

Summary

- High response rates achieved in difficult to treat patient populations
  - 39% ORR in recurrent OC
  - 50% ORR in advanced BTC
- NUC-1031 + platinum agents are well tolerated over multiple cycles
- Clinical observations coupled with known mechanisms of action support hypothesis that NUC-1031 is synergistic with platinum agents
- Future clinical studies will explore platinum combinations in:
  - Recurrent OC (Phase II/III planned)
  - Advanced BTC (Phase III, NuTide:121, to open in 2019)

References: 1: Slusarczyk; *et al. J Med Chem* 2014; 57:1531-1542. 2: Blagden *et al Br J Cancer* 2018; 119:815-822. 3: Blagden *et al Cancer Res* 2016; 76: Suppl abstr 2514. 4: McNamara *et al Ann Oncol* 2018; 29 :Suppl 8 Abstract ID: TPS544. 5: Valle *et al. N Engl J Med* 2010; 362:1273-1281.
DBD: Distal bile duct IHC: Intrahepatic cholangiocarcinoma Hilar: Hilar cholangiocarcinoma GB: Gallbladder Amp: Ampullary

PRO-002 data current as of Sept 1 2017. Data cleaning ongoing. ABC-08 data current as of Aug 30 2018. Data cleaning ongoing.