A Phase Ib open label study to assess the safety and pharmacokinetics of NUC-3373, a nucleotide analog, given in combination with standard agents used in colorectal cancer treatment (NuTide:302)

SP Blagden1, TRJ Evans2, E Ghazaly3, C Gnanaranjan3, A De Gramont4, J Tabernero5, JD Berlin6

1) Early Phase Clinical Trials Unit, Churchill Hospital, University of Oxford NHS Trust, Oxford, UK. 2) University of Glasgow, Beatson Institute for Cancer Research, Glasgow, UK.
3) Centre for Haematology, National Health Service Institute, London, UK. 4) Department of Medical Oncology, Institut Hospitalier Franco-Britannique, Levallois-Perret, France.
5) Early Drug Development Unit, Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology, CBERONC, Universitat Autonoma de Barcelona, Barcelona, Spain.
6) Henry-Joyce Cancer Clinic, The Vanderbilt Clinic, Nashville, TN, USA.

Background

- Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women1 and has a 5-year survival rate of 10% for patients with metastatic disease
- 5-Fluorouracil (5-FU) remains standard of care for patients with CRC, either as monotherapy or in combination with other chemotherapies
- Fluorodeoxyuridine-monophosphate (FUDR-MP) is the main anti-cancer metabolite of 5-FU, which binds to and inhibits thymidylate synthase (TS), reducing the pool of deoxynucleoside monophosphate (dNMP), leading to cancer cell death
- Key cancer resistance mechanisms are linked to reduced efficacy, poor prognosis and off-target toxicity with 5-FU regimen2
- Poor PK properties of 5-FU, including a plasma half-life of 8-14 minutes, necessitate prolonged administration times, often over 46 hours
- Effective new agents and combinations are required

5-FU Resistance Mechanisms

Susceptibility to breakdown
- Over 85% of 5-FU is broken down by dihydrouridine dehydrogenase (DHPD)3
- Thymidine phosphorylase (TP), commonly overexpressed in tumors2 or introduced by mycoplasma infection4, also breaks down 5-FU
- Metabolic degradation results in generation of toxic metabolites such as dihydrofluorouracil (dHFU), which is associated with hand-foot syndrome

Requirement of activation
- 5-FU is a pro-drug that requires complex intracellular enzymatic activation to generate FUDR-MP5
- Deficient enzymatic activation is linked to poor prognosis

Reliance on active transport
- Low expression of the nucleoside transporter hENT1 is associated with 5-FU resistance5

ProTides: NucleoTide Analogs

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

NUC-3373: A ProTide Transformation of 5-FU

- Designed to overcome key 5-FU resistance mechanisms6,7
- Generates 366x higher intracellular levels of FUDR-MP than 5-FU in human CRC cells in vitro
- Up to 330x significantly greater cytotoxicity than 5-FU in vitro
- Significantly greater anti-cancer activity in vivo compared to 5-FU
- Not degraded by DPD or TP
- Favorable toxicology profile

NuTide:301 Study

NUC-3373 first-in-human study in advanced solid tumors

- This study is ongoing and the results are based on interim data (n=21)8
- Patients had 10 primary cancer types, with the majority (57%) being CRC
- NUC-3373 showed an advantageous pharmacokinetic (PK) and pharmacodynamic (PD) profile compared to 5-FU, which may allow for a more convenient dosing regimen, favorable safety profile and enhanced efficacy
- Intracellular FUDR-MP detectable at 5 minutes post-infusion with 1/3 of 14.9±1.4 hours and still present at 48 hours
- TS was efficiently inhibited and sequestered into ternary complexes, depleting the pool of dTMP within 2-4 hours
- The toxic metabolite dHFU was undetectable, suggestive of an improved tolerability profile compared to 5-FU
- Based on these data, the NuTide:302 study was initiated to investigate NUC-3373 in combination with other anti-cancer agents in patients with recurrent CRC

NuTide:302 Study Design

Primary objective
- Determine a recommended dose of NUC-3373 in combination with agents commonly used in the treatment of CRC

Secondary objectives
- Safety and tolerability in each combination
- Effects of each combination agent on PK of NUC-3373
- Anti-tumor activity of each combination
- Effect of leucovorin (LV) when added to NUC-3373 on PK and PD parameters

Exploratory objectives
- Assess markers of resistance to 5-FU in blood and pre-treatment tumor samples
- Relationships between NUC-3373 PK, PD and clinical activity

Patient Population
- Aged ≥18 years with an ECOG performance status of 0-1
- Locally advanced/unresectable or metastatic CRC
- Relapse after ≥2 prior lines of therapy; one must be an oxaliplatin + 5-FU containing regimen and one must be an irinotecan + 5-FU containing regimen
- Measurable disease as defined by RECIST

Methods
- Patients treated every 2 weeks until disease progression

NuTide:302: Patients with recurrent metastatic CRC

Table: NUC-3373 PK profile comparison with 5-FU

<table>
<thead>
<tr>
<th></th>
<th>NUC-3373</th>
<th>5-FU</th>
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</thead>
<tbody>
<tr>
<td>Plasma t1/2</td>
<td>9.7 hours</td>
<td>8-14 minutes</td>
</tr>
<tr>
<td>FUDR-MP (vd/FU)</td>
<td>Detected (dose proportional)</td>
<td>Undetected</td>
</tr>
<tr>
<td>TS inhibition</td>
<td>Strong</td>
<td>Weak</td>
</tr>
<tr>
<td>Intracellular levels of dTMP</td>
<td>Strong</td>
<td>Weak</td>
</tr>
<tr>
<td>Toxic metabolite (dHFU)</td>
<td>Undetected</td>
<td>High levels</td>
</tr>
</tbody>
</table>

Summary

NUC-3373 is specifically designed to overcome the key cancer cell resistance mechanisms associated with 5-FU
The NuTide:302 study will determine the optimal dose of NUC-3373 in combination with agents commonly used in the treatment of patients with CRC
NUC-3373 has the potential to offer a more effective and safer treatment option than 5-FU

Study Status

- Study open with sites in the US, UK, Spain and France

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References
1. GLOBOCAN, 2012
9. Detected (dose proportional) Undetected