9-ING-41, a small molecule selective Glycogen Synthase Kinase-3 Beta (GSK-3β) inhibitor -

Progress to date in adult patients with cancer

May 2020
9-ING-41 has dose-proportional pharmacokinetics

It is well tolerated with no attributable SAEs

Antitumor activity as monotherapy: ongoing CR in a patient with refractory BRAF-mutated melanoma

Disease stability in combination with chemotherapy in patients previously exposed to the same chemotherapy agent(s)

Phase 2 study of 9-ING-41 plus gemcitabine/nab-paclitaxel in previously untreated advanced pancreatic cancer patients underway

Phase 2 study in patient with advanced myelofibrosis underway

Phase 1 pediatric study underway

Oral formulation in development
The relevance of Glycogen Synthase Kinase-3 Beta (GSK-3β) in cancer

- Constitutively active serine-threonine kinase
- The increased expression and aberrant function has been implicated in the biology of numerous diseases, including cancer, inflammation, fibrosis, and neurodegeneration
- Positive regulator of NF-kB, promoting cancer cell survival and proliferation by facilitating chemoresistance
- In the nucleus, it regulates NF-kB binding to its target gene promoters and modulates oncogenes (e.g., b-catenin, cyclin D1, and c-Myc)
- ATR-mediated DNA damage response (DDR), cell cycle arrest, and tumor immune surveillance
9-ING-41 - First clinically relevant small molecule potent selective GSK-3β inhibitor

- Reversible ATP-competitive inhibitor
- Inhibition of nuclear GSK-3β leads to its rapid degradation and is followed by downregulation of anti-apoptotic molecules (e.g., Bcl-2, XIAP, Bcl-XL)
- Significant pre-clinical antitumor activity in a broad spectrum of malignancies, including pancreatic cancer, GBM, lymphoma, neuroblastoma, breast cancer, ovarian cancer and bladder cancer models

![Chemical Structure](image)
9-ING-41 shows pre-clinical activity in pancreatic cancer

- 9-ING-41 potentiates the antitumor effect of standard agents in pancreatic cancer cells.
- 9-ING-41 enhances the antitumor effect of gemcitabine and liposomal irinotecan in pancreatic PDX Tumors In Vivo.
9-ING-41 sensitizes pancreatic cancer cells to chemotherapy

- Impairs TopBP1/ATR-mediated DNA damage response induced by gemcitabine

![Pathway Diagram]

- GSK-3β inhibits TopBP1/ATR-mediated DNA damage response.
- Gemcitabine induces cell cycle arrest and DNA repair.
- 9-ING-41 compromises DNA repair, sensitizing cells to chemotherapy.

Benedito A. Carneiro, MD, MS
Part 1: Enrolling specific patient cohorts @ RP2D of single agent 9-ING-41

Part 2: Define RP2D of 9-ING-41 in combination with standard chemotherapy chosen by investigator based on diagnosis and prior treatment: 9-ING-41 plus

- Gemcitabine
- Doxorubicin
- Carboplatin
- Irinotecan
- Lomustine
- Nab-Paclitaxel plus Gemcitabine
- Paclitaxel plus Carboplatin
- Pemetrexed plus Carboplatin

Part 3: Simon 2-Stage design Phase II studies

9-ING-41 plus Nab-Paclitaxel 125 mg/m2 IV and Gemcitabine 1000 mg/m2 IV Days 1, 8 and 15 - 28-day cycle

- 9-ING-41 is given IV twice a week, on days 1 and 4
Study 1801 objectives

► Phase 1 (parts 1 and 2):
  ■ Evaluate the safety of 9-ING-41 as monotherapy (Part 1) and in combination with chemotherapies (Part 2) in patients with advanced malignancies using standard 3+3 dose escalation design
  ■ Determine the maximum tolerated dose (MTD) or the recommended Phase 2 study dose (RP2D)

► Key eligibility:
  ■ Relapsed or refractory malignancies
  ■ Adequate organ function
  ■ For part 2, patient must have received the chemotherapy for treatment of the same malignancy
Study 1801 part 1 and 2 results to date – data cutoff April 27th, 2020

► Part 1: 9-ING-41 Single Agent Cohorts
  - 1 – 1 mg/kg
  - 2 – 2 mg/kg
  - 3 – 3.3 mg/kg
  - 4 – 5 mg/kg
  - 5 – 7 mg/kg
  - 6 – 9.3 mg/kg
  - 7 – 12.4 mg/kg
  - 8 – 15 mg/kg

N = 57 pts enrolled

► Part 2: Chemotherapy + 9-ING-41
  - Carboplatin
  - Carboplatin/Paclitaxel
  - Doxorubicin
  - Gemcitabine
  - Gemcitabine/Nab-Paclitaxel
  - Irinotecan
  - Lomustine

N = 116 pts enrolled
## Patient demographics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Part 1</th>
<th>Part 2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(N = 56)</td>
<td>(N = 99)</td>
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<tr>
<td><strong>Median age, years (range)</strong></td>
<td>61 (28–88)</td>
<td>61 (30–90)</td>
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<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (53.6%)</td>
<td>52 (52.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (46.4%)</td>
<td>47 (47.5%)</td>
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<tr>
<td><strong>Tumor Types, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>26</td>
<td>58</td>
</tr>
<tr>
<td>Thoracic</td>
<td>5</td>
<td>8</td>
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<tr>
<td>GYN</td>
<td>2</td>
<td>8</td>
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<tr>
<td>Breast</td>
<td>0</td>
<td>7</td>
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<tr>
<td>GU</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Melanoma/Skin</td>
<td>8</td>
<td>2</td>
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<tr>
<td>Sarcoma</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Lymphoma/Leukemia</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Head/Neck</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>GBM/Gliomas</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Prior systemic treatments, median (range)</strong></td>
<td>2 (1–13)</td>
<td>3 (1–14)</td>
</tr>
<tr>
<td><strong>ECOG Performance Status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS 0</td>
<td>19 (33.9%)</td>
<td>32 (32.3%)</td>
</tr>
<tr>
<td>PS 1</td>
<td>36 (64.3%)</td>
<td>63 (63.6%)</td>
</tr>
<tr>
<td>PS 2</td>
<td>1 (1.8%)</td>
<td>3 (3.0%)</td>
</tr>
</tbody>
</table>
9-ING-41 pharmacokinetics: dose-proportional exposure

- The mean concentration-time profiles do not change with the repeated dosing at 3 and 4-day intervals.
- Most exposure occurs within 6 hours of start of infusion (SOI). Concentrations decline ~70-75% from peak by 6 hours after SOI, and by 80-90% from peak by 24 hours after SOI.
9-ING-41 single-agent pharmacokinetics

9-ING-41’s mean terminal half-life is 12-20 hrs

$C_{\text{max}}$ and $\text{AUC}_{0-72}$ are dose proportional with no accumulation

R² = 0.6055
9-ING-41 single-agent attributable adverse events (N= 56)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1 N (%)</th>
<th>Grade 2 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Vision Change</td>
<td>20 (35.7%)</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Infusion Reaction</td>
<td>2 (3.5%)</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3.5%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>1 (1.7%)</td>
</tr>
</tbody>
</table>

¬ No Grade 3 or Grade 4 attributable SAEs
9-ING-41 attributable adverse events combinations (interim)

- No Grade 3 or Grade 4 9-ING-41 attributable SAEs
- No new or additional AEs
- No evidence of increased 9-ING-41 toxicity with chemotherapy
- Potential RP2D 15 mg/kg
9-ING-41 complete response in a patient with advanced melanoma

► 55 yo male with BRAF V600K mutated metastatic melanoma
► Refractory to immune checkpoint and BRAF/MEK inhibitors

MRI on Prior Treatment
Stable Disease

MRI During Washout
Apparent Growth

Baseline PET Scan
Baseline

6 weeks on 9-ING-41
Excellent Response

12 weeks on 9-ING-41
Complete Metabolic Response

18 weeks on 9-ING-41
Complete Metabolic Response
Patients with pancreatic cancer in phase I (N=42)

Duration of Treatment (Weeks)

- Part 1
- Part 2: Nab-paclitaxel and Gemcitabine
- Part 2: Irinotecan
- Part 2: Gemcitabine
- Pts receiving >1 dose 9-ING-41
- On Study
Actuate 1801: 9-ING-41 phase I/II study schema

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Conclusions

► 9-ING-41 has dose-proportional pharmacokinetics
► It is well tolerated with no 9-ING-41 attributable SAEs
► Antitumor activity as monotherapy: ongoing CR in a patient with refractory BRAF-mutated melanoma
► Disease stability in combination with chemotherapy in patients previously exposed to the same chemotherapy agent(s)
► Phase 2 study of 9-ING-41 plus gemcitabine/nab-paclitaxel in previously untreated advanced pancreatic cancer patients underway
9-ING-41 development

Indication | 2019 | 2020 | 2021 | 2022
--- | --- | --- | --- | ---
Cancers | | 1801 – Phase 1 / 2 Trial | | |
Myelofibrosis | | | 1901 – Phase 2 Myelofibrosis | |
Neuroblastoma | | | | 1902 Pediatric Phase 1 - 2001 Phase 2 Neuroblastoma
Pancreatic Cancer | | Phase 2 | | |
Checkpoint Inhibitor Failure | | | Phase 2 | |

Oral Formulation | Prototype Development | Oral Formulation Development / Testing | Manufacturing / Formulation Phase 1 Oral Bridging Study - NHV | |
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fgiles@actuatetherapeutics.com