NMS-01940153E, an MPS1 Inhibitor with Anti-tumor Activity in Relapsed or Refractory Unresectable Hepatocellular Carcinoma

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Declaration of Interests

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MPS1 (Monopolar spindle 1) kinase regulates the spindle assembly checkpoint*

Inhibition of MPS1 leads to cancer death through excess mitotic instability*

NMS-153 (NMS-01940153E) is an inhibitor of MPS1 active against a variety of cancer cell lines

NMS-153 is a Novel Therapeutic Strategy for HCC

High Unmet Medical Need
- HCC third line has few options; novel mechanism needed.

Reig M et al J Hepatol. 2022 Mar;76(3):681-693.
**High Unmet Medical Need**

- Hepatodellular Carcinoma (HCC) third line has few options; novel mechanism needed.
- Jiang et al (UIGM 2021) showed high expression of MPS1 in HCC; correlations with clinical factors.

**Preliminary Signs of Clinical HCC Activity**

- NMS-153 (also known as S81694) first-in-human, solid tumors*;
- 38 patients, 4-135 mg/m²/w (3 of 4 weeks), 35 evaluable;
- One, out of two, HCC patient (both with RECIST stable disease lasting 6 months) had transient decrease in target lesions:
  - 27% reduction in liver target lesion; three prior systemic therapies; 135 mg/m²/w.

*Servier Pharmaceuticals; Schöffski et al, Eur J Cancer 2022

**New Preclinical Data Shows Direct Anti-proliferative Effect in HCC**

NMS-153 is highly active in HCC cell lines

HCC-panel (7 cell lines) shows sensitivity of NMS-153 relative to traditional HCC agents

* Doxorubicin was used as a positive internal control
Phase I/II Study on Safety and Efficacy of NMS-01940153E (NMS-153) in Adult Patients with Unresectable Hepatocellular Carcinoma (HCC) Previously Treated with Systemic Therapy

**MPSA-153-001**

**Phase I**
- dose-finding; HCC patients who failed standard options;
- maximum tolerated dose (MTD);
- recommended phase 2 dose (RP2D);
- safety and tolerability;
- preliminary anti-tumor activity;
- 3+3 Design

**Phase II**
- expansion cohort (up to 40 patients; stopping rule at N=10);
- 3L+ HCC patients having failed at least an Immune-Checkpoints inhibitor in 1st line and one tyrosine kinase inhibitor line

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**RP2D**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>112</td>
</tr>
</tbody>
</table>

NMS-153 IV Continue until progression* or intolerability

*patients allowed to continue beyond progression if potential benefit in the opinion of the investigator
## MPSA-153-001 HCC Patient Characteristics
### Phase I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Safety Population N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age years</strong> – median (range)</td>
<td>64 (28-76)</td>
</tr>
<tr>
<td><strong>Sex, Male</strong> – n (%)</td>
<td>11 (91.7)</td>
</tr>
<tr>
<td><strong>Disease Extent</strong> – n (%)</td>
<td></td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>6 (50)</td>
</tr>
<tr>
<td><strong>Measurable Disease</strong></td>
<td>12 (100%)</td>
</tr>
</tbody>
</table>

### AlphaFetoprotein (AFP) Category Level – n (%)
- ≤ ULN: 4 (33.3)
- < ULN - < 400 ug/L: 4 (33.3)
- ≥ 400 ug/L: 4 (33.3)

### Sites of Metastases* – n (%)
- Lung: 4 (33.3)
- Lymphnode: 3 (25)
- Bone: 1 (8.3)
- Abdominal muscles: 1 (8.3)
- Left portal vein neoplastic thrombosis: 1 (8.3)
- Peritoneum: 1 (8.3)

### ECOG Performance Status – n (%)
- 0: 6 (50)
- 1: 6 (50)

### Child-Pugh Class A – n (%)
- 12 (100)

### ALBI Grade – n (%)
- 1: 10 (83.3)
- 2: 2 (16.7)

### No. Prior Anticancer Regimens – median (range)
- 2 (1-3)

### Prior Anticancer Therapies# – n (%)
- Sorafenib: 9 (75)
- Cabozatinib: 4 (33.3)
- Regorafenib: 3 (25)
- Lenvatinib: 3 (25)
- Nivolumab: 1 (8.3)
- Pembrolizumab + Regorafenib: 1 (8.3)
- Atezolizumab + Bevacizumab: 1 (8.3)
- Durvalumab: 1 (8.3)

*Patients with more than one metastatic site are counted for each reported site; # Patients with more than one line of therapy are counted for each reported one.
## Safety – Drug related TEAEs

### Phase I

<table>
<thead>
<tr>
<th></th>
<th>100 mg/m²/wk N=6</th>
<th>135 mg/m²/wk N=6</th>
<th>All Patients N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Max CTC AE Grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max CTC AE Grade</td>
<td>G 1-2</td>
<td>G3</td>
<td>G4</td>
</tr>
<tr>
<td>Preferred Term</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0 (0)</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Platelet Count Decreased</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chromaturia</td>
<td>1 (16.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (16.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Systemic Hypertensive Crisis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (16.7)</td>
</tr>
</tbody>
</table>

All categories with at least one ≥G3 drug related TEAE or with a frequency of at least 10% in the total population of any grade drug related TEAEs

- **No grade 5 Adverse Events (AEs)**
- **MTD = 100 mg/m²/w**
- **2 G4 neutropenia-related DLTs at 135 mg/m²/w**;
- Neutropenia recovery to ≤G1 from onset of a ≥G3 was 9.5 days average (SD 7.4);
- One discontinuation due to AE: 135 mg/m²/w; end of Cycle 2; related asthenia Gr 3 and platelet count decrease Gr 3;
- 2 patients missed doses during the first two cycles: 1 pt at 100 mg/m²/w (Gr 2 neutropenia); 1 pt at 135 mg/m²/w (Covid infection);
- 1 pt at 100 mg/m²/w interrupted C1D15 infusion due to infusion reaction.

Data cut-off 16Aug2022

TEAEs = Treatment Emergent Adverse Events

MTD = Maximum Tolerated Dose
Patients 003 and 012 continued treatment beyond first radiographic progression;
11/12 patients were evaluable for RECIST1.1 (pt 005 experienced cycle 1 DLT - Gr 4 neutropenia with Gr 4 sepsis - and was withdrawn for >1 week treatment delay from day 28).

AFP = Alpha Fetoprotein; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease
Minimum AUC projected for clinical activity based on mouse tumor stabilization model

$C_{max} (\mu M)\newline
\begin{align*}
1.35, \text{range } 0.7-3.0, \text{ SD } 1.10 \\
1.59, \text{range } 0.8-4.2, \text{ SD } 1.31
\end{align*}$

$AUC_{\text{weekly}} (\mu M*\text{h})\newline
\begin{align*}
32.5, \text{range } 24.8-39.1, \text{ SD } 6.51 \\
39.1, \text{range } 26.8-67.7, \text{ SD } 14.8
\end{align*}$

$T_{\text{half}} (\text{days}) \newline
\begin{align*}
\text{NMS-153} = 4.4 \ (\text{SD } 2.65) \ [100 \ mg/m^2/w] \\
4.8 \ (\text{SD } 1.15) \ [135 \ mg/m^2/w]
\end{align*}$

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Patient 0011 did not receive Cycle 1 Day 15 infusion due to Covid-19 infection, patient 0012 had Cycle 1 Day 15 infusion interrupted due to early infusion site reaction.

AUC = Area Under the Curve

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$100 \ mg/m^2/w \ N=4^#$
$135 \ mg/m^2/w \ N=6$

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Minimum average concentration throughout dosing interval projected for clinical activity based on mouse tumor stabilization model

Minimum AUC projected for clinical activity based on mouse tumor stabilization model
Patient 002 (100 mg/m²/week) RECIST 1.1 Partial Response

- 29 years old, Black, male;
- Chronic Hepatitis B under treatment;
- Normal Liver function, no Cirrhosis.

Status at study entry: Liver recurrence – Metastatic, lymph nodes and lung (02/2021)

Prior therapies:
- Surgery (12/2019)
- 1. Lenvatinib (04/2020 – 08/2020)

Start NMS-153: 08-Feb-21

<table>
<thead>
<tr>
<th>04-Feb-21</th>
<th>26 mm</th>
<th>19 mm</th>
<th>27 mm</th>
<th>14 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 6</td>
<td>16 mm</td>
<td>13 mm</td>
<td>12 mm</td>
<td>5 mm</td>
</tr>
</tbody>
</table>

relevant diameters in the plane of measurement as reported in eCRF

At progression at Cycle 6, patient had tumor burden still -24.4% compared to baseline with AFP with a marked reduction (baseline 16493 ng/mL and cycle 6 at 334.5 ng/mL); patient died for progression 11.6 months after study entry.

Best Response: PR (-46.5%) at Cycle 4
Duration of Response (DoR): 2.6 months
Progression at Cycle 6:
Increase >20% in target lesions (both liver, lymph node and lung lesions)
Patient 004 (135 mg/m²/week) RECIST 1.1 Partial Response

- 66 years old, White, male;
- Prior Hepatitis C Infection;
- Liver Cirrhosis at CT scan.

Status at study entry: multinodal liver recurrence - Metastatic, Lymph nodes (05/2021)

Prior therapies:
- Trans arterial embolisation (UN/2017)
- Radiotherapy (UN/2017)
1. Sorafenib (10/2019 – 04/2020)
2. Capecitabine (05/2020 – 08/2020)
3. Cabozantinib (09/2020 – 04/2021)

Start NMS-153: 25-May-21

<table>
<thead>
<tr>
<th>06-May-21</th>
<th>100 mm</th>
<th>25 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 2</td>
<td>60 mm</td>
<td>/</td>
</tr>
</tbody>
</table>

relevant diameters in the plane of measurement as reported in eCRF

At progression at Cycle 13, baseline target lesions still -44% compared to baseline; patient still alive at data cut-off (and currently) after 12.3 months from study entry.

Best Response: PR (-52%) at Cycle 2
Duration of Response (DoR): 9.3 months
Progression at Cycle 13: New Liver lesion

Alpha Fetoprotein (AFP) Levels
Conclusions

➢ NMS-153 targets a novel mitotic mechanism

➢ HCC cell lines are highly sensitive to NMS-153

➢ In the phase I part of MPSA-153-001, a treatment-experienced HCC clinical trial:
  ▪ The most common adverse event was neutropenia;
  ▪ RP2D = 100 mg/m²/week (3 of 4 weeks);
  ▪ Clinical activity was observed at both the 100 and 135 mg/m²/week (3 of 4 week schedule) dose levels, including two RECIST v1.1 partial responses, out of 11 evaluable patients;
  ▪ Pharmacokinetics (PK) was in a meaningful active range relative to preclinical predictions.
We thank the patients, their families, and caregivers that have made this study possible;

We thank the investigators and the investigational sites staff of this study;

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