Hafnium oxide nanoparticles activated by SBRT for the treatment of hepatocellular carcinoma and liver metastasis: a phase I/II trial

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Disclosure of interest

• I have the following conflict of interest to declare:
  • Nanobiotix: honorarium and travel expenses
Background

• Underlying liver dysfunction and concomitant malignancies limit treatment options for patients with hepatocellular carcinoma (HCC) or liver metastases (Mets)

• Stereotactic body radiation therapy (SBRT) is a well-tolerated treatment for patients ineligible for surgery, local ablation or chemoembolization

• SBRT dose is limited by hepatic function, which is commonly impaired in patients with HCC, as well as by the organs at risk near the tumor

• Thus, there is an unmet need for therapies able to increase the effectiveness of RT in this population, while sparing surrounding healthy tissues
Background:
NBTXR3 radiation-enhancing hafnium oxide nanoparticles

- NBTXR3 is inert unless exposed to radiotherapy (RT)
- Injected once directly into the tumor
- **Amplifies energy deposit and radiobiological effects**, when exposed to RT
- **Radioenhances** by generating photons and secondary electrons in the local area where the nanoparticles are present
- Not metabolized by the liver
- **Approved in the EU** (CE marking) for the treatment of advanced soft tissue sarcoma (STS) of the extremity and trunk wall

Dose enhancement determined by Monte Carlo simulation (CEA Saclay, France)

Maggiorella et al., Future Oncol 2012;8:1167-81.
Material/Methods:
Study design: Phase I dose escalation

Patient Population
- Age ≥ 18
- ECOG 0 or 1
- Hepatocellular Carcinoma (HCC) patients
  - Unsuitable for surgery or local treatment
  - Child Pugh A - B7
  - With or without portal vein thrombosis
  - Life expectancy > 3 months
- Liver metastases (Mets) patients
  - Unresectable tumor(s)
  - Life expectancy > 6 months

3 + 3 Design to assess 5 dose levels
- 10%
- 15%
- 22%
- 33%
- 42%

injected volume calculated as a % of tumor volume determined on an MRI performed ≤28 days prior to injection

Endpoints
- Assess DLTs, RP2D, MTD
- Safety and tolerability
- Liver function: Child-Pugh score (ALBI also explored)
- Early signs of anti-tumor activity per mRECIST (HCC) / RECIST 1.1 (Mets)

Single intratumoral injection of NBTXR3 activated by Radiotherapy
Material/Methods:
Study design: Phase I dose escalation
Material/Methods: Patient baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Level 1 - 10% N=6</th>
<th>Level 2 - 15% N=4</th>
<th>Level 3 - 22% N=4</th>
<th>Level 4 - 33% N=3</th>
<th>Total N=17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>2 (33.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>2 (11.8%)</td>
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<tr>
<td>Male</td>
<td>4 (66.7%)</td>
<td>4 (100.0%)</td>
<td>4 (100.0%)</td>
<td>3 (100.0%)</td>
<td>15 (88.2%)</td>
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<tr>
<td><strong>Age (Years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>66</td>
<td>69</td>
<td>79</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>Min ; Max</td>
<td>56-78</td>
<td>55-76</td>
<td>70-80</td>
<td>68-70</td>
<td>55-80</td>
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<tr>
<td><strong>Tumor /lesion Volume (ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>16.8</td>
<td>21.5</td>
<td>9.1</td>
<td>26.2</td>
<td>19.4</td>
</tr>
<tr>
<td>Min ; Max</td>
<td>3.4-66.7</td>
<td>3.3-30.5</td>
<td>4.8-45.9</td>
<td>20.2-30.6</td>
<td>3.3-66.7</td>
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<td><strong>Cancer Type</strong></td>
<td></td>
<td></td>
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<tr>
<td>HCC</td>
<td>4 (66.7%)</td>
<td>3 (75.0%)</td>
<td>2 (50.0%)</td>
<td>2 (66.7%)</td>
<td>11 (64.7%)</td>
</tr>
<tr>
<td>Liver mets</td>
<td>2 (33.3%)</td>
<td>1 (25.0%)</td>
<td>2 (50.0%)</td>
<td>1 (33.3%)</td>
<td>6 (35.3%)</td>
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<tr>
<td><strong>ECOG</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>2 (33.3%)</td>
<td>4 (100.0%)</td>
<td>0 (0.0%)</td>
<td>2 (66.7%)</td>
<td>8 (47.1%)</td>
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<tr>
<td>1</td>
<td>4 (66.7%)</td>
<td>0 (0.0%)</td>
<td>4 (100.0%)</td>
<td>1 (33.3%)</td>
<td>9 (52.9%)</td>
</tr>
</tbody>
</table>

Cut-off date: June 10, 2019
Results:
NBTXR3/SBRT safety profile similar to SBRT alone

• Four dose levels completed to date: 10%, 15%, 22%, and 33%
• N= 17 patients : 11 HCC and 6 Mets
• No DLTs
• One serious AE related to RT and NBTXR3 administration
  • Bile duct stenosis
• NBTXR3 remained in the injected tumor
Results:
Safety – No NBTXR3 related DLT

Adverse events related to NBTXR3 and/or NBTXR3 administration procedure

<table>
<thead>
<tr>
<th>NBTXR3 dose</th>
<th>Preferred term</th>
<th>Worse grade</th>
<th>AE (n)</th>
<th>SAE (n)</th>
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<tbody>
<tr>
<td>10%</td>
<td>Malaise</td>
<td>Grade 2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15%</td>
<td>Abdominal pain</td>
<td>Grade 3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>22%</td>
<td>Pleural effusion</td>
<td>Grade 1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Bile duct stenosis</td>
<td>Grade 3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>33%</td>
<td>Fatigue</td>
<td>Grade 1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Cut-off date: June 10, 2019
Results:
NBTXR3 remains localized within the tumor

• No leakage of NBTXR3 over time

CT-scan 24h post injection  

CT-scan post SBRT  
(15 weeks post NBTXR3 injection)
## Results:
### Liver Function

#### Liver Function in HCC Patients

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Patient</th>
<th>Score</th>
<th>Screening</th>
<th>NBTXR3 administration</th>
<th>Day 36</th>
<th>End of Treatment</th>
<th>Follow up 1</th>
<th>Follow up 2</th>
<th>Follow up 3</th>
<th>Follow up 4</th>
<th>Follow up 5</th>
<th>Follow up 6</th>
<th>Follow up 7</th>
<th>Follow up 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>1004</td>
<td>Child-Pugh</td>
<td>B7</td>
<td>B7</td>
<td>-</td>
<td>A5</td>
<td>A5</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>1006</td>
<td>Child-Pugh</td>
<td>A5</td>
<td>ND</td>
<td>A5</td>
<td>A5</td>
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<td>A5</td>
<td>A6</td>
<td>A5</td>
<td>A5</td>
<td>A6</td>
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<td>-</td>
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<tr>
<td></td>
<td>1011</td>
<td>Child-Pugh</td>
<td>A5</td>
<td>ND</td>
<td>A5</td>
<td>A6</td>
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<td>-</td>
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<tr>
<td></td>
<td>1012</td>
<td>Child-Pugh</td>
<td>A5</td>
<td>A5</td>
<td>A5</td>
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<td>ND</td>
<td>A5</td>
<td>ND</td>
<td>A6</td>
<td>A6</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>15%</td>
<td>1013</td>
<td>Child-Pugh</td>
<td>A5</td>
<td>ND</td>
<td>A5</td>
<td>A5</td>
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<tr>
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<td>1015</td>
<td>Child-Pugh</td>
<td>A5</td>
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<td>A5</td>
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<td>A5</td>
<td>ND</td>
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<tr>
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<td>A6</td>
<td>A6</td>
<td>A6</td>
<td>A5</td>
<td>A5</td>
<td>A6</td>
<td>A6</td>
<td>A7</td>
<td>B7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>22%</td>
<td>1023</td>
<td>Child-Pugh</td>
<td>A6</td>
<td>A5</td>
<td>A5</td>
<td>A5</td>
<td>B8</td>
<td>C10</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>1028</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>33%</td>
<td>1030</td>
<td>Child-Pugh</td>
<td>A5</td>
<td>A5</td>
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<td>ND</td>
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<td>-</td>
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</tr>
</tbody>
</table>

**ND**: Not Done

Cut-off date: June 10, 2019
Results:

HCC Patients: MRI injected lesion response - mRECIST

- **HCC Patients: MRI injected lesion response - mRECIST**

- **Results:**
  - **HCC Patients:** MRI injected lesion response - mRECIST

- **Treatment period:**
  - NBTXR3 + Radiotherapy (1 week)
  - Recovery (12 weeks)

- **Follow-up period:**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Evaluable Patients n</th>
<th>Complete Response n, (%)</th>
<th>Partial Response n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>8</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
</tr>
</tbody>
</table>

- **Legend:**
  - Complete response
  - Partial response
  - Stable disease
  - New lesion(s)
  - Local progressive disease
  - Death
  - Liver Transplant
  - Follow-up

- **Notes:**
  - † Non cancer-related death
  - * Patient response evaluation is performed by CT-scan only due to pacemaker
  - # patient with secondary cancer (myeloma)
  - § patient on liver transplant list
  - ** patient non evaluable for tumor response of target lesion

Cut-off date: 10 JUN 2019
Results:
Liver Mets Patients: MRI injected lesion response – RECIST1.1

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Evaluable Patients</th>
<th>Complete Response n, (%)</th>
<th>Partial Response n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>6</td>
<td>0 (0.0)</td>
<td>3 (50.0)</td>
</tr>
</tbody>
</table>

Cut-off date: 10 JUN 2019
Results:
Efficacy: 3-D CT-scan reconstruction

- **15% NBTXR3**
- **Complete Tumor Response**

- **24h post IT injection**
  - 6 JANUARY 2017
- **3 months post RT**
  - 21 APRIL 2017
- **9.5 months post RT**
  - 24 OCTOBER 2017
Summary

• Intratumoral injection of NBTXR3 in the liver is feasible

• NBTXR3 remains consistently localized within the tumor over time

• NBTXR3 was well tolerated up to the 33% dose level
  • No DLTs in dose levels tested

• Recruitment is ongoing for the 42% dose level

• NBTXR3 might represent a valuable option for patients with HCC not amenable to curative local treatment or with unresectable liver metastases
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Jérôme Durand-Labrunie  
Eric Deutsch

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