Novel Radioenhancer NBTXR3 Activated by Radiotherapy in Cisplatin-Ineligible Locally Advanced HNSCC Patients: Final Results of a Phase 1 Trial

October 5, 2023

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• our ability to successfully develop and commercialize NBTXR3, including through the License Agreement by and between Janssen Pharmaceutica NV and Nanobiotix, dated July 7 2023 (the “Janssen Agreement”);
• our ability to complete clinical trial NANORAY-312 within the expected time-frame due to a number of factors, including delays in patient enrollment or in manufacturing sufficient quantities of NBTXR3 necessary to conduct the trial in a timely manner;
• our ability to expand our product pipeline by developing and commercializing NBTXR3 in additional indications, in combination with chemotherapies or I-O treatment;
• our ability to complete applicable pre-marketing regulatory requirements and/or our ability to maintain regulatory approvals and certifications for our products and product candidates and the rate and degree of market acceptance of our product candidates, including NBTXR3;
• our ability to raise additional capital through public and private offerings of debt or equity;
• our ability to maintain relationships with key collaborators, including Janssen, and their ability to continue their support of development activities;
• our ability to develop and commercialize NBTXR3 on our own or on a co-development basis;
• our ability to protect our intellectual property rights and to compete effectively in the industry;
• our ability to achieve the milestones under the Janssen Agreement;
• our ability to achieve our strategic and operational plans;
• the potential for disagreements or disputes to arise in connection with the terms of the Janssen Agreement;
• delays in clinical trials;
• delays in obtaining, maintaining or enforcing necessary regulatory approvals or marketing authorizations;
• our ability to comply with applicable product manufacturing and other regulatory requirements;
• our ability to effectively control our expenses and manage our cash;
• our ability to continue to receive necessary support from our current and future collaborators, including Janssen;
• the potential for Janssen to terminate our collaboration for any reason, including our failure to achieve certain milestones or other reasons;
• the potential for our current and future collaborators, including Janssen, to develop, manufacture, market, distribute, and sell products covered by our licenses, and to design and conduct clinical studies; and
• our ability to protect our intellectual property rights and to compete effectively in the industry.

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NBTXR3: A First-In-Class Radioenhancer

Aqueous suspension of inorganic crystalline hafnium oxide (HfO$_2$) nanoparticles

High atomic number (Z=72) and electron density

Inert in the absence of ionizing radiation: “Off” status
Activated by ionizing radiation: “On” status

One-time intratumoral administration, remains in tumor

Efficacy and safety demonstrated in a randomized Phase 2/3 trial in locally advanced soft tissue sarcoma$^1$

Universal mode of action targeting all solid tumors

Radiotherapy (RT) alone

Increased absorption of ionizing radiation and cell death

Radiotherapy (RT) alone

Increased absorption of ionizing radiation and cell death

NBTXR3 activated by RT

Presented at ASTRO 65th annual meeting by Christophe Le Tourneau, MD, PhD: Abstract #: 55260

1 Bonvalot, Sylvie et al. The Lancet. Oncology (2019); RT: Radiotherapy
## Evaluating Tumor Agnostic, Combination Agnostic Potential of NBTXR3 in Solid Tumors with an Initial Focus in HNSCC

### Pipeline-in-a-product strategy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial Name</th>
<th>Approach</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and Neck Locally Advanced</td>
<td>NANORAY-312</td>
<td>NBTXR3-RT* ± cetuximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 102</td>
<td></td>
<td>NBTXR3-RT*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and Neck Recurrent and/or Metastatic</td>
<td>TBD - Planning</td>
<td>NBTXR3-RT* + anti-PD-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1100</td>
<td></td>
<td>NBTXR3-RT* + anti-PD-1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Demonstrated safety, feasibility and clinical activity of NBTXR3-RT* across multiple solid tumors**

**Completed Studies**

- Soft Tissue Sarcoma (Ph 2/3) – NBTXR3-RT*
- Head and Neck (Ph 1/2)** – NBTXR3-RT* + ChT
- Rectal (Ph 1/2)** – NBTXR3-RT* + ChT
- Liver (Ph 1) – NBTXR3-RT*
- Rectal (Ph 1/2) – NBTXR3-RT* + ChT

**Exploring safety, feasibility and efficacy of NBTXR3-RT* in solid tumors**

**Ongoing Studies**

- Head and Neck (Ph 2) – NBTXR3-RT* + anti-PD-1
- Head and Neck (Ph 2) – NBTXR3-RT* + anti-PD-1/L-1
- Pancreatic (Ph 1) – NBTXR3-RT*
- Esophageal (Ph 1) – NBTXR3-RT* + ChT
- NSCLC (Ph 1) – NBTXR3-RT*
- Advanced cancers (Ph 1/2) – NBTXR3-RT* + anti-PD-1/L-1

*NBTXR3-RT: NBTXR3 activated by radiotherapy; **Study terminated prior to completion as result of conclusion of collaboration, results presented at ASCO 22
New Treatments are Needed for LA-HNSCC

<table>
<thead>
<tr>
<th>Standard of care for LA-HNSCC</th>
<th>Surgery or definitive cisplatin-based chemoradiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin ineligibility and challenges</td>
<td>Approximately 1/3 of patients are ineligible for cisplatin</td>
</tr>
<tr>
<td>Comorbidities in LA-HNSCC*</td>
<td>ACCI: age and 19 comorbidities (diabetes, cardiovascular, liver, pulmonary disease, etc.) ACCI ≥ 4: correlated with lower OS in LA-HNSCC(^1); ~20-30% of patients with LA-HNSCC(^2)</td>
</tr>
<tr>
<td>Elderly patient concerns</td>
<td>~30% of HNSCC patients &gt; 70 years old and have poor outcomes (PFS ~9 months(^3); OS ~12 months(^3,4,5))</td>
</tr>
</tbody>
</table>

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Literature Suggests ~12 Months mOS in LA-HNSCC Patients with Better Prognosis Treated with Radiotherapy Alone

**Median OS in literature in patient populations with better prognosis**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Median OS (months)</th>
<th>Treatment</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amini et al. (2016)</td>
<td>1504</td>
<td>12-13</td>
<td>RT alone</td>
<td>70% patients with mCCI &lt; 4; ~10% high comorbidity index; 75% T3–T4</td>
</tr>
<tr>
<td>Bourhis et al. (2006)</td>
<td>266</td>
<td>~12</td>
<td>RT alone</td>
<td>100% T3–T4</td>
</tr>
<tr>
<td>Moye et al. (2015)</td>
<td>96</td>
<td>~12</td>
<td>RT or surgery</td>
<td>100% stage III &amp; IV</td>
</tr>
</tbody>
</table>

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Study Design: Phase 1

Key Inclusion Criteria
- Aged:
  - ≥70 yrs or
  - ≥65 and <70 yrs cisplatin ineligible or
  - < 65 yrs if not deemed to receive cetuximab
- KPS ≥70
- T3, T4 or Stage III/IVA HNSCC* of the oral cavity or oropharynx
- Tumor amenable to injection

Key Exclusion Criteria
- Tumor ulceration with vascular risk

Dose Escalation Completed 1
3 + 3 design: 4 dose levels
5%; 10%; 15%; 22%
N=19 patients
no DLT or TRAE grade ≥3

Cohort Expansion
RP2D
NBTXR3 dose = 22%
N=56 patients

Study Treatment
- Injection of NBTXR3 in the primary tumor
- CT-Scan/CT-Sim visualization of NBTXR3 (radiopacity of NBTXR3)
- Radiotherapy (IMRT) 70 Gy, 35 x 2 Gy, 7 weeks

Endpoints
- Efficacy
  - ORR of primary tumor (injected lesion)
  - ORR (injected and non-injected lesion)
  - Duration of Objective Response
- Safety
  - PFS
  - OS

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Primary tumor was injected with NBTXR3 and activated by IMRT (RT dose = 70 Gy)

Involved lymph nodes were non-injected and treated with the same dose of RT regimen as the primary tumor (RT dose = 70 Gy)
Baseline Characteristics Show Frail High Comorbidities Patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>All Treated Population N=56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n(%) Male</td>
<td>40 (71.4)</td>
</tr>
<tr>
<td>Age (yrs), Median [min-max]</td>
<td>72 [44 – 89]</td>
</tr>
<tr>
<td>Age-adjusted Comorbidity Index (ACCI) ≥4</td>
<td>36 (66.7)</td>
</tr>
<tr>
<td>Karnofsky Score ≤ 80%</td>
<td>28 (50)</td>
</tr>
<tr>
<td><strong>Tumor Location, n(%)</strong></td>
<td></td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>25 (44.6)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>31 (55.4)</td>
</tr>
<tr>
<td><strong>HPV status for oropharynx, n(%)</strong></td>
<td></td>
</tr>
<tr>
<td>p 16 -</td>
<td>16 (51.6)</td>
</tr>
<tr>
<td>p 16 +</td>
<td>14 (45.2)</td>
</tr>
<tr>
<td>Not done</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td><strong>AJCC Stage, n(%)</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>II</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td>III</td>
<td>21 (37.5)</td>
</tr>
<tr>
<td>IVa</td>
<td>22 (39.3)</td>
</tr>
<tr>
<td>IVb</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (3.6)</td>
</tr>
</tbody>
</table>

56 patients treated across 20 sites in 4 European countries

- 61% aged ≥ 70
- 67% had ACCI scores of ≥4
- 80% had T3–T4; 43 % had N2–N3 disease
- 14/56 (26%) were p16+ OPC

Mean duration of follow-up: 18.2 months

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Summary: R3 Consistently Appears Safety and Feasible

- TEAEs related to NBTXR3 or implantation grade ≥ 3
  - Represented 1.3% of all AEs

- Feasibility of NBTXR3 Injection
  - All patients received at least 90% of the planned injected volume of NBTXR3 in Oral cavity or Oropharynx

- Completion of IMRT
  - Completion of IMRT in 50 (89%) patients

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Evaluable Patients and High Comorbidity at Baseline

10 deaths within 180 days after treatment initiation

- 1 treatment related sepsis, 1 related to progression
- 8/10 patients had severe comorbidities (ACCI ≥ 4)
- 8 had no post-treatment assessment: not part of “Evaluable Population for Objective Tumor Response”

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RT-Activated NBTXR3 Associated with Locoregional Control

Best Overall Response Based on Investigator Assessment
Measurement of tumor change as per RECIST v1.1

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<td></td>
</tr>
<tr>
<td>CR</td>
<td>28 (63.6%)</td>
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<tr>
<td>PR</td>
<td>8 (18.2%)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (11.4%)</td>
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<tr>
<td>PD</td>
<td>3 (6.8%)</td>
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<tr>
<td>ORR (CR + PR)</td>
<td>36 (81.8%)</td>
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- Evaluable patients for Objective Tumor Response
  Underwent at least one post-treatment assessment, and received at least 80% of the planned dose of NBTXR3 and 60 Gy of IMRT

- 12 patients were non-evaluable:
  - not received 60 Gy of IMRT: 4 patients (3 TEAE, 1 consent withdraw)
  - No post treatment assessment: 8 early deaths

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<th>Injected and Non-Injected Lesion</th>
<th>Evaluable Patients (n=44)</th>
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<tbody>
<tr>
<td>Best Overall Response, n(%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>23 (52.3%)</td>
</tr>
<tr>
<td>PR</td>
<td>12 (27.3%)</td>
</tr>
<tr>
<td>SD</td>
<td>4 (9.1%)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (11.4%)</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>35 (79.5%)</td>
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</tbody>
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- **Evaluable patients for Objective Tumor Response**
  Underwent at least one post-treatment assessment, and received at least 80% of the planned dose of NBTXR3 and 60 Gy of IMRT

- **12 patients were non-evaluable:**
  - not received 60 Gy of IMRT: 4 patients (3 TEAE, 1 consent withdraw)
  - No post treatment assessment: 8 early deaths

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**Locoregional Control and Duration of Response**

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<table>
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<tr>
<th>Duration of Objective Response</th>
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<tbody>
<tr>
<td>NBTXR3-injected lesion (n=36)</td>
</tr>
<tr>
<td>Median [95%CI], months</td>
</tr>
<tr>
<td>Injected and non injected lesion (n=35)</td>
</tr>
<tr>
<td>Median [95%CI], months</td>
</tr>
</tbody>
</table>

Involved Lymph node(s) = non-injected lesion(s) $GTV_{70}$

Primary tumor = injected lesion $GTV_{70}$
Treatment Failure Pattern Consistent with Active NBTXR3

The cumulative incidence of **local treatment failure** was*:

- 4.2% among patients with OPC
- 21.3% among patients with OCC
- 11.4% among patients with LC
- 11.1% among patients with HPC

The cumulative incidence of **regional nodal failure** was*:

- 2.9% among patients with OPC
- 8.4% among patients with OCC
- 5.6% among patients with LC
- 2.2% among patients with HPC

“*Our study demonstrated that, in definitive cases, 87.3% of regional recurrences occurred at the sites of gross disease, with isolated recurrences in elective nodal volumes occurring in less than 1% of cases, similar to prior work.”

* Historical control; OPC: oropharyngeal cancer; OCC: oral cavity carcinoma; LC: laryngeal cancer; HPC: hypopharyngeal carcinoma

Median PFS of 16.9 Months in Evaluable Patients

By Independent Central Review

All Treated Population N=56

Evaluable Population* N=44

Among the 12 patients who were non-evaluable for objective tumor response, 9 had severe comorbidities (ACCI≥4)

~30% of HNSCC patients > 70 years old and have poor outcomes (PFS ~9 months; OS ~12 months)

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Median Overall Survival 23.1 Months in Evaluable Patients

All Treated Population N=56

Evaluable Population* N=44

Among the 12 patients who were non-evaluable for objective tumor response, 9 had severe comorbidities (ACCI≥4)

~30% of HNSCC patients > 70 years old and have poor outcomes (PFS ~9 months\(^3\); OS ~12 months\(^{3,4,5}\))

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Study 102 Key Messages

- NBTXR3 injection is feasible and has a manageable safety profile in an elderly population with high burden of comorbidities.
- High overall ORR (79.5%) with highest ORR in the NBTXR3 injected lesion (81.8%).
- Median duration of objective response was higher for NBTXR3 injected lesions (NR) than for injected and non-injected lesions (12.4 months).
- The change in the pattern of recurrence may be driven by the radioenhancer effect of NBTXR3 as injected and non-injected lesions (involved lymph nodes) are both treated with the same dose of radiotherapy.
- mPFS = 16.9 months and mOS = 23.1 months in the evaluable population.
- Longer mPFS and mOS compared with historical data (mPFS = 9 months, mOS = 12 months).
- Ongoing NANORAY-312:

  “A Phase 3 Study of NBTXR3 Activated by Investigator’s Choice of Radiotherapy Alone or Radiotherapy in Combination with Cetuximab for Platinum-based Chemotherapy-ineligible Elderly Patients with Locally Advanced Head & Neck Squamous Cell Carcinoma” [NCT04892173]

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NANORAY-312:
Global Phase 3 registration trial locally advanced HNSCC
Designed to provide robust evidence for survival superiority

Key Inclusion Criteria
- Age ≥65 years
- Eligible for definitive RT
- At least one measurable and IT injectable tumor
- Ineligible for platinum-based chemotherapy
- No prior systemic Rx or RT
- Life expectancy ≥ 6 months

Endpoints
- Primary: PFS
- Key Secondary: OS
- Secondary: time to local-regional progression, time to distant progression, ORR, AEs, QOL

Statistics
- Expected mPFS in control arm: ~9 months/Expected HR on PFS: 0.692
- Expected mOS in control arm: ~12 months / Expected HR on OS: 0.75
- Analysis for futility and interim efficacy
- Power for final PFS analysis: 89%
- Power for final OS analysis: 80%

First patients randomized in Europe (Jan 22), Asia (Aug 22) and in the US (Dec 22)
Differences Between Study 102 Expansion and NANORAY-312

**Comorbidities**

- **Study 102 Expansion**: 67% had ACCI ≥ 4*
- **NANORAY-312**: Stratification factor (ACCI ≥ 4)

**NBTXR3 injected lesions**

- **Study 102 Expansion**: Only primary tumor
- **NANORAY-312**: Primary tumor + lymph node if N stage ≥2

ACCI ≥ 4 as stratification factor to ensure that this negative prognosis factor will be well-balanced between both arms.

Higher loco-regional control in arm NBTXR3 in 312.

Potential for higher difference between Arms, and longer mPFS and mOS in NANORAY-312 vs. 102 expansion part.
Concluding Messages

NBTXR3 injection is **feasible** and showed a **manageable safety profile** in an elderly population with high burden of comorbidities.

Very **strong efficacy signal**, ORR, PFS and OS.

Compared with historical data these results potentially **strengthen the hypothesis** currently being tested in the ongoing global, **registrational Phase 3 study** (NANORAY-312) for elderly patients with locally advanced head and neck cancer.

Potentially the **first indication to be commercialized by J&J and LianBio**.
Q&A
The End