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

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NANOBIOTIX

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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, including 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 about the initiation, timing, progress and results of our preclinical studies and clinical trials, including those trials to be conducted under our collaborations with the MD Anderson Cancer Center of the University of Texas ("MD Anderson"), Lian Oncology Limited ("LianBio"), Cancer Center of the University of Texas ("MD Anderson"),
- our ability to obtain raw materials and maintain and operate our facilities to manufacture our product candidates, to market and distribute our products upon successful completion of applicable pre-marketing regulatory requirements, specifically NBTXR3;
- our reliance on Janssen to conduct the NBTXR3 co-development and commercialization activities in accordance with the Janssen Agreement, including the potential for disagreements or disputes; the risk that Janssen may exercise its discretion in a manner that limits the resources contributed toward the development of NBTXR3; and the ability of Janssen to exercise its termination rights under the Janssen Agreement without cause;
- our ability to obtain funding for our operations.

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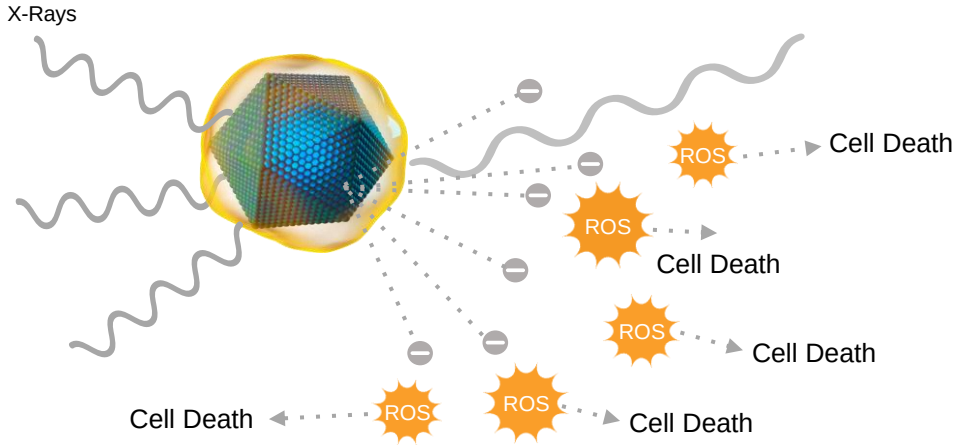
# NBTXR3: A First-In-Class Radioenhancer

- 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


## NBTXR3 activated by RT




**Increased absorption of ionizing radiation and cell death**

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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

| Indication | Trial Name | Approach | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|---|
| Head and Neck Locally Advanced | NANORAY-312 | NBTXR3-RT* ± cetuximab | | | |
| | Study 102 | NBTXR3-RT* | | | |
| Head and Neck Recurrent and/or Metastatic | *TBD - Planning* | NBTXR3-RT* + anti-PD-1 | | | |
| | Study 1100 | NBTXR3-RT* + anti-PD-1 | | | |

NANOBIOTIX EXPANDING LIFE

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

### Completed Studies

**Soft Tissue Sarcoma** (Ph 2/3) – NBTXR3-RT*

**Rectal** (Ph 1/2)** – NBTXR3-RT* + ChT

**Head and Neck** (Ph 1/2)** – NBTXR3-RT* + ChT

**Liver** (Ph 1) – NBTXR3-RT*

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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

### Ongoing Studies

**Head and Neck** (Ph 2) – NBTXR3-RT* + anti-PD-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

| | |
|---|---|
| **Standard of care for LA-HNSCC** | Surgery or definitive cisplatin-based chemoradiotherapy |
| **Cisplatin ineligibility and challenges** | Approximately 1/3 of patients are ineligible for cisplatin |
| **Comorbidities in LA-HNSCC*** | ACCI: age and 19 comorbidities (diabetes, cardiovascular, liver, pulmonary disease, etc.)<br>ACCI ≥ 4: correlated with lower OS in LA-HNSCC[1]; ~20-30% of patients with LA-HNSCC[2] |
| **Elderly patient concerns** | ~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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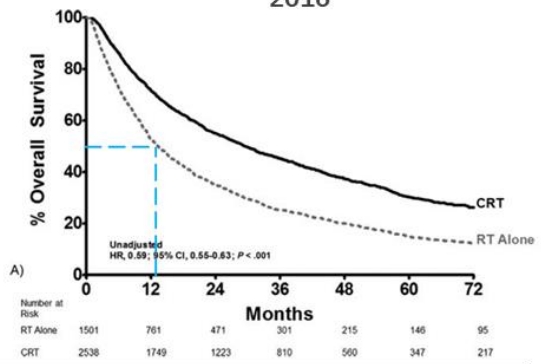
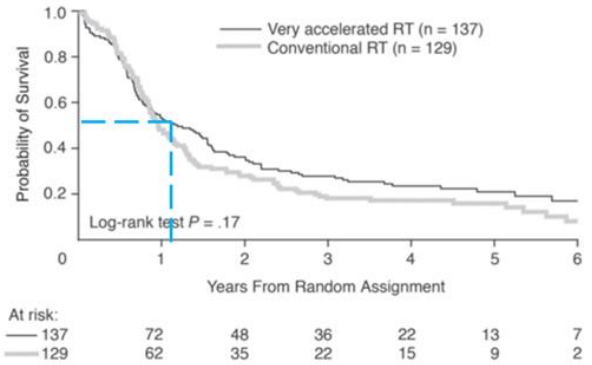
*Assessed by Age-adjusted Charlson Comorbidity Index (ACCI) Sources: 1. Zumsteg et al. Cancer (2017); 2. Göllnitz, Irene et al. Cancer Medicine (2016); 3. Moye et al., Oncologist (2015); 4. Amini A, et al., Cancer (2016), 5. Shia et al. Cancers (2020)

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

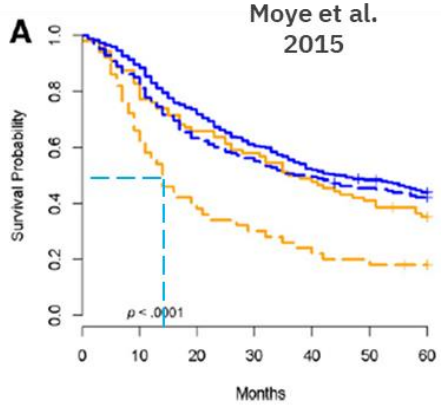
Amini et al. 2016




Bourhis et al. 2006




Moye et al. 2015




| Median OS in literature in patient populations with better prognosis[1–4] | | | | |
|---|---|---|---|---|
| | N | Median OS (months) | Treatment | Population |
| **Amini et al. (2016)** | 1504 | **12-13** | RT alone | 70% patients with mCCI < 4;<br>~10% high comorbidity index;<br>75% T3–T4 |
| **Bourhis et al. (2006)** | 266 | **~12** | RT alone | 100% T3–T4 |
| **Moye et al. (2015)** | 96 | **~12** | RT or surgery | 100% stage III & IV |

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1. Zumsteg ZS, et al., Cancer 2017;123:1345-53; 2. Amini et al. (2016); 3. Bourhis et al. (2006); 4. Moye et al. (2015);
mCCI: modified Charlson Comorbidity Index, RT: radiotherapy

# 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

**Dose Expansion part Endpoints**

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

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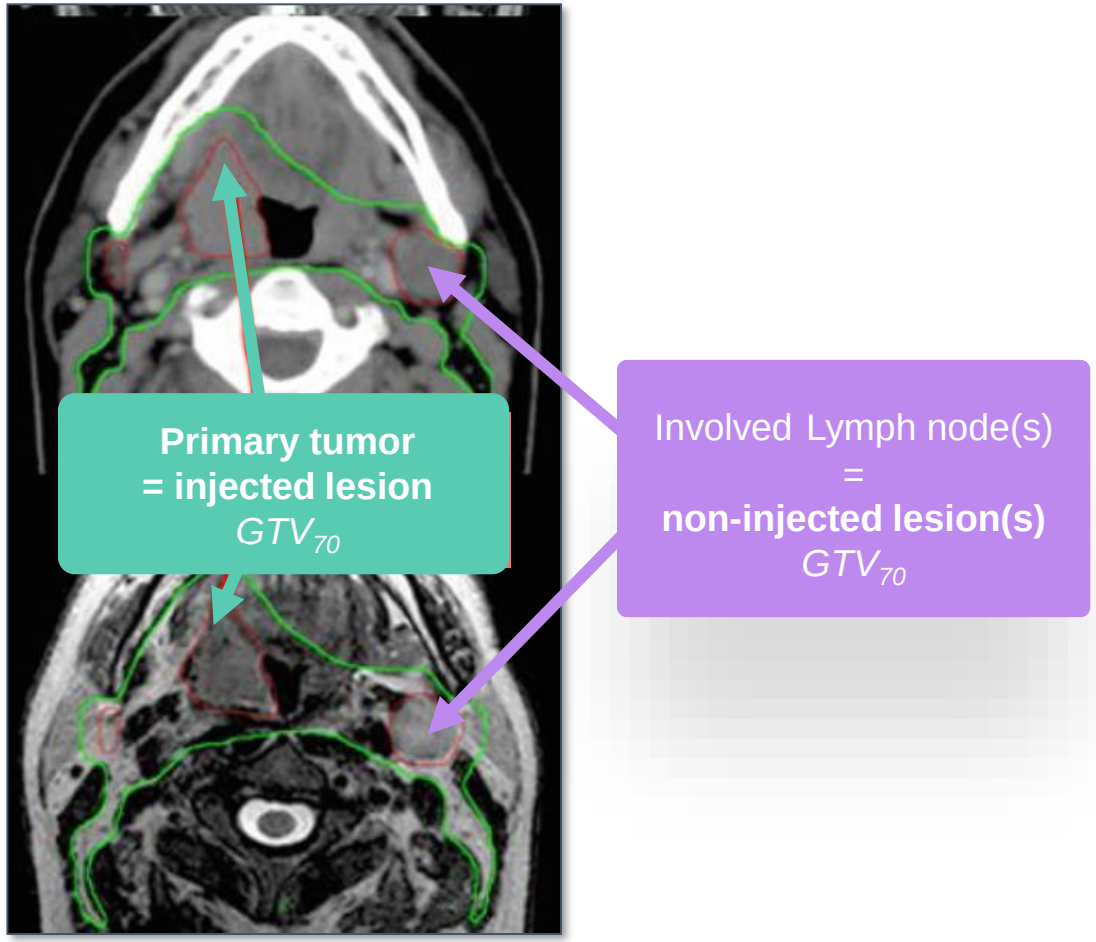
1. Hoffmann C, et al. Eur J Cancer. 2021 Mar;146:135-144. *According to AJCC 7th edition for the dose escalation and 8th edition for the dose expansion.

# RT of the Primary Tumor and Involved Lymph Nodes




**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)

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Image from Target Volume delineation for Conformal and IMRT, Lee 2015

# Baseline Characteristics Show Frail High Comorbidities Patients

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

- **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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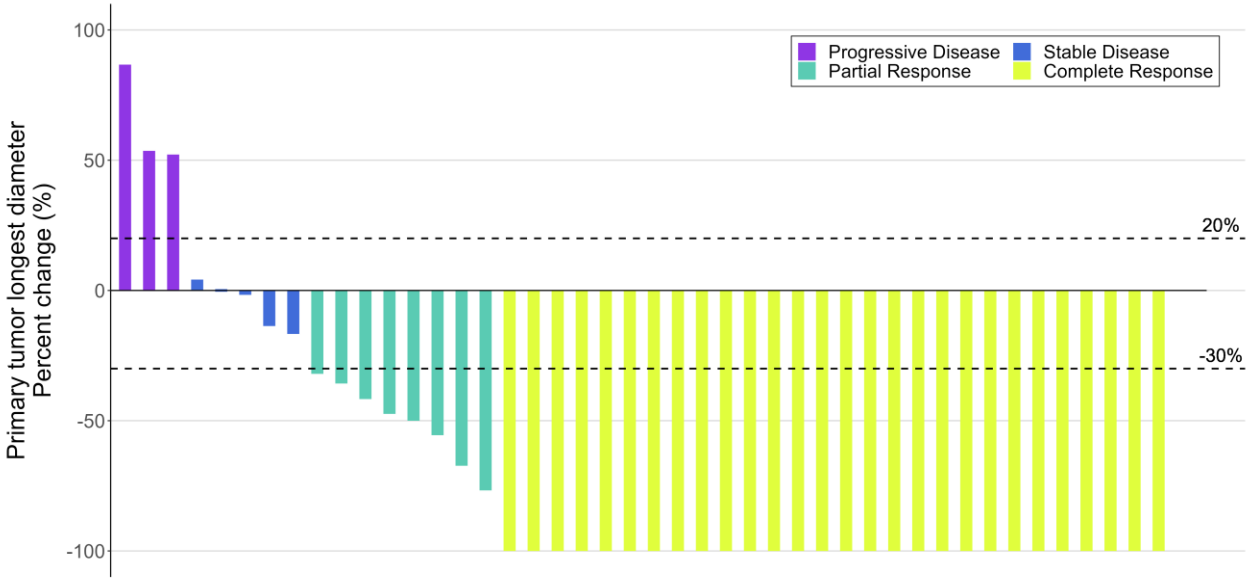
# RT-Activated NBTXR3 Associated with Locoregional Control




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

| NBTXR3 Injected Lesion | Evaluable Patients (n=44) |
|---|---|
| **Best Overall Response, n(%)** | |
| CR | 28 (63.6%) |
| PR | 8 (18.2%) |
| SD | 5 (11.4%) |
| PD | 3 (6.8%) |
| **ORR (CR + PR)** | **36 (81.8%)** |

- **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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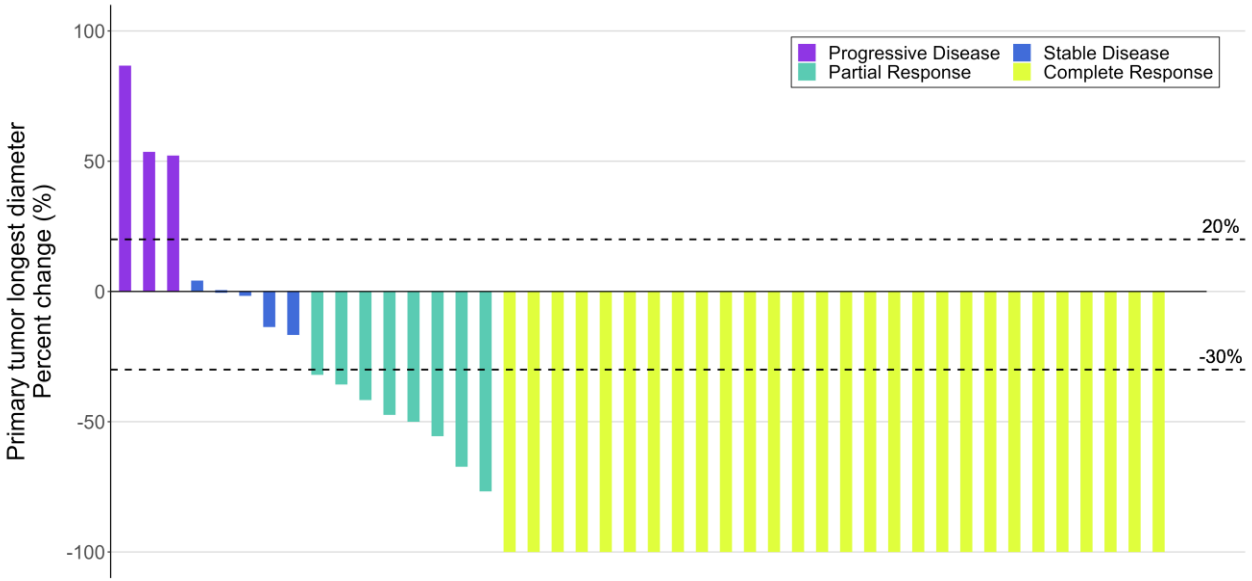


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| Injected and Non-Injected Lesion | Evaluable Patients (n=44) |
|---|---|
| **Best Overall Response, n(%)** | |
| CR | 23 (52.3%) |
| PR | 12 (27.3%) |
| SD | 4 (9.1%) |
| PD | 5 (11.4%) |
| **ORR (CR + PR)** | **35 (79.5%)** |

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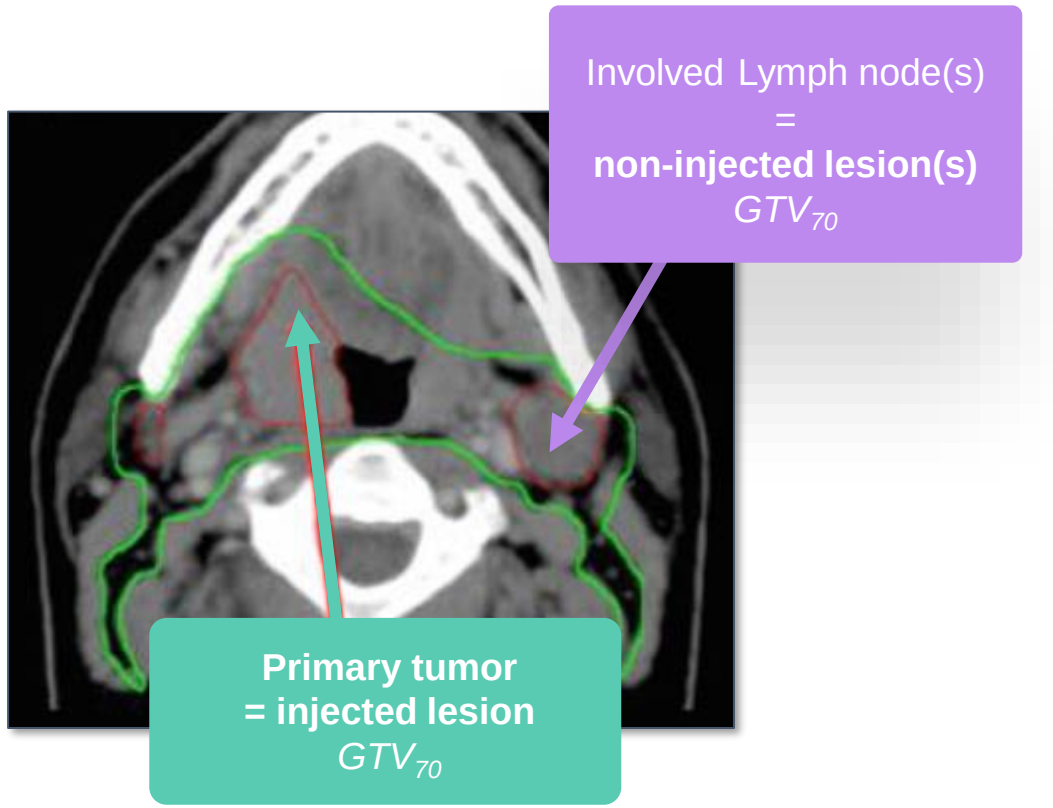
# Locoregional Control and Duration of Response




**Duration of Objective Response**

**NBTXR3-injected lesion (n=36)**

Median [95%CI], months Not Reached [7.2, NR*]

**Injected and non injected lesion (n=35)**

Median [95%CI], months 12.4 [6.6, NR*]

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*NR: Not Reached

# Treatment Failure Pattern Consistent with Active NBTXR3

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

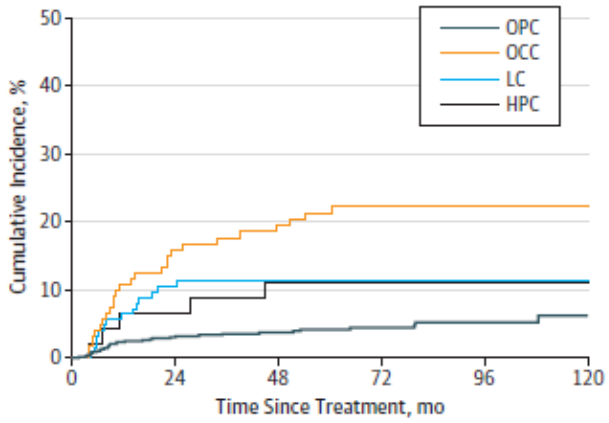
- 4.2% among patients with OPC
- **21.3% among patients with OCC**
- 11.4% among patients with LC
- 11.1% among patients with HPC

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

Cumulative incidence of Treatment Failures Across Subsites

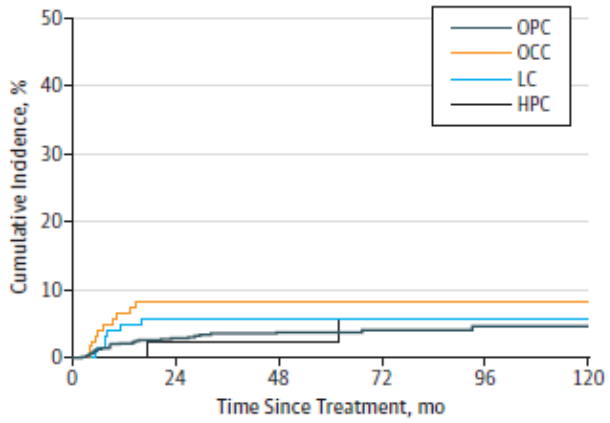
Local treatment failure
(primary tumor)




No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| OPC | 703 | 578 | 427 | 228 | 114 | 39 |
| OCC | 125 | 68 | 53 | 29 | 16 | 4 |
| LC | 126 | 85 | 61 | 38 | 16 | 2 |
| HPC | 46 | 32 | 20 | 10 | 4 | 1 |

Regional treatment failure
(lymph nodes)




No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| OPC | 703 | 567 | 413 | 224 | 113 | 39 |
| OCC | 125 | 75 | 63 | 38 | 21 | 4 |
| LC | 126 | 88 | 60 | 37 | 16 | 2 |
| HPC | 46 | 32 | 21 | 10 | 4 | 1 |

"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."



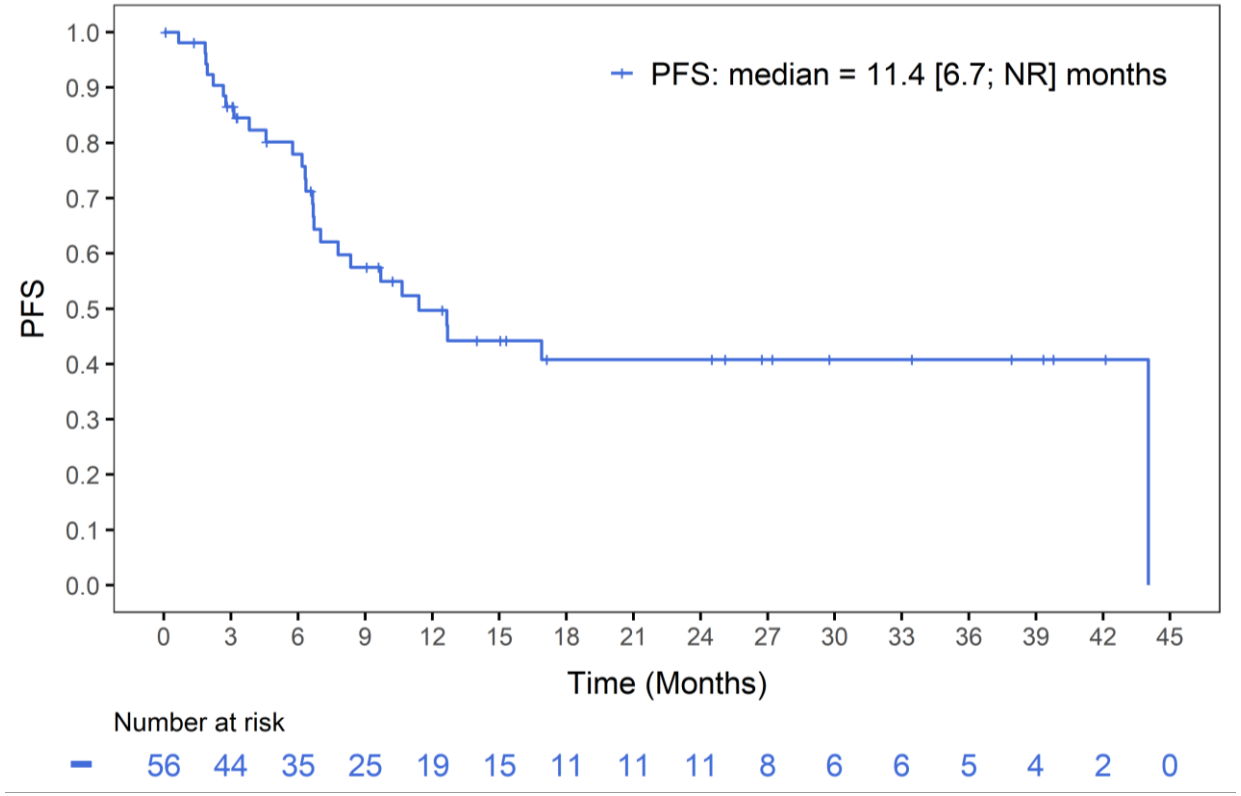
* Historical control; OPC: oropharyngeal cancer; OCC: oral cavity carcinoma; LC: laryngeal cancer; HPC: hypopharyngeal carcinoma

Source: Leeman JE, Li JG, Pei X, et al. Patterns of Treatment Failure and Postrecurrence Outcomes Among Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma After Chemoradiotherapy Using Modern Radiation Techniques. *JAMA Oncol*. 2017;3(11):1487-1494. doi:10.1001/jamaoncol.2017.0973

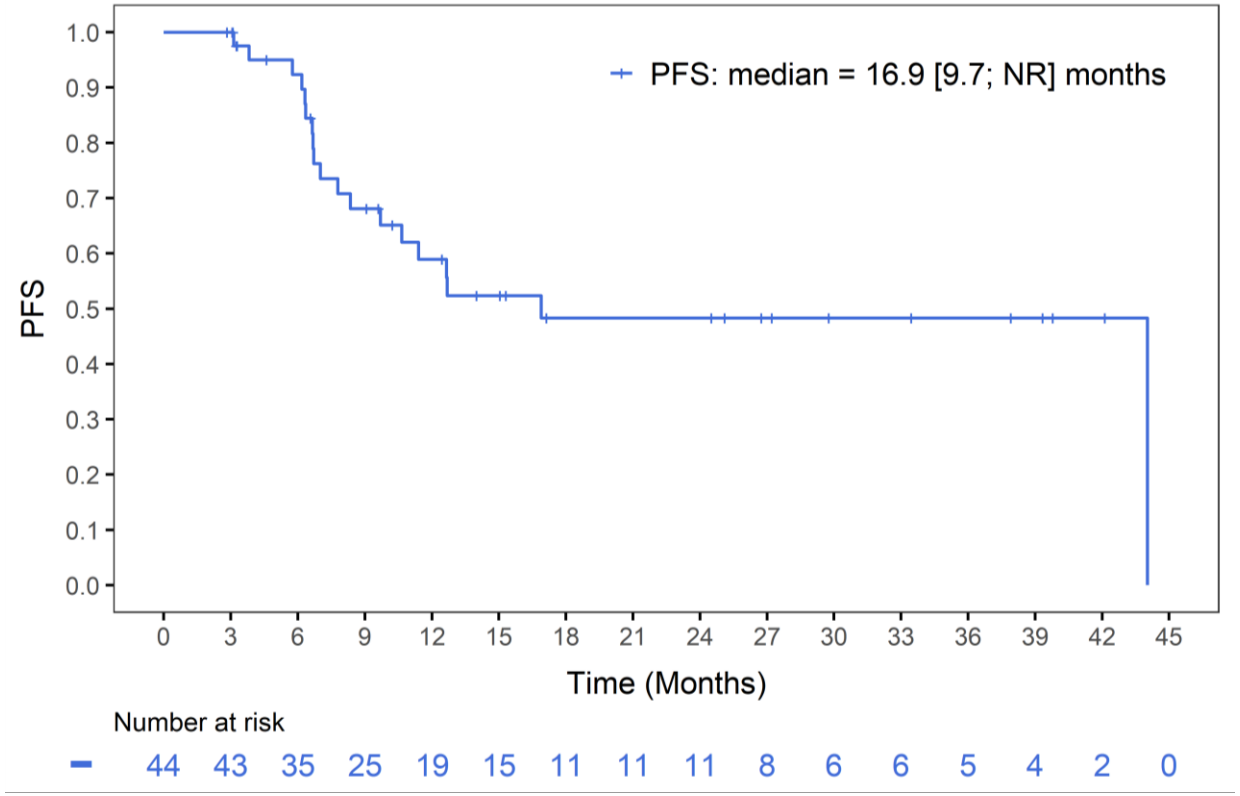
# Median PFS of 16.9 Months in Evaluable Patients

## 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[3]; OS ~12 months[3,4,5])

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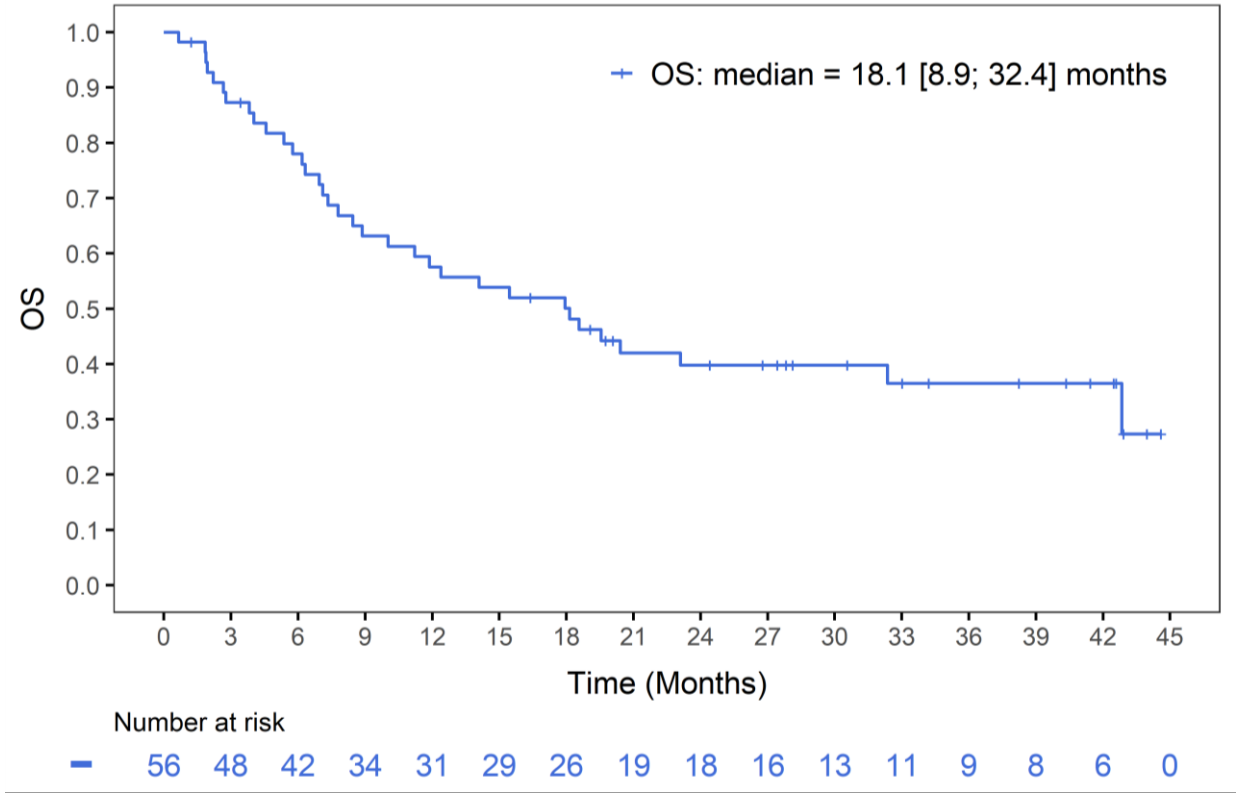
*Patients who underwent at least one post-treatment assessment, and received at least 80% of the planned NBTXR3 dose and 60 Gy of IMRT. Sources: 1. Zumsteg et al. Cancer (2017); 2. Göllnitz, Irene et al. Cancer Medicine (2016); 3. Moye et al., Oncologist (2015); 4. Amini A, et al., Cancer (2016), 5. Shia et al. Cancers (2020)

# Median Overall Survival 23.1 Months in Evaluable Patients

## All Treated Population N=56

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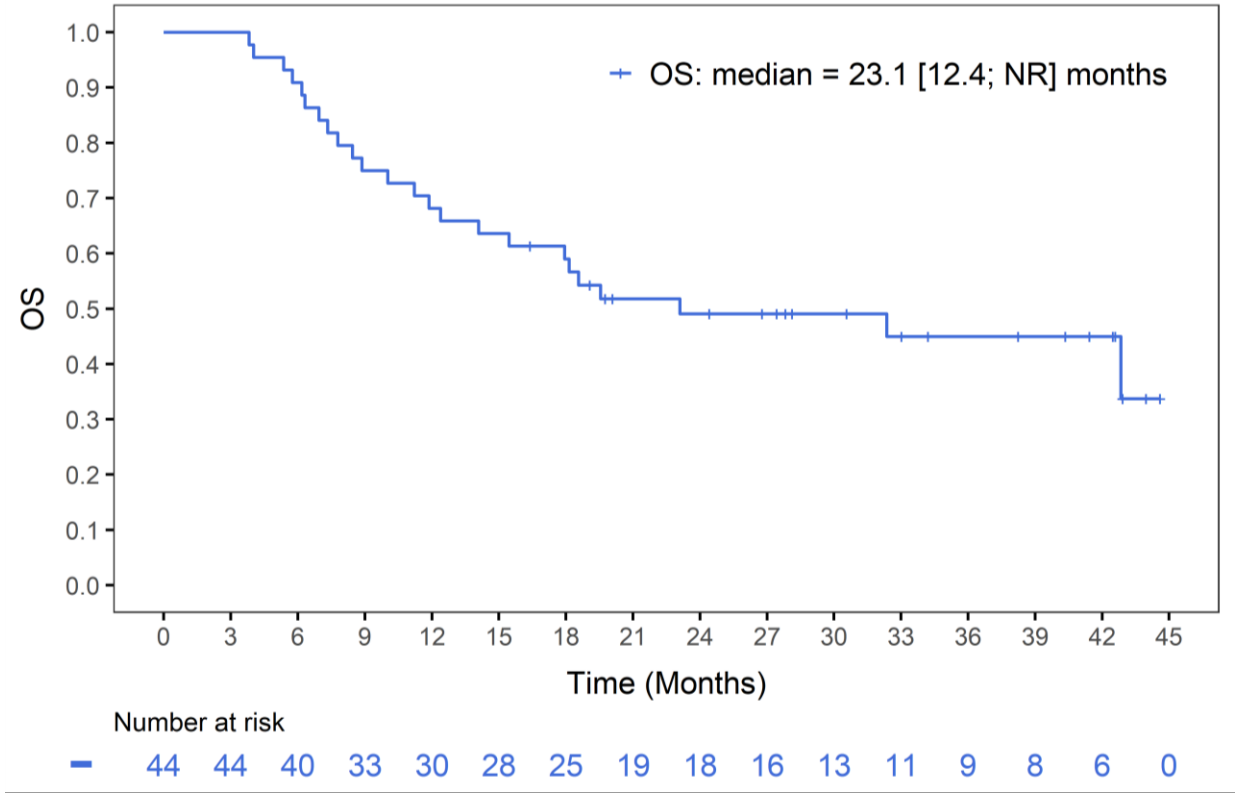


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*Patients who underwent at least one post-treatment assessment, and received at least 80% of the planned NBTXR3 dose and 60 Gy of IMRT. Sources: 1. Zumsteg et al. Cancer (2017); 2. Göllnitz, Irene et al. Cancer Medicine (2016); 3. Moye et al., Oncologist (2015); 4. Amini A, et al., Cancer (2016), 5. Shia et al. Cancers (2020)

# 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]**

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

# 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

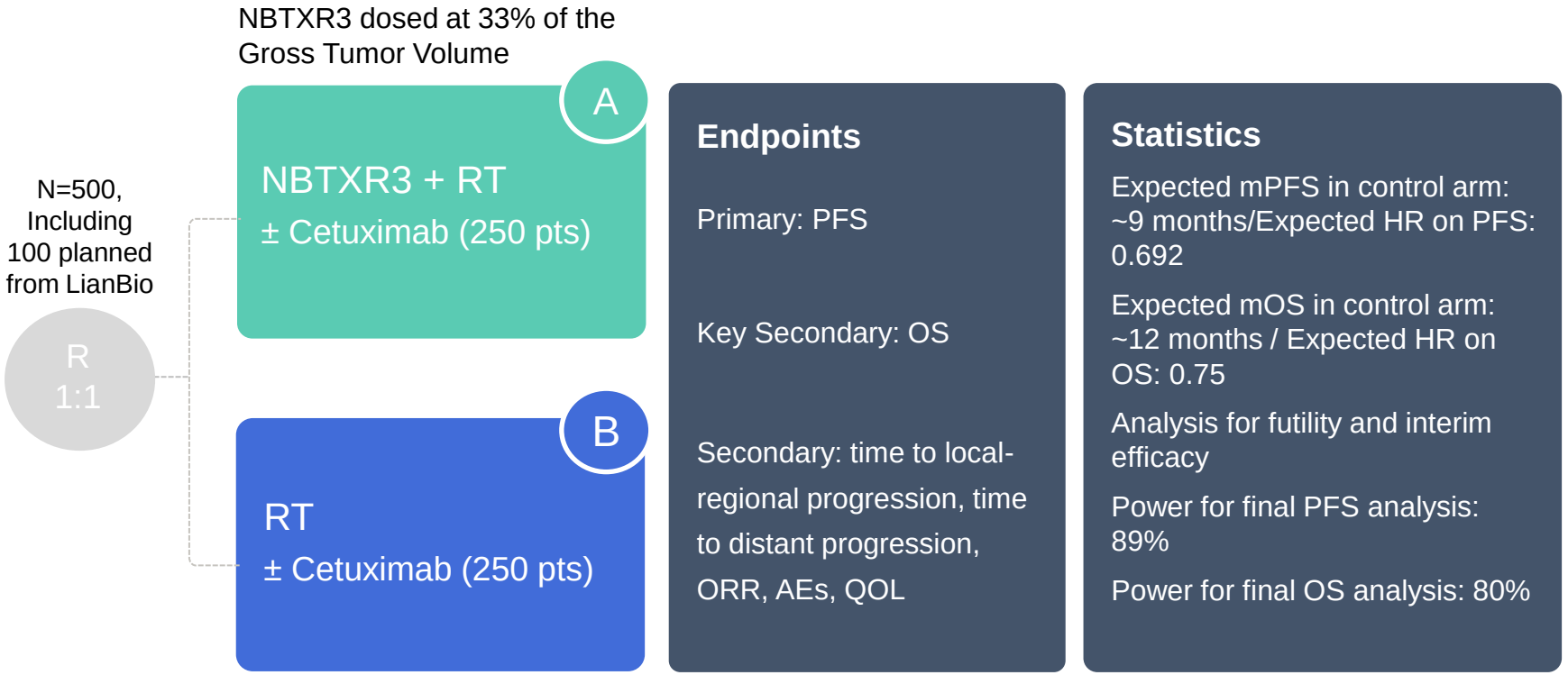
At least one measurable and IT injectable tumor

**Ineligible for platinum-based chemotherapy**

No prior systemic Rx or RT

**Life expectancy ≥ 6 months**

Stratification: mCCI, HPV status, cetuximab usage, geography




**First patients randomized in Europe** (Jan 22), **Asia** (Aug 22) **and in the US** (Dec 22)

# Differences Between Study 102 Expansion and NANORAY-312

| | Study 102 Expansion | NANORAY-312 | |
|---|---|---|---|
| ***Comorbidities*** | 67% had ACCI ≥ 4* | Stratification factor (ACCI ≥ 4) | ACCI ≥ 4 as stratification factor to ensure that this negative prognosis factor will be well-balanced between both arms |
| ***NBTXR3 injected lesions*** | Only primary tumor | Primary tumor + lymph node if N stage ≥2 | 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**

* Age-adjusted Charlson Comorbidity Index scores (ACCI) as presented at ASTRO 65th annual meeting by Christophe Le Tourneau, MD, PhD: Abstract #: 55260

# 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