Abstract # 2805

PHASE I STUDY OF NOVEL RADIOENHANCER NBTXR3 ACTIVATED BY RADIOTHERAPY IN CISPLATIN-INELIGIBLE LOCALLY ADVANCED HNSCC PATIENTS

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Data cut off: 3 SEP 2021

BACKGROUND

By 2030, 70% of all cancers will be diagnosed in older adults (aged ≥65 years). However, limited participation of older adults in clinical trials leaves patients in this group vulnerable to suboptimal cancer treatment and increased risk of poor outcomes.[1,2]

There is a need to broaden clinical trial access to older adults with cancer. However, conducting clinical trials in this population is challenging because they have an increased prevalence of comorbidities and ageing-related conditions.[3]

The comorbidity status can be assessed by the Charlson Comorbidity Index (CCI) that has been adjusted to age: mCCI. In Head and Neck, mCCI ≥ 4 is correlated with worse survival.[4]

In the Head and Neck population, the literature suggests that 20-30 % of patients had an mCCI ≥ 4.[5] Indeed, the number of elderly patients diagnosed with locally advanced head and neck squamous cell carcinoma (LA-HNSCC) is continuously increasing[2], yet not all are eligible to receive concurrent chemoradiation, the non-surgical standard of care (SOC), and they may not benefit from cetuximab. The global elderly Head and Neck population treated with radiotherapy only without concomitant therapy has an overall survival ranging around 12-13 months.[6-8]

Our study was designed to address this high unmet need in an elderly LA-HNSCC population with a higher burden of disease & comorbidities than the global elderly population. This Phase I dose escalation/dose expansion study was conducted to evaluate the feasibility, safety and preliminary efficacy of a potentially first-in-class radioenhancer, NBTXR3, administered as an intratumoral injection, followed by Intensity Modulated Radiation Therapy (IMRT), in elderly or fragile patients with LA-HNSCC.

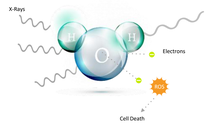
In the dose escalation part of this study (N=19), NBTXR3 was demonstrated to be well-tolerated: no DLTs or SAEs related to NBTXR3 or the injection procedure were observed, and RT-related toxicity was as expected with IMRT.[9] The recommended phase 2 dose (RP2D) was determined to be 22% of baseline tumor volume.[9] Currently, recruitment in the dose expansion cohort is being finalized.

Here, we present results of patients either enrolled or in follow-up during the COVID-19 pandemic that had a negative impact on healthcare organization and cancer outcomes in Europe.[10]

NBTXR3 MODE OF ACTION

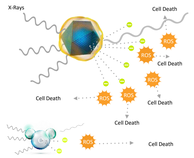
NBTXR3, a first-in-class radioenhancer, composed of functionalized hafnium oxide nanoparticles, is administered by one-time intratumoral injection and activated by radiotherapy (RT).[11,12] The product's physical mechanism of action (MoA) is designed to amplify the localized tumor-killing effect of radiotherapy without adding radiation-induced toxicity to surrounding healthy tissue.[9,11-13] NBTXR3 has also been shown to prime the adaptive immune response in cancer models. The clinical proof of concept for NBTXR3 was established in a randomized, controlled Phase II/III clinical trial and NBTXR3 obtained EU marketing approval in preoperative treatment of locally advanced soft tissue sarcomas.[13]

Radiotherapy (RT) Alone[11,12]



Interaction of X-rays with water molecules in tumor cells generates electrons and secondary photons, generating ROS (oxidative stress) and DNA damage, leading to subsequent cell death.

RT + NBTXR3[11,12]



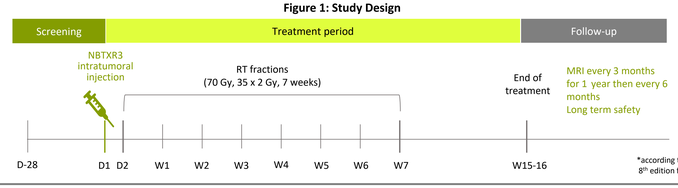
Interaction of X-rays with high electron density nanoparticles is higher and generates many more electrons and oxidative stress, and increases cell death more efficiently as demonstrated in the STS randomized trial.[13]

TRIAL DESIGN

Here we present the Phase I dose expansion part of a multicenter, open-label, non-randomized, Phase I dose escalation / dose expansion study in patients with LA-HNSCC (T3 or T4 or Stage III or IVa*) of the oral cavity or oropharynx, not eligible for cisplatin or cetuximab or aged ≥ 65 years old [NCT01946867].

Study design: The Phase I dose expansion part investigates a single dose of NBTXR3 at the RP2D (22% of baseline tumor volume). Primary endpoints of the dose expansion are Objective Response Rate (ORR) and Complete Response Rate (CRR) of the primary tumor, by imaging according to RECIST 1.1.

Figure 1: Study Design



*according to AJCC guidelines, 8th edition for dose expansion

BASELINE CHARACTERISTICS OF DOSE EXPANSION POPULATION

- Overall, 54 patients were recruited to the dose expansion part of the study, of which 41 were evaluable for objective tumor response. Patients were elderly (median age 71.8; range 44.5-89.9) and predominantly male, with tumors of the oral cavity (46.3%) and oropharynx (53.7%). Most patients were assessed with primary tumor Stage III (38.9%) or IVa (40.7%)

Baseline Characteristics	All Patients Treated (n=54)
Gender, n(%) Male	39 (72.2%)
Age at inclusion (Years)	
Median (Min-Max)	71.8 (44.5 - 89.9)
Tumor Location, n(%)	
Oral Cavity	25 (46.3%)
Oropharynx (OPSCC)	29 (53.7%)
AJCC Stage, n(%)	
Missing	2 (3.7%)
I	2 (3.7%)
II	6 (11.1%)
III	21 (38.9%)
IVa	22 (40.7%)
IVb	1 (1.9%)

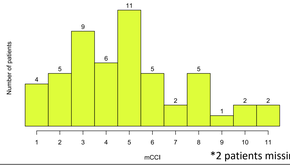
Baseline Characteristics	All Patients Treated (n=54)
HPV status for oropharynx, n(%)	
n	29 (53.7%)
HPV 16 +	12 (41.4%)
HPV 16 -	16 (55.2%)
Not Done	1 (3.4%)
Tumor Volume at baseline (ml)*	
Median (Min-Max)	43.6 (1.3 - 222.3)
Karnofsky Score, n(%)	
70%	7 (13.0%)
80%	19 (35.2%)
90%	17 (31.5%)
100%	11 (20.4%)

Baseline Characteristics	All Patients Treated (n=54)
Smoking Status, n(%)	
Current smoker	18 (33.3%)
Former smoker	22 (40.7%)
Never smoked	14 (25.9%)
Alcohol Status, n(%)	
Current drinker	12 (22.2%)
Former drinker	17 (31.5%)
Non drinker	25 (46.3%)
Number of medications ongoing at baseline (class), n(%)	
Missing	9 (16.7%)
<=2	8 (14.8%)
3-4	13 (24.1%)
5-7	10 (18.5%)
>=8	14 (25.9%)

According to AJCC 8th edition
* As per local imaging data

Safety Population: 54 patients
Efficacy population: 41 patients – 13 patients non evaluable for objective tumor response

Modified Comorbidity Index (mCCI) for Dose Expansion (All Patients Treated: n=54*)

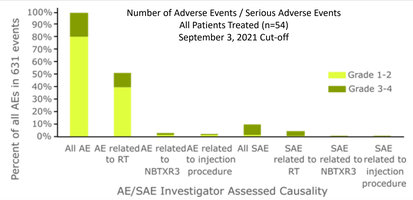


*2 patients missing data

- 63.0% of patients had an mCCI ≥ 4 at study entry. The mCCI in our study population was 2-3 times higher than what has been reported in the literature[5]
- Severe cardiovascular, diabetes-related complications and other second malignancies are at high prevalence in this patient population

ONGOING SAFETY RESULTS OF DOSE EXPANSION

- NBTXR3 administration followed by activation with RT was confirmed to be feasible and well tolerated in this population of HNSCC patients
- A total of 8 Grade 3-4 NBTXR3 related AEs were observed in 8 patients, representing 1.3% of all AEs
- 5 were Grade 3-4 Serious (SAEs) related to NBTXR3, observed in 5 patients. These were dysphagia, sepsis, soft tissue necrosis, stomatitis and tumor haemorrhage
- Of these, 1 death from sepsis possibly related to NBTXR3, RT, and cancer was observed



PATIENT EVALUABILITY FOR ORR

Evaluable Population for Objective Tumor Response includes all patients who have had at least:

- 80% of the intended intratumoral dose of NBTXR3 **AND**
- 60 Gy of IMRT **AND**
- The required imaging for tumor burden evaluation (target lesions assessments) at baseline and at least once post treatment (i.e. post NBTXR3+RT)

At the data cut-off date (3 Sept 2021), 41 of the 54 patients in the all patients treated constituted the evaluable population for objective tumor response.

Of the 13 non-evaluable patients, 2 have pending evaluability assessment.
Of the 11 remaining:
- 8 had an mCCI ≥ 4
- 7 had an early death**. Only 1 patient died from progressive disease

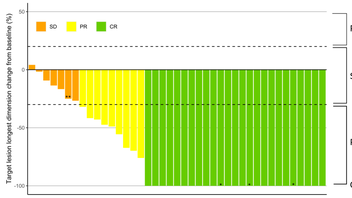
A similar correlation between mCCI ≥ 4 and early death was observed In the all patients treated:
- 8 of the 10 patients with early death had an mCCI ≥ 4

Reason for non evaluability	N (number of patients)
Patient died prior to required post-treatment imaging for tumor burden	4
Patient died after 8Gy (week 1)	1
Required post-treatment imaging for tumor burden not done	1
Withdrawal of consent prior to required post-treatment imaging for tumor burden	1
Withdrawal of consent after 20Gy (week 2)	1
Patient definitely interrupted radiotherapy after 50 Gy due to death	1
Patient definitely interrupted radiotherapy after 24 Gy due to AE	1
Patient definitely interrupted radiotherapy after 36 Gy due to Covid19 infection	1
Patients pending evaluability assessment as required post-treatment imaging for tumor burden not yet done as of cut-off date	2

** Early death is defined as death within 180 days after initiation of treatment, and used throughout as "early death"

ONGOING EFFICACY RESULTS OF DOSE EXPANSION

Best Observed Target (Injected) Lesion Response as per Investigator Assessment (based on RECIST 1.1)



* unconfirmed complete response
** CR as per investigator

Antitumor activity	Evaluable Patients (n=41)
Best Observed Target (Injected) Lesion Response, n(%)	
CR	26 (63.4%)
PR	9 (22.0%)
SD	6 (14.6%)
ORR (CR + PR)	**35 (85.4%)**

- At a median follow-up of 9.5 months after NBTRX3 injection, the 41 evaluable patients demonstrated a high target injected lesion response rate of **85.4%**, and a **63.4%** complete response rate in line with the response rates observed in the dose escalation cohort.[9]
- The 22 evaluable OPSCC patients had a target injected lesion best ORR of 100.0% including:
  - 12 HPV 16 – achieved a 66.7% complete response rate
  - 10 HPV 16 + achieved a 90.0% complete response rate

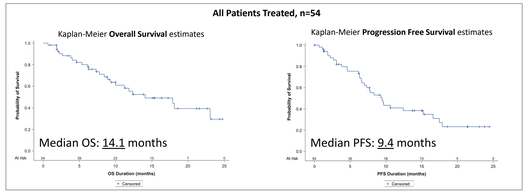
Best Observed Overall Response as per Investigator Assessment (based on RECIST 1.1)

- Of the 21 patients with best observed overall response of CR, only 1 died from disease progression and 6 from non-oncology related reasons
- These preliminary data suggest that NBTXR3+RT might reduce the overall tumor burden

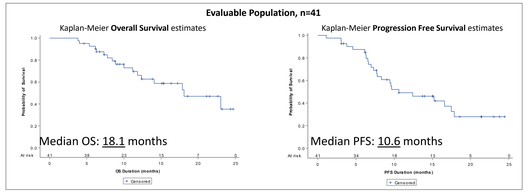
Antitumor activity	Evaluable Patients (n=41)
Best Observed Overall Response, n(%)	
CR	21 (51.2%)
PR	14 (34.1%)
SD	6 (14.6%)
ORR (CR + PR)	**35 (85.4%)**

Ongoing Survival Outcomes

All Patients Treated, n=54



Evaluable Population, n=41



- Median OS was 18.1 months in the evaluable population for objective tumor response (n=41) and 14.1 months in all patients treated (n=54)
  - 9 of 13 of non-evaluable patients included in the survival analysis of the all patients treated had an mCCI ≥ 4
  - The risk of early death was associated with an mCCI ≥ 4[4]
  - These data suggest that the lower mOS observed in the all patients treated population (14.1 months) compared with the evaluable population (18.1 months) may be driven by the high mCCI score in the non-evaluable population
- Of the 21 patients with CR as best observed overall response, the mOS was not reached at the cut-off date (mean follow-up 16.1 months)
- Median PFS was 10.6 months in the evaluable population for objective tumor response (n=41). Of note, the mPFS described in real world evidence data from 256 patients aged ≥ 65 years diagnosed with head and neck cancer (T-any, N1 or more, M0) treated with either RT or RT+cetuximab was of 7.3 months.[14]

CONCLUSIONS

- Results from this expansion group are consistent with the initial results from the dose escalation part of the trial that demonstrated NBTXR3 injection is feasible, well tolerated and safe in an elderly population with significant comorbidities.
- The high best objective response rate in target injected lesions (85.4%), consistent with the dose escalation part suggested that NBTXR3+RT is effective in our study population.
- The prevalence of a negative prognostic factor of survival (mCCI ≥ 4) in our population is higher than the prevalence described in real word evidence data. Despite the significant burden of comorbidities in our population, preliminary overall survival data showed a median OS of 18.1 months in the evaluable population and 14.1 months in the all patients treated. This suggests that treatment with NBTXR3+RT might result in a higher mOS in a population with lower burden of comorbidities.
- To develop a treatment for the elderly population, a Phase III Study comparing NBTXR3/RT±cetuximab versus RT±cetuximab in cisplatin unfit patients with LA-HNSCC: NANORAY 312 (NCIT04892173), is being implemented. Although the population enrolled in the phase III study could be different with lower burden of comorbidities, the negative prognostic factor of survival, mCCI, has been determined as a stratification parameter to ensure well-balanced arms in NANORAY 312.

References
(1) SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Cited 2020 Apr 15]. Available from https://seer.cancer.gov/explorer/. (2) Sung H, et al., CA: A Cancer Journal for Clinicians 2021;71(3):209-49. (3) Hurria A, et al. J Clin Oncol. 2014;32(24):2587-94. (4) Charlson ME, et al., J clin epidemiol. 2008;61(12):1234-40. (5) Zumsteg ZS, et al., Cancer 2017;123:1345-53. (6) Amini A, et al., Cancer. 2016;122(10):1533-43. (7) Bourhis J, et al. , J Clin Oncol. 2006;24(18):2873-8. (8) Bonner JA, et al., The Lancet Oncology. 2010;11(1):21-8. (9) Hoffmann C, et al. Eur J Cancer. 2021 Mar;146:135-144. (10) Bodilsen J, et al. BMJ 2021;373:n1135. (11) Marill J, et al. Radiat Oncol. 2014;9:150. (12) Maggiorella L, et al., Future oncology. 2012 Sep;8(9):1167-81. (13) Bonvalot S, et al., Lancet Oncol. 2019; 20 (8):1148-1159. (14) Le Tourneau, et al., Int J Radiat Oncol Biol Phys. 2020. 106(5):1142-1143.

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Disclaimer
The scientific information discussed in this presentation related to NBTXR3 is preliminary and investigative. NBTXR3 is not approved by the US Food and Drug Administration; therefore, no conclusions can nor should be drawn regarding the safety or effectiveness of the investigational product.