Abstract #2739

NBTXR3 activated by radiotherapy in combination with nivolumab or pembrolizumab in patients with advanced cancers: a phase I trial

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INTRODUCTION

Increasing the response rate to immune checkpoint inhibitors (ICIs) is a current challenge of cancer immunotherapy.[1] In patients with locoregional recurrent or recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) the durable response as well as the objective response rate (ORR) to anti–PD-1 monotherapy remains low with an ORR of 13.3% for nivolumab and 14.4%-16.9% for pembrolizumab due to the primary and secondary resistance to ICIs.[2,3]

Combining immunotherapy with radiotherapy (RT) can prime the immune response in advanced cancers. However, the combination of ICI inhibitors with RT/CRT in LA HNSCC did not improve outcomes based on the results of several recent trials.[4,5,6]

NBTXR3 – a potential first-in-class radioenhancer in combination with RT and anti-PD-1 improves both local and systemic control in pre-clinical studies.[7,8]

This phase I study aims at assessing the safety and preliminary efficacy of NBTXR3 activated by RT and combined with anti-PD-1 in patients with R/M HNSCC as well as in patients with liver and lung metastases from other solid tumors.

PATIENTS AND METHODS

Multicenter, open-label, non-randomized, Phase I dose escalation with dose expansion study to establish the RP2D of NBTXR3 + RT + anti-PD-1 in 3 cohorts of patients with advanced cancers (NCT03589339).

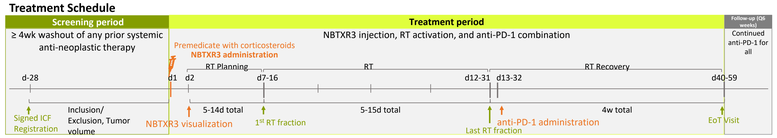
Study Design: 3+3 dose-escalation design with a limited safety dose expansion of up to 6 additional participants at the RP2D. The dose escalation will investigate increasing doses of NBTXR3 activated by a fixed (tumor site-specific) dose of RT, in combination with anti-PD-1 therapy. Cohorts 1 and 2 will investigate 2 doses of NBTXR3 (22% and 33% of baseline gross tumor volume (GTV)). Cohort 3 will investigate 3 doses of NBTXR3 (22%, 33%, and 42% of baseline GTV).

Cohort 1	Cohort 2	Cohort 3
		
Locoregional recurrent (LRR) or recurrent and metastatic (R/M) HNSCC amenable to re-irradiation of the HN	**Lung metastases** from any primary cancer eligible for anti-PD-1	**Liver metastases** from any primary cancer eligible for anti-PD-1
35Gy will be delivered in 5 fractions of 7Gy	**45Gy will be delivered in 5 fractions of 9Gy**	**45Gy will be delivered in 3 fractions of 15Gy**

Study treatment:

- NBTXR3 is given as a single intratumoral injection on Day 1. Corticosteroid premedication is required prior to NBTXR3 intratumoral injection.
- RT delivery follows an every-other day schedule (2-3 fractions per week, ≥40 hours between fractions with the option to exclude weekends/holidays) over 5-15 days depending on the Cohort and starts on day 7-16 after NBTXR3 administration*.
- An approved, commercially available anti-PD-1 antibody is given by intravenous route as per SOC starting the day after last RT fraction (received until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, death, or maximal duration allowed per FDA-approved label). Anti-PD-1 therapy is dosed according to FDA-approved package labeling and physician's discretion.

Treatment Schedule



*Decisions to dose adjust ±1Gy (per fraction) within the target volume by simultaneous integrated boost techniques or normalization will be left to the discretion of the treating radiation oncologist depending on tumor size and localization.

Key Inclusion Criteria:

- ECOG performance status of 0-2
- Life expectancy >12 weeks
- At least 1 measurable and injectable lesion (RECIST 1.1)
- Anti-PD-1 naïve or prior anti-PD-1 exposure, including:
  - Anti-PD-1 primary resistance: anti-PD-1 exposure between 6 weeks and 6 months, and BOR of SD or PD
  - Anti-PD-1 secondary resistance: anti-PD-1 exposure >6 months and disease progression after BOR on active therapy

Key Exclusion Criteria:

- History of severe immune-related AEs related to anti-PD-1
- Extensive metastatic disease unamenable for RT
- More than 1 prior line of immunotherapy
- Not recovered from AEs due to prior therapies

Primary Endpoints

- DLTs, MTDs, RP2D(s) of NBTXR3 + RT + anti-PD-1

Secondary Endpoints

- ORR (as defined by RECIST 1.1 and iRECIST)
- Safety and feasibility of NBTXR3+ RT + anti-PD-1
- Body kinetic profile of intratumorally injected NBTXR3

BASELINE CHARACTERISTICS

	Cohort 1 - HNSCC		Cohort 2 - Lung Mets		Cohort 3 - Liver Mets	
Baseline Characteristics	**Level 1 - 22% (n=7)**	**Level 2 - 33% (n=1)**	**Level 1 - 22% (n=4)**	**Level 2 - 33% (n=3)**	**Level 1 - 22% (n=3)**	**Level 2 - 33% (n=3)**
Age (years) Median [Min-Max]	71.0 [60.0 - 80.0]	67.0 [67.0 - 67.0]	64.5 [45.0 - 73.0]	69.0 [66.0 - 85.0]	64.0 [59.0 - 73.0]	65.0 [54.0 - 72.0]
Sex, n (%)						
Female	2	1	0	0	1	0
Male	5	0	4	3	2	3
ECOG, n (%)						
0	2	0	0	1	1	2
1	5	1	4	2	2	1
Primary cancer diagnosis, n (%)						
ANAPLASTIC THYROID CANCER	0	0	0	0	0	1
HNSCC	7	1	2	2	2	2
NSCLC	0	0	2	0	1	0
RECTAL	0	0	0	1	0	0
Prior anti-PD-1, n (%)	2	1	4	2	2	3
Prior radiotherapy, n(%)	7	1	2	3	1	1
Baseline tumor volume (mL) Median [Min-Max]	14.8 [3.9 - 80.2]	13.2 [13.2 - 13.2]	19.9 [6.0 - 95.1]	3.8 [1.9 - 19.1]	5.3 [1.7 - 60.0]	23.4 [9.9 - 214.1]

16 of 21 all patients treated (76%) in the study are current or former smoker and 14 of 21 all patients treated (67%) are current or former drinkers. Smoking and alcohol status being particularly relevant in the 16 patients with HNSCC.

Safety Population: 21 patients : Naïve (n=7), Non-responder (n=14)
Efficacy population: 16 patients : Naïve (n=5), Non-responder (n=11)
Non-evaluable for tumor response: 5 patients. Of them 2 patients died with no post-treatment scans; 1 patient with no post-baseline scan at the cut-off date; 2 patients did not receive at least 80% of NBTXR3. (*Of these 2 patients, patient B, that has been previously included in the efficacy population, is now excluded due to the evaluability definition change. This patient, despite being treated with a lower dose of NBTXR3, had a* ***best objective response of PR in both all target lesions and overall*** *assessed by RECIST 1.1)*

SAFETY

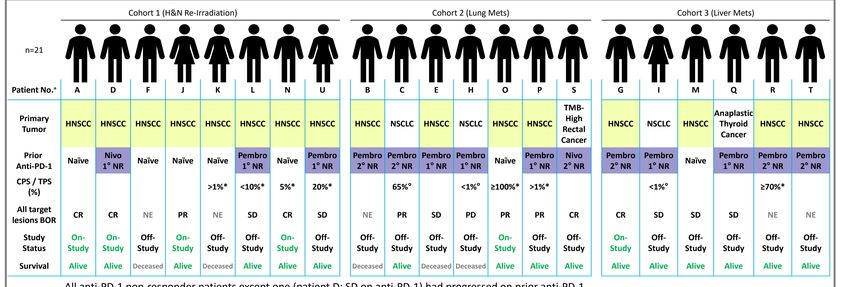
Injection and/or NBTXR3 related adverse events (AEs) grade ≥ 3

All Patients Treated	Cohort 1 - HNSCC Level 1 (22%) nPt=7		Cohort 3 - Liver Mets Level 1 (22%) nPt=3		Overall nPt=21	
Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Facial Paresis	1	1	0	0	1	1
Hyperglycaemia	1	1	0	0	1	1
Lymphocyte Count Decreased	0	0	1	1	1	1
Pneumonitis	1	1	0	0	1	1
Soft Tissue Necrosis	1	1	0	0	1	1
Weight Decreased	1	1	0	0	1	1
Total number of AEs	**5**	**5**	**1**	**1**	**6**	**6**

- A total of 6 injection and/or NBTXR3 related AEs grade ≥ 3 were observed in 4 patients
- No injection and/or NBTXR3 related AEs grade ≥ 3 were observed in the Lung Mets cohort
- No injection and/or NBTXR3 related AEs grade ≥ 3 were observed at dose level 33%
- 4 injection and/or NBTXR3 related SAEs grade ≥ 3 occurred in 3 patients in the HNSCC cohort
- 1 HNSCC anti-PD-1 naïve patient (cohort 1) died from pneumonitis approximately 2 months post-NBTXR3 injection, related to anti-PD-1 and possibly related to NBTXR3
- No injection and/or NBTXR3 related SAE, nor death was observed in the Lung Mets and Liver Mets cohorts

nPt: number of patients

INDIVIDUAL PATIENT RESPONSE



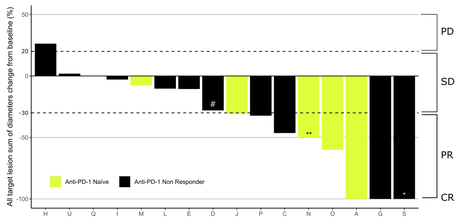
All anti-PD-1 non-responder patients except one (patient D: SD on anti-PD-1) had progressed on prior anti-PD-1

1°NR: Primary Anti-PD-1 Non-Responder
2°NR: Secondary Anti-PD-1 Non-Responder
TPS: Tumor Proportion Score
CPS: Combined Positive Score

NE: Not evaluable
*CPS (%) in patients with HNSCC primary tumor
°TPS (%) in patients with NSCLC primary tumor
ºLetters used for illustrative purposes only

BEST OBSERVED TUMOR RESPONSE

Best Observed Target Lesion Response (Evaluable Population: n=16)



Patient D: pCR based on biopsy sample located in the target lesion
* Patient S: Patient with unconfirmed complete response
** Patient N: Lymph node size is 8mm; complete response as per RECIST 1.1

Note: patient B, that has been previously included in the efficacy population, is now excluded due to the evaluability definition change. This patient, despite being treated with a lower dose of NBTXR3, had a **best objective response of PR in both all target lesions and overall** assessed by RECIST 1.1

Response as per Investigator Assessment based on RECIST 1.1 (Evaluable Population: n=16)

Best Observed Target Lesion Response (Injected and Non-Injected Lesion/s)	Naive	NR	All
CR	2**	3*, *	31%
PR	2	2	25%
SD	1	5	38%
PD		1	6%
Best Objective Response (Target Lesions) (CR + PR)	80%	45%	56%
Best Disease Control Rate (CR + PR + SD)	100%	91%	94%

#Patient D: pCR based on biopsy sample located in the target lesion
*Patient S: Patient recorded as unconfirmed CR by PI as per eCRF
**Patient N: Lymph node size is 8mm; CR per RECIST 1.1

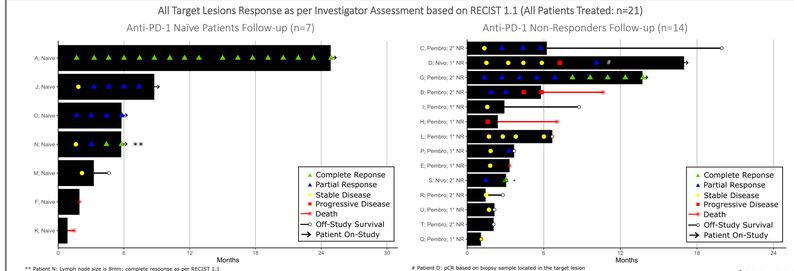
Best Observed Overall Response	Naive	NR	All
CR	1	2#	19%
PR	3	2	31%
SD	1	4	31%
PD		3	19%
Best Objective Response (Overall) (CR + PR)	80%	36%	50%
Best Disease Control Rate (CR + PR + SD)	100%	73%	81%

Preliminary data demonstrate the correlation between the local and systemic response in both anti-PD-1-naïve and post-anti-PD-1-failure patients irrespective to the tumor origin as a result of the treatment with a single intratumoral injection of NBTXR3 in combination with RT and anti-PD-1.

ABSCOPAL EFFECT AND SYSTEMIC IMMUNE RESPONSE

- The promising effects of NBTXR3 + RT in combination with anti-cancer immunotherapy are not limited to boost NBTXR3 immune response in anti-PD-1-naïve patients but also are capable of "re-sensitizing" the patient's cancer to anti-PD-1 achieving the response also in non-irradiated lesions: the latter is also seen as the one of the approaches of abscopal effect assessment
- In this study, in 3 patients that already failed response on prior IO treatment, **NBTXR3 + RT + anti-PD-1 circumvent or reverse resistance to previous anti-PD-1 treatment through the abscopal effect**
- Of 3 anti-PD-1 non-responders, best observed response indicates that NBTXR3 + RT + anti-PD-1 may:
  - **Improve the control of the disease in 2 patients (I and L) with highly progressive disease** (PD on anti-PD-1 within 6 months of therapy). These patients achieved best observed response of SD on non-target, non-irradiated lesion
  - **Reverse resistance in 1 patient (C)**: this patient achieved best observed response of CR in non-target, non-irradiated lesion
- Furthermore, **patient G** with a liver metastasis from a Stage IV HNSCC with prior secondary resistance, showed a **delayed and confirmed response that has deepened over time**, with a best observed response (BOR) of CR (-100%) based on RECIST 1.1

EFFICACY (NAÏVE AND NON-RESPONDERS)



** Patient N: Lymph node size is 8mm; complete response as per RECIST 1.1

Patient D: pCR based on biopsy sample located in the target lesion
* Patient S: Patient with unconfirmed complete response

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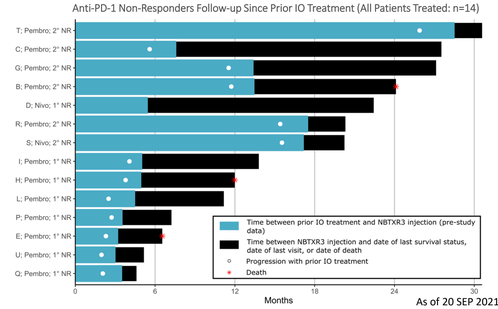
NON-RESPONDERS CUMULATIVE FOLLOW-UP (PRIOR IO & NBTXR3 + RT + ANTI-PD-1)

- Benefits of NBTXR3 are observed:
  - In a population of patients who had previously progressed on anti-PD-1 (except patient D)
  - Regardless of the time to progression on the previous anti-PD-1 (primary or secondary resistant)
- Median time alive after anti-PD-1 administration prior entry in the study plus NBTXR3 + RT + anti-PD-1= 17.02 months



As of 20 SEP 2021

CONCLUSIONS

- NBTXR3 administration by intratumoral injection was feasible and well tolerated in all patients irrespective to the tumor type, previous lines of therapy including immunotherapy, type of progression before study entry, NBTXR3 dose level, radiotherapy dose and schedule and location of the injection site
- NBTXR3 + RT + anti-PD-1 demonstrated preliminary efficacy at all tested doses with the signals of disease response or disease control in patients who had previously progressed on anti-PD-1 treatment with the ability to prolong patients' lives after the initial anti-PD-1 therapy failure
- While almost all non-responder patients had progressed on anti-PD-1 (only one SD on anti-PD-1), the rate of best objective response suggests that the combination of NBTXR3 + RT with anti-PD-1 might reverse resistance to immunotherapy
- NBTXR3 + RT demonstrated the ability to boost the therapeutic effect of anti-PD-1 therapy in anti-PD-1 naïve patients
- Moreover, the preliminary data demonstrate the correlation between the local and systemic response in both anti PD-1-naïve and post-anti-PD-1-failure patients
- The preliminary data showed the potential of NBTXR3 + RT + anti-PD-1 to prime a systemic immune response with the ability to trigger an abscopal effect in non-irradiated lesions
- The available data warrant the further development of NBTXR3 + RT in patients with local recurrent or metastatic solid tumors in combination with immunotherapy

References
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