255P

NBTXR3 activated by SBRT in combination with nivolumab or pembrolizumab for the treatment of patients with lung metastases from NSCLC or other solid tumors in the phase I trial Study 1100

Colette Shen[1], Aditya Juloori[2], William A Stokes[3], Jason Akulian[1], Jared Weiss[1], Kedar Kirtane[4], Laurent Mayrargue[5], David Rolando[5], Romain Gineste[5], Omar I. Vivar[5], George Q. Yang[4], Jimmy Caudell[4], Ammar Sukari[6], Nabil F Saba[3], Septimiu Murgu[2], Ari Rosenberg[2]

[1]University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA; [2]The University of Chicago, Chicago, Illinois, USA; [3]Winship Cancer Institute of Emory University, Atlanta, Georgia, USA; [4]Moffitt Cancer Center, Tampa, Florida, USA; [5]Nanobiotix, Paris, France; [6]Karmanos Cancer Institute, Detroit, MI, USA

Data cut off: 20 SEP 2024

BACKGROUND

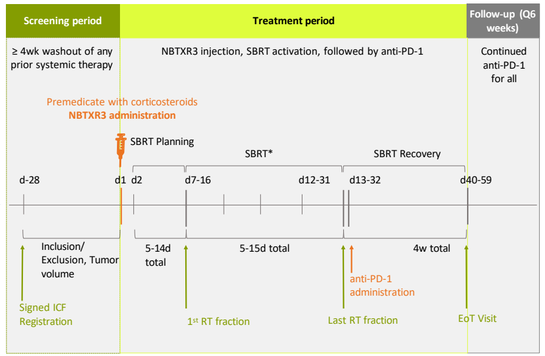
- Improving response and reversing resistance to immune checkpoint inhibitors (ICIs) is a current challenge of cancer immunotherapy[1]
- Combining ICIs with radiotherapy (RT) can prime the immune response in some advanced cancers
- NBTXR3 is a potential first-in-class nanoparticle radioenhancer, injected intra-tumorally. Pre-clinical models suggest NBTXR3, once activated by RT and followed by ICI, can improve both local and systemic control, by priming the immune response, increasing CD8+ T cell recruitment to tumors, and modulating TCR repertoire [2,3,4,5]
- The dose-escalation part of the phase I Study 1100 has established feasibility, safety, and RP2D of NBTXR3 activated by SBRT and followed by standard dose anti-PD-1, the ongoing dose-expansion part aims to evaluate early signs of efficacy in both ICI naïve and ICI resistant patients with advanced cancers
- **Here we report the feasibility and safety of NBTXR3 activated by SBRT and followed by ICI in patients with metastatic lung lesions in combination with ICIs from the ongoing Study 1100**

METHODS

Multicenter phase I dose escalation with dose expansion study to establish the RP2D of NBTXR3/SBRT/anti-PD-1 in 3 cohorts of anti-PD-1 resistant or naïve patients with advanced cancers (NCT03589339).

ICI Naïve Patients
Pre-treated with prior:
- Chemotherapy and/or
- Radiotherapy

ICI Resistant Patients (per SITC guidelines)
Pre-treated with at least one cycle of anti-PD-1, and generally pre-treated with prior:
- Chemotherapy and/or
- Radiotherapy



*RT dose schedule to site of treatment as per site of treated lesion:
H/N 35 Gy/ 5 fxns; Lung 45 Gy/ 5 fxns; Liver 45 Gy/ 3 fxns; Soft tissue as per investigator

Key Inclusion Criteria

ECOG PS of 0-2
Life expectancy >12 weeks
At least 1 measurable and injectable lesion (RECIST 1.1)
Anti-PD-(L)1 naïve or
Prior anti-PD-(L)1 exposure, including:
primary and secondary resistance per SITC guidelines

Key Exclusion Criteria

Extensive metastatic disease burden defined as:
>5 distant metastases overall excluding primary tumor and regional lymph nodes for patients with newly diagnosed metastatic disease
or
>5 progressive lesions with radiological progression (RECIST 1.1) confirmed by 2 consecutive imaging assessments 3 months apart for each individual progressive lesion including the unambiguous appearance of new lesions (oligoprogression)

BASELINE CHARACTERISTICS

	Lung primary cancer N=5			Other primary cancer N=24			All patients injected in lung N=29		
	ICI naive N=0	ICI resistant N=5	All N=5	ICI naive N=8	ICI resistant N=16	All N=24	ICI naive N=8	ICI resistant N=21	All N=29
Sex									
Male		4 (80.0)	4 (80.0)	8 (100)	14 (87.5)	22 (91.7)	8 (100)	18 (85.7)	26 (89.7)
Female		1 (20.0)	1 (20.0)		2 (12.5)	2 (8.3)		3 (14.3)	3 (10.3)
Age (years)									
Median		66.0	66.0	61.5	65.0	63.0	61.5	65.0	64.0
Min ; Max		63 ; 77	63 ; 77	50 ; 66	29 ; 85	29 ; 85	50 ; 66	29 ; 85	29 ; 85
Primary cancer diagnosis									
HNSCC				8 (100)	13 (81.3)	21 (87.5)	8 (100)	13 (61.9)	21 (72.4)
NSCLC		5 (100)	5 (100)					5 (23.8)	5 (17.2)
COLORECTAL					1 (6.3)	1 (4.2)		1 (4.8)	1 (3.4)
Injected lesion location									
Peripheral		2 (40.0)	2 (40.0)	4 (50.0)	15 (93.8)	19 (79.2)	4 (50.0)	17 (81.0)	21 (72.4)
Central		3 (60.0)	3 (60.0)	4 (50.0)	1 (6.3)	5 (20.8)	4 (50.0)	4 (19.0)	8 (27.6)
ECOG Performance status									
0		1 (20.0)	1 (20.0)	6 (75.0)	7 (46.7)	13 (56.5)	6 (75.0)	8 (40.0)	14 (50.0)
1		3 (60.0)	3 (60.0)	2 (25.0)	8 (53.3)	10 (43.5)	2 (25.0)	11 (55.0)	13 (46.4)
2		1 (20.0)	1 (20.0)					1 (5.0)	1 (3.6)
Prior anti-PD-1									
Yes		5 (100)	5 (100)	2 (25.0)	15 (100)	17 (73.9)	2 (25.0)	20 (100)	22 (78.6)
No				6 (75.0)		6 (26.1)	6 (75.0)		6 (21.4)
Combined Positive Score (CPS) testing (%)									
Missing		5	5	1	7	8	1	12	13
n		0	0	7	9	16	7	9	16
[1%-20%[				6 (85.7)	3 (33.3)	9 (56.3)	6 (85.7)	3 (33.3)	9 (56.3)
>= 20%				1 (14.3)	3 (33.3)	4 (25.0)	1 (14.3)	3 (33.3)	4 (25.0)
< 1%					3 (33.3)	3 (18.8)		3 (33.3)	3 (18.8)
Last pre-study treatment[1]									
Immunotherapy		5 (100)	5 (100)	2 (25.0)	10 (62.5)	12 (50.0)	2 (25.0)	15 (71.4)	17 (58.6)
Radiotherapy				5 (62.5)	2 (12.5)	7 (29.2)	5 (62.5)	2 (9.5)	7 (24.1)
Anti-cancer pharmaceuticals		1 (20.0)	1 (20.0)		3 (18.8)	3 (12.5)		4 (19.0)	4 (13.8)
Number of prior treatment lines									
Missing		1	1	0	1	1	0	2	2
n		4	4	8	15	23	8	19	27
0				1 (12.5)		1 (4.3)	1 (12.5)		1 (3.7)
1		3 (75.0)	3 (75.0)	4 (50.0)		4 (17.4)	4 (50.0)	3 (15.8)	7 (25.9)
2				3 (37.5)	4 (26.7)	7 (30.4)	3 (37.5)	4 (21.1)	7 (25.9)
3		1 (25.0)	1 (25.0)		6 (40.0)	6 (26.1)		7 (36.8)	7 (25.9)
5					5 (33.3)	5 (21.7)		5 (26.3)	5 (18.5)

(1) IO naive subjects may have received IO as an adjuvant therapy.

INJECTION FEASIBILITY

Lung Lesions	Lung primary cancer N=5			Other primary cancer N=24			All patients injected in lung N=29		
	IO naive N=0	IO resistant N=5	All N=5	IO naive N=8	IO resistant N=16	All N=24	IO naive N=8	IO resistant N=21	All N=29
Central lesions									
Injected lesion volumes (mL)									
n		3	3	4	1	5	4	4	8
Median		95.10	95.10	9.53	26.80	16.75	9.53	60.95	21.78
Min ; Max		6.0 ; 372.5	6.0 ; 372.5	1.9 ; 101.7	26.8 ; 26.8	1.9 ; 101.7	1.9 ; 101.7	6.0 ; 372.5	1.9 ; 372.5
NBTXR3 injected volume (mL)									
n		3	3	4	1	5	4	4	8
Median		20.90	20.90	3.13	8.00	5.50	3.13	14.45	6.75
Min ; Max		1.3 ; 42.0	1.3 ; 42.0	0.6 ; 33.6	8.0 ; 8.0	0.6 ; 33.6	0.6 ; 33.6	1.3 ; 42.0	0.6 ; 42.0
Peripheral lesions									
Injected lesion volumes (mL)									
n		2	2	4	15	19	4	17	21
Median		1.00	1.00	10.65	4.60	8.46	10.65	4.40	4.60
Min ; Max		0.3 ; 1.7	0.3 ; 1.7	2.2 ; 12.6	0.9 ; 32.3	0.9 ; 32.3	2.2 ; 12.6	0.3 ; 32.3	0.3 ; 32.3
NBTXR3 injected volume (mL)									
n		2	2	4	15	19	4	17	21
Median		0.33	0.33	3.52	1.52	1.87	3.52	1.45	1.52
Min ; Max		0.1 ; 0.6	0.1 ; 0.6	0.7 ; 5.0	0.3 ; 10.7	0.3 ; 10.7	0.7 ; 5.0	0.1 ; 10.7	0.1 ; 10.7

SAFETY

	Central lesion Patients=8	Peripheral lesion Patients=21	All injection sites Patients=29
	n (%) [e]	n (%) [e]	n (%) [e]
All TEAEs	7 (87.5) [54]	19 (90.5) [101]	26 (89.7) [155]
Grade ≥3 TEAEs	2 (25.0) [5]	5 (23.8) [6]	7 (24.1) [11]
Grade ≥3 TEAEs related to NBTXR3	0 [0]	0 [0]	0 [0]
Grade ≥3 TEAEs related to injection procedure	0 [0]	2 (9.5) [2] Pneumothorax Gr 3 Pulseless Electrical Activity Gr 4	2 (6.9) [2]
Grade ≥3 TEAEs related to radiotherapy	0 [0]	1 (4.8) [1] Dyspnea Gr 3	1 (3.4) [1]
Grade ≥3 TEAEs related to anti-PD1	0 [0]	0 [0]	0 [0]
Grade ≥3 TEAEs related to NBTXR3, injection procedure, radiotherapy or anti-PD1	0 [0]	2 (9.5) [3] Dyspnea Gr 3 Pneumothorax Gr 3 Pulseless Electrical Activity Gr 4	2 (6.9) [3]
Serious grade ≥3 TEAEs related to NBTXR3, injection procedure, radiotherapy or anti-PD1	0 [0]	2 (9.5) [2] Pneumothorax Gr 3 Pulseless Electrical Activity Gr 4	2 (6.9) [2]

AE occurrences are grouped in episodes when there is a chronologic continuity and no change in relationship to NBTXR3, injection, radiotherapy, anti-PD1, disease or other; n = number of patients with at least one TEAE and e = number of events; Events are considered treatment related when reported as 'Possibly related' or 'Related' to NBTXR3, injection procedure, radiotherapy and/or anti-PD1

EFFICACY

27 patients were evaluable for efficacy*

Best overall response (RECIST 1.1)	ICI naive N=8		ICI resistant N=19		All injected in lung N=27	
	Injected lesion response[1]	Overall response[2]	Injected lesion response[1]	Overall response[2]	Injected lesion response[1]	Overall response[2]
CR	2 (25.0)	2 (25.0)	1 (5.3)	0	3 (11.1)	2 (7.4)
PR	3 (37.5)	2 (25.0)	8 (42.1)	5 (26.3)	11 (40.7)	7 (25.9)
SD	3 (37.5)	2 (25.0)	10 (52.6)	9 (47.4)	13 (48.1)	11 (40.7)
PD	0	2 (25.0)	0	5 (26.3)	0	7 (25.9)
ORR (= CR + PR)	5 (62.5)	4 (50.0)	9 (47.4)	5 (26.3)	14 (51.9)	9 (33.3)
95% CI	[24.5 - 91.5]	[15.7 - 84.3]	[24.4 - 71.1]	[9.1 - 51.2]	[31.9 - 71.3]	[16.5 - 54.0]
Median duration (days)[3][5]		169.0		43.0		93.0
DCR (= SD + CR + PR)	8 (100)	6 (75.0)	19 (100)	14 (73.7)	27 (100)	20 (74.1)
95% CI	[63.1 - 100]	[34.9 - 96.8]	[82.4 - 100]	[48.8 - 90.9]	[87.2 - 100]	[53.7 - 88.9]
Median duration (days)[4]		170.0		39.5		63.5
Median RECIST follow-up duration (days)[5]		148.0		49.0		51.0

*2 patients were not evaluable for efficacy because post treatment imaging was not available. (1) Injected lesion response has been derived as single best diameter change observed for all patients (PD above or equal to +20% / PR below or equal to -30% / SD in-between / CR if equal to -100%); (2) Best overall response have been derived as single best overall response observed for 6 patients still ongoing (1 CR, 2 PR, 2 SD and 1 PD); (3) Number of days from first to last RECIST assessment with CR or PR; (4) Number of days from first to last RECIST assessment with CR, PR or SD; (5) Number of days from first to last RECIST assessment with CR, PR, SD or PD

	All patients injected in lung N=27 n (%)
Patients with overall progression	18 (66.7)
Progression pattern[1]:	
Injected lesion[2]	0
All target lesions	4 (22.2)
Non-target lesions	7 (38.9)
New lesion	14 (77.8)

(1) Progression pattern percentages are based on the number of patients with progression.
(2) Injected lesion response has been derived with diameter change observed for all patients (PD above or equal to +20% / PR below or equal to -30% / SD in-between / CR if equal to -100%).

CONCLUSIONS

- NBTXR3 injection in both peripheral and central lung lesions was feasible and well tolerated
  - One patient (1/29) experienced a procedure related pneumothorax requiring a chest tube
- NBTXR3/RT was also well tolerated in combination with anti-PD-1
- Among patients evaluable for efficacy, ORR was 51.9% in injected lesions, and 33.3% overall
  - An ORR of 47.4% in injected lesions, and 26.3% overall was achieved in patients who were resistant to ICI
  - Promising local control was observed, with DCR of 100% in injected lesions, and 74.1% overall
  - Progressive disease was largely due to new lesions or non target lesions, with no progression observed in injected lesions
- These results support that NBTXR3 can be safely injected in the lung, with promising preliminary efficacy, particularly in local control
- These results warrant further evaluation of NBTXR3/RT in combination with ICI in a randomized trial

References
(1) Haslam A, et al., JAMA Network Open. 2019. (2) Zhang P, et al., Int J Nanomedicine. 2020. (3) Hu Y, et al., International Journal of Radiation Oncology, Biology, Physics. 2021. (4) Darmon A, et al., Cancer Cell Int. 2022. (5) Bonvalot S, et al., Lancet Oncol 2019.

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.

Acknowledgements
All participating centers, all site staff, all patients and their families
Contact Information
Nanobiotix Medical Affairs: medicalaffairs@nanobiotix.com