

A PHASE I STUDY EVALUATING NBTXR3 ACTIVATED BY RADIOTHERAPY IN COMBINATION WITH NIVOLUMAB OR PEMBROLIZUMAB IN PATIENTS WITH ADVANCED CANCERS

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PATIENTS AND METHODS

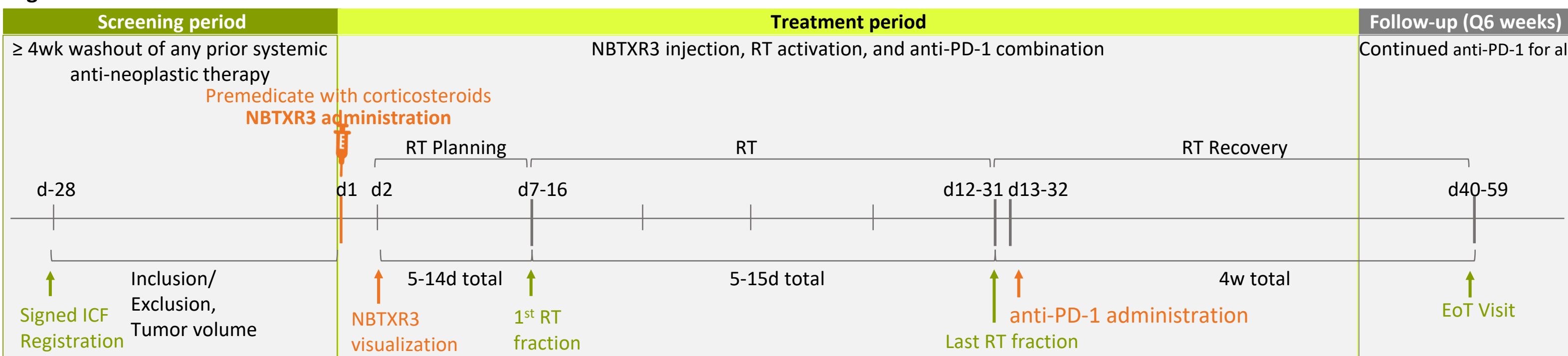
Multicenter, open-label, non-randomized, Phase I dose escalation with dose expansion study to establish the RP2D of NBTXR3/RT/anti-PD-1 in 3 cohorts of patients with advanced cancers (NCT03589339).¹

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
		
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. RT delivery follows an every-other day schedule (2-3 fractions per week, ≥40 hours between fractions with the option to include 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 intravenously 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.

Figure 2: Treatment Schedule



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-PD1 primary resistance (exposure between 6 weeks and 6 months, and BOR of SD or PD) and secondary resistance (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 OF PATIENTS²

Baseline Characteristics	Level 1 (22%)		Level 2 (33%)	
	Cohort 1 – HNSCC (N=7)	Cohort 2 – Lung Mets (N=4)	Cohort 3 – Liver Mets (N=3)	Cohort 2 – Lung Mets (N=2)
Median age, years (range)	71.0 (60.0 - 80)	64.5 (45.0 - 73.0)	64.0 (59.0 - 73.0)	75.5 (66.0 - 85.0)
Gender, n (%)				
Female	2 (28.6)	0	1 (33.3)	0
Male	5 (71.4)	4 (100.0)	2 (66.7)	2 (100)
ECOG, n (%)				
0	2 (28.6)	0	1 (33.3)	1 (50)
1	5 (71.4)	4 (100.0)	2 (66.7)	1 (50)
Primary cancer diagnosis, n (%)				
HNSCC	7 (100.0)	2 (50.0)	2 (66.7)	2 (100)
NSCLC	0	2 (50.0)	1 (33.3)	0
Prior anti-PD-1, n (%)	2 (28.6)	4 (100)	2 (66.7)	1 (50)
PD-L1 Expression, n (%)				
≥50%	0	0	0	1 (50)
<50%	4 (57.1)	0	0	0
Unknown / not reported	3 (42.9)	4 (100)	3 (100)	1 (50)
Prior radiotherapy, n (%)	7 (100.0)	2 (50.0)	1 (33.3)	2 (100)
Median baseline tumor volume, ml (range)	14.8 (3.9 - 80.2)	19.9 (6.0 - 95.1)	5.3 (1.9 - 60.0)	10.5 (1.9 - 19.1)
Patients evaluable for efficacy, n (%)	5 (71.4)	4 (100)	3 (100)	1 (50)

SAFETY: NBTXR3 or Injection Related AEs/Serious AEs and Deaths²

- The AE profile has not differed in type or grade from what is expected with RT or anti-PD-1 agents.
- 16 serious AEs were observed, of which 4 were identified as NBTXR3 or injection related, which included fall, hyperglycemia, pneumonitis, and soft tissue necrosis.
- 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.

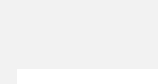
All treated population	Level 1 (22%)				Level 2 (33%)				Overall (N =16)	
	Cohort 1 – HNSCC (N =7)		Cohort 2 - Lung Mets (N =4)		Cohort 3 - Liver Mets (N =3)		Cohort 2 - Lung Mets (N =2)			
Preferred Term	Any Grade	Grade sup.3	Any Grade	Grade sup.3	Any Grade	Grade sup.3	Any Grade	Grade sup.3	Any Grade	Grade sup.3
Fall	0	0	1	1	0	0	0	0	1	1
Hyperglycemia	1	1	0	0	0	0	0	0	1	1
Pneumonitis	1	1	0	0	0	0	0	0	1	1
Soft Tissue Necrosis	1	1	0	0	0	0	0	0	1	1

Note: Incidence is calculated as the number of patients with at least an AE in a given category (PT, grade) on the total number of patients, by level and cohort or overall.

INDIVIDUAL PATIENT LEVEL EXPERIENCE TO DATE²

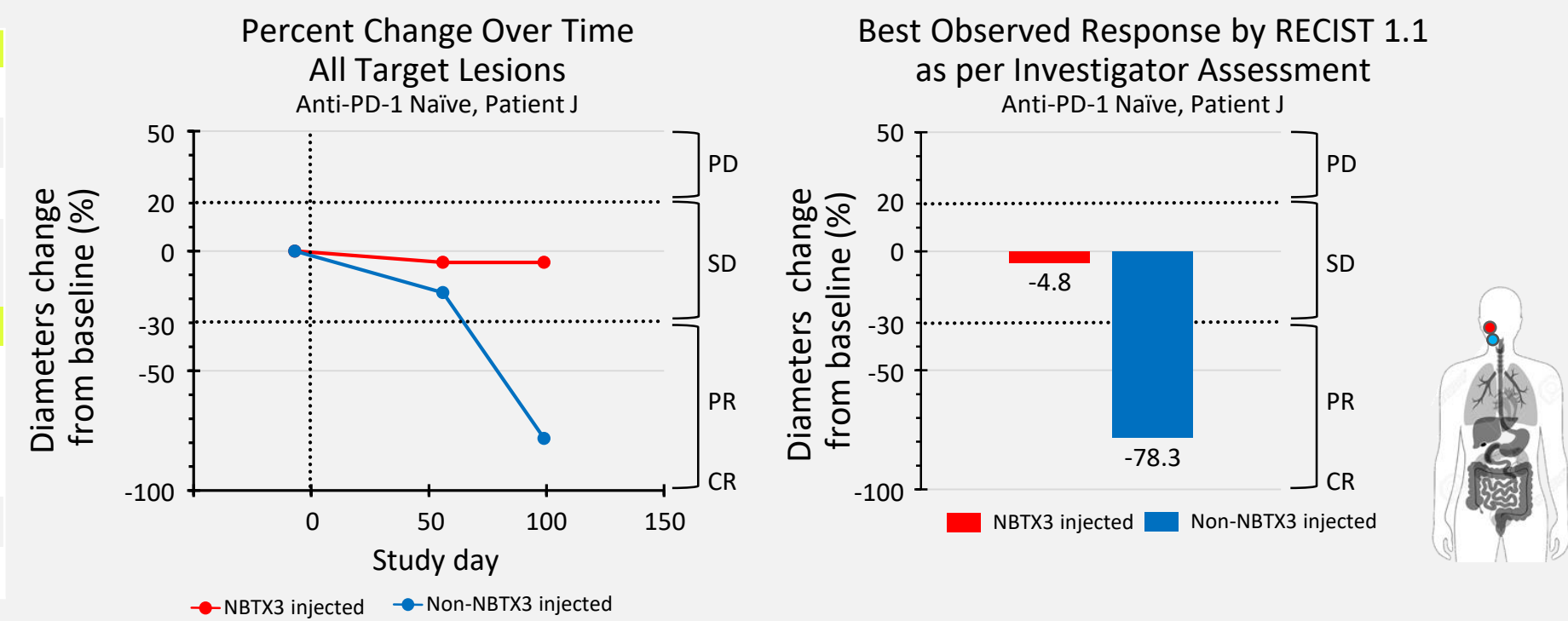
Case 1: Anti-PD-1 Naïve Patient Treated in Cohort 1 (HNSCC)

Patient J
Diagnosis: Stage IV p16- HNSCC with LRR in lymph node
Prior RT: 72 Gy in 66 fractions in 2016
Prior IO: IO naïve
PD-L1 Expression: PD-L1 expression is equal to 0% by TPS
Treatment: Study 1100 Began in Dec 2020 12.7 mL NBTXR3 ITI into 57.8 mL tumor 35 Gy SBRT in 5 fractions 480 mg nivo Q4W
Efficacy BOR: PR
Status: Currently in follow-up



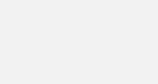
Dose Level 1: 22%

- IO naïve patient with a PD-L1 negative (TPS=0%), p16 negative Stage IV HNSCC, previously treated with induction chemotherapy, received NBTXR3/RT/anti-PD-1 as per protocol.
- The patient had two post-treatment scans and achieved an unconfirmed PR (-31%) with tumor regression in both target lesions.

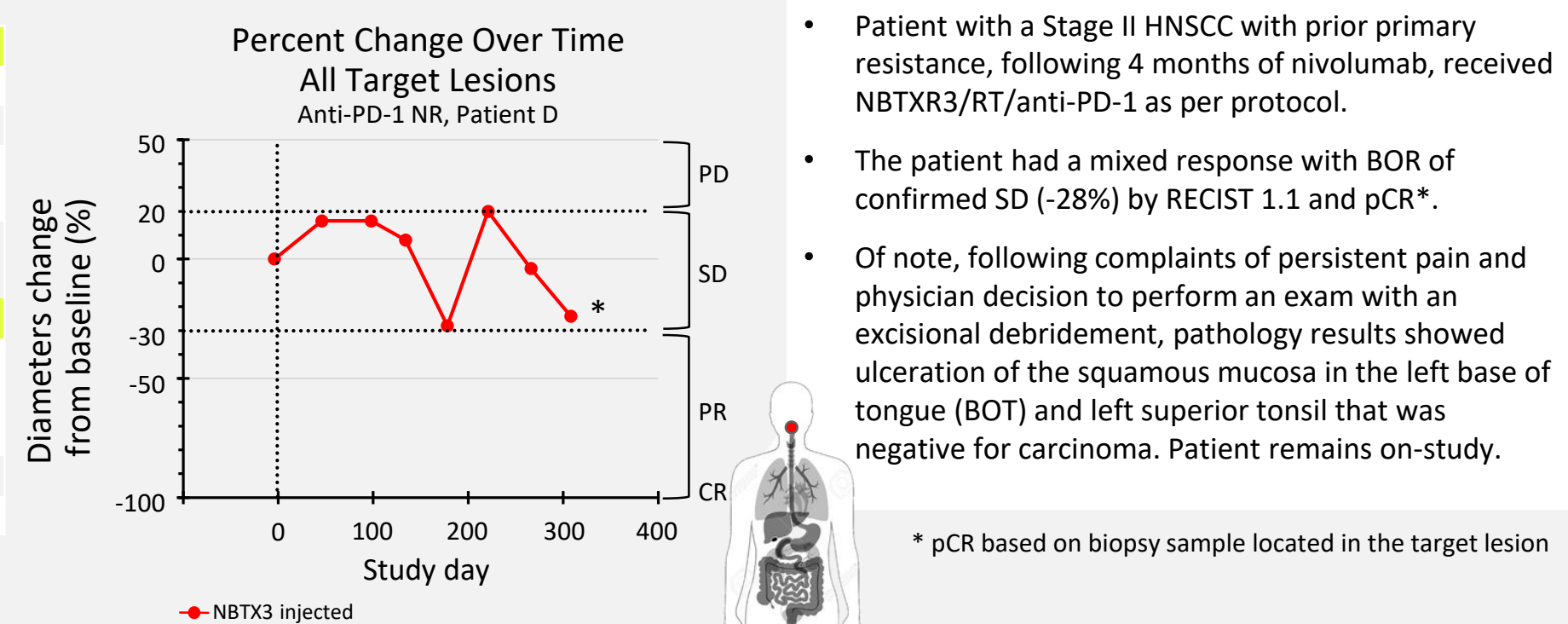


Case 2: Anti-PD-1 Non-Responder Patient Treated in Cohort 1 (HNSCC)

Patient D
Diagnosis: Stage II p16+ HNSCC with LRR in BOT
Prior RT: 70 Gy in 35 fractions in 2016
Prior IO: 480 mg nivo Q4W in 2019/20 (BOR: SD) Anti-PD-1 primary resistance / non-responder PD-L1 expression is unknown
PD-L1 Expression: Study 1100 Began in March 2020
Treatment: 2.68 mL NBTXR3 ITI into 12.2 mL tumor 35 Gy SBRT in 5 fractions 480 mg nivo Q4W SD*
Efficacy BOR: SD*
Status: Currently in follow-up

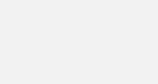


Dose Level 1: 22%



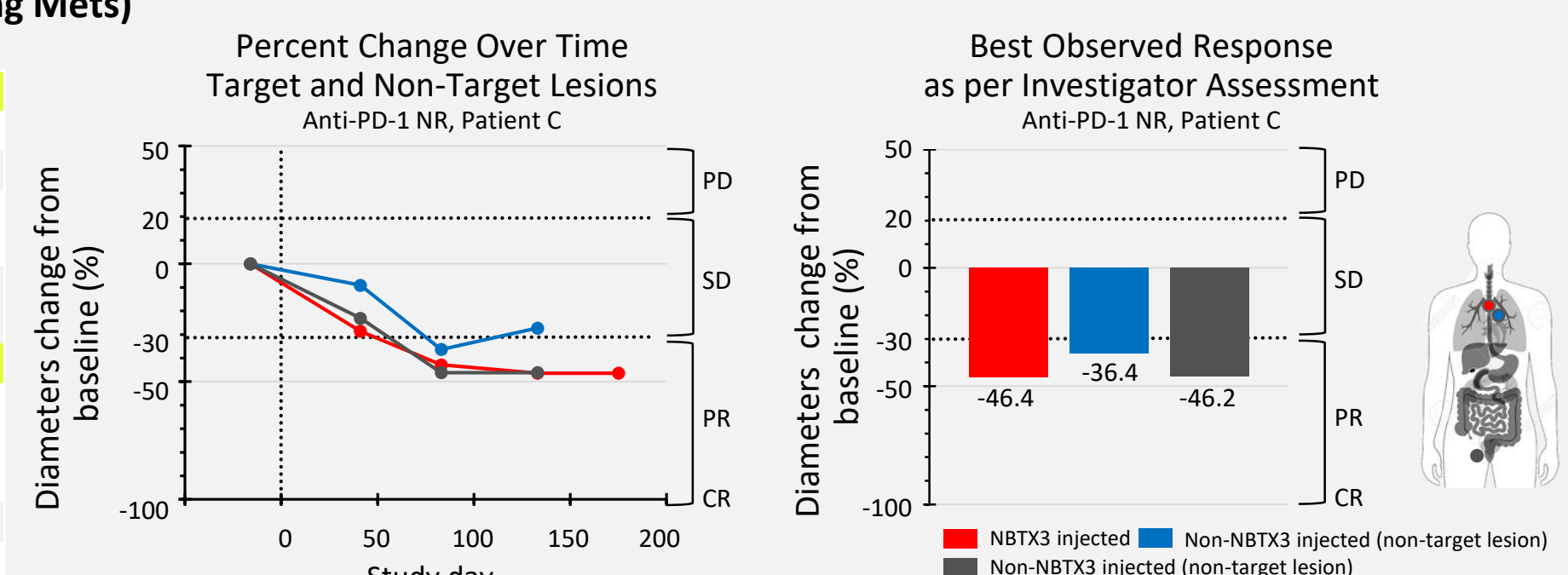
Case 3: Anti-PD-1 Non-Responder Patient Treated in Cohort 2 (Lung Mets)

Patient C
Diagnosis: PD-L1+ Stage IV NSCLC with Lung Mets
Prior RT: RT Naïve
Prior IO: 200 mg pembro Q3W in 2019 (BOR: PD) Anti-PD-1 primary resistance / non-responder PD-L1 expression is equal to 65%
PD-L1 Expression: Study 1100 Began in January 2020
Treatment: 20.9 mL NBTXR3 ITI into 95.1mL tumor 40 Gy SBRT in 5 fractions 200 mg pembro Q3W PR
Efficacy BOR: PR
Status: Alive



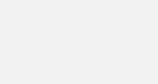
Dose Level 1: 22%

- Patient with lung and distant metastases from Stage IV NSCLC, with prior primary resistance following six months of pembrolizumab (monotherapy and with chemo), received NBTXR3/RT/anti-PD-1 as per protocol.
- Patient had a confirmed PR (-46%) at injected lesion.
- In addition to systemic anti-PD-1, the APW lesion may have received low-dose RT due to its vicinity to the injected target/irradiated lesion, while the distant inguinal lymph node (LN) was outside RT field. Patient withdrew from study due to travel concerns amidst COVID-19 pandemic.

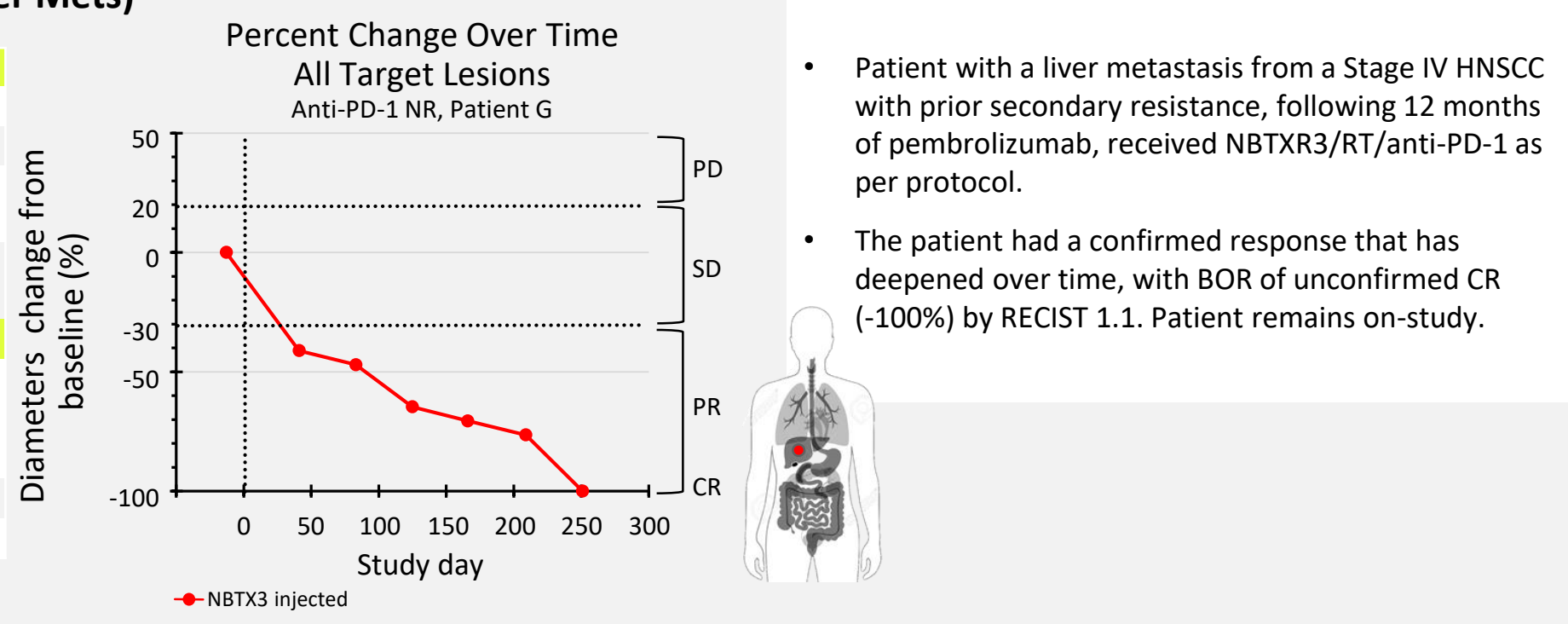


Case 4: Anti-PD-1 Non-Responder Patient Treated in Cohort 3 (Liver Mets)

Patient G
Diagnosis: PD-L1+, p16- Stage IV HNSCC with Liver Mets
Prior RT: RT Naïve
Prior IO: 200 mg pembro Q3W in 2019 (BOR: PD) Anti-PD-1 secondary resistance / non-responder Unknown PD-L1 expression in database
PD-L1 Expression: Study 1100 Began in June 2020
Treatment: 1.2 mL NBTXR3 ITI into 5.3 mL tumor 45 Gy SBRT in 3 fractions beginning on day 12 200 mg pembro Q3W beginning on day 19
Efficacy BOR: Unconfirmed CR
Status: Currently in follow-up



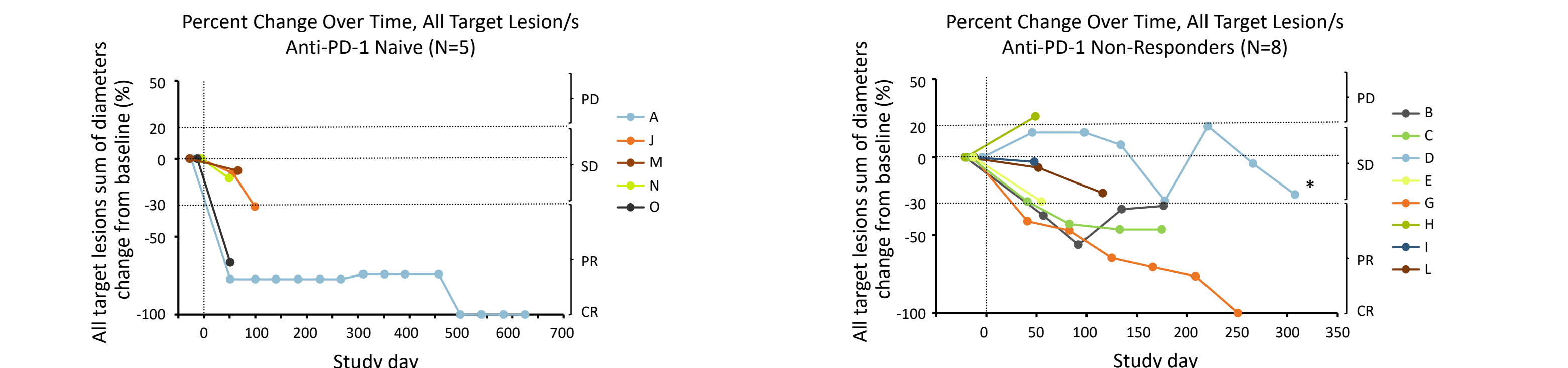
Dose Level 1: 22%



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Percent Change from Baseline in Tumor Size Over Time Stratified by Anti-PD-1 Status²

- Regardless of prior anti-PD-1 exposure (i.e., IO naïve, primary resistance, secondary resistance), tumor regression was observed in 10 of 13 patients evaluable for tumor response.

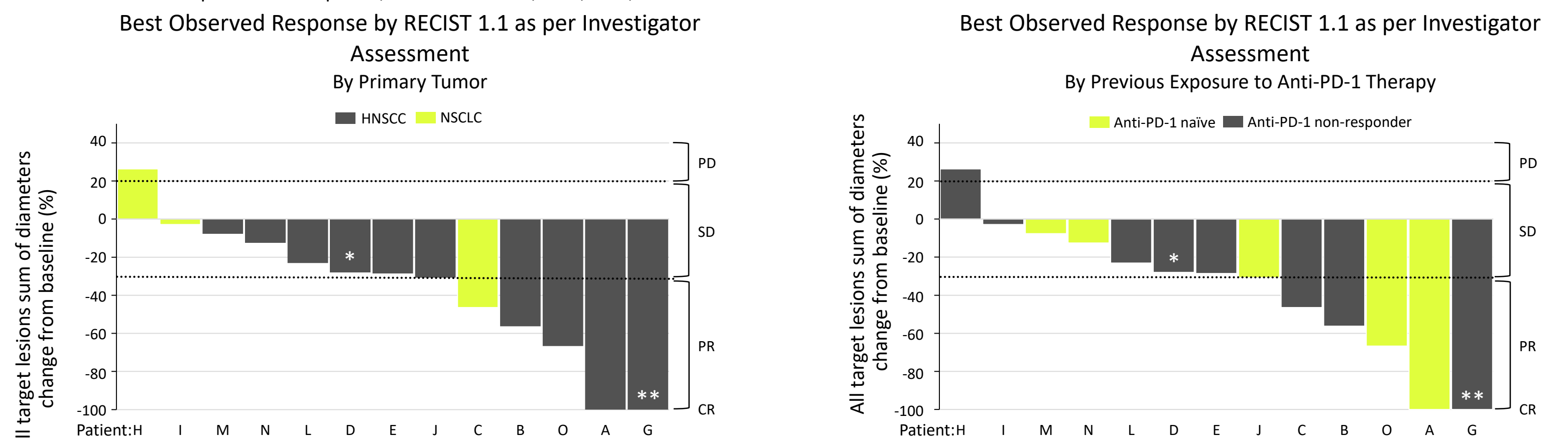


- In patients who were naïve to anti-PD-1, tumor regression was observed in 4 of 5 patients evaluable for tumor response.
- 60% (3/5) of patients had investigator-assessed OR, including 1 CR by RECIST 1.1.
- In patients who had primary or secondary resistance to prior anti-PD-1, tumor regression was observed in 6 of 8 patients evaluable for tumor response.
- 50% (4/8) had investigator-assessed OR (1 CR and 2 PR by RECIST 1.1, and 1 pCR).

* Patient D: pCR based on biopsy sample located in the target lesion

Best Observed Response (as of April 23, 2021)²

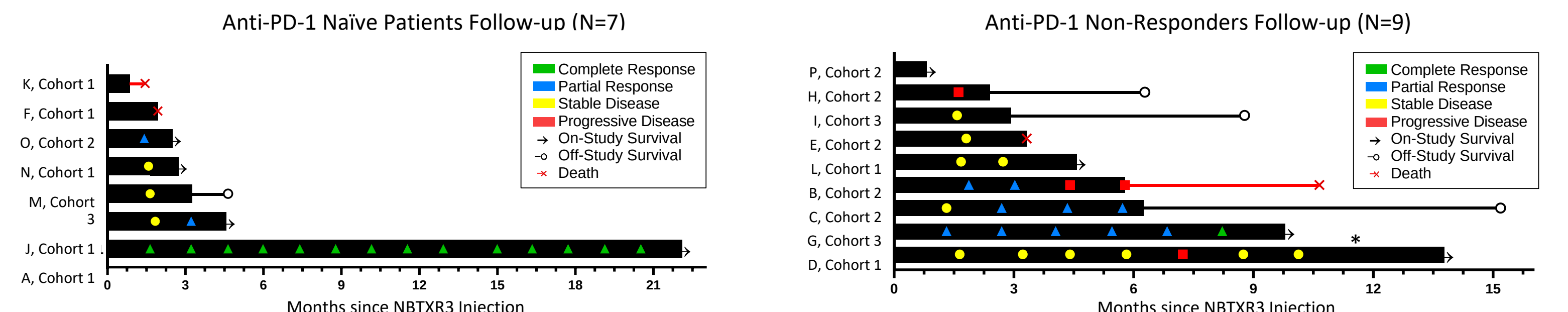
- Best observed responses as of April 23, 2021 were: 2 CR, 4 PR, 6 SD, 1 PD.



* Patient D: pCR based on biopsy sample located in the target lesion; ** Unconfirmed Response

All Treated Patients by Anti-PD-1 Naïve and Anti-PD-1 Non-Responders (as of May 01, 2021)³

- At data cut-off, 16 subjects (all treated population) received NBTXR3 and/or RT, with 13 patients evaluable for tumor response.
- Three patients were not evaluable for tumor response: patient K and F died, while patient P had yet to undergo post-treatment scans.



CONCLUSIONS

- Safety:** NBTXR3 administered by ITI was feasible and well tolerated in all patients (cohort 1: locoregional recurrent (LRR) or recurrent and metastatic (R/M) HNSCC, cohort 2: lung metastases, and cohort 3: liver metastases).
- Overall to date, the AE profile has not differed in type or grade from what is expected with RT or anti-PD-1 agents and safety for every cohort fit the expected profile.
 - Of note, in one isolated case, after two cycles of nivolumab, an anti-PD-1 naïve patient experienced G5 pneumonitis, that was investigator-assessed to be related to anti-PD-1 and possibly related to NBTXR3.
- Efficacy:** Regardless of prior anti-PD-1 exposure, 10 out of 13 patients evaluable for tumor response on study had tumor regression:
 - 4 of 5 anti-PD-1 naïve patients showed regression, 6 of 8 anti-PD-1 non-responder patients had post-treatment tumor regression.
 - Abscopal effect observed, as well as delayed responses
- These data support continued development of NBTXR3/RT in combination with anti-PD-1 across multiple tumor types regardless of prior IO exposure.
- This new study suggests that the combination of NBTXR3/RT and anti-PD-1 can yield a sustained response in both anti-PD-1 naïve patients and patients having progressed on prior anti-PD-1 therapy and NBTXR3/RT could be a promising next step after anti-PD-1/CI resistance.
- NBTXR3/RT has demonstrated potential to stimulate an immune response and to turn anti-PD-1 non-responders into responders.

Abbreviations

AE, adverse event; anti-PD-1, anti-programmed cell death protein 1; APW, aortopulmonary window; BOR, best overall response; chemo, chemotherapy; CR, complete response; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; EoT, end of treatment; G, grade; GTV, gross tumor volume; HNSCC, head and neck squamous cell carcinoma; HN, head and neck; ICF, informed consent form; HPX, hypopharynx; ICI, immune checkpoint inhibitors; IO, immuno-oncology; iRECIST, modified RECIST for immunotherapy; ITI, intratumoral injection; LRR, locoregional recurrent; MTD, maximum tolerated dose; nivo, nivolumab; NR, non-responder; NSCLC, non-small cell lung cancer; PD, progressive disease; pembro, pembrolizumab; qCR, pathological CR; PR, partial response; Q3W, every 3 weeks; RP2D, recommended Phase II dose; RECIST, Response Evaluation Criteria In Solid Tumors; R/M, recurrent/metastatic; RT, radiotherapy; SAE, serious adverse events; SBRT, stereotactic body radiation therapy; SD, stable disease; UNC = University of North Carolina.

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.

References

¹<https://clinicaltrials.gov/ct2/show/NCT03589339>. ²In House Data, cut-off date: 23APR2021. ³In House Data, cut-off date: 01MAY2021.

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