Early Phase 2 Clinical Results of IL-15RαFc Superagonist N-803 With BCG in BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer (NMIBC) Patients Demonstrating 86% CR of Carcinoma In Situ (CIS)

Karim Chamie[1], Amy Rock[2], Peter Rhode[2], John Lee[2], Patrick Soon-Shiong[2]

[1]Department of Urology, UCLA Medical Center, Los Angeles, CA; [2]NANT Cancer Immunotherapy Inc., Culver City, CA

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Background

BCG-Unresponsive NMIBC

- There were approximately 81,190 new bladder cancer cases and 17,240 deaths from the disease in the US in 2018[1]
- At least 70% of all bladder cancers present as non-muscle-invasive disease (NMIBC)[2]
- Immunotherapy with Bacillus Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, is standard-of-care (SoC) therapy[2]
  - BCG triggers an immune response in the bladder and is associated with high initial response rates
- However, recurrence rates for high-risk cases are > 50% at 1 year and about 90% by 5 years (patients with tumors classified as high-grade and patients with carcinoma in situ [CIS] are part of this high-risk group)[2]
- Cystectomy is the SoC for high-risk patients following BCG failure, but is associated with significant morbidity[3]
- New noninvasive treatment options are greatly needed

Augmenting Immunity With an IL-15 Superagonist: N-803 (Figure 3)

- N-803 (also known as ALT-803) is a novel IL-15 receptor superagonist engineered to have a longer serum half-life and 30-fold greater activity vs. IL-15[4,5]
- N-803 promotes natural killer (NK) and CD8+ T-cell expansion and activation in vivo without expanding immunosuppressive regulatory T cells[6,7]

Previous Studies of N-803 in NMIBC

- Preclinical data have shown that N-803 activates NK cells and reduces tumor burden when combined with BCG[8]
- In a phase 1b trial in BCG-naïve patients (n = 9), N-803 + BCG induced complete responses in all patients without recurrence for 24 months (NCT02138734)[9] **(Figure 1)**
- No serious adverse events (SAEs) and no grade > 3 adverse events (AEs)
- An 89-year old, BCG-unresponsive patient received N-803 + BCG under a single patient IND (compassionate use) starting in June 2015 (received 6 weekly intravesical doses) and showed durable response for 33 months[10]

Figure 1: **N-803 + BCG in High-Risk NMIBC – Phase I Results**
Durable Complete Responses in 9 out of 9 Patients

Dose (intravesicular instillation)	Patient	Stage	Response Assessments W12	6M	9M	12M	15M	18M	21M	24M
100 µg	1	T1	CR	CR	CR	CR	CR	CR	CR	CR
	2	Ta	CR	CR	CR	CR	CR	CR	CR	CR
	3	T1	CR	CR	CR	CR	CR	CR	CR	CR
200 µg	4	T1	CR	CR	CR	CR	CR	CR	CR	CR
	5	Tis (CIS)	CR	CR	CR	CR	CR	CR	CR	CR
	6	T1	CR	CR	CR	CR	CR	CR	CR	CR
400 µg	7	T1	CR	CR	CR	CR	CR	CR	CR	CR
	8	Tis (CIS)	CR	CR	CR	CR	CR	CR	CR	CR
	9	Ta	CR	CR	CR	CR	CR	CR	CR	CR

9 of 9 (100%) patients disease-free at 24 months

N-803 has earned ***Fast Track*** **designation** from the FDA based on the strength of these results.

Methods

Study Design

- This trial is a phase 2, open-label, single-arm, multicenter study of intravesical N-803 plus BCG in BCG-unresponsive patients with NMIBC (NCT03022825). The detailed study schema is shown in **Figure 2** below
- Two patient cohorts: (1) BCG-unresponsive CIS [with or without Ta/T1 papillary disease]
  (2) BCG-unresponsive high-grade Ta or T1 papillary disease

Enrollment Criteria

- BCG-unresponsive NMIBC, defined as:
  - Persistent or recurrent CIS (+/- recurrent Ta/T1 disease) within 12 months of receiving adequate BCG
  - Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG
  - T1 high-grade disease at the first evaluation following an induction BCG course alone
- ECOG status 0 – 2 and life expectancy > 2 yrs
- Absence of resectable disease after transurethral resection (TURBT) procedures

Figure 2: Study Schema

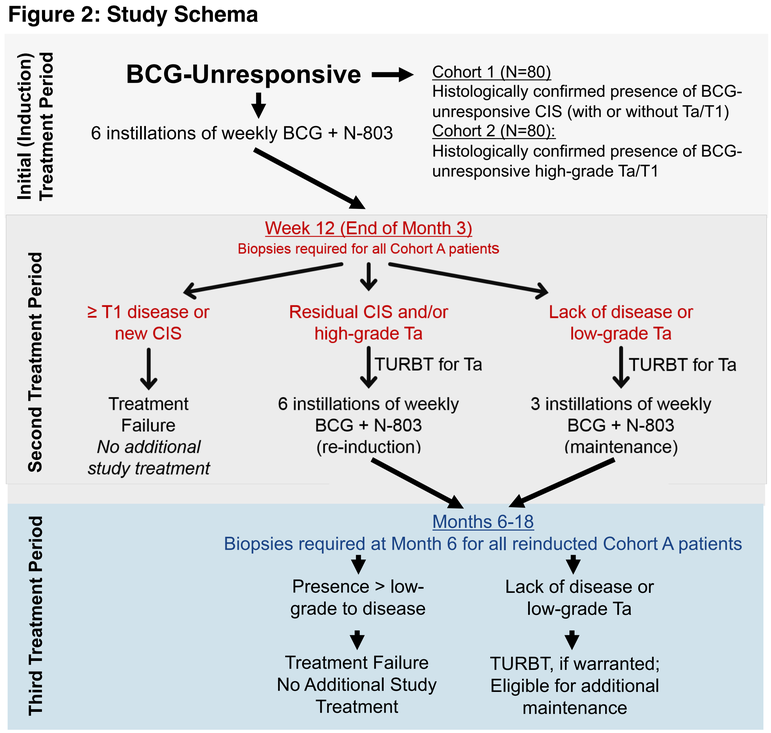
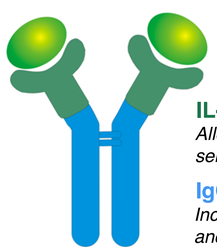


Figure 3:

N-803

IL-15 Superagonist



IL-15N72D
IL-15 alteration N72D enhances binding 10-fold to βγ complex

IL-15Rα
Allows transpresentation selectively to IL-2R βγ chain

IgG1 Fc
Increases serum half-life and lymphoid distribution

N-803 promotes natural killer (NK) and CD8+ T-cell expansion and activation in vivo without expanding immunosuppressive regulatory T cells[6,7]

Results

Efficacy

- 25 subjects have been enrolled to date (the 15 evaluable for response are shown in **Table 1**). Enrollment is ongoing
- **Cohort 1:** 6 of 7 (86%) subjects in the CIS with or without Ta/T1 papillary disease cohort had a complete response (CR)
- **Cohort 2:** 8 of 8 (100%) remain disease free (DF) with no evidence of disease recurrence in any of the patients in the high-grade Ta/T1 papillary disease cohort to date, ranging from 3 to 12 months in duration.

Table 1: Efficacy Assessments Per Subject

Cohort	Sex / Age	Stage	Response Assessments* 3 Months	6 Months	9 Months	12 Months
Cohort 1 Unresponsive Carcinoma In-Situ (CIS) [with or without Ta/T1 papillary disease]	M / 72	CIS	CR	CR	CR	CR →
	M / 73	CIS	PR	PD ✖		
	M / 55	CIS + T1	PR	CR →		
	M / 68	CIS + T1	CR →			
	M / 63	CIS + T1	CR →			
	M / 80	CIS + Ta	CR →			
	M / 66	CIS + Ta	CR →			
Cohort 2 Unresponsive high-grade Ta/T1 papillary disease	M / 64	T1	DF	DF	DF	DF →
	F / 66	T1	DF	DF	DF	**
	M / 89	Ta	DF	DF	DF →	
	F / 63	Ta	DF	DF →		
	M / 90	T1	DF	DF →		
	M / 74	T1	DF →			
	M / 63	T1	DF →			
	M / 88	T1	DF →			

→ Subject ongoing in study ✖ Progressive disease

CR, complete response; DF, disease free; PD, progressive disease. * For the CIS with or without Ta/T1 papillary disease cohort, CR is defined as negative cystoscopy and negative (including atypical) urine cytology; or positive cystoscopy with biopsy-proven benign or low-grade Ta NMIBC and negative cytology; or negative cystoscopy with malignant urine cytology if cancer is found in the upper tract or prostatic urethra and random bladder biopsies are negative. For the high-grade Ta/T1 papillary disease cohort, disease-free is defined as absence of high-grade Ta (excluding low-grade Ta), any grade T1, persistent or new CIS, disease progression, cystectomy, change in therapy, and death (any cause). ** Patient had treatment delays due to AEs of dysuria and urgency and then decided to discontinue treatment after 4 doses; patient was alive at 6-month and 9-month follow up and survival status will continue to be collected per protocol.

N-803 + BCG Safety (Based on > 175 Intravesical Doses)

- 90% of AEs were grade 1 or 2
- The most common AEs (AEs occurring in ≥ 2 subjects) were:
  - Chills (n = 3)
  - Pain or burning on urination (n = 3)
  - Abdominal cramps (n = 2)
  - Bladder spasms (n = 2)
  - Hematuria (n = 2)
  - Hypertension (n = 2)
  - Nausea (n = 2)
  - Urgency (n = 2)
- 2 SAEs have occurred, likely unrelated to N-803 (*E. coli* infection; anemia)
- No immune related AEs have been observed to date

Conclusions

- **CIS Cohort: 6 out of 7 (86%) complete response (CR)** in subjects in the CIS [with or without Ta/T1 papillary disease] cohort.
- **Papillary Cohort: 8 out of 8 (100%) remain disease free (DF)** with no evidence of disease recurrence in any of the patients in the high-grade Ta/T1 papillary disease cohort to date, ranging from 3 to 12 months in duration.
- Treatment is well tolerated with no immune related AEs
- AE profile was generally consistent with what would be expected in subjects receiving BCG alone[11]
- Enrollment is actively proceeding
- N-803 + BCG demonstrated promising evidence of clinical activity in patients who failed BCG therapy, in both the CIS and papillary disease cohorts.

References

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