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

Karim Chamie1, Amy Rock2, Peter Rhode2, John Lee2, Patrick Soon-Shiong2
1Department of Urology, UCLA Medical Center, Los Angeles, CA; 2NANT Cancer Immunotherapy Inc., Culver City, CA

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.
- At least 70% of all bladder cancers present as non-muscle-invasive disease (NMIBC).
- Immunotherapy with Bacillus Calmette-Guérin (BCG), an attenuated strain of Mycobacterium bovis, is standard-of-care (SoC) therapy. 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 around 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).
- Cystectomy is the SoC for high-risk patients following BCG failure, but is associated with significant morbidity.
- 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.
- N-803 promotes natural killer (NK) and CD8+ T-cell expansion and activation in vivo without expanding immunosuppressive regulatory T cells.

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.
- In a phase 1b trial in BCG-naive patients (n = 9), N-803 + BCG induced complete responses in all patients without recurrence for 24 months (NCT02138341).
- 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.

Methods

Study Design

- This trial is a phase 2, open-label, single-arm, multicenter study of intravesical N-803 plus BCG in BCG-unresponsive NMIBC patients (NCT03228285). 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 therapy.
  - ECOG status 0–2 and life expectancy >2 yrs.
  - Absence of resectable disease after transurethral resection (TURBT) procedures.

Results

Efficacy

- 25 subjects have been enrolled to date (the 15 evaluable for response are shown in Table 1).
- Recruitment is ongoing.

Table 1: Efficacy Assessments Per Subject

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Sex / Age</th>
<th>Stage</th>
<th>3 Months</th>
<th>6 Months</th>
<th>9 Months</th>
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<tr>
<td>Cohort 1</td>
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<tr>
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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 (occurring in ≥2 subjects) were:
  - Chills (n = 3)
  - Hematuria (n = 2)
  - Pain or burning on urination (n = 3)
  - Hypertension (n = 2)
  - Abdominal cramps (n = 2)
  - Nausea (n = 2)
  - Bladder spasms (n = 2)
  - Urgency (n = 2)

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, 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.
- 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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