Preliminary phase 2 clinical results of IL-15RαFc superagonist N-803 with BCG in BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) patients

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Background
BCG-Unresponsive NMIBC
- There were approximately 81,190 new 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).
- Immuno-therapy 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 that is associated with high initial response rates.
- However, recurrence rates for high-risk cases may be > 50%, at year 1 and about 50% by year 5. Patients with tumors classified as high-grade and patients with carcinoma in situ (CIS) are part of this high-risk group.
- Cisplatin is the SoC for high-risk patients following BCG failure, but is associated with significant morbidity and mortality.

New noninvasive treatment options are greatly needed

Augmenting Immunity With an IL-15 Superagonist: N-803 (Figure 1)
- N-803 (formerly 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-2.
- 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 1/2 trial in patients with BCG-refractory NMIBC (n = 5), N-803 plus BCG induced a complete response (CR) in one patient with CIS or no recurrence (NR; patients with Ta or T1 high-grade papillary disease) for 24 months.

Methods

Study Design
- This is a phase 2, open-label, single-arm, multicenter study of N-803 plus BCG in patients with BCG-unresponsive NMIBC (NCT02328253).
- The detailed study schema is shown in Figure 3.

- Two patient cohorts:
  1. Cohort 1: 18 of 20 (90%) CR
  2. Cohort 2: 12 of 16 (75%) CR

- The most common AEs (AEs occurring in ≥ 5% of the population) in subjects receiving BCG alone are:
  - Abdominal cramps – Nausea
  - Pain or burning on urination – Hypertension
  - Chills – Hematuria
  - Fever – Insomnia
  - Pain or swelling of joints – Urticaria


Cohort 1: 18 of 20 (90%) CR in subjects with CIS (with or without Ta/T1 papillary disease)

Cohort 2: 12 of 16 (75%) CR in subjects with high-grade Ta/T1 papillary disease

Enrollment Criteria
- BCG-unresponsive NMIBC, defined as:
  - Persistent or recurrent BCG-related cystitis (CT) or Ta/T1 disease within 12 months of receiving adequate BCG.
  - Persistent or recurrent Ta/T1 disease within 6 months of completion of adequate BCG.
  - High-grade disease at the first evaluation following an induction BCG course alone.

- 1/2 CRs have been enrolled to date (Table 1). Enrollment is ongoing.

Results

Efficacy
- 83 subjects have been enrolled to date (Table 1).
- Cohort 1: 18 of 20 (90%) CR (with or without Ta/T1 papillary disease cohort) and had a CR
- Cohort 2: 12 of 16 (75%) CR at 6 months and 7 of 13 (54%) at 9 months remain disease free (DF) in the high-grade Ta/T1 papillary disease cohort to date

- 50% of AEs observed are grade 1 or 2
- The most common AEs (AEs occurring in ≥ 2 subjects) are:
  - Chills
  - Pain or burning on urination
  - Abdominal cramps
  - Bladder spasm

- 5 SAEs have occurred, unlikely related to N-803
- No immune related AEs have been observed to date

- Safety data collection ongoing

Conclusions
- Cohort 1: 18 of 20 (90%) CR in subjects with CIS (with or without Ta/T1 papillary disease)
- Cohort 2: 12 of 16 (75%) disease-free at 6 months and 7 of 13 (54%) at 9 months in subjects with high-grade Ta/T1 papillary disease
- Treatment is well tolerated with no immune related AEs
- AE profile is generally consistent with what would be expected in subjects receiving BCG alone
- Enrollment is actively proceeding

N-803 + BCG demonstrates promising evidence of clinical activity in patients who failed BCG therapy, in both the CIS and papillary disease cohorts

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<th>Table 1: Efficacy Assessments Per Subject</th>
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<td>CR: Complete Response; NR: No Response; E: Evaluated; N: Not Done; TA: Ta; TC: Ta-Related Complete Response</td>
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<td>9 of 10 (90%) patients disease-free at 24 months</td>
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Acknowledgments

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References

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