Future Oncology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ifon20

N-803 Plus BCG Treatment for BCG-Naïve or -Unresponsive Non-Muscle Invasive Bladder Cancer: A Plain Language Review

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To cite this article: Karim Chamie, Sam S. Chang, Charles J. Rosser, Eugene Kramolowski, Mark L. Gonzalgo, Wade J. Sexton, Patricia Spilman, Lennie Sender, Sandeep Reddy & Patrick Soon-Shiong (02 Jul 2024): N-803 Plus BCG Treatment for BCG-Naïve or -Unresponsive Non-Muscle Invasive Bladder Cancer: A Plain Language Review, Future Oncology, DOI: 10.1080/14796694.2024.2363744

To link to this article: https://doi.org/10.1080/14796694.2024.2363744

Published online: 02 Jul 2024.

Plain Language Summary of Publication

N-803 plus BCG treatment for BCG-naïve or -unresponsive non-muscle invasive bladder cancer: a plain language review

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Affiliations can be found at the end of the article.

First draft submitted: 29 November 2023; Accepted for publication: 31 May 2024.

Where can I find the original articles?

The original paper on the Phase 1b study is called 'Safety, Tolerability, and Long-Term Clinical Outcomes of an IL-15 analogue (N-803) Admixed with Bacillus Calmette-Guérin (BCG) for the Treatment of Bladder Cancer.

It can be accessed, for free, using this link: https://www.tandfonline.com/doi/full/10.1080/2162402X.2021.1912885

The original paper on the Phase 2/3 study is called 'IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer'.

It can be accessed for free using this link: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200167

Summary

What is this summary about?
This is a summary of two studies that looked at the safety and effectiveness of a potential new treatment, N-803 (Anktiva), in combination with a standard treatment bacillus Calmette-Guerin (BCG) for people with **non-muscle invasive bladder cancer (NMIBC)**.

One study was a **Phase 1b study** that tested increasing doses of N-803 in combination with the same dose of BCG in people with NMIBC who had never received BCG previously (BCG-naïve). The other study is a **Phase 2/3 study** of N-803 and BCG in people with NMIBC whose cancer wasn't eliminated by BCG alone (BCG-unresponsive).

What happened in the studies?
In the Phase 1b study, the nine participants were split into three groups of 3 participants who received a dose of 100, 200, or 400 µg N-803 along with a standard 50 mg dose of BCG. In the Phase 2/3 study, one group (cohort A) of participants with **carcinoma in situ (CIS)** disease and another group (cohort B) with **papillary disease** were treated with 400 µg N-803 plus 50 mg BCG. There was also a cohort C that received only 400 µg N-803. Treatments were delivered directly into the bladder once a week for 6 weeks in a row.

Non-muscle invasive bladder cancer (NMIBC): Cancer found on the interior surface of the bladder that has not yet grown through the lining of the bladder to the underlying muscle.
Phase 1b study: The first study of a potential new treatment in a small number of people, focused on assessing safety, but also records treatment effects.
Phase 2/3 study: A Phase 2 study still assesses safety, but focuses on treatment effects in a much larger number people who have a specific condition than in Phase 1; in Phase 3, the study is even larger and the test treatment is typically compared to a standard treatment. In this Phase 2/3 study, N-803 plus BCG was not compared to BCG alone because the person's NMIBC was already known to not respond to BCG alone.
Carcinoma in situ (CIS): CIS is NMIBC that lies flat with a likelihood of growing quickly. It can be Ta disease found only on the bladder lining or T1 disease that has grown into the tissue beneath the bladder lining.
Papillary disease: NMIBC that does not lie flat but has tiny projections on the surface.

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Published by Informa UK Limited, trading as Taylor & Francis Group

ISSN 1479-6694

Summary cont.

What were the key takeaways?
N-803 plus BCG eliminated NMIBC in all nine BCG-naïve participants and the effects were long-lasting, with participants remaining NMIBC-free for a range of 8.3 to 9.2 years.

As reported in 2022, cancer was eliminated in 58 of 82 (71%) participants with BCG-unresponsive CIS disease and the effect was also long-lasting. Importantly, approximately 90% of the successfully treated participants avoided surgical removal of the bladder. In cohort B participants with papillary disease, 40 of 72 (55.4%) were cancer-free 12 months after treatment. N-803 used alone was only effective in 2 of 10 participants. In both studies, the combination of N-803 and BCG was found to be associated with very few adverse events.

Based on results from the Phase 2/3 study, the U.S. Food and Drug Association (FDA) approved the use of N-803 plus BCG for the treatment of BCG-unresponsive bladder CIS with or without Ta/T1 papillary disease.

Who sponsored the studies?

A sponsor is a company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyses the information that was generated during the study. Both studies were sponsored by ImmunityBio, Inc., manufacturer of N-803 (Anktiva).

Who is this review for?

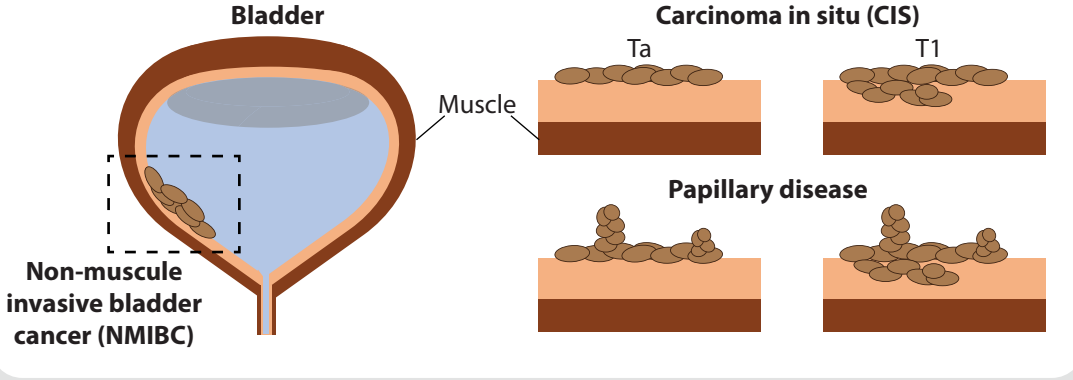
This review is for participants who have either newly diagnosed or previously treated NMIBC, their physicians, patient advocates, the general public, healthcare professionals, or anyone who is interested in new treatment options being studied for either BCG-naïve or BCG-unresponsive NMIBC.

The purpose of this plain language summary is to help you to understand the findings from recent research

- Anktiva (N-803) is approved by the U.S. FDA to treat BCG-unresponsive bladder carcinoma in situ with or without Ta/T1 papillary disease.
- Health professionals should make treatment decisions based on all available evidence not only the results of a single study.
- Phase 2b of the study for people with BCG-naïve NMIBC is ongoing.
- The Phase 2/3 study for people with BCG-unresponsive NMIBC was still ongoing at the time this report was written, therefore the final outcomes of this study may differ from the outcomes described in this summary.

What is NMIBC?

NMIBC is a type of cancer that grows on the inside lining of the bladder, but has not grown past the lining into the muscular wall of the bladder. NMIBC is also known as 'carcinoma in situ' (CIS). If it has not grown into the underlying tissue it is considered 'Ta' and if it has (but not as far as the muscle) it is 'T11'. If it has not grown into the underlying tissue it is considered 'Ta' and if it has (but not as far as the muscle) it is 'T1'. If the NMIBC is not flat, but has little projections, it is called 'papillary' NMIBC. Papillary NMIBC can also be Ta or T1.



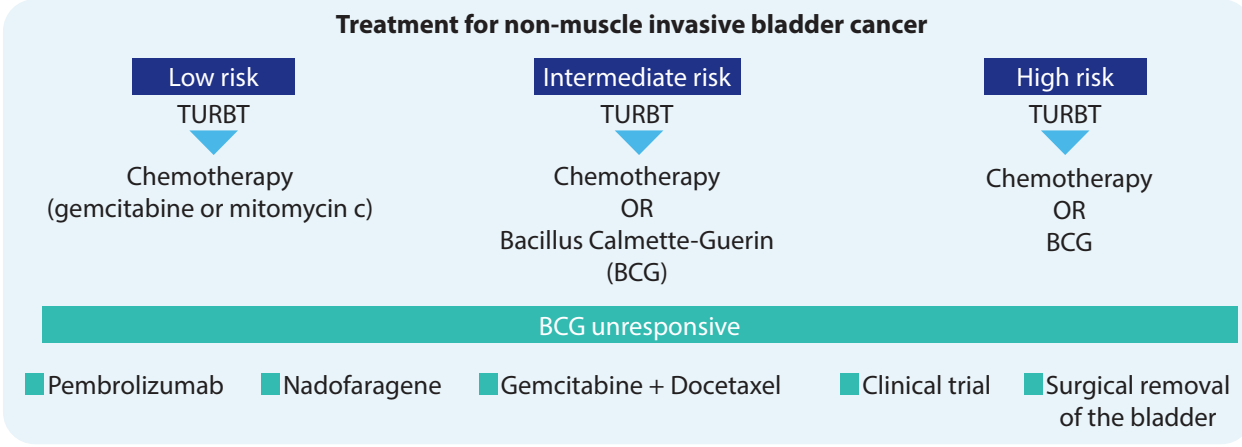
Assessing bladder cancer involves the use of a small camera called a cystoscope that can be inserted through the urethra and into the bladder so that the physician can see the bladder and urethra more thoroughly. Typically, biopsies (tissue samples) and resections (removed tumor tissue) are taken to be prepared and viewed under a microscope by a pathologist (an expert in identifying cancer tissue) to determine the disease type and severity.

What are some treatments currently used for NMIBC?

For NMIBC of all types, treatment typically starts with surgical removal of as much of the tumor as possible in a procedure called a 'transurethral resection of the bladder tumor' or TURBT. About 4-6 weeks after TURBT for NMIBC with a low risk of growing rapidly, chemotherapy is delivered directly to the bladder using a tube (urinary catheter). Treatment for intermediate-risk disease is similar, but BCG may be used instead of chemotherapy. For high-risk CIS disease, the standard treatment after TURBT is 6 weeks of BCG and further rounds of BCG up to 3 years, as well as frequent check-ups to assure the cancer has been eliminated.

If disease persists, BCG may be used a again, but if the cancer cannot be successfully treated with BCG, it is considered 'BCG-unresponsive'. Treatments currently approved for BCG-unresponsive NMIBC include pembrolizumab, nadofaragene, and a combination of gemcitabine and docetaxel.

In all cases where the cancer is not eliminated by standard treatments, the doctor may suggest surgical removal of the bladder or that the person participate in a clinical study.



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What were the Phase 1b and Phase 2/3 studies?

The studies were conducted to determine if combination of a standard treatment for NMIBC, BCG, delivered directly to the bladder, and the known **immune system enhancer** N-803 is effective in eliminating cancer in participants who had never received BCG or for whom BCG was not effective. Assessing the safety of the treatment combination was also important in both studies. In the Phase 1b study, increasing doses of N-803 were tested in combination with BCG to help with the choice of dose for the Phase 2/3 study. In the Phase 2/3 study, N-803 was also tested alone to see if it could be effective without BCG.

Immune system enhancer: A treatment that activates cells of the immune system to attack and eliminate a target, such as a cancerous cell.

How do BCG and N-803 work together in NMIBC?

BCG is a bacteria that is safe to deliver directly to the bladder. After delivery, it interacts with the cancer cells on the bladder lining and, in many people with NMIBC, triggers a response by cells of the immune system – our natural defense against infection and cancer - that clears the cancerous cells.

N-803 is an **interleukin-15 (IL-15)** '**superagonist**', that is, it has effects similar to natural IL-15, but is more powerful. N-803 (like IL-15) causes two types of immune cells – natural killer and T cells – to increase in numbers and become more active.

In people whose NMIBC does not respond to BCG alone, it is thought the cancer-killing activity of the natural killer and T cells cells is too weak to be effective. In many people with NMIBC, the addition of N-803 to BCG increases the activity of these immune cells enough to result in the elimination of the cancer.

Interleukin-15 (IL-15): A type of molecule called a 'cytokine', it specifically interacts with immune cells to activate them.
Superagonist: A potent agonist that increases an effect to a far greater level than is found naturally.

What did the Phase 1B and Phase 2/3 studies look at?

In the early, smaller Phase 1 study, investigators wanted to see if N-803 and BCG would be effective in BCG-naïve (who had not previously received BCG) people with NMIBC. They also wanted to establish what the best dose would be for the larger Phase 2/3 study, based on effects and, in particular, safety and tolerability.

In the second, larger study, investigators wanted to see if N-803 could sufficiently increase the immune response to the cancer to result in the elimination of cancer (referred to as a 'complete response'), in people for whom BCG alone was not effective, particularly in the study participants with CIS disease. In participants with papillary disease, investigators looked at the length of time they lived without disease (disease-free survival).

A smaller number of participants with CIS disease received N-803 alone to see if it could be effective without BCG.

In both studies, the association of treatment and a reduced need for the surgery to remove the bladder was also determined.

Safety, as assessed by the number of medical issues or 'adverse events', was important in both studies. The participants themselves also reported how they felt while on the study ('Patient Reported Outcomes' or PROs.').

Other responses to treatment assessed included:

- The length of time a complete response lasted
- How many participants avoided the need for surgical removal of the bladder
- How long participants went without disease getting worse (even if tumor tissue wasn't completely eliminated) called 'progression-free survival (PFS)'
- How long participants survived without evidence of NMIBC (disease-specific survival; DSS)
- How long participants survived (overall survival; OS)

For cohort B participants with papillary disease that received N-803 plus BCG, disease-specific survival (how long a participant continued without worsening disease) at 12 months was the main assessment. Safety and response to treatment were assessed as described for the Phase 1b study.

What happened in the studies?

The Phase 1b study in BCG-naïve NMIBC

The Phase 1b study was started in July 2014 and is now completed. The Phase 1b study initially looked at the safety and **efficacy** (ability to eliminate the cancer) of N-803 plus BCG in BCG-naïve participants. The study also established the dose for the following Phase 2/3 study.

Efficacy: How well the tested treatment works to eliminate the cancer.
Cytoscopy: A method to view the lining of the bladder using a cystoscope, which is a long flexible tube with a light and a lens.
µg: One millionth of a gram.

In both the Phase 1b and Phase 2/3 studies, participants had to be adults (older than 18 years) to participate, and could not have other health problems that would interfere with their ability to participate in the studies. Both men and women were in the studies.

People with NMIBC interested in participating in the study were screened to make sure they could take part in the study. All participants had NMIBC that was considered intermediate or high risk (likely to grow and spread without treatment) that was confirmed by tissue samples taken from their bladders. They could have either CIS or papillary disease, and could also have NMIBC that was considered CIS 'Ta' where the cancer is just in the innermost layer of the bladder lining, or 'T1' where the cancer has started to grow into the tissue beneath the bladder lining. It was important that none of the participants had previously received BCG, that is, they were BCG-naïve, but people with NMIBC routinely undergo the TURBT procedure whereby the cancer cells are scraped off the bladder wall by a physician. All participants started the study within less than 2 months of their last TURBT, and within a month of their most recent **cystoscopy**.

The Phase 1b study was called an open-label dose-escalation study, meaning both the participant and the doctor conducting the treatment knew what the participant would receive, and different doses would be tested in different participants. The BCG dose was kept at 50 mg, but the N-803 dose increased, with the first 3 participants receiving 100 **µg** (with the BCG) and – if no severe adverse events occurred (here, referred to as 'dose-limiting toxicities' or DLTs) – then the next 3 participants would receive 200 µg. If that was found to be safe, the final 3 participants would receive 400 µg. The two drugs were mixed and delivered via a catheter directly to the bladder weekly for 6 consecutive weeks. If there were no safety problems, the physicians and participants were encouraged to receive additional treatments of BCG alone every 3 months up to 3 years.

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About the participants in the Phase 1b study for BCG-naïve NMIBC

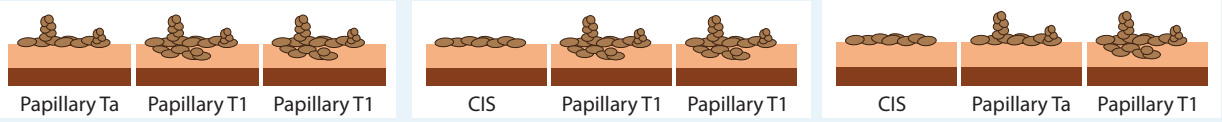
Overall, the participants in the Phase 1b study were newly diagnosed people with high risk (more likely to grow and spread than low risk) NMIBC. The age range, sex and disease types for participants in each of the 3 N-803 dose groups (100, 200, and 400 µg) are shown below.

About the BCG-naïve patients in the Phase 1b trial

N-803 Dose Group

100 µg	**200 µg**	**400 µg**
Age range: 43-70 years	Age range: 64-78 years	Age range: 61-65 years
Women: 1	Men: 3	Men: 3
Men: 2	Asian: 1	Asian: 2
Asian: 3	White: 1	White: 1
	Other: 1	

Disease type



The Phase 2/3 study for BCG-unresponsive NMIBC

The Phase 2/3 study was for people with NMIBC that had cancer return even after repeated BCG treatments (BCG-unresponsive) with a focus on efficacy and safety. These people may have never responded to BCG ('BCG refractory') or responded at one time, then failed to respond to BCG later when the cancer returned ('BCG-relapsed). The Phase 2/3 study was started in June 2017 and was ongoing at the time this report was written.

The Phase 2/3 participants were placed in cohorts A, B or C. Cohort A and C participants had high-risk BCG-unresponsive CIS disease with or without Ta or T1 status. Cohort B participants had high-grade (likely to grow and spread) Ta/T1 papillary NMIBC. All participants had to be free of cancer that could be removed by TURBT at the start of the study. This may seem to mean that the cancer is gone, but for high-risk NMIBC, TURBT alone is not enough to prevent the cancer from returning - that is why additional treatment is needed.

Participants in cohorts A and B received 50 mg BCG plus 400 µg N-803 (the highest dose tested in the Phase 1b study, and found to be safe) directly to the bladder, and cohort C participants received only 400 µg N-803. Just as in the Phase 1b study, they received the treatment weekly for 6 consecutive weeks. At 3 months, they underwent studies to assess their response to treatment, including cystoscopy, urine collection, and bladder tissue collection (biopsy). After that, these assessments took place every 3 months up to 5 years, but biopsies were only performed if it was suspected the cancer had returned. If at 3 months the participant had not achieved a complete response (some cancer remained), they had the option of another 6 weeks of treatment. For these participants, biopsies were taken at month 6.

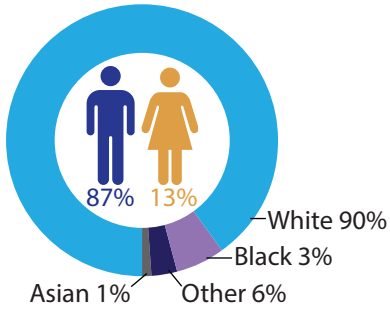
About the participants in the Phase 2/3 study for BCG-unresponsive NMIBC

This study had 3 groups or cohorts, cohort A participants had CIS with or without Ta/T1 disease and cohort B participants had high-grade papillary disease, and both of these groups received BCG (Anktiva) plus N-803 (Anktiva). Cohort C participants had CIS with or without Ta/T1 disease and received N-803 alone. The number of participants in each group, their age range, how many were male or female, and the percentage of each race represented is shown below.

About the BCG-unresponsive patients in the Phase 2/3 trial

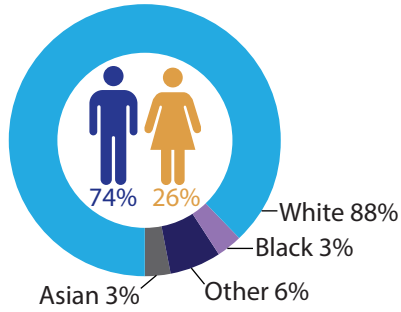
Cohort A

Anktiva + BCG
82 participants
Age range: 50-91 years



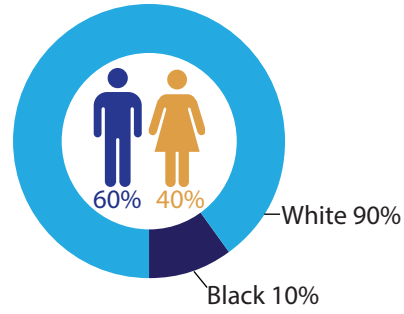
Cohort B

Anktiva + BCG
72 participants
Age range: 46-93 years



Cohort C

Anktiva
10 participants
Age range: 67-82 years



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What were the results?

The study for people with BCG-naïve NMIBC started in July of 2014 and the data presented in the publication was collected before March 2021. At each dose level, adverse events were manageable and most were mild or moderate (grades 1 and 2) and just a few severe (severe is grade 3). During the 2-year follow-up (a check-in with the participants to see if the cancer returned), all 9 participants were disease free and remained so for 6 years in the initial report. In the recent follow-up (September 2023), 4 of 6 evaluable participants (2 died of non-NMIBC causes and one could not be contacted) were still disease-free, with 2 having relatively recent (2023) return of or new bladder cancer, with responses being maintained for a range of 8.3 to 9.2 years from the first recorded complete response on the study.

The results from the Phase 2/3 study in BCG-unresponsive NMIBC are shown in the box:

Results from the Phase 2/3 trial in BCG-Unresponsive NMIBC

Cohort A CIS +/- Ta or T1 disease

Bladder cancer eliminated in 71%

Duration: 26.6 months (**median**)

Preserved bladder: 89.2% at 24 months

Cohort B Papillary disease

55.4% cancer-free at 12 months

Median: A value in the middle of values recorded for a group of people.

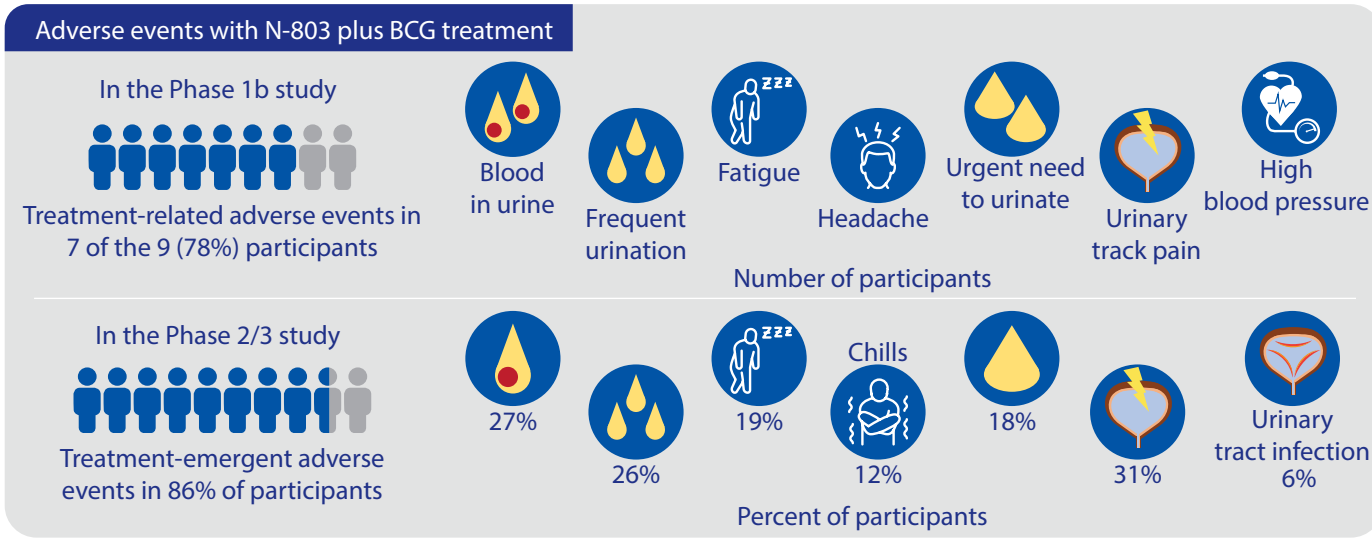
In the Phase 2/3 study, participants themselves had few complaints about the effects of treatment, as recorded in questionnaires about how they felt. Their Patient Recorded Outcomes, which covered both their perception of their own globalhealth and physical function, remained stable throughout the study.

How many study participants had adverse events?

Medical problems described by the participant (symptoms) or observed by the doctor or health care provider (signs) that occur during the course of the study were recorded. These medical problems or 'adverse events' may or may not be due to the treatment being studied. All adverse events that are recorded are referred to as 'treatment-emergent' (they appeared during the course of the study), only some as 'treatment-related' (actually due to the treatment itself), but all adverse event are important, as it can be difficult to know if an adverse event is treatment-related or not. Larger studies and use of the treatment over time are needed to confirm which adverse events are most likely to be related to the treatment.

In the Phase 1b study, none of the adverse events were considered serious, and use of N-803 did not need to be stopped in any case. Adverse events are also graded, with Grade 1 being mild, Grade 2 moderate, Grade 3 severe, Grade 4 life-threatening, and Grade 5 resulting in death. Almost all adverse events in the Phase 1 study were Grade 1 or 2, and only a few grade 3.

In the Phase 2/3 study in BCG-unresponsive NMIBC, cohorts A and B participants both received BCG and N-803. The most common adverse events considered treatment-related for participants who received N-803 plus BCG were similar to those reported in the Phase 1b study and were associated with the urinary tract. Most adverse events were grade 1 or 2 (86%), with 20% of participants having at least one grade 3 adverse event. Three participants had a grade 4 adverse events and there was one grade 5.



Key findings

- Use of N-803 plus BCG resulted in complete responses – the elimination of non-muscle invasive bladder cancer – in all nine BCG-naïve participants in the Phase 1b study
- The complete responses were extremely long-lasting, being more than 8 years in participants that could be followed-up.
- Every tested dose of N-803 was safe, whether it was100, 200, and 400 µg. For the second, larger Phase 2/3 study, the highest dose of 400 µg is being used.
- Use of N-803 plus BCG in BCG-unresponsive participants was also very effective, producing an approximately 70% complete response rate.
- Duration of complete responses in BCG-unresponsive participants were also long-lasting being more than 26 months at the time the data was published.
- Almost all of the successfully treated participants avoided the need for surgical removal of the bladder.
- Disease-free survival was above 50% for participants with papillary NMIBC.
- The combination of N-803 and BCG was found to be associated with very few adverse events.
- Participants themselves reported stable quality-of-life on the Phase 2/3 study.

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What are the next steps?

The Phase 1b study for BCG-naïve participants is completed. A Phase 2 study for BCG-naïve participants is underway to assess the effects of treatment in a larger group.

The Phase 2/3 study in BCG-unresponsive participants was ongoing at the time this report was written. Based on the data gathered up to the end of 2023, the U.S. FDA approved the use of N-803/Anktiva plus BCG for BCG-unresponsive CIS with or without Ta/T1 papillary disease. You can read more about this approval here: https://www.medscape.com/viewarticle/fda-approves-new-bladder-cancer-drug-2024a10007t5

Where can I find more information on the studies?

You can read more about the studies on https://www.clinicaltrials.gov by entering either 'NCT02138734' for the Phase 1b study or 'NCT03022825' for the Phase 2/3 study into the 'Other terms' search field.

In the Phase 1b study 'A Study of Intravesical BCG in Combination With ALT-803 in Patients With Non-Muscle Invasive Bladder Cancer' participants joined from July 2014 to July 2015, with follow-up through January 2021.

The original article on the Phase 1b was titled 'Safety, Tolerability, and Long-Term Clinical Outcomes of an IL-15 analogue (N-803) Admixed with Bacillus Calmette-Guérin (BCG) for the Treatment of Bladder Cancer'. It was published in Oncoimmunology on May 3, 2021 10(1):1912885. doi: 10.1080/2162402X.2021.1912885. This article is open access and can be viewed here: https://www.tandfonline.com/doi/full/10.1080/2162402X.2021.1912885

The Phase 2/3 study 'QUILT-3.032: A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination With ALT-803 (N-803) in Patients With BCG-Unresponsive High-Grade Non-Muscle-Invasive Bladder Cancer' began in June, 2017 and was ongoing at the time this report was written. All study sites are in the U.S.

The original article on the Phase 2/3 was titled 'IL-15 Superagonist NAI in BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer'. It was published in the New England Journal of Medicine (NEJM) Evidence in January 2023 2(1):EVIDoa2200167. doi: 10.1056/EVIDoa2200167. Epub 2022 Nov 10. This article is open access and can be viewed here: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200167

Learn more about non-muscle invasive bladder cancer on the American Urological Association's Urology Care website: https://www.urologyhealth.org/urology-a-z/n/non-muscle-invasive-bladder-cancer

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Acknowledgments

The authors would like to thank the Phase 1b and 2/3 study participants, their families and caregivers. They also thank the study investigators and staff who cared for study participants.

Financial disclosure

Authors with an ImmunityBio affiliation are employees of ImmunityBio, Inc. the manufacturer of N-803 and sponsor of the studies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Company review disclosure

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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10.1080/14796694.2024.2363744