ImmunityBio

Non-Muscle Invasive Bladder Cancer

NEJM Evidence

Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

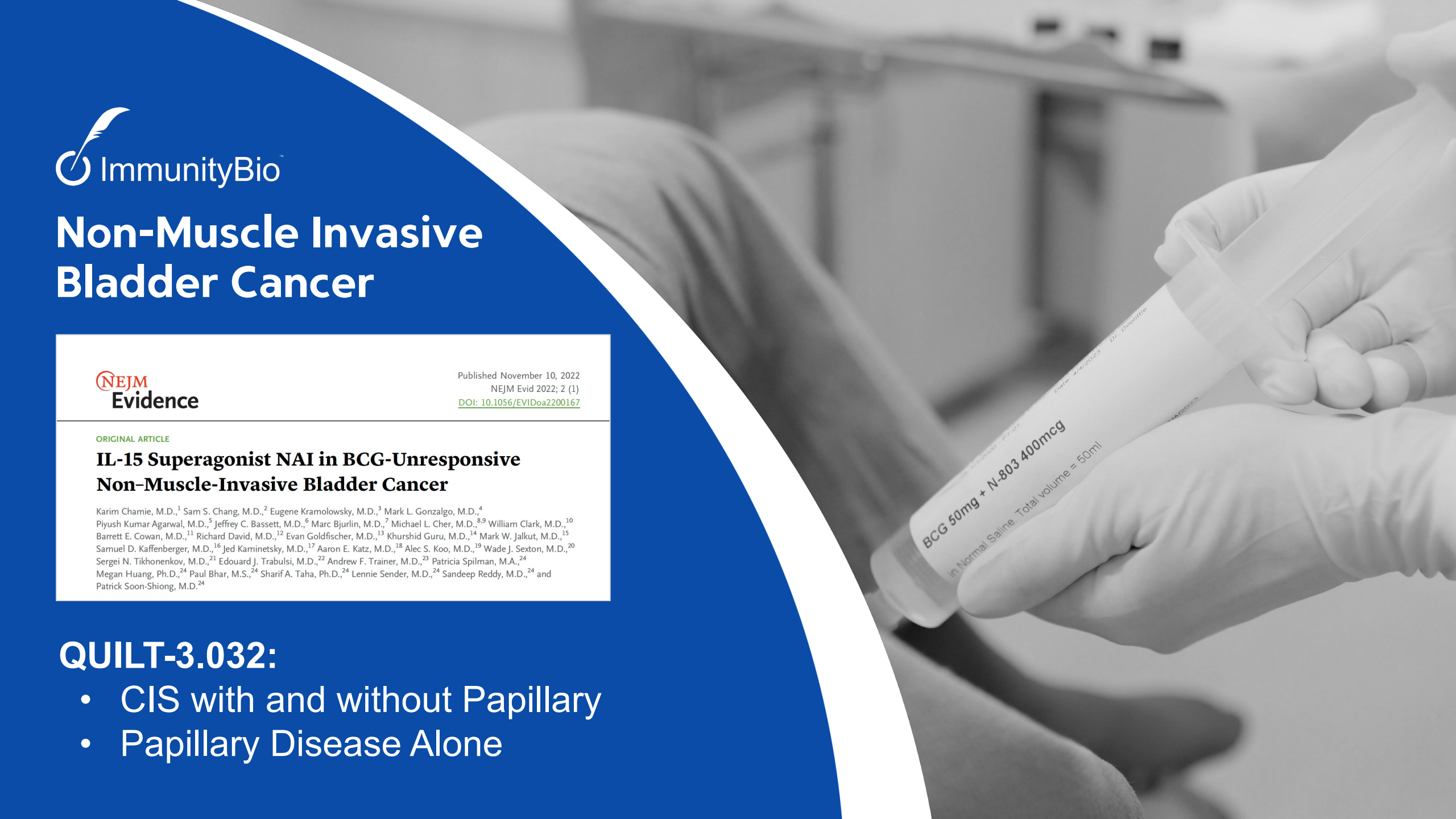
ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

QUILT-3.032:

- CIS with and without Papillary
- Papillary Disease Alone



The Ideal Profile of an Immunotherapy Therapeutic in the Treatment of NMIBC:

A locally (intravesical) administered immunotherapy molecule to achieve:

- A high complete remission rate
- A durable CR extending beyond 24 months
- A durable remission in both CIS & Papillary disease
- A high cystectomy avoidance rate
- A tolerable and safe adverse event profile
- A low treatment-related discontinuation rate
- No severe immune-related adverse events

Unmet Need in NMIBC BCG Unresponsive CIS & Papillary Disease

NEJM Evidence

Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

Abstract

BACKGROUND Patients with Bacillus Calmette–Guérin (BCG)–unresponsive non–muscle-invasive bladder cancer (NMIBC) have limited treatment options. The immune cell–activating interleukin-15 (IL-15) superagonist Nogapendekin alfa inbakicept (NAI), also known as N-803, may act synergistically with BCG to elicit durable complete responses (CRs) in this patient population.

METHODS In this open-label, multicenter study, patients with BCG-unresponsive bladder carcinoma in situ (CIS) with or without Ta/T1 papillary disease were treated with intravesical NAI plus BCG (cohort A) or NAI alone (cohort C). Patients with BCG-unresponsive high-grade Ta/T1 papillary NMIBC also received NAI plus BCG (cohort B). The primary end point was the incidence of CR at the 3- or 6-month assessment visit for cohorts A and C, and the disease-free survival (DFS) rate at 12 months for cohort B. Durability, cystectomy avoidance, progression-free survival, disease-specific survival (DSS), and overall survival were secondary end points for cohort A.

RESULTS In cohort A, CR was achieved in 58 (71%) of 82 patients (95% confidence interval [CI]=59.6 to 80.3; median follow-up, 23.9 months), with a median duration of 26.6 months (95% CI=9.9 months to [upper bound not reached]). At 24 months in patients with CR, the Kaplan–Meier estimated probability of avoiding cystectomy and of DSS was 89.2% and 100%, respectively. In cohort B (n=72), the Kaplan–Meier estimated DFS rate was 55.4% (95% CI=42.0% to 66.8%) at 12 months, with median DFS of 19.3 months (95% CI=7.4 months to [upper bound not reached]). Most treatment-emergent adverse events for patients receiving BCG plus NAI were grade 1 to 2 (86%); three grade 3 immune-related treatment-emergent adverse events occurred.

Drs. Chamie and Chang contributed equally to this article and are coprincipal investigators.

The author affiliations are listed at the end of the article.

Dr. Soon-Shiong can be contacted at PSS@immunitybio.com or at ImmunityBio, Inc., 9920 Jefferson Blvd., Culver City, CA 90232.

EFFICACY RESULTS

CIS with or without Papillary (Cohort A)

In cohort A, CR was achieved in 58 (71%) of 82 patients (95% confidence interval CI=59.6 to 80.3; median follow-up, 23.9 months), with a median duration of 26.6 months (95% CI=9.9 months to [upper bound not reached]). At 24 months in patients with CR, the Kaplan–Meier estimated probability of avoiding cystectomy and of DSS was 89.2% and 100%, respectively.

Papillary Disease Alone (Cohort B)

In cohort B (n=72), the Kaplan–Meier estimated DFS rate was 55.4% (95% CI=42.0% to 66.8%) at 12 months, with median DFS of 19.3 months (95% CI=7.4 months to [upper bound not reached]).

Editorial

An Interleukin-15 Superagonist with BCG — A Major Therapeutic Advancement or Just a Small Step in the Right Direction?

Eugene J. Pietzak, M.D. and Harry W. Herr, M.D.

December 27, 2022

NEJM Evid 2023;2(1) DOI: 10.1056/EVIDe2200264 VOL. 2 NO. 1

The author affiliation is listed at the end of the article.

Dr. Pietzak can be contacted at pietzake@mskcc.org or at Urology Service, Department of Surgery, Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, 353 E. 68th St., New York, NY 10065.

For more than 40 years, intravesical Bacillus Calmette–Guérin (BCG) has remained the most effective treatment for non–muscle-invasive bladder cancer (NMIBC); however, tumor recurrence and progression are common, especially for those patients with carcinoma in situ (CIS).[1] Therapeutic options are limited when treatment with BCG fails, and radical cystectomy remains the only curative treatment. BCG-unresponsive NMIBC criteria were developed in 2015 to identify patients for whom additional BCG would likely not be effective and to facilitate clinical trials of novel therapies.[2,3] Because randomized controlled trials comparing investigational approaches versus radical cystectomy are infeasible, the U.S. Food and Drug Administration allows for drug approval on the basis of single-arm phase 2 trials in BCG-unresponsive CIS; the first such approval was given for the immune checkpoint inhibitor pembrolizumab in 2020. However, pembrolizumab has a 12-month complete response rate (CRR) of only 20% and is associated with a ≥13% risk of serious immune-related adverse events.[4] The second major trial reported for BCG-unresponsive NMIBC assessed a viral gene therapy, nadofaragene firadenovec, with a similar 12-month CRR of only 24%; in contrast to pembrolizumab, however, it is an intravesical treatment that avoids systemic toxicity and has convenient dosing of every 3 months.[5] Nonetheless, issues around the complex manufacturing process for this viral gene therapy have prevented U.S. Food and Drug Administration approval to date and may limit its future clinical use.

In this issue of *NEJM Evidence*, Chamie et al.[6] report on the third major single-arm trial in BCG-unresponsive NMIBC, which evaluated intravesical administration of an interleukin-15 superagonist, nogapendekin alfa inbakicept, in combination with BCG (NAI/BCG). Although the primary end point for the CIS cohort in this trial, CRR at "any time", is of unclear clinical significance, the 12- and 18-month CRRs were clinically meaningful at 45% and 33%, respectively. The efficacy and minimal toxicity of this combination represent a major advance for the care of patients with BCG-unresponsive NMIBC, and the authors should be congratulated.

Eugene J. Pietzak, M.D.

Harry W. Herr, M.D.

"This promising combination offers a potential alternative to cystectomy"

"...the 12- and 18-month CRRs were clinically meaningful at 45% and 33%"

"The efficacy and minimal toxicity of this combination represent a major advance for the care of patients with BCG-unresponsive NMIBC, and the authors should be congratulated."

References

1. Fernandez-Gomez J, Solsona E, Unda M, et al. Prognostic factors in patients with non–muscle-invasive bladder cancer treated with Bacillus Calmette–Gu erin: multivariate analysis of data from four randomized CUETO trials. Eur Urol 2008;53:992-1002. DOI: 10.1016/j.eururo.2007.10.006.
2. Jarow JP, Lerner SP, Kluetz PG, et al. Clinical trial design for the development of new therapies for non–muscle-invasive bladder cancer: report of a Food and Drug Administration and American Urological Association public workshop. Urology 2014;83:262-265. DOI:10.1016/j.urology.2013.10.030.
3. Kamat AM, Sylvester RJ, B€ohle A, et al. Definitions, end points, and clinical trial designs for non–muscle-invasive bladder cancer: recommendations from the International Bladder Cancer Group. J Clin Oncol 2016;34:1935-1944. DOI: 10.1200/JCO.2015.64.4070.
4. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non–muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. Lancet Oncol 2021;22:919-930. DOI: 10.1016/S1470-2045(21)00147-9.
5. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non–muscleinvasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. Lancet Oncol 2021;22:107-117. DOI: 10.1016/S1470-2045(20)30540-4.
6. Chamie K, Chang SS, Kramolowsky E, et al. IL-15 superagonist NAI in BCG-unresponsive non–muscle-invasive bladder cancer. NEJM Evid. 2022;2(1). DOI: 10.1056/EVIDoa2200167.
7. Prasad NNG, Muddukrishna SN. Quality of transurethral resection of bladder tumor procedure influenced a phase III trial comparing the effect of KLH and mitomycin C. Trials 2017;18:123. DOI: 10. 1186/s13063-017-1843-5.

European Association of Urology

Words of Wisdom

Re: IL-15 Superagonist NAI in BCG-Unresponsive Non–muscle-invasive Bladder Cancer

Chamie K, Chang SS, Kramolowsky E, et al.

NEJM Evid 2022;2:EVIDoa2200167

Experts' summary:

This single-arm trial tested the IL-15 superagonist nogapendekin α-inbakicept (NAI, also known as N-803) plus bacillus Calmette-Guérin (BCG) in patients with BCG-unresponsive high-grade non–muscle-invasive bladder cancer (NMIBC). A complete response (CR) at any time was observed in 71% (95% confidence interval [CI] 59.6–80.3%) of patients with BCG-unresponsive carcinoma in situ (CIS) ± Ta/T1 and the median duration of response was 26.6mo. The disease-free survival (DFS) rate at 12 mo for patients with Ta/T1 tumors without CIS was 55.4% (95% CI 42.0–66.8%). CR was observed in only two of ten patients treated with NAI alone. The results show that the therapy was safe, with a low rate of adverse events [1].

Experts' comments:

This trial sets a new benchmark for 3–6-mo CR and 12-mo durability of response in patients with BCG-unresponsive CIS. Although there are limitations to comparisons across trials, these single-arm trials are designed for comparison to historic controls, so some cross-trial comparison is reasonable. The 71% CR rate for NAI compares favorably to the 3-mo CR rates of 40% for pembrolizumab and 53% for nadofaragene firadenovec (NF), both of which have now been approved by the US Food and Drug Administration (FDA) [2,3]. A key difference for NAI is that the trial allowed repeat induction. For pembrolizumab and NF, only 19% and 24% of patients, respectively, were disease-free at 12 mo, compared to 45% for NAI. This appears to be a major advance in disease control in this patient population, especially when the low rate of serious adverse events is considered.

Intravesical gemcitabine/docetaxel has evolved as a standard treatment in North America for patients with BCG-unresponsive CIS who are ineligible for or decline cystectomy. A multicenter retrospective series demonstrated 50% high-grade recurrence-free survival at 2 yr [4]. One could make the argument that NAI should now become the standard of care given its more rigorous clinical trial data, provided it is approved by the FDA. Nonetheless, gemcitabine/docetaxel remains attractive owing to its low cost and the excellent results reported to date.

The encouraging results from this trial also fuel the ongoing discussion about the adequacy of single-arm trials in BCG unresponsive NMIBC. This trial design and the associated path to regulatory approval have spurred a lot of activity in this disease setting. However, the stage appears to be set to build on the novel treatments that have emerged and to proceed with randomized multi arm comparison trials. Both NAI and gemcitabine/docetaxel offer an adequate durability of response to warrant randomization to either of these treatments as a standard of care. Testing of combination therapies would be a logical next step to augment the response rates. Comparison trials should also include patients with Ta/T1 tumors so that drug approval can also extend to these patients.

Conflicts of interest: Jonathan Suderman and Marie-Pier St-Laurent have nothing to disclose. Peter C. Black has served on advisory boards for AbbVie, AstraZeneca, Astellas, Bayer, BMS, EMD-Serono, Ferring, Fergene, Janssen, Merck, miR Scientific, Nonagen, NanOlogy, Prokarium, Protara Therapeutics, QED Bioscience, Roche, Sanofi, Sesen Bio, STIMIT, TerSera, Tolmar, Urogen, and Verity, has spoken on behalf of AbbVie, Biosyent, Janssen, Minogue, Ferring, TerSera, and Pfizer, and has participated in clinical trials with Genentech, Janssen, BMS, AstraZeneca, Therelase, Pacific Edge, and Pfizer.

References

[1] Chamie K et al. IL-15 superagonist NAI in BCG-unresponsive non–muscle-invasive bladder cancer. NEJM Evid 2022;2:EVIDoa2200167. https://doi.org/10.1056/EVIDoa2200167.
[2] Balar AV et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. Lancet Oncol 2021;22:919–30.
[3] Boorjian SA et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single arm, open-label, repeat-dose clinical trial. Lancet Oncol 2021;22:107–17.
[4] Steinberg RL et al. Multi-institution evaluation of sequential gemcitabine and docetaxel as rescue therapy for nonmuscle invasive bladder cancer. J Urol 2020;203:902–9.

Jonathan Suderman, Marie-Pier St-Laurent, Peter C. Black*
Department of Urologic Sciences, University of British Columbia, Vancouver, Canada
** Corresponding author. Department of Urologic Sciences, University of British Columbia, Vancouver, BC V6T 1Z4, Canada.*
E-mail address: j.suderman@alumni.ubc.ca (J. Suderman).

Peter C. Black

Jonathan Suderman

Marie-Pier St-Laurent

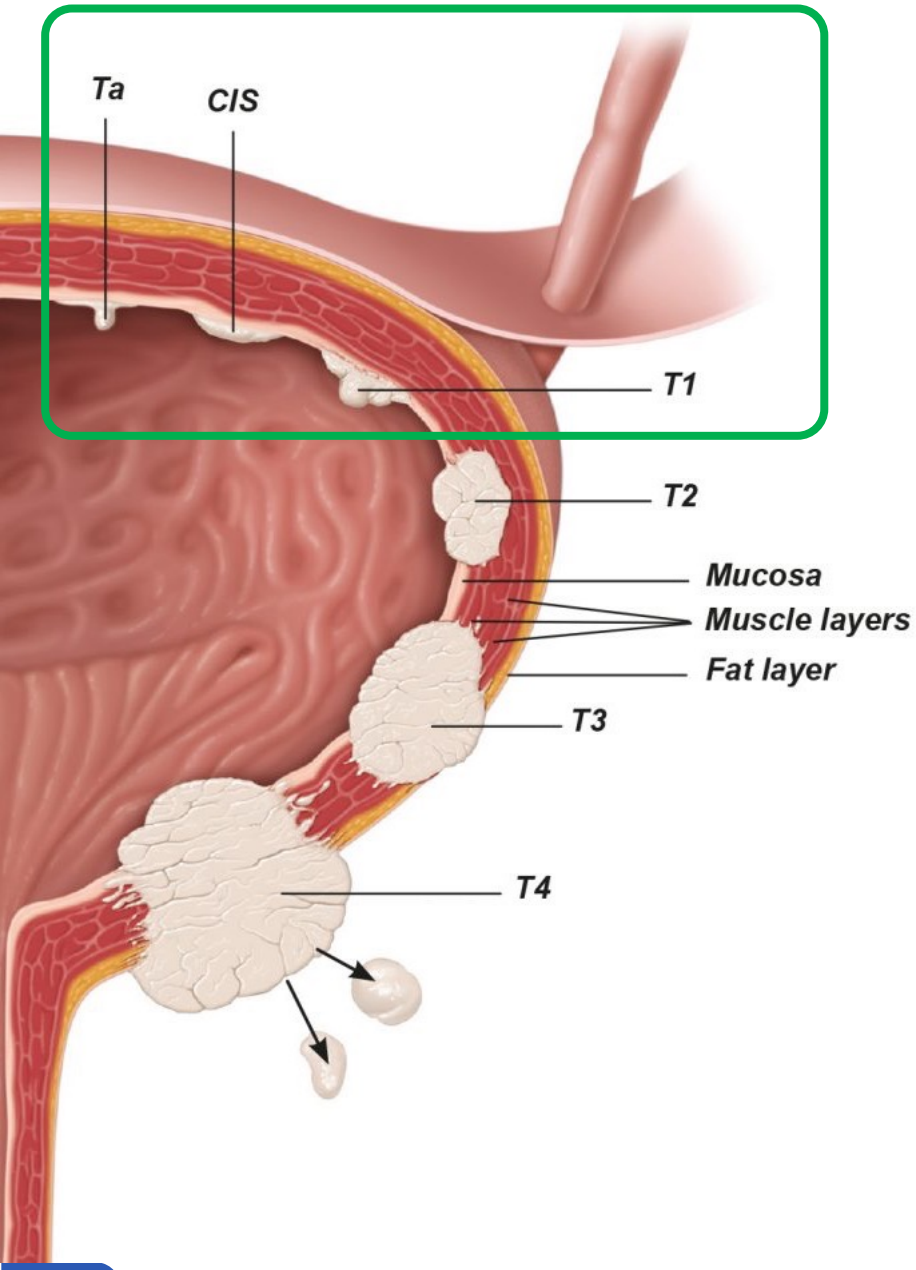
"This trial sets a new benchmark for 3–6-mo CR and 12-mo durability of response in patients with BCG-unresponsive CIS."

"...cross-trial comparison is reasonable. The 71% CR rate for NAI compares favorably to the 3-mo CR rates of 40% for pembrolizumab and 53% for nadofaragene..."

"This appears to be a major advance in disease control in this patient population, especially when the low rate of serious adverse events is considered."

"One could make the argument that NAI should now become the standard of care given its more rigorous clinical trial data, provided it is approved by the FDA."

ASCO 2022 Annual Meeting Oral Presentation



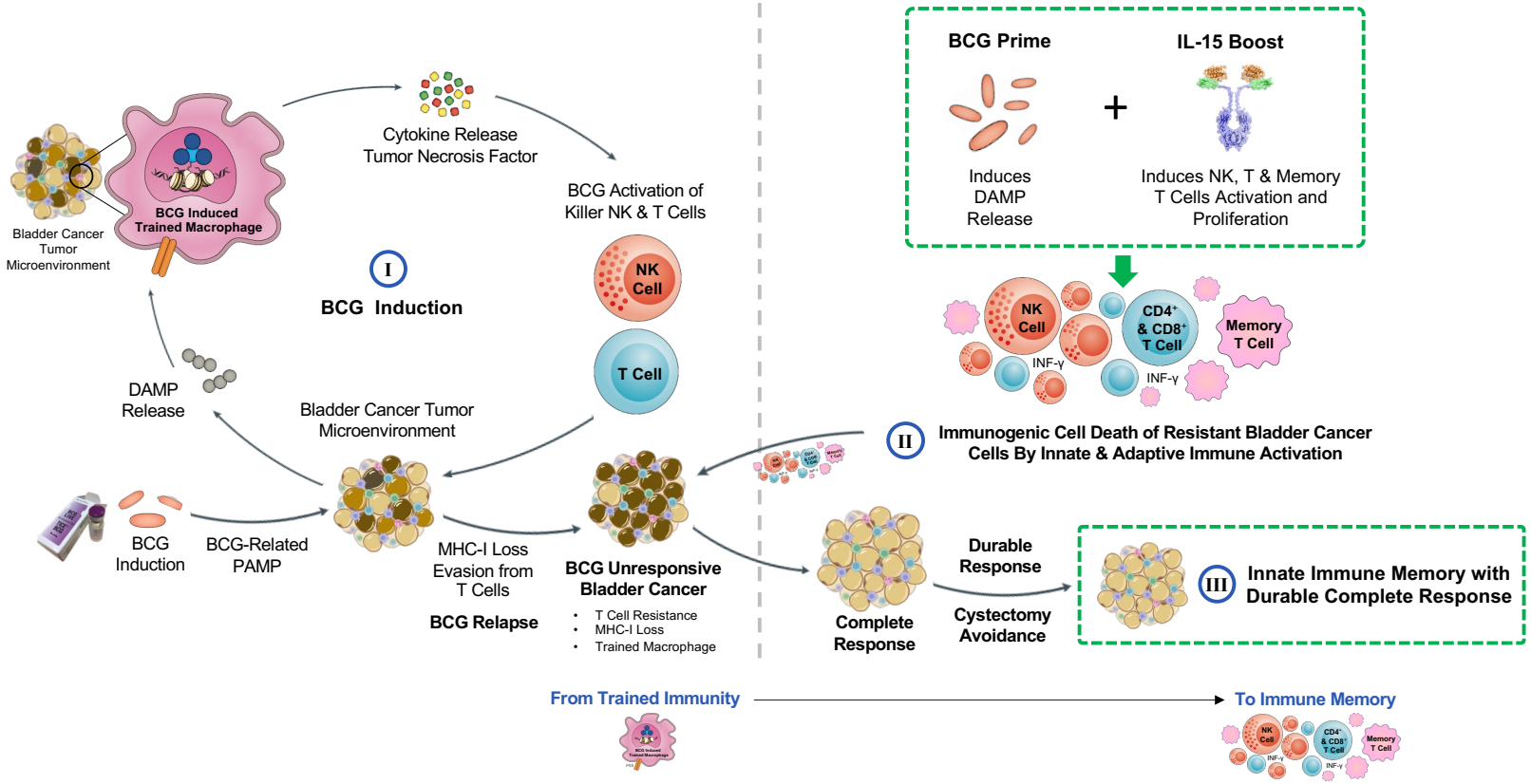
2022 ASCO ANNUAL MEETING

QUILT 3032: Final clinical results of pivotal trial of IL-15RαFc superagonist N-803 with BCG in BCG-unresponsive CIS and papillary nonmuscle-invasive bladder cancer (NMIBC)

QUILT 3032

Dr. Karim Chamie, UCLA

UROToday 2022

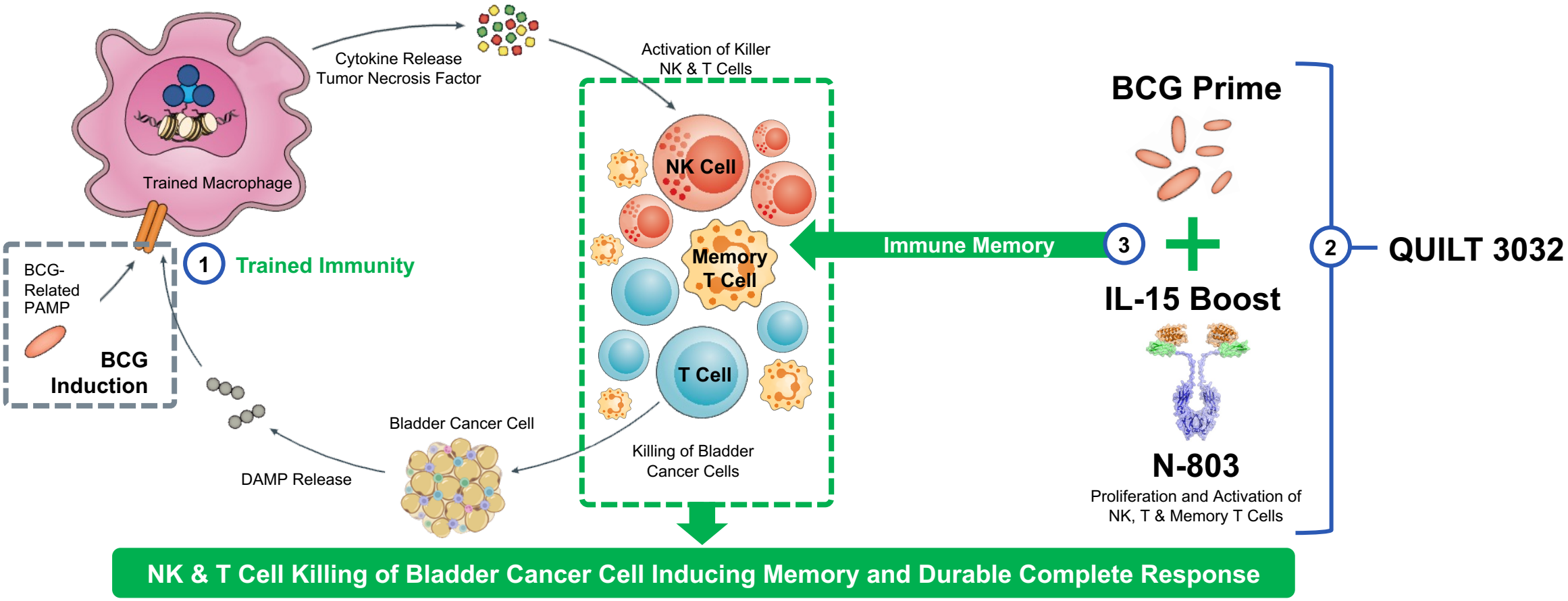


Published October 27, 2022

Underlying Mechanism of Action of N-803 + BCG Inducing Durable Complete Response in BCG Unresponsive NMIBC -Patrick Soon-Shiong

https://bit.ly/3sNIzXa

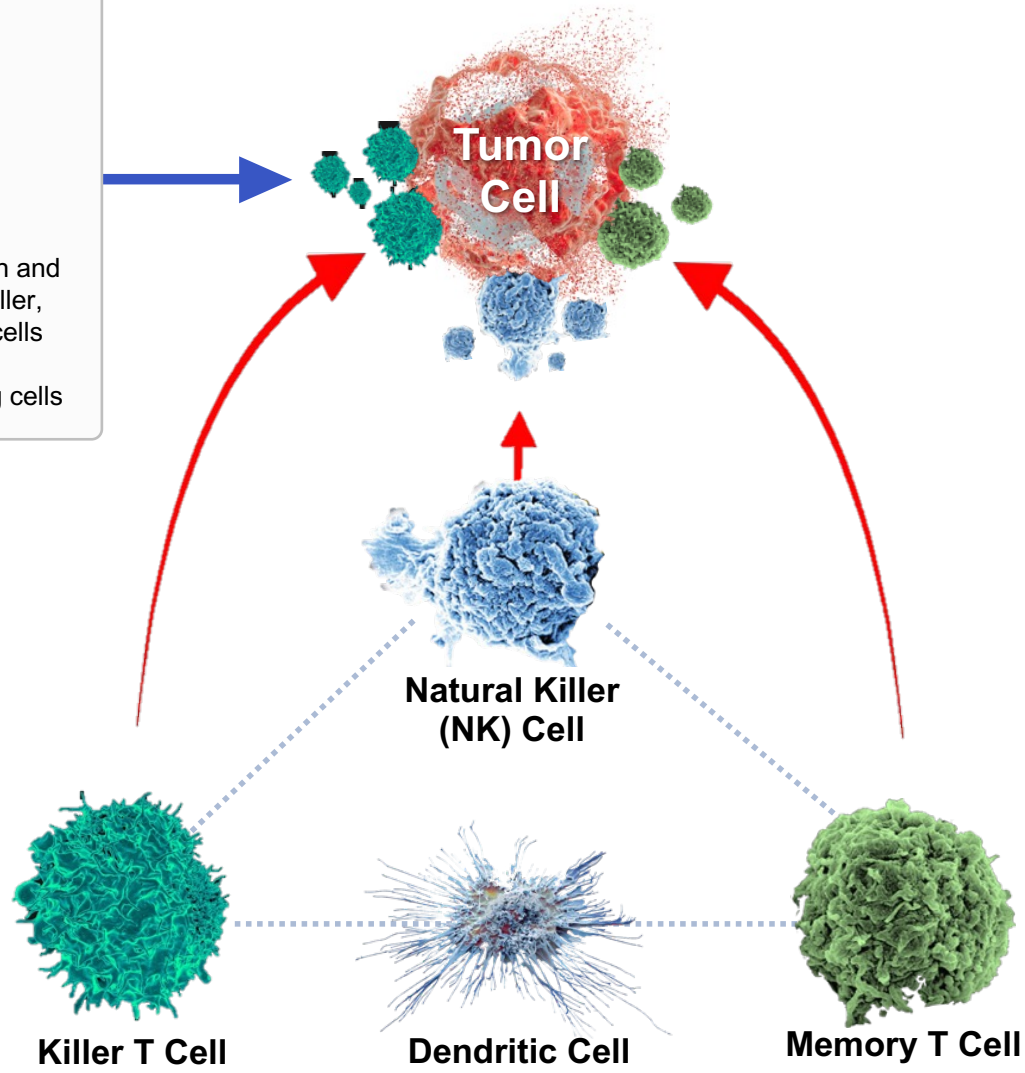
Underlying Mechanism of Action of N-803 + BCG Inducing Durable Complete Response in BCG Unresponsive CIS and Papillary Disease



Source: Urotoday.com "Underlying Mechanism of Action of N-803 + BCG Inducing Durable Complete Response in BCG Unresponsive NMIBC -Patrick Soon-Shiong. Retrieved April 2023

N-803

N-803 promotes activation and proliferation of natural killer, CD8+ T and memory T cells without expanding immunosuppressive T reg cells



1 BCG: Trained Immunity

- NK cells are essential for effective BCG immunotherapy (Brandau 2001)
- Trained immunity as a molecular mechanism for BCG immunotherapy in bladder cancer (van Puffelen 2020)
- BCG therapy downregulates HLA-I on malignant cells to subvert antitumor immune responses in bladder cancer (Rouanne 2022)

2 N-803: NK and T Cell Activation

- The IL-15-based superagonist N-803 promotes the antigen-independent conversion of memory CD8+ T cells into innate-like effector cells with antitumor activity (Wong 2013)
- IL-15 superagonist/IL-15RαSushi-Fc fusion complex markedly enhances specific subpopulations of NK and memory CD8+ T cells, and mediates potent anti-tumor activity (Kim 2016)
- Phase I trial characterizing the pharmacokinetic profile of N-803, a chimeric IL-15 superagonist, in healthy volunteers (Rubinstein 2022)

3 BCG Plus N-803: Immune Memory

- Intravesical N-803 and BCG treatment reduces tumor burden in a carcinogen induced bladder cancer rat model; a role for cytokine production and NK cell expansion (Gomes-Giacoia 2014)
- Innate immune memory is associated with increased disease-free survival in bladder cancer patients treated with BCG (Graham 2021)
- Intravesical BCG in patients with non-muscle invasive bladder cancer induces trained immunity and decreases respiratory infections (van Puffelen 2022)
- Tumor Escape Phenotype in Bladder Cancer is Associated with Loss of HLA Class I Expression, T-Cell Exclusion and Stromal Changes (Gil-Julio, 2021)

N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency.
PDUFA Date May 23, 2023

N-803 + BCG in BCG Unresponsive CIS with or without Papillary

NEJM Evidence

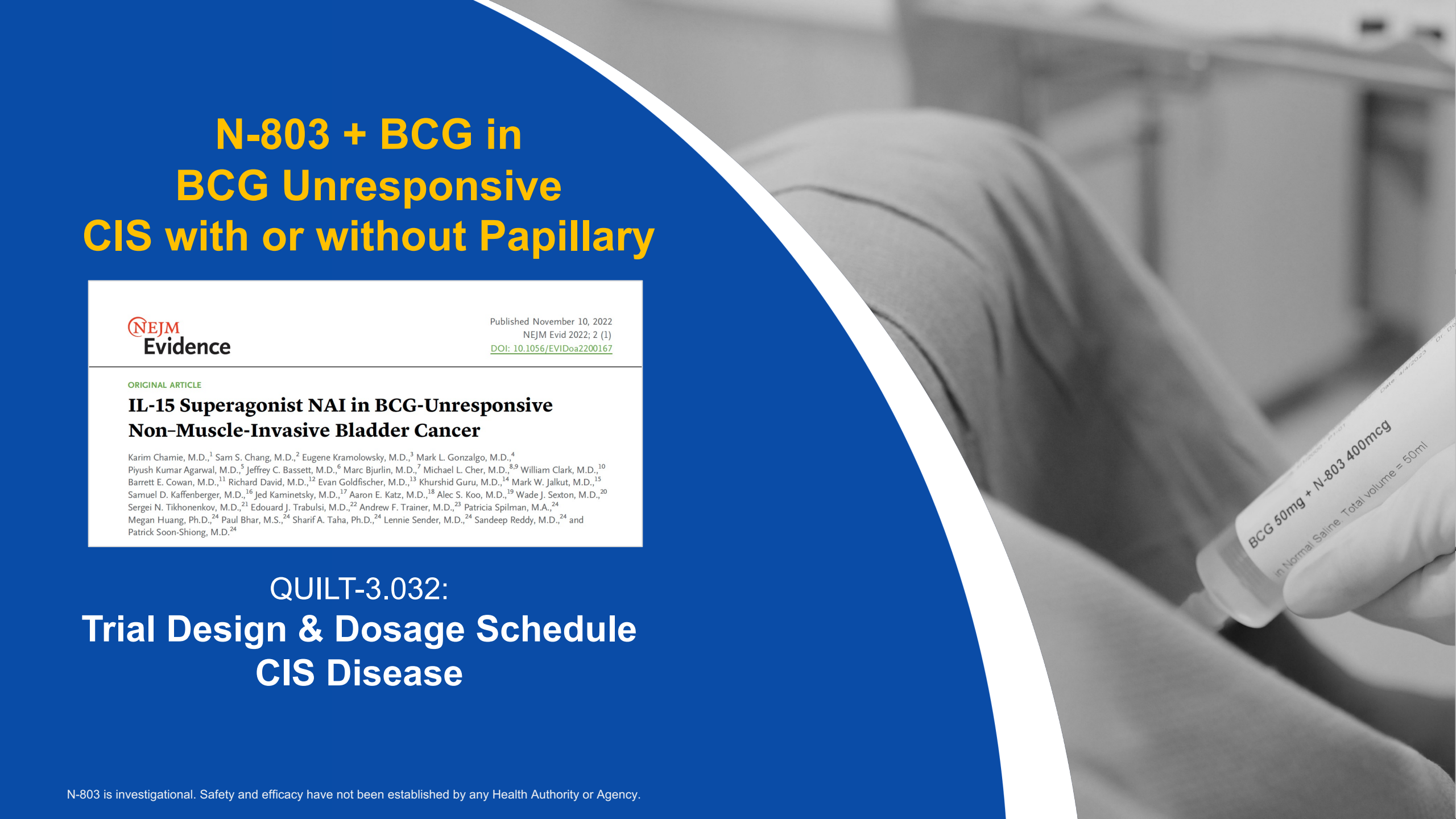
Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

QUILT-3.032:
Trial Design & Dosage Schedule
CIS Disease



N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency.

QUILT 3.032: IL-15 Superagonist N-803 with BCG in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer CIS with and without Papillary

CIS with and without Papillary

Patients
Adult BCG-Unresponsive Bladder Cancer CIS with and without Papillary

Cohort A, N=100

NMIBC BCG Unresponsive CIS

- Histologically confirmed
- Persistent or recurrent CIS (+/- recurrent Ta/T1 disease) within 12 months of receiving adequate BCG

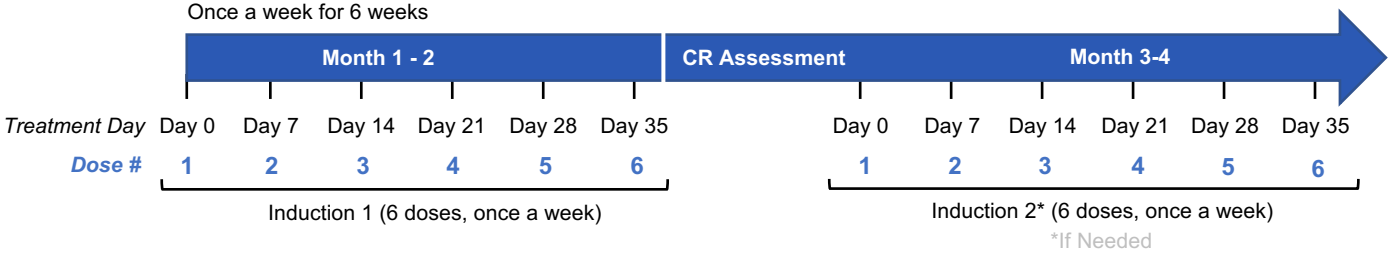
Intravesical N-803 + BCG

6 weekly induction treatments followed by maintenance for up to 36 months; one time re-induction for eligible patients included

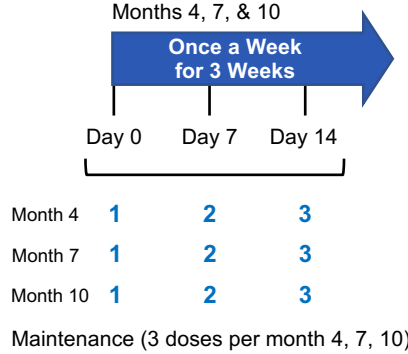
Primary Endpoint
- Biopsy confirmed complete response (CR) at any time

Secondary Endpoints:
- Duration of CR
- Cystectomy Avoidance
- Time to Cystectomy
- Safety

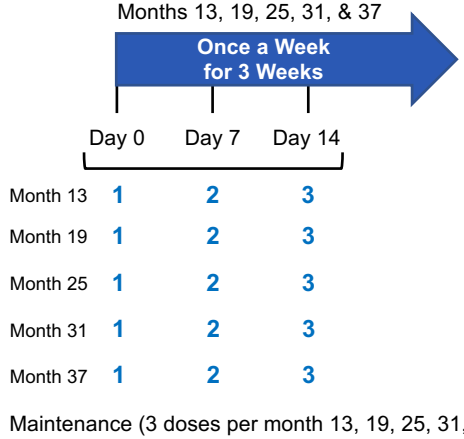
Induction Period
Once a week for 6 weeks



Maintenance
Months 4, 7, & 10



Ongoing Maintenance
Months 13, 19, 25, 31, & 37



Source: NCT03022825 https://clinicaltrials.gov/ct2/show/NCT03022825

N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency.

N-803 + BCG in BCG Unresponsive CIS with or without Papillary

NEJM Evidence

Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

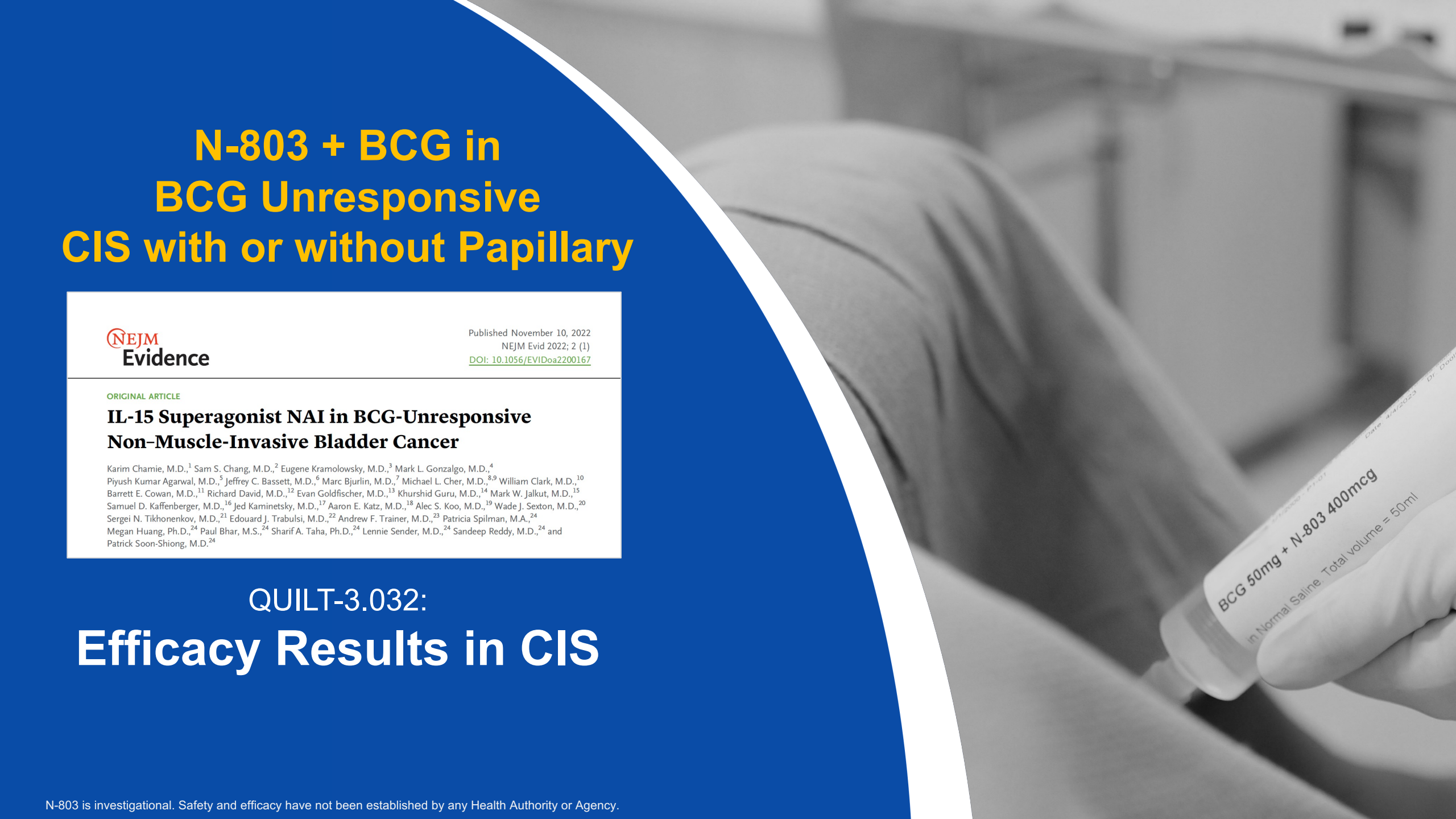
ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

QUILT-3.032:

Efficacy Results in CIS



N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency.

Summary of Efficacy in CIS with or without Papillary

71%
CR Rate
At Any Time

62%
12 Months
Complete Response

53%
24 Months
Complete Response

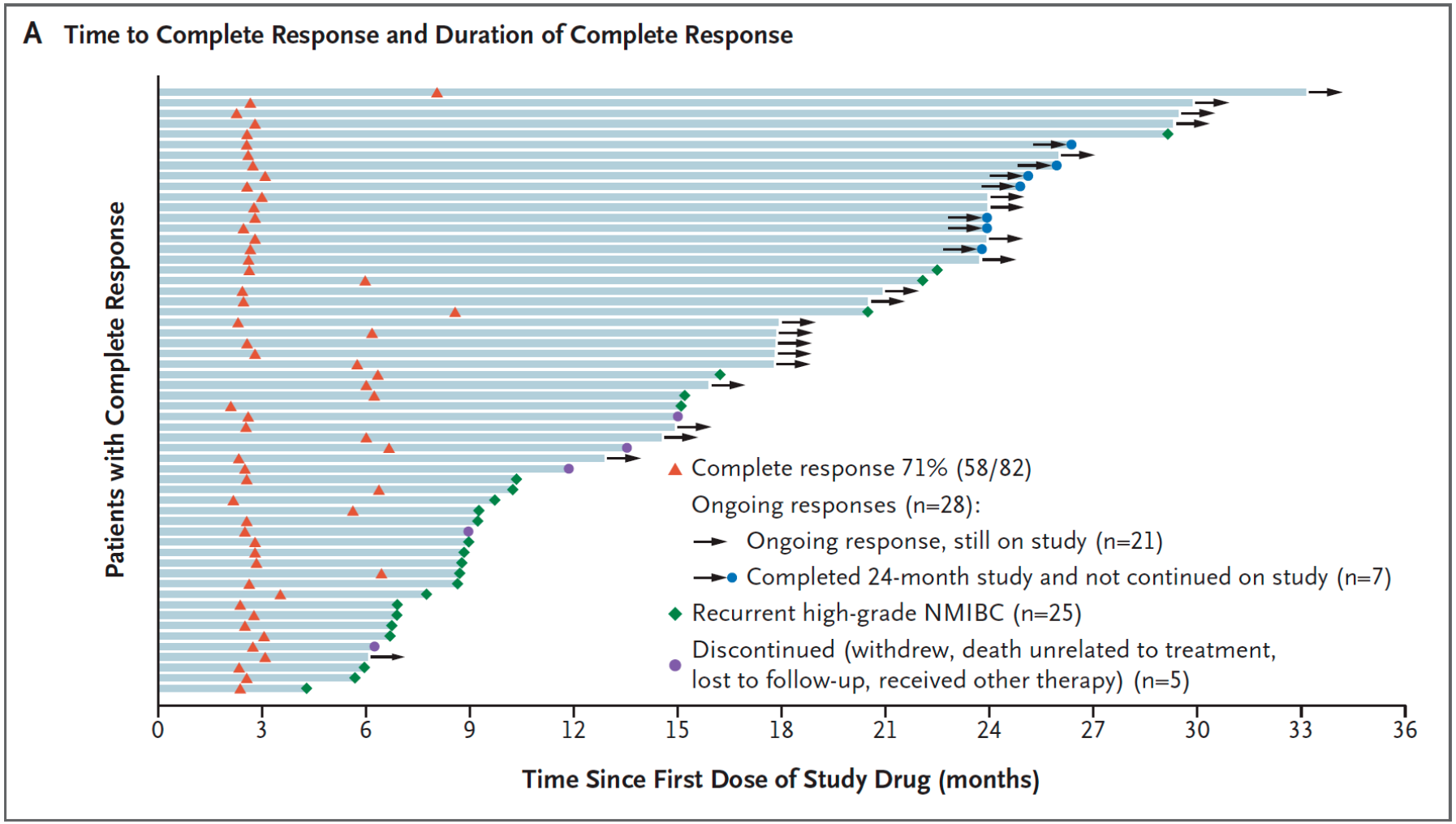
26.6
Months Median
Duration of CR

89%
Cystectomy Free
At 24 Months

90%
Avoidance of
Cystectomy
In Responders

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer. Chamie et al.
DOI: https://doi.org/10.1056/EVIDoa2200167

Figure 1. Duration of Complete Response, Disease Progression, and Survival in Cohort A Patients with Carcinoma In Situ.

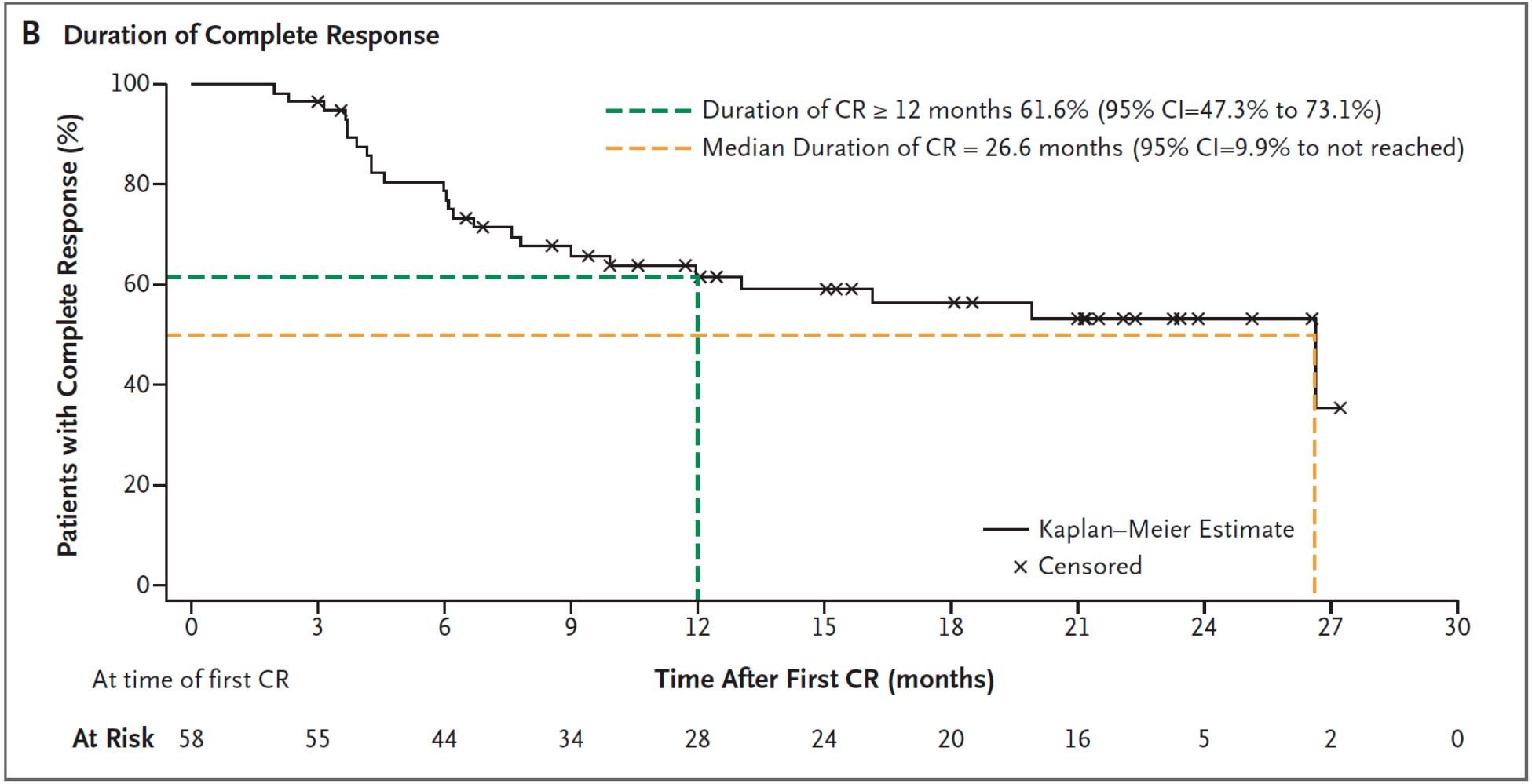


(Panel A) Time to complete response (CR) and duration of CR for individual patients are shown.

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer. Chamie et al.

DOI: https://doi.org/10.1056/EVIDoa2200167

Figure 1. Duration of Complete Response, Disease Progression, and Survival in Cohort A Patients with Carcinoma In Situ.



(Panel B) Duration of response showing probability of duration ≥12 months and median duration of CR (26.6 months) are shown.

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer. Chamie et al.
DOI: https://doi.org/10.1056/EVIDoa2200167

N-803 + BCG in BCG Unresponsive CIS with or without Papillary

NEJM Evidence

Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

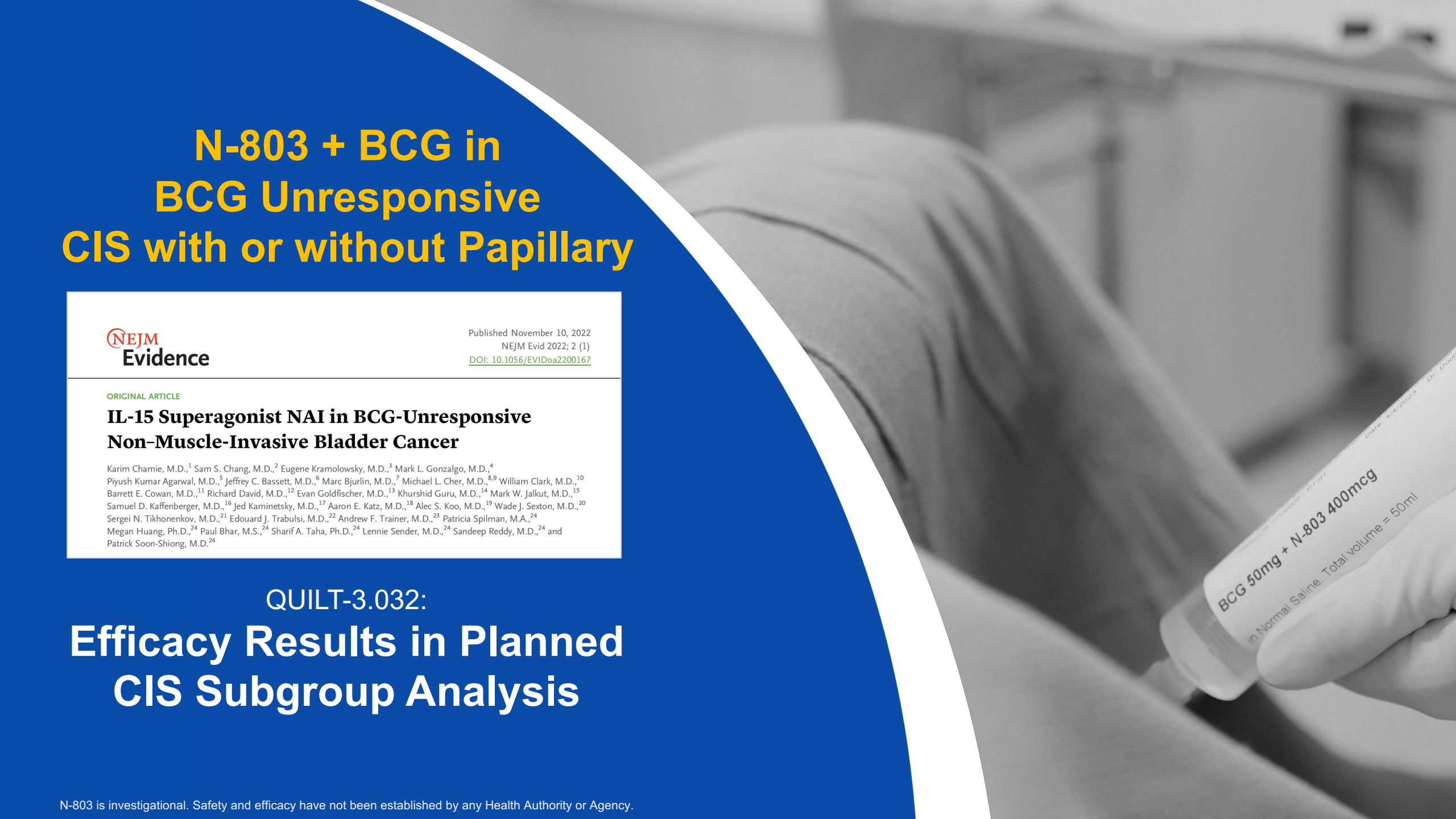
ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

QUILT-3.032:

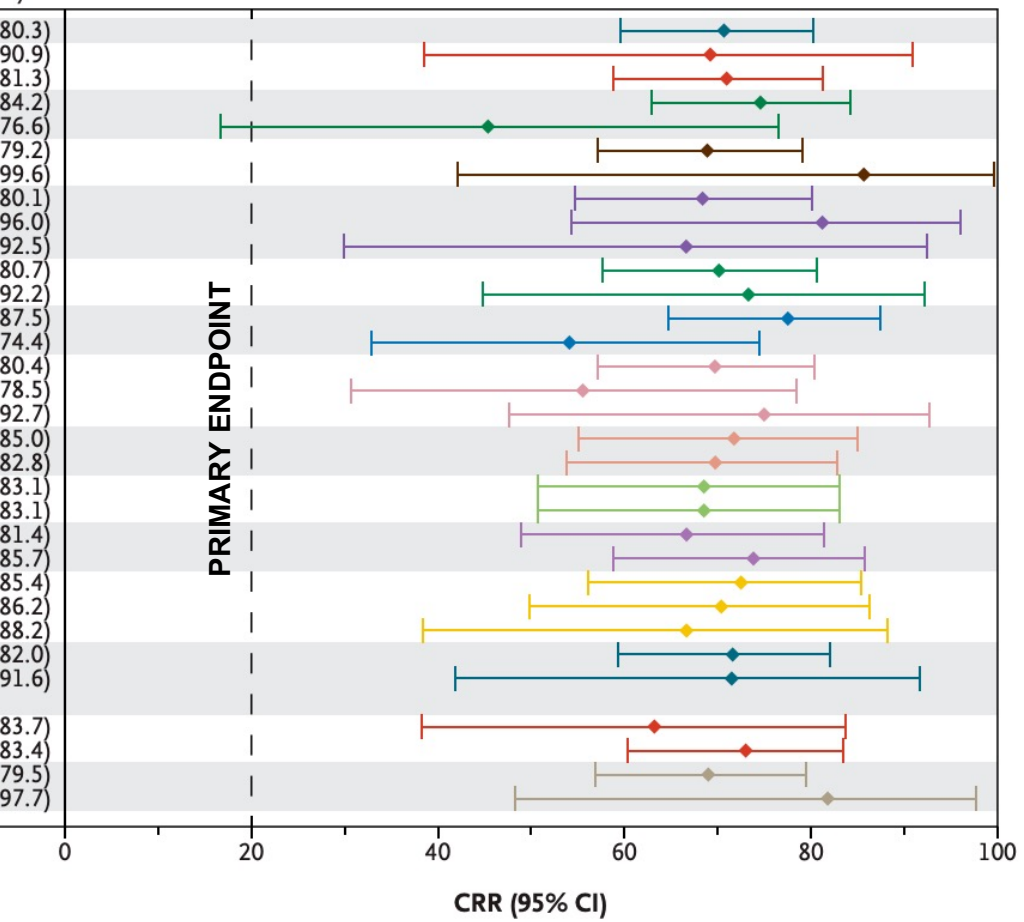
Efficacy Results in Planned CIS Subgroup Analysis



N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency.

Complete Response Rate (CRR) Consistent Across Subgroups in CIS with or without Papillary Disease

	# response/N	CRR (95% CI)
Overall	58/82	71% (59.6, 80.3)
Age < 65 yr	9/13	69% (38.6, 90.9)
Age ≥ 65 yr	49/69	71% (58.8, 81.3)
Gender: Male	53/71	75% (62.9, 84.2)
Gender: Female	5/11	45% (16.7, 76.6)
Race: White	51/74	69% (57.1, 79.2)
Race: Non-White	6/7	86% (42.1, 99.6)
Baseline Disease Type: CIS	39/57	68% (54.8, 80.1)
Baseline Disease Type: CIS/Ta	13/16	81% (54.4, 96.0)
Baseline Disease Type: CIS/T1	6/9	67% (29.9, 92.5)
Baseline Disease ECOG Status: 0	47/67	70% (57.7, 80.7)
Baseline ECOG Status: 1–2	11/15	73% (44.9, 92.2)
Reinduction: No	45/58	78% (64.7, 87.5)
Reinduction: Yes	13/24	54% (32.8, 74.4)
Number Prior BCG: ≥12	46/66	70% (57.1, 80.4)
BCG-Unresp., Given BCG	10/18	56% (30.8, 78.5)
Number Prior BCG: <12	12/16	75% (47.6, 92.7)
Prior BCG Only	28/39	72% (55.1, 85.0)
Prior BCG + Other Therapy	30/43	70% (53.9, 82.8)
Number Prior TURBT: ≤3	24/35	69% (50.7, 83.1)
Number Prior TURBT: >3	24/35	69% (50.7, 83.1)
BCG Refractory	24/36	67% (49.0, 81.4)
BCG Relapse	34/46	74% (58.9, 85.7)
Last Prior BCG to Study Entry: 0–6 mo	29/40	73% (56.1, 85.4)
Last prior BCG to Study Entry: >6–12 mo	19/27	70% (49.8, 86.2)
Last Prior BCG to Study Entry: >12 mo	10/15	67% (38.4, 88.2)
Last Prior BCG to 1st Recurrence: 0–6 mo	48/67	72% (59.3, 82.0)
Last Prior BCG to 1st Recurrence: >6–12 mo	10/14	71% (41.9, 91.6)
Last Prior BCG to 1st Recurrence: >12 mo	0/0	
Other Prior Therapy: Yes	12/19	63% (38.4, 83.7)
Other Prior Therapy: No	46/63	73% (60.3, 83.4)
Full Doses Prior BCG	49/71	69% (56.9, 79.5)
< Full Doses Prior BCG	9/11	82% (48.2, 97.7)

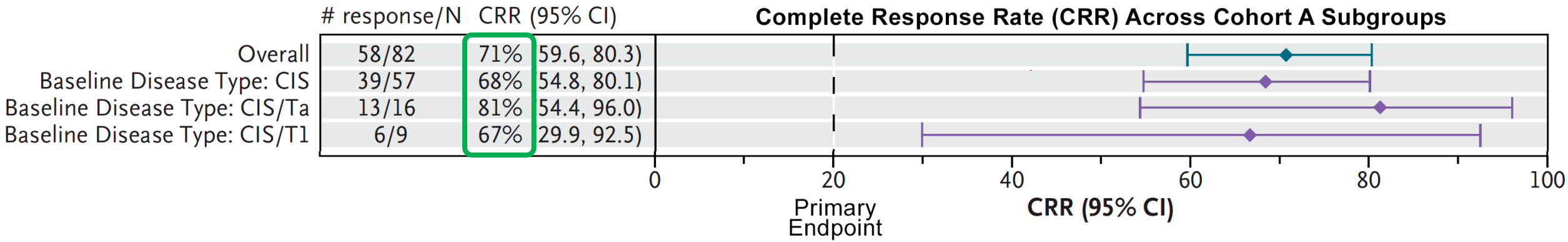


Response rates for subgroups are shown. The vertical dashed line represents the threshold required for the lower limit of the 95% confidence interval (CI) to meet the primary end point. 'BCG-unresp. Given BCG' represents patients previously defined as bacillus Calmette–Guerin (BCG) unresponsive who were given additional BCG. CIS denotes carcinoma in situ; ECOG, Eastern Cooperative Oncology Group; and TURBT, transurethral resection of the bladder tumor.

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer. Chamie et al.

DOI: https://doi.org/10.1056/EVIDoa2200167

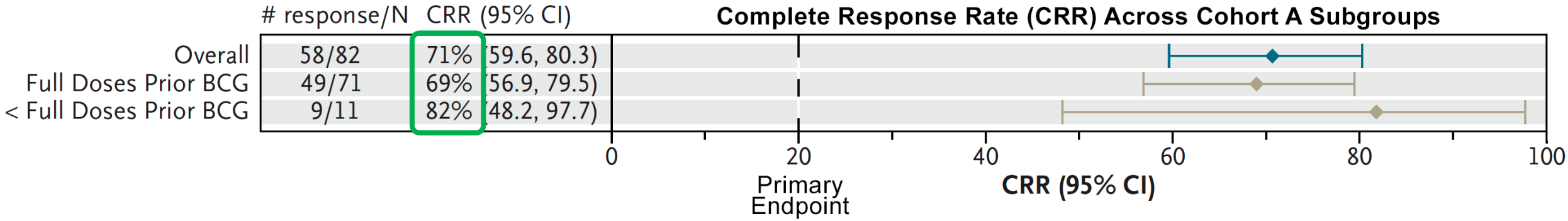
Complete Response Rate in CIS Alone and CIS + Papillary



All Subgroups (CIS Alone & CIS/Ta and CIS/T1) Met the Primary Endpoint With a CR Rate from 67% to 81%

Chamie, K. et. al. *IL-15 superagonist NAI in BCG-unresponsive non–muscle-invasive bladder…* https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200167

Complete Response Rate in Subjects with Full Dose versus Partial-Dose Prior BCG



Complete Response Rate (CRR) for Subjects with Partial Dose BCG and Full Dose BCG Were No Different from Overall CRR Ranging from 69% to 82% CRR

Chamie, K. et. al. *IL-15 superagonist NAI in BCG-unresponsive non–muscle-invasive bladder…* https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200167

N-803 + BCG in BCG Unresponsive Papillary Disease

NEJM Evidence

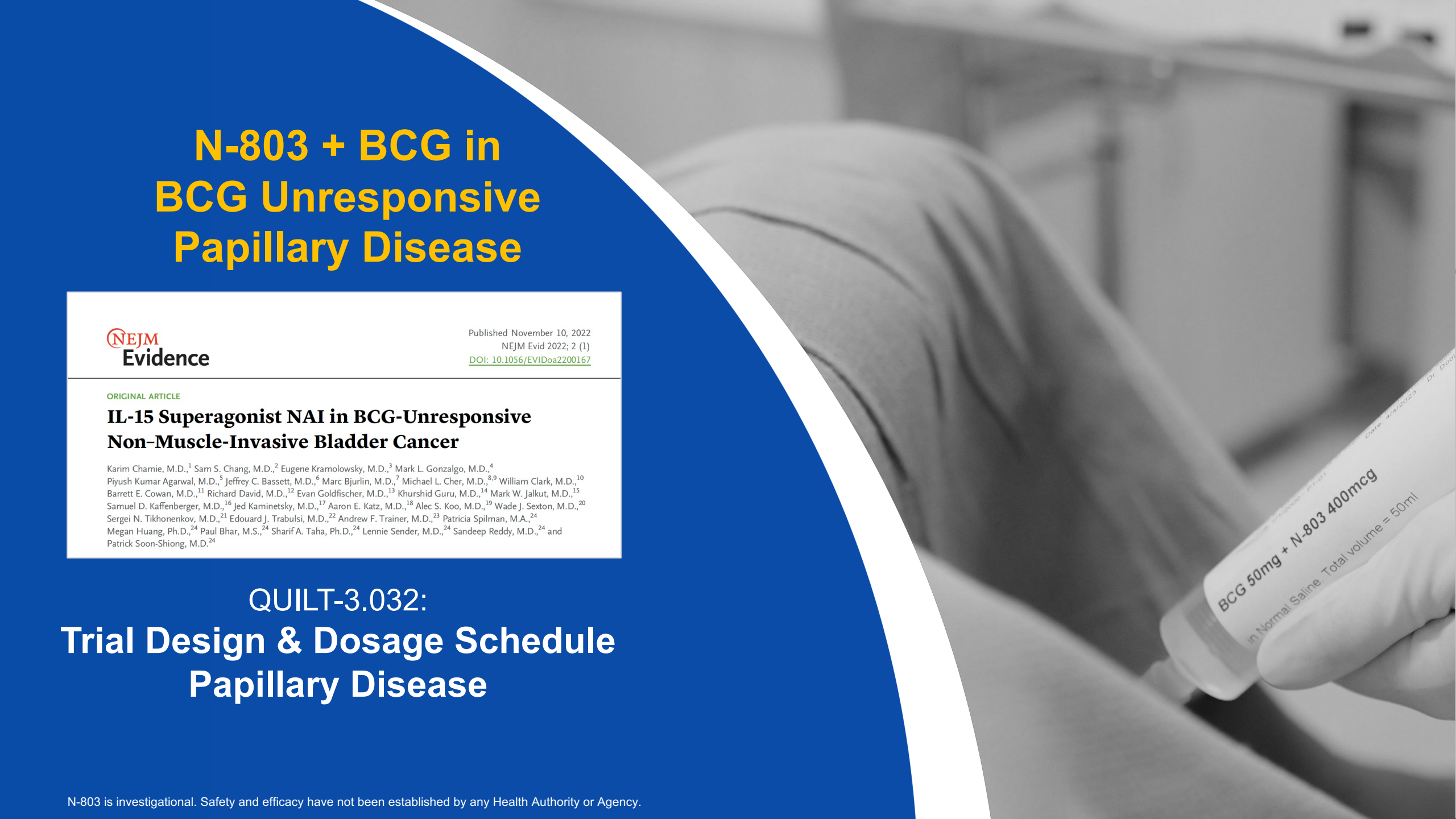
Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

QUILT-3.032:
Trial Design & Dosage Schedule Papillary Disease



N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency.

QUILT 3.032: IL-15 Superagonist N-803 with BCG in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer Papillary Disease

Papillary Disease Only

Patients
Adult BCG-Unresponsive Bladder Cancer Papillary Disease

Cohort B, N= 80

NMIBC BCG Unresponsive Papillary

- Histologically confirmed
- Persistent or recurrent Ta/T1 papillary disease within 6 months of completion of adequate BCG

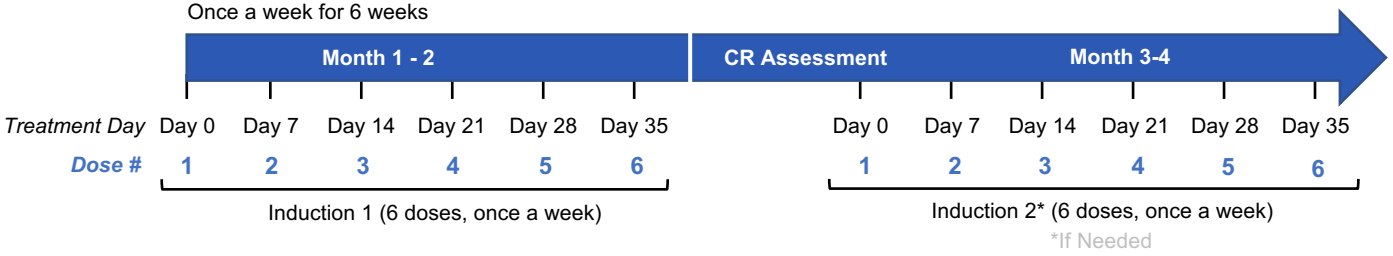
Intravesical N-803 + BCG

6 weekly induction treatments followed by maintenance for up to 36 months; one time re-induction for eligible patients included

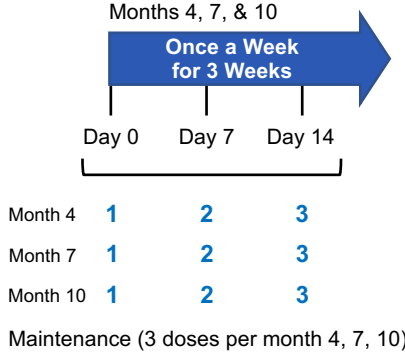
Primary Endpoint:
- Disease free rate at 12 months

Secondary Endpoints
- Disease free survival
- Cystectomy Avoidance
- Time to Cystectomy
- Safety

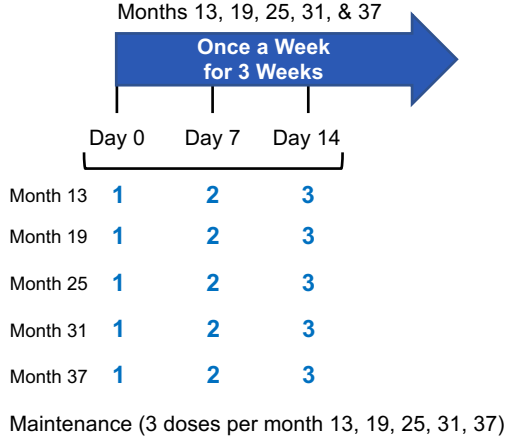
Induction Period
Once a week for 6 weeks



Maintenance
Months 4, 7, & 10



Ongoing Maintenance
Months 13, 19, 25, 31, & 37



Source: NCT03022825 https://clinicaltrials.gov/ct2/show/NCT03022825

N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency.

N-803 + BCG in BCG Unresponsive Papillary Disease

NEJM Evidence

Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

QUILT-3.032:

Efficacy Results in Papillary Disease

N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency.

Duration of Recurrence Free Disease in Papillary: >19 Months with Higher Point of CI Not Yet Reached

Table 2. Summary of Efficacy in Cohort B.*

Response	Value
Median duration of follow-up — mo	20.7
Range of follow-up of all patients — mo	2.9–37.1
Disease-free survival (n=72)	
Median disease-free survival — mo (95% CI)†	19.3 (7.4 to upper bound not reached)
Disease-free survival rate — % (95% CI)†	
12 mo	55.4 (42.0–66.8)
18 mo	51.1 (37.6–63.1)
24 mo	48.3 (34.5–60.7)
Progression-free survival rate — % (95% CI)†	
12 mo	97.1 (88.8–99.3)
18 mo	94.8 (84.3–98.3)
24 mo	88.8 (74.1–95.4)
Disease-specific survival — % (95% CI)†	
12 mo	100 (100–100)
24 mo	97.7 (84.6–99.7)
Overall survival — % (95% CI)†	
12 mo	98.6 (90.2–99.8)
18 mo	94.3 (82.9–98.1)
24 mo	91.7 (79.0–96.9)
Cystectomy rate — no. (%)	5 (7)

* Disease-free survival, progression-free survival, disease-specific survival, overall survival, and cystectomy rate in cohort B (n=72) are shown. CI denotes confidence interval.

† Kaplan–Meier analysis methods were used.

Chamie, K. et. al. *IL-15 superagonist NAI in BCG-unresponsive non–muscle-invasive bladder…* https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200167

N

Median Duration of Response >19 Months with Upper Bound Not Reached in Papillary Disease

Table 2. Summary of Efficacy in Cohort B.*

Response	Value
Disease-free survival (n=72)	
Median disease-free survival — mo (95% CI)†	19.3 (7.4 to upper bound not reached)
Disease-free survival rate — % (95% CI)†	
12 mo	55.4 (42.0–66.8)
18 mo	51.1 (37.6–63.1)
24 mo	48.3 (34.5–60.7)

* Disease-free survival, progression-free survival, disease-specific survival, overall survival, and cystectomy rate in cohort B (n=72) are shown. CI denotes confidence interval.

† Kaplan–Meier analysis methods were used.

Chamie, K. et. al. *IL-15 superagonist NAI in BCG-unresponsive non–muscle-invasive bladder…* https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200167

N-803 + BCG in BCG Unresponsive Papillary Disease

Table 2. Summary of Efficacy in Cohort B.*

Response	Value
Progression-free survival rate — % (95% CI)†	
12 mo	97.1 (88.8–99.3)
18 mo	94.8 (84.3–98.3)
24 mo	88.8 (74.1–95.4)
Disease-specific survival — % (95% CI)†	
12 mo	100 (100–100)
24 mo	97.7 (84.6–99.7)
Overall survival — % (95% CI)†	
12 mo	98.6 (90.2–99.8)
18 mo	94.3 (82.9–98.1)
24 mo	91.7 (79.0–96.9)
Cystectomy rate — no. (%)	5 (7)

* Disease-free survival, progression-free survival, disease-specific survival, overall survival, and cystectomy rate in cohort B (n=72) are shown. CI denotes confidence interval.

† Kaplan–Meier analysis methods were used.

Chamie, K. et. al. *IL-15 superagonist NAI in BCG-unresponsive non–muscle-invasive bladder…* https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200167

N-803 + BCG Safety in CIS and Papillary

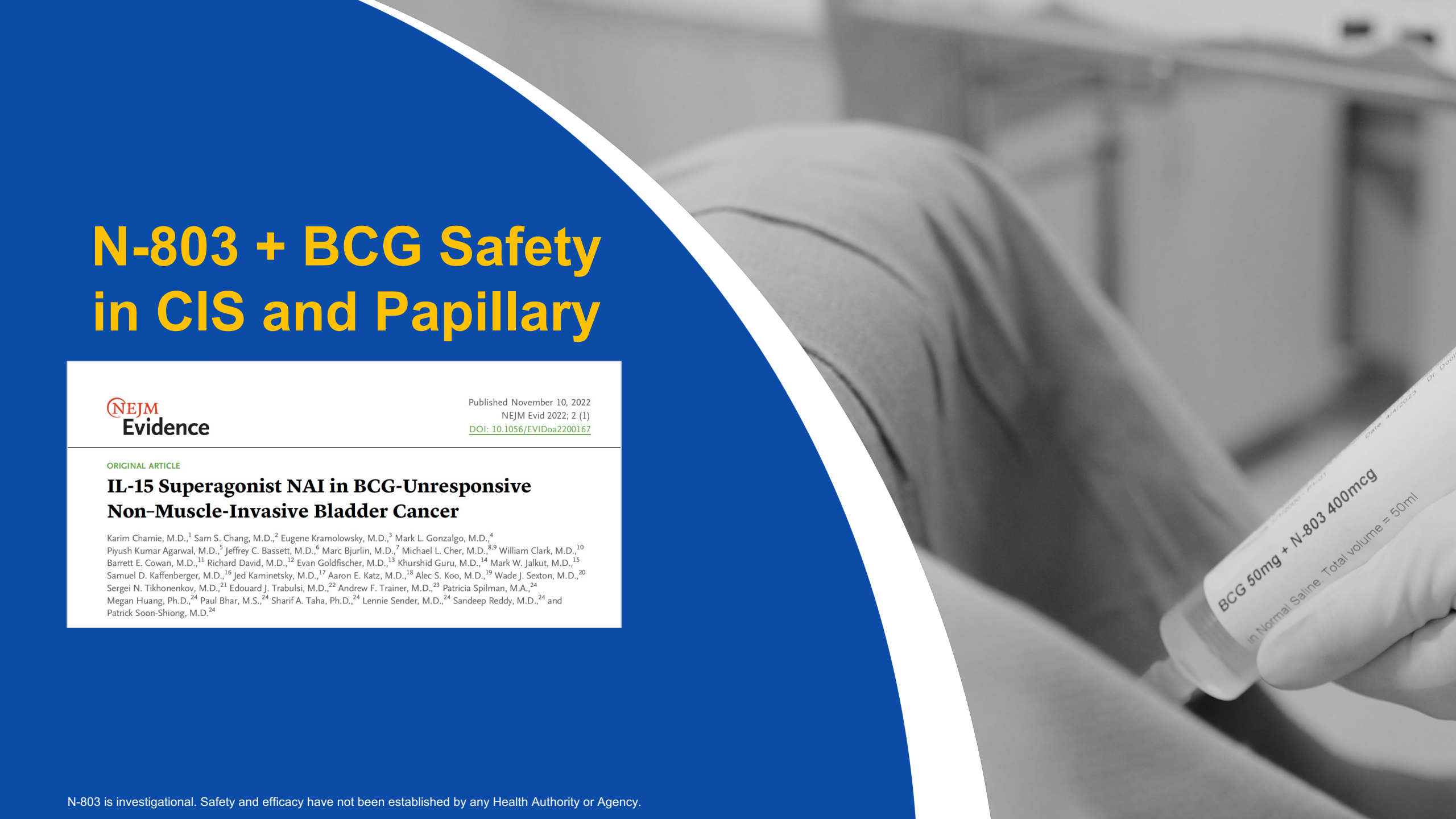
NEJM Evidence

Published November 10, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200167

ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]



N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency.

Summary of Safety

n = 161

Safety and tolerability profile comparable to BCG alone

N-803 (Anktiva) + BCG

1%
Treatment Related SAEs

0%
Immune Related SAEs

0%
Treatment Related Grade 4 and 5 AEs

2%
Treatment Related Discontinuation

The AE profile is consistent with PK results showing no systemic absorption

Adverse reactions considered related to treatment leading to interruption of N-803 in combination with BCG occurred in 13% of Patients

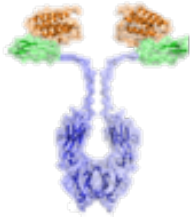
Most common treatment related AEs were those expected for intravesical instillation and included dysuria, pollakiuria and hematuria

N-803 Activity is **Local to the Bladder** with **Zero Systemic** IL-15 Levels per PK

- UroToday Oct 27, 2022 - Underlying Mechanism of Action of N-803 + BCG Inducing Durable Complete Response in BCG Unresponsive NMIBC
- IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer. Chamie et al. DOI: https://doi.org/10.1056/EVIDoa2200167

Immunotherapy Platform Scale

IL-15 Superagonist Anktiva (N-803)

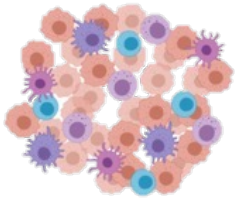


- NK & T Cell Activators

NK Cell Therapy

- NK-92
- Memory-Like Cytokine NK

DAMP Inducers



- Aldoxorubicin
- Nanatinostat

DNA Vaccine

- hAd5 Adenovirus

RNA Vaccine

- Self-Amplifying RNA (saRNA)

Toll Receptor Activators

- TLR 4, 7, 8, 9
- 3M-052

Notes:

ImmunityBio™

info@immunitybio.com