Phase II/III clinical results of IL-15RαFc superagonist N-803 with BCG in BCG-unresponsive non-muscle invasive bladder cancer (NMIBC)

QUILT-3.032 NCT03022825

VANDERBILT-INGRAM CANCER CENTER

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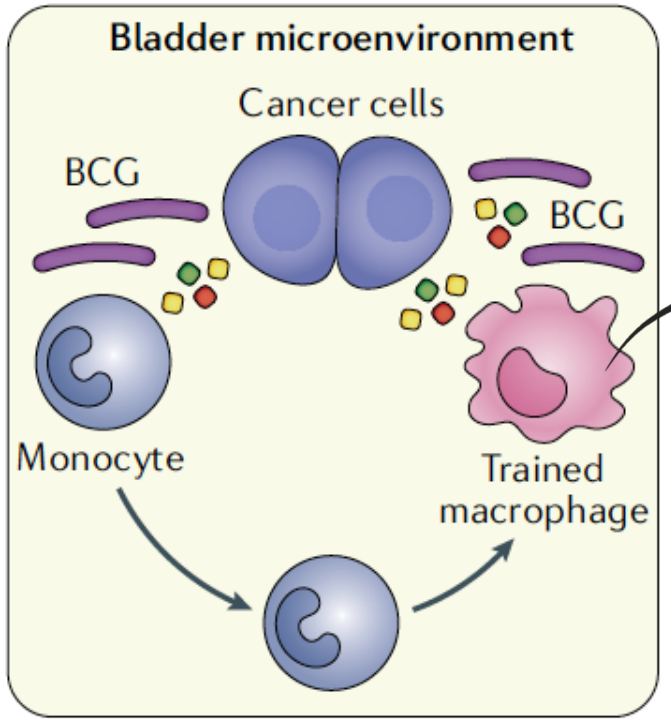
BCG Induces (Primes) Trained Immunity

BCG: THE PRIME



Trained Immunity

Int. J. Cancer: **92,** 697–702 (2001)
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Publication of the International Union Against Cancer

NK CELLS ARE ESSENTIAL FOR EFFECTIVE BCG IMMUNOTHERAPY

Sven Brandau[1], Josef Riemensberger[1], Marc Jacobsen[1], Don Kemp[3], Weicheng Zhao[4], Xiuqin Zhao[4], Dieter Jocham[2], Timothy L. Ratliff[4] and Andreas Böhle[2]*
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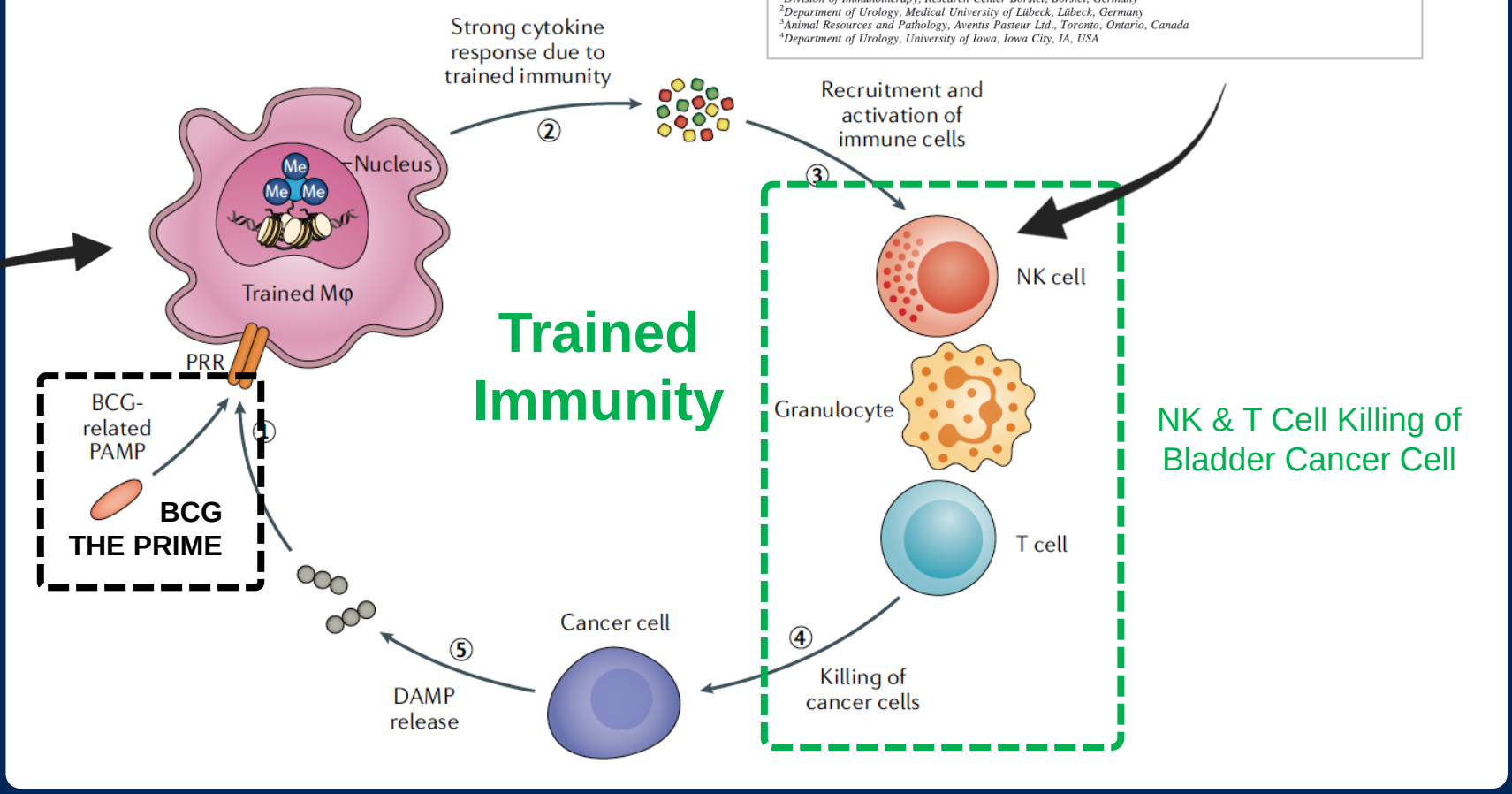

NK & T Cell Killing of Bladder Cancer Cell

Adapted from Jelmer H. van Puffelen et al.

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Innate Immune Memory Results in Prolonged Durable Complete Remission

nature reviews urology

nature > nature reviews urology > perspectives > article

Perspective | Published: 16 July 2020

Trained immunity as a molecular mechanism for BCG immunotherapy in bladder cancer

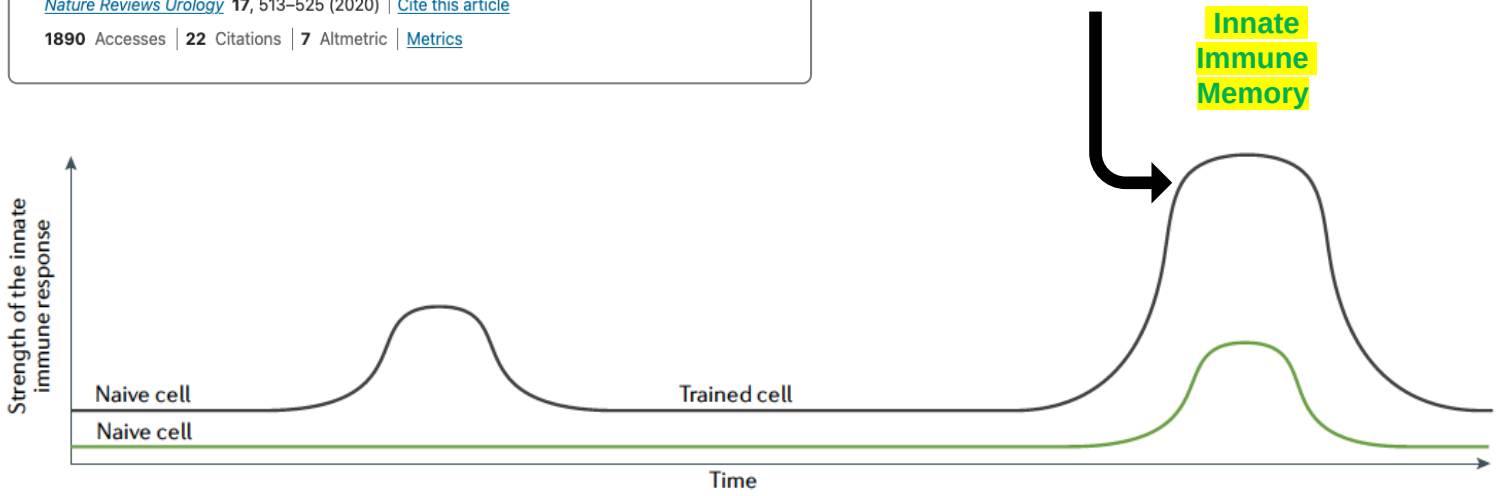
Jelmer H. van Puffelen, Samuel T. Keating, Egbert Oosterwijk, Antoine G. van der Heijden, Mihai G. Netea, Leo A. B. Joosten & Sita H. Vermeulen

Nature Reviews Urology **17**, 513–525 (2020) | Cite this article

1890 Accesses | **22** Citations | **7** Altmetric | Metrics

CAN WE POTENTIATE THIS INNATE IMUNE RESPONSE?

BCG + N-803 SEEMS TO DO THIS



ORIGINAL RESEARCH

Innate immune memory is associated with increased disease-free survival in bladder cancer patients treated with bacillus Calmette-Guérin

Charles H. Graham, PhD[1,2]; Jean-François Paré, PhD[1]; Tiziana Cotechini, PhD[1]; Wilma Hopman, MSc[3]; Charles C.T. Hindmarch, PhD[4]; Abdi Ghaffari, PhD[1]; Diana Marginean, MSc[1]; Stephen Chenard, MSc[1]; Madhuri Koti, PhD[1,2]; D. Robert Siemens, MD[1,2]

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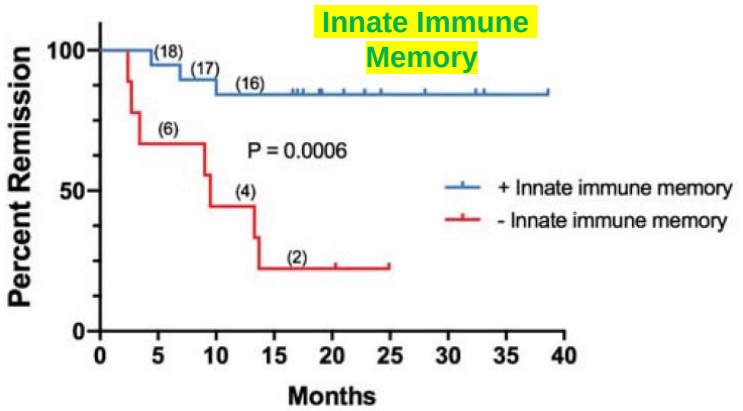
Cite as: Graham CH, Paré J-F, Cotechini T, et al. Innate immune memory is associated with increased disease-free survival in bladder cancer patients treated with bacillus Calmette-Guérin. *Can Urol Assoc J* 2021;15(8):E412-7. http://dx.doi.org/10.5489/cuaj.7066

responses. Further validation will increase our understanding of the mode of action of BCG and, therefore, will be used to enhance its effectiveness.



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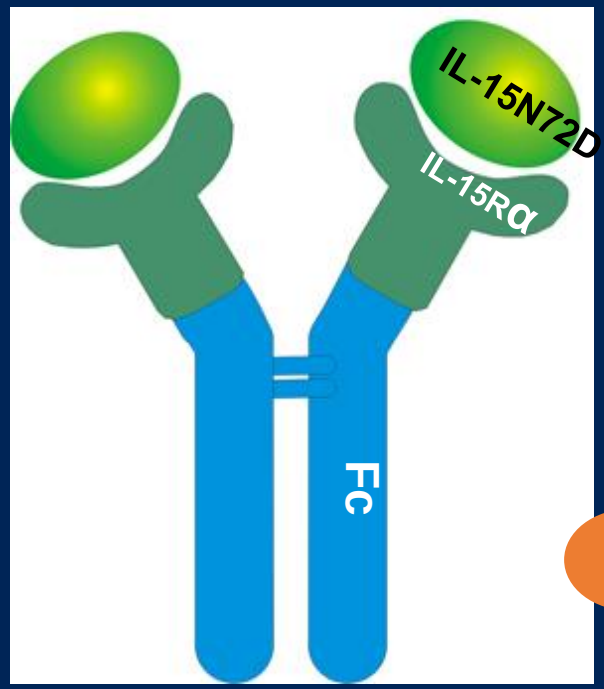
N-803: First-in-Class IgG1-Fc IL-15 Cytokine Agonist



N-803

Unique Mechanisms of Action

1 **IL-15N72D**

IL-15 N72D mutation enhances binding to IL-2Rβ, driving proliferation and activation of NK and T cells

2 **IL-15Rα**

Allows transpresentation selectively to only IL-2Rβγ chain of NK and $CD8^+$ T cells without binding to Tregs

3 **IgG1 Fc**

Increases half-life and lymphoid recycling and homing
Specific binding to NK, $CD8^+$ T cells, dendritic cells and macrophages

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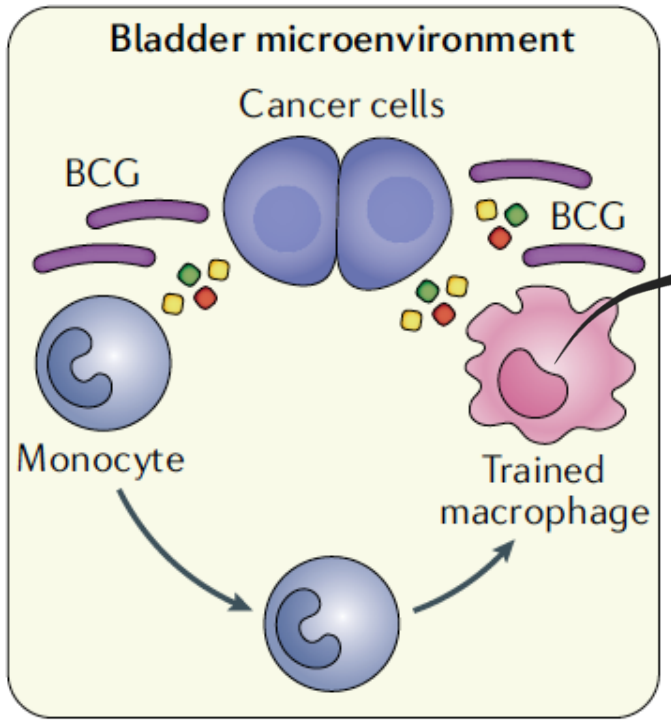
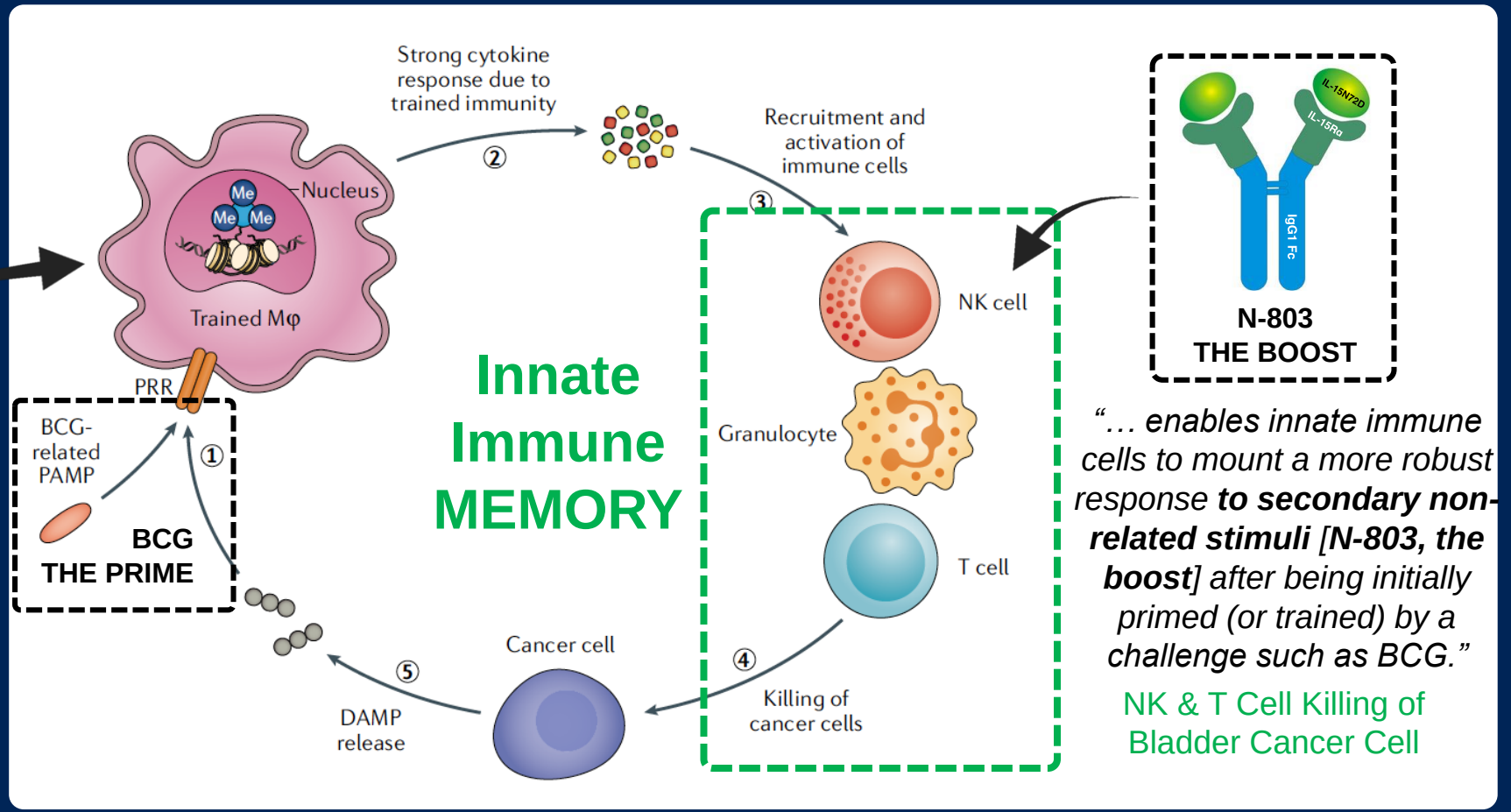
Synergistic MoA of BCG (Prime) + N-803 (Boost) to Induce Innate Immune Memory with Prolonged Duration of Response

BCG: THE PRIME



BCG induction

BCG + N-803



N-803: THE BOOST

N-803
THE BOOST

*"… enables innate immune cells to mount a more robust response **to secondary non-related stimuli** [**N-803, the boost**] after being initially primed (or trained) by a challenge such as BCG."*

NK & T Cell Killing of Bladder Cancer Cell

Adapted from Jelmer H. van Puffelen et al.

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Phase 1: NMIBC – Complete Response in 9 of 9 Subjects

With Durable 24 Month Response When N-803 is Combined with BCG (Innate Immune Memory Response)

Phase I
NCT02138734
QUILT 2.005

Phase I (N=9)
A Study of Intravesical BCG in Combination With N-803 in Patients With Non-Muscle Invasive Bladder Cancer

N-803 + BCG Inducing 24 Month Durable Response

Durable Complete Responses (CR) or No Recurrence (NR) in 9 out of 9 Patients

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

9 of 9 (100%) Patients Disease-Free at 24 Months

BCG naïve alone (SoC): Historical response rate is 55-75% at 3-6 months post BCG alone

Based on this data, FDA granted Fast Track Designation to the Pivotal Trial

*CR termed as No Recurrence (NR) in Papillary Disease **Negative Cystoscopy Inconclusive Cytology

IC: Inconclusive Cystoscopy

ONCOIMMUNOLOGY
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ORIGINAL RESEARCH

OPEN ACCESS

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

Charles J. Rosser[a], Sergei Tikhonenkov[a], Jeffrey W. Nix[b], Owen T.M. Chan[a], Irina Ianculescu[c], Sandeep Reddy[d,c], and Patrick Soon-Shiong[d]

[a]Clinical & Translational Research Program, University of Hawaii Cancer Center,Honolulu, Hawaii; [b]Department of Urology, University of Alabama, Birmingham, Alabama; [c]ImmunityBio, Inc., Culver City, California; [d]NantHealth Inc, Culver City, California

ABSTRACT

Intravesical BCG is active against non-muscle invasive bladder cancer (NMIBC), but bladder cancer will recur and even progress in a significant number of patients. To improve the response rate, N-803, an IL-15 superagonist was administered in combination with BCG. To evaluate the safety and efficacy associated with the use of intravesical N-803 and BCG in patients with BCG-naïve NMIBC. This phase 1b clinical trial used a 3 + 3 dose-escalation design. Participants were enrolled from July 2014 and July 2015, with follow-up and analyses through January 15, 2021. Eligibility criteria included histologically confirmed non-muscle invasive urothelial carcinoma of intermediate or high risk who had not received prior treatment with intravesical BCG (ie, BCG-naïve). All 9 participants met the eligibility criteria, received treatment according to the protocol, and were included in all analyses. Treatment was done once weekly for 6 consecutive weeks with bladder infusion of the standard dose of BCG, 50 mg/instillation, in combination with increasing doses of N-803 (100, 200, or 400 µg N-803 per instillation). No DLTs were noted in any of the dose cohorts. All adverse events (AEs) were manageable and less than grade 3. During the 2-year follow-up, all 9 participants were disease free. Furthermore, 6 y after treatment, all 9 participants (100%) were disease free with no evidence of disease progression and an intact bladder. This phase 1b trial found the combination of intravesical N-803 and BCG to be associated with modest toxic effects, low immunogenicity, and substantial prolonged antitumoral activity; phase 2 trials are in progress.

ARTICLE HISTORY
Received 3 March 2021
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KEYWORDS
Non-muscle invasive bladder cancer; IL15; BCG

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QUILT 3.032: N-803 + BCG in CIS (Cohort A) and Papillary (Cohort B) in NMIBC

Study Schema

BCG Unresponsive Disease

- Histologically Confirmed
- COHORT A (CIS): Persistent or recurrent CIS (+/- recurrent Ta/T1 disease) within 12 months of receiving adequate BCG
- COHORT B (Papillary): Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG

Treatment

50 mg BCG **plus** 400 µg N-803 intravesically weekly x 6 induction or re-induction x 6 + maintenance for up to three years

N = 160

Efficacy Endpoints

Primary Endpoint:

- COHORT A (CIS): Biopsy confirmed complete response (CR) at 3 or 6 months, with lower bound of the 95% CI of CR rate ≥ 20%
- COHORT B (Papillary): Disease-free rate at 12 months, with lower bound of the 95% CI of disease-free rate at 12 months ≥ 20%

Secondary Endpoints:

- Duration of CR
- Cystectomy Avoidance
- Time to Cystectomy

Safety Endpoints

Serious Adverse Events

Immune Adverse Events

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Demographics

	Cohort A CIS	Cohort B Papillary	ALL
N	83	77	160
AGE (yrs)	72.8	71.7	72.3
>65 yrs (%)	84	74	79
M:F (%)	87 / 13	74 / 26	81 / 19
ECOG 0 (%)	82	77	79
ECOG 1 (%)	18	17	18
ECOG 2 (%)	0	6	3

Number of Prior TURBT			
Mean	4	4	4

Total Number of Prior BCG Doses	Cohort A CIS	Cohort B Papillary
Median	12.0	12.0
Mean	16.6	12.3

Time From Last Prior BCG Dose to Enrollment in Study	Cohort A CIS	Cohort B Papillary
Median	6.2 Months	4.9 Months
Mean	7.9 Months	6.0 Months

Disease Type Prior to Enrollment		
CIS	70%	1%
CIS / Ta	19%	1%
CIS / T1	11%	5%
HG Ta	0	43%
T1	0	44%
Ta / T1	0	4%

Median Number of N-803 + BCG Doses Administered		
Median	12.0	12.0

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Efficacy
COHORT A (CIS)

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Clinically Meaningful Efficacy Results Cohort A (CIS)

	Overall Intent to Treat Population	QUILT-3.032
Complete Response	Complete Response (n)	59 / 83
	CR Rate (95% CI)	71% (60.1, 80.5)
Duration of Response	Median Duration of Response in Months (95% CI)	24.1 (9.9, NR)
	% (n) with duration >=12 Months per KM	62% (48.0, 73.5)
	% (n) with duration >=18 Months per KM	55% (40.1, 67.3)
	% (n) with duration >=24 Months per KM	52% (37.0, 64.9)
Bladder Cancer Specific Progression Free Survival	Overall Bladder Cancer Specific Progression Free Survival	
	24 Months per KM	91% (81.2, 95.4)
	Bladder Cancer Specific Progression Free Survival in Responders	
	24 Months per KM	96% (86.5, 99.1)
Impact on Cystectomy Rate	Cystectomy Avoidance Rate in Responders	93% (55 / 59)
	Cystectomy Rate in Responders	7% (4 / 59)
	Recurrence Delayed Cystectomy in Responders	5.1 Months
Disease Specific Overall Survival	Bladder Cancer Specific Overall Survival	100%
Duration of Follow Up	Median Duration of Follow Up	23.9 Months
	Range of Follow Up of All Subjects (months)	0.3 to 37.5 Months

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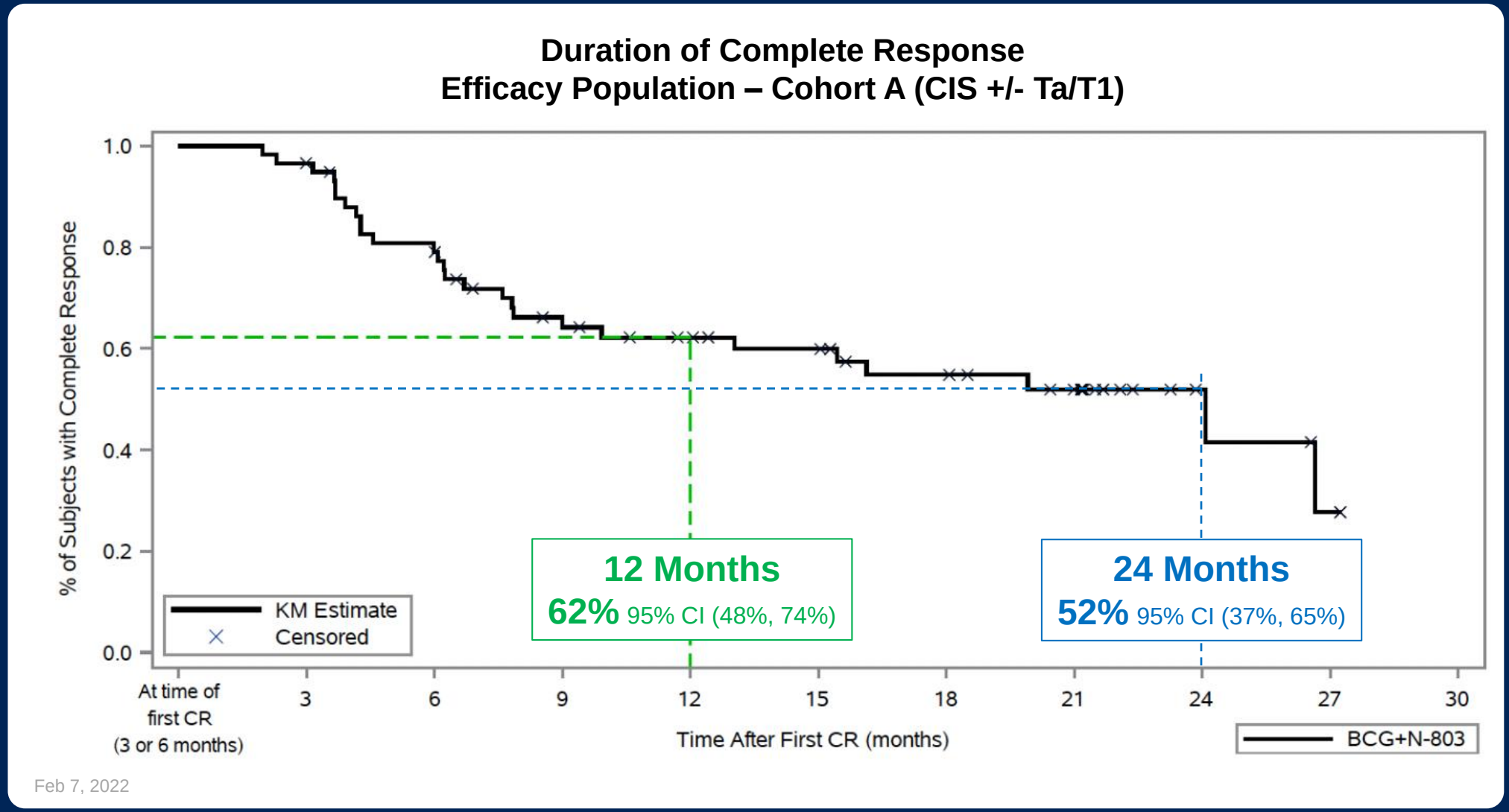
12 and 24 Month Durable Complete Response in CIS (Cohort A)



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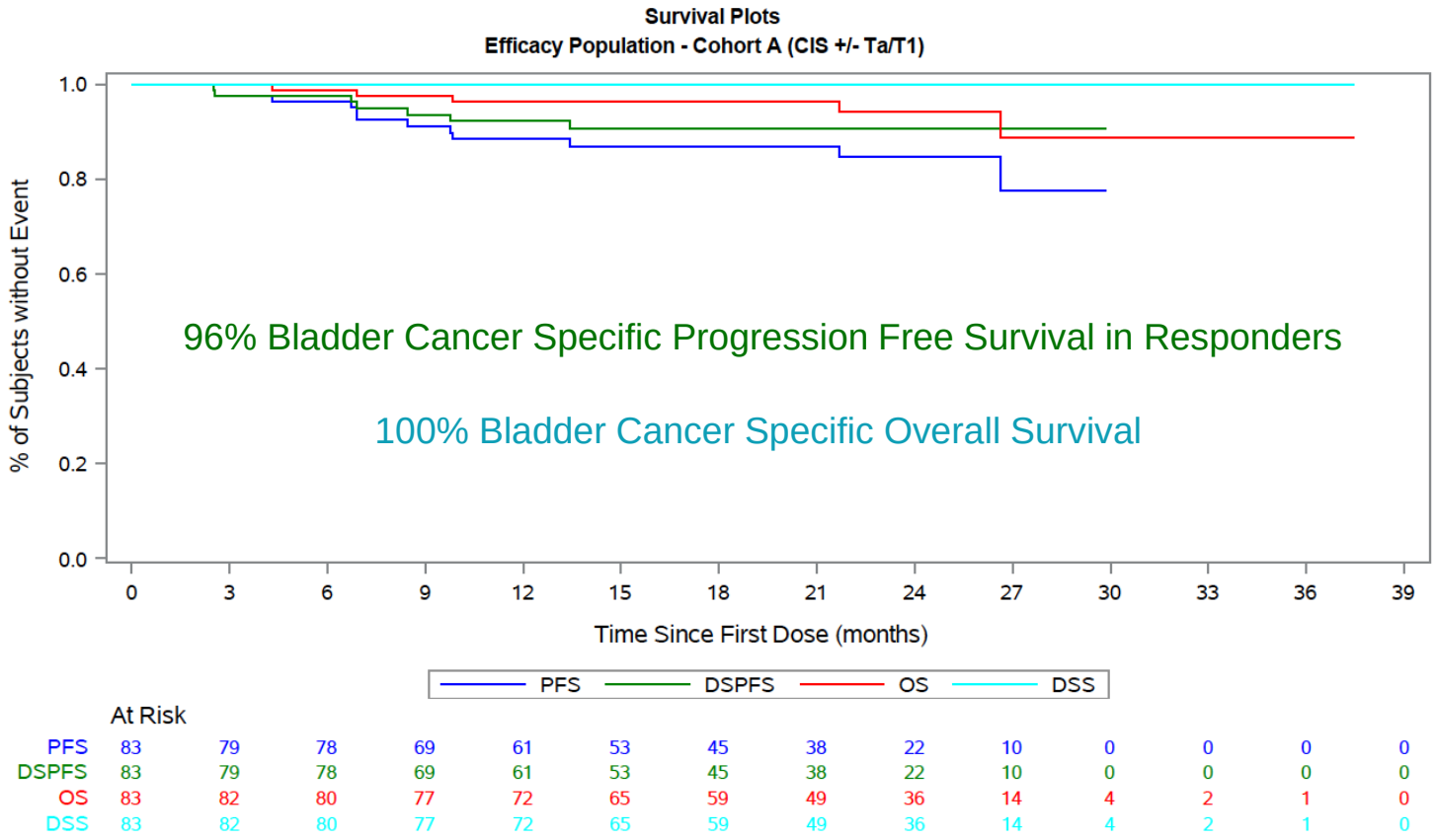
Sustained Durable Response, Bladder Cancer Progression Free Survival and Overall Survival (Cohort A: CIS)

Variable	Responders (n=59)
Subjects with Bladder Cancer Progression n (%)	2 (3%)
Median Disease Specific Progression-Free Survival (DSPFS) (Months)	NR
95% CI for the Median DSPFS	NR, NR
DSPFS Rate at:	
Month 12	96.4% (86.5, 99.1)
Month 15	96.4% (86.5, 99.1)
Month 18	96.4% (86.5, 99.1)
Month 21	96.4% (86.5, 99.1)
Month 24	96.4% (86.5, 99.1)

Source: Feb 07 Data Extraction

Summary of Survival Analysis



PRESENTED BY: SAM CHANG, MD

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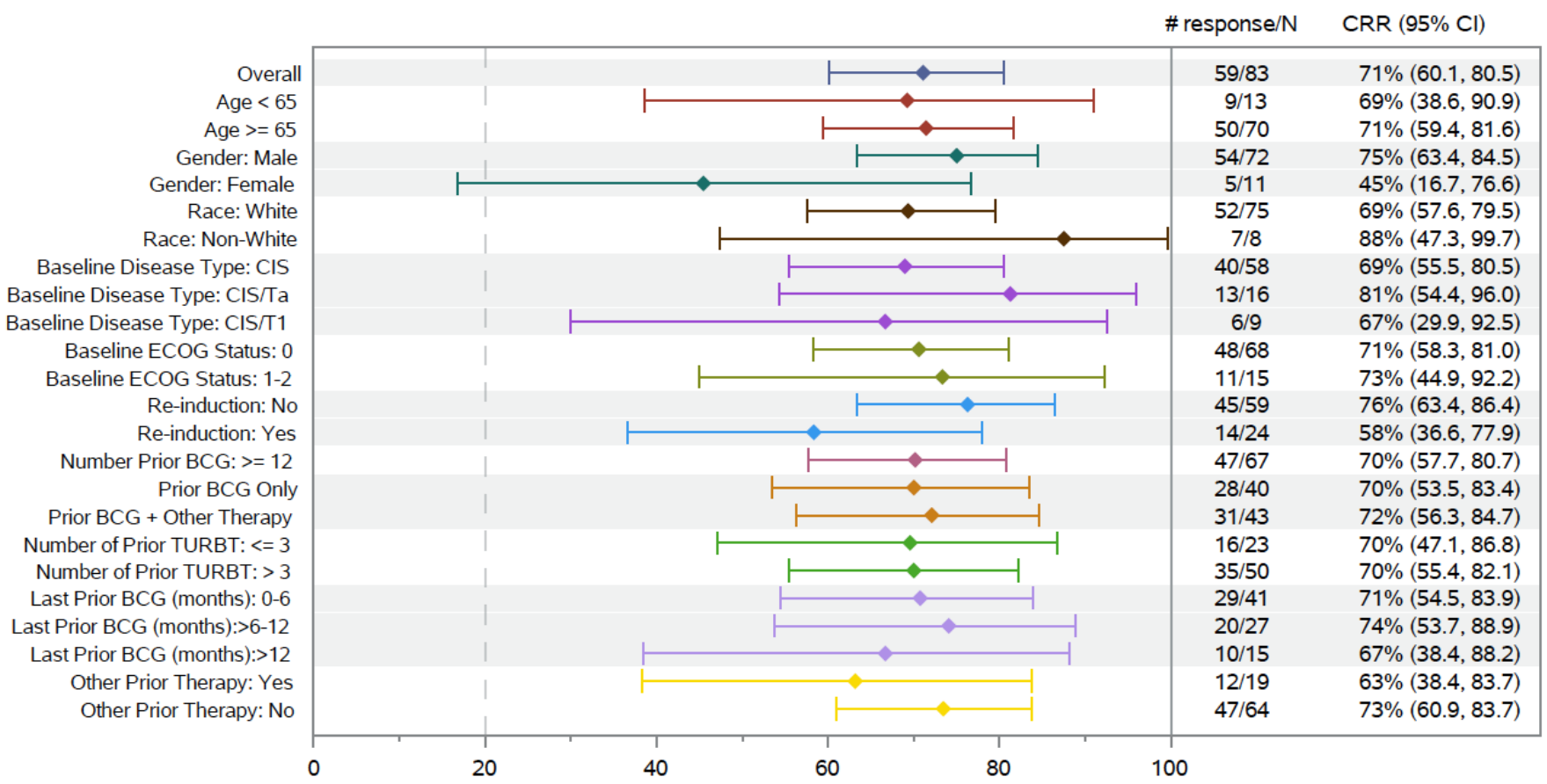
Efficacy Retained Across All Subgroups

COHORT A (CIS +/- Ta T1)



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Efficacy
COHORT B (PAPILLARY)

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Efficacy Results Cohort B (Papillary)

	Overall Intent to Treat Population	QUILT-3.032
Number Enrolled	Total Number of Patients	77
Disease Free Survival	Median Disease Free Survival	23.6 months
	DFS rate at 12 months	57% (95% CI: 44%, 68%)
	DFS rate at 18 months	53% (95% CI: 40%, 65%)
	DFS rate at 24 months	48% (CI 95%: 34%, 60%)
Cystectomy Avoidance	Cystectomy Avoidance Rate	95% (73/77)
Disease Specific Overall Survival	Bladder Cancer Specific Overall Survival	99%
Duration of Follow Up	Median Duration of Follow Up	20.7 months

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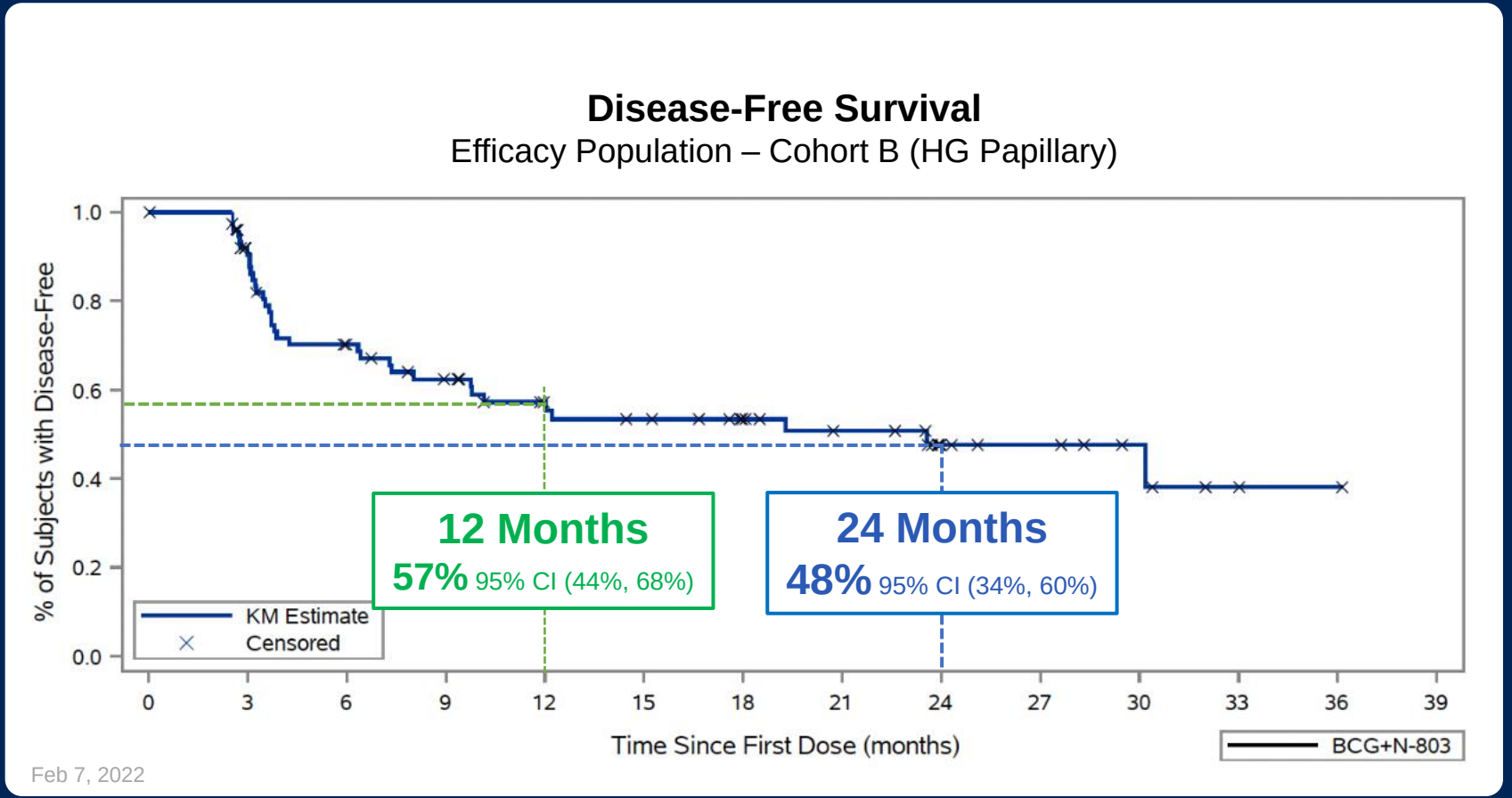
Durable 24 Month Disease Free Survival

Cohort B (Papillary) patients also seemed to retain durable disease-free states



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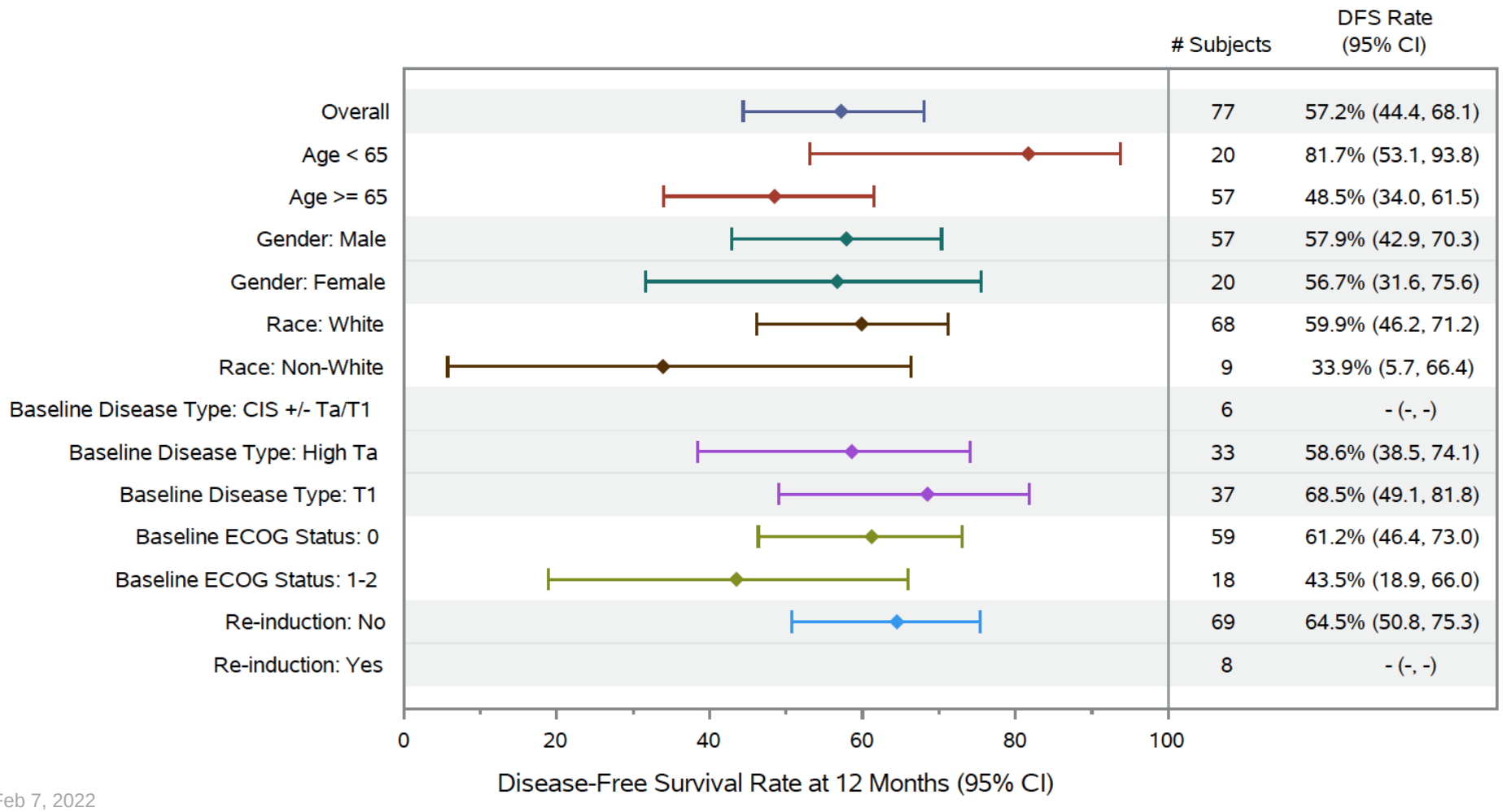
Efficacy Retained Across All Subgroups

COHORT B Papillary (Ta /T1)



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Adverse Events: Cohorts A (CIS) + B (Papillary) Profile

Treatment-Related AE's

GRADE 1-2

Adverse Event (AE)	%
Dysuria	**22%**
Pollakiuria	**19%**
Haematuria	**18%**
Fatigue	16%
Micturition urgency	12%
Chills	7%
Bladder spasm	6%
Pyrexia	5%
Urinary tract infection	5%
Cystitis noninfective	4%
Nocturia	3%
Diarrhea	3%
Nausea	2%
Bacterial test positive	2%
Cystitis	2%
Influenza like illness	2%
Urinary tract pain	2%

GRADE 3

Adverse Event (AE)	%
Arthralgia	<1%
Bacteraemia	<1%
Dysuria	<1%
Encephalopathy	<1%
Escherichia bacteraemia	<1%
Haematuria	<1%
Myalgia	<1%
Pain in extremity	<1%
Pollakiuria	<1%
Sepsis	<1%
Urinary tract infection	<1%
Urine flow decreased	<1%

Treatment-Related Grade 4 & 5

0% CIS

0% Papillary

Treatment-Related SAE's

0% CIS

0% Papillary

Immune-Related AE

0% CIS

0% Papillary

N-803 Activity is Local to the Bladder with No Systemic IL-15 Levels per PK

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Clinically Meaningful Benefit: BCG + N-803 in CIS

- **Excellent safety and tolerability profile** of N-803 + BCG (QUILT-3.032)
  - **0%** grade 4 and 5 AE
  - **0%** treatment-related SAEs
  - **0%** immune-related AE
- **71%** Complete remission (CR) rate at anytime
- **24.1** Months median durable complete remission
- **96%** Avoidance of bladder cancer progression at 24 months in responders
- **91%** Avoidance of cystectomy at 24 months in responders
- **100%** Bladder cancer specific overall survival at 24 months
- Favorable & familiar dosing schedule with activity localized to the bladder

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Clinically Meaningful Benefit: BCG + N-803 in Papillary

- **Excellent safety and tolerability profile** of N-803 + BCG (QUILT-3.032)
  - **0%** grade 4 and 5 AE
  - **0%** treatment-related SAEs
  - **0%** immune-related AE
- **57%** Disease free survival rate at 12 months
- **99%** Overall bladder cancer specific survival
- **95%** Cystectomy avoidance rate
- Favorable & familiar dosing schedule with activity localized to the bladder

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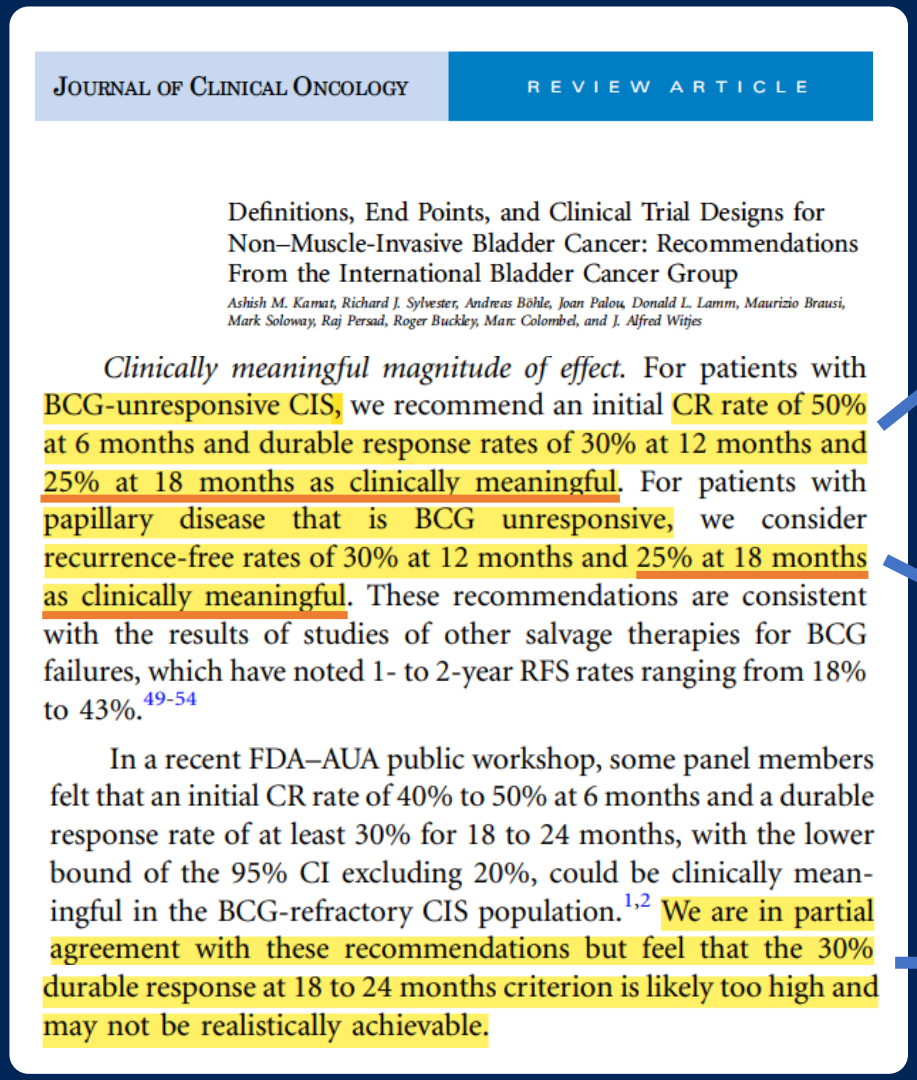
Clinically Meaningful Magnitude of Effect of N-803 + BCG in CIS & Papillary Exceeds Expectations



JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Definitions, End Points, and Clinical Trial Designs for Non–Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group

Ashish M. Kamat, Richard J. Sylvester, Andreas Böhle, Joan Palou, Donald L. Lamm, Maurizio Brausi, Mark Soloway, Raj Persad, Roger Buckley, Marc Colombel, and J. Alfred Witjes

Clinically meaningful magnitude of effect. For patients with BCG-unresponsive CIS, we recommend an initial CR rate of 50% at 6 months and durable response rates of 30% at 12 months and 25% at 18 months as clinically meaningful. For patients with papillary disease that is BCG unresponsive, we consider recurrence-free rates of 30% at 12 months and 25% at 18 months as clinically meaningful. These recommendations are consistent with the results of studies of other salvage therapies for BCG failures, which have noted 1- to 2-year RFS rates ranging from 18% to 43%.[49-54]

In a recent FDA–AUA public workshop, some panel members felt that an initial CR rate of 40% to 50% at 6 months and a durable response rate of at least 30% for 18 to 24 months, with the lower bound of the 95% CI excluding 20%, could be clinically meaningful in the BCG-refractory CIS population.[1,2] We are in partial agreement with these recommendations but feel that the 30% durable response at 18 to 24 months criterion is likely too high and may not be realistically achievable.

BCG + N-803 (CIS)

As of Feb 07, 2022:

CR rate 71% (59 / 83) with 28 / 83 (34%) Maintaining Complete Remission at **18** Months

BCG + N-803 (Papillary)

As of Feb 07, 2022:

Disease Free Rate:

57% Probability of Disease Free at 12 Months

53% Probability of Disease Free at 18 Months

Exceeds Expectations of Complete Response and Duration of Response

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Thomas Jefferson University, PA	Philadelphia, PA	Edouard Trabulsi, MD
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UCLA, CA	Los Angeles, CA	Karim Chamie, MD
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Skyline Urology - Sherman Oaks, CA	Sherman Oaks, CA	Richard David, MD
U of Miami	Miami, FL	Mark Gonzalgo, MD
Vanderbilt University, TN	Nashville, TN	Sam Chang, MD
Madigan Army Medical, WA	Tacoma, WA	Timothy Brand, MD
Clinical Research Solutions	Middleburg Heights, OH	Michael Barkoukis
Toledo Clinic	Toledo, OH	Rex Mowat, MD
Manhattan Medical, NY	New York, NY	Jed Kaminetsky, MD
West Coast Urology	Los Angeles, CA	Earnest Agatstein, MD
Urology Associates, CO	Denver, CO	Barrett Cowan, MD
U Chicago, IL	Chicago, IL	Scott Eggener, MD
Eisenhower Army Medical	Augusta, GA	Aaron Brothers, MD
Premier Medical, NY	Poughkeepsie, NY	Evan Goldfischer, MD
UNC Chapel Hill, NC	Chapel Hill, NC	Ray Tan, MD
Virginia Urology, VA	Richmond VA	Gene Kramolowsky, MD
Adult & Pediatric Urology, NE	Council Bluffs, NE	Andrew Trainer, MD
Assoc. Urologists, NC	Raleigh, NC	Mark Jalkut, MD
University of Michigan	Ann Arbor, MI	Samuel Kaffenberger, MD
Accument Rx, NM	Albuquerque, NM	Fredrick Snoy, MD
Arkansas Urology	Little Rock, AK	Richard D'Anna
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Thank You to all the patients, caregivers, and investigators

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