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

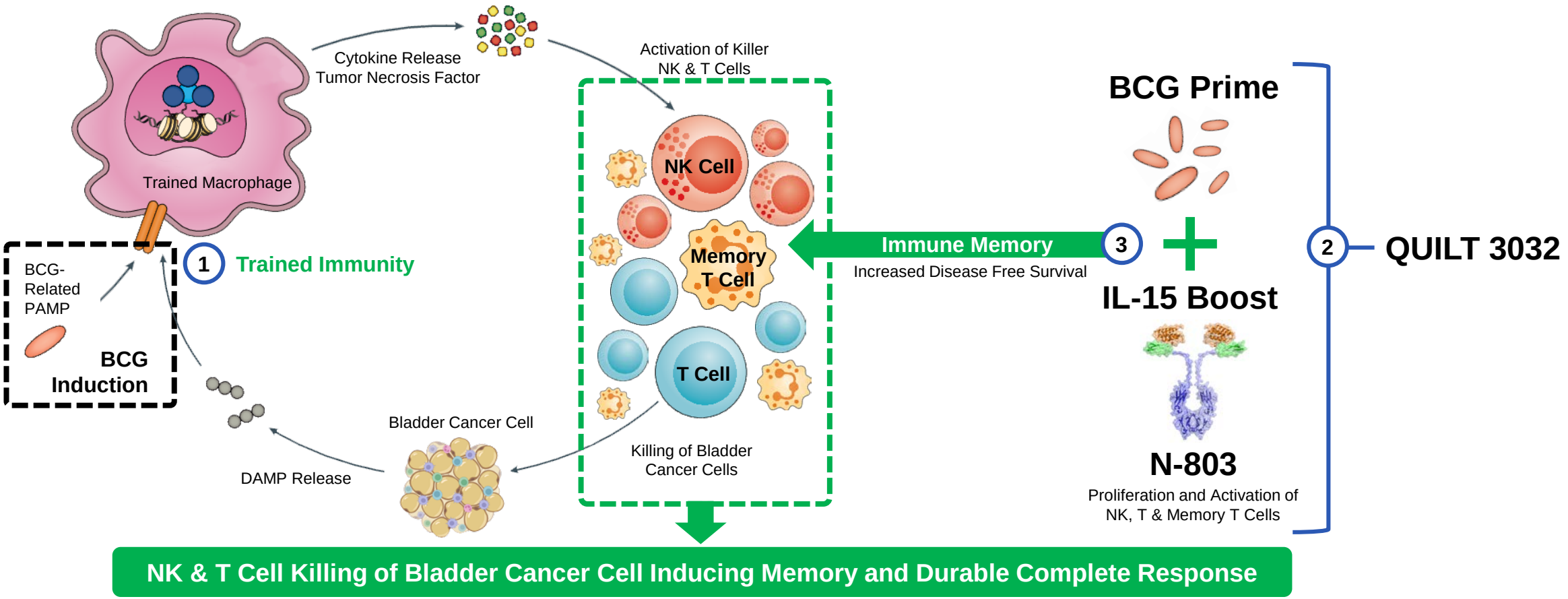
Dr. Karim Chamie, UCLA

Disclosures

- Urogen Pharma: Consultant and Scientific Advisory Board
- BMS: Speaker and Advisory Board
- Merck: Scientific Advisory Board
- ImmunityBio: Scientific Advisory Board

PRESENTED BY:
Dr. Karim Chamie, MD, MSHS – UCLA Department of Urology

QUILT 3032: BCG Induces Trained Immunity
BCG (Prime) + N-803 (Boost) in NMIBC for Immune Memory



Mechanism of Action References

① **BCG**
- NK Cells Are Essential for Effective BCG Immunotherapy. Sven Brandau, 2001 April. Wiley, Intl Journal of Cancer
- Trained Immunity as a Molecular Mechanism for BCG Immunotherapy in Bladder Cancer. Jelmer H van Puffelen, 2020 Jul Nature Rev Urology
- BCG therapy downregulates HLA-I on malignant cells to subvert antitumor immune responses in bladder cancer. Mathieu Rouanne et al., 2022 May, Journal of Clinical Investigation

② **N-803**
- 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. Hing Wong., 2013 Nov, OncoImmunology
- IL-15 superagonist/IL-15RαSushi-Fc fusion complex markedly enhances specific subpopulations of NK & memory CD8+ T cells, & mediates potent anti-tumor activity. Peter S. Kim, 2016. Oncotarget
- Phase I Trial Characterizing the Pharmacokinetic Profile of N-803, a Chimeric IL-15 Superagonist, in Healthy Volunteers. Mark P. Rubinstein et al., 2022 Feb. Journal of Immunology

③ **N-803 + BCG**
- 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. Evan Gomes-Giacoia, June 2014 PLos One
- Innate Immune Memory is Associated with Increased Disease-Free Survival in Bladder Cancer Patients Treated with BCG. Charles H. Graham, 2021 Aug Can Urol Assoc J.
- Intravesical BCG in Patients with Non-Muscle Invasive Bladder Cancer Induces Trained Immunity and Decreases Respiratory Infections. Jelmer H van Puffelen, 2021 Feb. BioRxiv

QUILT 3032

Phase 2 / 3: IL-15RαFc Superagonist N-803 with BCG in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer CIS & Papillary

BCG Unresponsive Disease

- Histologically Confirmed
- Persistent or recurrent CIS (+/- recurrent Ta/T1 disease) within 12 months of receiving adequate BCG
- CIS (Cohort A), Papillary (Cohort B)

QUILT 3032 - Treatment

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

Safety Endpoints

- Serious Adverse Events
- Immune Adverse Events

Efficacy Endpoints

Primary Endpoint:

- CR at any time, with lower bound 95% CI of ≥ 20%

Secondary Endpoints:

- Duration of CR,
- Cystectomy Avoidance
- Time to Cystectomy

Data extract: Nov 2021

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QUILT 3032
Demographics: Heavily Pre-treated NMIBC Subjects

Demographics	Cohort A - CIS	Cohort B - Papillary
N	84	77
AGE (yrs)	73	72
>65 yrs (%)	85	74
M:F (%)	87 / 13	74 / 26
ECOG 0 (%)	81	77
ECOG 1 (%)	19	17
ECOG 2 (%)	0	6

Number of Prior TURBT

Mean	4	4

Disease Type	Cohort A - CIS	Cohort B - Papillary
CIS	70%	1%
CIS / Ta	19%	1%
CIS / T1	10%	5%
CIS/Ta/T1	1%	0%
HG Ta	0	43%
T1	0	45%
Ta / T1	0	4%

Number Prior BCG Doses

Mean	16.6	12.3

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QUILT 3032
Adverse Events: Cohorts A (CIS) & Cohort B (Papillary)

Treatment-Related AE's

GRADE 1-2 (CIS & Papillary)

Adverse Event (AE)	%
Dysuria	22%
Pollakiuria	20%
Haematuria	17%
Fatigue	16%
Micturition urgency	12%
Chills	7%
Bladder spasm	6%
Pyrexia	5%
Urinary tract infection	6%
Cystitis noninfective	4%
Nocturia	3%
Diarrhoea	3%
Nausea	2%
Bacterial test positive	2%
Cystitis	2%
Influenza like illness	2%
Urinary tract pain	2%

GRADE 3 (CIS & Papillary)

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

Treatment-Related SAE's

1%

Immune-Related SAE

0%

Treatment-Related Deaths

0%

No Treatment Related Grade 4 or 5 Events

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

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Efficacy
COHORT A (CIS)

(Data Cutoff: January 15, 2022)

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Clinically Meaningful Efficacy Results Cohort A (CIS)

	Overall Intent to Treat Population Efficacy	QUILT 3032
Complete Response	Complete Response (n)	58 / 82
	CR Rate	71% (95% CI: 59.6, 80.3)
Median DoR	Median Duration of Response in Months	26.6 Months (95% CI: 9.9, Not Reached)
Duration of Response	Duration of Response ≥12 Months per KM	61.6% (95% CI: 47.3, 73.1)
	Duration of Response ≥18 Months per KM	56.3% (95% CI: 41.5, 68.8)
	Duration of Response ≥24 Months per KM	53.2% (95% CI: 38.0, 66.2)

Clinically Meaningful Efficacy Results Cohort A (CIS)

Duration of Follow Up

Cystectomy Rate

Bladder Cancer Specific Progression Free Survival

Disease Specific Overall Survival

Overall Intent to Treat Population	QUILT-3.032
Median Duration of Follow Up	23.9 Months
Cystectomy Rate	
Responders	9%
Overall	16%
Bladder Cancer Specific Progression Free Survival	
12 Months per KM	96.4% (95% CI: 86.2, 99.1)
18 Months per KM	96.4% (95% CI: 86.2, 99.1)
24 Months per KM	96.4% (95% CI: 86.2, 99.1)
Bladder Cancer Specific Overall Survival	100%

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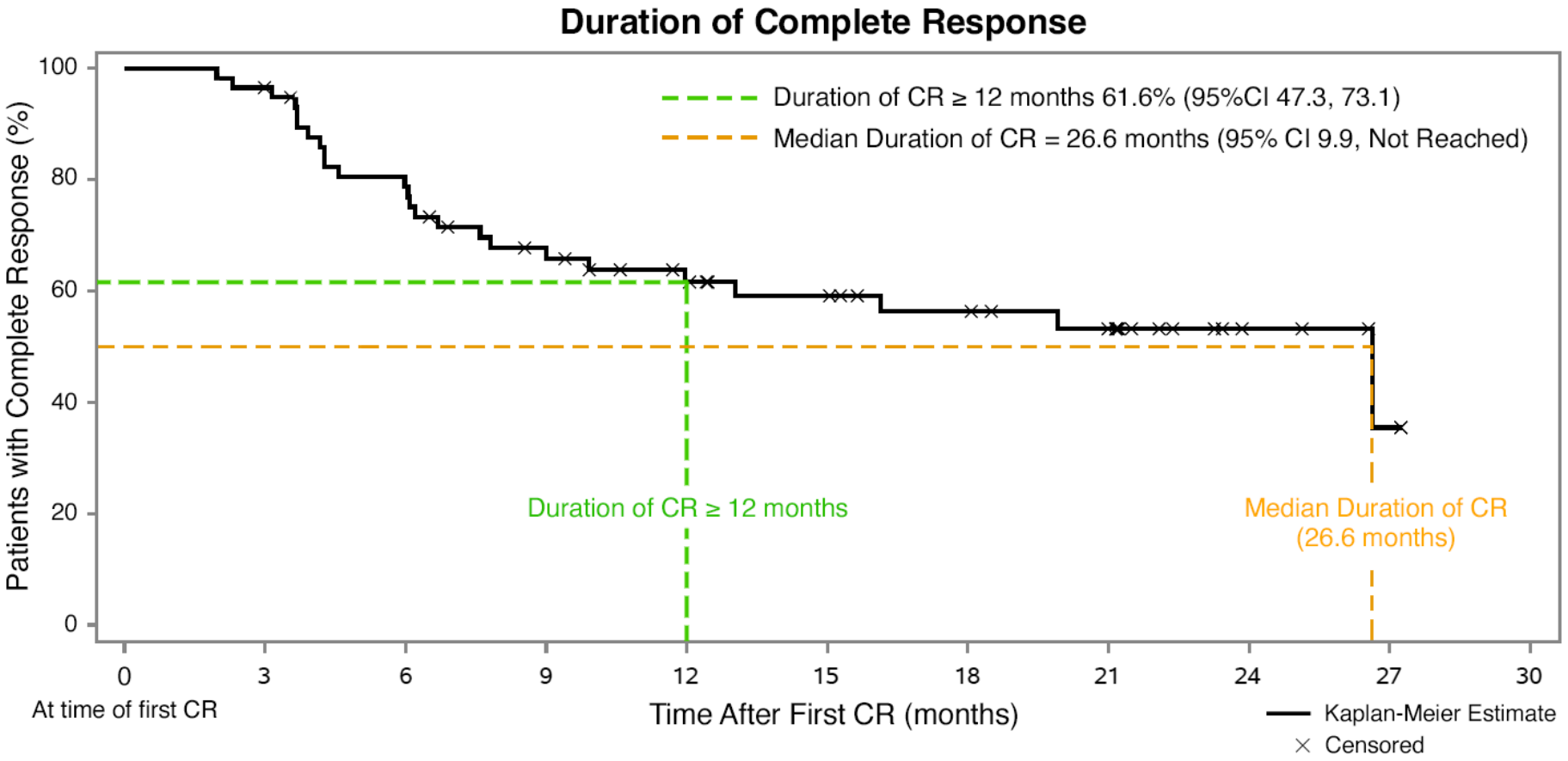
QUILT 3032
26.6 Month Durable Complete Remission in CIS (Cohort A)



Median Duration of CR
26.6 Months

Ongoing Response, Still on Study
21 / 58 (36%)

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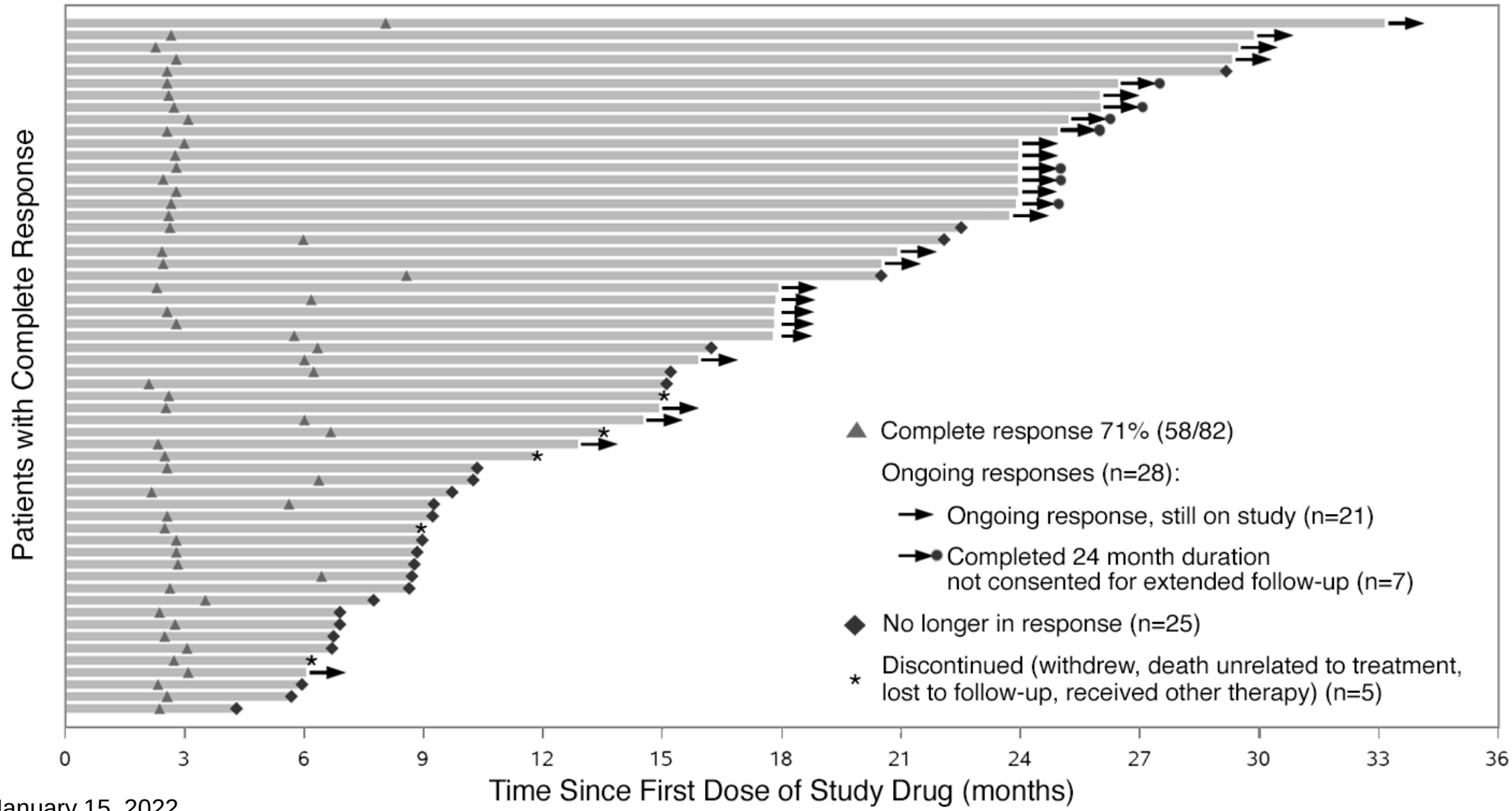
Overall Complete Response & Duration of Response

Time to Complete Response and Duration of Complete Response (Overall Responder Population)



Data Cutoff: January 15, 2022

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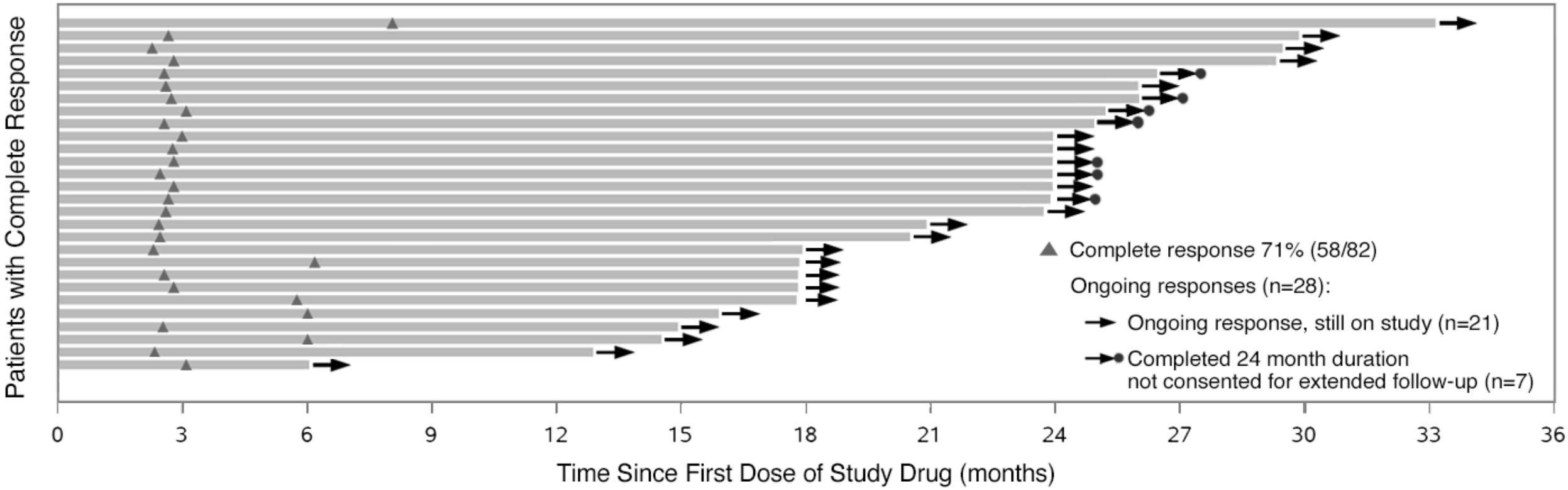
Durable Response: Responders Still Ongoing

Data Cutoff: January 15, 2022

Time to Complete Response and Duration of Complete Response (Ongoing Responder Population)



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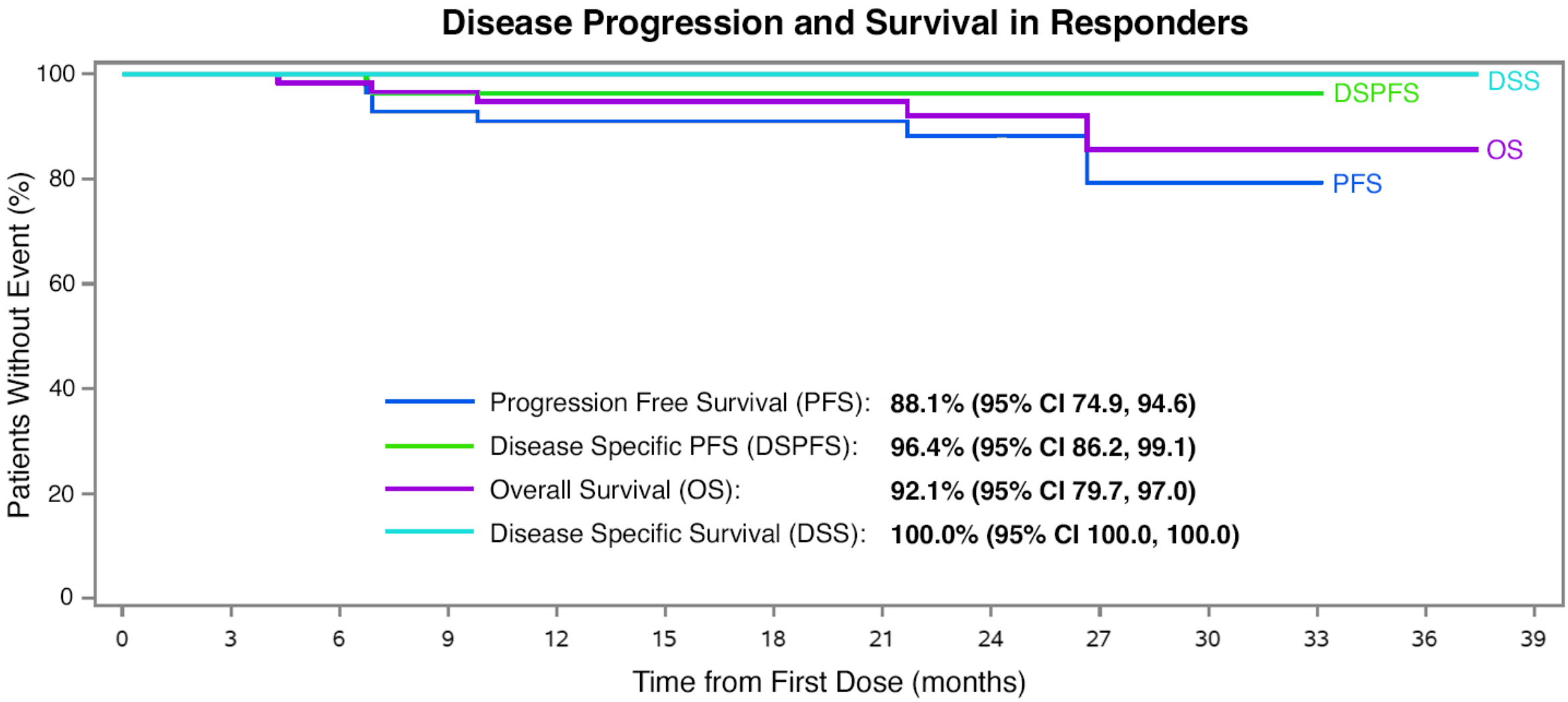
Progression Free Survival and Overall Survival (Cohort A: CIS)



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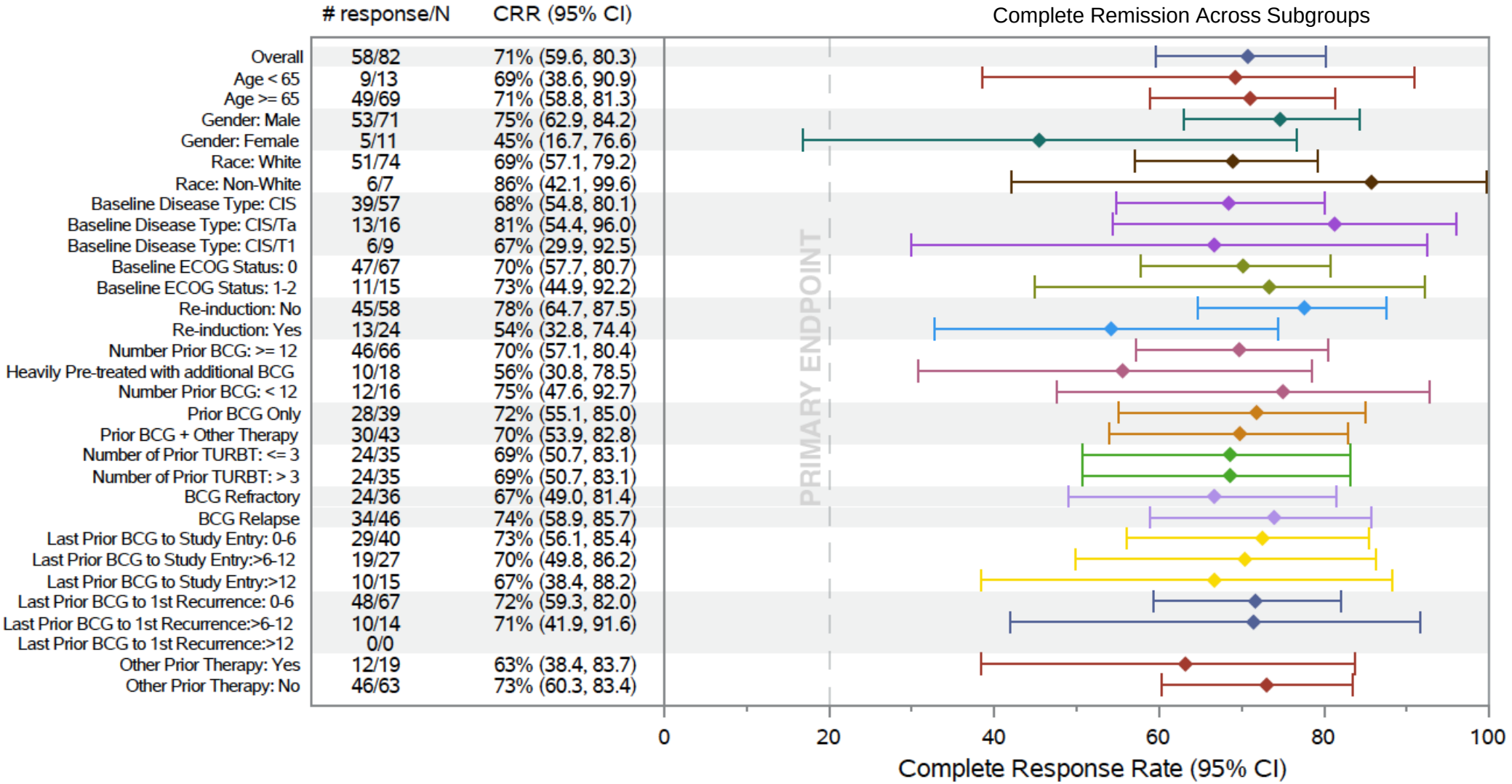
Efficacy Retained Across All Subgroups

COHORT A (CIS +/- Ta T1)



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Comparison with KEYNOTE-057 (Slides 16-20)

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QUILT 3032 Compared to KEYNOTE-057 in NMIBC BCG Unresponsive CIS Disease

Primary Endpoint: Efficacy

Study	N-803 + BCG QUILT-3.032	Pembrolizumab (Balar 2021, ODAC)
STUDY DESIGN	**Pivotal phase 2/3 open-label**	**Phase 2 open-label (KEYNOTE-057)**
Overall Efficacy Population	82	96
Median Duration of Follow-up (months)	23.9	24.1
COMPLETE RESPONSE (CR)		
CR Rate at Anytime		
CR Rate	71%	41%
CR Rate 95% CI	(59.6, 80.3)	(31, 52)
CR Rate in US Population % (n)		
CR Rate, United States Population	71% (58/82) (95% CI: 59.6, 80.3)	29% (10/34) (95% CI: 15.1, 47.5)
CR Rate, International	No Internationally Enrolled Subjects	47% (29/62) (95% CI: 34.0, 59.9)
CR Rate in High Risk Disease State % (n)		
CIS/HG Ta at baseline	81% (13/16) (95% CI: 54.4, 96.0)	29% (7/24) (95% CI: 12.6, 51.1)
CIS/T1 at baseline	67% (6/9) (95% CI: 29.9, 92.5)	42% (5/12) (95% CI: 15.2, 72.3)

Primary Endpoint: 30% CR rate with the lower bound 95% confidence interval at ≥ 20%

Lower bound 95% CI of QUILT 3032 **>** Upper bound 95% CI of KEYNOTE-057

CR Rate of US Population Differs

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QUILT 3032 Compared to KEYNOTE-057 in NMIBC BCG Unresponsive CIS Disease

Duration of Response

Study	N-803 + BCG QUILT-3.032	Pembrolizumab (Balar 2021, ODAC)
STUDY DESIGN	**Pivotal phase 2/3 open-label**	**Phase 2 open-label (KEYNOTE-057)**
Overall Efficacy Population	82	96
DURATION OF RESPONSE (DOR)		
Number of Patients with Durable Response		
Number of complete responders at any time	58	39
Durable CR ≥ 6 months	45	30
Durable CR ≥12 months	30	17
Durable CR ≥18 months	20	8
Number of Ongoing Responders	28	11
Ongoing CR, Still on Study	21	NA
CR at 24 Months, Completed Study	7	NA
Median Duration of CR (months)	26.6	16.2

Durable Response in QUILT 3032 at Median 26.6 Months

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QUILT 3032 Compared to KEYNOTE-057 in NMIBC BCG Unresponsive CIS Disease

Cystectomy Avoidance

Study	N-803 + BCG QUILT-3.032	Pembrolizumab (Balar 2021, ODAC)
STUDY DESIGN	**Pivotal phase 2/3 open-label**	**Phase 2 open-label (KEYNOTE-057)**
Overall Efficacy Population	82	96
CYSTECTOMY AVOIDANCE		
Number of Cystectomy, n (%)		
Cystectomy Rate	13 (15.8%)	40 (41.6%)
Cystectomy Avoidance, No Cystectomy	69 (84%)	56 (58%)
Cystectomy in Non-Responders	8 / 24 (33%)	29 / 57 (51%)
Cystectomy After Initial CR	5 / 58 (9%)	11 / 39 (28%)

Higher cystectomy rate in KEYNOTE-057

KEYNOTE-057: **42%** subjects overall population and **28%** subjects in responders

VS

QUILT 3032: **16%** subjects overall population and **9%** subjects in the responders

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QUILT 3032 Compared to KEYNOTE-057 in NMIBC BCG Unresponsive CIS Disease

Clinically Meaningful Efficacy Benchmarks (International Bladder Cancer Group, IBCG)

Study	N-803 + BCG QUILT-3.032	Pembrolizumab ODAC
STUDY DESIGN	**Pivotal phase 2/3 open-label**	**Phase 2 open-label (KEYNOTE-057)**
Overall Efficacy Population	82	102
BENCHMARKS		
Expert Benchmark for Clinically-Meaningful Efficacy (International Bladder Cancer Group)	Exceeded	Did Not Meet
≥ 30% CR rate at 12 months assessment	45% (37/82)	20% (20/102)
≥ 25% CR rate at 18 month assessment	33% (27/82)	13% (13/102)

Clinically meaningful efficacy in QUILT 3032 exceeded benchmark expectations

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QUILT 3032 Compared to KEYNOTE-057 in NMIBC BCG Unresponsive CIS Disease

Safety: Immune Related AEs

Study	N-803 + BCG QUILT-3.032	Pembrolizumab (Balar 2021)
Study design	**Pivotal phase 2/3 open-label**	**Phase 2 open-label (KEYNOTE-057)**
Safety population	171	101
Any adverse immune-mediated events	4.1%[a]	22%
Treatment-related grade 3-5 immune-related AEs	0%	2.9%
Treatment-related serious immune-related AEs	0%	4.9%
Steroid Treatment for Immune Mediated Adverse Events (n)	0	7

- N-803 + BCG Well Tolerated with AEs Comparable to BCG Alone
- Pembrolizumab with Systemic Immune Related AEs Requiring Steroid Therapy

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Efficacy
COHORT B (PAPILLARY)

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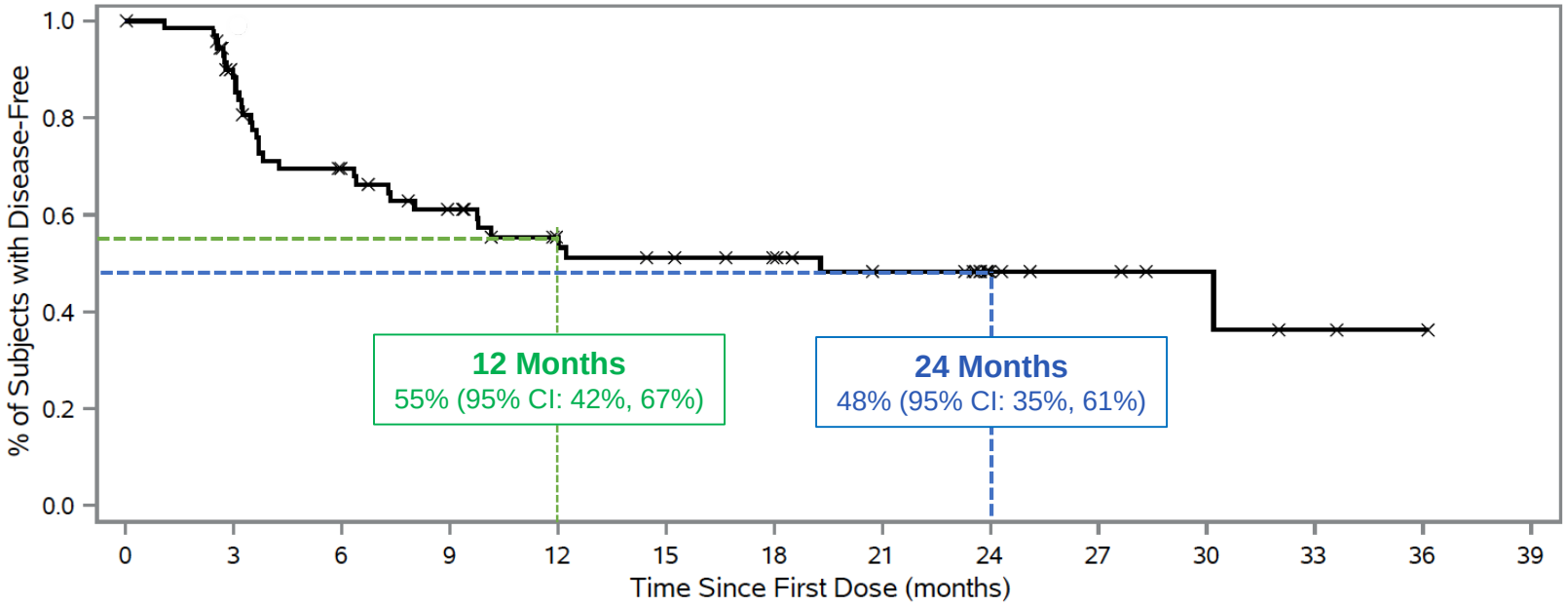
Durable 24 Month Disease Free Survival in Papillary

- 77 patients have been accrued
- Median DFS: 19.3 months
- 55% DFS rate at 12 months
- 51% DFS rate at 18 months
- 48% DFS rate at 24 months
- Primary endpoint met
- Median F/U is 20.7 months
- 72 of 77 (94%) radical cystectomy avoidance

Disease-Free Survival

Efficacy Population (N=72): Cohort B (HG Papillary)



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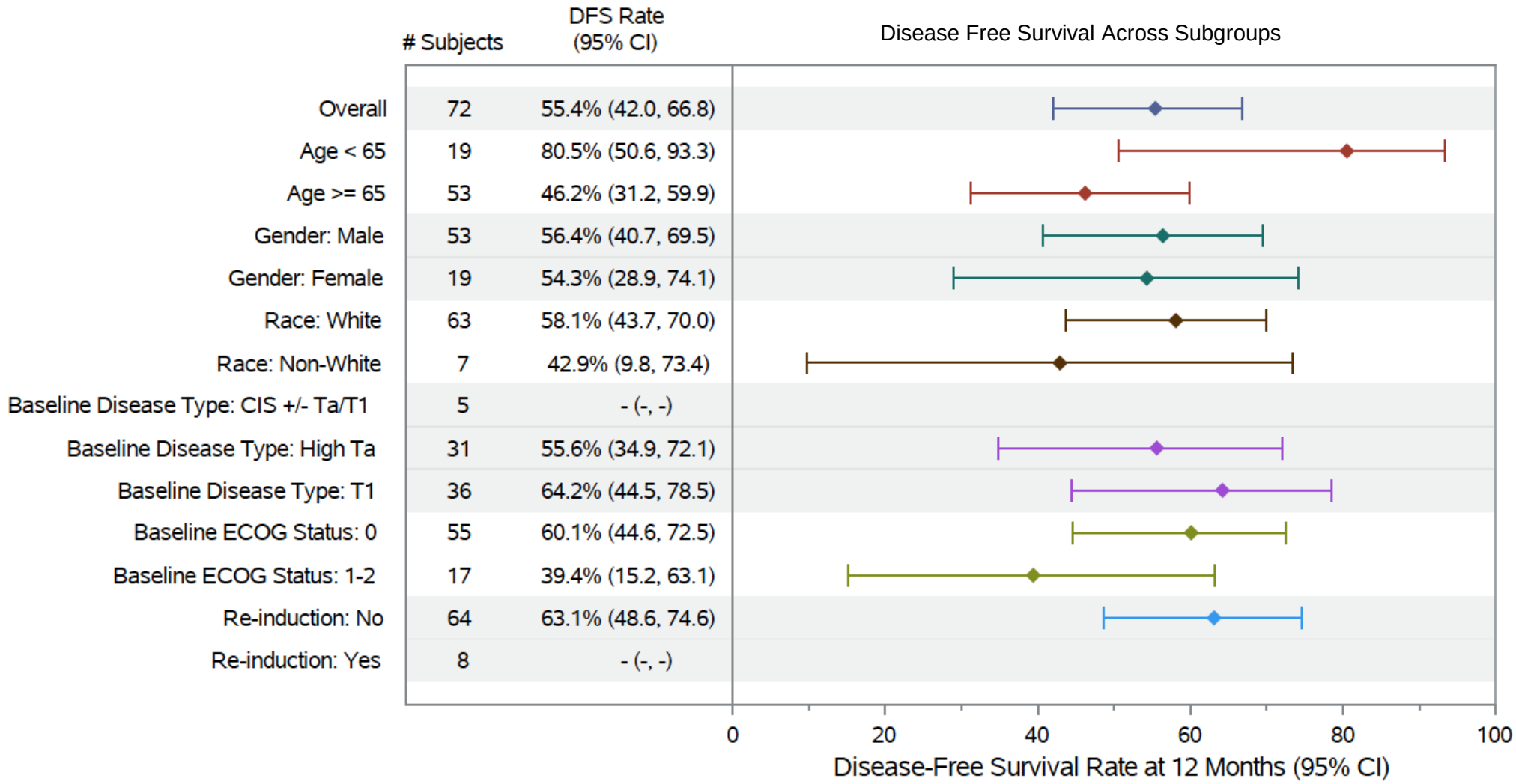
Efficacy Retained Across All Subgroups

COHORT B Papillary (Ta /T1)



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QUILT 3032: Clinically Meaningful Benefit: N-803 + BCG in CIS

High Efficacy Rate and Durable Response

- **71%** Complete remission (CR) rate at anytime
- **26.6** Months median durable complete remission
- **96%** Avoidance of bladder cancer progression at 24 months in responders
- **89%** Avoidance of cystectomy at 24 months in responders
- **100%** Bladder cancer specific overall survival at 24 months

Excellent Safety and Tolerability Profile Comparable to BCG Alone

- **1%** treatment related SAEs
- **0%** immune related SAEs
- **2%** treatment related discontinuation
- **0%** treatment related grade 4 or 5 AEs

Favorable & Familiar Dosing Schedule with Activity Localized to the Bladder

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QUILT 3032: Clinically Meaningful Benefit: N-803 + BCG in Papillary

High Efficacy Rate and Durable Response

- **55%** Disease free survival rate at 12 months
- **19.3 months** median disease free survival
- **99%** Overall bladder cancer specific survival
- **95%** Cystectomy avoidance rate

Excellent Safety and Tolerability Profile

- **0%** treatment related SAEs
- **0%** immune related SAEs
- **6%** treatment related discontinuation
- **0%** treatment related grade 4 or 5 AEs

Favorable & Familiar Dosing Schedule with Activity Localized to the Bladder

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Institution	Location	PI
Moffitt Cancer Center	Tampa, FL	Wade Sexton, MD
U of Hawaii, HI	Honolulu, HI	Sergei Tikhonenkov, MD
Roswell Park CC, NY	Buffalo, NY	Khurshid Guru, MD
University of Rochester, NY	Rochester, NY	Edward Messing, MD
Thomas Jefferson University, PA	Philadelphia, PA	Edouard Trabulsi, MD
Karmanos Cancer Center, MI	Detroit, MI	Michael Cher, MD
UCLA, CA	Los Angeles, CA	Karim Chamie, MD
Winthrop-NYU, NY	Garden City, NY	Aaron Katz, MD
Alaska CRC, AK	Anchorage, AK	William Clark, MD
Skyline Urology - Torrance, CA	Torrance, CA	Fredrick Wolk, MD
ECHO	Norwich, CT	Dennis Slater, MD
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
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Clinical Research Center FL	Pompano, FL	Herman Kester, MD

Thank You to all the patients, caregivers, and investigators