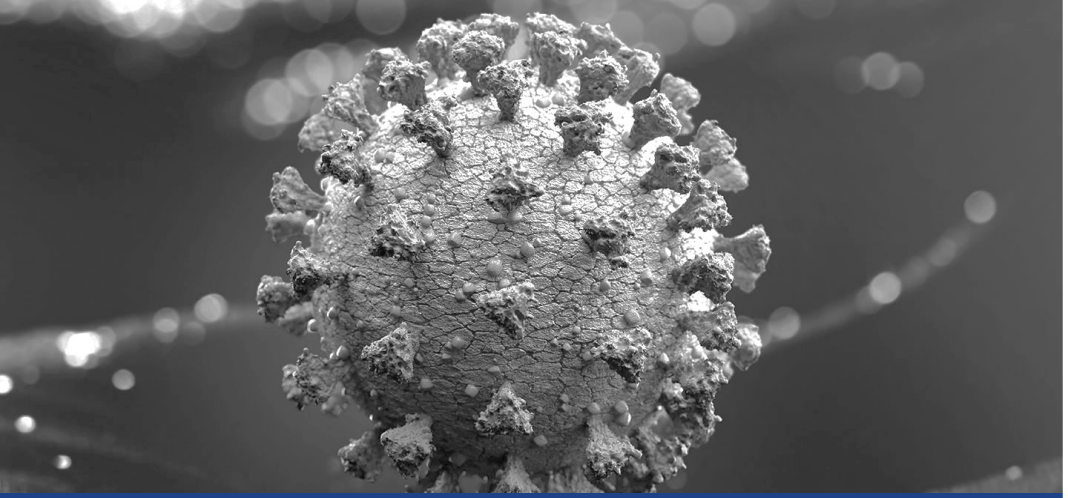
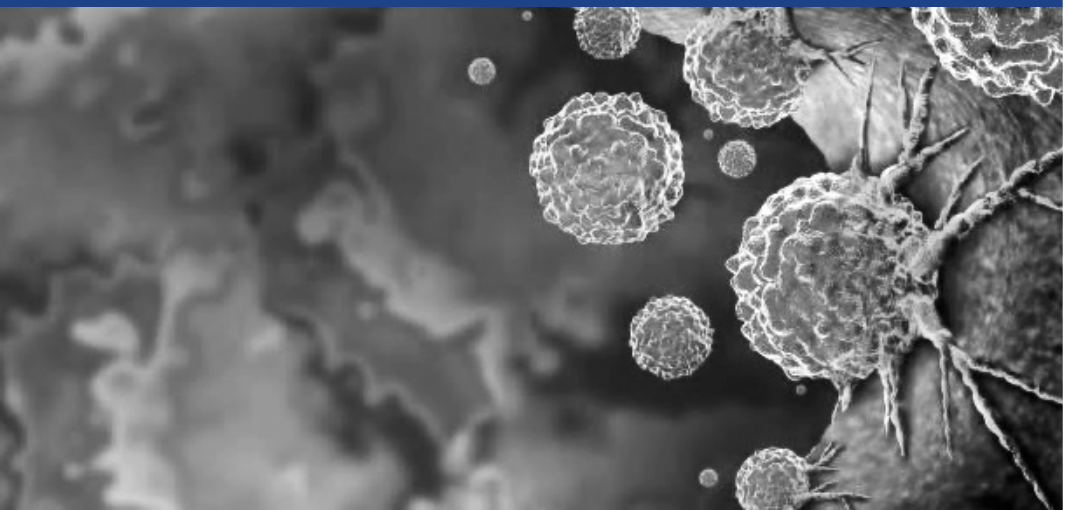


ImmunityBio®



ANKTIVA Synergizes with T Cell Activity of BCG in Both the Naïve and Unresponsive Setting by Activating NK Cells, Interferon Gamma, and Driving Memory CD8+ Killer T Cells

May 2024

Confirmation of the Contribution of Effect of ANKTIVA by a Randomized Control Trial Comparing BCG Alone Versus BCG + ANKTIVA in BCG Naïve NMIBC CIS and Papillary Disease

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Confirmation of the Contribution of Effect of ANKTIVA by a Randomized Control Trial Comparing BCG Alone Versus BCG + ANKTIVA in BCG Naïve NMIBC CIS and Papillary Disease

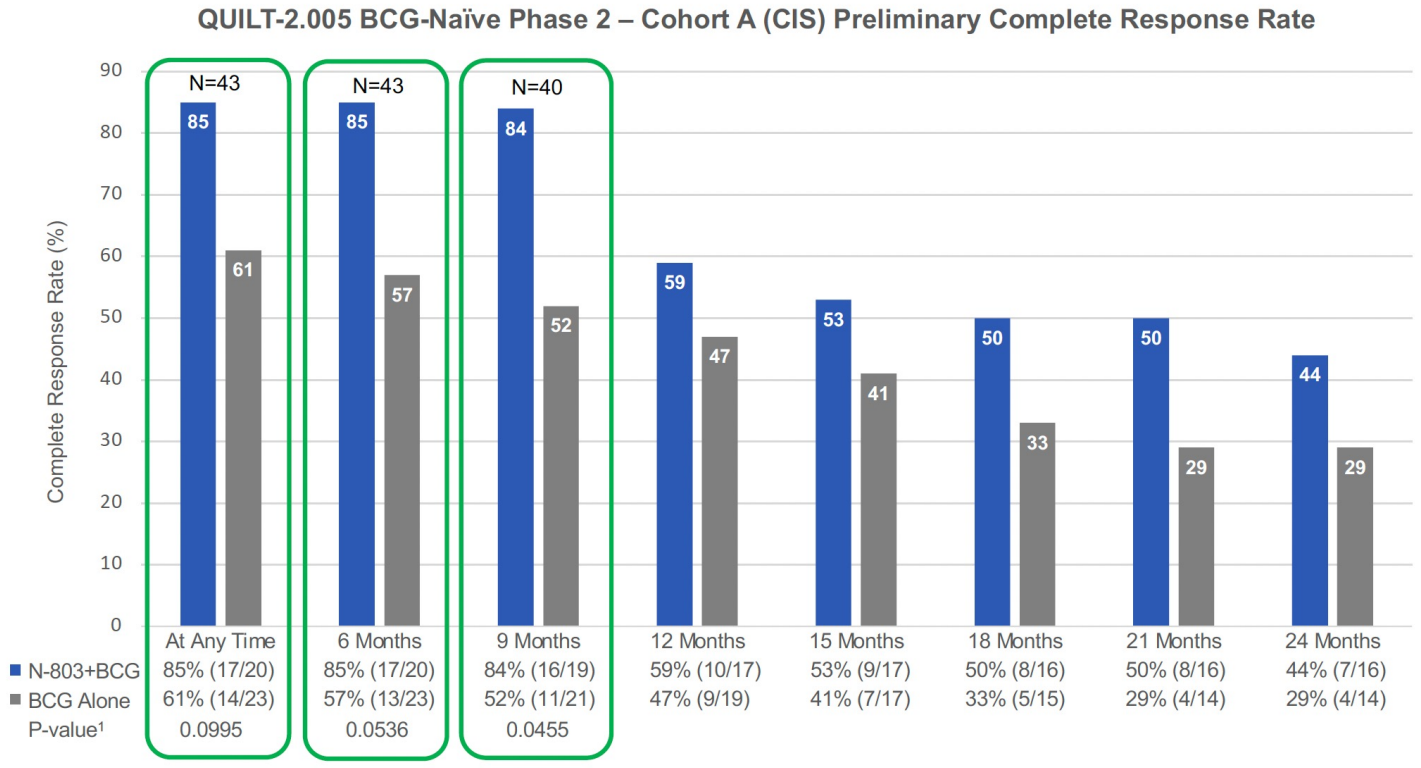
- QUILT 2.005 is a randomized controlled trial examining complete response and disease free status in BCG Naïve NMIBC patients receiving standard of care BCG alone versus BCG plus ANKTIVA.
- Primary endpoints was CR in CIS and disease free status in Papillary with duration of response as secondary endpoints.
- In Oct 2019, to determine that the contribution of effect in enhanced efficacy outcome in CIS and Papillary disease was due to ANKTIVA, the FDA requested that Sponsor unblind the ongoing QUILT 2.005 and perform an interim analysis to confirm that the enhanced effect was based on ANKTIVA and not BCG.
- The data below demonstrates that when ANKTIVA is combined with BCG, the complete response is increased and importantly, even though the numbers of evaluable patients during this interim analysis was n=43, by nine (9) months, statistical significance was achieved when the duration of complete response was compared between BCG alone (52% [11/21] of evaluable patients) versus (84% [16/19] of evaluable patients) P-value 0.0455.

Confirmation of the Contribution of Effect of ANKTIVA by a Randomized Control Trial Comparing BCG Alone Versus BCG + ANKTIVA in BCG Naïve NMIBC CIS and Papillary Disease

- The safety analysis of both QUILT 2.005 and QUILT 3.032 demonstrated no serious adverse events that were not consistent with those seen with BCG alone
- The figure (right) confirms the contribution of effect of ANKTIVA and provides support that combining BCG with ANKTIVA in the Naïve setting results in a clinically meaningful benefit of complete response, duration of complete response without additional adverse events.

Efficacy Results in CIS (QUILT-2.005) Phase 2 (Unplanned Interim Analysis, as Requested by the Agency)

Improvement of CR Rate Over Time and Contribution of Effect of N-803 Inducing Memory T Cells

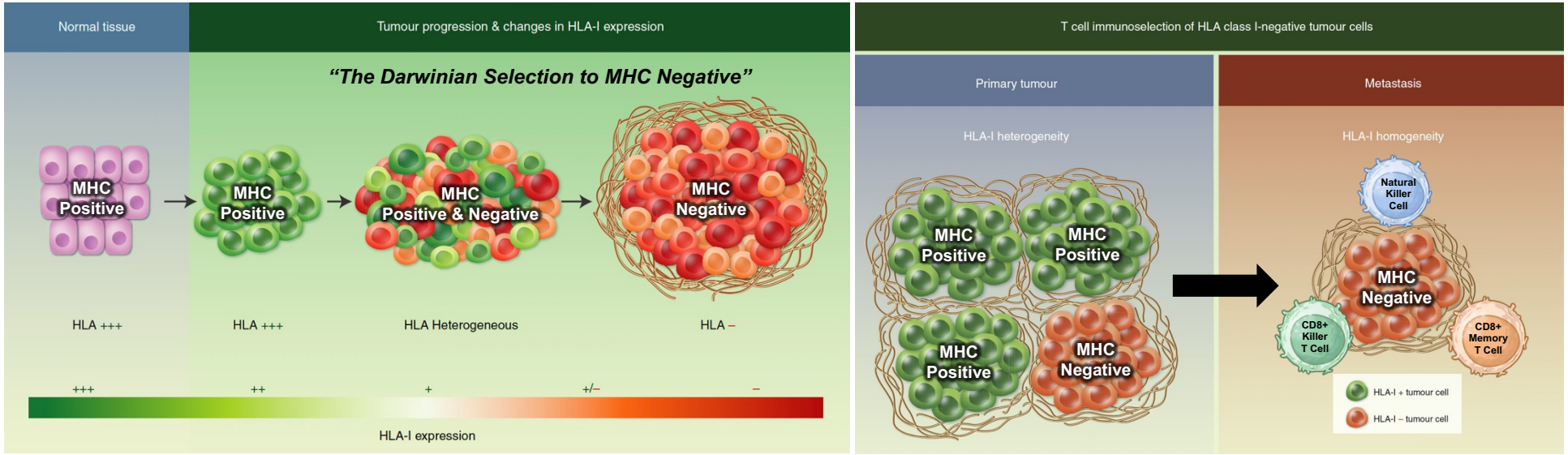


II. Mechanism of Action of ANKTIVA, Activating and Proliferating Natural Killer Cells and Interferon Gamma Which Rescues T Cells in BCG Relapsed NMIBC and Checkpoint Failures: Revealing How NK Cells and Interferon Rescue and Restore Cold Tumors to Hot and Re-Activates Killer and Memory T Cells for All Tumors

ANKTIVA: The Next Generation Immunotherapy Vaccine Beyond T Cells For All MHC-I Negative Tumors

Immunogenic Cell Death by ANKTIVA in the Triangle Offense:
The Three Steps to Transforming the MHCscore From a Cold Tumor (MHC-I Negative) to Hot (MHC-I Positive) and to Rescue Killer T Cells and Memory T Cells with NK

- **Step 1:** Conversion of MHC Negative (Cold) to MHC Positive Tumor (Hot)
- **Step 2:** Activation of IL-15 Receptor in Killer NK and T Cells
- **Step 3:** Proliferation of NK, CD8+ Killer, and CD8+ Memory Cells



Transforming a Cold Tumor (MHC-Negative) to Hot (MHC-Positive) with ANKTIVA for Durable Complete Response

Modified From: Garrido F, Aptsiauri N. Cancer immune escape: MHC expression in primary tumours versus metastases. Immunology. 2019 Dec;158(4):255-266. doi: 10.1111/imm.13114. Epub 2019 Oct 1. PMID: 31509607; PMCID: PMC6856929.

II. Mechanism of Action of ANKTIVA, Activating and Proliferating Natural Killer Cells and Interferon Gamma Which Rescues T Cells in BCG Relapsed NMIBC and Checkpoint Failures: Revealing How NK Cells and Interferon Rescue and Restore Cold Tumors to Hot and Re-Activates Killer and Memory T Cells for All Tumors

- T cell tumor evasion resulting in BCG and checkpoint inhibitor relapse
- Mechanism by which the tumor cells evades CD8+ T cells by retracting MHC-I, rendering the T cell inactive
- Mechanism to restore the T cell ligand (MHC-I) on the tumor cell by interferon gamma (IFN-y)
- Mechanism by which NK cells target MHC-I negative tumor cells
- Mechanism by which NK cells rescue and restore CD8+ killer and memory T cells by IFN-y stimulation
- Activated NK cells, CD8+ killer and memory T cells express IL-15 receptor in order to proliferate
- ANKTIVA (IL-15 Receptor Alpha / IL-15) mimics a dendritic cell and binds to the activated NK, CD8+ killer and memory T cells to drive proliferation and achieve a durable complete response for 47+ months and ongoing
- Introducing the **MHCscore** and the concept of ANKTIVA converting a cold tumor (MHC-Negative) to a hot tumor (MHC-Positive) harnessing the triangle offense of NK, Killer T and Memory T cells:
  - Rescuing T cells with NK cells attacking tumor cells which are MHC-I negative
  - Converting MHC-I negative tumors to MHC-I positive tumors
  - Activating IL-15 receptors on all the killer and memory cells resulting in long-term duration of complete response

ANKTIVA: The Next Generation Immunotherapy Vaccine Beyond T Cells For All MHC-I Negative Tumors

Immunogenic Cell Death by ANKTIVA in the Triangle Offense:
The Three Steps to Transforming the MHCscore From a Cold Tumor (MHC-I Negative) to Hot (MHC-I Positive) and to Rescue Killer T Cells and Memory T Cells with NK

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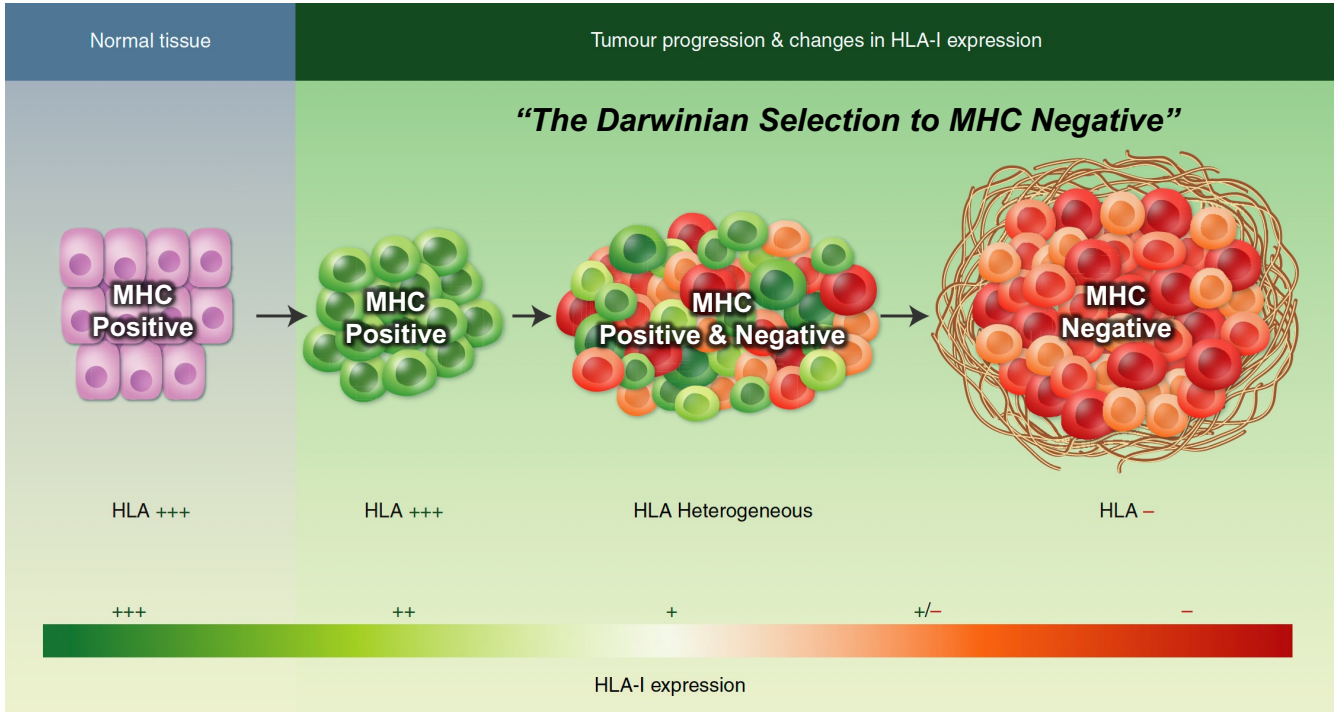

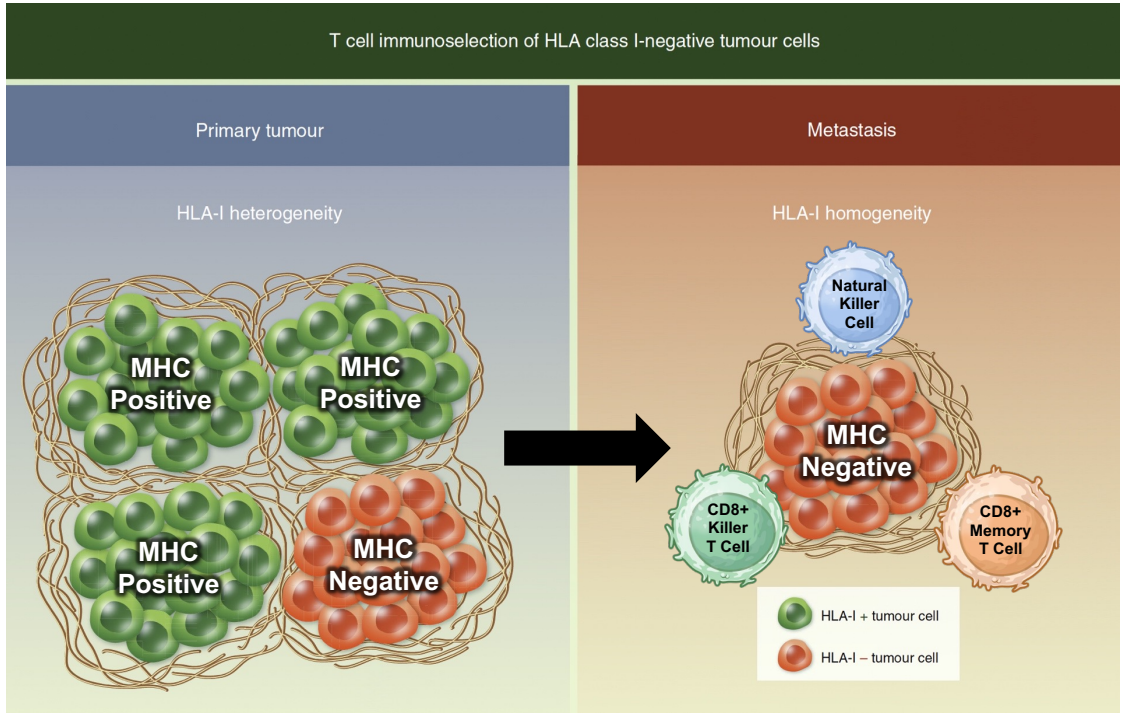

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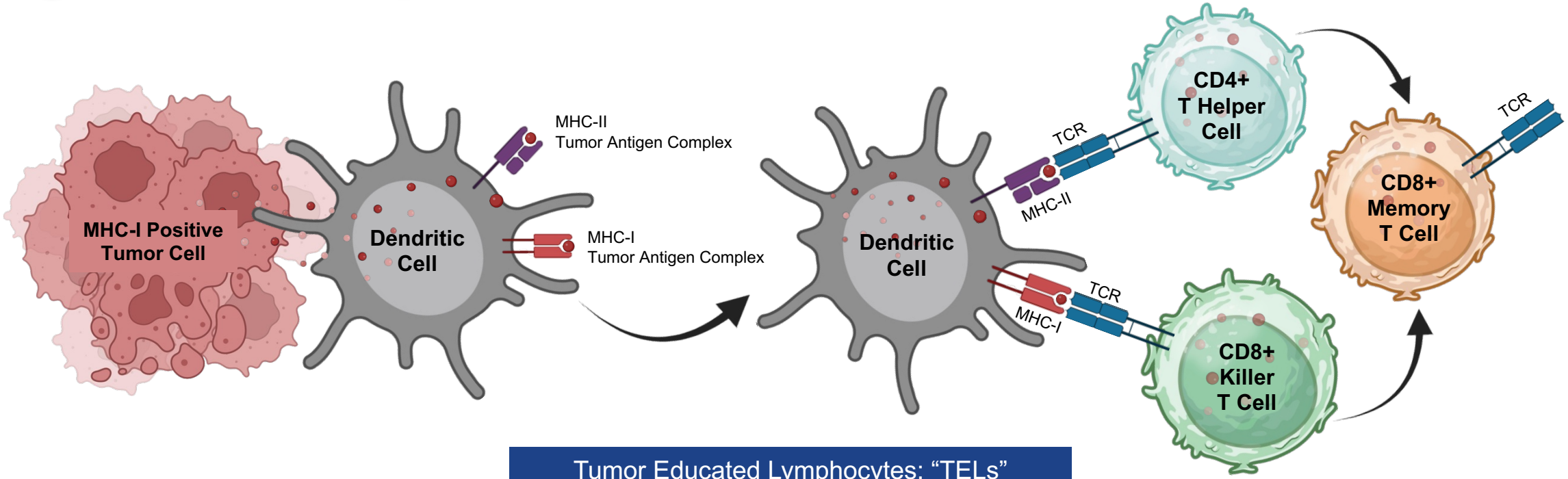
Dendritic Cell Activation of CD8+ Killer & CD8+ Memory T Cells Through MHC-I

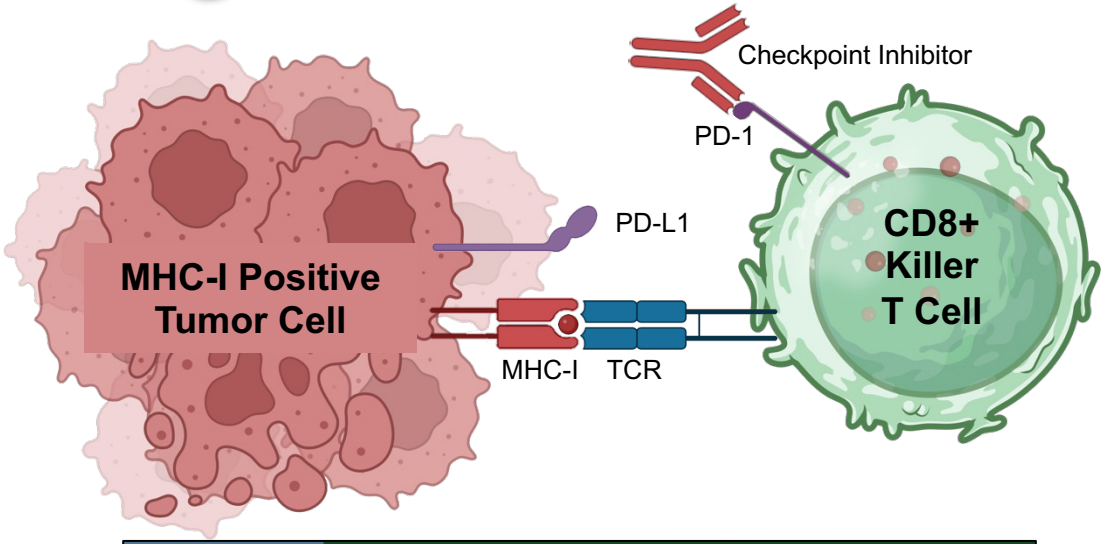
1. Antigen Shedding by Tumor DAMPS
2. Antigen Presentation by Dendritic Cell Generating MHC-I and MHC-II Tumor Antigen Complexes
3. Tumor Specific Education of CD8+ and CD4+ T Cells with Generation of CD8+ Memory T Cell

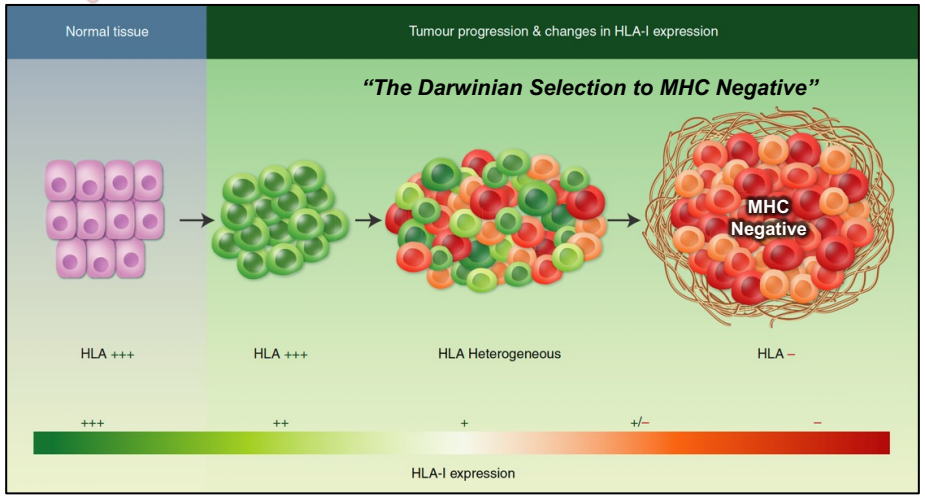


Tumor Educated Lymphocytes: “TELs”

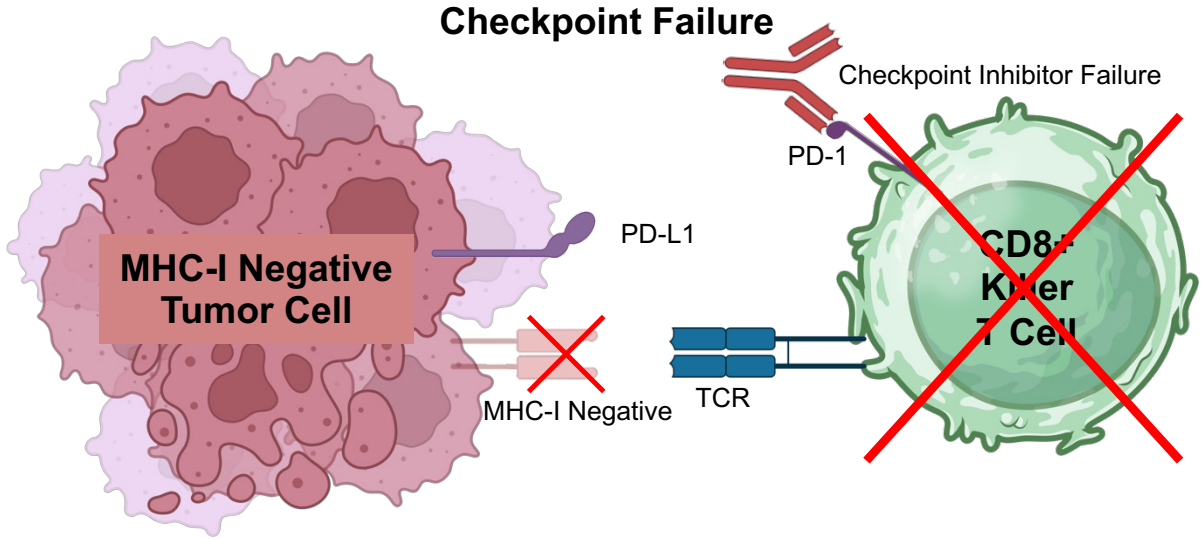
Checkpoint Inhibitor Failure:
Tumor Evasion by MHC-I Positive Converting to MHC-I Negative

4 CD8+ Killer T Cell Cytotoxicity Via MHC-I





5 Tumor Evasion to T Cells: MHC-I Negative and Acquired Resistance to Checkpoint Inhibitors

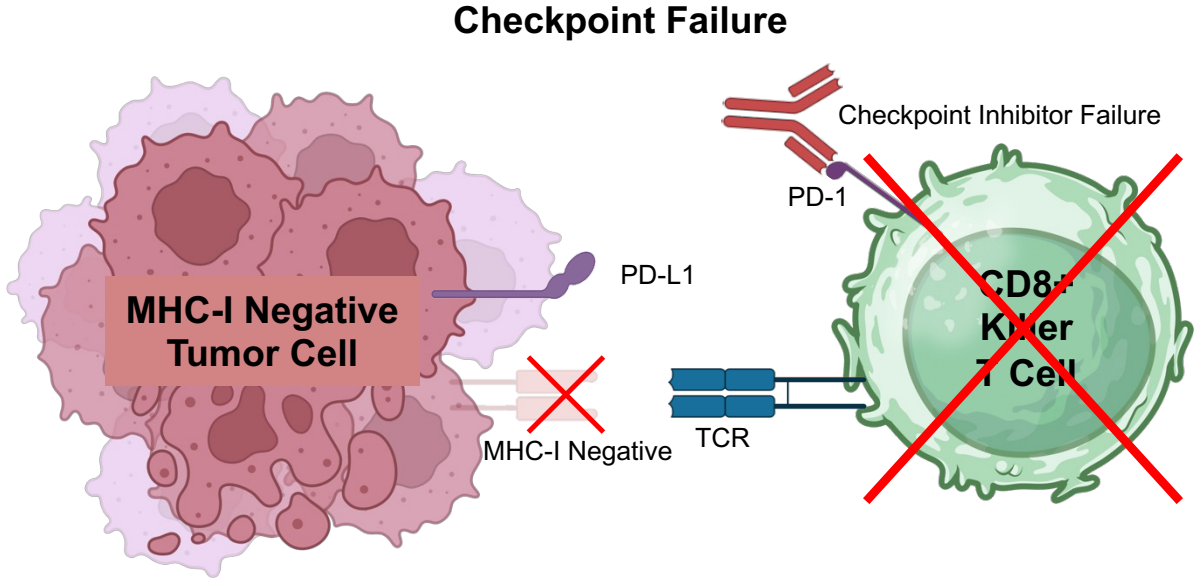


MHC-I Negative as a Universal Target for
All Checkpoint Failures Across all Tumor Types

Standard of Care Overall Survival ~7 Months

MHC-I Negative Tumor Cells Are a Target for Natural Killer Cells Across All MHC-I Negative Tumor Types

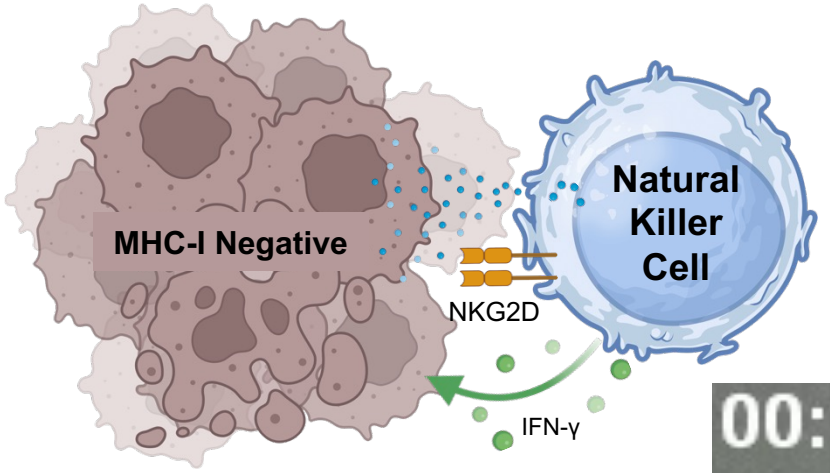
6 Tumor Evasion to T Cells: MHC-I Negative and Acquired Resistance to Checkpoint Inhibitors



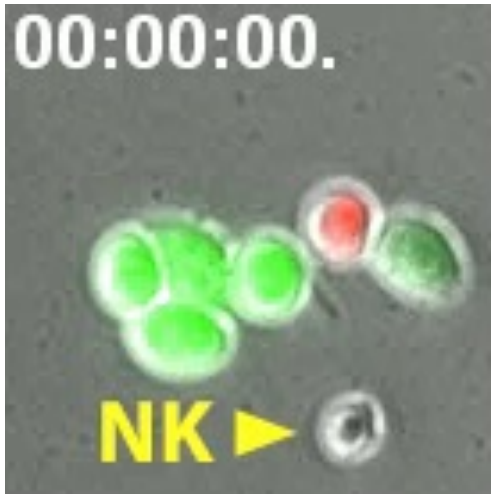
MHC-I Negative as a Universal Target for All Checkpoint Failures Across all Tumor Types

Standard of Care Overall Survival ~7 Months

7 MHC-I Negative Tumor Cell is a Target for Natural Killer Cells (Missing-Self)

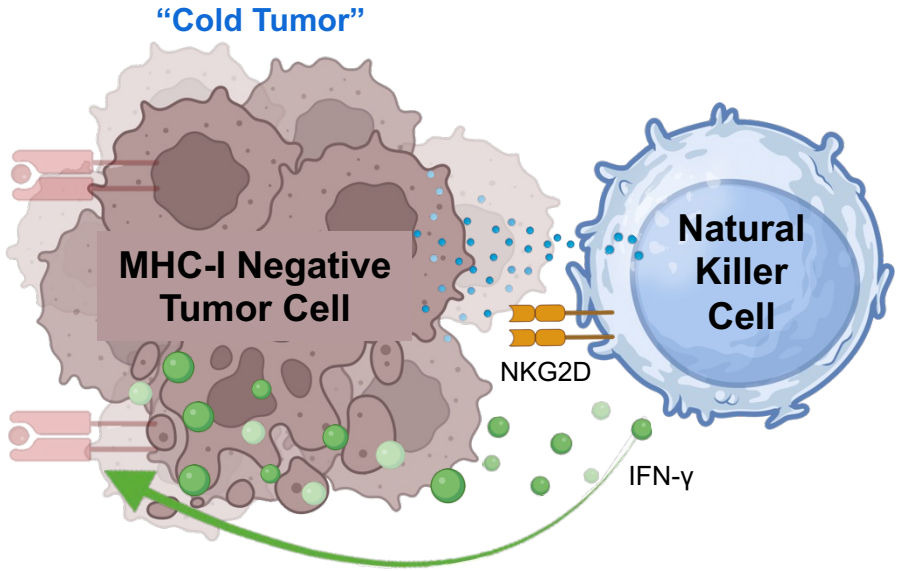


Activation of Natural Killer Cells as a Universal Killer for all MHC-I Negative Cells



Interferon-Gamma (IFN-y) Upregulates MHC-I and Reactivates T Cells Conversion of MHC-I Negative (Cold Tumor) to MHC-I Positive (Hot Tumor)

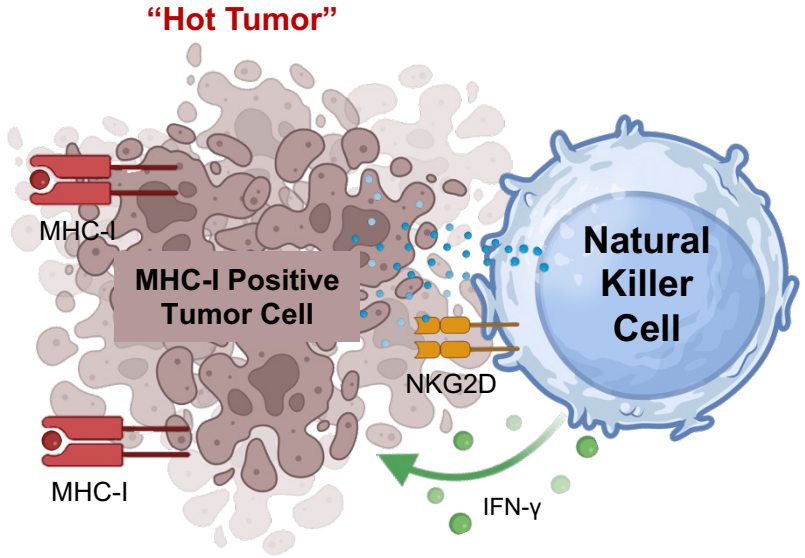
8 Upregulation of MHC-I in Tumor and Rescue of Checkpoint Inhibitors



Natural Killer Cells, a Universal Killer for all MHC-I Negative Tumor Cells.

IFNy Reactivates MHC-I Expression in Tumor Cells

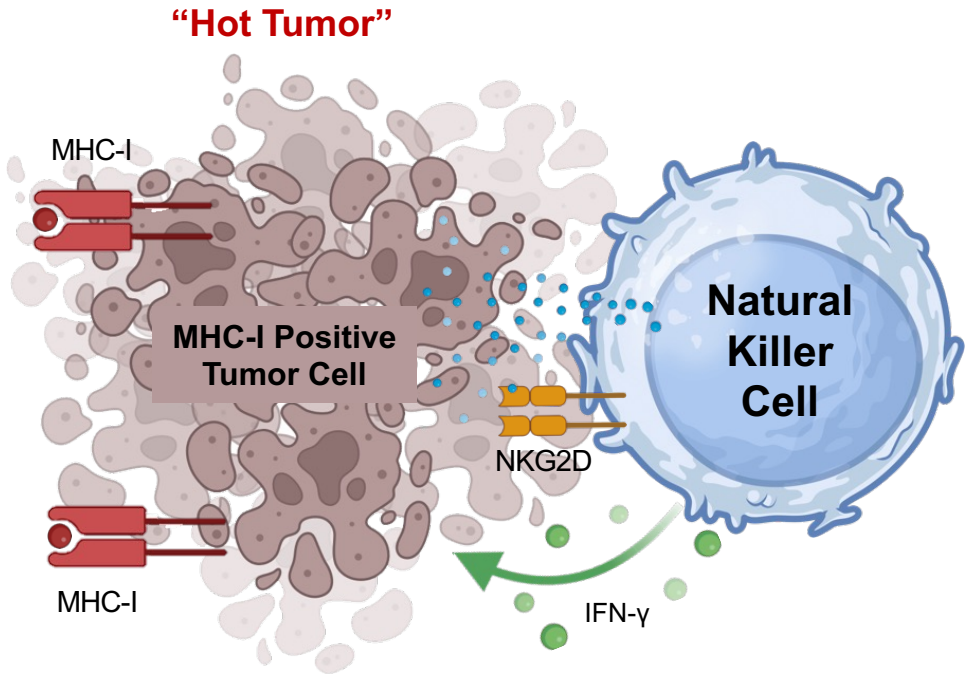
9 Interferon Gamma (IFN-y) Reverses the Darwinian Selection from MHC Negative to MHC Positive



CD8+ Killer T Cell and CD8+ Memory Killer T Cells Re-Engages Tumor with Tumor Specific T Cells

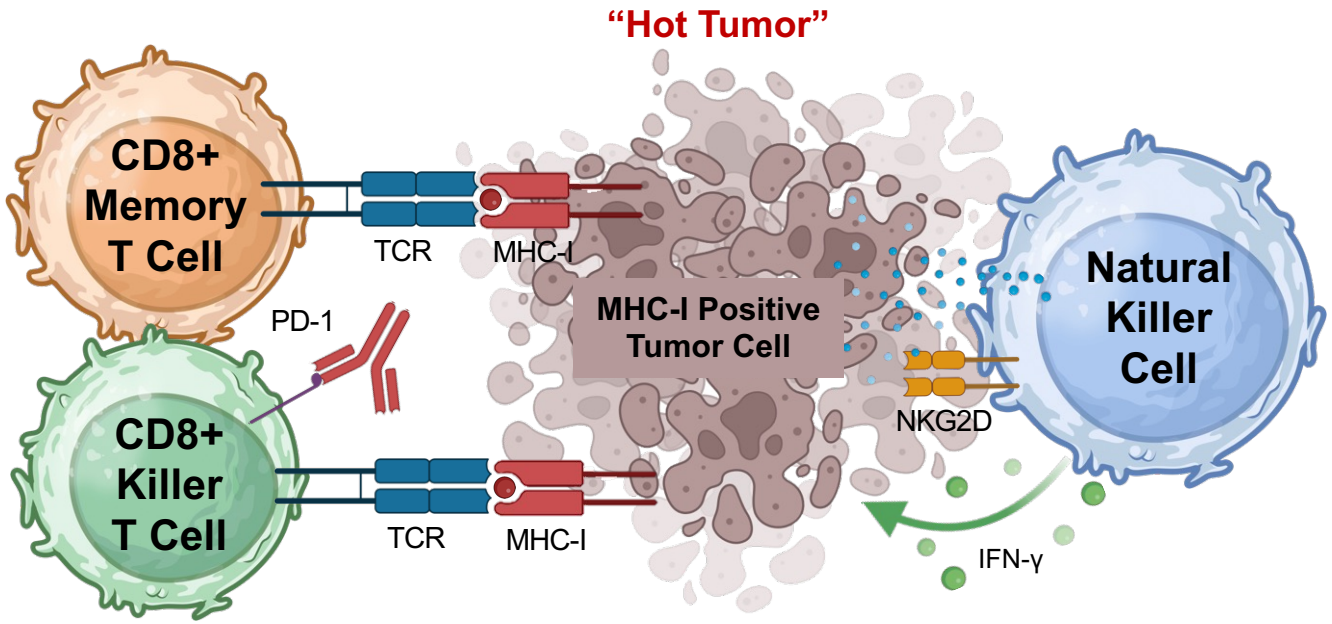
Rescue of Killer T Cells and Checkpoint Inhibitor With Reversal of MHC-I Negative to MHC-I Positive

10 Interferon Gamma (IFN-γ) Reverses the Darwinian Selection from MHC Negative to MHC Positive



CD8+ Killer T Cell and CD8+ Memory Killer T Cells Re-Engages Tumor with Tumor Specific T Cells

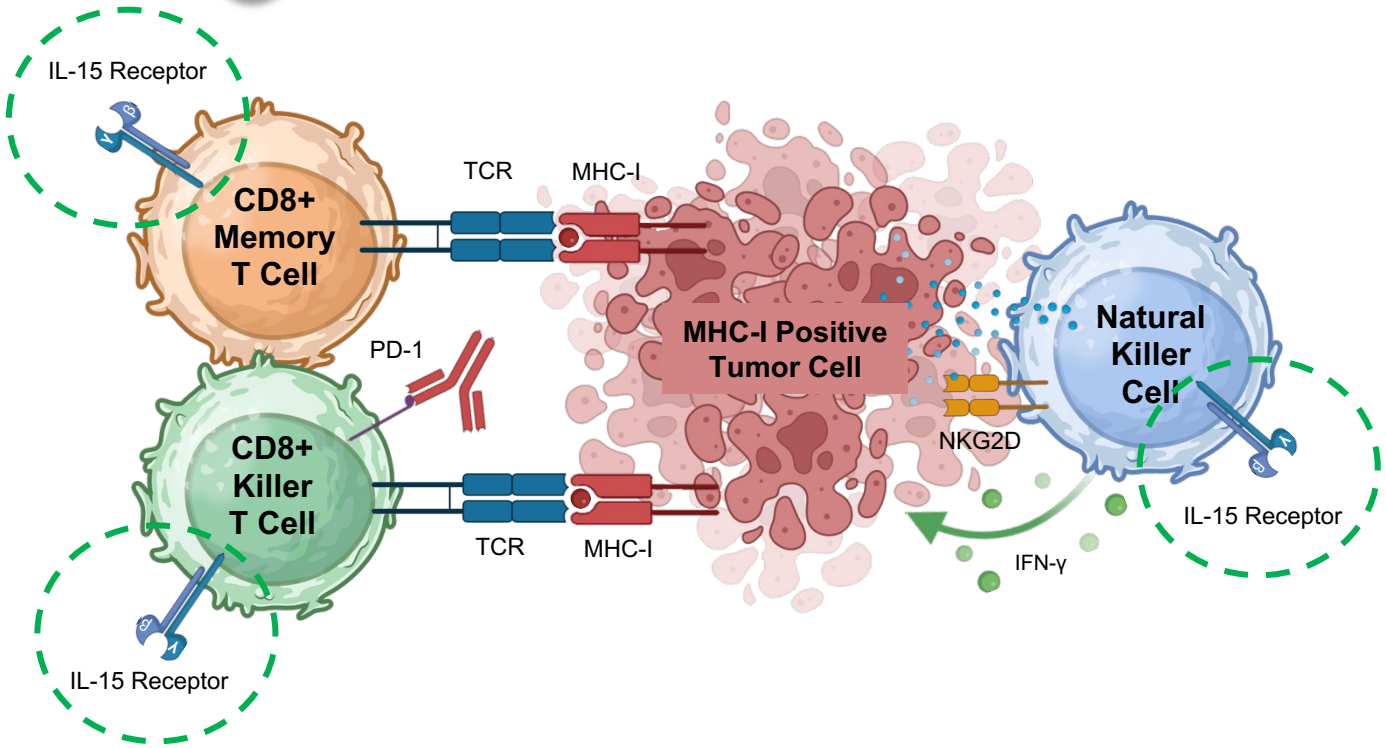
11 CD8+ Killer T Cell and CD8+ Memory T Cell Re-Activated and Checkpoint Inhibitor Rescued



CD8+ Killer T Cell and CD8+ Memory Killer T Cells Re-Engages Tumor with Tumor Specific T Cells

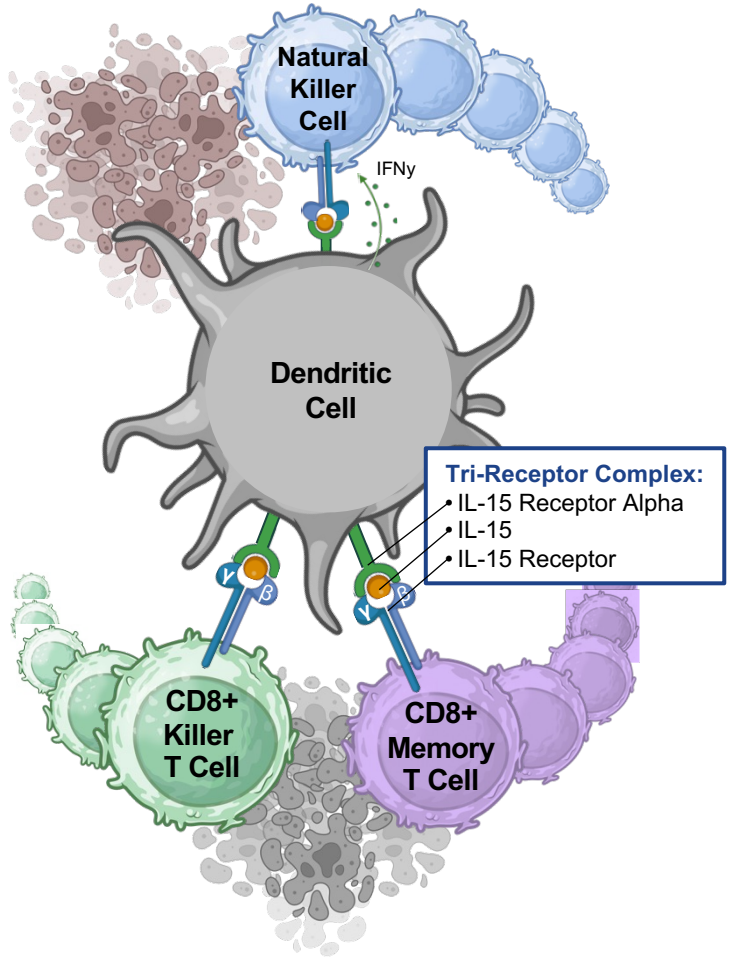
Immune Killer Cells Express IL-15 Receptor to Generate Proliferation by Cell-to-Cell Contact with Dendritic Cells

12 IL-15 Receptor Expression on NK and T Cells



CD8+ T Cells and Natural Killer Cells Express IL-15 Receptor Which Activates and Proliferates Killer T and NK Cells When Bound with IL-15 Receptor Alpha / IL-15 From an Activated Dendritic Cell

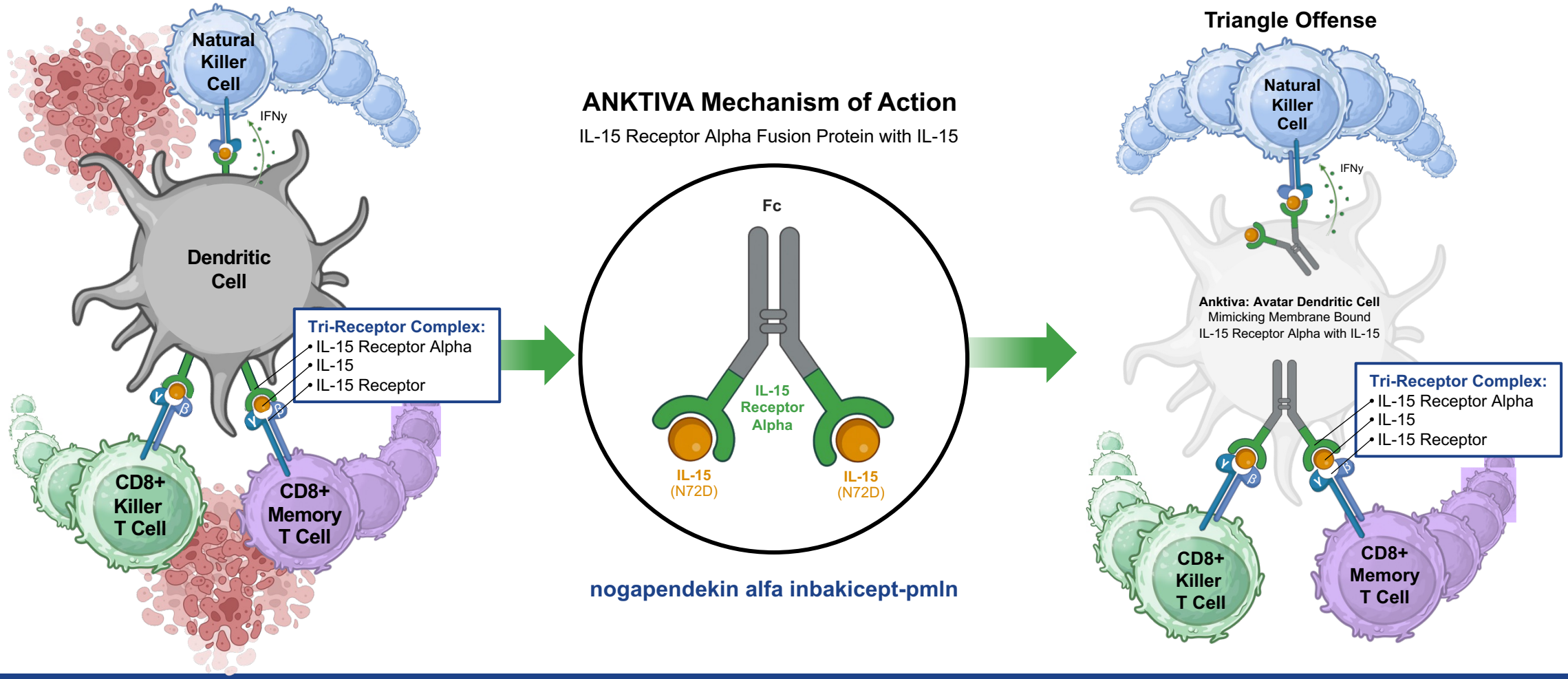
13 IL-15 Receptor Alpha / IL-15 From a Dendritic Cell Proliferates NK Cell and Killer T Cells via IL-15 Receptor



ANKTIVA: IL-15 Receptor Alpha / IL-15 Mimics a Dendritic Cell to Induce Proliferation of Immune Killer Cells

14 IL-15 Receptor Alpha / IL-15 From a Dendritic Cell Proliferates NK Cell and Killer T Cells via IL-15 Receptor

15 ANKTIVA Mechanism of Action Mimicking the Activity of an Activated Dendritic Cell to Proliferate Killer Cells with the Power of IL-15 Receptor Alpha / IL-15



Introducing The **MHCscore** and The Concept of ANKTIVA Converting a Cold Tumor (MHC-Negative) to a Hot Tumor (MHC-Positive) Harnessing The Triangle Offense of NK, Killer T and Memory T Cells:

- Rescuing T cells with NK cells attacking tumor cells which are MHC-I negative
- Converting MHC-I negative tumors to MHC-I positive tumors
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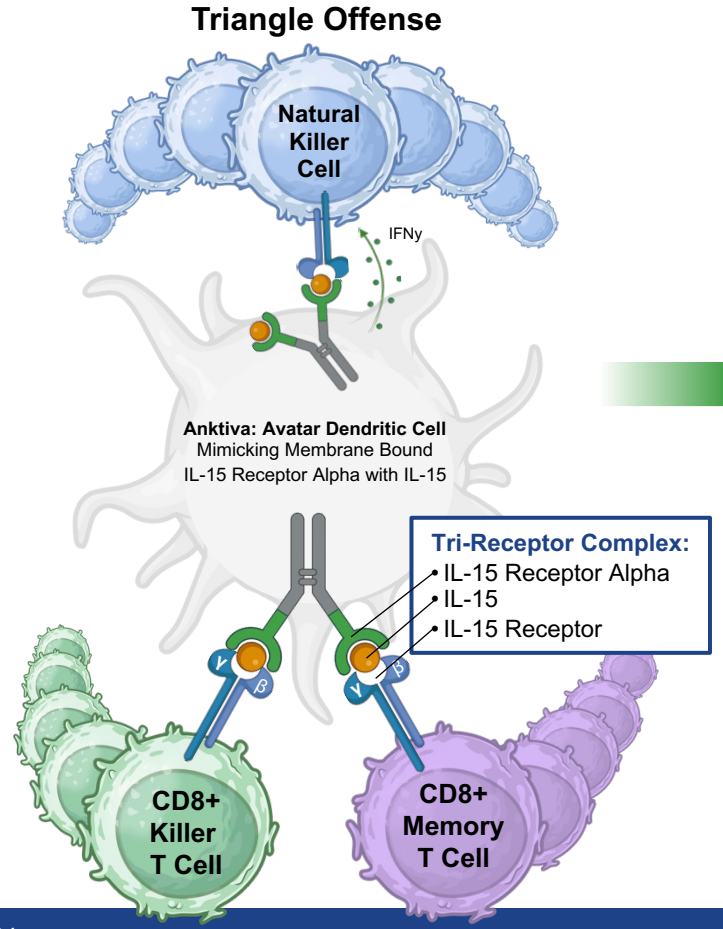
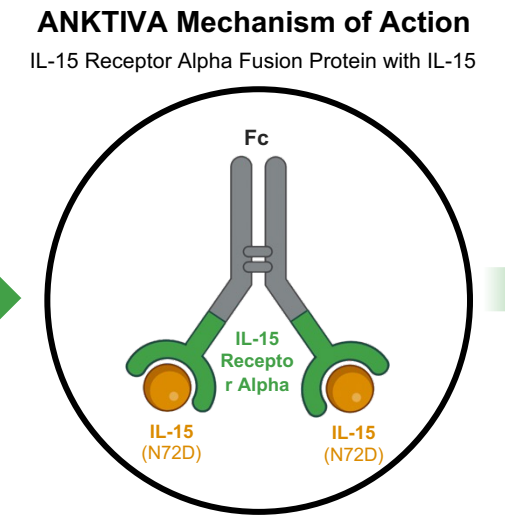
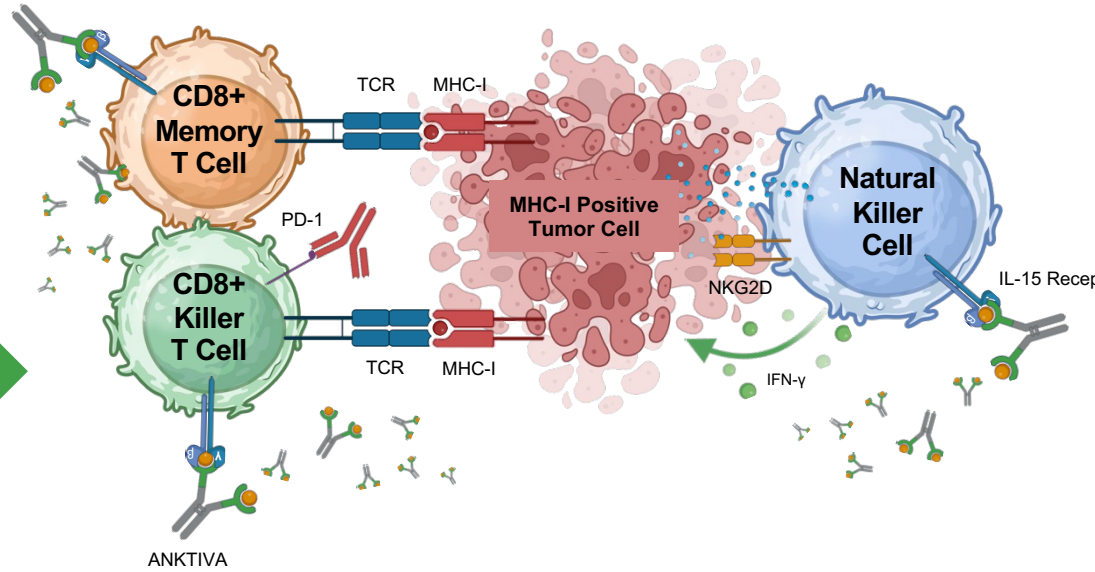




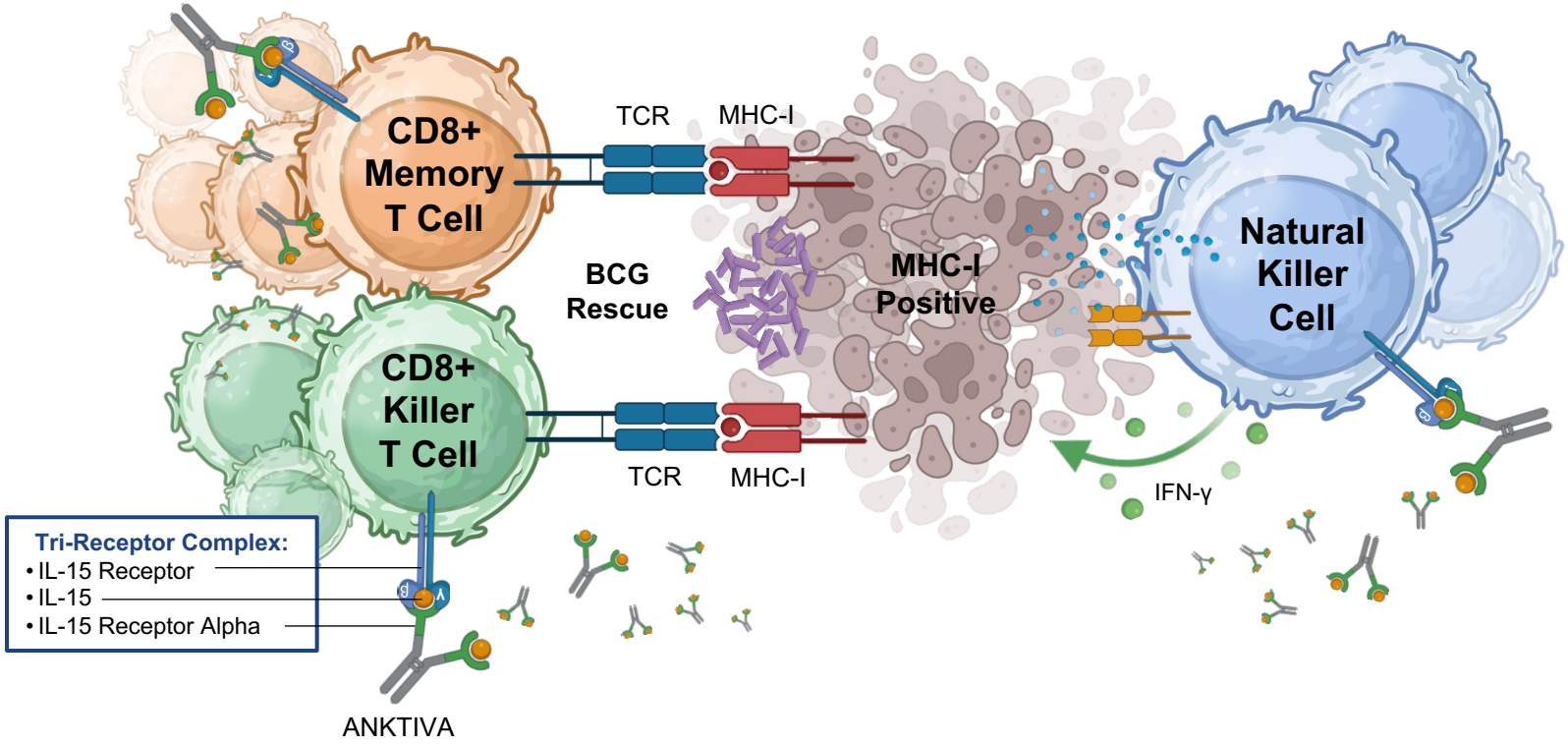
nogapendekin alfa inbakicept-pmln

17 Activation by ANKTIVA (IL-15 Receptor Alpha / IL-15) of CD8+ Killer T Cells, CD8+ Memory T Cells, and Natural Killer Cells



IL-15 Receptor Alpha / IL-15 of ANKTIVA Binds to IL-15 Receptor and Proliferates CD8+ T Cells and Natural Killer Cells

ANKTIVA: Rescue of BCG and T Cells in NMIBC



Immunogenic Cell Death by ANKTIVA in the Triangle Offense: The Three Steps to Transforming the MHCscore™

- **Step 1:** Conversion of MHC Negative (Cold) to MHC Positive Tumor (Hot)
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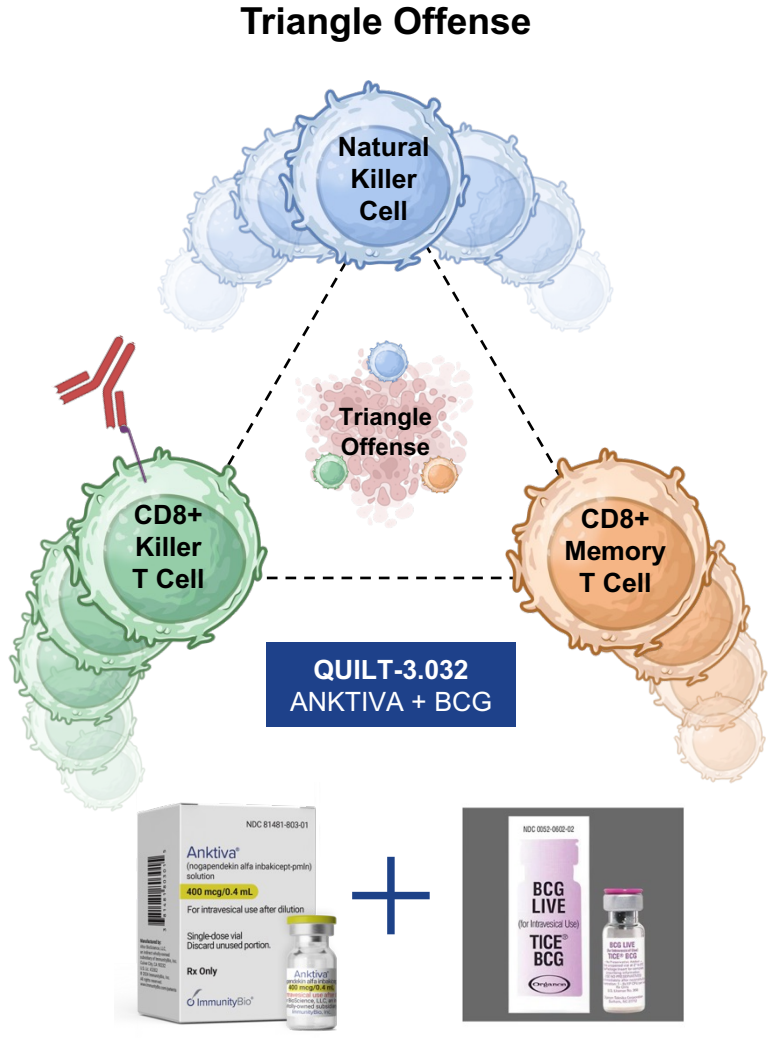

Long Term, Cancer Free Overall Survival
BCG Unresponsive in NMIBC: 47+ Months and Ongoing

I. Confirmation of the Contribution of Effect of ANKTIVA by a Randomized Control Trial Comparing BCG Alone Versus BCG + ANKTIVA in BCG Naïve NMIBC CIS and Papillary Disease

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QUILT-2.005: Phase I Complete Response Data in CIS and Papillary BCG Naïve Disease

ONCOIMMUNOLOGY
2021, VOL. 10, NO. 1, e1912885 (7 pages)
https://doi.org/10.1080/2162402X.2021.1912885

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ORIGINAL RESEARCH

OPEN ACCESS Check for updates

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
Revised 31 March 2021
Accepted 31 March 2021

KEYWORDS
Non-muscle invasive bladder cancer; IL15; BCG

Complete Response in CIS and Papillary BCG Naïve NMIBC Patients with Duration of Complete Response and Disease Free in 9 out of 9 (100%) at Time of Publication with Follow-Up for 6 Years After Treatment

ONCOIMMUNOLOGY
2021, VOL. 10, NO. 1, e1912885 (7 pages)
https://doi.org/10.1080/2162402X.2021.1912885

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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

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KEYWORDS
Non-muscle invasive bladder cancer; IL15; BCG

Dose (intravesicular instillation)	Patient	CIS Papillary	Response Assessments							
			W12	6M	9M	12M	15M	18M	21M	24M
100 µg	1	Pap T1	NR	NR	NR	NR	NR	NR	NR	NR
	2	Pap Ta	NR	NR	NR	NR	NR	ND	NR	NR
	3	Pap T1	NR	NR	NR	NR	NR	NR	NR	NR
200 µg	4	Pap T1	IC	NR	NR	NR	NR	ND	NR	NR
	5	CIS	No CR	IC	IC	CR	CR	CR	CR	CR
	6	Pap T1	NR	NR	NR	NR	NR	NR	NR	NR
400 µg	7	Pap T1	NR	NR	NR	NR	NR	NR	NR	NR
	8	CIS	CR	CR	CR	CR	CR	CR	CR	CR
	9	Pap Ta	NR	NR	NR	NR	NR	NR	NR	NR

NR = no recurrence, ND = not done, IC = Inconclusive

>6 Year Follow-Up

I. Confirmation of the Contribution of Effect of ANKTIVA by a Randomized Control Trial Comparing BCG Alone Versus BCG + ANKTIVA in BCG Naïve NMIBC CIS and Papillary Disease

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QUILT 205: Long Term Follow-Up Beyond 6 Years in 6 out of 9 Evaluable Patients

QUILT 205 Findings

- 6 out of 9 were evaluable in 2023
- 2 subjects died of natural causes independent of bladder cancer
- 1 lost to follow up
- Quality of life high in all 6 subjects
- All 6 out of 6 (100%) remain in complete response (CIS) or disease free (Papillary) for >8.5 years
- All 6 patients avoided cystectomy for >8.5 years

Dose (intravesicular instillation)	Patient	CIS Papillary	Response Assessments							
			W12	6M	9M	12M	15M	18M	21M	24M
100 µg	1	Pap T1	NR	NR	NR	NR	NR	NR	NR	NR
	2	Pap Ta	NR	NR	NR	NR	NR	ND	NR	NR
	3	Pap T1	NR	NR	NR	NR	NR	NR	NR	NR
200 µg	4	Pap T1	IC	NR	NR	NR	NR	ND	NR	NR
	5	CIS	No CR	IC	IC	CR	CR	CR	CR	CR
	6	Pap T1	NR	NR	NR	NR	NR	NR	NR	NR
400 µg	7	Pap T1	NR	NR	NR	NR	NR	NR	NR	NR
	8	CIS	CR	CR	CR	CR	CR	CR	CR	CR
	9	Pap Ta	NR	NR	NR	NR	NR	NR	NR	NR

NR = no recurrence, ND = not done, IC = Inconclusive

9 Year Follow-Up

Conclusion: ANKTIVA + BCG in BCG Naïve Patients Results in Durable Complete Response with Quality of Life and Adverse Events Consistent with BCG Alone

I. Confirmation of the Contribution of Effect of ANKTIVA by a Randomized Control Trial Comparing BCG Alone Versus BCG + ANKTIVA in BCG Naïve NMIBC CIS and Papillary Disease

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QUILT-2.005: Randomized Control Pivotal Trial of BCG versus BCG + ANKTIVA in BCG Naïve NMIBC CIS & Papillary: FDA Request Interim Analysis

Oct 2019, the FDA requested a interim analysis of QUILT-2.005 to confirm contribution of effect of ANKTIVA

Efficacy Results in CIS (QUILT-2.005) Phase 1 and Phase 2 (Unplanned Interim Analysis, as Requested by the Agency) October 2019

3.1. Efficacy in Patients with BCG-Naïve NMIBC

3.1.1. Phase 1b BCG-Naïve NMIBC (QUILT-2.005)

Appendix 4 show the study design and summary of patient response data during the 24 months of the first phase of QUILT 2.005 (refer to IND 121,976, sequence 0039, dated 14 May 2019, for the full QUILT-2.005 Phase 1b Clinical Study Report).

3.1.2. Phase 2 BCG-Naïve CIS (QUILT-2.005)

While efficacy data collection is ongoing, preliminary response data for patients with CIS is shown in Appendix 5. The preliminary evaluation was an unplanned interim analysis in response to FDA's request during review of ImmunityBio's Preliminary Breakthrough Therapy Designation Advice submission (IND 121,976, sequence 0035, dated 25 March 2019) and does not include papillary data as time to recurrence analyses have not yet been conducted.

In this phase, 85% of assessable patients with CIS treated in the combination arm have a CR compared to 57% in the BCG arm at month 6. At every time point of evaluation (6, 9, 12, 15, 18, 21, and 24 months), the CR rate in the CIS population of assessable patients is markedly higher in the N-803 plus BCG combination arm compared to BCG alone. Moreover, in addition to the increased response rate seen at each time point, the durability of response is longer when N-803 is administered in combination with BCG.

The preliminary data in the BCG-naïve CIS population provides supporting evidence that N-803 enhances the immune activity of local BCG, thereby increasing overall tumor clearance.

N-803 — ImmunityBio, Inc.
Request for Breakthrough Therapy Designation – NMIBC CIS

REQUEST FOR BREAKTHROUGH THERAPY DESIGNATION

For

N-803 in Combination with Bacillus Calmette-Guérin (BCG) for the Treatment of Patients with Non-muscle Invasive Bladder Cancer (NMIBC) Carcinoma in Situ (CIS)

Product Name:	N-803 (also known as ALT-803, a recombinant human agonist interleukin-15 (IL-15) fusion complex; INN *nogapendekin alfa inbakicept*) is the "working name" of the drug under investigation. N-803 has also been referred to as IL-15N72D:IL-15RuSu/IgG1 Fc complex. A trade name for commercial distribution has not been selected.
Proposed Indication:	In combination with Bacillus Calmette-Guérin (BCG) for the treatment of patients with non-muscle invasive bladder cancer (NMIBC) carcinoma in situ (CIS).
Contact Person (Name, Address, email, telephone and fax):	Melissa Luras, Director, Regulatory Affairs Melissa.Luras@ImmunityBio.com Phone: 310-633-3123 Fax: 310-853-7408 9920 Jefferson Blvd, Culver City, CA 90232
Submitted to:	Food and Drug Administration Center for Drug Evaluation and Research Office of Hematology and Oncology Products Division of Oncology Product 1 (DOP1)
IND Number:	121,976

Submitted October 4, 2019

Complete Response Rate and Durability of Response in Evaluable Patients with CIS BCG Naïve NMIBC Receiving ANKTIVA + BCG

These data provide evidence that the addition of N-803 to BCG increases initial CR rate and the durability of response for BCG-naïve patients with CIS. Furthermore, treatment was well tolerated by all patients in the phase 1b study, and well tolerated and balanced between treatments arms in the phase 2.

Table 4: Response Data in NMIBC Patients with BCG-Naïve CIS (N-803 + BCG Arm)

Time point	Evaluable Patients (Phase 1b & 2)	Complete Response Rate	95% Confidence Interval
At any time	n = 22	86% (19 / 22)	65%, 97%
6 Months[a]	n = 22	82% (18 / 22)	60%, 95%
12 Months	n = 19	63% (12 / 19)	38%, 84%

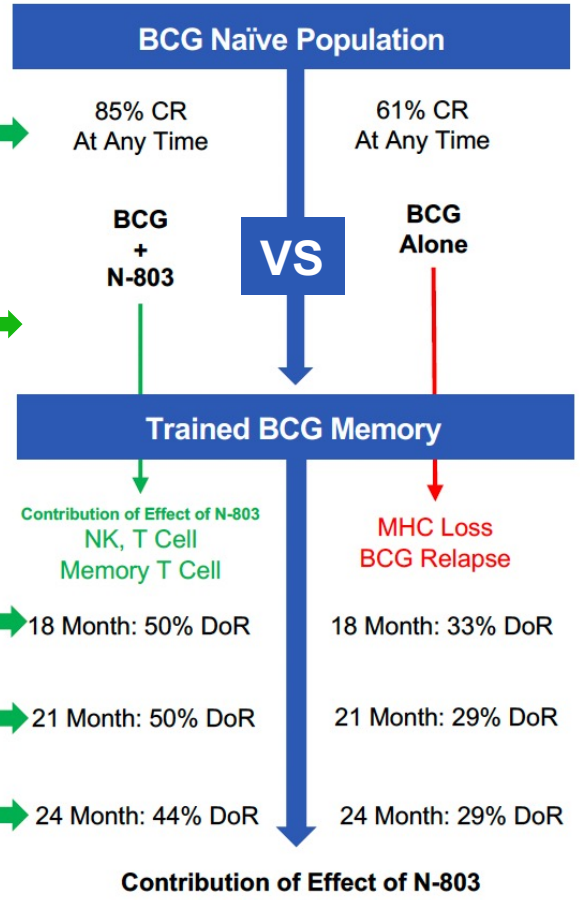
[a] Patients who had an absent or inconclusive assessment and had a CR at 3 or 9 months are assigned CR at 6 months.

Data Submitted to the FDA at Their Request of Interim Analysis of BCG Naïve Subjects, Demonstrating Statistical Significant Difference in Duration of Response by 9 Months for ANKTIVA + BCG versus BCG Alone

APPENDIX 5. QUILT-2.005 PHASE 2 PRELIMINARY EFFICACY DATA PATIENTS WITH BCG-NAÏVE CIS WITH OR WITHOUT PAPILLARY DISEASE

Table 11: QUILT 2.005 BCG-Naïve Phase 2 Preliminary Efficacy Data

Time point	Arm	Subjects with a CR	Evaluable Subjects	% of all Evaluable Subjects
At any time	N-803+BCG	17	20	85
	BCG	14	23	61
6 months	N-803+BCG	17	20	85
	BCG	13	23	57
9 months	N-803+BCG	16	19	84
	BCG	11	21	52
12 months	N-803+BCG	10	17	59
	BCG	9	19	47
15 months	N-803+BCG	9	17	53
	BCG	7	17	41
18 months	N-803+BCG	8	16	50
	BCG	5	15	33
21 months	N-803+BCG	8	16	50
	BCG	4	14	29
24 months	N-803+BCG	7	16	44
	BCG	4	14	29



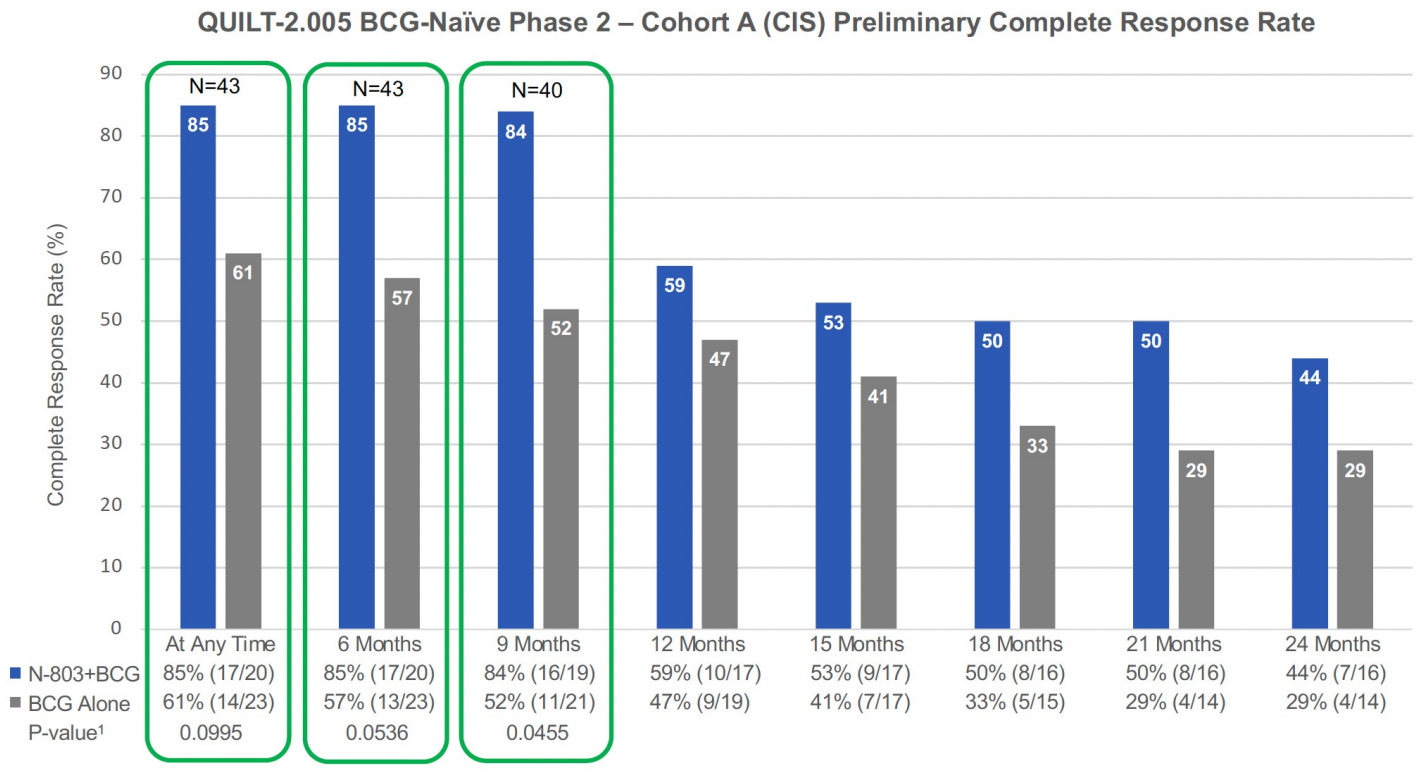
★ P Value 0.0455

Randomized Control Data Demonstrating the Clinical Meaningful Benefit and Contribution of Effect of ANKTIVA + BCG in BCG Naïve CIS and Papillary NMIBC

- The safety analysis of both QUILT 2.005 and QUILT 3.032 demonstrated no serious adverse events that were not consistent with those seen with BCG alone
- Complete response rate of 85% with BCG and ANKTIVA versus 61% at any time
- Duration of response statistically significant at 9 months at 84% versus 52%
- Continued trend of long duration of response at 12, 15, 18, 21 and 24 months when ANKTIVA is combined with BCG

Efficacy Results in CIS (QUILT-2.005) Phase 2 (Unplanned Interim Analysis, as Requested by the Agency)

Improvement of CR Rate Over Time and Contribution of Effect of N-803 Inducing Memory T Cells



I. Confirmation of the Contribution of Effect of ANKTIVA by a Randomized Control Trial Comparing BCG Alone Versus BCG + ANKTIVA in BCG Naïve NMIBC CIS and Papillary Disease

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ANKTIVA Label

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ANKTIVA safely and effectively. See full prescribing information for ANKTIVA.

ANKTIVA® (nogapendekin alfa inbakicept-pmln) solution, for intravesical use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
ANKTIVA is an interleukin-15 (IL-15) receptor agonist indicated with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG-unresponsive nonmuscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors. (1)

----------DOSAGE AND ADMINISTRATION----------
For Intravesical Use Only

- For induction: 400 mcg administered intravesically with BCG once a week for 6 weeks. A second induction course may be administered if complete response is not achieved at month 3. (2.1)
- For maintenance: 400 mcg administered intravesically with BCG once a week for 3 weeks at months 4, 7, 10, 13 and 19. For patients with an ongoing complete response at month 25 and later, additional maintenance instillations with BCG may be administered once a week for 3 weeks at months 25, 31, and 37. (2.1)
- Instill intravesically only after dilution. Total time from vial puncture to the completion of the intravesical instillation should not exceed 2 hours. (2.2)

See full Prescribing Information for dilution and administration instructions.

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Delaying cystectomy can lead to the development of metastatic bladder cancer, which can be lethal. (5.1)

----------ADVERSE REACTIONS----------
The most common (≥15%) adverse reactions, including laboratory test abnormalities, are increased creatinine, dysuria, hematuria, urinary frequency, micturition urgency, urinary tract infection, increased potassium, musculoskeletal pain, chills and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Altor BioScience, LLC, an indirect wholly-owned subsidiary of ImmunityBio, Inc. at toll-free phone 877-265-8482 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2024

Recommended Duration of Treatment: 37 Months

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

For Intravesical Use Only. Do NOT administer by subcutaneous or intravenous or intramuscular routes.

- For induction: ANKTIVA is recommended at a dose of 400 mcg administered intravesically with BCG once a week for 6 weeks. A second induction course may be administered if complete response is not achieved at month 3.
- For maintenance: After BCG and ANKTIVA induction therapy, ANKTIVA is recommended at a dose of 400 mcg administered intravesically with BCG once a week for 3 weeks at months 4, 7, 10, 13 and 19 (for a total of 15 doses). For patients with an ongoing complete response at month 25 and later, maintenance instillations with BCG may be administered once a week for 3 weeks at months 25, 31, and 37 for a maximum of 9 additional instillations.

The recommended duration of treatment is until disease persistence after second induction, disease recurrence or progression, unacceptable toxicity, or a maximum of 37 months.

No Change in Urology Workflow

2.2 Preparation and Administration

Preparation of Agent

See BCG Prescribing Information for information on preparation and handling of BCG.

- ✓ One Day Delivery
- ✓ 24 Month Shelf Life
- ✓ No Special Freezers
- ✓ No Special Cleaning Agents
- ✓ No Change in BCG Workflow
- ✓ Same Order Flow as BCG

ANKTIVA Mechanism of Action
Activation and Proliferation of NK, CD4+, CD8+ Killer & Memory T Cells, Without Proliferation of Immuno-Suppressive T Regulatory Cells

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nogapendekin alfa inbakicept-pmln is an IL-15 receptor agonist. IL-15 signals through a heterotrimeric receptor that is composed of the common gamma chain (γc) subunit, the beta chain (βc) subunit, and the IL-15-specific alpha subunit, IL-15 receptor α. IL-15 is *trans*-presented by the IL-15 receptor α to the shared IL-2/IL-15 receptor (βc and γc) on the surface of $CD4^+$ and $CD8^+$ T cells and NK cells.

Binding of nogapendekin alfa inbakicept-pmln to its receptor results in proliferation and activation of NK, $CD8^+$, and memory T cells without proliferation of immuno-suppressive Treg cells. In vivo, intravesicular nogapendekin alfa inbakicept-pmln alone or in combination with BCG showed anti-tumor activity when compared to BCG alone, in a carcinogen-induced model of bladder cancer in immunocompetent rats.

ANKTIVA Efficacy Results with Duration of Response 47+ Months and Ongoing

Table 3: Efficacy Results in QUILT-3.032

	ANKTIVA with BCG (n=77)
Complete Response Rate (95% CI)	62% (51, 73)
Duration of Response[a]	
Range in months	0.0, 47.0+
% (n) with duration ≥ 12 months	58% (28)
% (n) with duration ≥ 24 months	40% (19)

+ Denotes ongoing response

[a] Based on 48 patients that achieved a complete response at any time; reflects period from the time complete response was achieved.

I. Confirmation of the Contribution of Effect of ANKTIVA by a Randomized Control Trial Comparing BCG Alone Versus BCG + ANKTIVA in BCG Naïve NMIBC CIS and Papillary Disease

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Safety Comparable to BCG Alone

Table 1 summarizes the adverse reactions in Cohort A of QUILT-3.032.

Table 1 Adverse Reactions Occurring in ≥15% of Patients in Cohort A in QUILT-3.032

Adverse Reaction	ANKTIVA with BCG (n=88)	
	All Grades %	Grades 3 or 4 %
Dysuria	32	0
Hematuria[1]	32	3.4
Urinary Frequency	27	0
Micturition Urgency[1]	25	0
Urinary Tract Infection[1]	24	2.3
Musculoskeletal Pain[1]	17	2.3
Chills	15	0
Pyrexia	15	0

[1] Includes other related terms

Clinically relevant adverse reactions in <15% of patients who received ANKTIVA with BCG included fatigue (14%), nausea (14%), bladder irritation (11%), diarrhea (9%), and nocturia (7%).