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## Nektar is Leading the Development of Cytokine-Based Therapies

#### Oncology



### **BEMPEG (Preferential IL-2 Pathway Agonist)**

Prime, Proliferate, Activate & Increase Tumor-Infiltrating Lymphocytes (TILs), Increase PD-1 expression

**Immune Activation** 



#### **NKTR-255 (IL-15 Receptor Agonist)**

Stimulate and expand NK Cells & Promote survival and expansion of memory CD8+ T cells

**Immune Stimulation** 

#### **Immunology**



### NKTR-358 (IL-2 Pathway Conjugate)

A conjugated IL-2 agonist biased for T regulatory cell expansion

Immune Regulation

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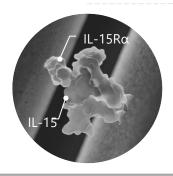
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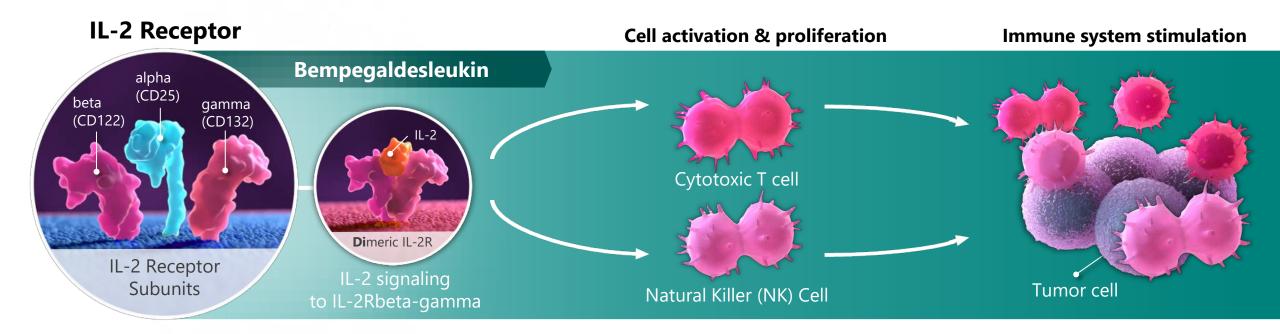
## IL-2 Pathway: Validated Pathway in Melanoma and Renal Cell Carcinoma

- High-dose (HD) interleukin-2 (IL-2) associated with complete responses (CRs)
  - CRs with IL-2 durable for decades without further therapy with complete responders being classified as "cures"
- ► HD IL-2 usage limited by receptor functionality and high dosing required
- Severe toxicities allowed HD IL-2 to be used in only a small population of patients
- Our goal was to create a new IL-2 molecule that solves the historical problems with IL-2

HD IL-2<sup>1</sup> in Melanoma (Approved 1998)

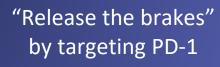
HD IL-2<sup>1</sup> in RCC (Approved 1992)

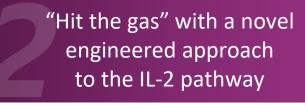
## Capturing the Potential of the IL-2 Pathway in Immuno-Oncology: Bempegaldesleukin Designed to Overcome Limitations of IL-2

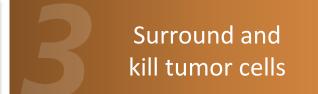


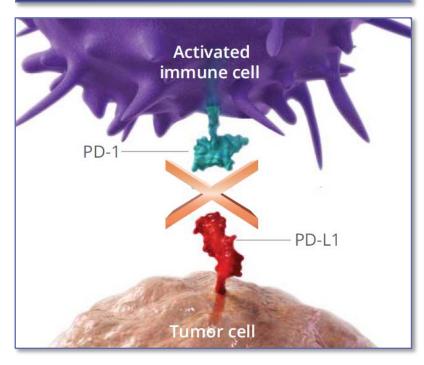
- Preferentially signals IL-2Rbeta-gamma complex to stimulate cytotoxic T cells
- Leverages native IL-2 sequence with no amino acid substitutions
- Retains some transient binding to the alpha receptor to enhance priming in lymph nodes
- Prodrug design and receptor bias eliminate over-activation of IL-2 pathway
- Achieves antibody-like dosing schedule in outpatient setting

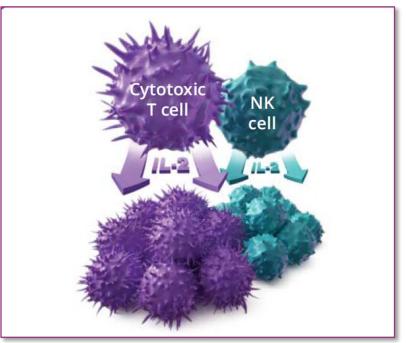
# Combining an IL-2 Mechanism with Checkpoint Inhibition: Release the Brakes, Hit the Gas

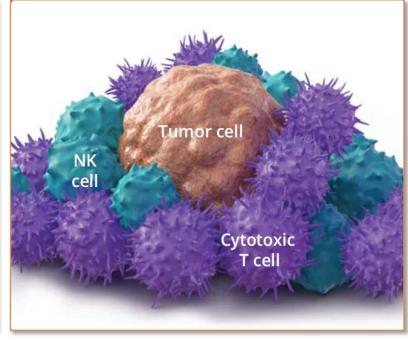




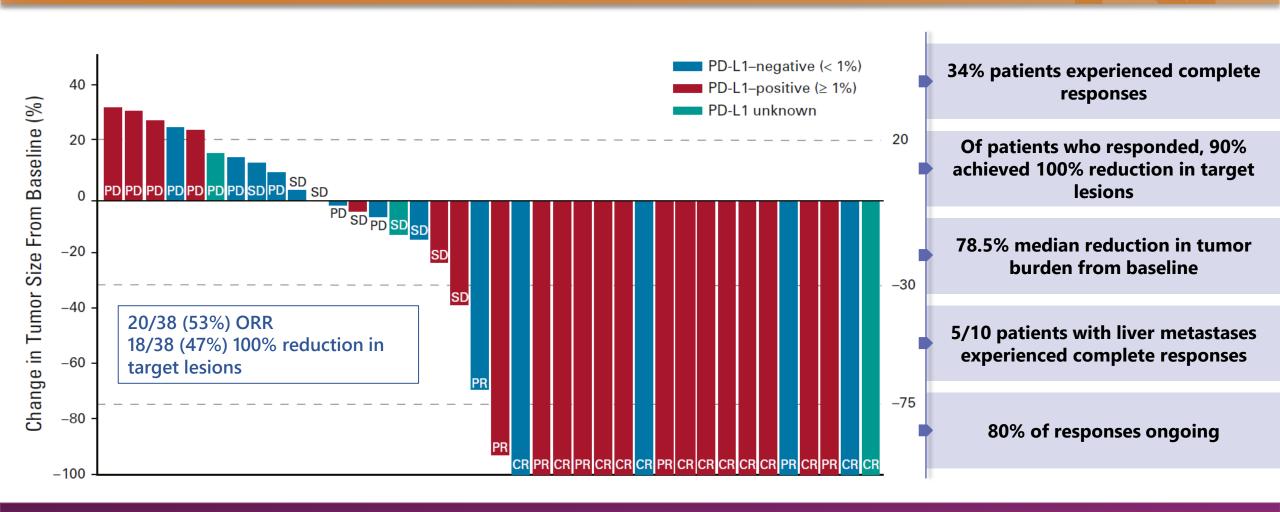








# BEMPEG plus NIVO in Patients with Stage IV 1L Melanoma: Best Overall Response by Independent Radiology

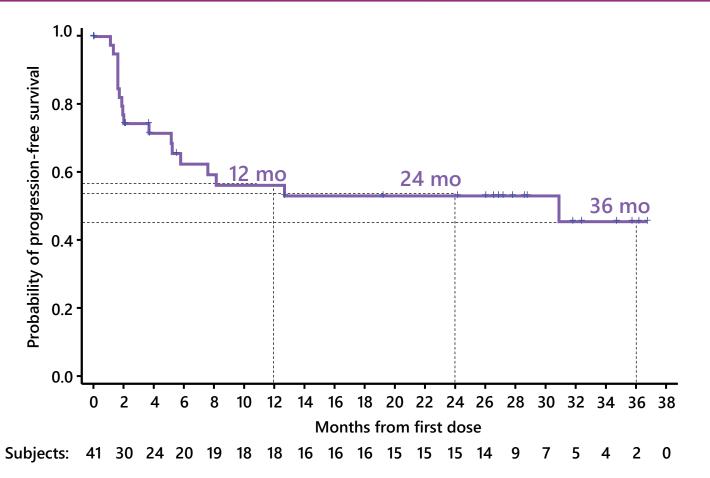


Data led to BEMPEG plus NIVO receiving Breakthrough Therapy Designation from FDA

# BEMPEG plus NIVO Demonstrated mPFS 30.9 Months in Stage IV 1L Melanoma

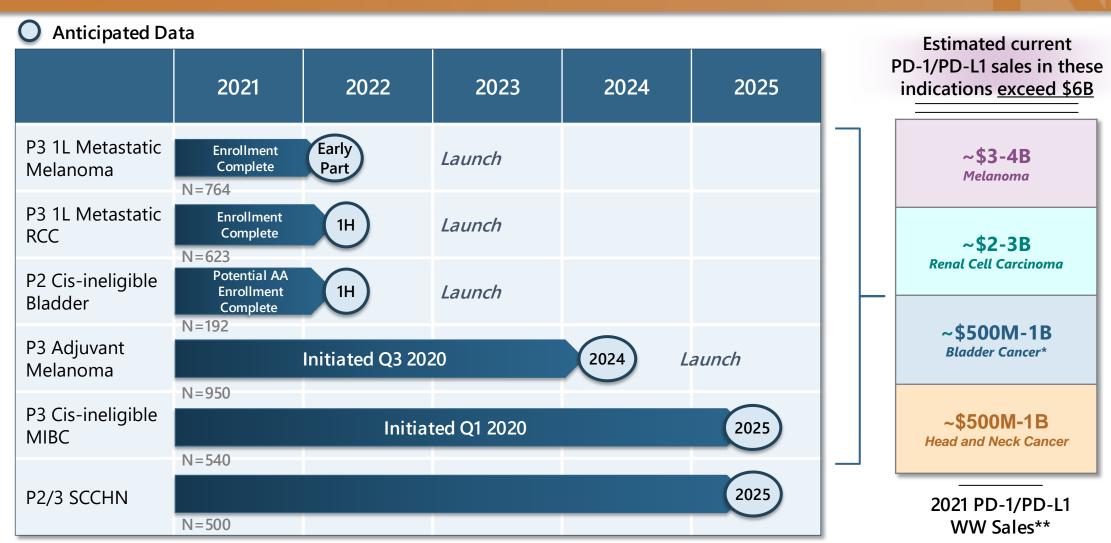
#### Median PFS 30.9 months

(95% CI: 5.3; NE)



Phase 3 Comparator						
Historical Ra	Median PFS					
Nivolumab Monotherapy	(CM-067)	6.9 months				
	(RELATIVITY-047)	4.6 months				
I-O Doublet						
Historical Rates Median PFS						
Ipilimumab+Niv	11.5 months					
Relatlimab+Niv	10.1 months					

## BEMPEG Poised for Multiple Potential Approvals in 2023-2025



**AA: Accelerated Approval** 

<sup>\*</sup>Bladder cancer sales WW represent indications of Muscle invasive bladder cancer and Metastatic Bladder Cancer (first-line and second-line across PD-L1 groups) as there are no approvals in 1L low PD-L1 expressing populations

<sup>\*\*</sup>Source for 2021 PD-1/PD-L1 (Opdivo, Keytruda, Tecentriq, Imfinzi, Bavencio) WW Sales: Evaluate Pharma. Represents sales ranges across all lines of therapy

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**Immune Stimulation** 

#### **Immunology**

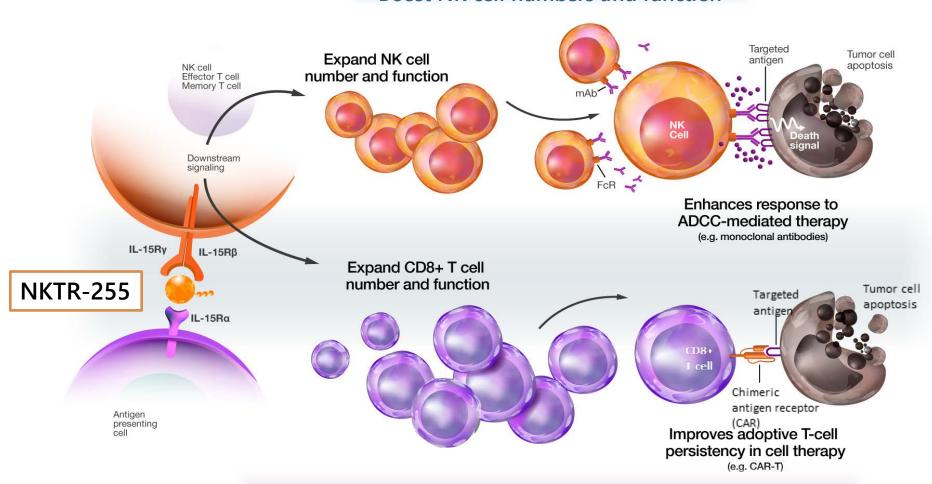


### **NKTR-358 (IL-2 Pathway Conjugate)**

A conjugated IL-2 agonist biased for T regulatory cell expansion

## NKTR-255 Designed to Boost Natural Killer Cells and Expand CD8+ T-cells

#### Boost NK cell numbers and function



#### **Enhancement of ADCC Antibodies**

Daratumumab **Rituximab** Cetuximab Potential to combine with any targeted antibody that utilizes an ADCC MOA

#### **Enhancement of CAR-T Regimens**

CD19 CAR-T **BCMA CAR-T** CD38 CAR-T Potential to expand into other hematological and solid tumor CAR-T and cellular therapies

Increase duration of response for CAR-T and cellular therapies

# NKTR-255 Clinical Program Captures Opportunity to Enhance NK-Mediated Mechanisms in Liquid and Solid Tumor Settings

	Program	Phase	Indication	Partner
Tumors	NKTR-255 + Rituxan°	Phase 1/2 Ongoing	R/R Non-Hodgkin's Lymphoma NCT04136756	
. Liquid	NKTR-255 + DARZALEX Faspro® (daratumumab and hyaluronidase-fihj) Injection for subcutaneous use   1,800mg/30,000units	Phase 1/2 Ongoing	R/R Multiple Myeloma NCT04136756	janssen <b>T</b>
Tumors	NKTR-255 + ERBITUX	Phase 1/2 Ongoing	R/R Colorectal Cancer R/R Head and Neck Squamous Cell Carcinoma NCT04616196	
Solid	NKTR-255 + BAVENCIO® avelumab lnjection avelumab 20 mg/mL	Phase 2 Planned	Bladder Cancer Planned Start 1H22	MERCK Pfizer

# Clinical Data Demonstrate that NKTR-255 Provides IL-15 Pathway Activation in Liquid and Solid Tumors

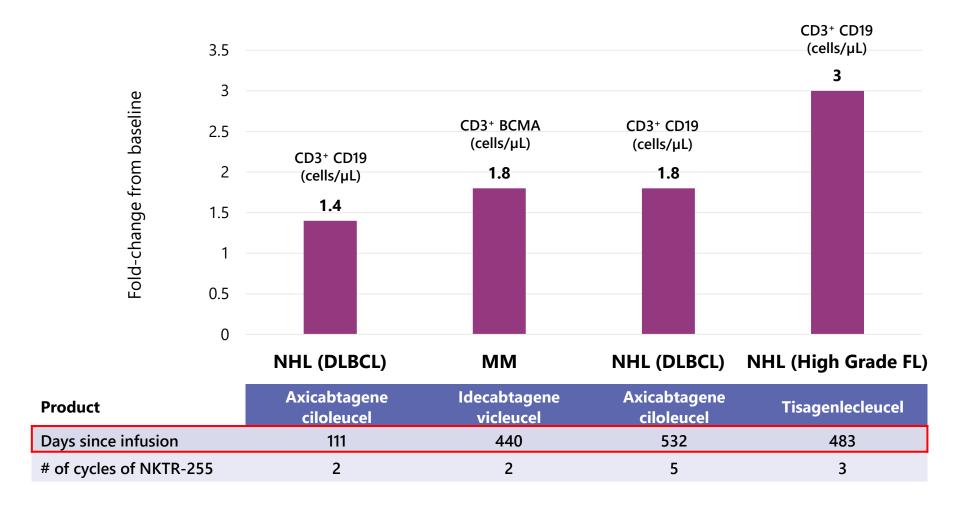
#### NKTR-255 is designed to capture the full IL-15 pathway to increase NK cells and cytotoxic function

	Liquid Tumor	Solid Tumor
<u>Parameter</u>	(NKTR-255-02)	(NKTR-255-03)
Route of Administration*	IV, q3wk	IV, q3wk
Antibody-Like Dosing Pharmacokinetics: IV t <sub>1/2</sub> (hr)	27-48 hr (ASH 2020)	27.8 hr (SITC 2020)
NK cell expansion	Yes, 8-fold (ASH 2020)	Yes, 9-fold (SITC 2020)
NK cell proliferation	<b>Yes</b> (ASH 2020)	<b>Yes</b> (SITC 2020)
CD8 T cell expansion	Yes, 2-fold (ASH 2020)	Yes, 3-fold (SITC 2020)
CD8 T cell proliferation	<b>Yes</b> (ASH 2020)	<b>Yes</b> (SITC 2020)
Upregulation of activation markers (HLA-DR, CD107a, NKp30, and Granzyme B) on NK cells	Yes (not yet publicly presented)	<b>Yes</b> (SITC 2020)

#### **Additional Messages:**

- Consistent level of NK and CD8 cell expansion and proliferation in multiple tumor types (NHL, MM, CRC, SCCHN)
- NK and CD8 cell elevations observed even in MM patients with compromised bone marrow
- Optimized PK/PD profile for both monotherapy and in combination with targeted antibodies

## ASH 2021: NKTR-255 Monotherapy Increased CAR-T Cell Levels in Patients Greater than 1 Year Past CAR-T Infusion



All patients had achieved a partial or complete response to prior CAR-T therapy. Pharmacodynamic data were analyzed for patients with measurable CAR-T cells at baseline; fold change was calculated as treatment with NKTR-255 over baseline (baseline=1); CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

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Source: ASH 2021

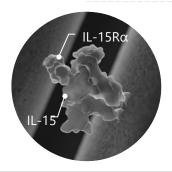
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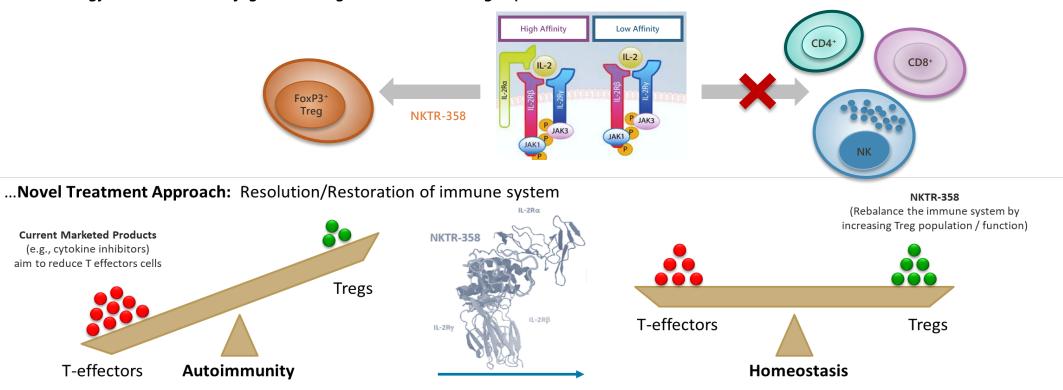
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Immune Regulation

## NKTR-358: Novel Biology & Novel Treatment Approach for Treatment of Auto-Immune Disorders

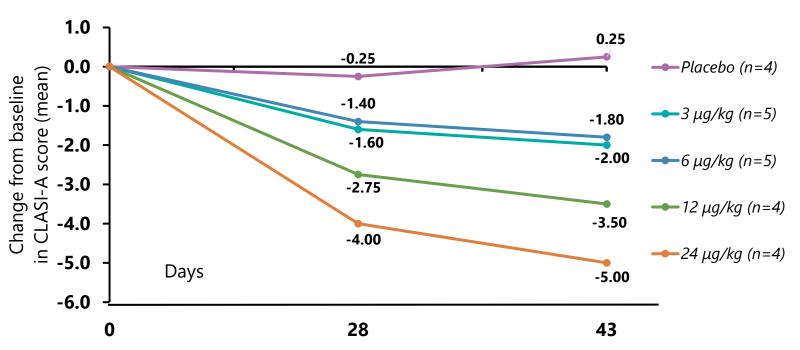
Novel biology: NKTR-358, a conjugated IL-2 agonist biased for Treg expansion, affords a...



Differential expression of high and low affinity IL-2 receptors allows IL-2 to regulate both pro-inflammatory T-effector cells and anti-inflammatory Treg cells. NKTR-358 is a stable pegylated IL-2 conjugate composition that preferentially stimulates expansion of Tregs with minimal effects on T-effectors.

# NKTR-358 Demonstrated a Dose-Dependent Reduction in CLASI-A Score in Patients with Mild Lupus

## Mean Change in CLASI-A Score Patients [N=22] with a CLASI-A score of ≥4 at baseline\*



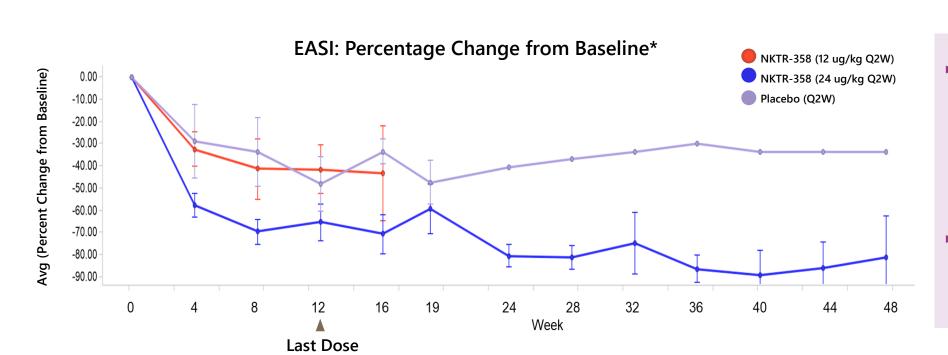
CLASI-A, cutaneous lupus erythematosus disease area and severity index-activity.

- 7 of 18 patients had a
   ≥4-point reduction in CLASI-A
   score from baseline by Day 43
- One patient (24 µg/kg)
   experienced a reduction in
   CLASI-A score from 22 at
   baseline to 5 by Day 43
   (2 weeks after last dose)
- No observed changes in SLEDAI or joint scores were noted due to the short treatment duration in this study

### Data led to Phase 2 Study of NKTR-358 in Moderate-to-Severe Lupus Patients

# NKTR-358 Phase 1B Proof-of-Concept Data Shows Sustained Disease Control in Patients with Atopic Dermatitis

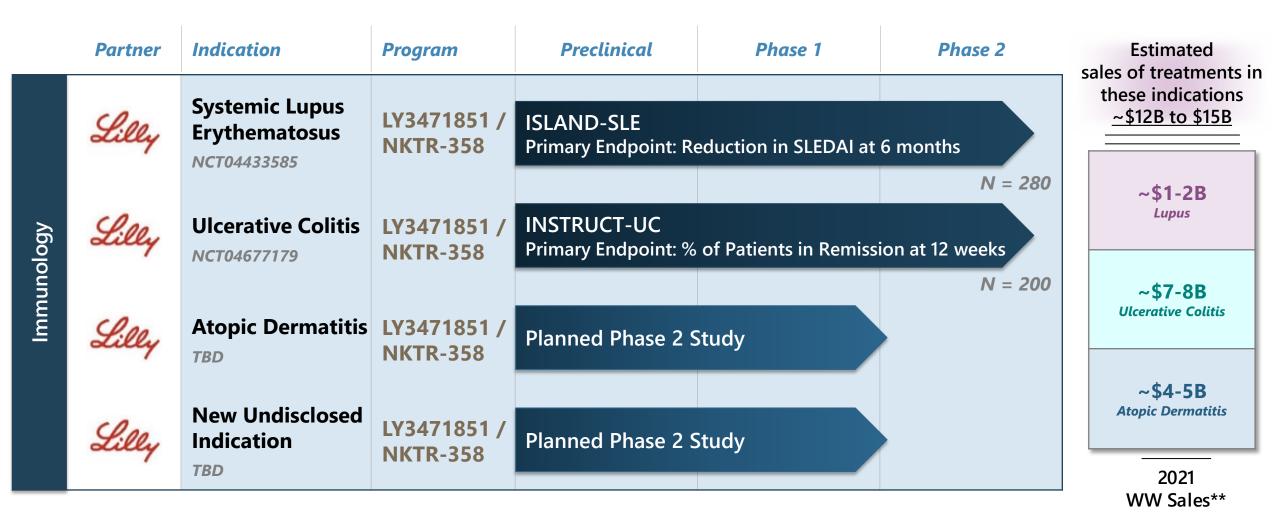
## PHASE 1B DATA FOR PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS (ECZEMA)



- Sustained disease control for at least 6 months after last dose demonstrates potential for NKTR-358 to differentiate from standard of care
- POC data demonstrates dose dependent reduction in EASI

<sup>\*</sup> Interim analysis; EASI = eczema area and severity index; Q2W = once every 2 weeks; POC = proof of concept Source: 2021 Lilly Investment Community Meeting

# LY3471851 / NKTR-358: Development Program with Lilly Advancing into Multiple Auto-Immune Conditions



### Nektar Clinical Pipeline

Immuno-oncology
Program

Program	Indication	Study	Preclinical	Phase 1	Phase 2	Phase 3	Partner
	Metastatic Melanoma	BEMPEG + OPDIVO® vs. OPDIVO®			Registratio	nal Study	ر <sup>اا</sup> ا Bristol Myers Squibb
	Renal Cell Carcinoma	BEMPEG + OPDIVO® vs. TKI			Registratio	nal Study	ر <sup>ااا</sup> Bristol Myers Squibb
	Adjuvant Melanoma	BEMPEG + OPDIVO® vs. OPDIVO®		Registrational Study			
Bempegaldesleukin	Muscle-invasive Bladder Cancer	BEMPEG + OPDIVO® vs. OPDIVO®		Į.	Registrational Stud		ر <sup>اال</sup> Bristol Myers Squibb
. •	Bladder Cancer	BEMPEG + OPDIVO®		AA Registratio	nal Study		ر <sup>اال</sup> Bristol Myers Squibb
(BEMPEG)	Head & Neck SCC	BEMPEG + KEYTRUDA®			Phase 2/3		
(NKTR-214)	Renal Cell Carcinoma	BEMPEG + OPDIVO® + TKI		Phase	1/2		ر <sup>ااا</sup> ا Bristol Myers Squibl
	1L NSCLC	BEMPEG + KEYTRUDA®		Phase 1/2			
	Multiple Solid Tumors (GU)	BEMPEG + OPDIVO® + TKI		Phase 1		<sup>(</sup> III)	Bristol Myers Squibb EXELIXIS
	Head & Neck SCC	BEMPEG + VB10.NEO	Pha	se 1/2a			vaccibody
NKTR-262	Genitourinary Tumors	NKTR-262 + BEMPEG		Phase 1/2			
	Bladder Cancer	NKTR-255 + BAVENCIO®		Phase 2			MERCK Pfize
NKTR-255	R/R NHL or Multiple Myeloma	NKTR-255 + RITUXAN® or DARZALEX FASPRO®		Phase 1/2			
	Head & Neck and Colorectal	NKTR-255 + ERBITUX®		Phase 1/2			

*Immunology* 

Program	Indication	Study	Preclinical	Phase 1	Phase 2	Phase 3	Partner
	Systemic Lupus Erythematosus	LY3471851 / NKTR-358	Phase 2				Lilly
LY3471851 /	Ulcerative Colitis	LY3471851 / NKTR-358			Phase 2		Lilly
•	Atopic Dermatitis	LY3471851 / NKTR-358		Phase 2	? Planned		Lilly
NKTR-358	Psoriasis	LY3471851 / NKTR-358	Phase 1b				Lilly
	Atopic Dermatitis	LY3471851 / NKTR-358	Pho	ase 1b			Lilly

Virology

Program	Indication	Study	Preclinical	Phase 1	Phase 2	Phase 3	Partner
BEMPEG	COVID-19	BEMPEG	Phase	1			

# 2022: A Year of Significant Milestones for Nektar Expect to End 2021 with ~\$800 Million in Cash & Investments

### BEMPEG (NKTR-214)

- Multiple registrational program data read-outs:
  - ► ORR/PFS data from Phase 3 metastatic melanoma study (early 2022)
  - ► First Phase 3 RCC Interim OS Analysis (1H 2022)
  - ► ORR/DOR data from Phase 2 cisplatin-ineligible bladder cancer study (1H 2022)
- ► Preliminary PROPEL data in 1L NSCLC patients treated with BEMPEG plus pembrolizumab plus chemotherapy (2H 2022)

#### NKTR-255

- ► Merck KGaA to initiate JAVELIN Bladder Medley study combining NKTR-255 with Bavencio®
- ► NKTR-255 initial Phase 2 data (combination with Rituxan, combination with Darzalex) in liquid tumors
- ► NKTR-255 initial Phase 2 data (combination with Erbitux) in solid tumors

### LY3471851 / NKTR-358

- ► Data from Phase 1b studies in AD and/or psoriasis patients presented at a major medical meeting
- ► Data from Phase 2 studies in lupus and ulcerative colitis available over the next 18 months
- ► Lilly to initiate Phase 2 trial in atopic dermatitis
- ► Lilly to initiate fourth Phase 2 trial in undisclosed auto-immune indication