
IMMUNOLOGY
Lilly

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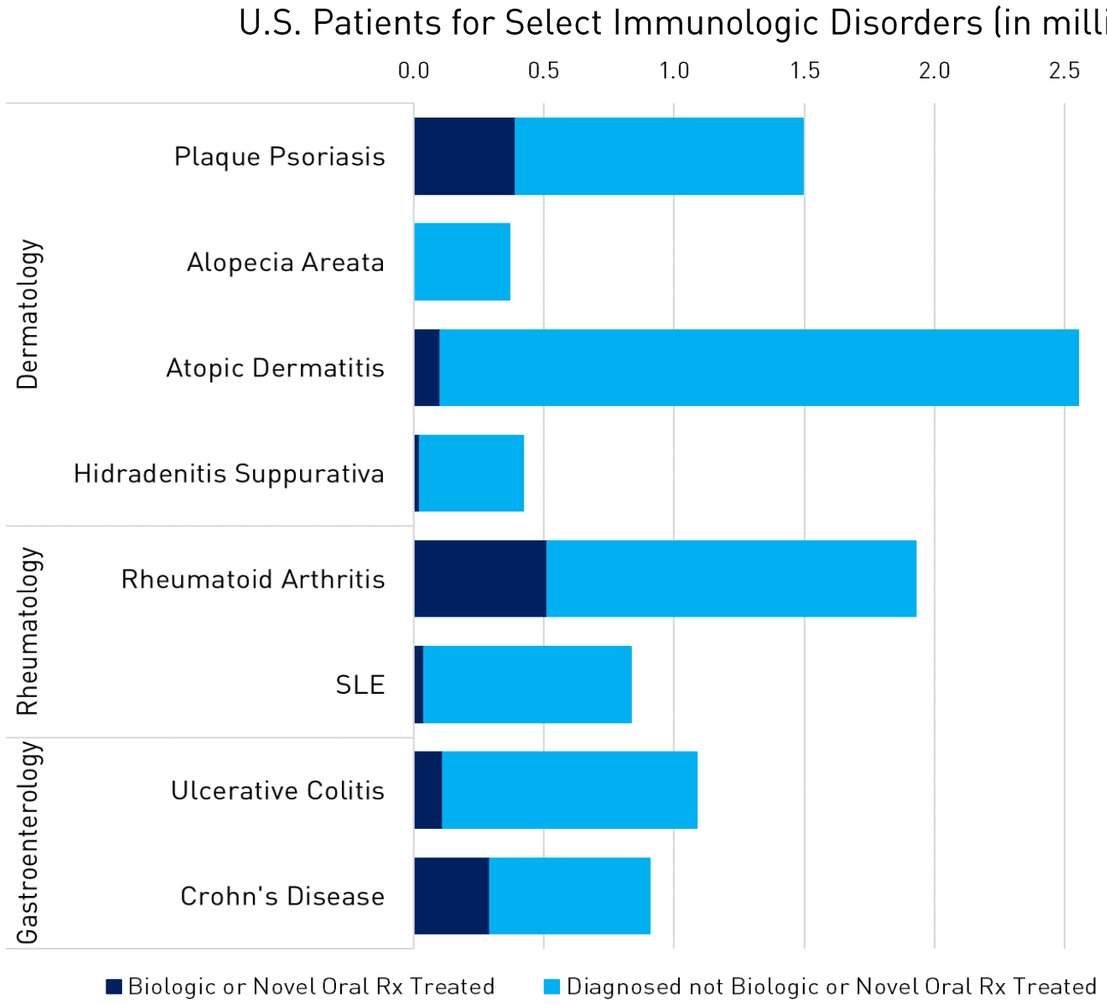
Lilly

2021 **INVESTMENT COMMUNITY MEETING**

PREVALENCE OF IMMUNOLOGIC DISORDERS

LARGE PATIENT POPULATIONS WITH SIGNIFICANT UNMET NEED



- Approximately 12 million people in U.S. have diagnosed auto-immune disorders, of which ~20% are treated with a biologic or novel oral medicine
- Lilly's pipeline has the potential to impact a broad spectrum of autoimmune disorders with high prevalence and unmet need
- In addition to internal research, external opportunities help to develop differentiated assets as demonstrated with Dermira acquisition as well as Nektar and Rigel collaborations

2020 US Data : Internal triangulation for select indications of Truven Health Analytics MarketScan Databases, Symphony APLD Database, IQVIA NPA Database, only primary indications are included; SLE = systemic lupus erythematosus

LATE-STAGE PIPELINE OPPORTUNITIES

POTENTIAL TO ADDRESS UNMET MEDICAL NEED IN KEY AREAS OF IMMUNOLOGY

MIRIKIZUMAB

- Anti-IL-23p19 monoclonal antibody
- Phase 3 induction and maintenance studies for people with moderately-to-severely active UC met primary and all key secondary endpoints; global submissions are planned for H1 2022
- Phase 3 study in Crohn's disease includes head-to-head versus Stelara and is expected to read out in early 2024

LEBRIKIZUMAB

- Potential best-in-class IL-13 monoclonal antibody with competitive profile in atopic dermatitis
- Phase 3 induction study demonstrated more than half of people with moderate to severe atopic dermatitis had at least 75% skin clearance as measured by EASI
- Upcoming Phase 3 read outs include combination with topical corticosteroids expected late 2021/early 2022 and 52-week maintenance data expected H1 2022

OLUMIANT

- The first JAK-inhibitor to demonstrate hair regrowth for alopecia areata in a Phase 3 program; Submitted in the U.S., Europe and Japan
- Phase 3 studies in SLE to read out before end of the year
- Approved in the EU and Japan for atopic dermatitis with U.S. regulatory action expected early 2022

Well positioned to become a leader in immunology with growing presence in dermatology and rheumatology as well as emergence in gastroenterology

UC = ulcerative colitis; EASI = eczema area and severity index; JAK = Janus kinase Inhibitors; SLE = systemic lupus erythematosus;

IMMUNOLOGY DEVELOPMENT STRATEGY

CORE AREAS OF FOCUS

ADAPTIVE IMMUNITY

- Offers potential of efficacy across many diseases
  - T cell biology
  - B cell biology
  - Cellular Signaling
- Most industry attention focused here with multiple approved assets

Taltz®
Mirikizumab (Ph 3)
Olumiant®
Lebrikizumab (Ph 3)
RIPK1 SM (Ph 1)

IMMUNE RESOLUTION

- Possibility of lasting remission
  - Checkpoints
  - Treg biology
  - Immunometabolism
  - Tolerance
- Key area of clinical focus for Lilly with industry-leading pipeline

IL-2 conjugate (Ph 2)
CD200R mAb (Ph 1)
PD-1 mAb (Ph 2)
BTLA mAb (Ph 1)

INNATE IMMUNITY

- Potential for efficacy in hard-to-treat targets
  - Myeloid cells/neutrophils
  - Dendritic cells
  - Fibrosis
- Emerging area of focus for Lilly

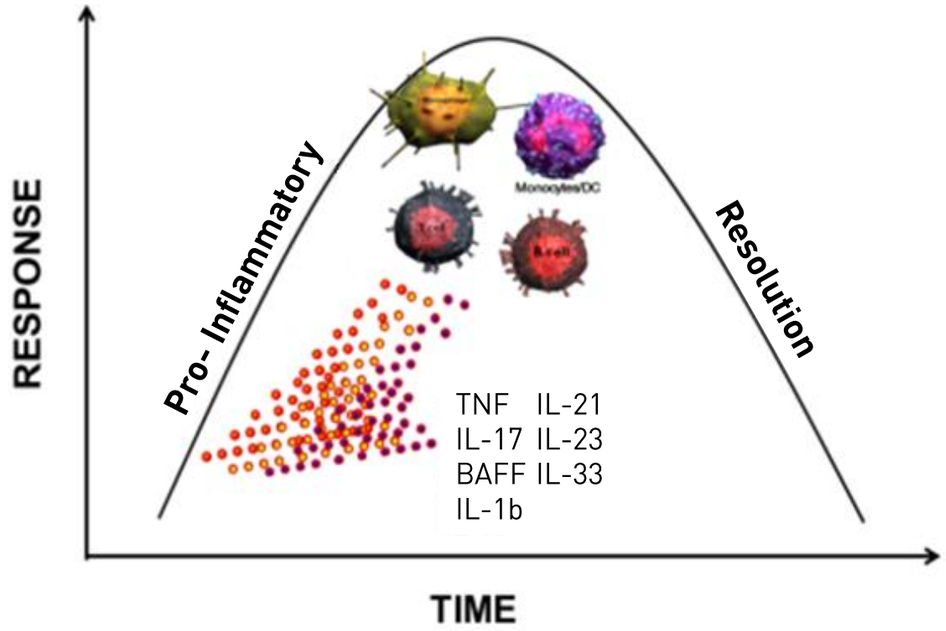
CXCR 1/2 mAb (Ph 2)

mAb = monoclonal antibody; SM = small molecule

CHECKPOINT RECEPTOR STRATEGY

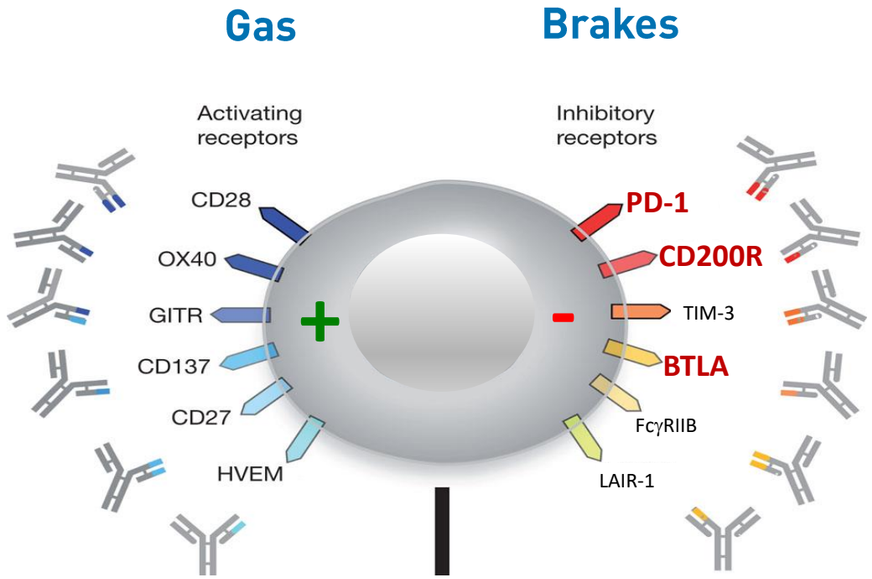
AGONIST ANTIBODIES (CD200R, BTLA, PD-1) INHIBIT IMMUNE RESPONSE AND PROMOTE A STATE OF RESOLUTION

HISTORICAL IMMUNOLOGY R&D



Prior efforts focused on pro-inflammatory response, whereas checkpoint agonists are focused on resolution

CHECKPOINT RECEPTOR FOCUS



Reasons to believe:

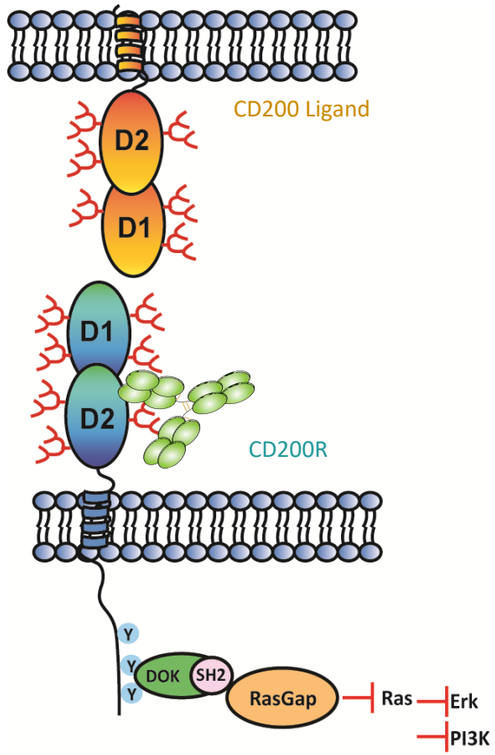
- Validated in immuno-oncology
- Associated with autoimmune side effects
- Agonists selectively impact activated cells

CD200R AGONIST AB (LY3454738)

LEAD CHECKPOINT AGONIST SHOWS POTENTIAL FOR EFFICACY AND DURABILITY

MECHANISM OF ACTION

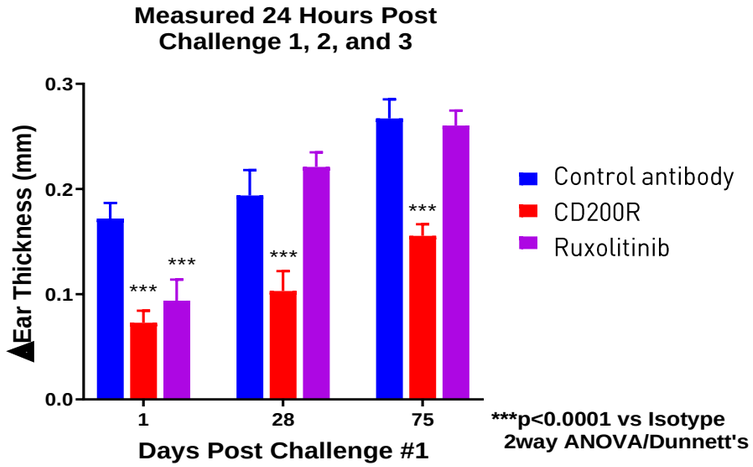
- Expressed on both innate and adaptive immune cells
- Agonism of the receptor leads to decreased cytokine release and decreased cell proliferation
- Pre-clinical data using an agonist antibody demonstrate inhibition of inflammation

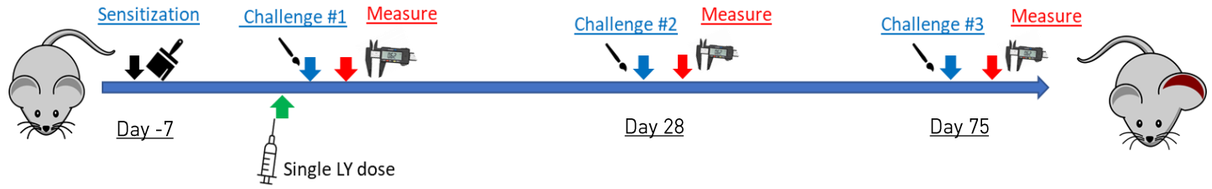


PRECLINICAL DATA

Long-term efficacy without measurable exposure suggest the potential for durable response after a single dose

Hapten-induced contact dermatitis*



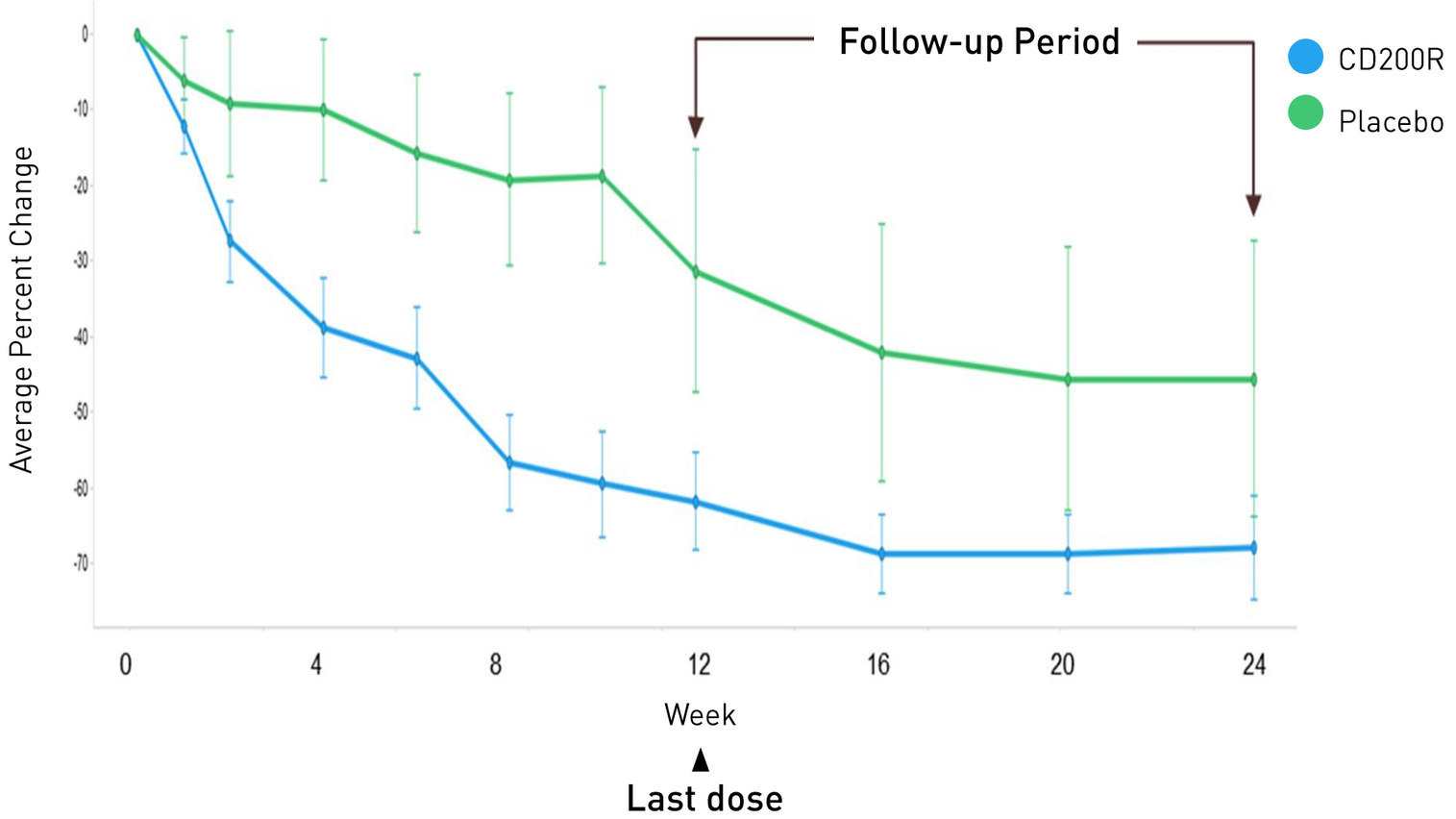


* Challenges are defined as hapten-induced dermatitis at predefined intervals

CD200R AGONIST AB (LY3454738)

FIRST CLINICAL POC FOR CHECKPOINT AGONISM ACROSS THE INDUSTRY

Mean EASI Percent Change from Baseline by Treatment in Atopic Dermatitis*



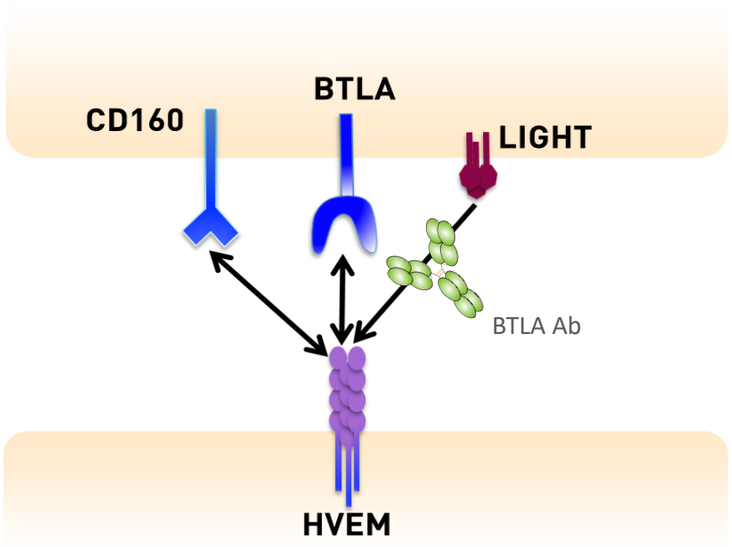
- EASI 75 of ~40% at week 12 established proof of concept for checkpoint agonists in Phase 1b study in atopic dermatitis
- Exploring durability of effect and potential for less frequent subcutaneous dosing
- Potential for enriching responses through biomarker-driven tailored approaches

*Interim analysis
EASI = eczema area and severity index; POC = proof of concept

BTLA AGONIST MAB (LY3361237)

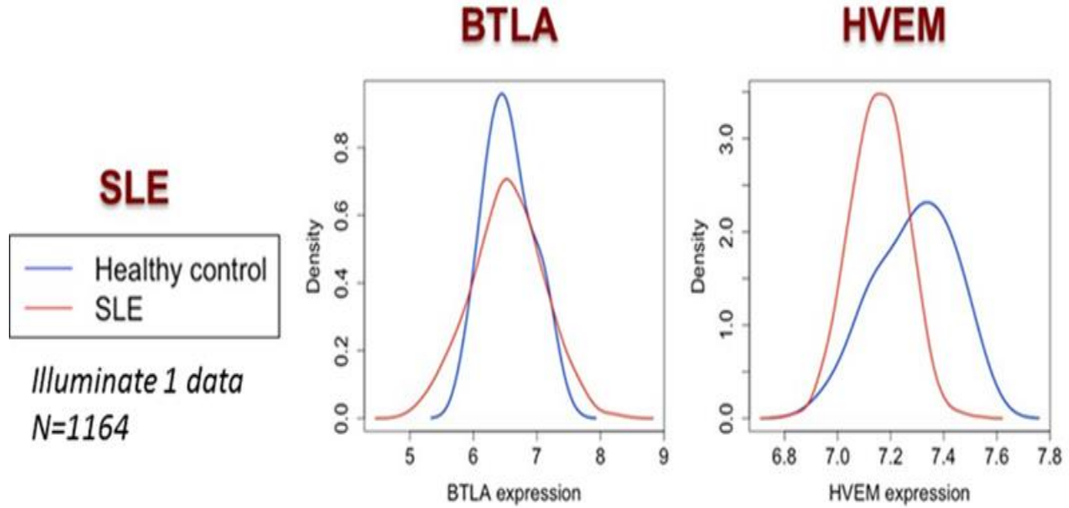
NOVEL FIRST-IN-CLASS CHECKPOINT AGONIST WITH PLANS FOR PHASE 2 SLE STUDY

MECHANISM OF ACTION



Binds BTLA on B cells, T cells, and dendritic cells to suppress immune activation

POTENTIAL TARGETED THERAPY IN SLE



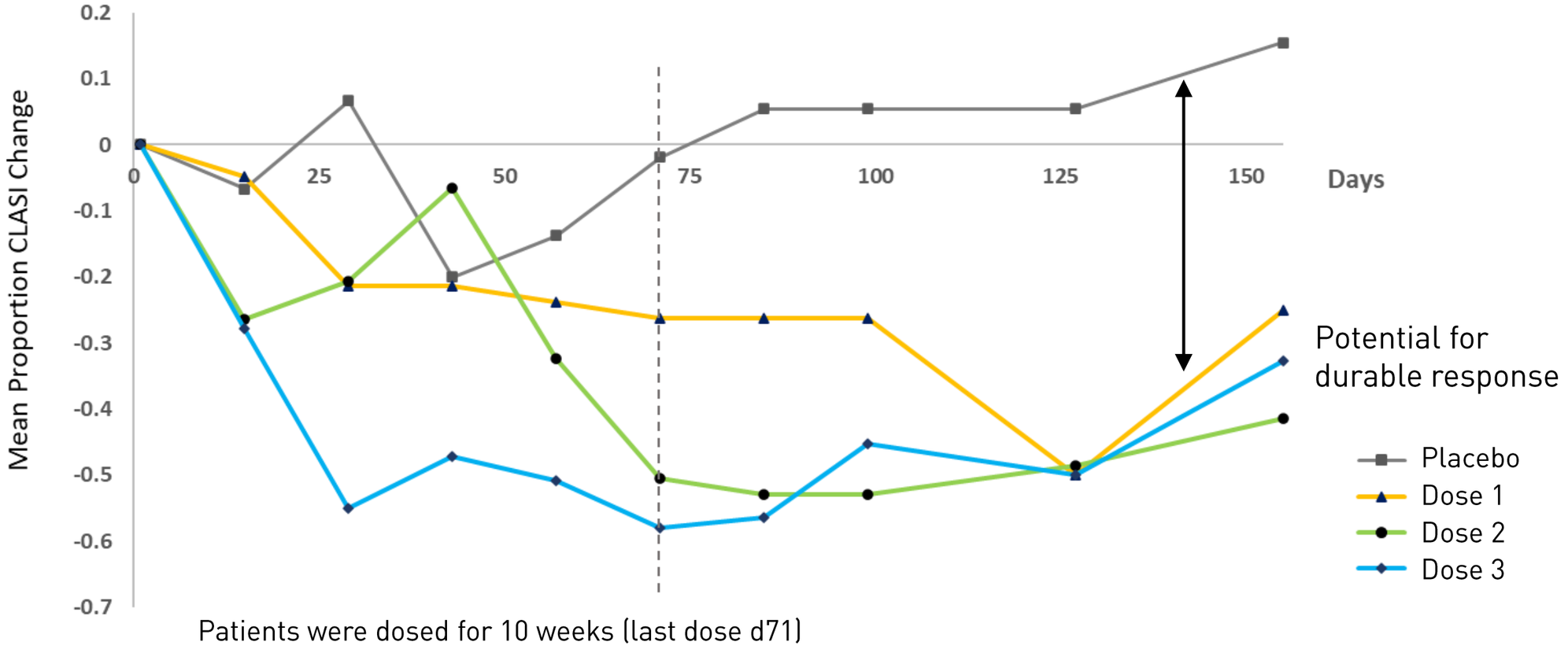
- HVEM, the BTLA ligand, is reduced in SLE patients
- BTLA agonist antibody may function as HVEM replacement therapy

BTLA = B- and T-lymphocyte attenuator; SLE = systemic lupus erythematosus; HVEM = herpesvirus-entry mediator

BTLA AGONIST MAB (LY3361237)

PHASE 1 DATA SHOWED THE POTENTIAL FOR DURABLE RESPONSE IN SLE

Phase 1 MAD Study: Skin Disease Improvement in SLE Patients with CLASI ≥ 4 at Baseline



Patients were dosed for 10 weeks (last dose d71)

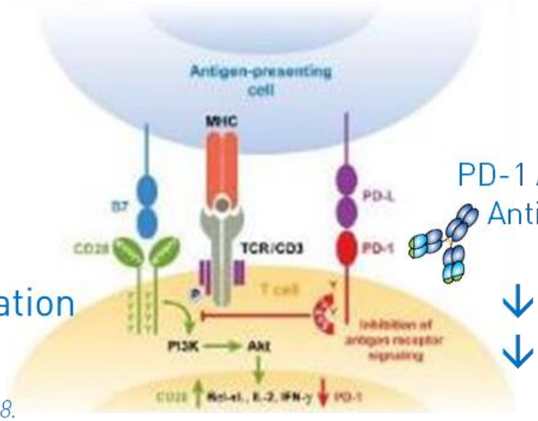
BTLA = B- and T-lymphocyte attenuator; MAD = multiple ascending dose; SLE = systemic lupus erythematosus; HVEM = herpesvirus-entry mediator; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index

PD-1 AGONIST MAB (LY3462817)

FIRST-IN-CLASS OPPORTUNITY TO AGONIZE A VALIDATED IMMUNE CHECKPOINT RECEPTOR

FIRST IN CLASS OPPORTUNITY

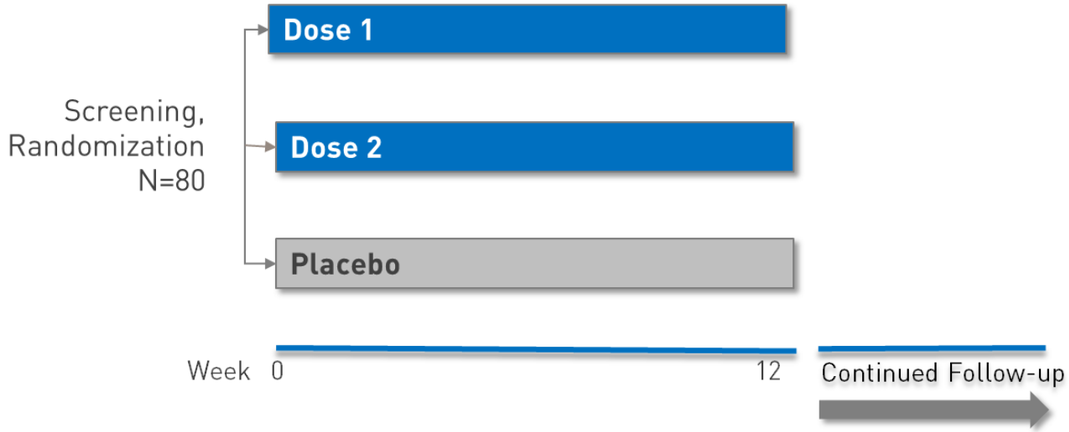
PD-1 agonism suppresses lymphocyte activation & expansion



Adapted from Keir ME, et al. 2008. Annu. Rev. Immunol. 26:677-704

- First-in-class development program will test the hypothesis of durability / disease resolution through checkpoint agonism
- PD-1 inhibition broadly associated with autoimmune side effects including colitis, autoimmune diabetes and inflammatory arthritis

ONGOING PHASE 2 POC IN RA



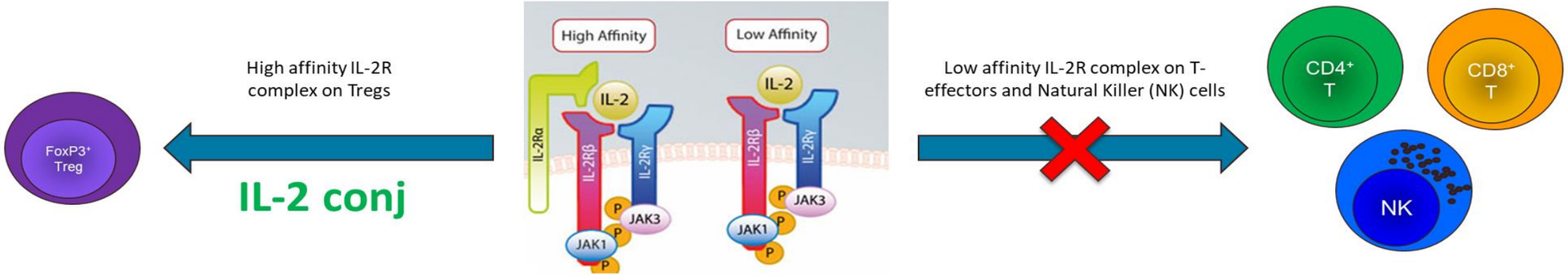
- **Patient Population**: Insufficient responders to conventional, biologic, or targeted synthetic disease modifying anti-rheumatic drugs
- **Primary Endpoint:** DAS28-hsCRP change from baseline at 12 weeks

RA = rheumatoid arthritis; POC = proof of concept; LDA = Low Disease Activity; CDAI = Clinical Disease Activity Index; PBO = placebo; RAMRIS = Rheumatoid Arthritis Magnetic Resonance Imaging Score; DAS28 = Disease Activity Score-28; hsCRP = high-sensitivity C-reactive protein

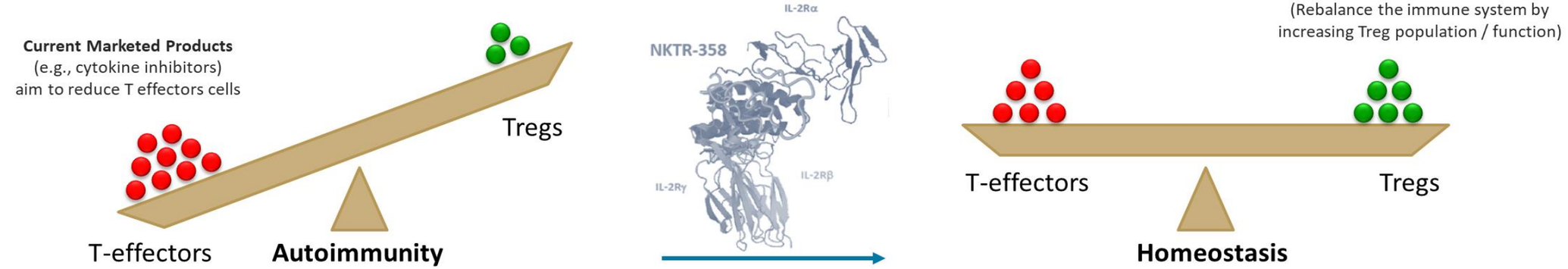
IL-2 CONJUGATE (NKTR-358)

NOVEL BIOLOGY & TREATMENT APPROACH IN PARTNERSHIP WITH NEKTAR

Novel Biology: IL-2 conjugate, An IL-2 Agonist biased for Treg expansion, affords a…



…Novel Treatment Approach: Resolution/Restoration of immune system

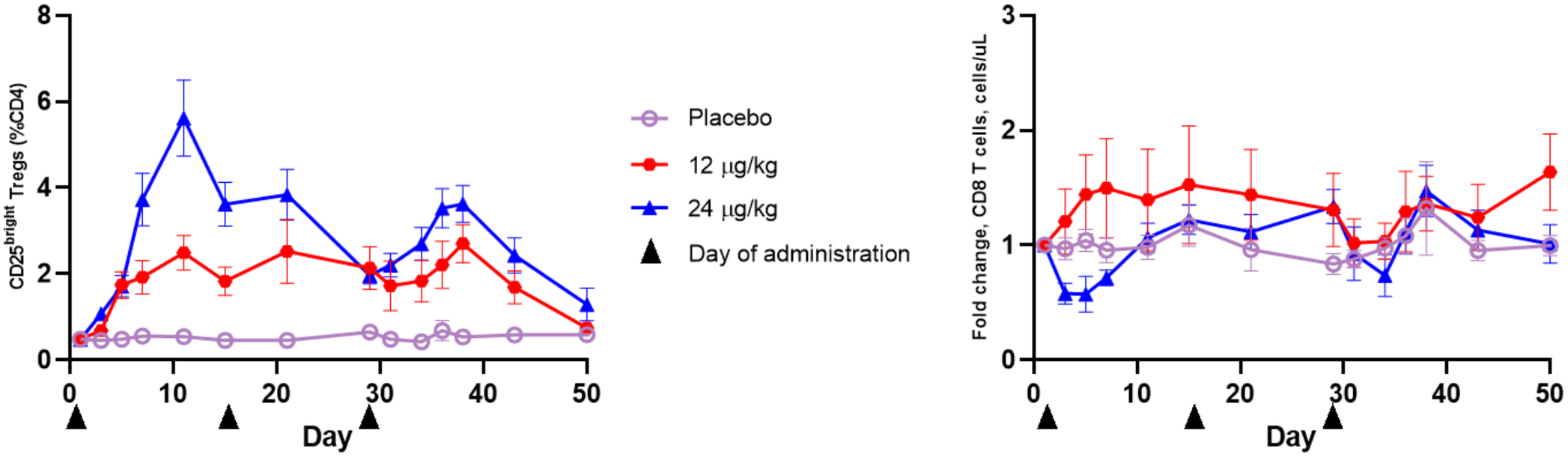


Differential expression of high and low affinity IL-2 receptors allows IL-2 to regulate both pro-inflammatory T-effector cells and anti-inflammatory Treg cells. NKTR-358 is a stable pegylated IL-2 conjugate composition that preferentially stimulates expansion of Tregs with minimal effects on T-effectors.

IL-2 CONJUGATE (NKTR-358)

ENCOURAGING MAD DATA IN SYSTEMIC LUPUS ERYTHEMATOSUS

Phase 1 MAD data in SLE demonstrated dose-dependent increase in CD25^{bright} Tregs (up to 20-fold) with no appreciable impact on T-effectors and an acceptable safety profile



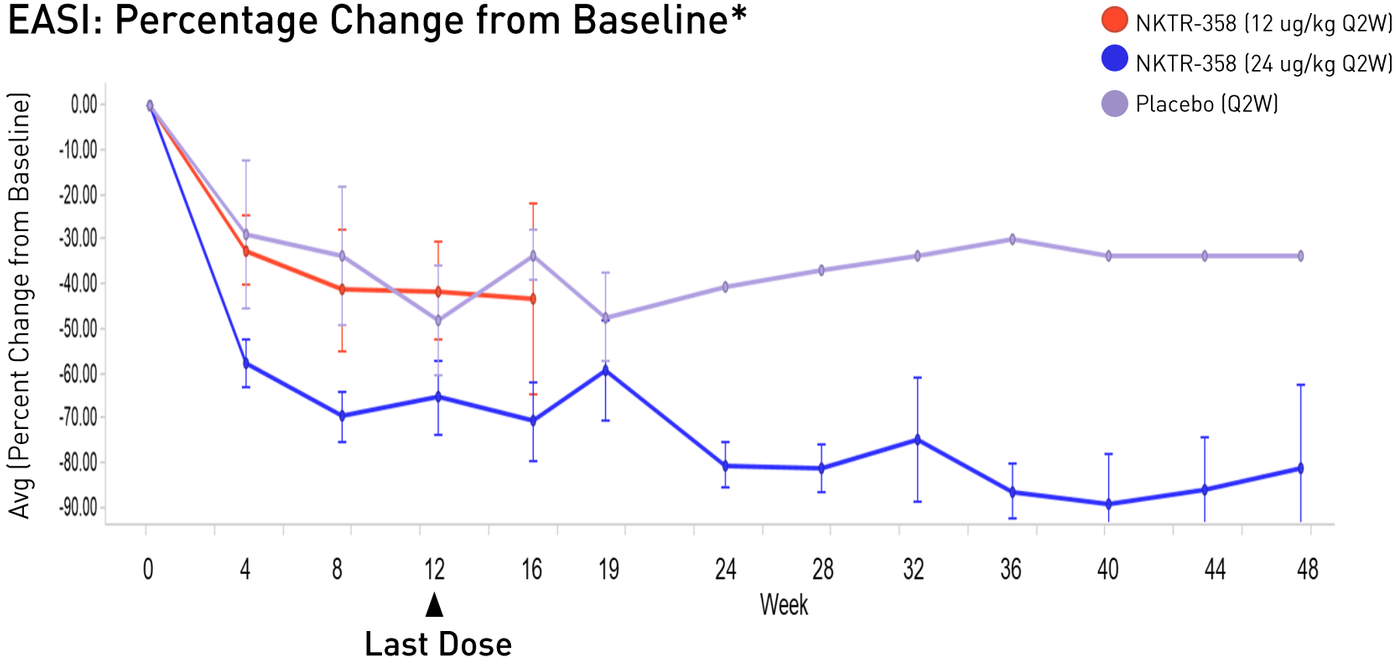
MAD = multiple ascending dose; SLE = systemic lupus erythematosus

IL-2 CONJUGATE (NKTR-358)

PHASE 1B POC DATA IN ATOPIC DERMATITIS SUPPORTS CLINICAL PROGRAM EXPANSION

PHASE 1B DATA FOR PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

EASI: Percentage Change from Baseline*



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

CLINICAL STATUS

SLE

Phase 2 trial recruiting (NCT04433585)); Encouraging Phase 1b data (NCT03556007)

ULCERATIVE COLITIS

Phase 2 trial recruiting (NCT04677179)

ATOPIC DERMATITIS

Encouraging Phase 1b data (NCT04081350)); Plan to initiate Phase 2 clinical study in 2022

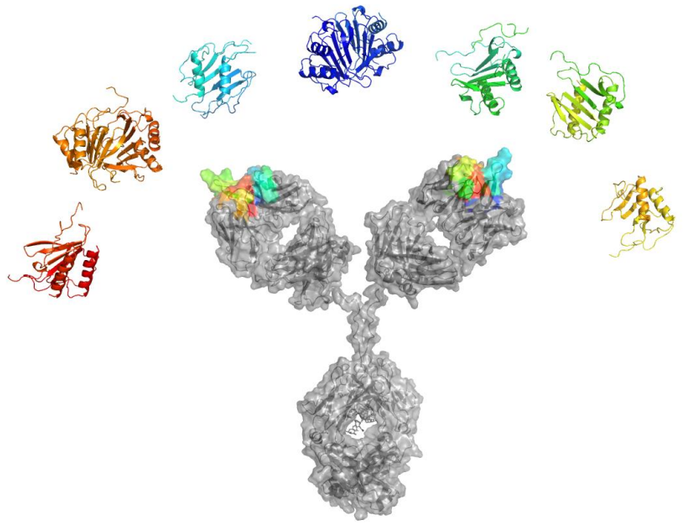
* Interim analysis; SLE = systemic lupus erythematosus; EASI = eczema area and severity index; POC = proof of concept

CXCR1/2L (LY3041658)

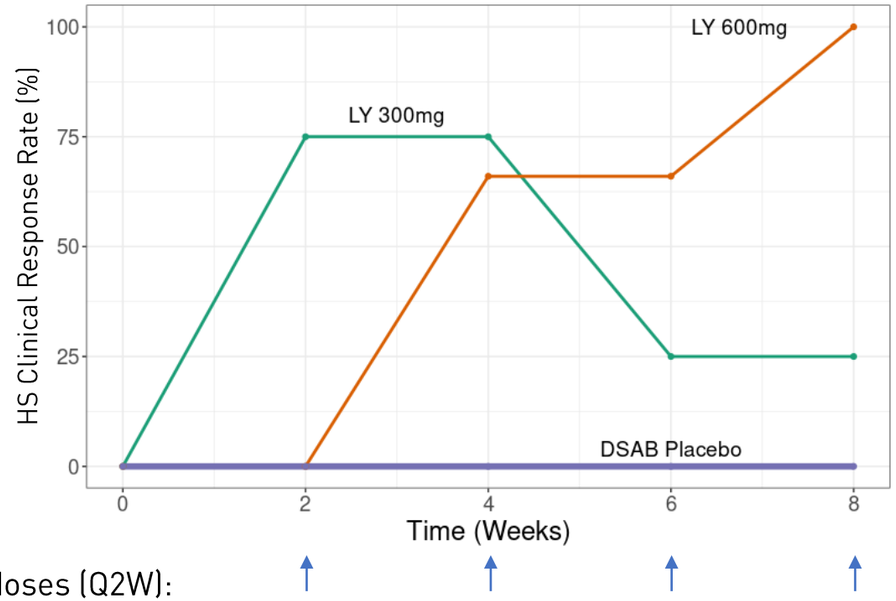
NOVEL NEUTROPHIL-TARGETED MAB BEING STUDIED IN HIDRADENITITIS SUPPURATIVA

MECHANISM OF ACTION

- Neutralizing all ELR+ chemokines acts as a dual CXCR1/CXCR2 antagonist, impacting the ability of neutrophils to migrate to sites of inflammation
- Due to the interplay between the innate and adaptive immune system, reducing neutrophil infiltration may result in downregulation of the adaptive autoimmune response



PHASE 1 MAD DATA IN HS



LY doses (Q2W):

- Potential application in neutrophil-driven autoimmune diseases including HS, ulcerative colitis and other neutrophilic skin diseases
- Full Phase 2 HS data expected H1 2022

HS = Hidradenitis Suppurativa; MAB = monoclonal antibody

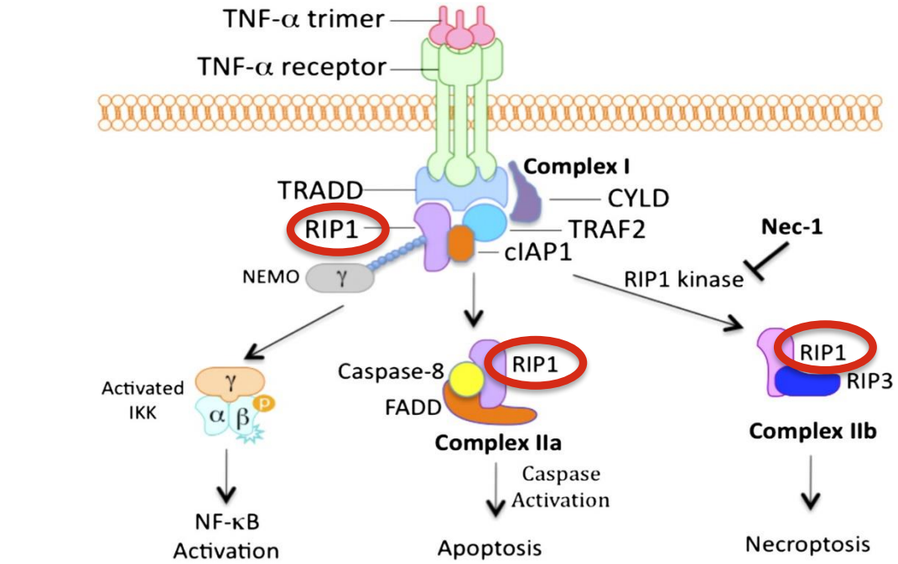
RIPK1 INHIBITOR R552 / LY3871801 (INLICENSED)

BROAD POTENTIAL AS AN ORAL THERAPY IN DISEASES TARGETED BY TNF INHIBITORS

BIOLOGIC RATIONALE

- Orally available, potent and selective inhibitor of RIP1 kinase, recently in-licensed from Rigel
- RIP1 kinase plays a key role in TNF signaling and in the induction of pro-inflammatory necroptosis, which could support indications in psoriasis, RA and IBD
- R552/LY3871801 could achieve best-in-class status relative to competition based on current Phase 1 data

DOWNSTREAM SIGNALING



Survival & proinflammatory cytokines	Programmed cell death & removal by phagocytosis	Cell death that leads to activation of immune response & inflammation

Adapted from Yuan J. & Kroemer G., Genes & Dev 2010

RIP1 = receptor-interacting serine/threonine-protein kinase 1; TNF = tumor necrosis factor; RA = rheumatoid arthritis; IBD = inflammatory bowel disease

LILLY IMMUNOLOGY PIPELINE

SELECT NME AND NILEX PIPELINE AS OF OCTOBER 22, 2021

Pre-Clinical

- TAU siRNA — Alzheimer's
- SARM1 INHIBITOR — Pain
- PI3Ka SELECTIVE — Cancer
- FGFR3 INHIBITOR — Cancer
- 2nd GENERATION RET INHIBITOR — Cancer
- BCL2 INHIBITOR — Cancer
- DACRA — Diabetes / Obesity
- LAARA — Diabetes / Obesity
- Glucose Sensing Insulin — Diabetes

PHASE 1

- RIPK1 INHIBITOR — Immunology ★
- P2X7 INHIBITOR — Pain
- PYY ANALOG — Diabetes
- RELAXIN-LA — Heart Failure
- NRG4 AGONIST — Heart Failure
- O-GLCNACASE INH — Alzheimer's
- OXYNTOMODULIN — Diabetes
- LP(a) siRNA — CVD
- N3PG Aβ MAB — Alzheimer's
- NOT DISCLOSED — Diabetes
- KHK INHIBITOR II — Diabetes / NASH
- KRAS G12C II — Cancer
- LP(a) INHIBITOR — CVD
- GIPR AGONIST LA II — Diabetes
- IDH1/2 INHIBITOR — Cancer
- IL-17A SMALL MOL INHIBITOR — Immunology
- CD200R MAB AGONIST — Immunology ★
- GIP/GLP COAGONIST PEPTIDE — Diabetes
- GIPR AGONIST LA — Diabetes
- ANGPTL3 siRNA — CVD
- AUR A KINASE INHIBITOR — Cancer
- BTLA MAB AGONIST — Immunology ★

PHASE 2

- TIRZEPATIDE — NASH
- IL-2 CONJUGATE — Ulcerative Colitis ★
- PIRTOBRUTINIB — B-Cell Malignancies
- GGG TRI-AGONIST — Obesity
- GBA1 GENE THERAPY — Gaucher Disease Type 2
- TRPA1 ANTAGONIST — Pain
- GLP-1R NPA — Obesity
- SSTR4 AGONIST — Pain
- GLP-1R NPA — Diabetes
- PACAP38 MAB — Migraine
- PD-1 MAB AGONIST — Rheumatoid Arthritis ★
- IL-2 CONJUGATE — Systemic Lupus Erythematosus ★
- MEVIDALEN — Symptomatic LBD
- GBA1 GENE THERAPY — Parkinson's Disease
- GRN GENE THERAPY — Frontotemporal Dementia
- EPIREG/TGFα MAB — Chronic Pain
- GGG TRI-AGONIST — Diabetes
- BEBTELOVIMAB (LY-CoV1404 MAB) — COVID-19
- CXCR1/2L MAB — Hidradenitis Suppurativa ★
- AUTOMATED INSULIN DELIVERY SYS — Diabetes
- BASAL INSULIN-FC — Diabetes

PHASE 3

- PIRTOBRUTINIB — R/R CLL Combination
- TIRZEPATIDE — CV Outcomes
- TIRZEPATIDE — Obesity
- SELPERCATINIB — 1L NSCLC
- TIRZEPATIDE — Heart Failure pEF
- PIRTOBRUTINIB — R/R MCL Monotherapy
- SELPERCATINIB — 1L Med Thyroid Cancer
- EMPAGLIFLOZIN* — Post MI
- MIRIKIZUMAB — Crohn's Disease ★
- BARICITINIB — Systemic Lupus Erythematosus ★
- EMPAGLIFLOZIN* — Chronic Kidney Disease
- ABEMACICLIB — HER2+ Early BC
- ABEMACICLIB — Prostate Cancer
- SOLANEZUMAB — Preclinical AD
- IMLUNESTRANT — ER+ HER2- mBC
- MIRIKIZUMAB — Ulcerative Colitis ★
- PIRTOBRUTINIB — R/R CLL Monotherapy
- DONANEMAB^ — Early Alzheimer's
- LEBRIKIZUMAB — Atopic Dermatitis ★

REG REVIEW

- EMPAGLIFLOZIN* — Heart Failure pEF
- CONNECTED CARE PREFILLED INSULIN PEN — Diabetes
- BARICITINIB — Alopecia Areata ★
- TIRZEPATIDE — Diabetes
- SINTILIMAB (US)* — NonSquam NSCLC 1L

LEGEND

- NME
- NILEX
- * *Commercial Collaboration*
- ^ *Rolling submission in the U.S. initiated*
- ☆ *Discussed in Dec 15 Investment Community Meeting*

Note: select pre-clinical assets listed, most of which were discussed at the Lilly Investment Community meeting on December 15, 2021; NME = new molecular entity; NILEX = new indication or line extension

IMMUNOLOGY SUMMARY

- Marketed products and late-stage assets, including Taltz, Olumiant, mirikizumab and lebrikizumab, support potential for continued growth and competitiveness in immunology
- Over the last decade, Lilly has built a deep early- and mid-stage portfolio with several potential first-in-class or best-in-class assets addressing improved efficacy, durability and formulations from both internal and external innovation
- Lilly is a leader in key areas of emerging science, including checkpoint agonism and Treg biology, and we are starting to deliver promising early phase data to validate these approaches

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