ESK-001, An allosteric TYK2 Inhibitor, Downregulates Biomarkers of Disease and TYK2 Activity

Biomarker Analysis of Phase 2 Psoriasis Study STRIDE

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Disclosures:
Commercial support was provided by Alumis Inc.
All authors are employed by Alumis. The authors have no other relationships or conflicts of interest to disclose.

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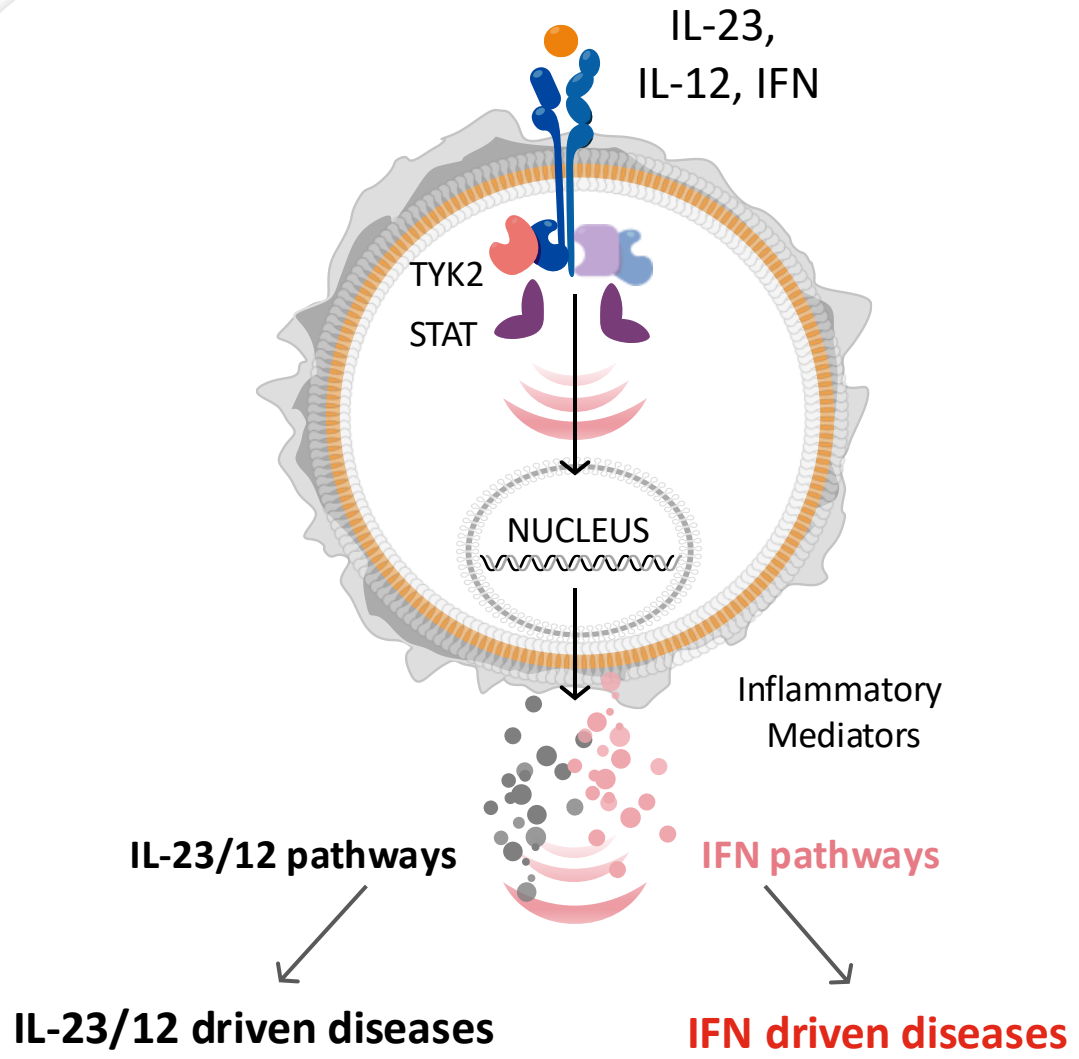
Conference: European Academy of Dermatology and Venereology, September 2024

TYK2 is Central to Key Pathways in Many Immune-mediated Diseases

- TYK2 mediates signaling from key proinflammatory cytokines, including **IL-23, IL-12 and type I IFN**
- Loss-of-kinase-function TYK2 genetic variants are protective for array of immune mediated diseases, including psoriasis
- P1104A loss-of-function variant is not associated with susceptibility to serious infections and malignancy
- Selectively targeting TYK2 **avoids safety liability** of JAK inhibitors



ESK-001: Potent and Selective Oral Allosteric TYK2i Designed to Achieve Maximal Target Inhibition

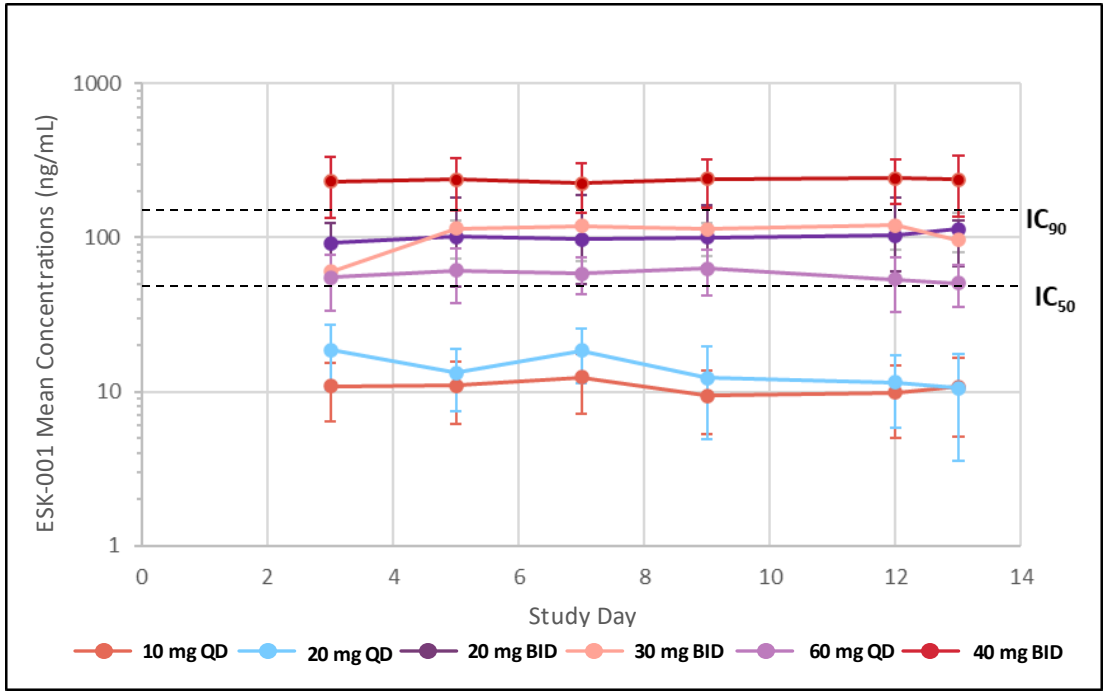
ESK-001, a highly selective allosteric TYK2 inhibitor

- Intrinsic TYK2 selectivity allows maximal target engagement while avoiding classic JAKi liabilities

Robust PK/PD relationship guided selection of Phase 2 doses

- Maximal target inhibition achieved at highest clinical dose
- Maintained across 24 hour-dosing period
- Highly predictable PK/PD

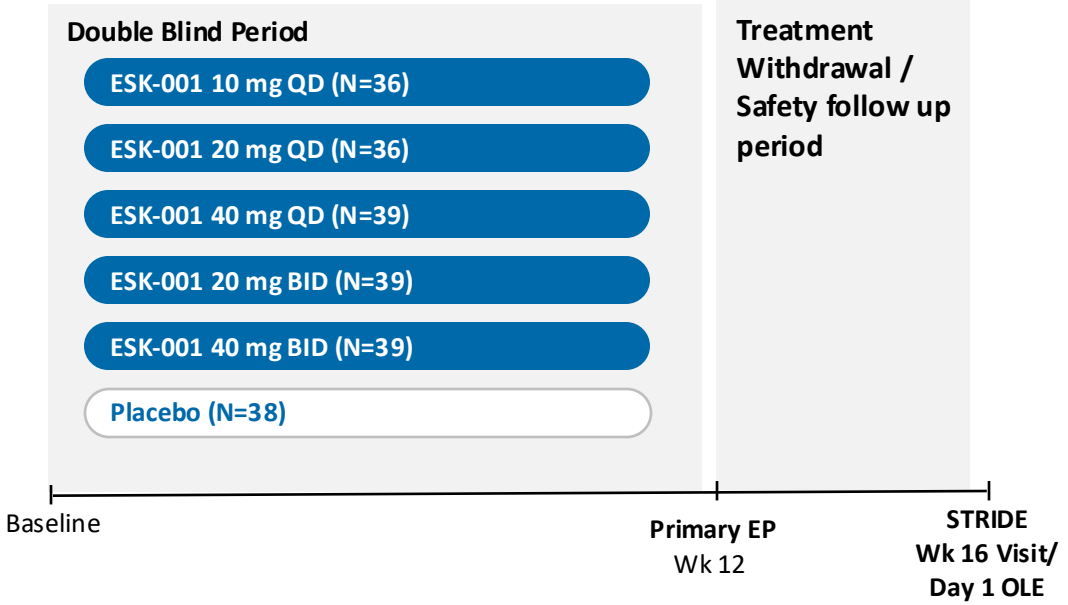
ESK-001 maintains IC90 coverage at trough with 40 mg BID dosing



ESK-001 Phase 1 Multidose Healthy Volunteers Study
PK measurements taken at trough, at steady state prior to next dose
IFNa stimulated human whole blood IC50 and IC90 (dotted lines)

ESK-001 Phase 2 STRIDE Evaluated Safety and Efficacy in Moderate-to-severe Psoriasis Patients with Extensive Exploratory Biomarker Sampling

STRIDE Phase 2 Trial



STRIDE Exploratory Biomarker Sampling

RNA*	Skin Biopsies*	Tape Stripping	Plasma Proteomics	DNA
Baseline	Baseline	Baseline	Baseline	Baseline
Week 2			Week 2	
Week 4			Week 4	
Week 8			Week 8	
Week 12	Week 12	Week 12	Week 12	
Week 16			Week 16	

* Data in this presentation

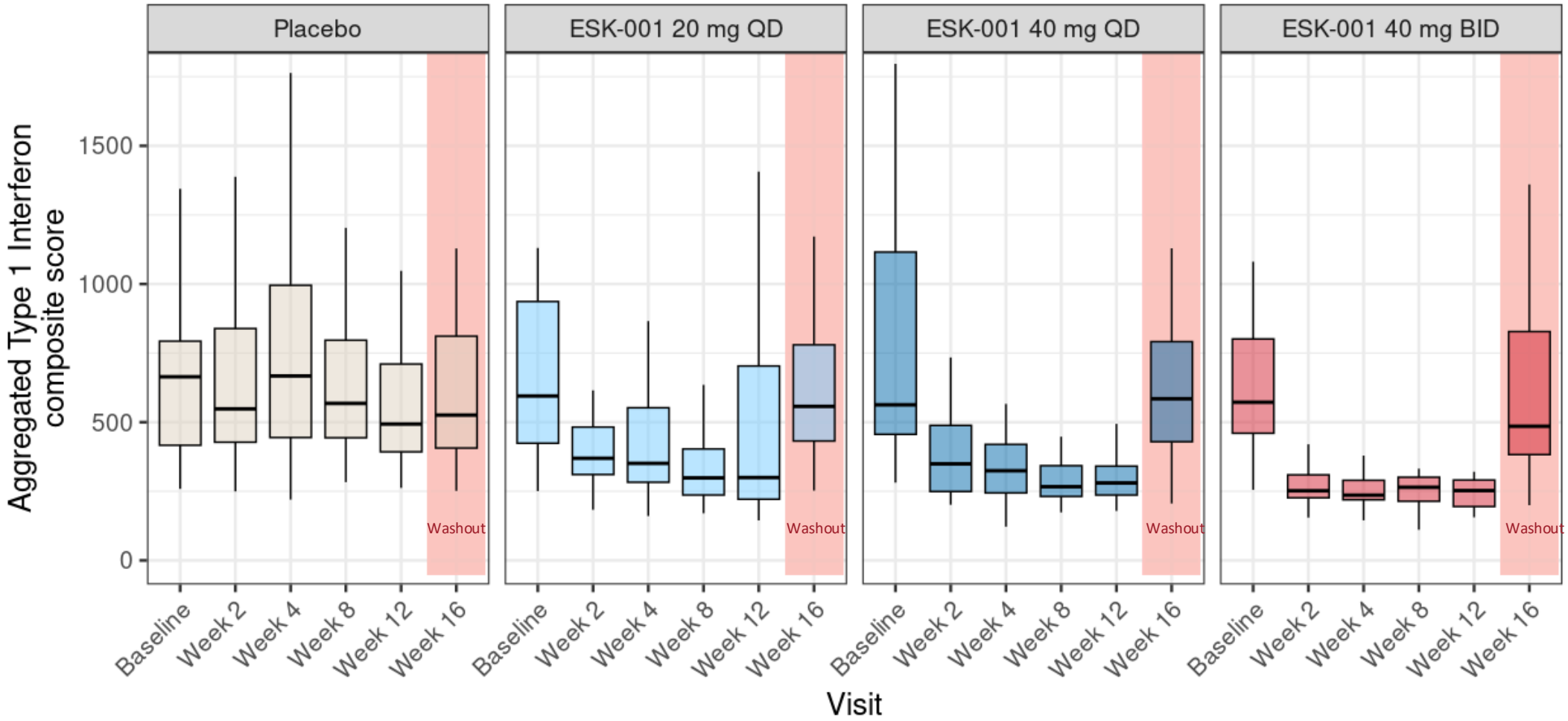
Stride Phase 2 Study

- **Key Inclusion Criteria:** adults 18-75 years with plaque psoriasis
  - PASI ≥ 12, sPGA ≥ 3, BSA ≥ 10%
- **Primary Endpoint :** PASI-75 Response at Week 12
- **Key Secondary Endpoint**: PASI-90, PASI-100, sPGA 0/1, sPGA 0 at week 12

Methods

- **Skin punch biopsies** of paired lesional and non-lesional samples at baseline, and a lesional sample at week 12 from subset of patients
- **RNA-seq blood and skin** Paired-end stranded libraries were generated and sequenced with a target depth of 100 million paired-end reads.
- **Spatial Transcriptomics** data also generated form skin biopsies using 10X Visium HD

STRIDE Ph2 Blood RNA-seq of Trough Drug Levels Shows Dose-Dependent Type I IFN Gene Signature Inhibition, Findings Consistent with Ph1



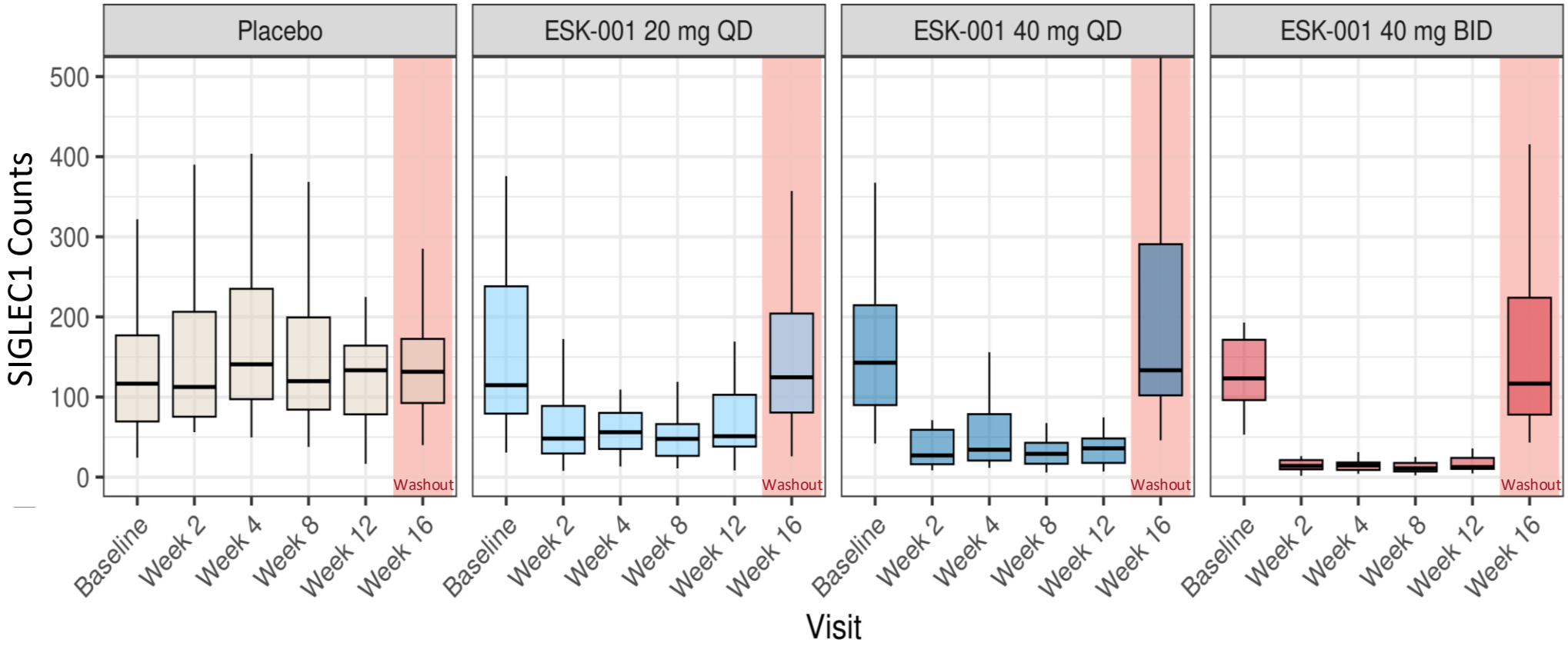
Note: Pink Bar Reflects Samples from End of Drug Washout Period (Week 12 to Week 16)

Composite IFN score: HERC5, IFI27, IFIT1 and RSAD2

Blood samples collected at trough. All patients on study with available samples included in analysis

Phase 2 Blood RNA-seq of Novel TYK2-Responsive Marker, SIGLEC1, Confirms Full Target Inhibition

Dose-dependent Inhibition of SIGLEC1



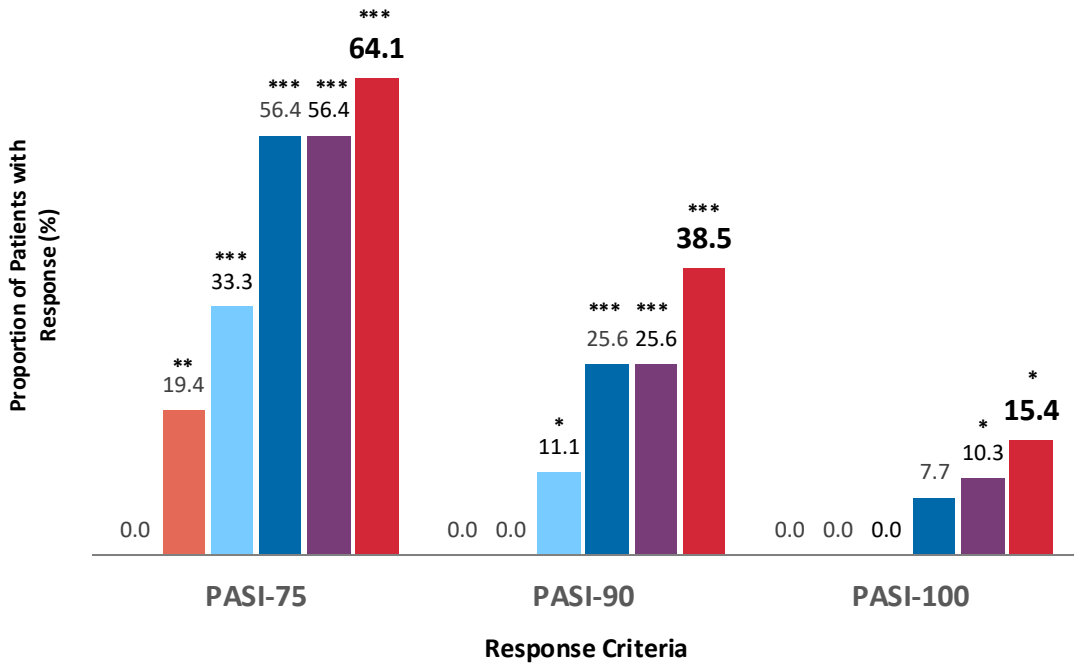
- SIGLEC-1 (CD169), a lectin-like receptor is expressed on monocytes, DCs, and microglia.
- Mediates binding of macrophages to Tregs
- Biomarker of severity in multiple inflammatory and immune-mediated diseases including Sjogrens Syndrome, SLE, and MS

Blood samples collected at trough. All patients on study with available samples included in analysis

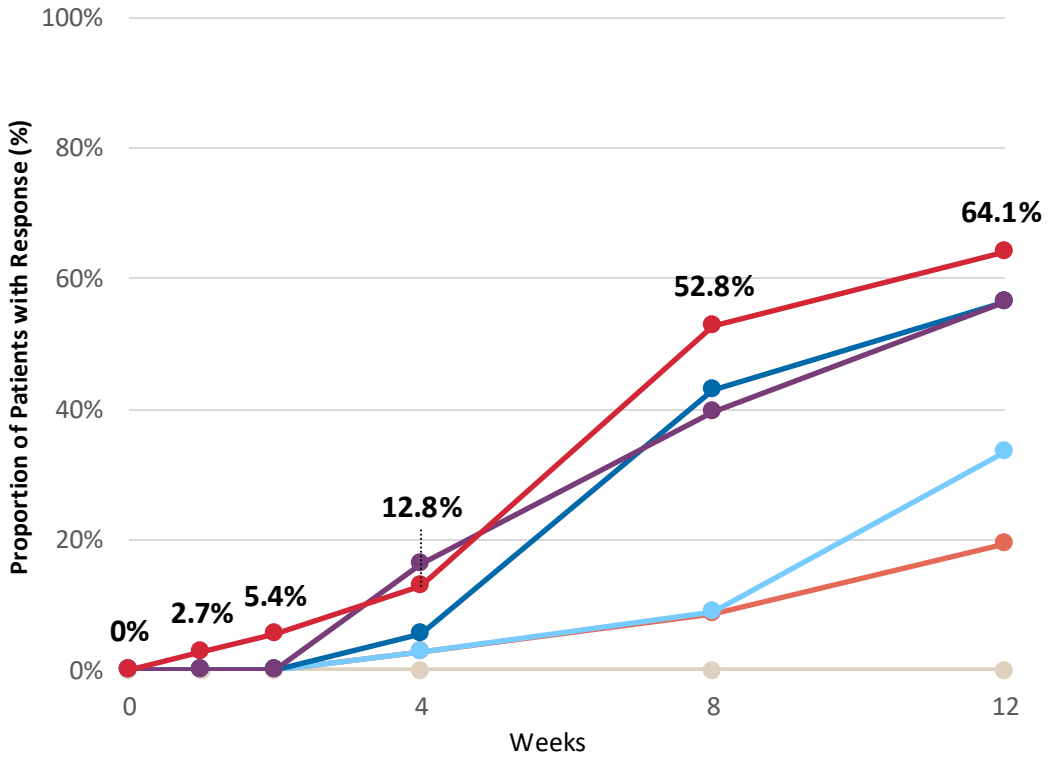
Note: Pink Bar Reflects Samples from End of Drug Washout Period (Week 12 to Week 16)

STRIDE Met Primary and Secondary Endpoints with High Statistical Significance and Dose Dependency (PASI-75: p < 0.001)

Clear Dose Dependent Efficacy



Increasing Efficacy Trajectory for PASI-75



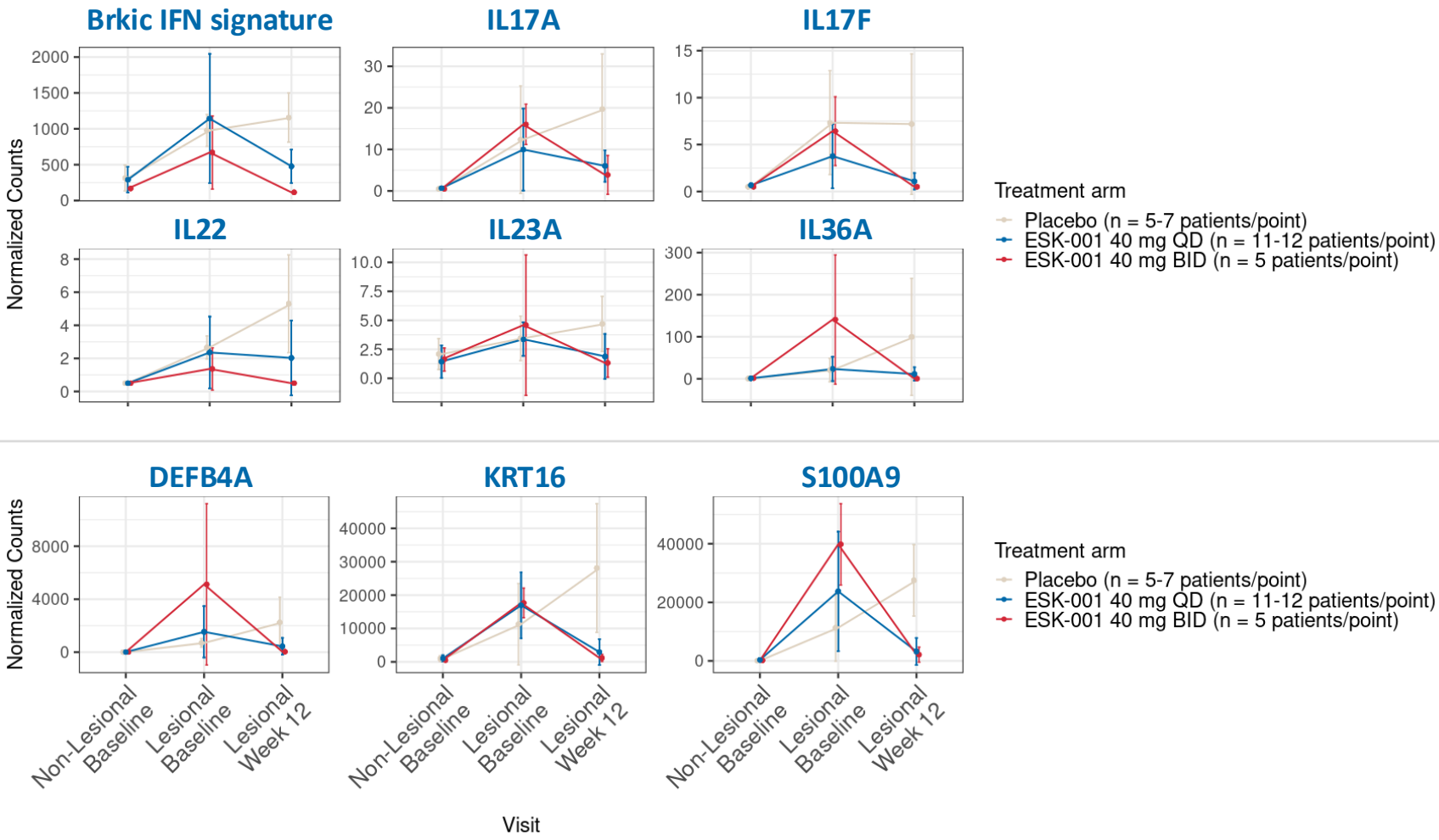
Placebo | 10 mg QD | 20 mg QD | 40mg QD | 20 mg BID | 40 mg BID

*p<0.05; **p< 0.005; ***p<0.001 . P-value is comparing proportion in each active arm vs placebo using the Cochran-Mantel-Haenszel test adjusted for stratification factors (prior use of biologics and geographic region (North American vs. ROW)).

RNA-seq Data in Lesional Tissue Confirm Maximal Inhibition with ESK-001

Lesional Skin Levels of Key Cytokines & Disease Related Biomarkers Return to Non-lesional Levels

Key TYK2 Pathway Cytokines



Key Keratinocyte Disease Biomarkers

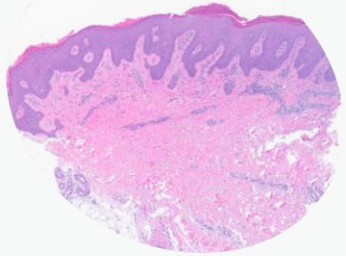
ESK-001 Psoriasis Phase 2 Skin biopsy RNA-seq, 12/05/2023 dataset.
Skin biopsies collected in subset of patients, all available skin biopsy samples with valid RNAseq data included in analysis.

ESK-001 Skin and Blood Biomarker Changes Reflected Histologically

ESK-001 40 mg BID

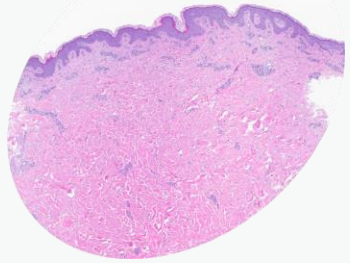
Day 1 lesional

PASI: 21.0



Week 12 lesional

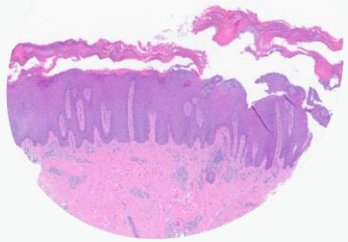
PASI: 13.0



ESK-001 Placebo

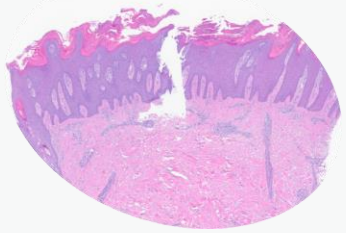
Day 1 lesional

PASI: 12.9



Week 12 lesional

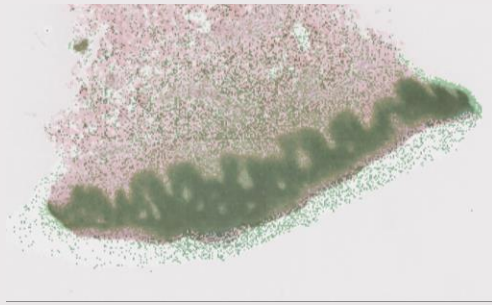
PASI: 9.0



ESK-001 40 mg QD

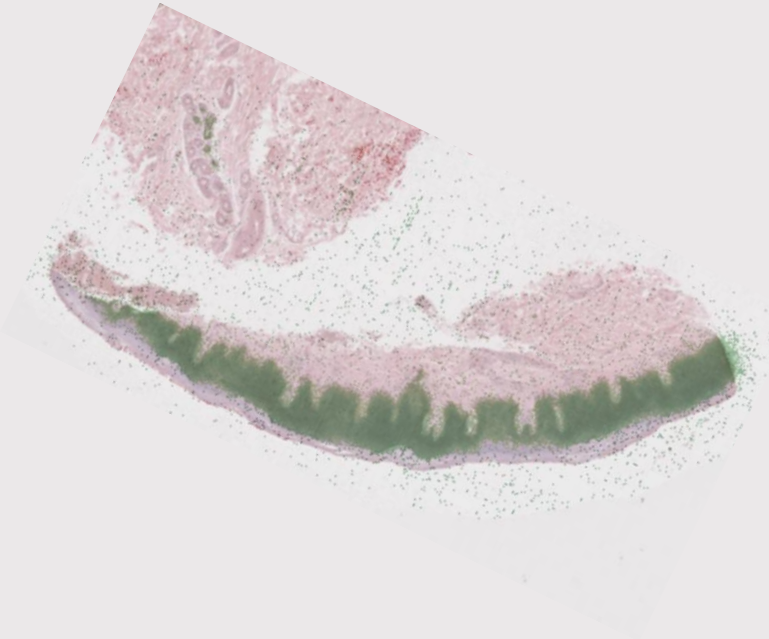
Day 1 lesional

PASI: 42.9



Week 12 lesional

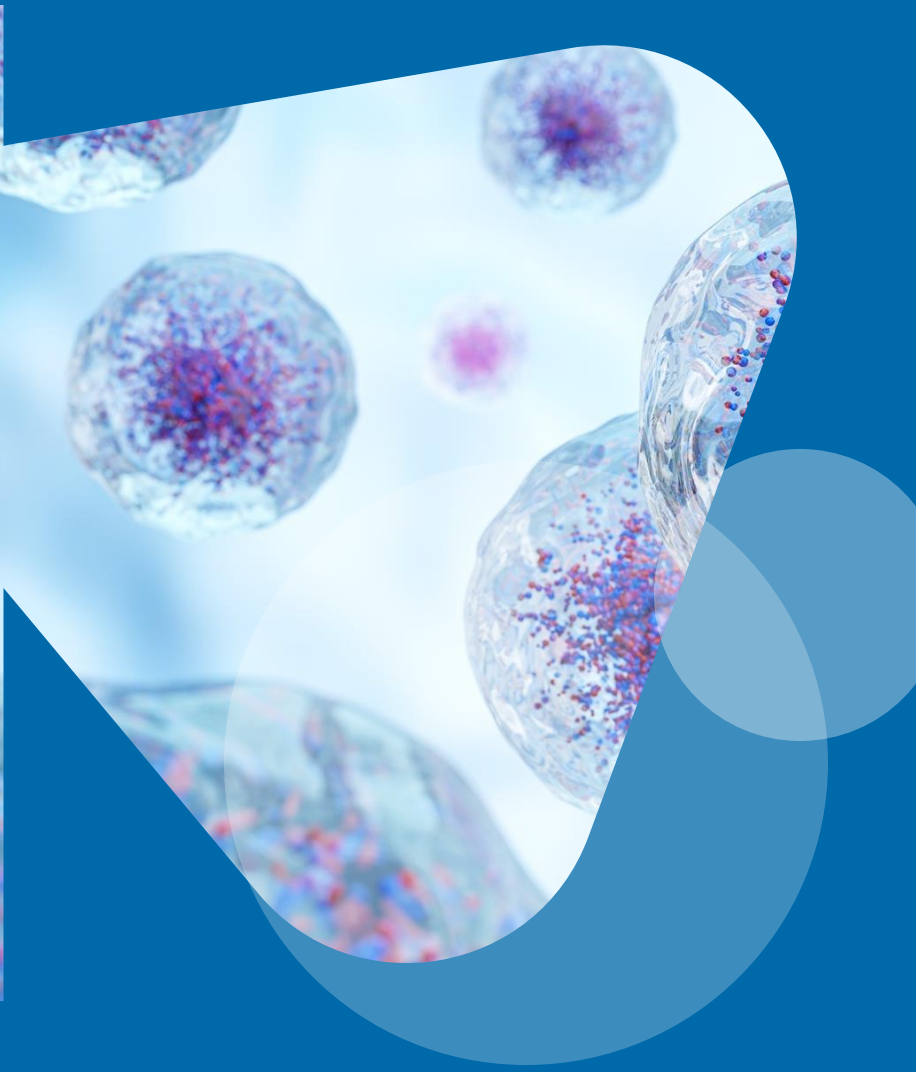
PASI: 4.8



Spatial scRNAseq expression of **KRT16 (green)** in Day 1 lesion vs Week 12 lesion for a representative subject visibly reduced post-treatment

Representative images shown for three separate subjects

Conclusions



- ESK-001 maximally inhibits TYK2, demonstrated by biomarkers in blood and confirmed in skin
- ESK-001 demonstrated clear dose-dependent effects on biomarkers
- ESK-001 returned key psoriasis disease biomarkers in lesional skin to baseline/non-lesional levels and improved histological outcomes
- Novel TYK2 PD biomarker identified, SIGLEC1, is also suppressed by ESK-001 in dose-dependent manner
- Modulation of TYK2 pathway and disease-related biomarkers closely mirrored clinical outcomes.

Late Breaker Session D3T01.3D: will present STRIDE OLE clinical results

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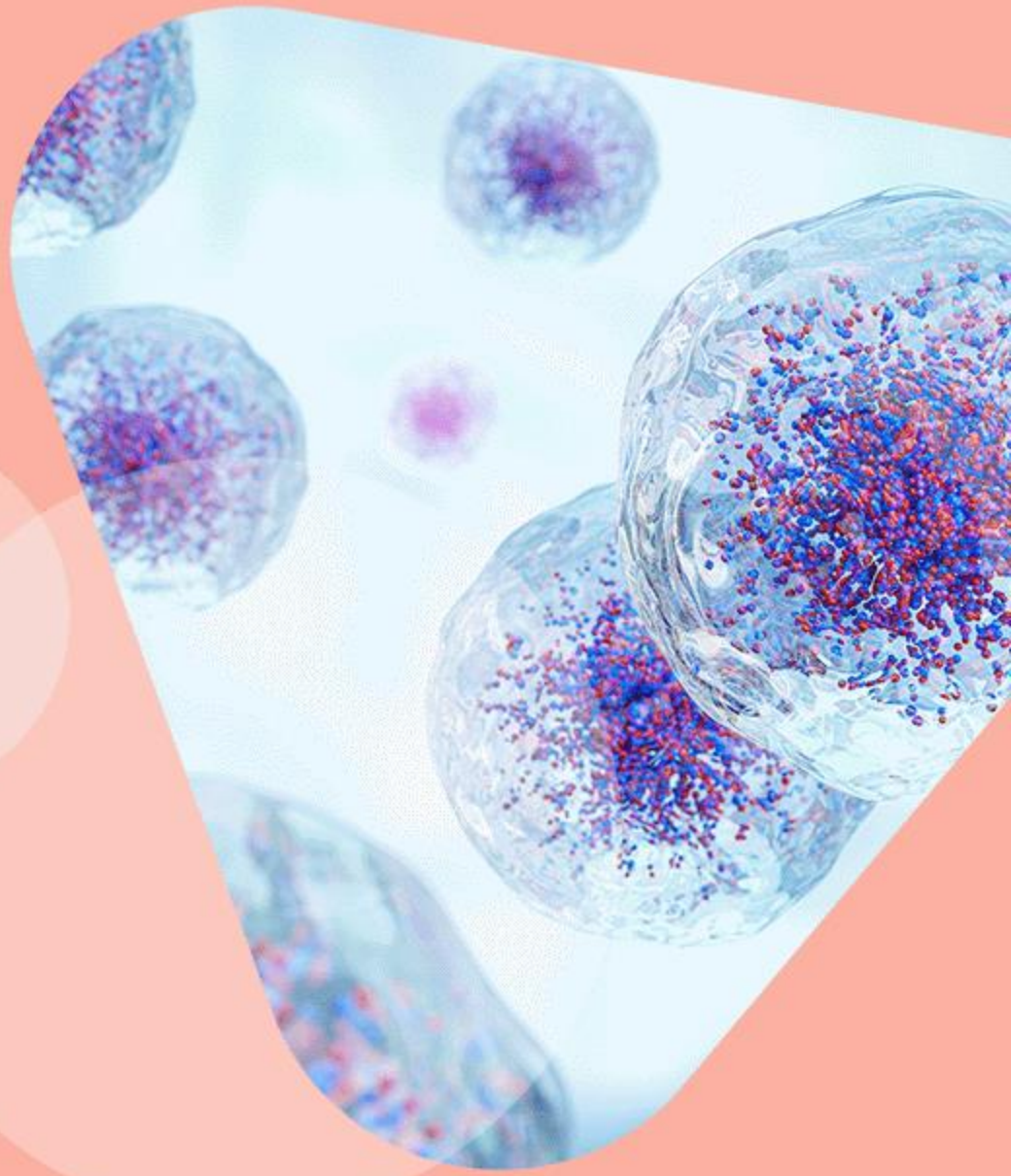
END



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SIGLEC1 is a novel, highly disease relevant TYK2-specific biomarker

SIGLEC-1 (CD169), a lectin-like receptor is expressed on monocytes, DCs, and microglia. The binding of macrophages to activated Tregs is mediated via Siglec-1. (Herzog 2022)

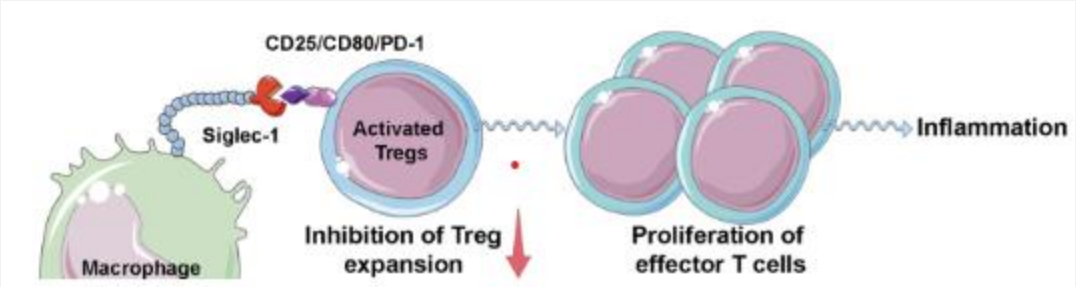

Image: Brzezicka 2023

SIGLEC1 is a biomarker of severity in multiple inflammatory and immune-mediated diseases

- High expression is marker of extraglandular manifestations in **Sjogren's syndrome** (Rose 2016)
- Changes in SIGLEC1 levels in **pediatric SLE** correlates with the change in SLEDAI-2k (von Stuckrad 2020)
- Upregulation of SIGLEC1 observed in DMARD-naïve patients who will subsequently develop persistent **inflammatory arthritis** (e.g. RA) (Seyhan 2020)
- Corelates with disease activity in idiopathic **inflammatory myopathies** (Graf 2022)
- SIGLEC1 is a marker of acute neuroinflammation in **multiple sclerosis** patients (Ostendorf 2021)