Overview

November 2026

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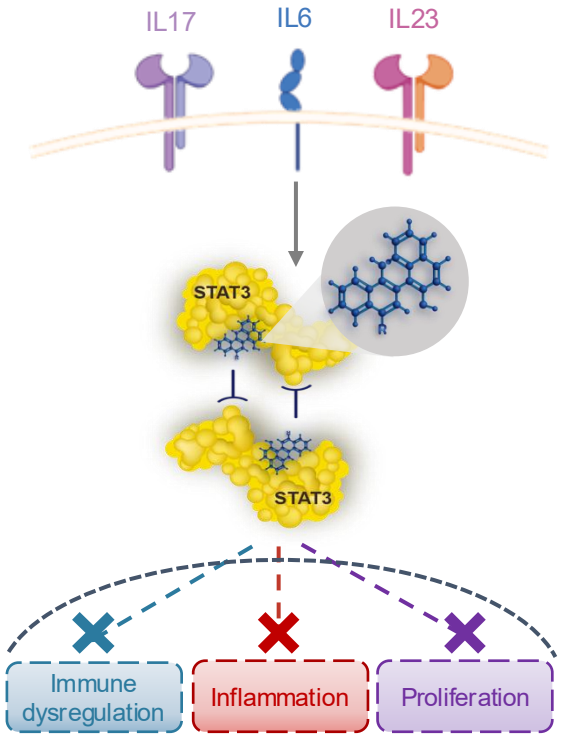
Our STAT3 Inhibitors are Designed to Address the Unmet Need in Inflammatory and Proliferative Diseases

STAT3: Highly Validated Convergent Node



STAT3: central mediator in inflammatory and proliferative disease

Translational Proof-of-Concept

Preclinical

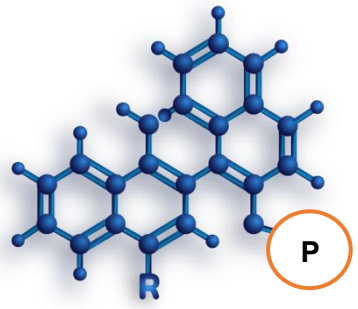
- ↓ pY-STAT3
- ↓ immune dysregulation
- ↓ inflammation
- ↓ proliferation

Confirmed in patients

Clinical

- ↓ pY-STAT3
- ↓ immune dysregulation
- ↓ inflammation
- ↓ proliferation

TTI-109 Validation in P1 Healthy Volunteers



TTI-109

- ✓ **PK**
- ✓ **GI tolerability**
- ✓ **Immune modulation**

TTI-109 Lead Indication



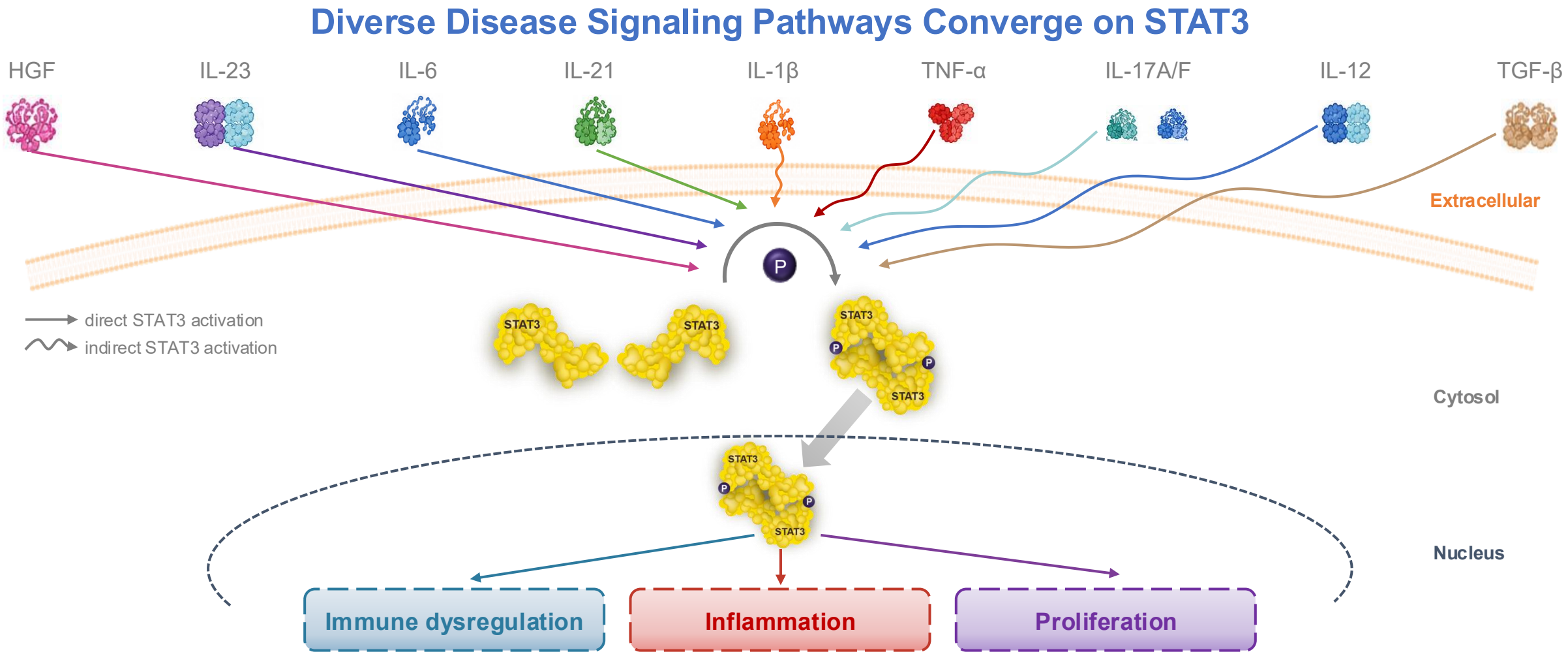
Ulcerative Colitis (UC)

- ✓ **Pre-IND FDA feedback supports IBD development plan**

tvardi THERAPEUTICS

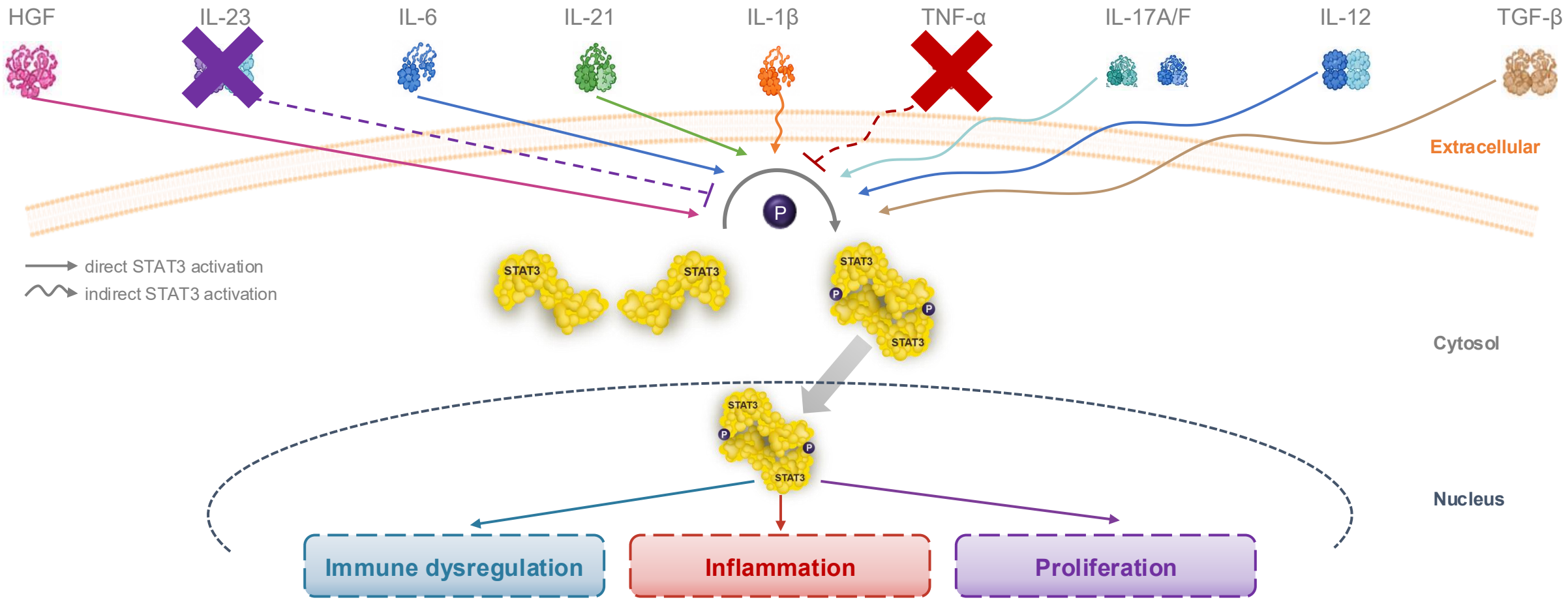
pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705; PK: pharmacokinetics; IBD: inflammatory bowel disease

Targeting STAT3: a Convergence Point of Inflammatory and Proliferative Disease



Targeting STAT3: a Convergence Point of Inflammatory and Proliferative Disease

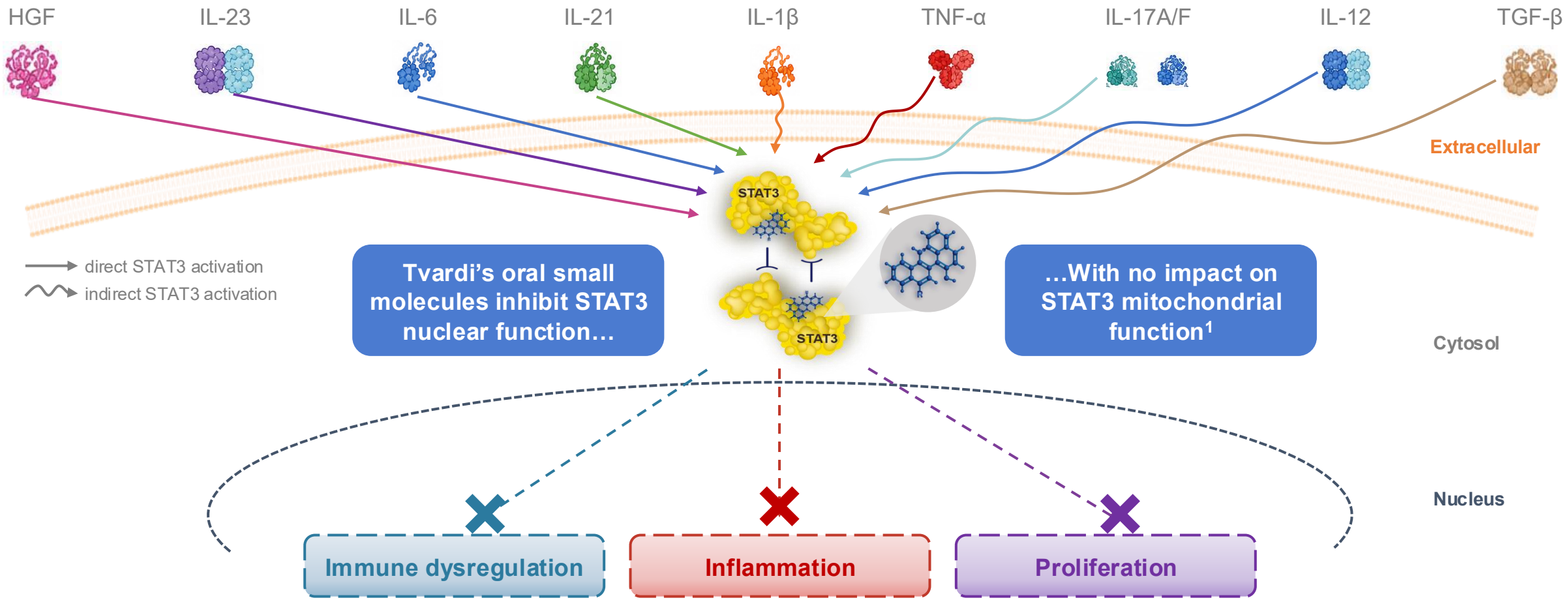
Current Therapies Target Individual Pathways



Single-pathway inhibition fails to suppress STAT3 due to redundant signaling cascades

Targeting STAT3: a Convergence Point of Inflammatory and Proliferative Disease

Diverse Disease Signaling Pathways Converge on STAT3



Selective inhibition of STAT3 nuclear function blocks three drivers of disease from a single target

1. Kasembeli et al. *Biochem Pharmacol.* 2021

Seasoned Leadership: Deep R&D and Operational Expertise

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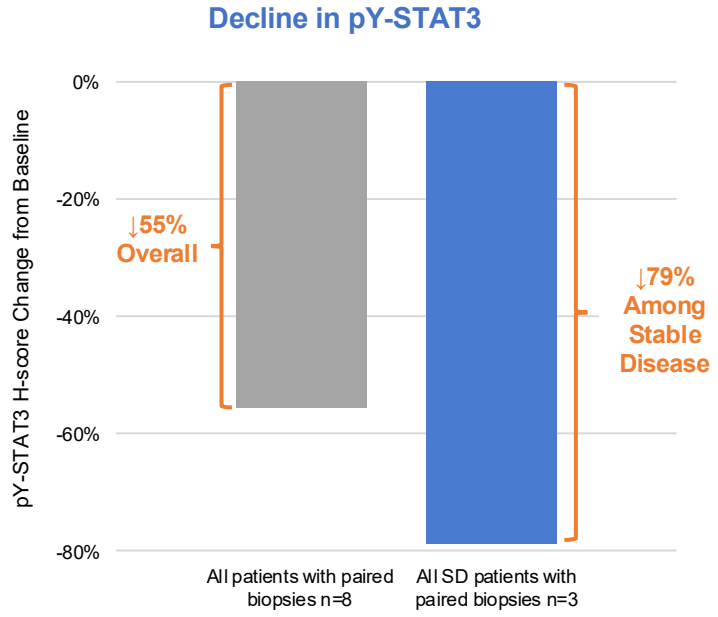
TTI-109

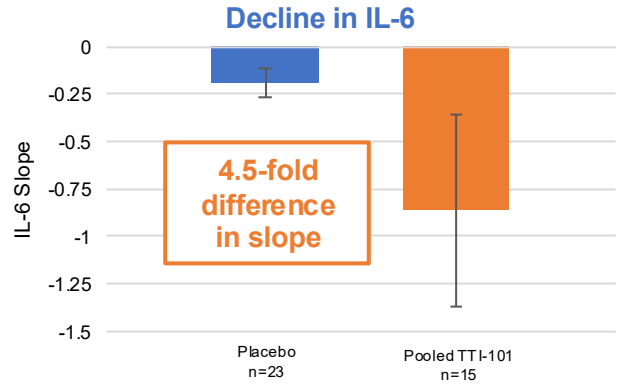
TTI-101 Clinical Foundation for Development of TTI-109

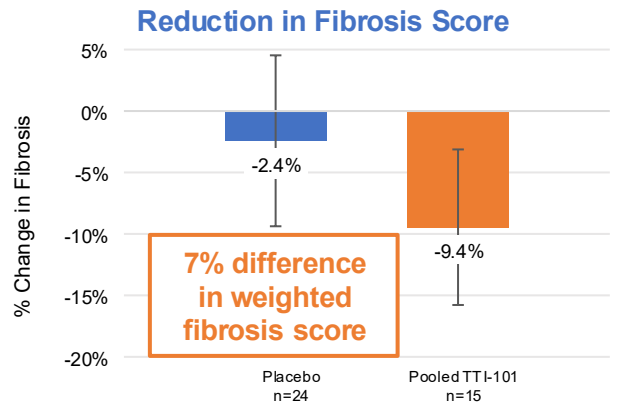
pY-STAT3 Target Engagement Oncology Phase 1[1]



100% of patients with elevated baseline pY-STAT3 demonstrated a decrease within ~6 weeks

IL-6 & Fibrosis Reduction REVERT IPF Phase 2[2]





Overall TTI-101 Safety

In over 300 subjects treated with TTI-101:

Mitochondrial toxicities observed with other STAT3 inhibitors[3] not observed with TTI-101:

- Peripheral neuropathy
- Lactic acidosis

Safety signals observed with JAK inhibitors[4] not observed with TTI-101:

- Major cardiovascular events
- Malignancy
- Cytopenias

Most commonly reported adverse event with TTI-101: diarrhea[1]

1. Tsimberidou et al. *Clin Cancer Res.* 2025; 2. Tvardi Press Release: January 8, 2026; Pooled results; TTI-101 vs placebo baseline-weighted percent change in fibrosis score; 3. Kasembeli et al. *Biochem Pharmacol.* 2021; 4. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions; pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705; SD: stable disease

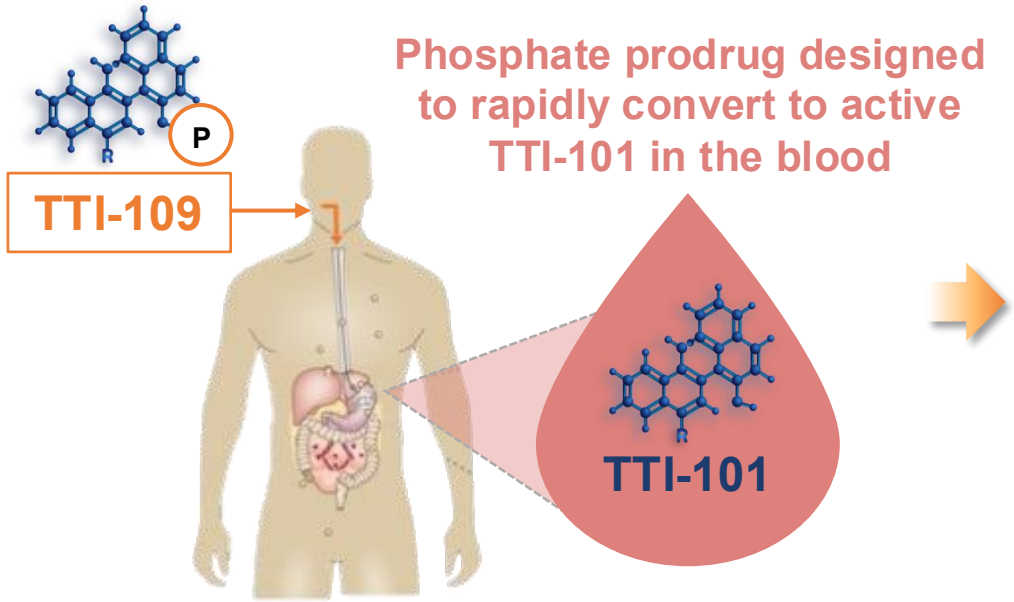
TTI-109 Designed as a Prodrug to Enhance Delivery of STAT3 Inhibitor and Establish Favorable Target Product Profile

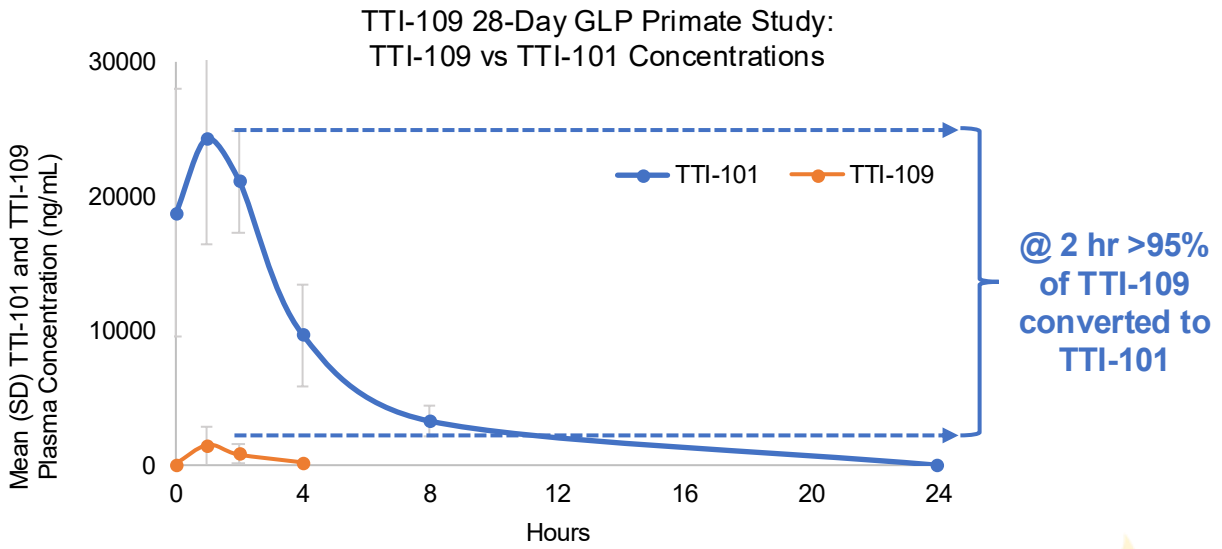
TTI-109 Design Objectives

- Preserve mechanism of action and observed clinical activity of TTI-101
- Improve drug delivery
- Diminish GI exposure

IND-Enabling GLP Results

- No toxicology findings with TTI-109, mirroring TTI-101
- At equal molar doses, TTI-109 and TTI-101 had equivalent exposures
- TTI-109 rapidly converted to active moiety TTI-101





*The pharmacokinetics of TTI-109 and TTI-101 were evaluated in GLP toxicology studies in rats and monkeys. Systemic exposures to TTI-101 from TTI-109 administration were predictable in terms of molar equivalent amounts of anticipated TTI-101.

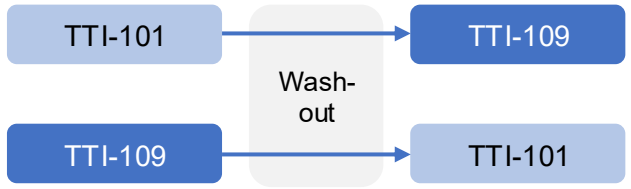
Phase 1 Clinical Program Validated TTI-109 as the Oral Prodrug of TTI-101

Part A: Single Ascending Dose (SAD)



Randomized, double blind, placebo-controlled
Single dosing of TTI-109 vs placebo

Part B: Bioequivalence Crossover Study



Randomized sequence of treatment of n=6 into each group

Part C: Multiple Ascending Dose (MAD)



Randomized, double blind, placebo-controlled
21-day BID dosing of TTI-109 vs placebo
with additional TTI-101 arm

Primary & Secondary Objectives:

- Confirm rapid PK conversion of TTI-109 to TTI-101 in humans
- Confirm equivalent exposures of active moiety with TTI-101 and TTI-109 dosing
- Demonstrate dose-dependent increases in TTI-101 exposures from TTI-109 administration
- Characterize safety/tolerability of TTI-109 relative to TTI-101 after repeated doses

Exploratory Objectives:

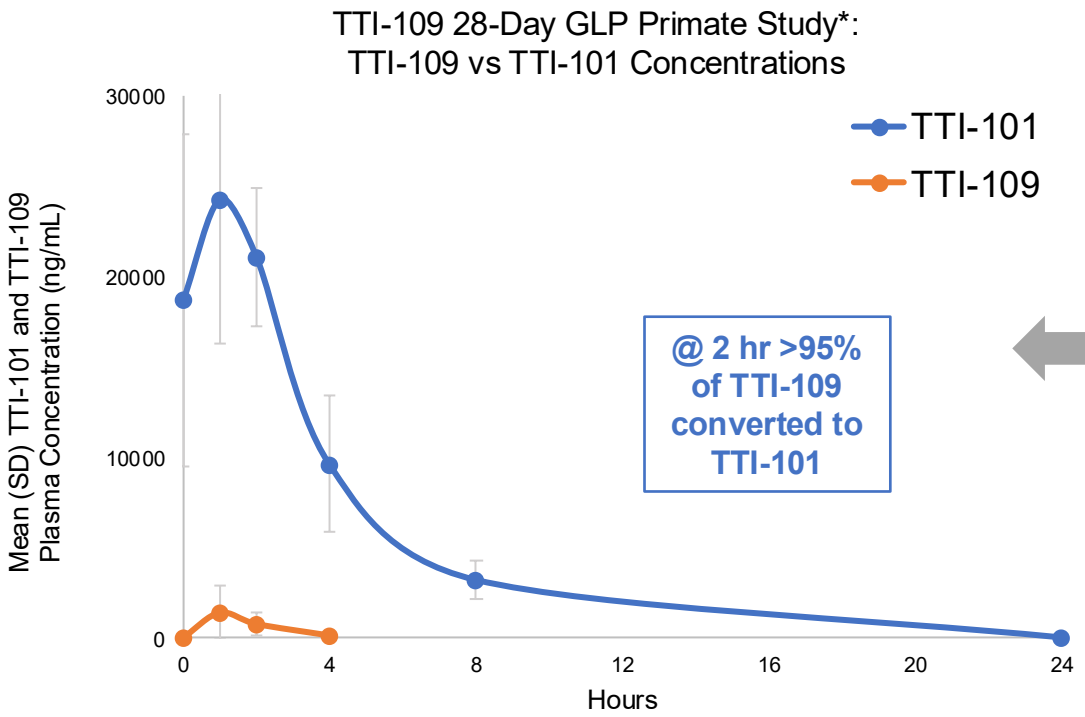
- Evaluate pharmacodynamics of TTI-109 in healthy participants

TTI-101 recommended phase 2 dose of TTI-101 (400mg BID) determined in oncology studies; PK: pharmacokinetics; BID: twice daily

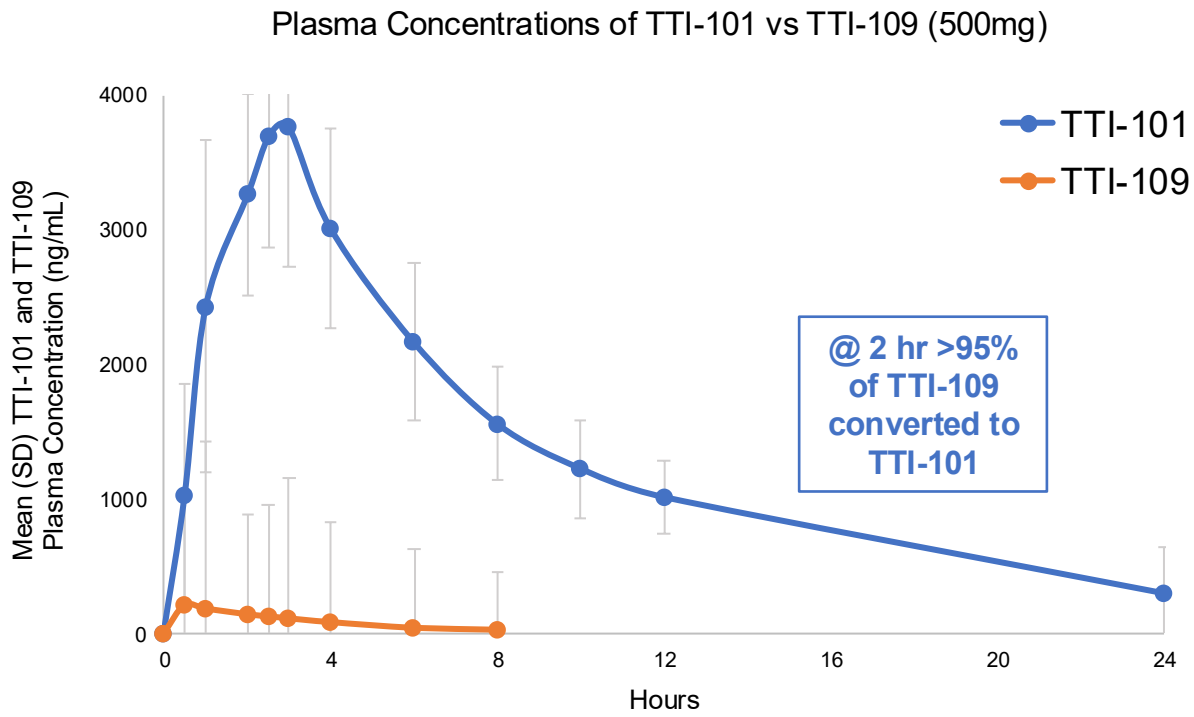
TTI-109 Rapidly Converted to Active TTI-101: Consistent from Primate to Human

SAD

Primate Study: Rapid conversion of TTI-109 to active moiety TTI-101



Human Study: Rapid conversion of TTI-109 to active moiety TTI-101

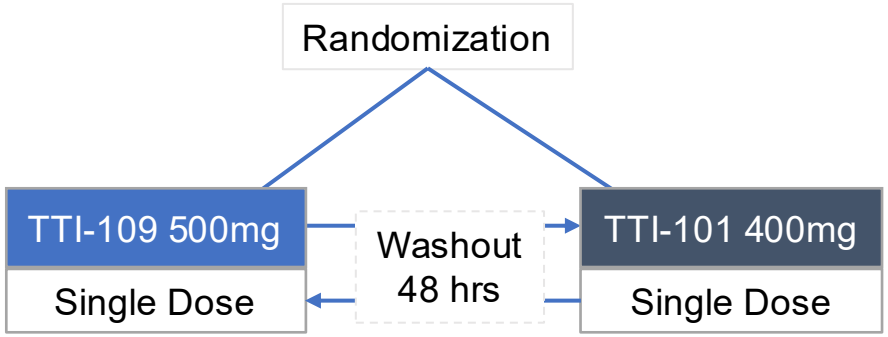


TTI-109 dosing yielded rapid conversion to the active moiety, TTI-101, consistent with animal studies

*The pharmacokinetics of TTI-109 and TTI-101 were evaluated in GLP toxicology studies in rats and monkeys. Systemic exposures of TTI-101 from TTI-109 administration were predictable in terms of molar equivalent amounts of anticipated TTI-101. SAD: Single Ascending Dose

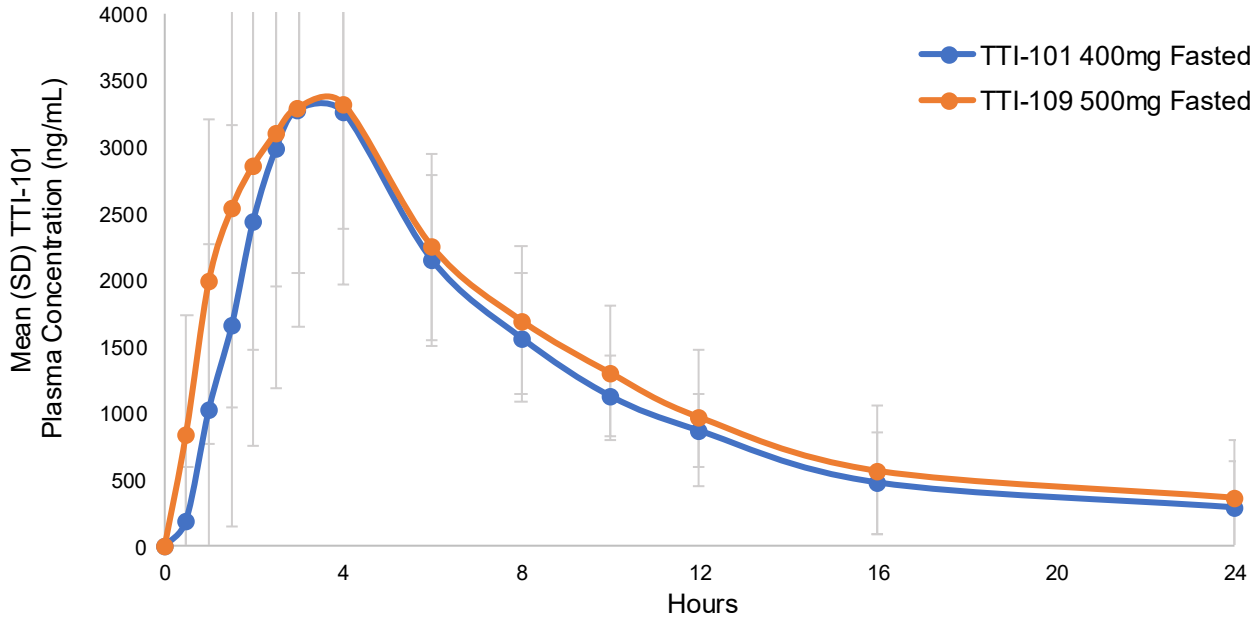
TTI-109 Achieved Equivalent Active Moiety Exposure to TTI-101

Bioequivalence Cross-over Study



TTI-109 500mg ≈ TTI-101 400mg
Near molar equivalent dosages

Plasma Concentrations of TTI-101 vs TTI-109 Dosing (molar equivalent doses)

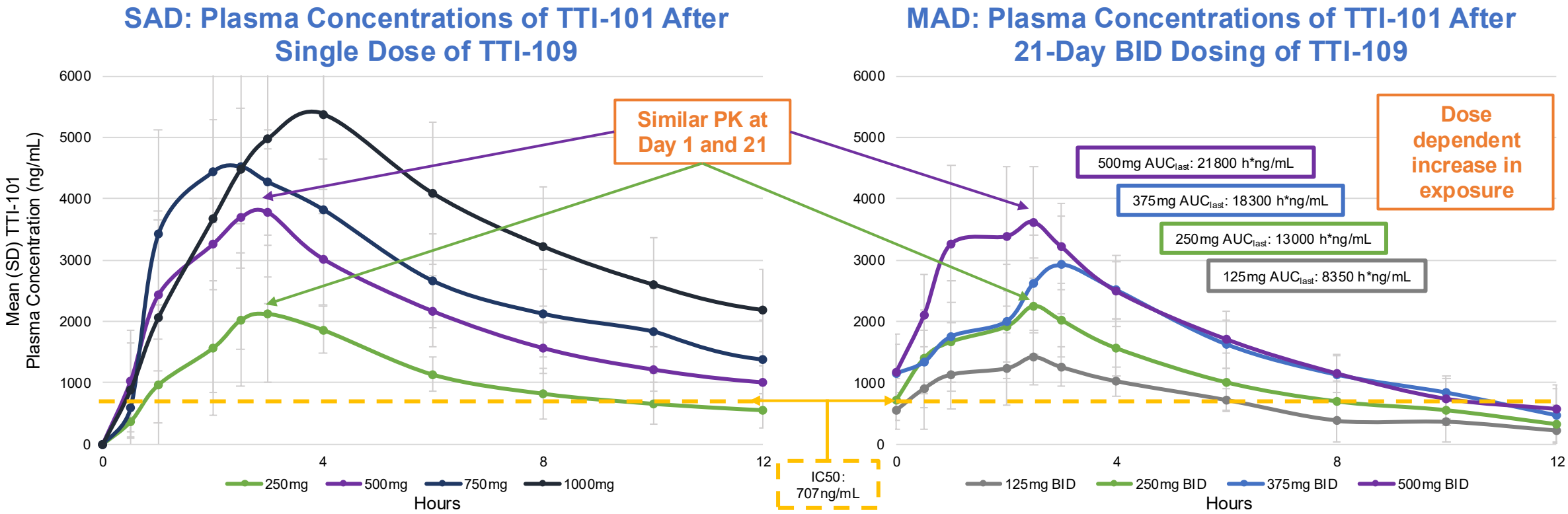


Equal molar dosing confirmed equivalent exposures of active moiety with TTI-101 and TTI-109

TTI-101 plasma concentrations following dosing with TTI-101 400 mg vs TTI-109 500 mg (427 mg TTI-101 molar eq.) in fasted state; Fed and fasted resulted in similar concentrations

TTI-109 Repeat Dosing Delivered Predictable Steady State Parameters

SAD MAD



Predictable, dose-proportional PK with exposures above STAT3 IC_{50}

SAD: Single Ascending Dose; MAD: Multiple Ascending Dose; PK = Pharmacokinetics; STAT3 IC_{50}: in a controlled system where proliferation is driven by pY-STAT3, TTI-101 inhibits cell growth with an IC_{50} of approximately 1.5μM (707ng/mL)

TTI-109 Phase 1 TEAE Profile

MAD

TTI-109 500mg ≈ TTI-101 400mg
Near molar equivalent dosages

Adverse Event Preferred Term	Placebo (N=8)		TTI-109 Doses 1-4 (N=32)		TTI-109 500mg (N=8)		TTI-101 400mg (N=8)	
No. of participants reporting at least one TEAE	5 (63%)		19 (59%)		6 (75%)		6 (75%)	
AEs leading to drug withdrawal	-		1 (3%)*		-		1 (3%)**	
TEAEs observed in ≥ 2 subjects per cohort	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2
Diarrhea	2 (25%)	-	10 (31%)	1 (3%)	2 (25%)	-	3 (38%)	-
Abdominal pain	-	-	3 (9%)	1 (3%)	2 (25%)	-	3 (38%)	-
Headache	1 (13%)	-	4 (13%)	1 (3%)	-	-	1 (13%)	-
Constipation	1 (13%)	-	1 (3%)	-	1 (13%)	-	1 (13%)	1 (13%)

*TTI-109 250mg BID subject discontinued due to grade 3 transaminitis; however, transaminases began to improve while on TTI-109, suggesting AE was unlikely related: bilirubin remained normal throughout treatment; **TTI-101 400mg BID subject discontinued due to diarrhea

- No serious adverse events
- No dose dependent pattern in the TEAEs
- No clinically relevant changes in vital signs or ECGs

Similar incidence of TEAEs across all groups

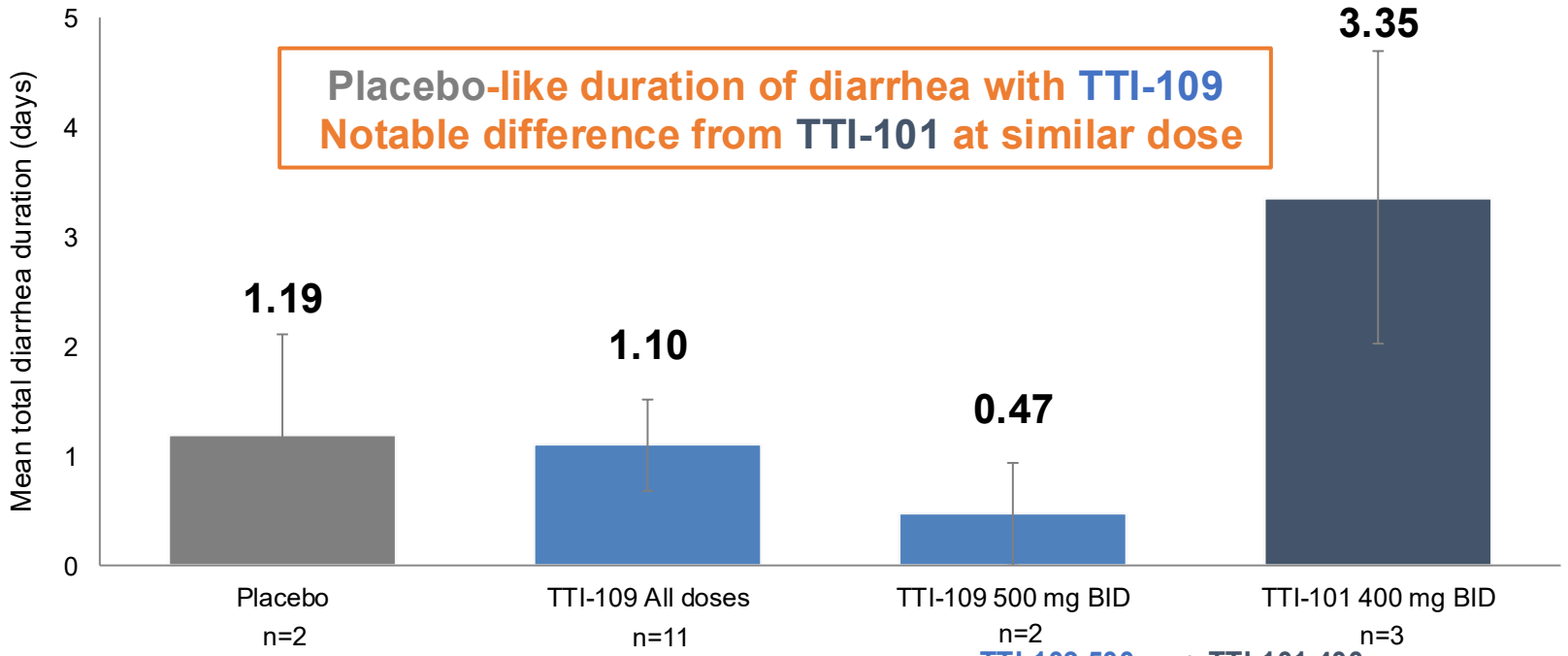
MAD: Multiple Ascending Dose; TTI-101 400 mg vs TTI-109 500 mg (427 mg TTI-101 molar eq.); TEAE: treatment emergent adverse event

Differential Diarrhea Pattern: TTI-109 vs. TTI-101

TTI-109 500mg ≈ TTI-101 400mg
Near molar equivalent dosages

MAD

Adverse Event Preferred Term	Placebo (N=8)		TTI-109 Doses 1-4 (N=32)		TTI-109 500mg (N=8)		TTI-101 400mg (N=8)	
	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2
Diarrhea	2 (25%)	-	10 (31%)	1 (3%)	2 (25%)	-	3 (38%)	-
Discontinuation	0 (0%)		0 (0%)		0 (0%)		1 (13%)	



TTI-109:

- Comparable to placebo
- Shorter duration than TTI-101
- Transient and resolved without interruption

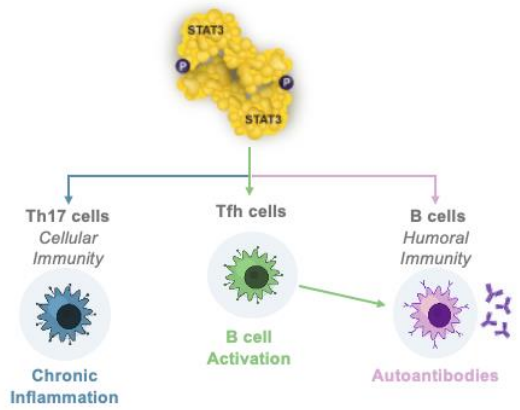
TTI-101:

- Trend for longer duration versus TTI-109 or placebo
- 1 subject discontinued due to diarrhea

MAD: Multiple Ascending Dose; TTI-101 400 mg vs TTI-109 500 mg (427 mg TTI-101 molar eq.); Duration calculated as total per subject

Preclinical Framework for Exploratory Pharmacodynamic Objectives

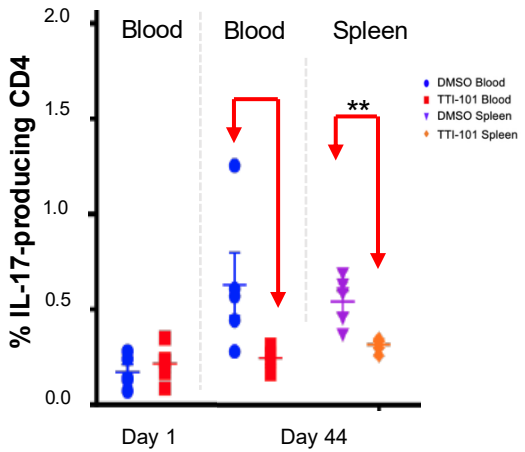
pY-STAT3 drives cellular and humoral immunity



STAT3 is an essential regulator of Th17 and B cells: T cell and B cell-specific STAT3 knockout mice are Th17-deficient and unable to produce autoantibodies, respecitvely[1]

Observed reduction of Th17 in healthy mice with TTI-101[2]

Th17 in healthy mice

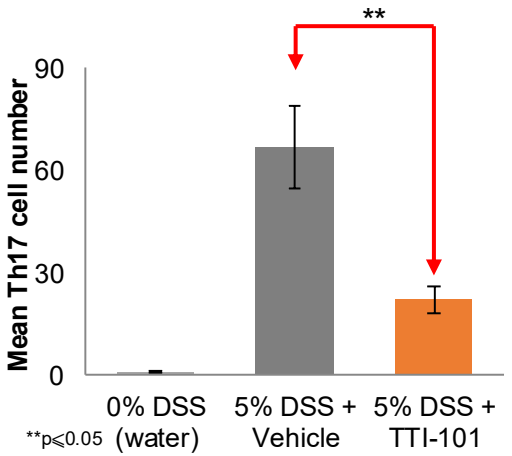


**TTI-101 vs DMSO treated mice p<0.05, ANOVA plus Tukey

In healthy mice, observed a 50% decrease in number of IL-17-producing CD4+ cells

Observed reduction of Th17 in diseased mice with TTI-101[3]

Colonic Th17 cells in IBD Model (5% DSS)[3]



Recapitulated modulation of the immune system in diseased mouse models

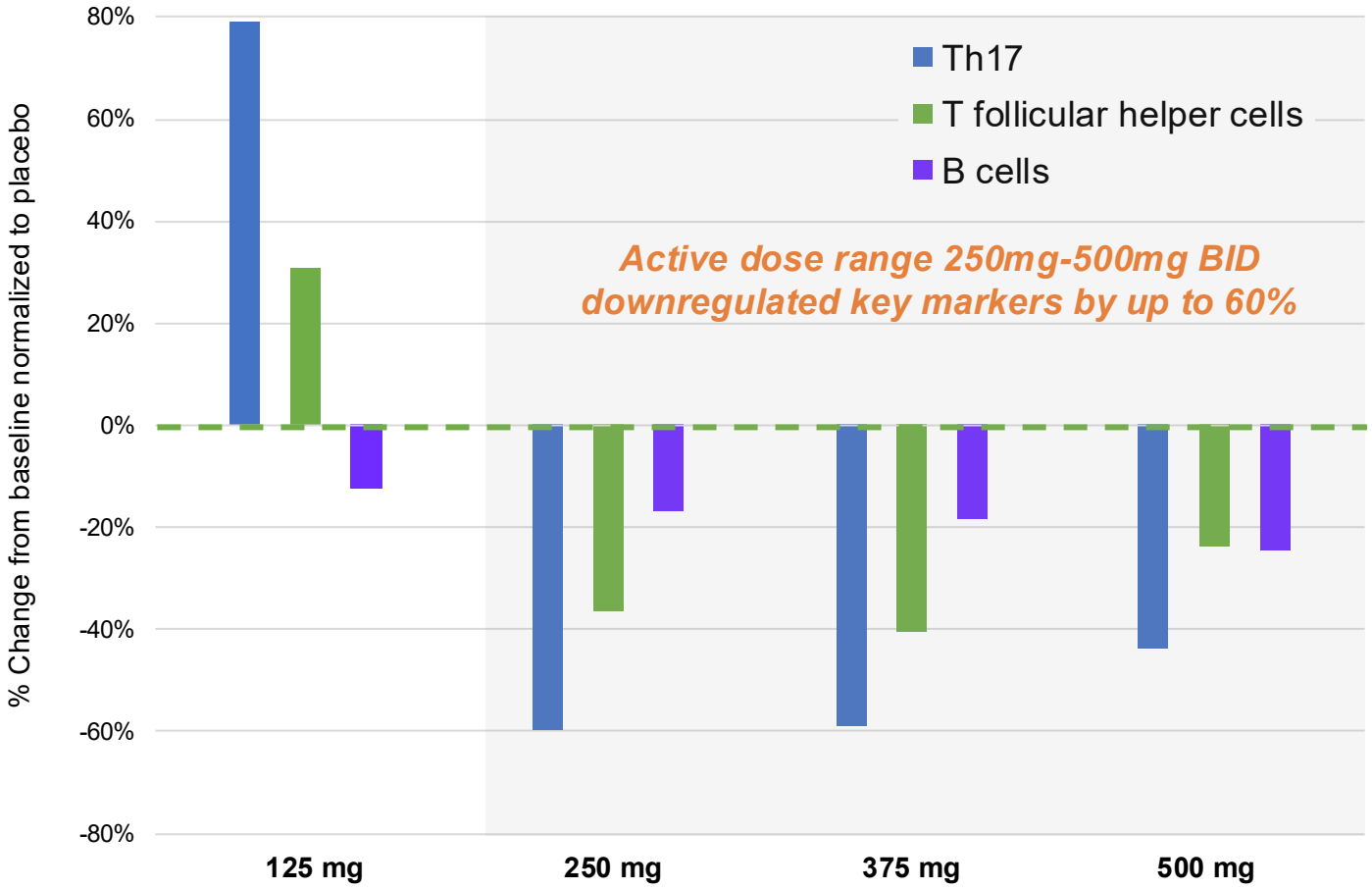
Evaluating pharmacodynamics from HV

- ↓ Th17 immune cell populations in healthy volunteers?
- Additional STAT3 driven-immune cell populations modulated in the expected direction?

1. Steward-Tharp et al. *Immunobiology* 2014; 2. Tweardy et al. *Trans Am Clin Climatol Assoc.* 2022; 3. Figures digitized from Robinson et al. *Cancers* 2023: Dextran sodium sulfate (DSS) model

TTI-109 Selectively Reduced Immune Cell Populations Driven by STAT3 in Phase 1 MAD Cohort

MAD



At active doses, downregulation of STAT3-driven immune populations observed:

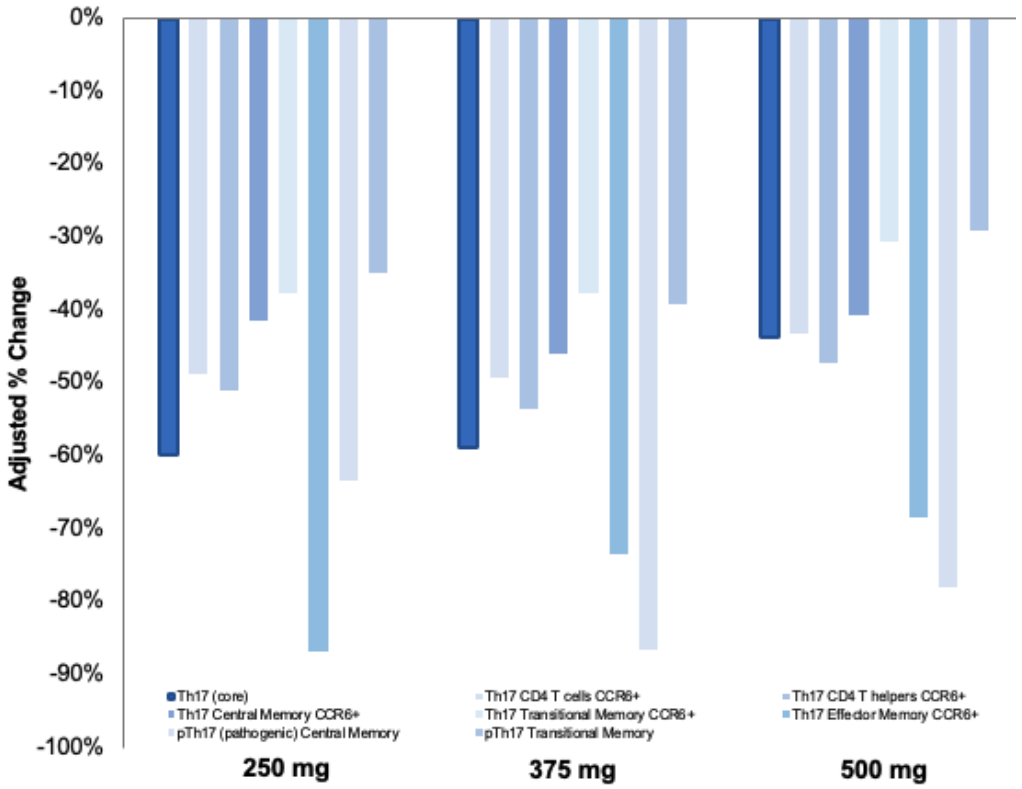
- ✓ Effects **sustained** across active dose range
- ✓ **Reduced** Th17, Tfh and B cell populations
- ✓ **Reductions** across 16 cellular and humoral immune subsets recognized as pathologic markers of inflammatory and proliferative diseases

TTI-109 modulated STAT3-driven cellular (T cell) and humoral (B cell) immune populations

TTI-109 by dose paired %Δ = (Post−Pre)/Pre; placebo-adjusted (n=8 per dose). Cell population changes assessed by flow cytometry (FACS) on peripheral blood mononuclear cells (PBMC) collected from subjects in the Phase 1 multiple ascending dose (MAD) cohort; values shown represent percentage change from baseline, normalized to placebo, for each active dose cohort. Th17, T follicular helper (Tfh), and B cell populations identified by surface marker immunophenotyping

TTI-109 Reduced Th17 Cells Implicated in UC Pathology

MAD



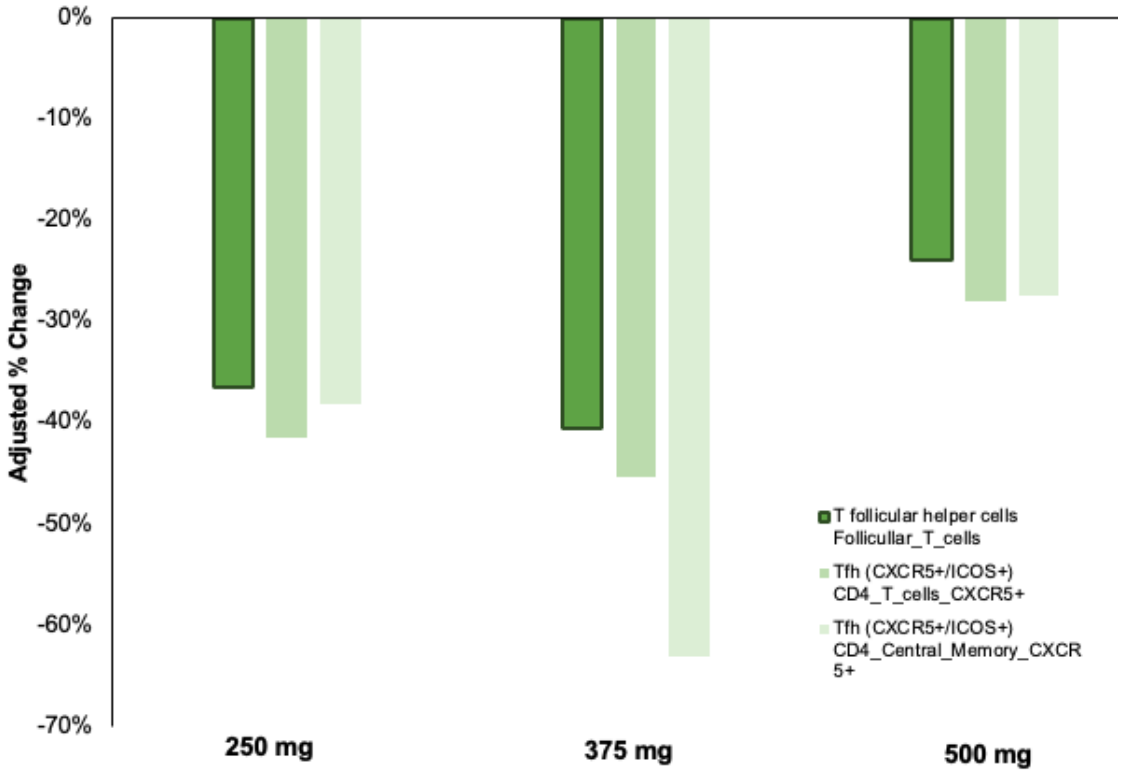
Broad suppression of pathogenic Th17-associated immune populations

Cell Type	%Δ	UC Rationale
Th17 cells (core)	**-54%**	**Central pathogenic effectors in UC and drive mucosal inflammation.**[1]
CD4 T cells CCR6+	-47%	Enriched in active UC biopsies.[2]
CD4 T helpers CCR6+	-51%	Drive IL-21-mediated B cell activation and pathogenic antibody production in UC.[2]
CD4 Central Memory CCR6+	-43%	Expanded in UC patients and drive pathogenic Th17 differentiation[2]
CD4 Transitional Memory CCR6+	-35%	Enriched in UC mucosa and contribute to the sustained Th17 cytokine milieu driving colonic inflammation.[1]
CD4 Effector Memory CCR6+	-76%	Accumulate in inflamed UC mucosa and are a major source of pathogenic IL-17 and IFN-γ.[1]
CD4 Central Memory CXCR3+CCR4−CCR6+ (pTh17)	-76%	Strongly associated with mucosal destruction and treatment-refractory UC.[1,4]
CD4 Transitional Memory CXCR3+CCR4−CCR6+ (pTh17)	-34%	Co-produce IL-17 and IFN-γ, accumulating in IBD mucosa and sustaining tissue-destructive inflammation.[1]

*Placebo-adjusted % change (**%Δ**)= TTI-109 dose-group mean − pooled placebo mean (per-subject % change). Paired n: D2=8, D3=8, D4=8; pooled placebo n=8. 1. Wen Y, et al. *Therap Adv Gastroenterol*. 2024; 2. Meitei HT, et al. *iScience*. 2025; 3. Sun L, et al. *Gastroenterol Res Pract*. 2021; 4. Paroni M, et al. *J Crohns Colitis*. 2026

TTI-109 Reduced T Follicular Cells Implicated in UC Pathology

MAD



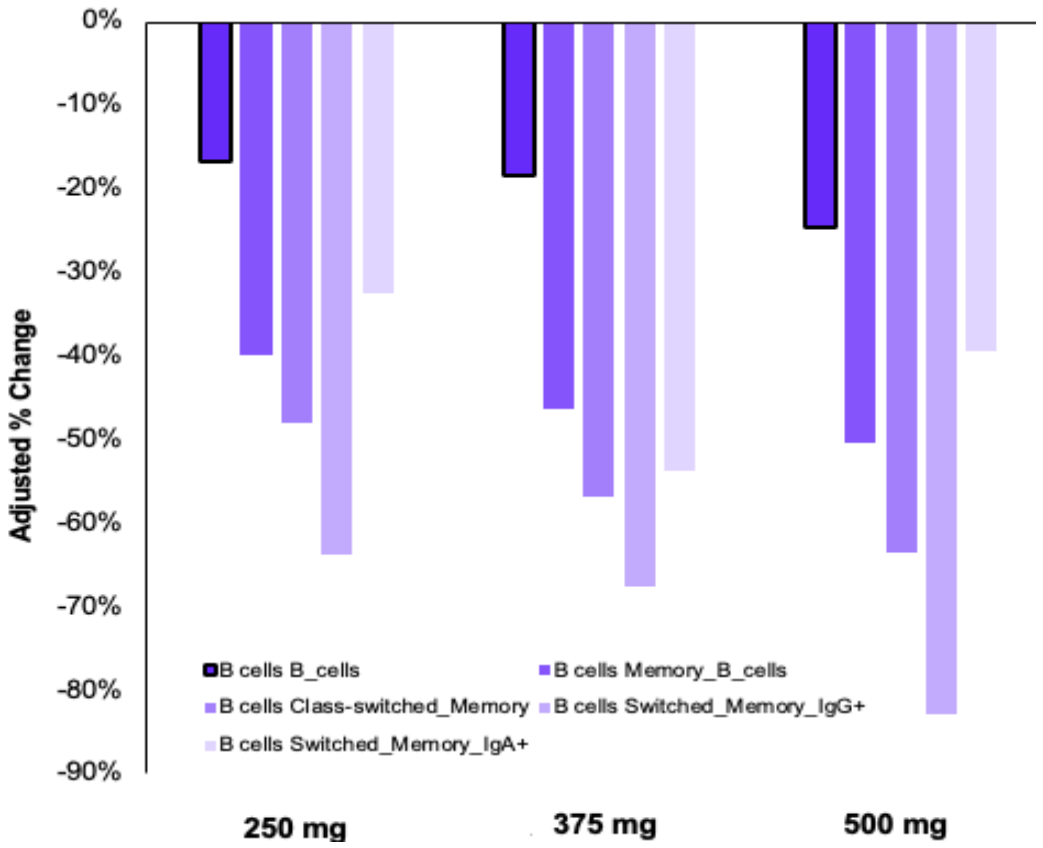
Cell Type	%Δ	UC Rationale
T follicular helper cells (Tfh)	-34%	**Drive UC through humoral autoantibody production and direct cellular Bcl6-dependent mucosal inflammation.[1,2]**
CD4 T cells CXCR5+	-38%	Track with UC disease activity and provide IL-21-driven B-cell help.[3]
CD4 Central Memory CXCR5+	-43%	Elevated in active UC, correlating with disease activity, memory B cell expansion, and plasmablast generation.[2]

Suppression extended beyond cellular immunity to the Tfh immune populations that drive mucosal B cell responses

*Placebo-adjusted % change (**%Δ**)= TTI-109 dose-group mean − pooled placebo mean (per-subject % change). Paired n: D2=8, D3=8, D4=8; pooled placebo n=8. 1. Sun L, et al. *Gastroenterol Res Pract*. 2021; 2. Long Y, et al. *Front Immunol*. 2020; 3. Xue G, et al. *Medicine*. 2019

TTI-109 Reduced B Cells Implicated in UC Pathology

MAD

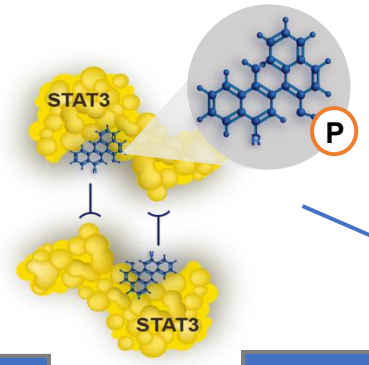


Cell Type	%Δ	UC Rationale
B cells	**-20%**	**Mucosal B-cell and plasma cell expansion is a hallmark of active UC, contributing directly to colonic inflammation and tissue injury.**[1]
Memory B cells	-46%	Track serum Ig levels and humoral activity in active UC.[2]
Class-switched Memory	-56%	Plasmablast-skewed, class-switched humoral response correlates with UC disease activity.[1]
Switched Memory IgG+	-71%	Accumulate in the inflamed colon and generate autoantibodies against the gut lining, directly linking class-switched IgG B cells to mucosal damage.[1]
Switched Memory IgA+	-42%	Aberrantly express cytotoxic granzyme B, contributing to epithelial damage.[3]

Suppression extended to B cell (humoral) immunity associated with colonic inflammation and tissue damage

*Placebo-adjusted % change (**%Δ**)= TTI-109 dose-group mean − pooled placebo mean (per-subject % change). Paired n: D2=8, D3=8, D4=8; pooled placebo n=8. 1. Uzzan M, et al. *Nat Med*. 2022; 2. Masaki Y, et al. *Clin Exp Immunol*. 2016; 3. Cupi ML, et al. J *Immunol*. 2014

We Believe TTI-109 Advances TTI-101's Clinical Profile Across PK, GI Tolerability and Immune Modulation



TTI-109 is designed to enhance delivery & improve tolerability while preserving mechanism of action

TTI-101 Clinical Observations[1,2]

- ✓ **Target Engagement**
  - ↓ pY-STAT3
- ✓ **Inflammation**
  - ↓ IL-6
- ✓ **Proliferation**
  - ↓ Fibrosis

+

TTI-109 Clinical Observations

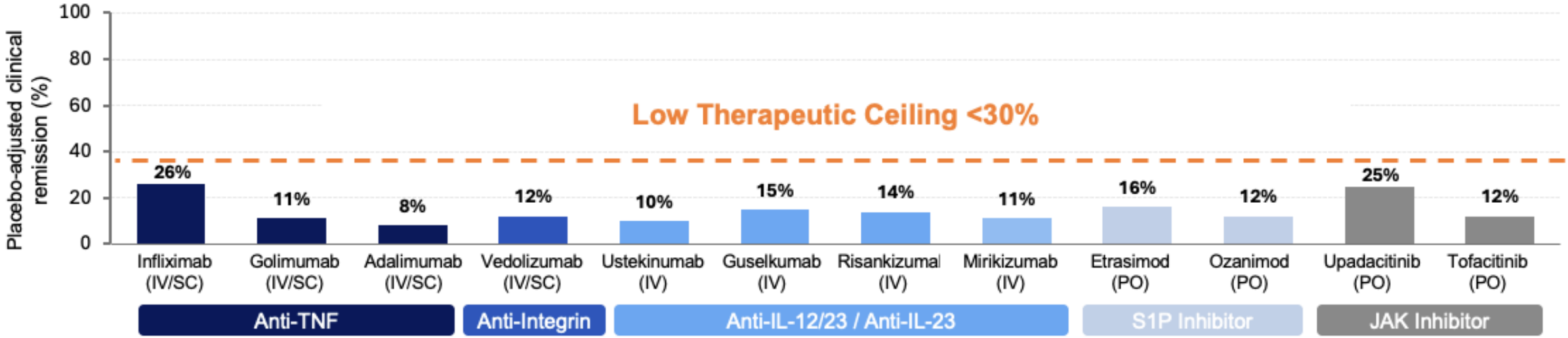
- ✓ **PK**
  - Rapid conversion with dose-proportional exposure >STAT3 IC_{50}
- ✓ **GI Tolerability**
  - Similar to placebo and improved over TTI-101
- ✓ **Immune Modulation**
  - ↓ Cellular and ↓ humoral disease related immune populations in UC

1. Tsimberidou et al. *Clin Cancer Res.* 2025; SD: Stable Disease; 2. Tvardi Press Release: January 8, 2026; pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705; STAT3 IC_{50}: in a controlled system where proliferation is driven by pY-STAT3, TTI-101 inhibits cell growth with an IC_{50} of approximately 1.5μM (707ng/mL)

UC: Large Market Opportunity with High Unmet Medical Need

UC Therapy Landscape

>1.25M[1]	$9B[2]	~$3B[2]
Diagnosed US Patients	Global Market (2024)	US Market (2024)



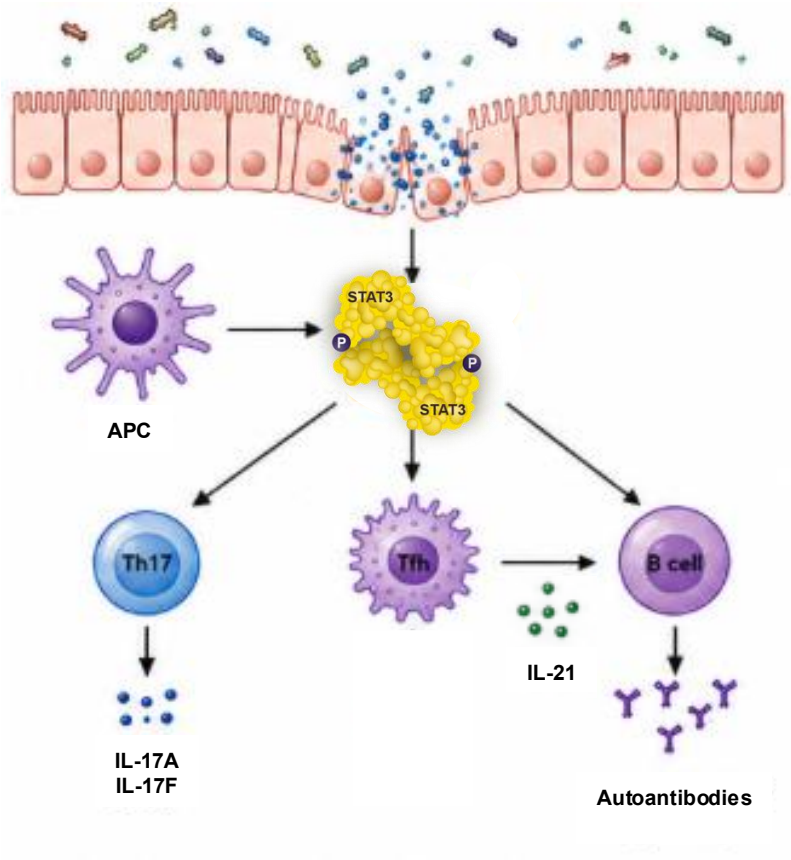
Placebo-adjusted clinical remission (induction) rates by MoA in UC[3]

>70% of patients do not achieve clinical remission with existing therapies

1. Lewis *Gastroenterology*. 2023; 2. S&S Insider. Estimate includes patients identified with indeterminate IBD. 3. Clinical remission rates from product labels; UC: ulcerative colitis; MoA: mechanism of action; IV: intravenous; SC: subcutaneous; PO: oral; MACE: major adverse cardiovascular events; Values represent placebo-adjusted clinical remission rates from pivotal induction studies and are intended for cross-mechanism comparison only. Direct comparisons across trials should be interpreted cautiously due to differences in study design, patient populations, and assessments

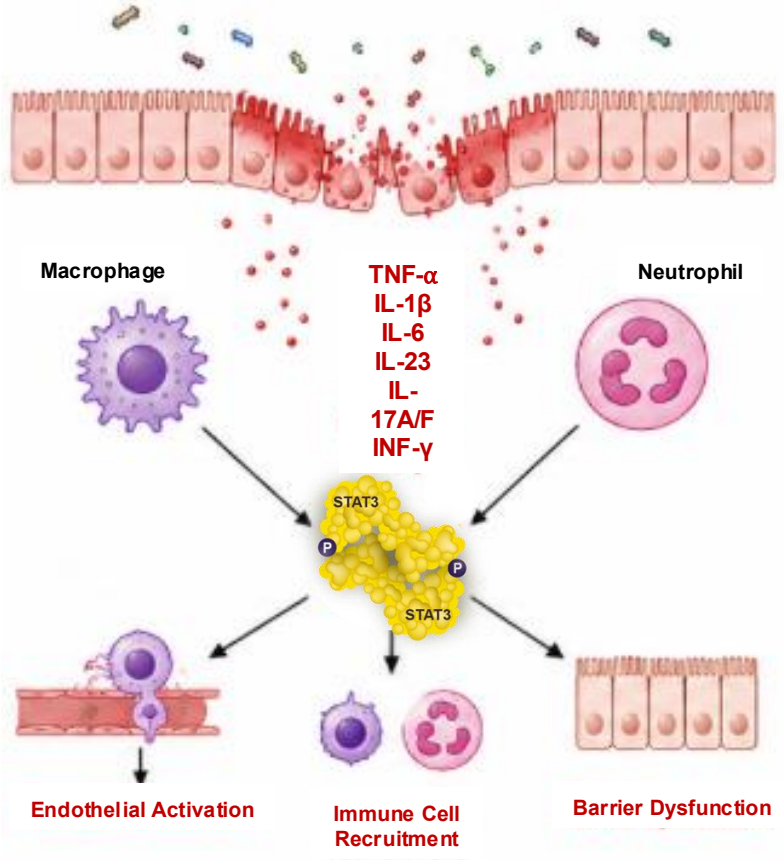
One Target, Three Mechanisms: pY-STAT3 Drives the Shared Biology of UC

Chronic immune activation and perpetuation of intestinal inflammation



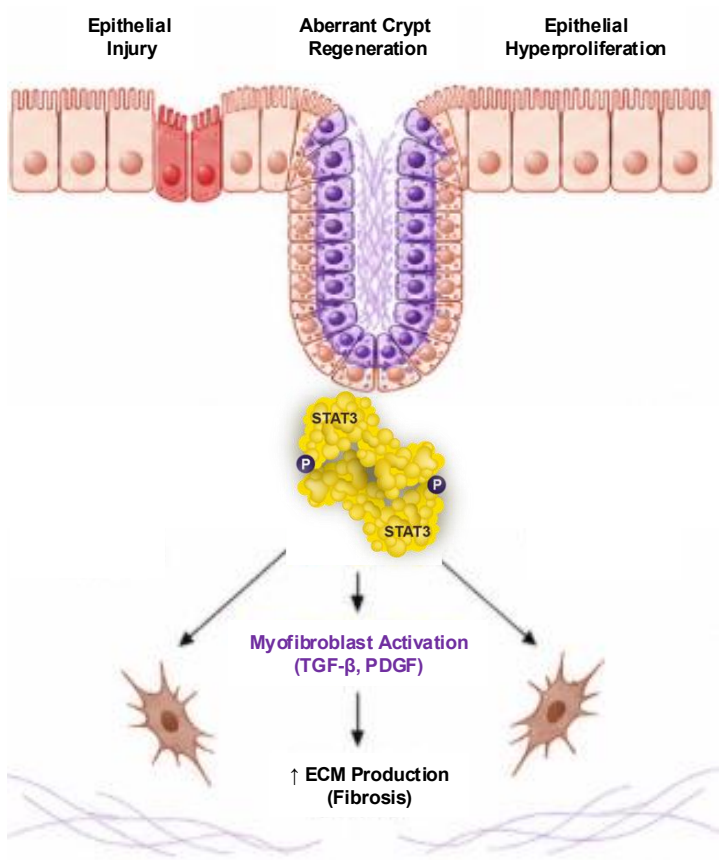
Immune Dysregulation

Persistent inflammation, tissue injury and ulceration



Inflammation

Chronic remodeling, fibrosis and increased dysplasia risk



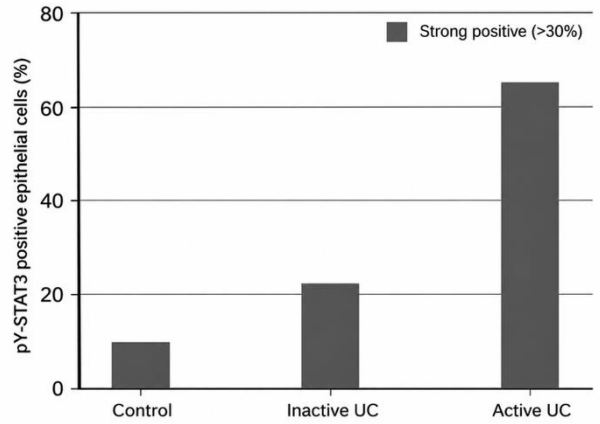
Proliferation

pY-STAT3 Reduction Demonstrated in Preclinical Models and Clinical Biopsies

Activated STAT3

pY-STAT3 is associated with UC clinical activity

Tissue pY-STAT3 increases with UC activity[1]



pY-STAT3 associated with clinical activity[2,3]

Reduced pY-STAT3

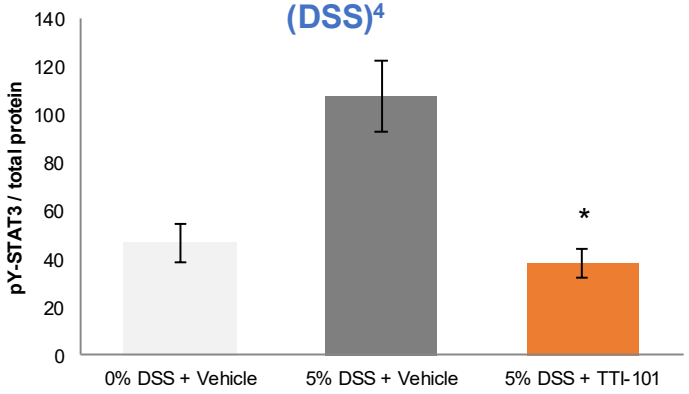
Clinical response

pY-STAT3

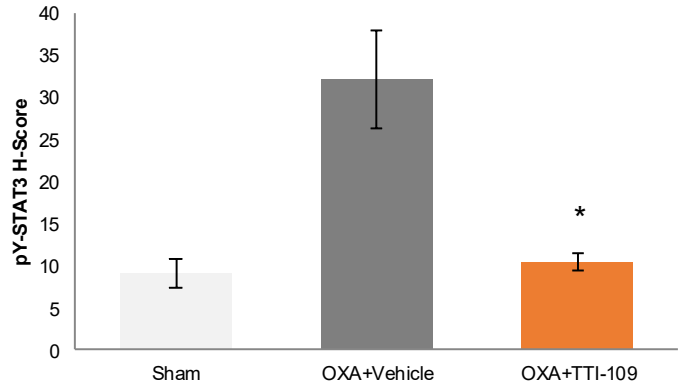


pY-STAT3 levels restored to baseline after TVRD STAT3 inhibitor treatment

GI model driven by innate immune axis (DSS)[4]

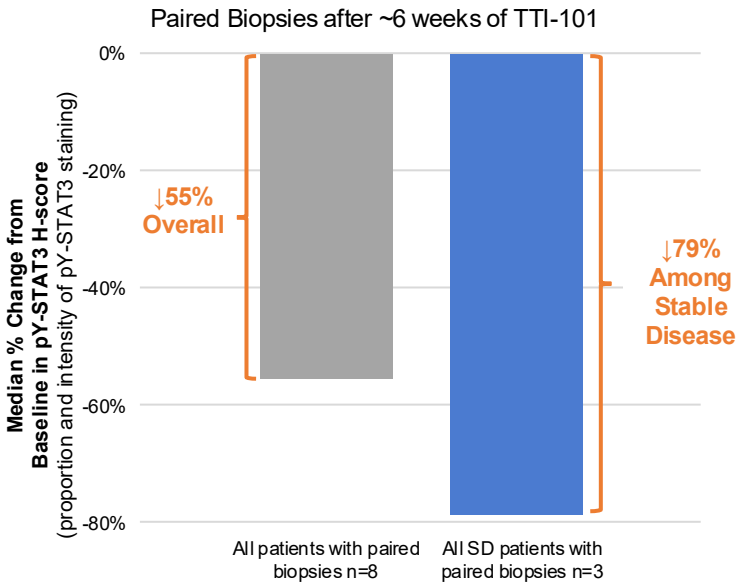


GI model driven by adaptive immune axis (OXA)[5]



Clinical PoC: Reduced pY-STAT3

Oncology Phase 1[6]



8/10 patients had elevated pY-STAT3 at baseline; elevated pY-STAT3 defined as H-score >30 on a 0-300 scale

100% of patients with elevated baseline pY-STAT3 demonstrated a decrease within ~6 weeks

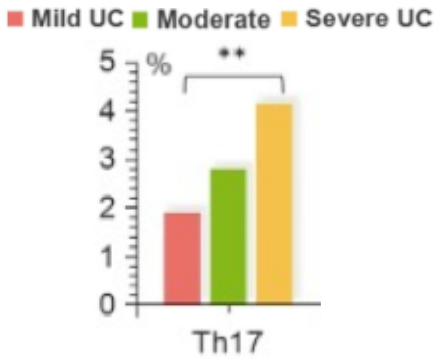
1.Adapted from Li et al. *Gut* 2010 ; 2. Schreiber et al *Gastroenterology* 2021; 3. Verstockt et al *J. Crohn's and Colitis* 2025; 4. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model; 5. Tvardi data generated with CRO: WuXi oxazolone (OXA) model; n=8 per group statistical comparison using exact Mann-Whitney + Kruskal-Wallis; 6. Tsimberidou et al. *Clin Cancer Res.* 2025; SD: Stable Disease; pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705; *p⩽0.05

STAT3 Inhibition Normalized Preclinical and Clinical Pathogenic Immune Cell Populations

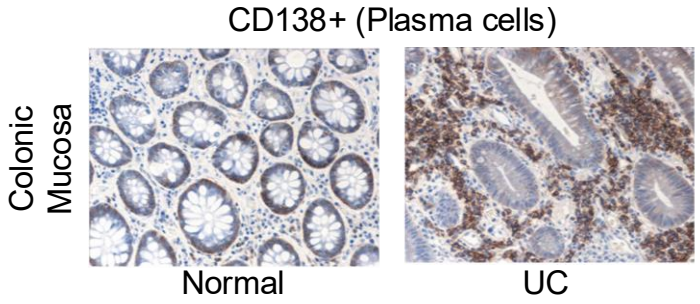
Immune dysregulation

Cellular (Th17) and Humoral (B cell) dysregulation in UC patients

Th17 cell frequency increases with UC disease severity (p<0.01). Th17 positively correlated with Mayo score (p < 0.001)[1]

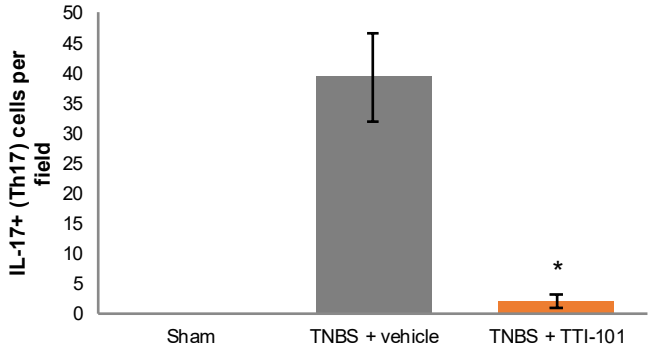


B cells/plasma cells heavily infiltrate the inflamed mucosa of UC patients[2]

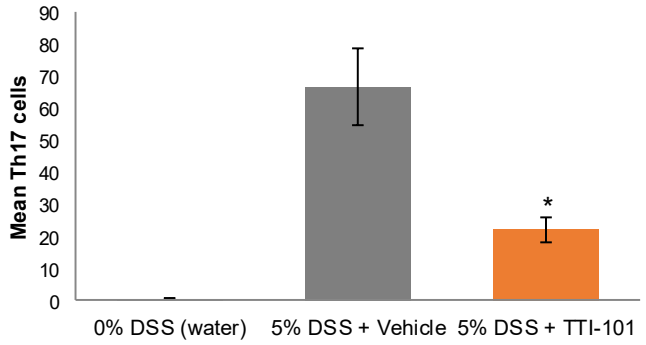


Th17 restored to homeostatic levels after TVRD STAT3 inhibitor

GI model driven by adaptive immune axis (TNBS)[3]

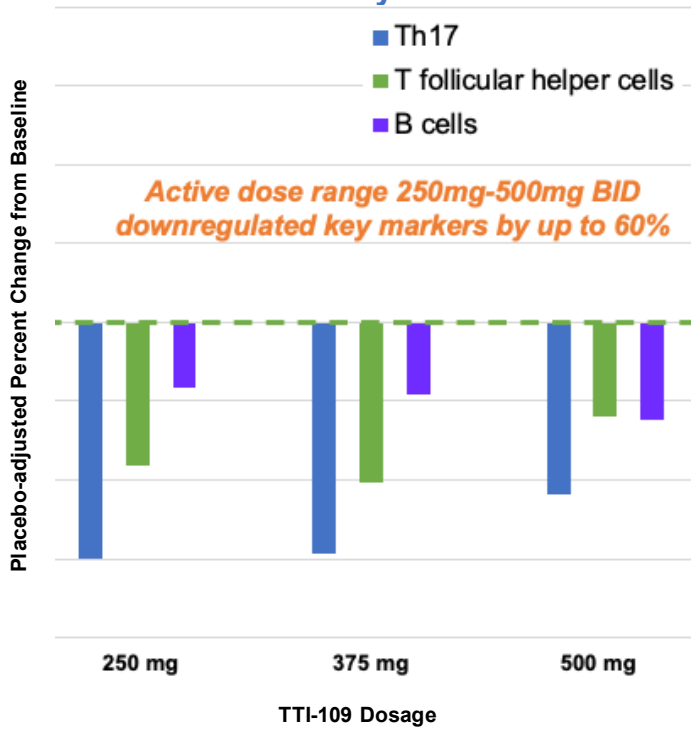


GI model driven by innate immune axis (DSS)[4]



Clinical PoC: Reduced key immune cell populations

Phase 1 Healthy Volunteers



Downregulation of STAT3-driven immune populations observed with TTI-109

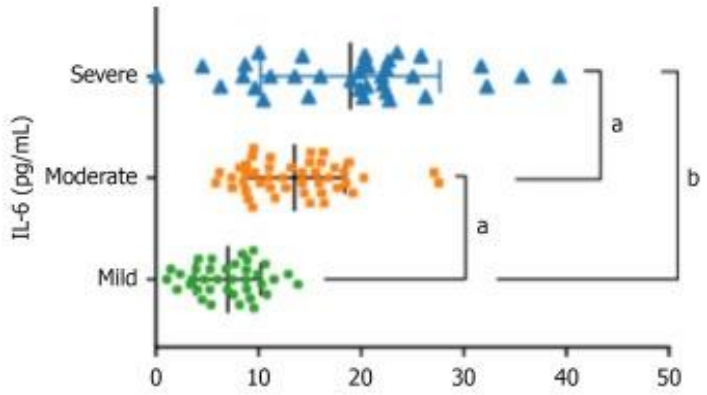
1. Zhang el al. *European Journal of Inflammation*. 2023; 2. Uo et al. *Gut* 2013; 3. Figures digitized from Robinson et al. *J Clin Med* 2022: 2,4,6-trinitrobenzene sulfonic acid (TNBS) model; 4. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model; *p⩽0.05 TTI-101 vs vehicle

STAT3 Inhibition Reduced IL-6 and Inflammation Preclinically and in Patients

Inflammation

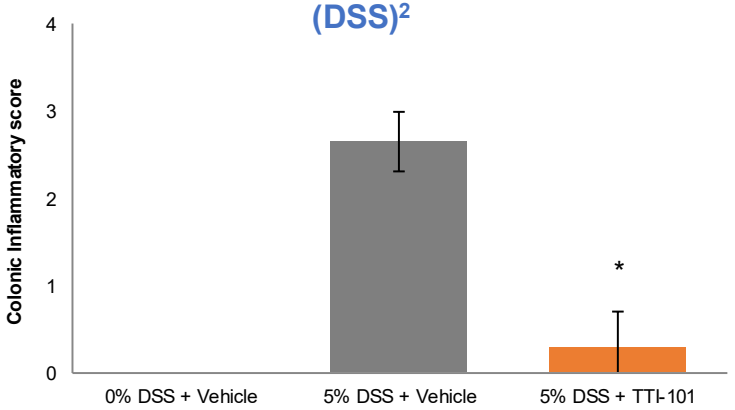
Inflammatory cytokine IL-6 correlates with UC severity

Increases in serum levels of inflammatory marker IL-6 significantly associated with worsening disease activity[1]

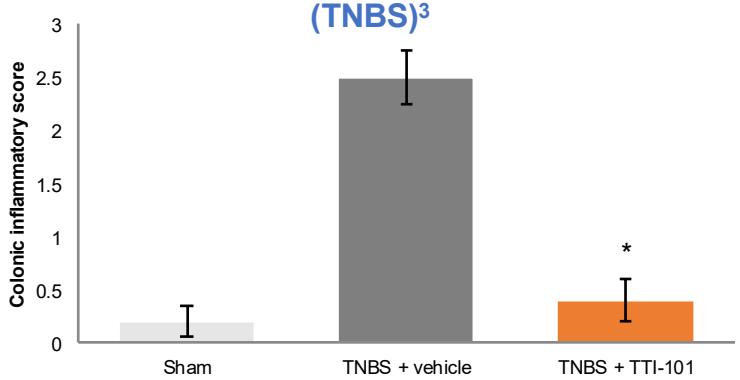


Colonic inflammation significantly attenuated with TVRD STAT3 inhibitor

GI model driven by innate immune axis (DSS)[2]



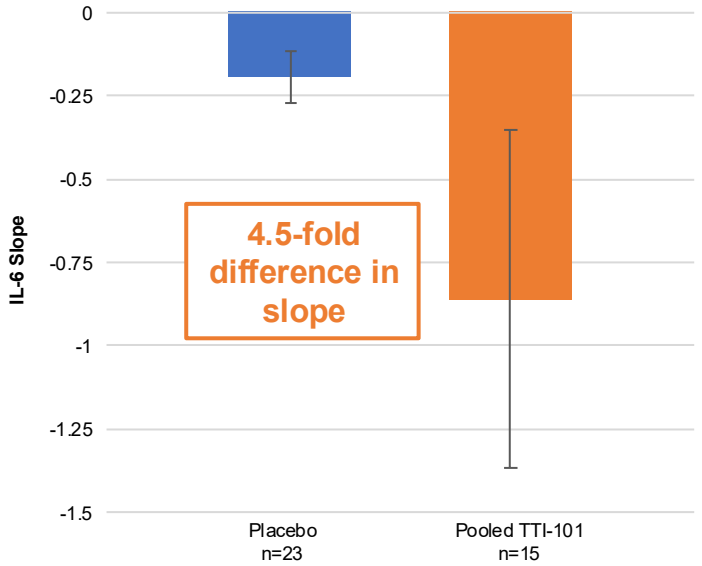
GI model driven by adaptive immune axis (TNBS)[3]



Clinical PoC: Reduced IL-6

IPF Phase 2[4]

TTI-101 vs Placebo Decline in IL-6



IL-6: a key pro-inflammatory cytokine that signals via STAT3

Greater decrease in IL-6 slope among pooled patients treated with TTI-101 vs placebo

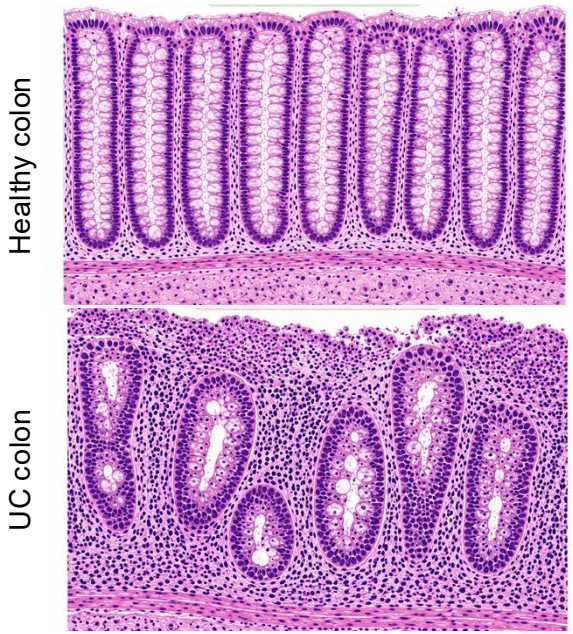
1. Fu et al. *World J Gastrointest Surg.* 2025; [a]*P* < 0.01; [b]*P* < 0.001; 2. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model; 3. Figures digitized from Robinson et al. *J Clin Med* 2022: 2,4,6-trinitrobenzene sulfonic acid (TNBS) model; 4. Tvardi Press Release: January 8, 2026; *p⩽0.05 TTI-101 vs vehicle

STAT3 Inhibition Reduced Proliferative Signaling and Fibrosis Preclinically and in Patients

Proliferation

Proliferation and fibrosis correlate with UC severity

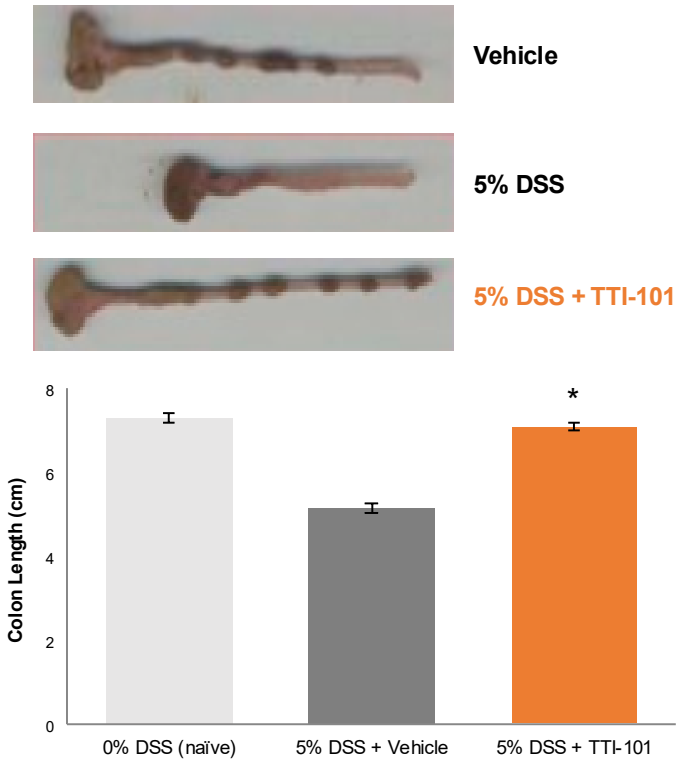
Disease severity indices integrate histologic architecture[1]



Submucosal fibrosis present in 100% of UC specimens and directly linked to severity and chronicity of mucosal inflammation[2]

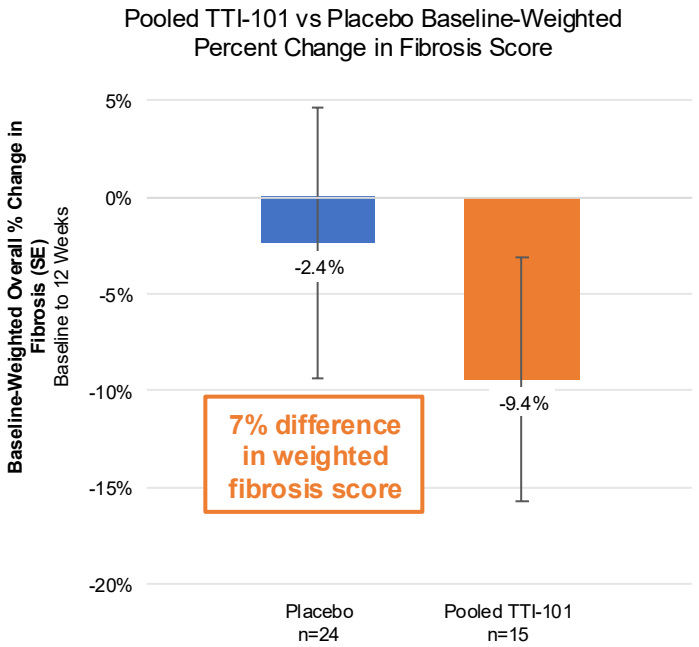
Preserved tissue integrity and colon length with TVRD STAT3 inhibitor

GI model driven by innate immune axis (DSS)[3]



Clinical PoC: Reduced fibrosis

IPF Phase 2[4]



Greater decrease in fibrosis score (improvement in fibrosis) among pooled patients treated with TTI-101 vs placebo

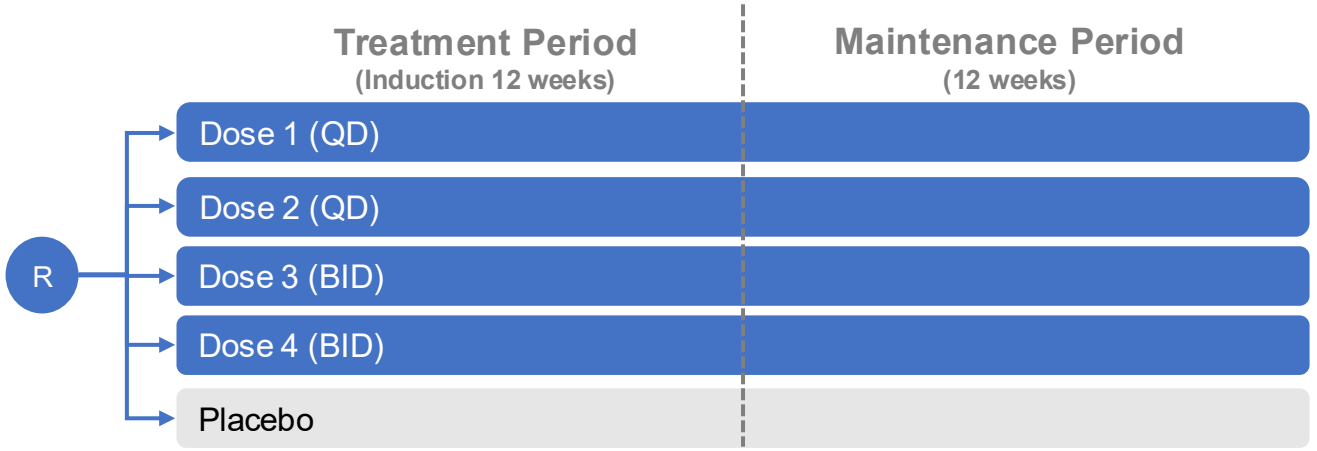
1. Vespa et al. *J. Clin Med.* 2022; 2. Gordon et al *Aliment Pharmacol Ther* 2018; 3. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model; 4. Tvardi Press Release: January 8, 2026;
*p≤0.05 TTI-101 vs vehicle

Proposed Clinical Trial Designed to Address Key Challenges in UC

Study Design

Key inclusion criteria:

- Moderate to severe UC
- Inadequate response to prior advanced therapies



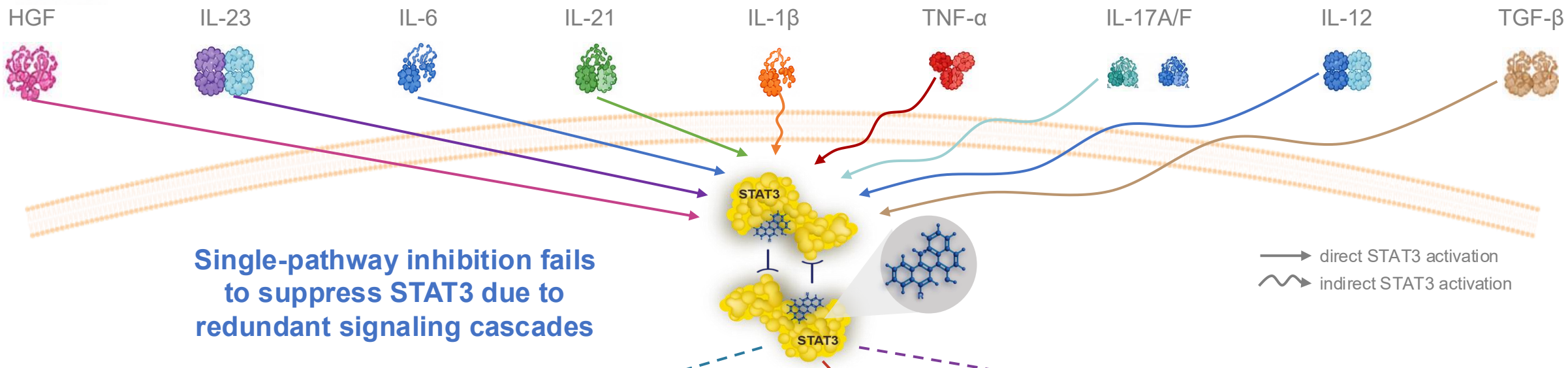
Endpoints

- Primary: Safety
- Secondary: Efficacy
  - Clinical remission at 12 weeks
- Exploratory: Pharmacodynamics
  - Serum biomarkers
  - Tissue analysis
  - Genetic SNPs

Key Challenges in UC	Why Target STAT3 with TTI-109?
Overcoming persistent disease biology	**STAT3 integrates multiple mechanisms of disease modification**
A differentiated oral therapy with targeted exposure	**Favorable safety profile, target-specific design with rapid biologic effect**
Enabling precision medicine	**Targeting STAT3 offers a distinct opportunity to develop a STAT3-mediated response signature**

QD: once daily dosing; BID: twice daily dosing; SNP: single nucleotide polymorphisms; Subject to IND submission and the availability of additional funding

Overcoming Persistent Disease Biology



Single-pathway inhibition fails to suppress STAT3 due to redundant signaling cascades

	Immune dysregulation	Inflammation	Proliferation
UC Murine Models with TTI-101/109	↓ Pathogenic Th17[2,3]	↓ Colonic inflammatory score[2,3,4]	Preserved colon integrity[2,3,4]
Human Data with TTI-101/109	↓ Key immune cell populations	↓ Inflammatory cytokine IL-6[5]	↓ Fibrosis score[5]

Predictor of relapse: 98% of patients in endoscopic remission have lesions composed of B- and T-cell aggregates, inflammatory infiltrates and distorted crypts[1]

1. Laterza et al *J Pers Med* 2024; 2. Robinson et al. *J Clin Med* 2022; 3. Robinson et al. *Cancers* 2023; 4. Tvardi data generated with CRO; 5. Tvardi Press Release: January 8, 2026

A Differentiated Oral Therapy with Targeted Exposure

Safety concerns

- Class-related safety risks with JAK inhibitors[1] and S1P[2,3] modulators:
  - MACE, venous thromboembolism, malignancy, immunosuppression

Exposure & durability limits

- Often require loading or extended induction periods
- Loss of response

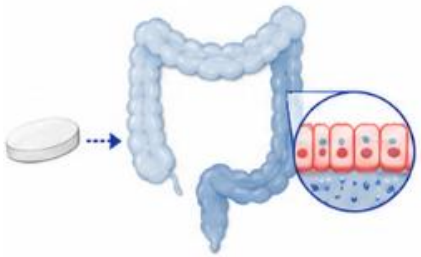
Differentiated safety profile

~400

subjects with up to **2-year exposure**

- Established clinical safety database
- Differentiated from JAK inhibitors and S1P modulators

Tissue-targeted exposure



>8x

colon tissue vs plasma

- Target-dependent accumulation in colon tissue (vs plasma) in UC models[4]

Rapid and durable biologic effect



83%

objective responses observed by **wk 8**; **durable responses** in refractory population[5,6]

- ↓ key immune subsets by day 21 (Ph 1 HV)
- ↓ fibrosis by week 12 (Ph 2 IPF)[7]

Favorable safety profile, target-specific design with rapid and durable biologic effect

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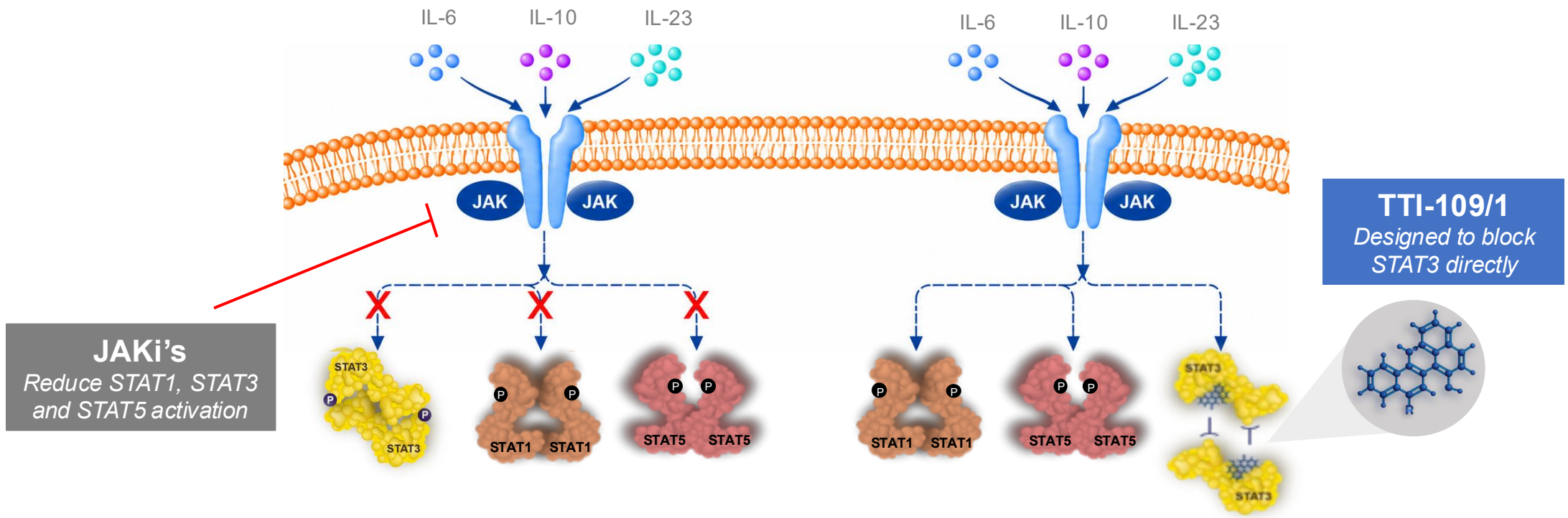
1. FDA Drug Safety Communication: September 1, 2021; 2. Ozanimod Prescribing Information; 3. Etrasimod Prescribing Information; 4. Robinson et al. *Int. J. Mol. Sci* 2025; 5. Tsimberidou et al. *Clin Cancer Res.* 2025; 6. Based on confirmed partial response rates and median time to treatment failure for patients with hepatocellular carcinoma; 7. Tvardi Press Release: January 8, 2026; MACE: major adverse cardiovascular event

Adverse Events Associated with JAK Inhibition Not Observed with TTI-109/1*



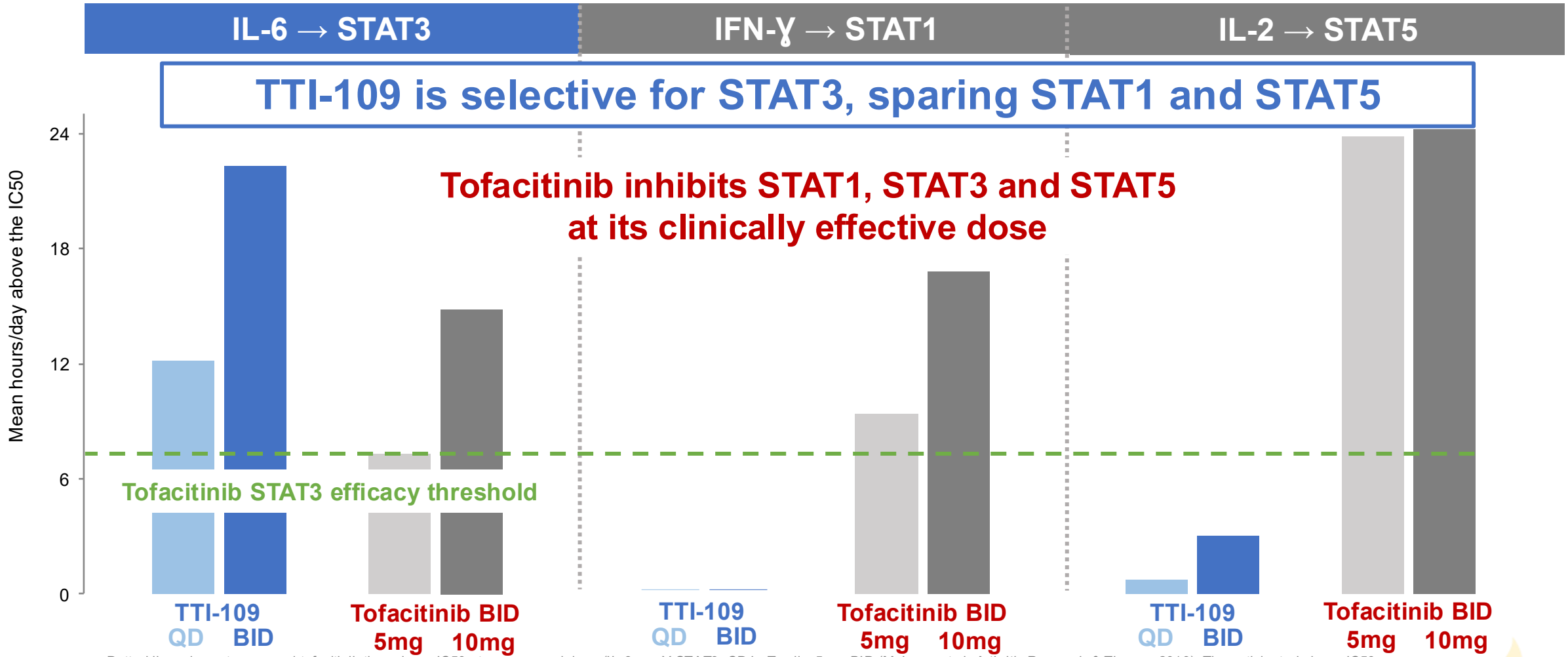
Domain related to STAT1/STAT5 with JAKs[1]	
Infections (STAT1)	Boxed warning for serious infections and opportunistic infections
Hematology (STAT5)	Anemia, thrombocytopenia and neutropenia
Malignancy	Boxed warnings for malignancy

pY-STAT3 inhibition using TTI-109/1

In over 400 subjects with exposure up to 2-years, differentiated profile from JAKi with **no signals of STAT1/5 effects** at the proposed doses

*Not observed in approximately 400 subjects treated with TTI-109/1 across clinical trials; 1. FDA Drug Safety Communication: September 1, 2021

TTI-109 is Expected to Selectively Inhibit STAT3: Sparing STAT1 and STAT5 at the Proposed Dosages



Dotted line = lowest measured tofacitinib time above IC50 at an approved dose (IL-6 → pY-STAT3, CD4+ T cells, 5 mg BID (McInnes et al. *Arthritis Research & Therapy* 2019). The anticipated above-IC50 coverage from the tofacitinib preclinical basis (FDA ClinPharm Review NDA 203214, §1.1.4A, pp. 53–54), derived from mouse collagen-induced arthritis concentrations against whole-blood IC50 estimates is 8.5–13 h/day. TTI-109 healthy volunteer study exposures of TTI-101 are estimated relative to in vitro STAT1, 3 and 5 inhibition of PBMCs of TTI-101. Certain data on this slide are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities and differences. The values shown in the cross-study comparisons are directional and may not be directly comparable

tvardi THERAPEUTICS

Enabling Precision Medicine

Limited Molecular Insight

- Broad, unselected patient populations
- Unpredictable response
- Molecular profiling remains an unmet need

pY-STAT3 associated with clinical activity[1,2]

Reduced pY-STAT3

Clinical response



- Reduction of pY-STAT3 correlated with clinical response
- Non-responders demonstrated little or no reduction of pY-STAT3

STAT3-associated genetic & immune signatures

Elevated UC risk[3,4]



STAT3 polymorphisms

rs744166 | rs2293152

Immune signatures



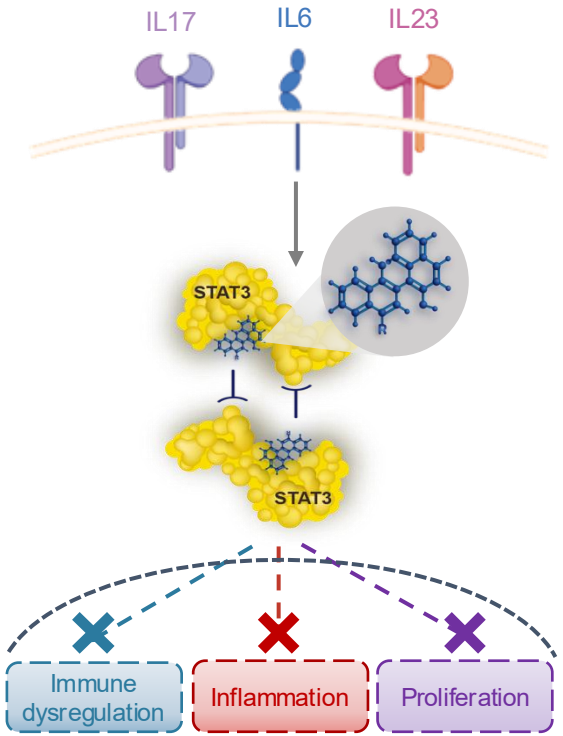
Pathogenic Th17 | Inflammatory macrophages | CD4+ Tfh

We believe targeting STAT3 offers a distinct opportunity to develop a STAT3-mediated response signature and may inform future patient enrichment strategy

1. Schreiber et al *Gastroenterology* 2021; 2. Verstockt et al *J. Crohn's and Colitis* 2025; 3. Zhang et al *Plos One* 2014; 4. Wang et al *Genet Mol Res.* 2014; pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705

Our STAT3 Inhibitors are Designed to Address the Unmet Need in Inflammatory and Proliferative Diseases

STAT3: Highly Validated Convergent Node



STAT3: central mediator in inflammatory and proliferative disease

Translational Proof-of-Concept

Preclinical

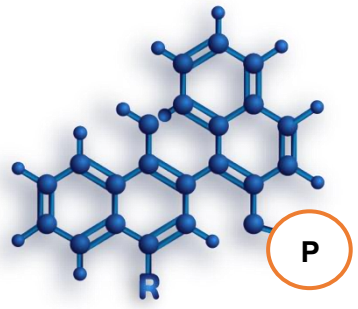
- ↓ pY-STAT3
- ↓ immune dysregulation
- ↓ inflammation
- ↓ proliferation

Confirmed in patients

Clinical

- ↓ pY-STAT3
- ↓ immune dysregulation
- ↓ inflammation
- ↓ proliferation

TTI-109 Validation in P1 Healthy Volunteers



TTI-109

- ✓ **PK**
- ✓ **GI tolerability**
- ✓ **Immune modulation**

TTI-109 Lead Indication



Ulcerative Colitis (UC)

- ✓ **Pre-IND FDA feedback supports IBD development plan**

tvardi THERAPEUTICS

pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705; PK: pharmacokinetics; IBD: inflammatory bowel disease

Our Pipeline

Program	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Milestones
TTI-109	Ulcerative Colitis (UC)	IND submission expected 2027*				• **November 2026: Pre-IND FDA feedback supports IBD development plan** • **Provides flexibility to advance UC and CD indications either in parallel or sequentially** • Study initiation expected 2027*
TTI-101	Hepatocellular Carcinoma (HCC)	Phase 1b/2				• Phase 1b/2 topline data 1Q:2027

*Tvardi's ability to initiate programs in inflammatory bowel diseases (IBD), specifically, ulcerative colitis (UC) and/or Crohn's disease (CD), is subject to clearance of Investigational New Drug (IND) application and the availability of additional funding

TTI-101 in HCC

TTI-101 Reversed Multiple Pathogenic Steps of Liver Cancer in a NASH-induced HCC Model

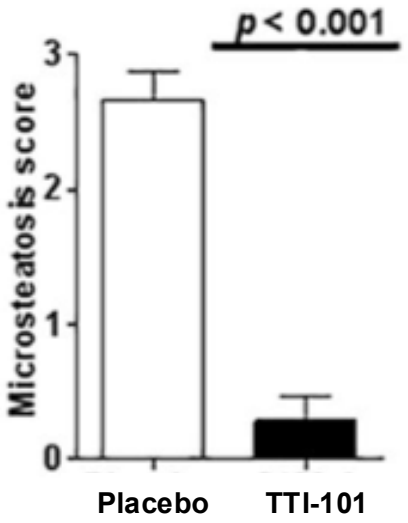
STAT3-mediated pathogenesis

Inflammation → Fibrosis/Cirrhosis → HCC

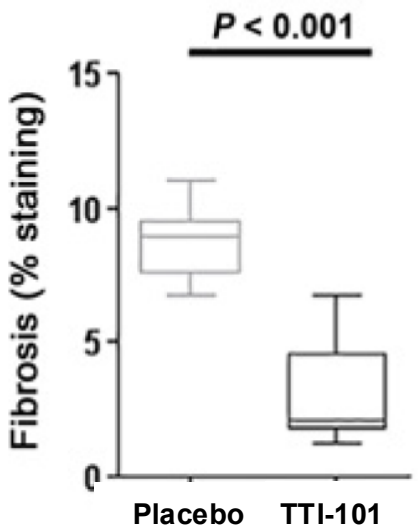


TTI-101 STAT3-inhibition in NASH-induced HCC

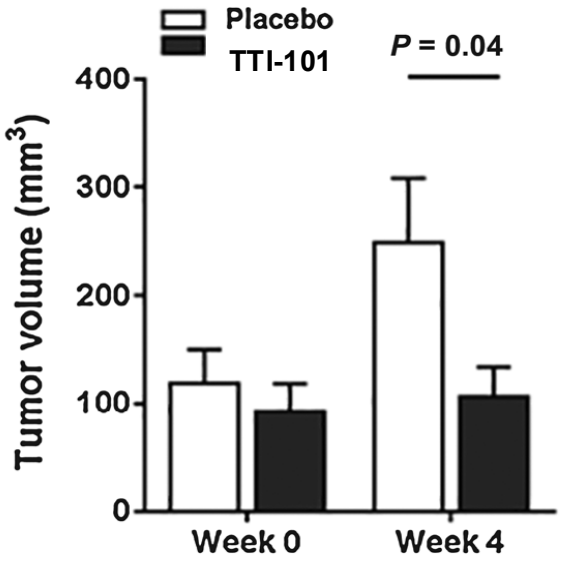
Microsteatosis



Fibrosis



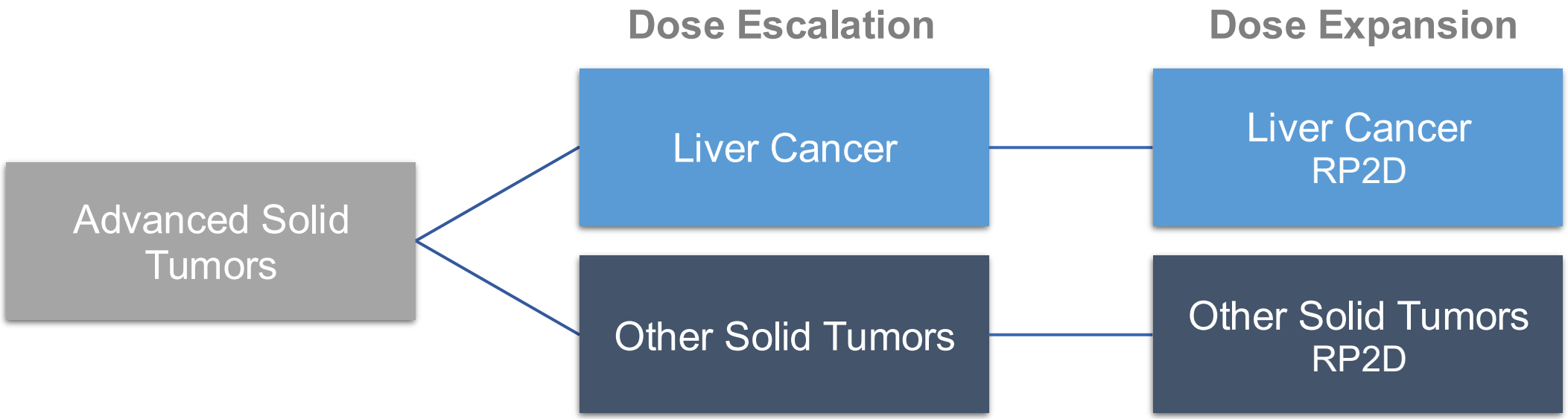
Tumor volume



After formation of tumors at 11 months, we observed treatment with TTI-101 therapeutically reduced inflammation, fibrosis, and tumor growth

Jung KH et al. *Clin Cancer Res.* 2017. Genetically engineered HepPTEN- murine model that replicates nonalcoholic steatohepatitis (NASH) induced hepatocellular carcinoma (HCC)

Phase 1 Clinical Trial: First in Human TTI-101 Monotherapy Study Design



Objectives:

- **Primary:** Maximum tolerated dose, safety, and pharmacokinetics
- **Secondary:** Clinical efficacy and pharmacodynamics

Tsimberidou et al. *Clin Cancer Res.* 2025

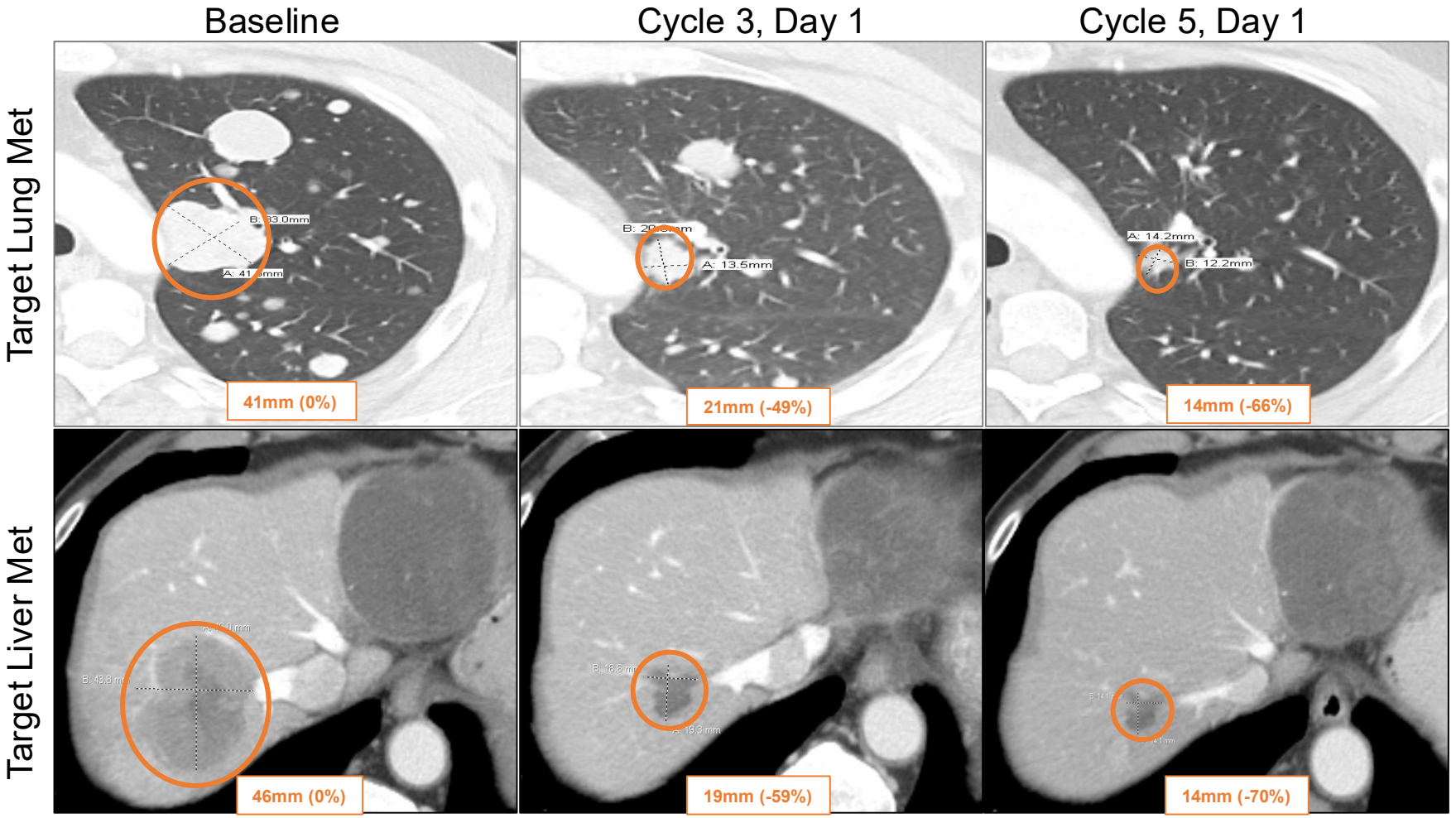
Phase 1 Clinical Trial: TTI-101 Monotherapy Led to Durable Partial Responses in Fibrotic Tumors

Partial Responder A: HCC

- Failed sorafenib, pembro, nivo, nivo+bev
- Best Response: **42% Reduction in Sum of Targets Overall**
- Sustained PR for 10 months

Partial Responder B: HCC

- Failed lenvatinib, nivo
- Best Response: **66% Reduction in Sum of Targets Overall**
- Sustained PR for 14 months



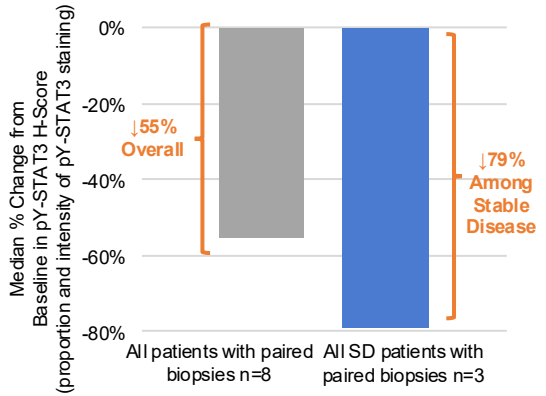
Tsimberidou et al. *Clin Cancer Res.* 2025

Phase 1: TTI-101 Monotherapy Clinical Trial Summary

PK / PD

- Exposures in humans above the level required for efficacy in preclinical inflammatory and proliferative models
- Linear PK from DL1-3
- Exposures above IC_{50} for STAT3 induced growth*
- Exposure plateaued at DL3, resulting in a RP2D of 12.8mg/kg/day
- 100% of patients with elevated pY-STAT3 levels at baseline demonstrated decrease within ~6 weeks of TTI-101 therapy
- 55% decrease in pY-STAT3 overall; 79% in SD

Paired Biopsies after ~6 weeks of TTI-101



8/10 patients had elevated pY-STAT3 at baseline; elevated pY-STAT3 defined as H-score >30 on a 0-300 scale

Tolerability

- Well-tolerated BID oral dosing
- No DLTs

TRAEs Occurring in >10% of Patients

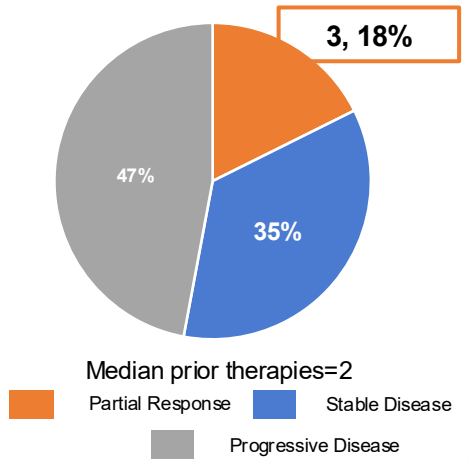
Formulation	F1 N=15		F2 N=47		F3 N=7**	
Grade, n (%)	G1/2	G3	G1/2	G3	G1/2	G3
Diarrhoea	3 (20)	3 (20)	16 (34)	6 (13)	2 (29)	0 (0)
Nausea	4 (26)	0 (0)	6 (13)	1 (2)	0 (0)	1 (14)
Fatigue	6 (40)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
Elevated ALT/AST***	1 (7)	1 (7)	1 (2)	4 (8)	1 (14)	1 (14)
Dose reduction	3 (20)		2 (4)		0 (0)	
Dose discont.	0 (0)		2 (4)		0 (0)	

*Most severe AE counted per subject by grade (G1/2=grade 1 or 2, G3=grade 3) **5 subjects started on F2 and transitioned to F3 ***Elevated alanine aminotransferase/aspartate aminotransferase (ALT/AST) is the sum of elevated ALT and AST events

Biological Activity

- Enhanced biological activity in fibrotic cancers with ORR that exceeds current standard of care in HCC
- Current expected ORR in 2L HCC is <5%

Best Overall Response Among HCC Patients, N=17

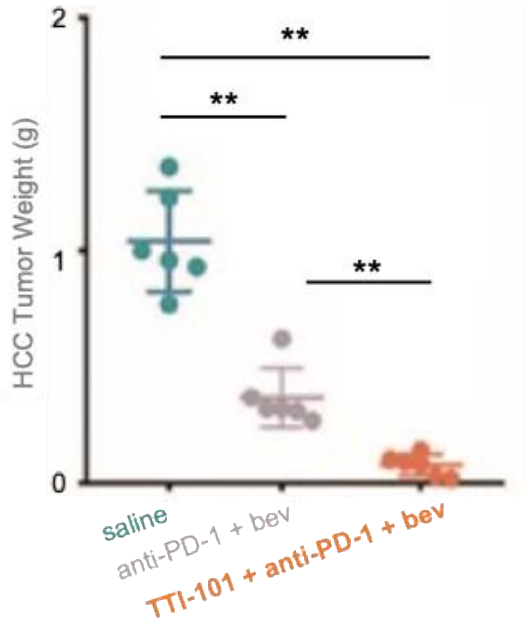


Tsimberidou et al. *Clin Cancer Res.* 2025; *STAT3 IC_{50}: in a controlled system where proliferation is driven by WT STAT3, TTI-101 inhibits cell growth with an IC_{50} of approximately 1.5µM; Kasembeli et al. *Blood.* 2022.
SD: Stable Disease; TRAE: Treatment related adverse events; F1-3: Formulation 1-3

Strong Rationale for TTI-101 and ICI Combination Therapy

Preclinical Model

TTI-101 additive to 1L SoC (ICI + Bev)[1]



POC Established for STAT3 Inhibition + ICI

Ph 2: Danvatirsen (STAT3 ASO) + Durvalumab (ICI) in 2L HNSCC[2]

	Durva[3]		Dan+Durva[2]
ORR	9%	→	**23%**
CR	0%	→	**7%**

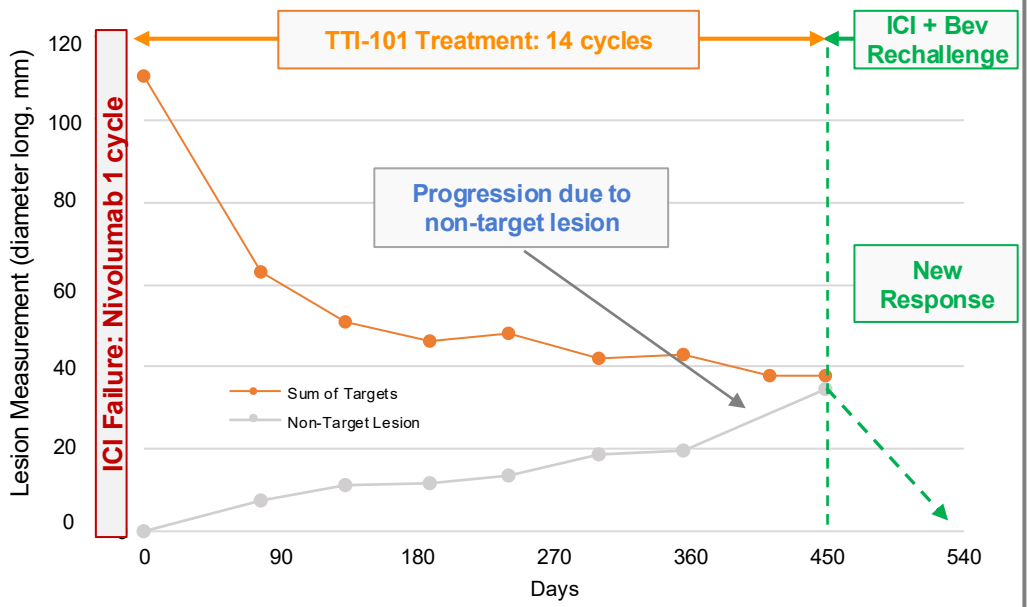
Danvatirsen key limitations:

- Observed AEs: Thrombocytopenia and transaminitis
- Onerous dosing: IV 3x week 1 then Q weekly
- Poor PD: Inhibition of STAT3 not observed in tumor, only in stroma

Danvatirsen development suspended by AZN/Ionis

Phase 1 Trial Responder Overcame ICI Resistance After TTI-101 Monotherapy

Sum of Tumor Responses After ICI Failure, On TTI-101 Therapy and After ICI+Bev Rechallenge[4]



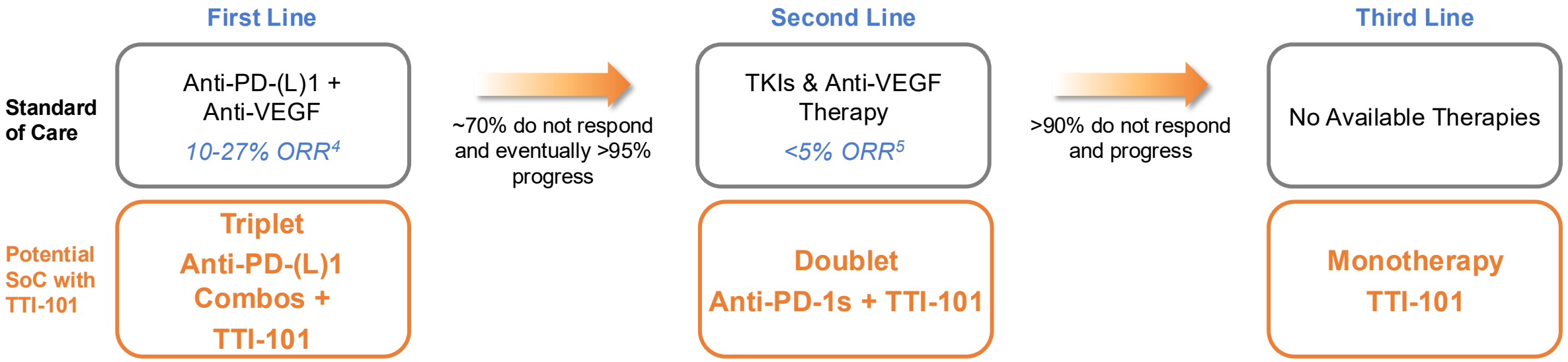
1. Adapted from Zhao, Y et al. *Hepatology*. 2021 2. Cohen et al. *Ann Oncol*. 2018 3. Siu et al. *JAMA Oncol*. 2019. ICI: Immune Checkpoint Inhibition; Bev: Bevacizumab. Certain data on this slide are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities and differences. The values shown in the cross-study comparisons are directional and may not be directly comparable. 4. Tsimberidou et al. *Clin Cancer Res*. 2025

TTI-101 is Designed to Provide a Distinct and Synergistic Mechanism for Unmet Need in HCC

HCC Disease Overview

- HCC is 3rd leading cause of cancer deaths in the world[1]
- Annually in the US, >42,000 new cases of HCC and ~32,000 deaths recorded[2]
- Incidence has more than tripled since 1980[3]

Overview of Current Treatment Landscape + Role of TTI-101



1. World Health Organization (WHO) 2. WHO US Statistics 3. American Cancer Society 4. Represents range of ORRs from previous studies (MORPHEUS, Tempest, IMBrave150). 5. 2nd line ORR expected to be <5% as 2nd line therapies inhibit VEGF/angiogenesis as common mechanism with bevacizumab and pembrolizumab (anti-PD-1) has common mechanism with atezolizumab (anti-PDL-1).

REVERT$_{\text{Liver Cancer}}$: Phase 2 Study of TTI-101 in HCC

	Phase 1b Dose Finding		Phase 2 Expansion (N=100)
A **Last Line:** no available therapies that will confer clinical benefit	TTI-101	RP2D	TTI-101 RP2D (N=30)
Last Line Rationale: Confirmation of P1 PoC TTI-101 monotherapy			
B **2nd Line:** progressed on anti-PD-(L)1 first line	TTI-101 + pembrolizumab	RP2D	TTI-101 RP2D + pembrolizumab (N=30)
2nd Line Rationale: TTI-101 overcomes anti-PD-(L)1 resistance			
C **1st Line:** treatment naïve	TTI-101 + atezo/bev	RP2D	TTI-101 RP2D + atezo/bev (N=40)
1st Line Rationale: TTI-101 is synergistic with anti-PD-L1 and anti-angiogenic inhibition			

FDA Fast Track

revert™ LIVER CANCER

(21 US Sites)

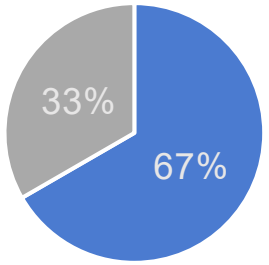
- Overall Response Rate (ORR)
- Duration of Response (DoR)
- Progression-free survival
- Liver stiffness (elastogram)
- Biomarkers (IL-6/AFP)
- pY-STAT3 in tumor

Early clinical data suggests clinical benefit across treatment lines

NCT05440708; Dayyani et al. *JCO.* 2024; Data as of April 2025

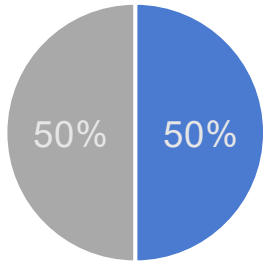
REVERT$_{\text{Liver Cancer}}$: Interim Phase 1b/2 Data

Cohort A: TTI-101 Monotherapy at RP2D



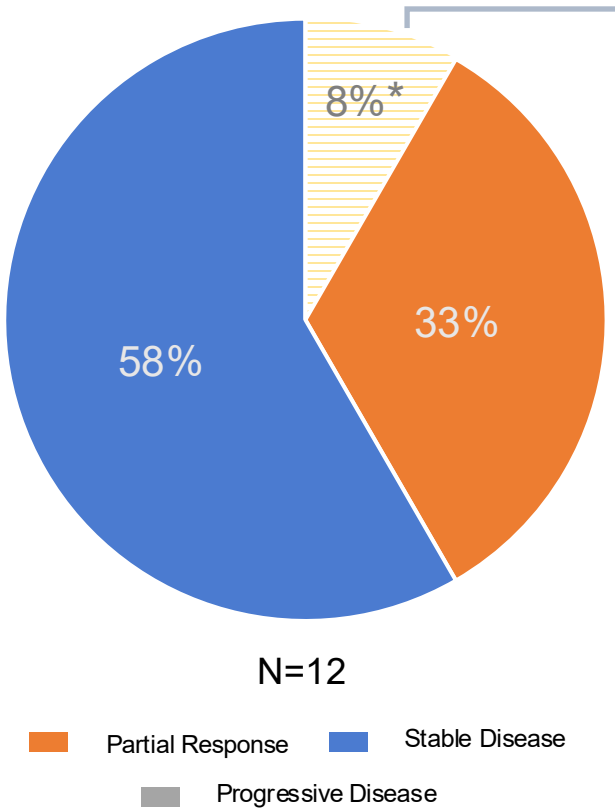
N=21

Cohort B: TTI-101 (RP2D) + Pembro



N=8

Cohort C: TTI-101 + Atezo/Bev



N=12

*One patient on protocol for 6 weeks. Patient discontinued combination due to an unrelated AE. After recovery from AE, patient continued with atezo/bev and investigator reported complete response.

Patient considered non-evaluable for efficacy. As DCR (disease control rate: CR+PR+SD) and ORR (objective response rate: CR+PR) are based on intent to treat population of all patients this patient is only included in denominator.

Early results compare favorably to 3rd party trials†:

Study	Publication Date	DCR	ORR
REVERT$_{\text{HCC}}$ Prelim	**Ongoing**	**92%**	**33%**
Tempest[1]	2023	63%	10%
MORPHEUS[2]	2023	56%	11%
IMBrave150[3]	2020-22	74%	27%

49% of patients in IMBrave150 atezo/bev arm had HBV-associated HCC and demonstrated a higher likelihood of benefit relative to non-HBV patients[4]
REVERT$_{\text{HCC}}$ Cohort C has **no patients with** HBV-associated HCC

Preliminary radiographic change from baseline RECIST measurements (best response). Data as of Aug 2024. This interim data set was not subject to the standard quality control measures typically associated with final clinical trial results. 1. Tempest press release 23 Apr 2023 of Phase 2 Study. Tempesttx.com 2. Roche Phase 2: Finn et al. *J Clin Oncol.* 2023 3. Roche Phase 3: Finn et al. *NEJM.* 2020. 4. Cheng et al. J Hepatol. 2022
† Certain data on this slide are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities and differences. The values shown in the cross-study comparisons are directional and may not be directly comparable.

Key Takeaways: TTI-101 in HCC

STAT3: Well-Established Biology

STAT3 long recognized as prime target in oncology; >95% of patients with HCC have activated STAT3 in their tumors

Differentiated Approach

Inhibition of STAT3 activation to have dual therapeutic effect on cancer cells – overcoming tumorigenesis and immune suppression

Encouraging Clinical Activity

Clinically meaningful activity in both monotherapy and combination therapy in areas of unmet need

Near-Term Clinical Milestone

Topline results from ongoing Phase 2 REVERT$_{\text{LIVER CANCER}}$ trial expected in 2H:2026

Appendix A.
Preclinical Support

TVRD STAT3 Inhibition Demonstrated Activity Across Multiple Validated IBD Immune Axes

Model Systems and Select Therapies Approved or Developed for IBD		TVRD STAT3i	Anti-TNFα	Anti-IL12/23	Anti-TL1A	Anti-IL-6	JAK1i	JAK2/3i	TyK2i	S1P1m
Model	**Immune Axis / Key Cytokines**									
DSS (UC)	• Innate → Th1/Th17 • IL-6, IL-1ß, IL-17	✅		✓	✓	✓				✓
TNBS (CD)	• Adaptive (Th1) • IFN-ɣ, TNF-α, IL-12	✅	✓	✓	✓	✓	✓		✓	✓
OXA (UC)	• Adaptive (Th2/NKT) • IL-13, IL-4	✅					✓	✓		

Unlike single-axis competitor mechanisms, TVRD STAT3-inhibitors demonstrated biologic activity across multiple, validated immune axes underlying IBD disease

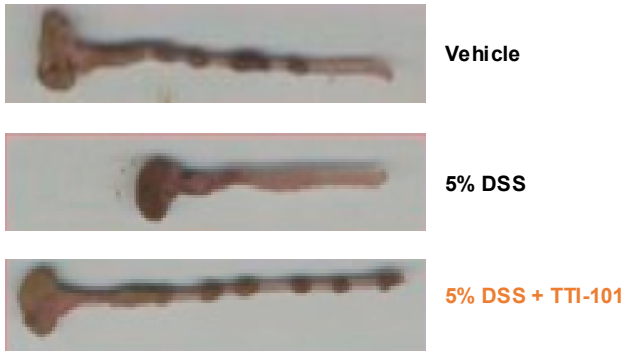
tvardi THERAPEUTICS

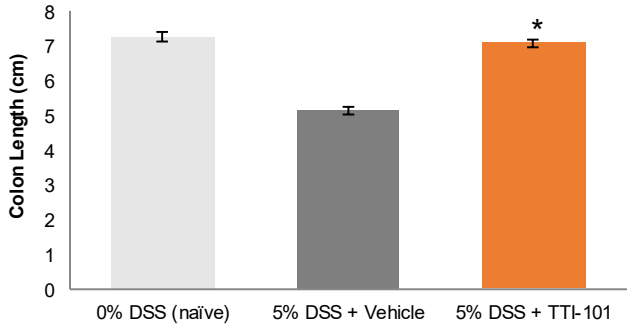
Tvardi data generated with CRO: WuXi; Comparative targets in the IBD space and select therapies approved or developed for IBD used for demonstrative purposes; DSS: dextran sodium sulfate ulcerative colitis (UC) model; TNBS: 2,4,6-trinitrobenzene sulfonic acid Crohn's disease (CD) model; OXA: oxazolone ulcerative colitis (UC) model

TVRD STAT3 Inhibitors in the DSS-UC Model

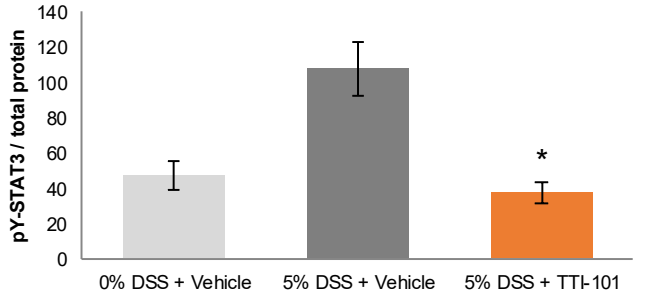
5% DSS UC Model with TTI-101[1]

Colon Morphology and Length

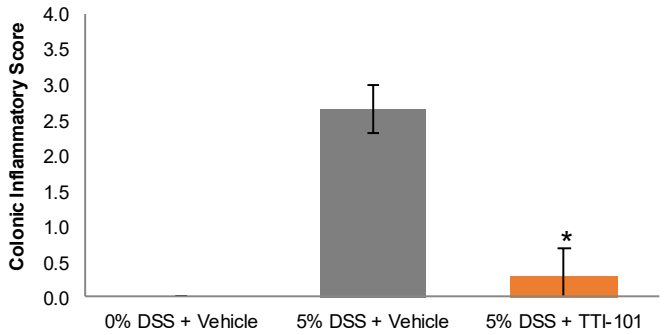




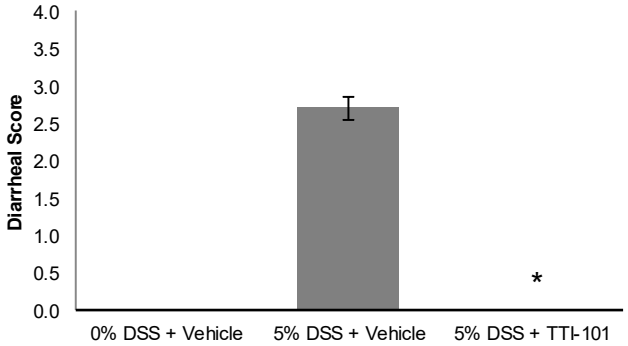
pY-STAT3



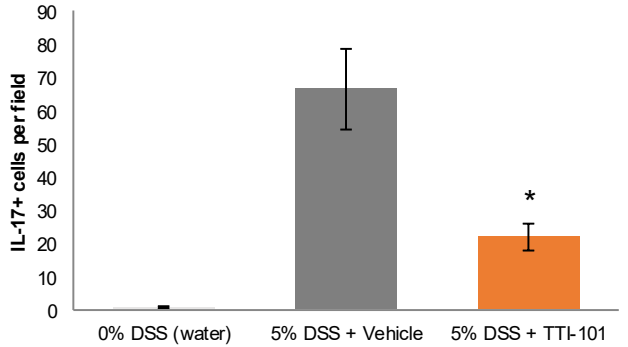
Colonic inflammation



Diarrhea



Colonic IL-17⁺ Cells



*p ⩽0.05 for all TTI-101 arms relative to DSS + vehicle

TTI-101 treatment in DSS model normalized all hallmarks of UC

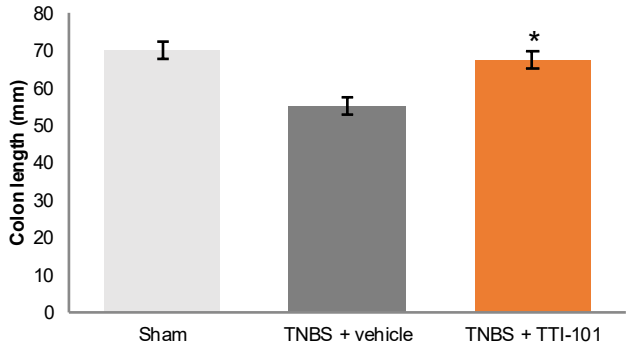
1. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model

TVRD STAT3 Inhibitors in the TNBS-CD Model

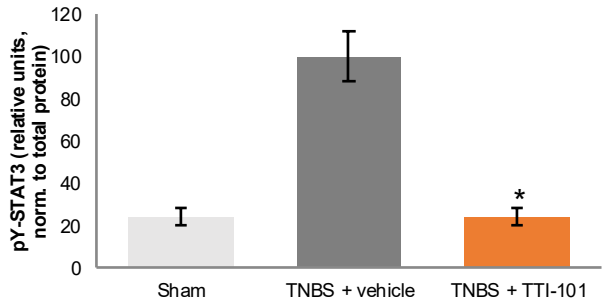
TNBS CD Model with TTI-101[1]

Colon Morphology and Length

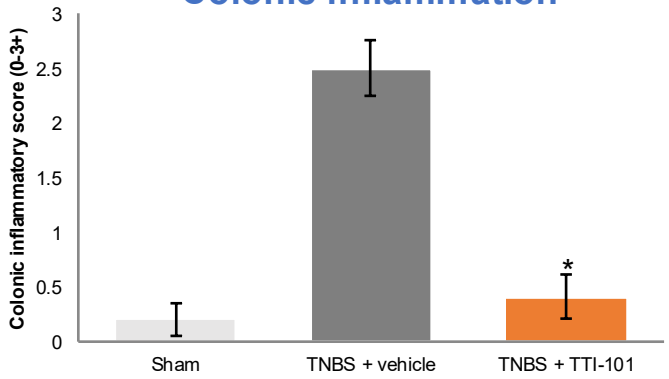




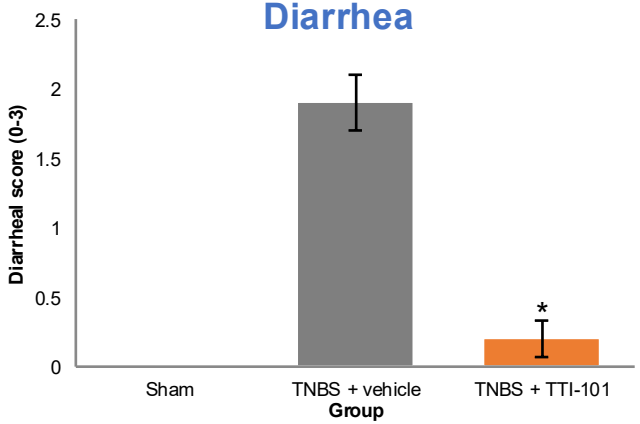
pY-STAT3



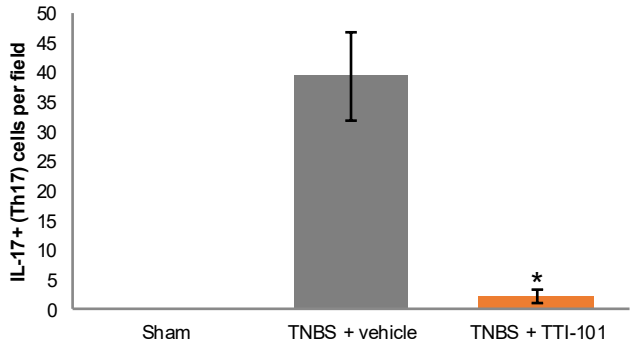
Colonic inflammation



Diarrhea



Colonic IL-17⁺ Cells



*p ⩽0.05 for all TTI-101 arms relative to TNBS + vehicle

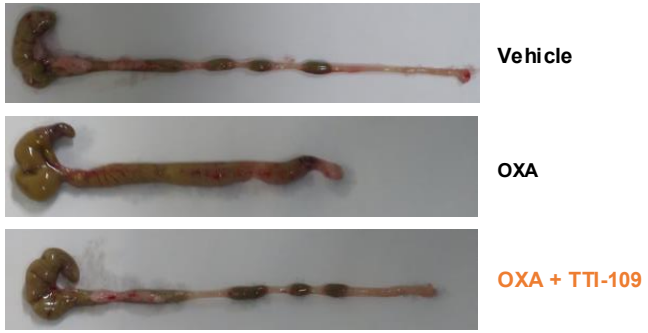
TTI-101 treatment in TNBS model normalized all hallmarks of CD

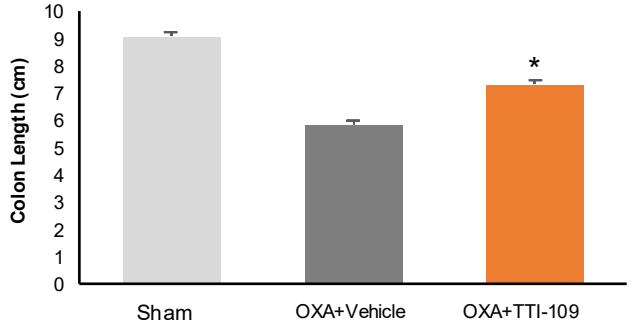
1. Figures digitized from Robinson et al. *J Clin Med* 2022: 2,4,6-trinitrobenzene sulfonic acid (TNBS) model

TVRD STAT3 Inhibitors in the OXA-UC Model

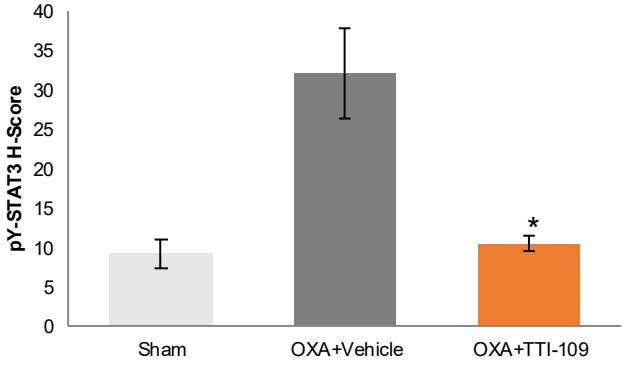
OXA UC Model with TTI-109[1]

Colon Morphology and Length

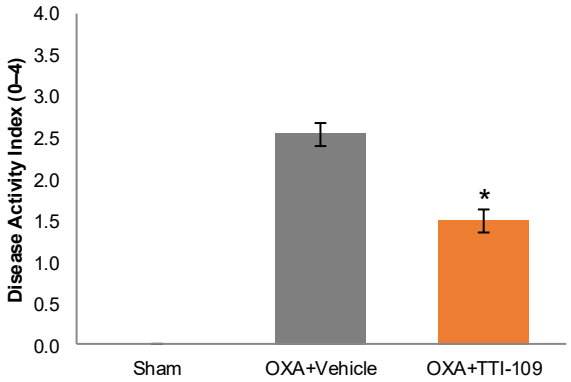




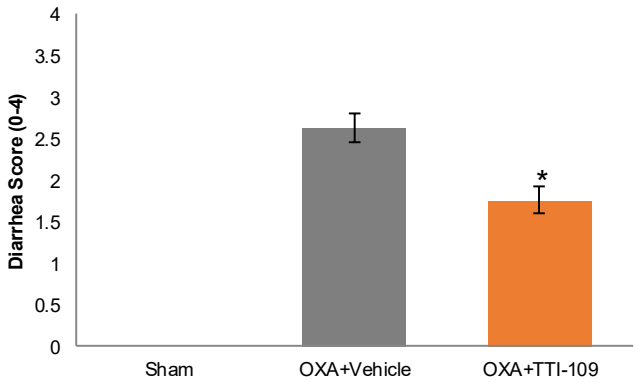
pY-STAT3



Colonic inflammation



Diarrhea



** p ⩽0.05 for all TTI-101 arms relative to OXA + vehicle

TTI-109 treatment in OXA model normalized all hallmarks of UC

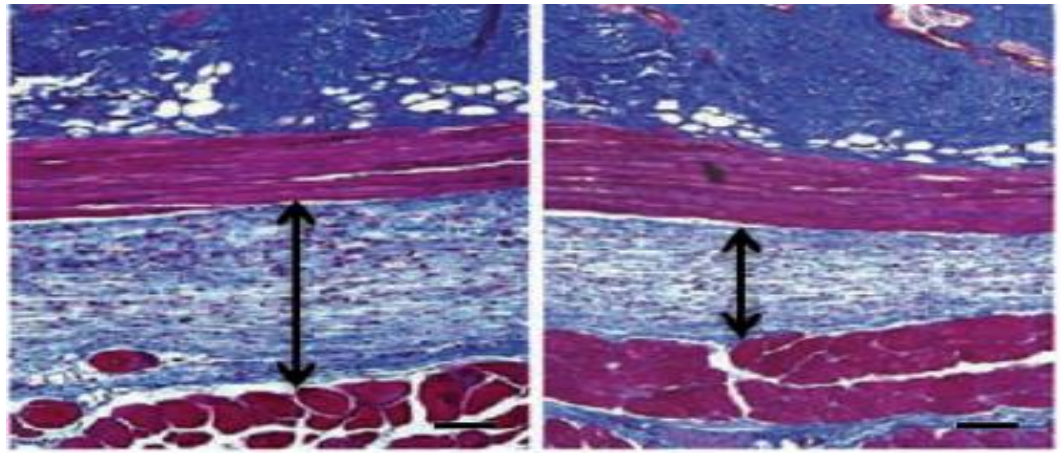
1. Tvardi data generated with CRO: WuXi; n=8 per group statistical comparison using exact Mann-Whitney + Kruskal-Wallis

TTI-101 Attenuated *Growth Factor* Driven Fibrosis and Dermal Thickening

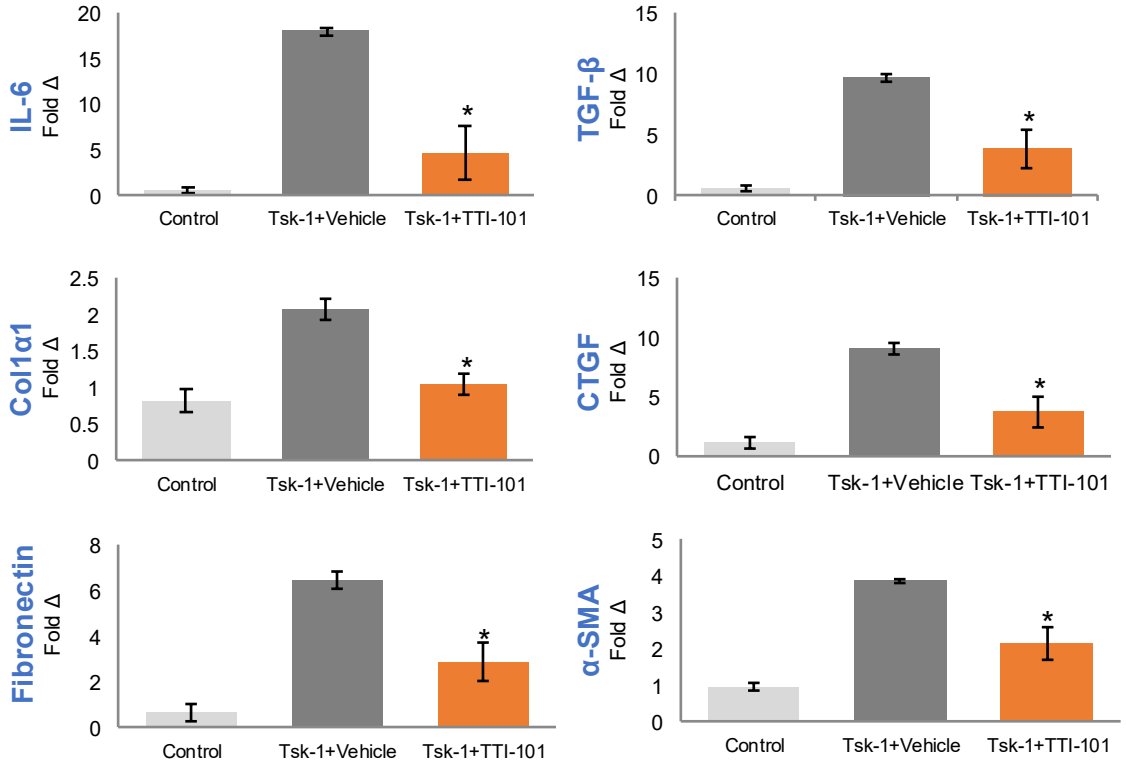
Genetically-induced proliferative skin model

Therapeutic treatment with TTI-101 significantly reduced dermal thickness…

Tsk-1 mice + Placebo | Tsk-1 mice + TTI-101



…and significantly reduced key drivers of inflammation and proliferation



* p ⩽0.05 for all TTI-101 arms relative to Tsk-1 + vehicle

TTI-101 reversed both dermal thickening and inflammatory/pro-fibrotic hallmarks of skin fibrosis

Figures digitized from Pedroza et al. *Rheum.* 2017: SSc: systemic sclerosis; Genetically engineered model (GEM) of Tight skin (Tsk-1) mice which spontaneously develop fibrosis as a result of a duplication in the fibrillin-1 gene and BLM (bleomycin-induced SSc) model; Fold Δ = Fold Change

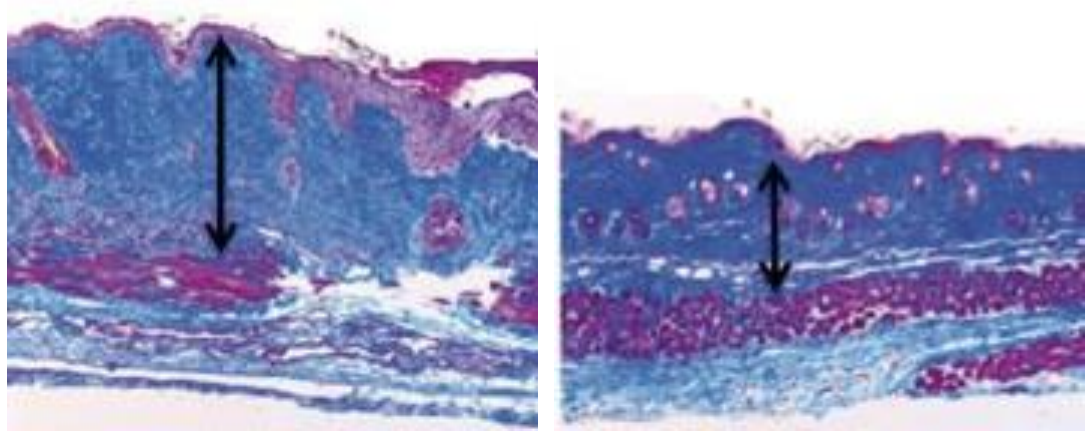
TTI-101 Attenuated *Inflammation* Driven Fibrosis and Dermal Thickening

Chemically-induced inflammatory skin model

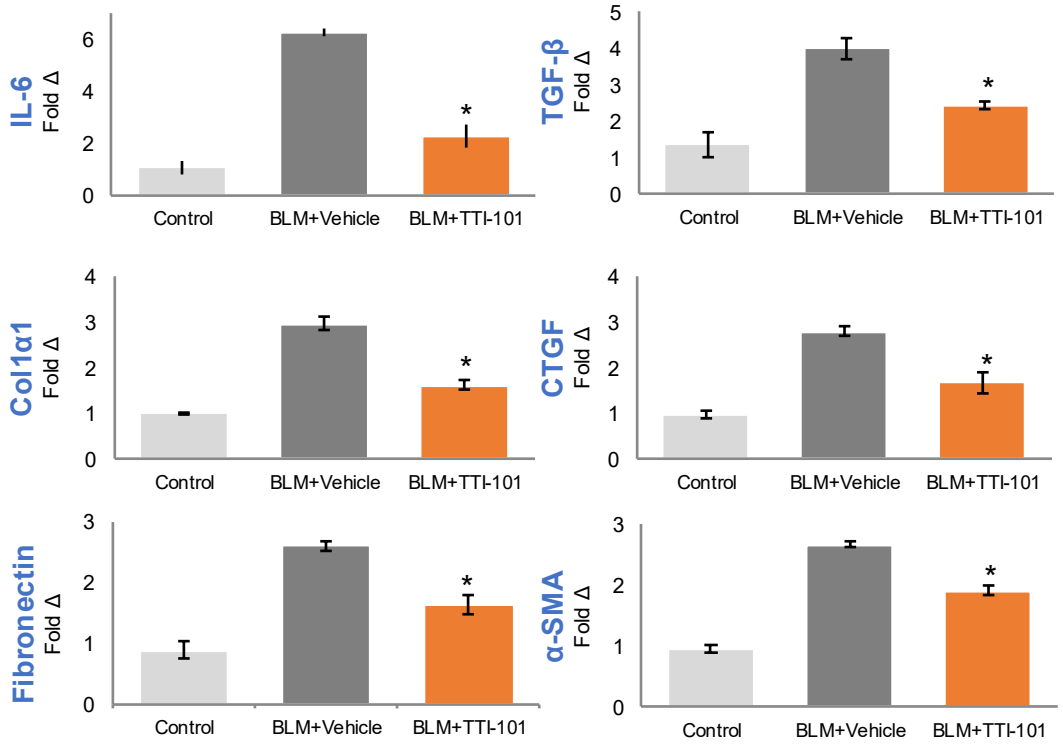
Therapeutic treatment with TTI-101 significantly reduced dermal thickness

BLM mice + Placebo

BLM mice + TTI-101



…and significantly reduced key drivers of inflammation and proliferation



* p ⩽0.05 for all TTI-101 arms relative to BLM + vehicle

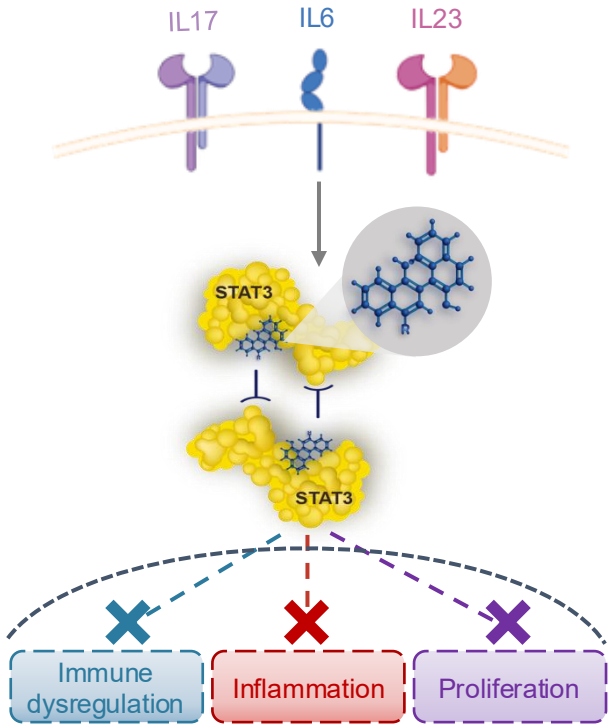
TTI-101 reversed both dermal thickening and inflammatory/pro-fibrotic hallmarks of skin fibrosis

Figures digitized from Pedroza et al. *Rheum.* 2017: SSc: systemic sclerosis; Bleomycin (BLM) treated mice develop fibrosis through an inflammatory mechanism; Fold Δ = Fold Change

Appendix B.
TTI-101 in IPF

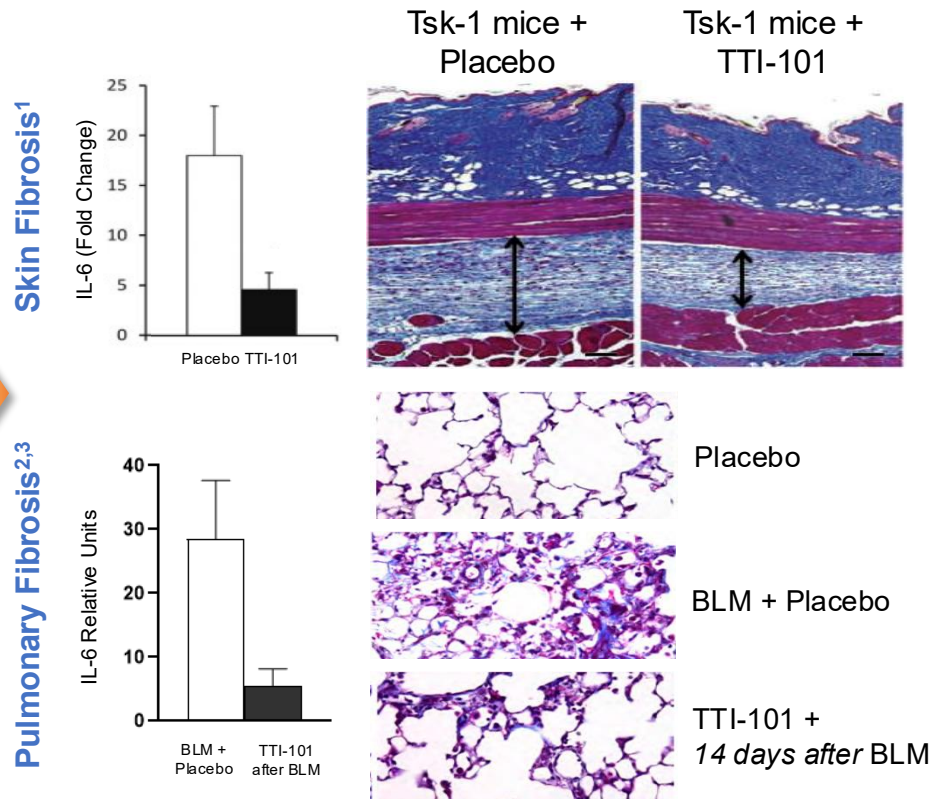
Our STAT3 Inhibitors are Designed to Address the Unmet Need in Inflammatory and Proliferative Diseases

Well-Established Target



STAT3: central mediator in inflammation and proliferative disease

Preclinical Biological Activity



↓ IL-6 levels and ↓ fibrosis in models of proliferative disease

Initial Clinical Proof of Mechanism: IPF

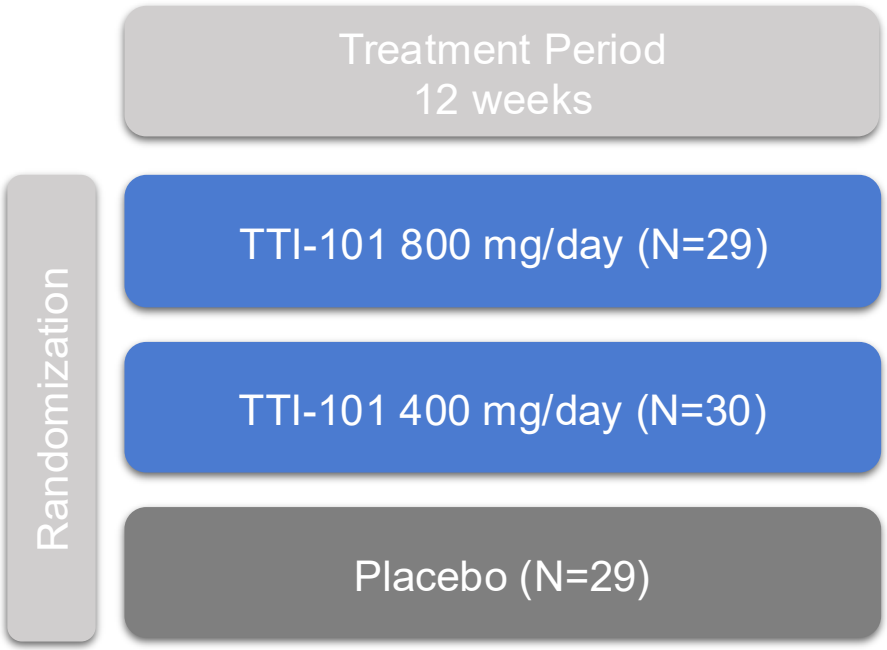
revert™ IPF

1. Pedroza et al. *Rheum.* 2017: Genetically engineered model of Tight skin (Tsk-1) mice which spontaneously develop fibrosis as a result of a duplication in the fibrillin-1 gene; 2. Pedroza et al. *FASEB J.* 2016; 3. Kauh et al. *CHEST.* 2024. Pulmonary fibrosis bleomycin (BLM) model

REVERT$_{IPF}$: Preliminary Conclusions Released October 2025

revert™ IPF

(28 US Sites, N = 88)



- Placebo arm overperformed compared to historical data
- FVC change from baseline overlapped between treatment arms, with large variability within each cohort
- Treatment emergent adverse events resulted in early discontinuations leading to a small number of patients available for efficacy analysis at the 12-week time point

Patient Characteristics

Characteristic	Placebo (n=29)	TTI-101 400mg/day (n=30)	TTI-101 800mg/day (n=29)
Age	72.0 (9.3)	72.4 (6.9)	72.8 (7.7)
Sex, Male – no. (%)	23 (79.3)	25 (83.3)	21 (72.4)
Time since diagnosis of IPF – yrs., mean (SD)	2.4 (2.0)	2.6 (1.7)	2.5 (1.5)
Standard of care use, nintedanib – no. (%)	17 (58.6)	18 (60.0)	17 (58.6)
FVC – L, mean (SD)	2.59 (0.75)	2.84 (0.71)	3.03 (1.00)
Percent of predicted FVC (ppFVC), mean (SD)	70.08 (16.72)	74.05 (13.38)	81.12 (19.90)
GI comorbidity at baseline, mean (%)[1]	21 (72.4)	26 (86.7)	20 (69.0)

GI comorbidities were prevalent among the patient population

SD: standard deviation; [1]GI comorbidity: gastrointestinal medical history collected at baseline

Summary of Treatment-Emergent Adverse Events

Characteristic	Placebo (n=29)	TTI-101 400mg/day (n=30)	TTI-101 800mg/day (n=29)
Any TEAEs	21 (72.4)	30 (100)	26 (89.7)
TEAE leading to death	1 (3.4)	1 (3.3)[1]	1 (3.4)
TEAE leading to discontinuation	3 (10.3)	17 (56.7)	18 (62.1)
Gastrointestinal disorders		6 (20.0)	11 (37.9)
Investigations (Labs)[2]		4 (13.3)	6 (20.7)
Respiratory, thoracic and mediastinal disorders	1 (3.4)	5 (16.7)	3 (10.3)

Incidence of respiratory adverse events leading to discontinuation is consistent with adverse events expected in this patient population

Treatment-emergent adverse event: any adverse event that emerges after treatment with TTI-101 or placebo. Safety analysis performed on all patients treated with at least one dose of TTI-101. [1]Occurred during safety follow-up after 12-week treatment period ended; [2]No instances of drug-induced liver injury reported across visits or treatment groups. All increases in investigations (labs) were transient

Treatment-Emergent Adverse Events Resulting in Discontinuations by Concomitant Nintedanib Use

Dose	Placebo (n=29)		TTI-101 400mg/day (n=30)		TTI-101 800mg/day (n=29)	
Reason for discontinuation by concomitant nintedanib use	**Nintedanib (n=17)**	**Placebo (n=12)**	**TTI-101 + Nintedanib (n=18)**	**TTI-101 alone (n=12)**	**TTI-101 + Nintedanib (n=16)**	**TTI-101 alone (n=13)**
Gastrointestinal disorders			2	4	7	4
Investigations (Labs)[1]			4		4	2
Respiratory, thoracic and mediastinal disorders		1	3	2	1	2

Majority of discontinuations were observed with concomitant nintedanib

Treatment emergent adverse event: any adverse event that emerges after treatment with TTI-101 or placebo. Safety analysis performed on all patients treated with at least one dose of TTI-101. [1]No instances of drug-induced liver injury reported across visits or treatment groups. All increases in investigations (labs) were transient

Most Common Adverse Events Reported in INPULSIS vs REVERT$_{IPF}$ Trials

	INPULSIS-1 and 2[1]		Pooled TTI-101	
	Placebo (N=423)	**Nintedanib (N=638)**	**TTI-101 alone (n=25)**	**TTI-101 + Nintedanib (n=34)**
Any adverse event	379 (89.6)	609 (95.5)	23 (92.0)	33 (97.1)
Diarrhea	78 (18.4)	398 (62.4)	11 (44.0)	25 (73.5)
Nausea	28 (6.6)	156 (24.5)	4 (16.0)	10 (29.4)
Nasopharyngitis	68 (16.1)	87 (13.6)	1 (4.0)	0 (0.0)
Cough	57 (13.5)	85 (13.3)	3 (12.0)	4 (11.8)
Progression of IPF	61 (14.4)	64 (10.0)	2 (8.0)	2 (5.9)
Bronchitis	45 (10.6)	67 (10.5)	2 (8.0)	0 (0.0)
Upper respiratory tract infection	42 (9.9)	58 (9.1)	0 (0.0)	4 (11.8)
Dyspnea	48 (11.4)	49 (7.7)	1 (4.0)	4 (11.8)

- TTI-101 treated patients reported adverse events consistent with overall expectations for an IPF population
- However, addition of nintedanib meaningfully increased incidence of diarrhea

Adverse events selected to align with INPULSIS categories; safety analysis performed on all patients treated with at least one dose of TTI-101. Certain data on this slide are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities and differences. The values shown in the cross-study comparisons are directional and may not be directly comparable. [1]Richeldi et al. *NEJM*. 2014

Preliminary Conclusions and Additional Analyses

EES[1] on Treatment at 12-weeks

- **Placebo** n=24
- **TTI-101 400mg/day** n=8
- **TTI-101 800mg/day** n=13

Assessment of Individual Patient Trajectory on Study[2]

Criteria: duration of treatment, PK data and adverse events

5 patients excluded as the following criteria were not met:

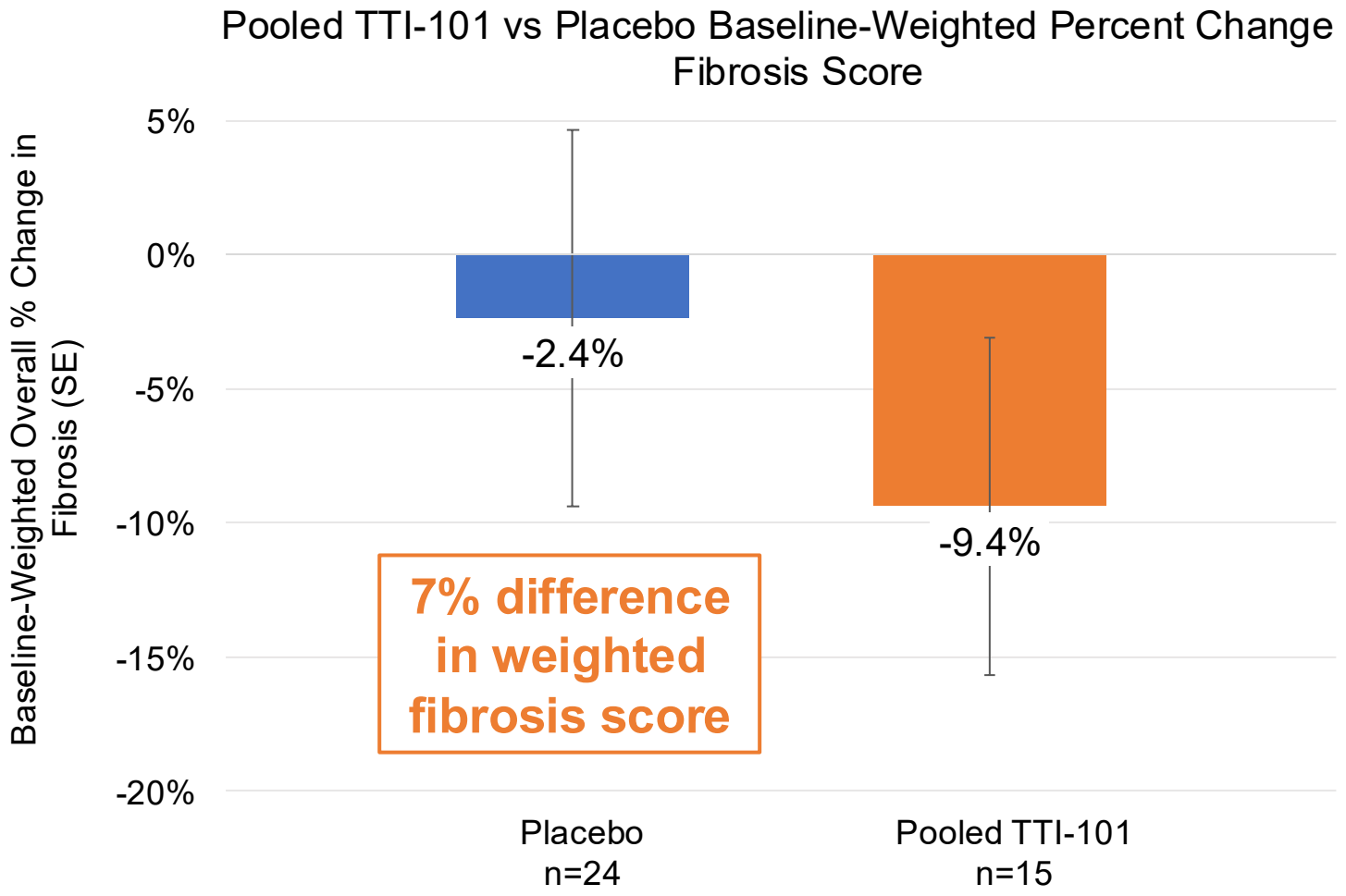
- Duration of treatment
- TTI-101 exposure + no adverse events observed
- One patient with initial improvement in FVC, subsequently impacted by acute bronchitis (non-related)

Post hoc Analysis Population

- **Placebo** n=24
- **Pooled TTI-101 400mg or 800mg** n=16

[1]The Efficacy Evaluable Set (EES) consists of all patients defined as all randomized patients who received at least one dose of IP and have at least one post-baseline acceptable or borderline acceptable forced vital capacity (FVC) result while on-treatment. On treatment is defined as spirometry values obtained when actively receiving IP at protocol-defined collection time points and spirometry values when on IP hold at protocol-defined collection time points; excludes spirometry values collected > 14 days of last IP dosing after they have been permanently discontinued from IP. [2] Post hoc analysis population: The additional analysis was limited to patients who were exposed to study drug for 12 weeks. One patient was not exposed to TTI-101 at 12 weeks; one patient was removed from the analysis due to receiving less than 60% of the expected dosing; two patients were removed due to no measurable TTI-101 observed in the blood as well as no reported adverse events; and one additional patient was removed as an outlier for the 12-week analysis as their pulmonary function initially improved on treatment, but was subsequently severely impacted by acute bronchitis deemed unrelated to study drug

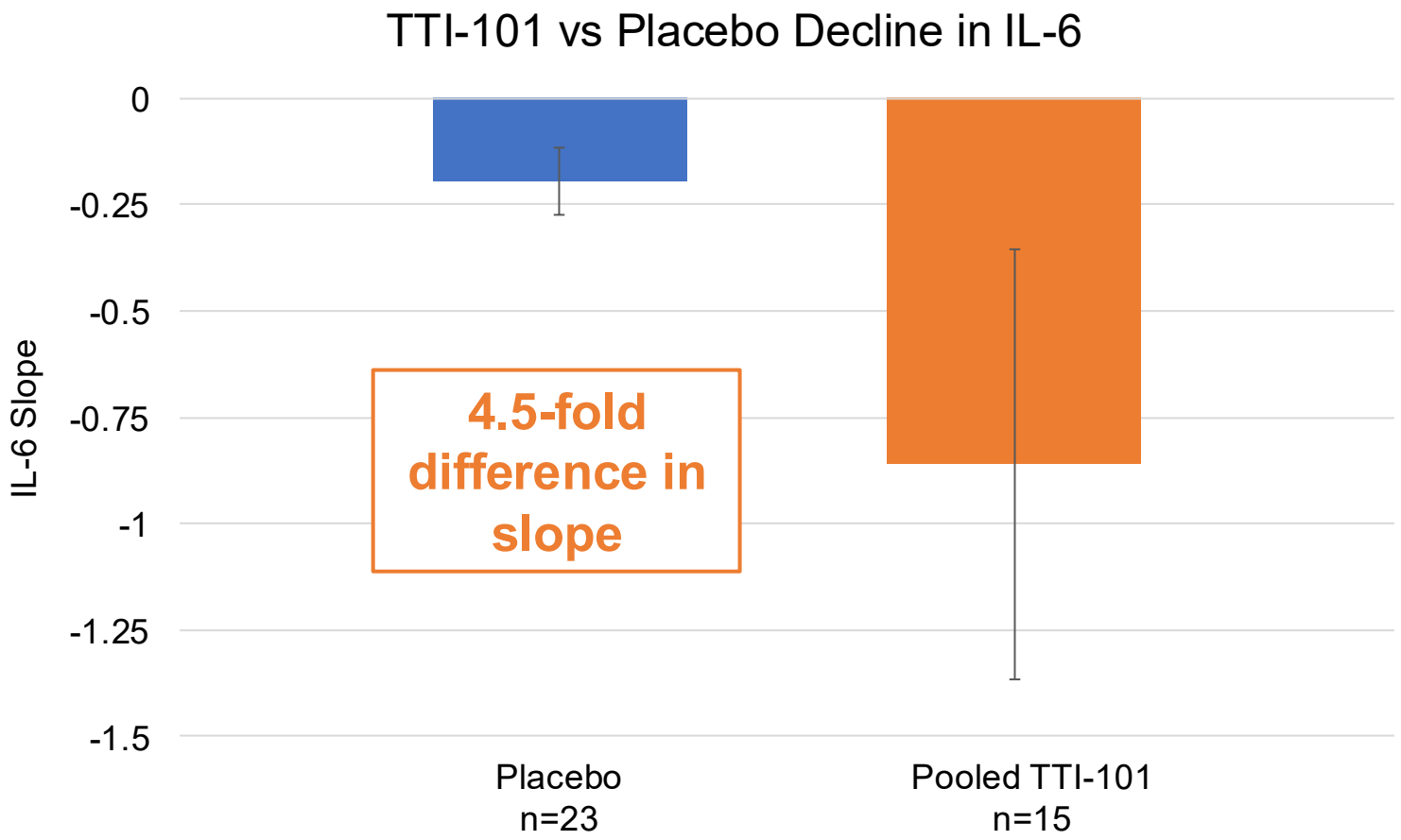
TTI-101-treated Patients Demonstrated Greater Decline in Fibrosis Score (Baseline to 12 Weeks) vs Placebo



Greater decrease in fibrosis score (improvement in fibrosis) among patients treated with TTI-101 (either arm) vs placebo

Analysis performed on post hoc analysis population comparing baseline to 12 weeks. One patient missing fibrosis score; overall percent change from baseline was calculated using baseline-weighted aggregation to account for differences in initial fibrosis severity with bootstrap-based standard error (SE)

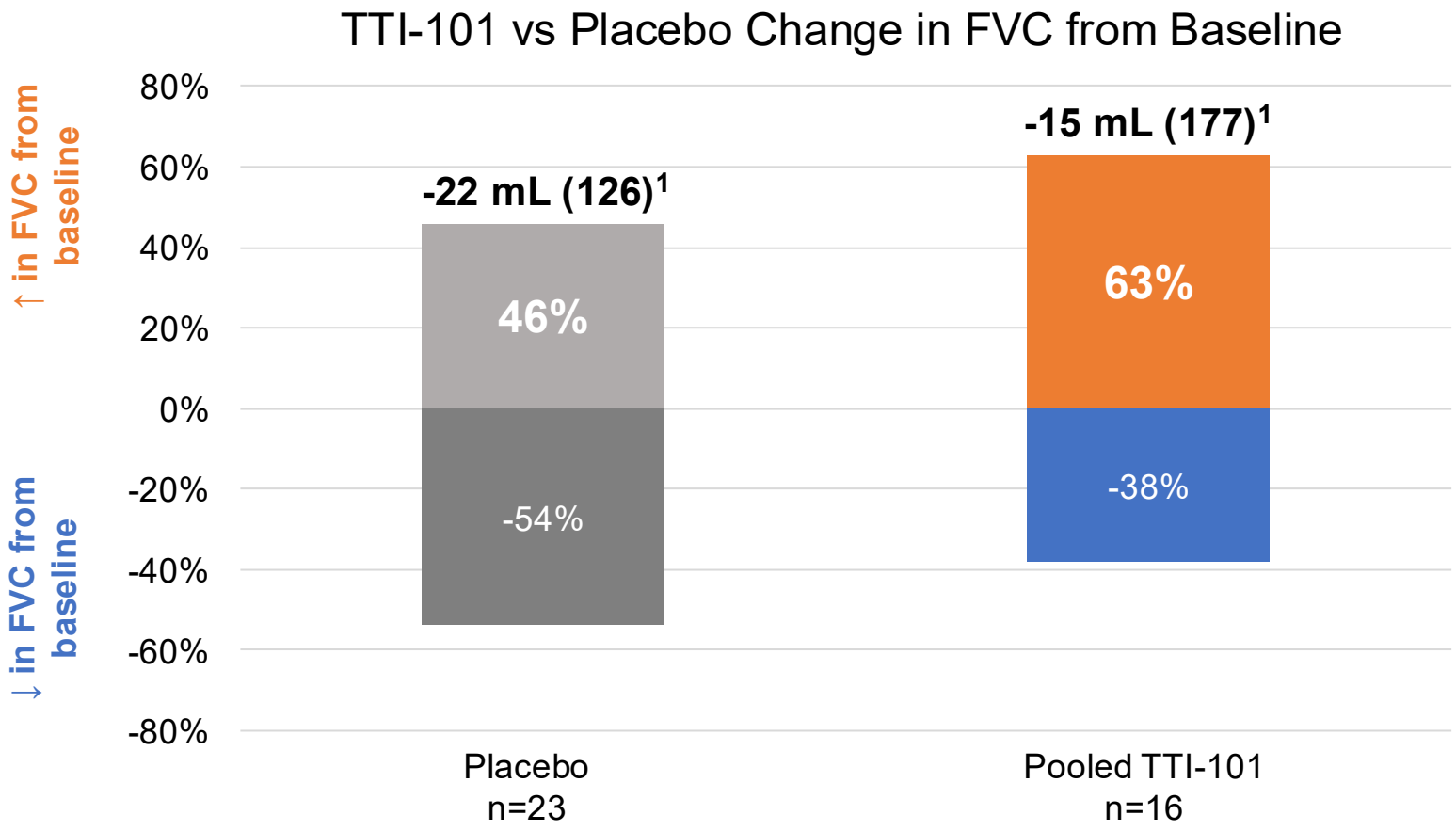
TTI-101-treated Patients Demonstrated Greater IL-6 Decline vs Placebo



IL-6 is a key pro-inflammatory cytokine that signals through STAT3; inhibition of STAT3 is expected to reduce downstream inflammatory signaling associated with disease

Analysis performed on post hoc analysis population comparing baseline to 12 weeks. Two patients missing IL-6 change scores (one placebo, one TTI-101); Decline assessed using OLS: ordinary least squares regression model and standard errors

A Greater Proportion of TTI-101-treated Patients Demonstrated Increase in FVC vs Placebo



63% of patients treated with TTI-101 demonstrated an increase in FVC at 12 weeks, and less of a decline when compared to the REVERT and historical placebo groups

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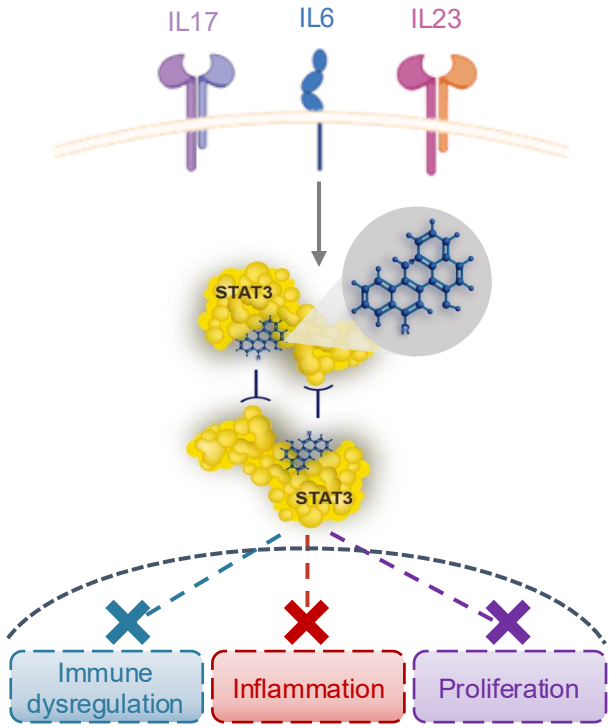
Analysis performed on post hoc analysis population comparing baseline to 12 weeks; [1]Actual mean FVC change in mL (SD) at 12 weeks

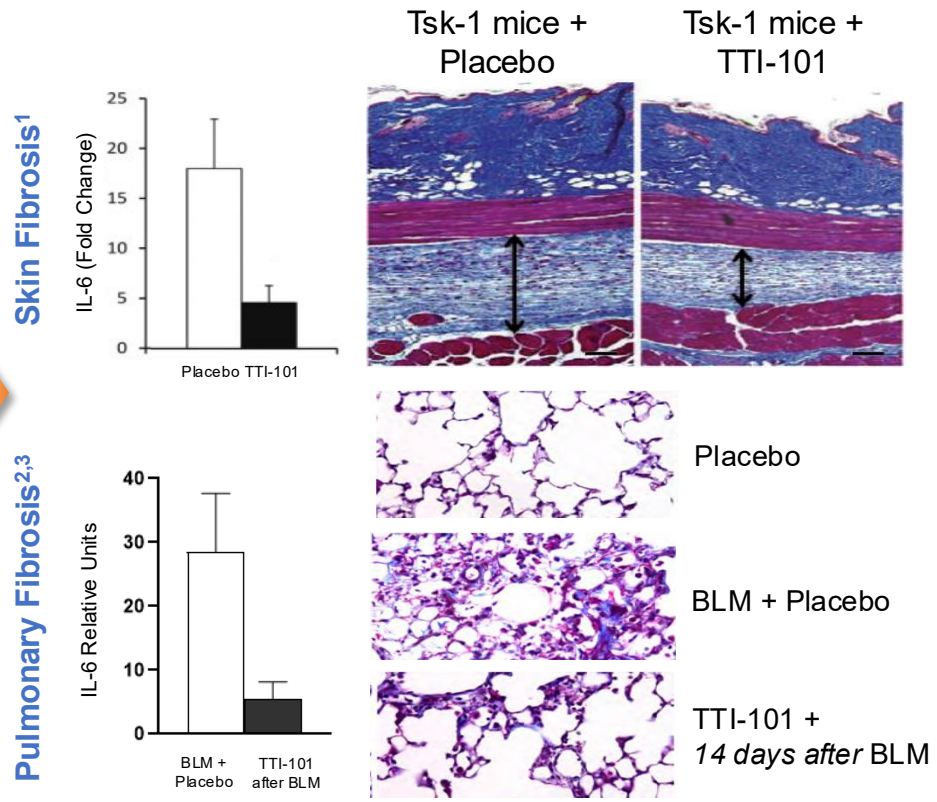
Our STAT3 Inhibitors are Designed to Address the Unmet Need in Inflammatory and Proliferative Diseases

Well-Established Target



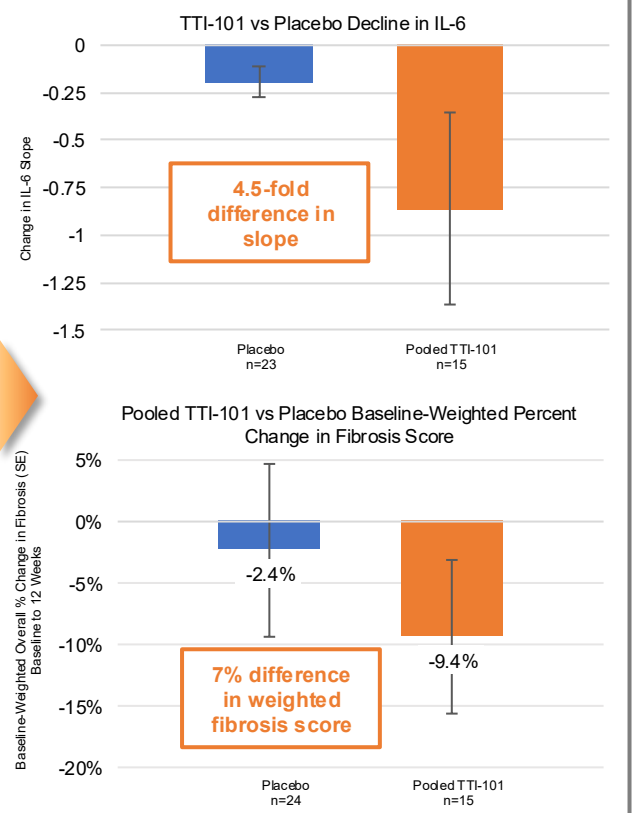
STAT3: central mediator in inflammation and proliferative disease

Preclinical Biological Activity



↓ IL-6 levels and ↓ fibrosis in models of proliferative disease

Clinical Proof of Mechanism



↓ IL-6 levels and ↓ fibrosis in humans

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1. Pedroza et al. *Rheum.* 2017: Genetically engineered model of Tight skin (Tsk-1) mice which spontaneously develop fibrosis as a result of a duplication in the fibrillin-1 gene; 2. Pedroza et al. *FASEB J.* 2016; 3. Kauh et al. *CHEST.* 2024. Pulmonary fibrosis bleomycin (BLM) model