UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K/A

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported):
December 17, 2024

CARA THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-36279**	**75-3175693**
(state or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**
400 Atlantic Street **Suite 500** **Stamford, CT**		**06901**
(Address of principal executive offices)		**(Zip Code)**

Registrant's telephone number, including area code: (203) 406-3700

Not applicable
(Former name or former address, if changed since last report.)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☒ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, $0.001 par value per share	**CARA**	**The Nasdaq Capital Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Explanatory Note

This Amendment No. 1 to the Form 8-K (this "Amendment") amends the Form 8-K (the "Original Form 8-K") of Cara Therapeutics, Inc. (the "Company"), which was filed with the Securities and Exchange Commission (the "SEC") on December 18, 2024. This Amendment is being filed solely to correct formatting errors and omitted text resulting from the conversion to the Electronic Data Gathering, Analysis, and Retrieval system ("EDGAR"), of the investor presentation attached as Exhibit 99.2 to the Original Form 8-K.

Except as described above, this Amendment does not update or modify any other information presented in the Original Form 8-K and does not reflect events occurring after the Original Form 8-K's filing date of December 18, 2024.

Cautionary Statement Regarding Forward-Looking Statements

Certain statements contained in this Current Report on Form 8-K regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include statements concerning the anticipated completion and effects of the proposed Merger and Asset Disposition and related timing, Tvardi's and the combined company's planned clinical programs, including planned clinical trials and the timing for anticipated trial results, the potential of Tvardi's product candidates, the expected trading of the combined company's stock on the Nasdaq Capital Market, management of the combined company and other statements regarding management's intentions, plans, beliefs, expectations or forecasts for the future, and, therefore, you are cautioned not to place undue reliance on them.

Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. These forward-looking statements are subject to a number of risks, including, among other things: the risk that the conditions to the closing of the Merger are not satisfied, including that the approval of the stockholders of Cara is not obtained on the timeline expected, if at all; uncertainties as to the timing of the closing of the Merger and the ability of each of Tvardi and Cara to consummate the Merger; risks related to the ability of Tvardi and Cara to correctly estimate and manage their respective operating expenses and expenses associated with the Merger pending the closing of the Merger; risks associated with the possible failure to realize certain anticipated benefits of the Merger, including with respect to future financial and operating results; the potential for the occurrence of any event, change or other circumstance or condition that could give rise to the termination of the Merger and any agreements entered into in connection therewith; the possible effect of the announcement, pendency or completion of the Merger on Tvardi's or Cara's business relationships, operating results and business generally; the risk that as a result of adjustments to the exchange ratio, Tvardi stockholders and Cara stockholders could own more or less of the combined company than is currently anticipated; risks related to the market price of Cara's common stock relative to the value suggested by the exchange ratio; unexpected costs, charges or expenses resulting from the Merger; the uncertainties associated with Tvardi's product candidates, as well as risks associated with the clinical development and regulatory approval of product candidates, including potential delays in the completion of clinical trials; the significant net losses each of Cara and Tvardi has incurred since inception; the combined company's ability to initiate and complete ongoing and planned preclinical studies and clinical trials and advance its product candidates through clinical development; the timing of the availability of data from the combined company's clinical trials; the outcome of preclinical testing and clinical trials of the combined company's product candidates, including the ability of those trials to satisfy relevant governmental or regulatory requirements; the combined company's plans to research, develop and commercialize its current and future product candidates; the clinical utility, potential benefits and market acceptance of the combined company's product candidates; the requirement for additional capital to continue to advance these product candidates, which may not be available on favorable terms or at all; the combined company's ability to attract, hire, and retain skilled executive officers and employees; the combined company's ability to protect its intellectual property and proprietary technologies; the combined company's reliance on third parties, contract manufacturers, and contract research organizations; the possibility that Tvardi, Cara or the combined company may be adversely affected by other economic, business, or competitive factors; risks associated with changes in applicable laws or regulations; those factors discussed in Cara's filings with the Securities and Exchange Commission, including the "Risk Factors" section of the Company's Annual Report on Form 10-K for the year ending December 31, 2023, and its other documents subsequently filed with or furnished to the Securities and Exchange Commission, including its Form 10-Q for the quarter ended September 30, 2024. All forward-looking statements contained in this Current Report on Form 8-K speak only as of the date on which they were made. Cara undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made, except as required by law.

Additional Information and Where to Find It

In connection with the proposed transaction between Cara and Tvardi, Cara intends to file relevant materials with the SEC, including a registration statement on Form S-4 that will contain a proxy statement and prospectus. CARA URGES INVESTORS AND STOCKHOLDERS TO READ THESE MATERIALS CAREFULLY AND IN THEIR ENTIRETY WHEN THEY BECOME AVAILABLE BECAUSE THEY WILL CONTAIN IMPORTANT INFORMATION ABOUT CARA, TVARDI, THE PROPOSED TRANSACTION AND RELATED MATTERS. Stockholders will be able to obtain free copies of the proxy statement, prospectus and other documents filed by Cara with the SEC (when they become available) through the website maintained by the SEC at www.sec.gov. In addition, stockholders will be able to obtain free copies of the proxy statement, prospectus and other documents filed by Cara with the SEC by contacting Investor Relations by email at investor@caratherapeutics.com. Stockholders are urged to read the proxy statement, prospectus and the other relevant materials when they become available before making any voting or investment decision with respect to the proposed transaction.

Participants in the Solicitation

Cara and Tvardi, and each of their respective directors and executive officers and certain of their other members of management and employees, may be deemed to be participants in the solicitation of proxies in connection with the proposed transaction. Information about Cara's directors and executive officers, consisting of Helen M. Boudreau, Jeffrey L. Ives, Ph.D., Christopher Posner, Susan Shiff, Ph.D., Martin Vogelbaum, Lisa von Moltke, M.D., Ryan Maynard and Scott Terrillion, including a description of their interests in Cara, by security holdings or otherwise, can be found under the captions, "Security Ownership of Certain Beneficial Owners and Management," "Executive Compensation" and "Director Compensation" contained in the definitive proxy statement on Schedule 14A for Cara's 2024 annual meeting of stockholders, filed with the SEC on April 22, 2024 (the "2024 Cara Proxy Statement"). To the extent that Cara's directors and executive officers and their respective affiliates have acquired or disposed of security holdings since the applicable "as of" date disclosed in the 2024 Cara Proxy Statement, such transactions have been or will be reflected on Statements of Change in Beneficial Ownership on Form 4 filed with the SEC. Additional information regarding the persons who may be deemed participants in the proxy solicitation, including the information about the directors and executive officers of Tvardi, and a description of their direct and indirect interests, by security holdings or otherwise, will also be included in a registration statement filed on Form S-4 that will contain a proxy statement (and prospectus and other relevant materials) to be filed with the SEC when they become available. Investors should read the registration statement, proxy statement/prospectus and the other relevant materials when they become available before making any voting or investment decision with respect to the proposed transaction. These documents can be obtained free of charge from the sources indicated above.

Non-Solicitation

This Current Report on Form 8-K shall not constitute an offer to sell or the solicitation of an offer to sell or the solicitation of an offer to buy any securities, nor shall there be any sale of securities in any jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such jurisdiction. No public offer of securities shall be made except by means of a prospectus meeting the requirements of Section 10 of the Securities Act of 1933, as amended.

Item 9.01 **Financial Statements and Exhibits.**

(d) Exhibits.

Exhibit No.	Description
2.1*	Agreement and Plan of Merger and Reorganization, dated December 17, 2024, by and among Cara Therapeutics, Inc., CT Convergence Merger Sub, Inc. and Tvardi Therapeutics, Inc. (incorporated by reference to Exhibit 2.1 to the Original Form 8-K)
10.1	Form of Cara Therapeutics, Inc. Stockholder Support Agreement, dated December 17, 2024 (incorporated by reference to Exhibit 10.1 to the Original Form 8-K)
10.2	Form of Tvardi Therapeutics, Inc. Stockholder Support Agreement, dated December 17, 2024 (incorporated by reference to Exhibit 10.2 to the Original Form 8-K)
10.3	Form of Lock-Up Agreement, dated December 17, 2024 (incorporated by reference to Exhibit 10.3 to the Original Form 8-K)
10.4*	Asset Purchase Agreement, dated December 17, 2024, by and among Cara Therapeutics, Inc. Cara Royalty Sub, LLC and Vifor Fresenius Medical Care Renal Pharma, Ltd. (incorporated by reference to Exhibit 10.4 to the Original Form 8-K)
99.1	Joint Press Release of Cara Therapeutics, Inc. and Tvardi Therapeutics, Inc. issued on December 18, 2024 (incorporated by reference to Exhibit 99.1 to the Original Form 8-K)
99.2	Investor Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

* Exhibits and/or schedules have been omitted pursuant to Item 601(a)(5) or 601(b)(2) of Regulation S-K, as applicable. The registrant hereby undertakes to furnish supplementally copies of any of the omitted exhibits and schedules upon request by the SEC; provided, however, that the registrant may request confidential treatment pursuant to Rule 24b-2 under the Exchange Act for any exhibits or schedules so furnished.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

CARA THERAPEUTICS, INC.

By: /s/ Ryan Maynard
Ryan Maynard
Chief Financial Officer

Dated: December 20, 2024


tvardi
THERAPEUTICS
CARA
THERAPEUTICS
Proposed
Merger
Overview
December 18, 2024

Disclaimer and Forward-Looking Statements

This presentation and any accompanying oral commentary have been prepared by Tvardi Therapeutics, Inc. ("Tvardi") and Cara Therapeutics, Inc. ("Cara") for informational purposes only and to as such parties in making their own evaluation with respect to the potential combination (the "Proposed Merger") of a wholly-owned subsidiary of Cara with and into Tvardi and related transactions and for any other purpose. All statements contained in this presentation and the accompanying oral commentary, other than statements of historical facts, are forward-looking statements, including: statements about the combined company's expectations regarding the potential benefits, activity, effectiveness, and safety of its product candidates; the combined company's expectations with rega to the design and results of its research and development programs, preclinical studies, and clinical trials, including the timing and availability of data from such studies and trials; the combined company's preclinical, clinical, and regulatory development plans for its product candidates, including the timing or likelihood of regulatory filings and approvals for the combined company's product candidates; the combined company's expectations with regard to its ability to license, acquire, discover, and develop additional products candidates and advance such product candidates into, and successfully complete, preclinical studies and clinical trials; the potential market size and size of the potential patient populations for the combined company's product candidates and any future prod candidates; ability to maintain existing, and establish new, strategic collaborations, licensing, or other arrangements; the scope of protection the combined company is able to establish and maintain intellectual property rights covering its initial product candidate and any future product candidates; the combined company's business strategy; the combined company's future results of operations a financial position; the combined company's expectations with respect to future performance and anticipated financial impacts of the Proposed Merger; the satisfaction of closing conditions to the Proposed Merger and the timing of the completion of the Proposed Merger, including obtaining the approval of the Proposed Merger and issuance of shares contemplated thereby by Cara's stockholders. These statements involve substantial known and unknown risks, uncertainties and other factors that may cause the combined company's actual results, timing of results, levels of activ performance, or achievements to be materially different from the information expressed or implied by these forward-looking statements. New risks emerge from time to time. It is not possible for Tva and Cara's management to predict all risks, nor can they assess the impact of all factors on the combined company's business or the extent to which any factor, or combination of factors, may cause actual results to differ materially and adversely from those anticipated or implied in the forward-looking statements.

Tvardi and Cara may not actually achieve the plans, intentions, or expectations disclosed in their forward-looking statements, and you should not place undue reliance on such forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements Tvardi and Cara make. The forward-looking statements in this presentation represent Tvardi's and Cara's views as of the date of this presentation. Tvardi and Cara anticipate that subsequent events and developments will cause their views to change. However, while Tvardi and Cara may elect to update these forward-looking statements at some point in the future, they have no current intention of doing so except to the extent required by applicable law. Except as required by law, neither Tvardi and Cara nor any other person assumes responsibility for the accuracy and completeness of the forward-looking statements in this presenta and the accompanying oral commentary. You should, therefore, not rely on these forward-looking statements as representing Tvardi's or Cara's views as of any date subsequent to the date of this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by Tvardi and Cara relating to market size and growth and other data about the combined company's industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estima of the combined company's future performance and the future performance of the markets in which it will operate are necessarily subject to a high degree of uncertainty and risk.

This presentation contains trademarks, service marks, trade names and copyrights of Tvardi, Cara and other companies which are the property of their respective owners.

This presentation shall not constitute an offer to sell or the solicitation of an offer to buy these securities, nor shall there be any sale of these securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

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Chris Posner

CEO, Cara Therapeutics

Merger of Tvardi and Cara Therapeutics

Overview	• Tvardi, a clinical-stage biopharmaceutical company focused on the development of novel, oral, small molecule therapies targeting STAT3 to treat fibrosis-driven diseases with significant unmet need, intends to merge with Cara Therapeutics, Inc. (Nasdaq: CARA) • Cara exploration of strategic alternatives initiated in July 2024 evaluating several potential merger candidates • Supported by the Board of Directors of both companies and is subject to stockholder approval and other customary closing conditions • Combined company will focus on advancing the development of Tvardi programs • Upon close, combined company is expected to be renamed "Tvardi Therapeutics, Inc." trading as Nasdaq: TVRD
Transaction Summary	• Merger expected to close in 1H:2025 • Pro forma company ownership: 83.0% Tvardi and 17.0% Cara, before giving effect to Tvardi financing • Combined company will be well capitalized including $28 million from concurrent financing, combined with Cara's anticipated cash at the closing of the merger • Merger and combined financings would fund the company into the 2H:2026, well past multiple Phase 2 readouts in IPF and HCC (expected 2H:2025) and prepare programs for Phase 3 development
Management & Board	• Tvardi management will operate pro forma company • Combined Board of Directors to contain to contain six representatives from Tvardi and one from Cara

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tvardi™ THERAPEUTICS

CARA THERAPEUTICS

Imran Alibhai, PhD

CEO, Tvardi Therapeutics

Targeting STAT3: Central Mediator of Fibrosis-Driven Diseases

Deep expertise in STAT3 biology

- Unlocking highly-validated, yet historically "undruggable" target within fibrosis-driven diseases

Potential to serve as a disease-modifying therapy in IPF[1]

- IPF models demonstrated reversal of fibrosis and restoration of lung function
- Phase 2 blinded data suggests encouraging trends in lung function

Well-positioned to differentiate therapeutic impact in HCC[2]

- Early signs of response in both mono- and combination therapy from completed and ongoing clinical trials

Multiple near-term data catalysts expected

- IPF Phase 2 unblinded data in H2:2025
- HCC Phase 1b/2 topline data in H2:2025
- TTI-109 IND[3] submission planned for H1:2025

1. Idiopathic pulmonary fibrosis. 2. Hepatocellular carcinoma. 3. Investigational new drug.

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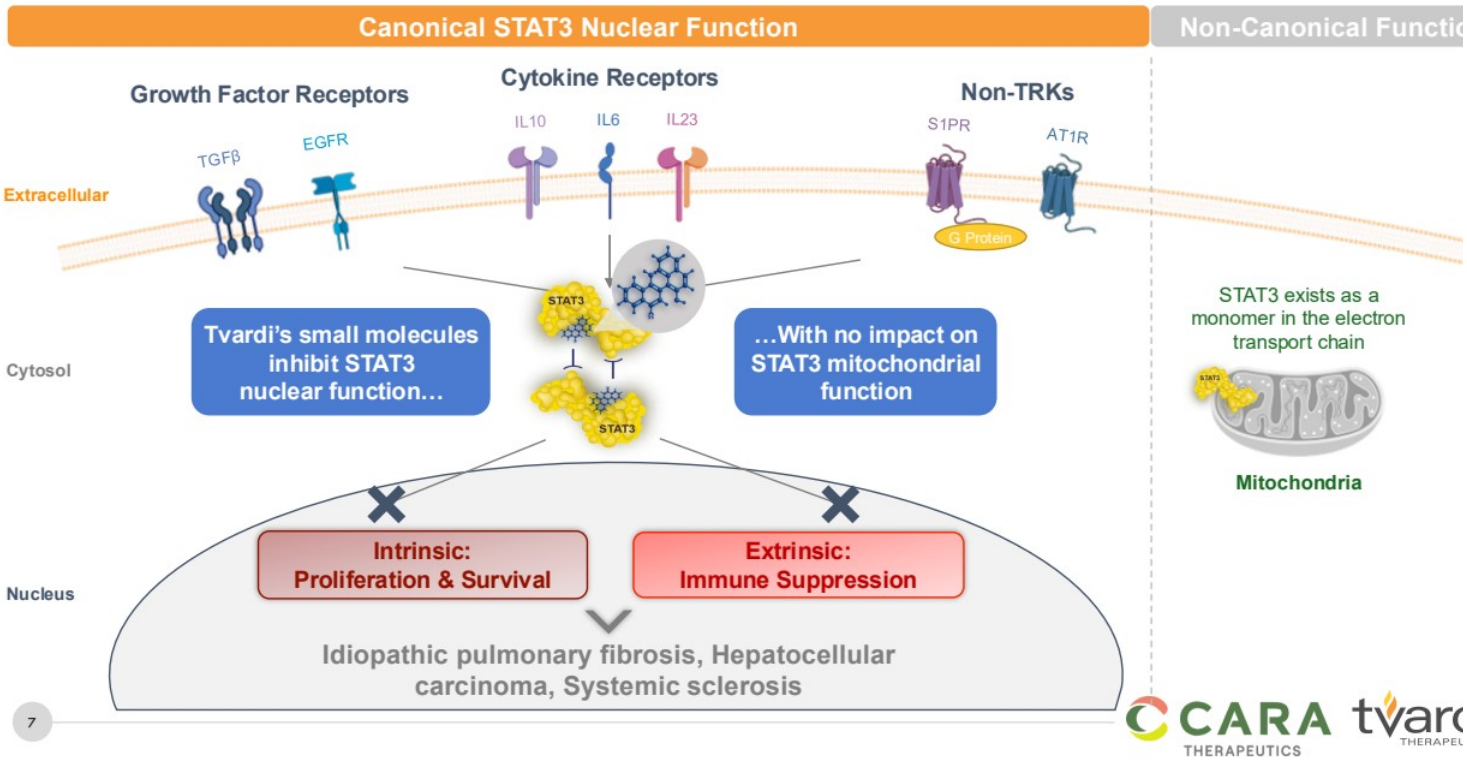
STAT3's Canonical Function Plays a Central Role in Fibrosis-Driven Diseases



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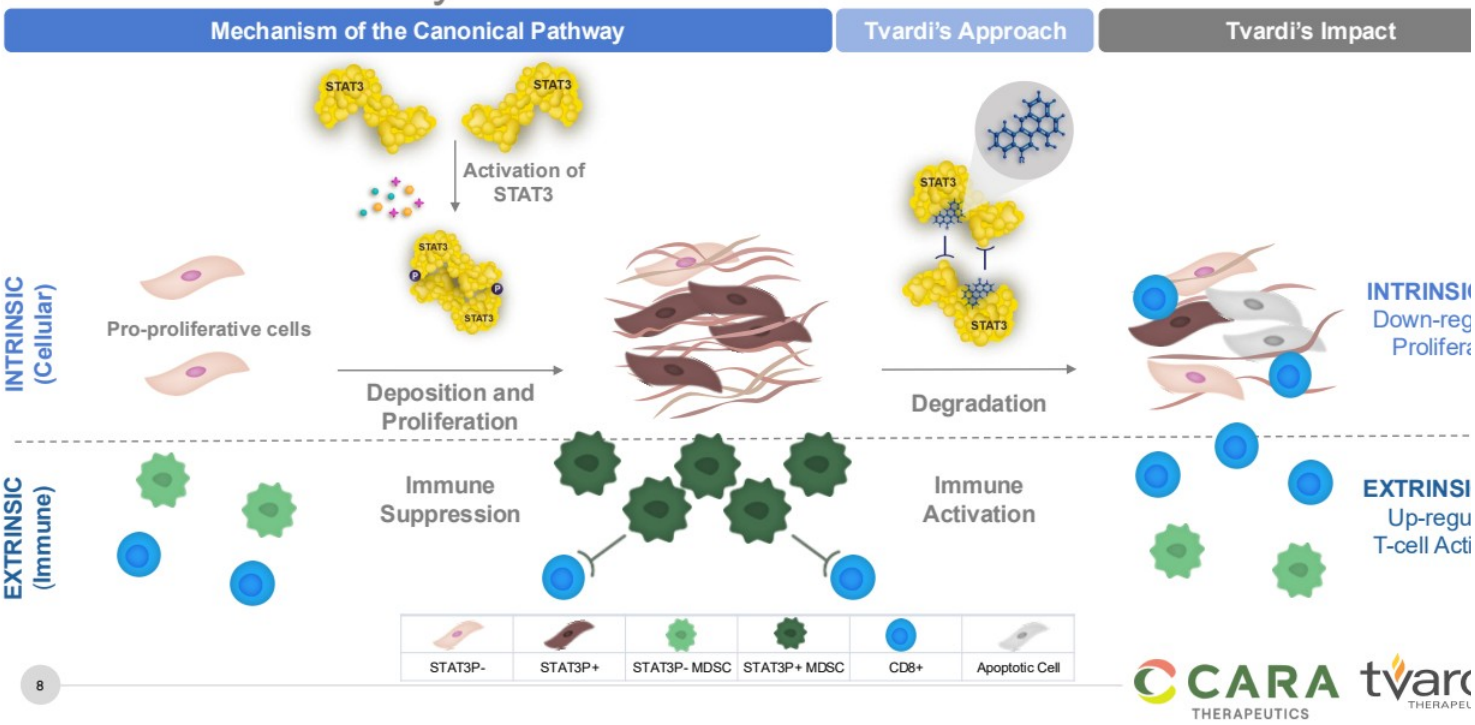
The Dual Mechanism of Action of STAT3's Function in the Canonical Pathway



Seasoned Leadership: Deep R&D and Operational Expertise & Strong Existing Support

Management Team

Imran Alibhai, PhD CEO & Director

Dan Conn, JD, MBA CFO

John Kauh, MD CMO

Scientific Advisory Board

David Tweardy, MD Founder & Advisor

Ron DePinho, MD Founder & Advisor

Keith Flaherty, MD Advisor (Oncology)

Lisa Lancaster, MD Advisor (IPF)

Jeff Swigris, DO Advisor (IPF)

Board of Directors

Sujal Shah Chairman

Michael Wyzga Director

Shaheen Wirk, MD Director

Wallace Hall Director

Cara Representative Director

Existing Investors

Our Pipeline

Program	Indication	Discovery & Preclinical	Phase 1	Phase 2	Phase 3	Anticipated Milestone
TTI-101	revert IPF Idiopathic Pulmonary Fibrosis			Phase 2		H2:2025 Phase 2 data
TTI-101	revert LIVER CANCER Hepatocellular Carcinoma			Phase 1b/2		H2:2025 Phase 1b/2 topline data
TTI-109	Fibrosis-driven Disease[1]					H1:2025 IND submission

1. We plan to commence clinical trials in fibrosis and/or oncology pending IND submission and FDA feedback.

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tvardi™ THERAPEUTICS

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TTI-101 in IPF

IPF Unmet Need Represents a Large Commercial Opportunity

- IPF is a rare, chronic, interstitial lung disease characterized by inflammation, progressive fibrosis, and lung dama
- Patients with IPF have a poor prognosis, poor quality of life, and are at a higher risk of early mortality

Prevalence	Incidence	Survival
~150K in US[1]	~50K in US[1]	Median <5 years[2] from time of diagnosis

Peak Sales[3]

OFEV (nintedanib) capsules 150mg ▶ **$3.8B** in 2023

Esbriet (pirfenidone) tablets ▶ **$1.1B** in 2020

High unmet need remains, even with two FDA approved drugs, Ofev® (nintedanib) and Esbriet® (pirfenidone)

- **Neither reverse / halt clinical decline: both only slow the progression of disease**
- Only ~25%[4] of US IPF patients initiate standard of care
  - Estimated >40% of patients discontinue therapy[4]

We believe there is a significant commercial opportunity for a differentiated IPF treatment

1. Raghu, G., Weycker, D., Edelsberg, J., Bradford, W. Z., & Oster, G. Incidence and prevalence of idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 174(7), 810–816 (2006). https://doi.org/10.1164/rccm.200602-163OC
2. Du, K., Zhu, Y., Mao, R. et al. Medium-long term prognosis prediction for idiopathic pulmonary fibrosis patients based on quantitative analysis of fibrotic lung volume. Respir Res 23, 372 (2022). https://doi.org/10.1186/s12931-022-02276-3
3. Based on $3.8B in sales of Ofev and $1.1B in sales of Esbriet from Boehringer Ingelheim and Genentech (Roche) filings.
4. Dempsey, T. M., Payne, S., Sangaralingham, L., Yao, X., Shah, N. D., & Limper, A. H. (2021). Adoption of the Antifibrotic Medications Pirfenidone and Nintedanib for Patients with Idiopathic Pulmonary Fibrosis. Annals of the American Thoracic Society, 18(7), 1121–1128. https://doi.org/10.1513/AnnalsATS.202007-901OC

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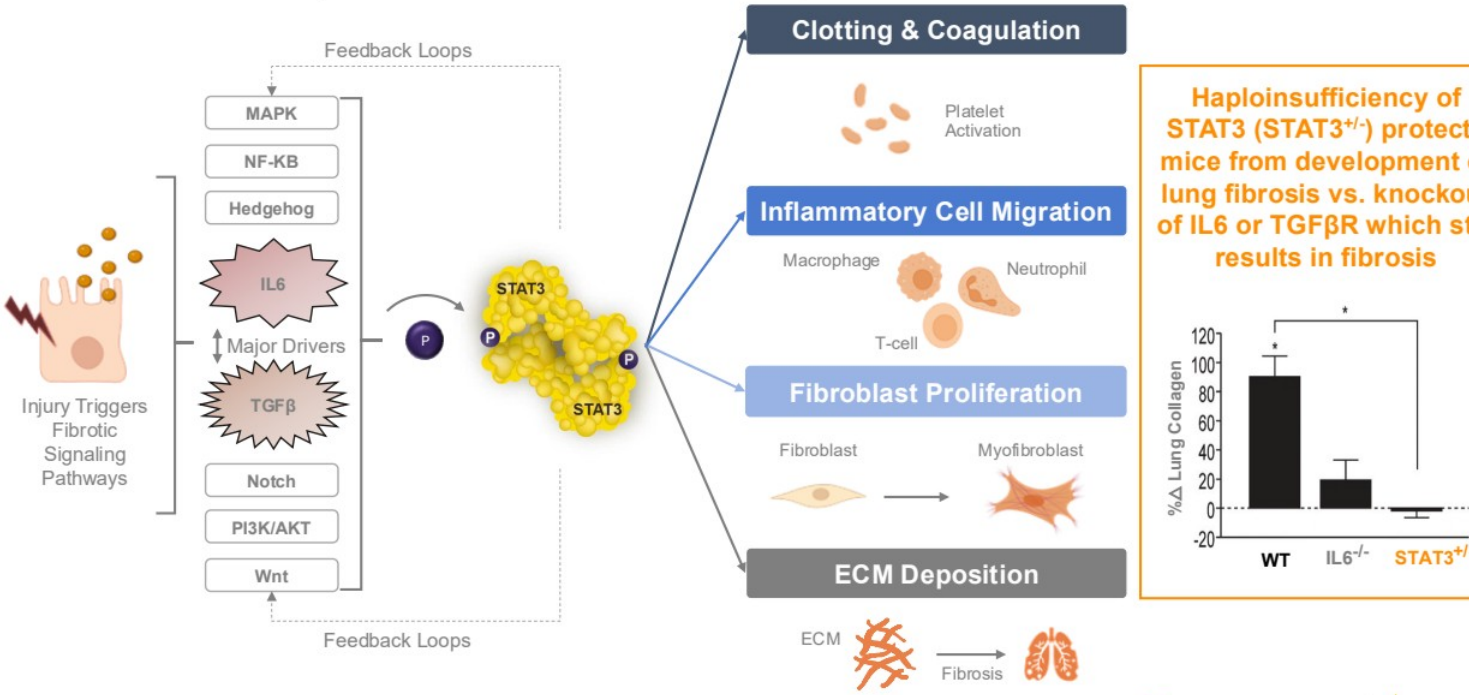
STAT3 Activation is a Central Catalyst in the Fibrotic Cascade



Haploinsufficiency of STAT3 (STAT3$^{+/-}$) protect mice from development lung fibrosis vs. knockou of IL6 or TGFβR which st results in fibrosis

Denton CP *Ann Rheum Dis* 2018; O'Donoghue RJ et al *EMBO Mol Med* 2012

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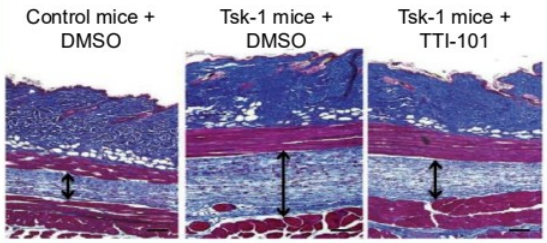
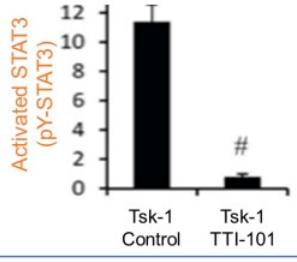
TTI-101 Inhibited Activation of STAT3 and Key Pro-fibrotic Mediators in Sclerosis

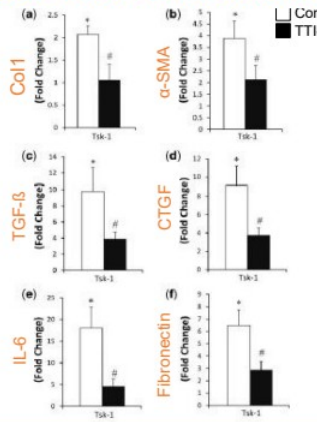
TTI-101 Decreased Hypodermal Fibrosis in Tsk-1 Mice



TTI-101 Inhibited STAT3 Activation



TTI-101 Inhibited Profibrotic Mediator



Results from this GEM model with TTI-101 also replicated in a chemically induced skin fibrosis model

These mechanisms are individual targeted in clinical trials; TTI-101 observed to down-regulat all factors simultaneously via STA inhibition

Pedroza et al *Rheum* 2017: Tight skin (Tsk-1) mice spontaneously develop fibrosis as a result of a duplication in the fibrillin-1 gene

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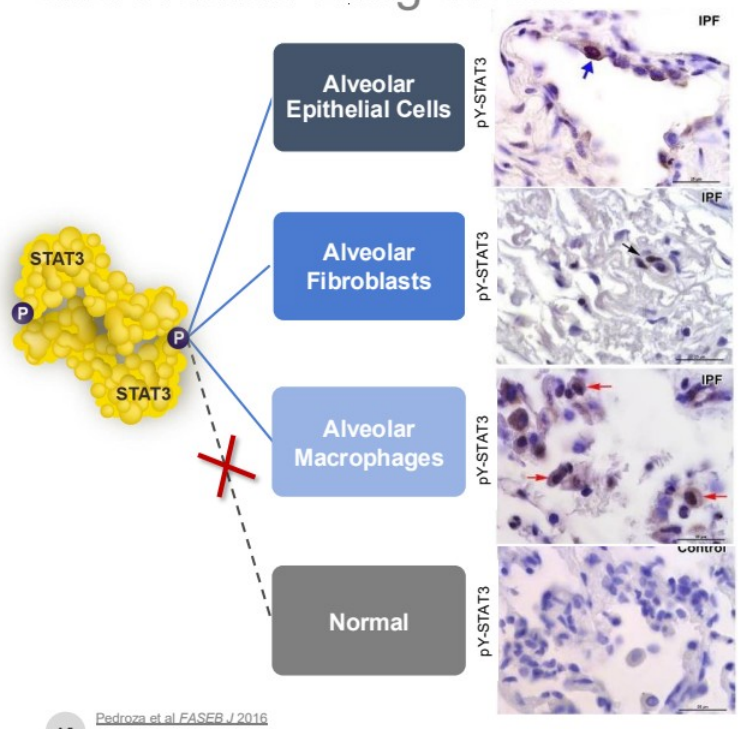
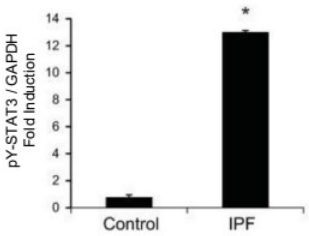
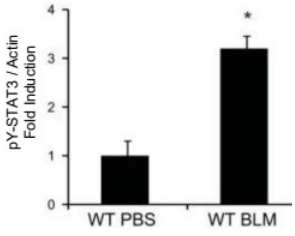
STAT3 is Activated in Major Compartments of IPF-Affected Mouse and Human Lung Tissue



Activated STAT3 is overexpressed in IPF human lung tissue



Activated STAT3 is similarly overexpresse lung tissue of murine



Pedroza et al *FASEB J* 2016

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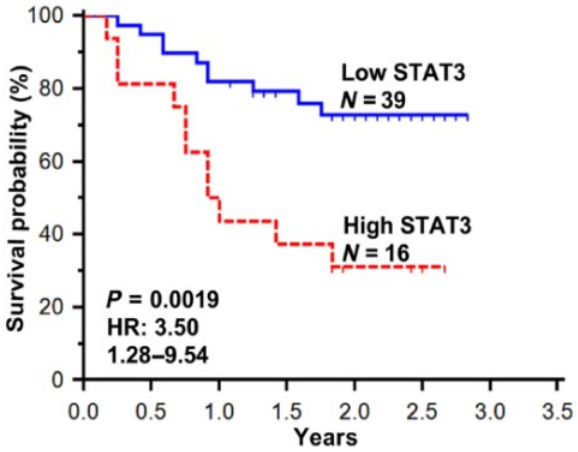
STAT3 Correlates with High Mortality in IPF Patients



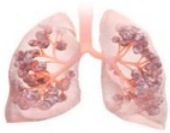
IPF Transplant-free survival over the course of 3.5 years post-diagnosis in a cohort of patients (n=55) based on STAT3 expression. Activated STAT3 (pSTAT3) induces the expression of STAT3 transcript.

Celada et al Sci Transl Med 2018

Reduction of Lung Fibrosis and Statistically Significant Improvement of Oxygen Saturation Observed with TTI-101

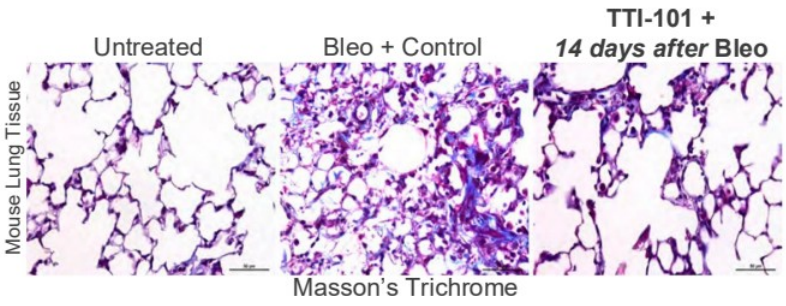
IPF pathogenesis

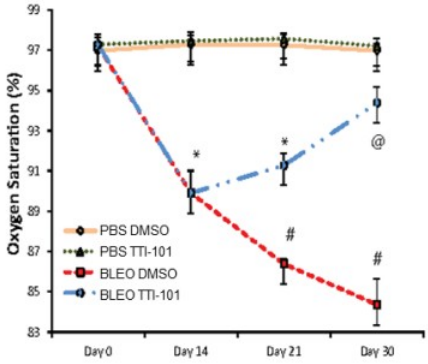
Fibrosis



Diminished Lung Function

IPF induced by bleomycin reversed with TTI-101





* TTI-101 dosed therapeutically 14 days after bleomycin (Bleo) induction of fibrosis; whereas, most experimental therapeutics are dosed prophylactically to demonstrate an effect of fibrosis

Pedroza et al *FASEB J* 2016

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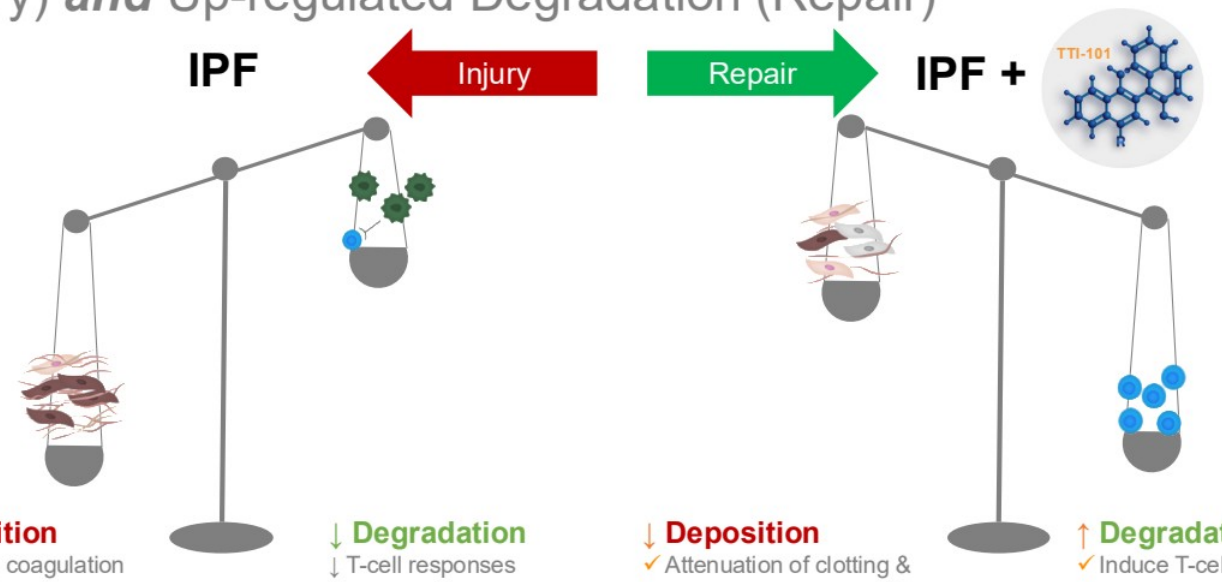
Mechanistic Data Revealed TTI-101 Down-regulated Deposition (Injury) ***and*** Up-regulated Degradation (Repair)



↑ Deposition
↑ Clotting & coagulation
↑ Immunomodulation
↑ Fibroblast proliferation
↑ ECM deposition

↓ Degradation
↓ T-cell responses

↓ Deposition
✓ Attenuation of clotting & coagulation
✓ Reverse fibroblast activation
✓ Reverse ECM deposition

↑ Degradation
✓ Induce T-cell maturatio and activation
✓ Induce cytotoxic effect of NK- and T-cells

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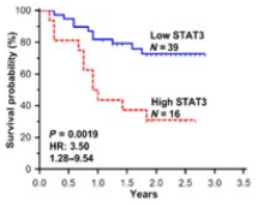
TTI-101 is Designed to Address the Unmet Need in IPF

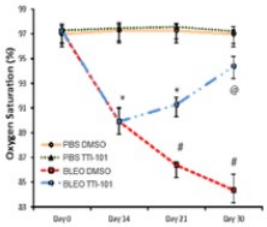
Well-Established Target



STAT3 correlates with high mortality in IPF patients[1]

- ✓ STAT3 is a central mediator in fibrosis
- ✓ TTI-101 designed to target the canonical pathway of STAT3

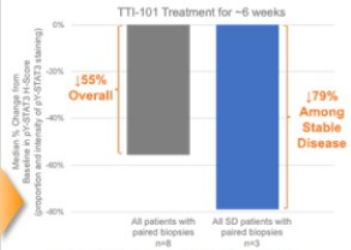
Preclinical Biological Activity



Observed to reduce fibrosis and improve lung function[2]

- ✓ Targets full pathogenesis of IPF
- ✓ TTI-101 in additional fibrotic mouse models demonstrated downregulation of key factors

Clinical Proof of Mechanism – Phase 1



Reduced pyY-STAT3 in humans[3]

- ✓ Well-tolerated
- ✓ High blood exposure (PK)
- ✓ Hits STAT3 target (PD)

Next Step: IPF Clinical POC

revert™ IPF

Phase 2 clinical trial underway

- ✓ No Phase 1 SAD / MAD study needed per FDA; progressed straight to Phase 2 REVERT$_{IPF}$ trial

1. Celada et al 2018. IPF Transplant-free survival over the course of 3.5 years post-diagnosis in a cohort of patients (n=55) based on STAT3 expression. Activated STAT3 (pY-STAT3) induces the expression of STAT3 transcript. 2. Pedroza et al *FASEB J* 2016. 3. Tsimberidou 2024 *accepted in Clin Cancer Research*. 8/10 patients had elevated pY-STAT3 at baseline; elevated pY-STAT3 defined as H-score >30 on a 0-300 scale.

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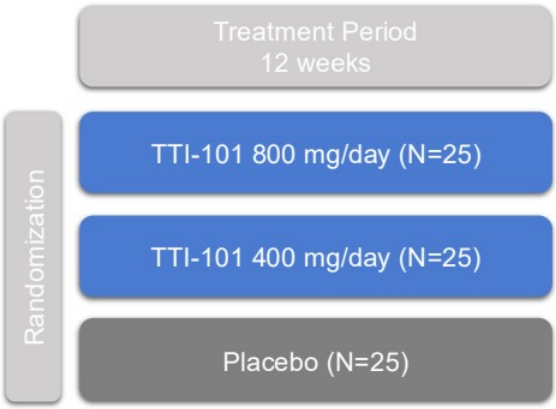
REVERT$_{IPF}$: Double Blind Randomized Phase 2 Study of TTI-101

revert™ IPF

(26 US Sites, N = 75)



- Oral dosing (BID)
- 12-week double blind, randomized, placebo-controlled study
- Alone or in combination with nintedanib
- Enrollment of mild and moderate IPF subjects
- 1º & 2º Objectives: Safety & PK
- Exploratory Objectives:
  - Phase 3 endpoints: △FVC, △DLCO, HRCT, 6MWT
  - Biomarkers

Early blinded clinical data has demonstrated encouraging trends

NCT05671835

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Key Takeaways: TTI-101 in IPF

STAT3: Well-Established Biology

Compelling and validated target → central mediator in fibrosis

Differentiated Approach

Driving inhibition of STAT3 activation to address both IPF disease pathologies (downregulating deposition and upregulating degradation)

Clinical PoC Underway

$REVERT_{IPF}$ Phase 2 trial ongoing with clinically relevant endpoints and collection of STAT3-mediated biomarkers

Near-Term Clinical Milestones

Results from ongoing Phase 2 $REVERT_{IPF}$ t expected in H2:2025

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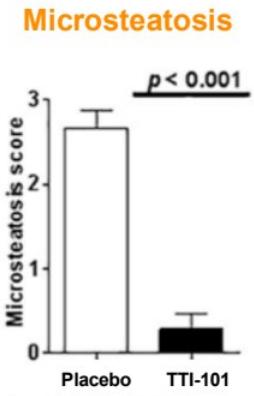
TTI-101 in HCC

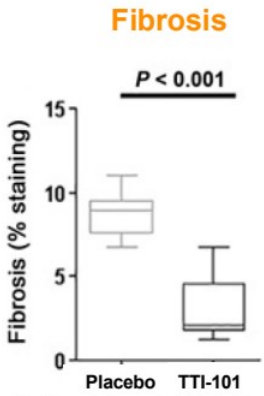
TTI-101 Reversed Multiple Pathogenic Steps of Liver Cancer in a NASH-induced HCC Model

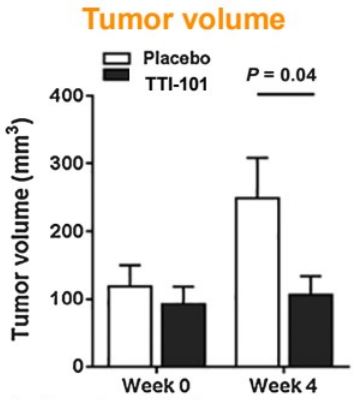
STAT3-mediated pathogenesis

Inflammation → Fibrosis/Cirrhosis → HCC

TTI-101 STAT3-inhibition in NASH-induced HCC







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

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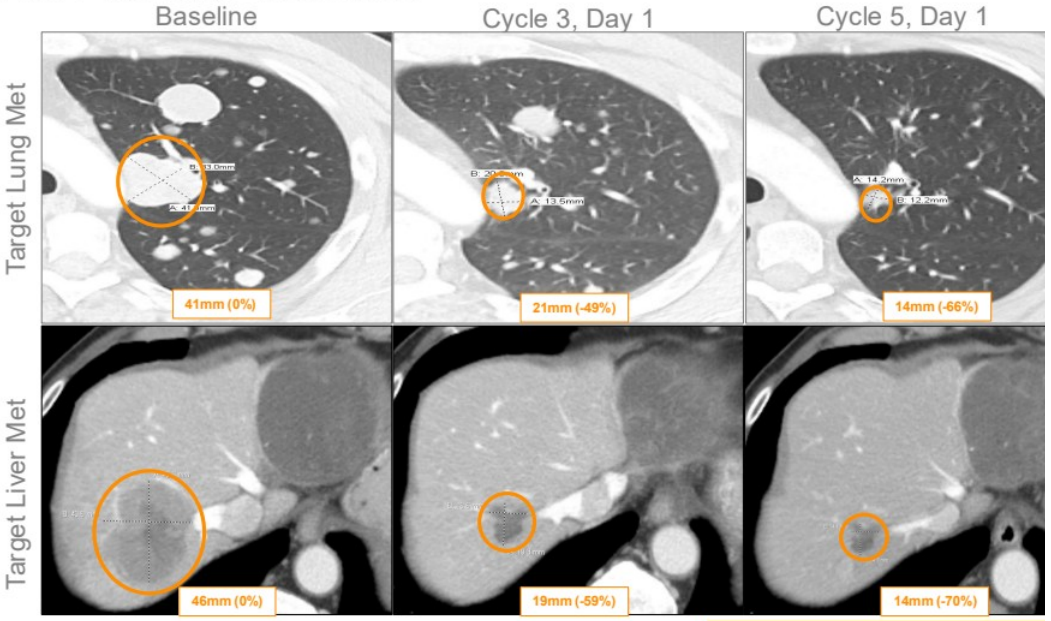
Phase 1 Clinical Trial: TTI-101 Monotherapy Led to Durable Partial Responses in Fibrotic Tumors

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 2023

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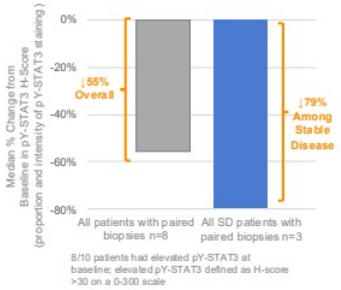
Phase 1: TTI-101 Monotherapy Clinical Trial Summary

PK / PD

- Exposures in humans above the level required for efficacy in preclinical oncology and fibrosis models
- Linear PK from DL1-3
- C_{min} above the IC_{90} 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

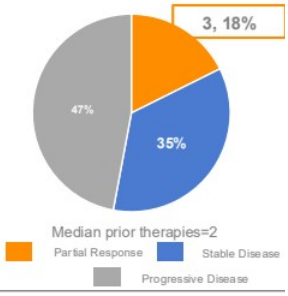
Formulation	F1 N=15		F2 N=47		F3 N=7**	
Grade, n (%)	G1/2	G3	G1/2	G3	G1/2	G3
Diarrhoea	3 (20)	3 (20)	16 (34)	6 (13)	2 (29)	0 (0)
Nausea	4 (26)	0 (0)	6 (13)	1 (2)	0 (0)	1 (14)
Fatigue	6 (40)	0 (0)	4 (8)	0 (0)	0 (0)	0 (0)
Elevated ALT/AST***	1 (7)	1 (7)	1 (2)	4 (8)	1 (14)	1 (14)
Dose reduction	3 (20)		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 2023: SD: Stable Disease; TREAE: Treatment related adverse events; F1-3: Formulation 1-3

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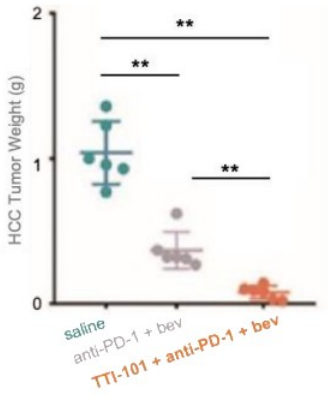
Strong Rationale for Combo Therapy with STAT3 TTI-101

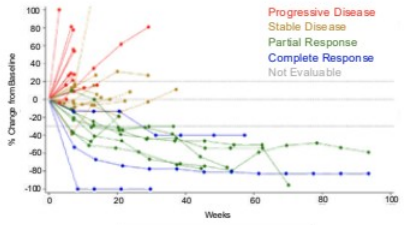
Preclinical Model

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]



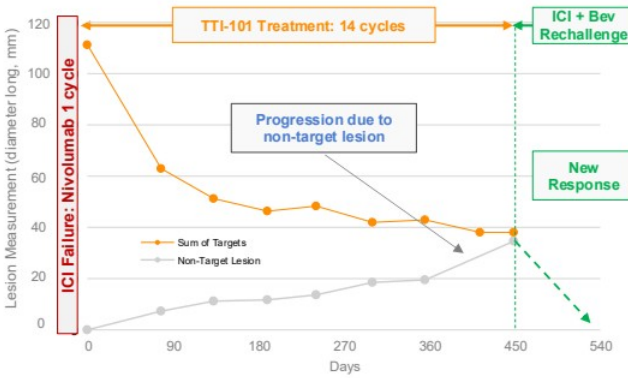
	Durva[3]	Dan+Durva[2]
ORR	9% →	23%
CR	0% →	7%

Danv. development suspended due to several limitations:

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

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 2018; 3. Siu et al 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 2024 *accepted in Clin Cancer Research*

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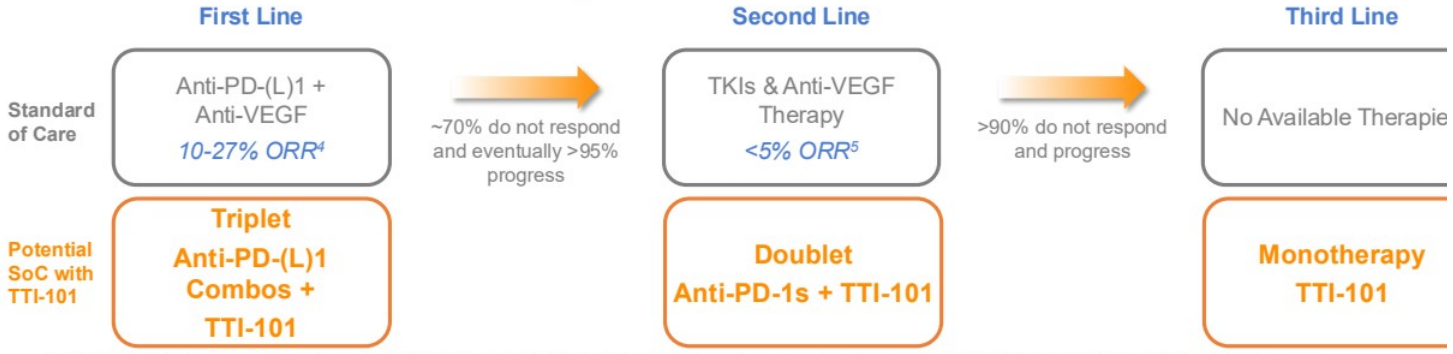
TTI-101 is Designed to Provide a Distinct and Synergistic Mechanism for Unmet Need in HCC

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. Listed 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).

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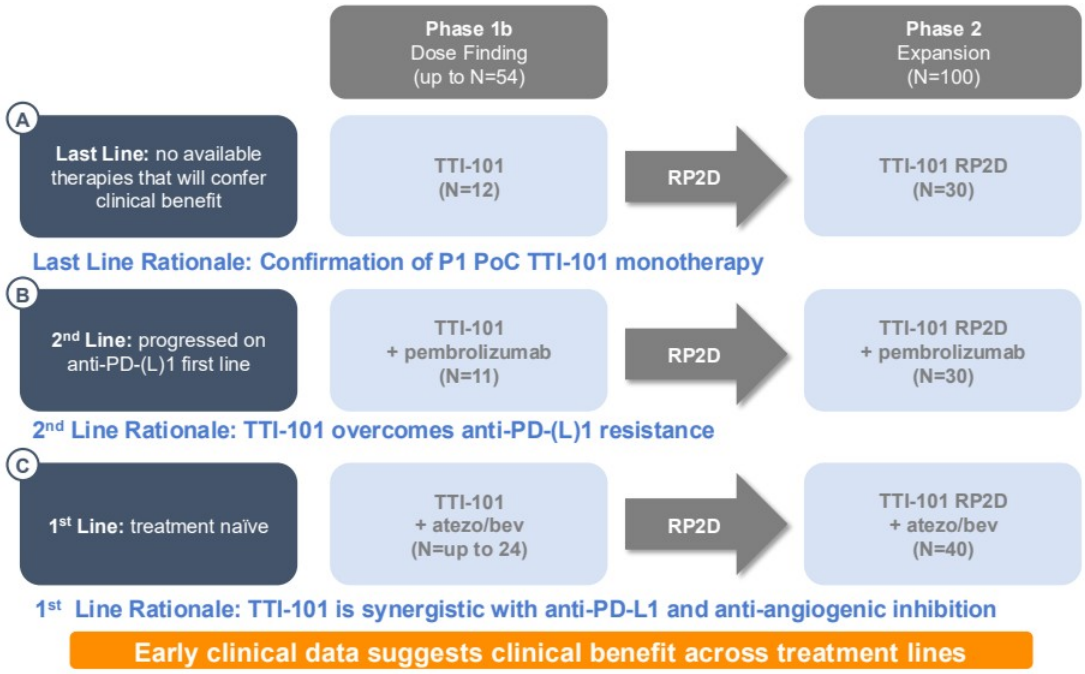
REVERT$_{HCC}$: Phase 2 Study of TTI-101 in HCC



FDA Fast Tr

revert™ LIVER CANCER

(21 US Sites)

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

NCT05440708

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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

Clinical PoC Underway

$REVERT_{HCC}$ trial Phase 2 assessing activity in both monotherapy and combination therapy in areas of unmet need

Near-Term Clinical Milestones

Topline results from ongoing Phase 2 $REVERT_{HCC}$ trial expe in H2:2025

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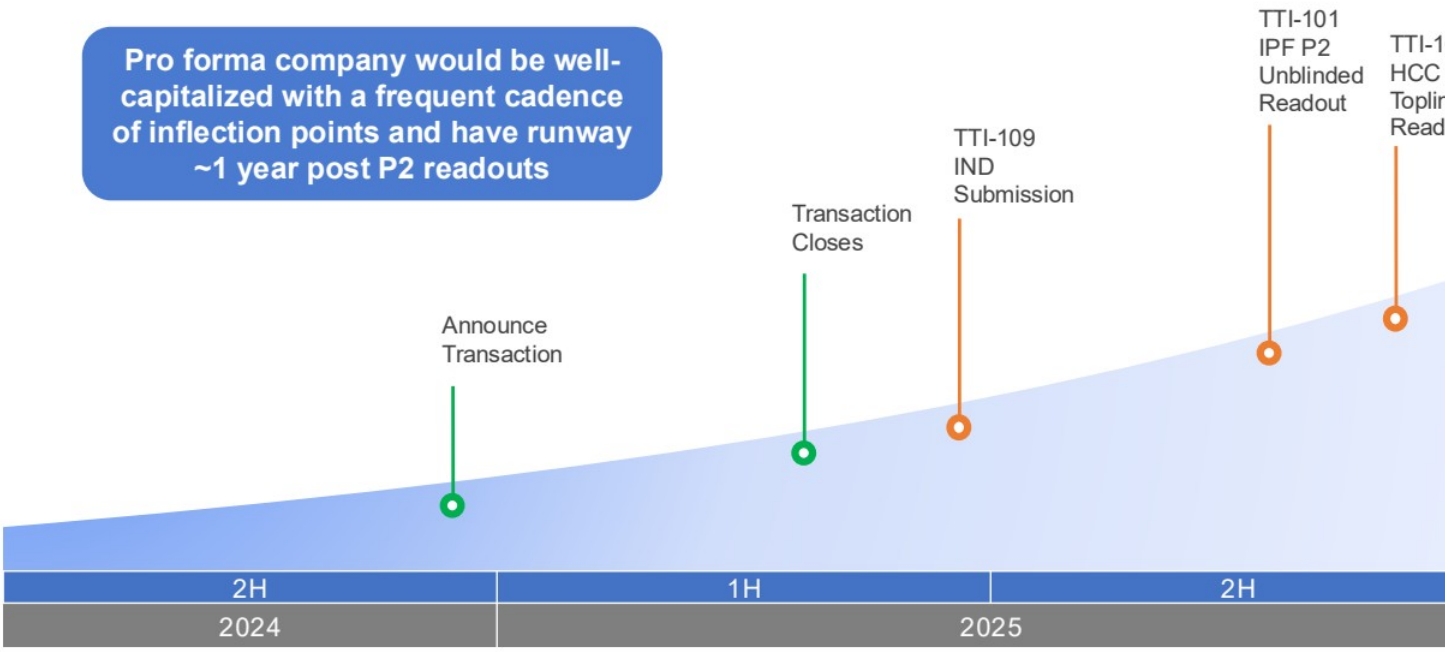
Near-Term Anticipated Value-Creating Milestones

Pro forma company would be well-capitalized with a frequent cadence of inflection points and have runway ~1 year post P2 readouts



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Targeting STAT3: Central Mediator of Fibrosis-Driven Diseases

Deep expertise in STAT3 biology

- Unlocking highly-validated, yet historically "undruggable" target within fibrosis-driven diseases

Potential to serve as a disease-modifying therapy in IPF[1]

- IPF models demonstrated reversal of fibrosis and restoration of lung function
- Phase 2 Clinical PoC ongoing

Well-positioned to differentiate therapeutic impact in HCC[2]

- Evaluating both mono- and combination therapy from an ongoing clinical trial

Multiple near-term data catalysts expected

- IPF Phase 2 unblinded data in H2:2025
- HCC Phase 1b/2 topline data in H2:2025
- TTI-109 IND[3] submission planned for H1:2025

1. Idiopathic pulmonary fibrosis. 2. Hepatocellular carcinoma. 3. Investigational new drug.

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