



A New Path to Medicine

34th Annual ROTH Conference

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Forward Looking Statements

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aTyr: A New Path to Medicine

Mission: Develop a new class of medicines based on proprietary tRNA synthetase biology platform

Efzofitimod (ATYR1923)

- Immunomodulator with novel MOA for severe inflammatory lung disease
- Favorable safety profile to date
- Clinical POC in pulmonary sarcoidosis supports program advancement and expansion to other ILD

Lead Indication: Pulmonary Sarcoidosis

- Major form of ILD with limited treatment options and poor outcomes for many patients
- Positive phase 1b/2a data for efzofitimod reported Sept. 2021
- Orphan drug designation granted for sarcoidosis in Jan. 2022
- Initiation of registrational trial planned in 2022

Platform and Target Validation

- Efzofitimod clinical POC validates tRNA synthetase platform and NRP2 as a therapeutic target
- NRP2 antibody program advancing to Phase 1 in 2022
- Future tRNA synthetase discovery work progressing

Financials: Cash, cash equivalents and investments at \$116.4m as of September 30, 2021

aTyr Development Pipeline

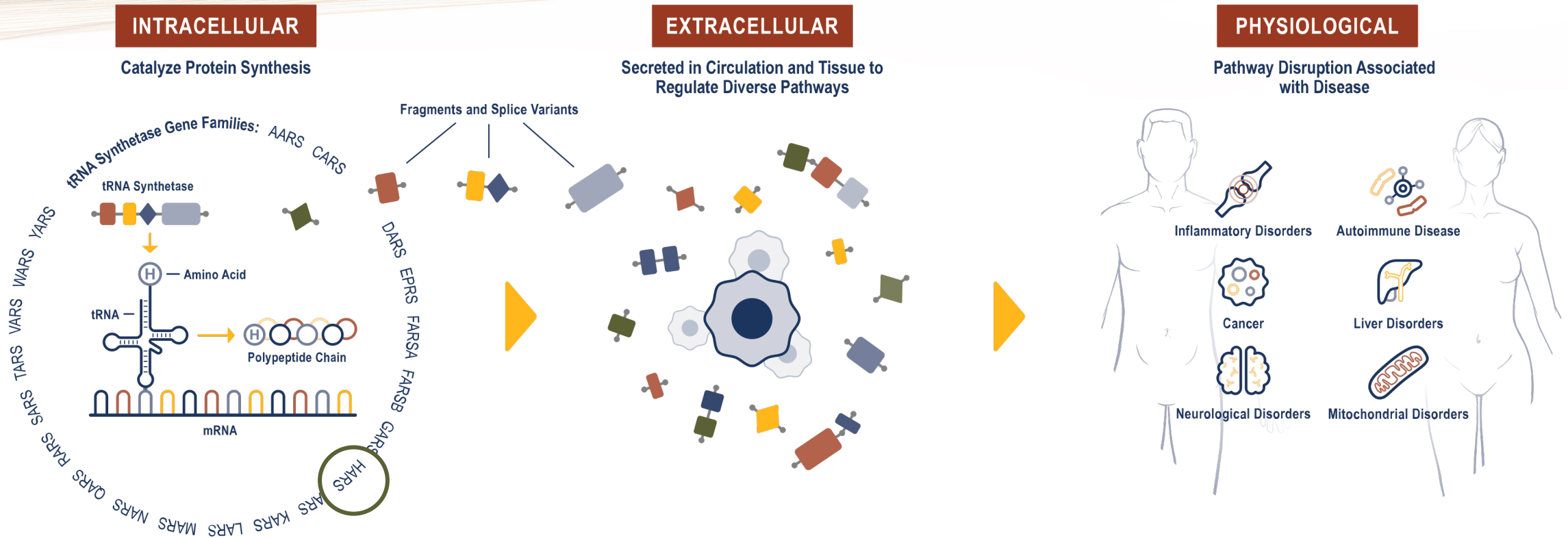
PROGRAM	INDICATION	RESEARCH	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
	Pulmonary Sarcoidosis					
Efzofitimod (ATYR1923)	Other ILDs (CTD-ILD; CHP) ⁽¹⁾					
	Healthy Japanese Volunteers ⁽²⁾					
ATYR2810	Solid Tumors					
NRP2 mAbs	Cancer; Inflammation					
AARS-1; DARS-1⁽³⁾	Cancer; Fibrosis; Inflammation					

(1) CTD-ILD: connective tissue disease-related ILD (e.g. Scleroderma-related ILD); CHP: chronic hypersensitivity pneumonitis

(2) In partnership with Kyorin Pharmaceutical Co., Ltd. Kyorin's Phase 1 study in healthy Japanese volunteers has been completed. Kyorin is eligible to participate in future efzofitimod trials sponsored by aTyr.

(3) The next two candidates from our tRNA synthetase platform; initial focus on NK cell biology

Foundational Science: Novel Functions of Extracellular tRNA Synthetases



tRNA synthetases are secreted extracellularly and occur in novel forms which lose their canonical function

Extracellular tRNA synthetase disruption (genetic/autoimmune) is associated with disease in humans

Validated synthetase platform is an engine for new protein therapeutics (e.g. efzofitmod) and new target identification (e.g. NRP2)

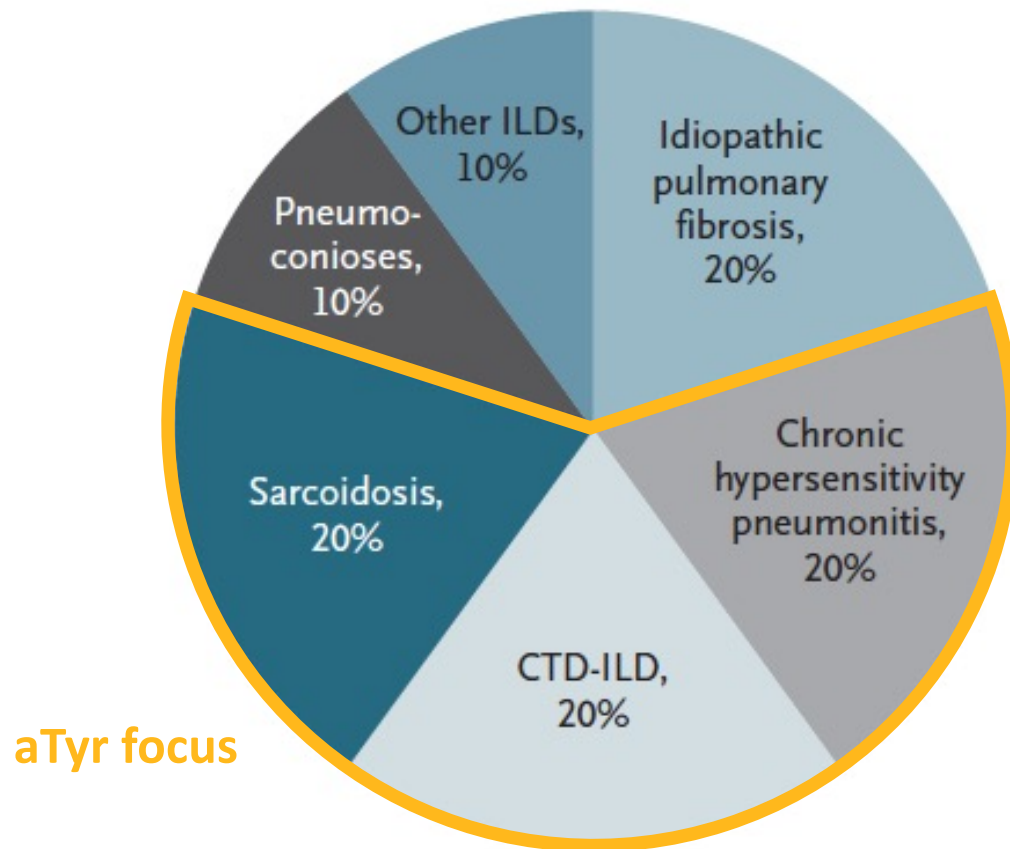


Efzofitimod (ATYR1923)

A Novel Immunomodulator for Severe Inflammatory Lung Disease

ILD: A Group of Immune-mediated Fibrotic Lung Diseases

Relative Distribution of ILDs in the USA⁽¹⁾



- >200 types of ILD: 4 major types comprise 80% of patients
- IPF is the archetypal fibrotic lung disease, but fibrosis occurs in all types – immune pathology is common to all
- Poor outcomes with limited therapeutic options – immunomodulatory therapy remains SOC outside of IPF
- aTyr focused on 3 main immune-driven types: >500k US patients⁽²⁾; ~3m globally
- \$2-3b global market opportunity⁽³⁾
- Orphan drug designation granted for sarcoidosis; orphan eligible for other ILD

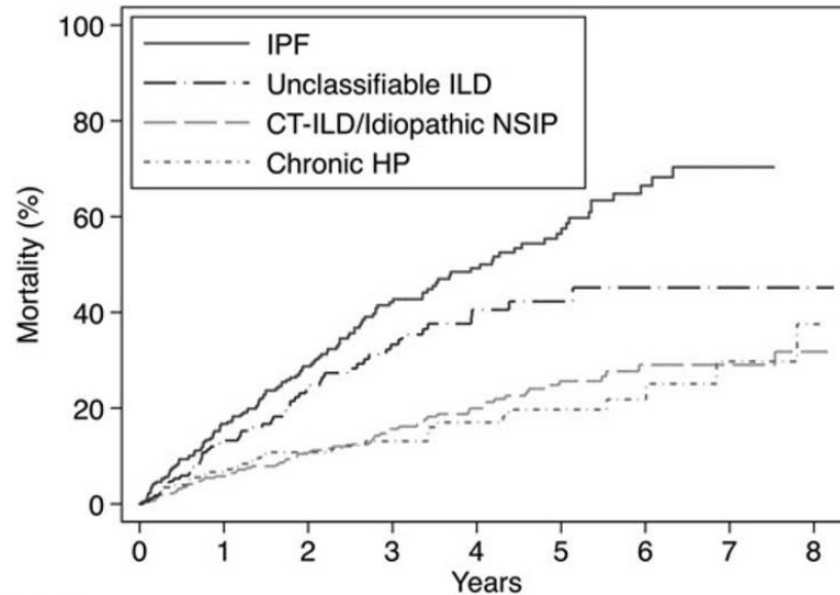
(1) Lederer, Martinez. NEJM 2018

(2) All ILDs individually have potential for orphan status

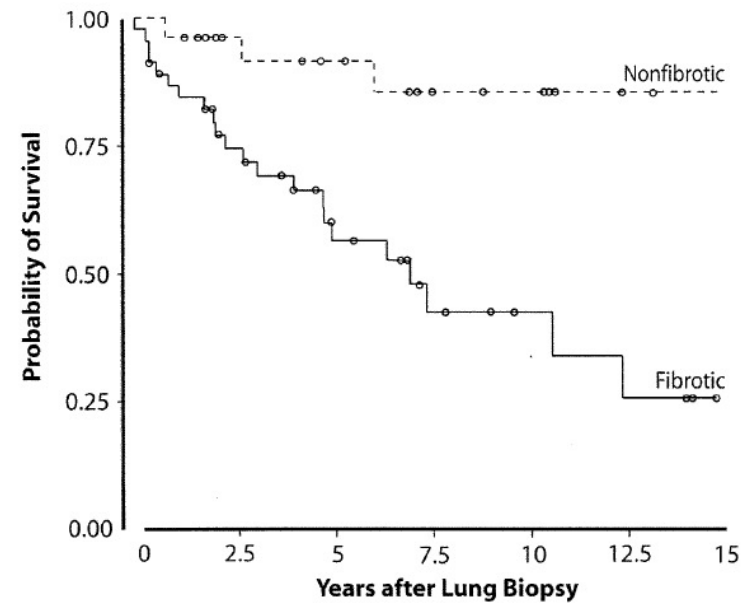
(3) aTyr estimates for efzofitimod in Pulmonary Sarcoidosis, CHP, CTD-ILD; excludes IPF

ILDs Share Poor Clinical Outcomes

High Mortality Burden



Outcomes Worsen with Fibrosis



Intervening early to restore immune balance and avoid progression to fibrosis could improve outcomes

First Efzofitimod Indication: Pulmonary Sarcoidosis

- Multisystem inflammatory disorder of unknown etiology, characterized by the formation of granulomas (clumps of immune cells)
- Lung affected in ~90% of all patients
- ~5x increased mortality in advanced disease
- SOC: corticosteroids; cytotoxic immunosuppressants; anti-TNFs – limited development pipeline
- High unmet need for treatments with improved safety and clinically established efficacy

Large orphan population



50-75% require treatment



Persistent or progressive disease in **30-50%**



10-30% develop fibrosis with **5-10%** mortality

Efzofitimod: Potential First-in-Class Therapy for Immune-Mediated Lung Disease

MOA

- Targets innate and adaptive immune cells during active inflammation to restore immune balance via selective modulation of NRP2
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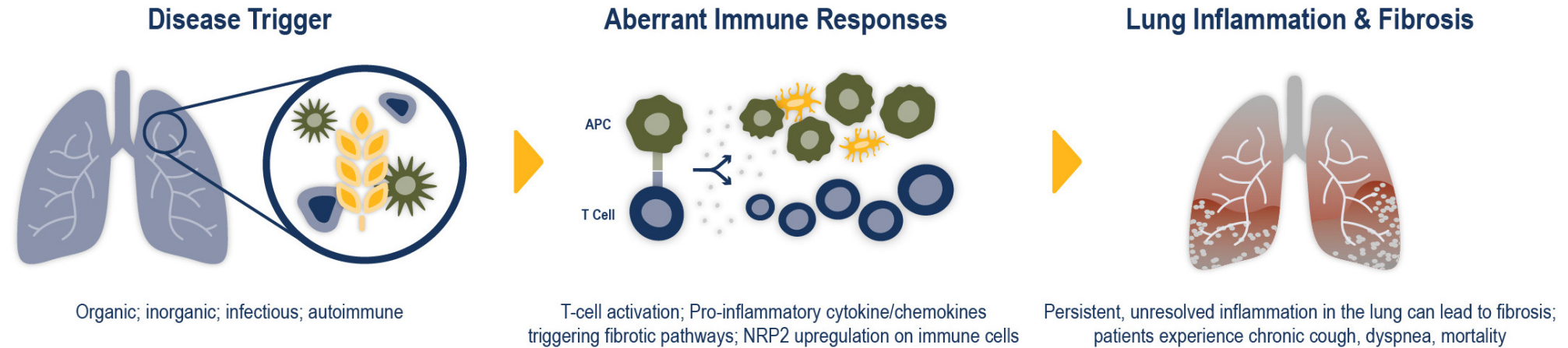
Pre-Clinical Evidence

- Anti-inflammatory and anti-fibrotic effects demonstrated in translational models of multiple ILDs
 - Reduces inflammatory cytokines and pro-fibrotic chemokines *in vitro* and *in vivo*
 - No toxicity observed in GLP toxicology rodents and non-human primates out to 6 months
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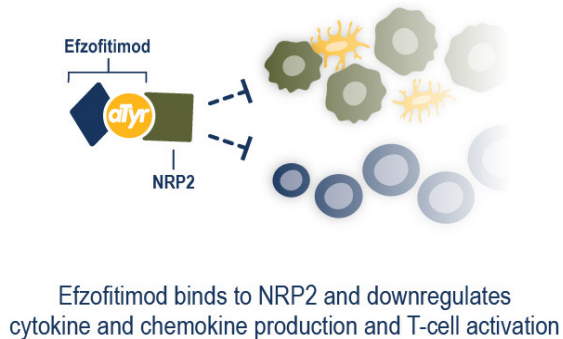
Clinical Experience

- Safe and well-tolerated in clinical trials to date with exposure to 24 weeks
- No immunogenicity observed
- Controls inflammation by downregulating cytokines implicated in sarcoidosis and other ILD
- Dose-dependent disease control demonstrated in pulmonary sarcoidosis patients

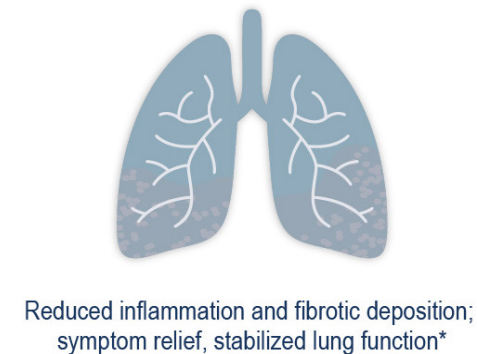
Efzofitimod Therapeutic Goal: Restore Immune Balance and Prevent Fibrosis



Efzofitimod Dampens Immune Responses



Stabilized Lung



*aTyr hypothesis

Phase 1b/2a Data Supports Proof-of-Concept and Clinical Advancement

- Efzofitimod was safe and well-tolerated
- Strong suggestion of efficacy: Dose-response and consistent positive trends across key efficacy endpoints and multiple analysis populations
- Clinically meaningful symptom improvements in dyspnea, cough, fatigue and King's Sarcoidosis scores
- Dose dependent control of inflammatory biomarkers confirms anti-inflammatory effect

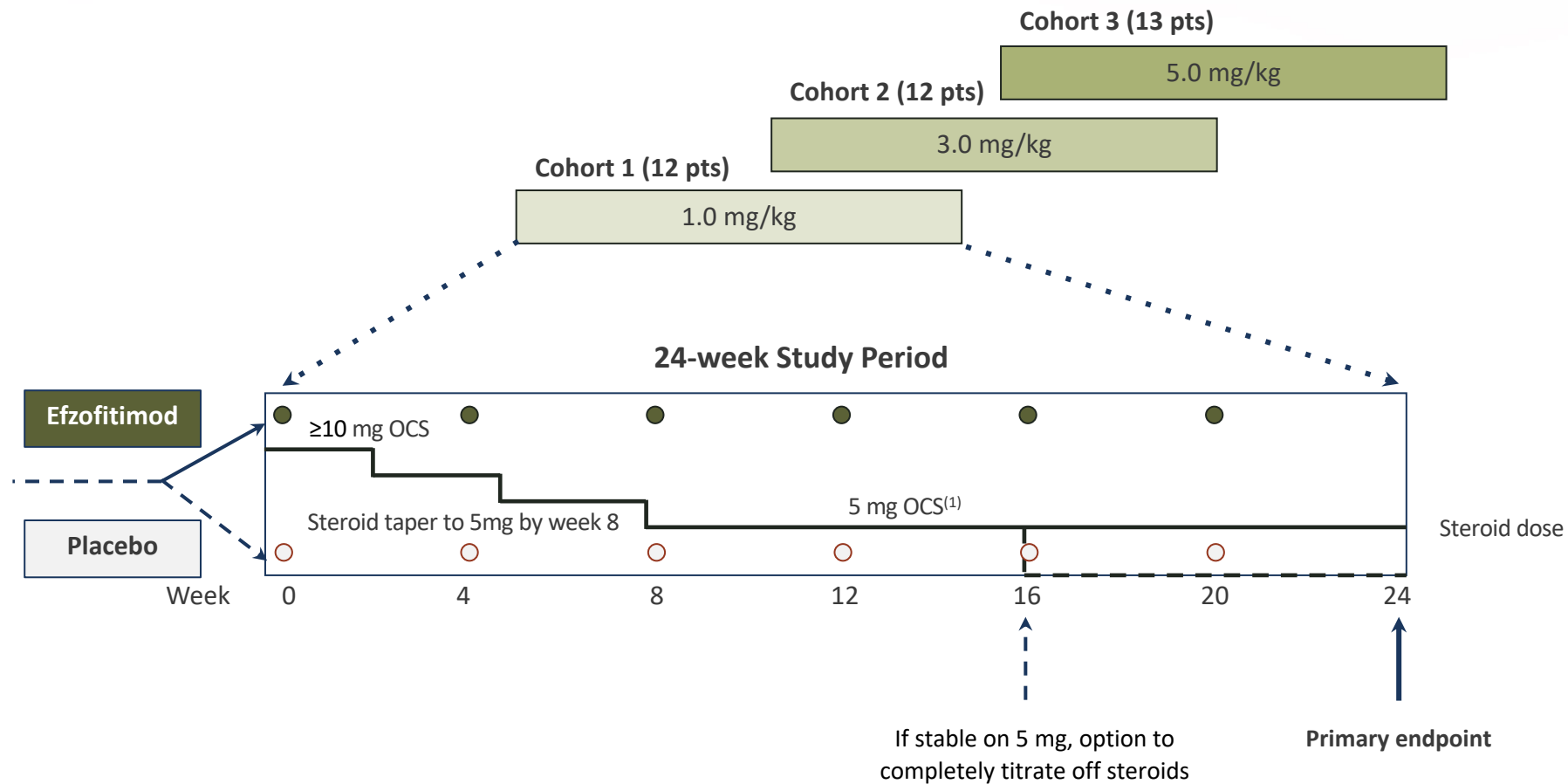
Platform and target validation

First tRNA synthetase derived and NRP2 targeting compound to demonstrate clinical POC

Trial Design

Design	• Randomized (2:1), double-blind, placebo-controlled, multiple ascending dose • 24 week study: 6 monthly IV doses of efzofitimod tested at 1.0, 3.0, and 5.0 mg/kg • Forced steroid taper to 5.0 mg by week 8; amendment to allow taper to 0 mg at week 16 in responders
Population	• 37 histologically confirmed pulmonary sarcoidosis patients • ≥ 10 mg stable oral corticosteroid treatment • Symptomatic/active disease at baseline
Primary Endpoint	• Safety and tolerability of multiple ascending IV efzofitimod doses
Secondary Endpoints	• Steroid-sparing effect • Immunogenicity • Pharmacokinetics (PK) • Exploratory: Lung function (FVC and other PFTs); sarcoidosis symptom scores and quality of life scales; inflammatory and sarcoidosis biomarkers; FDG-PET/CT imaging

Study Schema



Baseline Demographics and Disease Characteristics Generally Balanced

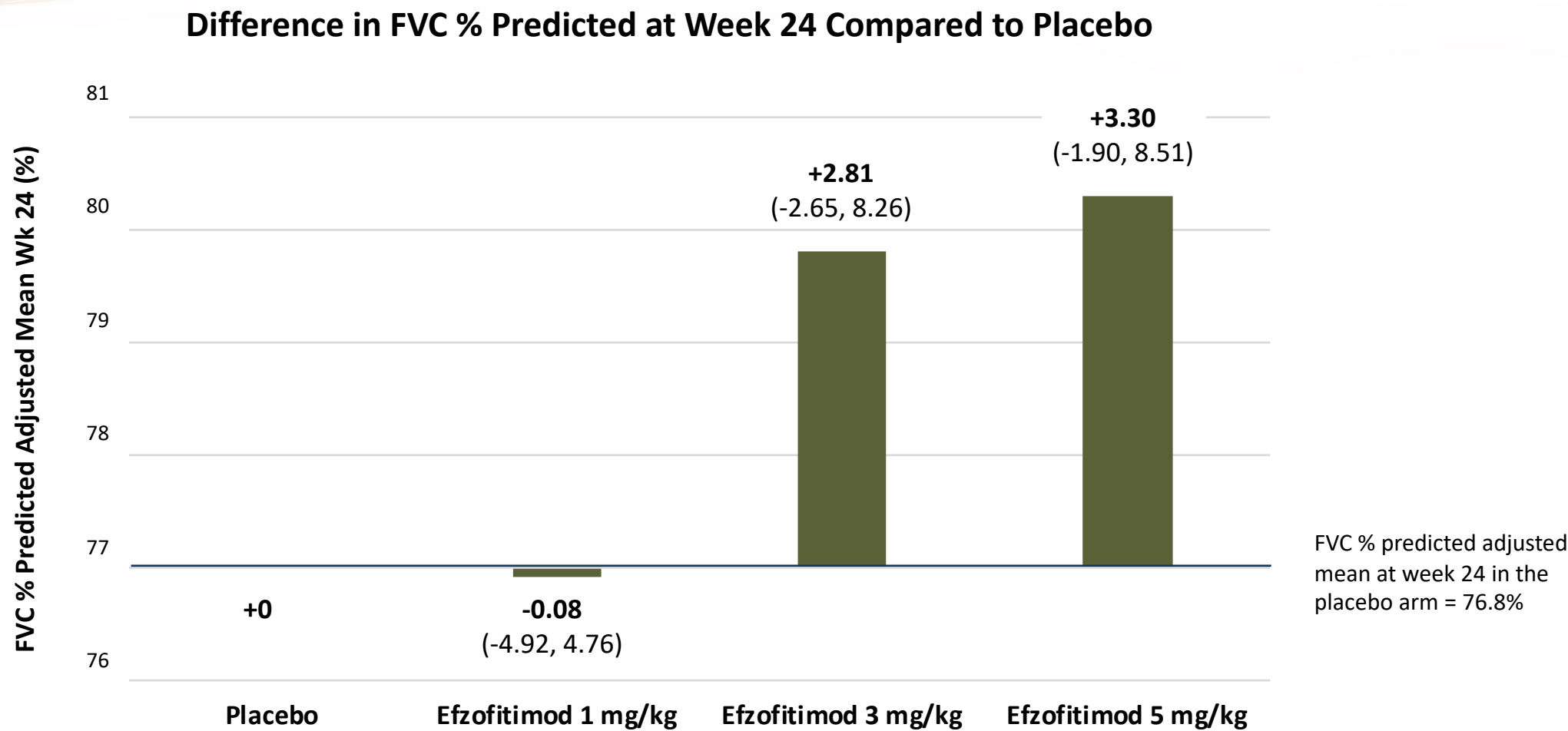
Demographics	Placebo N=12	Efzofitimod 1 mg/kg N=8	Efzofitimod 3 mg/kg N=8	Efzofitimod 5 mg/kg N=9
Age (Years); mean (SD), ≥65	52.5 (10.2), 0	54.5 (11.3), 1	51.8 (11.4), 2	50.8 (9.2), 0
Sex (Male); n (%)	5 (42)	4 (50)	4 (50)	4 (44)
Race; White / African American	9 / 3	5 / 3	6 / 2	3 / 6
Disease characteristics Mean (SD)				
FVC (% predicted)	77.3 (11.5)	68.3 (9.7)	83.8 (7.3)	83.8 (16.6)
Duration of disease (Years)	4.2 (3.3)	7.4 (6.1)	5.9 (5.1)	7.7 (9.9)
Baseline Dyspnea Index Score	4.8 (2.0)	4.3 (1.8)	7.6 (3.0)	6.3 (2.5)
Background Therapy				
Steroid dose (mg/day), mean	13.3	11.3	14.4	13.9
Immunomodulator; n (%)	6 (50)	3 (38)	1 (13)	4 (44)

Monthly Dosing of Efzofitimod was Safe and Well-Tolerated

n (%)	Placebo N=12	Efzofitimod 1 mg/kg N=8	Efzofitimod 3 mg/kg N=8	Efzofitimod 5 mg/kg N=9
AEs	10 (83)	8 (100)	7 (88)	8 (89)
Drug-related AEs	4 (33)	3 (38)	1 (13)	3 (33)
Severe AEs (Grade 3 or 4)	4 (33)	2 (25)	0	2 (22)
SAEs	1 (8)	1 (13)	0	0

- No new or unexpected findings with repeat dosing
- No dose-response relationship observed
- Most frequent AEs were consistent with underlying disease: Cough, fatigue, wheezing
- No signal of immunogenicity
- No drug related SAEs
- No deaths

Dose-dependent Improvement in FVC % Predicted Compared to Placebo



Dose-dependent Reduction in Steroid Utilization Compared with Placebo

Post-taper Period	Placebo N=12	Efzofitimod 1 mg/kg N=8	Efzofitimod 3 mg/kg N=8	Efzofitimod 5 mg/kg N=9
Average daily dose (mg), adjusted mean	7.17	6.83	6.54	5.62
- relative reduction vs placebo (%)	-	-5%	-9%	-22%
Change from baseline (%), mean	-46	-41	-49	-58
- difference in adjusted means (%), mean (95% CI)	-	1.2 (-20, 22)	-2.3 (-23, 19)	-12.3 (-33, 8)
Tapered to 0 mg and maintained taper, n (%)	0	0	0	3 (33)

- 58% overall steroid reduction from baseline and 22% relative reduction compared to placebo in steroid utilization post taper in the 5.0 mg/kg treatment group
- 33% of patients able to taper off of steroids completely in 5.0 mg/kg treatment group while controlling disease symptoms

Dose-dependent Clinically Meaningful Symptom Improvements Compared with Placebo

Differences in Adjusted Means vs Pbo at Week 24	Efzofitimod 1 mg/kg N=8	Efzofitimod 3 mg/kg N=8	Efzofitimod 5 mg/kg N=9
• Dyspnea	-0.76	3.33	4.49
• Cough	-3.49*	2.98*	2.05
• Fatigue	0.76	-4.78	-7.77*
• King's Sarcoidosis Score: Lung	-6.41	11.29	16.17*
• King's Sarcoidosis Score: General Health	-5.1	2.13	18.33*

 = clinically meaningful improvement based on published MCID

*p<0.05 on difference between adjusted means from MMRM; Pbo = Placebo

19 MCIDs: TDI - Witek 2003; LCQ – Raj 2009; FAS - de Kleijin 2011 (Negative score is better for Fatigue); KSQ Lung – Baughman 2021; KSQ Lung – Baughman 2021
TDI: Table 14.2.20.1.1; LCQ: Table 14.2.22.1.1, FAS: Table 14.2.23.1.1, Gen Health: Table 14.2.21.1.1, Lung: Table 14.2.21.1.1

Dose Response and Consistent Positive Trends of Efficacy Across all Evaluable Endpoints

- The trial met its primary endpoint: efzofitimod was safe and well-tolerated
- 58% overall steroid reduction from baseline and 22% relative reduction in steroid utilization post taper in the 5.0 mg/kg treatment group
- 33% of patients able to taper completely off steroids in the 5.0 mg/kg treatment group
- 3.3% absolute improvement in lung function as measured by FVC % predicted at week 24 in the 5.0 mg/kg treatment group
- Dose-dependent clinically meaningful improvement in all sarcoidosis symptom measures in the 5.0 mg/kg treatment group
- Dose-dependent improvement on inflammatory biomarkers including IL-6, MCP-1, IFN- γ , IP-10 and TNF α as well as sarcoidosis markers ACE, IL-2Ra and SAA with tightest control in the 5.0 mg/kg treatment group

Efzofitimod Data Supports Expansion to Other ILD with High Unmet Need

Connective Tissue Disease related-ILD

- ILD secondary to autoimmune diseases, such as systemic sclerosis (SSc-ILD) and rheumatoid arthritis (RA-ILD)
- ILD occurs in up to 80% of SSc patients
- ~10% of RA patients have clinically significant lung disease
- ILD is the leading cause of death in these diseases
- Treatment options remain limited

Chronic Hypersensitivity Pneumonitis

- Exaggerated, chronic immune response to inhaled environmental antigens
- Comprises up to 15% of all ILD
- Commonly misdiagnosed as IPF
- Median survival: 7 years
- No approved therapies

Proof-of-Concept Supports Advancement in Pulmonary Sarcoidosis and Other ILD

Pulmonary Sarcoidosis

- Meet with regulators to present data and clinical development plans
- Anticipate initiating a registrational trial in 2022
- Worldwide registrational trial expected to be conducted in collaboration with our partner Kyorin

Other ILD

- Efzofitimod MOA, proof-of-concept and safety data support investigation in other ILD
 - Phase 2 ready in other ILD, including CTD-ILD (e.g. Scleroderma-ILD) and CHP
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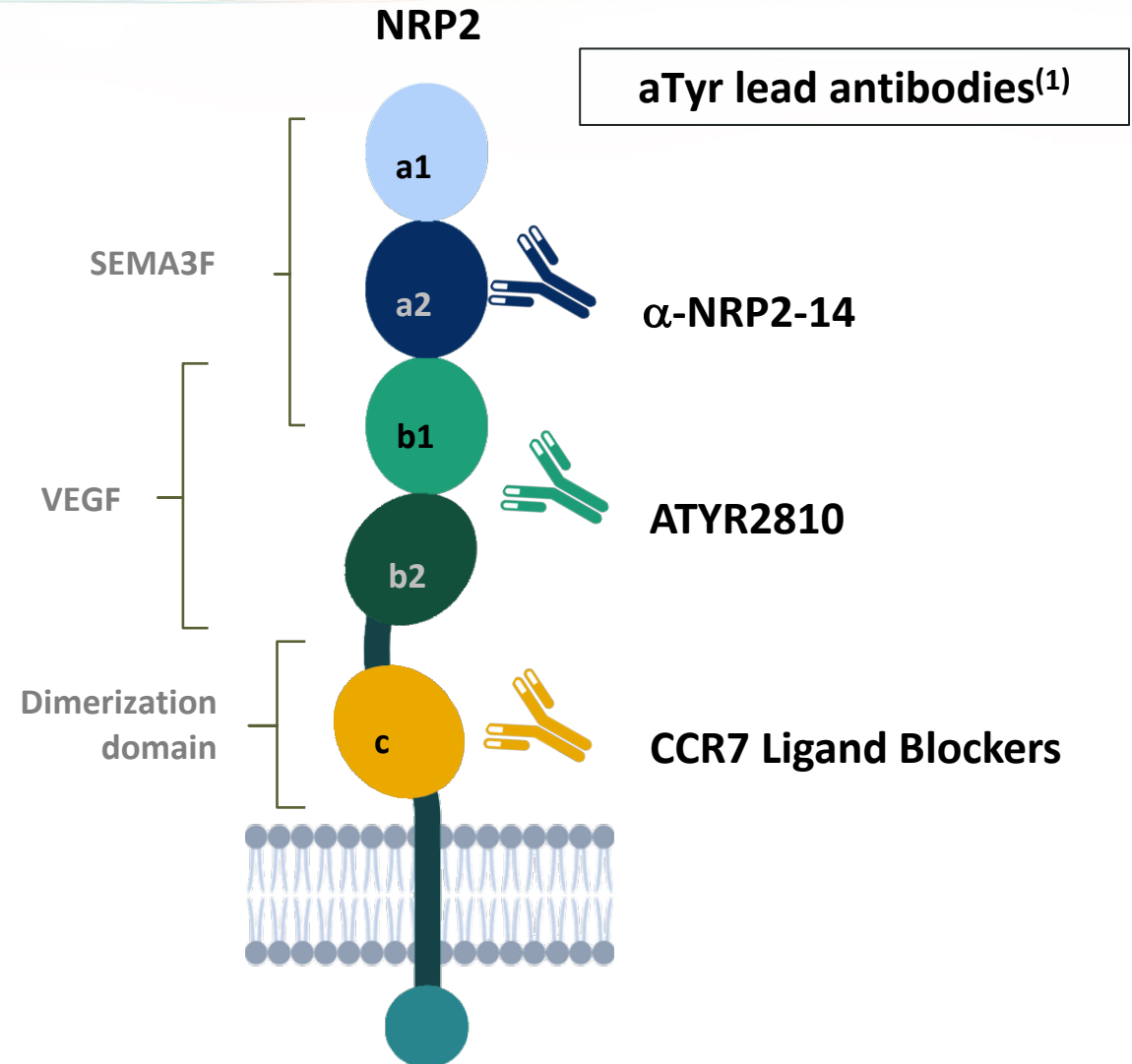


NRP2 Antibodies

Regulating Diverse Disease Pathways

NRP2: A Novel Therapeutic Target

- NRP2 is a potentially novel drug target for cancer and inflammatory disorders
- Acts as a co-receptor for VEGF, semaphorins and certain chemokines (e.g., CCL21)
- Highly expressed on certain solid tumors (e.g. breast, lung, renal); expression is associated with worse outcomes in many cancers
- aTyr mAbs selectively target distinct epitopes for differentiated therapeutic applications
- Superior specificity and sensitivity compared to commercially available antibodies in preclinical studies



ATYR2810: Lead Anti-Neuropilin-2 Antibody IND Candidate for Cancer

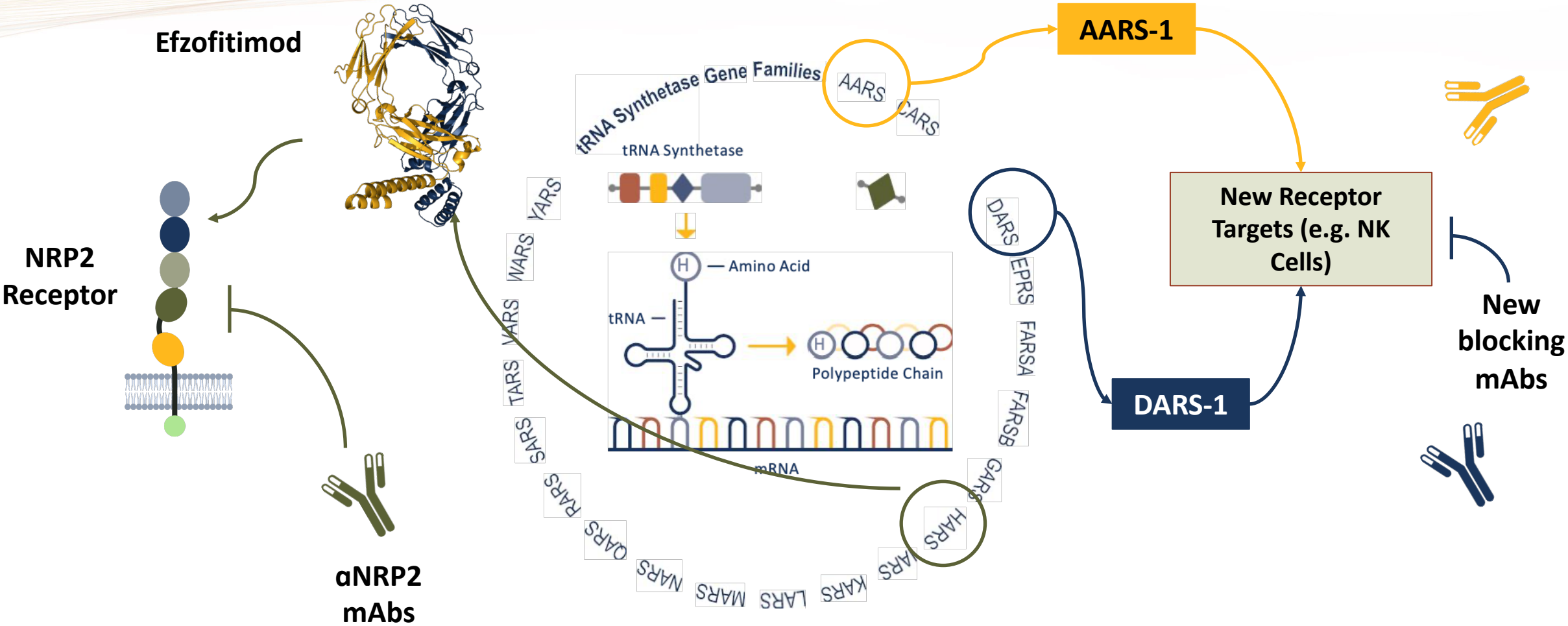
- Fully humanized mAb that specifically and functionally blocks the interaction between NRP2 and VEGF
- VEGF is a validated mediator of tumor growth and plays a role in immune evasion in the tumor microenvironment
- Blocking VEGF signaling through NRP2 is differentiated from targeting VEGF or VEGF-R directly
- Blocking the NRP2 / VEGF nexus may impact cancer through multiple mechanisms, including downregulation of key drivers of epithelial-mesenchymal transition
- Significant effects on tumor growth in pre-clinical models suggest that ATYR2810 could potentially be effective in certain aggressive solid tumors
- Plan to initiate clinical trial in patients in 2022



tRNA Synthetases

A Potential New Therapeutic Protein Class

tRNA Synthetase Engine



aTyr owns IP covering all 20 tRNA synthetase gene families



A New Path to Medicine

aTyr: A New Path to Medicine

- Clinically validated platform of proprietary new biology
- Clinical program: efzofitimod (ATYR1923)
 - Novel MOA for severe inflammatory lung disease
 - Favorable safety profile
 - Proof-of-concept in pulmonary sarcoidosis supports program advancement and expansion to other ILD
 - Orphan drug designation granted for sarcoidosis
- Pipeline in cancer and immunology
 - Lead anti-NRP2 antibody IND candidate for cancer
 - NRP2 antibody research program for distinct therapeutic applications
 - Discovery programs for tRNA synthetases AARS and DARS initially focusing on NK cell biology
- Cash, cash equivalents, and investments at \$116.4m as of September 30, 2021

Future Milestones

Efzofitimod (ATYR1923)

- Publication of Phase 1b/2a results in pulmonary sarcoidosis patients
- Initiation of registrational trial in pulmonary sarcoidosis patients expected in 2022
- Phase 2 ready for initiation of trials in other ILD

ATYR2810

- Initiate Phase 1 clinical trial in 2022

Discovery pipeline

- New NRP2 mAb opportunities targeting distinct NRP2 epitopes
- Advance AARS and DARS derived product candidates



Thank You