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

FORM 8-K

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

Date of Report (Date of earliest event reported): June 25, 2021

PIERIS PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Nevada	**001-37471**	**30-0784346**
(State or other jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

225 State Street, 9th Floor	**02109**
Boston, MA	
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: 857-246-8998
N/A
(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:

☐ 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(s)	Name of each exchange on which registered
Common Stock, $0.001 par value per share	**PIRS**	**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 (17 CFR §230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR §240.12b-2).

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. ☐

Item 7.01 Regulation FD Disclosure.

On June 25, 2021, Pieris Pharmaceuticals, Inc. issued a press release furnished as Exhibit 99.1 to this report.

Attached hereto as Exhibit 99.2 and incorporated by reference herein is the June 2021 Investor Presentation of Pieris Pharmaceuticals, Inc.

The information set forth under this "Item 7.01. Regulation FD Disclosure," including Exhibits 99.1 and 99.2 attached hereto, shall not be deemed "filed" for any purpose, and shall not be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, regardless of any general incorporation language in any such filing except as shall be expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits

(d) *Exhibits.*

99.1 Press Release, Dated June 25, 2021.

99.2 Investor Presentation, Dated June 2021.

SIGNATURE

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.

PIERIS PHARMACEUTICALS, INC.

Dated: June 25, 2021

/s/ Tom Bures
Tom Bures
Vice President, Finance

PRESS RELEASE

PIERIS PHARMACEUTICALS ANNOUNCES INHALED CTGF INHIBITOR PRS-220 FOR IDIOPATHIC PULMONARY FIBROSIS AND 17 MILLION DOLLAR GRANT FROM BAVARIAN GOVERNMENT TO ACCELERATE PROGRAM DEVELOPMENT FOR POST-COVID-19 PULMONARY FIBROSIS

- **PRS-220, an oral inhaled Anticalin protein targeting CTGF, a fully proprietary drug candidate for respiratory disease, is being developed as a local treatment for idiopathic pulmonary fibrosis**
- **Grant to enable the evaluation of PRS-220 for the treatment of post-COVID-19-related pulmonary fibrosis for clinical-readiness in general and initial clinical development of PRS-220 in the post-COVID-19 setting**
- **Clinical development of PRS-220 expected to begin in 2022**

BOSTON, MA, June 25, 2021 - ***Pieris Pharmaceuticals, Inc. (NASDAQ: PIRS)***, a clinical-stage biotechnology company advancing novel biotherapeutics through its proprietary Anticalin® technology platform for respiratory diseases, cancer, and other indications, today announced the development of PRS-220, an oral inhaled Anticalin protein targeting connective tissue growth factor (CTGF), also known as CCN2, for the treatment of idiopathic pulmonary fibrosis (IPF). The Company also announced it has been selected to receive a 14.2 million euro (approximately 17 million USD) grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy for the research and development of PRS-220 for post-acute sequelae of SARS-CoV-2 infection (PASC) pulmonary fibrosis (PASC-PF), also known as post-COVID-19 syndrome pulmonary fibrosis or “long COVID”. Clinical development of the program for both indications is expected to begin next year.

PRS-220 follows Pieris’ strategy of deploying its proprietary Anticalin proteins for local interventions on clinically validated targets with the objective of developing superior medicines through more efficient biology. CTGF, a protein localized in the extracellular matrix, is a driver of fibrotic tissue remodeling as a consequence of an aberrant wound healing process. Over-expression of this target in lung tissue is observed in patients suffering from IPF, and clinical data indicate inhibition of CTGF reduces the decline in lung function among these patients. IPF affects over three million patients worldwide and roughly 130,000 patients in the United States. Mean survival is two to five years from the time of diagnosis, with standard of care conferring only modest benefit. The critical function of CTGF in fibrosis, as well as its induced expression upon tissue injury and fibrotic remodeling, render it a compelling intervention for PASC-PF. Persistent symptoms following severe COVID-19 have been reported by different studies in more than one third of hospitalized patients. Pathological changes include impairment of lung function and reduced diffusion capacity of lung for carbon monoxide (DLCO), as well as radiologically detected interstitial lung abnormalities indicative of fibrotic-like impairment of lung tissues. A sub-population of these patients is expected to benefit from an anti-fibrotic treatment, such as PRS-220. There is currently no approved therapy to address PASC-PF.

The grant announced today, intended to support the evaluation of PRS-220 in PASC-PF beyond the intended IPF population, will support clinical-readiness activities and initial clinical development for the program, including GLP tox studies, GMP manufacturing, and phase 1 clinical development. PRS-220 has passed the drug candidate nomination stage within Pieris’ pipeline and has several features that reflect its best-in-class potential, including a developability profile demonstrating suitability for inhaled delivery. Pieris intends to present preclinical data for PRS-220 later this year, around which time the Company also plans to provide further program details in IPF and PASC-PF.

"The health consequences of the COVID-19 pandemic will affect our health system for a long time to come. Bavaria's biotech and pharmaceutical companies are at the forefront of developing new therapies to combat the effects of this virus. Through the strategic grants of the Bavarian Ministry of Economic Affairs, we are providing financial support for particularly innovative therapeutic research projects. We are

convinced of the great potential of the PRS-220 program and are therefore promoting its development through a grant of 14.2 million euros," said Huber Aiwanger, Bavarian State Minister of Economic Affairs, Regional Development and Energy.

"We are excited to unveil our most advanced proprietary inhaled respiratory program and look forward to sharing more details on this program later this year, while actively working to begin clinical development next year. The Bavarian government's support of innovative drug development is invaluable for both the local biotech ecosystem and broader public health initiatives, and we are grateful for having been selected as a recipient of this grant for PRS-220, which will allow us to accelerate its development and broaden clinical investigation beyond IPF to address an evolving medical need precipitated by the global COVID-19 pandemic that we believe will persist," said Stephen S. Yoder, President and Chief Executive Officer of Pieris. "Pieris is a pioneer in the inhaled biologics space, and it is gratifying to leverage our respiratory platform to improve the lives of those affected by respiratory diseases such as IPF and COVID-19."

***About IPF**:*

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and ultimately fatal type of interstitial lung disease of unknown cause, characterized by a radiological or histopathological pattern of usual interstitial pneumonia. It is the most commonly occurring type of idiopathic interstitial pneumonia, with an estimated mean survival of two to five years from the time of diagnosis. Estimated mortality rates are 64.3 deaths per million in men and 58.4 deaths per million in women.

About PASC-PF:

Post-acute sequelae of SARS-CoV-2 infection (PASC) pulmonary fibrosis (PASC-PF), also known as pulmonary fibrosis secondary to COVID-19 or "long COVID", affects patients who have recovered from acute COVID-19 but continue to suffer from or remain at risk for pulmonary fibrotic abnormalities. Persistent symptoms, reflected by impairment of lung function and reduced diffusion capacity of lung for carbon monoxide (DLCO), as well as radiologically detected interstitial lung abnormalities indicative of fibrotic-like impairment of lung tissues, have been reported following severe COVID-19 in more than a third of hospitalized patients who have recovered from acute COVID-19, according to reported clinical studies. There is currently no approved therapy to address PASC-PF.

***About Pieris Pharmaceuticals**:*

Pieris is a clinical-stage biotechnology company that combines leading protein engineering capabilities and deep understanding into molecular drivers of disease to develop medicines that drive local biology to produce superior clinical outcomes for patients. Our pipeline includes inhalable Anticalin proteins to treat respiratory diseases and locally-activated bispecifics for immuno-oncology. Proprietary to Pieris, Anticalin proteins are a novel class of therapeutics validated in the clinic and by respiratory and immuno-oncology focused partnerships with leading pharmaceutical companies. For more information, visit www.pieris.com.

***Forward Looking Statements**:*

This press release contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Statements in this press release that are not purely historical are forward-looking statements. Such forward-looking statements include, among other things, the timing for initiation of clinical trials of PRS-220, whether PRS-220 will provide a clinical benefit in the treatment of IPF and PASC-related fibrosis, whether the combination of cinrebafusp alfa with other therapies could address a high medical need in HER2 gastric cancer patients who do not respond to traditional HER2-targeted therapies; whether the effects of the combination of cinrebafusp alfa with other therapies seen in preclinical studies will be observed in clinical trials; whether data from patients enrolled to date will be sufficient to inform the recommended phase 2 dose for the Company's planned proof of concept study of cinrebafusp alfa in

gastric cancer; the expected timing and potential outcomes of the reporting by the Company of key clinical data from its programs, references to novel technologies and methods and our business and product development plans, including the Company's cash resources, the advancement of our proprietary and co-development programs into and through the clinic and the expected timing for reporting data, making IND filings or achieving other milestones related to our programs, including PRS-060/AZD1402, cinrebafusp alfa, PRS-344, and PRS-352 and the expected timing of the initiation of the next stage of cinrebafusp alfa's development in gastric cancer. Actual results could differ from those projected in any forward-looking statements due to numerous factors. Such factors include, among others, our ability to raise the additional funding we will need to continue to pursue our business and product development plans; the inherent uncertainties associated with developing new products or technologies and operating as a development stage company; our ability to develop, complete clinical trials for, obtain approvals for and commercialize any of our product candidates, including our ability to recruit and enroll patients in our studies; our ability to address the requests of the U.S. Food and Drug Administration; competition in the industry in which we operate; delays or disruptions due to COVID-19; and market conditions. These forward-looking statements are made as of the date of this press release, and we assume no obligation to update the forward-looking statements, or to update the reasons why actual results could differ from those projected in the forward-looking statements, except as required by law. Investors should consult all of the information set forth herein and should also refer to the risk factor disclosure set forth in the reports and other documents we file with the Securities and Exchange Commission available at www.sec.gov, including without limitation the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2020 and the Company's Quarterly Reports on Form 10-Q.

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PIERIS PHARMACEUTICALS

CORPORATE PRESENTATION
June 2021

Forward-Looking Statements

This presentation contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Statements in this presentation that are not purely historical are forward-looking statements. Such forward-looking statements include, among other things, the timing for initiation of clinical trials of PRS-220, whether PRS-220 will provide a clinical benefit in the treatment of IPF and PASC-related fibrosis, whether the combination of cinrebafusp alfa with other therapies could address a high medical need in HER2 gastric cancer patients who do not respond to traditional HER2-targeted therapies; whether the effects of the combination of cinrebafusp alfa with other therapies seen in preclinical studies will be observed in clinical trials; whether data from patients enrolled to date will be sufficient to inform the recommended phase 2 dose for the Company's planned proof of concept study of cinrebafusp alfa in gastric cancer; the expected timing and potential outcomes of the reporting by the Company of key clinical data from its programs, references to novel technologies and methods and our business and product development plans, including the Company's cash resources, the advancement of our proprietary and co-development programs into and through the clinic and the expected timing for reporting data, making IND filings or achieving other milestones related to our programs, including PRS-060/AZD1402, cinrebafusp alfa, PRS-344, and PRS-352 and the expected timing of the initiation of the next stage of cinrebafusp alfa's development in gastric cancer. Actual results could differ from those projected in any forward-looking statements due to numerous factors. Such factors include, among others, our ability to raise the additional funding we will need to continue to pursue our business and product development plans; the inherent uncertainties associated with developing new products or technologies and operating as a development stage company; our ability to develop, complete clinical trials for, obtain approvals for and commercialize any of our product candidates, including our ability to recruit and enroll patients in our studies; our ability to address the requests of the U.S. Food and Drug Administration; competition in the industry in which we operate; delays or disruptions due to COVID-19; and market conditions. These forward-looking statements are made as of the date of this presentation, and we assume no obligation to update the forward-looking statements, or to update the reasons why actual results could differ from those projected in the forward-looking statements, except as required by law. Investors should consult all of the information set forth herein and should also refer to the risk factor disclosure set forth in the reports and other documents we file with the Securities and Exchange Commission available at www.sec.gov, including without limitation the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2020 and the Company's Quarterly Reports on Form 10-Q.

Our Formula for Success

We combine leading protein engineering capabilities and deep insights into molecular drivers of disease to develop medicines that drive local biology to produce superior clinical outcomes for patients

Executive Summary

Superior Medicines via Efficient Biology	• Protein therapeutics that exploit biology validated by mAbs yet are engineered for focused activity at disease locus • Improved activity, reduced side effects, increased convenience
Two Focus Areas	• Oral inhaled antagonists for respiratory disease • Locally activated immuno-oncology bispecifics • 2 POC readouts in '22; several follow-on candidates
Supportive Partnerships	• ~$200M since 2017 in upfronts, milestones and equity investments • Several co-developed and out-licensed programs • Clinical supply for combination studies and development expertise

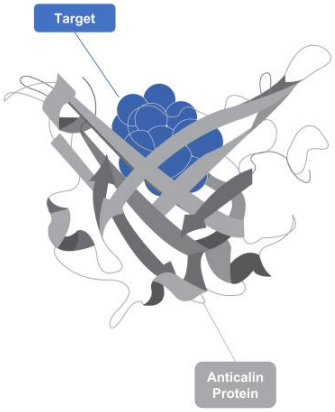
Anticalin® Proteins as Therapeutic Modalities

A Novel Therapeutic Class with Favorable Drug-Like Properties

- **Human –** Derived from lipocalins (human extracellular binding proteins)
- **Small** – Monomeric, monovalent, small size (~18 kDa vs ~150kDa mAbs)
- **Stable** – Inhalable delivery
- **Simple** – Bi/multispecific constructs
- **Proprietary** – Broad IP position on platform and derived products

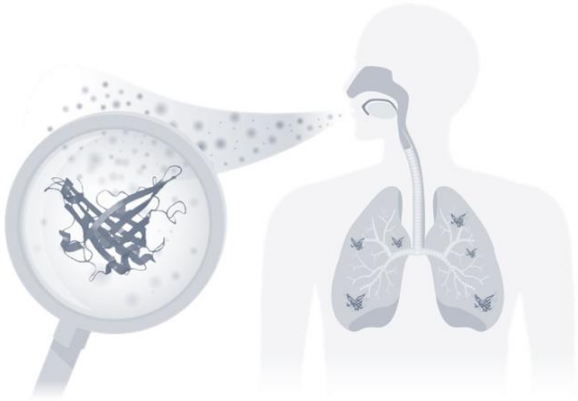
Translational Science Expertise to Deploy Platform in Meaningful Way

- Immunology expertise underpins IO and respiratory focus
- A leader in 4-1BB and costim biology
- Patient phenotyping efforts for improved stratification and novel intervention points in, e.g., asthma

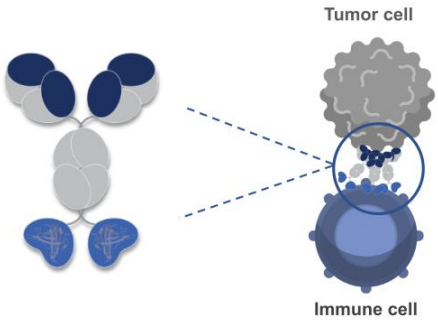


Two-fold Focus of Anticalin Platform Deployment

Inhalable formulations to treat respiratory diseases locally



Bispecifics for local immune agonism to treat cancer



Our Pipeline

RESPIRATORY								
CANDIDATE	**TARGETS**	**INDICATION**	**PARTNER**	**OUR COMMERCIAL RIGHTS**	**DISCOVERY**	**PRECLINICAL**	**PHASE I**	**PHASE II**
PRS-060/AZD1402	IL4-Rα	Asthma	AstraZeneca	Worldwide Profit-Share Option				
PRS-220	CTGF	IPF, PASC-PF	n/a	Worldwide				
AstraZeneca Programs*	n.d.	n.d.	AstraZeneca	Worldwide Profit-Share Options				
Genentech Programs*	n.d.	n.d.	Genentech	Royalties				
*4 respiratory programs in collaboration with AstraZeneca, 2 of which carry co-development and co-commercialization options for Pieris								
†Collaboration includes 1 respiratory program and 1 ophthalmology program								

IMMUNO-ONCOLOGY								
CANDIDATE	**TARGETS**	**INDICATION**	**PARTNER**	**OUR COMMERCIAL RIGHTS**	**DISCOVERY**	**PRECLINICAL**	**PHASE I**	**PHASE II**
Cinrebafusp Alfa (PRS-343)	4-1BB/HER2	HER2-High GC**	n/a	Worldwide				
		HER2-Low GC**						
PRS-344/S095012	4-1BB/PD-L1	n.d.	Servier	US Rights; ex-US Royalties				
PRS-352	n.d.	n.d.	Servier	Royalties				
PRS-342/BOS-342	4-1BB/GPC3	n.d.	Boston Pharmaceuticals	Royalties				
Seagen Programs‡	Co-stim Agonist	n.d.	Seagen	US Co-Promotion Option; Royalties				
‡3 bispecific programs in collaboration with Seagen, with Pieris retaining a US co-promotion option for the second program								
** Phase 2 study includes HER2-high arm in combination with ramucirumab and paclitaxel and HER2-low arm in combination with tucatinib; drug supply agreements with Lilly and Seagen, respectively								

Validating Partnerships with Leading Companies

AstraZeneca

- PRS-060/AZD1402 + 4 additional programs
- Upfront & milestones to date: $70.5M
- $10M equity investment from AstraZeneca
- Eligible to receive up to approximately $5.4B in potential milestone payments plus royalties
- Retained co-development and co-commercialization (US) options on PRS-060 and up to 2 additional programs

BOSTON pharmaceuticals

- Boston Pharmaceuticals holds exclusive license for PRS-342/BOS-342
- Upfront & milestones to date: $10M
- Eligible to receive up to approximately $353M in potential milestone payments
- Entitled to tiered royalties

Genentech
A Member of the Roche Group

- 1 respiratory program + 1 ophthalmology program
- Upfront & milestones to date: $20M
- Eligible to receive over $1.4B million in potential milestone payments
- Entitled to tiered royalties
- Genentech has option to select additional targets in return for an option exercise fee

Seagen

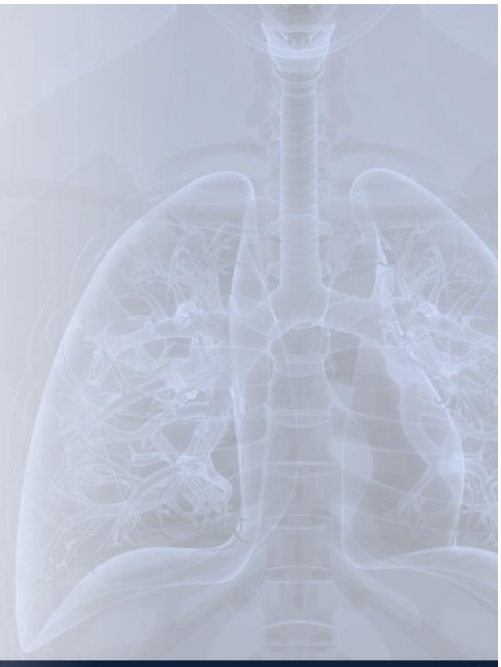
- 3-program IO bispecific partnership
- Upfront & milestones to date: $35M
- Eligible to receive up to approximately $1.2B in potential milestone payments plus royalties
- $13M equity investment from Seagen
- Tucatinib drug supply for phase 2 combination trial of cinrebafusp alfa in HER2-low gastric cancer

SERVIER

- PRS-344/S095012: PD-L1/4-1BB antibody-Anticalin bispecific, for which Pieris holds full U.S. rights
- Upfront & milestones to date: ~$40M
- Eligible to receive up to approximately $447M in potential milestone payments
- Entitled to tiered royalties

Anticalin Technology Advantages: Differentiated Respiratory Platform

- Lipocalin templates deployed by Pieris in respiratory programs are abundant in the human lung and can permeate lung epithelium
- Stable, monovalent molecules with high melting temperatures and insensitivity to mechanical stress
- Inhalation pharmacokinetics suitable for once or twice daily administration and compatible with flexible treatment regimens
- Control of particle size distribution in critical size range in both “wet” and “dry” formulations to enable tailored delivery to discrete lung regions



PRS-060/AZD1402: Inhaled IL-4Rα Antagonist

Candidate	PRS-060/AZD1402
Function/MoA	Inhibiting IL4-Rα (disrupts IL-4 & IL-13 signaling)
Indications	Moderate-to-severe asthma
Development	Phase 2a in moderate asthmatics
Commercial Rights	Co-development and U.S. co-commercialization options, including gross margin share

PRS-060/AZD1402

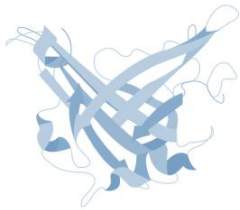
PRS-060 Phase 2a Trial

Part 1	**Patient Population:** Moderate controlled asthmatics **Primary Endpoint:** Safety and tolerability **Number of Patients:** ~45
Part 2	**Patient Population:** Moderate uncontrolled asthmatics with blood eosinophil count of ≥ 150 cells/µL and FeNO ≥ 25 ppb at screening **Primary Endpoint:** Improvement of FEV1 over four weeks relative to placebo **Number of Patients:** ~360

- Enrollment initiated 1Q 2021
- Dry powder formulation, administered b.i.d. over four weeks
- Up to three dose levels plus placebo
- Study is sponsored and funded by AstraZeneca

PRS-220: Inhaled CTGF Antagonist

Candidate	PRS-220
Function/MoA	Inhibiting CTGF/CCN2
Indications	IPF and PASC-PF*
Development	Entering phase 1 in 2022
Commercial Rights	Fully proprietary

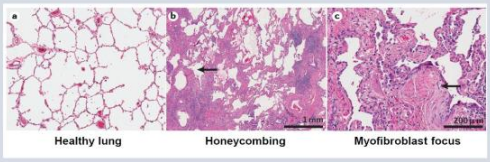


PRS-220

*Idiopathic Pulmonary Fibrosis and Post-Acute sequelae of SARS-CoV-2 infection (PASC) Pulmonary Fibrosis

IPF: High Unmet Medical Need and Significant Commercial Opportunity

IPF is a chronic, progressive, and ultimately fatal lung disease of unknown cause characterized by chronic lung inflammation and progressive scarring (fibrosis) of the tissues between the alveoli of the lung



Martinez, Nature Rev Dis Primer, 2017

3 to 5 million people affected worldwide with increasing global incidence, with ~130K affected in the US each year[1,2]

2 to 5 years mean survival from the time of diagnosis[2]

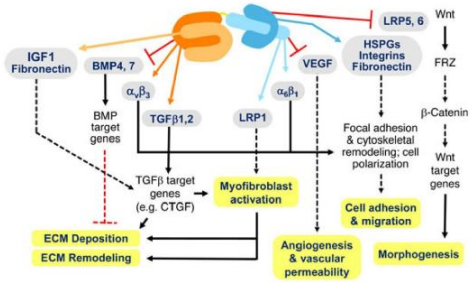
>$3B current market in sales

Currently approved treatments provide modest benefit, in addition to having side effects that require management

1 – Glassberg, AJMC 2019
2 - Meltzer, Orphanet Journal of Rare Diseases 2008

CTGF: Clinically Validated Intervention for IPF

- Connective tissue growth factor (CTGF), or CCN2, a protein localized in the extracellular matrix, is a driver of fibrotic remodeling as consequence of an aberrant wound healing process
- Over-expression of the protein in lung tissue is observed in patients suffering from IPF
- Competitor clinical data indicate inhibition of CTGF reduces the decline in lung function among patients with IPF
- Competitor compound requires high-dose infusions to effectively target lung-resident CTGF



CTGF affects multiple signaling pathways and processes important in pathophysiology. CTGF interacts with a variety of molecules, including cytokines and growth factors, receptors and matrix proteins. These interactions alter signal transduction pathways, either positively or negatively, which results in changes in cellular responses.

(Lipson, Fibrogenesis & Tissue Repair, 2012)

PRS-220: Inhaled Solution

The only CTGF inhibitor in clinical trials for IPF is a monoclonal antibody administered by IV infusion, 30 mg/kg every three weeks

The objective of PRS-220 is to more efficiently engage a clinically validated target via oral inhalation directly to the lung epithelium and interstitium

Benefits of inhaled administration:

- Inhaled administration eliminates the need for additional clinic visits required for systemic drug administration
- Direct administration into the lungs may result in more efficient CTGF inhibition in the site of the disease
- Patients with IPF frequently take inhaled medications and thus no additional training required
- This approach supports add-on to SOC, whereas patients on SOC are excluded from current studies of reference mAb

Grant From Bavarian Government to Support Program Acceleration and Evaluation of Efficacy in PASC-PF

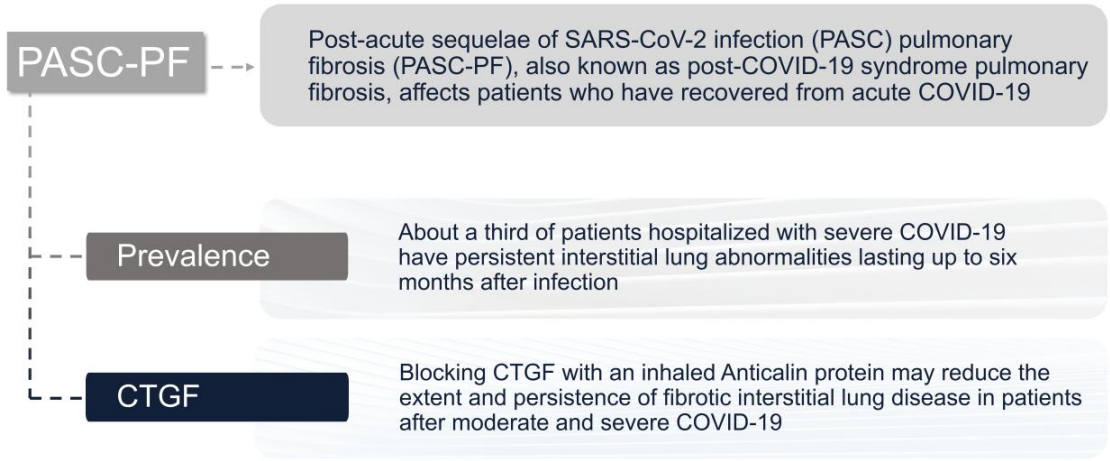
~$17M

approximately 14 million euro grant from the Bavarian government for the research and development of PRS-220 for post-acute sequelae of SARS-CoV-2 infection (PASC) pulmonary fibrosis (PASC-PF)

Grant will:

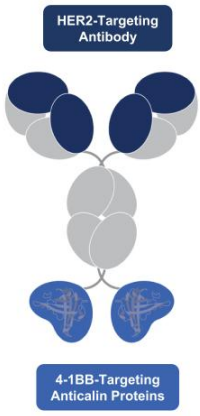
- Allow Pieris to accelerate development of the program – IND planned 2022
- Support clinical-readiness activities and initial clinical development for the program, including GLP tox studies, GMP manufacturing, and phase 1 clinical development
- Broaden scope of the program beyond the original IPF indication by including the evaluation of PRS-220 for the treatment of post-COVID-19-related pulmonary fibrosis

PRS-220 for PASC-PF



Cinrebafusp Alfa (PRS-343): Lead IO Asset

Candidate	Cinrebafusp alfa (PRS-343)
Function/MoA	Tumor-targeted 4-1BB agonism and HER2 antagonism
Indications	HER2-high and HER2-low gastric cancer
Development	Initiating phase 2
Commercial Rights	Fully proprietary



Cinrebafusp Alfa Phase I Summary

- Acceptable profile observed at all doses tested with no dose-limiting toxicities
- Clinical benefit at active dose levels (≥2.5 mg/kg), including confirmed complete response and several confirmed partial responses
- Dose-dependent immune activation and 4-1BB modulation in both HER2-high and HER2-low expressing patients
- Durable anti-tumor activity in heavily pre-treated patient population, including "cold" tumors
- Moving into phase 2 in HER2-high and HER2-low gastric cancer
- As lead IO program, cinrebafusp alfa provides key validation of 4-1BB franchise and follow-on programs, including PRS-344 and PRS-342

Cinrebafusp Alfa Phase 1 Monotherapy Study

Study Objectives

Primary: Characterize Safety Profile
Identify MTD or RP2D

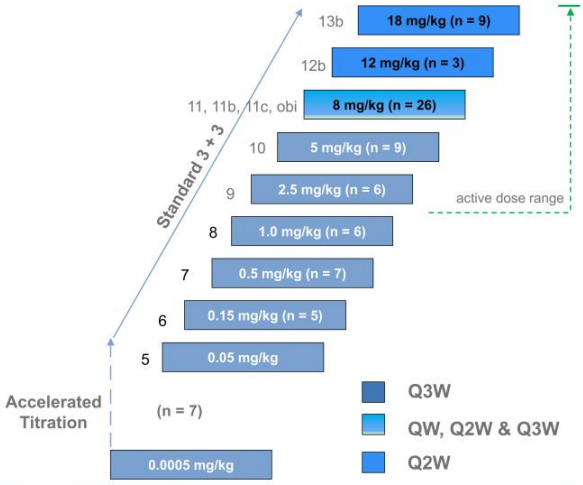
Secondary: Characterize PK/PD & Immunogenicity
Preliminary anti-tumor activity

Key Eligibility Criteria

Inclusion: Metastatic HER2+ solid tumors
Breast & Gastric/GEJ ≥ 1 prior anti-HER2 Tx
Measurable disease (RECIST v1.1)
ECOG 0 or 1

Exclusion: Symptomatic or unstable brain metastasis
Abnormal cardiac EF (< 45%)

Dose Escalation Study Design



Phase 1 Monotherapy Treatment Related Adverse Events at Active Doses (≥ 2.5 mg/kg)

Treatment Related Adverse Events (TRAEs occurring in > 1 patient; n = 53)	All Grades n (%)	Grade 1-2 n (%)	Grade 3-4 n (%)
Infusion related reaction	13 (25%)	9 (17%)	4 (8%)
Nausea	7 (13%)	7 (13%)	
Chills	6 (11%)	6 (11%)	
Vomiting	6 (11%)	6 (11%)	
Dyspnea	4 (8%)	4 (8%)	
Fatigue	4 (8%)	4 (8%)	
Arthralgia	3 (6%)	2 (4%)	1 (2%)
Decreased appetite	3 (6%)	3 (6%)	
Non-cardiac chest pain	3 (6%)	3 (6%)	
Asthenia	2 (4%)	2 (4%)	
Diarrhea	2 (4%)	2 (4%)	
Dizziness	2 (4%)	2 (4%)	
Headache	2 (4%)	2 (4%)	
Paresthesia	2 (4%)	1 (2%)	1 (2%)
Pruritus	2 (4%)	2 (4%)	
Pyrexia	2 (4%)	2 (4%)	
Rash	2 (4%)	2 (4%)	

1 Gr 3 Ejection Fraction dec and 1 Gr 3 Heart Failure; both events occurred in one patient and resolved w/o sequelae.

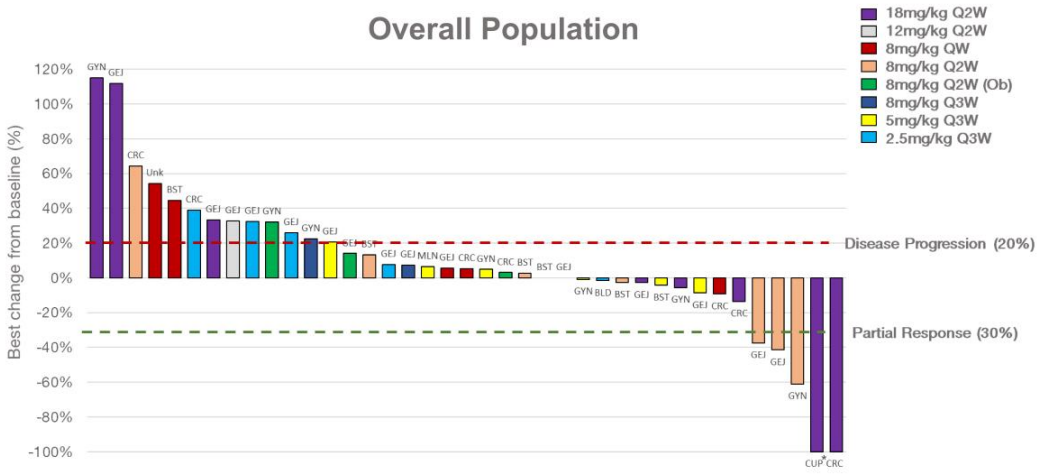
Data cut-off: 25-Feb-21

Summary of Responses in Phase 1 Monotherapy Study

Cohort	13b	12b	11c	Obi	11b	11	10	9	Total
Best Response	18 mg/kg, Q2W	12 mg/kg, Q2W	8 mg/kg, QW	8 mg/Kg, Q2W	8 mg/kg, Q2W	8 mg/kg, Q3W	5 mg/kg, Q3W	2.5 mg/kg, Q3W	
Evaluable Patients	8	2	5	4	7	4	7	5	42
CR	1	-	-	-	-	-	-	-	1
PR	1	-	-	-	3	-	-	-	4
SD	3	-	1	2	3	3	3	2	17
ORR	25%	0%	0%	0%	43%	0%	0%	0%	12%
DCR	63%	0%	20%	50%	86%	75%	43%	40%	52%

Data cut-off: 25-Feb-21

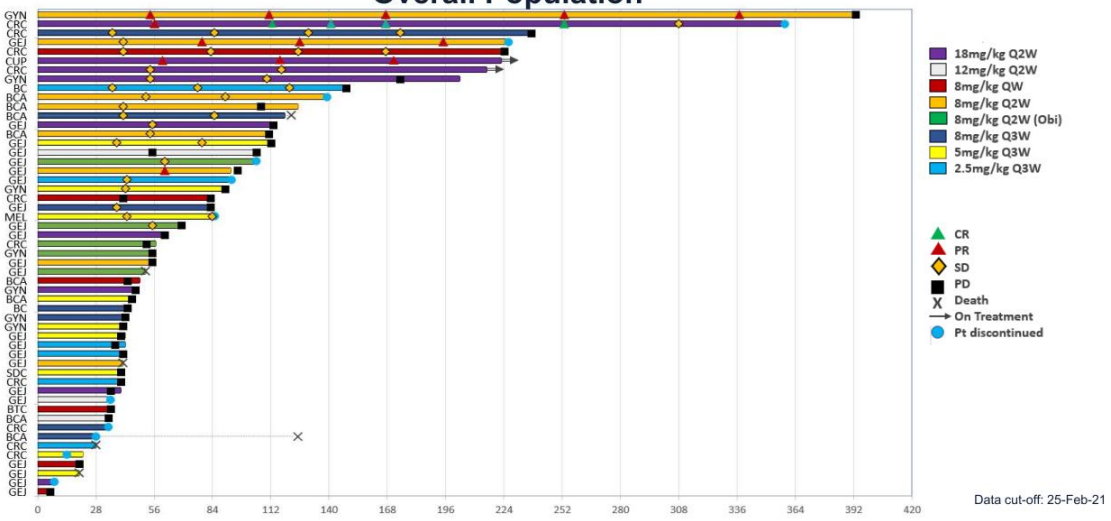
Cinrebafusp Alfa Phase 1 Monotherapy Efficacy Data: Analysis of Patients Treated at Active Doses



Data cut-off: 25-Feb-21
*Manual update for CUP patient from Medidata 9-Apr-21

Durable Responses with Cinrebafusp Alfa Among Heavily Pre-treated Population

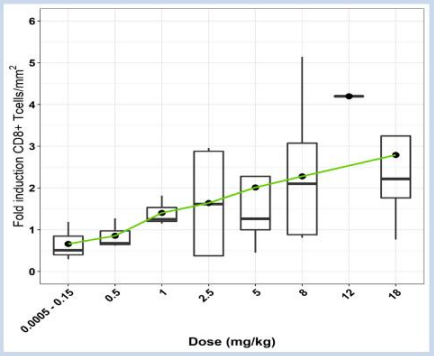
Overall Population



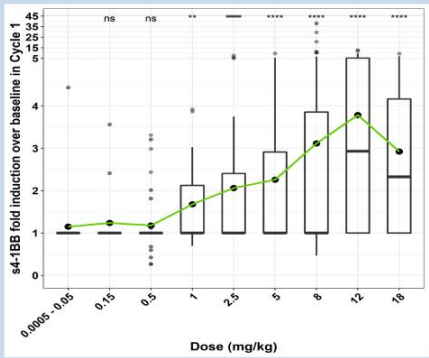
Data cut-off: 25-Feb-21

Cinrebafusp Alfa Shows Dose-dependent Activity Across Key Pharmacodynamic Parameters

Tumor (CD8+)



Serum (s4-1BB)



Connects group averages

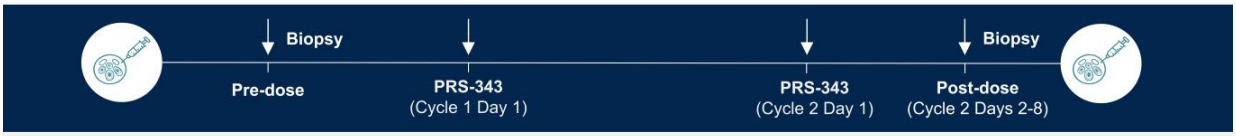
Median

Mann-Whitney U Test

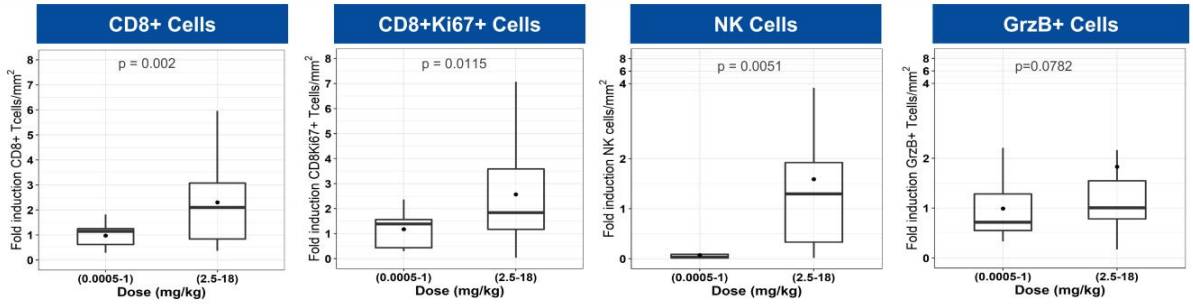
Dose at 8 mg/kg incorporates patients treated at Q1W, Q2W, or Q3W

Data cut-off: 25-Feb-21

Cinrebafusp Alfa Activates Adaptive and Innate Immunity in the Tumor



Based on preclinical and clinical data, serum concentration of > 20 µg/ml defines active dose range beginning at 2.5 mg/kg (Cohort 9)



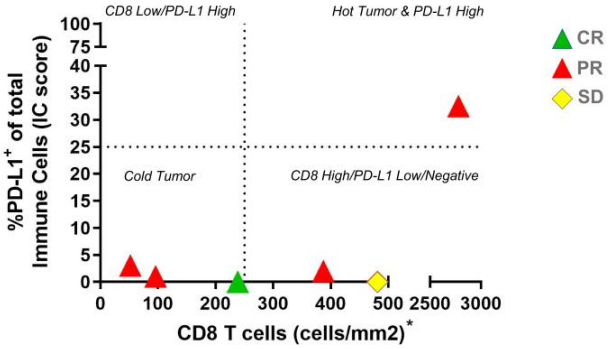
● Denotes group averages
— Median

Unpaired One-Tailed Welch`s

Data cut-off: 25-Feb-21

Single-Agent Activity in Both "Hot" and "Cold" Tumors

PD-L1 status and CD8+ T cells levels in tumor biopsies



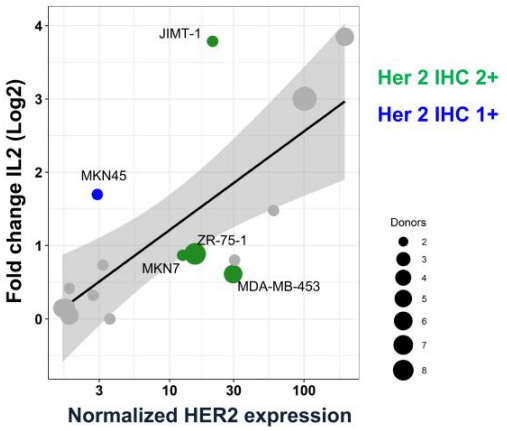
* Threshold informed by (Tumeh et al., 2014 and Blando et al., 2019)

Several patients with clinical benefit have low/negative PD-L1 status and low CD8 T cell numbers

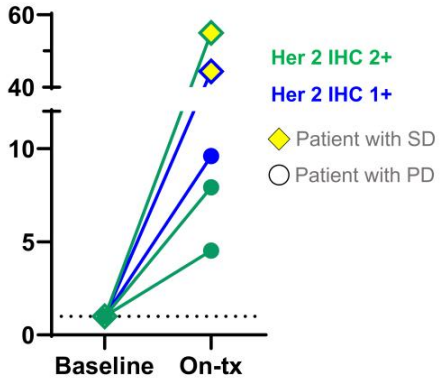
Data cut-off: 25-Feb-21

Signs of Preclinical and Clinical Activity in the HER2-Low Setting

PRS-343 enhances T cell activation in *in vitro* co-cultures with HER2-low tumor cell lines[1]



PRS-343 increases soluble 4-1BB in HER2-low-expressing patients

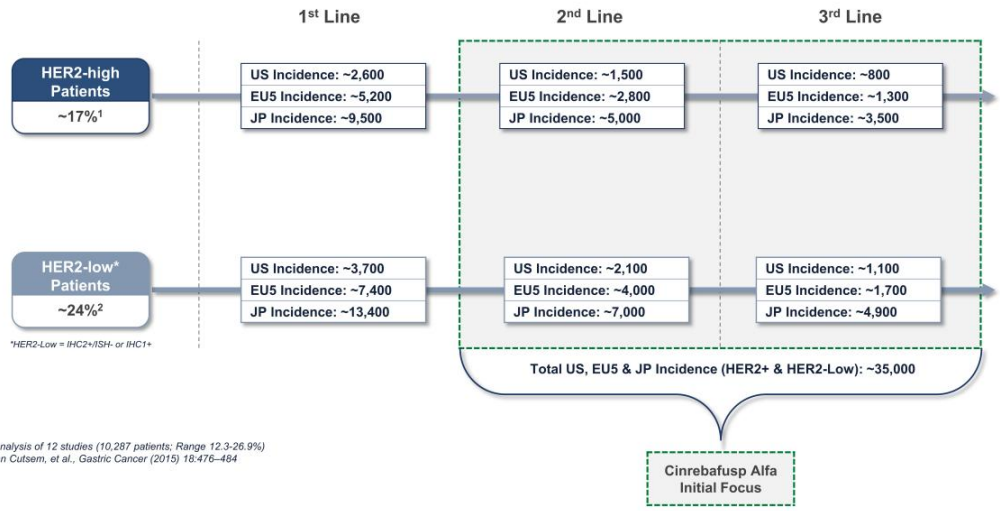


Data cut-off: 25-Feb-21

[1]*Hinner et al Clin Can Res 2019*

Cinrebafusp Alfa Clinical Development Plan

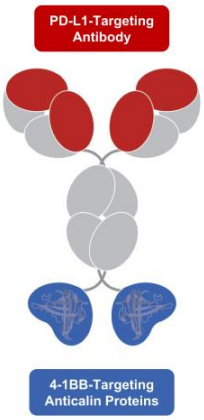
Cinrebafusp Alfa Opportunity in HER2-High & HER2-Low Gastric Cancer



1) *Meta Analysis of 12 studies (10,287 patients; Range 12.3-26.9%)*
2) *Eric Van Cutsem, et al., Gastric Cancer (2015) 18:476–484*

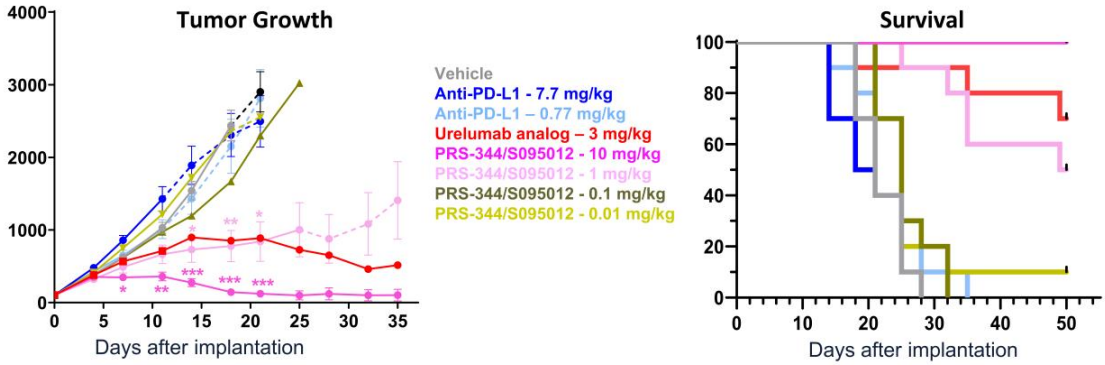
PRS-344/S095012: Meaningfully Building on Localized MoA of Cinrebafusp Alfa

Candidate	PRS-344/S095012
Function/MoA	Localized 4-1BB agonism with PD-L1 antagonism
Indications	N.D.
Development	2021 IND expected (in co-dev with Servier)
Commercial Rights	Co-development with full U.S. commercial rights; royalty on ex-U.S. sales



PRS-344 Drives Strong Anti-tumor Activity in Anti-PD-L1 mAb-resistant Mouse Model

h-4-1BB knock-in mice subcutaneously implanted with MC-38-huPD-L1 cells



- Dose-dependent anti-tumor response that leads to significant extension of survival
- Superior to equimolar doses of anti-PD-L1 mAb treatment alone

Financial Overview (As of 3/31/21)

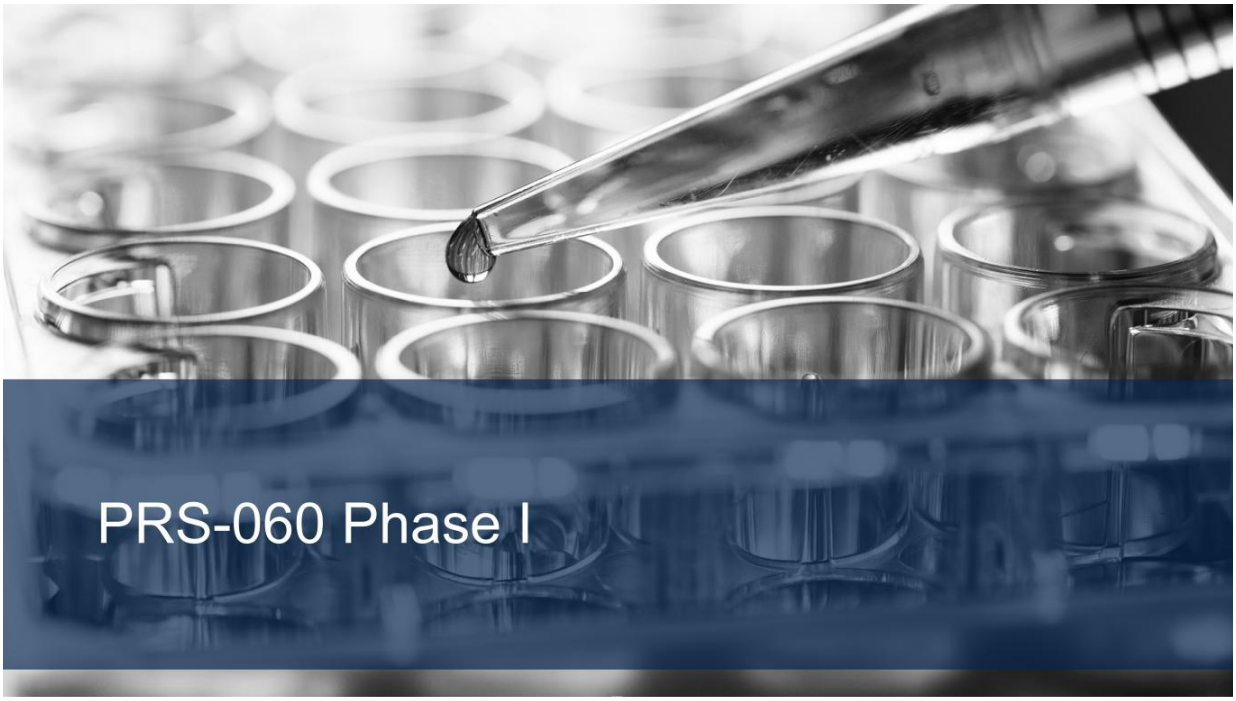
$66.8M* (~$120M proforma)	$0.0	59.7M*
Cash & Cash Equivalents	Debt	CSO

>$175M non-dilutive capital from partnerships since 2017

>$17M grant announced in 2021

*Excludes $23M from PRS-060 phase 2a milestone and AstraZeneca equity investments (along with ~3.6M common shares issued), $10 million from Boston Pharmaceuticals, and $20 million from Genentech

Appendix


PRS-060 Phase I

PRS-060 Phase I Multiple Ascending Dose Trial

Strategic Objectives	Ascertain PK/PD with a reliable biomarker to confirm local target engagement and inform Phase II dosage regimen
Trial Design Highlights	Dosing patients with mild asthma with elevated FeNO levels (≥35 ppb), to receive inhaled PRS-060 or pbo b.i.d.* over a 10-day period

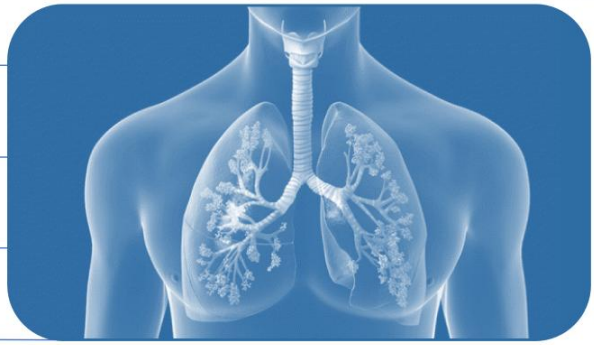
*q.d. on Day 10

Initiated in July 2018

Evaluating safety, tolerability, PK, PD and will also evaluate FeNO reduction vs. placebo

Measuring safety, tolerability and FeNO changes days 1-10,17, and 40

Pieris is sponsoring the trial, AstraZeneca is reimbursing Pieris for all associated costs



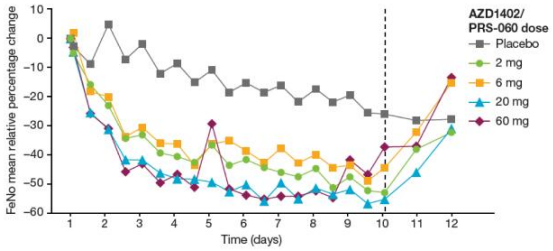
Phase 1b Interim Results: Favorable Safety Profile

- All doses of AZD1402/PRS-060 tested in the study were well tolerated
- No treatment-related serious AEs were observed

System organ class AE Preferred Terms[b]	Placebo (N = 12) n (%) m	AZD1402/PRS-060[c] (N = 30) n (%) m	Overall (N = 42) n (%) m
Gastrointestinal disorders	**4 (33.3) 4**	**13 (43.4) 14**	**17 (40.5) 18**
Dry mouth	1 (8.3) 1	2 (6.7) 2	3 (7.1) 3
Nausea	1 (8.3) 1	3 (10.0) 3	4 (9.5) 4
Infections and infestations	**1 (8.3) 1**	**7 (23.3) 8**	**8 (19.0) 9**
Upper respiratory tract infection	1 (8.3) 1	3 (10.0) 4	4 (9.5) 5
Nervous system disorders	**5 (41.7) 9**	**13 (43.4) 18**	**18 (42.9) 27**
Headache	3 (25.0) 6	5 (16.7) 7	8 (19.0) 13
Presyncope	0	4 (13.3) 6	4 (9.5) 6
Respiratory, thoracic and mediastinal disorders	**6 (50.0) 6**	**14 (46.7) 15**	**20 (47.6) 21**
Cough	1 (8.3) 1	4 (13.3) 4	5 (11.9) 5
Rhinorrhoea	2 (16.7) 2	1 (3.3) 1	3 (7.1) 3
Wheezing	2 (16.7) 2	4 (13.3) 5	6 (14.3) 7

Phase 1b Interim Results: Robust FeNO Reduction

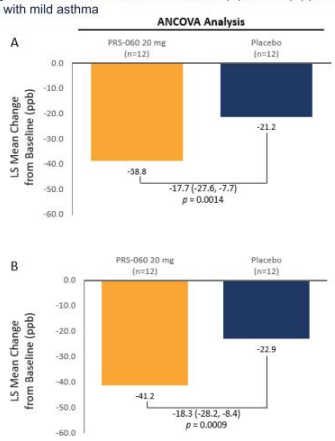
PRS-060 Relative FeNO Reduction (Emax Analysis)



PRS-060, mg (delivered)	n	Reduction vs. placebo, % (95% CI)	p-value
2	6	24.0 (1.8–41)	0.04
6	6	24.3 (2.7–41)	0.03
20	12	36.4 (22–48)	<0.0001
60	6	30.5 (10–46)	0.005
Placebo	12		

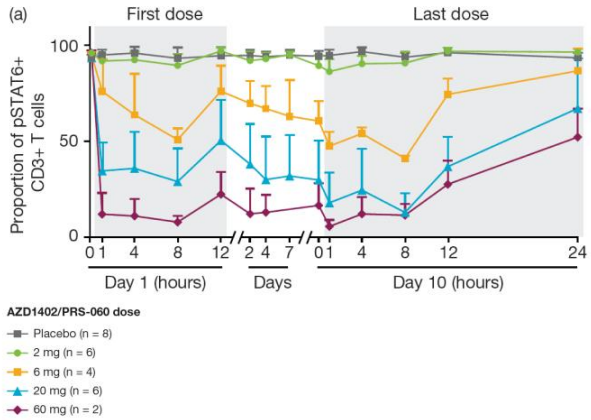
PRS-060 Relative FeNO Reduction (ANCOVA Analysis)

Mean change from baseline in FeNO levels at 0.5h (A) and 2h (B) post-dose on Day 10 in participants with mild asthma



Phase 1b Interim Results: Pharmacological Versatility

pSTAT6 levels over time following inhalation of PRS-060



No systemic target engagement and minimal systemic exposure was observed at the 2mg dose, suggesting that local target engagement by the drug is sufficient to reduce airway inflammation

Pharmacological versatility, given low-dose FeNO reduction with no observed systemic activity (pSTAT6) versus high-dose FeNO reduction with systemic activity

Cinrebafusp Alfa – Phase I Monotherapy

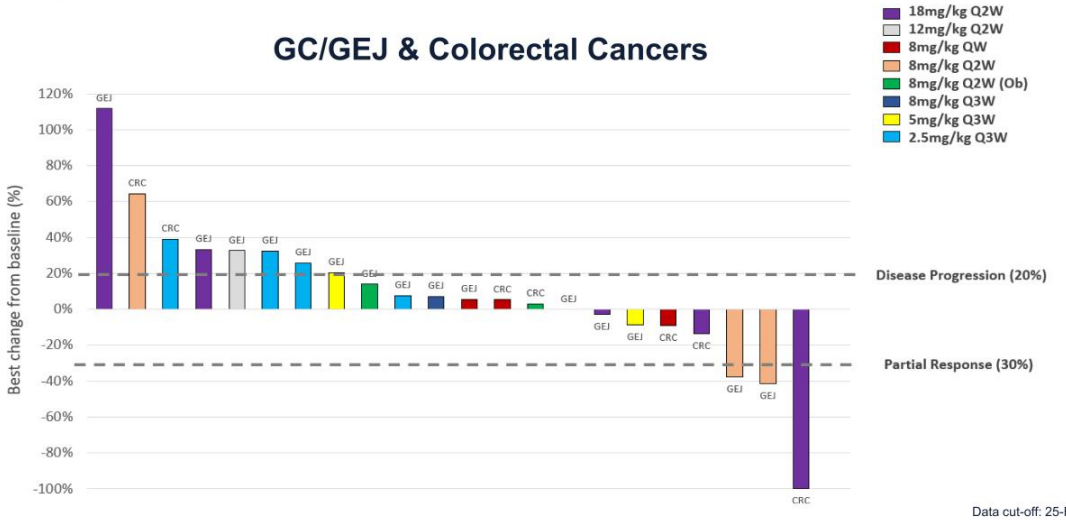
Phase 1 Monotherapy Baseline Characteristics (N = 78)

Characteristic	n (%)
Age, Median (range)	**63 (24–92)**
Gender	
F	**46 (59%)**
M	**32 (41%)**
ECOG PS	
0	**19 (24%)**
1	**59 (76%)**
Prior Therapy Lines	
1	**11 (14%)**
2	**10 (13%)**
3	**16 (21%)**
4	**12 (15%)**
5+	**29 (37%)**
Median # of anti-HER2 Tx	
Breast	**6**
Gastric	**2**

Primary Cancer Type	n (%)
Gastroesophageal	**34 (44%)**
Breast	**16 (21%)**
Colorectal	**12 (15%)**
Gynecological	**9 (12%)**
Bladder	**2 (3%)**
Pancreatic	**1 (1%)**
Other – Cancer of Unknown Origin	**2 (3%)**
Other – Salivary Duct	**1 (1%)**
Melanoma	**1 (1%)**

Data cut-off: 25-Feb-21

Cinrebafusp Alfa Phase 1 Monotherapy Efficacy Data: Analysis of Patients Treated at Active Doses



Data cut-off: 25-Feb-21

Case Studies: PR in Gastric Cancer and CR in Rectal Cancer

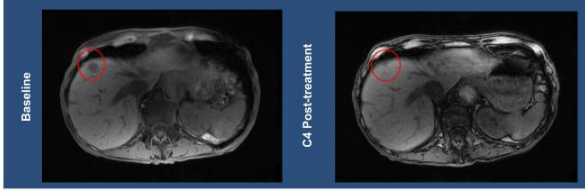
Patient Profile, Treatment History and Treatment Outcome

Gastric Cancer Patient with Partial Response

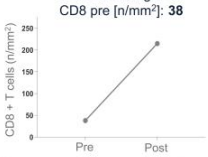
- 80-year-old woman; initial diagnosis in June 2017
- Gastric adenoca with mets to liver, LN and adrenals
- Treated with 8 mg/kg Q2W of PRS-343
- HER2 IHC 3+; PD-L1 positive (CPS=3) ; NGS: ERBB2 amplification

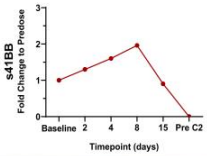
Prior Treatment includes:

- Trastuzumab, Pembrolizumab + Capecitabine/oxaliplatin
- Nivolumab with IDO1 inhibitor (investigational drug)



CD8 fold change: **5.7**
CD8 pre [n/mm²]: **38**



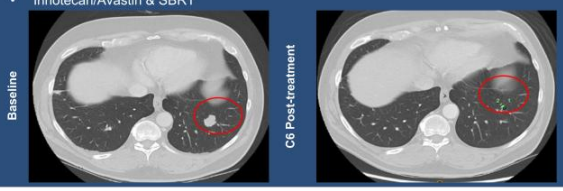


Rectal Cancer Patient with Complete Response

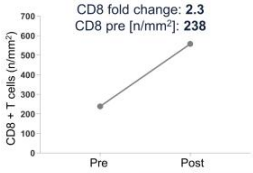
- 59-year-old male; initial diagnosis in March 2017
- Rectal cancer with cardiac and lung mets
- Treated with 18 mg/kg Q2W of PRS-343
- Foundation One Her2 amplification; verified in-house to be IHC 3+; MSS, TMB low

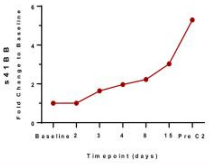
Prior Treatment includes:

- Folfiri/Avastin
- 5FU/Avastin maintenance
- Irinotecan/Avastin & SBRT



CD8 fold change: **2.3**
CD8 pre [n/mm²]: **238**





Case Study: PR in Cancer of Unknown Primary

Patient Profile, Treatment History and Treatment Outcome

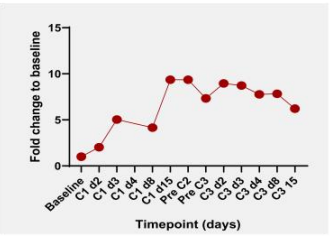
Patient Profile

82-year-old male
Initial diagnosis October 2019
Carcinoma of Unknown Primary
Stage 4
HER2 amplification via MD Anderson
NGS; MSS- stable; TMB unknown

Treatment History

Open Radical Prostatectomy
Radiation
Carboplatin + gemcitabine

s4-1BB Serum



Lesions	Lesion Site	Lesion Size (mm)			
		Pre-treatment	Post-treatment		
			Cycle 2	Cycle 4	Cycle 6
Target 1	Lung, right lower lobe mass	25	13	0	0
	Total	25	13	0	0
	% Change from Baseline		-48%	-100%	-100%
Non-target 1	Lung, bilateral pulmonary masses	Present	Not assessed	Present	Present
Non-target 2	Lymph nodes, mediastinal and hilar	Present	Not assessed	Present	Present
Overall Response			PR	PR	PR

Data cut-off: 25-Feb-21

Case Study: SD in Colorectal Cancer

Patient Profile, Treatment History and Treatment Outcome

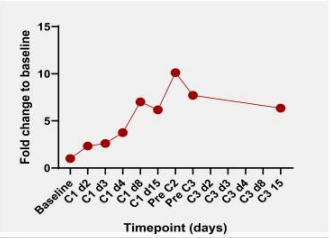
Patient Profile

56-year-old female
Initial diagnosis Jan 2009
Stage 4 Colorectal Adenocarcinoma Cancer
Archival HER2 3+
MSI stable; KRAS, NRAS, BRAF wt

Treatment History

9 prior lines of therapy, including:
Folfiri
Folfox + Avastin
5-FU + bevacizumab
trastuzumab/pertuzumab
Investigational agent (immune stimulator antibody conjugate (ISAC) with antibody similar to trastuzumab

s4-1BB Serum



Lesions	Lesion Site	Lesion Size (mm)			
		Pre-treatment	Post-treatment		
			Cycle 2	Cycle 4	Cycle 6*
Target 1	Lung, right upper lobe pulmonary nodule	10	8	8	-
Target 2	Lung, right lower lobe pulmonary nodule	12	11	11	-
	Total	22	19	19	-
	% Change from Baseline		-14%	-14%	-
Non-target 1	Lung, multiple pulmonary nodules	Present	Present	Present	-
CEA		<1.9	1.1	1.3	-

Data cut-off: 25-Feb-21
*Data not yet available due to COVID-related delays

Cinrebafusp Alfa – Biomarkers

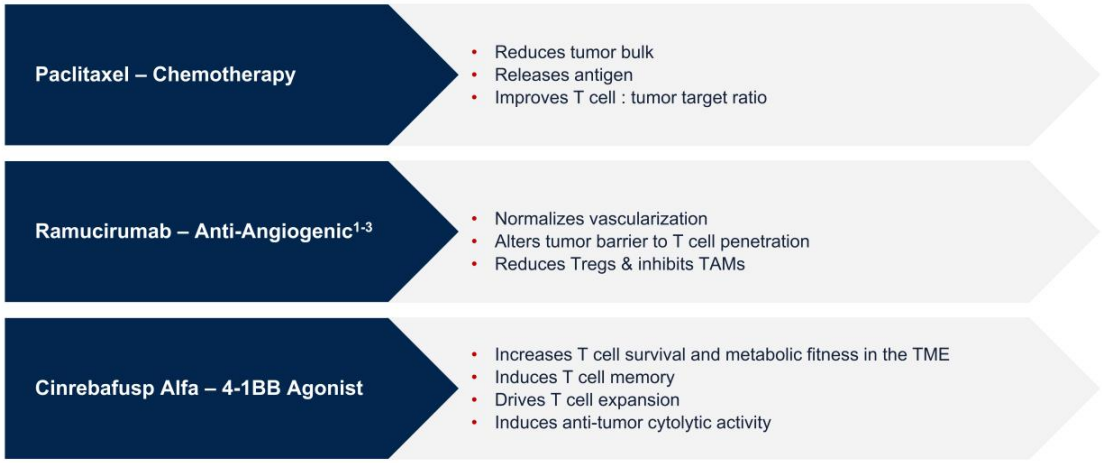
Soluble 4-1BB (s4-1BB): Blood-based Biomarker of Cinrebafusp Alfa Engagement

- s4-1BB is an alternatively spliced form of 4-1BB receptor lacking the transmembrane encoding exon (Setareh et al., 1995; Shao et al., 2008)
- s4-1BB is **released by leukocytes in an activation-dependent manner** (Michel et al., 2000; Salih et al., 2001; Schwarz et al., 1996)
- s4-1BB is **produced with a slightly delayed kinetic to pathway activation**. Hypothesized role is as a negative regulator, keeping 4-1BB-mediated co-stimulation in check

s4-1BB utility as a pathway specific biomarker provides ability to track cinrebafusp target engagement and activity using serum samples

Cinrebafusp Alfa – Phase II Rationale

Scientific Rationale for Combining Cinrebafusp Alfa & SoC



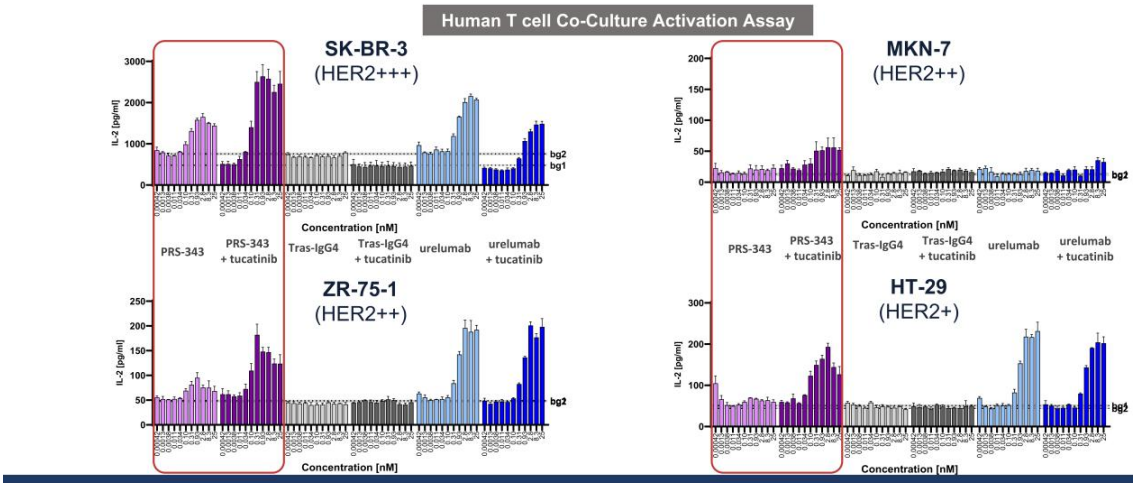
1 - Allen et al., Science Translational Medicine 2017
2 - Juang et al. Front Immunology 2018
3 - Tada et al., Journal for Immunotherapy of Cancer 2018

Scientific Rationale for Combining Cinrebafusp Alfa & Tucatinib

Tyrosine kinase inhibitors (tucatinib)	• Upregulates or stabilizes tumor cell surface HER2 expression[2,3,4] • Increases clustering potential of cinrebafusp alfa on tumor cells to drive enhanced 4-1BB cross-linking
Cinrebafusp Alfa – Dual MoA	• Inhibits HER2 signaling AND activates tumor-specific T cells in tumor microenvironment
Complements Both MoAs	• Enhances inhibition of HER2 signaling by concurrent binding to HER2 on the tumor cell surface and TKI inhibition of the internal kinase signaling domain[1] • *In vitro*, combination leads to significantly increased T cell activation in the presence of HER2-Low cell lines

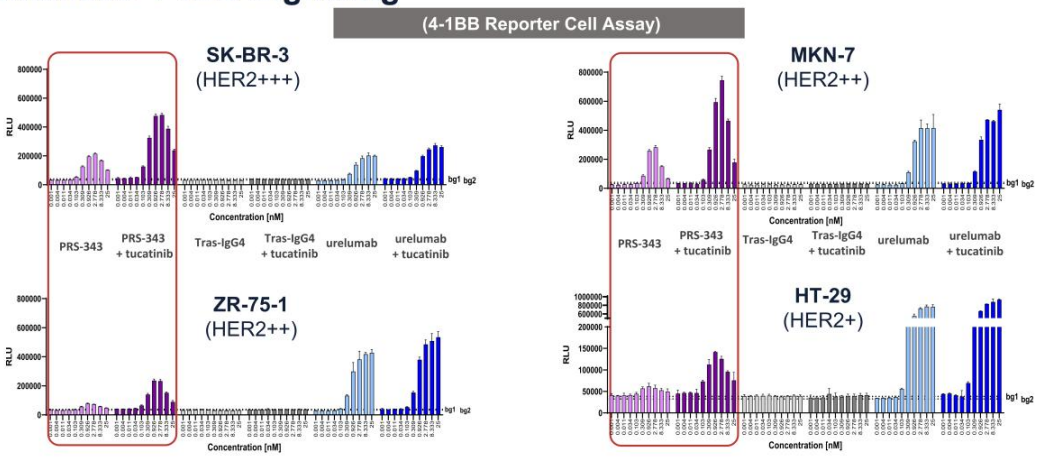
1 - Baselga J., Lancet, 2012;
2 - Maruyama T., et al, Anticancer Res., 2011
3 - Scaltriti M., et al, Oncogene, 2009
4 - Hartmans, et al, Oncotarget,, 2017

Cinrebafusp Alfa and Tucatinib Combination Enhances T-cell Activation



Increased IL-2 secretion observed when cinrebafusp alfa was combined with fixed dose tucatinib in a co-culture assay with SK-BR-3 (high HER2), MKN-7, ZR-75-1 (medium HER2) and HT-29 (low HER2) tumor cell lines

Cinrebafusp Alfa and Tucatinib Combination Leads to Enhanced 4-1BB Signaling



Increased 4-1BB signaling observed when cinrebafusp alfa was combined with fixed dose tucatinib in a reporter assay with SK-BR-3 (high HER2), MKN-7, ZR-75-1 (medium HER2) and HT-29 (low HER2) tumor cell lines

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