# 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): January 24, 2022**

# 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.)** |

| | |
|---|---|
| **255 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 2.02 Results of Operations and Financial Condition.**

On January 24, 2022, Pieris Pharmaceuticals, Inc. (the "Company") presented the January 2022 Investor Presentation announcing certain unaudited financial results for the fiscal year ended December 31, 2021. A copy of the presentation is furnished as Exhibit 99.1 to this report.

The information set forth under this "Item 2.02. Results of Operations and Financial Condition," including Exhibit 99.1 furnished hereto, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, except as shall be expressly set forth by specific reference in such filing.

**Item 7.01 Regulation FD Disclosure.**

Furnished hereto as Exhibit 99.1 is the January 2022 Investor Presentation of the Company.

The information set forth under this "Item 7.01. Regulation FD Disclosure," including Exhibit 99.1 furnished 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 Investor Presentation, dated January 2022.

104 Cover Page Interactive Data File (embedded within the Inline XBRL document)

**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: January 24, 2022

/s/ Tom Bures
Tom Bures
Chief Financial Officer

# PIERIS PHARMACEUTICALS

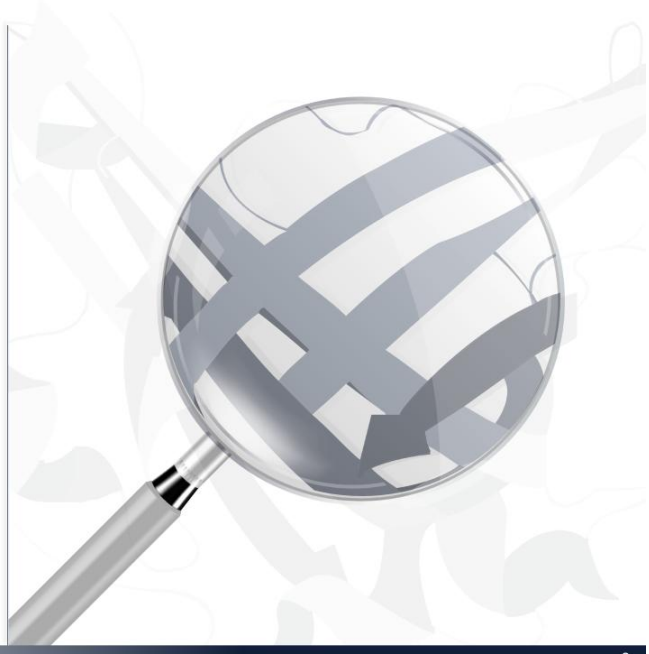
*CORPORATE PRESENTATION*
*January 2022*

# 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 subsequent 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 this year; 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

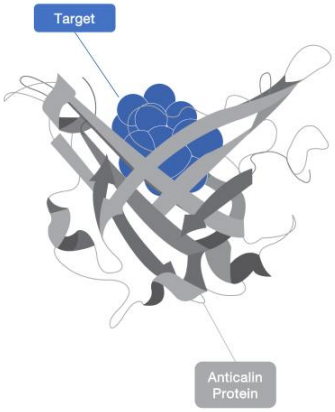
# Anticalin® Proteins as Therapeutic Modalities

## 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

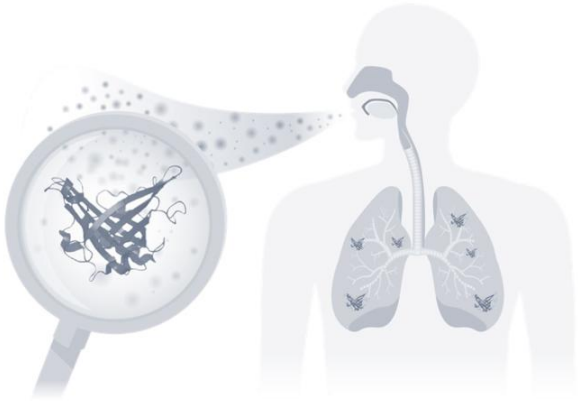
## Translational Science Expertise to Deploy Platform in Meaningful Way

- 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

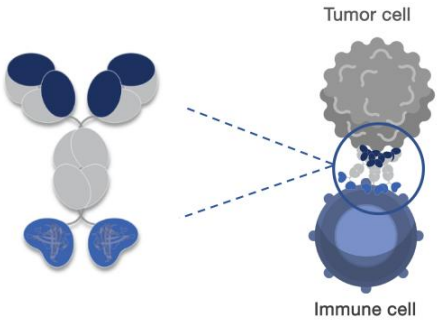


# Two-fold Focus of Anticalin Platform Deployment

## 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 1 | Phase 2 |
| PRS-060/AZD1402 | IL4-Rα | Asthma | AstraZeneca | Worldwide Gross Margin Option | | | | |
| PRS-220 | CTGF | IPF, PASC-PF | n/a | Worldwide | | | | |
| AstraZeneca Programs* | n.d. | n.d. | AstraZeneca | Worldwide Gross Margin 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 1 | Phase 2 |
| 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 over $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**

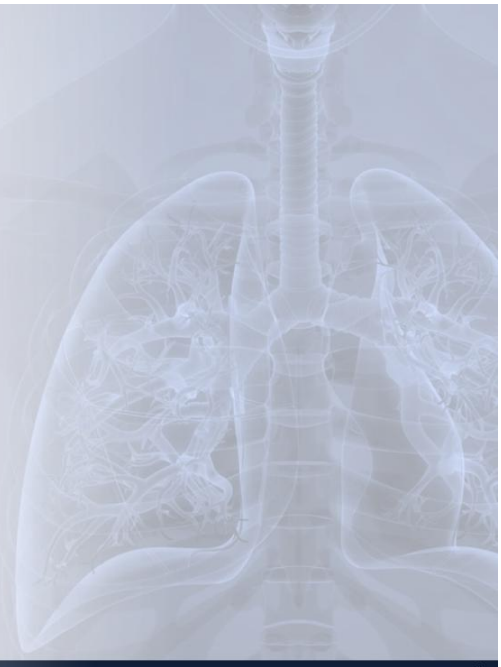
- 3-program IO bispecific partnership
- Upfront & milestones to date: $35M
- Eligible to receive up to approximately $1.2B in potential milestone payments plus royalties
- $13M equity investment from Seagen
- Tucatinib drug supply for phase 2 combination trial of cinrebafusp alfa in HER2-low gastric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

**SERVIER**

- PRS-344/S095012: PD-L1/4-1BB antibody-Anticalin bispecific, for which Pieris holds full U.S. rights
- Upfront & milestones to date: ~$41M
- Eligible to receive up to approximately $261M 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 uncontrolled asthmatics |
| Commercial Rights | Co-development and U.S. co-commercialization options, including gross margin share |

PRS-060/AZD1402

# PRS-060/AZD1402 Progressed into Efficacy Portion of Phase 2a

| | | |
|---|---|---|
| Part 1 (Safety) | ✓ Part 1a: Low + Med Dose<br>❑ Part 1b: High Dose | **Participant Population:** Moderate asthmatics controlled on ICS/LABA<br>**Primary Endpoint:** Safety and tolerability compared to placebo from baseline until follow-up (approximately 56 days)<br>**# of Participants:** ~45 (randomized: 1:1:1 for part 1a; 2:1 for part 1b) |
| Part 2 (Efficacy) | ❑ Part 2a: Low + Med Dose<br>❑ Part 2b: High Dose | **Participant Population:** Moderate uncontrolled asthmatics on ICS/LABA with blood EO count of ≥ 150 cells/µL and FeNO ≥ 25 ppb at screening*<br>**Primary Endpoint:** Improvement of FEV1 at four weeks relative to placebo<br>**# of Participants:** ~300 (randomized: 1:1:1 for part 2a; 2:1 for part 2b) |

Parts 1b & 2a initiated 1Q 2022

Dry powder formulation, administered b.i.d. over four weeks on top of standard-of-care therapy (medium dose ICS with LABA)

Up to three dose levels plus placebo

Study is sponsored, conducted, and funded by AstraZeneca

*In addition to uncontrolled asthmatics with threshold EO count and FeNO profile, there are other enrollment criteria associated with part 2 not in part 1, including FEV1, and a different ACQ score.

# DPI Formulation of PRS-060/AZD1402 Passed Safety Review

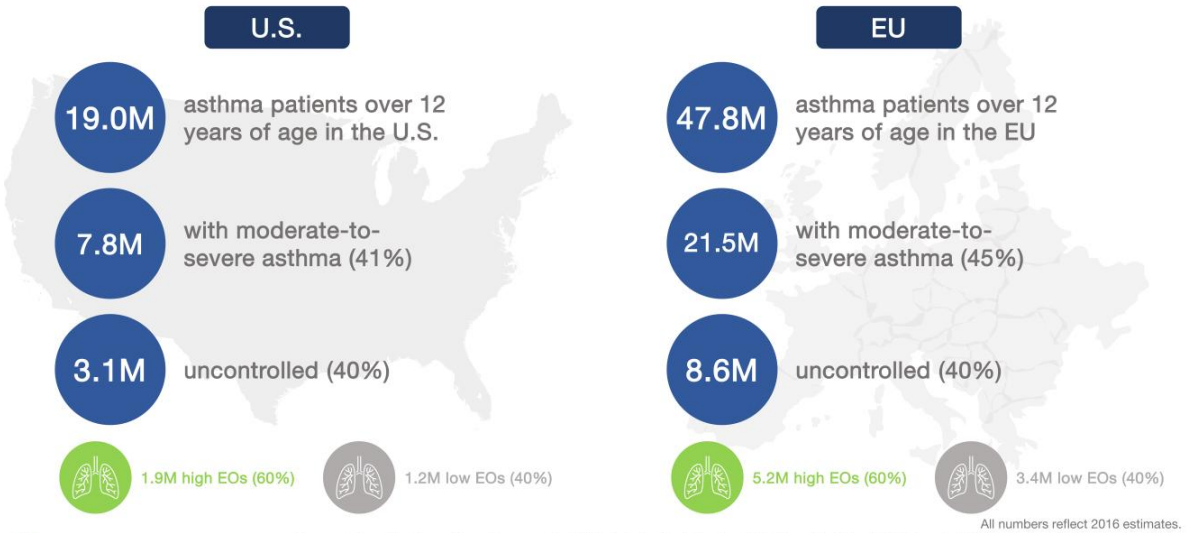
31 moderate asthmatics controlled on standard-of-care (medium dose ICS with LABA) asthma therapy were dosed twice daily over four weeks randomized across two dose levels and placebo arm (1:1:1)

Safety review successfully completed for two different dose levels that will now be explored for efficacy in participants with asthma uncontrolled on medium dose ICS-LABA

Safety review performed of the following (compared to placebo):

- ☑ Incidence of adverse events
- ☑ Changes in laboratory markers (immune biomarkers, clinical chemistry, and hematology)
- ☑ Forced expiratory volume in 1 second (FEV1)
- ☑ Pharmacokinetics

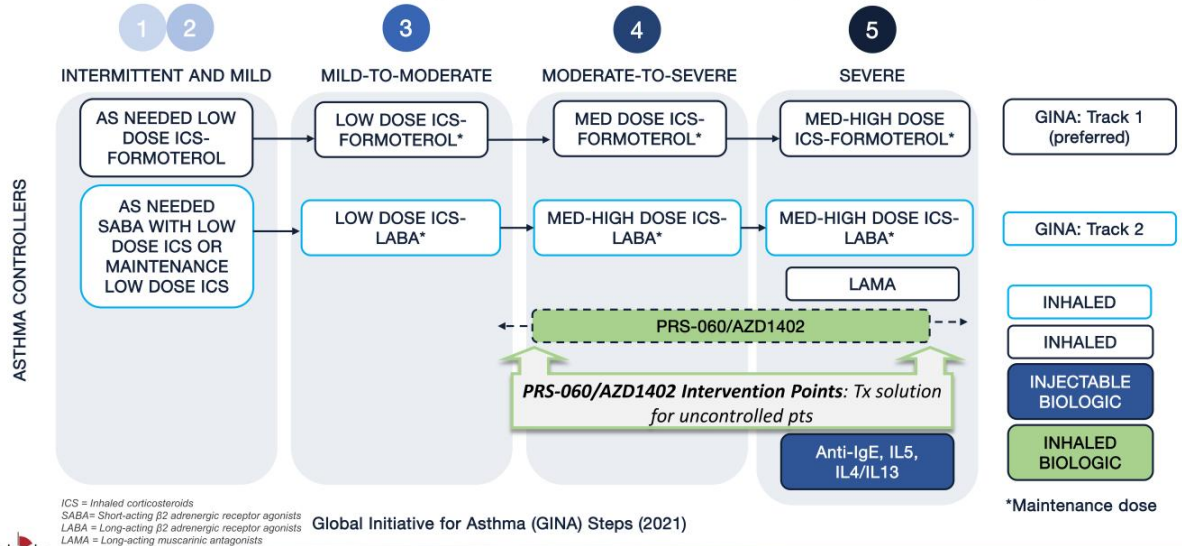
# Moderate-to-Severe Asthma Market Opportunity




All numbers reflect 2016 estimates.

Source: Artisan Healthcare Consulting analysis (2016), including the following: CDC, Eurostat, Rabe (2004), Cazzoletti (2007), Colice (2012), Hekking (2015).

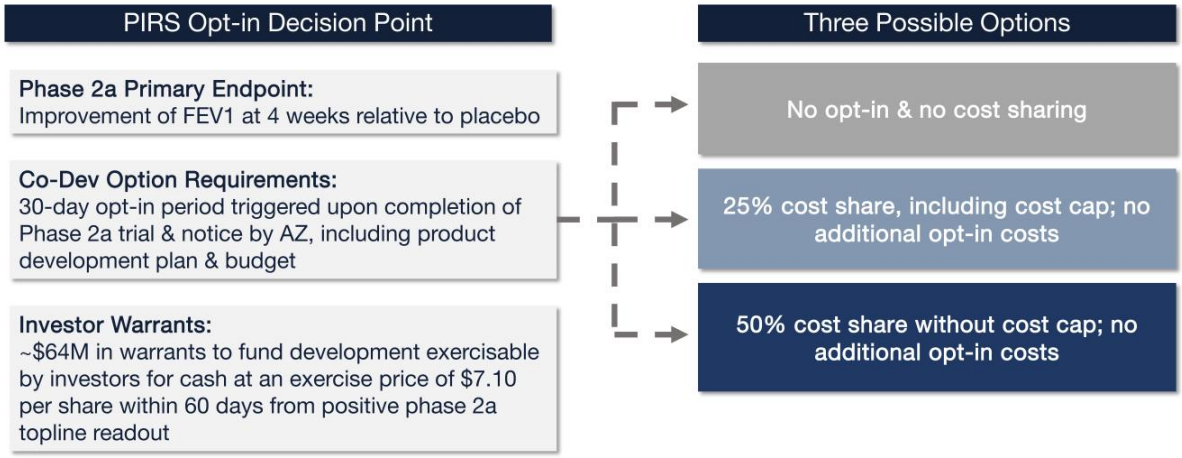
# Potential Large Market Opportunity in Moderate-to-Severe Asthma not Addressed by ICS/LABA before Injectable Biologics




ICS = Inhaled corticosteroids
SABA= Short-acting β2 adrenergic receptor agonists
LABA = Long-acting β2 adrenergic receptor agonists
LAMA = Long-acting muscarinic antagonists

Global Initiative for Asthma (GINA) Steps (2021)

# Co-Development Options for PRS-060/AZD1402



# PRS-220: Inhaled CTGF Antagonist

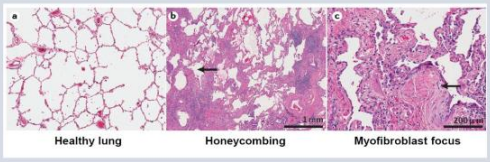
| | |
|---|---|
| Candidate | PRS-220 |
| Function/MoA | Inhibiting CTGF/CCN2 |
| Indications | IPF and PASC-PF* |
| Development | Entering phase 1 in healthy subjects this year |
| Commercial Rights | Fully proprietary |

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]

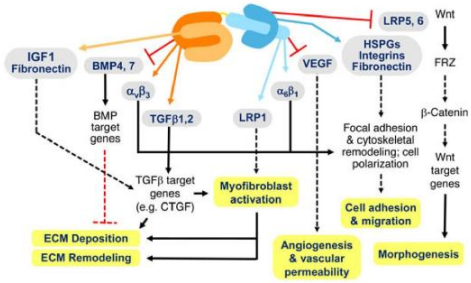
**>$3B** current market in sales

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

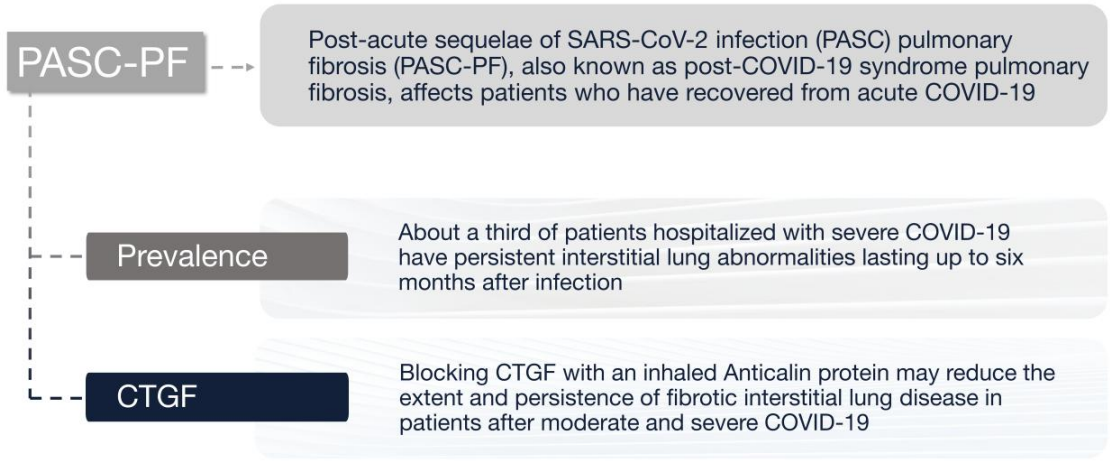
**~$17M**

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:

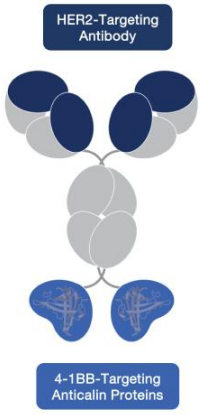
- Allow Pieris to accelerate development of the program – IND planned 2022
- Support clinical-readiness activities and initial clinical development for the program, including GLP tox studies, GMP manufacturing, and phase 1 clinical development
- Broaden scope of the program beyond the original IPF indication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

# PRS-220 for PASC-PF



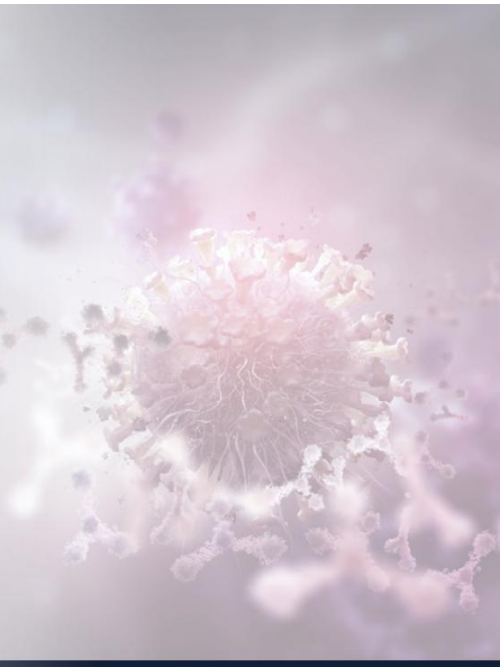
# Cinrebafusp Alfa (PRS-343): Lead IO Asset

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



## Cinrebafusp Alfa Phase 1 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
- 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

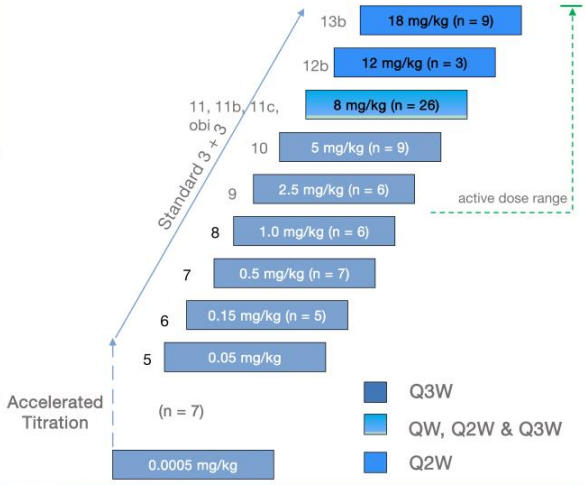
**Secondary:** Characterize PK/PD & immunogenicity
Preliminary anti-tumor activity

**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.

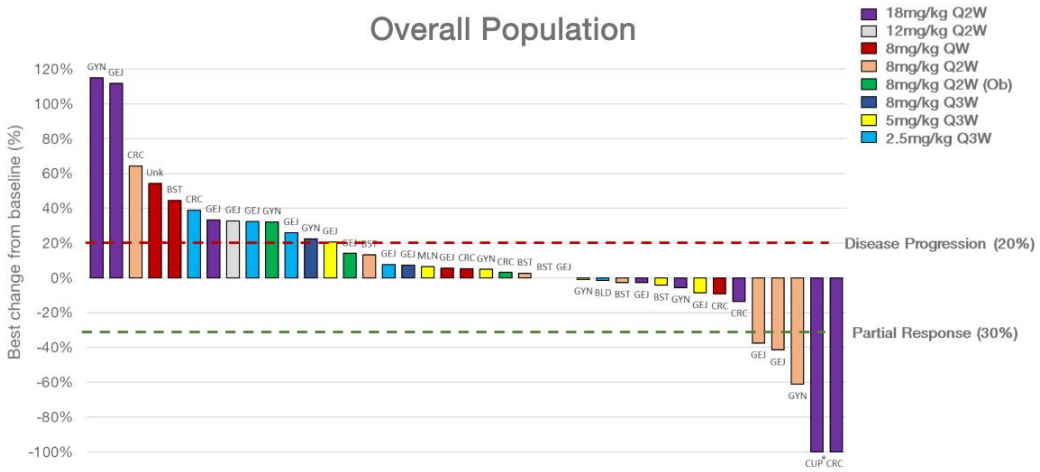
Data cut-off: 25-Feb-21

# 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% |

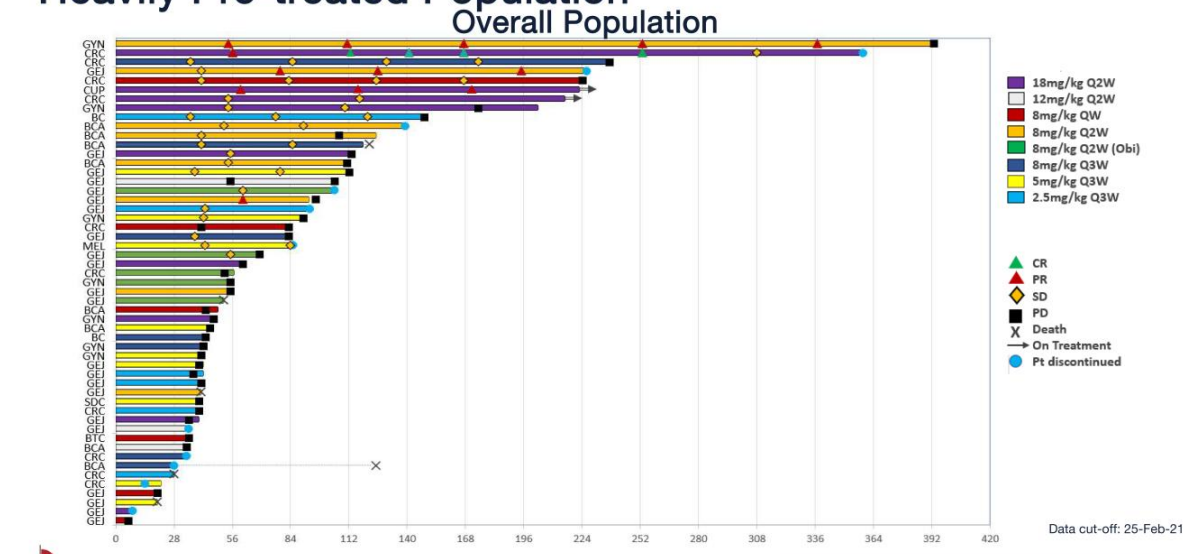
Data cut-off: 25-Feb-21

# 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

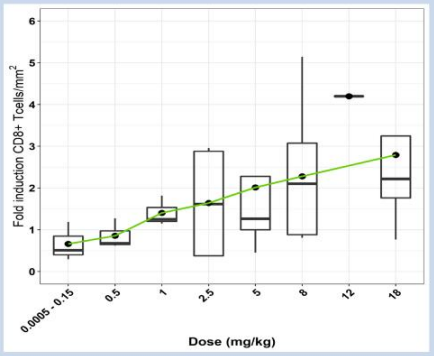
# Durable Responses with Cinrebafusp Alfa Among Heavily Pre-treated Population



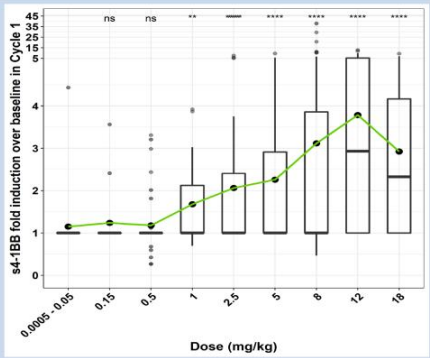

Data cut-off: 25-Feb-21

# Cinrebafusp Alfa Shows Dose-dependent Activity Across Key Pharmacodynamic Parameters

Tumor (CD8+)




Serum (s4-1BB)




Connects group averages

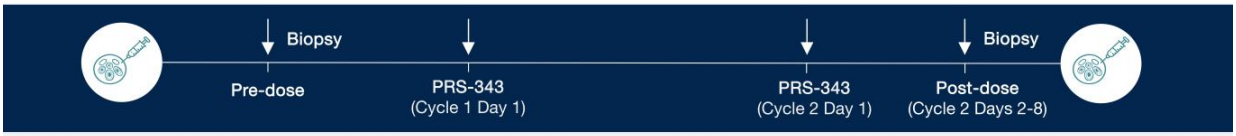
Median

Mann-Whitney U Test

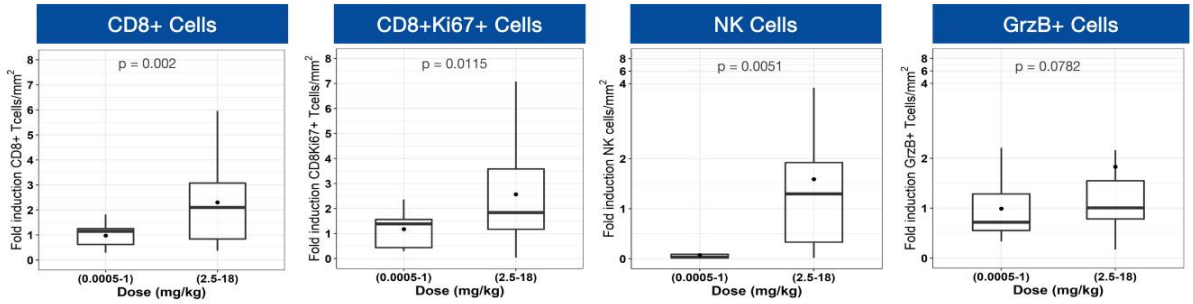
Dose at 8 mg/kg incorporates patients treated at Q1W, Q2W, or Q3W

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)



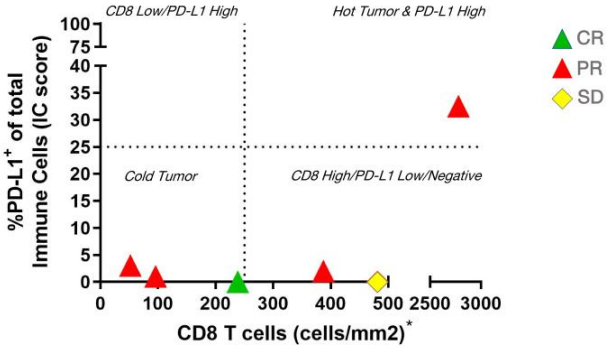

Denotes group averages
Median

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



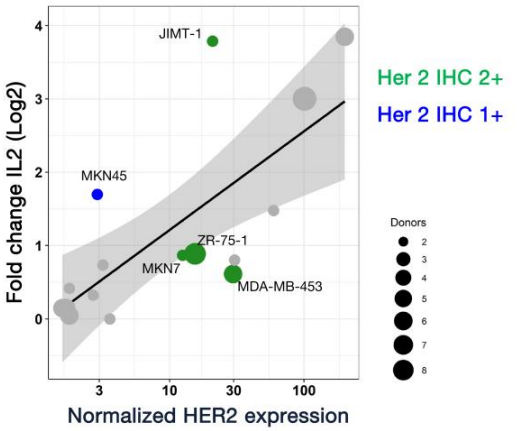

* Threshold informed by (Tumeh et al., 2014 and Blando et al., 2019)

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

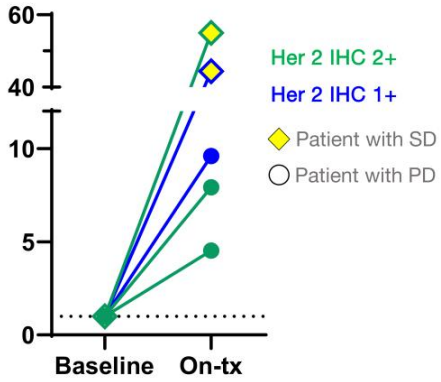
Data cut-off: 25-Feb-21

# 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**

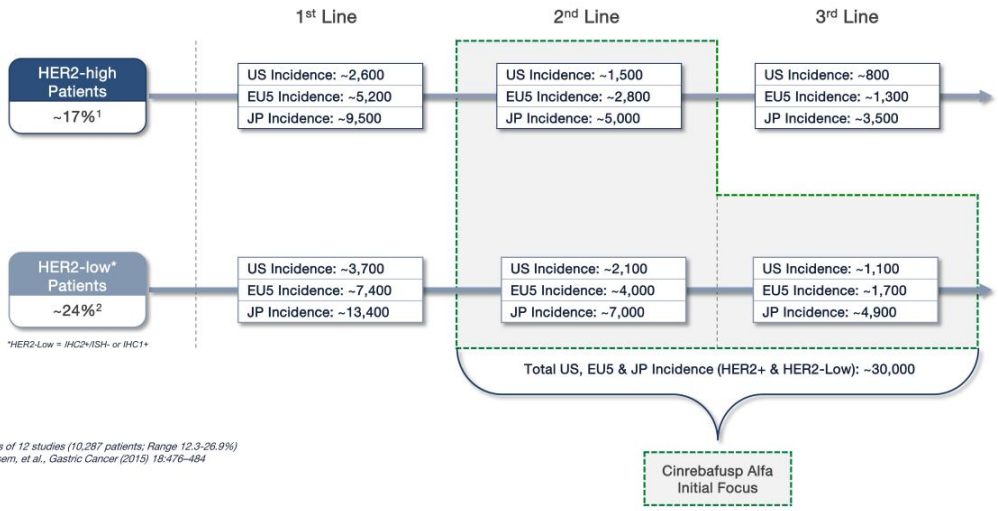



Data cut-off: 25-Feb-21

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

# Cinrebafusp Alfa Clinical Development Plan

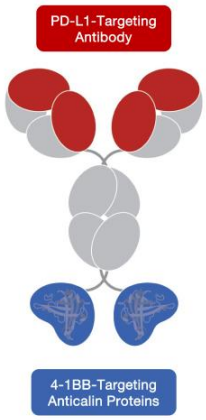
# Cinrebafusp Alfa Opportunity in HER2-High & HER2-Low Gastric Cancer




*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*

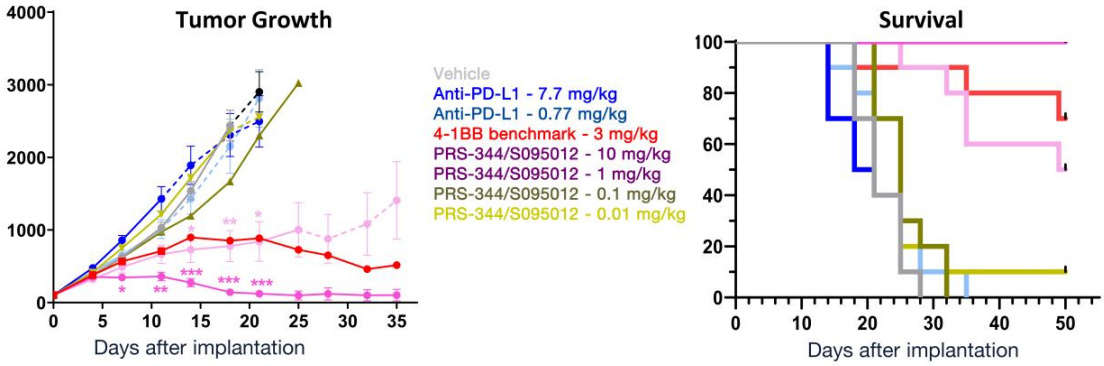
# PRS-344/S095012: Meaningfully Building on Localized MoA of Cinrebafusp Alfa

| | |
|---|---|
| Candidate | PRS-344/S095012 |
| Function/MoA | Localized 4-1BB agonism with PD-L1 antagonism |
| Indications | N.D. |
| Development | Phase 1 (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

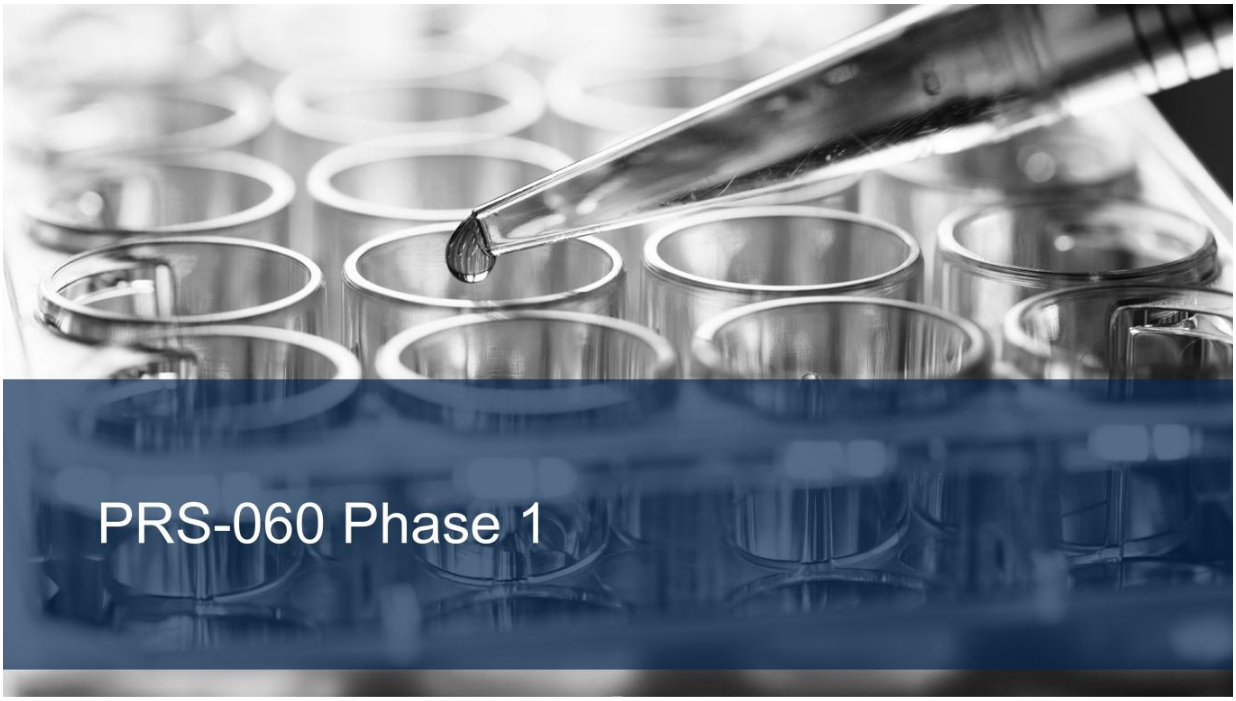
# Financial Overview (Unaudited, as of 12/31/21)

| $117.8M | $0.0 | 72.2M |
| --- | --- | --- |
| Cash & Cash Equivalents | Debt | CSO |

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

>$17M grant announced in 2021

# Appendix


PRS-060 Phase 1

# PRS-060 Phase 1 Multiple Ascending Dose Trial

| | |
|---|---|
| Strategic Objectives | Ascertain PK/PD with a reliable biomarker to confirm local target engagement and inform Phase 2 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, and 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

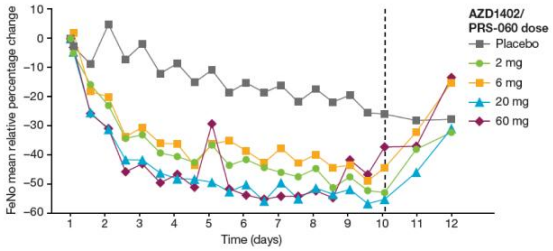
# Phase 1b Interim Results: Favorable Safety Profile

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

| System organ class<br>AE Preferred Terms[b] | Placebo<br>(N = 12)<br>n (%) m | AZD1402/PRS-060[c]<br>(N = 30)<br>n (%) m | Overall<br>(N = 42)<br>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

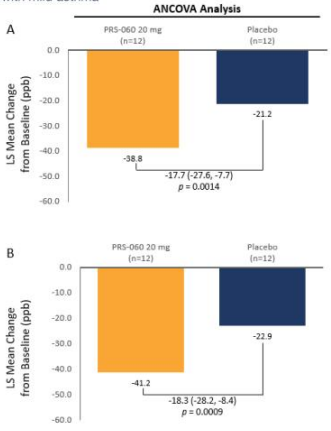
## PRS-060 Relative FeNO Reduction (Emax Analysis)




| 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 | | |

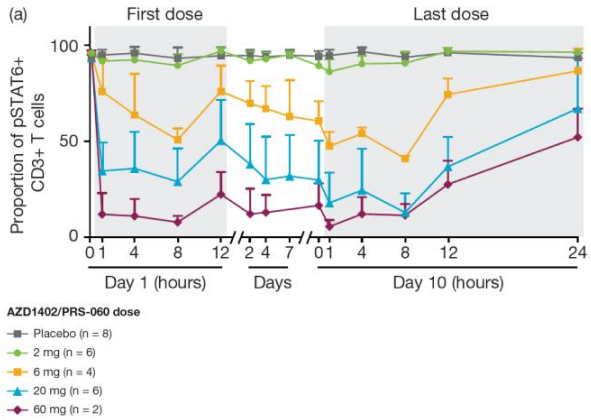
## PRS-060 Relative FeNO Reduction (ANCOVA Analysis)

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




AZD1402/PRS-060 dose

- Placebo (n = 8)
- 2 mg (n = 6)
- 6 mg (n = 4)
- 20 mg (n = 6)
- 60 mg (n = 2)

No systemic target engagement and minimal systemic exposure was observed at the 2 mg 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 1 Monotherapy

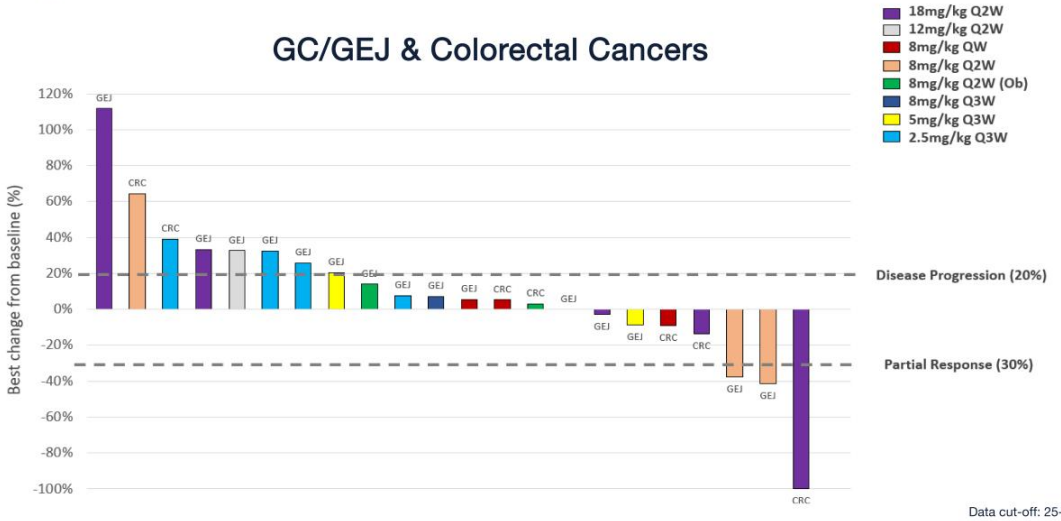
# Phase 1 Monotherapy Baseline Characteristics (N = 78)

| 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

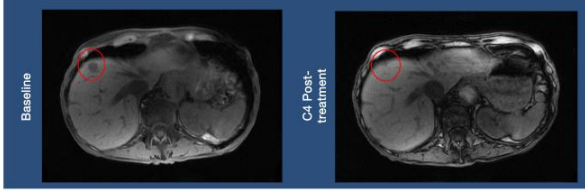
## Patient Profile, Treatment History and Treatment Outcome

**Gastric Cancer Patient with Partial Response**

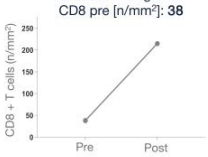
- 80-year-old woman; initial diagnosis in June 2017
- Gastric adenoca with mets to liver, LN and adrenals
- Treated with 8 mg/kg Q2W of PRS-343
- HER2 IHC 3+; PD-L1 positive (CPS=3); NGS: ERBB2 amplification

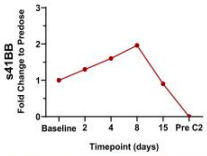
**Prior Treatment includes:**

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




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



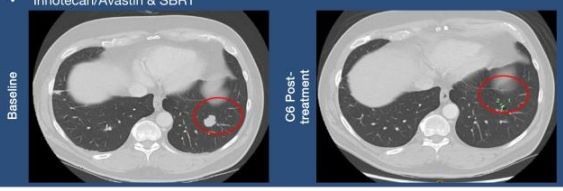




**Rectal Cancer Patient with Complete Response**

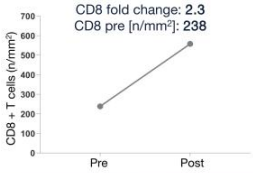
- 59-year-old male; initial diagnosis in March 2017
- Rectal cancer with cardiac and lung mets
- Treated with 18 mg/kg Q2W of PRS-343
- Foundation One Her2 amplification; verified in-house to be IHC 3+; MSS, TMB low

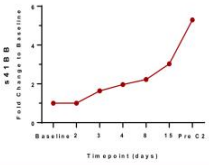
**Prior Treatment includes:**

- 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

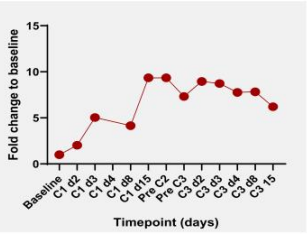
### Patient Profile

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

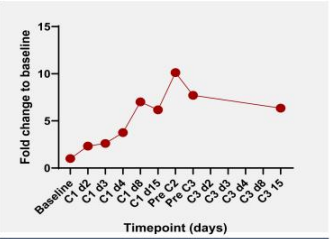
### Patient Profile

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

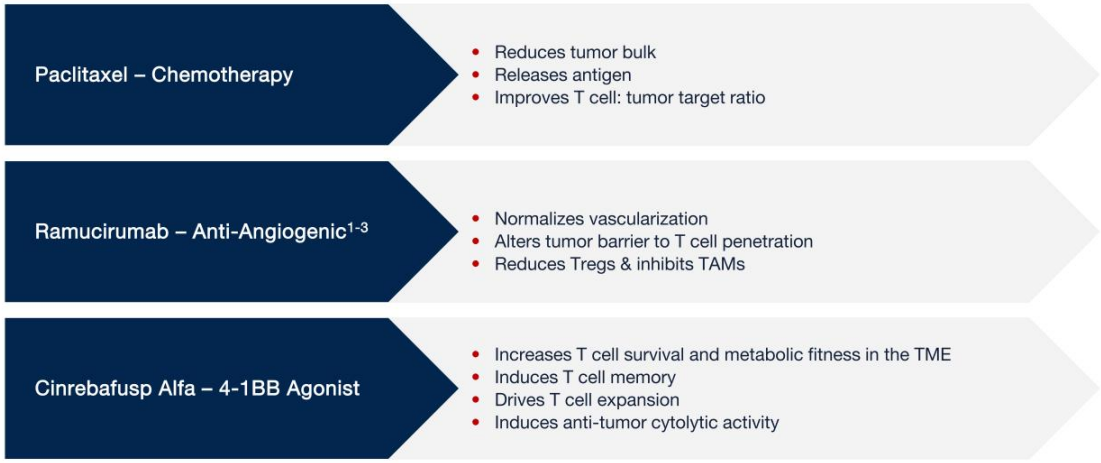
# Soluble 4-1BB (s4-1BB): Blood-based Biomarker of Cinrebafusp Alfa Engagement

- 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 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

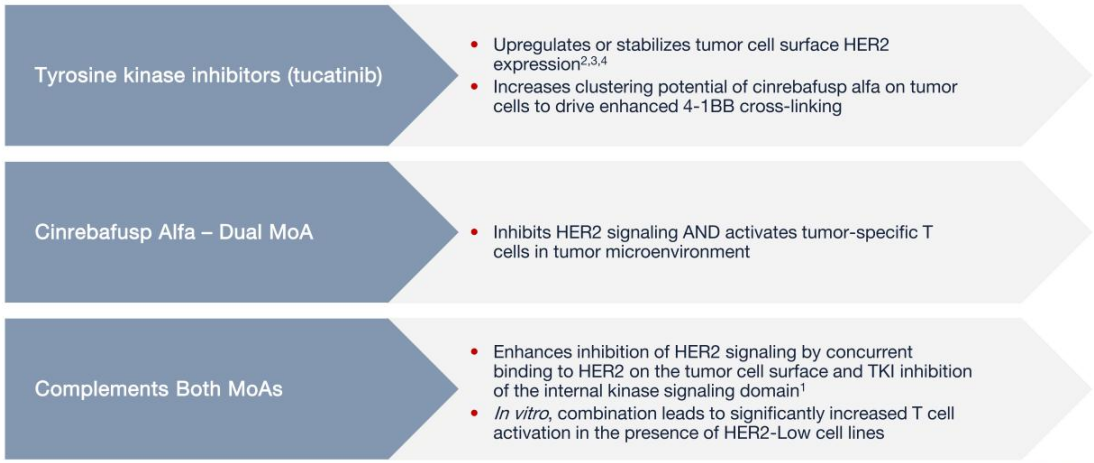
# Cinrebafusp Alfa – Phase 2 Rationale

# Scientific Rationale for Combining Cinrebafusp Alfa & SoC



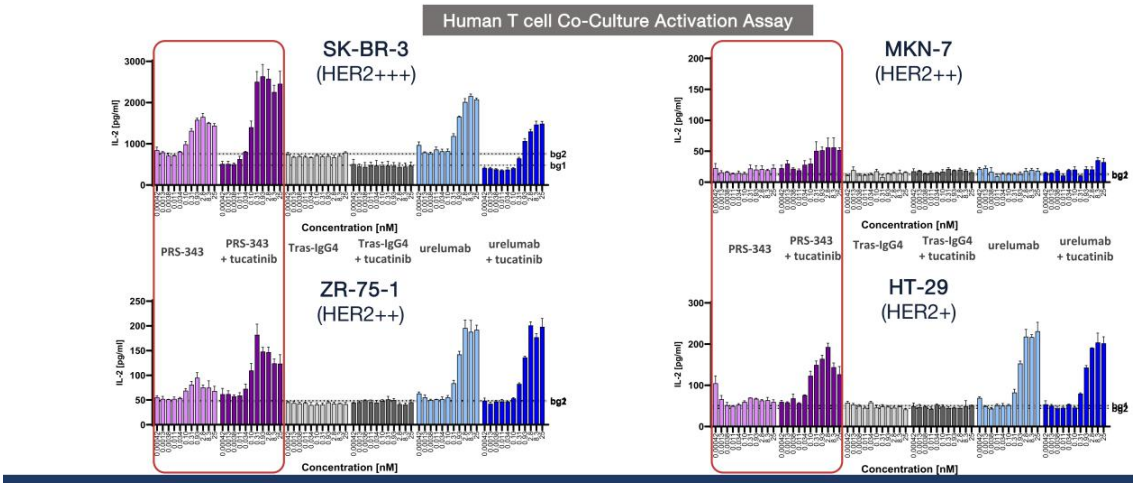

1 - Allen et al., Science Translational Medicine 2017
2 - Juang et al., Front Immunology 2018
3 - Tada et al., Journal for Immunotherapy of Cancer 2018

# Scientific Rationale for Combining Cinrebafusp Alfa & Tucatinib



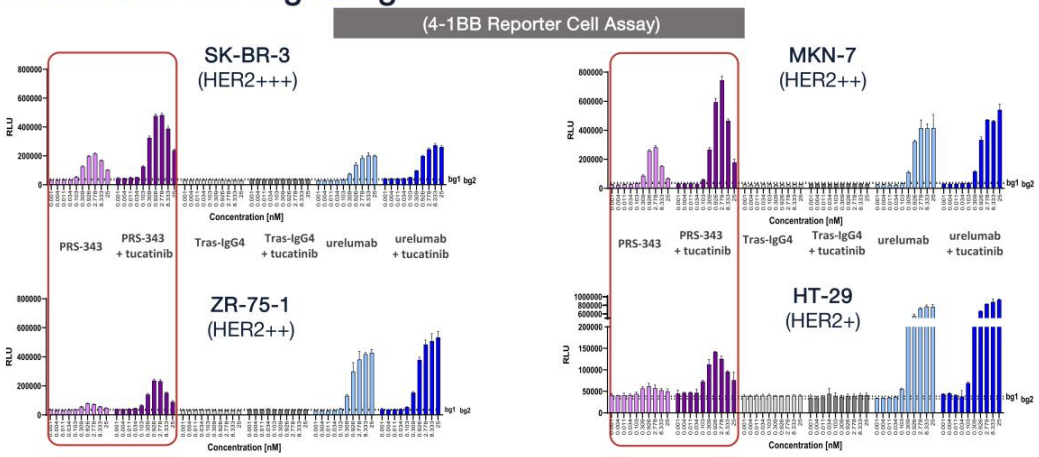

*1 - Baselga J., Lancet, 2012*
*2 - Maruyama T., et al, Anticancer Res., 2011*
*3 - Scaltriti M., et al, Oncogene, 2009*
*4 - Hartmans, et al, Oncotarget,, 2017*

# 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

255 State Street
Boston, MA 02109
USA

Zeppelinstraße 3
85399 Hallbergmoos
Germany

Nasdaq: PIRS