



What`s new and hot in pulmonary hypertension in 2025

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Abteilung für Pneumologie
II. Medizinische Klinik und Poliklinik



CENTRUM FÜR PULMONAL-ARTERIELLE HYPERTONIE
UKE HAMBURG



Speaker fees, consulting activities, support for scientific projects by:

Janssen, Astra Zeneca, Boehringer Ingelheim, GSK, Pfizer, Bayer, MSD, Berlin Chemie, Chiesi, BTG, AOP, OMT

8. November 1865 in Vienna

XXI. Jahrgang. N^o 45. 8. November 1865.

Wochenblatt

der
Zeitschrift der k. k. Gesellschaft der Aerzte
in Wien.
(Beilage zu den mediz. Jahrbüchern.)

Preis der Gesamt-Zeitschrift
ganzzählig 10 fl. ö. W.
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Pränumeration bei der Redaction (Stadt, Universitätsplatz Nr. 2), sowie durch die k. k. Postämter oder durch
die Heinrich'sche Buchhandlung in Leipzig. — Sendungen an die Redaction frankirt.

Kleine pathologisch - anatomische Mittheilungen aus der
Prosectur des Rudolf-Spitals.

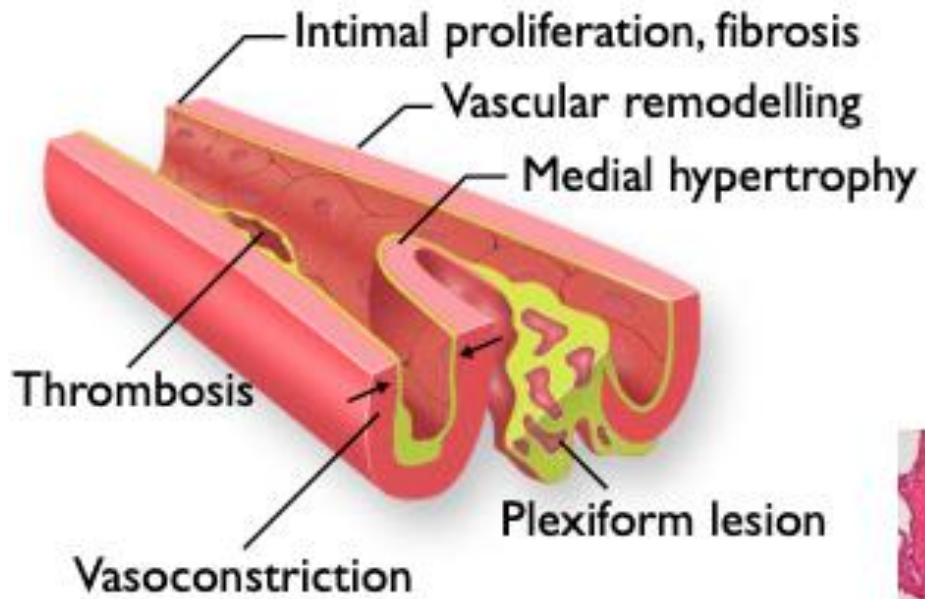
Von

Professor Dr. Julius Klob.

I. Endarteriitis pulmonalis deformans.

The term endarteritis (inflammation of the vessel) deformans is used because this term is currently used by many. The disease consists of an increase in the mass of the inner vascular skin due to the outgrowth to a pseudomembranous connective tissue formation. However, it is not always caused by inflammation alone.

Pulmonary vasculopathy

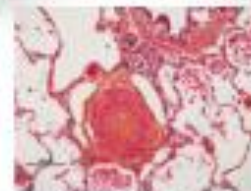


Pulmonary artery



Medial hyperplasia

Vascular obstruction



Intimal proliferation



Plexiform lesions

Right heart failure

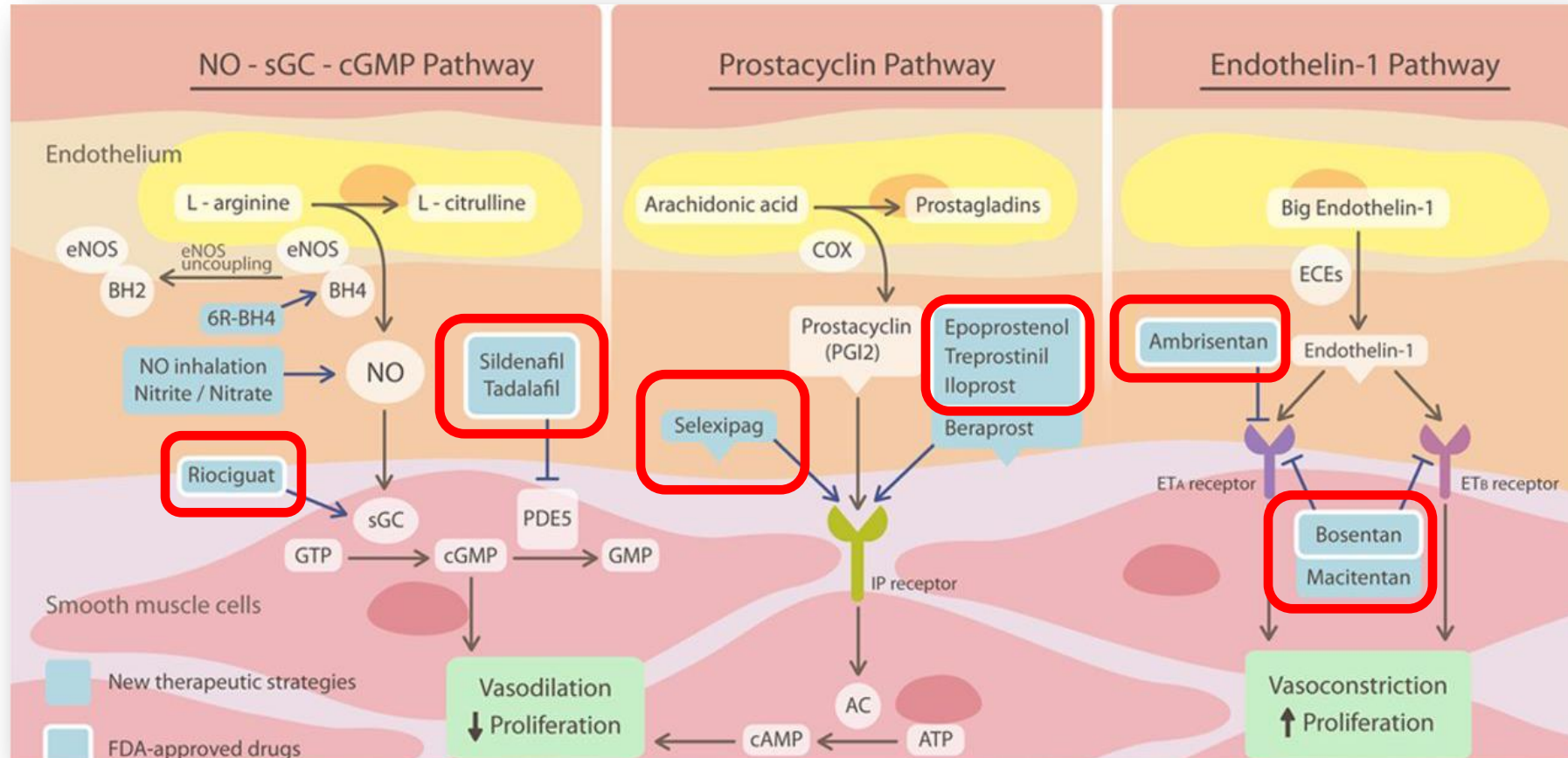


Right ventricular remodelling / dysfunction

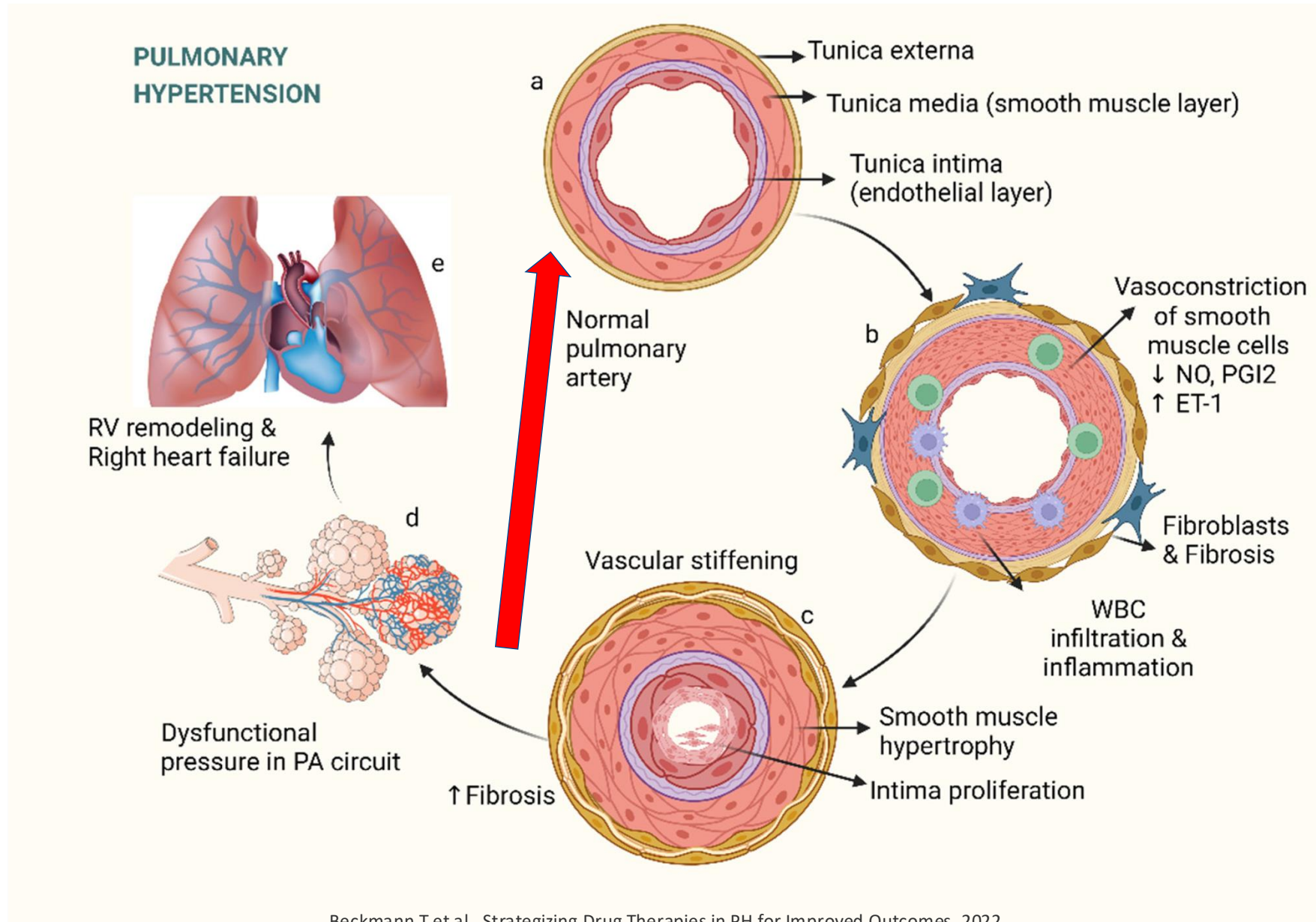
Development of targeted drugs since 1995

3 signaling pathways - 5 drug groups

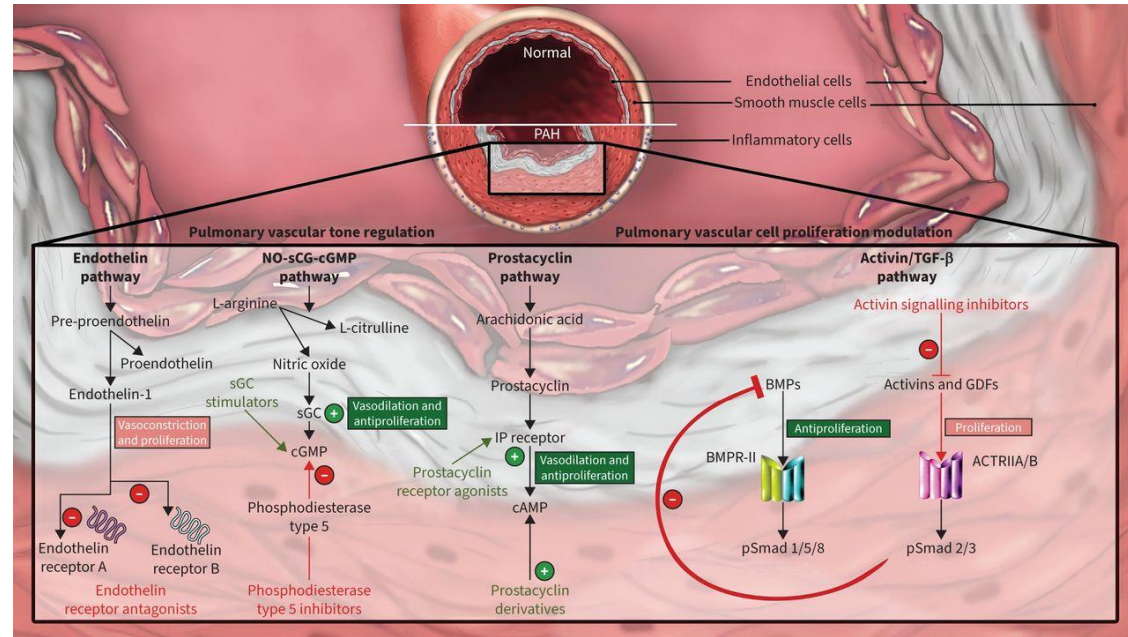
10 approved drugs



Re-remodeling as a (new) treatment goal

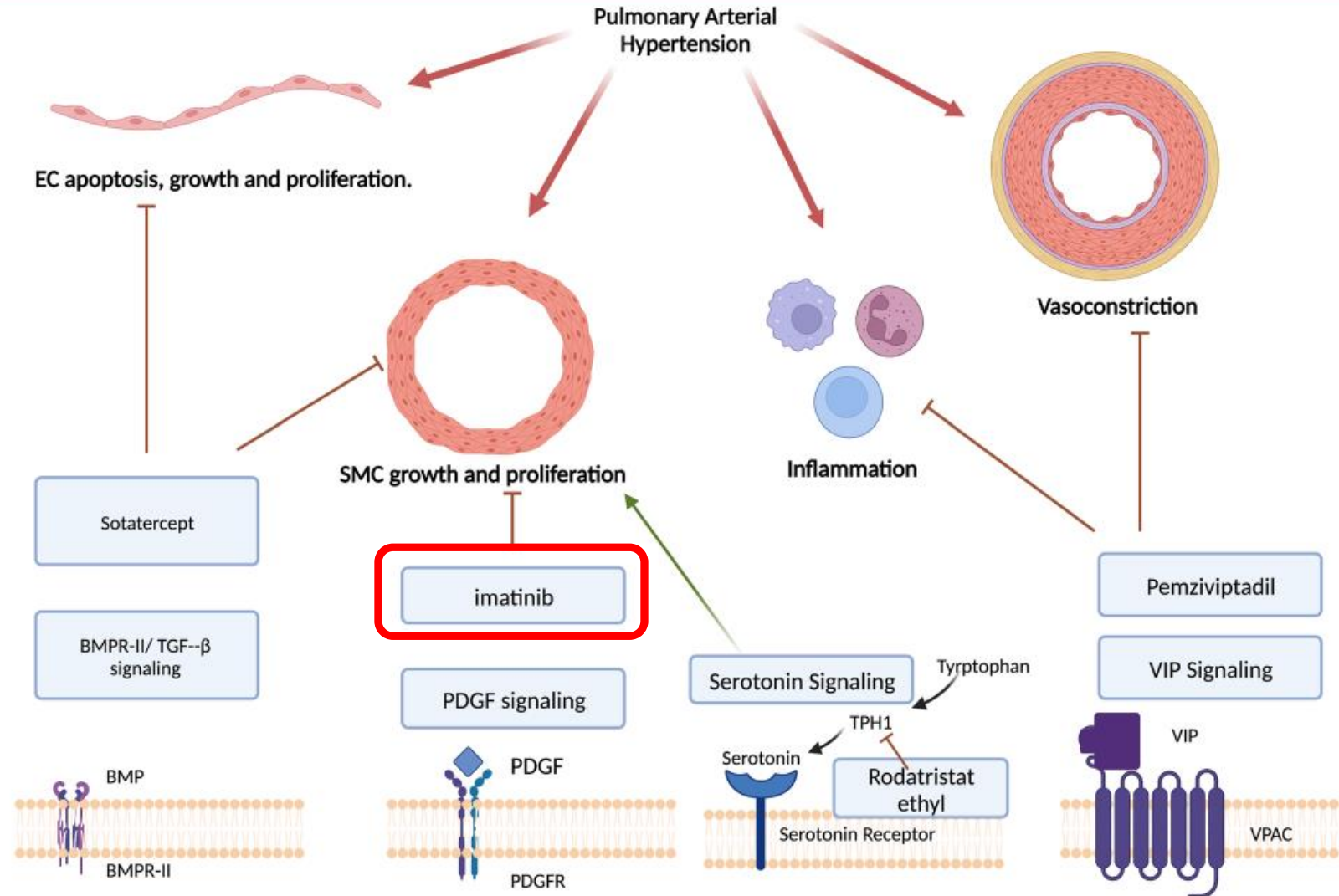


Further potential therapeutic approaches



- Vasoactive intestinal peptid (VIP Signaling)
- PDGF-Signaling (Imatinib, Seralutinib)
- BMPR II / TGF β Signaling (Activin pathway Sotatercept)
- Serotonin-Signaling
- Gen therapy

Novel Pathways

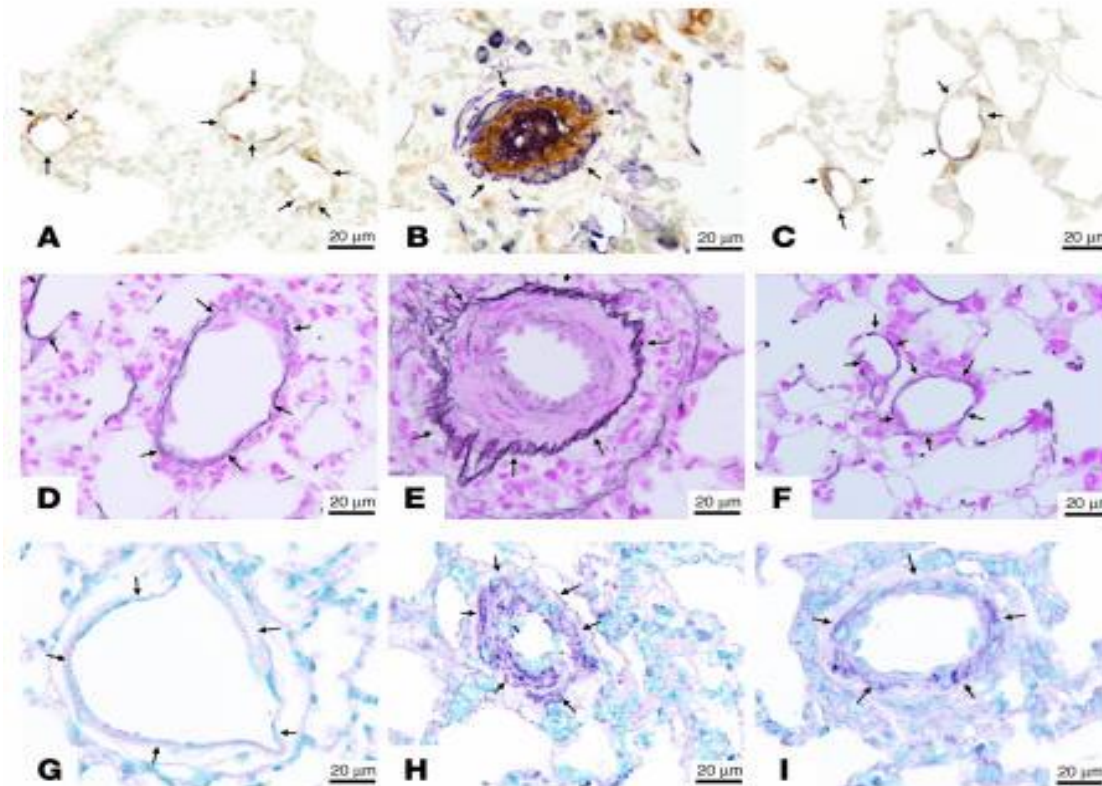




Reversal of experimental pulmonary hypertension by PDGF inhibition

Ralph Theo Schermuly, Eva Dony, Hossein Ardeschir Ghofrani, Soni Pullamsetti, Rajkumar Savai, Markus Roth, Akylbek Sydykov, Ying Ju Lai, Norbert Weissmann, Werner Seeger, and Friedrich Grimminger

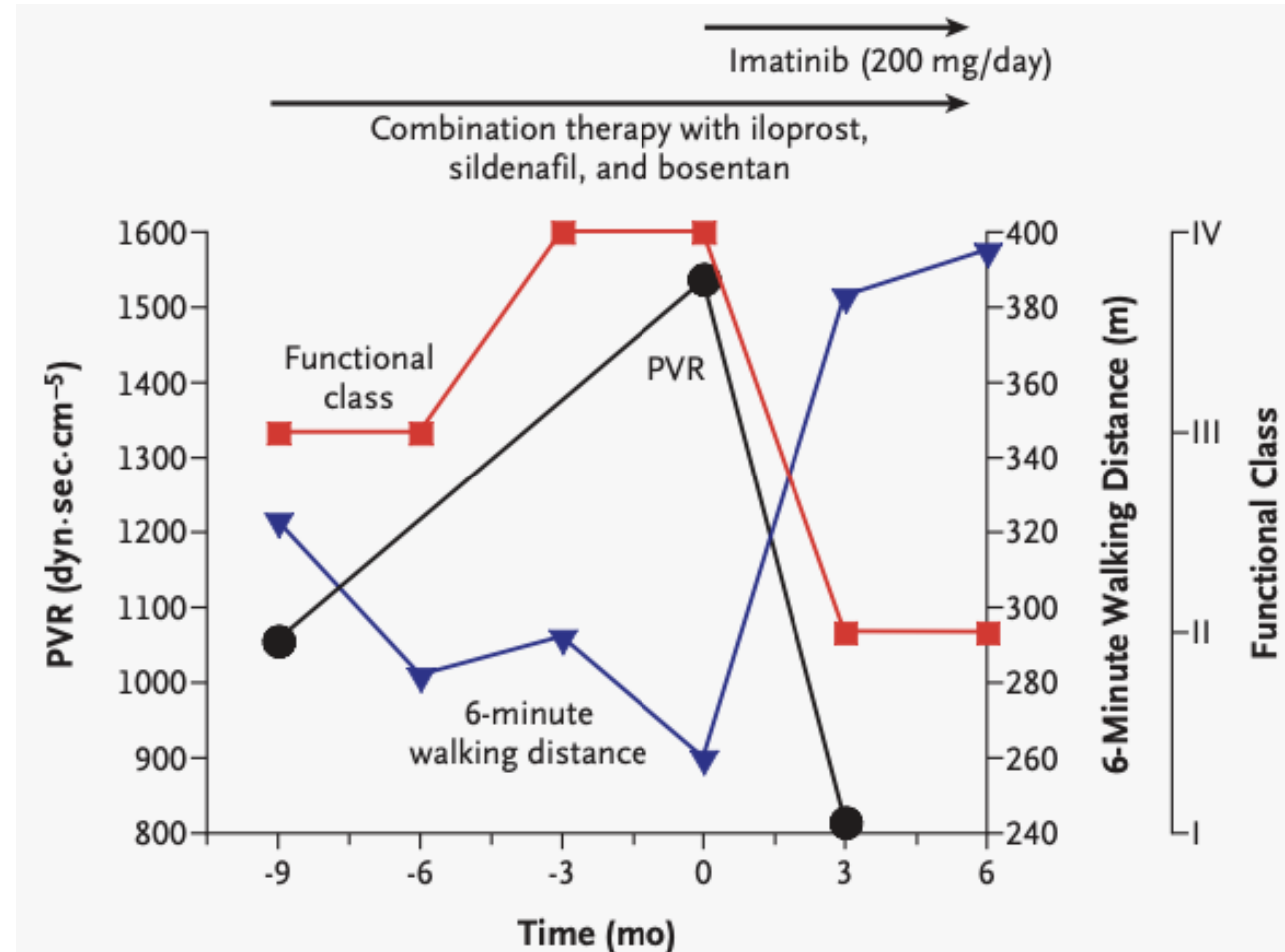
Department of Internal Medicine, Justus-Liebig-University Giessen, Giessen, Germany.



CORRESPONDENCE



Imatinib for the Treatment of Pulmonary Arterial Hypertension

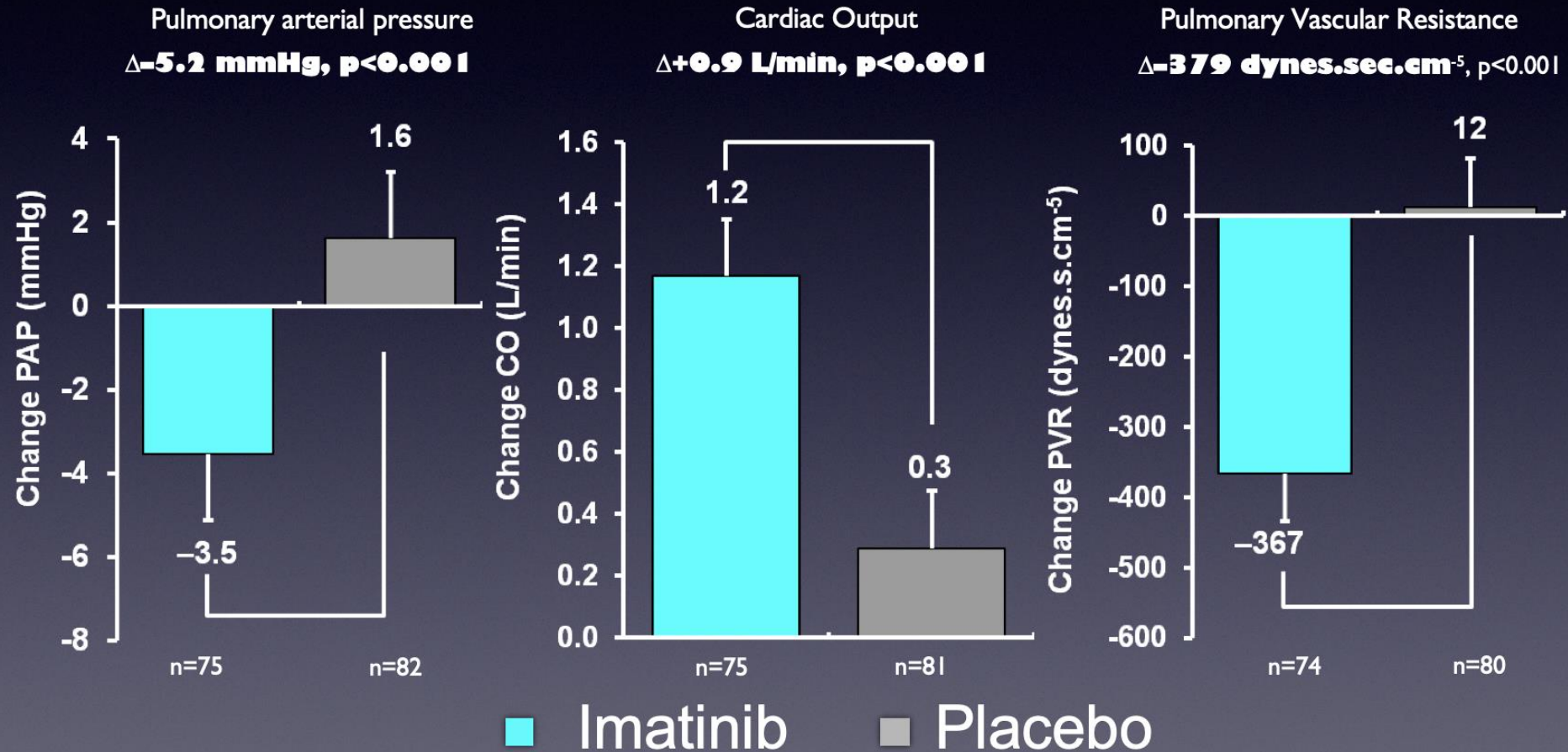


Imatinib in pulmonary arterial hypertension, a randomized, efficacy study (IMPRES)

M. Hoeper, R. J. Barst, N. Galié, P. Hassoun, N. Morrell, A. Peacock, G. Simonneau, V. Tapson, F. Torres, K. Lu, D. Quinn, H.A. Ghofrani (Hannover, Giessen, Germany; New York, Baltimore, Durham, Dallas, East Hanover, Cambridge, United States of America; Bologna, Italy; Cambridge, Glasgow, United Kingdom; Orsay, France)



Change in haemodynamics at Week 24



Positioning Imatinib for Pulmonary Arterial Hypertension: A Dose Finding
Phase 2 Study

Alexander M K Rothman^{1,2}, Sofia Villar^{3,4}, Jennifer Middleton^{1,2}, Andreas A. Roussakis⁵, Frances Varian^{1,2}, Hamza Zafar^{1,2}, Martin Law^{3,4}, Jane Apperley⁶, Imke H Bartelink^{7,8}, Medhat M Said^{7,8}, Juan A Delgado-SanMartin⁵, David G Kiely^{1,2}, Luke Howard^{5,9}, Mark Toshner¹⁰, S. John Wort^{5,11}, Martin R Wilkins⁵

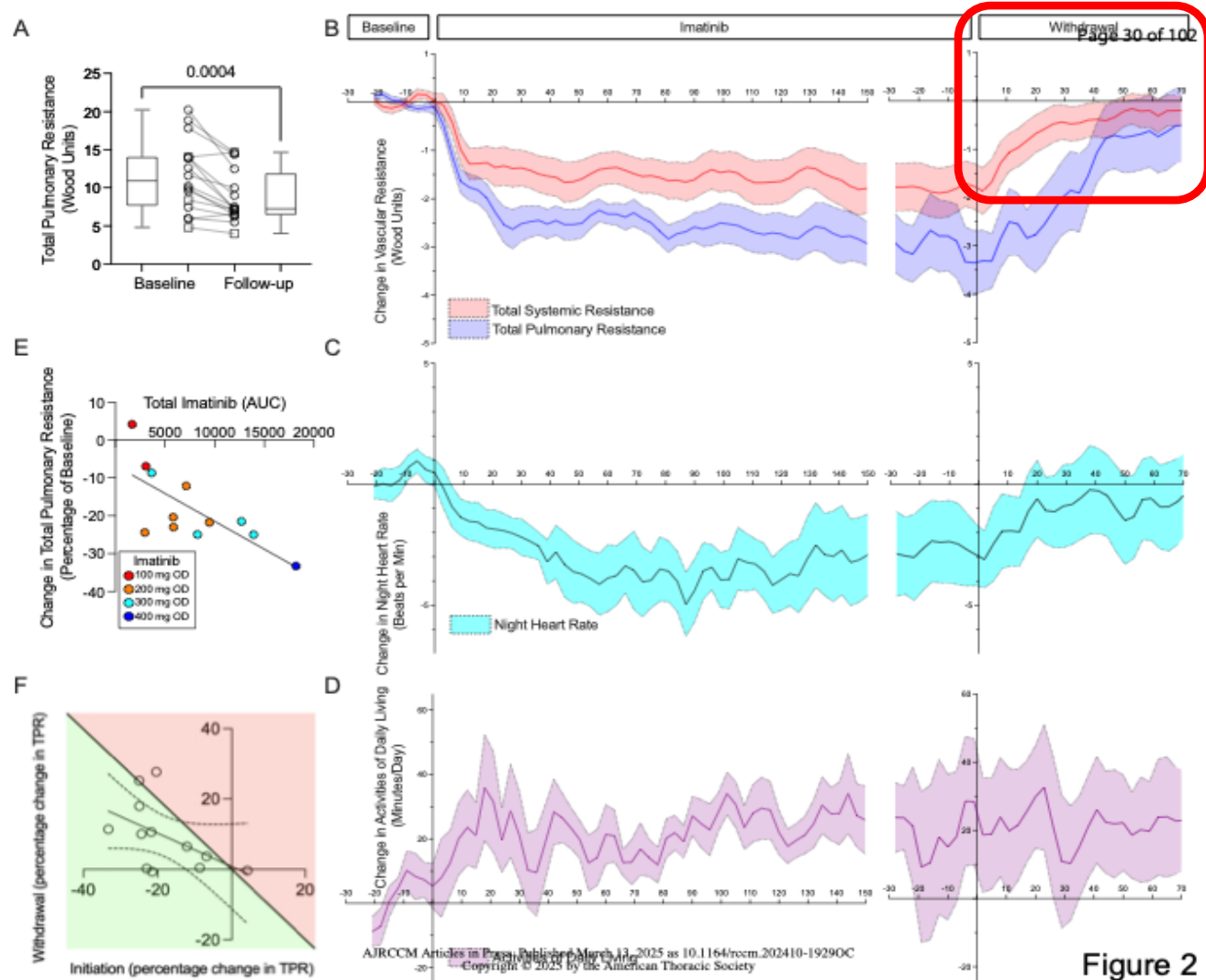
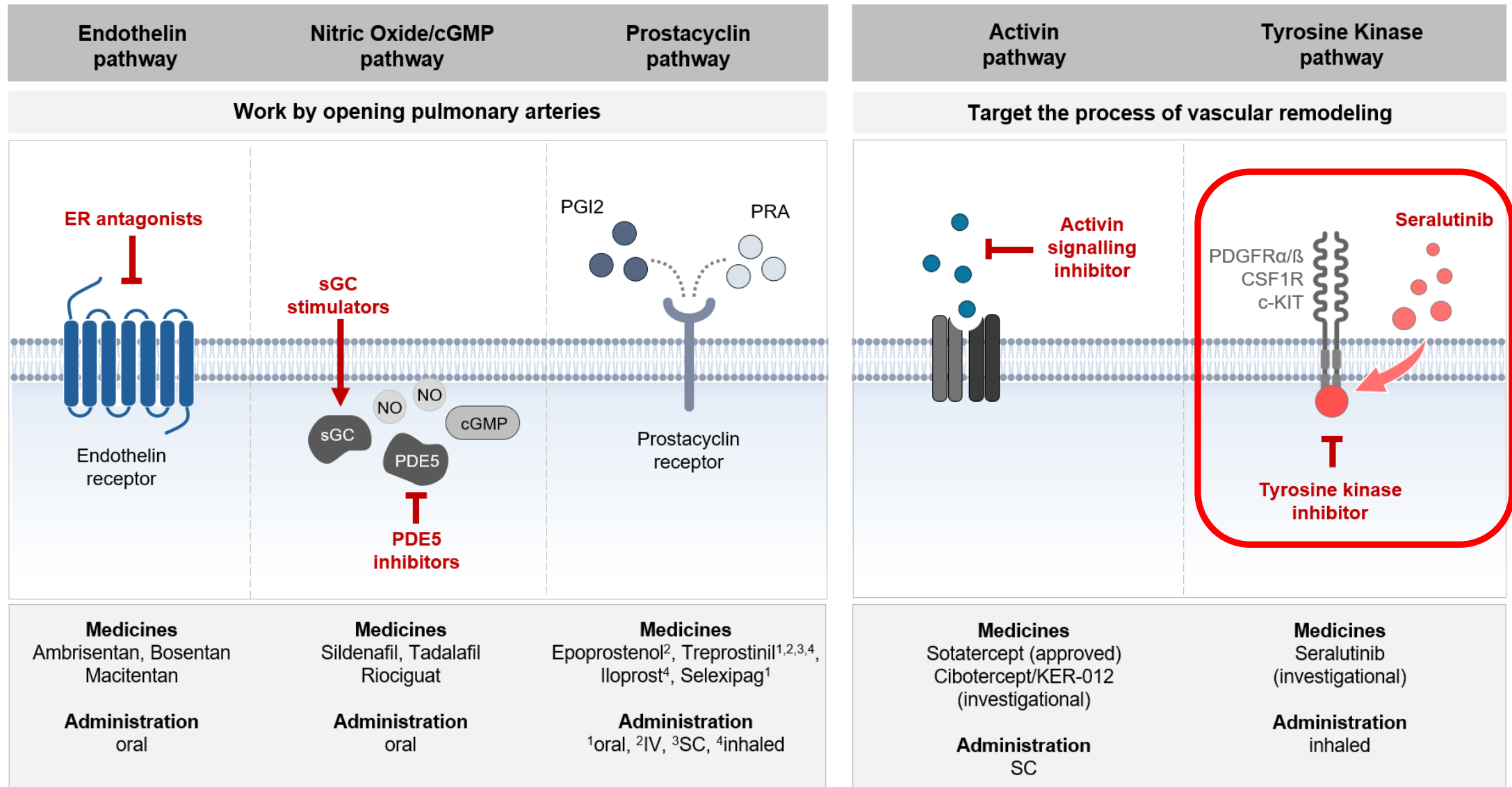
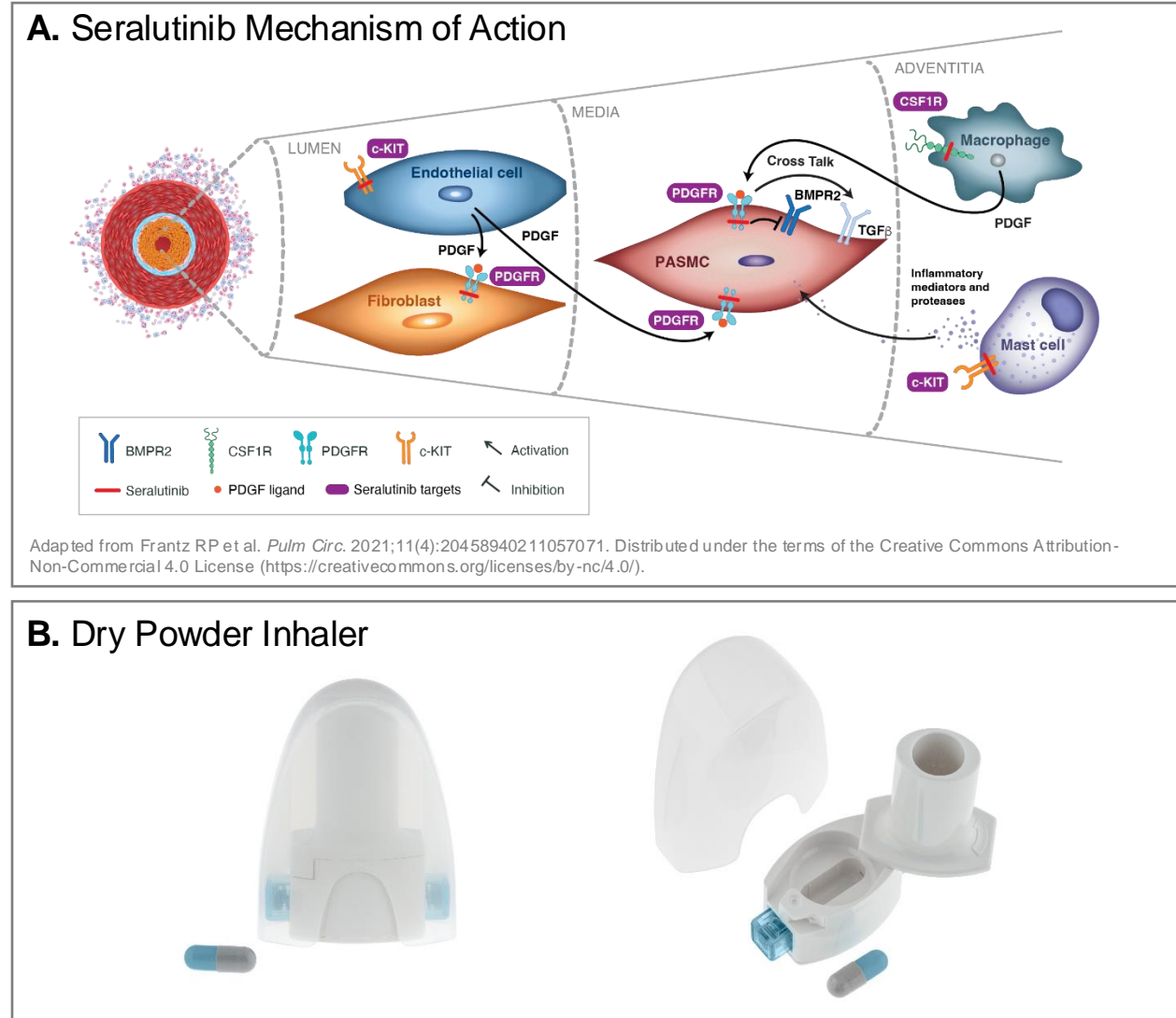


Figure 2

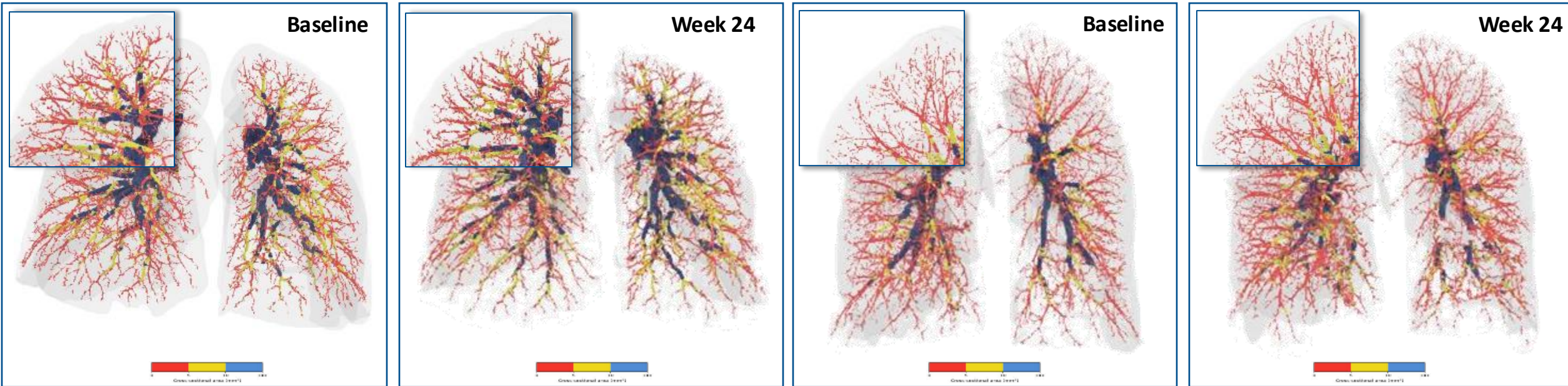
Medicines for PAH Work in Different Ways



- Potent small molecule PDGFR α/β , CSF1R, and c-KIT kinase inhibitor (**A**)
- New mechanism of action that targets inflammatory, proliferative, and fibrotic processes implicated in pulmonary vascular remodeling
- First and only tyrosine kinase inhibitor intentionally designed as an inhaled treatment for PAH
 - Administered by dry powder inhaler for deep lung deposition (**B**)
 - Low oral bioavailability and rapid clearance characteristics to minimize systemic exposure to mitigate adverse events



Examples of Imaging (Torrey Study): Placebo vs. Seralutinib



Placebo patient

Female, 24 y, iPAH, FC II, treated with PDE5-i + prostacyclin

PVR change, $\text{dyne} \cdot \text{s} / \text{cm}^5$ (%)	283 (+65.4)
$\Delta\text{BV510ARatio}$ (% change)	-0.70 (-28.9)

Seralutinib patient

Female, 58 y, iPAH, FC II, treated with ERA + PDE5-i + prostacyclin

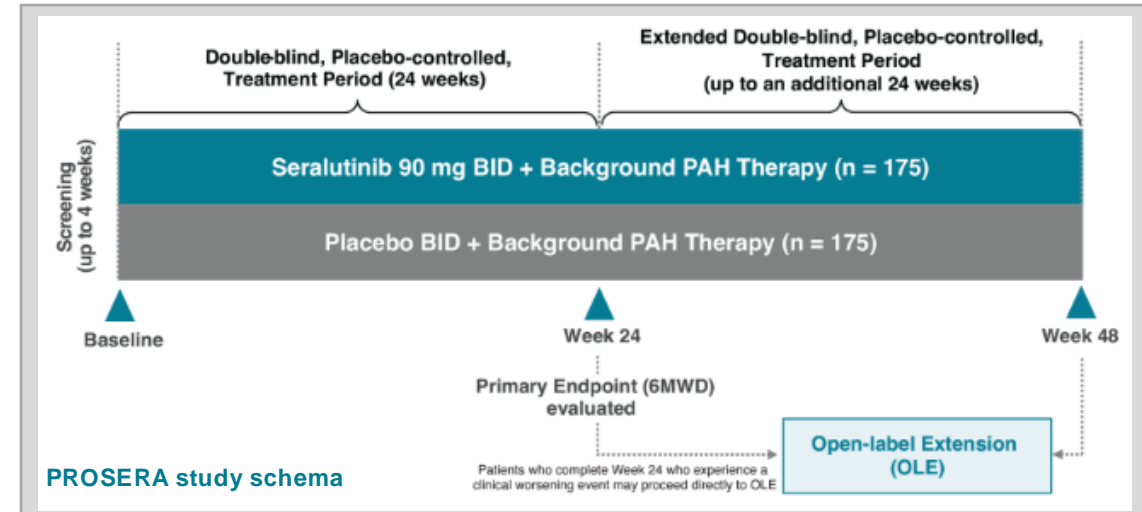
PVR change, $\text{dyne} \cdot \text{s} / \text{cm}^5$ (%)	-159 (-39.0)
$\Delta\text{BV510ARatio}$ (% change)	+2.5 (+78.0)

The images shown are representative examples. The highlighted sections were chosen to illustrate changes in the pulmonary vasculature.

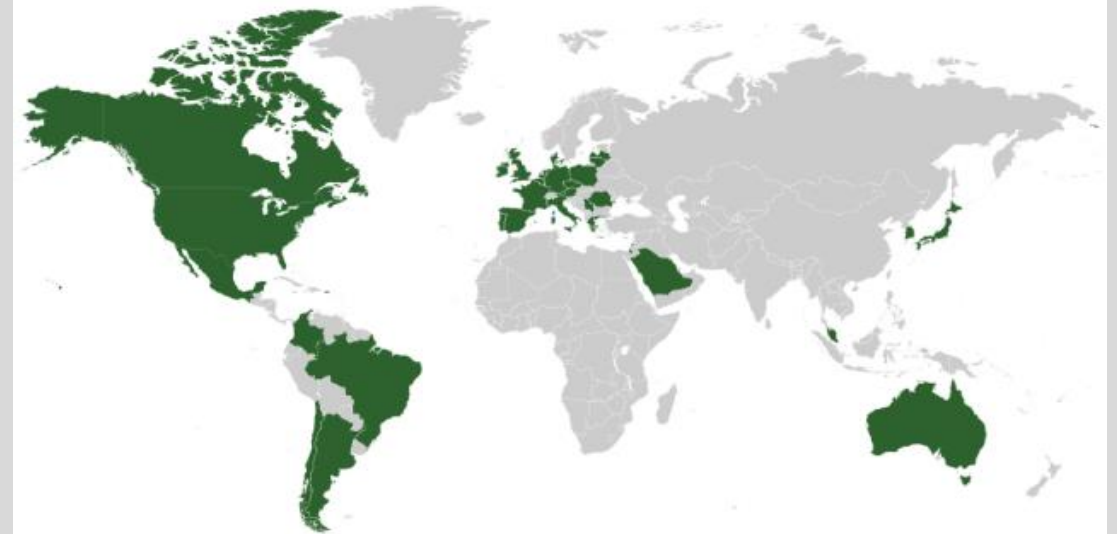
- Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of inhaled seralutinib
- 350 patients to be enrolled at ~160 sites globally
- Eligible patients randomized 1:1 to receive seralutinib or placebo BID by dry powder inhalation

Key Inclusion Criteria

- Adults ≥ 18 and ≤ 75 years old
- WHO Group 1 PH
- WHO FC II or III
- $PVR \geq 400 \text{ dyne}\cdot\text{s}/\text{cm}^5$
- Baseline 6MWD 150 – 475 m
- Either REVEAL Lite 2 Risk Score ≥ 5 **OR** NT-proBNP $\geq 300 \text{ ng/L}$ **OR** $PVR \geq 800 \text{ dyne}\cdot\text{s}/\text{cm}^5$
- Stable treatment with at least one SOC PAH background therapy

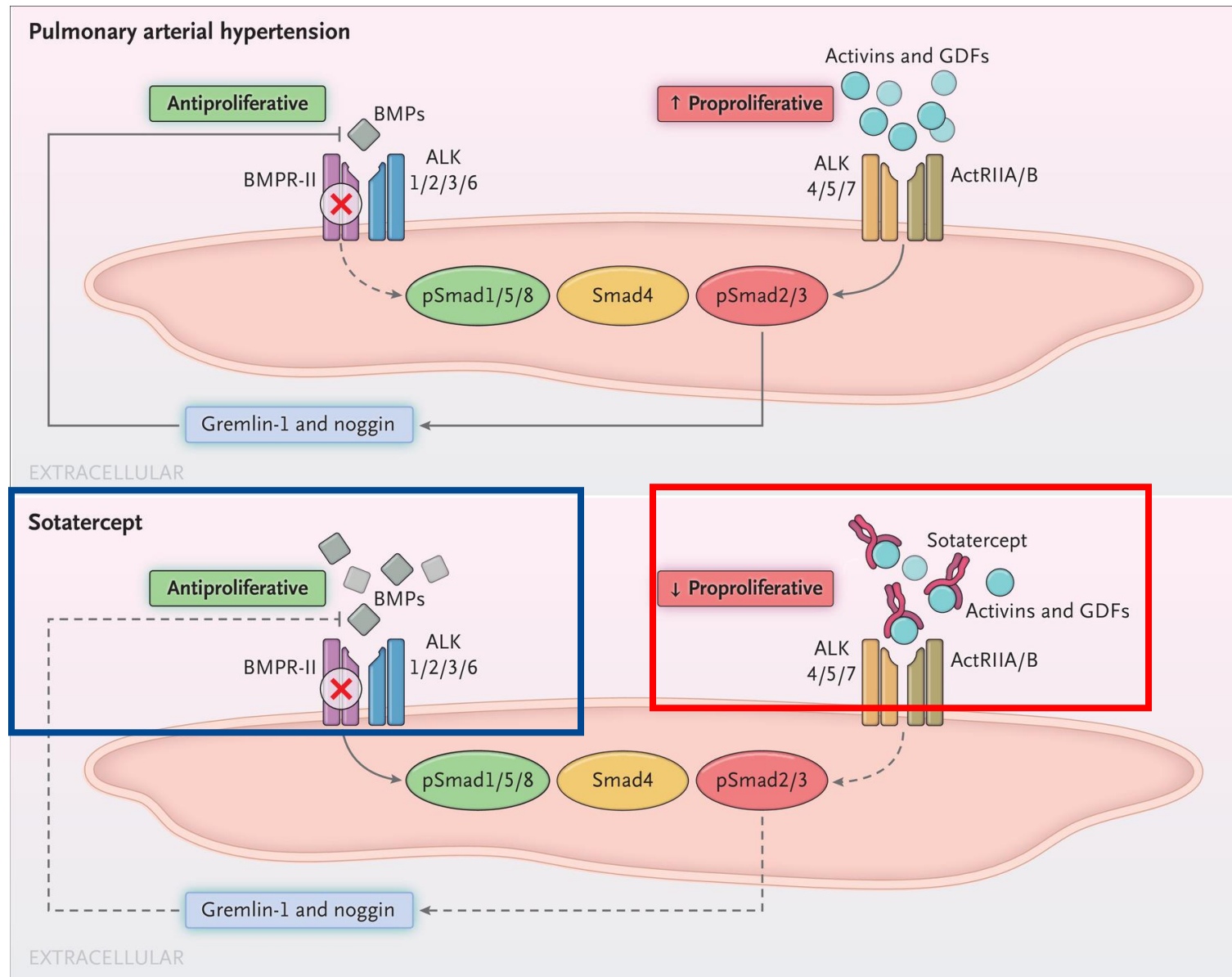


PROSERA study schema

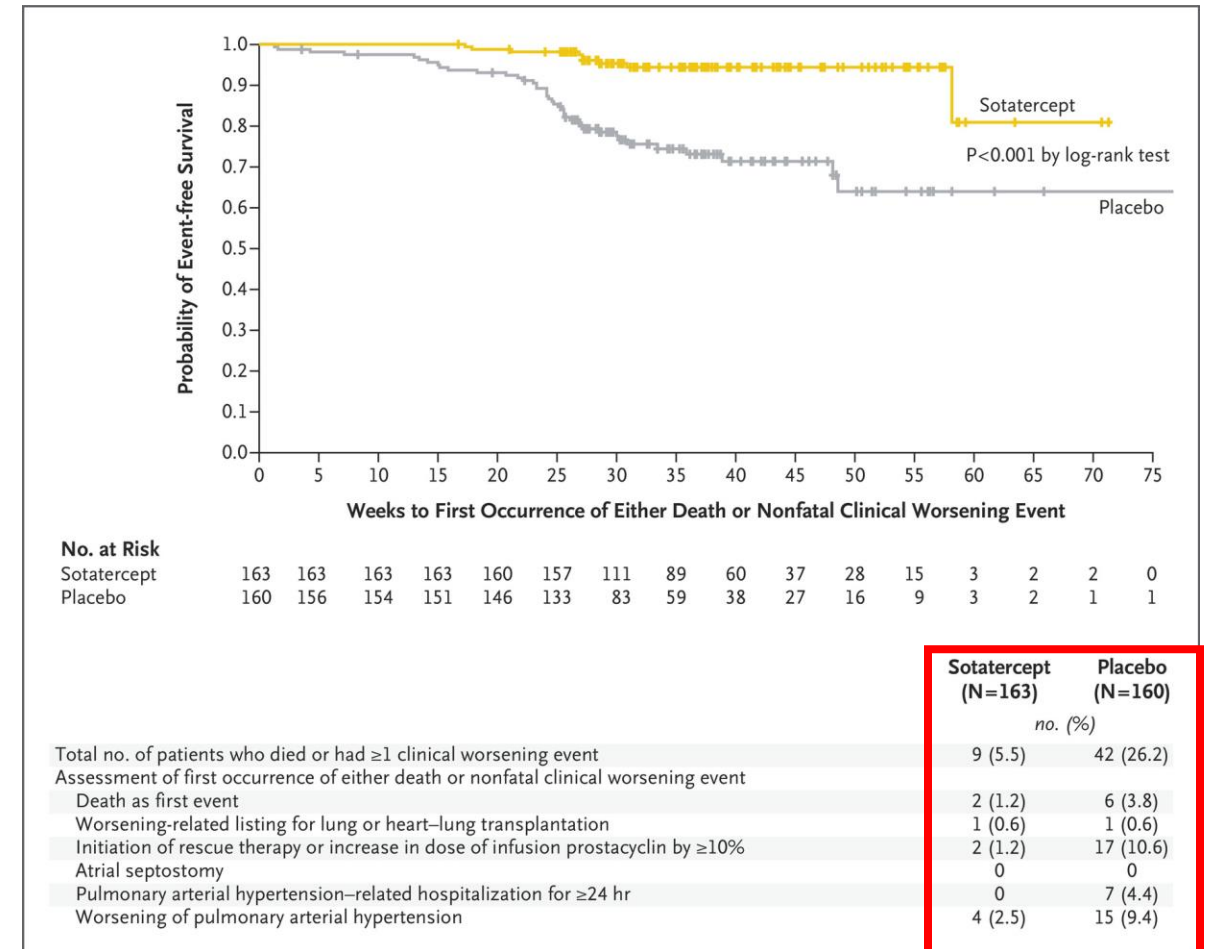
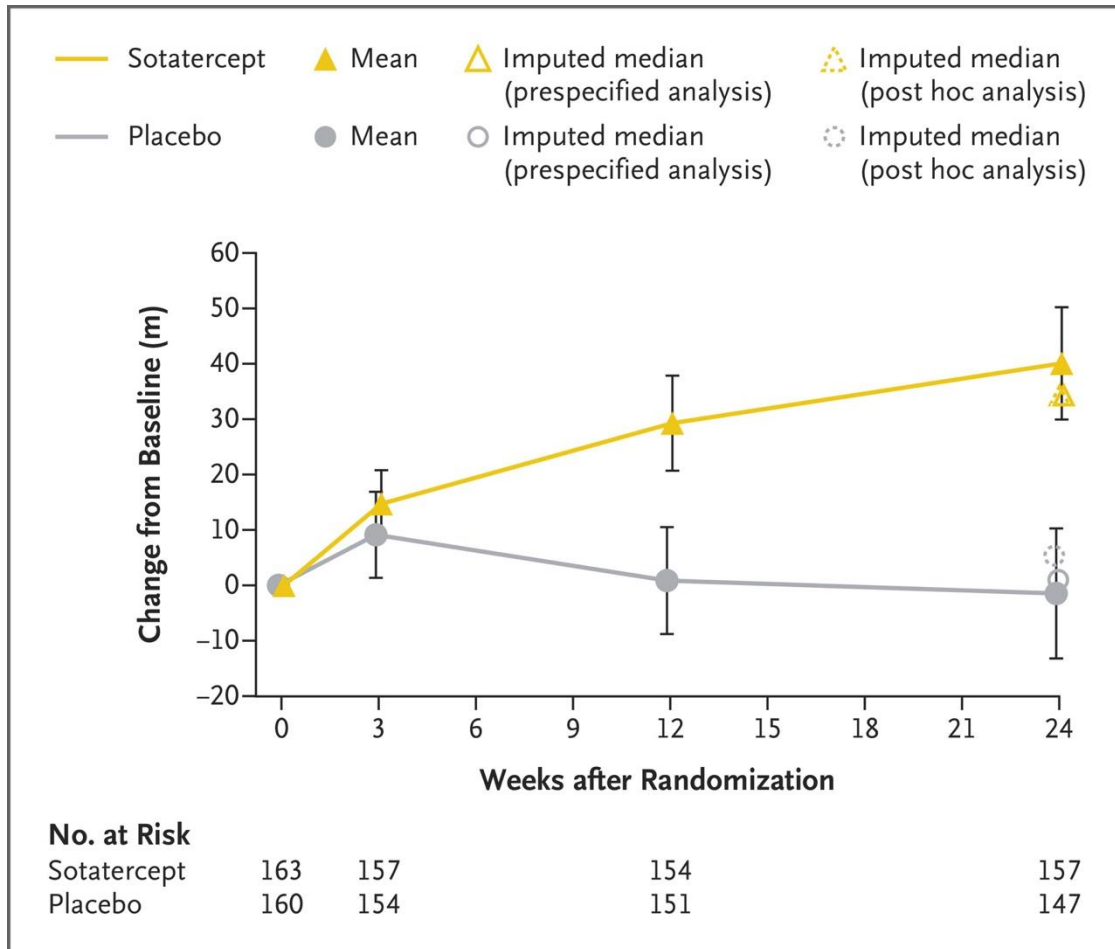


Countries with PROSERA study sites

Mechanism of action of sotatercept: effects at the molecular level



STELLAR trial results (selection)



KEY POINTS

- Merck is buying Acceleron Pharma for about \$11.5 billion, broadening its portfolio beyond aging cancer drug Keytruda with potential treatments that could bring in fresh revenue.
- The deal gives Merck access to Acceleron’s rare disease drug candidate, sotatercept, which the company expects to be a multi-billion dollar peak sales opportunity, and comes as Keytruda moves toward the loss of market exclusivity in 2028.
- Sotatercept is currently in a late-stage study, testing it as a treatment for a rare cardiovascular disease called pulmonary arterial hypertension (PAH), a type of high blood pressure that affects blood vessels in the lungs. Merck sees PAH as a roughly \$7.5 billion market by 2026.

In this article

MRK -0.10 (-0.11%) 🌙 +

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MERCK (MRK)	75.38	+0.29	[+0.39%]
ACCELERON INC (XLRN)	175.65	+0.29	[+0.17%]

VIDEO 02:04
MERCK DEAL VALUES
ACCELERON AT \$11.5B
Merck to acquire Acceleron Pharma in \$11.5 billion deal

Nov 25, 2024 6:45 AM Eastern Standard Time

Merck Announces Pivotal Phase 3 ZENITH Trial Evaluating WINREVAIR™ (sotatercept-csrk) Met Primary Endpoint at Interim Analysis

Share      ...

WINREVAIR met primary endpoint of time to first morbidity or mortality event for the treatment of patients with pulmonary arterial hypertension (PAH) functional class III or IV at high risk of mortality

Study to be stopped early and participants will be offered the opportunity to receive WINREVAIR

Second positive phase 3 trial adds to growing body of evidence for WINREVAIR, an activin signaling inhibitor therapy that targets an underlying cause of PAH

Like ‘a miracle’

In July 2019, Barry had rented an apartment for the summer in Greece, where she was looking forward to volunteering at a children’s hospital. But while she was abroad, some shortness of breath that she had been asking doctors about for more than two years suddenly worsened.

Barry was diagnosed shortly after her surgery in October 2019, and she jumped at the chance to try sotatercept in the spring of 2020. The improvements weren’t instant, but after a few months, she went from not being able to even fold her laundry to being able to do a little more. She was able to go for short hikes and kayak a bit.

After a year, Barry said, she was able to come off her continuous oxygen therapy and use it only at night. She was eventually able to stop using it at night, too.

After about 18 months, doctors were able to remove her central line and the bulky, ever-pr CNN logo pump, allowing her to switch from the IV versions of her vasodilating drugs to the pill forms.

“For me, that was so life-changing,” Barry said.

FDA approves new drug that may help stop a rare, fatal condition that doctors call a ‘ticking time bomb’

By Brenda Goodman, CNN
11 minute read · Updated 1:37 PM EDT, Wed March 27, 2024



Doctors diagnosed Katrina Barry with pulmonary arterial hypertension after she had a heart attack at age 25, courtesy Katrina Barry



Katrina Barry hiking in Greece in 2022 courtesy Katrina Barry

A new day has come: Sotatercept for the treatment of pulmonary arterial hypertension



Thomas M. Cascino, MD, MSc,^a Sandeep Sahay, MSc,^b Victor M. Moles, MD,^a
and Vallerie V. McLaughlin, MD^a

Cascino et al. Sotatercept for PAH

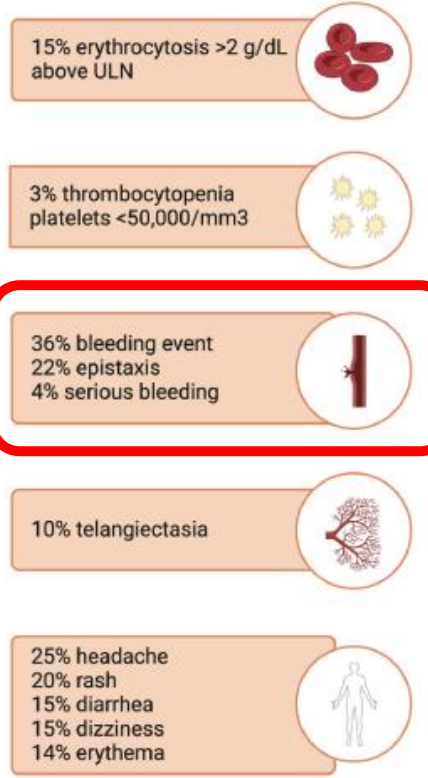
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Sotatercept for the management of pulmonary arterial hypertension

Benefits



Adverse Events



Key Unknowns



- Sotatercept first antiproliferative therapy option, very effective but:
 - do not forget established therapy
 - Long-term side effects not know
 - There are further promising ideas



Thank you for your attention and best regards from Hamburg

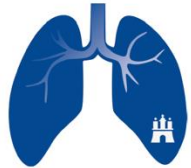


Questions ?





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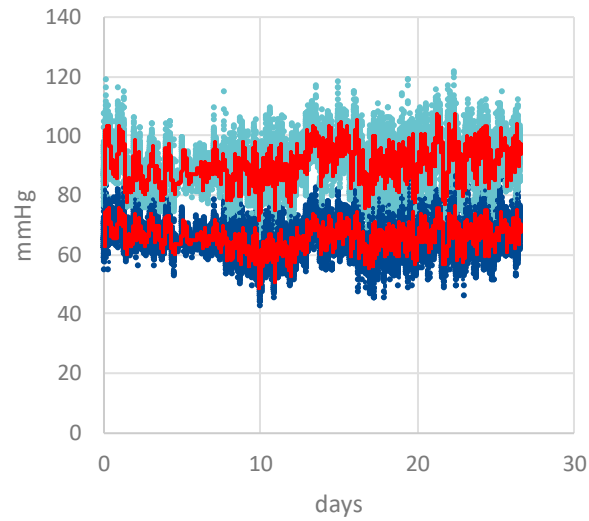
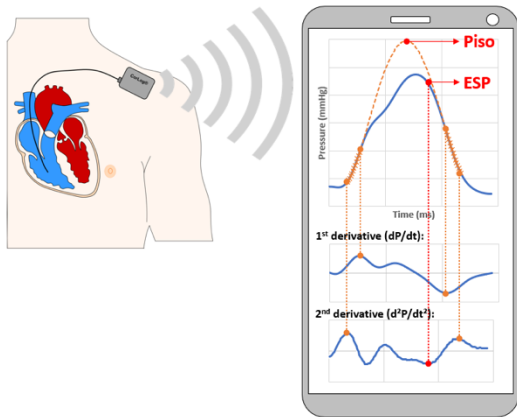
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***Personal Diagnostics:
The future of medicine?***

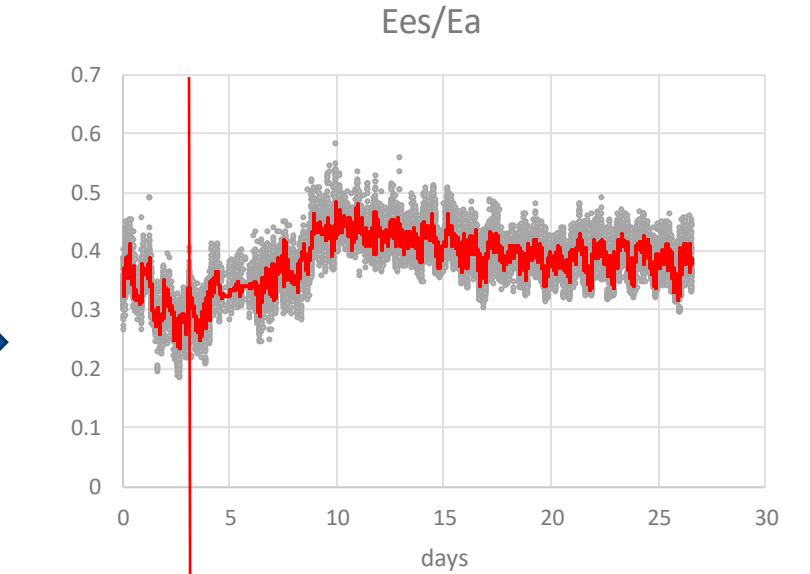


Pressure based analysis of Treprostinil Titration



• EESP • PMAX

$$\frac{Ees}{Ea} = \frac{Piso}{ESP} - 1$$



Start Treprostinil i.v.