Genetic background: differential response to Sotatercept?

Pr David MONTANI

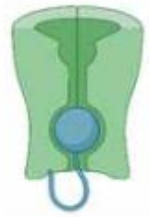
Centre Coordonnateur du CRMR PulmoTension,
Service de Pneumologie et Soins Intensifs Respiratoires
Hôpital Bicêtre (APHP) – Université Paris-Saclay – INSERM UMR_S999
Le Kremlin-Bicêtre – France
david.montani@aphp.fr

Disclosures

- ❑ I have no real or perceived conflicts of interest that relate to this presentation.
- ☑ I have the following real or perceived conflicts of interest that relate to this presentation:

Affiliation / Financial interest	Commercial company
Grants/research support	Actelion, Bayer, Boerhinger, Ferrer, GSK, Janssen, Pfizer, Acceleron Pharma, Inc., a wholly owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), and MSD
Honoraria or consultation fees	Actelion, Bayer, Boerhinger, Chiesi, Ferrer, GSK, Janssen, Pfizer, MSD, and Acceleron Pharma, Inc., a wholly owned subsidiary of MSD

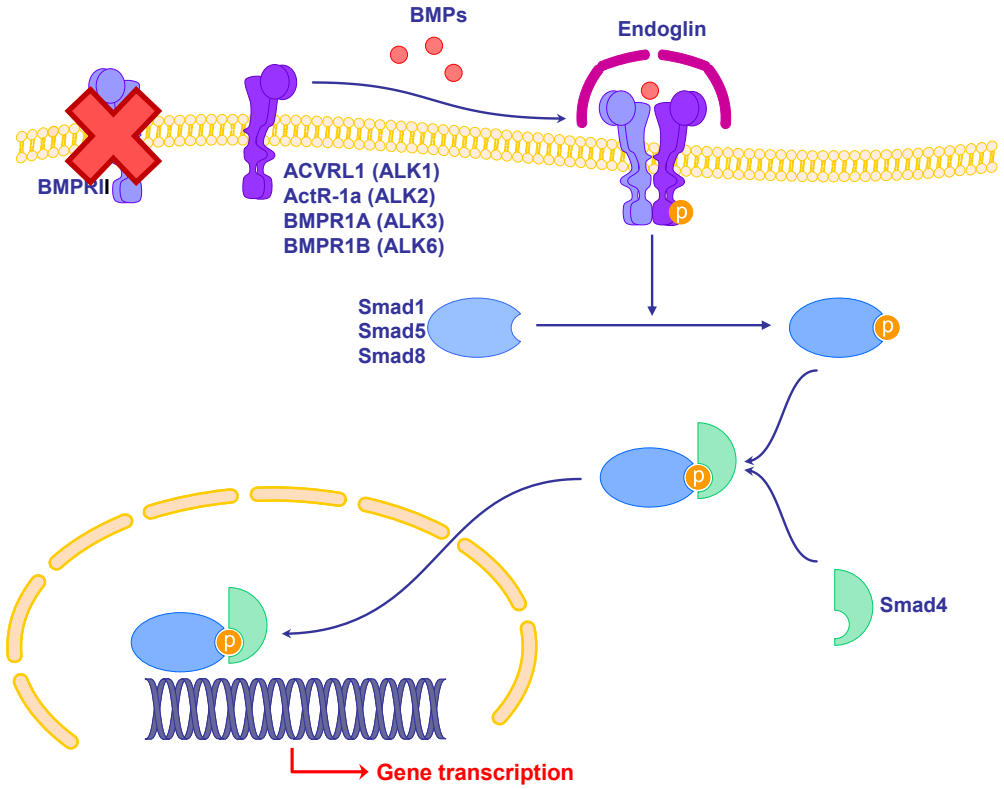
Genetic variants in *BMPR2* are an important cause of PAH



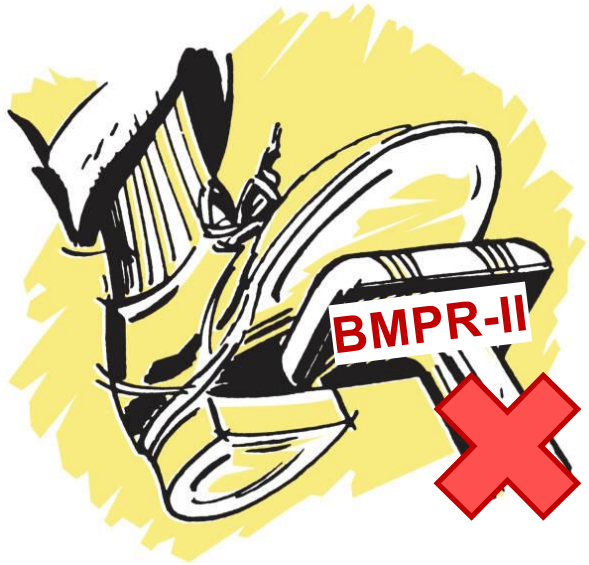
BMP/TGF-β family	Channels	Transcription factors	Other
ACVRL1 (ALK1)#	*ATP13A3* (ATPase 13A3)	*EIF2AK4* (GCN2)¶	*KDR* (VEGFR2)
BMPR2 (BMPR2)	*KCNK3* (TASK1)	*SOX17* (SOX17)+	*TET2* (TET2)
ENG (endoglin)#	*ABCC8* (MRP8)	*TBX4* (TBX4)+	*GGCX* (GGCX)
GDF2 (BMP9)			
SMAD9 (SMAD8)			
CAV1 (caveolin-1)			

Eichstaedt CA, et al. *Eur Respir J*. 2023;61(2):2201471.
#, genes associated with hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease); ¶, gene associated with pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis; +, genes associated with lung development abnormalities. Protein symbols/names/aliases are given in brackets.

Genetic variants in *BMPR2* are an important cause of PAH

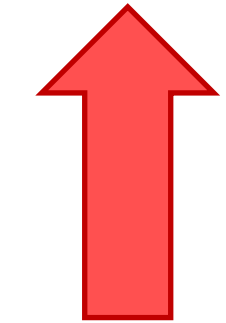


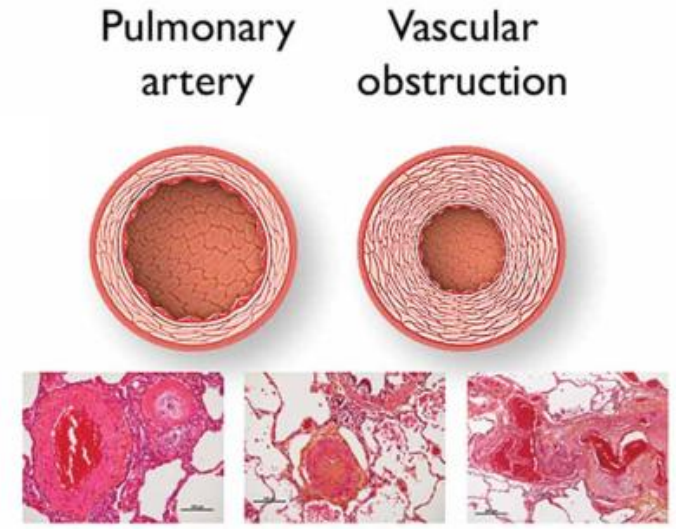
1. Promotes regeneration of small arteries
2. Induces apoptosis of cells that occlude the vessel
3. Maintains elastic fibers
4. Blocks inflammation
5. Preserves mitochondria, repairs damaged DNA



BMPR-II
= Brake

Cell proliferation

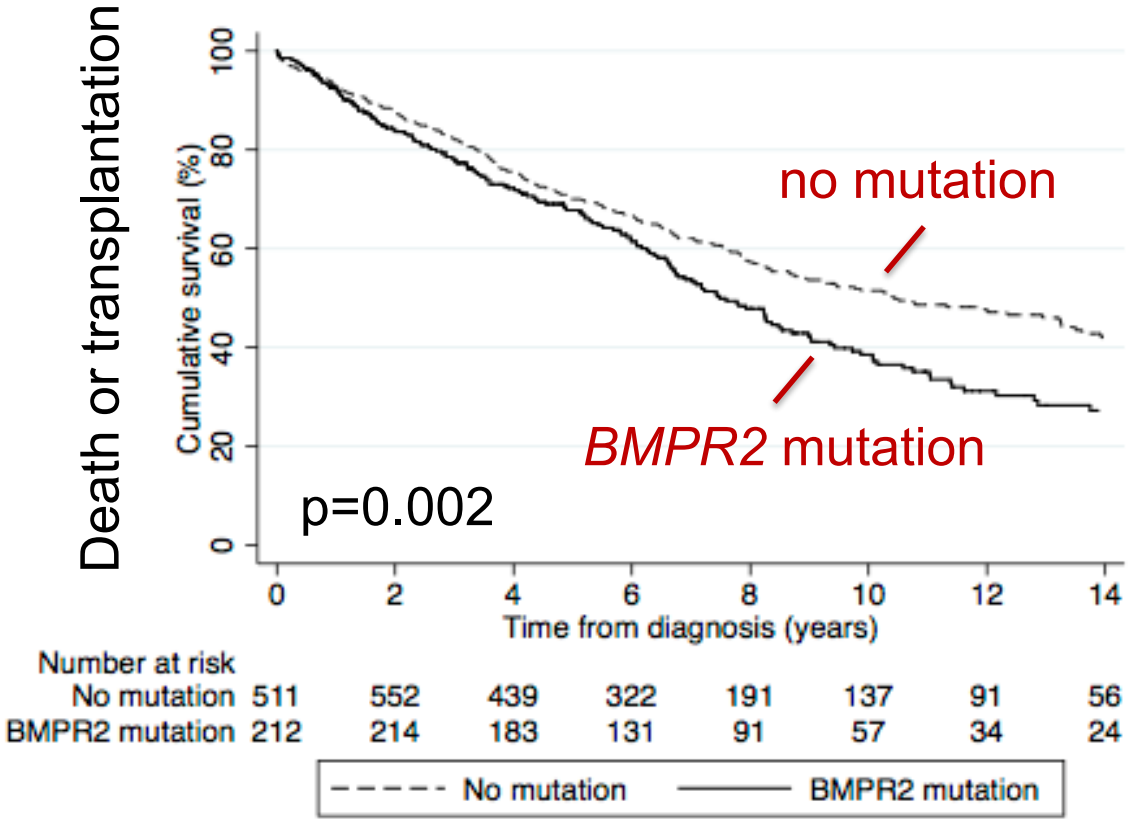




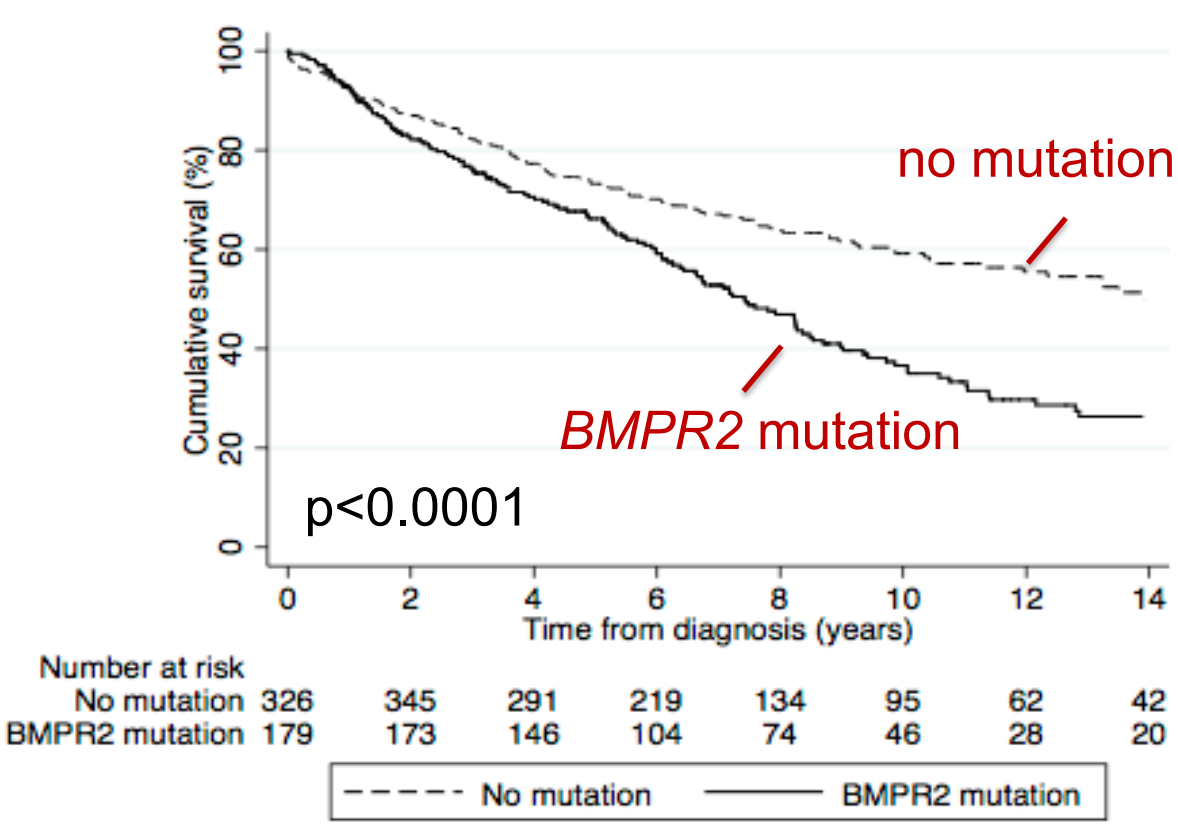
BMPR2 mutation carriers present with more severe disease

Time to Death or Transplantation

Total population

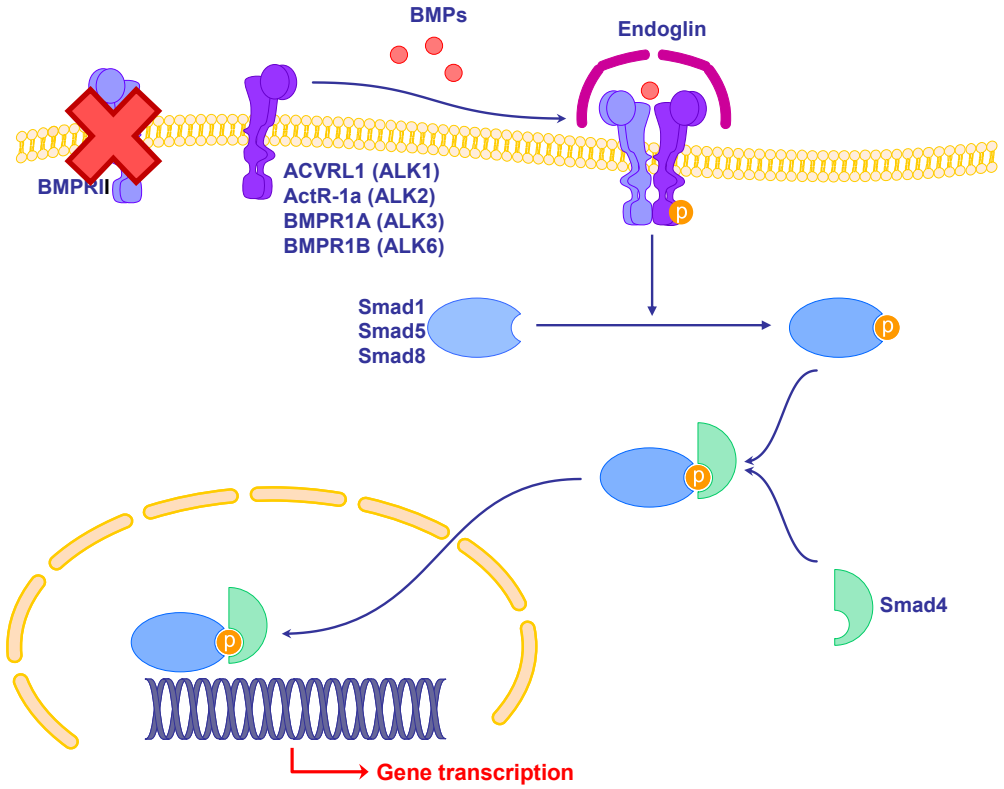


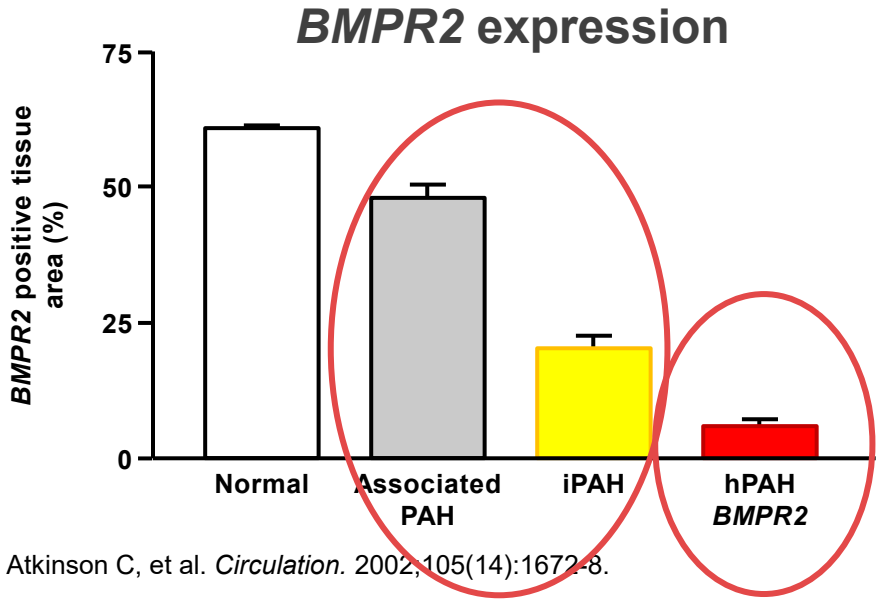
Age<50 at diagnosis



Evans et al, *Lancet Respir Med* 2016

Genetic variants in *BMPR2* are an important cause of PAH





Atkinson C, et al. *Circulation.* 2002;105(14):1672-8.

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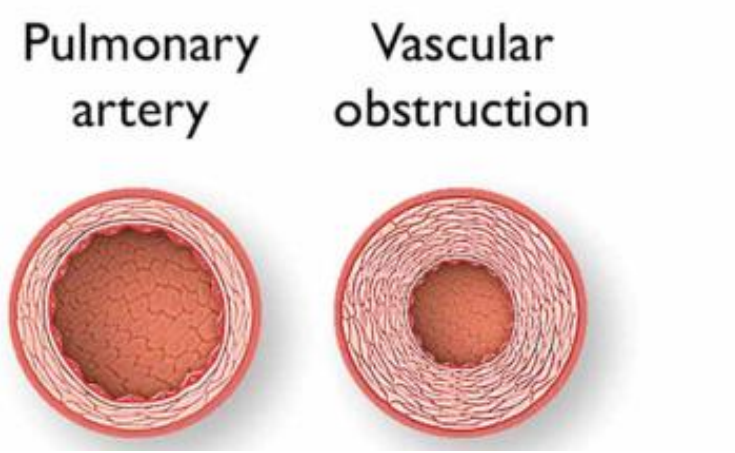
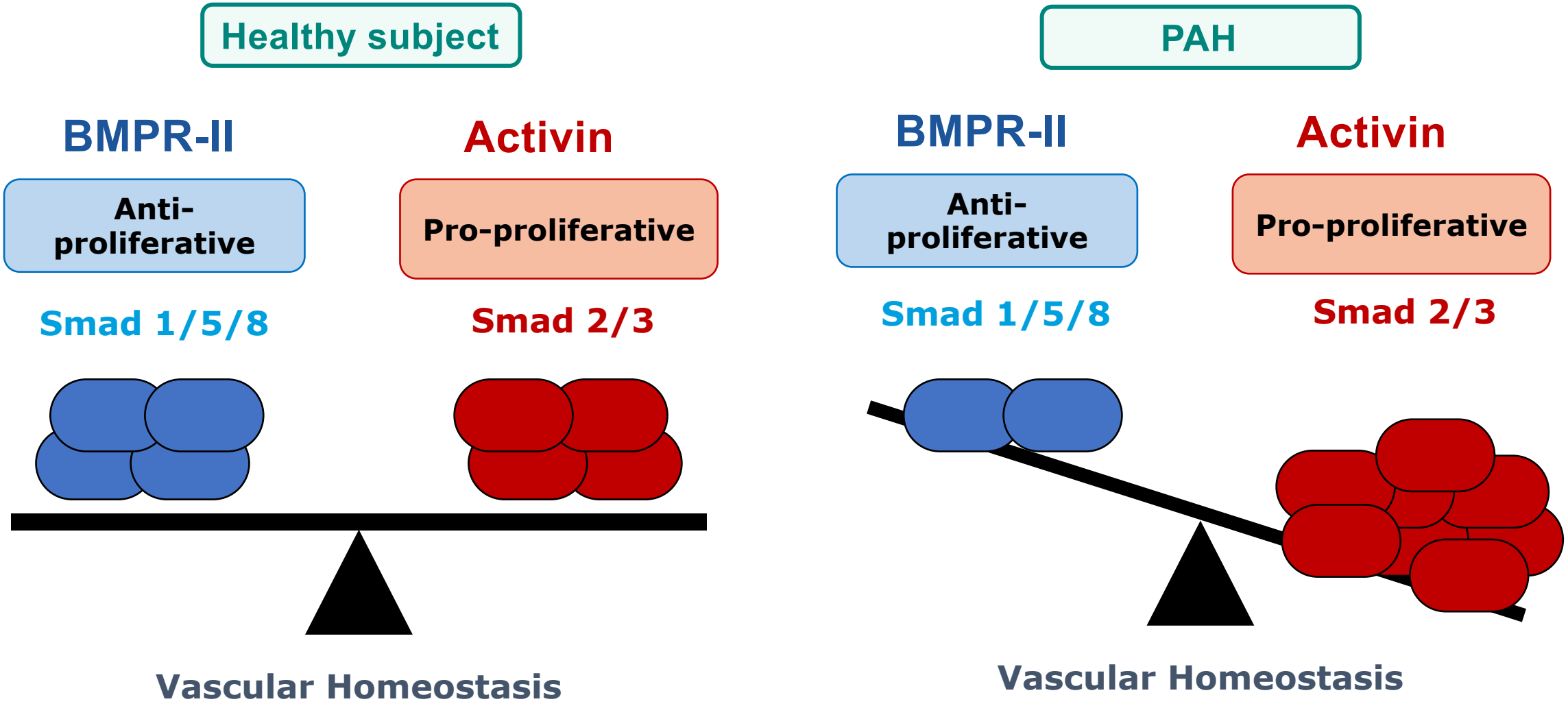
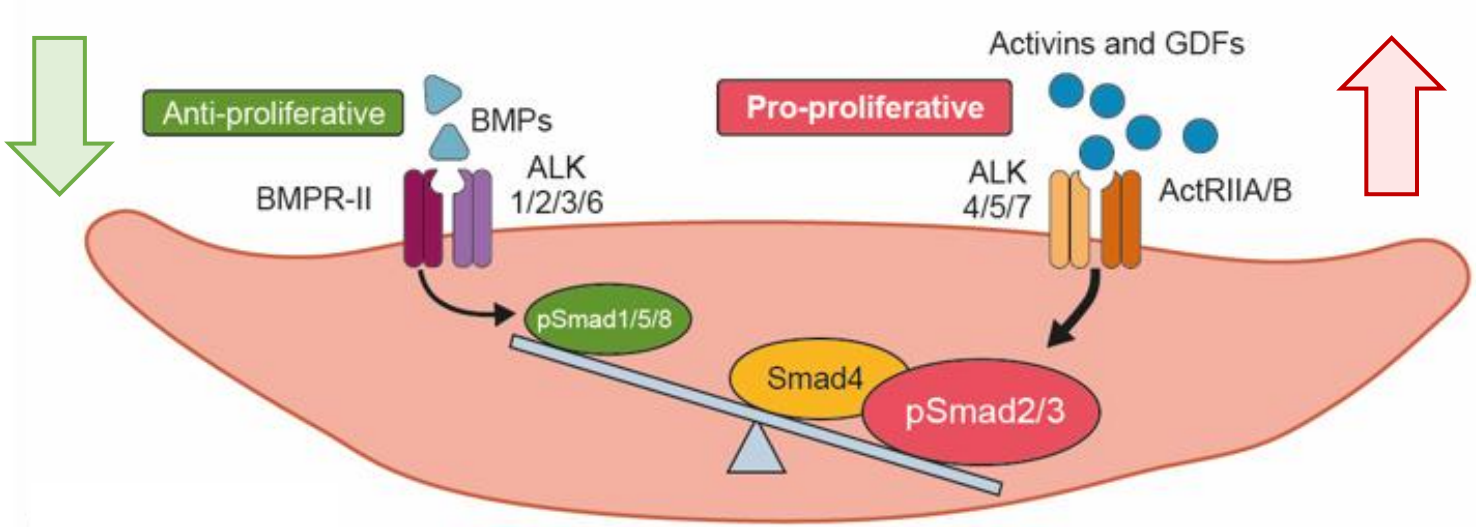


BMPR-II/ActRII Balance: Pulmonary Vascular Homeostasis



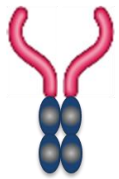
Restoring the BMPR-II/Activin Receptor IIA (ActRIIA) Balance in PAH

PAH



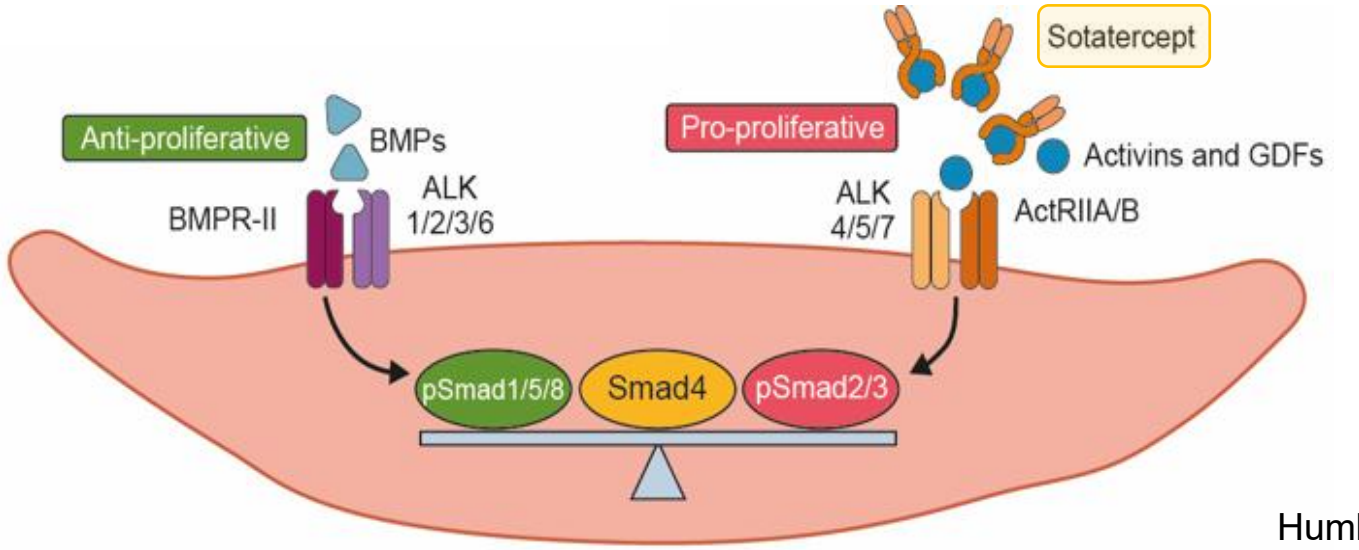
Sotatercept

ACTRIIA-Fc



Selectivity for

Activin A
Activin B
GDF-11
GDF-8

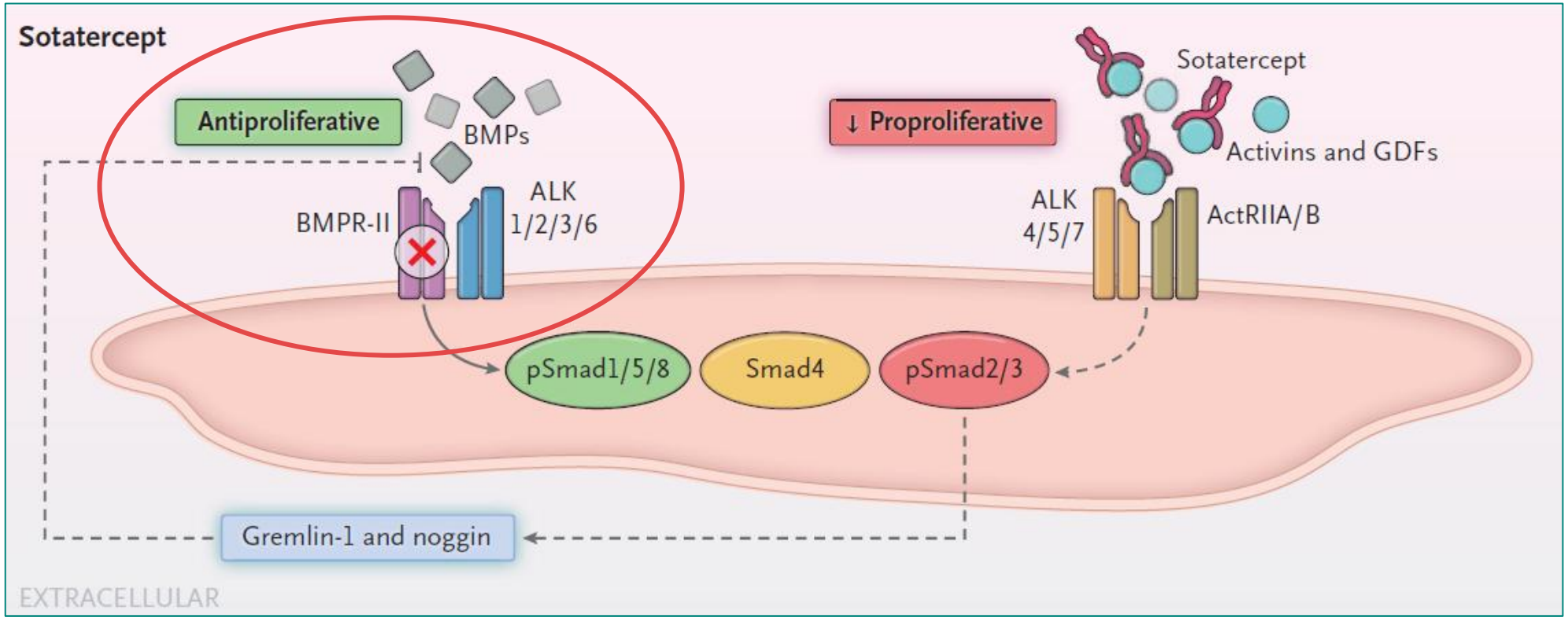


Humbert et al. *N Engl J Med* 2021

BMPR-II and Activins balance

***BMPR2* mutation**

?



BMPR2, bone morphogenetic protein receptor type II; PAH, pulmonary arterial hypertension.

Humbert M, et al. *N Engl J Med.* 2021;384(13):1204-1215. 2. Humbert M, et al. *Eur Respir J.* 2023;61(1):2201347.

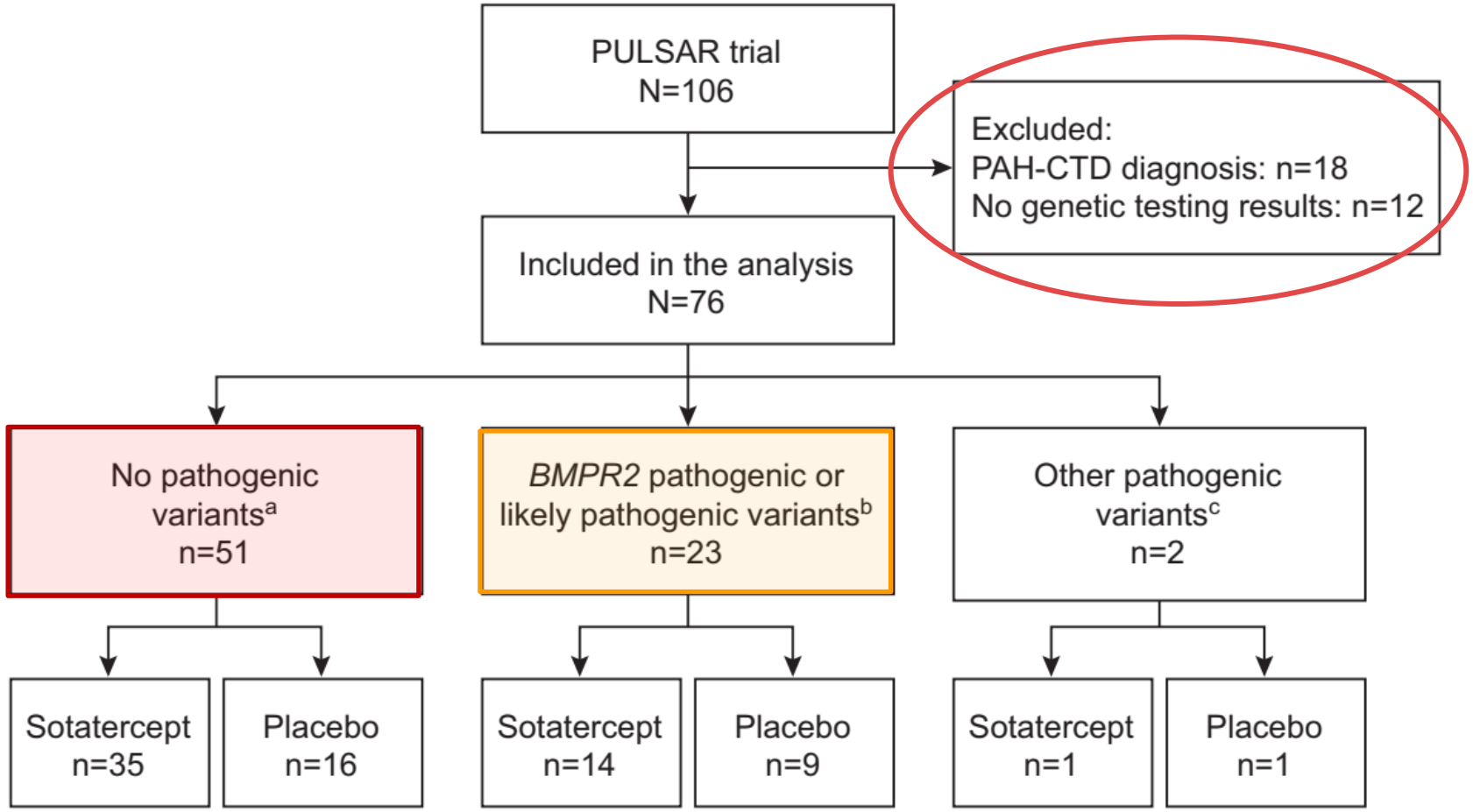
Consistent Safety and Efficacy of Sotatercept for Pulmonary Arterial Hypertension in *BMPR2* Mutation Carriers and Noncarriers: A Planned Analysis of a Phase II, Double-Blind, Placebo-controlled Clinical Trial (PULSAR)

David Montani[1]; Vallerie V. McLaughlin[2]; J. Simon R. Gibbs[3]; Mardi Gomberg-Maitland[4]; Marius M. Hoeper[5]; Ioana R. Preston[6]; Rogerio Souza[7]; Aaron B. Waxman[8]; Pilar Escribano Subias[9]; Jeremy Feldman[10]; Gisela Meyer[11]; Karen M. Olsson[5]; Solaiappan Manimaran[12]; Yujie Zhao[12]; Anna Lau[12]; Janethe de Oliveira Pena[12]; David B. Badesch[13]; Marc Humbert[1]

[1]Université Paris-Saclay, Le Kremlin-Bicêtre, France; [2]University of Michigan, Ann Arbor, MI, USA; [3]National Heart & Lung Institute, Imperial College London, London, UK; [4]George Washington University, Washington, DC, USA; [5]Hannover Medical School, Hannover, Germany; [6]Tufts Medical Center, Boston, MA, USA; [7]University of São Paulo, São Paulo, Brazil; [8]Brigham and Women's Hospital, Boston, MA, USA; [9]Centro de Investigación en Red en Enfermedades Cardiovasculares, Hospital Universitario 12 de Octubre, Universidad Complutense, Madrid, Spain; [10]Summit Health, Bend, OR, USA; [11]Irmandade da Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil; [12]Merck & Co., Inc., Rahway, NJ, USA; [13]University of Colorado Hospital, Aurora, CO, USA

Montani D et al. *Am J Respir Crit Care Med* 2025

Participant disposition



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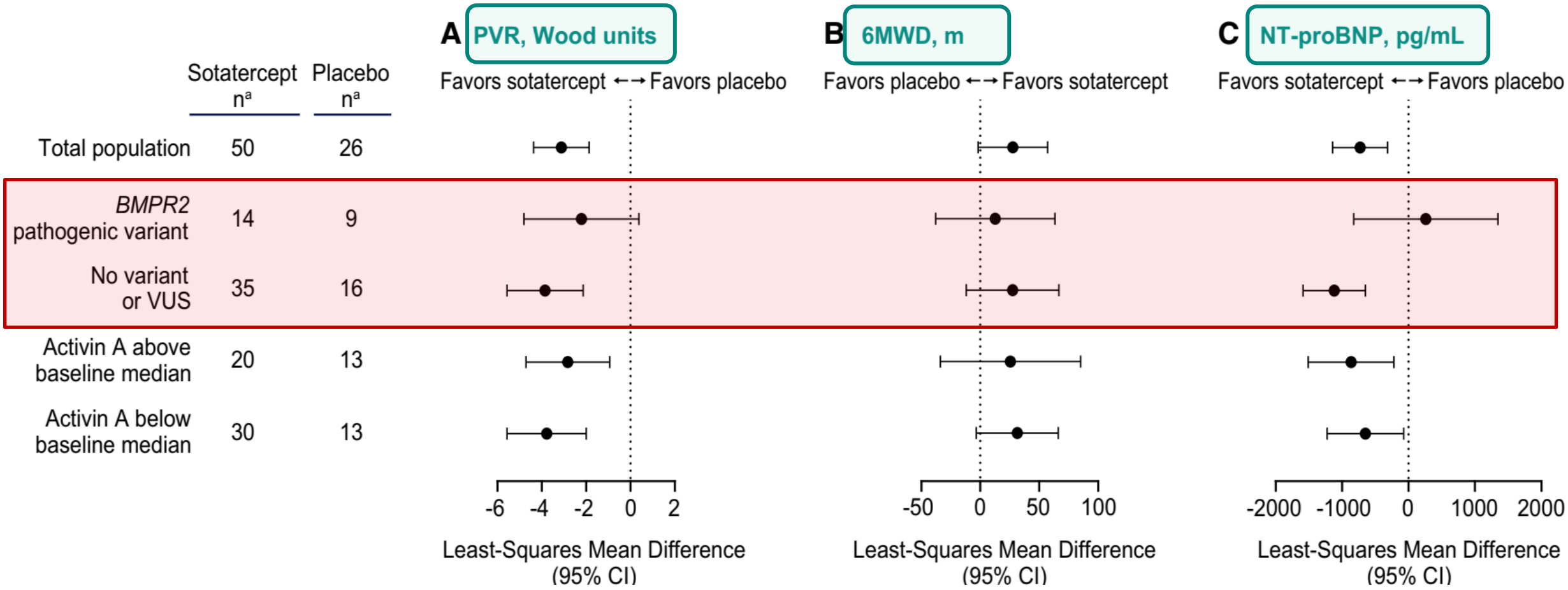
Baseline demographics and clinical characteristics[a]

		BMPR2 pathogenic variant (n=23)	VUS (variants of uncertain significance) or no variant (n=51)	Total (N=76[b])
Age, years	Mean (SD)	38.5 (13.1)	49.5 (13.7)	45.7 (14.4)
Sex, n (%)	Female/male	21 (91.3)/2 (8.7)	42 (82.4)/9 (17.6)	65 (85.5)/11 (14.5)
Time since PAH diagnosis, years	Mean (SD)	10.2 (6.6)	7.5 (5.5)	8.3 (5.9)
WHO functional class, n (%)	II	15 (65.2)	23 (45.1)	40 (52.6)
	III	8 (34.8)	28 (54.9)	36 (47.4)
Background therapy, n (%)	Monotherapy	0	8 (15.7)	8 (10.5)
	Double therapy	5 (21.7)	20 (39.2)	26 (34.2)
	Triple therapy	18 (78.3)	23 (45.1)	42 (55.3)
PVR, WU[c]	Mean (SD)	10.7 (3.8)	10.1 (4.9)	10.2 (4.5)
6MWD, m	Mean (SD)	442.3 (45.7)	384.6 (88.9)	404.0 (81.8)
NT-proBNP, pg/mL	Mean (SD)	541.4 (673.8)	1056.0 (1664.0)	897.4 (1434.5)
Activin A, ng/L	Median (range)	177.0 (117.0, 343.0)	241.0 (104.0, 537.0)	211.0 (104.0, 537.0)
***BMPR2* mRNA, ΔC_t**	Mean (SD) [n][d]	5.2 (2.7) [20]	6.0 (1.5) [40]	5.8 (2.0) [62]

[a]Participants with PAH-CTD were excluded from the analysis.
[b]Data for the 2 participants with pathogenic variants in genes other than *BMPR2* are included in the total population but not shown individually. View e-poster #8491 for more details.
[c]PVR in WU was calculated from PVR in $dyn \cdot s \cdot cm^{-5}$ using the conversion factor of 1 WU = 80 $dyn \cdot s \cdot cm^{-5}$. [d]The number of participants in each group with available data is shown in brackets.
6MWD, 6-minute walk distance; AVCRL1, activin receptor-like kinase 1; *BMPR2*, bone morphogenetic protein receptor type II; *EIF2AK4*, eukaryotic translation initiation factor 2-alpha kinase 4; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SD, standard deviation; WHO, World Health Organization; WU, Wood Units.

Between-group differences in change from baseline at week 24 in clinical endpoints



[a]Data for the 2 participants with other pathogenic variants are included in the total population and in above/below baseline median activin A groups but not shown individually.
VUS - variants of uncertain significance

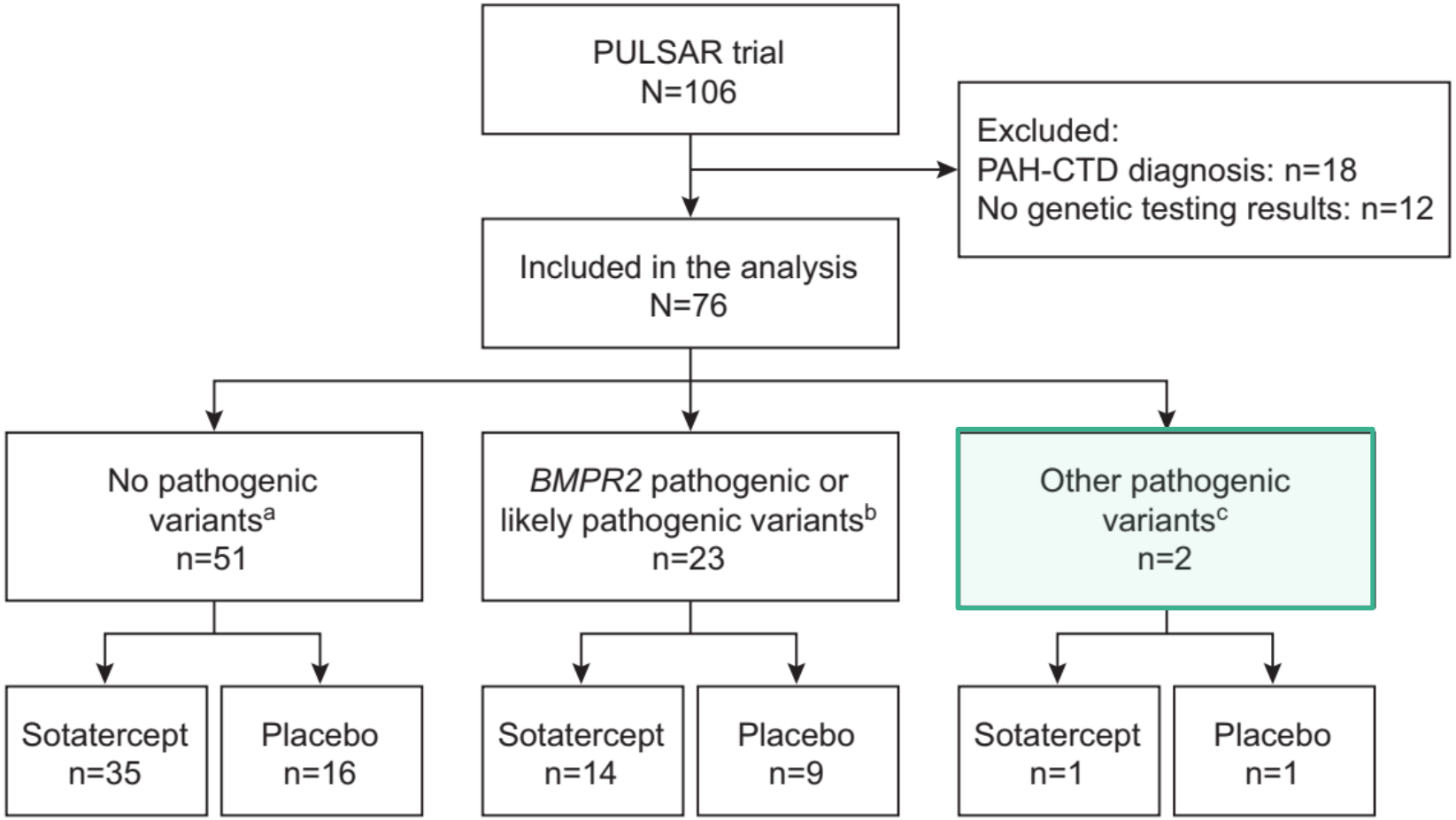
Summary of safety by variant status

No. (%) of participants with	*BMPR2* pathogenic variant (N=23)		VUS or no variant (N=51)		Total (N=76)[a]	
	Sotatercept (n=14)	Placebo (n=9)	Sotatercept (n=35)	Placebo (n=16)	Sotatercept (n=50)	Placebo (n=26)
Any TEAE	13 (92.9)	9 (100.0)	29 (82.9)	14 (87.5)	43 (86.0)	24 (92.3)
Related to treatment	11 (78.6)	3 (33.3)	11 (31.4)	5 (31.3)	23 (46.0)	8 (30.8)
Leading to treatment discontinuation	1 (7.1)	1 (11.1)	4 (11.4)	0	5 (10.0)	1 (3.8)
Leading to death	0	0	1 (2.9)	0	1 (2.0)	0
Of special interest	2 (14.3)	0	7 (20.0)	0	10 (20.0)	0
Serious TEAE	**2 (14.3)**	0	**6 (17.1)**	2 (12.5)	8 (16.0)	2 (7.7)
Related to treatment	**1 (7.1)**	0	**1 (2.9)**	1 (6.3)	2 (4.0)	1 (3.8)

TEAE, treatment-emergent adverse event with a start date on or after the first dose of treatment and up to 8 weeks after the last dose of treatment; VUS, variants of uncertain significance. TEAEs of special interest include fertility disorders with a focus on suppression of FSH; hepatic toxicity; cardiac events, embolic and thrombotic events, thrombocytopenia, leukopenia, and neutropenia.

[a]Data for the 2 participants with other pathogenic variants are included in the total population but not shown individually.

Participant disposition

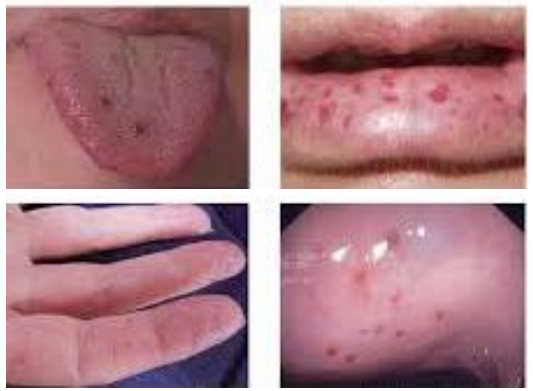


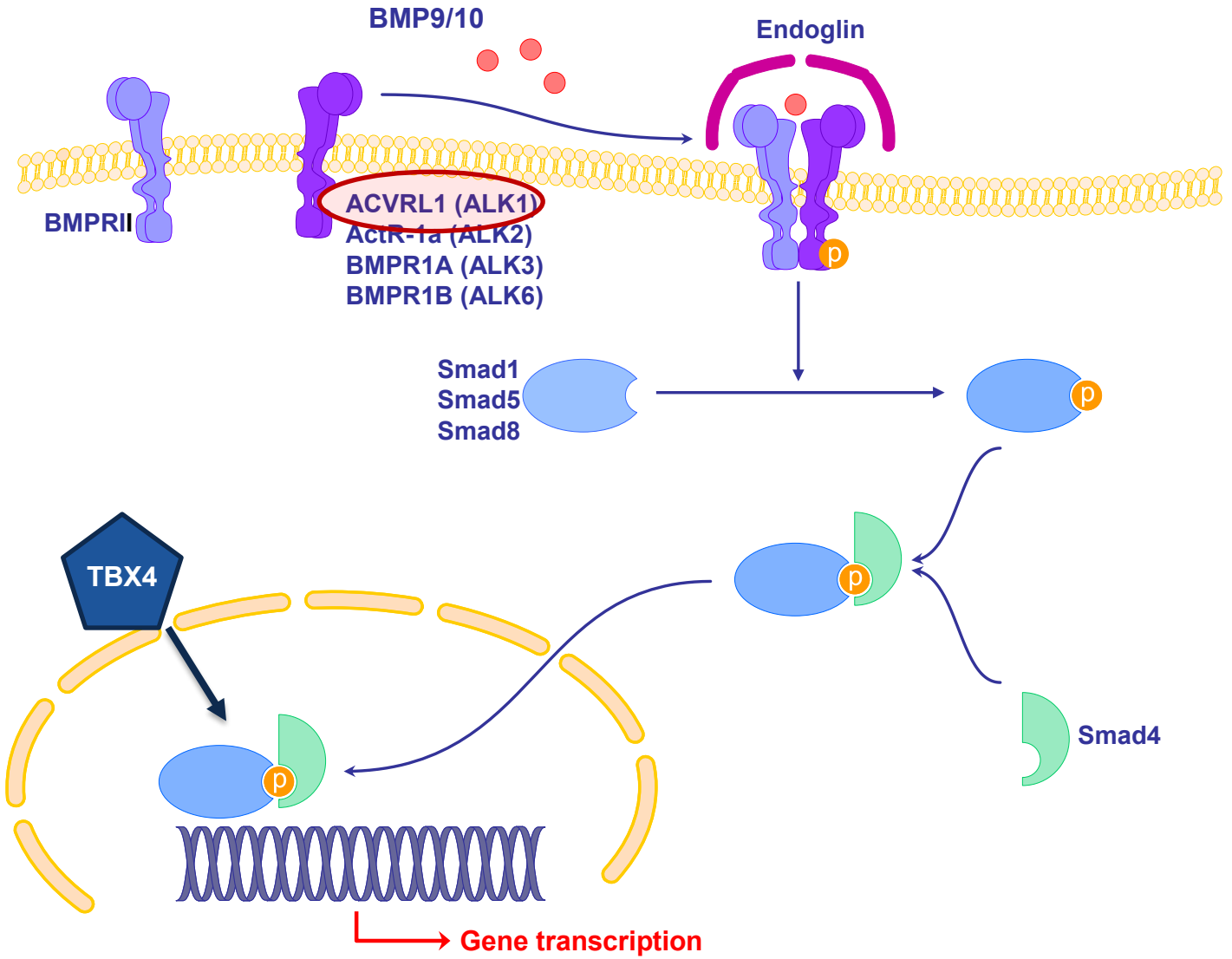
ACVRL1 mutation

Biallelic *EIF2AK4* mutations

Montani D, et al. *ARCCMJ* 2025

PREDISPOSING GENES IN PAH : ACVRL1





Vignettes of 2 participants with pathogenic variants in the *ACVRL1* and *EIF2AK4* genes

HHT : *ACVRL1* +/-

- Randomized to sotatercept 0.3 mg/kg treatment
- At week 24:
  - PVR was 7.5 WU (−2.1 WU from baseline)
  - 6MWD was 585 m (+108 m from baseline)
  - NT-proBNP was 700 pg/mL (−1162 pg/mL from baseline)
  - WHO functional class II was maintained
- Extension Period: Escalated to sotatercept 0.7 mg/kg, then deescalated to 0.3 mg/kg for new onset of telangiectasia and gum bleeding (both nonserious and mild)
- Hemoglobin levels increased from 10.9 g/dL at baseline to 11.0 g/dL at week 24, to 11.2 g/dL at study completion

- At study completion (24 months since randomization):
  - PVR was 7.7 WU, **−1.9 WU** from baseline
  - 6MWD was 604 m , **+127 m** from baseline
  - NT-proBNP was 523 pg/mL, **−1339 pg/mL** from baseline

- No serious adverse events were reported for this participant during the study

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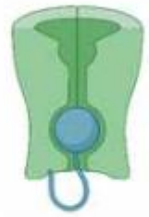
Predisposing PAH genes



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ENG (endoglin)#	*ABCC8* (MRP8)	*TBX4* (TBX4)+	*GGCX* (GGCX)
GDF2 (BMP9)			
SMAD9 (SMAD8)			
CAV1 (caveolin-1)			

Eichstaedt CA, et al. *Eur Respir J*. 2023;61(2):2201471.
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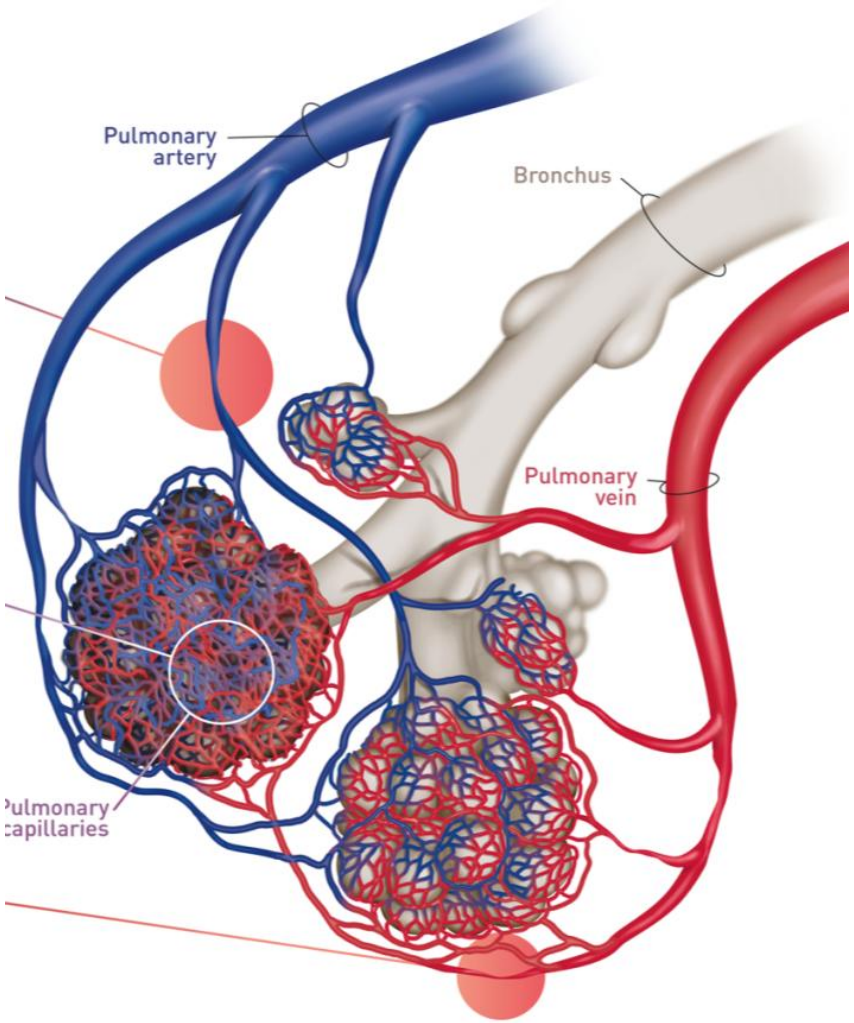
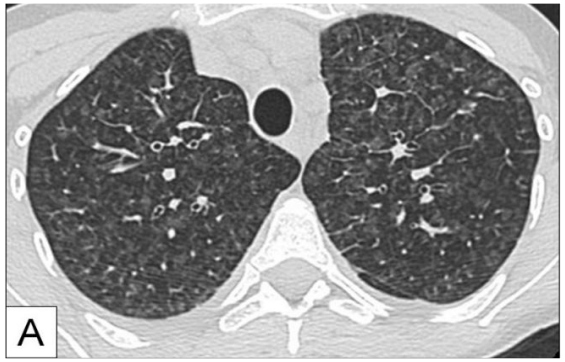
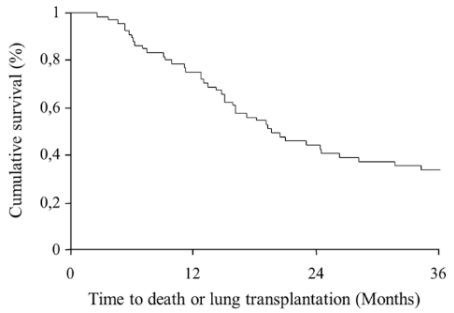
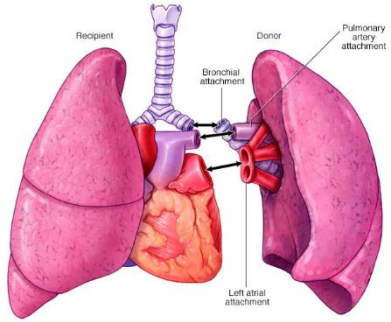
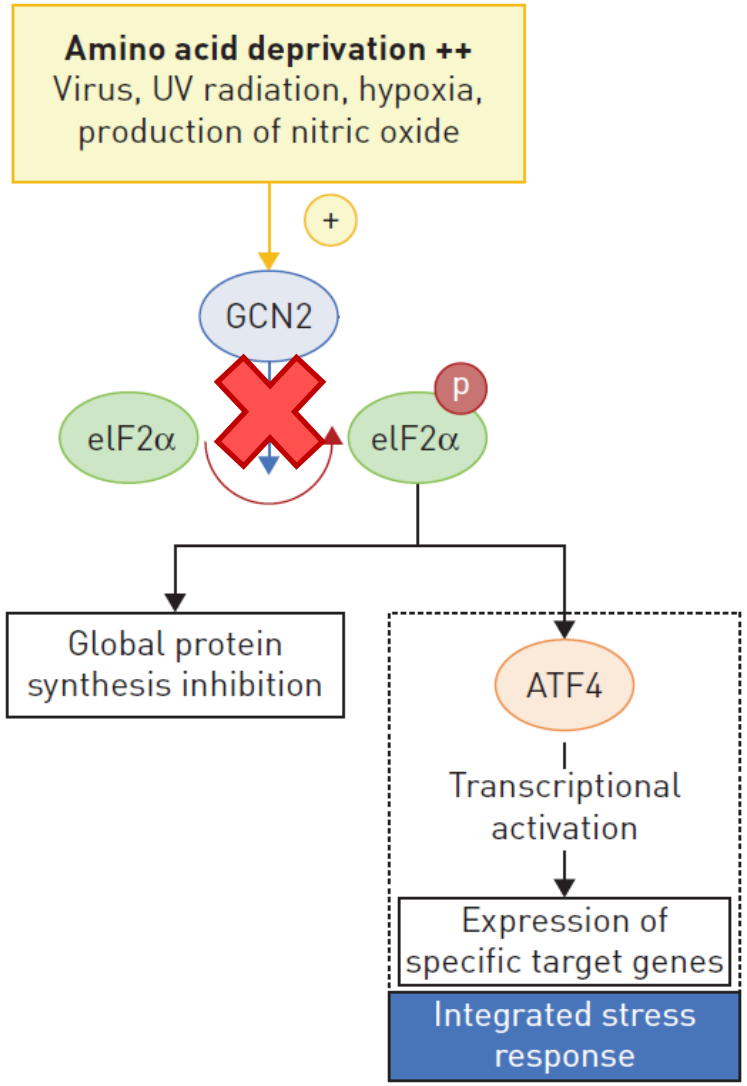
PULMONARY VENO-OCCLUSIVE DISEASE











Montani D et al. *Eur Respir J* 2016

Vignettes of 2 participants with pathogenic variants in the *ACVRL1* and ***EIF2AK4*** genes

Heritable PVOD : *EIF2AK4* -/-

- Randomized to placebo treatment
- At week 24:
  - PVR was 6.3 WU (−0.1 WU from baseline)
  - 6MWD was 440 m (−2.5 m from baseline)
  - NT-proBNP was stable at 29 pg/mL (+1 pg/mL from baseline)
  - WHO functional class II was maintained
- Extension Period: sotatercept 0.3 mg/kg
- Hemoglobin levels were 13.6 g/dL at baseline, 13.4 g/dL at week 24, and 16.1 g/dL at study completion

- At study completion (24 months since randomization):
  - PVR was 2.2 WU, **−4.2 WU** from baseline
  - 6MWD was 454 m, **+11.5 m** from baseline
  - NT-proBNP was 26 pg/mL

- No serious adverse events or adverse events of special interest were reported for this participant during the study

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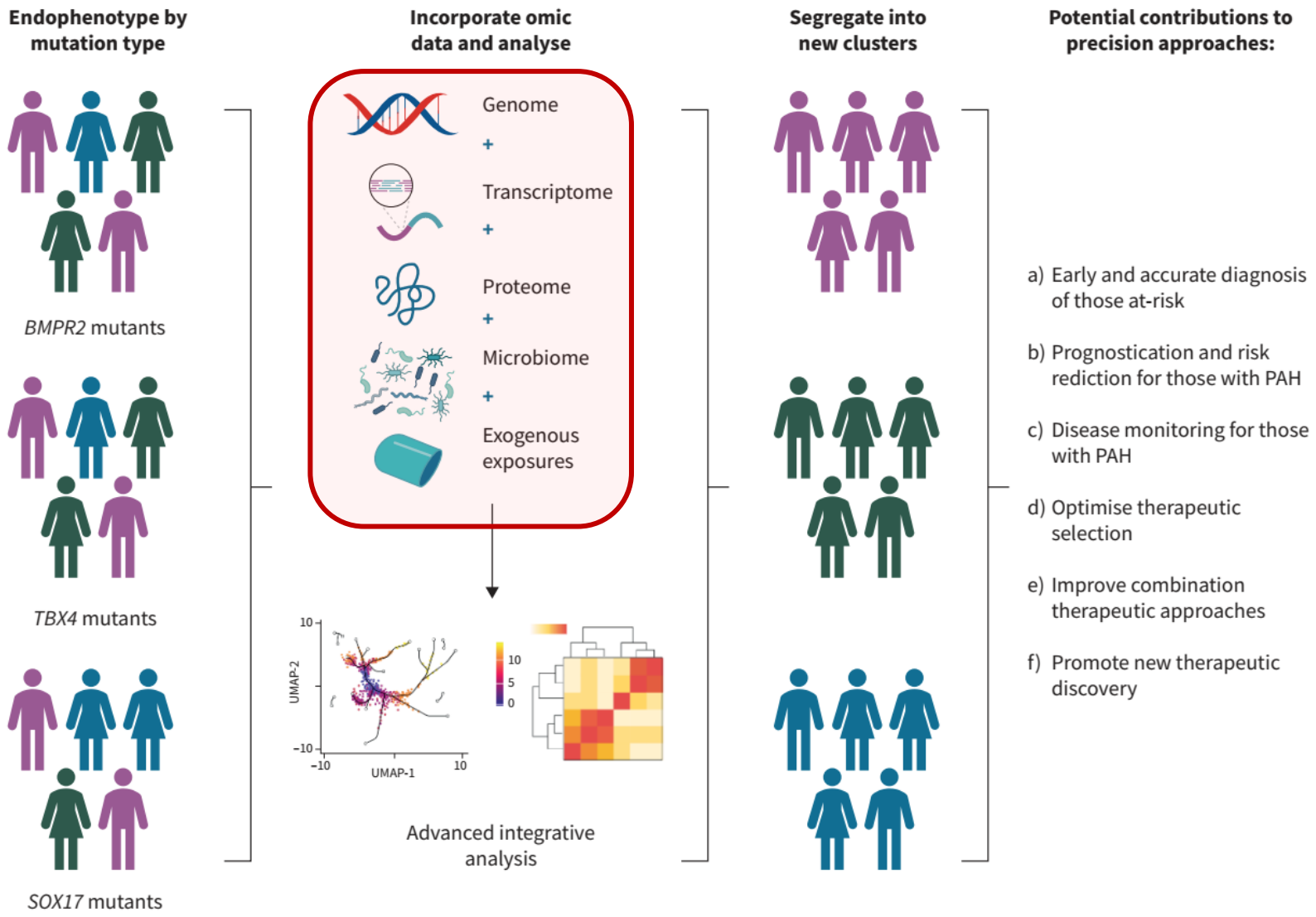
Summary and conclusions

- Participants with pathogenic variants were more likely to be **younger, to be in WHO class II, and to be on triple therapy**. They presented with **higher 6MWD, and lower NT-proBNP** at baseline
- Despite differences in baseline characteristics, the **treatment effect of sotatercept on PVR and 6MWD was generally consistent** across the *BMPR2* pathogenic variant and VUS or no variant subgroups
- The **adverse events profile was consistent** with that seen in the parent PULSAR study, with no new safety concerns emerging by variant status
- Further investigation of sotatercept treatment in the context of genetic background is warranted

VUS, variants of uncertain significance

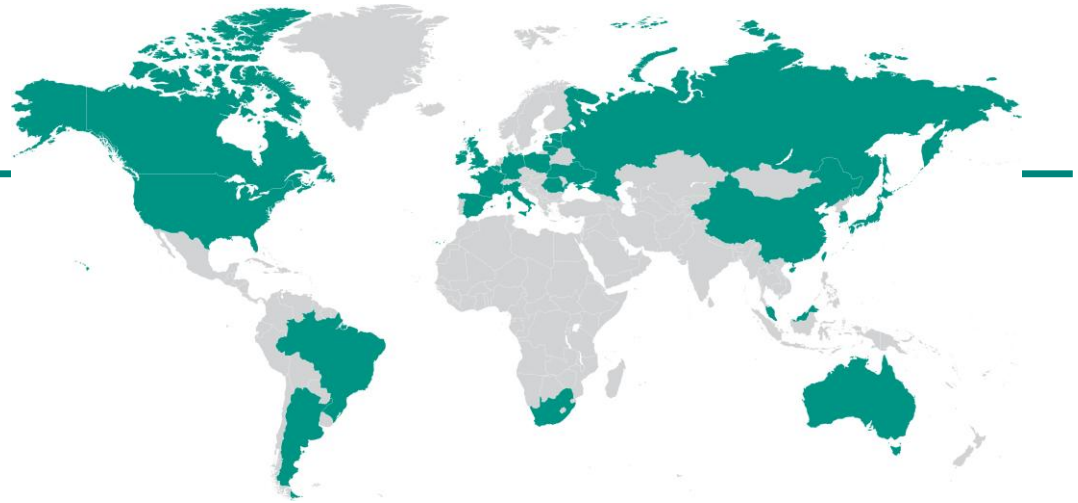
Perspectives

Endophenotype



Personalized medicine

Acknowledgments



Professor Florence Coulet,
Genetics Department, Pitié-Salpêtrière Hospital, Sorbonne Université, Paris, for help with the classification of the genetic variants

Patients and families who participated in the PULSAR trial,
and the investigators and their research teams who collaborated on the trial.

The PULSAR study, including these analyses, were funded by Acceleron Pharma, Inc., a wholly own subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Centre Coordonnateur du CRMR PulmoTension,
Service de Pneumologie et Soins Intensifs Respiratoires
Hôpital Bicêtre (APHP) – Université Paris-Saclay – INSERM UMR_S999
Le Kremlin-Bicêtre – France
david.montani@aphp.fr