DESTINATION 2024

DETECTION, ASSESSMENT AND TREATMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Unique multidisciplinary partnership of highly recognized specialists with first class imaging and pharma partners work together to:

- revolutionize outcomes in CTEPH patients and contribute to saving lives by identifying and properly managing the disease
- achieve a personalized management of CTEPH patients who are candidate for interventional treatment with BPA
- improve standard of care with an ambition to develop a treat-to-cure approach

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- Assistance Publique-Hôpitaux de Paris (AP-HP, coordinator) hosting the French Reference Centre for PH (PulmoTension), a leading member of the ERN- LUNG and of RespiFIL where it is in charge of French and European guidelines for diagnosis and treatment of PH.
- Janssen (through Actelion) has been a pioneer in the field of CTEPH.
- GE Healthcare, a leading provider of medical imaging equipment and solutions, enables precision health through intelligent devices, data analytics, applications and services.
- The Groupe Hospitalier Paris Saint-Joseph through its Marie-Lannelongue Hospital hosting the PulmoTension Constitutive Site in charge of surgery and interventional radiology with more than 100 procedures per year for CTEPH patients, is the only national surgical PH centre and one of the four largest worldwide pulmonary endarterectomy programs.
- Université Paris-Saclay and Inserm host the laboratory UMR_S 999 (Pulmonary Hypertension: Pathophysiology and Novel Therapies), recipient of the «Fondation pour la Recherche Médicale Team» label in 2012 and 2015, and founding member of a Laboratory of Excellence in Research on Medication and Innovative Therapeutics in 2011, which displays a successful history of clinical and translational research in pulmonary hypertension.

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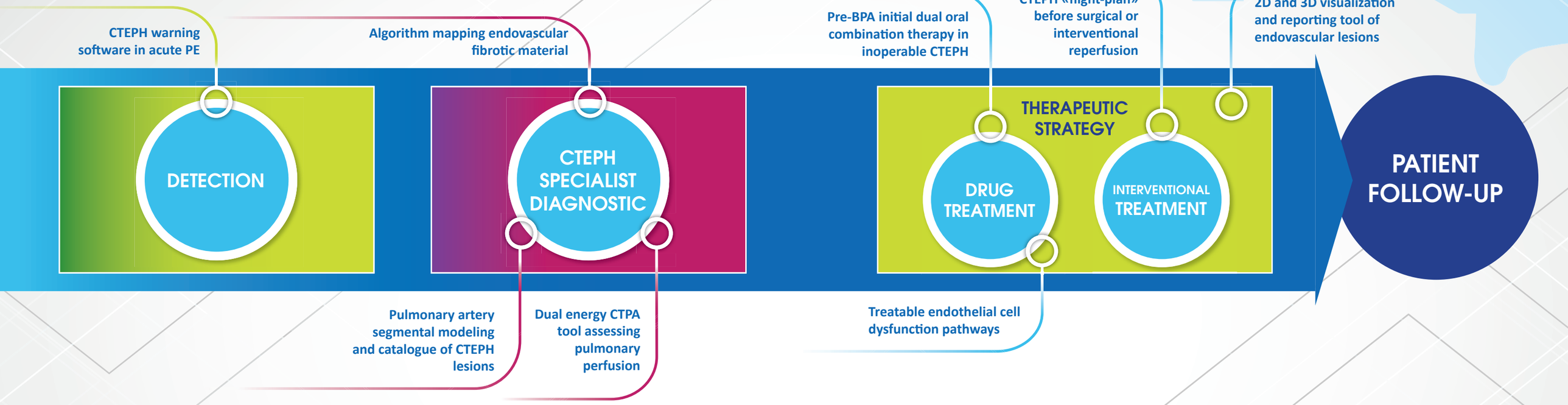
"When Thomas P. turned 42, he became increasingly tired and suffered from progressive shortness of breath at exercise. As his symptoms worsened, he began experiencing pleuritic chest pain 10 months after the first signs of dyspnea. At this stage, his medical history only showed a life-long hormonal treatment for hypothyroidism, diagnosed at the age of 26. Computed tomography pulmonary angiography (CTPA) revealed a bilateral lobar acute pulmonary embolism and Thomas was treated with a vitamin K antagonist for 6 months. This partly relieved his fatigue, and both the chest pain and dyspnea lessened. However, his physical condition remained unsatisfactory and impacted his daily life and career, leading him to take on a not-physically-demanding job and stop training with his tennis club. After two years of medical wandering, Thomas, who still endured those persistent symptoms, underwent an echocardiography showing elevated estimated systolic pulmonary artery pressure, a ventilation/perfusion lung scintigraphy showing multiple segmental perfusion defects and another computed tomography pulmonary angiography (CTPA) detecting pulmonary artery lesions typical of chronic thromboembolic pulmonary disease. Severe pre-capillary pulmonary hypertension was confirmed by right-heart catheterization and this case was discussed at a multidisciplinary meeting in a Reference Centre confirming a diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) which was not suitable for surgical endarterectomy. Thomas was offered a multimodal management associating medical therapy with anticoagulation and a pulmonary hypertension drug, followed by balloon pulmonary angioplasty. Thanks to this treatment approach, his condition improved markedly and Thomas is now back to a normal life."

It is estimated that about 1-3% of patients suffering from acute pulmonary embolism will develop this life-threatening complication. Patients with CTEPH have an average diagnostic delay of 12 months and for most cases the disease is detected at a late-stage, resulting in significant mortality if left untreated (survival rate of 60% at 5 years).

The RHU DESTINATION 2024 aims to improve awareness and help with the early detection of CTEPH for Thomas and other patients in order to enable rapid diagnosis and timely management which will translate into better outcomes. An early identification and proper management of the disease will increase survival rate of patients while allowing them to benefit from a personalized management of a treat-to-cure approach. In addition, it is also expected to improve the cost-effectiveness of treatment and lessen its economic burden on healthcare systems.

CONSOLIDATED APPROACH TO IMPROVE ALL STEPS OF CTEPH PATIENTS' JOURNEY



DETECTION – DIAGNOSIS – INTERVENTIONAL TREATMENT

The RHU DESTINATION 2024 intends to provide a complete care pathway ranging from the early detection assistance to the therapy planning and interventional guidance. This will be achieved using artificial intelligence tools embedded into an image processing platform.

- Enable the early detection of CTEPH patients by using a warning software that assesses the CTEPH risk in CTPA scans imaged for acute PE patients
- Facilitate a specialist diagnosis of the disease with a tool to localize and flag occlusions, and determine their type. We will also produce automatic lung perfusion mapping by dual energy CTPA protocols, and a decision-support tool capable of assessing the pulmonary hypoperfusion
- Elaborate a personalized strategy for patient's management from simplified 2D and 3D representations of the pulmonary arteries and standardized reporting of the endovascular lesions
- Contribute to the interventional treatment with 'flight-plan' design recommendations and/or tools on the existing interventional software

DRUG TREATMENT: PROOF OF CONCEPT & CLINICAL TRIAL

When the obstruction by residual organized thrombi occurs in small pulmonary vessels, surgery and interventional treatment are not possible. The RHU DESTINATION 2024 will deliver a preclinical proof-of-concept as a strong basis for testing initial combination therapies to treat patients with inoperable CTEPH. Then, we will show that initial dual oral combination therapy followed by balloon pulmonary angioplasty (BPA) improves the global efficacy of a strategy using these 2 complementary therapies. This will be demonstrated through the IMPACT-CTEPH study, a randomized controlled trial of an initial oral combination medical therapy with a guanylate cyclase stimulator plus an endothelin receptor antagonist versus an initial oral monotherapy with a guanylate cyclase stimulator alone on pulmonary vascular resistance (PVR) (primary end-point) before BPA.

- Describe endothelial alterations resulting in imbalanced production of relaxing and contracting factors
- Provide a preclinical proof-of-concept that a restoration of the endothelium-dependent vasodilation is beneficial in CTEPH
- Demonstrate that initial dual oral combination therapy followed by BPA improves the global efficacy of a therapeutic strategy that uses two complementary medicines for treating the 40% patients with inoperable CTEPH