ISHLT JOURNAL WATCH
May 2023 | Pulmonology

Arun Jose, MD, MS
University of Cincinnati, Cincinnati, OH USA

Kavita Dave, M.D.
EDITOR
ISHLT.ORG

Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

Hoeper MM, et al. *N Engl J Med* 2023 | https://doi.org/10.1056/nejmoa2213558

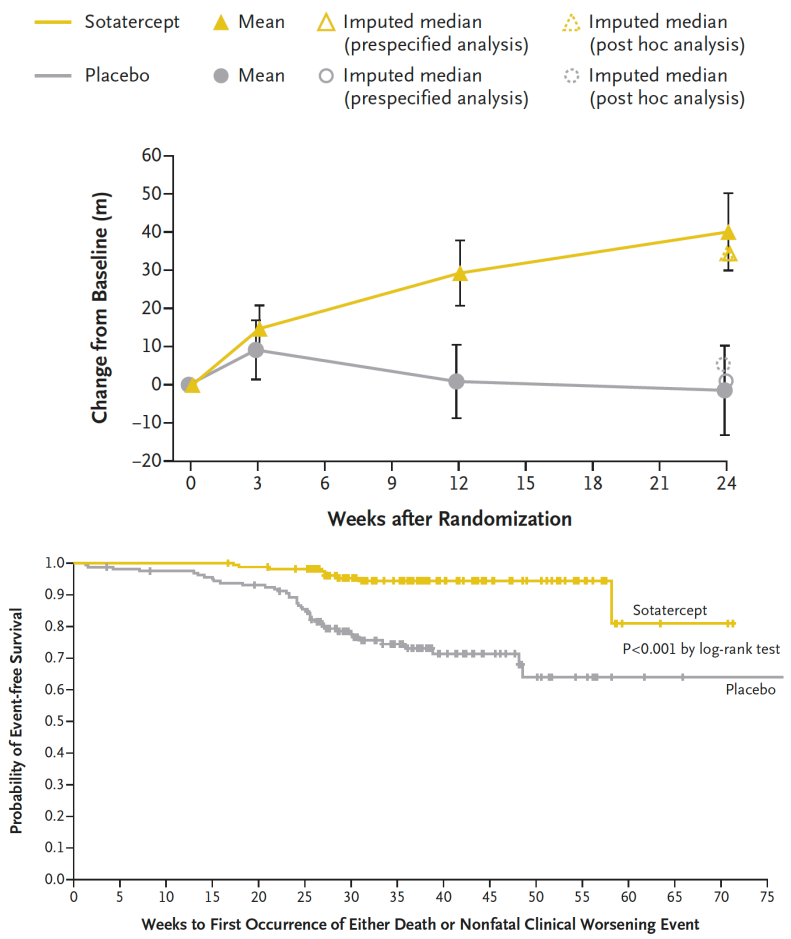
Study Highlights

Objective: Dysfunctional activin-growth differential factor (GDF) pathway signaling is believed to drive pulmonary arterial hypertension (PAH) pathogenesis. The continued high morbidity and mortality in PAH highlight the need for additional treatment options targeting new pathways.

Methods: Phase 3 multicenter randomized controlled study of sotatercept, a soluble activin/GDF ligand trap. 323 adult PAH subjects, on stable background PAH therapy, were randomized 1:1 to drug or placebo. The primary endpoint was change in six-minute walk test (6MWT) at 24 weeks.

Results: Subjects were well balanced on demographics, PAH disease severity, and PAH treatment regimens. Sotatercept significantly increased 6MWT compared to placebo. Significant improvements in multiple secondary endpoints (PAH hemodynamics, natriuretic peptide levels, time to clinical worsening) were also seen. Sotatercept side effects included increased hemoglobin, development of telangiectasias, and more bleeding events.

Conclusions: Sotatercept significantly improved multiple measures of PAH disease severity when added to stable background therapy in PAH patients. The risk of death or non-fatal clinical worsening events, was 84% lower with sotatercept than with placebo.



Legend: Change in 6MWT (top) and time to clinical worsening (bottom) for Sotatercept versus placebo

Reviewer's Comments

- Sotatercept acts differently from current PAH medications (nitric oxide/vasodilation).
- Sotatercept resulted in significant hemodynamic, functional, and clinical improvements in PAH patients when added to background therapy.
- Sotatercept may represent a significant step forward in the management of PAH
- Sotatercept may be effective for incident PAH patients.

Limitations

- Important PAH subtypes (portopulmonary, HIV-PAH) excluded, limiting generalizability.
- Few CTD-PAH subjects (may be more sensitive to bleeding) enrolled impacting safety.
- No change in cardiac function (improvements driven primarily by pulmonary arterial pressures) was disappointing given the stronger predictive power of cardiac function for PAH outcomes.
- The median treatment period of 7.5 months precluded the ability to establish the long-term durability of the treatment response, including safety and adverse event profile.

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Kavita Dave, MD, FRCP
Harefield Hospital, UK

Kavita Dave, M.D.
EDITOR
ISHLT.ORG

Elexacaftor/tezacaftor/ivacaftor projected survival and longterm health outcomes in people with cystic fibrosis with homozygous *F508del*

Lopez, et al. *Journal of Cystic Fibrosis* 2023 | https://doi.org/10.1016/j.jcf.2023.02.004

Study Highlights

Objective: Clear evidence that elexacaftor/tezacaftor/ivacaftor (ETI) is beneficial and safe in people with cystic fibrosis (pwCF). The impact on lifetime outcomes and survival is yet to be assessed.

Methods: A person-level microsimulation model was developed to estimate the benefits of ETI against other modulator combinations in pwCF with *F508del/F508del*.

Results: Median projected survival in pwCF treated with ETI was71.6 years. Treatment with ETI reduced disease severity, the number of pulmonary exacerbations and lung transplants. 0.1% of the ETI cohort received a lung transplant versus 9.6% of the best supportive cohor (BSC).

Conclusion: The magnitude of improvements in clinical and patient outcomes achieved with ETI have established ETI as a new benchmark for CFTR modulator therapy. Early intervention in CF is key in minimizing functional loss and maximizing survival.

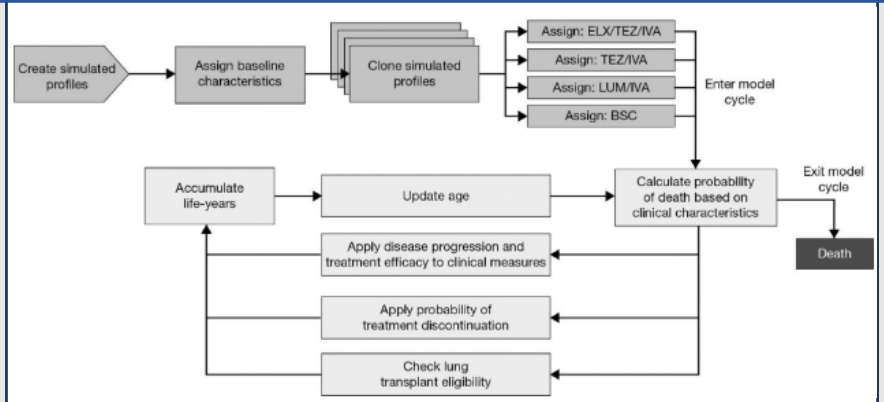
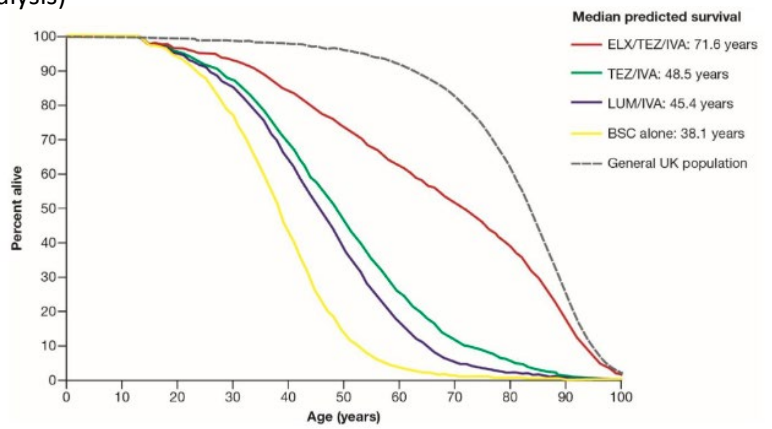


Figure 1. Simulation model structure
Abbreviations: BSC = best supportive care; ELX/TEZ/IVA = elexacaftor plus tezacaftor plus ivacaftor; LUM/IVA = lumacaftor plus ivacaftor; TEZ/IVA = tezacaftor plus ivacaftor.

Figure 2. Projected survival for pwCF homozygous for F508del-CFTR who receive ELX/TEZ/IVA, TEZ/IVA, LUM/IVA, or BSC alone (base case analysis)



Reviewer's Comments

- In addition to increasing the proportion of pwCF homozygous for F508del remaining alive at 10 years, there were considerable reductions in healthcare resource utilization over this period.
- There were significantly fewer hospitalizations, intravenous antibiotics (to treat exacerbations) and complete elimination for lung transplantation.
- Those requiring lung transplant in the future will be older with more comorbidities, and so higher risk.
- As life expectancy increases, increased risk for other diseases, particularly those prevalent in older populations (e.g., cancer, cardiovascular disease)

Limitations

- Cox proportional hazards equation, was developed in a CFTR modulator-naive population, to estimate the impact of clinical characteristics on survival, and not the impact of treatment.
- The simulation model can only evaluate variables selected for inclusion in the equation.
- The model assumes that the modulator treatment effects observed over 2–3 years would apply over the lifetime model horizon

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Mary Claire R. Orden, MD, FPCCP
Lung Center of the Philippines

Kavita Dave, M.D.
EDITOR

ISHLT.ORG

Triaging donor lungs based on a micro-aspiration signature that predicts adverse recipient outcome

Ramendra, et al. *J Heart Lung Transplant* Jan 2023 | https://doi.org/10.1016/j.healun.2022.12.024

Study Highlights

Objective: Determine total bile acids (TBA) – a marker of aspiration – utility in donor lung airway bronchial wash (LABW) to predict donor lung performance and recipient outcomes.

Methods: A single center retrospective cohort study measuring TBA in 605 consecutive lung donors 2012-2018 with LABW. TBA were compared in lungs unsuitable for transplant, needing assessment on ex-vivo lung perfusion (EVLP), and for transplantation.

Results: Donor TBA levels were highest in lungs unsuitable for transplant correlating with clinical assessment of aspiration. TBA concentration correlated with calcium, decreased pH, and increased pro-inflammatory mediators in EVLP perfusate. High donor TBA level was associated with an increased primary graft dysfunction rate and time to extubation, and shorter time to chronic lung allograft dysfunction.

Conclusion: Donor TBA level was associated with donor lung suitability, EVLP performance, and adverse lung transplant recipient outcomes.

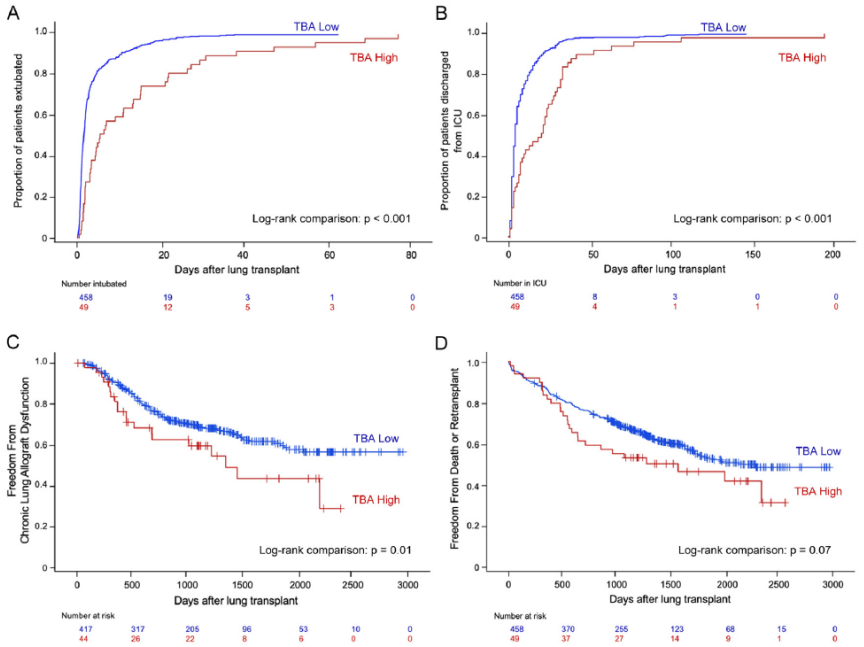

Figure 1. Kaplan-Meier curves for time to extubation and ICU discharge as well as cumulative risk of CLAD or death/retransplant in donors with high vs low LABW TBA level. TBA high = TBA>1245nM; TBA low = TBA<1245nM. p-values were calculated using log-rank comparisons.

Reviewer's Comments

- Large population size highlighted the impact of donor lung quality in patient outcomes.
- Identifying donor lungs with significant aspiration may allow targeted treatments and improve recipient outcomes.
- TBA point-of-care testing would help retrieval teams improve their decision-making capability to improve recipient outcomes.
- EVLP – even if TBA are high – appears to improve outcomes of lung transplant recipients though more work is needed to understand the pathophysiology.

Limitations

- TBA levels in this study had high specificity but very low sensitivity to predict unacceptable donor lungs.
- Multicenter studies needed.
- The baseline characteristics did not include ethnicity or the cause of pulmonary fibrosis in native lungs.
- There were no profile comparison between patients with good outcomes and those with bad (functional capacity, post-operative complications).

ISHLT JOURNAL WATCH
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Justin Rosenheck, DO
Ohio State University, Columbus, OH USA

Kavita Dave, M.D.
EDITOR
ISHLT.ORG

Subphenotypes of Frailty in Lung Transplant Candidates

JP Singer, et al. *Am J Transplant* Apr 2023 | https://doi.org/10.1016/j.ajt.2023.01.020

Study Highlights

Objective: Pre-lung transplant (LT) frailty has been shown to affect post-transplant outcomes; however, findings have been inconsistent. Using latent class analysis, sub-phenotypes of frailty may be identified.

Methods: This sub-study of a multicenter prospective cohort study identified 422 adult LT candidates with pre-frailty and frailty as measured by a short performance physical battery score <12. Biomarkers and clinical variables known to be associated with frailty were collected.

Results: Compared to frailty sub-phenotype 1 (SP1), SP2 was associated with higher systemic inflammation, dysregulated metabolism, sarcopenia, malnutrition, low adiposity, anemia and shorter 6-minute walk distance. The hazard ratio for SP2 candidate waitlist delisting or death was 4.0; (95%CI: 1.8-9.1). Post LT, SP2 patients had significantly longer median hospital lengths of stay and more unplanned returns to the operating room.

Conclusion: Distinct sub-phenotypes of frailty are identifiable and may explain differences in pre- and post-LT outcomes.

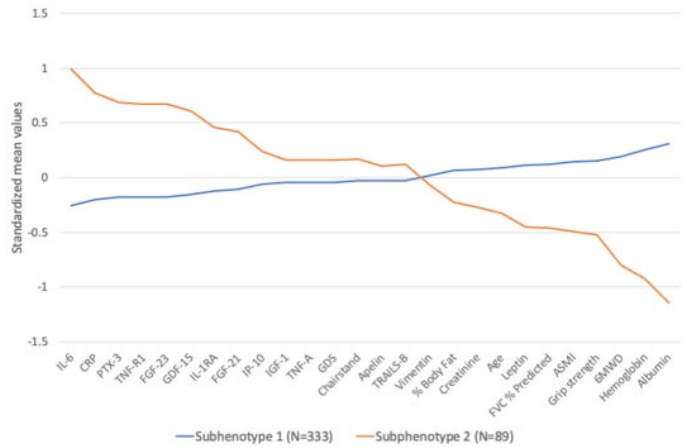

Figure 1: Differences in standardized mean values of variables by frailty subphenotypes

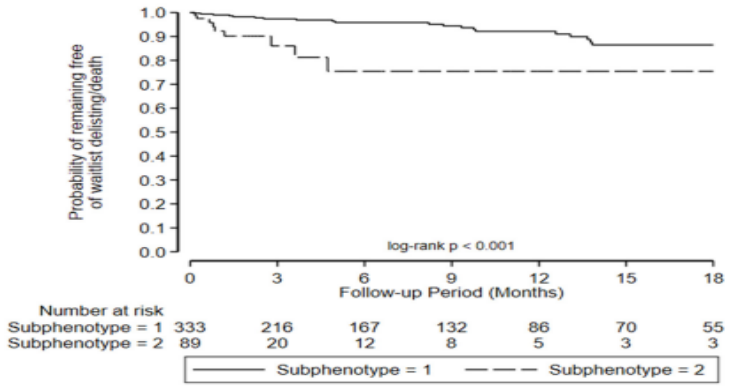

Figure 2: Time to waitlist delisting/death by frailty subphenotype

Reviewer's Comments

- Currently utilized phenotypic assessment tools and cumulative deficits models conceptualize pre-LT frailty as a continuum.
- Utilizing a battery of clinical variables and biomarkers representative of pathophysiologic pathways associated with frailty may be able to distinguish between sub-phenotypes of either hyperinflammatory or "benign" frailty.
- Sub-phenotyping frailty may allow for improved discrimination of pre- and post-transplant risk in LT candidates and offer a meaningful construct to design interventional and therapeutic studies.

Limitations

- Data missingness, and a relative lack of severely frail or severely ill patients may have obscured identification of additional sub-phenotypes.
- Effects of changes in pre-LT immunosuppression, and effects of subclinical infections were not captured by researchers.
- Few patients underwent serial assessments, thus conclusions on whether frailty sub-phenotypes are fixed or dynamic states could not be drawn.