Association of the novel clinical trial endpoint multicomponent improvement (MCI) with event-free survival in patients living with pulmonary arterial hypertension in the US

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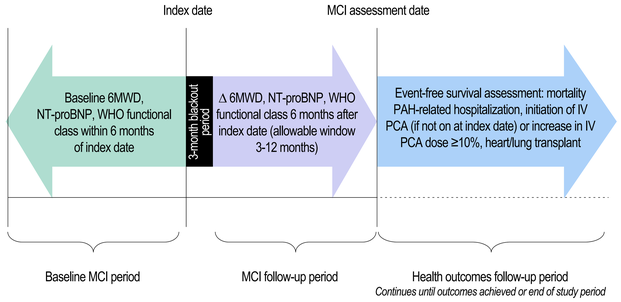
Purpose

- Pulmonary arterial hypertension (PAH) is a rare, progressive disorder in which remodeling of the pulmonary vasculature leads to increased pulmonary arterial pressure (PAP), eventually leading to right ventricular failure and death
- Three noninvasive measures – 6-minute walk distance (6MWD), World Health Organization functional class (WHO FC), and N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) – are used to assess clinical and risk status
- Multicomponent improvement (MCI) is a novel endpoint in the phase 3 trial for activin signaling inhibitor sotatercept. It is defined by attaining all 3 criteria of:
  - 6MWD increase of >30 m
  - WHO FC improvement or FC II maintenance
  - NT-proBNP reduction of ≥30% or NT-proBNP <300 pg/mL
- We conducted an exploratory evaluation of the association between MCI and event-free survival in real-world (RW) patients living with PAH in the US

Methods

- A retrospective cohort study was conducted in the TriAxia Health dataset, comprising electronic medical record data for 3,180 patients living with PAH from 4 academic medical centers (Massachusetts General Brigham, Stanford University, University of Pittsburgh Medical Center, University of Arizona)
- As shown in **Figure 1**, 3 study time periods were defined:
  - Baseline MCI period: 6-month window when all 3 baseline MCI components were collected, ending with observation of third MCI component at the "index date"
  - MCI follow-up period: 3-12 months after index date, ending with observation of third MCI component at "MCI assessment date"
  - Health outcomes follow-up period: Continues from MCI assessment date until outcome achieved or end of study period

Figure 1. Schematic of study time periods



- PAH was identified 1 of 3 ways:
  - Formal Dx by academic pulmonologist or cardiologist diagnosis
    or
  - Diagnostic right-heart catheterization (RHC) results consistent with PAH (mPAP >20 mmHg, PAWP ≤15 mmHg, and PVR >2WU). (Note: Criteria can be met by a single RHC or by data from multiple RHCs obtained within a 90-day period)
    or
  - Coding-based (ICD-9/ICD-10) diagnosis of PAH (I27.0, I27.20, I27.21, I27,81, I27.83, I27.89, I27.9) with no recorded codes for causes of other PH groups (I27.22, I27.23, I27.24, I27.29)
- All PAH patients aged ≥18 years receiving PAH therapy and with baseline 6MWD, WHO FC, and NT-proBNP and follow-up NT-proBNP and 6MWD (3-12 months later) were included
  - Per standard clinical practice, WHO FC was assumed unchanged at follow-up if not otherwise noted
- MCI achievement was evaluated at follow-up
- The proportion of patients with event-free survival was stratified by MCI achievement
- A time-to-event analysis for event-free survival over 10 years using Cox proportional hazards model with log-rank test was performed
  - Events were PAH-related hospitalization, initiation or titration of prostacyclin analogue, or heart/lung transplantation. R version 4.4.2 survival package performed computations

Disclosures

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TW, DL, and DR are employees of MSD and are Merck & Co., Inc., Rahway, NJ, USA shareholders.
BL & VV are employees of TriAxia Health, who was paid to perform this analysis by MSD. VM has received consulting fees from MSD.

Results

- The analysis included 116 patients. Mean (±SD) follow-up was 4.79 ±3.34 years. Key demographic and clinical characteristics of the study cohort are in **Table 1**

Table 1. Study population characteristics

Patient characteristics		N = 116	%	Mean (SD)
Age at index date	—	—	—	53.1 (15.6)
Sex	Female	80	68.9%	
Timing of diagnosis	Newly Dx (<6 months of index date)	65	56.0%	
	Prevalent	51	44.0%	
PAH subtype	IPAH+HPH+DTI	65	56.0%	
	PAH-CTD	26	22.4%	
	PAH-OTHER	25	21.6%	
PAH treatment at baseline	Monotherapy	39	33.6%	
	Dual	22	19.0%	
	Triple	1	0.9%	
	Other/None/Unknown	54	46.6%	
PAH treatment at follow-up	Monotherapy	48	41.4%	
	Dual	49	42.2%	
	Triple	4	3.5%	
	Other/None/Unknown	15	12.9%	

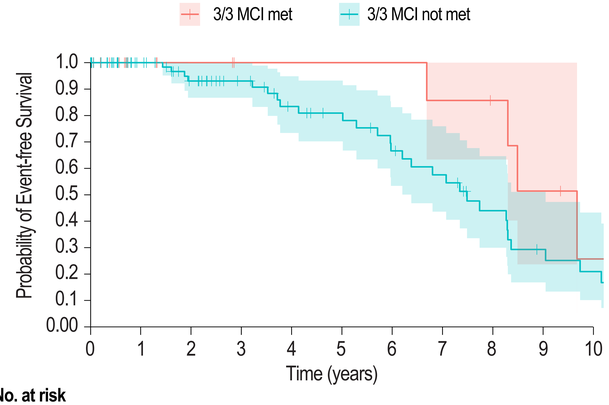
Limitations

- Real-world data from US academic centers is not representative of all US PAH patients
- No data collected prospectively; analysis limited to data recorded during clinical practice

Clinical implications

- New endpoints that show improvement are needed in PAH clinical trials. Future prospective evaluation of MCI could support it as a meaningful prognostic indicator, but improved assessment of 6MWD, WHO FC, and NT-proBNP are needed for risk and MCI achievement to have clinical utility

Figure 2. Time-to-event analysis Kaplan-Meier curve for event-free survival



No. at risk

3/3 MCI met	18	11	9	7	7	7	7	6	5	3	1
3/3 MCI not met	89	63	51	41	33	29	23	19	12	7	5

- 19 patients (16.4%) achieved MCI
- Over 10 years, 31/96 patients not achieving MCI (32.3%) and 4/19 patients achieving MCI (21.1 %) experienced an event (HR 0.343 [95%CI, 0.118-0.996])
- This result is borderline significant with a log-rank $P = 0.049$. Due to small sample size, the results must be interpreted with caution (**Figure 2**)

Conclusion

- Achievement of MCI was associated with 10-year event-free survival in a real-world US cohort of PAH patients

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