ISHLT 2022
42nd Annual Meeting & Scientific Sessions
John B. Hynes Memorial Convention Center
Boston, Massachusetts, USA
Wednesday, 27 April – Saturday, 30 April

Extended Cold Preservation Times Are Not Associated With Increased Post-transplant Mortality After Ex Vivo Lung Perfusion (EVLP) at a Dedicated Facility Using a Centralized Lung Evaluation System (CLES)

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Relevant Financial Relationship Disclosure Statement

Extended Cold Preservation Times Are Not Associated With Increased Post-transplant Mortality After Ex Vivo Lung Perfusion (EVLP) At A Dedicated Facility Using A Centralized Lung Evaluation System (CLES)

Jorge M. Mallea, MD

I have the following relationships with ACCME defined ineligible companies:

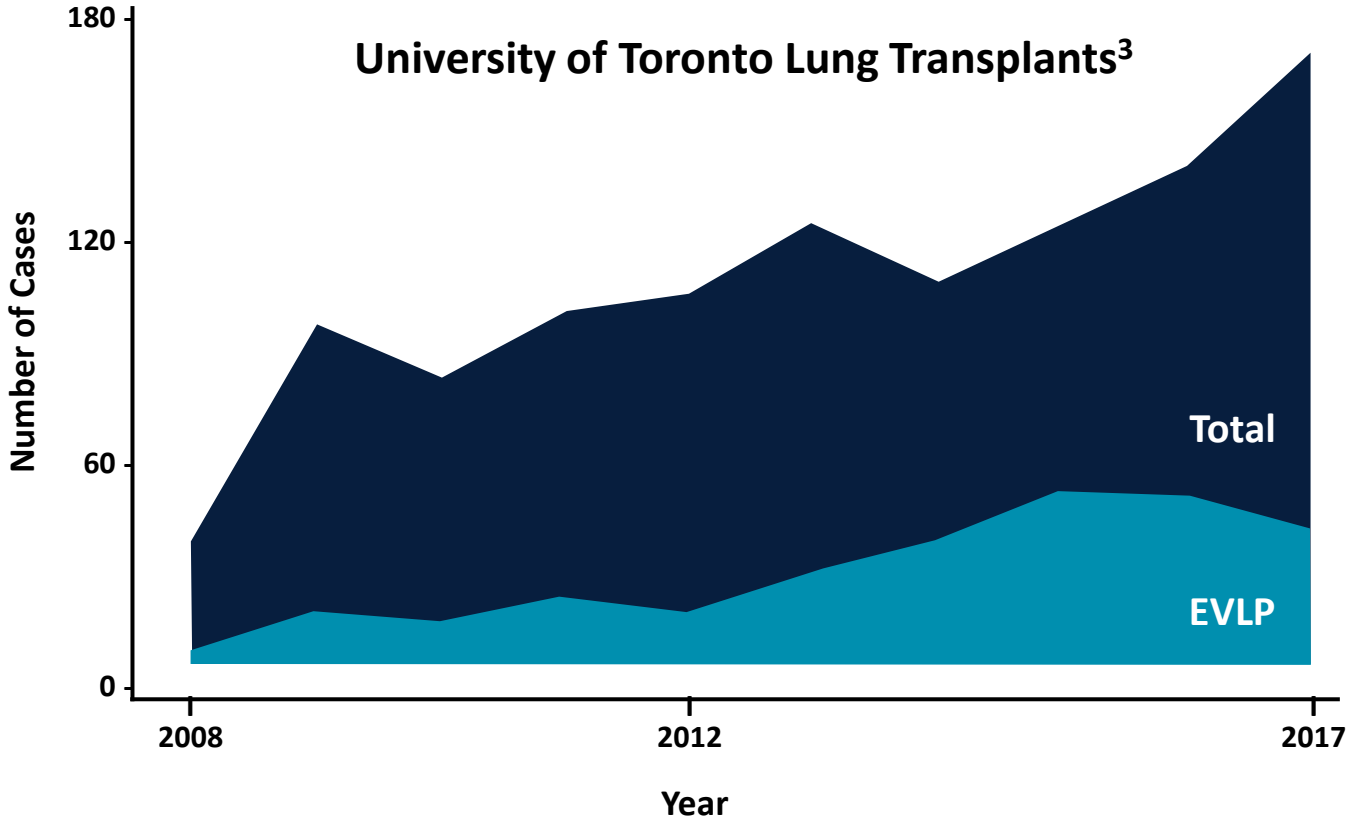
Lung Bioengineering, Medical Director
United Therapeutics Corp, Consultant

I **will** discuss off-label use and/or investigational use of the following drugs or devices:

Centralized Lung Evaluation System (CLES)

Background

- In the US, only 23% of lungs offered for transplantation are recovered[1]
- EVLP allows for the evaluation of additional lung grafts
- **Centralized Lung Evaluation Systems (CLES)** could safely expand access to EVLP, overcoming limitations due to equipment, resources, and expertise
- Extended preservation times have been suggested to be associated with increased 1-year mortality[2]

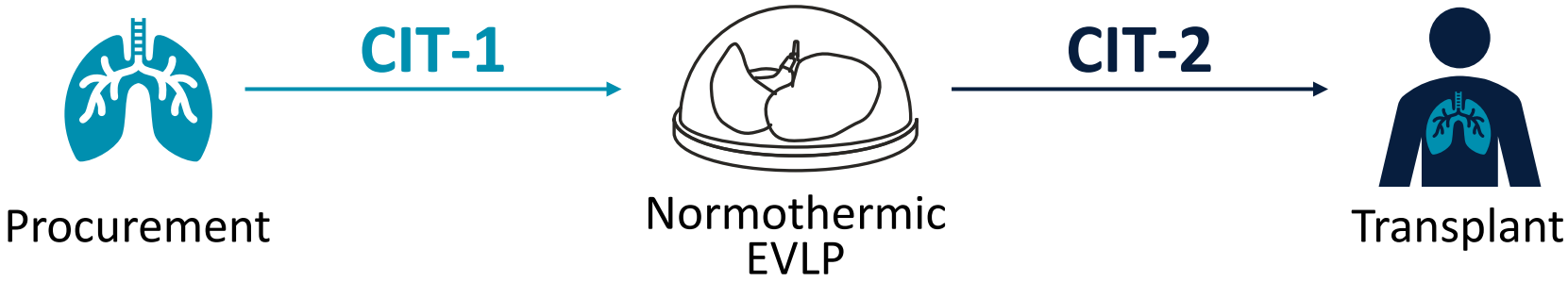


EVLP = Ex Vivo Lung Perfusion; CLES = Centralized Lung Evaluation System

1.Valapour M, Lehr CJ, Skeans MA, et al. *Am J Transplant*. 2021;21(S2):441-520.
2.Leiva-Juárez, MM, Urso A, Arango Tomás E, et al. *J Heart Lung Transplant*. 2020;39(9):954-961.
3.Figure representative of Cypel M, Yeung JC, Donahoe L, et al. *J Thorac Cardiovasc Surg*. 2019; S0022-5223(19)31732-5.

Aim

To address the association of extended Cold Ischemia Times before (CIT-1) and after EVLP (CIT-2) on 1-year mortality in the CLES feasibility trial



Centralized Lung Evaluation System (CLES)

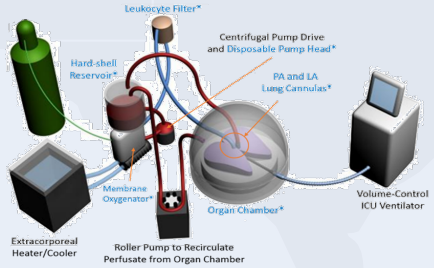
DONOR HOSPITAL

LB-1

CLES

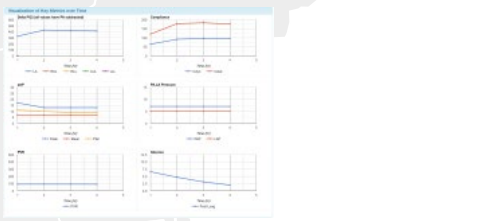
RECIPIENT HOSPITAL

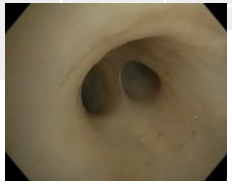
Toronto Ex Vivo Lung Perfusion System (TES)

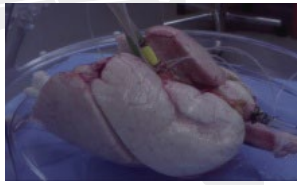


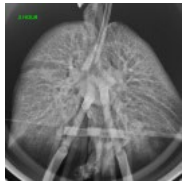
Case Management Exchange (CMX)

Key Assessment Parameters			
Hour	1	2	3
PAP	7	7	7
LAP	5	5	5
PVR	91.4	91.4	91.4
Peak	17	13	13
Cdyn	65	92	96
Cstat	121	178	183
PvO2/FiO2	417.8	513.6	502.4
Delta pO2	325.9	428	417.8









CMX = Case Management Exchange

Study Design and Plan

Unblinded, Non-randomized, Feasibility Study

7 US Study Sites within 750 mi of CLES facility

ClinicalTrials.gov number NCT02234128

18+ Years
Jul 2015 – Nov 2019

Rejected for standard transplant
N=63

SAMPLE SIZE = **112 DONORS**

Accepted for standard transplant
N=49

1 CLES GROUP
N=66
(63 Donors)

SAMPLE SIZE = **115 RECIPIENTS**

2 CONTROL GROUP
N=49
(49 Donors)

Matched with the EVLP by:
- ✓ Study Center
- ✓ Single or Double lung transplant
- ✓ Lung Allocation Score Disease Diagnosis Group (LAS-DDG)

Inclusion and Exclusion Criteria

X CLES ELIGIBILITY- EXCLUSION CRITERIA

- Donor lungs were excluded for
  - confirmed pneumonia/aspiration
  - persistent purulent secretions
  - significant mechanical injury/trauma
  - HIV, HCV, HBV, or other active infectious disease
  - CIT-1 expected to exceed ten hours

+ RECIPIENT INCLUSION CRITERIA

✓18+

✓Informed consent prior to study

✓ CLES TRANSPLANT- ACCEPTANCE CRITERIA

✓**Final CLES PaO_2/FiO_2 ratio of ≥ 350 mmHg** at the end of EVLP

✓**<15% increase PAP** and **PVR**, and **<15% decrease Cstat** from first hour of EVLP to final measurements

AND

✓Physician must be clinically satisfied with the lung evaluation

– RECIPIENT EXCLUSION CRITERIA

- Same side lung re-transplantation
- Multiple-organ transplantation
- Live donor lobar transplant
- HIV, Hep B, Hep C or *Burkholderia cepacia* infection
- Subjects in the ICU at the time of the initial lung offer requiring mechanical ventilation, or extracorporeal life support (ECLS)

Main Study Objectives

Objective: **Evaluate the feasibility and safety of the CLES** to evaluate lungs not otherwise used for transplantation

PRIMARY ENDPOINTS

PGD3 MEASURED AT 72H POST TRANSPLANT

SURVIVAL AT 30 DAYS

SECONDARY & EXPLORATORY ENDPOINTS

SUBJECT SURVIVAL AT 12 MONTHS

PGD SCORE (GRADES 0-3) MEASURED AT 0H 24H 48H 72H POST TRANSPLANT

TIME TO FIRST EXTUBATION

ICU LENGTH OF STAY (LOS)

TOTAL PRESERVATION TIME (TPT)

HOSPITAL LOS

ADVERSE EVENTS

BOS AT 1-YR POST-TRANSPLANT

FEV_1 AT 1-YR POST-TRANSPLANT

REHOSPITALIZATIONS WITHIN 1-YR POST-TRANSPLANT

Results have been **submitted** for publication.

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Transplant Center	Time to LB-1*
1 Mayo Clinic Jacksonville, FL	2 hrs 50 min
2 Loyola University Medical Center Chicago, IL	2 hrs 55 min
3 Cleveland Clinic Cleveland, OH	2 hrs
4 Duke University Health System Durham, NC	1 hr 50 min
5 UPMC Pittsburgh, PA	1 hr 40 min
6 University of Maryland Medical Center Baltimore, MD	25 min
7 Inova Fairfax Medical Campus Falls Church, VA	25 min

*Times provided by Nationwide Organ Recovery Transport Alliance (NORA)

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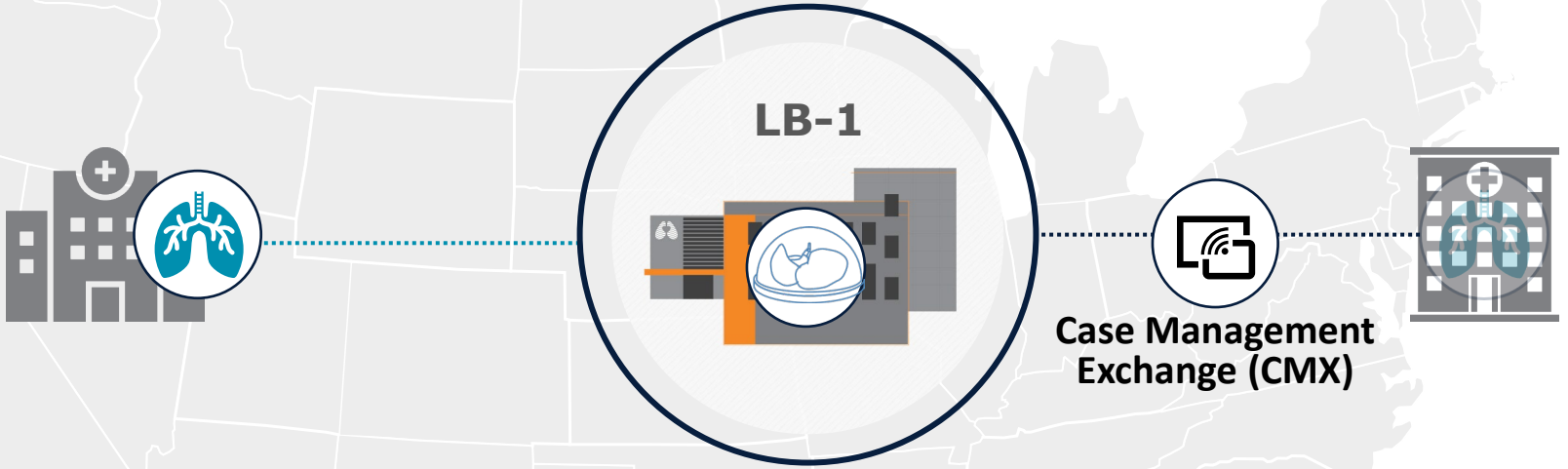
Cold Ischemia Times (CIT)



	CIT-1	EVLP	CIT-2
Time allowed by trial protocol	10 h max	3-6 h	6 h max
	Donor cross clamp to EVLP start	Normothermic Perfusion	EVLP end to **removal from cold storage**

CIT = cold ischemia time

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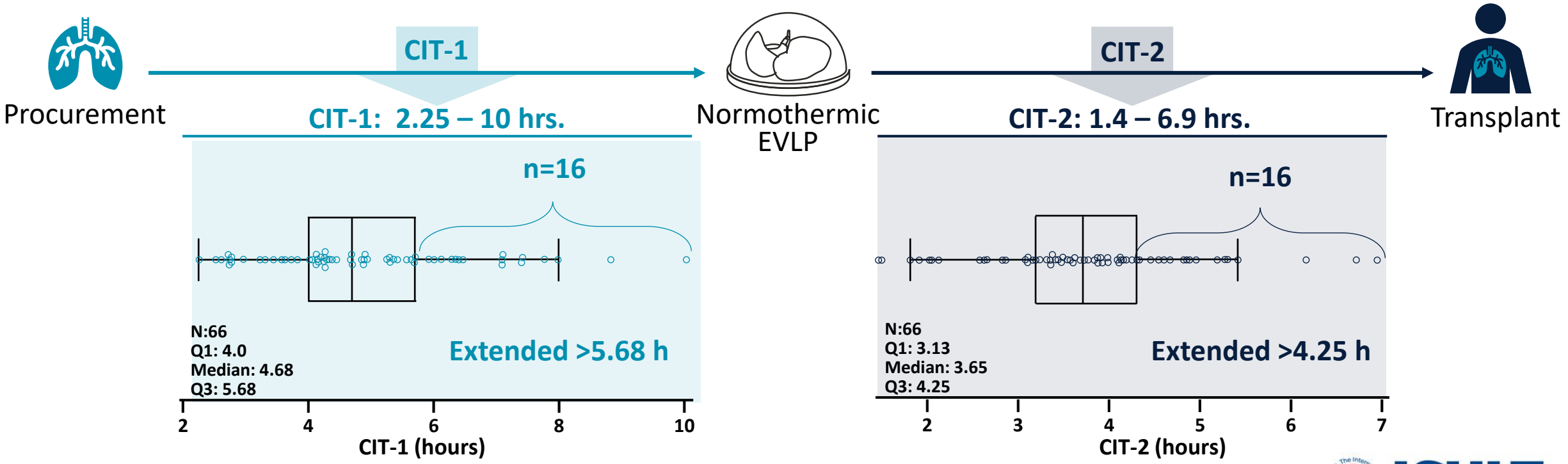
Methods

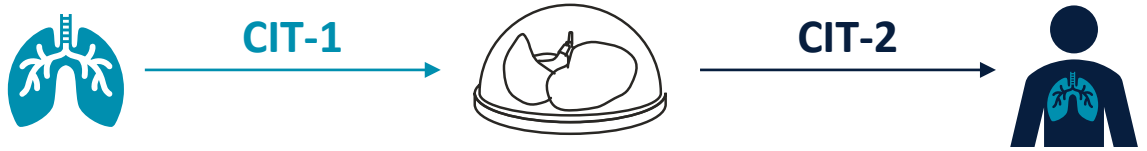
- Subgroup analysis of the 66 recipients of EVLP lungs in the CLES feasibility trial
- The top quartile of CITs were classified as Extended
- Recipient 1-year survival compared for Extended (n = 16) and Non-Extended CITs (n = 50)



Donor Demographic Characteristics

	CIT-1 (Pre-EVLP)			CIT-2 (Post-EVLP)		
CHARACTERISTIC	**Non-Extended** (n=50)	**Extended** (n=16)	**p-value**	Non-Extended (n=50)	Extended (n=16)	p-value
Female, n (%)	23 (46)	7 (43.75)	1.00	23 (46)	7 (43.75)	1.00
Age, years (range)	33.5 (16-66)	32 (11-55)	0.298	37 (15-66)	26 (11-59)	**0.012**
Last PaO2, mmHg (range)	323 (82-515)	390 (77-615)	0.139	342 (82-615)	367.5 (77-515)	0.565
Type of Donor, n (%)			0.324			0.743
DBD	39 (78)	10 (62.5)		38 (76)	11 (68.75)	
DCD	11 (22)	6 (37.5)		12 (24)	5 (31.25)	
Cause of Death, n (%)			0.573			**0.033**
Anoxia/cardiac arrest	24 (48)	7 (43.75)		28 (56)	3 (18.75)	
Head trauma	13 (26)	4(25)		11 (22)	6 (37.5)	
Cerebrovascular/stroke	12 (24)	4 (25)		10 (20)	6 (37.5)	
CNS tumor	0 (0)	1 (6.25)		0 (0)	1 (6.25)	
Other	1 (2)	0 (0)		1 (2)	0 (0)	
Pulmonary edema, n (%)	7 (14)	4 (25)	0.440	9 (18)	2 (12.5)	0.720
≥10 units transfusion, n (%)	3 (6)	1 (6.25)	1.00	3 (6)	1 (6.25)	1.00

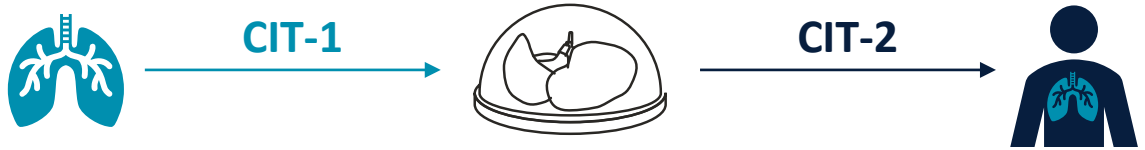
Age and Last PaO2 expressed as median (range). Comparisons for categorical variables were made using exact test for Pearson's Chi-square. Comparisons for continuous variables across groups are based on the Mann-Whitney test.

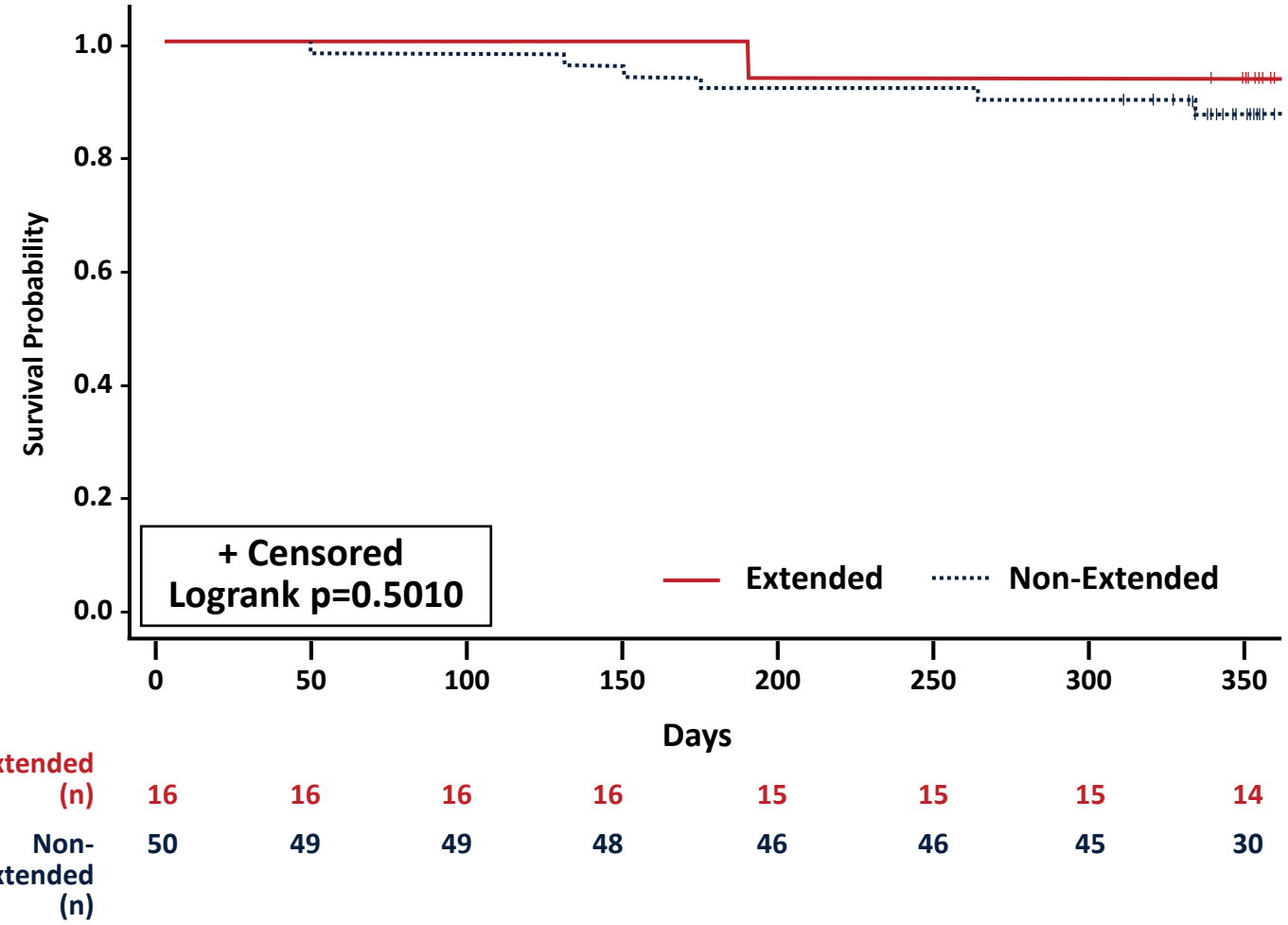


Recipient Demographic Characteristics

	CIT-1 (Pre-EVLP)			CIT-2 (Post-EVLP)		
CHARACTERISTIC	**Non-Extended** (n=50)	**Extended** (n=16)	**p-value**	Non-Extended (n=50)	Extended (n=16)	p-value
Female, n (%)	20 (40)	11 (68.75)	0.082	25 (50)	6 (37.5)	0.407
Age, years (range)	62.5 (20-72)	61 (29-68)	0.157	63 (20-72)	61 (29-72)	0.463
LAS, score (range)	35.43 (32.2-78.9)	35.30 (32.2-57.1)	0.570	35.77 (32.24-78.93)	35.21 (32.18-54.94)	0.616
CIT-1, hours (range)	4.25 (2.25-5.7)	7.07 (5.9-10)	**<0.0001**	4.4 (2.25-8.8)	5.44 (3.22-10)	0.080
EVLP time, hours (range)	4.03 (3.5-5.8)	3.81 (3.5-5.7)	0.342	3.98 (3.5-5.7)	4.36 (3.5-5.8)	0.234
CIT-2, hours (range)	3.57 (1.4-6.9)	3.89 (2.6-6.1)	0.108	3.4 (1.4-4.25)	4.87 (4.27-6.9)	**<0.0001**
Bilateral transplant, n (%)	21 (42)	14 (87.5)	**0.002**	26 (52)	9 (56.25)	0.783
Diagnosis, n (%)			0.747			0.689
Group A	22 (44)	8 (50)		24 (48)	6 (37.5)	
Group B	1 (2)	0 (0)		1 (2)	0 (0)	
Group C	1 (2)	1 (6.2)		1 (2)	1 (6.25)	
Group D	26 (52)	7 (43.8)		24 (48)	9 (56.25)	

Age, LAS, CIT-1, EVLP, and CIT-2 expressed as median (range). Comparisons for categorical variables were made using exact test for Pearson's Chi-square. Comparisons for continuous variables across groups are based on the Mann-Whitney test. UNOS group A: Obstructive lung disease; UNOS group B: Pulmonary vascular disease; UNOS group C: Cystic Fibrosis; UNOS group D: Restrictive lung disease





CIT-1

1 year-mortality

6.25% Extended

12.0% Non-Extended

(*p*=0.67)

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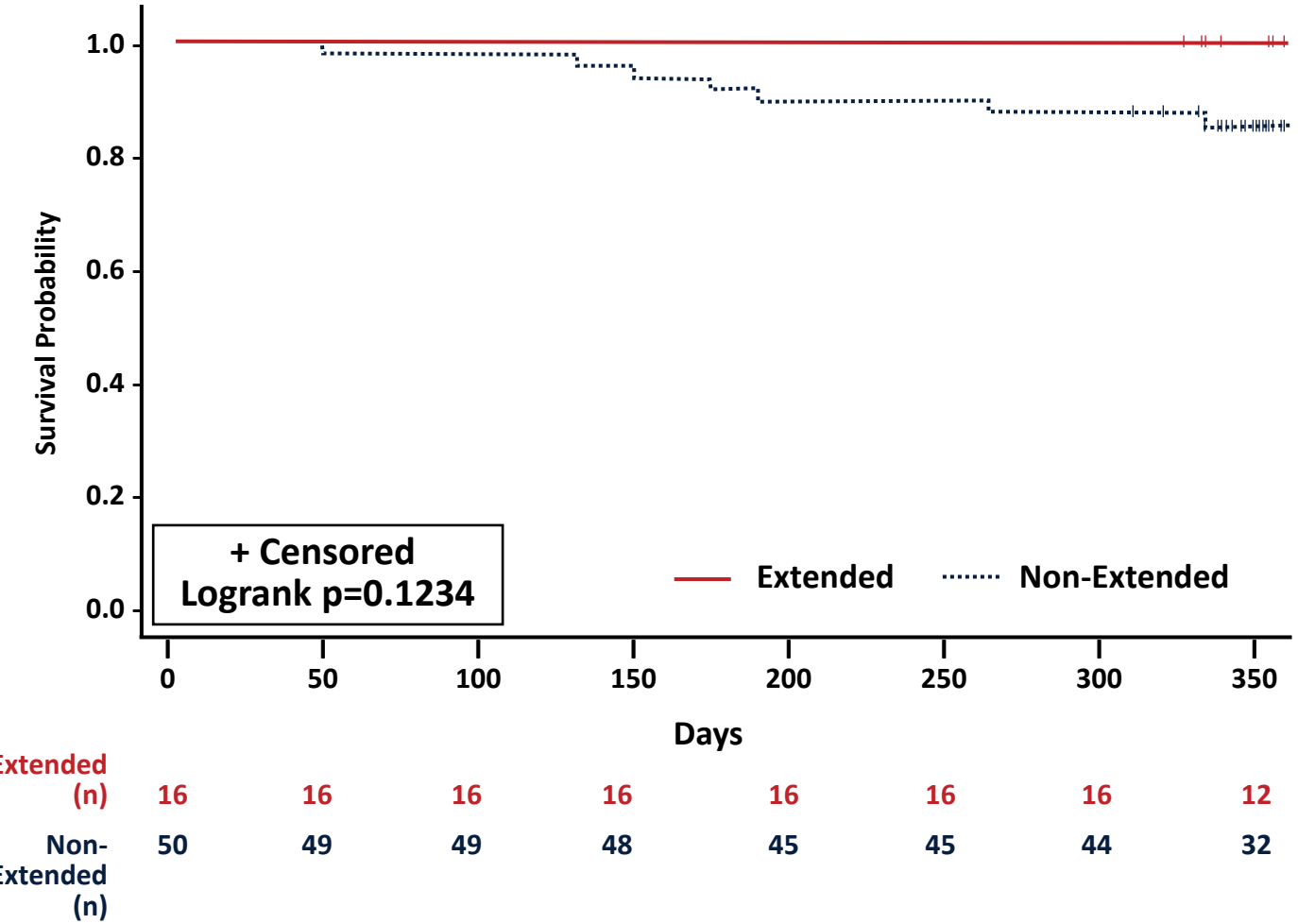
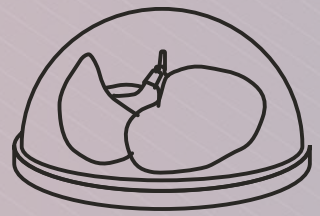
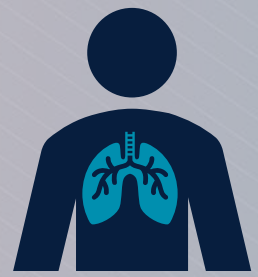




CIT-2



1 year-mortality

0.0% Extended

14.0% Non-Extended

(*p*=0.18)

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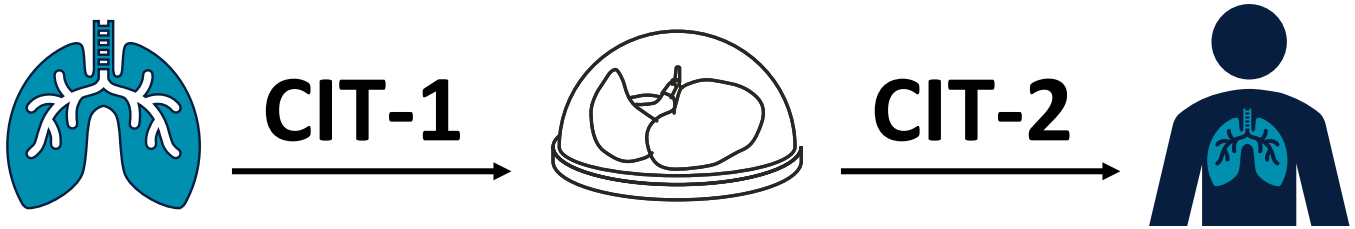
Summary

In recipients of lungs that underwent EVLP at a Dedicated Facility using a Centralized Lung Evaluation System (CLES):



Extended CIT-1 **was <u>not</u> associated with** increased 1-year mortality

Extended CIT-2 **was <u>not</u> associated with** increased 1-year mortality

Results support that extended cold ischemic times are not associated with 1-year mortality, which **may allow longer timelines and increased use of donor lungs**

SCAN ME

CLES Pivotal Trial is ongoing
(EVP-DEV-LTX-301)
Primary Endpoint:
Survival at 1-Year

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Thank you!

- Donors and their families
- Recipients and caregivers
- Clinical trial investigators and coordinators
- Marcelo Cypel, Thomas K Waddell, and Shaf Keshavjee at the Lung Transplant Program, University of Toronto

Clinical Trial Transplant Centers:

- Cleveland Clinic
- Duke University Health System
- Inova Fairfax Medical Campus
- Loyola University Medical Center
- Mayo Clinic Florida
- University of Maryland Medical Center
- University of Pittsburgh Medical Center