mesoblast

the regenerative medicine company

Top-line Results for Remestemcel-L in COVID-19 ARDS

2021 Stem Cells, Cell Therapies, and Bioengineering in Lung Biology and Diseases

JULY 2021

ASX: MSB; Nasdaq: MESO

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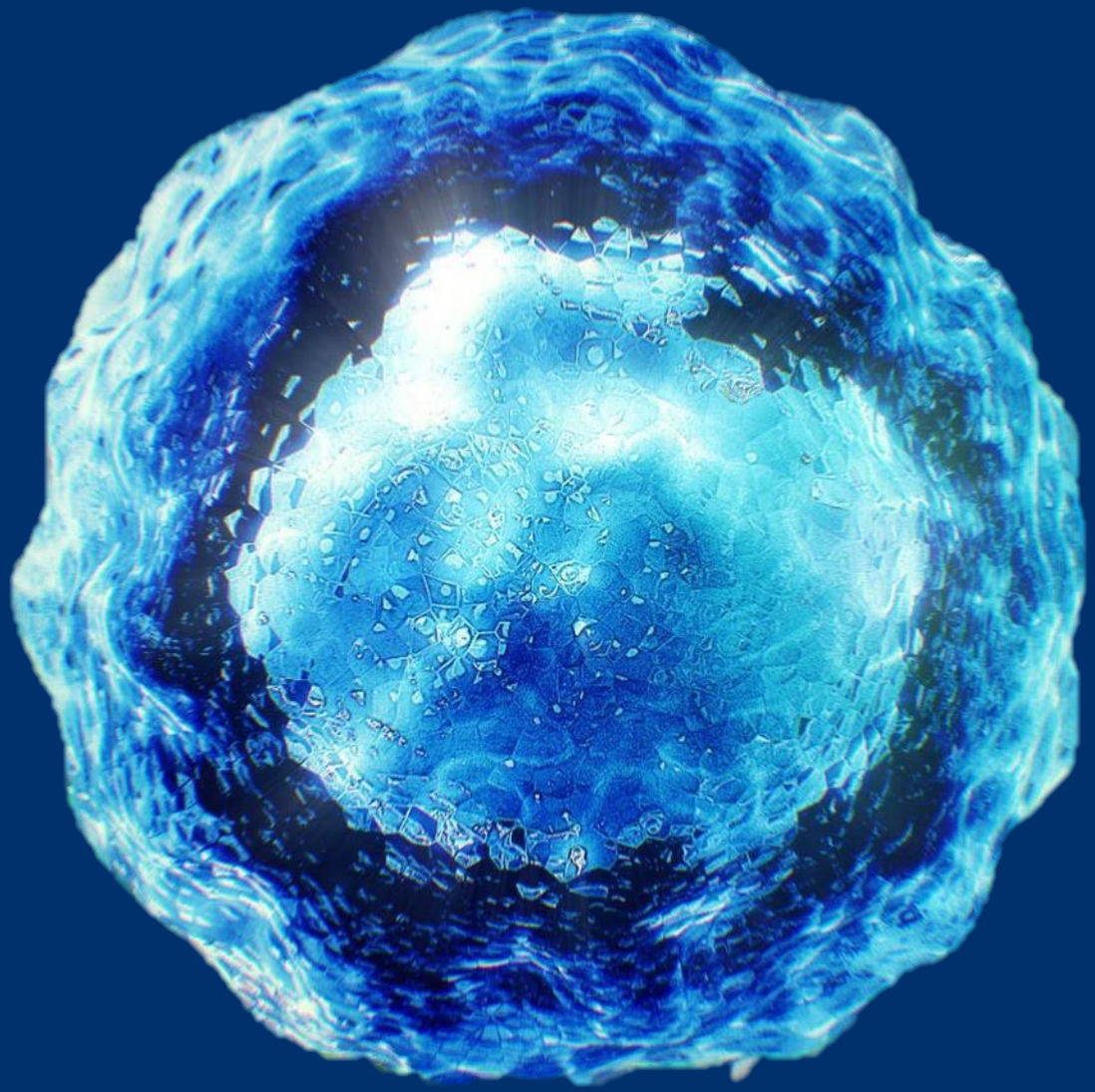
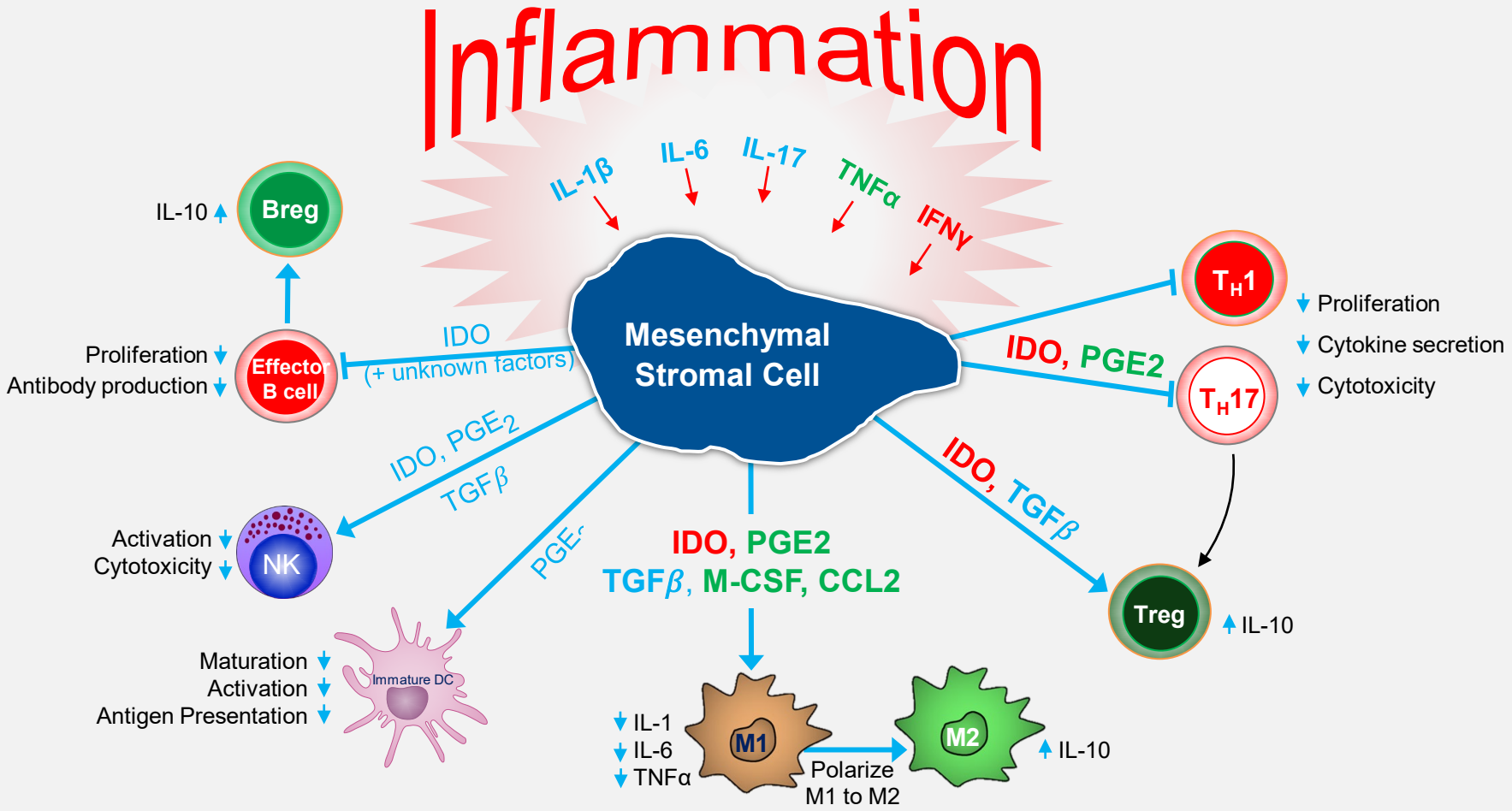
Our Mission

Mesoblast is committed to bringing to market innovative cellular medicines to treat serious and life-threatening illnesses



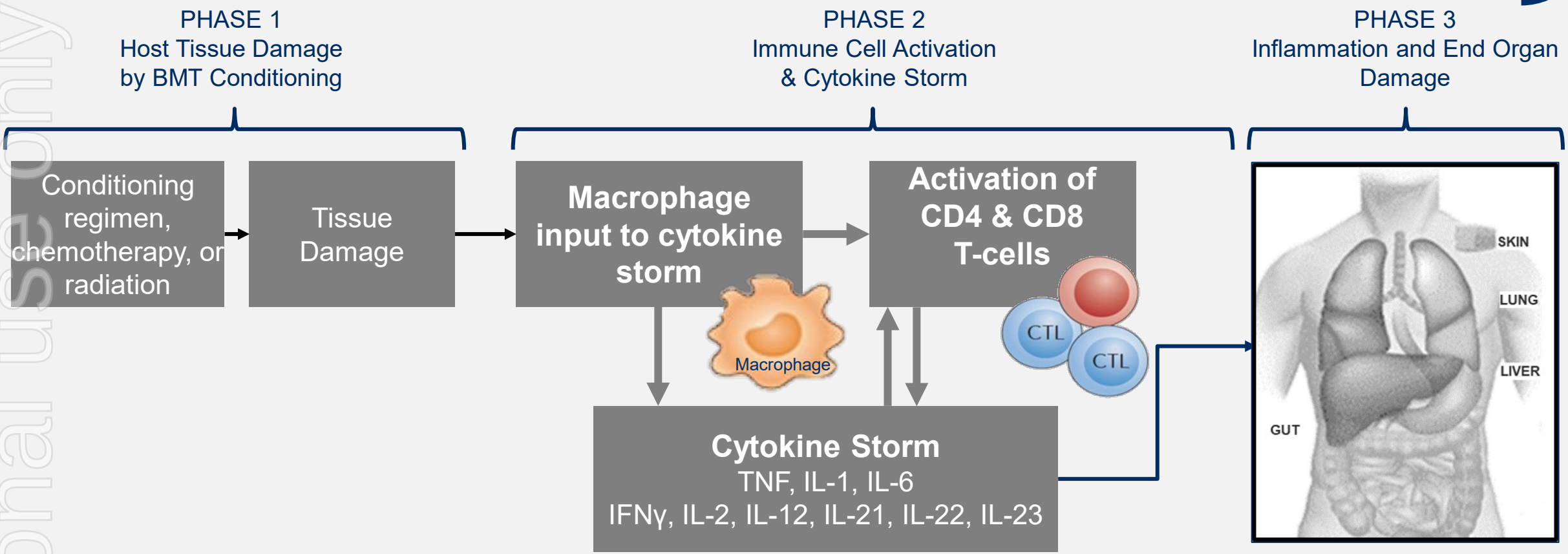
Platform Technology – Mechanism of Action (MOA)

Our mesenchymal stromal cells respond to and are activated by multiple inflammatory cytokines through surface receptors, resulting in orchestration of an anti-inflammatory cascade



Source: Data on file

Acute Graft versus Host Disease (GVHD): A Prototypic Disease Driven by Cytokine Storm



Modified from Blazar et al., Nature Reviews Immunology 12: 443 – 458

Remestemcel-L in Steroid Refractory Acute GVHD: Clinical Evidence for a MOA Applicable to Various Inflammatory Conditions

Consistent efficacy and safety outcomes in a total of 309 children from three studies:

- Remestemcel-L was used as first-line therapy in a randomized controlled Phase 3 trial of 260 patients, with SR-aGVHD, including 27 children
- Remestemcel-L was used as salvage therapy in an expanded access program in 241 children with SR-aGVHD, 80% of whom had Grade C/D disease, and failed institutional standard of care
- Remestemcel-L was used as first-line therapy in Mesoblast's open-label Phase 3 trial in 54 children with SR-aGVHD, 89% of whom had Grade C/D disease

		Protocol 280 (pediatric)		EAP 275	Study 001
	MAGIC[1] N=30[2]	Placebo N=13	Remestemcel-L N=14	Remestemcel-L N=241	Remestemcel-L N=54[3]
Day 28 Overall Response	**43%**	**38%**	**64%**	**65%**	**69%**
Day 100 Survival	**57%**	**54%**	**79%**	**66%**	**74%**

Source: ODAC Advisory Committee Briefing Document and Presentation August 2020.

1. Mount Sinai Acute GVHD International Consortium (MAGIC) - a group of ten BMT centers throughout the US and Europe whose purpose is to conduct ground-breaking clinical trials in GVHD, including developing informative biorepositories that assist in developing treatments that can guide GVHD therapy.
2. Two subjects in the MAGIC cohort had follow-up <100 days; these subjects are excluded from the respective survival analyses.
3. GVHD001 had 55 randomized patients, however one patient dropped out before receiving any dose of remestemcel-L

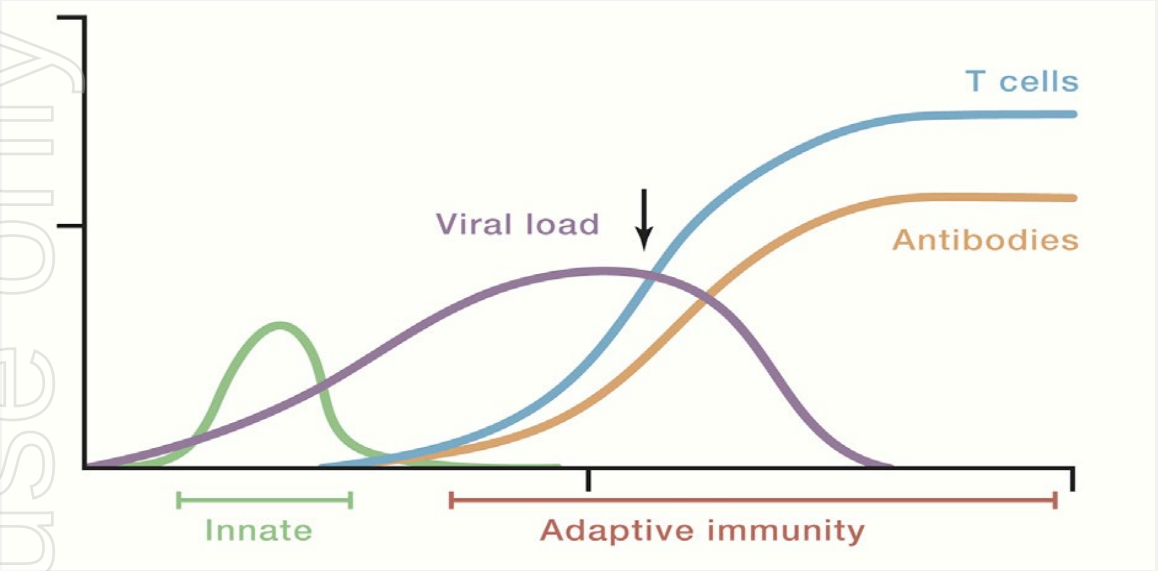
Cytokine Storm in COVID-19 ARDS Closely Resembles Secondary Hemophagocytic Lymphohistiocytosis (sHLH): A T Cell Driven Disease

- Secondary (or acquired) hemophagocytic lymphohistiocytosis (sHLH) is a life-threatening disease characterized by lymphocyte and macrophage hyperinflammation triggered by viral infections such as EBV, CMV, HHV)[1]
- Lung involvement including ARDS is common and of poor prognosis (>50% mortality)[2]
- Hematological manifestations involve severe anemia due to activated macrophages engulfing red blood cells.
- Excessive immune activation driven by cytotoxic T cells and macrophages resulting in cytokine storm and release of IFN-γ, IL-6 and TNF-α, and reduction in regulatory T cells[3]
- Activated CD8 T cells producing IFN-γ appear to be central to disease pathogenesis

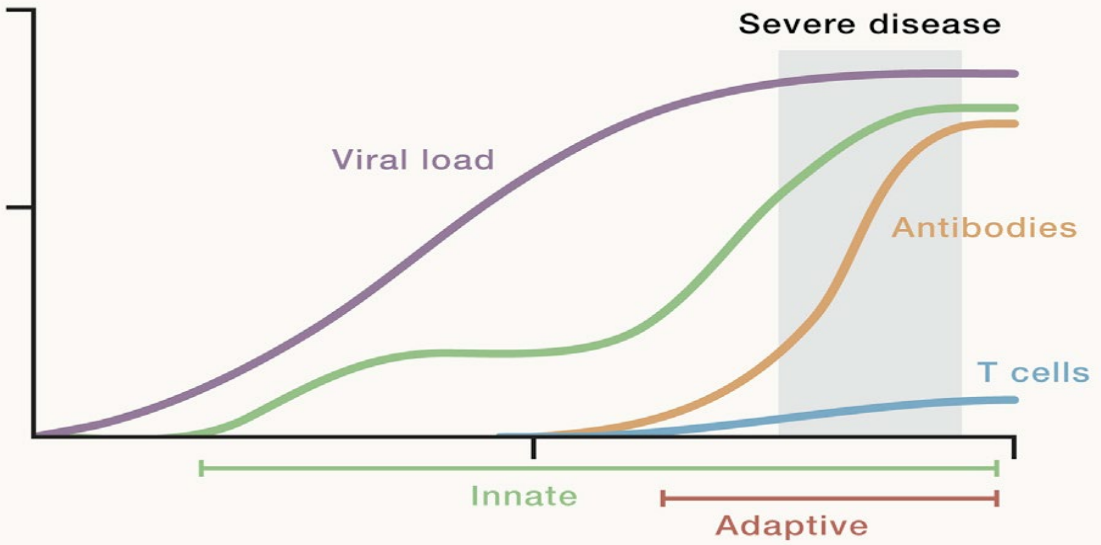
1. Bode et al. Recent advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis. *Arthritis Res Ther*. 2012 Jun 8;14(3):213
2. Seguin et al. Pulmonary Involvement in Patients With Hemophagocytic Lymphohistiocytosis. *Chest*. 2016 May;149(5):1294-301
3. Humblet-Baron et at. IFN-γ and CD25 drive distinct pathological features during hemophagocytic lymphohistiocytosis. *J Allergy Clin Immunol*. 2019 Jun; 143(6): 2215–2226.e7

Robust Adaptive *Naïve* T Cell Response in COVID-19 is Critical for Viral Clearance
Lack of Adequate T Cell Response Results in Increased Viral Load and Severe Disease

Average SARS2 infection



Severe SARS2 infection



- Analysis of SARS-CoV-2-specific adaptive immune responses during acute COVID-19 identifies coordination between SARS-CoV-2-specific CD4 T cells and CD8 T cells to limit disease severity
- Aged individuals often exhibit uncoordinated adaptive responses, potentially tied to scarcity of naive T cells highlighting immunologic risk factors linked to disease severity

Rydyznski Moderbacher et al., Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. 2020, Cell 183, 996–1012; doi.org/10.1016/j.cell.2020.09.038
Sette A and Crotty S. Adaptive immunity to SARS-CoV-2 and COVID19.https://doi.org/10.1016/j.cell.2021.01.007

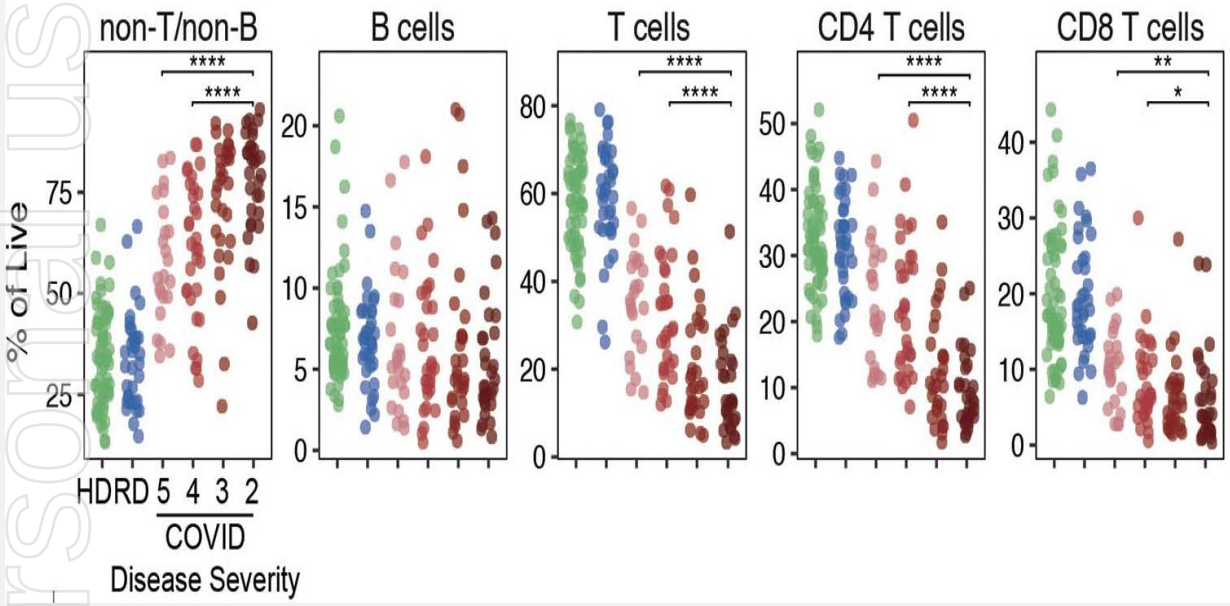
Severe COVID-19 Disease is Associated with Progressive **Depletion** of *Naïve* T Cells, and Aberrant **Activation** of *Non-Naïve* CD4 and CD8 T Cells

Death	COVID 1	Death
	COVID 2	Invasive mechanical ventilation
	COVID 3	Non-invasive ventilation
	COVID 4	Supplemental Oxygen
	COVID 5	No supplemental Oxygen; Requires medical care
	COVID 6	No supplemental Oxygen; No medical care
	COVID 7	Limitation in activities and/or requiring Oxygen
Mild	COVID 8	No limitation in activities

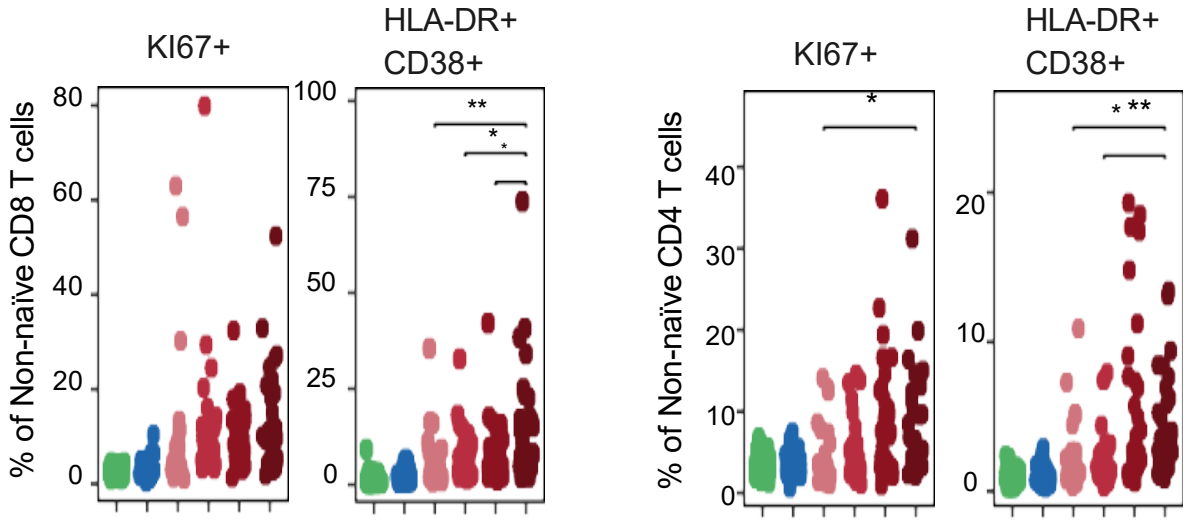
Hospitalization

Based off NIH Ordinal Scale

Naïve T Cells



Non-Naïve Activated T Cells



Frequencies of activated CD8 or CD4 T cells, shown as percent of non-naïve CD8 and CD4 T cells expressing KI67⁺ and HLA-DR⁺CD38⁺

D. Mathew et al., Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications Science 369, eabc8511 (2020). DOI:10.1126/science.abc8511

Severity of COVID-19 Infection is Associated with Increased Activated T Cells Producing IFN-γ and GM-CSF

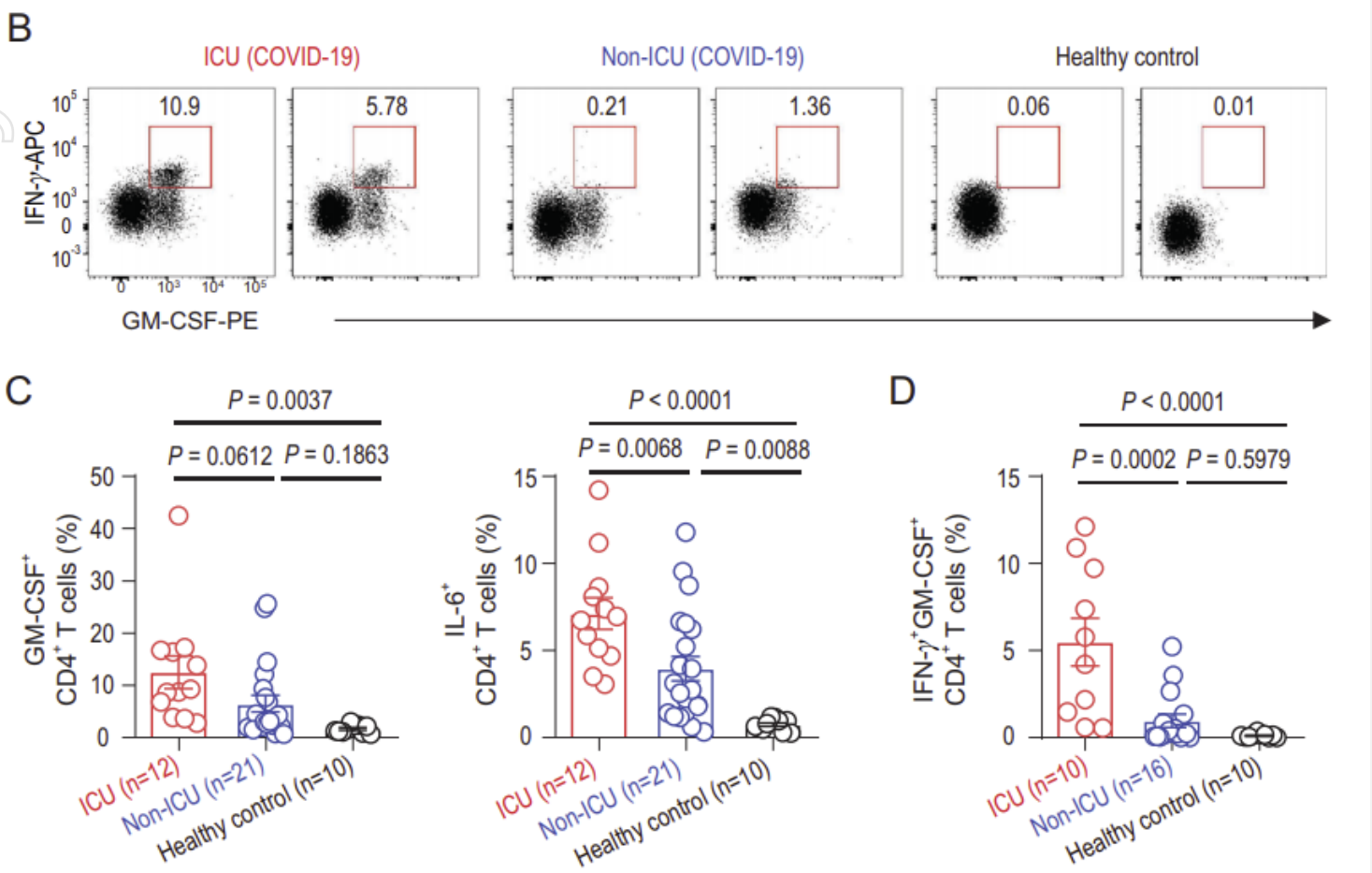


Figure: Pathogenic Th1 cells with high expression of GM-CSF in COVID-19 patients.

(B) Representative density plots showing an analysis of co-expression of GM-CSF and IFN-γ in gated CD45+CD3+CD4+ T-cells isolated from peripheral blood in healthy controls, ICU and non-ICU patients of COVID-19.

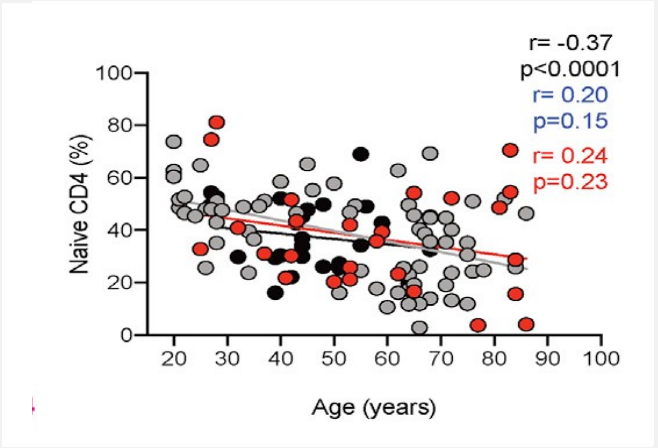
(C) Statistics calculated by the percentage of GM-CSF+ or IL-6+ cells from CD4+ T-cells.

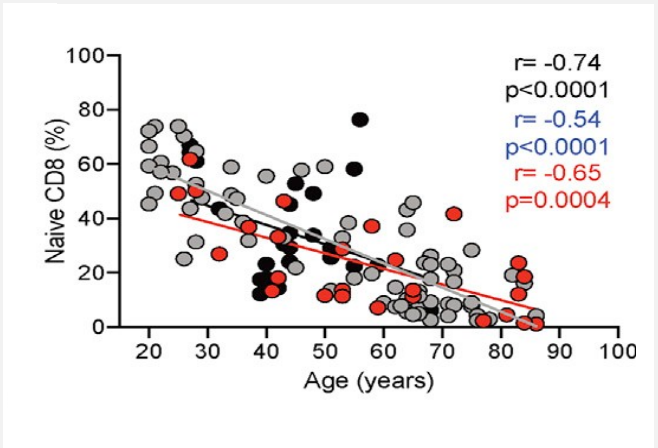
(D) Statistics calculated by the percentage of GM-CSF+ and IFN-γ + co-expressing CD4+ T-cells. Data represent the mean ± SEM. One-way ANOVA. P < 0.05 was considered statistically significant.

Zhou Y, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev. 2020;nwaa041

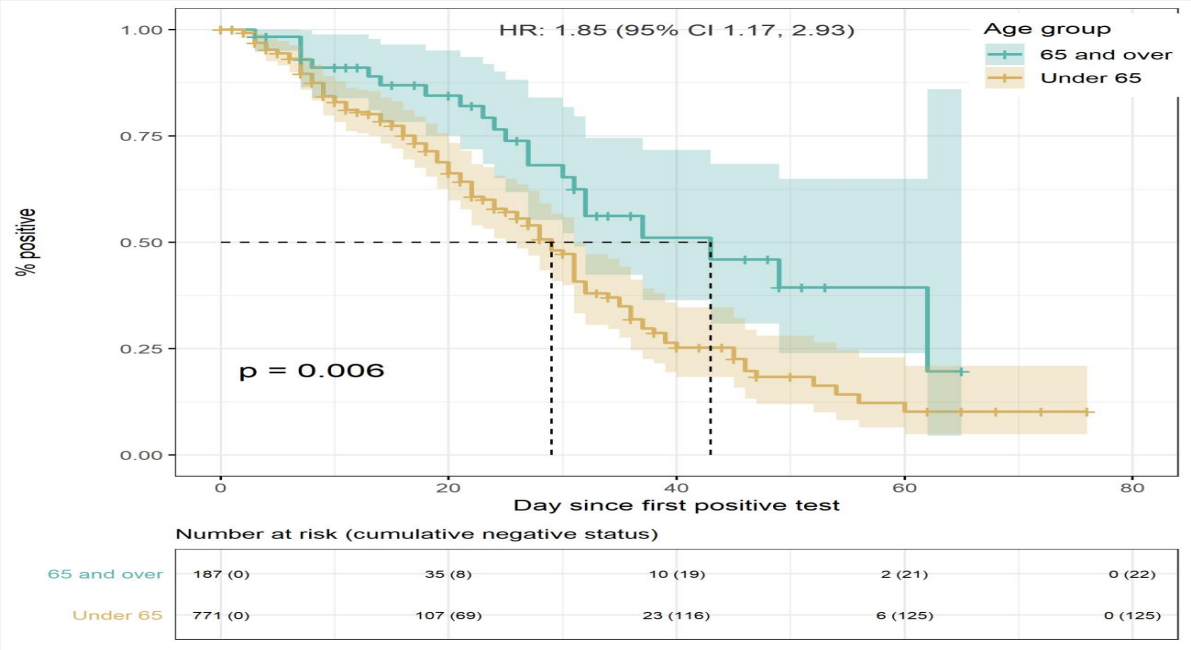
Age > 65 years is Associated with Reduced Naïve T Cell Response to SARS-CoV-2, Delayed Viral Clearance and Greater Disease Severity

Naïve CD4 and CD8 T Cells reduced in age > 65

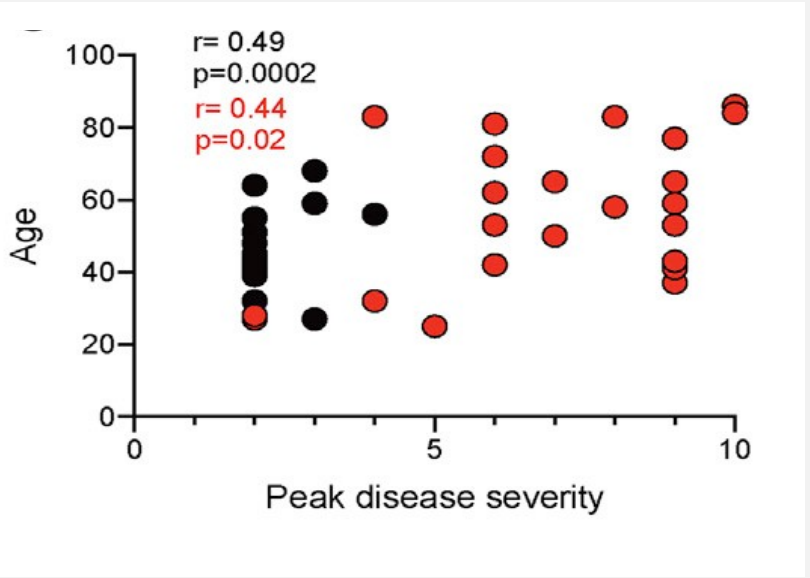




Median duration to negative status longer in subjects over 65 years (43 days) compared with under 65 years (29 days)



Age > 65 associated with greater COVID-19 peak disease severity

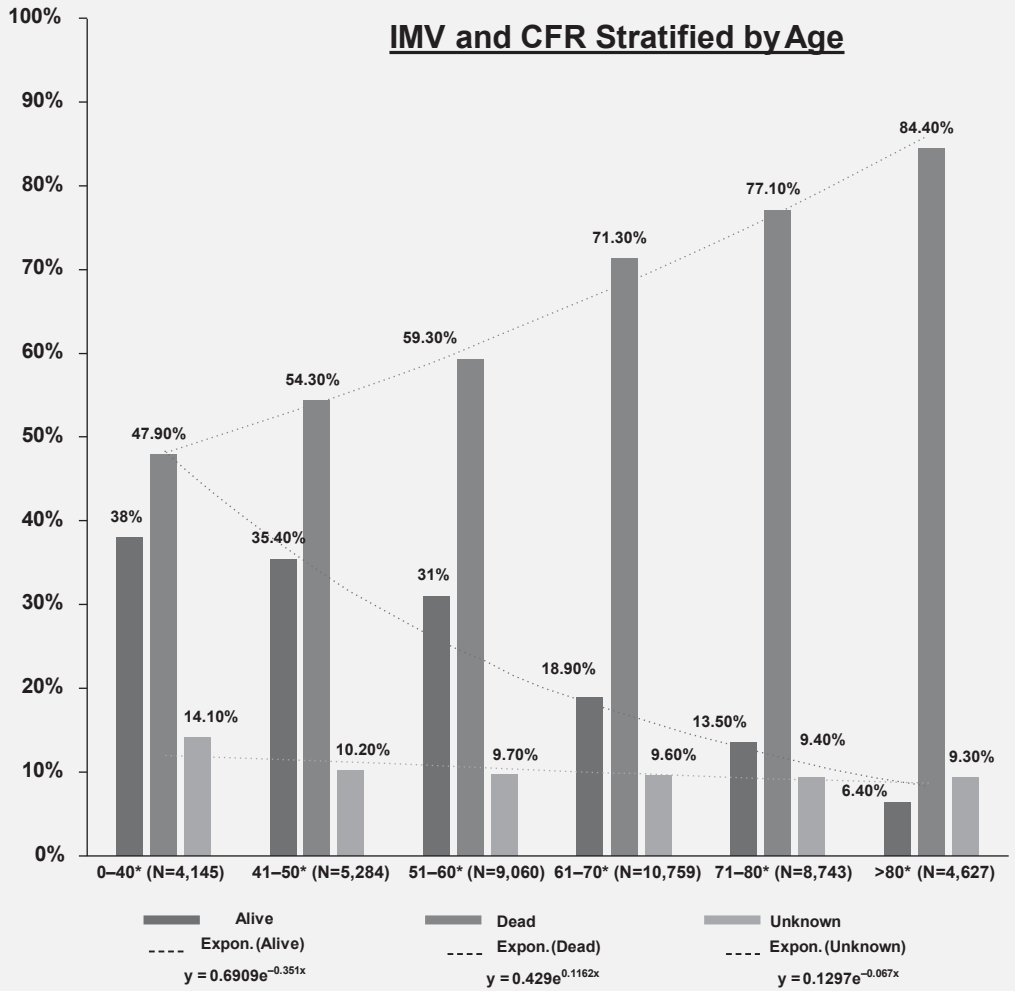


Rydyznski Moderbacher et al., Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. 2020, Cell 183, 996–1012; doi.org/10.1016/j.cell.2020.09.038
Stehlik P et al. Repeat testing for SARS-CoV-2: persistence of viral RNA is common, and clearance is slower in older people. Medical Journal of Australia 2021; doi:10.5694/mja2.51036

Meta-Analysis of Case Fatality Rates (CFR) for COVID-19 Patients on Invasive Mechanical Ventilation (IMV): Mortality Significantly Increases with Age

Age	Alive n (%, 95% CI)	Dead n (%, 95% CI)	Unknown n (%, 95% CI)
≤40* (N=4,145)	1,575 (38.0, 36.5–39.5)	1,985 (47.9, 46.4–49.4)	585 (14.1, 13.1–15.2)
41–50* (N=5,284)	1,872 (35.4, 34.1–36.7)	2,870 (54.3, 53.0–55.7)	542 (10.2, 9.5–11.1)
51–60* (N=9,060)	2,809 (31.0, 30.1–32.0)	5,373 (59.3, 58.3–60.3)	878 (9.7, 9.1–10.3)
61–70* (N=10,759)	2,033 (18.9, 18.2–19.6)	7,676 (71.3, 70.5–72.2)	1,050 (9.6, 9.2–10.3)
71–80* (N=8,743)	1,180 (13.5, 12.8–14.2)	6,740 (77.1, 76.2–78.0)	823 (9.4, 8.8–10.0)
>80* (N=4,627)	295 (6.4, 5.7–7.1)	3,903 (84.4, 83.3–85.4)	429 (9.3, 8.5–10.1)

Reported case fatality rates for patients receiving invasive mechanical ventilation stratified by age, reported in six studies. *Age stratification for ICNARC was 16–39, 40–49, 50–59, 60–69, 70–79, and >80. CFR = case fatality rate; CI = confidence interval; Expon. = exponential; ICNARC = Intensive Care National Audit and Research Centre; IMV = invasive mechanical ventilation.



Source: Am J Respir Crit Care Med Vol 203, Issue 1, pp 54–66, Jan 1, 2021. Sixty-nine studies were included, describing 57,420 adult patients with COVID-19 who received IMV. Fifty-four of 69 studies stated whether hospital outcomes were available but provided a definitive hospital outcome on only 13,120 (22.8%) of the total IMV patient population.

Objectives of Immunomodulation with Remestemcel-L in COVID ARDS

MSCs have the potential to:

- Reduce activated *non-naïve* CD4 and CD8 T cells
- Reduce inflammatory cytokines produced by *non-naive* T cells to reduce macrophage and neutrophil influx, activation and cytokine storm
- Expand and enhance survival of *naïve* CD4 and CD8 T cells to accelerate viral clearance
- Improve pulmonary epithelial integrity

Clinical Experience with Remestemcel-L in COVID-19 ARDS

Emergency IND in Ventilator-Dependent COVID-19 ARDS

- 11 patients (10/11 were < 65 years) with moderate or severe ARDS on ventilators, received two infusions of remestemcel-L 2 million cells/kg within five days at Mt. Sinai Hospital in New York City
- Nine patients (82%) successfully came off ventilator and were discharged from the ICU
- Experience under the emergency IND informed the dosing regimen for the randomized controlled Phase 2b/3 trial, however no data on this dosing regimen in patients ≥ 65 years

Phase 3 Randomized Controlled Trial in COVID-19 ARDS

- Multi-center, randomized, controlled, blinded study to assess safety and efficacy of remestemcel-L versus placebo in ventilator-dependent patients with moderate/severe ARDS due to COVID-19
- Up to 300 patients randomized 1:1 to receive placebo or two infusions of remestemcel-L within 3-5 days
- 222 patients enrolled before the study was stopped by DSMB as unlikely to meet primary endpoint of 43% overall mortality reduction
- The median age increased from 59 in the first half of the trial to 67 in the second half ($p<0.0001$)
- Preliminary results based on 60-day patient follow-up post randomization
- Pre-specified analysis of results stratified by age < or ≥ 65: 125 patients < 65 years, 97 patients ≥ 65 years

Baseline Summary Data: Intent to Treat Patients Pre-Specified Age < 65 & ≥ 65

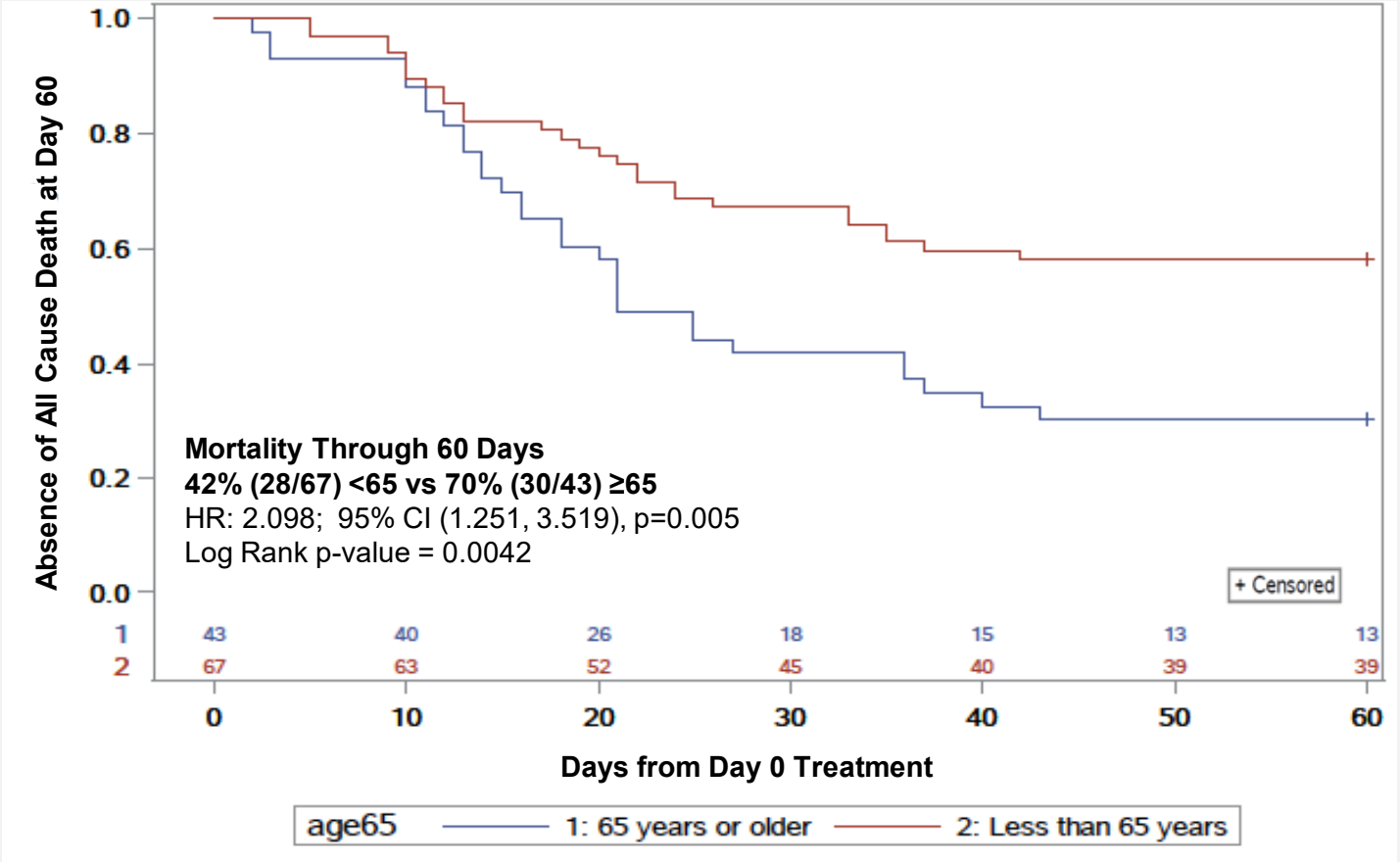
Category	ITT Patients < 65 years		ITT Patients ≥ 65 years	
	REM Mean n=58	Control Mean n=67	REM Mean n=54	Control Mean n=43
Sex (%) Male Female	 76% 24%	 70% 30%	 65% 35%	 65% 35%
Age (Yrs)	**52 (9.9)**	**51 (9.8)**	**72 (5.7)**	**73 (5.5)**
BMI (kg/m^2)	34.1 (7.7)	36.6 (8.2)	32 (7)	32(6)
CRP (mg/L)	29.8 (58.8)	19.5 (17.5)	17.2 (27.8)	26.4 (51.9)
PF Ratio **ARDS Severity (mild, moderate, severe)**	**163 (79)** **17.%, 48%, 24%** **(11% missing or no ARDS)**	**144 (85)** **9.%, 48%, 37%** **(6% missing or no ARDS)**	**132 (50)** **13.%, 57%, 28%** **(2% missing or no ARDS)**	**150 (54)** **14%, 67%, 14%** **(5% missing or no ARDS)**
SOFA Score	6.3 (2.4)	6.6 (1.8)	6.3 (2)	6.4 (1.9)
Any Steroids at Baseline Dexamethasone at Baseline	67% 50%	84% 67%	98% 78%	93% 67%
Remdesivir at Baseline	62%	63%	72%	74%
Anti-IL6 at Baseline	3%	4%	7%	5%

Baseline Summary Data: Increased Co-Morbid Conditions in Patients ≥ 65

All Patients - ITT	ITT Patients < 65 years		ITT Patients ≥ 65 years		< 65 vs ≥ 65
	REM Mean n=58	Control Mean n=67	REM Mean n=54	Control Mean n=43	Chi-Squared P-Value
Medical History					
COPD	2%	1%	13%	12%	0.0004
Asthma	10%	10%	6%	9%	
Pulmonary Fibrosis.	0%	0%	4%	0%	
CF	0%	0%	0%	0%	
MI last 12 months	0%	0%	2%	2%	
CHF	2%	6%	9%	0%	
Cancer	3%	4%	19%	19%	0.0002
Renal Disease	7%	7%	19%	19%	0.0047
Immunological Disorder	3%	3%	4%	2%	
Smoker	27%	27%	43%	37%	0.0464
Hepatic	7%	0%	0%	12%	
Diabetes	45%	36%	39%	42%	
Hypertension	50%	49%	67%	70%	0.0069
Neurological	5%	1%	13%	7%	0.0074

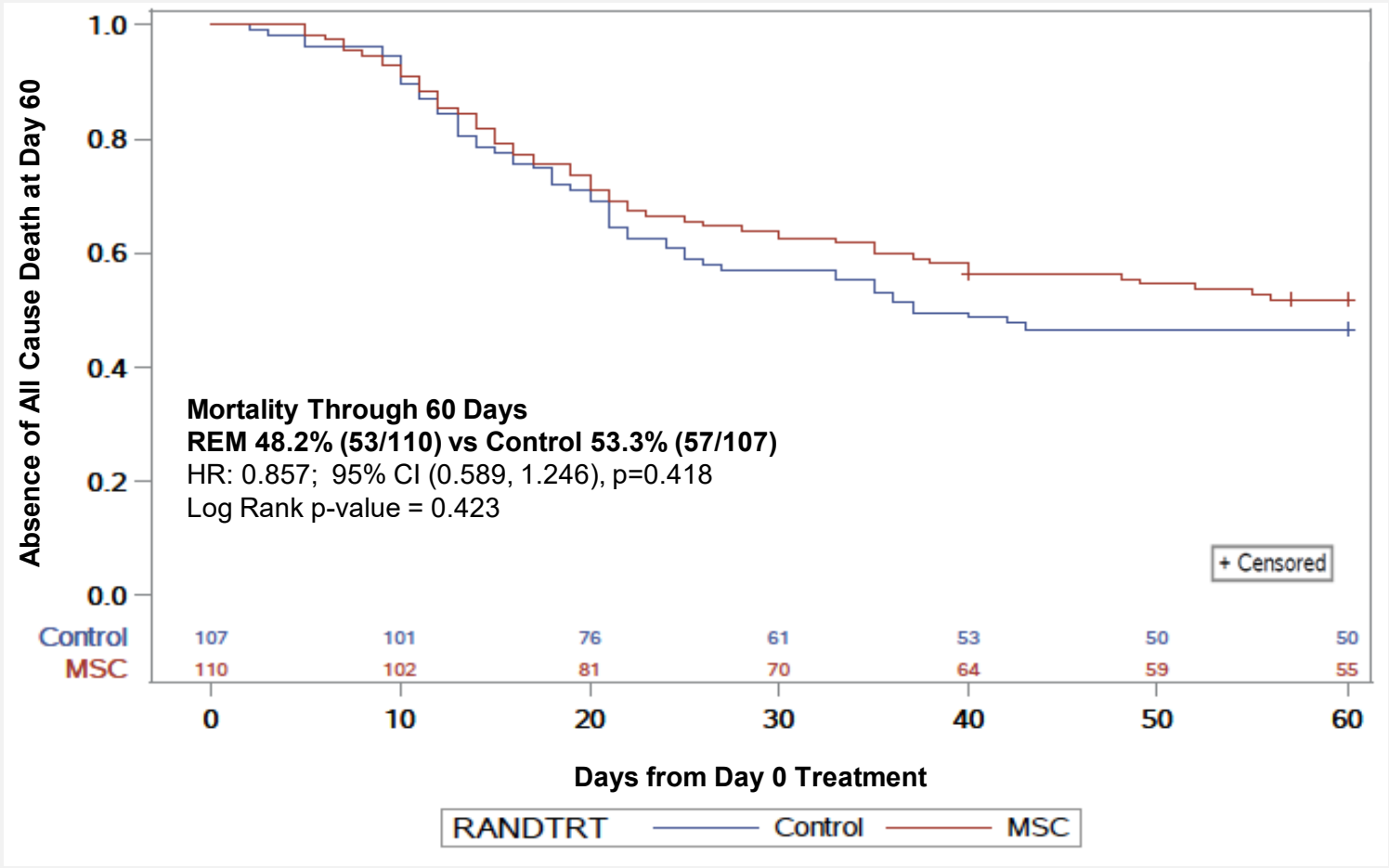
Greater Mortality through Day 60 in Control Patients Older than 65, Consistent with Other Trials

Controls Age < 65 vs ≥ 65 (n=110)



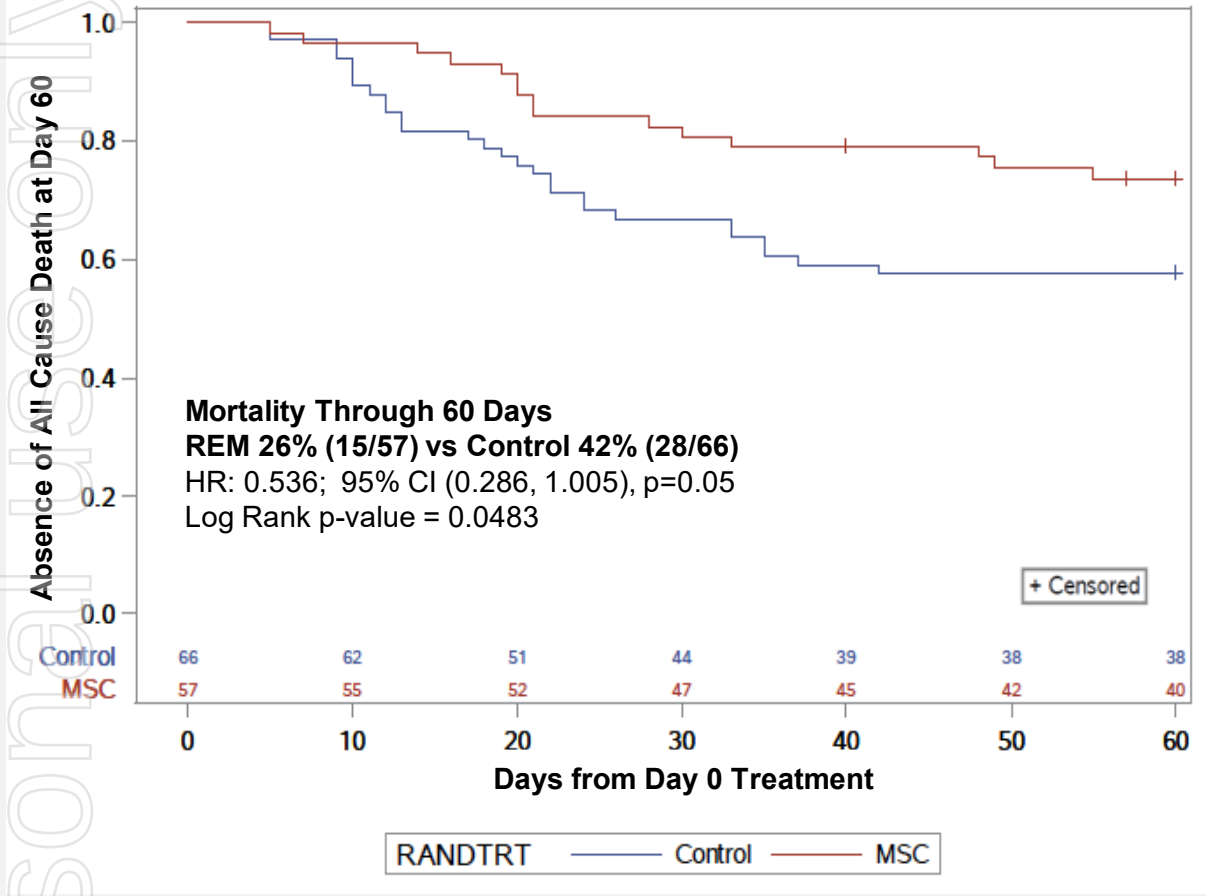
Remestemcel-L vs Controls with COVID-19 ARDS: Mortality through 60 Days in Treated Patients

All **Modified Intent to Treat** Patients (n=217), Remestemcel-L vs Control

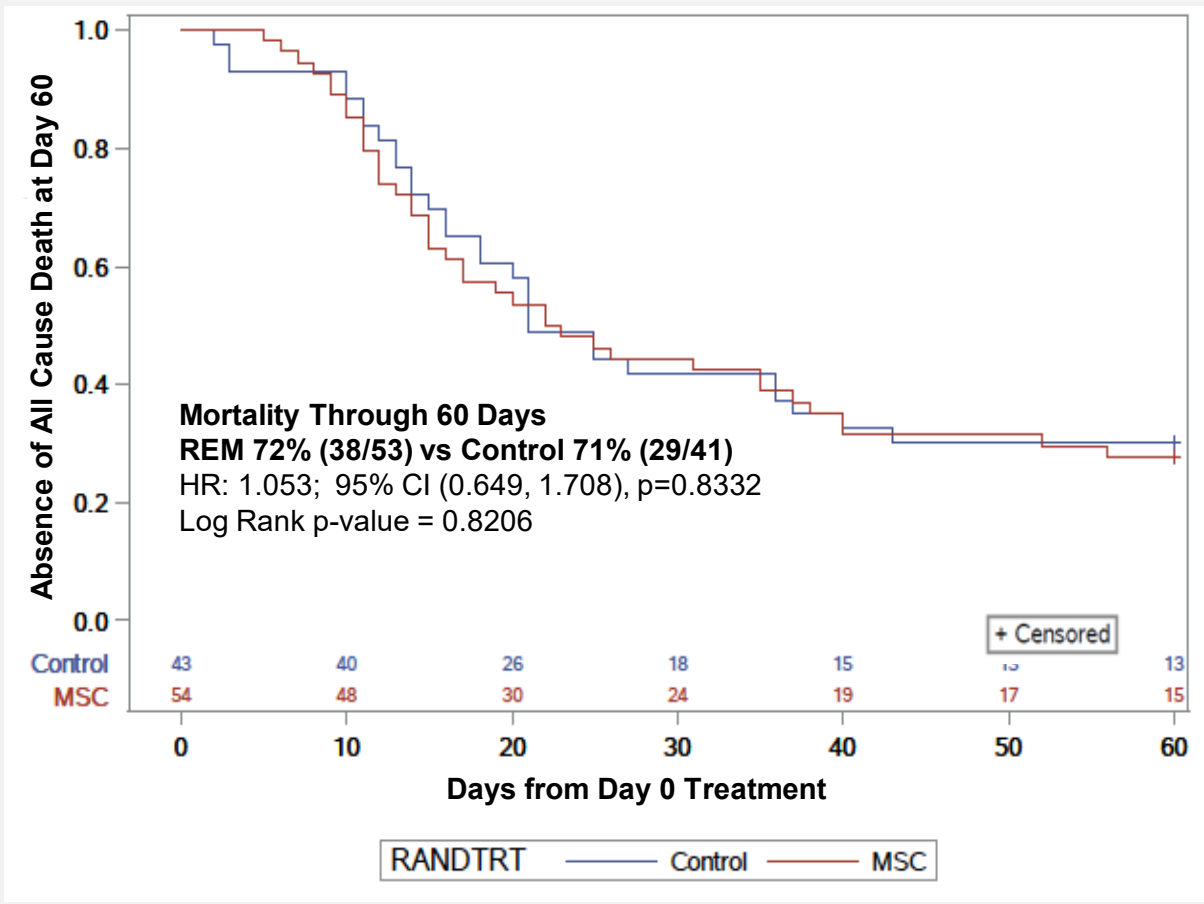


Remestemcel-L vs Controls:
Pre-Specified Mortality Analysis through 60 Days < or ≥ 65 Years Old

Modified Intent to Treat Patients **< 65 years old** (n=123)
REM vs Control

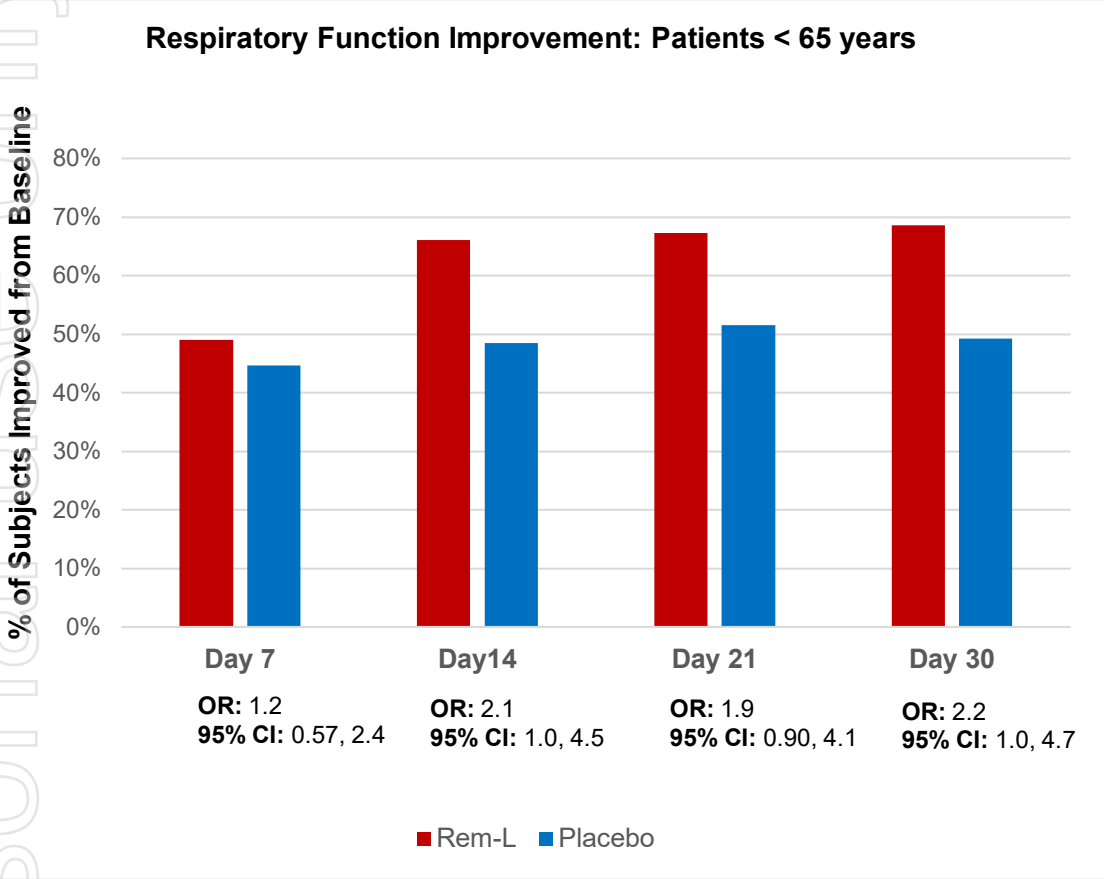


Modified Intent to Treat Patients **≥ 65 years old** (n=94)
REM vs Control

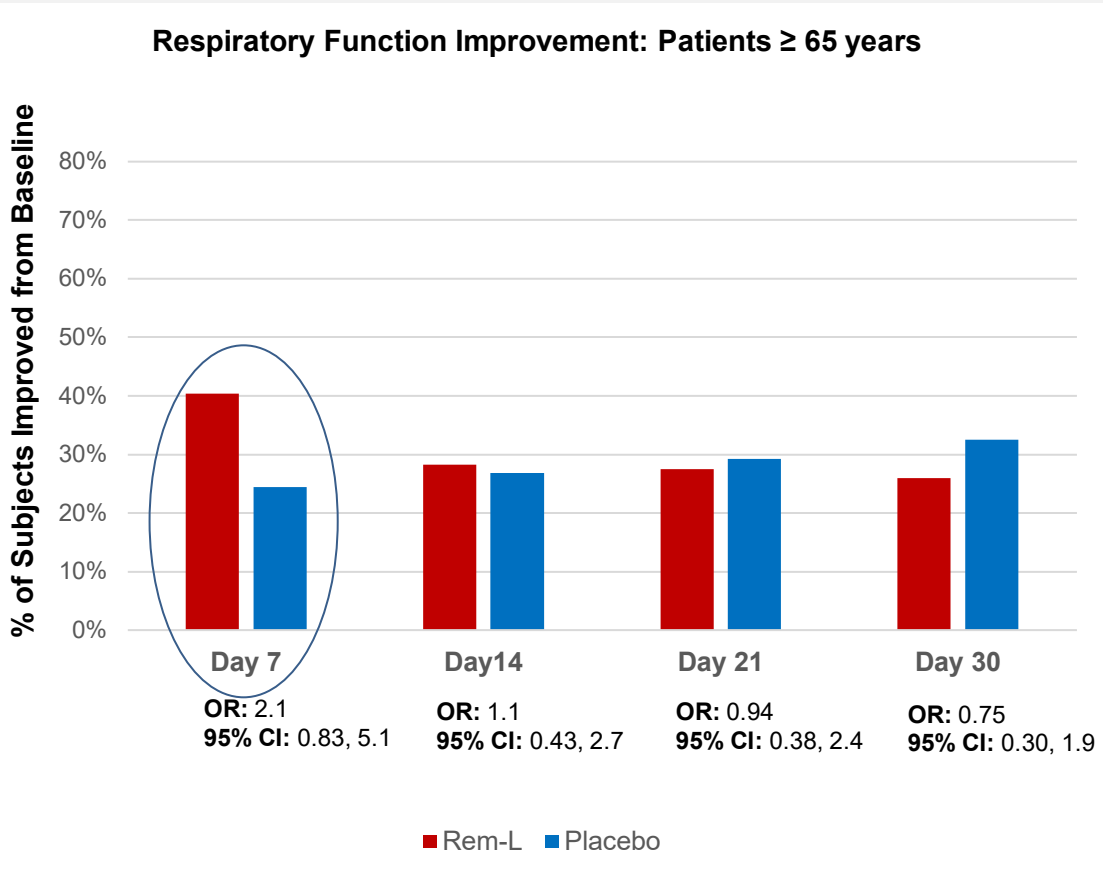


Remestemcel-L vs Controls: Analysis of Respiratory Function Improvement*

Treated Patients (mITT) **< 65 years old** (n=123) Remestemcel-L vs Control

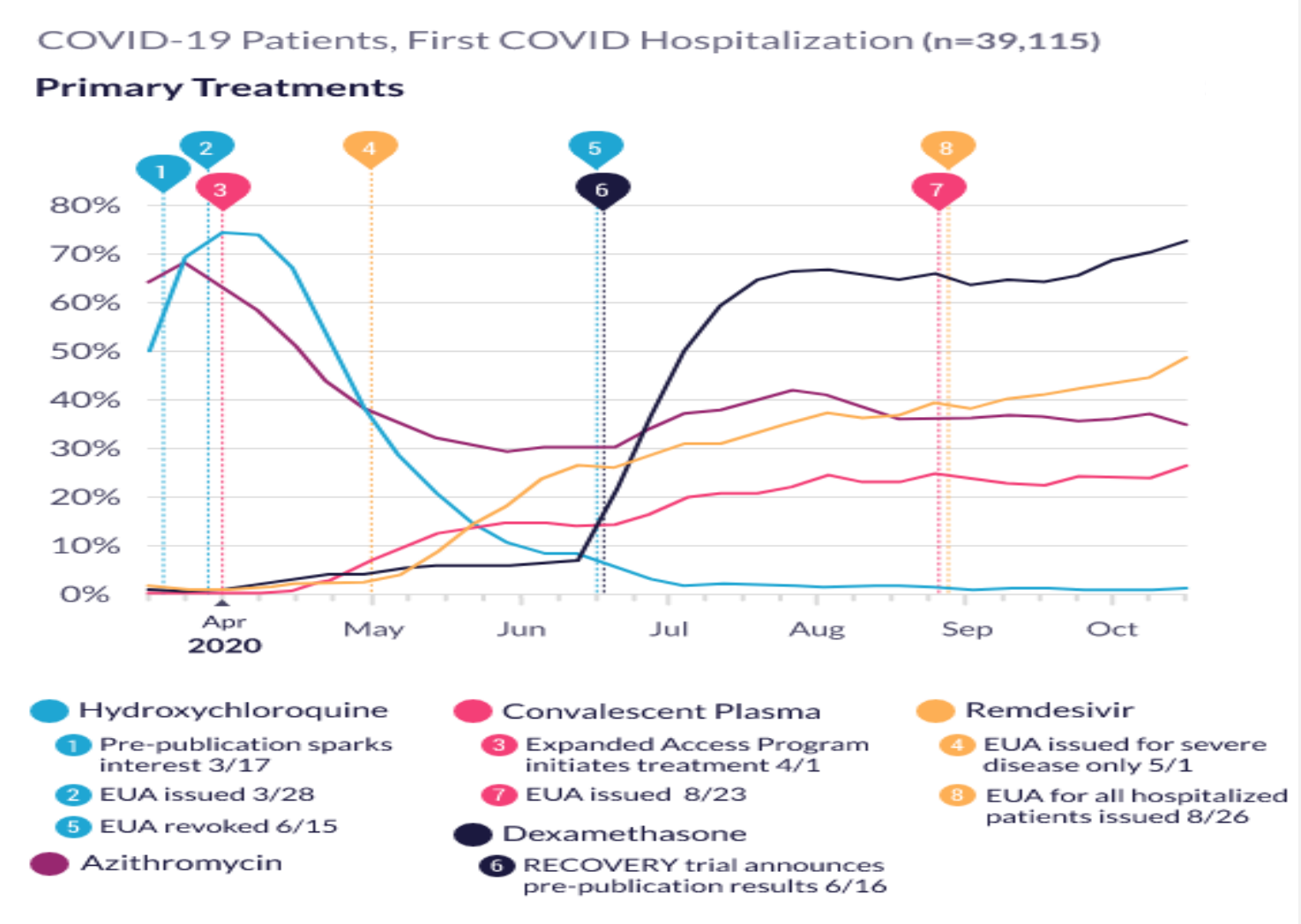


Treated Patients (mITT) **≥ 65 years old** (n=94) Remestemcel-L vs Control



* Measured as resolution and/or improvement of ARDS as defined by the Berlin criteria at Days 7, 14, 21, and 30 post-randomizations

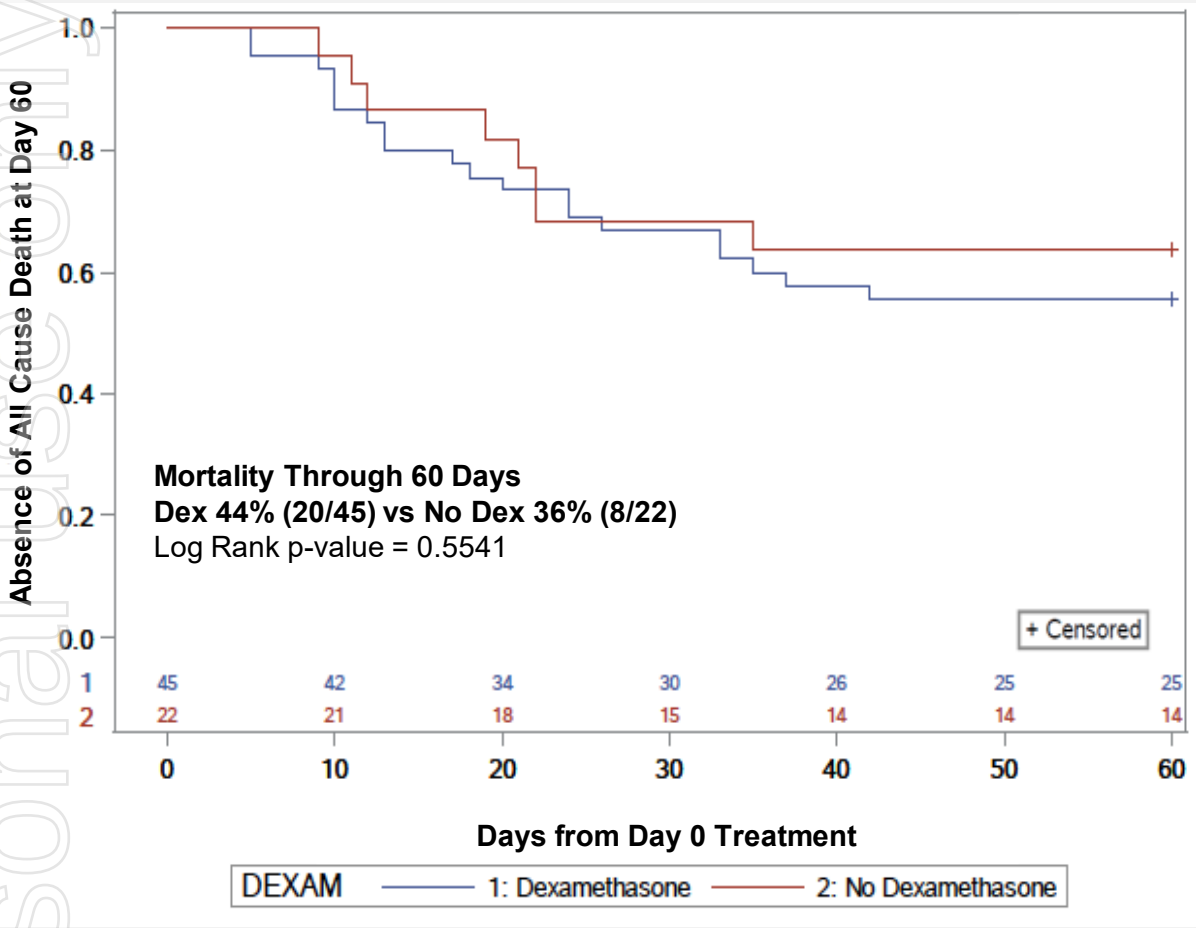
Dynamic Changes in the Treatment Regimes During the Trial



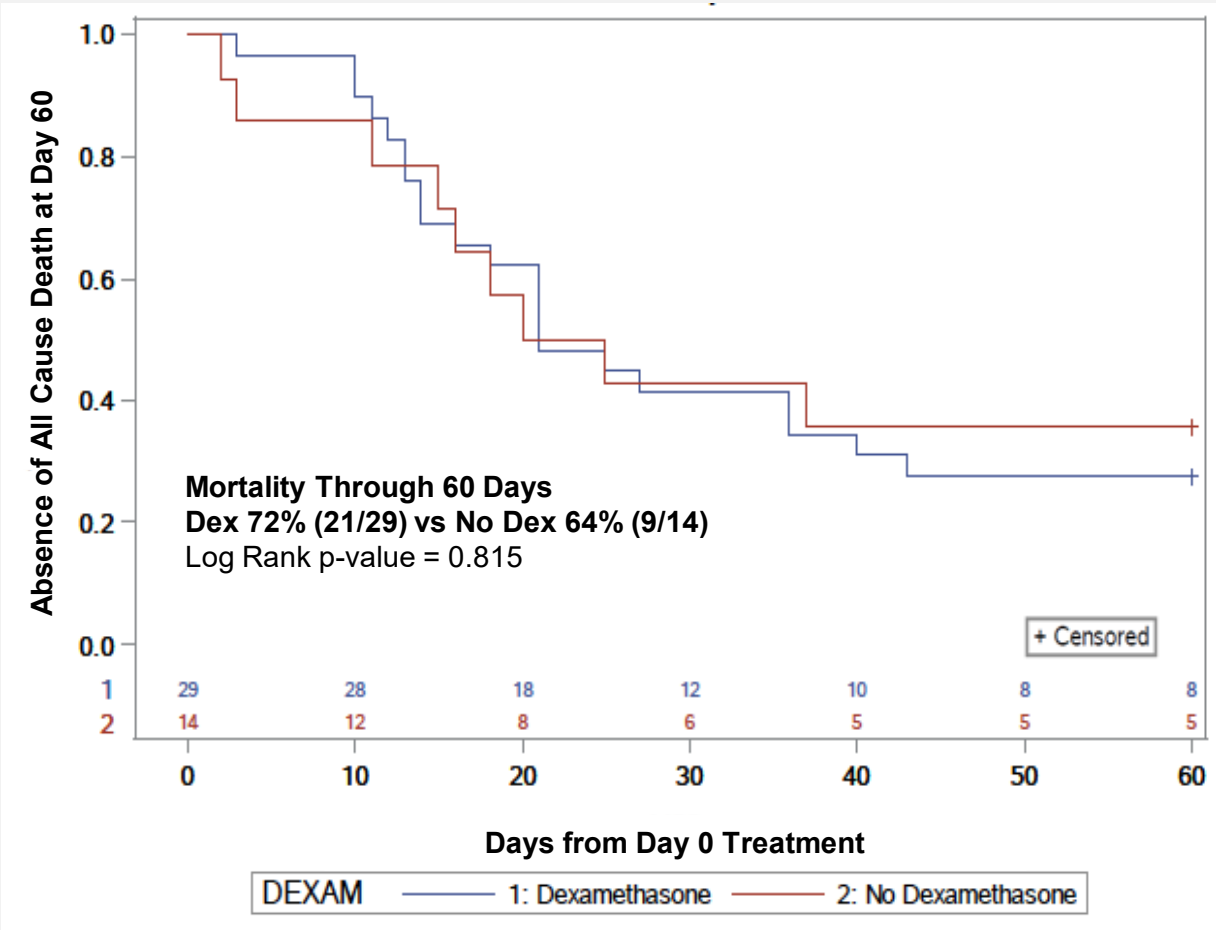
Source: Noel A. et al. Epic Health Research Network. Nov 2020

Dexamethasone did not Reduce Mortality in Controls on Invasive Mechanical Ventilation with Moderate/Severe COVID-19 ARDS

Controls < 65 years old +/- Dexamethasone (ITT n=67)

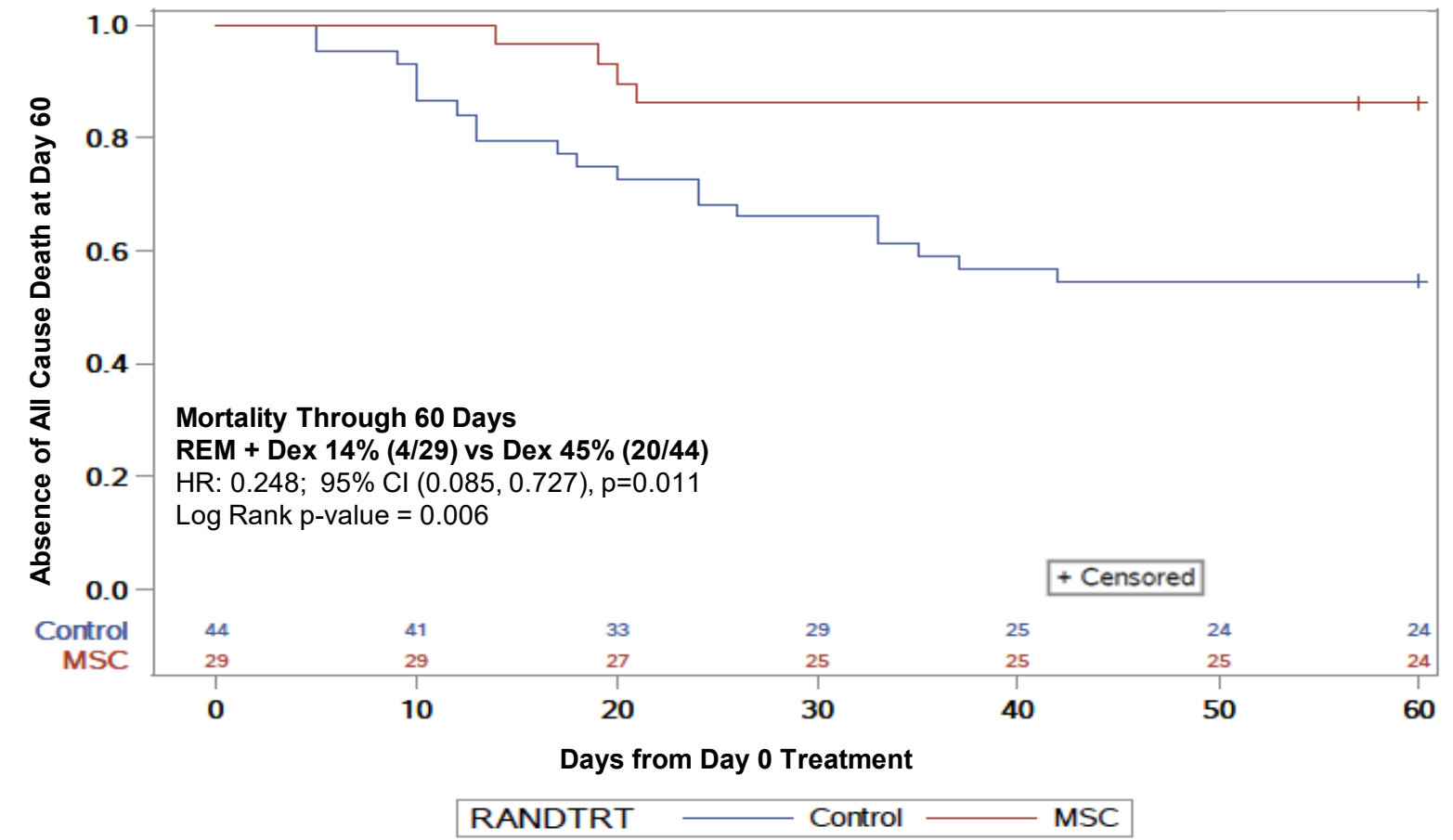


Controls ≥ 65 years old +/- Dexamethasone (ITT n=43)



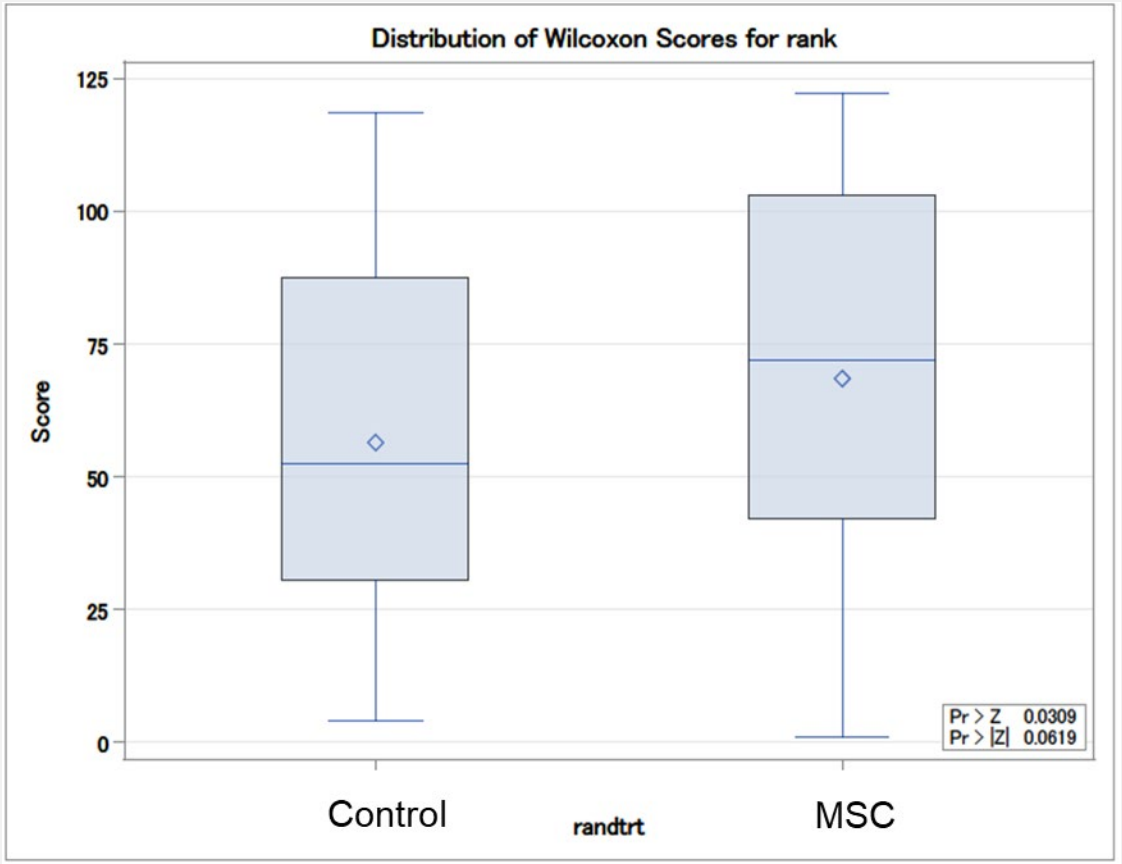
Remestemcel-L plus Dexamethasone: Synergistic in Reducing Mortality in Exploratory Population < 65 years old

All Treated Patients < 65 years old on Dexamethasone (n=73)



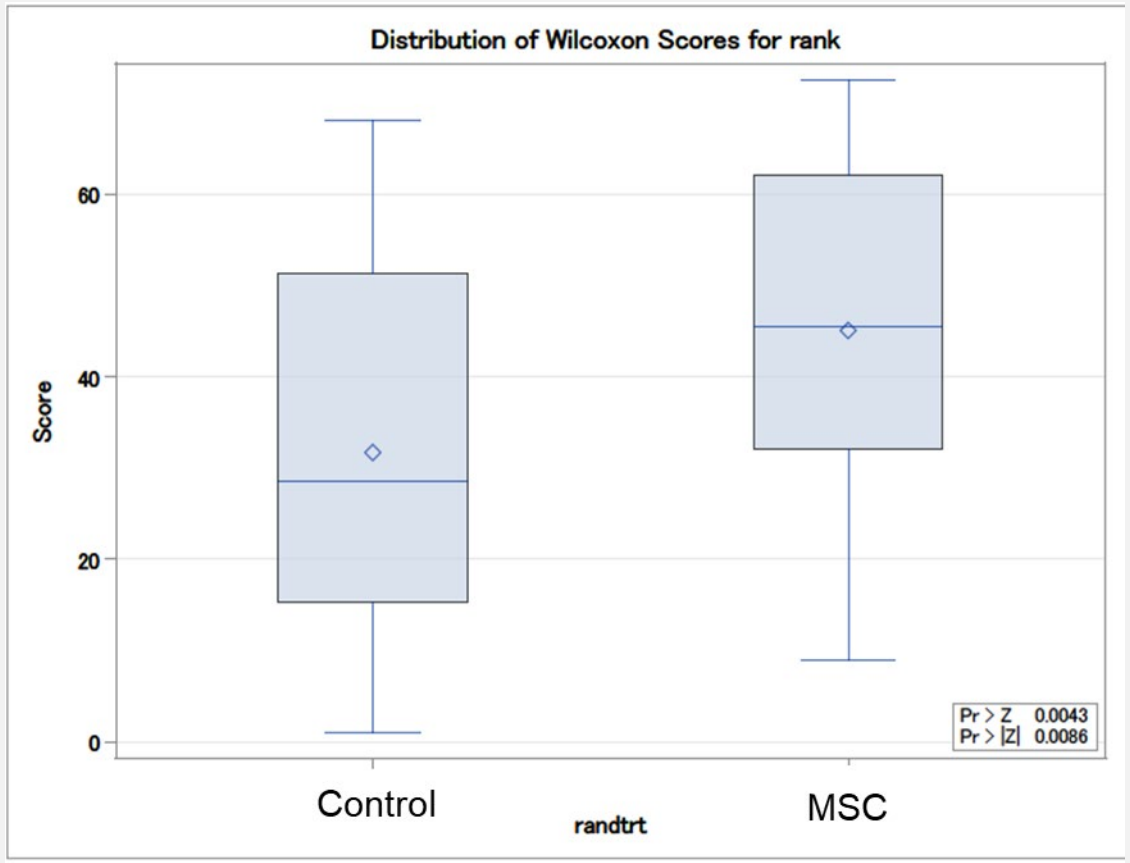
Remestemcel-L Increases Ventilator-Free Days Alive through 60 Days in Patients < 65 years old

All Treated Patients < 65 years old (n=123)



Ventilator-Free Days Alive Through Day 60

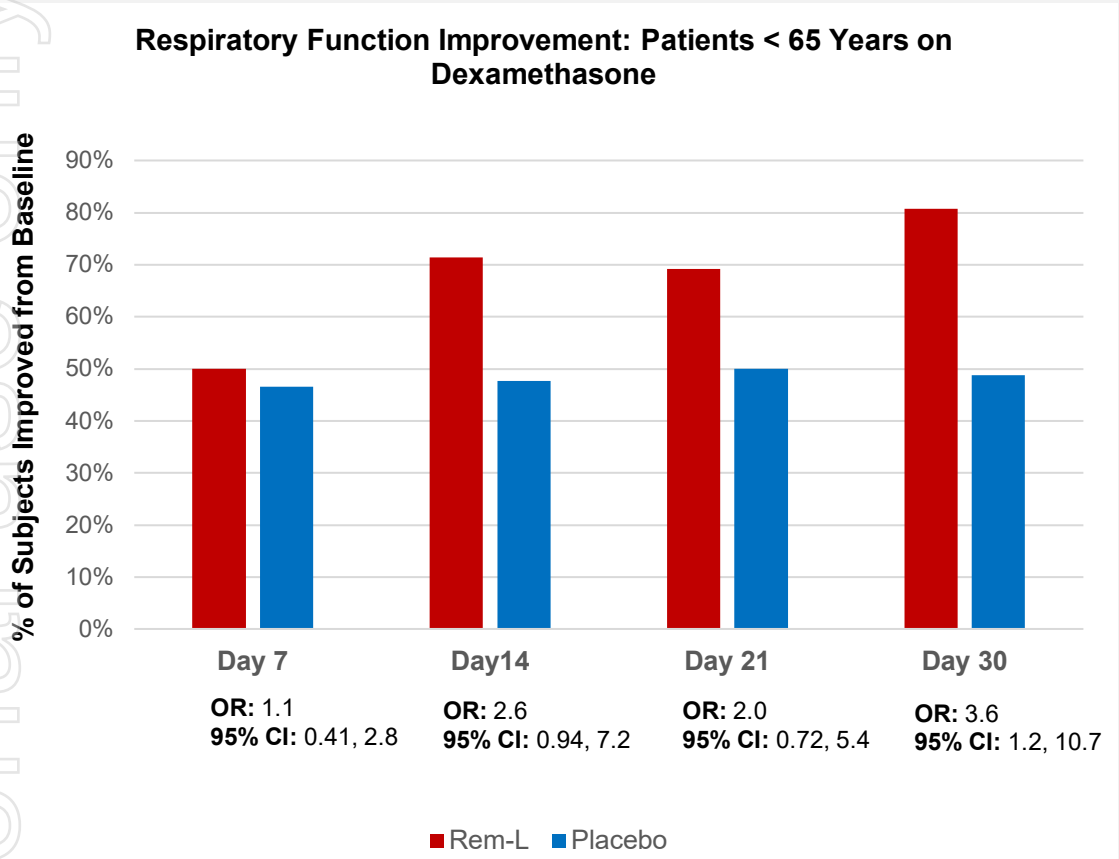
All Treated Patients < 65 years old on Dexamethasone (n=73)



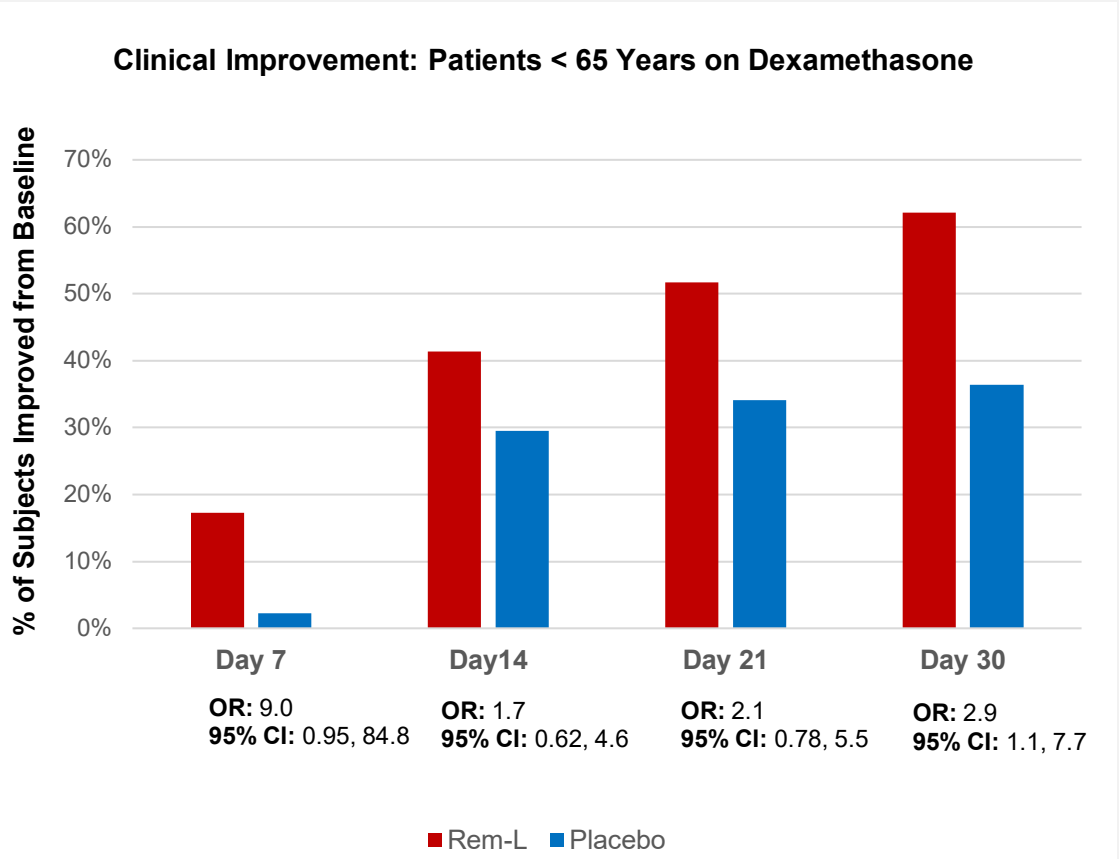
Ventilator-Free Days Alive Through Day 60

Remestemcel-L plus Dexamethasone: Analysis of Respiratory Function and Clinical Improvement* in Exploratory Population < 65 years old

Treated Patients (mITT) **< 65 years old** on Dexamethasone (n=73)



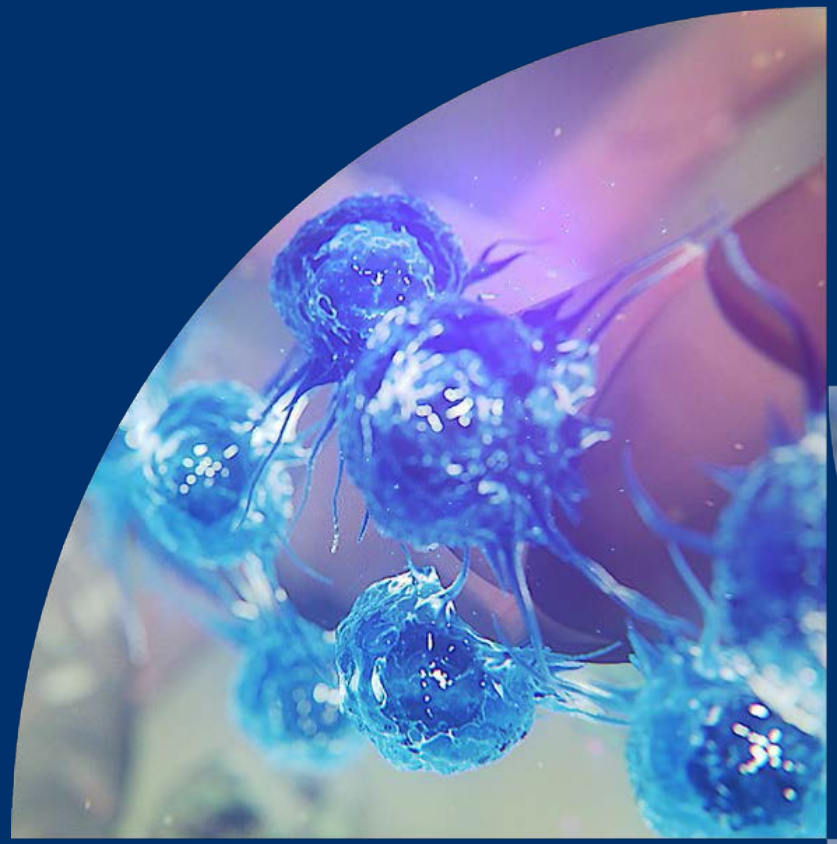
Treated Patients (mITT) **< 65 years old** on Dexamethasone (n=73)



* Respiratory Function Improvement measured as resolution and/or improvement of ARDS as defined by the Berlin criteria at Days 7, 14, 21, and 30 post-randomizations; Clinical Improvement was assessed based on a 7-point ordinal scale at baseline and on Days 7, 14, 21, and 30 and discharge from hospital

Conclusions and Next Steps for Remestemcel-L in ARDS Due to COVID-19

- Remestemcel-L did not significantly reduce overall mortality
- Remestemcel-L reduced mortality and increased ventilator-free days through 60 Days in pre-specified patient population < 65 years old
- Addition of remestemcel-L to dexamethasone was synergistic in reducing mortality and increasing days alive off ventilator through 60 Days in exploratory analysis of patients < 65
- Plan to meet with U.S. Food and Drug Administration (FDA) to discuss potential next steps
- Confirmatory Phase 3 trial in COVID-19 ARDS patients < 65 years of age with dexamethasone, explore additional remestemcel-L dosing regimens for patients with ARDS ≥ 65 years of age



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