Remestemcel-L for Pediatric Patients with SR-aGVHD

Mesoblast, Inc.

Oncologic Drugs Advisory Committee (Clinical Session)

August 13, 2020

Introduction to Remestemcel-L

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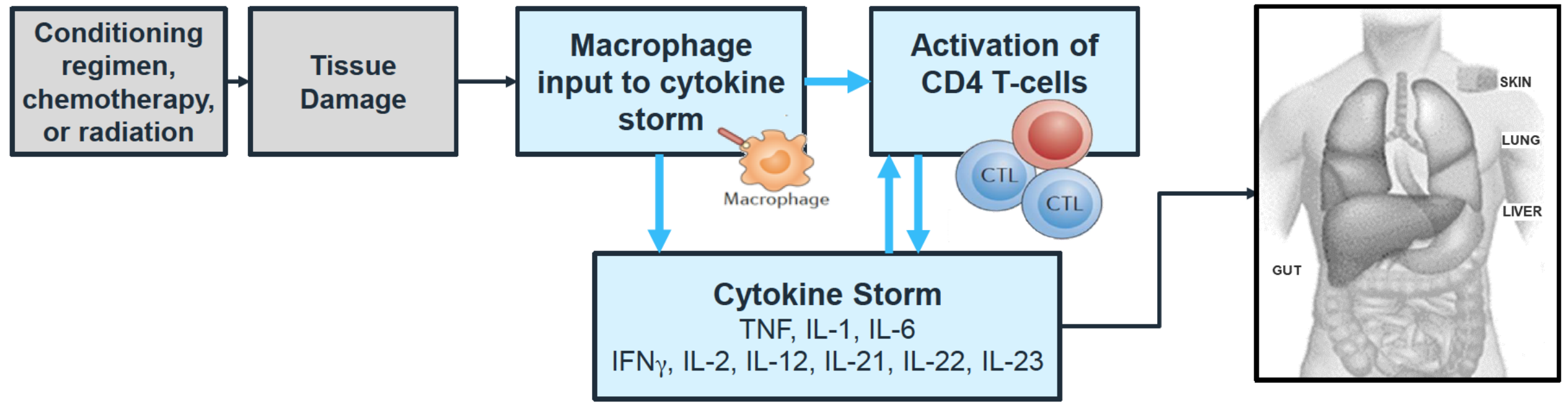
Mesoblast, Inc.

Acute GVHD: Serious and Fatal Complication of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

PHASE 1
Host Tissue Damage by BMT Conditioning

PHASE 2
Immune Cell Activation & Cytokine Storm

PHASE 3
Inflammation and End Organ Damage



Children with Steroid-Refractory Acute GVHD at High Risk of Treatment Failure and Death

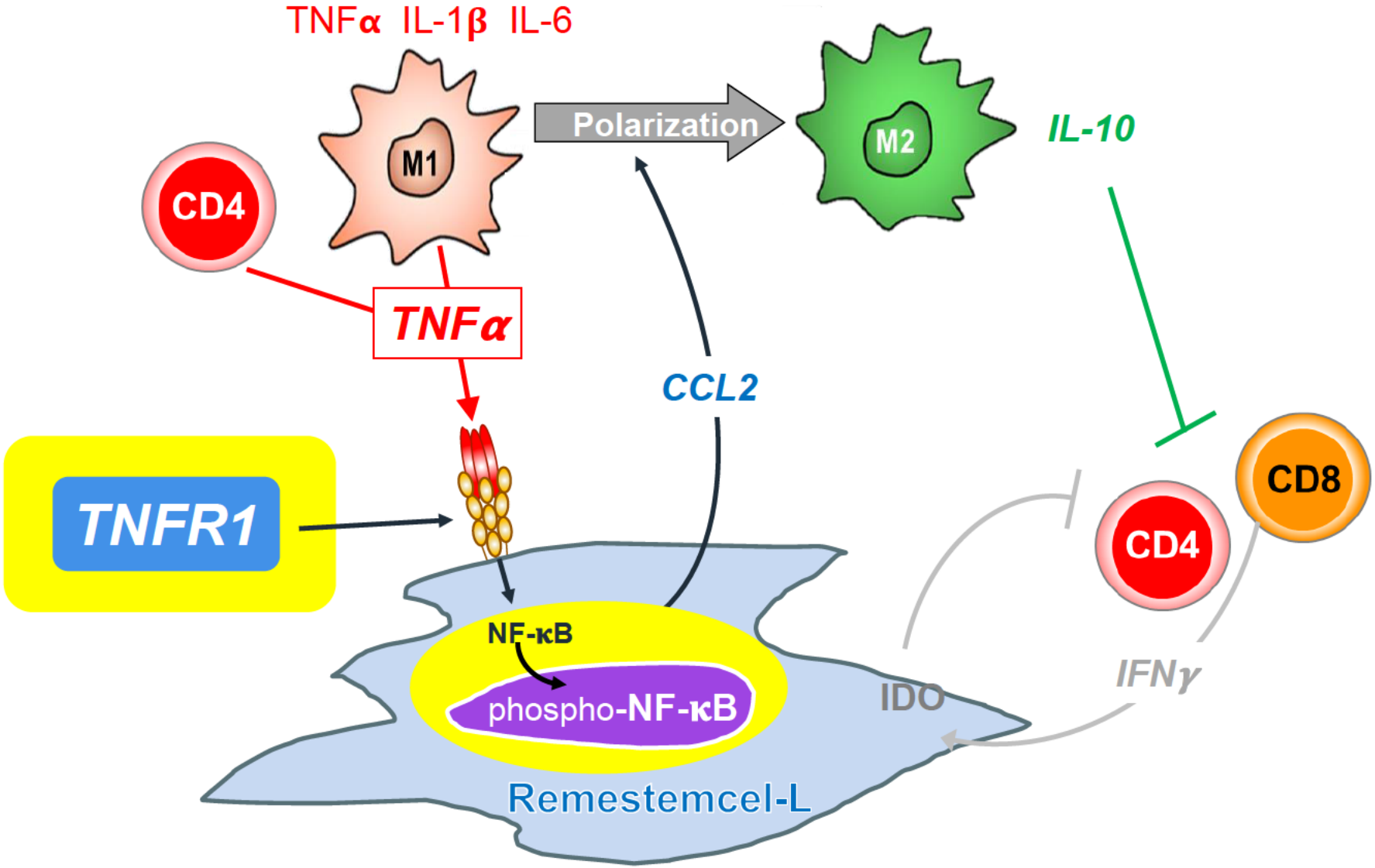
- As high as 70 – 90% mortality[1,2,3]
- No available therapies considered standard of care
- Children < 12 years of age have no approved treatment

1. MacMillan et al. 2020; 2. Jagasia et al. 2012; 3. Arai et al. 2002

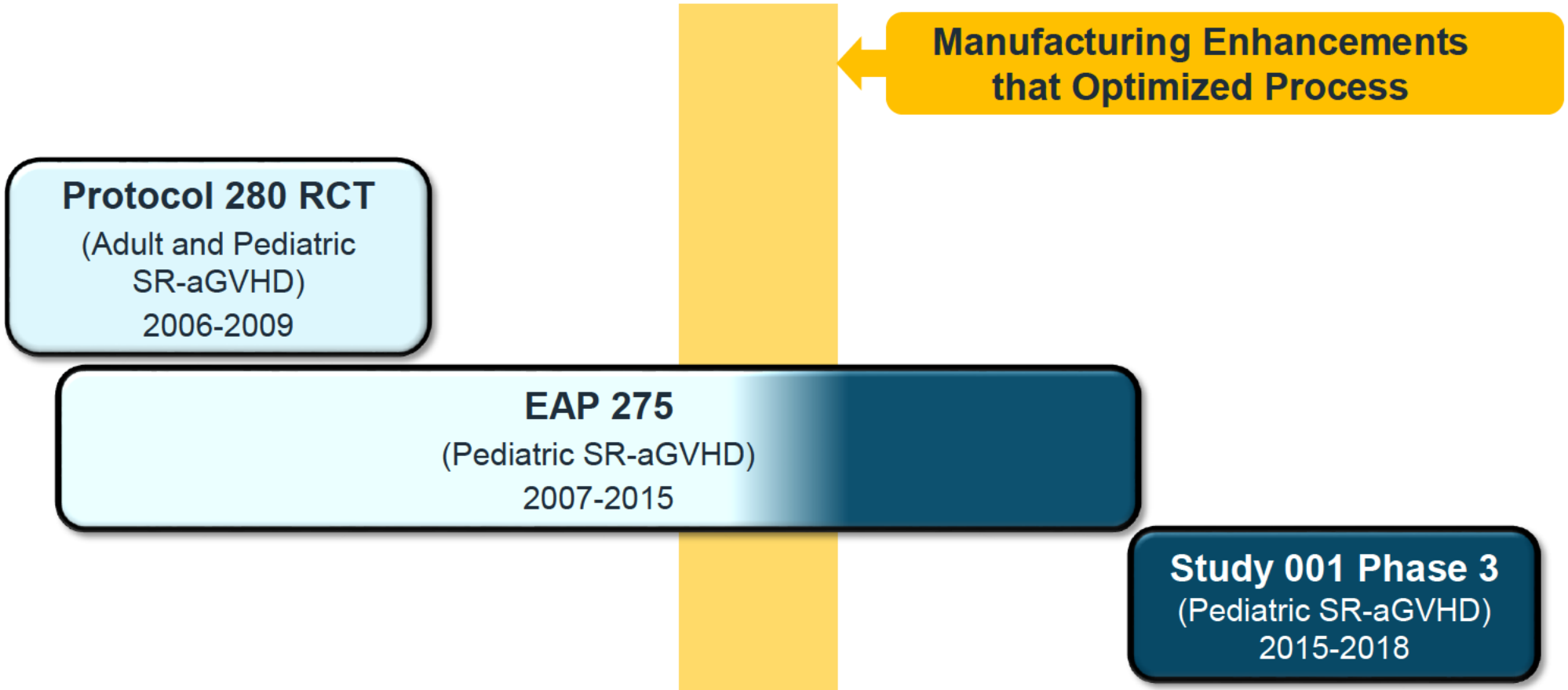
Remestemcel-L: Novel, Off-the-Shelf Cellular Therapy

- Comprises culture-expanded mesenchymal stromal cells (ceMSC)
  - Unique immunological profile
- Hypo-immunogeneic allogeneic product
  - Used without tissue matching or immunosuppressives
- Multi-modal mechanism of action
  - Modulates immune response allowing patient's body to adjust and recover

Immunomodulatory Activities of Remestemcel-L in Response to Inflammation



Development History Leading to Pivotal Study 001 / 002 in Children with SR-aGVHD



- Orphan Drug Designation and Fast Track status granted by FDA

Agenda

Unmet Need in SR-aGVHD	**Joanne Kurtzberg, MD** Director, Marcus Center for Cellular Cures Director, Pediatric Blood and Marrow Transplant Program Director, Carolinas Cord Blood Bank Duke University School of Medicine
Remestemcel-L Clinical Efficacy and Safety	**Fred Grossman, DO** Chief Medical Officer Mesoblast, Inc.
Clinical Perspective	**Joanne Kurtzberg, MD**

Additional Expert

Mount Sinai Acute GVHD International Consortium (MAGIC)	**John Levine, MD** Professor of Medicine, Hematology and Medical Oncology, and Pediatrics Icahn School of Medicine at Mount Sinai Co-director, MAGIC

Unmet Need in SR-aGVHD

Joanne Kurtzberg, MD

Jerome Harris Distinguished Professor of Pediatrics

Professor of Pathology

Director, Marcus Center for Cellular Cures

Director, Pediatric Blood and Marrow Transplant Program

Director, Carolinas Cord Blood Bank

Duke University School of Medicine

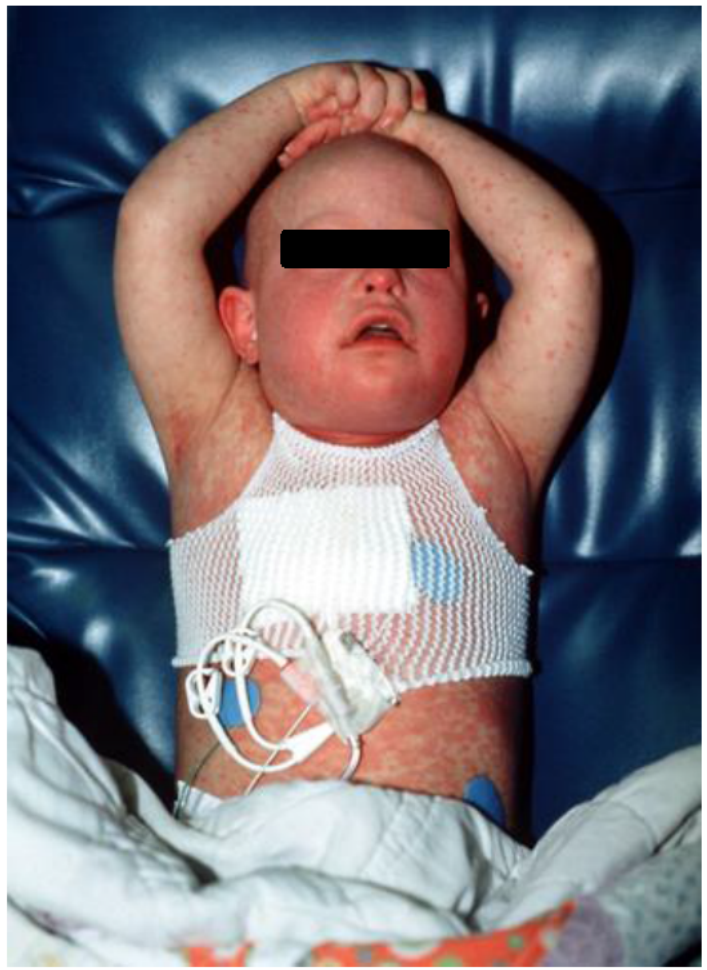
aGVHD: Progressive and Fatal Complication of Allogeneic HSCT

- ~1,300 allogeneic HSCTs in children in US[1]
  - Despite prophylaxis, 25 – 80% will develop aGVHD
- First-line treatment is corticosteroids, usually IV
- Response rate is ~50%, thus ~500 new cases of SR-aGVHD per year
- SR-aGVHD mortality as high as 70 – 90%[2,3,4]

1. CIBMTR, 2019; 2. MacMillan et al. 2020; 3. Jagasia et al. 2012; 4. Arai et al. 2002

Acute GVHD Primarily Affects Skin, GI Tract, and Liver

- Classic skin rash
- Abdominal cramps
- Large volumes of diarrhea
- Rising serum bilirubin
- 70 – 90%[1,2,3] likelihood of death when involving gut and liver



1. MacMillan et al. 2020; 2. Jagasia et al. 2012; 3. Arai et al. 2002

Pediatric aGVHD: Typical Clinical Course

- Transplant with GVHD prophylaxis

3 – 6 weeks post transplant	▪ Itchy rash that burns the skin ▪ Some get fever ▪ Prescribed IV steroids
Days to weeks later	▪ Diarrhea/anorexia/vomiting ▪ Prescribed second-, third- and fourth-line agents
Persistent symptoms	▪ Failure to thrive, total parenteral nutrition dependency, renal insufficiency, very poor immune reconstitution, opportunistic infections (often multiple)
Death	▪ Death from multi-system organ failure

No Available Therapies Considered Standard Of Care

- No drugs approved for treatment of SR-aGVHD in patients < 12 years
- Only Category 2A (lower level) evidence for currently available therapies
  - No sufficient data for guidelines to recommend use of one agent over others
- Off-label immunosuppressants have mixed efficacy and high toxicity
  - Renal injury/renal failure
  - Further immunosuppression leading to life-threatening infections
- Ruxolitinib only FDA-approved treatment available
  - Not approved for children < 12 years due to safety concerns

Ruxolitinib Not FDA-Approved For Patients < 12 Years

- Pediatric patients have poor compliance with oral therapies
- Patients with GI involvement often cannot tolerate oral drug
- Thrombocytopenia can limit patients from continuing therapy
- *"…the lowest available strength of ruxolitinib precluded safe treatment in infants and children, the indication was limited to patients 12 years and older"*[1]

1. FDA Briefing Book

Pediatric Patients with SR-aGVHD Urgently Need Safe and Effective Therapy to Reduce Mortality

- Children are immunosuppressed and highly vulnerable
  - Need for well-tolerated therapies with low morbidity risk
- Currently there are limited to no approved treatment options
  - Only 1 approved option for patients 12+ years of age
  - No FDA-approved option for children under 12 years of age
- Remestemcel-L has potential to meet treatment need and significantly reduce high mortality in these children

Placebo-Controlled RCT in Children With Severe Refractory Disease Would Not Be Possible

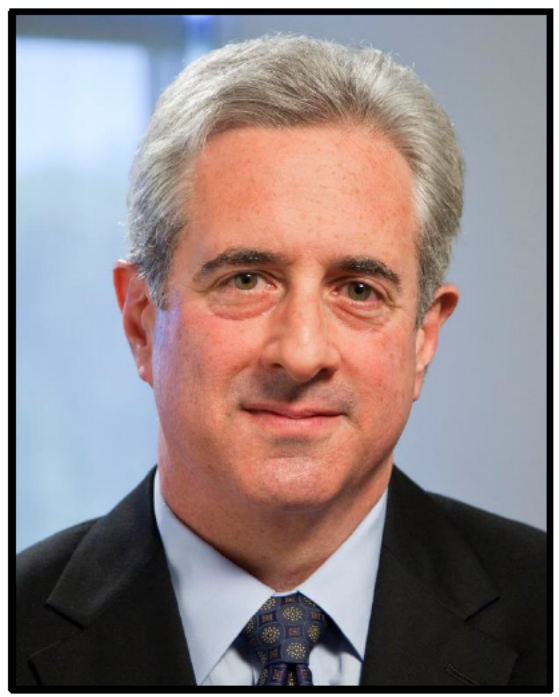
- Investigators would not enroll children with SR-aGVHD in a randomized-controlled trial
- EAP 275 data showed favorable safety and high response and survival
  - Single-arm trial allowed all enrolled patients to receive remestemcel-L

Remestemcel-L Clinical Efficacy and Safety

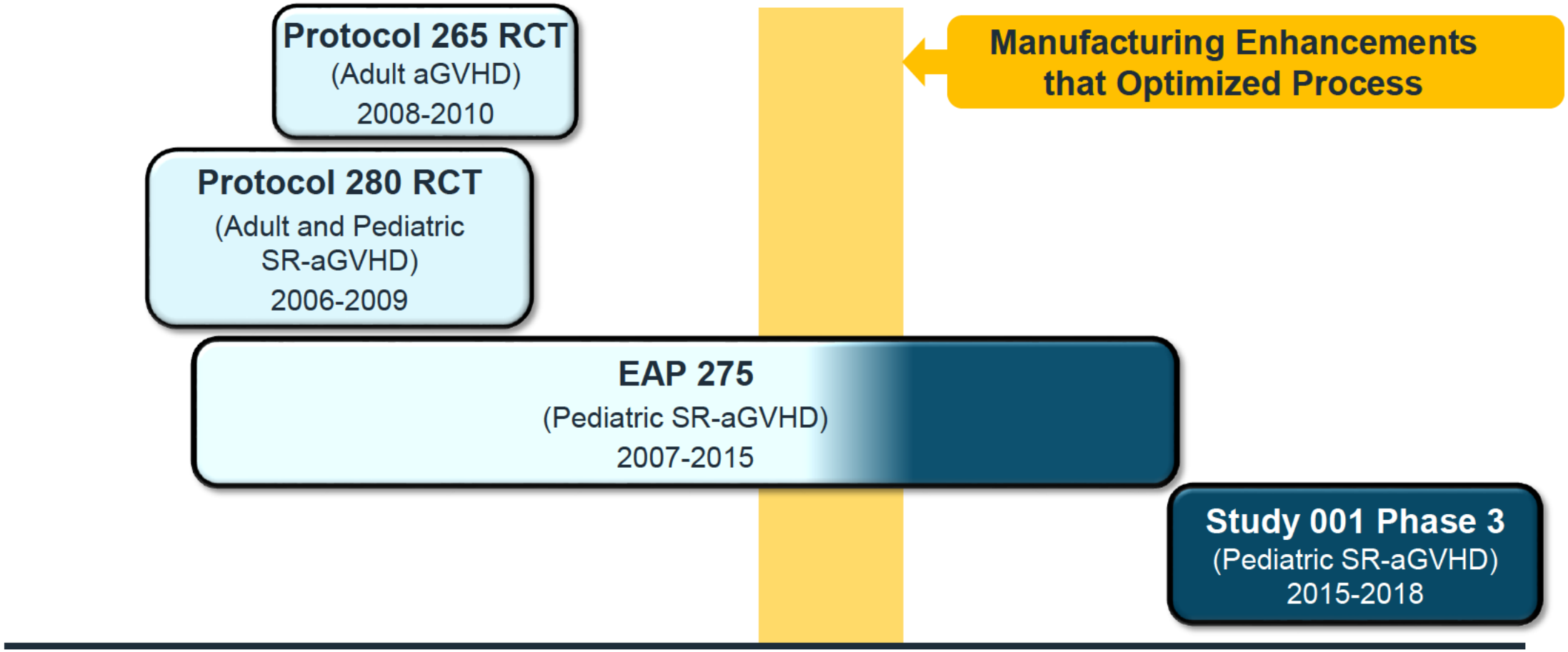
Fred Grossman, DO

Chief Medical Officer

Mesoblast, Inc.



Development History Leading to Pivotal Study 001 / 002 in Children with SR-aGVHD



Study 001 Provides Substantial Evidence of Efficacy in Children with SR-aGVHD

- We agree with FDA conclusions
  - *"the primary endpoint results in Study 001 were statistically significant, the measured response was durable, and the results were consistent across subpopulations and secondary efficacy endpoints"*
  - *"no safety signal of concern was identified in the studies of remestemcel-L"*
  - *"… did not reveal remarkable differences in safety between remestemcel-L and placebo"*

Two Trials in Adults > 10 Years Ago Did Not Meet Their Primary Endpoints

	Protocol 265	Protocol 280
Phase	Phase 3	Phase 3
Ages	Adult	Adult and pediatric
Population	Treatment naive aGVHD Grade B-D (NOT STEROID REFRACTORY)	SR-aGVHD Grade B-D (skin only Grade B allowed)
Design	Randomized, double-blind, placebo-controlled, multicenter	Randomized, double-blind, placebo-controlled, multicenter
Primary endpoint	Composite Treatment Response*	Durable Complete Response**
Control arm	Steroids + placebo	SOC + placebo
Treatment arm	Steroids + remestemcel-L 2 infusions/ week x Weeks 1-2, then 1 infusion/ week x Weeks 3-4	SOC + remestemcel-L 2 infusions/ week x Weeks 1-4, then 1 infusion/ week x Weeks 5-8***

* Composite Treatment Response = Decrease in 2 Grades by Day 28 with maintenance through Day 56, clinically managed CR after Day 28 with no escalation of therapy, and survival status

** Durable Complete Response = achieving a complete response of ≥ 28 days duration within 100 days after starting study drug.

***Only for partial and mixed responders at Day 28

Protocol 280

Protocol 280: Randomized Placebo-Controlled Trial in Adults and Children with SR-aGVHD

- N=260 patients with SR-aGVHD* (Grades B – D) including 28 pediatric patients
- Patients received remestemcel-L or placebo in addition to institutional standard second-line treatment for SR-aGVHD
- Primary endpoint = durable complete response (DCR)
  - CR of ≥ 28 days within 100 days post treatment initiation
  - DCR not met (34.7% vs 29.9% on placebo)

*** No improvement after 3 days and a duration of ≤ 2 weeks, while receiving treatment with methylprednisolone (≥ 1 mg/kg/day) or equivalent.**

Day 28 OR Became Accepted and Validated Endpoint Predictive of Survival

- FDA-NIH public workshop in 2009 concluded that Day 28 OR is valid marker for trials designed to assess efficacy outcomes for treatment of aGVHD[1]
- Day 28 OR highly correlated with long-term survival[2,3]

1. Center for International Blood and Marrow Transplant Research. aGVHD Workshop. May 19, 2009. 2. Martin et al., 2009 3. Martin et al., 2012

Protocol 280: Clinically Meaningful Efficacy vs Placebo in Patients with Severe Disease

	Remestemcel-L N=162		Placebo N=81	
	N (%)	95% CI	N (%)	95% CI
Overall Response at Day 28	162 (57%)	(49, 65)	81 (51%)	(40, 62)
Grade C	82 (65%)	(53, 75)	47 (49%)	(34, 64)
Grade D	44 (50%)	(35, 65)	14 (36%)	(13, 65)
Grade C / D	126 (60%)	(50, 68)	61 (46%)	(33, 59)

Protocol 280: Clinically Meaningful Efficacy vs Placebo in Pediatric Cohort

	Remestemcel-L n=14	Placebo n=13
Day 28 OR	64%	38%
Day 100 Survival	79%	54%
Day 180 Survival	64%	54%

Expanded Access Protocol (EAP) 275

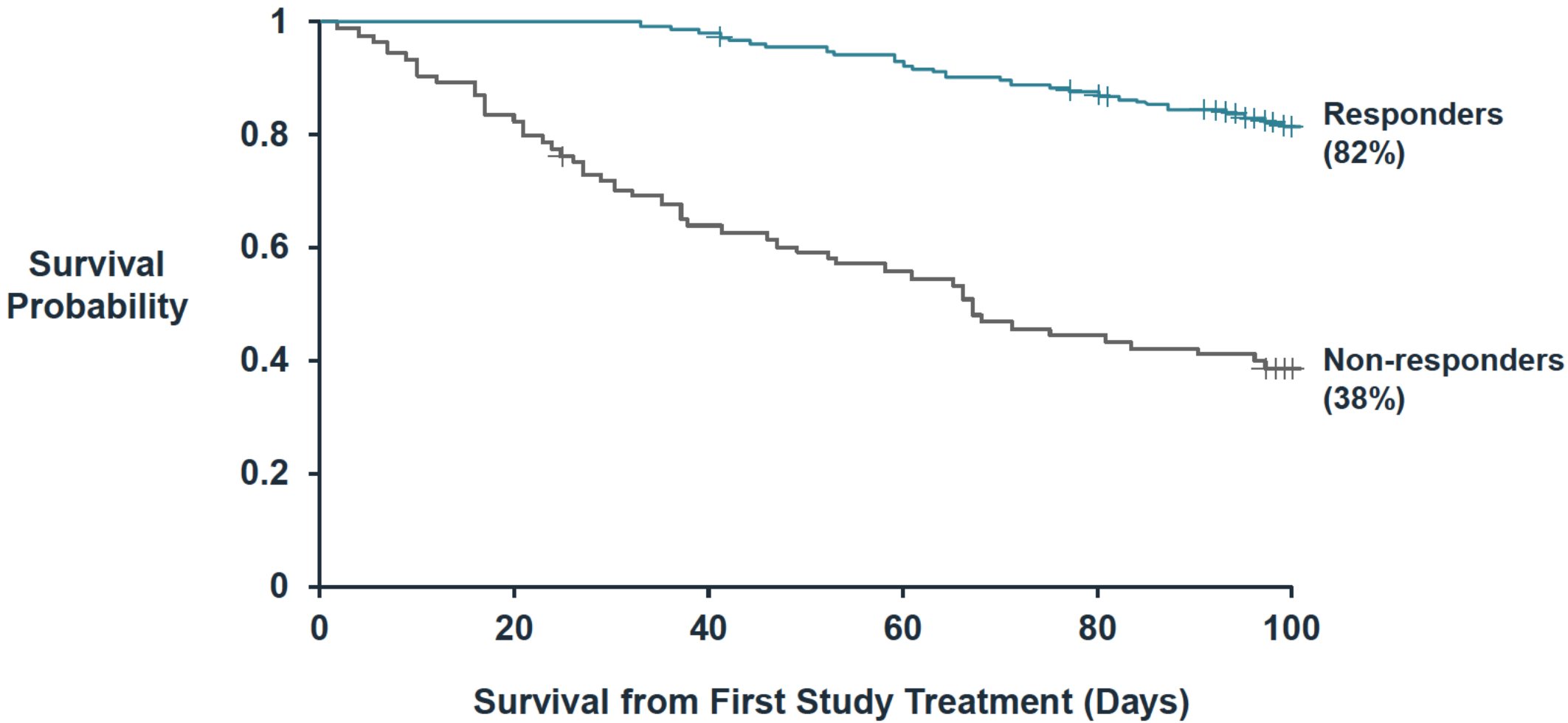
EAP 275 Represents Real-World Population

- N=241 pediatric patients with SR-aGVHD Grades B – D
  - Refractory to multiple lines of off-label treatment
  - 80% of patients Grade C / D
- Remestemcel-L treatment used as salvage ± concomitant therapy

EAP 275: High Day 28 OR and Day 100 Survival with Remestemcel-L as Salvage Therapy

Outcomes, n/N (%)	Remestemcel-L N=241
Day 28 overall response	157/241 (65%)
Day 28 OR by Grade	
Grade B	35/48 (73%)
Grade C	49/73 (67%)
Grade D	73/120 (61%)
Grade C or D	122/193 (63%)
Day 100 survival	160/241 (66%)

EAP 275: Response at Day 28 Significantly Associated with Day 100 Survival



Pivotal Study 001 / 002

Study 001 Provides Substantial Evidence of Efficacy in Children with SR-aGVHD

- We agree with FDA conclusions
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  - *"no safety signal of concern was identified in the studies of remestemcel-L."*

FDA Guidance for Single-arm Trials to Support Marketing Approval

- *"FDA has considered single-arm trials to support a marketing approval in instances*
  - *where there are no available therapies that would be considered standard of care,*
  - ***where the effect of response is presumed to be attributable to the investigational product."***

FDA Guidance for Industry Clinical Trials Endpoints for Approval of Cancer Drugs and Biologics.

Expectations for Identifying Appropriate External Control

- FDA Briefing Book
  - *"appropriate external controls can be a group of patients treated at an earlier time (historical control) or a group treated during the same time period but in another setting"*
- Used International Conference on Harmonisation (ICH) E10 guidance to identify appropriate external controls
- Similar baseline characteristics between controls and study patients is essential
- Standard of care should include physician choice of therapies

Identification of Appropriate External Pediatric Controls to Establish Study 001 Null Hypothesis

	Primary Endpoint	Day 28 OR	Experimental Single Agent	First line SR-aGVHD
Multi-agent Standard of Care				
Rashidi et al., BBMT 2019 (N=61)	Day 28 OR	34%	No	Yes
Protocol 280 Control Arm Pediatric Subgroup (N=14)	Day 28 OR	36%	No	Yes
Mount Sinai Acute GVHD International Consortium (MAGIC) database (N=30)	Day 28 OR	43%	No	Yes
Experimental Single Agent				
Sleight et al., BMT 2007 (N=27)	Maximal response within 56 days	NA	infliximab	No
Faraci et al., BBMT 2019 (N=25)	ORR at Day 7	NA	etanercept	Yes
Khandelwal, et al., BBMT 2016 (N=15)	ORR at 4 weeks	47%*	alemtuzamab	Yes

*47% OR at 4 weeks in alemtuzamab only as first line after steroids, 64% including those receiving additional salvage therapy

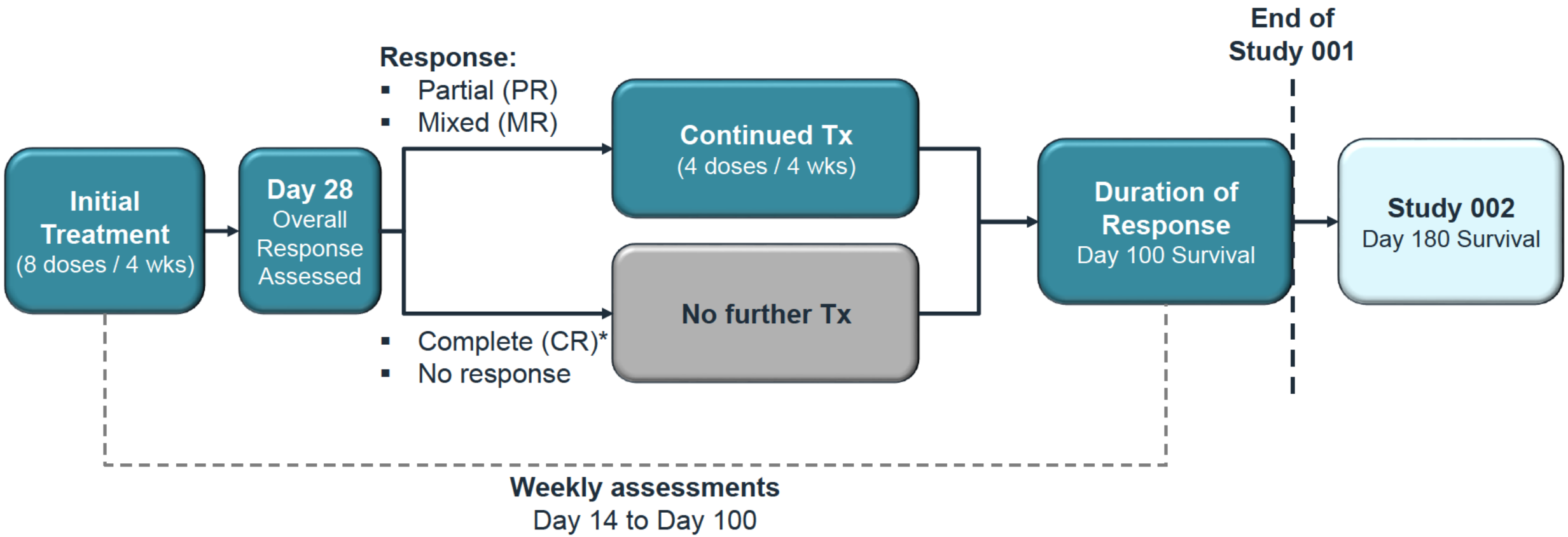
External Controls Justify and Validate Study 001 Null Hypothesis of 45%

Control Cohort	ORR at Day 28	Similar Patient Characteristics to Study 001 Population
Rashidi et al., 2019 (N=61)	**34%**	▪ Single-center ▪ 203 patients total treated from 1990 – 2016 ▪ 61 pediatric patients ▪ SR-aGVHD Grades 1 – 4
Protocol 280 Control Arm Pediatric Subgroup (N=14)	**36%**	▪ Multi-center ▪ 14 pediatric control group from randomized controlled study of remestemcel-L from 2006 – 2009 ▪ SR-aGVHD Grades B – D
MAGIC (N=30)	**43%**	▪ Multi-center ▪ 30 pediatric patients treated from 2009 – 2019 matched to study 001 eligibility criteria ▪ SR-aGVHD Grades B – D excluding Grade B skin-only

Pivotal Study 001: Phase 3, Single-arm Open-label Trial in Children with SR-aGVHD

- **Study Objective:** To show significant increase in Day 28 OR attributable to remestemcel-L as initial second-line therapy following steroids
- 55 children ages 2 mos – 17 yrs
- SR- aGVHD Grades B – D (Grade B skin only excluded)
- Null hypothesis = Day 28 OR 95% lower CI excludes 45%

Pivotal Phase 3 Study 001 / 002 Design



*Flare Tx if needed by day 70 (8 doses / 4 weeks)

Study 001 / 002 Endpoints

Study 001

Primary

- Overall Response at Day 28*
  - Complete Response (CR)
  - Partial Response (PR)

Secondary

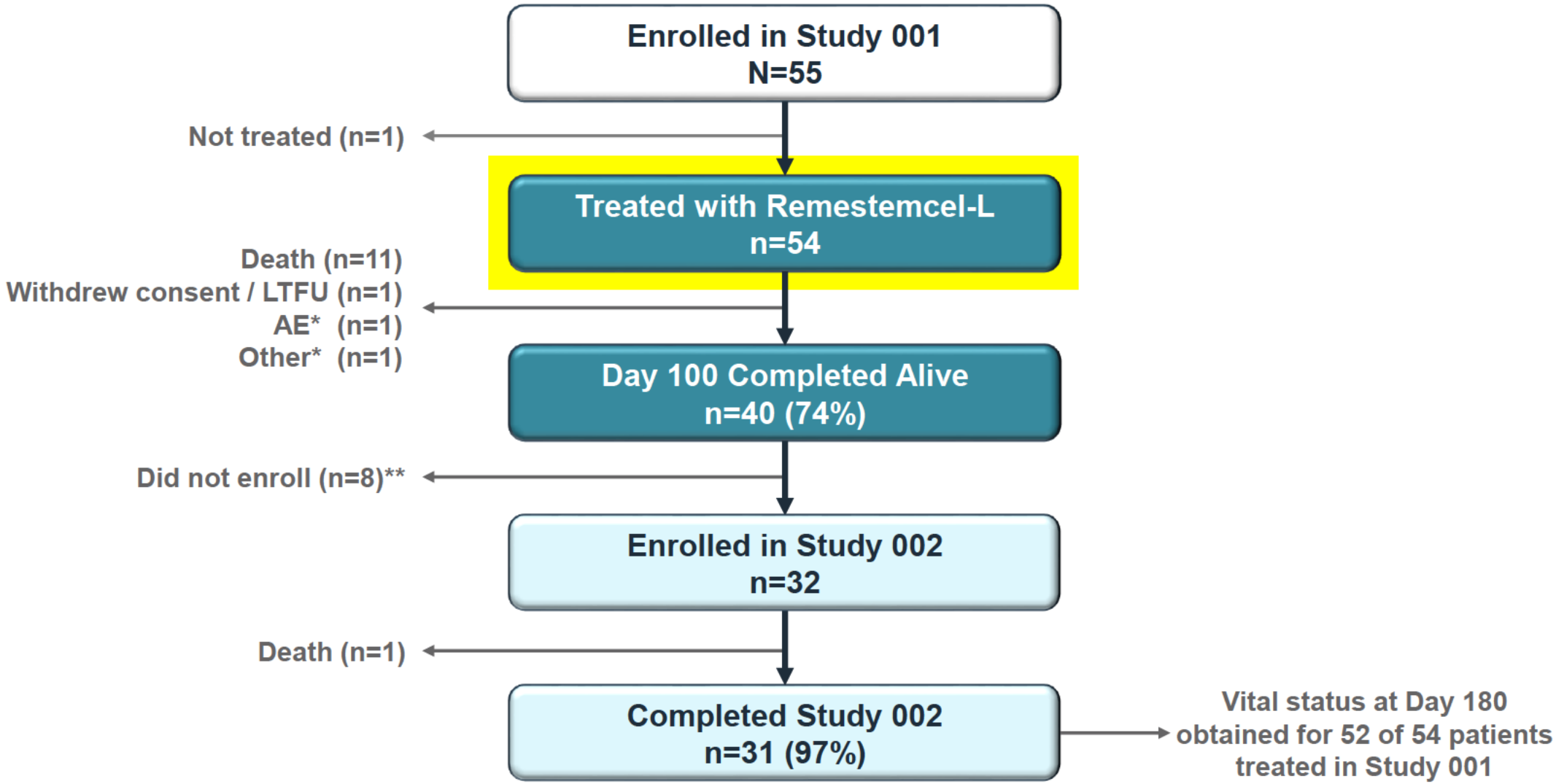
- Overall Survival (OS) at Day 100

Study 002

- Safety
- Overall Survival (OS) at Day 180
- Duration of response

*Assessed by skin, GI tract and liver

Study 001 / 002: Patient Disposition



* Withdrew from study, vital status collected - reported death before Day 100

**Did not enroll (n=8): 4 did not consent, 2 site did not have IRB approval, 1 moved out of state, and 1 per sponsor's decision; 2 deaths while not in the study

Study 001: Demographics

		Remestemcel-L N=54
Age	Median (Min, Max)	7 years (7 months, 17 years)
Gender, n (%)	Male	65%
	Female	35%
Race, n (%)	White	56%
	Black or African American	15%
	Asian	6%
	American Indian or Alaska Native	6%
	Other	19%
Weight (kg)	Mean (SD)	29 (19)

Study 001: Transplant Characteristics

Transplant Characteristics (%)		Remestemcel-L N=54
Type of Transplant	Bone Marrow	54%
	Peripheral Blood Stem Cells	26%
	Cord Blood	20%
HLA Compatibility	Matched / Related	11%
	Mismatched / Related	13%
	Unrelated	76%

Study 001: Disease Severity

Disease Severity (%)		Remestemcel-L N=54
aGvHD Grade (IBMTR)*	Grade B (excluding skin-only)	11%
	Grade C	43%
	Grade D	46%
Organ involvement	Skin only	26%
	Lower GI only	39%
	Multi-organ	35%

* International Bone Marrow Transplantation Registry

Study 001 Meets Primary Endpoint: 95% Lower CI Excluded 45% Null Hypothesis

Analysis Set	N	Day-28 CR	Day-28 PR	Day-28 ORR	
		% (n)	% (n)	% (n)	95% CI
Full Analysis Set (ITT)	55	29.1 (16)	40.0 (22)	69.1 (38)	(55.2, 80.9)
Treated Set	54	29.6 (16)	40.7 (22)	70.4 (38)	(56.3, 82.0)
Sensitivity Set 1	45	33.3 (15)	42.2 (19)	75.6 (34)	(60.5, 87.1)
Sensitivity Set 2	55	27.3 (15)	34.5 (19)	61.8 (34)	(47.8, 74.6)

- Sensitivity Set 1 removed patients who received concomitant medications or improved prior to treatment initiation
- Sensitivity Set 2 considered these patients as treatment failures

Adapted from FDA Briefing Book Table 2

Study 001 / 002: Meaningful Outcomes Across Disease Severity

Outcomes, n/N (%)	Remestemcel-L N=54
Day 28 overall response	38/54 (70%)
Day 28 OR by Grade	
Grade B	3/6 (50%)
Grade C	16/23 (70%)
Grade D	19/25 (76%)
Grade C or D	35/48 (73%)

Study 001 Durable Day 28 Response

Definition Used	Duration of ORR days n=38	
	Median	Range
Mesoblast DOR	70.5	1, 171
FDA-defined DOR	54	7, 159+
FDA-defined alternative measure of durability	111.5	9, 182+

Day 28 OR Consistent in Pediatric Patients Treated with Remestemcel-L

	Study 001	EAP 275	Protocol 280 (Pediatric)	
	Remestemcel-L N=54	Remestemcel-L + SOC N=241	Remestemcel-L + SOC N=14	Placebo + SOC N=13
Day 28 OR (95% CI)	**69% (55, 81)**	**65% (59, 71)**	**64% (35, 87)**	**38% (14, 68)**

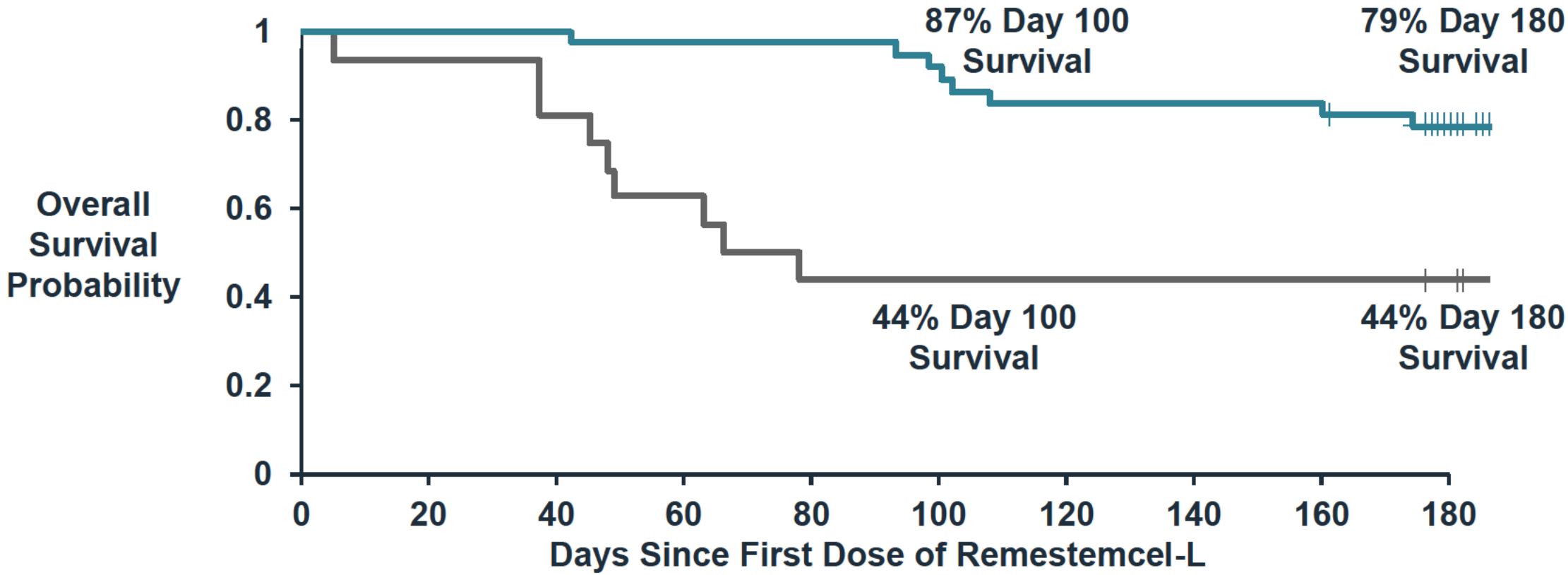
Effect of Response Attributable to Remestemcel-L

- Primary endpoint Day 28 OR results in Study 001 were statistically significant
- All sensitivity analyses excluded null hypothesis
- Appropriate external controls justified and validated null hypothesis
- Measured response was durable
- Results were consistent across 3 separate pediatric cohorts

Consistent Survival Outcomes in Pediatric Patients Treated with Remestemcel-L

	MAGIC N=30	Protocol 280 (pediatric) Placebo N=13	Protocol 280 (pediatric) Remestemcel-L N=14	EAP 275 Remestemcel-L N=241	Study 001 Remestemcel-L N=54
Day 100 Survival	57%	54%	79%	66%	74%
Day 180 Survival	54%	54%	64%	NA	69%

Study 001/002: Day 28 Responders Have High Survival Through Day 180 with Remestemcel-L



Number at Risk

Day 28 Responder	38	38	38	37	37	35	32	32	32	22
Day 28 Non-Responder	16	15	13	10	7	7	7	7	7	6

p-value based on a Cochran-Mantel-Haenszel test

Safety

Remestemcel-L Safety Profile Similar to Placebo

	Study 001	All aGHVD		All Non-GVHD	
	Remestemcel-L N=54	Remestemcel-L +/- SOC N=654*	Placebo + SOC N=173	Remestemcel-L +/- SOC N=460	Placebo + SOC N=230
Any AEs	100%	100%	100%	88%	90%
AEs grade ≥ 3	56%	87%	82%	31%	27%
AEs leading to discontinuation	15%	9%	9%	2%	0.4%
SAEs	65%	72%	79%	35%	35%
SAEs leading to death	20%	45%	42%	2%	2%

*N=344 for AEs; EAP 275 did not collect AEs

Overall Safety Profile of Remestemcel-L in Pediatric Patients with SR-aGVHD

	Study 001	EAP 275	Protocol 280	
	Remestemcel-L N=54	Remestemcel-L N=241	Remestemcel-L N=14	Control N=13
Any AE	54 (100%)	-	14 (100%)	13 (100%)
AE ≥ Grade 3	30 (56%)	-	7 (50%)	5 (39%)
Any SAE	35 (65%)	131 (54%)	12 (86%)	12 (92%)
AE/SAE leading to death	11* (20%)	77 (32%)	5 (36%)	6 (46%)
AE/SAE leading to discontinuation	8 (15%)	26 (11%)	1 (7%)	1 (8%)

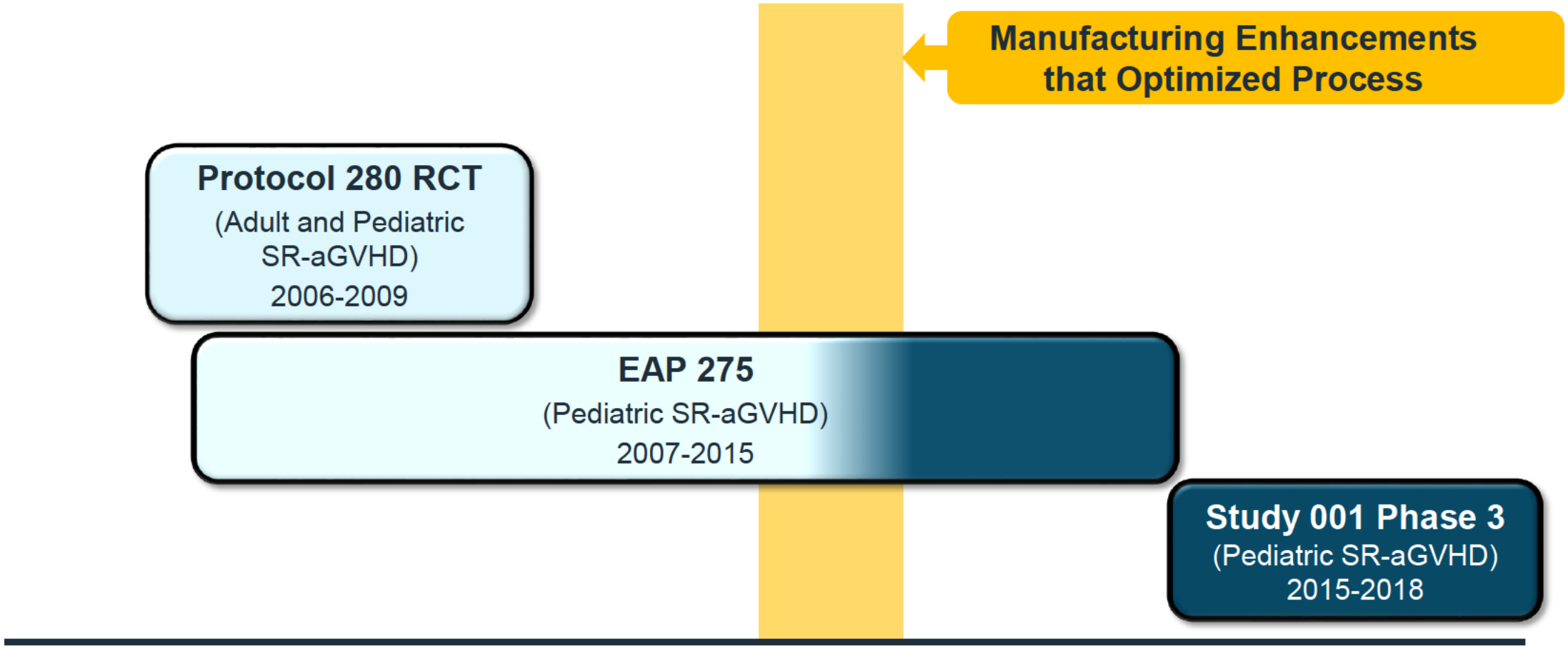
* 3 additional deaths occurred after study conclusion

No Safety Differences Between Remestemcel-L and Placebo

- No safety signal of concern was identified in the studies of remestemcel-L

Positive Results in Pivotal Study 001 in Context of Other Studies

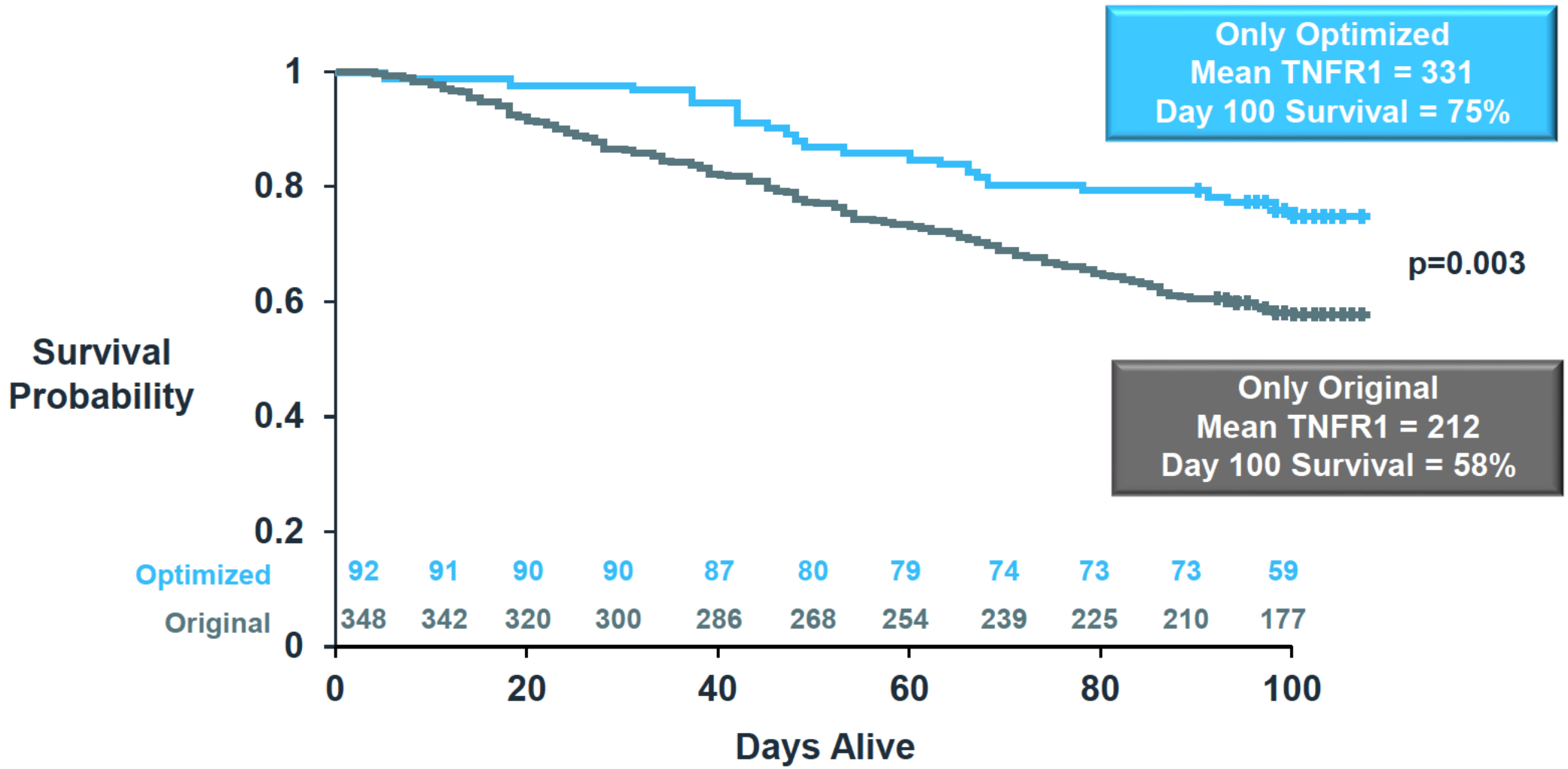
Manufacturing Improvements During Remestemcel-L Product Development Associated with Improved Outcomes in SR-aGVHD



Manufacturing Improvements Resulted in Improved Potency Quality Attributes

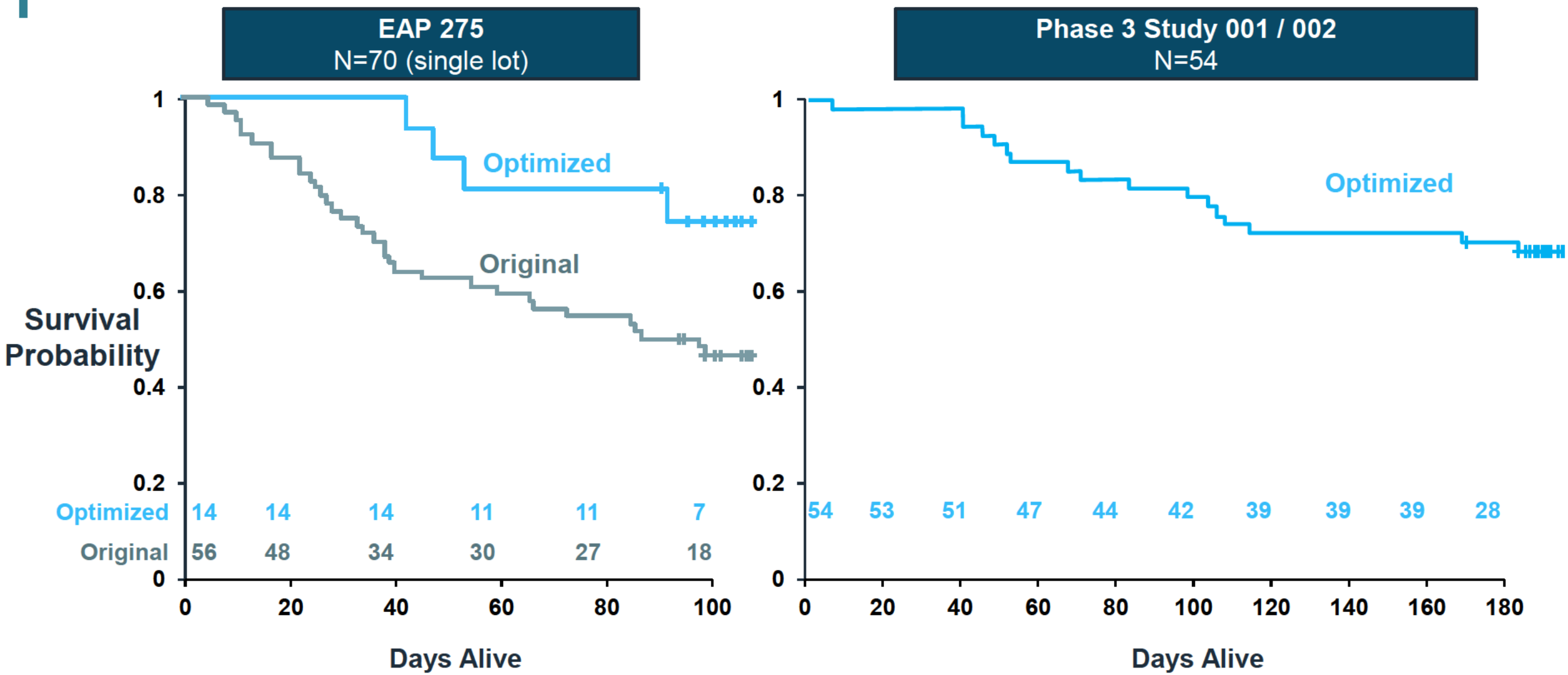
	Dates of Product Manufacture	TNFR1 (SD) (pg/mL)	IL-2Rα (SD) (% inhibition)	Day 28 OR	Day 100 OS
Protocol 280 (N=163)	2006-2008	206 (45)	65 (11)	58%	52%
EAP 275 (N=241)	2006-2009	241 (55)	69 (11)	65%	66%
Phase 3 Study 001 (N=54)	2009-2015	322 (56)	81 (7)	70%	74%

Survival Benefit in Patients Across All Trials who Received Only Product Made with Optimized vs Original Process



Log-rank p-value

Product Made with Optimized Process Provides Survival Benefit in Pediatric EAP 275 and Study 001



Log-rank p-value

Pivotal Study 001 Provides Substantial Evidence of Efficacy in Children with SR-aGVHD

- Successfully met primary endpoint with Day 28 OR 70% vs 45% null hypothesis
  - Null hypothesis validated using appropriate external controls
  - 95% lower CI in every sensitivity analysis excluded null hypothesis
- Study 001 demonstrates that remestemcel provides meaningful clinical benefit in children with SR-aGVHD

Remestemcel-L Meets FDA Guidance for Single-arm Trials to Support Marketing Approval

- *"FDA has considered single-arm trials to support a marketing approval in instances*
  - *where there are no available therapies that would be considered standard of care,*
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FDA Guidance for Industry Clinical Trials Endpoints for Approval of Cancer Drugs and Biologics.

Mesoblast Committed to Post-marketing Study in Adults with Severe SR-aGVHD

- Utilize remestemcel-L manufactured with optimized process
- Advisory Board of GVHD experts convened on Aug 1, 2020
- Planning underway for randomized controlled trial of remestemcel-L vs standard of care
  - Designed to demonstrate improved overall response and survival
  - Focus on adults with continued high unmet need despite approved therapies or who have not responded to existing therapies

Clinical Perspective

Joanne Kurtzberg, MD

Jerome Harris Distinguished Professor of Pediatrics

Professor of Pathology

Director, Marcus Center for Cellular Cures

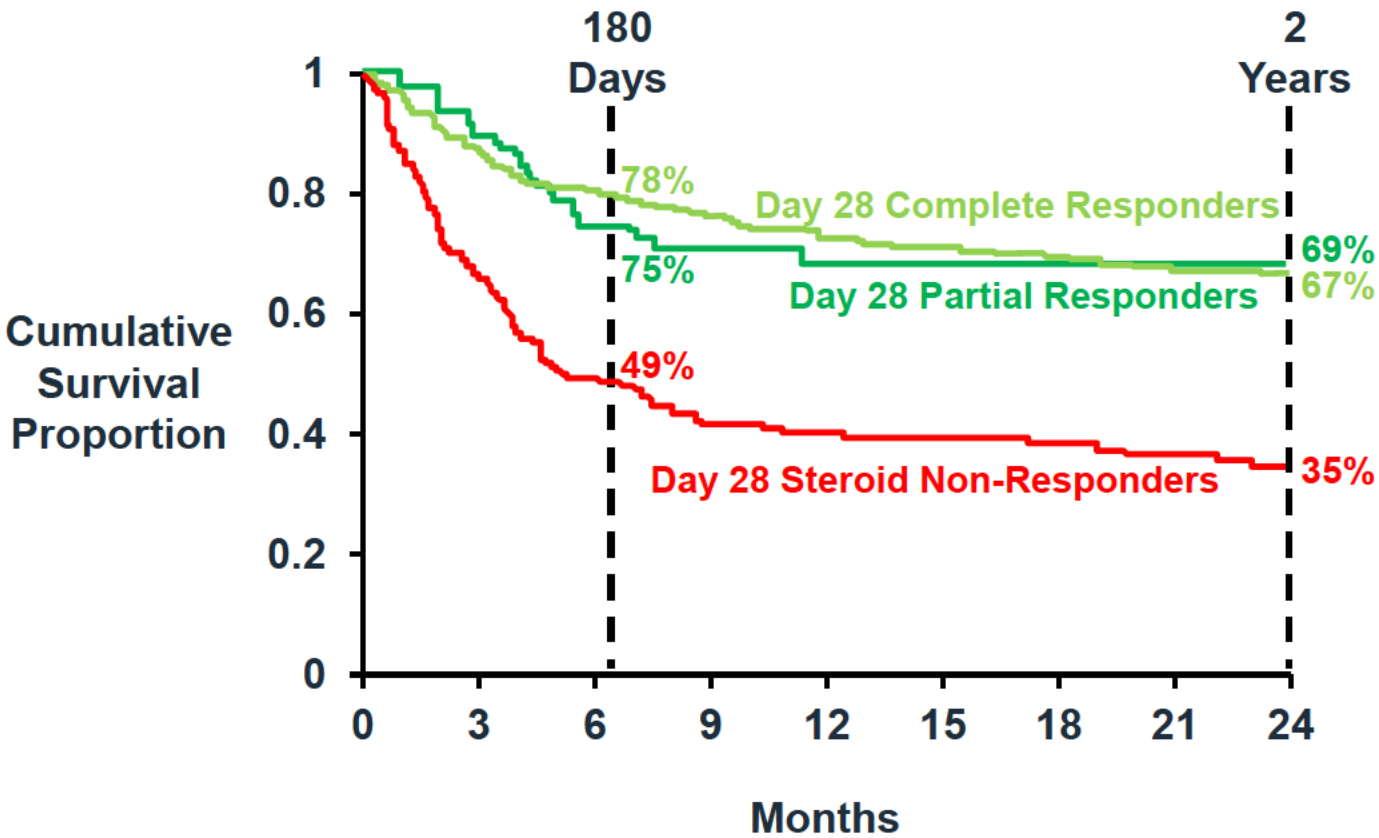
Director, Pediatric Blood and Marrow Transplant Program

Director, Carolinas Cord Blood Bank

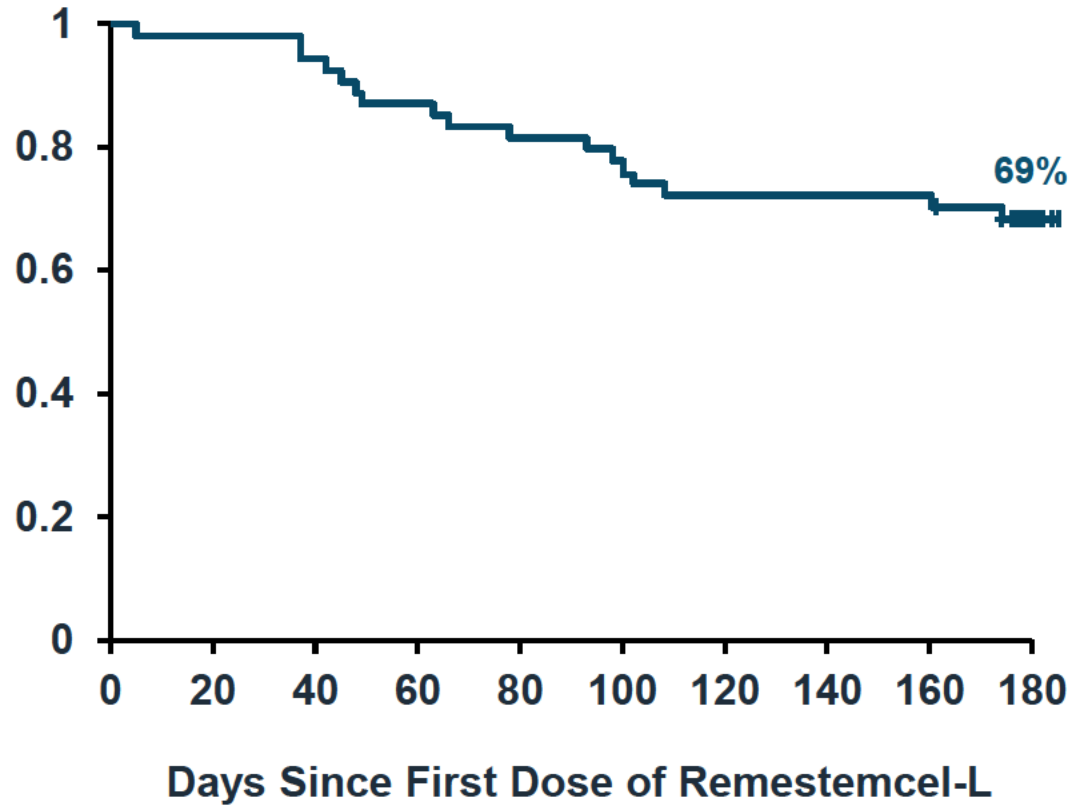
Duke University School of Medicine

Children with SR-aGVHD Have Dismal Survival at 2 Years

2-Year Survival in Pediatric Patients Treated with Steroids[1]
N=370



Study 001 / 002 Survival through Day 180
N=54



1. Redrawn from Figure 2 of MacMillan et al. 2020

Efficacy and Safety Data Reported For Remestemcel Support Positive Benefit-Risk

- Children < 12 years of age have no approved treatments
- Unapproved treatments carry risk for high toxicity
- High morbidity and mortality in children treated with other options
- Study 001 results vs historical controls are accurate
- Need remestemcel to reduce number of children dying from aGVHD
- Safety profile and mode of administration allow use without concerns of AEs or inability to tolerate oral medications

Remestemcel-L for Pediatric Patients with SR-aGVHD

Mesoblast, Inc.

Oncologic Drugs Advisory Committee (Clinical Session)

August 13, 2020