Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

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elivaldogene autotemcel (eli-cel) for the Treatment of Patients with Early Active Cerebral Adrenoleukodystrophy

betibeglogene autotemcel (beti-cel) for the Treatment of Patients with β-Thalassemia who Require Regular Red Blood Cell Transfusions

June 9 and 10, 2022

bluebird bio, Inc.

Cellular, Tissue and Gene Therapies Advisory Committee

bluebirdbio®

beti-cel & eli-cel Advisory Committee Meeting: Introduction – June 9, 2022, Morning

Anne-Virginie Eggimann, MSc

Chief Regulatory Officer

bluebird bio, Inc.

bluebirdbio®

Sponsor Presentations

TODAY

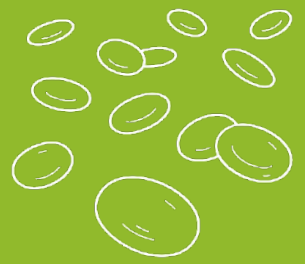
elivaldogene autotemcel (eli-cel)

Morning

Treatment of early active cerebral adrenoleukodystrophy (CALD)
BLA 125755

Benefit-Risk Discussion

Sponsor Presentations

	TODAY	TOMORROW
	elivaldogene autotemcel (eli-cel)	**betibeglogene autotemcel (beti-cel)**
Morning	 **Treatment of early active cerebral adrenoleukodystrophy (CALD) BLA 125755** ***Benefit-Risk Discussion***	 **Treatment of β-thalassemia requiring regular transfusions BLA 125717** ***Benefit-Risk Discussion***

Sponsor Presentations

TODAY

elivaldogene autotemcel (eli-cel)

Morning

Treatment of early active cerebral adrenoleukodystrophy (CALD)
BLA 125755

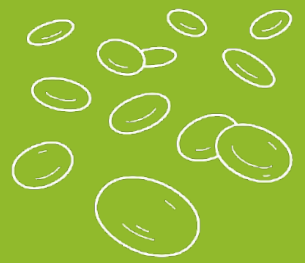
Benefit-Risk Discussion

Afternoon

Lentiviral Vector (LVV) Safety
(eli-cel, beti-cel and lovo-cel*)

TOMORROW

betibeglogene autotemcel (beti-cel)



Treatment of β-thalassemia requiring regular transfusions
BLA 125717

Benefit-Risk Discussion

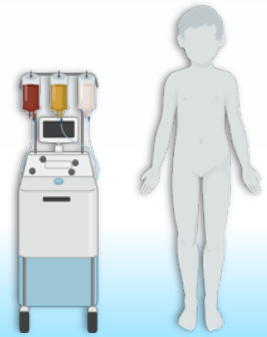
*lovo-cel = lovotibeglogene autotemcel in Phase 3 clinical development for the treatment of sickle cell disease

eli-cel and beti-cel are Two Different Products that Share Some Key Features

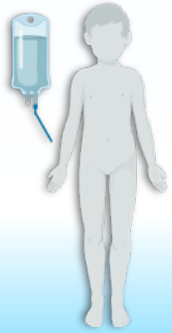
- First-in-class, one-time, gene therapy products
- Consist of patient's own blood stem cells genetically modified ex vivo with a lentiviral vector
- Address underlying cause of disease by adding functional copies of a gene

Treatment Steps are Similar for Both Gene Therapies

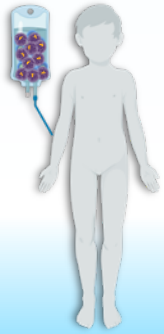
Mobilization and Cell Collection (Apheresis)



Conditioning

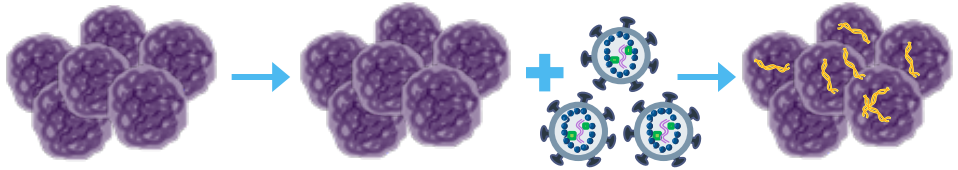


Drug Product IV Infusion



Minimum dose:
5×10^6 CD34+ cells/kg

Manufacturing



Select CD34+ cells

Transduce Cells with Lentiviral Vector (LVV)

Cryopreserve, Test, and Release Drug Product

Manufacturing process starts and ends with each patient

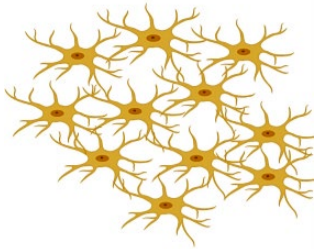
IV: intravenous

eli-cel Produces Functional ALD Protein in the Brain

Mobilization and Cell Collection (Apheresis)

Conditioning

Drug Product IV Infusion



Manufacturing

Select CD34+ cells

Transduce Cells with Lentiviral Vector (LVV)

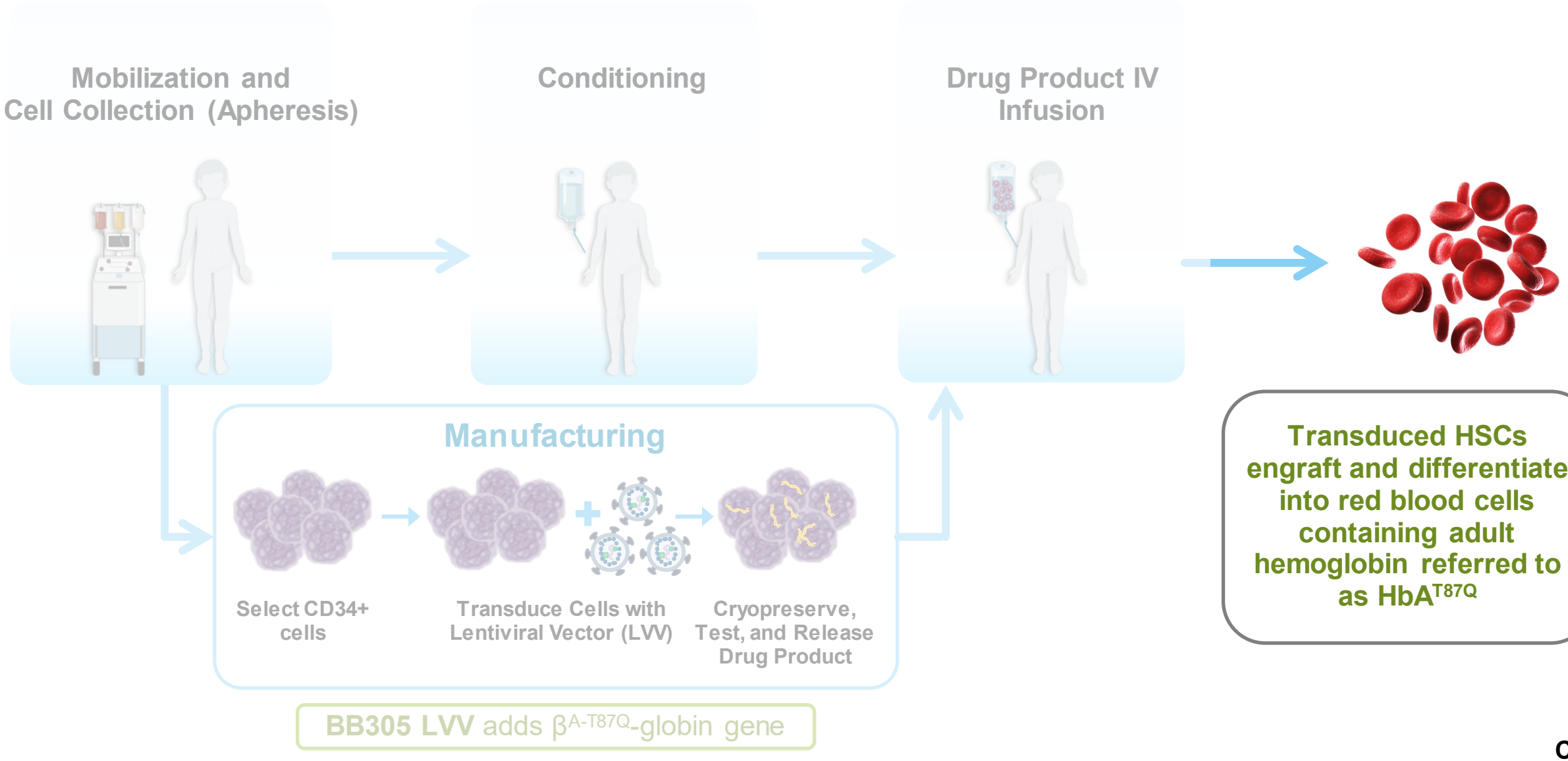
Cryopreserve, Test, and Release Drug Product

Lenti-D LVV adds *ABCD1* gene

Putative Mechanism of Action:
Transduced HSCs engraft and differentiate into cerebral microglia expressing adrenoleukodystrophy protein (ALDP)

HSCs: hematopoietic stem cells, IV: intravenous

beti-cel Produces Functional Adult Hemoglobin in Blood



Distinct Benefit/Risk Assessments: Both Positive

eli-cel key outcomes

JUNE 9

- Stabilize CALD w/ preservation of physical & intellectual function in majority of patients
- Improved OS and EFS compared to allo-HSCT patients treated without a matched sibling donor
- Majority of adverse events consistent with mobilization, apheresis and conditioning
- 3 MDS cases likely mediated by Lenti-D LVV

eli-cel is **an essential life-saving therapy for patients with unmatched donors**, and a meaningful option for those with a MUD

67 patients treated with up to 7 yrs follow-up

beti-cel key outcomes

JUNE 10

- High rate of durable transfusion independence
- Trends of improvement in iron overload and erythropoiesis
- Safety profile largely reflects known side effects of mobilization and conditioning agents
- No BB305 LVV mediated safety event

beti-cel is a **potentially curative option** for patients with β-thalassemia who require regular red blood cell transfusions

63 patients treated with up to 7 yrs follow-up

Allo-HSCT=allogeneic hematopoietic stem cell transplant, MDS=Myelodysplastic Syndrome, EFS=Event free survival, OS=Overall survival, MUD=Matched unrelated donor

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67 patients treated with up to 7 yrs follow-up

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Proposed indication for eli-cel

Treatment of patients with
early active cerebral adrenoleukodystrophy

Proposed indication for eli-cel

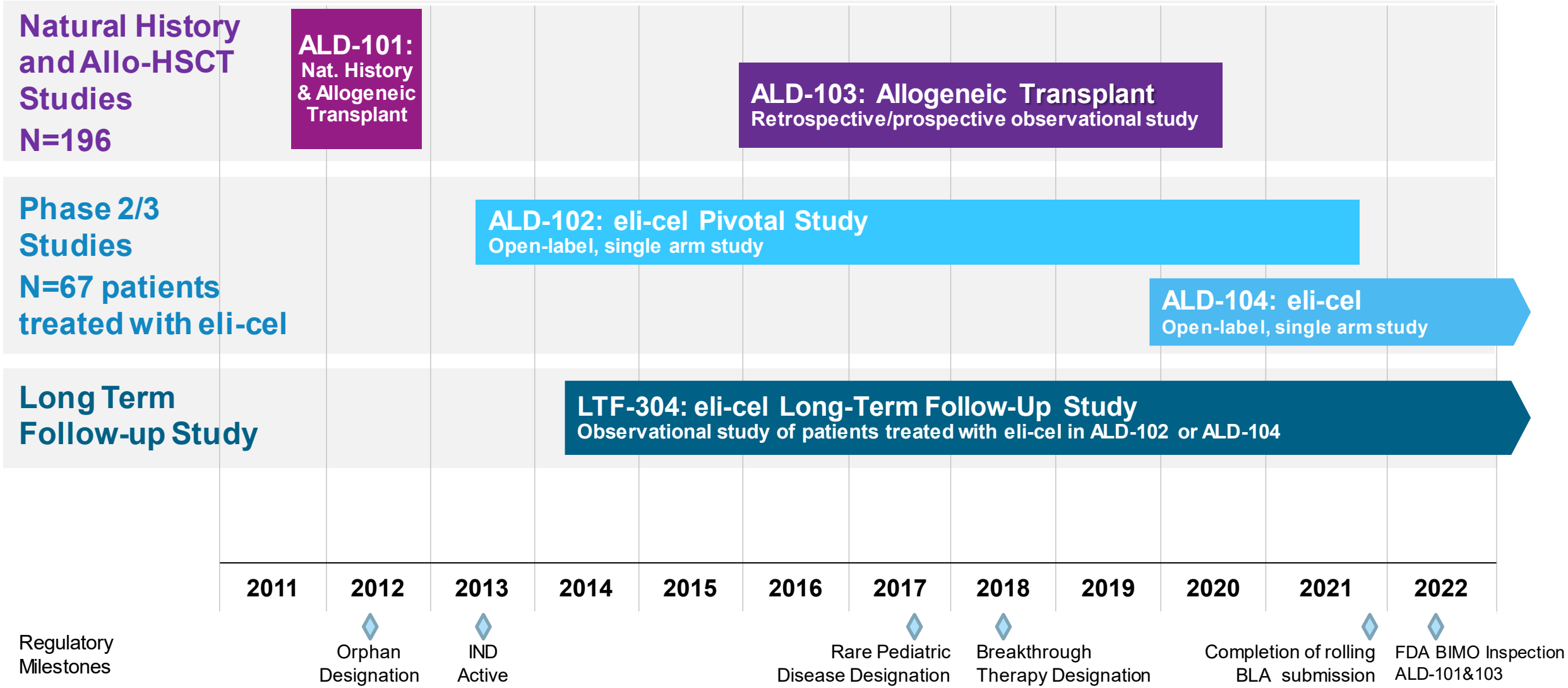
Treatment of patients with
early active cerebral adrenoleukodystrophy
who are less than 18 years of age

Proposed indication for eli-cel

Treatment of patients with
early active cerebral adrenoleukodystrophy
who are less than 18 years of age
and do not have an available and willing
HLA-matched sibling
hematopoietic stem cell donor

HLA = human leukocyte antigen

Overview of eli-cel clinical development



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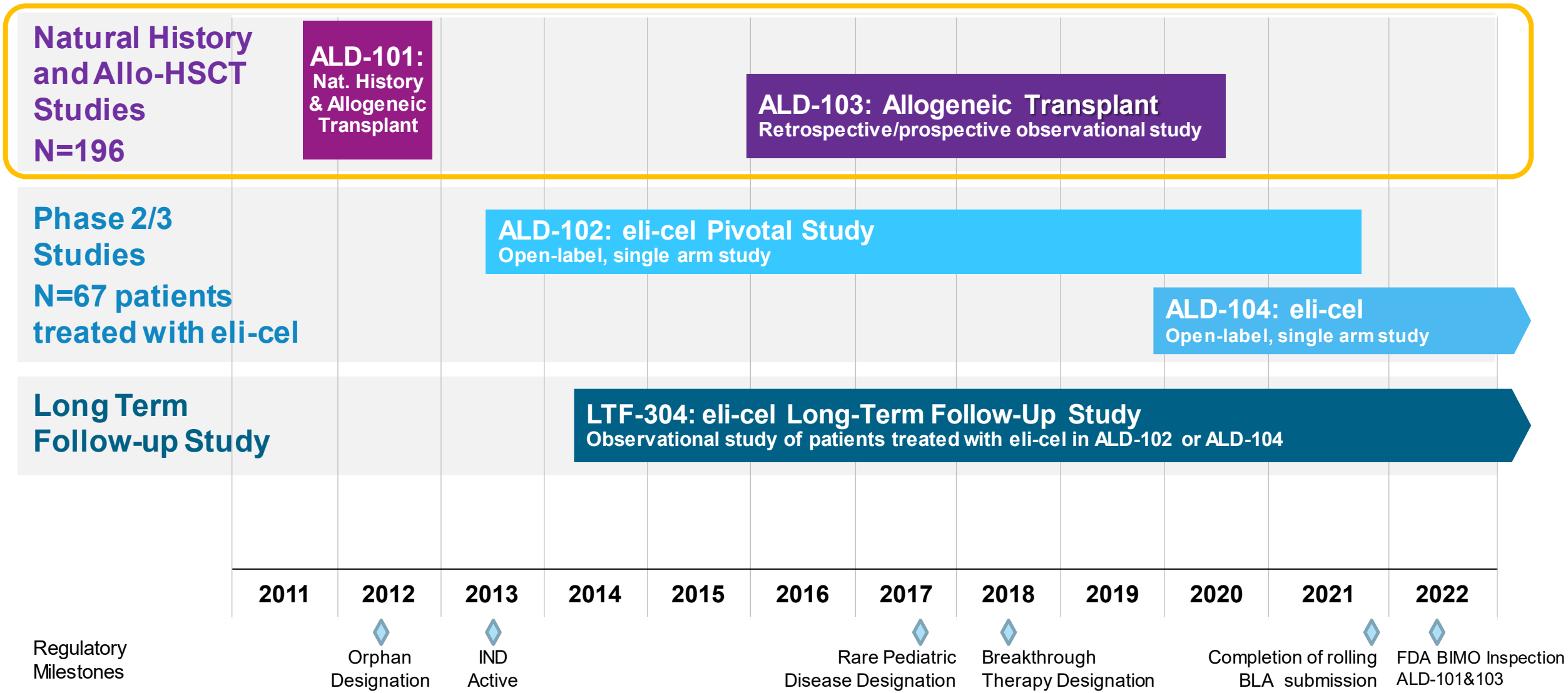
Overview of eli-cel clinical development



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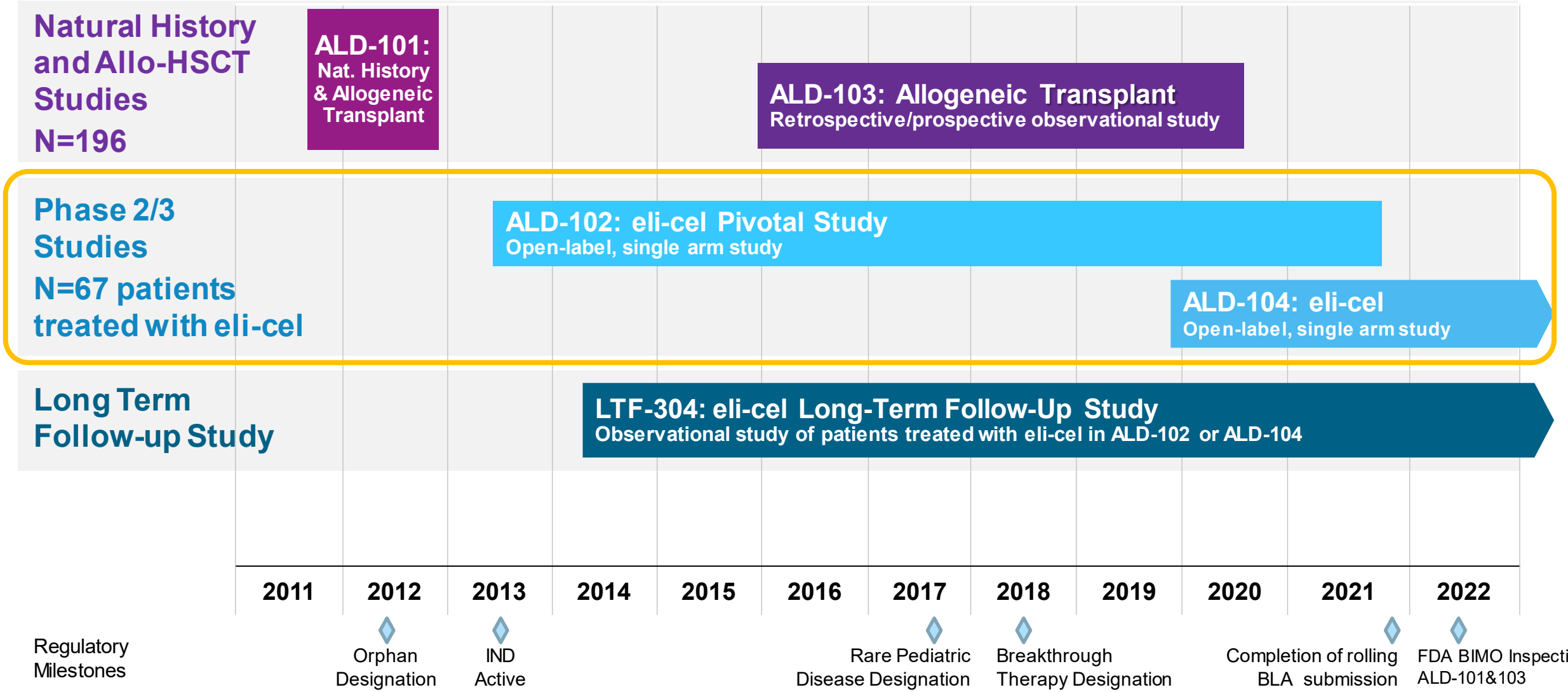

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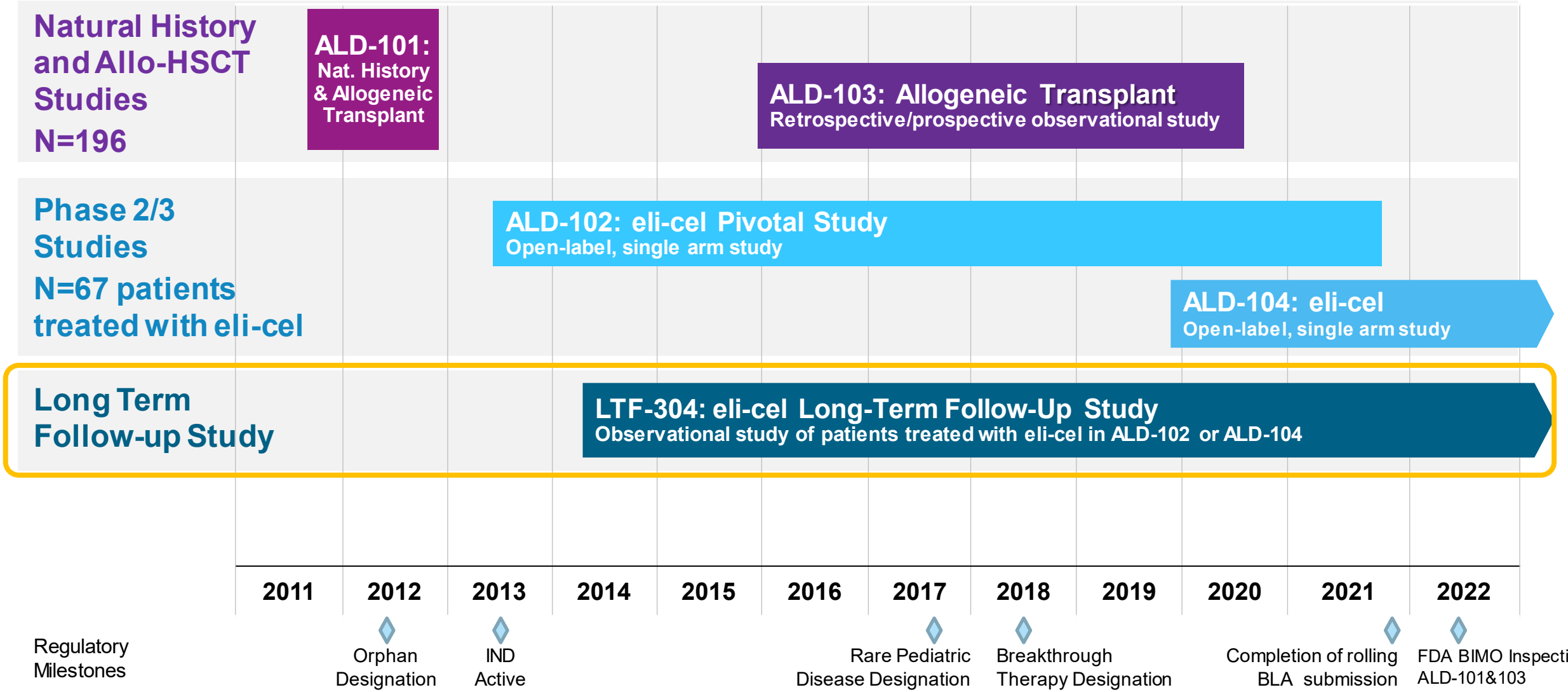

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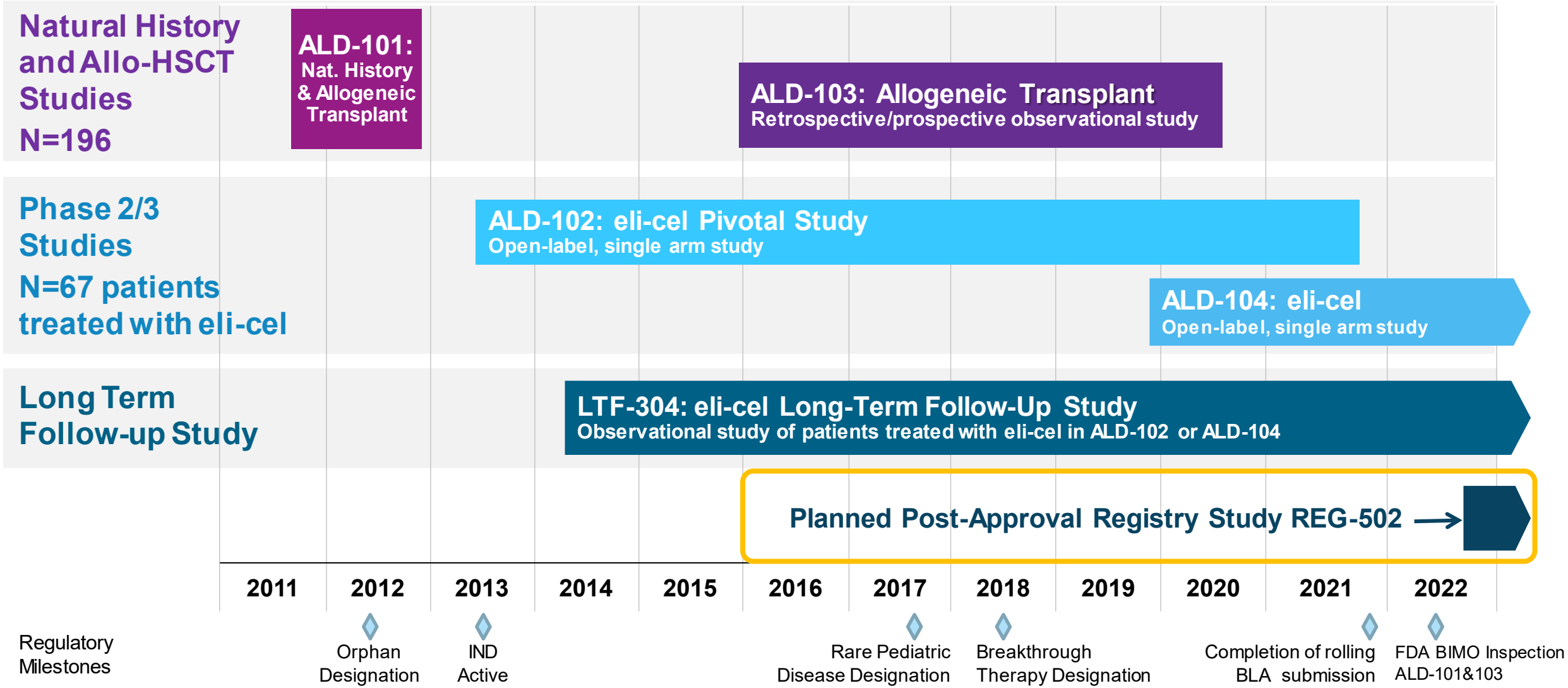

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Agenda for Sponsor Presentations – June 9, 2022

Morning: eli-cel Benefit/Risk	
Introduction	**Anne-Virginie Eggimann, MSc** Chief Regulatory Officer, bluebird bio, Inc.
Cerebral Adrenoleukodystrophy	**Florian Eichler, MD** Director, Leukodystrophy Service, Massachusetts General Hospital Associate Professor of Neurology, Harvard Medical School
Efficacy	**Jakob Sieker, MD** Senior Medical Director, Clinical Research and Development, bluebird bio, Inc.
Safety and Benefit/Risk	**Laura Demopoulos, MD** Vice President, Pharmacovigilance, bluebird bio, Inc.
Clinical Perspective: **The Role of eli-cel**	**Christine Duncan, MD** Sr. Physician, Dana-Farber/Boston Children's Hospital Cancer and Blood Disorders Center Medical Director of Clinical Research & Development, Gene Therapy, Boston Children's Hospital Associate Professor of Pediatrics, Harvard Medical School
Moderator	**Frederic Prince, PhD** Program Lead, eli-cel
Afternoon: Lentiviral Vector Safety	
Introduction	**Anne-Virginie Eggimann, MSc** Chief Regulatory Officer, bluebird bio, Inc.
Lentiviral Vector Safety (relevant to both eli-cel and beti-cel)	**Melissa Bonner, PhD** Senior Vice President, Head of Research, bluebird bio, Inc.

Additional Experts – June 9, 2022

Bone Marrow Assessments	**Robert Hasserjian, MD** Professor of Pathology Harvard Medical School
Hematologic Oncology	**R. Coleman Lindsley, MD, PhD** Assistant Professor, Medical Oncology Dana-Farber Cancer Institute
Cerebral MRI Scoring	**Daniel J. Loes, MD, FACR** Neuroradiologist Retired, Private practice and University of Minnesota
Neurologic Function Score (NFS) and Major Functional Disabilities (MFDs)	**Gerald V. Raymond, MD** Professor of Genetics and Neurologist Johns Hopkins Hospital and the Kennedy Krieger Institute
Gene Therapy Principal Investigator for ALD-102 and HGB-207	**Adrian Thrasher, MD, PhD** Professor of Pediatric Immunology Lead for the Cell, Stem Cell, and Gene Therapy theme UK NIHR Great Ormond Street Hospital NHS Trust Biomedical Research Centre
Gene Therapy Principal Investigator for ALD-102	**David A. Williams, MD** Chief of Hematology/Oncology at Boston Children's Hospital Senior Vice President, Chief Scientific Officer at Boston Children's Hospital Professor of Pediatrics at Harvard Medical School

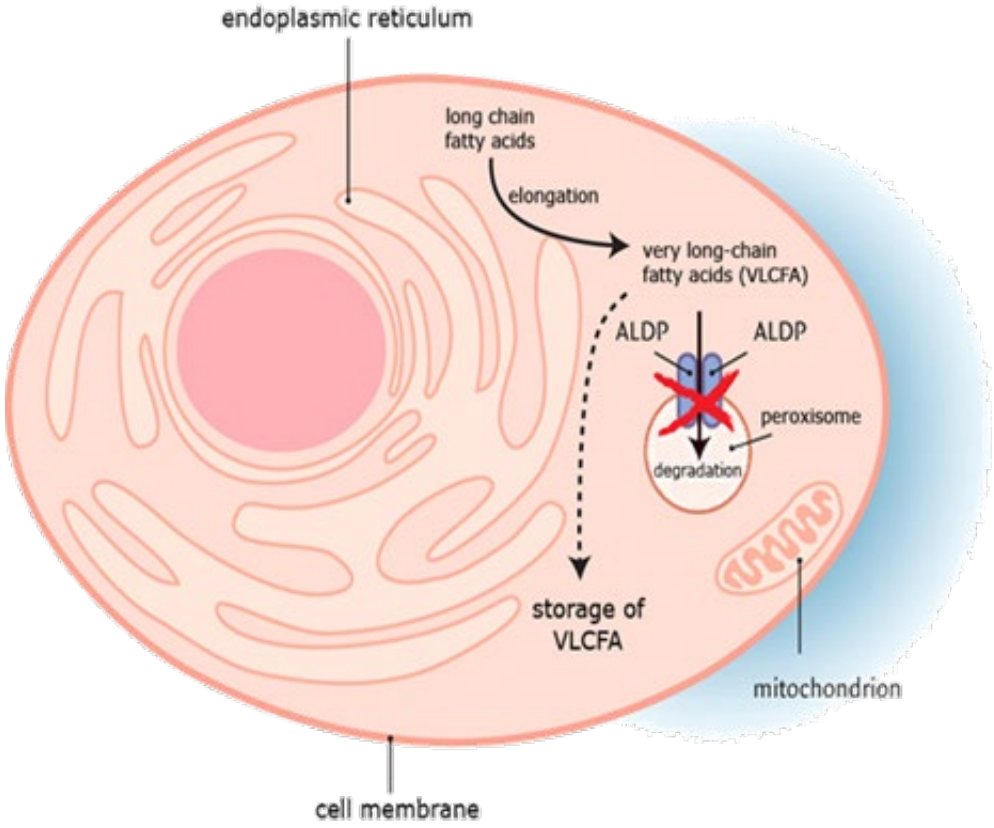
Cerebral Adrenoleukodystrophy

Florian Eichler, MD

Director, Leukodystrophy Service, Massachusetts General Hospital

Associate Professor of Neurology, Harvard Medical School

Adrenoleukodystrophy (ALD)



- X-linked metabolic disease
- Mutations in *ABCD1* gene lead to impaired expression of the peroxisomal ALDP needed to transport VLCFA into the peroxisome for degradation[1]
- VLCFA accumulate and tissue damage occurs, primarily in adrenal gland and nervous system
- There are 4 main forms of ALD that range in severity

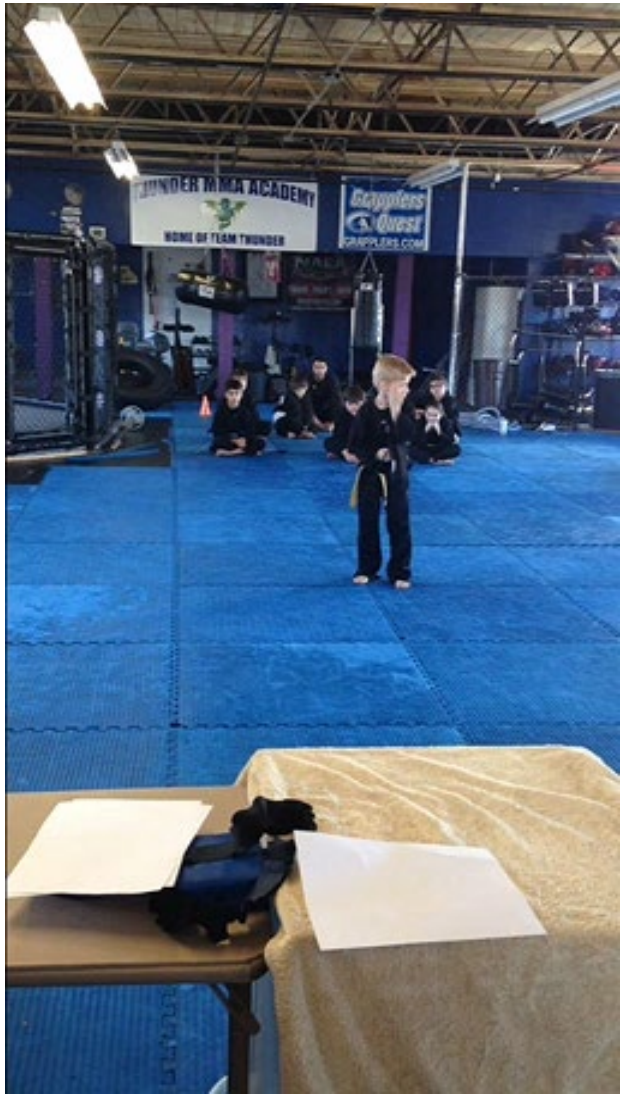
Asymptomatic	Adrenal insufficiency	Adrenomyelo-neuropathy (AMN)	Cerebral ALD (CALD)

- The estimated incidence of ALD is ~1:20,000 to 1:30,000 males[2]
- **~40% of boys with ALD will develop CALD[3]**

VLCFA=very long chain fatty acids

1. Moser HW. *Brain* 1997;120:1485.; 2. Wiesinger C et al. *Appl Clin Genet*. 2015;8:109-21.; 3. Engelen M. et al. *Orphanet J Rare Dis* 2012;7:51.

Cerebral adrenoleukodystrophy (CALD)



Evaluating severity of neurologic dysfunction in CALD

Neurologic Function Score (NFS)[1]

Component	Score
Hearing/auditory processing problems	1
Aphasia/apraxia	1
Loss of communication	3
Vision impairment	1
Cortical blindness	2
Swallowing dysfunctions	2
Tube feeding	2
Running difficulties	1
Walking difficulties/spasticity	1
Spastic gait (need assistance)	2
Wheelchair dependence	2
No voluntary movement	3
Episodes of incontinence	1
Total incontinence	2
Nonfebrile seizures	1
Possible Total	25

1. Moser HW, Raymond GV, et al. *Neuropediatrics.* 2000;31(5):227-39.; 2. Raymond GV, et al. *JICNA* 2020

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Major Functional Disabilities (MFD)

Loss of communication
Cortical blindness
Tube feeding
Wheelchair dependence
No voluntary movement
Total incontinence

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Major Functional Disabilities (MFD)

Loss of communication
Cortical blindness
Tube feeding
Wheelchair dependence
No voluntary movement
Total incontinence

MFD presence: ≥97% interrater agreement [2]

1. Moser HW, Raymond GV, et al. *Neuropediatrics.* 2000;31(5):227-39.; 2. Raymond GV, et al. *JICNA* 2020

Neurologic and radiographic progression of CALD

Progression					
Clinical Status	**Asymptomatic**	**Initial symptoms[1]**	**Moderate disability[1]**	**Major functional disability[1,2]**	**Death**
Symptoms	N/A	• Poor school performance • Behavioral problems • May be misdiagnosed as ADHD	• Hearing • Aphasia/apraxia • Vision impairment • Dysphagia • Walking/running difficulties • Episodes of incontinence • Seizures	• Cortical blindness • Loss of communication • Tube feeding • Wheelchair dependence • No voluntary movement • Total incontinence	

ADHD=attention-deficit hyperactivity disorder; CALD,=cerebral adrenoleukodystrophy; MRI=magnetic resonance imaging; N/A=not applicable.

1. Engelen M, et al. *Orphanet J Rare Dis.* 2012;7:51-64. 2. Raymond GV, et al. *Biol Blood Marrow Transplant.* 2019;25(3):538-48. 3. Cartier N, et al. *Science.* 2009;326:818-23.

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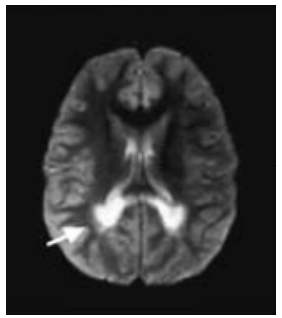
Symptoms	N/A	• Poor school performance • Behavioral problems • May be misdiagnosed as ADHD	• Hearing • Aphasia/apraxia • Vision impairment • Dysphagia • Walking/running difficulties • Episodes of incontinence • Seizures	• Cortical blindness • Loss of communication • Tube feeding • Wheelchair dependence • No voluntary movement • Total incontinence	

MRI

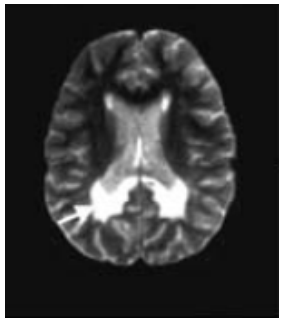
Lesions precede symptoms

Symptom severity does not always correlate with the extent of demyelination.

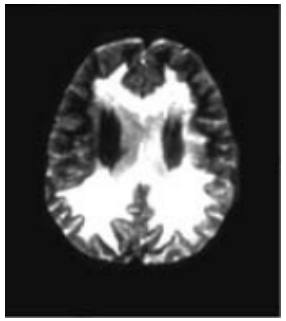
At diagnosis[3]



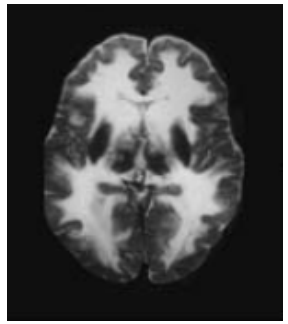
12 months after diagnosis[3]



18 months after diagnosis[3]



24 months after diagnosis[3]



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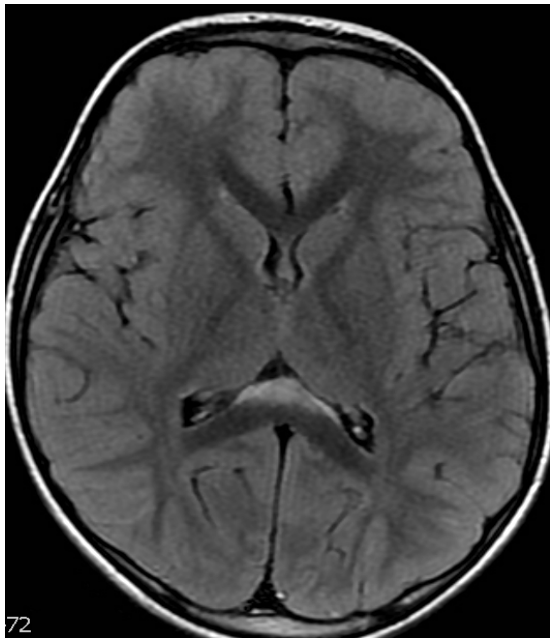
Measuring radiographic extent of CALD

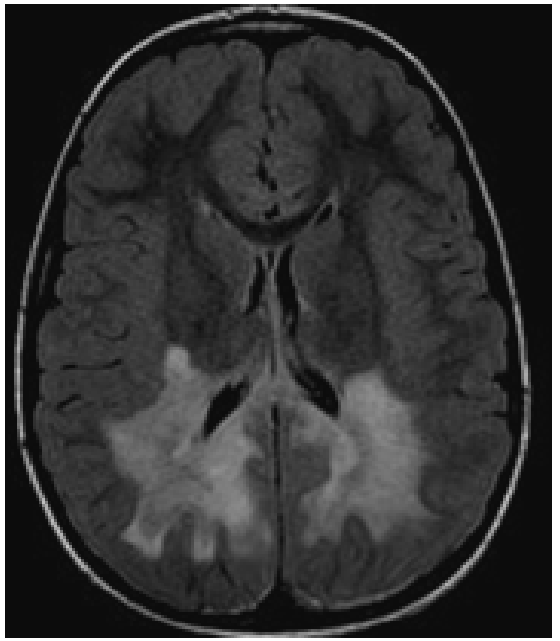
Loes Scoring[1,2]

Location/Feature	Score
Parieto-occipital white matter	**up to 4**
Anterior temporal white matter	**up to 4**
Frontal white matter	**up to 4**
Corpus callosum	**up to 5**
Visual pathway	**up to 4**
Auditory pathway	**up to 4**
Projection fibers	**up to 2**
Cerebellum	**up to 2**
Basal ganglia	**up to 1**
Atrophy	**up to 4**
Possible Total	**34**

Example of Loes Scoring[3]



Loes Score = 1



Loes Score = 15

CALD=cerebral adrenoleukodystrophy; MRI=magnetic resonance imaging.
1. Loes DJ, et al. *AJNR.* 1994;15:1761-6. 2. Loes DJ, et al. *Neurology.* 2003;61:369-74. 3. Images courtesy of Dr. Florian Eichler

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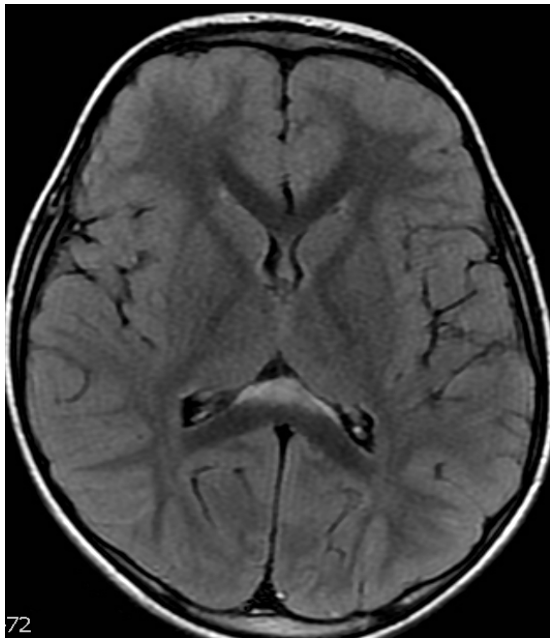
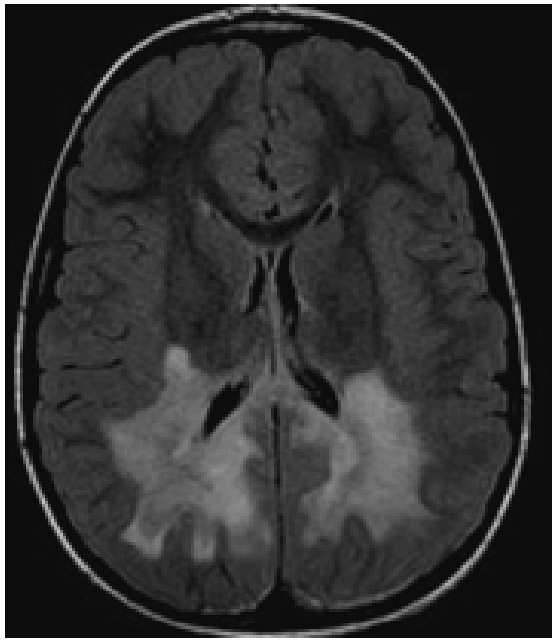


Loes Score = 1



Loes Score = 15

<u>Early</u> CALD is defined as Loes scores from 0.5 to 9 and NFS of 0 or 1.

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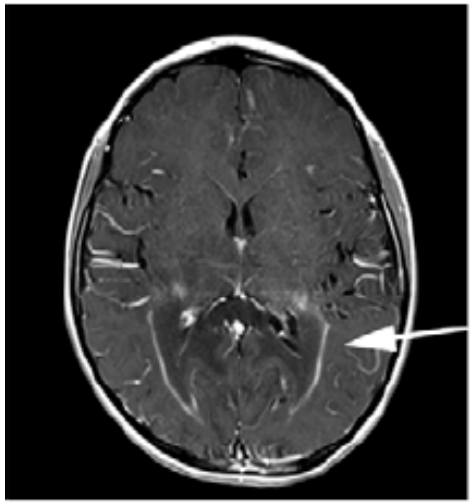
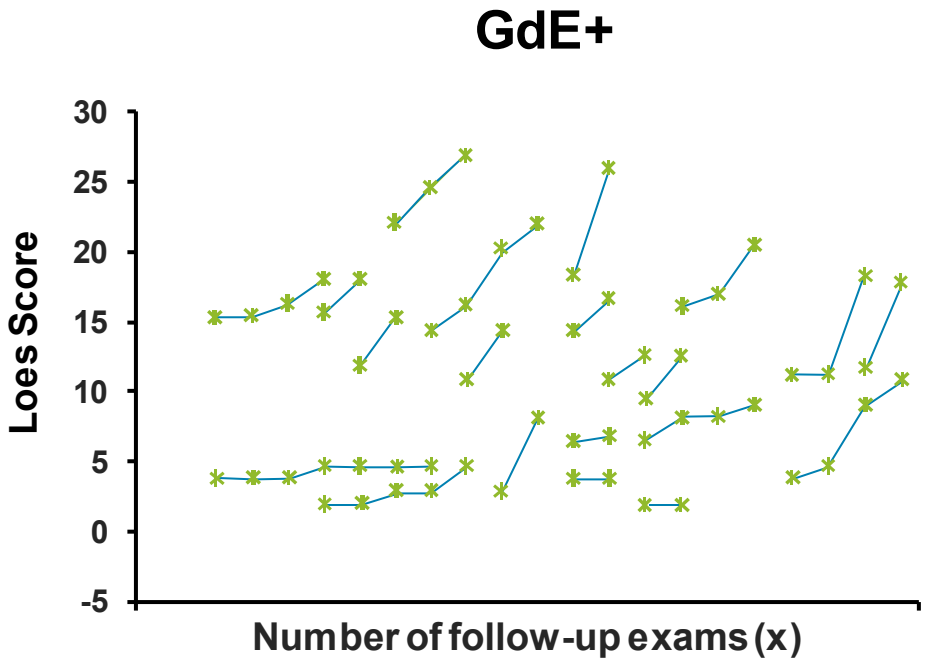
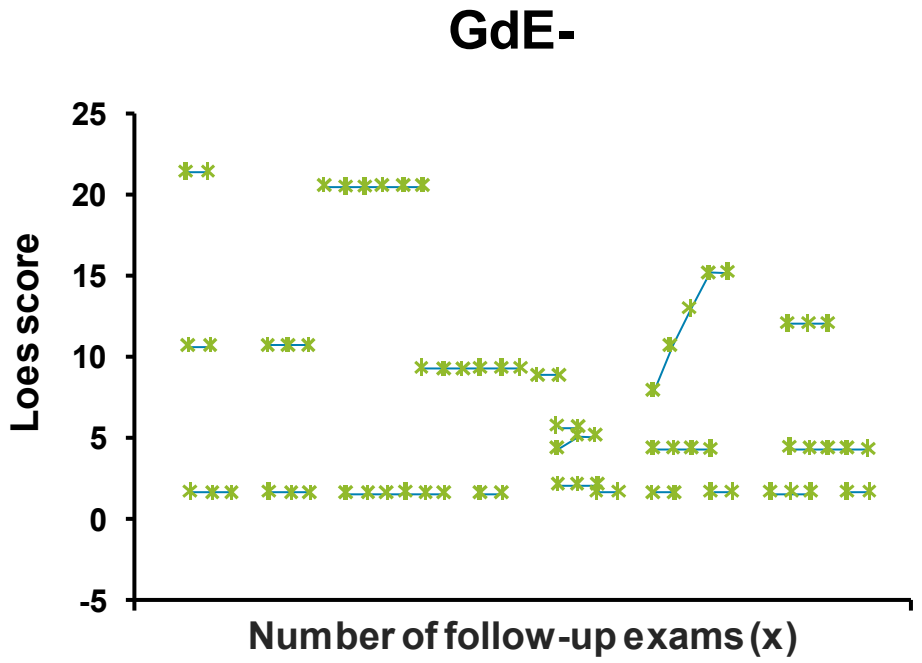
1. Loes DJ, et al. *AJNR.* 1994;15:1761-6. 2. Loes DJ, et al. *Neurology.* 2003;61:369-74. 3. Images courtesy of Dr. Florian Eichler

Gadolinium enhancement (GdE+) predicts rapid progression[1,2,3]







CALD=cerebral adrenoleukodystrophy; GdE+ or –, positive or negative for gadolinium enhancement.

1. Orchard PJ, et al. Blood. 2019. 2. Melhem ER, et al. AJNR. 2000. 3. Raymond GV, et al. BBMT. 2019.

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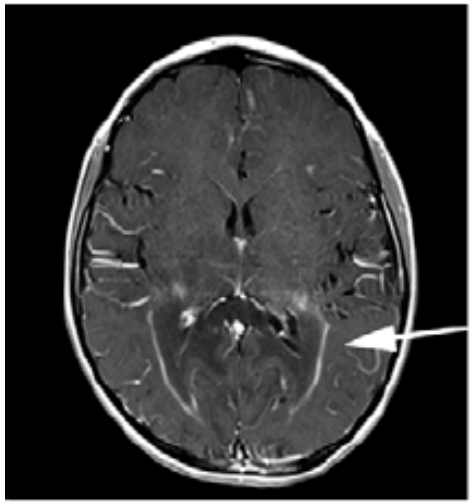
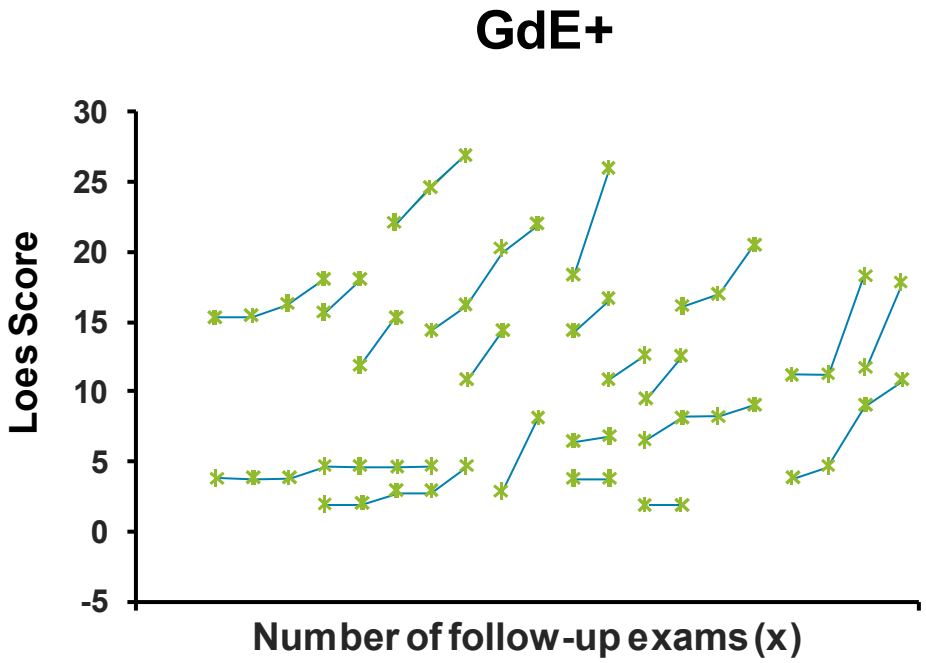
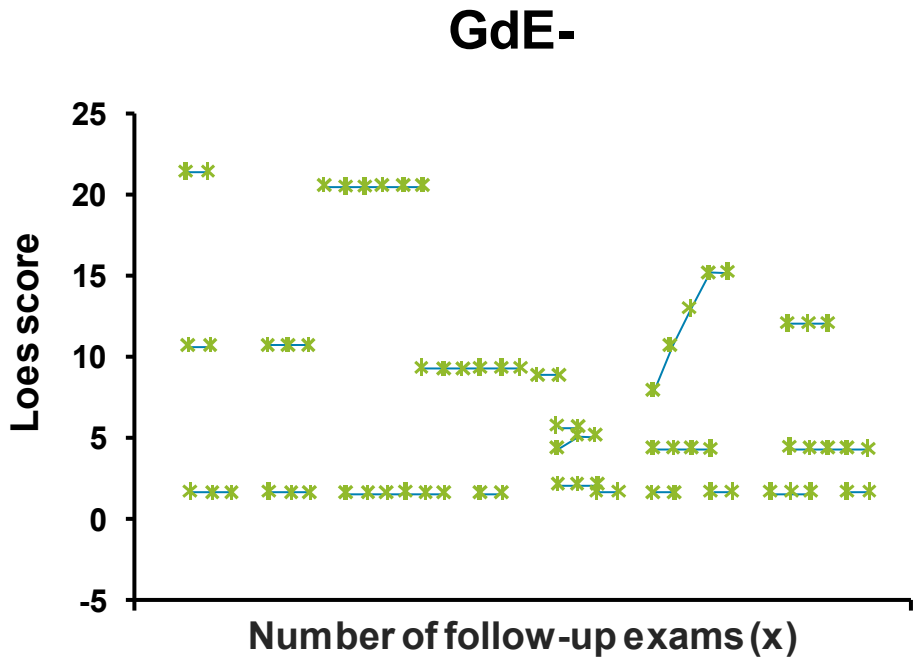




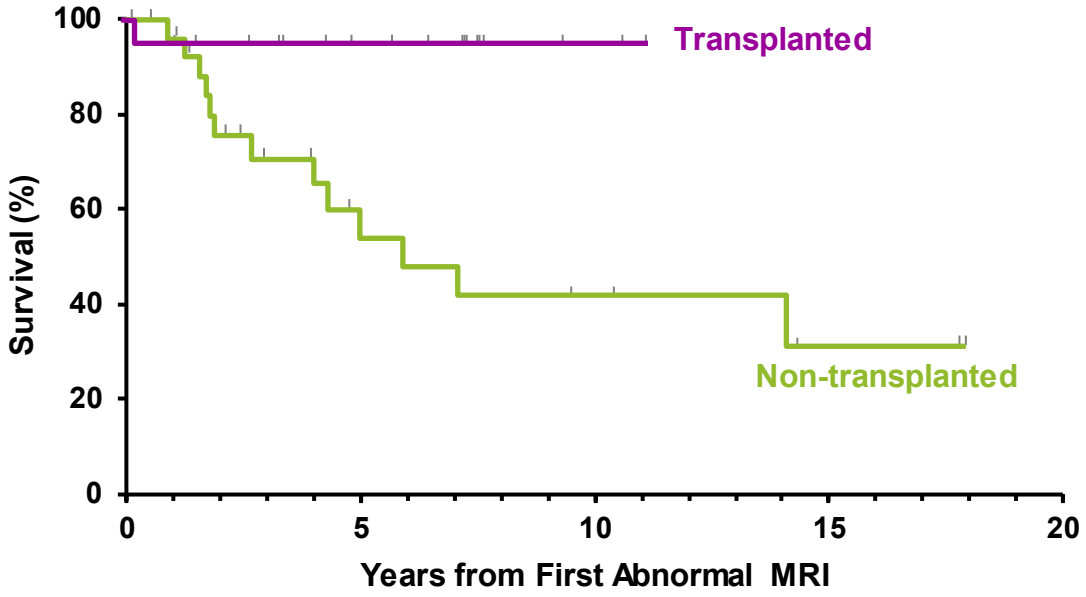


GdE+ indicates <u>active</u> CALD and impacts treatment decisions [4,5]

CALD=cerebral adrenoleukodystrophy; GdE+ or –, positive or negative for gadolinium enhancement. 1. Orchard PJ, et al. *Blood*. 2019. 2. Melhem ER, et al. *AJNR*. 2000. 3. Raymond GV, et al. *BBMT*. 2019. 4. Engelen M, et al. *OJRD*. 2012. 5. Engelen M, et al.: International recommendations for the diagnosis and management of patients with adrenoleukodystrophy (submitted)

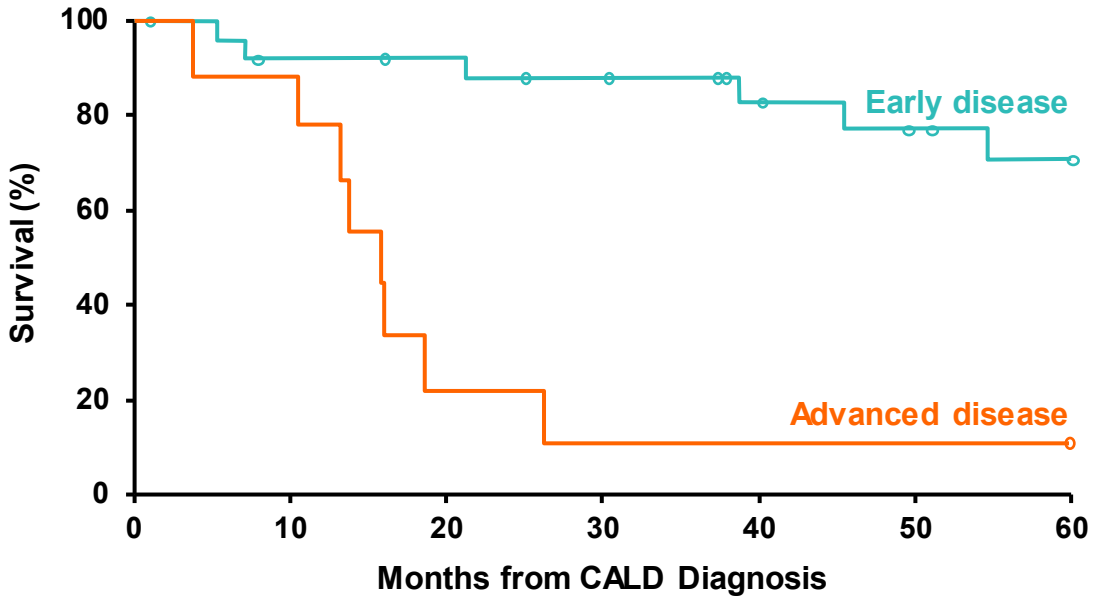
Allogeneic stem cell transplantation (allo-HSCT) improves survival and functional outcomes in early active CALD

Transplanted vs. Non-transplanted (Overall Survival) [1,2]



N=					
Transplanted	19	10	2	..	..
Non-transplanted	30	10	5	3	..

Transplanted in Early vs. Advanced CALD (MFD-free Survival) [3]



N=							
Early disease	27	23	22	20	16	13	11
Advanced disease	9	8	2	1	1	1	1

CALD= cerebral adrenoleukodystrophy; MRI=magnetic resonance imaging; Early CALD defined as Loes scores of 0.5–9.0 and neurologic function score (NFS) of 0–1;

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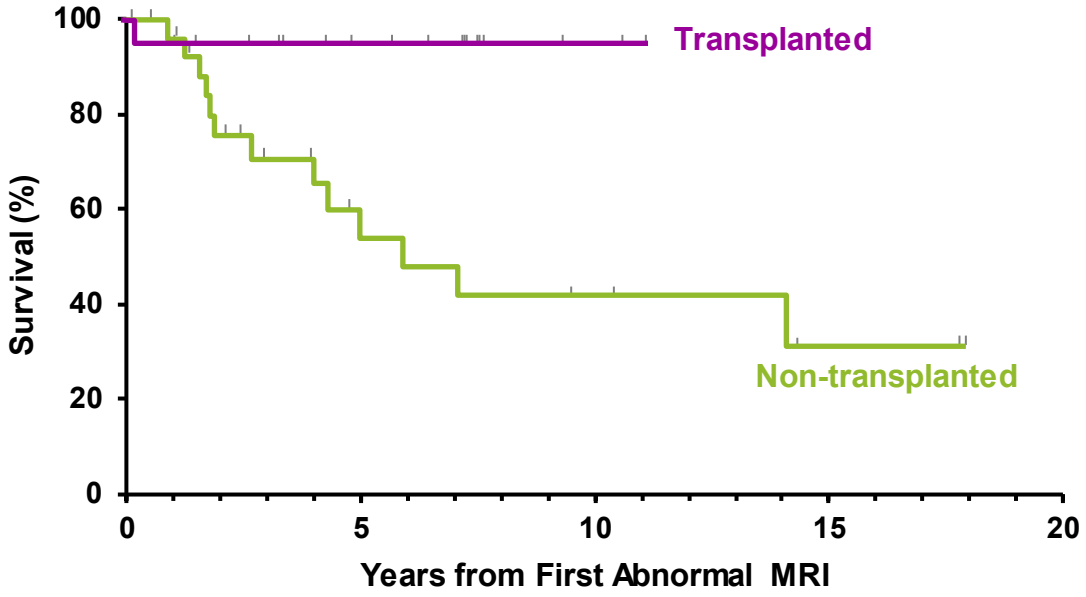

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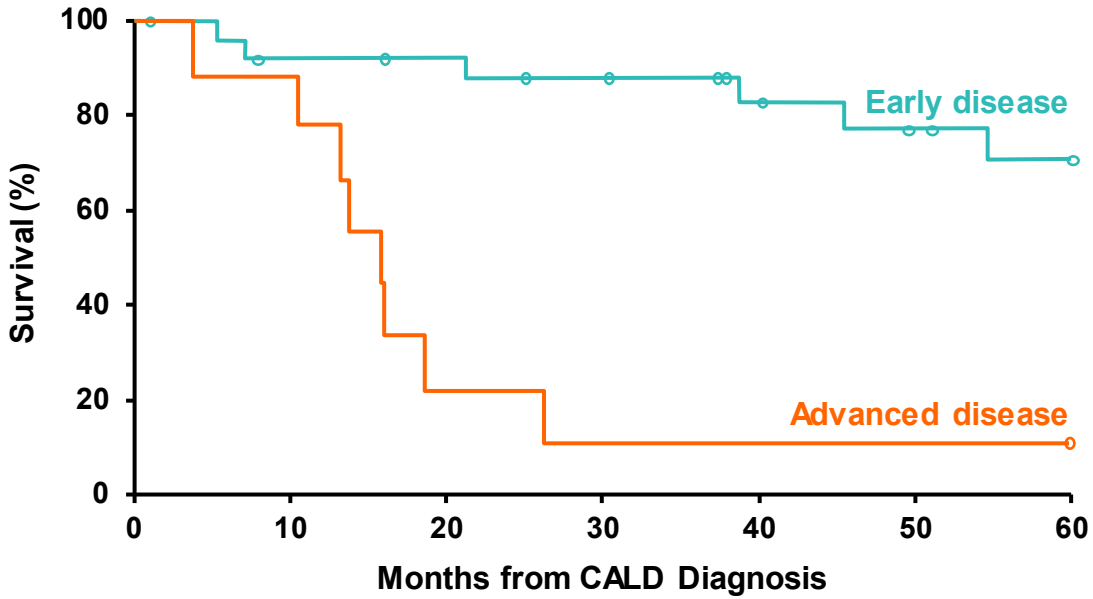

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The goal of treatment is to halt disease – treatment does not reverse previous deficits.

CALD, cerebral adrenoleukodystrophy; MRI, magnetic resonance imaging; Early CALD defined as Loes scores of 0.5–9.0 and neurologic function score (NFS) of 0–1;

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Allo-HSCT has substantial risks, particularly with HLA-mismatched donors

- **Transplant related mortality**
- **Graft failure**
- **Graft versus host disease (GVHD)**

1. CIBMTR center volume dataset (2013-2017)

Allo-HSCT has substantial risks, particularly with HLA-mismatched donors

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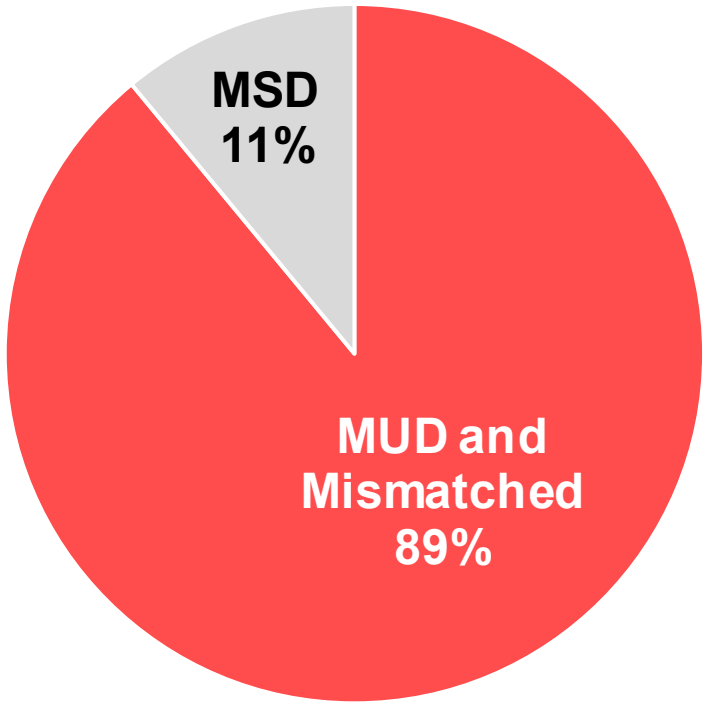
- **Graft failure**
- **Graft versus host disease (GVHD)**

~90% of patients without access to matched sibling donor[1]



MSD=matched sibling donor; MUD=matched unrelated donor; Mismatched=HLA-mismatched donor; 1. CIBMTR center volume dataset (2013-2017)

Conclusion

- **CALD is characterized by inflammatory demyelination leading to progressive loss of neurologic function and death**

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Conclusion

- **CALD is characterized by inflammatory demyelination leading to progressive loss of neurologic function and death**
- **Allo-HSCT can stabilize disease progression if performed at the early stage of cerebral involvement**
- **Patients without MSD, have substantial risks associated with allo-HSCT, particularly for those with only HLA-mismatched donor**
- **Ex-vivo gene therapy using autologous cells is therefore particularly appropriate for these patients and provides benefit and new options**

Clinical Program and Efficacy

Jakob Sieker, MD

Senior Medical Director

Clinical Research and Development

bluebird bio, Inc.

Five trials support the eli-cel application

CALD=cerebral adrenoleukodystrophy; allo-HSCT=allogeneic hematopoietic stem cell transplantation
Early CALD defined as Loes scores of 0.5–9.0 and neurologic function score (NFS) of 0–1; active defined as Gadolinium enhancement positive (GdE+)

Five trials support the eli-cel application

ALD-101 Completed

- Early and advanced CALD
- N=72 untreated
- N=65 allo-HSCT in 1997-2010

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- N=32 eli-cel

ALD-104 Ongoing

- Active early CALD, <18 years of age
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- N=35 eli-cel

ALD-103 Completed
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LTF-304 Ongoing
- Long-term follow up (15y)
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Efficacy data presented

eli-cel compared to no treatment	• versus pre-specified benchmark (primary efficacy analysis) • versus untreated population with early active disease (rUTES-101)

rUTES-101=ALD-101 re-coded untreated population strictly eligible for ALD-102; allo-HSCT=allogeneic hematopoietic stem cell transplantation; TPES=transplant population strictly eligible for ALD-102; NMSD=no matched sibling donor; PrvIQ=composite of performance/reasoning/visual IQ from age-appropriate Wechsler tests

Efficacy data presented

eli-cel compared to no treatment	• versus pre-specified benchmark (primary efficacy analysis) • versus untreated population with early active disease (rUTES-101)
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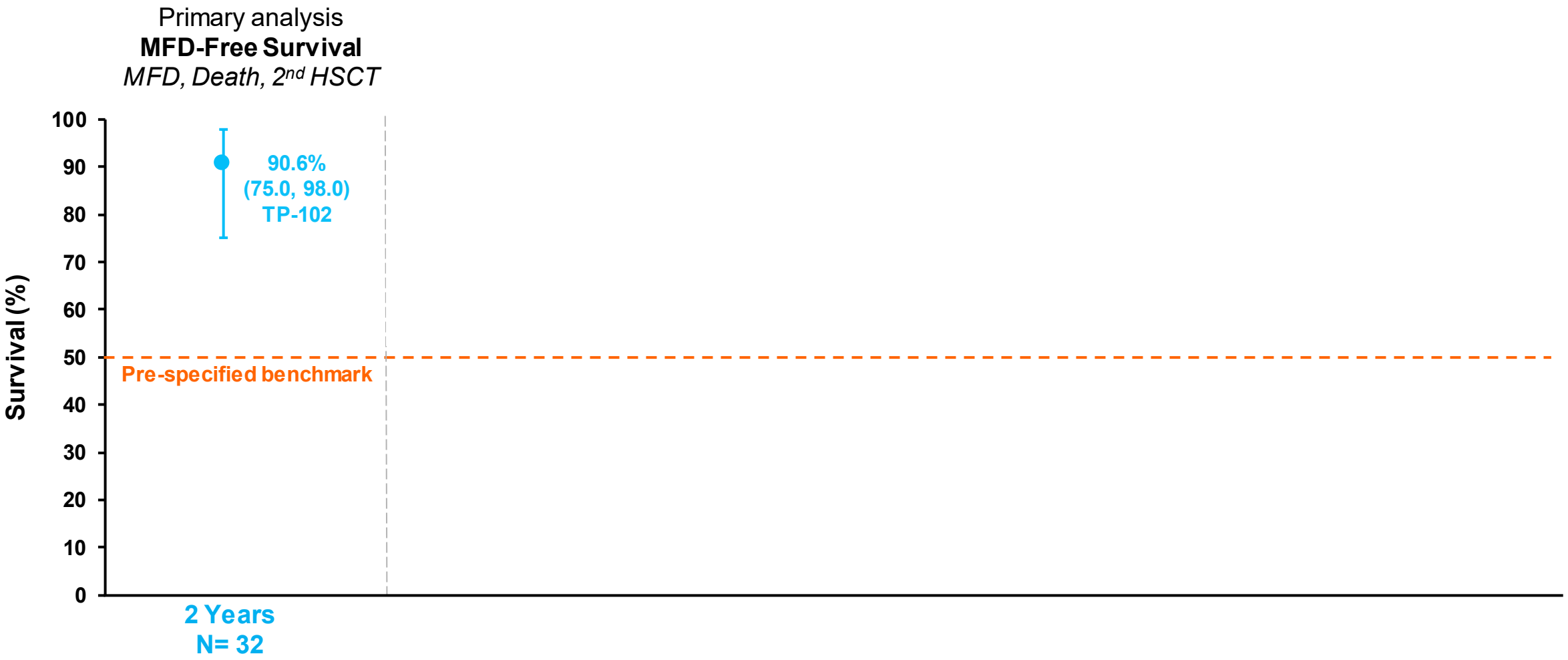
ALD-102 met success criterion for primary efficacy endpoint



Jan2022 data; MFD=major functional disability; HSCT= hematopoietic stem cell transplantation; MDS=myelodysplastic syndrome

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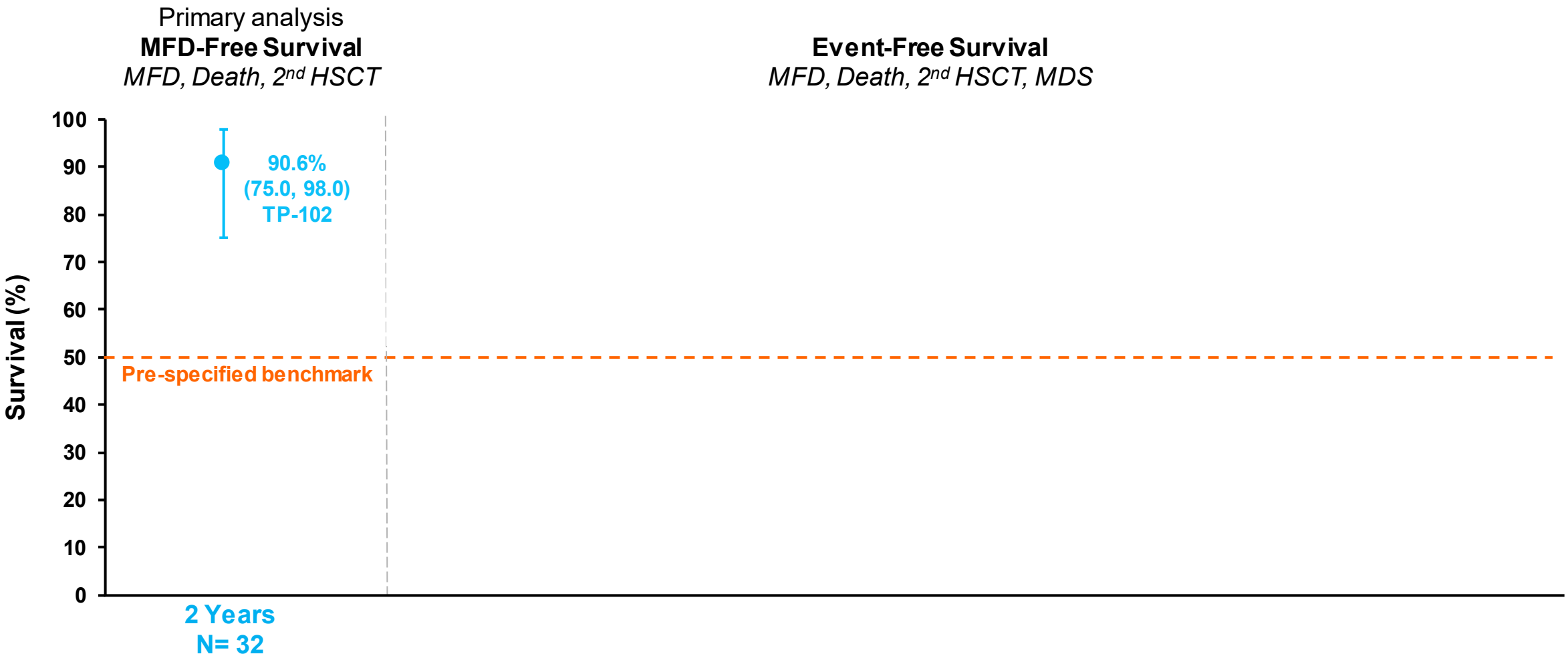

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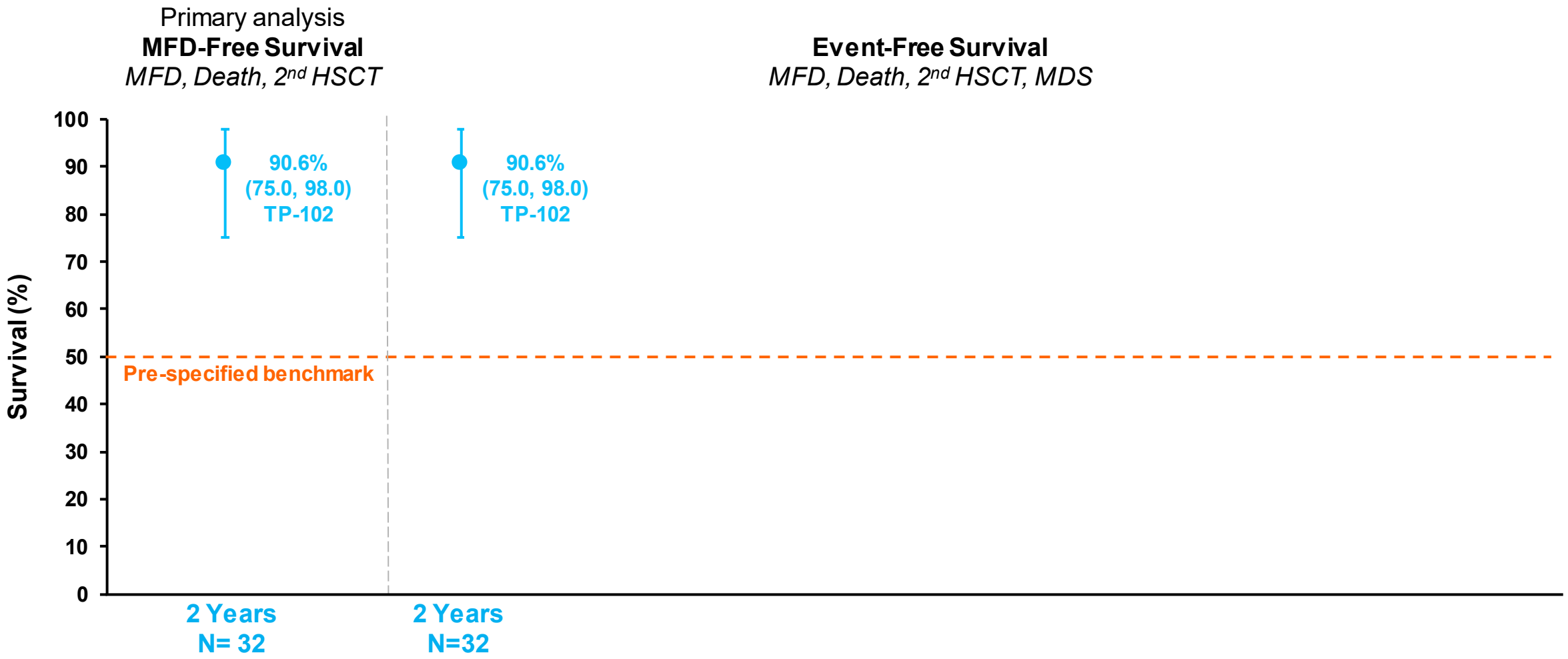

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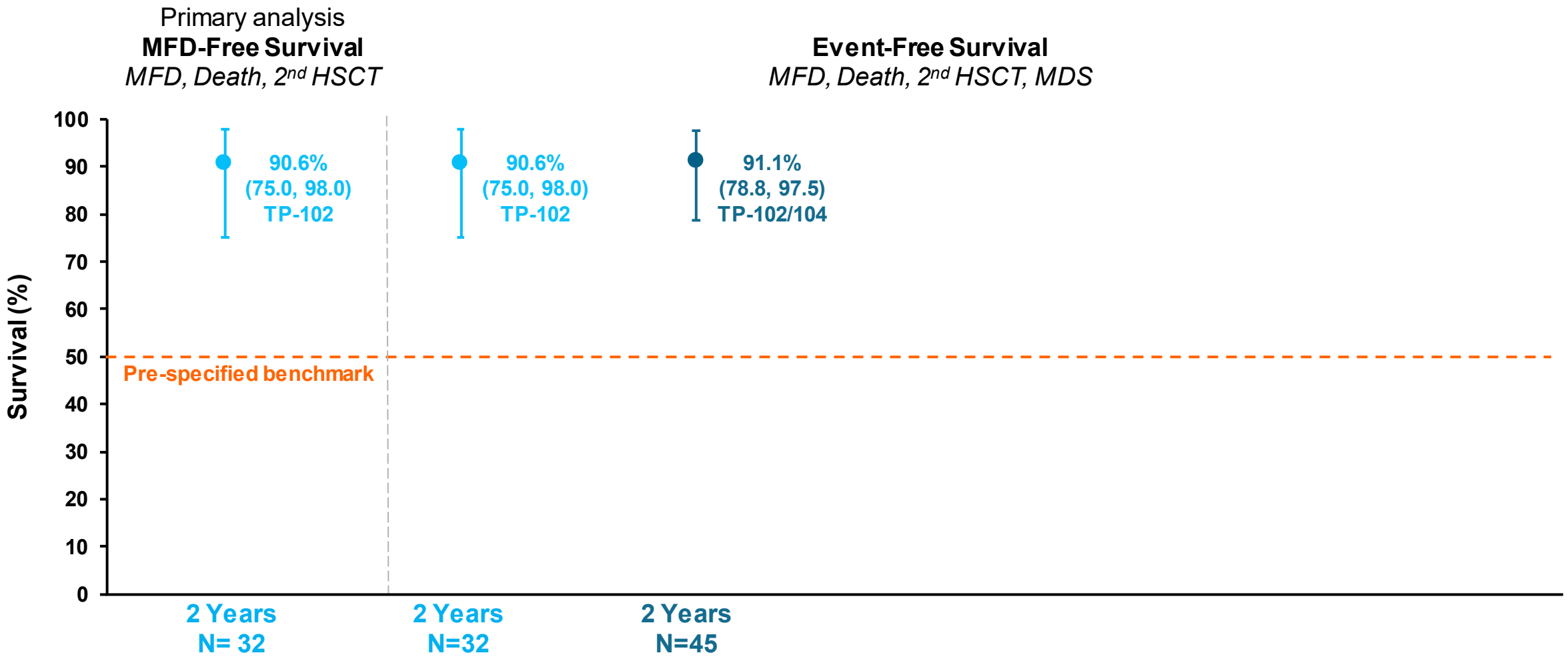

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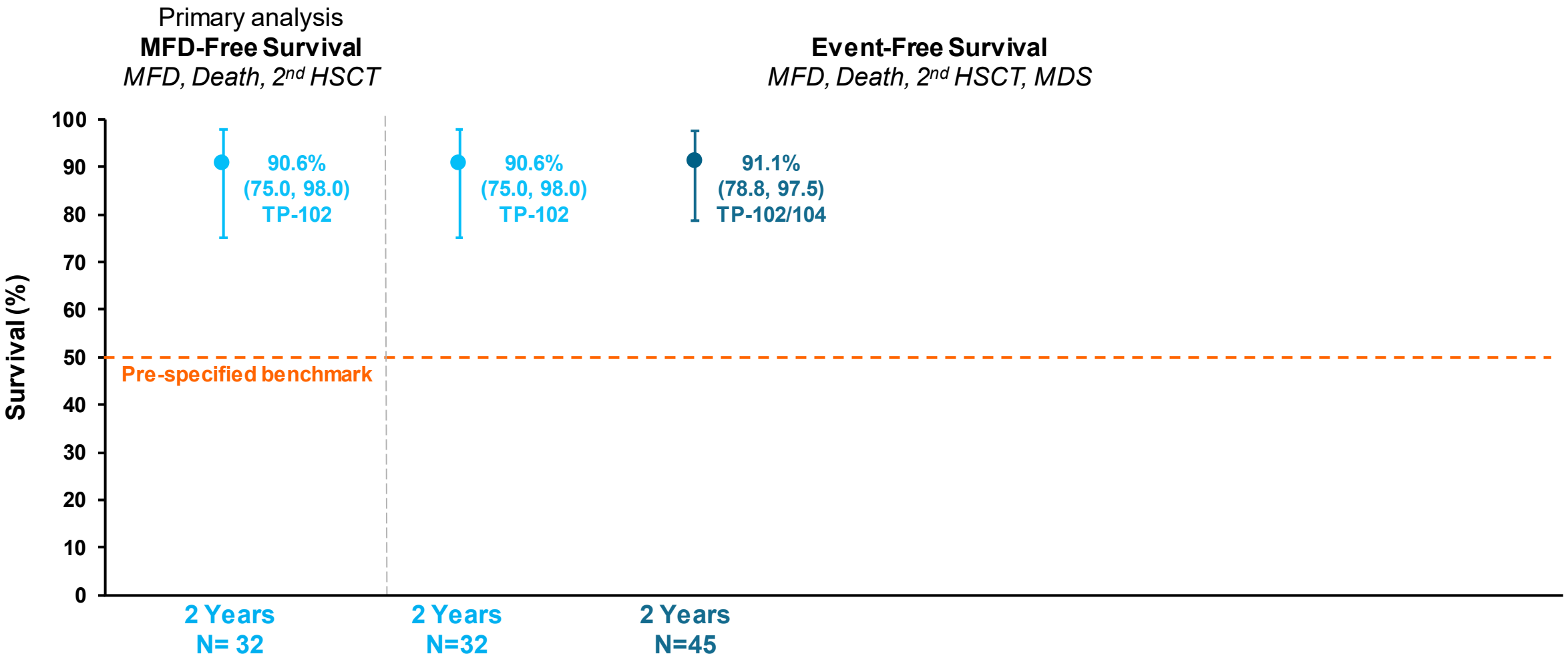
Event-free survival: eli-cel continued to exceed benchmark beyond two years



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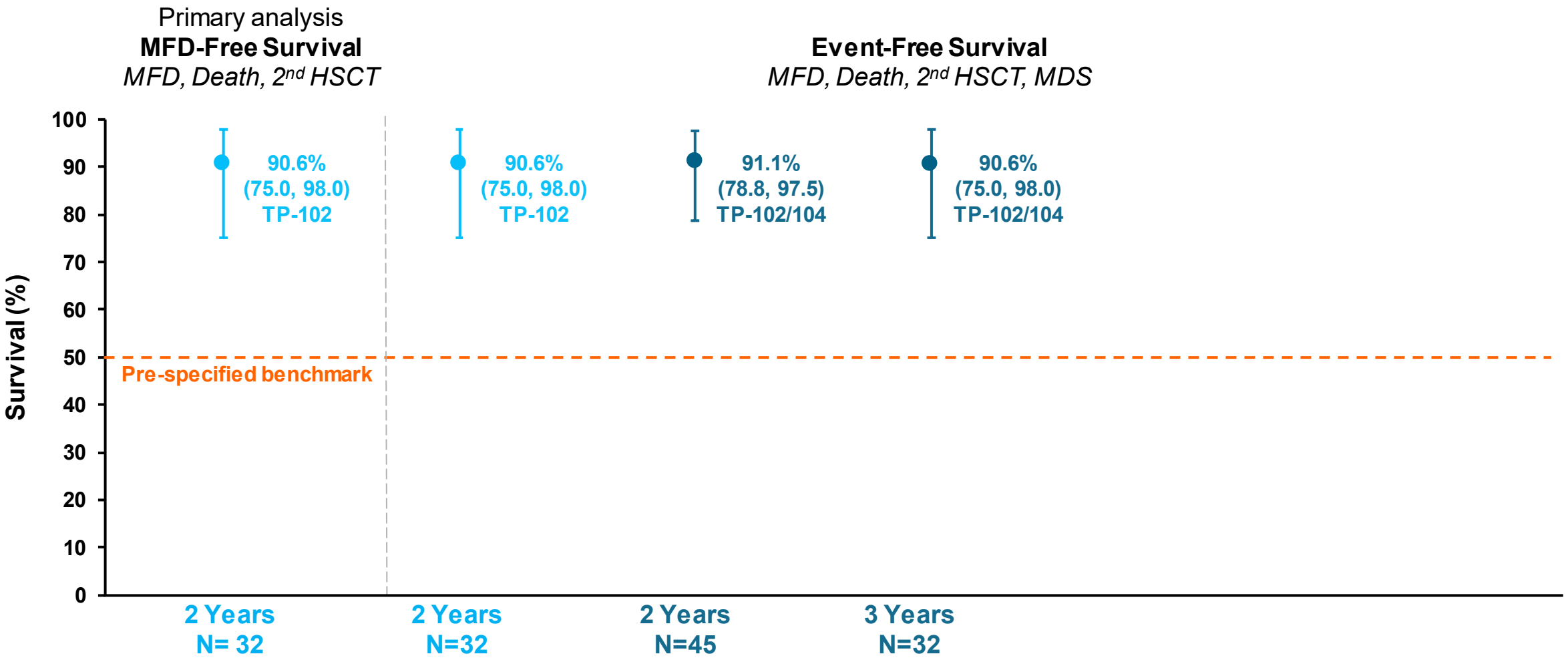

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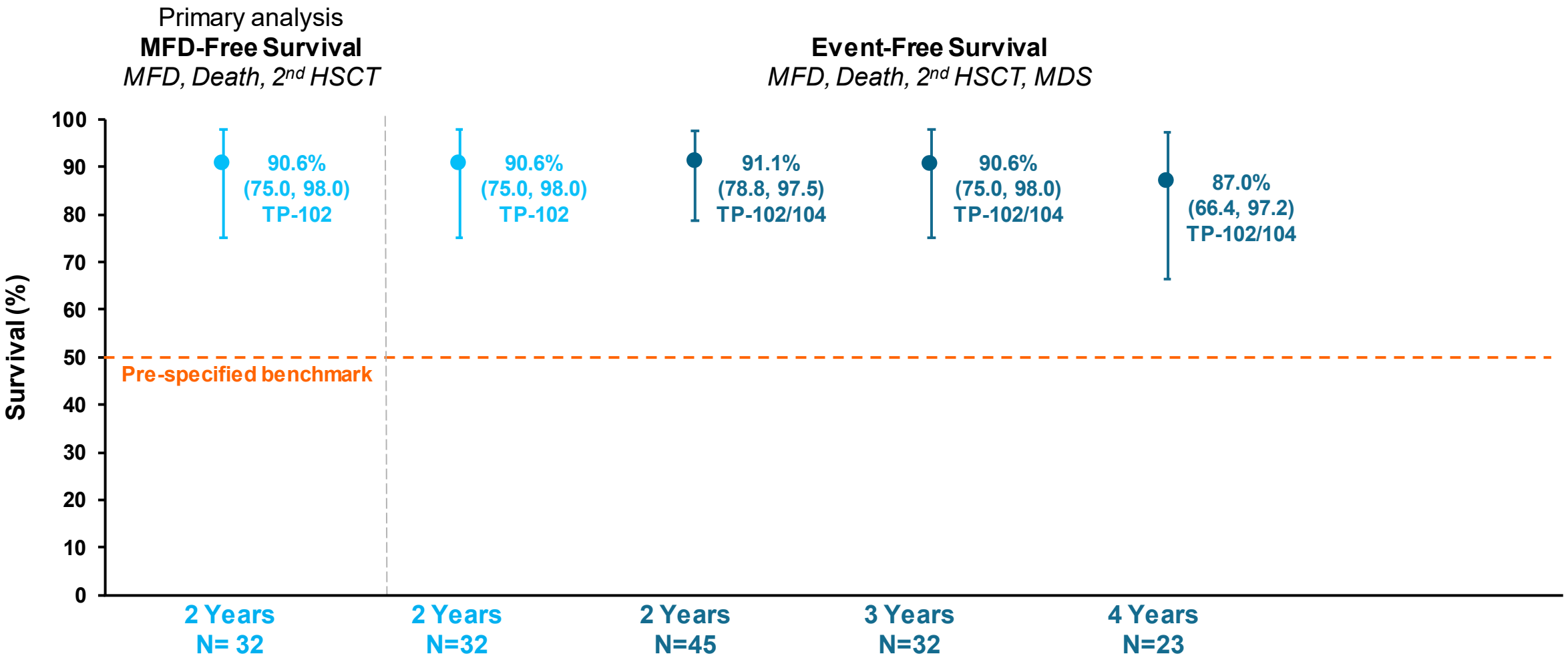

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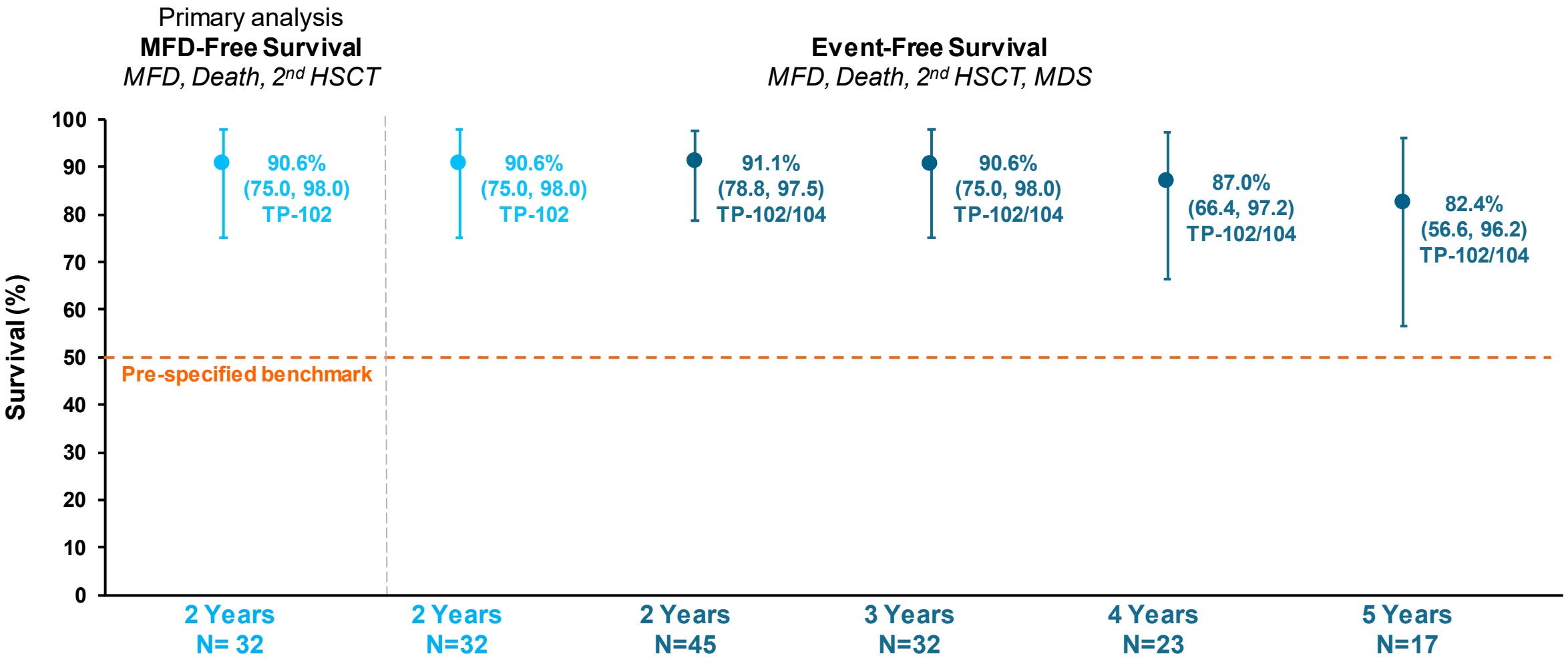
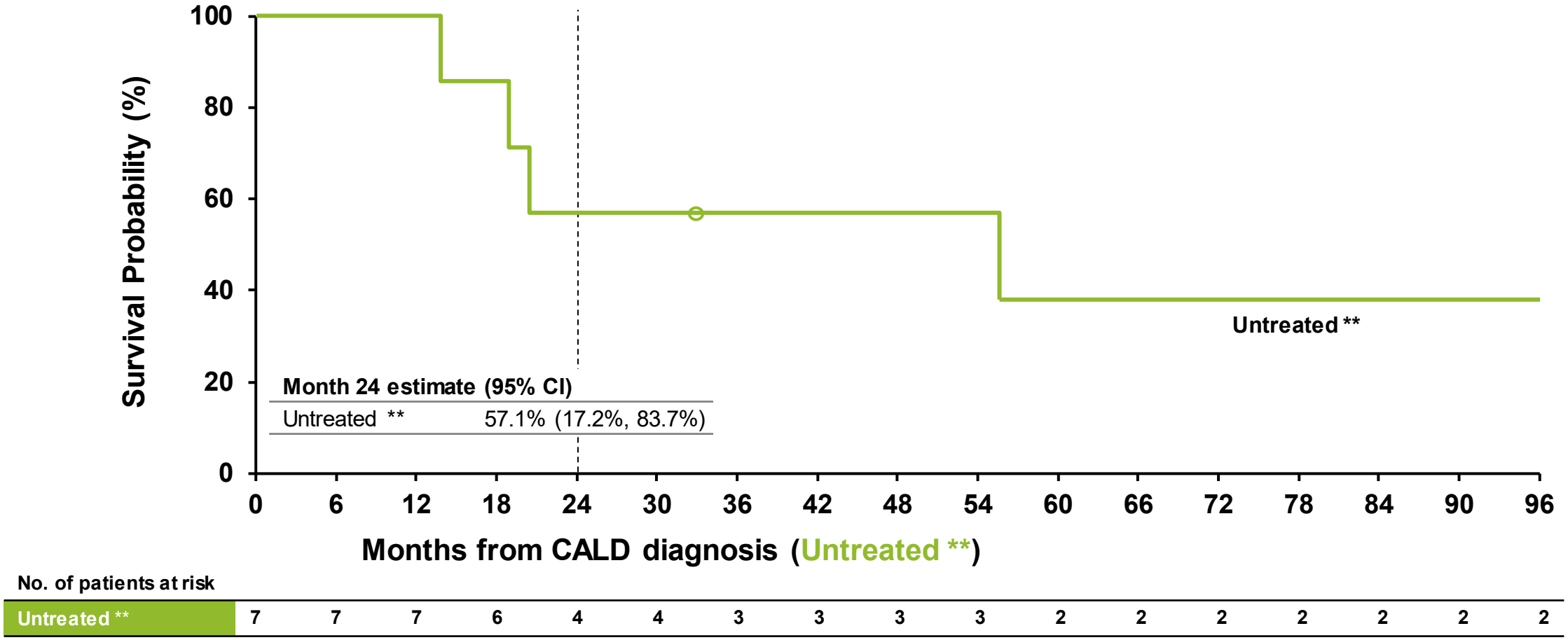


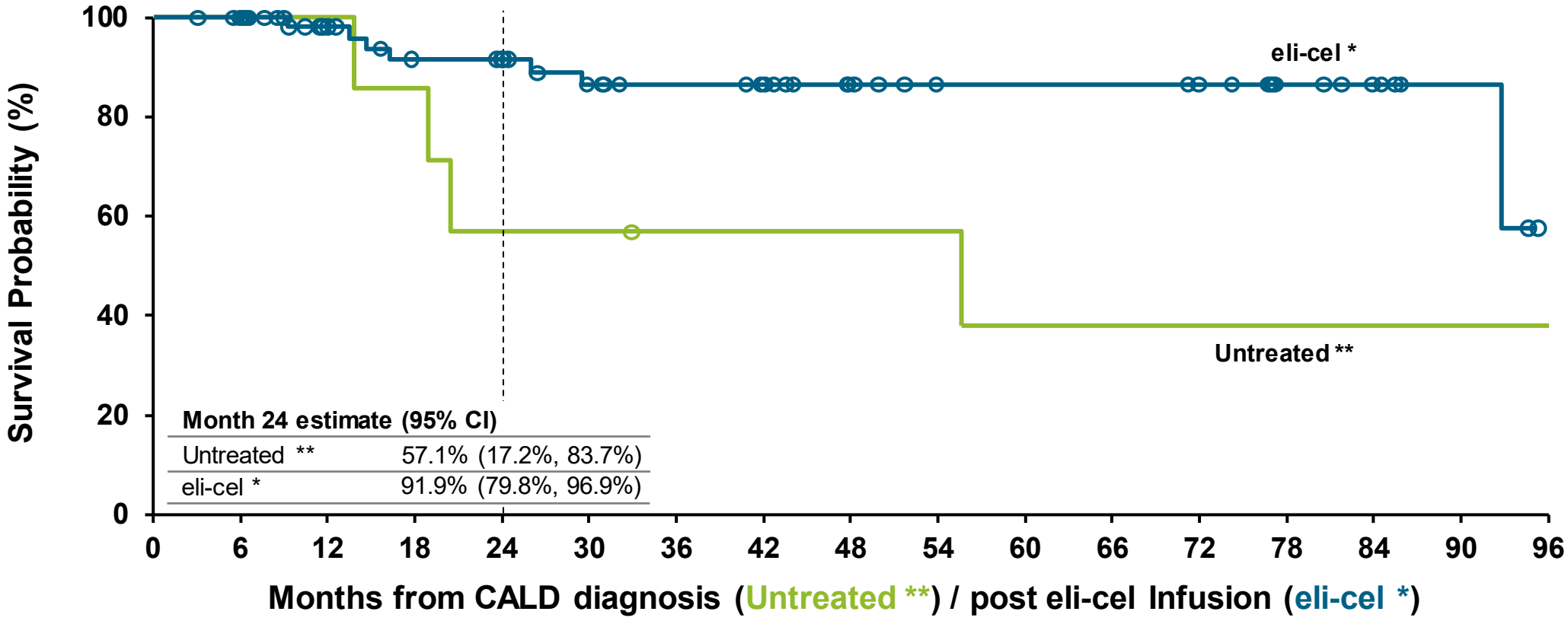
Jan2022 data; MFD=major functional disability; HSCT= hematopoietic stem cell transplantation; MDS=myelodysplastic syndrome

Event-free survival: untreated patients with early active disease developed MFD within two years



* TP-102/104; ** rUTES-101=recoded; MFD=major functional disability, MDS=myelodysplastic syndrome, HSCT=hematopoietic stem cell transplantation
Jan2022 data; Event definition: Death, MFD, MDS, second HSCT; Note: data for the untreated population beyond 8 years are not shown

Event-free survival: eli-cel compared favorably to no treatment



No. of patients at risk

Untreated **	7	7	7	6	4	4	3	3	3	3	2	2	2	2	2	2	2
eli-cel *	67	65	50	42	38	32	28	25	19	14	14	14	12	8	6	3	0

* TP-102/104; ** rUTES-101=recoded; MFD=major functional disability, MDS=myelodysplastic syndrome, HSCT=hematopoietic stem cell transplantation
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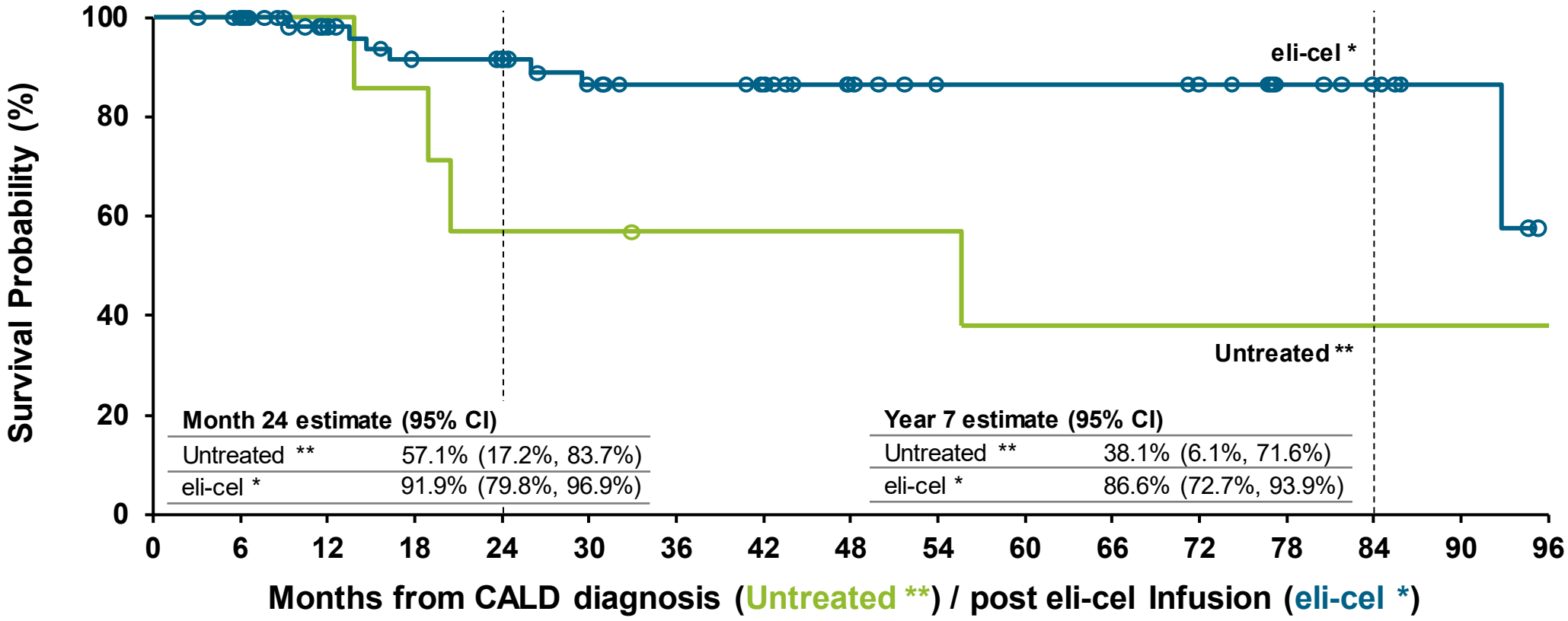

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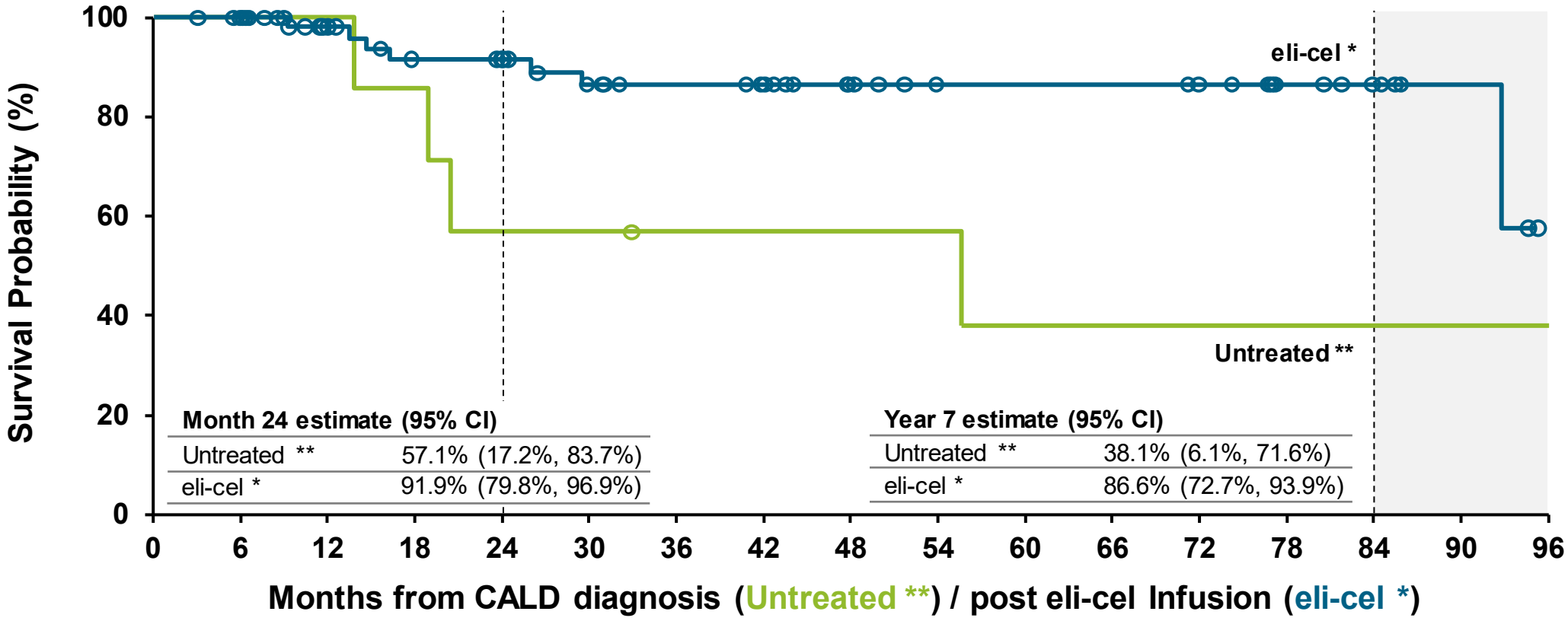

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Baseline characteristics of eli-cel and allo-HSCT efficacy populations were comparable

	eli-cel TP-102/104 N=67	allo-HSCT TPES-103 NMSD N=17
Age at CALD diagnostic, (year)		
Median	6	7
Min., Max.	1, 13	0, 11
Age at HSC infusion, (year)		
Median	6	8
Min., Max.	4, 14	5, 11
Baseline neurologic function score (NFS), n (%)		
0	64 (95.5)	16 (94.1)
1	3 (4.5)	1 (5.9)
Baseline Loes score		
Median	2	2
Min., Max.	1, 9	1, 9
Baseline GdE Status, n (%)		
GdE+	66 (98.5)	17 (100.0)
GdE-	1 (1.5)*	0

Early CALD defined as Loes scores of 0.5 – 9.0 and neurologic function score (NFS) of 0 – 1; active defined as Gadolinium enhancement positive (GdE+)
*One patient enrolled into ALD-104 with a GdE+ screening MRI, a subsequent MRI prior to conditioning was GdE- and is considered baseline

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Baseline GdE Status, n (%)		
GdE+	66 (98.5)	17 (100.0)
GdE-	1 (1.5)*	0

Early CALD defined as Loes scores of 0.5 – 9.0 and neurologic function score (NFS) of 0 – 1; active defined as Gadolinium enhancement positive (GdE+)
*One patient enrolled into ALD-104 with a GdE+ screening MRI, a subsequent MRI prior to conditioning was GdE- and is considered baseline

Baseline characteristics of eli-cel and allo-HSCT efficacy populations were comparable

	eli-cel TP-102/104 N=67	allo-HSCT TPES-103 NMSD N=17
Age at CALD diagnostic, (year)		
Median	6	7
Min., Max.	1, 13	0, 11
Age at HSC infusion, (year)		
Median	6	8
Min., Max.	4, 14	5, 11
Baseline neurologic function score (NFS), n (%)		
0	64 (95.5)	16 (94.1)
1	3 (4.5)	1 (5.9)
Baseline Loes score		
Median	2	2
Min., Max.	1, 9	1, 9
Baseline GdE Status, n (%)		
GdE+	66 (98.5)	17 (100.0)
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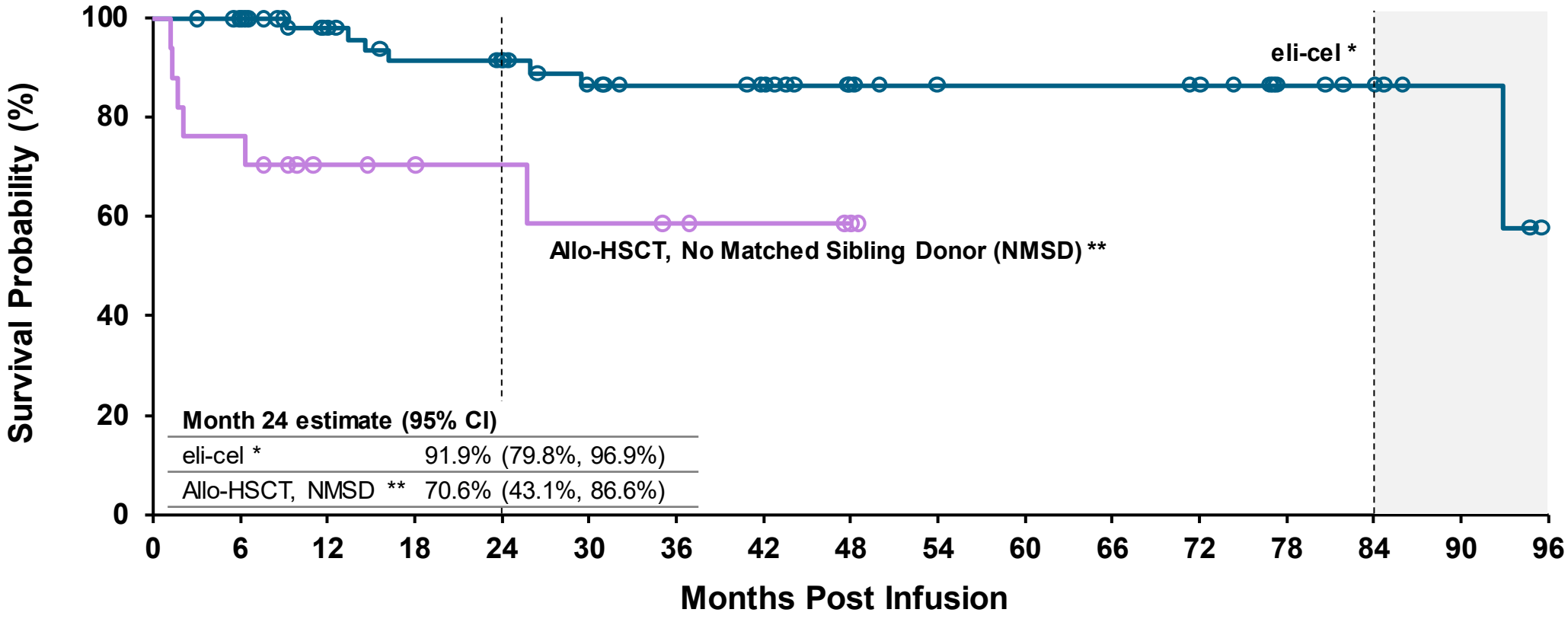
Event-free survival: eli-cel compared favorably with allo-HSCT without MSD (NMSD)

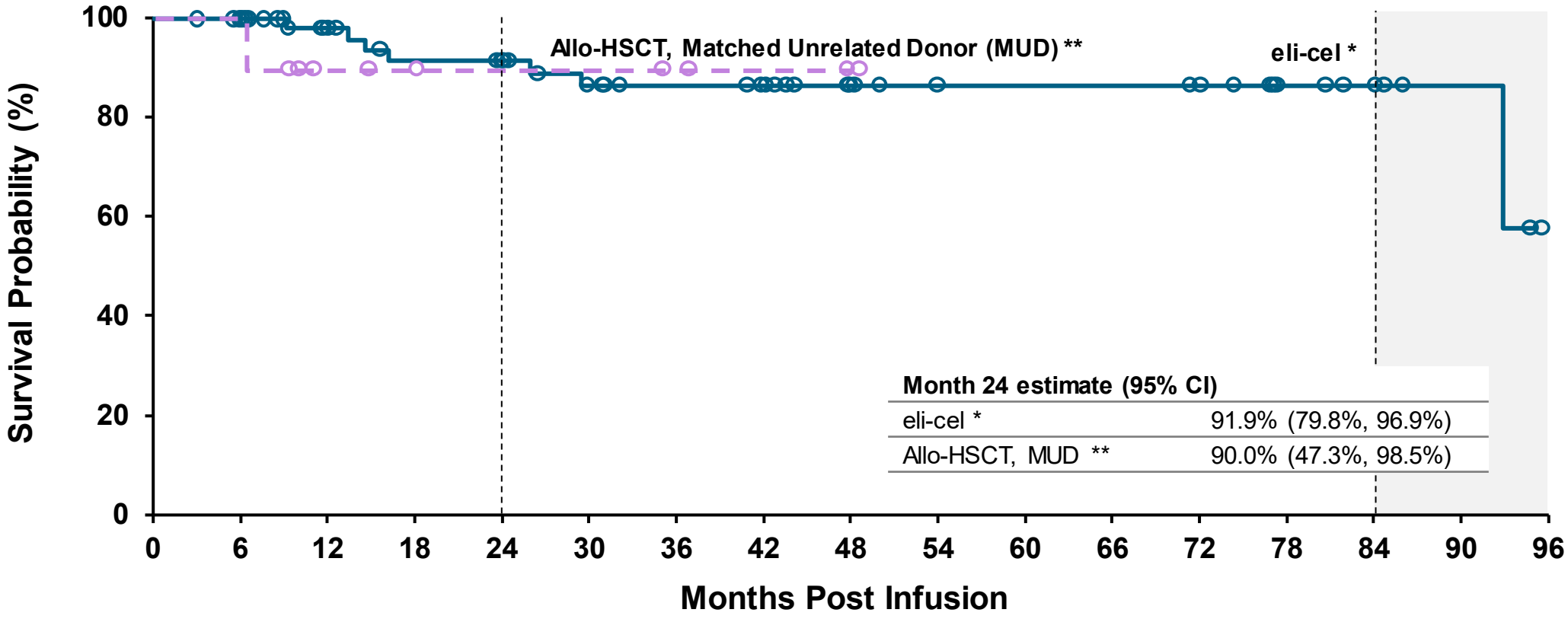


No. of patients at risk

eli-cel *	67	63	48	42	38	32	28	24	18	14	14	14	12	8	5	3	0
Allo-HSCT, NMSD **	17	13	8	7	6	5	4	3	2	0							

NMSD=No Matched sibling donor; MFD=major functional disability; MDS=myelodysplastic syndrome; allo-HSCT=allogeneic hematopoietic stem cell transplant
Jan2022 data; Event definition: Death, MFD, MDS, second HSCT; * TP-102/104; ** TPES-103-NMSD

Event-free survival: eli-cel compared favorably with allo-HSCT without MSD, particularly when using an HLA-mismatched donor



No. of patients at risk

eli-cel *	67	63	48	42	38	32	28	24	18	14	14	14	12	8	5	3	0
Allo-HSCT, MUD **	10	10	6	5	4	4	3	2	1	0							

NMSD=No Matched sibling donor; MFD=major functional disability; MDS=myelodysplastic syndrome; allo-HSCT=allogeneic hematopoietic stem cell transplant
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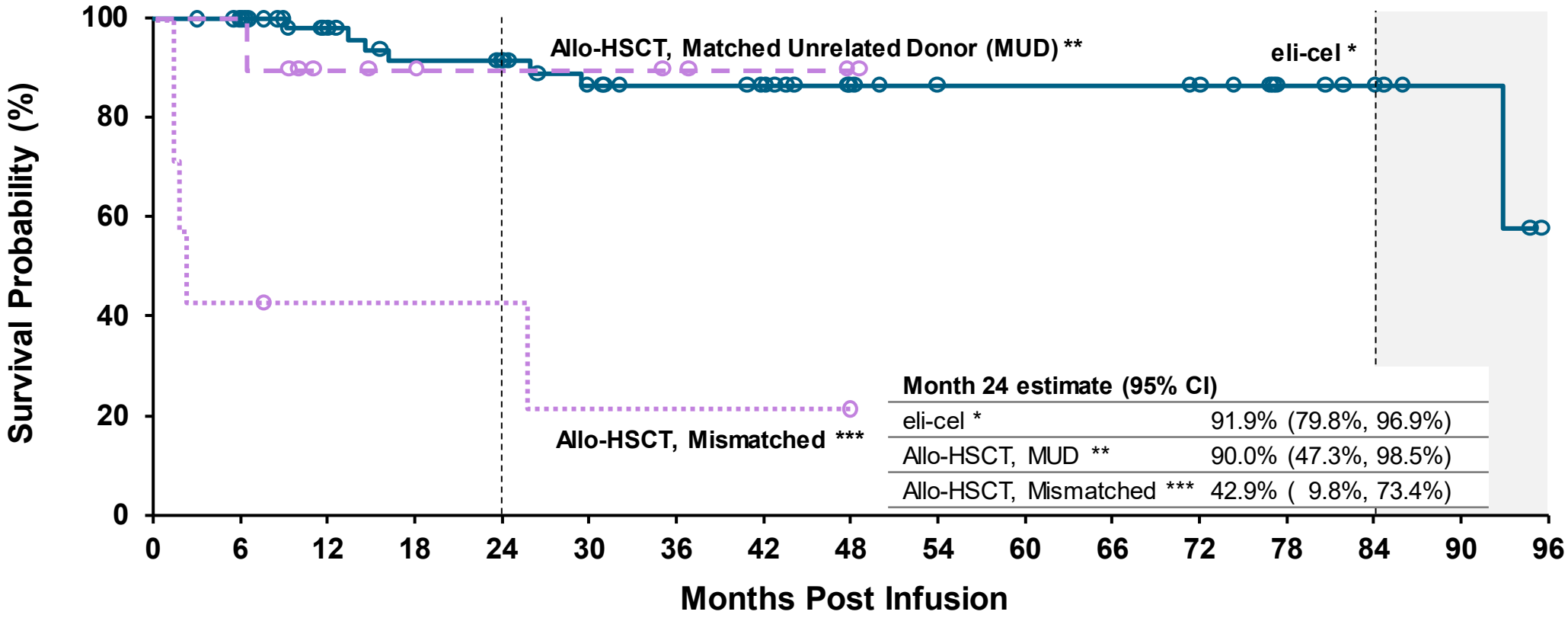

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Allo-HSCT, MUD **	10	10	6	5	4	4	3	2	1	0							
Allo-HSCT, Mismatched	7	3	2	2	2	1	1	1	1	0							

MUD=Matched Unrelated donor; MFD=major functional disability; MDS=myelodysplastic syndrome; allo-HSCT=allogeneic hematopoietic stem cell transplant
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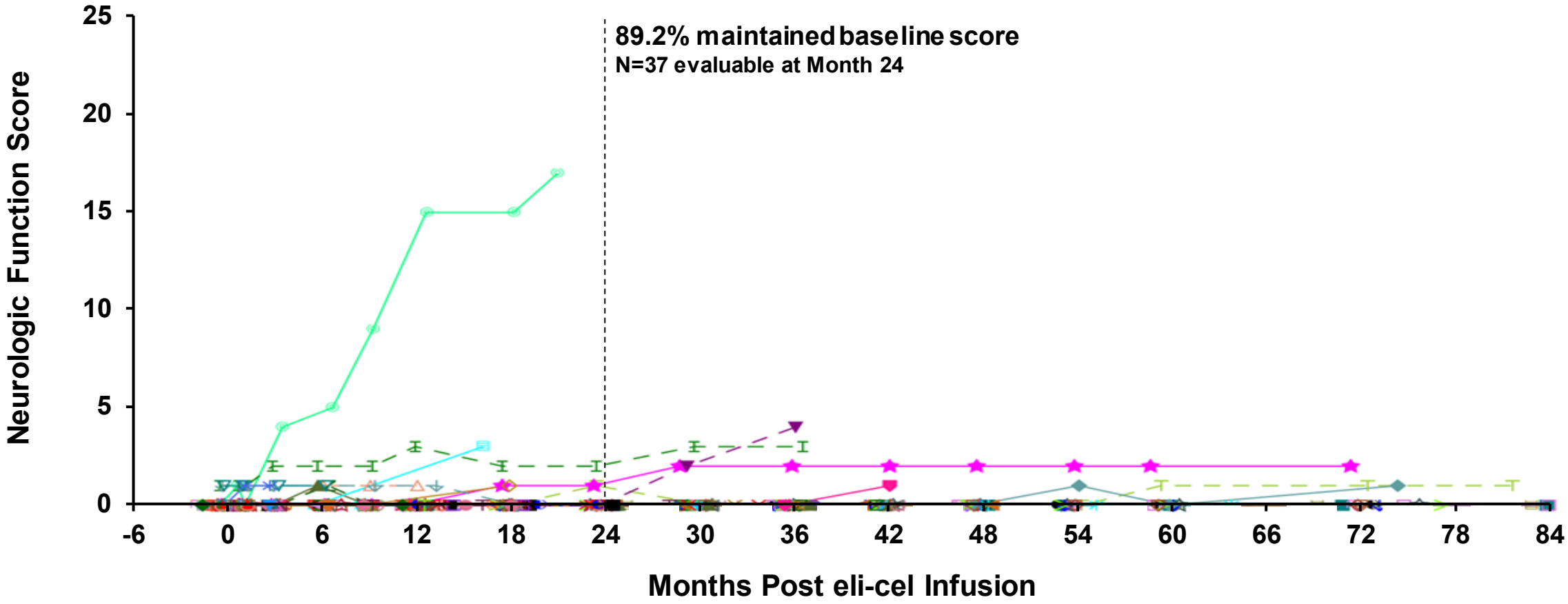
Efficacy data presented

eli-cel compared to no treatment	• versus pre-specified benchmark (primary efficacy analysis) • versus untreated population with early active disease (rUTES-101)
eli-cel compared to allo-HSCT	• versus contemporaneous external control study (TPES-103-NMSD)
durability of eli-cel efficacy	• NFS and Performance IQ (PrvIQ) in eli-cel treated patients

rUTES-101=ALD-101 re-coded untreated population strictly eligible for ALD-102; allo-HSCT=allogeneic hematopoietic stem cell transplantation; TPES=transplant population strictly eligible for ALD-102; NMSD=no matched sibling donor; PrvIQ=composite of performance/reasoning/visual IQ from age-appropriate Wechsler tests

Neurologic function: majority of patients maintained their baseline neurologic function after eli-cel treatment



Aug2021 data; TP-102/104 population

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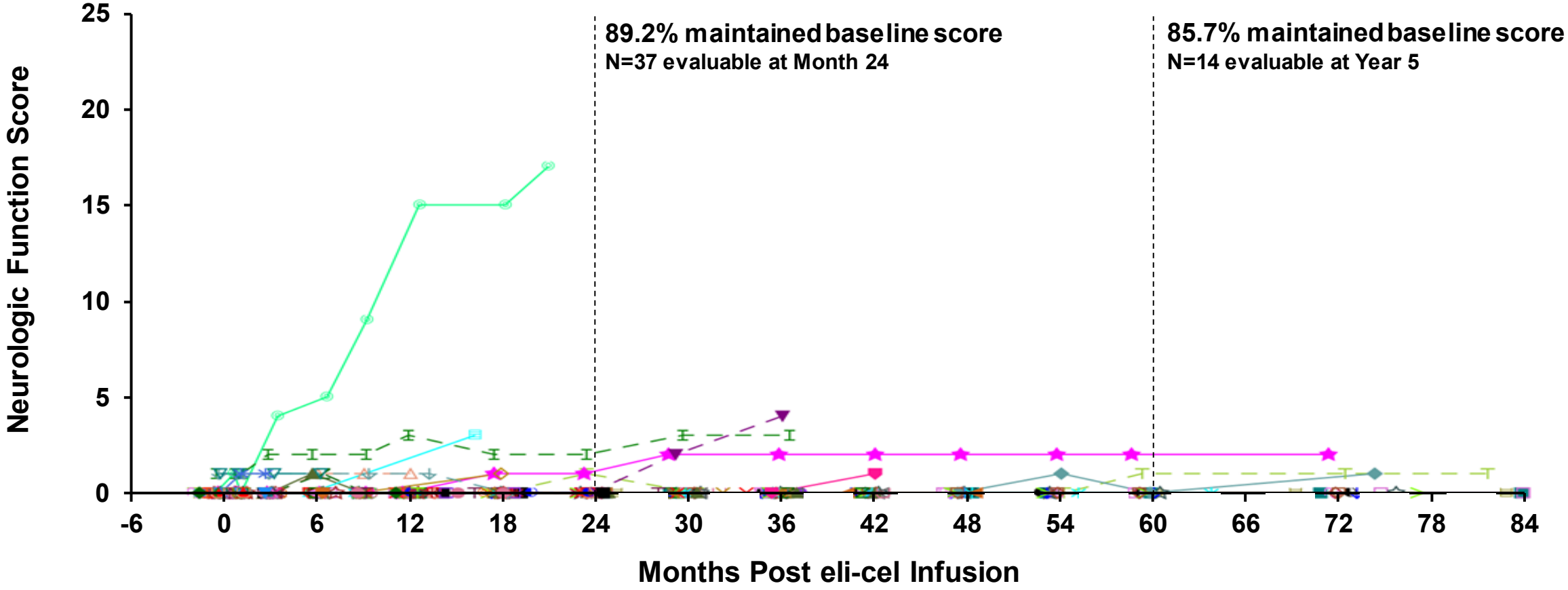
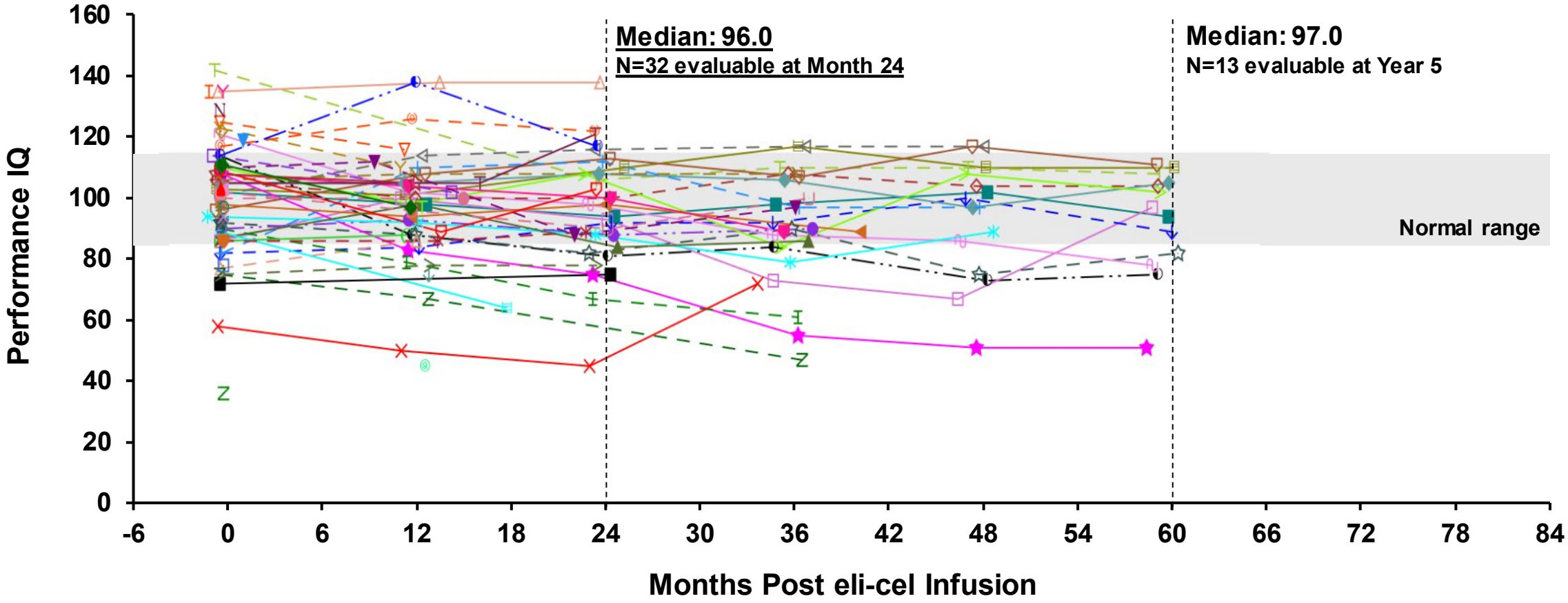


Aug2021 data; TP-102/104 population

Cognition: majority of patients maintained normal performance IQs after eli-cel treatment (PrvIQ)



Aug2021 data; TP-102/104 population; 85 to 115 is considered normal and shown as gray bar on the graph

Efficacy conclusions

M24=Month 24; 95% Confidence Intervals are shown in parentheses

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- **eli-cel compares favorably to no treatment**

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  - Event-free survival rate after eli-cel is similar to allo-HSCT with MUD: 90% at M24

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- **eli-cel efficacy is durable**
  - eli-cel maintained event-free-survival of 86.8% (72.7, 93.9) through 7 years
  - Majority of eli-cel treated patients maintained baseline neurologic function and normal IQ

M24=Month 24; 95% Confidence Intervals are shown in parentheses; MUD=matched unrelated donor; IQ=intelligence quotient

eli-cel Safety

Laura Demopoulos

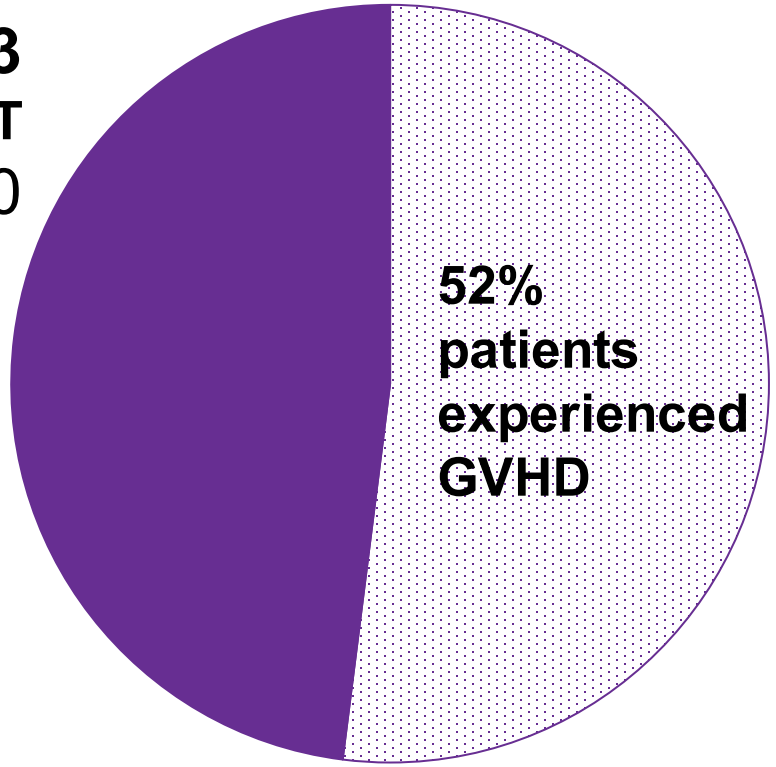
Vice President, Pharmacovigilance

bluebird bio, Inc.

Significant reduction in proportion of evaluable[1] patients who experienced either ≥ Grade II acute or chronic GVHD

TP-102
eli-cel
n=32

TP-103
allo-HSCT
n=50



p<0.0001

Primary success criterion was met

Aug21 datacut; GVHD=graft versus host disease; TP=transplant population
[1]Evaluable are those who had the respective event by Month 24 in any allo-HSCT Period or had been followed for at least 12 months in the latest allo-HSCT Period if no events

Fatal outcomes more common after allo-HSCT than eli-cel

TP-102/104 1.5% (1/67)	**1 died** Rapid disease progression starting 2 weeks after infusion with development of 4 MFDs and cardio-respiratory arrest 2 yrs after treatment. Not related to eli-cel.

Aug21 datacut; MFD=major functional disability; TP=transplant population

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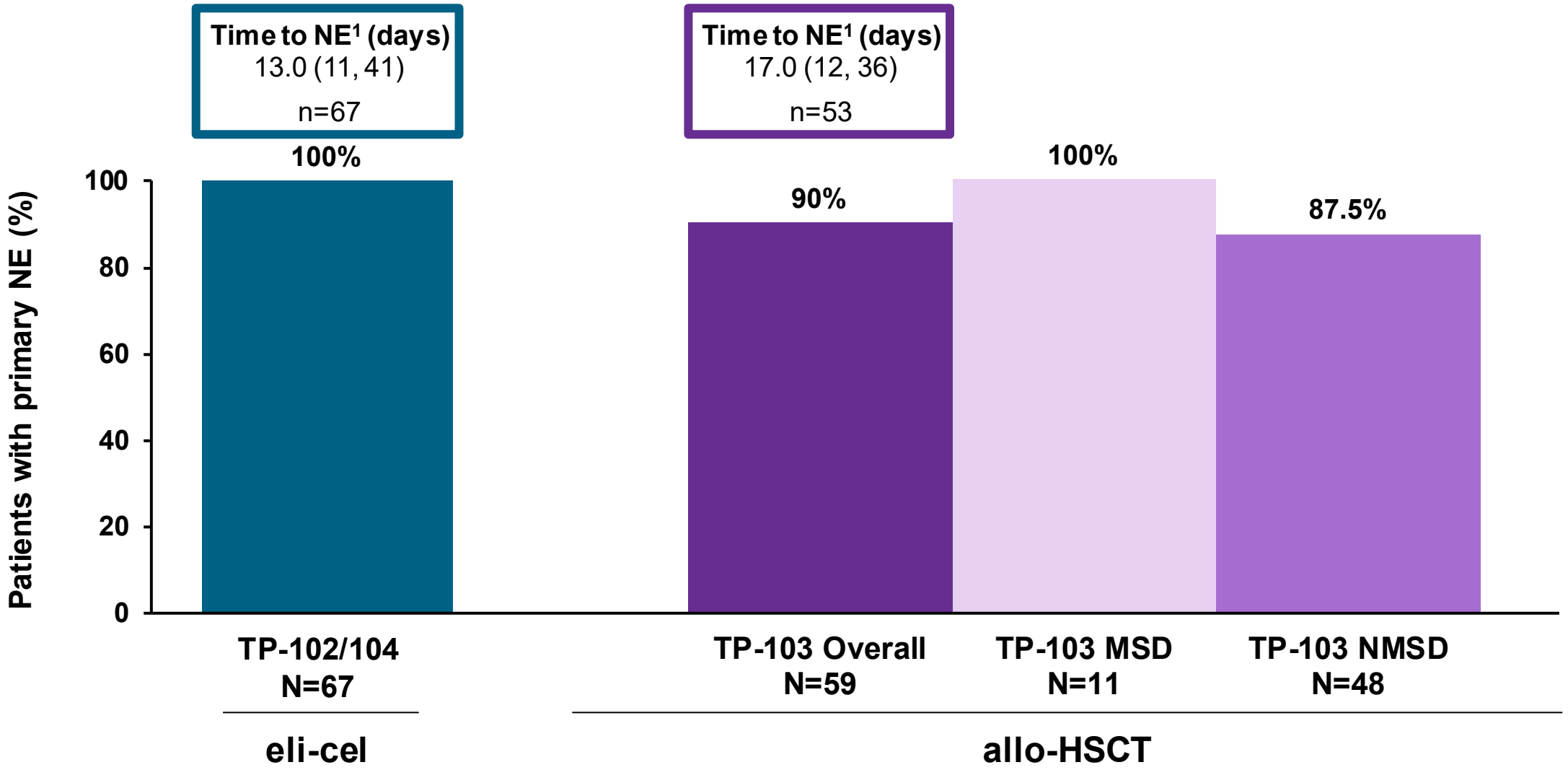
TP-102/104 1.5% (1/67)	**1 died** Rapid disease progression starting 2 weeks after infusion with development of 4 MFDs and cardio-respiratory arrest 2 yrs after treatment. Not related to eli-cel.	
TP-103 25.4% (15/59)	**MSD (n=11)** **2 died after 1st allo-HSCT** • 1 transplant related (GVHD) • 1 septic shock	**NMSD (n=48)** **10 died after 1st allo-HSCT** • 6 transplant related (all had GVHD) • 2 progressive disease • 1 cardiac arrest • 1 unknown **3 died after 2nd allo-HSCT** • 2 transplant related • 1 progressive disease

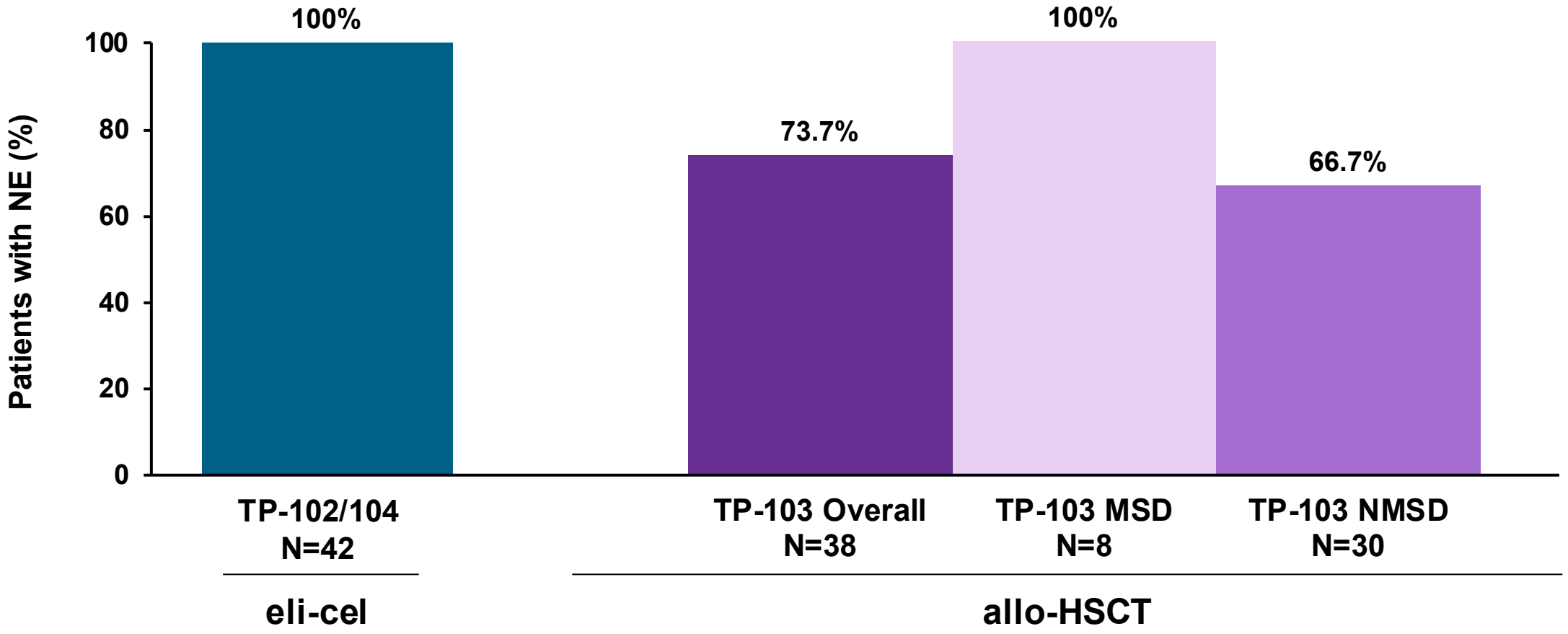
Aug21 datacut; MFD=major functional disability; MSD=matched sibling donor; NMSD=not a matched sibling donor; GVHD=graft versus host disease; TP=transplant population

All eli-cel patients had primary neutrophil engraftment



Jan22 datacut; [1]median (min, max); NE=neutrophil engraftment; MSD=matched sibling donor; NMSD=not a matched sibling donor; TP=transplant population

Primary/secondary NE failure only occurred following allo-HSCT



Jan2022 datacut NE=neutrophil engraftment; MSD=matched sibling donor; NMSD=not a matched sibling donor; TP=transplant population
Evaluable include patients who achieved NE and either had primary or second engraftment failure or had been followed for at least 24 months if no events

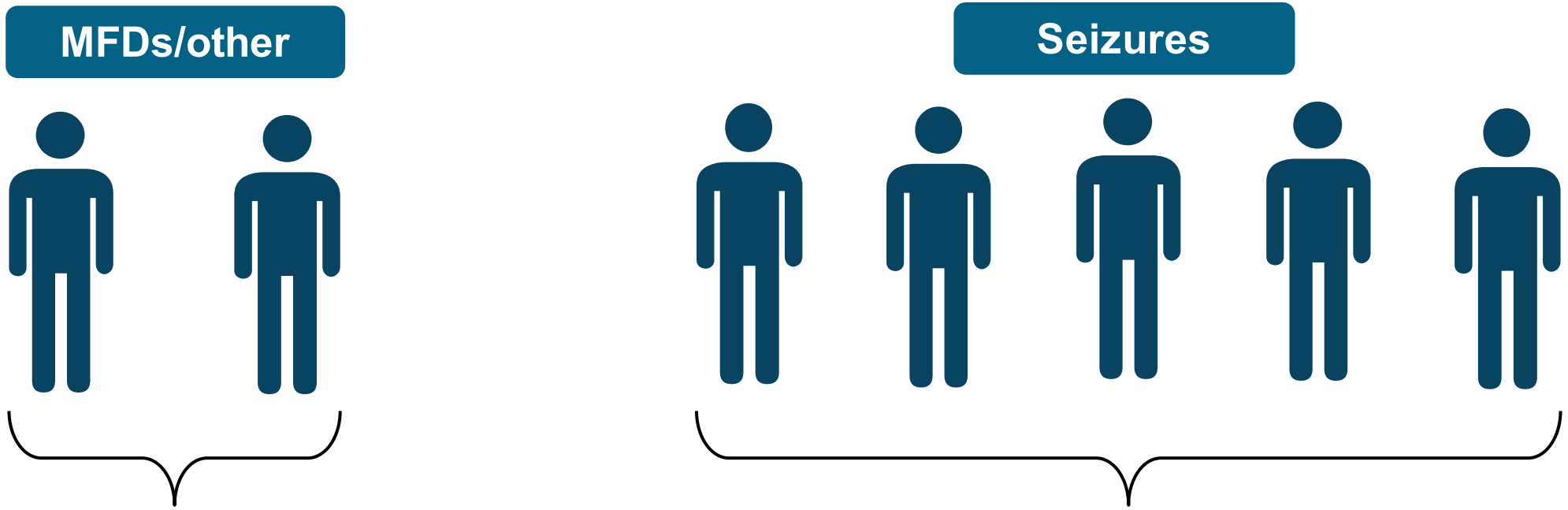
Safety of eli-cel Treatment Regimen

Treatment emergent SAEs in ≥2 patients were attributed to conditioning, eli-cel, or underlying disease

Conditioning	eli-cel	CALD
• **Febrile neutropenia** (12) • **Pyrexia** (12) • **CVC infection** (2) • **Pseudomonas bacteremia** (2) • **Stomatitis** (2) • **Vomiting** (2)	• **Myelodysplastic syndrome** (3) • **Pancytopenia** (2)	• **Seizure** (5) • **Major functional disability** (2)

Aug21 datacut (Jan22 datacut for myelodysplastic syndrome and major functional disability), SAE=serious adverse event; CVC=central venous catheter

Most neurologic SAEs were seizures



2 with MFDs and other neuro SAEs

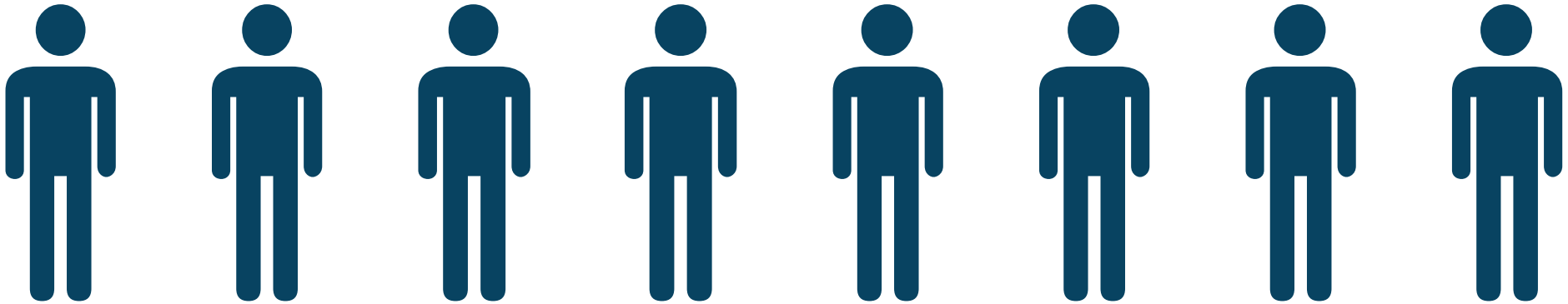
- 1 with SAE of dyskinesia ~2 wks after eli-cel, followed by 4 MFDs and death
- 1 with SAE of transverse myelitis followed by MFD of total incontinence

5 with SAEs of seizure

- All with onset ≥2yrs from eli-cel
- 4 maintained a stable NFS
- Followed for 1 to 5 yrs since onset

Aug21(Jan22 datacut for major functional disability (MFD)); SAE=serious adverse event; NFS=neurologic function score

Adverse drug reactions occurred in 8 of 67 patients



Jan22 datacut

CE-101

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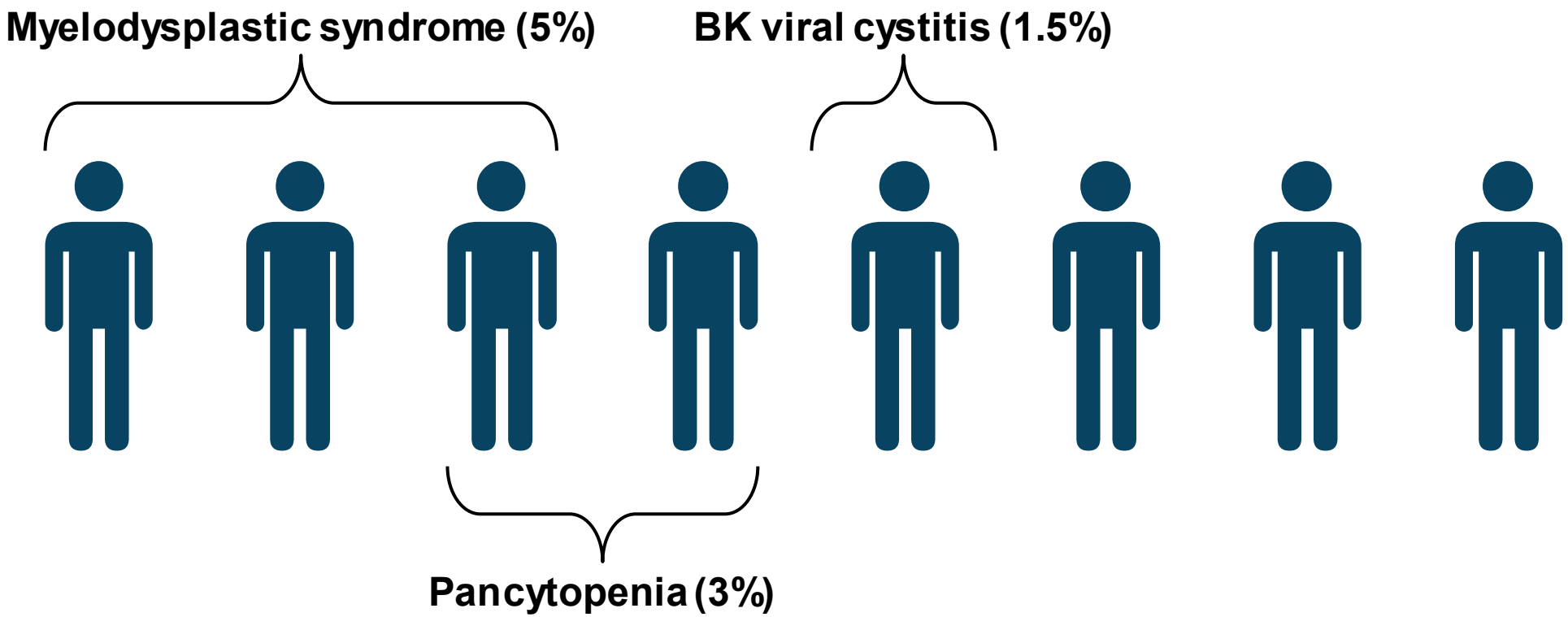

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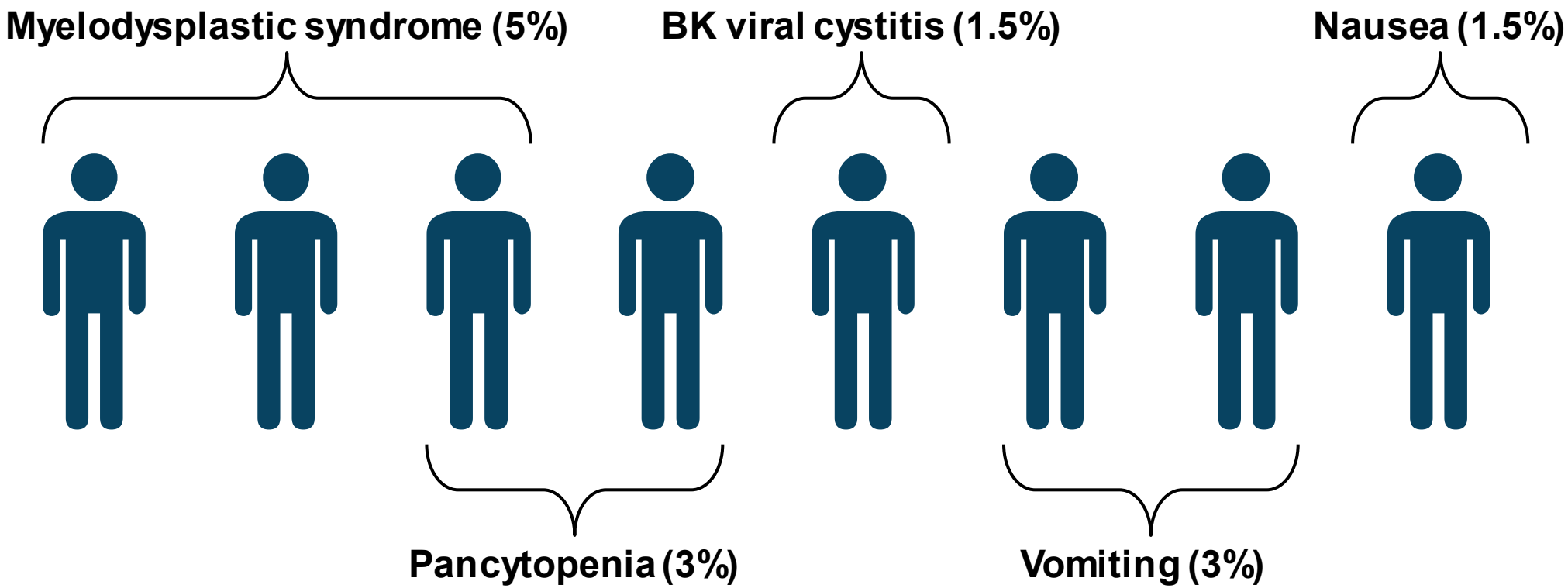

Jan22 datacut

Insertional oncogenesis

MDS in 3 patients likely mediated by Lenti-D LVV insertion

104-18
MDS-single lineage; megakaryocytic

Age at consent: 11yrs

Day of NE/PE: 14/106

ISA: clonal contribution >50% at M6. Increased EVI1 expression of MECOM locus in whole blood

Molecular testing: no known leukemic mutations or chromosomal aberrations

Day of diagnosis: Rel Day 444

CBC at time of diagnosis: WBC: 2.6 × 10^9/L; ANC: 1.3 × 10^9/L; platelets: 123 × 10^9/L

BM morphology: Markedly hypocellular marrow with dysmegakaryopoiesis

Treatment: allo-HSCT (D582)

Outcome: Remission (D685)

104-08
MDS-single lineage; megakaryocytic

Age at consent: 12yrs

Day of NE/PE: 12/104

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Molecular testing: no known leukemic mutations or chromosomal aberrations

Day of diagnosis: Rel Day 784

CBC at time of diagnosis: WBC: 2.2 × 10^9/L; ANC: 0.8 × 10^9/L; platelets: 19 × 10^9/L

BM morphology: Trilineage hematopoiesis with dysmegakaryopoiesis

Treatment: allo-HSCT (D896)

Outcome: Remission (D955)

102-03
MDS-EB-2

Age at consent: 4yrs

Day of NE/PE: 37/37

ISA: clonal contribution >50% at time of diagnosis, with IS in PRDM16

Molecular testing: KRAS and NRAS

Day of diagnosis: Year 7.5

CBC at time of diagnosis: WBC: 8.8 cells/μL; platelets: 25 × 10^9/L;

BM morphology: 15% myeloblasts, concurrent with 3% blasts/LVV in blasts in the peripheral blood

Treatment: chemotherapy + allo-HSCT (Y8)

Outcome: post allo-HSCT: bone marrow showed 5% cellularity with 0.15% myeloblasts

Jan22 datacut; WBC=white blood count; ANC=absolute neutrophil count; LVV=lentiviral vector; Rel=relative day; MDS=myelodysplastic syndrome; EB=excess blasts; ISA=integration site analysis; NE=neutrophil engraftment; PE=platelet engraftment

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Treatment: allo-HSCT (D896)

Outcome: Remission (D955)

102-03
MDS-EB-2

Age at consent: 4yrs

Day of NE/PE: 37/37

ISA: clonal contribution >50% at time of diagnosis, with IS in PRDM16

Molecular testing: KRAS and NRAS

Day of diagnosis: Year 7.5

CBC at time of diagnosis: WBC: 8.8 cells/μL; platelets: 25 × 10^9/L;

BM morphology: 15% myeloblasts, concurrent with 3% blasts/LVV in blasts in the peripheral blood

Treatment: chemotherapy + allo-HSCT (Y8)

Outcome: post allo-HSCT: bone marrow showed 5% cellularity with 0.15% myeloblasts

Jan22 datacut; WBC=white blood count; ANC=absolute neutrophil count; LVV=lentiviral vector; Rel=relative day; MDS=myelodysplastic syndrome; EB=excess blasts; ISA=integration site analysis; NE=neutrophil engraftment; PE=platelet engraftment

Post-marketing monitoring for MDS

- **In-depth analyses for early detection and risk mitigation**
  - Routine CBC (every 6 months)
    - Patients with CBC abnormalities such as platelet engraftment after Day 100 and recurrent cytopenias should be evaluated to determine the cause, including malignancy
  - PB VCN, prolonged thrombocytopenia, clonal hematopoiesis
- **Limited network of qualified treatment centers and rare disease**
  - Maintain chain of identity, training on US prescribing information and AE reporting
- **REG-502**
  - CBC every 6 months (proposed in US prescribing information)
  - PB VCN and ISA at M6, M12, and annually thereafter
- **Continuous assessment of benefit/risk**
  - Revision of recommended monitoring and US prescribing information, as needed

CBC=complete blood count; PB VCN=peripheral blood vector copy number; ISA=integration site analysis; M=month; US=United States; AE: adverse events; MDS=myelodysplastic syndrome

Safety conclusions

- **Primary safety success criterion was met**
- **eli-cel avoids the key immune-mediated complications of allo-HSCT (GVHD, graft failure, TRM) and the complications of post-transplant immunosuppression**
- **Adverse drug reactions:**

<u>Serious</u>
- **Myelodysplastic syndrome**
- **Pancytopenia**
- **BK viral cystitis**

<u>Nonserious</u>
- **Infusion reactions**
  - **Nausea**
  - **Vomiting**

- **Comprehensive post-marketing surveillance for malignancy**

GVHD=graft versus host disease; TRM=transplant related mortality

Benefit/Risk

Benefit/Risk context

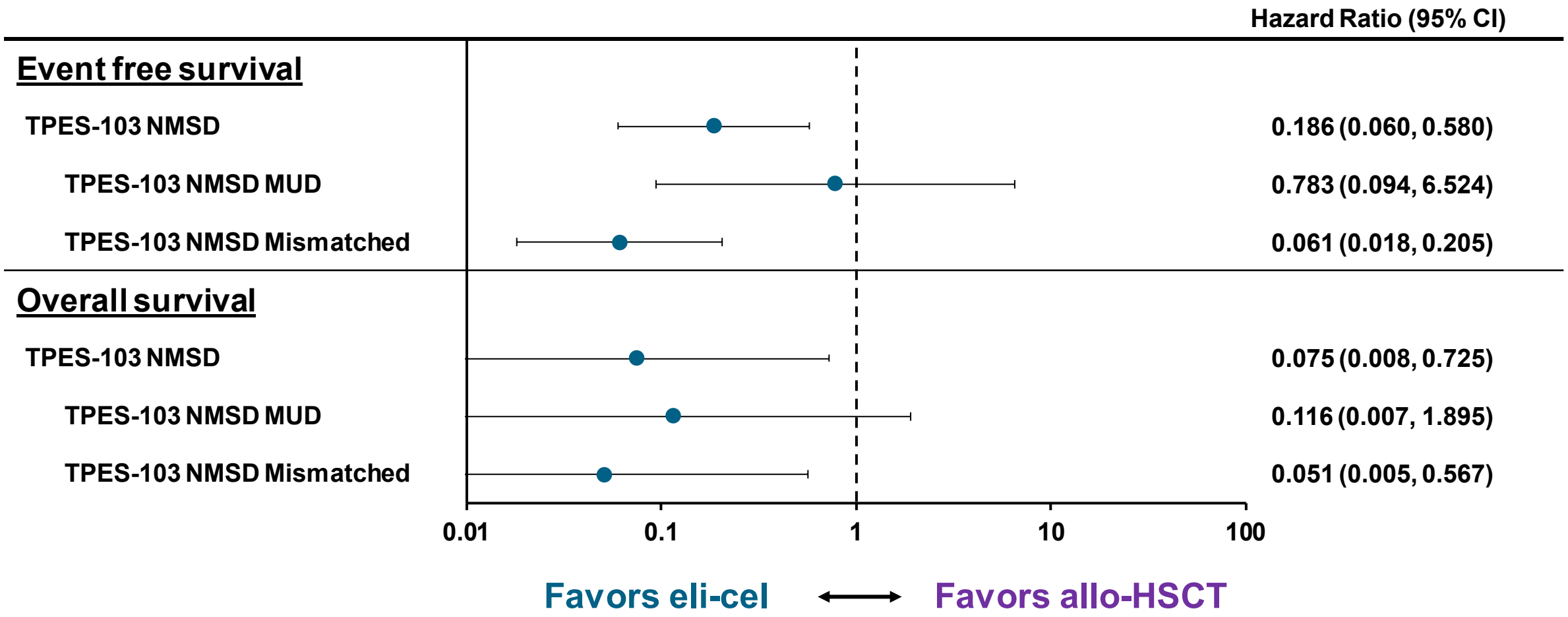
- **Natural history of untreated CALD is characterized by neurologic decline and death**

- **Allo-HSCT is only therapeutic option**
  - MSD confers good outcomes, available to approximately 10%
  - NMSD morbidity/mortality result from immune incompatibility

- **Balance the immune complications of NMSD allo-HSCT with gene therapy specific complications of autologous treatment with eli-cel**

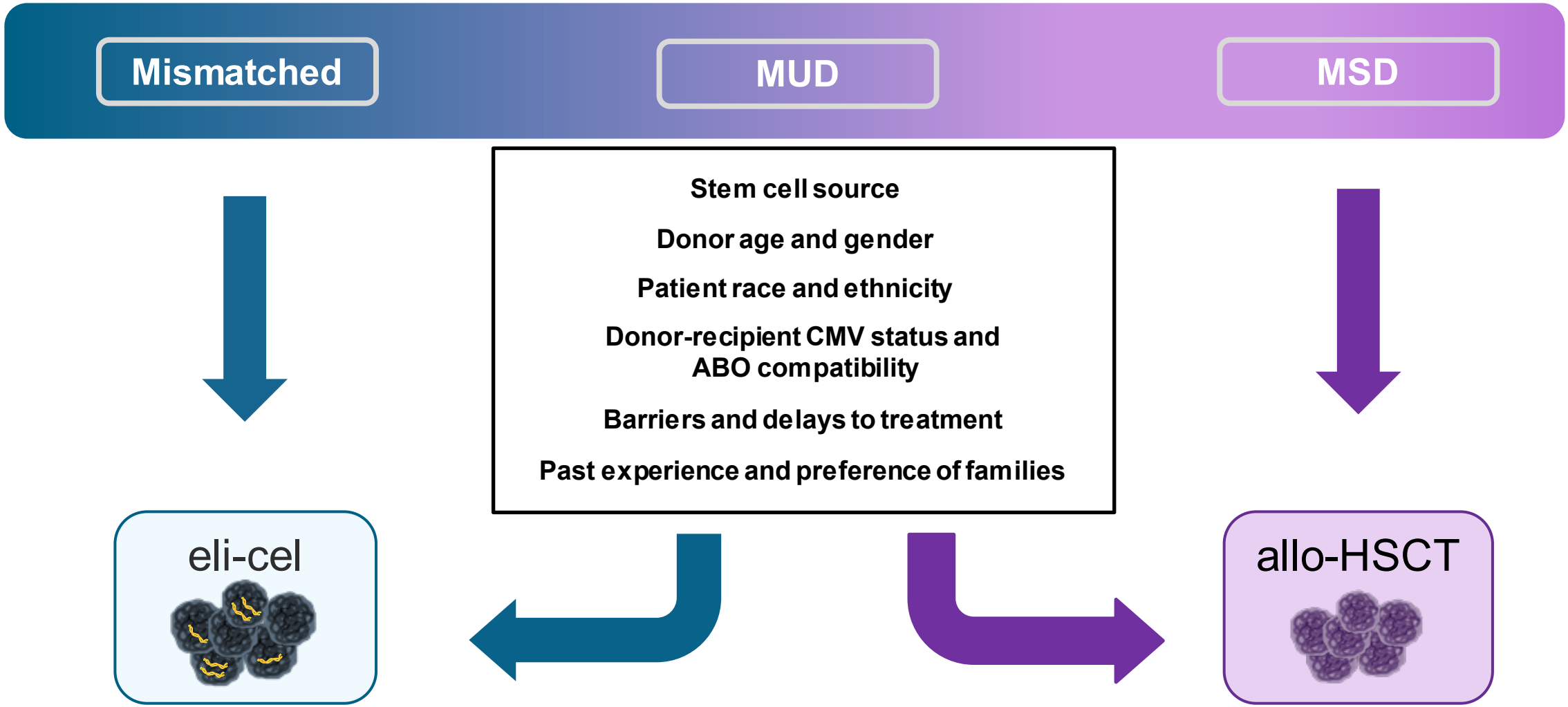
MSD=matched sibling donor; NMSD=not a matched sibling donor

Hazard ratios for event free and overall survival



Jan22 datacut; MSD: matched sibling donor; NMSD: not a matched sibling donor: MUD=matched unrelated donor; CI=confidence interval;
TPES=strictly ALD-102 eligible transplant population
The hazard ratio of TP-102/014 vs. the allo-HSCT analysis population is based on an univariate Cox regression model with treatment group as the predictor

Patients with life-threatening diseases benefit from having multiple treatment options



MSD=matched sibling donor; MUD=matched unrelated donor; CMV=Cytomegalovirus

Clinician Perspective: the Role of eli-cel

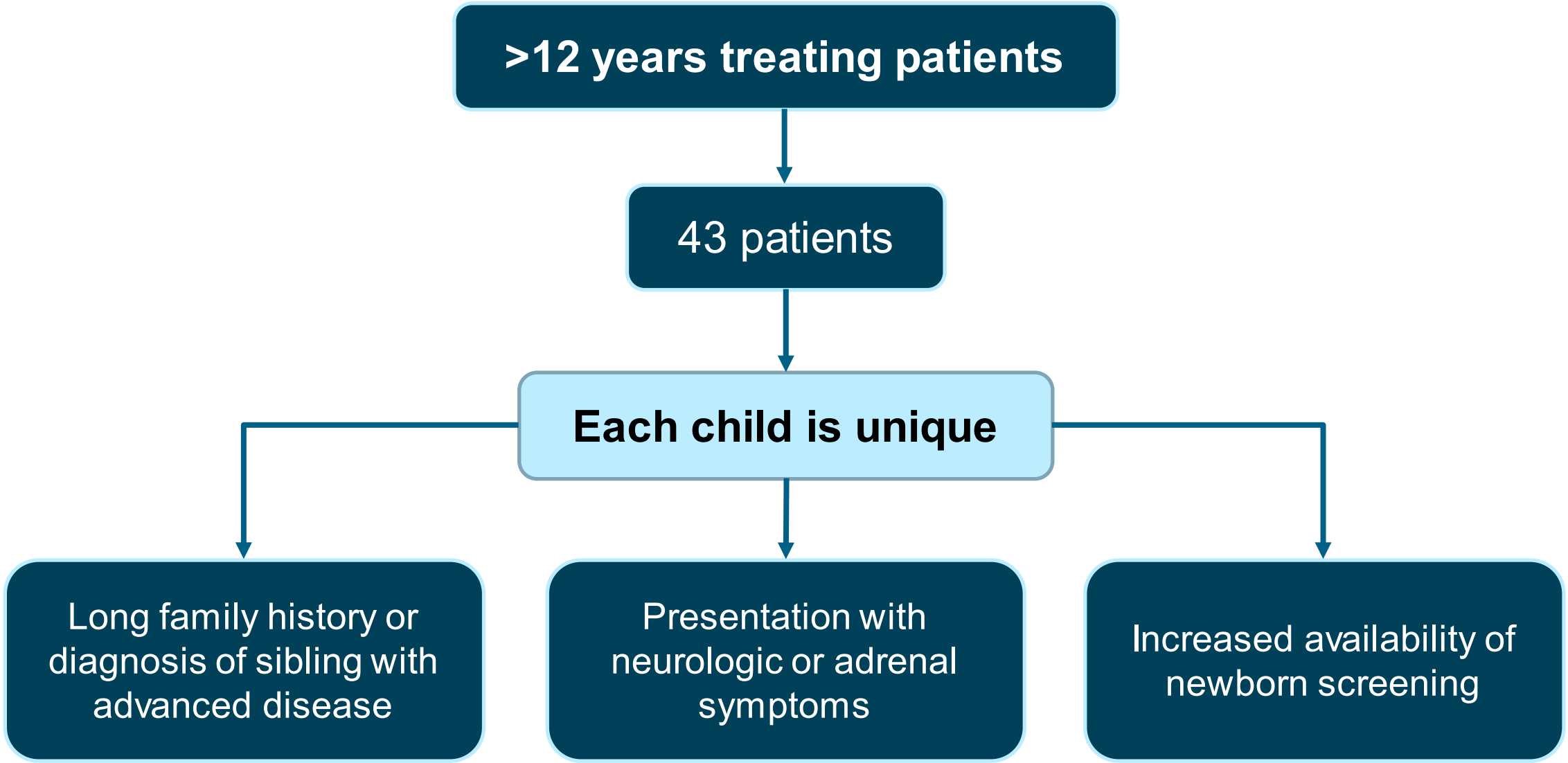
Christine Duncan, MD

Sr. Physician, Dana-Farber/Boston Children's Hospital Cancer and Blood Disorders Center

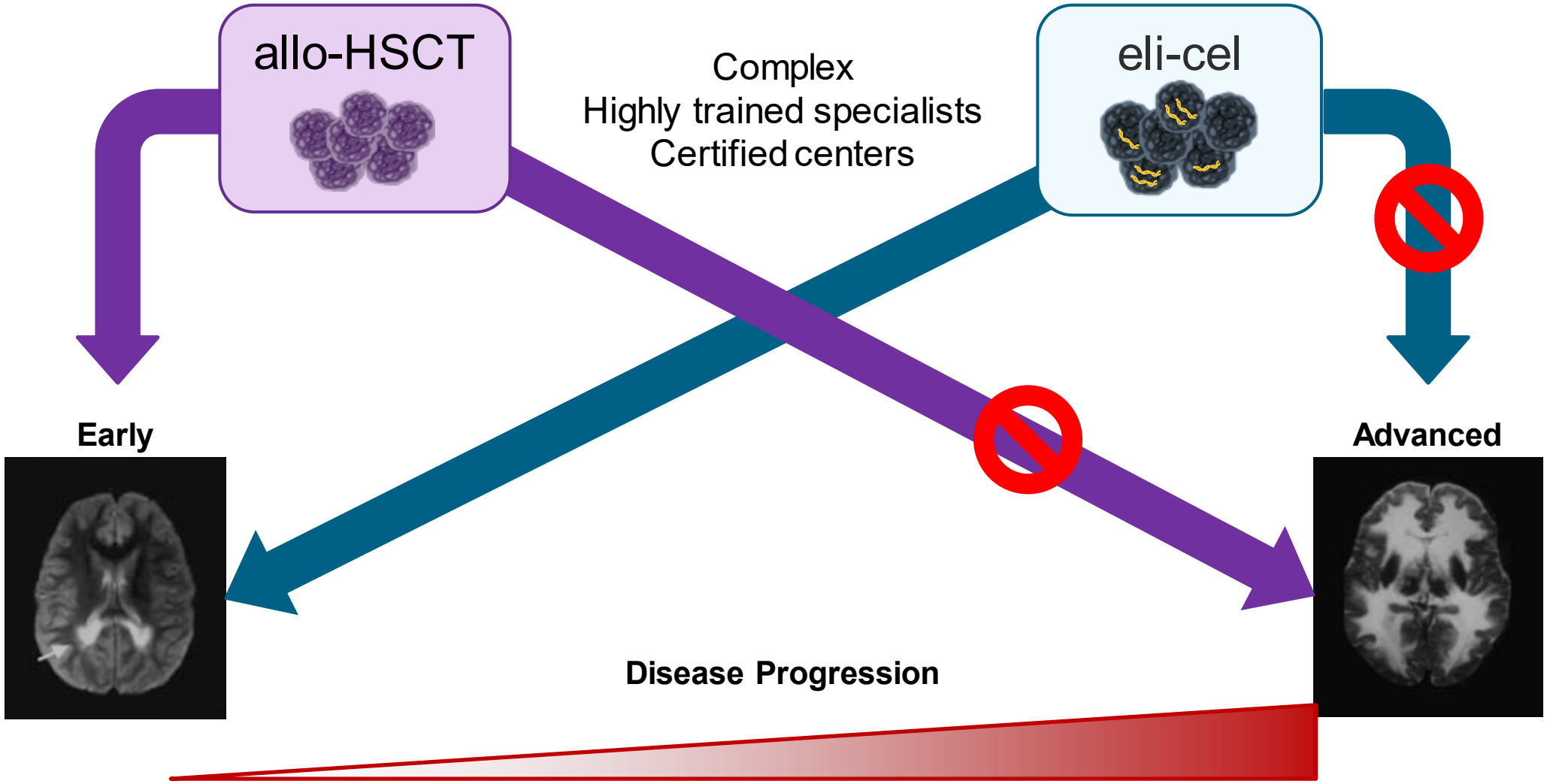
Medical Director of Clinical Research & Clinical Development, Gene Therapy Program, Boston Children's Hospital

Associate Professor of Pediatrics, Harvard Medical School

My experience with cerebral adrenoleukodystrophy



Therapeutic options in CALD



Considerations in allogeneic-HSCT

Donor Type
Bone Marrow
Peripheral Blood
Cord Blood

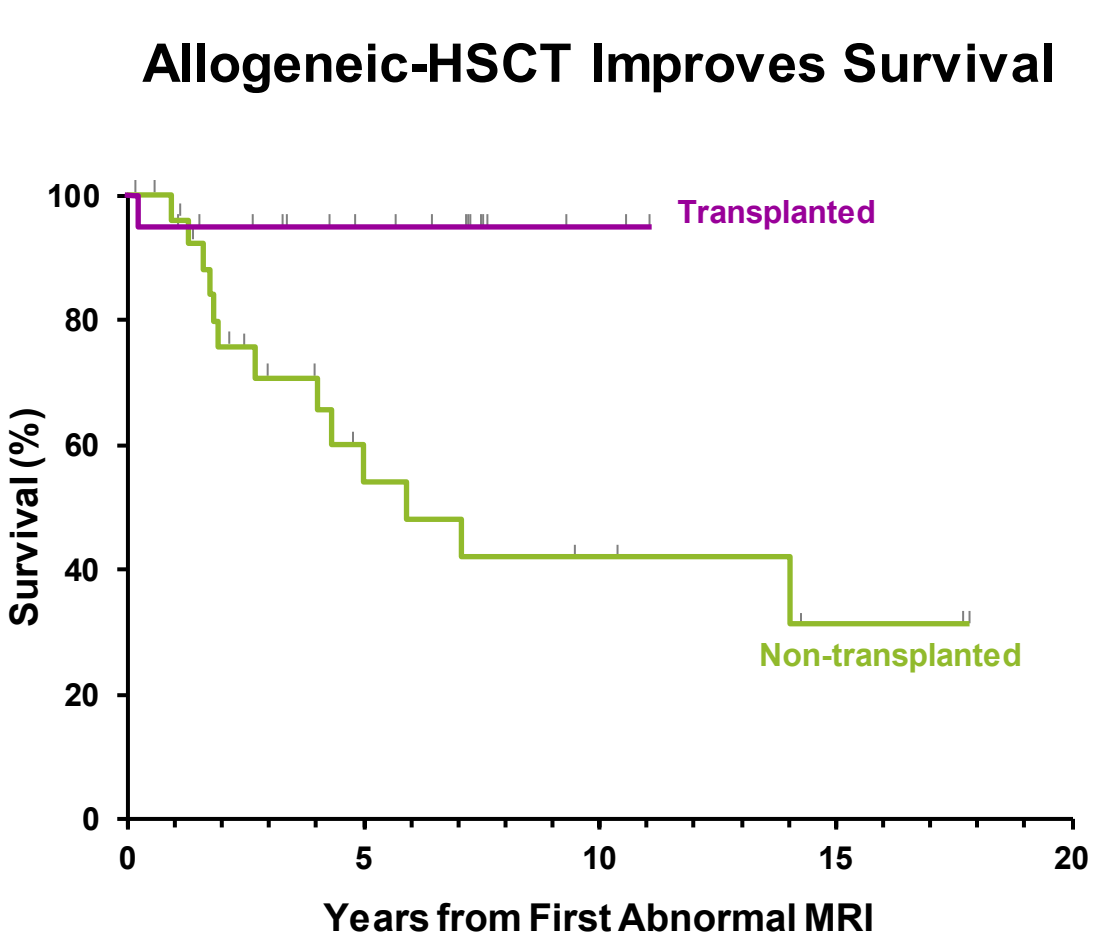
Donor Source
Related
Unrelated

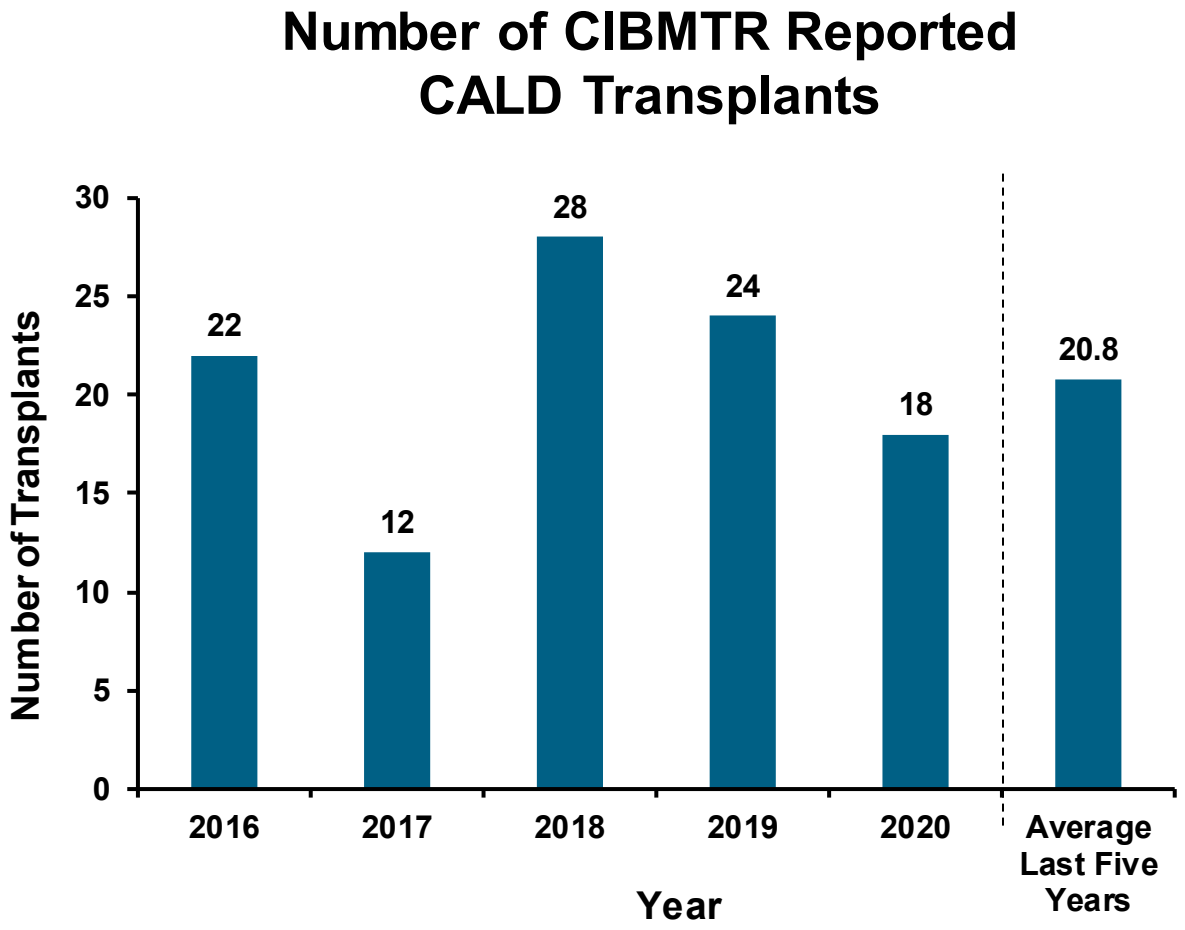
Conditioning Regimen Choices

Medications to Prevent Rejection and GVHD

Multiple Additional Factors

Data about allogeneic-HSCT in CALD

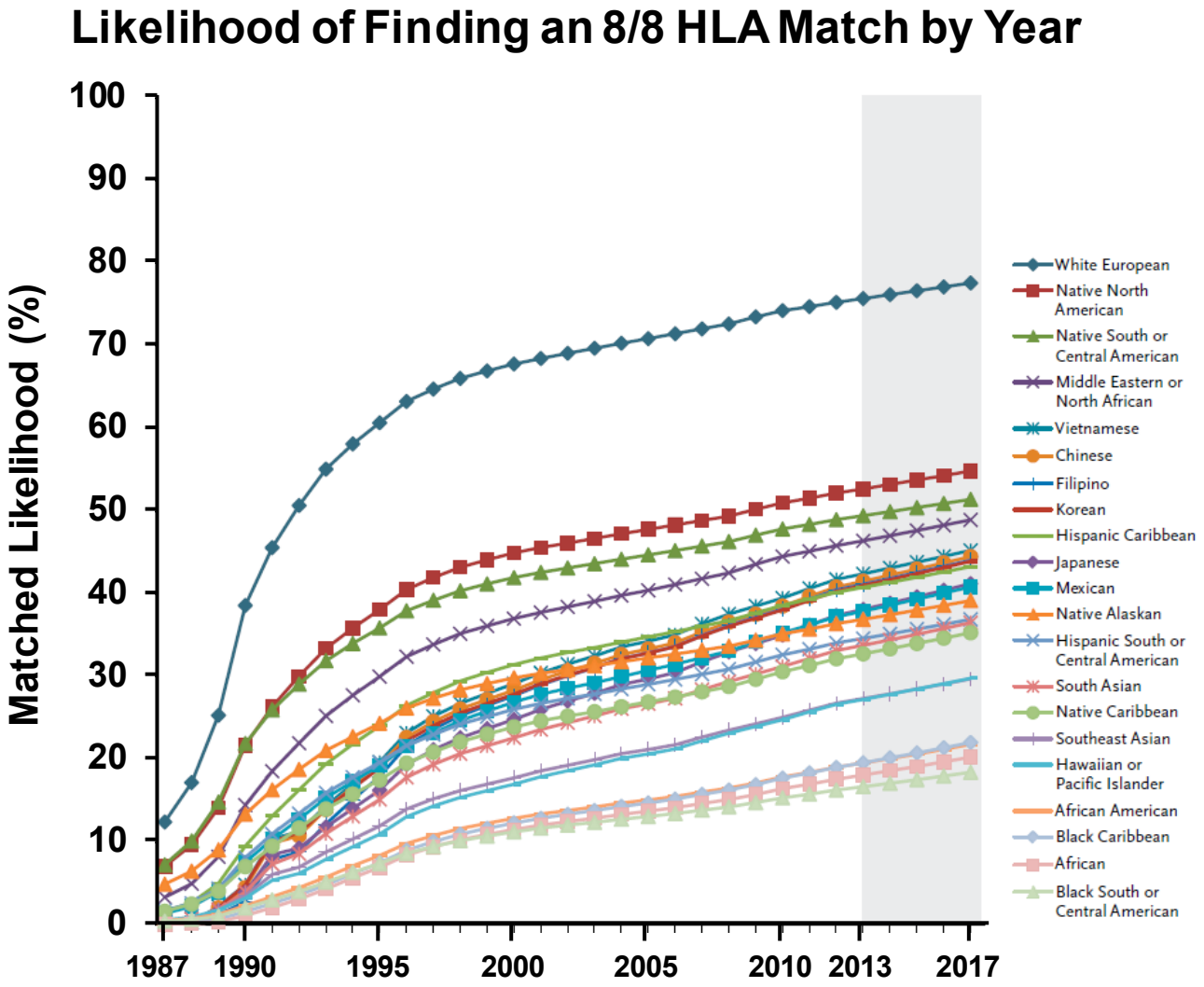




~10% MSD and ~2% other related/haplo

Left figure: Mahmood A, et al. *Lancet Neurol*. 2007;6:687-92

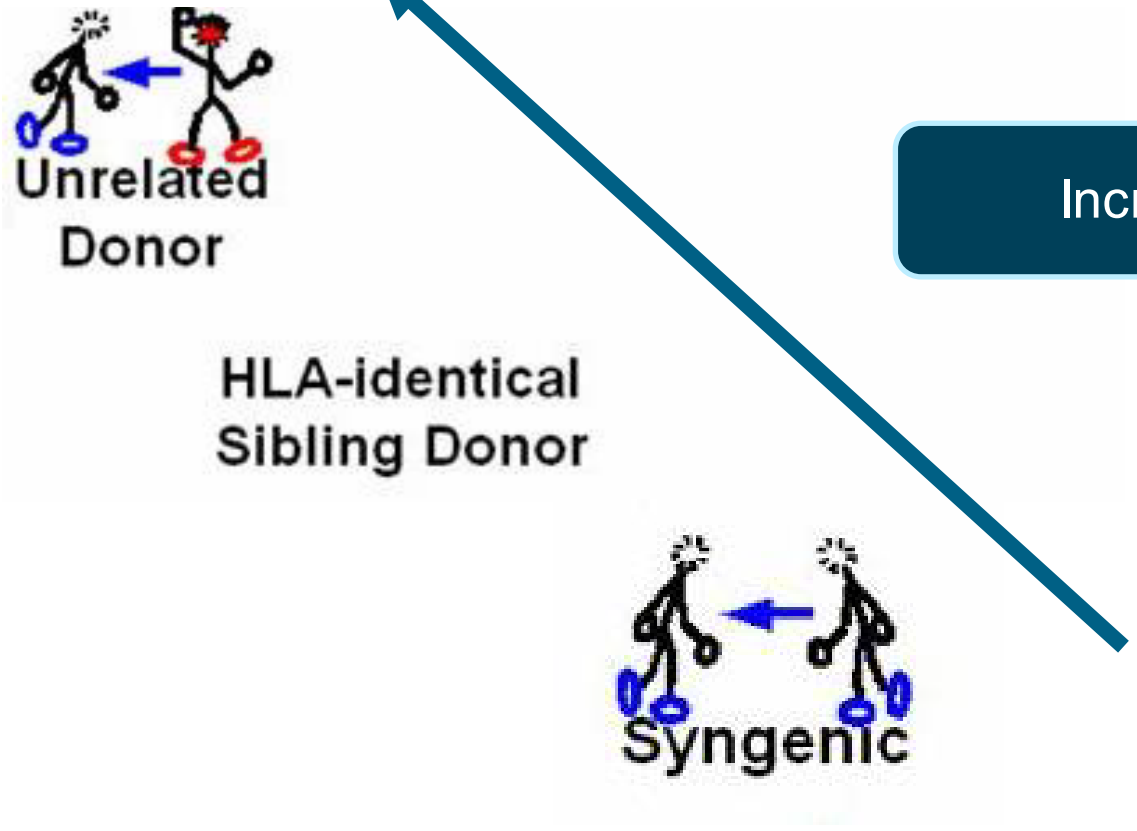
Diversity in treatment: increasing options



TP-102/104 Demographics	
Race	
White	54%
Black	4%
Asian	1%
Other	10%
Unknown	30%
Ethnicity	
Hispanic	25%
Non-Hispanic	61%
Unknown	13%

Source (figure): Gragert et al. *NEJM* 2014

Allogeneic-HSCT complications regardless of HLA match



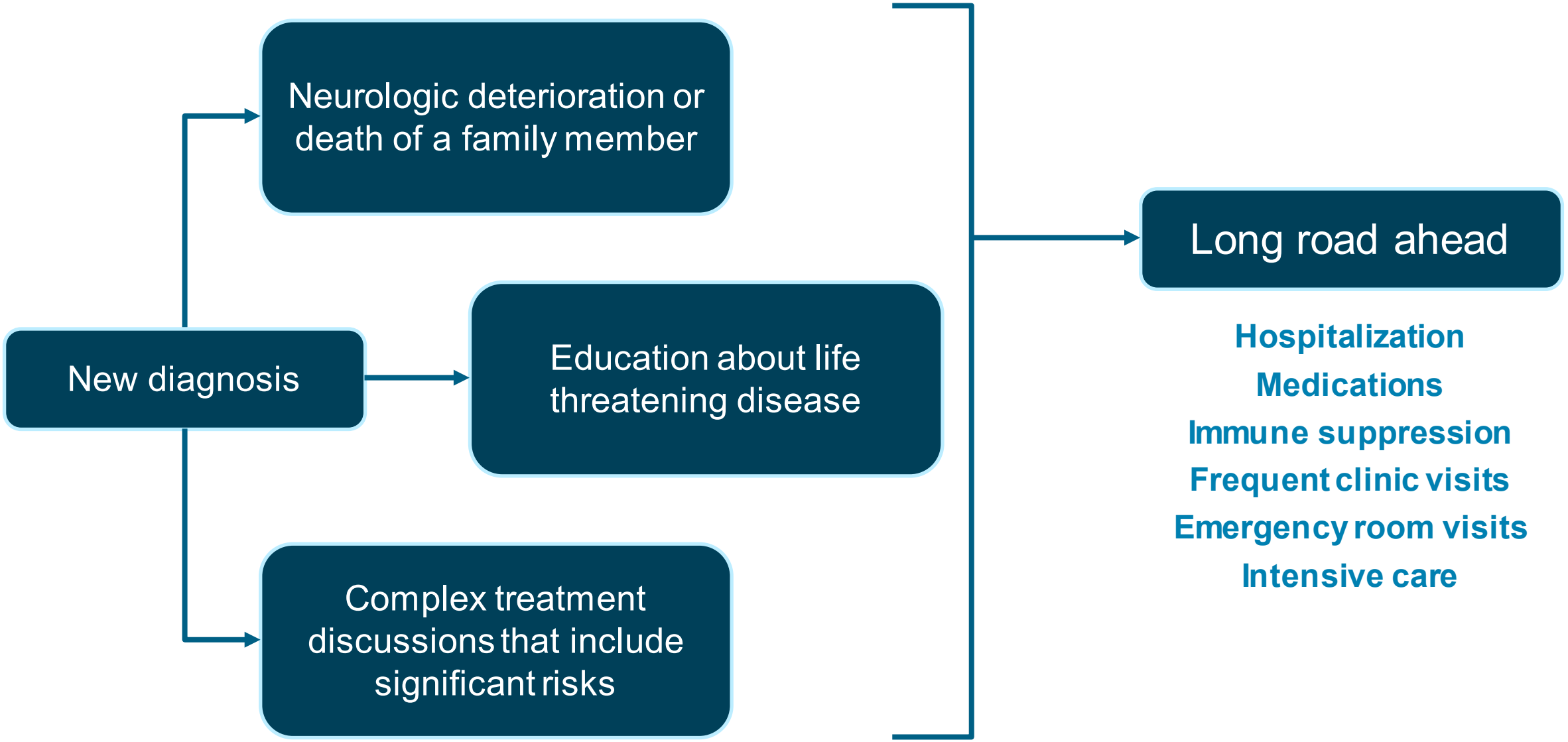
Increasing GVHD

Increasing Graft Rejection

Increasing TRM

HLA=Human Leukocyte Antigen; GVHD=graft vs. host disease; TRM=treatment related mortality

Impact on patients and families



Length of in-patient hospitalization is an important factor for many patients and caregivers

	eli-cel	allo-HSCT
	TP-102/104 N=67 n (%)	TP-103 NMSD N=48 n (%)
Total duration of in-patient hospitalizations (days)		
n	66	47[1]
Median	28.0	52.0
Min, Max	15, 59	25, 240
p-value		<0.0001

Subjects who received eli-cel were observed to have shorter in-patient hospitalizations (median of 28 days) compared to subjects who received allo-HSCT from a NMSD (52 days; p<0.0001)

Aug21 datacut; 1 one patient was excluded due to a data entry error; NMSD: not a matched sibling donor

Study ALD-102 was a success

Success criteria for primary efficacy and safety endpoints were met

- ✓ **90.6% (95% CI: 75.0, 98.0) Month 24 MFD-free survival**
  - Significant effect compared to a pre-specified benchmark that reflects untreated CALD

- ✓ **0% ≥ Grade II acute or chronic GVHD**
  - Significant reduction in proportion of patients who experienced either ≥ Grade II acute or chronic GVHD (0% vs. 52%, p<0.0001)

MFD=major functional disability; CALD=cerebral adrenoleukodystrophy; GVHD=graft vs. host disease

Difficult outcomes and challenging clinical situations

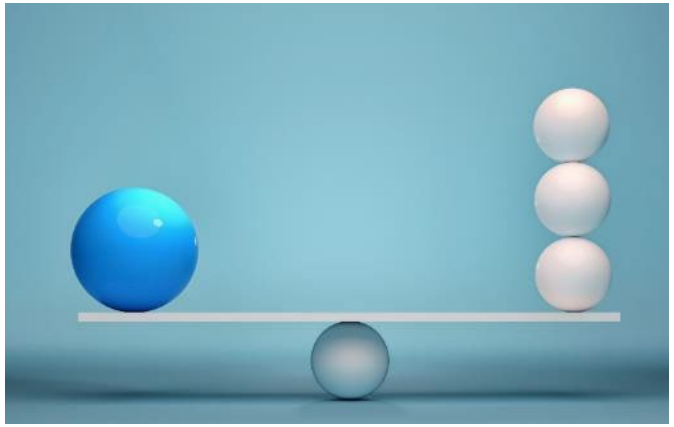
Serious Issues, Intense Therapies, Arduous Processes

Insertional oncogenesis

Allo-HSCT complications

There are multiple considerations that must be balanced, including downstream therapeutic implications

Occurrence of MDS has required patients to undergo a second (allo) transplant



Occurrence of graft failure has required patients to undergo a second transplant

HSCT=hematopoietic stem cell transplant; MDS=myelodysplastic syndrome

Conclusions: selection of a treatment option

- **Matched sibling donor – comfortable with allo-HSCT**

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- **No related or unrelated donor – need an option for these patients (eli-cel)**

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Conclusions: selection of a treatment option

- **Matched sibling donor – comfortable with allo-HSCT**
- **No related or unrelated donor – need an option for these patients (eli-cel)**
- **In between is complex – need to allow for open dialogue (allo-HSCT or eli-cel)**
- **Multiple therapeutic options allows for better treatment conversations**

Questions and Answers

Frederic Prince, PhD

eli-cel Program Lead

bluebirdbio®