Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

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FDA Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) June 9, 2022

Elivaldogene Autotemcel (Eli-cel): BLA 125755 Clinical Considerations for Efficacy and Specific Safety in Early Cerebral Adrenoleukodystrophy

Shelby Elenburg, MD and Leah Crisafi, MD, FASA, CDR, USPHS
and AC Planning Working Group
Office of Tissues and Advanced Therapies (OTAT)
CBER, FDA

Outline

- Disease background
- Eli-cel product
- Studies submitted in support of BLA
- Study ALD-102 protocol
- Efficacy results and issues
- Product-specific safety results and issues
- Benefit-risk summary

Cerebral Adrenoleukodystrophy (CALD)

- Rare, X-linked neurodegenerative metabolic disorder
- *ABCD1* mutations lead to accumulation of very long chain fatty acids (VLCFAs) and neuroinflammation
- Presents in boys 3-10 years of age
- Progressive neurologic deterioration
- Death by 2nd decade
- Heterogeneous
- No approved treatment in the US, but allogeneic HSCT is standard of care

Neurologic Function Score (NFS) and Major Functional Disabilities (MFDs)

Neurologic Function Score[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, et al. Neuropediatrics. 2000; 31(5):227-39

- Neurologic Function Score (NFS):
  - Used to rate clinical severity of CALD
  - Score of 0 (asymptomatic) to 25
- Major Functional Disabilities (MFDs):
  - Loss of communication
  - Cortical blindness
  - Tube feeding
  - Wheelchair dependence
  - Loss of voluntary movement
  - Total incontinence

MRI Findings: Loes Score and Gadolinium Enhancement

- Demyelination on brain MRI
- Loes score:
  - Scores 0 (normal, no lesions) to 34
  - Location, extent, and presence or absence of atrophy
- Gadolinium enhancement (GdE+):
  - Active inflammatory disease
  - Increased probability of progression and higher 5-year mortality

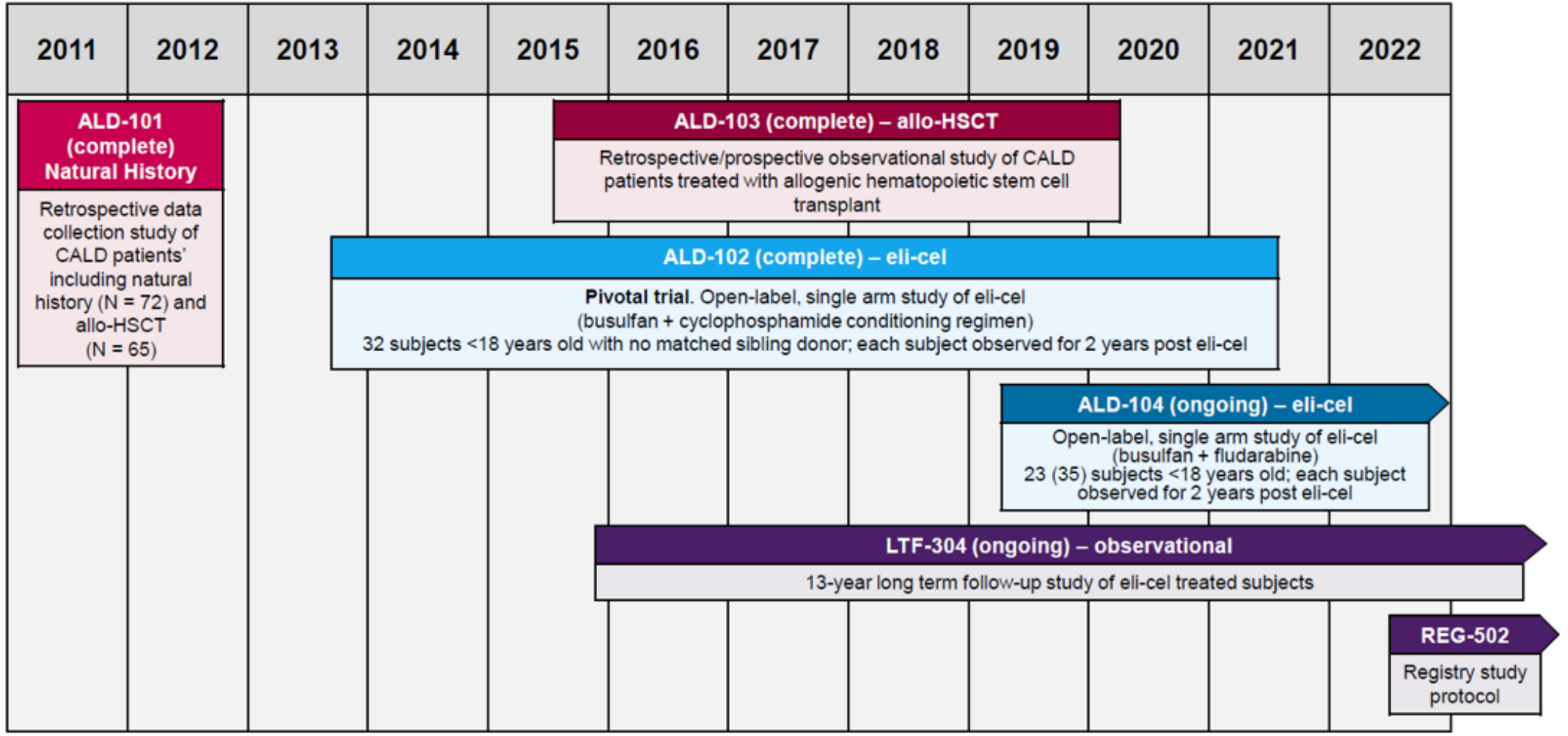
- MRI findings useful for:
  - Pre-HSCT clinical decision-making
  - Post-HSCT monitoring
- MRI findings limitation:
  - Do not always correlate with clinical symptoms

Drug Product: eli-cel

- Lentiviral vector (LVV) gene therapy
- Replace *ABCD1*

Source: bluebird bio, Inc. original BLA submission; plasmid map available in RAC presentation materials, available at: https://osp.od.nih.gov/wp-content/uploads/2013/12/1073_Williams.pdf

Clinical Development Program



Source: bluebird bio, Inc. Application Orientation Meeting slides

Study ALD-102

- Study Design:
  Open label, externally- controlled 24-month study
- Primary objectives:
  Safety and efficacy of eli-cel as single IV dose
- Inclusion Criteria:
  - Males ≤ 17 years of age Active CALD :
    - Elevated VLCFA levels
    - Loes score 0.5 - 9
    - Gadolinium enhancement (GdE+)
  - NFS ≤ 1
- Exclusion Criteria:
  - Prior HSCT or gene therapy
  - 10/10 HLA-matched sibling donor

- Primary Efficacy Endpoint:
  - Month 24 MFD-Free Survival, compared to a benchmark value
- Primary Safety Endpoint:
  - Acute (≥ Grade II) or chronic graft versus host disease (GVHD) by Month 24

Defining "Strictly ALD-102- Eligible"

- Subjects in Studies ALD-101 or ALD-103 eligible for enrollment in Study ALD-102 (**early active disease**):
  - NFS ≤ 1
  - Loes score 0.5 to 9
  - GdE+

- Strictly ALD-102- Eligible Populations:
  - **HSCT: TPES**
    - **TPES-101** (n=26), **TPES**-103 (n=27)
  - Untreated: UTES
    - UTES-101 (n=1)

Primary Efficacy Endpoint: Month 24 MFD-Free Survival

- At Month 24, a subject must:
  - Be alive
  - Not have developed any MFDs
  - Not have received rescue cells or allo-HSCT
  - Not have withdrawn or been lost to follow-up
- Success:
  - Month 24 MFD-free survival compared to a clinical benchmark of >50%
- The benchmark populations:
  - **Population #1 (UTG-101):**
  - **Untreated, GdE+ (advanced disease)**
    - Month 24 MFD-free survival : 21%
      - 95% CI of 6.1% to 45.6%
  - **Population #2 (TPES-101):**
  - **HSCT, strictly ALD-102-eligible, no matched sibling donor (NMSD)**
    - Month 24 MFD-free survival: 76%
      - 95% CI of 50.1% to 93.2%

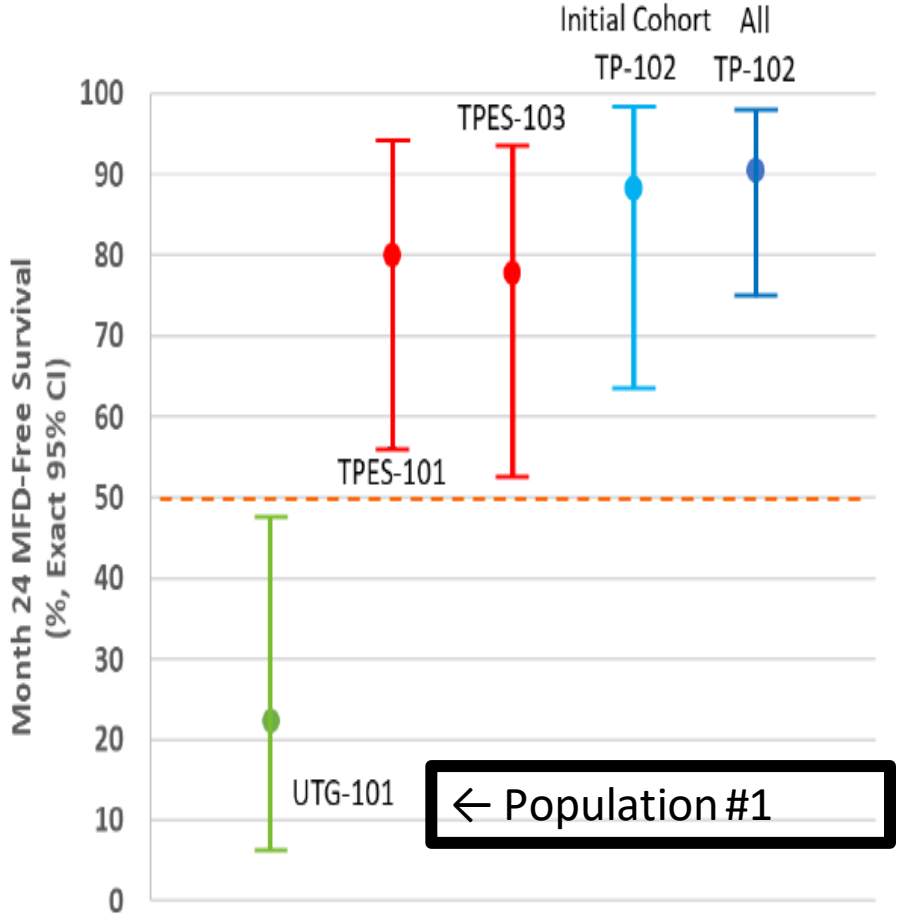
Baseline Demographics and Disease Characteristics- Benchmark Populations and eli-cel

Parameter	Population #1: UTG-101 (n=21)	Population #2: TPES-101 NMSD (n=21)	Eli-cel ALD-102: TP-102 (n=32)
Age (Years) Median (Min, Max)	8 (4,15)	8 (4,14)	6 (4,14)
Age at Diagnosis (Years) Median (Min, Max)	8 (4,15)	7 (3,12)	6 (1,13)
Baseline Loes Median (Min, Max)	11 (2.0,15.0)	4.5 (0.5, 9.0)	2 (1.0, 9.0)
Baseline NFS Median (Min, Max)	3.5 (0, 25)	0 (0,1)	0 (0,1)

Source: Reviewer's analysis of ADSL datasets
Abbrev: UTG, GdE+ Untreated population; TP, Transplant Population; TPES, Strictly ALD-102-eligible Transplant Population; NMSD, No Matched Sibling Donor subgroup; NFS, Neurologic Function Score

Primary Efficacy Endpoint: Month 24 MFD-Free Survival

- Eli-cel was successful:
  - point estimate of 90.6%
  - 95% CI of 75.0% to 98.0%
- There were 3 failures of MFD-free survival by Month 24:
  - 1 MFD at Month 9
  - 2 rescue allo-HSCT due to progressive disease on brain MRI (at Months 13 and 17)



Source: bluebird bio BLA 2.5 Clinical Overview, Figure 5

Primary Efficacy Endpoint: Month 24 MFD-Free Survival

Issues with Study ALD-101 and the benchmark populations:

- **Lack of comparability between study groups**
- Imputation methods used in the calculation of the benchmark
- Other potential for bias
- Insufficient duration to establish efficacy

- Unknown benchmark
- Eli-cel cohort may have been treated at an earlier, less advanced stage of disease

Primary Efficacy Endpoint: Month 24 MFD-Free Survival

Issues with Study ALD-101 and the benchmark populations:

- Lack of comparability between study groups
- **Imputation methods used in the calculation of the benchmark**
- Other potential for bias
- Insufficient duration to establish efficacy

Repeat HSCT for engraftment failure is not the same as MFD or death and should not be imputed as such.

Primary Efficacy Endpoint: Month 24 MFD-Free Survival

Issues with Study ALD-101 and the benchmark populations:

- Lack of comparability between study groups
- Imputation methods used in the calculation of the benchmark
- **Other potential for bias**
- Insufficient duration to establish efficacy

1. Retrospective data collection
2. Assessment of MFDs

Primary Efficacy Endpoint: Month 24 MFD-Free Survival

Issues with Study ALD-101 and the benchmark populations:

- Lack of comparability between study groups
- Imputation methods used in the calculation of the benchmark
- Other potential for bias
- **Insufficient duration to establish efficacy**

1. Few events by Month 24
2. Unclear what would happen with lack of treatment in early active disease

Secondary and Exploratory Efficacy Analyses

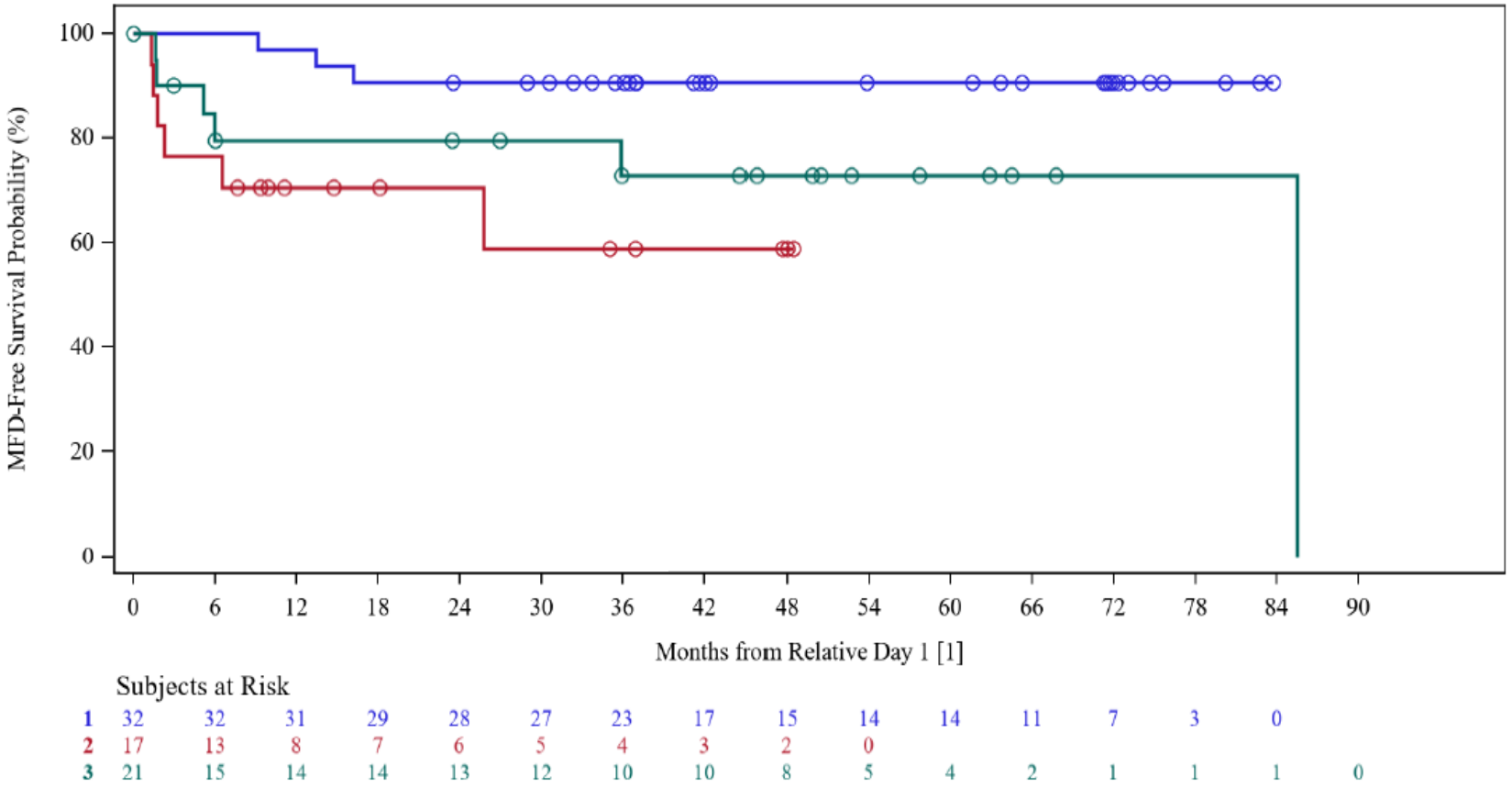
Baseline Demographics and Disease Characteristics for Relative Efficacy Analyses: TPES-103 NMSD, Pooled TPES NMSD, and eli-cel Populations

Parameter	HSCT: TPES- 103 NMSD (n=17)	HSCT: Pooled TPES-101 and TPES-103 NMSD (n=38)	Eli-cel: TP-102 (n=32)	Eli-cel: Pooled TP-102 and TP-104 (n=45)
Age (Years) Median (Min, Max)	8 (5,11)	8 (4,14)	6 (4,14)	6 (4,14)
Age at Diagnosis (Years) Median (Min, Max)	7 (0,11)	7 (0,12)	6 (1,13)	6 (1,13)
Baseline Loes Median (Min, Max)	2.0 (1.0, 9.0)	3.8 (0.5, 9.0)	2.0 (1.0, 9.0)	2.0 (1.0, 9.0)
Baseline NFS Median (Min, Max)	0 (0,1)	0 (0,1)	0 (0,1)	0 (0,1)

Source: Reviewer's analysis of ADSL datasets

Abbrev: TP, Transplant Population; TPES, Strictly ALD-102-eligible Transplant Population; NMSD, No Matched Sibling Donor subgroup; NFS, Neurologic Function Score.

Major Functional Disability (MFD)-Free Survival Over Time: eli-cel, Strictly ALD-102-Eligible HSCT populations (TPES) with No Matched Sibling Donor (NMSD)



- Populations
  - **eli-cel (TP-102)**
  - **TPES-101 NMSD**
  - **TPES-103 NMSD**
- Repeat HSCT is imputed as failure of MFD-free survival

Source: bluebird bio, Inc., Original BLA submission, Figure 2.1.1.1.2

MFD-Free Survival Over Time

Issues with Study ALD-103 and the HSCT comparator cohorts:

- Lack of comparability to eli-cel populations
- Imputation methods used
- Partial retrospective data collection, potential bias in assessment of MFDs
- Study ALD-103 was terminated early, resulting in significant amounts of missing data; only 9/17 (53%) subjects in TPES-103 NMSD had at least 24 months of data following HSCT
- MFD capture may have been influenced by knowledge of treatment assignment

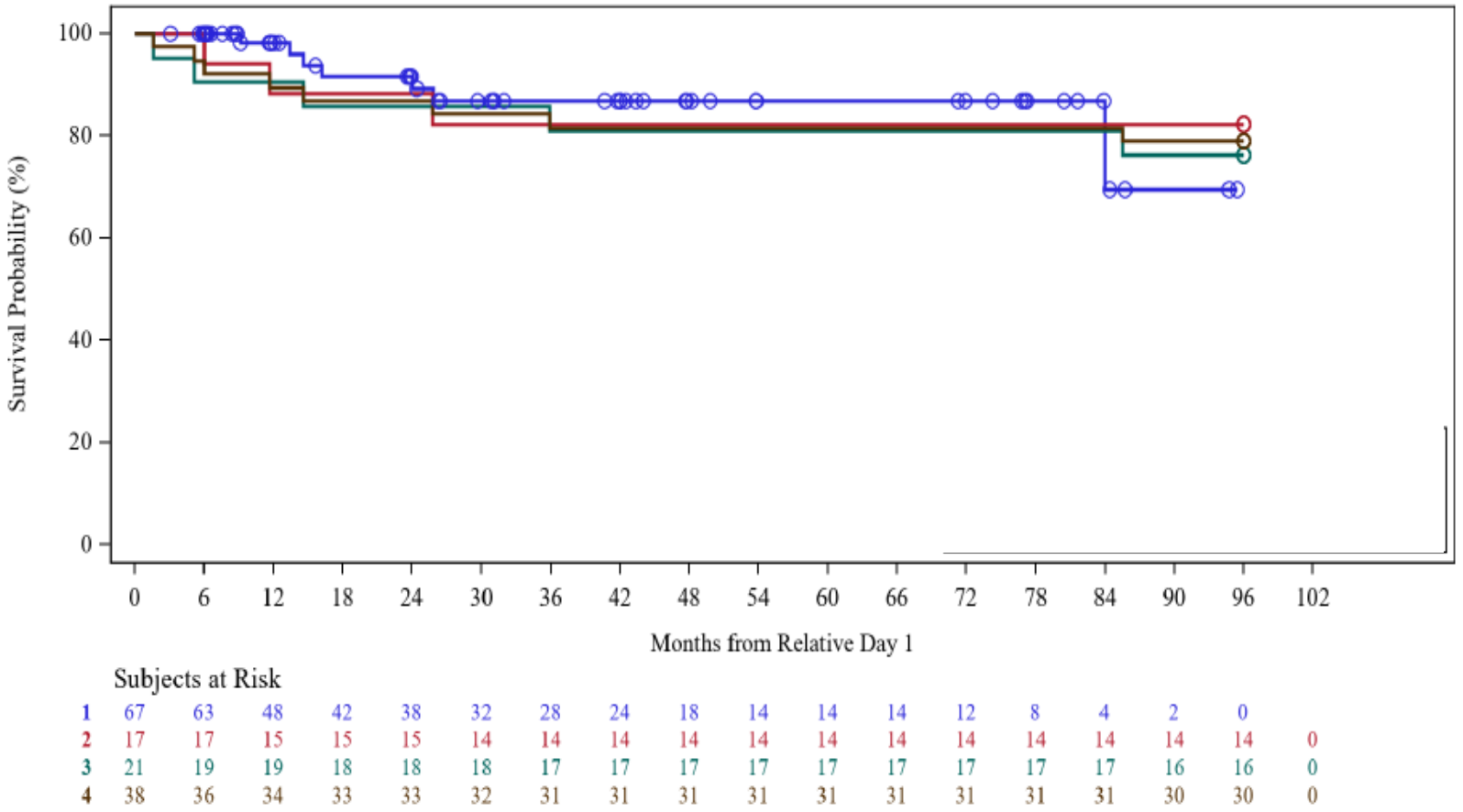
MFD-Free Survival Over Time: Exploratory Analysis

- Populations used:
  - Pooled TP-102 and TP-104 eli-cel treated subjects
  - Pooled TPES-101 and TPES-103 NMSD

- Imputation scheme used for failure of MFD-free survival:
  - For allo-HSCT cohorts: MFD and death only
  - For eli-cel cohorts: MFD, rescue allo-HSCT, death, and MDS

MFD-Free Survival Over Time Exploratory Analysis: Pooled eli-cel, Strictly ALD-Eligible HSCT (TPES) Populations with No Matched Sibling Donor (NMSD)

- Populations:
  - **eli-cel (pooled TP-102 and TP-104)**
  - **TPES-101 NMSD**
  - **TPES-103 NMSD**
  - **Pooled TPES-101 and TPES-103 NMSD**
- Repeat HSCT is NOT imputed as failure of MFD-free survival, MDS was

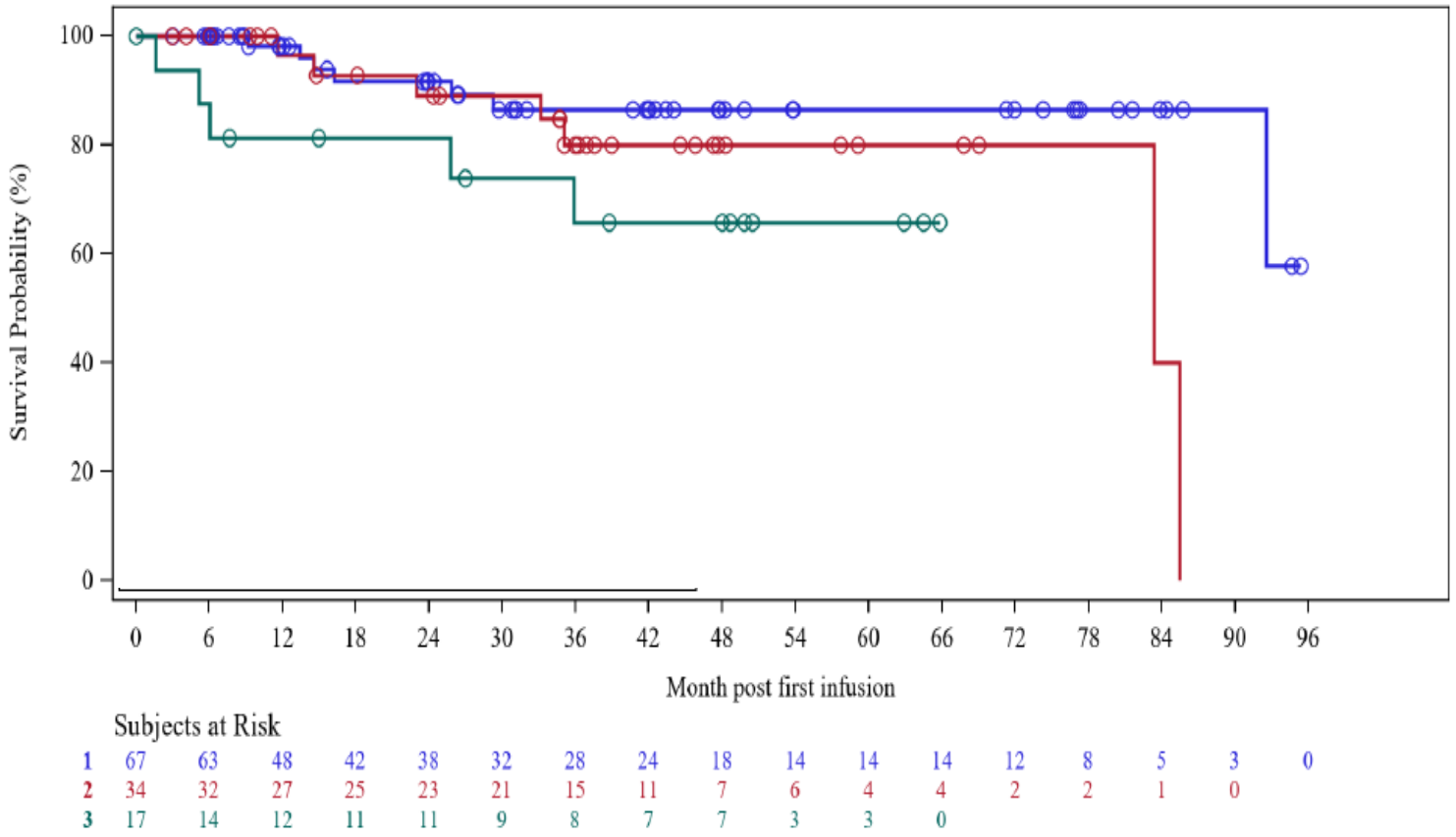


Source: bluebird bio, Inc., BLA ad hoc Figure 80.2.6

MFD-Free Survival Over Time: Subgroup Exploratory Analysis

- Traditionally understood that matched sibling donor (MSD) is superior to other donor types for allo-HSCT
- HLA-matching of donors regardless of relatedness to patient may be more important
  - Events in ALD-101 and ALD-103: trends toward worse outcomes for those with unmatched donor compared to those with matched
  - Increased number of events (including death) which appear to occur sooner in those with unmatched donor compared to matched

MFD-Free Survival Over Time Exploratory Analysis: Pooled eli-cel, Pooled Strictly ALD-102- Eligible HSCT (TPES) by HLA Donor Matching

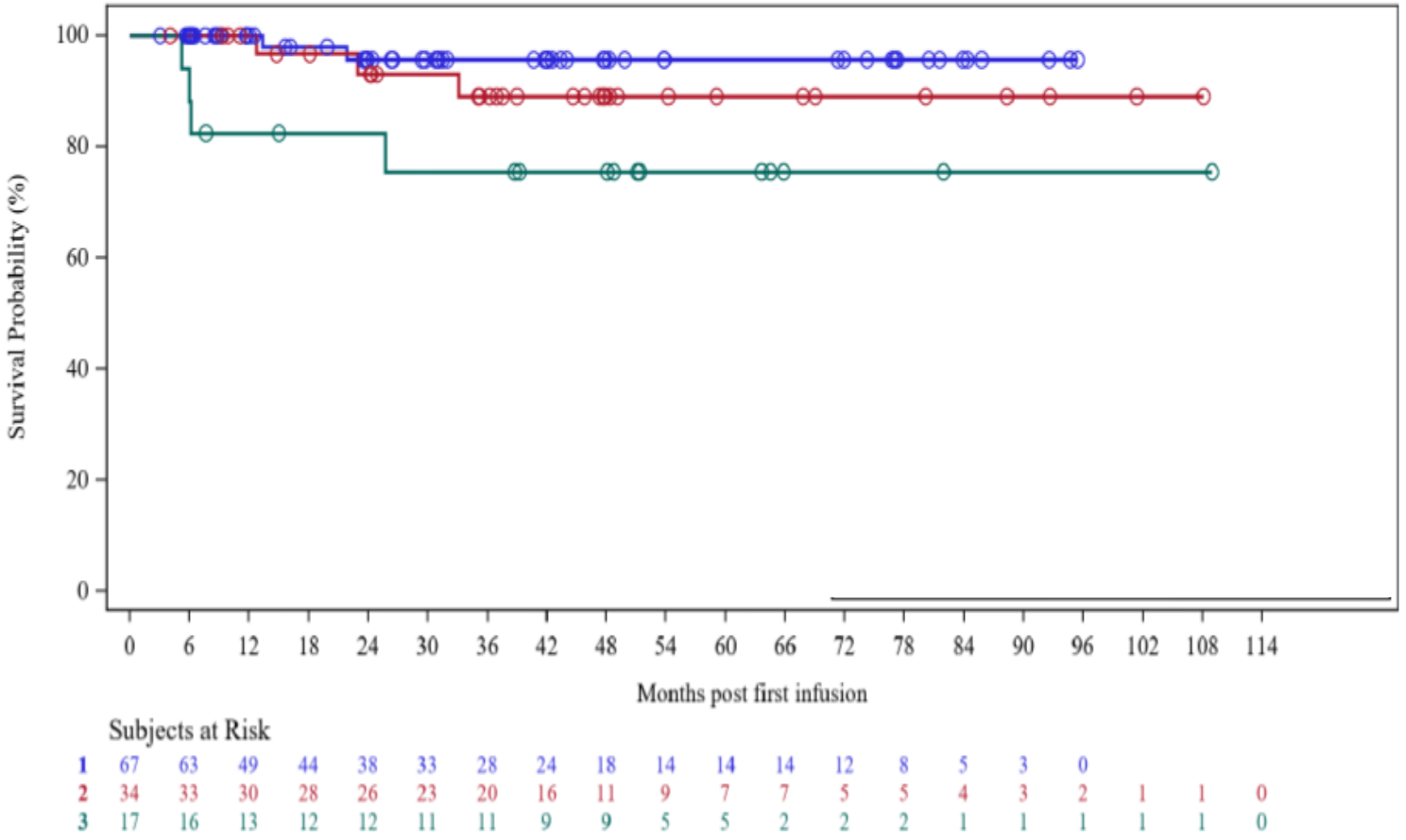


Source: bluebird bio, Inc., BLA ad hoc Figure 80.2.34

- Pooled TPES-101 and TPES-103 by HLA Donor Matching:
  - **HLA-matched**
  - **HLA-unmatched**
- Pooled TP-102 and TP-104:
  - **Eli-cel**
- Repeat HSCT NOT imputed as failure of MFD-free survival, MDS was

Donor Type	First MFD (months), median	Death (month), median
Matched	35	23
Unmatched	19	6

Overall Survival, Exploratory Analysis: Pooled eli-cel, Pooled Strictly ALD-102- Eligible HSCT (TPES) by HLA Donor Matching

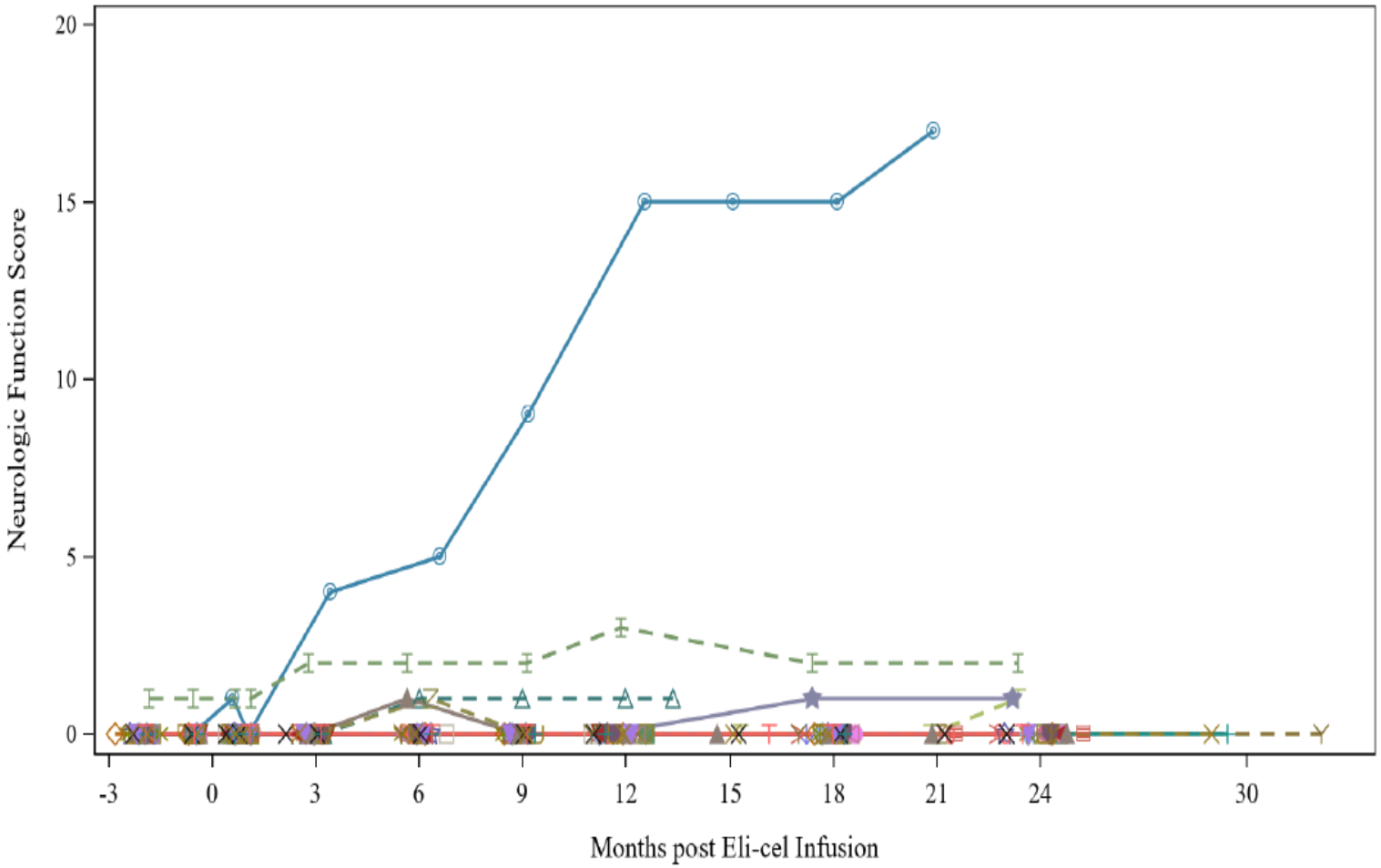


Source: bluebird bio, Inc., BLA ad hoc Figure 80.14.4

- Pooled TPES-101 and TPES-103 by HLA Donor Matching:
  - **HLA-matched**
  - **HLA-unmatched**
- Pooled TP-102 and TP-104:
  - **Eli-cel**
- Death only (no imputations)

- More than double the deaths in HLA-unmatched (24%) than HLA-matched (9%)

Change in NFS at Month 24



Source: bluebird bio, Inc. Original BLA submission, Figure 14.2.4

Change in Loes Score at Month 24

Parameter	Change	Pooled eli-cel TP-102 and TP-104[1] (n=35)	Pooled HSCT TPES-101 and TPES-103[1] (n=30)
Change in Loes from Baseline at Month 24, n (%)	Decreased	1 (2.9)	4 (13.3)
--	No Change	7 (20.0)	4 (13.3)
--	Increased by 0.5-3.5	10 (28.6)	16 (53.3)
--	Increased by ≥ 4	17 (48.6)	6 (20.0)

[1]Subjects evaluable for Loes Score at Month 24
Source: reviewer's analysis of ADSL and ADEFF datasets

Efficacy Summary

- Issues with benchmark derivation make primary efficacy endpoint difficult to interpret.

- Limited duration of follow-up in studies impacts interpretability:
  - Not clear disease progression would have occurred in 24 months without treatment in early active CALD
  - Paucity of long-term follow-up data

- Additional issues that affect interpretability:
  - Comparability of populations
  - Potential bias (retrospective data collection and assessment of MFDs)

- It is unclear whether eli-cel's efficacy is non-inferior to allo-HSCT at Month 24 for early active CALD in subjects without matched sibling donors

- Patients without HLA-matched donors may be a more appropriate target population.

Brief Overview of Safety

Safety Issues

- Engraftment failure
- Persistent cytopenias
- Opportunistic infections
- Insertional oncogenesis
- Short period of follow-up

Engraftment Failure

- Neutrophil engraftment failure
  - Failure to achieve three consecutive absolute neutrophil counts ≥ 0.5 x10^9/L *without granulocyte colony stimulating factor (G-CSF) support* by 42 days
  - 9% incidence (6 of 64 subjects)

- Platelet engraftment failure
  - Failure to achieve three consecutive platelet counts of ≥ 20 x10^9/L without platelet transfusion in the preceding 7 days and *without thrombopoietin mimetic support by 42 days*
  - 22% incidence (14 of 64 subjects)

Safety Issues

- Engraftment failure
- **Persistent cytopenias**
- Opportunistic infections
- Insertional oncogenesis
- Short period of follow-up

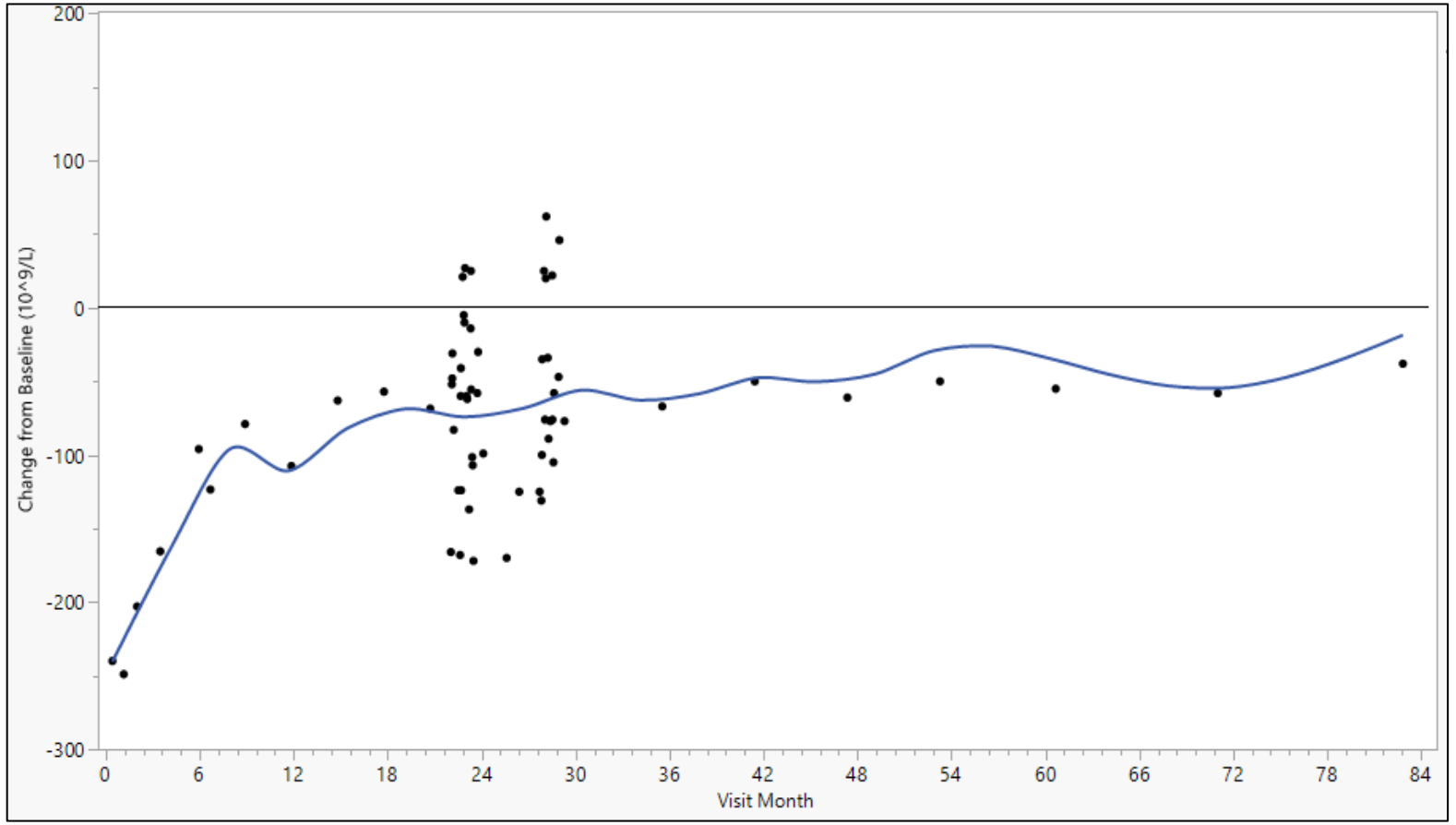
Persistent Cytopenias at 60 and 100 days

- Severe neutropenia
  - Neutrophils $< 1 \times 10^9/L$
  - 21% at Day 60
  - 11% at Day 100
- Severe thrombocytopenia
  - Platelets $< 50 \times 10^9/L$
  - 15% at Day 60
  - 8% at Day 100

Persistent Cytopenias: Platelets

- Blood counts not returning to baseline
  - **Platelets**
  - Hemoglobin
  - White blood cells

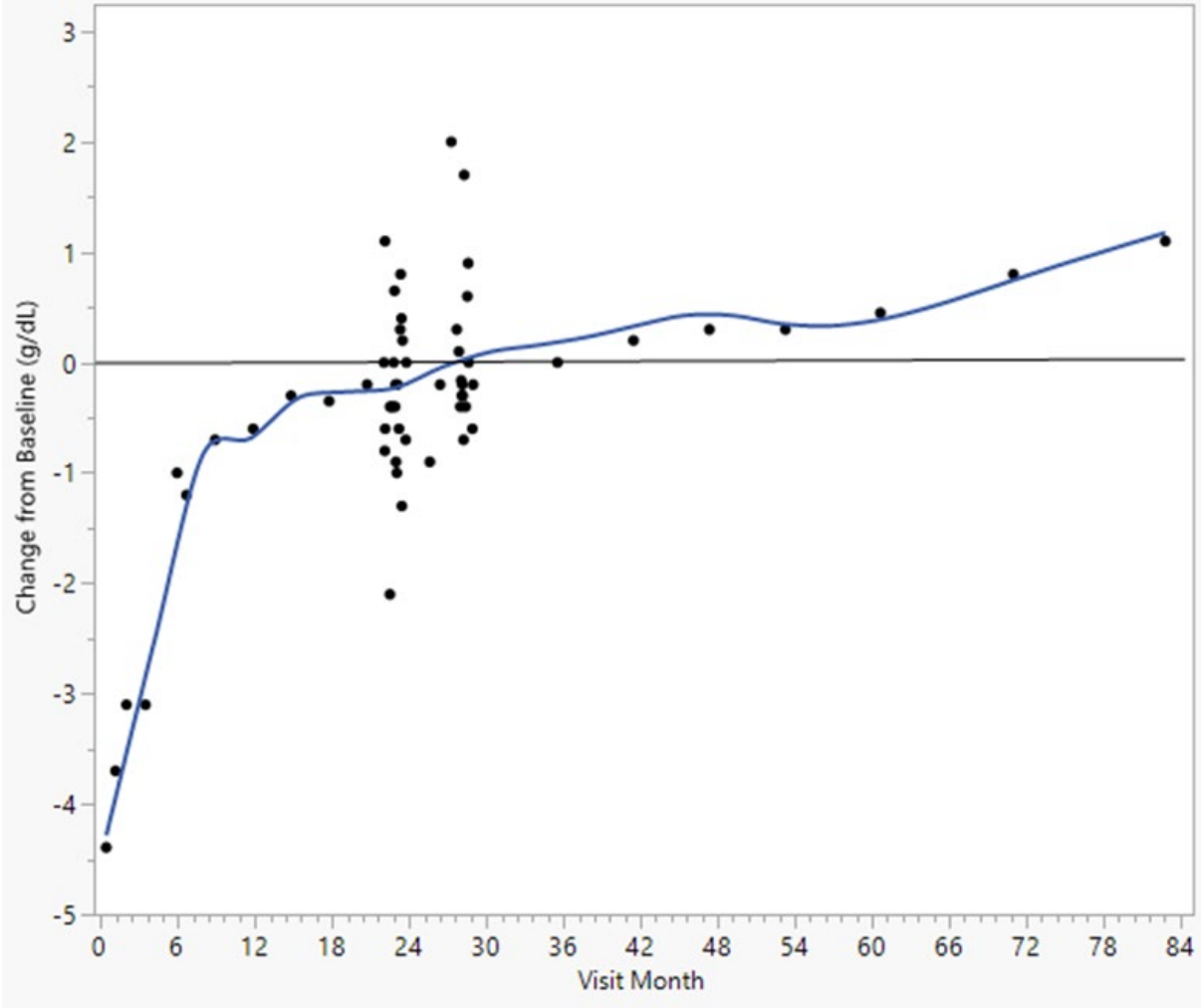
Platelet Count Change from Baseline



Persistent Cytopenias: Hemoglobin

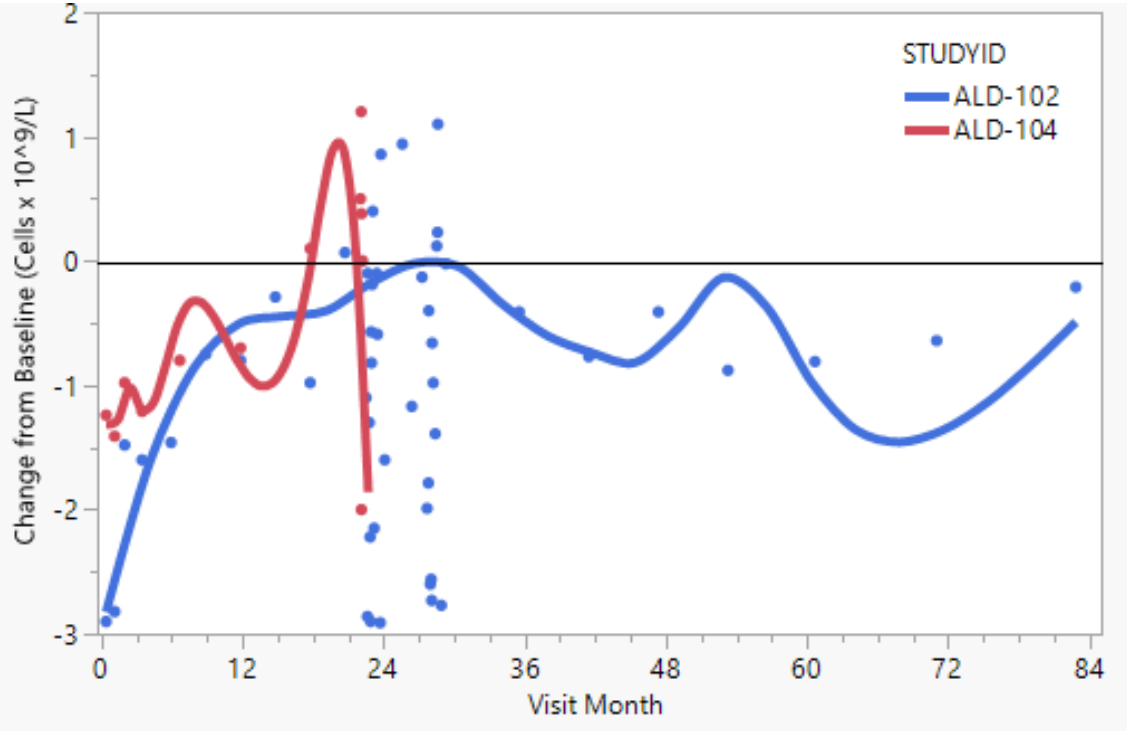
- Blood counts not returning to baseline
  - Platelets
  - **Hemoglobin**
  - White blood cells

Hemoglobin Change from Baseline

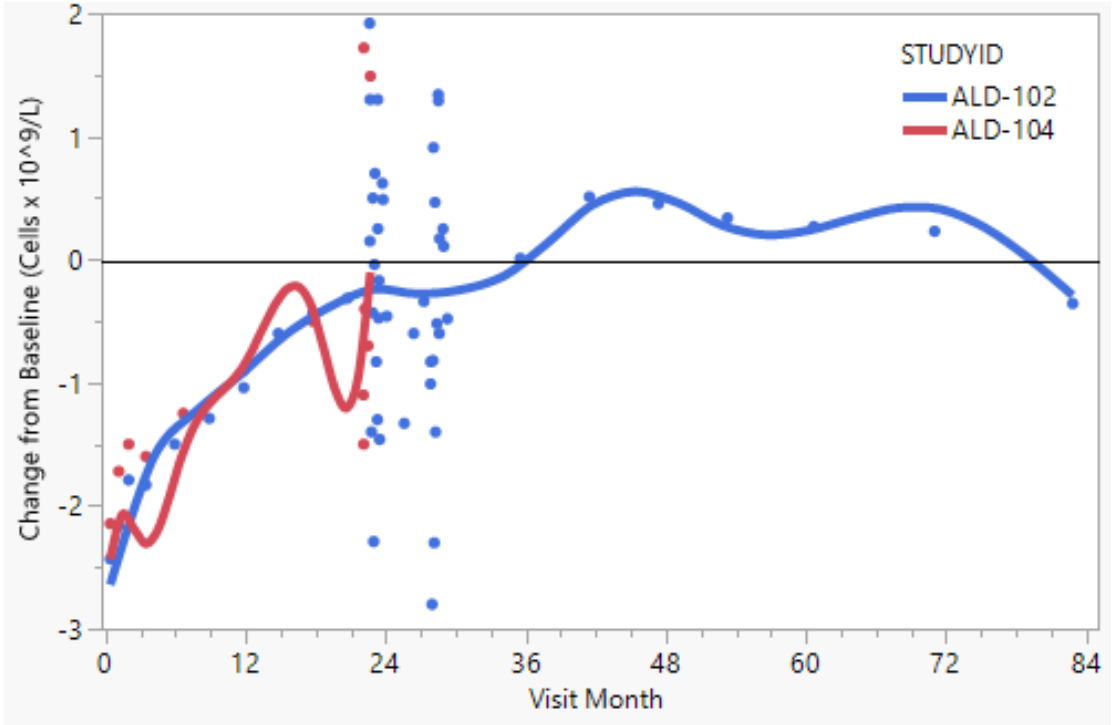


Persistent Cytopenias: White Blood Cells

- Blood counts not returning to baseline
  - Platelets
  - Hemoglobin
  - **White blood cells**



Neutrophil Count Change from Baseline



Lymphocyte Count Change from Baseline

Safety Issues

- Engraftment failure
- Persistent cytopenias
- **Opportunistic infections**
- Insertional oncogenesis
- Short period of follow-up

Opportunistic Infections

Time of Onset	Early Post-engraftment: Days 0 to 30	Early Post-engraftment: Days 31 to 100	Late Post-engraftment: Days 101 to 180	After Day 180
Serious or severe	• Clostridium difficile • Catheter infection x 2 • Bacteremia • Soft tissue infection • Pneumonia	• Central line infection • BK bladder infection • Pseudomonal bacteremia • Stenotrophomonas bacteremia	• Streptococcal bacteremia • Central line infection (atypical mycobacteria)	• Pseudomonal bacteremia • EBV reactivation
Otherwise notable	• Candidiasis x 3	• Candidiasis • Central line infection x 2 • HHV6 viremia • EBV viremia • CMV reactivation	--	--

Safety Issues

- Engraftment failure
- Persistent cytopenias
- Opportunistic infections
- **Insertional oncogenesis**
- Short period of follow-up

Insertional Oncogenesis

- 3 cases of hematologic malignancy
  - All diagnosed within the last 1 year
  - All treated with hematopoietic stem cell transplant

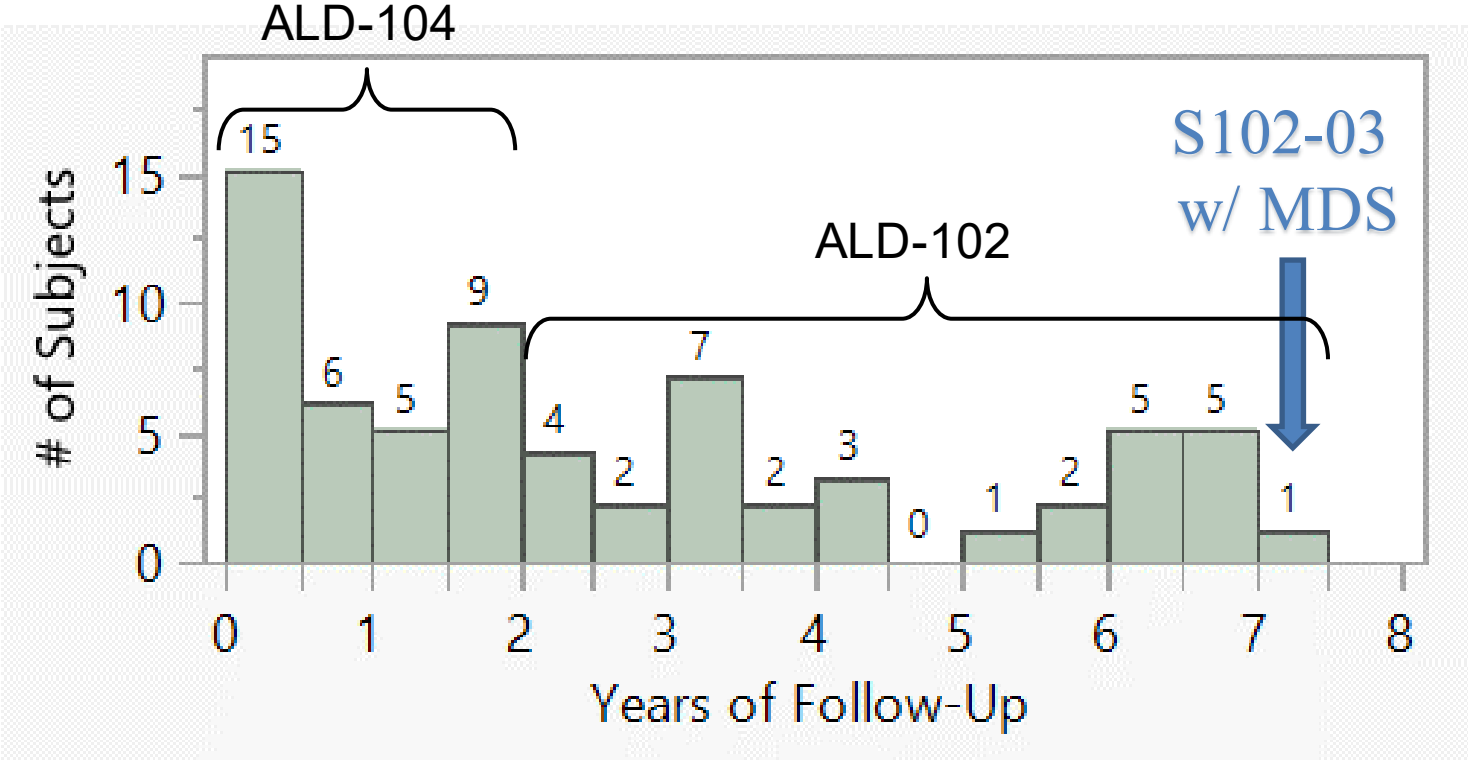
- 98% of eli-cel-treated subjects have integration into MECOM
  - A cancer-causing gene associated with poor prognosis
  - Implicated in 2 of the 3 hematologic malignancy cases

Safety Issues

- Engraftment failure
- Persistent cytopenias
- Opportunistic infections
- Insertional oncogenesis
- **Short period of follow-up**

Short Period of Follow-Up

- Study ALD-102
  - 27 in long-term follow-up
  - Follow-up duration:
    - Median 4 years
    - Range 2 to 7 years
- Study ALD-104
  - 32 followed for safety
  - Follow-up duration:
    - Median 6 months
    - Range 1 to 27 months



Benefit-Risk

Benefit- Risk Analysis

Efficacy Assessment:

- Limitations of study design and comparator data challenge the conclusion that eli-cel is efficacious, even though successful on the primary endpoint.

- Patients without HLA-matched donors may be a more appropriate target population due to increased morbidity and mortality with allo-HSCT in this population.

Safety Assessment:

- Significant risk of hematologic malignancy

Benefit- Risk Summary:

- The overall benefit-risk profile is difficult to characterize because of the uncertain benefit and the uncertain magnitude of the risk of life-threatening MDS.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