Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

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

Risk of Insertional Oncogenesis with Eli-cel, Lovo-cel, and Beti-cel

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Office of Tissues and Advanced Therapies (OTAT)

CBER, FDA

Overview of Malignancy Cases

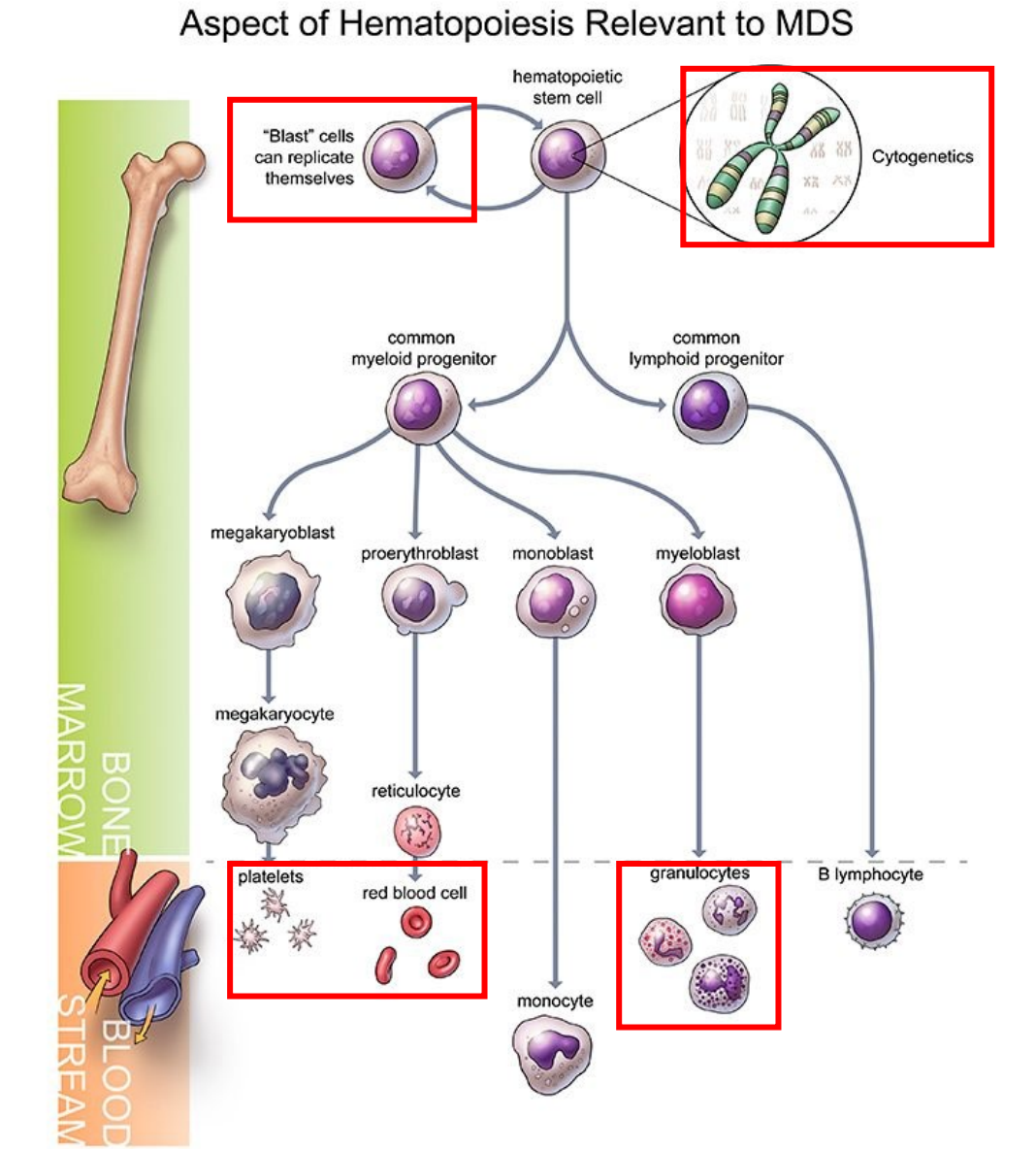
- Eli-cel for cerebral adrenoleukodystrophy (CALD)
  - Myelodysplastic syndrome (MDS) incidence - 3/67 (4%)
  - 4 additional cases of concern
  - High incidence of MECOM integration - 53/54 (98%)
- Lovo-cel for sickle cell disease
  - Acute myeloid leukemia (AML) incidence - 2/49 (4%)
  - Confounded assessment of causality
  - 3 additional cases of concern
- Beti-cel for beta-thalassemia
  - No diagnosed cases of malignancy - 0/59 (0%)
  - Prolonged thrombocytopenia of unclear etiology
  - Integration pattern similarity with lovo-cel

Outline

- Myelodysplastic syndrome (MDS)
- Potential for lentiviral vector (LVV)-mediated malignancy
- Eli-cel, lovo-cel, and beti-cel product comparison
- Observed malignancies and other cases of concern
- Integration site patterns

Myelodysplastic Syndrome

- Hematologic malignancy with 3 components
  - Dysplastic stem cells
  - Persistent, unexplained peripheral cytopenia
  - Genetic evidence of clonal hematopoiesis
- No association with CALD
- Rare in pediatrics (1 to 4 cases per million children per year)
- Variable prognosis
  - 35% 3-year overall survival after HSCT with matched unrelated donor
  - Poor prognosis after progression AML



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Potential for LVV-mediated Malignancy

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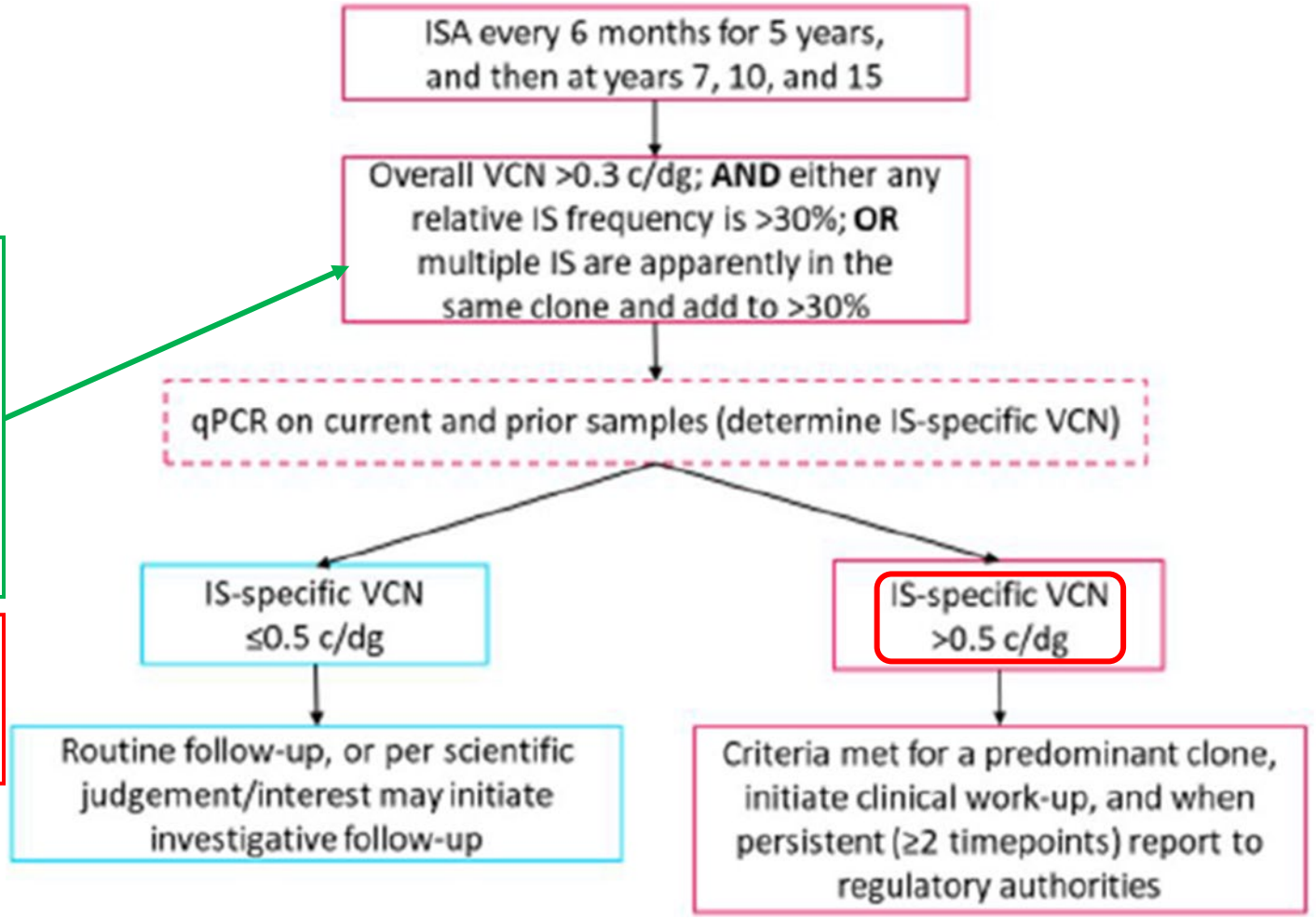
- Permanent genome alteration
- Potential mechanisms of oncogenesis
  - Viral activation of cellular gene transcription
  - Altered host cell RNA processing
  - Tumor suppressor gene inactivation
- Observed in multiple diseases with gammaretroviral gene therapy
- FDA Guidance recommends assays to assess the pattern of vector integration sites in relevant surrogate cells (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products)

Potential for of LVV-mediated malignancy (cont'd)

- Monitored via S-EPTS/LM-PCR integration site analysis

- Overall vector copy number (VCN) - copies of vector per cell in a mixed population of cells
- Integration site (IS) relative frequency - % of vector integrations that occur within a specific site

- IS-specific VCN - Copies of vector within a specific integration site per cell in a mixed population of cells



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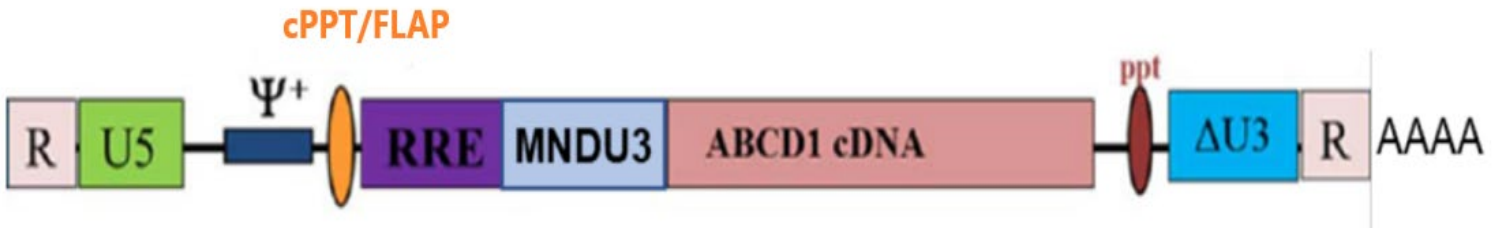
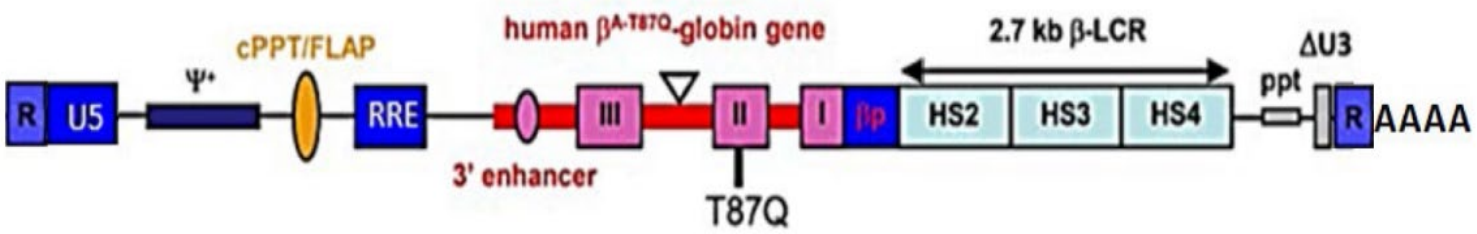
Product Comparison

Eli-cel Lenti-D lentiviral vector



Lovo-cel and beti-cel BB305 lentiviral vector



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Malignancy after Eli-cel

Eli-cel Diagnosed Malignancy Cases

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Subject Number	Subject 104-08	Subject 104-18	Subject 102-03
Age at treatment	13 years	11 years	5 years
Age at malignancy	14 years	12 years	12 years
Time to malignancy	22 months	14 months	7.5 years
Neutrophil engraftment	Primary engraftment failure (Day 188)	Day 27	Day 37
Platelet engraftment	**Primary engraftment failure**	**Primary engraftment failure (Day 106)**	Day 37
Integration sites	**MECOM**, ACTR, RAP2C, STGAL6	**MECOM**, SLC6A16	**PRDM16**, **GAB3, CAMK2A, MIR106A, TYK2,** SNX12
Gene expression	**Increased EVI1**	**Increased EVI1**	> 3-fold increased expression of PRDM16, GAB3, and CAM2KA
BM Bx date, Diagnosis	May 2021, **MDS w/ single lineage dysplasia**	July 2021, **MDS w/ single lineage dysplasia**	Nov 2021, **MDS w/ excess blasts-2**
BM morphology	80% cellularity, **dysplastic megakaryocytes**	10-20% cellularity, **dysmegakaryopoesis**	60-70% cellularity, overall 15% myeloblasts
Cytogenetic abnormalities	None	Karyotype: del(14)(q11.2q13) vs. inv(14)(p11.2q11.2)	Variants in KRAS, NRAS
WBC / Hgb / Plt	2.2 / 10.7 / 19	2.6 / 13 / 123	14.9 / 10 / 17

Integration Site Relative Frequency

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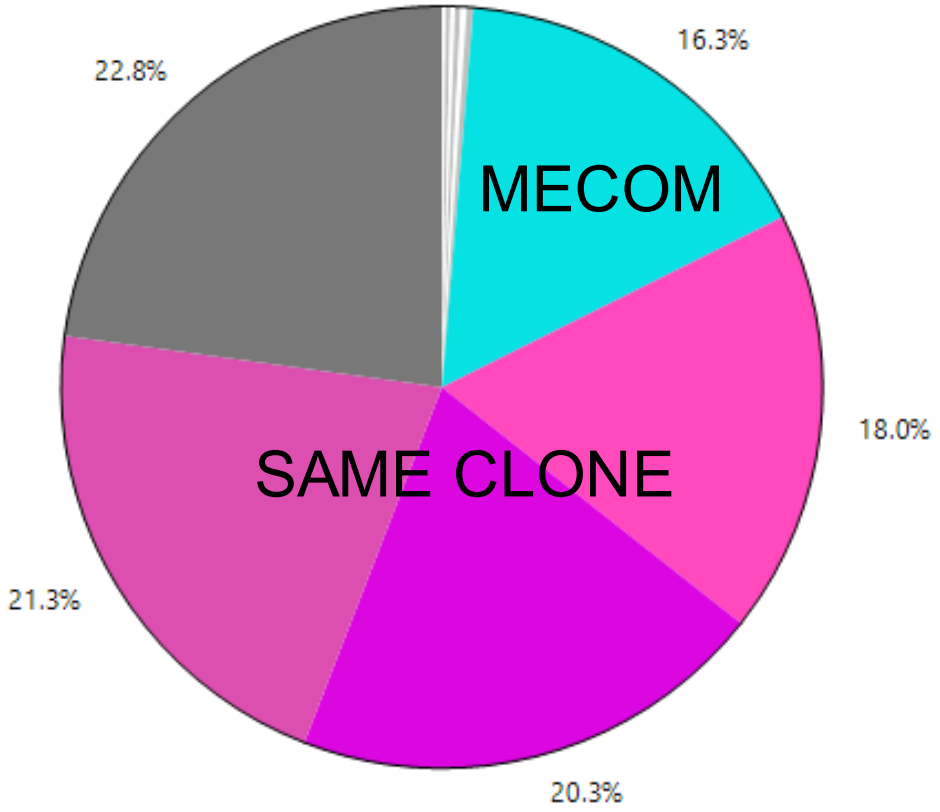
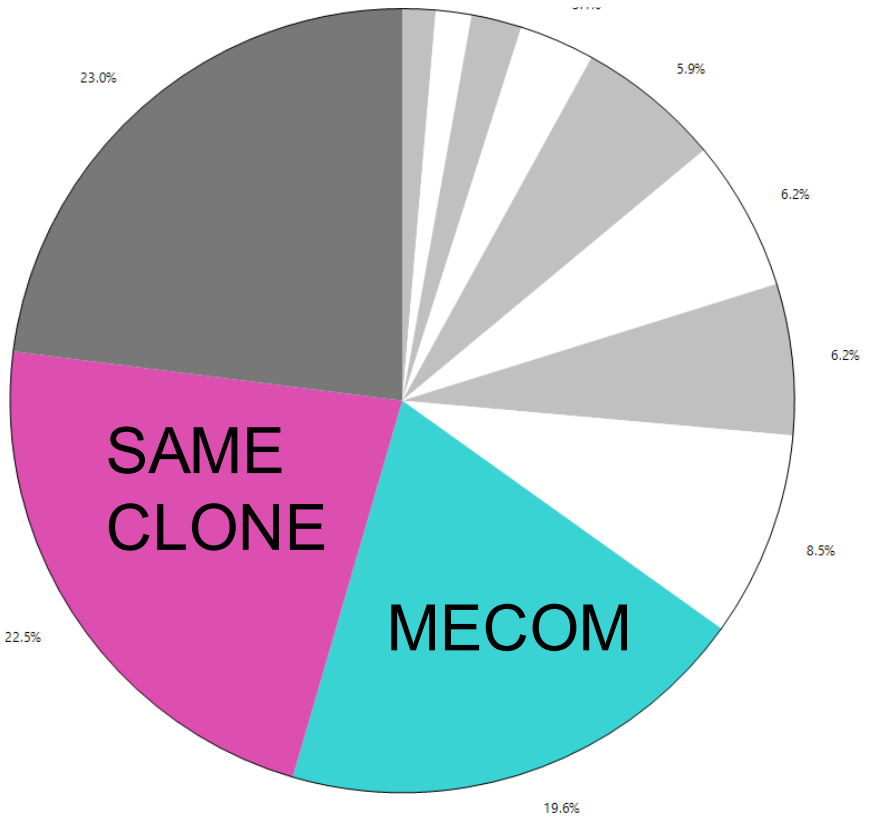
Subject 104-08 at 22 months



Subject 104-18 at 14 months



Eli-cel Diagnosed Malignancy Cases

U.S. FOOD & DRUG ADMINISTRATION

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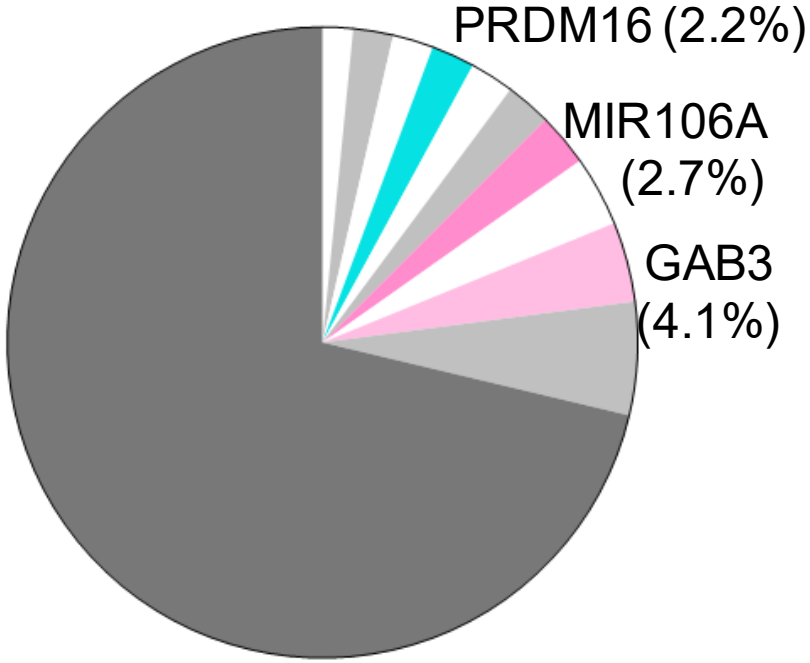
BM morphology	80% cellularity, **dysplastic megakaryocytes**	10-20% cellularity, **dysmegakaryopoesis**	60-70% cellularity, overall 15% myeloblasts
Cytogenetic abnormalities	None	Karyotype: del(14)(q11.2q13) vs. inv(14)(p11.2q11.2)	Variants in KRAS, NRAS
WBC / Hgb / Plt	2.2 / 10.7 / 19	2.6 / 13 / 123	14.9 / 10 / 17

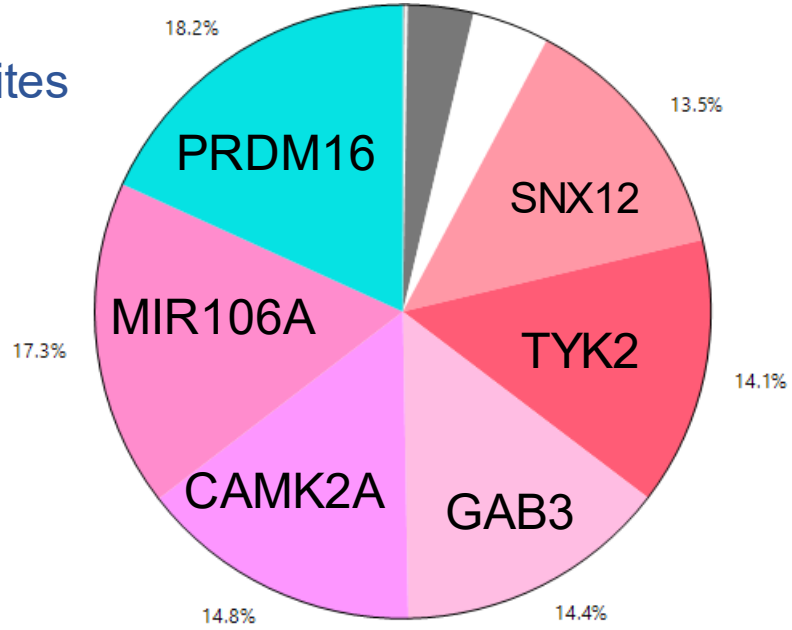
Subject 102-03

- Unremarkable integration site analysis (ISA) at Year 5
- Clone with six integration sites at Year 7.5
  - PRDM16 (a proto-oncogene and MECOM paralog)
  - MIR106A, CAM2KA, TYK2, and GAB3 may have contributed
- Bone marrow biopsy: MDS vs. acute myeloid leukemia – blasts comprise overall 15-20% of cellularity, focally up to 20-30%, “worrisome for evolving AML”

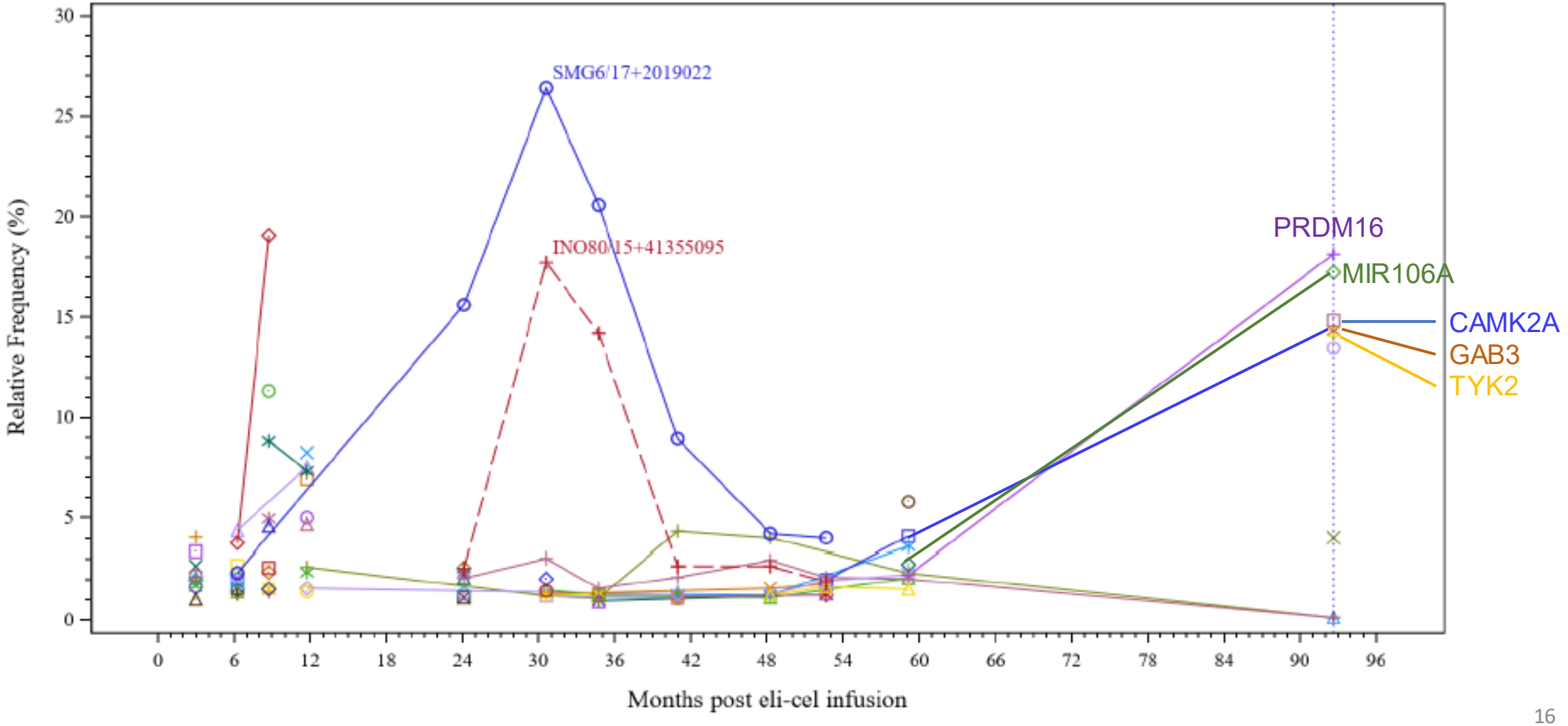
Integration Sites at Year 5



Integration Sites at Year 7.5



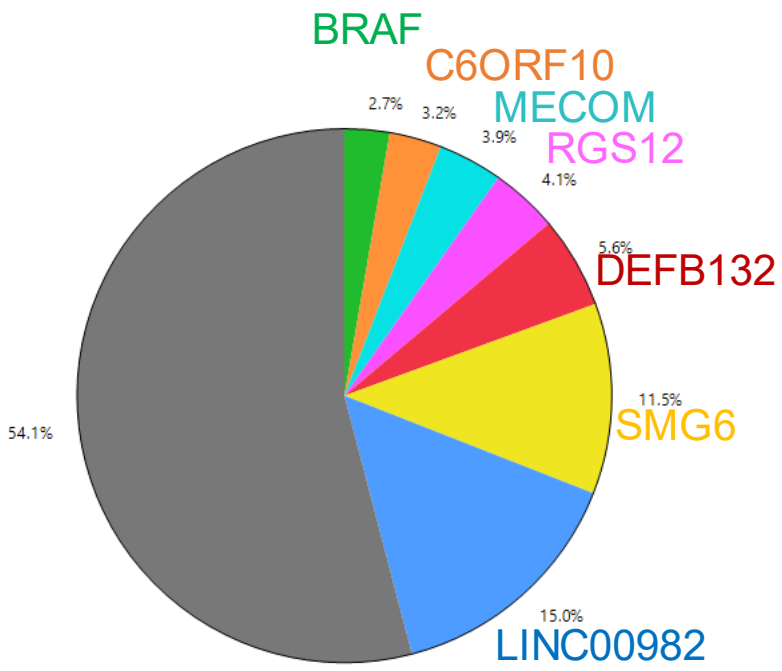
Subject 102-03 Integration Site Analysis Relative Frequency

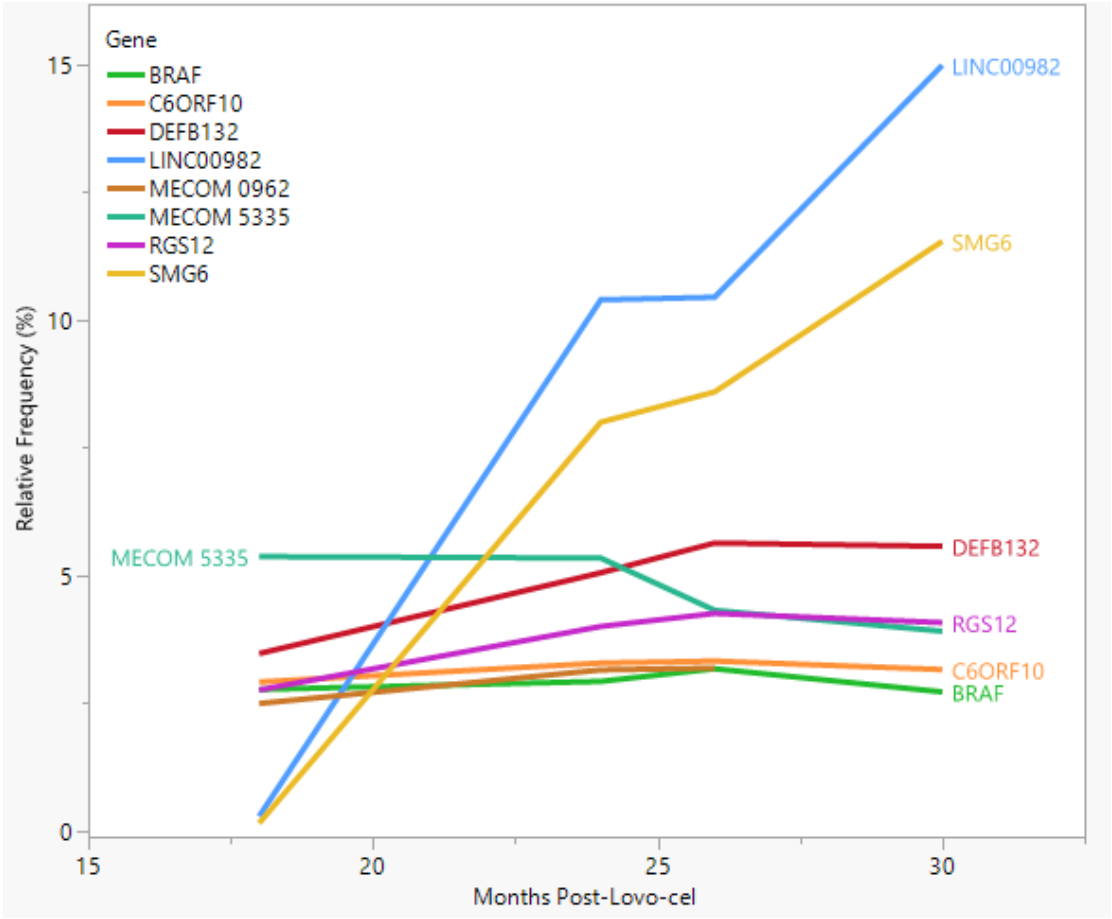


Eli-cel Cases of Concern of Malignancy

- **Subject 102-11**
  - Bone marrow:
    - 30-40% cellularity
    - Megakaryocytes with overall normal morphology and some small forms
  - ISA: Monoclonal with MECOM integration
  - Increased EVI1
- **Subject 102-31**
  - Primary platelet engraftment failure
  - Anemia (Hgb 11.2 g/dL)
  - Bone marrow: 40-50% cellularity
  - ISA: Multiple large clones and MECOM integration
  - Increased EVI1
- **Subject 104-09**
  - Primary neutrophil and platelet engraftment failure
  - Thrombocytopenia (Plt 100 x 10^9)
  - Bone marrow:
    - Parvovirus detected by PCR
    - 30% cellularity
    - Atypical megakaryocytes of small size
  - Cytogenetics: MPL variant
  - ISA: Multiple large clones and MECOM integration
- **Subject 104-22**
  - Thrombocytopenia (Plt 118 x 10^9)
  - ISA: Multiple expanding clones with MECOM integration sites

Subject 104-09 Integration Site Analysis





Subject 104-09 VCN data

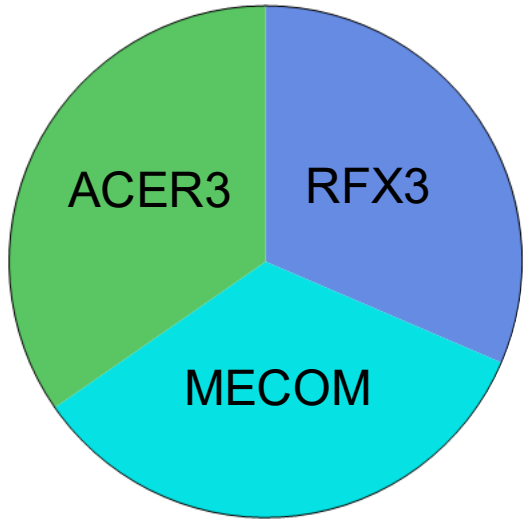
Gene	IS-specific VCN in CD15+ cells (c/dg)	S-EPTS/LM-PCR Relative Frequency in Whole Blood
LINC00982	0.59	14.0%
SMG6	0.59	11.5%
MECOM 5335	0.11	3.9%

Drug Product VCN (c/dg)	Vector Copies per Transduced Cell	Month 6 VCN (c/dg)	Month 12 VCN (c/dg)	Month 18 VCN (c/dg)	Month 24 VCN (c/dg)	Month 26 VCN (c/dg)
1.8	2.7	2.29	2.70	0.88	2.77	3.01

Subject 102-11

- Monoclonality with integration sites in MECOM, ACER3, and RFX3
- Rising vector copy number
  - ACER3 IS-specific VCN of 0.9846 c/dg in CD15+ cells
- Increased expression of EVI1

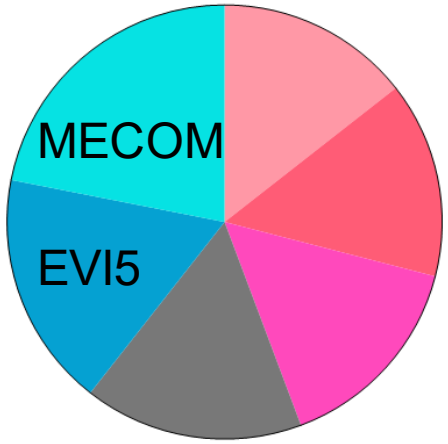
IS-Specific Frequency at Year 6.5



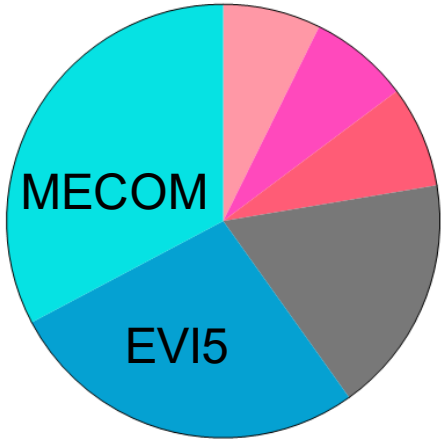
Subject 102-31

- Two notable clones:
  - Predominant clone with integration sites in MECOM and EVI5 (blues)
  - Second clone with integration sites in SECISBP2, PLAG1, and PUM3 (pinks)
- Increased expression of EVI1

Integration Site Analysis at Month 42



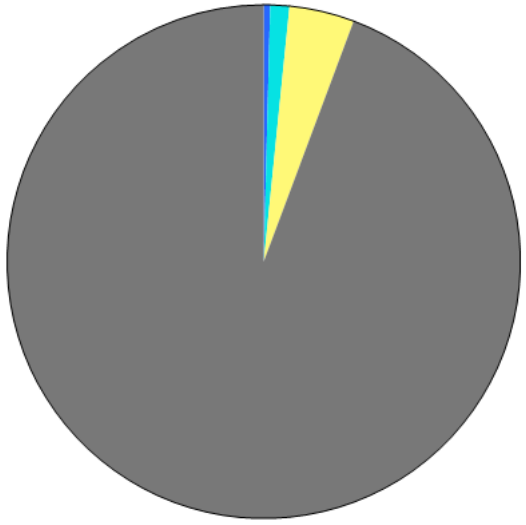
Integration Site Analysis at Month 48



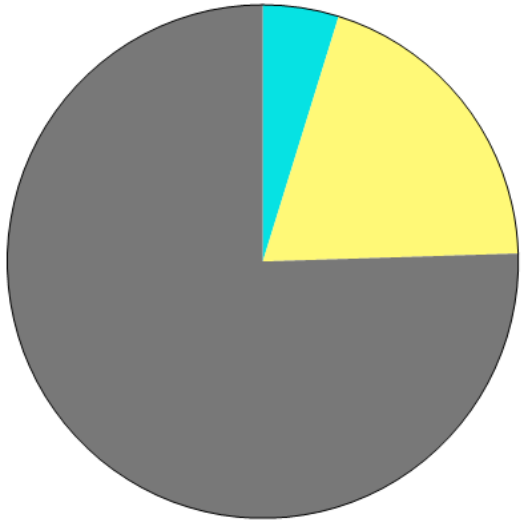
Subject 104-22

- Increasing relative frequency in MECOM and MPL proto-oncogenes

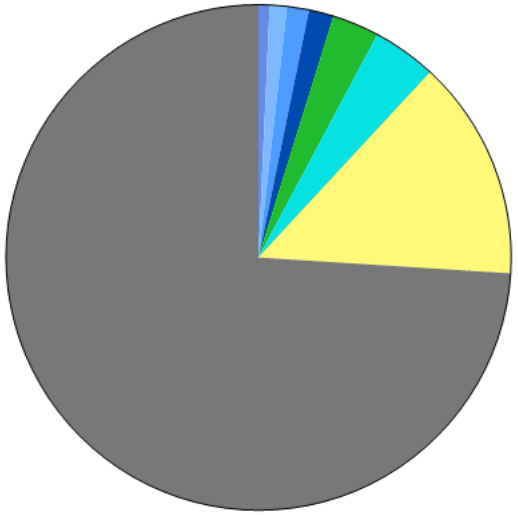
Integration Site Analysis at Month 6



Integration Site Analysis at Month 12



Integration Site Analysis at Month 18



MPL – yellow
MECOM – blues
C7orf60 - green

Eli-cel Proto-oncogene Integration

- MECOM = MDS1 and EVI1 complex locus
  - A known myeloid oncogene
  - EVI1 overexpression
    - Confers poor prognosis in MDS and AML
  - Integrations in 53 of 54 (98%) with CALD
- PRDM16
  - Causal of hematologic malignancy that is phenotypically similar to MECOM
  - Integrations in 5 of 49 (9%) with CALD
- MPL integrations – 15 of 49 (31%) with CALD
- MIR100HG integrations – 5 of 49 (10%) with CALD

Malignancy after Lovo-cel

Malignancy after Eli-cel

Sickle Cell Disease Malignancy Risk

California Cancer Registry and the California Patient Discharge Data and Emergency Department Utilization databases

- 0.1% incidence of AML in sickle cell disease (6 of 6,243)

Table 1. Age, sex, race/ethnicity, and time-adjusted SIRs for selected cancers among patients with SCD, California, 1988-2014

	Observed cases	Expected cases	SIR	95% CI
Hematologic tumors	31	18.03	1.72	(1.17-2.44)
Lymphoma	15	10.38	1.45	(0.81-2.38)
Leukemia	12	5.17	2.32	(1.20-4.05)
ALL	3	1.64	1.83	(0.38-5.35)
CLL	3	0.62	4.83	(1.00-14.11)
AML	6	1.67	3.59	(1.32-7.82)

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia.

Source: Brunson, 2017

Lovo-cel Leukemia Cases

- 2 cases of acute myeloid leukemia (AML) in 49 subjects
  - 4% incidence vs 0.1% incidence in California Cancer Registry

Characteristic	Subject 206-A-01	Subject 206-A-02
Time to onset of MDS/AML	5.5 years to AML	3 years to MDS followed 5 months later by AML
Presence of predominant clone	Yes	No
Presence of LVV integration sites in blasts	Yes - VAMP4 integration site	No
Cytogenetic abnormalities in blasts	**Monosomy 7** Partial loss of 11p **RUNX1** (p.Ala149*fs) **PTPN11** (p.Ala72Val) Del/repl at 147,036,771 Del at 231,212,613 4 CNAs near VAMP4	**Monosomy 7** Abnormal 19p **RUNX1** (p.Asp198Gly) **PTPN11** (p.Phe71Leu) KRAS (p.Gly12Ala)

Lovo-cel Cases of Concern for Malignancy

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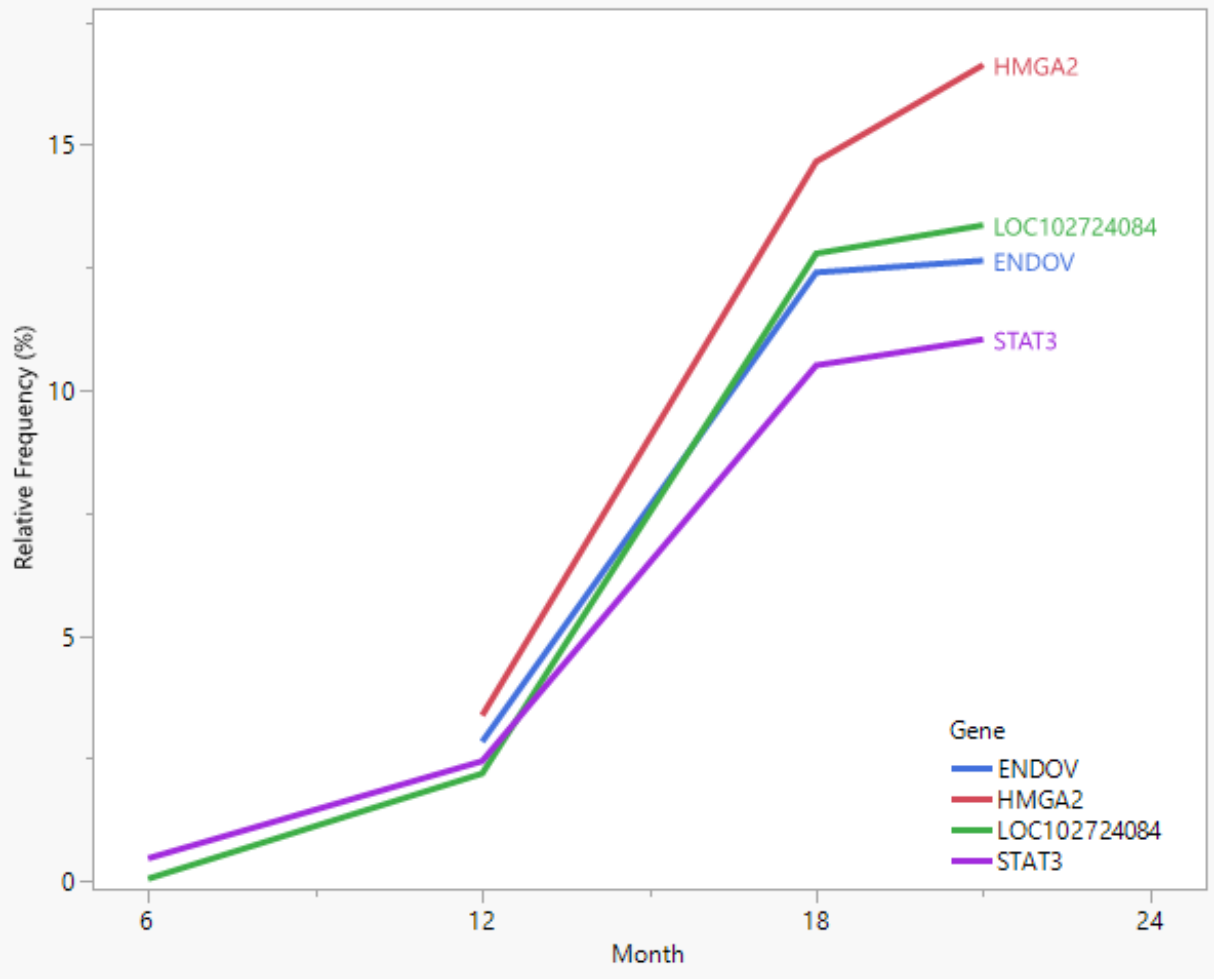
Characteristic	Subject 206-C-27	Subject 206-C-32
Age	20 years	14 years
Sickle cell disease genotype	βS/βS and alpha-thalassemia with two α-globin gene deletions	βS/βS and alpha-thalassemia with two α-globin gene deletions
Neutrophil engraftment	Day 35	Day 26
Platelet engraftment	Primary engraftment failure (Day 134)	Day 37
Integration sites	KDM2A – 0.425% relative frequency	KDM2B – 0.205% relative frequency ABL1 – 0.122% relative frequency
Vector Copy # (c/dg)	Unreliable data due to frequent pRBC transfusions	Increasing (3.3 at Month 6 and 12, 4.1 at Month 18)
Bone Marrow	Smear shows erythroid hyperplasia with 10-15% dysplasia. Normal megakaryocytes.	Biopsy shows erythroid hyperplasia with 5-15% dysplasia. Overall normal megakaryocytes with 2% small hypolobated forms.
Diagnosis	**Erythroid hyperplasia w/ dyserythropoiesis**, most likely stress erythropoiesis; ongoing vaso-occlusive events & transfusion-dependent anemia	**Normocellular with moderate dyserythropoiesis**, likely stress erythropoiesis; mild pancytopenia and vitamin B12 deficiency
Cytogenetic abnormalities	**Transient trisomy 8, tetrasomy 8.** **Pathogenic variant: ATM** (VAF 27%). Variants of unknown significance: TET2 (VAF 42%); TERT (VAF 59%); IKZF (VAF 38%)	**Trisomy 8, tetrasomy 8.** Variant of unknown significance: TET2 (VAF 47.5%)

Subject 206-C-23

- Predominant clone with 4 integration sites
  - Include proto-oncogenes STAT3 & HMGA2
  - Combined relative frequency of > 50%
- Near-normal CBC
- Increasing peripheral blood vector copy number
  - 1.14 c/dg at Month 6,
  - 1.34 c/dg at Month 12,
  - 1.86 c/dg at Month 18



Overview of Malignancy Cases

- Eli-cel for CALD
  - Myelodysplastic syndrome (MDS) incidence - 3/67 (4%)
  - 3 cases of greatest concern
  - Consistent integration into proto-oncogene - 53/54 (98%)
- Lovo-cel for sickle cell disease
  - Acute myeloid leukemia incidence - 2/49 (4%)
  - 2 cases of “stress erythropoiesis”
  - 1 clonal predominance
  - Confounded assessment of causality
- Beti-cel for beta-thalassemia
  - No diagnosed cases of malignancy - 0/59 (0%)
  - Prolonged thrombocytopenia of unclear etiology
  - Integration pattern similarity with lovo-cel

Outline

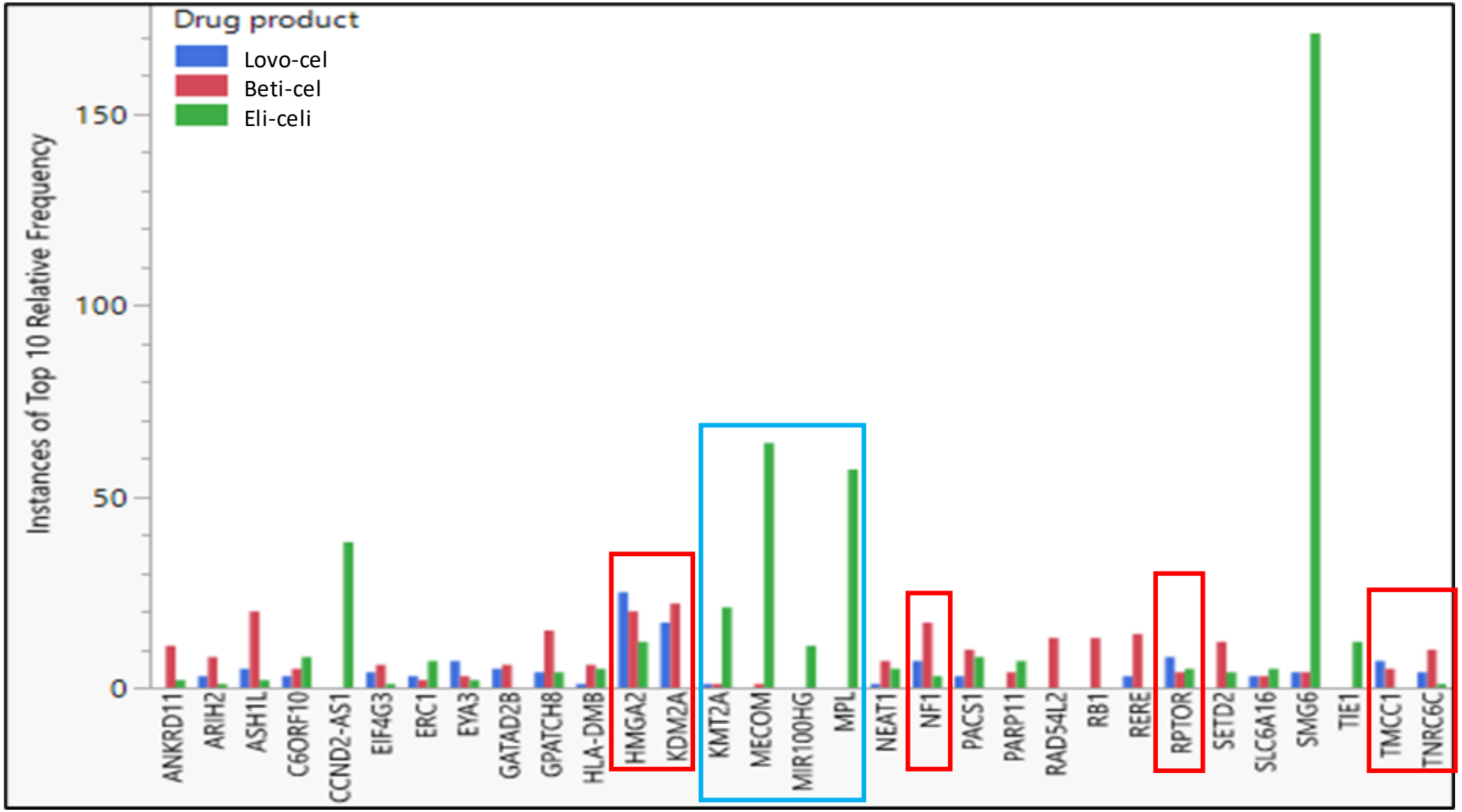
- Myelodysplastic syndrome
- Potential for LVV-mediated malignancy
- Eli-cel, lovo-cel, and beti-cel product comparison
- Observed malignancies and other cases of concern
- **Integration site patterns**

Integration Site Patterns

- MECOM integration sites
  - 53 of 54 (98%) with eli-cel

- VAMP4 integration sites
  - 25 of 35 (71%) with lovo-cel
  - 31 of 55 (56%) with beti-cel

Integration Site Patterns



Summary

- High risk of hematologic malignancy with eli-cel
  - Current incidence of 4% may increase
  - Limited duration of follow-up vs. time to develop malignancy
    - Median follow-up 23.5 months, range 1 month to 7 years
  - Numerous additional cases of concern
  - Universal integration into the MECOM proto-oncogene
- High incidence of acute myeloid leukemia after lovo-cel
  - 4% after lovo-cel vs. 0.1% in the overall sickle cell population
  - Unclear causality
  - Parallels between AML cases and between “stress erythropoiesis” cases suggest common tumorigenesis pathways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EXTRA SLIDES

Topics for Committee Discussion:

- Which population, if any, has clinically meaningful benefit with eli-cel
- Risk of insertional oncogenesis from LVV integration in eli-cel-treated subjects
- Relevance of safety data from lovo-cel and beti-cel to eli-cel
- Recommendations on post-treatment monitoring for risk of insertional oncogenesis and risk mitigation

Committee Discussion Questions:

1. There were a multitude of problems with the benchmark calculation that make the primary efficacy endpoint difficult to interpret. Additionally, issues of comparability between populations, potential for bias, imputation methods, few events during a limited duration of follow-up, and limited sample size for treatment and control populations challenge interpretation of efficacy. Please discuss whether the efficacy data support the presence of a clinically meaningful benefit of eli-cel. If so, in what population (e.g., children without a matched and willing sibling donor, children without a matched donor)?

Committee Discussion Questions:

2. In addition to the occurrence of MDS in eli-cel-treated subjects, there have been diagnoses of myeloid malignancies diagnosed in subjects with sickle cell disease after administration of a related product, lovo-cel. Please discuss whether the diagnosis of myeloid malignancy in subjects receiving lovo-cel increases concern for malignancy with eli-cel.

Committee Discussion Questions:

3. Eli-cel has a risk of hematologic malignancy, a potential fatal adverse event. The number of cases of malignancy (currently 3/67, or 4.4%) seems likely to increase over time. There are at least four cases with concern for impending MDS in addition to the three recognized cases of MDS. In addition, although the clinical significance is unclear, 98% of subjects in the study population have integration sites in MECOM, a proto-oncogene. Please discuss the acceptability of the risk of insertional oncogenesis in the proposed patient population.

Committee Voting Questions:

1. Are the lovo-cel safety data relevant to the safety assessment of eli-cel?

Committee Voting Questions:

2. Does the evidence demonstrate that the benefits of elivaldogene autotemcel for the treatment of any sub-population of children with early active CALD outweigh the risks, including the potential for insertional oncogenesis?

   a) If you voted "yes," please discuss the following:

      i. The sub-population of children with early active CALD for whom there is a favorable benefit-risk.

      ii. Recommendations for post-approval risk monitoring and mitigation.

   b) If you voted "no," please discuss what additional information you would consider necessary to support a favorable benefit-risk profile.