Familial Acute Myeloid Leukemia with Germline *CEBPA* Mutation

SH/EAHP Workshop 2017
Case #SH2017-0283

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Clinical History

19 year-old man with no significant past medical history presented with one-month history of bruising, petechiae, rib and shoulder pain, and night sweats

PMH: Asthma

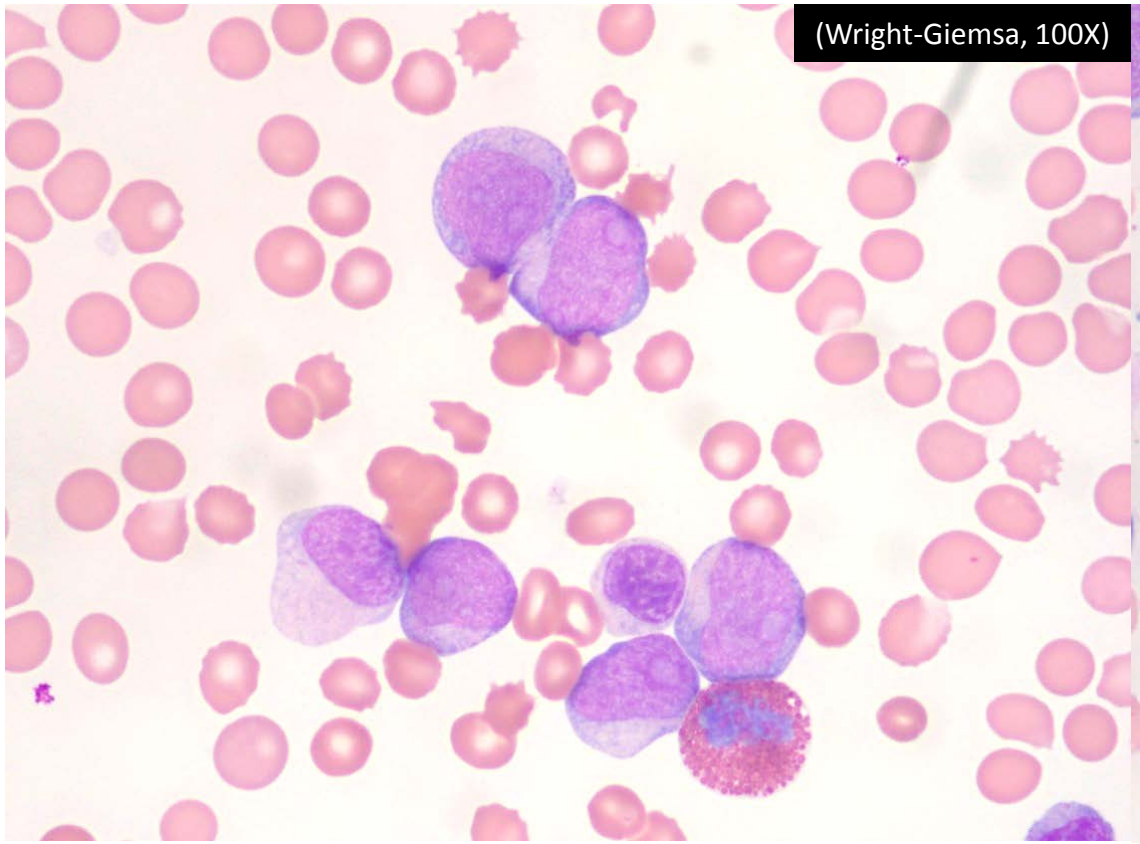
PSH: Fracture surgery

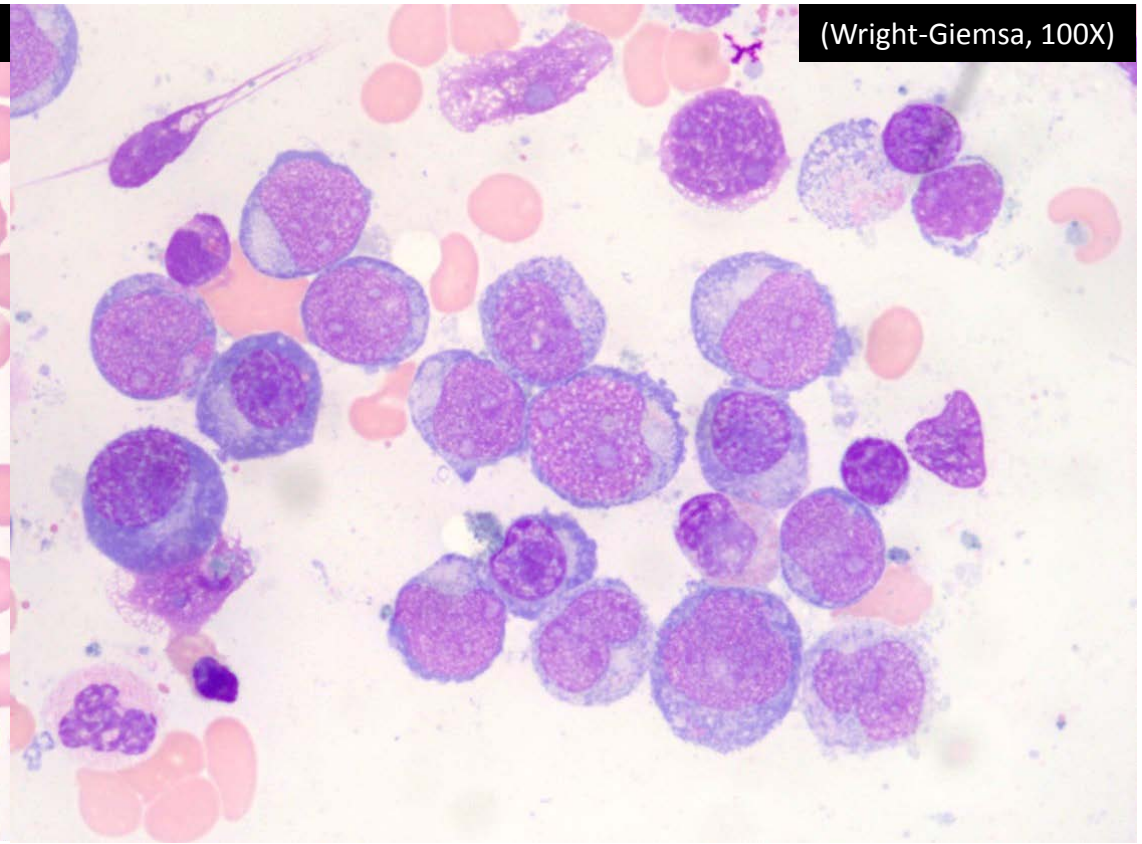
FH: No history of leukemia

Chest XRAY demonstrated small pleural effusions and atelectasis

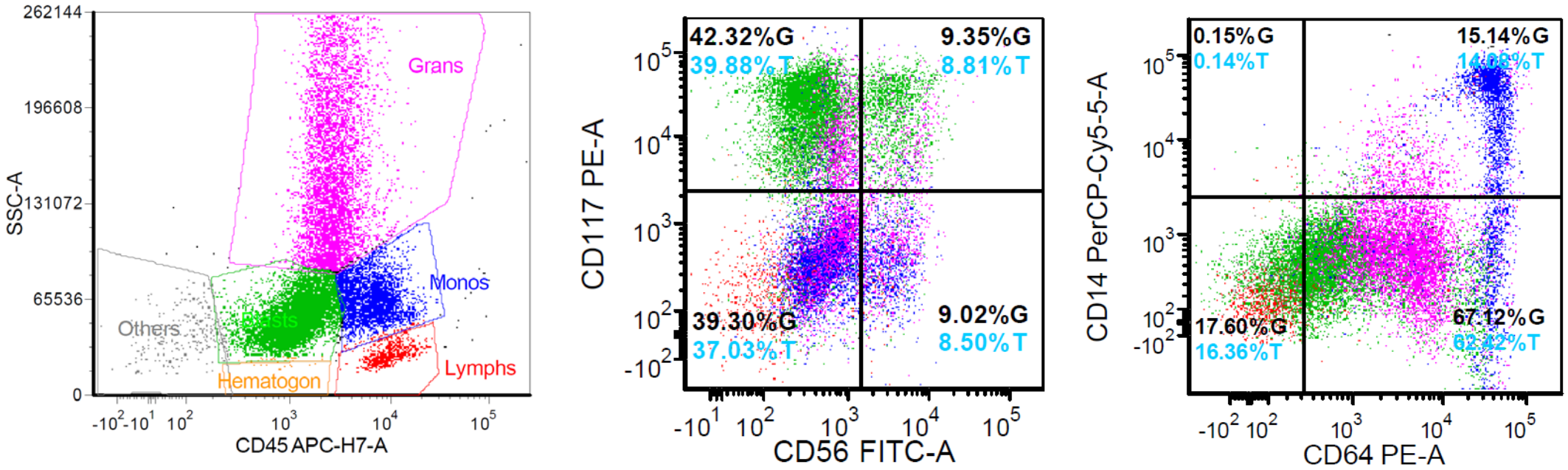
CBC showed marked leukocytosis to 119,000/uL comprising mostly immature cells

Peripheral Smear and Bone Marrow Aspirate Smears Showed Numerous Blasts





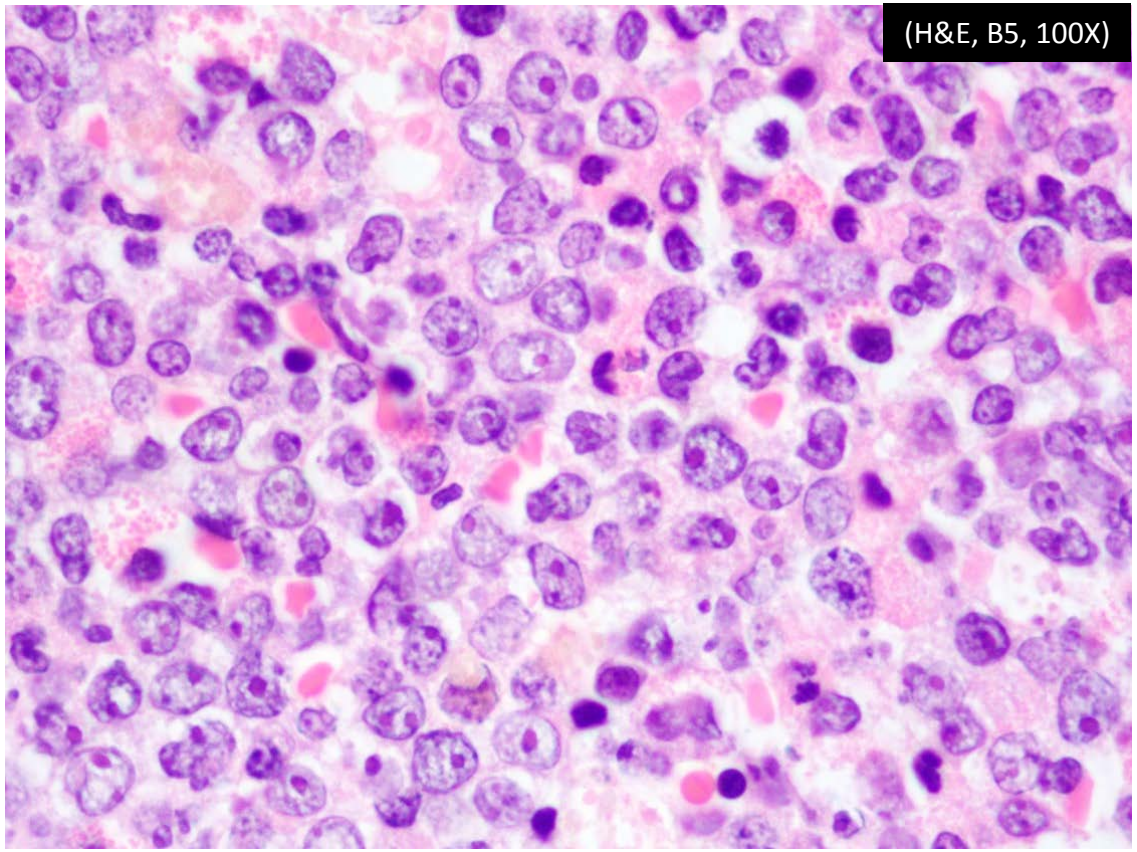
Bone Marrow Flow Cytometry Demonstrated Increased Myeloblasts and Monocytic Cells



- Blasts: CD7 (subset), CD13 (dim), CD33 (bright), CD34 (bright), CD38 (bright), CD56 (subset), CD117, HLA-DR (subset), icMPO

- Monocytic cells: CD14 (heterogeneous), CD36 (heterogeneous), CD56 (subset)

Bone Marrow Biopsy Showed Sheets of Blasts



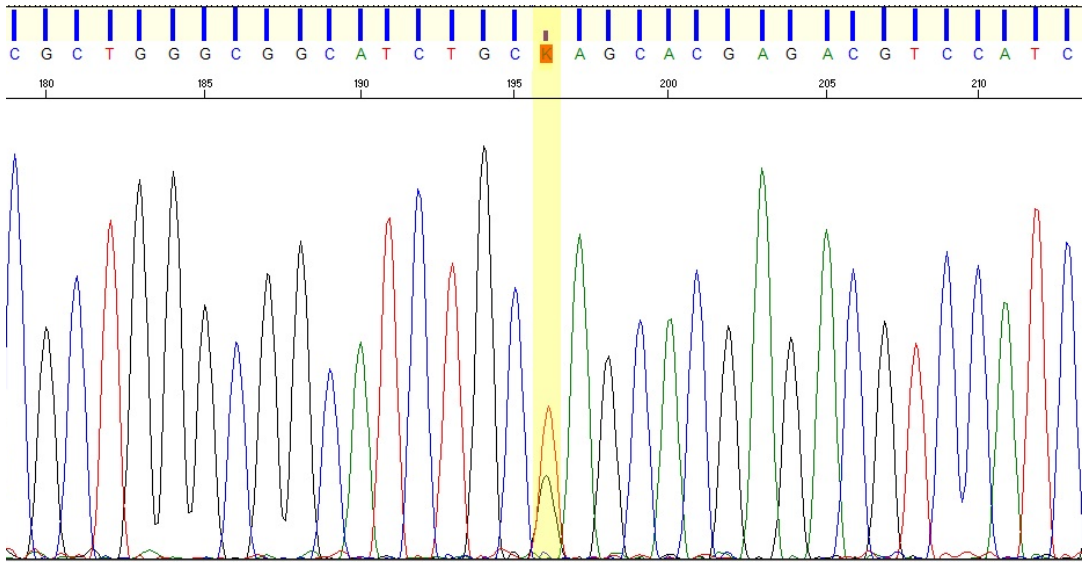
Final Diagnosis:
Acute myeloid leukemia

Conventional cytogenetics:
Normal male karyotype, 46,XY[20]

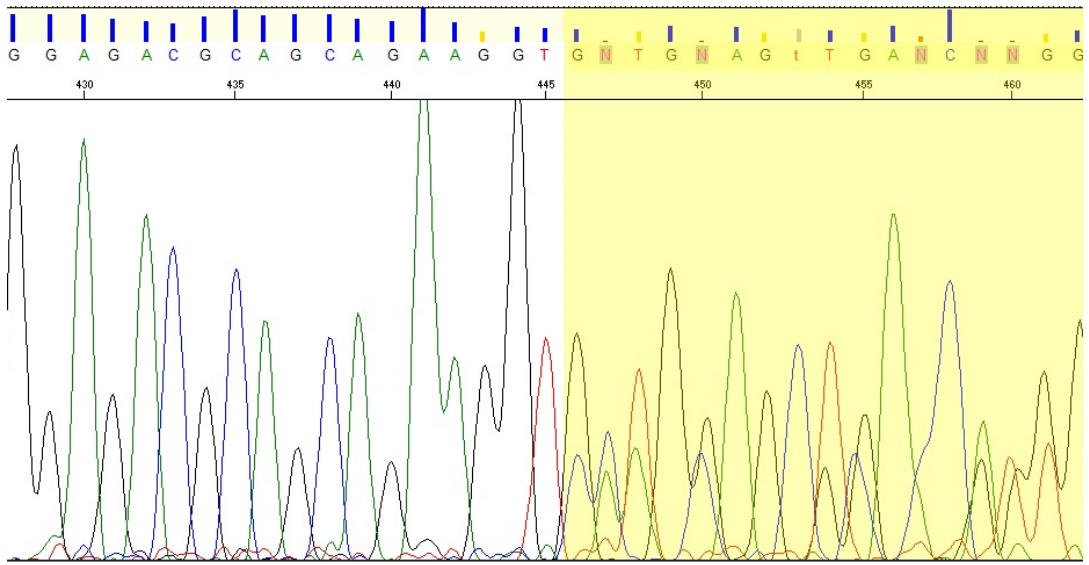
FISH:
No evidence of *AML1/ETO1, BCR-ABL1, CBFB, EV1, MLL*, or *PML-RARA* rearrangement

Sanger Sequencing Studies Identified Two *CEBPA* Mutations

Fragment 1
N-terminus c.169G>T (p. Glu57*)



Fragment 2
C-terminus c.909_941dup (p. Lys304_Val314dup)



Next-Generation Sequencing Studies Identified Additional Mutations

CLINICALLY SIGNIFICANT MUTATIONS

Gene	Mutation	COSMIC ID	Mutation Location	Mutant Allele Frequency
CEBPA	c.169G>T (p.E57*)	COSM42116	Exon 1	48%
CEBPA	c.909_941dup (p.K304_V314dup)	NA	Exon 1	NA

Next-Generation Sequencing Studies Identified Additional Mutations

CLINICALLY SIGNIFICANT MUTATIONS

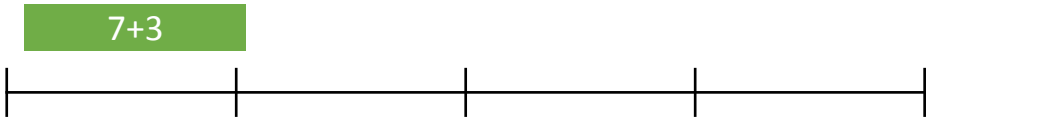
Gene	Mutation	COSMIC ID	Mutation Location	Mutant Allele Frequency
CEBPA	c.169G>T (p.E57*)	COSM42116	Exon 1	48%
CEBPA	c.909_941dup (p.K304_V314dup)	NA	Exon 1	NA
GATA2	c.953C>T (p.A318V)	COSM255084	Exon 4	46%
NRAS	c.38G>A (p.G13D)	COSM573	Exon 2	42%

MUTATION OF UNDETERMINED CLINICAL SIGNIFICANCE

Gene	Mutation	COSMIC ID	Mutation Location	Mutant Allele Frequency
NRAS	c.35G>A (p.G12D)	COSM564	Exon 2	2%

Final Diagnosis: Acute myeloid leukemia with (likely) biallelic mutations of *CEBPA*

Clinical Course



Day 1
Diagnosis

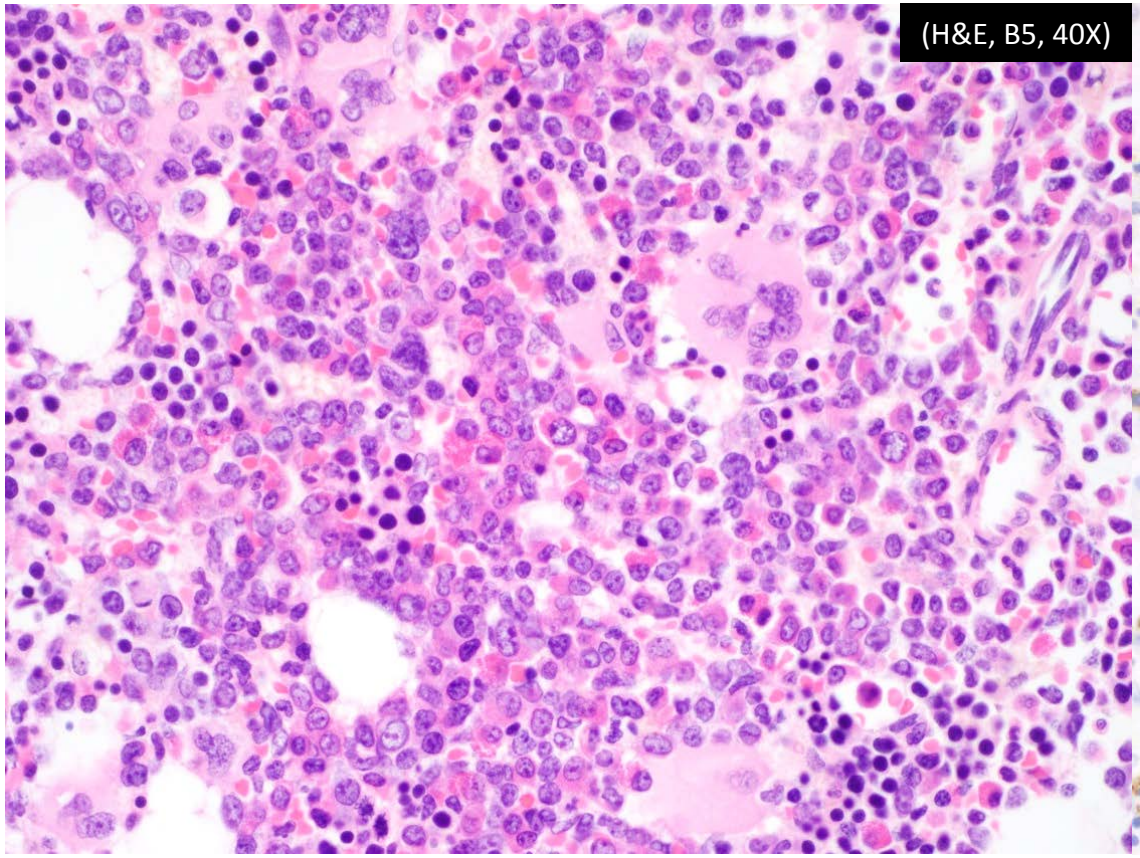
AML with biallelic *CEBPA*
CEBPA c.169G>T (p.E57*)
CEBPA c.909_941dup (p.K304_V314dup)
GATA2 c.953C>T (p.A318V)
NRAS c.38G>A (p.G13D)
NRAS c.35G>A (p.G12D)

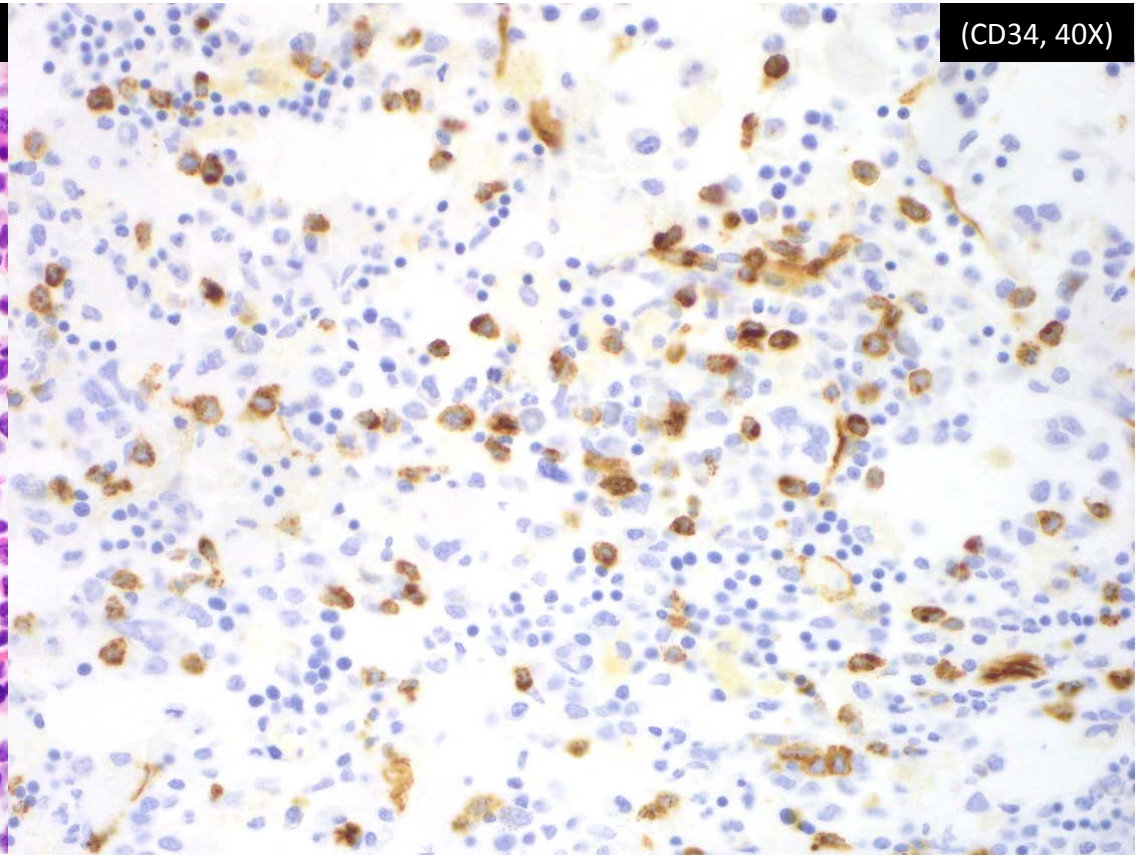
Day 14
Bone Marrow

No excess blasts

Day 30
Bone Marrow

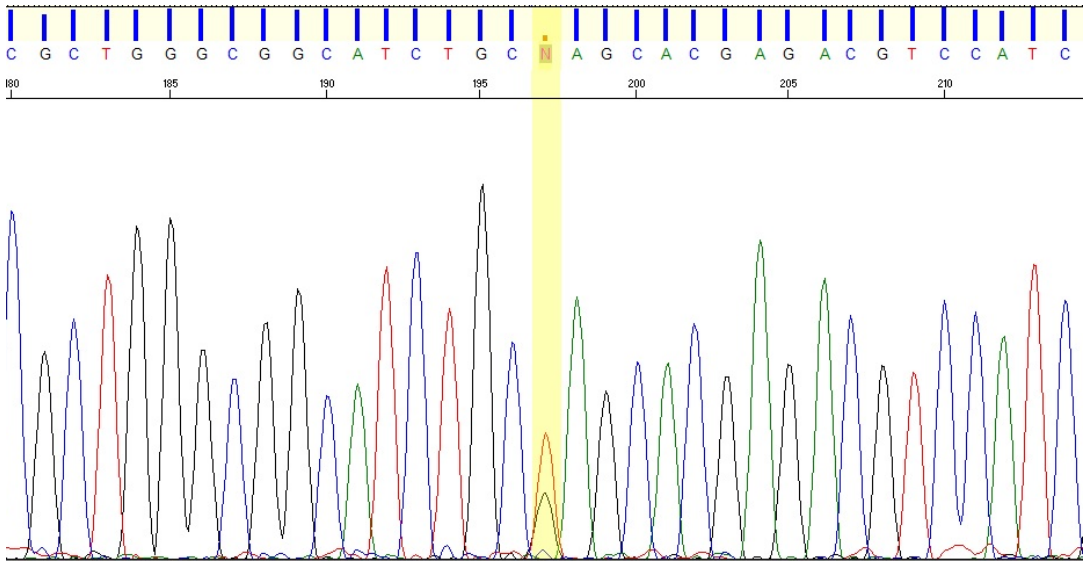
Day 30 Bone Marrow Showed 15-20% Blasts



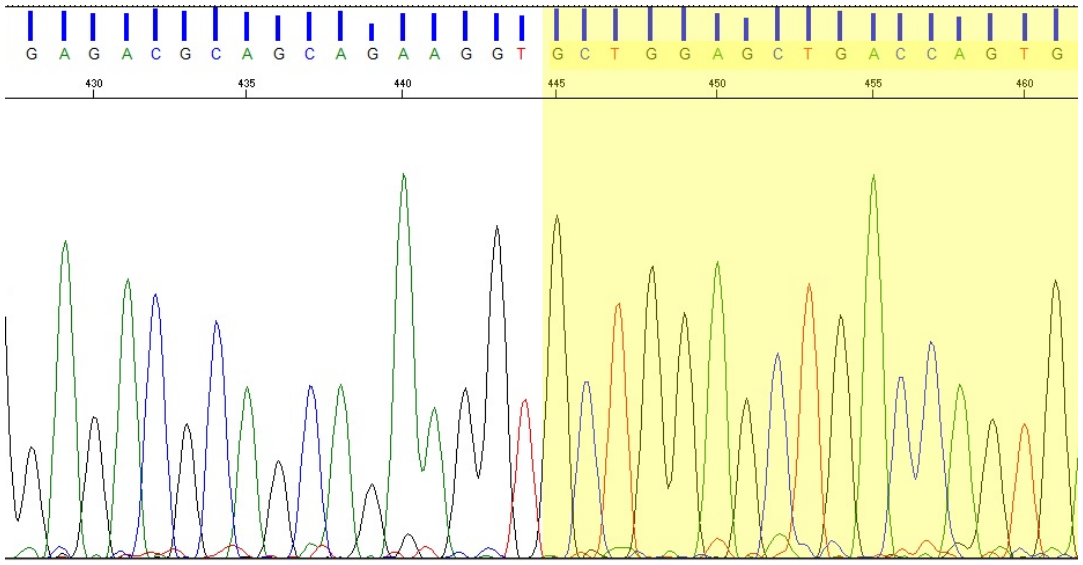


Next Generation Sequencing and Sanger Sequencing Demonstrated Persistence of the N-terminus *CEBPA* Mutation Without Other Mutations

Fragment 1
Positive for N-terminus c.169G>T (p. Glu57*)



Fragment 2
No Mutations Detected



Clinical Course

Day 1
Diagnosis

AML with biallelic *CEBPA*
CEBPA c.169G>T (p.E57*)
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NRAS c.38G>A (p.G13D)
NRAS c.35G>A (p.G12D)

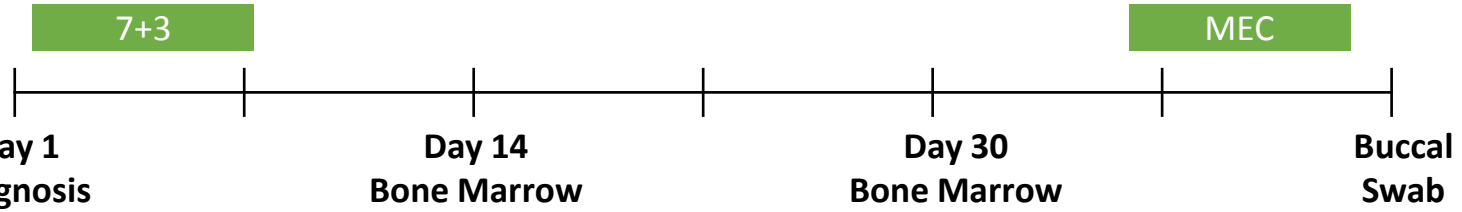
Day 14
Bone Marrow

No excess blasts

Day 30
Bone Marrow

15-20% blasts
CEBPA c.169G>T (p.E57*) 51%

Clinical Course



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No excess blasts

15-20% blasts
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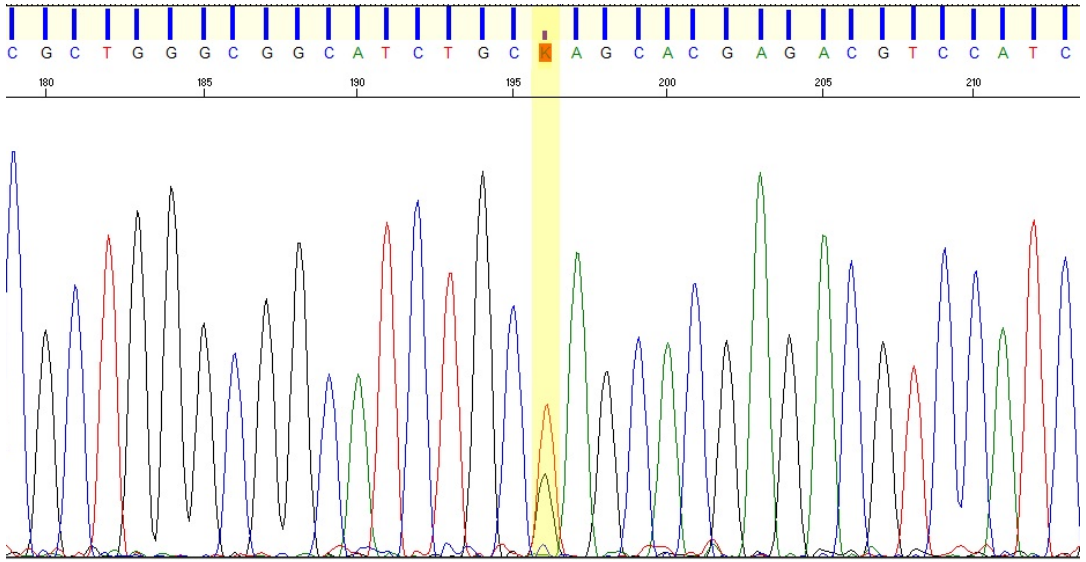
Sanger Sequencing of Buccal Swab Identified N-terminus *CEBPA* Mutation

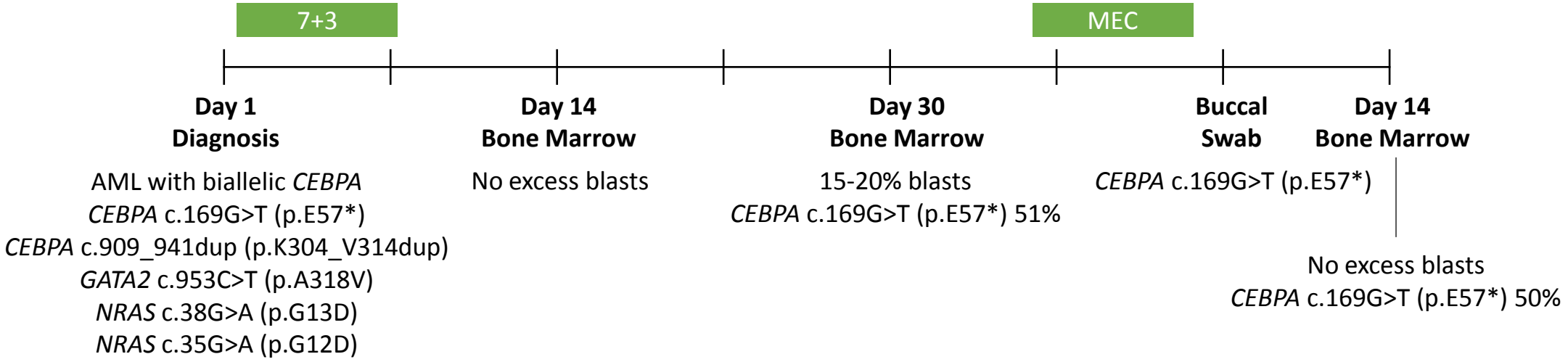
Fragment 1

Positive for N-terminus c.169G>T (p. Glu57*)

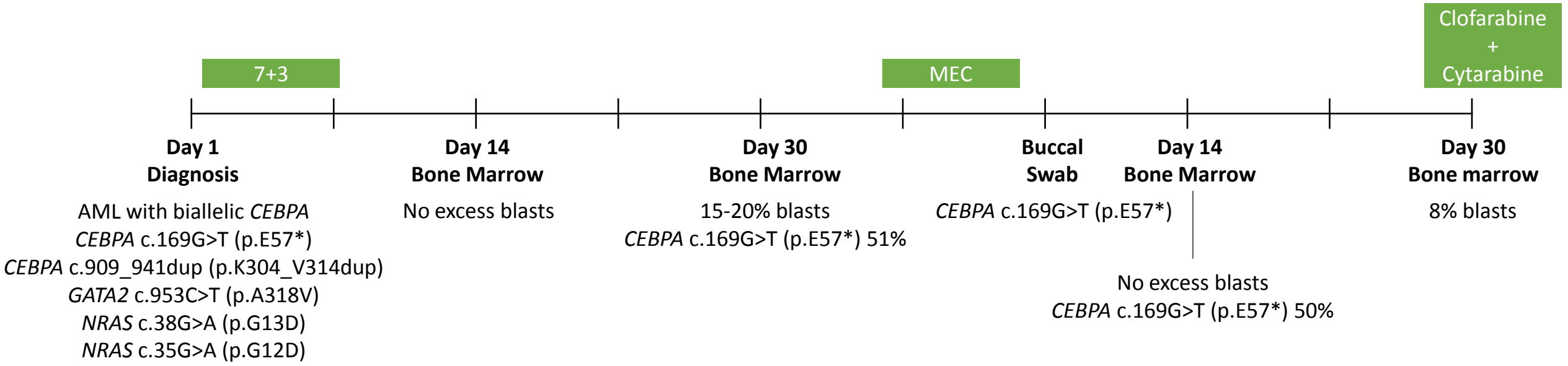


Final Diagnosis: Acute myeloid leukemia with germline *CEBPA* mutation

Clinical Course

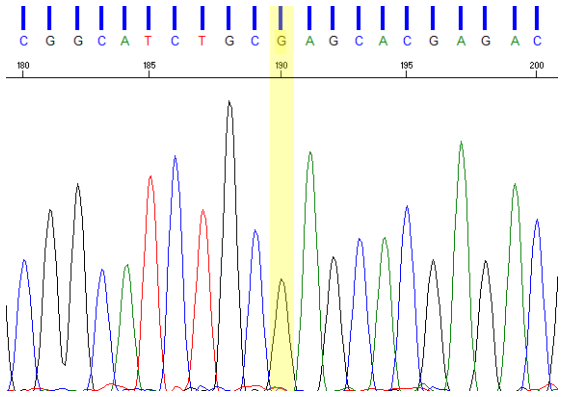


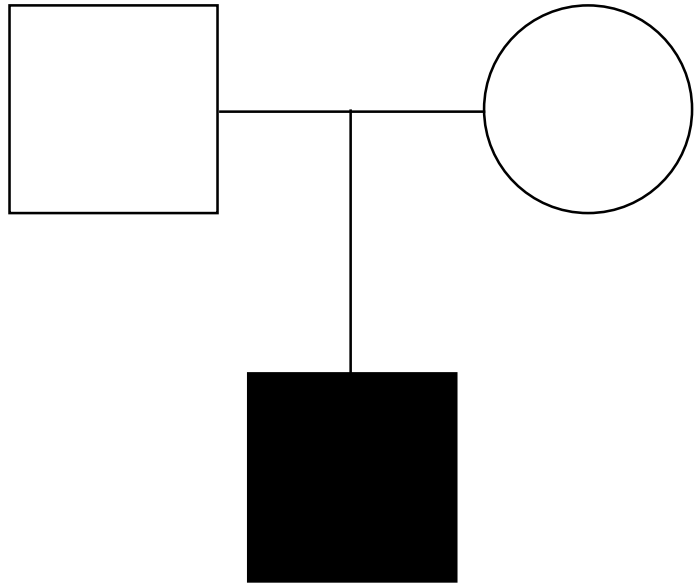
Clinical Course

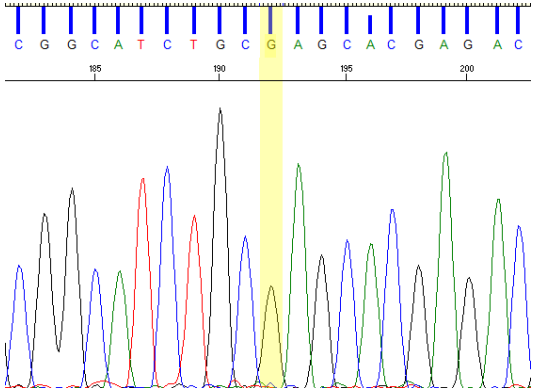


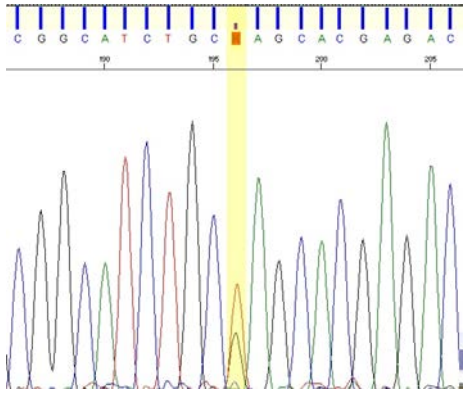
- Patient received allogeneic hematopoietic stem cell transplant 9 months after initial diagnosis
- Genetic counseling was provided
- Parental blood samples were submitted for germline *CEBPA* testing

Sanger Sequencing of Parental Samples Demonstrated Absence of Germline *CEBPA* Mutation







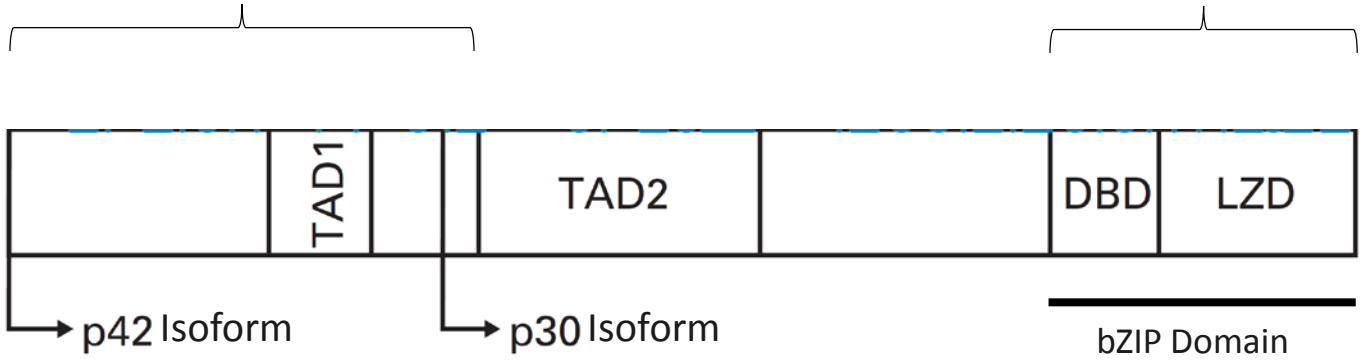


Final Diagnosis: Acute myeloid leukemia with *de novo* germline *CEBPA* mutation

CCAAT/Enhancer Binding Protein Alpha (*CEBPA*) Encodes a Transcription Factor

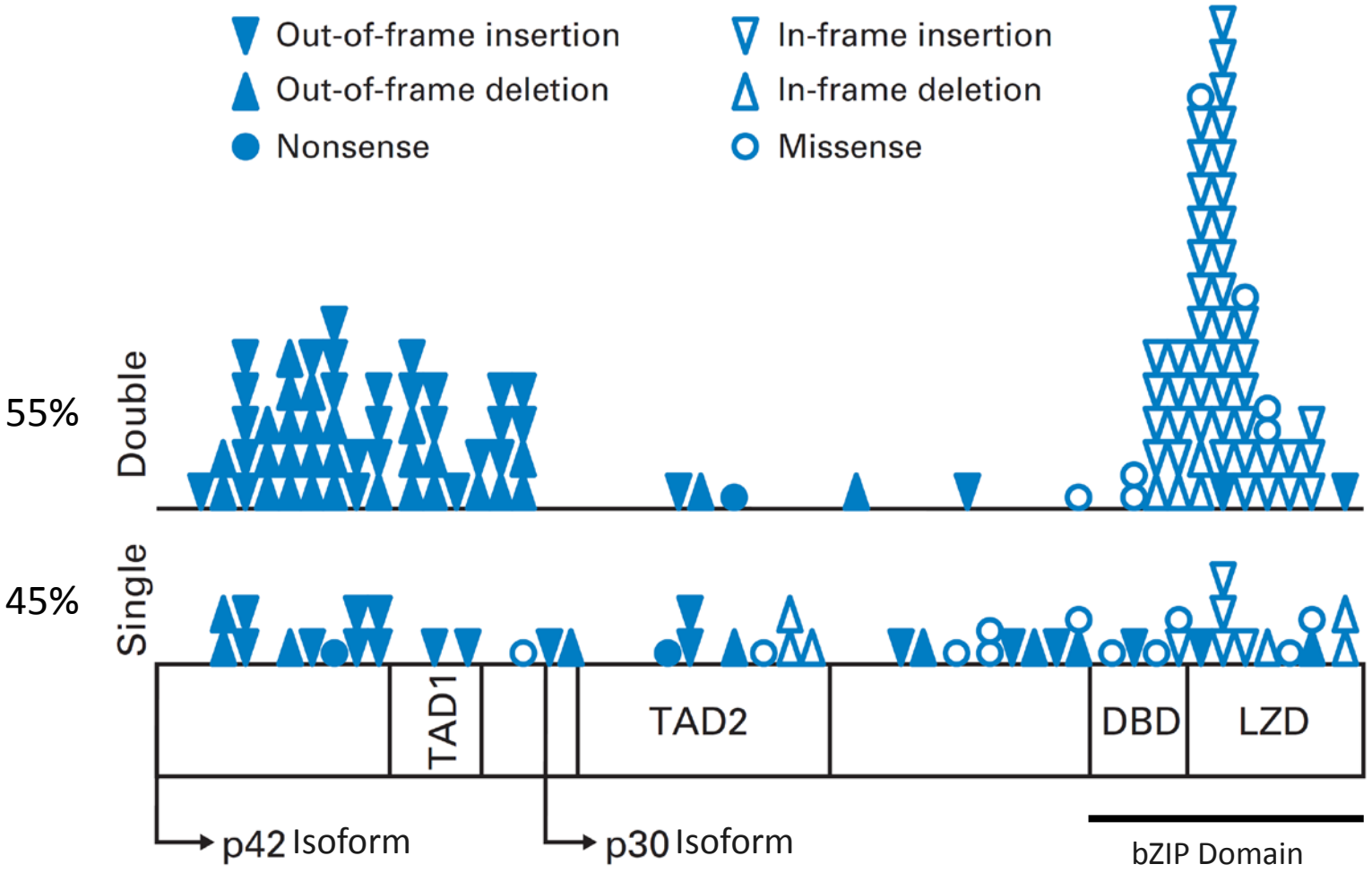
Alternative start sites can give rise to different isoforms

Recognizes the CCAAT promoter motif, and forms homodimers and heterodimers



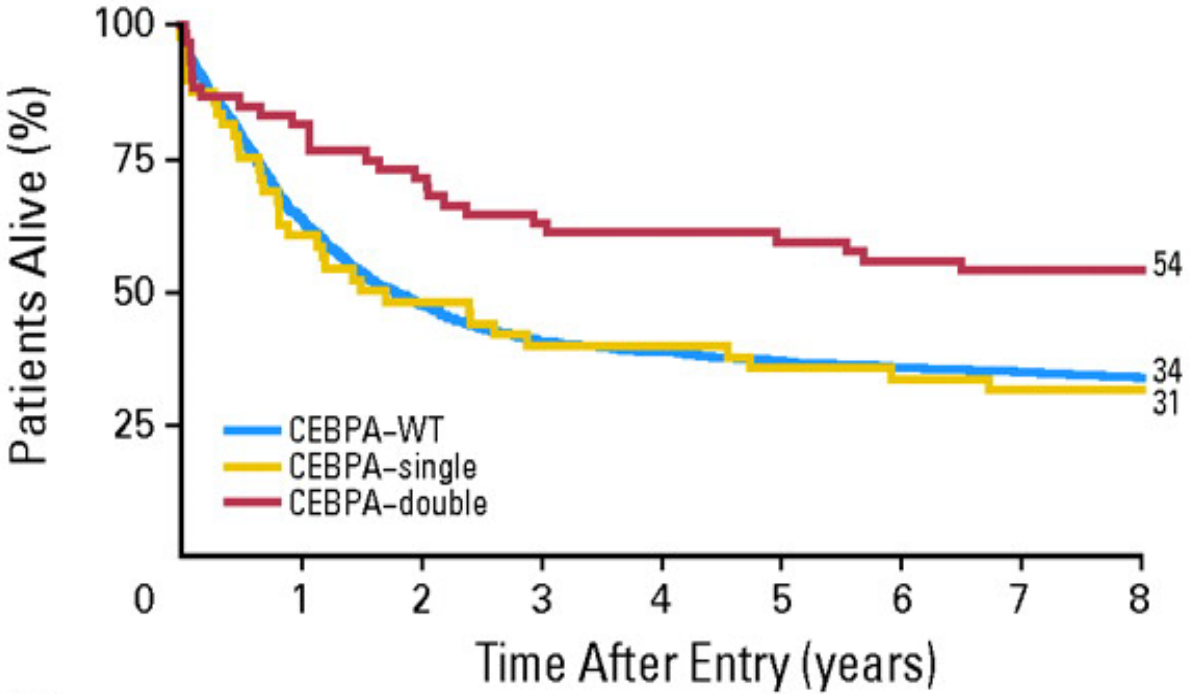
(Adapted from Green, CL *et al*, *JCO,* 2010)

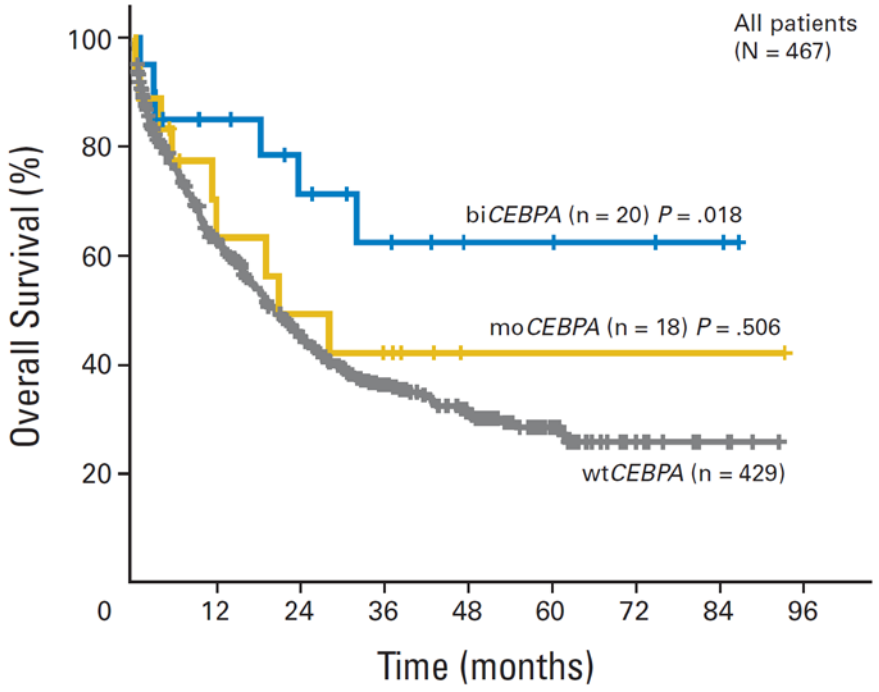
Somatic *CEBPA* Mutations Occur in the N- and C-terminus



(Adapted from Green, CL *et al*, *JCO,* 2010)

Somatic Bi-allelic *CEBPA* Mutations Are Associated With a Favorable Prognosis in AML

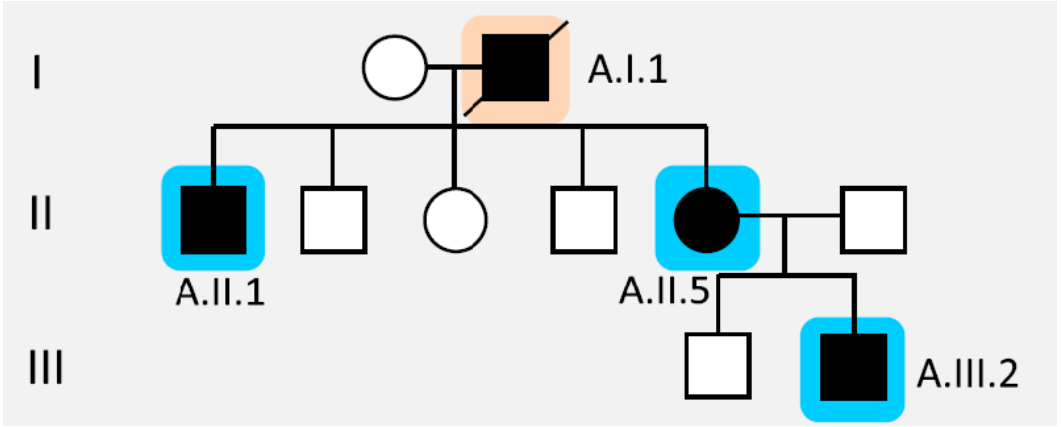




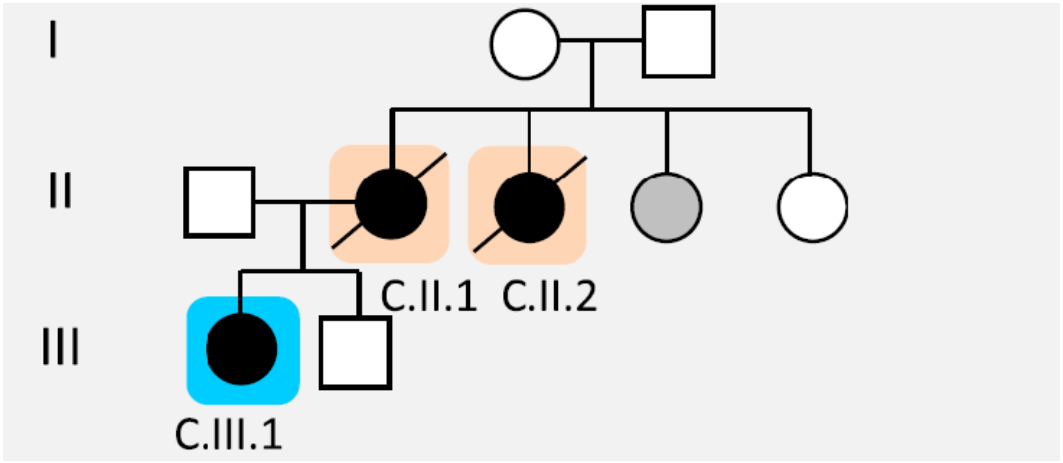
(Green, CL *et al*, *JCO,* 2010)
(Dufour A, *et al, JCO*, 2009)

Familial AML with Germline *CEBPA* Mutations Are Autosomal Dominant

- Early-onset primary AML
- Often M1 or M2 with aberrant CD7
- Median age 24.5 years (1.75 to 46 years)

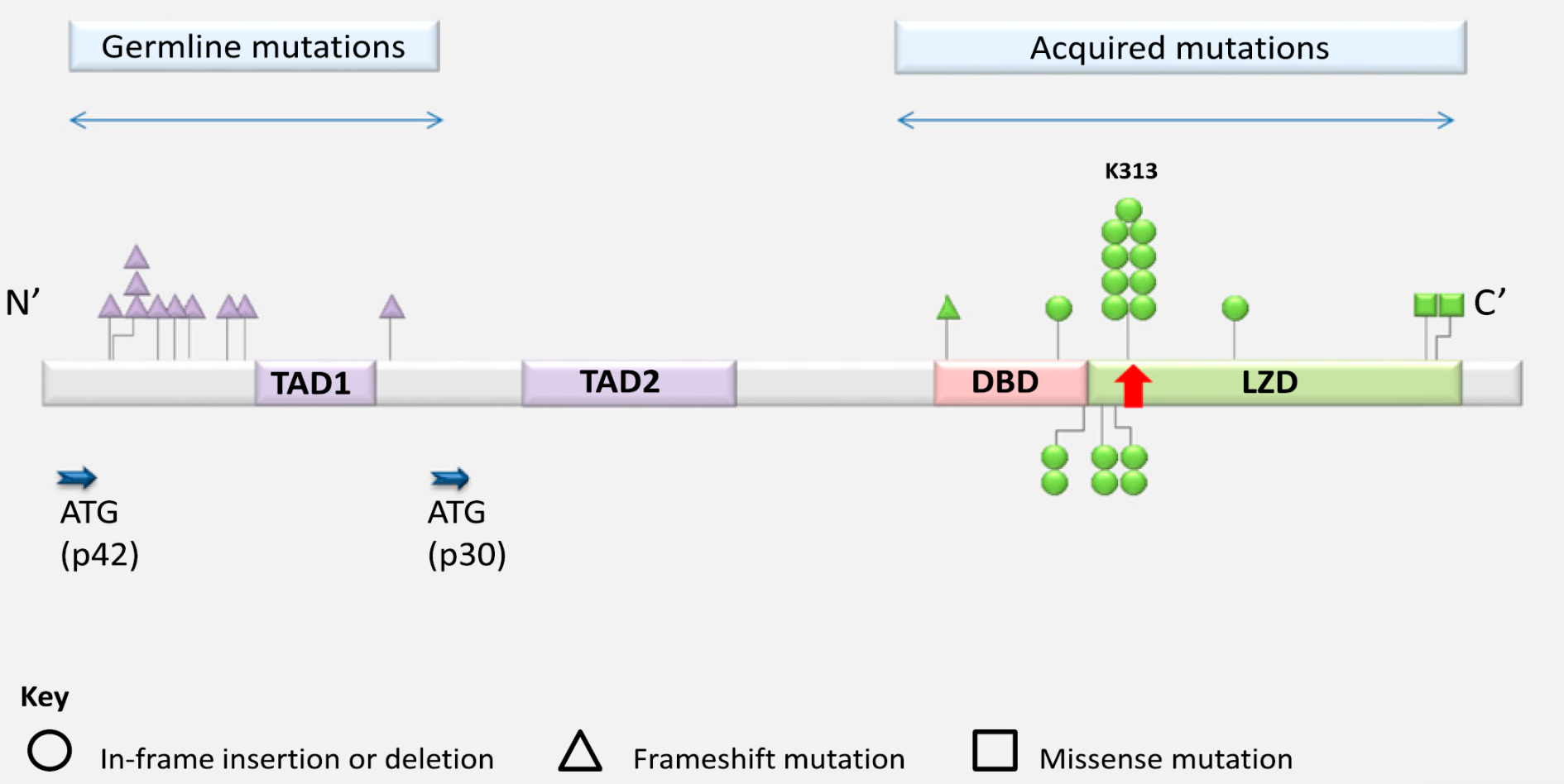


- Penetrance is high with rare unaffected carriers



(Adapted from Tawana K, *et al*, *Blood*, 2015)

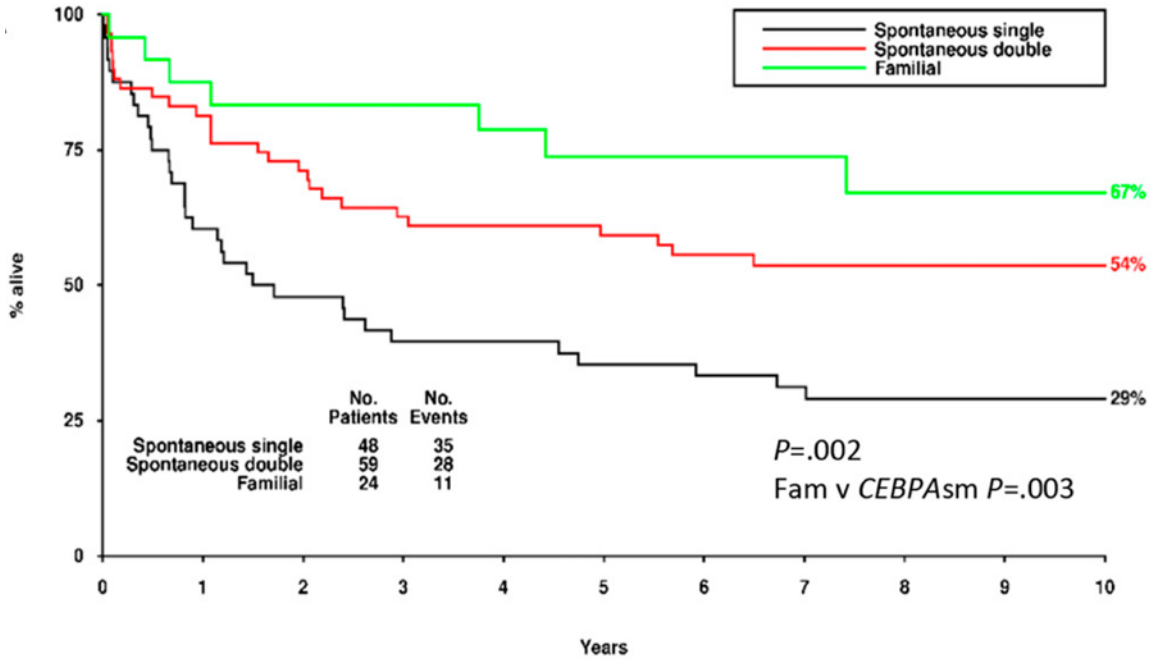
Germline *CEBPA* Mutations Occur in the N-terminus



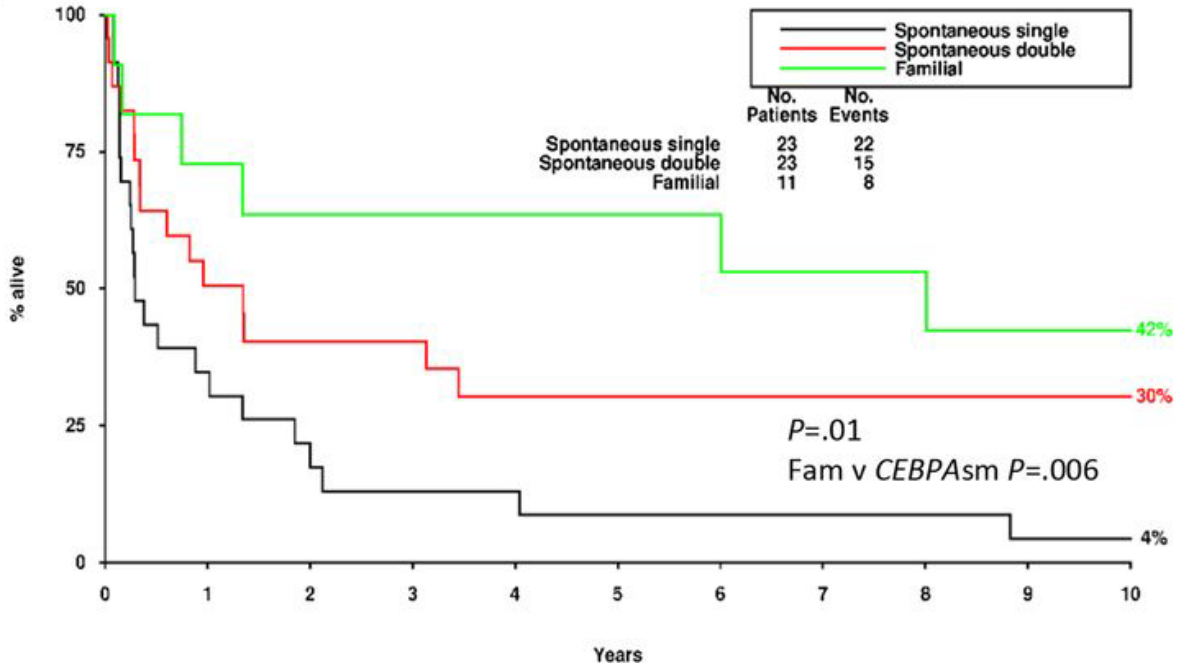
(Tawana K, *et al*, *Blood*, 2015)

Familial AML with Germline *CEBPA* Mutations Demonstrates Favorable Prognosis

Overall Survival



Survival After Relapse



(Tawana K, *et al, Blood*, 2015)

Case Summary

- 19 year-old man with primary AML with two *CEBPA* mutations
- Found to have one *de novo* germline N-terminus *CEBPA* mutation with a somatic C-terminus *CEBPA* mutation
- Allogeneic stem-cell transplant was pursued for refractory disease and germline predisposition to AML
- Familial AML with *CEBPA* mutations are autosomal dominant with high penetrance
- Overall survival is superior to survival in somatic *CEBPA*-mutated AML

Final Panel Diagnosis:
Acute myeloid leukemia with biallelic mutations of *CEBPA* (one germline, one somatic)

References

1. Dufour A, Schneider F, Metzeler KH, Hoster E, Schneider S, Zellmeier E, Benthaus T, Sauerland MC, Berdel WE, Büchner T, Wörmann B. Acute myeloid leukemia with biallelic CEBPA gene mutations and normal karyotype represents a distinct genetic entity associated with a favorable clinical outcome. Journal of clinical oncology. 2009 Dec 28;28(4):570-7.
2. Green CL, Koo KK, Hills RK, Burnett AK, Linch DC, Gale RE. Prognostic significance of CEBPA mutations in a large cohort of younger adult patients with acute myeloid leukemia: impact of double CEBPA mutations and the interaction with FLT3 and NPM1 mutations. Journal of Clinical Oncology. 2010 May 3;28(16):2739-47.
3. Preudhomme C, Sagot C, Boissel N, Cayuela JM, Tigaud I, de Botton S, Thomas X, Raffoux E, Lamandin C, Castaigne S, Fenaux P. Favorable prognostic significance of CEBPA mutations in patients with de novo acute myeloid leukemia: a study from the Acute Leukemia French Association (ALFA). Blood. 2002 Oct 15;100(8):2717-23.
4. Tawana K, Wang J, Renneville A, Bödör C, Hills R, Loveday C, Savic A, Van Delft FW, Treleaven J, Georgiades P, Uglow E. Disease evolution and outcomes in familial AML with germline CEBPA mutations. Blood. 2015 Sep 3;126(10):1214-23.

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Hyung Suh
Gary Schiller

Thank you.
Questions?