panel Discussion

Hematopoietic stem cell transplantation for patients with AML in first complete remission

MODERATOR

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Hematologist and Medical oncologist

PANELISTS

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PhD Laboratory Hematology and Transfusion Sciences

Case Study 1 (1400/5/3)

- A 51-year-old man presents to the emergency department complaining of fatigue and shortness of breath.
- he reports a two-week history of worsening exercise tolerance and a rather abrupt onset of shortness of breath over the past several hours
- The patient has no major past medical history
- Prior to this illness, he exercised three to four times weekly.

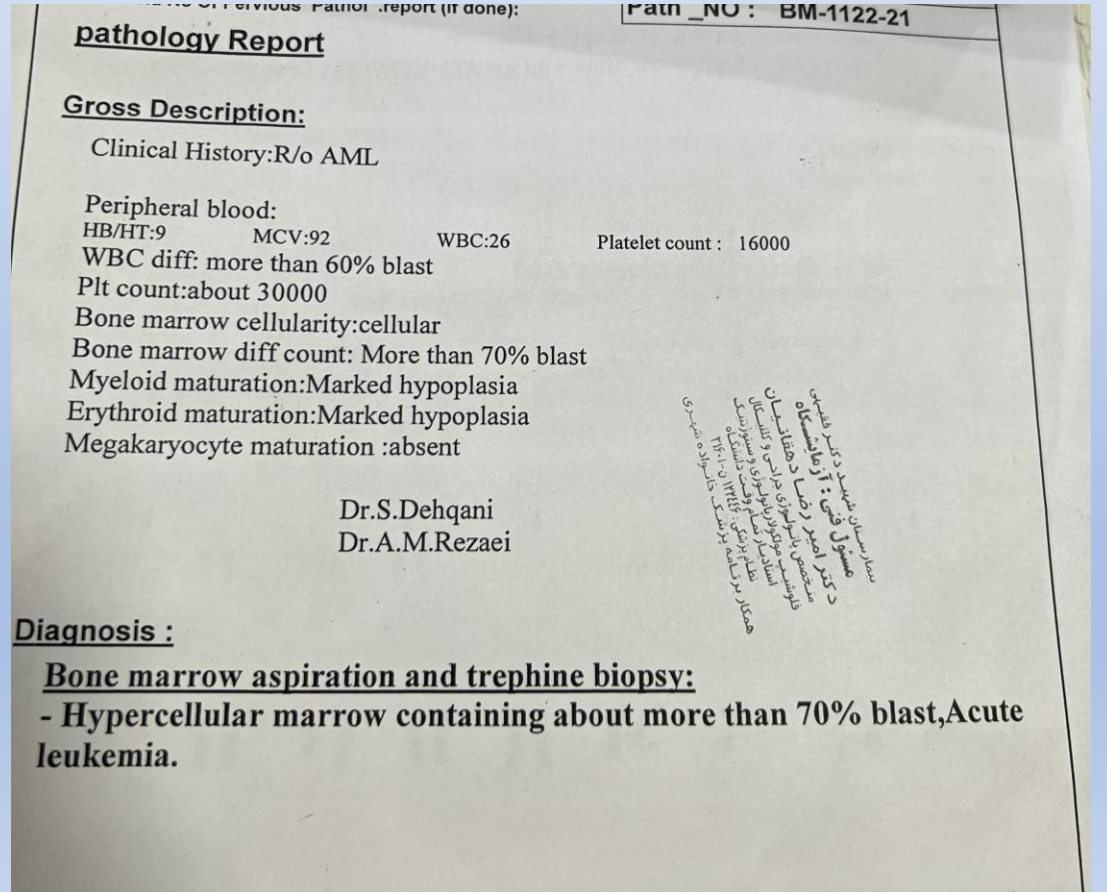
Count	Value	Reference Range
White blood cells	$8.6 \times 10^9/L$	$4 \times 10^9/L - 10 \times 10^9/L$
Hemoglobin	10 g/dL	14 – 18 g/dL
Platelet count	$70 \times 10^9/L$	$150 \times 10^9/L - 450 \times 10^9/L$

White blood cell (WBC) differential is notable for 30 percent blasts. Peripheral blood smear shows a vast majority of cells are large blasts with occasional cytoplasmic granules

INR: 1.2
PTT: 36
Fibrinogen level: 250

Bone marrow aspiration and biopsy

- Bone marrow aspiration and biopsy is performed, revealing a hypercellular marrow involved with blasts comprising 70 percent of bone marrow cellularity



Path _NO : BM-1122-21

pathology Report

Gross Description:

Clinical History:R/o AML

Peripheral blood:
HB/HT:9 MCV:92 WBC:26 Platelet count : 16000
WBC diff: more than 60% blast
Plt count:about 30000
Bone marrow cellularity:cellular
Bone marrow diff count: More than 70% blast
Myeloid maturation:Marked hypoplasia
Erythroid maturation:Marked hypoplasia
Megakaryocyte maturation :absent

Dr.S.Dehqani
Dr.A.M.Rezaei

Diagnosis :

Bone marrow aspiration and trephine biopsy:

- Hypercellular marrow containing about more than 70% blast,Acute leukemia.

PCR Report

P _NO : M-6197

Description:

This patient is a case of AML and FLT3 mutation is detected as prognostic. DNA was extracted from bone marrow aspiration and FLT3 mutations was analysed by multiplex PCR, restriction enzyme digestion and gel analysis to see whether an internal tandem duplication (ITD) and/or mutation at D835 is present. Mutation of FLT3 is associated with increase in risk of relapse. In this patient no mutation in FLT3 was detected in either ITD or D835.

Diagnosis: Bone marrow aspiration, Multiplex PCR for detection of FLT3 mutation as prognostic factor :

- Negative for FLT3 Internal Tandem Duplication.
- Negative for FLT3 D835 mutation.

Ar. Dehghanian, M.D. A. Safaei, M.D. S.

Description:

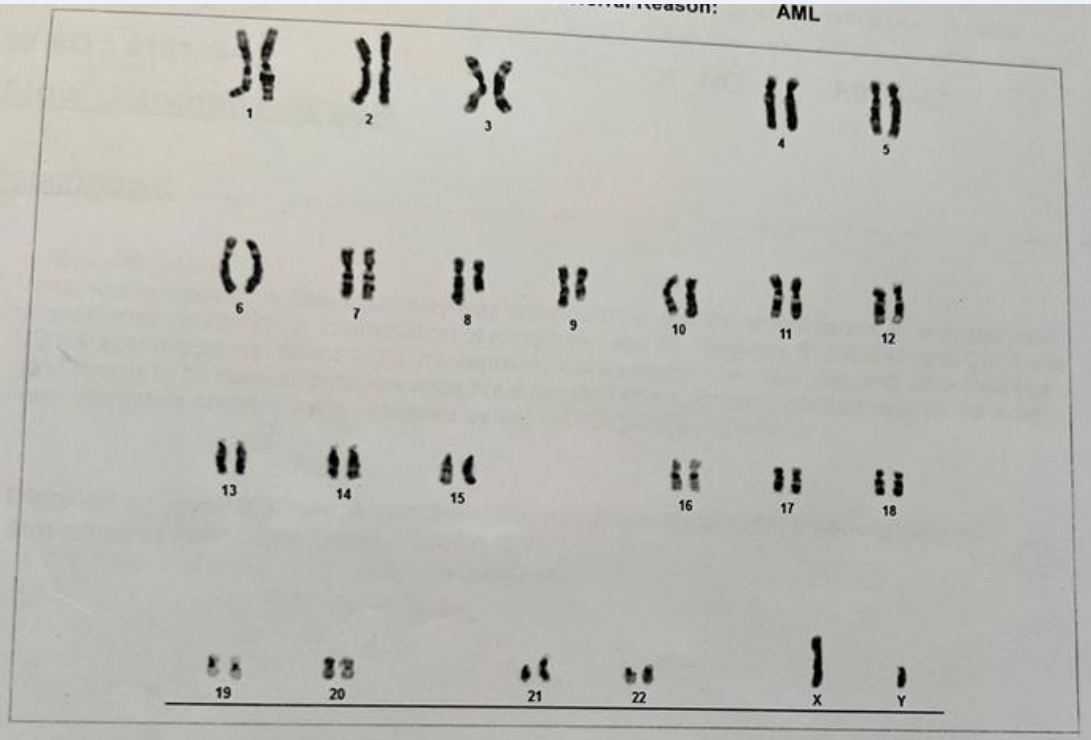
This patient is a well documented case of AML. RNA was extracted from bone marrow aspiration. Qualitative RT-PCR examination for the detection of t(8;21)/*RUNX1-RUNX1T1* transcript and inv (16) *CBFB-MYH11* transcript(AB2) fusion genes was performed. Co-amplification of ABL gene was done to check for the quality of RNA and absence of inhibitors. RNA from a well documented positive case was also amplified simultaneously as positive control. Patient's sample showed a single sharp band of amplification at 395 bp indicative of presence of t(8;21)[AML1-ETO].

Final diagnosis:

-Positive for **t(8;21)**/*RUNX1-RUNX1T1* transcript.

-No RT-PCR evidence of inv(16) *CBFβ-MYH11* transcript.
-No RT-PCR evidence of t(16;16) *CBFβ-MYH11* transcript.

A. Monabati, MD



AML

N Results: **Karyotype study with G banding method revealed:**
46,XY,t(8;21)(q22:q22),del(9)(q21q22)

by: Hosseini.M

ked by: Z.Kargar MD

e: *t(8;21)(q22;q22) compatible with RUNX1-RUNX1T1 gene rearrangement and associated with favorable prognosis.*

Impact of 9q Deletions on the Classification in AML

- In 1 % of AML pts a del(9q) was present. Del(9) frequently co-occured with *RUNX1-RUNX1T1* , biallelic *CEBPA* and *NPM1* mutations, *NUP98* -rearrangements and other AML-typical translocations.
- A mutation signature typical for s-AML was infrequent.
- it seems reasonable that the del(9q) is no longer regarded as a defining cytogenetic abnormality for AML with myelodysplasia-related changes, in particular as prognosis in del(9q) cases with non-complex karyotype is favorable

What are the translocation events in core binding factor acute myeloid leukemia?

- The core-binding factor alpha and beta subunits form heterodimers to bind to DNA and regulate hematopoietic differentiation, cell cycles, and ribosome biogenesis
- genes that are necessary for maturation of these blood cells cannot function, and the cells are arrested at an earlier stage. The resultant differentiation block leads to the development of leukemia.

What are the treatment options for core binding factor AML?

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Acute Myeloid Leukemia (Age ≥18 years)

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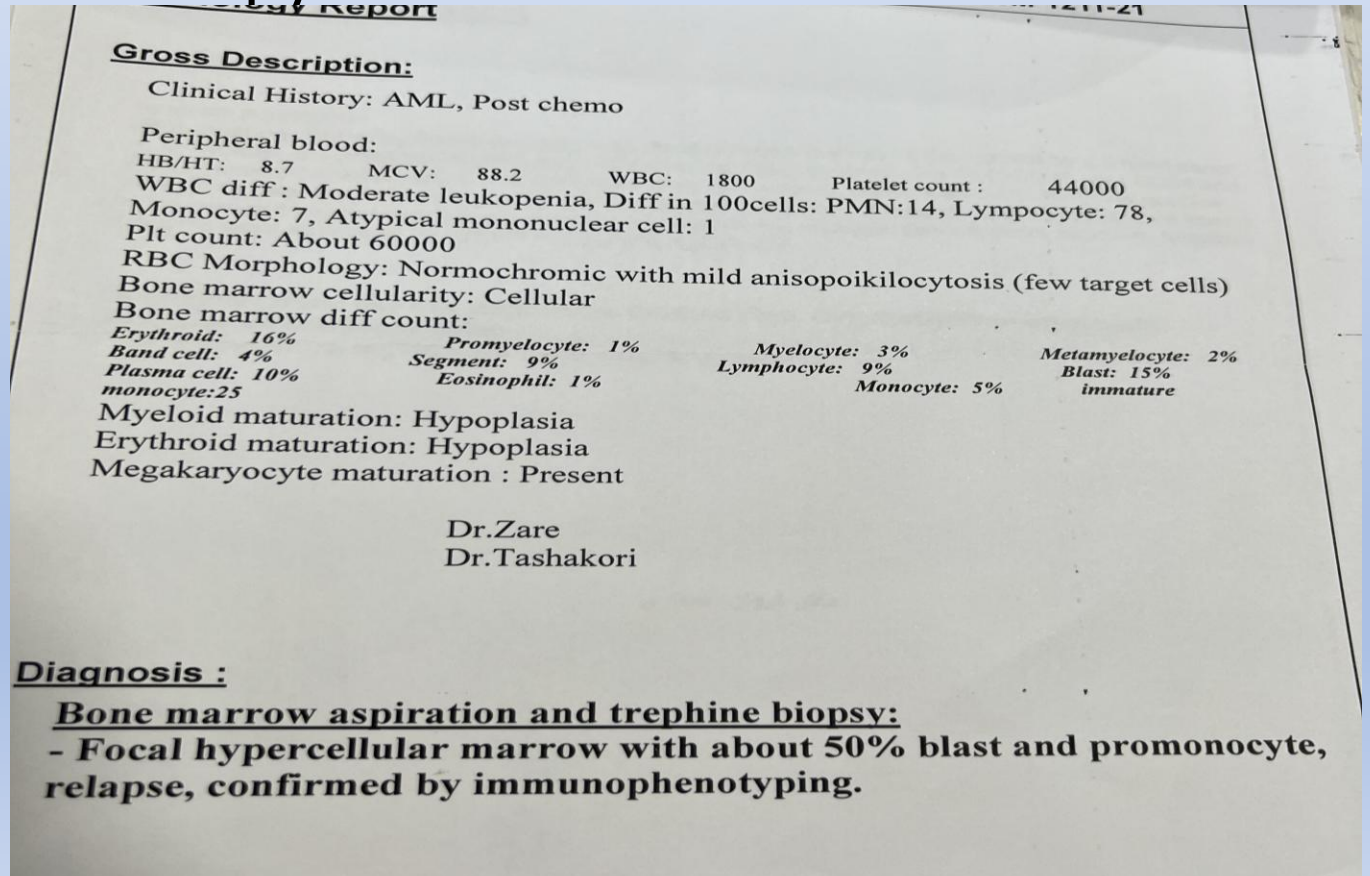
AGE<60 y INDUCTION ELIGIBLE	TREATMENT STRATEGIES	TREATMENT INDUCTION[g,h,i,j]
	Favorable-risk cytogenetics	Options: • Standard-dose cytarabine 200 mg/m^2 continuous infusion x 7 days with daunorubicin 60 mg/m^2 x 3 days and a single dose of gemtuzumab ozogamicin 3 mg/m^2 (up to one 4.5 mg vial) given on day 1, or day 2, or day 3, or day 4; alternatively, three total doses may be given on days 1, 4, and 7[k,l] (CD33-positive)[m] (preferred) • Standard-dose cytarabine 100–200 mg/m^2 continuous infusion x 7 days with idarubicin 12 mg/m^2 or daunorubicin 60–90 mg/m^2 x 3 days[n,o] (category 1) • Fludarabine 30 mg/m^2 days 2–6, high-dose cytarabine (HiDAC) 2 g/m^2 over 4 hours starting 4 hours after fludarabine infusion on days 2–6, idarubicin 8 mg/m^2 IV on days 4–6, and granulocyte colony-stimulating factor (G-CSF)[p] subcutaneously (SC) daily days 1–7 plus a single dose of gemtuzumab ozogamicin 3 mg/m^2 in first course (category 2B)[q]

- Induction chemotherapy (7+3) start for him
- 17 days after induction chemotherapy BM:



Gross Description:

Clinical History: AML, Post chemo

Peripheral blood:

HB/HT: 8.7 MCV: 88.2 WBC: 1800 Platelet count : 44000

WBC diff : Moderate leukopenia, Diff in 100cells: PMN:14, Lympocyte: 78, Monocyte: 7, Atypical mononuclear cell: 1

Plt count: About 60000

RBC Morphology: Normochromic with mild anisopoikilocytosis (few target cells)

Bone marrow cellularity: Cellular

Bone marrow diff count:

Erythroid: 16% *Promyelocyte: 1%* *Myelocyte: 3%* *Metamyelocyte: 2%*
Band cell: 4% *Segment: 9%* *Lymphocyte: 9%* *Blast: 15%*
Plasma cell: 10% *Eosinophil: 1%* *Monocyte: 5%* *immature*
monocyte:25

Myeloid maturation: Hypoplasia

Erythroid maturation: Hypoplasia

Megakaryocyte maturation : Present

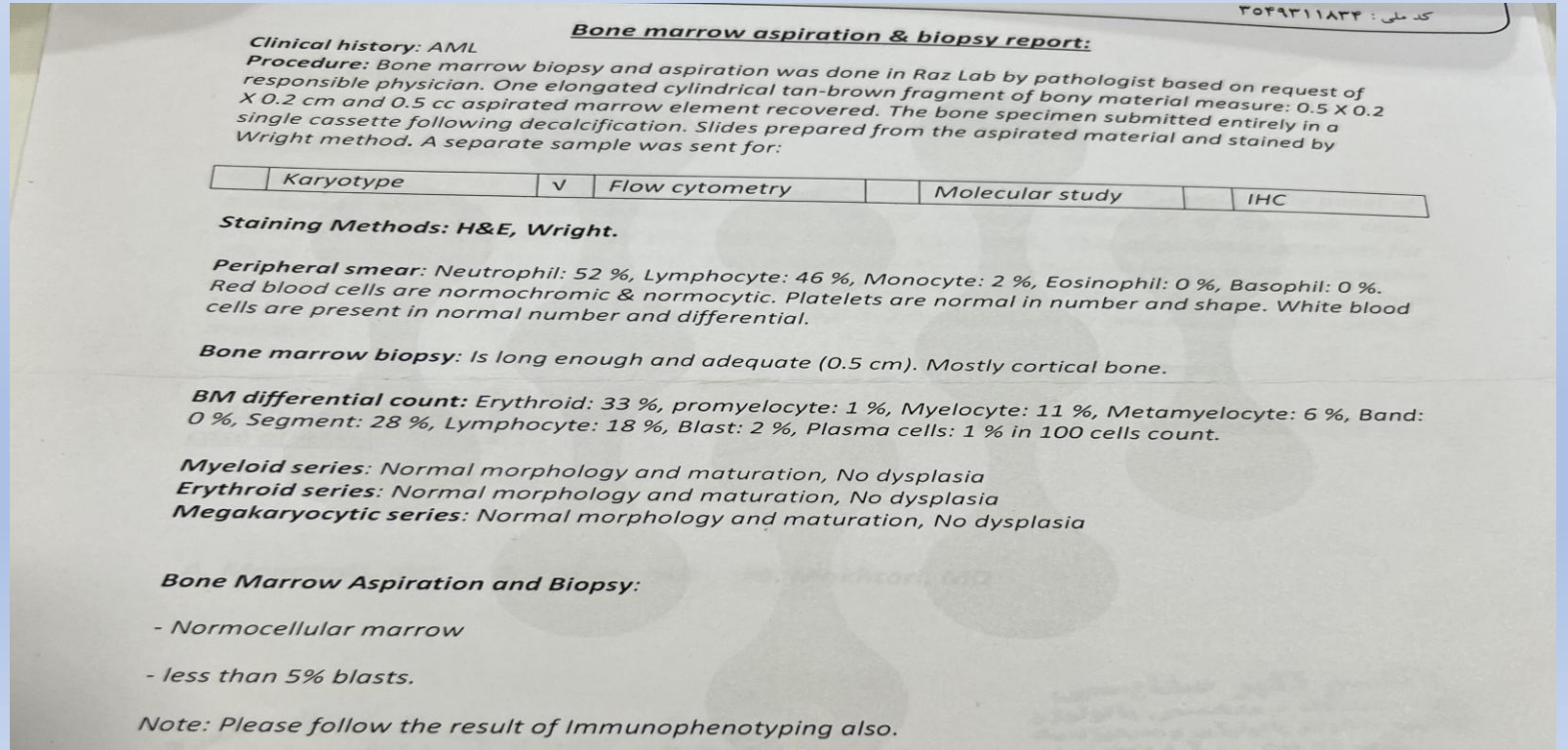
Dr.Zare
Dr.Tashakori

Diagnosis :

Bone marrow aspiration and trephine biopsy:

- Focal hypercellular marrow with about 50% blast and promonocyte, relapse, confirmed by immunophenotyping.

- Before reinduction chemotherapy, The patient was infected with corona virus
- Chemotherapy stop for 2 weeks and due to nl CBC , BM aspiration repeated :



کد ملی : ۳۵۴۹۳۱۱۸۳۴

Bone marrow aspiration & biopsy report:

Clinical history: AML

Procedure: Bone marrow biopsy and aspiration was done in Raz Lab by pathologist based on request of responsible physician. One elongated cylindrical tan-brown fragment of bony material measure: 0.5 X 0.2 X 0.2 cm and 0.5 cc aspirated marrow element recovered. The bone specimen submitted entirely in a single cassette following decalcification. Slides prepared from the aspirated material and stained by Wright method. A separate sample was sent for:

	Karyotype	√	Flow cytometry		Molecular study		IHC

Staining Methods: H&E, Wright.

Peripheral smear: Neutrophil: 52 %, Lymphocyte: 46 %, Monocyte: 2 %, Eosinophil: 0 %, Basophil: 0 %. Red blood cells are normochromic & normocytic. Platelets are normal in number and shape. White blood cells are present in normal number and differential.

Bone marrow biopsy: Is long enough and adequate (0.5 cm). Mostly cortical bone.

BM differential count: Erythroid: 33 %, promyelocyte: 1 %, Myelocyte: 11 %, Metamyelocyte: 6 %, Band: 0 %, Segment: 28 %, Lymphocyte: 18 %, Blast: 2 %, Plasma cells: 1 % in 100 cells count.

Myeloid series: Normal morphology and maturation, No dysplasia
Erythroid series: Normal morphology and maturation, No dysplasia
Megakaryocytic series: Normal morphology and maturation, No dysplasia

Bone Marrow Aspiration and Biopsy:

- Normocellular marrow

- less than 5% blasts.

Note: Please follow the result of Immunophenotyping also.

Case Report

Spontaneous Complete Remission of Acute Myeloid Leukemia in the Absence of Disease-Modifying Therapy following Severe Pulmonary Involvement by Coronavirus Infectious Disease-19

Maryam Barkhordar, Fatemeh Tajic Rostami, Marjan Yaghmaie, Mehrdad Abbaszadeh, Bahram Chahardouli, and Seied Asadollah Mousavi

Hematology Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran

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Despite the high capacity of the immune process to eliminate the malignant cells, the spontaneous immunerelated remission in the absence of disease-modifying therapy, similar to what happens following the induction chemotherapy, is usually transient

Delayed Hematologic Recovery in AML Patients after Induction Chemotherapy

blood®

617. ACUTE MYELOID LEUKEMIA: BIOLOGY, CYTOGENETICS, AND MOLECULAR MARKERS IN DIAGNOSIS AND PROGNOSIS: INTEGRATING GENOMICS INTO RISK STRATIFICATION AND THERAPEUTIC DECISIONS | NOVEMBER 29, 2018

Delayed Hematologic Recovery in AML Patients after Induction Chemotherapy Is Associated with Inferior Relapse-Free Survival and Persistence of Preleukemic Mutations

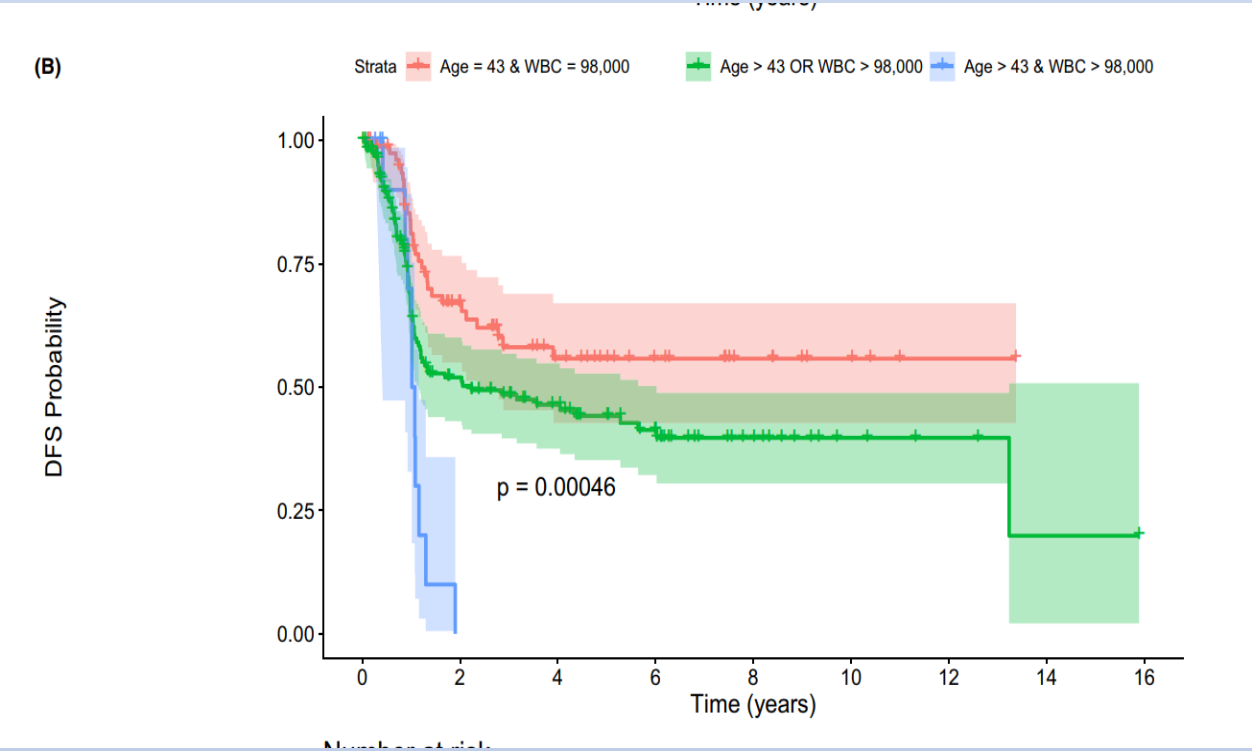
Conclusion:Delayed hematologic recovery in AML patients after induction chemotherapy is associated with inferior RFS and persistence of preleukemic mutations (i.e., DTAS mutations). Our results support a model in which progenitors harboring DTAS mutations have reduced repopulation capacity leading to delayed hematologic recovery after induction chemotherapy.

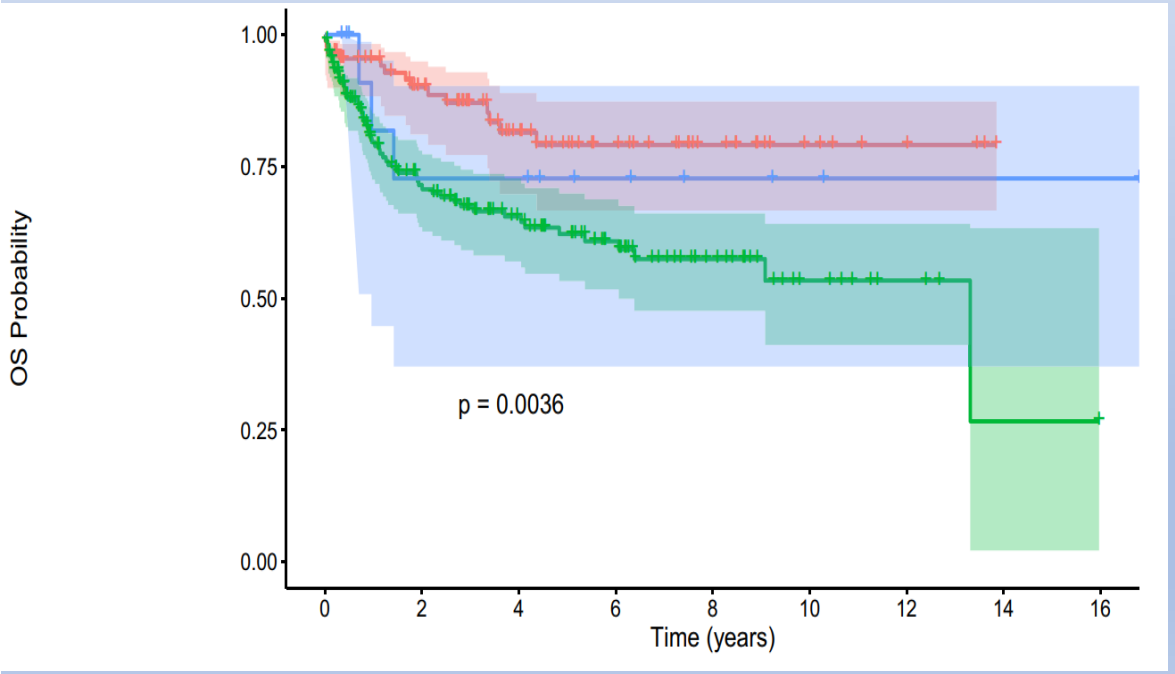
Are there ways to tailor treatment to particular patients?

- average rate of survival is approximately 50%.
- 40% to 50% of patients are still relapsing and dying from the disease
- Two important risk factors are older age and persistence of MRD.
- Patients who do not achieve an optimal molecular response have higher rates of relapse and death from disease.
- A nonrandomized study from China suggested that patients without an optimal qPCR response might benefit from allogeneic transplant rather than continued chemotherapy.

High risk AML with inv 16

- **Older age and high white blood cell count are risk factors for treatment failure**





Int J Lab Hematol. 2020;00:1–7

- Several investigative groups have reported that the mutation in the *KIT* gene indicates high risk.
- Patients who have *KIT* mutations tend to relapse more often.
- At MD Anderson, we have not been able to confirm this finding in the context of fludarabine- and cytarabine-based regimens, and this observation was not borne out in the pediatric setting.
- it is not yet known whether the *KIT* mutation necessarily indicates a higher-risk patient population that requires treatment modification.

Mutatin anlysis testing for C-KIT in Acute Myeloid Leukemia

Mutation description: *Mutations are mainly of substitution type, distributed in exon 8 and 17.*

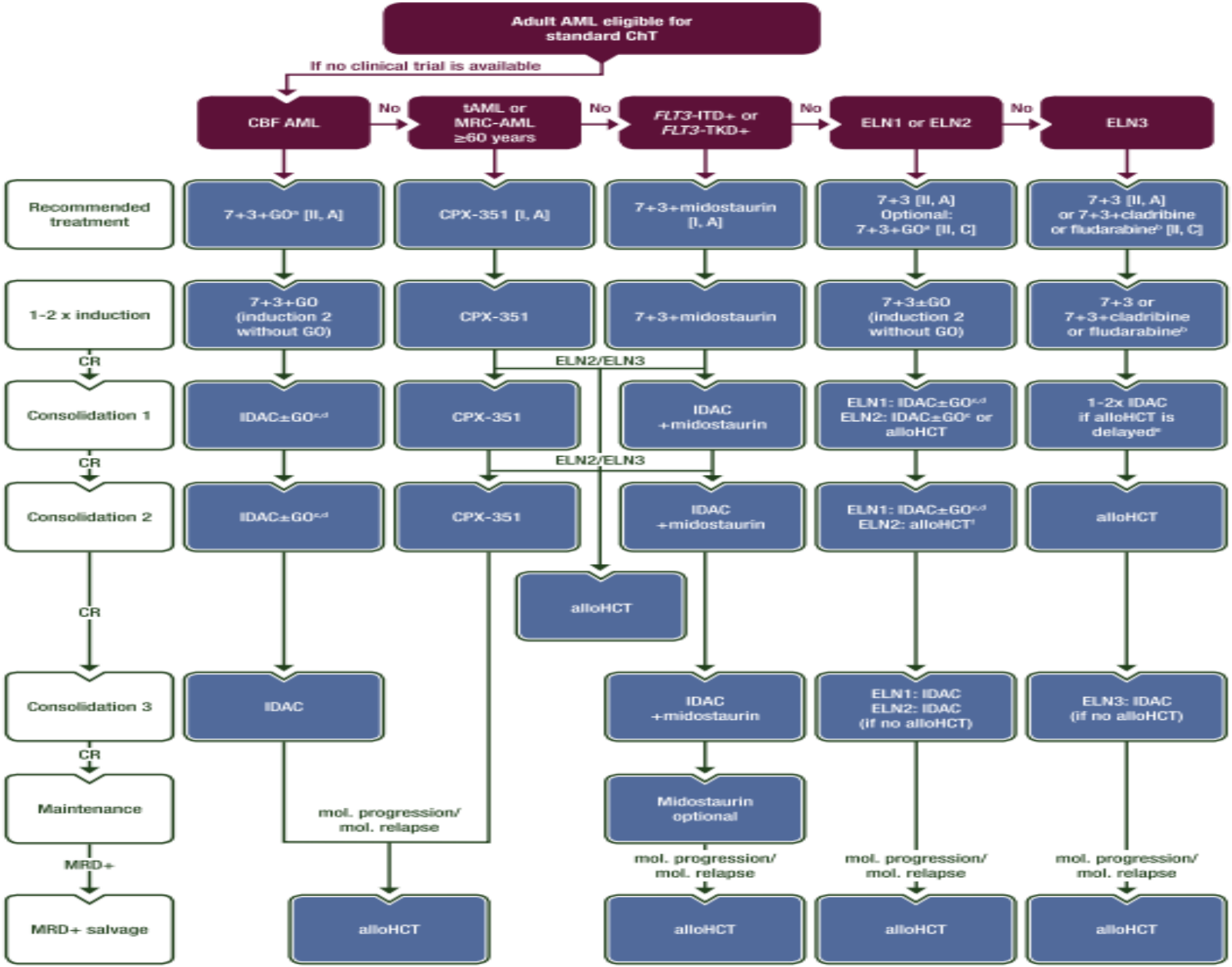
Procedure description*: This test has been developed and validated in Raz lab. The test is done on DNA extracted from bone marrow. This assay utilizes PCR amplification of exons 8 and 17 followed by Sanger sequencing. This test has high specificity but limited sensitivity.*

Performed by: M. Sarikhani

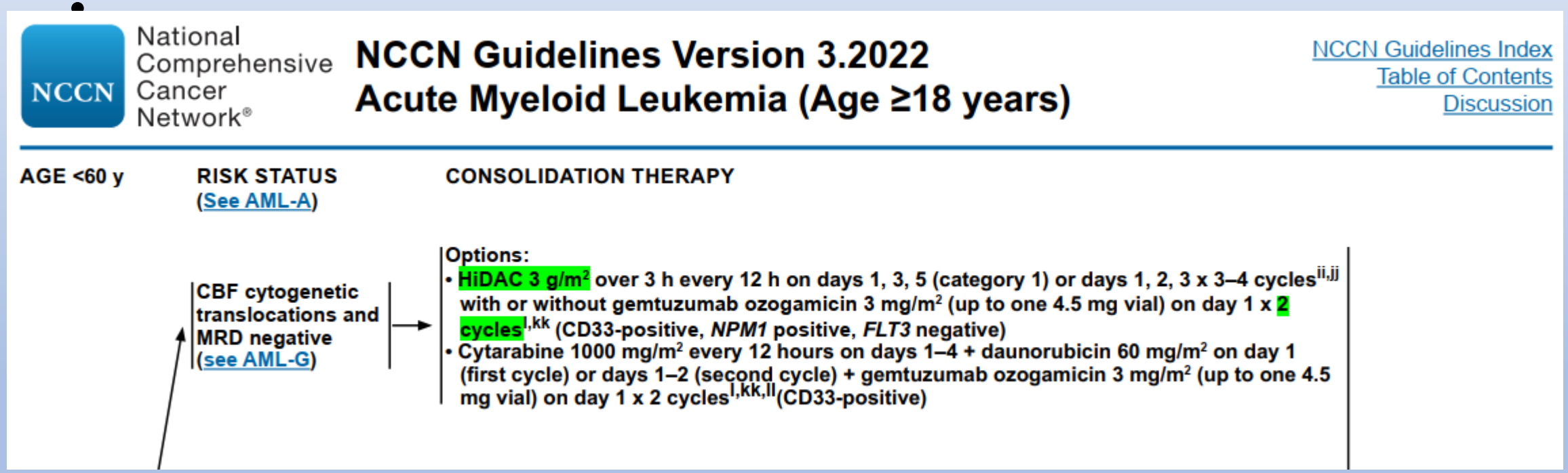
Final result*: C-KIT mutation testing on bone marrow by PCR and Sanger sequencing show:*

- Wild type C-KIT gene.

A. Monabati, MD ***A. Safaei, MD*** ***M. Mokhtari, MD***


Adult AML eligible for standard ChT
If no clinical trial is available
CBF AML
No
tAML or MRC-AML ≥60 years
No
FLT3-ITD+ or FLT3-TKD+
No
ELN1 or ELN2
No
ELN3
Recommended treatment
7+3+GO[a] [II, A]
CPX-351 [I, A]
7+3+midostaurin [I, A]
7+3 [II, A] Optional: 7+3+GO[a] [II, C]
7+3 [II, A] or 7+3+cladribine or fludarabine[b] [II, C]
1-2 x induction
7+3+GO (induction 2 without GO)
CPX-351
7+3+midostaurin
7+3±GO (induction 2 without GO)
7+3 or 7+3+cladribine or fludarabine[b]
CR
ELN2/ELN3
Consolidation 1
IDAC±GO[c,d]
CPX-351
IDAC +midostaurin
ELN1: IDAC±GO[c,d] ELN2: IDAC±GO[c] or alloHCT
1-2x IDAC if alloHCT is delayed[e]
CR
ELN2/ELN3
Consolidation 2
IDAC±GO[c,d]
CPX-351
IDAC +midostaurin
ELN1: IDAC±GO[c,d] ELN2: alloHCT[f]
alloHCT
CR
alloHCT
Consolidation 3
IDAC
IDAC +midostaurin
ELN1: IDAC ELN2: IDAC (if no alloHCT)
ELN3: IDAC (if no alloHCT)
CR
Maintenance
mol. progression/ mol. relapse
Midostaurin optional
MRD+
mol. progression/ mol. relapse
mol. progression/ mol. relapse
mol. progression/ mol. relapse
MRD+ salvage
alloHCT
alloHCT
alloHCT
alloHCT

- IDAC start for him x 4 cycle
-



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Acute Myeloid Leukemia (Age ≥18 years)

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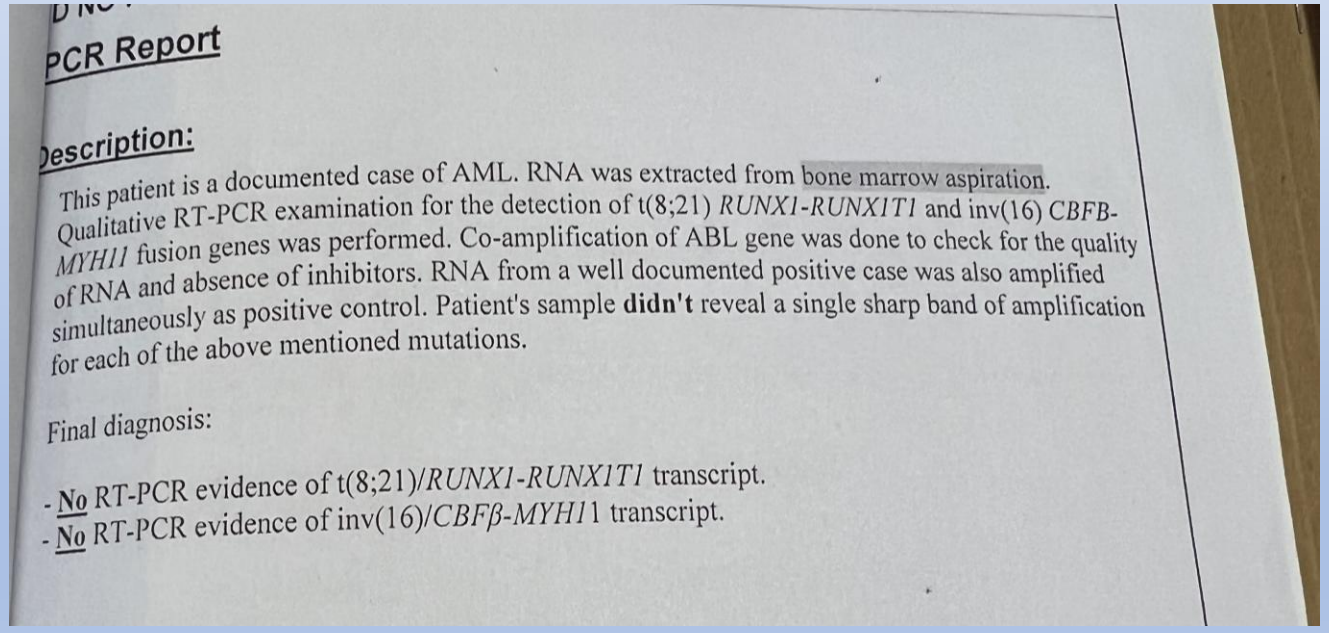
AGE <60 y	RISK STATUS (See AML-A)	CONSOLIDATION THERAPY
	CBF cytogenetic translocations and MRD negative (see AML-G)	Options: • HiDAC 3 g/m² over 3 h every 12 h on days 1, 3, 5 (category 1) or days 1, 2, 3 x 3–4 cycles[ii,jj] with or without gemtuzumab ozogamicin 3 mg/m² (up to one 4.5 mg vial) on day 1 x 2 cycles[l,kk] (CD33-positive, *NPM1* positive, *FLT3* negative) • Cytarabine 1000 mg/m² every 12 hours on days 1–4 + daunorubicin 60 mg/m² on day 1 (first cycle) or days 1–2 (second cycle) + gemtuzumab ozogamicin 3 mg/m² (up to one 4.5 mg vial) on day 1 x 2 cycles[l,kk,ll](CD33-positive)

- At end of consolidation :



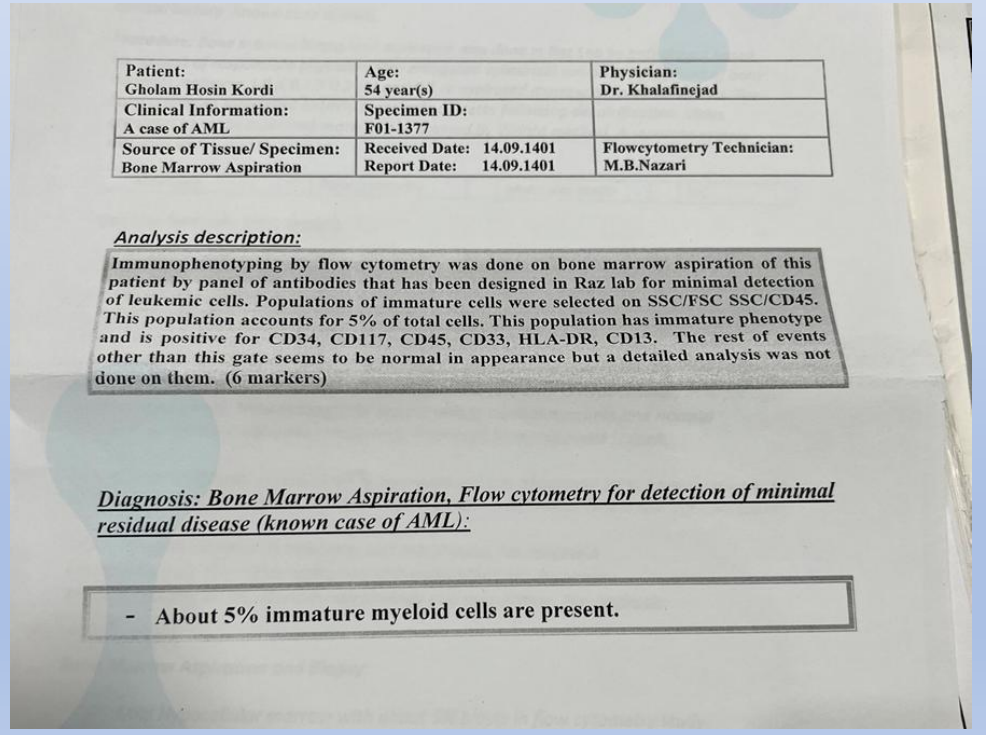
PCR Report

Description:

This patient is a documented case of AML. RNA was extracted from bone marrow aspiration. Qualitative RT-PCR examination for the detection of t(8;21) *RUNX1-RUNX1T1* and inv(16) *CBFB-MYH11* fusion genes was performed. Co-amplification of ABL gene was done to check for the quality of RNA and absence of inhibitors. RNA from a well documented positive case was also amplified simultaneously as positive control. Patient's sample **didn't** reveal a single sharp band of amplification for each of the above mentioned mutations.

Final diagnosis:

- No RT-PCR evidence of t(8;21)/*RUNX1-RUNX1T1* transcript.
- No RT-PCR evidence of inv(16)/*CBFβ-MYH11* transcript.



Patient: Gholam Hosin Kordi	Age: 54 year(s)	Physician: Dr. Khalafinejad
Clinical Information: A case of AML	Specimen ID: F01-1377	
Source of Tissue/ Specimen: Bone Marrow Aspiration	Received Date: 14.09.1401 Report Date: 14.09.1401	Flowcytometry Technician: M.B.Nazari

Analysis description:

Immunophenotyping by flow cytometry was done on bone marrow aspiration of this patient by panel of antibodies that has been designed in Raz lab for minimal detection of leukemic cells. Populations of immature cells were selected on SSC/FSC SSC/CD45. This population accounts for 5% of total cells. This population has immature phenotype and is positive for CD34, CD117, CD45, CD33, HLA-DR, CD13. The rest of events other than this gate seems to be normal in appearance but a detailed analysis was not done on them. (6 markers)

Diagnosis: Bone Marrow Aspiration, Flow cytometry for detection of minimal residual disease (known case of AML):

- **About 5% immature myeloid cells are present.**

Does this patient need more treatment?

MAINTENANCE THERAPY

- **Patient with intermediate or adverse risk disease:**
  - **Who received prior intensive chemotherapy and is now in remission**
  - **Completed no consolidation, some consolidation or a recommended course of consolidation and**
  - **No allogeneic stem cell transplant is planned**

→ **Oral azacitidine 300 mg PO daily on Days 1–14 of each 28-day cycle until progression or unacceptable toxicity[ooo]**

Post allogeneic stem cell transplantation, in remission, and history of *FLT3*-ITD → ***FLT3* inhibitor maintenance**
- **Sorafenib[sss,ttt]**

Neither of the above scenarios is applicable → **Maintenance therapy not recommended**

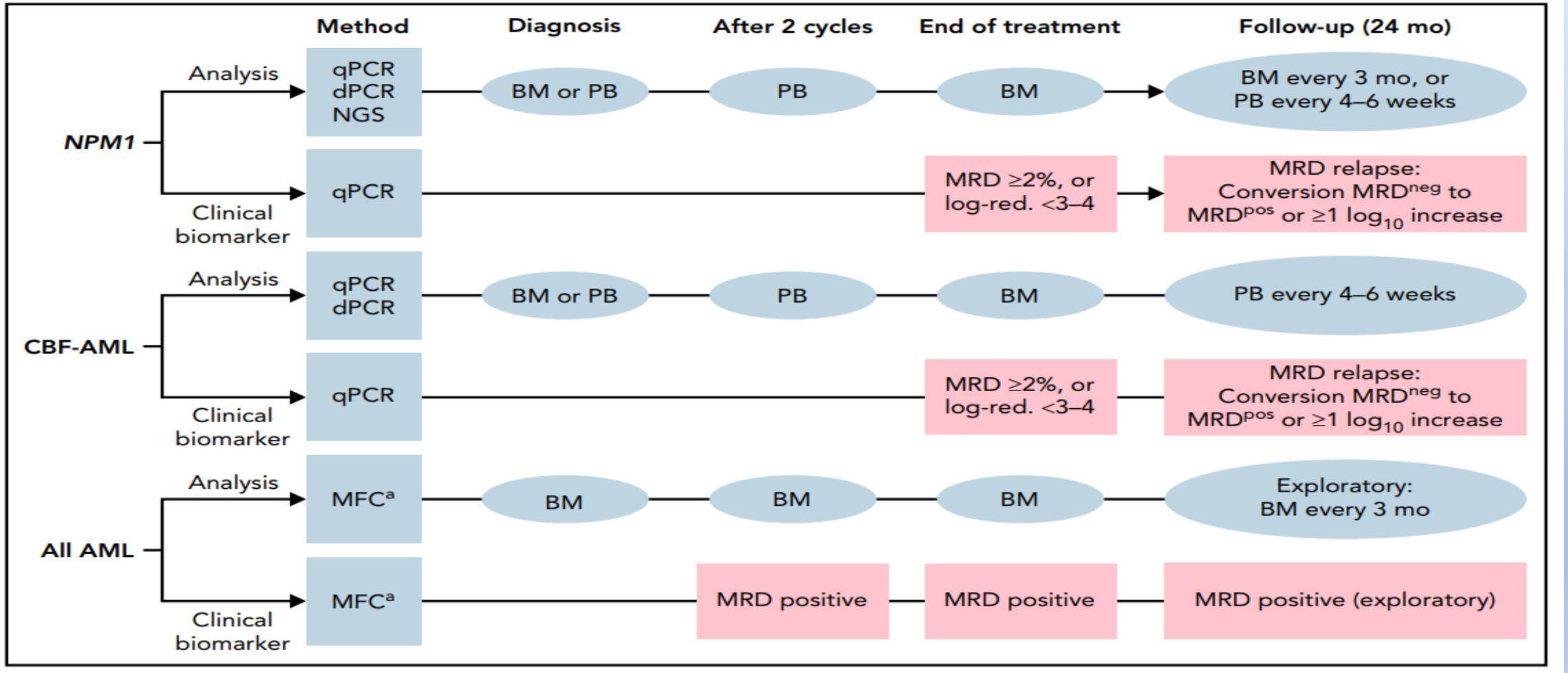
→ **See Surveillance (AML-11)**

Monitoring of measurable residual disease

How Should We Test Patients for MRD?

	Method	Target	Sensitivity	Applicable in % of AML	Turn-around time (days)	Limitations/ problems
Established	Multi-parameter flow cytometry (MFC)	Leukemia-associated immunophenotype (LAIP) or different from normal (DfN)	10^{-3} to 10^{-4}	85-90	2	Less sensitive, more subjective analysis
Established	Real-time quantitative PCR (RT-qPCR)	Robust data: *NPM1*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1* Less validated: *KMT2A*::*MLLT3*, *DEK*::*NUP214*, *BCR*::*ABL1*, *WT1*	10^{-4} to 10^{-5}	40-50*	3-5	Limited applicability
Exploratory	Next-generation sequencing (NGS)†,‡	Potentially any somatic mutation†	10^{-2} to 10^{-4}	~100	5-10	Less sensitive, costly, technically challenging
Exploratory	Digital PCR (dPCR)	Specific targeted mutations	10^{-3} to 10^{-4}	~70	3-5	Specific assay necessary for every mutation, limited sensitivity

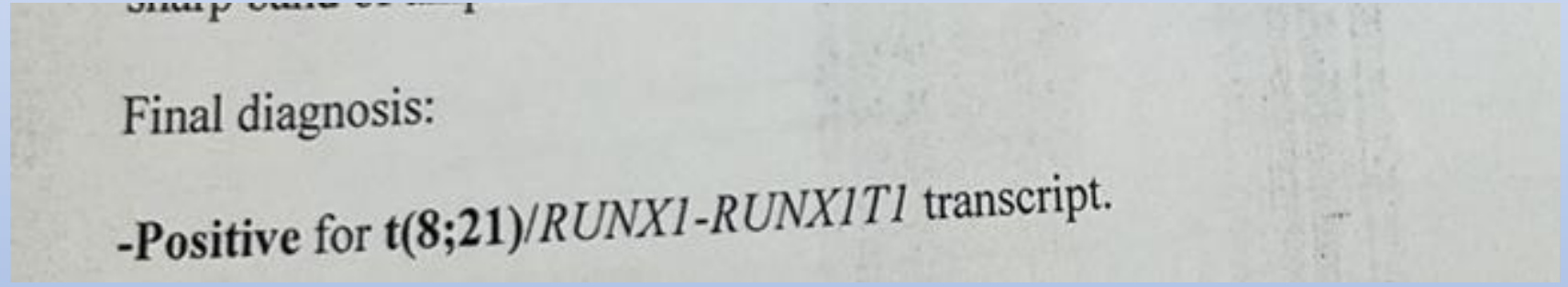
At What Time Points Should We Test for MRD?



What Is the Significance of MRD-Positive Status at First Complete Remission?

- **MRD negativity is associated with longer remissions** and potentially longer rates of survival
- negative MRD test result may not indicate complete disease eradication
- not all patients who are MRD positive will relapse.
- Mol-MRD may remain detectable at low levels (CR_{MRD-LL}) without prognostic significance
- in CBF-AML and NPM1-mutant AML, the transcripts may show persistent low level expression after treatment, but this is not prognostic of relapse.
- For favorable-risk patients, if MRD is persistently positive after induction and/or consolidation, consider a clinical trial or alternative therapies, including allogeneic transplantation(NCCN)

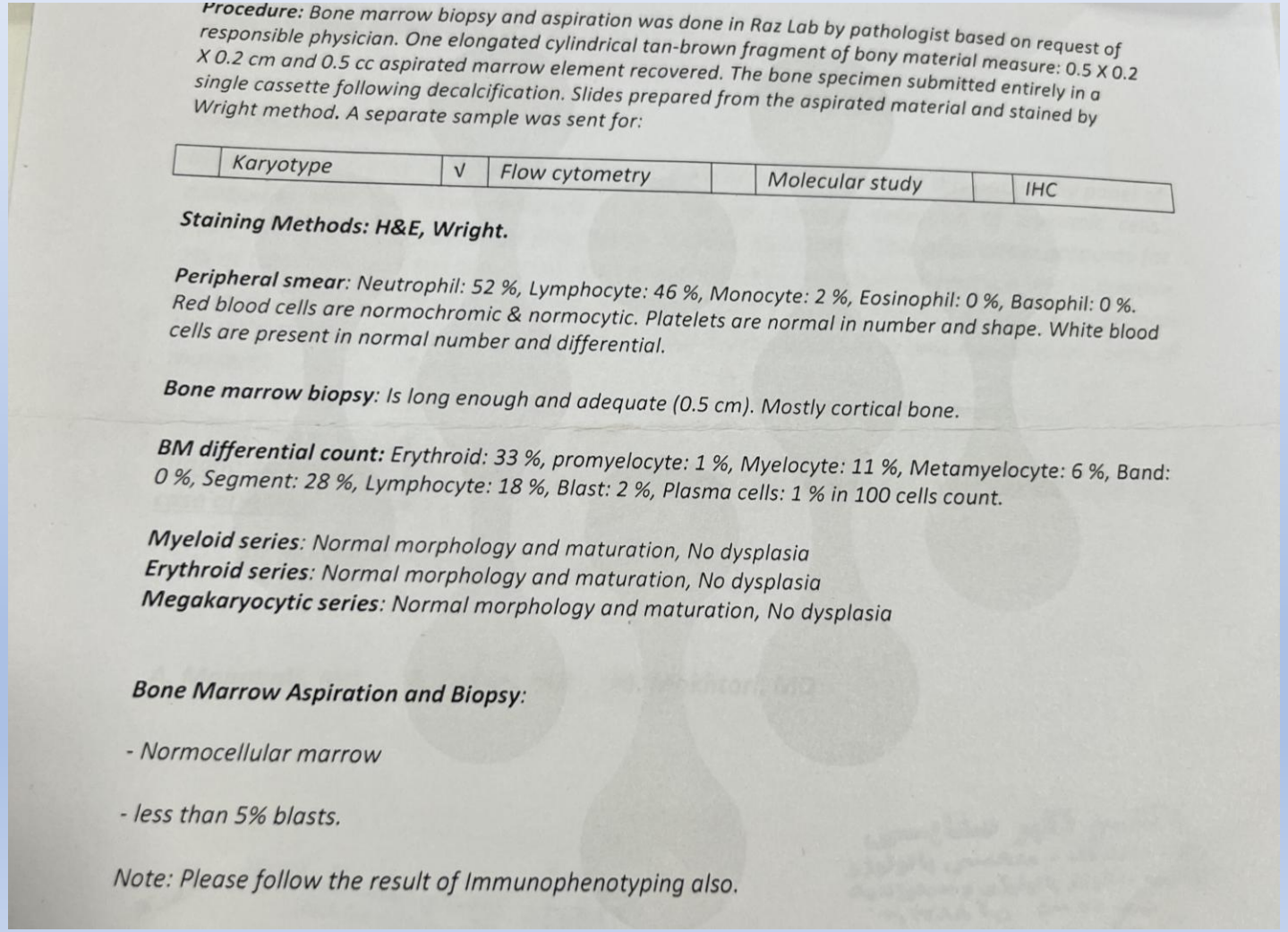
- After 3 m/o MRD recheck for pt:



Final diagnosis:

-**Positive** for **t(8;21)**/*RUNX1-RUNX1T1* transcript.

BM aspiration



Procedure: Bone marrow biopsy and aspiration was done in Raz Lab by pathologist based on request of responsible physician. One elongated cylindrical tan-brown fragment of bony material measure: 0.5 X 0.2 X 0.2 cm and 0.5 cc aspirated marrow element recovered. The bone specimen submitted entirely in a single cassette following decalcification. Slides prepared from the aspirated material and stained by Wright method. A separate sample was sent for:

	Karyotype	√	Flow cytometry		Molecular study		IHC

Staining Methods: H&E, Wright.

Peripheral smear: Neutrophil: 52 %, Lymphocyte: 46 %, Monocyte: 2 %, Eosinophil: 0 %, Basophil: 0 %. Red blood cells are normochromic & normocytic. Platelets are normal in number and shape. White blood cells are present in normal number and differential.

Bone marrow biopsy: Is long enough and adequate (0.5 cm). Mostly cortical bone.

BM differential count: Erythroid: 33 %, promyelocyte: 1 %, Myelocyte: 11 %, Metamyelocyte: 6 %, Band: 0 %, Segment: 28 %, Lymphocyte: 18 %, Blast: 2 %, Plasma cells: 1 % in 100 cells count.

Myeloid series: Normal morphology and maturation, No dysplasia
Erythroid series: Normal morphology and maturation, No dysplasia
Megakaryocytic series: Normal morphology and maturation, No dysplasia

Bone Marrow Aspiration and Biopsy:

- Normocellular marrow

- less than 5% blasts.

Note: Please follow the result of Immunophenotyping also.

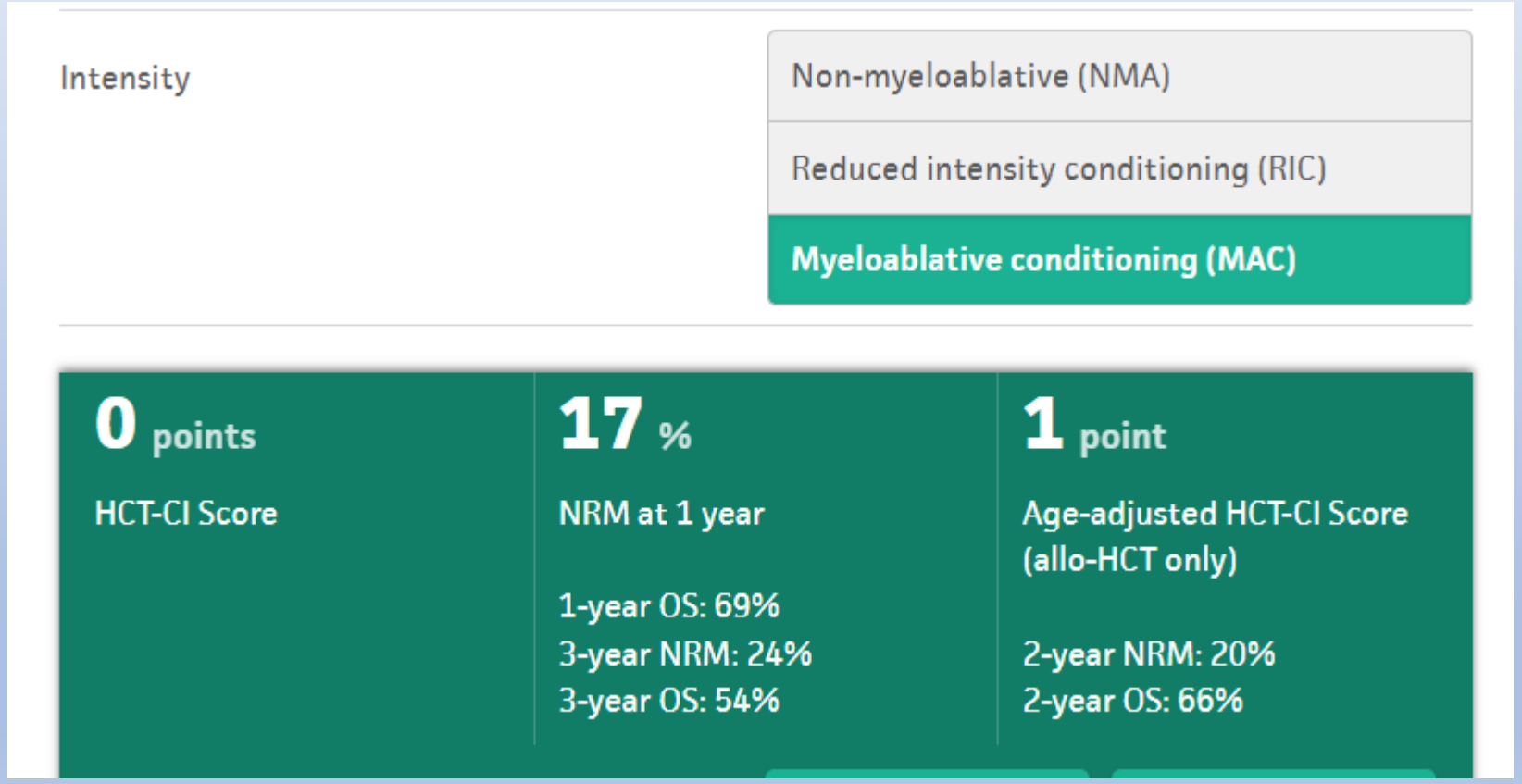
Can We Use MRD-Directed Treatment to Prevent Relapse after Initial Chemotherapy?

- The presence of detectable MRD before transplant is an independent unfavorable predictor of posttransplant outcome.
- However, there is currently no evidence showing benefit of additional courses of intensive chemotherapy prior to transplant in CR1 patients who are MRD positive.

For Whom Is Transplant Indicated?

- GIMEMA AML1310 randomized control trial compared outcomes in favorable and intermediate risk patients . Among the MRD-positive intermediate risk patients who underwent allo-HSCT, outcomes were similar to favorable risk patients (2-year overall survival was 58% and disease-free survival was 61%), suggesting a strong benefit to transplant
- AML17 trial data, patients with AML without the *NPM1* mutation demonstrated more benefit from allo-HSCT if MRDpositive (HR 0.72) than MRD-negative (HR 1.68)
- AML05 trial reported allo-HSCT outcomes in patients with favorable risk t(8;21) AML based on MRD response after the second consolidation . In patients with persistent MRD (<0.3-log reduction in *RUNX1::RUNX1T1* transcripts), allo-HSCT resulted in a lower cumulative incidence of relapse

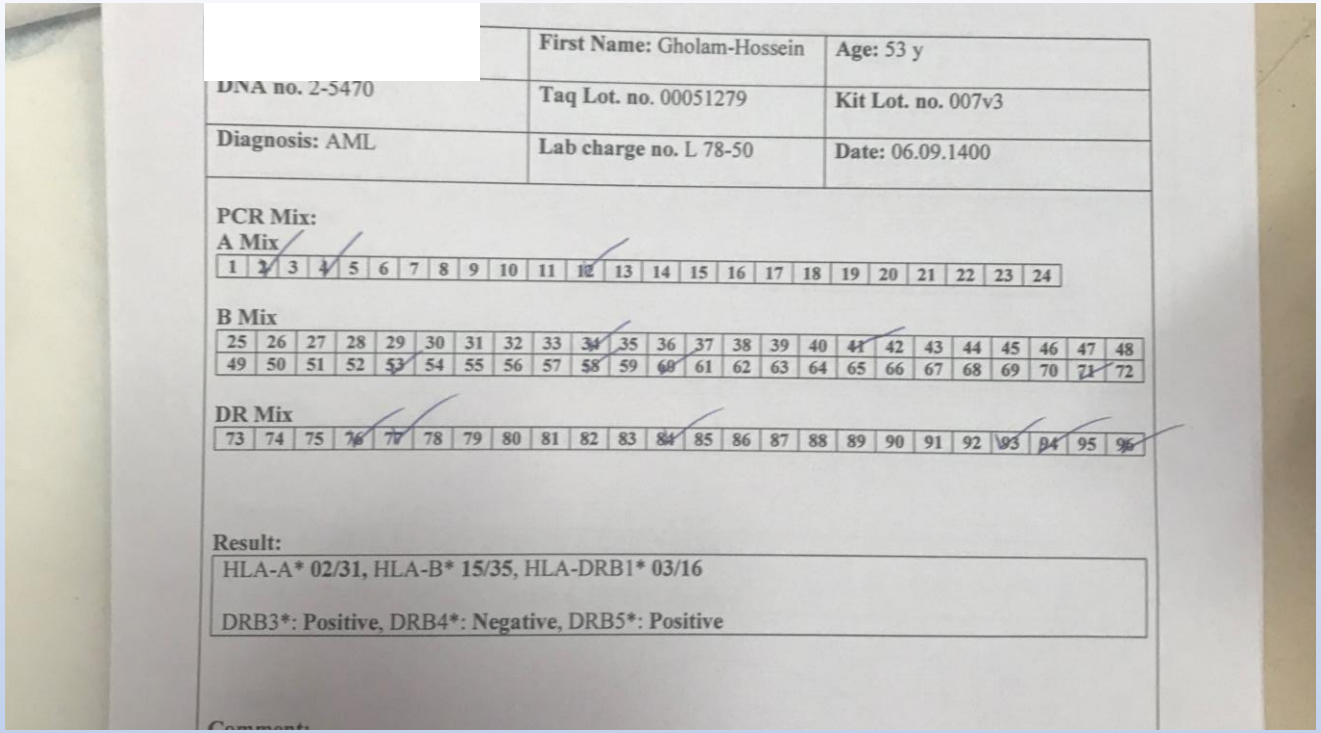
Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI)



MRD, Relapse Risk and TRM

	MRD Satus	Relapse Risk at 1-2 y without Allo-HSCT	TRM (%)	Preferred Post-Remission Therpay
Favorable	Negative	CBF 10% $NPM1^{+}$ $FLT3^{neg}$ 15-20%	none	Chemotherapy /ASCT
	Positive	CBF 40-50% $NPM1^{+}$ $FLT3^{neg}$ 50-60%	< 20-25	Allo-HSCT (MSD, MUD) **If TRM risk acceptable**
Intermediate	Negative	20%	<10	Allo-HSCT (MSD, MUD) **If TRM risk acceptable**
	Positive	60-75%	<30	Allo-HSCT (MSD, MUD, Haplo, CB)
Adverse	Negative	60%	20-25	Allo-HSCT (MSD, MUD, Haplo, CB)
	Positive	90-100%	40-50	Allo-HSCT (MSD, MUD, Haplo, CB)

MRD, Minimal Residual Disease; TRM, Transplnt Related Mortality



	First Name: Gholam-Hossein	Age: 53 y
DNA no. 2-5470	Taq Lot. no. 00051279	Kit Lot. no. 007v3
Diagnosis: AML	Lab charge no. L 78-50	Date: 06.09.1400

PCR Mix:

A Mix

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

B Mix

25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72

DR Mix

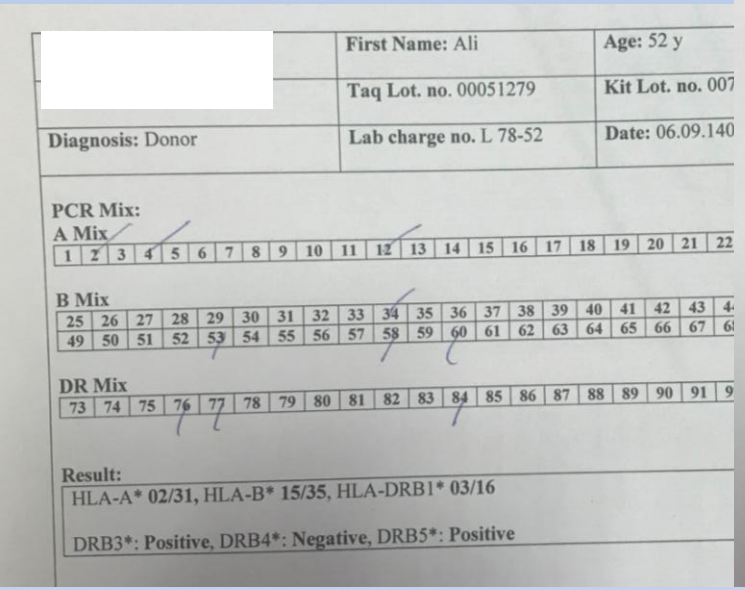
73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96

Result:

HLA-A* **02/31**, HLA-B* **15/35**, HLA-DRB1* **03/16**

DRB3*: **Positive**, DRB4*: **Negative**, DRB5*: **Positive**

Comment:



	First Name: Ali	Age: 52 y
	Taq Lot. no. 00051279	Kit Lot. no. 007
Diagnosis: Donor	Lab charge no. L 78-52	Date: 06.09.140

PCR Mix:

A Mix

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22

B Mix

25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68

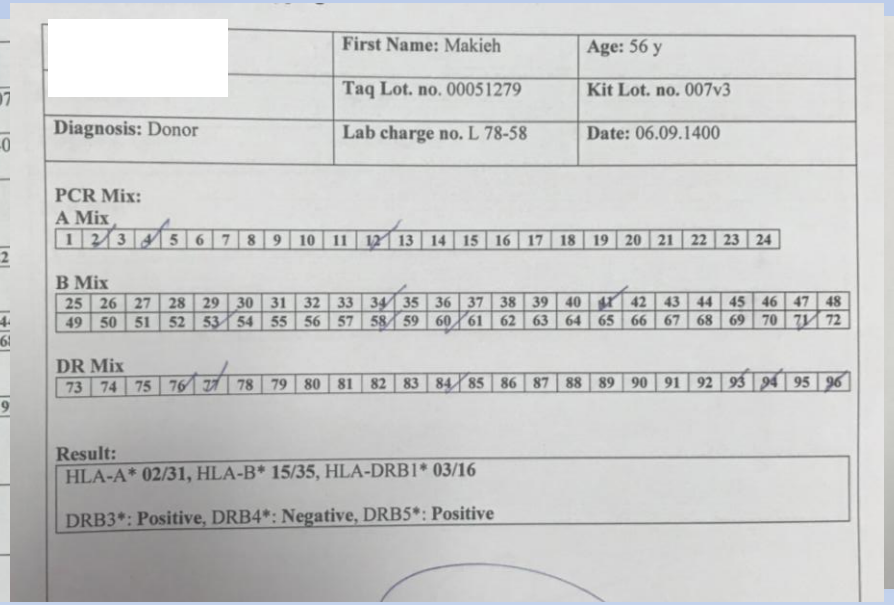
DR Mix

73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	9

Result:

HLA-A* **02/31**, HLA-B* **15/35**, HLA-DRB1* **03/16**

DRB3*: **Positive**, DRB4*: **Negative**, DRB5*: **Positive**



	First Name: Makieh	Age: 56 y
	Taq Lot. no. 00051279	Kit Lot. no. 007v3
Diagnosis: Donor	Lab charge no. L 78-58	Date: 06.09.1400

PCR Mix:

A Mix

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

B Mix

25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72

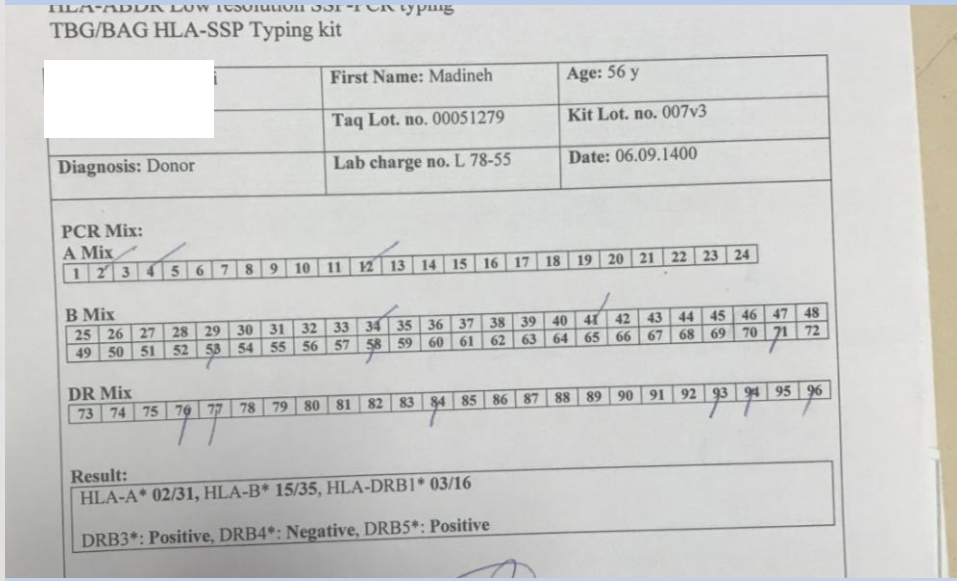
DR Mix

73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96

Result:

HLA-A* **02/31**, HLA-B* **15/35**, HLA-DRB1* **03/16**

DRB3*: **Positive**, DRB4*: **Negative**, DRB5*: **Positive**



HLA-ABDR Low resolution SSP-PCR typing

TBG/BAG HLA-SSP Typing kit

	First Name: Madineh	Age: 56 y
	Taq Lot. no. 00051279	Kit Lot. no. 007v3
Diagnosis: Donor	Lab charge no. L 78-55	Date: 06.09.1400

PCR Mix:

A Mix

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

B Mix

25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72

DR Mix

73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96

Result:

HLA-A* **02/31**, HLA-B* **15/35**, HLA-DRB1* **03/16**

DRB3*: **Positive**, DRB4*: **Negative**, DRB5*: **Positive**

Prognostic Value of MRD Prior to Transplant

- Araki et al. demonstrated similar 3-year overall survival and relapse rates in patients transplanted with active disease versus MRD-positive CR (23% vs. 26%, 65% vs. 67%); compared to these cohorts, outcomes were improved in patients in MRD-negative CR (3 year overall survival 73%, relapse rate 22%)
- Jentzsch et al., wherein 392 patients in either MRD-negative CR, MRD-positive CR, or with active disease had progressively worse event-free survival after allo-HSCT
- Gilleece et al. similarly found higher 2-year relapse rates in MRD-positive (40%) versus MRD-negative (24%) patients
- Jentzsch et al. identified MRD-positive status prior to HSCT as a significant factor for relapse in the ELN favorable and intermediate groups, but not in the adverse group

Can Changes in Conditioning and GVHD Prophylaxis Alter the Impact of Pre-Transplant MRD?

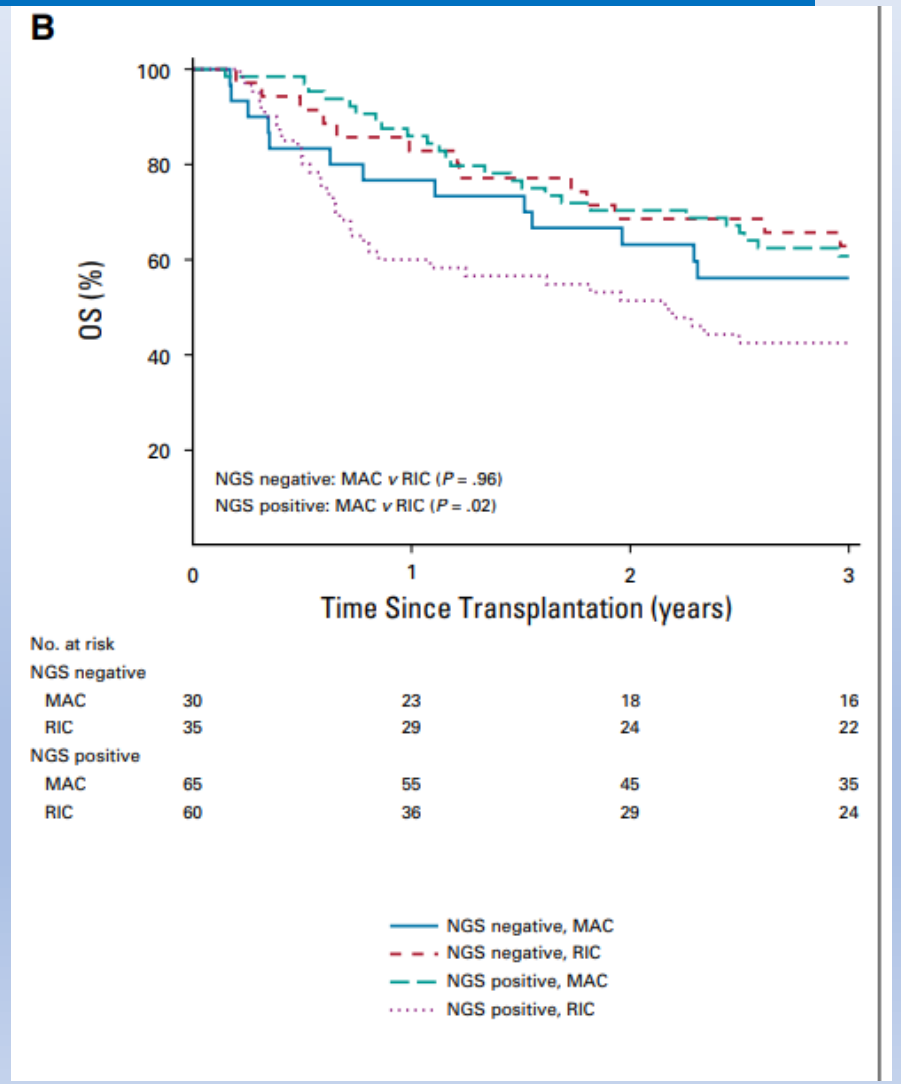
J Clin Oncol. 2020 Apr 20;38(12):1273-1283. doi: 10.1200/JCO.19.03011. Epub 2019 Dec 20.

Impact of Conditioning Intensity of Allogeneic Transplantation for Acute Myeloid Leukemia With Genomic Evidence of Residual Disease

CONCLUSION: This study provides evidence that MAC rather than RIC in patients with AML with genomic evidence of MRD before alloHCT can result in improved survival.

in patients transplanted with a MAC regimen, levels of MRD pre-transplant

did not appear to affect outcomes post-transplant.



Can We Use MRD to Determine Optimal Donor Type?

- Few prospective studies compare outcomes after haploidentical (haplo-HSCT) versus HLA-matched sibling donor transplant (MSDT)
- Among patients who were MRD positive prior to transplant in a study that combined retrospective and prospective data, haplo-HSCT was associated with lower relapse (19% vs. 55%) and improved overall survival (83% vs. 38%) at 4 years when compared to MSDT
- patients who received haplo-HSCT had lower rates of post-transplant MRD compared to MSDT (18% vs. 42%)
- This difference was attributed to a greater graft-versus-leukemia effect in haplo-HSCT.

How Should We Treat MRD Relapse during Post-Transplant Surveillance?

- treatment for patients with MRD relapse after allo-HSCT can include matched DLI with the reduction or withdrawal of immunosuppression.

- the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation recommends the use of pre-emptive matched DLI for patients with evidence of MRD post-allo-HSCT

Back to the case

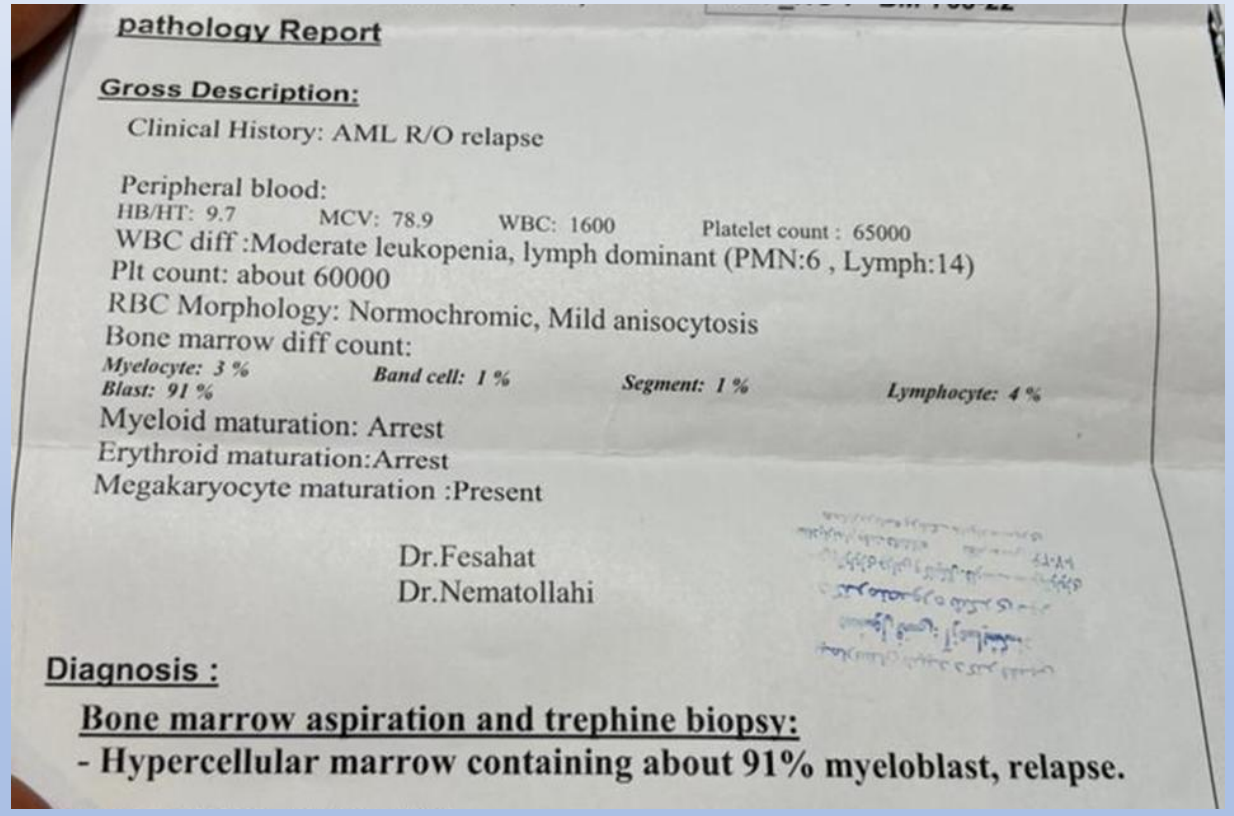
- After MRD was positive, the patient was referred for transplantation, but during the time that passed for the preparation of transplantation, the patient returned with pancytopenia .

Count	Value	Reference Range
White blood cells	$2.2 \times 10^9/L$	$4 \times 10^9/L – 10 \times 10^9/L$
Hemoglobin	9.6 g/dL	14 – 18 g/dL
Platelet count	$36 \times 10^9/L$	$150 \times 10^9/L – 450 \times 10^9/L$

White blood cell (WBC) differential is notable for 75 percent blasts. Peripheral blood smear shows a vast majority of cells are large blasts with occasional cytoplasmic granules

Bone marrow aspiration and biopsy

Bone marrow aspiration and biopsy is performed, revealing a hypercellular marrow involved with blasts comprising 91 percent of bone marrow cellularity



pathology Report

Gross Description:

Clinical History: AML R/O relapse

Peripheral blood:
HB/HT: 9.7 MCV: 78.9 WBC: 1600 Platelet count : 65000
WBC diff :Moderate leukopenia, lymph dominant (PMN:6 , Lymph:14)
Plt count: about 60000
RBC Morphology: Normochromic, Mild anisocytosis
Bone marrow diff count:
Myelocyte: 3 % *Band cell: 1 %* *Segment: 1 %* *Lymphocyte: 4 %*
Blast: 91 %
Myeloid maturation: Arrest
Erythroid maturation:Arrest
Megakaryocyte maturation :Present

Dr.Fesahat
Dr.Nematollahi

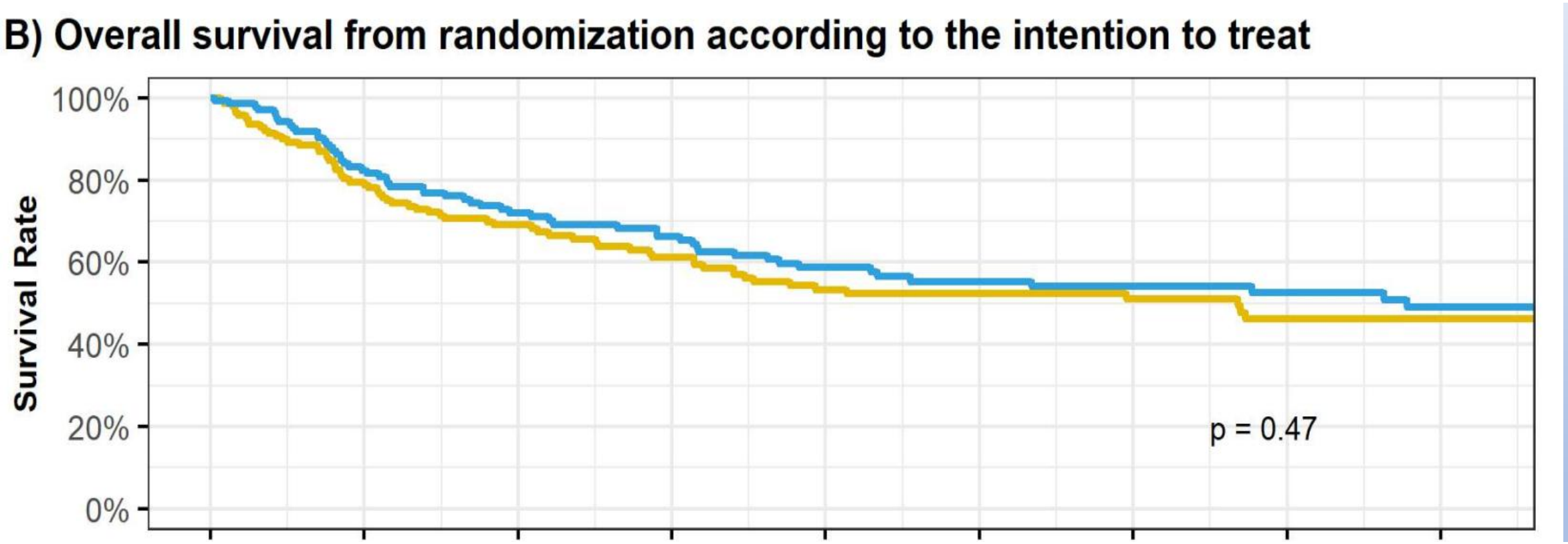
Diagnosis :

Bone marrow aspiration and trephine biopsy:
- Hypercellular marrow containing about 91% myeloblast, relapse.

What is the best decision to continue treating the patient?

- Salvage chemotherapy then transplantation
- Upfront transplantation

4 In Patients with Relapsed/Refractory AML Sequential Conditioning and Immediate Allogeneic Stem Cell Transplantation (allo-HCT) Results in Similar Overall and Leukemia-Free Survival Compared to Intensive Remission Induction Chemotherapy Followed By Allo-HCT: Results from the Randomized Phase III ASAP Trial



This is the first randomized controlled trial, which questioned the benefit of intensive remission induction CT prior to alloHCT for pts with r/r AML. Chemotherapy with high-dose cytarabine and mitoxantrone before alloHCT did not result in a higher overall success rate and did not confer a survival advantage. Watchful waiting followed by sequential conditioning and alloHCT resulted in comparable overall CR rates and survival. These data support sequential conditioning and alloHCT without prior remission induction CT whenever a stem cell donor is readily available. Finally, these results underline the importance of facilitating alloHCT as most effective anti-leukemic therapy in patients with r/r AML and stress the need for starting donor search at diagnosis.