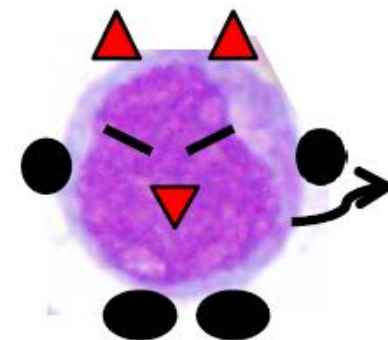




The outcome of AML by ELN 2022 risk stratification in real practice

Chantiya Chanswangphuwana, MD

16 Mar 2025





Disclosure

None

Scope of my talk

- AML and ELN 2022 risk stratification
- Outcome of AML from TALWG and KCMH
- Non-HSCT outcome for intermediate- and high-risk AML from TALWG
- *FLT3*-ITD mutated AML from TALWG
- Secondary AML from TALWG
- Favorable-risk AML from TALWG and KCMH

Acute myeloid leukemia (AML)

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

1. Acute myeloid leukemia with defining genetic abnormalities
2. Acute myeloid leukemia, defined by differentiation
3. Myeloid sarcoma

Secondary myeloid neoplasm

(Addition term as qualifiers to relevant myeloid disease types in the classification)

- Myeloid neoplasms post cytotoxic therapy (AML pCT or MDS pCT)
- Myeloid neoplasms associated with germline predisposition



Acute myeloid leukaemia with defining genetic abnormalities

Acute promyelocytic leukaemia with *PML::RARA* fusion

Acute myeloid leukaemia with *RUNX1::RUNX1T1* fusion

Acute myeloid leukaemia with *CBFB::MYH11* fusion

Acute myeloid leukaemia with *DEK::NUP214* fusion

Acute myeloid leukaemia with *RBM15::MRTFA* fusion

Acute myeloid leukaemia with *BCR::ABL1* fusion ★

Acute myeloid leukaemia with *KMT2A* rearrangement

Acute myeloid leukaemia with *MECOM* rearrangement

Acute myeloid leukaemia with *NUP98* rearrangement

Acute myeloid leukaemia with *NPM1* mutation

Acute myeloid leukaemia with *CEBPA* mutation ★

Acute myeloid leukaemia, myelodysplasia-related ★

Acute myeloid leukaemia with other defined genetic alterations

Not require blast
≥20% except ★

Cytogenetic and molecular abnormalities defining AML-MR



Defining cytogenetic abnormalities

Complex karyotype (≥ 3 abnormalities)

5q deletion or loss of 5q due to unbalanced translocation

Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation

11q deletion

12p deletion or loss of 12p due to unbalanced translocation

Monosomy 13 or 13q deletion

17p deletion or loss of 17p due to unbalanced translocation

Isochromosome 17q

idic(X)(q13)

Defining somatic mutations

ASXL1

BCOR

EZH2

SF3B1

SRSF2

STAG2

U2AF1

ZRSR2

Or history of MDS or MDS/MPN are required for diagnosing AML-MR.

การพยากรณ์โรคของ AML at diagnosis ตาม 2022 ELN risk stratification



กลุ่มความเสี่ยง	ความผิดปกติที่ตรวจพบ
Favorable	• t(8;21)(q22;q22.1)/<i>RUNX1::RUNX1T1</i> โดยไม่ขึ้นกับ <i>KIT</i>* หรือ <i>FLT3</i> mutation • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/<i>CBFB::MYH11</i> โดยไม่ขึ้นกับ <i>KIT</i> หรือ <i>FLT3</i> mutation • Mutated <i>NPM1</i> without <i>FLT3-ITD</i> และไม่มี adverse cytogenetic abnormality • Basic leucine zipper in-frame mutated <i>CEBPA</i> แบบ single หรือ biallelic ก็ได้
Intermediate	• Mutated <i>NPM1</i> with <i>FLT3-ITD</i>** และไม่มี adverse cytogenetic abnormality • Wild-type <i>NPM1</i> with <i>FLT3-ITD</i>** (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/<i>MLL T3::KMT2A</i> โดยไม่ขึ้นกับ gene mutation อื่นที่พบ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

*การตรวจพบ *KIT* mutation ใน favorable risk leukemia ตาม ELN 2565 พบว่าไม่ส่งผลต่อ prognosis หากมีการตรวจติดตามระดับ measurable residual disease แต่หากตรวจไม่ได้ สามารถพิจารณาเป็น high risk ได้เพื่อให้ผู้ป่วยได้รับประโยชน์จากการรักษาสูงสุดด้วยการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด

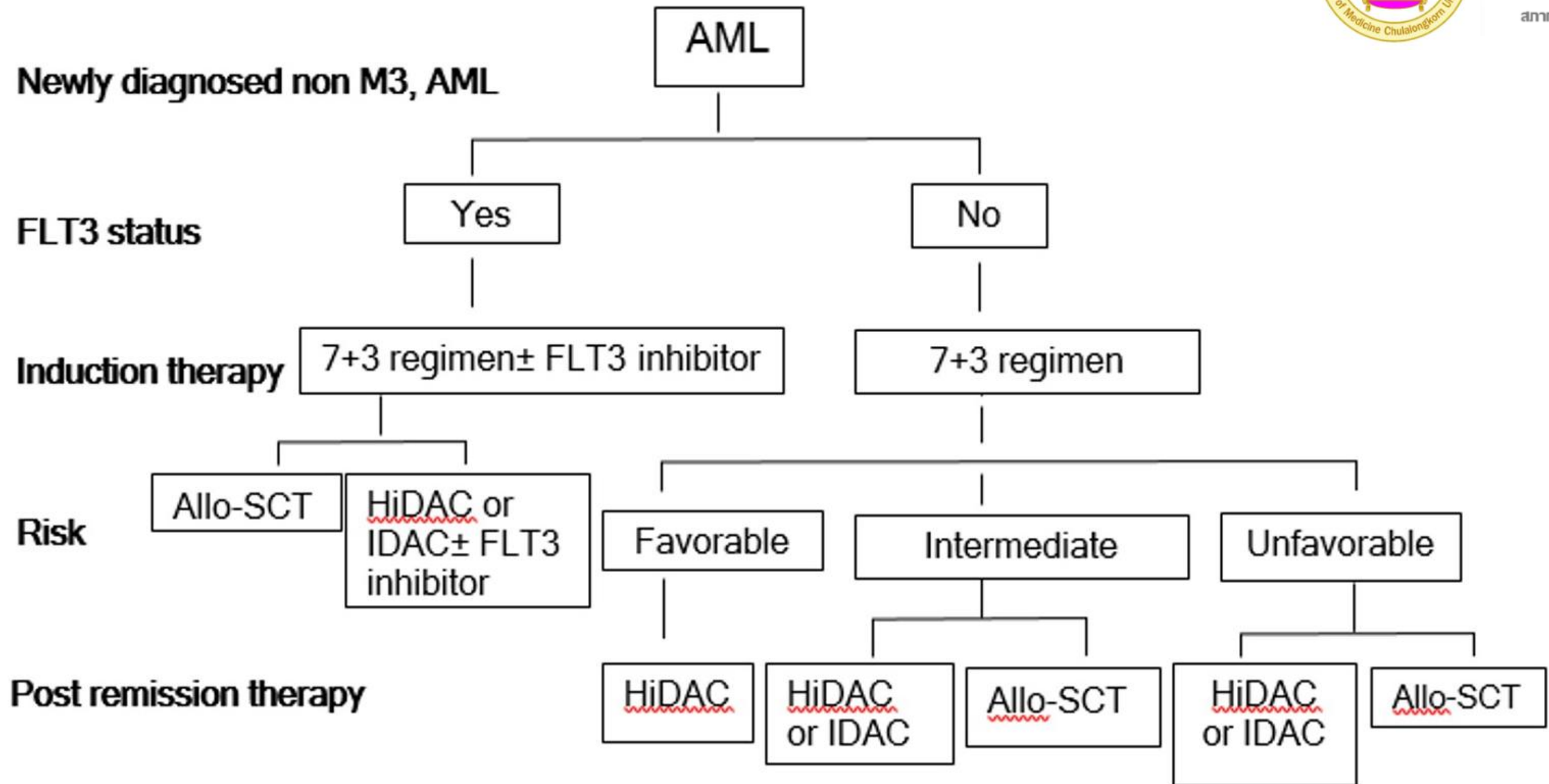
**การตรวจพบ *FLT3-ITD* mutation ใน ELN 2565 จัดเป็น intermediate risk โดยไม่ขึ้นกับ allelic ratio เนื่องจากการตอบสนองที่ดีต่อยา *FLT3* inhibitor แต่สำหรับประเทศไทยที่การตรวจ *FLT3-ITD* ไม่ทราบถึง allelic ratio รวมทั้งไม่สามารถเข้าถึงยา *FLT3* inhibitor สามารถพิจารณาเป็น high risk ได้เพื่อให้ผู้ป่วยได้รับประโยชน์จากการรักษาสูงสุดด้วยการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด

การพยากรณ์โรคของ AML at diagnosis ตาม 2022 ELN risk stratification



Adverse	• t(6;9)(p23.3;q34.1)/<i>DEK::NUP214</i> • t(v;11q23.3)/<i>KMT2A</i>-rearranged (ที่ไม่ใช่ partial tandem duplication) • t(9;22)(q34.1;q11.2)/<i>BCR::ABL1</i> • t(8;16)(p11.2;p13.3)/<i>KAT6A::CREBBP</i> • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/<i>GATA2, MECOM(EVI1)</i> • t(3q26.2;v)/<i>MECOM(EVI1)</i>-rearranged • -5 or del(5q); -7; -17/abnormal (17p) • Complex karyotype (ตั้งแต่ 3 structural abnormalities ขึ้นไป โดยไม่นับ hyperdiploid, trisomy ที่มากกว่า 3 chromosome หรือ polysomies) • Monosomal karyotype • Mutated <i>ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1</i>, and/or <i>ZRSR2</i> • Mutated <i>TP53</i> (อย่างน้อยที่ variant allele frequency $\geq 10\%$)
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Treatment plan for adult AML age < 60 years



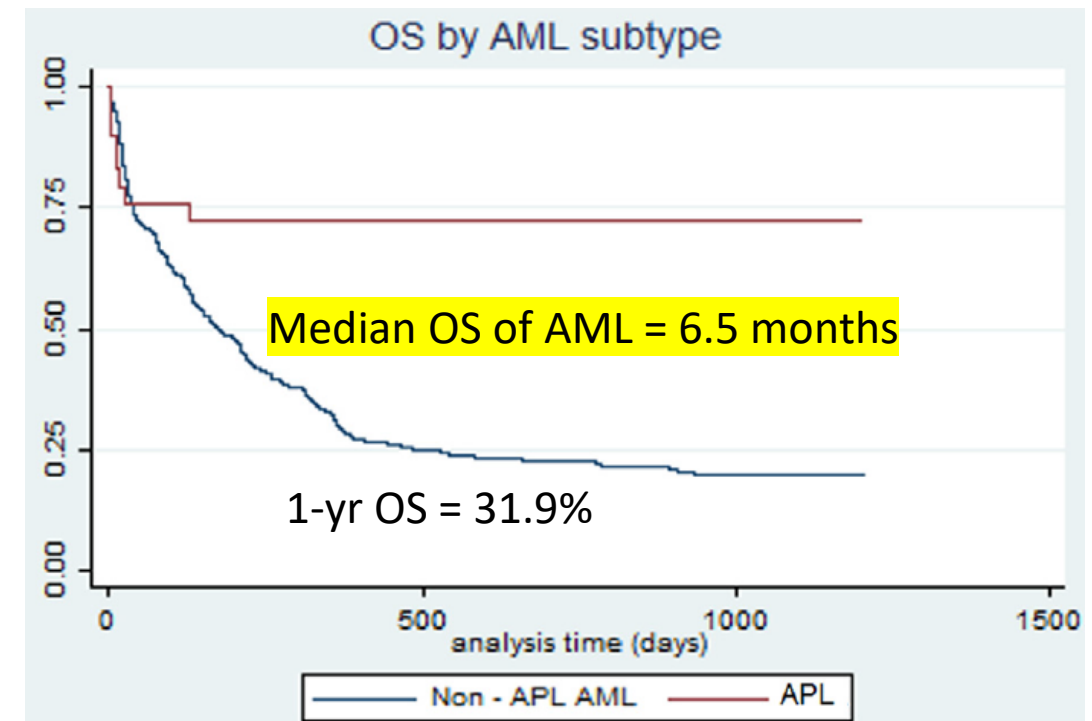
Types, Clinical Features, and Survival Outcomes of Patients with Acute Myeloid Leukemia in Thailand: A 3-Year Prospective Multicenter Study from the Thai Acute Leukemia Study Group (TALSG)



Chinadol Wanitpongpun, et al.

(9 tertiary hospitals; Year 2014 – 2017)

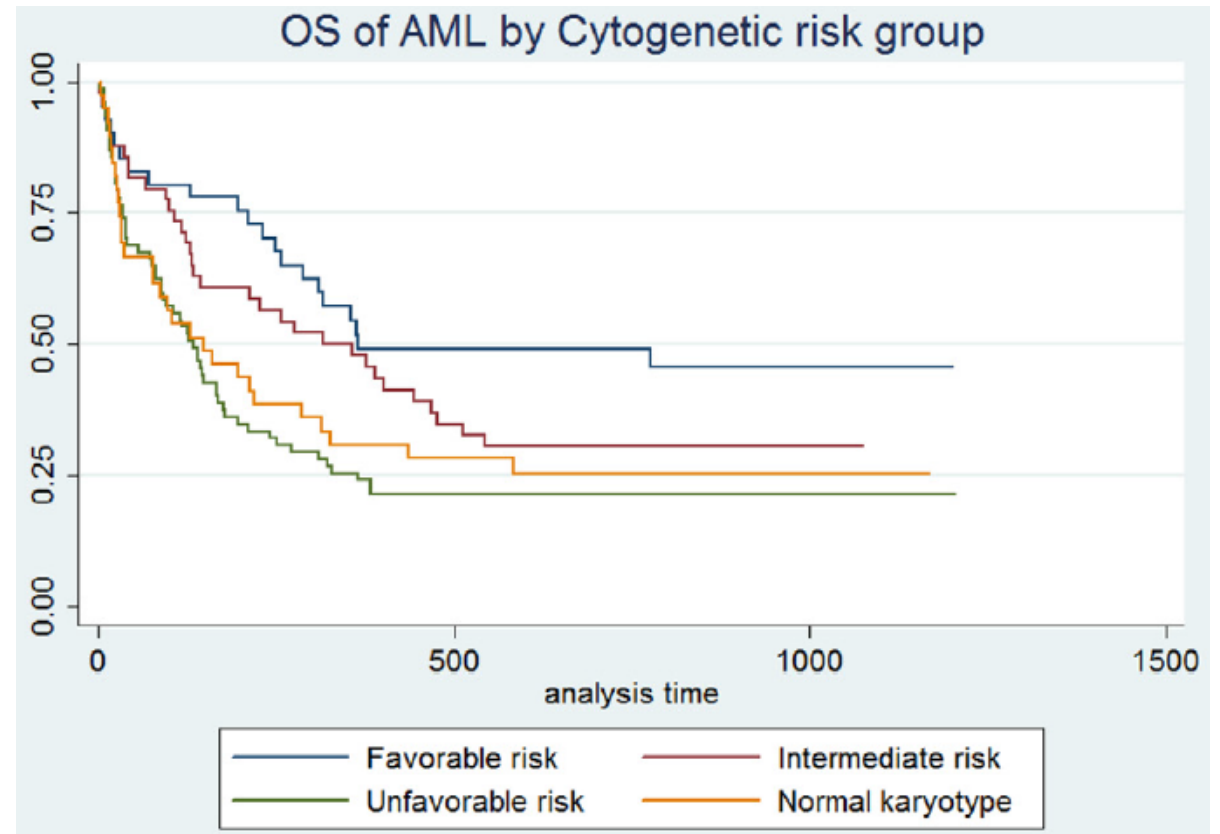
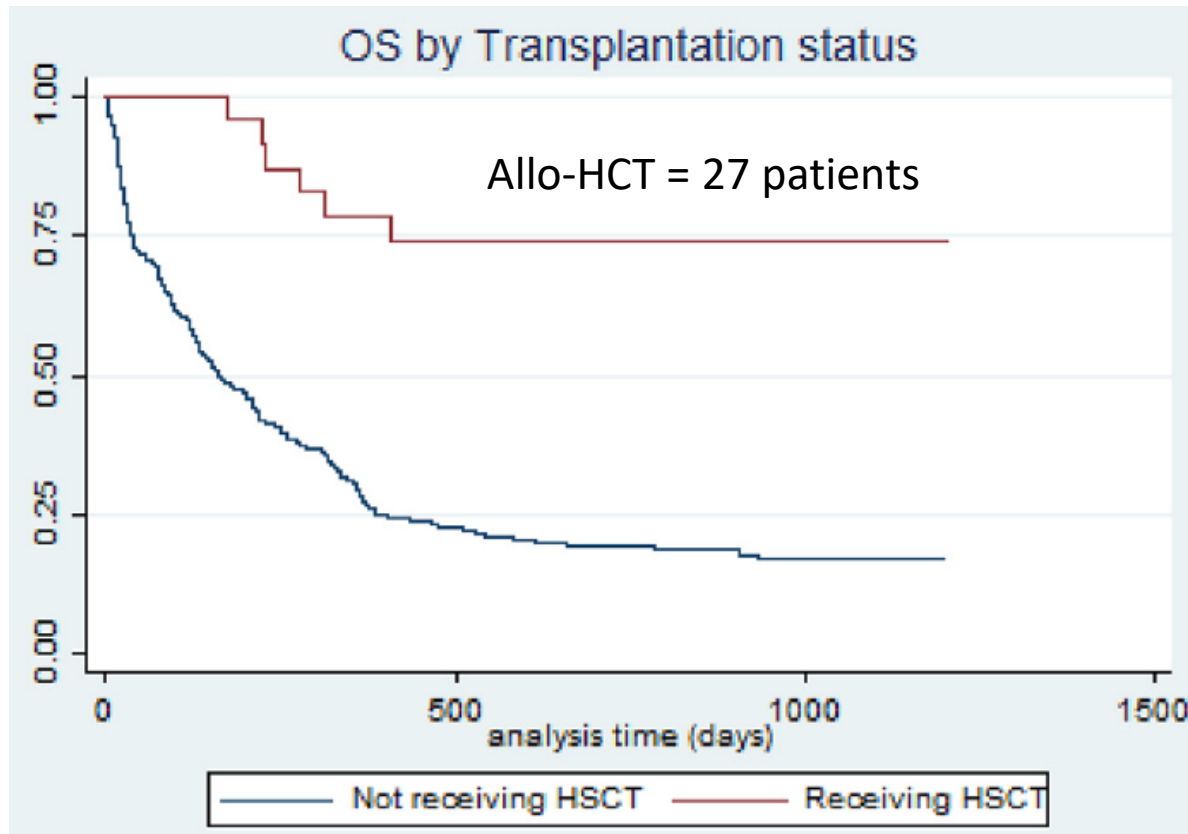
- AML (non-APL) patient = 618 patients
- Median age = 55 (42 – 64) years old
- Favorable cytogenetic risk 16.6%
- Intermediate cytogenetic risk 21.7%
- Poor cytogenetic risk 34.4%
- Receive 7+3 regimen = 55.7%
- Complete remission after 1st induction = 60.2%



Types, Clinical Features, and Survival Outcomes
of Patients with Acute Myeloid Leukemia in
Thailand: A 3-Year Prospective Multicenter Study
from the Thai Acute Leukemia Study Group
(TALSG)



Currently 1668 cases in AML registry (11 centers)
→ update OS is ongoing.

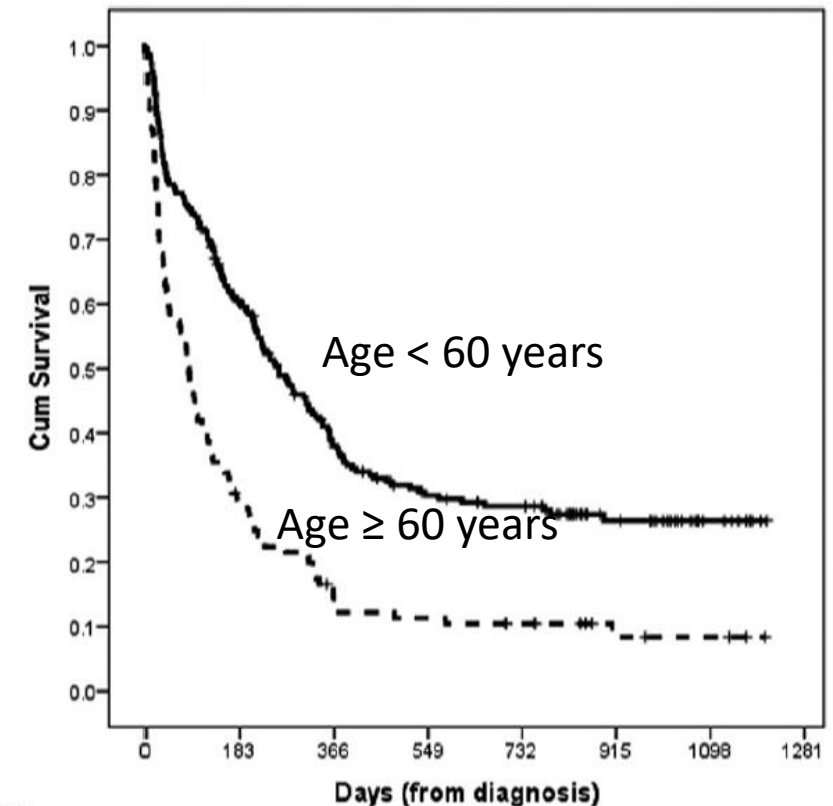


Improved Survival of Elderly-fit Patients With Acute Myeloid Leukemia Requiring Intensive Therapy: 3-Year Multicenter Analysis From TALWG (Year 2014 – 2016)



Weerapat Owattanapanich, et al.

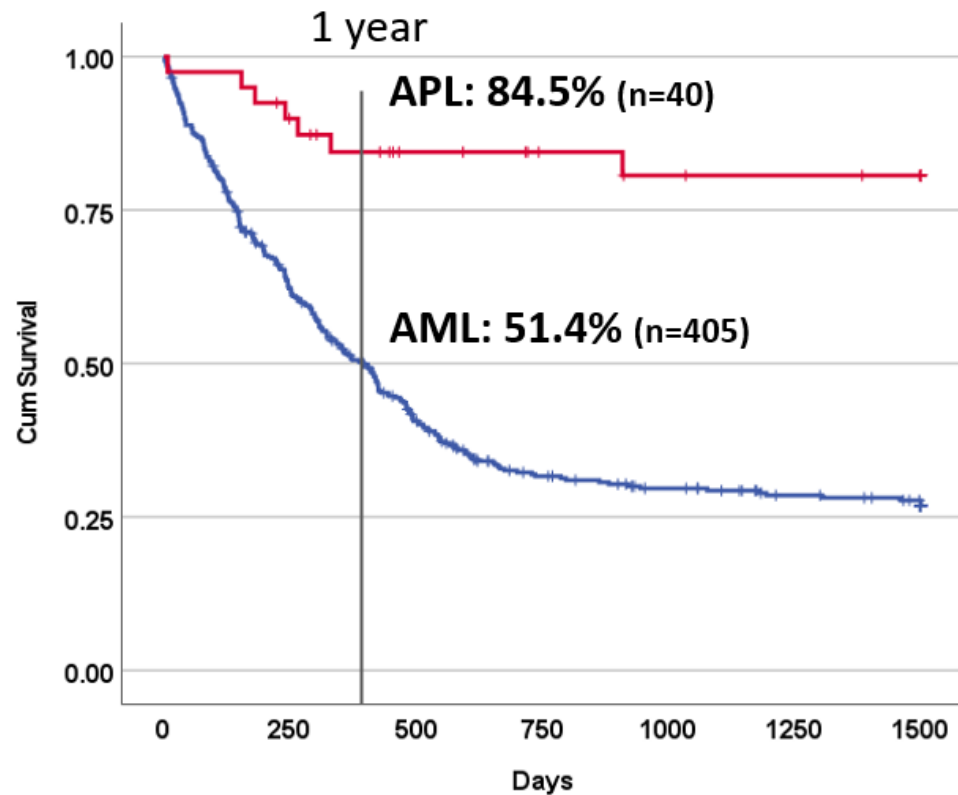
- Elderly patients: ≥ 60 years old $\rightarrow$ 235 patients
- Median age of elderly patients = 70 years old
- Intermediate risk 73.8%, Adverse risk 22.6%
- Compared with younger patient: 445 patients
- Median OS of elderly patient = 128.2 days (4 months)
- The significant factors associated with an improved long-term OS were patients with ECOG 0 - 2 and those receiving intensive therapy.



Age <60 years								
N patients at risk	219	126	76	56	50	27	10	
N cumulative death	87	132	147	150	153	153	153	
Age ≥ 60 years								
N patients at risk	124	35	15	13	10	4	3	
N cumulative death	88	107	109	110	111	111	111	

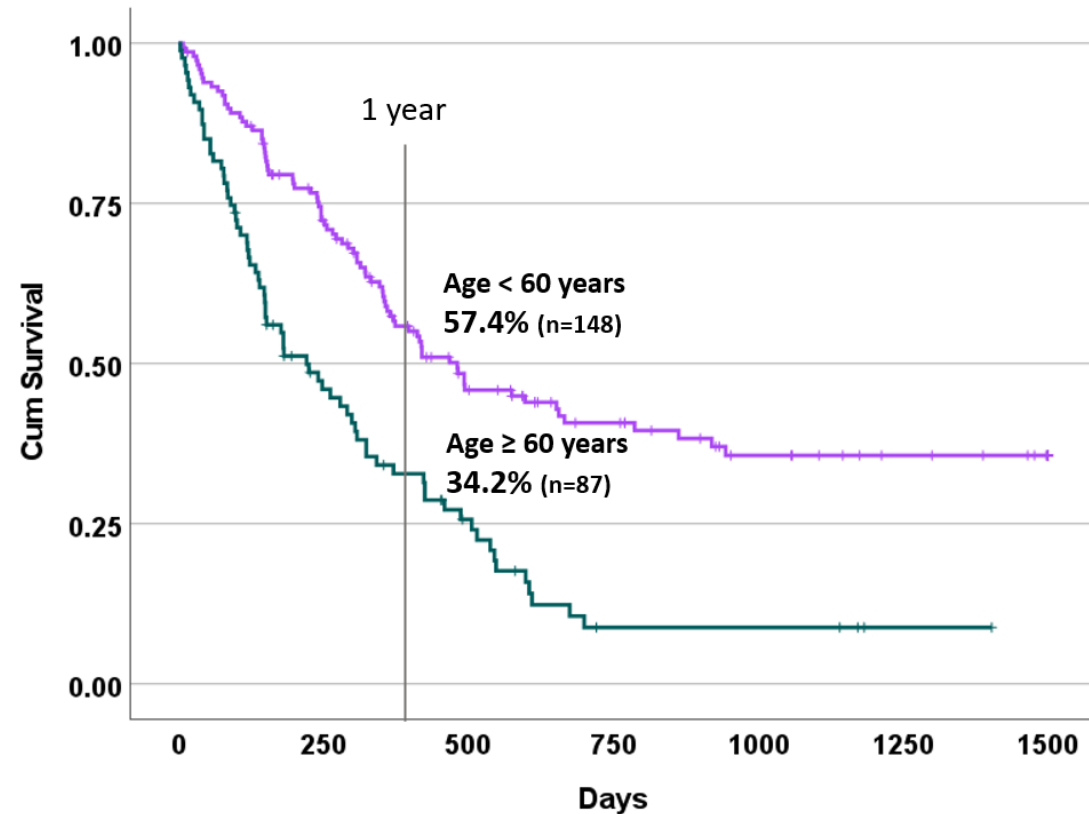
King Chulalongkorn Memorial Hospital (DSC-AML)

Overall Survival of AML patients
(KCMH) from 2015-2024 (N = 445)



Median OS in AML = 395 days (1.1 years)

Overall Survival of AML patients (KCMH) from 2019-2024 (N = 235) by age



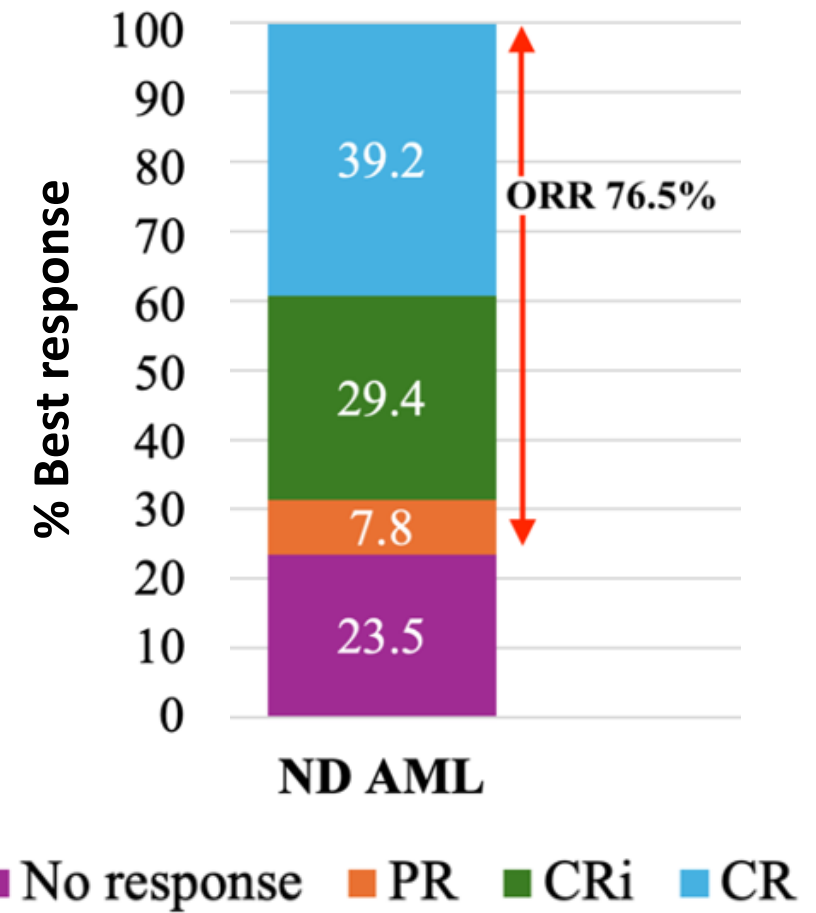
Median OS in elderly = 182 days (6 months)

Real-World Efficacy and Toxicity of Azacitidine Plus Venetoclax in Adult Acute Myeloid Leukemia: A Multicenter Thai cohort

Thanawat Rattanathammethee, et al

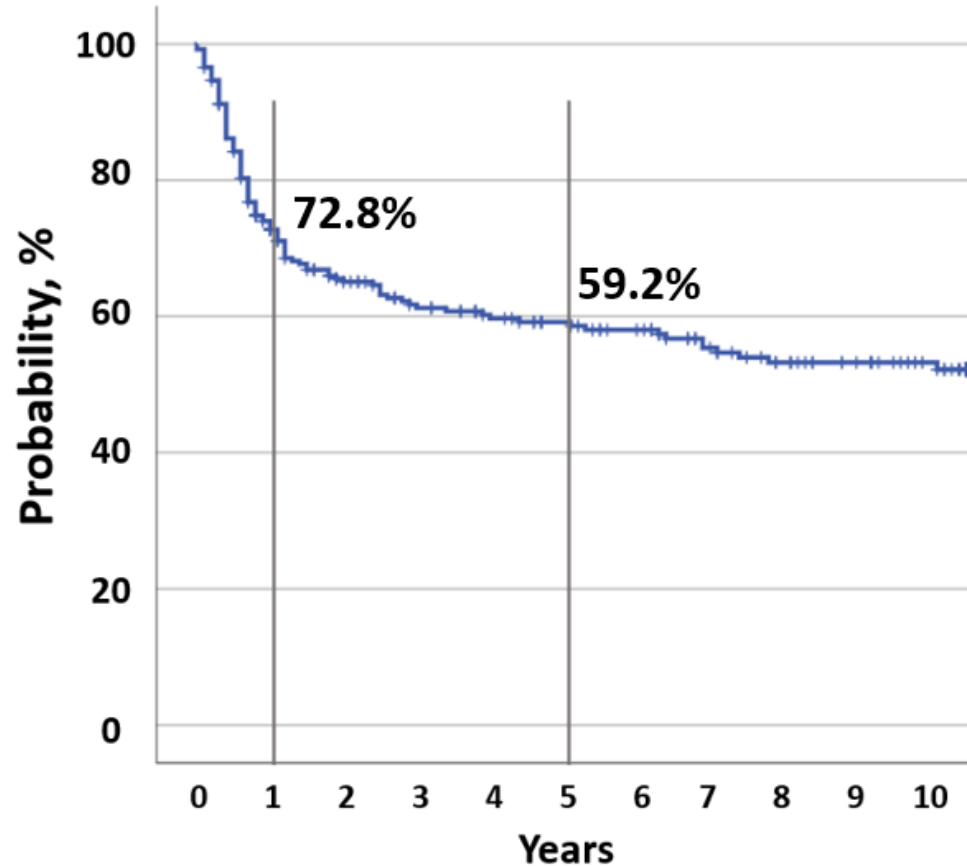
(Year 2021 – 2024)

- 54 newly Dx elderly AML patients (median age 68 years)
- ECOG 0-1 = 70.4%, prior MDS/MPN 27.8% (no prior Aza)
- Favorable 18.5%, Int risk 46.3%, Adverse risk 32.2%
- Azacitidine 75mg/m² sc * 7 days
- Ven 100 mg * 28 (14-28) days + Posaconazole/Voriconazole
- 60.9% CR+CRi (1st cycle), 68.6% CR+CRi (best response)
- Induction dead 5%, Allo-HCT 9.3%
- Median duration of each cycle = 35 days (4 cycles; 1-24)
- Median OS = 14.4 months (median RFS 8.5 months)



King Chulalongkorn Memorial Hospital (DSC-AML)

Overall Survival after Allo-HCT for AML (KCMH), 1991-2024 (N = 262)



Prognostic factors and impact of CMV reactivation on acute myeloid leukemia patients after HLA-matched myeloablative allogeneic stem cell transplantation in a high CMV prevalence country

- 85 AML patient CR in underwent Allo-HCT (2011-2021)
- 3-yr RFS and OS = 72.2% and 80.8%, respectively
- HCT beyond CR1 and absence of cGVHD are powerful prognostic factors associated with inferior RFS and OS.

Covariate	Multivariate analysis	
	aHR (95% CI)	p-value
For RFS		
Failure of 7+3 induction	2.23 (0.71 – 7.05)	0.17
> CR1 (vs CR1)	5.13 (2.04 – 12.87)	< 0.001
CMV reactivation	0.59 (0.25 – 1.41)	0.23
Acute GVHD (yes vs no)		
Chronic GVHD (yes vs. no)	0.13 (0.05 – 0.42)	< 0.001

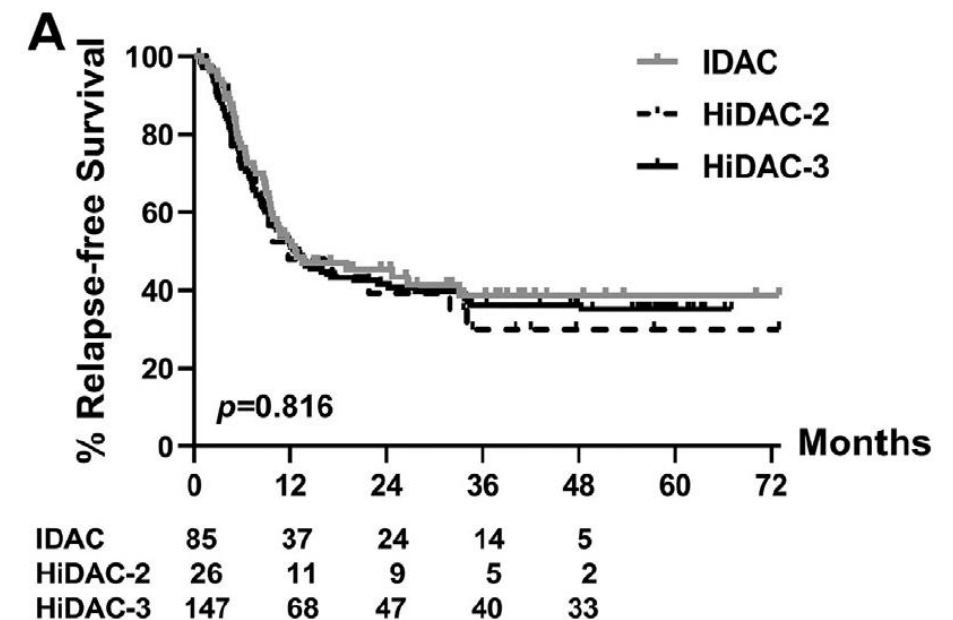
Comparison of Three Doses of Cytarabine Consolidation for Intermediate- and Adverse-risk Acute Myeloid Leukemia: Real World Evidence From Thai Acute Myeloid Leukemia Registry



Chantiya Chanswangphuwana, et al.

(9 tertiary hospitals; Year 2014 – 2021)

- Among 992 patients → CR after 1-2 induction cycles 452 patients → intermediate- and adverse-risk 381 patients → received single-agent cytarabine for post-remission therapy = 258 patients
- Median age = 48 (15 – 65) years old
- Intermediate risk (81.8%), adverse risk (15.9%)
- 7+3 induction = 91.2%
- CR after 1 cycle (82.9%), CR after 2 cycles (17.1%)



Univariate & Multivariate Analysis for Relapse-free Survival of AML Patients



Covariates	Median RFS (mo)	Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P-Value	HR (95% CI)	P-Value
Age					
- Less than 50 y	13.5	1			
- 50 - 59 y	11.6	1.18 (0.84-1.67)	.334		
- 60 - 65 y	33.1	0.88 (0.50-1.56)	.662		
Type of AML					
- De novo	13.9	1		1	
- Secondary	9.4	1.54 (1.05-2.26)	.028	1.71 (1.15-2.54)	.008
Risk stratification					
- Intermediate	13.9	1	.134		
- Adverse	9.8	1.38 (0.91-2.10)			
WBC count					
- $\leq 100 \times 10^9/L$	15.8	1		1	
- $> 100 \times 10^9/L$	7.1	1.93 (1.34-2.80)	< .001	1.97 (1.35-2.89)	< .001
Consolidation	IDAC = 12.6	1			
- HiDAC-2 versus IDAC	11.7	1.18 (0.68-2.07)	.558		
- HiDAC-3 versus IDAC	13.0	1.09 (0.76-1.56)	.636		
- HiDAC ^a versus IDAC	13.0	1.12 (0.78-1.57)	.577		
Cytarabine					
- 1 - 2 cycles	5.4	1		1	
- 3 - 4 cycles	24.3	0.34 (0.25-0.48)	< .001	0.36 (0.26-0.51)	< .001





Take home message 1.

- 7+3 induction for fit and <60 newly diagnosed AML patients.
- Intermediate- and adverse-risk AML: consolidation after CR1 with allogeneic HSCT with HLA matched donor (prefer) or cytarabine 1.5 g/m² IV q 12 hours for 3 days, 3-4 cycles (4 weeks/cycle)
- Encourage hematologists to refer intermediate- and adverse-risk patient in CR1 for allogeneic HCT (reimbursement program).
- Azacitidine and Venetoclax is feasible for elderly AML in Thailand, however the management of toxicity still be a concern.



Real-world data on adult AML with *FLT3*-ITD mutation from the Thai Acute Leukemia Working Group (TALWG)

Thanawat Rattanathammethee, et al

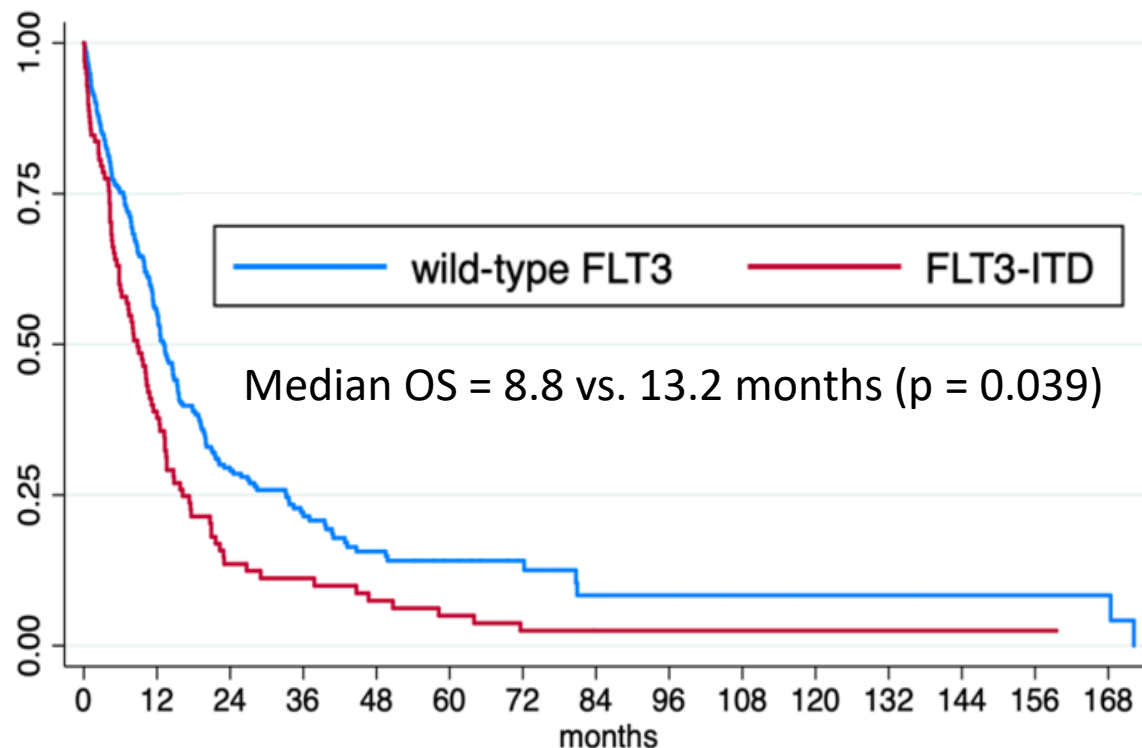
(11 hospitals; 2016 – 2023)

- 360 AML patients who were tested for *FLT3*-ITD → 28.1% (101) had *FLT3*-ITD mutation
- Mutated *NPM1* = 45.6%
- ELN2022: *FLT3*-ITD: Int- and adverse-risk 86.1% and 4.9% (Fav-risk 8.9%)
- ELN2022: *FLT3*-WT: Int- and adverse-risk 58.3% and 21.2% (Fav-risk 20.5%)
- Median age was 51 years (range 16-90).
- CR rate (7+3): 55.7% for *FLT3*-ITD and 66.5% for WT patients (without *FLT3* inhibitor).
- Median follow up time was 10.7 months. (HCT 13.9%)
- No difference in relapse-free survival (ITD 7.3 vs. WT 7.8 months, $p = 0.704$)

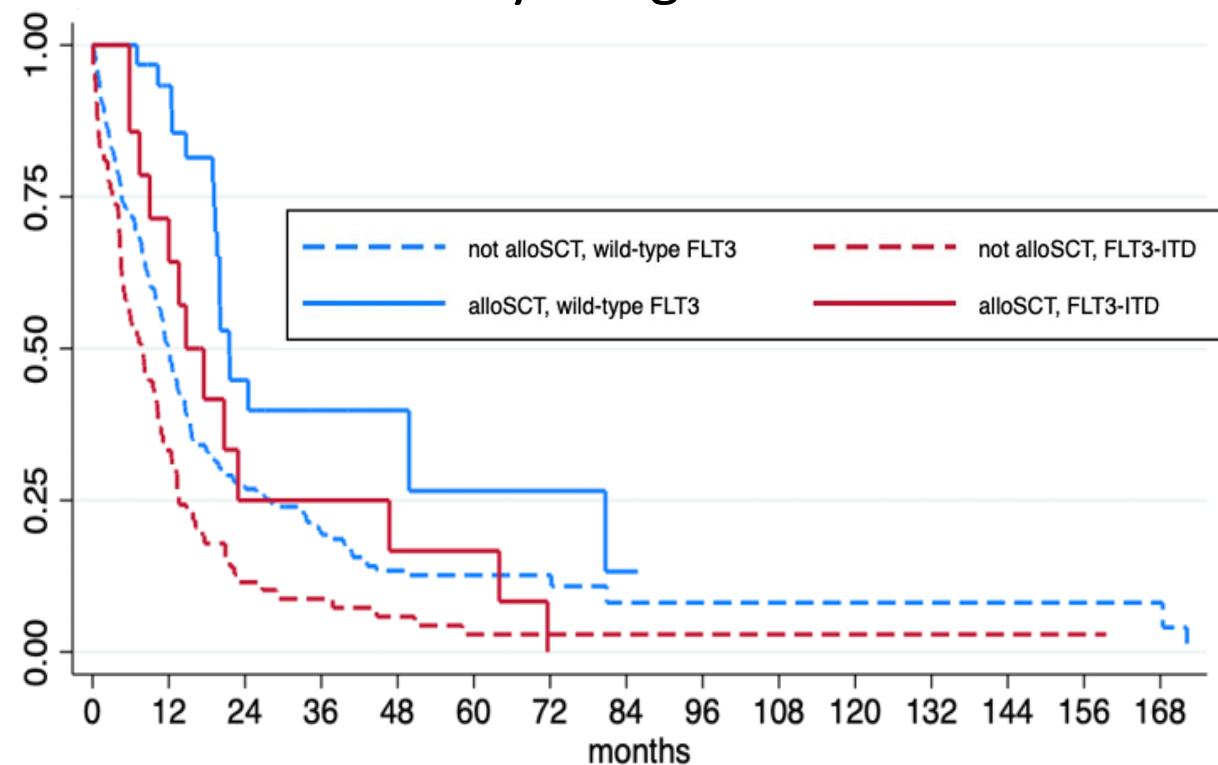
Real-world data on adult AML with *FLT3*-ITD mutation from the Thai Acute Leukemia Working Group (TALWG)



Overall survival



OS by Allogeneic HCT



Allo-HCT: ITD 14.7 months vs. WT 21.5 months ($p = 0.019$)

Non-HCT: ITD 7.8 months vs. WT 12 months ($p < 0.001$)



Take home message 2.

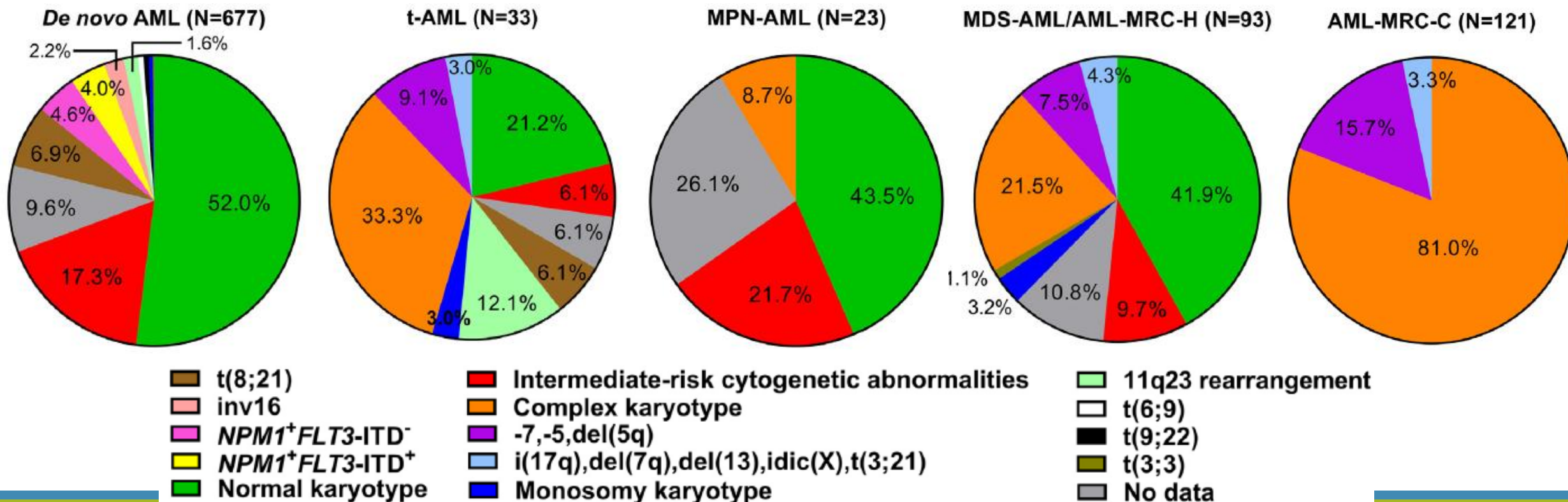
- ELN2022: *FLT3*-ITD without adverse genetic lesion ($\pm$ *NPM1* mutation) = Int-risk, due to combine *FLT3* inhibitor and intensive chemotherapy.
- In Thailand, because of non-reimbursement of *FLT3* inhibitor → please consider *FLT3*-ITD as adverse risk and proceed to allogeneic HCT as consolidation treatment in CR1.

Characteristics and Outcomes of Secondary Acute Myeloid Leukemia and Acute Myeloid Leukemia With Myelodysplasia-Related Changes: Multicenter Study From the Thai Acute Leukemia Study Group



Chantiya Chanswangphuwana, et al.

Cytogenetics abnormalities and molecular genetic profiles of AML subtypes.



Characteristics and Outcomes of Secondary Acute Myeloid Leukemia and Acute Myeloid Leukemia With Myelodysplasia-Related Changes: Multicenter Study From the Thai Acute Leukemia Study Group



Old definition: Secondary AML includes antecedent hematologic disorder-AML (from MPN or MDS) and t-AML. AML-MRC by ELN 2017

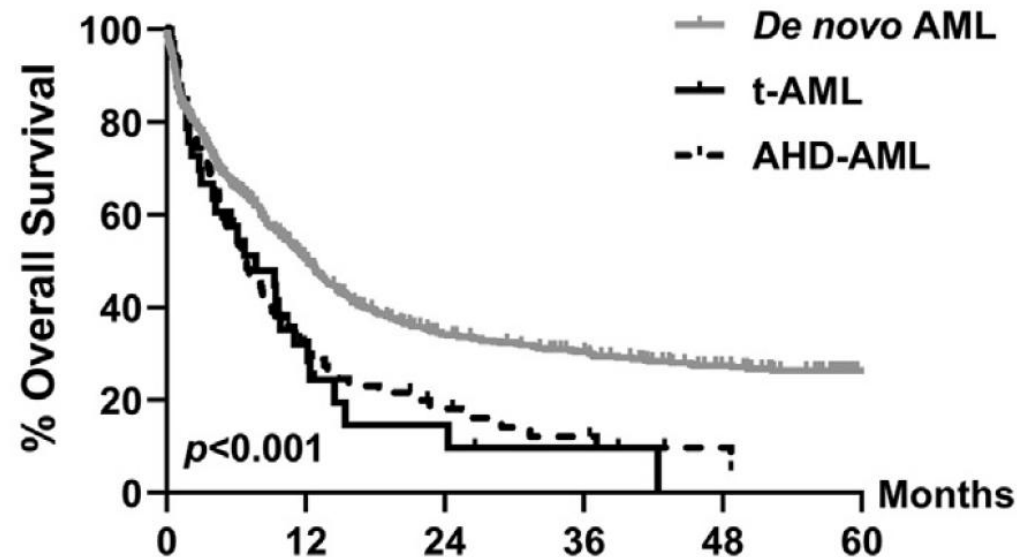
Table 3 Treatment Response After First-Line Treatment and Consolidation Therapy.

Treatment	<i>De Novo</i> AML N = 677	Secondary AML N = 149	P Value ^a	AML-MRC N = 259	P Value ^a
First 7+3 regimen	N = 431	N = 34		N = 96	
CR rate (%)	269 (62.4)	12 (35.3)	.002	41 (42.7)	<.001
HMA/Low-intensity chemotherapy	N = 71	N = 35		N = 54	
CR rate (%)	29 (40.8)	5 (20.0)	.033	11 (20.4)	.015
Reinduction treatment	N = 109	N = 18		N = 42	
CR rate (%)	70 (64.2)	8 (44.4)	.110	19 (45.2)	.034

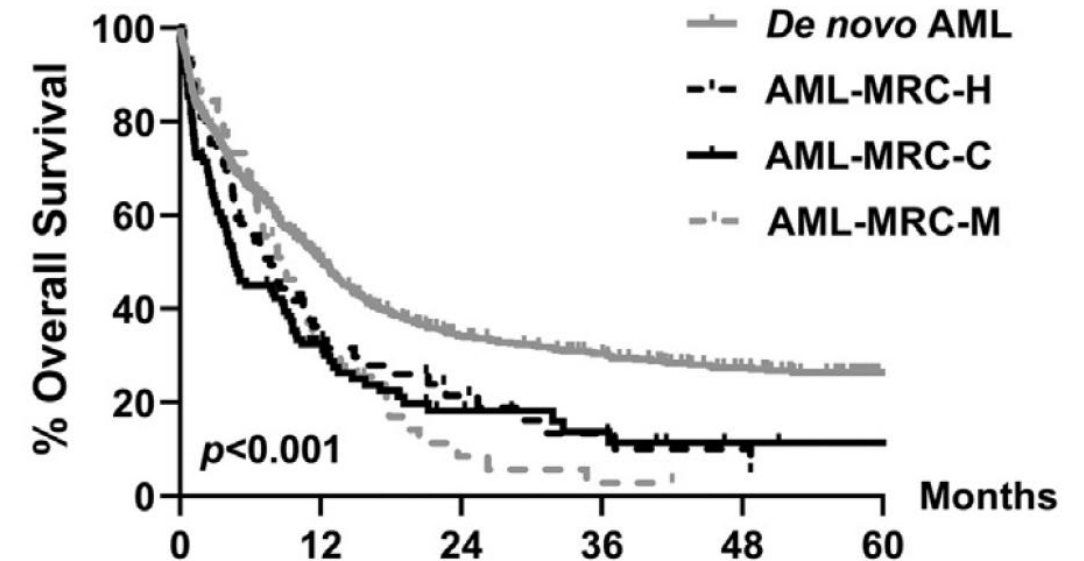
Characteristics and Outcomes of Secondary Acute Myeloid Leukemia and Acute Myeloid Leukemia With Myelodysplasia-Related Changes: Multicenter Study From the Thai Acute Leukemia Study Group

Median OS: 12.2 vs. 7.7 vs. 6.9 months

Median OS: 12.2 vs. 7.7 vs. 4.7 vs. 8.9 months



<i>De novo</i>	677	287	159	123
t-AML	33	9	3	1
AHD-AML	116	28	10	6



<i>De novo</i>	677	287	159	123
MRC-H	93	25	9	5
MRC-C	121	27	10	6
MRC-M	45	15	3	1



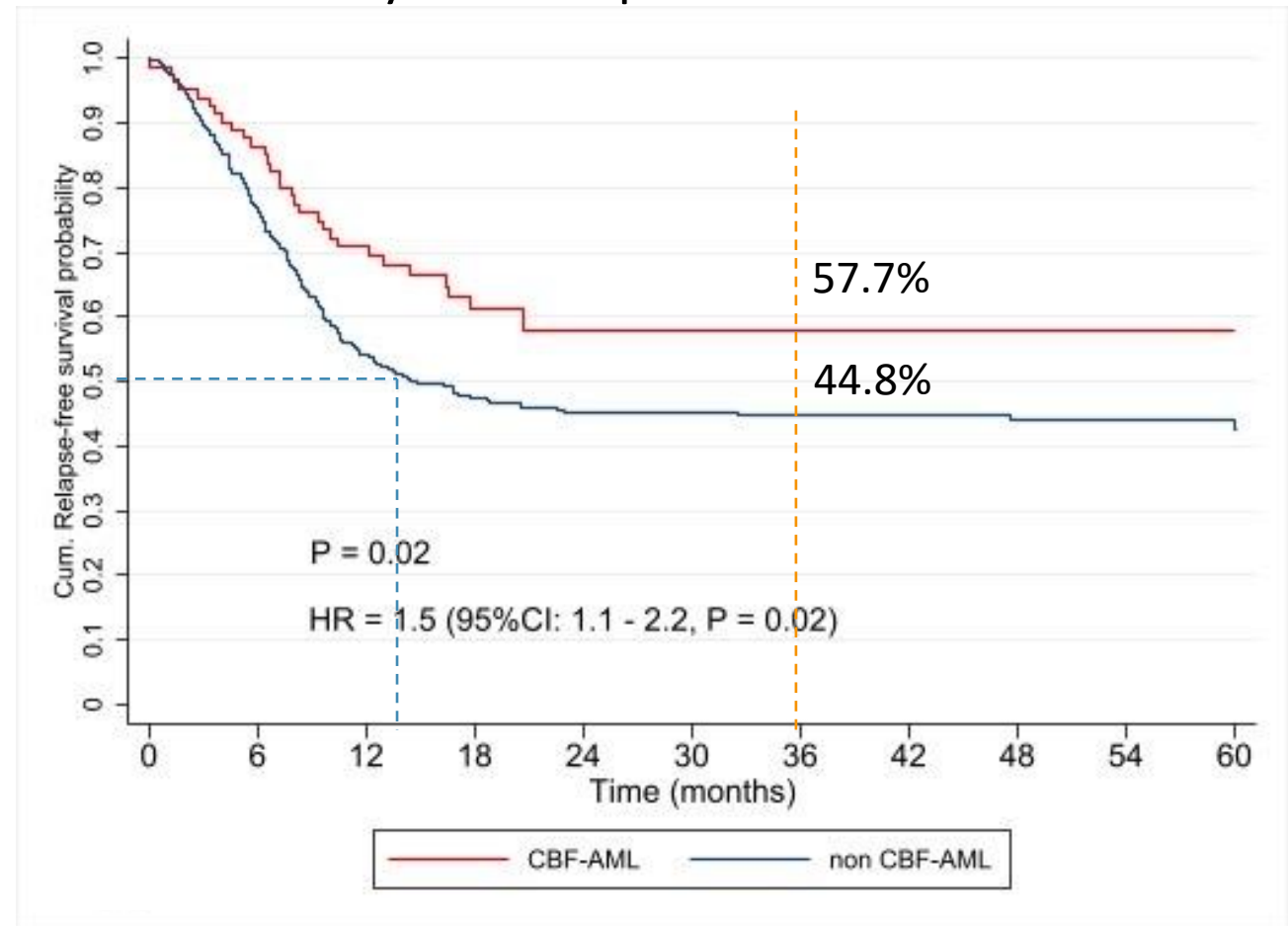
Take home message 2.

- ELN2022: *FLT3*-ITD without adverse genetic lesion ($\pm$ *NPM1* mutation) = Int-risk, due to combine *FLT3* inhibitor and intensive chemotherapy.
- In Thailand, because of non-reimbursement of *FLT3* inhibitor → please consider *FLT3*-ITD as adverse risk and proceed to allogeneic HCT as consolidation treatment in CR1.
- Secondary AML (AML post cytotoxic therapy) and AML-MR still had adverse outcome.

Clinical and genetic factors associated with prognostic determination in CBF-AML: results from a Thai Acute Leukemia Working Group

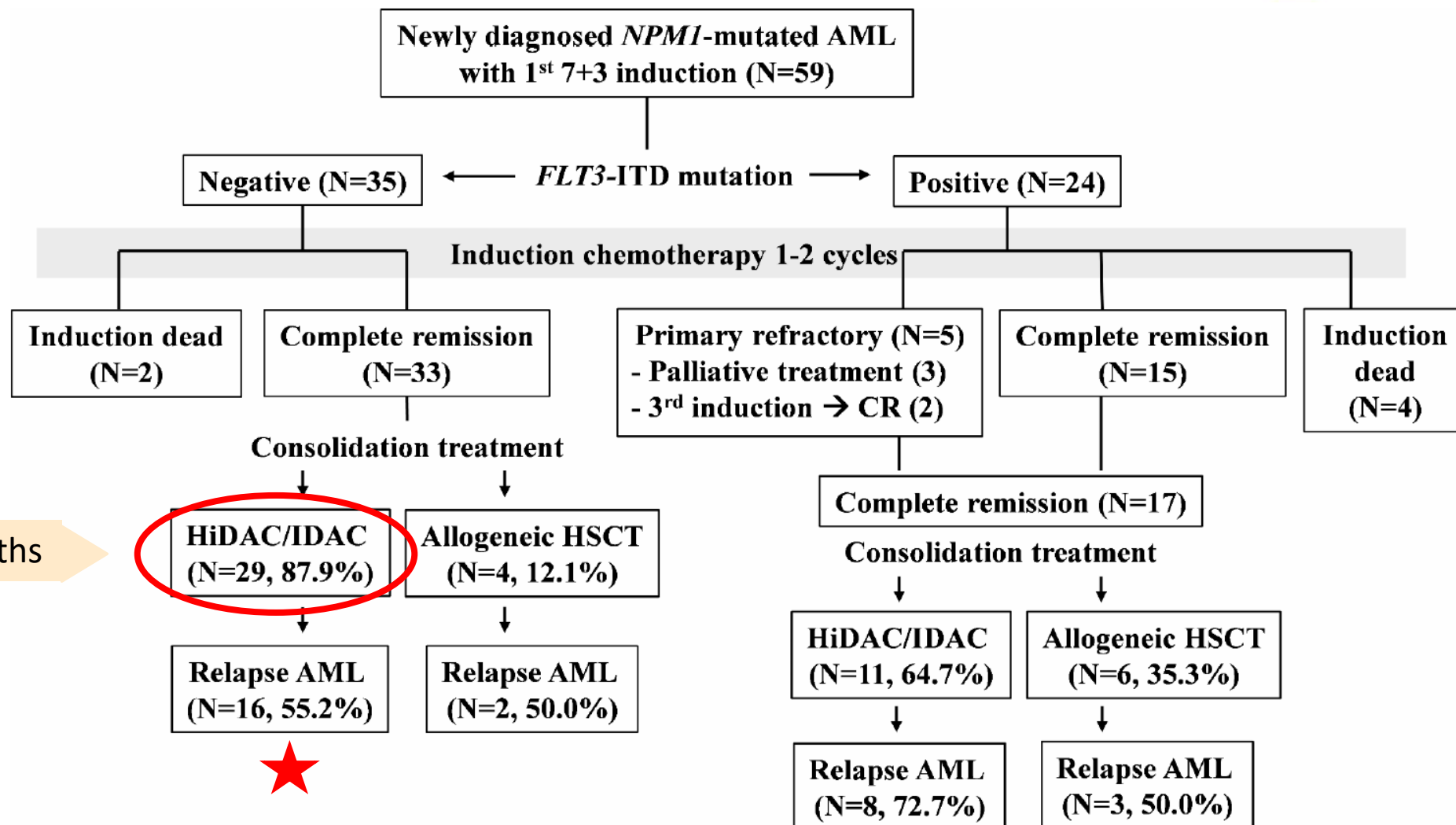
- Among 1,330 AML (non-M3) cases:
CBF-AML 8.5%;
 - $t(8;21)(q22;q22) = 6.6\%$
 - $inv(16)(p13q22)/t(16;16) = 1.9\%$
- CBF-AML: 64.6% had concurrent cytogenetic abnormalities (-X, -Y, trisomy 22, and del(9q)).
- CR after 7+3: CBF 77% vs. non-CBF 54.6% ($p < 0.001$)

3 years Relapsed-free survival



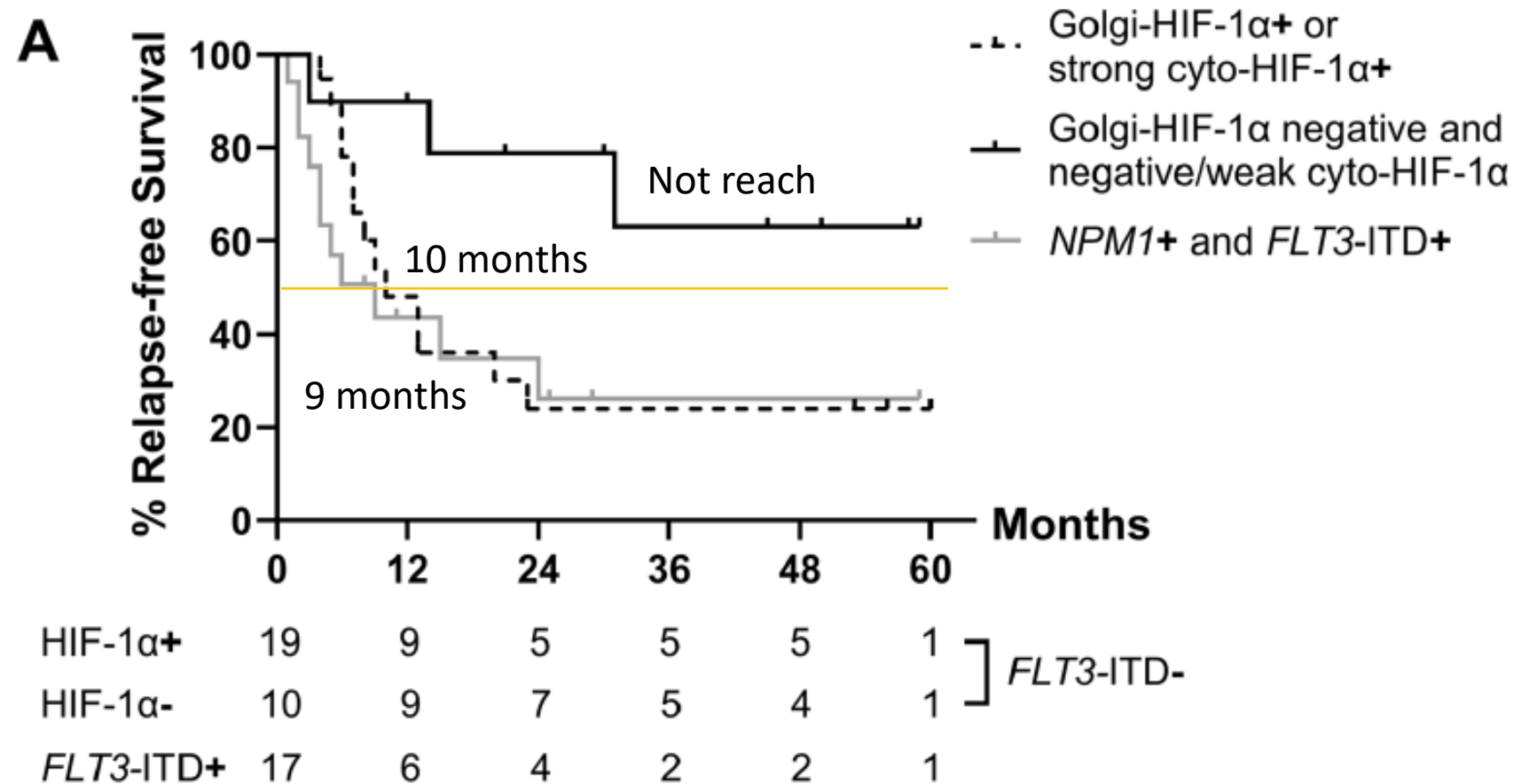
Survival impact of hypoxia-inducible factor-1 alpha (HIF-1 α) in *Nucleophosmin1* mutated acute myeloid leukemia

KCMH cohort



Median RFS = 23 months

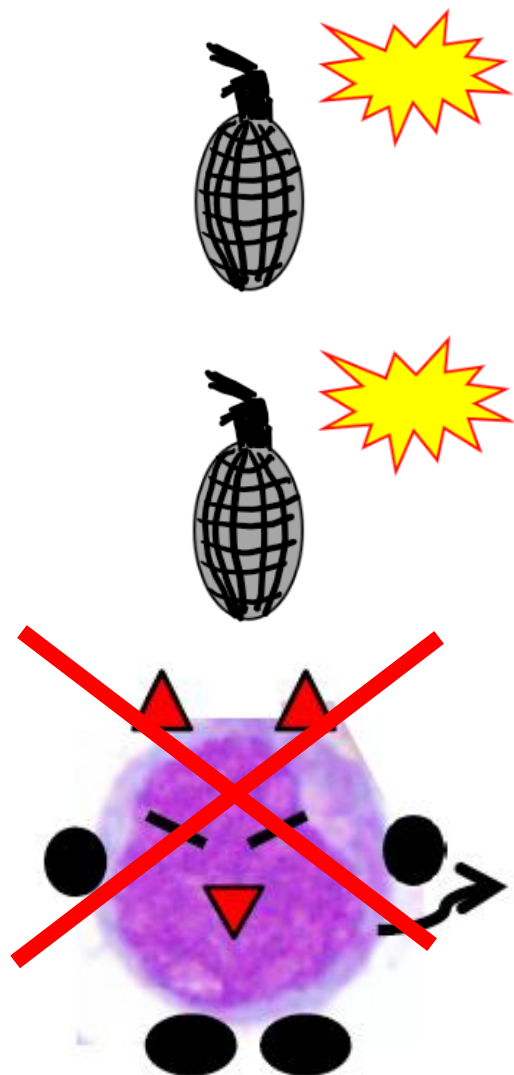
Median RFS of *NPM1*+*FLT3*-ITD- AML (CR1, non-HCT, n=29) = 23 months.





Take home message 3.

- CBF-AML in Thailand: Low incidence, high CR rate after 7+3 and superior 3-year RFS compare with non-CBF AML.
- *NPM1* mutated AML without *FLT3*-ITD is favorable-risk AML. However, ~50% of patients still relapse within 2 years (KCMH data). Identification poor-risk *NPM1* mutated AML patients is needed such as MRD monitoring and significant genetic co-mutation for initiate HCT in CR1 in some patients.



Thank you for your attention

QUESTION?