# Clinical implications of gene alterations in risk-adapted treatment of AML

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# Acute myeloid leukemia (AML)

AML is a heterogeneous group of diseases with great variability in the pathogenesis, clinical course and response to treatment.

Risk-adapted treatment may not only improve the prognosis, but also reduce the toxicity from the therapy.

# Main Risk-Factors in AML

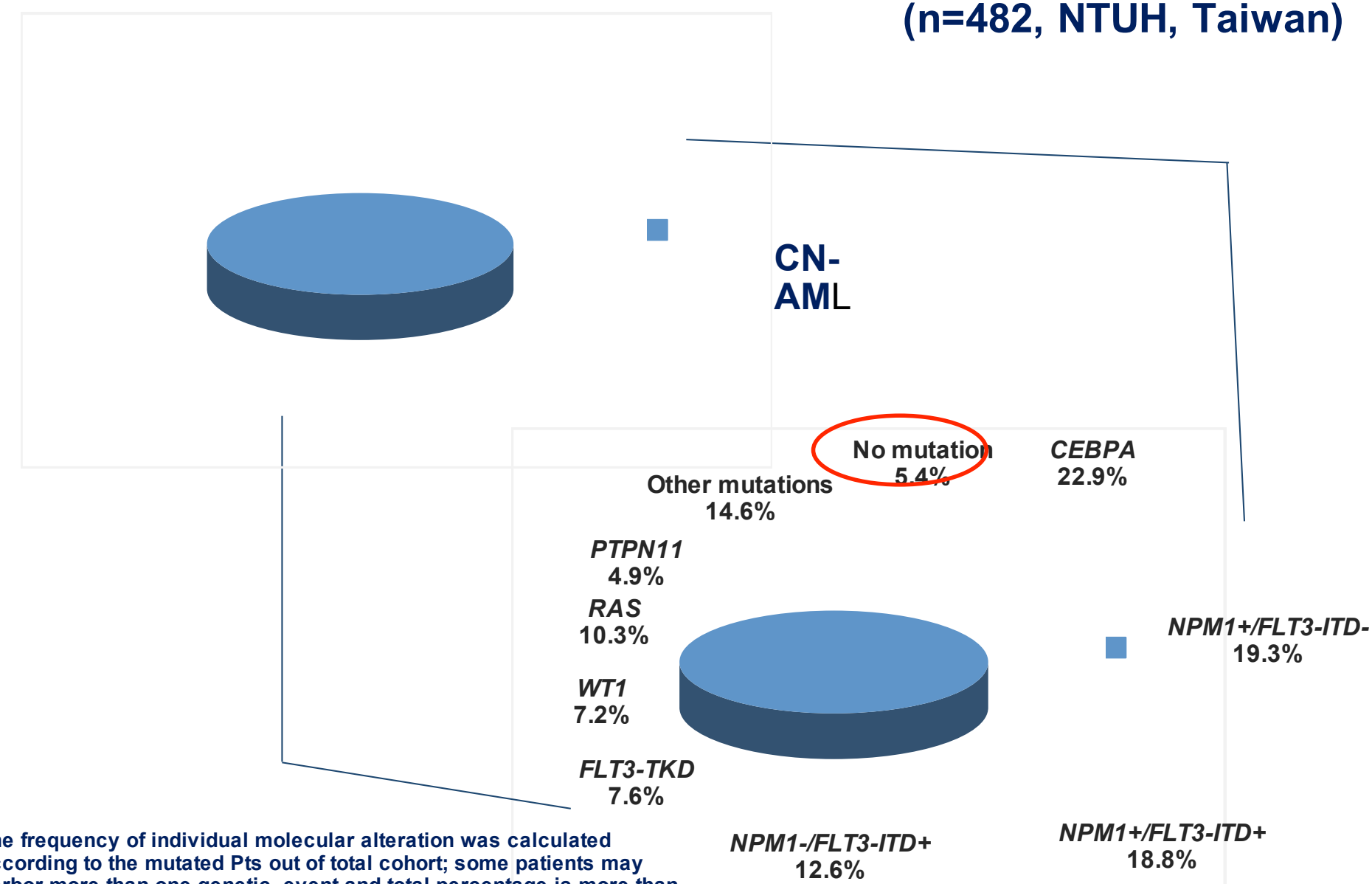
1. **Age**
2. **White blood cell count**
3. **Genetic alterations**

**Chromosomal abnormalities**

**Molecular gene mutations**

# Genetic alterations in AML patients with cytogenetic data

## (n=482, NTUH, Taiwan)




The frequency of individual molecular alteration was calculated according to the mutated Pts out of total cohort; some patients may harbor more than one genetic event and total percentage is more than 100%

*NTUH, Taiwan: Clin Can Res 2005;11:1372; Cancer Res 2006;66:3310; Blood 2009; 114(26):5352; Blood 2010; 115:2149*

# Pathogenesis of Acute Myeloid Leukemias

## Class I mutations

Proliferative and/or survival advantage (signal transduction)

*FLT3* mutations (*FLT/ITD,TKD)*

*KIT* mutation

*N-RAS* and *K-RAS* mutations

*WT1* mutation

## Class II mutations

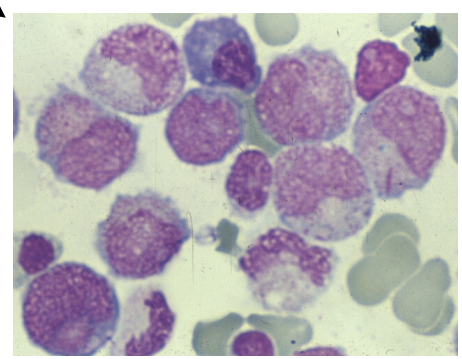
Impair differentiation and subsequent apoptosis ( transcription factors)

t(8;21); t(15;17); inv(16)

t(v;11q23); *MLL*- PTD

*CEBPA, RUNX1* mutations

*NPM1* mutation



*IDH1/2, ASXL1, TET2, DNMT3A mutations*

Epigenetic deregulation

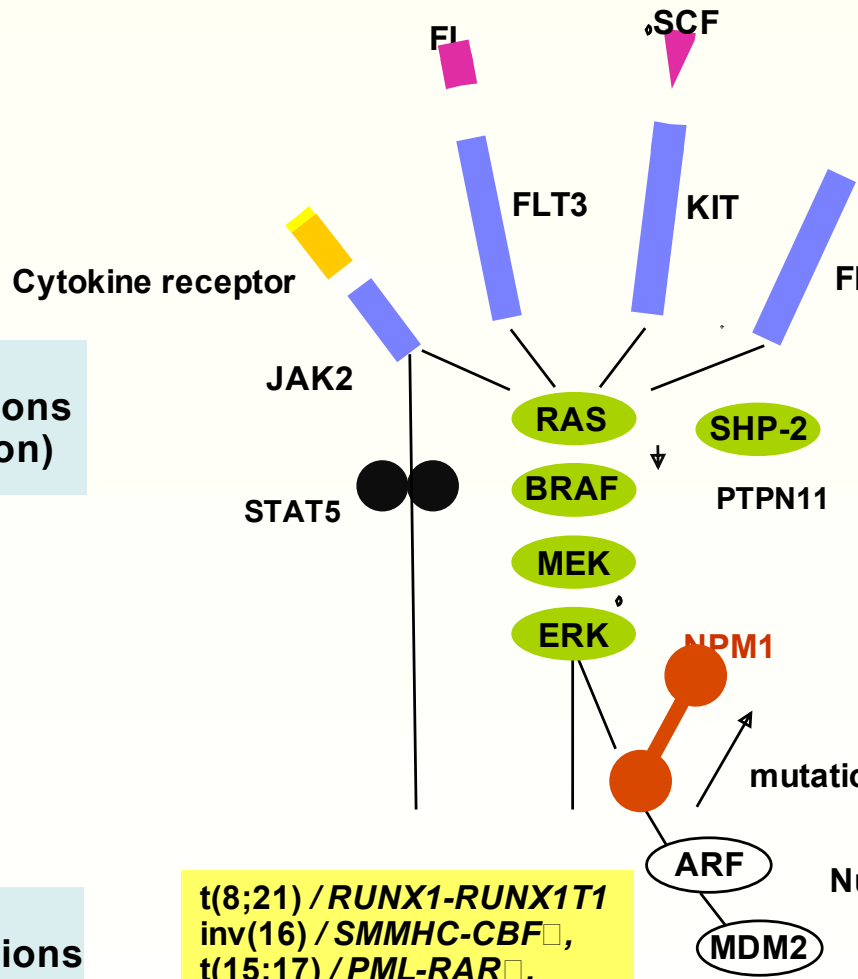
## Class III mutations

DNA methylation, Histone methylation, acetylation

## Epigenetic deregulation

*Modified from Ann Rev Genomics Hum Genet 3:179, 2002*

# Leukemogenesis of Acute Myeloid Leukemia




Ligands

Receptor tyrosine kinase

RAS-BRAF signaling pathway

Transcription factors or cofactors

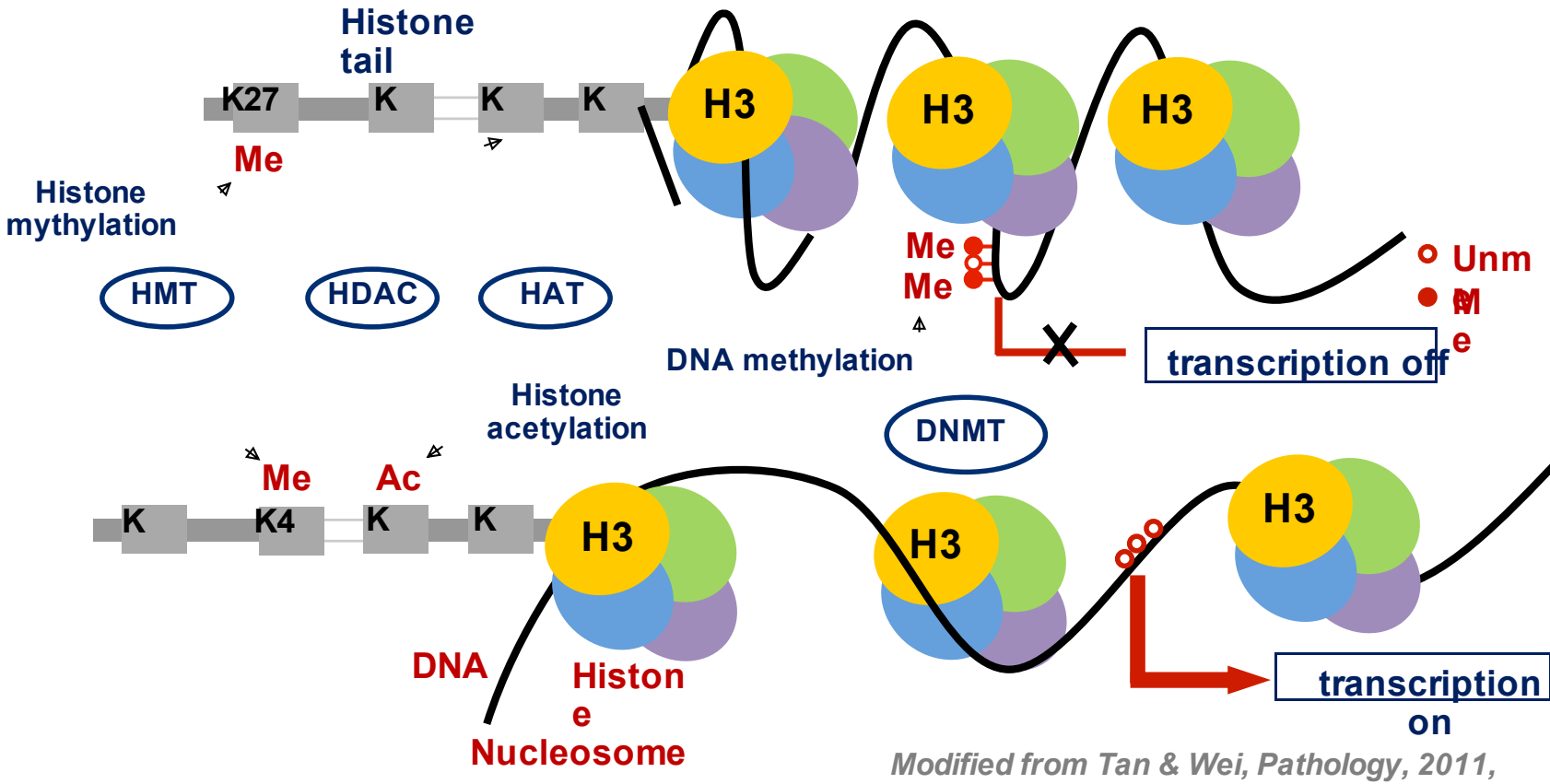
**Class I mutations (proliferation)**

**Class II mutations (differentiation)**

t(8;21) / *RUNX1-RUNX1T1*
inv(16) / *SMMHC-CBF*□,
t(15;17) / *PML-RAR*□,
t(11;v) / *MLL fusion, MLL/PTD*
*CEBPA, RUNX1 mutations*

*Modified from Leukemia (2008) 22,240–248*

# Class III mutations- epigenetic deregulation




*Modified from Tan & Wei, Pathology, 2011, 43:536*

**Class III mutations involve genes related to epigenetic modifications**

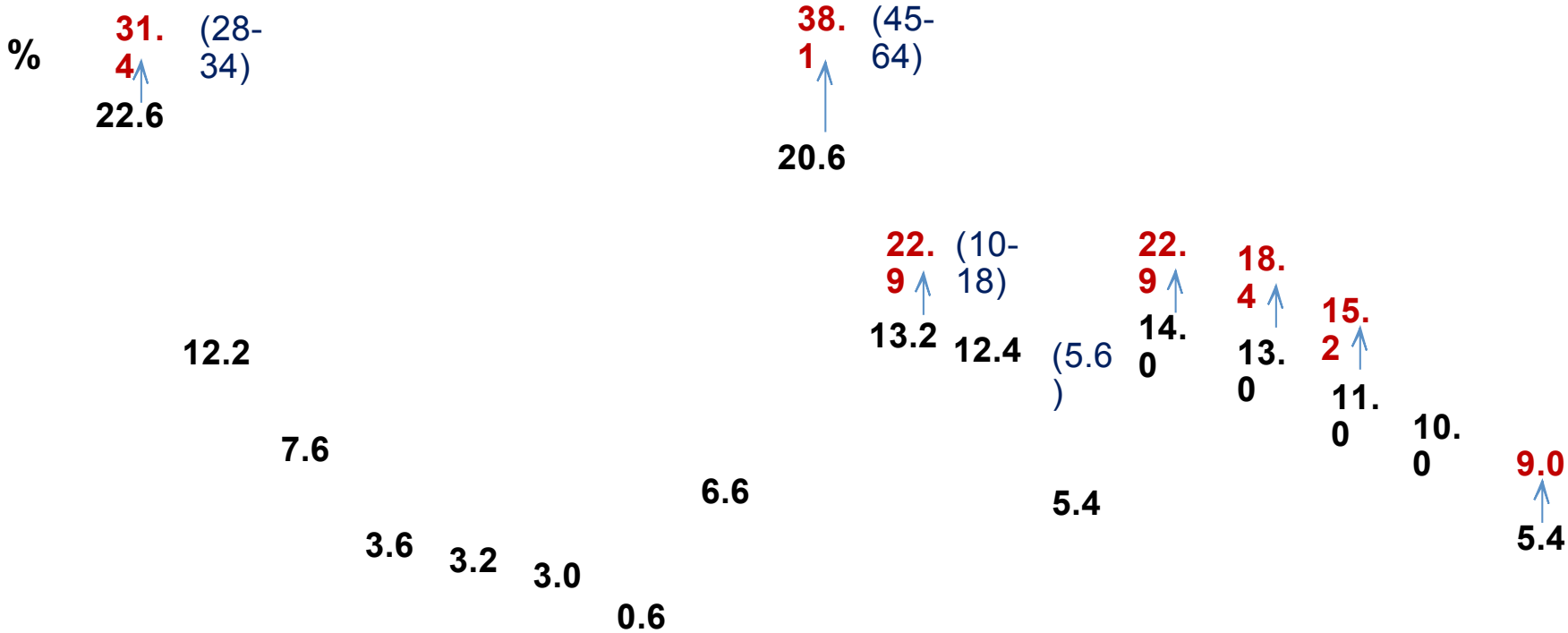
**DNMT3A:** A DNA methyltransferase

**TET2:** Can catalyze the conversion of 5-mc to 5-hmc and may be involved in DNA demethylation

**IDH1/2:** Mutations result in decrease of □- KG, a coenzyme for TET2

**ASXL1:** Polycomb group protein, possibly involved in histone methylation

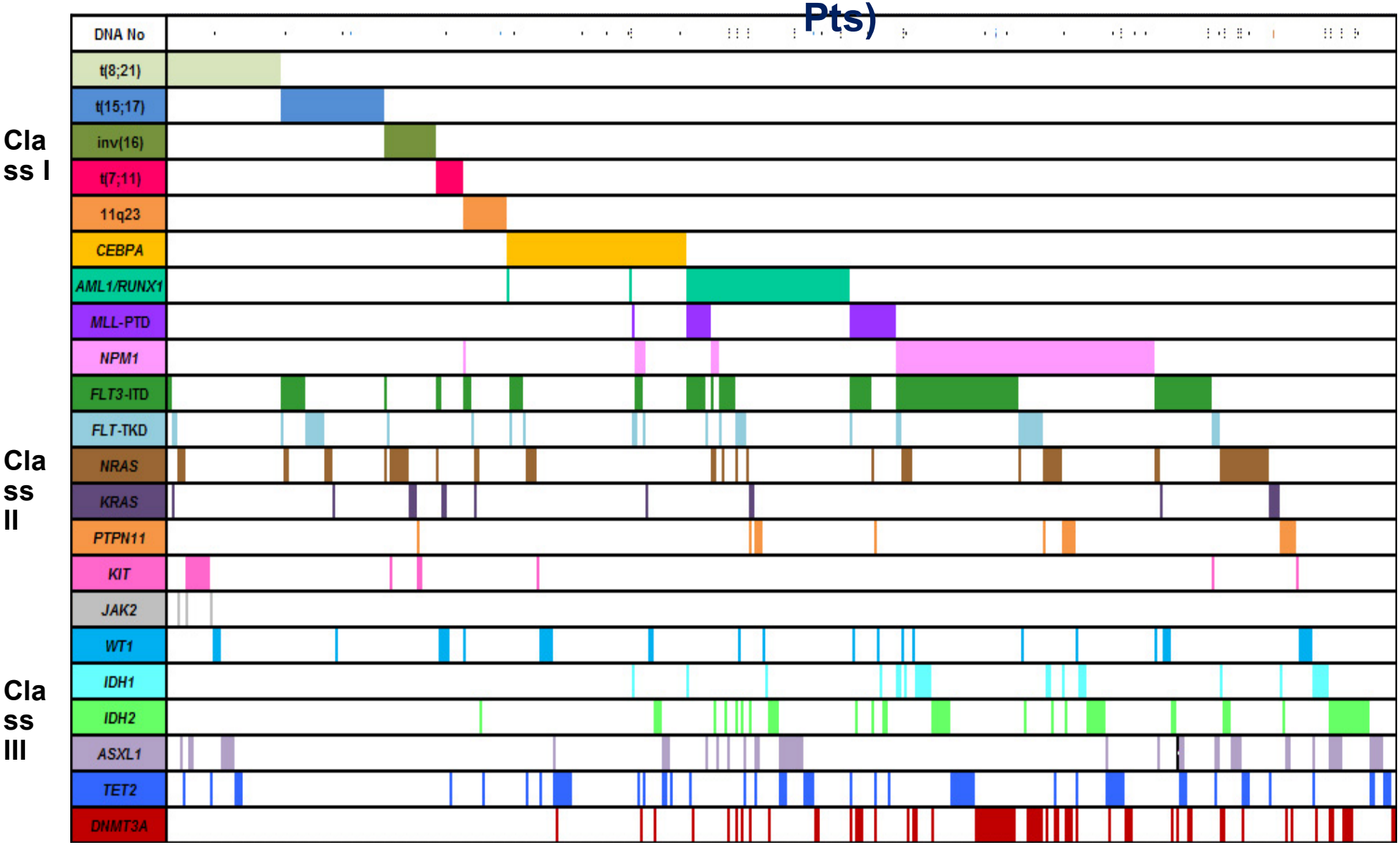
# Molecular Gene Mutations in 500 AML Patients (NTUH , *Taiwan*)




***NTUH , Taiwan*** *: Clin Can Res 2005;11:1372; Cancer Res 2006;66:3310; Blood 2009;114(26); 5352; Blood 2010; 115:2149; Blood 2010, 115:2749; Blood 2010, 116:4086; Leukemia 2011, 25:246; Blood 2011, 118:3803; Blood 2012, 119:559*

# Interaction of Genetic Alterations in AML

## (NTUH, Taiwan, 500 AML Pts)

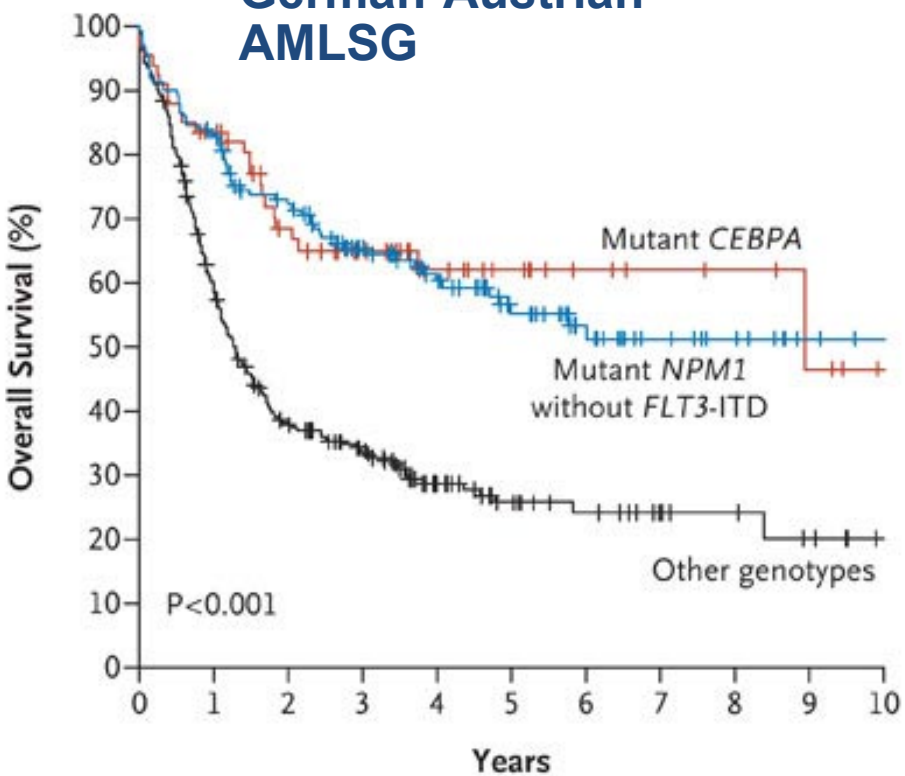



Forty-eight patients who did not have any genetic alterations at diagnosis were not enrolled in this figure.

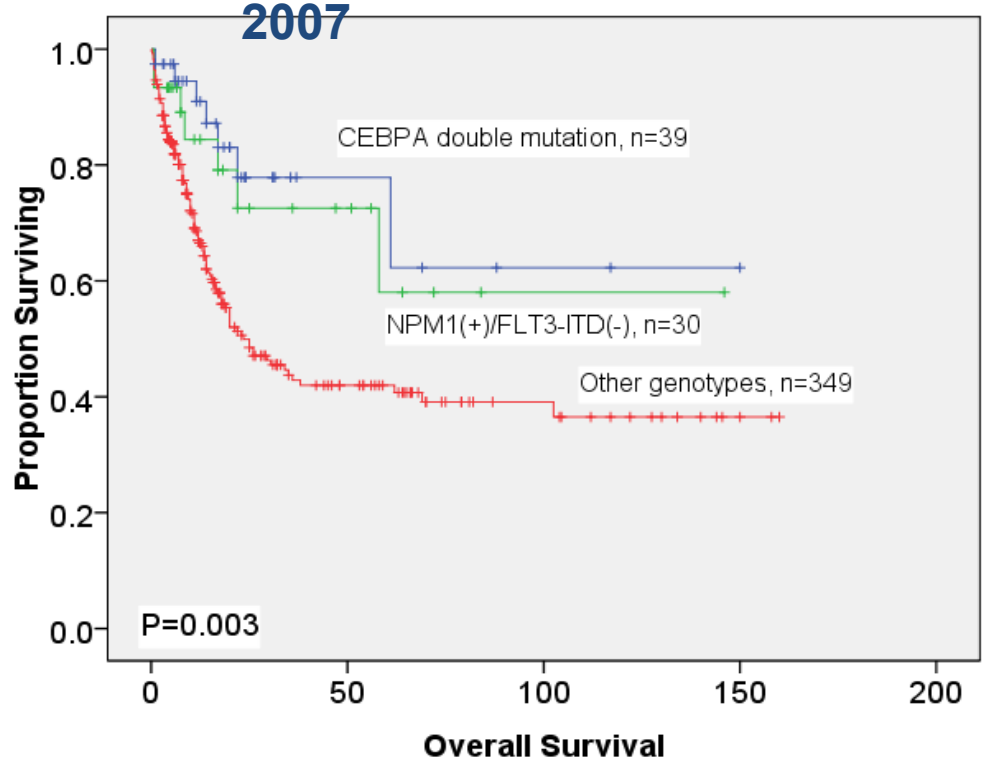
# Gene mutations can predict prognosis

## *CEBPA* mutation and *NPM1* mutation without *FLT3-ITD* predict longer survival- good-risk genotypes

### German-Austrian AMLSG

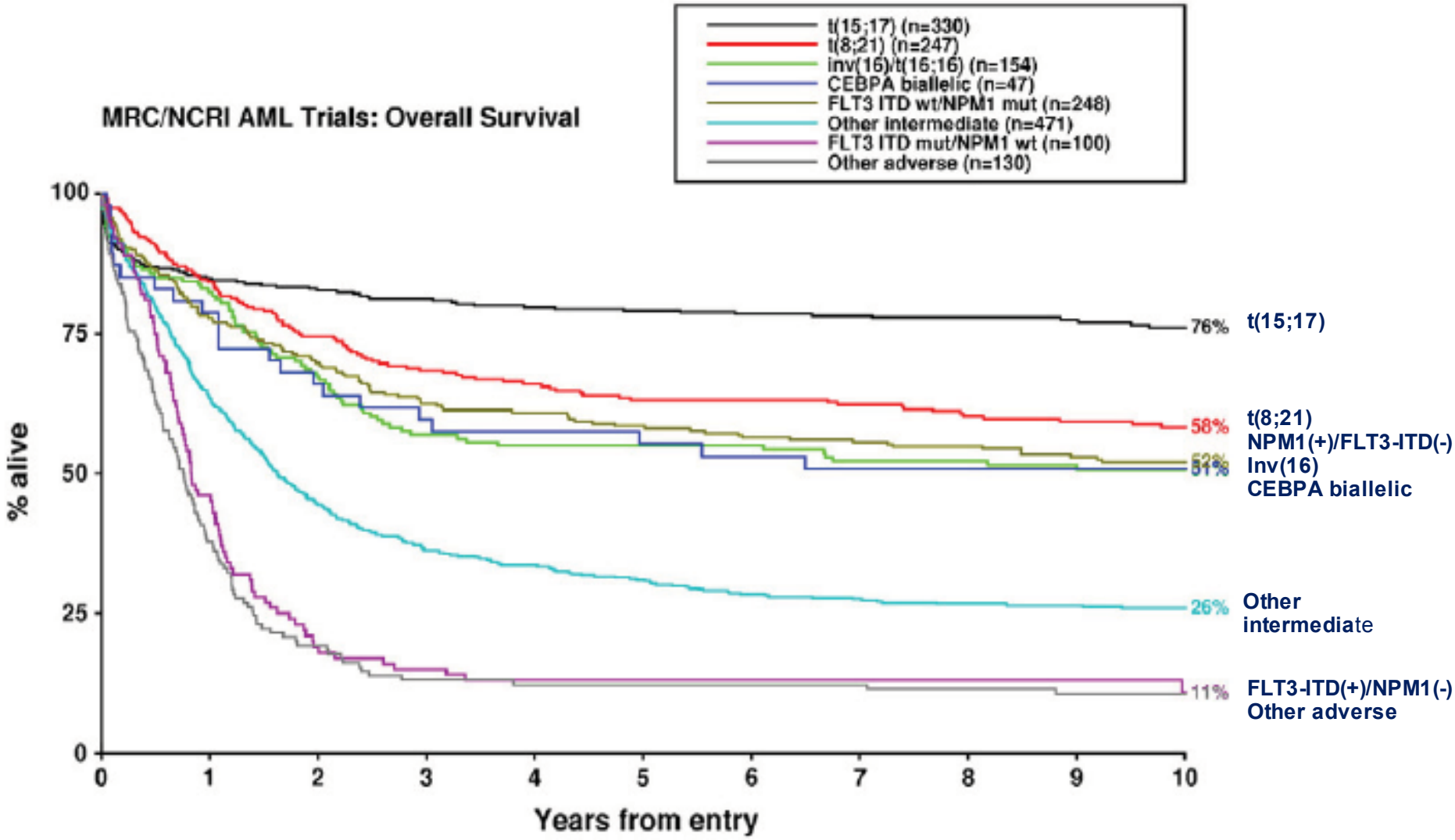



### NTUH, Taiwan, 1995-2007




*NEJM 358:1909,2008*

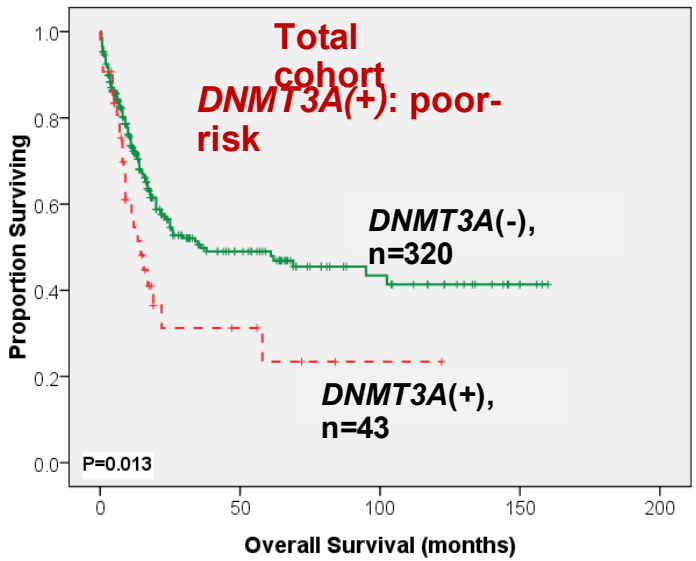
# Outcome according to cytogenetic and molecular abnormalities

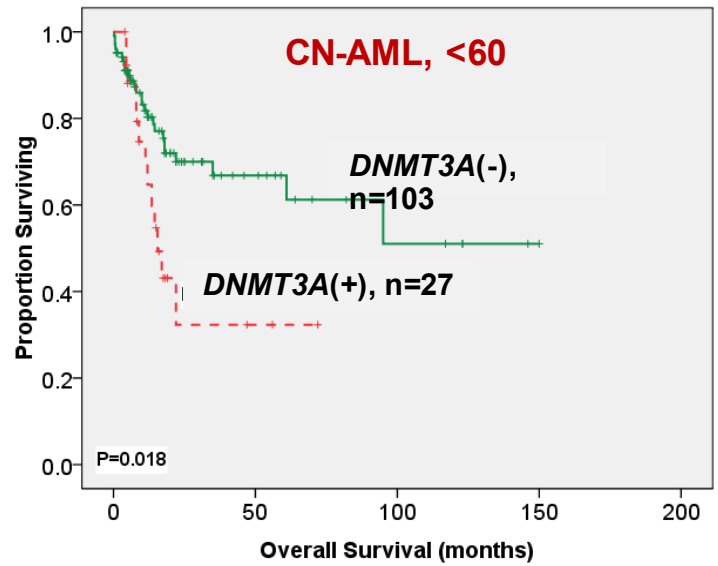


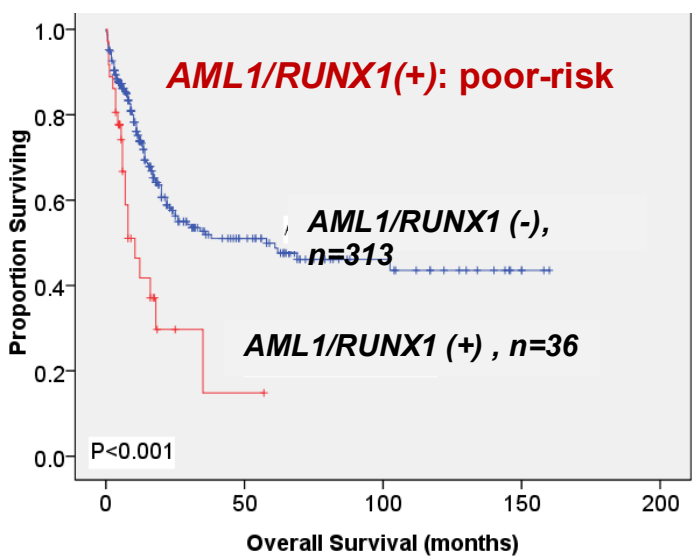

*United Kingdom Medical Research Council*
*Blood Rev. 2011; 25:39*

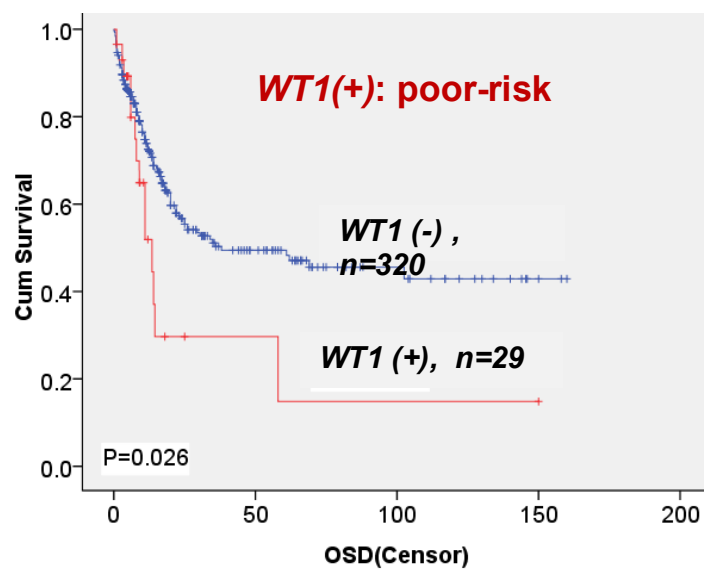
# Gene mutations can predict prognosis

## NTUH, Taiwan, 1995-2007




***NTUH, Taiwan,*** *Br J Can 101:738, 2009; Blood* 2009; 114(26):5352;

*Blood* 2010; 115:2149 ; *Blood, 2012, 119:559*

# Multivariate Analysis of Prognostic Factors

## (500 adult AML patients, *NTUH, taiwan, 1995-2007)*

| variables | Overall Survival | |
|---|---|---|
| | RR | *P value* |
| Age□ | 2.531 | <0.001* |
| WBC§ | 1.970 | <0.001* |
| Karyotype□ | 3.078 | <0.001* |
| *NPM1+/FLT3-ITD-*□ | 0.261 | 0.001* |
| *CEBPA double mut*‡ | 0.423 | 0.015* |
| *WT1* | 2.576 | 0.001* |
| *DNMT3A* | 2.218 | 0.002* |
| *AML1/RUNX1* | 1.963 | 0.017* |
| *IDH2* | 0.573 | 0.099 |
| *ASXL1* | 1.439 | 0.227 |
| *TET2* | 1.033 | 0.906 |

Abbreviation: RR, relative risk; *Statistically significant (P < 0.05)
† Age □ 50 relative to Age □50 (the reference); §WBC greater than 50,000/□L versus less than 50,000/□L
□*NPM1*mut/*FLT3-ITD*neg *versus other subtypes;* ‡*CEBPA* double-mutation *versus others*
□ unfavorable cytogenetics versus others

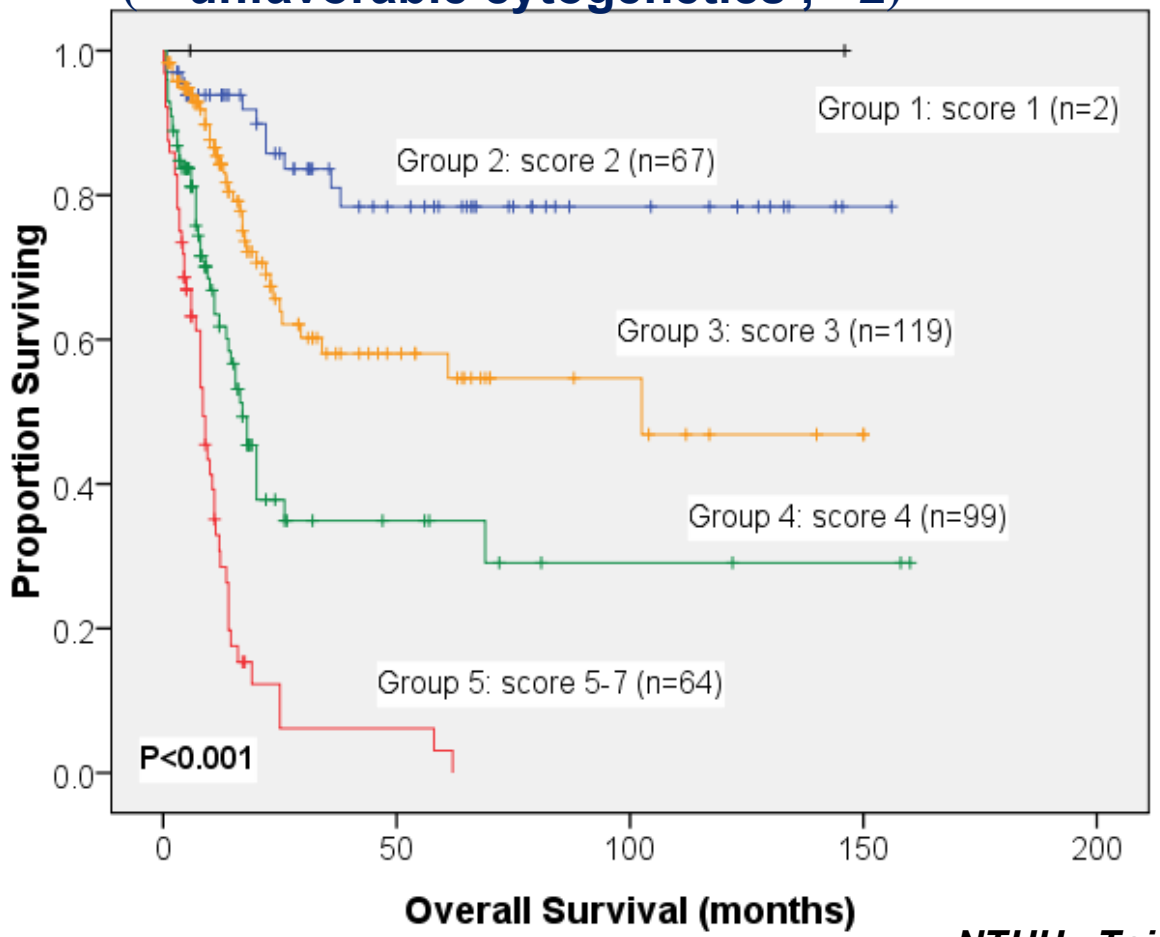
***NTUH,*** *Taiwan, Blood 2012, 119:559*

# Risk-Stratification According to Scoring System

**-1(good prognostic factor): *CEBPA*double-mutation, *IDH2* mutation , *NPM1mut/FLT3-ITDneg***

**+1(poor prognostic factor): older age, high WBC count, intermediate cytogenetics, *WT1, DNMT3A,* 及*RUNX1* mutation**

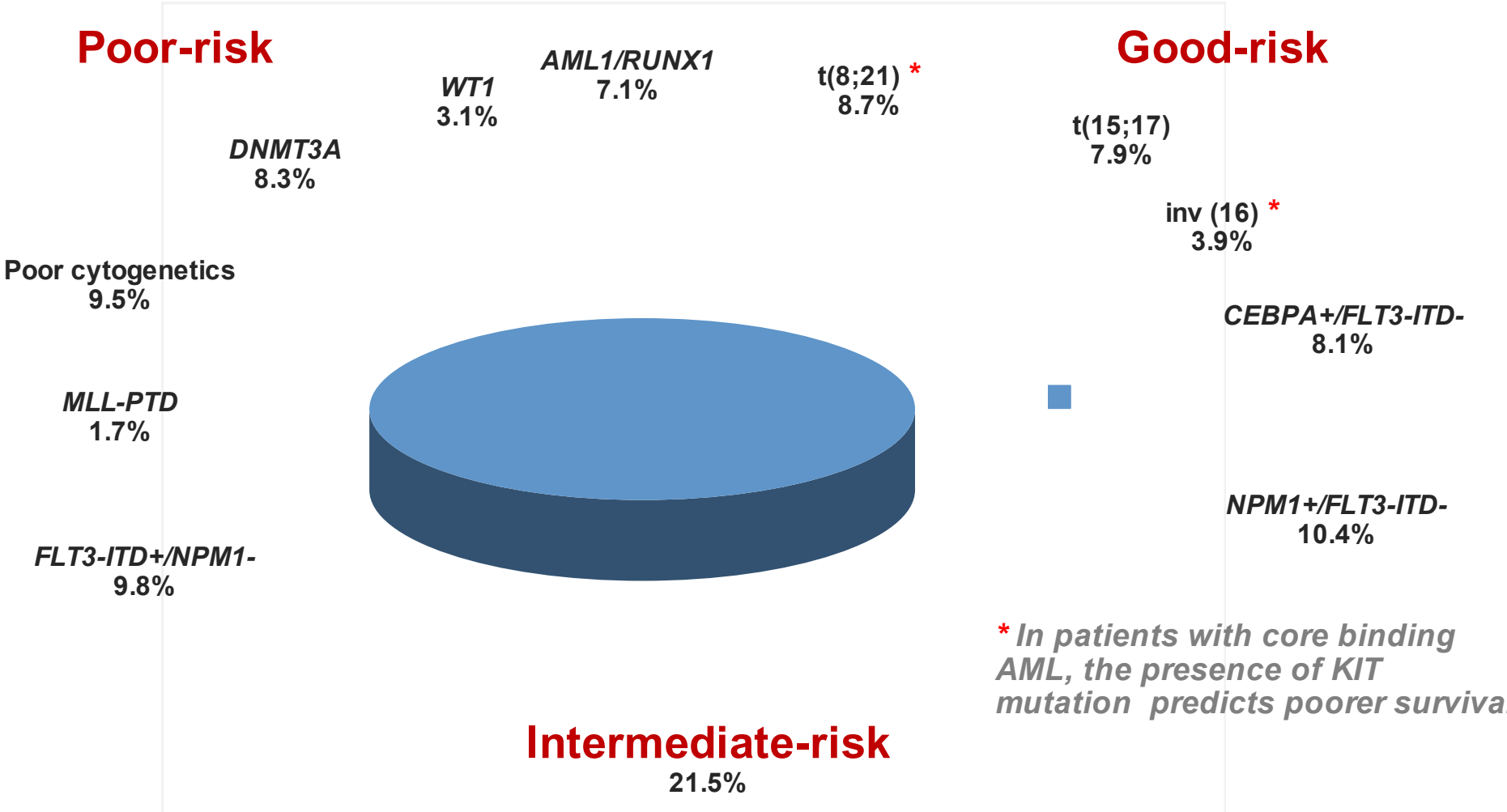
**(＊unfavorable cytogenetics , +2)**




***NTUH, Taiwan**, Blood*

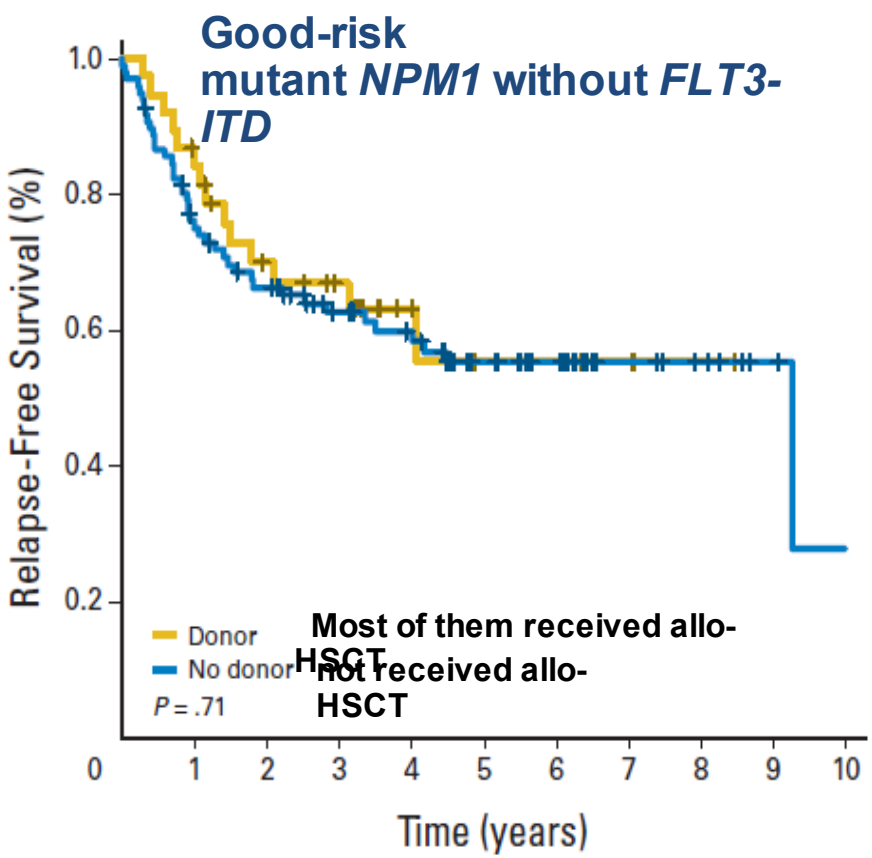
# Risk- Stratification by Genetic Alterations

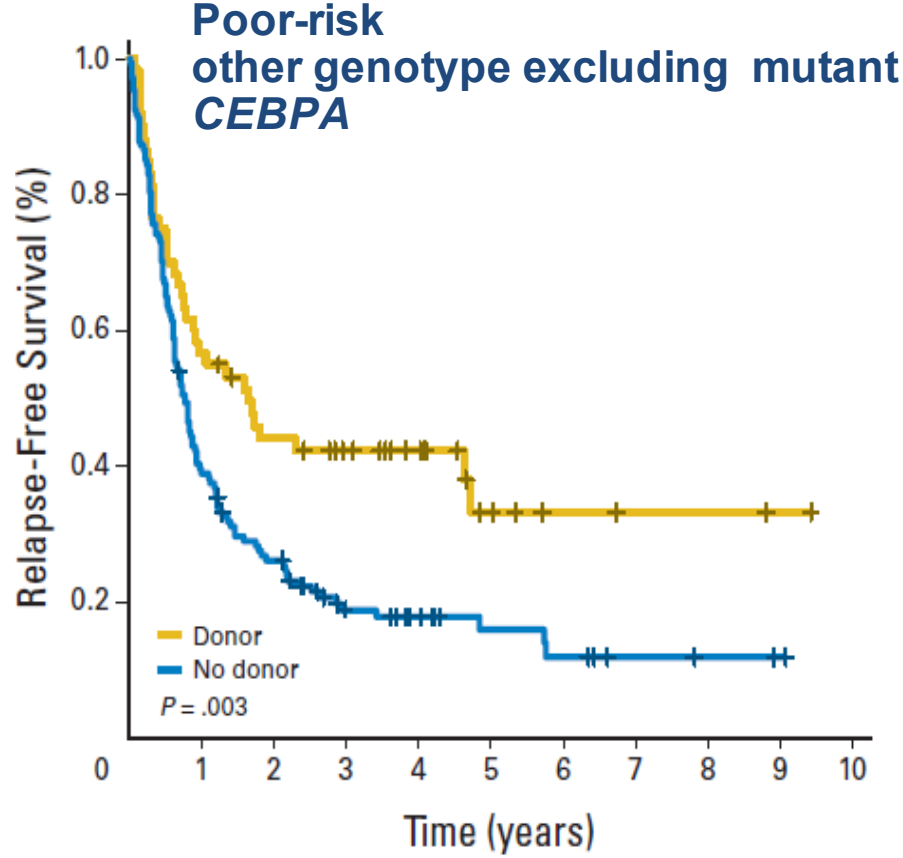
## (NTUH, 482 patients with cytogenetic data)




**Good-risk genotypes: Respond well to high dose post remission C/T alone**
**Poor-risk genotypes: HSCT**

# Relapse-free Survival According to the Availability of an Matched Related Donor



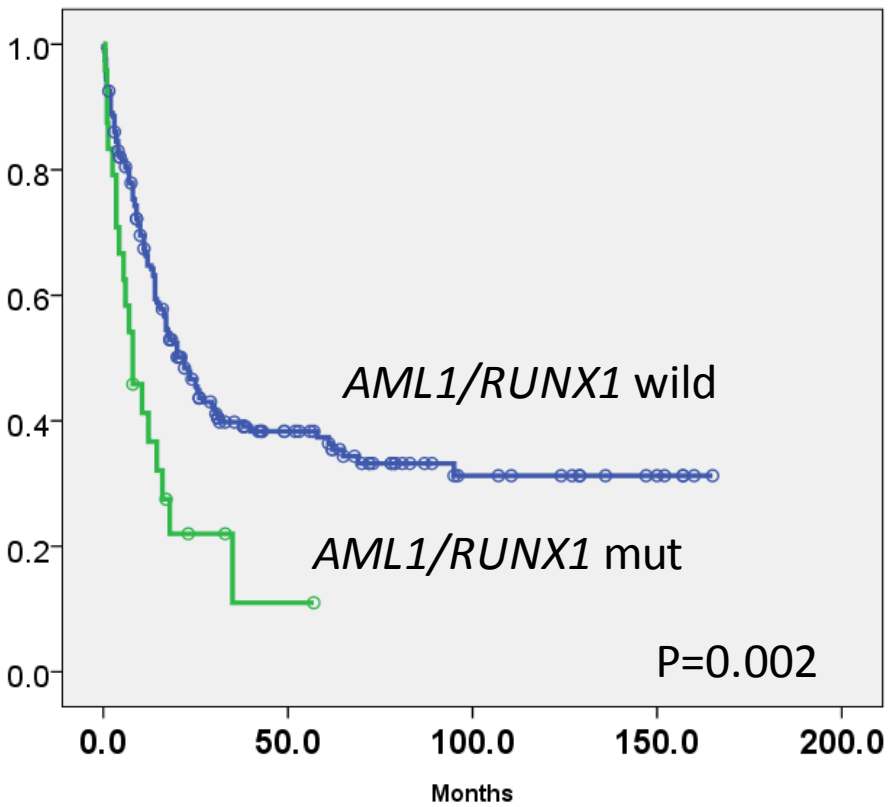




*German-Austrian AMLSG, NEJM 358:1909,2008*

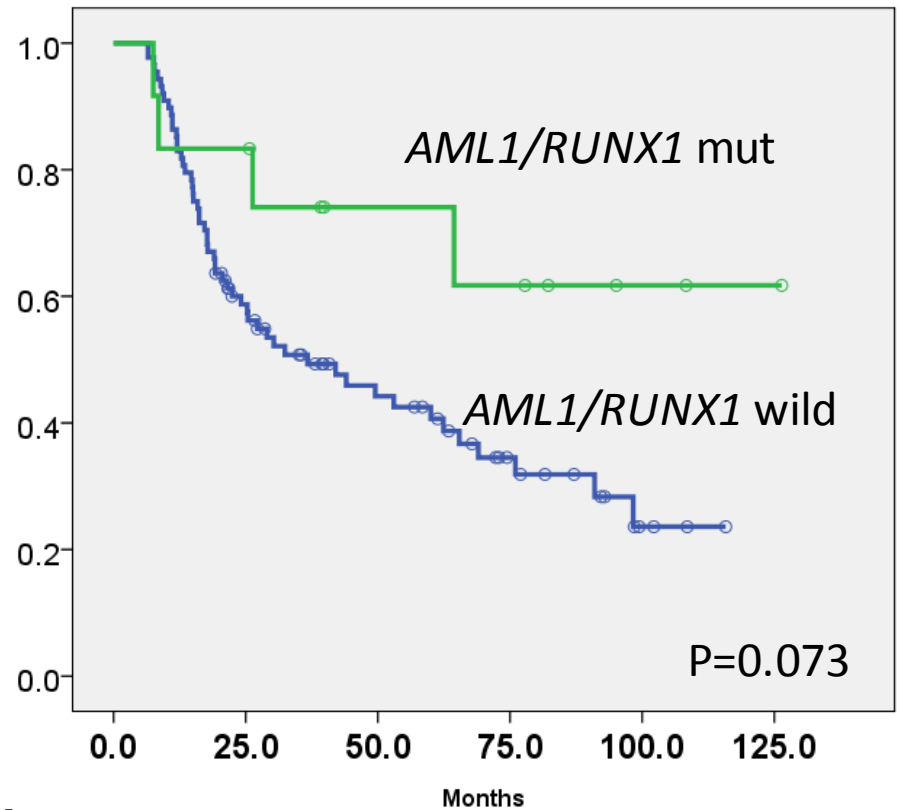
**Suggestion:**
**Patients with good-risk genotypes need not receive allo-HSCT in 1st CR**

# Allo-HSCT Improve the Survival of Patients with *RUNX1* Mutations

**non allo-HSCT group**




**allo-HSCT group**

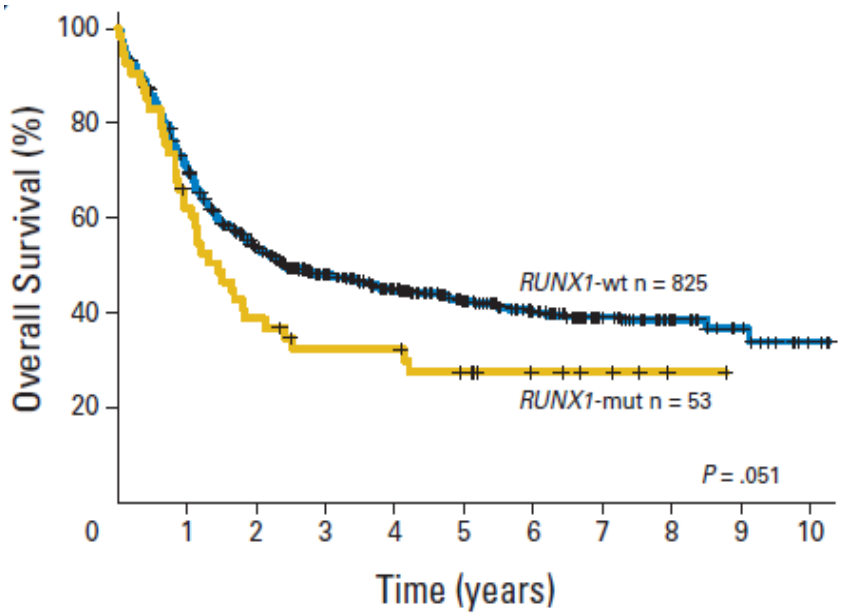


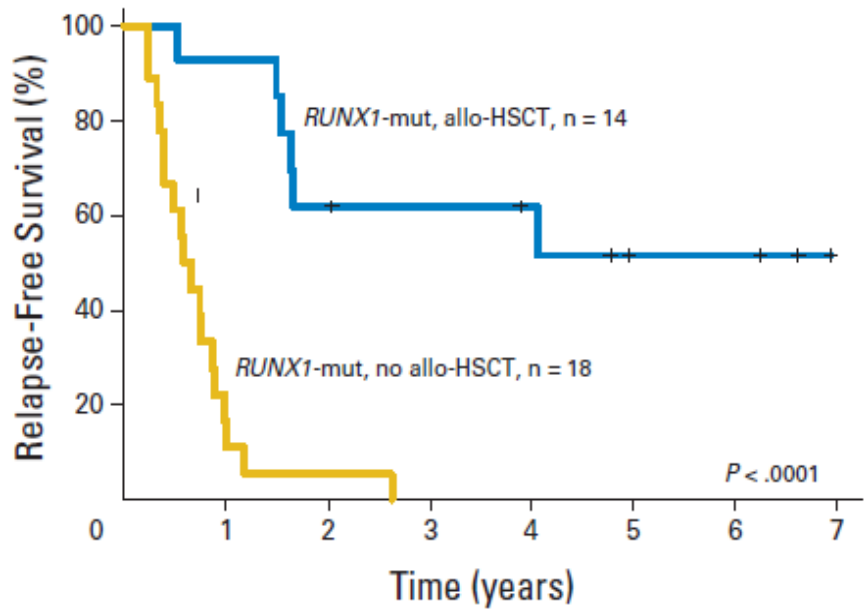

**NTUH, Taiwan**

**Suggestion:**
**Patients with poor-risk genotypes receive allo-HSCT in 1st CR.**

# Allo-HSCT Improve the Survival of Patients with *RUNX1* Mutations

## German-Austrian AML Study Group



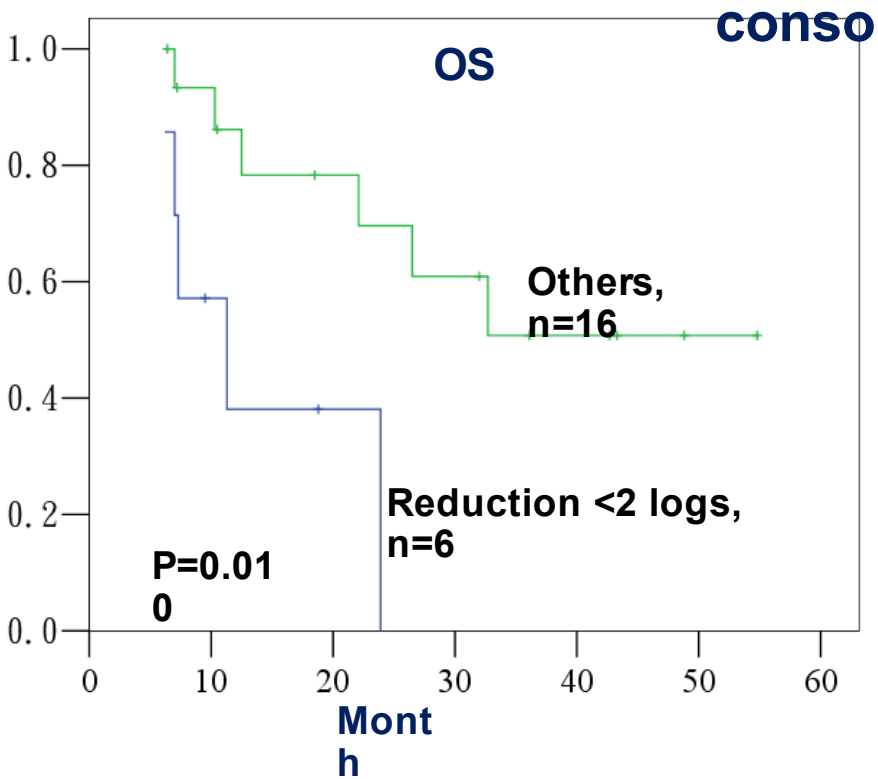



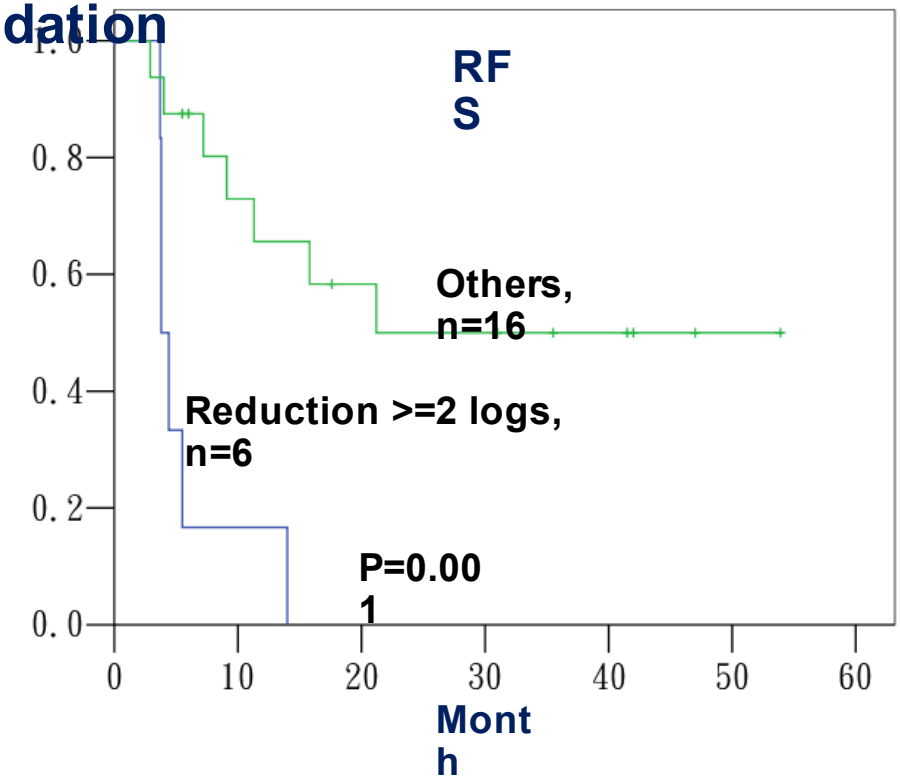

*JCO,2011, 29:1364*

# Gene mutations as biomarkers to monitor MRD

## Monitoring of *NPM1*-mutant in *NPM1*-mutated patients

**After consolidation**




**Patients with less than 2 logs reduction of *NPM1* mutants after consolidation C/T had shorter OS and RFS**

**More aggressive treatment may be needed for this group of patients.**

***NTUH:* *Leukemia 21:998, 2007***

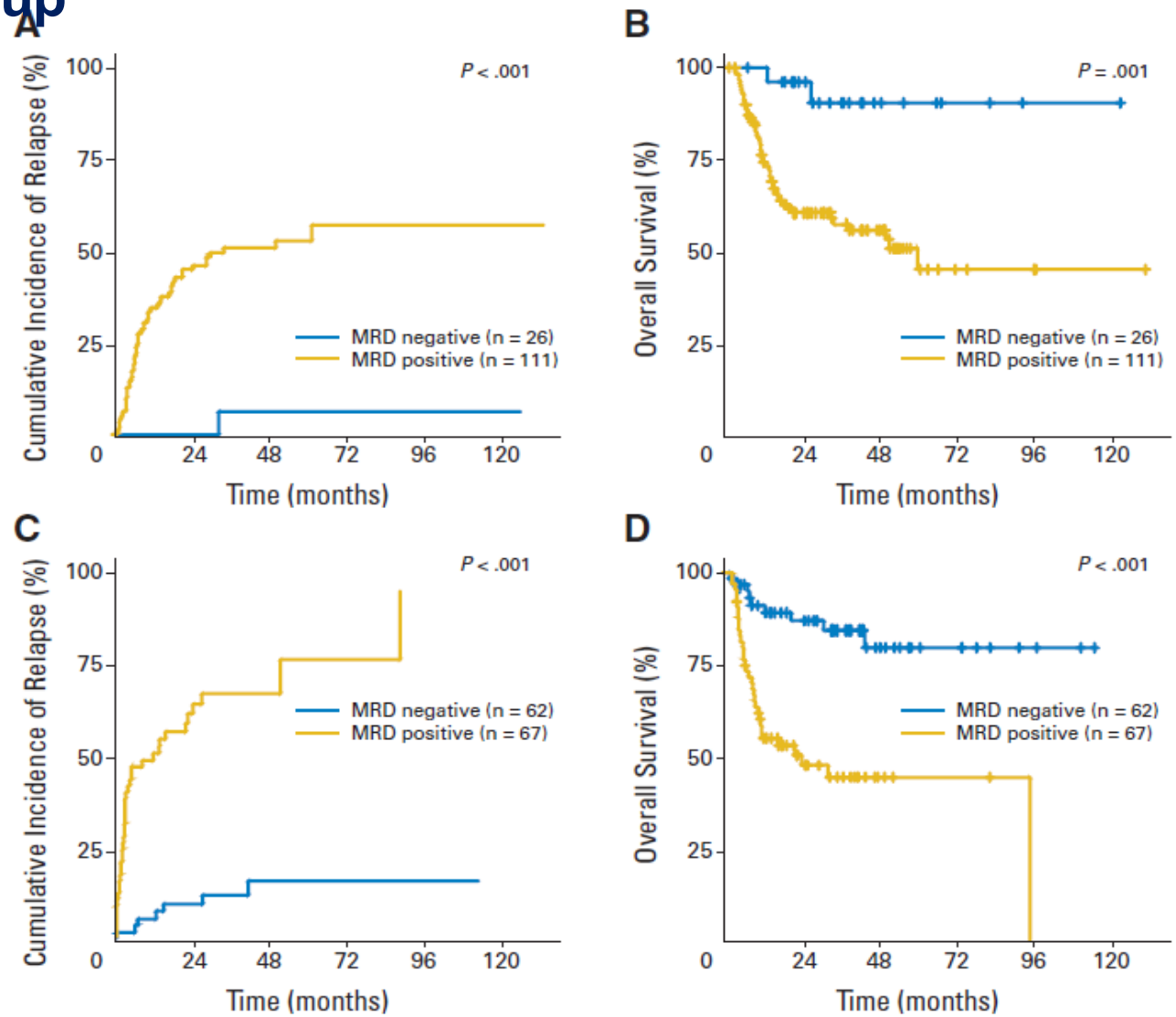
# Gene mutations as biomarkers for MRD monitoring

## *NPM1 mutation:* German-Austrian AML Study Group

**CR patients**

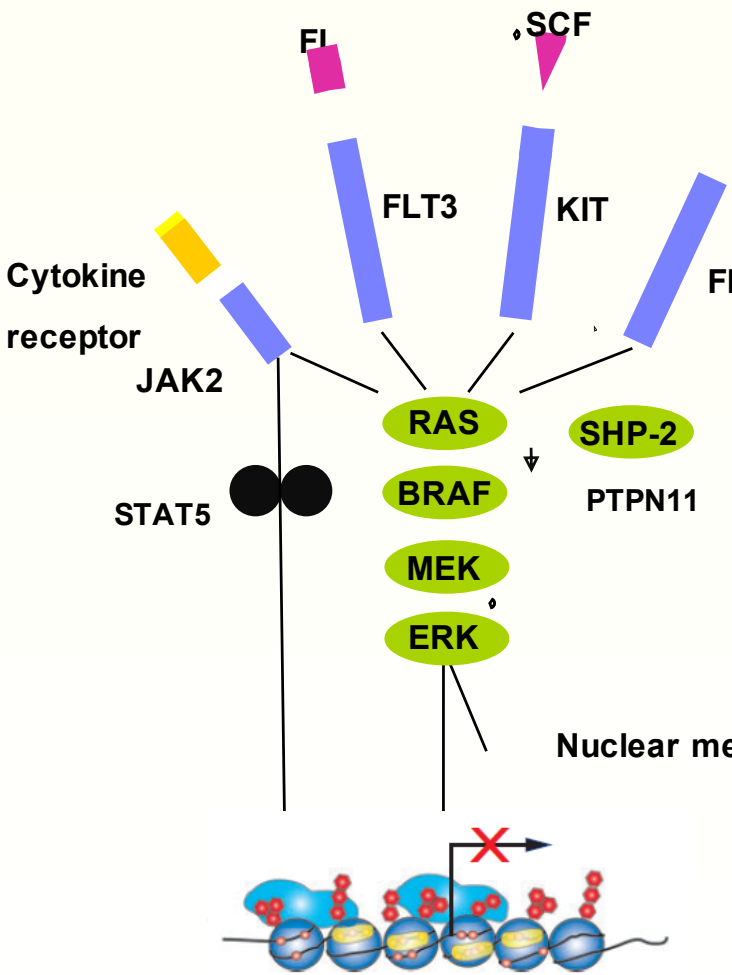
**after induction chemotherapy**

**after completion of therapy**




*JCO, 2011, 29:2709*

# Targeted Therapy in Acute Myeloid Leukemia




**Receptor tyrosine Kinases** — FLT3 inhibitors

**RAS-BRAF signaling** — Farnesyl-transferase Inhibitor: tipifarnib

**Transcription Factors PML/RARα** — All-trans retinoic acid; Arsenic trioxide

**Epigenetic modification** — DNA demethylation Agents (*TET, DNMT3A* mutations); Histone deacetylase inhibitors

# Summary

1. Most AML patients have genetic aberrations, and usually with 2 or more hits.
2. Genetic abnormalities can predict clinical outcome .
3. Gene alterations can be used as therapeutic targets as well as biomarkers to monitor MRD.
4. Risk-adapted treatment according to genotype at diagnosis and MRD after treatment may improve the clinical outcome of patients while reduce the side effects of treatments.

# Acknowledgement

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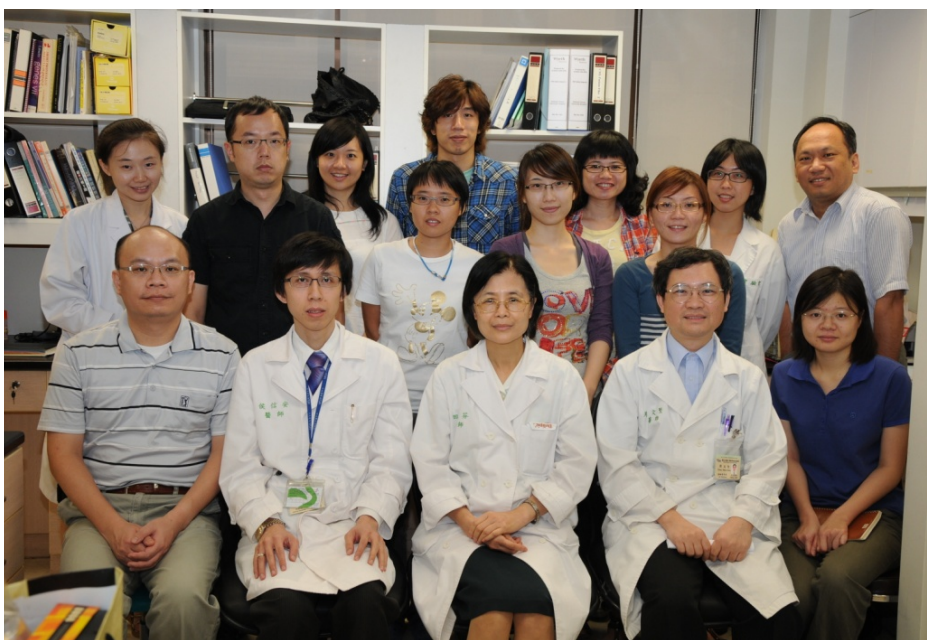
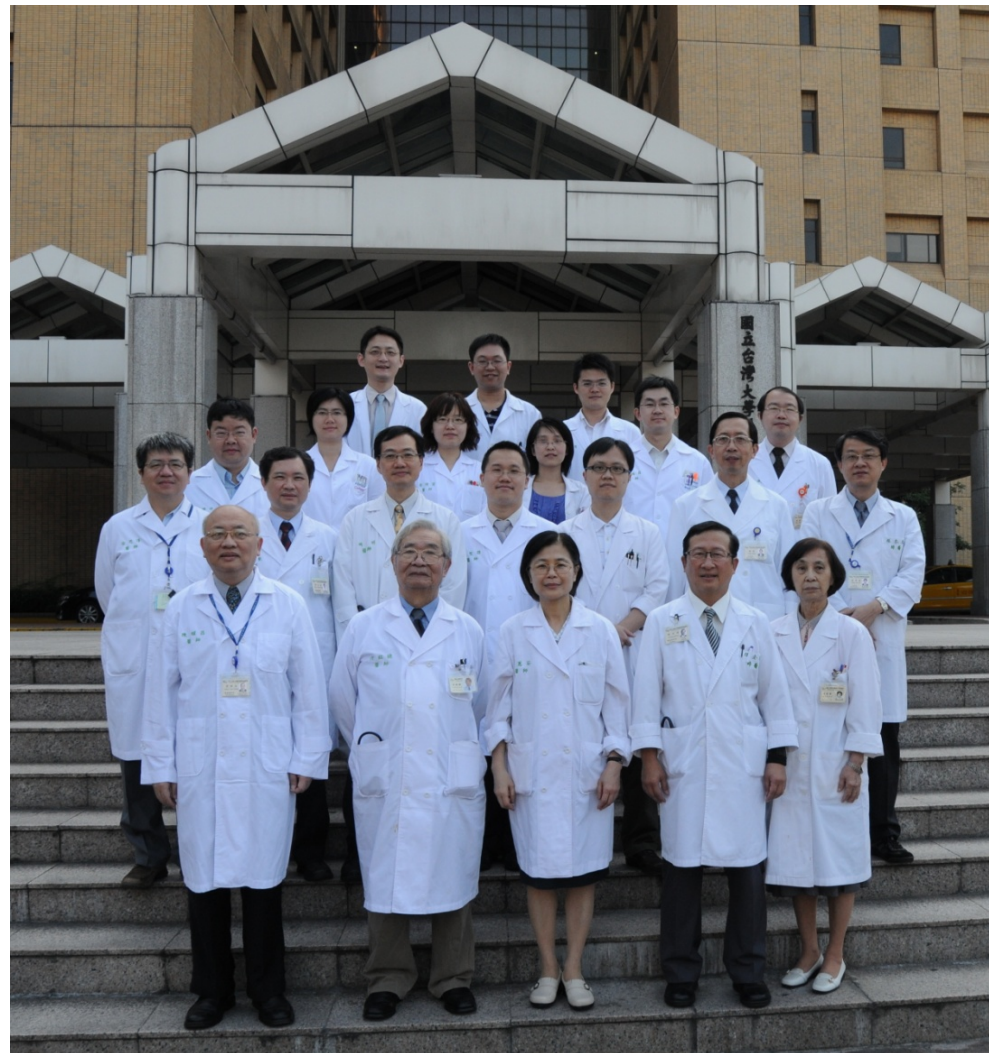
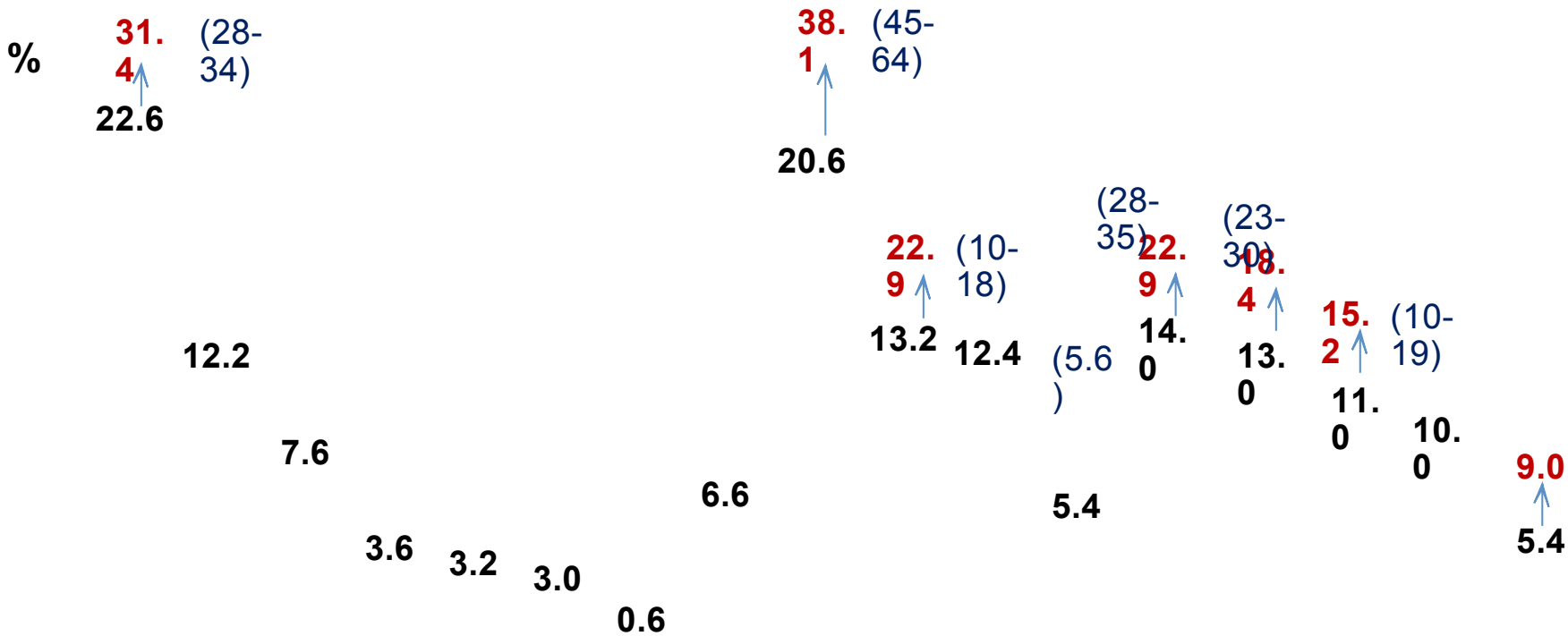





# 台灣藍鵲（
# Formosan Blue

# Molecular Gene Mutations in 500 AML Patients (NTUH)




***NTUH**: Clin Can Res 2005;11:1372; Cancer Res 2006;66:3310; Blood 2009;114(26); 5352; Blood 2010; 115:2149; Blood 2010, 115:2749; Blood 2010, 116:4086; Leukemia 2011, 25:246; Blood 2011, 118:3803; Blood 2012, 119:559*

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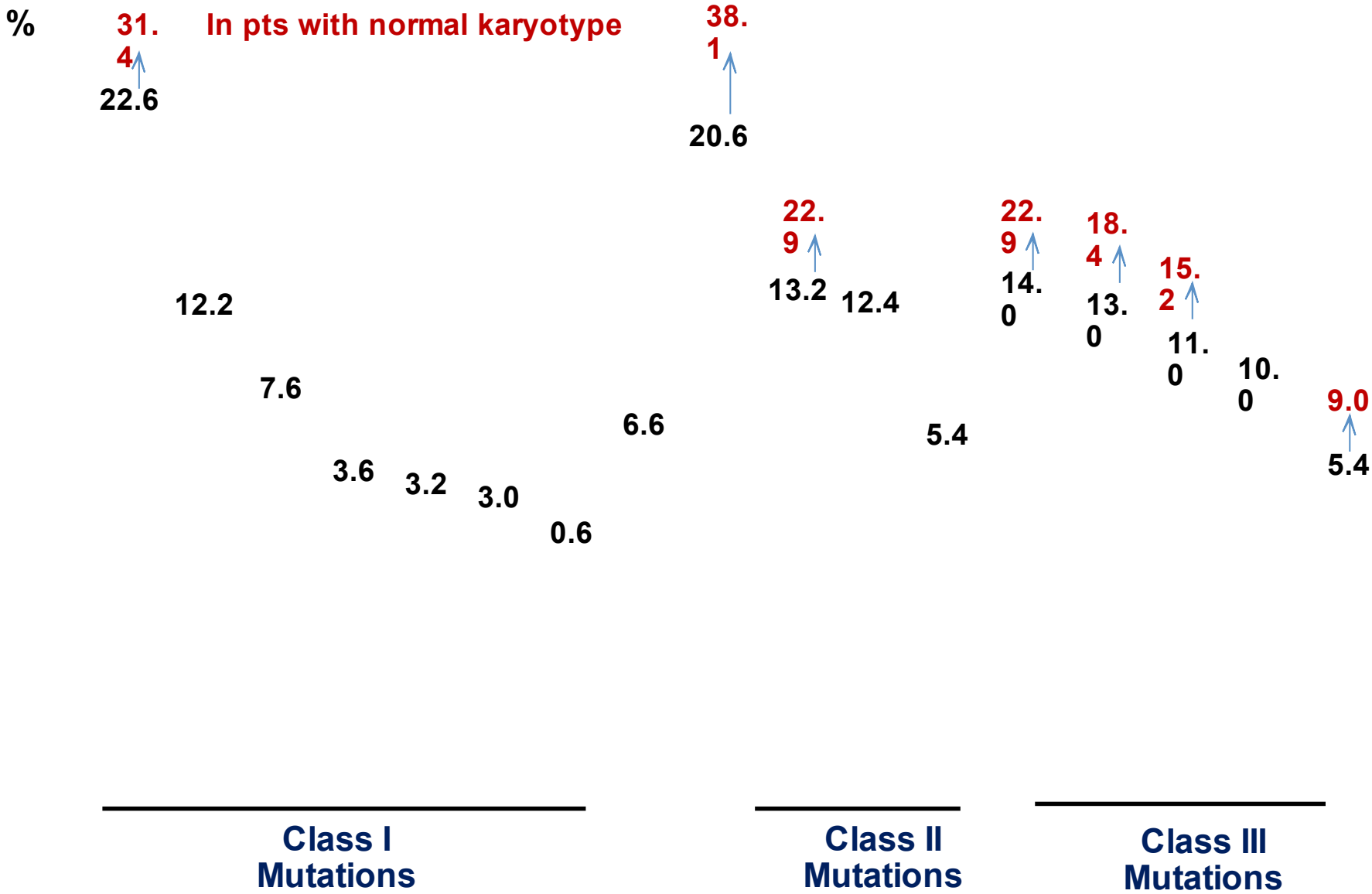
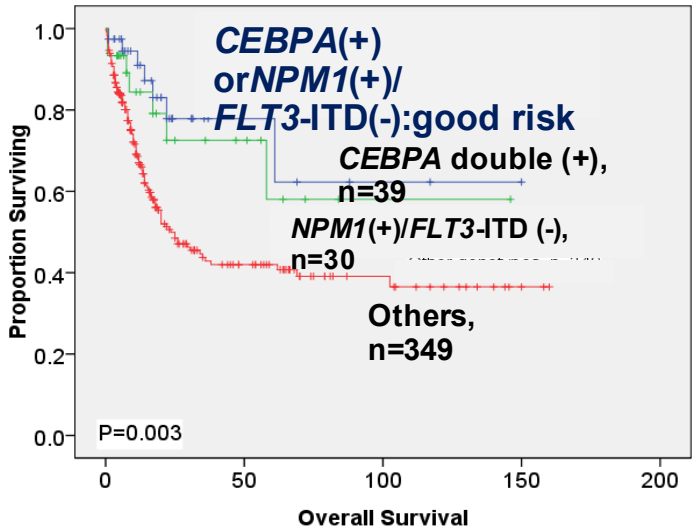
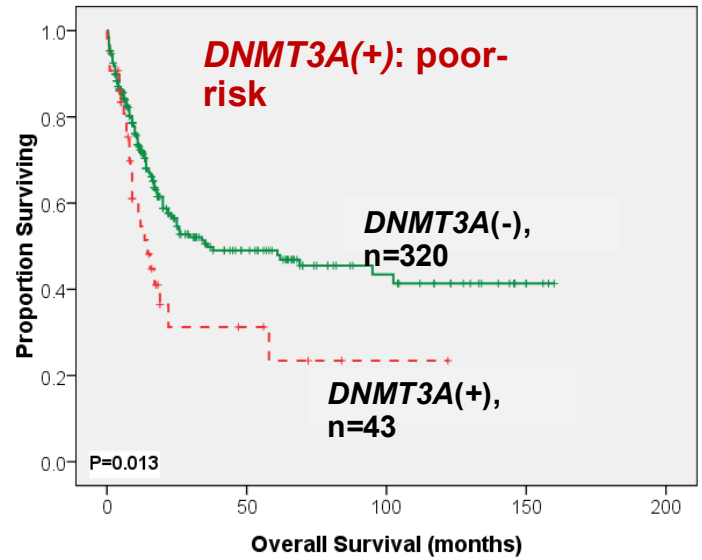


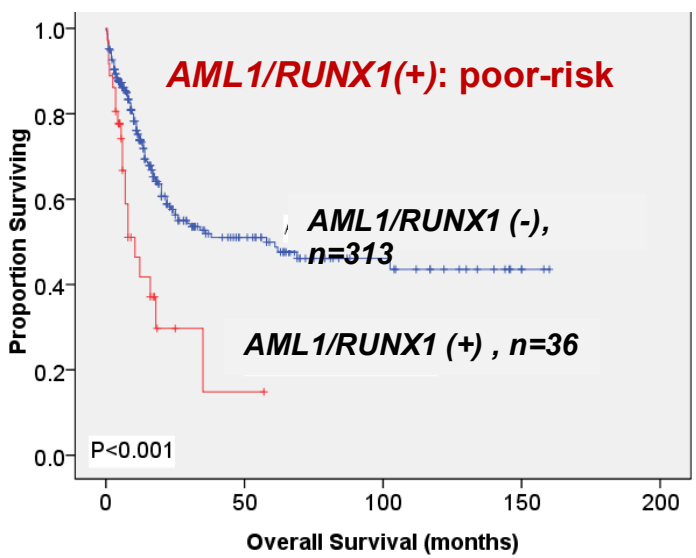

***NTUH***: *Clin Can Res 2005;11:1372*; *Cancer Res 2006;66:3310*; *Blood 2009;114(26); 5352*; *Blood 2010; 115:2149; Blood 2010, 115:2749; Blood 2010, 116:4086*; *Leukemia 2011, 25:246; Blood 2011, 118:3803; Blood 2012, 119:559*

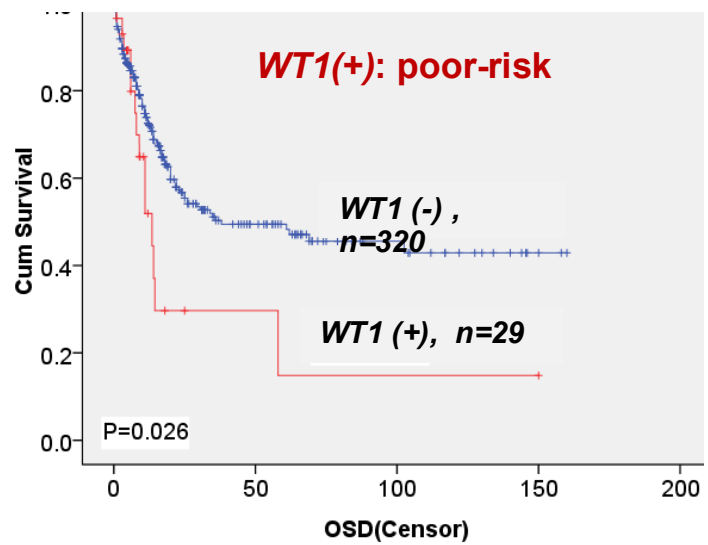
# Gene mutations predict prognosis

## NTUH, Taiwan, 1995-2007




***NTUH,*** *Br J Can 101:738, 2009; Blood* 2009; 114(26):5352;

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