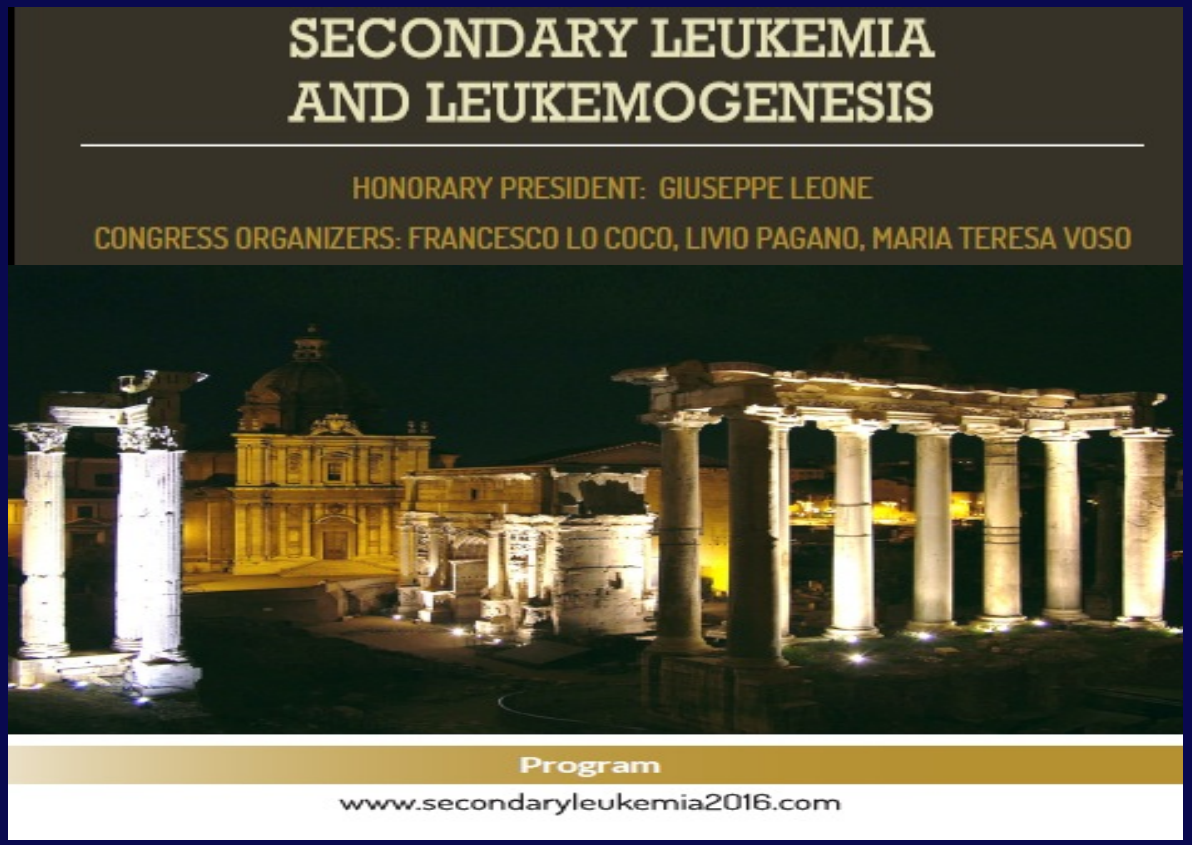
# Epidemiology of t-MN: an evolving scenario?




*Safaa Ramadan, Hemato-oncology, IEO Milan, Italy*

**t-AML as a late complication in cancer survivors**

**Baseline characteristics:** The Italian registry
**Outcome analysis:** EORTC experince

**Risk factors of t-AML among lymphoma patients**

# t-AML as a late complication in cancer survivors

# Risk of t-AML among cancer patients from 9 registries of SEER Program (1975-2008)

## Standardized Incidence Ratio (SIRs) of t-AML and type of primary disease

A **426.068** adults treated with chemotherapy for primary malignancy over 3 decades

**801 t-AML** cases were identified, ***4.70 times more than expected*** in the general population ***(p < .001)***

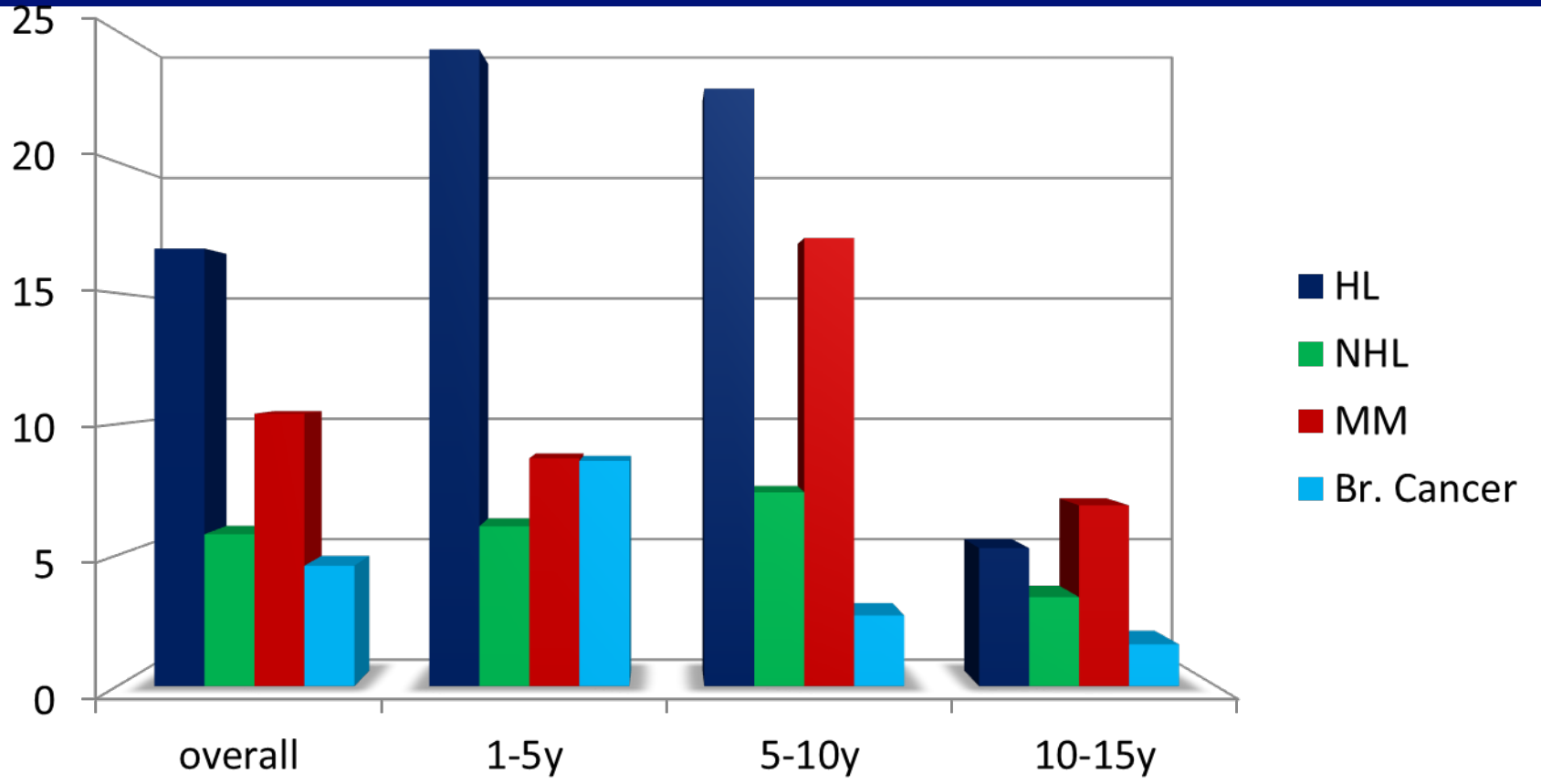
**50%:** breast cancer and NHL

- Breast: n =223, **SIR=4.60**; NHL: n=158, **SIR=5.85**

Morton L M et al, Blood. 2013

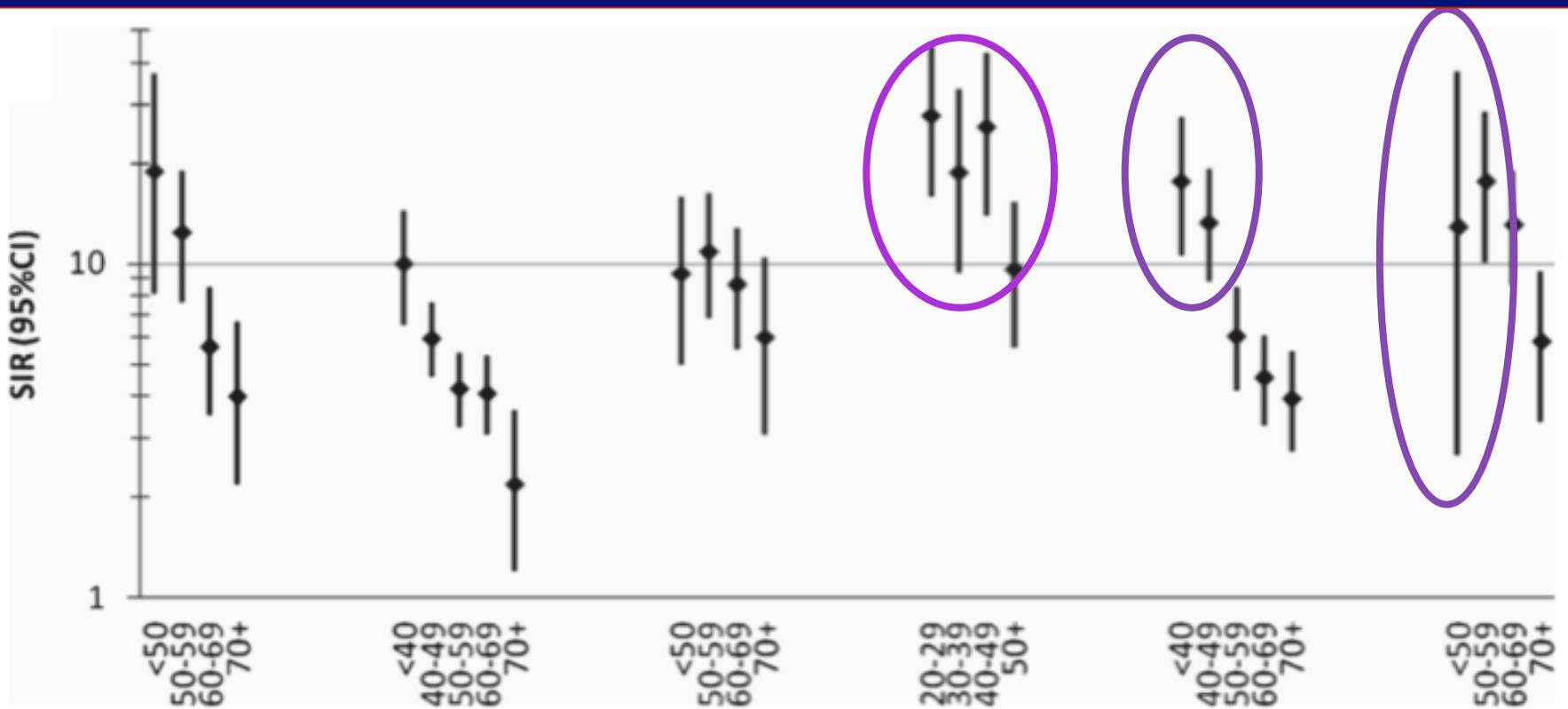
# SIR of t-AML by latency period
# SEER data (1975-2008)

Risks of t-AML declines after 5 years in solid tumors
But persistent for >10 years in HL, NHL, and myeloma.




Morton L M et al, Blood. 2013

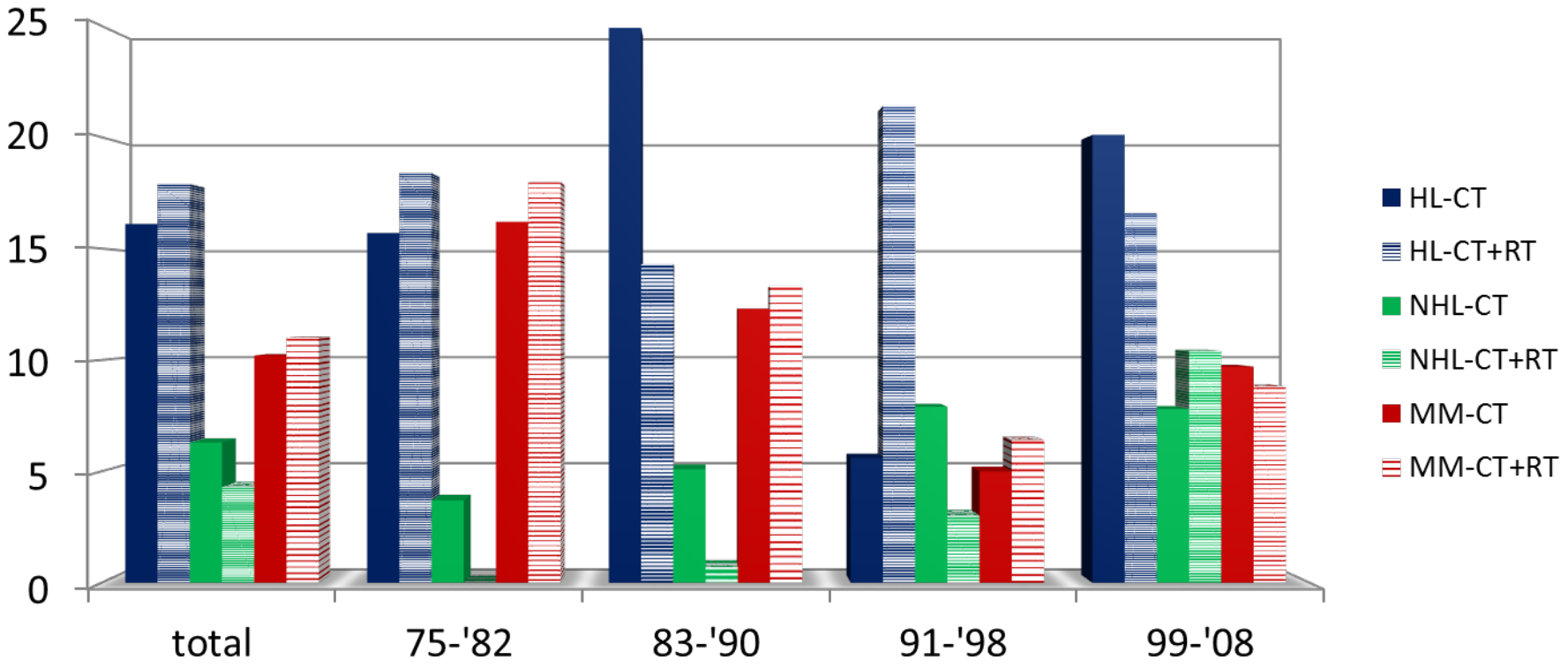
# Standardized Incidence Ratio (SIRs) of t-AML by age after chemotherapy of first primary malignancies in adulthood, 9 SEER registries, 1975-2008




| Lung, bronchus | Female breast | Ovary | Hodgkin lymphoma | Non-Hodgkin lymphoma | Myeloma |
|---|---|---|---|---|---|
| $P_{hom}$<0.001 | $P_{hom}$<0.001 | $P_{hom}$=0.051 | $P_{hom}$<0.001 | $P_{hom}$<0.001 | $P_{hom}$=0.012 |
| $P_{trend}$<0.001 | $P_{trend}$<0.001 | $P_{trend}$=0.009 | $P_{trend}$<0.001 | $P_{trend}$<0.001 | $P_{trend}$=0.004 |

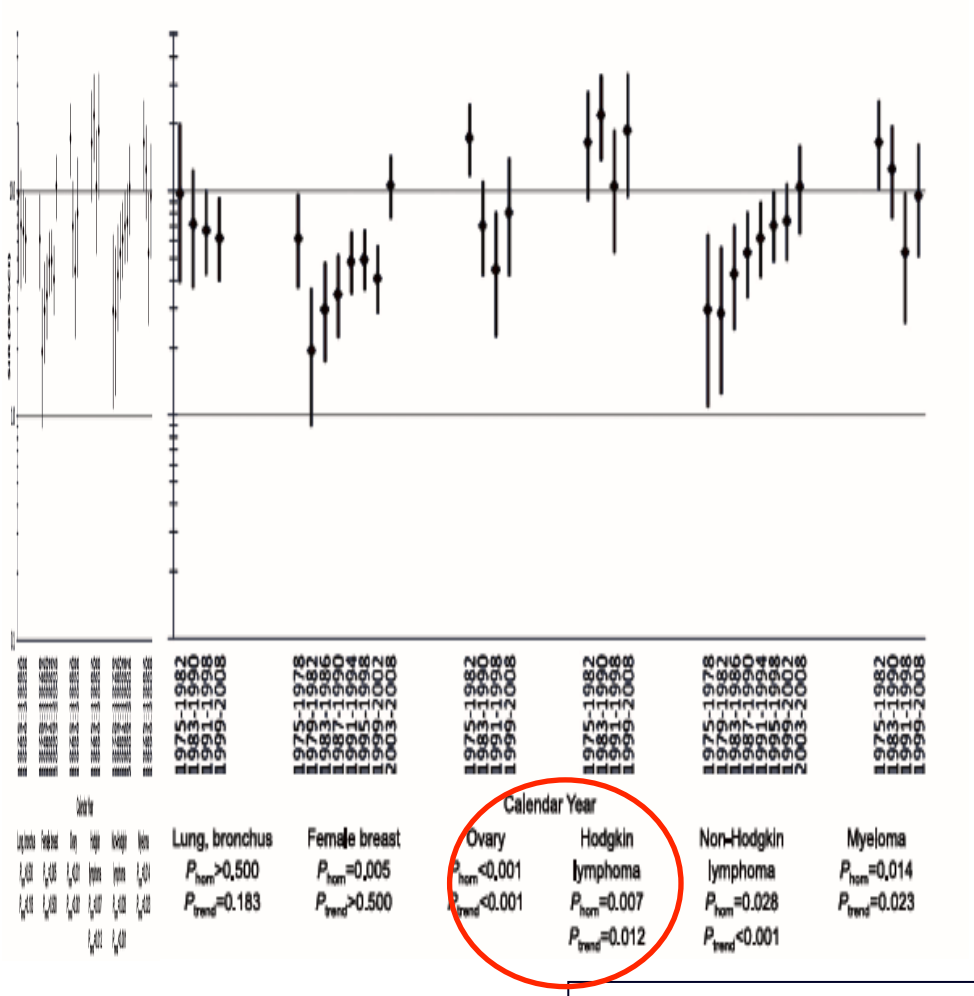
Morton L M et al, Blood. 2013

# SIRs of t-AML by calendar period treated with or without RT: Hodgkin's Lymphoma, non-Hodgkin's Lymphoma and Multiple Myeloma




Morton L M et al, Blood. 2013

# SIRs of t-AML by calendar period for the three main lymphoid malignancies: there is a steady increase in t-AML risk in NHL




Morton L M et al, Blood. 2013

## Conclusion 1:

- **In NHL:** there is a steady increase in t-AML risk
- **In HL and MM:** the risk of t-AML remains high despite the introduction of novel agents

# Baseline characteristics and outcome of t-MN: The Italian registry data

# Characteristics and outcome of therapy-related myeloid neoplasms: Report from the Italian network on secondary leukemias

**42 Italian Centers afferent to GIMEMA**

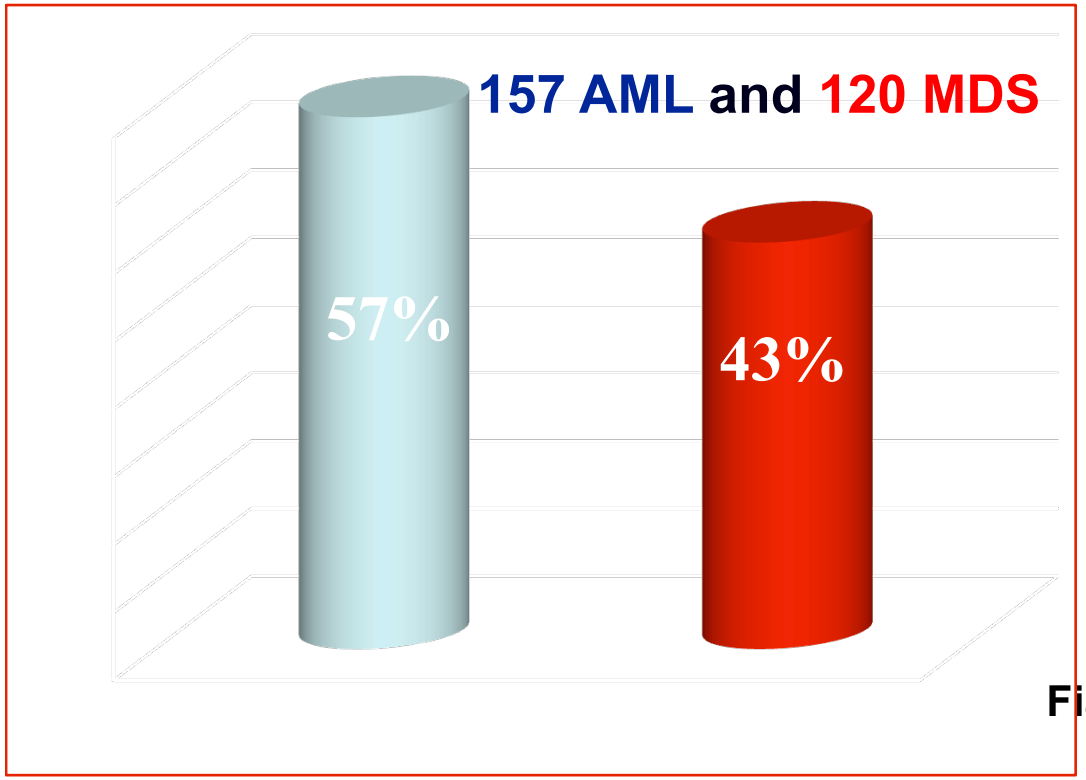
**277 t-MN patients**, recruited between 1999 and 2013

(104 retrospectively and 173 prospectively registered).

**Cortesy of L. Fianchi**
**Fianchi et al, Am J Hem 2015**

# t-MN Italian Multicenter Registry: patient charateristics

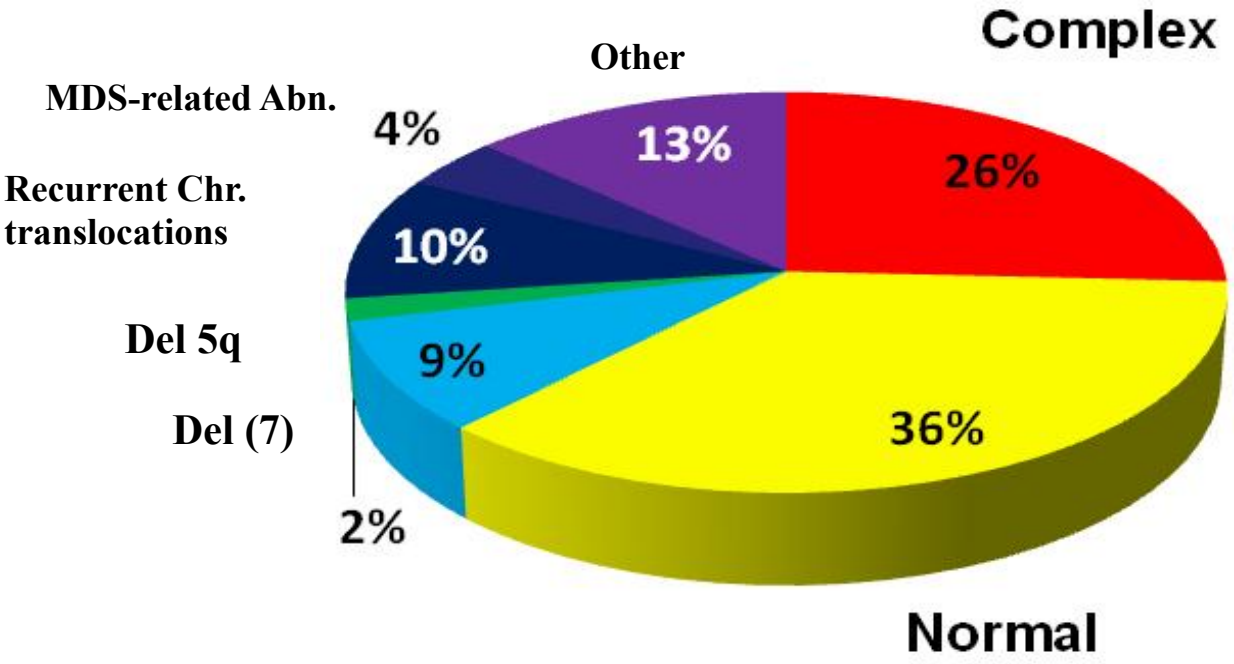
| Patient Characteristics | Retrospective series (n= 104) | Prospective series (n=173 ) | p |
|---|---|---|---|
| Median age – years | 64 (27-83) | 64 (21-87) | 0.28 |
| Sex (M/F) | 44/60 | 73/100 | 1.0 |




Fianchi et al, Am J Hem 2015

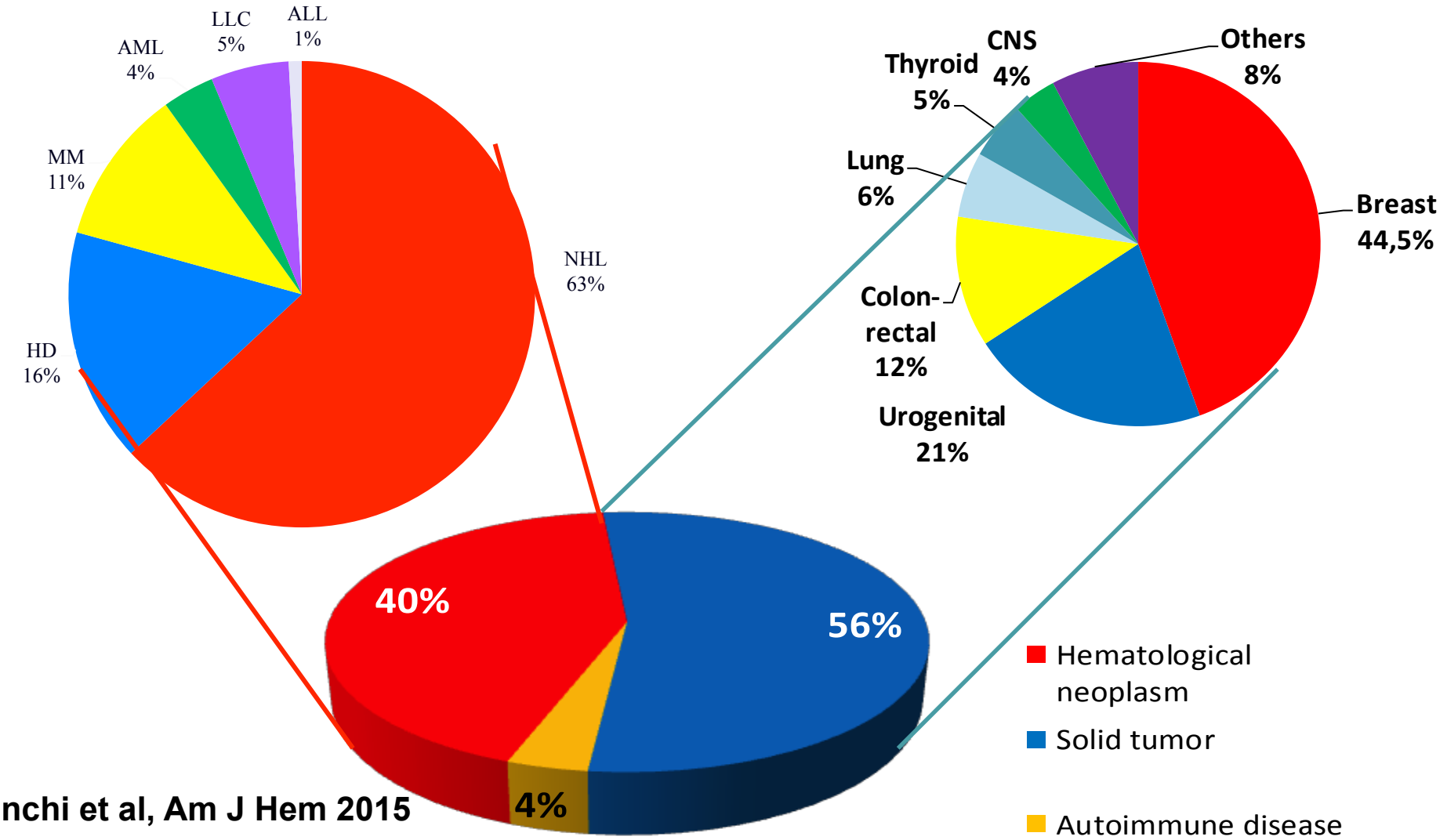
# t-MN Italian Multicenter Registry: Distribution of cytogenetic abnormalities

**Cytogenetic risk classification: 39% had Unfavorable AML, 50% intermediate and 11% favorable.**



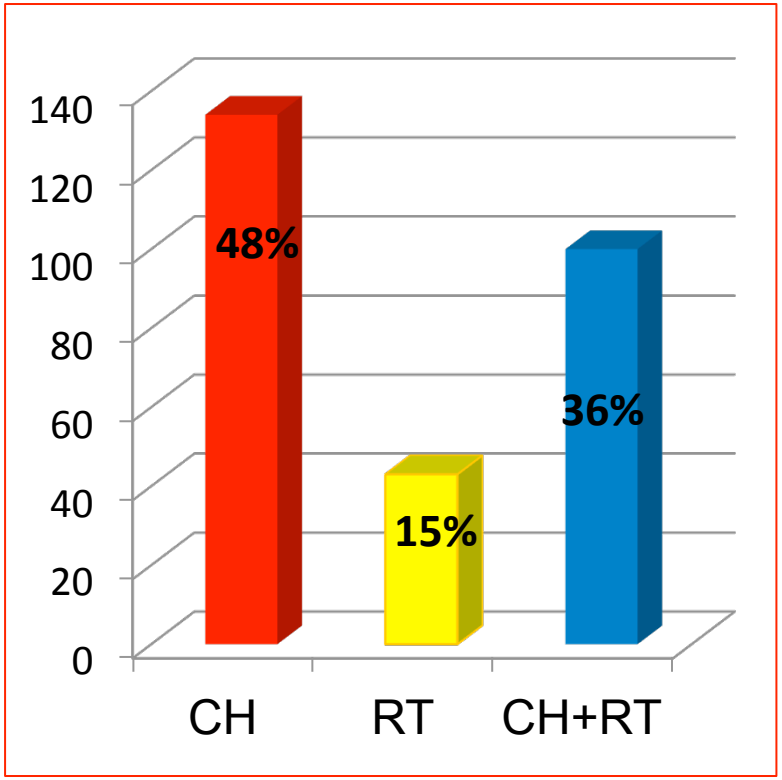

Fianchi et al, Am J Hem 2015

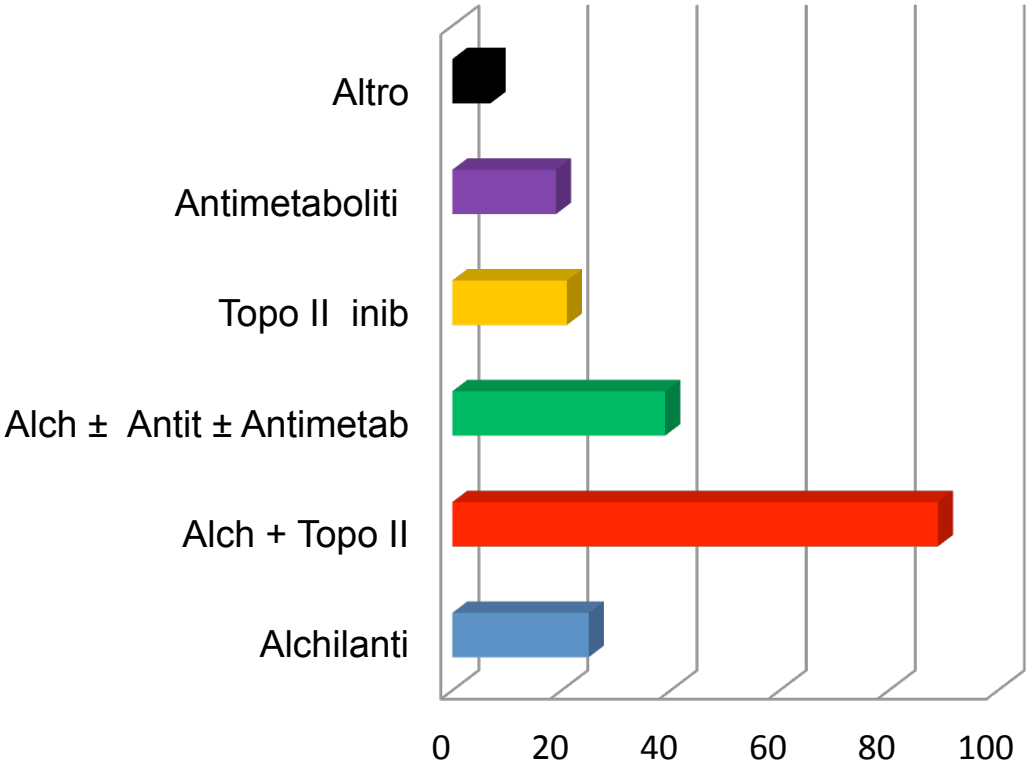
# t-MN Italian Multicenter Registry: Primary malignancy




Fianchi et al, Am J Hem 2015

# Italian Multicenter Registry: Primary treatment




**Fianchi et al, Am J Hem 2015**

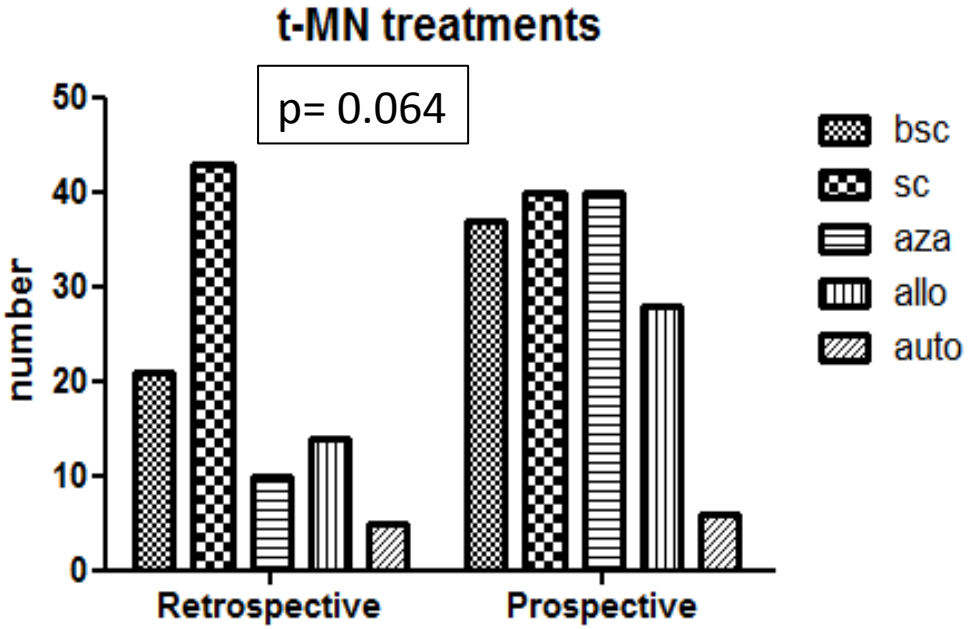
# t-MN Italian Multicenter Registry: Latency period

| Treatment | Median latency |
|---|---|
| Ch | 5,7 years |
| RT | 11.2 ± 1.8 years |
| RT + CH | 7.1 ± 0.4 years |
| Alk | 8.4 ± 1.1 years |
| Alk + Topo-Inh | 6 ± 0.5 years |

Fianchi et al, Am J Hem 2015

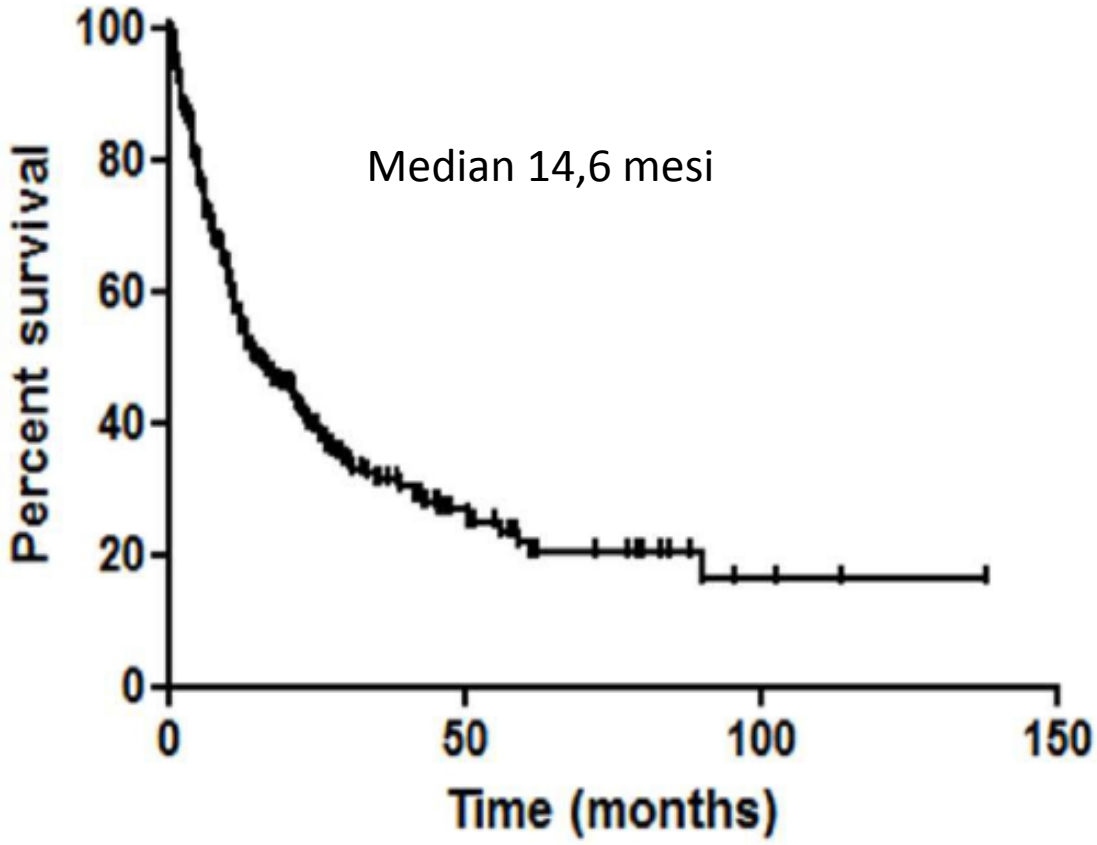
# t-MN Italian Multicenter Registry: AML/MDS Treatment (n=244)

| Treatment | N° (%) |
|---|---|
| Standard chemotherapy | 83 (34%) |
| Hypomethylating | 50 (20%) |
| BSC | 58 (24%) |
| Allo-SCT | 42 (17%) |
| Auto-SCT | 11 (4,5%) |




Fianchi et al, Am J Hem 2015

# t-MN Italian Multicenter Registry: Overall survival




Fianchi et al, Am J Hem 2015

# Survival improvement of secondary acute myeloid leukemia (s-AML) over time: Experience from 960 patients included in 13 EORTC-GIMEMA-HOVON Leukemia Group Trials

Safaa M.Ramadan, Stefan Suciu, Marian J.P.L.Stevens-Kroef, Roelof Willemze, Sergio Amadori, Theo de Witte, Bob Lowenberg, Petra Muus, Boris Labar, Liv Meert, Gaetan de Schaetzen, Giovanna Meloni, Giuseppe Leone, Marco Vignetti, Franco Mandelli, Frédéric Baron, and Jean Pierre Marie

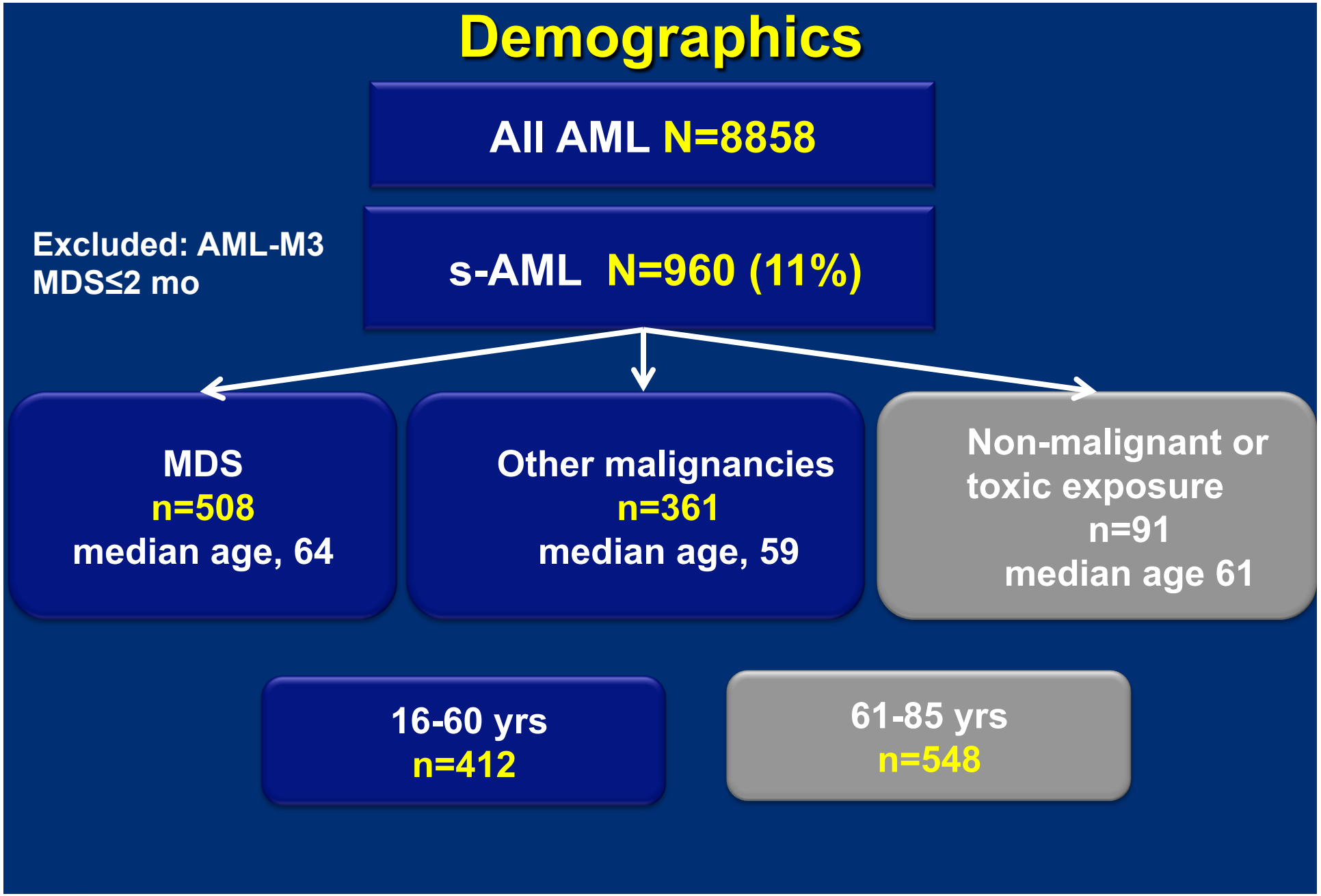
on behalf of the

EORTC, GIMEMA and HOVON Leukemia groups.

Presented at the 55th ASH annual meeting, New Orleans.

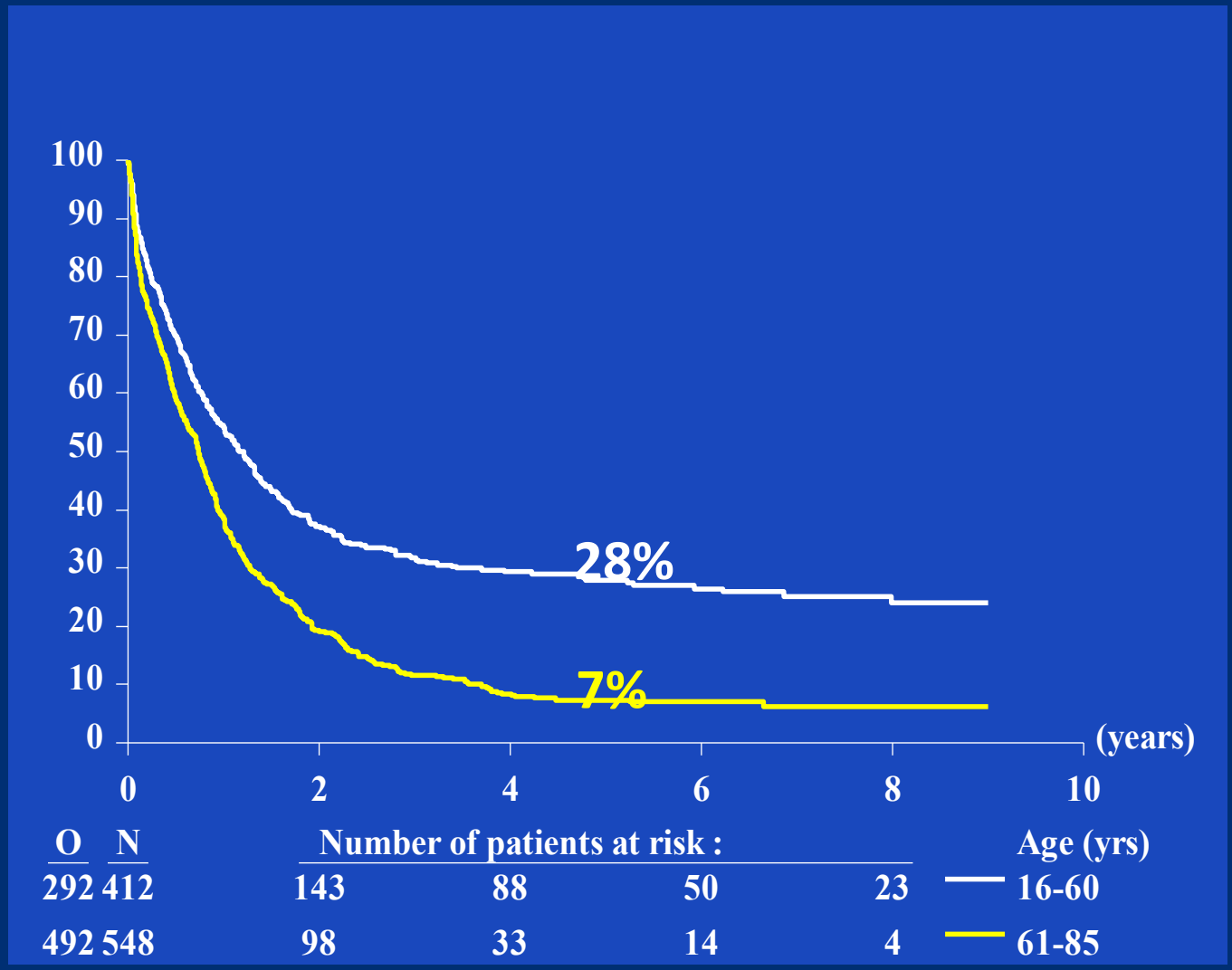
EORTC The future of cancer therapy

# Demographics




EORTC *The future of cancer therapy*

# 5-year OS of the all s-AML patients by age
## (median follow-up 6 yrs)

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# Baseline characteristics of patients (age 16-60 yrs) with s-AML following MDS or other malignancies

| | MDS (*n* = 181) | Other malignancies (*n* = 186)* |
|---|---|---|
| Age: 16-45 years | 26.5% | 42.5% |
| 46-60 years | 73.5% | 57.5% |
| Female | 40% | 60% |
| Latency (yrs): Median (range) | 0.6 (0.17, 14.8) | 3.7 (0.2, 30.3) |
| WBC: ≥25 x$10^9$/L | 23% | 65 (35%) |
| Cytogenetic risk: | | |
| Good-intermediate | 49% | 52% |
| Poor | 20% | 12% |
| Unknown | 31% | 36% |

*Solid tumors *n*=131 (BC=55); Hematologic *n*=45 (HD=25); Unknown *n* = 10

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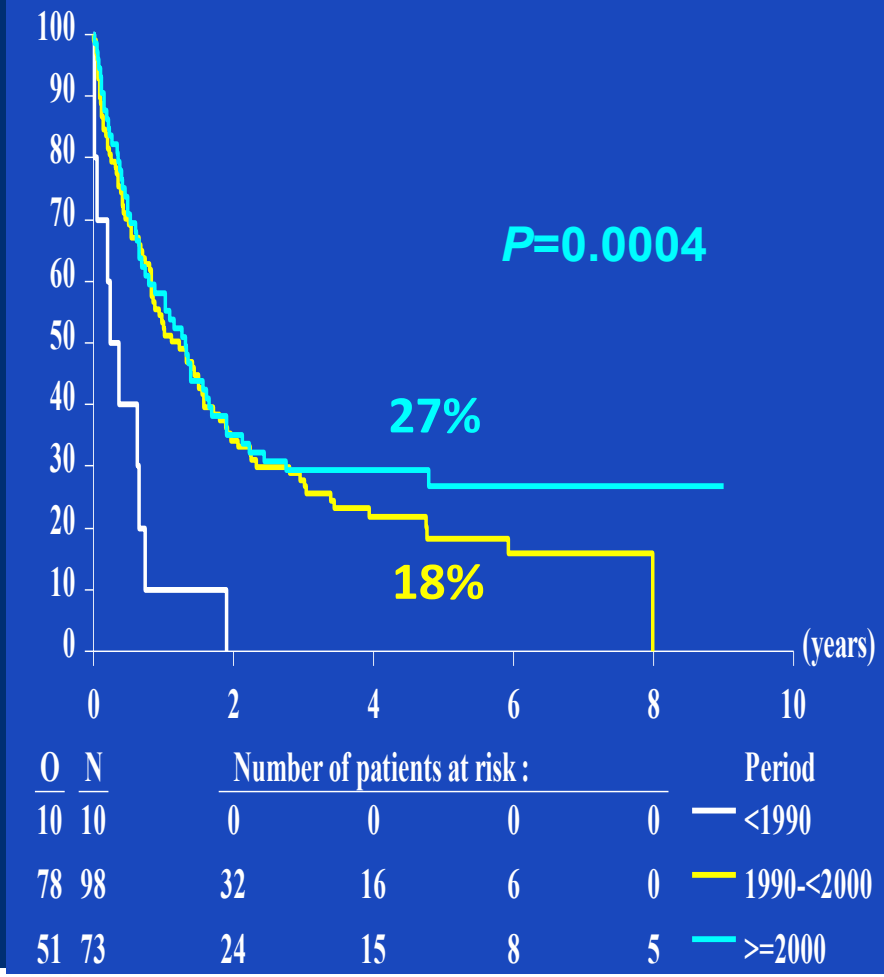
# Treatment type and outcome (age 16-60 yrs)

| | MDS (*n* = 181) | Other malignancies (*n* = 186) |
|---|---|---|
| Intensity Induction | | |
| Standard (SD-Ara-C) | 90% | 84% |
| Intensive (HD-Ara-C) | 10% | 16% |
| CR/CRi after induction | 51% | 65% |
| Relapse rate after CR/CRi | [58%] | [37%] |
| SCT in CR1 | | |
| AutoSCT | [18%] | [36%] |
| AlloSCT | [25%] | [19%] |

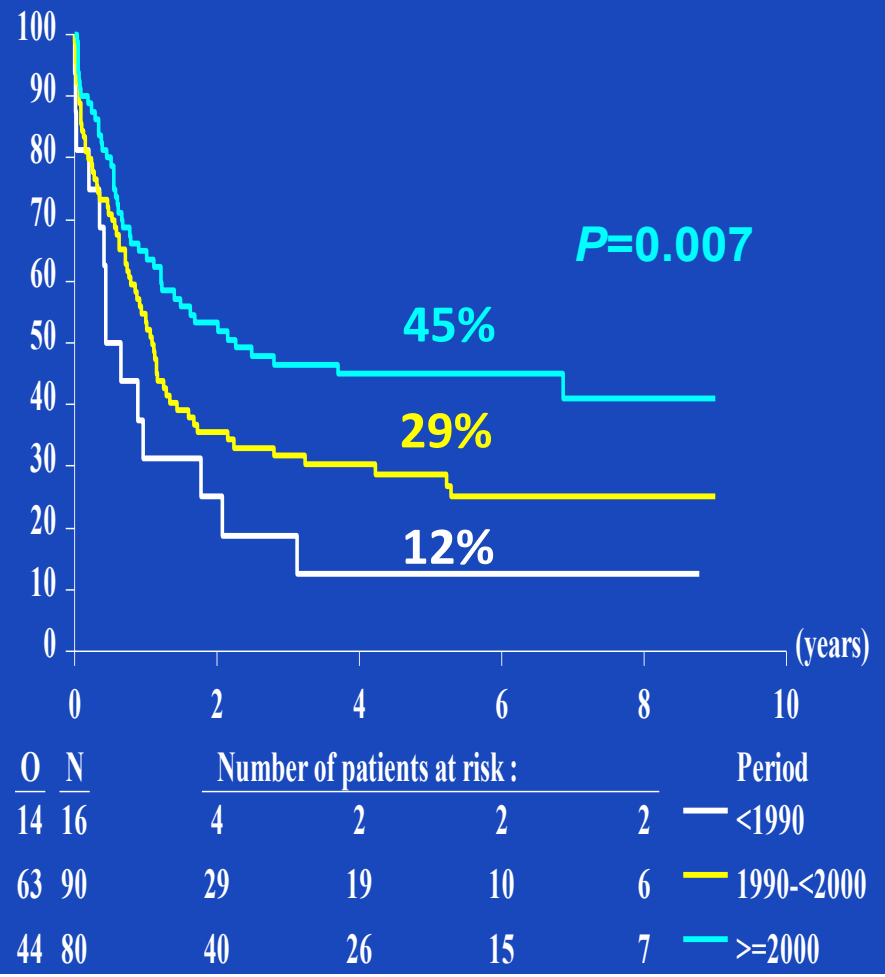
# 5-year OS by treatment period (age 16-60 yrs)

## s-AML following MDS




| O | N | Number of patients at risk : | | | | Period |
|---|---|---|---|---|---|---|
| 10 | 10 | 0 | 0 | 0 | 0 | <1990 |
| 78 | 98 | 32 | 16 | 6 | 0 | 1990-<2000 |
| 51 | 73 | 24 | 15 | 8 | 5 | >=2000 |

## s-AML following other malignancies




| O | N | Number of patients at risk : | | | | Period |
|---|---|---|---|---|---|---|
| 14 | 16 | 4 | 2 | 2 | 2 | <1990 |
| 63 | 90 | 29 | 19 | 10 | 6 | 1990-<2000 |
| 44 | 80 | 40 | 26 | 15 | 7 | >=2000 |

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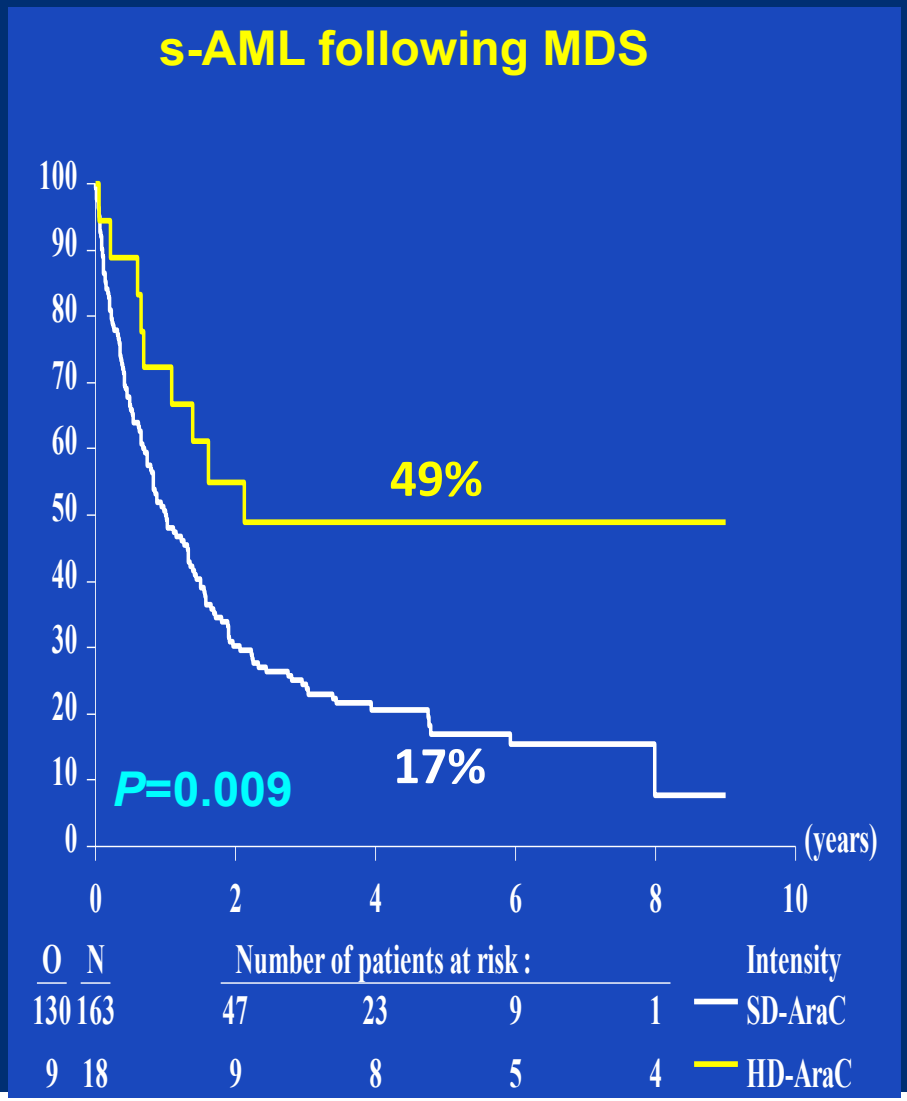
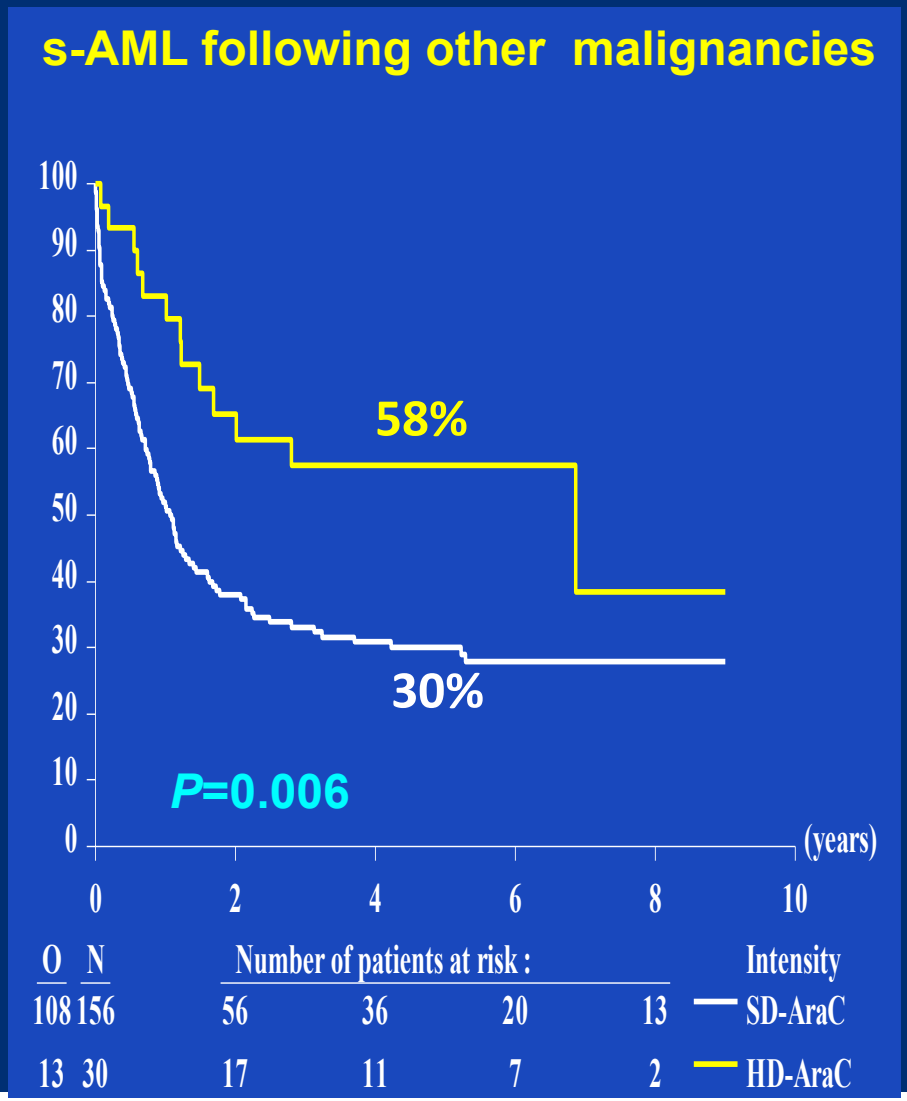
# 5-year OS by induction intensity (HD-AraC vs SD-AraC*)

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*regardless the treatment period

# Multivariate analysis* (restricted to s-AML following MDS and other malignancies, age 16-60 years)

| | HR (95% CI) | P-value |
|---|---|---|
| Age : ≥45 vs. <45 yrs | 1.7 (1.3-2.2) | <0.0001 |
| Gender: Male vs. Female | 1.4 (1.1-1.8) | 0.01 |
| WBC: 25 ≥ vs. < 25 x 10E9/L | 1.9 (1.5-2.5) | <0.0001 |
| Cytogenetics: Poor vs. Other | 2.0 (1.5-2.8) | <0.0001 |
| Treatment period: 1990 - 1999 vs. <1990 | 0.5 (0.3-0.7) | <0.0001 |
| ≥ 2000 vs. <1990 | 0.4 (0.2-0.6) | <0.0001 |
| HD- vs. SD-AraC | 0.5 (0.3-0.9) | 0.01 |

*Stratified by Group

## Conclusion 2:

- The outcome of s-AMLis generally poor
- In younger patients, induction schedules containing HD-AraC were associated with improvement in survival

# Risk factors for t-MN in lymphoma patients

MEDITERRANEAN JOURNAL OF HEMATOLOGY AND INFECTIOUS DISEASES
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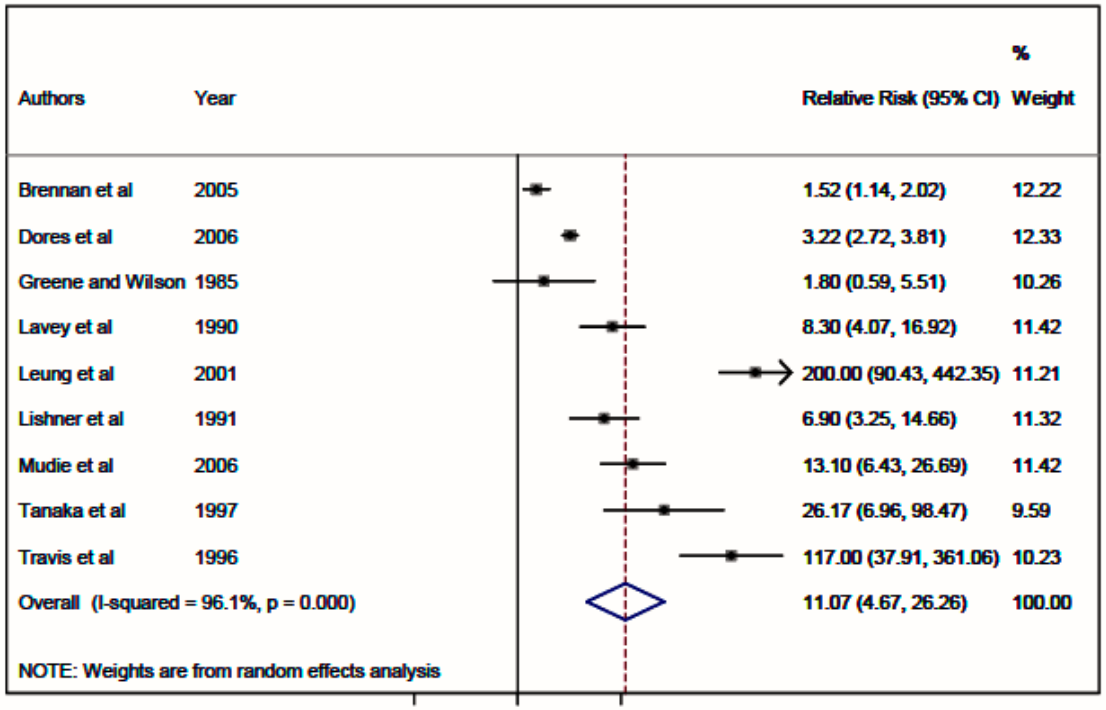
**Review Articles**

# Therapy-Related Myeloid Neoplasm in Non-Hodgkin Lymphoma Survivors

Alessia Bari[1], Luigi Marcheselli[1], Raffaella Marcheselli[1], Eliana Valentina Liardo[1], Samantha Pozzi[1], Paola Ferri[2] and Stefano Sacchi[1]

The RR for AML among 197,456 NHL survivors recruited from 19 studies (1935-2004): was 11.07 (95% CI: 4.67-26.26)



The risk of second cancer among
1,347 patients with lymphoma treated with the HDS program
between 1985 and 2005 at 11 Italian centers

VOLUME 29 · NUMBER 7 · MARCH 1 2011

JOURNAL OF CLINICAL ONCOLOGY

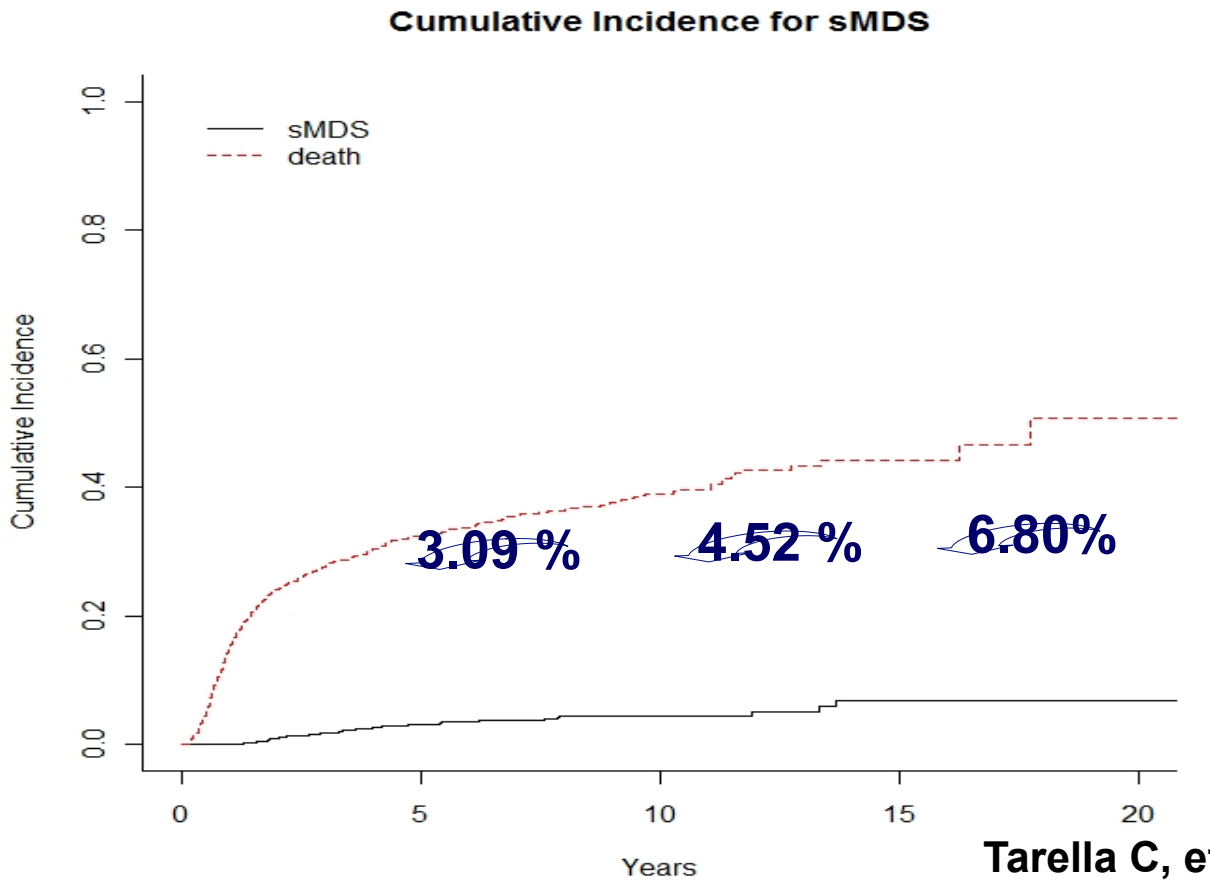
ORIGINAL REPORT

# Risk Factors for the Development of Secondary Malignancy After High-Dose Chemotherapy and Autograft, With or Without Rituximab: A 20-Year Retrospective Follow-Up Study in Patients With Lymphoma

*Corrado Tarella, Roberto Passera, Michele Magni, Fabio Benedetti, Andrea Rossi, Angela Gueli, Caterina Patti, Guido Parvis, Fabio Ciceri, Andrea Gallamini, Sergio Cortelazzo, Valerio Zoli, Paolo Corradini, Alessandra Carobbio, Antonino Mulé, Marco Bosa, Anna Barbui, Massimo Di Nicola, Marco Sorio, Daniele Caracciolo, Alessandro M. Gianni, and Alessandro Rambaldi*

# Overall incidence of s-MDS-AML

**53 out of 1,347 patients developed MDS/AML:**
**-crude incidence: 3.9%, SIR: 2.6 (95% CI, 2.007 to 3.421)**
**-latency 3.3 years since HDS**




Tarella C, et al, JCO 2012

# *Multivariate Analysis of Risk Factors of sMDS/AL*

| *Variable* | | SDHR | *p* = |
|---|---|---|---|
| ***Sex*** | M **vs** F | **2.66 (1.34-5.29)** | **0.005** |
| ***Type of PBSC*** | post-EDX **vs** post-AraC | **2.32 (1.30-4.14)** | **0.004** |

❖ **the analysis suggests that the quality of graft employed may be critical for sMDS/AL development**

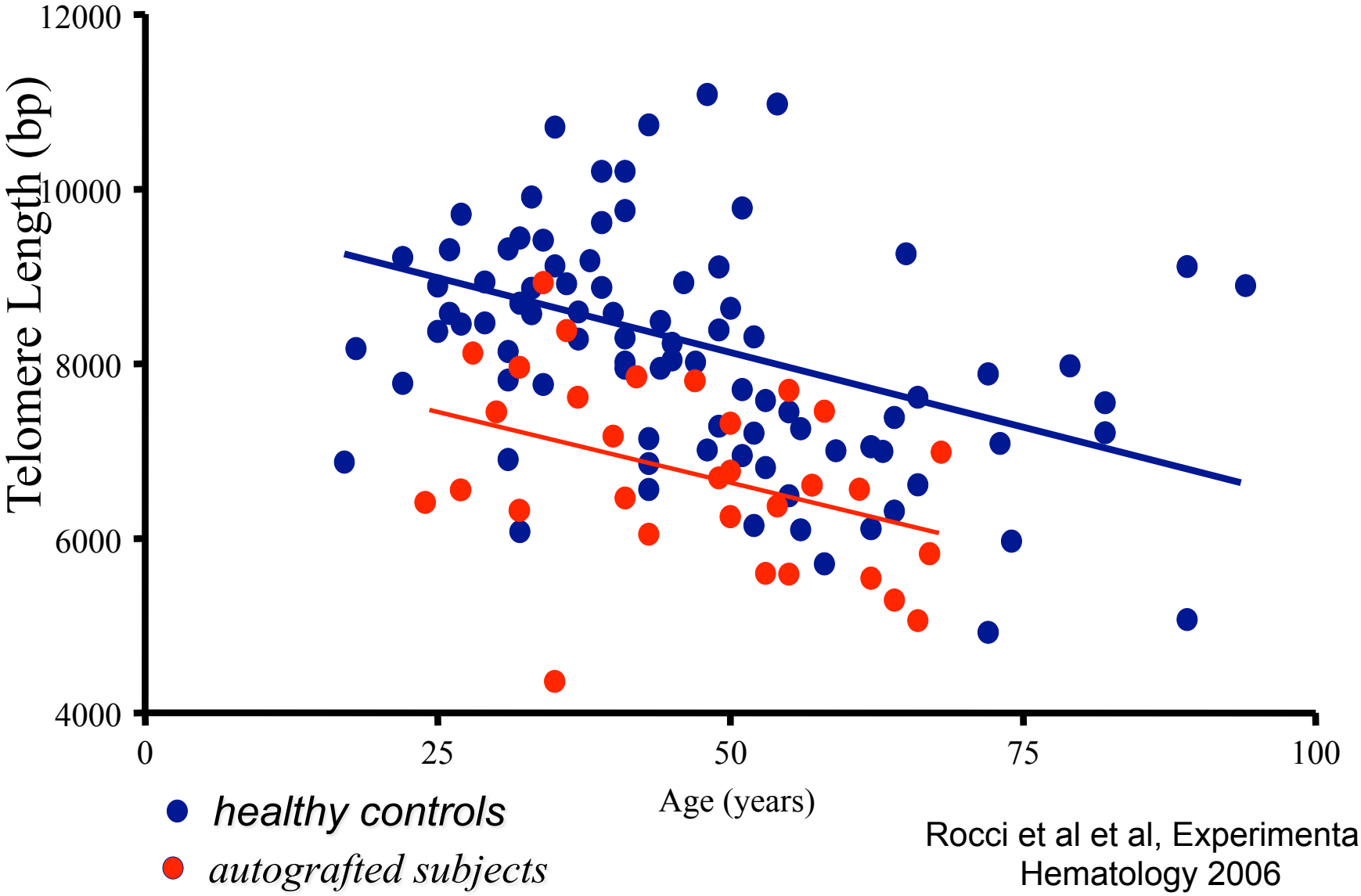
**Tarella C, et al, JCO 2012**

- **increased dose of chemotherapy is associated with increased risk of t-MDS/AL**

**--→ raised a debated about high-risk of t-MDS/AML occurrence following high-dose therapy and autograft**

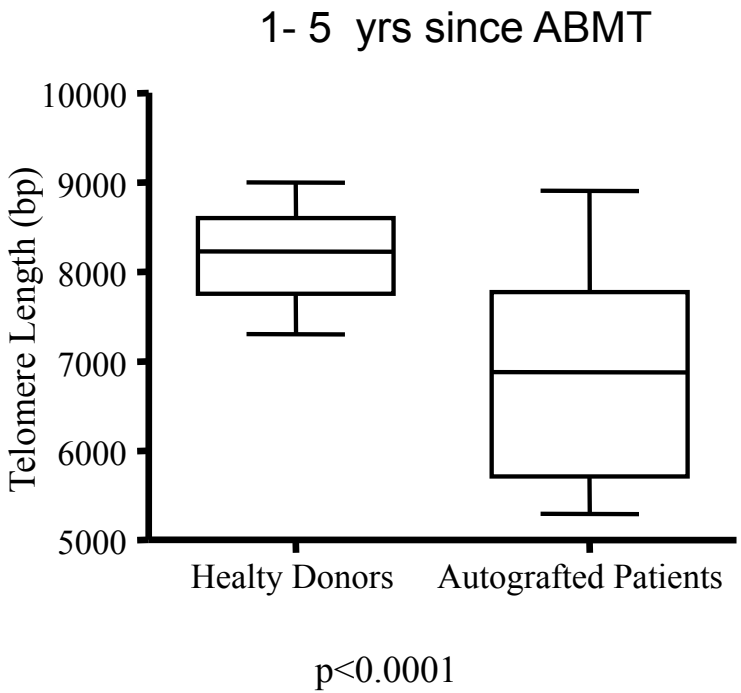
Monitoring of **Telomere Lenght** modifications in hematopoietic cells as a simple and reliable tool to indirectly evaluate the extent of DNA damages induced by exposure to cytotoxic agents

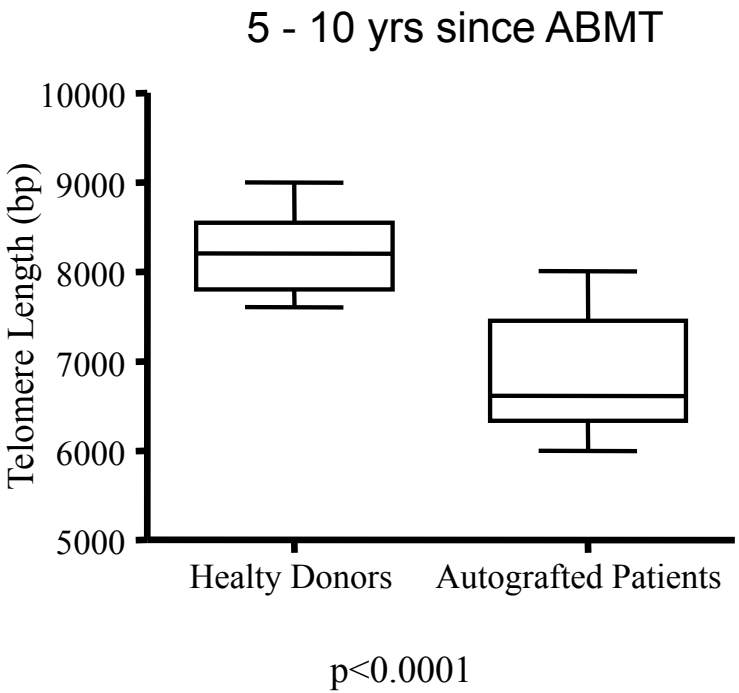
# TELOMERE LENGTH OF PB GRANULOCYTES IN HEALTHY CONTROLS




Rocci et al et al, Experimental Hematology 2006

# PERSISTENCE OF TELOMERE LOSS AT LONG-TERM FOLLOWING PBPC AUTOGRAFT



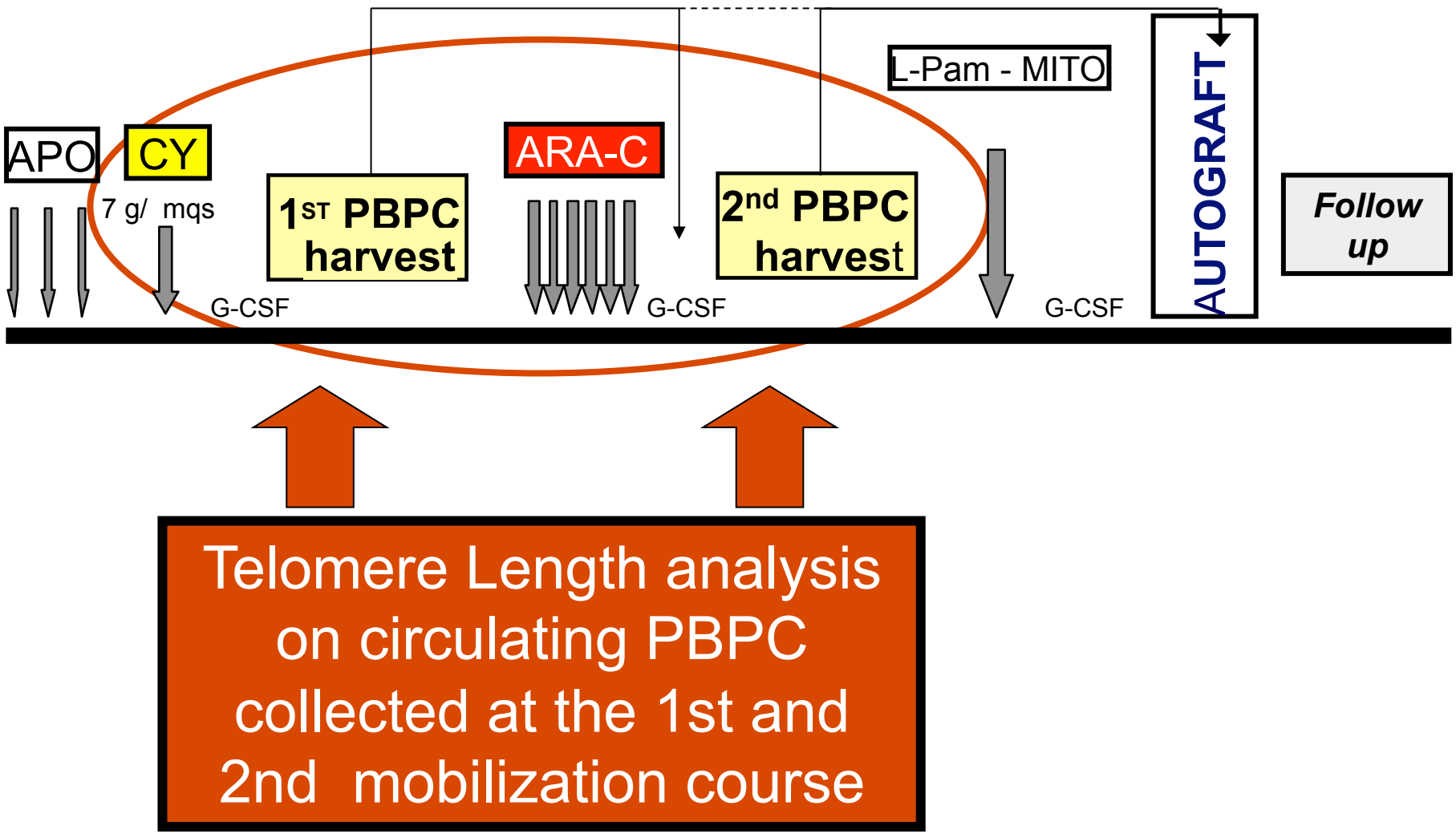




ufortunately, telomere loss is maintained at long term and it thus represents an *irreversible damage*

The use of large amounts of autologous stem cells did not prevent the *"early cell ageing" of hematopoietic progenitors* following autograft

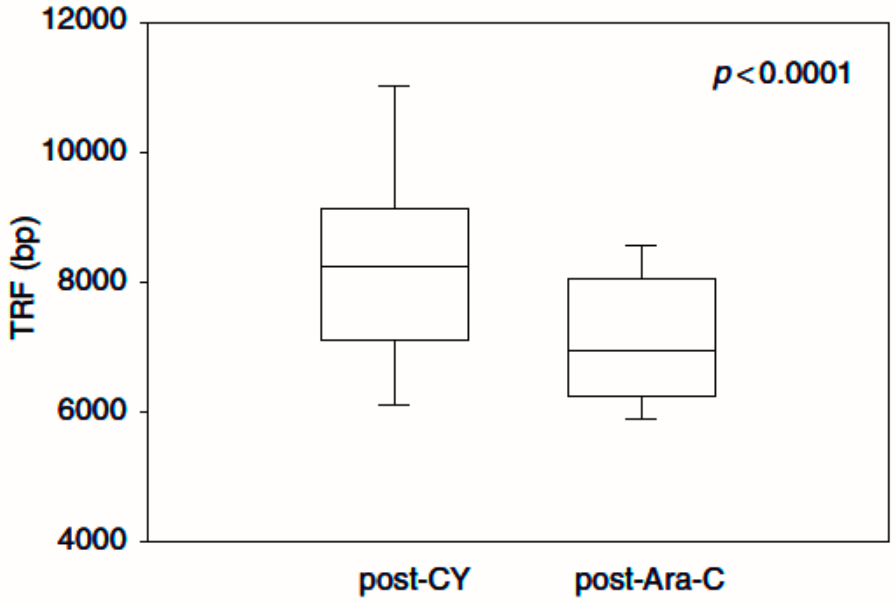
Rocci et al et al, Experimental Hematology 2006

# HDS Protocol for aggressive lymphoma



# TELOMERE LOSS IN AUTOGRAFT AFTER HD-ARA-C:

**TL of mononuclear cells from harvest products after hdcyclophosphamide (CY) and hd-Ara-C in 37 patients**




The median telomere shortening after completion of the two courses corresponds approximately to the decrease occurring in normal subjects after 20 years of life

I Ricca et al, Leukemia 2005

## Summary and conclusion

t-MN is a fatal complication of cancer treatment among cancer survivros

The incidence remains high over the years

Breast cancer and lymphoma patients are at high risk for t-MN.

The outcome is generally poor, in younger patients, the induction schedules containing HD-AraC warrants further exploration

There is a need for molecular assays to identify critical DNA abnormalities that may be predictive of the risk of t-MDS-AL

# Thanks you

**University of Torino, Hematology Division at S. Giovani Hospitals**

R Bruna, D Caracciolo, M Ladetto & R Passera

**University of Torino, Hematology**

Division at Mauriziano Hospital

A Cignetti, A De Crescenzo, D Gottardi, M Mezzabotta, M Ruella,

**Italian network on S.MN**

Prof. Leone, L.Fianchi, MT Voso

**I.E.O., Milan Hematology Division:** Prof. Tarella C.

A. Gueli

E. Derenzini,

S.Sammassimo

F. Gigli

**EORTC leukemia Group**

Jean-Pierre Marie

F. Baron

Stefan Suciu

Theo de Witte

Roel Willemze

GITMO

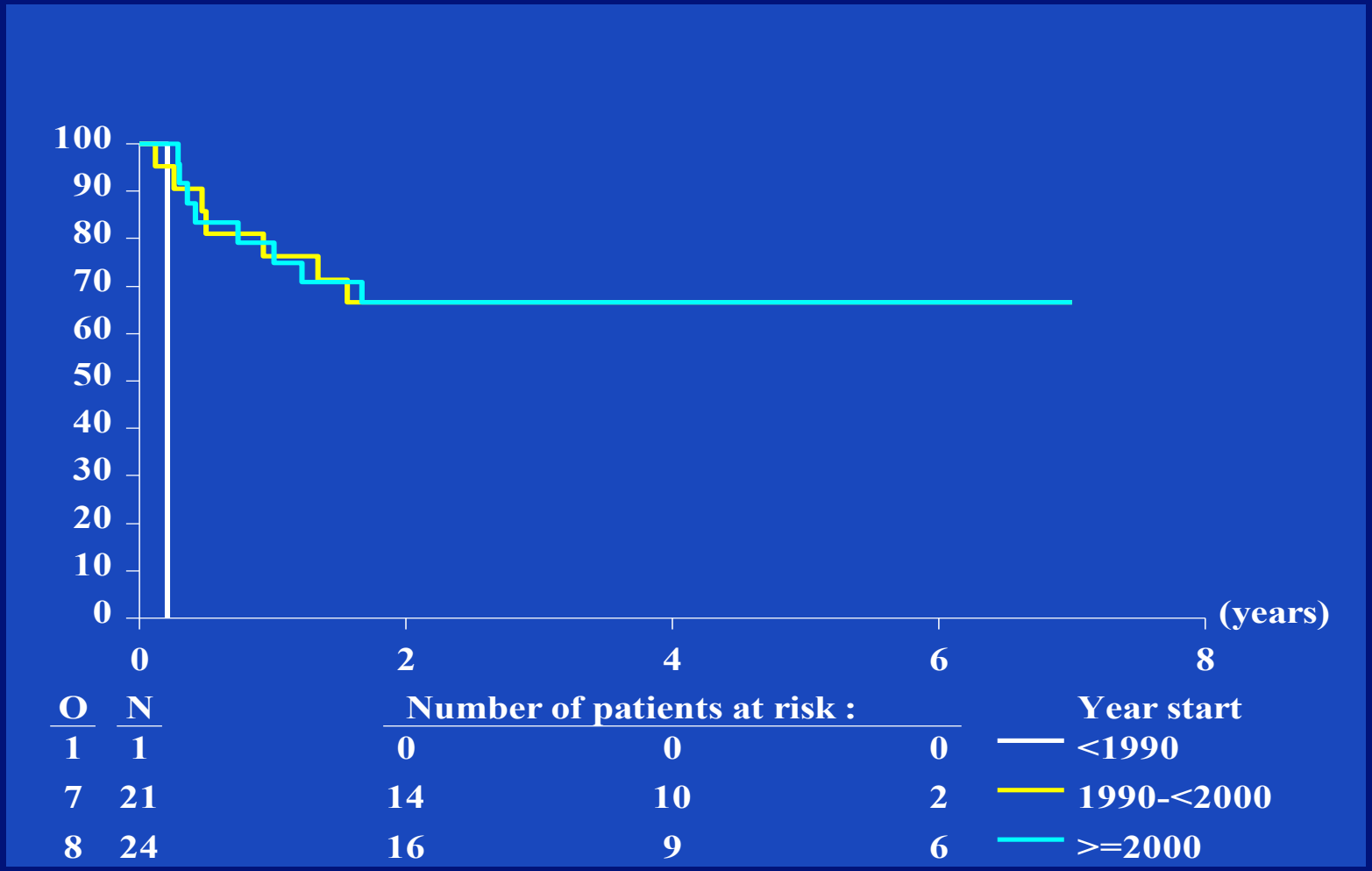
GRUPPO ITALIANO TRAPIANTO MIDOLLO OSSEO

FONDAZIONE FIL ITALIANA LINFOMI

**G I T I L**

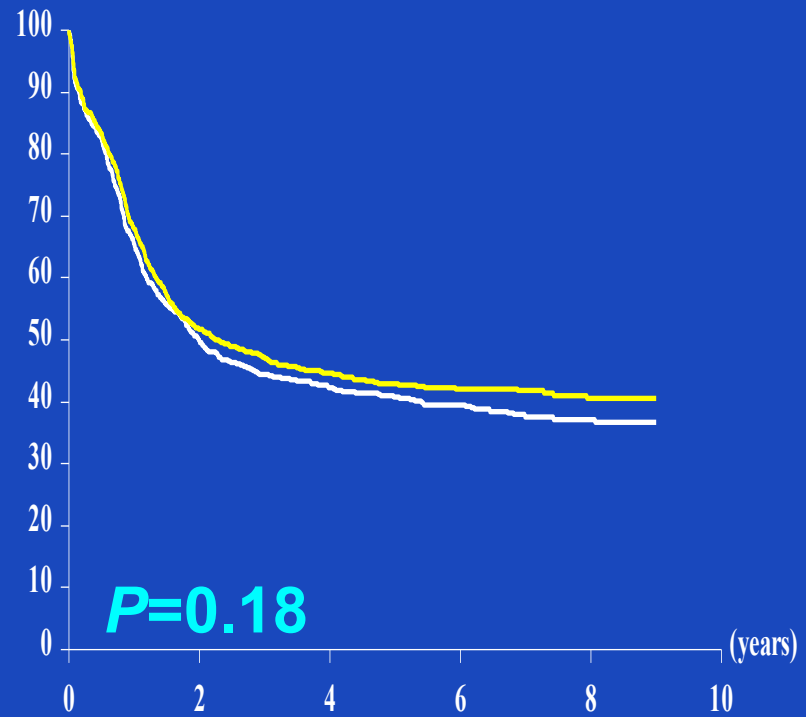
***multicenter group***

# 5-year OS from Allo-SCT for patients in CR1
# By treatment period



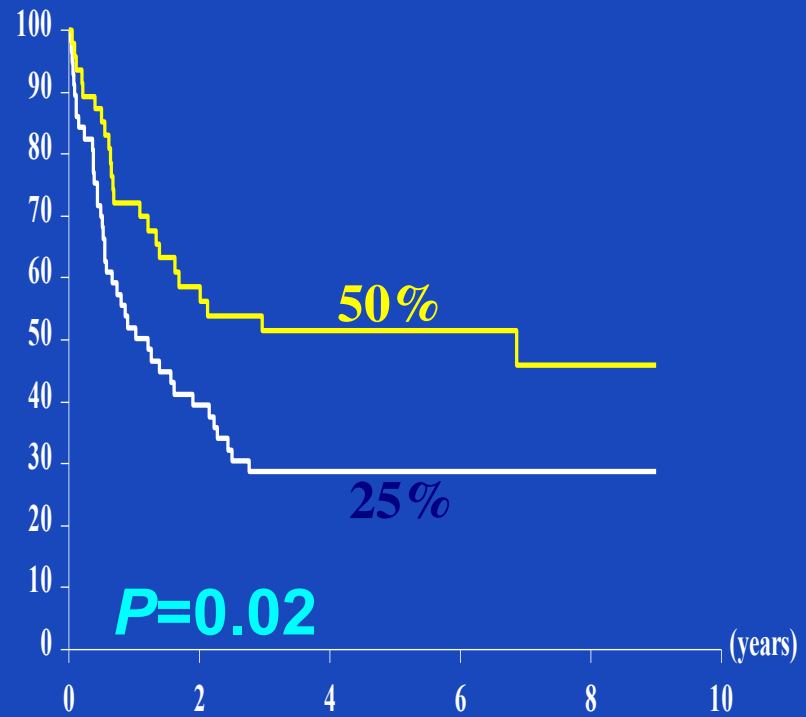
# EORTC-GIMEMA AML-12: OS by randomized treatment

## *de novo* AML




| O | N | Number of patients at risk : | | | | Treatment |
|---|---|---|---|---|---|---|
| 535 | 906 | 431 | 320 | 171 | 66 | SD-AraC |
| 511 | 919 | 450 | 333 | 198 | 84 | HD-AraC |

## *s*-AML




| O | N | Number of patients at risk : | | | | Treatment |
|---|---|---|---|---|---|---|
| 40 | 58 | 22 | 11 | 7 | 4 | SD-AraC |
| 23 | 47 | 25 | 18 | 13 | 5 | HD-AraC |

R. Willemze et al, JCO (*in press*)