

Highlights from EHA

Report dei gruppi di lavoro >>
[Leucemie acute mieloidi]

Relatore: **F. FERRARA**

27-28 ottobre 2008

Borgo S. Luigi – Monteriggioni (Siena)

Gruppo di lavoro

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[Leucemie acute mieloidi]

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MARIA ENZA MITRA

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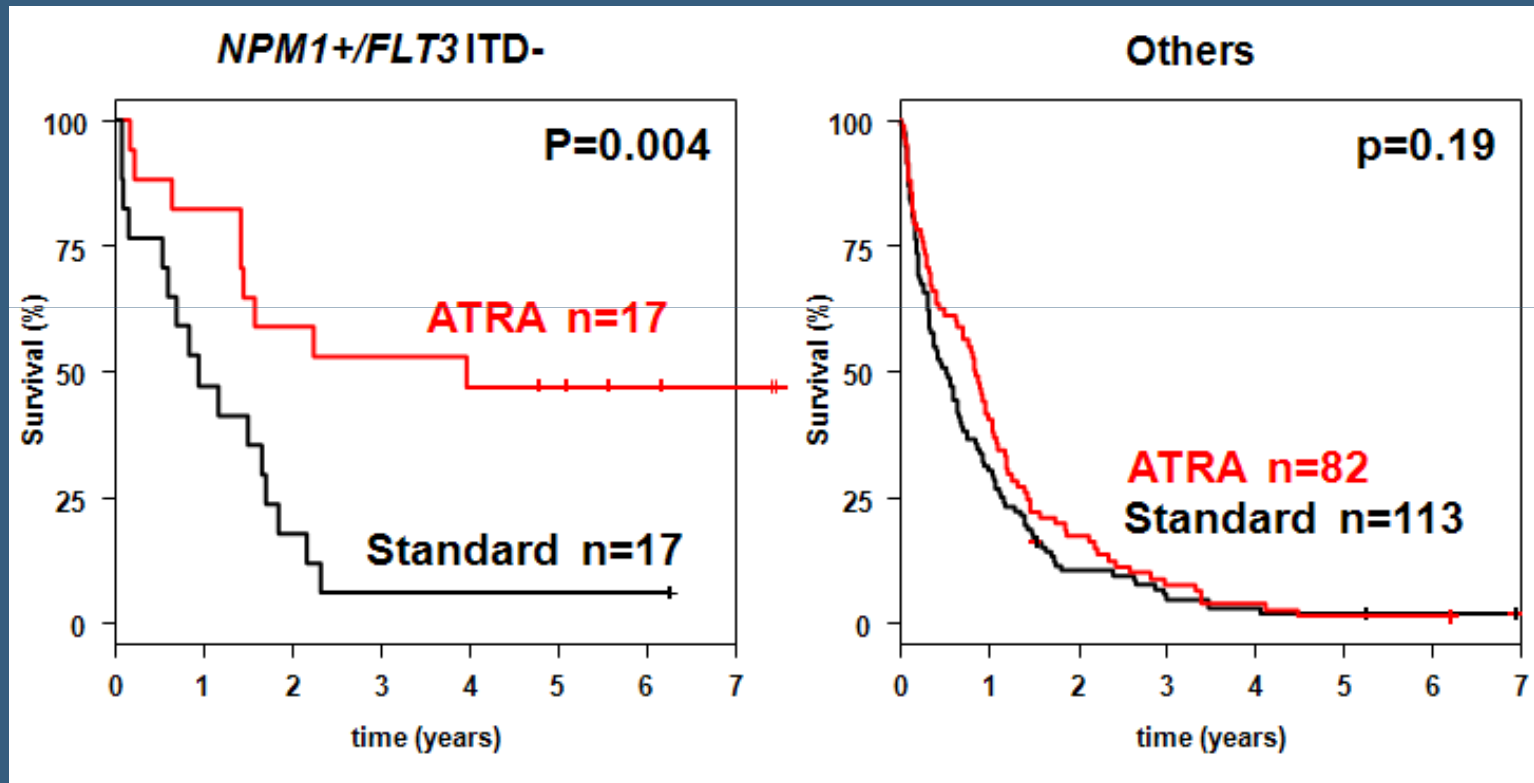
SIMONA SICA

MONICA MESTRINER

DONATELLA VINCELLI

Genetic Subgroup Analysis: OS*

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* allo-SCT excluded n=17

ASH, 2007

Martelli et al: Silencing of NPM1 mut. by ATRA (# 17)

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Randomized study in older AML NPM1+patients

DNR + ARA-C + ATRA

vs.

DNR + ARA-C

WT1: an universal marker for AML ?

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- WT1 mutations in 12%

Younger age, increased WBC

Association with FLT3-ITD (P=.0008)
and CBPA mut (P= .001)

WT1mut alone no impact on prognosis

WT1mut -FLT3-ITD worst prognosis

- Comments: WT1mut + FLT3-ITD potentially identifies RD

WT1: an universal marker for AML ?

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- Background: WT1 overexpressed in >90% AMLs
Suitable “universal” MRD marker for AML
- Methods: Comparison of sensitivity & specificity of 9 different R-Q-PCR assays
729 diagnostic & 106 f-up samples
11 European labs (LeukemiaNet)

WT1: an universal marker for AML ?

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- Results: Failure to normalize WT1 transcripts post-ind. correlates with relapse in 100% of cases (independent predictive factor)

Decreased levels post-treatment non fully informative on outcome
- Comments: Important early information, most relevant (if confirmed) to adjust post-induction therapy

WT1: an universal marker for AML to combine with

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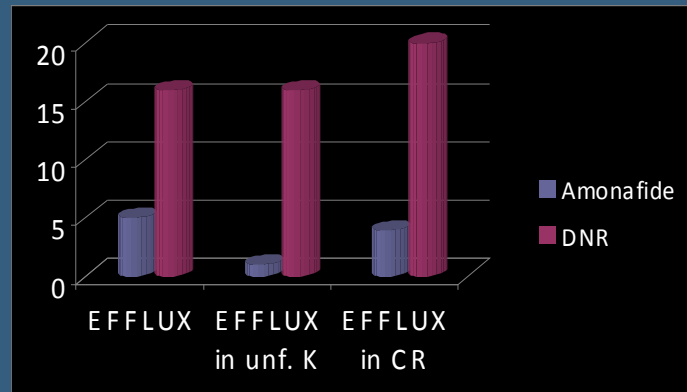
- immunophenotype
- early blast clearance
- cytogenetic response?
- to be validated in prospective trials

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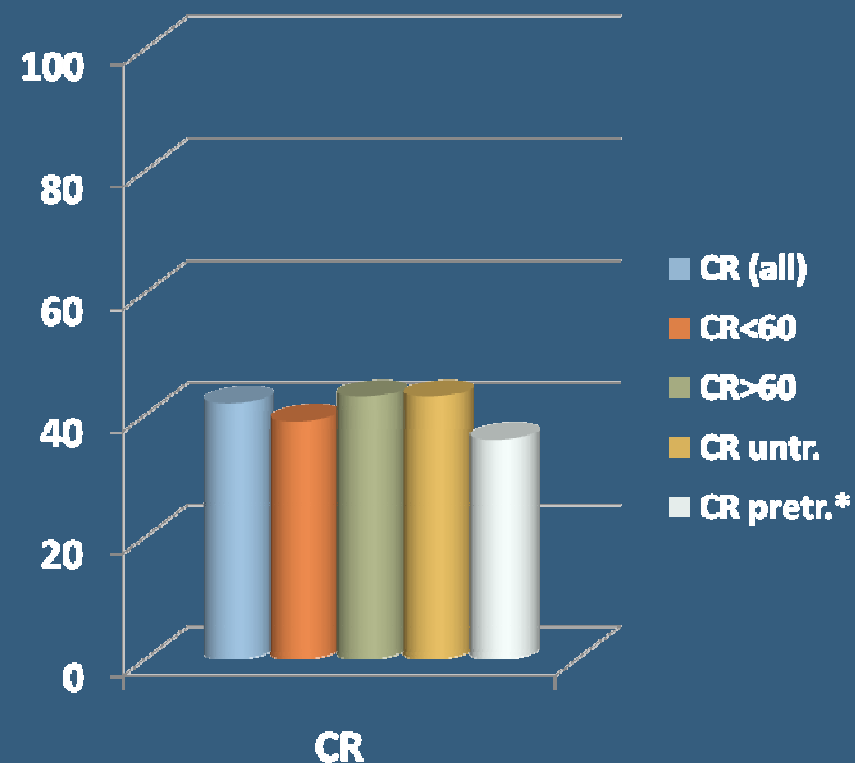
Discussione

AMONAFIDE: A TOPO II INHIBITOR WITH NOVEL PHARMACOLOGICAL PROPERTIES AND UNIQUE ACTIVITY FOR THE TREATMENT OF SEC. AML (Capizzi et al, #890)

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- Median CR duration : 10 mos.
- CCR at 12 mos: 44%
- Death within 28 days: 20%
- Marrow recovery: 1 mo.
- 6% moderate diarrhea and skin rash



VNP40101M in Elderly Patients with De Novo Poor Risk AML

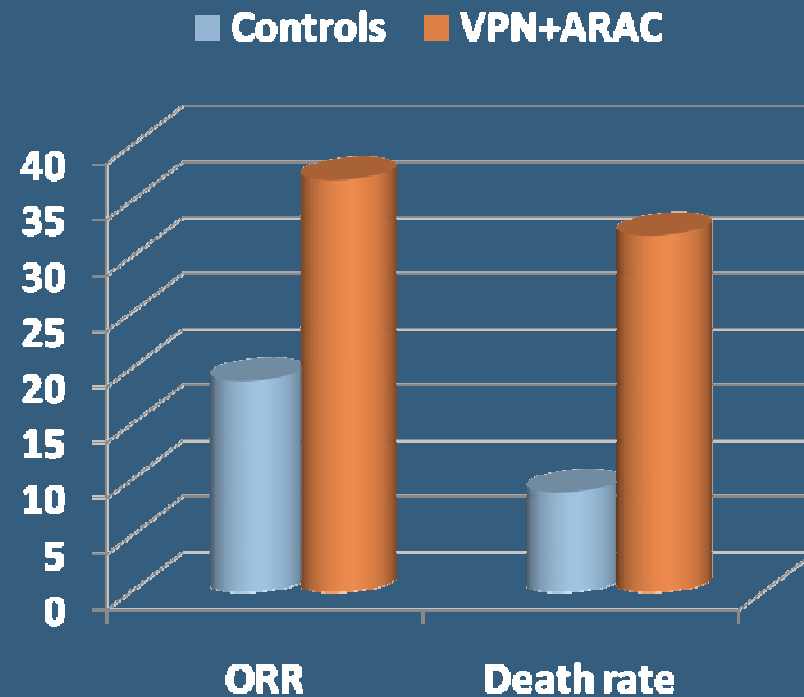
- **86 pts; median age 73 yrs (60-87)**
- **ECOG PS 2 43%**
- **Adverse CG 49%**
- **Response and outcome:**
 - **CR 25%; CRp 10%**
 - **OR \geq 70 yrs 34%; OR adverse CG 23%**
 - **OR \geq 70 yrs and adverse CG 20%**
 - **IM (\leq 30 d) 15%**
 - **93% of responses with single dose**

Schiller GJ, et al. Blood 2007; 110: abs 917

A DOUBLE BLIND PLACEBO-CONTROLLED RANDOMIZED PHASE III STUDY OF HIGH DOSE CONTINUOUS INFUSION ARAC WITH OR WITHOUT CLORETAZINE IN FIRST RELAPSE AML (Norbert et al, #35)

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- Median age for 210 patients was 59 yrs;
- 63% patients had CR1 <12 months (median 290 days).



67% of treatment group deaths were due to infection, sepsis, or pneumonia.
18% to pulmonary events (8/10 ARDS)

PHASE II STUDY OF SINGLE AGENT CLOFARABINE IN UNTREATED ELDERLY PATIENTS WITH AML UNLIKELY TO BENEFIT FROM STANDARD INDUCTION CHEMOTHERAPY (Erba et al, #892)

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- AML (*de novo* or secondary) according to WHO
- Age \geq 60 years
- ECOG performance status (PS) 0-2 and adequate renal, hepatic, and cardiac function
- At least 1 of the following adverse prognostic factors:
 - ▣ Age \geq 70 years
 - ▣ ECOG PS 2
 - ▣ Antecedent hematologic disorder (AHD)
 - ▣ Intermediate- or unfavorable-risk blast karyotype

PHASE II STUDY OF SINGLE AGENT CLOFARABINE IN UNTREATED ELDERLY PATIENTS WITH AML UNLIKELY TO BENEFIT FROM STANDARD INDUCTION CHEMOTHERAPY (Erba et al, #892)

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**RESPONSE
CATEGORY**

**RESPONSE
RATE (95% CI)**

ORR (CR + CRp)

45.2% (35.9%, 54.8%)

CR

40.0% (31.0%, 49.5%)

CRp

5.2% (1.9%, 11.0%)

Failure

53.0% (43.5%, 62.4%)

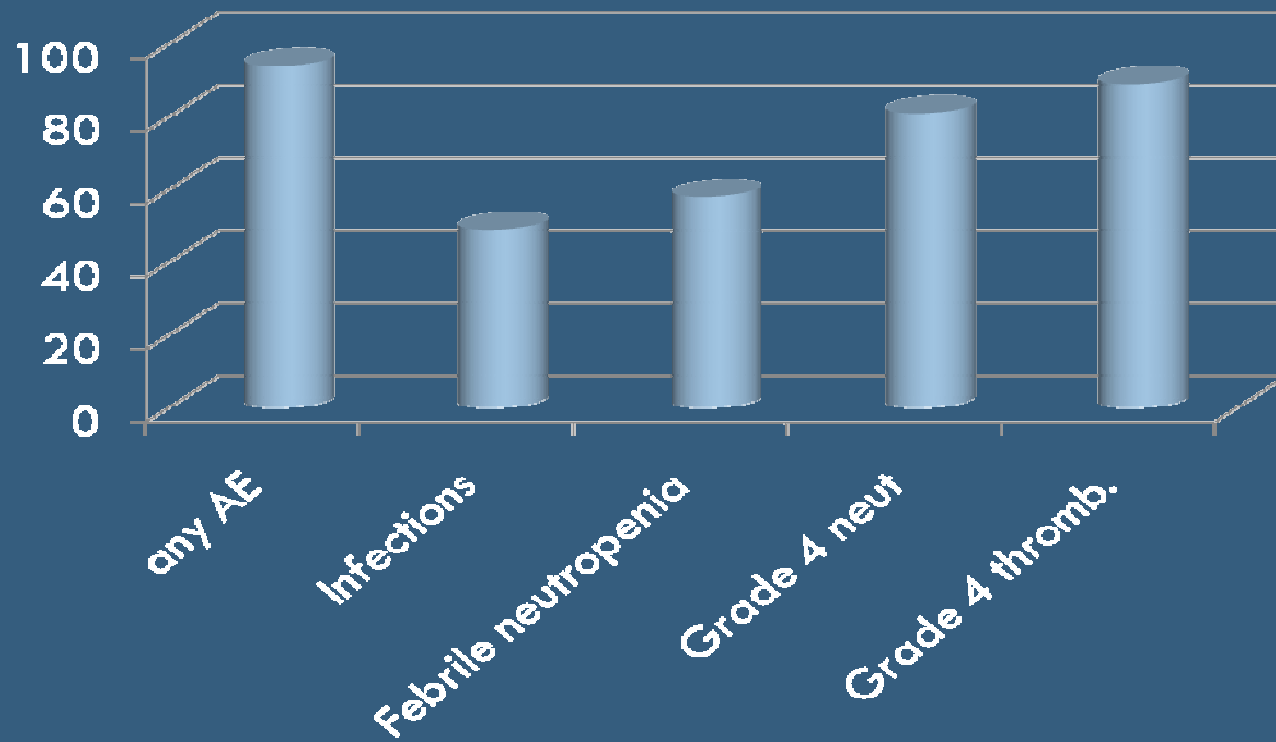
Unknown

2

- Remissions (CR + CRp) after cycles 1 and 2 of therapy (N=52):
 - 35/52 remissions after cycle 1 (induction)
 - 17/52 remissions after cycle 2 (re-induction)

Adverse Events (%)

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All-cause 30-day mortality = 9.6%

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Cause of Death

Respiratory failure secondary to pneumonia*

Gram negative sepsis*

Acute respiratory distress*

Intracranial hemorrhage

Cardiopulmonary arrest

Cardiac ischemia/infarction

Invasive *Aspergillus fumigatus*

Respiratory failure

Aspergillus pneumonia

Multiorgan failure

AML (septic shock, DIC, asystole and cardiac arrest)

Comparisons EU/US data

Clofarabine: BIOV-121 phase II study in elderly 'unfit' patients with AML – Patient demographics

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- $n = 66$
- Median age, years 71 (64–81)
- Patients aged ≥ 70 years 55% (36/66)
- Type of disease
 - *De novo* 76% (50/66)
 - Secondary 24% (16/66)
- Cytogenetic risk
 - Intermediate 65% (43/66)
 - Adverse 29% (19/66)
- ≥ 2 ECOG performance score 29% (17/59)
- ≥ 1 Comorbidity 74% (49/66)

Patient Characteristics

	<u>BIOV-121</u>	<u>CLO-243</u>
Number of patients	66	115
Age, median (range)	71 (64-81)	71 (60-88)
- 60-69	25 (38%)	43 (37%)
- 70+	41 (62%)	72 (63%)
Male:Female	33:33	53:62
ECOG PS 2+	18 (27%)	27 (24%)
AHD		42 (37%)
Secondary AML	16 (24%)	
Cytogenetics		
- Intermediate	43 (65%)	46 (40%)
- Unfavorable	19 (29%)	56 (49%)
- Not available	4 (6%)	13 (11%)

Responses

	<u>BIOV-121</u>	<u>CLO-243</u>
Number of patients	66	115
- CR + CRi + PR	32 (48%)	-
- CR + CRi/CRp	29 (44%)	52 (45%)
- CR	14 (21%)	46 (40%)
- CRi/CRp	15 (23%)	6 (5%)
- PR	3 (5%)	-

CR + CRi/CRp Rates by Risk Factors

	<u>BIOV-121</u>	<u>CLO-243</u>
Number of patients	66	113
Age < 70	10/25 (40%)	24/43 (56%)
Age ≥ 70	22/41 (54%)	28/70 (40%)
ECOG PS 2+		10/26 (38%)
ECOG PS 0-1		42/87 (48%)
Prior AHD		21/42 (50%)
No prior AHD		29/66 (44%)
Unknown AHD		2/5 (40%)
Secondary AML	5/16 (31%)	
De Novo AML	24/50 (48%)	
Cytogenetics		
- Intermediate	20/43 (47%)	24/46 (52%)
- Unfavorable	9/19 (47%)	24/56 (43%)
- Not available		4/11 (36%)

More promising drugs in AML

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- ❑ Clofarabine (CR rate 40-45 %)
- ❑ Cloretazine (30-35 %)
- ❑ Amonafide (particularly active in s-AML?)

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Discussione