

Highlights from EHA

Novità dall'EHA >> [Leucemie acute mieloidi]

Relatore: **F. LO COCO**

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Biologic & Clinical Studies Selection Criteria

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- Not presented at ASH or considerable expansion of previously presented studies (updates, additional findings etc.)
- Unpublished, in press, or *very recently* published
- For **biologic studies**, emphasis on studies with potential impact into the clinics in the near future
- For **clinical studies**, emphasis on promising new agents (most likely to be further explored) and on randomised studies

AML Biology : Overview (selection)

I. Basic studies

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- Martelli et al: Silencing of NPM1 mut. by ATRA (# 17)
- Brundiers et al: miRNA in AML with different K (# 18)
- Iacobucci et al: DNA copy number analysis by SNPs (# 23)
- Kronke et al: SNPs analysis in NK-AML (# 459)
- McLoman et al: c-FLIP as a regulator of cell survival (# 30)
- Hasan et al: Genomic analysis of t(15;17) in sAPL(# 944)

AML Biology : Overview (selection)

II. Translational studies

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- Chamuleau et al: INDO mRNA and AML outcome (# 20)
- Fiskus et al: Panobinostat + decitabine effect in vitro (#24)
- Maiso et al: Panobinostat + doxorubicin effect in vitro (# 33)
- Gaidzik et al: Prognostic impact of WT1 mut (adults # 943)
- Hollink et al: Prognostic impact of WT1 mut (children # 457)
- Cilloni et al: WT1 as an MRD marker (# 421)

PROGNOSTIC IMPACT OF WT1 MUTATIONS IN THE CONTEXT OF OTHER MOLECULAR MARKERS IN NK-AML: A STUDY OF THE AMLSG (Gaidzik et al, # 943)

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- Background: WT1 mutations reported in 10% NK-AML
Suggested negative impact on prognosis
Influence on other markers unknown
- Methods: Analyse impact of WT1 mutations in the context of NPM1, CEBPa, FLT3, RAS mutations

602 pts with NK-AML, three AMLSG trials

PROGNOSTIC IMPACT OF WT1 MUTATIONS IN THE CONTEXT OF OTHER MOLECULAR MARKERS IN NK-AML: A STUDY OF THE AMLSG (Gaidzik et al, # 943)

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- Results: 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

WILMS' TUMOR GENE MUTATIONS IN CHILDHOOD AML: CHARACTERISTICS, PROGNOSTIC VALUE AND CONSEQUENCES FOR MRD DETECTION (Hollink et al, #457)

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- Background: Approximately 10% of adult AML with NK carry mutations in the WT1 gene. Suggested association with poor prognosis
- Methods: Screening of 298 diagnostic childhood AMLs using PCR-based direct sequencing. Paired dx.-rel. samples studied in 39 cases

WILMS' TUMOR GENE MUTATIONS IN CHILDHOOD AML: CHARACTERISTICS, PROGNOSTIC VALUE AND CONSEQUENCES FOR MRD DETECTION (Hollink et al, #457)

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- Result: Mutations found in 35/298 (12%)
Association with NK, FLT-ITD and high WBC
Mutations gained at relapse in 4/28 (14%)
Lower CR, OS and EFS
- Comments: New relevant prognostic marker; problematic
for MRD monitoring

EARLY ASSESSMENT OF MRD BY OPTIMIZED REAL-TIME PCR FOR DETECTION OF WT PROVIDES AN INDEPENDENT PREDICTOR OF DFS IN AML (Cilloni et al, #421)

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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)

EARLY ASSESSMENT OF MRD BY OPTIMIZED REAL-TIME PCR FOR DETECTION OF WT PROVIDES AN INDEPENDENT PREDICTOR OF DFS IN AML (Cilloni et al, #421)

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- Result: 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

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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Background:

Secondary AML (sAML) portends a poor prognosis due to disease and patient-related factors. Newer therapies are needed.

Aims:

- Comparison of amonafide to classical TOPO II inhibitors (anthracyclines, mitoxantrone, etoposide)
- Efflux from patient-derived sAML blasts

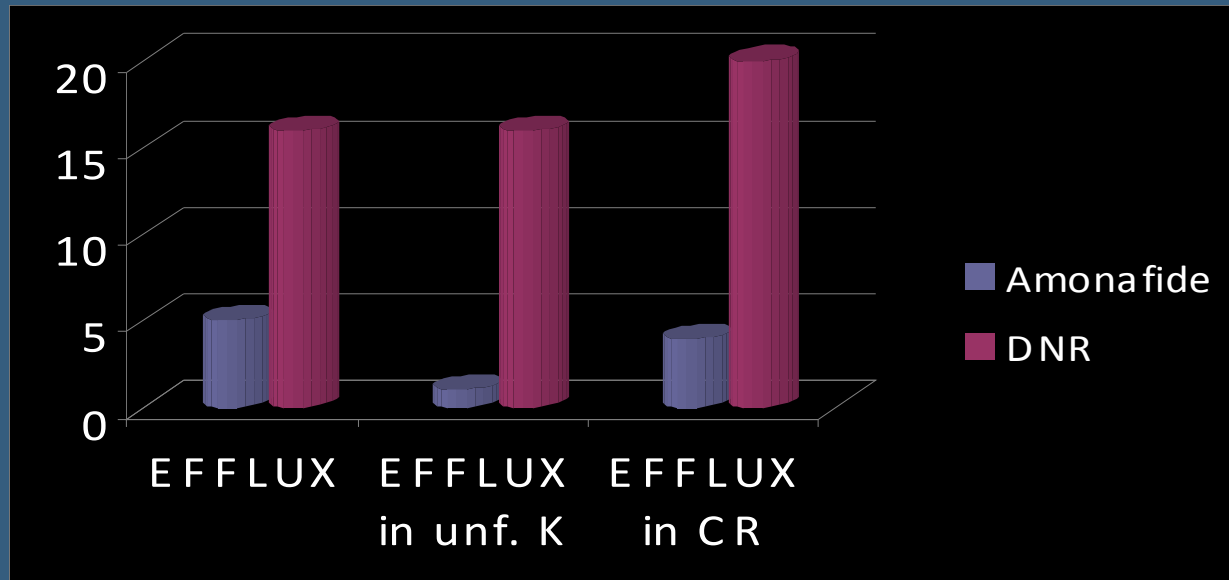
AMONAFIDE: A TOPO II INHIBITOR WITH NOVEL PHARMACOLOGICAL PROPERTIES AND UNIQUE ACTIVITY FOR THE TREATMENT OF SEC. AML (Capizzi et al, #890)

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- combination of amonafide (600mg/m²/day1-5 and ara-C, 200 mg/m²/day 1-7 c.i.)
- 88 sAML patients
- Median age 63 yrs (range 23-87)
- prior MDS: 45.5%; t-AML: 54.5%
- unfavorable cytogenetics: 47%

Results (I)

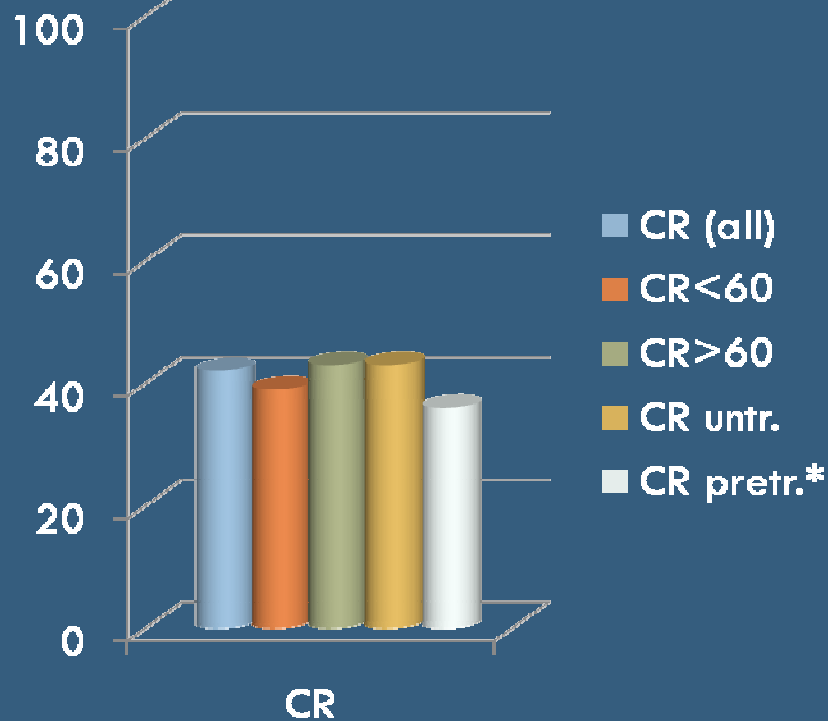
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- Amonafide had equal cytotoxicity in both the wild type and MDR cells.
- Additional studies showed that amonafide was neither a substrate nor an inhibitor of Pgp.

Results (II)

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*: azacytidin

- 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

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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- VNP40101M is a novel alkylating agent which preferentially targets the O6 position of guanine resulting in DNA cross-links and which showed anti-leukemic activity in clinical trials.
- Multi-center phase III study to compare overall response rate (CR,CRp,safety of VNP40101M + araC vs placebo + araC, in patients with AML in first relapse.
- Secondary endpoints were response duration, progression-free and overall survival (OS).

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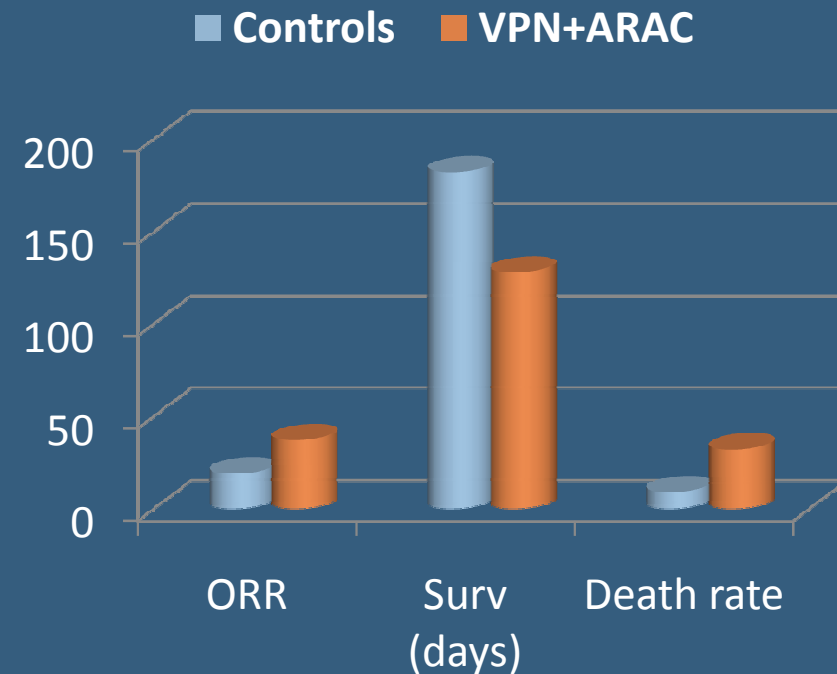
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- ≥18 yrs, and in first relapse after CR1 of 3-24 mos.
- Randomized (2:1) to ara-C 1.5 g/m² (d1-3)+ VNP40101M 600 mg/m², or ara-C 1.5 g/m² (d1-3) + placebo.
- Patients with at least 20% blast reduction in the bone marrow could receive a second induction.
- Patients with CR or CRp could be consolidated according to original randomization, but at a lower dose of VNP40101M (400 mg/m²) or placebo.

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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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- Phase II, open-label, single arm
- Multicenter, conducted in North America
- 26 sites eligible to enroll
 - ▣ 20 sites enrolled patients
 - ▣ Median number per site 4; range 1-26
- First patient registration: 27 October 2006
- Last patient registration: 27 November 2007

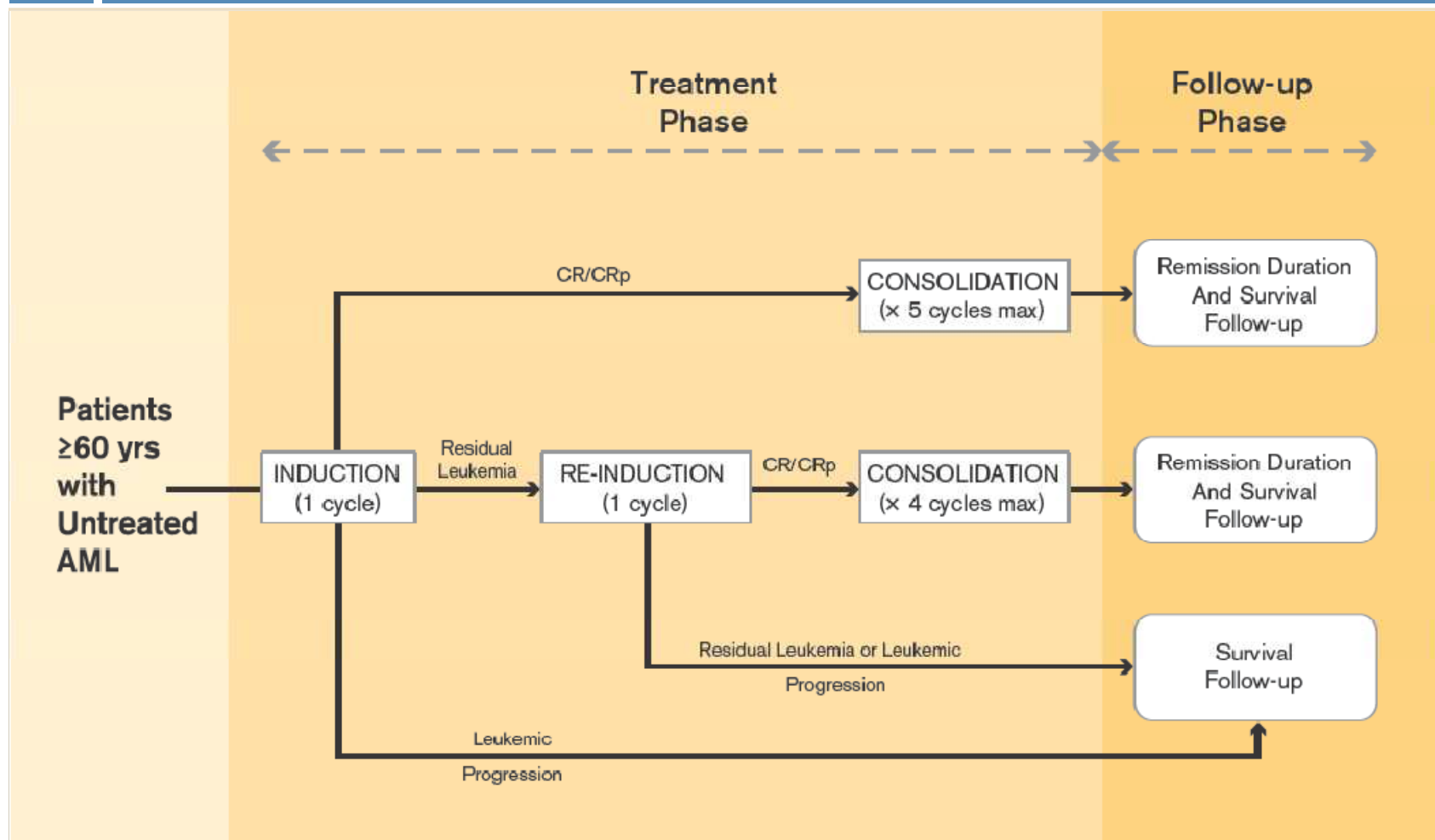
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- AML (*de novo* or secondary) according to WHO
- Age \geq 60 years
- ECOG performance status (PS) 0-2 and adequate renal, hepatic, and cardiac function
- At least 1 of the following adverse prognostic factors:
 - ▣ Age \geq 70 years
 - ▣ ECOG PS 2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

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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)

Overall Remission Rates (ORR) by Baseline Prognostic Factors (Investigator-assessed, N=113)*

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Number of Risk Factors	Patients in Subset	CR + CRp (n)	CR + CRp (%)
1	22	11	50%
2	50	24	48%
3	38	16	42%
4	1	0	0%

Overall Remission Rates (ORR) by Baseline Prognostic Factors (Investigator-assessed, N=113)*

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Prognostic Factor	Patients in Subset	CR + CRp (n)	CR + CRp (%)
Age			
≥ 70	70	26	40%
< 70	43	87	56%
Performance Status			
ECOG 2	28	10	38%
ECOG 0-1	24	42	48%

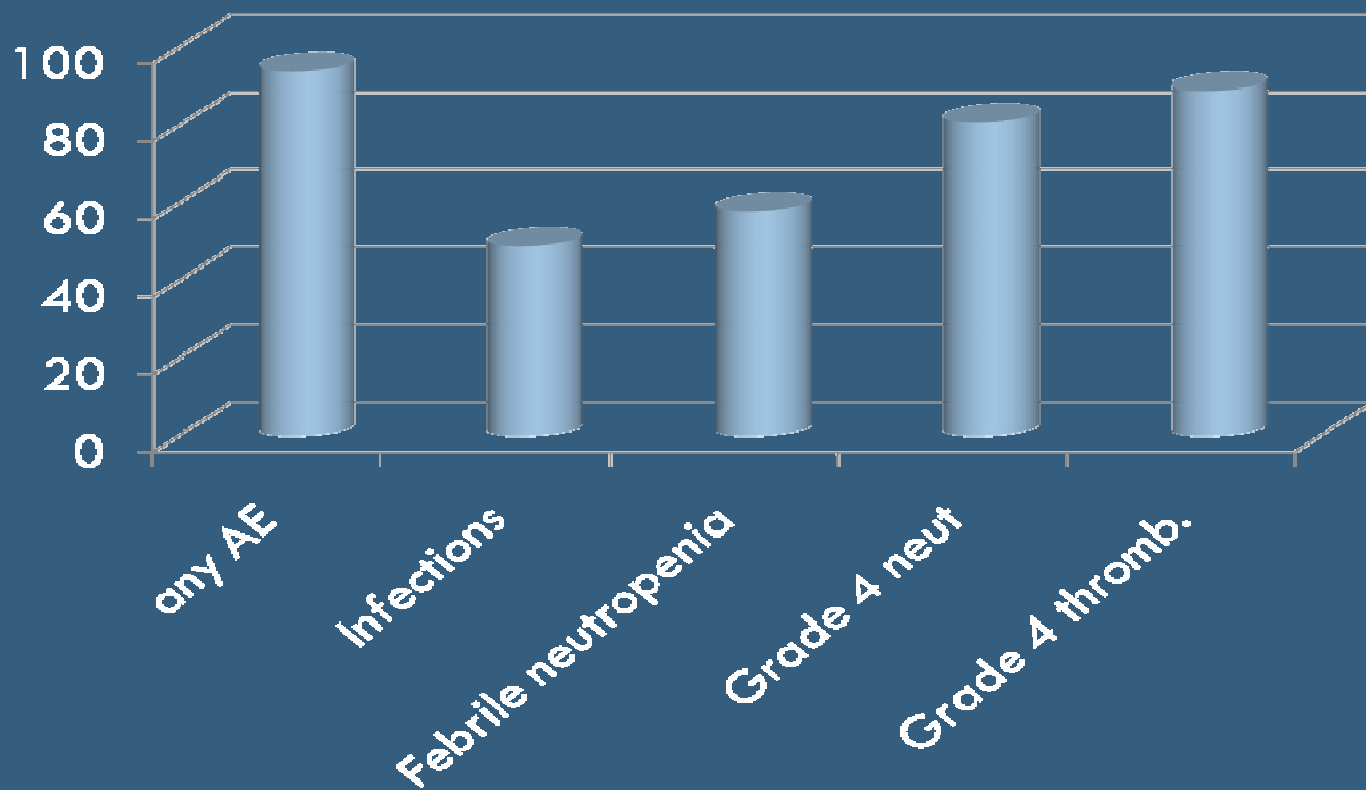
Overall Remission Rates (ORR) by Baseline Prognostic Factors (Investigator-assessed, N=113)*

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Prognostic Factor	Patients in Subset	CR + CRp (n)	CR + CRp (%)
Presence of AHD			
Yes	42	21	50%
No	66	29	44%
Unknown	5	2	40%
Cytogenetics			
Intermediate/Unfavorable	102	48	47%
Intermediate	46	24	52%
Unfavorable	56	24	43%
Favorable	0	--	--
Not reported	11	4	36%

Adverse Events (%)

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CLO243: Conclusions

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- ORR :45% (CR 40%; 1/3 after 2 cycles)
- RR not affected by adverse risk factors such as age over 70, PS 2, AHD, and unfavorable K.
- All-cause 30-day mortality: 9.6%.
- Clofarabine is active with acceptable toxicity in a poor risk population of older AML pts unlikely to benefit from standard induction chemotherapy.