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The ELN risk classification has prognostic relevance also in elderly patients with secondary acute myeloid leukemia and may support treatment decisions. A retrospective multicenter study of the Rete Ematologica Lombarda (REL)

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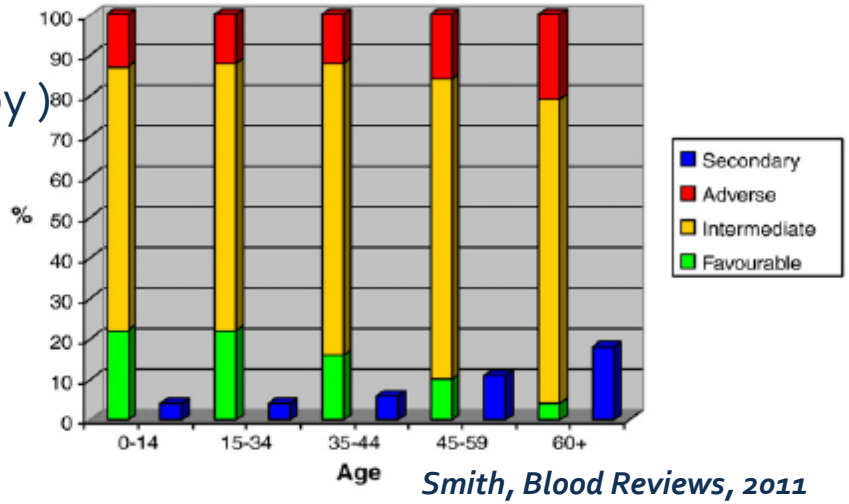
Background
Secondary AML
(post AHD, therapy-related)

- (?) **Poor outcome** compared to "de novo" AML
  - **Yes** (*Goldstone, ASH 2002-Larson ASH,2007- Wheatley, BJH 2009*)
  - **No** (*Pagano, Annals of Oncology 2005-Ostgard, Eur J Haemal 2010-Smith, Blood Reviews, 2011), in elderly (Hulegärdh, AJH 2015*)

- Higher frequency in **older** patients (25%> 60y)

  Leone, Haematologica 1999
  Smith, Blood Reviews, 2011
  Hulegärdh, AJH 2015



Smith, Blood Reviews, 2011

- High frequency of **unfavourable cytogenetics**

  Grimwade, Blood 2001;
  Smith, Blood 2003;
  Kayser, Blood 2011

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Background
sAML & ELN

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Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet

AML-related prognostic factors includes white blood count (WBC), existence of prior MDS, previous cytotoxic therapy for another disorder (see section 9), and cytogenetic and molecular genetic changes in the leukemic cells at diagnosis. Various other

Besides age, the most important covariates are cytogenetics and secondary AML (following MDS or MDS/MPN), WBC, performance status, and comorbidities.[209] No specific comorbidity index

unfavorable cytogenetics.[216,217,220-223] In multivariable analyses, however, t-AML appears to remain an independent adverse prognostic factor.[221,222] Scarce data are available regarding whether

Table 4. Standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	−5 or del(5q); −7; abnl(17p); complex karyotype‡

Döhner, Blood, 2009

older adult median OS=0.5 years) [98•]. However, due to the few numbers of patients with s-AML in studies validating the ELN classification, caution is advised when extrapolating those results to s-AML [99]. A comparative analysis

Zeichner, Curr. Treat. Options in Oncol., 2015

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Background
Treatment of sAML

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- Patients who have an HLA-matched donor should be considered for allogeneic HSCT (considered the only approach with curative potential)

Zeichner, *Curr. Treat. Options in Oncol. 2015*
Döhner, *Blood, 2011*
Litwoz, *Blood, 2010*
Larson, *ASH educational book 2007*

- Elderly ➔ most **not elegible** for HSCT (age and comorbidity)

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Patients

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- Secondary AML (s-AML) encompasses:
  1) **AML with an antecedent hematological disease (AHD-AML)**:
  - evolving from myelodysplasia (AML-MDS)
  - evolving from myeloproliferative neoplasms (AML-MPN)
  2) **AML "therapy-related" (t-AML)**

- From 2008 to 2015

- Eight Hematological Departments of the Rete Ematologica Lombarda (REL)

- **280 of 699 (40%)** consecutive elderly AML patients

	s-AML
Median age	73 years (65-96)
ECOG > 3	20.7%
Female/male ratio	93/187 (37%/63%)

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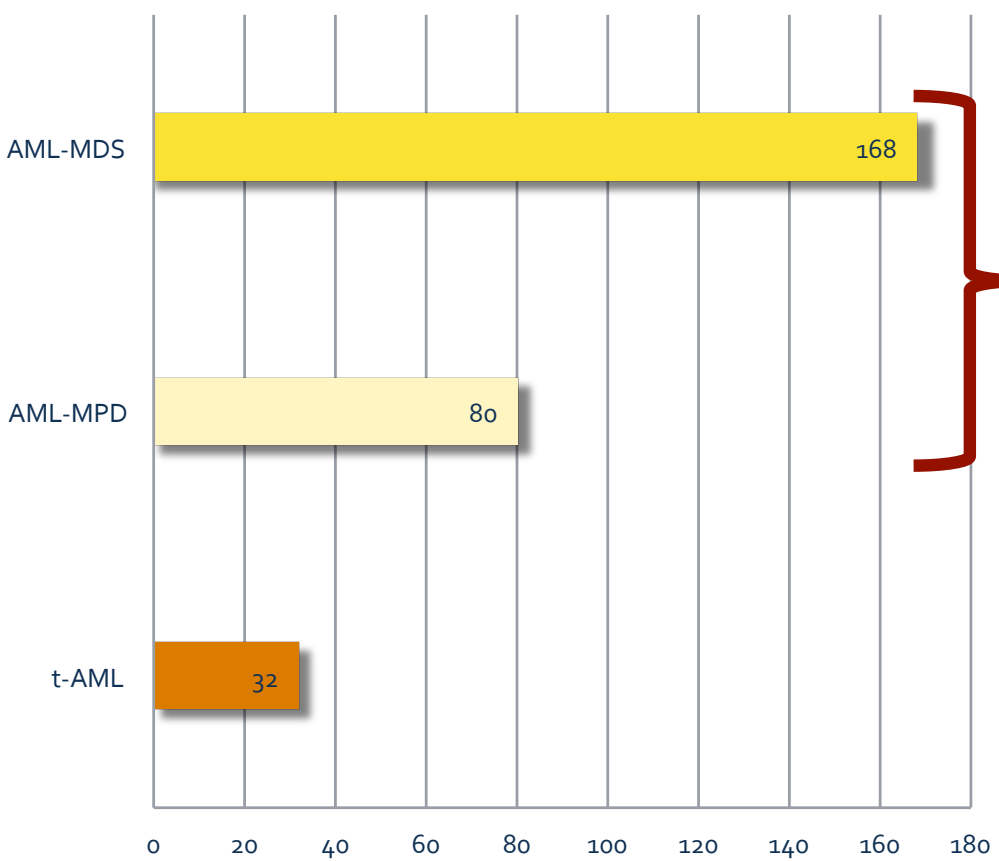
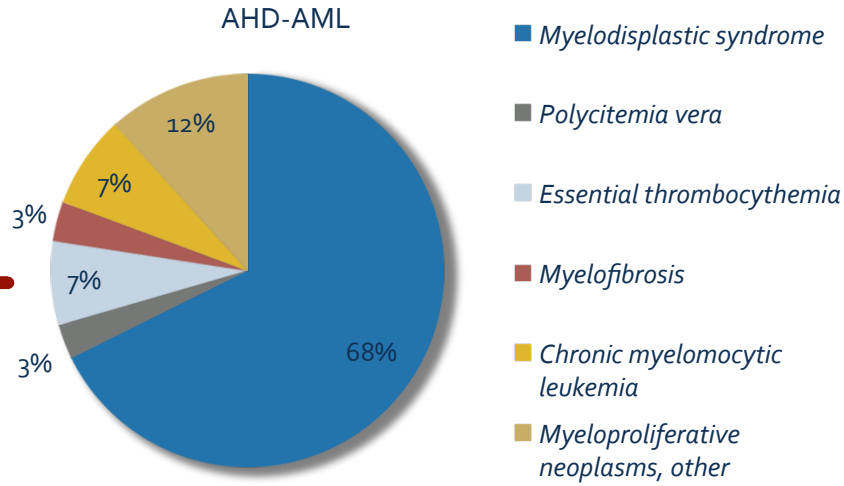
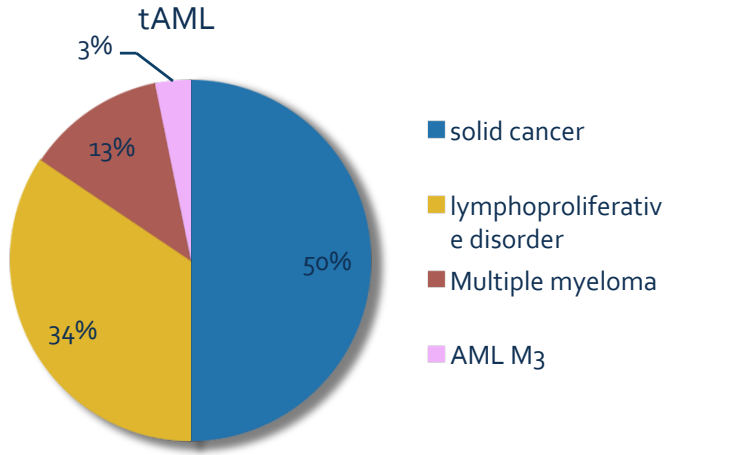
Distribution of s-AML







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Patient's characteristics

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	s-AML	AHD-AML		t-AML	
	280	to MDS 168	to MPD 80	32	
Median age	**74 (65-94)**	74 (65-94)	74 (65-86)	71 (66-83)	**ns**
ECOG-PS>3	59 (21%)	38 (22.6%)	13 (16.2%)	8 (25%)	ns
Fitness**					
FIT	110 (39.2%)	64 (38.1%)	32 (40%)	14 (43.8%)	**ns**
UNFIT	123 (44%)	77 (45.8%)	32 (40%)	14 (43.8%)	
FRAIL	44 (15.7%)	26 (15.5%)	14 (17.5%)	4 (12.5)	
Not eval	**3 (1.1%)**	1 (0.6%)	2 (2.5%)		
Treatment					
i-T°°	97 (34.5%)	61 (36.3%)	20 (25%)	16 (50%)	**ns**
ni-T§§	54 (19.3%)	29 (17.3%)	18 (22.5%)	7 (21.9%)	
BSC^^	129 (46.1%)	78 (46.4%)	42 (52.5%)	9 (28.1%)	

°°i-T= standard induction: antracyclin + ara-c (3+7 or equivalent)
§§Ni-T= low dose ara-C, HMA, non myelotossic sperimental drugs
^^BSC= Best Supportive Care

**Ferrara, Leukemia 2013
Borlenghi, ASH 2014-EHA2015

53.8% of patients were treated

Treatment in 95.4% of non-frail patients

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ELN-risk distribution

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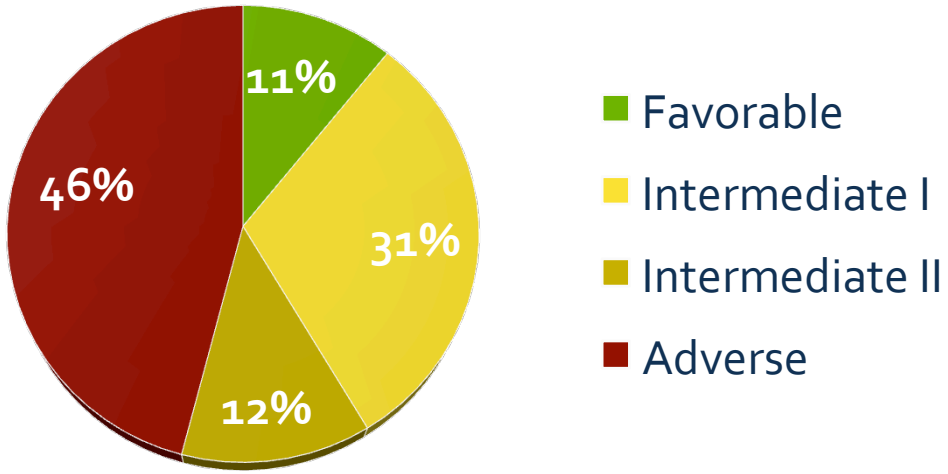
	s-AML
ELN in Treated patients	**111/151 (73.5%)**
Favorable	12 (10.8%)
Intermediate I	34 (30.6%)
Intermediate II	14 (12.6%)
Adverse	51 (45.9%)



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ELN & Outcome

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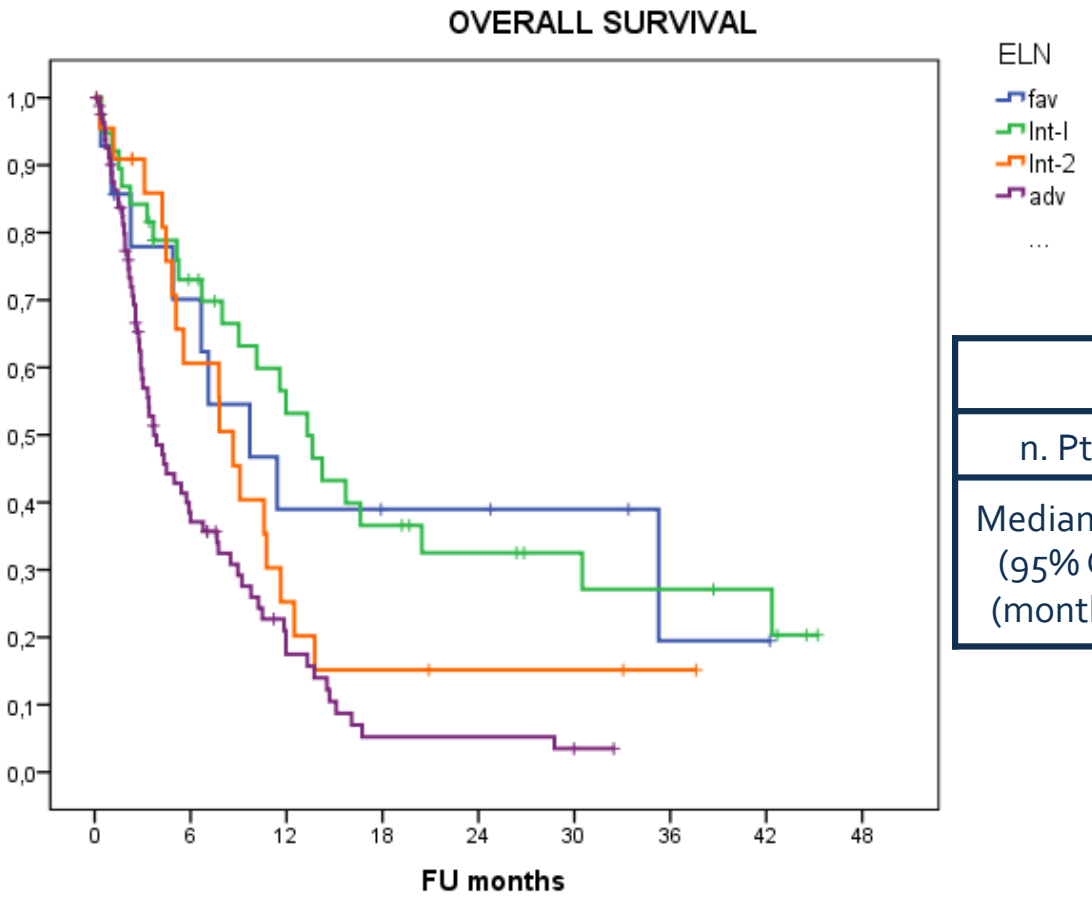

	Fav	Int-1	Int-2	Adv
n. Pts	14	38	23	83
Median OS (95% CI) (months)	9,7 (4,2-15,2)	13,3 (8,8-17,8)	8,7 (6,9-10,5)	3,7 (2,5-4,9)

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OS Treatment

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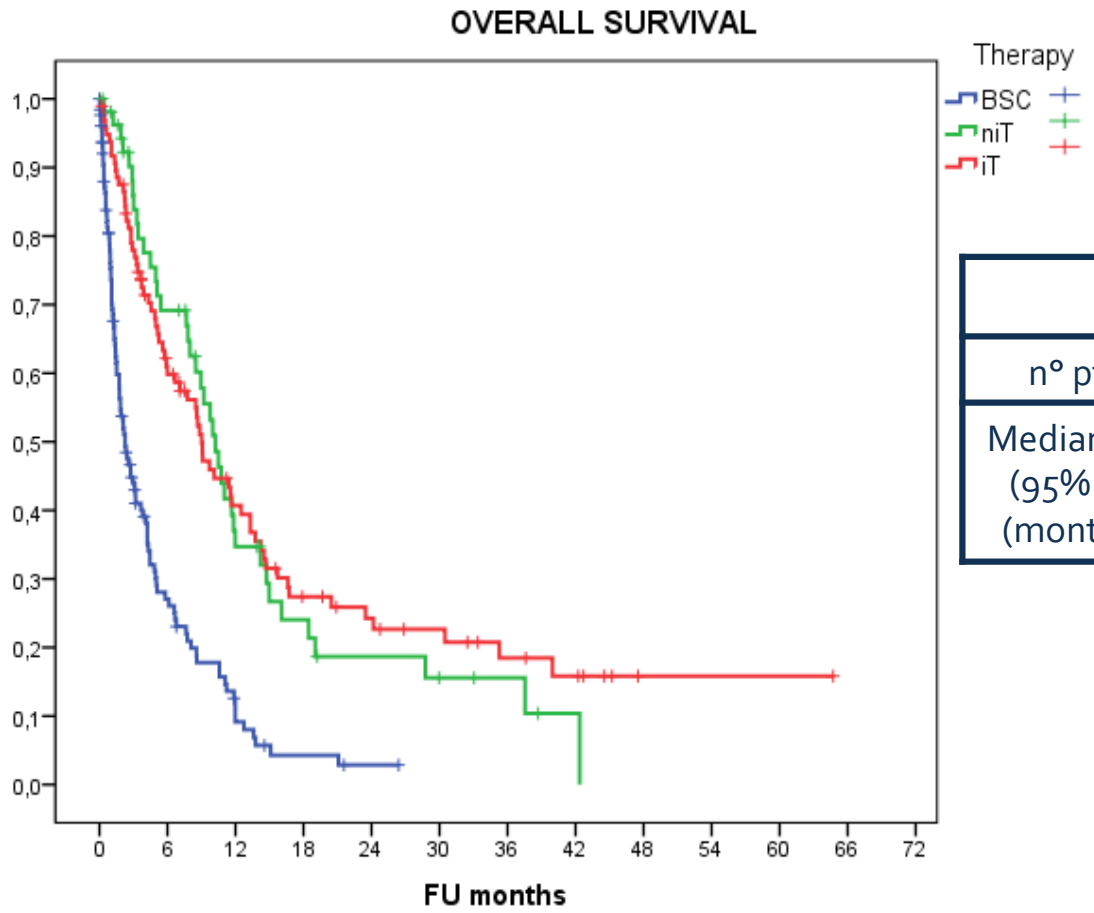

	i-T	ni-T	BSC
n° pts	97	54	129
Median OS (95% CI) (months)	9 (6,8-11,1)	10,2 (8,3-12,2)	2,3 (1,5-3)

p 0.8

p 0.00

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ELN & CR

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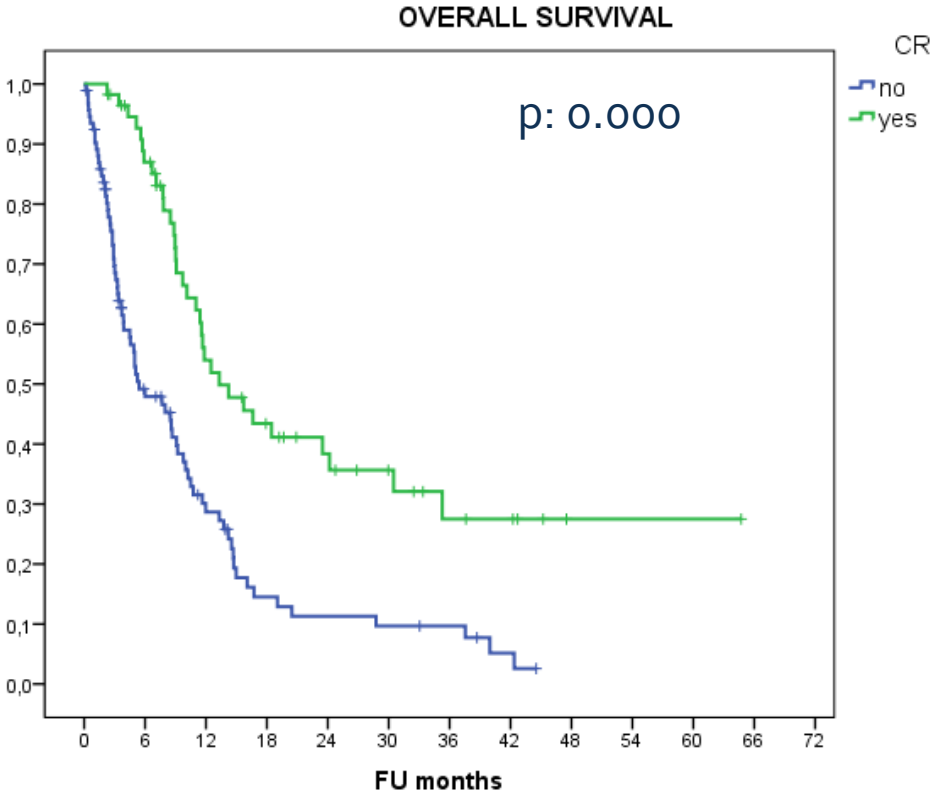
CR achievement in intensitive-treated patients: 41.3%

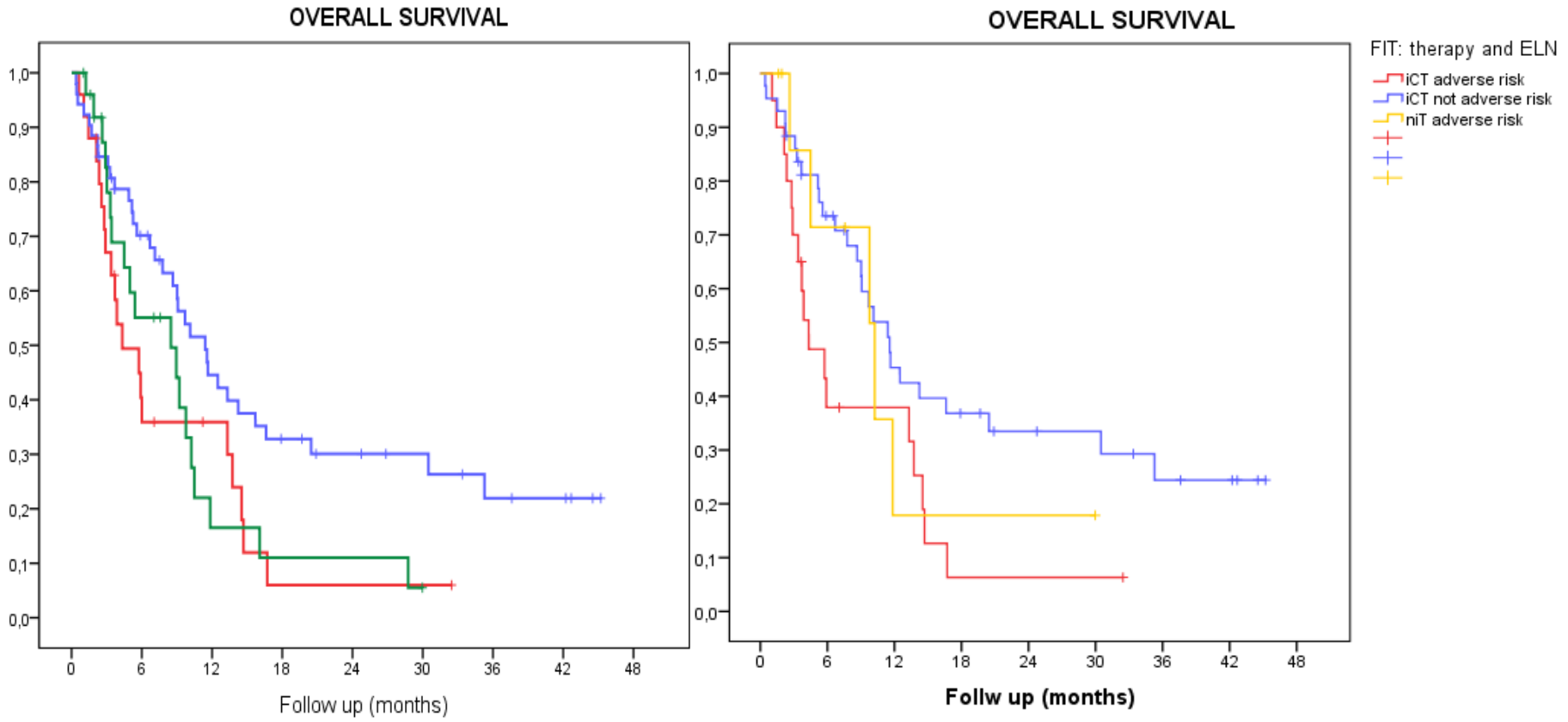


CR yes (CI 95%)	CR no (CI 95%)
13,3 (7,8-18,8)	5,4 (2,1-8,6)

CR was inversely related to ELN risk (p 0.00)

	CR achievemnt
Favorable	75%
Intermediate I	52.9%
Intermediate II	57.1%
Adverse	21.6%

OS:
ELN & Intensity of treatment



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Multivariable analysis

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	HR for OS	P value	IC 95,0% for HR
Therapy i-T-ni-T (n=111) BSC (n=47)	1 1.822	0.006	1,193 - 2,784
Complete remission yes (n=46) no (n=112)	0.516 1	0.009	0,314 - 0,846
ELN Class Risk adverse risk (n=83) other (n=75)	1.76 1	0.006	1,179 - 2,629

- **Treatment**
- **CR**
- **ELN risk**

are **indipendent parameters predicting survival**

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Conclusion

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- ELN risk classification was applicable and useful also in these population
- It identifies groups of patients at significant different prognosis
- Non frail elderly patients with sAML merit to be considered for antileukemic treatment even if they are not eligible for allogenic HSCT
- CR achievement in FIT patients treated with intensive chemotherapy impacts favorably on survival
- In sAML patients at adverse ELN risk ni-T obtained a better overall survival than i-T

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Criteria used for defining fitness to conventional intensive chemotherapy

CONCEPTUAL CRITERIA	OPERATIONAL CRITERIA	
	"UNFIT" to intensive chemotherapy	**Unfit to non-intensive therapy = "FRAIL"**
Age	Older than **75 years**	
Cardiac comorbidity severe > very severe	**Congestive heart failure** or documented cardiomyopathy with an EF ≤50%	**Refractory congestive heart failure**
Pulmonary comorbidity		Documented **pulmonary disease** with DLCO ≤ 65% or FEV1 ≤ 65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
Renal comorbidity	**On dialysis** and age older than 60 years or uncontrolled renal carcinoma	
Hepatic comorbidity severe > very severe	Documented liver disease with marked **elevation of transaminases** (>3 times normal values)	**Liver cirrhosis Child B or C or acute viral hepatitis**
Infectious comorbidity		**Active infection** resistant to anti-infective therapy
Cognitive impairment		Current **mental illness** requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
ECOG performance status	**PS > 2** not related to leukemia	
Oher comorbidities/ neoplasia	**Any other comorbidity that the physician judges** to be incompatible with conventional intensive chemotherapy	Uncontrolled **neoplasia**