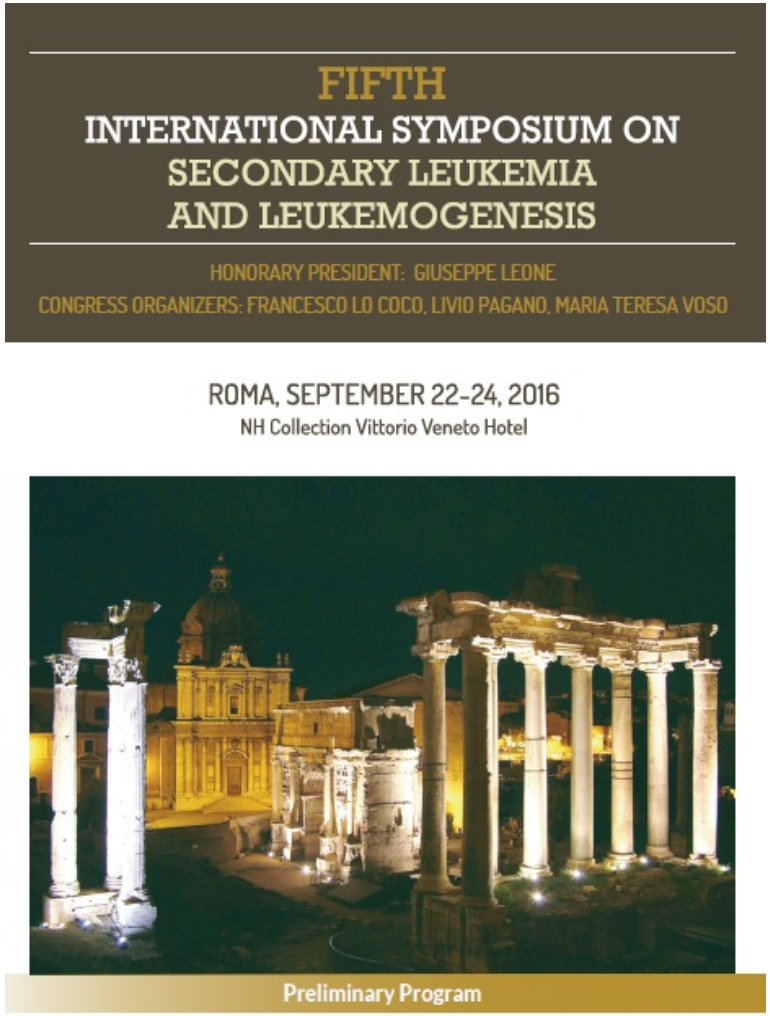


Treatment of Low-Blast Count AML

Maria Teresa Voso
Dipartimento di Biomedicina e Prevenzione
Università di Roma Tor Vergata

Università di Roma
Tor Vergata

Definition of Low-Blast Count AML

Blast counts 20-30% , or > 10% ?

- Retrospective study on patients with MDS or AML and >10% blasts seen at MD Anderson from January 2000 to April 2014 (n=1652)

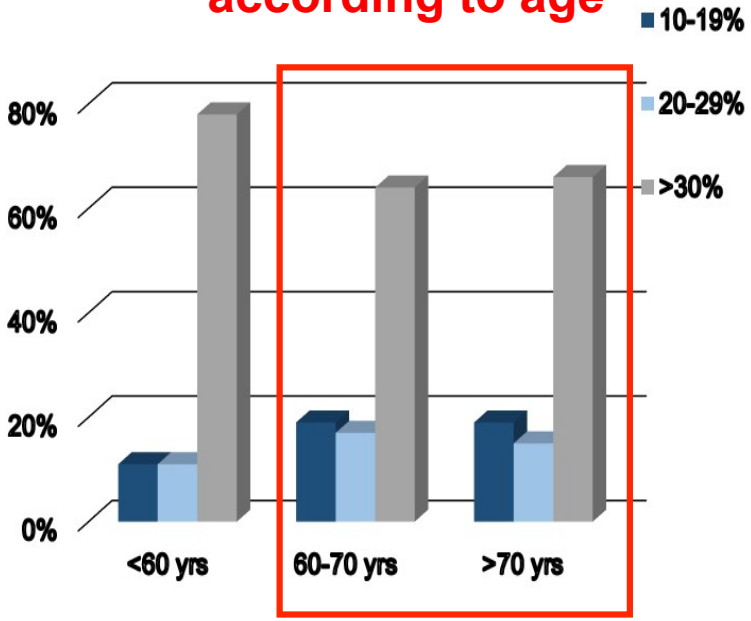
  10-19%: n=263 20-29%: n=230 >30%: n=1159

  AML with 20–29% blasts were similar to those with 10-19% blasts for

  - ✓ advanced age
  - ✓ increased frequency of poor-risk cytogenetics
  - ✓ lower WBC counts
  - ✓ less frequent NPM1 and FLT3-ITD mutations.

Di Nardo et al, Am J Hematol 2016

Distribution of MDS and AML according to age



Median OS according to age and blasts

BM-blasts (%)	Age <60 n=635	*p*	Age 60-69 n=470	*p*	Age 70+ n=537	*p*
10-19	39 m	0.98	15 m	0.006	15 m	<0.001
20-29	18 m		21 m		9 m	
>30	24 m		11 m		7 m	

- **Multivariate analysis** showed inferior survival associated with
  - ✓ older age
  - ✓ poor-risk cytogenetics
  - ✓ therapy-related disease
  - ✓ proliferative disease (WBC> 25 10^9/L, elevated LDH, peripheral blasts)

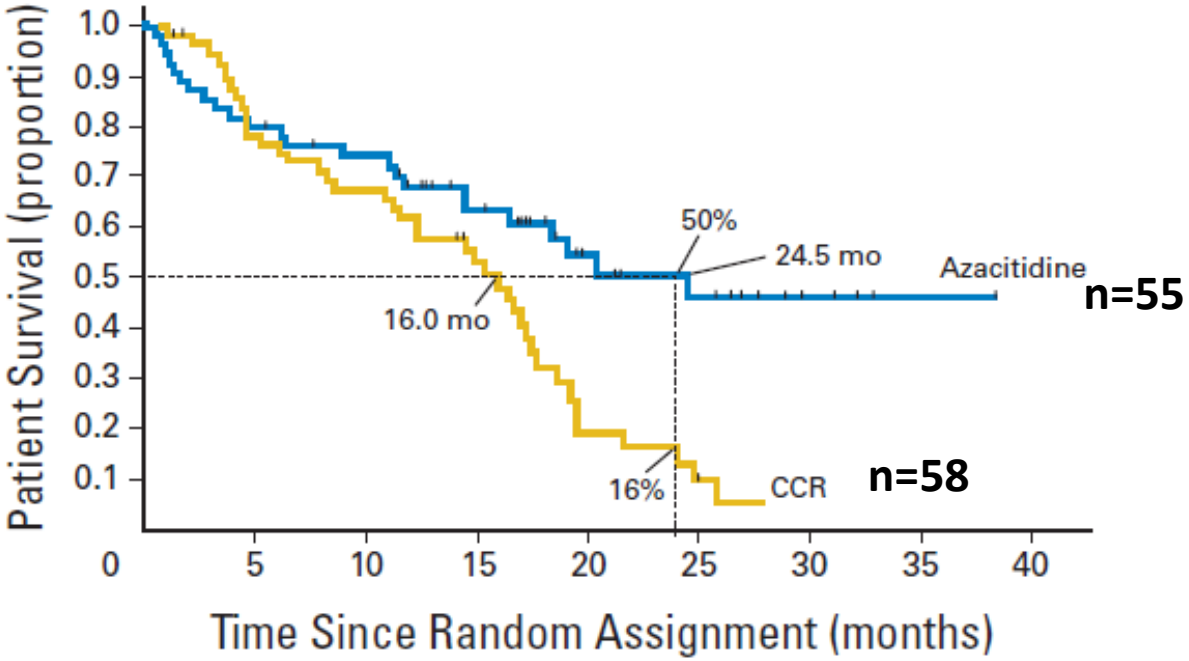
Di Nardo et al, Am J Hematol 2016

LBC AML: Hypomethylating Agents, Azacitidine

- Patients with 23% median BM blast counts (range 20-34%)
- Median age: 70 years (50-83)
- Randomized to receive AZA-SD (MDS-001 trial) versus CCR (pre-selection)
  - BSC: n= 27
  - LD-Cytarabine: n = 20
  - Intensive CHT: n = 11

Complete remission Rate

- ✓ AZA: 18%
- ✓ CCR: 16%
  - LD-ARA-C: 15%
  - I-CHT: 55%



No. of patients at risk

Azacitidine	55	43	38	26	15	10	4	1	0
CCR	58	43	36	22	6	3	0	0	0

Fenaux et al, J Clin Oncol 2010

Real-life: Austrian Azacitidine Registry

Patient characteristics (n=302)

Median age (range):
73 (30–93)

WHO diagnosis†

t-AML:	8%
AML-RCA:	20%
AML-MRF:	67%
AML-NOS:	20%

BM blasts

<30%:	43%
≥30%:	57%

MRC cytogenetics

good:	4%
intermediate:	67%
high:	19%

WBC count

<10 x 10^9/L:	50%
>10 x 10^9/L:	50%

ECOG PS

0–1:	76%
≥2:	24%

Comorbidities

0–1:	50%
≥2:	50%

Prior Treatment of AML

none:	38%
yes:	62%

Regimen*

AZA d1–7:	53%
AZA d5–2–2:	24%
AZA d1–5:	15%
AZA others:	7%

Route

SC:	85%
IV:	10%
IV and SC:	5%

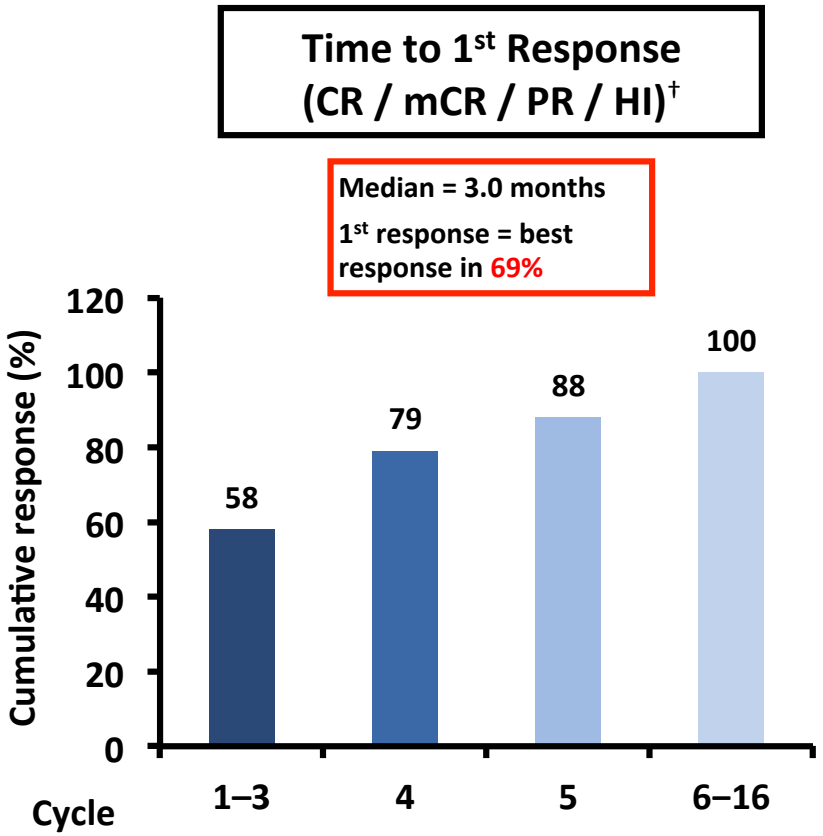
Pleyer L, et al. Ann Hematol 2014, 93: 1825-1838

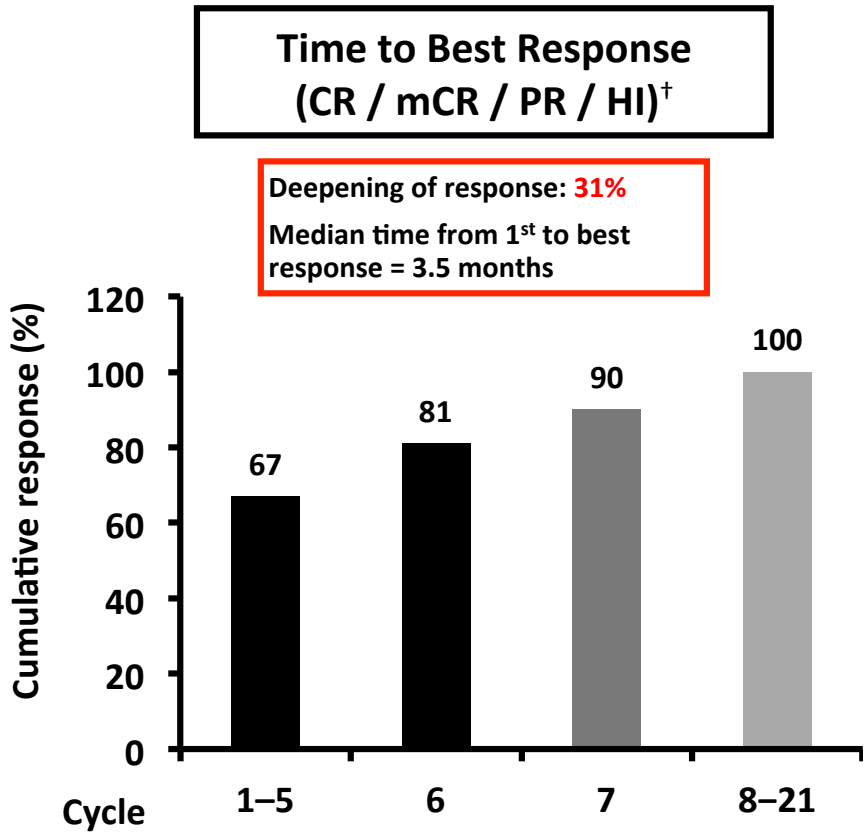
Austrian Azacitidine Registry: response*

	ITT n = 302 %	At least 2. cycles %
ORR (CR + mCR + PR + HI),		
Yes	48	72
No	52	28
Transfusion independence,		
PLT-TI	42	62
RBC-TI	39	60
Haematological		
improvement, Any,	39	60
HI-platelet	29	44
HI-neutrophil	15	23
HI-erythrocyte	30	45
No HI	61	41
Marrow response,		
Yes	30	65
CR	13	28
mCR	4	9
PR	13	28
No, mSD	11	24
Primary PD	5	10

Plever L. et al. Ann Hematol 2014. 93: 1825-1838

Austrian Azacitidine Registry: time to response



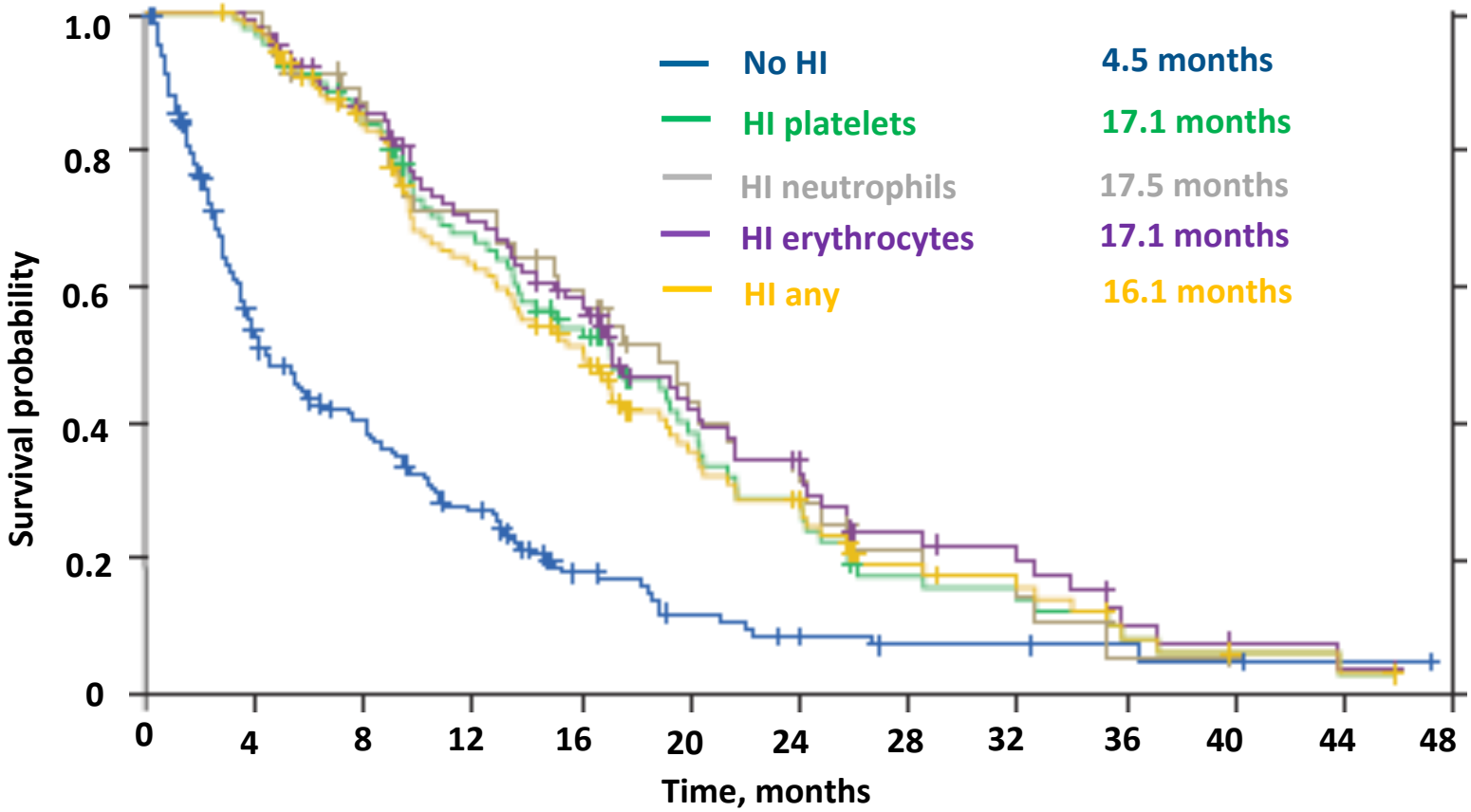


Median duration of response, months (range): 3.4 (0.3–33.0)

Pleyer L, et al. Ann Hematol 2014, 93: 1825-1838

Austrian Azacitidine Registry:

OS according to haematological improvement (n=302)

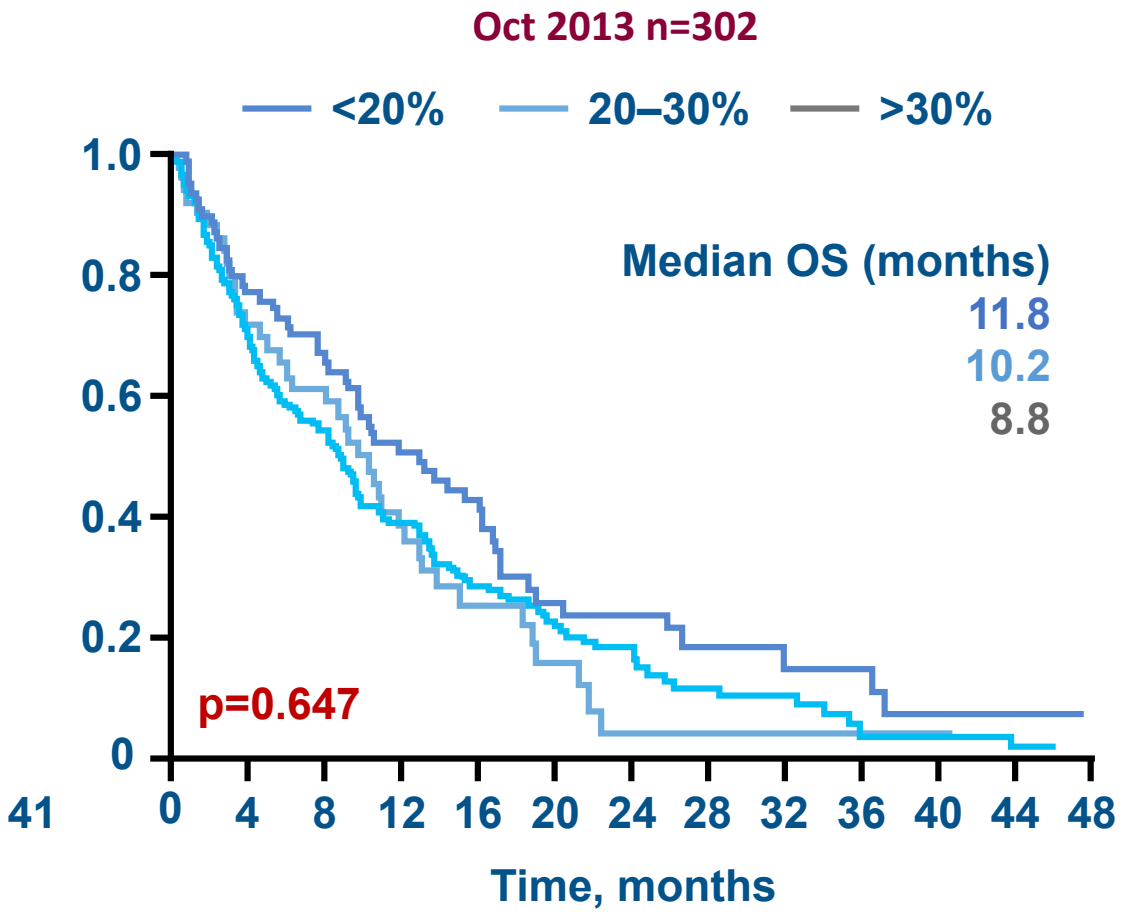


Significant survival benefit in patients with any type of haematological improvement (16.1 vs 4.5 months)

Pleyer L, et al. Ann Hematol 2014

Austrian Azacitidine Registry:

effect of BM blast percentage on OS



BM blast count did not significantly affect OS, irrespective of whether the whole cohort was analysed, or whether pre-treated patients were excluded

1. Pleyer L, et al. J Hematol Oncol 2013;6:32
2. Pleyer L, et al. Ann Hematol 2014

Italian Series: patients characteristics

	n 103 (%)
Age, years	
Median	75
Range	61-88
≥ 70 yrs	78 (76)
Sex	
Male	63 (61)
Female	40 (39)
WBC (x 10^9/L)	
Median	2.6
Range	0.27-105.0
PB blasts count (%)	
Median	5
range	0-94
BM blasts count (%)	
Median	30
Range	20-90
<30%	45 (44)
≥30%	58 (56)
AML	
De novo	54 (52.4)
sAML	49 (47.6)
therapy related	12 (11.6)

	n 103 (%)
Karyotype	
intermediate	60 (58.3)
normal	49 (47.6)
adverse	23 (22.3)
favorable	-
failure	20 (19.4)
Performance status (ECOG)	
0	28 (27.2)
1	50 (48.6)
2	25 (24.2)
Azacitidine dose	
75 mg/m^2/d	79 (76.7)
100 mg/d fixed dose	24 (23.3)
Time from DG to Aza (days)	
median (range)	24 (5-85)
Number of cy delivered	6 (range 1-60)
Number of cy to response	4 (range 2-12)
Duration of response	6 (range 2-18)

Maurillo et al, in preparation

Response to AZA

	No.	%
Patients	102*	
Overall response	**44**	**43**
CR/CRi	22/2	23
PR	20	20
No Response	58	57

*1 patient lost to follow up after 2 cycles

Maurillo et al, in preparation

Multivariate analysis

Parameter		*p*	Hazard Ratio	95% HR CI	
age	<70 vs >70	0.4606	1.243	0.697	2.217
cytogenetics	Intermediate vs adverse	**0.0106**	2.112	1.190	3.749
WBC	$<10x10^9/L$ vs $\geq 10x10^9/L$	**0.0097**	0.444	0.240	0.821
PS	0 vs 1	**0.0093**	2.362	1.236	4.513
PS	0 vs 2	**<.0001**	4.496	2.188	9.238
response	Yes vs No	**<.0001**	3.216	1.859	5.564

Maurillo et al, in preparation

Elderly AML
AML-001: Phase III Study

Investigator preselection of CCR

Randomization

Older (≥65 years) pts with newly diagnosed AML (>30% BM blasts) (N=480)

AZA (n=241)

- **75 mg/m^2/day SC x 7 days every 28 days + BSC, ideally for at least 6 cycles**

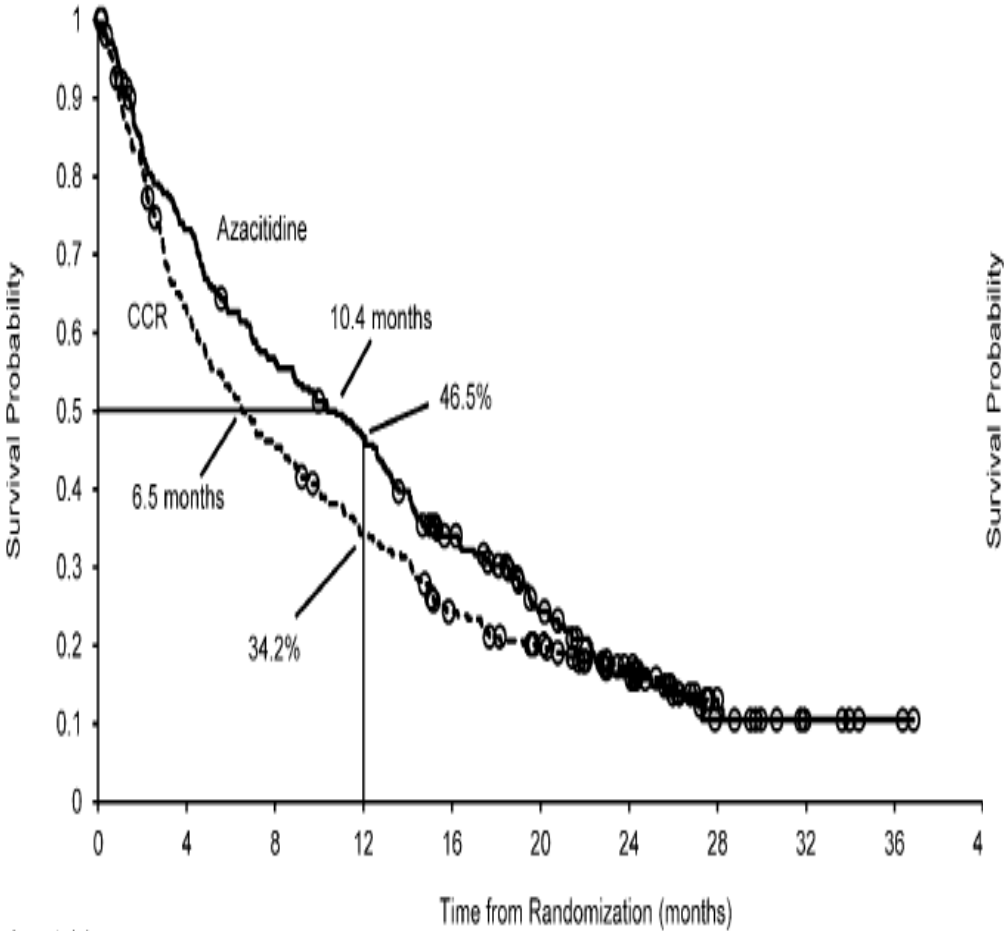
CCR (n=240)

- **IC (cytarabine 100-200 mg/m^2 IV 7 d + anthracycline IV 3 days) induction, with up to 2 subsequent cycles (re-induction or consolidation) (45 pts)**
- **LDAC (20 mg SC BID 10 d, q 28 (158 pts)**
- **BSC only (44 pts)**

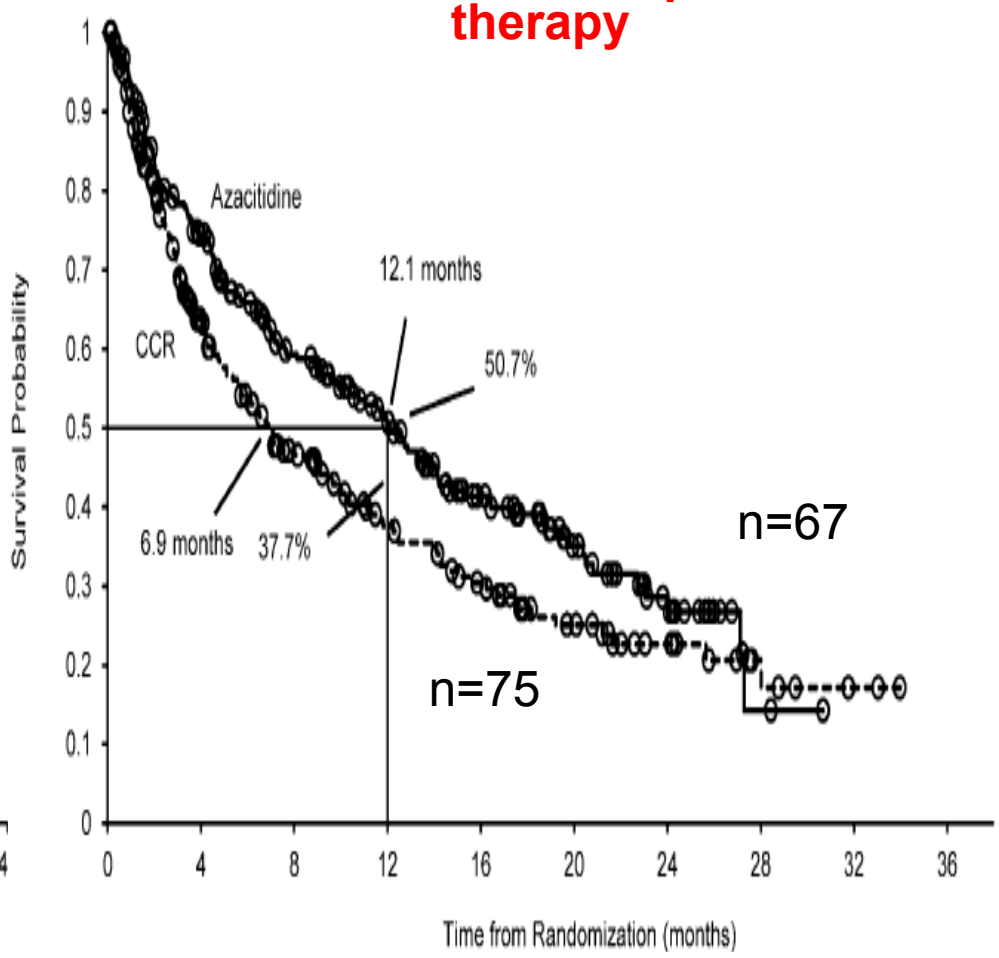
Patients in each arm followed for survival

Dombret et al, Blood 2015

Overall Survival



Preplanned sensitivity Analysis Censored for subsequent AML therapy



Dombret et al, Blood 2015

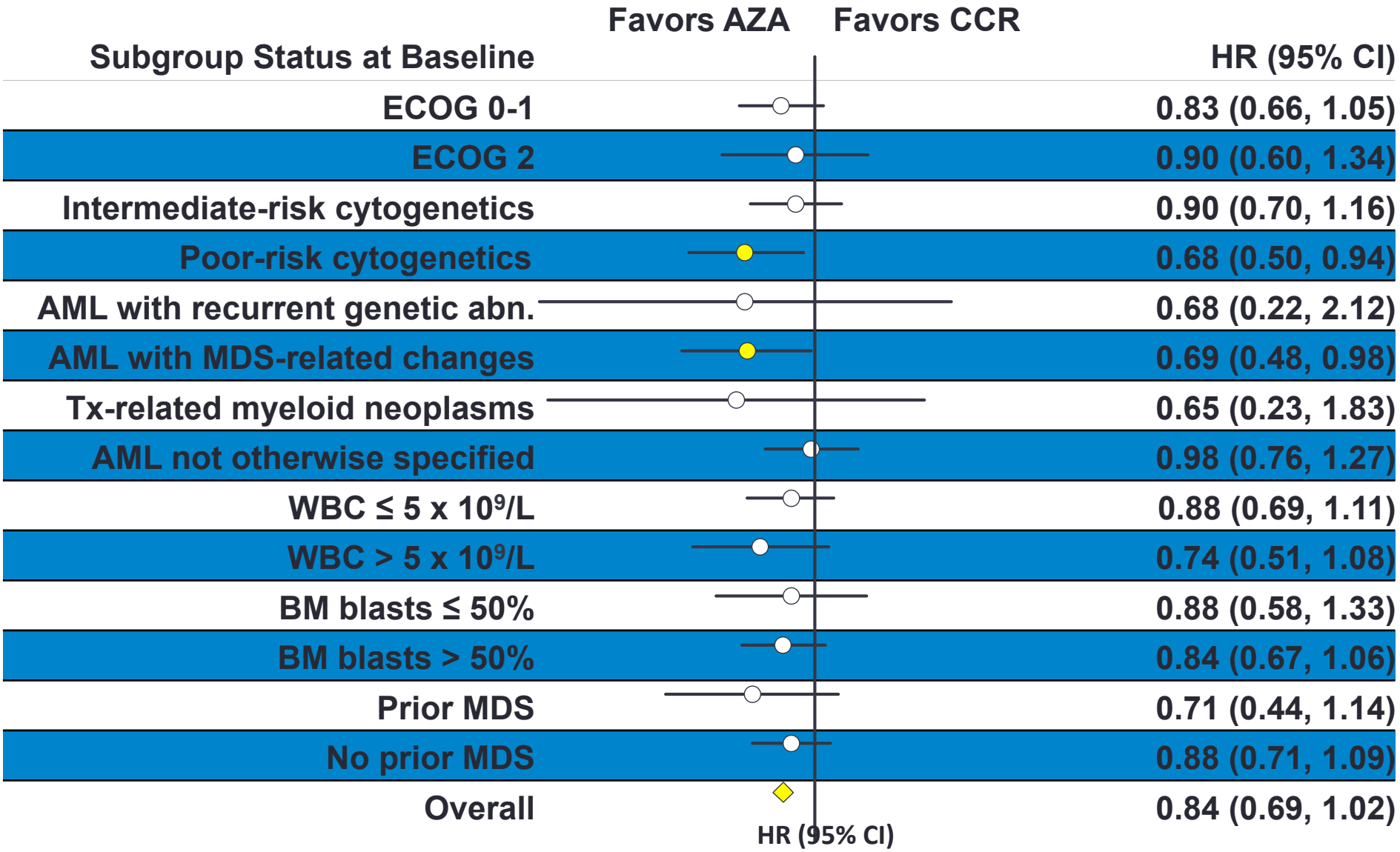
First Subsequent Therapy After Study Discontinuation

First subsequent therapy	AZA n=69	CCR n=75
AZA,* n (%)	9 (13)	31 (41)
Decitabine,* n (%)	2 (3)	2 (3)
Cytarabine-based,* n (%)	37 (54)	22 (29)
Other,* n (%)	21 (30)	20 (27)

Dombret et al, Blood 2015

Prognostic Factors for Overall Survival

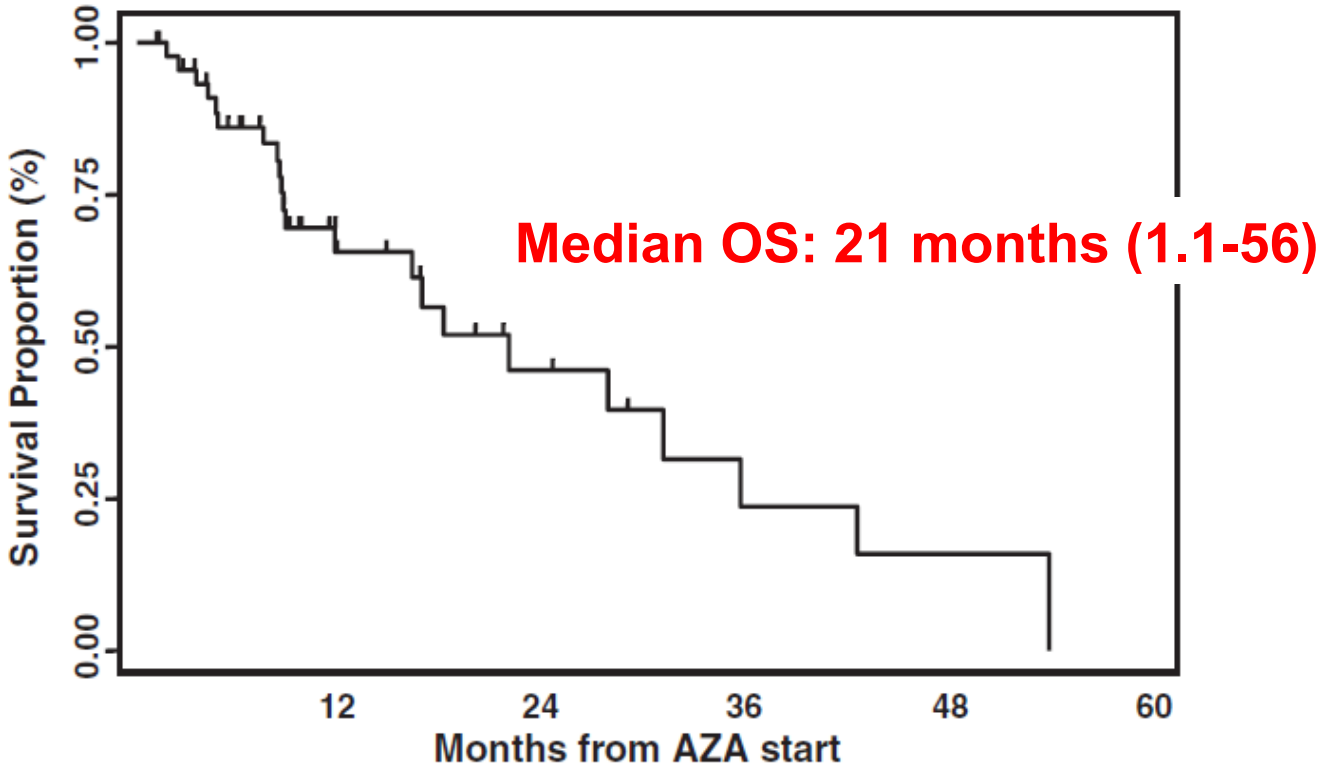
(Univariate Analysis)



Dombret et al, Blood 2015

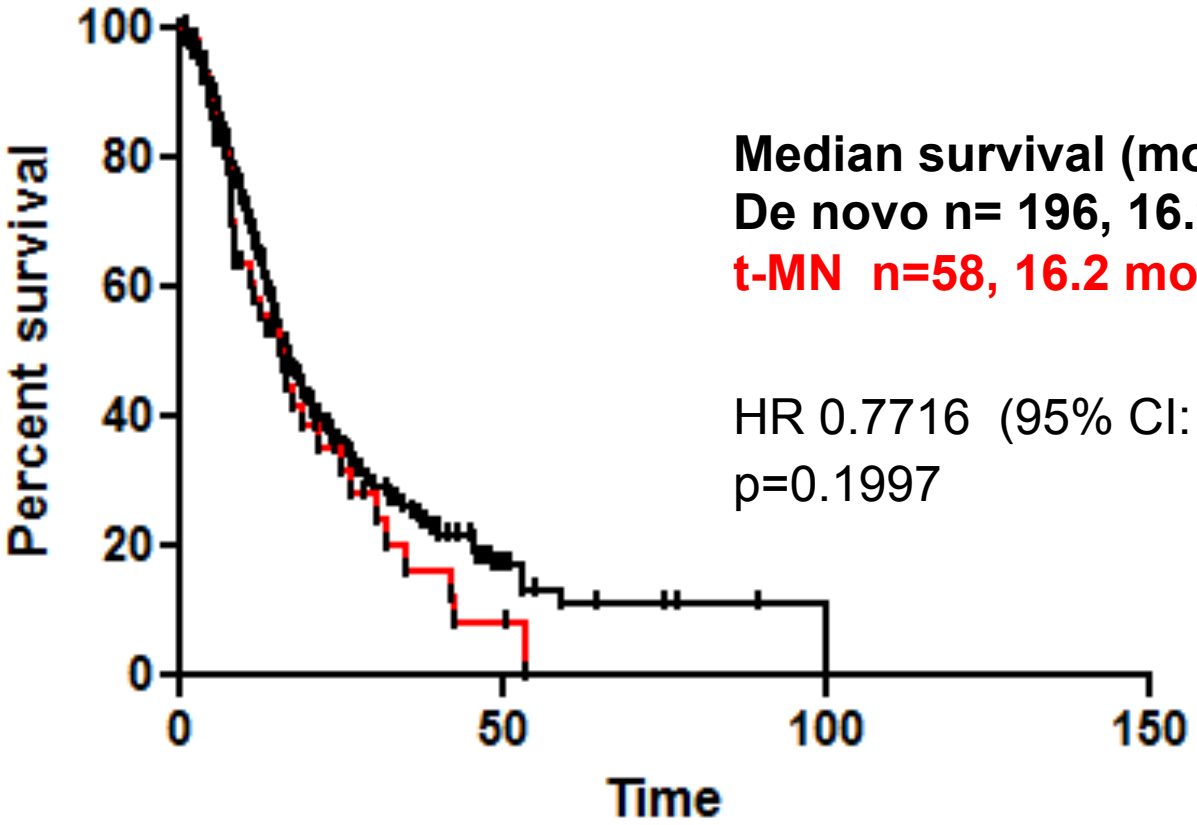
Azacitidine in Therapy-related Myeloid Neoplasms

- n= 50 pts with a t-MN, treated with Azacitidine
  - CR 21%, PR 4.2%, HI 16.7%, SD 31%



Fianchi et al, J Hematol Oncol 2012

Overall Survival
t-MN vs De novo HR-MDS



Median survival (months)
De novo n= 196, 16.9 months
t-MN n=58, 16.2 months

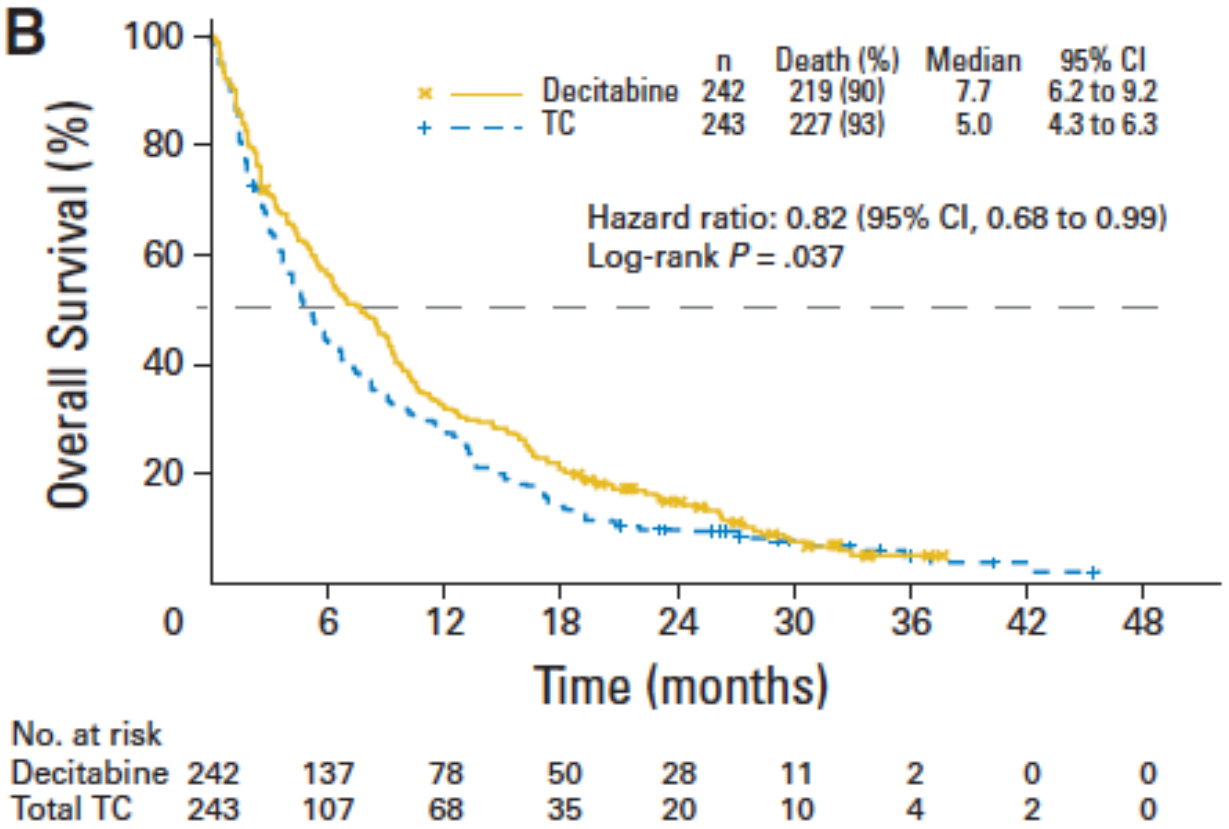
HR 0.7716 (95% CI: 0.5191 to 1.147)
p=0.1997

Fianchi, Voso et al, in preparation

Decitabine, Phase III Trial in AML

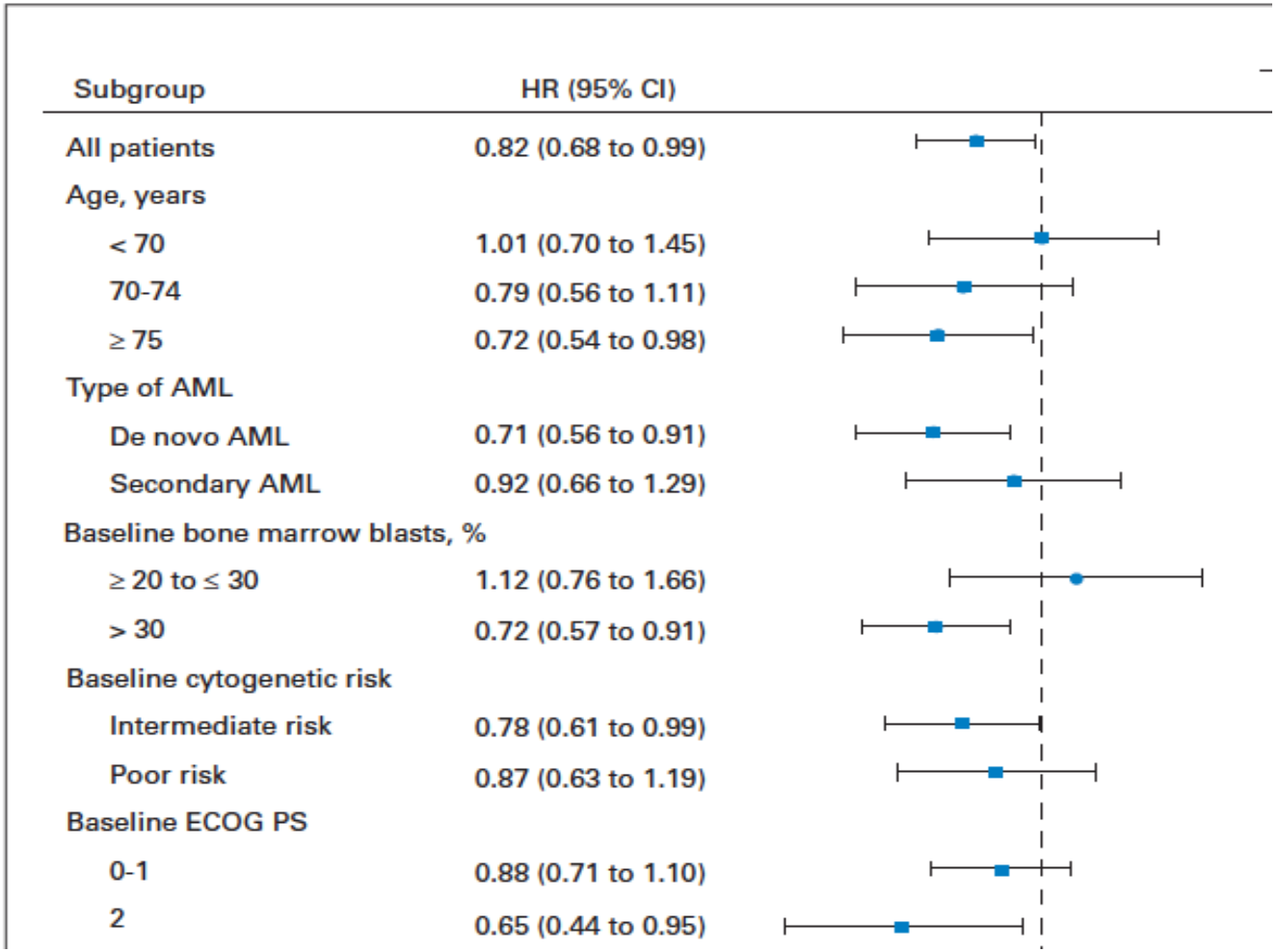
Elderly AML (73 yrs (64-91 yrs)
DAC 20 mg/m^2 IV 10 d, every 4 we (n=242),
Vs LDARAC 20 mg/m^2/day sc 10 days, every 4 we (n=215),
Or Supportive care (n=28)

CR: DAC: 18% vs 8%*



Kantarjian et al, JCO 2012

Prognostic Factors for Survival



Favors DAC

Kantarjian et al, JCO 2012

How to Improve?

Still high rate of early relapse or progression:

Prognostic factors

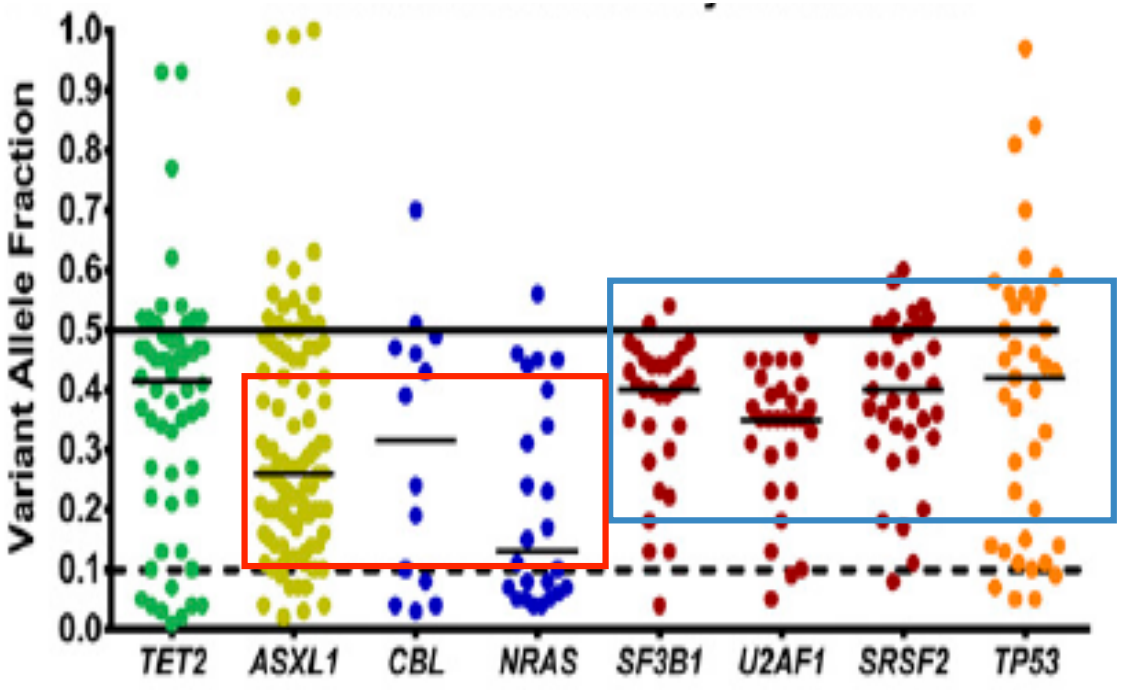
Allogeneic SCT

Combination Treatment

Prognostic Factors: Mutations

- 40 genes sequenced in 213 patients treated with Azacitidine or Decitabine
- 94% of patients had a mutation in at least one gene.
- The overall response rate (47%) was not different between agents.

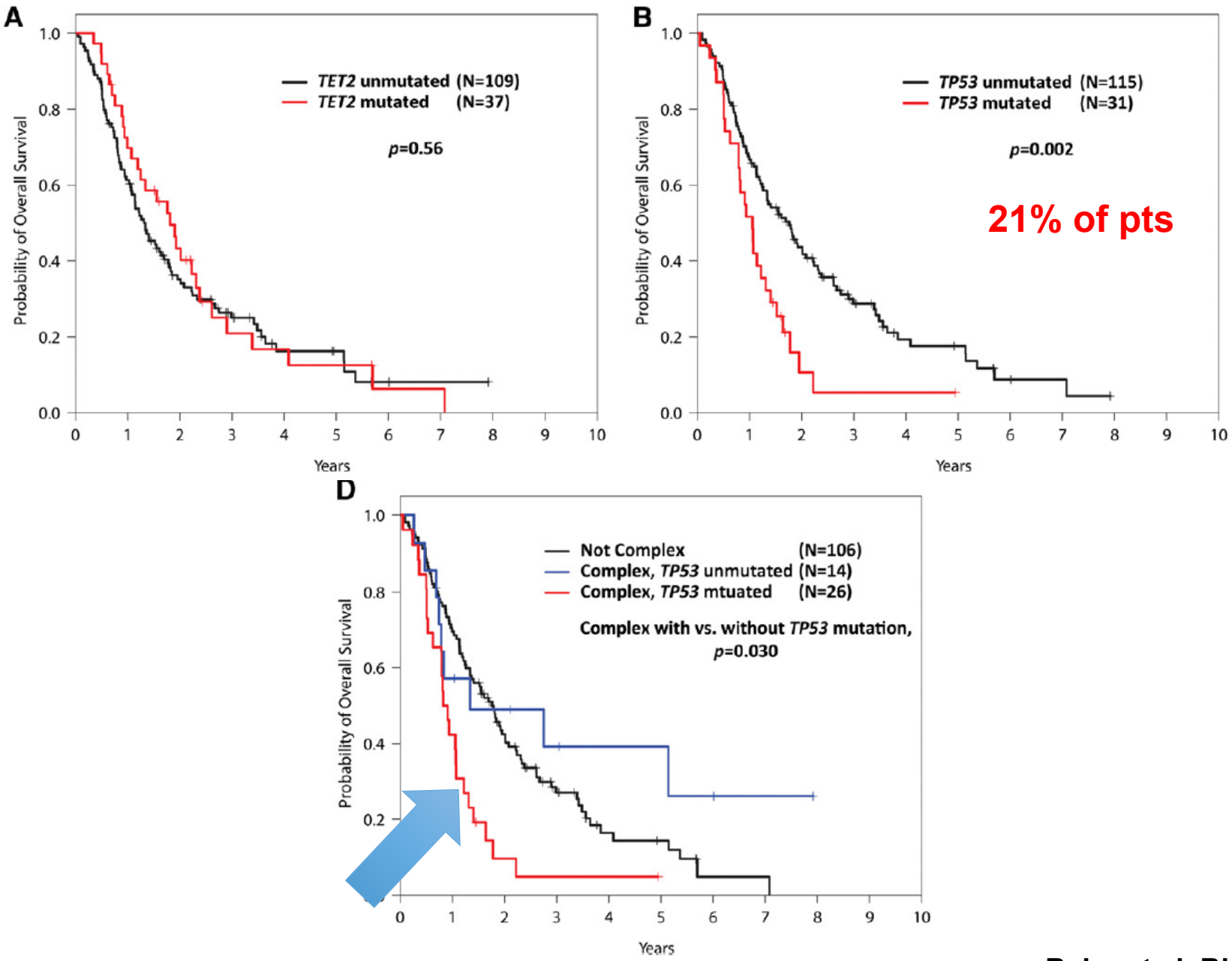
Subclonal?



- ✓ None of the mutations was predictive of response per se
- ✓ TET2 mutations predicted response only at over 10% VAF

Bejar et al, Blood 2014

Mutations and overall survival

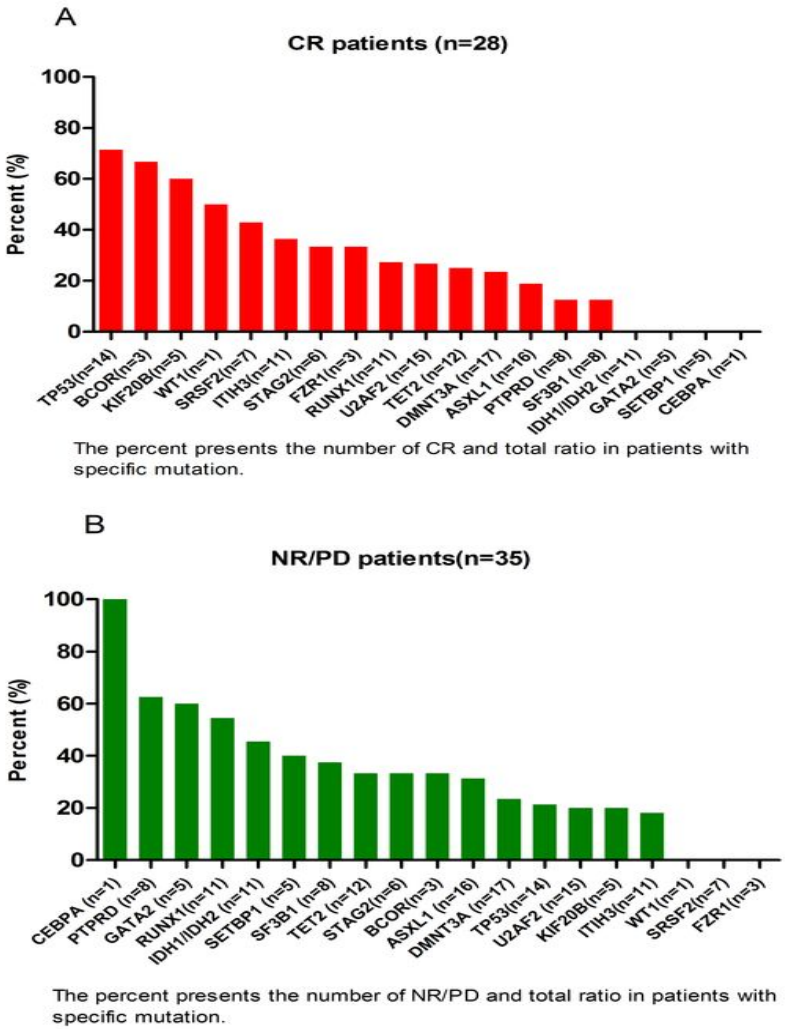


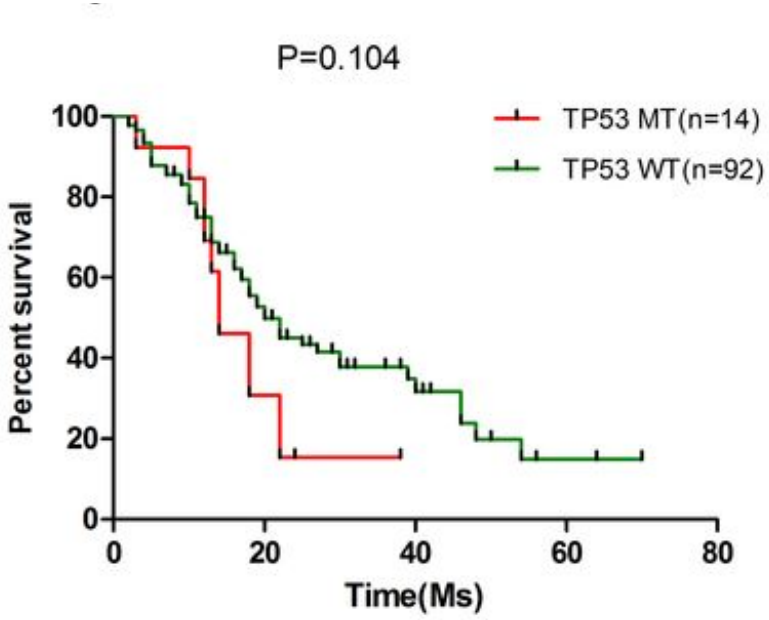
Bejar et al, Blood 2014

Mutations and HMT

- 106 pts with MDS, treated with Decitabine
- Among the 14 TP53 mutated patients, ten achieved CR (71.4%).

Fig.1



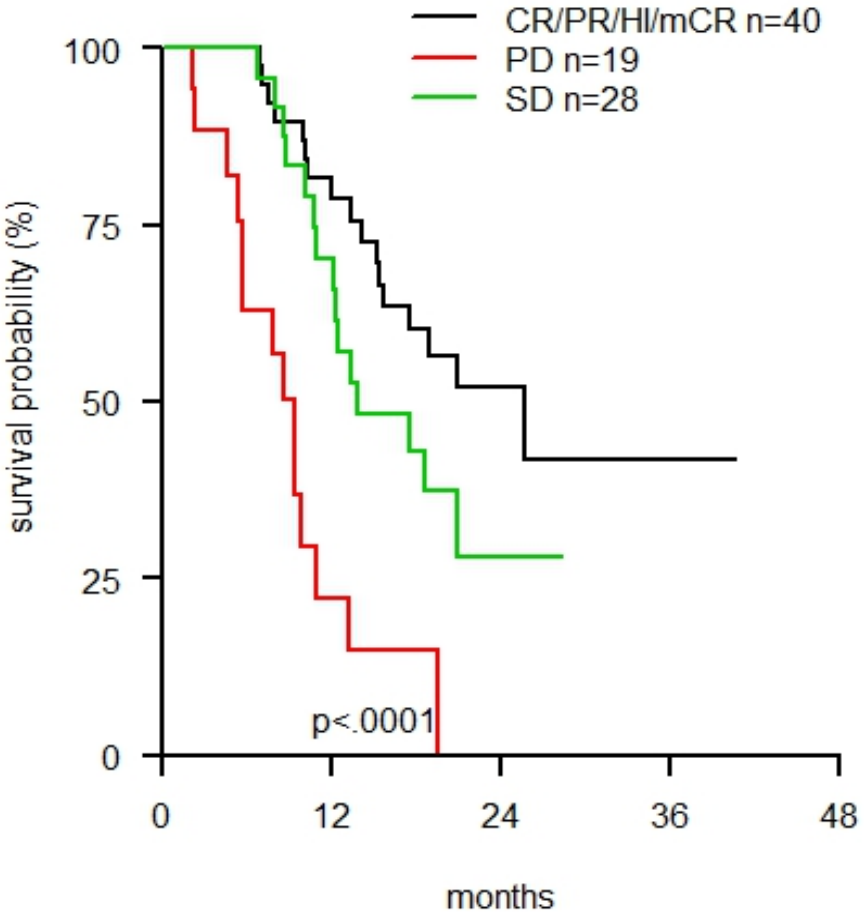


Chunkang Chang et al. Blood 2015;126:1689

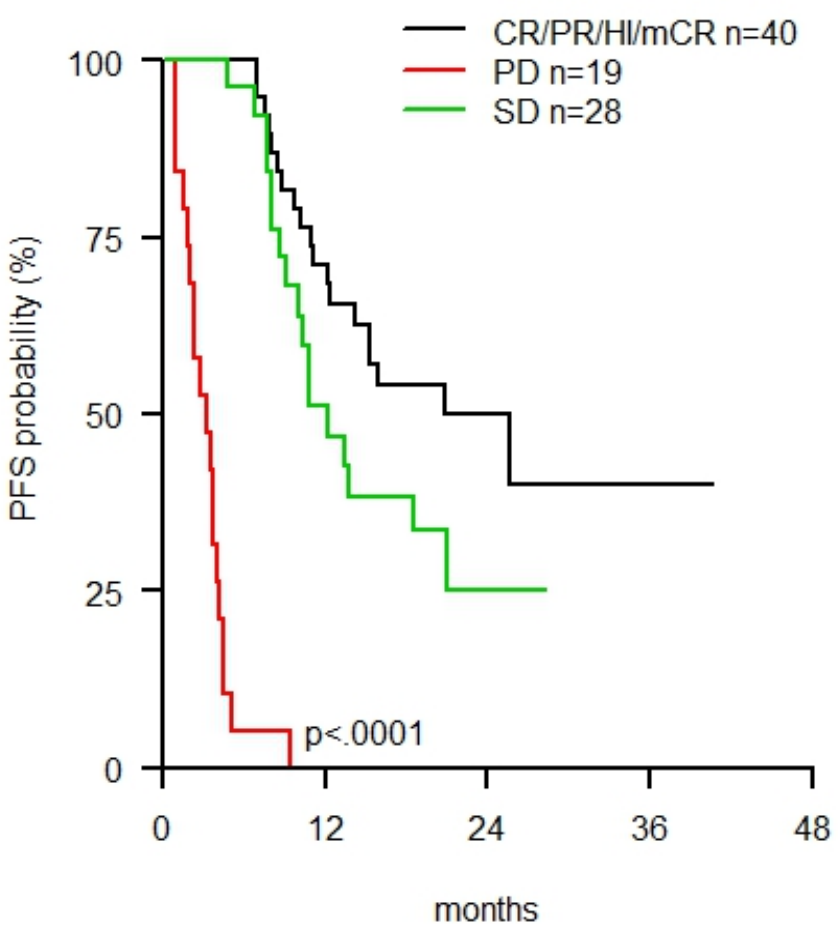
blood

AlloSCT: BMT-AZA Protocol
n =97 pts
AZA: 4 cy (1-11)
HSCT: 54 pts (74% with a donor)

Overall Survival



Progression-free Survival



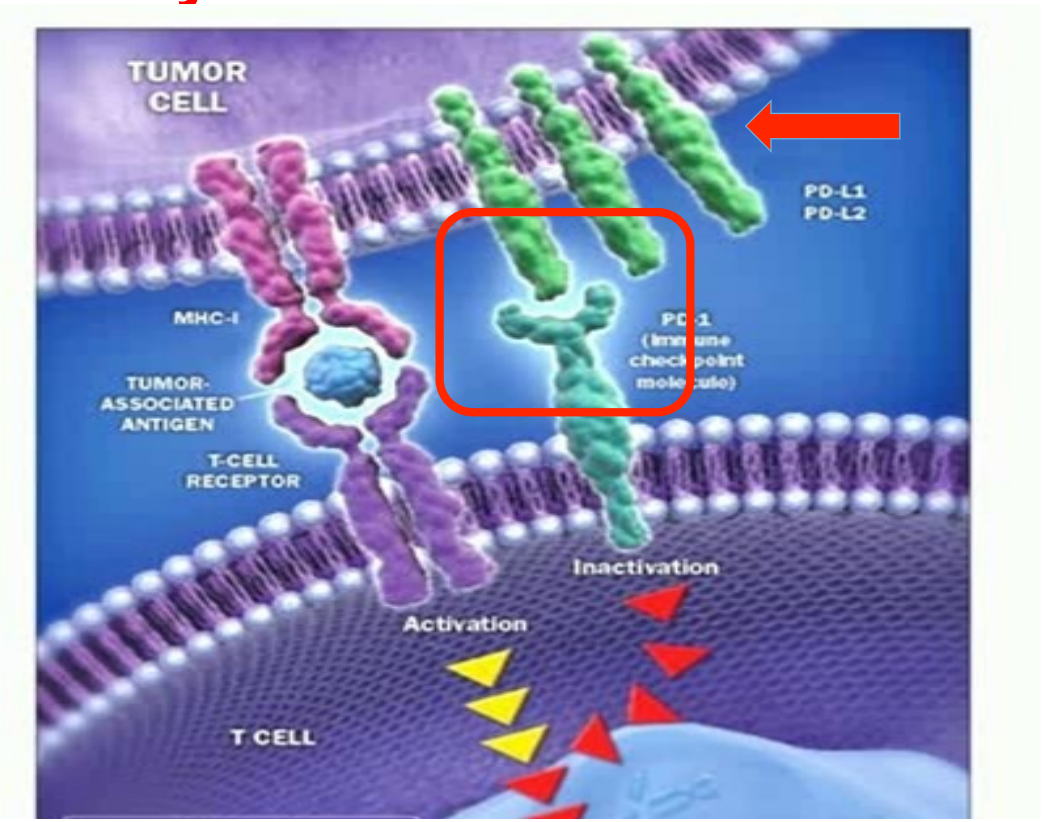
Submitted

Combination Therapy

Study	Drugs	Patients (n)	Median age (range)	ORR (%)	Median OS, months
Prebet	Aza ± Entinostat	97 MDS 52 AML	72 (25-87)	32% vs 27% (Aza vs AZA/Ent)	18 vs 13 (Aza vs AZA/Ent)
Issa	DAC ± VPA	87 MDS 62 AML (70 DAC vs 79 DAC/VPA)	69 (20-89)	51% vs 58% (DAC vs DAC/ VPA)	12 vs 11 (DAC vs DAC/VPA)
Kirschbaum	DAC + Vorinostat	11 MDS 60 AML (29 rel/ refractory; 31 untreated)	68 (18-75)	30% (untreated: 46%, relapsed/refractory AML:15%)	n.r.
Zhao	DAC ±Thalid	107 MDS (52 DAC, 55 DAC/Thal)	66 (65-82)	67% vs 65% (DAC vs DAC/ Thal)	2-year OS 71.2 vs 78.6% (low-risk) 40.2 vs 50.6% (high-risk)

PD1 Pathway and Immune Surveillance

Tumor cell

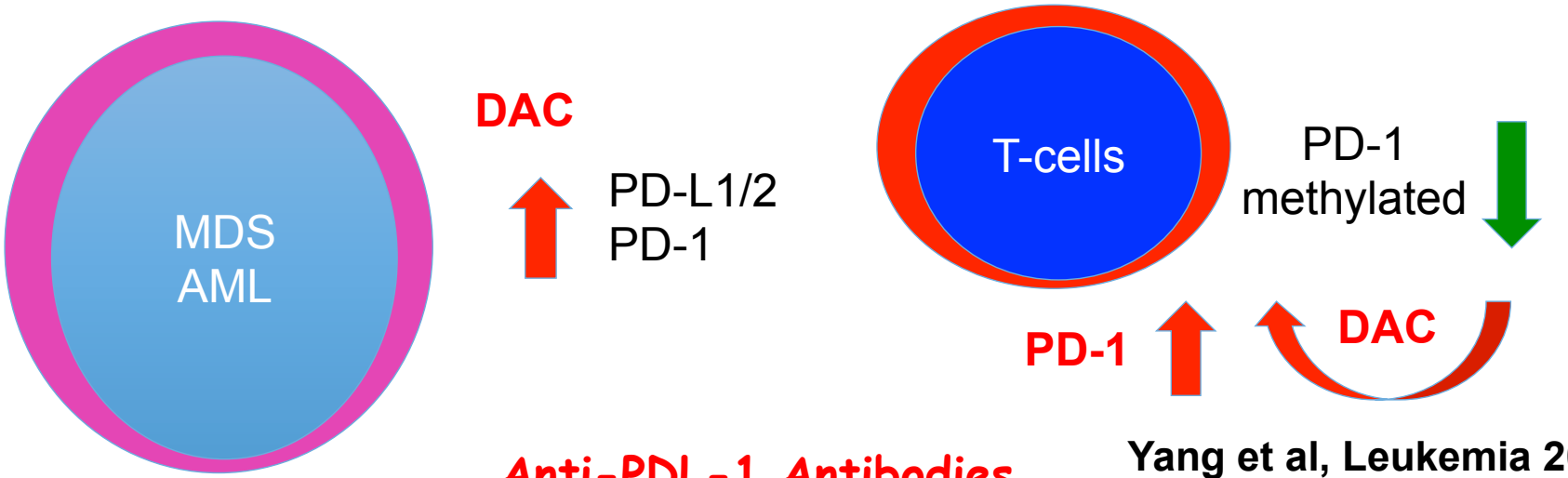


T-cell

- PD-1 is a negative co-stimulatory receptor primarily expressed on activated B-cells
- Binding of PD-1 to its ligands PDL-1 and PDL-2 inhibits effector T-cell function
- Expression of PD-L1 on tumor cells and macrophages can suppress immune surveillance and permit neoplastic growth
- Anti-PD-1 antibodies (pembrolizumab, durvalumab, etc) have clinical activity

PD1 Pathway in MDS/AML

- PD-L1, PD-L2, PD-1 and CTLA4 are upregulated in CD34+ cells from MDS, CMML and AML patients and in PBMNC.
- The relative expression of PD-L1 from PBMNC was significantly higher in MDS and CMML compared to AML.
- PD-L1, PD-L2, PD-1 and CTLA4 expression was upregulated is patients undergoing decitabine (PD-1 was demethylated)
- Patients resistant to therapy had relative higher increments in gene expression compared to patients that achieved response.
- A significantly higher baseline methylation level of the PD-1 promoter was observed in T cells of non-responding patients compared to healthy controls



Yang et al, Leukemia 2014
Ørskov et al, Oncotarget 2015

An Efficacy and Safety Study of Azacitidine Subcutaneous in Combination With Durvalumab (MEDI4736) in Previously Untreated Subjects With Higher-Risk Myelodysplastic Syndromes (MDS) or in Elderly Subjects With Acute Myeloid Leukemia (AML)

This study is currently recruiting participants. (see Contacts and Locations)

Verified July 2016 by Celgene Corporation

Sponsor:
Celgene Corporation

Information provided by (Responsible Party):
Celgene Corporation

ClinicalTrials.gov Identifier:
NCT02775903

First received: May 16, 2016
Last updated: July 5, 2016
Last verified: July 2016
History of Changes

Purpose

This is a Phase 2, multicenter, randomized, parallel-group, open-label study consisting of 3 phases: Screening, Treatment, and Follow-up.

To confirm the safety, ie, the absence of overlapping toxicities of the combination treatment regimen, an early safety monitoring will be performed based on approximately the first 12 subjects randomized.

A total of approximately 72 subjects will be included in the Myelodysplastic syndromes (MDS) cohort and approximately 110 subjects in the Acute Myeloid Leukemia (AML) cohort.

Summary

- Low-blast count AML are frequent in elderly patients, and are characterized by poor-risk cytogenetics, lower WBC counts, less frequent NPM1 and FLT3-ITD mutations
- Hypomethylating treatment, and azacitdine in particular, induces response and prolongs survival in LBC-AML and AML, *de novo* and therapy-related
- Duration of response is however short
- Somatic mutations may predict survival
- Strategies to improve outcome include : allogeneic SCT and combination therapy
- Association of HMT to immune-response checkpoint inhibitors is a promising approach

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Con la ricerca, contro il cancro.

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