DIFFERENTIAL TREATMENT APPROACHES FOR THERAPY-RELATED ACUTE LEUKEMIAS

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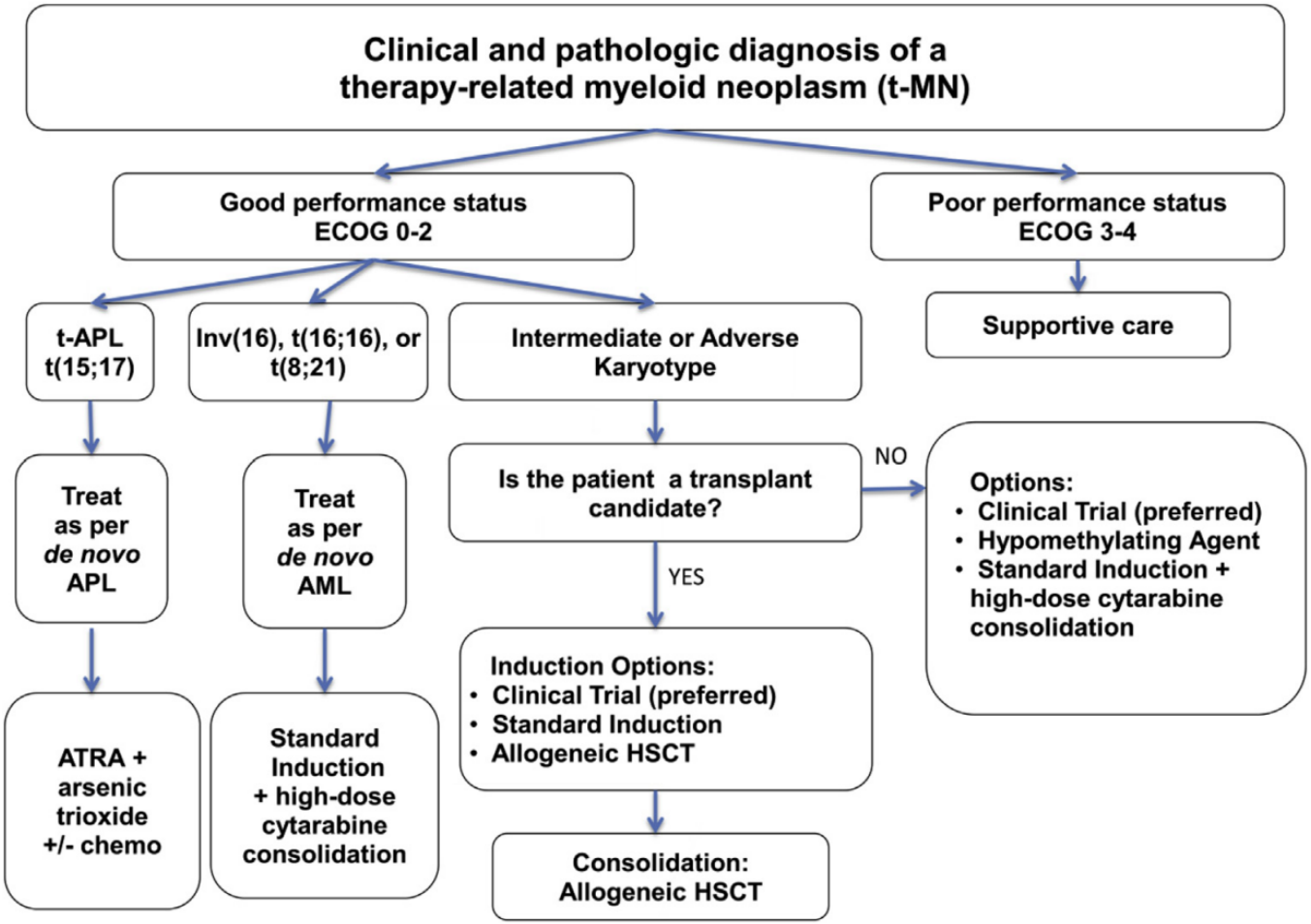
Algorithm for the treatment of t-MN



Churpek & Larson, BPRCH 2013

TREATMENT OF t-AML

- Investigational agents (Clinical trials)
- Hypomethylating agents

INVESTIGATIONAL AGENTS

- Amonafide
  - ✓ Topoisomerase II inhibitor that is not a substrate for gp170
- CPX-351
  - ✓ Liposomal formulation of daunorubicin and cytarabine at an "optimal" (1:5) molar ratio
- Anti-CD33 MoAbs
  - ✓ Gentuzumab Ozogamicin (GO)
  - ✓ SGN-CD33A (Vadastuximab Talirine)

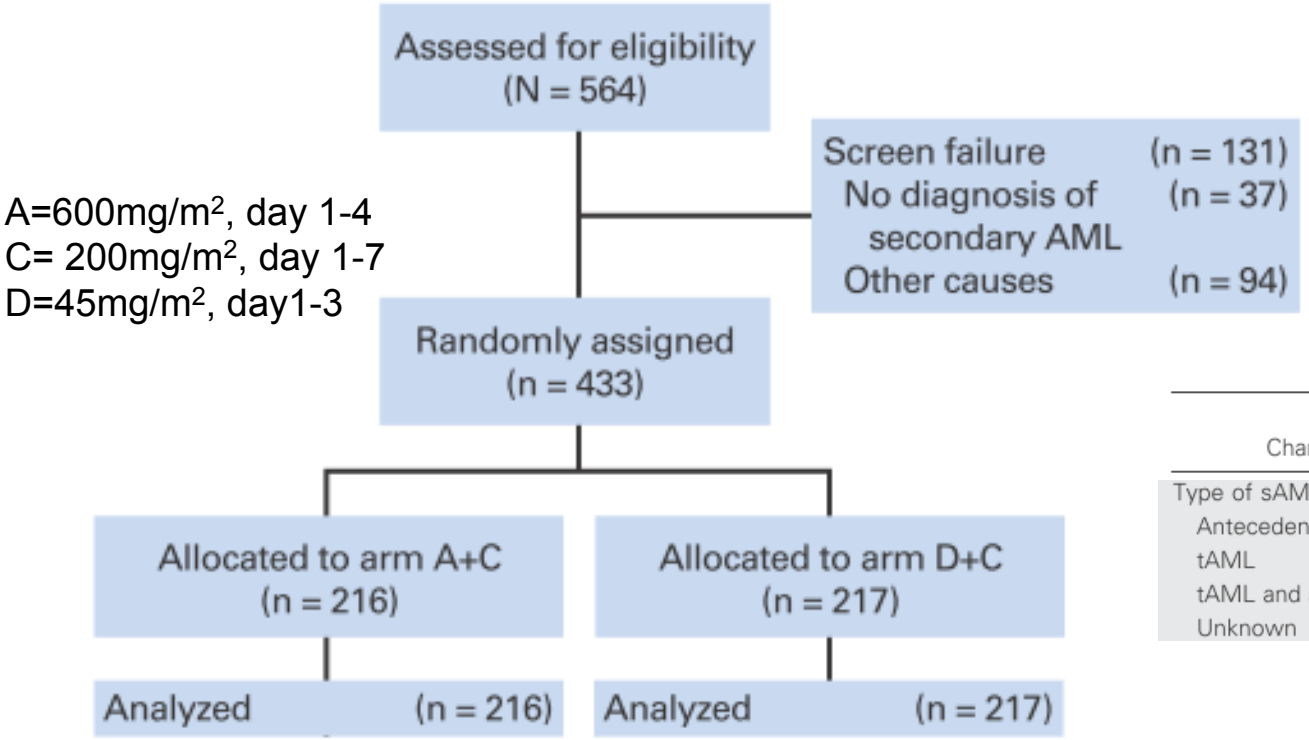
Stein et al, Blood 2016; Stone et al, JCO 2015; Feldman et al, Clin Lymphoma, Myeloma & Leukemia 2014

AMONAFIDE

Phase III open-label randomized study of ARAC in combination with Amonafide or DNR as induction therapy for patients with sAML

- Primary end-point: ORR (CR/CRi) in both arms

A=600mg/m^2, day 1-4
C= 200mg/m^2, day 1-7
D=45mg/m^2, day1-3



Patient Demographic and Clinical Characteristics

Characteristic	A + C Arm (n = 216)	D + C Arm (n = 217)	Total (N = 433)
Type of sAML			
Antecedent MDS	104	111	215
tAML	88	85	173
tAML and antecedent MDS	24	20	44
Unknown	0	1	1

Stone et al, JCO 2015

AMONAFIDE: Phase III open-label randomized study

CR Rate by Treatment Arm

Characteristics	A+C No. (%)	D+C No. (%)	P
All patients	99 (46)	97 (45)	0.81
Age			
< 60	42 (54)	37 (45)	0.27
>60	57 (41)	60 (44)	0.60
Sex			
M	48 (44)	61 (48)	0.54
F	51 (47)	36 (40)	0.28
Type of sAML			
aMDS	43 (41)	44 (40)	0.80
t-AML	49 (56)	49 (58)	0.79
t-AML+aMDS	7 (29)	4 (20)	0.48

Stone et al, JCO 2015

AMONAFIDE: Phase III open-label randomized study

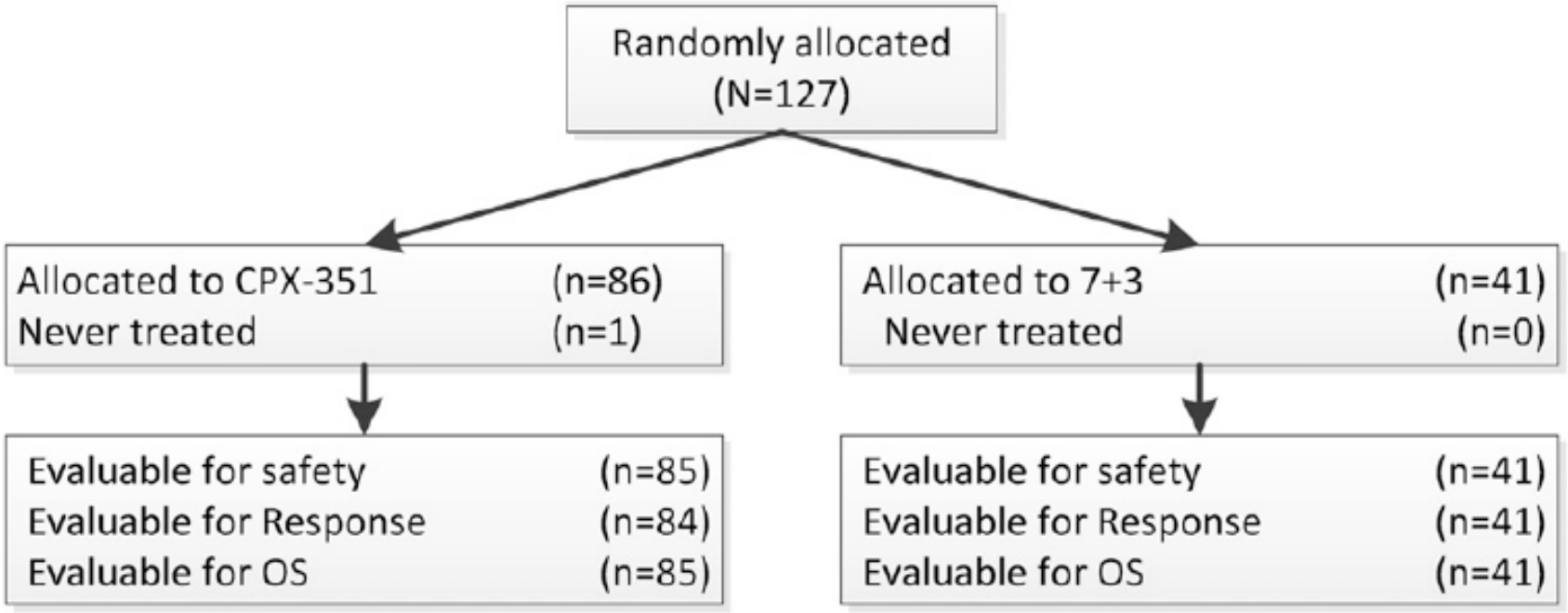
Grade 4 toxicities

Toxicity	A+C No.	D+C No.	Total No.
Cardiac	15	13	28
GI	14	1	15
Hematologic	60	61	121
Hepatic	2	2	4
Infectious disease	24	19	43
Neurologic	4	4	8
Renal	10	7	17
Respiratory	14	15	29

Stone et al, JCO 2015

CPX-351

Phase II trial of CPX-351 vs ARAC/DNR in older adults with untreated AML



CPX-351 = 100U/m^2, day 1-3-5
ARAC = 100mg/m^2, day 1-7
DNR =60mg/m^2, day1-3

Lancet et al, Blood 2014;

CPX-351

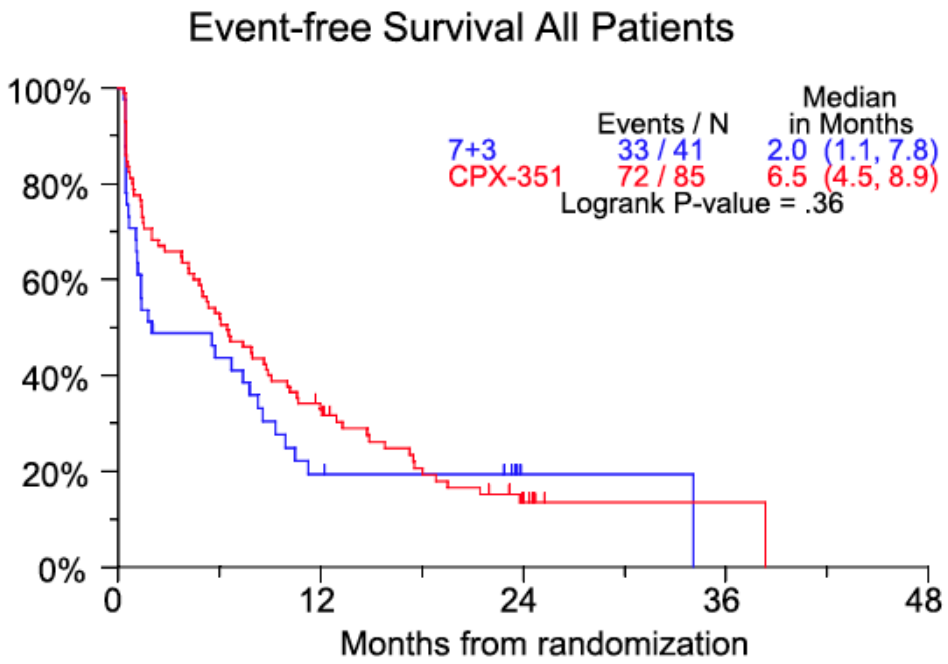
Phase II trial of CPX-351 vs ARAC/DNR in older adults with untreated AML

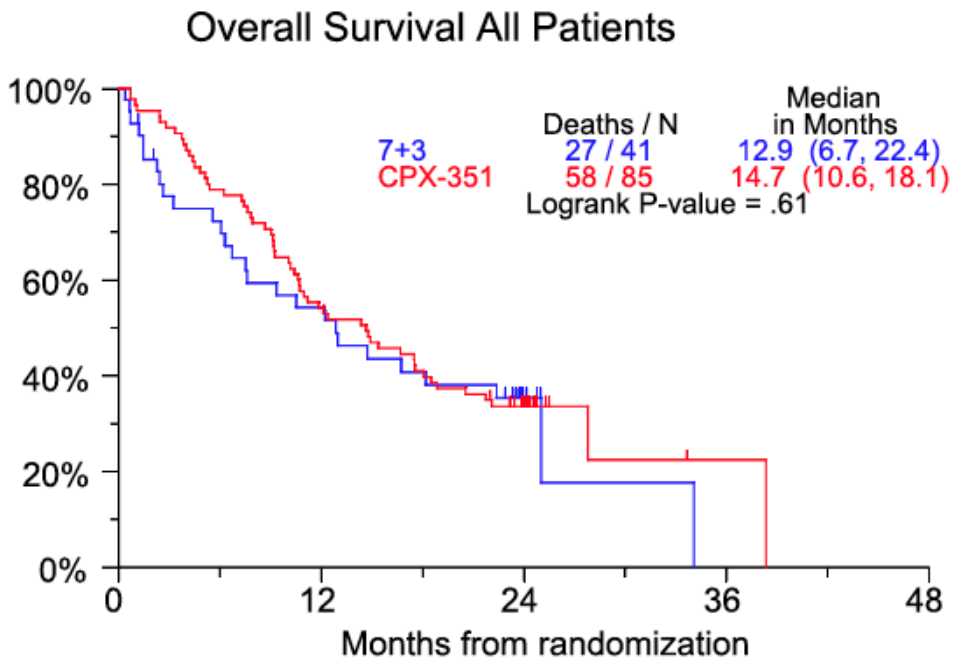
	CPX-351	3+7	P
CR (%)	41/84 (48.8)	20/41 (48.8)	
CRi (%)	15/84 (17.9)	1/41 (2.4)	
Overall (%)	56/84 (66.7)	21/41 (51.2)	0.07

Lancet et al, Blood 2014;

CPX-351

Phase II trial of CPX-351 vs ARAC/DNR in older adults with untreated AML





Lancet et al, Blood 2014;

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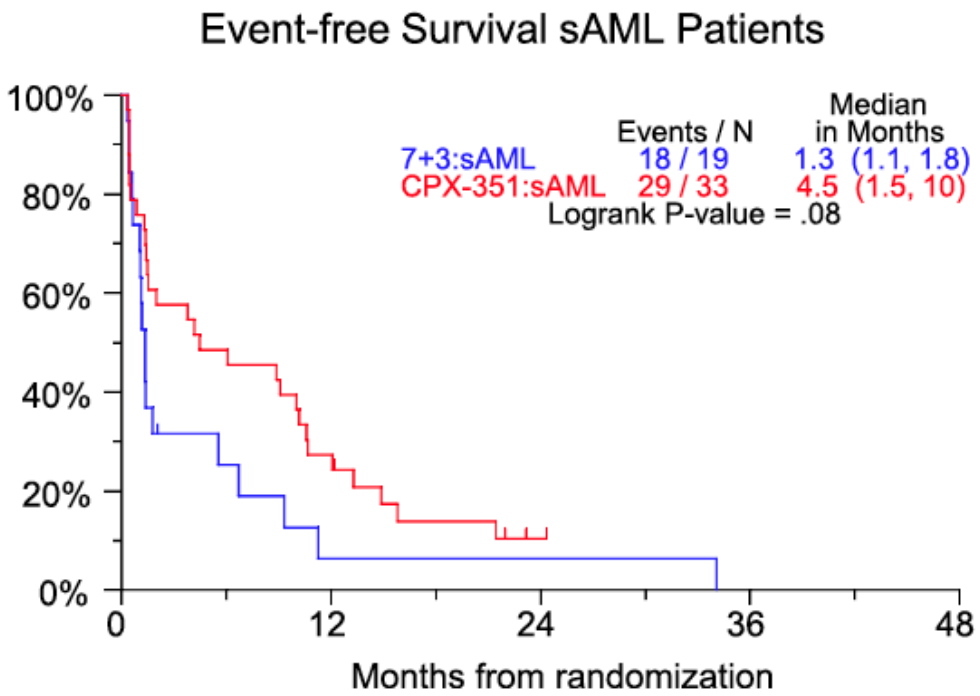
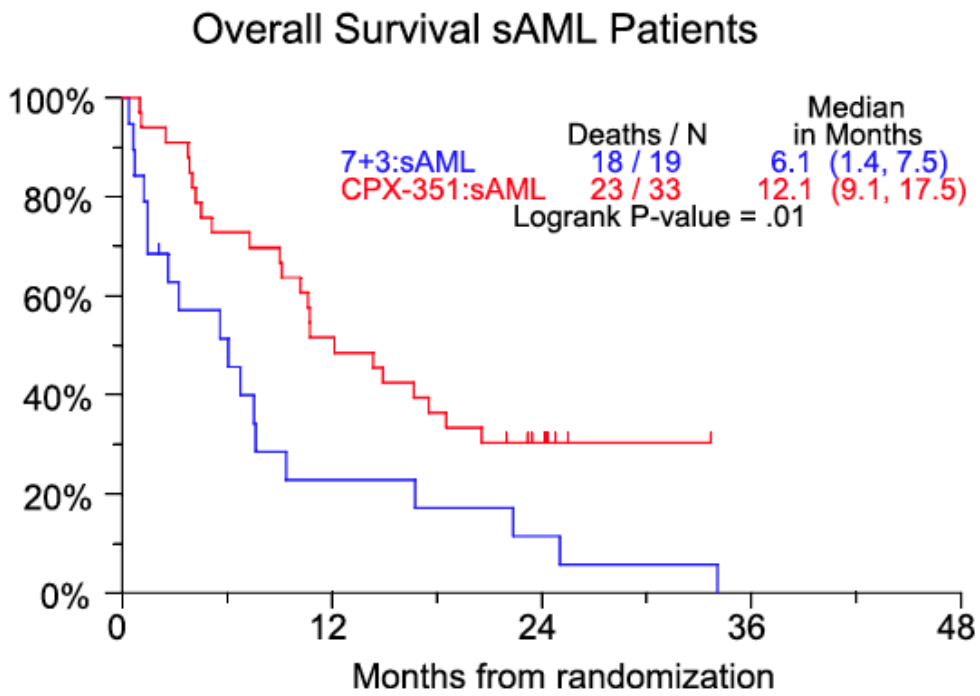




Lancet et al, Blood 2014;

CPX-351 PHASE III STUDY

Open-label, randomized phase 3 study of CPX-351 vs daunorubicin ($60mg/m^2$)-cytarabine for sAML in patients between the ages of 60 and 75 years (NCT01696084)

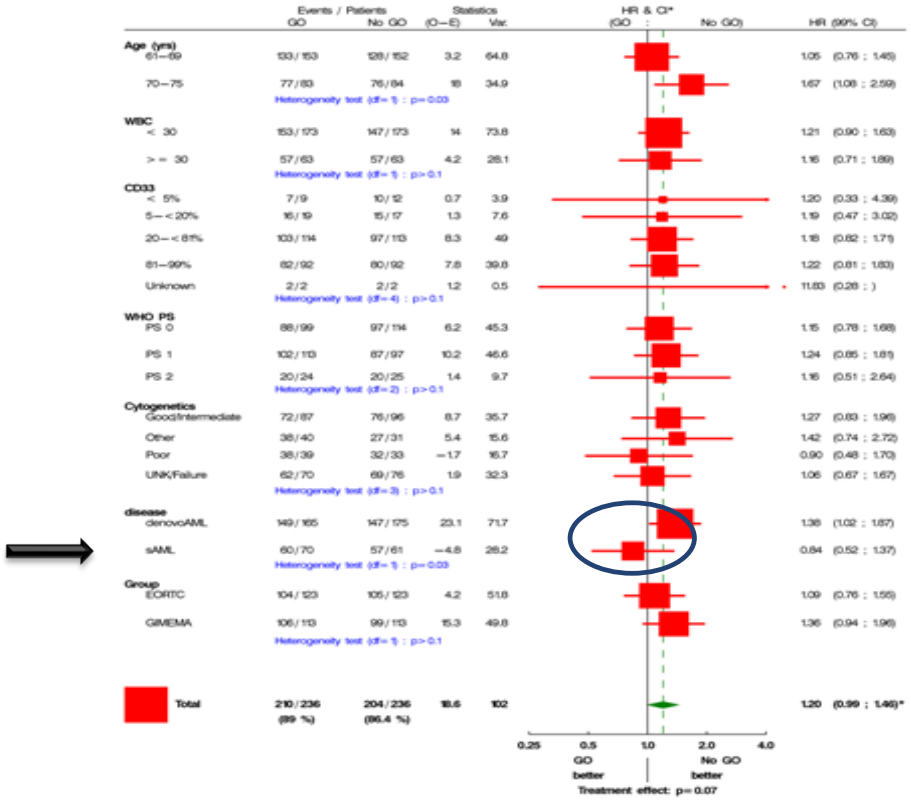
CPX-351: CONSIDERATIONS

- NCRI AML17 trial: DNR 60 mg/m^2 equivalent to 90 (Burnett et al, Blood 2015) but 90 better than 60 in FLT3-ITD^{mut} AML (Russel et al, EHA 2016)
- CPX-351 better than 3+7 in FLT3-ITD^{mut} AML (Lancet, EHA 2016)
- CPX-351equivalent to DNR 90 mg/m^2?
- CPX-351 potential candidate for high-risk AML?

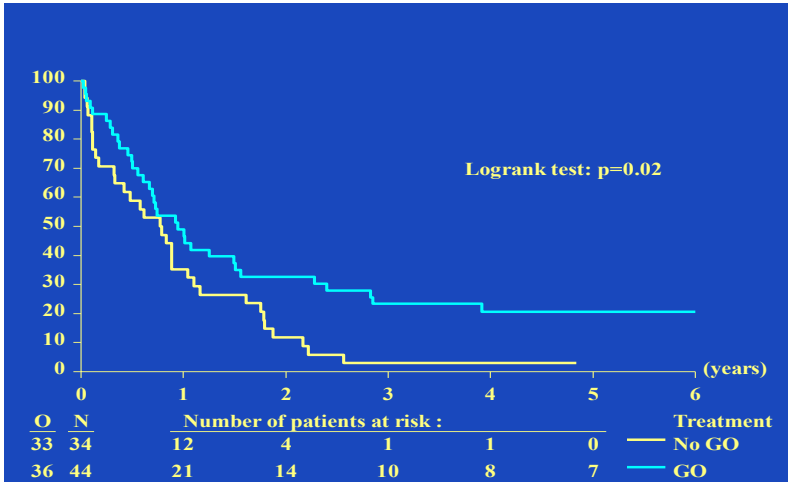
ANTI-CD33 MOABS

Phase III EORTC/GIMEMA Protocol of GO ± iCHT for elderly patients (AML17)

sAML age <70

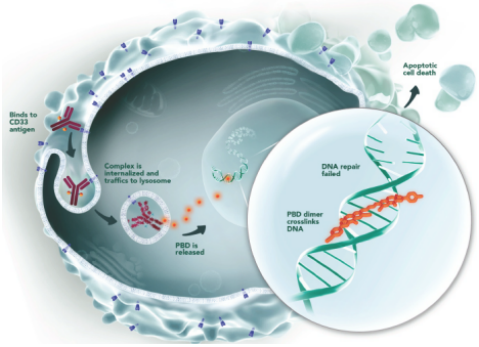


	GO (N=44)	No GO (N=34)	OR/HR (99% CI)	p-value
CR+CRp rate	50.0 %	29.4 %	2.32 (0.71-7.60)	0.10
No response	34.0 %	55.9 %		
Induction death	13.6 %	11.7 %		
2.5 y OS	27.9 %	5.9 %	0.57 (0.30-1.09)	0.02
2.5 y EFS	13.6 %	2.9 %	0.70 (0.37-1.29)	0.049
2.5 y DFS	27.2%	10.0 %	0.67 (0.23-1.96)	0.33



Amadori et al, JCO 2013

ANTI-CD33 MOABS



- SGN-CD33A MoAb (Vadastuximab Talirine)
  - ✓ Fully humanized anti-CD33 MoAb linked with a pyrrolbenzodiazepin dimer (PBD), which binds DNA with high intrinsic affinity
  - ✓ In xenotransplanted mices, it exhibits a potent cytotoxicity against p53 mutated or MDR-1 efflux positive AML cells
  - ✓ It exhibits synergy with HMA to enhance anti-leukemic activity
  - ✓ CR rate 29% in a escalating-phase I study of relapsed/refractory AML
  - ✓ Devoided of liver toxicity (VOD/SOS)

Stein et al, Blood 2016; Feldman et al, Clin Lymphoma, Myeloma & Leukemia 2014,Sutherland et al, Blood 2015

ANTI-CD33 MOABS

Phase I study of SGN-CD33A in combination with an HMA (AZA or DAC) (NCT01902329)

- SGN-CD33A 10 mcg/Kg i.v., every 4 weeks on the last day of HMA
- 53 pts treated with the combination therapy
- Median age 75 (60-87)
- Median BM blast infiltration 46%
- 5 pts (9%) previuosly treated
- 19 pts (36%) with adverse cytogenetics risk

Fathi et al, EHA 2016

ANTI-CD33 MOABS

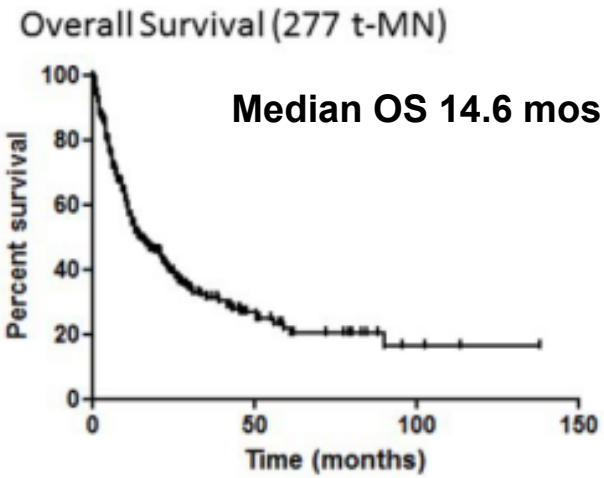
Phase I study of SGN-CD33A in combination with an HMA (AZA or DAC) (NCT01902329)

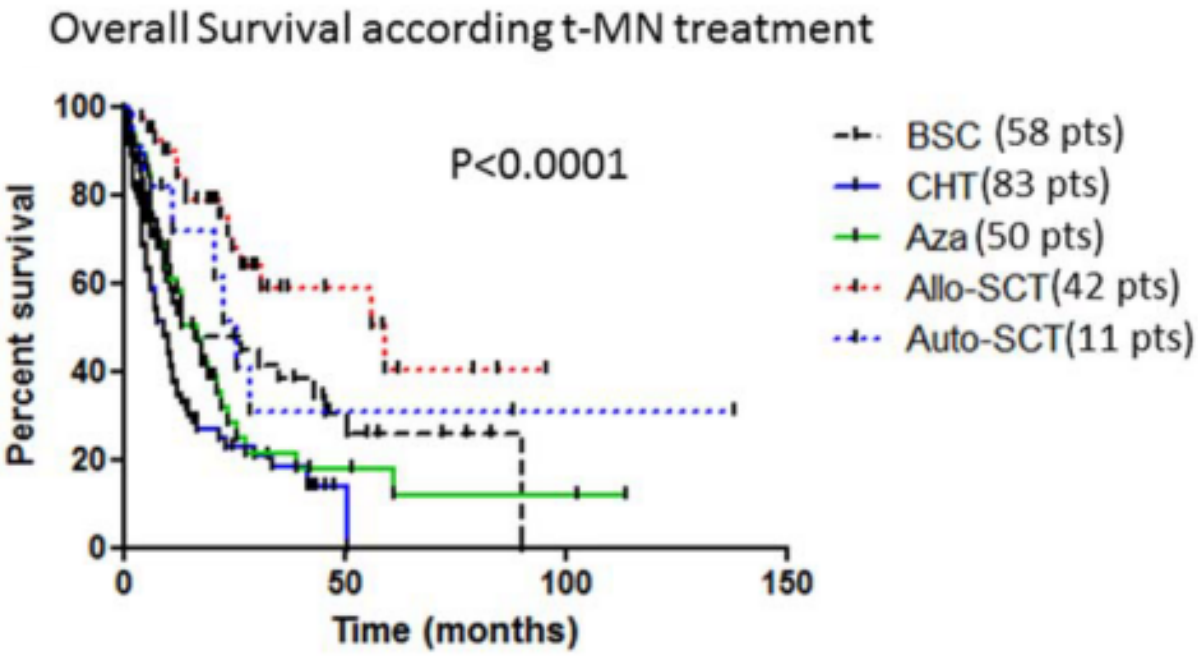
- 49/53 evaluable for efficacy
- 37/49 (76%) achieved CR+CRi+PR (1)
- Median time to response 2 cycles (range 1-4)
- 13/17 (76%) with adverse cytogenetic risk achieved remission
- Median RFS in CR/CRi pts 6.9 months
- 37 pts (70%) still alive with a median follow-up of 4.9 months
- Combination well tolerated and capable of inducing deep and durable remission

Fathi et al, EHA 2016

REPORT FROM THE ITALIAN NETWORK ON T-AML

- 277 patients with t-MN
  - ✓ 157 t-AML
  - ✓ 120 t-MDS





Fianchi et al, AJH 2015

Austrian Azacitidine Registry: outcomes in patients with t-AML

Retrospective analysis of AZA in patients with t-AML vs other WHO-AML subgroups

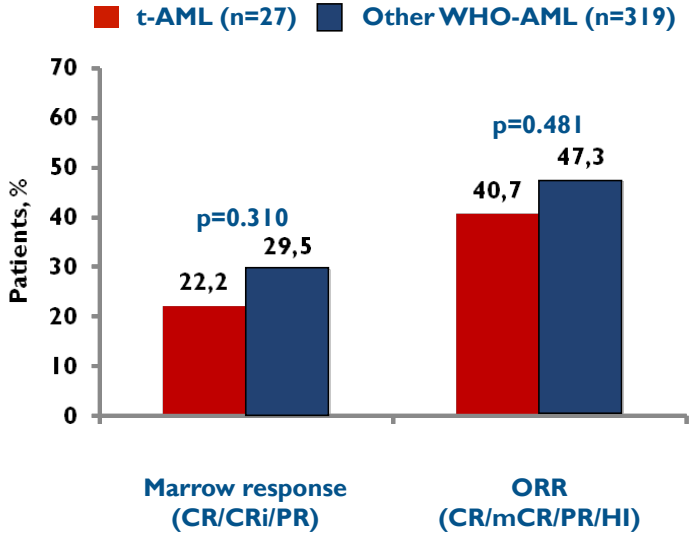
Baseline characteristic	t-AML (n=27)	Other WHO-AML (n=319)	p-value
Median age, years (range) Age ≥75 years, %	73 (48–88) 38	73 (23–93) 45	1.0 0.453
Male/female, %	56/44	59/41	0.779
WBC, % ≥10G/L ≥15G/L	 19 19	 21 14	 0.691 0.408
ECOG PS >2, %	19	4	0.002
>3 comorbidities, %	33	9	<0.001
Cytogenetic risk, % int high	 41 37	 68 20	 <0.001
Median BM blasts, %	26	32	0.431
PB blasts >0%, %	74	64	0.390
LDH >225IU/L, %	56	55	0.975

Pleyer L, et al. Poster presentation at ASH 2014. Abstract 2284

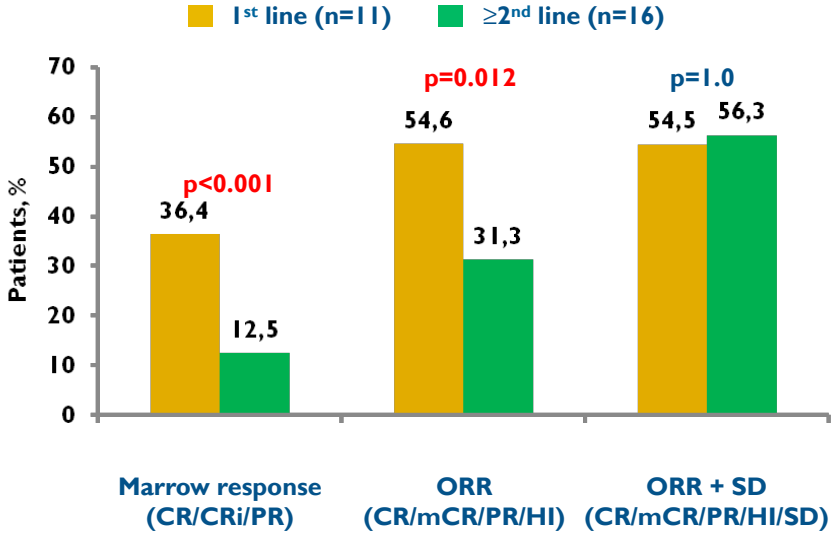
Austrian Azacitidine Registry: outcomes in patients with t-AML

Median AZA cycles, n (range): tAML 4 (1–25); other WHO-AML 4 (1–46)

Response in the ITT population according to AML type



Response in t-AML patients according to line of treatment

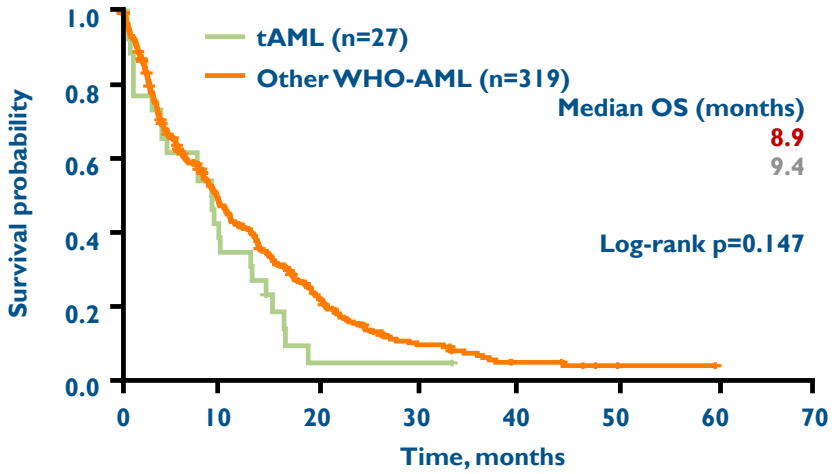


Overall, response to AZA was similar for patients with t-AML and other WHO-AML;
Response to AZA was significantly higher in t-AML patients treated 1st line than ≥2nd line;
When SD was included, response was similar

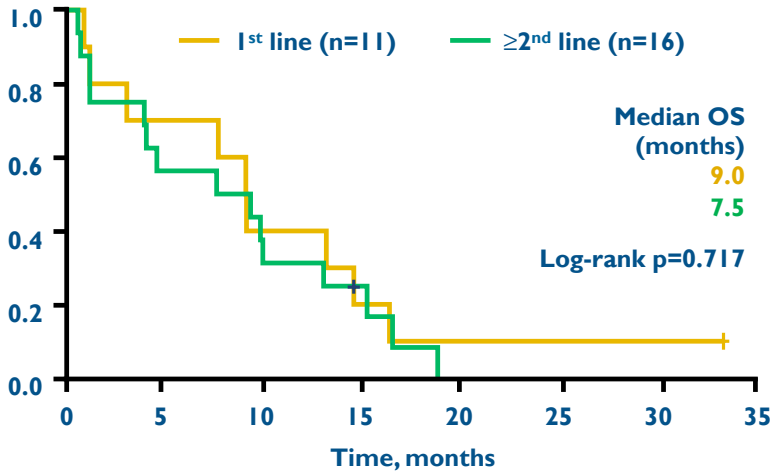
Pleyer L, et al. Poster presentation at ASH 2014. Abstract 2284

Austrian Azacitidine Registry: outcomes in patients with t-AML

OS by presence of tAML (tAML vs other WHO-AML*)



OS by treatment line in patients with tAML (AZA 1st line vs ≥2nd line)

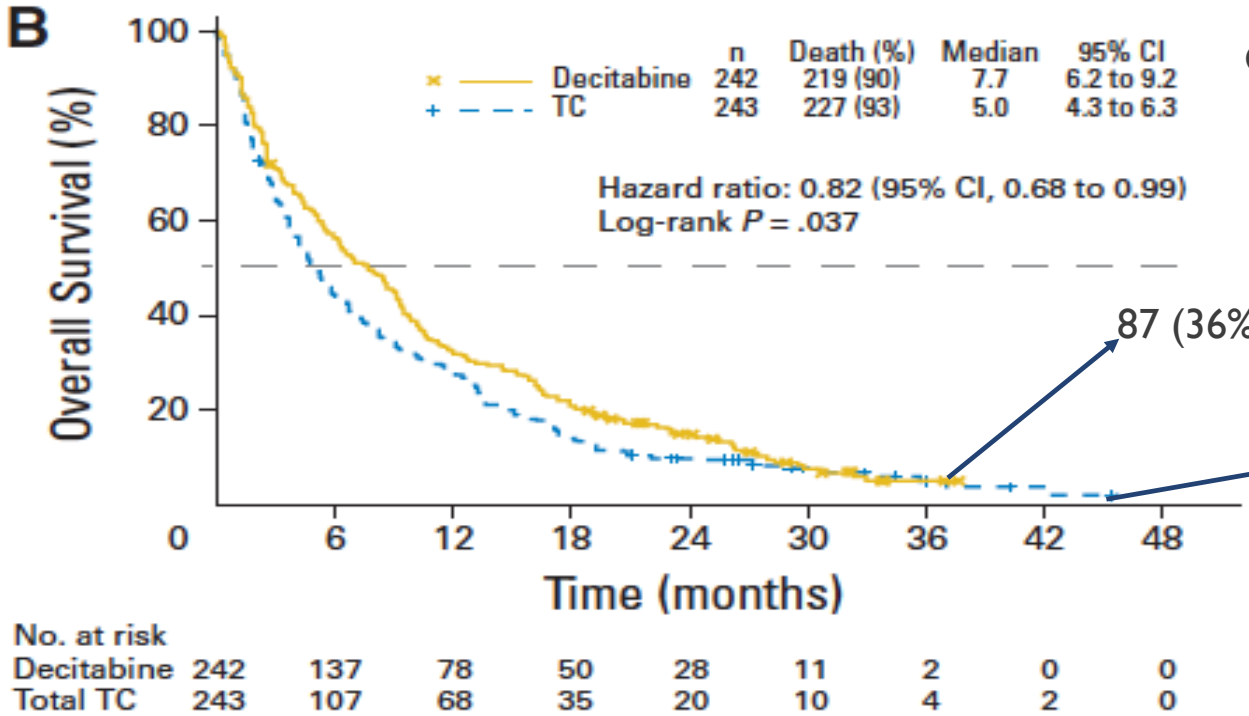


OS was similar for patients with t-AML and patients with other WHO-AML
OS was similar for patients with t-AML treated with AZA 1st line and ≥2nd line

Pleyer L, et al. Poster presentation at ASH 2014. Abstract 2284

DECITABINE PHASE III IN AML

- Elderly AML: median age 73 yrs (64-91 yrs)
- DAC 20 mg/m^2 IV 10 d, every 4 weeks (n=242), vs LDARAC 20 mg/m2/day sc 10 days, every 4 weeks (n=215), or supportive care (n=28)



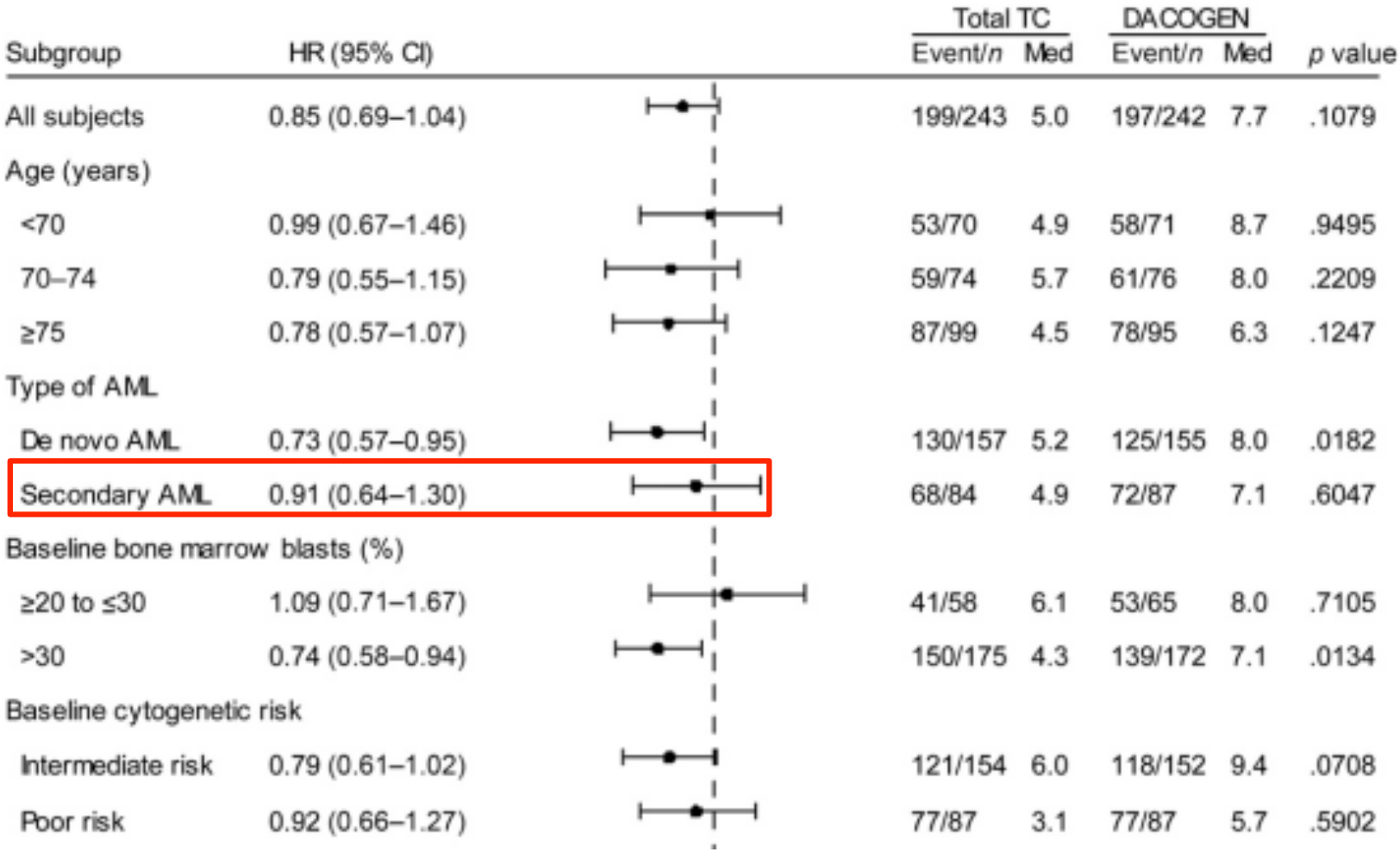
CR: DAC: 18% vs 8%*

87 (36%) pts with sAML

84 (35%) pts with sAML

Kantarjian et al, JCO 2012

PROGNOSTIC FACTORS FOR OS



Subgroup	HR (95% CI)	Total TC Event/*n*	Total TC Med	DACOGEN Event/*n*	DACOGEN Med	*p* value
All subjects	0.85 (0.69–1.04)	199/243	5.0	197/242	7.7	.1079
Age (years)						
<70	0.99 (0.67–1.46)	53/70	4.9	58/71	8.7	.9495
70–74	0.79 (0.55–1.15)	59/74	5.7	61/76	8.0	.2209
≥75	0.78 (0.57–1.07)	87/99	4.5	78/95	6.3	.1247
Type of AML						
De novo AML	0.73 (0.57–0.95)	130/157	5.2	125/155	8.0	.0182
Secondary AML	0.91 (0.64–1.30)	68/84	4.9	72/87	7.1	.6047
Baseline bone marrow blasts (%)						
≥20 to ≤30	1.09 (0.71–1.67)	41/58	6.1	53/65	8.0	.7105
>30	0.74 (0.58–0.94)	150/175	4.3	139/172	7.1	.0134
Baseline cytogenetic risk						
Intermediate risk	0.79 (0.61–1.02)	121/154	6.0	118/152	9.4	.0708
Poor risk	0.92 (0.66–1.27)	77/87	3.1	77/87	5.7	.5902

Kantarjian et al, JCO 2012

CONCLUSION

- t-AML among the most difficult disease to treat
- For patients who achieve an initial CR, ASCT represents the best chance for long-term OS
- Need of continued development of novel agents
  - ✓ Enroll in clinical trials
  - ✓ Cytotoxic agents, MoAbs
  - ✓ Drugs targeting genetic changes (p53 inhibitors, Dot1L inhibitors, combinations of p53 inhibitors and Bcl2 inhibitors)