AML - Underhållsbehandling

SK-kurs 26-28 April 2021

Gunnar Juliusson

Behandling - terminologi

- **Induktion** - Intensivbehandling ledande till remission
  - Oftast en eller två cykler, kan inkludera sviktbehandling
- **Konsolidering** - Intensivbehandling för att upprätthålla remission
  - Hur många cykler? 1 till 3 (- 16).
- **Underhåll** - Lågintensiv behandling för att förebygga recidiv
- **Preemptiv behandling** – tidig sviktbehandling vid molekylär sjukdom
- **Recidivbehandling** – vid fulminant recidiv

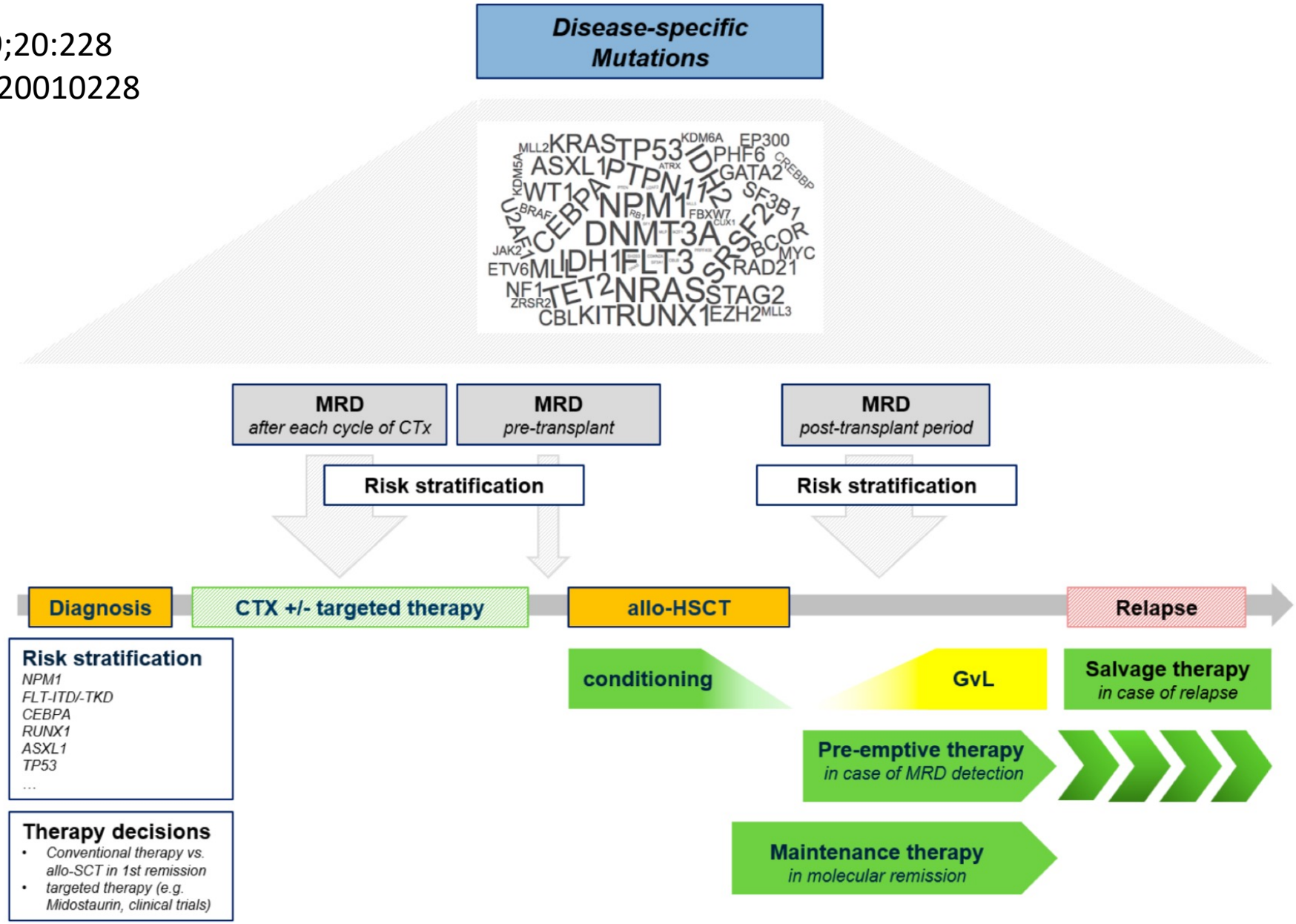
Leuk Lymphoma 1991;3(5-6):355-64. doi: 10.3109/10428199109070279.

A Randomized Comparison of Doxorubicin and Doxorubicin-DNA in the Treatment of Acute NonLymphoblastic Leukemia

C Paul, U Tidefelt, G Gahrton, M Björkholm, M Järnmark, A Killander, E Kimby, J Liliemark, A Lindeberg, R Lindquist, D Lockner, B Lönnqvist, H Mellstedt, K Merk, J Palmblad, C Peterson, B Simonsson, A M Stalfelt, C Sundström, B Wadman, C Wedelin, A M Udén, G Öberg, Å Öst. PMID: 27467426 DOI: 10.3109/10428199109070279

In the light of previous findings that treatment of leukemia patients with DNA-linked doxorubicin gave higher doxorubicin concentrations in leukemic cells than treatment with doxorubicin alone, the Leukemia Group of Middle Sweden performed a randomized clinical trial to compare the effects of doxorubicin and doxorubicin-DNA in patients with acute non-lymphoblastic leukemia. One hundred and twenty consecutive patients within the age range 15 to 60 years were randomized to one of three treatment groups. In two of these, remission induction treatment was performed with prednisolone, vincristine, ara-C and thioguanine combined with either doxorubicin or doxorubicin-DNA. Patients entering a complete remission received intensive consolidation during 16 months with 4 courses each of doxorubicin (+/ - DNA)/ara-C, doxorubicin (+/ - DNA)/azacytidine, ara-C and amsacrine. The third treatment group followed a protocol from a previous study with daunorubicin and ara-C for induction therapy and a less intensive maintenance therapy. No further patients were assigned to this "control" group after 3 years or to the two other groups after 6 years. This report is based on a follow-up 31 months thereafter. The overall rate of complete remission was 67% and the mean time to complete remission was 71 days, with no differences between the treatment groups. Patients treated with the doxorubicin-DNA conjugate had a significantly longer survival [median for all patients 27.2 months ($p < 0.01$) and for patients in CR 47.0 months ($p < 0.025$)] and longer duration of first remission (median 23.6 months, $p < 0.025$) than the other groups. There were significantly fewer reports of cardiotoxicity ($p < 0.05$) and severe intestinal toxicity ($p < 0.02$) in patients treated with the doxorubicin-DNA conjugate and there was a tendency towards less hepatic ($p < 0.08$) and renal toxicity ($p < 0.08$). The frequency of myelosuppression, fever and infectious complications was similar in all three groups. Complex binding to DNA appears to increase the therapeutic effects and reduce some toxic effects of doxorubicin in patients with ANLL.

Rautenberg et al,
Int J Mol Sci 2019;20:228
doi:10.3390/ijms20010228



Underhållsbehandling AML (utan/efter SCT)

- **Kemoterapi**
- **Immunterapi**
  - Cytokiner
    - IL2 +/- Histamin
    - IFN
  - Lenalidomid
  - Vaccination
    - BCG, WT1 (Anguille S, et al. Blood 2017;130:1713-21)
  - Allogen Stamcellstransplantation
- **Hypometylering**
  - Azacytidin / Decitabin
- **Målriktad terapi**
  - *FLT3*-hämmare
  - *IDH*-hämmare, dasatininb *(KIT)*
- **Andra**
  - Venetoclax, PD1-hämmare, HDAC hämmare

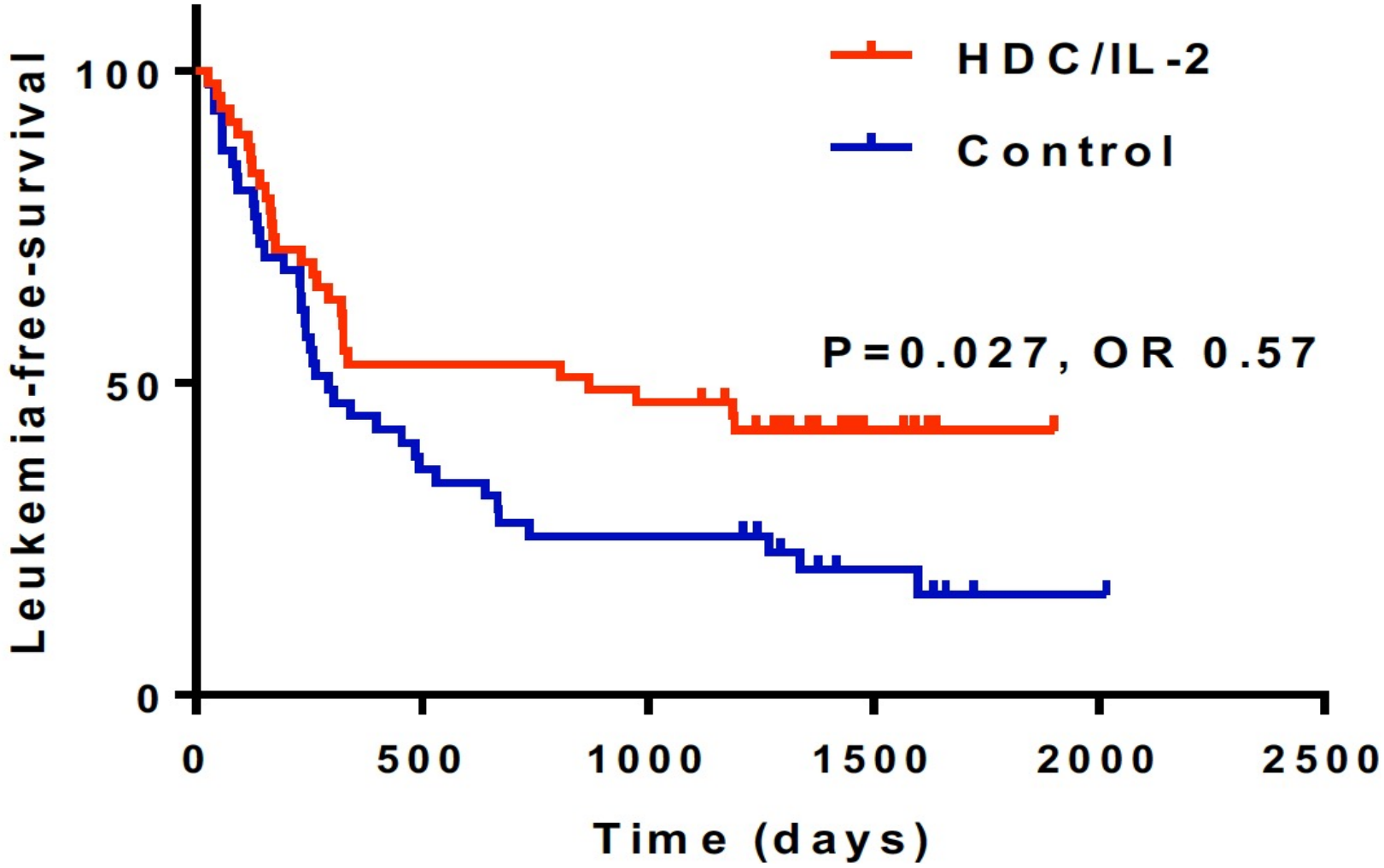
Immunterapi som underhåll

TABLE 3 Studies/trials which include immunotherapy as maintenance therapy

Trial	Age	Number of patients treated with maintenance therapy	Maintenance treatment regimen (s)	Median follow-up	Disease free survival (DFS)	Overall survival (OS)
Cancer and leukemia group B study 9720[a]	60-81 years	81	14-day cycles of low-dose rIL-2	NR	6.1 months	14.7 months
ELAM02[b]	<18 years	154	Monthly courses of IL-2 for 1 year	5-years	64%	NR
Multileft trial[39]	18-84 years	160	10 consecutive 3-week cycles of histamine dihydrochloride plus IL-2	36 months	34%	46%
ALFA-9801 study[c]	50-70 years	161	IL-2 for 12 months	4-years	NR	41%
Finnish study[33]	16-59 years	15	IFN-α administration until relapse or for 3 years	5-years	15 months	22%
United Kingdom medical research council AML11 trial[d]	>55 years	182	IFN-α maintenance for one year	5-years	20%	21%
English group[e]	Any	20	Bacille Calmette-Guérin (BCG) vaccination	NR	35 weeks	90 weeks

Am J Hematol 2019;94:1254

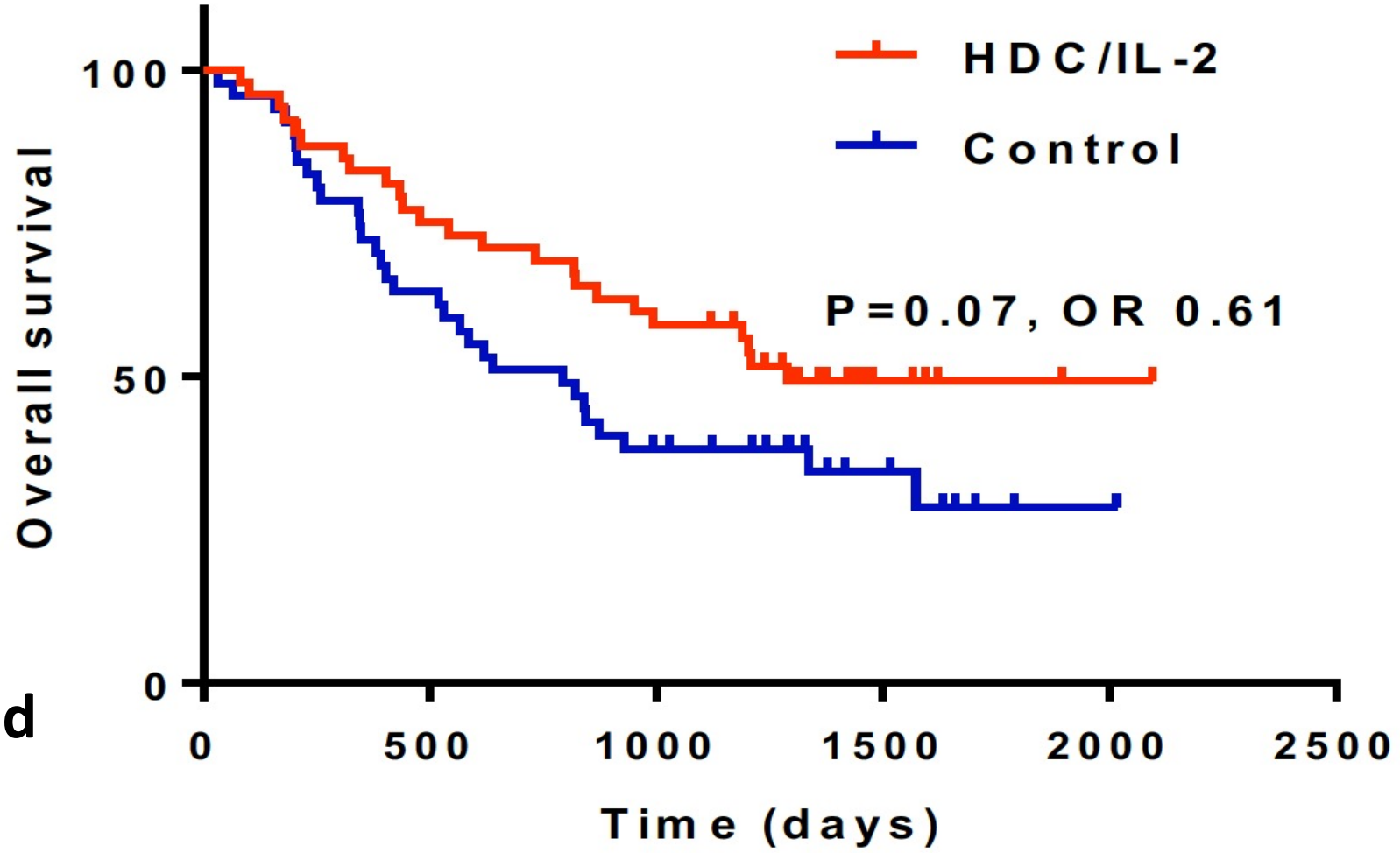
Maintenance with low dose IL-2 and Histamine



AML
CR1
50-70 yrs

Brune et al.
Blood 2006;
108(1):88-96

Maintenance immunotherapy with IL-2 and Histamine



AML
CR1
50-70 yrs

Bäst effekt vid
AML FAB M5

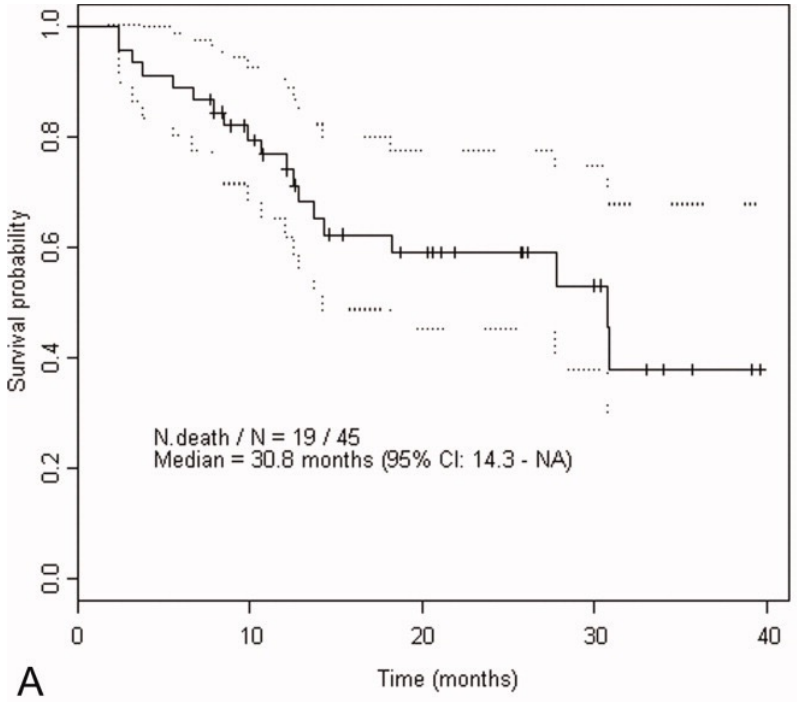
Brune et al.
Blood 2006

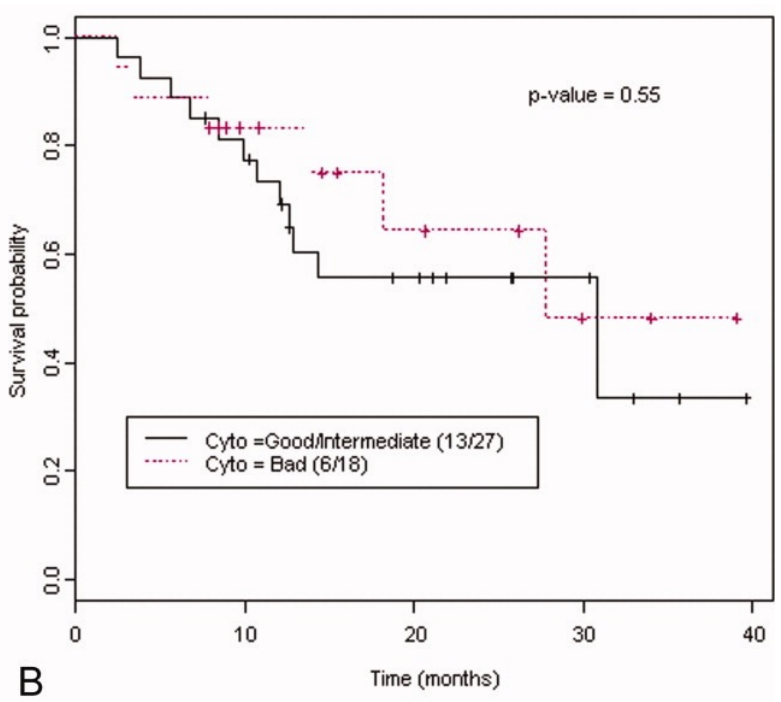
HMA
Lenalidomid

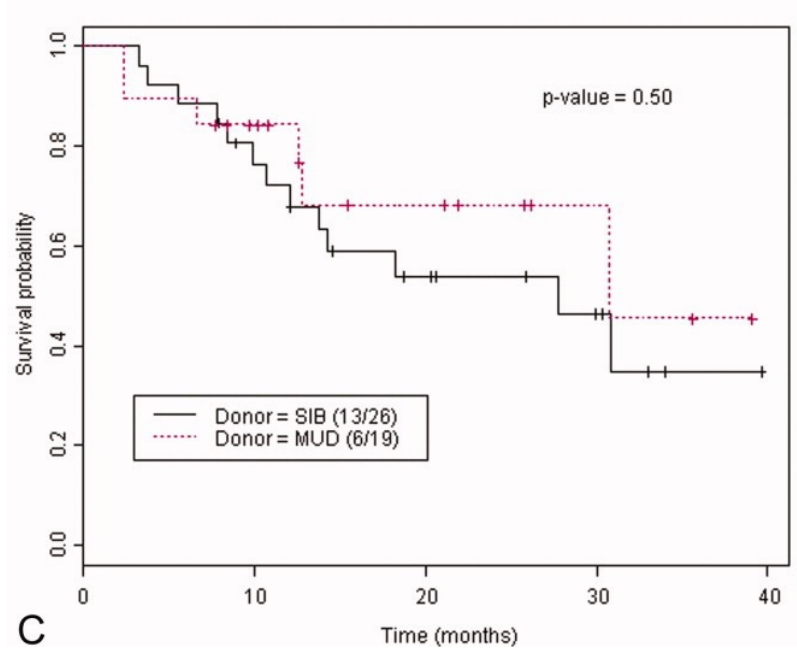
TABLE 2 Studies/trials which include hypomethylating agents (HMAs), lenalidomide and the association between these drugs as maintenance therapy in post consolidation and post-transplant phases

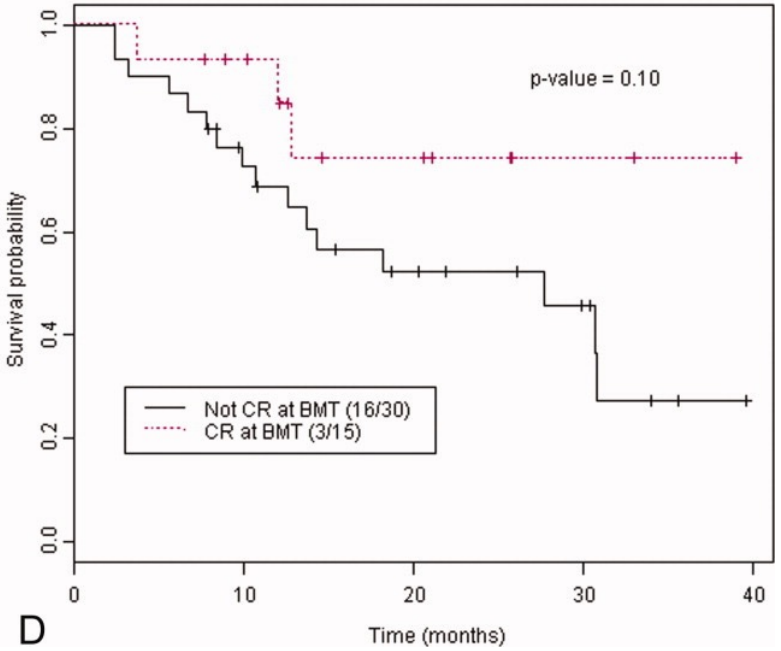
trial	Age	Post-consolidation or post alloHSCT treatment	Number of patients treated with maintenance therapy	Maintenance treatment regimen (s)	Median follow-up	Disease free survival (DFS)	Overall survival (OS)
HOVON97[22]	>65 years	Post-consolidation	56	5-azacitidine until relapse for a maximum of 12 weeks	12 months	63%	NR
UK NCRI AML16 TRIAL[a]	>65 years	Post-consolidation	226	5-azacitidine for nine 6-week courses	5-years	NR	24%
Japanese trial[27]	17-65 years	Post-alloHSCT	10	5-azacitidine and GO every 4 weeks for up to 4 cycles	12 months	70%	60%
MDACC trial[b]	24.3-73.8 years	Post-alloHSCT	45	Low-doses 5-azacitidine for 4 cycles	12 months	NR	77%
CALGB 10503[25]	<60 years	Post-consolidation	134	Decitabine for 8 cycles	12 months 3-years	79% 54%	–96% –68%
MDACC trial[26]	24–79 years	Post-consolidation	20	Decitabine for maximum 12 cycles	44.9 months	NR	45%
Pursic et al[28]	21-68 years	Post-alloHSCT	24	Decitabine for maximum 8 cycles	2-years	56%	48%
Australasian leukaemia and lymphoma group[29]	18-65 years	Post-consolidation	28	Lenalidomide for 12 months	2-years	78% (favorable karyotype), 48% (intermediate karyotype), 75% (*NPMc* mutation), 31% (*FLT3-ITD*) and 53% (*FLT3-ITD* and *NPMc* double negative)	91%
FILO[30]	>60 years	Post-consolidation	65	12 cycles of alternating 5-azacitidine and lenalidomide	2-years	12.3%	21.4%
Australian trial[c]	43-79 years	Post-consolidation	40	Lenalidomide in combination with 5-azacitidine	NR	12 months for patients in first CR, 11 months for patients in second CR	20 months for patients in first CR

Molica et al.
Maintenance therapy in AML: The past, the present and the future.
Am J Hematol 2019;94:1254









Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome

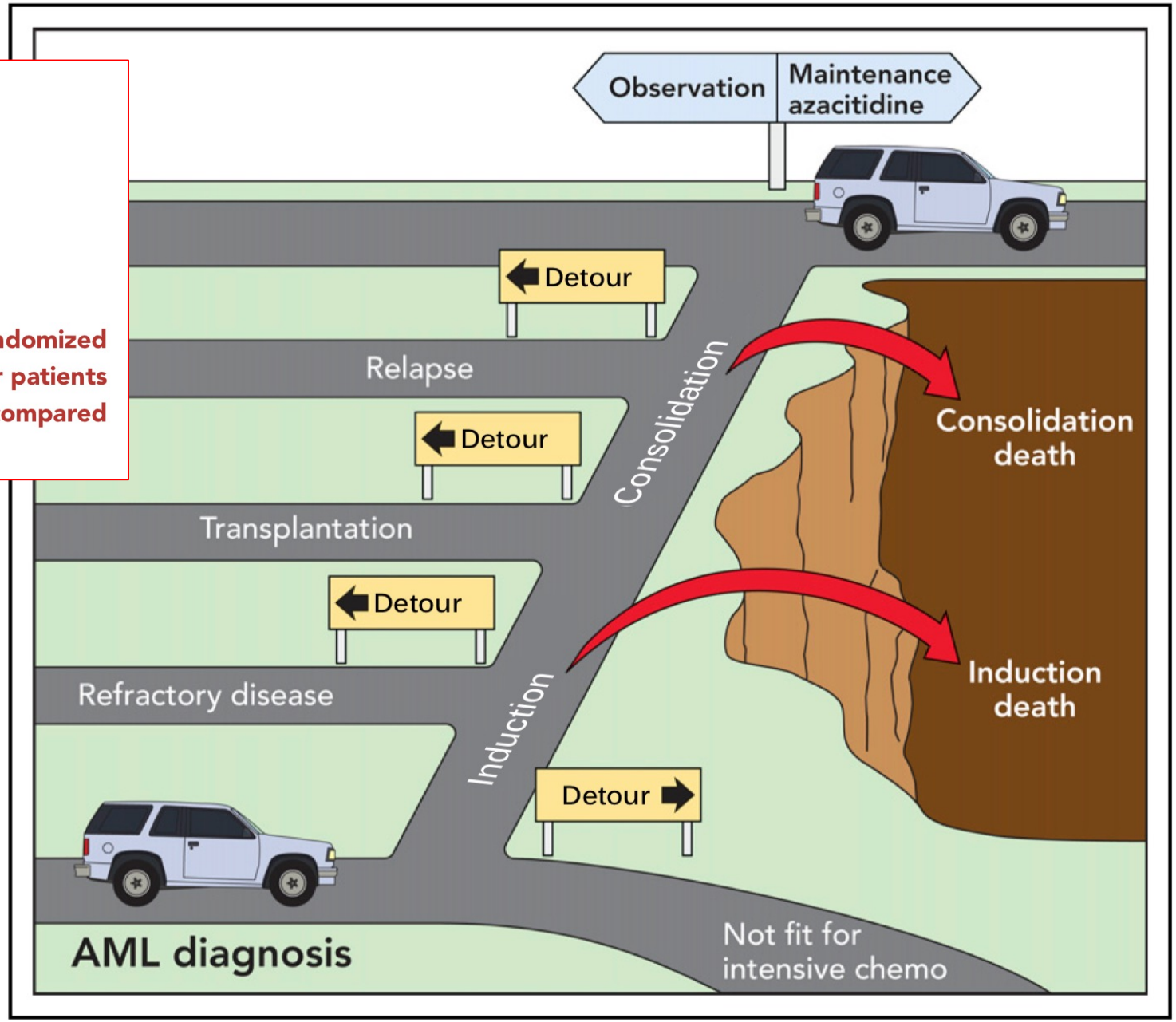
Cancer 2010; 116(23): 5420-5431
DOI: (10.1002/cncr.25500)
MD Anderson Houston

Comment on Huls et al, page 1457

Maintenance therapy for AML: are we there yet?

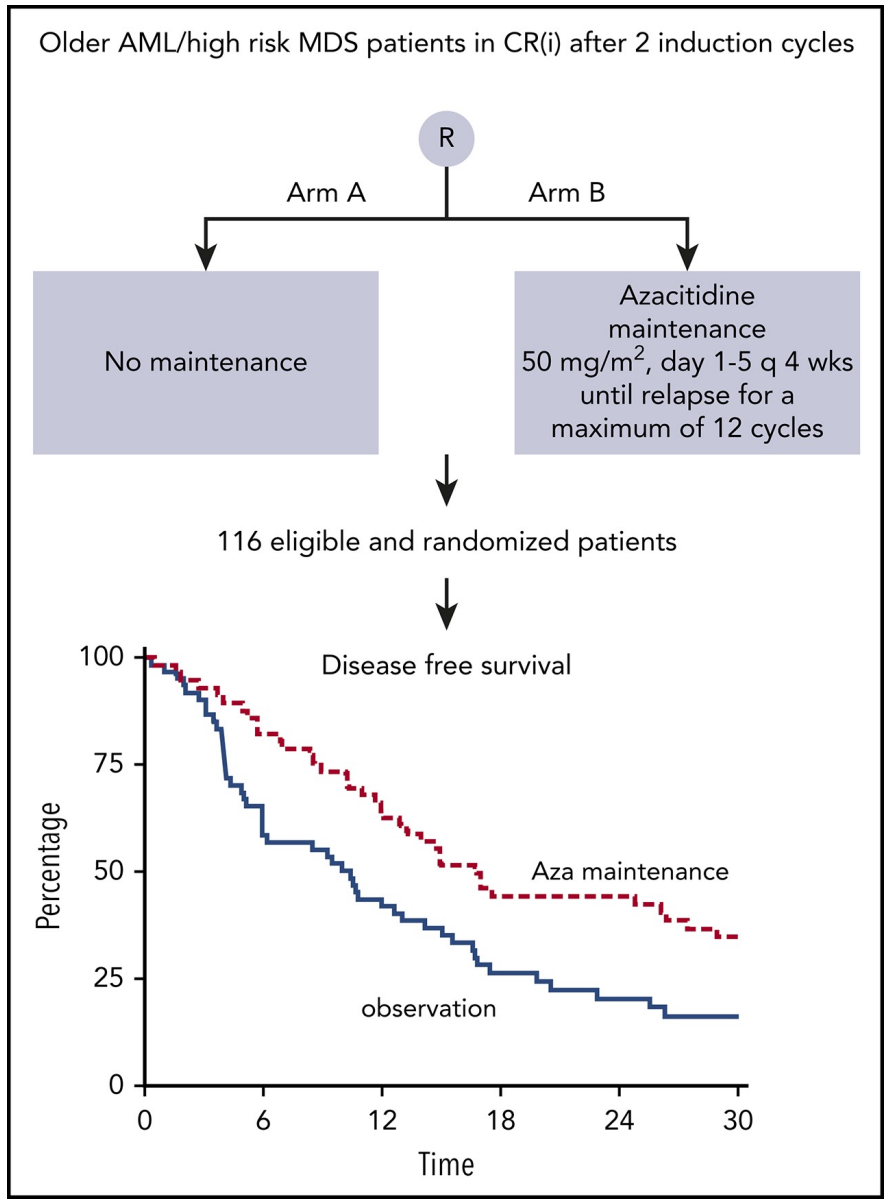
Andrew H. Wei | The Alfred Hospital; Monash University

In this issue of *Blood*, Huls et al present positive results from a randomized study (HOVON97) showing that disease-free survival (DFS) in older patients with acute myeloid leukemia (AML) was improved by azacitidine compared with postremission observation.[1]



The hazardous and detour-laden road to maintenance therapy in AML. chemo, chemotherapy. Professional illustration by Patrick Lane, ScEYEnce Studios.

HOVON 97



Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients

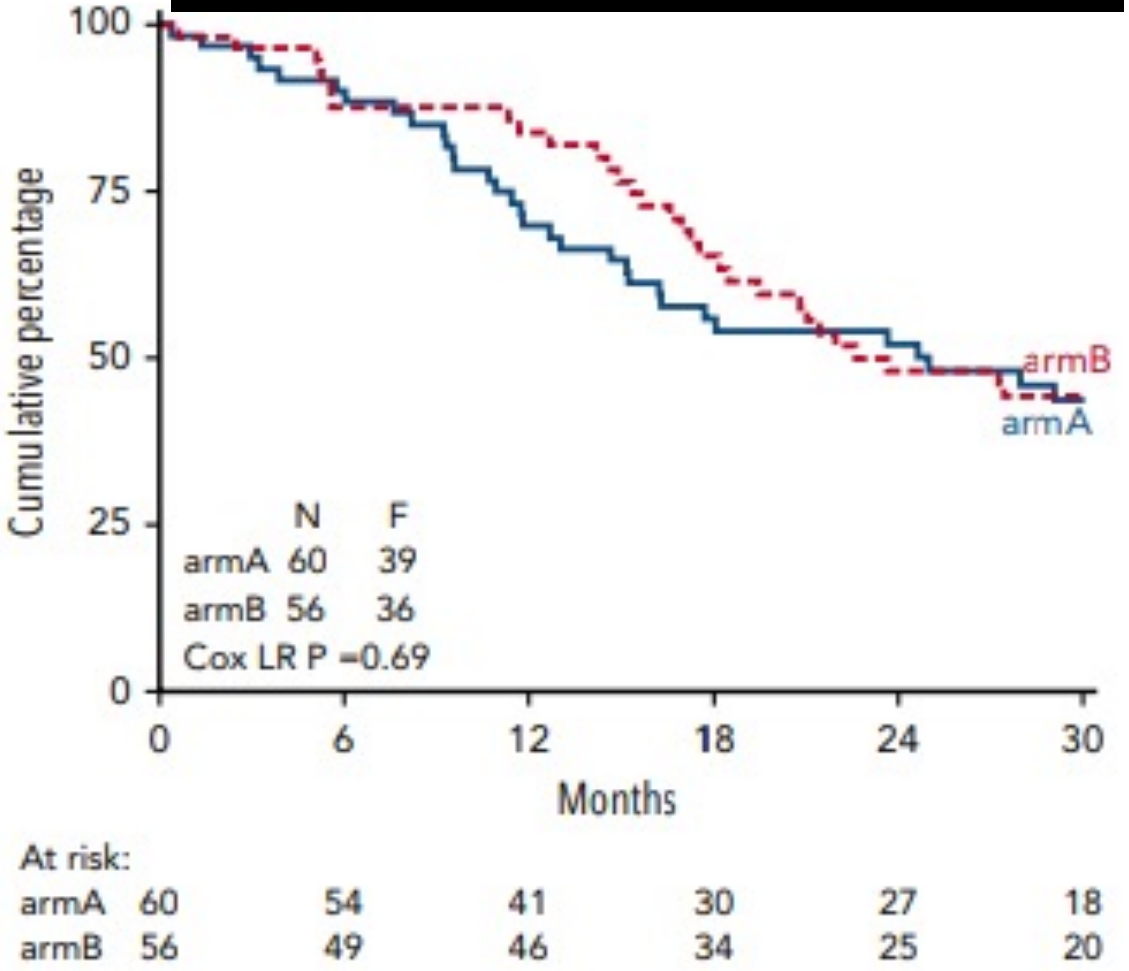
AML / MDS RAEB (IPSS ≥ 1.5)
≥ 60 yrs of age
< 5% BM blasts after
2 cycles intensive chemo
(N = 116)

Gerwin Huls, …, Gert J. Ossenkoppele, Edo Vellenga, Bob Löwenberg, the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON).

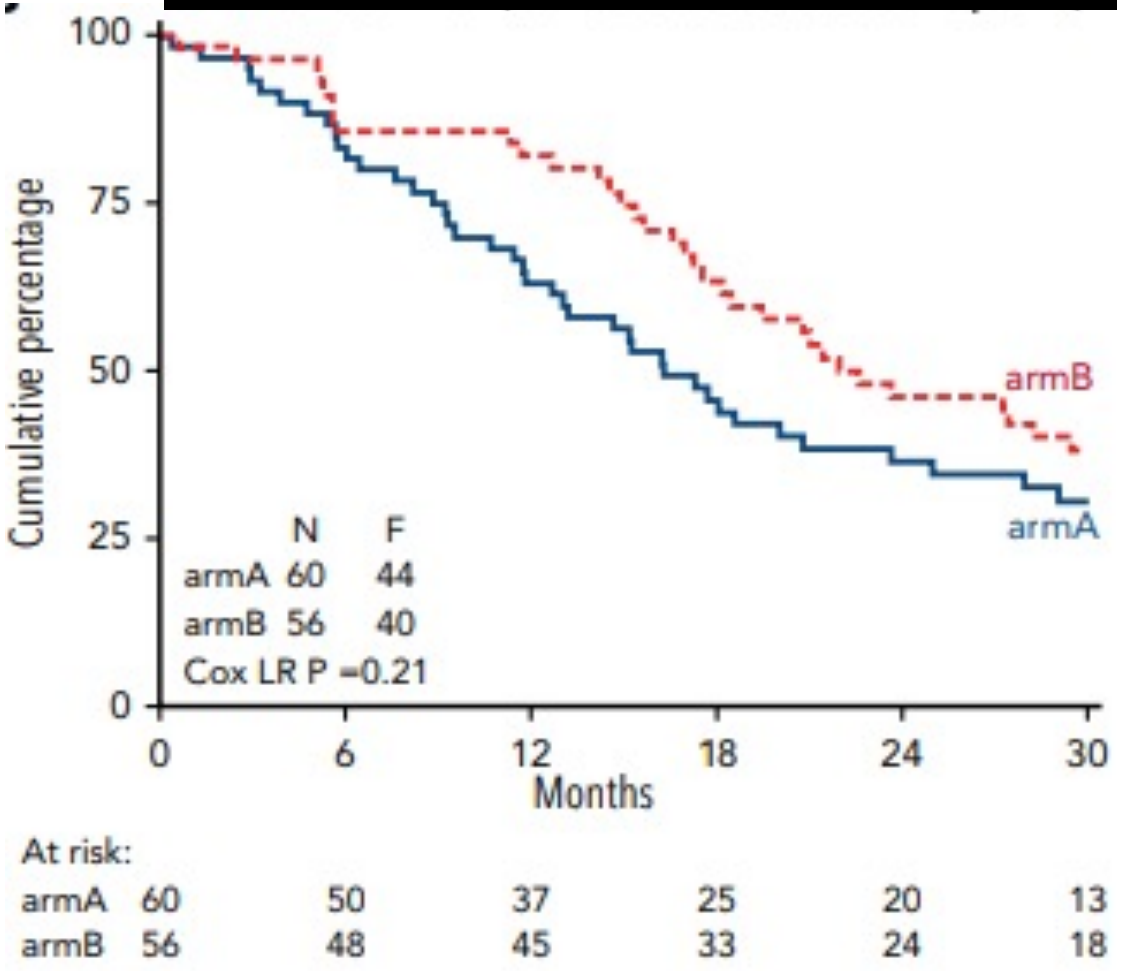
Blood, 2019; 133(13):1457

Maintenance Azacitidine in AML (HOVON 97): OS

OS, all randomized patients (N = 116)



OS after censoring 15 patients at HCT



Huls. Blood. 2019;133:1457.

ORIGINAL ARTICLE

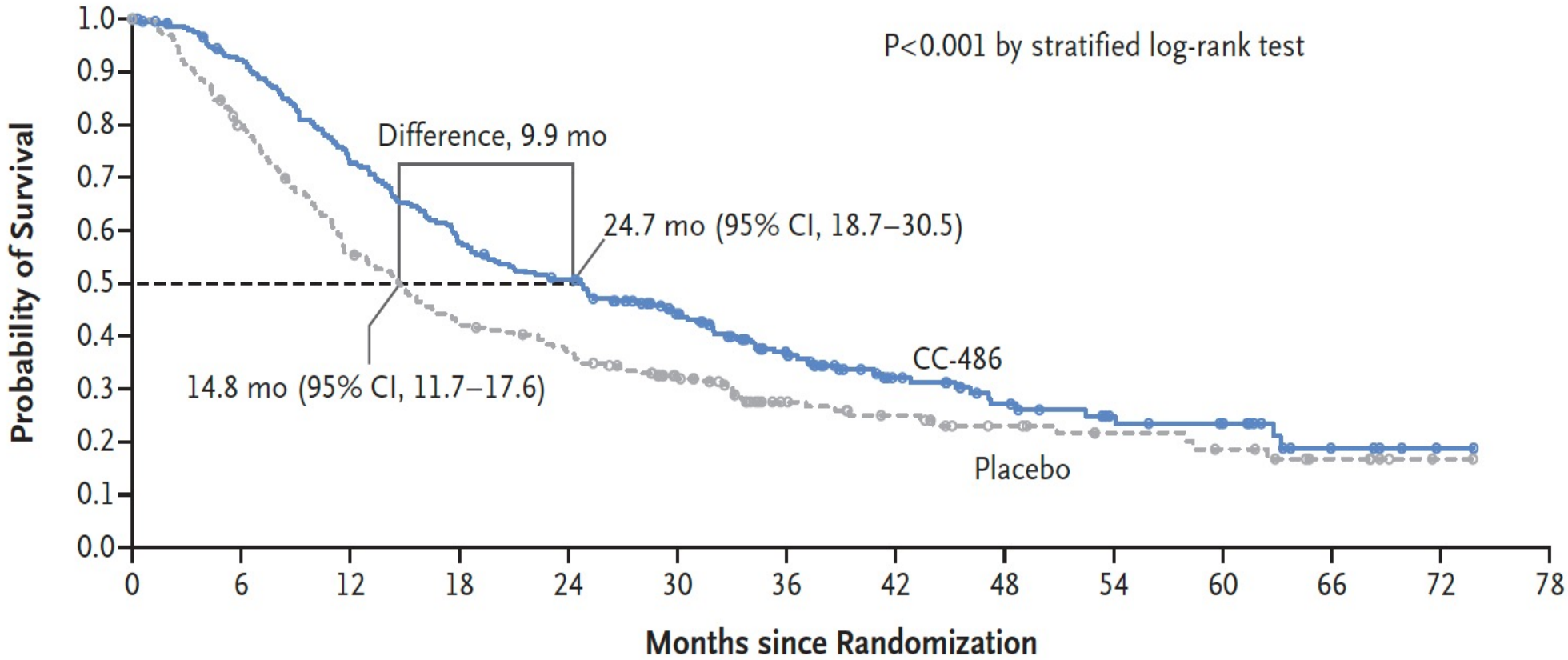
Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

A.H. Wei, H. Döhner, C. Pocock, P. Montesinos, B. Afanasyev,* H. Dombret, F. Ravandi, H. Sayar, J.-H. Jang, K. Porkka, D. Selleslag, I. Sandhu, M. Turgut, V. Giai, Y. Ofran, M. Kizil Çakar, A. Botelho de Sousa, J. Rybka, C. Frairia, L. Borin, G. Beltrami, J. Čermák, G.J. Ossenkoppele, I. La Torre, B. Skikne, K. Kumar, Q. Dong, C.L. Beach, and G.J. Roboz, for the QUAZAR AML-001 Trial Investigators†

Just approved by CHMP

N Engl J Med 383;26:2526-2537, December 24, 2020

A Overall Survival



No. at Risk

CC-486	238	213	168	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	127	96	82	58	34	27	19	14	11	6	1	0

REGULAR ARTICLE

blood advances

A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients

Betül Oran,[1] Marcos de Lima,[2] Guillermo Garcia-Manero,[3] Peter F. Thall,[4] Ruitao Lin,[4] Uday Popat,[1] Amin M. Alousi,[1] Chitra Hosing,[1] Sergio Giralt,[5] Gabriela Rondon,[1] Glenda Woodworth,[1] and Richard E. Champlin[1]

[1]Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX; [2]University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH; [3]Department of Leukemia and [4]Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX; and [5]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Blood Advances 2020;4(21):5580

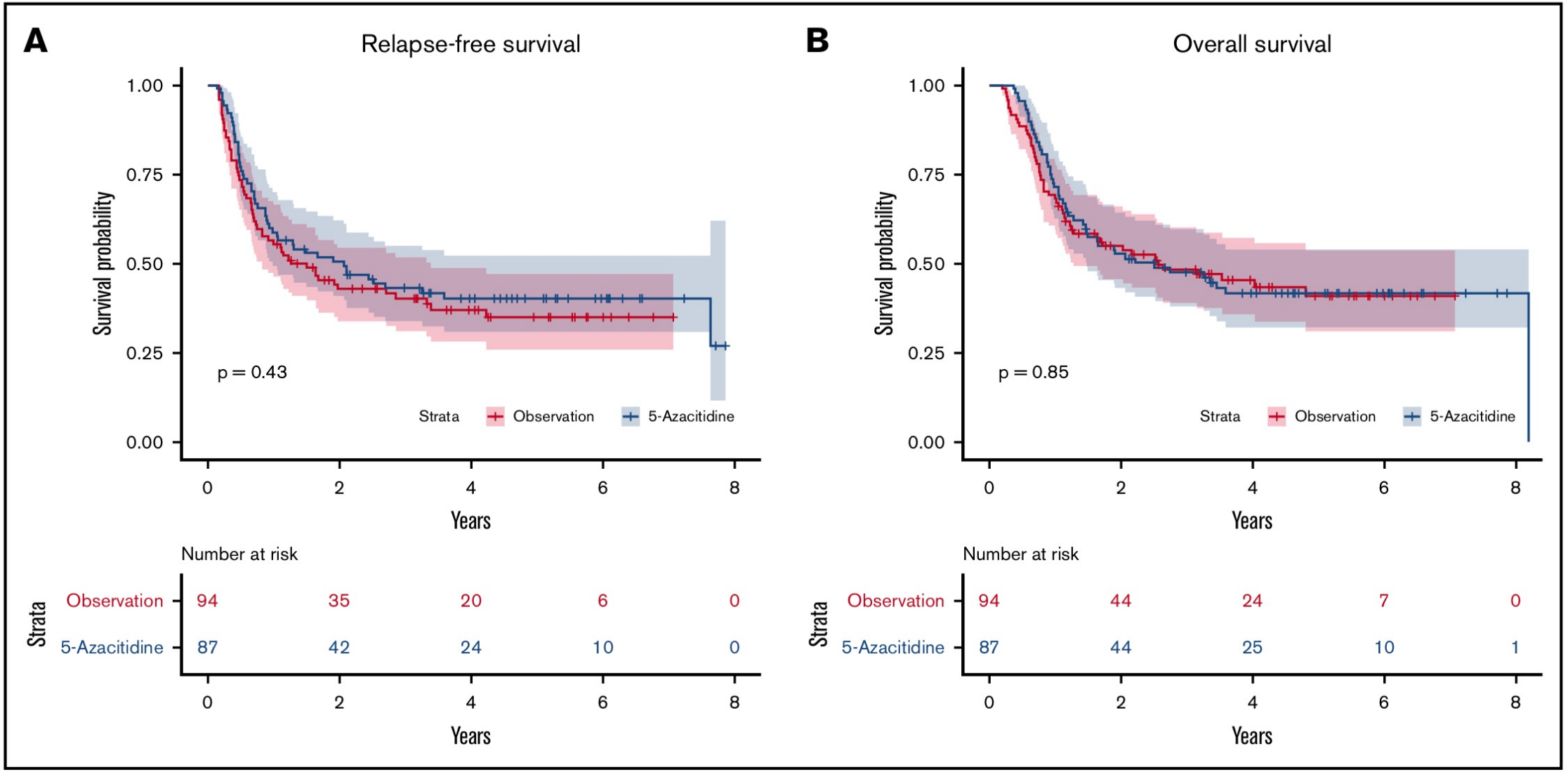


Figure 2. Relapse free and overall survial. The use of subcutaneous 5-azacitidine as posttransplant maintenance strategy was not associated with improved relapse-free survival (A) and overall survival (B) compared with observation arm.

Underhåll vid *FLT3*-ITD

- Midostaurin registrerat som underhåll utifrån RATIFY-studien
  - få patienter fick underhåll – ingen påvisad nytta
  - RATIFY <60 år
  - Tyska data 60-70 år ‘feasible’ men ingen kontrollgrupp
- I Sverige
  - AlloSCT i CR1 för de flesta <70 år

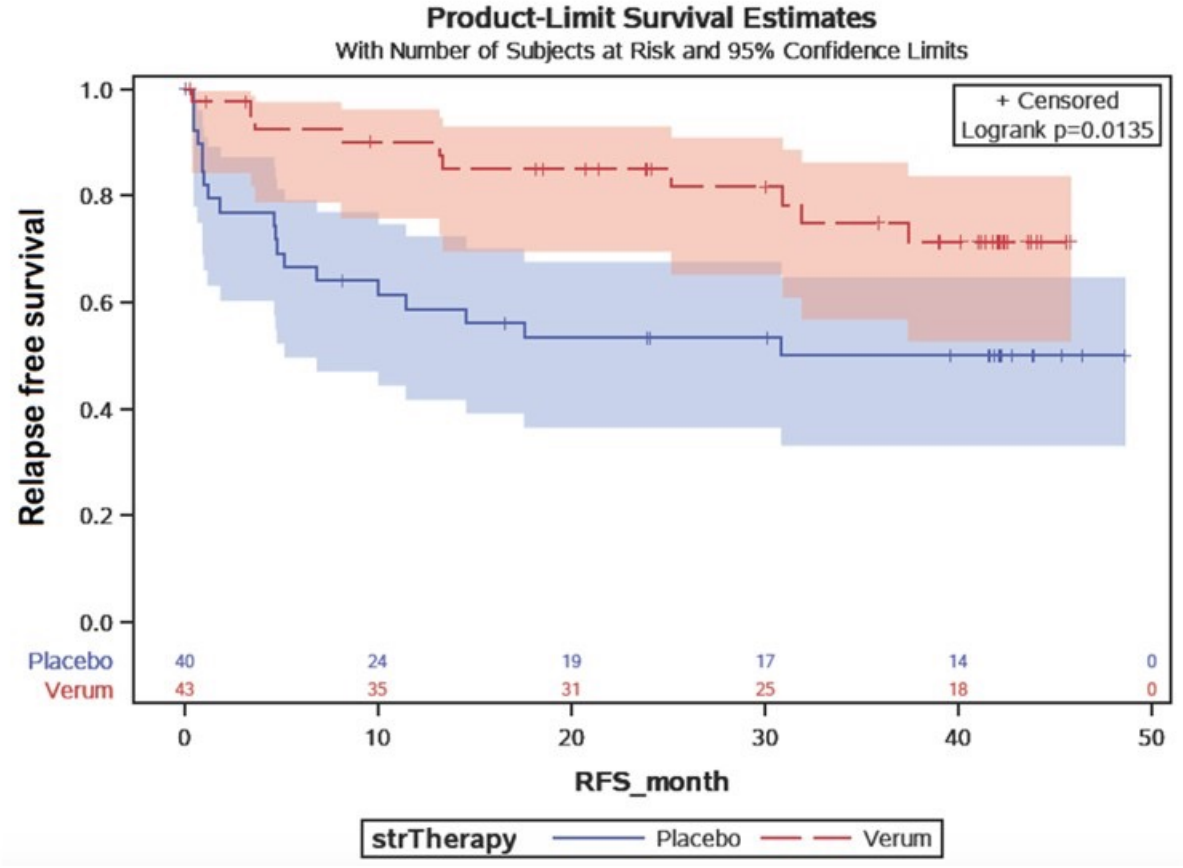
- Underhåll mest relevant efter allo-SCT

ASH 2019 #661

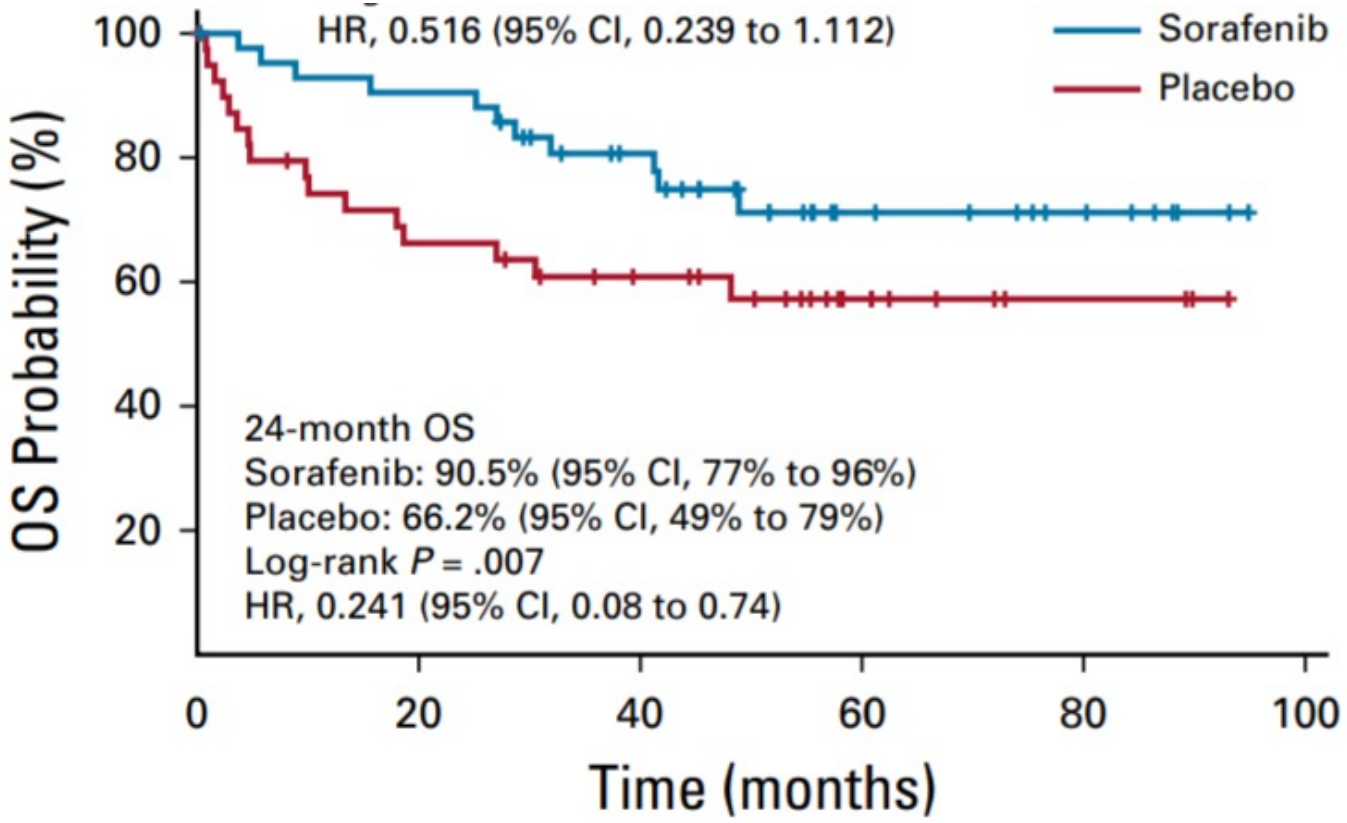
Sorafenib As **Maintenance** Therapy Post Allogeneic Stem Cell Transplantation for *FLT3*–ITD Positive AML: Results from the Randomized, Double-Blind, Placebo-Controlled Multicentre **Sormain** Trial.

Burchert et al, SAL, Germany, Austria

- AML, ***FLT3***-ITD, CR 1-3 månader post Allo-SCT
- Sorafenib 200-400 mg x 2 vs Placebo, 24 mån
- N=83, median 54 år, uppföljning 42 mån post rand.
- 2-year RFS
  - Placebo: **53** % (95% CI 36.5 - 67.5)
  - Sorafenib: **85** % (69.5 - 93.0)
  - HR **0.39** (0.18 - 0.85); P=0.0135



SORMAIN: OS with Sorafenib Maintenance After Allogeneic HCT in *FLT3*+ AML



No. at risk:						
Placebo	40	25	19	9	3	0
Sorafenib	43	38	28	12	7	0

P = .0855

OS, %	Sorafenib (n = 43)	Placebo (n = 40)	HR
At 2 yrs	90.5	66.2	0.24 (95% CI: 0.08-0.74); *P* = .007

Burchert. J Clin Oncol. 2020;38:2993.

Sorafenib maintenance in patients with *FLT3*-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial

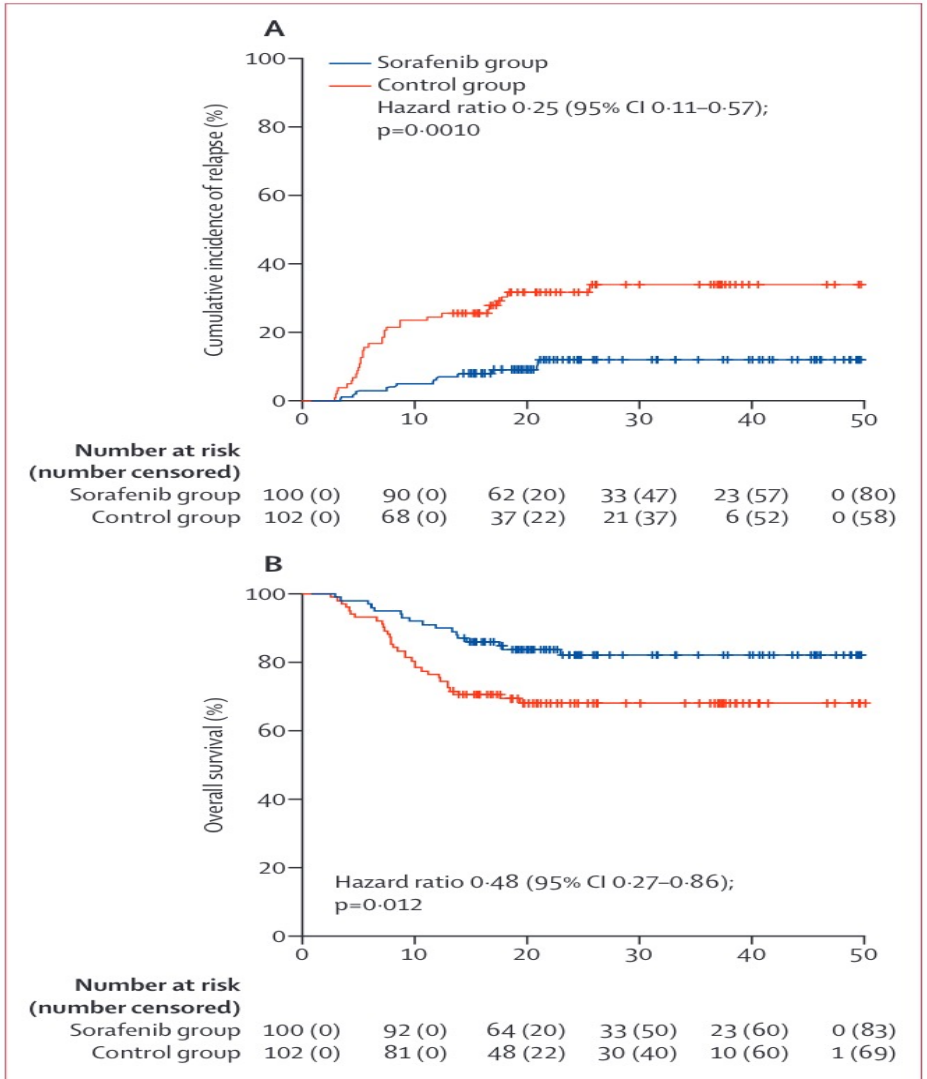
Li Xuan, Yu Wang*, Fen Huang*, Zhiping Fan*, Yajing Xu, Jing Sun, Na Xu, Lan Deng, Xudong Li, Xinquan Liang, Xiaodan Luo, Pengcheng Shi, Hui Liu, Zhixiang Wang, Ling Jiang, Chunzi Yu, Xuan Zhou, Ren Lin, Yan Chen, Sanfang Tu, Xiaojun Huang, Qifa Liu*

Lancet Oncol 2020; 21: 1201–12

Published Online
August 10, 2020
https://doi.org/10.1016/S1470-2045(20)30455-1

Summary

Background Findings of retrospective studies suggest that sorafenib maintenance post-transplantation might reduce relapse in patients with *FLT3* internal tandem duplication (*FLT3*-ITD) acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation. We investigated the efficacy and tolerability of sorafenib maintenance post-transplantation in this population.



	Sorafenib group (events, n/ patients, N)	Control group (events, n/ patients, N)	Cumulative incidence of relapse in sorafenib group at 2 years (95% CI)	Cumulative incidence of relapse in control group at 2 years (95% CI)	Hazard ratio (95% CI)
Gender					
Male	7/50	16/52	15·0% (6·4–27·0)	30·1% (17·8–43·4)	0·35 (0·15–0·86)
Female	4/50	16/50	8·8% (2·7–19·6)	33·2% (20·2–46·7)	0·21 (0·07–0·62)
Patient age, years*					
≥35	4/50	18/49	8·0% (2·5–17·7)	38·7% (24·4–52·7)	0·17 (0·06–0·50)
<35	7/50	14/53	16·1% (6·8–28·9)	25·1% (14·2–37·7)	0·45 (0·18–1·11)
White blood cell count at diagnosis*					
≥64×10⁹ per L	5/46	16/55	11·2% (4·0–22·5)	30·0% (18·2–42·7)	0·31 (0·11–0·85)
<64×10⁹ per L	6/54	16/47	13·1% (5·1–25·0)	33·9% (20·1–48·2)	0·26 (0·10–0·66)
Cytogenetic risk					
Low	0/6	0/4	0·0% (0·0–0·0)	0·0% (0·0–0·0)	NA
Intermediate	8/80	27/85	11·1% (5·0–19·7)	31·5% (21·7–41·8)	0·26 (0·12–0·57)
High	1/7	1/5	14·3% (0·5–49·6)	26·7% (0·2–75·1)	0·71 (0·04–11·32)
Unknown	2/7	4/8	28·6% (2·9–64·1)	50·0% (12·5–79·4)	0·54 (0·10–2·96)
***NPM1* mutation**					
Without	7/71	22/76	10·6% (4·6–19·6)	28·6% (18·7–39·4)	0·28 (0·12–0·66)
Concomitant	4/29	10/26	15·1% (4·5–31·7)	41·3% (20·4–61·2)	0·26 (0·08–0·84)
Sorafenib pretransplantation					
No use	6/41	19/45	15·3% (6·1–28·4)	43·9% (28·4–58·2)	0·23 (0·09–0·59)
Use	5/59	13/57	9·5% (3·3–19·6)	21·7% (11·8–33·5)	0·34 (0·12–0·96)
Disease status at transplantation					
CR1	8/79	20/84	11·5% (5·2–20·4)	24·0% (15·1–34·0)	0·35 (0·15–0·80)
≥CR2	3/21	12/18	14·3% (3·4–32·7)	66·7% (38·5–84·2)	0·13 (0·04–0·48)
CRc status at transplantation					
CRp or CRi	4/27	11/23	15·2% (4·6–31·5)	47·8% (26·2–66·6)	0·23 (0·07–0·74)
CR	7/73	21/79	10·8% (4·6–20·0)	26·7% (17·1–37·3)	0·29 (0·12–0·69)
MRD at transplantation					
Negative	4/69	15/68	6·9% (2·1–15·5)	21·6% (12·4–32·5)	0·21 (0·07–0·64)
Positive	7/31	17/34	23·1% (9·9–39·5)	51·5% (32·7–67·4)	0·33 (0·14–0·79)
Transplant modality					
MSD	2/44	13/39	5·6% (0·9–17·1)	31·0% (17·2–45·9)	0·11 (0·03–0·50)
MUD	1/8	1/6	12·5% (0·5–44·8)	16·7% (0·5–54·9)	0·66 (0·04–10·53)
HID	8/48	18/57	17·5% (8·0–30·0)	33·6% (21·1–46·6)	0·42 (0·18–0·96)
MRD at the time of enrolment post-transplantation					
Negative	8/91	24/91	9·8% (4·5–17·6)	26·3% (17·5–36·0)	0·28 (0·13–0·62)
Positive	3/9	8/11	33·3% (6·5–64·2)	77·3% (24·3–95·4)	0·25 (0·06–0·94)
Acute GVHD					
No	4/56	23/60	7·3% (2·3–16·2)	37·7% (25·1–50·1)	0·14 (0·05–0·41)
Yes	7/44	9/42	17·7% (7·5–31·5)	23·0% (11·1–37·4)	0·65 (0·24–1·76)
Chronic GVHD†					
No	8/52	20/54	16·9% (7·6–29·3)	35·1% (21·9–48·5)	0·35 (0·15–0·77)
Yes	3/47	12/45	6·8% (1·7–17·0)	27·3% (15·0–41·1)	0·21 (0·06–0·74)
All patients	**11/100**	**32/102**	**11·9% (6·2–19·6)**	**31·6% (22·6–41·1)**	**0·29 (0·15–0·58)**

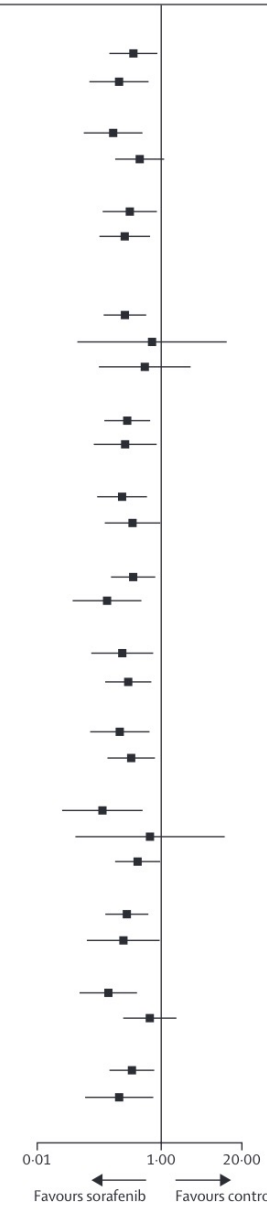


Figure 3: **Subgroup analysis of cumulative incidence of relapse at 2 years in patients receiving sorafenib maintenance or control (non-maintenance) post-transplantation**
CR=complete remission. CR1=first complete remission. CR2=second complete remission. CRc=composite complete remission. CRi=complete remission with incomplete haematological recovery. CRp=complete remission with incomplete platelet recovery. GVHD=graft-versus-host disease. HID=HLA-haploidentical donor. MRD=minimal residual disease. MSD=HLA-matched sibling donor. MUD=HLA-matched unrelated donor. NA=not available. *Cutoffs were the median value. †Excluded patients who died before day 100 post-transplantation.

Konklusion

- Visst, men inte enhälligt stöd för underhåll
  - AML FAB M5: IL2 – histamin
  - Vaccination
  - Azacytidin
  - *FLT3*-hämmare efter alloSCT (Sorafenib)
- Många kandidater/kombinationer studeras
  - andra kinashämmare (*FLT3, IDH*)
  - efter allo-SCT (bl.a. gilteritinib)
- Effekt beroende av konsolideringens intensitet
  - intensiv konsolidering – mindre effekt av underhåll
- Dos, duration mm mm oklart