Akut leukæmi og MDS

LYLE 14042018

Hans Beier Ommen

Disposition

- Del 1: Nuværende behandling af AL/MDS
  - (Kort) overblik over sygdomme
  - Behandling af Akut leukæmi og MDS
    - Kemoterapi
      - Intensiv kemoterapi ved akut leukæmi
      - Azacitidin ved MDS eller mindre intensiv AML
    - Transplantation

Disposition II

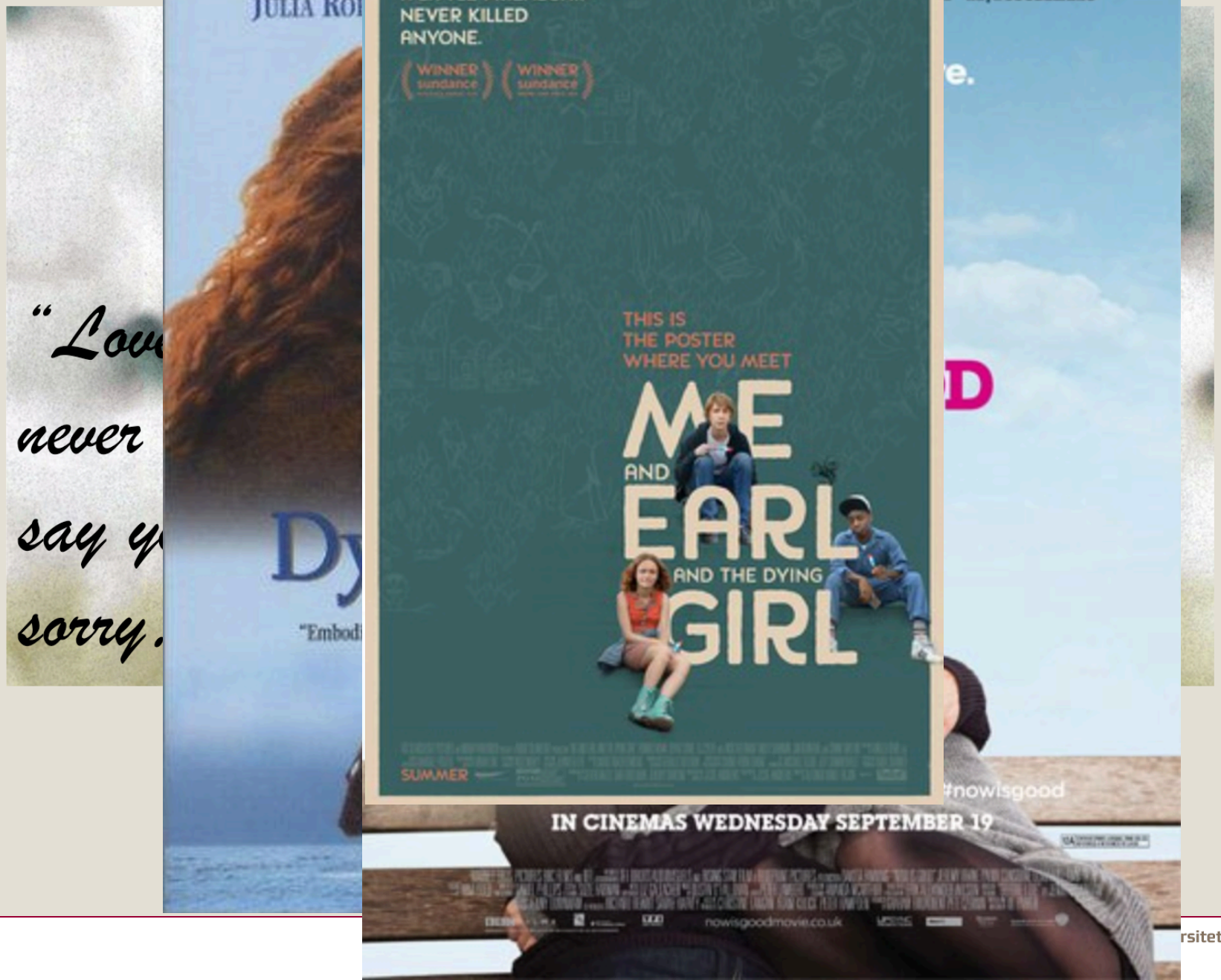
- Del 2: Fremtidig behandling af AL/MDS
  - Akut leukæmi:
    - Forbedret behandlingsovervågning
    - ALL: CAR-T celleterapi
    - AML: subtypespecifik behandling
  - MDS:
    - Højrisiko
      - Behandling til patienter der fejler azacitidin
    - Lavrisiko
      - Behandling til patienter der fejler epo

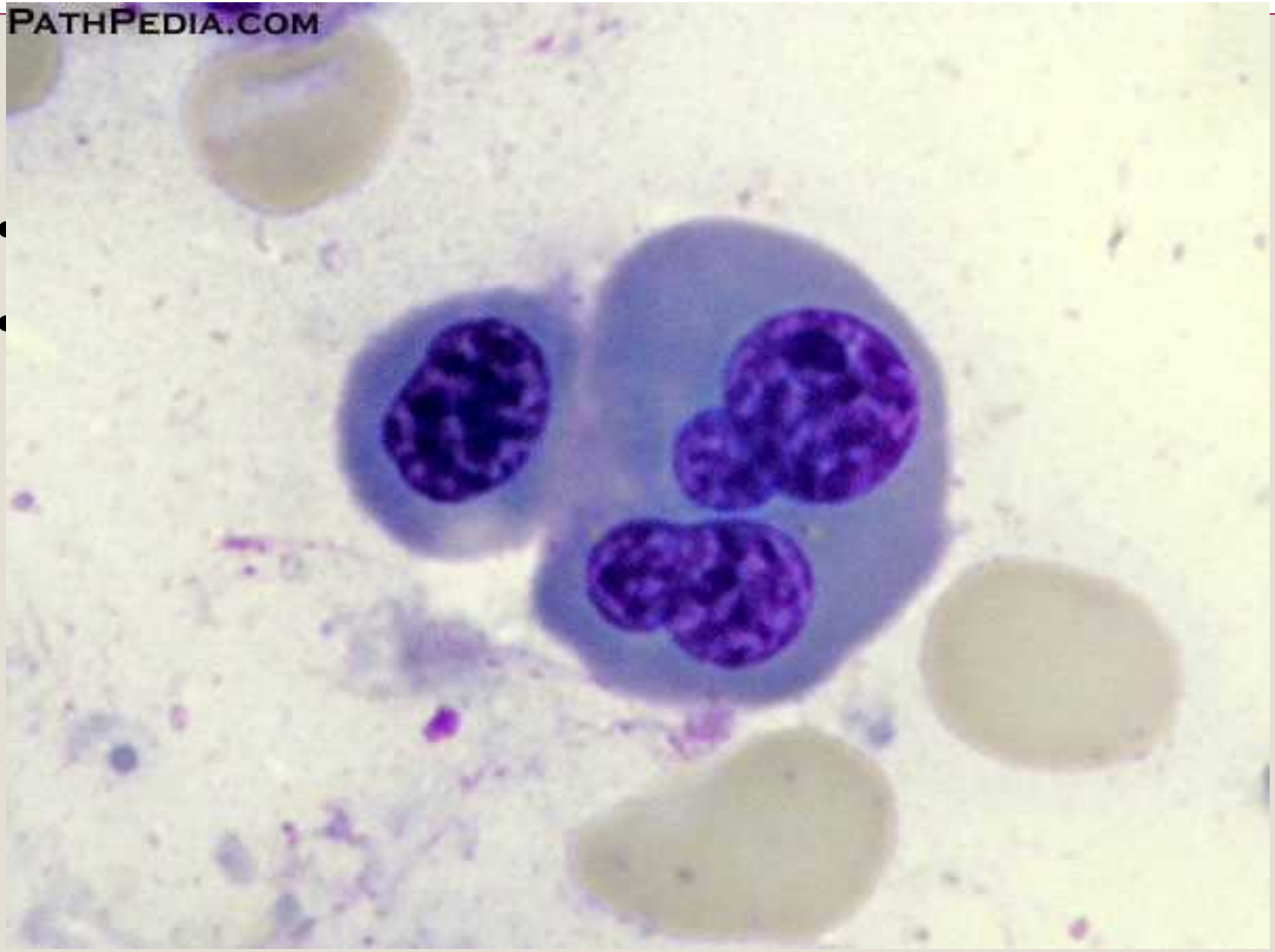
Præsentation

- Hans Beier Ommen
- 42 år, gift, 2 børn
- Overlæge Blodsygdomme
  - Funktionsleder
  - Ser Akut leukæmi og MDS patienter
- Forskningsbaggrund:
  - Ph.d. 2009: Minimal restsygdom ved AML
  - Vejleder for 4 ph.d. studerende

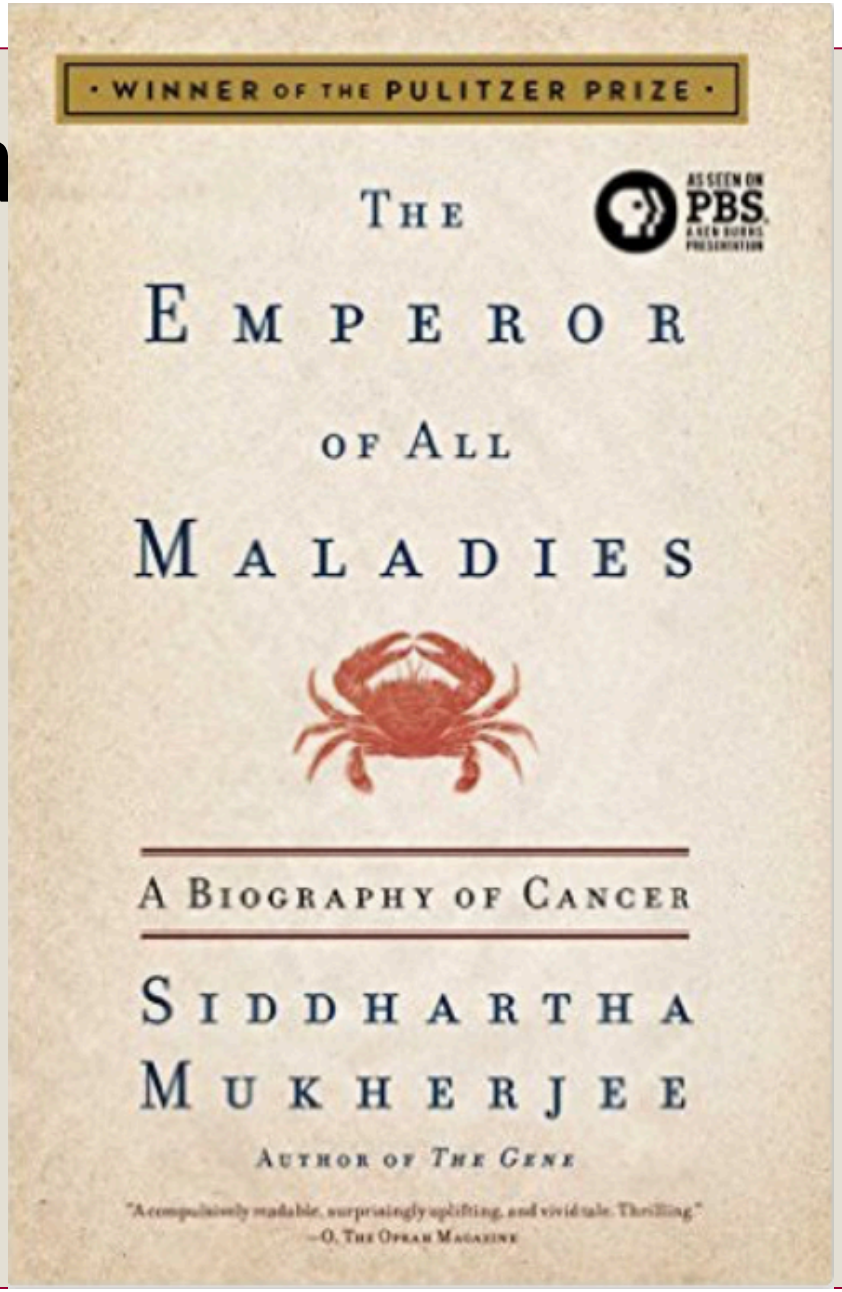
Sygdommene

- Akut leukæmi


A LITTLE FRIENDSHIP
NEVER KILLED
ANYONE.
WINNER sundance
WINNER sundance
THIS IS
THE POSTER
WHERE YOU MEET
ME
AND
EARL
AND THE DYING
GIRL
SUMMER
IN CINEMAS WEDNESDAY SEPTEMBER 19
nowisgoodmovie.co.uk
#nowisgood
Kaya SCODELARIO


PATHPEDIA.COM

Beha n om


· WINNER OF THE PULITZER PRIZE ·
AS SEEN ON PBS
A KEN BURNS PRESENTATION
THE
EMPEROR
OF ALL
MALADIES
A BIOGRAPHY OF CANCER
SIDDHARTHA
MUKHERJEE
AUTHOR OF THE GENE
"A compulsively readable, surprisingly uplifting, and vivid tale. Thrilling."
—O, THE OPRAH MAGAZINE

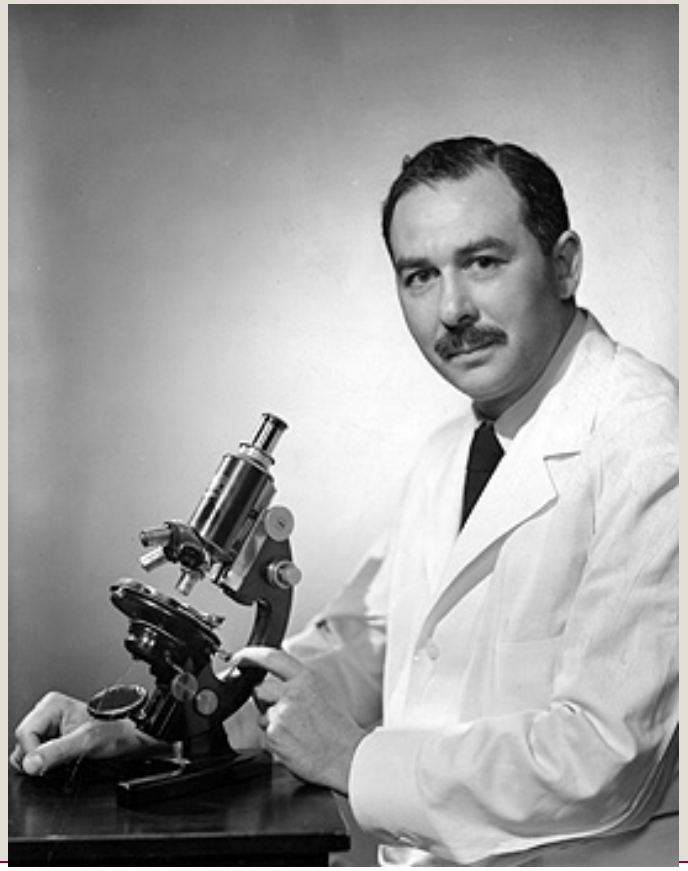
1948

- Cancerbehandling:
  - Solide tumorer
    - Kirurgi & strålebehandling
  - Leukæmi
    - uhelbredelig
- Penicillin
- Blodtransfusioner

Boston, Massachusetts

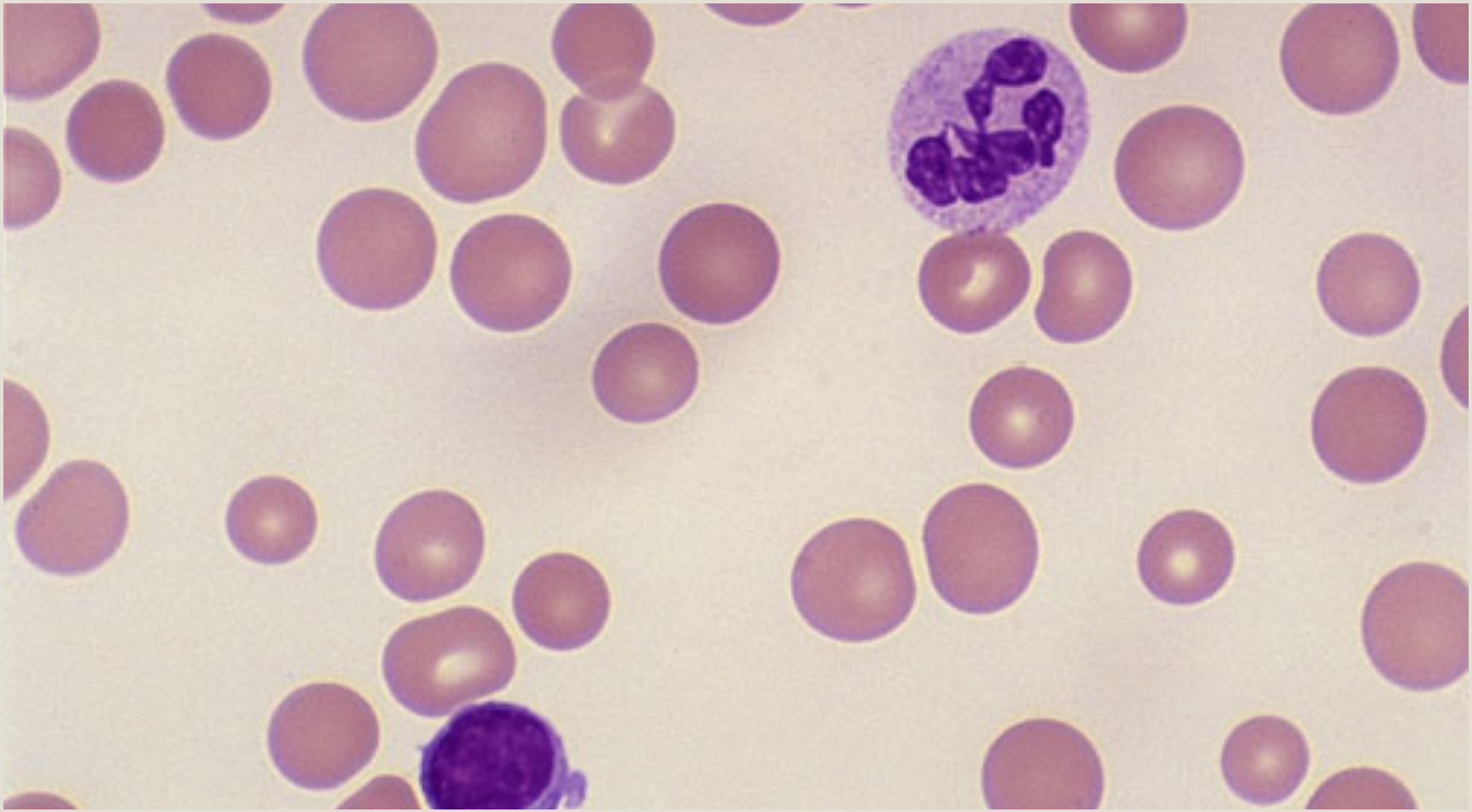
- Børnehospitalet, patologisk afdeling

Dr Sydney Farber i 1948



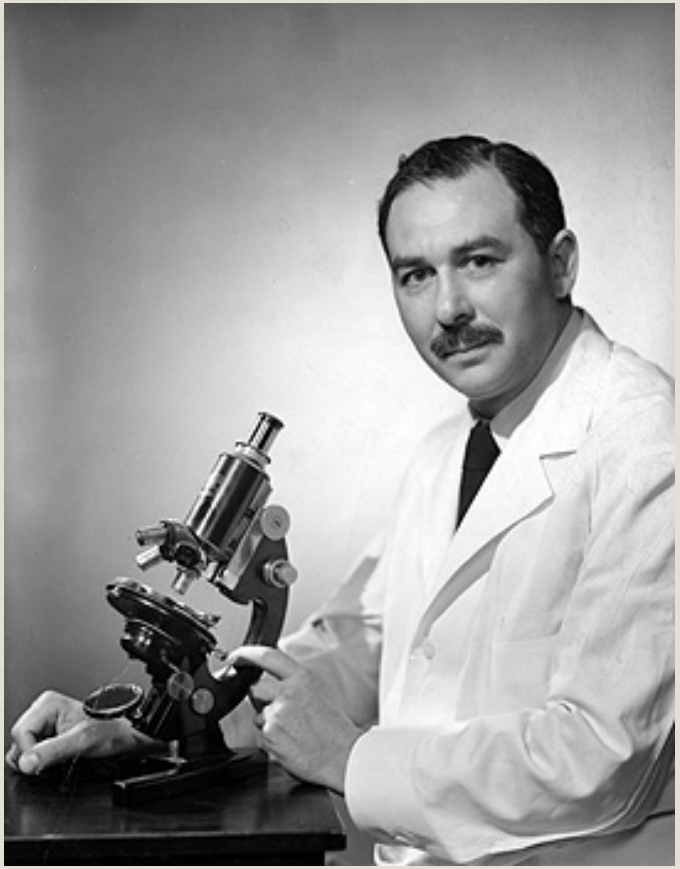
- 200 obduktioner af døde leukæmibørn

Megaloblastær anæmi



Folinsyre til leukæmibørn

- Ingen effekt
- Obduktioner forestås af Sydney Farber
- Folinsyremodgift (Aminopterin) forsøges



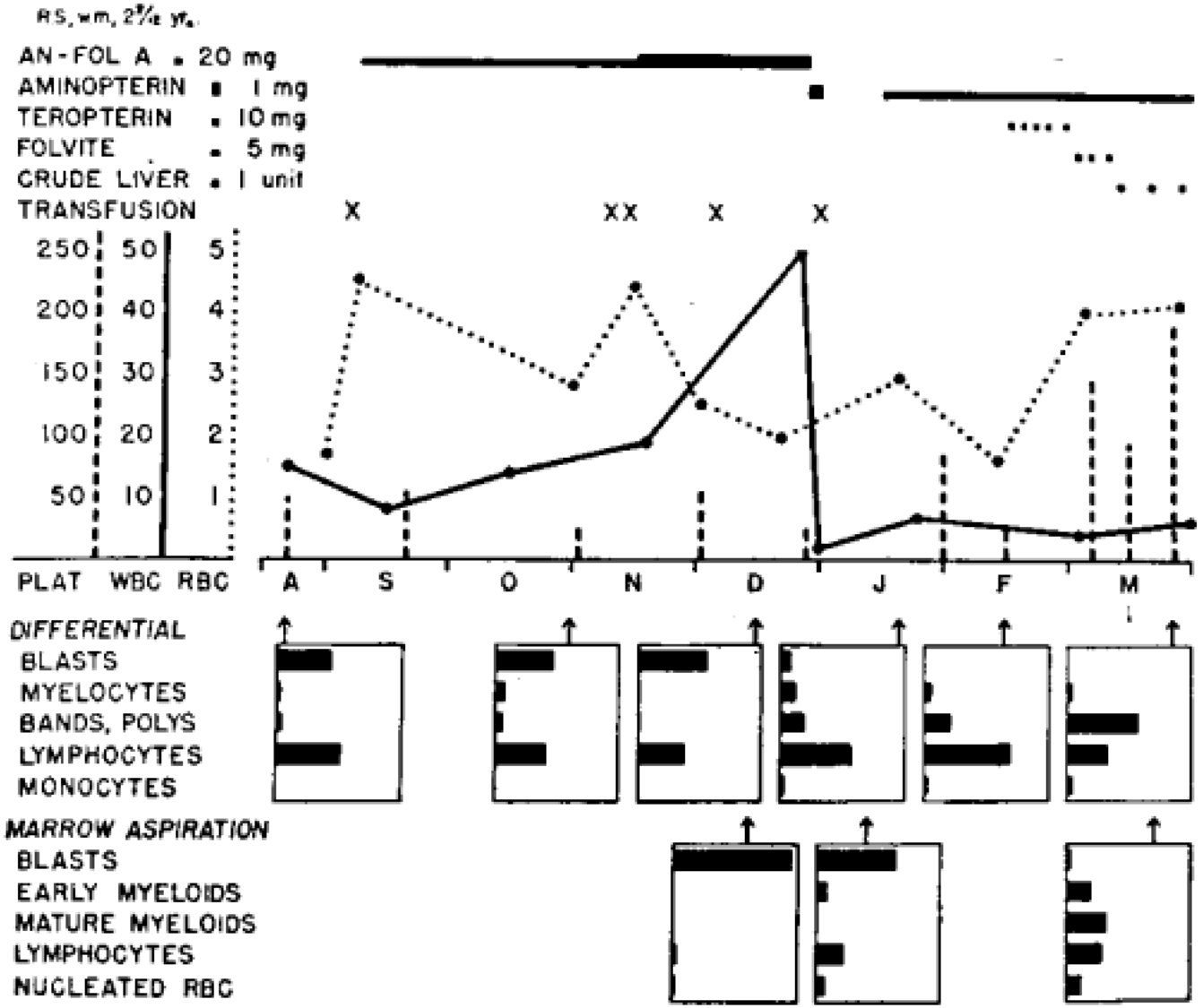


FIGURE 6. *Course of Leukemia in Case 5.*

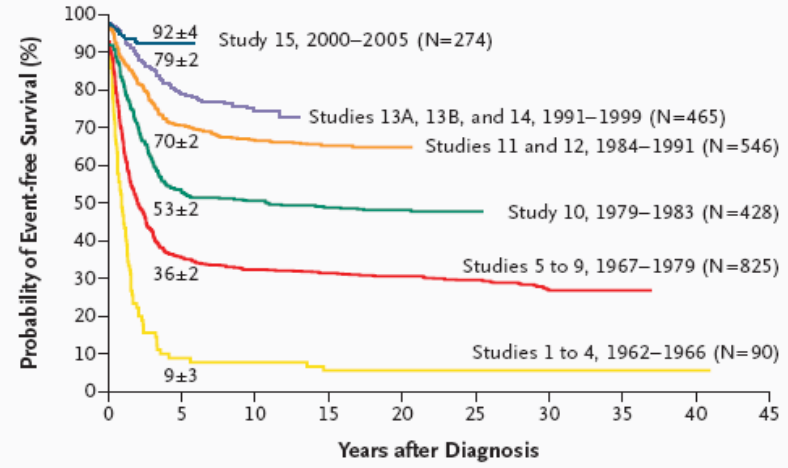
The New England
Journal of Medicine

Volume 238 JUNE 3, 1948 Number 23

TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§
ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.‖

BOSTON



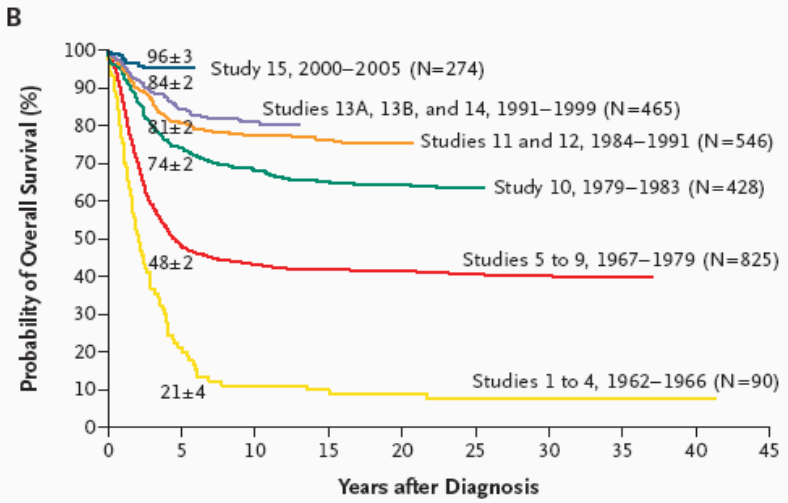


Figure 1. Kaplan–Meier Analyses of Event-free Survival (Panel A) and Overall Survival (Panel B) in 2628 Children with Newly Diagnosed ALL.

The patients participated in 15 consecutive studies conducted at St. Jude Children's Research Hospital from 1962 to 2005. The five-year event-free and overall survival estimates (±SE) are shown, except for Study 15, for which preliminary results at four years are provided. The results demonstrate steady improvement in clinical outcome over the past four decades. The difference in event-free and overall survival rates has narrowed in the recent periods, suggesting that relapses or second cancers that occur after contemporary therapy are more refractory to treatment.

Dana-Farber Cancer Institute

Behandling af AML idag

Aktuelt behandlingsprincip

Cytosine Arabinoside With Daunorubicin or Adriamycin for Therapy of Acute Myelocytic Leukemia: A CALGB Study

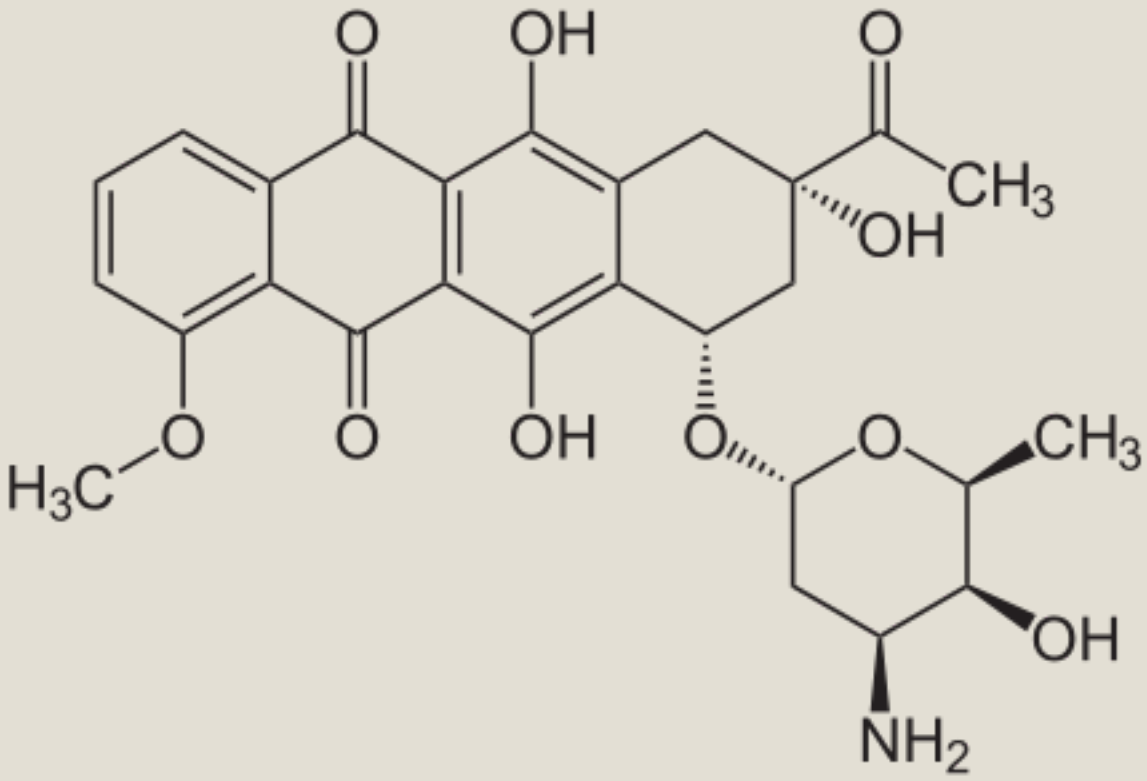
By Jerome Yates, Oliver Glidewell, Peter Wiernik, M. Robert Cooper, David Steinberg, Harvey Dosik, Robert Levy, Clark Hoagland, Patrick Henry, Arlan Gottlieb, Cornelius Cornell, Jeffrey Berenberg, J. Lawrence Hutchison, Peter Raich, Nis Nissen, Rose Ruth Ellison, Robert Frelick, G. Watson James, Geoffrey Falkson, Richard T. Silver, Farid Haurani, Mark Green, Edward Henderson, Louis Leone, and James F. Holland

A randomized comparison of the relative efficacy and toxicity of daunorubicin (DNR) at 30 or 45 mg/sq m or adriamycin (ADM) at 30 mg/sq m, given on the first 3 days of a 7-day continuous infusion of cytosine arabinoside (ara-C) at 100 mg/sq m/day, shows the outcome to be dependent on anthracycline, dose, and patient age. DNR 45 is significantly better than DNR 30 or ADM 30 for inducing complete remissions (CR) in patients younger than 60 yr, (72%, 59%, 58% CRs, respectively). DNR 30 is better than DNR 45 or ADM 30 for inducing CR in patients older than 60 yr (47%, 31%, 35%, respectively). There was a corresponding shift in the induction mortality for the age, dose, and anthracycline groups. Adriamycin was significantly more toxic to the gastrointestinal tract than daunorubicin. The duration of complete remission, with cyclic courses of maintenance therapy, was independent of the patient's age, the dose, or choice of anthracycline used in induction, and of whether the maintenance courses were given every 4 wk or every 8 wk.

BLOOD 1982

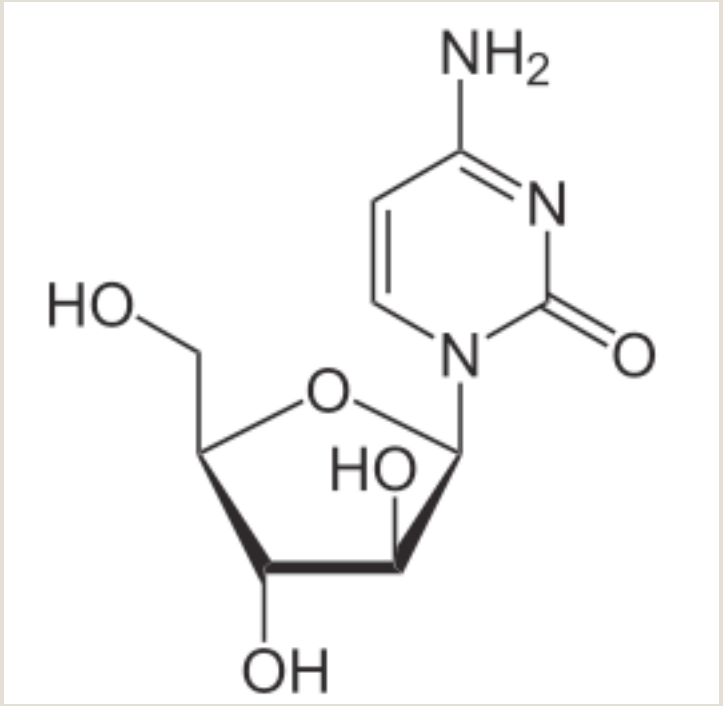
Behandling - 1

- Kemoterapi 1: topoisomerasehæmmer

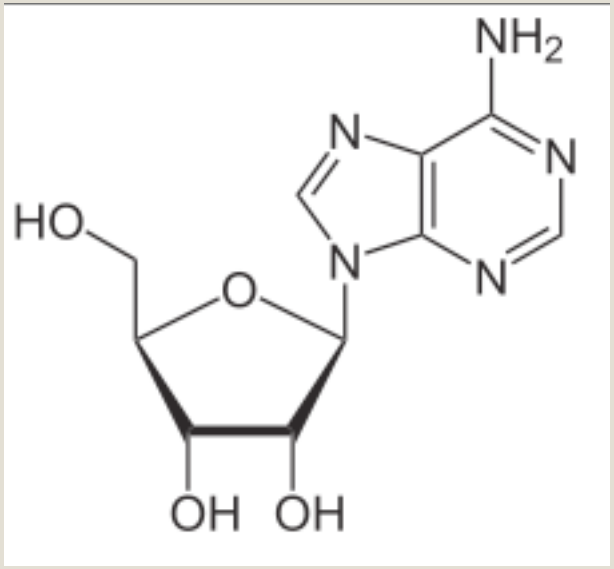


Behandling - 2

- Kemoterapi 2: Nucleosidanalog



Cytarabin

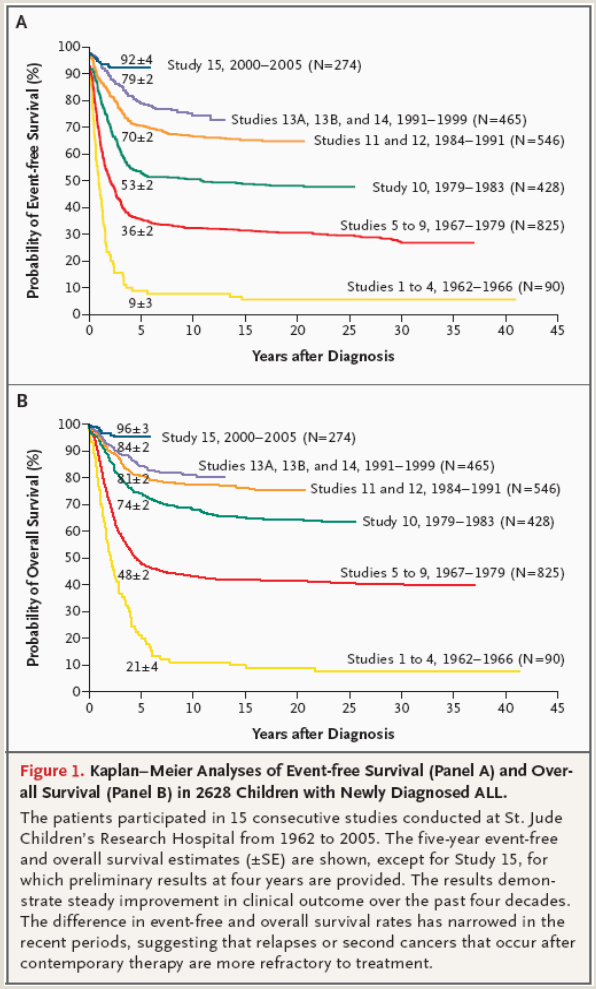


Adenosin

Behandling - 3

- Kombinationskemoterapi – hvorfor?
  - Synergi mellem stoffer med forskelligt angrebspunkt
  - Nedsat risiko for tilstedeværelse af resistente cancerceller mod alle stoffer
  - Forskellig bivirkningsprofil
    - Standard kemoterapeutika
    - Targeterede stoffer

Børne-ALL



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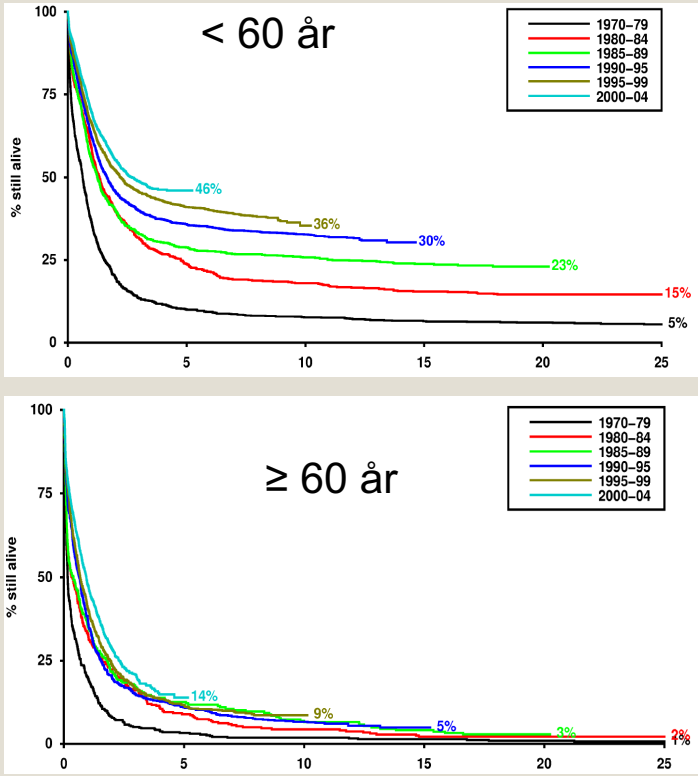
Pui *et al.*
N Engl J Med 2006;354:166-78.

AML



Burnett *et al.*
Survival in MRC AML trials

Ændringer i AML behandling de sidste 10 år

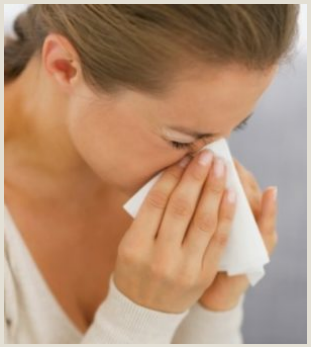
- Int
  hje dling

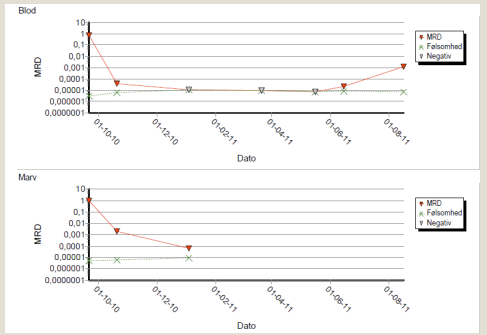
Ændringer i AML behandling de sidste 10 år

- Introduktion af hjemmeenheder/semiambulant behandling
  - Forbedret 3 års overlevelse Århus (Under 60-årige)
    - 2006-2011: 33%
    - 2012-2016: 61%

Hjemmeenheder

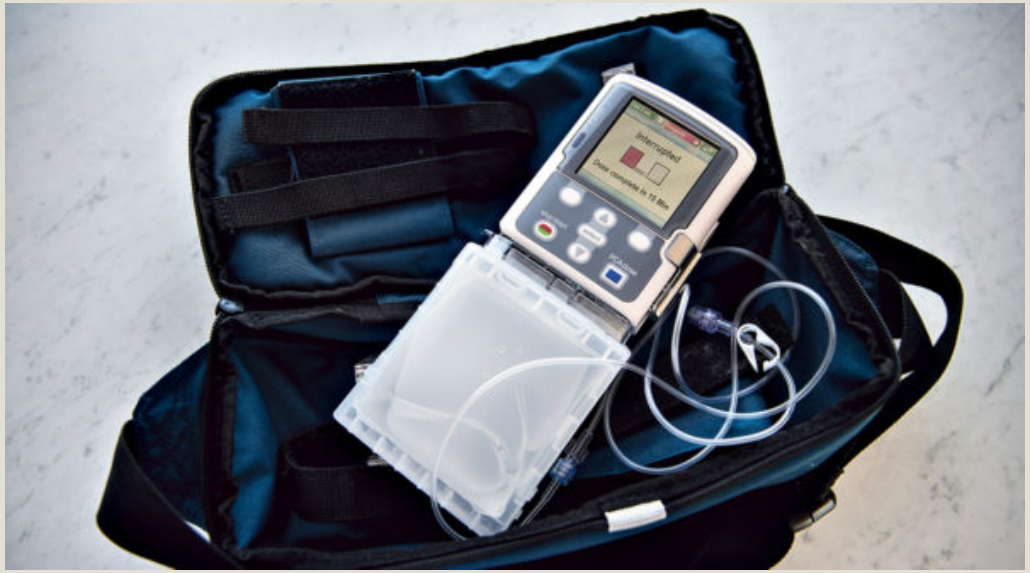
- Infektionsovervågning og tidlig handling
- Profylaktisk antibiotika
- Profylaktiske blodpladetransfusioner
- Løbende overvågning af sygdom
  - Rettidig ændring af behandlingsstrategi





Ændringer i AML behandling de sidste 10 år

- Introduktion af hjemmeenheder/semiambulant behandling
- Hjemmekemoterapi



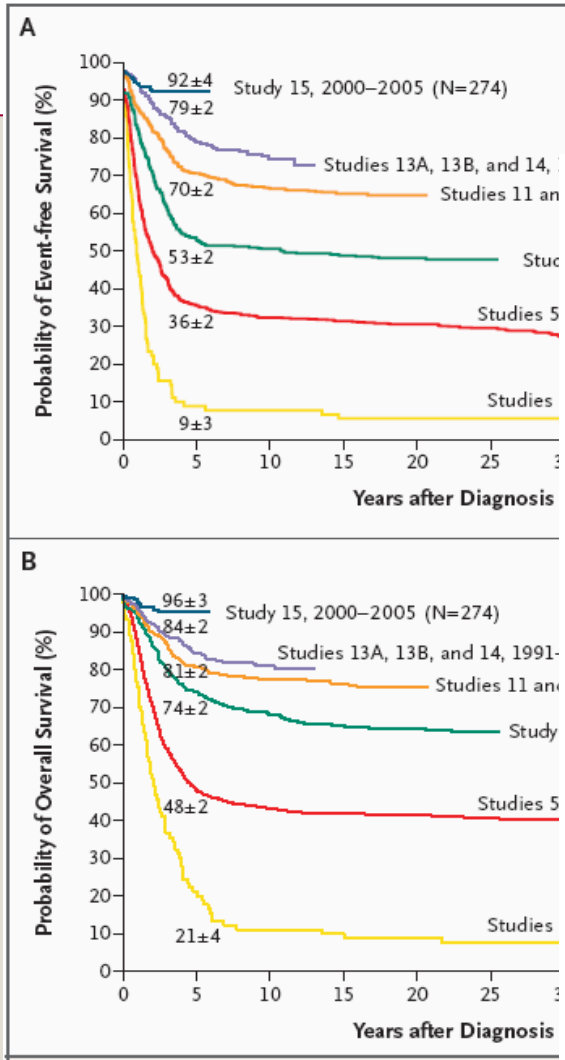
Dilemmaer ved hjemmekemoterapi

- Gode ting:
  - Man kan være der hjemme
  - Man er mindre syg
  - Mindre ressourceforbrug for samfund
- Dårlige ting:
  - Pres for at være der hjemme
  - Belastning af pårørende

Ændringer i AML behandling de sidste 10 år

- Introduktion af hjemmeenheder/semiambulant behandling
- Hjemmekemoterapi
- Øget transplantationsfrekvens ved ældre
  - 3 års overlevelse blandt over 60 årige i Aarhus
    - 2005-2008: 13 %
    - 2013-2016: 42%

ALL ved yngre voksne



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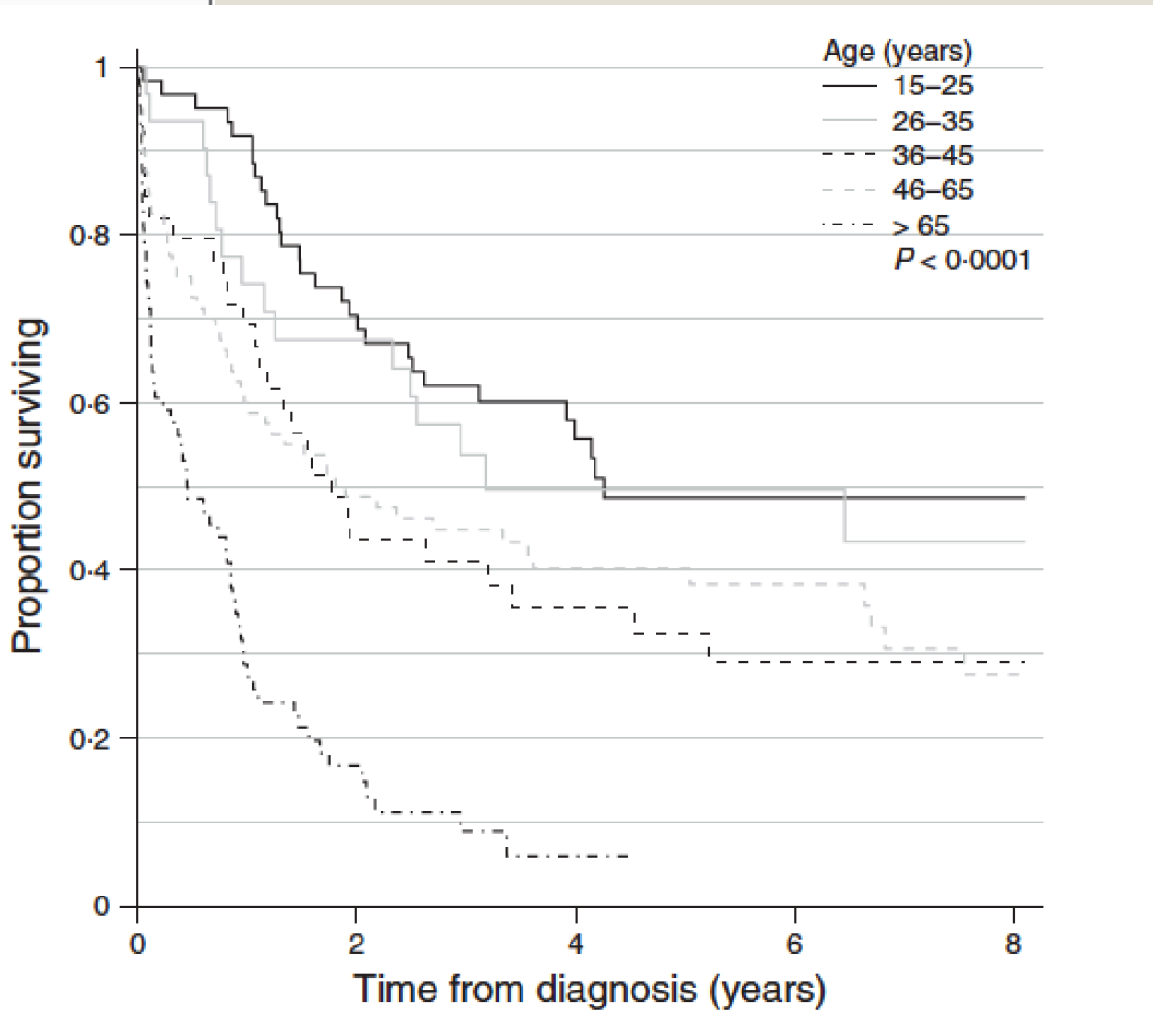


CANCER TREATMENT REVIEWS (2004) **30**, 37–51

ELSEVIER

www.elsevierhealth.com/journals/ctrv

TUMOUR REVIEW

Prognosis in childhood and adult acute lymphoblastic leukaemia: a question of maturation?☆

Sabine L.A. Plasschaert[a], Willem A. Kamps[a], Edo Vellenga[b], Elisabeth G.E. de Vries[c], Eveline S.J.M. de Bont[a,*]

CORRESPONDENCE

Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric *vs* adult protocols in the Netherlands

JM de Bont[1]
B van der Holt[2]
AW Dekker[3]
A van der Does-van den Berg[4]
P Sonneveld[5]
R Pieters[1,4]

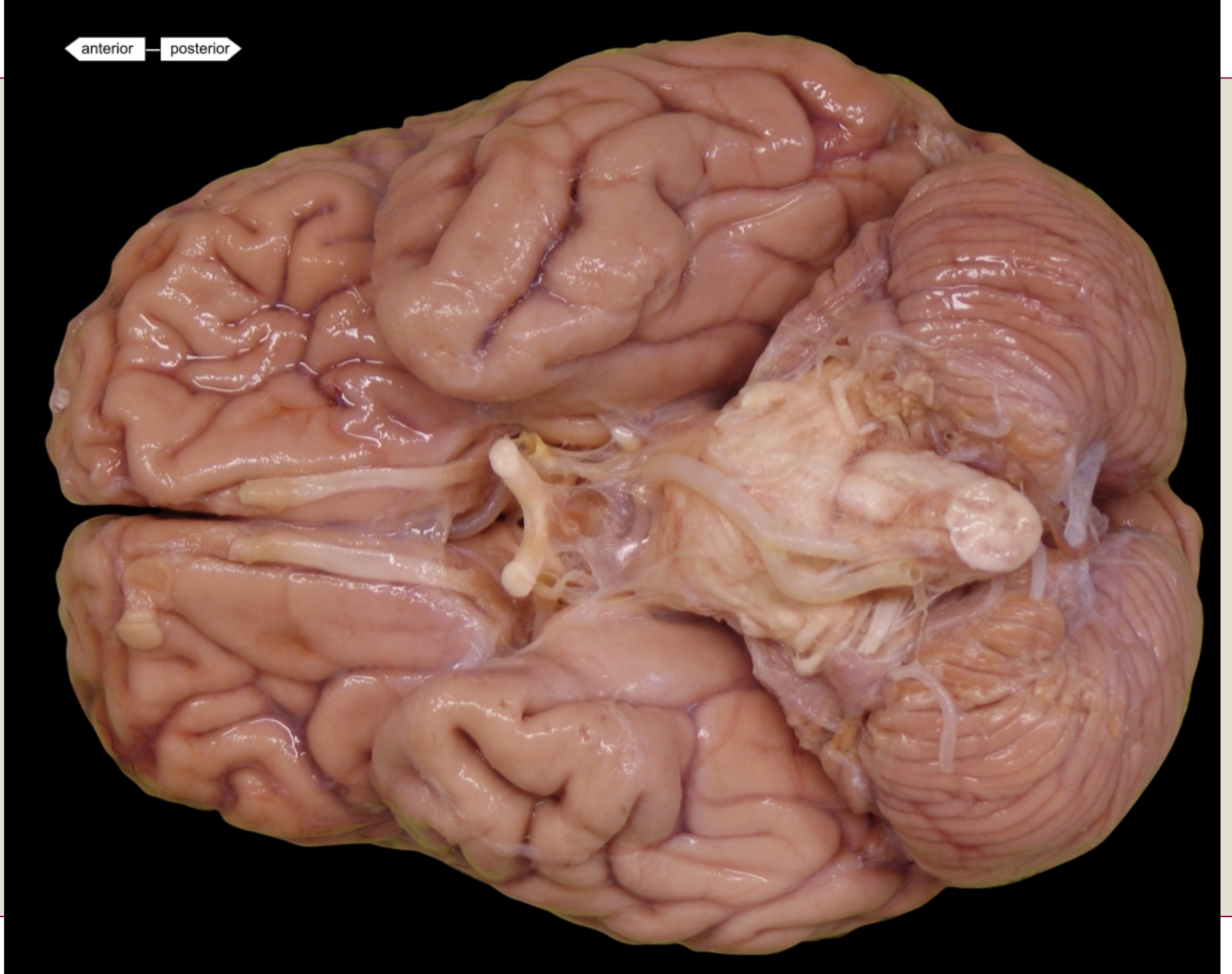
[1]*Erasmus MC, Sophia Children's Hospital, Rotterdam, The Netherlands;*
[2]*Erasmus MC, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands;*
[3]*UMC Utrecht, Utrecht, The Netherlands;*
[4]*DCOG, The Hague , The Netherlands; and*
[5]*Erasmus MC, Rotterdam, The Netherlands*

Behandling voksne vs. børn

- Voksenbehandling:
  - 10 stoffer, 2 år
- Børnebehandling:
  - 10 stoffer, 2,5 år
  - Højere doser (specielt MTX)
  - Mere intracerebral kemoterapi
  - Omhyggelig risikostratificering

CNS leukæmi

- Frygtet komplikation, særlig til ALL
- Høj dødelighed
- Undgås ved at administrere hd MTX + isp kemoterapi


anterior
posterior

NOPHO 2008

- Børnebehandlingsprotokol
- Unge voksne 15-44 år kan inkluderes
- Observationer:
  - Flere med dårlige prognostika i voksengruppe
  - Flere transplanteres
  - Voksne tåler intensiv kemoterapi dårligere
  - Nogle toksiske dødsfald
- Men: 5 års overlevelse for voksne
  - 45% -> 80%

Label (lille)

Behandlingsdag:		FORFASE?	1	8	15	22	29	30
Behandlingsuge:		1		2	3	4	5	
År:	Dato:	/	/	/	/	/	/	/
Højde:	Vægt:							
	Overflade i m^2:							
Afdeling:								
Ordineret af (sign.):								
Vinkristin i.v. **2 mg** Infusion 5-15 min.	Dosis %		**2**	**2**	**2**	**2**	**2**	
Doxorubicin i.v. **40 mg/m^2** Infusion 4 timer	Dosis %					*		
Prednison p.o. **60 mg/m^2**	Dosis i mg	5-20 mg/m^2 i 1-7 dage	daglig dosis "dag 1-29" - *fordel* på daglige 3 doser				* aftrapning	
Pegyleret asparaginase i.m. **(Medac) med lidokain** **1.000 IE/m^2**	Dosis %							*
Merkaptopurin (Puri-nethol) **p.o. 25 mg/m^2 dgl.** Puri-nethol-tabl. à 50 mg	Dosis %							**start!** se protokol (afsnit 14.3.1)
Givet af (sign.):								
Methotrexat isp. **12 mg**	Dosis		**12**	*	*		*	
Givet intraspinalt af (sign.):								
Evt. allopurinol p.o. *Hvis* ja, *angiv* dosis mg								
Faxet (dato/sign.):							*fax* til 2 dg.	

* *Udsæt* evt. doxorubicin "dag 22" ved alvorlig infektion - samt *hvis* neutrofile < 0,2 mia/l, og KM "dag 15" viser lavt MRD-niveau

* *Aftrap* prednison med 30 mg/m^2 i 3 dage, 15 mg/m^2 i 3 dage og 7,5 mg/m^2 i 3 dage

NOPHO: ALL-konsolidering standard og IR risiko

(ingen IR/HR-cytogenetik og MRD < 10^{-3})

ALL NOPHO-protokol (2 SR/2IR), 18 - < 45 år (EuDraCT nr. 2008-003235-20)

Revideret 3.11.11

ALL NOPHO konsolidering - standard- og intermediær risiko/15.3.17

Label (lille)

Behandlingsdag:	35	36	37	43	56	57	58	64	71	77	78	79	85
Behandlingsuge:	6			7	9			10	11	12			13
År: Dato:	/	/	/	/	/	/	/	/	/	/	/	/	/
Højde: Vægt:													
Overflade i m^2:													
Afdeling:													
Ordineret af (sign.):													
Methotrexat i.v. 5000 mg/m^2 Dosis *Anvend* særskilt skema ("NOPHO-MTX 5 g/m^2")	hydr. kl. 22	andet skema			hydr. kl. 22	andet skema				hydr. kl. 22	andet skema		
Folininsyre (Calciumfolinat) *Anvend* skema: "NOPHO-folininsyre-rescue"			andet skema				andet skema					andet skema	
Vinkristin i.v. 2 mg Dosis Infusion 5-15 min.				2				2					
Pegyleret asparaginase i.m. (Medac) med lidokain 1.000 IE/m^2 Dosis				*		*			*				*
Merkaptopurin (Puri-nethol™) p.o. 25 mg/m^2 dgl. Dosis (Puri-nethol™-tabl. à 50 mg)	*Giv kontinuerligt* fra "dag 30" til "dag 85" Dosisreduktion ved TPMT-mangel til 5 mg/m^2 og ved KM-depression - *se* protokol afsnit 14.3.1												
Givet af (sign.):													
Methotrexat isp. 12 mg Dosis			12				12					12	
Givet intraspinalt af (sign.):													
Evt. allopurinol p.o. Hvis ja, angiv dosis mg													
Faxet (dato/sign.):	fax til 1 dg.			fax til 1 dg.	fax til 1 dg.			fax til 1 dg.	fax til 1 dg.	fax til 1 dg.			fax til 1 dg.
Udleveret medicin:													

NOPHO: ALL (IR) - sen intensifikation I og konsolidering II

ALL NOPHO-protokol (3 IR), 18 - < 45 år (EuDraCT nr. 2008-003235-20)

Label (lille)

Revideret 11.7.11

ALL NOPHO intermediær risiko - sen intensifikation I og konsolidering II/15.3.17

Behandlingsdag:		92 *	99	106	113	127 *	129	130	131	132	136	137	138	139	141
Behandlingsuge:		14	15	16	17	19					20				21
År:	Dato:	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Højde:	Vægt:														
Overflade i m^2:															
Afdeling:															
Ordineret af (sign.):															
Vinkristin i.v. **2 mg** Infusion 5-15 min.	Dosis %	2	2	2	2										
Daunorubicin i.v. **30 mg/m^2** Infusion 4 timer	Dosis %														
Dexamethason p.o. **10 mg/m^2** (Dexamethason-tabl. à 4 mg)	Dosis i mg	"dag 92-98" *3 dgl. doser*		"d. 106-112" *3 dgl. doser*	* aftrap-ning										
Peg. asparaginase i.m. (Medac) med lidokain **1.000 IE/m^2**	Dosis %		*		*	*									*
Cyclophosphamid i.v. **1000 mg/m^2** Infusion 60 min.	Dosis %														
Cytarabin i.v. **75 mg/m^2** Bolusinfusion	Dosis %														
Givet af (sign.):															
Thioguanin p.o. **60 mg/m^2 dgl.** (Lanvis®-tabl. à 40 mg)	Dosis %					*Dosér* i mg til om aftenen i 14 dage (doser delelig med 20) Dosisreduktion ved TPMT-mangel til 20 mg/m^2									
Methotrexat isp. **12 mg**	Dosis	12				12									
Givet intraspinalt af (sign.):															
Evt. allopurinol p.o. Hvis ja, angiv dosis mg															
Faxet (dato/sign.):		*fax til 1 dg.*	*fax til 1 dg.*	*fax til 1 dg.*	*fax til 1 dg.*	*fax til 6 dg.*					*fax til 4 dg.*				*fax til 1 dg.*
Udleveret medicin:															

NOPHO: ALL (IR) - vedligeholdelse I

ALL NOPHO-protokol (4 IR), 18 - < 45 år (EuDraCT nr. 2008-003235-20)

Revideret 6.11.11

ALL NOPHO intermediær risiko - vedligeholdelse I/15.3.17

Label (lille)

Behandlingsdag:	148 *	154 *	155	156	169	183	197	210 *	211	212	225	239
Behandlingsuge:	22	23			25	27	29	31			33	35
År: Dato:	/	/	/	/	/	/	/	/	/	/	/	/
Højde: Vægt:												
Overflade i m^2:												
Afdeling:												
Ordineret af (sign.):												
Merkaptopurin * **(Puri-nethol™) p.o.** **75 mg/m^2 dgl.** (Puri-nethol™-tabl. à 50 mg) — Dosis / %	*Giv merkaptopurin p.o. kontinuerligt* fra "uge 22" til 2½ år fra ALL-diagnose. Dosisreduktion ved TPMT-deficiency og -heterozygocitet til hhv. 5 og 50 mg/m^2. *Se* protokol 11.2.2											
Methotrexat p.o. * **20 mg/m^2 x 1 ugtl.** (Methotrexat-tabl. à 2,5 mg) — Dosis / %	*Giv ldMTX p.o. kontinuerligt x 1 ugtl.* fra "uge 22" (også uge 24+26+28+30) til 2½ år fra ALL-diagn. *Giv dog ikke* ldMTX p.o. i "ugen med hdMTX 5000 mg/m^2". *Se* også appendiks 33.11											
Vinkristin i.v. **2 mg** Infusion 5-15 min. — Dosis / %						2						2
Dexamethason p.o. **6 mg/m^2, 5 dage** (Dexamethason-tabl. à 4 mg) — Dosis i mg						5 dage *3 dgl. doser*						5 dage *3 dgl. doser*
Methotrexat i.v. * **5000 mg/m^2** — Dosis		hydr. kl. 22	andet skema						hydr. kl. 22	andet skema		
Anvend særskilt skema ("NOPHO-MTX 5 g/m^2")				andet skema						andet skema		
Folininsyre (Calciumfolinat) — Dosis												
Anvend skema: "NOPHO-folininsyre-rescue"			*		*	*	*		*		*	
Peg. asparaginase i.m. (Medac) med lidokain **1.000 IE/m^2** — Dosis / %												
Givet af (sign.):				12						12		
Methotrexat isp. **12 mg** — Dosis												
Givet intraspinalt af (sign.):												
Evt. allopurinol p.o. Hvis ja, angiv dosis mg												
Faxet (dato/sign.):		fax til 2 dg.		fax til 2 dg.	fax til 1 dg.	fax til 1 dg.	fax til 1 dg.	fax til 2 dg.		fax til 2 dg.	fax til 1 dg.	fax til 1 dg.
Udleveret medicin:												

Status	Koder	Registrér
Indl.	BWHA 2	Dag 435
Amb.	BWHA 1	Dag 414, 421, 428, 435

NOPHO: ALL (IR) - sen intensifikation II og kons. III

ALL NOPHO-protokol (5 IR), 18 - < 45 år (EuDraCT nr. 2008-003235-20)

Revideret 5.3.12

ALL NOPHO intermediær risiko - forsinket intensifikation II og konsolidering III/15.3.17

Label (lille)

Behandlingsdag:		414	421	428	435 *	436	437	438	439	442	443	444	445	449
Behandlingsuge:		60	61	62	63					64				65
År:	Dato:	/	/	/	/	/	/	/	/	/	/	/	/	/
Højde:	Vægt:													
Overflade i m^2:														
Afdeling:														
Ordineret af (sign.):														
Vinkristin i.v. **2 mg** Infusion 5-15 min.	Dosis %	2	2	2	2									
Dexamethason p.o. **10 mg/m^2** (Dexamethason-tabl. à 4 mg)	Dosis i mg	"d. 414-420" *3 dgl. doser*		"d. 428-434" *3 dgl. doser*	* aftrap-ning									
Cyclophosphamid i.v. **1000 mg/m^2** Infusion 60 min.	Dosis %				*									
Cytarabin i.v. **75 mg/m^2** Bolusinfusion	Dosis %													
Givet af (sign.):														
Thioguanin p.o. **60 mg/m^2 dgl.** (Lanvis®-tabl. à 40 mg)	Dosis %				*Dosér* i mg til om aftenen i 14 dage (doser delelig med 20) Dosisreduktion ved TPMT-mangel til 20 mg/m^2									
Methotrexat isp. **12 mg**	Dosis	12												12
Givet intraspinalt af (sign.):														
Evt. allopurinol p.o. Hvis ja, angiv dosis mg														
Faxet (dato/sign.):		*fax til 1 dg.*	*fax til 1 dg.*	*fax til 1 dg.*	*fax til 5 dg.*					*fax til 4 dg.*				*fax til 1 dg.*
Udleveret medicin:														

Status	Koder	Registrér
Indl.	-	-
Amb.	HWHA119	Ved fremmøde
	HWHA1	Ved fremmøde
	HWHA162	Dag 512, 568, 624, 680, 736 osv.

NOPHO: ALL (IR) - vedligeholdelse II

ALL NOPHO-protokol (6 IR), 18 - < 45 år (EuDraCT nr. 2008-003235-20)

Revideret 26.1.15

ALL NOPHO intermediær risiko - vedligeholdelse II/15.3.17

Label (lille)

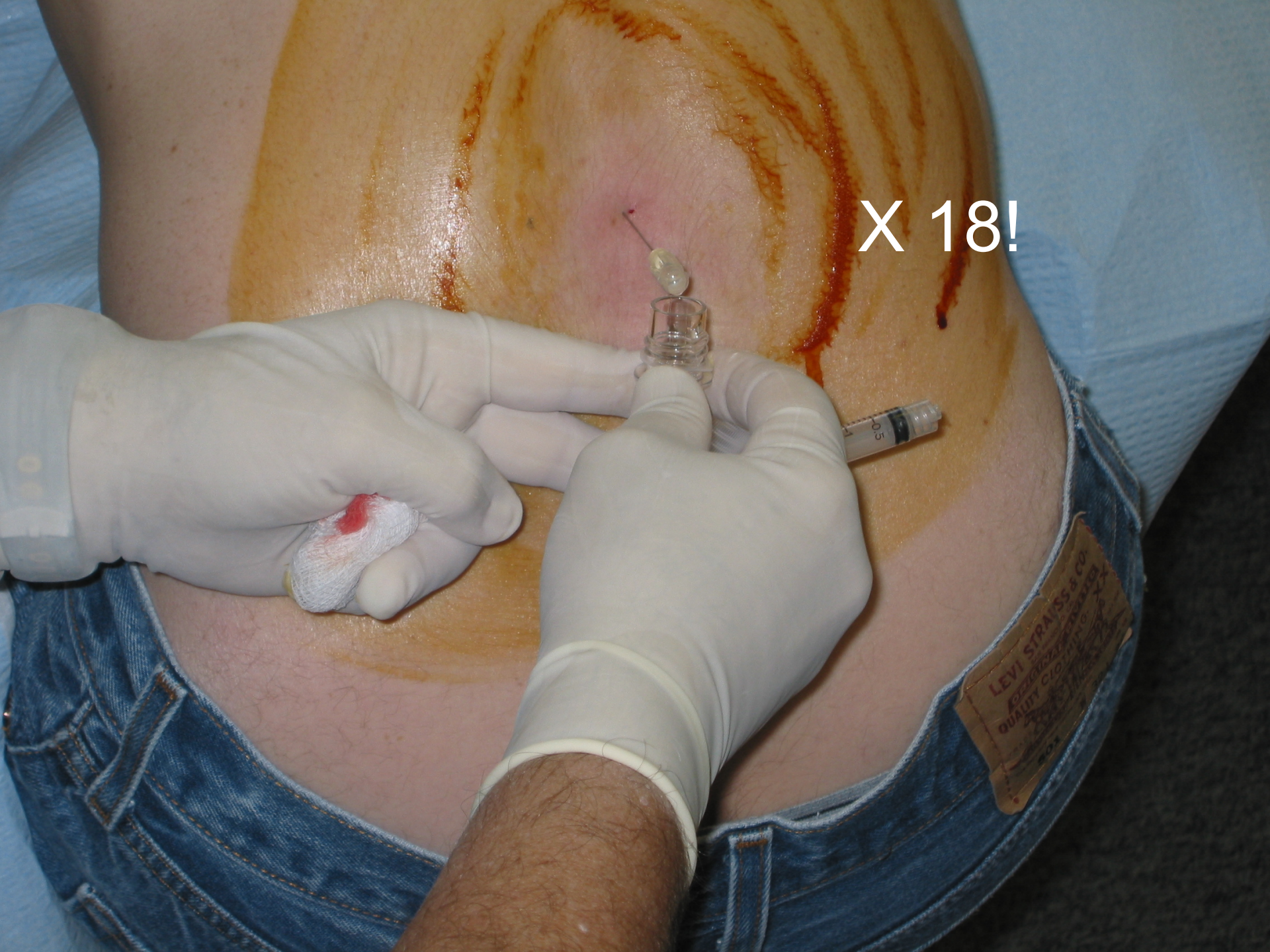
Behandlingsdag:	456-511	512	519-567	568	575-623	624	631-679	680
Behandlingsuge:	66-73	74	75-81	82	83-89	90	91-97	98
År: Dato:	/ - /	/	/ - /	/	/ - /	/	/ - /	/
Højde: Vægt:								
Overflade i m²:								
Afdeling:								
Ordineret af (sign.):								
Merkaptopurin * (Puri-nethol™) p.o. **75 mg/m² dgl.** Puri-nethol™-tabl. à 50 mg — Dosis	*Giv* merkaptopurin kontinuerligt til 2½ år fra ALL-diagnose. Dosisreduktion ved TPMT-deficiency og -heterozygoticitet til hhv. 10 og 50 mg/m². *Se* protokol 11.2.2							
%								
Methotrexat p.o. * 20 mg/m² x 1 ugtl. Methotrexat-tabl. à 2,5 mg — Dosis	*Giv* ldMTX p.o. kontinuerligt til 2½ år fra ALL-diagnose. *Giv* dog ikke ldMTX p.o. i "ugen med MTX intraspinalt". *Se* også appendiks 33.11							
%								
Methotrexat isp. 12 mg Dosis		12		12		12		12
Givet intraspinalt af (sign.):								
Evt. allopurinol p.o. *Hvis* ja, *angiv* dosis mg								
Faxet (dato/sign.):		fax til 1 dg.		fax til 1 dg.		fax til 1 dg.		fax til 1 dg.
Udleveret medicin:								

Behandlingsdag:	687-735	736	743-791	792	799-847	848	855-903	904
Behandlingsuge:	99-105	106	107-113	114	115-121	122	123-129	130
År: Dato:	/ - /	/	/ - /	/	/ - /	/	/ - /	/
Højde: Vægt:								
Overflade i m²:								
Afdeling:								
Ordineret af (sign.):								
Merkaptopurin * (Puri-nethol™) p.o. **75 mg/m² dgl.** Puri-nethol™-tabl. à 50 mg — Dosis	*Giv* merkaptopurin kontinuerligt til 2½ år fra ALL-diagnose. Dosisreduktion ved TPMT-deficiency og -heterozygoticitet til hhv. 10 og 50 mg/m². *Se* protokol 11.2.2							
%								
Methotrexat p.o. * 20 mg/m² x 1 ugtl. Methotrexat-tabl. à 2,5 mg — Dosis	*Giv* ldMTX p.o. kontinuerligt til 2½ år fra ALL-diagnose. *Giv* dog ikke ldMTX p.o. i "ugen med MTX intraspinalt". *Se* også appendiks 33.11							
%								
Methotrexat isp. 12 mg Dosis		12		12		12		12
Givet intraspinalt af (sign.):								
Evt. allopurinol p.o. *Hvis* ja, *angiv* dosis mg								
Faxet (dato/sign.):		fax til 1 dg.		fax til 1 dg.		fax til 1 dg.		fax til 1 dg.
Udleveret medicin:								

Kommentar:
Kvalmegruppe 0.

* *Giv* **ldMTX p.o.** x 1 ugentligt - dog ikke i "ugen med MTX intraspinalt". "Target-dosis" af merkaptopurin og ldMTX: leukocytter 1,5-3,0 mia/l (*se* appendiks 33.11).

Hæmatologisk afdeling R, Aarhus Universitetshospital


X 18!

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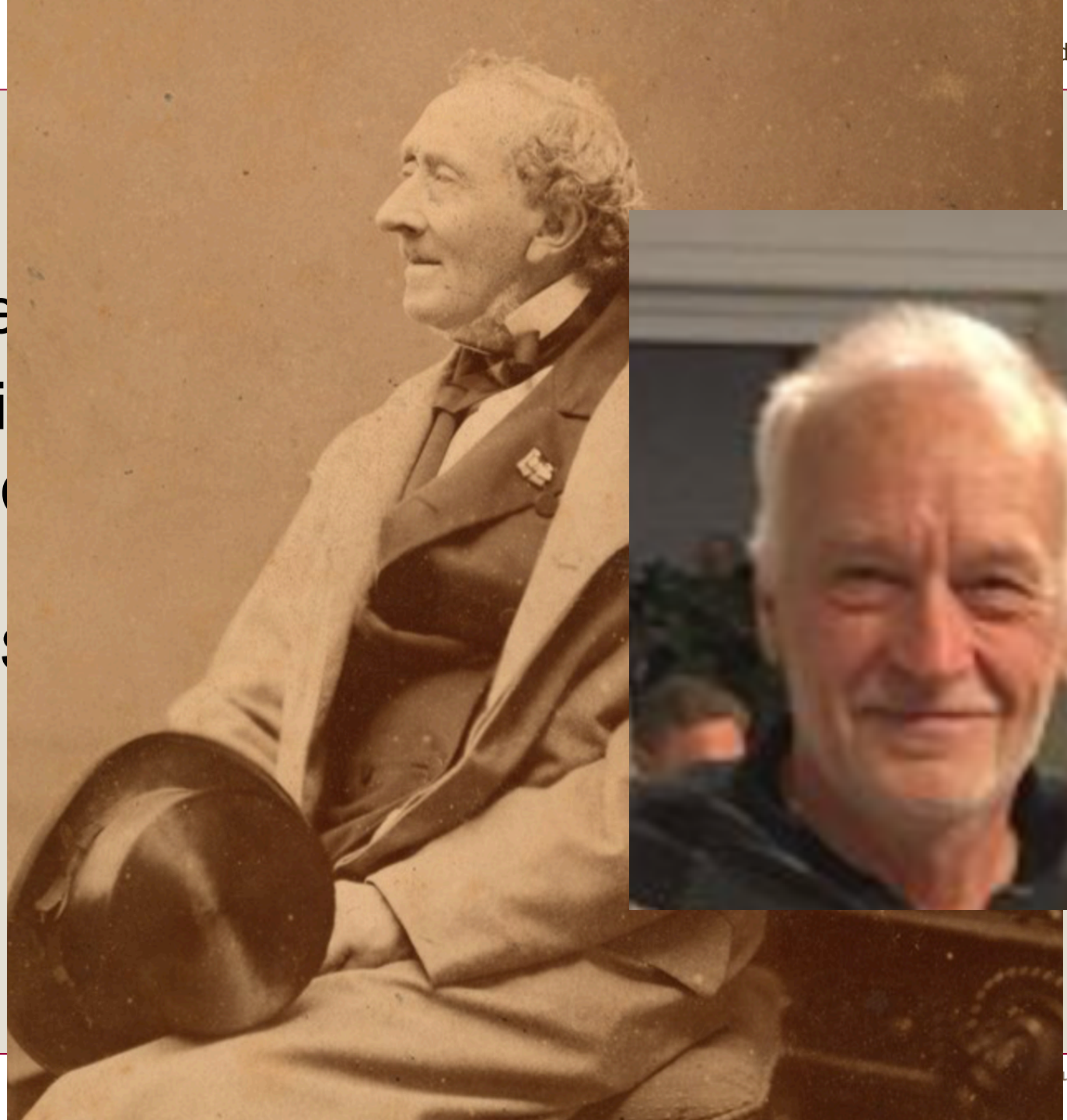
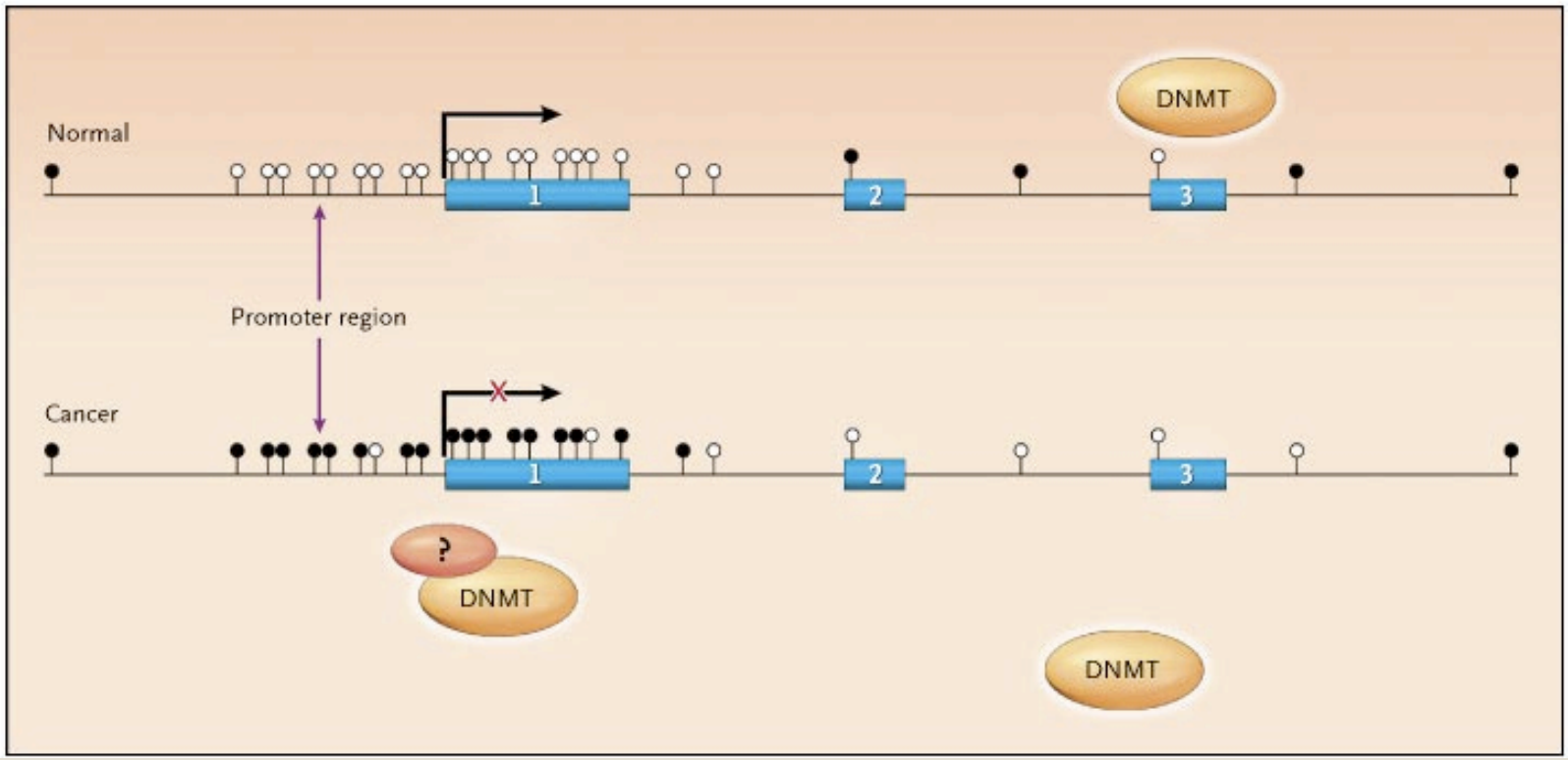


Dilemma: intensiv kemoterapi ved AML patient omkring 70

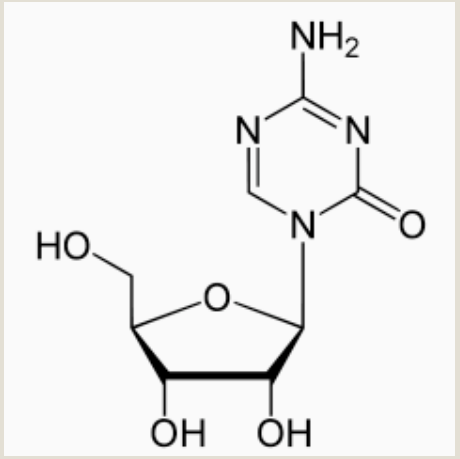
- For:
  - Nogle (få) kan helbredes, afhængigt af undertype. Kræver transplantation
  - Nogle patienter er i god almentilstand
- Imod:
  - Intensiv kemoterapi er bivirkningstungt
  - Hvor stor skal chancen være?

Azacitidin ved MDS og AML

- Meget kort om methylering

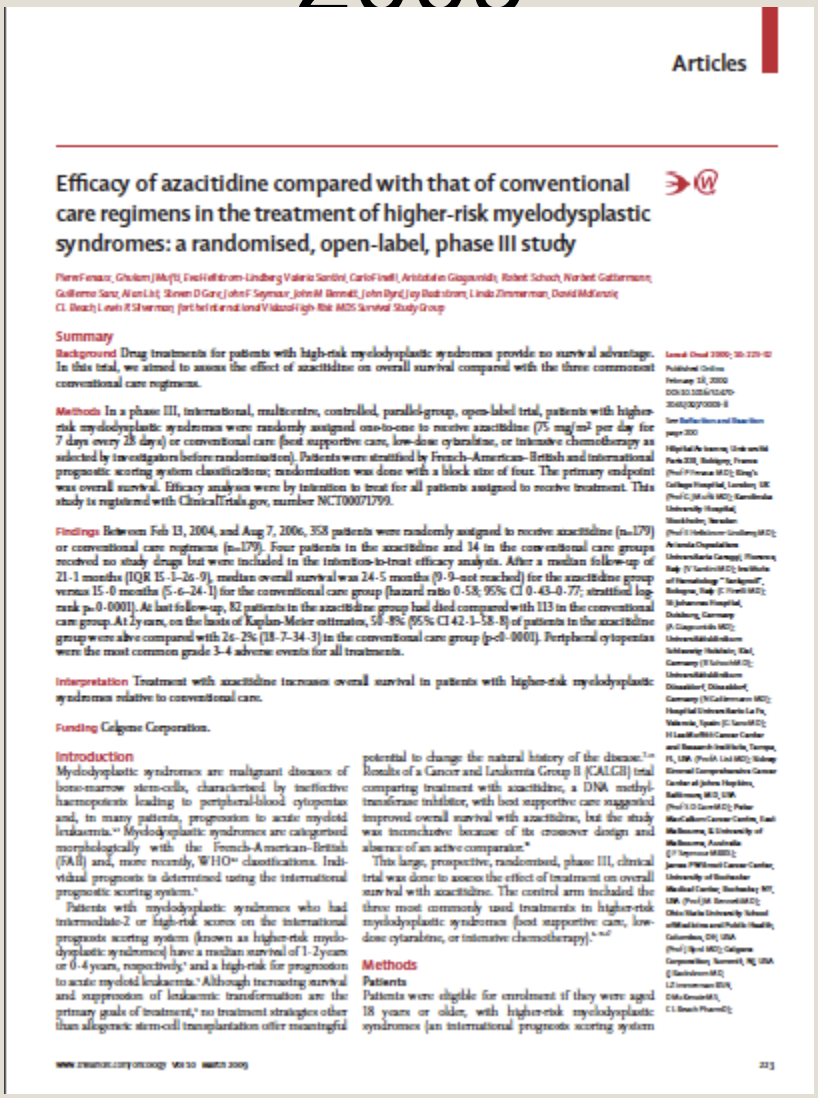


Azacytidin



- antimetabolit
- Indbygges i RNA - og DNA
- Demethylering

Fenaux et al, Lancet Oncology 2009



Articles

Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study

Pierre Fenaux, Ghulam J Mufti, Eva Hellstrom-Lindberg, Valeria Santini, Carlo Finelli, Aristoteles Giagounidis, Robert Schoch, Norbert Gattermann, Guillermo Sanz, Alan List, Steven D Gore, John F Seymour, John M Bennett, John Byrd, Jay Backstrom, Linda Zimmerman, David McKenzie, Cl. Beach, Lewis R Silverman, for the International Vidaza High-Risk MDS Survival Study Group

Summary

Background Drug treatments for patients with high-risk myelodysplastic syndromes provide no survival advantage. In this trial, we aimed to assess the effect of azacitidine on overall survival compared with the three commonest conventional care regimens.

Methods In a phase III, international, multicentre, controlled, parallel-group, open-label trial, patients with higher-risk myelodysplastic syndromes were randomly assigned one-to-one to receive azacitidine (75 mg/m² per day for 7 days every 28 days) or conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy as selected by investigators before randomisation). Patients were stratified by French-American-British and international prognostic scoring system classifications; randomisation was done with a block size of four. The primary endpoint was overall survival. Efficacy analyses were by intention to treat for all patients assigned to receive treatment. This study is registered with ClinicalTrials.gov, number NCT00071799.

Findings Between Feb 13, 2004, and Aug 7, 2006, 358 patients were randomly assigned to receive azacitidine (n=179) or conventional care regimens (n=179). Four patients in the azacitidine and 14 in the conventional care groups received no study drugs but were included in the intention-to-treat efficacy analysis. After a median follow-up of 21·1 months (IQR 15·1–26·9), median overall survival was 24·5 months (9·9–not reached) for the azacitidine group versus 15·0 months (5·6–24·1) for the conventional care group (hazard ratio 0·58; 95% CI 0·43–0·77; stratified log-rank p=0·0001). At last follow-up, 82 patients in the azacitidine group had died compared with 113 in the conventional care group. At 2 years, on the basis of Kaplan-Meier estimates, 50·8% (95% CI 42·1–58·8) of patients in the azacitidine group were alive compared with 26·2% (18·7–34·3) in the conventional care group (p<0·0001). Peripheral cytopenias were the most common grade 3–4 adverse events for all treatments.

Interpretation Treatment with azacitidine increases overall survival in patients with higher-risk myelodysplastic syndromes relative to conventional care.

Funding Celgene Corporation.

Introduction

Myelodysplastic syndromes are malignant diseases of bone-marrow stem-cells, characterised by ineffective haemopoiesis leading to peripheral-blood cytopenias and, in many patients, progression to acute myeloid leukaemia.[1–3] Myelodysplastic syndromes are categorised morphologically with the French-American-British (FAB) and, more recently, WHO[4] classifications. Individual prognosis is determined using the international prognostic scoring system.[5]

Patients with myelodysplastic syndromes who had intermediate-2 or high-risk scores on the international prognostic scoring system (known as higher-risk myelodysplastic syndromes) have a median survival of 1·2 years or 0·4 years, respectively,[5] and a high risk for progression to acute myeloid leukaemia.[6] Although increasing survival and suppression of leukaemic transformation are the primary goals of treatment,[7] no treatment strategies other than allogeneic stem-cell transplantation offer meaningful potential to change the natural history of the disease.[7–10] Results of a Cancer and Leukaemia Group B (CALGB) trial comparing treatment with azacitidine, a DNA methyltransferase inhibitor, with best supportive care suggested improved overall survival with azacitidine, but the study was inconclusive because of its crossover design and absence of an active comparator.[11]

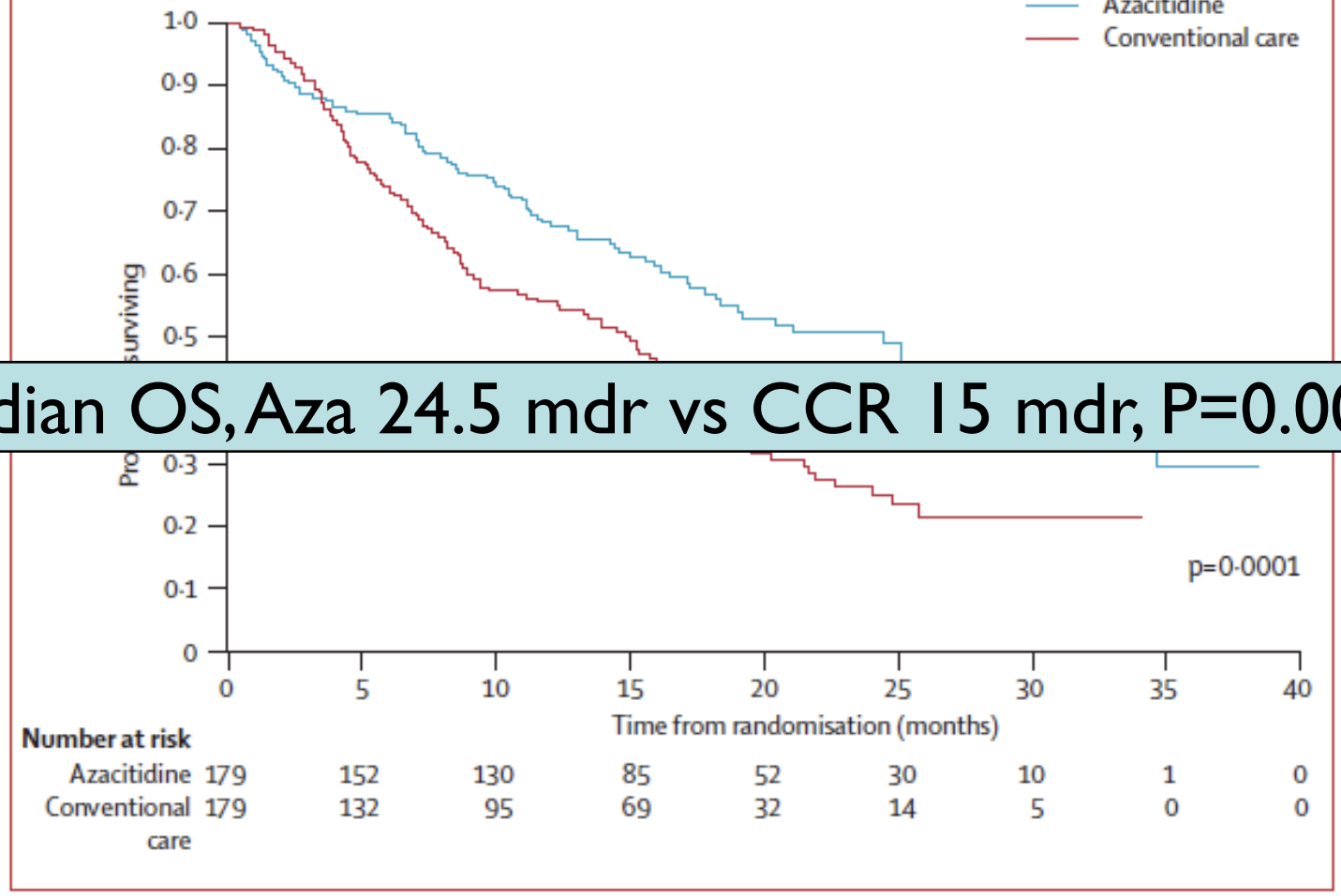
This large, prospective, randomised, phase III, clinical trial was done to assess the effect of treatment on overall survival with azacitidine. The control arm included the three most commonly used treatments in higher-risk myelodysplastic syndromes (best supportive care, low-dose cytarabine, or intensive chemotherapy).[6,8,12]

Methods

Patients

Patients were eligible for enrolment if they were aged 18 years or older, with higher-risk myelodysplastic syndromes (an international prognostic scoring system

Resultater



Median OS, Aza 24.5 mdr vs CCR 15 mdr, P=0.0001

Figure 3: **Overall survival**

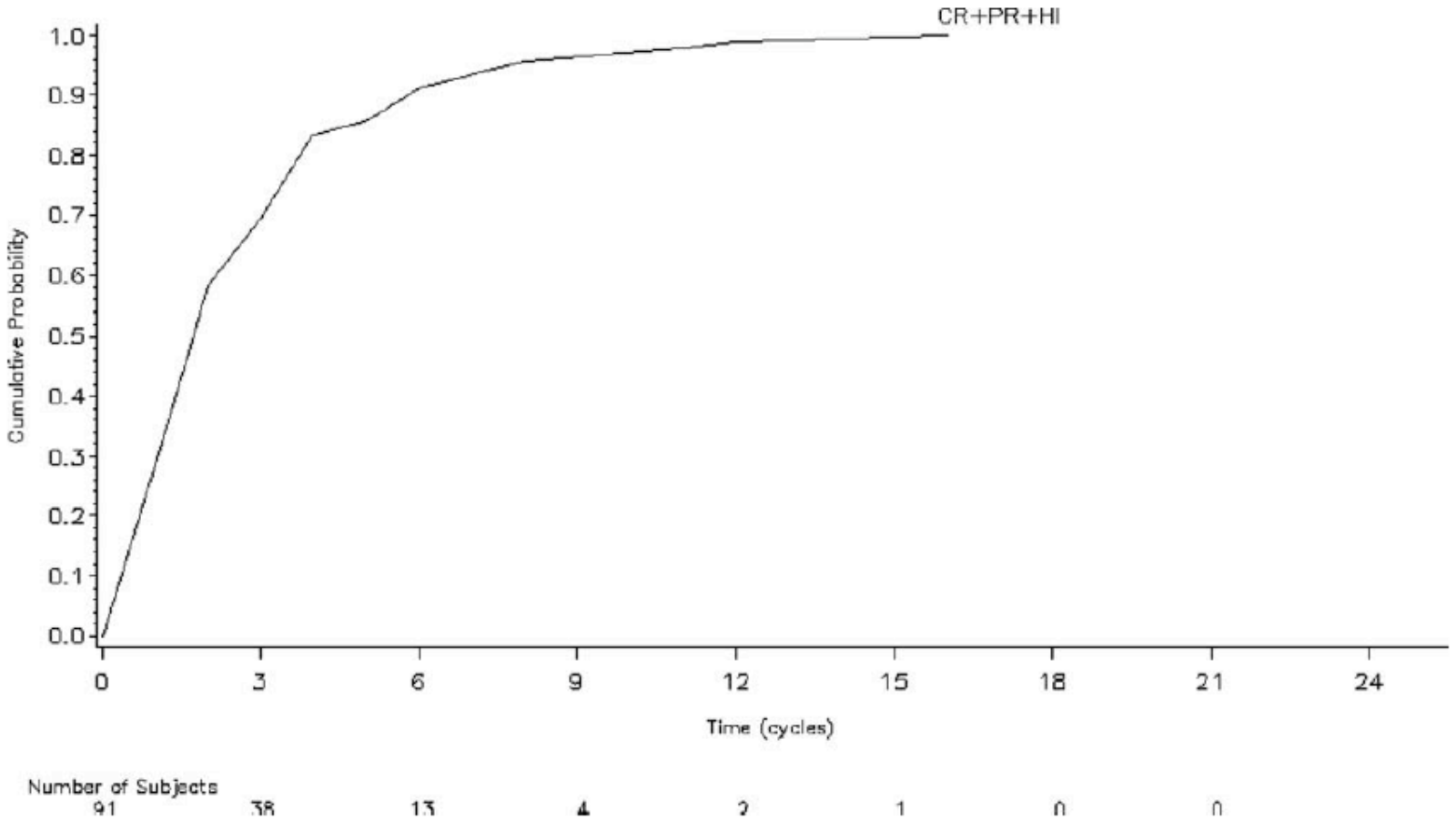
Resultater (2)

- Effekt i alle subgrupper - dvs inkl dårlige prognostiske
- Færre infektioner, sammenlignelig mængde andre bivirkninger

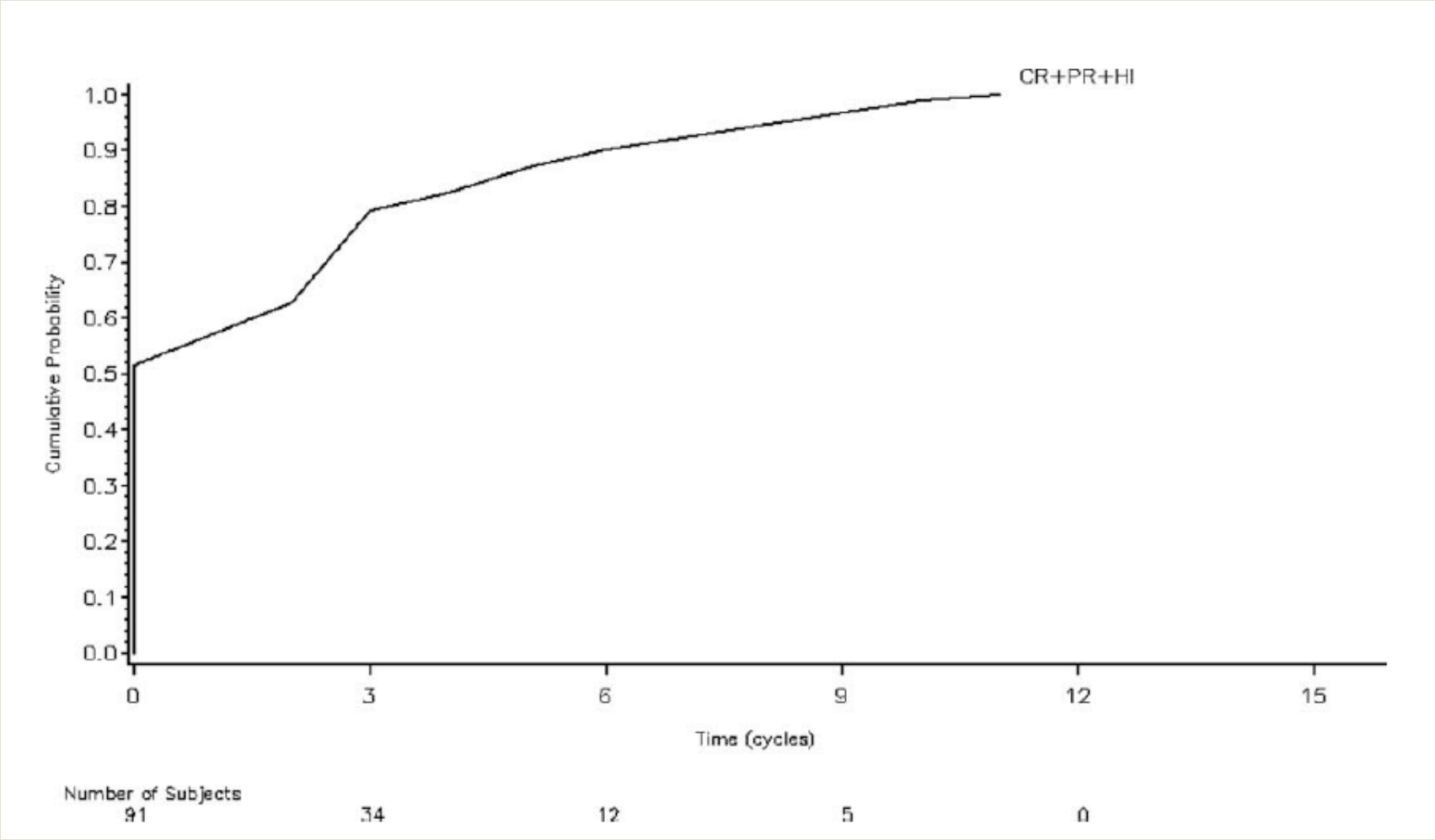
Konklusion

- Azacytidin giver bedre overlevelse
- Uafhængigt af prognostisk gruppe
- Effekt bedst vist ved patienter bedst egnet til BSC

Administration



Administration (2)

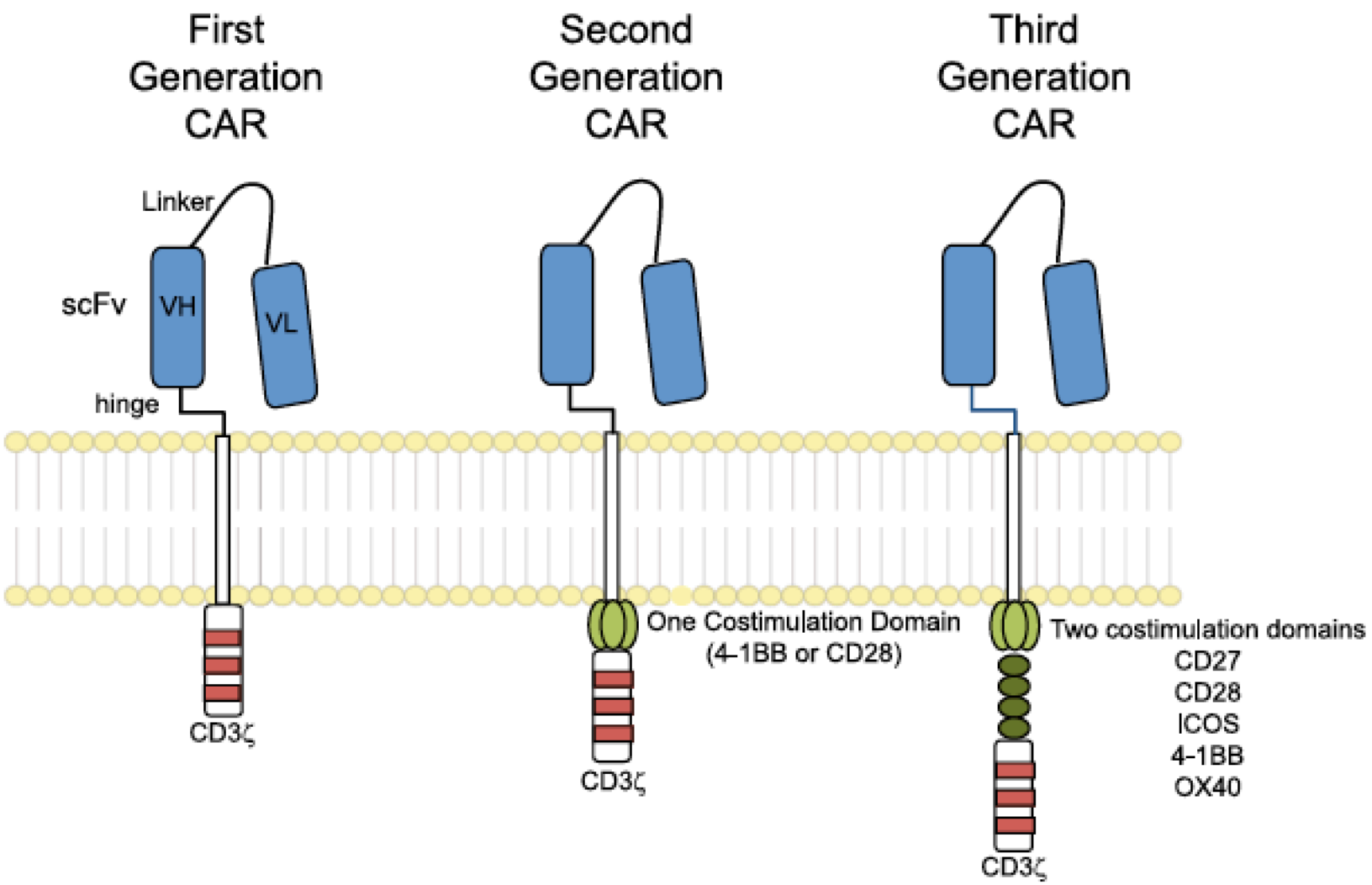


Celgenes aktier

Marts 2009, Fenaux et al

(Pris pr 19/3: ca 30.000kr/5dages behandling)

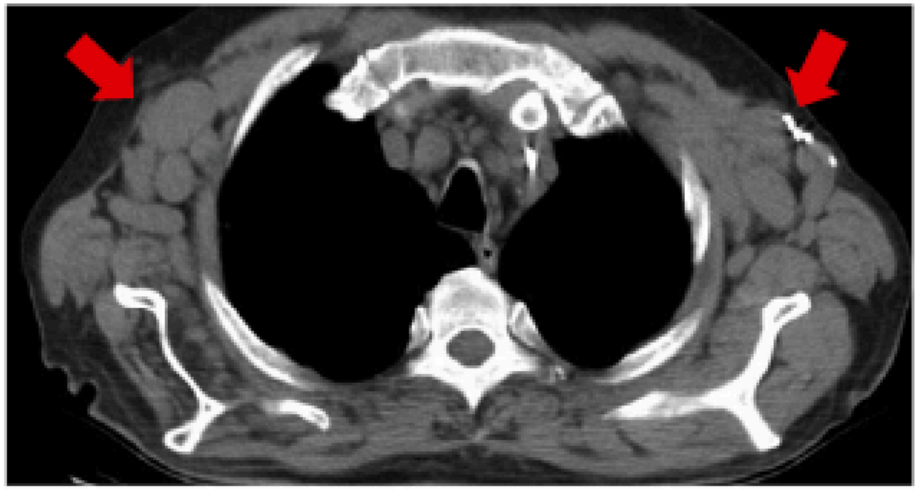
Del 2: Nuværende og fremtidig



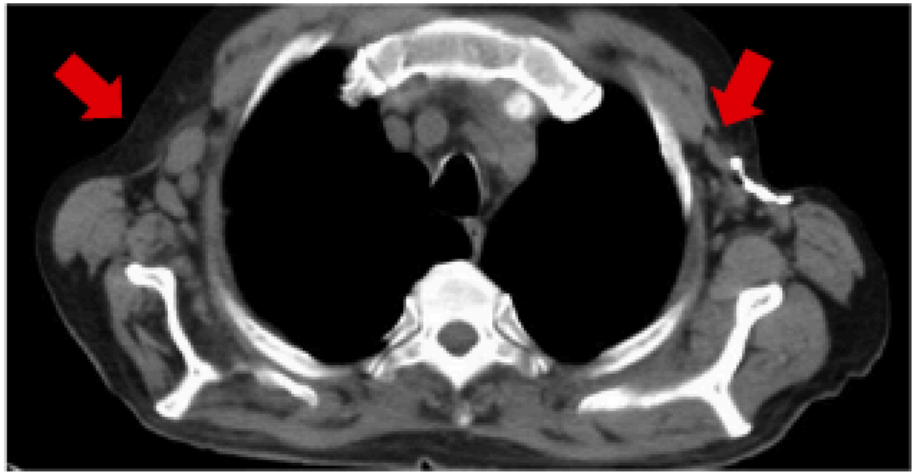
Maus et al Blood 2014

E

Before cell infusion



26 days after cell infusion



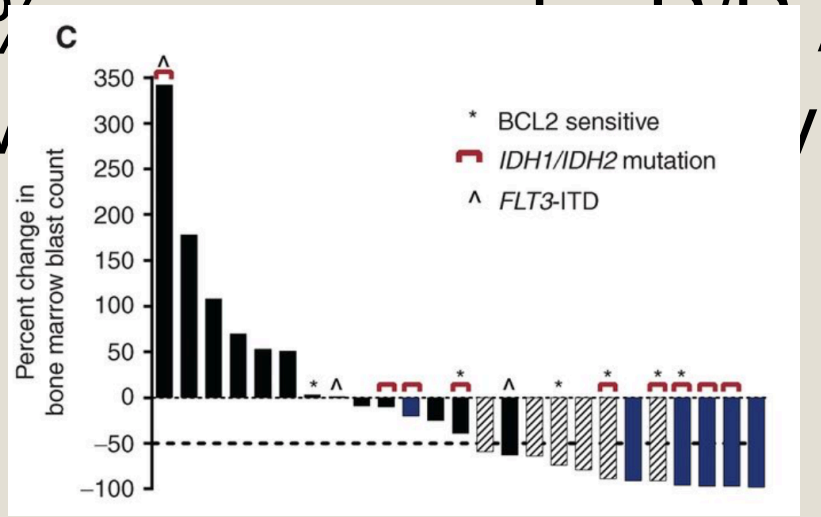
Kochendercher et al Blood 2013

Udfordringer

- Tumorlysis syndrom
- Cytokinstorm

Venetoclax i AML

- Bcl-2 inhibitor
- Ikke alt for imponerende single agent data (19% AML) - Konoplev very 2016



Pollyea et al: aza+venetoclax

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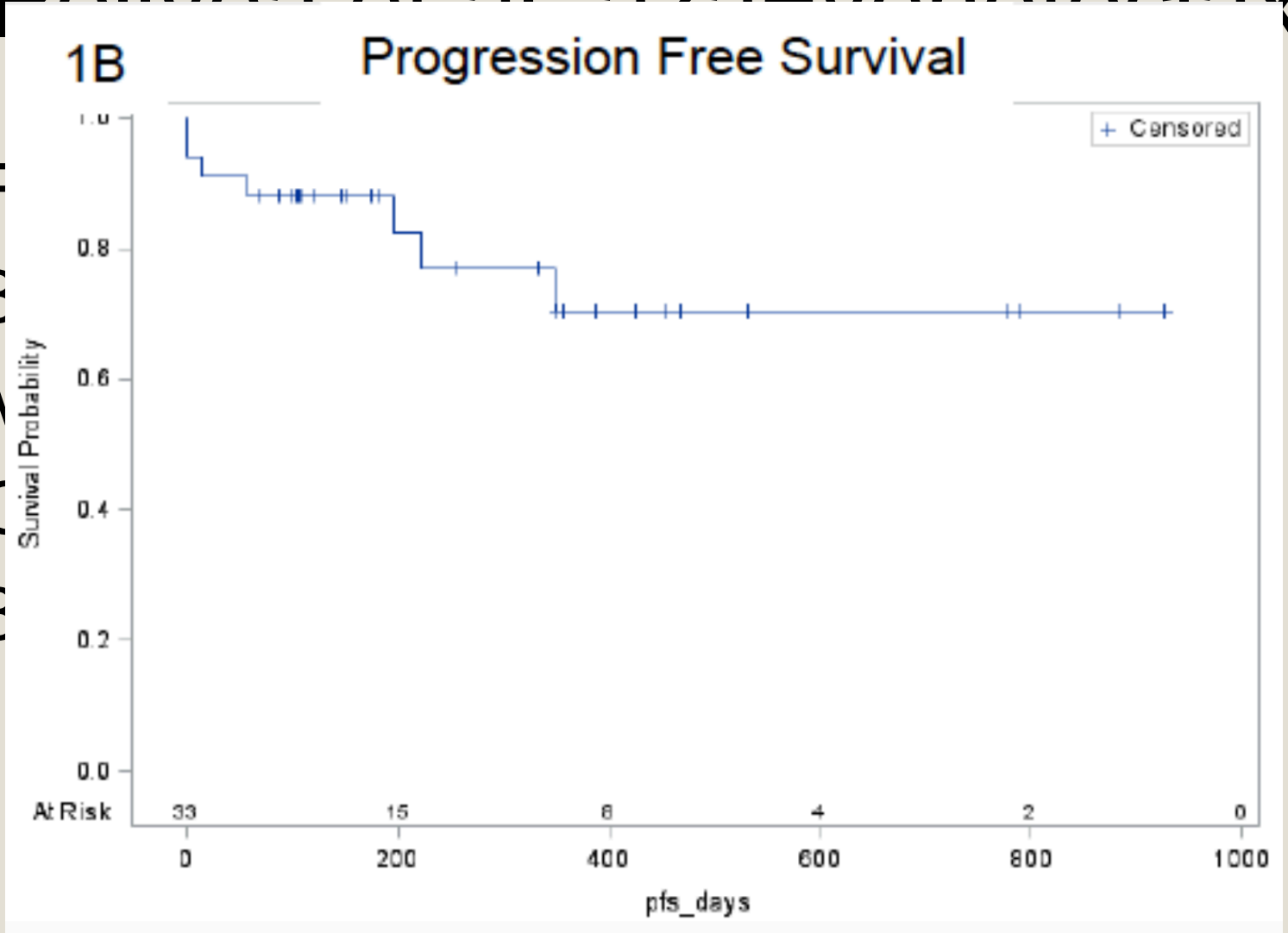
- 3
- M
- C
- 8



AML: særlig behandling af specielle undertyper

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 30, 2013 VOL. 368 NO. 22

Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia

The Cancer Genome Atlas Research Network

- Sekventering af hele genomet (50pts), hele exomet (150 pts)


Mutation Type
Exclusive across categories
Co-occurring across categories
Co-occurring within category
2-Hit mutation
Cytogenetic Risk
Unfavorable
Intermediate
Favorable
Unknown
Dendrix++ Group
A
B
C
TF Fusions
PML-RARA
MYH11-CBFB
RUNX1-RUNX1T1
PICALM-MLLT10
NPM1
Tumor Suppressors
TP53
WT1
PHF6
DNA Methylation
DNMT3A
DNMT3B
DNMT1
TET1
TET2
IDH1
IDH2
Activated Signaling
FLT3
KIT
Other Tyr kinases
Ser–Thr kinases
KRAS/NRAS
PTPs
Myeloid TFs
RUNX1
CEBPA
Other myeloid TFs
Chromatin Modifiers
MLL-X fusions
MLL-PTD
NUP98-NSD1
ASXL1
EZH2
KDM6A
Other modifiers
Cohesin
Spliceosome
Cytogenetic Risk
200 AML Samples

AML: særlig behandling i undertyper

- Midostaurin: 6% overlevelsesgevinst ved FLT3-ITD AML
- Mylotarg: 15% overlevelsesgevinst ved CBF AML
- Enasidenib: 50% respons ved terminal IDH2 AML

Erfaring fra Aarhus

- Terminal IDH2+ AML behandlet med Enasidenib, startet 7/2 2017

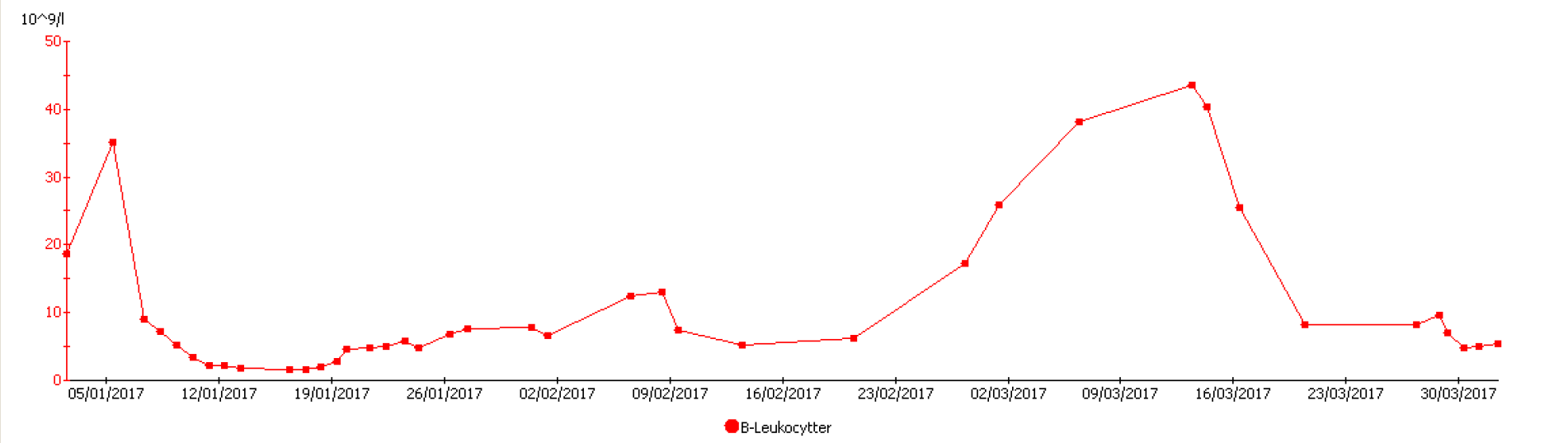
13.02.17 11:40, Hans Beier Ommen, Overlæge, Hæmatologisk Overafd. R - AUH / birtjr

AUH, Hæm. R Amb.

Klinisk kontrol

Journalnotat
Ualmindelig velbefindende. Har ikke haft feber siden 2 dage efter han startede på AG-221. Tager ikke længere Panodil.
Siger han har det bedre nu end når han tager Panodil.

De næste måneder



Regular Article

blood

CLINICAL TRIALS AND OBSERVATIONS

Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia

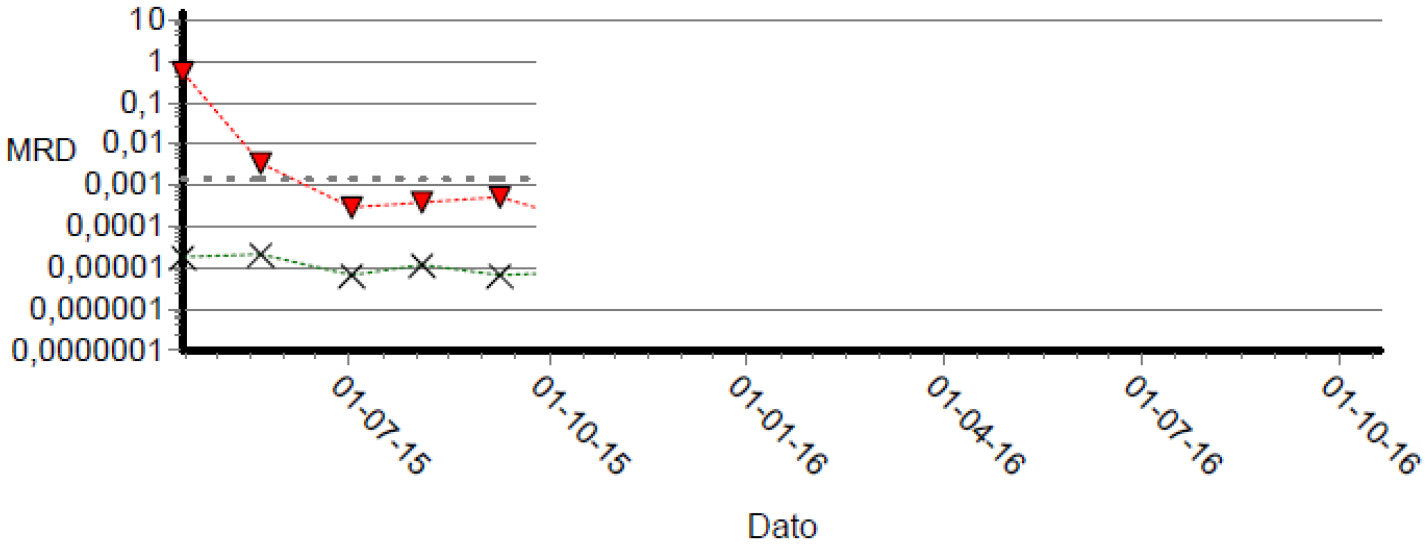
Eytan M. Stein,[1,2,*] Courtney D. DiNardo,[3,*] Daniel A. Pollyea,[4] Amir T. Fathi,[5,6] Gail J. Roboz,[2,7] Jessica K. Altman,[8] Richard M. Stone,[9] Daniel J. DeAngelo,[9] Ross L. Levine,[1] Ian W. Flinn,[10] Hagop M. Kantarjian,[3] Robert Collins,[11] Manish R. Patel,[12] Arthur E. Frankel,[11] Anthony Stein,[13] Mikkael A. Sekeres,[14] Ronan T. Swords,[15] Bruno C. Medeiros,[16] Christophe Willekens,[17,18] Paresh Vyas,[19,20] Alessandra Tosolini,[21] Qiang Xu,[21] Robert D. Knight,[21] Katharine E. Yen,[22] Sam Agresta,[22] Stephane de Botton,[17,18,†] and Martin S. Tallman[1,2,†]

Blood aug 2017

- Patienter der opnår CR: medianoverlevelse 20 måneder

Overvågning af AL mhp tidlig behandling

Blod


10
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MRD 0,01
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01-10-15
01-01-16
01-04-16
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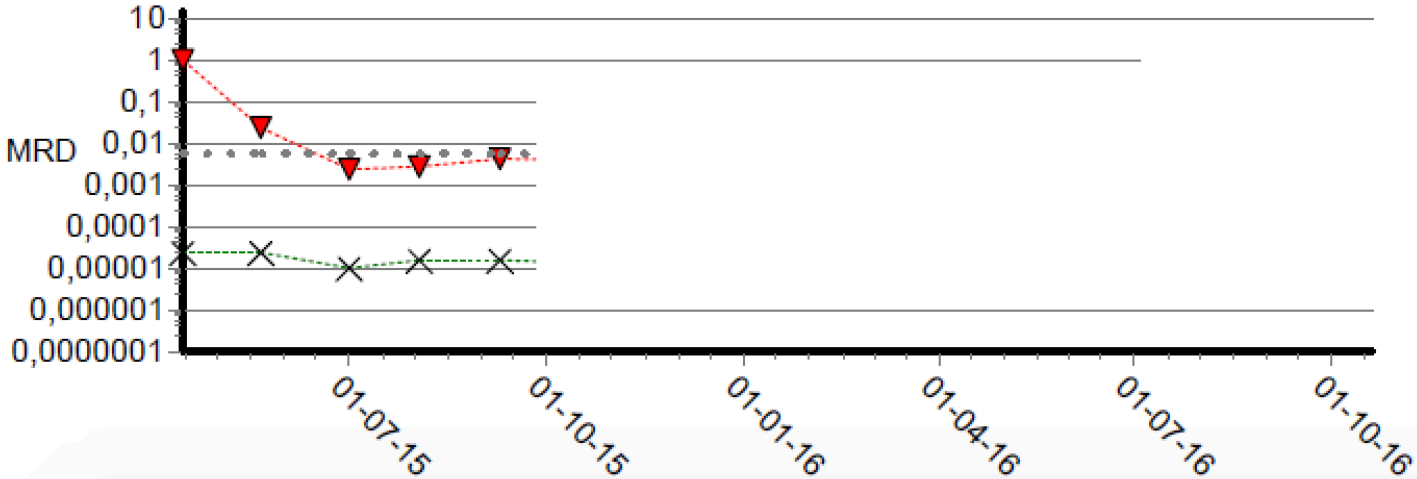
01-10-16
Dato
MRD
Følsomhed
Negativ
Normalniveau Blod

Marv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MRD 0,01
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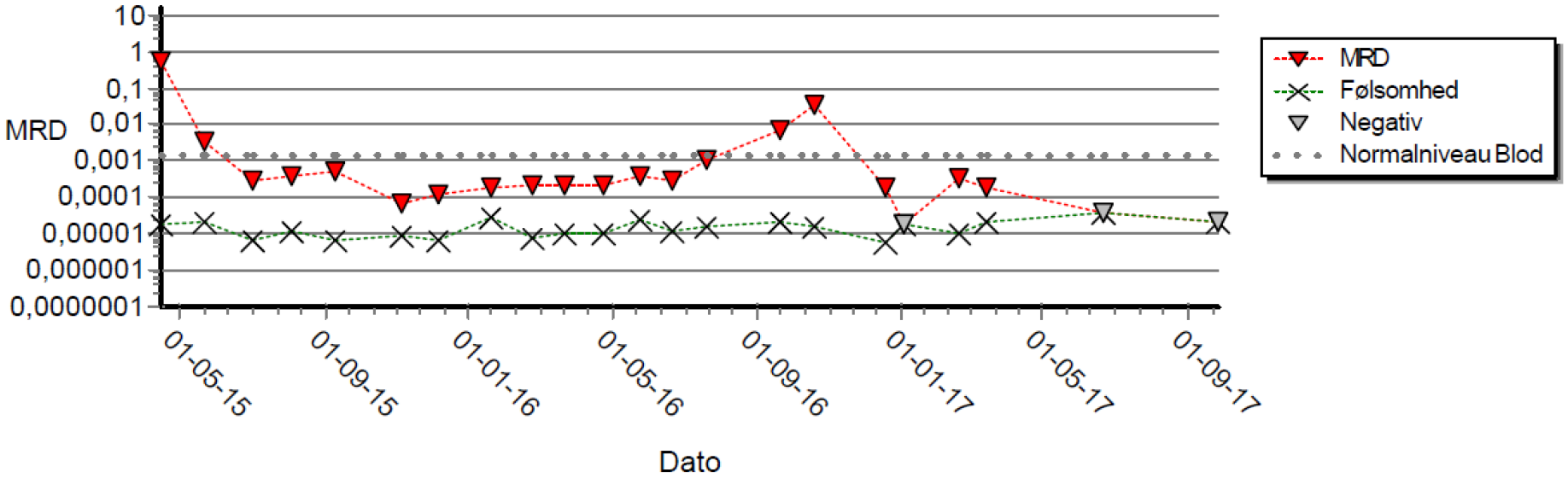
01-07-16
01-10-16
MRD
Følsomhed
Negativ
Normalniveau Marv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Dato
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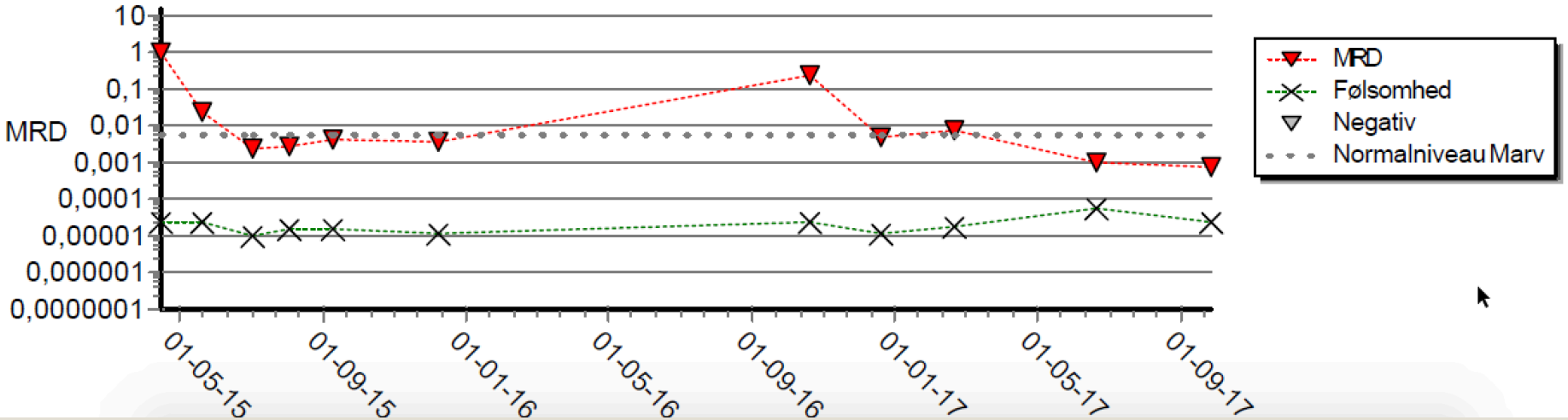
Følsomhed
Negativ
Normalniveau Blod

Marv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01-01-16
01-05-16
01-09-16
01-01-17
01-05-17
01-09-17
MRD
Følsomhed
Negativ
Normalniveau Marv