

3rd edition

Unmet challenges in high-risk
hematological malignancies:
from benchside to clinical practice

Turin, September 21-22, 2023

Starhotels Majestic

Scientific board:

Marco Ladetto (Alessandria)

Umberto Vitolo (Candiolo-TO)



Biology of high-risk ALL

Sabina Chiaretti



SAPIENZA
UNIVERSITÀ DI ROMA

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						X	
Incyte						X	
Pfizer						X	
Abbvie						X	
Gilead						X	

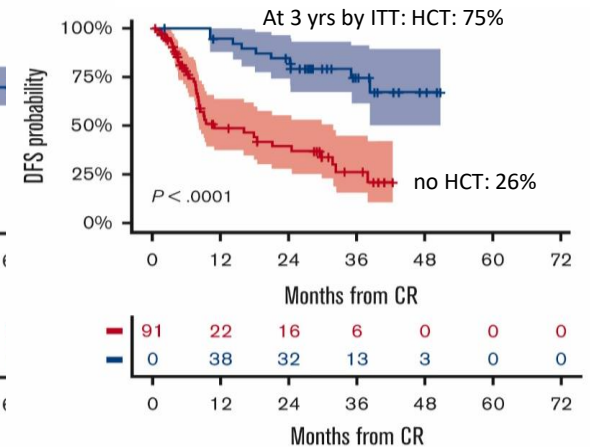
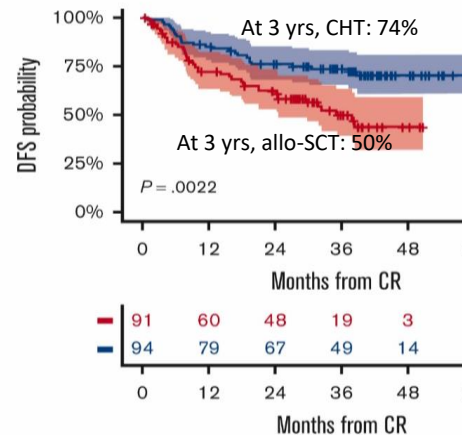
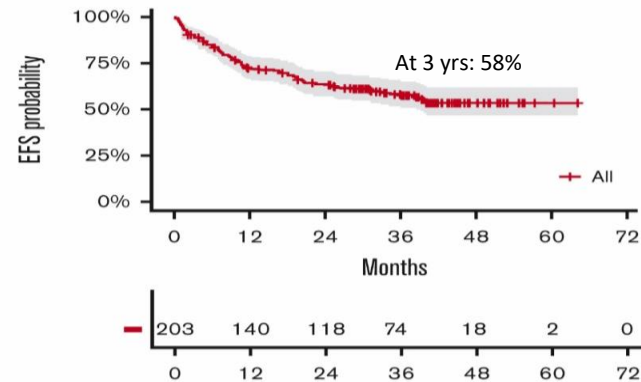
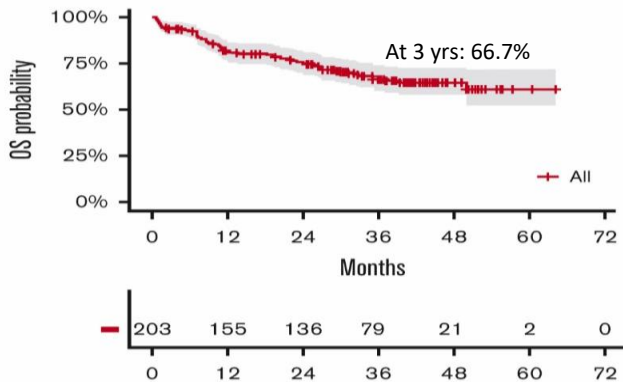
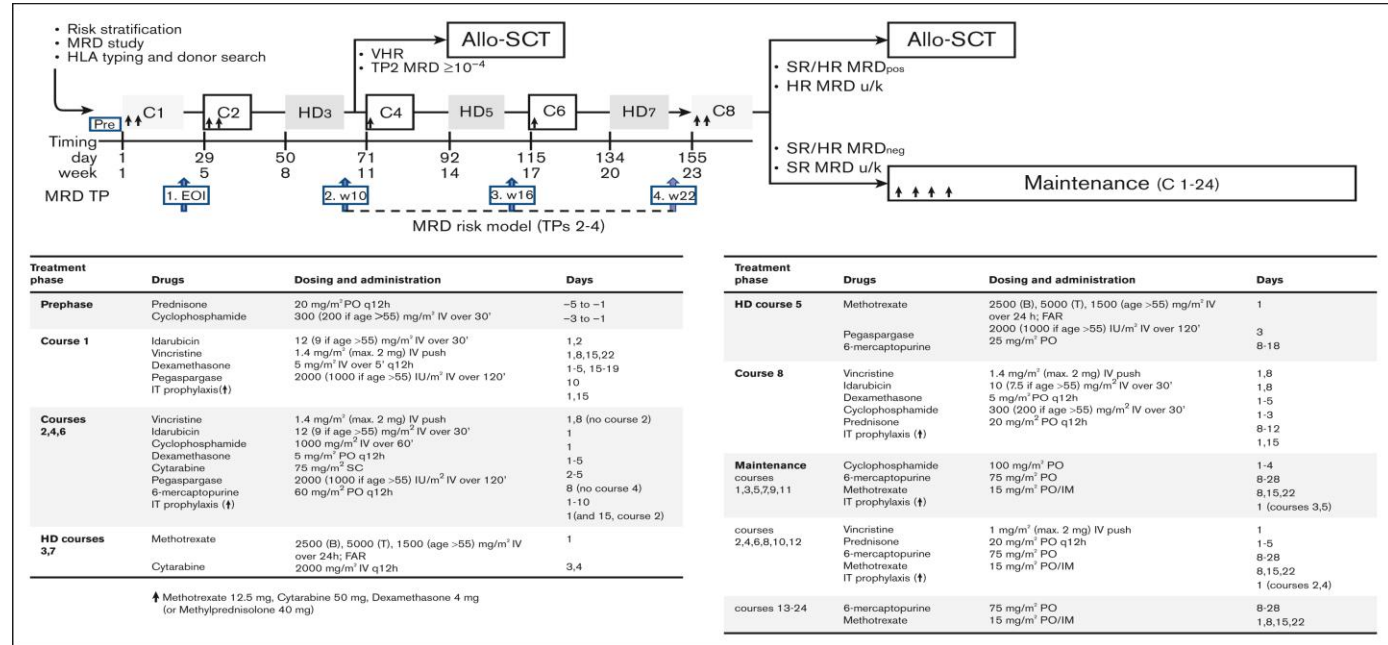
ALL in adults: where do we stand?

Inclusion criteria

Ph-ALL: both B- and T- ALL

203 patients enrolled

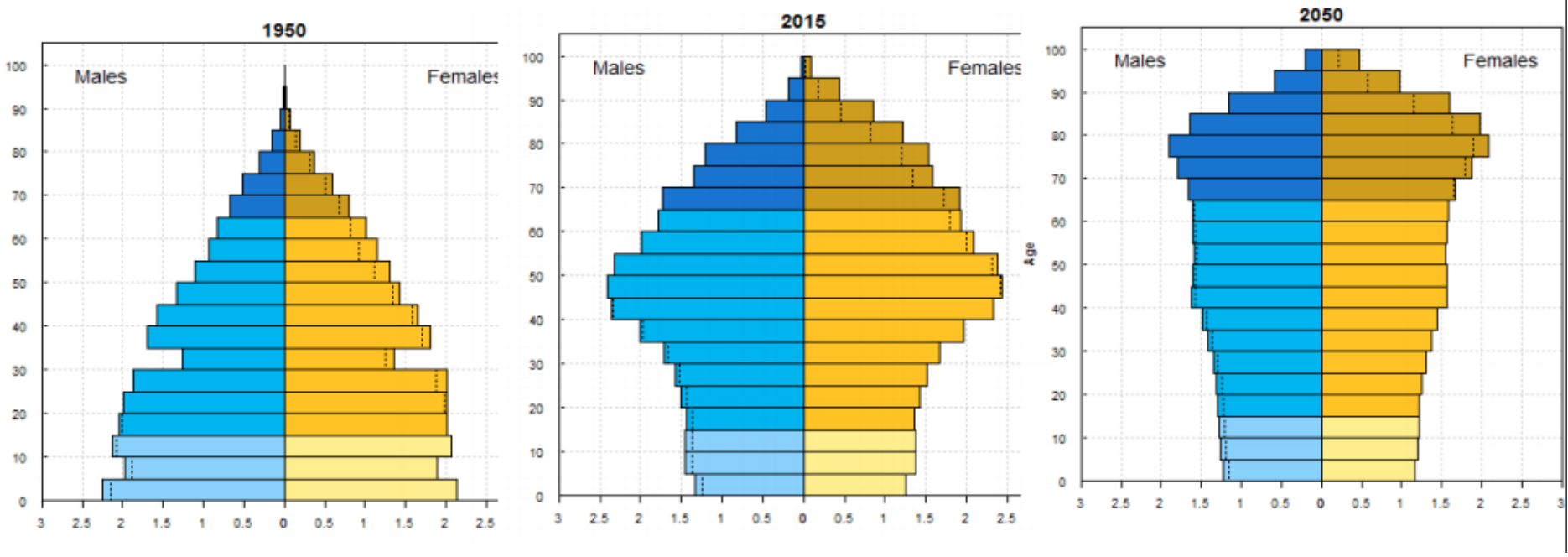
Age: 18-65 yrs



Who is high-risk nowadays?

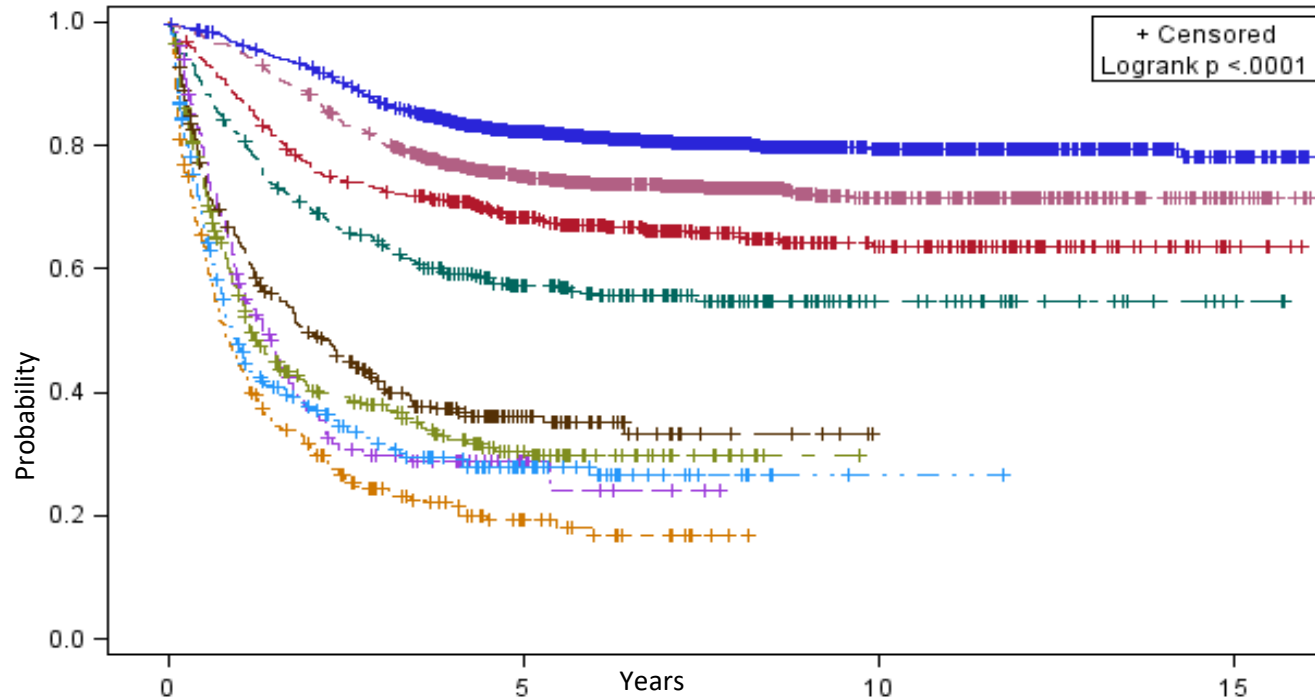
- Age
- Biological findings
- MRD
- CNS

Ageing: probabilistic projections in Italy



<https://greenvoices.files.wordpress.com/2011/08/population-japan.jpg>

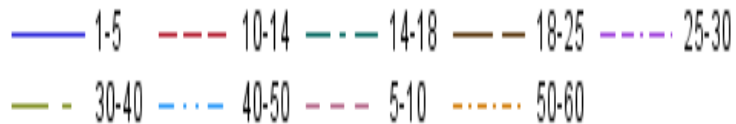
Overall outcome according to age



Reasons for poorer outcome in adults:

- Presence of comorbidities
- Higher/lower compliance to treatment
- Non-intensive treatment
- Different incidence of molecular transcripts
- Improvement with introduction of monoclonal antibodies, but results still suboptimal

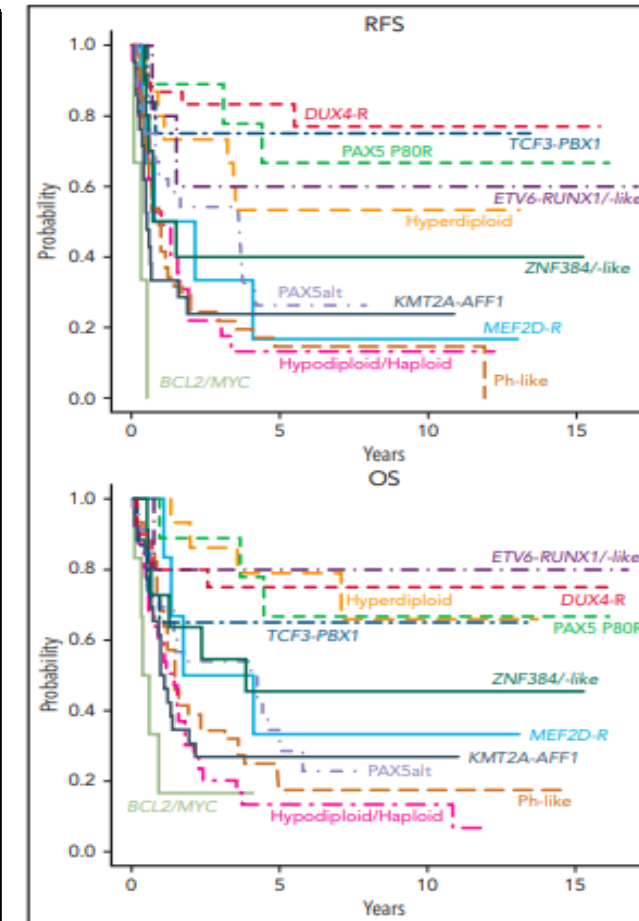
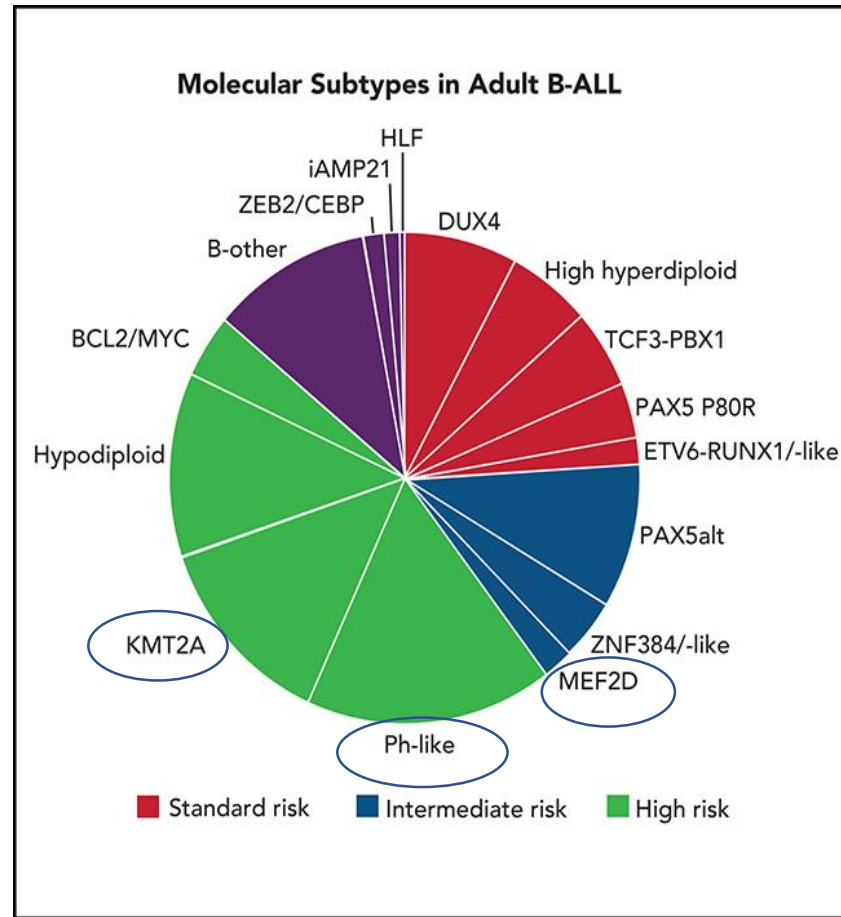
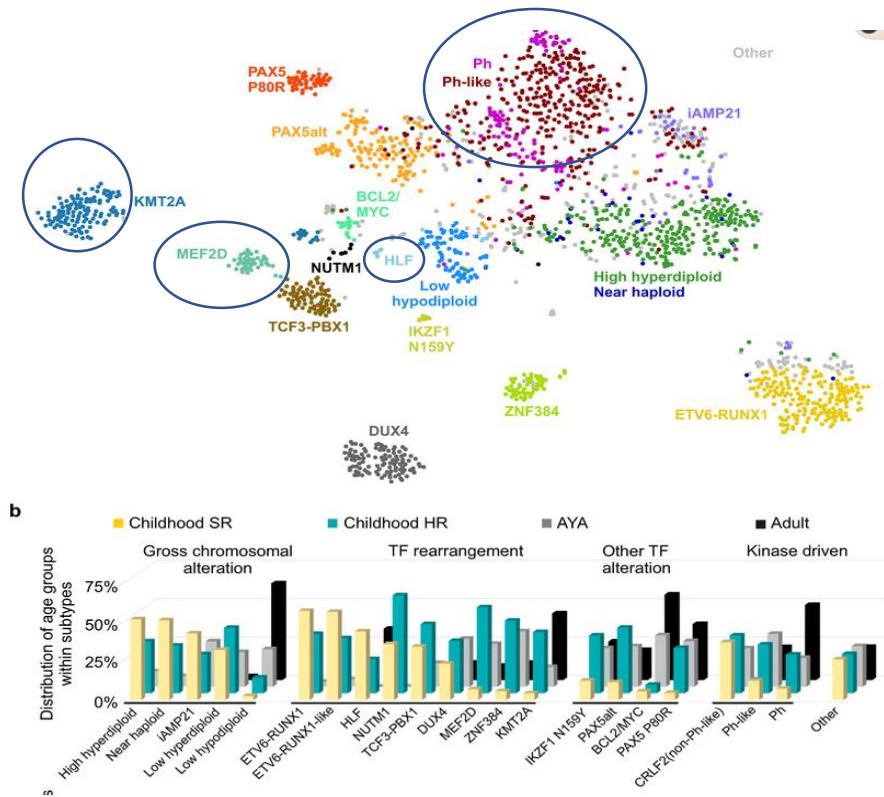
Age cohorts



Who is high-risk nowadays?

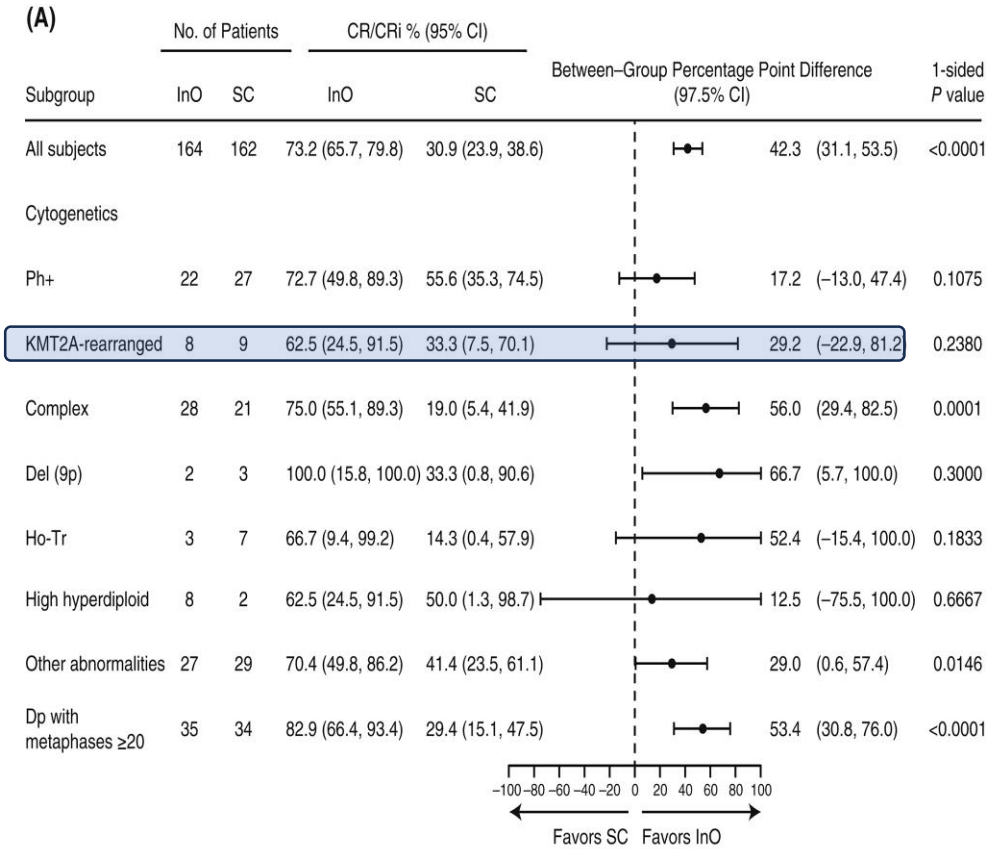
- Age
- **Biological findings**
- MRD
- CNS

Molecular classification: the new

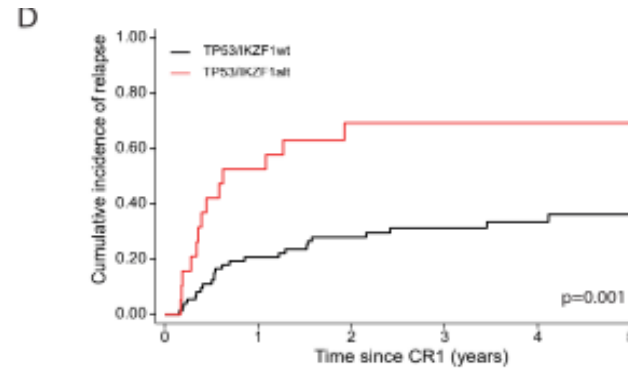


KMT2A-r: more than one group?

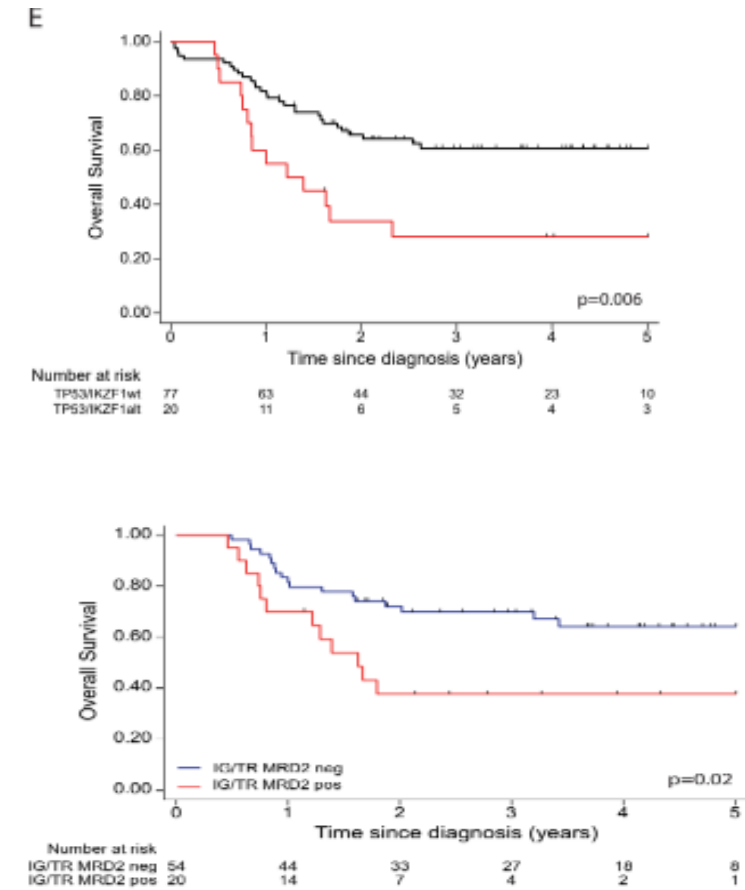
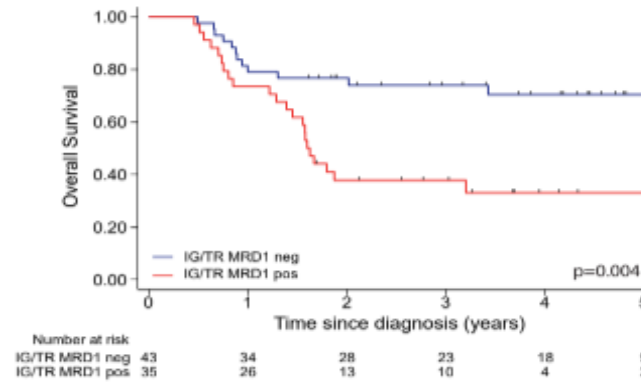
Setting: R/R ALL treated with Ino



Additional lesions



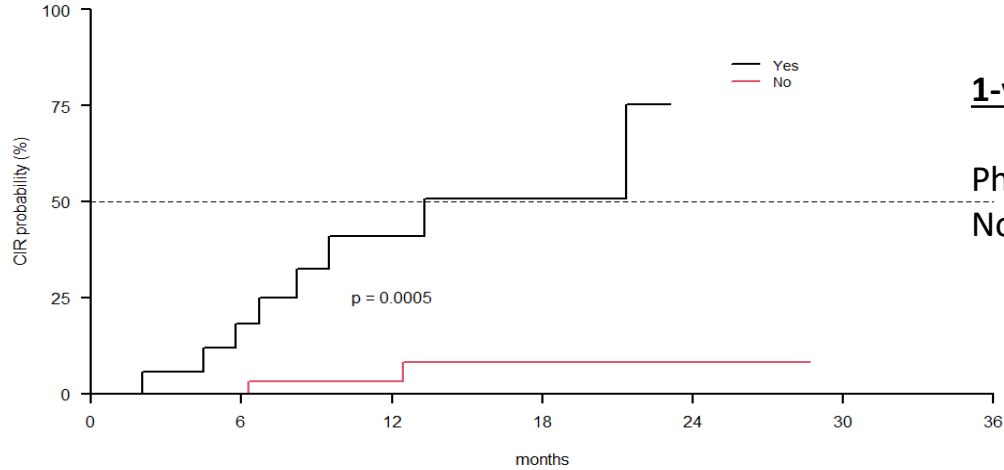
MRD



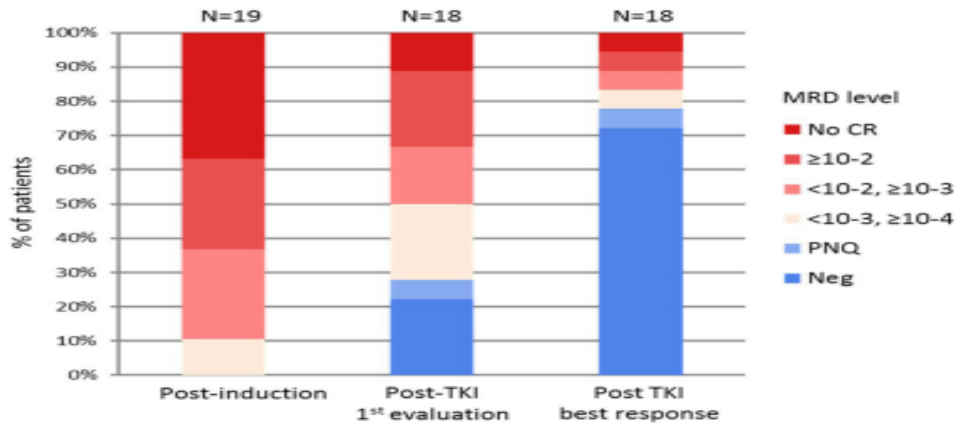
Ph-like ALL

Combination of Ponatinib Plus Chemotherapy As Frontline Treatment For Patients With BCR/ABL1-Like Acute Lymphoblastic Leukemia (BCR/ABL1-Like ALL) - BALLik

GIMEMA LAL2317: 31 Ph-like cases, median follow-up:13 ms (0.5-31)

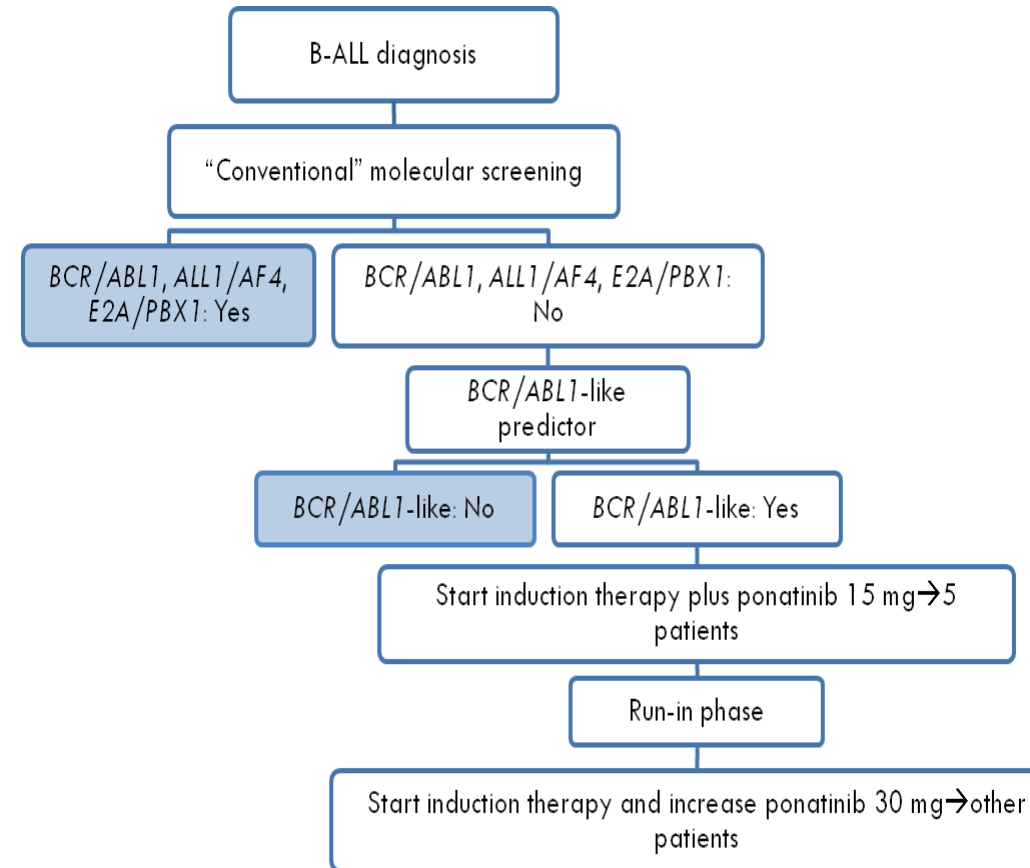


Bassan, Chiaretti et al; EHA 2021



Tanasi et al, Blood 2019

GIMEMA ALL2922



ARTICLE

Received 7 Feb 2016 | Accepted 23 Sep 2016 | Published 8 Nov 2016

DOI: 10.1038/ncomms13331

OPEN

Genomic analyses identify recurrent *MEF2D* fusions in acute lymphoblastic leukaemia

Zhaohui Gu¹, Michelle Churchman¹, Kathryn Roberts¹, Yongjin Li², Yu Liu², Richard C. Harvey³, Kelly McCastlain¹, Shalini C. Reshmi⁴, Debbie Payne-Turner¹, Ilaria Iacobucci¹, Ying Shao^{1,2}, I-Ming Chen³, Marcus Valentine⁵, Deqing Pei⁶, Karen L. Mungall⁷, Andrew J. Mungall⁷, Yussanne Ma⁷, Richard Moore⁷, Marco Marra⁷, Eileen Stonerock^{8,9,10}, Julie M. Gastier-Foster^{8,9,10}, Meenakshi Devidas¹¹, Yunfeng Dai¹¹, Brent Wood¹², Michael Borowitz¹³, Eric E. Larsen¹⁴, Kelly Maloney¹⁵, Leonard A. Mattano Jr¹⁶, Anne Angiolillo¹⁷, Wanda L. Salzer¹⁸, Michael J. Burke¹⁹, Francesca Gianni²⁰, Orietta Spinelli²⁰, Jerald P. Radich²¹, Mark D. Minden²², Anthony V. Moorman²³, Bella Patel²⁴, Adele K. Fielding²⁵, Jacob M. Rowe²⁶, Selina M. Luger²⁷, Ravi Bhatia²⁸, Ibrahim Aldoss²⁸, Stephen J. Forman²⁹, Jessica Kohlschmidt^{30,31}, Krzysztof Mrózek³⁰, Guido Marcucci²⁹, Clara D. Bloomfield³⁰, Wendy Stock³², Steven Kornblau³³, Hagop M. Kantarjian³³, Marina Konopleva³³, Elisabeth Paietta³⁴, Cheryl L. Willman³, Mignon L. Loh^{35,36}, Stephen P. Hunger^{37,38} & Charles G. Mullighan¹



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BIOLOGY OF NEOPLASIA

MEF2D-BCL9 Fusion Gene Is Associated With High-Risk Acute B-Cell Precursor Lymphoblastic Leukemia in Adolescents

Kyogo Suzuki, Yusuke Okuno, Nozomu Kawashima, Hideki Muramatsu, Tatsuya Okuno, Xinan Wang, Shinsuke Kataoka, Yuko Sekiya, Motoharu Hamada, Norihiro Murakami, Daiei Kojima, Kotaro Narita, Atsushi Narita, Hirotoshi Sakaguchi, Kimiyoshi Sakaguchi, Nao Yoshida, Nobuhiro Nishio, Asahito Hama, Yoshiyuki Takahashi, Kazuko Kudo, Koji Kato, and Seiji Kojima

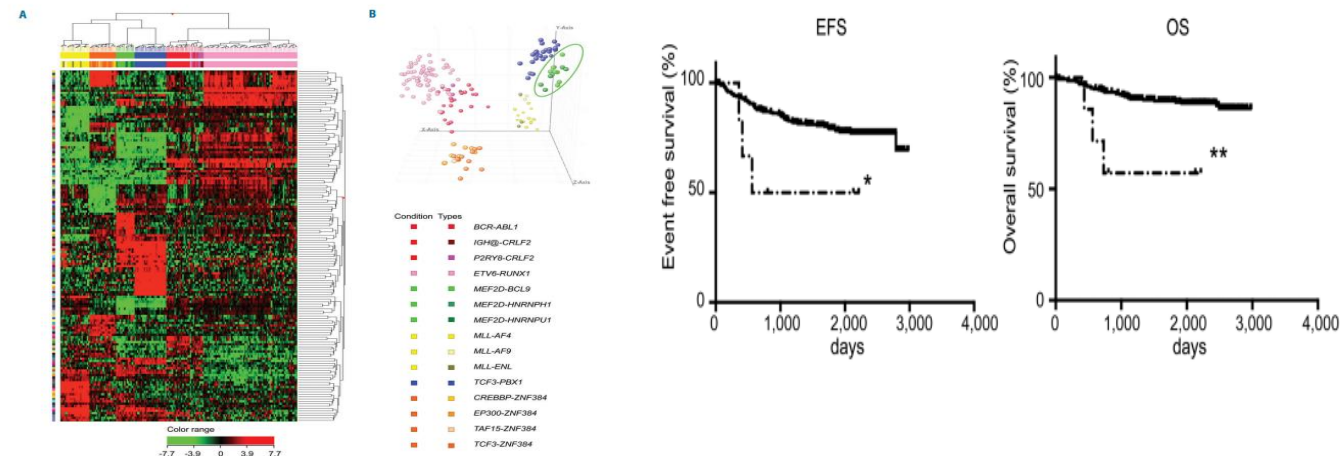
Haematologica 2019
Volume 104(1):128-137

Clinical and molecular characteristics of *MEF2D* fusion-positive B-cell precursor acute lymphoblastic leukemia in childhood, including a novel translocation resulting in *MEF2D-HNRNP1* gene fusion

Kentaro Ohki,¹ Nobutaka Kiyokawa,¹ Yuya Saito,^{1,2} Shinsuke Hirabayashi,^{1,3} Kazuhiko Nakabayashi,⁴ Hitoshi Ichikawa,⁵ Yukihide Momozawa,⁶ Kohji Okamura,⁷ Ai Yoshimi,^{1,8} Hiroko Ogata-Kawata,⁹ Hiromi Sakamoto,⁵ Motohiro Kato,⁷ Keitaro Fukushima,⁹ Daisuke Hasegawa,⁷ Hiroko Fukushima,¹⁰ Masako Imai,¹¹ Ryosuke Kajiwara,¹² Takashi Koike,¹³ Isao Komori,¹⁴ Atsushi Matsui,¹⁵ Makiko Mori,¹⁶ Koichi Moriwaki,¹⁷ Yasushi Noguchi,¹⁸ Myoung-ja Park,¹⁹ Takahiro Ueda,²⁰ Shohei Yamamoto,²¹ Koichi Matsuda,²² Teruhiko Yoshida,⁹ Kenji Matsumoto,²³ Kenichiro Hata,⁴ Michiaki Kubo,⁹ Yoichi Matsubara,²⁴ Hiroyuki Takahashi,²⁵ Takashi Fukushima,²⁶ Yasuhide Hayashi,²⁷ Katsuyoshi Koh,¹⁵ Atsushi Manabe² and Akira Ohara²⁸ for the Tokyo Children's Cancer Study Group (TCCSG)

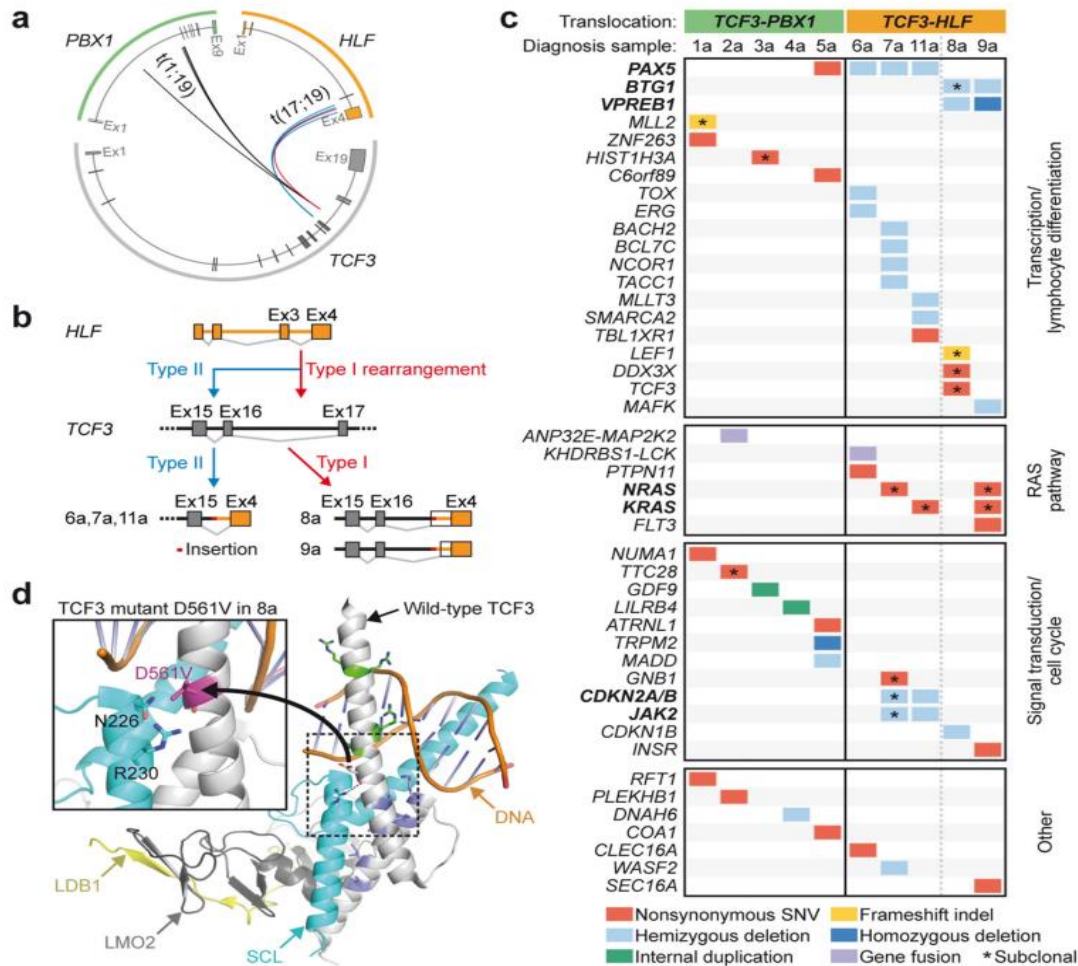
17/328 (4.8%)

Often overexpressing cytoplasmic μ



59 children analyzed, 4 with *MEF2D-BCL9*
Morphology resembling that of mature leukemia
All refractory/very early relapse
HDAC inhibitors (vorinostat and quisinostat) as well Bortezomib, showed inhibitory activity in vitro

TCF3-HLH: a rare subset with dismal prognosis



Type 1 rearrangements: alteration in coagulation
 Type 2 rearrangements: hypercalcemia

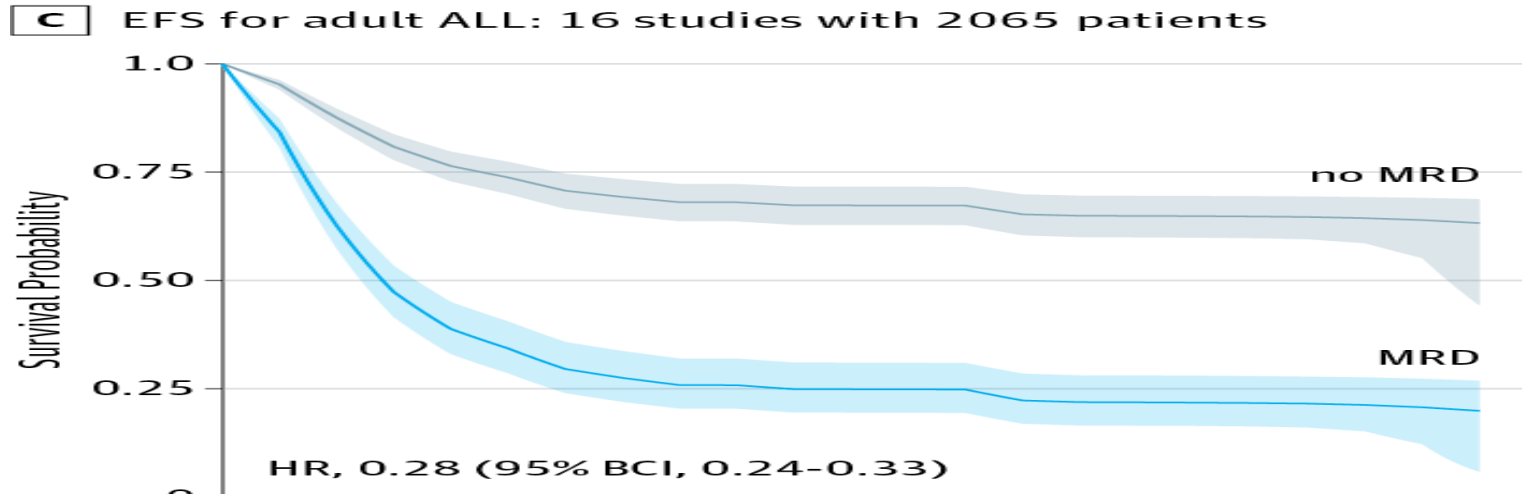
In all cases: very early relapse

Potential therapeutic compounds, among others;
 venetoclax and navitoclax

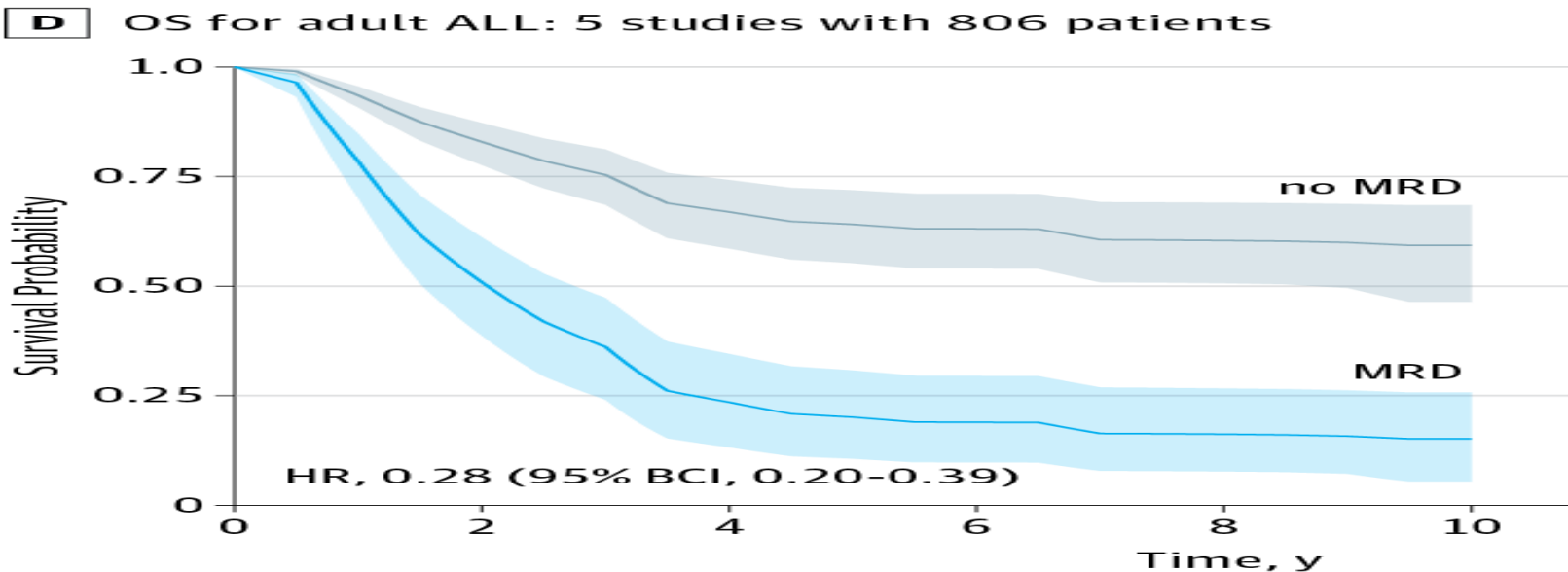
Who is high-risk nowadays?

- Age
- Biological findings
- **MRD**
- CNS

Clinical value of MRD

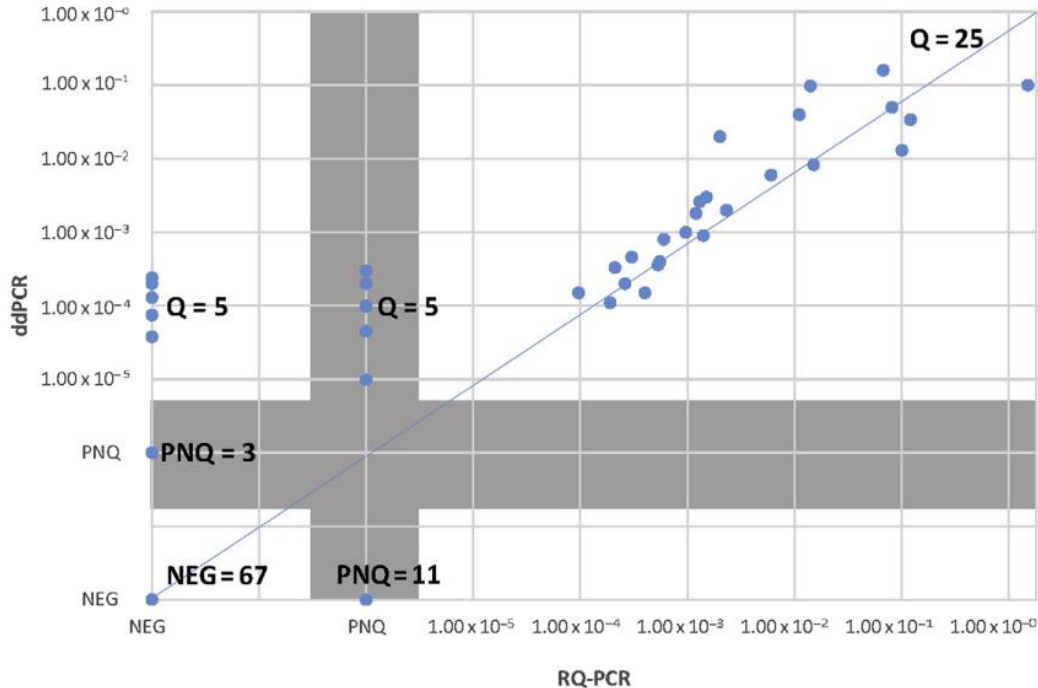


MRD is one of the most important prognostic factors



Are new techniques more informative than RQ-PCR (I)?

116 samples (44 patients) evaluated



High concordance rates between the two techniques.
5 RQ-PCR negative and 5 RQ-PCR PNQ samples proved positive by ddPCR

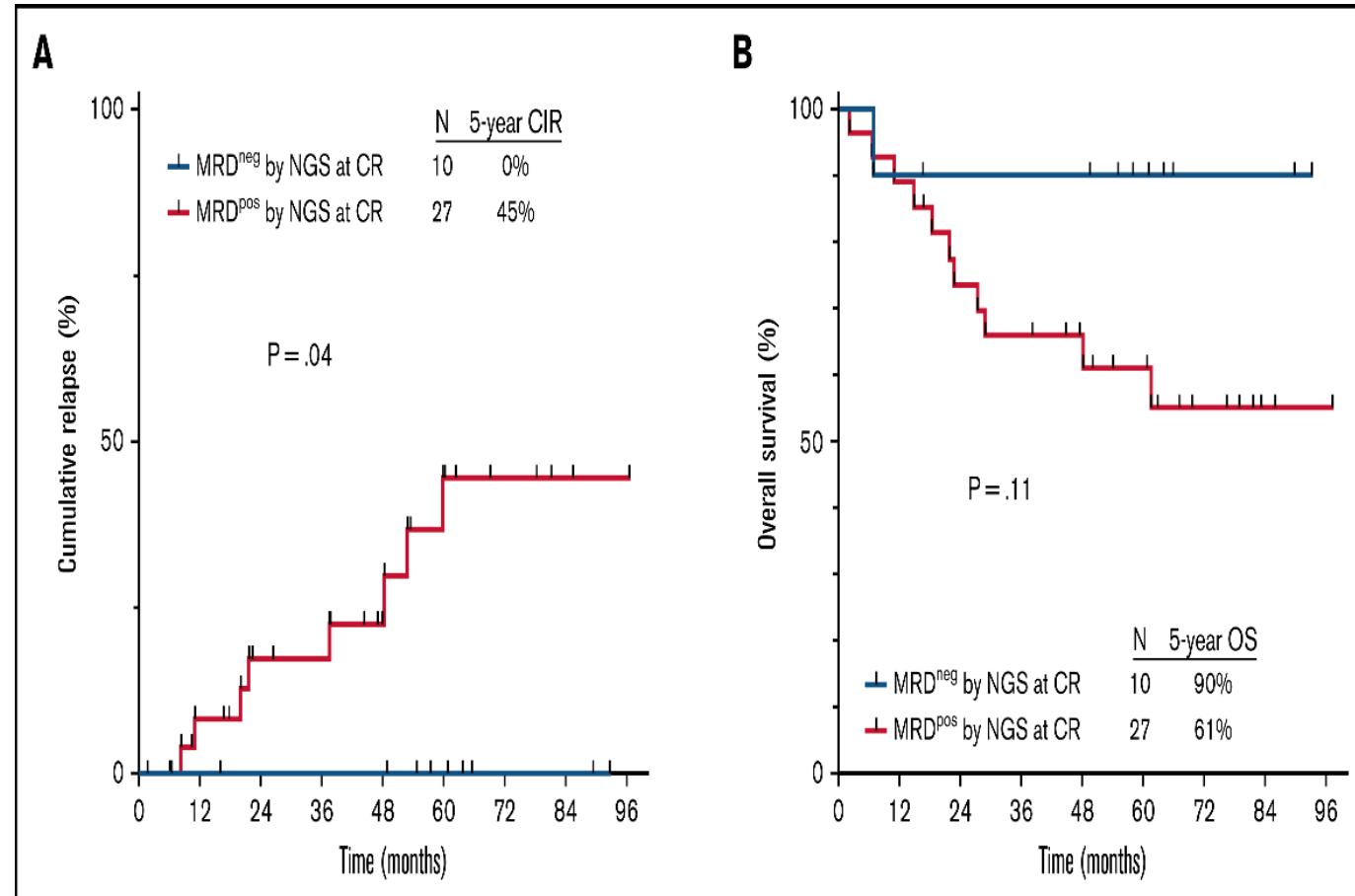
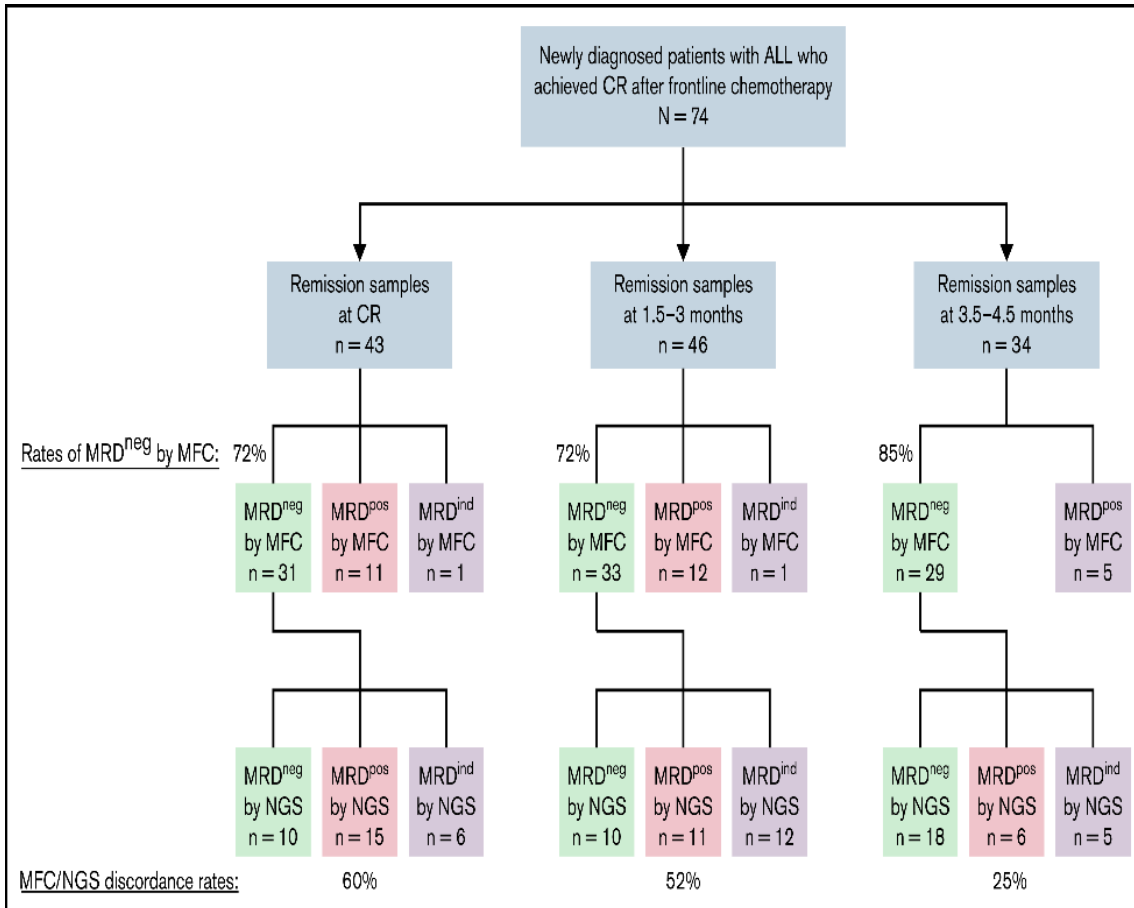
Recovery of quantificability

RQ-PCR	NGS			Total
	Q	PNQ	NEG	
Q	10	0	0	10
PNQ	5	0	1	6
NEG	6	0	25	31
Total	21	0	26	47

ddPCR	NGS			Total
	Q	PNQ	NEG	
Q	18	0	0	18
PNQ	0	0	1	1
NEG	3	0	25	28
Total	21	0	26	47

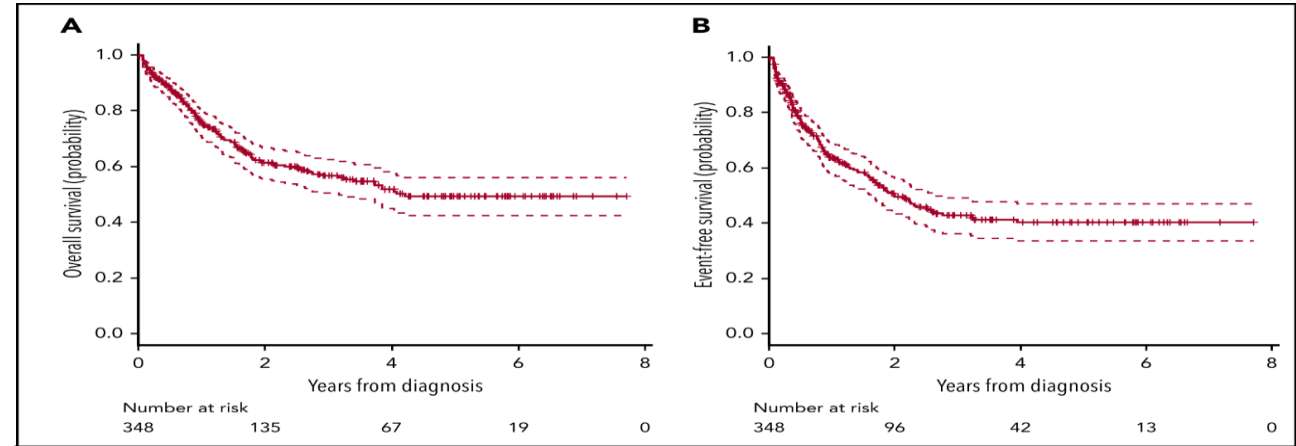
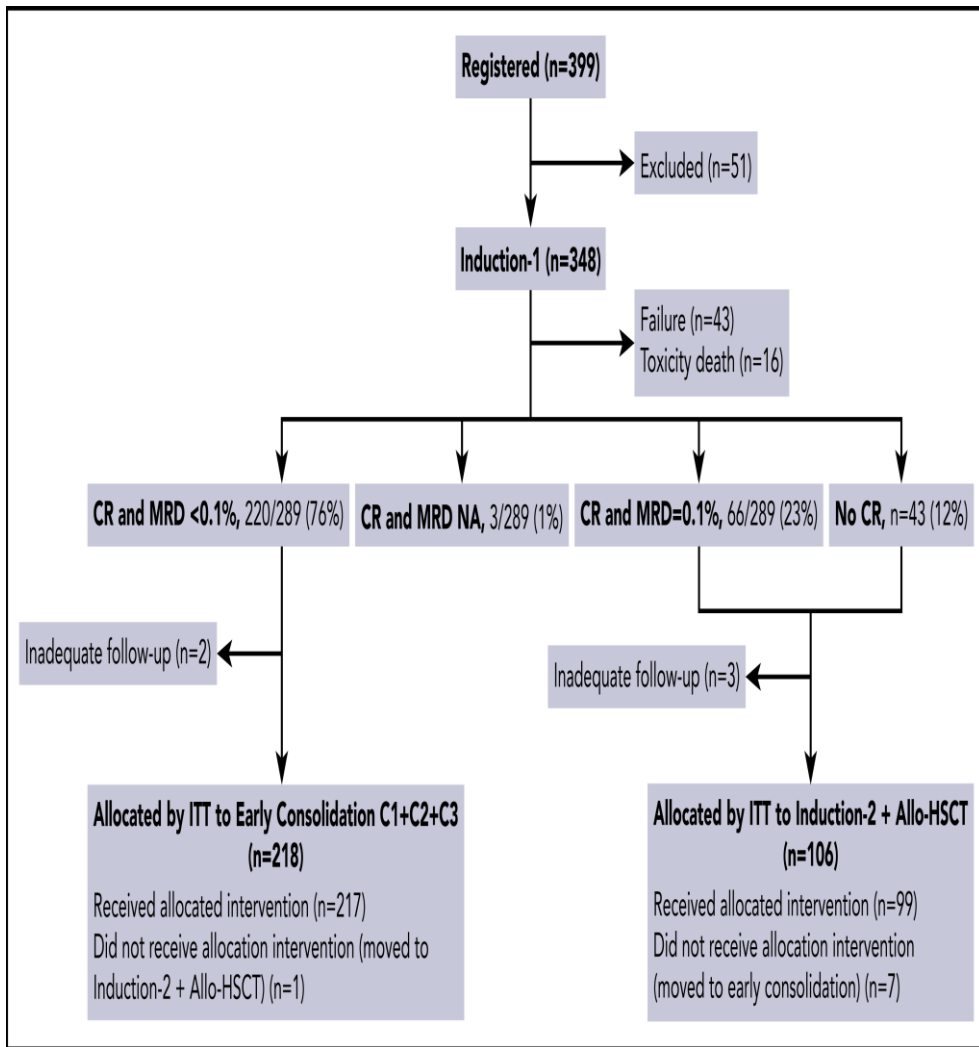
Higher concordance rate between NGS and ddPCR: 92% versus 75% between NGS and RQ-PCR

Adult ALL: FC vs HTS

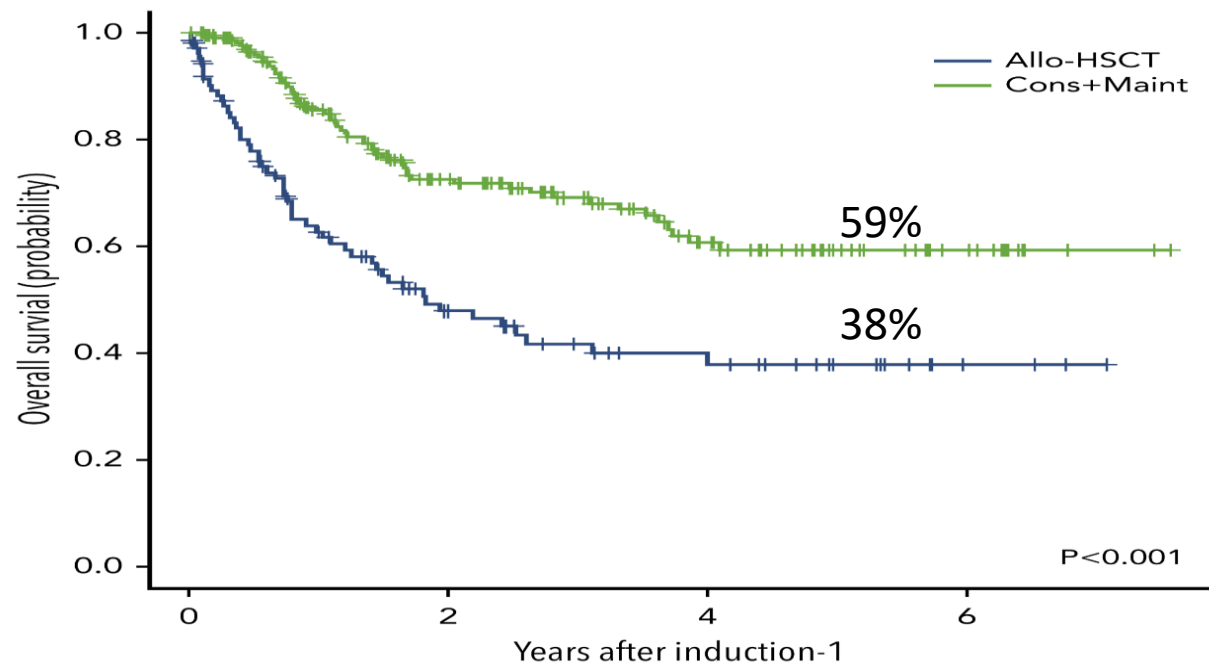


Better prediction of CIR and OS by HTS

Spanish experience in high risk patients



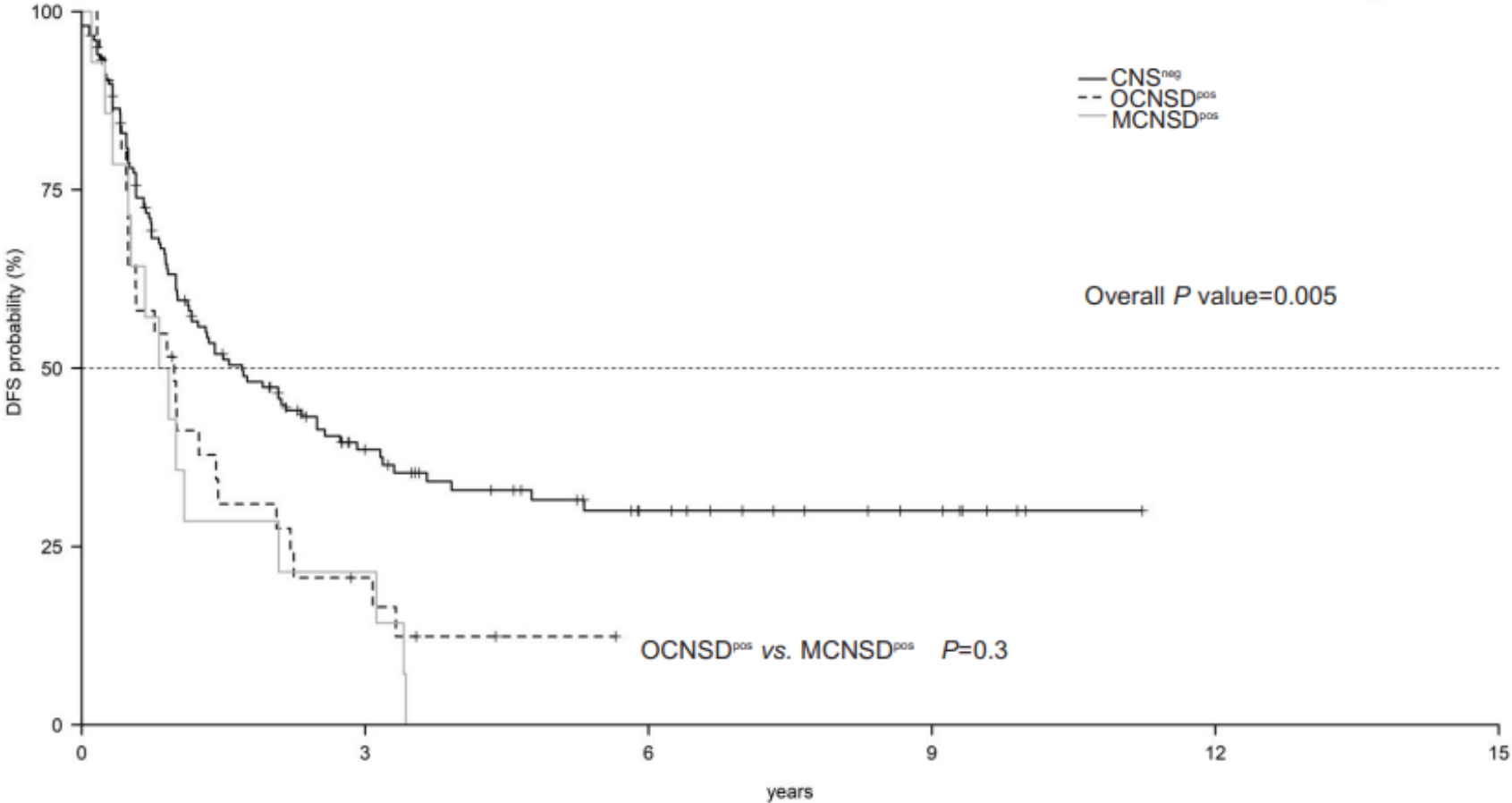
5-year OS and EFS for the whole series: 43%, 49%



Who is high-risk nowadays?

- Age
- Biological findings
- MRD
- **CNS**

CNS involvement



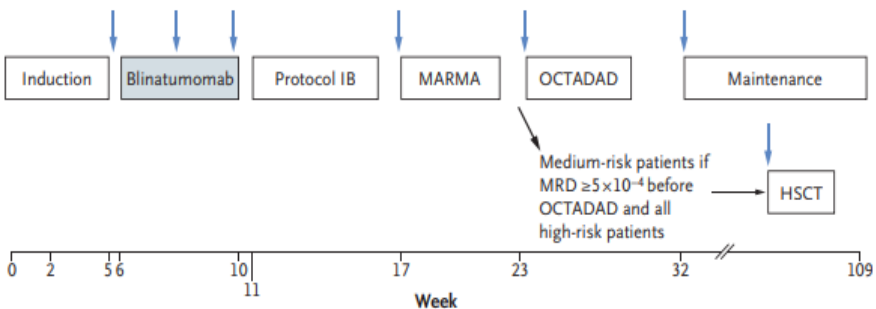
CNS disease significantly affects outcome

Del Principe MI, et al. Haematologica. 2021;106():39-45.

ORIGINAL ARTICLE

Blinatumomab Added to Chemotherapy in Infant Lymphoblastic Leukemia

Inge M. van der Sluis, M.D., Ph.D., Paola de Lorenzo, Ph.D., Rishi S. Kotecha, M.B., Ch.B., Ph.D., Andishe Attarbaschi, M.D., Gabriele Escherich, M.D., Karsten Nysom, M.D., Ph.D., Jan Stary, M.D., Ph.D., Alina Ferster, M.D., Benoit Brethon, M.D., Franco Locatelli, M.D., Ph.D., Martin Schrappe, M.D., Peggy E. Scholte-van Houtem, M.Sc., Maria G. Valsecchi, Ph.D., and Rob Pieters, M.D., Ph.D.



30 patients enrolled
 Median follow-up: 26 ms (3.9-48.2)
 MRD response in 28 patients (93%)
 8 patients underwent transplant
4 relapses, all involving CNS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2020 VOL. 383 NO. 17

Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults

Robin Foà, M.D., Renato Bassan, M.D., Antonella Vitale, M.D., Loredana Elia, M.D., Alfonso Piciocchi, M.S., Maria-Cristina Puzzolo, Ph.D., Martina Canichella, M.D., Piera Viero, M.D., Felicetto Ferrara, M.D., Monia Lunghi, M.D., Francesco Fabbiano, M.D., Massimiliano Bonifacio, M.D., Nicola Fracchiolla, M.D., Paolo Di Bartolomeo, M.D., Alessandra Mancino, M.S., Maria-Stefania De Propriis, Ph.D., Marco Vignetti, M.D., Anna Guarini, Ph.D., Alessandro Rambaldi, M.D., and Sabina Chiaretti, M.D., Ph.D., for the GIMEMA Investigators*

63 patients enrolled
 At 18 months:
 OS: 95%; DFS: 88%

At 53 months:
 OS: 80.7%; DFS 75.8%
 9 relapses, of which 4 CNS



Chemotherapy-free treatment with inotuzumab ozogamicin and blinatumomab for older adults with newly-diagnosed, Ph-negative, CD22-positive, B-cell acute lymphoblastic leukemia: Alliance A041703

Matthew J. Wieduwilt, Jun Yin, Oudom Kour, Rebecca Teske, Wendy Stock, Kenneth Byrd, Kimberly Doucette, James Mangan, Gregory Masters, Alice Mims, Katarzyna J. Jamieson, Shira Dinner, Ali Bseiso, Harry Erba, Mark Litzow, Geoffrey L. Uy, Richard M. Stone

Best cumulative response (N=33)	N (%)
Composite CR (CR + CRh + CRi)	32 (96%)
CR	20 (60)
CRh	11 (33)
CRi	1 (3)
Refractory/progressive	1 (3)

Events	N (%)
Total (of N=33)	12 (36)
Relapse	9 (27)
Systemic +CNS	2
Isolated CNS	0
CD19 negative	3
CD22 negative (<20%)	1
Death with refractory ALL	1 (3)
Death in remission	2 (6)
On study therapy	1
After allogeneic HCT	1

Conclusions

- ALL outcome has dramatically improved over the last decade
- Old (*KMT2A-r*) and novel lesions (Ph-like, *MEFD2-r* and *TCF3-HLH*) still represent an unmet need : 1) RNA sequencing and NGS allow their prompt recognition; 2) therapeutic targeting should be pursued
- MRD, and its integration with biologically-defined categories, is improving patient's stratification
- CNS: emerging issue; efforts ongoing for the identification of predictive signatures (Sapienza MR, et al. Hematol Oncol. 2023; doi: 10.1002/hon.3136)