

Comprehensive Cancer Center
Tübingen-Stuttgart

Post ASH 2024 San Diego

Akute lymphatische Leukämie

Christoph Faul

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN



Comprehensive
Cancer Center
Tübingen - Stuttgart



Universitätsklinikum
Tübingen

GMALL Trial 08/2013. Chemotherapy or SCT



Nicola Gökbüget. 961 Chemotherapy or Stem Cell Transplantation in Adult High Risk Ph/BCR::ABL1-Negative ALL Patients with Early MRD Negativity: Results of the Randomized GMALL Trial 08/2013.

GMALL Trial 08/2013. Chemotherapy or SCT

Chemotherapy or Stem Cell Transplantation in Adult High Risk Ph/BCR::ABL1-Negative ALL Patients with Early MRD Negativity: Results of the Randomized GMALL Trial 08/2013

Nicola Goekbuget, MD , Folker Schneller, MD , Kathrin Nachtkamp Sr., MD , Joachim Beck, MD , Christoph Faul, MD , Ralph Wäsch, MD , Tobias Gaska, MD , Nael Alakel, MD , Kerstin Schaefer-Eckart, MD , Thomas Kubin, MD , Sonja Martin, MD , Lino L. Teichmann, MD , Karsten Spiekermann, MD , Walter Fiedler, MD , Christian Junghanss, MD , Claudia D Baldus, MD , Monika Brüggemann, Stefan Schwartz, MD , Axel Benner , Nicholas Schreck , Lena Reiser, Hubert Serve, MD and Andreas Viardot, MD*



GMALL Trial 08/2013. Chemotherapy or SCT



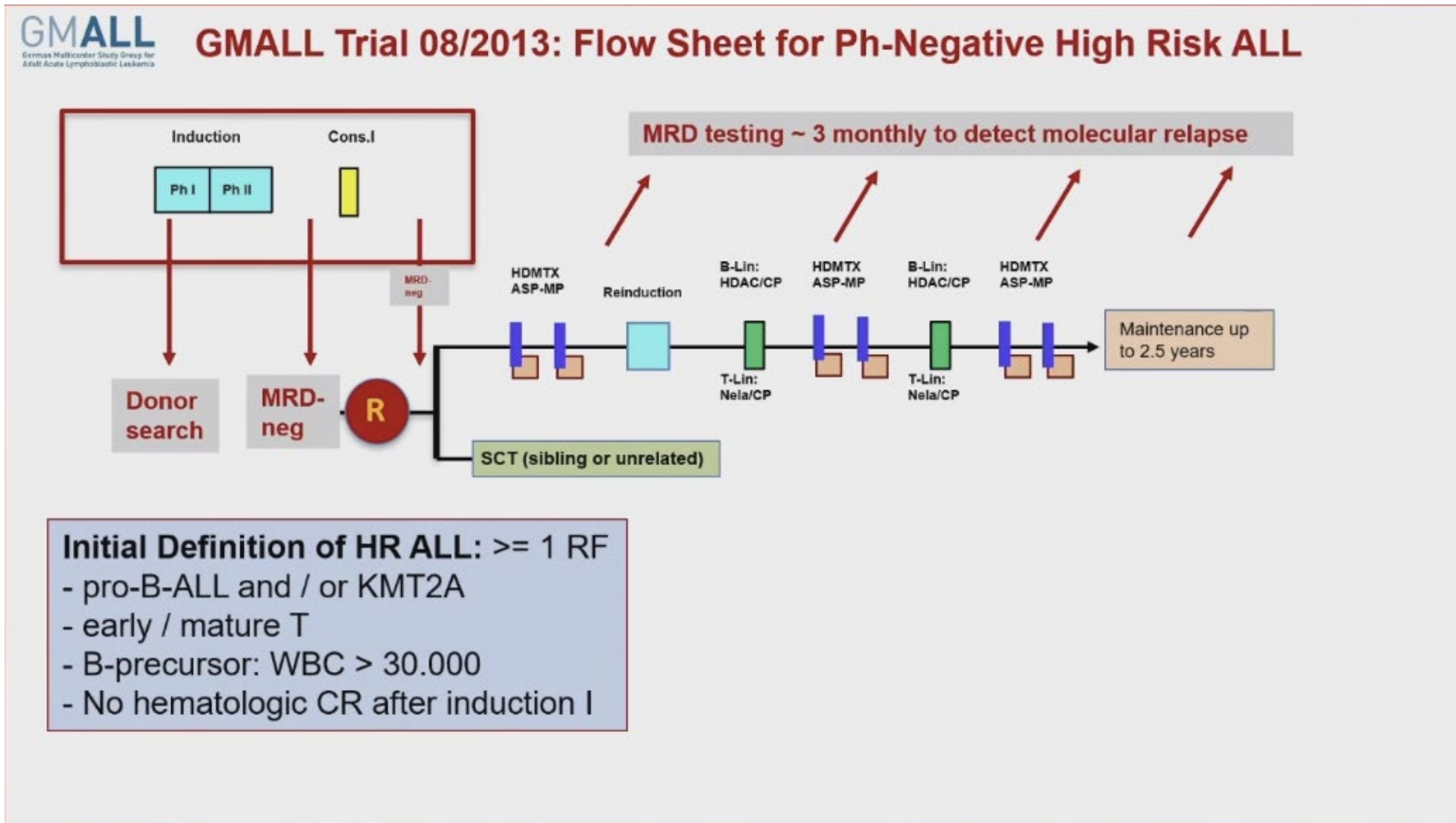
GMALL Trial 08/2013: Flow Sheet for Ph-Negative High Risk ALL

Initial Definition of HR ALL: ≥ 1 RF

- pro-B-ALL and / or KMT2A
- early / mature T
- B-precursor: WBC > 30.000
- No hematologic CR after induction I



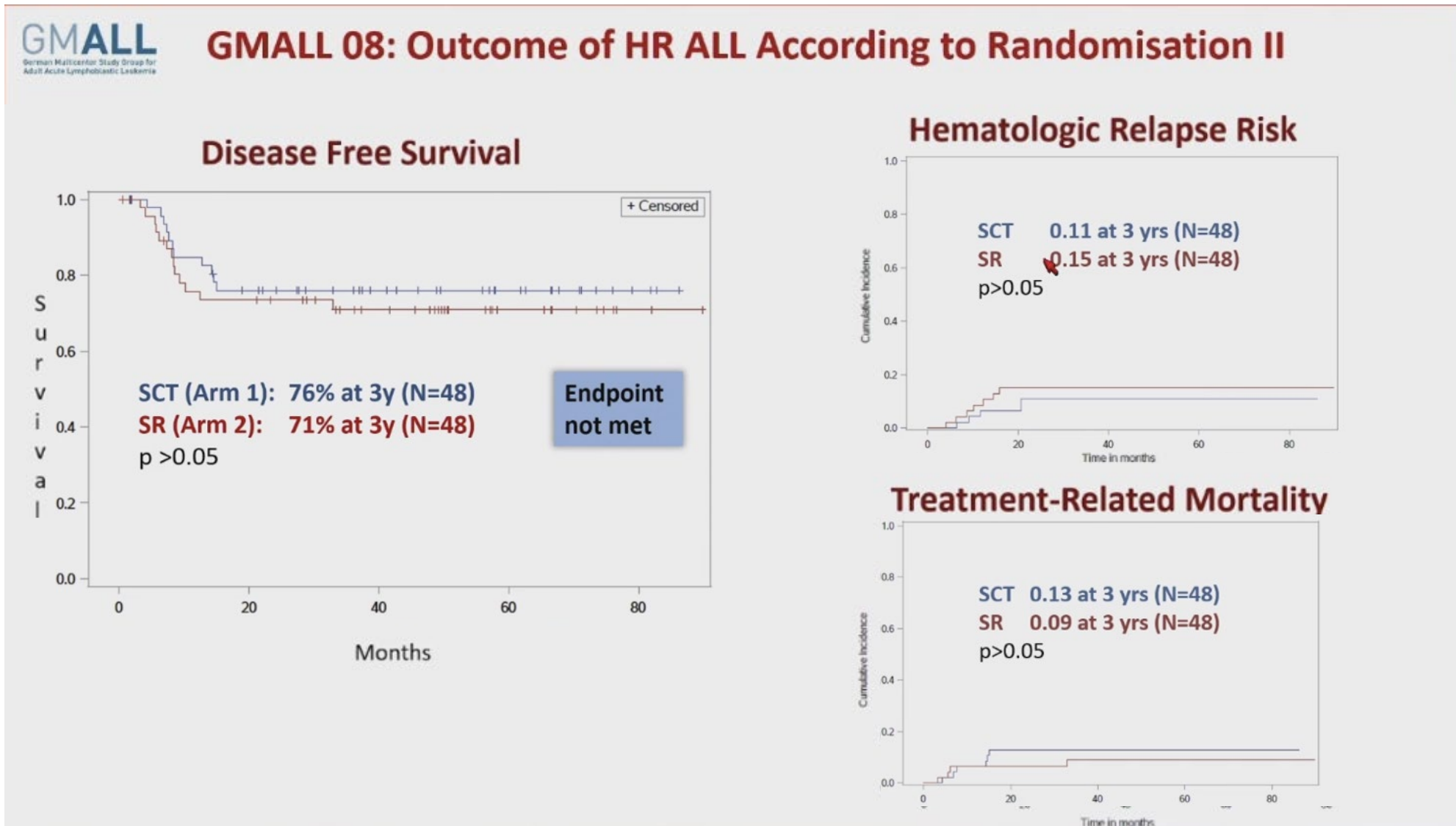
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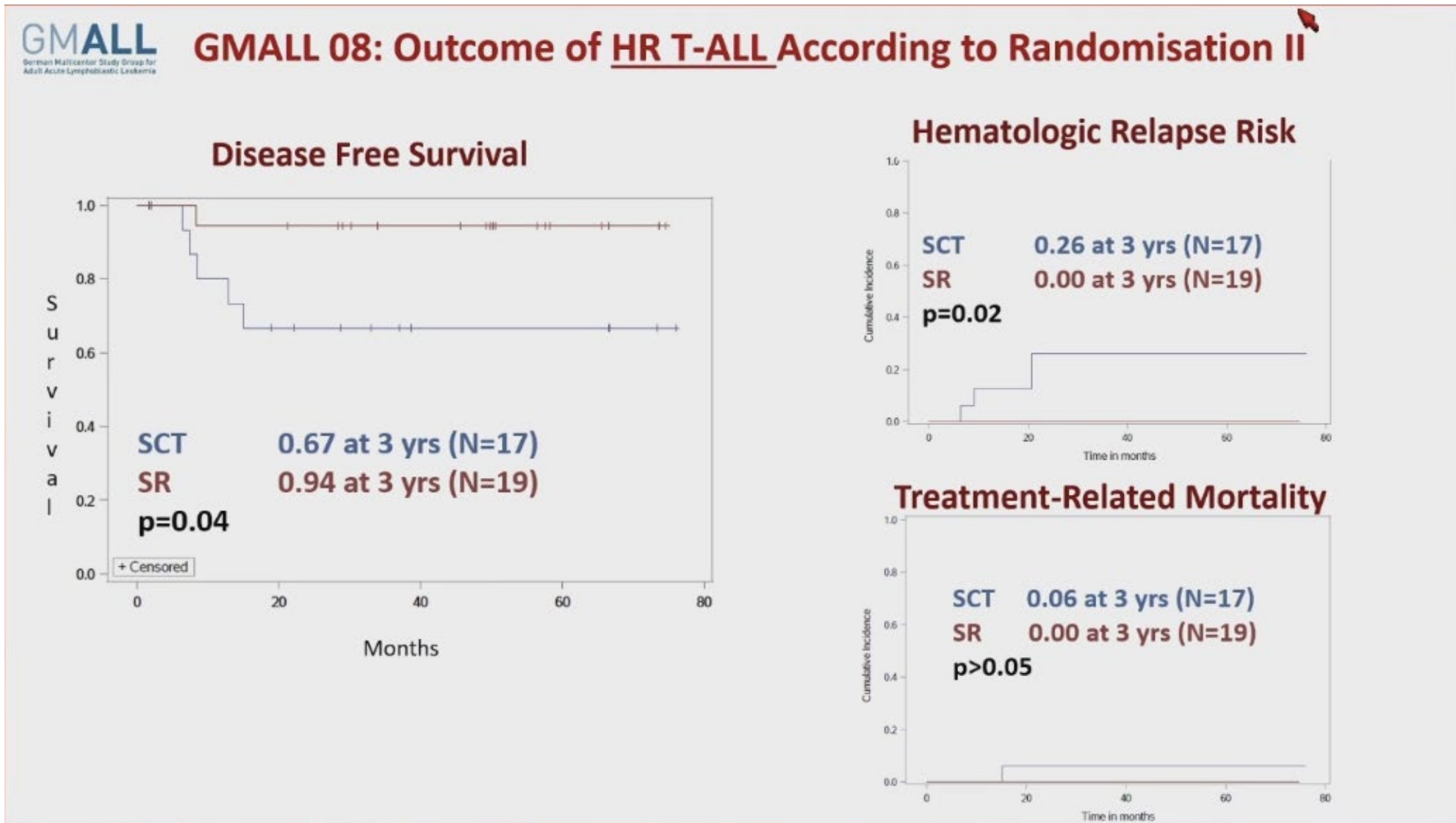
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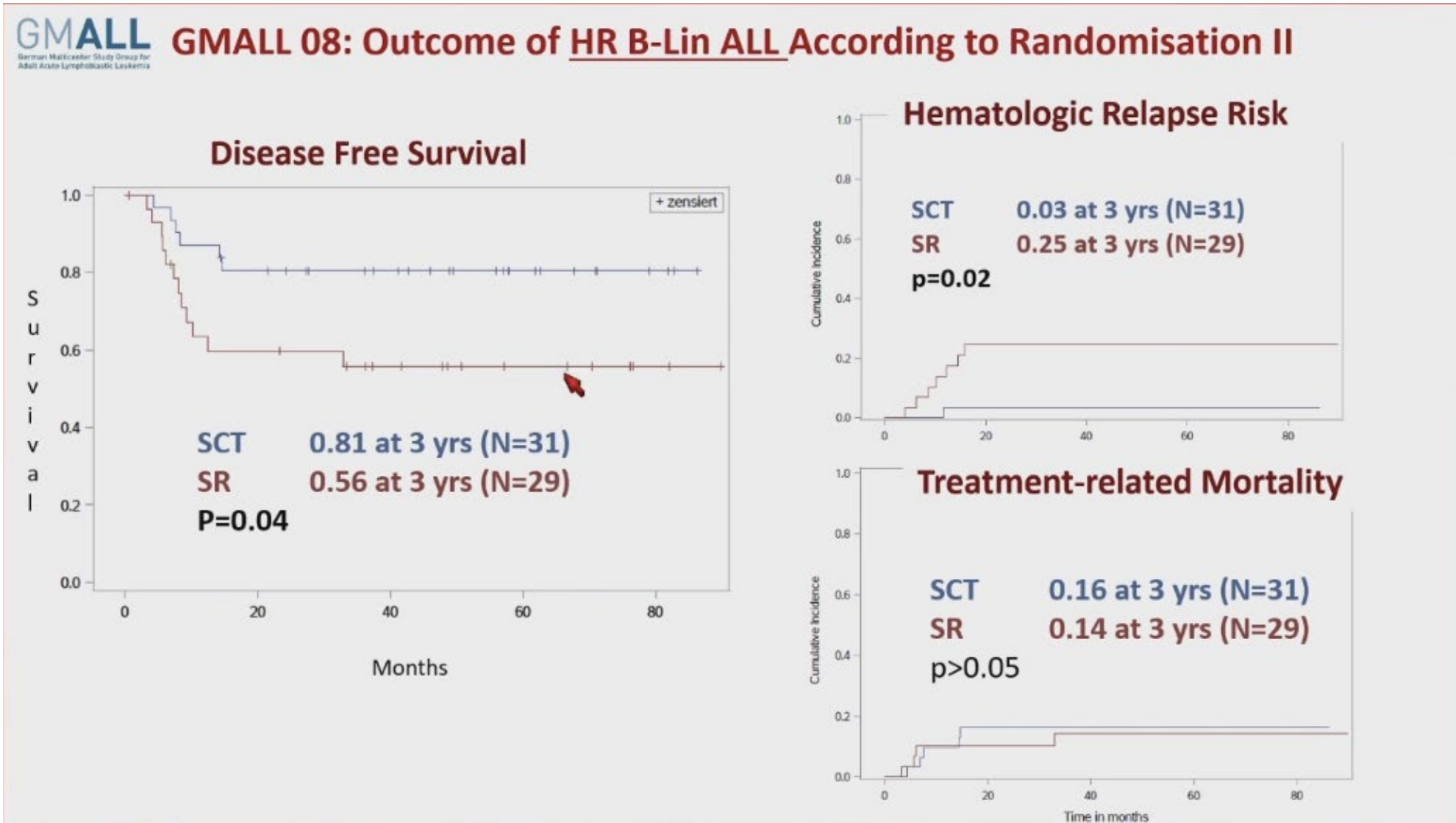
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GMALL Trial 08/2013. Chemotherapy or SCT



GMALL 08: Outcome of Molecular and Hematologic Relapse after Randomization II

Alive: 2/14

B-precursor (N=9)

Mol Relapse 7

SR Therapy (N=6)

- Cyt relapsed/died: 5

- SCT/alive: 1

SCT (N=1)

Cyt relapsed/died: 1

Direct Cyt Relapse: 2

SR Therapy (N=2)

Died: 2

T-ALL (N=5)

MolRelapse 4

SR Therapy (N=1)

SCT/alive: 1

SCT (N=3)

Cyt relapsed/died: 3

Direct Cyt Relapse 1

SCT (N=1)

Died: 1



GMALL Trial 08/2013. Chemotherapy or SCT

GMALL 08: Randomisation II - Summary

- Randomisation process overall successful in a complex multicenter setting
- Excellent outcome in MRD negative HR ALL
- Primary endpoint not met: No DFS advantage for SR therapy compared to SCT
- Trend to higher TRM in SCT arm and higher RR in SR arm
- **Different trends in T- vs B-lineage with extraordinary good outcomes**
 - **T-lineage: Better outcome with SR therapy (less relapses); *chemo backbone highly effective***
 - **B-lineage: Better outcome with SCT (less relapses); *more aggressive biologic subgroups may benefit from SCT***
- Upcoming relapses successfully identified with regular MRD testing
- Salvage of molecular / cytologic relapse extremely poor
- So far no differences between SCT and SR therapy in terms of late effects (data collection ongoing)
- **Future: Omission of SCT in patients with molecular CR after induction 2 with potential exceptions and addition of Blinatumomab in B-precursor ALL**

Nicola Gökbüget. 961 Chemotherapy or Stem Cell Transplantation in Adult High Risk Ph/BCR::ABL1-Negative ALL Patients with Early



GMALL Trial 08/2013. Outcome Ph+ALL



11 Heike Pfeifer. 840 Update on GMALL Trial 08/2013 Shows Durable Favorable Outcome of Newly Diagnosed Adult Philadelphia-Positive Acute Lymphoblastic Leukemia (Ph+ALL) with Imatinib, Dose-Reduced Induction Followed By Stem Cell Transplantation .



GMALL Trial 08/2013. Outcome Ph+ALL

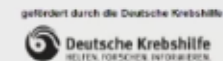


Update on GMALL Trial 08/2013 Shows Durable Favorable Outcome of Newly Diagnosed Adult Philadelphia-Positive Acute Lymphoblastic Leukemia (Ph+ALL) with Imatinib, Dose-Reduced Induction Followed By Stem Cell Transplantation

Eudra-CT-Number: 2013-003466-13

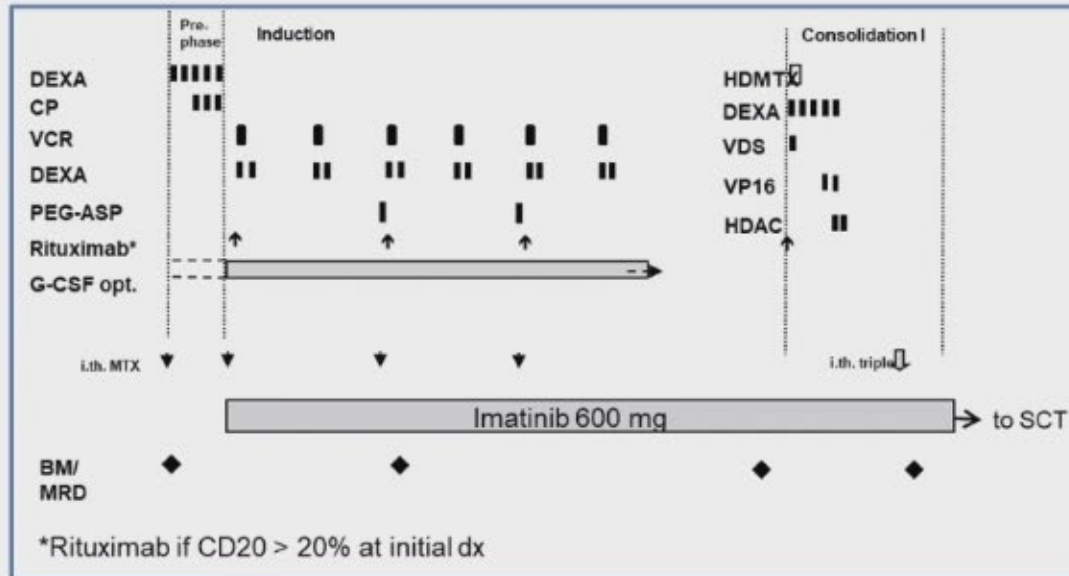
Heike Pfeifer, Fabian Lang, Walter Fiedler, Matthias Stelljes, Folker Schneller, Björn Steffen, Boris Böll, Andreas Viardot, Christoph Faul, Lino L. Teichmann, Hendrik Poeck, Joerg Westermann, Kerstin Schäfer-Eckart, Thomas Heinicke, Thomas Burmeister, Stefan Schwartz, Monika Brueggemann, Hubert Serve and Nicola Goekbuget on behalf of the GMALL study group

GMALL Study Center



GMALL Trial 08/2013. Outcome Ph+ALL

Induction und Consolidation I for Ph+ ALL within GMALL08/2013 trial



GMALL Trial 08/2013. Outcome Ph+ALL



Overall Response after Induction and Consolidation Ph+ALL within GMALL 08/2013

	after Induction I	pre Consolidation I	after Consolidation I
Evaluatable <u>cytology</u>	165	174	174
CR/CRu	85%	96%	94%
PR	9%	2%	0%
Failure	4%	1%	2%
Early Death	1%	1%	3%**

* incl. 3 pro-B-ALL

** 4 Death in CR



GMALL Trial 08/2013. Outcome Ph+ALL



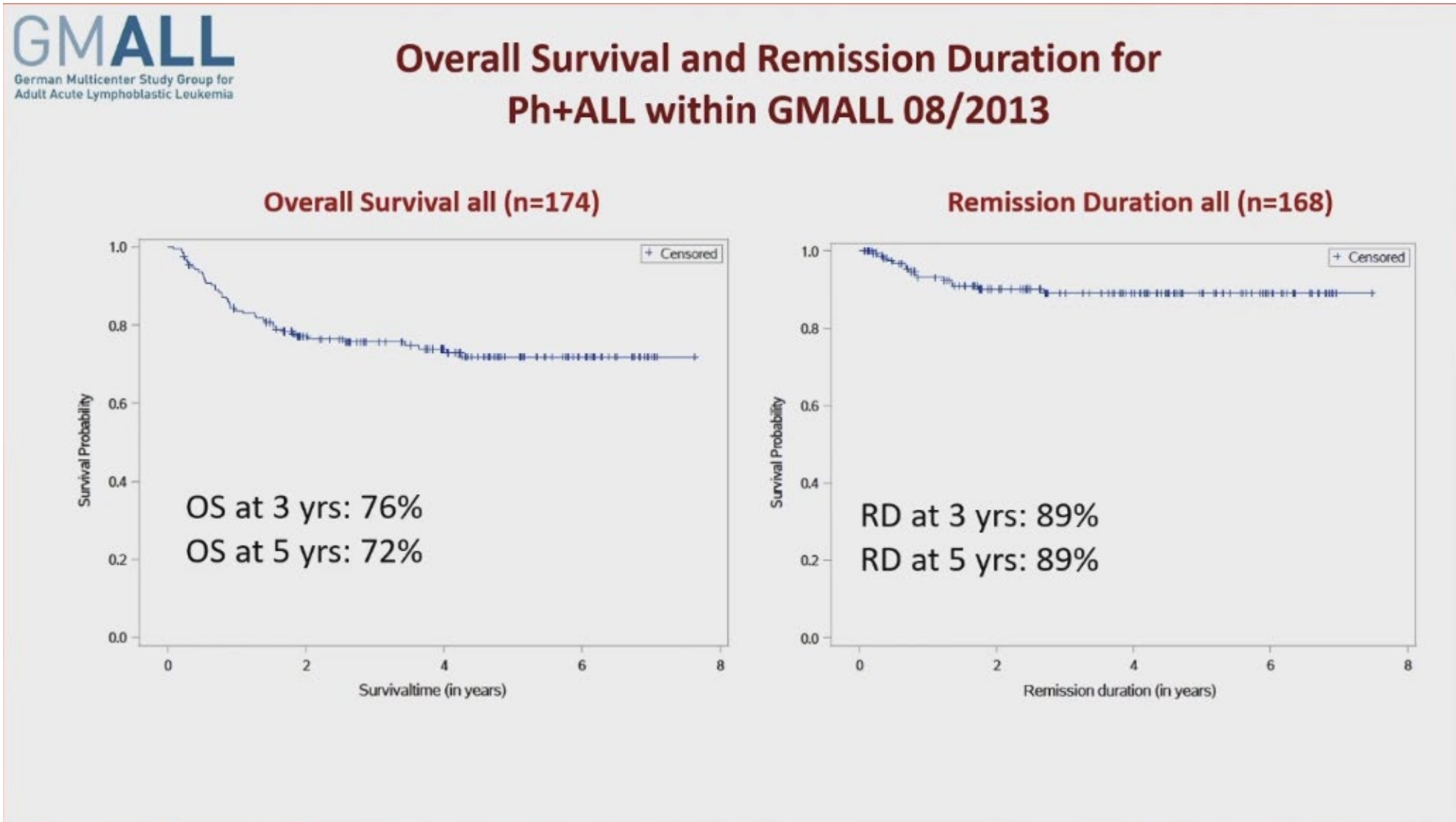
MRD Response after Induction and Consolidation for Ph+ALL within GMALL 08/2013

	After Induction I		Pre Consolidation I		After Consolidation I	
MRD Total	174		150		144	
MRD Evaluable	139	(80 %)	150	(87%)	144	(87%)
Mol CR	9 %		24 %		42%	
Mol Fail	81%		58%		38%	
$\geq 10^{-2}$					17%	
$<10^{-2} \geq 10^{-3}$					41%	
$<10^{-3} \geq 10^{-4}$					43%	
Mol IMR	25%		18%		21 %	

- MolCR: MRD negative with at least 10.000 ABL1 copies
- MolFail: MRD positive, quantifiable, with Ratio $>1E-04$
- Mol IMR: MRD positive below $<1E-04$ (with at least 10 000 ABL1 copies)



GMALL Trial 08/2013. Outcome Ph+ALL

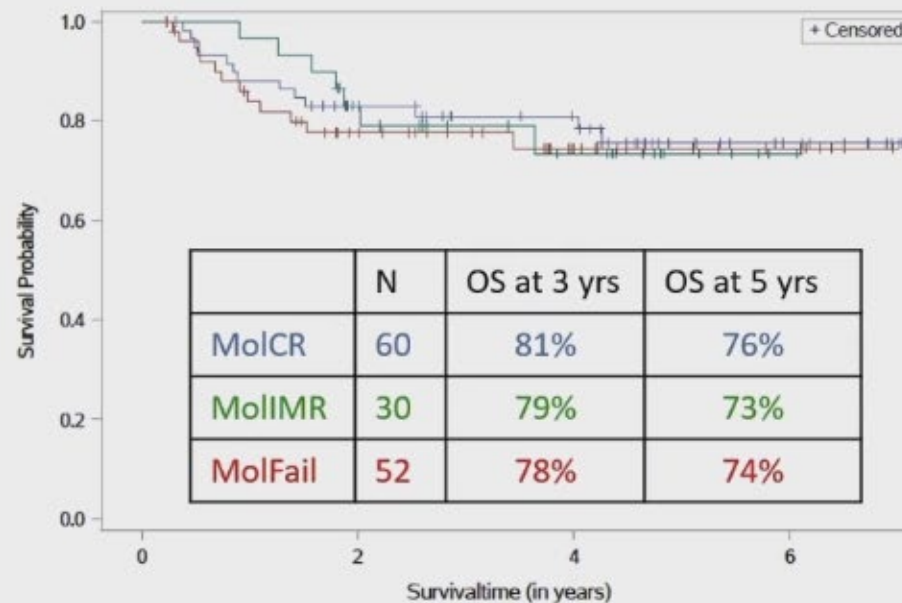


GMALL Trial 08/2013. Outcome Ph+ALL

GMALL
German Multicenter Study Group for
Adult Acute Lymphoblastic Leukemia

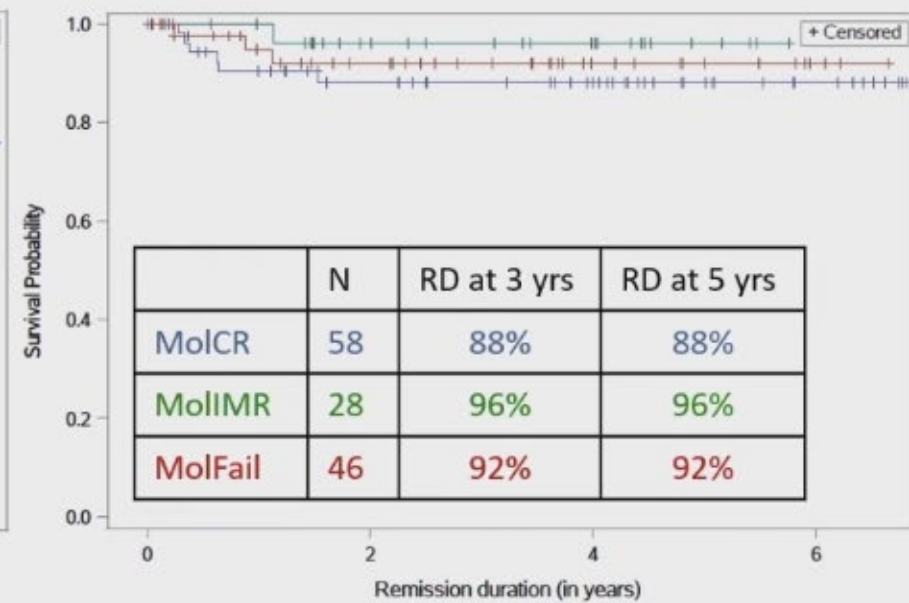
Outcome for Patients with CR after Cons I
According to MRD Response for Ph+ALL
within GMALL 08/2013

Overall Survival all



$p > 0.05$

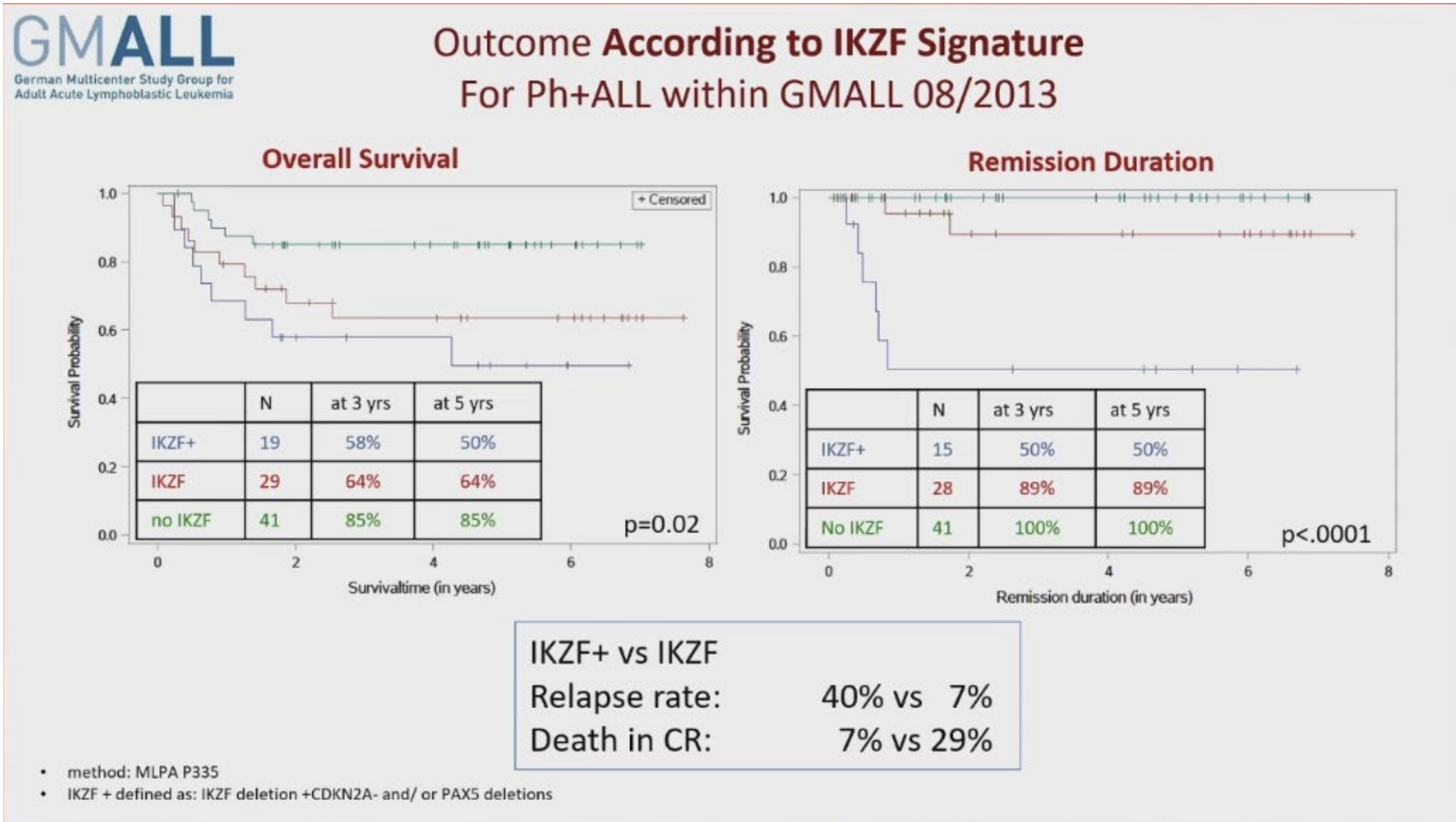
Remission Duration all



$p > 0.05$



GMALL Trial 08/2013. Outcome Ph+ALL



GMALL Trial 08/2013. Outcome Ph+ALL



Summary

- Dose reduced induction including PEG-ASP in combination with Imatinib was feasible and yielded high response rates with a molecular CR rate of 43% already after CI.
- A very high SCT realization rate (98%) was obtained at approximately 3 months from diagnosis likely contributing to the favorable overall outcome with a low relapse rate.
- Nevertheless, a relevant TRM especially in a higher patient age (>45 yrs) was observed, leading to recommendations for dose-reduced TBI-based conditioning regimens in older patients
- IKZF+positive patients showed a higher relapse rate despite allogeneic SCT
- Randomized prospective trials are required to define the future role of SCT considering
 - Response
 - Risk factors
 - Standardized SCT procedures



Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients



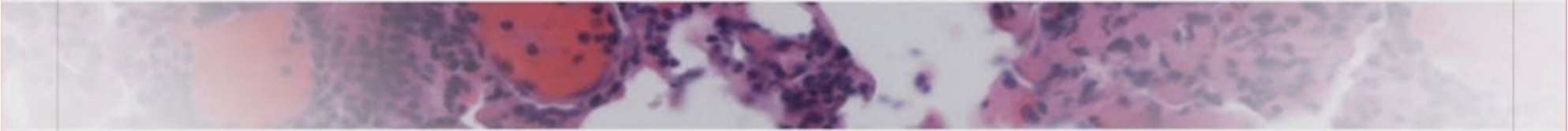
Sabina Chiaretti. 835 Efficacy and Toxicity of Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients of All Ages. Intermediate Analysis of the Gimema ALL2820



Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients



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Efficacy and Toxicity of Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients of All Ages. Intermediate Analysis of the GIMEMA ALL2820

Sabina Chiaretti, Matteo Leoncin, Loredana Elia, Stefano Soddu, Alfonso Piciocchi, Mabel Matarazzo, Mariangela Di Trani, Maurizio Martelli, Erika Borlenghi, Marina Parisi, Valentina Mancini, Caterina Alati, Daniele G. Mattei, Maria Paola Martelli, Prassede Salutati, Patrizia Chiusolo, Ernesta Audisio, Mario Luppi, Lara Pochintesta, Crescenza Pasciolla, Bianca Serio, Barbara Scappini, Antonella Cucca, Martina Chiarucci, Massimiliano Bonifacio, Nicola Fracchiolla, Silvia Imbergamo, Lucia Ammirati, Federico Mosna, Patrizia Zappasodi, Sara Mastaglio, Daniela Pietrasanta, Monica Bocchia, Monia Lunghi, Elisabetta Todisco, Paola Fazi, Alessandro Rambaldi, Robin Foà



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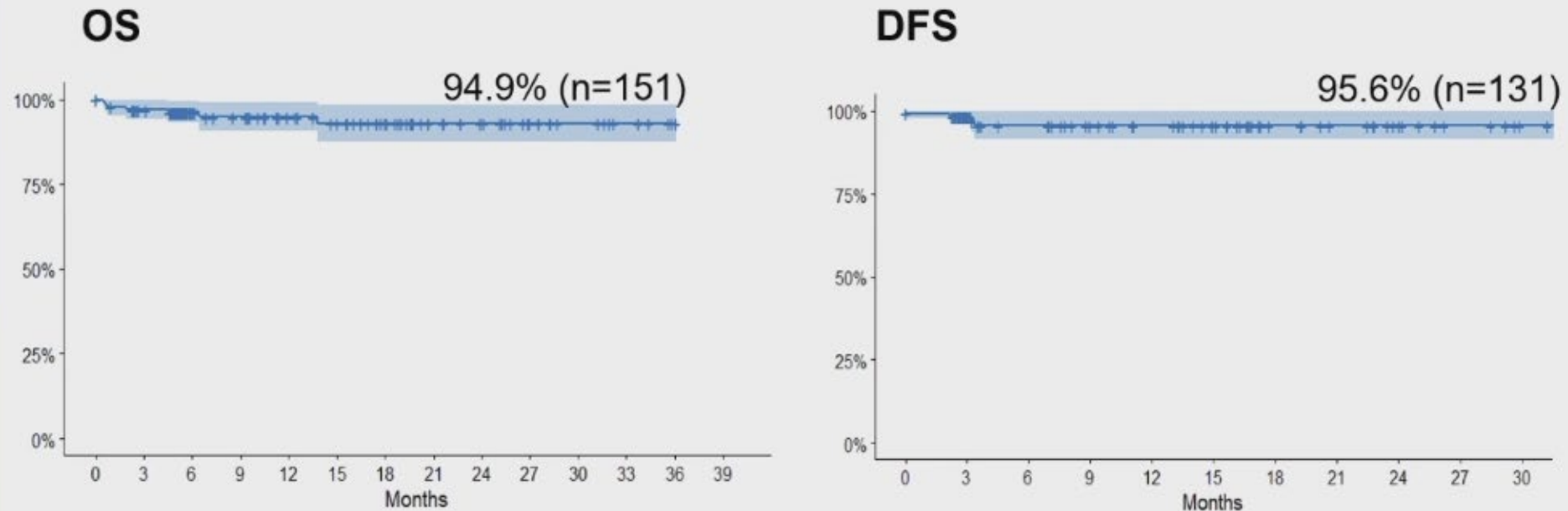


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Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients

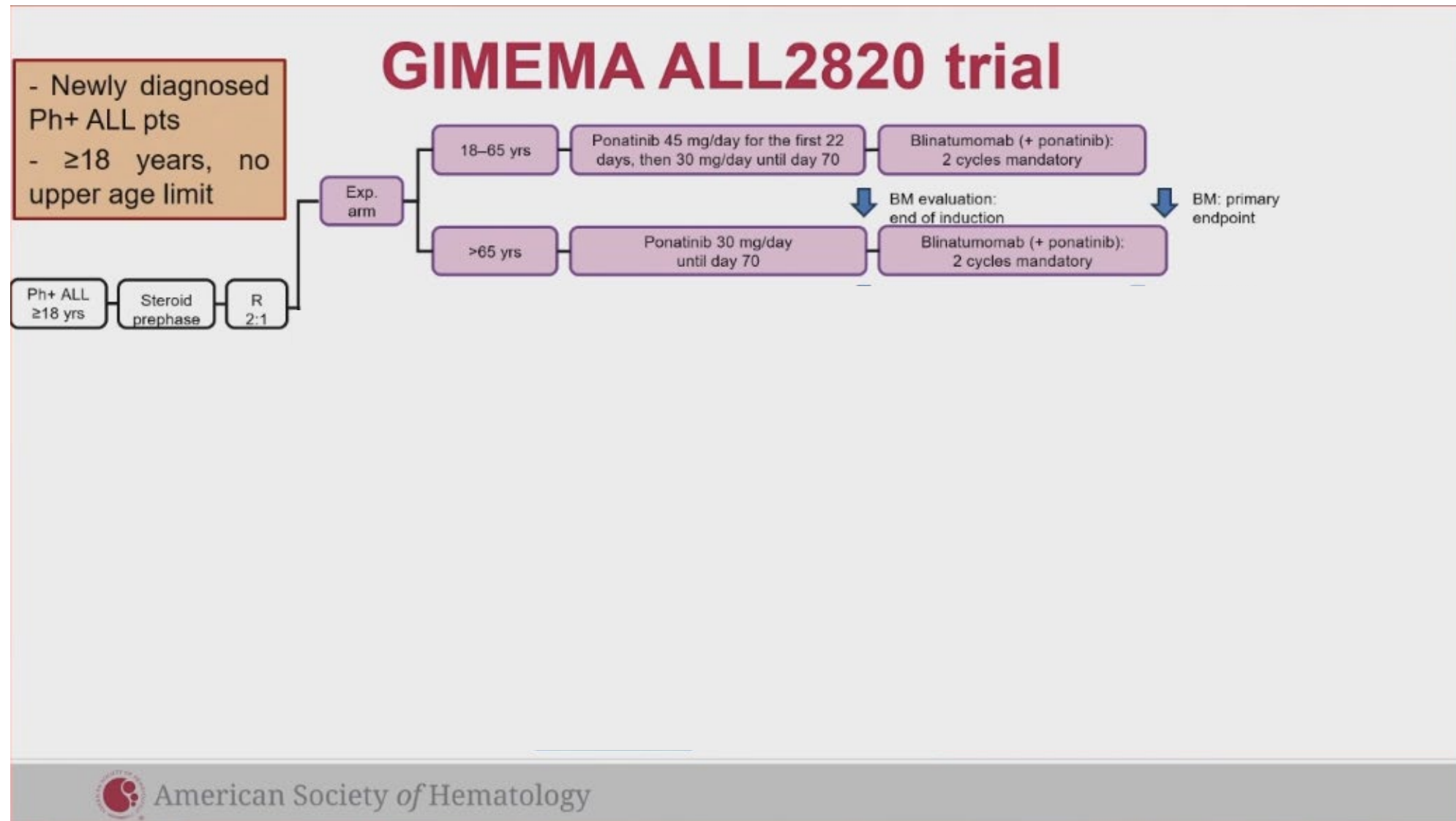
Estimated 12-months OS and DFS



Median follow-up: 8.5 months (0.1 - 36.1)



Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients



Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients

Experimental arm: hematologic & molecular responses

End of induction (d +70)	n=137
CHR	131 (96%)
Deaths	4 (3%)
Off treatment	2 (1%)

	No molecular responses (%)	CMR	PNQ	Overall molecular responses (%)
End of induction (d +70)	71/131 (54)	40/131	20/131	60/131 (46)
After 2 cycles of blinatumomab	30/117 (26)	59/117	27/117	86/117 (74)



Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients

Deaths and relapses

- **Deaths: 7**
 - 4 deaths occurred during induction: 1 paralytic ileus (age 68 yrs), 2 pneumonia (age 65 and 67 yrs), 1 sudden death during sleep (age 77 yrs)
 - 1 in CHR: general conditions deterioration (age 71 yrs)
 - 2 after relapse
- **Relapses: 4** (median time: 5 months)
 - 1 *IKZF1*^{plus} and T315I
 - 2 *IKZF1*^{plus}; CNS involvement in 1
 - 1 Ph- ALL, nodal



American Society of Hematology

Sabina Chiaretti. 835 Efficacy and Toxicity of Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients of All Ages. Intermediate



Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients

Transplant allocation in 1st CHR

	N=16
Age, median (range)	49 (27-67)
>65 years	1 (27)
Gender: M/F (%)	13/3 (50/50)
WBC, median (range)	23 (2-207)
p190	10
p210, p190/210	5, 1
<i>IKZF1</i> ^{plus}	9



Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients

Transplant allocation in 1st CHR

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p190	10
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<i>IKZF1^{plus}</i>	9

Reasons for transplant

- MRD persistence (n=7)
- *IKZF1^{plus}* (n=9)
- Both (n=5)

**So far, no relapses nor
transplant-related deaths**



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Sabina Chiaretti. 835 Efficacy and Toxicity of Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients of All Ages. Intermediate



Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients

Conclusions

- The combination of ponatinib in induction followed by a consolidation with blinatumomab has further improved the results achieved in the D-ALBA trial.
- This strategy was effective and feasible: 12-months OS and DFS are 94.9% and 95.6%.
- SAEs, leading to interruption or discontinuation were rare and mostly observed in the elderly population.
- The biologically-driven allo-SCT allocation has further reduced the rate of allografts. No fatal events have so far been recorded.
- Given these results, a strategy for TKI discontinuation after an optimal time on TKI needs to be implemented*.

**Dragani et al, Haematologica in press*



Blinatumomab and Ponatinib for Adults with Ph+ ALL



Nicholas J. Short. 837 Blinatumomab and Ponatinib for Adults with Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Updated Results and Predictors of Relapse.



Blinatumomab and Ponatinib for Adults with Ph+ ALL

Blinatumomab and Ponatinib for Adults with Newly Diagnosed Ph+ ALL: Updated Results and Predictors of Relapse

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O Karrar, TM Kadia, K Chien, K Sasaki, E Kugler, R Garriss, F Ravandi, E Jabbour

Department of Leukemia

The University of Texas MD Anderson Cancer Center, Houston, TX

Nicholas J. Short. 837 Blinatumomab and Ponatinib for Adults with Newly Diagnosed Philadelphia Chromosome-Positive Acute

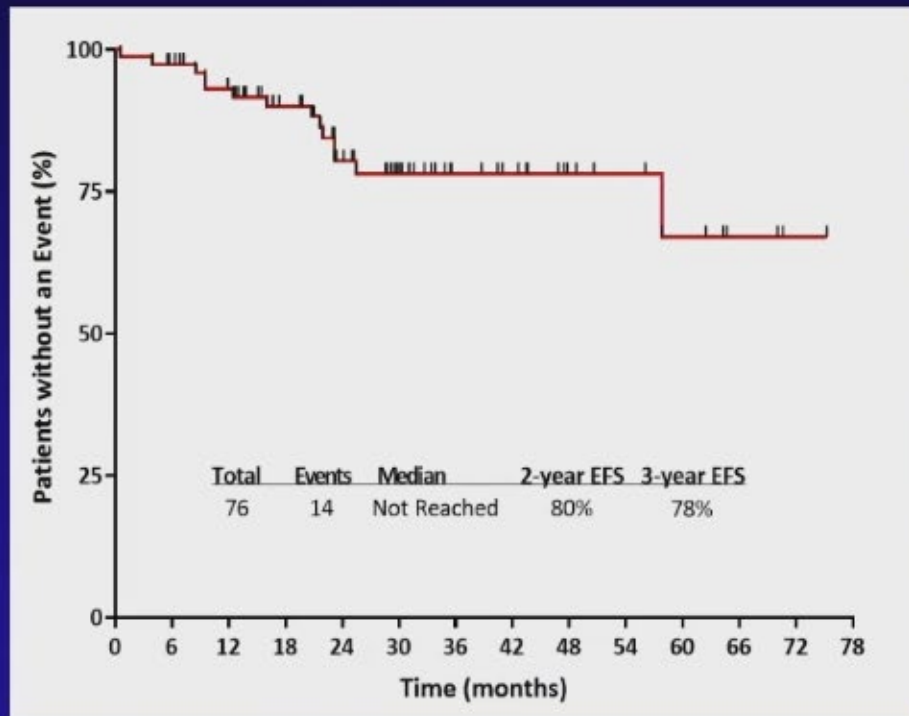


Blinatumomab and Ponatinib for Adults with Ph+ ALL

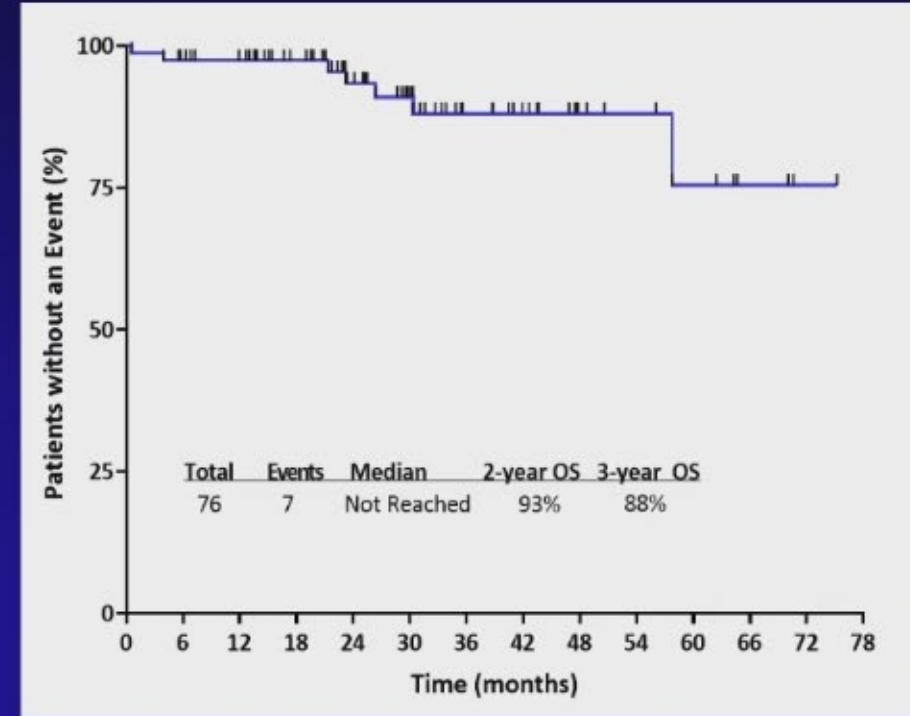
Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes

Median follow-up: 29 months (range, 5-75 months)

Event-Free Survival



Overall Survival



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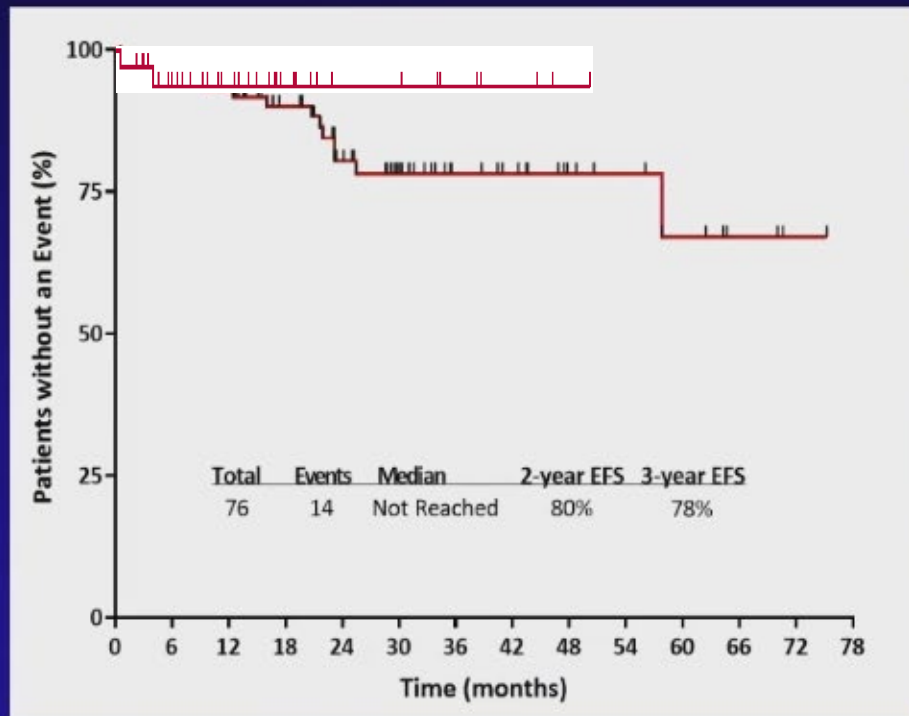


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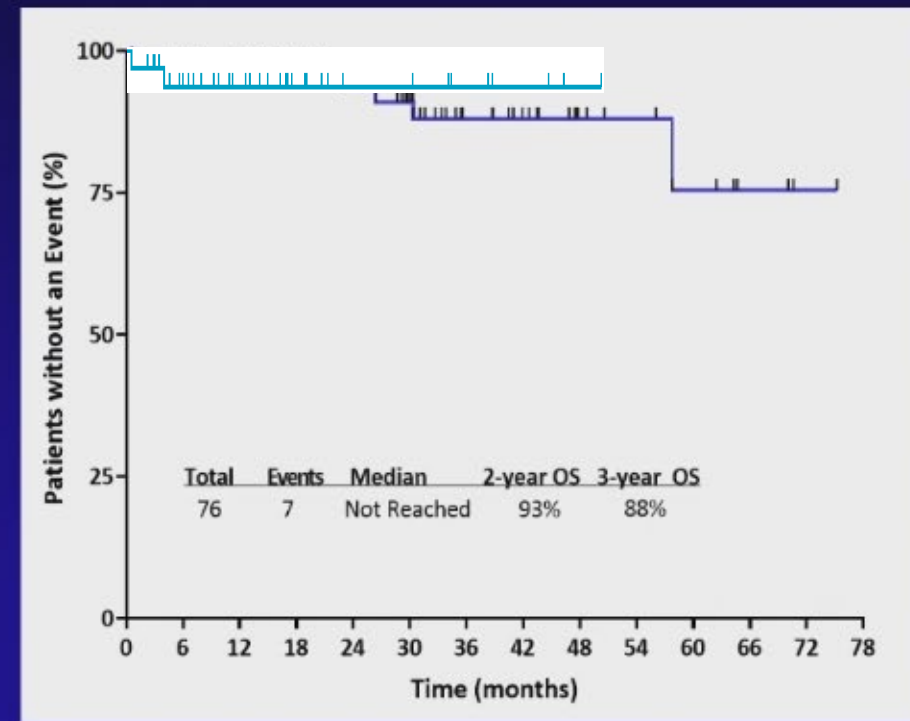
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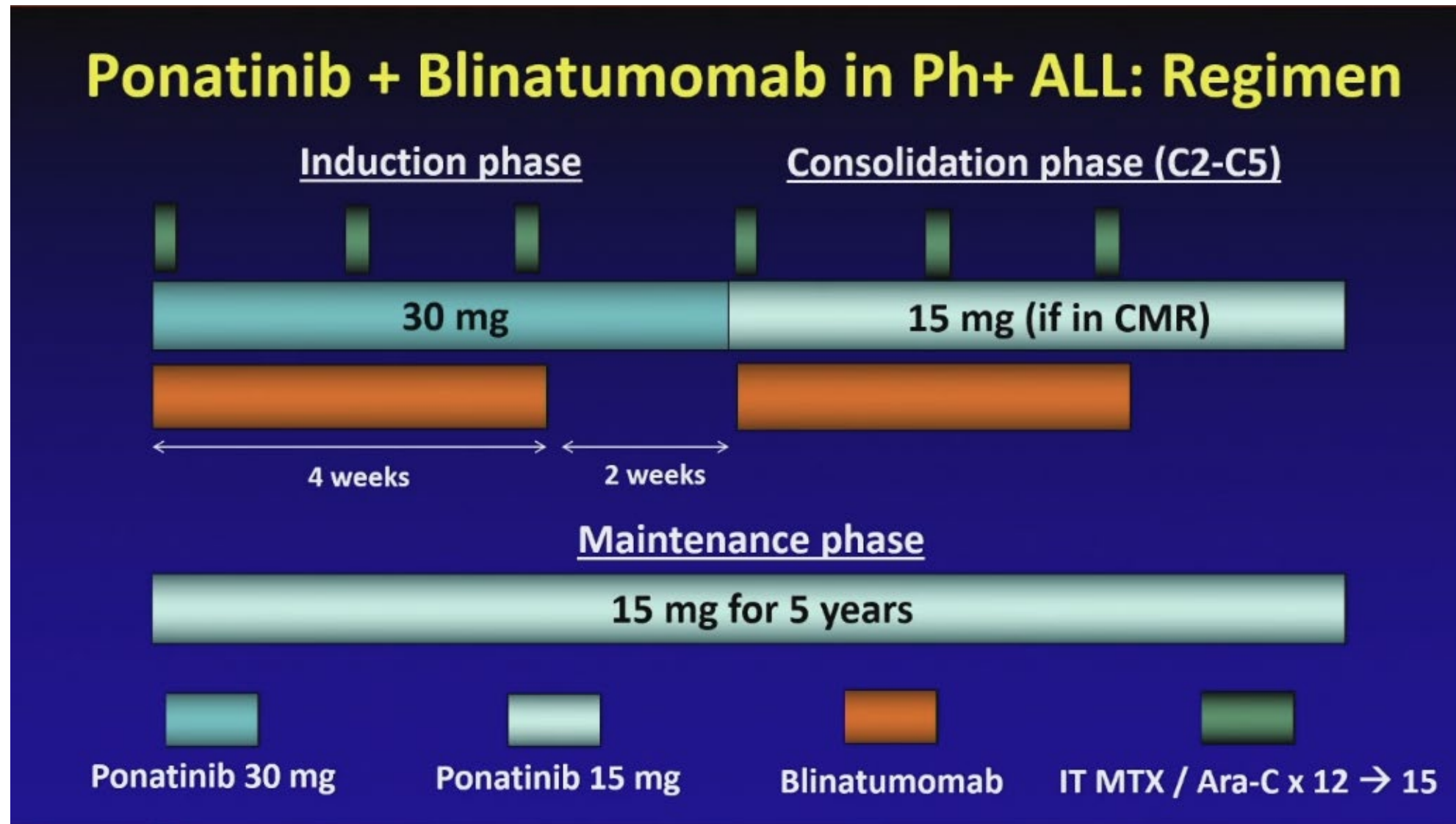
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Blinatumomab and Ponatinib for Adults with Ph+ ALL

Ponatinib + Blinatumomab in Ph+ ALL: Response Rates

Response, n/N (%)	N = 76
CR/CRi*	52/53 (98)
CR	51/53 (96)
CRi	1/53 (2)
Early death	1/53 (2)
MMR**	64/66 (97)
CMR**	57/69 (83)
After 1 cycle	41/69 (59)
NGS MRD negative	55/57 (96)
After 1 cycle	17/36 (47)

* 23 pts in CR at start

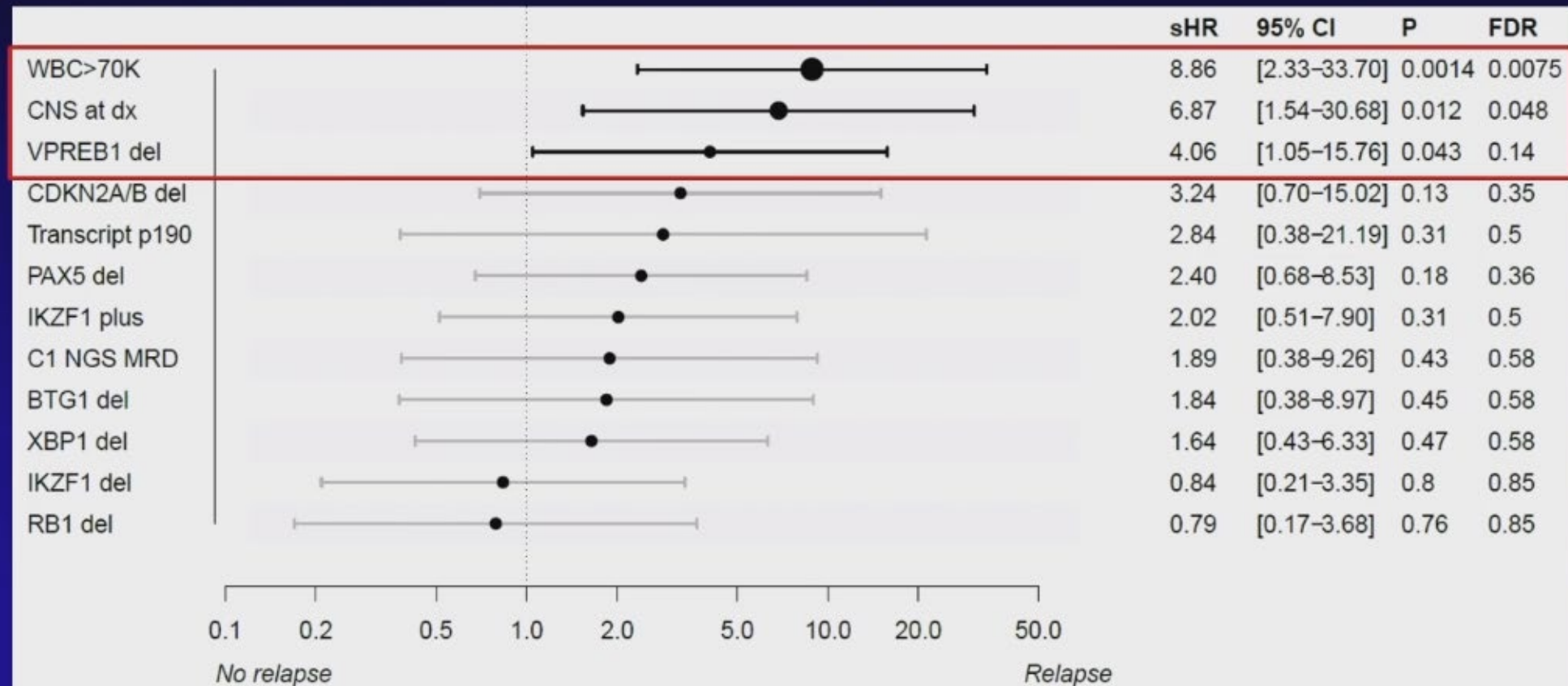
** 10 pts were in MMR, 7 were in CMR, and 2 were NGS MRD negative at start

Nicholas J. Short. 837 Blinatumomab and Ponatinib for Adults with Newly Diagnosed Philadelphia Chromosome-Positive Acute



Blinatumomab and Ponatinib for Adults with Ph+ ALL

Ponatinib + Blinatumomab in Ph+ ALL: UVA for Relapse Risk

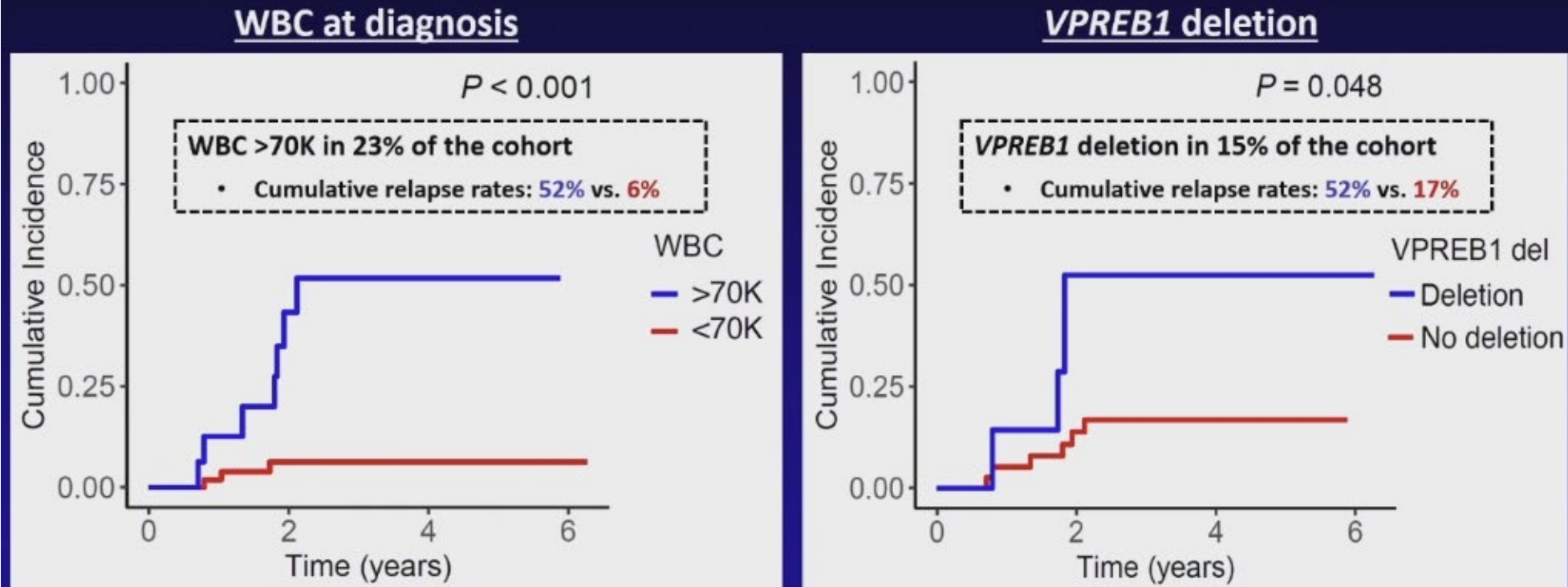


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Blinatumomab and Ponatinib for Adults with Ph+ ALL

Ponatinib + Blinatumomab in Ph+ ALL: Relapse Risk by WBC and *VPREB1* deletion



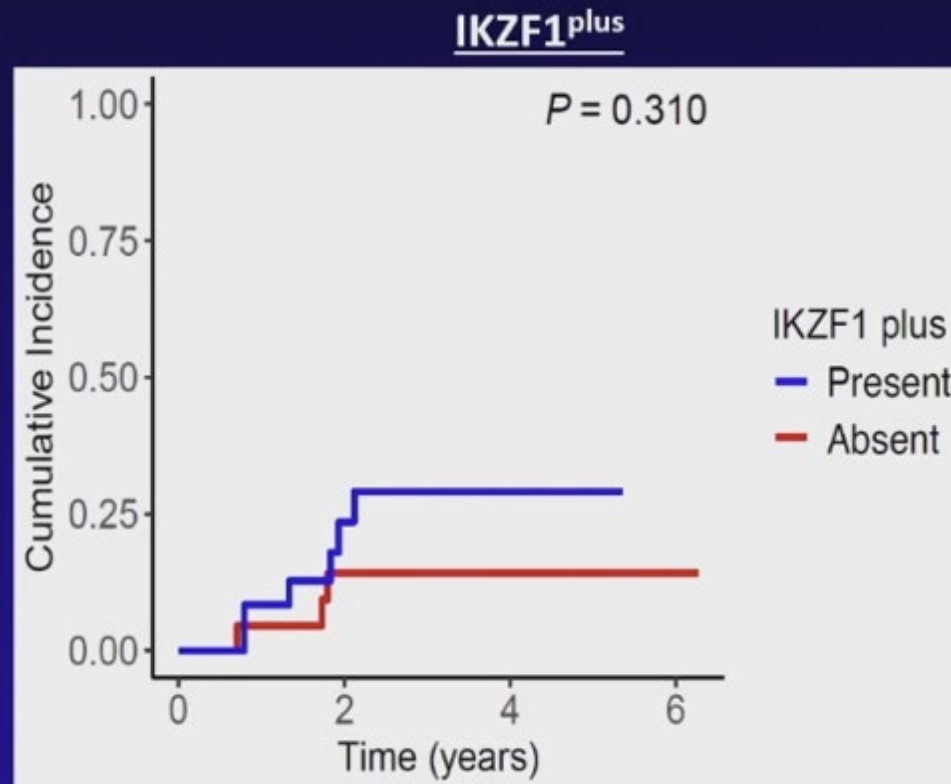
Among 3 pts with WBC <70K who relapsed: 2 had *VPREB1* del and 1 was not tested

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Blinatumomab and Ponatinib for Adults with Ph+ ALL

Ponatinib + Blinatumomab in Ph+ ALL: Relapse Risk by Transcript Type and *IKZF1*^{plus}

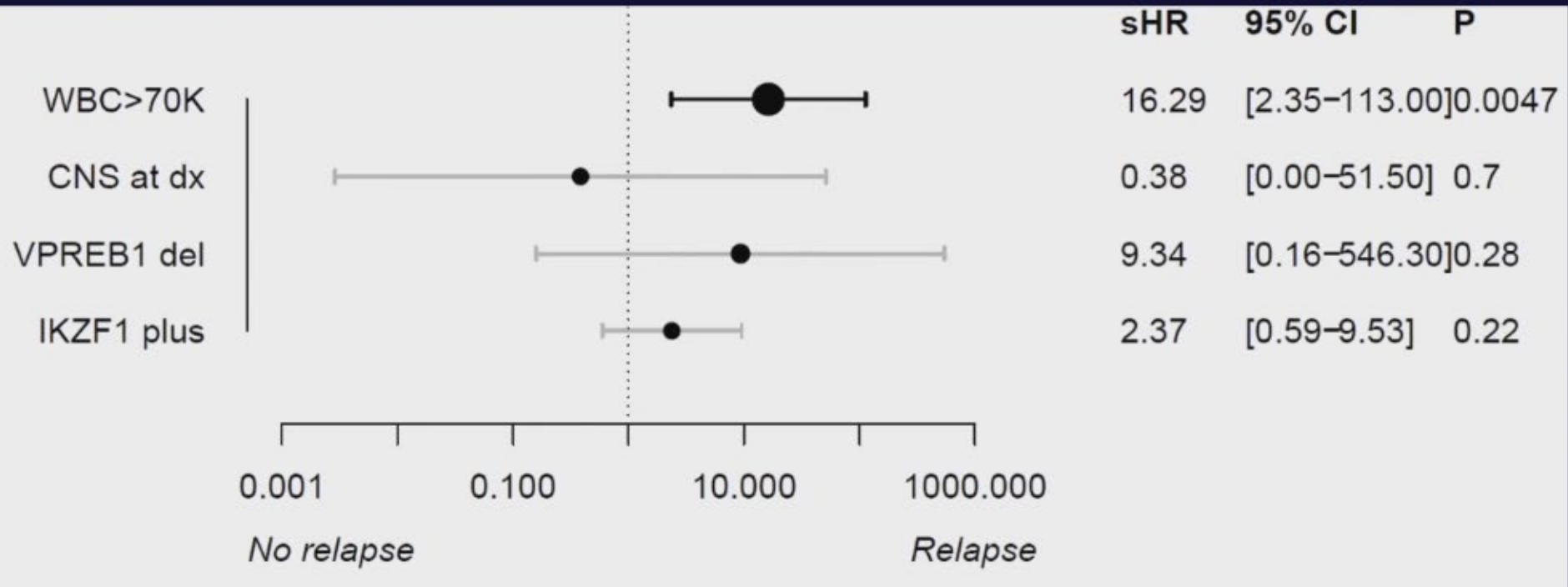


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Blinatumomab and Ponatinib for Adults with Ph+ ALL

Ponatinib + Blinatumomab in Ph+ ALL: MVA for Relapse Risk



WBC > 70K at diagnosis was only factor independently predictive of relapse risk on MVA

Nicholas J. Short. 837 Blinatumomab and Ponatinib for Adults with Newly Diagnosed Philadelphia Chromosome-Positive Acute



Blinatumomab and Ponatinib for Adults with Ph+ ALL

Ponatinib + Blinatumomab in Ph+ ALL: Conclusions

- Chemotherapy-free combination of ponatinib + blinatumomab achieves deep responses in pts with newly diagnosed Ph+ ALL
 - CR/CRI 98%, CMR 83%, **NGS MRD negativity 96%**
- Durable remissions without HSCT in first remission
 - Estimated 3-year RFS 78%; **3-year OS 88%**
 - Only 2 pts (3%) underwent HSCT in first remission
 - 10 relapses to date (**13% relapse rate; half in CNS**)
- **WBC >70K only factor predictive for relapse; ? role of *VPREB1* deletion**
 - Very high-risk feature → CIR rate ~50%
- Novel strategies needed for pts with high-risk Ph+ ALL

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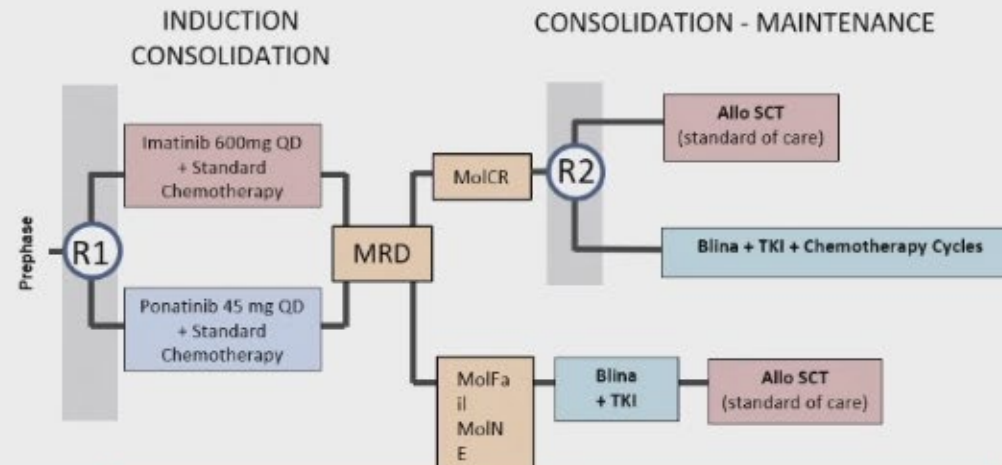


GMALL Trial 08/2013. Outcome Ph+ALL



GMALL Evolve Trial in Ph+ ALL

Lang et al, Oncology Research and Treatment, 2024



**Vielen Dank für
Ihre Aufmerksamkeit**