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Cologne Post ASH 2022
– Breaking News –

Fortbildungsveranstaltung der
Klinik I für Innere Medizin

18. Januar 2023 | 17:00 - 19:30 Uhr

Foto: New Orleans Ernest N Morial Convention Center

CIO
Centrum für Integrierte Onkologie
Aachen Bonn Köln Düsseldorf

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Handout Cologne Post ASH 2022

Mittwoch, 18. Januar 2023

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Hereditäre Hämoglobinopathien/ITP

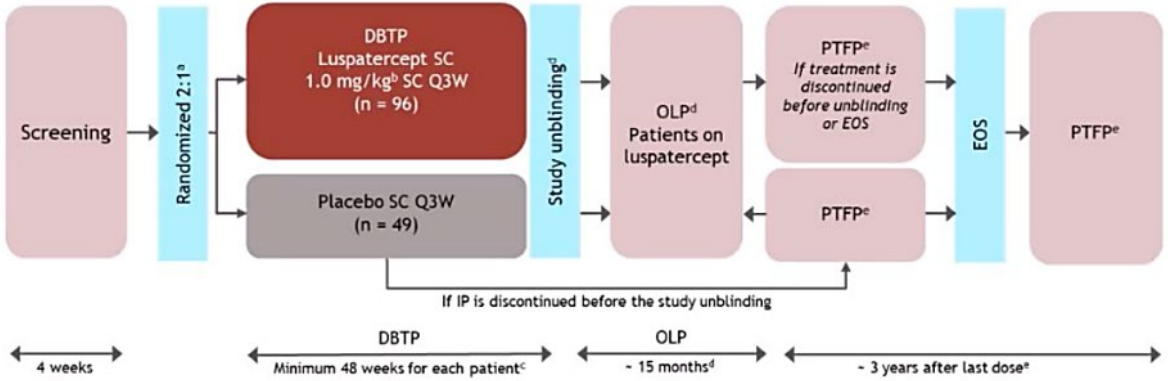
Janine Böll

18.01.2023 Cologne Post ASH Köln 2022

Offenlegung potentieller Interessenskonflikte

Anstellungsverhältnis, Führungsposition	keine
Beratungs-/ Gutachtertätigkeit	Novartis, Global Blood Therapeutics, BMS, BluebirdBio
Besitz von Geschäftsanteilen, Aktien oder Fonds	keine
Patent, Urheberrecht, Verkaufslizenz	keine
Honorare	Novartis, Global Blood Therapeutics, BMS, BluebirdBio
Finanzierung wissenschaftlicher Untersuchungen	STAND-Studie
Andere finanzielle Beziehungen	keine
Immaterielle Interessenkonflikte	keine

Abs # 3669: Erythroid Response in Patients with Non-Transfusion-Dependent β-Thalassemia Treated with Luspatercept: Long-Term Data from the BEYOND Trial



Assessment:

- Mean change from baseline Hb for continuous 12-wk intervals up to wk 144
- Erythroid response = mean Hb change from baseline of ≥ 1 g/dL, assessment over rolling 12-wk intervals
- Incidence of RBC transfusions (events and units)

Data cut: 22.09.2021	LUSP (n = 96)	PBO (n = 49)
≥ 96 wk of treatment	83 (86.5%)	16 (32.7%)
≥ 120 wk of treatment	72 (75.0%)	11 (22.4%)
≥ 144 wk of treatment	55 (57.3%)	0
Median treatment duration	150.1 (15.0–185.4) wk	61.1 (3.0–138.0) wk
discontinuation	18 (18.8%)	31 (63.3%)

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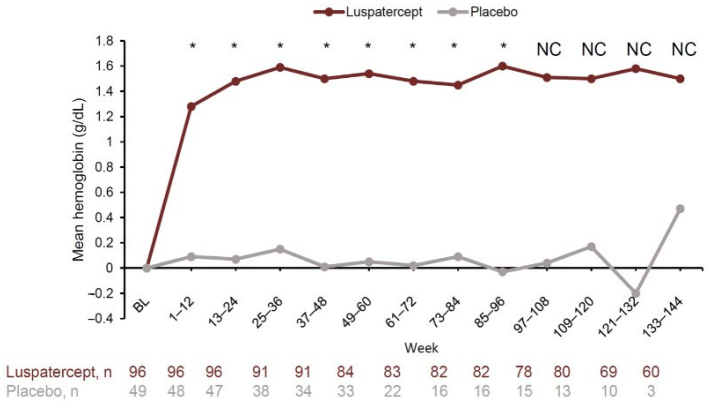
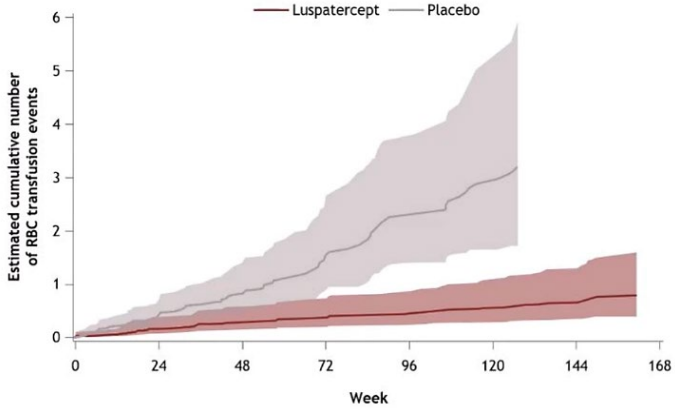
Abs # 3669: Erythroid Response in Patients with Non-Transfusion-Dependent β-Thalassemia Treated with Luspatercept: Long-Term Data from the BEYOND Trial



Mean Hb change from baseline (LUSP):
> Wk 1-12: 1.28 g/dL (SE: 0.069)
> Wk 13-24: 1.48 g/dL (SE: 0.078)

- increase maintained through all time points
- improvements in Hb levels from baseline were nominally significant vs. placebo at 12-wk intervals up to wk 96
- Erythroid response: 93.8% (90/96) at current data cut off vs. 91.7% (88/96) at primary cut off

Mean cumulative plot of RBC transfusion events in the ITT population



Week 1 – 96: ≥ 2 RBC transfusions

- LUSP: 10.4% [10/96 pat.] vs PBO=: 32.7% [16/49 pat.])
- mean number of transfusion events (LUSP: 0.4 vs PBO: 1.3)

Week 97 – 144:

- LUSP: mean number of transfusion events (0.2 events)

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Abs #12: Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Severe Sickle Cell Disease

Background:

- BCL11A => gamma-globin ↓ => HbF ↓
- Exa-cel: non-viral, ex vivo editing of erythroid-specific enhancer region of BCL11A in CD34+ HSPCs
  => reduces erythroid-specific expression of BCL11A
  => reactivates gamma-globin expression
  => HbF increase

International, multicenter, open-label, single-arm pivotal study (NCT03745287)

- Inclusion criteria: 12-35 years with severe SCD and history of ≥ 2 VOCs/year in previous 2 years
- Primary Endpoint: No severe VOC for 12 months after exa-cel
- Clinical Assessment: Engraftment, total Hb, HbF, BCL11A edited alleles, transfusion, VOCs, AEs

Characteristics	CLIMB SCD-121 SCD (n = 31)
Sex n (%)	M: 16 (51.6) F: 15 (48.4)
Genotype n (%)	
$ß^S/ß^S$	29 (93.5)
$ß^S/ß^0$	2 (6.5)
Age at baseline, years, mean (min, max)	22.5 (12, 34)
VOCs/year, mean (min, max)	3.9 (2.9, 9.5)

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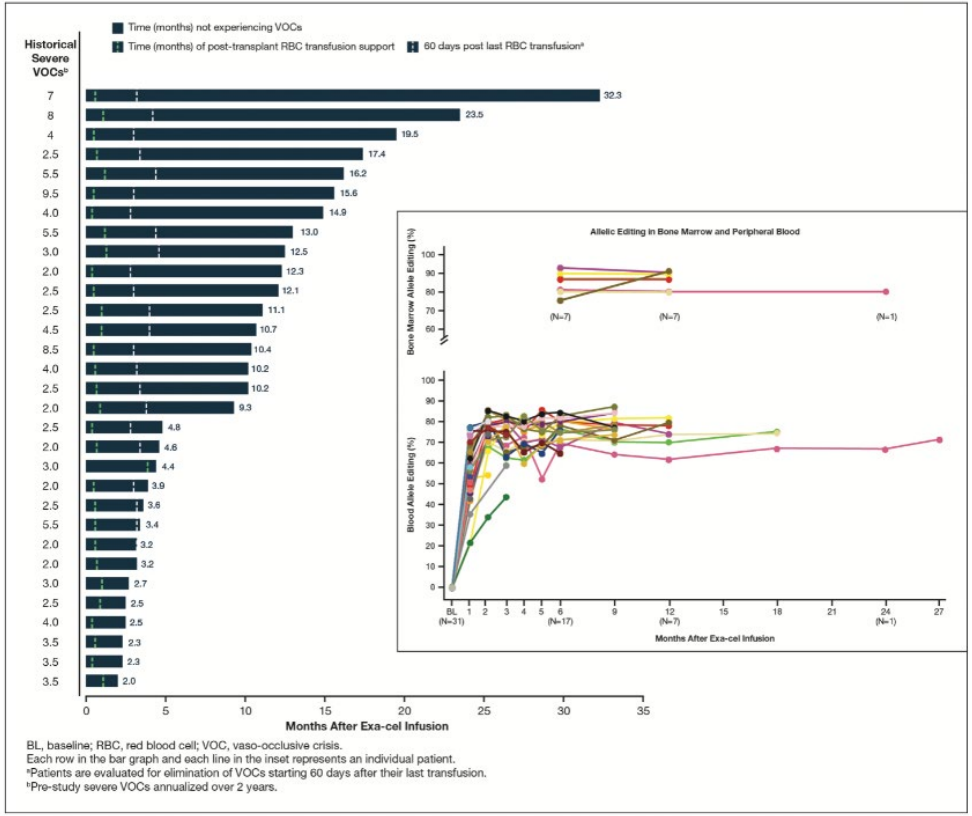
Abs #12: Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Severe Sickle Cell Disease



BL, baseline; RBC, red blood cell; VOC, vaso-occlusive crisis.
Each row in the bar graph and each line in the inset represents an individual patient.
[a]Patients are evaluated for elimination of VOCs starting 60 days after their last transfusion.
[b]Pre-study severe VOCs annualized over 2 years.

- Engraftment neutrophils/PTL: median 27/ 32 days
- Median duration FU: 10.2 months
- all pat VOC-free
- Median time from infusion to last transfusion:

  19 days
- Month 6 edited *BCL11A* alleles :
  - BM CD34+HSPCs: 86.6%
  - pB mononuclear cells: 76.0%
  - Stable ≥1 year of FU
- Safety:
  - consistent with busulfan myeloablation + autologous transplant
  - None: related SAE, deaths, discontinuations, malignancies

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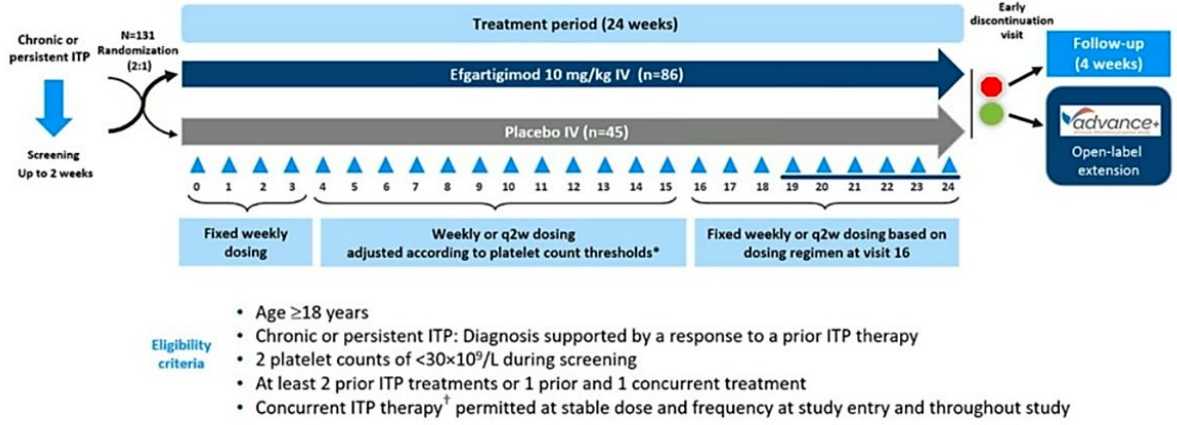
Plenary Abs #3:Efficacy and Safety of Intravenous Efgartigimod in Adults with Primary Immune Thrombocytopenia: Results of a Phase 3, Multicenter, Double-Blinded, Placebo-Controlled, Randomized Clinical Trial (ADVANCE IV)



<u>EFG (n=86)</u>

- medium age: 46.9 years
- time since diagnosis 10.3 years
- splenectomy: 32
- ≥ 3 prior therapies: 59

<u>PBO (n=45)</u>

- medium age: 51.7 years
- time since diagnosis 11.1 years
- splenectomy: 17
- ≥ 3 prior therapies: 29

<u>Primary endpoint (chron. ITP-pat.):</u>

- sustained PLT response (PLT of ≥ 50nL ≥ 4 of 6 visits between weeks 19 + 24)

<u>Secondary endpoints:</u>

- disease control (cumulative weeks PLTs of ≥50nL in chron. pat.)
- sustained PLT response in overall population (chon. + persistent)
- incidence of bleeding events
- durable sustained PLT response (≥ 50nL in ≥ 6 of 8 visits between weeks 17 + 24) in overall population

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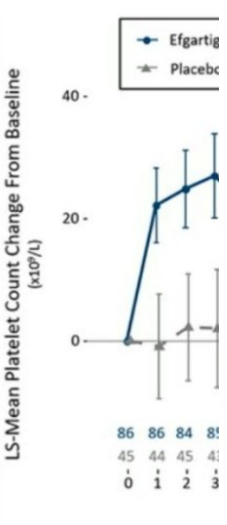
Plenary Abs #3:Efficacy and Safety of Intravenous Efgartigimod in Adults with Primary Immune Thrombocytopenia: Results of a Phase 3, Multicenter, Double-Blinded, Placebo-Controlled, Randomized Clinical Trial (ADVANCE IV)



Endpoint	Population	Efgartigimod	Placebo	*P*-value
Primary endpoint				
Sustained platelet count response	Chronic	17/78 (21.8%)	2/40 (5.0%)	.0316*
Key Secondary endpoints				
Extent of disease control[a]	Chronic	6.1 (7.66), 2.0 (0.0, 11.0)	1.5 (3.23), 0.0 (0.0, 1.0)	.0009*
Sustained platelet count response	Overall	22/86 (25.6%)	3/45 (6.7%)	.0108*
Incidence of WHO bleeding events[b]	Overall	6.2 (6.39), 4.0 (1.0, 10.0)	8.3 (8.01), 5.0 (2.0, 14.0)	.8287
Durable sustained platelet count response	Overall	19/86 (22.1%)	3/45 (6.7%)	.0265

- ✓ EFG achieved primary and all PLT-related secondary endpoints
- ✓ EFG response regardless of age, sex, severity of disease, time since diagnosis, prior ITP treatment, background medication
- ✓ Mean IgG levels in EFG decreased steadily over first 4 weeks of treatment (mean max. reductions from baseline > 60%)
- ✓ Well tolerated (no increased risk of infection, no deaths):
  - AE (bruising, headache, hematuria, and petechiae): 93.0% (EFG) vs. 95.6& (PBO)
  - SAE (not related) (bleeding (n=5), infection (n=4), worsening ITP (n=3)): 8.1% (EFG) vs. 15.6% (PBO)

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ASH 2022: Take-Home Botschaften

1. Long-term luspatercept treatment in NTD ß-thalassemia leads to nominally significant Hb increase maintained up to week 96 + 144 with only a few patients requiring RBC transfusions, also leading to stabilization in iron-related parameters.

2. Exa-cel led to elimination of VOCs in all patients with SCD, with clinically meaningful increases in HbF and total Hb. It has the potential to be the first CRISPR/Cas9-based therapy to provide a functional cure for severe SCD.

3. Efgartigimod showed early PLT increase with higher sustained PLT response and more weeks with PLT ≥50nL and long-term efficacy and safety data are being evaluated in the open-label extension trial (ADVANCE+; NCT04225156).

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Best of ASH: Hämostaseologie

PD Dr. Paula Cramer

Uniklinik Köln

18.01.2023 Cologne Post ASH Köln 2022

Offenlegung potentieller Interessenskonflikte: P. Cramer

Anstellungsverhältnis, Führungsposition	-
Beratungs-/ Gutachtertätigkeit	AbbVie, Acerta, AstraZeneca, BeiGene, Janssen-Cilag and Novartis
Besitz von Geschäftsanteilen, Aktien oder Fonds	-
Patent, Urheberrecht, Verkaufslizenz	-
Honorare	AbbVie, AstraZeneca, BeiGene, BMS, F. Hoffmann-LaRoche und Janssen-Cilag
Finanzierung wissenschaftlicher Untersuchungen	Acerta, AstraZeneca, BeiGene, F. Hoffmann-LaRoche, Gilead, Janssen-Cilag und Novartis
Andere finanzielle Beziehungen: Reiseunterstützung	AbbVie, AstraZeneca, BeiGene, F. Hoffmann LaRoche, Gilead and Janssen-Cilag
Immaterielle Interessenkonflikte	-

LBA-5 (S. Middeldorp, Nijmegen/NL) : **Low-Molecular-Weight Heparin** Versus Standard Pregnancy Care for **Women with Recurrent Miscarriage and Inherited Thrombophilia (ALIFE2):** An Open-Label, Phase III Randomized Controlled Trial

Background

- known association between recurrent miscarriage and inherited thrombophilia
- anticoagulant therapy often used to reduce risk of miscarriages and adverse pregnancy outcomes

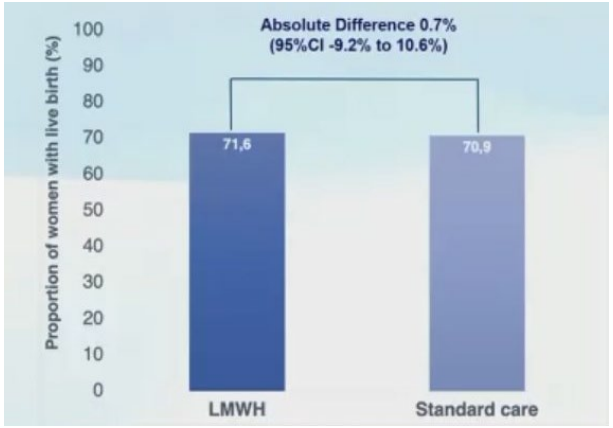
Methods

- 326 women ≤7 weeks pregnant from 41 sites in 5 countries (IIT trial) with history of ≥2 miscarriages and inherited thrombophilia (FVL or PT mutation, antithrombin, protein C or protein S deficiency)
- 164 women randomized to receive LMWH (mostly enoxaparin) and 162 to standard surveillance

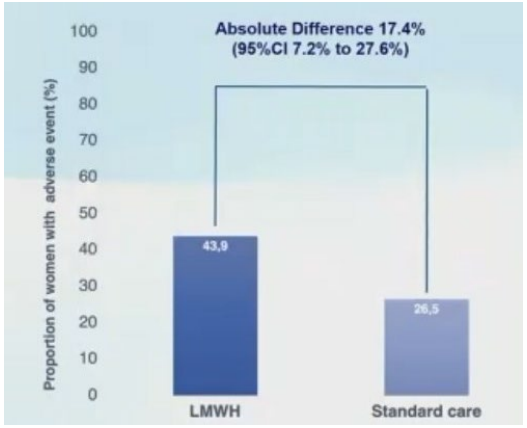
LBA-5 (S. Middeldorp, Nijmegen/NL) : **LMWH** vs Standard Pregnancy Care for **Women with Recurrent Miscarriage and Inherited Thrombophilia (ALIFE2):**

Results

- Primary outcome: live birth rates 71.6 vs 70.9%



- AEs: 43.9 vs 26.5%



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LBA-5 (S. Middeldorp, Nijmegen/NL) : **LMWH** vs Standard Pregnancy Care for **Women with Recurrent Miscarriage and Inherited Thrombophilia (ALIFE2):**

Society for Maternal-Fetal Medicine

Conclusions

The ALIFE2 study showed that with standard pregnancy care – and without expensive testing and burdensome medication use – slightly more than

70% of women had a live birth.

Home >> Publications & Guidelines >> Choosing Wisely: Twenty Things Physicians and Patients Should Question

Choosing Wisely: Twenty Things Physicians and Patients Should Question

1. Don't do an inherited thrombophilia evaluation for women with histories of pregnancy loss, fetal growth restriction (FGR), preeclampsia and abruption.

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Abstract-519 (F. Moik, Graz/AT):
Early Dynamics of C-Reactive Protein Predict Risk of Venous Thromboembolism in Patients with Cancer Treated with Immune Checkpoint Inhibitors

Background

- pts with cancer treated with immune checkpoint inhibitors (ICI) have a substantial risk of venous thromboembolism (VTE)
- conventional prothrombotic risk factors seem inefficient in the prediction of VTE in these pts

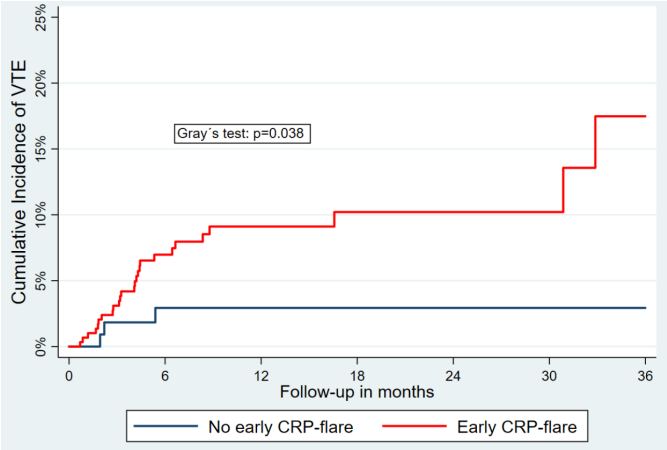
Methods

- 405 patients with ICI; most commonly: melanoma (33%) and lung cancer (26%); 91% in stage IV
- CRP levels measured at baseline and at 1, 2, and 3 months after ICI-initiation. CRP dynamics:
  - CRP-flare: increase by the factor of 2.5 relative to baseline measurements
  - CRP-response: 50% relative decrease in CRP-levels
- median follow-up of 7.9 months (IQR: 4-16)

Abstract-519 (F. Moik, Graz/AT):
Early Dynamics of C-Reactive Protein Predict Risk of Venous Thromboembolism in Patients with Cancer Treated with Immune Checkpoint Inhibitors

Results

- 29 VTE events in 405 patients (12.7%)
  - 296 pts (73%) had CRP-flare:
    cumulative incidence of VTE 17.5%
  - 62 pts (15%) with CRP-response without prior flare:
    cumulative incidence of VTE 1.6%



Conclusion

- potential link between the ICI-induced systemic inflammatory response and subsequent risk of VTE

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Abstract-522 (K. Snow, Hartford/CT):

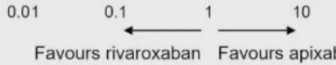
Rivaroxaban vs Apixaban for Treatment of Cancer-Associated Venous Thromboembolism: A Head-to-Head Analysis of the United States Cohort of the Observational Study in Cancer-Associated Thrombosis for Rivaroxaban: (H2H-OSCAR-US)

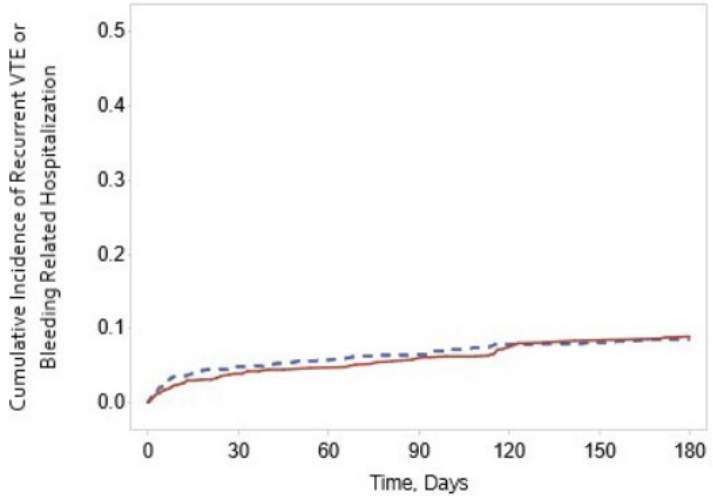
Methods

- retrospective study with De-Identified electronic health data from US (2013 – 2020)
- 2437 pts with active solid cancer an VTE treated with apixaban (1344 pts) or rivaroxaban (1093 pts)

Results

	Rivaroxaban N=1093, %	Apixaban N=1344, %	IPTW-HR* (95% CIs)	IPTW-HR* (95% CIs)
Recurrent VTE or bleeding related hospitalization	5.3	6.0		0.87 (0.60–1.27)
Recurrent VTE	3.8	4.2		0.92 (0.59–1.42)
Bleeding related hospitalization	2.4	2.3		1.05 (0.59–1.88)
Critical organ bleed	0.2	0.4		0.49 (0.09–2.59)
Recurrent VTE or critical organ bleed	3.8	4.5		0.85 (0.56–1.31)





Abstract-520 (A. Leader, Tel-Aviv/IL):
Thrombin Generation Is Differentially Affected By Anticoagulants in Patients with Acute Lymphoblastic Leukemia – an Ex-Vivo Study

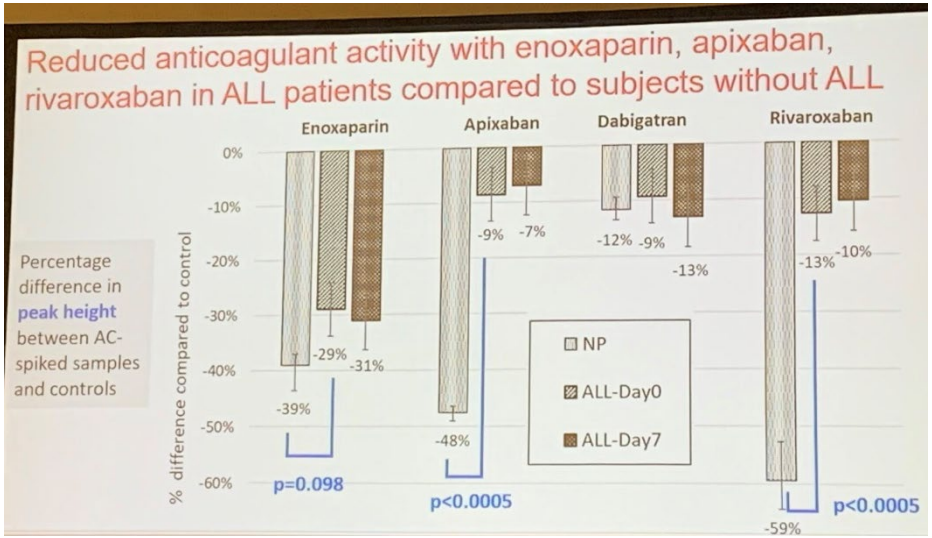
Background

- suboptimal effect of LMWH in preventing VTE in pts with ALL: possibly due to anti-thrombin deficiency with asparaginase

Methods

- thrombin generation assay testing ex-vivo effect of:
  - LMWH (enoxaparin)
  - direct Xa inhibitors (apixa-/rivaroxaban)
  - direct thrombin inhibitor (dabigatran)

Results



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ASH 2022: Take-Home Messages (Hämostaseologie)

1. Gynäkologie/Reproduktionsmedizin:

   Frauen mit Z.n. rezidivierenden Aborten und Thrombophilie benötigen **keine Heparin-Gabe in der Schwangerschaft**, sofern hierfür keine andere Indikation (z.B. frühere Thrombose/Embolie) besteht. Es sollte auch kein Screening auf eine hereditäre Thrombophilie erfolgen.

2. Onkologie:

   Deutlich erhöhtes Risiko für Thrombosen/Embolien bei Pat. mit soliden Tumoren und CRP-Anstieg um das ≥2,5-fache unter Immuncheckpoint-Blockade

   Rivaroxaban scheint zumindest gleichwertig zu Apixaban zu sein bzgl. der Vermeidung von Rezidivthrombosen/embolien und schweren Blutungen bei Pat. mit aktiven soliden Tumoren

3. Hämatologie:

   3. **Ex-vivo Daten** legen nahe, dass **Dabigatran zur VTE Prophylaxe bei Pat. mit ALL ggf. besser** geeignet ist als Apixaban und Rivaroxaban, sowie LMWH

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Cologne Post ASH 2022
- aggressive B-NHL und Hodgkin Lymphom -

Peter Borchmann

Uniklinik Köln

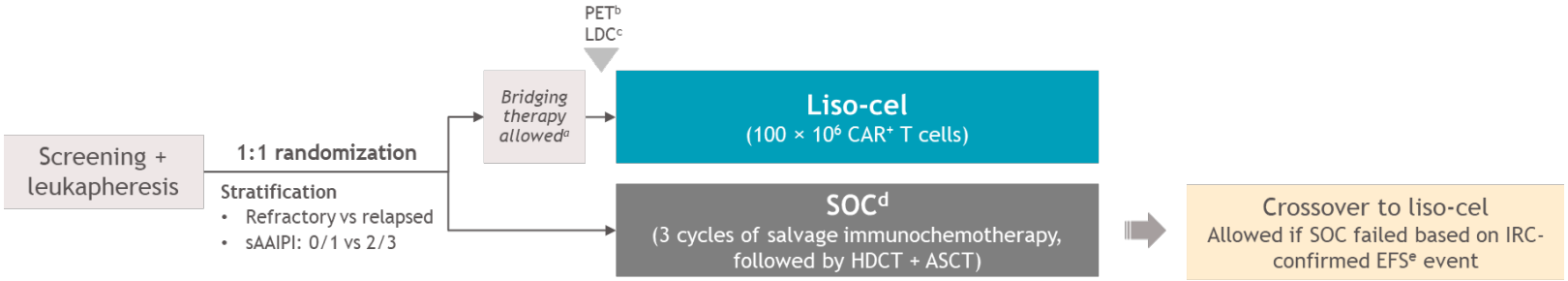
Cologne Post ASH 2022
- aggressive B-NHL und Hodgkin Lymphom -

1. DLBCL: CD19 CAR T-Zelltherapie im der Zweitlinie obligat?
   TRANSFORM Studie

2. PCNSL: Stellenwert der Hochdosistherapie?
   MATRIX/IELSG43 Studie

3. HL: Gibt es was besseres als eBEACOPP?
   GHSG HD21 Studie

Abs 655. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma: primary analysis of the randomized, phase 3 TRANSFORM study. Abramson et al.



– Primary enpoint EFS: time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurred first.

– median follow-up from randomization of 17.5 months

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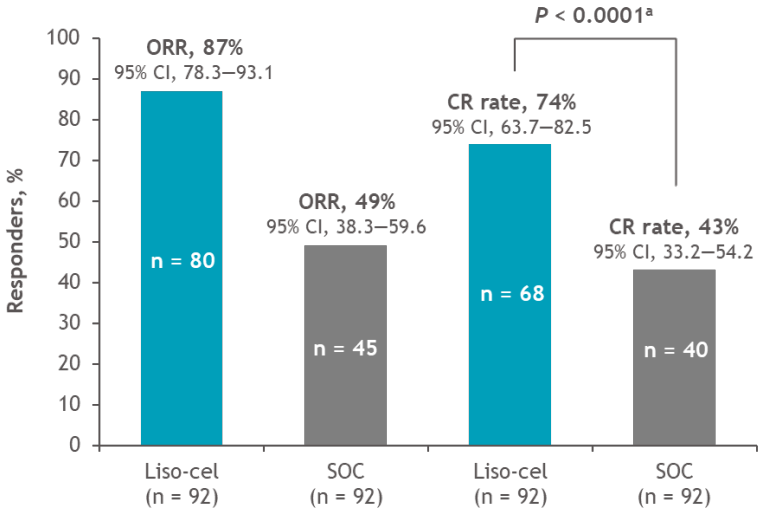
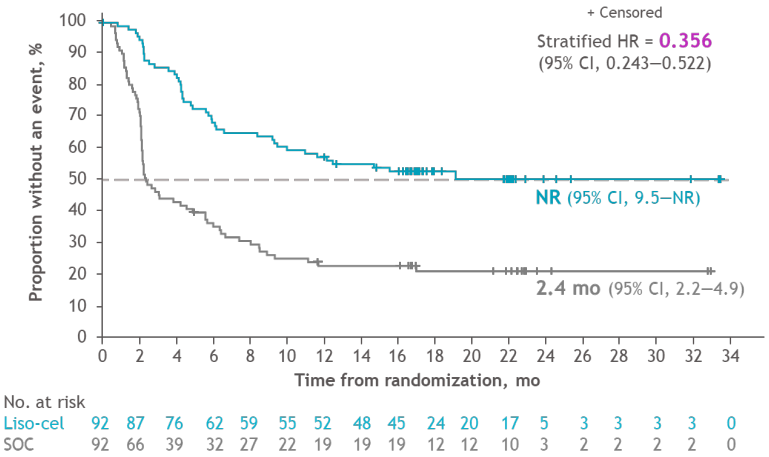
TRANSFORM: RR and EFS per IRC (ITT set; primary endpoint)



18-month EFS rate	
Liso-cel	SOC
52.6%	20.8%
(95% CI, 42.3–62.9)	(95% CI, 12.2–29.5)
Median follow-up: 17.5 mo	



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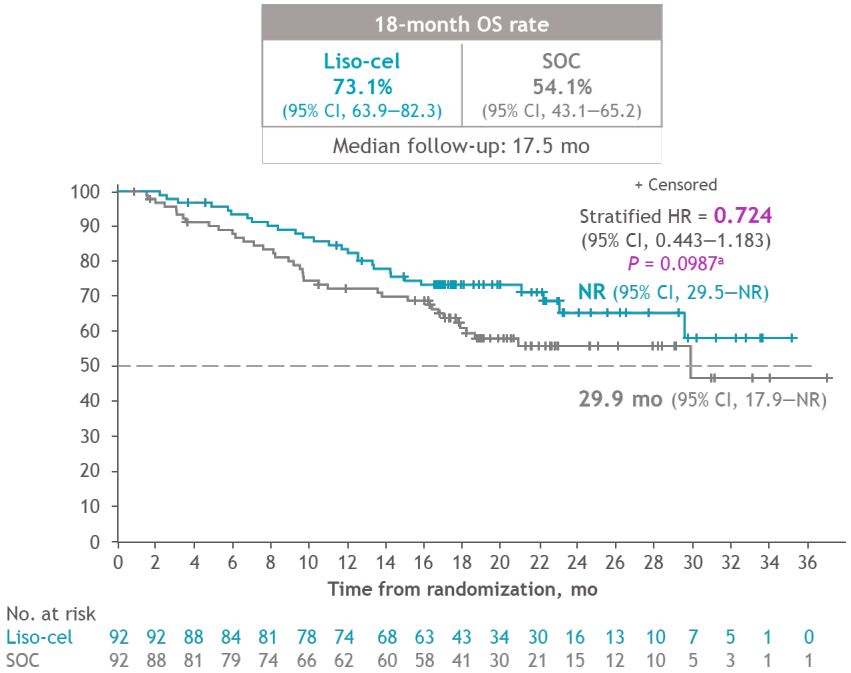
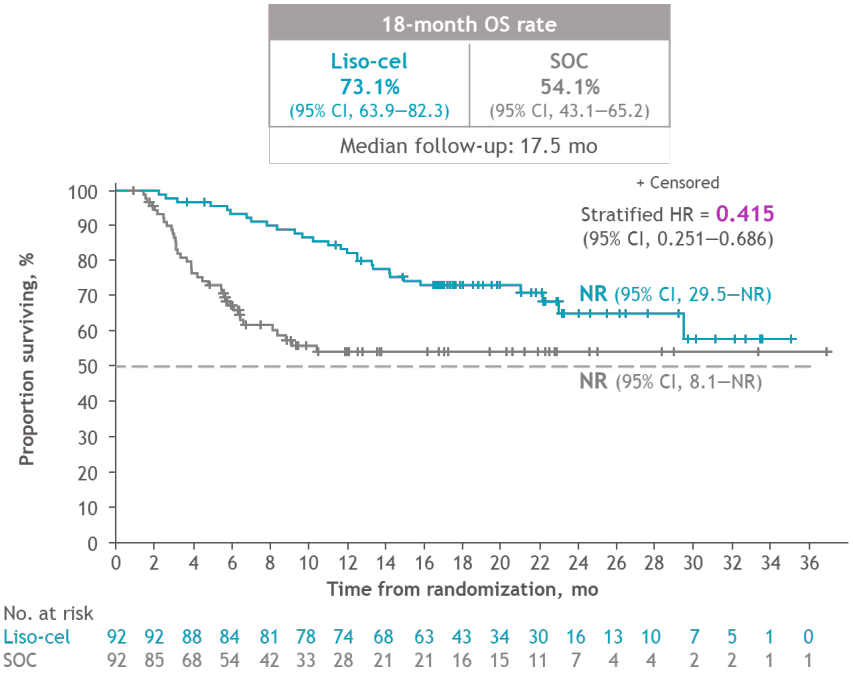
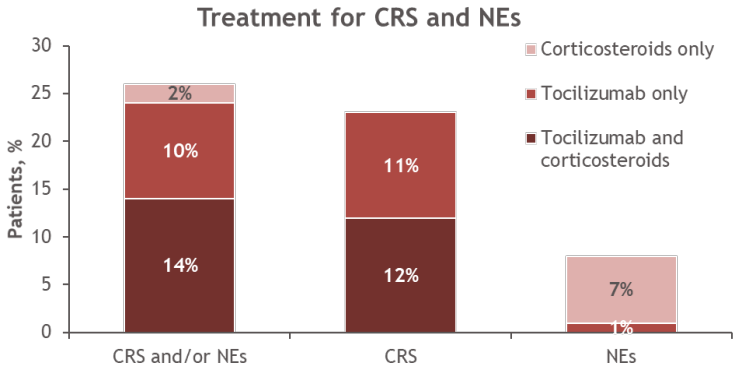
TRANSFORM: OS per IRC (ITT set)



Adjusted for crossover (2-stage accelerated failure time model)



TRANSFORM: TEAEs of special interest (safety set)



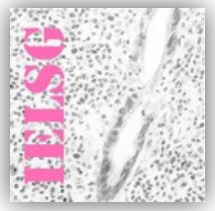
• No vasopressors or prophylactic corticosteroids were used

Other adverse events of special interest	Liso-cel arm (n = 92)	SOC arm (n = 91)
Prolonged cytopenia[c]	40 (43)	3 (3)
Grade ≥ 3 infection	14 (15)	19 (21)

Keine Grad 4 oder 5 Ereignisse!

- Nach ZUMA-7 die zweite CD19 CAR T-Zell Studie mit jetzt ausreichend langem FU und positivem Ergebnis
- Wirksamkeit klinisch relevant und Verträglichkeit jedenfalls sicher, jedoch auch relativ gut

➢ Frühe Rezidive des DLBCL *sollen* mit CARs behandelt werden!



Kooperative Studiengruppe ZNS-Lymphome

Klinikum Stuttgart

ASH, New Orleans, December 2022

Effects on Survival of Non-Myeloablative Chemoimmunotherapy Compared to High-Dose Chemotherapy Followed By Autologous Stem Cell Transplantation As Consolidation Therapy in Patients with Primary CNS Lymphoma – Results of an International Randomized Phase III Trial (MATRix/IELSG43)

Gerald Illerhaus, A.J.M. Ferreri, M. Binder, P. Borchmann, J. Hasenkamp, S. Stilgenbauer, A. Roeth, T. Weber, G. Egerer, T. Ernst, B. Hertenstein, G. Lenz, G. Kobbe, U. Brunnberg, C. Schmidt, M. Kneba, M. Dreyling, R. Möhle, J. Panse, T. Heinicke, S. Schroll, T.S. Larsen, H. Salwender, R. Naumann, G. Hess, L. Thurner, T. Pukrop, U. Keller, A.K. Blystadt, F.P. Kroschinsky, F. Re, E. Pulczynski, L. Orsucci, L. Pospiech, M. Deckert, M. Ponzoni, J. Wendler, E. Valk, T. Calimeri, B. Kasenda, M. Trepel, H. Fricker, P. v. Gottberg, E. Burger, G. Ihorst, O. Grishina, C. Hader, E. Zucca, J. Finke and Elisabeth Schorb

On behalf of the German Cooperative Study Group CNS Lymphoma and the International Extranodal Lymphoma Study Group (IELSG)

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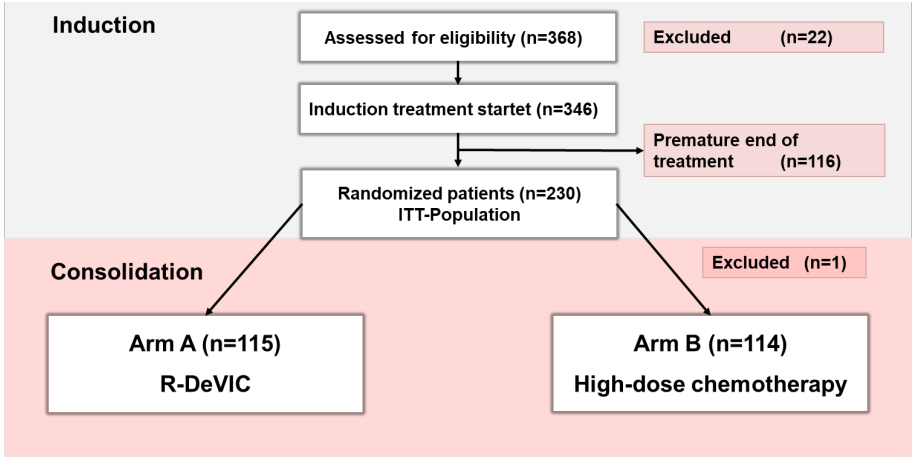
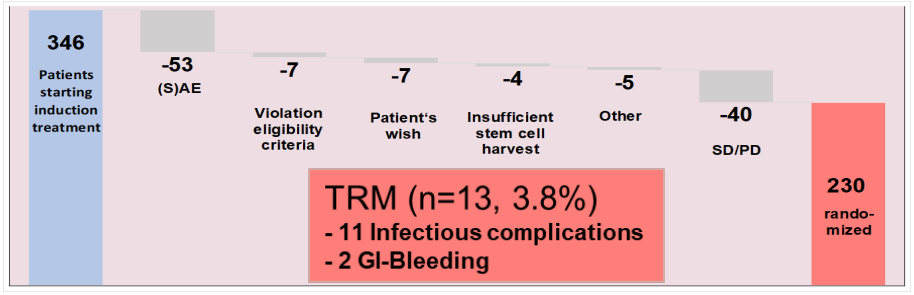
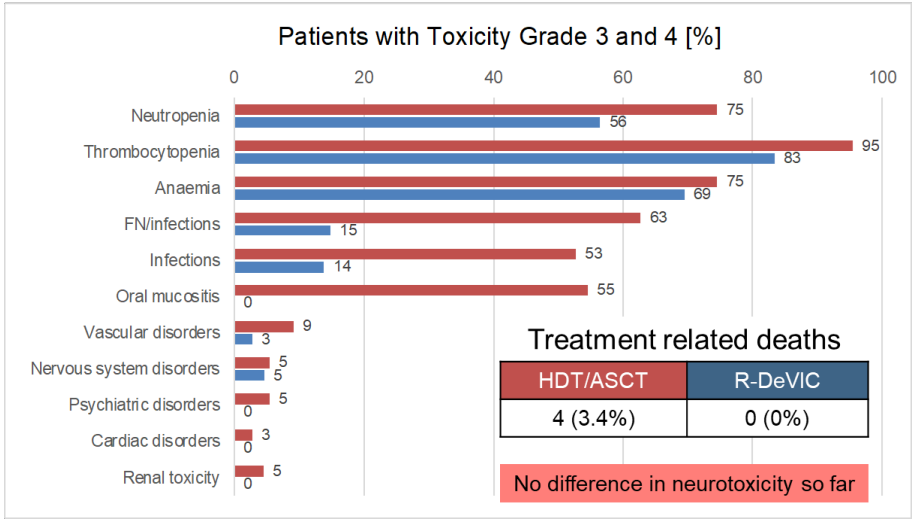
MATIRX: Treatment algorithm and tolerability







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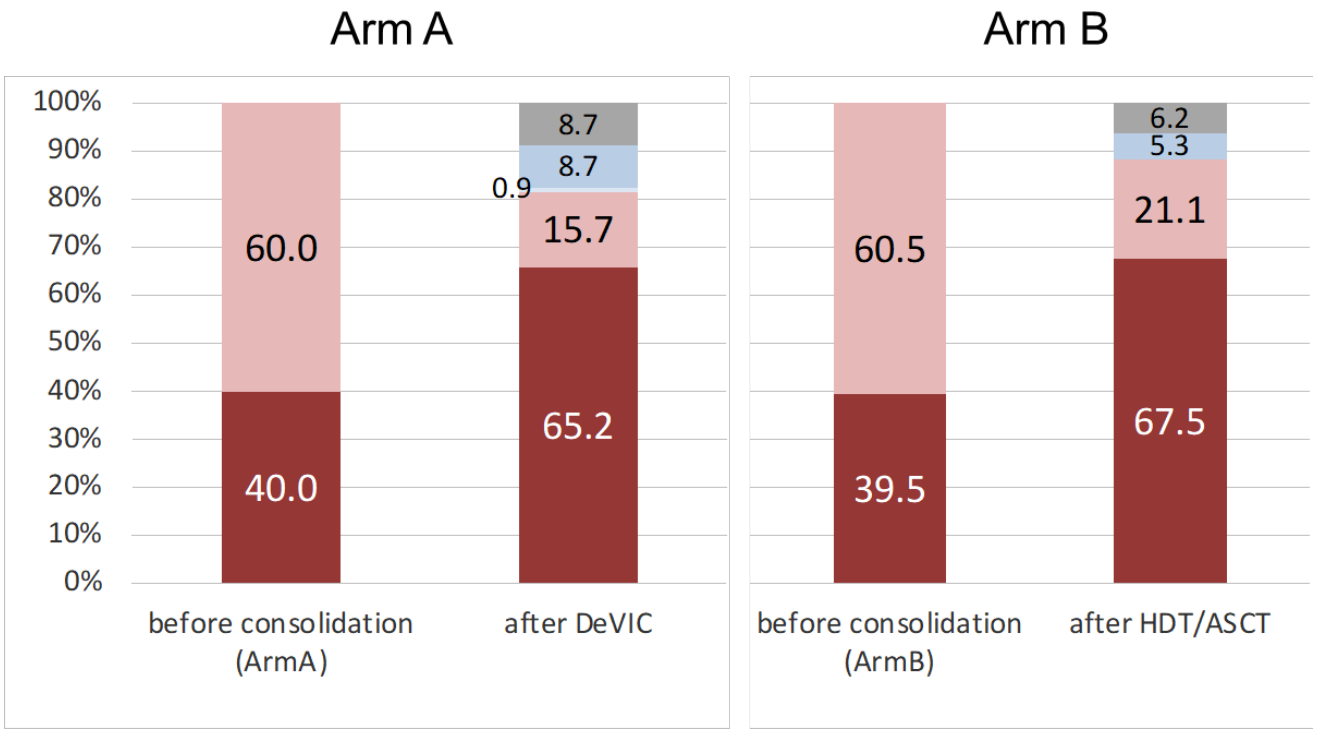
Response (randomized patients)



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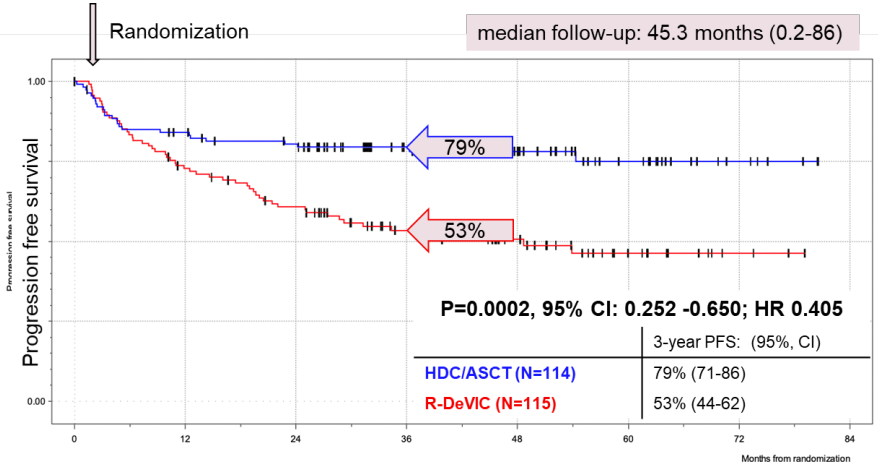
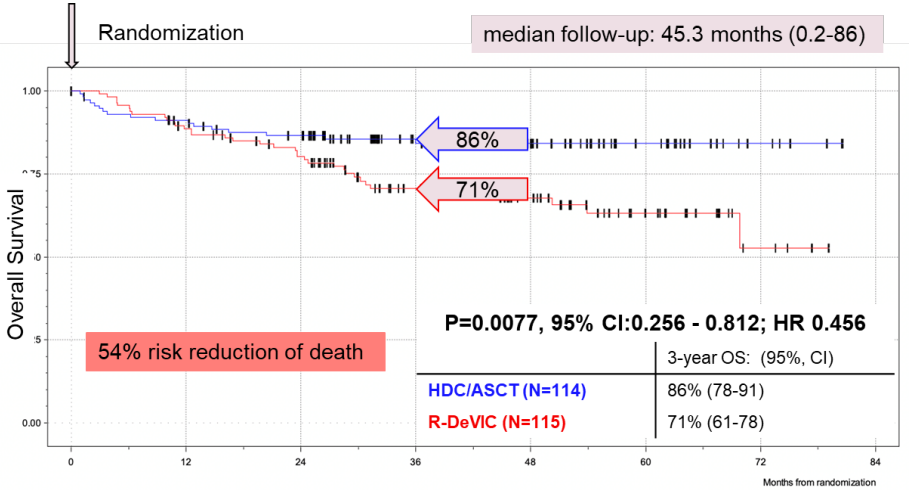
MATRIX: PFS and OS





- Die Hochdosistherapie ist der konventionellen Therapie signifikant und relevant überlegen ohne mehr Neurotoxizität zu verursachen (im Gegensatz zur konsolidierenden Ganzhirn-Radiotherapie)

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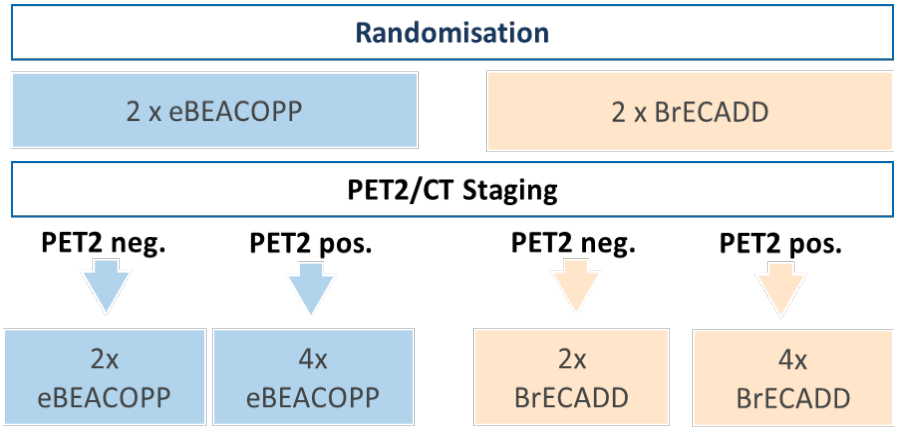
Abs 140: Treatment related morbidity in patients with classical Hodgkin Lymphoma: results of the ongoing, randomized phase III HD21 Trial by The German Hodgkin Study Group. P. Borchmann et al.

Drug	Day	BEACOPP[1] Dose (mg/m²)	BrECADD Dose (mg/m²)
Bleomycin	8	10	-
Etoposide	1–3	200	*150*
Doxorubicin	1	35	*40*
Cyclophosphamide	1	1250	*1250*
Vincristine	8	1.4	-
Brentuximab vedotin	1	-	*1.8 mg/kg*
Procarbazine	1–7	100	-
Prednisone	1–14	40	-
Dacarbazine	2–3	-	*250*
Dexamethasone	1–4	-	*40*



superiority for treatment related morbidity (TRMB)

- Acute non-hematological organ toxicity of CTCAE grade 3 or 4
- Acute hematological toxicity: grade 4 anemia, grade 4 thrombocytopenia, and grade 4 infections
- during primary chemotherapy up to 12m

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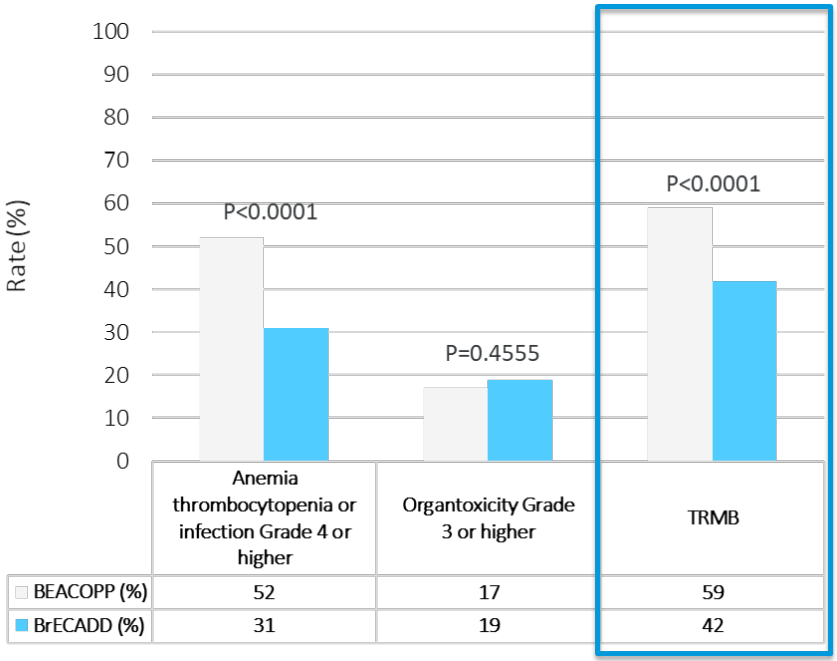
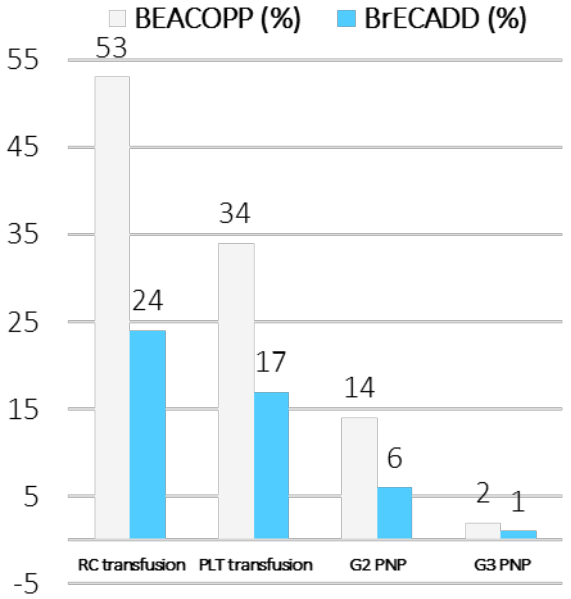
GHSG HD21 primary safety endpoint TRMB analyses results



	Anemia thrombocytopenia or infection Grade 4 or higher	Organtoxicity Grade 3 or higher	TRMB
BEACOPP (%)	52	17	59
BrECADD (%)	31	19	42



	eBEACOPP (%)	BrECADD (%)
TRM	< 1%	0%

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GHSG HD21: gonadal dysfunction

female patients (18-39) per arm

	BEACOPP (N=326)		BrECADD (N=331)	
	N	Mean	N	Mean
N (min FU12 m)	145	27,2 U/l	149	13,4 U/l

- FSH normal values (cycle dependent): 1,7 – 21,5 U/l
- FSH documented in: 58 % in BEACOPP and 57 % in BrECADD

male patients (18-49) per arm

	BEACOPP (N=418)		BrECADD (N=417)	
	N	Mean	N	Mean
N (min FU12 m)	189	20,5 U/l	178	11,9 U/l

- FSH normal values: FSH: 1.5 – 12.4 U/l
- FSH was documented in: 45 % in BEACOPP and 45 % in BrECADD

PFS entire study cohort

- Signifikante Toxizitäts-Unterschiede zugunsten von BrECADD, praktisch relevant
- PFS mit 94% nach fast 3 Jahren besser als angenommen: IA genehmigt!

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Cologne Post ASH 2022
- aggressive B-NHL und Hodgkin Lymphom -

1. DLBCL *DLBCL: CD19 CAR T-Zelltherapie im der Zweitlinie obligat?*
   Ja. Was machen wir mit fragilen Patienten und Therapieversagern?

2. PCNSL: *DLBCL: CD19 CAR T-Zelltherapie im der Zweitlinie obligat?*
   Standard. Verbesserung der Induktion?

3. HL: *Gibt es was besseres als eBEACOPP?*
   Sehr gut möglich, PFS abwarten kommt noch 2023

UNIKLINIK
KÖLN

Indolente Lymphome und Mantelzelllymphom

Ron D. Jachimowicz

18.01.2023 Cologne Post ASH Köln 2022

Offenlegung potentieller Interessenskonflikte

Anstellungsverhältnis, Führungsposition	Oberarzt, Uniklinik Köln; Max Planck Forschungsgruppenleiter, MPI-Age
Beratungs-/ Gutachtertätigkeit	entfällt
Besitz von Geschäftsanteilen, Aktien oder Fonds	entfällt
Patent, Urheberrecht, Verkaufslizenz	entfällt
Honorare	entfällt
Finanzierung wissenschaftlicher Untersuchungen	entfällt
Andere finanzielle Beziehungen - Reisekosten	Beigene
Immaterielle Interessenkonflikte	entfällt

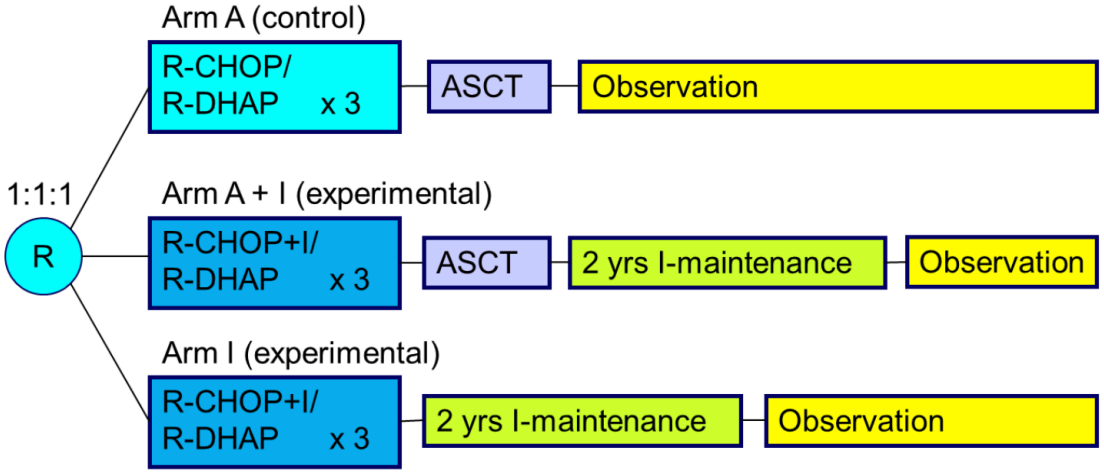
UNIKLINIK KÖLN

Abstr. No 1: Efficacy and Safety of Ibrutinib combined with standard 1st-line Treatment as substitute for Autologous Stem Cell Tx in Younger Pts with Mantle Cell Lymphoma

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

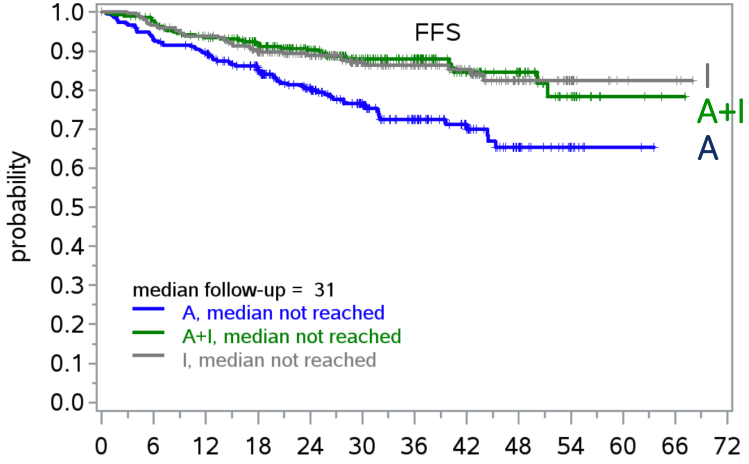
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

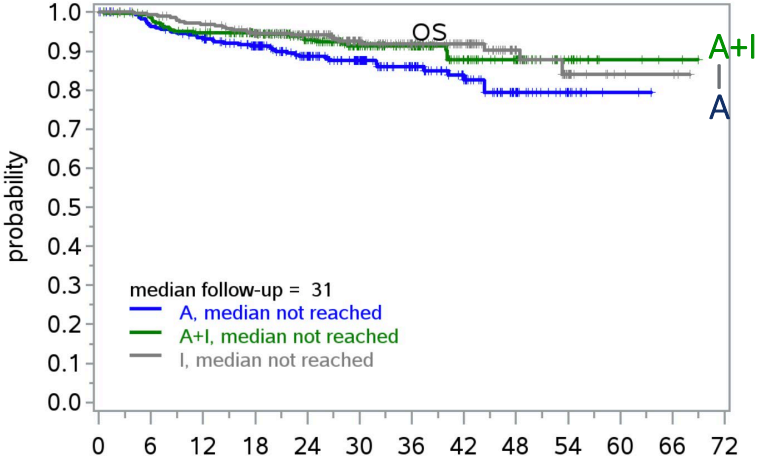


Response at End of Induction

	Overall	A	A+I/I	A+I	I
ED	2 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	0 (0%)
PD	17 (2%)	11 (4%)	6 (1%)	3 (1%)	3 (1%)
SD	7 (1%)	4 (1%)	3 (0.5%)	1 (0.4%)	2 (0.7%)
PR	458 (55%)	158 (58%)	300 (54%)	152 (54%)	148 (53%)
CR	347 (42%)	98 (36%)	249 (45%)	124 (44%)	125 (45%)
CR+PR	805 (97%)	256 (94%)	549 (98%)	276 (98%)	273 (98%)
Total	831	272	559	281	278

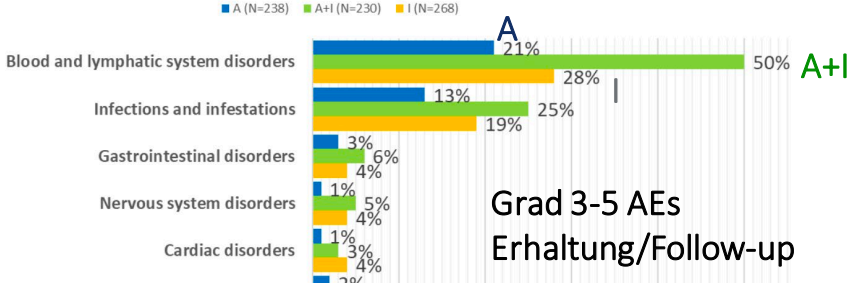
Abstr. No 1: Efficacy and Safety of Ibrutinib combined with standard 1st-line Treatment as substitute for Autologous Stem Cell Tx in Younger Pts with Mantle Cell Lymphoma





3-year FFS: **A+I**: 88%; **A**: 72% -> HR=0.52
3-year FFS: **A**: 72%; **I**: 86% -> HR=1.77
Test **A+I** vs. **I**: ausstehend

3-year OS: **A**: 86%; **A+I**: 91%; **I**: 92%
zu früh für eine statistische Auswertung

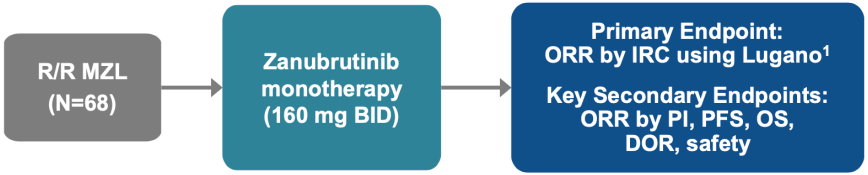


Grad 3-5 AEs
Erhaltung/Follow-up

UNIKLINIK KÖLN

Abstr. No 234: Long-Term Efficacy and Safety of Zanubrutinib in Patients with Relapsed/Refractory (R/R) Marginal Zone Lymphoma (MZL): Final Analysis of the Magnolia (BGB-3111-214) Trial

A Phase 2, Multicenter, Open-Label, Single-Arm Study



- Patients with R/R MZL who received ≥1 CD20-directed regimen
- Response based on the Lugano classification for NHL[1]
  - PET-based criteria for patients with IRC-confirmed FDG-avid disease
  - CT-based criteria for non-FDG-avid patients
  - Additional sensitivity analysis for all evaluable patients using CT-based criteria
- Biomarker correlative sub-study by the Australasian Leukaemia and Lymphoma Group

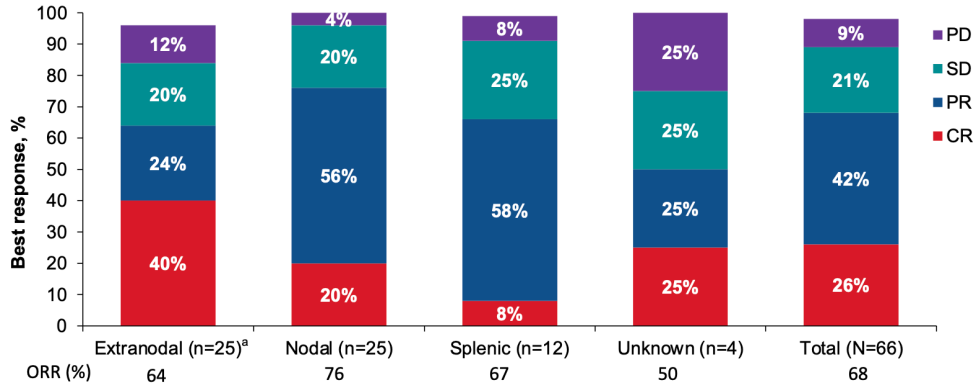
Characteristics, n (%)	Total (N=68)
Median age (range), years	70 (37-95)
≥65	41 (60)
≥75	19 (28)
Male	36 (53)
ECOG PS 0/1[a]	63 (93)
MZL subtypes	
Extranodal	26 (38)
Nodal	26 (38)
Splenic	12 (18)
Unknown	4 (6)
Disease status	
Relapsed	44 (65)
Refractory	22 (32)
Stage III/IV	59 (87)
FDG-avid (by IRC)	61 (90)
Extranodal site involvement	53 (78)
Bone marrow infiltration	29 (43)
Median prior lines of systemic therapy (range)	2 (1-6)
Immunochemotherapy	61 (90)[b]
Rituximab monotherapy	7 (10)

CT, computerized tomography; DOR, duration of response; FDG, fluorodeoxyglucose; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PI, principal investigator.
1. Cheson et al. *J Clin Oncol* 2014;32(27):3059-3067.

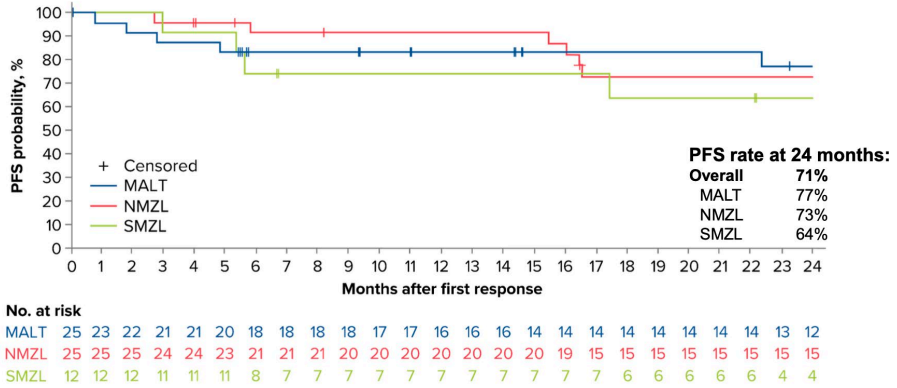
UNIKLINIK KÖLN

Abstr. No 234: Long-Term Efficacy and Safety of Zanubrutinib in Patients with Relapsed/Refractory (R/R) Marginal Zone Lymphoma (MZL): Final Analysis of the Magnolia (BGB-3111-214) Trial

Best Overall Response by IRC and MZL Subtypes



PFS by MZL Subtypes by IRC Assessment



TEAEs of interest, n (%)	N=68	
	All grade	Grade ≥3
Infections	38 (56)	15 (22)[a]
Hemorrhage	28 (41)	1 (1.5)[b]
Cardiac		
Hypertension	3 (4)[c]	2 (3)
Atrial fibrillation/flutter	2 (3)[d]	1 (1.5)
Ventricular extrasystole	1 (1.5)[e]	0
Second primary malignancy	5 (7)[f]	3 (4)

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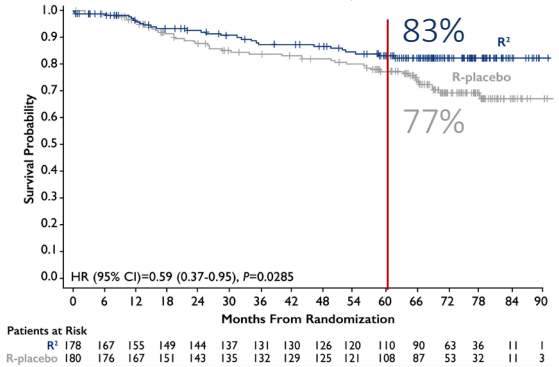
Abstr. No 609: Subcutaneous Epcoritamab with Rituximab + Lenalidomide in Patients with Relapsed or Refractory Follicular Lymphoma: Phase 1/2 Trial Update

OS: medianes follow-up 65.9 Monate



Leonard, ASH2022

A phase 1b/2, open-label trial evaluating the safety and antitumor activity of epcoritamab + R² in adults with R/R FL[a]

Key inclusion criteria

- R/R CD20⁺ FL
  - Grade 1, 2, or 3A
  - Stage II–IV
- Need for treatment based on symptoms or disease burden, as determined by GELF criteria[1]
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Data cutoff: September 16, 2022
Median follow-up: 6.4 mo

	Treatment Regimen Epcoritamab SC 48 mg + R²						
Agent	C1	C2	C3	C4	C5	C6–C12	C13+
R² Epcoritamab SC 48 mg	QW	QW	Q4W	Q4W	Q4W	Q4W	Q4W Up to 2 years
R² Rituximab IV 375 mg/m²		Q4W					
R² Lenalidomide oral 20 mg	Daily for 21 d (for 12 cycles)						

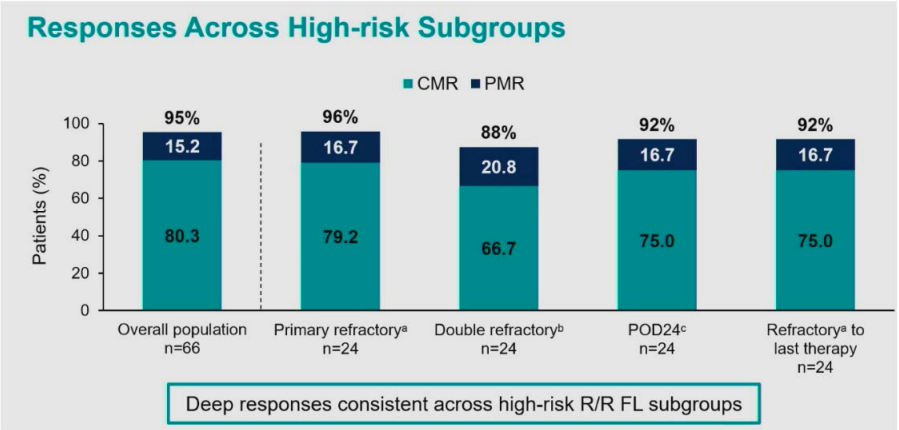
Primary objective: Safety and antitumor activity[b]

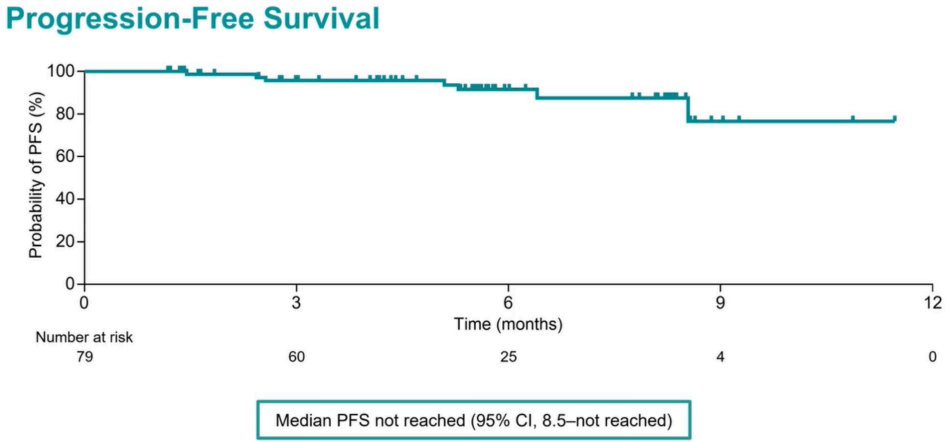
Demographics and Disease Characteristics	Total N=76
Median age, y (range)	64 (30–79)
Female, n (%)	37 (49)
Ann Arbor stage, n (%)	
II	12 (16)
III	19 (25)
IV	45 (59)
Histologic grade, n (%)[a]	
1	6 (8)
2	37 (49)
3A	24 (32)
FLIPI, n (%)[b]	
0–1	7 (9)
2	24 (32)
3–5	39 (51)
ECOG PS, n (%)	
0	48 (63)
1	25 (33)
2	3 (4)

Treatment History	Total N=76
Median time from diagnosis to first dose, mo (range)	59 (4–331)
Median time from end of last line of therapy to first dose, mo (range)	16 (0.2–198)
Median number of prior lines of therapy (range)	1 (1–9)
1 prior line, n (%)	41 (54)
2 prior lines, n (%)	21 (28)
≥3 prior lines, n (%)	14 (18)
Primary refractory[c] disease, n (%)	29 (38)
Double refractory[d] disease, n (%)	30 (39)
POD24[e], n (%)	32 (42)
Refractory[c] to last line of therapy, n (%)	29 (38)
Prior ASCT, n (%)	8 (11)
Prior CAR T, n (%)	2 (3)

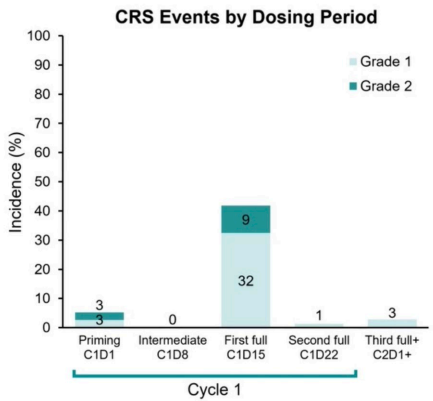
UNIKLINIK KÖLN

Abstr. No 609: Subcutaneous Epcoritamab with Rituximab + Lenalidomide in Patients with Relapsed or Refractory Follicular Lymphoma: Phase 1/2 Trial Update





Data cutoff: October 31, 2022. Median follow-up: 5.6 mo (range, 1.2+ to 11.5+).



UNIKLINIK KÖLN

ASH 2022: Take-Home Botschaften

1. ED Mantelzell-Lymphom jüngere Pat.: Ibrutinib neuer Standard in 1. Linie! Zusätzlicher Benefit von auto-Tx+I vs. I noch nicht abschließend geklärt, aber erhöhte Toxizität von auto-Tx+I vs. I in Erhaltung! Auto-Tx nur noch in ausgewählten Fällen?

2. r/r Marginalzonen-Lymphom: Zanubrutinib ist zugelassen ab der 2. Linie! Längeres Follow-up zeigt weiterhin gute Aktivität und Verträglichkeit.

3. r/r Follikuläres Lymphom: R^2 als Standard in der Rezidivtherapie bestätigt. Bispezifische Antikörper in Kombination mit R^2 zeigen verbesserte Wirksamkeit! Mosunetuzumab zugelassen ab der 3. Linie!

UNIKLINIK KÖLN

Chronische lymphatische Leukämie

Petra Langerbeins

18.01.2023 Cologne Post ASH Köln 2022

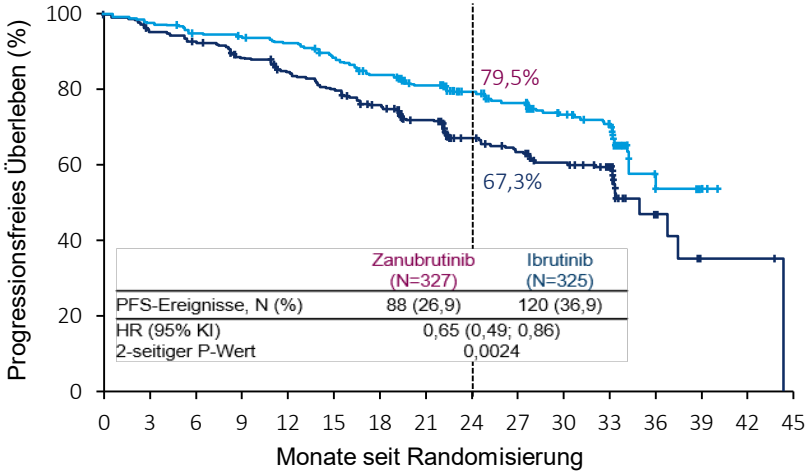
Offenlegung potentieller Interessenskonflikte

Anstellungsverhältnis, Führungsposition	
Beratungs-/ Gutachtertätigkeit	AstraZeneca, Beigene, Janssen, Abbvie
Besitz von Geschäftsanteilen, Aktien oder Fonds	
Patent, Urheberrecht, Verkaufslizenz	
Honorare	AstraZeneca, Beigen, Janssen, Roche, Abbvie
Finanzierung wissenschaftlicher Untersuchungen	Janssen
Andere finanzielle Beziehungen	
Immaterielle Interessenkonflikte	

ALPINE: Zanubrutinib compared with ibrutinib for treatment of R/R CLL

Jennifer Brown, Abstract LBA6

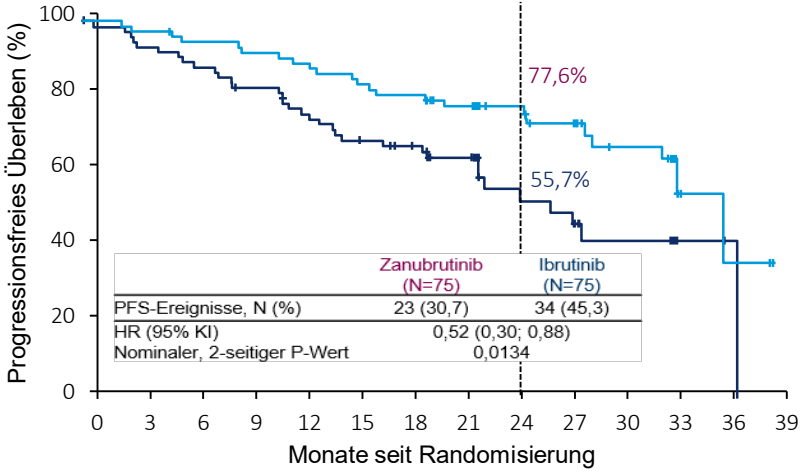
PFS (IRC)



Anzahl Patient:innen

Zanu	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0
Ibru	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

PFS bei Patient:innen mit del(17p)/*TP53*m



Anzahl Patient:innen

Zanu	75	71	68	67	64	62	58	49	35	30	21	19	3	0
Ibru	75	70	66	60	55	49	45	34	18	16	10	10	2	0

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ALPINE: Zanubrutinib compared with ibrutinib for treatment of R/R CLL

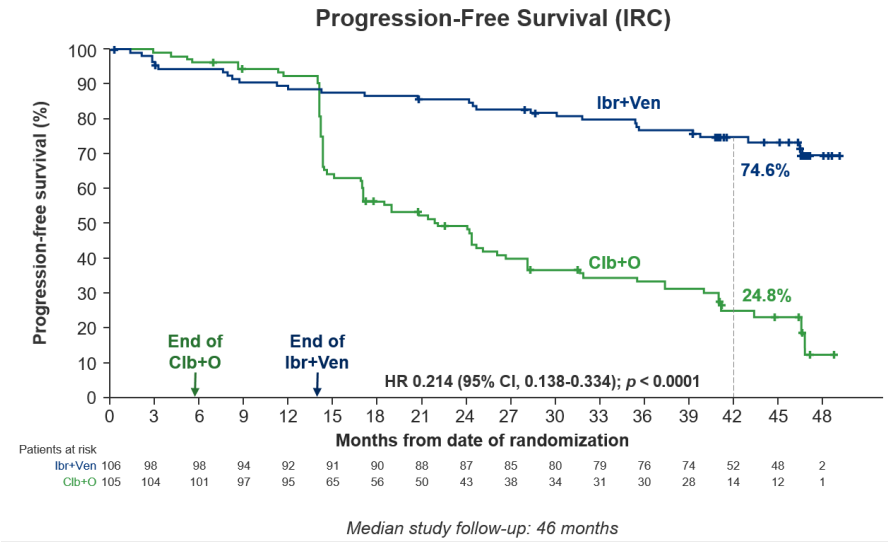
Jennifer Brown, Abstract LBA6

Sicherheitsprofil	Zanubrutinib (N=324)	Ibrutinib (N=324)
Mediane Behandlungszeit, Monate	28,4	24,3
AE jeglichen Grades, N (%) Grad 3-5 Grad 5	318 (98,1) 218 (67,3) 33 (10,2)	321 (99,1) 228 (70,4) 36 (11,1)
Schwerwiegendes AE, N (%)	136 (42,0)	162 (50,0)
AE, die zu folgenden Konsequenzen führten, N (%) Dosisreduktion Dosisunterbrechung Behandlungsabbruch	 40 (12,3) 162 (50,0) 50 (15,4)	 55 (17,0) 184 (56,8) 72 (22,2)
Kardiale AE, N (%)	69 (21,3)	96 (29,6)
Schwerwiegende kardiale AE, N (%)	6 (1,9)	25 (7,7)
Kardiale AE, die zum Behandlungsabbruch führten, N (%)	1 (0,3)	14 (4,3)

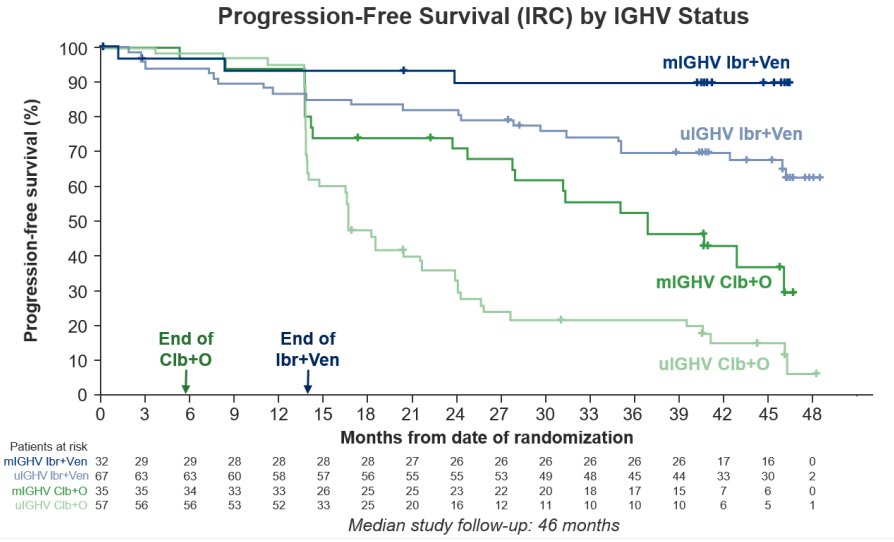
UNIKLINIK KÖLN

GLOW: Ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab

Carsten Niemann, Abstract 93



Median study follow-up: 46 months

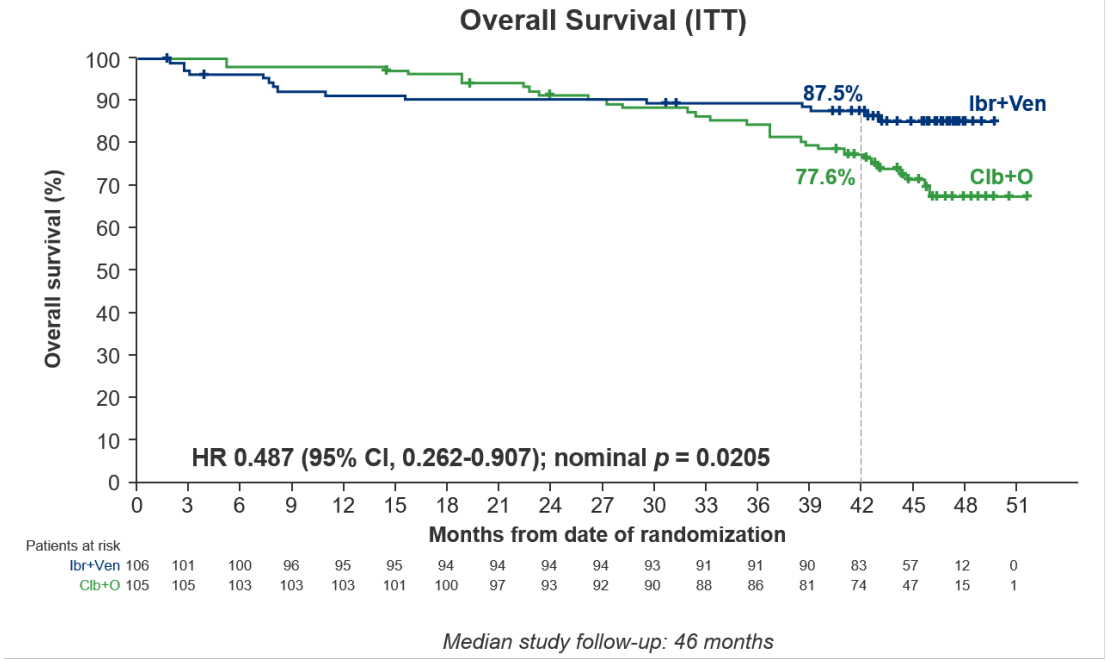


Median study follow-up: 46 months

UNIKLINIK KÖLN

GLOW: Ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab

Carsten Niemann, Abstract 93



Cause of death N(%)	Ibr + Ven N=106	Clb + O N=105
PD	1 (0.9)	2 (1.9)
Infection	4 (3.8)	11 (10.5)
Other	10 (9.4)	17 (16.2)
Unknown	4	5
Cardiac	2	4
CNS	2	3
Neoplasm	1	3
Euthanasia	1	-
Hepatobiliary	-	1
Respiratory	-	1
Total	15 (14.2)	30 (28.6)

UNIKLINIK KÖLN

BRUIN: Pirtobrutinib in BTKi pre-treated R/R CLL

Anthony Mato, Abstract

13.9 Monate FU-Update einer Phase I/II Studie mit 276 Patienten mit CLL

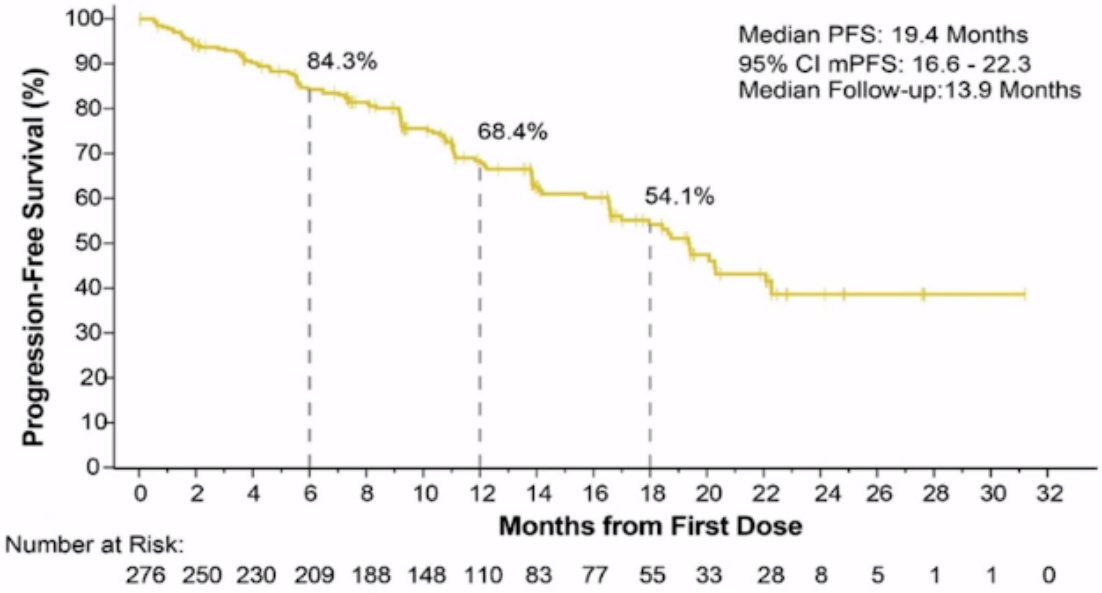
		BTKi pre-treated CLL/SLL, n	Response Evaluable Cohort, n	ORR, % (95% CI)	Median PFS, months (95% CI)	Estimated 12-month PFS rate, % (95% CI)	Estimated 18-month PFS rate, % (95% CI)
Overall		276	273	74 (68-79)	19.4 (16.6-22.3)	68 (62-74)	54 (46-61)
Age	≥75	57	56	71 (58-83)	20.1 (15.7- NE)	78 (63-87)	62 (44-75)
	<75	219	217	74 (68-80)	18.7 (16.6- NE)	66 (58-73)	52 (43-60)
At least prior BTKi and BCL2i	Yes	122	119	73 (64-81)	14.1 (11.1-18.7)	58 (47-68)	42 (29-55)
	No	154	154	74 (66-81)	22.1 (18.4-NE)	75 (67-82)	62 (52-70)
Del(17p) and/or *TP53* mutation	Yes	99	98	80 (70-87)	16.6 (13.8-22.1)	69 (58-78)	47 (33-59)
	No	107	107	67 (58-76)	19.4 (14.1-NE)	66 (55-75)	58 (46-68)
BTK C481 status*	Mutated	85	85	81 (71-89)	17.0 (13.8-20.3)	69 (57-79)	49 (35-61)
	Unmutated	91	91	65 (54-75)	20.3 (13.8-NE)	63 (52-73)	54 (40-65)
Reason for Prior BTKi discontinuation	Disease progression	206	205	73 (66-79)	18.6 (13.9-20.3)	66 (58-73)	50 (41-59)
	Intolerance & Other	68	66	76 (64-85)	NE (18.4-NE)	77 (64-86)	67 (51-79)

*Pts with available mutation data who progressed on any prior covalent BTKi, excluding those who were covalent BTKi intolerant.
Del(17p)- deletion 17p; PFS- median progression-free survival; DOR- median duration of response; CI- confidence interval; ORR- overall response rate; N- number of patients; n- number of response evaluable patients in sample; NE- not evaluable

UNIKLINIK KÖLN

BRUIN: Pirtobrutinib in BTKi pre-treated R/R CLL

Anthony Mato, Abstract



UNIKLINIK KÖLN

ASH 2022: Take-Home Messages

ALPINE Zanubrutinib zeigt einen PFS-Vorteil im direkten Vergleich mit Ibrutinib bei PatientInnen mit rezidivierter CLL - auch mit TP53-Mutation.

Die Rate an kardialen Nebenwirkungen & frühzeitigen Therapieabbrüchen ist geringer unter Zanubrutinib.

GLOW Das geschätzte 3,5-Jahres PFS ist 75% von alten ± komorbiden CLL PatientInnen, die mit Ibrutinib plus Venetoclax first-line behandelt wurden.

Im Vergleich zur Chemoimmuntherapie zeigt sich ein Überlebensvorteil.

BRUIN Pirtobrutinib ist bei BTKi-vorbehandelten CLL-PatientInnen effektiv.

Das mediane PFS beträgt ca. 20 Monate.

UNIKLINIK KÖLN

ASH 2022: Multiples Myelom

Christof Scheid

18.01.2023 Cologne Post ASH Köln 2022

Offenlegung potentieller Interessenskonflikte

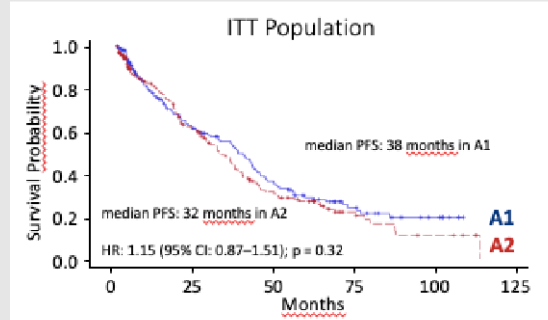
Anstellungsverhältnis, Führungsposition	
Beratungs-/ Gutachtertätigkeit	Amgen, BMS, GSK, Janssen, Roche
Besitz von Geschäftsanteilen, Aktien oder Fonds	
Patent, Urheberrecht, Verkaufslizenz	
Honorare	Amgen, BMS, GSK, Janssen, MSD, Novartis, Roche, Takeda
Finanzierung wissenschaftlicher Untersuchungen	Janssen, Novartis, Takeda
Andere finanzielle Beziehungen	
Immaterielle Interessenkonflikte	

Long-Term Outcome of a Prospective Randomized Trial Comparing Continuous Lenalidomide/Dexamethasone with Lenalidomide/Dexamethasone Induction, MEL140 with Autologous Blood Stem Cell Transplantation and Single Agent Lenalidomide Maintenance in Patients of Age 60-75 with Newly Diagnosed Multiple Myeloma (#116)

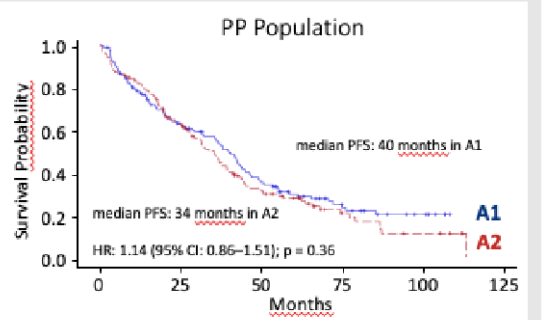
- Introduction
- High-dose melphalan with autologous stem cell transplantation (ASCT) is standard of care in patients with NDMM up to age 65 years
- Median age at diagnosis is > 70 years
- Do patients > 65 years also benefit from ASCT?
- Methods
- DSMM XIII-Study in NDMM
- Age 60 – 75 years (median 68 years, 29% > 70 years)
- A1: Lenalidomid 25 mg/Dexamethason 40mg weekly until progression
- A2: Len/Dex 3 cycles, apheresis, 1-2 x MEL 140 mg/m2 + ASCT, Len maintenance 10mg until progression

Long-Term Outcome of a Prospective Randomized Trial Comparing Continuous Lenalidomide/Dexamethasone with Lenalidomide/Dexamethasone Induction, MEL140 with Autologous Blood Stem Cell Transplantation and Single Agent Lenalidomide Maintenance in Patients of Age 60-75 with Newly Diagnosed Multiple Myeloma (#116)

DSMM XIII: Progression-free survival (PFS) in the ITT and PP population



A1	174	88	60	29	14	7	0
A2	174	87	47	28	9	5	0



A1	142	87	60	29	14	7	0
A2	131	83	45	26	9	5	0

- For the primary study endpoint PFS, there was no significant difference between arms A1 and A2 in the ITT and the PP population.
- The prespecified per-protocol (PP) analysis included patients with at least 6 months of study treatment (also including patients with progression or death during this period).

ITT: intention to treat; PFS: progression-free survival; PP: per protocol.

8

UNIKLINIK KÖLN

Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of the Phase 3 MAIA Study (#4559).

- Introduction
- Rd was a standard treatment for transplant-ineligible patients with NDMM with a median PFS of 26 months and a median OS of 59 months (FIRST study, Facon et al. Blood 2018)
- DRd is an established treatment for relapsed MM (POLLUX study, Facon et al. NEJM 2018)

- Methods

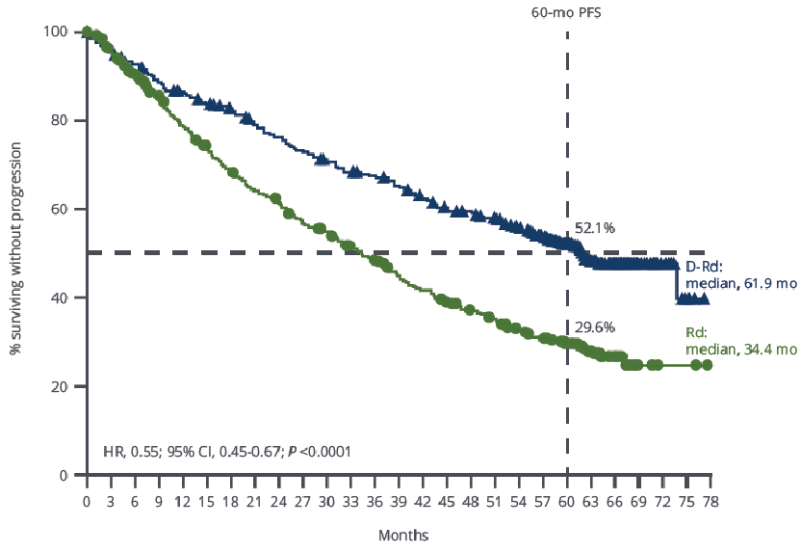
737 patients with a median age of 74 years were randomised to DRd or Rd until progression

Data with a median follow up of 64.5 months were reported

Still on study treatment: 36% with DRd, 14.9% with Rd

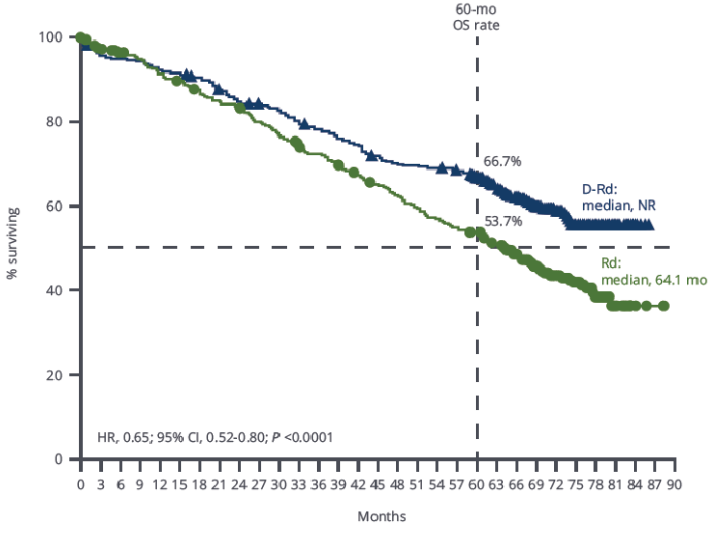
Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of the Phase 3 MAIA Study (#4559)

FIGURE 1: PFS with D-Rd and Rd in the ITT population[a]



PFS, progression-free survival; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval.
[a]Data are based on a median follow-up of 64.5 months.

FIGURE 2: OS with D-Rd and Rd in the ITT population[a]

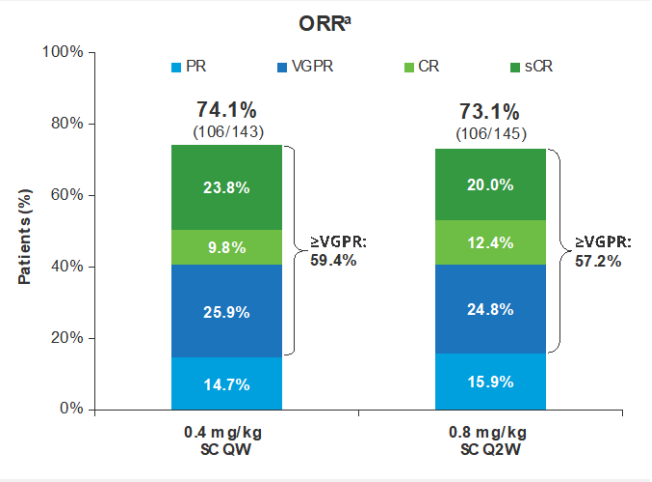


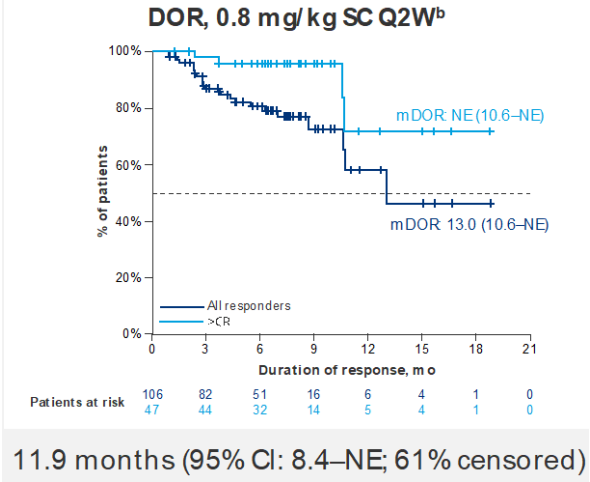
OS, overall survival; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; ITT, intent-to-treat; NR, not reached; HR, hazard ratio; CI, confidence interval.
[a]Data shown in the figure are based on a median follow-up of 73.6 months. At a median follow-up of 64.5 months, median OS was NR with D-Rd versus 65.5 months with Rd (HR, 0.66; 95% CI, 0.53-0.83; $P = 0.0003$), and the estimated 60-month OS rate was 66.6% with D-Rd and 53.6% with Rd.

UNIKLINIK KÖLN

Clinical activity of BMS-986393 (CC-95266), a G protein–coupled receptor class C group 5 member D (GPRC5D)–targeted chimeric antigen receptor (CAR) T cell therapy, in patients with relapsed and/or refractory (R/R) multiple myeloma (MM): first results from a phase 1, multicenter, open-label study (#364)

- Introduction and methods
- GPRC5D is a well established new target for myeloma therapy
- Talquetamab is a GPRC5D x CD3 bispecific antibody and will be available in 2023
- BMS-986393 is a new GPRC5D-specific CART construct





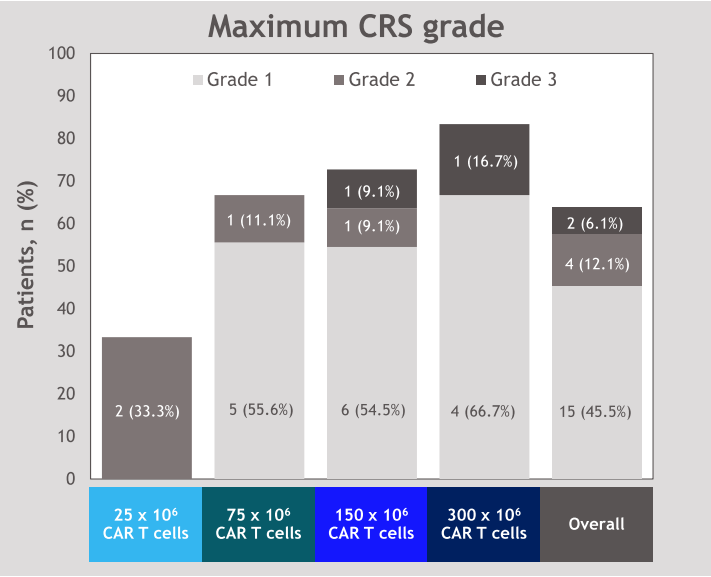
11.9 months (95% CI: 8.4–NE; 61% censored)

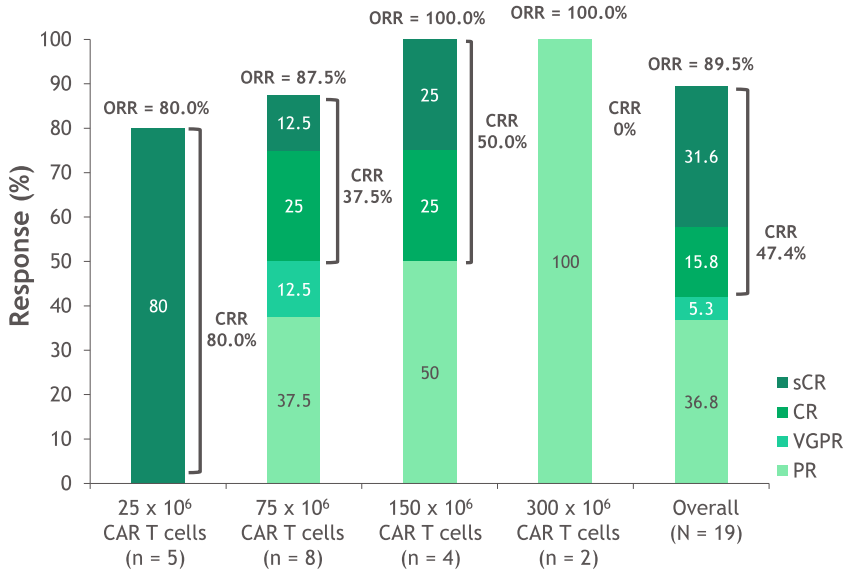
MONUMENTAL-1
Chari et al.
ASH 2022
#157

UNIKLINIK KÖLN

Clinical activity of BMS-986393 (CC-95266), a G protein–coupled receptor class C group 5 member D (GPRC5D)–targeted chimeric antigen receptor (CAR) T cell therapy, in patients with relapsed and/or refractory (R/R) multiple myeloma (MM): first results from a phase 1, multicenter, open-label study (#364)

- 33 patients, 16 high risk genetics, 15 with extramedullary disease
- 18 with prior BCMA-directed therapy, 15 with prior CART therapy





UNIKLINIK KÖLN

ASH 2022: Take-Home Botschaften

1. Kein gesicherter Benefit einer Hochdosistherapie über 65 Jahre
2. Medianes PFS > 5 Jahre mit DRd bei älteren Patienten (median 73,5 Jahre)
3. BCMA-gerichtete Therapie 2023 als Teil der Routine (ide-cel, cilta-cel, teclistamab, elranatamb, belantamab mafodotin)
4. GPRC5D als neues Target, insbesondere nach BCMA-gerichteter Therapie (talquetamab, neue CART)
5. ASCO/EHA 2023: KarMMa-3 + CARTITUDE-4 (randomisierte Phase III Studien)
6. Immuntherapie auf dem Weg in die Erstlinientherapie: ide-cel (KarMMa-9), cilta-cel (CARTITUDE-6), teclistamab (GMMG HD10/DSMM XX)

UNIKLINIK RWTH AACHEN

Centrum für Integrierte Onkologie – CIO Aachen

GERMAN STUDY GROUP MPN

Highlights vom ASH 2022 zu Myeloproliferativen Neoplasien

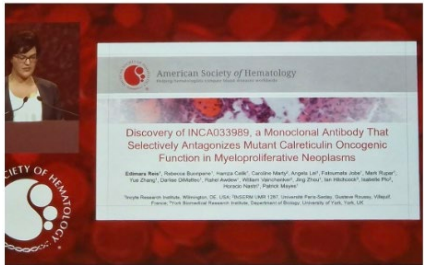
Dr. med. Susanne Isfort,
Uniklinik RWTH Aachen

18.01.2023

Interessenkonflikte

Anstellungsverhältnis, Führungsposition	Uniklinik RWTH Aachen
Beratungs-/ Gutachtertätigkeit	Pfizer, Novartis, Incyte
Besitz von Geschäftsanteilen, Aktien oder Fonds	-
Patent, Urheberrecht, Verkaufslizenz	-
Honorare	Pfizer, Novartis, Incyte, Abbvie, BMS-Celgene
Finanzierung wissenschaftlicher Untersuchungen	-
Andere finanzielle Beziehungen	Zuschüsse für Reisetätigkeiten: Pfizer, AOP Orphan, Hexal, Alexion, Novartis
Immaterielle Interessenkonflikte	

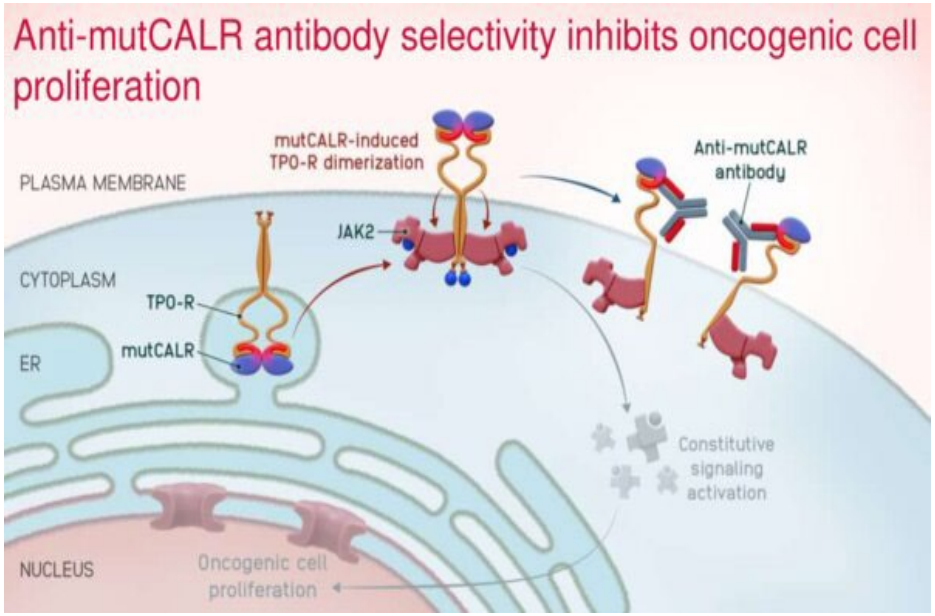
ET/PMF: Reis E. et al.; Discovery of INCA033989



UNIKLINIK RWTH AACHEN

HINTERGRUND:

- Calreticulin (CALR)-Mutationen verantwortlich für die Krankheitsentwicklung in 20-30% der Patienten mit MPN
- Der Komplex aus mutiertem CALR und TPO-Rezeptor führt zu einer konstitutiven Stimulierung des JAK2/STAT Signalweges
- Bisher keine/kaum kurative Therapieoptionen für ET/PMF



METHODEN:
Entwicklung eines monoklonalen Antikörpers gegen mutiertes CALR
INC

→ Gewinnung mittels Phagen-/Hefen-Displays
→ Selektion mittels zusätzlicher Sequenzierung
→ Testung +/- RUX in Ba/F3-TPO-R/mutCALR Zellinien
→ Evalierung des Effekts auf CD34+-Zellen von MPN-Patienten
→ Kompetitives Transplantations-MPN-Mausmodell (10 Wochen Behandlung)

Quelle: Reis E. et al; *Blood* (2022) 140 (Supplement 1): 14–15.

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ET/PMF: Reis E. et al.; Discovery of INCA033989

ERGEBNISSE:

Zellinien:

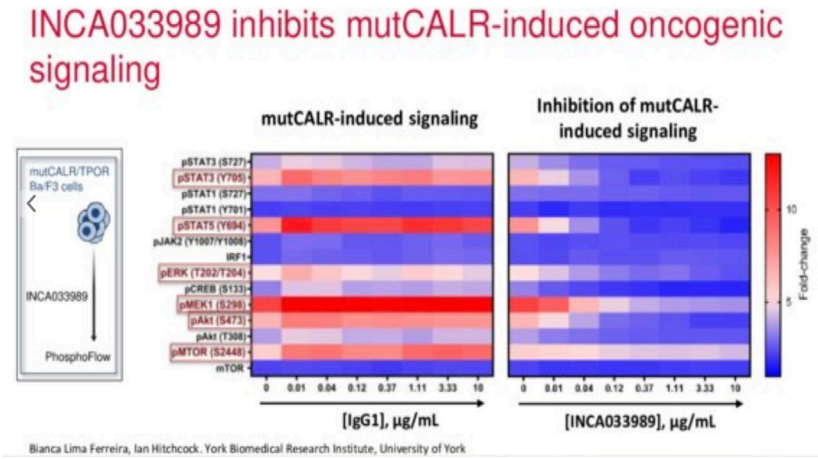
- Unterbricht die mutCALR-abhängige TPO-R Dimerisierung, onkogene Signaltransduktion und Zellproliferation
- Induziert Zelltod
- Synergistische Effekte mit RUX gezeigt

MPN-Zellen:

- Inhibiert dosisabhängig mutCALR-vermittelte JAK2/STAT-Aktivierung
- Kein Effekt auf JAK2V617F-mutierte Zellen oder Zellen von Gesunden

Maus-Modell:

- Verhinderte Thrombozytose
- Hemmte die Megakaryozytose im KM
- Reduzierte die CALR-mutierte hämatopoetischen Stammzellen
- Keine Krankheitsentwicklung bei seriell transplantierten Mäusen



FAZIT:

- Entwicklung eines hochwirksamen und selektiven monoklonalen Antikörpers gegen mutiertes Calreticulin

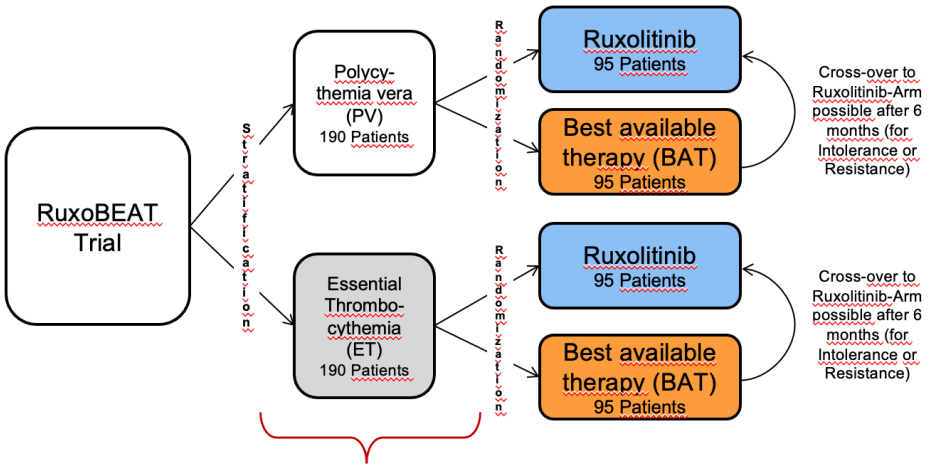
→ Phase 1-Studie geplant für 2023

Quelle: Reis E. et al; *Blood* (2022) 140 (Supplement 1): 14–15.

ET: Koschmieder S., Isfort S. et al.: Ruxolitinib vs. BAT – RuxoBEAT

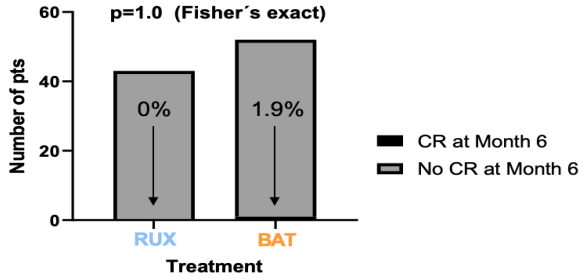
UNIKLINIK RWTH AACHEN

- **Pre-specified interim analysis of 95 ET pts randomized 1:1 to RUX vs. BAT**
  - ET pts were allowed to have had previous ET-directed therapy or no therapy

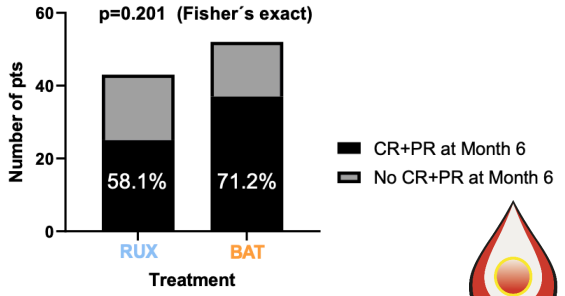


Data cutoff date: 1-NOV-2022

1°EP: Complete Remission at Month 6



2°EP: Overall Remission (CR + PR) at Month 6



Primary endpoint
Clinico-hematologic complete response (CR) rate at month 6, as defined by Barosi et al (Blood 2009)

Secondary and exploratory endpoints
Overall response rate (CR+PR), changes in blood counts, spleen size, PROM, using p values descriptively

Quelle: Koschmieder S. et al; Blood (2022) 140 (Supplement 1): 1790–1793.

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ET: Koschmieder S., Isfort S. et al.: Ruxolitinib vs. BAT – RuxoBEAT

	RUX			BAT		
Time point	**BL**	**M6**	**p**	**BL**	**M6**	**p**
Platelets, median /nl [IQR]	646 [503, 923]	552 [464, 731]	**0.002**	586.5 [423.5, 851.5]	445.5 [364.5, 590]	**<0.001**
WBC, median /nl [IQR]	7.9 [5.7, 11]	6.8 [5.6, 8.9]	**0.007**	7.5 [5.8, 10.6]	6.6 [4.7, 8.1]	**0.006**
Hgb, median g/dl [IQR]	14 [12.8, 15]	12.3 [11.4, 13.2]	**<0.001**	13.5 [12.8, 14.7]	13.5 [12.7, 14.4]	0.435
Spleen size, median cm [IQR]	12 [10.2, 13.4]	10.7 [9.0, 11.9]	**0.008**	12 [11.2, 13.7]	12.1 [10.5, 14.4]	0.759
PROM headache, median points [IQR]	1.0 [0.0, 3.0]	0.5 [0, 2]	0.054	1.0 [0.0, 3.0]	2.0 [0, 4]	0.946
PROM pruritus, median points [IQR]	0 [0, 5]	0 [0, 1]	**0.002**	0 [0, 3]	1 [0, 3]	0.547
PROM concentration pbs, median points [IQR]	2 [0, 5]	1.5 [0, 4]	**0.012**	3 [0, 6]	3 [1, 7]	0.401
PROM dizziness, median points [IQR]	1 [0, 5]	1 [0, 3]	0.114	2 [0, 4]	2 [0, 6]	0.283

RUX: Ruxolitinib; BAT: best available therapy; BL: baseline; M6: month 6; p: p value; IQR: Interquartile range; WBC: white blood count; Hgb: hemoglobin; PROM: patient-reported outcome measures; pbs: problems. p: p value for BL vs. M6.

Fazit:

- Ruxolitinib war BAT nicht überlegen hinsichtlich Induktion einer CR
- **Ruxolitinib zeigte bessere Symptomkontrolle und Milzgrößenreduktion**

Quelle: Koschmieder S. et al; Blood (2022) 140 (Supplement 1): 1790–1793.

CIO Centrum für Integrierte Onkologie Aachen Bonn Köln Düsseldorf

GERMAN STUDY GROUP MPN

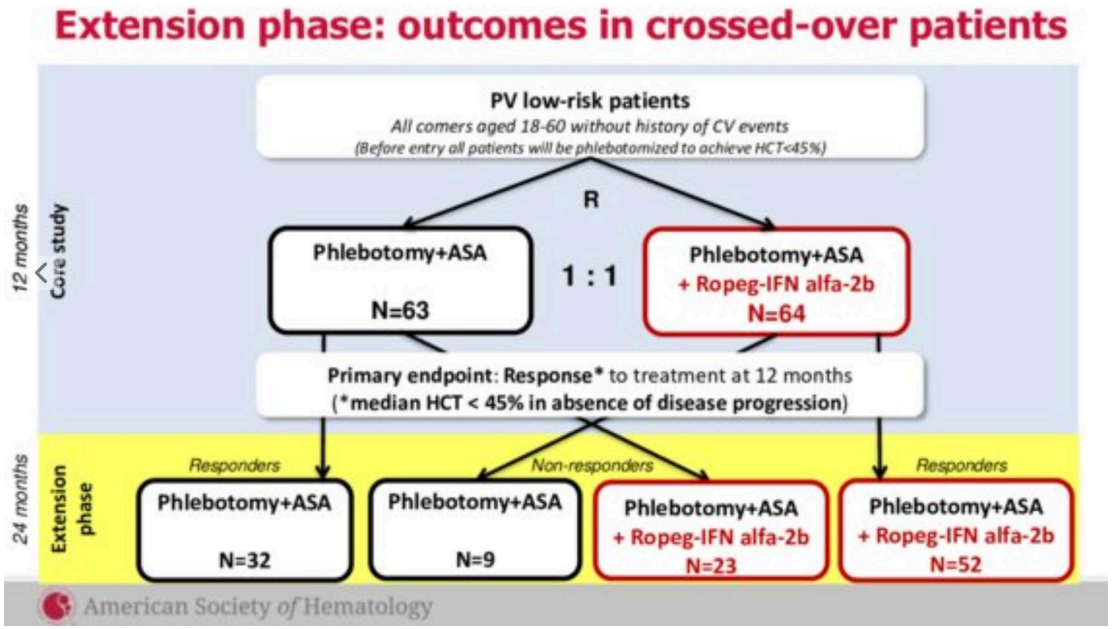
PV: Barbui T. et al; Low-PV Phase II trial

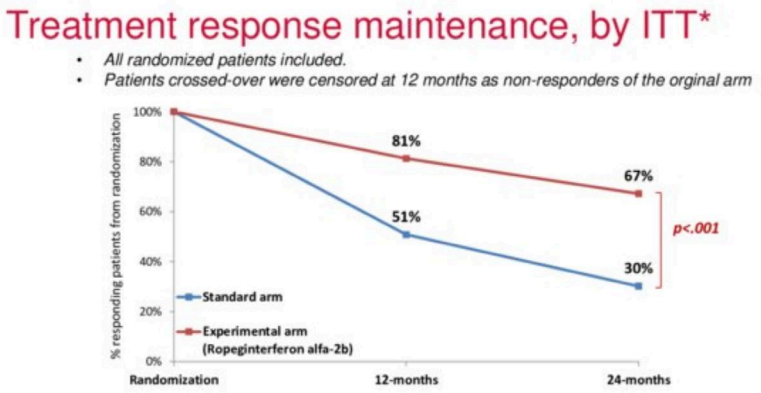
HINTERGRUND:

- Standardtherapie bei Niedrigrisiko-PV:

→ ASS und Aderlässe

- Unklar, ob zytoreduktive Substanzen das weiterhin erhöhte thrombembolische Risiko bei diesen Patienten senken können





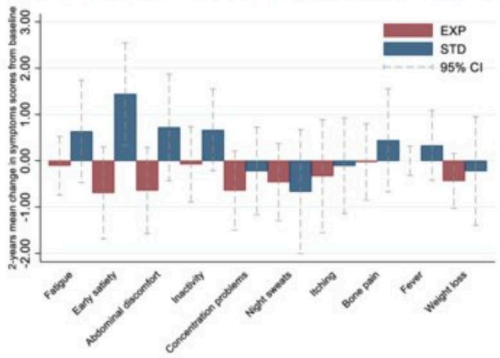
ERGEBNISSE NACH 1 JAHR:

- (n=100) Composite-Endpunkt erreicht (Kontrolle von Hkt & Fortschreiten)
- 6x Thrombozytose , 2x Thromembolie
- Neurekrutierung wurde 2020 gestoppt
- Studie lief weiter mit bislang eingeschlossenen Patienten

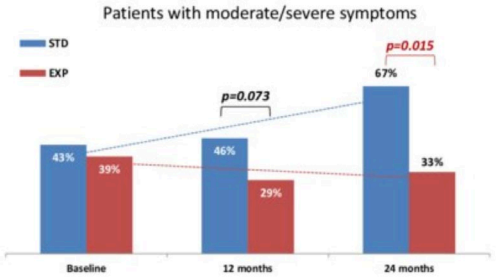
Quelle: Barbui T. et al; Blood (2022) 140 (Supplement 1): 1797–1799.

PV: Barbui T. et al; Low-PV Phase II trial

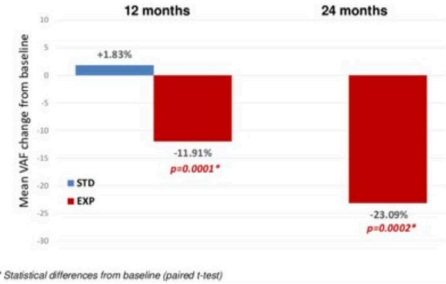
Responders: symptoms changes from baseline



Responders: overall quality of life*



Responders: *JAK2*V617F VAF



FAZIT:

- IFN besser in Kontrolle von Hkt und Fortschreiten
- IFN sicher, aber mit mehr NW verbunden
- Bisher kein direkter Nachweis, dass IFN protektiv hinsichtlich Thrombosen ist
- IFN zeigt Effektivität bei Surrogatparametern, die in anderen Studien mit höherem Thromboserisiko verbunden waren
- Etwa bei 1/3 der Patienten kein Ansprechen (ggf. höhere Dosis notwendig)?

Safety

	Ropeg	Phlebotomy	p
	*N=87**	*N=72**	
Patients with AE	73 (84%)	36 (50%)	<.001
Patients with treatment-related AE	48 (55%)	4 (6%)	<.001
Patients with grade 3 or 4§ AE	8 (9%)	6 (8%)	0.948
AE that caused therapy discontinuation	7 (8%)	0 (0%)	0.016

** AE are counted under the treatment actually received (i.e., n=87 patients received Ropeg, (n=64 since randomization and n=23 after crossover, respectively). N=72 patients received phlebotomy-only, (n=63 since randomization and n=9 after crossover, respectively).*

§ Only one grade 4 AE (hypertriglyceridemia), occurred under Ropeg

Quelle: Barbui T. et al; Blood (2022) 140 (Supplement 1): 1797–1799.

Centrum für Integrierte Onkologie
Aachen Bonn Köln Düsseldorf

GERMAN STUDY GROUP MPN

ASH 22: Take-Home Messages

- Mit der Entwicklung eines Antikörpers gegen mutiertes Calreticulin steht uns in Kürze eine neue vielversprechende Therapieoption bei PMF/ET im Rahmen einer Studie zur Verfügung.

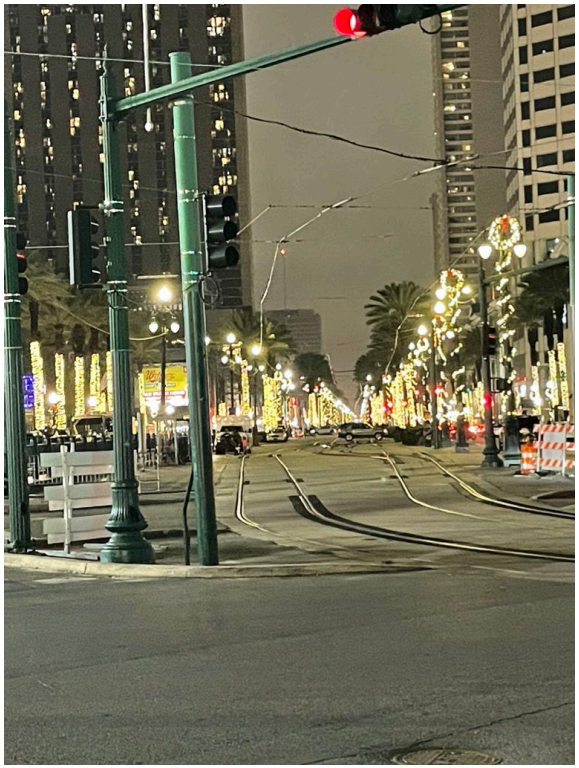
- Ruxolitinib zeigt gegenüber BAT in der Interimanalyse der RuxoBEAT-Studie zwar keine Unterschiede bezüglich der CR-Rate, aber eine verbesserte Symptomkontrolle und Milzgrößenreduktion

- Ropeginterferon zeigt bei Niedrig-Risiko-PV Vorteile gegenüber der Therapie mit Aderlass+ASS und scheint die Progression der Erkrankung zu limitieren.

Danke für Ihre Aufmerksamkeit!

Fragen?

GERMAN
STUDY
GROUP
M P N



UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

40 Jahre MDS Register Düsseldorf

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

ABCD

D·MDS
Deutsche MDS-Studiengruppe

Myelodysplastische Syndrome
Köln, 18.1.23

MDS Center of Excellence
of the International MDS Foundation

UTZ Universitätstumorzentrum Düsseldorf
Comprehensive Cancer Center
Als Onkologisches Spitzenzentrum gefördert durch die Deutsche Krebshilfe e.V.

Offenlegung potentieller Interessenskonflikte

Ulrich Germing, UK Düsseldorf

Anstellungsverhältnis, Führungsposition	Keine
Beratungstätigkeit	1 x Celgene
Besitz von Geschäftsanteilen, Aktien oder Fonds	Keine
Patent, Urheberrecht, Verkaufslizenz	Keine
Vortragshonorare	BMS, Novartis, Jansen
Institutionelle Forschungsförderung	Celgene, Novartis, Abbvie
Andere finanzielle Beziehungen	Keine
Immaterielle Interessenkonflikte	Keine

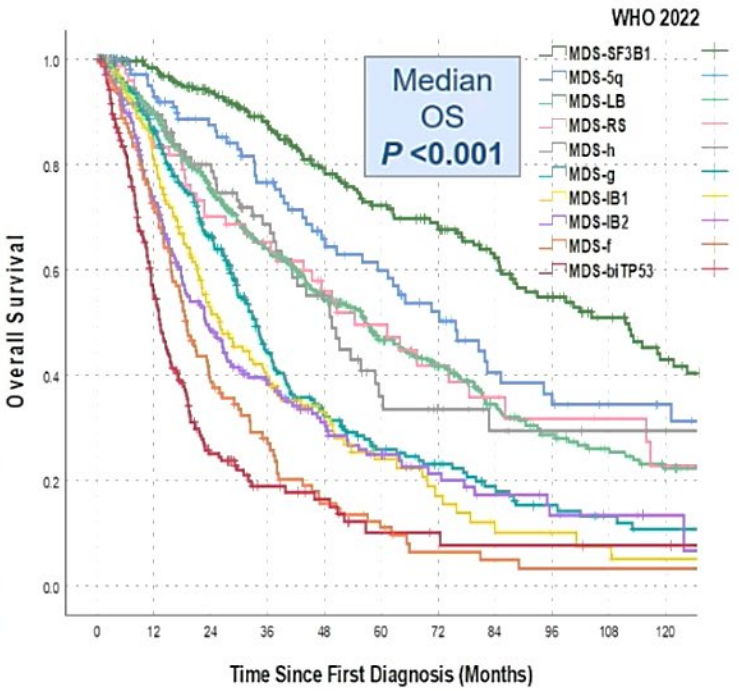
WHO2022	Dysplastic lineages and special morphologic features	BM and PB Blasts	Cytogenetics	Mutations
MDS with low blast count and SF3B1 mutation	≥1, ≥5% RS, or ≥15% RS without SF3B1 mutation	<5% BM <2% PB	Any, except isolated del(5q), -7/del(7q) or complex	SF3B1, no multi-hit TP53
MDS with del(5q) - with TP53 mut - with SF3B1 mut	≥1	<5% BM <2% PB	Del(5q) with up to 1 additional aberration, except -7/del(7q)	Any, except multi-hit TP53
MDS with biallelic TP53 alteration		<20% BM <20% PB	any	multi-hit TP53 alteration
MDS, NOS with single lineage dysplasia	1	<5% BM <2% PB	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit TP53; not meeting criteria for MDS-SF3B1
MDS, NOS with multilineage dysplasia	≥2	<5% BM <2% PB	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit TP53; not meeting criteria for MDS-SF3B1
MDS, hypoplastic	≥1, <25% cellularity, age-adjusted	<5% BM <2% PB	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit TP53; not meeting criteria for MDS-SF3B1
MDS IB1	≥1	5-9% BM 2-4% PB	any	Any, except multi-hit TP53
MDS IB2	≥1, Auer rods possible	10-19% BM 5-19% PB	any	Any, except multi-hit TP53
MDS with fibrosis	≥1, grade 2/3 fibrosis	5-19% BM <19% PB	any	Any, except multi-hit TP53

Cytopenia of at least one cell line in blood is a prerequisite for all MDS types

WHO Subgroups with Survival

Subgroups	No. (%)	mLFS	mOS
Overall	2231 (100%)	30.9 mo	40.9 mo
MDS-*SF3B1*	276 (12%)	**109.4** mo	**111.6** mo
MDS-5q	110 (5%)	62.9 mo	75.6 mo
MDS-LB	595 (27%)	47.8 mo	56.8 mo
MDS-RS	82 (4%)	50.5 mo	54.3 mo
MDS-h	98 (4%)	42.3 mo	49.6 mo
MDS -g *	325 (15%)	22.1 mo	33.3 mo
MDS-IB1	193 (9%)	21.0 mo	25.9 mo
MDS-IB2	224 (10%)	**10.0** mo	22.9 mo
MDS-f	118 (5%)	13.7 mo	18.9 mo
MDS-bi*TP53*	210 (9%)	**10.0** mo	**13.2** mo

* Low or increased blasts with *RUNX1*, *IDH*1/2, Cohesin complex mutations, *SF3B1* with blast ≥5%; [LFS- Leukemia free survival, OS- Overall survival]



Somedeb Ball et al., Abstract #463, ASH 2022.

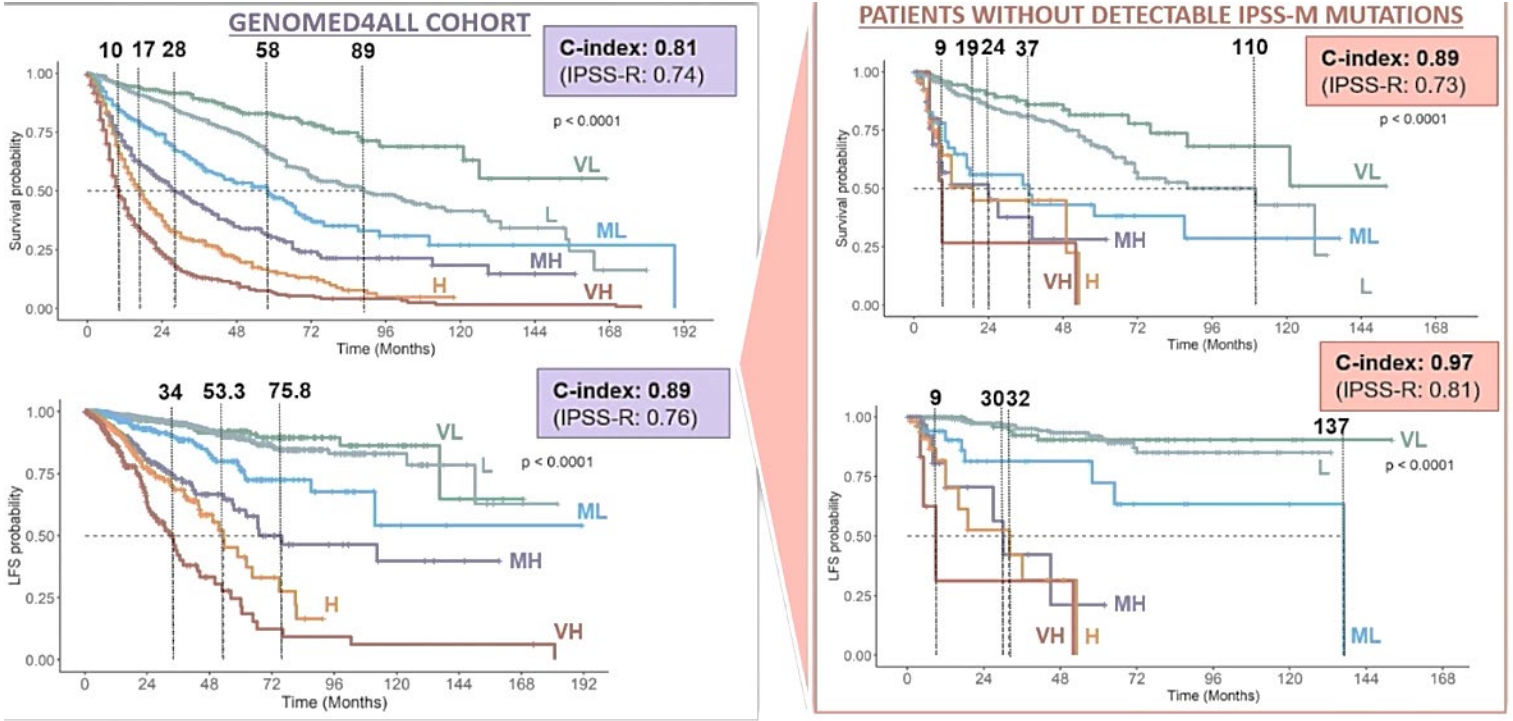
MV analysis: independent predictors of survival

Variables	LFS		OS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Number of Dysplastic Lineages	**1.73** (1.35-2.21)	**<0.001**	**1.68** (1.31-2.16)	**<0.001**
Blast Count Category*	1.46 (0.53-3.99)	0.453	1.39 (0.51-3.80)	0.514
BM Fibrosis Grade	1.11 (0.98-1.26)	0.086	**1.14** (1.00-1.30)	**0.038**
***SF3B1* Mutation**	**0.57** (0.44-0.74)	**<0.001**	**0.59** (0.46-0.77)	**<0.001**
Multi-hit *TP53***	**3.09** (2.06-4.61)	**<0.001**	**3.39** (2.25-5.12)	**<0.001**

* Blast <5% vs. 5-9% vs. ≥ 10%
** *TP53*-VAF ≥ 50% or, ≥ 2 *TP53* mutations (VAF > 10% each) or, 1 *TP53* mutation plus loss of 17p (by Karyotyping or FISH)

Somedeb Ball et al., Abstract #463, ASH 2022.

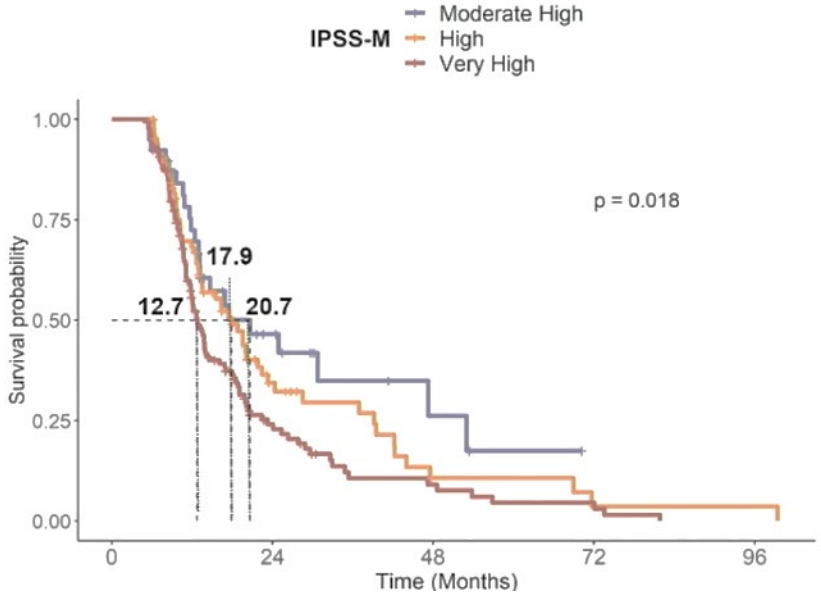
Results real-world validation of IPSS-molecular



Elisabetta Sauta et al., Abstract #464, ASH 2022.

Results clinical efficacy

268 patients of the GenoMed4All cohort not eligible for transplant were treated with **HMA**



- The probability of overall response was 42%, without significant differences among IPSS-M categories (P= 0.19)
- Median OS in the whole population treated by HMA was 13.9 months
- Response duration and probability of survival were inversely related to the IPSS-M risk model

Elisabetta Sauta et al., Abstract #464, ASH 2022.

IMerge (MDS3001; NCT02598661) Phase 2/3 Study Design

Part 1[1,2]
Phase 2, single-arm, open-label
Overall N=57

Target population of non-del(5q)/len/HMA-naive
N=38
Enrollment Complete

Imetelstat
7.5 mg/kg IV q4w

Part 2
Phase 3, randomized, double-blind, placebo-controlled
N=170
Enrollment complete; Top line results early Jan 2023

RANDOMIZE 2:1

Imetelstat (n~115)

Placebo (n~55)

Stratification: transfusion burden (≤6 vs >6 units); IPSS risk group (low vs intermediate-1)

- **Patients with LR-MDS**[1,2]
  - IPSS low or intermediate-1
  - Relapsed/refractory to ESA or sEPO >500 mU/mL
  - Transfusion dependent: ≥4 units RBC/8 weeks over the 16-week prestudy period
  - Non-del5(q), len/HMA-naive
- **Primary endpoint**: ≥8-week RBC TI
- **Key secondary endpoints**: safety, ≥24-week TI rate, HI-E, OS, PFS, and time to progression to AML

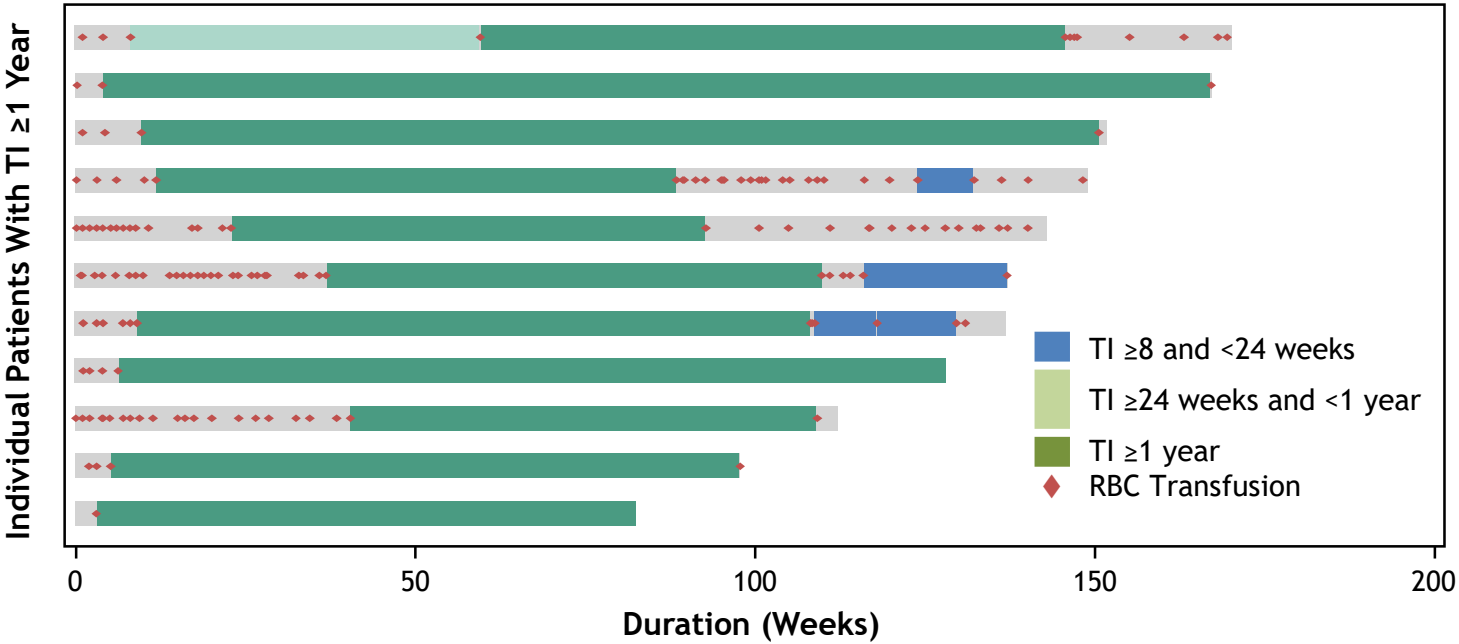
Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent
Pre-medication: diphenhydramine, hydrocortisone 100-200mg (or equivalent)
Supportive care: transfusions, myeloid growth factors per local guidelines

AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IV, intravenous; len, lenalidomide; LR, lower-risk; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; q4w, every 4 weeks; RBC, red blood cell; sEPO, serum erythropoietin; TI, transfusion independence.

1. Steensma DP, et al. J Clin Oncol. 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 3113.

Uwe Platzbecker et al., Abstract #459, ASH 2022.

LR-MDS Patients Treated With Imetelstat Achieved Sustained, Continuous TI ≥1 Year



- Median onset of 8-week TI was 9.29 weeks (range, 3.3 - 40.7)

Data cutoff: October 13, 2022.
LR, lower-risk; MDS, myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.
Uwe Platzbecker et al., Abstract #459, ASH 2022.

ASH 2022: Take-Home Botschaften

1. NEUE WHO KLASSIFIKATION DER MDS HAT 3 NEUE SUBGRUPPEN, ZYTOLOGIE, HISTOLOGIE, ZYTOGENETIK UND SF3B1, TP53 ERFORDERLICH

2. IPSS-MOL IM ALLTAG ANWENDBAR, SOFERN NGS MIT mind. TP53 incl. VAF VORLIEGT

3. IMETELSTAT ANTIANÄMISCH WIRKSAM BEI NIEDRIG RISIKO MDS, PHASE 3 LÄUFT

UNIKLINIK RWTH AACHEN

Centrum für Integrierte Onkologie – CIO Aachen

Neues vom ASH 2022: Akute myeloische Leukämie (AML)

Edgar Jost

Klinik für Hämatologie, Onkologie, Hämostaseologie und Stammzelltransplantation der Uniklinik der RWTH Aachen

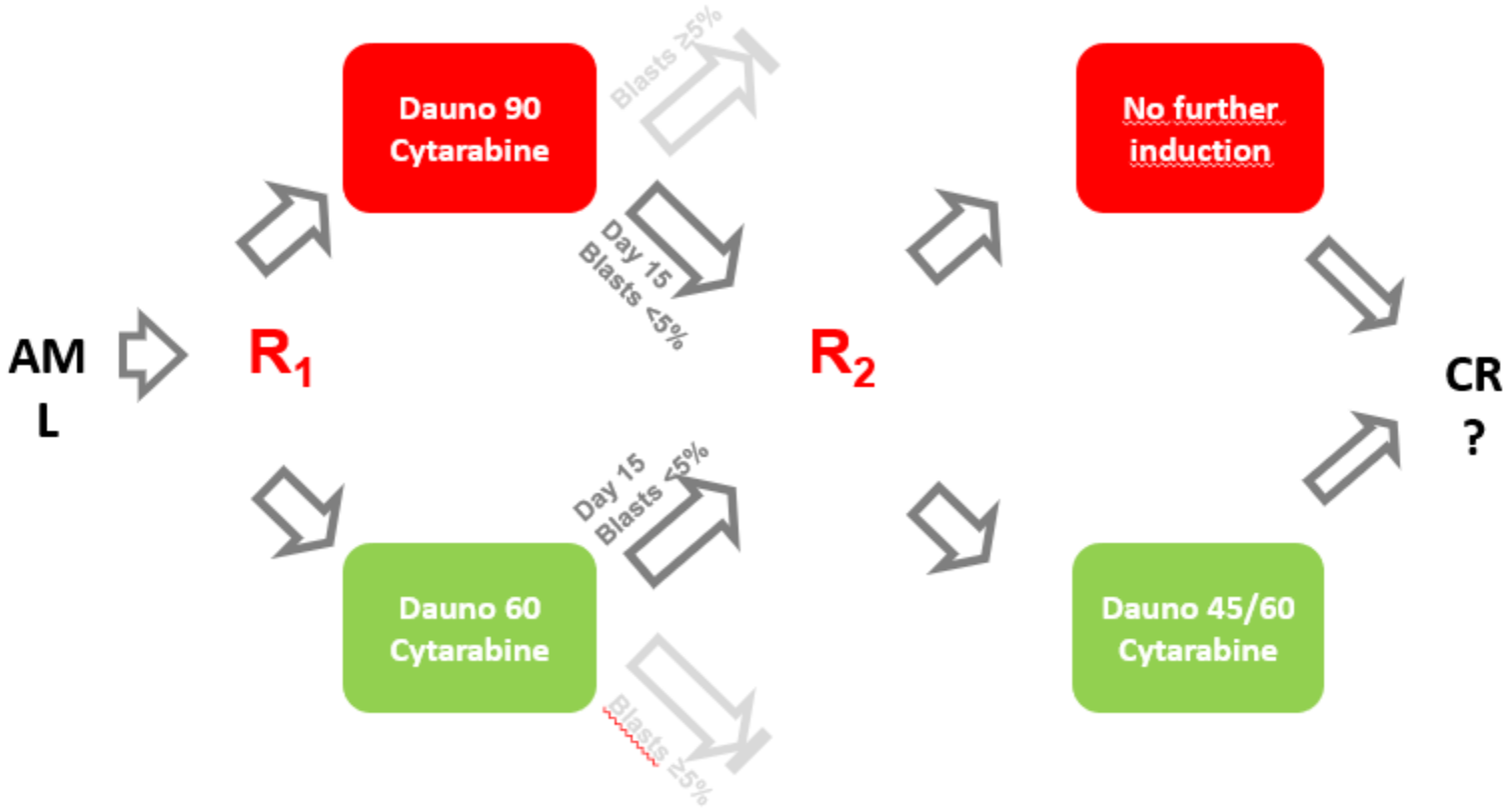
Köln, 18.01.2023

CIO
Centrum für Integrierte Onkologie
Aachen Bonn Köln Düsseldorf

Single versus double induction with “7+3” containing 60 versus 90 mg daunorubicin for newly diagnosed AML

Results from the randomized controlled SAL-DaunoDouble trial

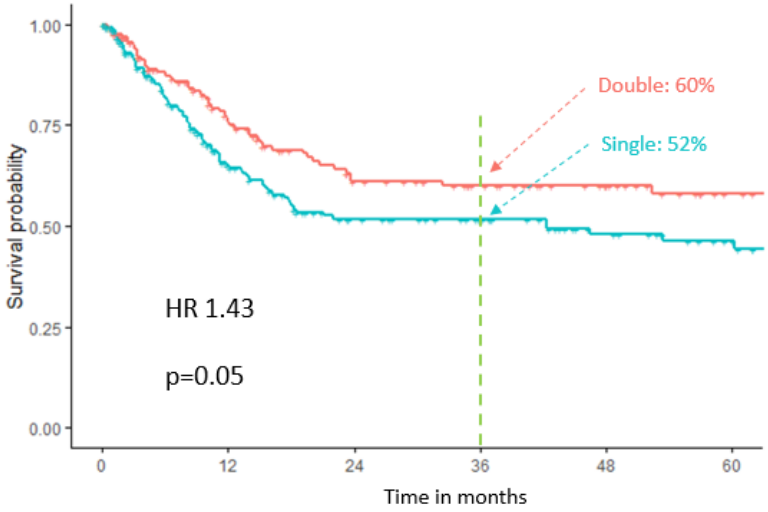
SAL
Study Alliance Leukemia

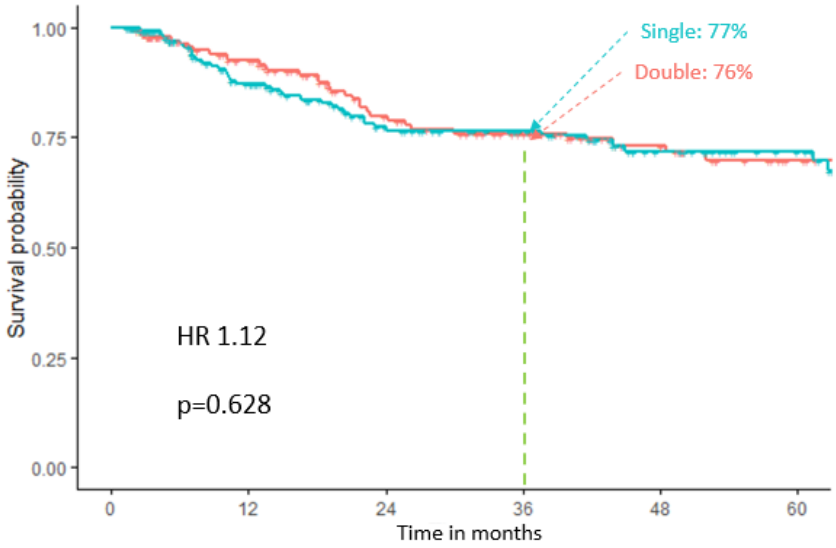


C. Röllig et al., ASH2022, #217

Relapse-free Survival Per-Protocol Population

Median Follow-up 44 months





C. Röllig et al., ASH2022, #217

Schlussfolgerungen DaunoDouble Studie

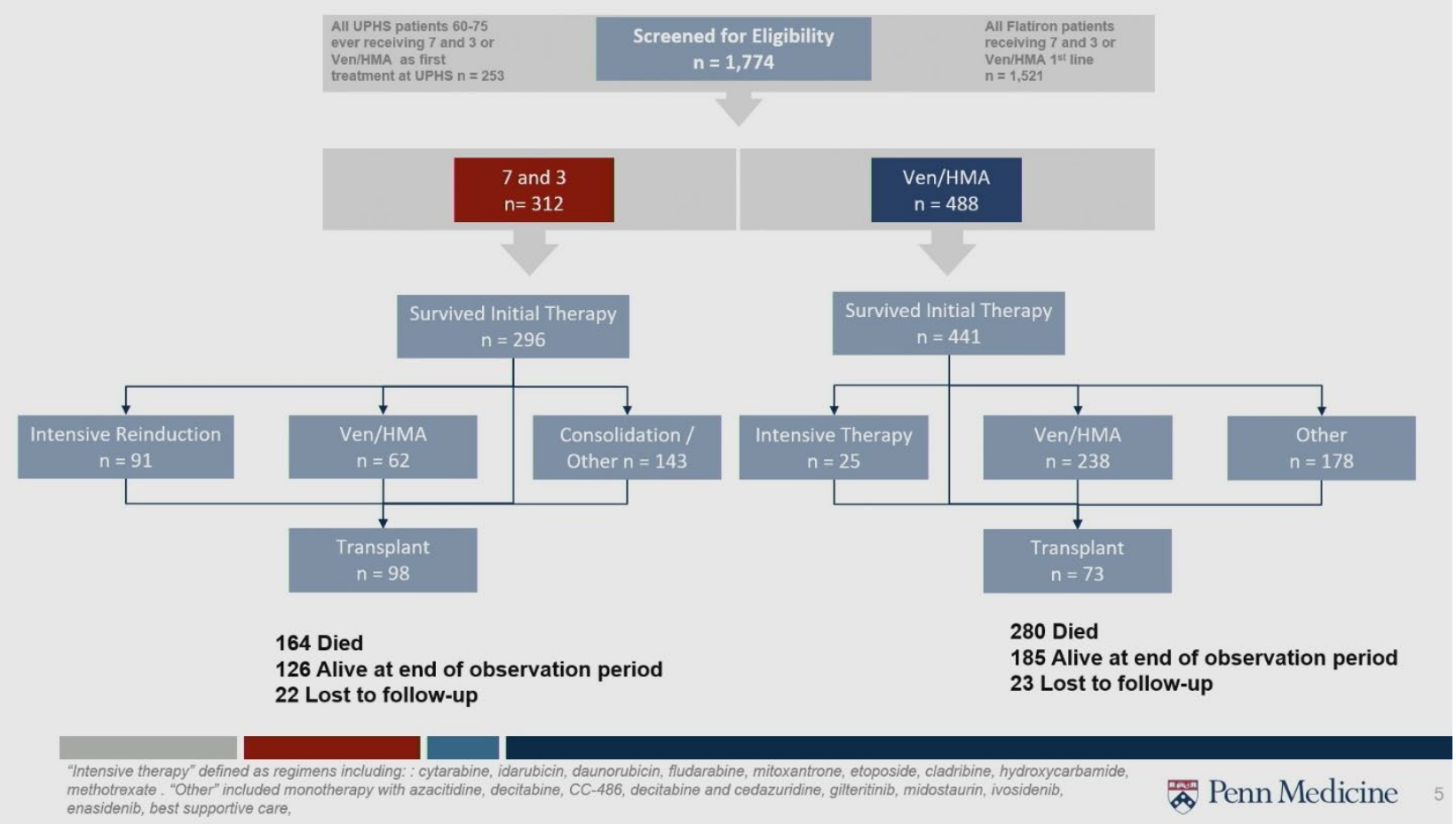
Für Patienten mit Blasten < 5 % an d15 nach 3+7 gilt:

- Die Remissionsraten CR/CRi sind nach einer Doppelinduktion etwas höher aber dies nicht statistisch signifikant
- Es besteht ein Trend für ein besseres Rezidivfreies Überleben nach Doppelinduktion in der Univariaten Analyse, jedoch nicht in der multivariaten Analyse
- Kein Unterschied im Gesamtüberleben zwischen einfacher Induktion und Doppelinduktion

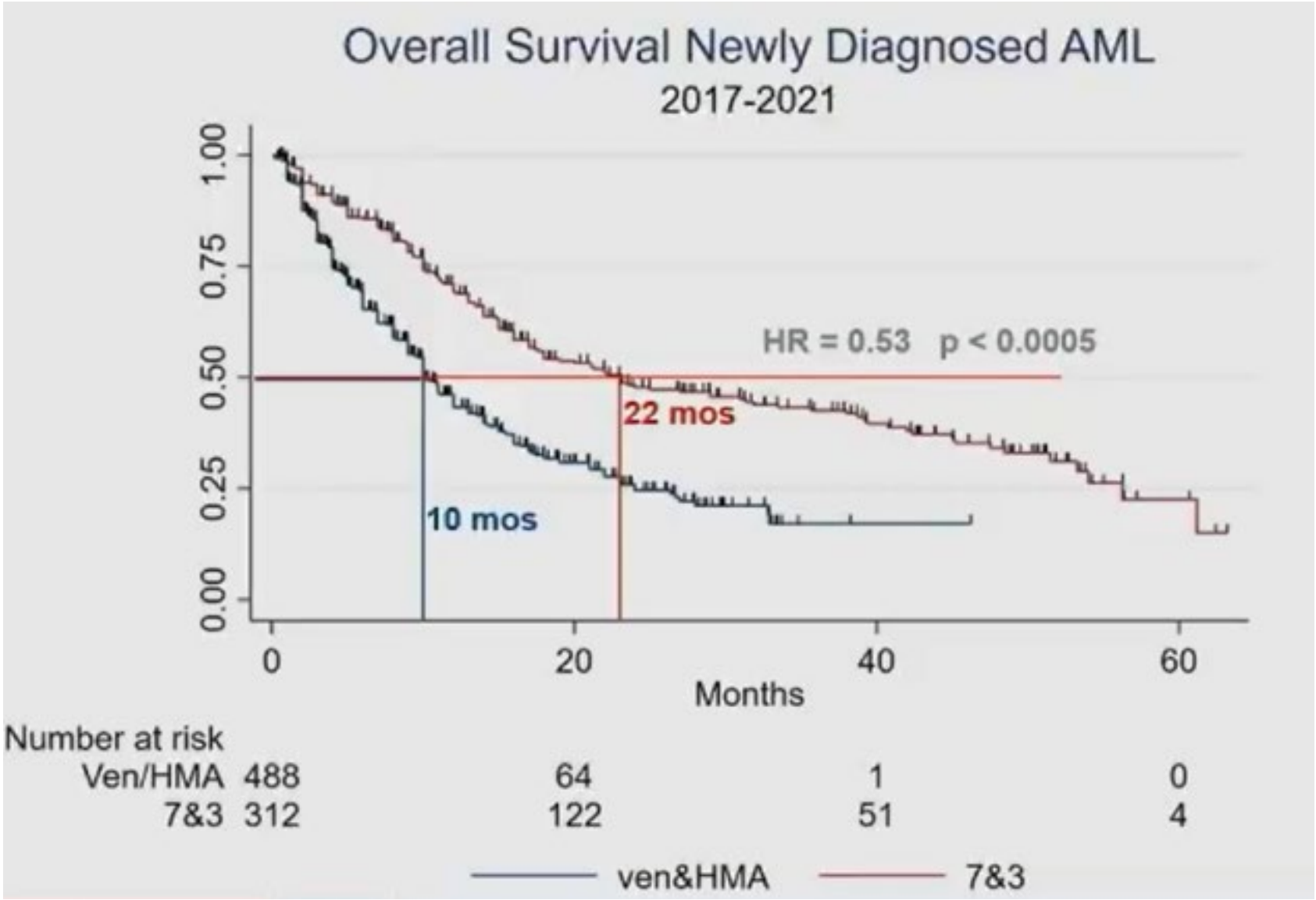
→ Für Patienten mit Blasten < 5 % an d15 kann auf die Doppelinduktion verzichtet werden

#426: Real World Effectiveness of “7 + 3” Intensive Chemotherapy vs Venetoclax and Hypomethylating Agent for Initial Therapy in Adult Acute Myeloid Leukemia

AH Matthews et al.



#426: Real world 3+7 vs. V/V



AH Matthews et al. ASH2022:#426

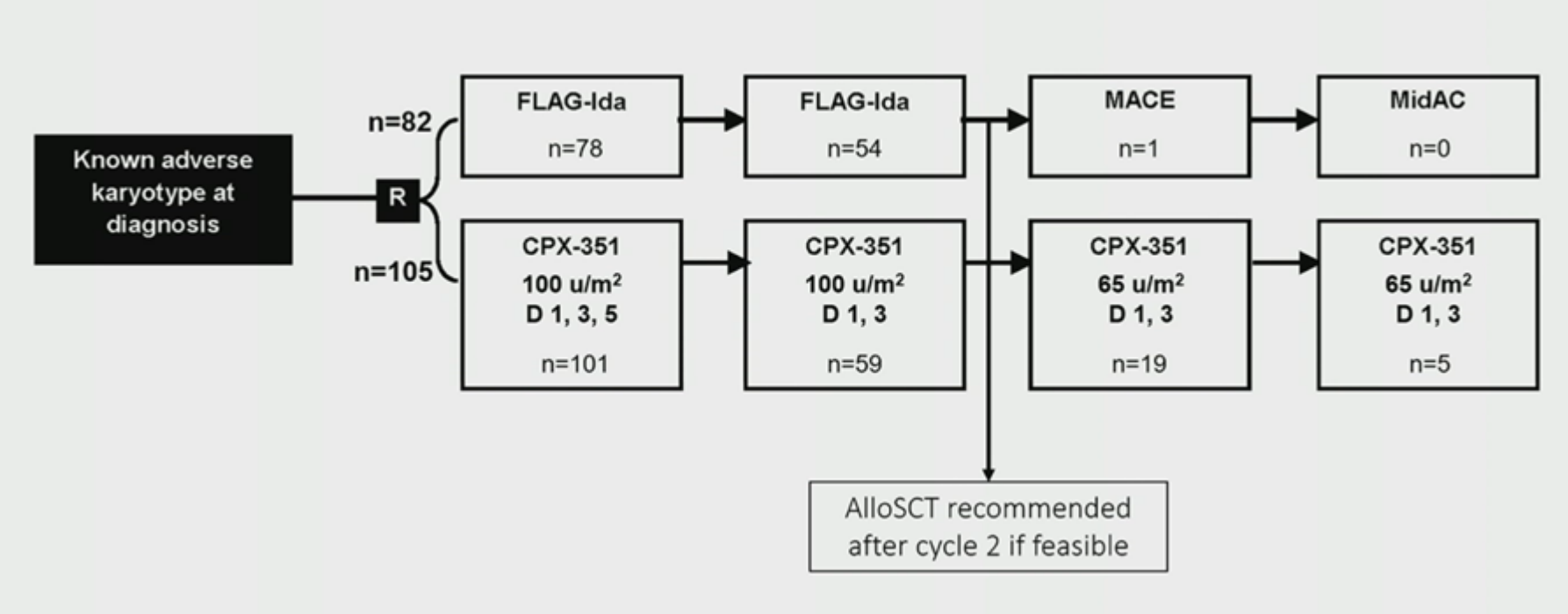
#426: Real world 3+7 vs. V/V: Schlussfolgerung

- Weiterhin kein Nachweis einer Überlegenheit von
  Vidaza/Ventoclax gegenüber 3+7
- Randomisierte Studien ausstehend

→ 3+7 bleibt Standard auch für Patienten > 60 Jahre die induktionsfähig sind
mit GO, Midostaurin oder ggf. Vyxeos
entsprechend Onkopedia Leitlinie

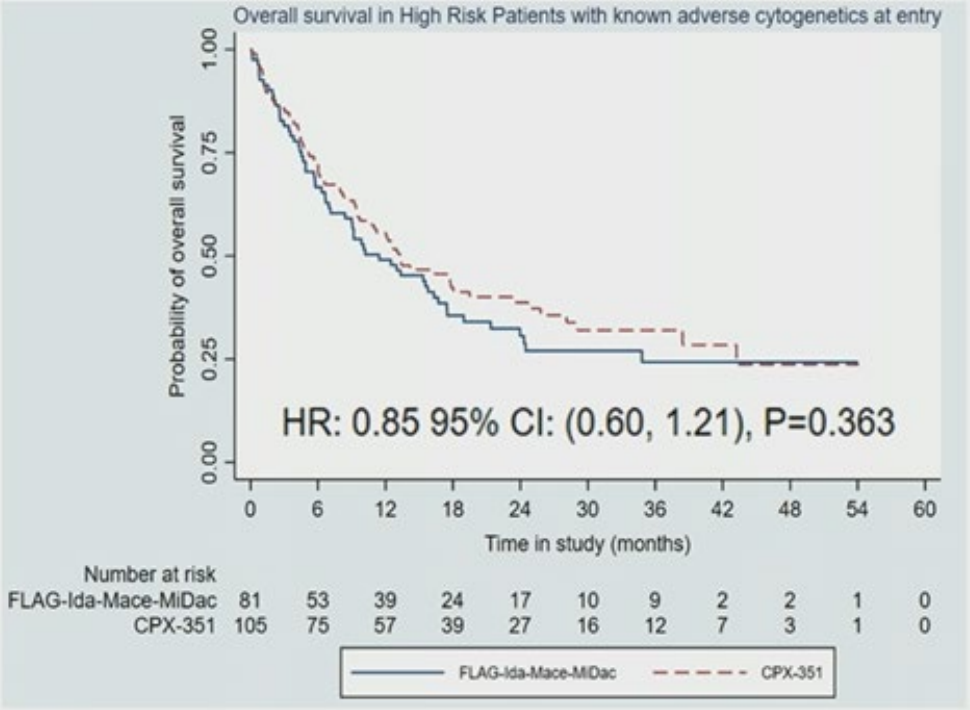
#431: Genomic Correlates of Outcome in a Randomised Comparison of CPX-351 and FLAG-Ida in High-Risk Acute Myeloid Leukaemia and Myelodysplastic Syndrome: Results from the UK NCRI AML19 Trial

J.Othman et al.



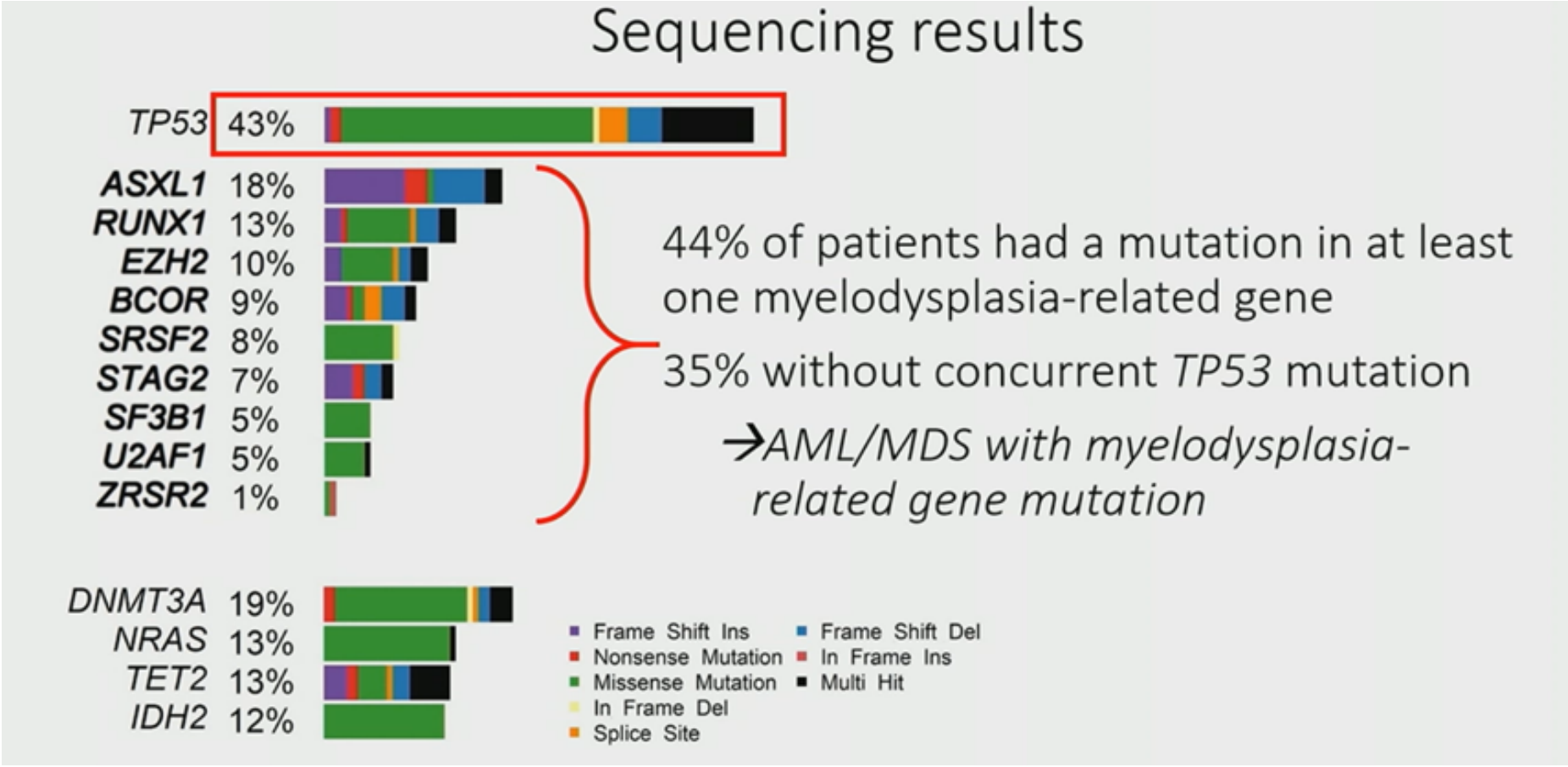
#431: UK NCRI AML19 Trial: Ergebnisse

3-yr outcomes	FLAG-Ida	CPX-351
OS	25%	32%
EFS	24%	25%
RFS	29%	39%



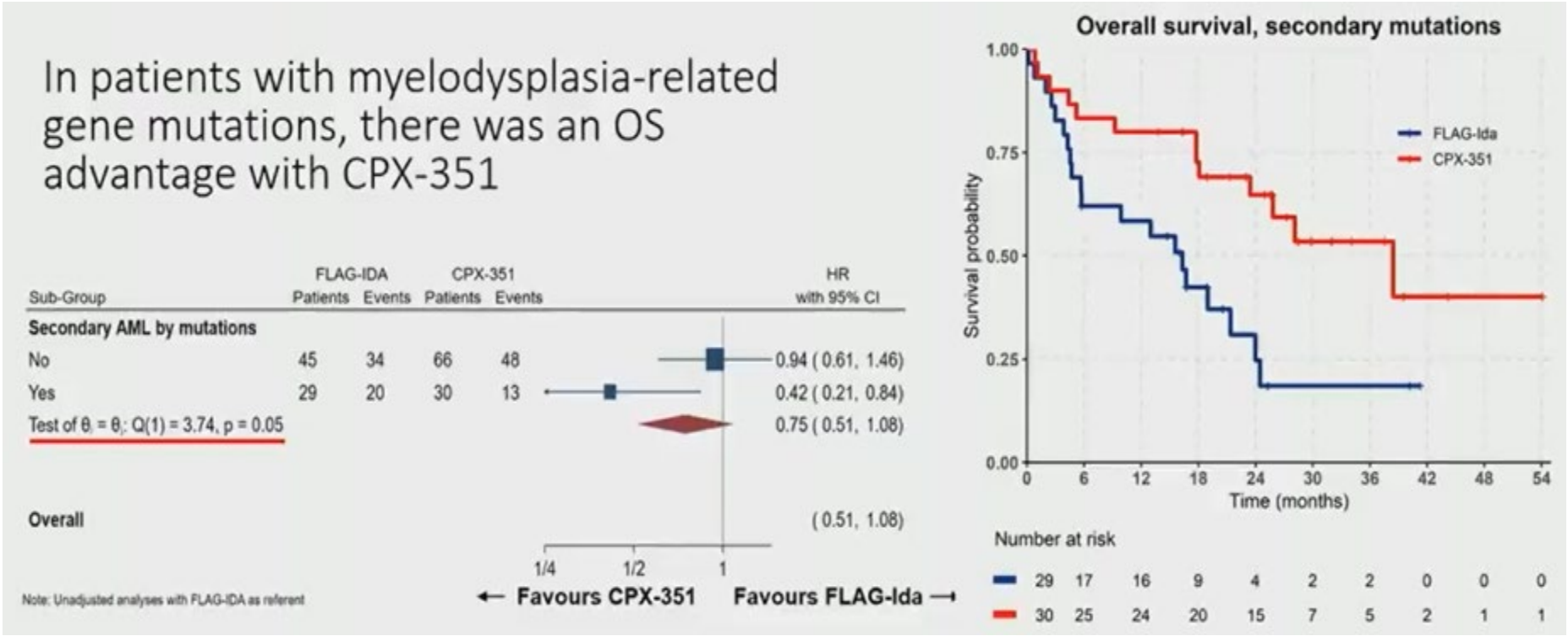
J. Othman et al. ASH2022:#431

#431: UK NCRI AML19 Trial: Ergebnisse



J. Othman et al. ASH2022:#431

#431: UK NCRI AML19 Trial: MDS Mutationen



J. Othman et al. ASH2022:#431

#431: UK NCRI AML19 Trial: Schlussfolgerung

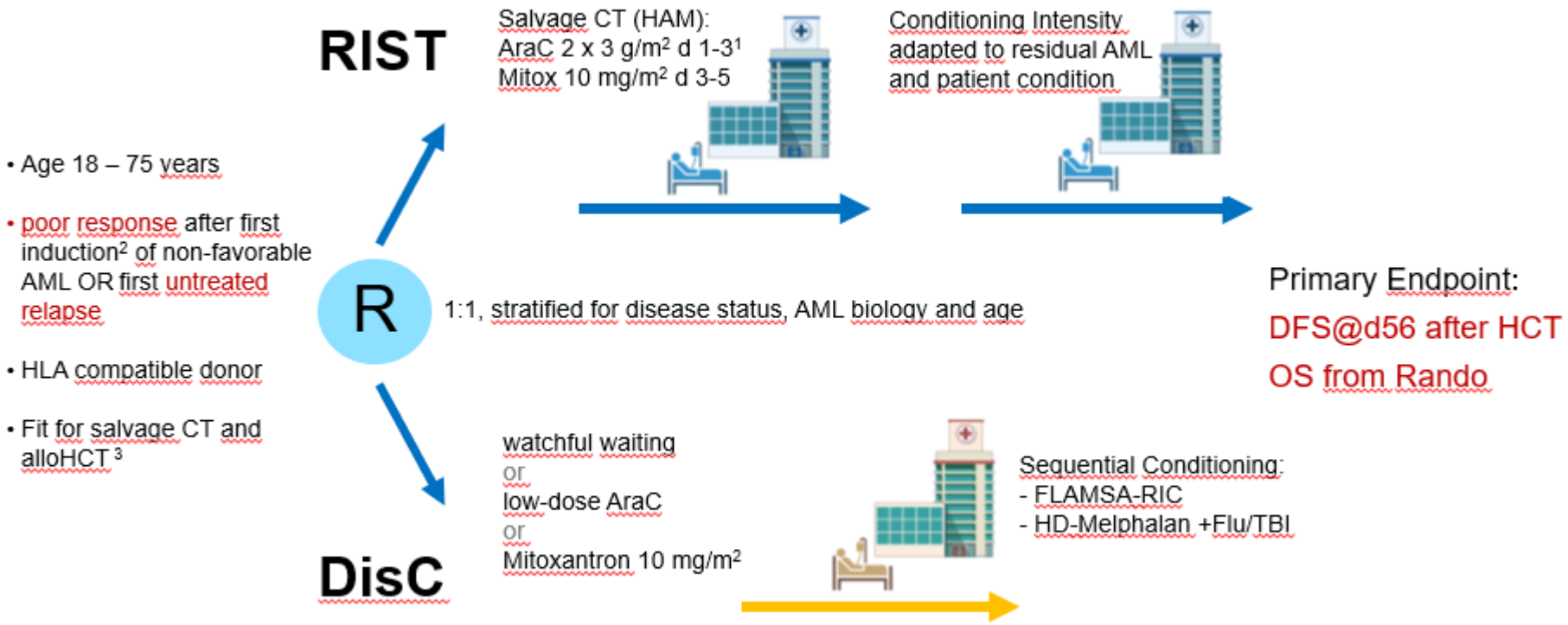
- FLAG-IDA und Vyxeos sind für Hochrisiko-AML und MDS gleichwertig
- Vyxeos zeigt Vorteile bei AML mit MDS Mutationen

→ Vyxeos bleibt in seiner Indikation bestehen (und der Einsatz kann auf die neue WHO Klassifikation der AML mit MD-Mutationen ausgedehnt werden)

In patients with relapsed/refractory AML sequential conditioning and immediate allogeneic stem cell transplantation (alloHCT) results in similar OS and LFS compared to intensive remission induction chemotherapy followed by alloHCT: Results from the randomized Phase III ASAP Trial

Matthias Stelljes, ..,Johannes Schetelig

on behalf of Study Alliance Leukemia and German Cooperative Transplant Study Group

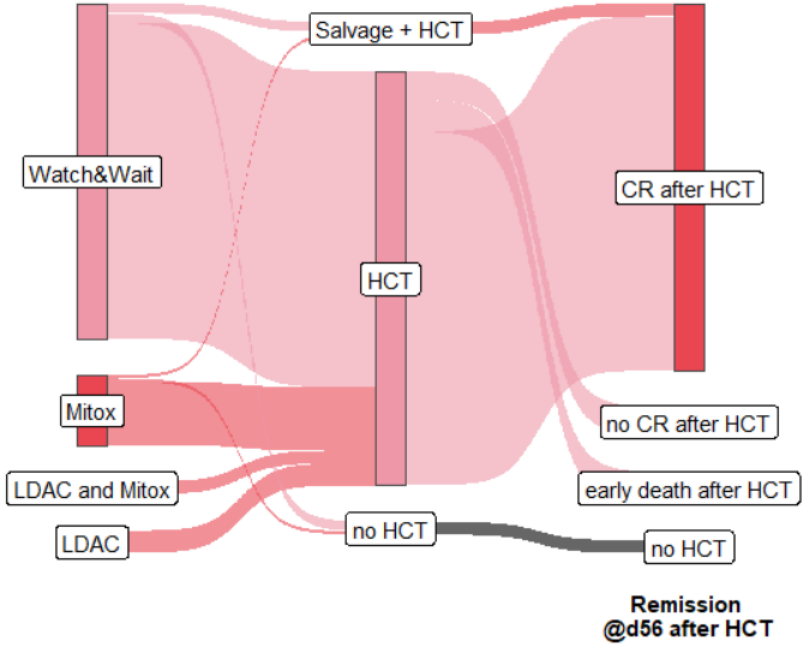


¹ Cytarabine 2 x 1 g/m² for patients >60 yrs
² poor response was defined as ≥5% marrow blasts after 1st induction; (see also Röllig *et al*, abstract 217, ASH 2022)
³ Patients with WBC≥50 GPT/L, CNS manifestations, prior alloHCT, LVEF <50%, O_2 supplementation., bilirubin >1.5xULN, GFR <50 ml/min were not eligible

Disease Control arm

76% of patients bridged by watchful waiting

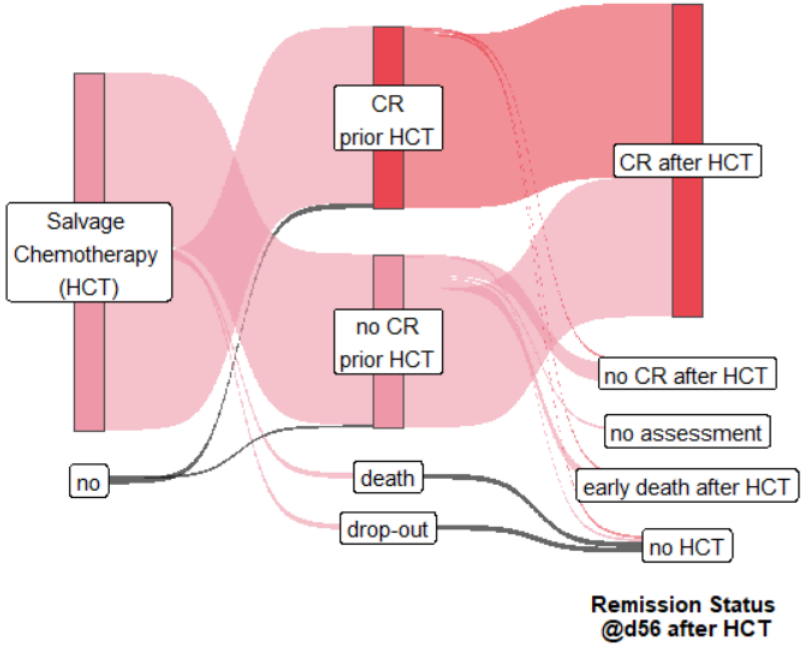
Median time to HCT 4 weeks; @16weeks 97% HCT



Remission Induction arm

Every second patient achieved a CR

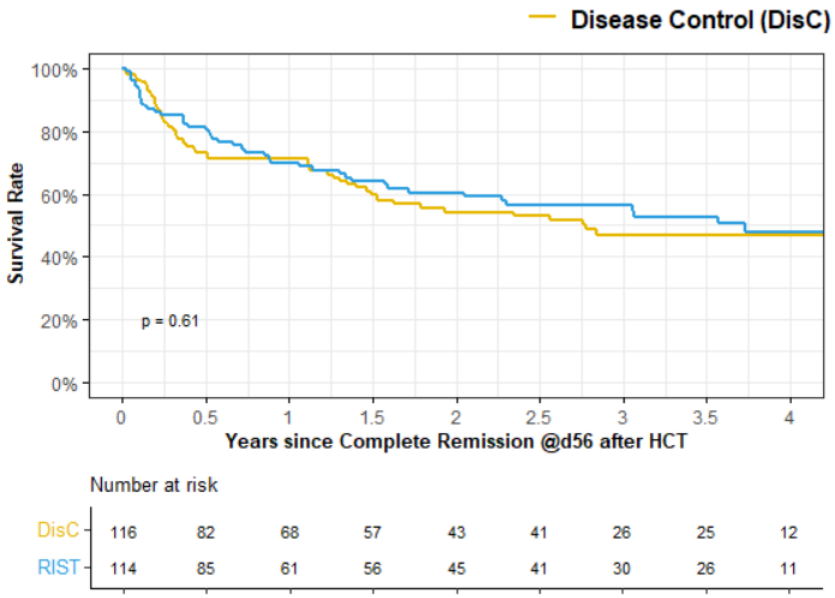
Median time to HCT 8 weeks; @16weeks 93% HCT



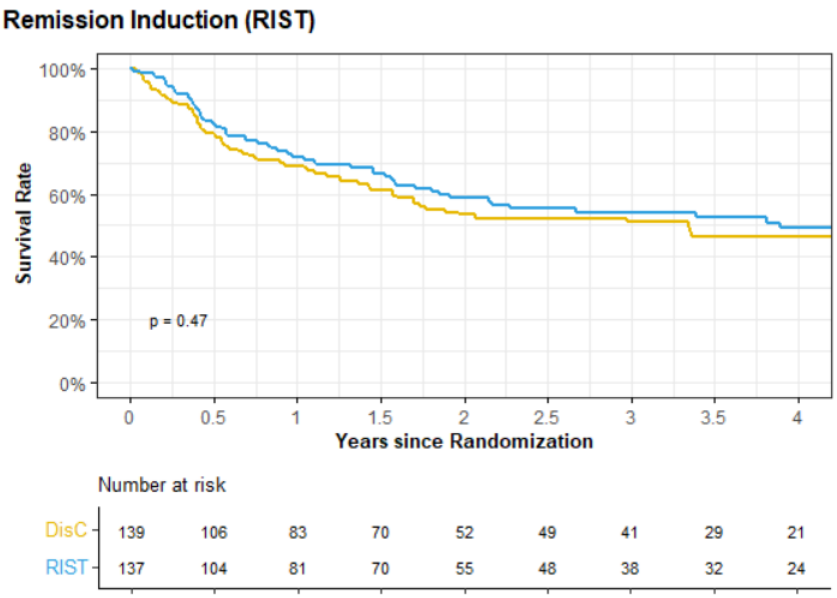
ITT populations, data lock 2022-07-19, analysis as of 2022-11-04

No Difference in Leukemia-free from DFS@d56 and Survival from randomization!

Leukemia-free Survival from d56



Overall Survival from Rando



Median follow-up from Randomization: 37 months

#4: ASAP: Schlussfolgerung

- Patienten mit einer R/R AML profitieren nicht von einer erneuten Induktionschemotherapie mit HAM
- Eine rasche allogene Stammzelltransplantation ergibt gleiche Raten von CR und OS
- Die Patienten verbringen weniger Zeit im Krankenhaus wenn eine allogene SZT unmittelbar erfolgt
- Der Remissionsstatus vor AlloTx ist nicht entscheidend
- Eine MRD Negarivität ist nicht Voraussetzung für einen guten Verlauf nach allogener SZT
- Der Nutzen einer erneuten Induktionstherapie mit dem Ziel einer Remission vor allogener SZT muss noch erwiesen werden

HERZLICHEN DANK!

CIO
Centrum für Integrierte Onkologie
Aachen Bonn Köln Düsseldorf

Save-the-Date: Mittwoch, 17. Januar 2024

Cologne Post ASH – Breaking News 2023 –

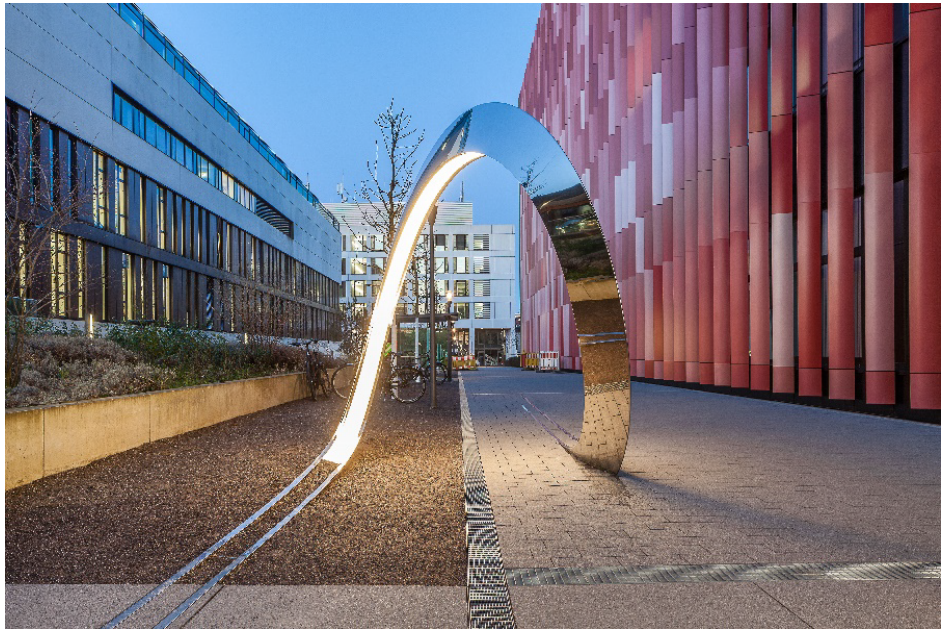


Foto: MFK, Christian Wittke

UNIKLINIK KÖLN