Bahnbrechendes vom ASH 2021

4. Hamburger AML Symposium

Prof. Dr. med. Claudia Baldus

Hämatologie/Onkologie -UKSH Kiel

UNIVERSITÄTSKLINIKUM Schleswig-Holstein

UCCSH | Universitäres Cancer Center Schleswig-Holstein

Christian-Albrechts-Universität zu Kiel

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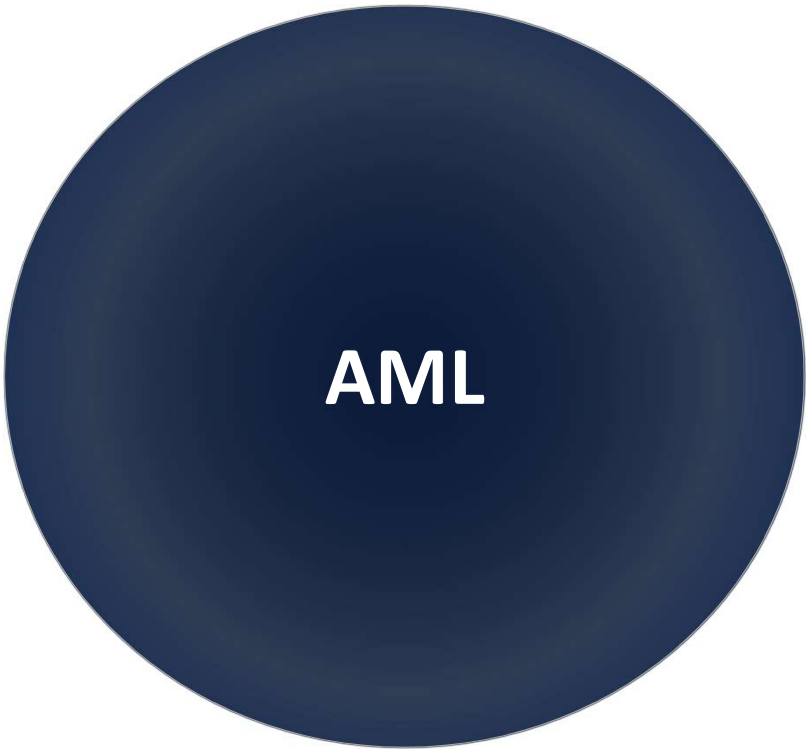
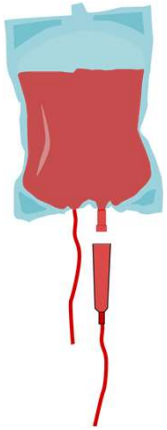

AML

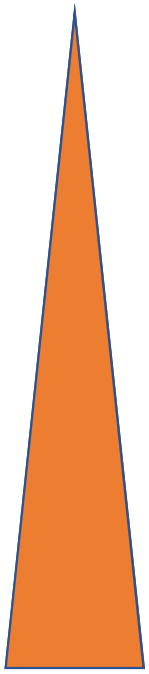
AML Fit

Genetische Risikogruppe -> Postremissionstherapie



ELN Risikogruppe	Aberrationen
Günstig **-> Chemo-Konsolidierung**	• t(8;21)(q22;q22); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) oder t(16;16)(p13.1;q22); *CBFB-MYH11* • Mutiertes *NPM1* ohne *FLT3*-ITD oder mit FLT3-ITD^{niedrig*} • Biallelisch mutiertes *CEBPA*
intermediär **-> allogene Transplantation/ Chemo-Konsolidierung**	• Mutiertes *NPM1* mit *FLT3*-ITD^{hoch*} (normaler Karyotyp) • Wildtyp-*NPM1* ohne *FLT3*-ITD (normaler Karyotyp) oder mit FLT3-ITD^{niedrig*} (mit oder ohne ungünstige genetische Aberrationen) • t(9;11)(p22;q23); *MLLT3-KMT2A*§ • Zytogenetische Aberrationen, die nicht als günstig oder ungünstig eingestuft wurden
Ungünstig **-> allogene Transplantation (Chemo-Konsolidierung)**	• t(6;9)(p23;q34); *DEK-NUP214* • t(v;11)(v;q23); *KMT2A*-Genumlagerung • t(9;22)(q34.1;q11.2); *BCR-ABL1* • inv(3)(q21q26.2) oder t(3;3)(q21;q26.2); GATA2, MECOM (*EVI1*) • -5 oder del(5q); -7; -17/abnl(17p) • komplexer Karyotyp (≥3 Aberrationen†) • monosomaler Karyotyp (eine Monosomie, assoziiert mit mindestens einer weiteren Monosomie oder einer anderen strukturellen, chromosomalen Aberration (außer CBF-AML)) • Wildtyp-*NPM1* mit *FLT3*-ITD^{hoch*} • Mutiertes *RUNX1*‡ • Mutiertes *ASXL1*‡ • Mutiertes *TP53*

Rezidiv Risiko



SCT Indikation

Röllig et al., Onkopedia-Leitlinie AML, www.onkopedia.de 2021

AlloSCT in pts ≤ 60 Years with Intermediate-Risk AML in 1. CR - Results of the Randomized Etal-1 Trial

Martin Bornhäuser, MD[1], *Christoph Schliemann, Prof., MD*[2*], *Johannes Schetelig, MD, MSc*[3], *Christoph Rollig, MD, MSC*[4*], *Michael Kramer, MSc*[3*], *Bertram Glass, MD*[5*], *Uwe Platzbecker, MD*[6], *Andreas Burchert, MD*[7], *Mathias Haenel*[8*], *Lutz Peter Mueller, MD*[9*], *Stefan Klein, MD*[10], *Gesine Bug*[11*], *Dietrich W. Beelen, MD*[12], *Wolf Roesler, MD*[13*], *Kerstin Schaefer-Eckart, MD*[14], *Christoph Schmid, MD*[15*], *Edgar Jost*[16*], *Georg Lenz, Prof., MD*[2], *Johanna Tischer, MD*[17*], *Karsten Spiekermann, MD*[18], *Markus Pfirrmann, PhD*[19*], *Hubert Serve, MD*[20], *Friedrich Stoelzel, PD, MD*[21], *Nael Alakel, MD*[22*], *Gerhard Ehninger, MD*[23], *Wolfgang E. Berdel, Prof., MD*[24] *and Matthias Stelljes, MD*[25]

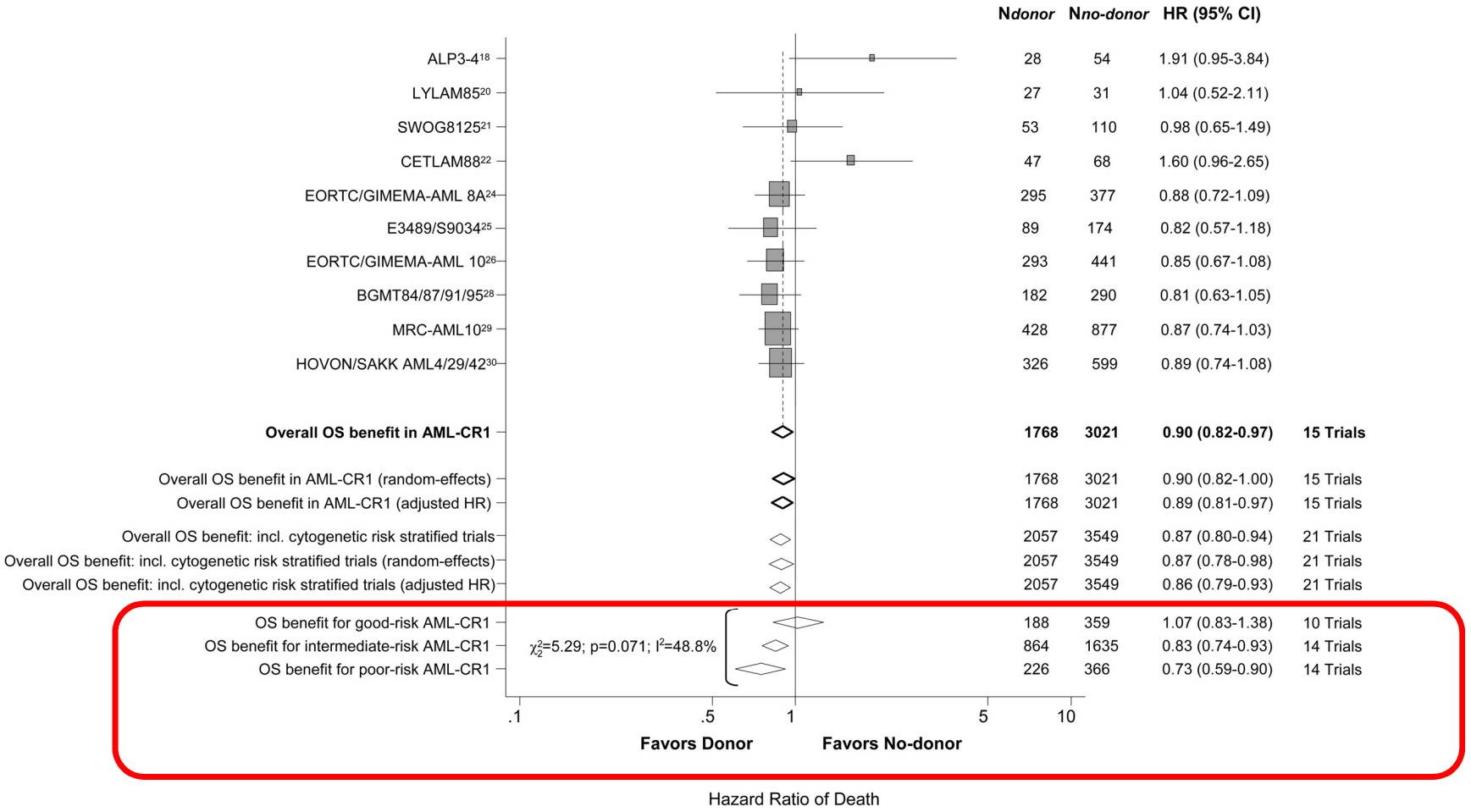
AlloSCT in 1. CR?

- **AlloSCT: hohes anti-leukämisches Potential im Vergleich zur Chemo-Konsolidierung**
- **AlloSCT: ist SOC für fitte pts < 60 Jahre mit high-risk AML**
- **Donor vs. no donor analyses: suggerieren Benefit für alloSCT auch in int.-risk AML**

- **Über die letzten Jahre:**

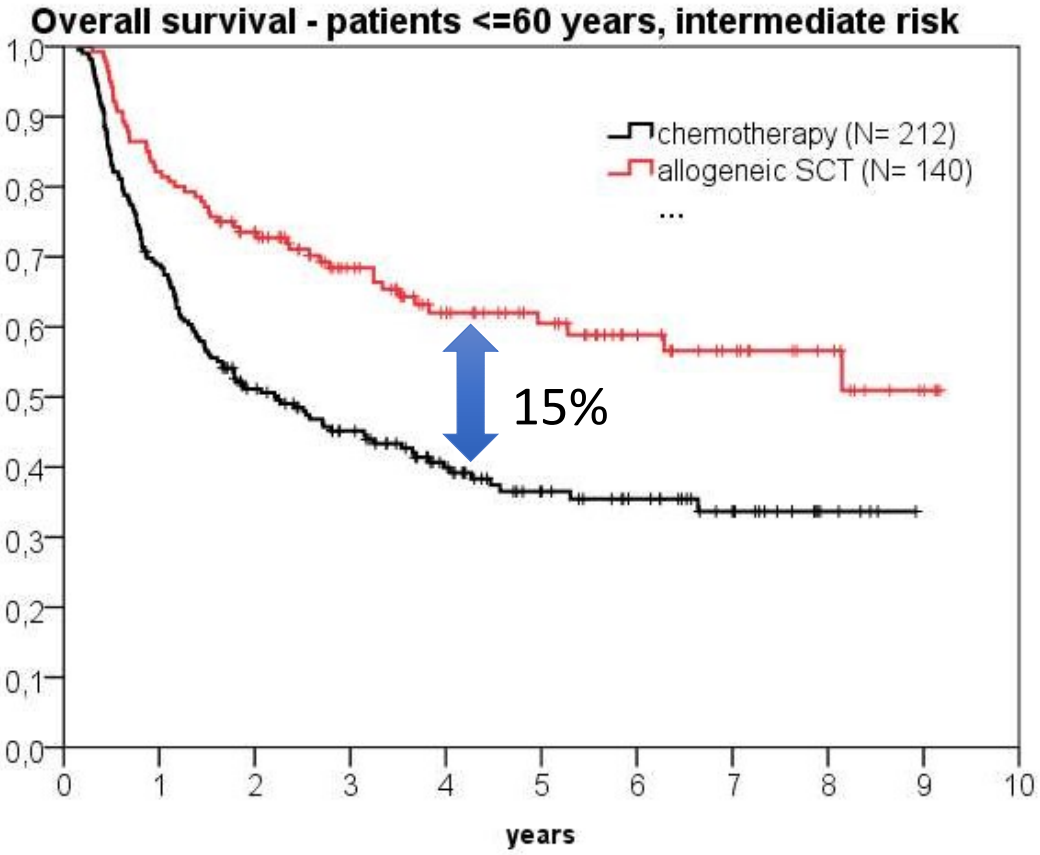
  verbesserte Spenderauswahl, RIC, supportive Therapien -> NRM post alloSCT < 15%

Survival Benefit der allogenen SCT in 1. CR AML (Metanalyse: donor vs no donor)



Koreth, J. et al. JAMA 2009;301:2349-2361.

SHG AML-96 Trial



ETAL-1 Trial

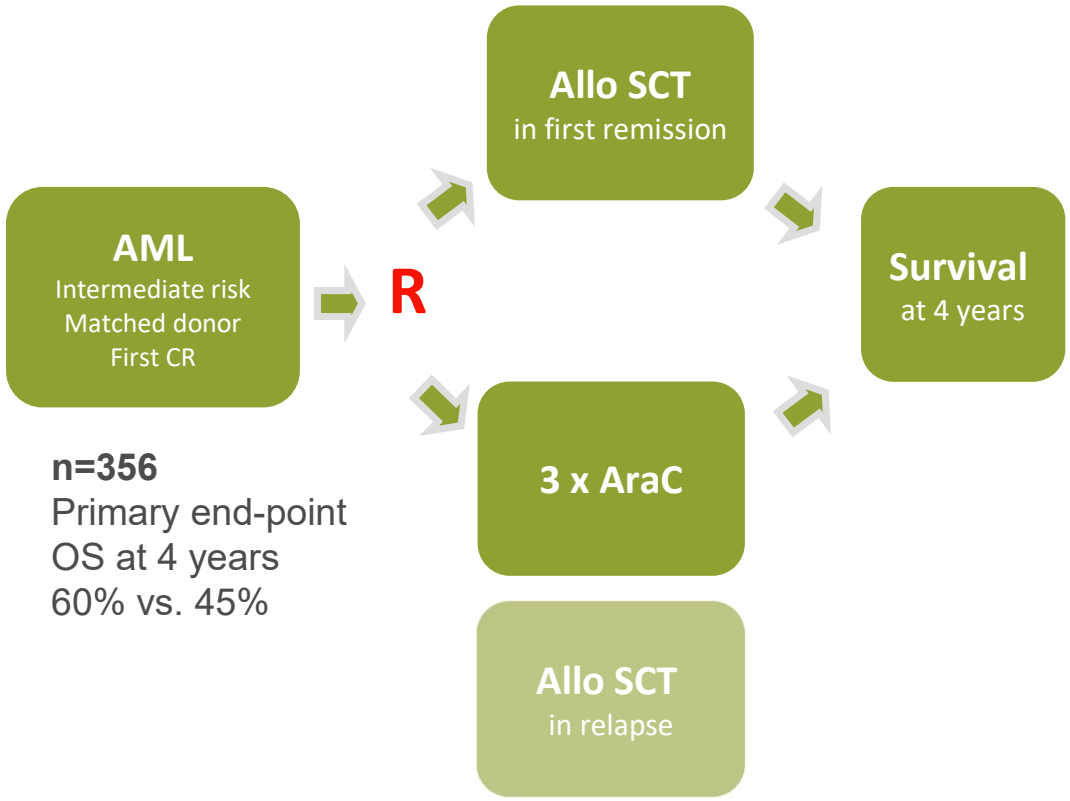
Inclusion criteria

- AML in 1st CR
- normal Karyotype
- Age 18-60
- „fit for transplant“

Exclusion criteria

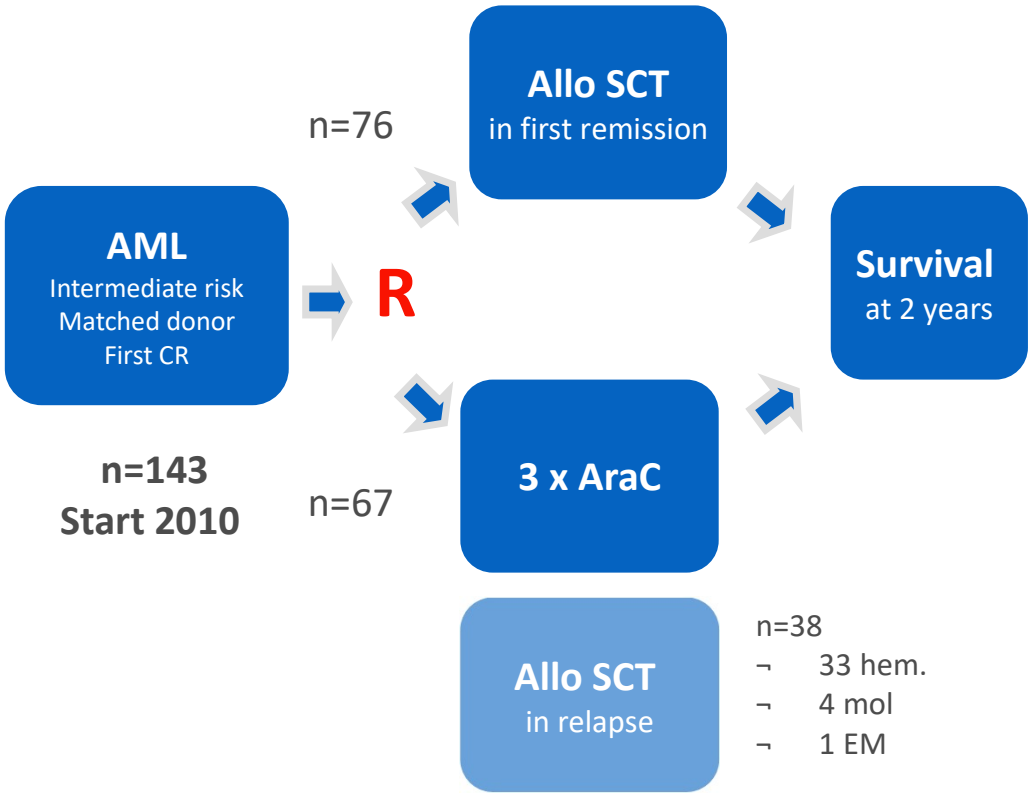
- Core-Binding-Factor Leukemia
- t(15;17)
- complex Karyotype
- -7, 7q-
- -5, 5q-
- abnorm. Chr. 3 or 11
- t(6;9)
- +8 + addit. abberrations

Plan ETAL-1-Studie



n=356
Primary end-point
OS at 4 years
60% vs. 45%

Durchführung



n=143
Start 2010

n=38
- 33 hem.
- 4 mol
- 1 EM

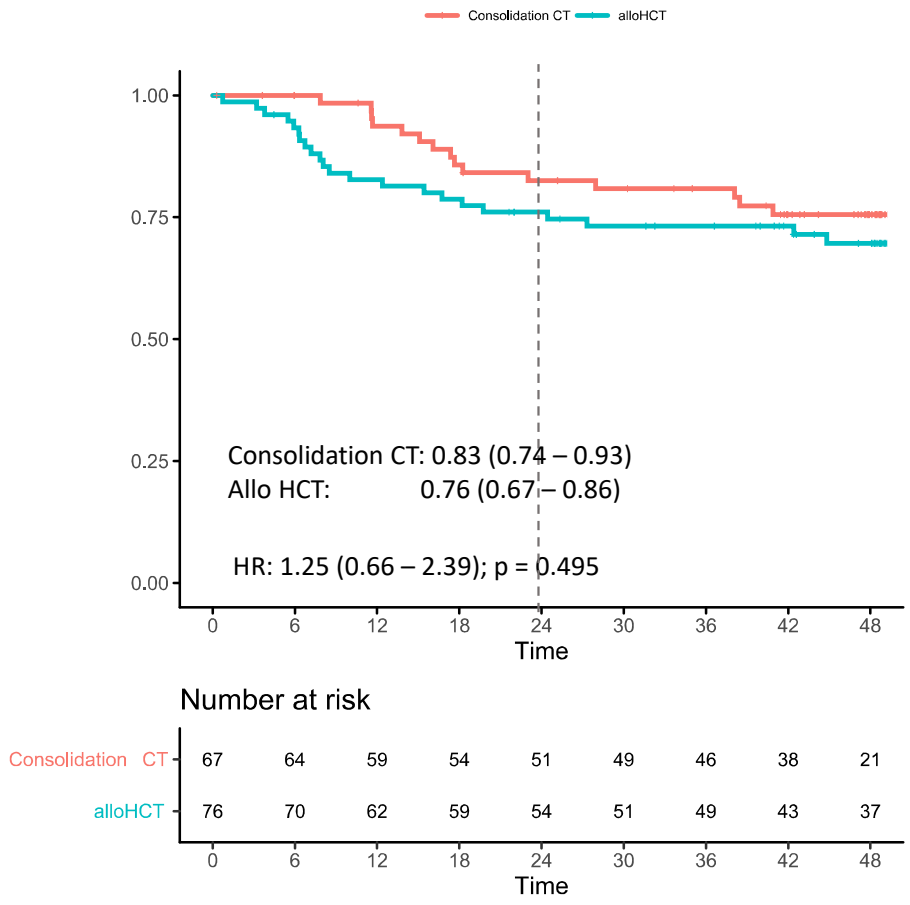
ETAL1 - Patienten

ELN 2017 noch in 2010 noch nicht berücksichtigt

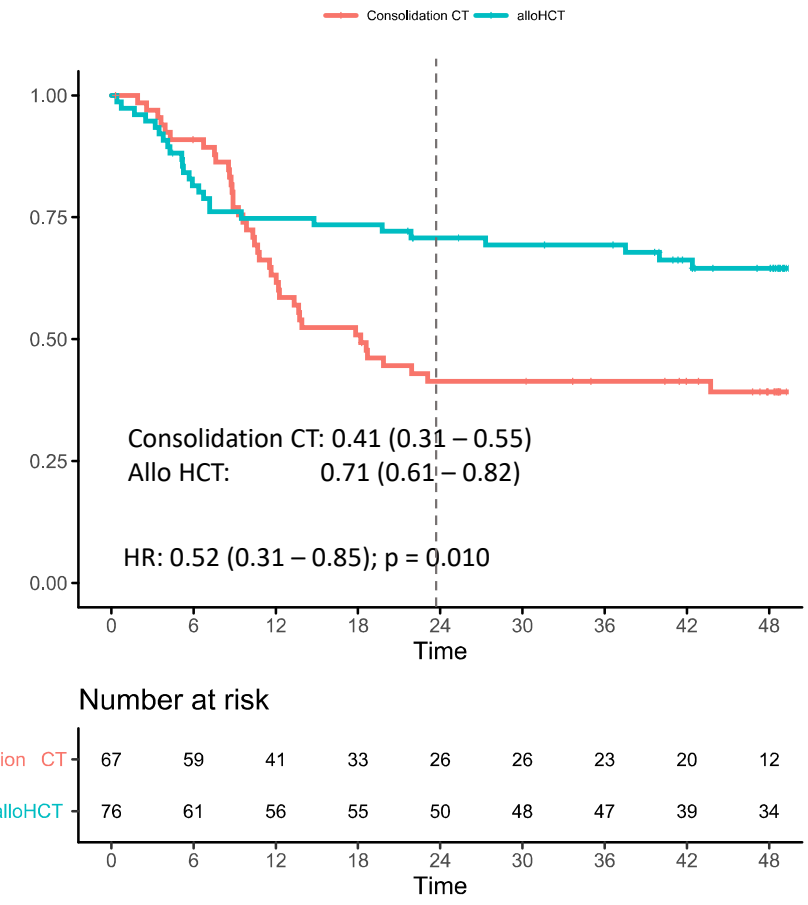
	Arm A, HCT (n = 76)	**Arm B, Chemo consol.** (n = 67)
Age [years]		
Median	50.5	51
Range	(19–60)	(24–60)
Age subgroup [No. (%)]		
18-40 years	16 (21)	11 (16)
41-60 years	60 (79)	56 (84)
Gender [No. (%)]		
Female	31 (41)	31 (46)
Male	45 (59)	36 (54)
Cytogenetics [No. (%)]		
Normal karyotype	54 (56)	65 (66)
Other intermediate abnormalities	16 (17)	12 (12)
CEBPA status		
Mutated	12 (13)	5 (5)
Wild-type	8 (8)	9 (9)
NPM1 Status/FLT3- ITD status [No. (%)]]		
Mutated/Mutated	12 (17)	13 (20)
Mutated/Wild-type	17 (25)	14 (22)
Wild-type/Mutated	5 (7)	3 (5)
Wild-type/Wild-type	35 (51)	34 (53)
FLT3-ITD ratio		
Median (range)	0.57 (0.36-1)	0.54 (0.22-0.63)
ELN Category		
Favorable	24 (32)	19 (28)
Intermediate	50 (66)	46 (69)
Adverse	2 (3)	2 (3)
Donor [No. (%)]		
Matched sibling	18 (24)	23 (34)
Matched unrelated (10/10)	51 (67)	28 (52)
1 allele mismatched unrelated (9/10)	7 (9)	12 (13)
CMV serostatus* [patient, No. (%)]		
Positive	41 (54)	36 (55)
Negative	35 (46)	29 (31)

Outcome

Overall survival

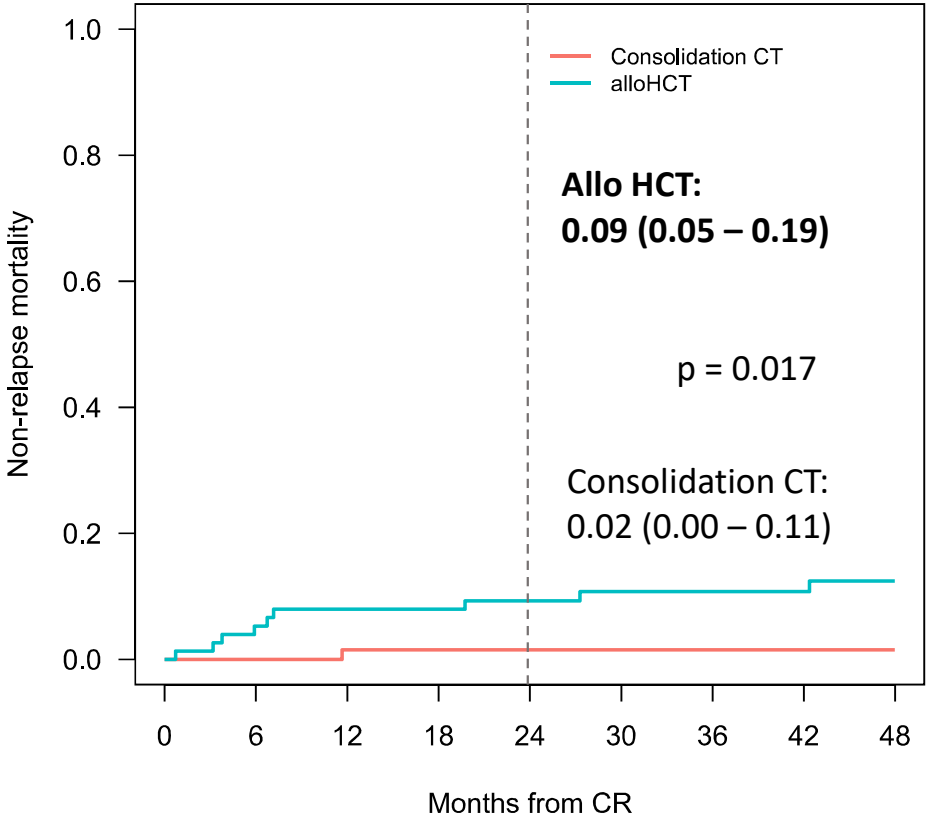


Disease-free survival

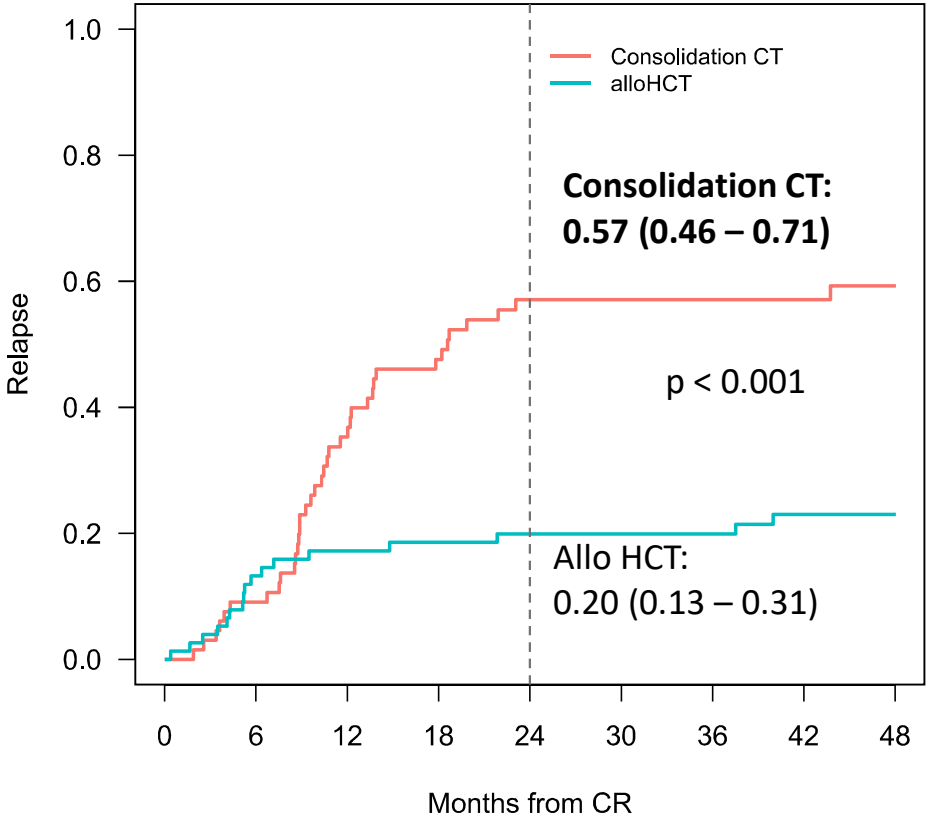


NRM and Relapse

Non-relapse mortality



Incidence of relapse



Summary

AlloSCT
in 1. CR
Nicht unbedingt

- Randomisierte alloSCT Studie!
  -> vergleichbares OS alloSCT vs Chemo int. AML
- DFS ist besser in alloSCT: bessere Leukämiekontrolle
- Chemotherapie Arm besser als angenommen (gute und schnelle Salvage SCT)
- NRM < 10%!
- QoL vergleichbar!
- Schnelle und frühe Spenderverfügbarkeit wesentlich!
- MRD Monitoring und als Therapiestratifizierung jetzt möglich!

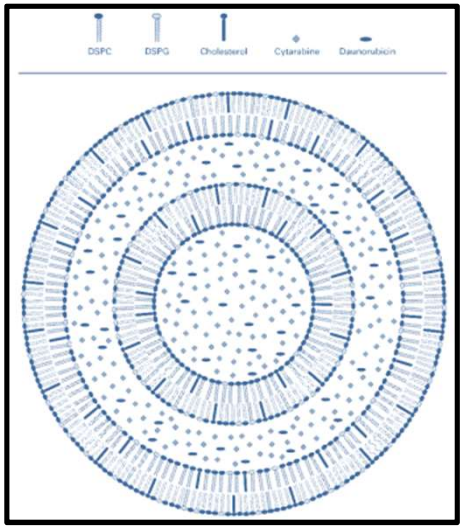
Real-World Experience of CPX-351 As First-Line Treatment in 188 Patients with Acute Myeloid Leukemia

Rautenberg C. *et al.,* Essen, Deutschland

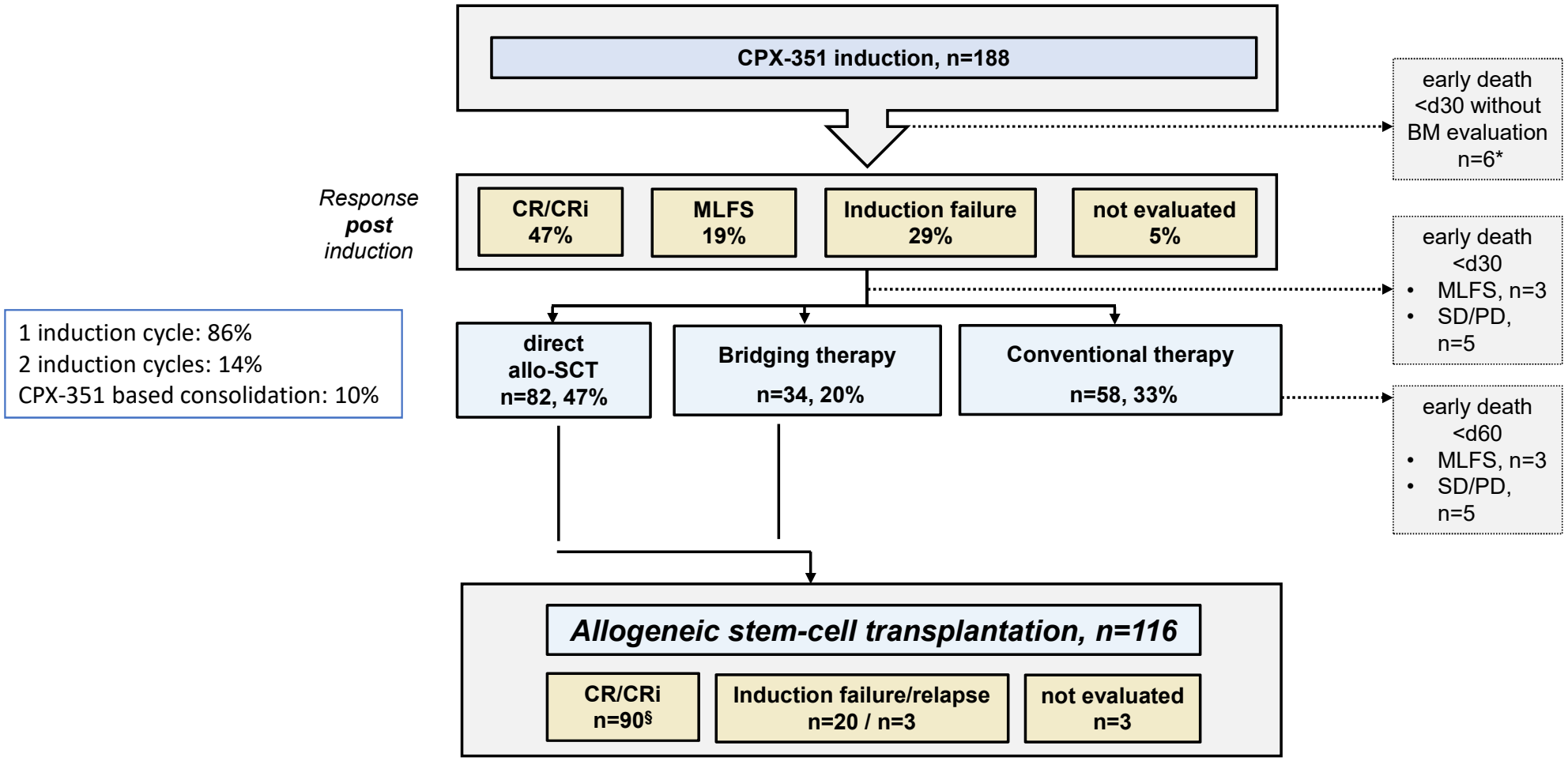
CPX351
->
SCT

CPX-351: real world Analyse von CPX-351 in AML Patienten mit neudiagnostizierter AML-MRC/t-AML und nachfolgender alloSCT in Deutschland (SAL/AML-SG)

Characteristic	n=188
Age, median (range)	65 (26-80)
Male sex, n (%)	118 (63)
HCT-CI, n (%)	
low	29 (18)
intermediate	55 (35)
high	74 (47)
Karnofsky Index, n (%)	
≥ 80%	135 (82)
< 80%	30 (18)
HMA pretreatment, n (%)	19 (10)

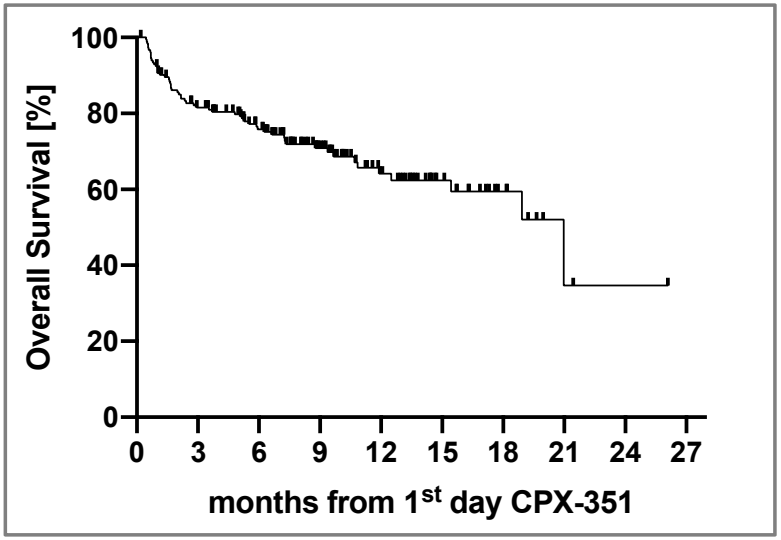


Real-World Experience of CPX-351 As First-Line Treatment



Outcome after Transplant

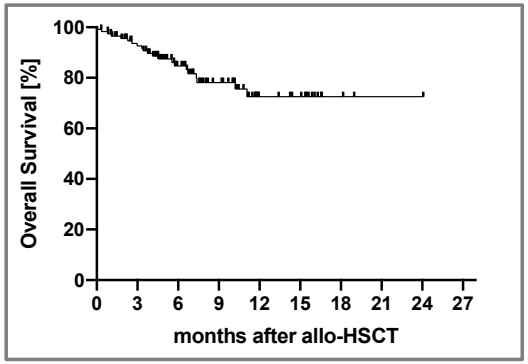
Overall Survival, n=188



Median OS: 21 months
1-year OS: 64%

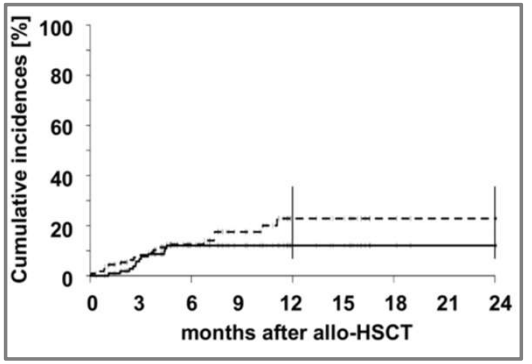
Follow-up: 9.3 months (0.2 – 26.1)

OS n=116



Median OS: not reached
1-year OS: 73%

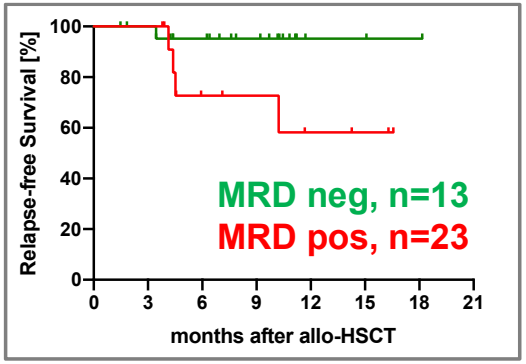
CIR/NRM n=116



1-year CIR: 23%
1-year NRM: 12%

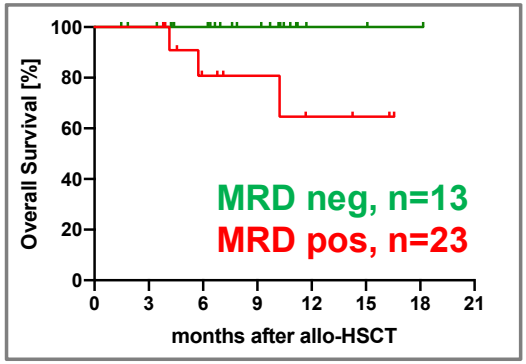
Outcome after allo-SCT - MRD status

RFS allo-cohort, n=36 (CR/CRi pre-SCT)



***p*=0.048**
HR 6.7 [1.1-41.2]

OS allo-cohort, n=36 (CR/CRi pre-SCT)



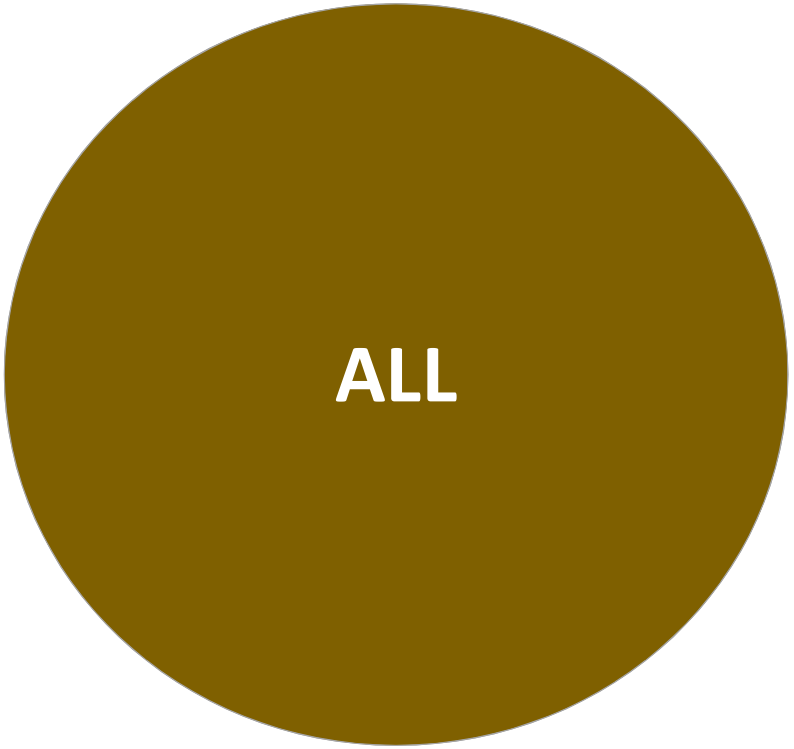
***p*=0.02**
HR 15.9 [1.5-167.8]

CPX-351 -> MRD -> SCT

Summary

CPX-351 in AML MRC real-world:

v.a. bei MRD Negativität vor alloSCT sehr gute Outcome Ergebnisse !


ALL

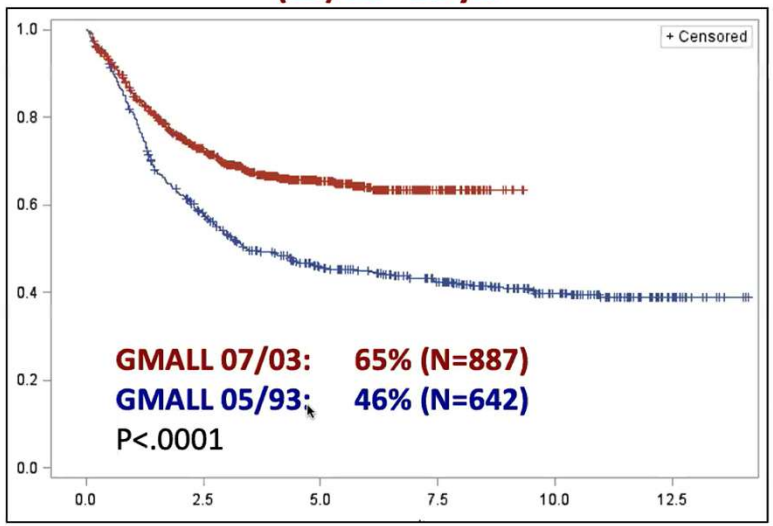
GMALL08 – Erste Daten

ALL
Verbesserung der
Erstlinientherapie

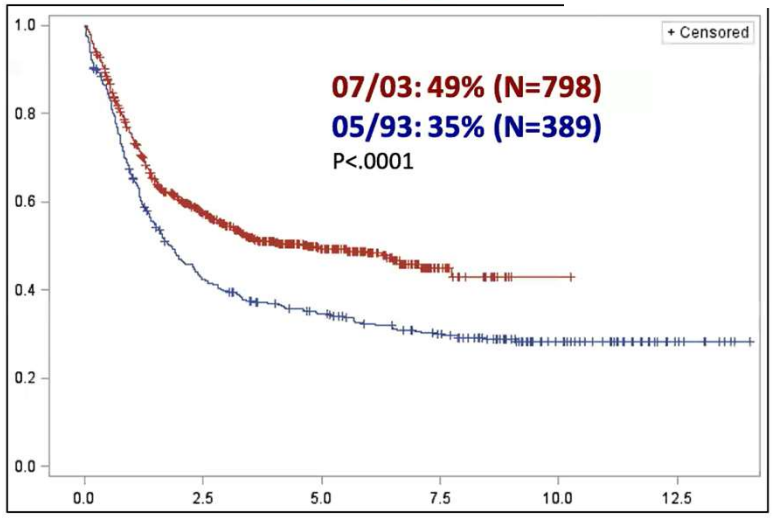
Overall Survival 07/2003 vs 05/93

Goekbuget et al, ASH 2014

(15) 18 - 35 yrs

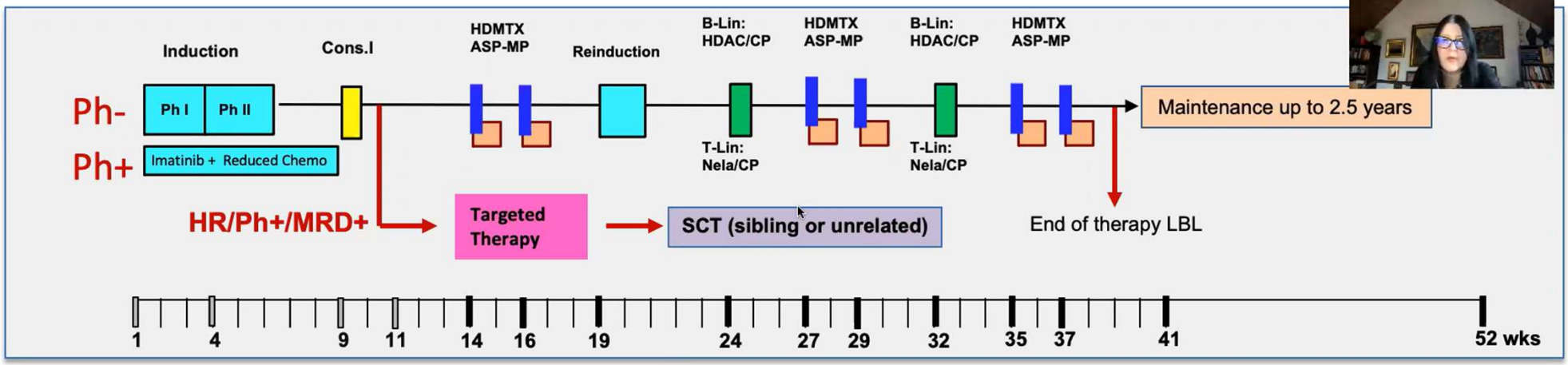


36 - 55 yrs



Improved with ‚pediatric-based' – adult optimised approach in all age groups

GMALL Trial 08/2013: Flow Sheet



- ➔ BFM-based ‚pediatric' regimen
- ➔ Dexa during induction/consolidation I
- ➔ 9 x PEG-asparaginase (2000 - 1000 – 500 U/m²)
- ➔ 7x HDMTX (1.5 g/m²)
- ➔ Reinduction
- ➔ Risk-adapted SCT indication

Risk stratifikation: HR: >= 1 risk factor
- pro-B-ALL and / or KMT2A
- early / mature T
- B-precursor: WBC > 30.000
- No CR after induction I

+ Molecular Failure after Consolidation I

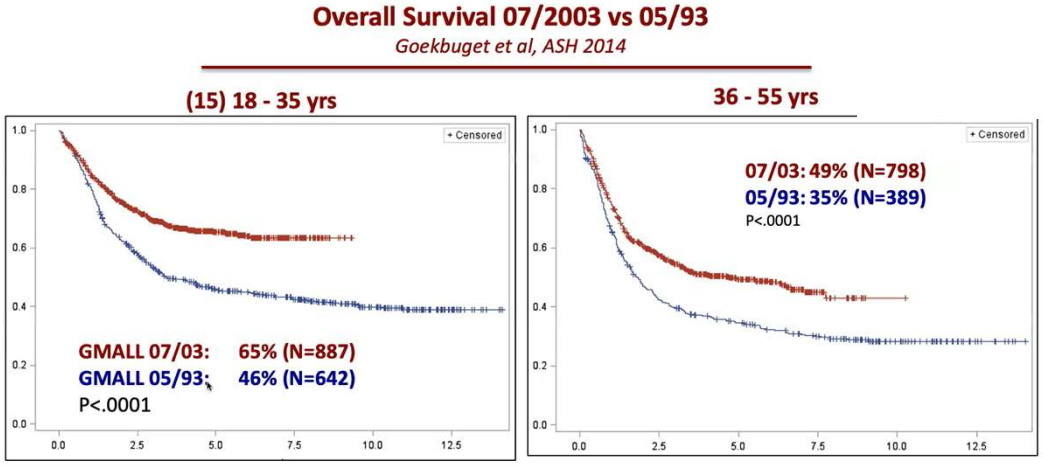
Randomization I:

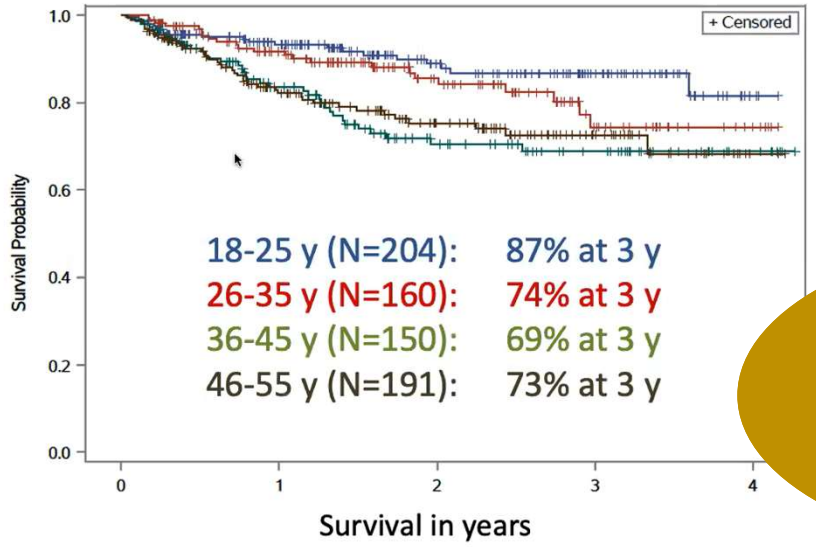
CNS irradiation versus i.th. prophylaxis in B-ALL/LBL

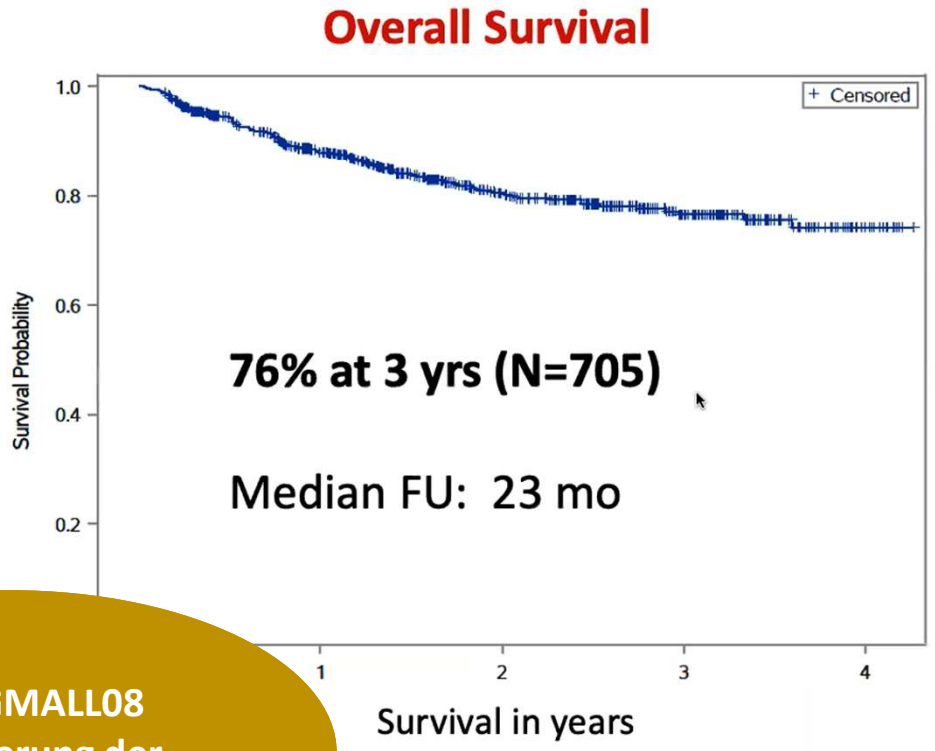
Randomization II:

SCT versus standard therapy in HR pts with MolCR after induction.

GMALL08 – Erste Daten

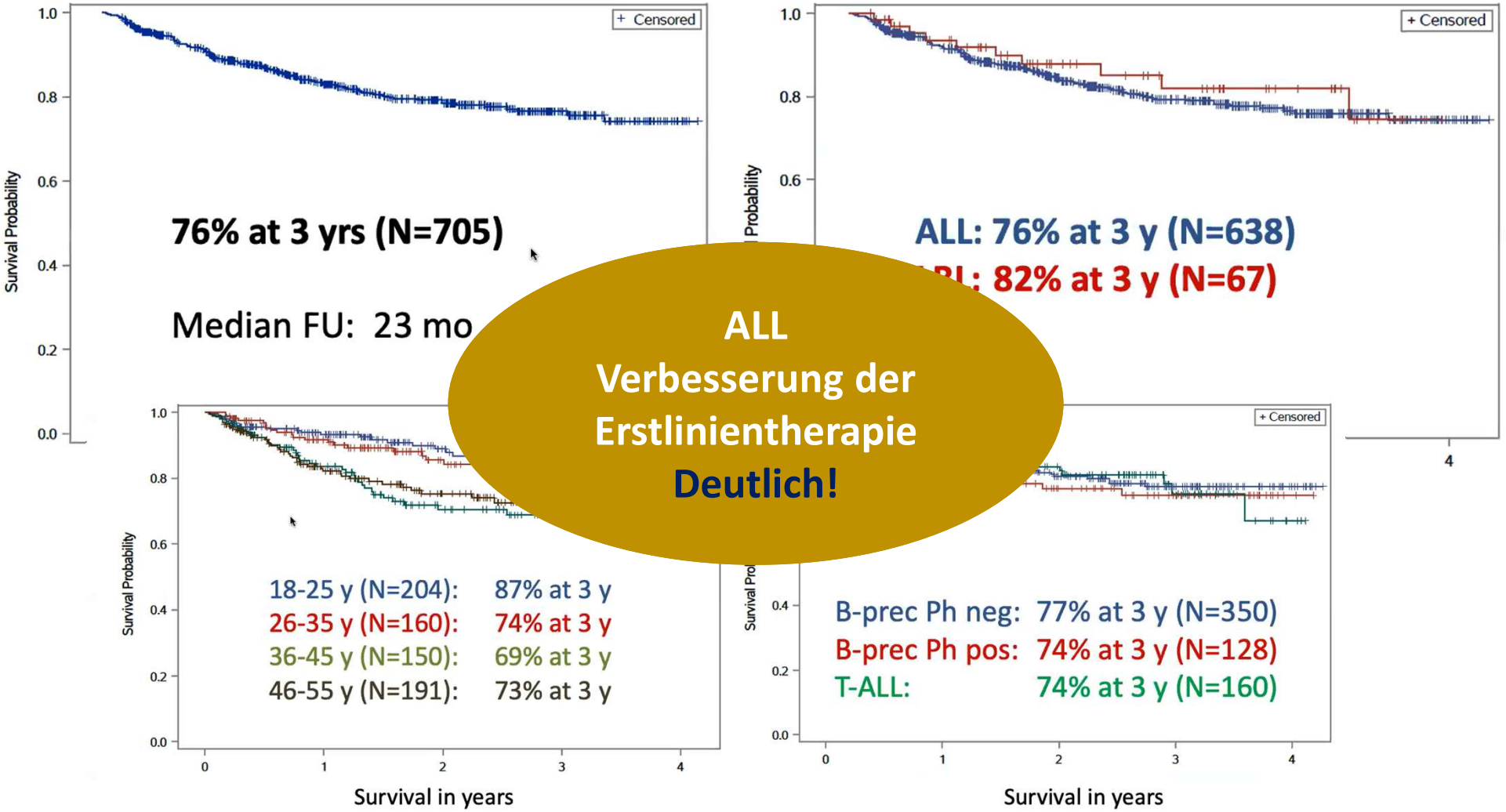






ALL – GMALL08
Verbesserung der Erstlinientherapie

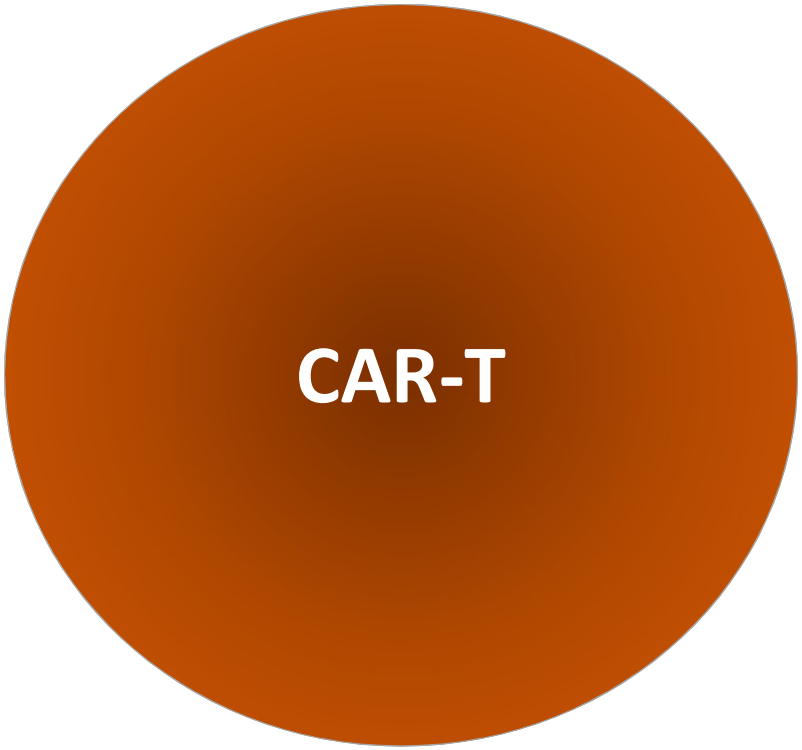
GMALL08 – Overall Survival



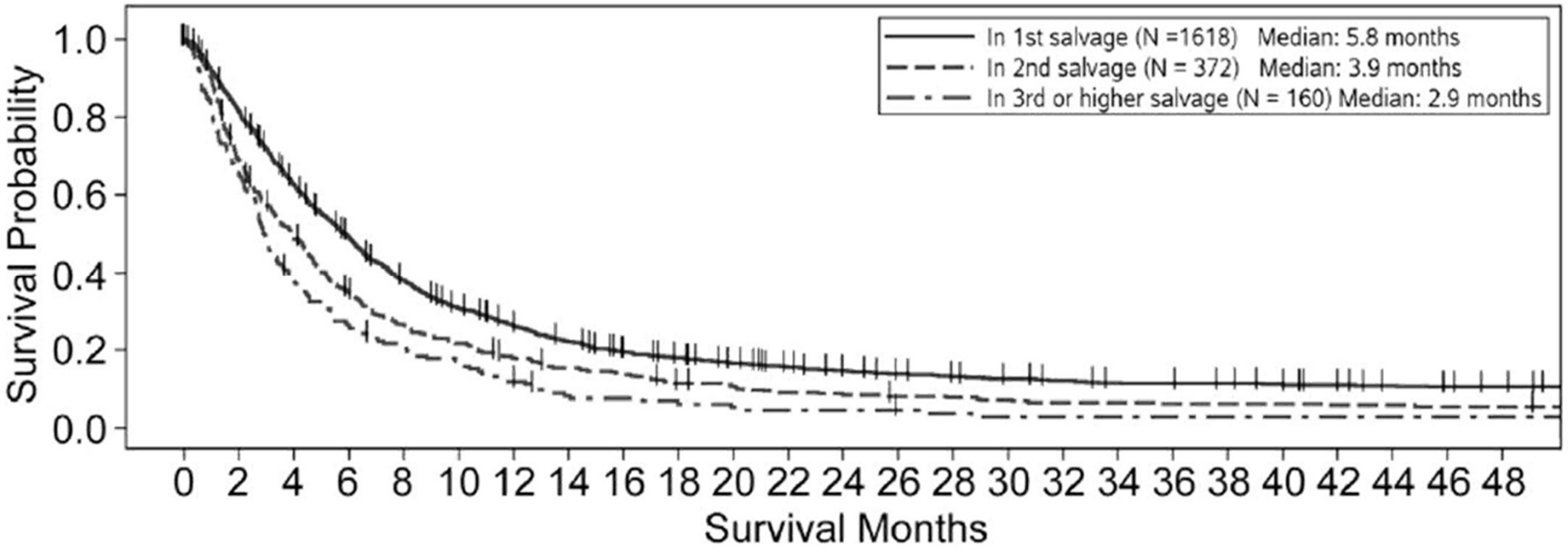
GMALL08

ALL
Verbesserung der Erstlinientherapie deutlich

- Sehr gute vorläufige Ergebnisse
- Pädiatrisch-basierter Therapiebackbone: bis 55 Jahre machbar
- MRD basierte Therapiestratifizierung: fast immer umgesetzt
- OS von molekularen Failure Patienten: besser als historische Daten
- AlloSCT: relevanter Therapieelement, aber stringentere Selektion
- Therapie in Studien essentiell!


CAR-T

Outcome und Therapieoptionen r/r adulte ALL



Gökbuget N *et al.* 2016

N=1706 adult pts Ph-neg r/r ALL
median OS 5.8 months

Salvage-Chemotherapie:	**CR: 18-45%**	**Medianes OS 3-9 Mo**
Blinatumomab:	**CR: 44%**	**Medianes OS 7.7 Mo**
Inotuzumab:	**CR: 80%**	**Medianes OS 7.7 Mo**

Metaanalyse CAR-T in r/r ALL

Anagnostau et al The Lancet 2020

35 Studien
953 Pts mit CAR-T behandelt
v.a. ped Patienten

80% CR Rate
72% MRD Negativität
1 Jahr PFS: 37%

Pitfalls
Kleine Fallzahlen
Überwiegend Kinder
Heterogene Settings
Kurzes follow-up

	Complete remission	Minimal residual disease negative	Overall survival at 1 year after anti-CD19 CAR T-cell infusion	Progression-free survival at 1 year after anti-CD19 CAR T-cell infusion	Cytokine release syndrome	Grade 3 or 4 cytokine release syndrome	Neurotoxicity	Grade 3 or worse neurotoxicity
Patients with available data	953	821	613	696	824	854	548	532
FMC63-derived anti-CD19 CAR T cells								
Yes (N=557)	78·5% (72·3–84·2)	73·1% (64·5–80·9)	61·0% (51·4–70·3)	35·8% (23·3–49·3)	81·3% (65·7–93·5)	28·7% (19·4–38·8)	31·1% (19·4–44·0)	13·0% (7·1–20·2)
No (N=257)	78·7% (66·0–89·4)	61·2% (41·5–79·4)	47·2% (28·9–65·8)	39·2% (24·9–54·4)	89·7% (78·5–97·6)	21·7% (7·4–39·9)	26·5% (14·3–40·6)	12·3% (0·0–35·5)
p value	0·95	0·24	0·19	0·71	0·31	0·48	0·63	1·00
T-cell origin								
Autologous (N=901)	82·6% (78·5–86·5)	74·1% (67·5–80·3)	59·0% (50·9–67·0)	37·2% (27·6–47·4)	85·9% (76·4–93·6)	25·6% (18·2–33·5)	33·2% (24·7–42·3)	15·1% (8·8–22·4)
Allogeneic (N=52)	55·3% (30·6–79·0)	49·5% (20·3–78·8)	49·6% (26·0–73·4)	36·5% (5·8–73·9)	53·9% (10·7–94·2)	37·0% (0·0–88·7)	3·1% (0·0–23·0)	0% (0·0–5·6)
p value	0·018	0·10	0·46	0·99	0·15	0·65	0·011	0·0032
Age group								
Adults (N=263)	75·3% (66·9–82·9)	61·0% (45·5–75·7)	48·5% (39–58·1)	28·3% (11·9–47·8)	79·2% (56·2–96·1)	29·1% (11·0–50·8)	15·3% (2·2–34·2)	10·4% (1·8–22·9)
Children (N=346)	80·5% (72·9–87·2)	74% (64·8–82·3)	61·7% (50·9–71·9)	46·3% (37·0–55·7)	86·5% (68·3–98·4)	23·1% (13·7–33·7)	43·0% (31·6–54·6)	14·7% (8·9–21·6)
p value	0·24	0·11	0·069	0·10	0·50	0·52	0·020	0·77
Anti-CD19 CAR T-cell construct								
4-1BB co-stimulated (N=527)	82·4% (76·2–87·9)	76·8% (69·3–83·6)	62·1% (53·1–70·8)	45·3% (37·1–53·6)	86·8% (76·3–94·9)	31·8% (21·1–43·3)	28·4% (21·1–36·2)	10·0% (5·0–16·0)
CD28 co-stimulated (N=273)	74·6% (66·0–82·5)	60·8% (52·5–68·8)	53·7% (45·3–62·0)	29·7% (12·3–50·4)	71·2% (38·4–96·1)	19·1% (8·2–32·4)	29·8% (6·5–59·1)	15·3% (4·8–29·2)
Third and fourth generation (N=153)	84·3% (74·1–92·7)	59·9% (24·9–90·8)	7·3% (0·0–36·6)	0% (0·0–18·5)	78·6% (70·9–85·6)	16·6% (6·9–28·7)	25·0% (4·6–69·9)	25·0% (4·6–69·9)
p value	0·14	0·0094	0·0030	0·0018	0·25	0·19	0·98	0·43
Risk of bias								
Low (N=489)	82·2% (76·7–87·2)	76·1% (68·2–83·2)	64·8% (57·3–71·9)	47·9% (40·9–54·9)	86·3% (75·7–94·5)	26·7% (16·5–38·3)	33·4% (23·1–44·4)	14·2% (7·1–22·9)
Moderate (N=464)	77·3% (68·6–85·1)	65·9% (53·9–77·3)	39·4% (25·0–54·6)	15·1% (3·6–31·0)	75·2% (55·9–91·0)	25·3% (14·7–37·5)	20·3% (8·7–34·4)	9·4% (1·0–22·4)
p value	0·21	0·13	0·0028	0·0004	0·19	0·98	0·20	0·77

ZUMA-3: KTE-X19 in adulter r/r ALL (EHA/ASCO 2021)

Phase 2 Results of the ZUMA-3 Study Evaluating KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy, in Adult Patients With Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

Bijal D. Shah, MD[1]; Armin Ghobadi, MD[2]; Olalekan O. Oluwole, MD, MPH, MBBS[3]; Aaron C. Logan, MD, PhD[4]; Nicolas Boissel, MD, PhD[5]; Ryan D. Cassaday, MD[6]; Edouard Forcade, MD, PhD[7]; Michael R. Bishop, MD[8]; Max S. Topp, MD[9]; Dimitrios Tzachanis, MD, PhD[10]; Kristen M. O'Dwyer, MD[11]; Martha L. Arellano, MD[12]; Yi Lin, MD, PhD[13]; Maria R. Baer, MD[14]; Gary J. Schiller, MD[15]; Jinghui Dong, PhD[16]; Tong Shen, PhD[16]; Francesca Milletti, PhD[16]; Behzad Kharabi Masouleh, MD[16]; Roch Houot, MD, PhD[17]

- **Ca. 40%–50% der erwachsenen Patienten mit BCP-ALL rezidivieren**
- **KTE-X19: autologes anti-CD19 CAR T-Zell Produkt – zugelassen für die Therapie des R/R MCL**
- **ZUMA-3: Phase 1/2, international, multicenter study, adult only!**
  Phase 1: overall CR/CRi Rate 83%, empfohlene Phase 2 Dosis: 1×10^6 CAR T cells/kg

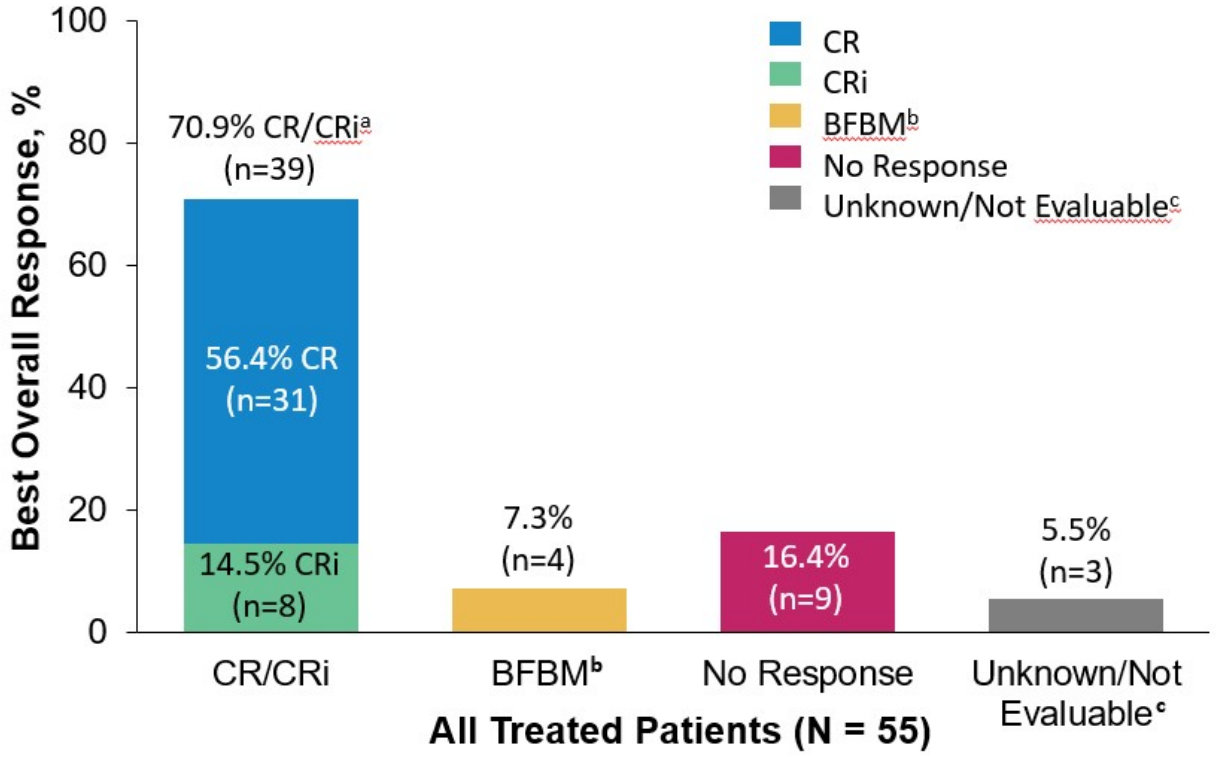
Shaha et al, Lancet 2021

ZUMA-3: KTE-X19 in adulter r/r ALL

- median follow-up for all treated patients:
  16.4 months (range, 10.3–22.1)
- KTE-X19 was successfully manufactured:
  in 65/71 of enrolled pts (**92%**)
  in 55/71 treated pts (**77%**)
- median time from leukapheresis to KTE-X19 release:
  13 days for US pts and 14.5 days for European pts

Characteristics	N=55
Age, median (range), years	40 (19–84)
Male, n (%)	33 (60)
ECOG PS of 1, n (%)	39 (71)
Philadelphia chromosome-positive, n (%)	15 (27)
CNS-1 disease at baseline, n (%)[a]	55 (100)
Number of prior therapies, median (range)	2 (1–8)
≥3 prior lines of therapy, n (%)	26 (47)
Prior blinatumomab, n (%)	25 (45)
Prior inotuzumab ozogamicin, n (%)	12 (22)
Prior alloSCT, n (%)	23 (42)
Relapsed/refractory subgroup, n (%)	
Primary refractory	18 (33)
Relapsed/refractory to ≥2 prior systemic therapy lines	43 (78)
First relapse with remission ≤12 months	16 (29)
Relapsed/refractory post-SCT[b]	24 (44)
BM blasts at screening, median (range), %	65.0 (5–100)
BM blasts at preconditioning after bridging chemotherapy, median (range), %[c]	59.0 (0–98)

ZUMA-3: A CR/CRi Rate of 70.9% and CR Rate of 56.4% by Central Assessment Was Observed, Meeting Primary Endpoint



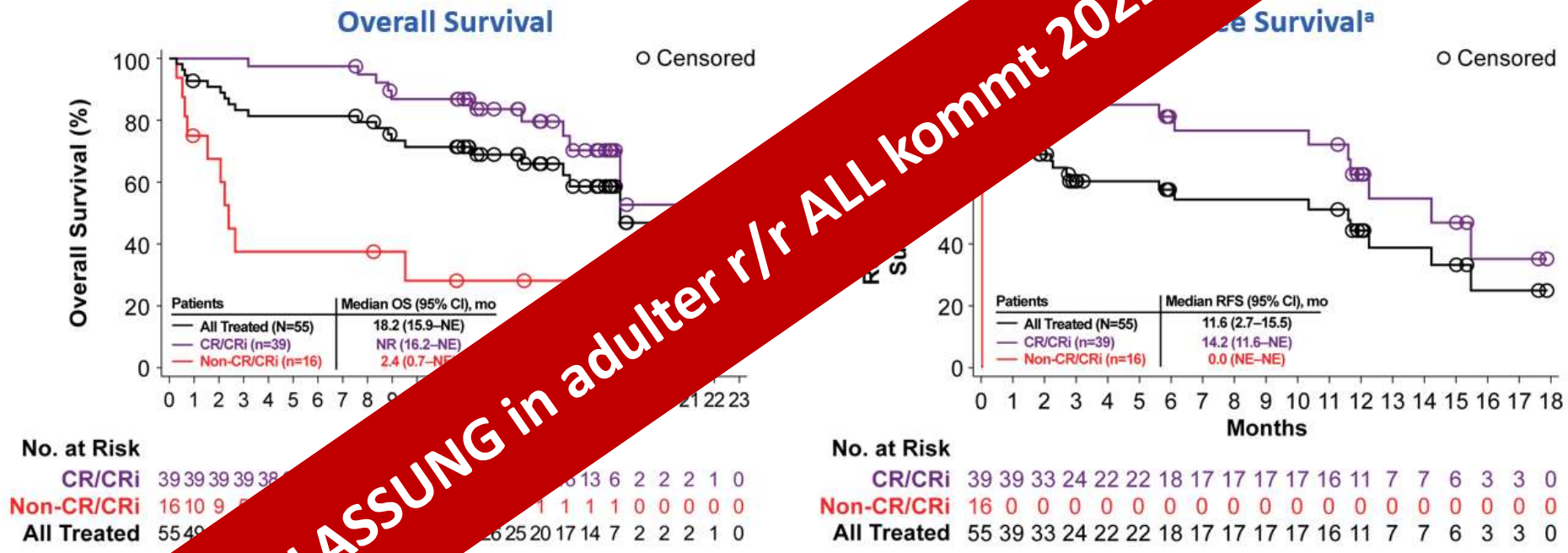
- The median time to initial CR/CRi was 1.1 months (range, 0.85–2.99)
- The MRD-negativity rate was 97% in responders, with samples unavailable for 1 patient
- Ten patients (18%), including 9 with CR/CRi and 1 with BFBM, received alloSCT at a median 98 days (range, 60–207) post–KTE-X19 infusion

ZUMA-3: CRS and Neurologic Events

Parameter	N=55
CRS	
Any grade CRS, n (%)[a,b]	49 (89)
Grade ≥3	13 (24)
Most common any grade symptoms, n (%)[c]	
Pyrexia	46 (94)
Hypotension	33 (67)
Median time to onset (range), days	5
Median duration of events, days	7.5
Neurologic Events	
Any grade neurologic event, n (%)[b]	33 (60)
Grade ≥3	14 (25)
Most common any grade symptoms, n (%)	
Tremor	15 (27)
Confusional state	14 (25)
Median time to onset (range), days	9
Median duration of events, days	7

- No Grade 5 CRS occurred
- One patient had Grade 5 brain herniation related to KTE-X19
- Tocilizumab, steroids, and vasopressors were given to 80%, 75%, and 40% of patients, respectively

ZUMA-3: Median OS Was 18.2 Months and Me…n RFS Was 11.6 Months



ZULASSUNG in adulter r/r ALL kommt 2022!

- Among p…, median OS was not reached and median RFS[a] was 14.2 months

RFS 11.6 Mont…
(with / without SCT censoring)
23% went on to SCT

Salvage-Chemotherapie:	**CR: 18-45%**	**Medianes OS 3-9 Mo**
Blinatumomab:	**CR: 44%**	**Medianes OS 7.7 Mo**
Inotuzumab:	**CR: 80%**	**Medianes OS 7.7 Mo**

ASH 2021
3844

The Comparison of KTE-X19 to Current Standards of Care: A Prespecified Synthetic Control Study Utilizing Individual Patient-Level Data from Historic Clinical Trials (SCHOLAR-3)

Bijal Shah[1], Imi Faghmous[2,3], Jim Whitmore[2], Behzad Kharabi Masouleh[2], and Hairong Xu[2]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Kite, a Gilead Company, Santa Monica, CA, USA; and [3]Universty of Maastricht Holland, Maastricht, Netherlands

SCHOLAR-3

Synthetic control anaylsis (SCA)
Vergleich zu historischen Patientenkohorten zum Vergleich der ZUMA-3 Daten

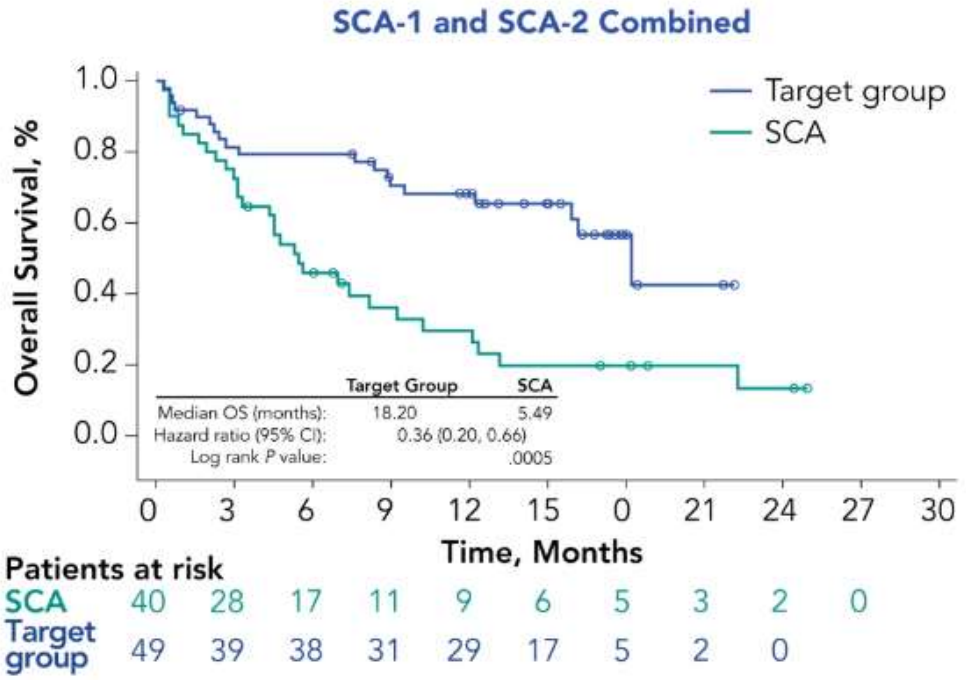
External control arms for primary analysis

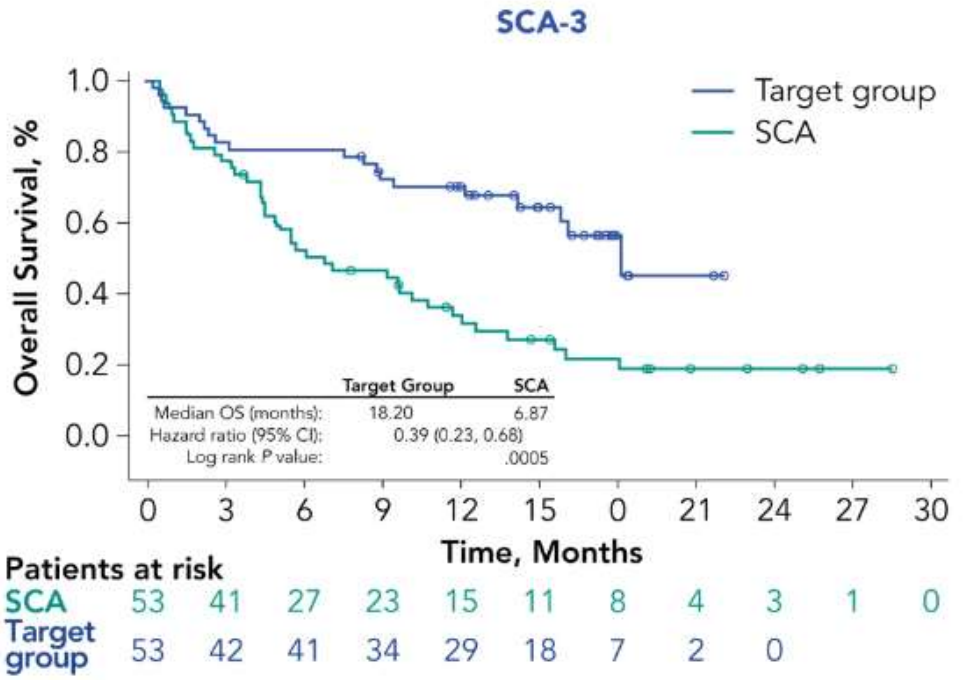
- SCA-1: External arm 1 consisted of matched patients who had previously been naive to blinatumomab and inotuzumab therapy
- SCA-2: External arm 2 consisted of matched patients who had previously failed treatment with blinatumomab and/or inotuzumab therapy

External control arm for sensitivity analysis

- SCA-3: External arm 3 consisted of patients who had previously been naive to blinatumomab and inotuzumab therapy matched to all ZUMA-3 patients (irrespective of whether patients were pretreated with blinatumomab or inotuzumab)
- The rationale for this analysis was to compare ZUMA-3 patients to a less heavily pretreated population

OS of All Matched Patients of SCA-1 and SCA-2 Combined and SCA-3





Cave: keine randomisierte Studie; kleine Fallzahlen

Deutlicher Benefit für CAR-T Therapie

Rolle SCT nicht adressiert

Bahnbrechendes ASH 2021

Studienregister
UCCSH - QuickQueck
https://www.quickqueck.de
https://www.uksh.de/uccsh

AML alloSCT

AlloSCT
in 1. CR
Nicht unbedingt

BLIVEN
IIT Studie
chemofree
In MRD + r/r ALL
Blina + Venetoclax

AML CPX -> MRD -> SCT

Sehr gute Daten!

ALL ED

ALL
Verbesserung der
Erstlinientherapie
Ja!

adulte r/r ALL

Zulassung für
CAR-T


Vielen Dank für die Aufmerksamkeit