Aktuelle Therapie der Akuten Myeloischen Leukämie

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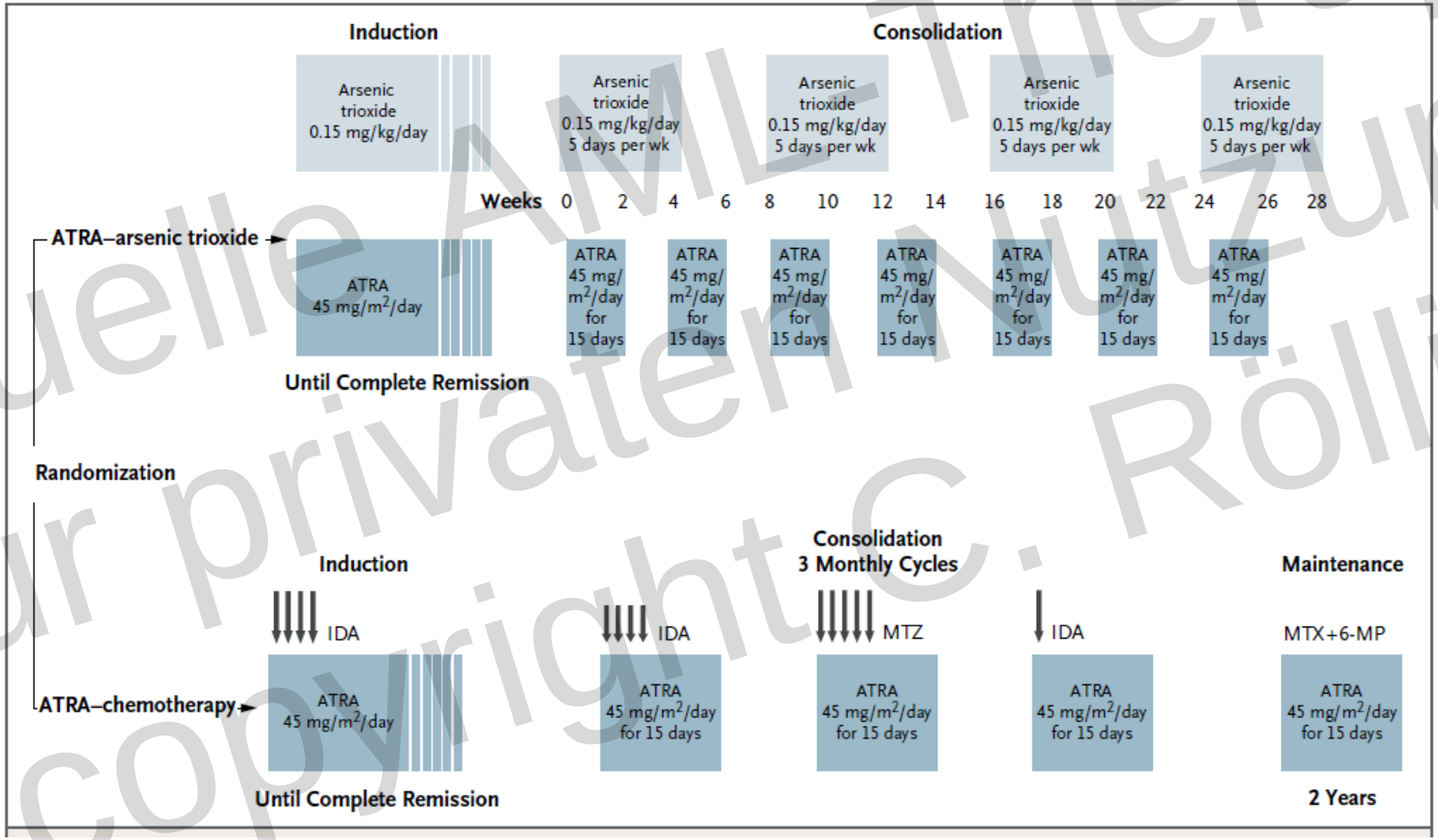
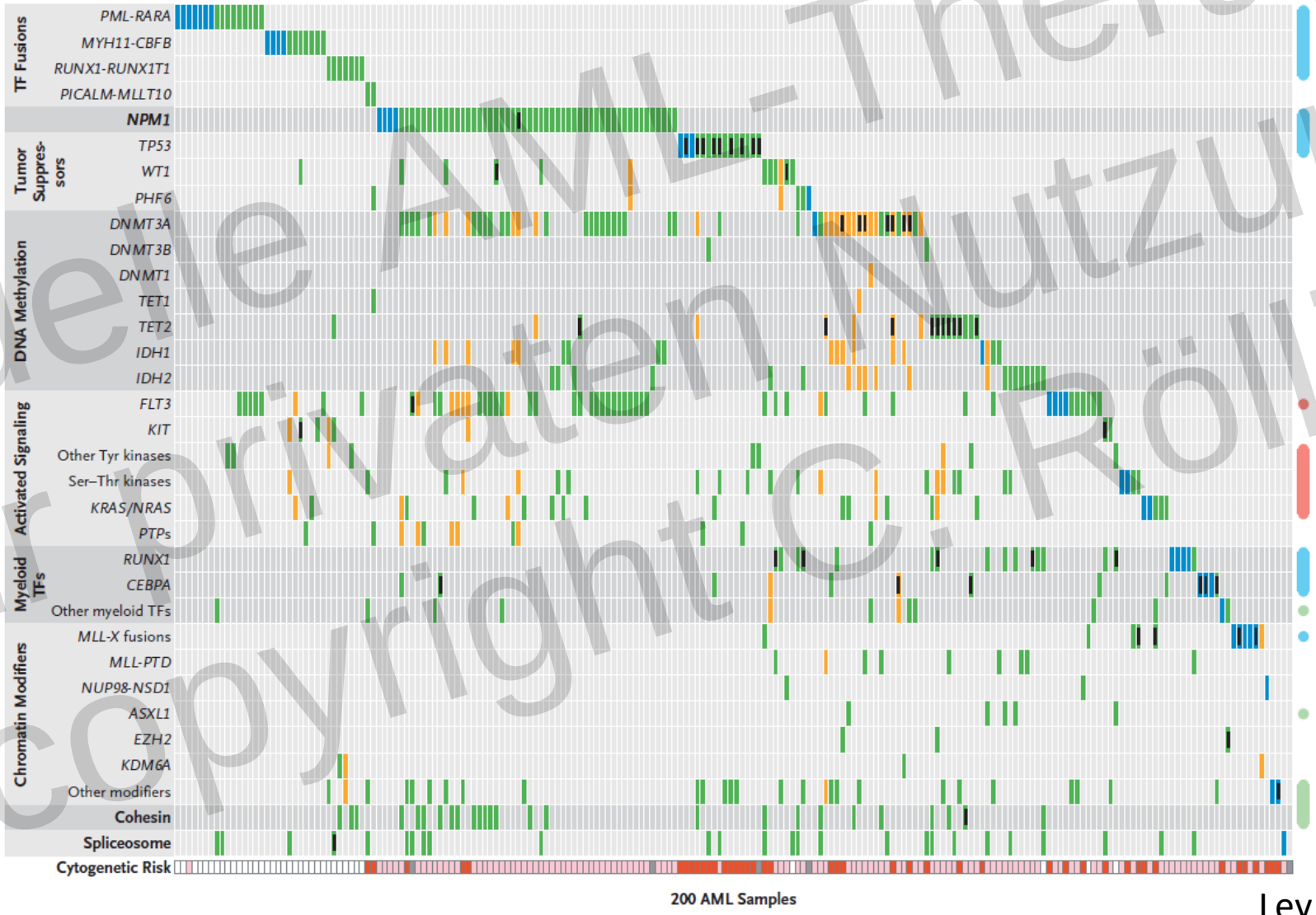
Therapie APL (M3)



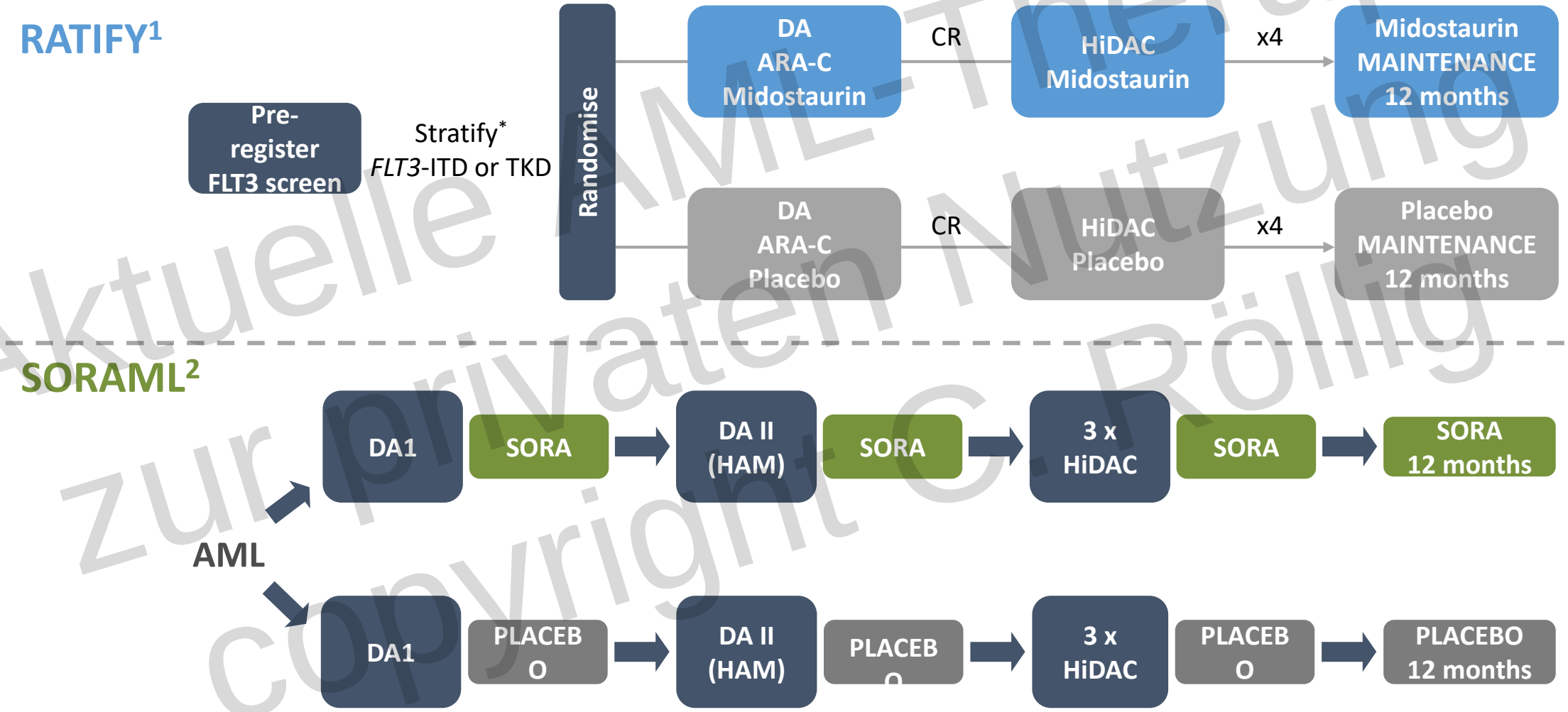
Lo Coco et al., NEJM 2013

AML ≠ AML



Ley et al., NEJM 2013

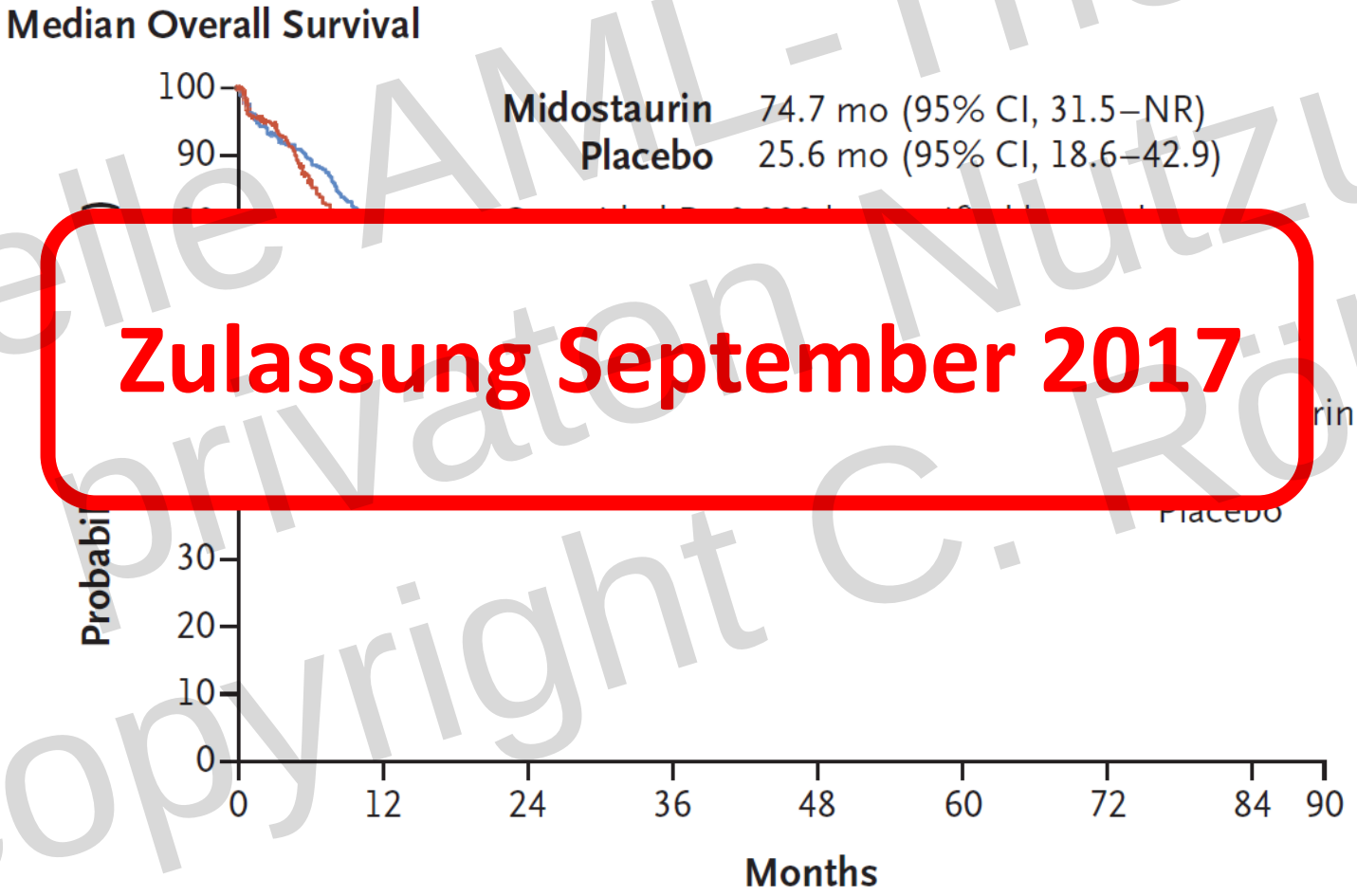
TKIs der 1. Generation in Kombination mit Chemo



1. Stone RM, et al. N Engl J Med 2017;377:454–64; 2. Röllig C, et al. Blood 2017;130:721

ARA-C, cytarabine; DA, daunorubicin; HAM, high-dose cytarabine and mitoxantrone; HiDAC, high-dose cytarabine; SORA, sorafinib

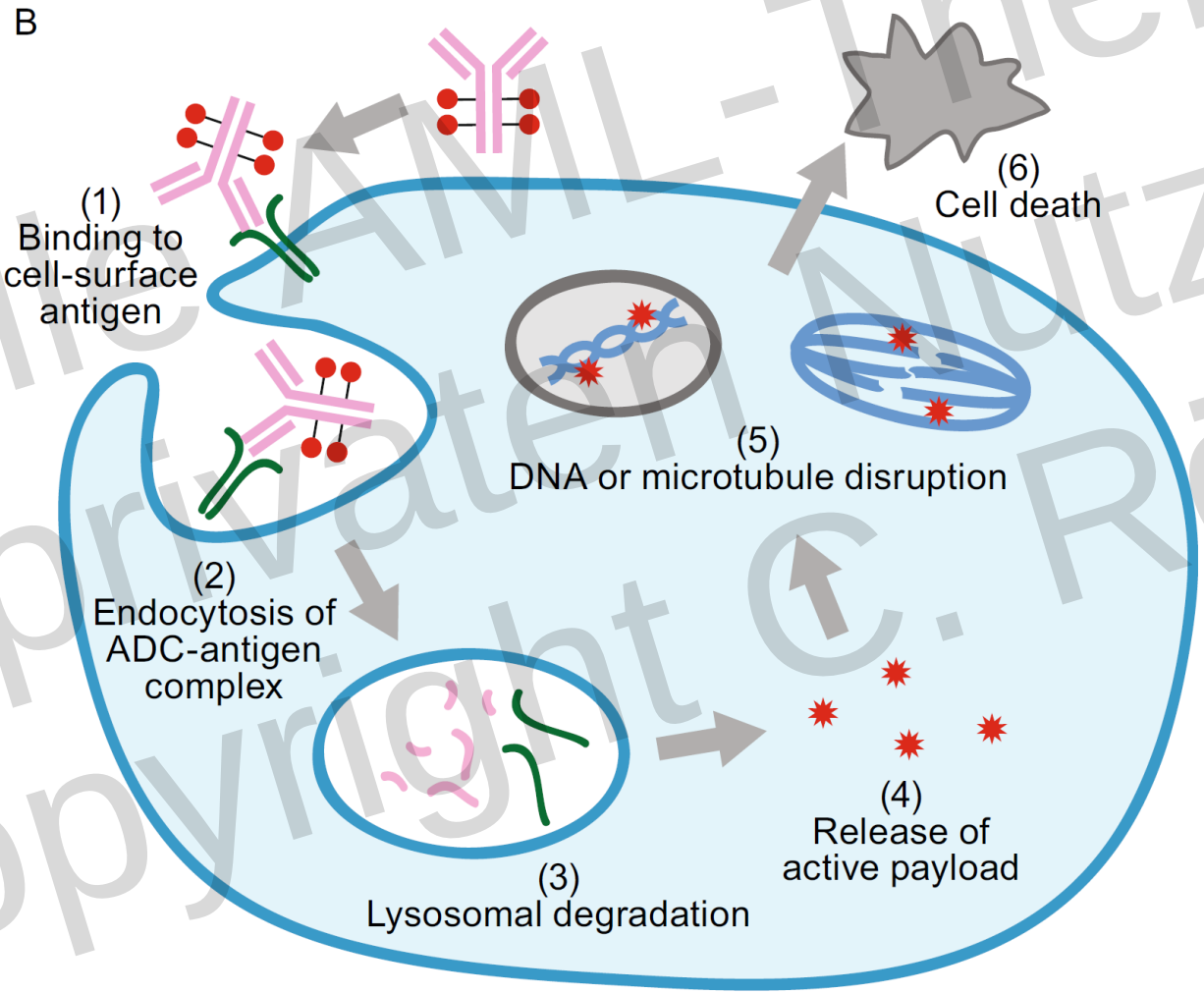
Signifikante Überlebensverlängerung mit Midostaurin (RATIFY trial)



Zulassung September 2017

Stone et al., NEJM 2017

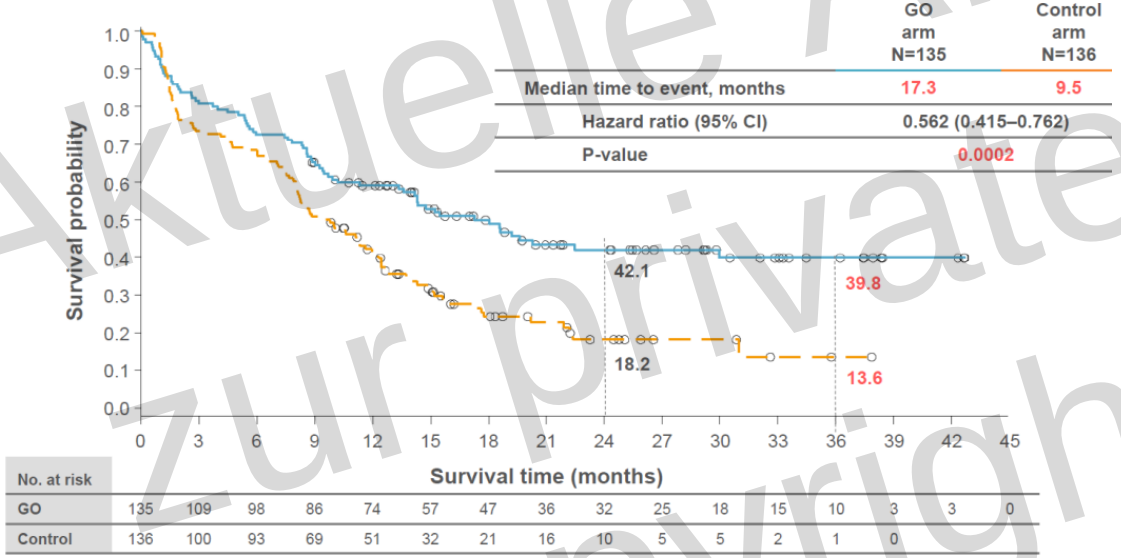
Konjugierter CD33 Antikörper: Gemtuzumab Ozogamicin



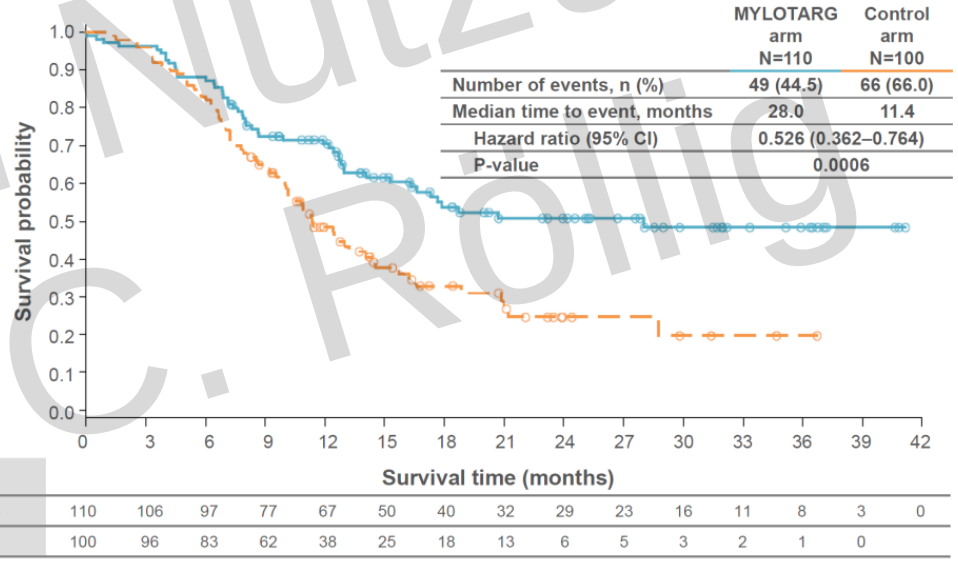
Tsuchikama & An, Prot Cel 2016

Gemtuzumab Ozogamicin plus Chemotherapie verlängert EFS und RFS bei AML

EFS



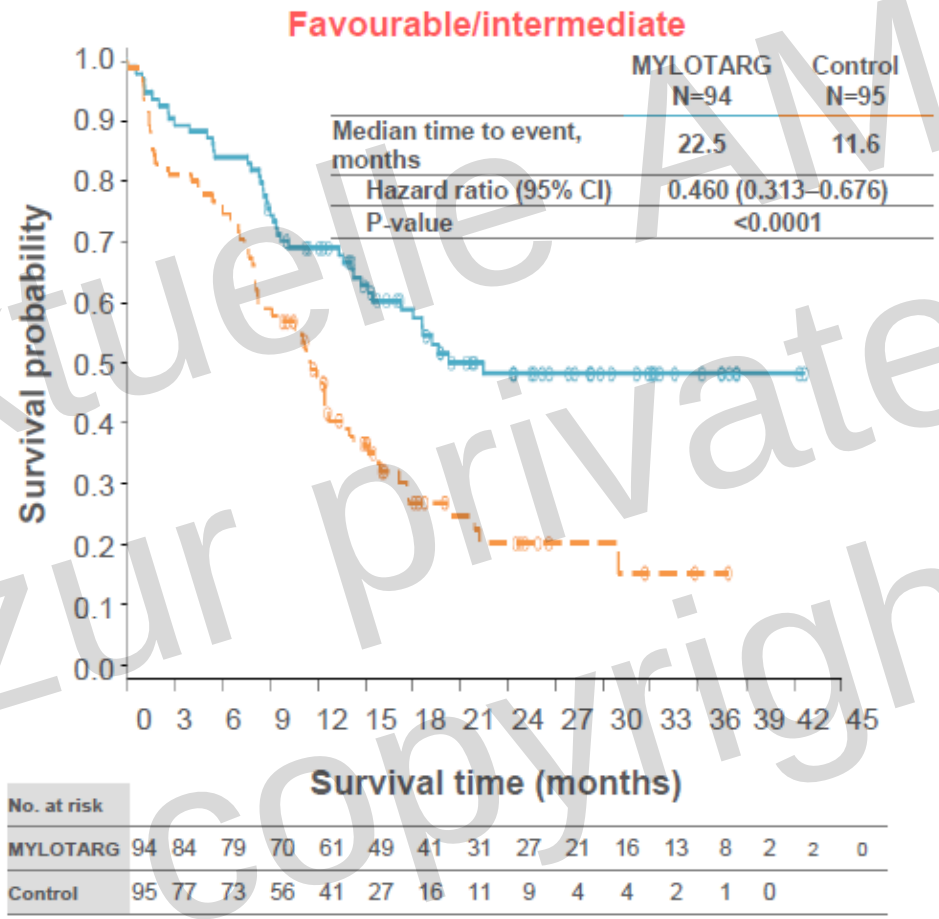
RFS

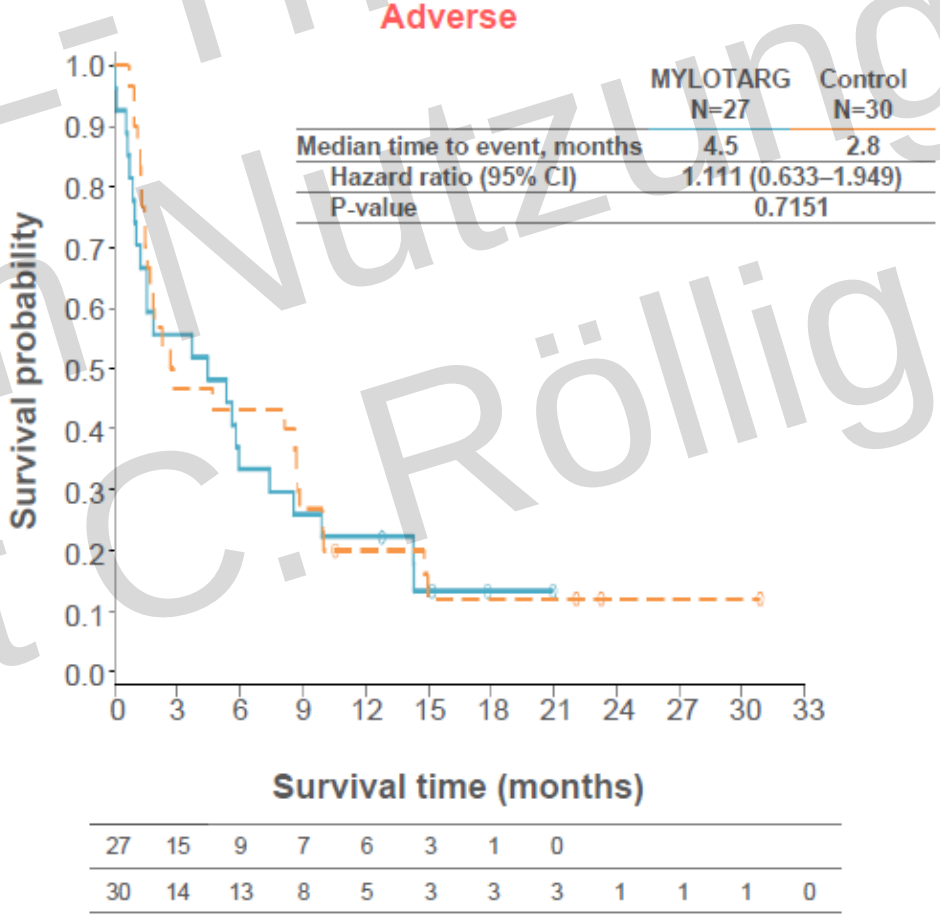


Lambert et al., *Haematologica 2018*

Patienten mit ungünstigem Risiko profitieren nicht

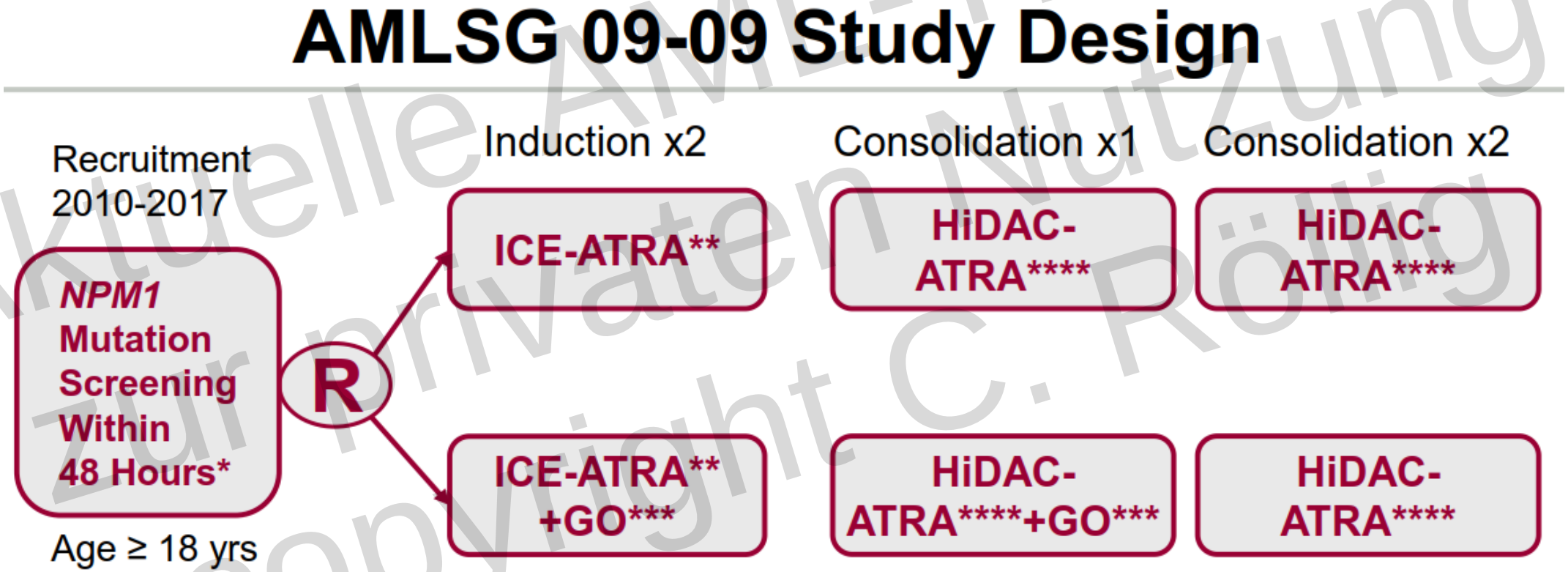
(EFS in ALFA-0701)





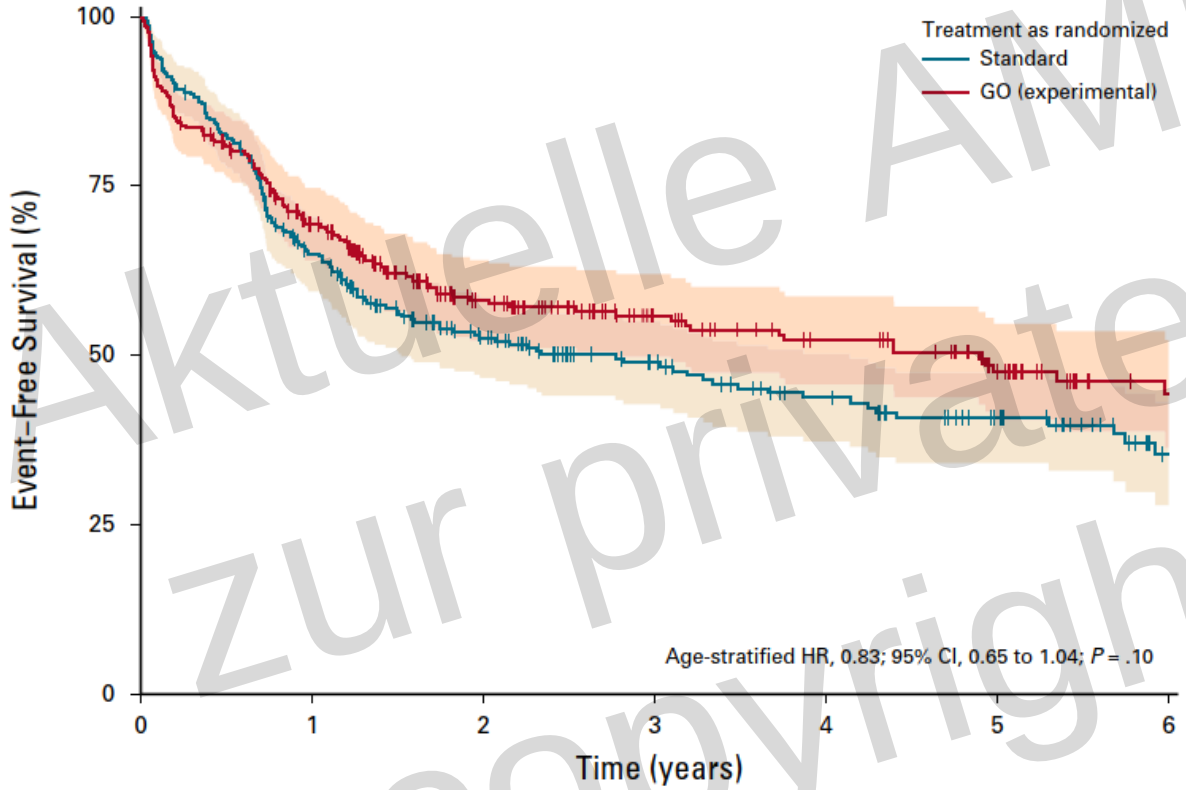
Lambert et al., *Haematologica 2018*

GO bei NPM1-mutierter AML

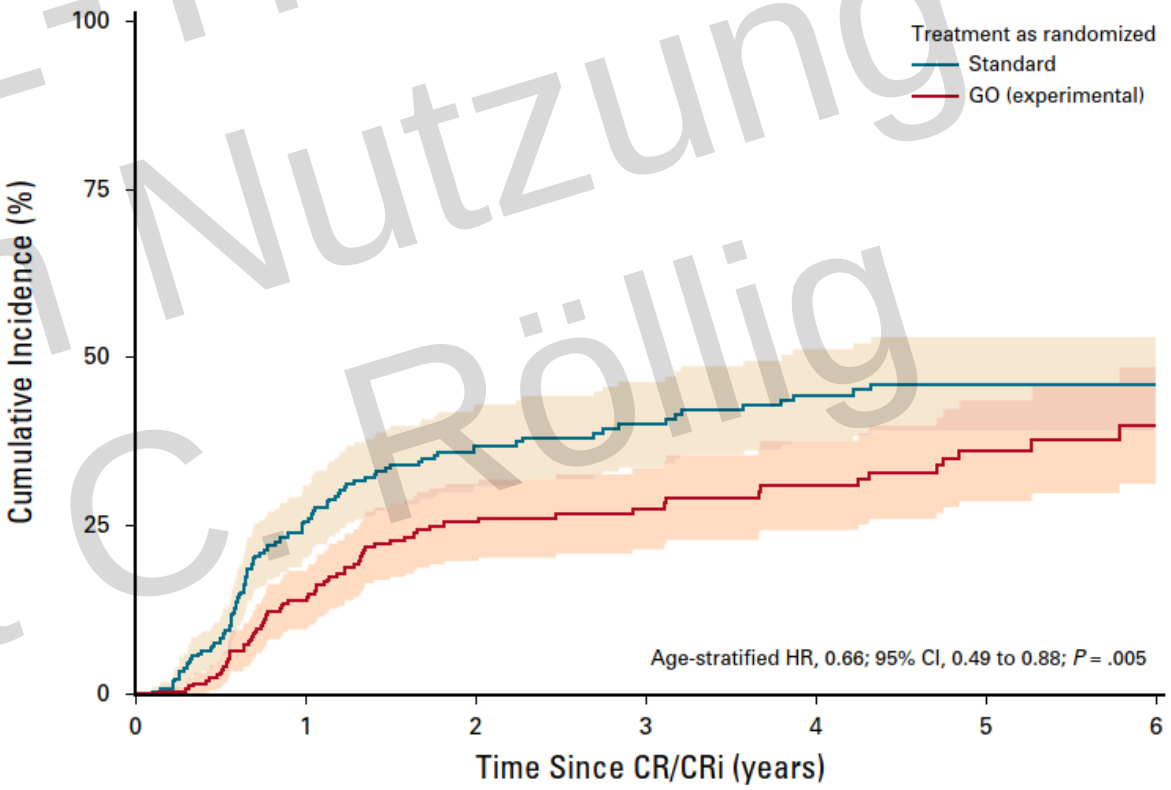


Schlenk et al., J Clin Oncol 2019

ICE plus GO:
mehr Frühtodesfälle, weniger Rezidive



Treatment as randomized							
Standard	296	179	113	81	62	45	21
GO (experimental)	292	185	117	81	64	47	24



Treatment as randomized							
Standard	269	171	107	75	58	42	20
GO (experimental)	254	180	114	80	64	39	22

Schlenk et al., J Clin Oncol 2019

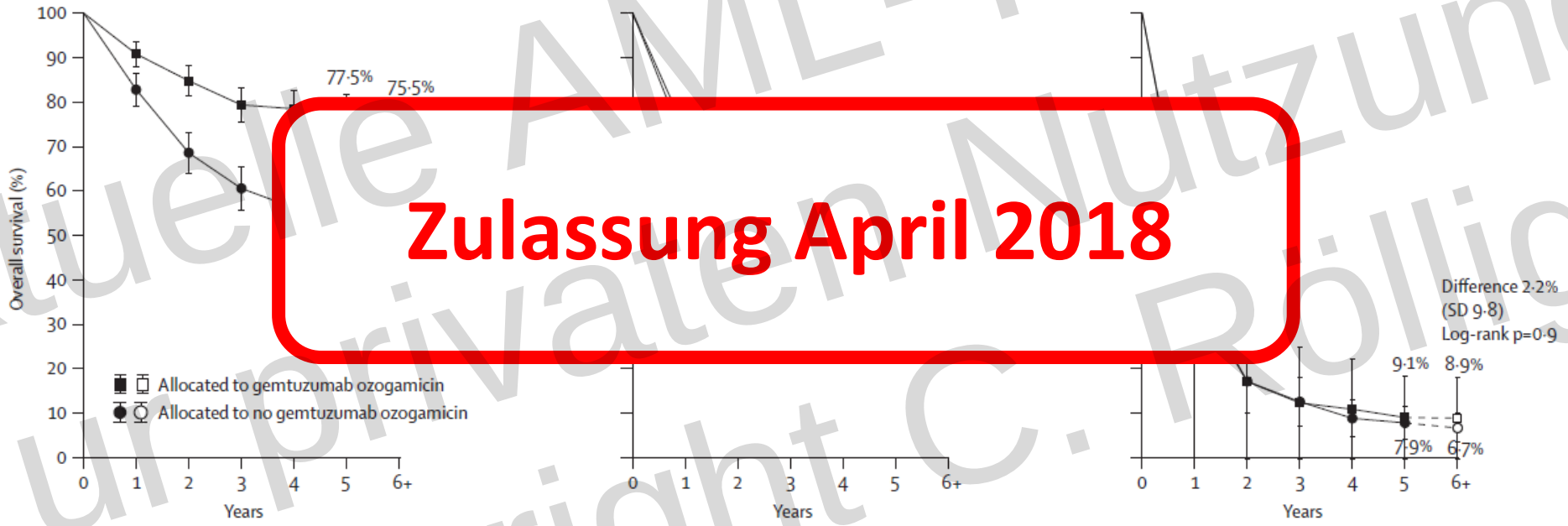
Frühtodesfälle v.a. bei älteren Patienten vermehrt
Cave: Kombination mit ICE!

Response to Induction Therapy

	Standard n=295 n (%)	GO-Experimental n=291 n (%)	p-value
CR	163 (55.2)	134 (46.0)	
CRi	99 (33.6)	107 (39.5)	
CR/CRi	262 (88.8)	249 (85.5)	0.28
Refractory Disease	16 (5.4)	12 (4.1)	0.56
Death	17 (5.7)	30 (10.3)	0.06
≤60yrs	6/165 (3.6)	11/160 (6.9)	
60-70yrs	9/81 (11.1)	9/83 (10.8)	
>70yrs	2/50 (4.0)	10/49 (20.4)	

Schlenk et al., J Clin Oncol 2019

Meta-Analyse über 5 randomisierte Studien (ohne AML-SG 09-09):
Gemtuzumab Ozogamicin plus Chemotherapie verlängert das Überleben bei AML mit Günstig- und Intermedär-Risiko



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

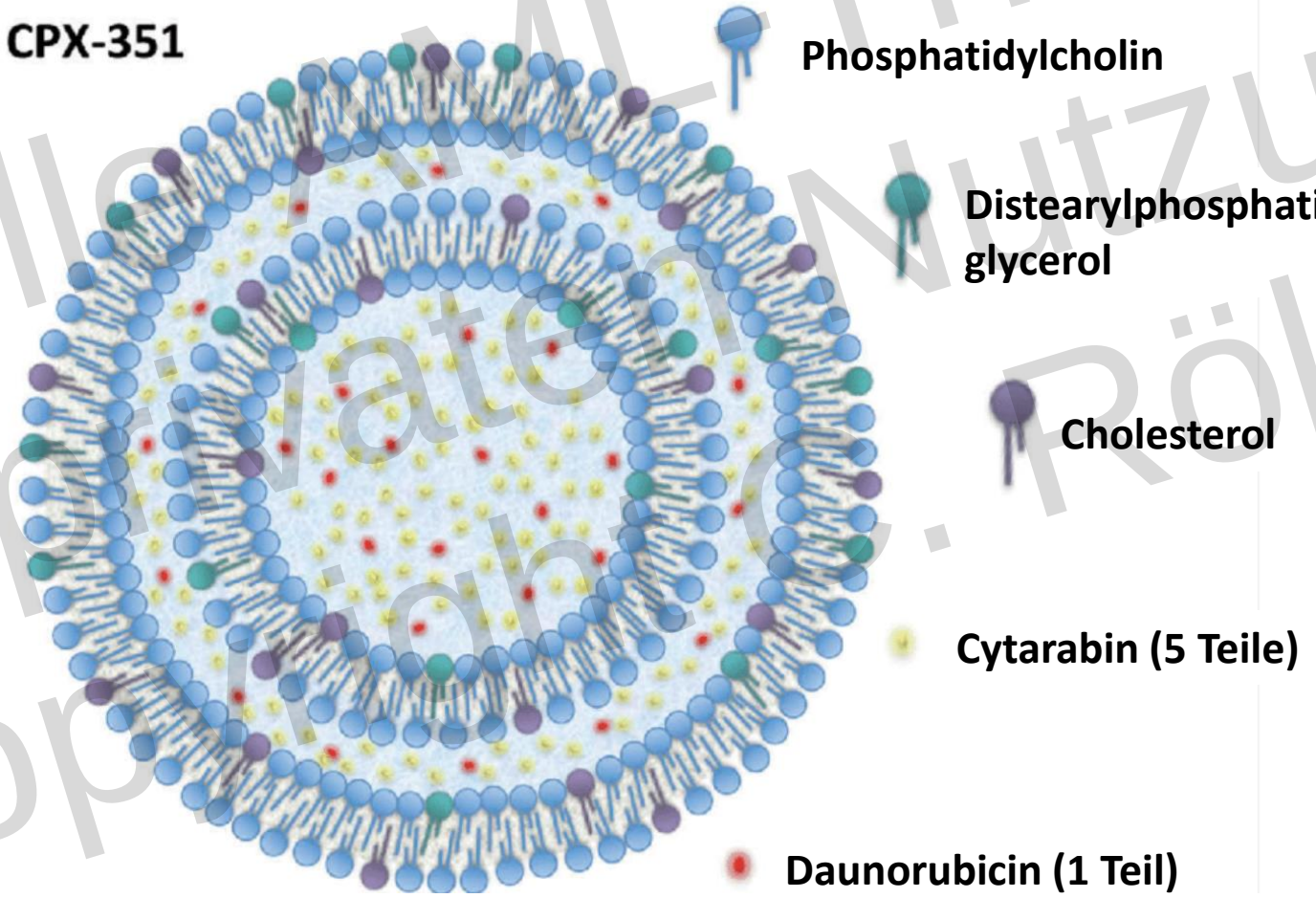
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

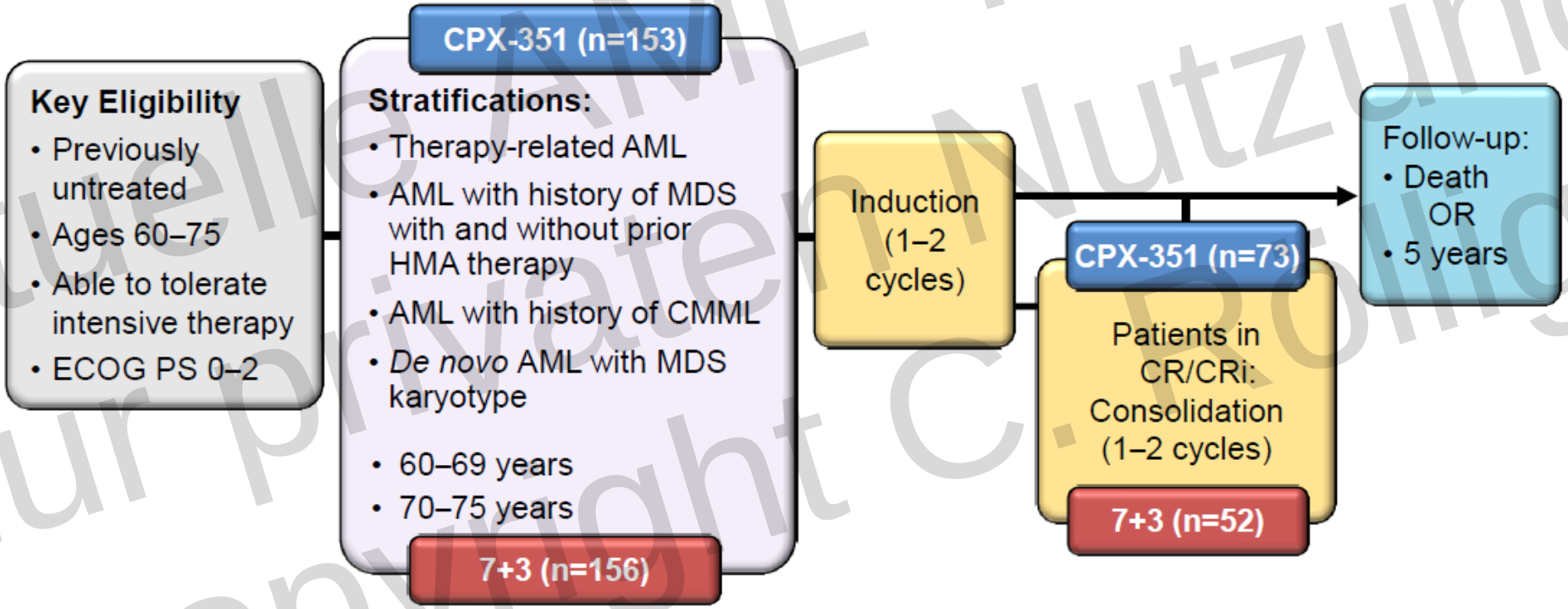
Zulassung April 2018

Hills et al., *Lancet Oncol* 2014

Liposomale Formulierung von Cytarabin (5 mol) und Daunorubicin (1 mol): CPX-351

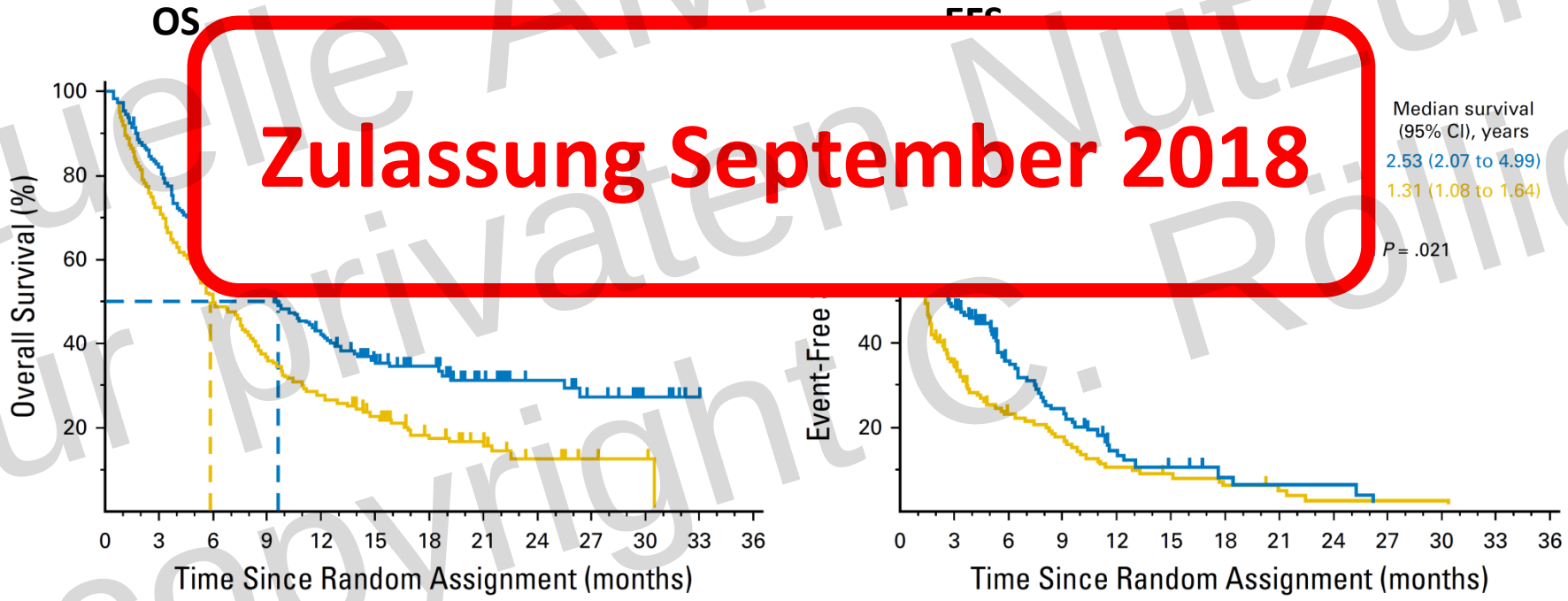


CPX-351 versus Standard 7+3 Chemo: Studiendesign



Lancet et al., *J Clin Oncol 2018*

Signifikant längeres Überleben gegenüber Standard-Chemotherapie bei tAML, sAML, AML-MDS >60 J



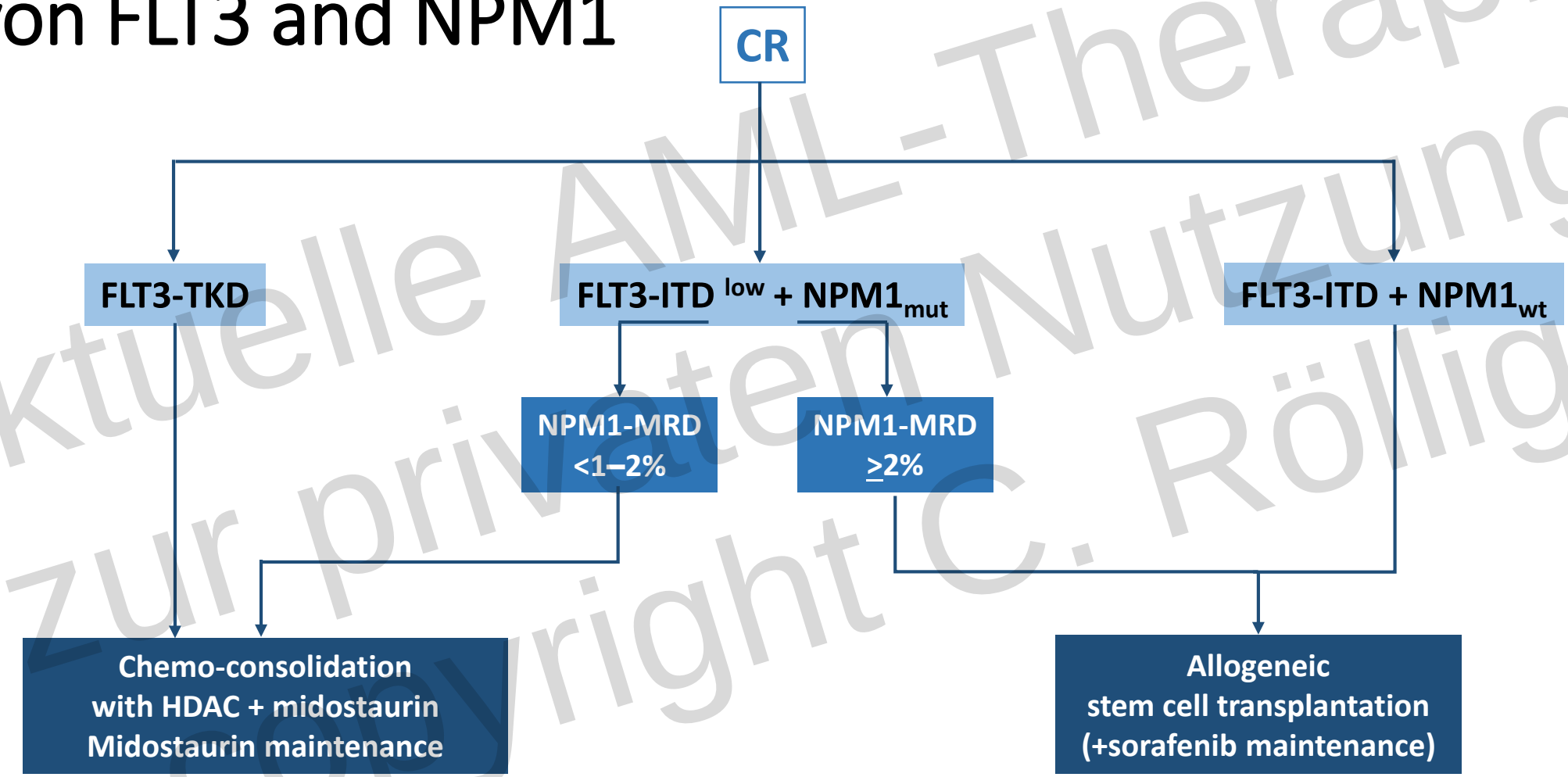
Lancet et al., *J Clin Oncol 2018*

Die genetische Risikogruppe bestimmt die 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	• 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	• 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*

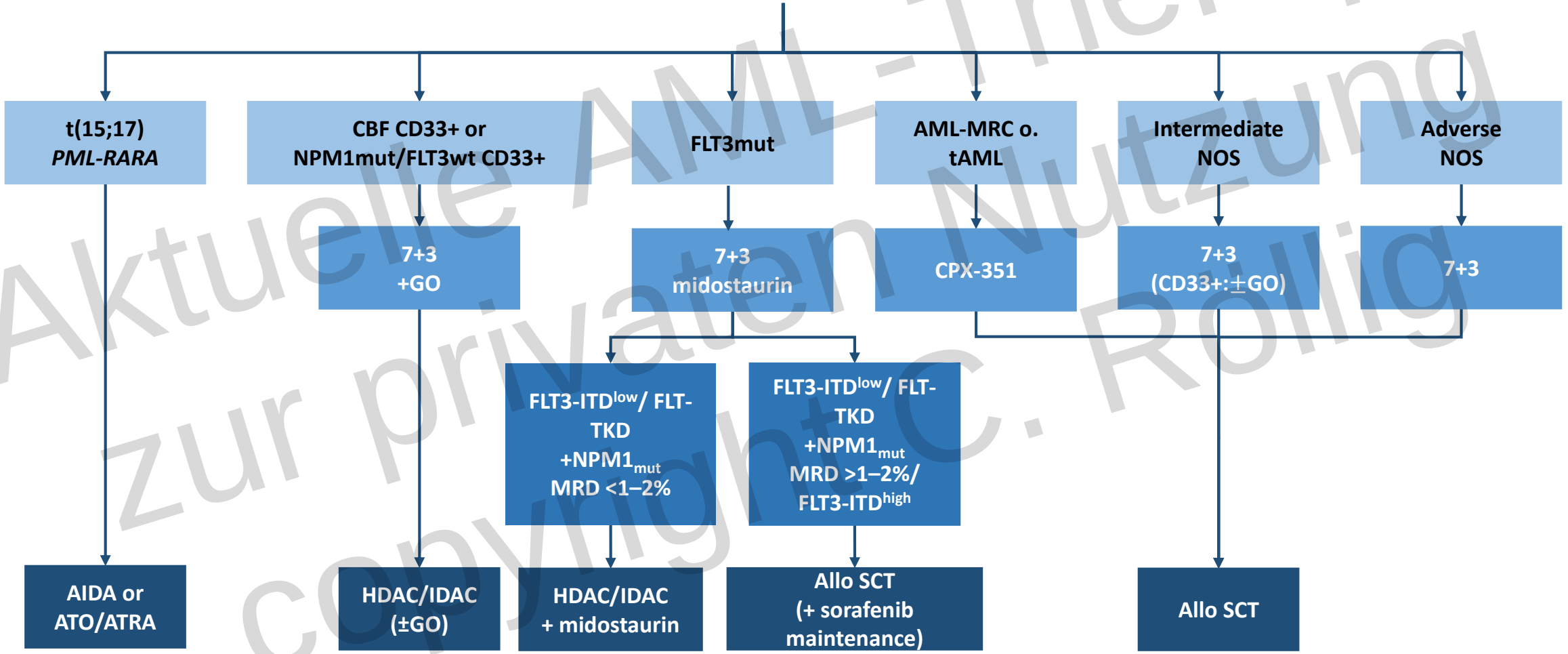
Röllig et al., Onkopedia-LL AML 2019

Wahl der Postremissionstherapie in Abhängigkeit von FLT3 and NPM1



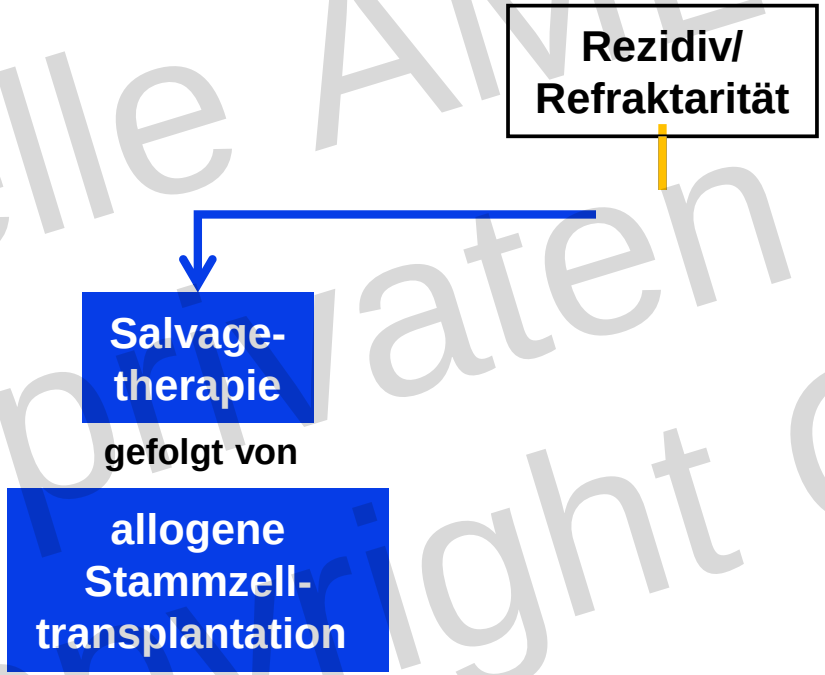
Röllig et al., Onkopedia-LL AML 2019

Therapie-Stratifikation bei fitten AML-Patienten



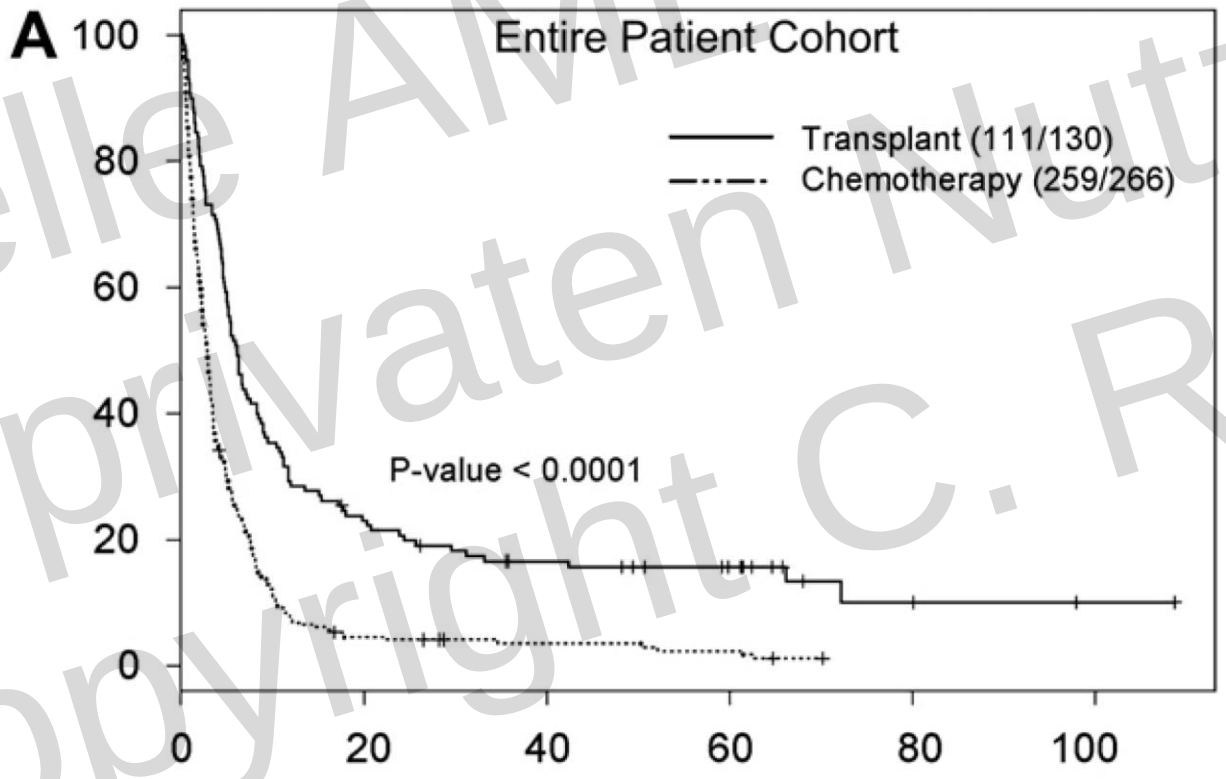
Röllig et al., Onkopedia-LL AML 2019

Intensive Therapie



Onkopedia-Leitlinie AML 2019

Keine Heilung ohne allogene SZT



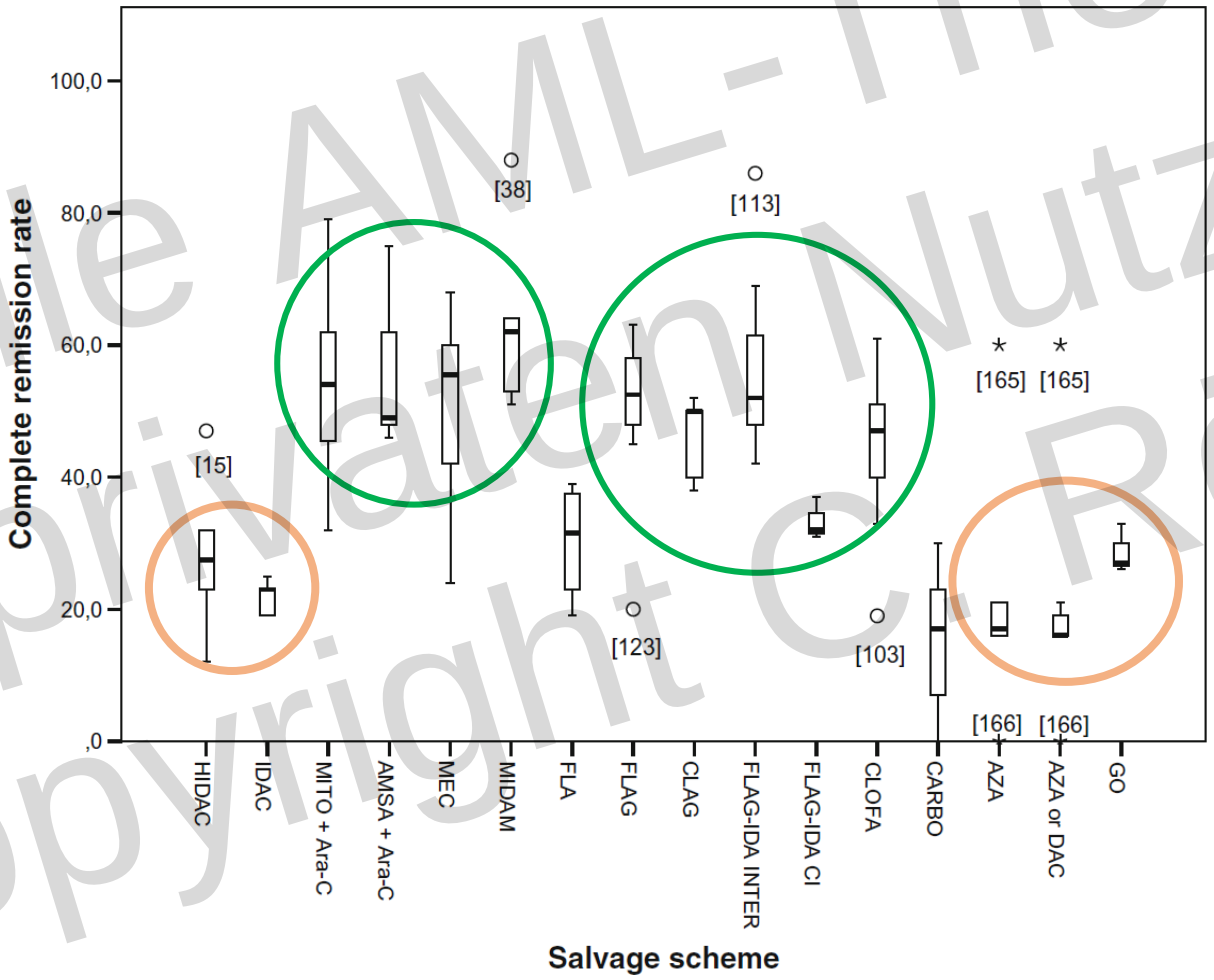
Armistead et al., BBMT 2009

Rezidiv-Therapien: Eine Menge Kombinationen, aber keine direkten Vergleiche.
Cytarabin ist ein Muss…

Reference	Study design	Regimens	Number of patients	Refractory/ relapsed	Median age (y)	% CR
51	Phase 2	HiDAC vs HiDAC + DXR or DNR	78	42/36	37	63 vs 65 (REF: 20 vs 56)
52	Phase 2	MTZ, etoposide	61	21/20	47	43
53	Phase 2	MTZ, etoposide, IDAC (MEC)	32	18/14	24	66
54	Phase 2	MTZ, etoposide, IDAC (MEC)	74	0/30	37	55
55	Phase 2	IDAC + IDA + etoposide	97	36/61	37	43 (REF: 29)
56	Phase 3, randomized	MTZ, etoposide, AraC + G-CSF vs MTZ, etoposide, AraC	50	6/44	43 vs 47	54 vs 42
57	Phase 3, randomized	HiDAC vs HiDAC + etoposide	131	n.g.	n.g.	31 vs 38
46	Phase 2	Etoposide, MTZ, AraC (EMA)	133	22/111	43	60 (REF: 44; REL: 76)
47	Phase 3, randomized	HiDAC + MTZ vs IDAC + MTZ	186	27/159	50	47 (REF <60 y: 46 vs 26)
58	Phase 3, randomized	HiDAC vs HiDAC + MTZ	162	56/106	48 vs 53	32 vs 44
59	Phase 3, randomized	Etoposide, MTZ, AraC (EMA) + GM-CSF vs EMA	192	120/72	47 vs 46	65 vs 59 REF: 51 vs 46; REL: 89 vs 81
45	Phase 2	FLAG-IDA	46	10/36	41	52
60	Phase 2	Cladribine, HiDAC, MTZ	118	78/40	45	58 (REF:51; REL: 54)
61	Phase 2	FLAG-IDA ± GO	71	10/61	48	29 (+GO) vs 39 (−GO) (ORR 56 vs 52)
62	Phase 2, randomized	IDAC + GO vs IDAC + liposomal DNR vs AraC, CTX, topotecan	82	29/53	60 vs 52 vs 53	12 vs 7 vs 4
63	Phase 1/2	HiDAC + clofarabine + G-CSF	50 (46 eval.)	18/32	53	46 (ORR 61) (REL: 32; REF: 67)
64	Phase 2	IDAC + clofarabine	47	20/27	51	51 (REF: 45)
65	Phase 2	BIDFA ± GO	93	n.g.	62	23 (ORR: 27)
48	Phase 3, randomized	IDAC + clofarabine vs IDAC	326	171/148	67	35 vs 18 (ORR: 47 vs 23) REF: 46 vs 23; REL: 49 vs 23
66	Phase 2	Homoharringtonine, AraC, aclarubicine	46	11/35	37	80 (REF: 67; REL: 96)
67	Phase 3, randomized	SHAI vs SHAI + fludarabine IDAC + GO vs IDAC + liposomal DNR vs AraC, CTX, topotecan	326	n.g.	57 vs 52	35 vs 44 (ORR: 42 vs 54)
62	Phase 2, randomized					
28	Phase 2	Fludarabine, HiDAC, liposomal DNR MTZ, etoposide	41	11/30	60	0 vs 73
49	Phase 3, randomized	Elacytarabine vs others	381	140/241	59 vs 60	15 vs 12 (ORR: 23 vs 21)
50	Phase 2	CPX-351 vs first salvage therapy	125	125	52 vs 56	37.0 vs 31.8

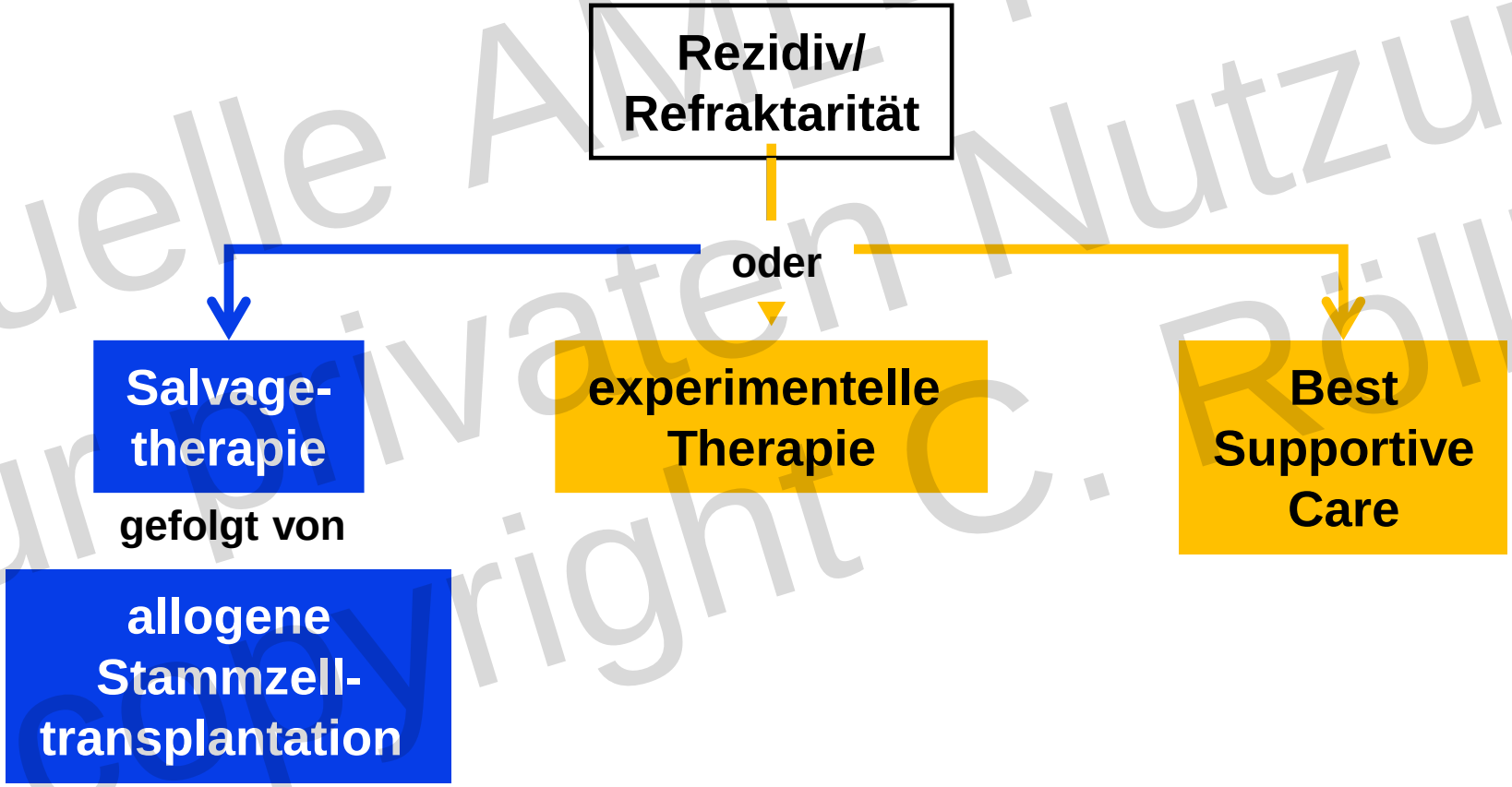
Thol et al., Blood 2015

… aber ein Anthracyclin sollte auch dabei sein…

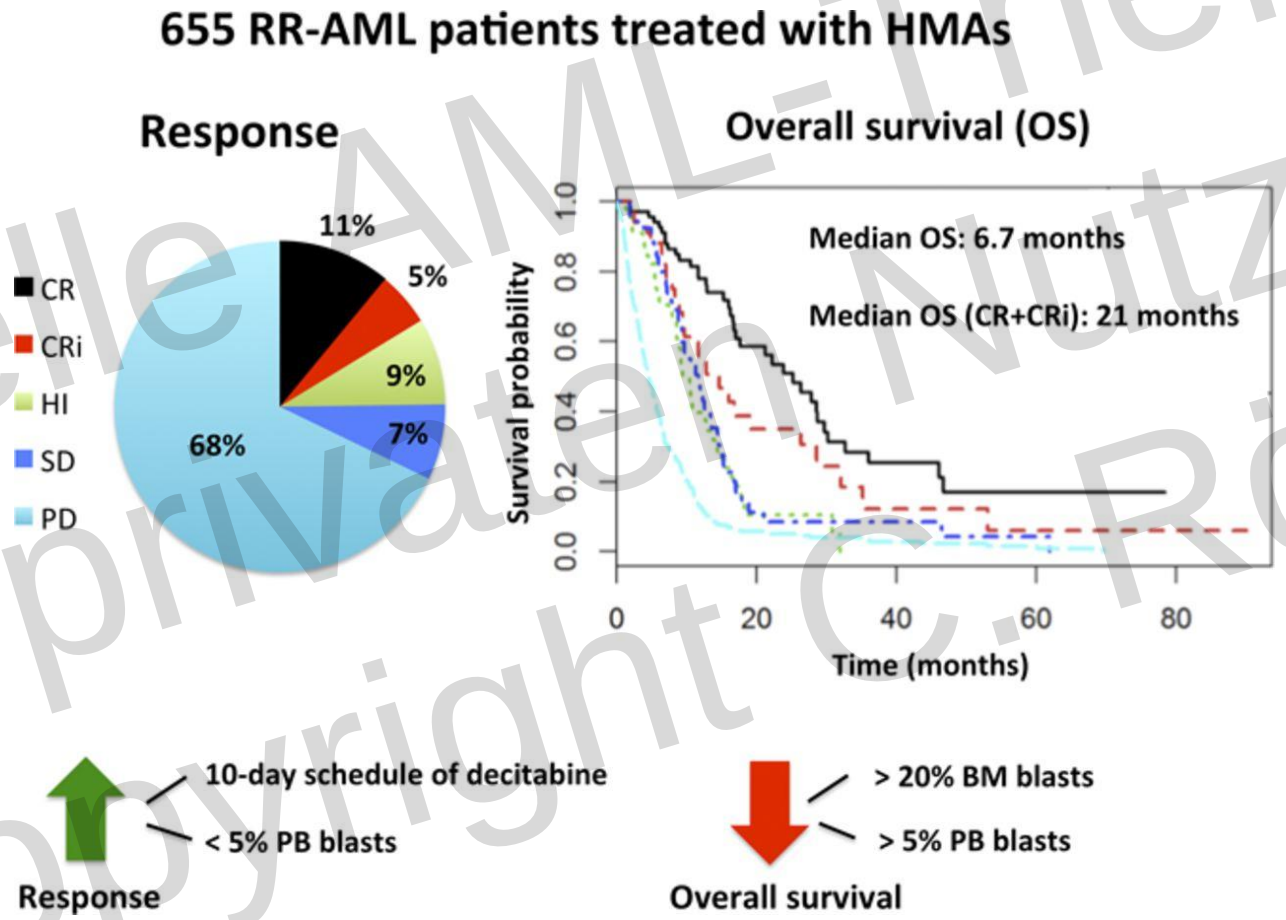


Megias-Vericat et al., Ann Hematol 2018

AML-Rezidiv



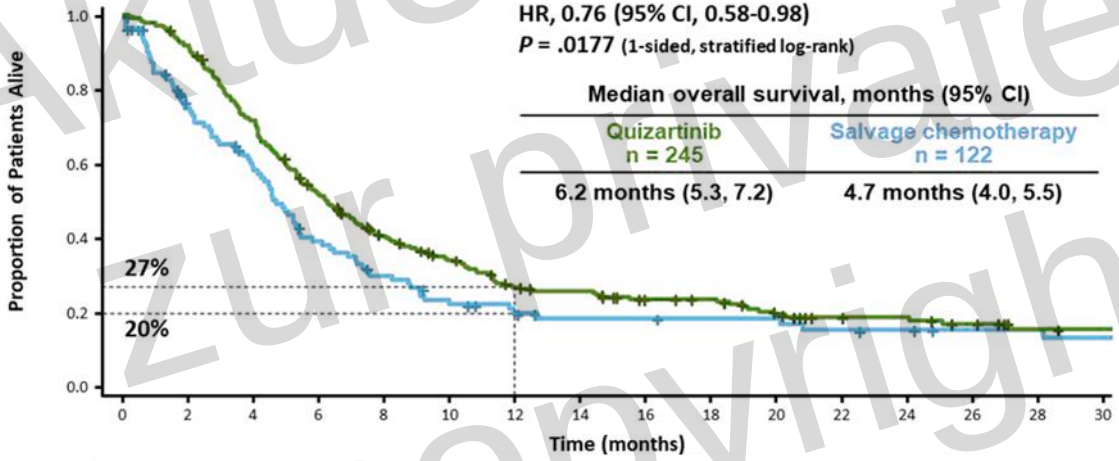
Hypomethylierende Substanzen (HMA) im Rezidiv



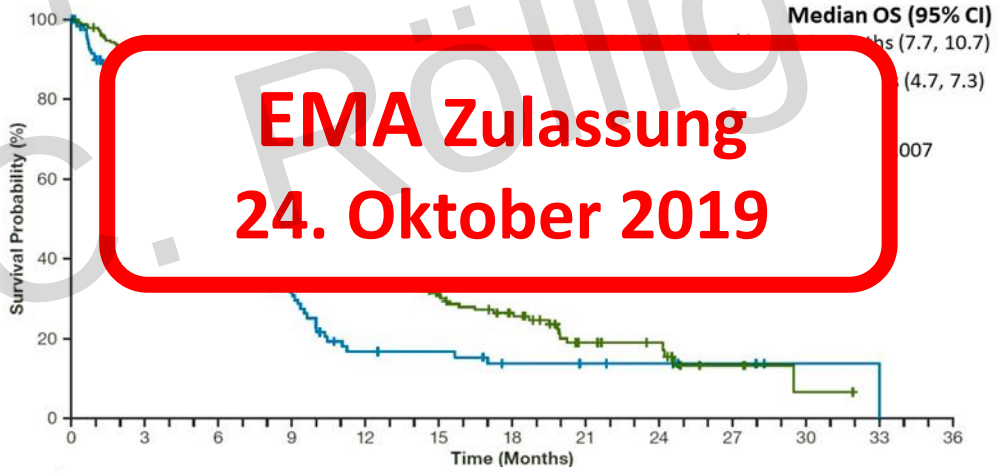
Stahl et al., Blood Adv 2018

Zweit-Generations-TKI Quizartinib and Gilteritinib haben Monowirksamkeit bei r/r AML mit FLT3-ITD- (+TKD-) Mutationen

OS quizartinib vs SOC in r/r FLT3-ITD AML (QuANTUM-R)[1]



OS gilteritinib vs SOC in r/r FLT3mut AML (ADMIRAL)[2]

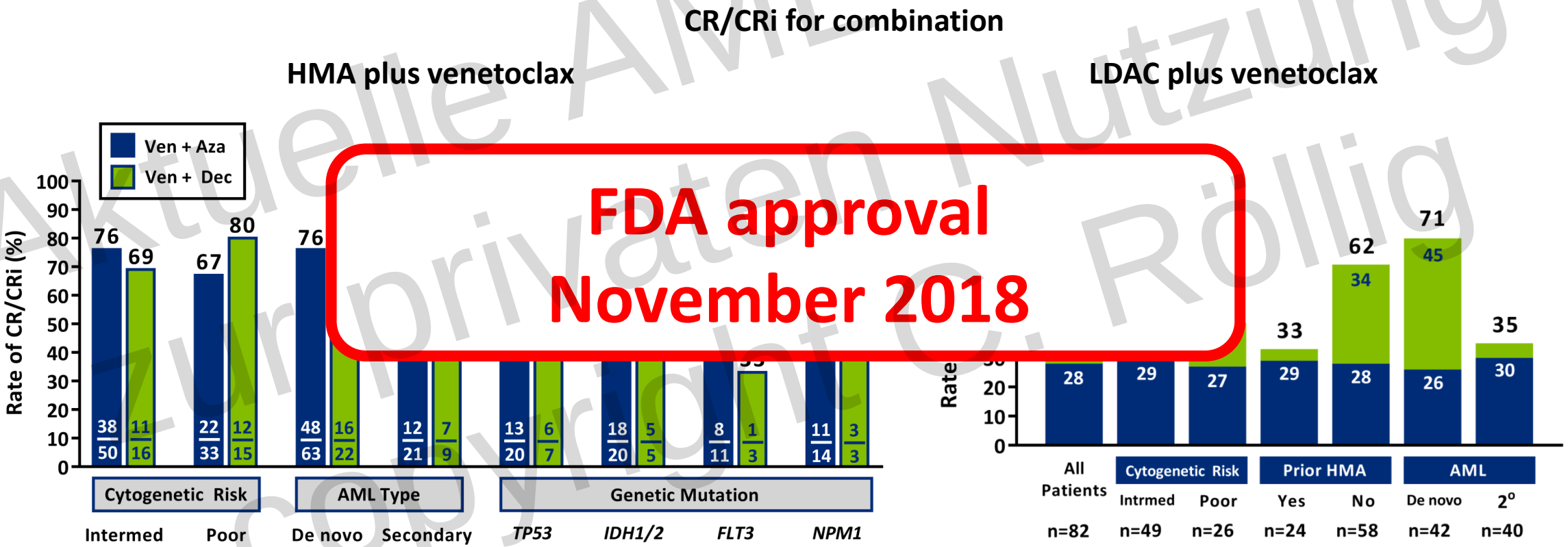


EMA Zulassung
24. Oktober 2019

1. Cortes JE, et al. Blood. 2018;132(6):563-607.
2. Perl AE, et al. Abstract presented at AACR 2019; CT184

SOC, standard of care

Kombination aus Venetoclax mit HMA oder LDAC führt zu hohen Remissionsraten in der Primärtherapie von unfitten AML-Patienten



Pollyea DA, et al. Blood 2018;132:285.

Wei A, et al. Blood 2018;132:284.

FDA-Zulassung von 8 neuen Substanzen: 5 davon mit Implikationen fürs Rezidiv

Substanz	Indikation	Zulassung
Midostaurin[1,2]	*De novo* AML with FLT3 mutation	FDA: 2017 EMA: 2017
Gemtuzumab ozogamicin[3,4]	*De novo* CD33^{+} AML (also R/R AML in the US)	FDA: 2017 EMA: 2018
CPX-351[5,6]	*De novo* t-AML or MRC-AML	FDA: 2017 EMA: 2018
Ivosidenib[7]	*De novo* R/R AML with IDH1 mutation	FDA: 2018
Enasidenib[8]	R/R AML with IDH2 mutation	FDA: 2017
Gilteritinib[9]	**R/R AML with FLT3 mutation**	**FDA: 2018** **EMA: 2019**
Glasdegib[10]	(+LDAC) *De novo* AML in patients ≥75 years old or who have comorbidities precluding use of intensive chemotherapy	FDA: 2018
Venetoclax[11]	(+LDAC/HMA) *De novo* AML in patients ≥75 years old or who have comorbidities precluding use of intensive chemotherapy	FDA: 2018

1. Novartis Pharmaceuticals. RYDAPT® (midostaurin) Prescribing Information. 2017; 2. Novartis Pharmaceuticals. RYDAPT® (midostaurin) summary of product characteristics. 2018; 3. Pfizer. MYLOTARG™ (gemtuzumab ozogamicin) Prescribing Information. 2017; 4. Pfizer. MYLOTARG™ (gemtuzumab ozogamicin) summary of product characteristics. 2018; 5. Jazz Pharmaceuticals. VYXEOS™ (daunorubicin and cytarabine) Prescribing Information. 2017; 6. Jazz Pharmaceuticals. VYXEOS™ (daunorubicin and cytarabine) summary of product characteristics. 2018; 7. Agios Pharmaceuticals, Inc. TIBSOVO® (ivosidenib) Prescribing Information. 2018; 8. Agios Pharmaceuticals, Inc. IDHIFA ® (enasidenib) Prescribing information. 2017; 9. Astellas. XOSPATA® (gilteritinib) Prescribing Information. 2018; 10. Pfizer. Daurismo™ (glasdegib) Prescribing information. 2018; 11. AbbVie Inc. Venclexta® (venetoclax) Prescribing Information. 2018

AML-Rezidiv