2. Hamburger AML Symposium

Therapie älterer AML Patienten

Walter Fiedler
Med. Klinik II
Universitätsklinikum Hamburg-Eppendorf

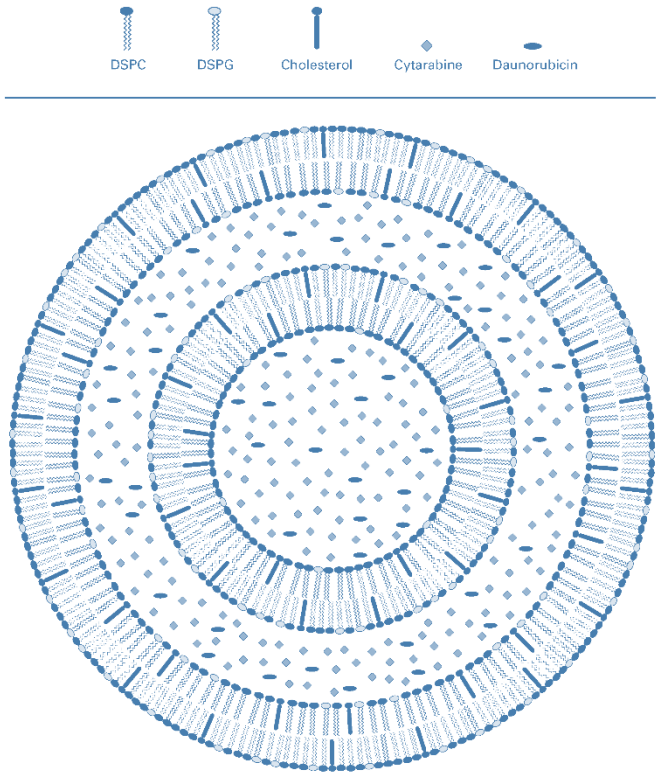
Disclosures

Disclosures of: Professor Dr. Walter Fiedler

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen	X					X	X
Pfizer						X	X
Jazz Pharmaceuticals						X	X
Daiichi Sankyo Oncology							X
Servier							X
Ariad/Incyte						X	
Novartis						X	
Abbvie							X
Celgene						X	

CPX-351

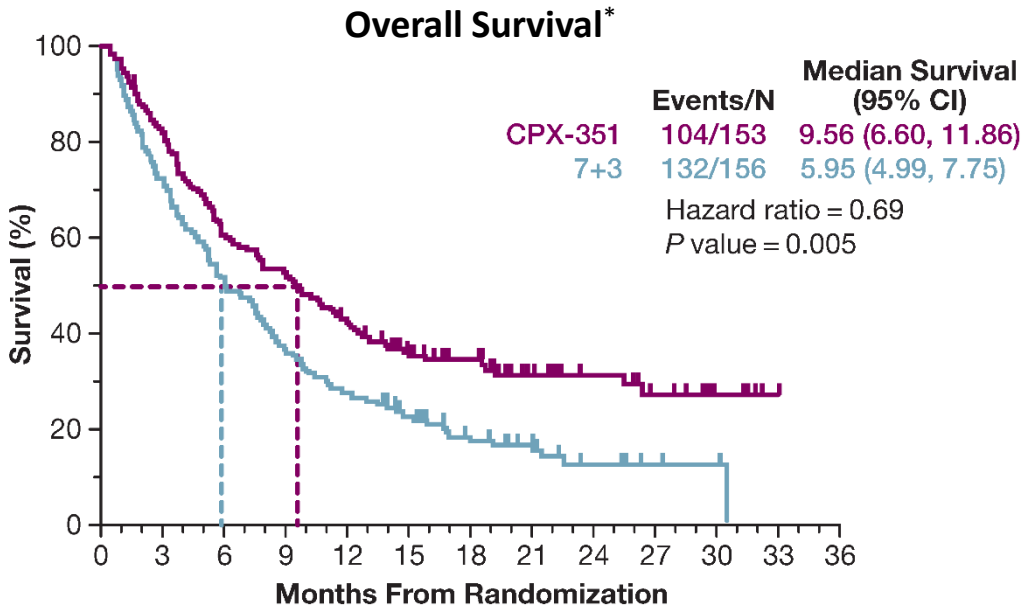
- CPX-351 is a liposomal formulation of cytarabine and daunorubicin
  encapsulated at a 5:1 molar ratio
  - Fixed molar ratio maintained in human plasma for at least 24 hours after final dose[1]
  - Drug exposure maintained for 7 days[1]
  - Selective uptake by leukemic vs normal cells in bone marrow of leukemia-bearing mice[2]



1. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979–985; 2. Lim WS et al. *Leuk Res.* 2010;34(9):1245–1223.

Clinical Results of Phase 3 Study

	CPX-351 (n=153)	7+3 (n=156)		
	Median Survival in Months (95% CI)		Hazard Ratio	*P* value
Event-Free Survival	2.53 (2.07, 4.99)	1.31 (1.08, 1.64)	0.74 (0.58, 0.96)	0.021
Remission Duration	6.93 (4.60, 9.23)	6.11 (3.45, 8.71)	0.77 (0.47, 1.26)	0.291
Deaths ≤ 60 Days*	13.8%	21.8%		
			Odds Ratio	*P* value
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
HCT	34.0%	25.0%	1.54 (0.92, 2.56)	0.098



*Kaplan-Meier estimate.

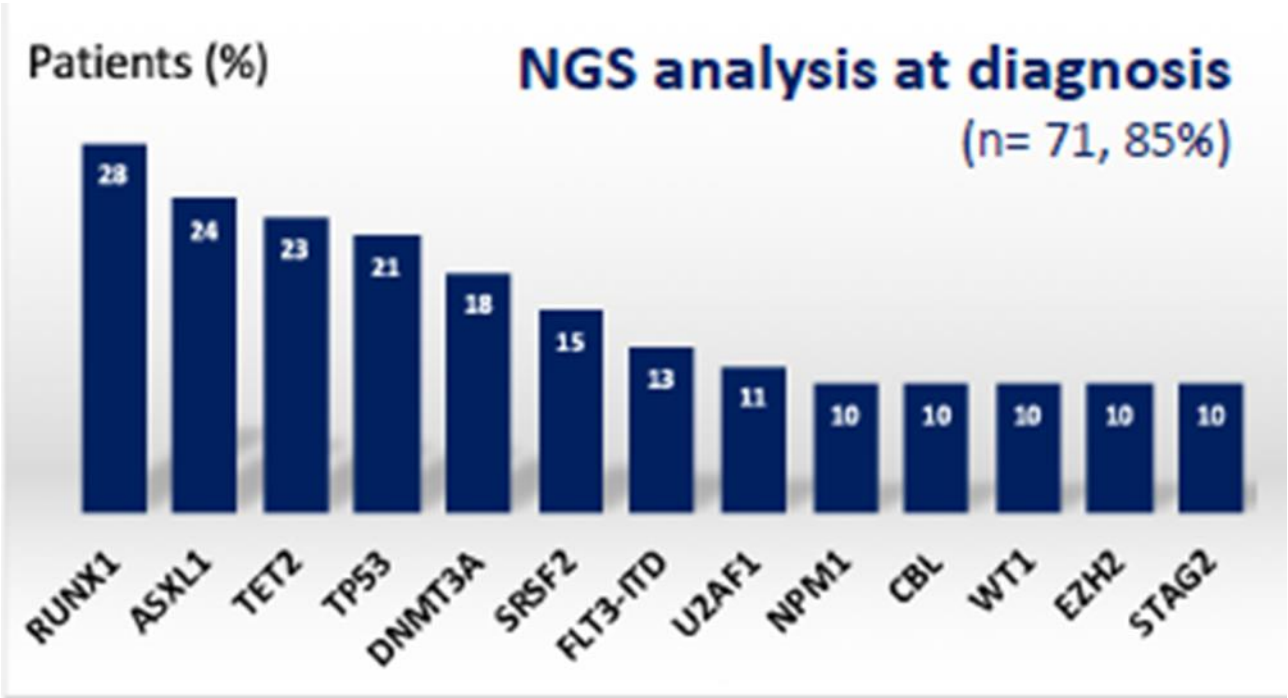
CI, confidence interval; CR, complete response; CRi, CR with incomplete platelet/neutrophil recovery; HCT, Hematopoietic Cell Transplant.

CPX-351 Induces Deep Response and Suppress the Impact of Poor Prognosis Mutations (TP53, ASXL1, RUNX1 and EVI1) Defined By ELN-2017 in t-AML and MRC AML: A Report from a Multicentric French Cohort

Edmond Chiche et al.

1/ *Patients characteristics* (n = 84)

Median age (years) [range]	67 [20-83]
Sex ratio M/F	44/40
AML subtypes	
MRC-AML	29%
MDS-AML	32%
CMML-AML	8%
t-AML	28%
Prior HMA exposure	16 (19%)
Complex karyotype	29 (35%)
Monosomal karyotype	24 (29%)
ELN 2017 genetic risk	
Favorable	2 (2%)
Intermediate	33 (39%)
Adverse	48 (57%)
Complex/Monosomal karyotype	29 (36%)/23 (28%)
Genetic ontogeny-based classifier (*Lindsley et al., Blood 2015*)	
de novo/pan-AML	21 (25%)
secondary type mutations AML	35 (42%)
TP53 mutated AML	18 (21%)



Response after induction

- **CR** : 49 (58%)
- **CRi** : 2 (3%)
- **PR** : 5 (6%)

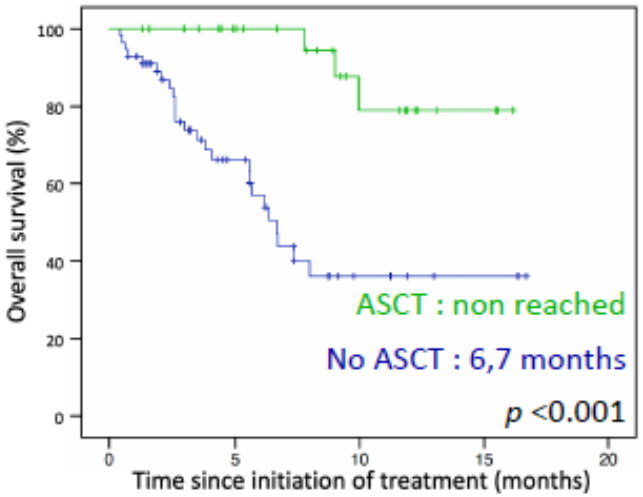
ORR = 61%

In 29 responders :

MRD < 10^{-3} = 55%

Median follow up : 6,7 months

Patients underwent an ASCT : 28 (33%)



Subgroup analysis of best response rate after induction

		CR /CRi (%)	P value
AML subtype			
	MRC-AML	71	0,004
	MDS-AML	37	
	CMML-AML	40	
	t-AML	77	
Prior/no **HMA experience**		25/69	0,001
Karyotype			
	Complex/no complex	52/63	0,29
	Monosomal/no monosomal	38/68	0,009
2017 ELN genetic risk stratification			
	Favorable and Intermediate	63	0,455
	Unfavorable	56	
Lindsley's classifier			
	de novo/pan-AML	81	
	secondary type mutations AML	54	0,047
	TP53 mutated AML	44	
Mutation status (mutated/non mutated)			
	TP53	44/62	0.207
	ASXL1	53/64	0.409
	RUNX1	50/65	0.264
	EVI1	25/62	0.157
	FLT3-ITD	67/60	0.714
	FLT3-TKD	50/60	0.631

ABSTRACT LBA-3

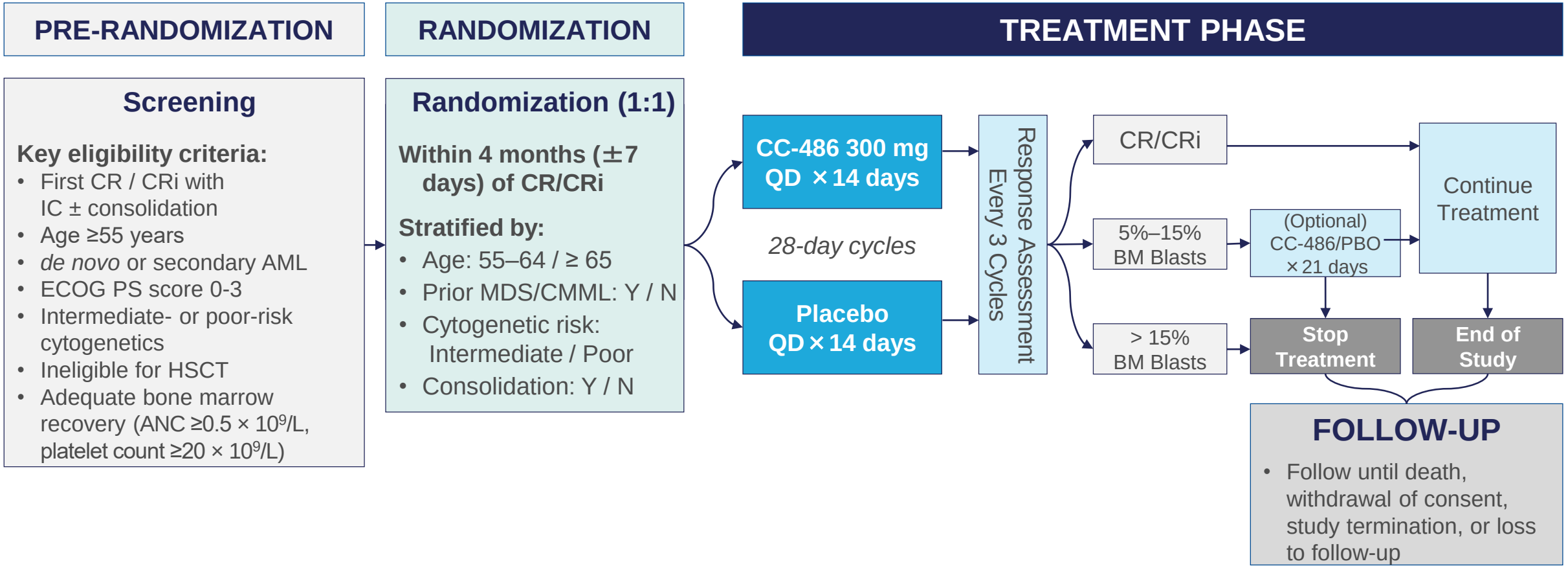
The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 in Patients with Acute Myeloid Leukemia (AML) in First Remission

Andrew H. Wei[1,2], Hartmut Döhner[3], Christopher Pocock[4], Pau Montesinos[5,6], Boris Afanasyev[7], Hervé Dombret[8], Farhad Ravandi[9], Hamid Sayar[10], Jun Ho Jang[11], Kimmo Porkka[12], Dominik Selleslag[13], Irwindeep Sandhu[14], Mehmet Turgut[15], Valentina Giai[16], Yishai Ofran[17,18], Merih Kizil Cakar[19], Aida Botelho de Sousa[20], Justyna Rybka[21], Chiara Frairia[22], Lorenza Borin[23], Germana Beltrami[24], Jaroslav Cermak[25], Gert Ossenkoppele[26], Ignazia La Torre[27], Barry Skikne[28], Keshava Kumar[28], Qian Dong[28], CL Beach[28], Gail J. Roboz[29,30]

[1]The Alfred Hospital, Melbourne, Australia; [2]Monash University, Melbourne, Australia; [3]Ulm University Hospital, Ulm, Germany; [4]Kent and Canterbury Hospital, Canterbury, United Kingdom; [5]Hospital Universitari i Politècnic La Fe, Valencia, Spain; [6]CIBERONC, Instituto Carlos III, Madrid, Spain; [7]First I. P. Pavlov State Medical University of St. Petersburg, Saint Petersburg, Russian Federation; [8]Hôpital Saint Louis, Institut de Recherche Saint Louis, Université de Paris, Paris, France; [9]The University of Texas MD Anderson Cancer Center, Houston, TX; [10]Indiana University Cancer Center, Indianapolis, IN; [11]Samsung Medical Center, Seoul, South Korea; [12]Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; [13]AZ Sint-Jan Brugge-Oostende, Brugge, Belgium; [14]University of Alberta Hospital, Alberta, Canada; [15]Ondokuz Mayis University, Samsun, Turkey; [16]Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; [17]Rambam Medical Center, Haifa, Israel; [18]Faculty of Medicine Technion, Haifa, Israel; [19]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey; [20]Hospital dos Capuchos (CHLC), Lisbon, Portugal; [21]Wroclaw Medical University, Wroclaw, Poland; [22]Città della Salute e della Scienza, Torino, Italy; [23]Ospedale San Gerardo Monza, Monza, Italy; [24]Ospedale Policlinico San Martino, Genoa, Italy; [25]Ústav Hematologie a Krevní Transfuze, Prague, Czech Republic; [26]Amsterdam UMC, Location VUMC, Amsterdam, Netherlands; [27]Celgene, A Bristol-Myers Squibb Company, Summit, NJ; [28]Bristol-Myers Squibb, Summit, NJ; [29]Weill Cornell Medicine, New York, NY; [30]New York Presbyterian Hospital, New York, NY

QUAZAR AML-001: STUDY DESIGN

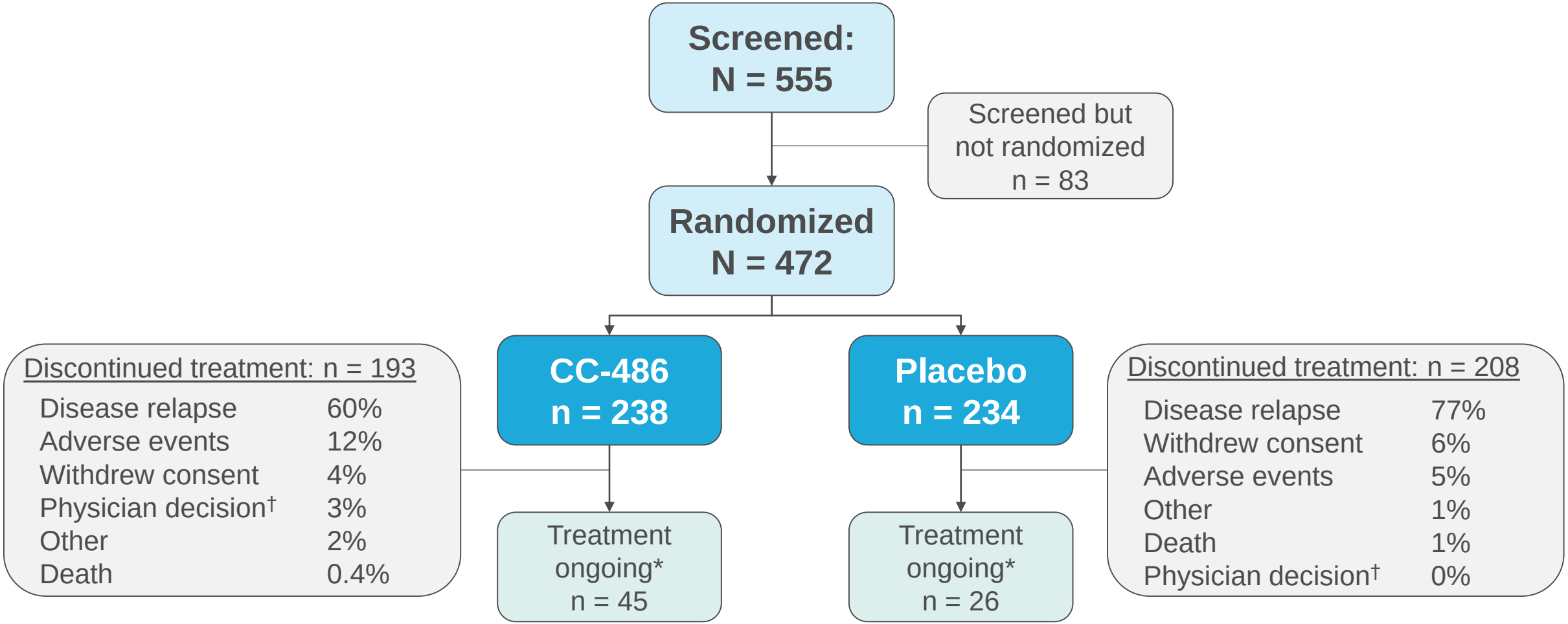
International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)



AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; BSC, best supportive care; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo.

Wei et al., Abstract LBA-3. Oral presentation, ASH 2019

PATIENT DISPOSITION



*Still receiving study drug at data cutoff (July 15, 2019).
†Became eligible for hematopoietic stem cell transplant during treatment.

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BASELINE CHARACTERISTICS

Parameter	CC-486 n = 238	Placebo n = 234
Age, years, median (range)	68 (55–86)	68 (55–82)
Age ≥65 years, n (%)	172 (72)	166 (71)
Sex, n (%)		
Male	118 (50)	127 (54)
Female	120 (50)	107 (46)
ECOG PS score, n (%)		
0	116 (49)	111 (47)
1	101 (42)	106 (45)
2	21 (9)	15 (6)
3	0	2 (1)

Parameter	CC-486 n = 238	Placebo n = 234
de novo AML, n (%)	213 (89)	216 (92)
WHO AML classification, n %)		
Not otherwise specified	148 (62)	145 (62)
Myelodysplasia-related changes	49 (21)	42 (18)
Recurrent genetic abnormalities	39 (16)	46 (20)
NCCN cytogenetic risk, n (%)		
Intermediate	203 (85)	203 (87)
Poor	35 (15)	31 (13)

AML, acute myeloid leukemia; ECOG PS, Eastern Cooperate Oncology Group performance status; NCCN, National Comprehensive Cancer Network; WHO, World Health Organization.

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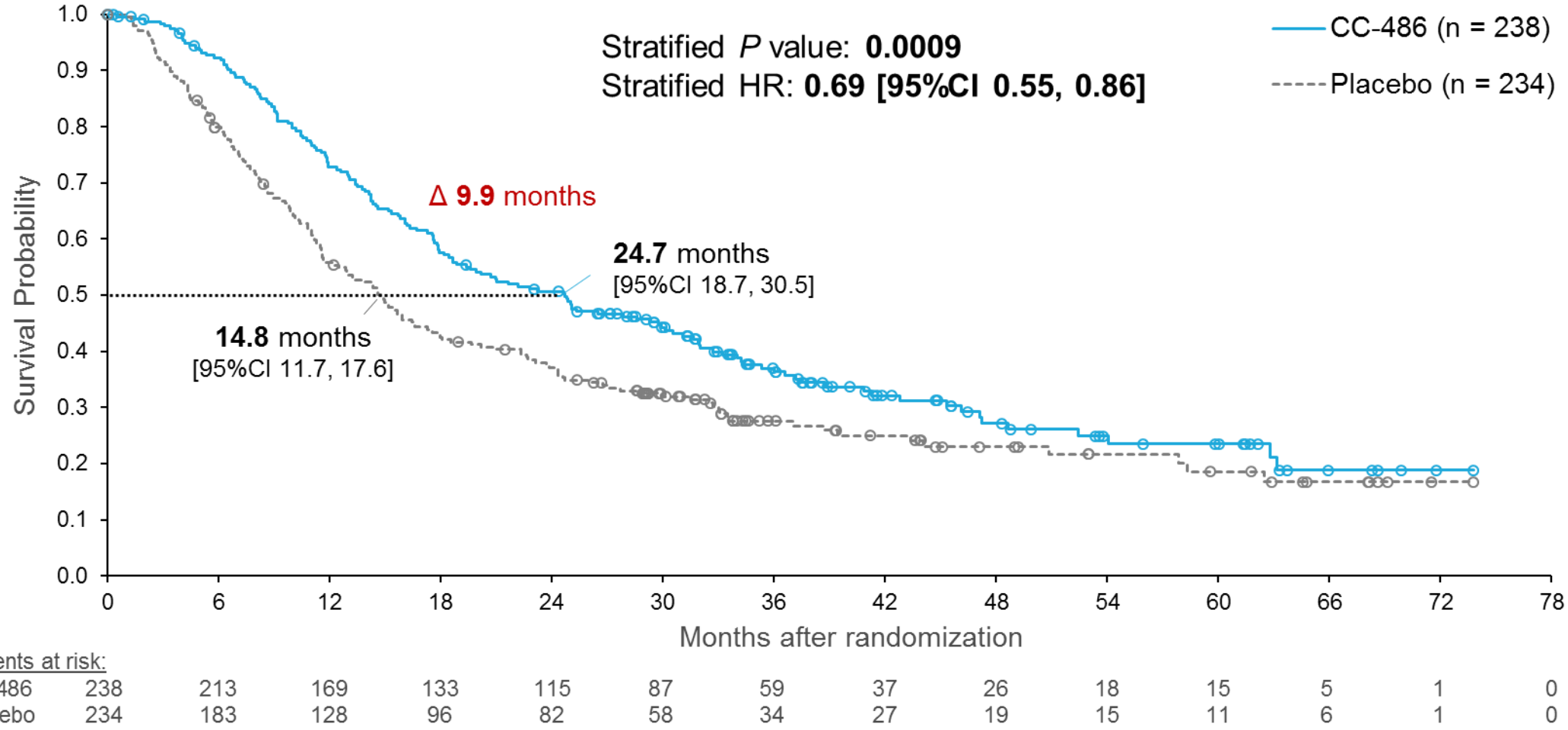
PRIMARY ENDPOINT: OVERALL SURVIVAL FROM RANDOMIZATION

- Median follow-up: 41.2 months



Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Data cutoff: July 15, 2019
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 *vs.* placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.
95%CI, 95% confidence interval; HR, hazard ratio.

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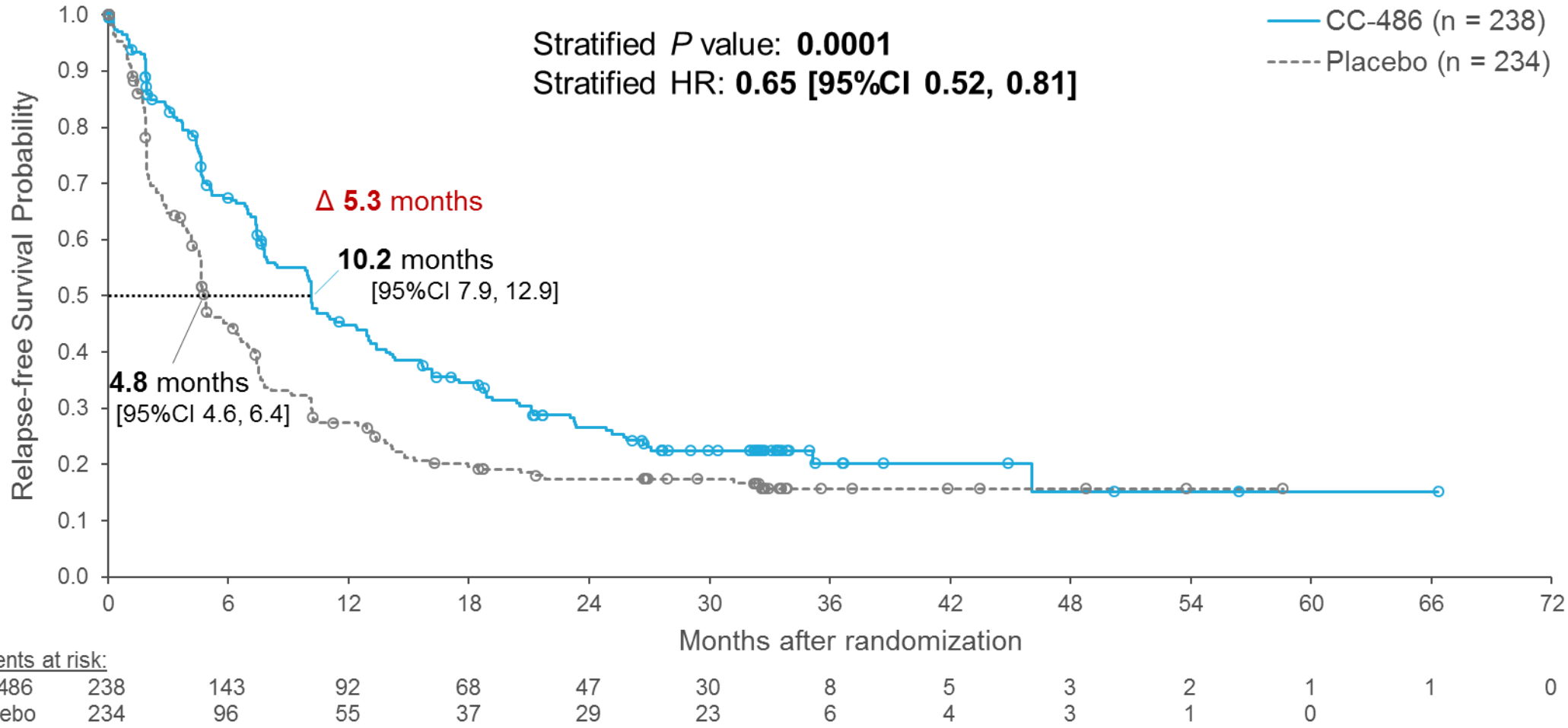
RELAPSE-FREE SURVIVAL FROM RANDOMIZATION



- 1-year relapse rate was 53% in the CC-486 arm [95%CI 46, 59] and was 71% in the placebo arm [65, 77]

Data cutoff: July 15, 2019

RFS was defined as the time from randomization to relapse or death by any cause, whichever occurred first. Kaplan-Meier estimated RFS was compared for CC-486 *vs.* placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.

95%CI, 95% confidence interval; HR, hazard ratio; PBO, placebo.

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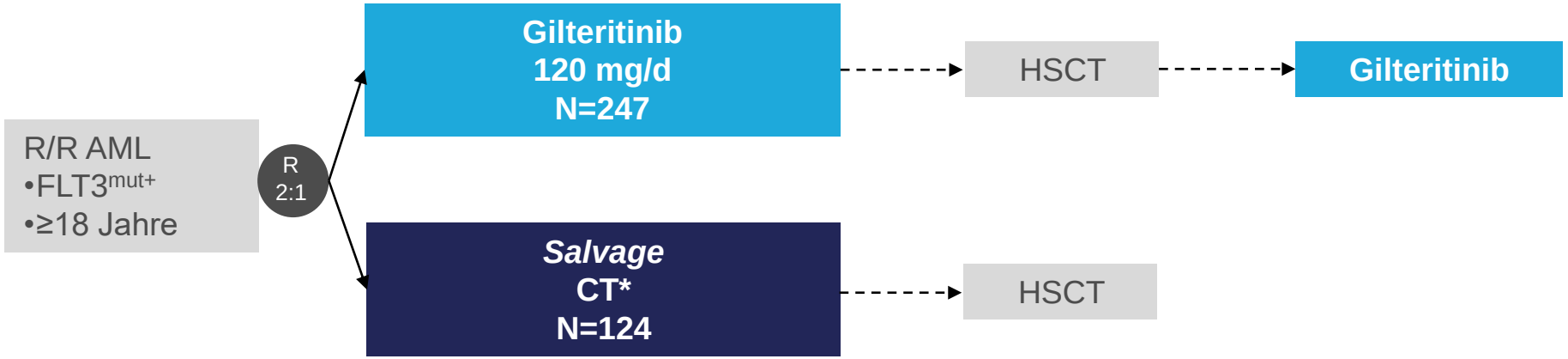
ADMIRAL

Studiendesign



Co-Primäre Endpunkte

- OS, CR/CRh-Rate

Wichtigste sekundäre Endpunkte:

- EFS, CR-Rate

**Salvage* CT-Regimen wurden vor Randomisierung gewählt*

MEC (Mitoxantron, Etoposid und Cytarabin)
FLAG-IDA (Fludarabin, Cytarabin, Idarubicin und G-CSF) } Hohe Intensität (1-2 Zyklen)

Niedrig-dosiertes Cytarabin
Azacitidin } Niedrige Intensität (bis Progression oder Intoleranz verabreicht)

HSCT: hämatopoetische Stammzelltransplantation

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Patienten- und Krankheitscharakteristika

Charakteristika	Gilteritinib 120 mg/d (N=247)	*Salvage*-CT (N=124)	Gesamt (N=371)
Medianes Alter, Jahre (Bereich)	62 (20-84)	61,5 (19-85)	62 (19-85)
Weiblich, N (%)	131 (53)	70 (56)	201 (54)
Zytogenetisches Risiko, N (%)			
Günstig	4 (2)	1 (1)	5 (1)
Mittel	182 (74)	89 (72)	271 (73)
Ungünstig	26 (11)	11 (9)	37 (10)
Sonstiges	35 (14)	23 (19)	58 (16)
Zentral-bestätigter FLT3 Mutationsstatus*, N (%)			
FLT3-ITG allein	215 (87)	113 (91)	328 (88)
FLT3-TKD allein	21 (9)	10 (8)	31 (8)
FLT3-ITD und FLT3-TKD	7 (3)	0	7 (2)
Vorherige AML Therapien, N (%)			
Anthracyclin-basiertes Regimen	201 (81)	102 (82)	303 (82)
FLT3 Tyrosinkinase-Inhibitor	32 (13)	14 (11)	46 (12)
HSCT	48 (19)	26 (21)	74 (20)
Ansprechen auf 1L, N (%)			
Primär refraktäre AML ohne HSCT	98 (40)	48 (39)	146 (39)
Rezidiv ≤6 Mon. nach HSCT	31 (3)	17 (14)	48 (13)
Rezidiv >6 Mon. nach HSCT	17 (7)	8 (6)	25 (7)
Rezidiv ≤6 Mon. nach CRc	67 (27)	34 (27)	101 (27)
Rezidiv >6 Mon. nach CRc	34 (14)	17 (14)	51 (14)

*Fünf Patienten hatten eine FLT3 Mutation, die nicht durch ein zentrales Labor bestätigt wurde

CRc: composite complete remission
ITD:internal tandem duplication
TKD: tyrosine kinase domain
HSCT: hämatopoetische Stammzelltransplantation

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Ergebnisse – Ansprechen (ITT Population, N=371)

Parameter*	Gilteritinib (N=247)	Salvage-CT (N=124)
CR, N (%)	52 (21)	13 (11)
CRh, N (%)	32 (13)	6 (5)
CRi, N (%)	63 (26)	14 (11)
CRp, N (%)	19 (8)	0 (0)
CRc, N (%)	134 (54)	27 (22)
CR/CRh, N (%)	84 (34)	19 (15)
PR, N (%)	33 (13)	5 (4)
ORR, N (%)	167 (68)	32 (26)
NR, N (%)	66 (27)	43 (35)
Mediane Therapiedauer (Bereich), Monate	4,1 (0,1-29,1)	0,9 (0,2-7,1)
Mediane Zeit bis CRc, Monate (KI 95%)	1,8 (0,9; 9,5)	1,1 (0,8; 2,9)
Median DoR[1], Monate (KI 95%)	11,0 (4,6; NE)	NE
Allogene HSCT, N (%)	63 (26)	19 (15)

*Ansprechen war bei 14 Patienten im Gilteritinib-Arm (6%) und bei 49 Patienten (40%) im Salvage-CT-Arm nicht verfügbar
[1]Remissionsdauer war definiert als die Dauer von CR/CRh

CRc: composite complete remission
CRh: complete remission with partial hematologic recovery
CRi: complete remission with incomplete hematologic recovery
CRp: complete remission with incomplete platelet recovery
HSCT: hematopoietic stem cell transplantation

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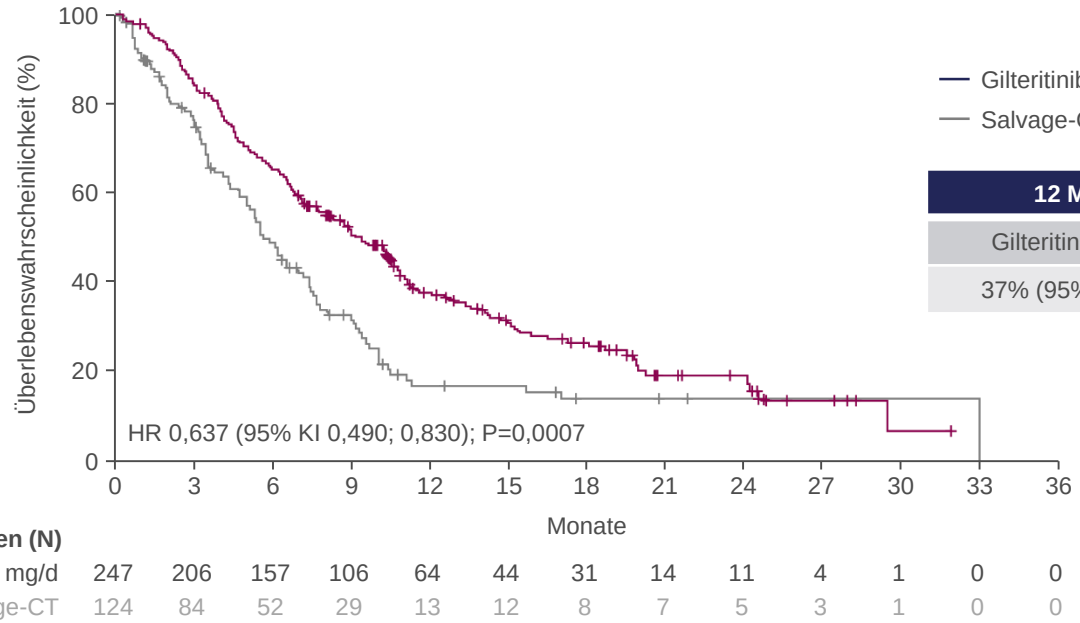
Ergebnisse – OS (ITT Population, N=371)



	Median OS (95% KI)
Gilteritinib 120 mg/d	9,3 Monate (7,7; 10,7)
Salvage-CT	5,6 Monate (4,7; 7,3)

12 Monate OS-Raten nach Therapiearm	
Gilteritinib (N=247)	Salvage-CT(N=124)
37% (95% KI 31; 44)	17% (95% KI 10; 25)

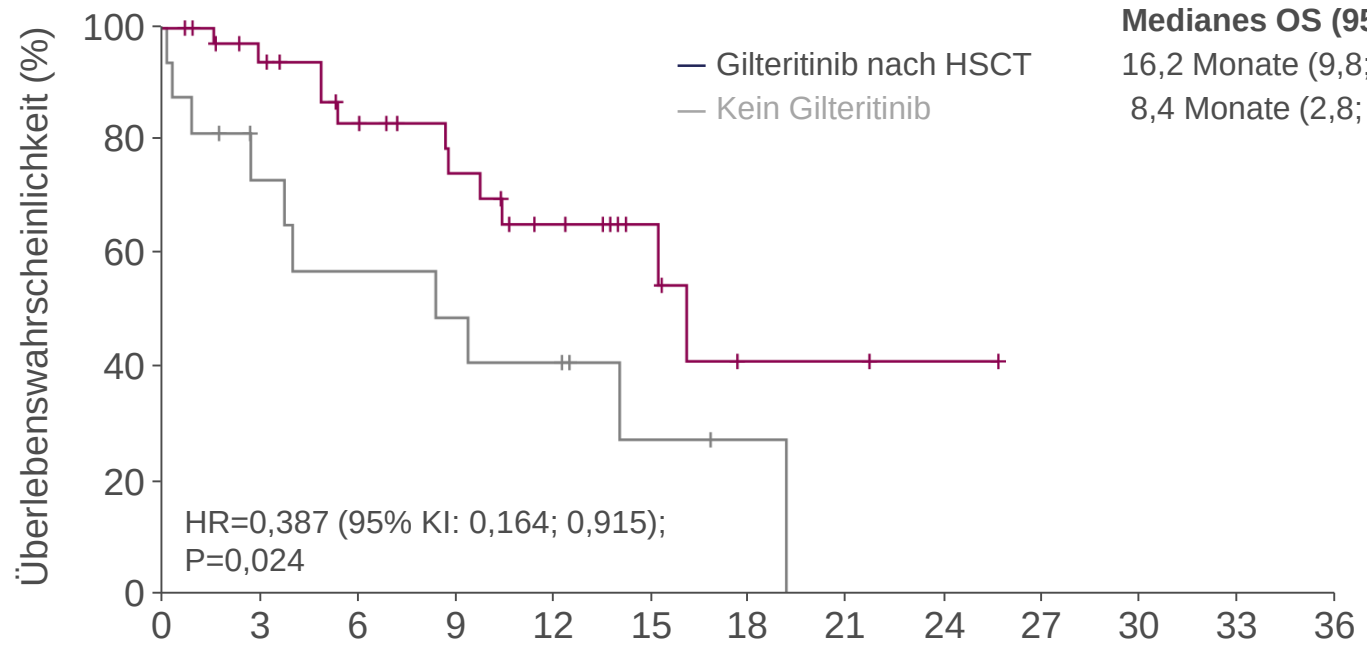
Beidseitige P-Werte wurden gemäß dem Log-Rank-Test festgestellt; die Kaplan-Meier-Methode kombiniert mit der Greenwood Formel wurden genutzt, um das OS und den dazugehörigen Konfidenzintervall zu bestimmen.

OS und CR je nach FLT3-Mutationstyp (ITT Population, N=371)

Ansprech-Parameter	FLT3-ITD allein			FLT3-TKD allein			FLT3-ITD + FLT3-TKD		
	Gilteritinib, N=215	Salvage-CT, N=113	P-Wert	Gilteritinib, N=21	Salvage-CT, N=10	P-Wert	Gilteritinib, N=7	Salvage-CT, N=0	P-Wert
Medianes OS, Monate	9,3	5,6	0,0007	8,0	5,7	0,4029	10,2	NE	NE
CR, N (%)	44 (21)	11 (10)	0,0131	4 (19)	2 (20)	1,0000	2 (29)	NE	NE

Ergebnisse – Post-HSCT Überleben

Post-HSCT Überleben im Gilteritinib-Arm: Auswirkung der Erhaltungstherapie (*Landmark* Analyse von Tag 60 Post-HSCT, N=51)



Medianes OS (95% KI)
16,2 Monate (9,8; NE)
8,4 Monate (2,8; 19,3)

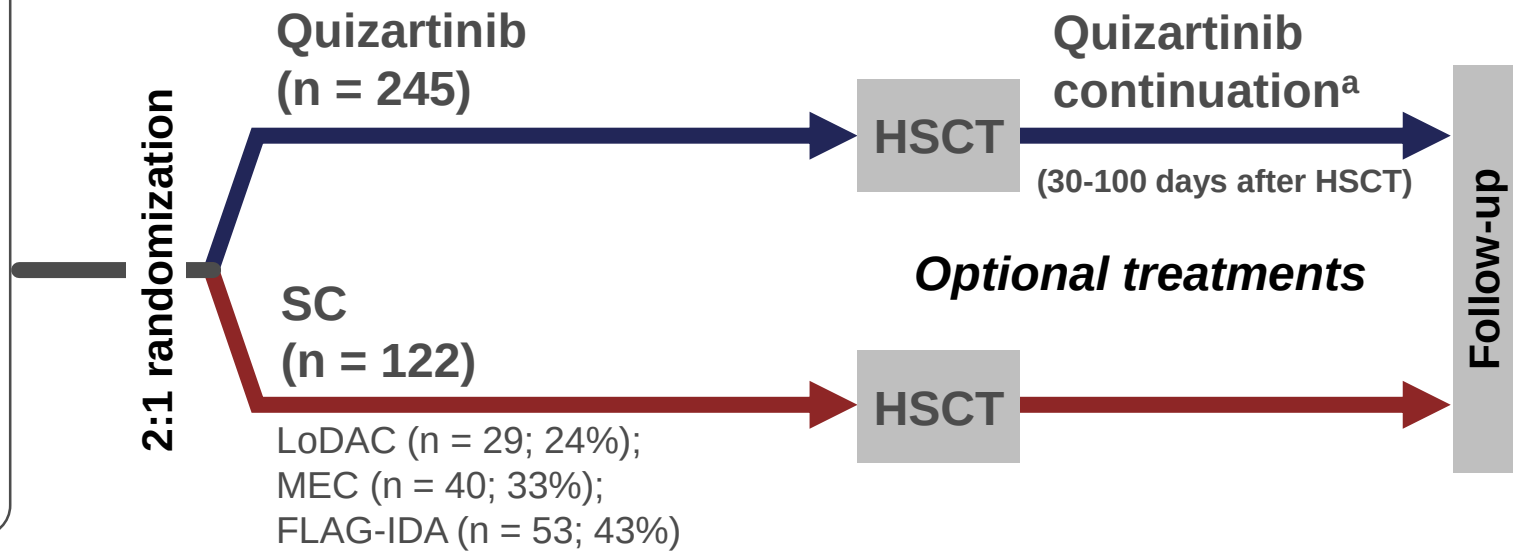
Anzahl Patienten													
Gilteritinib nach HSCT	35	29	22	17	12	6	2	2	1	0	0	0	0
Kein Gilteritinib	16	9	7	6	5	2	1	0	0	0	0	0	0

Beidseitige P-Werte wurden gemäß dem Log-Rank-Test festgestellt; die Kaplan-Meier-Methode kombiniert mit der Greenwood Formel wurden genutzt um das OS und den dazugehörigen Konfidenzintervall zu bestimmen.
*Zeit gerechnet ab 60 Tagen nach HSCT

QUANTUM-R STUDY DESIGN
A RANDOMIZED, CONTROLLED, GLOBAL, PHASE 3 STUDY

Patients with *FLT3*-ITD AML

- Age ≥ 18 years
- Refractory AML or relapse within 6 months of first remission (± HSCT)
- ≥ 1 cycle of standard-dose anthracycline- or mitoxantrone-containing induction therapy



Primary endpoint
OS

Secondary and exploratory endpoints
EFS,
CRc rate and duration, HSCT rate

HSCT based on institutional policies

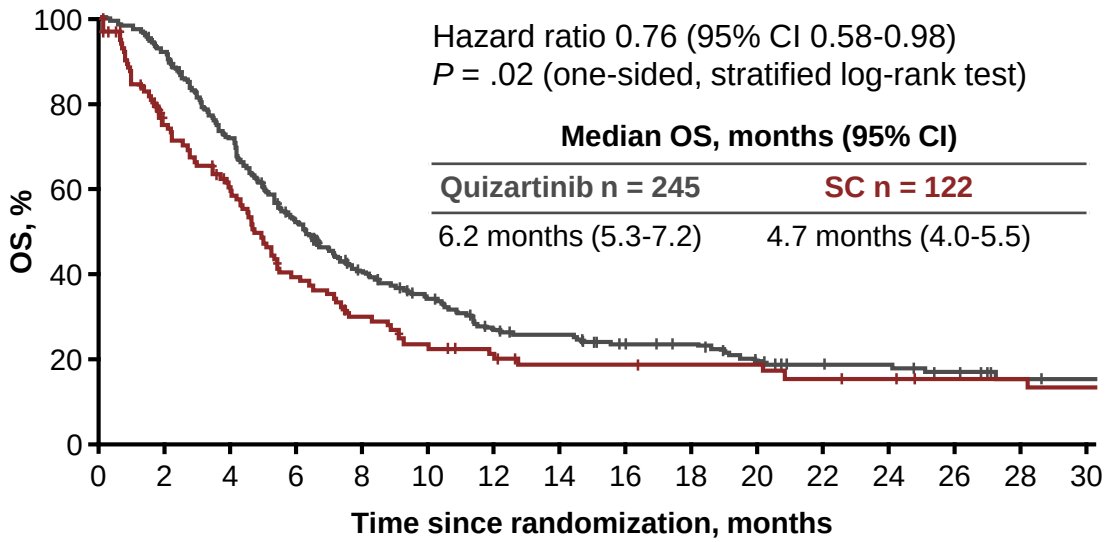
- Disease control and reduction
- Performance status
- Comorbidities
- Donor availability

[a]Patients could resume quizartinib treatment 30 to 100 days after allo-HSCT per institutional policies and if certain conditions were met, including adequate blood count recovery and absence of significant graft-vs-host disease.

CRc, composite complete remission; EFS, event-free survival; FLAG-IDA, fludarabine, cytarabine, idarubicin, granulocyte-colony stimulating factor; HSCT, hematopoietic stem cell transplant; LoDAC, low-dose cytarabine; MEC, mitoxantrone, etoposide, cytarabine; OS, overall survival; SC, salvage chemotherapy

Cortes J, et al. *Lancet Oncol*. 2019;20:984-997.

Characteristic	Quizartinib (n = 245)	SC (n = 122)
Median age (range), years	55 (19-81)	58 (18-78)
Relapsed/Refractory, %	67/33	66/34
Median duration of first CR (IQR), months	3.5 (2.4-4.7)	3.7 (2.4-4.6)
Median OS, months[a]	6.2	4.7
Best response		
CRc, n (%)[a]	118 (48)	33 (27)
CR, n (%)	10 (4)	1 (1)
CRp, n (%)	9 (4)	0
CRi, n (%)	99 (40)	32 (26)
Time to first CRc, median (range), months	1.1 (0.9-4.5)	0.9 (0.5-3.4)
Duration of CRc, median (95% CI), months	2.8 (2.4-6.2)	1.2 (0.8-2.9)
Transplant rate[b], n (%)	78 (32)	14 (12)



- QuANTUM-R was the first study to demonstrate an OS benefit with a FLT3 inhibitor in patients with R/R *FLT3*-ITD–positive AML
  - OS benefit was seen across patient subgroups and was reproduced consistently across sensitivity analyses
  - Transplant rates were higher with quizartinib (32%) compared with salvage chemotherapy (12%)

[a] *P* = .02 (one-sided, stratified log-rank test)
[b] Transplant rate is the percent of subjects undergoing allogeneic HSCT directly following the protocol treatment with no intervening AML therapy.
CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; IQR, interquartile range; R/R, relapsed/refractory; OS, overall survival; SC, salvage chemotherapy.
Cortes J, et al. *Lancet Oncol*. 2019;20:984-997.

Anti-leukemic activity of single agent venetoclax in newly diagnosed acute myeloid leukemia: a sub-set analysis of the CAVEAT study

(CAVEAT: Chemotherapy And Venetoclax in Elderly AML Trial)

INTERIM REPORT DATA CUTOFF 23 SEP 2019

Chong Chyn Chua[1, 2], John Reynolds[3], Jessica Salmon[2], Chun Y. Fong[4], Stephen B. Ting[5], Ing S. Tiong[1], Shaun Fleming[1], Sarah MacRaild[2], Donia M. Moujalled[2], Giovanna Pomilio[2], Nik Cummings[2], Julie McManus[1], Adam Ivey[1], Purvi M. Kakadia[6], Stefan K. Bohlander[6], Andrew W. Roberts[7], Andrew H. Wei[1,2]

[1]The Alfred Hospital and Monash University, Melbourne, Victoria, Australia; [2] Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria, Australia; [3]The Alfred and Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia, [4]Department of Haematology, Austin Hospital, Heidelberg, Victoria, Australia, [5]Department of Haematology, Box Hill Hospital, Victoria, Australia,, [6]The University of Auckland, Auckland, New Zealand, [7]Department of Haematology, Royal Melbourne Hospital, Parkville, Victoria, Australia.

American Society of Hematology 61st Annual Meeting and Exposition 2019, Orlando

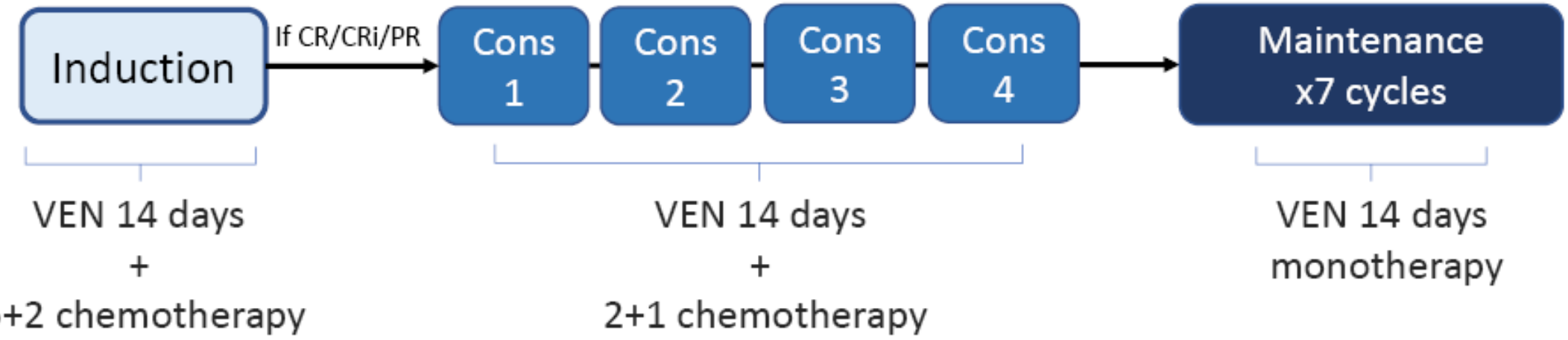
Key eligibility criteria

Main inclusion criteria	**Main exclusion criteria**

▪ *De novo,* secondary or therapy-related AML without prior exposure to induction chemotherapy
  ▪ prior LDAC or HMA was allowed in cohorts A-E
▪ Age
  ▪ ≥65 or
  ▪ ≥60 and monosomal karyotype
▪ ECOG 0-1
▪ Fit for intensive chemotherapy
▪ WCC<$25x10^9$/L (hydroxyurea permitted)
	▪ Prior venetoclax or other BCL-2 inhibitor exposure
	▪ Prior anthracycline exposure
	▪ Use of potent CYP3A inducers or warfarin within 7 days of study treatment initiation

HU, hydroxyurea. LDAC, low dose cytarabine. HMA, hypomethylating agents. WCC, white cell count.

Study design



Cons: consolidation

5+2 chemotherapy: Ara-C 100mg/m^2/day D1-5 plus Idarubicin 12mg/m^2/day D2-3

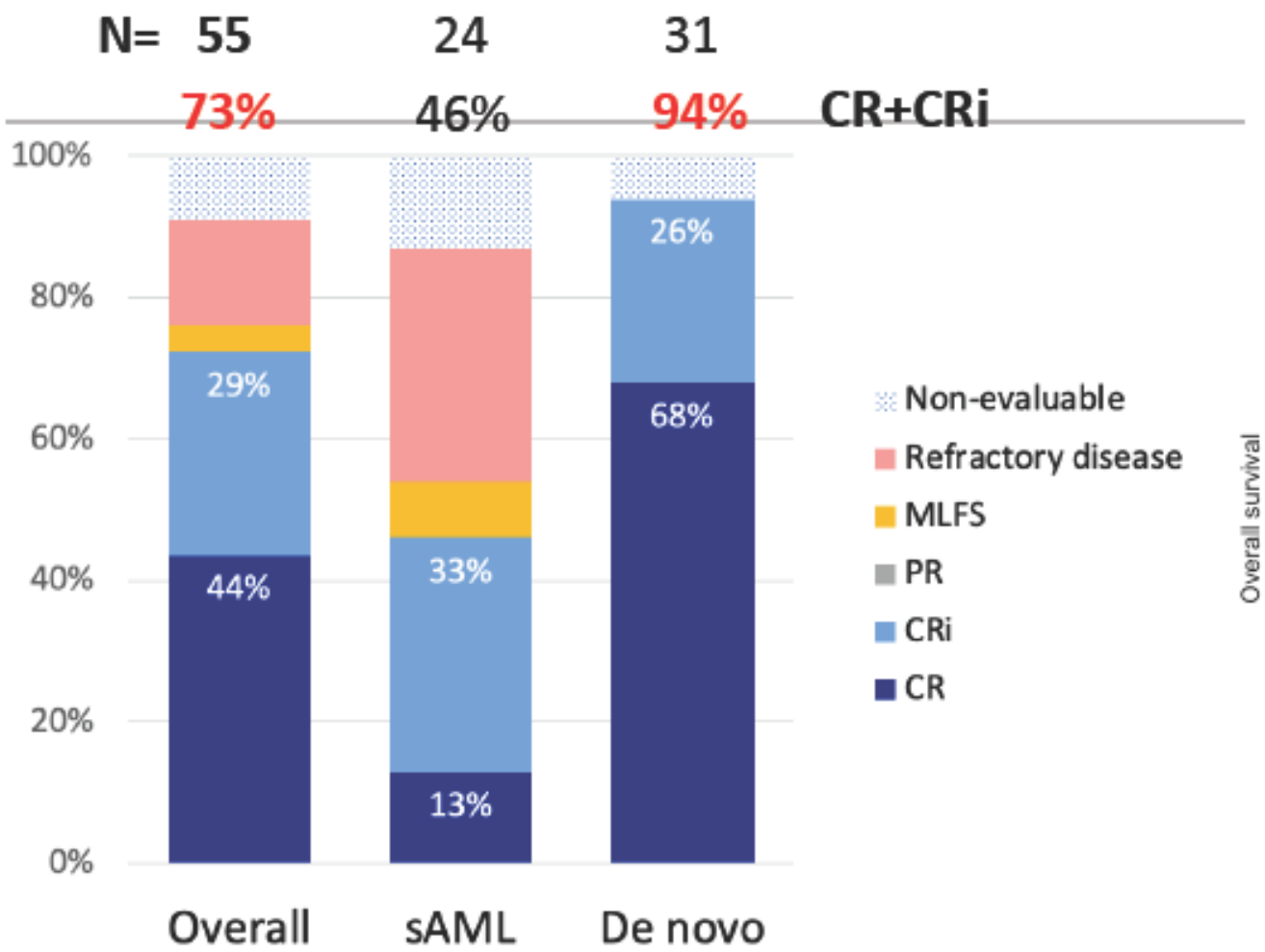
2+1 chemotherapy: Ara-C 100mg/m^2/day D1-2 plus Idarubicin 12mg/m^2/day D1

Patient characteristics (n=55)

Characteristics	Total (n=55)
Median age, years (range)	**71 (63-80)**
Males, n (%)	35 (64)
ECOG 1, n (%)	35 (64)
Secondary AML, n (%)	**24 (44)**
Prior HMA, n (%)	**16 (29)**
MRC 2010 cytogenetic risk, n (%)	
Favorable	-
Intermediate	38 (69)
Adverse	**15 (27)**
Failed	2 (4)
ELN 2017 classification, n (%)	
Favorable	12 (22)
Intermediate	17 (31)
Adverse	**26 (47)**

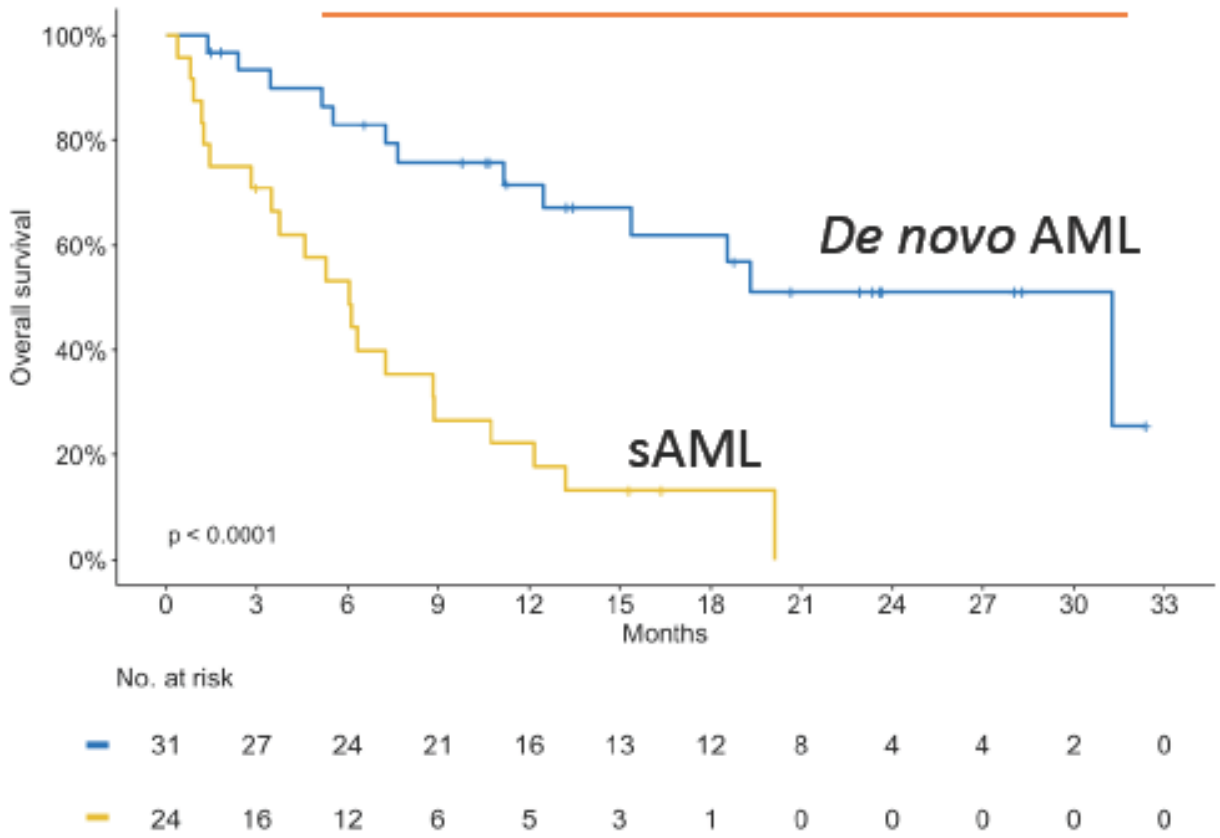
MRC: Medical Research Council; ELN: European LeukemiaNet

Excellent efficacy in *de novo* AML



Median follow up: 20.2 months

	OS at 12m	OS at 18m
Overall	50%	40%
De novo AML	72%	**62%**
sAML	22%	13%



Outcomes In Molecular Subgroups And Resistance Patterns With Ten-day Decitabine And Venetoclax In Acute Myeloid Leukemia

A. Maiti, C.R. Rausch, J.E. Cortes, G. Borthakur, N. Pemmaraju, C.B. Benton, T.M. Kadia, K. Takahashi, K. Naqvi, F. Ravandi, Y. Alvarado, N.J. Short, N.G. Daver, K. Sasaki, M. Ohanian, G. Garcia-Manero, P.A. Thompson, S.M. Kornblau, L. Masarova, N. Jain, E.J. Jabbour, M. Andreeff, R. Maduike, J.A. Guerrero, Q. Zhang, A. Cavasos, H. Ma, C.A. Bivins, K. Vaughan, S.A. Pierce, J. Ning, W. Qiao, J.S. Welch, K.P. Patel, H.M. Kantarjian, M.Y. Konopleva, C.D. DiNardo.

Department of Leukemia,

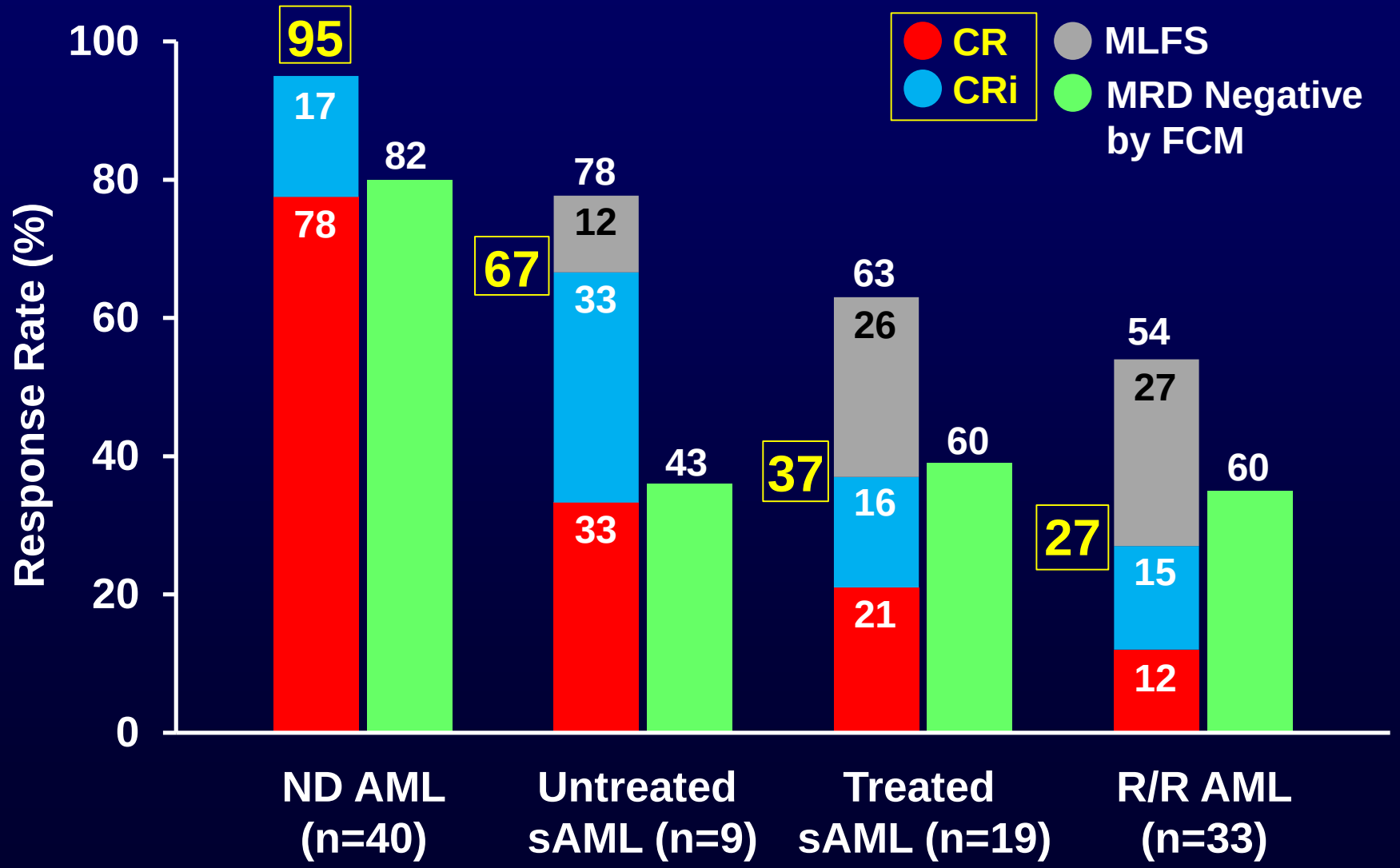
The University of Texas MD Anderson Cancer Center, Houston, TX.

DEC10-VEN: Molecular Subgroups & Resistance
Results: All Patients (N=101)

Patient characteristics	n (%), median [range]
Age ≥ 70 years	52 (51)
ECOG PS ≥2	28 (28)
Diagnosis	
Newly diagnosed AML	40 (40)
Untreated secondary AML	9 (9)
Treated secondary AML	19 (19)
Relapsed/refractory AML	33 (32)
ELN 2017 risk group	
Favorable	18 (18)
Intermediate	15 (15)
Adverse	68 (67)
Prior therapies in treated patients	2 [1-8]
HMA	31 (31)
Intensive chemotherapy	33 (32)
Stem-cell transplantation	18 (18)

DEC10-VEN: Molecular Subgroups & Resistance

Results: Response



DEC10-VEN: Molecular Subgroups & Resistance Results: Untreated AML – ND + untreated sAML

Mutational Subgroups	ORR	CR/CRi	MRD-	DOR	OS	1 year OS
	n (%) or n/N (%)			median, months		%
NPM1 (n=13)	13 (100)	13 (100)	13/13 (100)	NR	NR	76
IDH1/2 (n=12)	12 (100)	11 (92)	9/12 (75)	NR	NR	83
RUNX1 (n=8)	8 (100)	8 (100)	4/8 (50)	9.7	NR	50
TP53 (n=13)	11 (85)	11 (85)	8/11 (73)	5.7	5.7	15
ASXL1 (n=9)	7 (78)	6 (67)	4/7 (57)	8.5	12.4	67
N/KRAS (n=13)	11 (85)	10 (77)	7/11 (64)	6.4	12.4	62

ORR = CR+CRi+MLFS, MRD tested by FCM

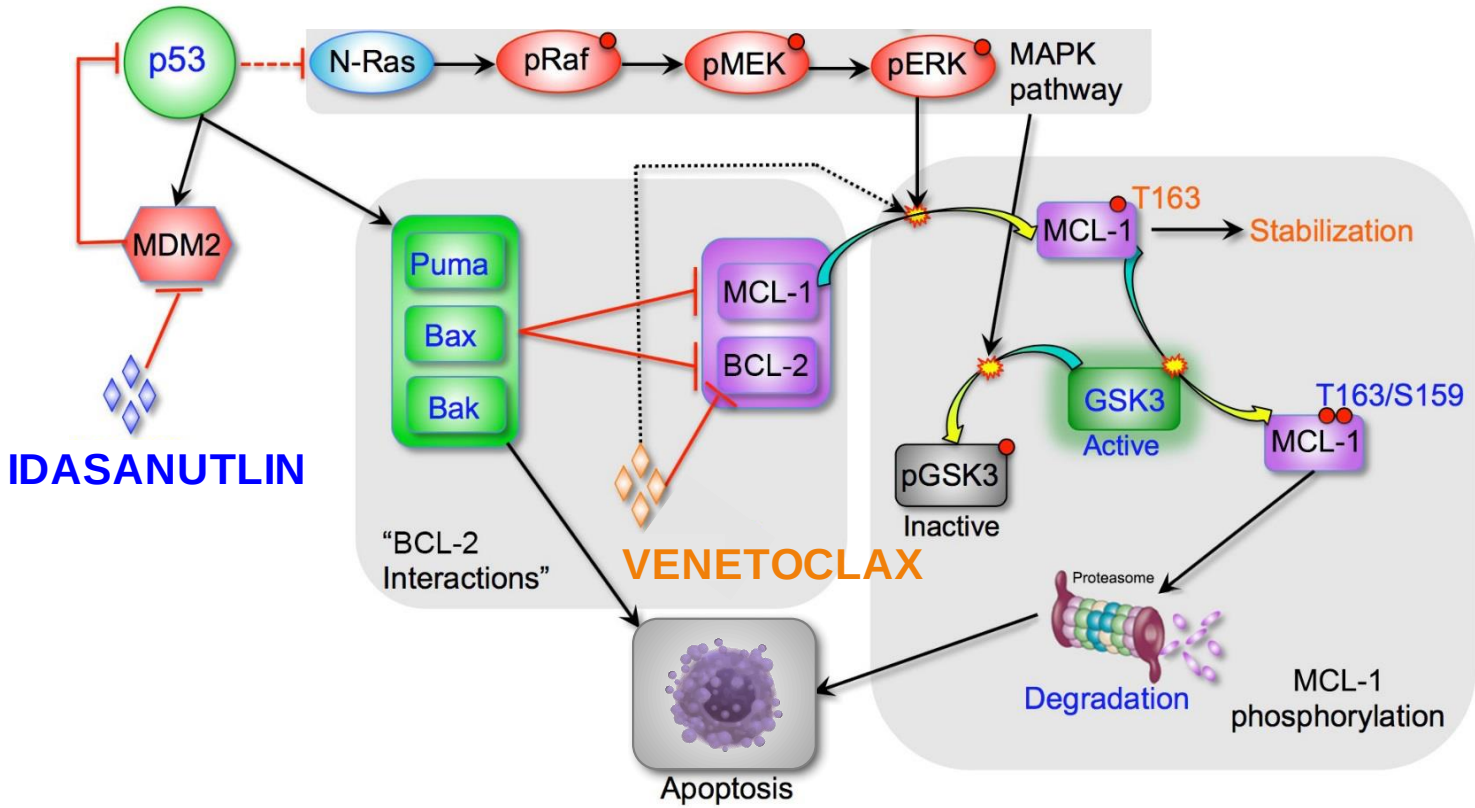
Updated results from the venetoclax (Ven) in combination with idasanutlin (Idasa) arm of a Phase 1b trial in elderly patients with relapsed or refractory AML ineligible for cytotoxic chemotherapy

Naval G Daver,[1] Jacqueline S Garcia,[2] Brian A Jonas,[3] Kevin R Kelly,[4] Sarit Assouline,[5] Joseph M Brandwein,[6] Pierre Fenaux,[7] Rebecca L Olin,[8] Giovanni Martinelli,[9] Stefania Paolini,[10] Arnaud Pigneux,[11] Daniel A Pollyea,[12] Bayard L Powell,[13] Gail J Roboz,[14] Agostino Tafuri,[15] Norbert Vey,[16] Giuseppe Visani,[17] Karen WL Yee,[18] Monique Dail,[19] Cherie Green,[19] Whitney P Kirschbrown,[19] Wan-Jen Hong,[19] Marion G Ott,[20] Maika Onishi,[19] Jue Wang,[19] Marina Y Konopleva,[1] Michael Andreeff[1]

[1]University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Center for Oncology Hematology Outcomes Research and Training (COHORT) Division of Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA, USA; [4]University of Southern California, Los Angeles, CA, USA; [5]Jewish General Hospital, Montreal, QC, Canada; [6]Division of Hematology, University of Alberta, Alberta, Canada; [7]Hôpital Saint-Louis, Université Paris Diderot, Paris, France; [8]University of California San Francisco, San Francisco, CA, USA; [9]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola (FC), Italy; [10]Department of Experimental, Diagnostic and Speciality Medicine, Institute of Hemetology "L. and A. Seràgnoli", University of Bologna, Bologna, Italy; [11]Bordeaux Haut-Leveque University Hospital, Pessac, France; [12]University of Colorado, Aurora, CO, USA; [13]Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC, USA; [14]Weill-Cornell Medical College, New York Presbyterian, New York, NY, USA; [15]Hematology, DMCM, University Hospital Sant'Andrea-Sapienza, Rome, Italy; [16]Hematologie Clinique, Institut Paoli Calmettes, Marseille, France; [17]Hematology, Ospedale San Salvatore, Pesaro, Italy; [18]Princess Margaret Cancer Centre, Toronto, ON, Canada; [19]Genentech, Inc., South San Francisco, CA, USA; [20]F. Hoffmann-La Roche Ltd, Basel, Switzerland

Mechanistic rationale for BCL-2 and MDM2 inhibition

- Combined inhibition of BCL-2 and MDM2 has been shown to have synergistic apoptotic effects in both *in vitro* and *in vivo* models
- MDM2 inhibition promotes degradation of MCL-1, overcoming resistance to BCL-2 inhibition in AML



Reprinted from Cancer Cell, Vol 32, Pan R, et al. Synthetic lethality of combined Bcl-2 inhibition and p53 activation in AML: mechanisms and superior anti-leukemic efficacy, 748–60.e6, 2017, with permission from Elsevier.

GSK3, glycogen synthase kinase 3; MCL-1 myeloid cell leukemia 1; PUMA, p53 upregulated modulator of apoptosis

Pan R, et al. Cancer Cell 2017;32:748–60.e6

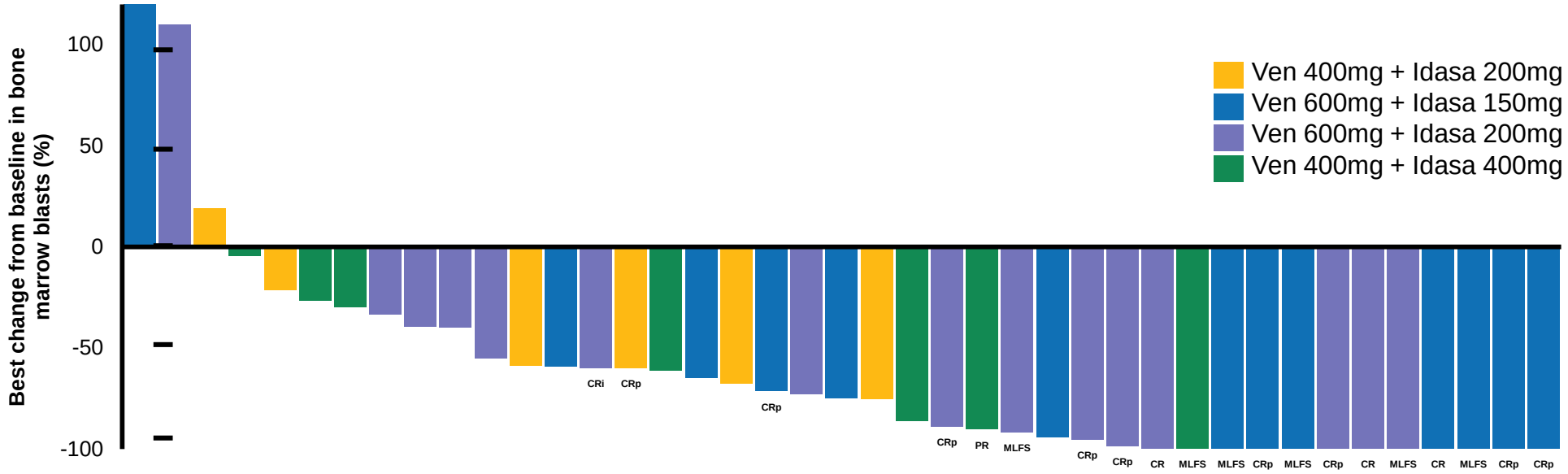
Ven + Idasa demonstrated a manageable safety profile

AEs (≥25% of patients), n (%)	Ven + Idasa (All doses, N=49)	
	All grades	Grade ≥3
Diarrhea*	44 (90)	2 (4)
Nausea	38 (78)	1 (2)
Vomiting	26 (53)	0
Febrile neutropenia	23 (47)	23 (47)
Hypokalemia	23 (47)	8 (16)
Decreased appetite	16 (33)	5 (10)
Hypomagnesemia	15 (31)	0
Neutropenia†	14 (29)	14 (29)
Thrombocytopenia	14 (29)	13 (27)
Anemia	13 (27)	9 (18)
Fatigue	13 (27)	5 (10)

Serious AEs (>5% patients), n (%)	Ven + Idasa (All doses, N=49)
Febrile neutropenia	18 (37)
Sepsis	7 (14)
Pneumonia	6 (12)
Septic shock	4 (8)
Pneumonia fungal	3 (6)
Other key AEs	
TLS‡	
Laboratory	3 (6)
Clinical	1 (2)
Early deaths	
30-day mortality	6%

*No grade 3 or higher diarrhea after implementation of mandatory anti-diarrheal prophylaxis (N=25); †Ven and Idasa dose modifications/interruptions due to neutropenia occurred in 16% and 14%, respectively; ‡All TLS events resolved with standard measures and did not result in treatment discontinuation
AE, adverse event; TLS, tumor lysis syndrome

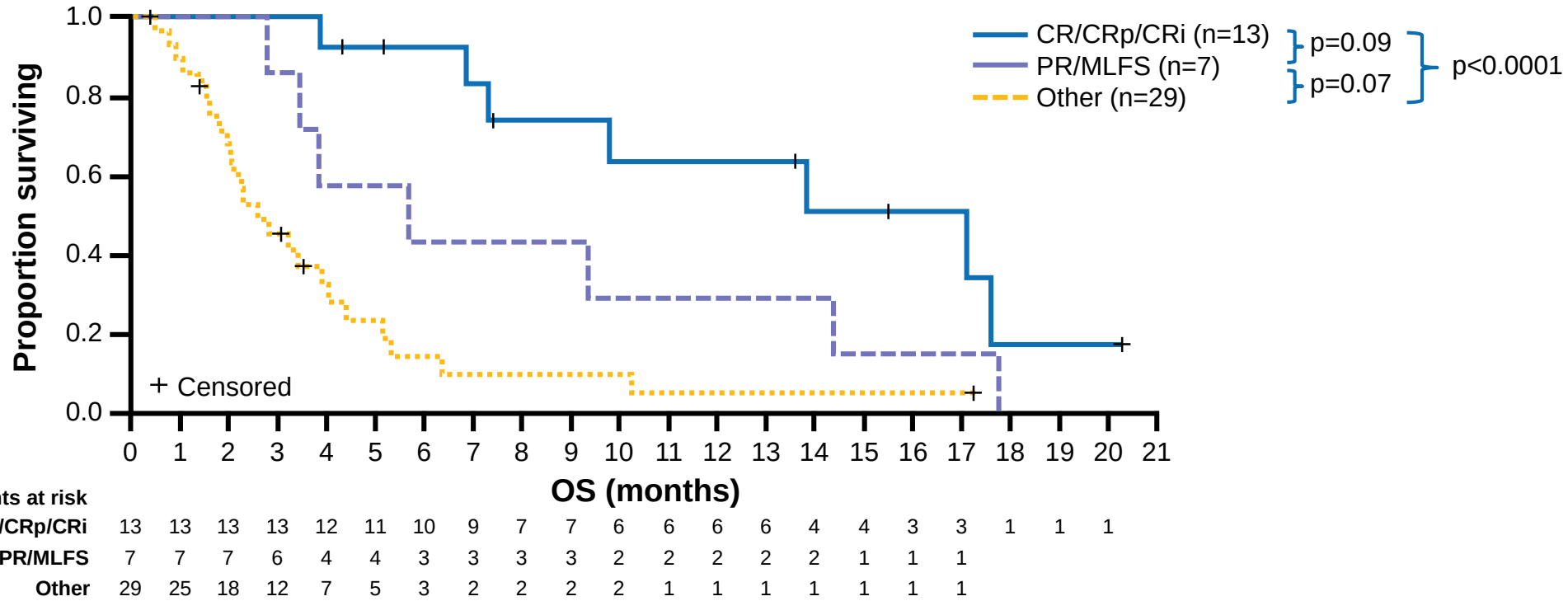
Ven + Idasa demonstrated encouraging efficacy (N=49, all doses)



Total patients treated, n (%)	Ven 400mg + Idasa 200mg (n=6)	Ven 600mg + Idasa 150mg (n=13)	Ven 600mg + Idasa 200mg (n=21)	Ven 400mg + Idasa 400mg (n=9)	Total (N=49)
Anti-leukemic response (cCR/PR/MLFS)	1 (17)	**8 (62)**	**9 (43)**	2 (22)	20 (41)
CR	0	1 (8)	2 (10)	0	3 (6)
CRp	1	4 (31)	4 (19)	0	9 (18)
CRi	0	0	1 (5)	0	1 (2)
PR	0	0	0	1 (11)	1 (2)
MLFS	0	3 (23)	2 (10)	1 (11)	6 (12)
cCR (CR/CRp/CRi)	1 (17)	**5 (38)**	**7 (33)**	0	13 (27)

cCR, composite complete response; CRi, complete response with incomplete blood count recovery; CRp, complete response with incomplete platelet count recovery; MLFS, morphologic leukemia-free state; PR, partial response. **Note:** 7 patients had missing baseline or post-baseline bone marrow blast count (not pictured in figure above)

Median OS was 17.1 months for CR/CRp/CRi responders versus 2.6 months for non-responders (n=49, all patients)



No. of patients at risk																					
CR/CRp/CRi	13	13	13	13	12	11	10	9	7	7	6	6	6	6	4	4	3	3	1	1	1
PR/MLFS	7	7	7	6	4	4	3	3	3	3	2	2	2	2	2	1	1	1			
Other	29	25	18	12	7	5	3	2	2	2	2	1	1	1	1	1	1	1			

Months (range)	Total N=49
Median OS	4.4 (0.4–20.3)
cCR (CR/CRp/CRi)	17.1 (3.8–20.3)*
PR/MLFS	5.7 (2.8–17.7)
Other	2.6 (0.4–17.2)
Median follow-up	3.8 (0.4–20.3)

*cCR vs PR/MLFS: p=0.09 (HR 0.42, 95% CI 0.14–1.20); cCR vs other: p<0.0001 (HR 0.17, 95% CI 0.06–0.42); PR/MLFS vs other: p=0.07 (HR 0.43, 95% CI 0.17–1.08).

61st American Society of Hematology (ASH) Annual Meeting & Exposition, December 7–10, 2019

A Phase 1b Study of Glasdegib in Combination With Azacitidine in Patients With Untreated Higher-Risk Myelodysplastic Syndromes, Acute Myeloid Leukemia, and Chronic Myelomonocytic Leukemia [Abstract 177]

Mikkael A Sekeres[1], Michael W Schuster[2], Magalie Joris[3], Jürgen Krauter[4], Johan A Maertens[5], Emmanuel Gyan[6], Tibor Kovacsovics[7], Amit Verma[8], Paresh Vyas[9], Eunice S Wang[10], Weidong Wendy Ma[11], Mirjana Zeremski[11], Arthur Kudla[11], Geoffrey Chan[11], Amer M Zeidan[12]

[1]Leukemia Program, Cleveland Clinic, Cleveland, OH , USA; [2]Stony Brook University Hospital Cancer Center, Stony Brook, NY, USA; [3]CHU Amiens-Picardie, Amiens, France; [4]Medizinische Klinikum Braunschweig GmbH, Braunschweig, Germany; [5]UZ Leuven, Leuven, Belgium; [6]CHU de Tours – Hôpital Bretonneau, Tours, France; [7]Huntsman Cancer Institute, Salt Lake City, UT, USA; [8]Montefiore Medical Center, Bronx, NY, USA; [9]MRC Molecular Haematology Unit, Oxford Centre for Haematology, University of Oxford and Oxford University Hospitals NHS Trust, Oxford, UK; [10]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [11]Pfizer Oncology, New York, NY, USA; [12]Yale University School of Medicine and Yale Cancer Center, New Haven, CT, USA

BRIGHT MDS & AML 1012 Study Design

- BRIGHT MDS & AML 1012 (NCT02367456) is an ongoing open-label, multicenter, phase 1b trial
- Key eligibility criteria:
  - Patients were aged ≥18 years
  - Newly diagnosed AML, higher-risk MDS, and CMML
  - Clinical indication for treatment with AZA for AML or MDS
  - No prior treatment with a Smoothened inhibitor and/or a hypomethylating agent

Population

AML cohort (n=30)
- De novo or secondary AML

MDS cohort (n=30)
- MDS (intermediate, high, or very high risk by IPSS-R) or CMML

Treatment

Glasdegib + AZA
- Glasdegib 100 mg once daily
- AZA (75 mg/m^2/day) on Days 1–7 of a 28-day cycle

Endpoints

Primary
- Rate of CR

Secondary
- Overall survival
- Disease-specific efficacy measures
- Time to and duration of CR
- Safety
- Pharmacokinetic analysis

Study start date: April 28, 2015. Data cut-off: September 11, 2019.

AML=acute myeloid leukemia; AZA=azacitidine; CMML=chronic myelomonocytic leukemia; CR=complete remission; IPSS-R=Revised International Prognostic Scoring System; MDS=myelodysplastic syndrome

Patient Demographics and Treatment

Characteristic	AML (n=30)	MDS* (n=30)
Male, n (%)	18 (60.0)	24 (80.0)
Age, years		
Median (range)	74 (56–87)	72 (55–89)
Disease history, n (%)		
De novo	19 (63.3)	27 (90.0)
Secondary	11 (36.7)	3 (10.0)
ELN genetic risk category, n (%)		
Favorable	2 (6.7)	N/A
Intermediate	9 (30.0)	N/A
Adverse	18 (60.0)	N/A
Unknown	1 (3.3)	N/A
IPSS-R MDS category, n (%)	**N/A**	**n=27**
Intermediate risk	N/A	4 (14.8)
High risk	N/A	14 (51.9)
Very high risk	N/A	9 (33.3)
MDS with ≥5% BM blasts	**N/A**	**N=27**
n (%)	N/A	20 (74.1)

	AML (n=30)	MDS* (n=30)
Treated, n (%)	30 (100.0)	30 (100.0)
Treatment duration, months		
Median (range)	5.0 (0.3–14.9)	4.7 (0.4–15.5)
Follow-up, months		
Median (95% CI)	11.5 (9.9–12.5)	9.9 (9.2–14.1)
End of study disposition, n (%)		
Death	15 (50.0)	10 (33.3)
Refused further follow-up	3 (10.0)	1 (3.3)

- **Cycle 2 dose delays**
  - 8.7% (2/23) of patients with AML
  - 11.5% (3/26) of patients with MDS

* Includes 3 patients with chronic myelomonocytic leukemia

AML=acute myeloid leukemia; BM=bone marrow; CI=confidence interval; ELN=European LeukemiaNet; IPSS-R=Revised International Prognostic Scoring System; MDS=myelodysplastic syndrome; N/A=not applicable

AML Cohort: All-Causality Treatment-Emergent Adverse Events

TEAEs ≥ Grade 3 in >1 Patient

	Glasdegib + AZA (n=30)			
TEAEs, n (%)	Grade 3	Grade 4	Grade 5	Total
Any AEs	10 (33.3)	10 (33.3)	8 (26.7)	28 (93.3)
Non-hematologic TEAEs				
Decreased appetite	6 (20.0)	0	0	6 (20.0)
Disease progression	0	0	3 (10.0)	3 (10.0)
ECG QT prolongation	2 (6.7)	1 (3.5)	0	3 (10.0)
ALT increased	2 (6.7)	0	0	2 (6.7)
Back pain	2 (6.7)	0	0	2 (6.7)
Diarrhea	2 (6.7)	0	0	2 (6.7)
Hypertension	2 (6.7)	0	0	2 (6.7)
Hyponatremia	1 (3.3)	1 (3.3)	0	2 (6.7)
Hypotension	2 (6.7)	0	0	2 (6.7)
Nausea	2 (6.7)	0	0	2 (6.7)
Renal failure	0	2 (6.7)	0	2 (6.7)
Sepsis	0	1 (3.3)	1 (3.3)	2 (6.7)
Syncope	2 (6.7)	0	0	2 (6.7)
Urinary tract infection	2 (6.7)	0	0	2 (6.7)
Vomiting	2 (6.7)	0	0	2 (6.7)
Weight decreased	2 (6.7)	0	0	2 (6.7)

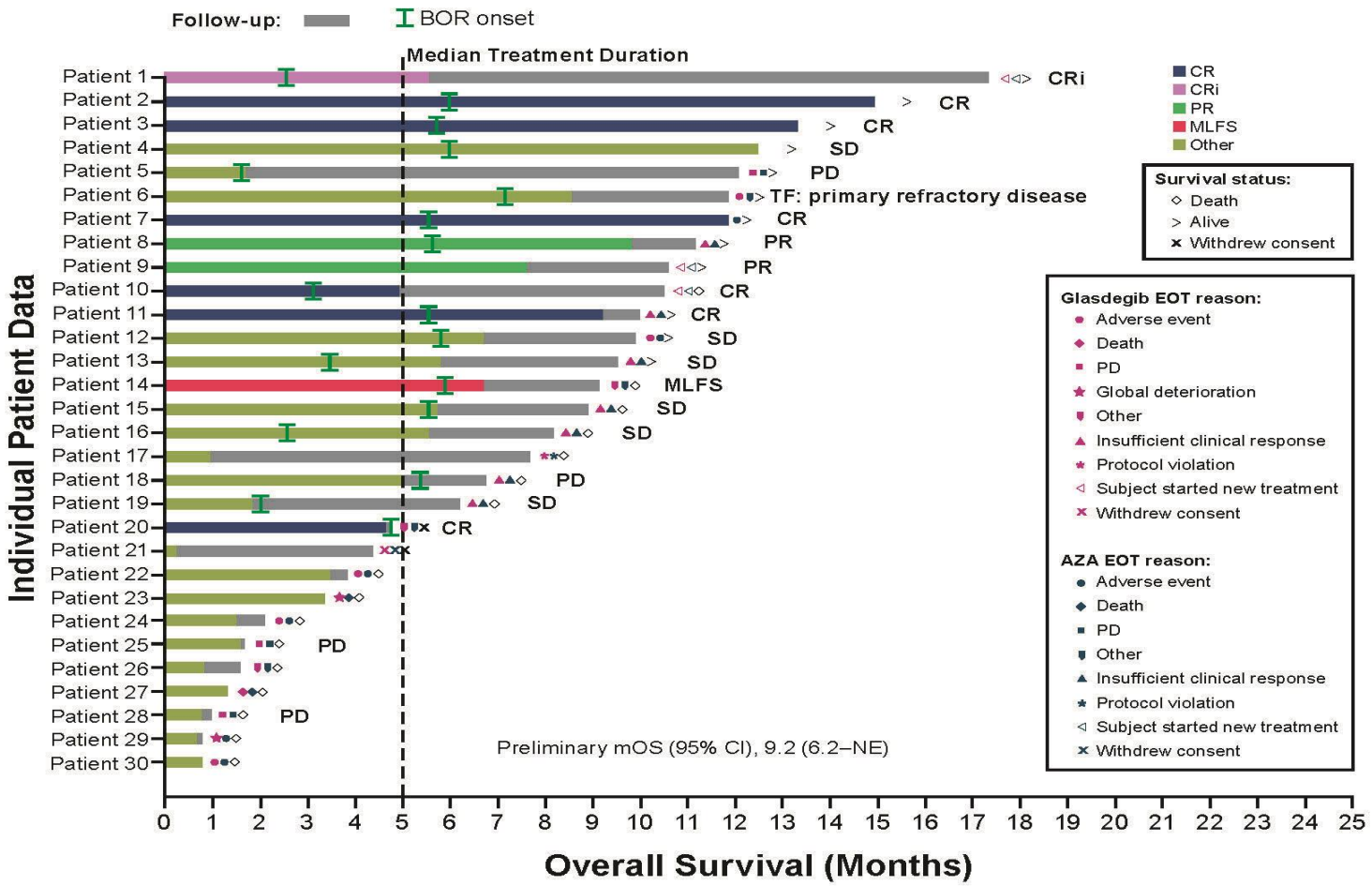
Smoothened Inhibitor–Associated TEAEs

	Glasdegib + AZA (n=30)			
TEAEs, n (%)	Grade 1	Grade 2	Grade 3–5	Total
Muscle spasms	4 (13.3)	4 (13.3)	0	8 (26.7)
Dysgeusia	4 (13.3)	3 (10.0)	0	7 (23.3)
Alopecia	1 (3.3)	0	0	1 (3.3)

Additional safety data for glasdegib + AZA in patients with AML:
Poster #3916; December 9, 2019: 6:00–8:00 PM.

AE=adverse event; ALT=alanine aminotransferase; AML=acute myeloid leukemia; AZA=azacitidine; ECG=electrocardiograph; TEAE=treatment-emergent adverse event

AML Cohort:
Overall Survival With Best Overall Response

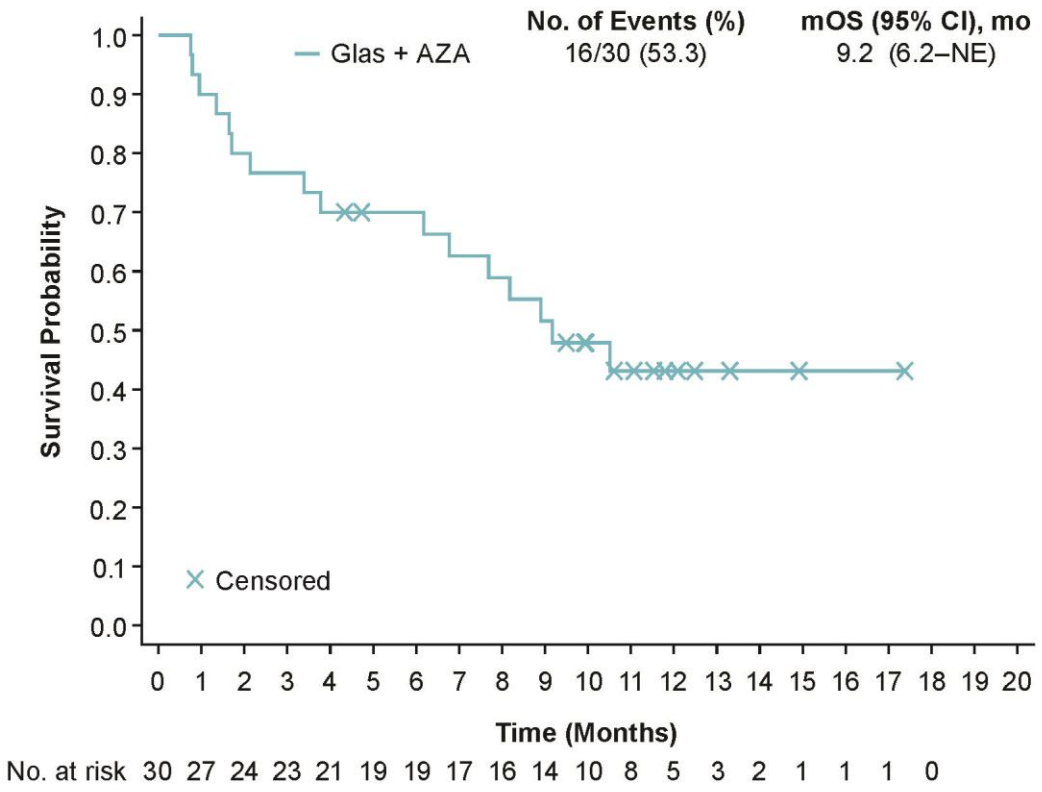


Response	n (%)
CR	6 (20.0)
CRi	1 (3.3)
CR + CRi	7 (23.3)
PR	2 (6.7)
MLFS	1 (3.3)
SD	6 (20.0)

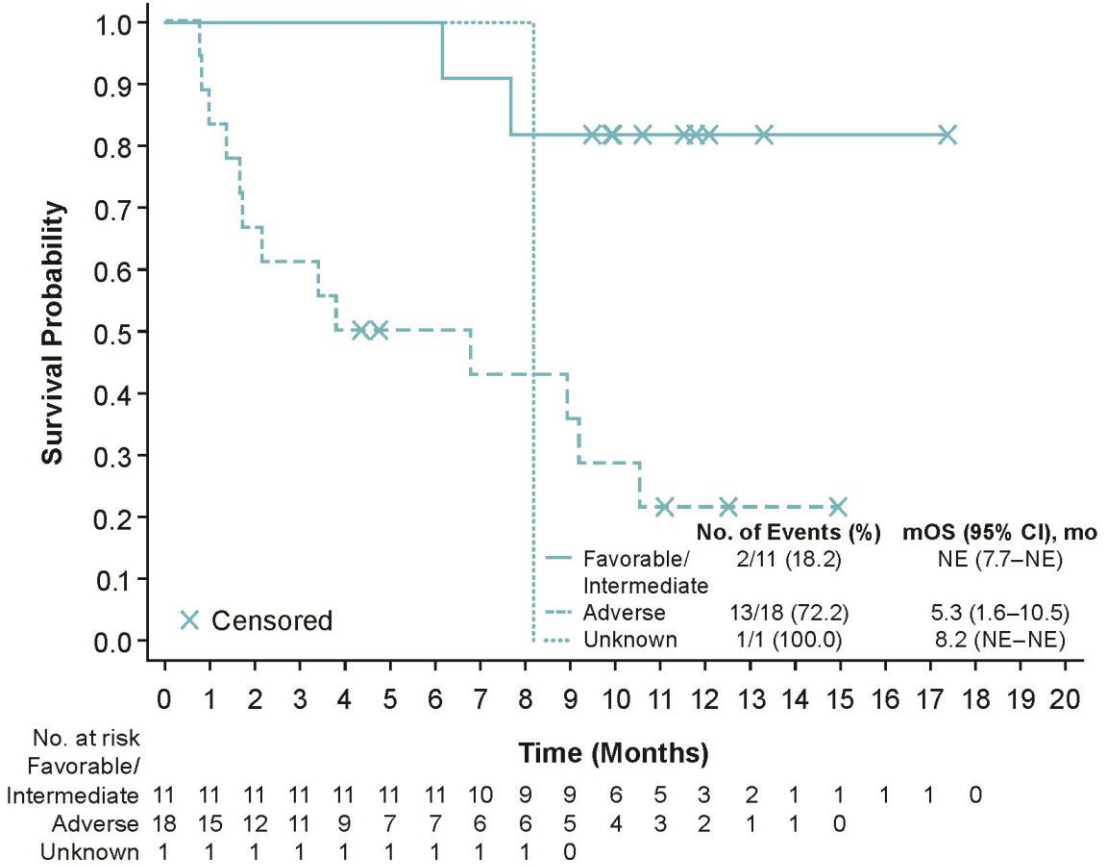
AML=acute myeloid leukemia; AZA=azacitidine; BOR=best overall response; CR=complete remission; CRi=complete remission with incomplete hematologic response; MLFS=morphologic leukemia-free state; PD=progressive disease; PR=partial remission; SD=stable disease; TF=treatment failure

AML Cohort: Preliminary Overall Survival

All Patients



ELN Genetic Risk Category



AML=acute myeloid leukemia; AZA=azacitidine; CI=confidence interval; ELN=European LeukemiaNet; Glas=glasdegib; mo=months; mOS=median overall survival; NE=not evaluable

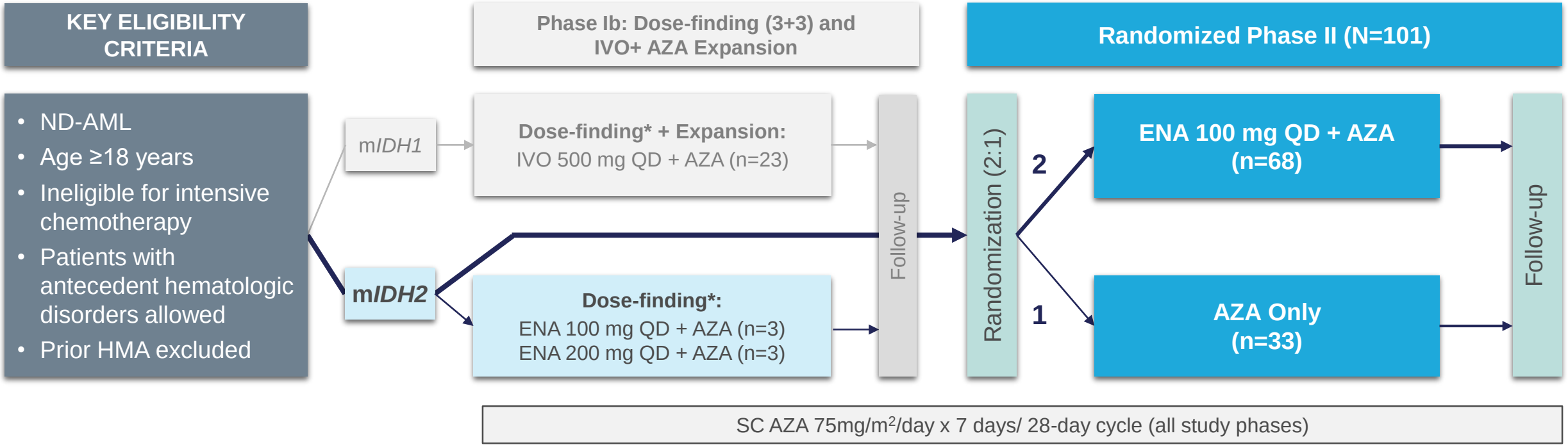
ABSTRACT 643

Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) with Isocitrate Dehydrogenase 2 (*IDH2*) Mutations: Interim Phase II Results from an Ongoing, Randomized Study

Courtney D. DiNardo[1], Andre C. Schuh[2], Eytan M. Stein[3,4], Pau Montesinos[5,6], Andrew Wei[7,8], Stephane de Botton[9], Amer M. Zeidan[10], Amir T. Fathi[11,12], Lynn Quek[13], Hagop M. Kantarjian[1], Mark G. Frattini[14], Frederik Lersch[15], Jing Gong[14], Aleksandra Franovic[14], Kyle MacBeth[14], Paresh Vyas[12] and Hartmut Döhner[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]Weill Cornell Medical College, New York, NY; [5]Hospital Universitario y Politécnico Le Fe, Valencia, Spain; [6]CIBERONC, Instituto Carlos III, Madrid, Spain; [7]The Alfred Hospital, Melbourne, Australia; [8]Australian Centre for Blood Diseases, Monash University, Melbourne, Australia; [9]Gustave Roussy, Villejuif Cedex, France; [10]Yale University School of Medicine and Yale Cancer Center, New Haven, CT; [11]Harvard Medical School, Boston, MA; [12]Massachusetts General Hospital, Cambridge, MA; [13]MRC Molecular Haematology Unit and Oxford Biomedical Research Centre, University of Oxford and Oxford University Hospitals, Oxford, United Kingdom; [14]Bristol-Myers Squibb, Summit, NJ; [15]Celgene, A Bristol-Myers Squibb Company, Summit, NJ; [16]Department of Internal Medicine III, University Hospital Ulm, Ulm, Germany

AG221-AML-005: STUDY DESIGN



Primary Endpoint: ORR

Key Secondary Endpoints: CR rate, safety, overall survival (OS), event-free survival (EFS)

*Dose finding for ENA or IVO; AZA dose remained constant.
AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; EFS, event-free survival; ENA, enasidenib; HMA, hypomethylating agent; IVO, ivosidenib; m*IDH1*/m*IDH2*, mutant-*IDH1*/mutant-*IDH2*; ND, newly diagnosed; ORR, overall response rate; OS, overall survival; SC, subcutaneous.

DiNardo et al., Abstract 643. Oral presentation, ASH 2019

BASELINE DEMOGRAPHIC AND DISEASE CHARACTERISTICS

	ENA + AZA (n=68)	AZA Only (n=33)
Age, years, median (range)	75 (62–85)	75 (57–85)
Age ≥65 years, n (%)	61 (90)	32 (97)
Gender, % Male / % Female	47 / 53	67 / 33
IDH2 mutation, n (%)		
IDH2-R140	51 (75)	24 (73)
IDH2-R172	16 (24)	7 (21)
Both	0	1 (3)
Missing	1 (1)	1 (3)
AML diagnosis, n (%)		
de novo AML	48 (71)	25 (76)
Secondary AML	20 (29)	8 (24)
ECOG PS score, n (%)		
0	15 (22)	7 (21)
1	42 (62)	16 (48)
2	11 (16)	10 (30)
Hemoglobin, g/dL, median (range)	9.2 (4.0–13.6)	9.0 (6.7–14.5)
Platelets, 10^9/L, median (range)	62 (6–788)	76 (6–1071)
WBC, 10^9/L, median (range)	3.0 (0.1–83.0)	3.5 (0.8–29.6)

	ENA + AZA (n=68)	AZA Only (n=33)
Co-mutations, n (%)	n=45	n=18
DNMT3A	20 (44)	6 (33)
ASXL1	17 (38)	8 (44)
RUNX1	8 (18)	3 (17)
FLT3–ITD	5 (11)	1 (6)
TP53	5 (11)	0
NRAS	4 (9)	0
NPM1	2 (4)	1 (6)
ELN risk, n (%)	n=45	n=18
Favorable	3 (7)	1 (6)
Intermediate	16 (36)	7 (39)
Adverse	26 (58)	10 (56)
Cytogenetic risk, n (%)	n=54	n=21
Good	1 (1)	0
Intermediate	43 (80)	19 (90)
Poor	10 (19)	2 (10)

AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; IDH2, isocitrate dehydrogenase-2; WBC, white blood cells.

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RESPONSE

- ORR and CR rate were both significantly higher with ENA + AZA *vs.* AZA Only

	ENA + AZA (n=68)		AZA Only (n=33)
Overall response (CR, CRi/CRp, PR, MLFS), n (%)	**48 (71)**		**14 (42)**
[ORR 95%CI]	[58, 81]		[26, 61]
***P* value**		**0.0064**	
CR, n (%)	**36 (53)**		**4 (12)**
[CR rate 95%CI]	[41, 65]		[3, 28]
***P* value**		**0.0001**	
CRi/CRp, n (%)	7 (10)		4 (12)
PR, n (%)	3 (4)		4 (12)
MLFS, n (%)	2 (3)		2 (6)
Stable disease, n (%)	13 (19)		13 (39)
Disease progression, n (%)	2 (3)		1 (3)
Not evaluable / Missing, n (%)	5 (7)		5 (15)
Time to first response, months, median (range)	1.9 (0.7–9.0)		2.0 (0.8–5.8)
Time to CR, months, median (range)	5.5 (0.7–19.5)		3.7 (3.0–4.1)
Duration of response, months, median [95%CI]	24.1 [11.1, NR]		12.1 [2.8, 14.6]

Data cutoff: August 19, 2019.
95%CI, 95% confidence interval; AZA, azacitidine; CR, complete remission; CRi/CRp, CR with incomplete hematologic or platelet recovery; ENA, enasidenib; MLFS, morphologic leukemia-free state; NR, not reached; ORR, overall response rate; PR, partial remission.

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Targeting CD70 with cusatuzumab eliminates acute myeloid leukemia stem cells in humans

ASH 2019

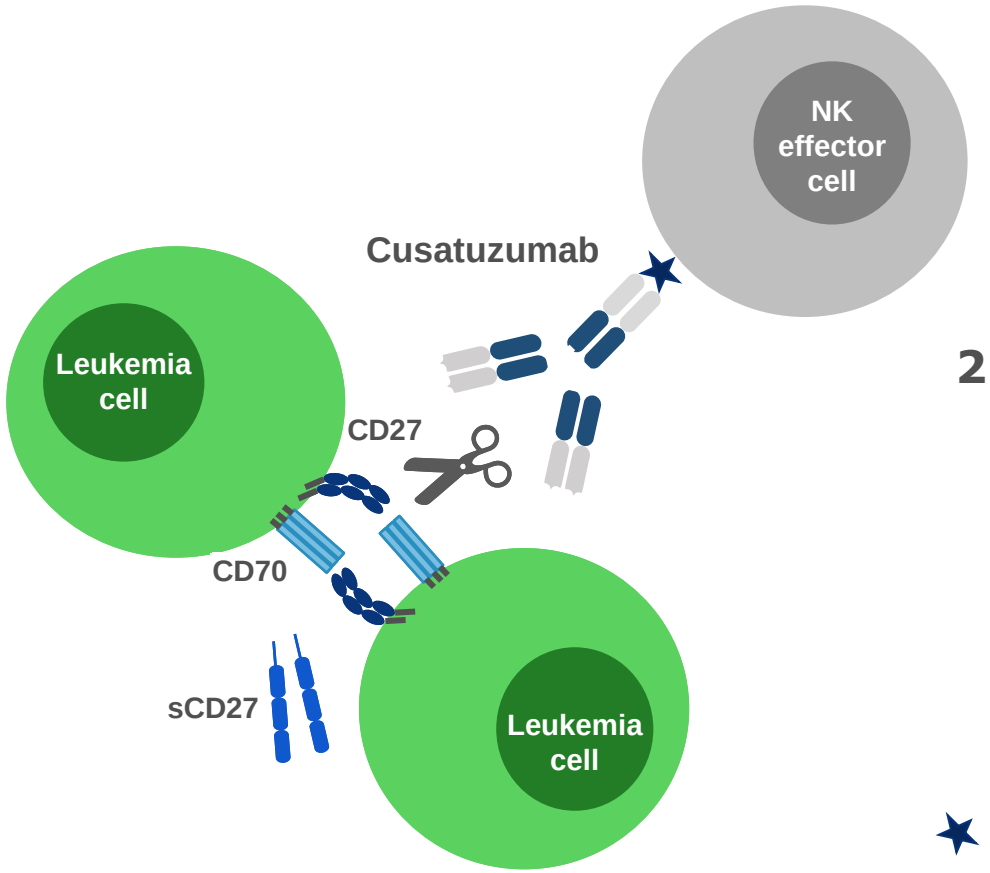
Adrian F. Ochsenbein[1,2], Thomas Pabst[1], Sabine Höpner[1,2], Ulrike Bacher[3], Magdalena Hinterbrandner[1,2,4], Yara Banz[5], Rouven Müller[6], Markus G. Manz[6], Walid H. Gharib[7], David Francisco[7], Remy Bruggmann[7], Luc van Rompaey[8], Mahan Moshir[8], Tim Delahaye[8], Domenica Gandini[8], Ellen Erzeel[8], Anna Hultberg[8], Samson Fung[8,9], Hans de Haard[8], Nicolas Leupin[8] and Carsten Riether[1,2]

[1]Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Switzerland; [2]Department of BioMedical Research (DBMR), University of Bern, Bern, Switzerland; [3]Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Switzerland; [4]Graduate School of Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland; [5]Institute of Pathology, University of Bern, Switzerland; [6]Department of Medical Oncology and Hematology, University Hospital Zürich and University of Zürich, Zürich, Switzerland; [7]Interfaculty Bioinformatics Unit and SIB Swiss Institute of Bioinformatics, University of Bern, Bern, Switzerland; [8]argenx BVBA, Zwijnaarde, Belgium; [9]Fung Consulting Healthcare & Life Sciences, Eching, Germany

Cusatuzumab targets CD70 with multiple mechanisms of action

1. **Blocking CD70-CD27 signaling,** which leads to myeloid differentiation and stops proliferation of LSCs

   - **Blocking release of soluble CD27,** which is generated by CD70-CD27 ligation



2. **Killing cells** via Fc-dependent, complement dependent cytotoxicity and enhanced antibody-dependent cellular cytotoxicity (ADCC)

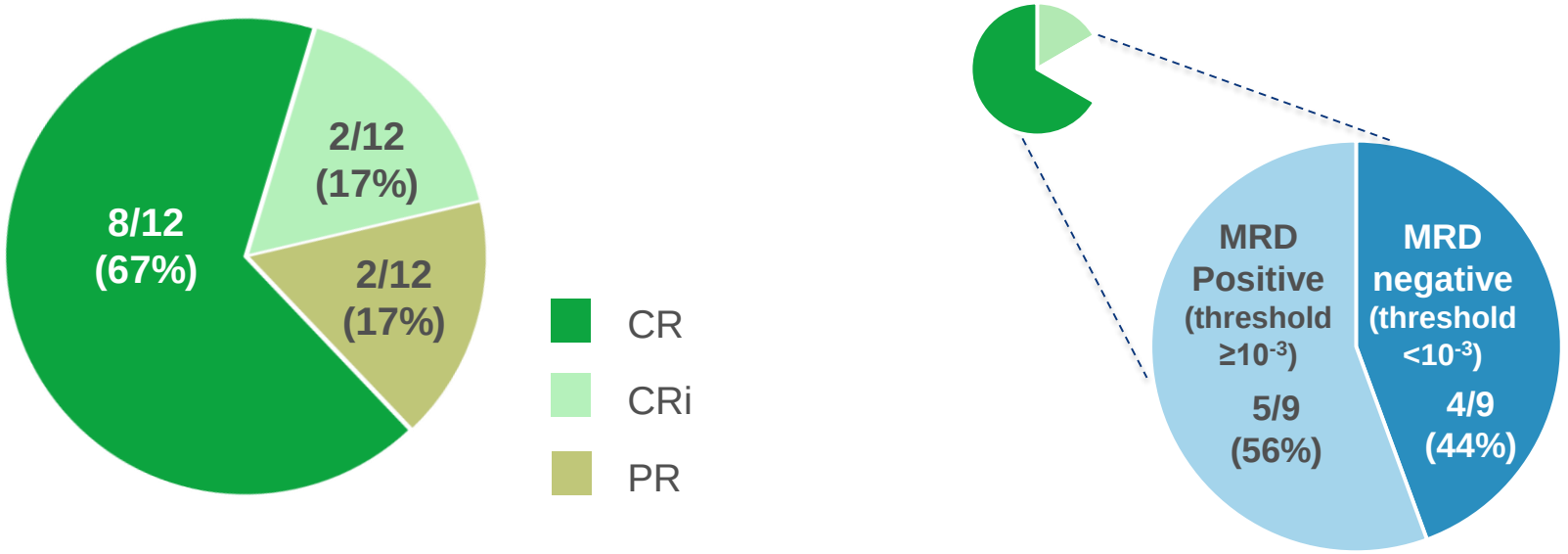
★ = ADCC enhanced antibody (using POTELLIGENT® for defucosylation)

LSC = leukemia stem cell

1. Bertrand et al, Genes. Chromosomes Cancer. 2013;52:764–774; 2. Liu et al, Onco Targets Ther. 2013;6:615–619; 3. Riether et al, J Exp Med. 2017;214:359–80; 4. Bowman et al, J Immunol. 1994;152:1756–1761; 5. Nolte et al, Immunol Rev. 2009;229:216–231

ARGX-110-1601: Phase 1 overall response rates
Encouraging hematologic response data*

100% response rate with 83% CR/CRi



- 3 patients responded after cusatuzumab monotherapy
- Significant blast reduction in bone marrow after cusatuzumab monotherapy

* Data cut-off: February 2019

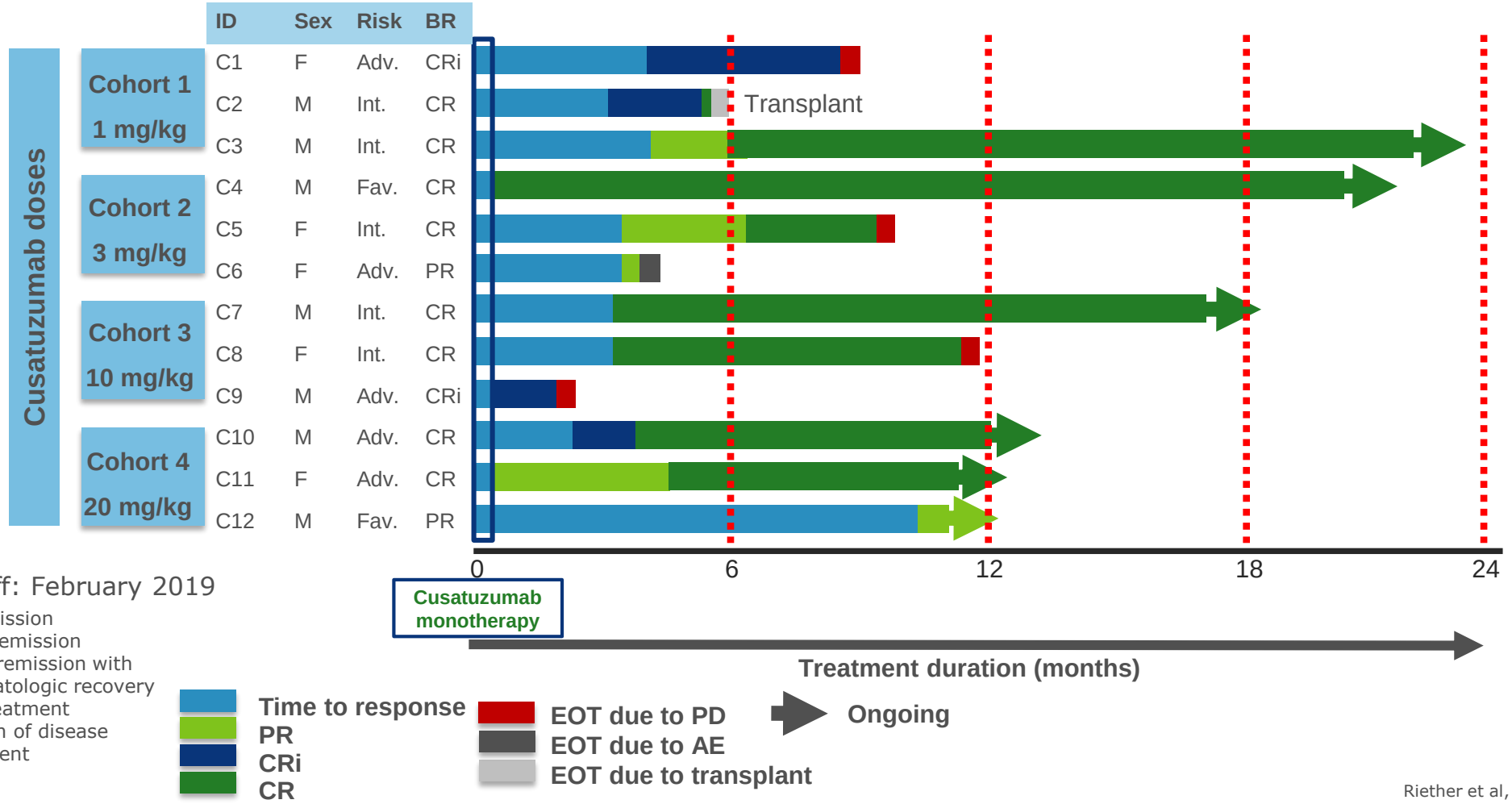
MRD data available on 9 of 10 patients; 1 flow cytometry sample result not available (due to short follow-up)
CR = complete remission; CRi = complete remission with incomplete hematologic recovery; MRD = minimal residual disease, measured by flow cytometry

NCT03030612

Riether et al, manuscript submitted

ARGX-110-1601: Individual patient responses (Phase 1)*

Swimmer plot illustrating response and outcome of AML patients treated with cusatuzumab in combination with azacitidine



* Data cut-off: February 2019

PR = partial remission
CR = complete remission
CRi = complete remission with incomplete hematologic recovery
EOT = end of treatment
PD = progression of disease
AE = adverse event

NCT03030612

Riether et al, manuscript submitted

Vielen Dank für die Aufmerksamkeit
Fragen?