Akute Myeloische Leukämie
Behandlungsstrategien und Studien der AMLSG

Prof. Hartmut Döhner

Ärztlicher Direktor, Klinik für Innere Medizin III
Universitätsklinikum Ulm

Hämatologie im Wandel 2019, Frankfurt, 22. März 2019

AMLSG: Algorithm of central diagnostics and trial portfolio*

Central Diagnostics

Molecular screening

- *PML-RARA*
- *RUNX1-RUNX1T1*
- *CBFB-MYH11*
- *MLLT3-KMT2A*
- *BCR-ABL1*
- *NPM1*
- *CEBPA*
- *FLT3*
- *IDH1/2*

within 24-48 hrs

- *RUNX1*
- *ASXL1*
- *TP53*

within 1st cycle

- *NGS gene panel*

Cytogenetics within 5-7 days

MFC (LAIP)

AMLSG-BiO [NCT01252485]

PML-RARA (high-risk)	APOLLO +/- ATO-ATRA-Ida	●
Core-binding factor AML	AMLSG 21-13 (n=203) ‚3+7' +/- Dasatinib	●
AML with *NPM1* mutations	AMLSG 09-09 (n=588) ‚3+7' + ATRA +/- GO	✓
AML with *FLT3* mutations	AMLSG 16-10 (n=440) ‚3+7' + Midostaurin	✓
	HOVON 156/ AMLSG 28-18 ‚3+7' + Mido. vs Gilt.	●
AML with *IDH1/IDH2* mutations	HOVON 150/ AMLSG 29-18 ‚3+7' +/- Ena. / Ivo.	●
AML – ELN intermediate-/high-risk	AMLSG 30-18 (n=533) ‚3+7' vs CPX-351	●
AML	*AMLSG 31-19/HOVON ‚3+7' +/- Venetoclax*	○

✓ Completed ● Active ● Activation Q2 / 2019 ○ Planned

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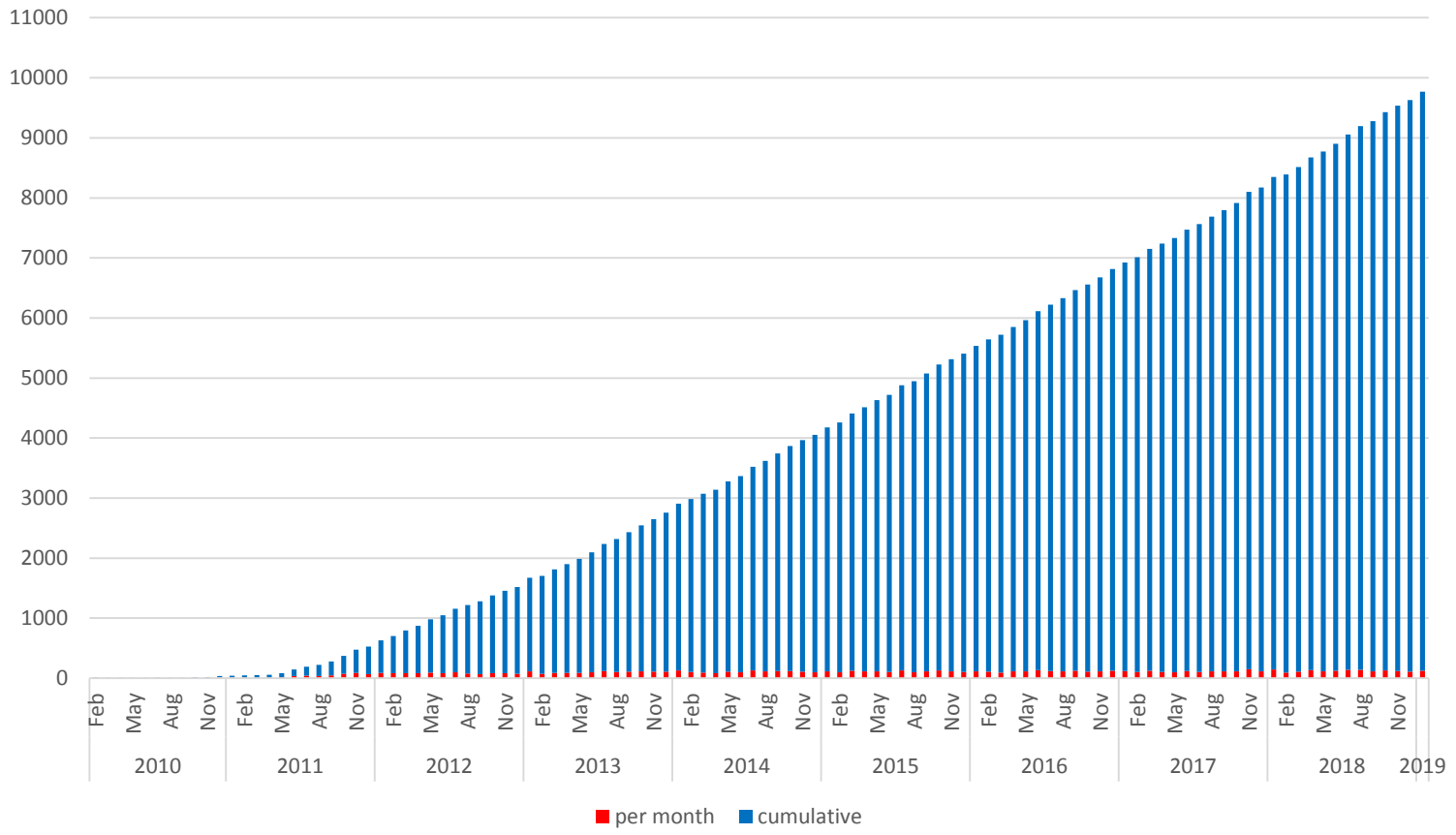
* Intensive first-line trials only
≥18 years, eligible for intensive chemotherapy

AMLSG BiO Registry



Time period:	7/2010-01/2019
No. of centers:	73
No. of pts:	9,646
Accrual/yr:	1,462 (2018)
	1,392 (2017)
	1,383 (2016)
Median age:	65 (18-98) yrs

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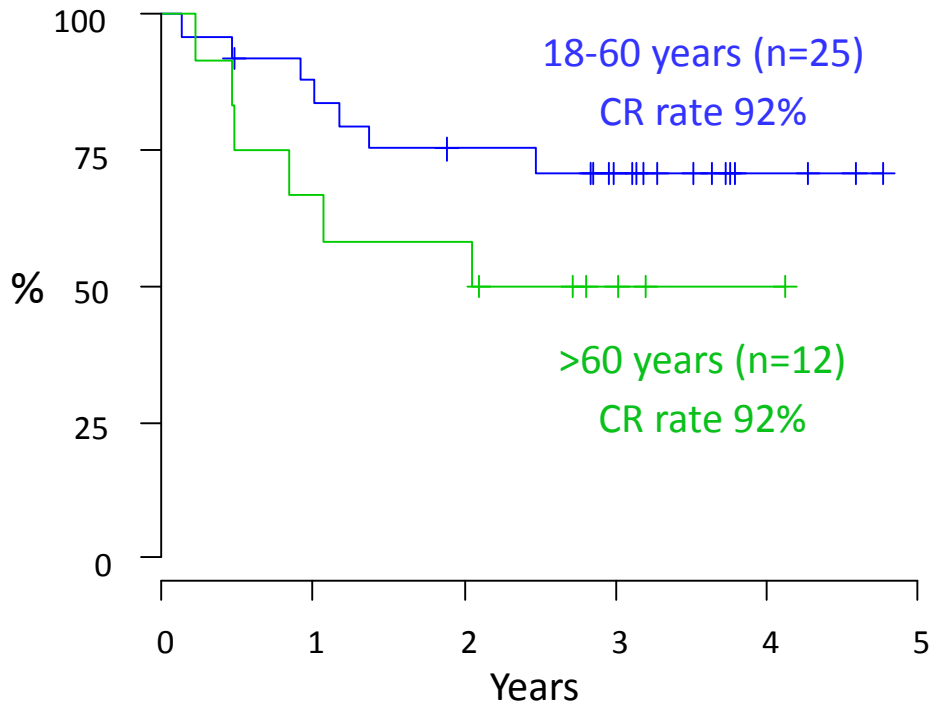
AMLSG-BiO [NCT01252485]

Phase Ib: Dasatinib plus chemotherapy for newly diagnosed CBF-AML: Overall survival by type of CBF-AML and age

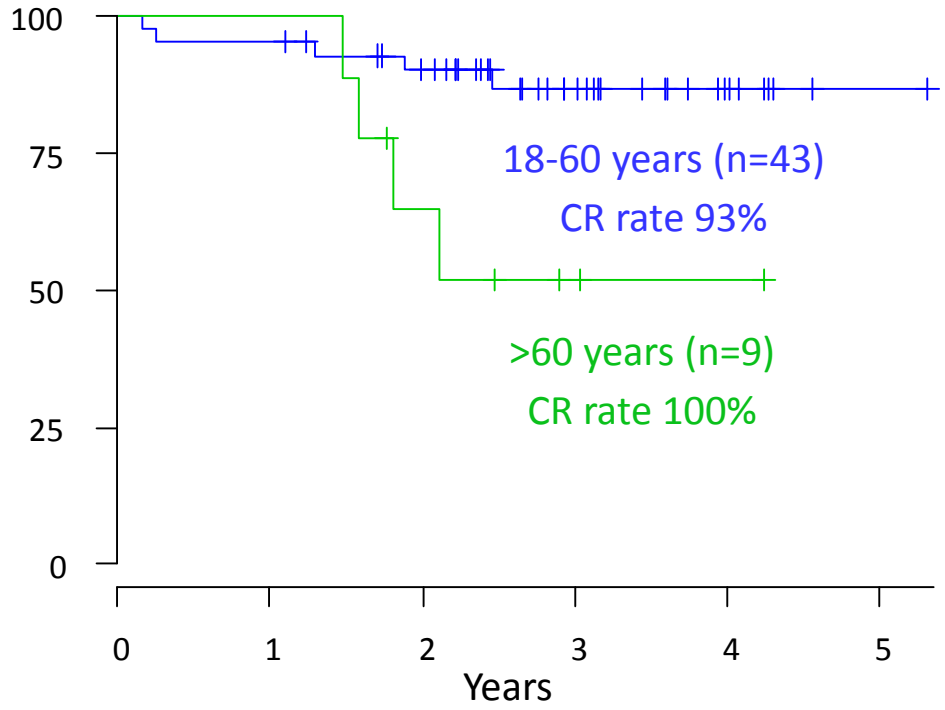
AML with t(8;21)

Age (yrs): 52 (27-73)



AML with inv(16)

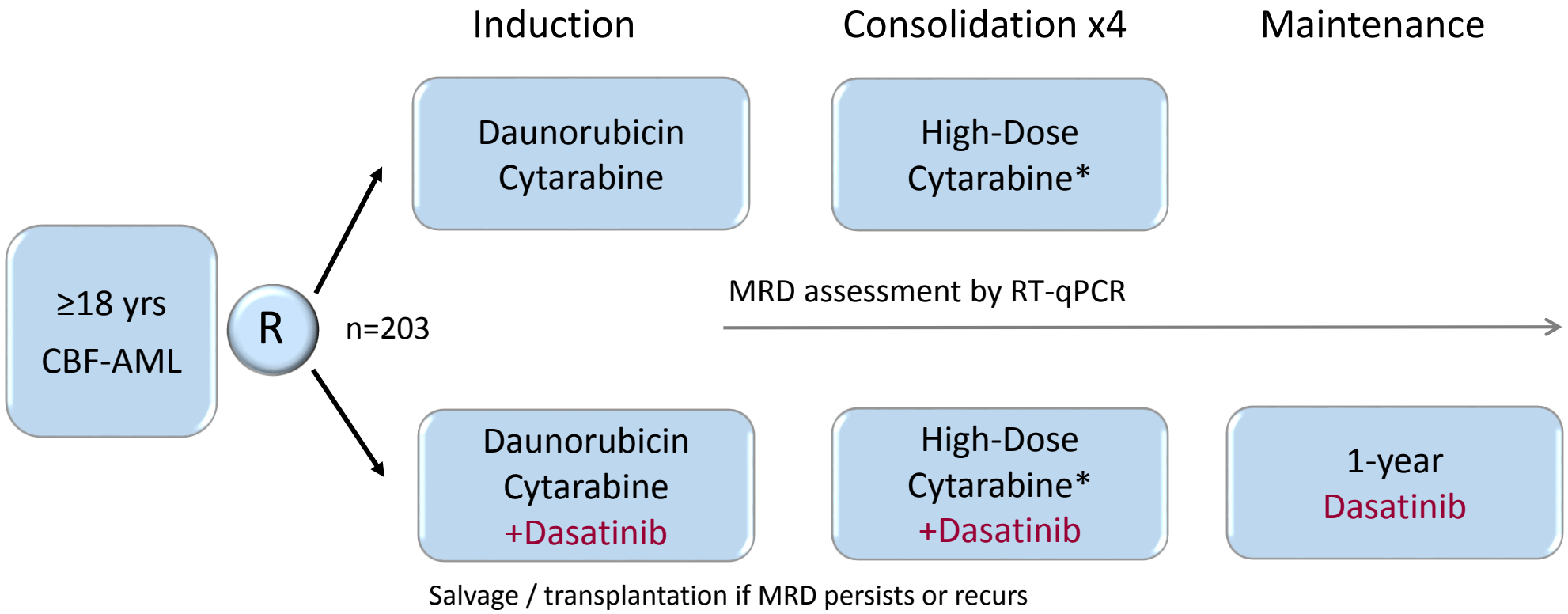
Age (yrs): 47 (19-72)



CBF, core-binding factor

Paschka P, et al. Leukemia. 2018;32(7):1621-1630.

Intensive chemotherapy with or without Dasatinib in patients with newly diagnosed Core-Binding Factor AML



Adult patients eligible for intensive therapy, no upper age limit

* Cytarabine: 18-60yrs: 3g/m^2, q12hr, d1-3; >60yrs: 1g/m^2, q12hr, d1-3

Primary endpoint: Event-free survival

Expected accrual: End of 2019

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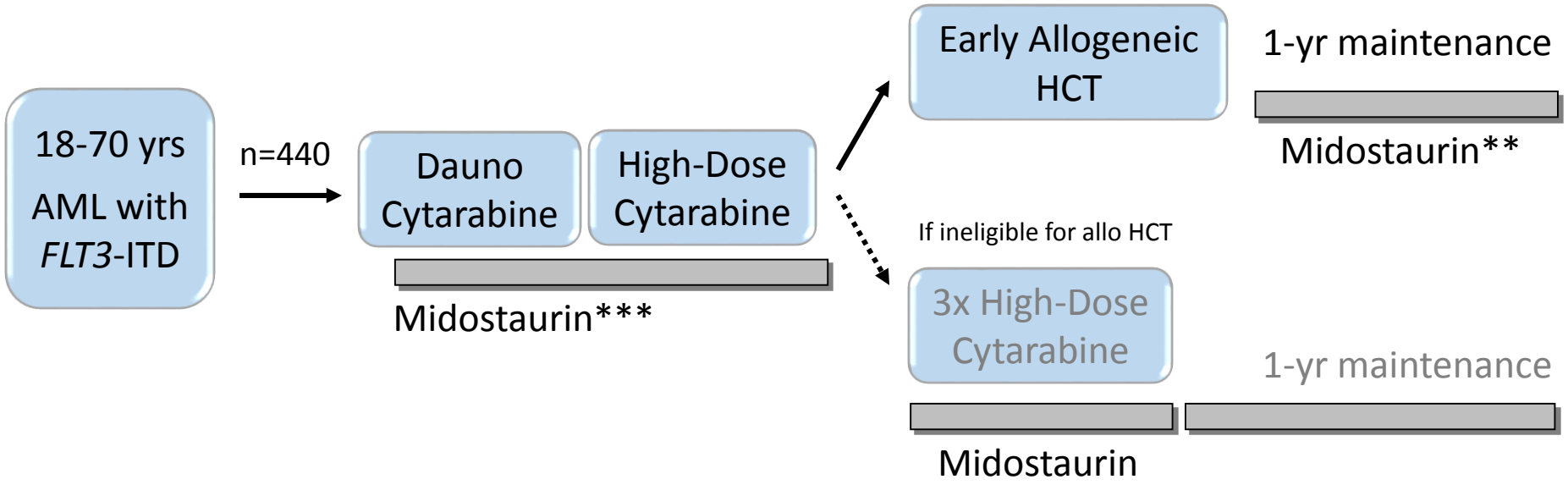
AMLSG 21-13; ClinicalTrials.gov NCT02013648

Midostaurin plus chemotherapy for AML with *FLT3*-ITD – AMLSG 16-10 trial



* Adult patients 18 – 70 years

** Midostaurin given also after allogeneic HCT (start d+30)

*** Continuous dosing of midostaurin (start on day 8; except days of chemotherapy)

ClinicalTrials.gov: NCT01477606 (accrual reached 02/2018)

Primary endpoint:	Event-free survival
Key secondary endpoint:	Overall survival
Accrual period:	June 2012 – Feb 2018

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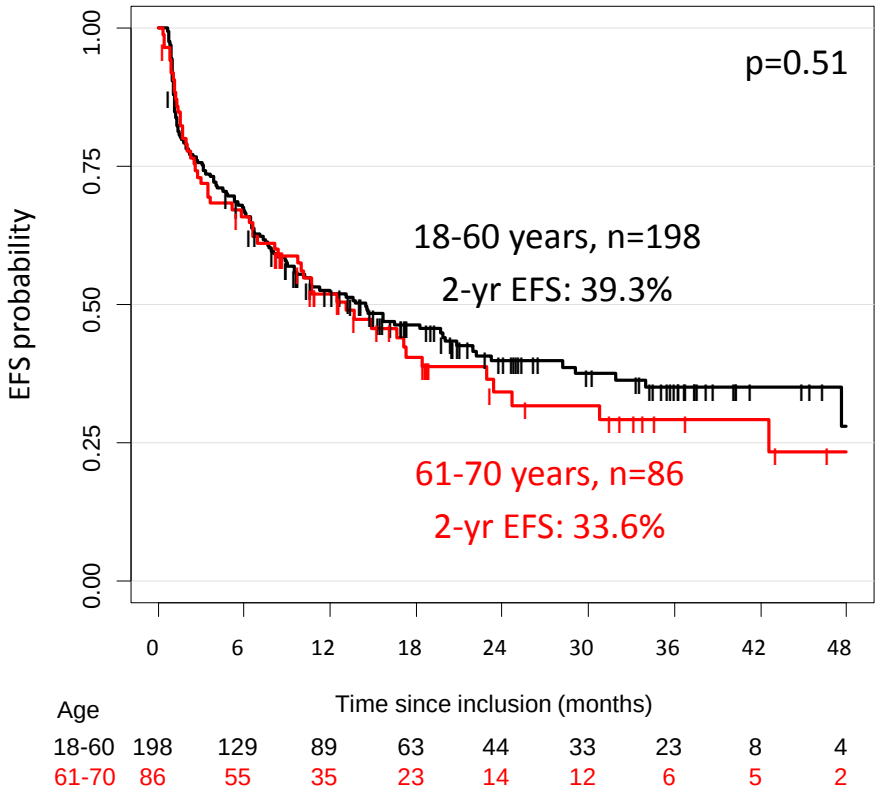
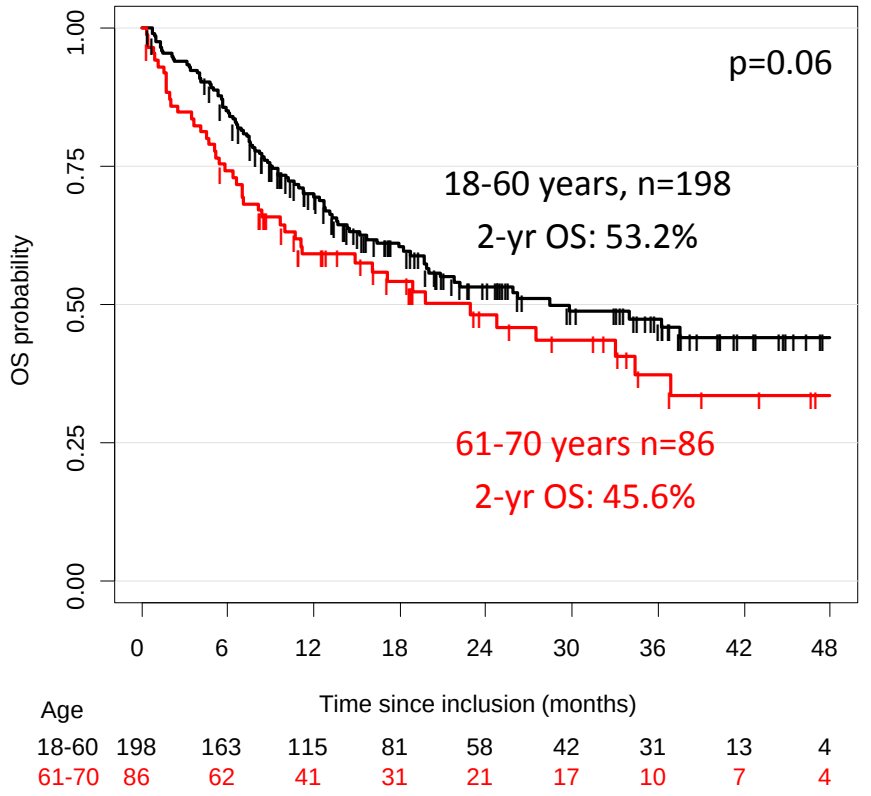
Interim analysis: Event-free and overall survival by age group

Event-free survival



Overall survival



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N= 284 patients with AML and *FLT3*-ITD

Schlenk RF, et al. Blood. 2019;133(8):840-851.

Gilteritinib clinical development program

NATIONAL CLINICAL TRIAL (NCT) #	PHASE OF DEVELOPMENT	STUDY NAME	STUDY DESCRIPTION
NCT02421939	Phase III	ADMIRAL	A Study of ASP2215 Versus Salvage Chemotherapy in Patients With Relapsed or Refractory Acute Myeloid Leukemia (AML) With FMS-like Tyrosine Kinase (FLT3) Mutation[5] Find out more
NCT02927262	Phase III	GOSSAMER	A Study of ASP2215 (Gilteritinib), Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects With FMS-like Tyrosine Kinase 3 (FLT3/ITD) Acute Myeloid Leukemia (AML) in First Complete Remission[6] Find out more
NCT02997202	Phase III	MORPHO	A Trial of the FMS-like Tyrosine Kinase 3 (FLT3) Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients With FLT3/Internal Tandem Duplication (ITD) Acute Myeloid Leukemia (AML)[7] Find out more
NCT02752035	Phase II/III	LACEWING	A Study of ASP2215 (Gilteritinib), Combination of ASP2215 Plus Azacitidine and Azacitidine Alone in the Treatment of Newly Diagnosed Acute Myeloid Leukemia With FMS-like Tyrosine Kinase (FLT3) Mutation in Patients Not Eligible for Intensive Induction Chemotherapy[8] Find out more
NCT02236013	Phase I		A Phase 1 Study of ASP2215 in Combination With Induction and Consolidation Chemotherapy in Patients With Newly Diagnosed Acute Myeloid Leukemia[9] *Trial being conducted in the United States Find out more
NCT02310321	Phase I		A Phase 1 Study of ASP2215 in Combination With Induction and Consolidation Chemotherapy in Patients With Newly Diagnosed Acute Myeloid Leukemia[10] *Trial being conducted in Japan Find out more

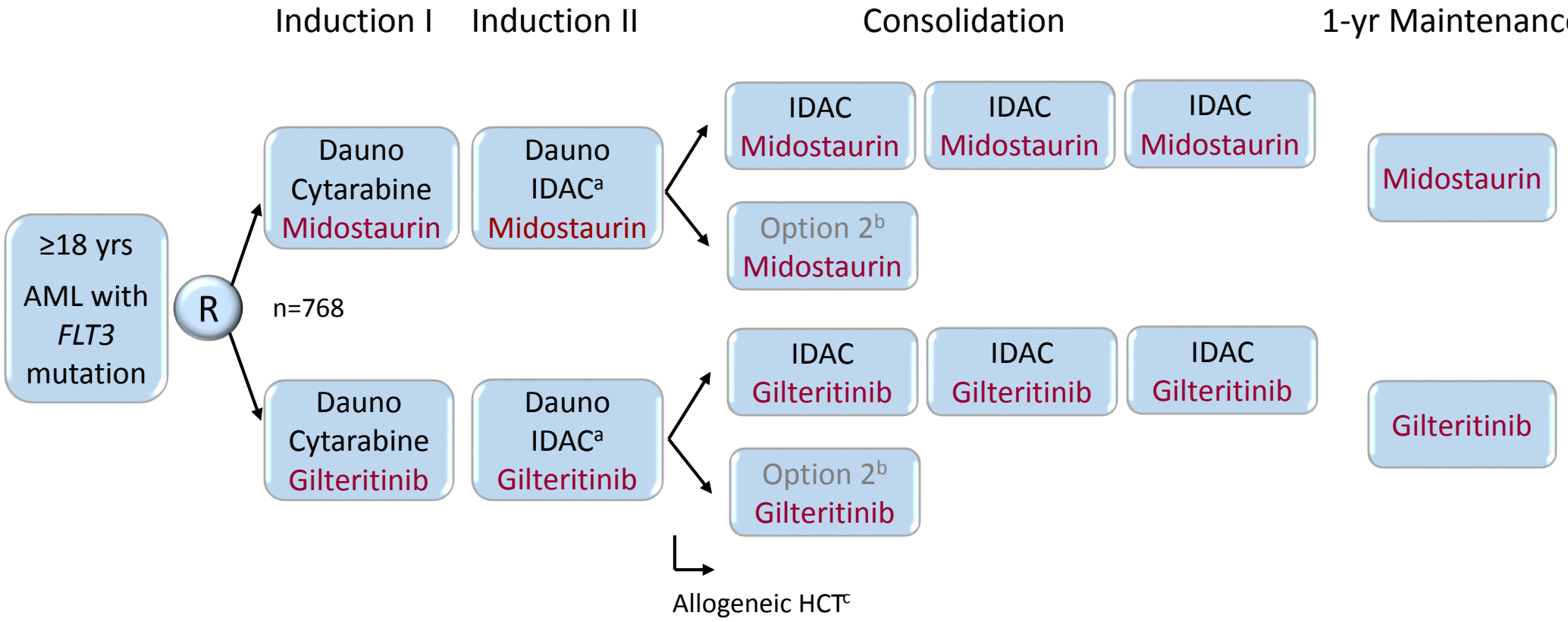
Gilteritinib in combination with "7+3" induction and HiDAC consolidation in newly diagnosed AML (Phase 1)

- Safe in combination with intensive induction chemotherapy (n=66)
- MTD with induction or consolidation: 120 mg/d
- Antileukemic activity in *FLT3*-mutated AML (n=33)
  - ➢ **CRc rate: 94%**

Pratz K, et al. ASH 2018, abstract #564.

http://www.astellasamltrials.com (assessed on January 20, 2019)

Midostaurin vs Gilteritinib plus chemotherapy for AML with *FLT3* mutation – HOVON 156 / AMLSG 28-18



Patients in CR/CRi after two cycles of induction proceed to AMLSG/HOVON-specific consolidation therapy; assignment to allogeneic hematopoietic cell transplantation (HCT) according to the local institutional or cooperative group prognostic algorithm; HCT can be performed at any time point following one induction cycle

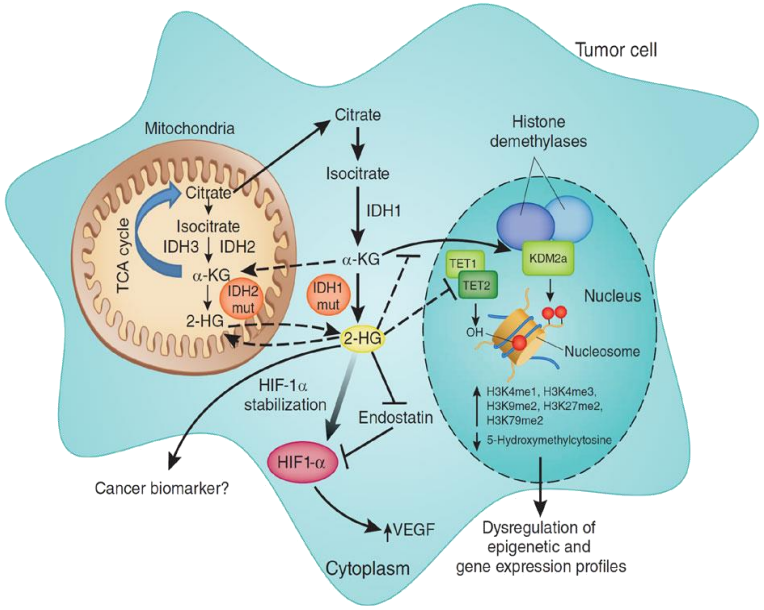
[a] IDAC, intermediate-dose cytarabine; age-adapted dosing; no anthracycline ≥60 yrs

[b] HOVON consolidation: autologous HCT; or mitoxantrone / etoposide

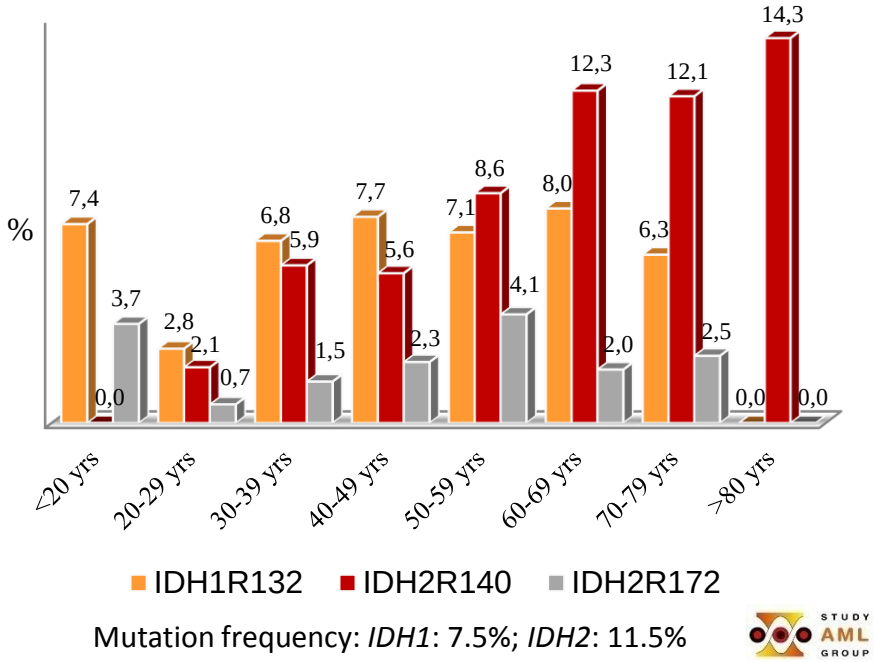
[c] Maintenance with TKI also after allogeneic HCT

Mutated IDH1 / IDH2 enzymes as targets in AML

Mutant *IDH1* and *IDH2* activity and 2-HG signalling in cancer[1]



Mutation frequency in AML (n=2,464 pts)[2]



Mutation frequency: *IDH1*: 7.5%; *IDH2*: 11.5%

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- Neomorphic activity of mutant *IDH1/2* enzymes → oncometabolite 2-HG
- Specific inhibitors of mutant *IDH* enzymes (enasidenib, ivosidenib) in clinical development

Dang L, et al. Nature. 2009;462(7274):739-44.
Ward PS, et al. Cell. 2010;17(3):225-34.
Gross S, et al. J Exp Med. 2010;207(2):339-44.
Xu W, et al. Cancer Cell. 2011;19(1):17-30.
Chaturvedi A, et al. Blood. 2013;122(16):2877-87.
Wang F, et al. Science. 2013;340(6132):622-6.
Stein E, et al. Blood. 2017;130(6):722-31; Blood. 2019;133(7):676-687.
DiNardo CD, et al. N Engl J Med. 2018;378(25):2386-2398.
DiNardo, et al. Blood. 2019 Jan 3;133(1):7-17

[1]Prensner JR & Chinnaiyan AM. Nat Med. 2011;17(3):291-3; [2]Paschka P, Döhner K. Unpublished data.

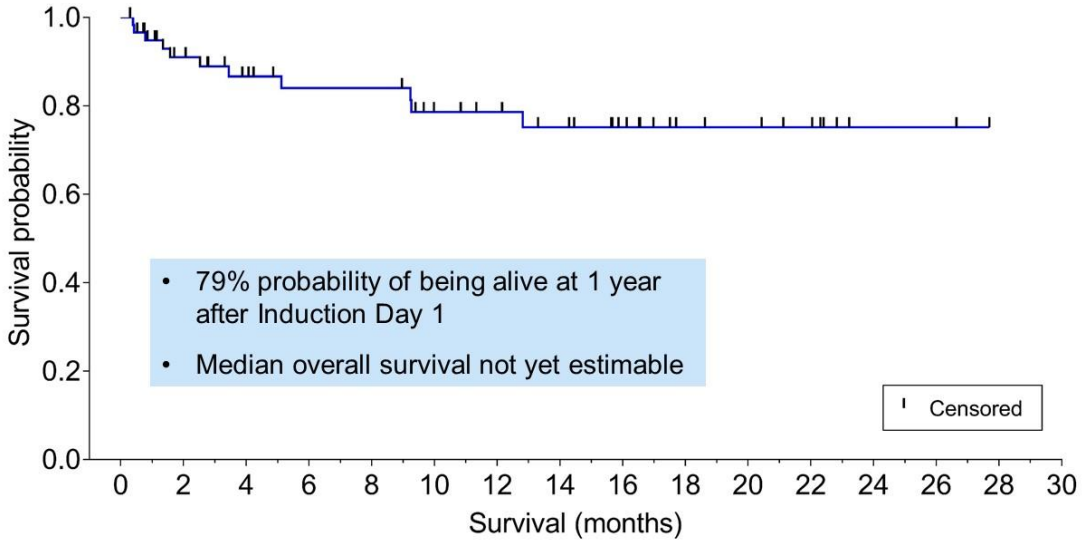
AML with *IDH1* and *IDH2* mutation: Development program of enasidenib (AG-221) and ivosidenib (AG-120)

	Phase 1/2	Phase 3
2nd or 3rd line therapy Relapsed/refractory AML		**Phase 3: AG221-AML-004 (IDHENTIFY)** Ena *vs* CCR N=280
First line treatment Unfit for intensive therapy	**Phase 1b/2: AG221-AML-005** Azacitidine + Ivo/Ena Azacitidine +/- Ena N=175 ✓	**Phase 3: AG120-C-009 (AGILE)** Azacitidine +/- Ivo N=392
First line treatment Fit for intensive therapy	**Phase 1: AG-221-120-C-001** Ivo / Ena + intensive Cx N=153 ✓	**Phase 3: HOVON 150 / AMLSG 29-18** Ivo / Ena + intensive Cx N=968 HOVON STUDY AML GROUP

AG-221-120-C-001: ‚7+3‘ plus Enasidenib / Ivosidenib

Ivosidenib (n=60)

- Median age: 62.5 yrs
- CRc: 80% (CR: 71%)

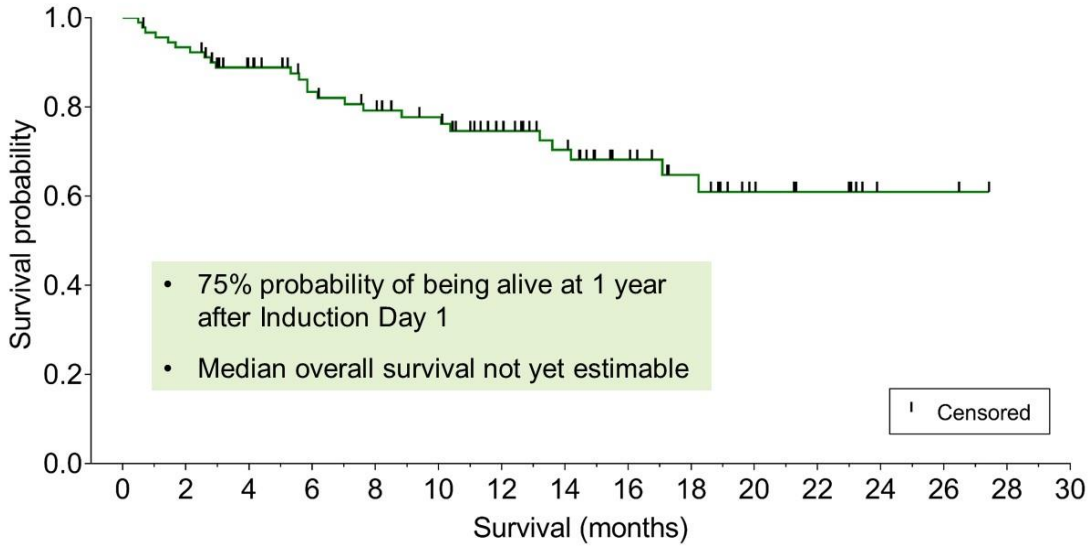


MRD- in patients with CRc

- MFC: 88%
- dPCR (*IDH1*^{mut}): 41%

Enasidenib (n=93)

- Median age: 63 yrs
- CRc: 72% (CR: 56%)

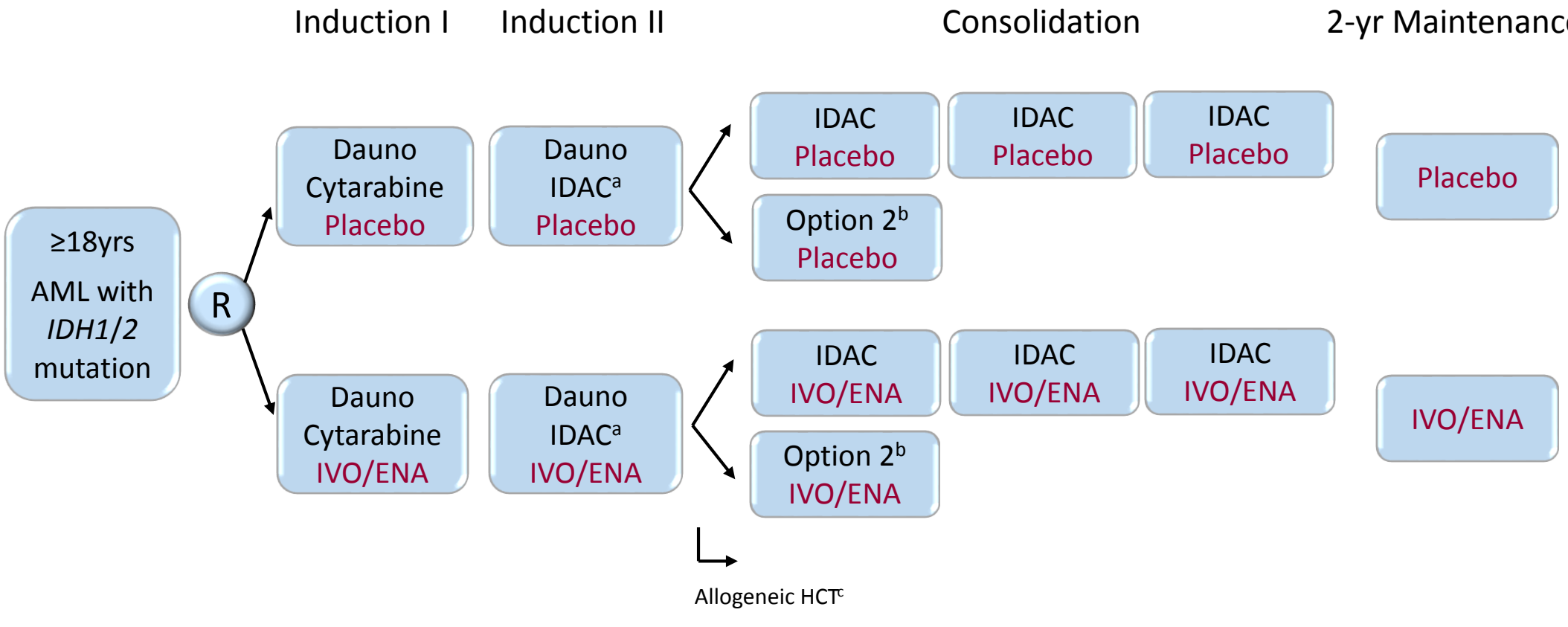


MRD- in patients with CRc

- MFC: 56%
- dPCR (*IDH2*^{mut}): 25%

Stein EM, et al. ASH 2018, abstract #560.

Chemotherapy plus Ivosidenib/Enasidenib *vs* placebo for AML with *IDH1*/*IDH2* mutation – HOVON 150 / AMLSG 29-18



Patients in CR/CRi after two cycles of induction proceed to AMLSG/HOVON-specific consolidation therapy; assignment to allogeneic hematopoietic cell transplantation (HCT) according to the local institutional or cooperative group prognostic algorithm; HCT can be performed at any time point following one induction cycle

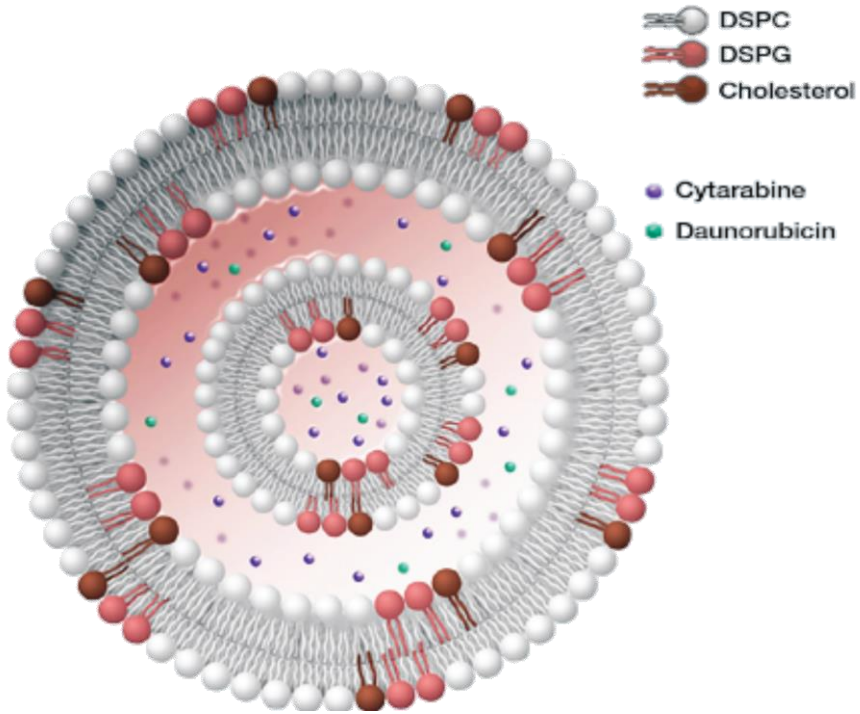
[a] IDAC, intermediate-dose cytarabine; age-adapted dosing; no anthracycline ≥60 yrs

[b] HOVON consolidation: autologous HCT; or mitoxantrone / etoposide

[c] Maintenance with TKI also after allogeneic HCT

CPX-351 (VYXEOS™)

- CPX-351 is a liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio within 100-nm diameter liposomes
  - Ratiometric dosing: Cytarabine/daunorubicin molar ratios of 1:1, 5:1, and 10:1 shown to be synergistic[1]
  - Fixed molar ratio maintained in human plasma for at least 24 hours after final dose[2]
  - Median half-life 31.1 hrs (cytarabine) and 21.9 hrs (daunorubicin)[2]
  - Drug exposure maintained for 7 days[2]
  - Evidence for selective uptake by leukemic vs normal cells in bone marrow of leukemia-bearing mice[3]
  - 1 unit: 1 mg cytarabine, 0.44 mg dauno



DSPC, desaturated phosphatidylcholine; DSPG, distearylphosphatidylglycerol.

Adapted from Lancet et al., EHA 2017 (P556).

[1]Mayer LD et al. Mol Cancer Ther. 2006;5(7):1854-63; [2]Feldman EJ et al. J Clin Oncol. 2011;29(8):979–85; [3]Lim WS et al. Leuk Res. 2010;34(9):1245–23.

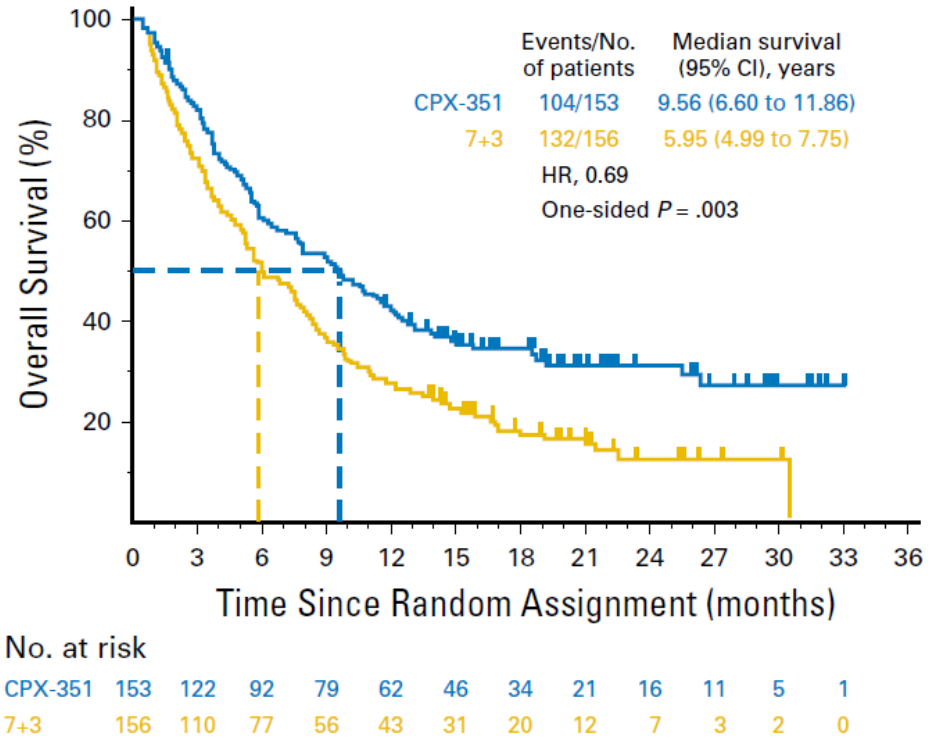
Randomized trial of CPX-351 vs '7+3'in older patients with high-risk AML

Key Eligibility
- Previously untreated
- Ages 60–75
- Able to tolerate intensive therapy
- ECOG PS 0–2

CPX-351 (n=153)

Stratifications:
- Therapy-related AML
- AML with history of MDS with and without prior HMA therapy
- AML with history of CMML
- *De novo* AML with MDS karyotype
- **60–69 years**
- **70–75 years**

7+3 (n=156)

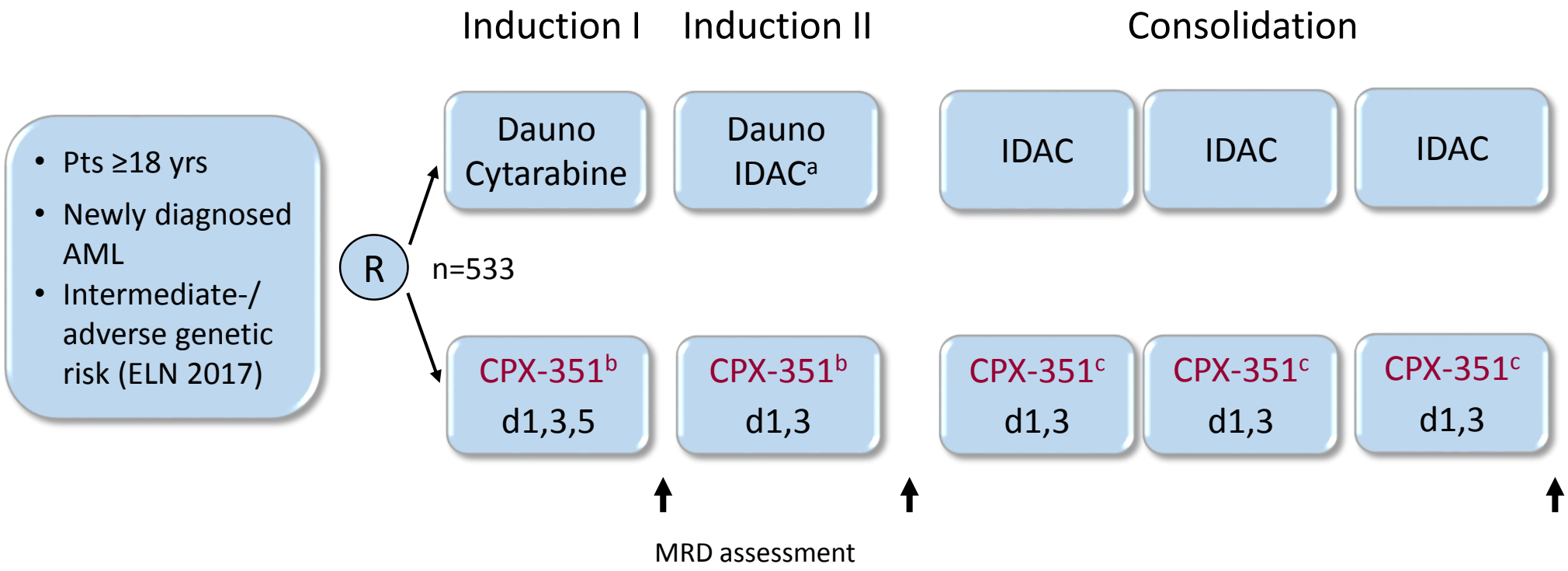


	CPX-351 n=153	„7+3" n=156	Odds Ratio	P
CR+CRi	47.7%	33.3%	1.77	0.016
HCT rate	34.0%	25.0%	1.54	0.098
Deaths within 60 days	13.8%	21.8%		

HCT, hematopoietic-cell transplantation

Lancet JE, et al. J Clin Oncol. 2018;36(26):2684-2692.

CPX-351 vs ‘3+7‘ chemotherapy for patients with genetic intermediate-/adverse-risk AML – AMLSG 30-18



Assignment to allogeneic hematopoietic-cell transplantation (HCT) according to the local institutional or cooperative group prognostic algorithm; HCT can be performed at any time point following one induction cycle

[a] IDAC, intermediate-dose cytarabine; age-adapted dosing; no anthracycline ≥60 yrs

[b] Patients 18-60 yrs: CPX-351 55/125 mg/m^2 (120 U/m^2); >60 yrs: CPX-351 44/100 mg/m^2 (100 U/m^2)

[c] Patients 18-60 yrs: CPX-351 35/80 mg/m^2 (80 U/m^2); >60 yrs: CPX-351 29/65 mg/m^2 (65 U/m^2)

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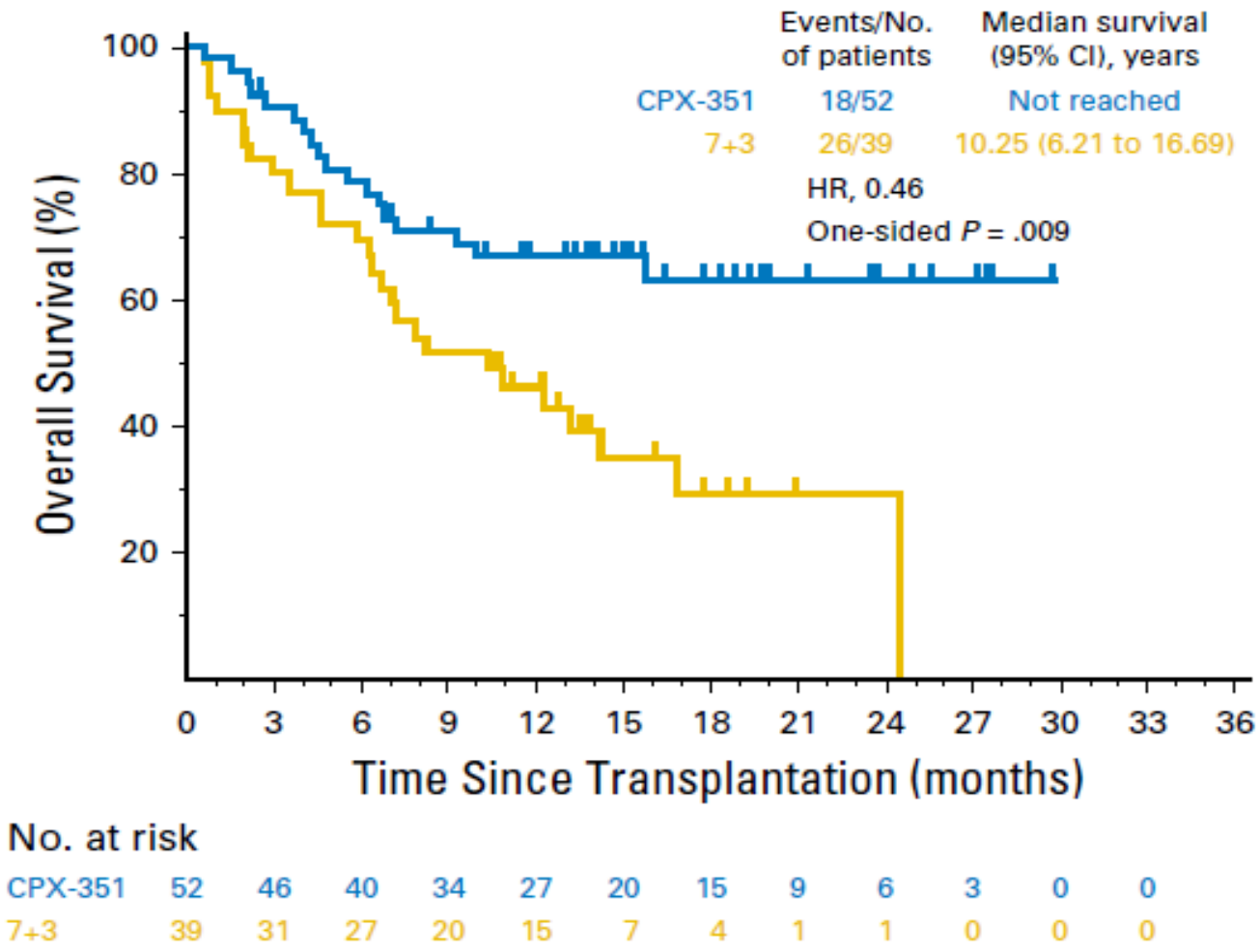
Landmark survival analysis at time of transplant: CPX-351 vs '7+3'



Lancet JE, et al. J Clin Oncol. 2018;36(26):2684-2692.

German-Austrian

AML Study Group (AMLSG)

Acknowledgement

M. Agrawal
S. Cocciardi
A. Corbacioglu
M. Feuring-Buske
M. Habdank
N. Jahn
S. Kapp-Schwörer
J. Krönke
L. Kubanek
V. Mayr
E. Panina
L. Schmalbrock
V. Teleanu
F. Theis

V. Gaidzik
C. Morlok
F. Rücker
A. Schrade
D. Weber
P. Paschka
K. Döhner

Ulm University

R.F. Schlenk
A. Gambietz
J. Krzykalla
A. Benner

DKFZ, Heidelberg

Charité, Berlin

T. Blätte
A. Dolnik
L. Bullinger

Hannover

M. Heuser
F. Thol
G. Göhring
B. Schlegelberger
A. Ganser

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R. Stone
R. Larson
C. Bloomfield

HOVON

J. Cloos
G. Ossenkoppele
M. Raaijmakers
P. Valk
B. Wouters
B. Löwenberg

Diese illustrative Abbildung wurde urheberrechtlichen Gründen entfernt.

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European Commission

SFB 1074

SFB 1074 Experimental Models and Clinical Translation in Leukemia

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