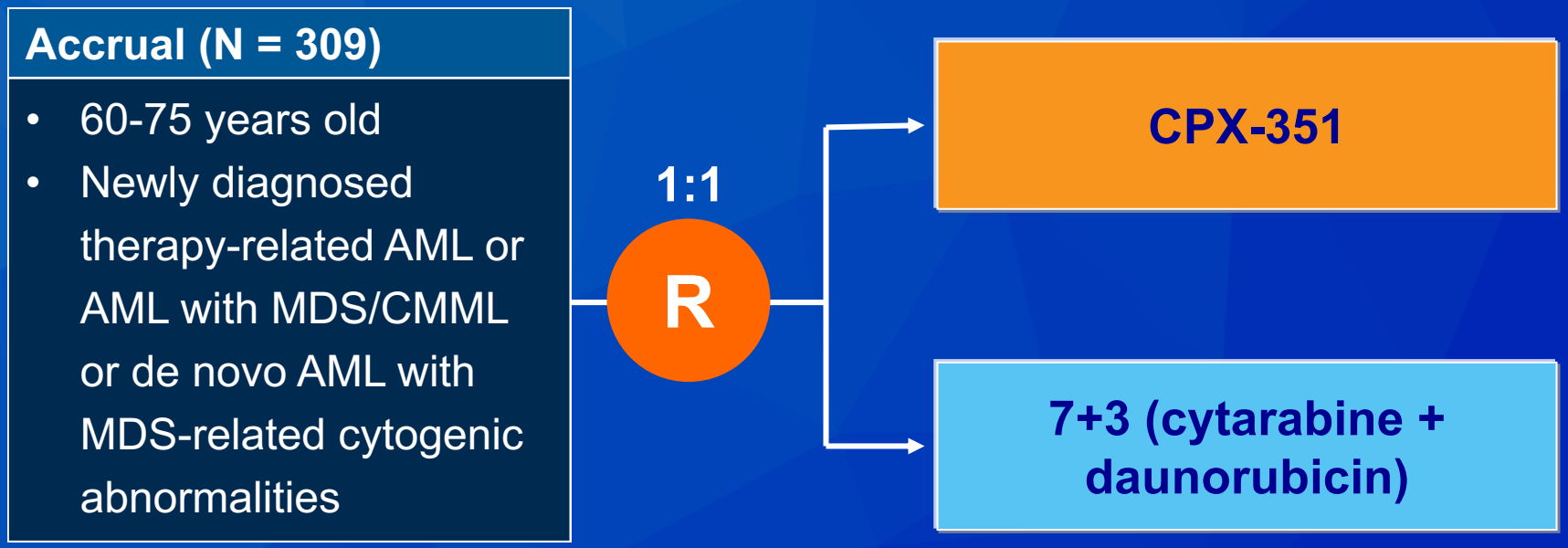
Acute Myeloid Leukemia (AML)

CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

Jeffrey E. Lancet, Geoffrey L. Uy, Jorge E. Cortes, Laura F. Newell, Tara L. Lin, Ellen K. Ritchie, Robert K. Stuart, Stephen A. Strickland, Donna Hogge, Scott R. Solomon, Richard M. Stone, Dale L. Bixby, Jonathan E. Kolitz, Gary J. Schiller, Matthew J. Wieduwilt, Daniel H. Ryan, Antje Hoering, Kamalika Banerjee, Michael Chiarella, Arthur C. Louie, and Bruno C. Medeiros

J Clin Oncol 2018;[Epub ahead of print].

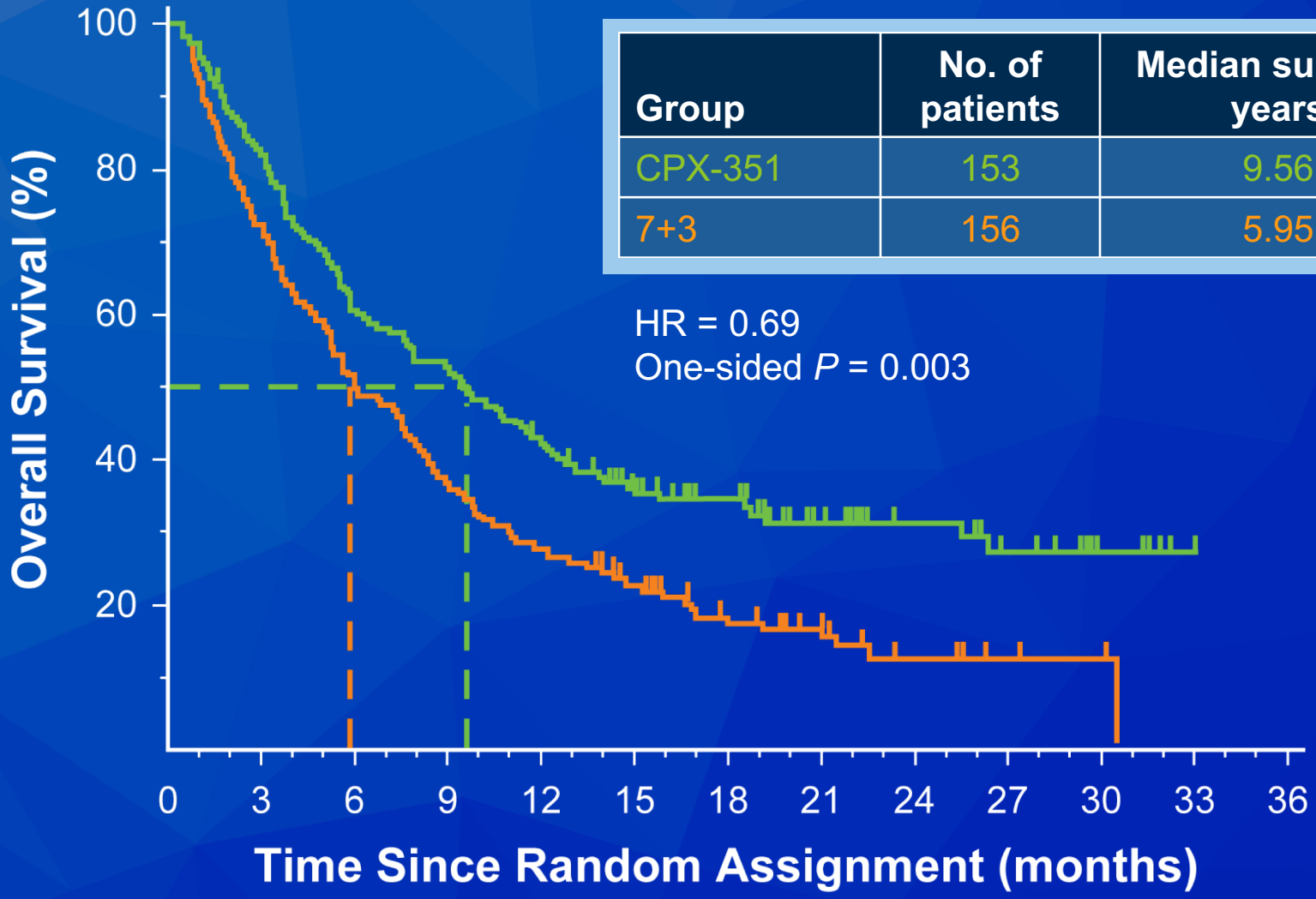
CLTR0310-301: Phase III Study of CPX-351 versus 7+3 Chemotherapy Induction and Consolidation



Primary Endpoint: Overall survival
Secondary Endpoints: Remission rate, remission duration, EFS

Lancet JE et al. *J Clin Oncol* 2018;[Epub ahead of print].

CLTR0310-301: Overall Survival

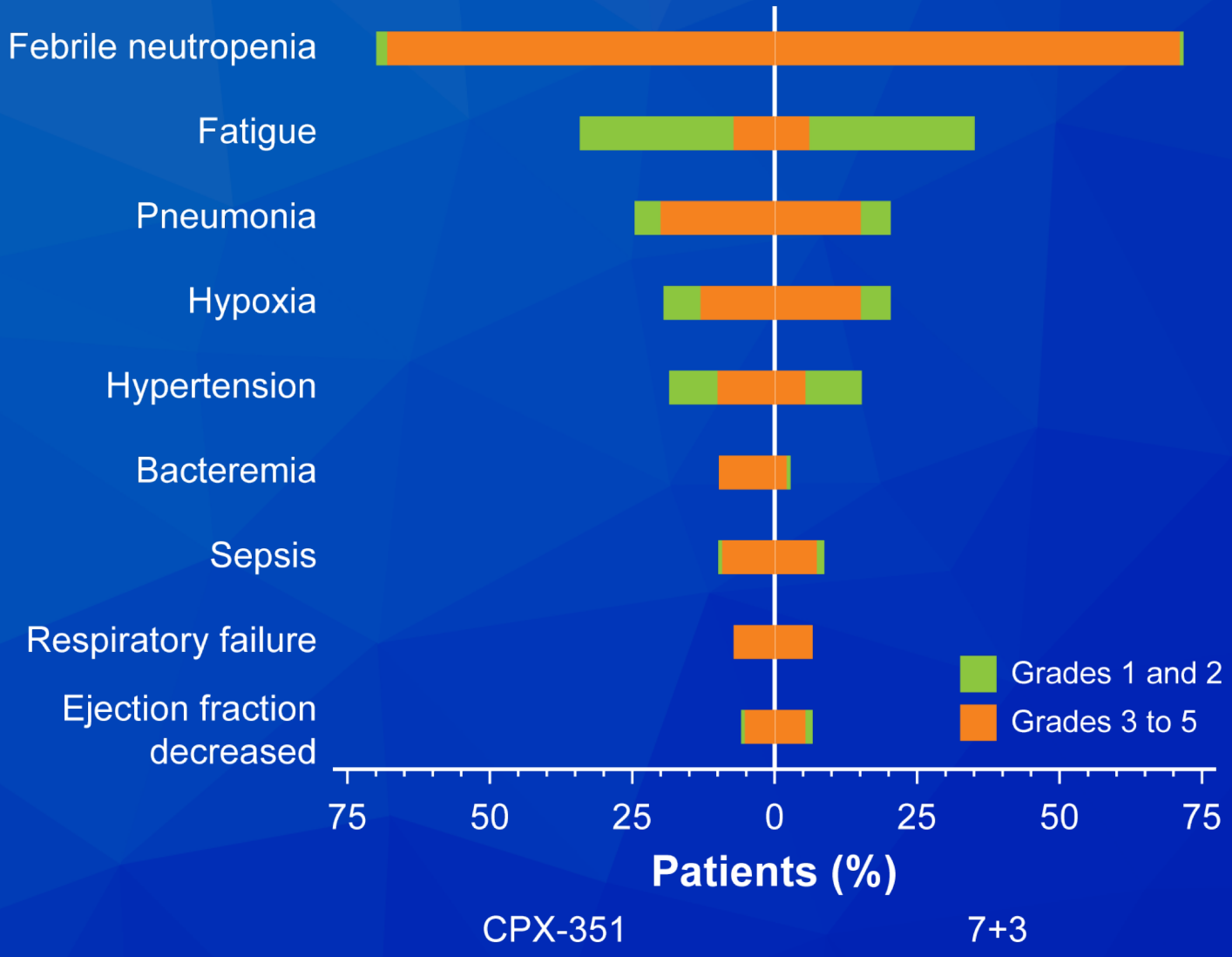


Group	No. of patients	Median survival, years
CPX-351	153	9.56
7+3	156	5.95

HR = 0.69
One-sided *P* = 0.003

Lancet JE et al. *J Clin Oncol* 2018;[Epub ahead of print].

CLTR0310-301: Most Frequently Reported Adverse Events



Lancet JE et al. *J Clin Oncol* 2018;[Epub ahead of print].

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

C.D. DiNardo, E.M. Stein, S. de Botton, G.J. Roboz, J.K. Altman, A.S. Mims, R. Swords, R.H. Collins, G.N. Mannis, D.A. Pollyea, W. Donnellan, A.T. Fathi, A. Pigneux, H.P. Erba, G.T. Prince, A.S. Stein, G.L. Uy, J.M. Foran, E. Traer, R.K. Stuart, M.L. Arellano, J.L. Slack, M.A. Sekeres, C. Willekens, S. Choe, H. Wang, V. Zhang, K.E. Yen, S.M. Kapsalis, H. Yang, D. Dai, B. Fan, M. Goldwasser, H. Liu, S. Agresta, B. Wu, E.C. Attar, M.S. Tallman, R.M. Stone, and H.M. Kantarjian

N Engl J Med 2018;378(25):2386-98.

Ivosidenib for Patients with an IDH1 Mutation: Efficacy

	R/R AML (n = 179)	Untreated AML (n = 34)
Overall response	39.1%	55.9%
CR	21.8%	20.6%
CRi or CRp	11.7%	20.6%
PR	0	2.9%
MLFS or bone marrow CR	5.6%	11.8%
Median duration of response	6.5 mo	9.2 mo

CR = complete response; CRi = CR with incomplete hematologic recovery; CRp = CR with incomplete platelet recovery; PR = partial response; MLFS = morphologic leukemia-free state

- Patients with R/R AML in the primary efficacy group (n = 125) had a median overall survival of 8.8 months

DiNardo C et al. *N Engl J Med* 2018;378(25):2386-98.

Ivosidenib for Patients with an IDH1 Mutation: Tolerability

Event	R/R AML, 500 mg/d starting dose (n = 179)	All patients (n = 258)
≥1 TRAE Grade 3 or higher	20.7%	25.6%
Prolongation of QT interval	7.8%	7.0%
IDH differentiation syndrome	3.9%	4.7%
Anemia	2.2%	2.3%
Thrombocytopenia	1.7%	1.9%
Leukocytosis	1.7%	1.2%
Febrile neutropenia	0.6%	1.2%

TRAE = treatment-related adverse event

DiNardo C et al. *N Engl J Med* 2018;378(25):2386-98.

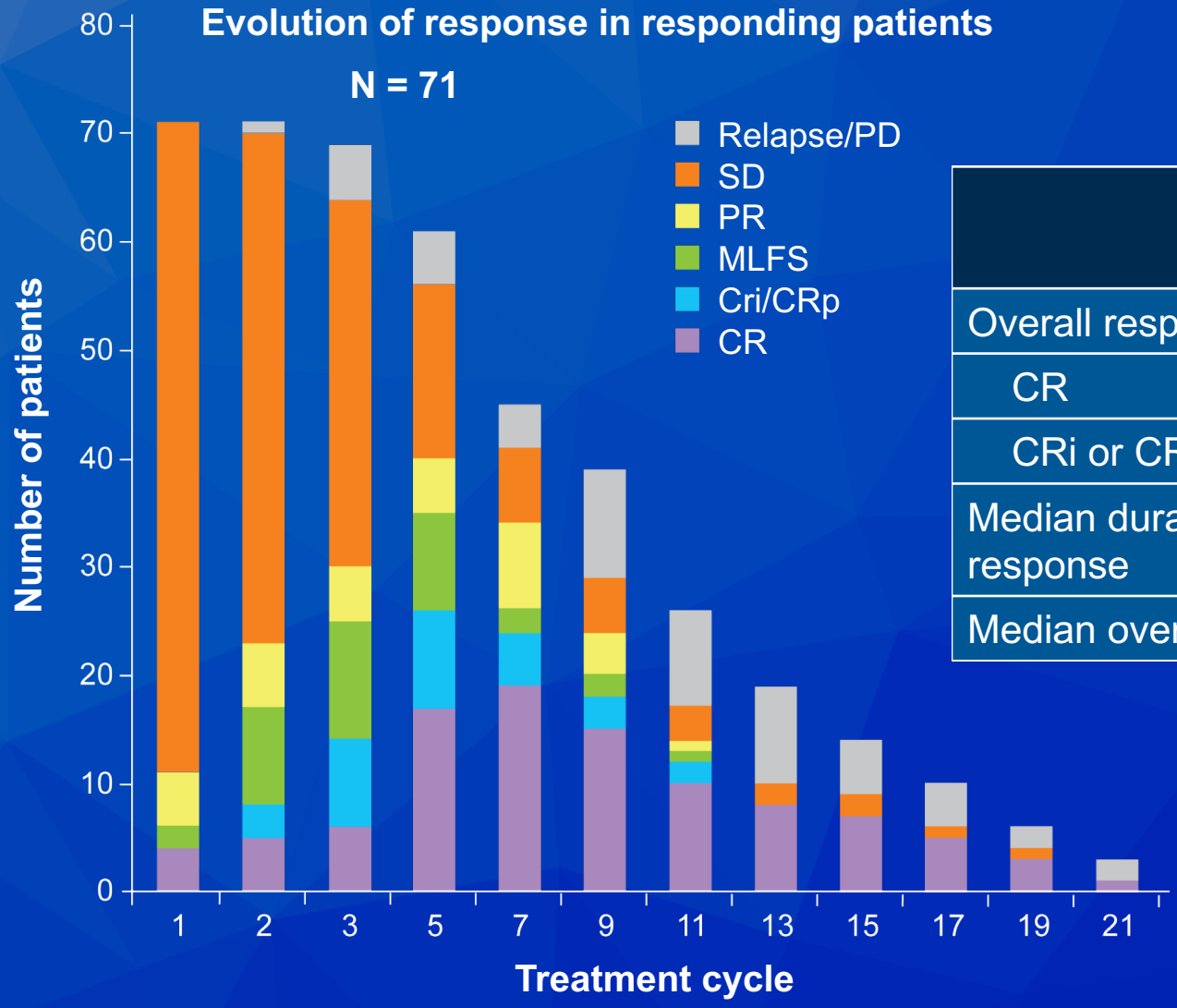
blood

Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia

Eytan M. Stein,[1,2,*] Courtney D. DiNardo,[3,*] Daniel A. Pollyea,[4] Amir T. Fathi,[5,6] Gail J. Roboz,[2,7] Jessica K. Altman,[8] Richard M. Stone,[9] Daniel J. DeAngelo,[9] Ross L. Levine,[1] Ian W. Flinn,[10] Hagop M. Kantarjian,[3] Robert Collins,[11] Manish R. Patel,[12] Arthur E. Frankel,[11] Anthony Stein,[13] Mikkael A. Sekeres,[14] Ronan T. Swords,[15] Bruno C. Medeiros,[16] Christophe Willekens,[17,18] Paresh Vyas,[19,20] Alessandra Tosolini,[21] Qiang Xu,[21] Robert D. Knight,[21] Katharine E. Yen,[22] Sam Agresta,[22] Stephane de Botton,[17,18,†] and Martin S. Tallman[1,2,†]

Blood 2017;130(6):722-31.

Enasidenib for Patients with an IDH2 Mutation: Efficacy



	All doses (n = 176)
Overall response	40.3%
CR	19.3%
CRi or CRp	6.8%
Median duration of response	5.6 mo
Median overall survival	9.3 mo

Stein EM et al. *Blood* 2017;130(6):722-31.

Enasidenib for Patients with an IDH2 Mutation: Select Grade 3 and 4 TRAEs

TRAE	100 mg dose (n = 153)	All patients (n = 239)
Hyperbilirubinemia	8%	12%
IDH differentiation syndrome	7%	6%
Anemia	7%	5%
Thrombocytopenia	5%	6%
Tumor lysis syndrome (TLS)	3%	3%
Leukocytosis	1%	3%
Lipase increased	1%	2%

- 5% of patients discontinued therapy as a result of TRAEs

Stein EM et al. *Blood* 2017;130(6):722-31.

Ivosidenib or Enasidenib Combined with Standard Induction Chemotherapy Is Well Tolerated and Active in Patients with Newly Diagnosed AML with an IDH1 or IDH2 Mutation: Initial Results from a Phase 1 Trial

Stein EM et al.
Proc ASH 2017;Abstract 726.

Ivosidenib or Enasidenib for Patients with Newly Diagnosed IDH-Mutated AML

	Ivosidenib + chemotherapy			Enasidenib + chemotherapy		
	De novo AML (n = 14)	Secondary AML (n = 9)	Overall (n = 23)	De novo AML (n = 18)	Secondary AML (n = 19)	Overall (n = 37)
Overall response	93%	67%	83%	83%	79%	81%
CR	71%	33%	57%	56%	32%	43%
CRi or CRp	14%	11%	13%	11%	26%	19%
MLFS	0	11%	4%	17%	21%	19%
PR	7%	11%	9%	0	0	0

Stein EM et al. *Proc ASH* 2017;Abstract 726.

Ivosidenib or Enasidenib for Patients with Newly Diagnosed IDH-Mutated AML

Select Grade ≥3 TEAEs	Ivosidenib + chemotherapy (n = 27)	Enasidenib + chemotherapy (n = 38)
Any adverse event	93%	92%
Febrile neutropenia	56%	63%
ALT increase	11%	0
AST increase	11%	0
Colitis	11%	8%
Hypertension	7%	11%
Respiratory failure	7%	5%
Rash	0	8%

TEAE = treatment-emergent adverse events

Stein EM et al. *Proc ASH* 2017;Abstract 726.

Mutant IDH (mIDH) Inhibitors, Ivosidenib or Enasidenib, with Azacitidine (AZA) in Patients with Acute Myeloid Leukemia (AML)

DiNardo CD et al.
Proc ASCO 2018;Abstract 7042.

mIDH Inhibitors with AZA for Patients with Newly Diagnosed AML Ineligible for Intensive Chemotherapy

Response	Ivosidenib + AZA (n = 23)	Enasidenib + AZA (n = 6)
Overall response	78%	67%
CR	44%	50%
CRi or CRp	22%	0
PR	0	0
MLFS	13%	17%

DiNardo C et al. *Proc ASCO* 2018;Abstract 7042.

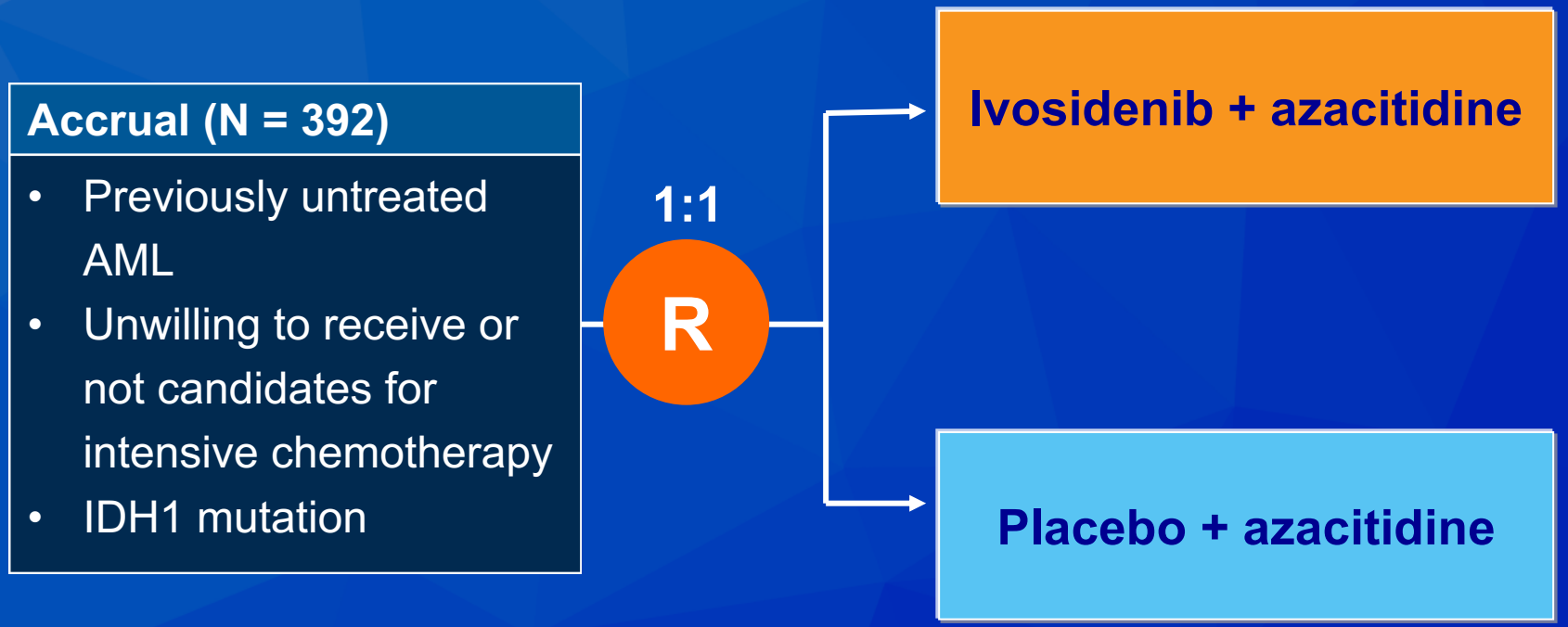
mIDH Inhibitors with AZA for Patients with Newly Diagnosed AML Ineligible for Intensive Chemotherapy

Select Grade 3/4 TEAEs	Ivosidenib + AZA (n = 23)	Enasidenib + AZA (n = 6)
Hyperbilirubinemia	NR	33%
Anemia	44%	50%
Thrombocytopenia	44%	50%
Neutropenia	39%*	33%
Lung infection	NR	33%
Pneumonia	NR	33%
Hypoxia	NR	17%
QT interval prolongation	13%	NR

* Febrile neutropenia
NR = Not reported

DiNardo C et al. *Proc ASCO* 2018;Abstract 7042.

AGILE: Phase III Study of Azacitidine with or without Ivosidenib



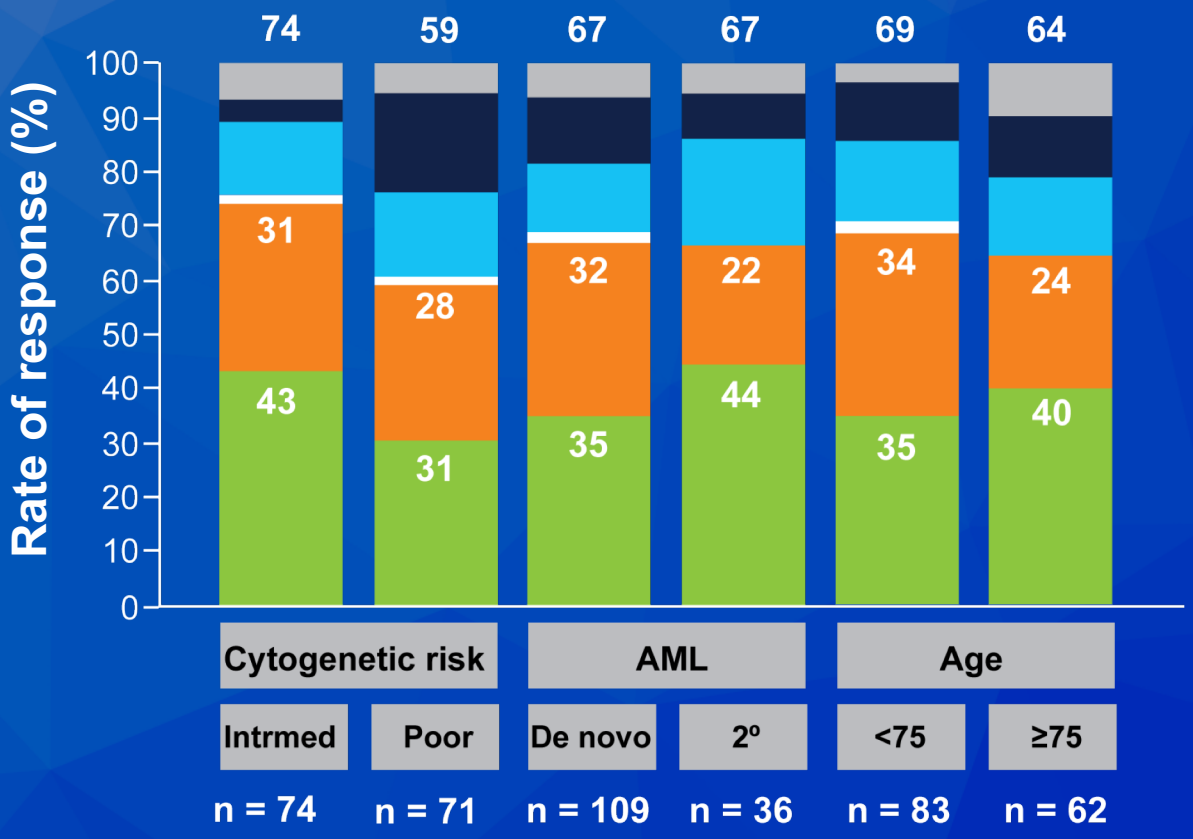
Primary endpoint: Overall survival
Secondary endpoints include remission rate, duration of response, EFS, safety

Stein E et al. *Proc ASCO* 2018;Abstract TPS7074.

Durable Response with Venetoclax in Combination with Decitabine or Azacitidine in Elderly Patients with Acute Myeloid Leukemia (AML)

DiNardo CD et al.
Proc ASCO 2018;Abstract 7010.

Venetoclax in Combination with Azacitidine or Decitabine: Response Rates by Subgroup



Patients (%) with CR/CRi shown at the top of each bar

Other
RD
MLFS
PR
CRi
CR

CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission; MLFS = morphogenic leukemia free state; RD = resistant disease
Other: disease progression, or discontinued prior to assessment

DiNardo CD et al. *Proc ASCO* 2018;Abstract 7010.

Venetoclax in Combination with Azacitidine or Decitabine: Tolerability

Serious AEs in ≥3% of patients	N = 145
Any event	70%
Febrile neutropenia	32%
Pneumonia	12%
Bacterial infection	6%
Lung infection	5%
Sepsis	4%
Hypotension	3%
Mental status changes	3%
Gastrointestinal hemorrhage	3%
Mucosal inflammation	3%

- No events of clinical or laboratory TLS were observed

DiNardo CD et al. *Proc ASCO* 2018;Abstract 7010.

Phase 1/2 Study of Venetoclax (VEN) with Low-Dose Cytarabine (LDAC) in Treatment-Naïve, Elderly Patients with Acute Myeloid Leukemia Unfit for Intensive Chemotherapy: 1-Year Outcomes

Wei A et al.
Proc ASH 2017;Abstract 890.

Response to VEN with LDAC in Elderly Patients with AML Not Eligible for Intensive Chemotherapy

Patients (n)	CR/CRi	Median duration of CR/CRi (months)	Median OS (months)
Cytogenetic risk			
Intermediate (37)	76%	NR	15.7
Poor (19)	47%	3.1	5.7
Biomarker			
NPM1 (7)	100%	NR	NR
DNMT3A (11)	82%	NR	NR
FLT3-ITD (9)	78%	7.4	14.0
TP53 (9)	44%	3.0	6.6
IDH1/2 (10)	70%	NR	9.3
SRSF2 (16)	75%	NR	9.0
RUNX1 (9)	56%	9.0	3.8

Wei A et al. *Proc ASH* 2017;Abstract 890.

Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial

Jorge Cortes, Alexander E Perl, Hartmut Döhner, Hagop Kantarjian, Giovanni Martinelli, Tibor Kovacsovics, Philippe Rousselot, Björn Steffen, Hervé Dombret, Elihu Estey, Stephen Strickland, Jessica K Altman, Claudia D Baldus, Alan Burnett, Alwin Krämer, Nigel Russell, Neil P Shah, Catherine C Smith, Eunice S Wang, Norbert Ifrah, Guy Gammon, Denise Trone, Deborah Lazzaretto, Mark Levis

Lancet Oncol 2018;19(7):889-903.

Quizartinib for R/R AML: Efficacy

- **Cohort 1**: Patients ≥60 years old, R/R AML within 1 year of first-line therapy (excluding stem cell transplant)
- **Cohort 2**: Patients 18 to 85 years old, R/R AML after salvage chemotherapy or hematopoietic stem cell transplant (HSCT)

	Cohort 1		Cohort 2	
	FLT3-ITD positive (n = 112)	**FLT3-ITD negative (n = 44)**	**FLT3-ITD positive (n = 136)**	**FLT3-ITD negative (n = 40)**
Overall response	77%	45%	74%	45%
CR	3%	5%	4%	3%
CRp	4%	2%	1%	3%
CRi	50%	30%	40%	25%
PR	21%	9%	29%	15%
Median overall survival (weeks)	25.4	19.1	24.0	25.1

Cortes J et al. *Lancet Oncol* 2018;19(7):889-903.

Quizartinib for R/R AML: Tolerability

Grade ≥3 TRAEs in ≥10% of patients	All patients (n = 333)
Febrile neutropenia	41%
Anemia	26%
Thrombocytopenia	15%
QTcF prolongation	11%
Neutropenia	11%
Leucopenia	7%
Decreased platelet count	8%
Pneumonia	13%

Cortes J et al. *Lancet Oncol* 2018;19(7):889-903.

Quizartinib Significantly Prolongs Overall Survival in Patients with FLT3-Internal Tandem Duplication–Mutated (Mut) Relapsed/Refractory AML in the Phase 3, Randomized, Controlled QuANTUM-R Trial

Cortes J et al.
Proc EHA 2018;Abstract LB2600.

Phase III QuANTUM-R: Efficacy

Survival	Quizartinib (n = 245)	Salvage chemotherapy (n = 122)	HR, *p*-value
Median OS	27 wk	20.4 wk	0.76, $p = 0.0177$
1 year OS	27%	20%	

Median drug exposure: Quizartinib 4 cycles, salvage chemotherapy 1 cycle

Cortes J et al. *Proc EHA* 2018;Abstract LB2600.

Phase III QuANTUM-R: Tolerability

Select Grade ≥3 AEs in >10% of patients	Quizartinib (n = 241)	Salvage chemotherapy (n = 94)
Thrombocytopenia	35%	34%
Anemia	30%	29%
Febrile neutropenia	31%	21%
Leukopenia	17%	16%
Sepsis/septic shock	16%	18%
Hypokalemia	12%	9%
Pneumonia	12%	9%

- 2 patients discontinued quizartinib due to QTcF prolongation

Cortes J et al. *Proc EHA* 2018;Abstract LB2600; http://www.ascopost.com/News/58973.

Low Relapse Rate in Younger Patients ≤ 60 Years Old with Newly Diagnosed FLT3-Mutated Acute Myeloid Leukemia (AML) Treated with Crenolanib and Cytarabine/Anthracycline Chemotherapy

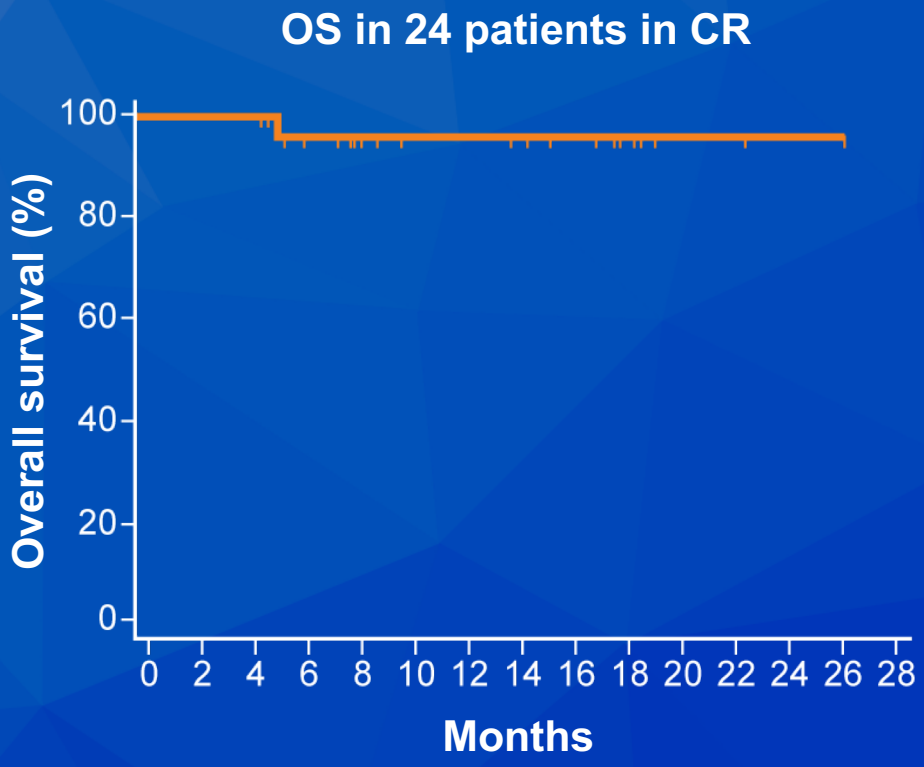
Wang ES et al.
Proc ASH 2017;Abstract 566.

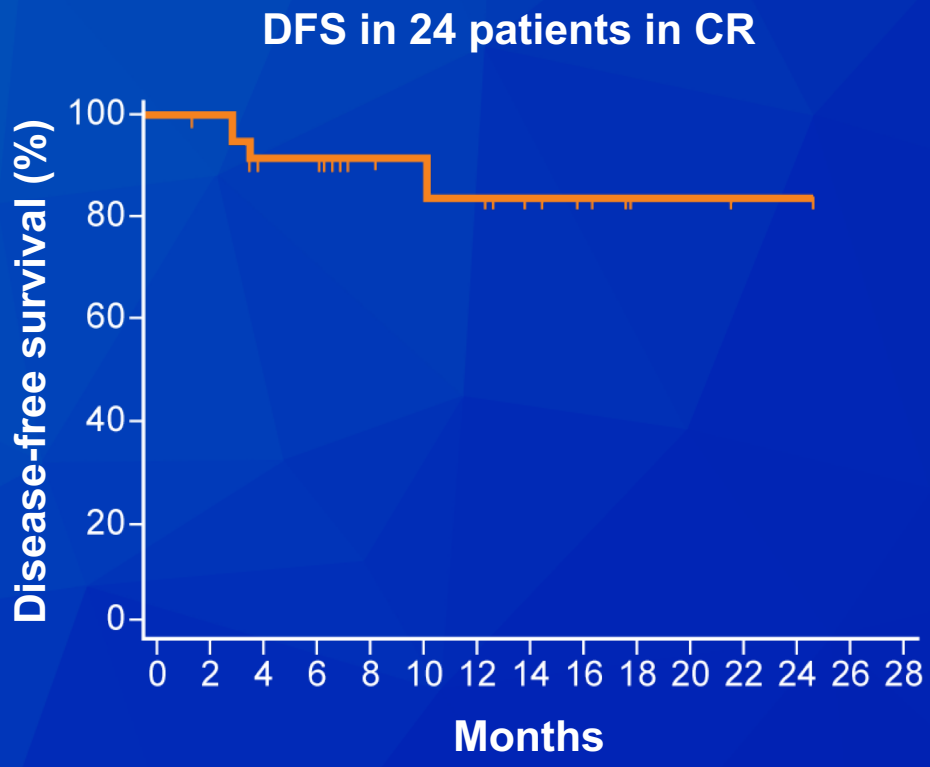
Crenolanib in Combination with Chemotherapy for Newly Diagnosed FLT3-Mutant AML

- 21 of 29 (72%) patients achieved a CR after one cycle of induction with chemotherapy with crenolanib
  - 3 additional patients achieved a CR after re-induction, 7+3 induction and high-dose cytarabine or HSCT
- 23 of 24 patients in CR in follow-up (median follow-up = 14 months)
  - 1 death (post-transplant complications)
  - 2 relapses:
    - 1 bone marrow
    - 1 CNS

Wang ES et al. *Proc ASH* 2017;Abstract 566.

Crenolanib in Combination with Chemotherapy for Newly Diagnosed FLT3-Mutant AML





Wang ES et al. *Proc ASH* 2017;Abstract 566.

Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1–2 study

Alexander E Perl, Jessica K Altman*, Jorge Cortes, Catherine Smith, Mark Litzow, Maria R Baer, David Claxton, Harry P Erba, Stan Gill, Stuart Goldberg, Joseph G Jurcic, Richard A Larson, Chaofeng Liu, Ellen Ritchie, Gary Schiller, Alexander I Spira, Stephen A Strickland, Raoul Tibes, Celalettin Ustun, Eunice S Wang, Robert Stuart, Christoph Röllig, Andreas Neubauer, Giovanni Martinelli, Erkut Bahceci, Mark Levis*

Lancet Oncol 2017;18(8):1061-75.

Gilteritinib for R/R AML: Efficacy

	FLT3-WT (n = 58)	FLT3-mutant (n = 191)	All patients (n = 249)
Overall response	12%	49%	40%
CR	2%	9%	8%
CRp	0	5%	4%
CRi	7%	22%	18%
PR	3%	12%	10%
Median duration of response	12 weeks	20 weeks	17 weeks
Median overall survival	17 weeks	30 weeks	25 weeks

Perl AE et al. *Lancet Oncol* 2017;18(8):1061-75.

Gilteritinib for R/R AML: Tolerability

Most common Grade 3-4 AEs	All patients (n = 252)
Febrile neutropenia	39%
Anemia	25%
Thrombocytopenia	13%
Sepsis	14%
Pneumonia	12%

- 9% of patients had a greater than 60 ms change in their maximum post-baseline QTcF relative to baseline

Perl AE et al. *Lancet Oncol* 2017;18(8):1061-75.

Preliminary Results from a Phase 1 Study of Gilteritinib in Combination with Induction and Consolidation Chemotherapy in Subjects with Newly Diagnosed Acute Myeloid Leukemia (AML)

Pratz KW et al.
Proc ASH 2017;Abstract 722.

Response and Safety with Gilteritinib and Induction and Consolidation Chemotherapy in AML

Response parameters	All patients (N = 49)	FLT3^{mut+} (n = 23)[1]
CRc	71.4%	91.3%
CR	57.1%	82.6%
Treatment-emergent adverse events (Grade ≥3)		
Febrile neutropenia	53.1%	
Thrombocytopenia	18.4%	
Neutropenia	16.3%	
Decreased platelet count	12.2%	
Sepsis	10.2%	
Decreased WBC	10.2%	

[1] FLT3 mutation status was unknown for 1 patient
CRc = complete response (CR) with incomplete platelet recovery + CR with incomplete hematologic recovery

Serious drug-related adverse events: febrile neutropenia (16.3%), sepsis (6.1%) and decreased ejection fraction (4.1%)

Pratz K et al. *Proc ASH* 2017;Abstract 722.

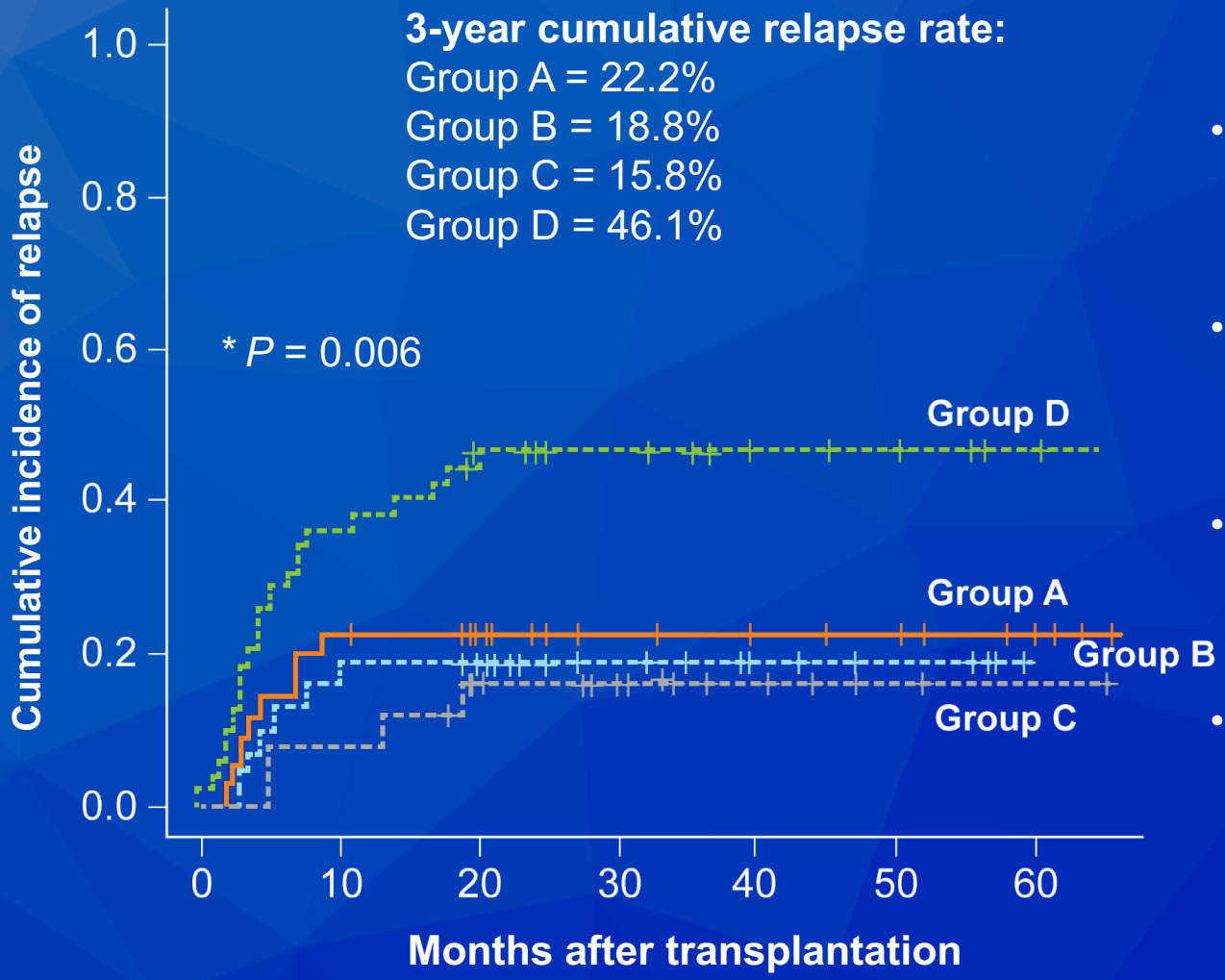
Original Article

Effect of Sorafenib on the Outcomes of Patients With FLT3-ITD Acute Myeloid Leukemia Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Li Xuan, MD, PhD[1]; Yu Wang, MD, PhD[2]; Fen Huang, MS[1]; Erlie Jiang, MD, PhD[3]; Lan Deng, MD[4]; Bingyi Wu, MS[4]; Zhiping Fan, MS[1]; Xinquan Liang, MS[5]; Na Xu, MD, PhD[1]; Jieyu Ye, MD, PhD[1]; Ren Lin, MD, PhD[1]; Changxin Yin, PhD[1]; Yuanyuan Zhang, MD, PhD[2]; Jing Sun, MS[1]; Mingzhe Han, MD, PhD[3]; Xiaojun Huang, MD, PhD[2]; and Qifa Liu, MS[1]

Cancer 2018;124(9):1954-63.

Relapse Mortality Stratified by Use of Sorafenib Before and After Transplantation



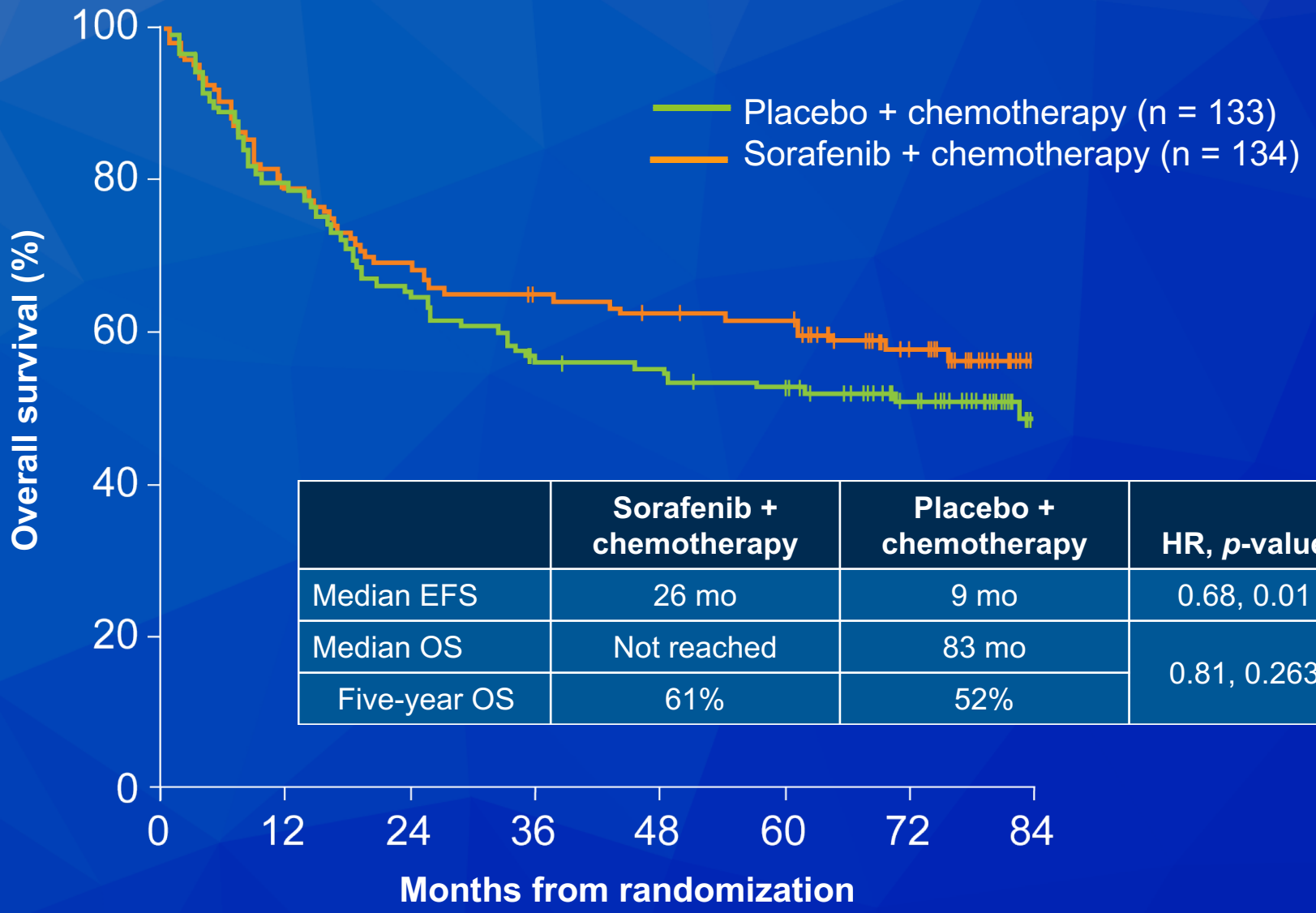
- **Group A** (n = 36): sorafenib before transplantation
- **Group B** (n = 32): sorafenib maintenance after transplantation
- **Group C** (n = 26): sorafenib both before and after transplantation
- **Group D** (n = 50): sorafenib neither before nor after transplantation

Xuan L et al. *Cancer* 2018;124(9):1954-63.

The Addition of Sorafenib to Standard AML Treatment Results in a Substantial Reduction in Relapse Risk and Improved Survival. Updated Results from Long-Term Follow-Up of the Randomized-Controlled Soraml Trial

Rollig C et al.
Proc ASH 2017;Abstract 721.

SORAML: Overall Survival



	Sorafenib + chemotherapy	Placebo + chemotherapy	HR, *p*-value
Median EFS	26 mo	9 mo	0.68, 0.01
Median OS	Not reached	83 mo	0.81, 0.263
Five-year OS	61%	52%	

Rollig C et al. *Proc ASH* 2017;Abstract 721.

Minimal-Residual Disease Guided Treatment with Azacitidine in MDS/AML Patients at Imminent Risk of Relapse: Results of the Prospective RELAZA2 Trial

Platzbecker U et al.
Proc ASH 2017;Abstract 565.

RELAZA2: MRD-Guided Treatment with Azacitidine

- 205 patients (n = 27 MDS, n = 178 AML) in CR after chemotherapy alone (n = 58) or allogeneic HSCT (n = 147)
- MRD monitored in peripheral blood or bone marrow monthly for two years
- Patients with MRD above a specific threshold but still in CR received 6 cycles of azacitidine preemptively
- Patients could receive up to 18 months of additional azacitidine-based treatment based on MRD
- Patients with a hematologic relapse came off study

Platzbecker U et al. *Proc ASH* 2017;Abstract 565.

RELAZA2: MRD-Guided Treatment with Azacitidine

- 53 of 205 patients (26%) became MRD positive while still in hematologic CR and received azacitidine
  - After 6 months, 31 of 53 patients were still in CR (58%)
    - 21 patients declined below the MRD threshold
    - 10 patients stabilized with no relapse
  - 22 patients relapsed after a median of 3 cycles of azacitidine
- After 6 months, 24 patients continued to receive median 9 cycles of azacitidine
  - 8 relapsed after a median of 397 days after an initial MRD detection

Platzbecker U et al. *Proc ASH* 2017;Abstract 565.

Phase 2 Study of Combination of Cytarabine, Idarubicin, and Nivolumab for Initial Therapy of Patients with Newly Diagnosed Acute Myeloid Leukemia

Ravandi F et al.
Proc ASH 2017;Abstract 815.

Nivolumab in Combination with Induction Chemotherapy for Newly Diagnosed AML

- 32 patients treated with nivolumab after induction with ara-C and idarubicin
  - 24 de novo AML
  - 2 therapy-related AML
  - 3 secondary AML
  - 1 therapy-related secondary AML
  - 2 high-risk MDS
- 23 patients achieved CR/CRi (72%)
- Median RFS: not reached
- Median OS: not reached
- Immune-related toxicities in 5 patients
  - Rash, pancreatitis and colitis

Ravandi F et al. *Proc ASH* 2017;Abstract 815.

The NEW ENGLAND JOURNAL of MEDICINE

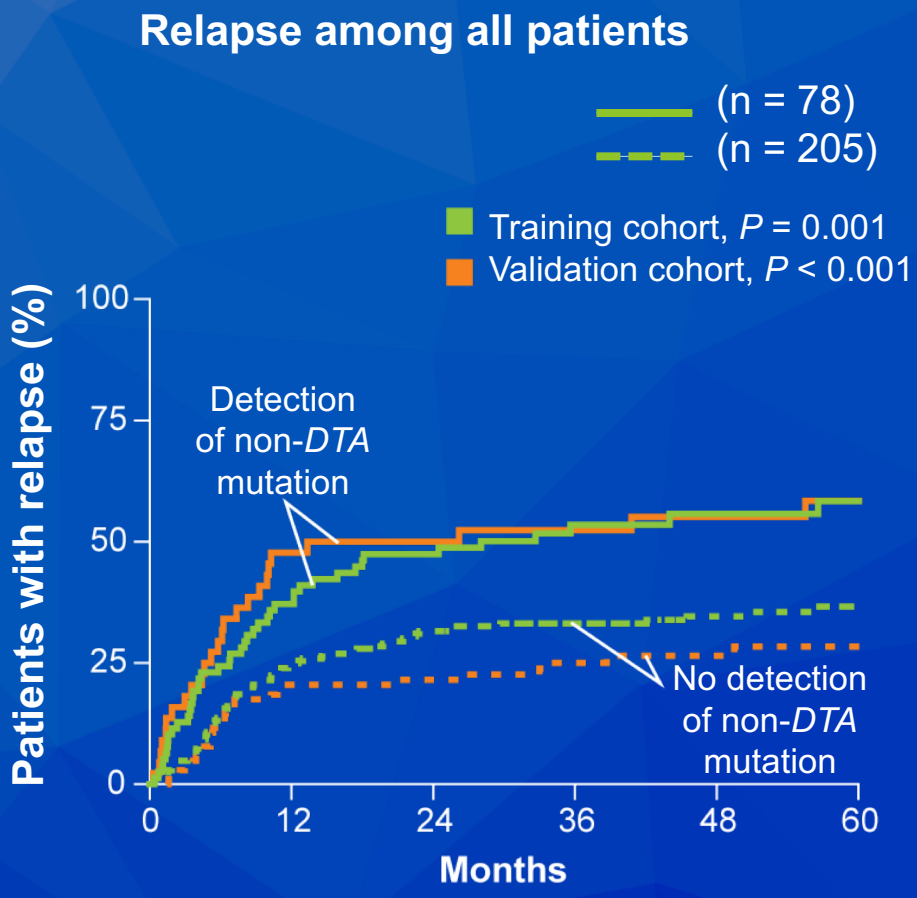
ORIGINAL ARTICLE

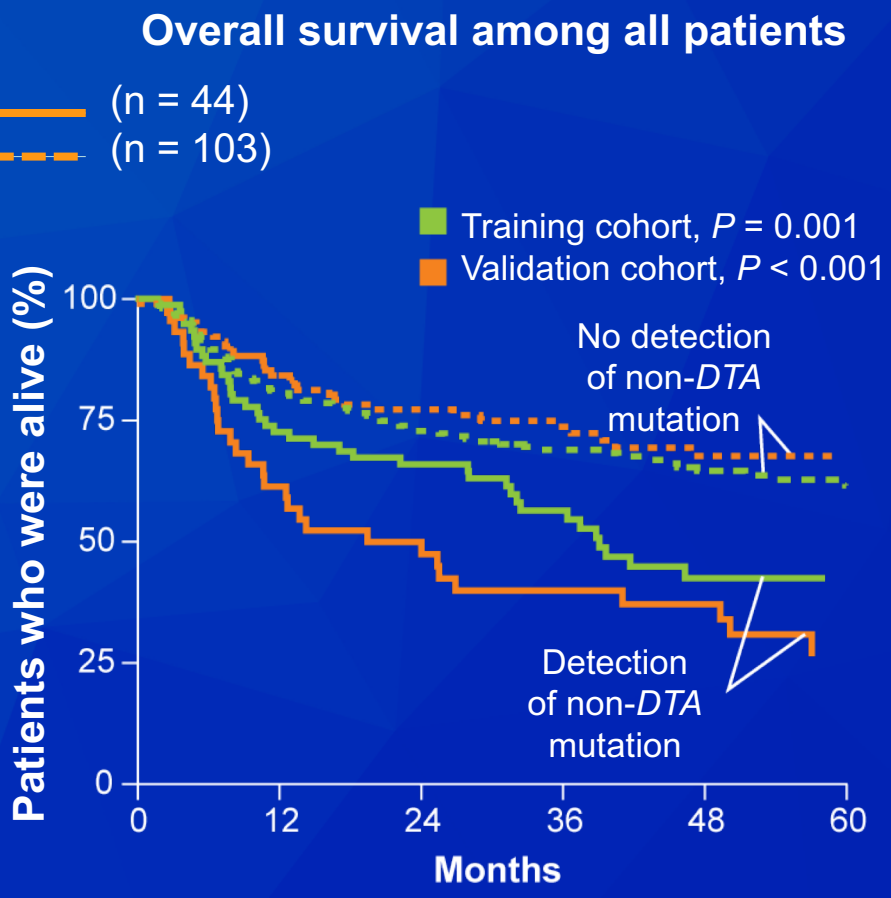
Molecular Minimal Residual Disease in Acute Myeloid Leukemia

M. Jongen-Lavrencic, T. Grob, D. Hanekamp, F.G. Kavelaars, A. al Hinai, A. Zeilemaker, C.A.J. Erpelinck-Verschueren, P.L. Gradowska, R. Meijer, J. Cloos, B.J. Biemond, C. Graux, M. van Marwijk Kooy, M.G. Manz, T. Pabst, J.R. Passweg, V. Havelange, G.J. Ossenkoppele, M.A. Sanders, G.J. Schuurhuis, B. Löwenberg, and P.J.M. Valk

N Engl J Med 2018;378(13):1189-99.

Detection of Persistent Non-*DTA* Mutations During CR Is Associated with Increased Risk of Relapse and Decreased OS

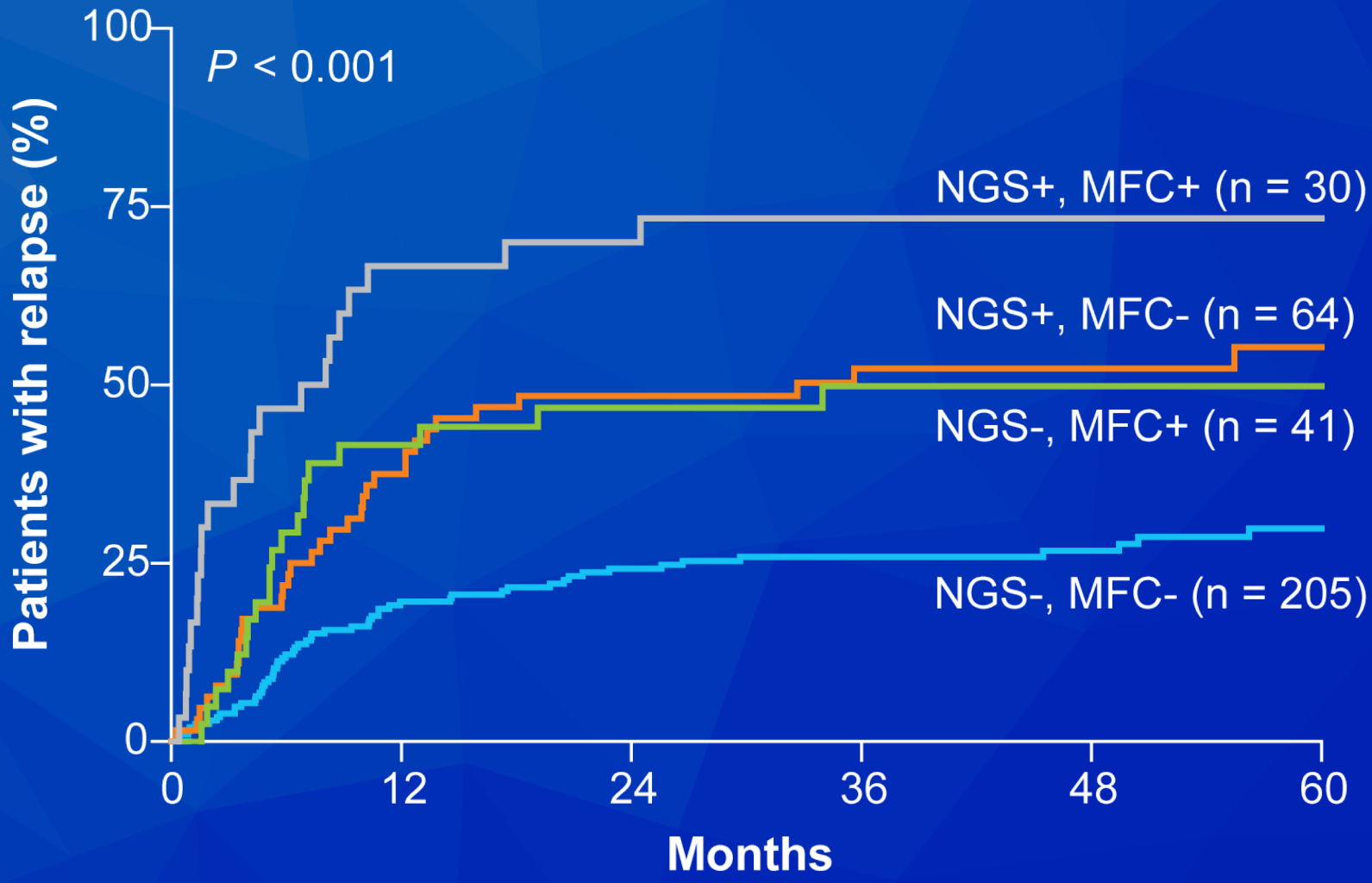




- The detection of persistent DTA mutations, which are often present in persons with age-related clonal hematopoiesis, was not associated with an increased relapse rate.

Jongen-Lavrencic M et al. *N Engl J Med* 2018;378(13):1189-99.

Rate of Relapse by Detection of Persistent Non-*DTA* Mutations During CR with Next-Generation Sequencing (NGS) and Multiparameter Flow Cytometry (MFC)



Jongen-Lavrencic M et al. *N Engl J Med* 2018;378(13):1189-99.

A Phase 2 Randomized Study of Low Dose Ara-C with or without Glasdegib (PF-04449913) in Untreated Patients with Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome

Cortes JE et al.
Proc ASH 2016;Abstract 99.

Overall Survival with Low-Dose Ara-C with or without Glasdegib for Untreated AML or High-Risk MDS

All patients	LDAC + glasdegib N = 88	LDAC alone N = 44	HR	*p*-value
Median follow-up (months)	14.3	12.4	0.511	0.0020
Median OS (months)	8.3	4.9		
Good/intermediate risk	**N = 55**	**N = 27**		
Median OS (months)	12.2	6.0	0.464	0.0035
Poor risk	**N = 33**	**N = 17**		
Median OS (months)	4.4	2.3	0.575	0.0422

Cortes JE et al. *Proc ASH* 2016;Abstract 99.

Acute Lymphoblastic Leukemia (ALL)

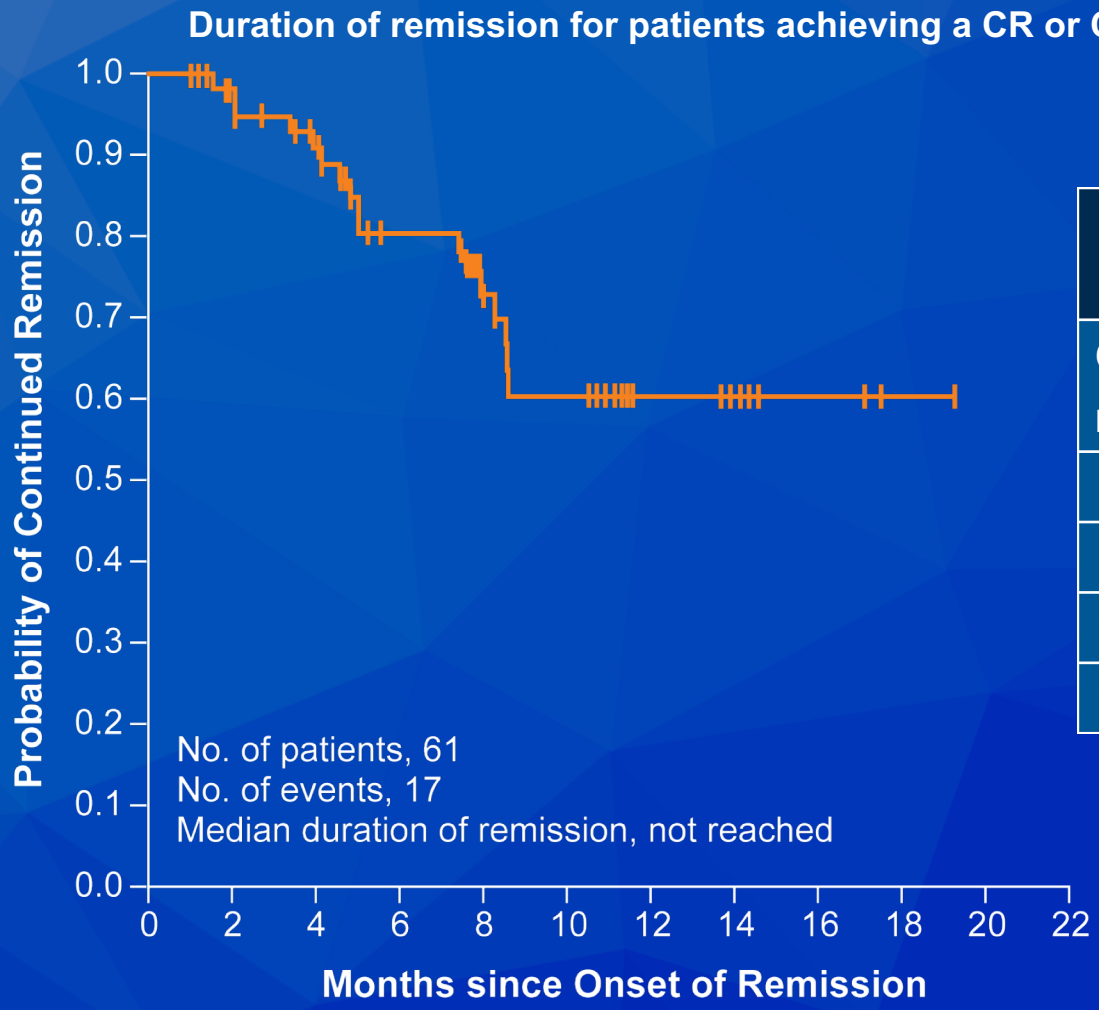
ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

N Engl J Med 2018;378(5):439-48.

Tisagenlecleucel for Children and Young Adults with R/R ALL: Efficacy



	Tisagenlecleucel (n = 75)
Overall remission rate	81%
CR	60%
CRi	21%
1-year EFS	50%
1-year OS	76%

- The median duration of persistence of tisagenlecleucel in blood was 168 days

Maude SL et al. *N Engl J Med* 2018;378(5):439-48.

Tisagenlecleucel for Children and Young Adults with R/R ALL: Tolerability

Select Grade 3 or 4 AE	≤8 weeks after infusion (n = 75)	
	Grade 3	Grade 4
Any event	25%	44%
Cytokine release syndrome	21%	25%
Hypotension	9%	8%
Neurologic event	13%	0
Decrease in lymphocyte count	7%	5%
Increase in blood bilirubin	11%	0
Increase in AST	7%	3%

- From 8 weeks to 1 year after infusion (n = 70):
  - 11% experienced a Grade 3 AE
  - 6% experienced a Grade 4 AE

Maude SL et al. *N Engl J Med* 2018;378(5):439-48.

Outcomes of Patients (pts) Treated with Prior Blinatumomab (Blin) in ZUMA-3: A Study of KTE-C19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Adult Pts with Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL)

Shah BD et al.
Proc ASCO 2018;Abstract 7006.

ZUMA-3: KTE-C19 for Adult Patients with R/R ALL: Efficacy After 8 Weeks Follow-Up

	Prior blin (n = 8)	Blin-naïve (N = 10)	Overall (n = 18)
CR rate	63%	80%	72%
CR	63%	80%	72%
CRi	0	0	0
Undetectable MRD	88%	100%	94%

- 5/6 patients who did not respond to prior blinatumomab achieved undetectable MRD response to KTE-C19

Shah BD et al. *Proc ASCO* 2018;Abstract 7006.

ZUMA-3: KTE-C19 for Adult Patients with R/R ALL: Tolerability

Grade ≥3 AE	Prior blin (n = 11)	Blin-naïve (N = 12)	Overall (n = 23)
CRS	27%	17%	22%
Neurologic events	36%	67%	52%

- Most frequent Grade ≥3 CRS symptoms:
  - Pyrexia (39%)
  - Hypotension (30%)
- Most frequent Grade ≥3 neurologic events:
  - Encephalopathy (22%)
  - Aphasia (17%)
  - Confusional state (13%)

Shah BD et al. *Proc ASCO* 2018;Abstract 7006.

The NEW ENGLAND JOURNAL of MEDICINE

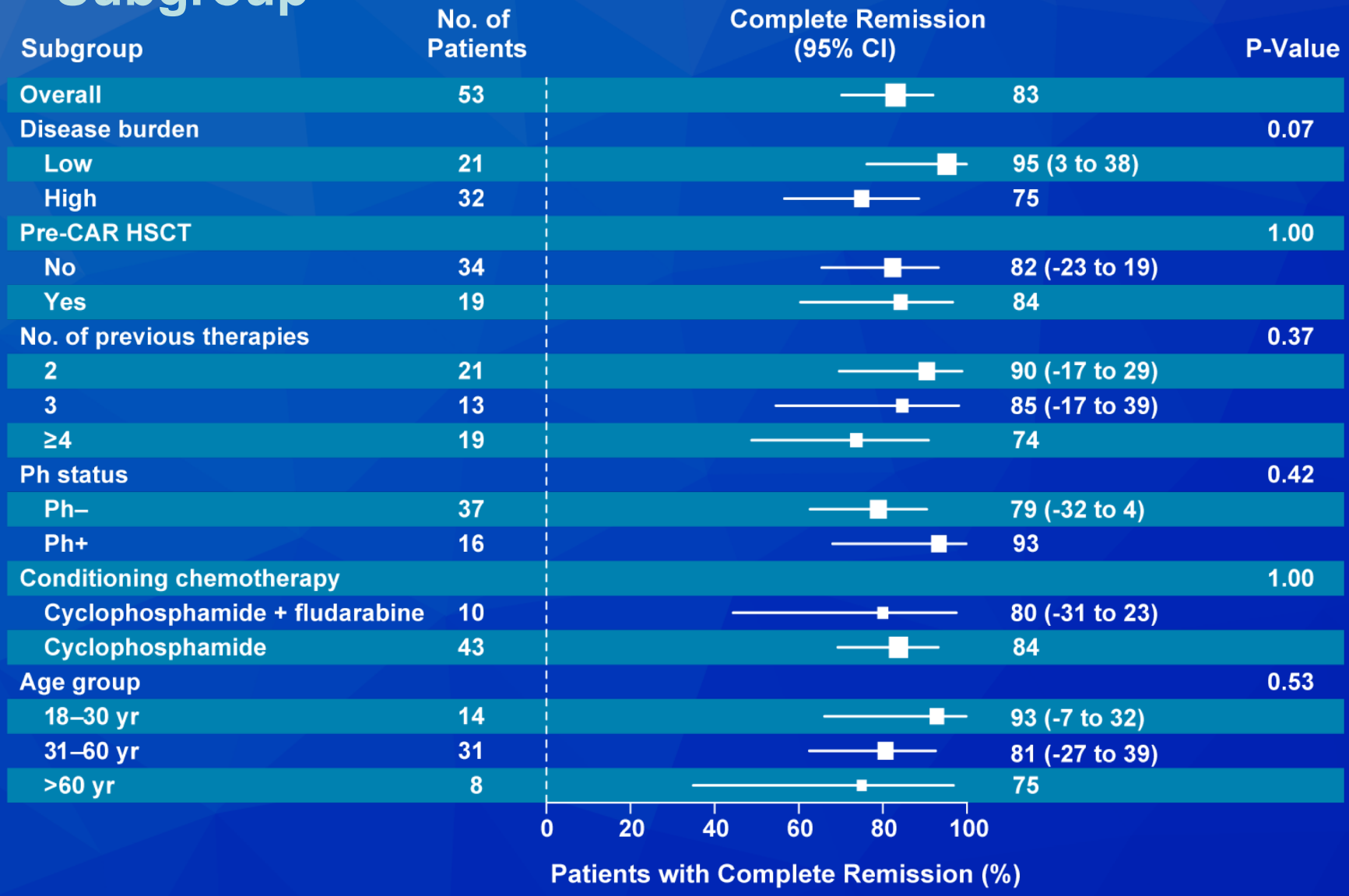
ORIGINAL ARTICLE

Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia

Jae H. Park, M.D., Isabelle Rivière, Ph.D., Mithat Gonen, Ph.D., Xiuyan Wang, Ph.D., Brigitte Sénéchal, Ph.D., Kevin J. Curran, M.D., Craig Sauter, M.D., Yongzeng Wang, Ph.D., Bianca Santomasso, M.D., Ph.D., Elena Mead, M.D., Mikhail Roshal, M.D., Peter Maslak, M.D., Marco Davila, M.D., Ph.D., Renier J. Brentjens, M.D., Ph.D., and Michel Sadelain, M.D., Ph.D.

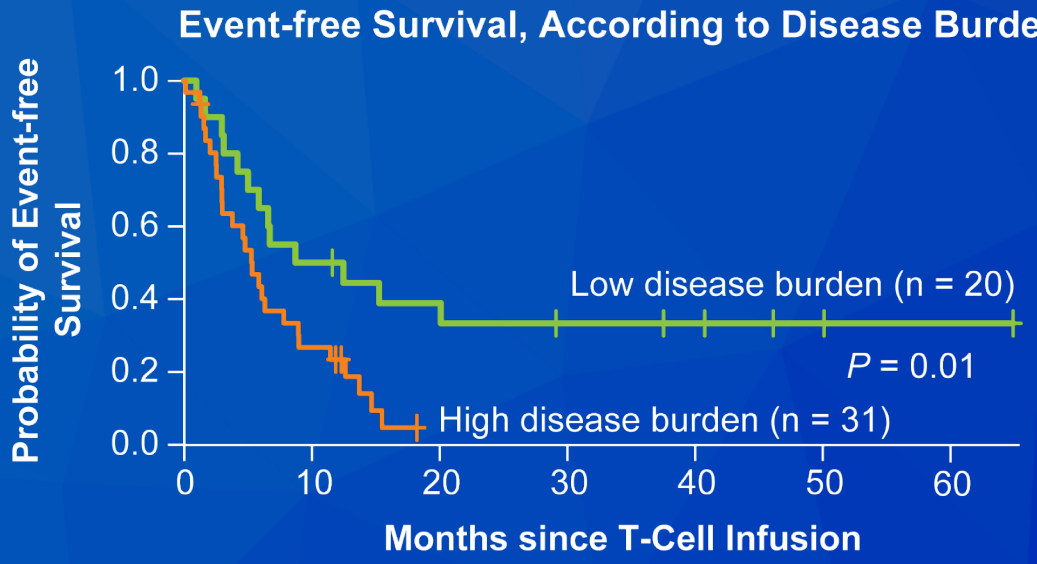
N Engl J Med 2018;378(5):449-59.

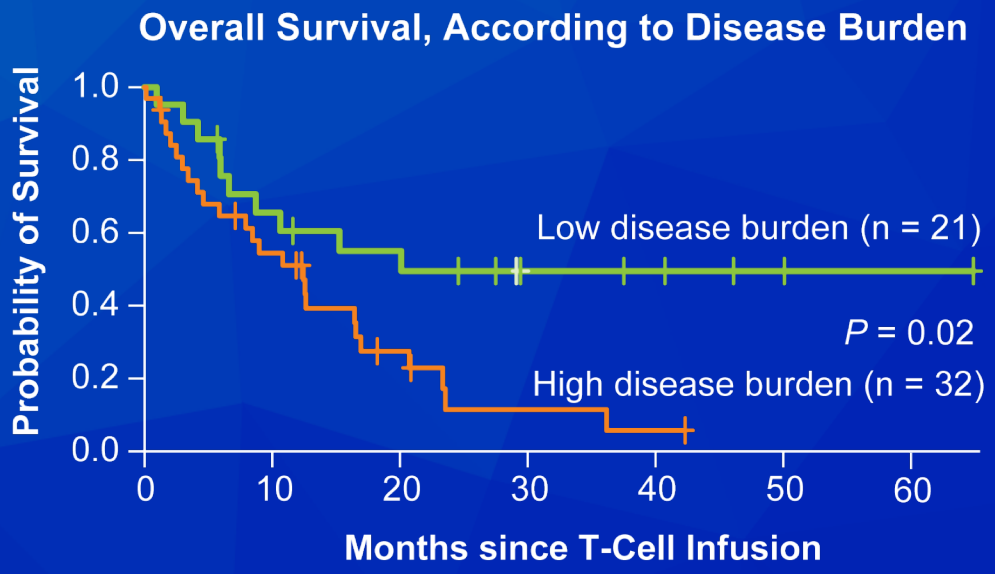
19-28z T Cells for R/R ALL: Remission Rates by Subgroup



Park JH et al. *N Engl J Med* 2018;378(5):449-59.

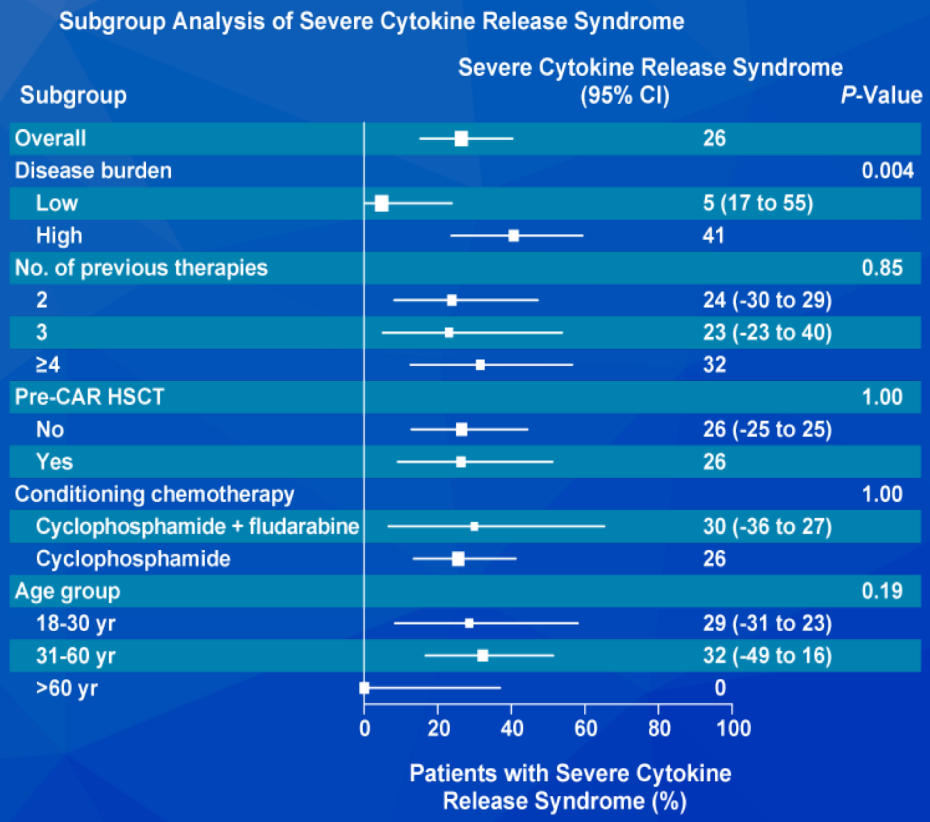
19-28z T Cells for R/R ALL: Survival by Disease Burden

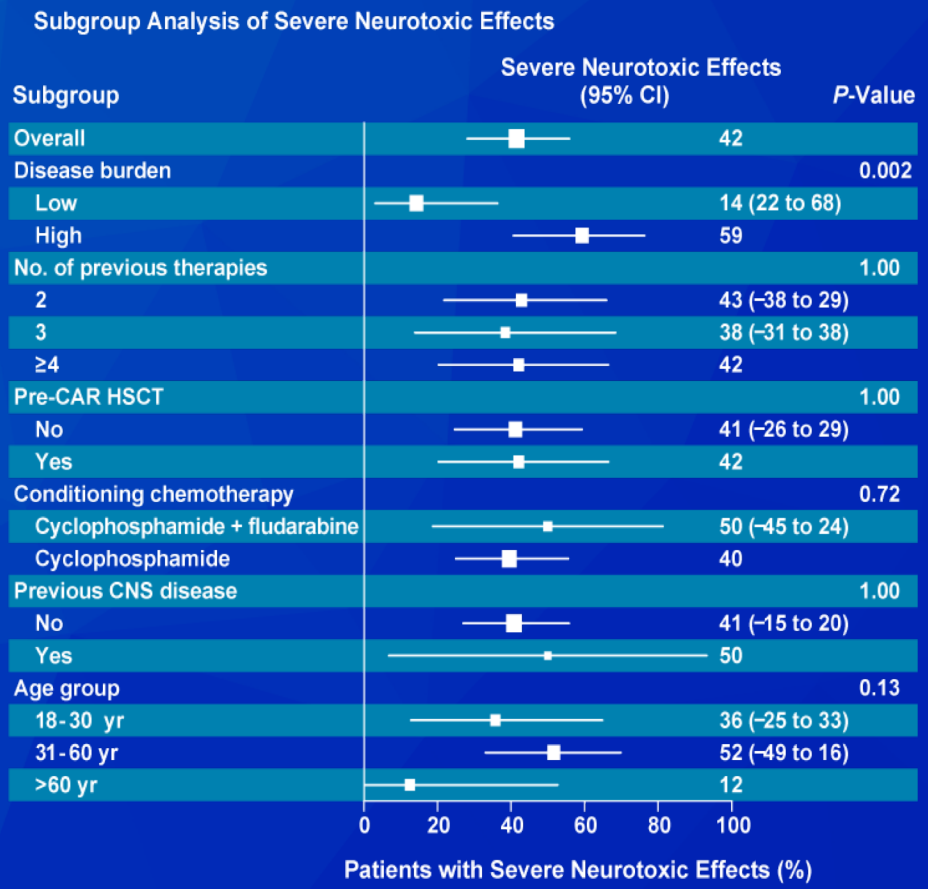




Park JH et al. *N Engl J Med* 2018;378(5):449-59.

19-28z T Cells for R/R ALL: Tolerability by Subgroup





Park JH et al. *N Engl J Med* 2018;378(5):449-59.

Tumor Gene Signature Associated with Neurotoxicity in R/R B-ALL Patients Treated with JCAR015, A CD19-Directed CAR T Cell Product

Olson NE et al.
Proc ASCO 2018;Abstract 7007.

Neurotoxicity associated with ALL subtype

- Analysis of patients enrolled on the ROCKET trial of JCAR015
  - Differential gene expression between low neurotoxicity (Grade 0-1) and high neurotoxicity (Grade 4-5)
  - Compared these genes to the TARGET database of 250 B-ALL samples
  - Grade 0-1 neurotoxicity genes were expressed in Ph+/Ph-like samples
  - Grade 4-5 neurotoxicity genes were expressed in non-Ph-like samples

Olson NE et al. *Proc ASCO* 2018;Abstract 7007.

Classification System Extrapolated to 3 Other B-ALL CD19 CAR T studies

BCR-ABL only

MSK 09-114 NCT01044069	Max neurotoxicity grade						
	Total	0	1	2	3	4	5
Not Ph+	36	14	5	0	14	3	0
Ph+	15	6	3	2	4	0	0
PHCRC2639 (B-ALL) NCT01865617							
Not Ph+	38	19	4	3	8	2	2
Ph+	9	3	2	2	2	0	0

BCR-ABL and Ph-like

PLAT-02 NCT02028455	Total	0-3	4	5
Non-Ph	35	32	3	0
Ph+/Ph-like	8	8	0	0

All trials	Total	Grade 0-3	Grades 4-5
Non-Ph	124	107	17
Ph+/Ph-like	48	48	0

Olson NE et al. *Proc ASCO* 2018;Abstract 7007.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

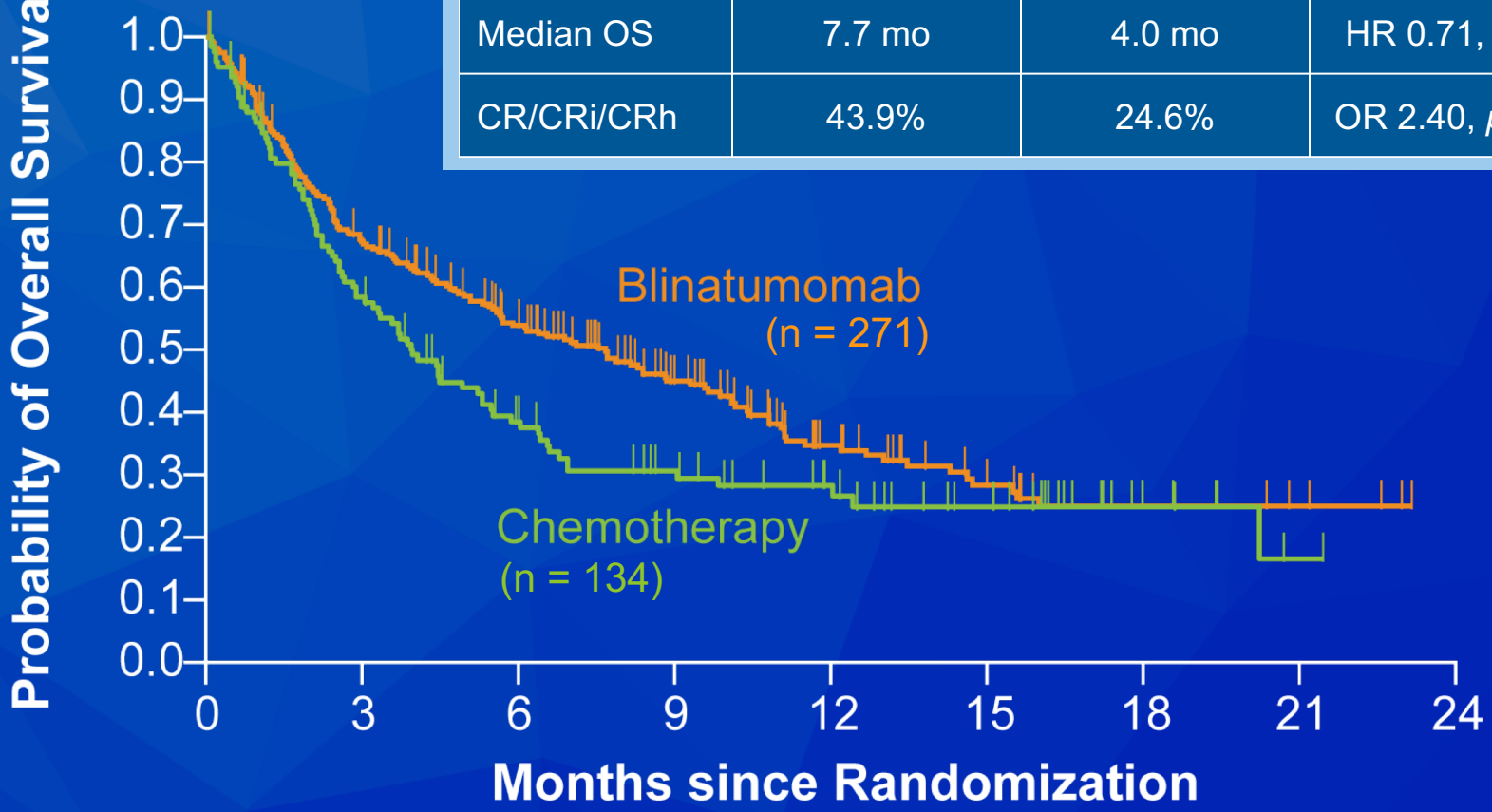
Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Hagop Kantarjian, M.D., Anthony Stein, M.D., Nicola Gökbuget, M.D., Adele K. Fielding, M.B., B.S., Ph.D., Andre C. Schuh, M.D., Josep-Maria Ribera, M.D., Ph.D., Andrew Wei, M.B., B.S., Ph.D., Hervé Dombret, M.D., Robin Foà, M.D., Renato Bassan, M.D., Önder Arslan, M.D., Miguel A. Sanz, M.D., Ph.D., Julie Bergeron, M.D., Fatih Demirkan, M.D., Ewa Lech-Maranda, M.D., Ph.D., Alessandro Rambaldi, M.D., Xavier Thomas, M.D., Ph.D., Heinz-August Horst, M.D., Ph.D., Monika Brüggemann, M.D., Wolfram Klapper, M.D., Ph.D., Brent L. Wood, M.D., Ph.D., Alex Fleishman, M.S., Dirk Nagorsen, M.D., Ph.D., Christopher Holland, M.S., Zachary Zimmerman, M.D., Ph.D., and Max S. Topp, M.D.

N Engl J Med 2017;376(9):836-47.

TOWER: Phase III Study of Blinatumomab vs SoC Chemo in R/R ALL — Survival and Response

	Blinatumomab n = 271	SoC chemo n = 134	HR or odds ratio, *p*-value
Median OS	7.7 mo	4.0 mo	HR 0.71, $p = 0.01$
CR/CRi/CRh	43.9%	24.6%	OR 2.40, $p < 0.001$

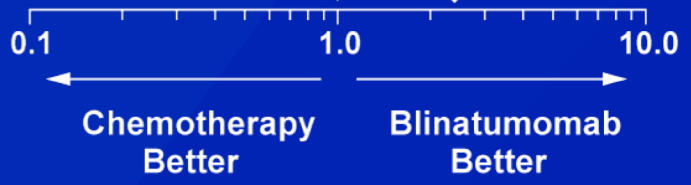


CRh = CR with partial hematologic recovery

Kantarjian H et al. *N Engl J Med* 2017;376(9):836-47.

TOWER: Phase III Study of Blinatumomab vs SoC Chemo in R/R ALL — Remission Rate by Subgroup

Subgroup	Blinatumomab no. of events/no. of patients (%)	Chemotherapy no. of events/no. of patients (%)	Odds Ratio
Age			
<35 yr	43.1	25.0	2.27
≥35 yr	44.6	24.3	2.50
Salvage-treatment phase			
First	52.6	35.4	2.03
Second	39.6	16.3	3.37
Third or later	34.8	11.5	4.10
Previous allogeneic stem-cell transplantation			
Yes	40.4	10.9	5.56
No	45.8	31.8	1.81
Bone marrow blasts			
<50%	65.5	34.2	3.65
≥50%	34.4	20.8	1.99
Overall	43.9	24.6	2.40



Kantarjian H et al. *N Engl J Med* 2017;376(9):836-47.

TOWER: Phase III Study of Blinatumomab vs SoC Chemo in R/R ALL — Tolerability

Event	Blinatumomab group (n = 267)	Chemotherapy group (N = 109)
	No. of patients, %	
Event leading to premature discontinuation of trial treatment	12.4	8.3
Fatal serious adverse event	19.1	17.4
Select Grade ≥3 AE in ≥3% of patients		
Neutropenia	37.8	57.8
Infection	34.1	52.3
Neurologic event	9.4	8.3
Cytokine release syndrome	4.9	0
Infusion reaction	3.4	0.9
Lymphopenia	1.5	3.7

Kantarjian H et al. *N Engl J Med* 2017;376(9):836-47.

blood

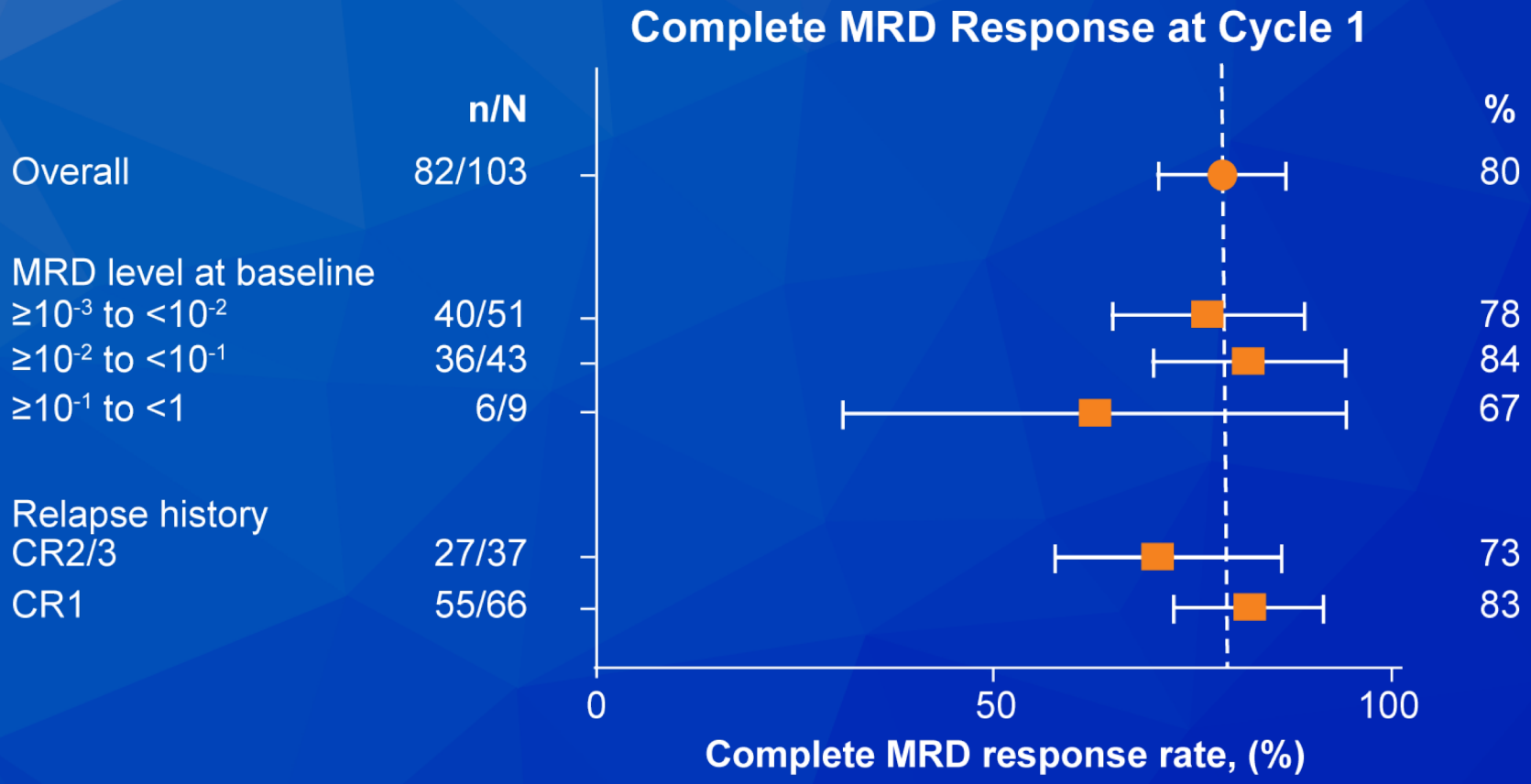
CLINICAL TRIALS AND OBSERVATIONS

Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia

Nicola Gökbuget,[1] Hervé Dombret,[2] Massimiliano Bonifacio,[3] Albrecht Reichle,[4] Carlos Graux,[5] Christoph Faul,[6] Helmut Diedrich,[7] Max S. Topp,[8] Monika Brüggemann,[9] Heinz-August Horst,[9] Violaine Havelange,[10] Julia Stieglmaier,[11] Hendrik Wessels,[11] Vincent Haddad,[12] Jonathan E. Benjamin,[13] Gerhard Zugmaier,[11] Dirk Nagorsen,[13] and Ralf C. Bargou[14]

Blood 2018;131(14):1522-31.

Blinatumomab for Patients in CR with MRD: Complete MRD Response



	MRD responders (n = 85)	MRD non-responders (n = 22)	*p*-value
Median OS	38.9 mo	12.5 mo	0.002

Gökbuget N et al. *Blood* 2018;131(14):1522-31.

Blinatumomab for Patients in CR with MRD: Tolerability

Select adverse events	All patients (n = 116)	
	Grade 3	Grade 4
Pyrexia	8%	0
Neutropenia	2%	14%
Leukopenia	4%	2%
Thrombocytopenia	2%	3%
Any neurologic AE	10%	3%
Tremor	5%	0
Encephalopathy	3%	2%

Gökbuget N et al. *Blood* 2018;131(14):1522-31.

The NEW ENGLAND JOURNAL of MEDICINE

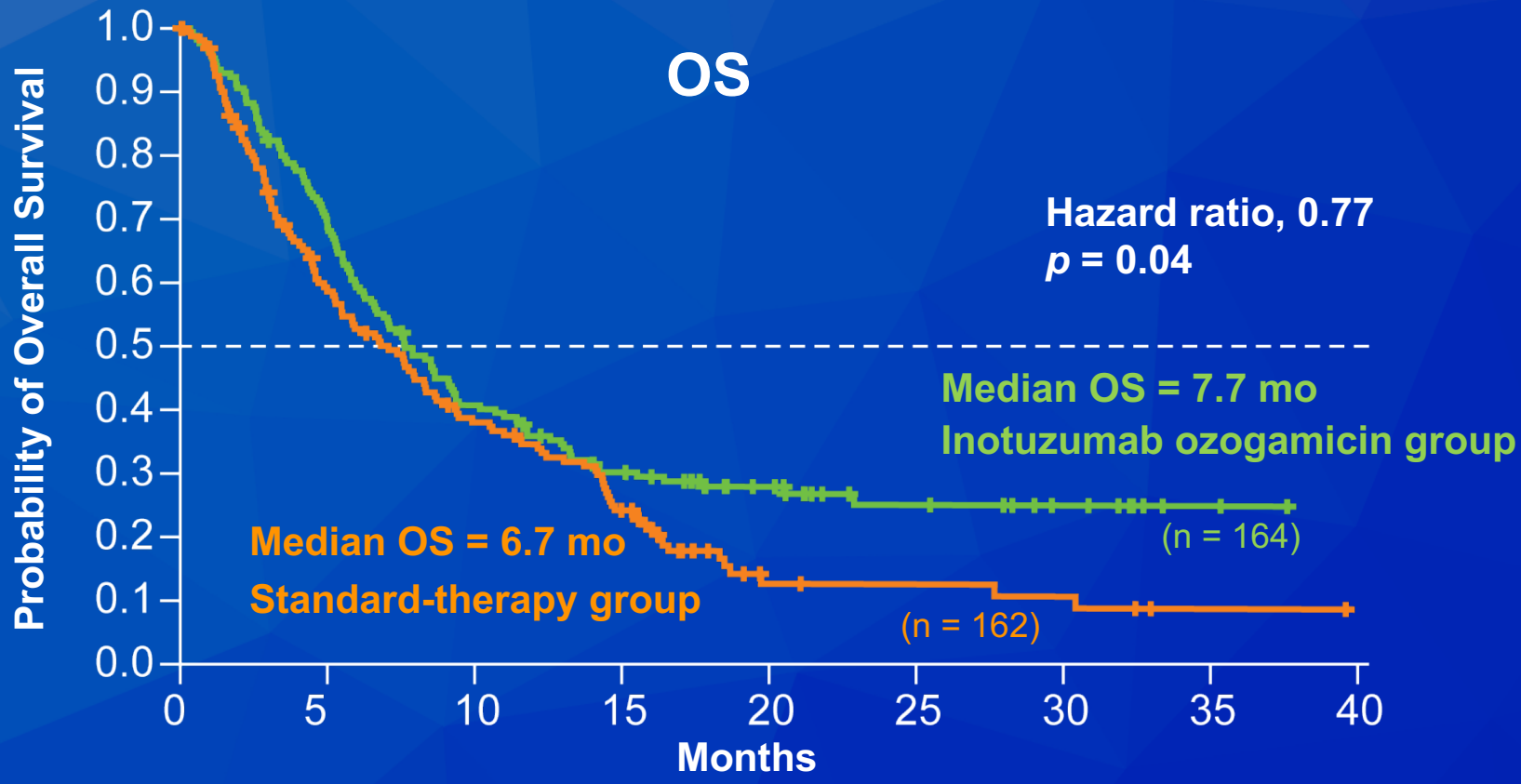
ORIGINAL ARTICLE

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

Hagop M. Kantarjian, M.D., Daniel J. DeAngelo, M.D., Ph.D., Matthias Stelljes, M.D., Giovanni Martinelli, M.D., Michaela Liedtke, M.D., Wendy Stock, M.D., Nicola Gökbuget, M.D., Susan O'Brien, M.D., Kongming Wang, Ph.D., Tao Wang, Ph.D., M. Luisa Paccagnella, Ph.D., Barbara Sleight, M.D., Erik Vandendries, M.D., Ph.D., and Anjali S. Advani, M.D.

N Engl J Med 2016;375(8):740-53.

Phase III INO-VATE ALL Trial: OS and Response



Response	Inotuzumab (n = 109)	Standard (n = 109)	*p*-value
CR	35.8%	17.4%	0.002
CRi	45.0%	11.9%	<0.001

Kantarjian HM et al. *N Engl J Med* 2016;375(8):740-53.

Phase III INO-VATE ALL Trial: Select Adverse Events

	Inotuzumab (n = 139)		Standard (n = 120)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Febrile neutropenia	16 (12%)	15 (11%)	22 (18%)	21 (18%)
Veno-occlusive disease	15 (11%)	13 (9%)	1 (1%)	1 (1%)
Pneumonia	5 (4%)	5 (4%)	1 (1%)	0
Sepsis	3 (2%)	3 (2%)	6 (5%)	6 (5%)
Respiratory failure	1 (1%)	1 (1%)	4 (3%)	4 (3%)
Tumor lysis syndrome	2 (1%)	1 (1%)	0	0
Acute renal failure	2 (1%)	1 (1%)	0	0

Kantarjian HM et al. *N Engl J Med* 2016;375(8):740-53.

Acute Promyelocytic Leukemia (APL)

blood

CLINICAL TRIALS AND OBSERVATIONS

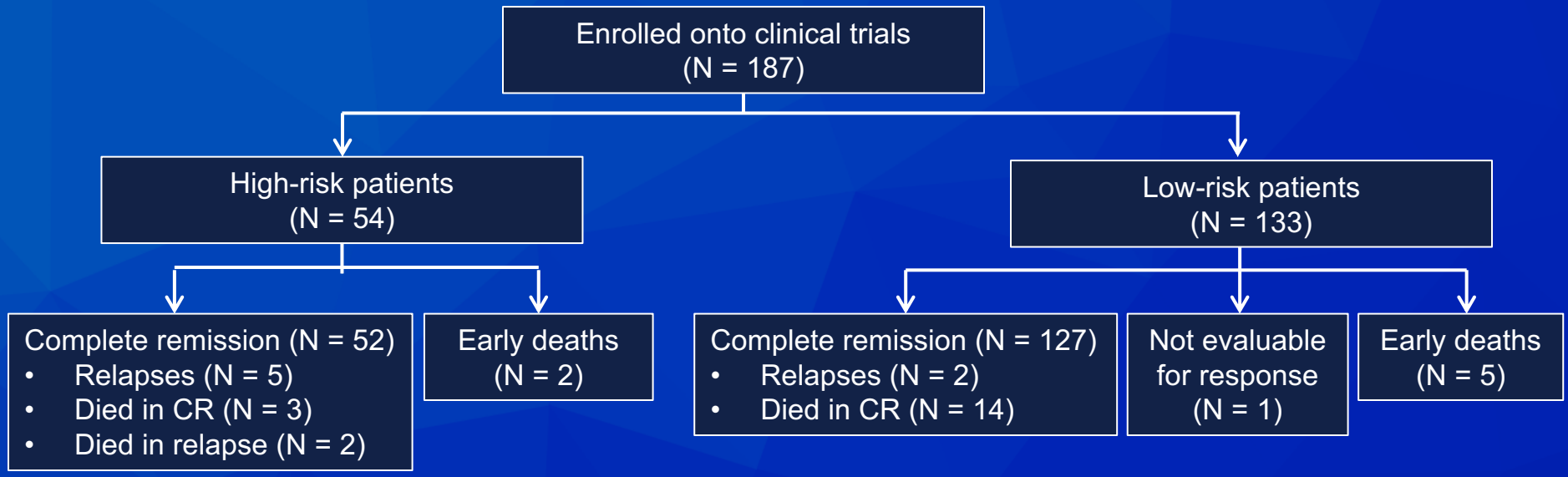
Long-term outcome of acute promyelocytic leukemia treated with all-*trans*-retinoic acid, arsenic trioxide, and gemtuzumab

Yasmin Abaza,[1] Hagop Kantarjian,[1] Guillermo Garcia-Manero,[1] Elihu Estey,[2] Gautam Borthakur,[1] Elias Jabbour,[1] Stefan Faderl,[3] Susan O'Brien,[4] William Wierda,[1] Sherry Pierce,[1] Mark Brandt,[1] Deborah McCue,[5] Rajyalakshmi Luthra,[6] Keyur Patel,[6] Steven Kornblau,[1] Tapan Kadia,[1] Naval Daver,[1] Courtney DiNardo,[1] Nitin Jain,[1] Srdan Verstovsek,[1] Alessandra Ferrajoli,[1] Michael Andreeff,[1] Marina Konopleva,[1] Zeev Estrov,[1] Maria Foudray,[1] David McCue,[1] Jorge Cortes,[1] and Farhad Ravandi[1]

Blood 2017;129(10):1275-83.

Gemtuzumab Ozogamicin (GO) in Combination with ATRA and ATO for Patients with APL

- Patients with high-risk APL (WBC count > 10 x 10^9/L on presentation) and patients with low-risk APL who developed high WBC counts to >10 x 10^9/L during the first 4 weeks of therapy received GO in addition to ATRA and ATO
- 96 patients (72%) of the low-risk group developed leukocytosis; 60 received treatment with GO

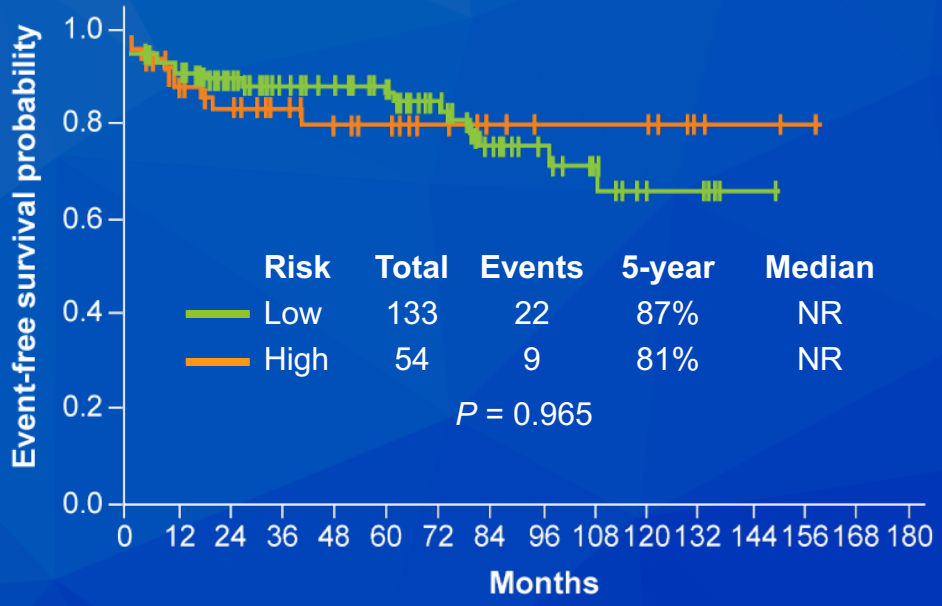


ATRA = all-trans retinoic acid; ATO = arsenic trioxide

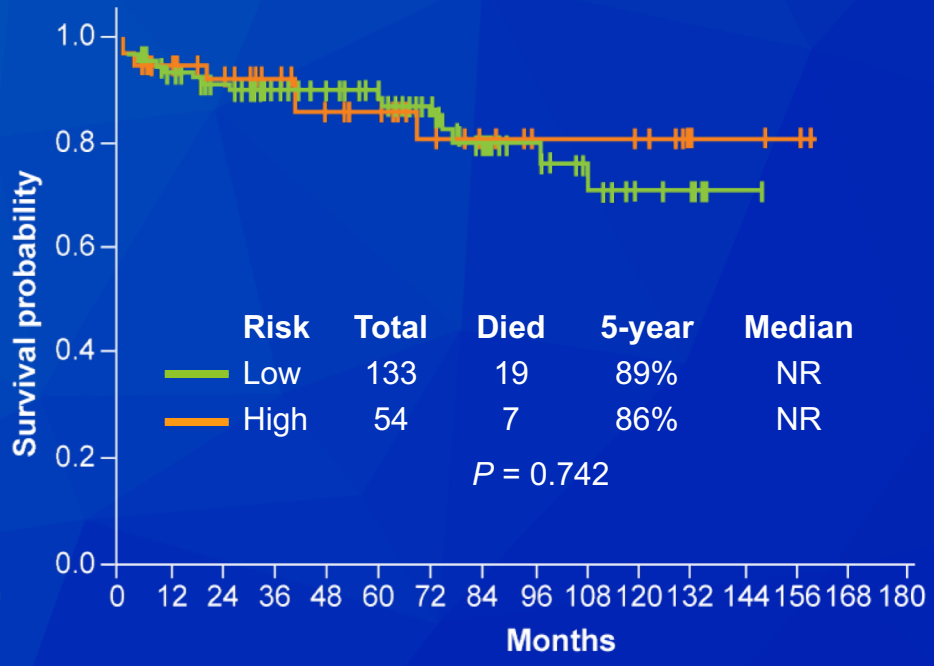
Abaza Y et al. *Blood* 2017;129(10):1275-83.

GO in Combination with ATRA and ATO for Patients with APL: Survival Outcomes by Risk Group

EFS



OS



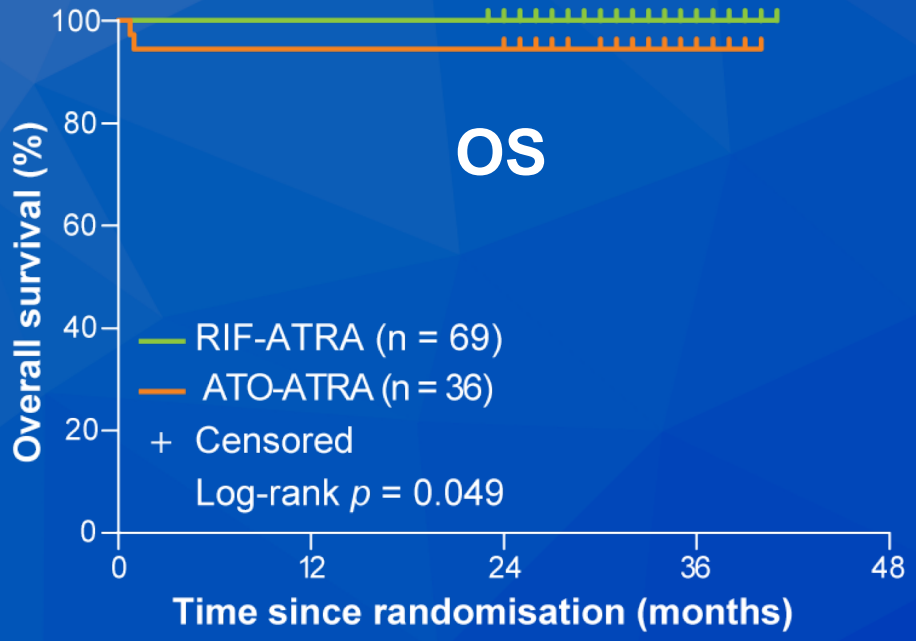
Abaza Y et al. *Blood* 2017;129(10):1275-83.

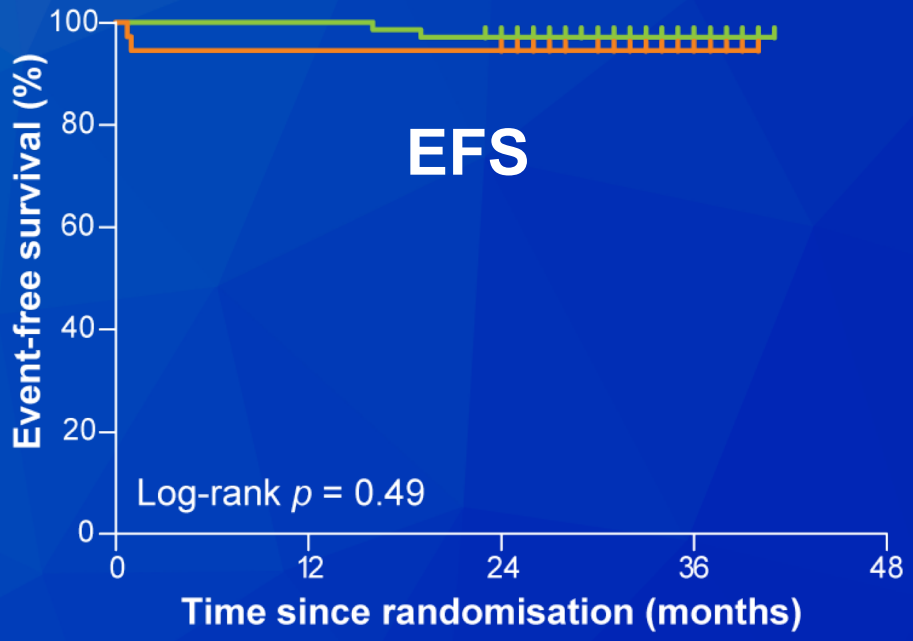
Oral arsenic plus retinoic acid versus intravenous arsenic plus retinoic acid for non-high-risk acute promyelocytic leukaemia: a non-inferiority, randomised phase 3 trial

Hong-Hu Zhu, De-Pei Wu, Xin Du, Xi Zhang, Lin Liu, Jun Ma, Zong-Hong Shao, Han-Yun Ren, Jian-Da Hu, Kai-Lin Xu, Jing-Wen Wang, Yong-Ping Song, Mei-Yun Fang, Juan Li, Xiao-Yan Yan, Xiao-Jun Huang

Lancet Oncol 2018;19(7):871-9.

Oral Arsenic (RIF) Plus ATRA Compared to IV ATO Plus ATRA for APL





	RIF-ATRA (n = 69)	ATO-ATRA (n = 36)	*p*-value
Complete remission	100%	94%	0.12
Molecular remission after consolidation	100%	100%	—
30-day mortality	0%	6%	0.11
2-year EFS	97%	94%	0.49
2-year OS	100%	94%	0.049
2-year cumulative incidence of relapse	3%	0%	0.32

Zhu HH et al. *Lancet Oncol* 2018;19(7):871-9.

RIF-ATRA versus IV ATO-ATRA: Select AEs

	RIF-ATRA (n = 69)			Arsenic trioxide-ATRA (n = 36)		
	Grades 1-2	Grade 3	Grade 4	Grades 1-2	Grade 3	Grade 4
Vomiting	12%	0%	0%	8%	0%	0%
Diarrhoea	9%	0%	0%	6%	0%	0%
Mucositis	9%	0%	0%	14%	3%	0%
Thrombosis or embolism	5%	0%	0%	0%	0%	0%
Haemorrhage	33%	2%	2%	25%	6%	3%
Cardiac	6%	2%	0%	6%	0%	3%
Prolonged QTc interval	19%	0%	0%	19%	0%	0%
Increased ALT/AST	49%	9%	0%	64%	11%	3%
Hyperbilirubinaemia	26%	0%	0%	36%	0%	0%
Neutropenia	9%	18%	64%	11%	19%	61%
Anaemia	33%	58%	8%	22%	53%	22%
Thrombocytopenia	8%	15%	68%	8%	25%	64%

Zhu HH et al. *Lancet Oncol* 2018;19(7):871-9.

Long-Term Outcome of Relapsed Acute Promyelocytic Leukemia Treated With Oral Arsenic Trioxide-Based Reinduction and Maintenance Regimens: A 15-Year Prospective Study

Harinder Gill, MB, BS[1]; Rita Yim, PhD[1]; Harold K. K. Lee, MB, ChB[2]; Vivien Mak, MB, BS[2]; Shek-Ying Lin, MB, BS[3]; Bonnie Kho, MB, ChB[4]; Sze-Fai Yip, FRCPath[5]; June S. M. Lau, MB, BS[6]; Wah Li, MB, ChB[7]; Ho-Wan Ip, FRCPA[8]; Yu-Yan Hwang, MB, BS[1]; Thomas S. Y. Chan, MB, BS[1]; Eric Tse, FRCPath[1]; Wing-Yan Au, FRCP[9]; Cyrus R. Kumana, FRCP[1]; and Yok-Lam Kwong, MD [1]

Cancer 2018;124(11):2316-26.

Oral ATO-Based Reinduction and Maintenance for Patients with Relapsed APL

- 73 patients in first relapse (R1) treated with ATO, ATRA, and ascorbic acid (AAA) reinduction and maintenance
- All 73 patients achieved CR2 in response to reinduction
  - 10-year leukemia-free survival rate: 56.8%
  - 10-year OS: 67.3%
- After median follow-up of 94 months, 43 were still in CR2 and 49 had finished 2 years of maintenance

Gill H et al. *Cancer* 2018;124(11):2316-26.

Oral ATO-Based Reinduction and Maintenance for Patients with Relapsed APL

- 30 patients experienced a second relapse and were treated with AAA
  - 27 patients (90%) achieved CR3
  - 11 patients remained in CR3 after median follow-up of 30 months
- 16 patients experienced a third relapse and were treated with AAA
  - 12 patients (75%) achieved CR4; 3 patients were refractory to AAA
- 10 patients experienced a fourth relapse and were treated with AAA
  - 5 patients (50%) achieved CR5
- 11 of the 30 patients who had a second relapse remain alive

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