Year in Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

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Orlando, Florida

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Disclosures

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Disclosure

No financial interests or affiliations to disclose.

Select Recently Approved Agents in Acute Leukemias

Acute myeloid leukemia		
Agent	**Approval date**	**Indication**
Midostaurin	4/28/17	Newly diagnosed FLT3-mutant AML with cytarabine and daunorubicin induction and cytarabine consolidation
Enasidenib	8/1/17	Relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 (IDH2) mutation
Liposomal daunorubicin/ cytarabine	8/3/17	Newly diagnosed therapy-related AML or AML with myelodysplasia-related changes
Gemtuzumab ozogamicin	9/1/17	Newly diagnosed and relapsed or refractory CD33-positive AML in combination with daunorubicin and cytarabine or as a stand-alone treatment

Acute lymphoblastic leukemia		
Agent	**Approval date**	**Indication**
Inotuzumab ozogamicin	8/17/17	Relapsed or refractory ALL
Tisagenlecleucel (CAR T-cell therapy)	8/30/17	Patients up to 25 with ALL that is refractory or in second or later relapse

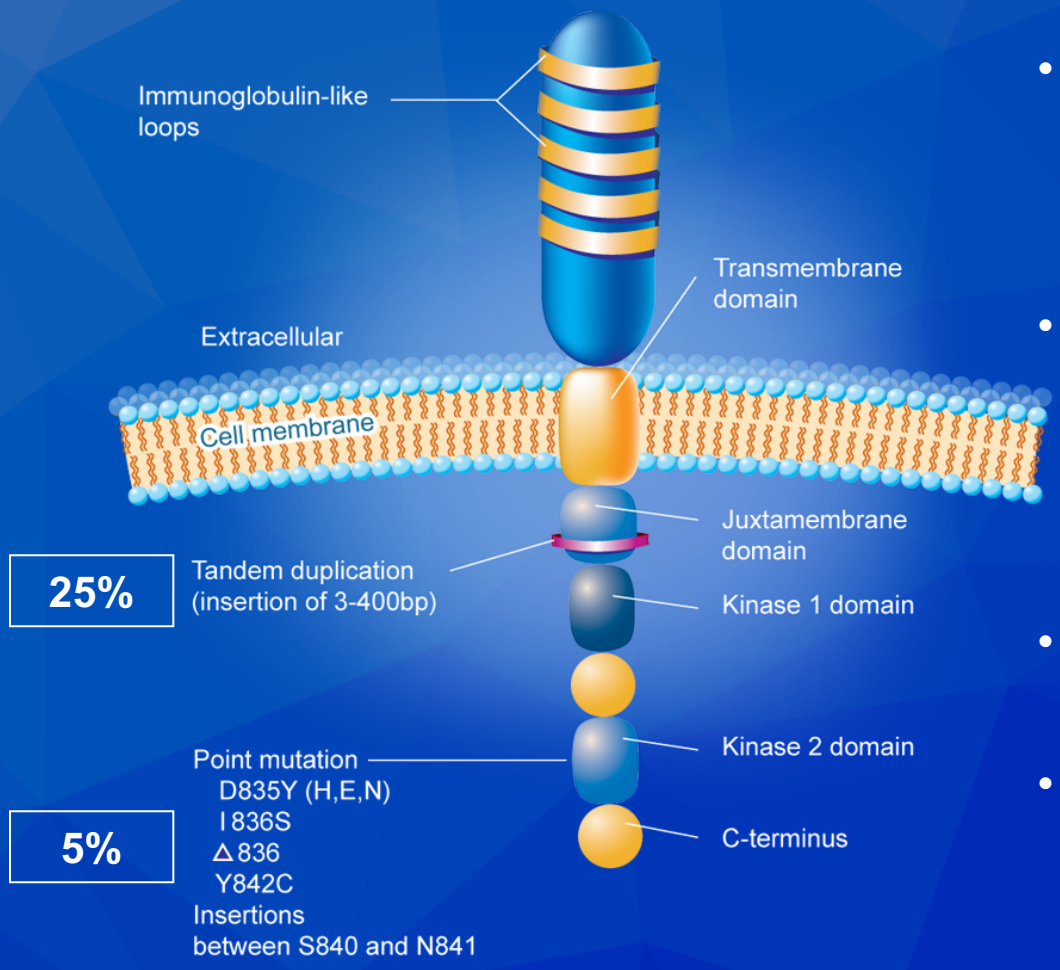
Acute Leukemias – Drs Erba and Kantarjian

Acute Myeloid Leukemia

Acute Lymphoblastic Leukemia

Acute Promyelocytic Leukemia

FLT3 Mutations in AML



- FLT3 is a type III transmembrane receptor tyrosine kinase found in blasts from 70%-90% of patients with AML.
- FLT3 ligand (FL) binding shifts receptor conformation and allows transphosphorylation of JM domain, activating downstream pathways (↑ cell proliferation).
- For ITD+ cells, FL binding is not a necessary step for FLT3 activation.
- FLT3 ITD has been associated with higher risk of relapse and lower overall survival in AML.

Litzow MR. *Blood* 2005;106:3331-2; Small D. *Hematology Am Soc Hematol Educ Program* 2006:178-84; Swords R et al. *Leukemia* 2012;26(10):2176-85; Griffith J et al. *Mol Cell* 2004;13(2):169-78.

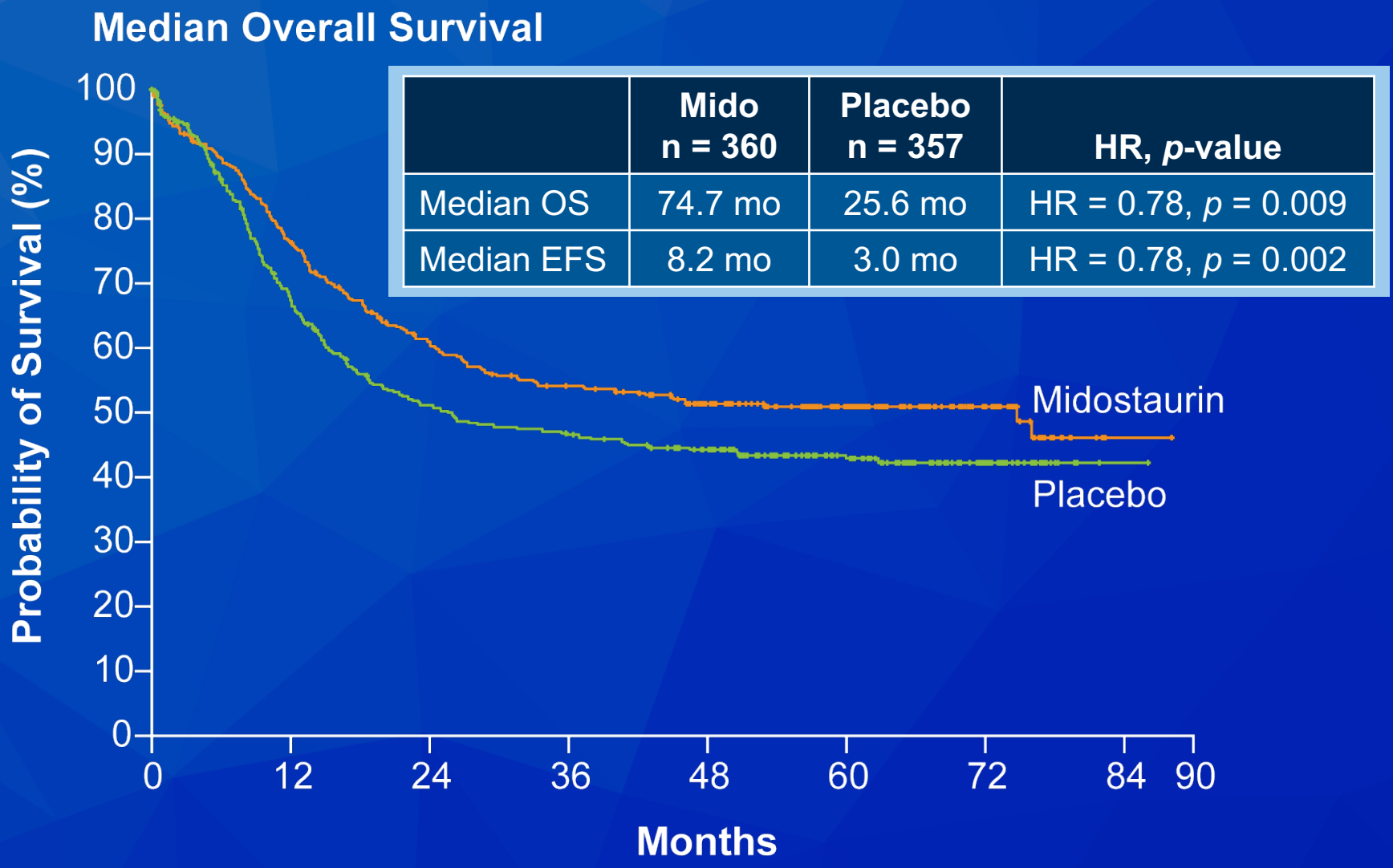
ORIGINAL ARTICLE

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner

N Engl J Med 2017;377(5):454-64.

RATIFY: Midostaurin with Chemotherapy for FLT3-Positive AML — Primary Endpoint OS



	Mido n = 360	Placebo n = 357	HR, *p*-value
Median OS	74.7 mo	25.6 mo	HR = 0.78, *p* = 0.009
Median EFS	8.2 mo	3.0 mo	HR = 0.78, *p* = 0.002

Stone RM et al. *N Engl J Med* 2017;377(5):454-64.

Editorial — Dr Kantarjian

This multi-institutional study randomized newly diagnosed young patients (age 18 to 59 years) with AML and FLT3 mutation to chemotherapy (3+7) and midostaurin (FLT3 inhibitor that affects both FLT3 ITD and TKD). 3,277 patients were screened; 896 had a FLT3 mutation, and 717 underwent randomization. The overall survival was significantly longer with midostaurin therapy (hazard ratio 0.78; p = 0.009). This difference was particularly notable among patients who underwent allogeneic stem cell transplant in first CR (55% to 59% of the randomized patients). The 4-year survival rates were 51.4% with midostaurin and 44.3% with placebo.

Editorial — Dr Kantarjian (continued)

This study with the positive data favoring midostaurin resulted in the FDA approval of midostaurin for the treatment of younger patients with AML and FLT3 mutations, which affect about 30% of patients with AML. Midostaurin should now be considered as standard front-line therapy for these patients. Midostaurin is given at the dose of 50 mg orally twice daily on Days 8 to 21 during induction and during consolidation, followed by maintenance using midostaurin 50 mg orally twice daily for 1 year. The FDA approval is for the induction and consolidation phases.

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: 1061–75

Deep molecular response to gilteritinib to improve survival in FLT3 mutation-positive relapsed/refractory acute myeloid leukemia

Altman JK et al. *Proc ASCO* 2017;Abstract 7003.

CHRYSALIS: Efficacy and Safety of Gilteritinib in Relapsed/Refractory AML

	All patients (n = 249)	FLT3 WT (n = 58)	FLT3 mutant (n = 191)
Composite complete remission	30%	9%	37%
Overall response	40%	12%	49%
Duration of response	17 wk	12 wk	20 wk
Overall survival	25 wk	17 wk	30 wk

Grade 3/4 adverse events	
Febrile neutropenia	97/252 (39%)
Anemia	61/252 (24%)
Thrombocytopenia	33/252 (13%)
Sepsis	28/252 (11%)
Pneumonia	27/252 (11%)

- Based on activity data, gilteritinib at 120 mg/day is being tested in Phase III trials

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

CHRYSALIS: OS by Molecular Response

- Subgroup of patients with FLT3 mutations treated with 120 or 200 mg/d gilteritinib

Molecular response	Achieved a molecular response		Did not achieve a molecular response		*p*-value
	n	Median OS, days	n	Median OS, days	
ITD signal ratio $\leq 10^{-2}$	20	417	60	199	<0.001
MMR	18	417	62	213	0.003
MRD-negative	13	417	67	213	0.002

MMR = major molecular response (ITD signal ratio $\leq 10^{-3}$); MRD-negative (ITD signal ratio $\leq 10^{-4}$)

Altman JK et al. *Proc ASCO* 2017;Abstract 7003.

Editorial — Dr Kantarjian

In this Phase I/II study, 250 patients with refractory relapsed AML received gilteritinib 20-450 mg daily with further expansion of patients in the dose range of 120-200 mg daily. The overall response rate in 169 patients treated at 80 mg daily or more was 52%. The median survival was 31 weeks; the median duration of response was 20 weeks.

The above 2 studies confirm the importance of gilteritinib as a novel FLT3 AXL inhibitor with potential activity in AML. If confirmed in randomized trials, this new FLT3 inhibitor may, hopefully, be added to the list of useful FLT3 inhibitors in FLT3-mutated AML therapy.

Editorial — Dr Kantarjian

Gilteritinib is a highly selective FLT3/AXL inhibitor that demonstrated activity in refractory relapsed AML (CHRYSALIS study), particularly when given at doses of 80 mg daily or more. In this analysis, the investigators evaluated the association between the depth of molecular response on gilteritinib therapy and improved survival. 147 patients received gilteritinib 120-200 mg daily. 80 were included in the analysis. The overall response rate was 55%. The authors noted a longer median survival by the depth of the ITD signal ratio. Patients with ITD signal ratio ($\leq 10^{-2}$) had a median survival of 417 days versus about 200 days for those who did not achieve this kind of a molecular response.

Quizartinib and bridge to transplant in FLT3-ITD AML patients after failure of salvage chemotherapy: A historical comparison with UK National Cancer Research Institute (NCRI) data

Hills R et al.
Proc EHA 2017;Abstract S475.

Quizartinib Compared to Historical Treatment: Efficacy Results

- Primary aim: Compare SCT rates and outcomes for patients with AML with FLT3 mutations treated with quizartinib in a cohort of the AC220-002 study to those of patients treated with standard chemotherapy from the UK NCRI database

	Quizartinib n = 58	Historic control Standard chemo n = 118	HR, *p*-value
CRi	40%	3%	OR = 0.05, $p < 0.0001$
Median OS	140 d	54 d	HR = 0.38, $p < 0.0001$
Proceeded to SCT	40%	8%	—

- 18-month survival
  - Patients who proceeded to SCT: 29%
  - Patients who did not proceed to SCT: 7%

} HR = 0.36, $p = 0.0005$

Hills R et al. *Proc EHA* 2017;Abstract S475.

Editorial — Dr Kantarjian

Quizartinib is a well-known effective FLT3 inhibitor with a reasonable toxicity profile. Randomized studies are ongoing aiming at potential FDA approval of this agent. In this historical comparison analysis, 58 patients with AML and FLT3 ITD mutation who received and had R/R AML on intensive chemotherapy were treated with quizartinib. These were compared to 118 patients who received chemotherapy. A landmark analysis was applied, excluding deaths before Day 90 of a transplant in the total sample. Overall, patients treated with quizartinib had higher remission rates (40% versus 3%; $p < 0.0001$) and longer median survival (140 days versus 54 days; hazard ratio 0.38; $p < 0.0001$).

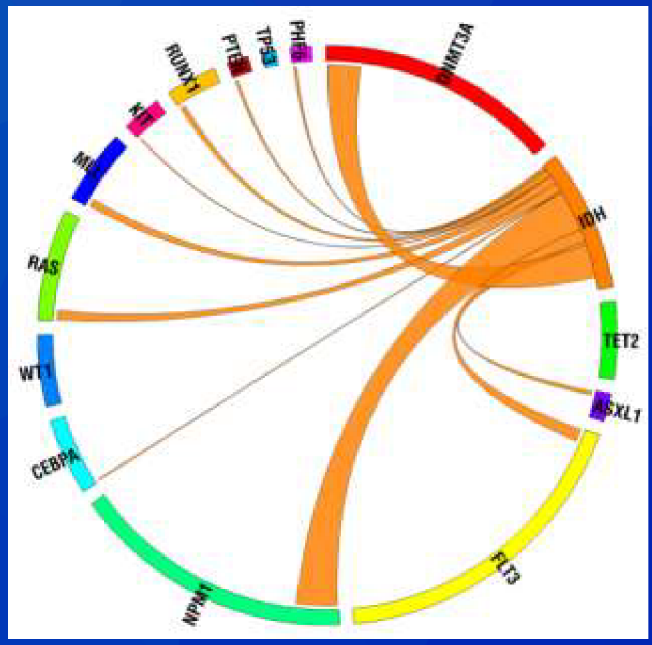
Editorial — Dr Kantarjian (continued)

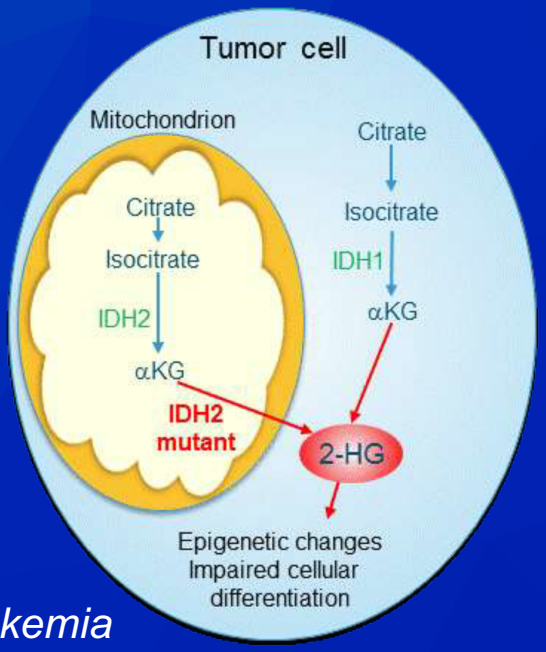
More patients on quizartinib proceeded to stem cell transplant (40% versus 8%). The 18-month survival was better post-SCT after quizartinib therapy (29% versus 7%; HR 0.36; p = 0.0005). This study provides a strong foundation for the beneficial effect of quizartinib as a FLT3 inhibitor in R/R FLT3-ITD AML, as well as its capacity to bridge more people to transplant and to improve the outcome post SCT.

In essence, all the above studies with FLT3 inhibitors support the notion that these agents are important in AML therapy and will become standards of care in the context of FLT3-mutated AML therapy, as front-line combinations with chemotherapy, in salvage combinations, and in the context of SCT.

IDH in Leukemia

- IDH mutations occur in ~20% of AML
  - Frequency: 6%-16% IDH1 and 8%-18% IDH2
  - Majority (85%) with diploid or +8 cytogenetics
  - ↑ prevalence with ↑ patient age
  - Strongly associated with NPM1+ and MPN-derived AML (21%-31%)
  - Mutated residues occur in conserved active site
    - IDH1-R132, IDH2-R172 or R140
    - Gain of function
  - Founder mutations, not progression
    - 0/225 pts WT IDH at dx develop IDH mutation during f/u





Dang L et al. *Trends Mol Med* 2010;16(9):387–97. Chou WC et al. *Leukemia* 2011;25(2):246-53. Patel JP et al. *N Engl J Med* 2012;366(2):1079-89.

Determination of IDH1 mutational burden and clearance via next-generation sequencing in patients with IDH1 mutation-positive hematologic malignancies receiving AG-120, a first-in-class inhibitor of mutant IDH1

DiNardo CD et al.
Proc ASH 2016;Abstract 1070.

Clinical Activity of Single-Agent Ivosidenib

	Dose escalation	
	R/R AML n = 63	Overall n = 78
CR	10 (16%)	14 (18%)
CRi	8 (13%)	8 (10%)
PR	1 (2%)	2 (3%)
Marrow CR/morphologic leukemia-free state	2 (3%)	6 (8%)
ORR	21 (33%)	30 (39%)

- Grade ≥3 AEs: febrile neutropenia, anemia, leukocytosis, pneumonia

DiNardo CD et al. *Proc ASH* 2016;Abstract 1070.

blood

CLINICAL TRIALS AND OBSERVATIONS

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,†]

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Safety of Enasidenib for Patients with IDH2-Mutant AML

	All patients (n = 239)
Treatment-related Grade 3/4 AEs	99 (41%)
Hyperbilirubinemia	29 (12%)
IDH inhibitor-associated differentiation syndrome	15 (6%)
Thrombocytopenia	15 (6%)
Anemia	12 (5%)
Grade 3/4 hematologic AEs	10%
Grade 3/4 infections	1%
Treatment-related AE leading to discontinuation	5%

- MTD was not reached at doses of up to 650 mg

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

Response and Survival Results for Enasidenib for Patients with IDH2-Mutant R/R AML

- Median OS
  - All patients with R/R AML: 9.3 mo
  - Patients who attained complete remission: 19.7 mo
  - Patients who attained partial remission: 14.4 mo

	100 mg QD n = 109	All doses n = 176
ORR	42 (38.5%)	71 (40.3%)
CR	22 (20.2%)	34 (19.3%)
CRi	7 (6.4%)	12 (6.8%)
PR	3 (2.8%)	11 (6.3%)
Morphologic leukemia-free state	10 (9.2%)	14 (8.0%)
Median time to first response	1.9 mo	1.9 mo
Median duration of response	5.6 mo	5.8 mo

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

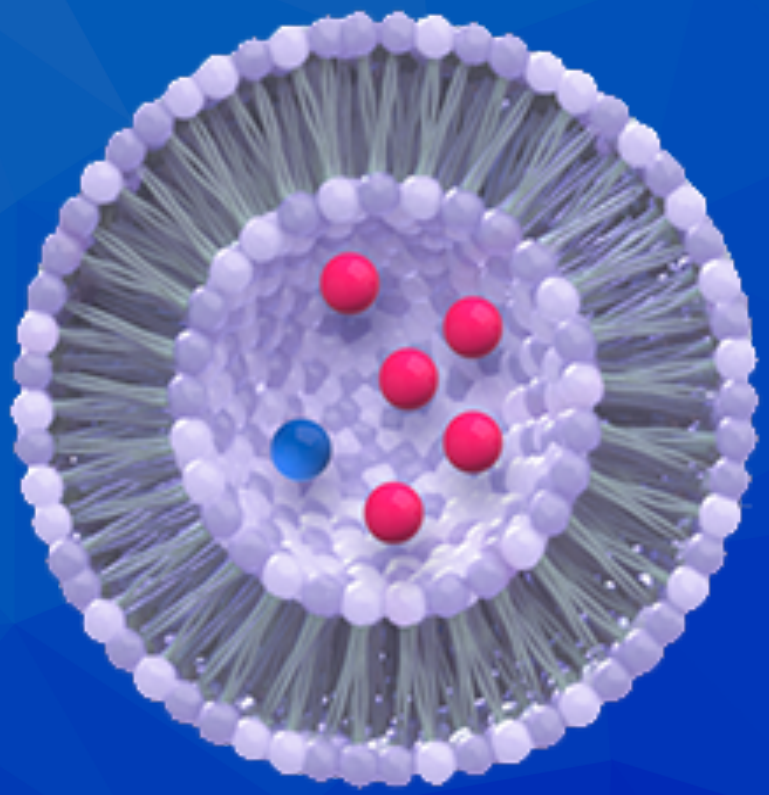
Editorial — Dr Kantarjian

IDH1/2 mutations occur in about 15% to 20% of patients with AML. Enasidenib (AG221) is a first-in-class oral selected small-molecule inhibitor of mutant IDH2. Ivosidenib (AG-120) is a similar IDH1 inhibitor under development. Both have shown exciting activity in R/R AML. In this study, Stein and colleagues evaluated enasidenib 30-150 mg BID and 50-650 mg daily. A total of 239 patients were treated. Clinical efficacy was evaluated in 176 patients with R/R AML. The MTD was not reached at dose ranges of 50-650 mg daily. A dose of 100 mg daily was chosen for the expansion phase. Grade 3-4 AEs included elevation of indirect bilirubin (12%) and differentiation syndrome (7%).

Editorial — Dr Kantarjian (continued)

The overall response rate was 40%, the median response duration 5.8 months, and the median survival 9.3 months. Among 34 patients (19%) achieving CR, the median survival was 19.7 months. This study resulted in the FDA approval of enasidenib for the treatment of IDH2 mutated R/R AML. This should now be considered a standard of care in this salvage setting, and all patients with AML should be tested for IDH1/2 mutations. Future studies will clarify the role of enasidenib in the front-line setting in combination with established anti-AML agents.

Liposomal Daunorubicin and Cytarabine (CPX-351)



- 1:5 molar ratio of daunorubicin to cytarabine
- Synergistic activity in both in vitro and animal models
- 100 nm bilamellar liposomes
- 1 unit = 0.44 mg daunorubicin and 1.0 mg cytarabine (1:5 molar ratio) complexed with copper
- Targets bone marrow and preferentially targets leukemic compared to normal marrow progenitors

Overall survival (OS) with CPX-351 versus 7+3 in older adults with newly diagnosed, therapy-related acute myeloid leukemia (tAML): Subgroup analysis of a phase III study

Efficacy by consolidation administration site: Subgroup analysis of a phase III study of CPX-351 versus 7+3 in older adults with newly diagnosed, high-risk acute myeloid leukemia (AML)

Lancet JE et al.
Proc ASCO 2017;Abstract 7035.

Kolitz JE et al.
Proc ASCO 2017;Abstract 7036.

Efficacy of CPX-351 in Older Patients with Therapy-Related AML

- Subgroup analysis of patients with therapy-related AML from the Phase III CLTR0310-301 study of CPX-351 compared to standard 7 + 3 regimen for older patients with newly diagnosed, secondary AML

	CPX-351 n = 30	7 + 3 n = 32	HR
Median OS	12.17 mo	6.64 mo	0.49
Median EFS	2.5 mo	1.64 mo	0.66
Remission duration	10.87 mo	6.11 mo	0.50
CR + CRi	47%	36%	—

Lancet JE et al. *Proc ASCO* 2017;Abstract 7035.

Efficacy of CPX-351 by Setting of Consolidation Therapy

- Subgroup analysis by consolidation site from the Phase III CLTR0310-301 study of CPX-351 compared to standard 7 + 3 regimen for older patients with newly diagnosed, high-risk AML

	Inpatient		Outpatient	
	CPX-351	**7 + 3**	**CPX-351**	**7 + 3**
Consolidation cycle 1	24/49 (49%)	30/32 (94%)	25/49 (51%)	2/32 (6%)
Median OS	14.72 mo	9.26 mo	25.43 mo	6.87 mo
HR	0.55		0.10	
Consolidation cycle 2	9/23 (39%)	12/12 (100%)	14/23 (61%)	0/12 (0%)
Median OS	NR	14.31	26.32	—
HR	0.45		—	

Kolitz JE et al. *Proc ASCO* 2017;Abstract 7036.

Editorial — Dr Erba

Outcomes for older patients with AML following an antecedent hematologic malignancy and treatment-related AML (t-AML) have remained poor for over 40 years, since the initial publication in 1973 of cytarabine and daunorubicin (7+3) induction therapy. Dose intensification of cytarabine and/or an anthracycline as well as addition of other cytotoxic agents have not improved outcomes during this time. Preclinical studies, including murine xenograft models, have shown that the cytotoxic effect of cytarabine and daunorubicin can be optimized by combining the agents at a fixed molar ratio (1:5). CPX-351 is a liposomal formulation of daunorubicin and cytarabine that maintains delivery of these two agents to the bone marrow in a 1:5 molar ratio for at least 24 hours. Adults ages 60 to 75

Editorial — Dr Erba (continued)

years with previously untreated AML following myelodysplastic syndrome or chronic myelomonocytic leukemia, t-AML, and de novo AML with poor-risk, myelodysplasia-related cytogenetic abnormalities were eligible for the phase III study of CPX-351 versus standard cytarabine and daunorubicin (7+3) induction therapy. Subjects had to have adequate performance status (ECOG PS 0-2) and be eligible for standard induction therapy. Subjects achieving CR or CRi received up to two cycles of consolidation with CPX-351 or 5+2. Allogeneic hematopoietic stem cell transplant (allo-HSCT) was allowed.

Editorial — Dr Erba (continued)

CPX-351 was associated with superior overall survival compared with 7+3: median survival 9.6 months vs 6.0 months, and 12-month survival 42% vs 28%. The rates of complete remission were higher with CPX-351: CR 37% vs 26%, and CRi 48% vs 33%. The early mortality was lower with CPX-351: 30-day mortality 6% vs 11%, and 60-day mortality 14% vs 21%. More patients were able to proceed to allo-HSCT following CPX-351. The survival of patients undergoing allo-HSCT was superior following CPX-351 compared to 7+3. The difference in mortality appeared to be due to a higher rate of persistent AML in the 7+3 cohort; mortality due to toxicity was similar in the two arms. The toxicity profile of CPX-351 was similar to that of 7+3 except for more prolonged myelosuppression following both induction and consolidation and a higher

Editorial — Dr Erba (continued)

rate of hemorrhage, including fatal intracranial hemorrhage (2% vs 0.7%) with CPX-351.

Several subset analyses from this phase III study of 304 patients with secondary AML and t-AML have since been presented. The benefit of CPX-351 was maintained in subjects ages 70-75 years. Older adults with t-AML experienced a higher rate of CR+CRi and longer median overall survival. Induction therapy with CPX-351 was given in the inpatient setting in almost all subjects. However, 51% of subjects received CPX-351 consolidation cycle #1 and 61% received CPX-351 consolidation cycle #2 as outpatients. The survival benefit was not diminished by receiving treatment as an outpatient. Since subjects receiving consolidation therapy have achieved complete remission with marrow recovery, and CPX-351 is given as a 90-minute infusion on days 1 and

Editorial — Dr Erba (continued)

3, outpatient consolidation is quite feasible. However, in my experience, the severity and the frequency of known complications associated with the initial cytotoxic chemotherapy for active AML are quite different from those seen during consolidation. Regardless of the site of initial induction therapy for AML, the treating physician should be prepared to react quickly to the expected life-threatening infectious and hemorrhagic complications.

After 40 years of 7+3, CPX-351 is clearly a step forward in the treatment of older patients with secondary or t-AML who are fit for chemotherapy. However, many questions regarding the optimal use of this agent remain. We have not yet seen the analysis of other subsets from this study, including the 50% of subjects with poor-risk karyotype, the 25% with de novo AML with myelodysplasia-related

Editorial — Dr Erba (continued)

cytogenetic changes, and those subjects with an antecedent MDS and CMML (the majority of whom had received a prior hypomethylating agent).

The FDA-approved indication is much broader than the eligibility for the clinical trial demonstrating superiority of CPX-351 over 7+3. The label indication includes all adults with previously untreated AML with t-AML and AML with myelodysplasia-related changes (AML-MRC). Younger AML patients may be able to tolerate more intensive cytotoxic treatment regimens than 7+3 followed by 5+2. We do not have data comparing CPX-351 with more intensive regimens such as Ida/FLAG or CLAG-M. The label indication includes all subsets of AML-MRC, including morphologic dysplasia. This subtype of AML-MRC is defined by the presence of dysplasia in more than

Editorial — Dr Erba (continued)

50% of the precursors in two or more lineages. These patients were not eligible for the phase III study of CPX-351. Morphologic dysplasia alone is not always associated with a worse outcome with intensive therapy. In fact, the WHO 2016 criteria now exclude the presence of nucleophosmin cytoplasmic mutations or biallelic CEBPA mutations from the subset of AML-MRC based on morphologic dysplasia alone, since morphologic dysplasia has not been shown to affect the outcome of de novo AML with these mutations. Subjects with AML following a myeloproliferative neoplasm (PCV, ET, PMF, CML) were excluded from the phase III study and are NOT included in the definition of AML-MRC. Furthermore, hydroxyurea was NOT considered a cause of t-AML in the phase III study.

Editorial — Dr Erba (continued)

Occasionally, core binding factor gene translocations, ie, t(8;21) and inv(16), are identified in patients with t-AML following the topoisomerase II inhibitors. Although there is some debate in the literature, these patients may not have the same poor outcome as t-AML with poor-risk karyotype or MLL gene rearrangements. Therefore, the optimal regimen for this rare subset of patients is not clear.

Finally, in 2017 the FDA approved two other agents for previously untreated AML patients: the kinase inhibitor midostaurin for AML with FLT3 mutations, in combination with daunorubicin and cytarabine, and the monoclonal antibody-drug conjugate gemtuzumab ozogamicin, in combination with standard AML induction therapy and consolidation. We will need to evaluate the safety and efficacy of these agents in combination with CPX-351.

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ORIGINAL REPORT

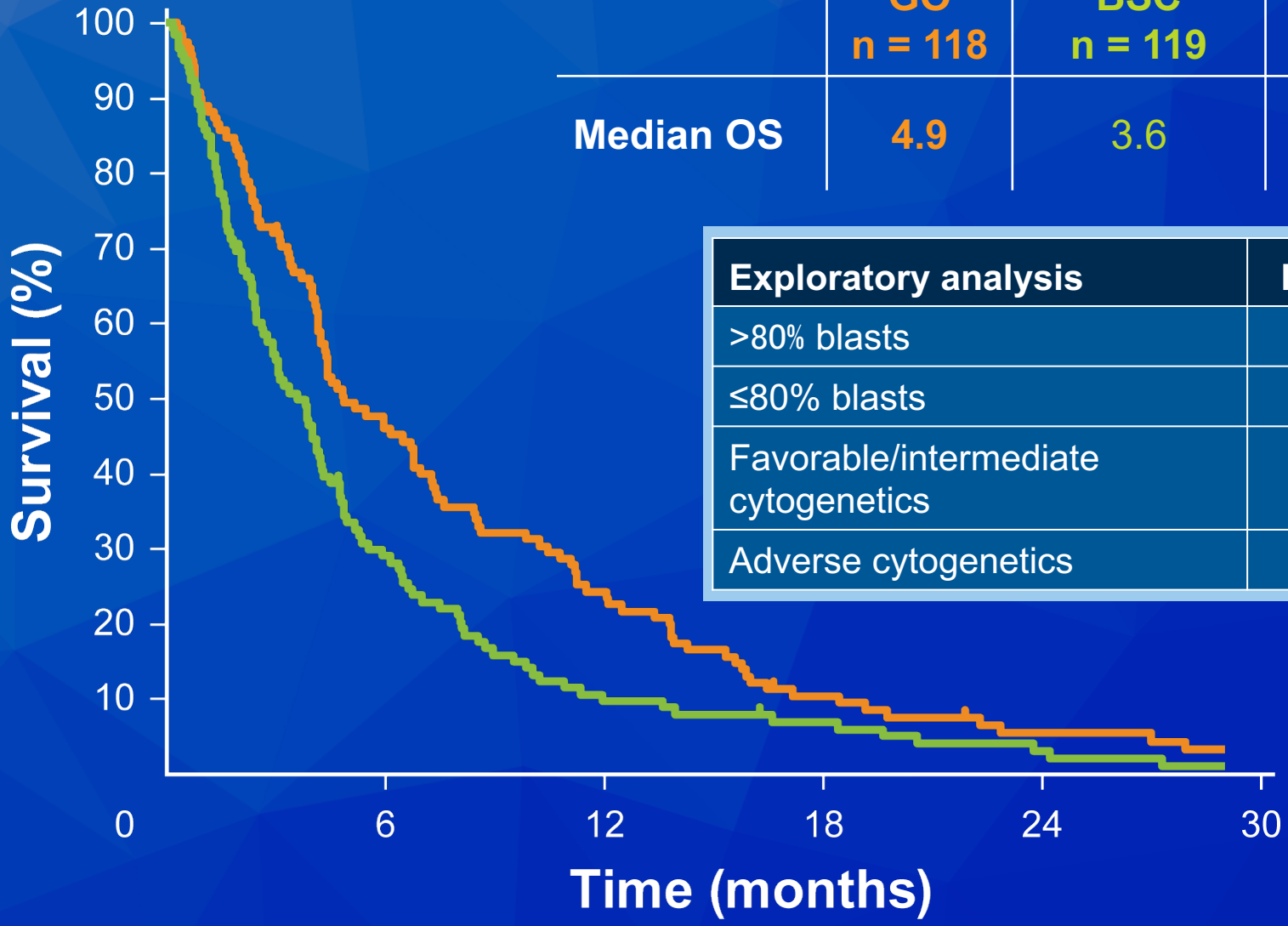
Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial

Sergio Amadori, Stefan Suciu, Dominik Selleslag, Franco Aversa, Gianluca Gaidano, Maurizio Musso, Luciana Annino, Adriano Venditti, Maria Teresa Voso, Carla Mazzone, Domenico Magro, Paolo De Fabritiis, Petra Muus, Giuliana Alimena, Marco Mancini, Anne Hagemeijer, Francesca Paoloni, Marco Vignetti, Paola Fazi, Liv Meert, Safaa Mahmoud Ramadan, Roel Willemze, Theo de Witte, and Frédéric Baron

AML-19: Overall Survival with Gemtuzumab Ozogamicin (GO)

	GO n = 118	BSC n = 119	HR (*p*-value)
Median OS	4.9	3.6	0.69 (0.005)

Exploratory analysis	HR (*p*-value)
>80% blasts	0.49 (0.001)
≤80% blasts	0.85 (0.36)
Favorable/intermediate cytogenetics	0.52 (0.001)
Adverse cytogenetics	1.12 (0.65)



Amadori S et al. *J Clin Oncol* 2016;34(9):972-9.

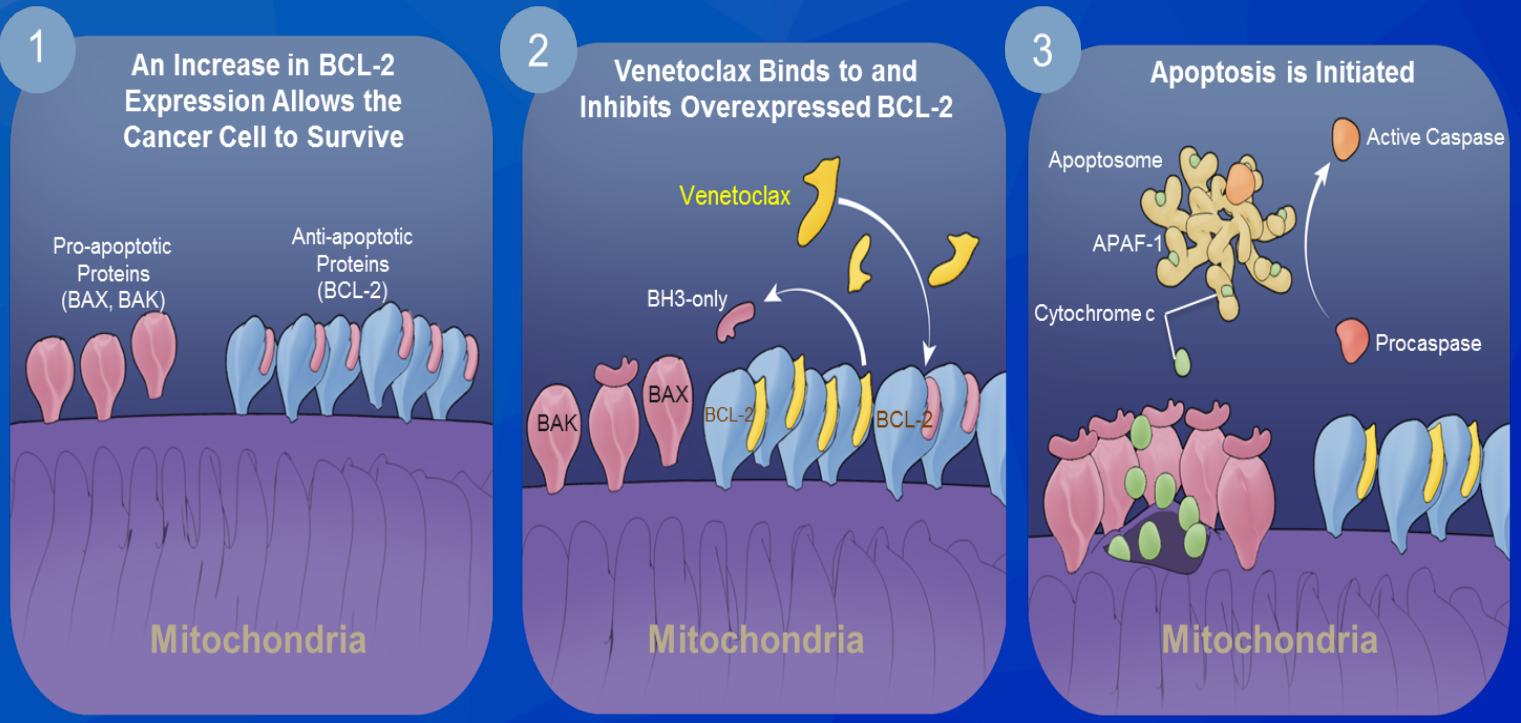
Editorial — Dr Kantarjian

GO is a CD33 monoclonal antibody bound to calicheamicin. Following investigations in R/R AML, GO was approved by the FDA for the treatment of salvage AML in May 2000, and subsequently withdrawn from the market in October 2010 following the negative results of the SWOG pivotal trial of front-line chemotherapy (3+7) with or without GO in younger patients with AML. Subsequently, 4 randomized trials and a meta-analysis confirmed the efficacy of GO in AML. This resulted in the FDA re-approval of GO for front-line therapy of AML in August 2017. The dose schedule is unclear since different studies used GO as 3 mg/m^2 on Days 1, 4 and 7 of induction or GO 3 mg/m^2 x 1 during one induction and one consolidation course (which I prefer).

Editorial — Dr Kantarjian (continued)

In this study, Amadori and colleagues from Italy evaluated GO versus best supportive care (BSC) in older patients with AML not suited for intensive chemotherapy. 237 patients were randomized. GO was given as 6 mg/m^2 on Day 1 and 3 mg/m^2 on Day 8 on a single induction course. Patients who did not progress continued GO 2 mg/m^2 x 1 every month x 8. The median survival was 4.9 months with GO and 3.6 months with BSC (HR 0.69; p = 0.005.). The 1-year survival rates were 24.3% with GO and 9.7% with BSC. The CR + CRi rate with GO was 30/111 = 27%. This study adds to the weight of evidence that GO is an important agent for the treatment of AML.

Venetoclax: Selective Bcl-2 Inhibitor



- Venetoclax is a potent, orally bioavailable agent with demonstrated single-agent activity in CLL
- Venetoclax was shown to synergize with HMA in preclinical models, suggesting that combination with HMA may be a promising approach in AML

Updated safety and efficacy results of phase 1/2 study of venetoclax plus low-dose cytarabine in treatment-naïve acute myeloid leukemia patients aged ≥65 years and unfit for standard induction therapy

Safety and efficacy of venetoclax (ven) in combination with decitabine or azacitidine in treatment-naive, elderly patients (≥65 years) with acute myeloid leukemia (AML)

Wei A et al.
Proc EHA 2017;Abstract S473.

Pratz K et al.
Proc EHA 2017;Abstract S472.

Safety and Efficacy of Venetoclax and Low-Dose Cytarabine in Elderly Patients with AML

- Phase I/II study in elderly patients (≥65 yo) with AML
  - Ineligible for standard induction therapy (N = 61)
- Venetoclax tested at 600-800 mg; 600 mg RP2D
- Grade 3/4 AEs (≥10% pts)
  - Febrile neutropenia (34%)
  - Hypokalemia (15%)
  - Hypophosphatemia (13%)
  - Hypertension (10%)
- No pts had TLS
- Overall response rate: 37/61 (61%)
- CR/CRi rate: 33/61 (54%)

Wei AH et al. *Proc EHA* 2017;Abstract S473.

Efficacy of Venetoclax in Combination with Decitabine or Azacitidine in AML

- Phase Ib study in elderly patients (≥65 yo) with AML
  - Ineligible for standard induction therapy
  - Intermediate- or poor-risk karyotype
- Pts received continuous 400-mg or interrupted 800-mg venetoclax in combination with HMAs
- Grade 3/4 febrile neutropenia: 41%
- No pts had TLS
- Overall response rate: 68%
- Promising activity with high ORRs was observed at the lower 400-mg venetoclax dose with decitabine or azacitidine

Pratz K et al. *Proc EHA* 2017;Abstract S472.

Editorial — Dr Kantarjian

Venetoclax is a selective BCL2 inhibitor with impressive activity in CLL. It is approved for the treatment of CLL. Modest activity of single agent venetoclax was noted in R/R AML. Based on the pathophysiology of AML and pre-clinical studies, combinations of venetoclax 400-800 mg with either azacitidine/decitabine or with low-dose cytarabine were conducted by 2 different groups.

In a first Phase I/II study reported by Pratz and colleagues, 100 patients were treated with azacitidine or decitabine in combination with venetoclax 400 mg continuous or 800 mg intermittent dosing. The overall response rate was 68%.

Editorial — Dr Kantarjian (continued)

The estimated 1-year survival was over 55%. In a second study reported by Wei and colleagues, venetoclax 600 mg daily was combined with low-dose cytarabine 20 mg/m^2 subcutaneously daily for 10 days. Again the overall response rate was 70% and the 12-month survival exceeded 60%. These two studies confirm the high efficacy of venetoclax in combination with low intensity/epigenetic therapy in newly diagnosed older patients with AML. Confirmatory randomized trials are ongoing, which we hope will establish the role of venetoclax in AML.

CC-486 (oral azacitidine) in patients with hematological malignancies who had received prior treatment with injectable hypomethylating agents (HMAs): Results from Phase 1/2 CC-486 studies

Garcia-Manero G et al.
Proc ASH 2016;Abstract 905.

Oral Azacitidine for Patients with Prior HMA Therapy: Efficacy and Safety

- Analysis of 40 pts with MDS, CMML or AML with prior HMA therapy from 3 Phase I/II studies of oral azacitidine
- Of 29 pts for whom outcomes with prior HMAs were known, 16 pts relapsed and 13 pts were refractory to the injectable HMA
- Two dosing regimens (28-d cycles):
  - 120-600 mg x 7 d following a single subcutaneous azacitidine cycle
  - 300 mg QD or 200 mg BID x 14 d or 21 d (extended dosing)
- Overall response rate: 35%
  - No statistical difference between 7-d and extended dosing (p = 0.288)
- Grade 3-4 hematologic TEAEs:
  - Anemia (33%)
  - Thrombocytopenia (23%)
  - Neutropenia (15%)
  - Febrile neutropenia (10%)

Garcia-Manero G et al. *Proc ASH* 2016;Abstract 905.

Editorial — Dr Kantarjian

Epigenetic therapies include subcutaneous azacitidine and IV decitabine. They are established treatment modalities in MDS and elderly AML. Oral formulations of these drugs may allow improved efficacy, convenience, and also the potential for using different oral dose schedules as investigational strategies. In this study, an oral formulation of azacitidine, CC-486, was investigated in 40 patients who had received prior hypomethylating agents (26 MDS, 2 CMML, 12 AML). The overall response rate was 35%. Five of 13 patients refractory to prior hypomethylation therapy responded (38%). This suggests that this oral agent can be effective and safe. It can also be investigated over longer periods of time than what is traditionally used for epigenetic therapy.

Editorial — Dr Kantarjian (continued)

Similar studies are being conducted with an oral formulation of decitabine. Second generation epigenetic therapies (guadecitabine [SGI-110]) are also under development.

In summary, the studies discussed highlight the very exciting areas of research in AML and MDS with novel targeted therapies. These include monoclonal antibodies targeting CD33 and CD123 (applicable to 100% of patients with AML); FLT3 inhibitors (may benefit 30% of patients with AML); IDH1 and 2 inhibitors (20% of patients with AML); BCL2 targeted therapy with venetoclax (100% of patients); and novel formulations of epigenetic therapies (oral azacitidine and decitabine; second generation of guadecitabine).

Editorial — Dr Kantarjian (continued)

As with the experiences in solid tumors and some hematologic malignancies with checkpoint inhibitors, pilot studies of checkpoint inhibitors in AML and MDS are producing interesting results.

VOLUME 35 · NUMBER 4 · FEBRUARY 1, 2017

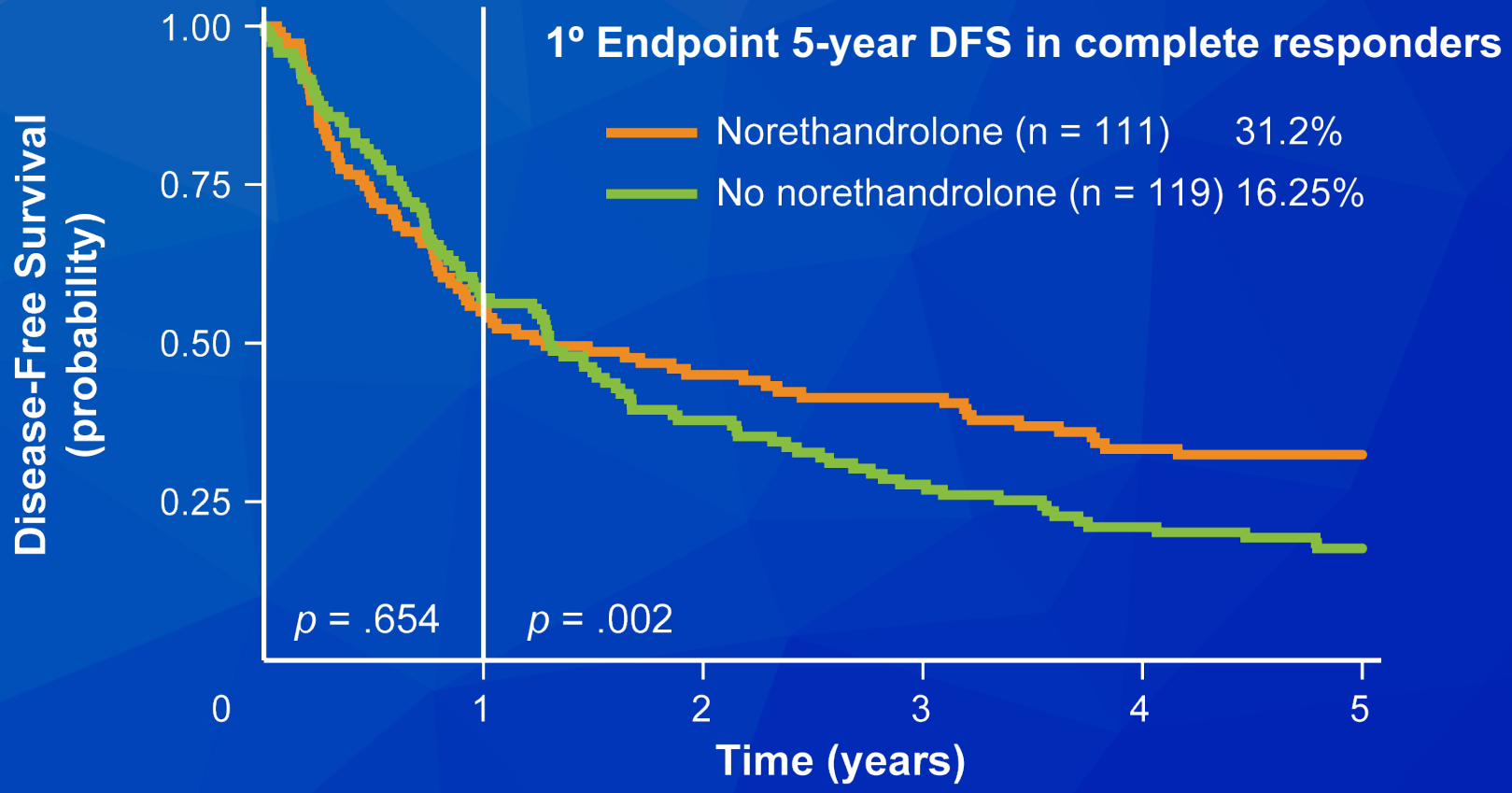
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Addition of Androgens Improves Survival in Elderly Patients With Acute Myeloid Leukemia: A GOELAMS Study

Arnaud Pigneux, Marie C. Béné, Philippe Guardiola, Christian Recher, Jean-Francois Hamel, Mathieu Sauvezie, Jean-Luc Harousseau, Olivier Tournilhac, Francis Witz, Christian Berthou, Martine Escoffre-Barbe, Denis Guyotat, Nathalie Fegueux, Chantal Himberlin, Mathilde Hunault, Martine Delain, Bruno Lioure, Eric Jourdan, Frederic Bauduer, Francois Dreyfus, Jean-Yves Cahn, Jean-Jacques Sotto, and Norbert Ifrah

Maintenance Androgens for Elderly Patients with AML: Survival Results



	Androgen (n = 162)	No androgen (n = 163)
5-year OS (all pts)	26.3%	17.2%
5-year EFS (all pts)	21.5%	12.9%

Pigneux A et al. *J Clin Oncol* 2017;35(4):387-93.

Editorial — Dr Kantarjian

In this study by the French group, 330 older patients (median age 70 years; range 66 to 73) with de novo or therapy-related AML received induction chemotherapy with idarubicin cytarabine and lomustine, followed by 6 consolidation courses. They were then randomly assigned to norethandrolone 10-20 mg daily or nothing for 2 years of maintenance. The overall response rate with chemotherapy was 76% (CR rate 71%). 165 patients were randomly assigned to the maintenance. The 5-year disease-free survival was 31% with androgens and 15% without.

Editorial — Dr Kantarjian (continued)

The 5-year overall survivals were 26% versus 17%. The authors concluded that maintenance androgen significantly improved survival in these elderly patients.

This beneficial fact was time dependent and became significant only among patients who remained in CR during the first year of therapy. While the reason behind the positive effect of norethandrolone is not clear, the authors hypothesize that this could be related to its enhancing effect on telomerase activity, thus decreasing proliferation of the persistent AML cells and exerting a beneficial effect on normal hematopoiesis. Whether androgen maintenance should become a standard of care in elderly patients with AML needs to be confirmed in additional studies.

Phase IB/II study of nivolumab in combination with azacytidine (AZA) in patients (pts) with relapsed acute myeloid leukemia (AML)

Daver N et al.
Proc EHA 2017;Abstract S474.

Safety and Efficacy of Nivolumab/Azacitidine for Patients with Relapsed AML

- Best response
  - CR/CRi: 14/63 (22%; 3 CR, 11 CRi)
  - Hematologic improvement (HI): 7/63 (11%)
  - ≥50% BM blast reduction: 13/63 (21%)
- Median OS (all patients): 5.7 months
  - Patients who obtained CR/CRi: 15.3 mo
  - Patients who obtained HI: 9.7 months
- Grade 3/4 AEs: 8/63 (12%)
  - Pneumonitis
  - Colitis
  - Nephritis
  - Skin rash
  - Hypophysitis

Daver N et al. *Proc EHA* 2017;Abstract S474.

Editorial — Dr Erba

Effector T-cell function is inhibited by engagement of the T-cell receptors CTLA-4 and PD-1 by their respective ligands. Tumors appear to evade the immune system by expressing the ligands for CTLA-4 and PD-1. The reported efficacy of single agent CTLA-4 and PD-1 blockade in AML has not been impressive. However, remarkable responses to CTLA-4 blockade with ipilimumab have been reported in subjects with extramedullary relapse of AML following allogeneic hematopoietic stem cell transplantation (Davids MS et al. *N Engl J Med* 2016). The response may be due to enhancement of a graft-versus-tumor effect. This observation suggests that CTLA-4 or PD-1 blockade may be effective adjuncts to overcome resistance mediated by immune mechanisms. Azacitidine appears to up-regulate both PD-1 and PD-L1 gene

Editorial — Dr Erba (continued)

expression, and increased expression of PD-1 and PD-L1 has been associated with resistance to azacitidine.

The MD Anderson Cancer Center conducted a phase I/II study of the PD-1 inhibitor nivolumab with azacitidine in relapsed/refractory AML. In the first six subjects there was one dose-limiting toxicity, so the study continued with nivolumab 3 mg/kg on days 1 and 14 and azacitidine 75 mg/m^2/day for seven days; cycles repeated every 4-5 weeks. The rate of CR/CRi was 18%, similar to the CR/CRi rate in a retrospective study of over 500 relapsed/refractory AML patients treated with hypomethylating agents (HMA) (16%, see Stahl et al. ASH 2016). The response was associated with higher marrow CD8+ effector T cells and lower Treg cells. The median survival was reported as 9.3 months, but this was only for

Editorial — Dr Erba (continued)

the 35 of 51 subjects evaluable for response (16 were too early, ie, less than 3 cycles). The median survival of subjects with AML in first relapse treated with the azacitidine-nivolumab combination was statistically superior to historical controls treated with other HMA combinations. Although the 4- and 8-week mortality were low (0% and 6%), there was the expected immune-mediated toxicities, including pneumonitis, nephritis, transaminase elevations, and rash, in 26% of subjects. One of the four patients post-allo-HSCT had a grade 3 flare of GVHD of skin and gut.

Currently, the goal of therapy for patients with relapsed/refractory AML is one of the following: bridge to a potentially curative allo-HSCT or extend survival without compromising quality of life. It is not clear from the data

Editorial — Dr Erba (continued)

presented in these two abstracts that either goal can be achieved with this combination. The complete remission rate appears similar to what can be achieved with azacitidine alone. The overall survival is only presented for the subset of subjects evaluable for response after 3 cycles, which may overestimate the survival compared with an intent-to-treat analysis. Furthermore, the survival benefit is in comparison to historical controls. Finally, the combination has added toxicities that are not commonly encountered with HMA alone. Nonetheless, there remains pre-clinical rationale to continue to evaluate the combination of PD-1 blockade with azacitidine. If loss of effector T-cell function due to an enhanced expression of PD-1 and PD-L1 contributes to a shorter duration of response with an HMA, then the addition of nivolumab to

Editorial — Dr Erba (continued)

HMA may help to improve duration of response and therefore survival. In fact, the SWOG-1612 study that will activate this year will compare the survival of older, previously untreated, less-fit AML patients treated with azacitidine alone compared with this combination of nivolumab and azacitidine. Only in this way can we truly estimate the benefit as well as the toxicity of this combination.

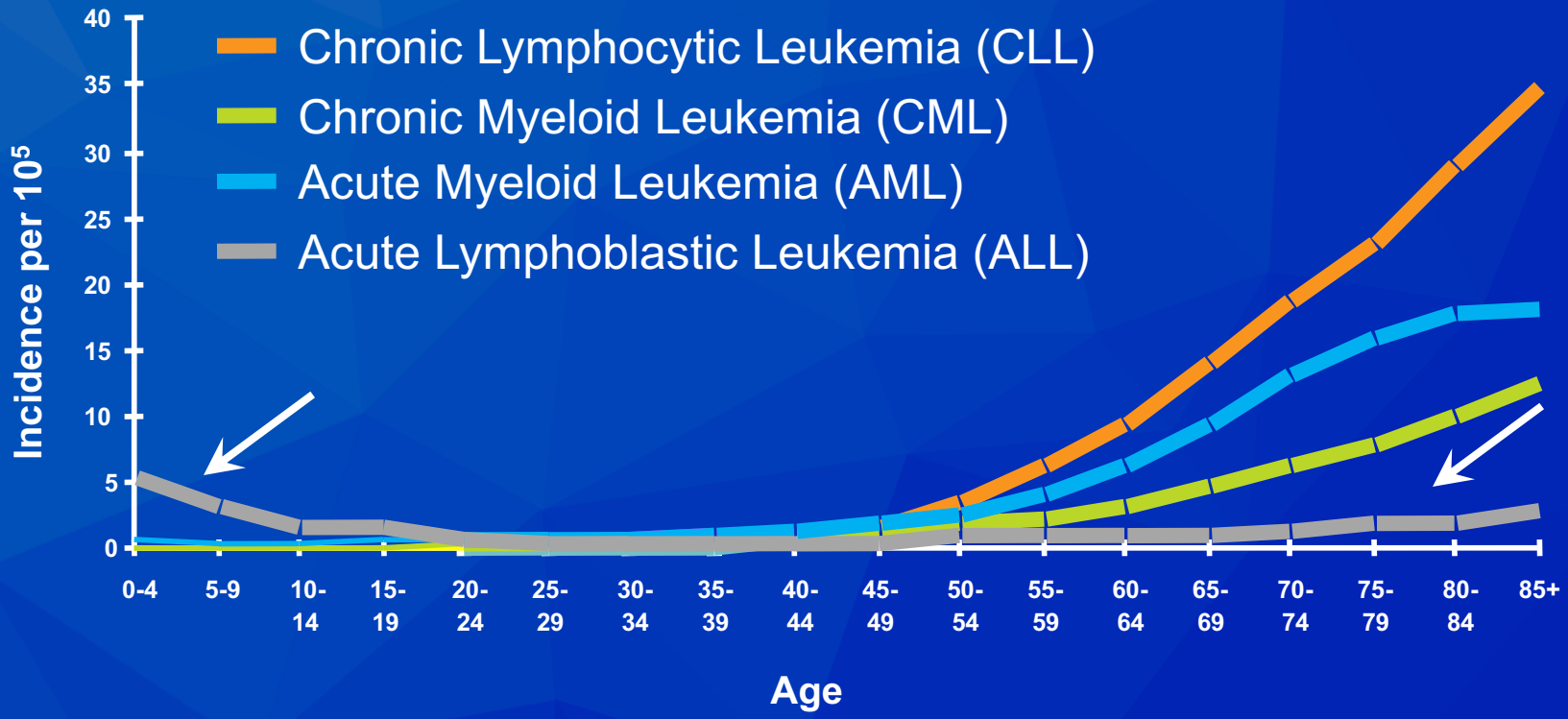
Acute Leukemias – Drs Erba and Kantarjian

Acute Myeloid Leukemia

Acute Lymphoblastic Leukemia

Acute Promyelocytic Leukemia

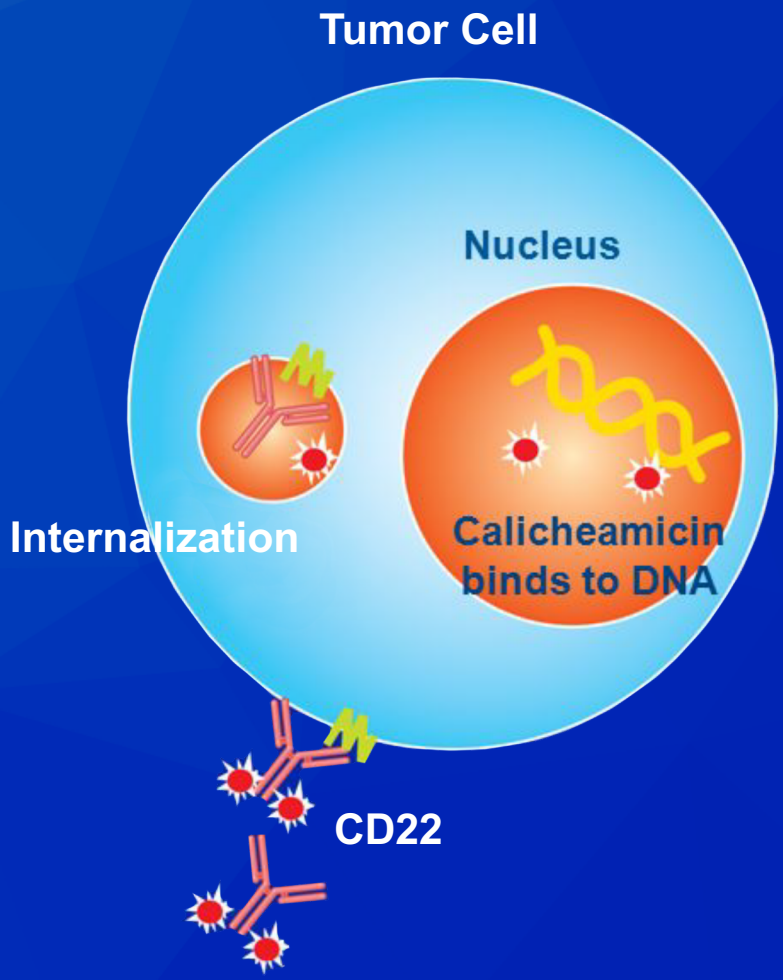
Incidence of Leukemia in the US by Age



SEER Data

Inotuzumab in ALL: Mechanisms of Action

- The antibody-antigen complex is rapidly internalized upon binding to CD22
- Calicheamicin is released inside the tumor cell
  - Calicheamicin is more potent than other cytotoxic chemotherapeutic agents
  - Calicheamicin binds to DNA, inducing double-stranded DNA breaks
  - Development of DNA breaks is followed by apoptosis of the tumor cell



With permission from Jabbour E et al. *Proc ASCO* 2012;Abstract 6501.

Factors associated with allogeneic hematopoietic stem cell transplantation (HSCT) outcomes in patients (pts) with relapsed/refractory acute lymphoblastic leukemia (R/R ALL) treated with inotuzumab ozogamicin (InO) versus (v) conventional chemotherapy (C)

Kebriaei P et al.
Proc ASCO 2017;Abstract 7007.

INO-VATE: Outcomes of Patients with R/R ALL Treated with InO or Chemo Undergoing HSCT

	InO n = 77	Chemo n = 31	*p*-value
Additional therapy before HSCT	14%	55%	$p < 0.0001$
MRD-negative	71%	26%	$p < 0.0001$
2-year nonrelapse mortality (NRM)	39%	31%	$p = 0.4904$
2-year relapse rate	33%	46%	$p = 0.3100$

- Fatal veno-occlusive disease (VOD) was observed within 100 days of the date of HSCT in 5 patients receiving InO and 0 patients receiving chemo
- Despite increased NRM and fatal VOD, long-term survival was attainable in patients treated with InO

Kebriaei P et al. *Proc ASCO* 2017;Abstract 7007.

Editorial — Dr Erba

Inotuzumab ozogamicin (InO) is an anti-CD22 humanized murine monoclonal antibody covalently linked to the anti-tumor antibiotic calicheamicin. Upon binding to CD22 on the surface of neoplastic B lymphoblasts, the antibody-drug conjugate is internalized and degraded in lysosomes, releasing calicheamicin to bind to DNA, causing double strand DNA breakage and apoptosis. In a multicenter, international phase III study, InO was compared with standard of care (SOC) chemotherapy regimens for adults with relapsed/refractory B ALL (Kantarjian H et al. *N Engl J Med* 2016). Patients were randomly assigned 1:1 to receive InO 0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15. Once achieving remission, patients received maintenance therapy with InO 0.5 mg/m^2 IV on day 1 of a 28 day cycle. The three SOC regimens were FLAG,

Editorial — Dr Erba (continued)

cytarabine and mitoxantrone, and high dose cytarabine alone.

The complete remission was higher with InO compared with SOC (81% vs 29%). Among the patients achieving CR and CRi, the rate of MRD negativity was also higher with InO vs SOC (78% vs 28%). The response benefit of InO over SOC was observed regardless of patient age (older or younger than age 55 years), salvage status (first vs second) or duration of first remission (more or less than 12 months), % marrow blasts, normal vs Ph+ karyotype, and prior allo HSCT. Duration of remission was longer with InO than SOC, and progression-free survival was significantly longer for patients after InO compared with SOC (5.0 vs 1.8 months). However, there was no difference in median overall survival (7.7 vs 6.7 months). More patients were able to proceed to

Editorial — Dr Erba (continued)

allo HSCT in CR following InO compared with SOC (41% vs 11%).

Hematologic toxicity was more common with SOC, including thrombocytopenia and febrile neutropenia. The rate of all serious adverse events was similar in the two treatment groups (InO 48%, SOC 46%). Hepatic toxicity, including transaminase elevations and hyperbilirubinemia, was more commonly seen in the InO group. Veno-occlusive disease / sinusoidal obstructive syndrome (VOD/SOS) of the liver was more commonly observed following InO (11%) vs SOC (1%). Ten of 48 patients undergoing allo-HSCT after InO developed VOD/SOS.

This abstract evaluates the factors associated with allo-HSCT outcomes in patients with relapsed/refractory B ALL treated with InO vs SOC chemotherapy. Nonrelapse

Editorial — Dr Erba (continued)

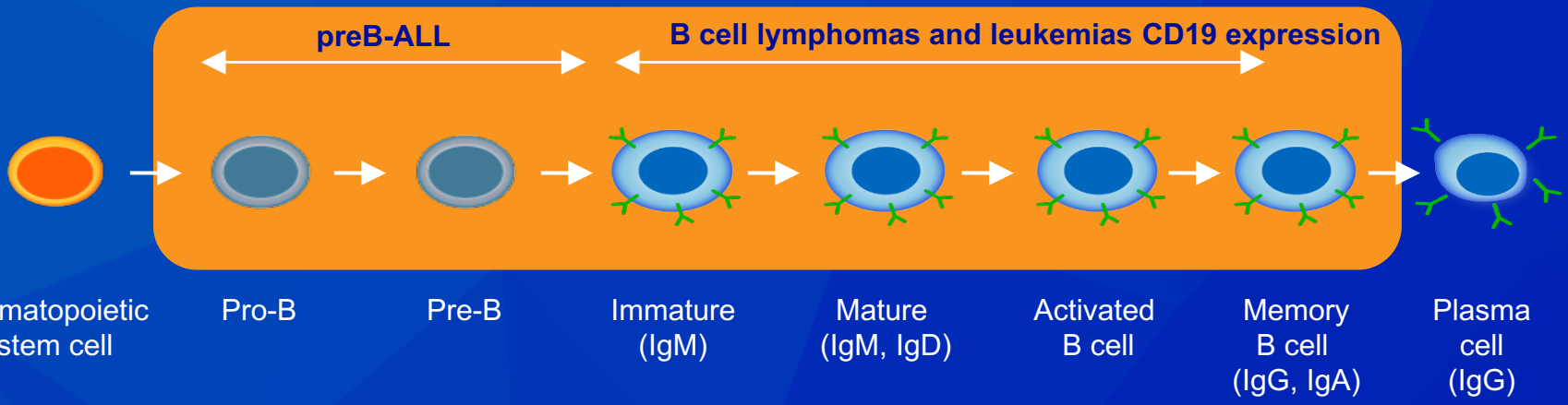
mortality was higher with InO compared with SOC at 1 year (36% vs 20%) and 2 years (39% vs 31%), but relapse rates were lower with InO at both 1 year (23% vs 29%) and 2 years (33% vs 46%). The rate of VOD/SOS in InO treated patients was 22% (17 of 77 allo-HSCT patients, 5 cases fatal). The incidence of VOD/SOS post-allo-HSCT was greater in older patients (over 55 years), history of liver disease, bilirubin above upper limit of normal before HSCT, and three or more cycles of InO. Conditioning regimens, including dual alkylating agents and thiotepa were associated with greater nonrelapse mortality and greater incidence of VOD/SOS. Therefore, there was no difference in post- allo-HSCT survival in the InO and SOC groups.

Editorial — Dr Erba (continued)

This data is potentially helpful to the treating physician in selecting therapy for patients with relapsed/refractory ALL. For patients with relapsed/refractory B ALL who remain candidates for allo-HSCT, blinatumomab may be a better initial choice for salvage therapy based on the absence of VOD/SOS. On the other hand, for older patients and those who are not candidates for allo-HSCT, InO can be delivered as a rapid infusion on a reasonable outpatient schedule, and InO has been associated with less hematopoietic toxicity and higher rates of complete remission compared with SOC chemotherapy regimens.

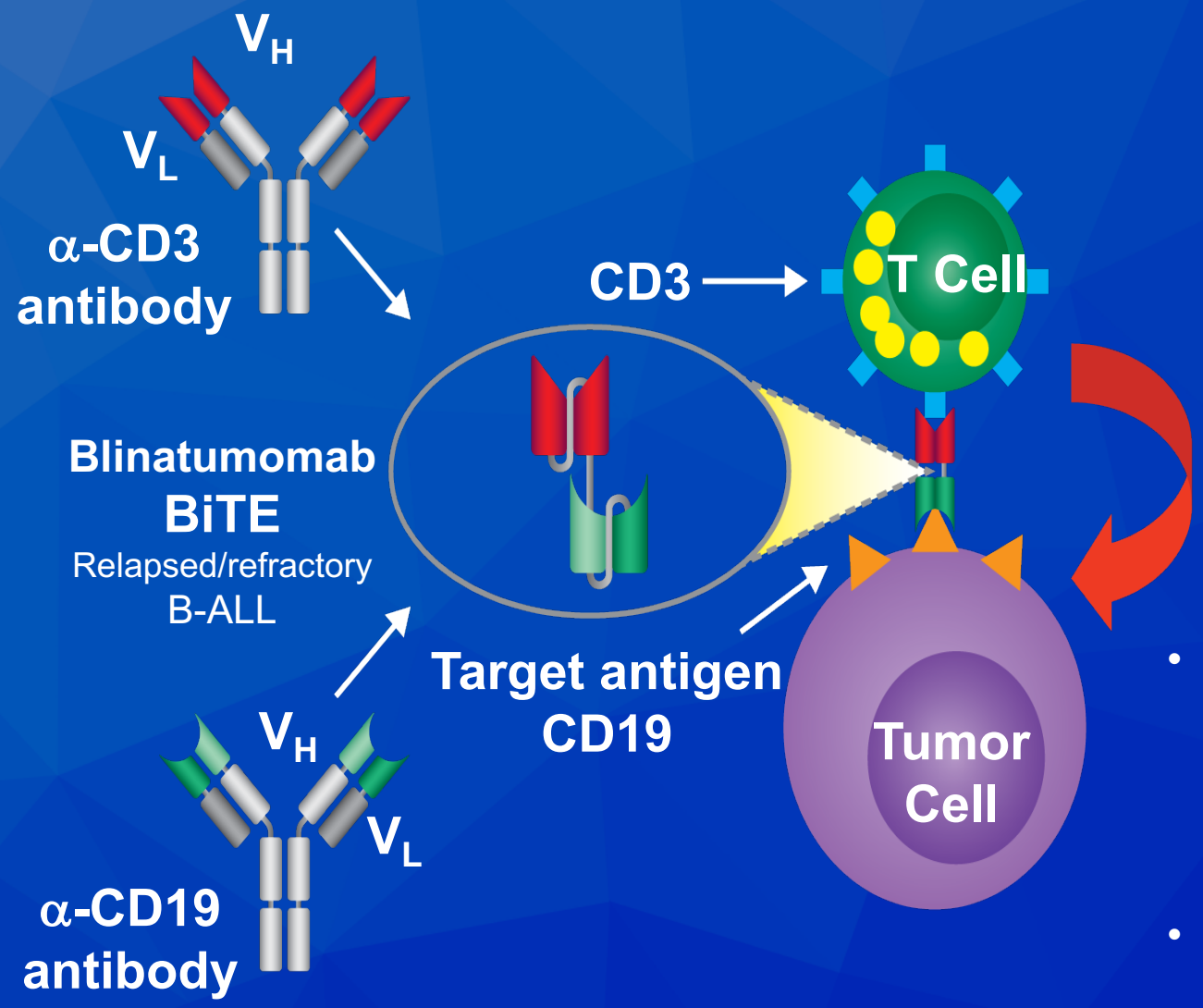
CD19: An Ideal Tumor Target in B-Cell Malignancies

- CD19 expression is generally restricted to B cells and B-cell precursors[1]
  - CD19 is not expressed on hematopoietic stem cells[1]
- CD19 is expressed by most B-cell malignancies[1]
  - CLL, B-ALL, DLBCL, FL, MCL[1]
- Antibodies against CD19 inhibit tumor cell growth



[1] Scheuermann RH, Racila E. *Leuk Lymphoma* 1995;18(5-6):385-97; Image adapted from Janeway CA et al. *Immunobiology* 2001:221-93; Scheuermann RH, Racila E. *Leuk Lymphoma* 1995;18(5-6):385-97; Feldman M, Marini JC. Cell cooperation in the antibody response. In: Roitt I, Brostoff J, Male D, eds. *Immunology* 2001:131-46.

Mode of Action of BiTE Antibody Blinatumomab



- **Blinatumomab:** A BiTE antibody designed to direct cytotoxic T cells to CD19-expressing cancer cells
- Approved for use in relapsed/refractory B-ALL

Bargou R et al. *Science* 2008;321;(5891):974-7.

VOLUME 35 · NUMBER 16 · JUNE 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome–Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study

Giovanni Martinelli, Nicolas Boissel, Patrice Chevallier, Oliver Ottmann, Nicola Gökbuget, Max S. Topp, Adele K. Fielding, Alessandro Rambaldi, Ellen K. Ritchie, Cristina Papayannidis, Lulu Ren Sterling, Jonathan Benjamin, and Anthony Stein

Efficacy and Safety of Blinatumomab for Patients with Relapsed/Refractory Ph+ ALL

- CR/CRh: 36% (16/45)
  - 14 CR, 2 CRh
  - 86% of CR/CRh responders achieved complete MRD
- Median OS: 7.1 mo
- Median RFS: 6.7 mo

	Grade 3	Grade 4
All AEs	33/45 (73%)	16/45 (36%)
Febrile neutropenia	12/45 (27%)	0
Anemia	7/45 (16%)	1/45 (2%)
Thrombocytopenia	5/45 (11%)	7/45 (16%)
Elevated liver enzymes	8/45 (18%)	2/45 (4%)
Neurologic events	3/45 (7%)	0

Martinelli G et al. *J Clin Oncol* 2017;35(16):1795-802.

Editorial — Dr Erba

Therapeutic options for patients with ABL tyrosine kinase inhibitor resistant and/or intolerant, BCR/ABL positive (Ph+) acute lymphoblastic leukemia (ALL) are limited. These patients have typically already been exposed to combination chemotherapy as well. Blinatumomab is a bispecific, anti-CD3/anti-CD19 T-cell engager. This agent was initially approved for Ph negative ALL based on response rates. The efficacy of blinatumomab in patients with relapsed/refractory Ph+ ALL was demonstrated in this phase II study. The overall response rate (CR + CRh) following two 28 day cycles of blinatumomab was 36%. Most responses were CR (14 of 16 responses). Most responses occurred following the first cycle. Among the 16 patients achieving CR or CRh, 14 were negative for minimal residual disease (MRD) as measured by RT-PCR

Editorial — Dr Erba (continued)

for the BCR/ABL fusion transcript. The response rate was not affected by patient age, type of BCR/ABL fusion (p190 vs p210), presence of the T315I mutation, number of prior TKI therapies, or prior allo-HSCT. The response rate appeared higher in those patients with less than 50% marrow blasts at study entry. The median relapse free survival and median overall survival were 6.7 months and 7.1 months, respectively. Interestingly, in a landmark analysis after 2 months of therapy, the RFS and OS were not affected by censoring at the time of allo-HSCT. The toxicities were as expected for blinatumomab, including febrile neutropenia, thrombocytopenia, anemia, transaminase elevations, and cytokine release reaction. There were 5 (of 45) subjects with fatal adverse events.

The FDA-approved indication for blinatumomab was

Editorial — Dr Erba (continued)

expanded in 2017 to include all relapsed/refractory B lineage ALL, including Ph+ ALL. Since the response rates appeared higher with a lower leukemic burden at initiation of therapy, we should investigate the use of some cytoreductive therapy prior to blinatumomab. Dexamethasone 10 mg IV twice daily for up to 5 days was required for those patients with greater tumor burden, including more than 50% marrow blasts, but this does not appear sufficient to improve response.

Of course, combination therapy of blinatumomab and ABL TKI must be explored in Ph+ ALL. SWOG-1318 is evaluating the use of the ABL TKI dasatinib with blinatumomab for previously untreated, Ph+ ALL patients over age 65 years; the trial is close to the accrual goal. The leukemia committees of the NCI cooperative groups

Editorial — Dr Erba (continued)

have collaborated to design a study for previously untreated adults with Ph+ ALL. The study will compare the rate of remission with and without minimal residual disease (MRD) between dasatinib and hyperCVAD vs dasatinib and blinatumomab. Patients who achieved complete remission without MRD will be randomly assigned to continuation of ABL TKI maintenance or allo-HSCT. ECOG will lead the study and will present the concept to the Leukemia Steering Committee in the near future for consideration.

Finally, how to sequence blinatumomab into the treatment of relapsed/refractory Ph+ ALL will need to be defined as other agents continue to be developed, such as CAR-T cells and other monoclonal antibody–drug conjugates such as inotuzumab ozogamicin.

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.

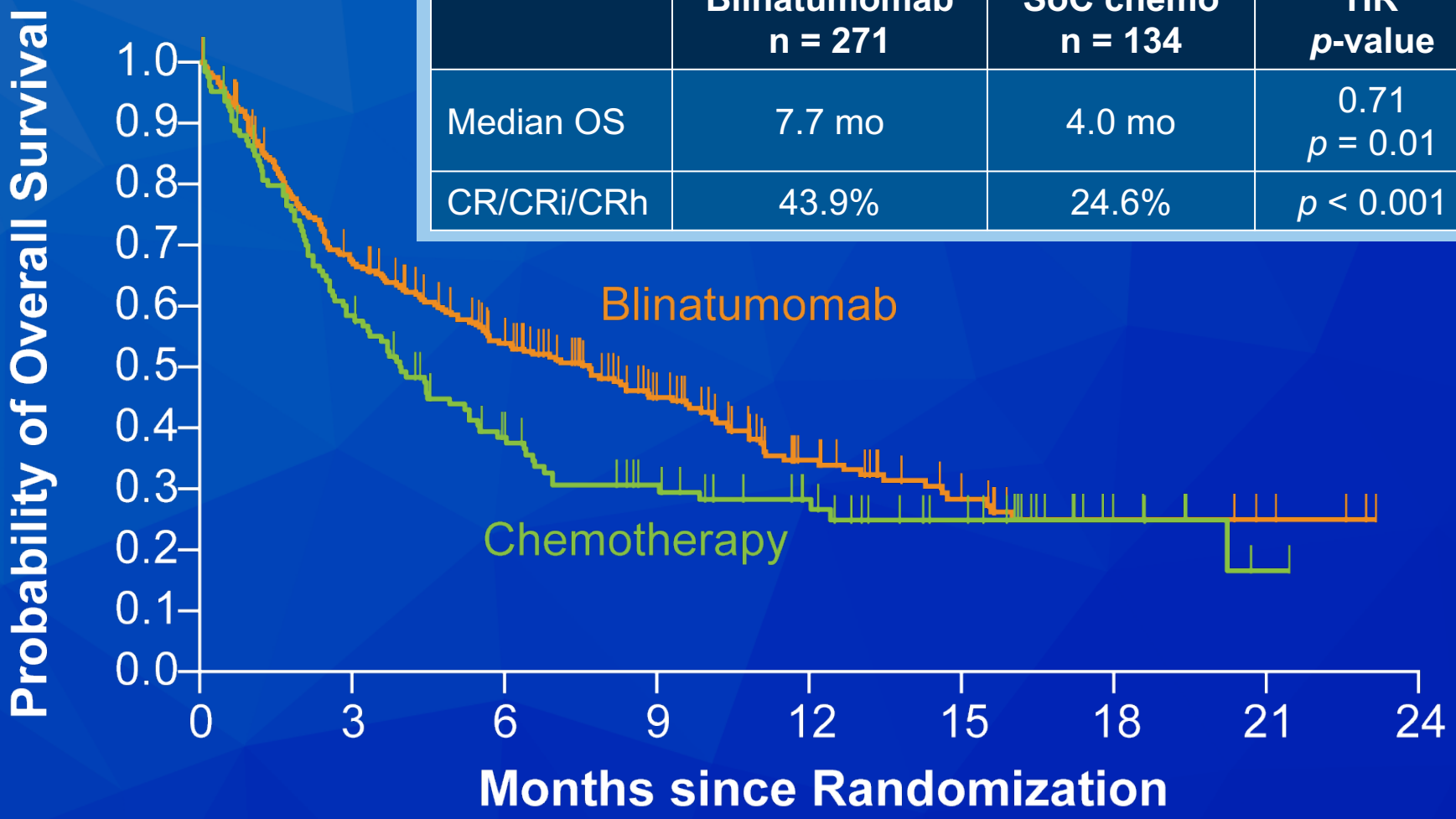
N Engl J Med 2017;376(9):836-47.

Blinatumomab vs SoC chemotherapy in first salvage compared with second or greater salvage in a phase 3 study

Dombret H et al. *Proc EHA* 2017;Abstract S478.

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

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



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

TOWER: Blinatumomab vs SoC Chemo for Patients with R/R ALL by Salvage Line

	No prior salvage		Any prior salvage	
	Blin n = 104	**SoC n = 63**	**Blin n = 167**	**SoC n = 71**
Prior HSCT	27.9%	31.7%	38.9%	36.6%
Median OS	11.1 mo	5.5 mo	5.1 mo	3.0 mo
HR, *p*-value	0.59, $p = 0.016$		0.72, $p = 0.055$	
CR/CRi/CRh	51%	36.5%	39.5%	14.1%
p-value	$p = 0.07$		$p < 0.001$	

Dombret H et al. *Proc EHA* 2017;Abstract S478.

Editorial — Dr Erba

Blinatumomab is a bispecific T-cell engager that links CD3 positive T cells and CD19 positive neoplastic B lymphoblasts to induce tumor cell lysis. Blinatumomab was compared with salvage chemotherapy for patients with relapsed/refractory B ALL (Kantarjian H et al. *N Engl J Med* 2017). Subjects were randomly assigned 2:1 to blinatumomab vs one of four standard of care (SOC) chemotherapy options (FLAG, high dose cytarabine, high dose methotrexate, and clofarabine based regimen). The primary endpoint of the study was achieved. The median overall survival was 7.7 months with blinatumomab, significantly longer that the 4.0 month median OS with SOC chemotherapy. The survival curves separated at 3 months but again converged at 15-18 months at 25%. The survival was superior with blinatumomab for subjects

Editorial — Dr Erba (continued)

receiving first or second salvage only, not for subjects receiving third or later salvage. Blinatumomab was also associated with a statistically significant survival benefit in subjects who had not received prior allo-HSCT. The complete remission rate was 34% vs 16% in favor of blinatumomab; the overall response rate was also higher with blinatumomab (CR+CRh+CRi 44% vs 25%). The response rates were superior with blinatumomab compared with SOC regardless of patient age, number of prior salvage therapies, prior allo-HSCT, and % marrow blasts. More patients with CR, CRh and CRi achieve an MRD-negative bone marrow following blinatumomab (76%) compared to SOC (48%). 24% of subjects in both groups received allo-HSCT, but more proceeded to allo-HSCT without additional therapy following blinatumomab

Editorial — Dr Erba (continued)

compared with SOC chemotherapy (14% vs 9%).

This abstract re-evaluates response and survival based on salvage status, but the salvage status was adjudicated separately from the prior randomization strata. The conclusions were similar, although all salvage statuses later than first were considered together in this analysis. The rate of CR and overall response were higher with blinatumomab compared with SOC chemotherapy in both the first salvage and second or later salvage cohorts. Median survival for the first salvage group was 11.1 months with blinatumomab compared to 5.5 months with SOC. The median survival for the second or later salvage group was also longer with blinatumomab than SOC (5.1 months vs 3.0 months), but the difference was not statistically significant. Grade 3 and grade 4 adverse

Editorial — Dr Erba (continued)

events were more commonly seen with the SOC chemotherapy compared with blinatumomab. Neurologic adverse events were similar in the two treatment groups; however, cytokine release syndrome was only seen with blinatumomab (4% first salvage and 5% second or later salvage). The authors conclude that blinatumomab should be used as first salvage therapy to maximize the survival benefit.

Blinatumomab is clearly superior to SOC chemotherapy for patients with B ALL refractory to or relapsed after standard multi-agent chemotherapy regimens, in terms of response rates and overall survival. The treating physician should be prepared to treat the expected blinatumomab-associated cytokine release syndrome. However, other agents are now approved for relapsed/refractory B ALL,

Editorial — Dr Erba (continued)

including inotuzumab ozogamicin and CAR-T cells for pediatric B ALL. Without comparative data for these novel agents, clinicians will be left to choose between approaches based on site of administration, ease of administration, cost of therapy, known toxicities, availability of allo-HSCT after achieving response, and (hopefully) available clinical trials to help improve outcomes further.

Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL): Update to the interim analysis

Grupp SA et al.
Proc EHA 2017;Abstract S476.

ELIANA: Phase II Safety and Efficacy of CD19-Targeted CAR T-Cell Therapy in R/R ALL

- Single infusion with CTL019 CAR T cells
- CR/CRi within 3 months of infusion: 52/63 (83%)
  - All CR/CRi responders were MRD-negative
- 6-month overall survival: 89%; 12-month OS: 79%
- Cytokine release syndrome (CRS) rate: 78%
  - 21% Grade 3, 27% Grade 4
  - No CRS-associated deaths
  - Received tocilizumab/other anti-cytokine therapy: 38%
- Grade 3/4 neutropenia with high fever occurred in 60% of pts
- Grade 3/4 nonhematologic AEs included:
  - Hypotension (22%)
  - Hypoxia (18%)
  - Increased AST (16%)
  - Neuropsychiatric AEs (15%)

Grupp SA et al. *Proc EHA* 2017;Abstract S476.

Editorial — Dr Erba

Chimeric antigen receptor T (CAR-T) cell therapy has emerged as a breakthrough in the cellular therapy of cancer. Autologous T cells are removed from patients by leukapheresis. The T cells are then transfected with a retroviral vector containing a gene construct. The gene construct encodes a transmembrane protein. The extracellular domain will have the antigen binding site of a monoclonal antibody. The antigen will be present on the tumor cells. The intracellular domain has T-cell stimulatory signals. The various constructs in development have different T-cell stimulatory domains. In the case of B-cell malignancies such as B lineage acute lymphoblastic leukemia, the target antigen is CD19, but others are being developed (eg, CD22). Following transfection the CAR-T cells are expanded in vitro and then re-infused into the

Editorial — Dr Erba (continued)

patient. The process of CAR-T cell production currently takes 3 weeks. Subjects receive a lymphodepletion regimen (eg, cyclophosphamide alone or fludarabine and cyclophosphamide) a few days prior to CAR-T cell infusion. After the CAR-T cells are infused, these cells bind to CD19 positive malignant and normal B cells and induce cell-mediated cytolysis. The major short term toxicity has been cytokine release syndrome (CRS), treated with steroids and IL6 blockade, and encephalopathy, including seizures. An expected long-term toxicity may include B-cell aplasia and hypogammaglobulinemia.

In this study, 88 pediatric patients with relapsed/refractory B ALL were enrolled. Patients may require some systemic therapy during the manufacturing process to control the

Editorial — Dr Erba (continued)

disease (not specified in this abstract). The manufacturing process failed for 8% of subjects, and 10% did not receive the product due to death or other adverse events during the manufacturing process. CR/CRi (with no evidence of minimal residual marrow disease) was achieved in 83% of subjects. The relapse-free survival was 75% at 6 months and 79% at 12 months. Almost 80% of subjects developed CRS (including fever, hypotension, hypoxia). There were no deaths due to CRS. Eleven of the 63 evaluable patients died (disease progression, cerebral hemorrhage, HHV6 encephalitis, pneumonia, and systemic fungal infection). Expansion of the CAR-T cells in vivo correlated with CRS severity, and persistence of the CAR-T was observed in some responders for over one year (and was associated with B-cell aplasia).

Editorial — Dr Erba (continued)

The ultimate role of CAR-T therapy has yet to be defined. At this point, the procedure has been performed at relatively few centers. These centers have developed the expertise and protocols to care for these patients, often forming multi-disciplinary teams (with specialists from oncology, intensive care, infectious disease, pulmonary, and neurology) to specifically care for this population of patients. The clinical benefit of this approach over bispecific T-cell engagers such as blinatumomab has not been evaluated. The optimal sequencing of CAR-T cell strategies with allo-HSCT also needs to be defined. The long term outcome of CAR-T cell therapy for ALL is also unclear. Loss of the target by the tumor cell population has already been identified as a cause of resistance. However, we need to understand other causes of primary resistance.

Editorial — Dr Erba (continued)

The toxicities of CAR-T cells are quite alarming; protocols to decrease CAR-T cell toxicity without affecting efficacy are needed. CAR-T cell strategies are also being developed for other malignancies.

CAR-T cell therapy is an exciting new area of clinical investigation in oncology. However, for the near future this treatment should only be performed at centers capable of investing resources into the support of these patients. The cost of the manufacturing process as well as the clinical care of these patients is likely to be significant.

Acute Leukemias – Drs Erba and Kantarjian

Acute Myeloid Leukemia

Acute Lymphoblastic Leukemia

Acute Promyelocytic Leukemia

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ORIGINAL REPORT

Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non–High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial

Uwe Platzbecker, Giuseppe Avvisati, Laura Cicconi, Christian Thiede, Francesca Paoloni, Marco Vignetti, Felicetto Ferrara, Mariadomenica Divona, Francesco Albano, Fabio Efficace, Paola Fazi, Marco Sborgia, Eros Di Bona, Massimo Breccia, Erika Borlenghi, Roberto Cairoli, Alessandro Rambaldi, Lorella Melillo, Giorgio La Nasa, Walter Fiedler, Peter Brossart, Bernd Hertenstein, Helmut R. Salih, Mohammed Wattad, Michael Lübbert, Christian H. Brandts, Mathias Hänel, Christoph Röllig, Norbert Schmitz, Hartmut Link, Chiara Frairia, Enrico Maria Pogliani,† Claudio Fozza, Alfonso Maria D'Arco, Nicola Di Renzo, Agostino Cortelezzi, Francesco Fabbiano, Konstanze Döhner, Arnold Ganser, Hartmut Döhner, Sergio Amadori, Franco Mandelli, Gerhard Ehninger, Richard F. Schlenk, and Francesco Lo-Coco

APL0406: Efficacy Results

- Noninferiority trial

	ATRA + ATO n = 77	ATRA + chemo n = 31	*p*-value
50-month OS	99.2%	92.6%	$p = 0.0073$
50-month EFS	97.3%	80.0%	$p < 0.001$
50-month DFS	97.3%	82.6%	$p < 0.001$
50-month cumulative incidence of relapse	1.9%	13.9%	$p = 0.0013$

- Grade 3/4 neutropenia and thrombocytopenia significantly higher with ATRA + chemo than with ATRA + ATO ($p < 0.001$)
- Grade 3/4 elevation of liver function tests:
  - ATRA + ATO: 44%
  - ATRA + chemo: 3%

Platzbecker U et al. *J Clin Oncol* 2017;35(6):605-12.

Editorial — Dr Erba

The Italian-German APL0406 trial was previously reported by Lo Coco (*NEJM* 2013). The combination of ATRA and ATO was found not to be inferior to ATRA and chemotherapy (CHT) for adults with low- and intermediate-risk APL. The manuscript by Platzbecker et al is the final report of the APL0406 study, including now more patients (N = 276) and longer follow-up (median follow-up 40.6 months). All 127 subjects randomly assigned to ATRA and ATO achieved a complete remission. The cumulative incidence of relapse was lower with ATRA and ATO compared with ATRA and CHT (2% vs 14%). The event free survival and the overall survival were statistically superior with the ATRA and ATO combination (EFS 97% vs 80%, OS 99% vs 93%). There were only 2 relapses and

Editorial — Dr Erba (continued)

one death in CR in the ATRA and ATO group. On the other hand, there were 15 relapses, 2 treatment-related myeloid neoplasms, and 5 deaths in CR in the ATRA plus CHT group.

The rates of hematologic toxicity and infection were higher in the ATRA plus CHT group; the rate of hepatic toxicity was greater in the ATRA and ATO group. All 117 subjects in the ATRA plus CHT group in CR after consolidation proceeded to maintenance; 9 patients experienced relapse during maintenance, and 20 discontinued maintenance therapy.

Editorial — Dr Erba (continued)

The regimen of ATRA plus ATO is now the standard of care for patients with low- and intermediate-risk APL. Immediate initiation of ATRA is incredibly important for preventing hemorrhagic complications and early death. If the physician suspects APL based on the morphology of the circulating blasts, then the first dose of ATRA should be given prior to confirmation of diagnosis by cytogenetic analysis, FISH analysis or RT-PCR. In fact, a bone marrow biopsy may not be required if the peripheral blood is diagnostic. I try to avoid invasive procedures, such as bone marrow biopsy and placement of a tunnel catheter, in patients with active APL complicated by DIC (disseminated intravascular coagulation). If the diagnosis of APL is suspected based on the morphology, then cytogenetic analysis for the t(15;17), FISH analysis for

Editorial — Dr Erba (continued)

PML/RARA fusion gene, and RT-PCR for PML/RARA fusion transcript should all be ordered. There are rare situations of PML/RARA positive APL where the fusion may not be detected by one of these tests.

The treating physician must be prepared to recognize and treat the most serious and potentially fatal complication of this therapy, the APL differentiation syndrome (DS), which will only occur during induction therapy. The APL0406 protocol prescribed prednisone 0.5 mg/kg/day as prophylaxis for APL DS. However, 17% of patients still developed moderate or severe APL DS. I typically do not give steroid prophylaxis but instead start dexamethasone 10 mg IV twice daily for early signs of APL DS such as dyspnea, edema, pulmonary rales, hypoxia, weight gain, and fever. The dexamethasone should be tapered after

Editorial — Dr Erba (continued)

the DS subsides. ATRA and ATO do not need to be discontinued unless the patient is having life-threatening DS. If the treating physician monitors and adjusts (when necessary) the electrolytes and concomitant medications, QT prolongation is manageable, and ventricular arrhythmias are rare. The recovery of the WBC count and ANC during induction therapy is typically a biphasic process. The initial recovery is due to differentiation and is then typically followed by recurrent neutropenia with subsequent improvement due to normal marrow recovery. I avoid the azole anti-fungals during ATRA therapy since these may inhibit the metabolism of ATRA and increase the risk of ATRA-induced toxicities. Significant neutropenia, infections, and transfusion requirement are very unlikely during consolidation. ATRA-induced

Editorial — Dr Erba (continued)

headache and mucocutaneous dryness as well as ATO-induced sensory neuropathy are the most common non-hematologic adverse events encountered during consolidation. The consolidation consisting of IV administration of 20 daily doses of ATO every 8 weeks, is not convenient for patients. The evaluation of an oral arsenic formulation is planned.

ATRA, arsenic trioxide (ATO), and gemtuzumab ozogamicin (GO) is safe and highly effective in patients with previously untreated high-risk acute promyelocytic leukemia (APL): Final results of the SWOG/Alliance/ECOG S0535 trial

Lancet JE et al.
Proc ASH 2016;Abstract 896.

ECOG S0535: Efficacy and Safety Results with ATRA, ATO and GO in High-Risk APL

- CR: 62/73 (85%)
- 3-year EFS: 79%
  - Historical rate: 50% ($p < 0.001$)
- 3-year OS: 88%
- 3-year RFS: 93%
- Grade 3/4 AEs included:
  - Febrile neutropenia (34%)
  - AST/ALT elevation (12%)
  - Hypoxia/differentiation syndrome (11%)
  - Hyperglycemia (11%)
  - Prolonged QTc (11%)

Lancet JE et al. *Proc ASH* 2016;Abstract 896.

Editorial — Dr Erba

High risk APL is defined by leukocytosis at presentation (WBC count >10,000). High risk APL accounts for 25% of patients with APL and is often associated with the presence of FLT3 ITD mutations. The optimal therapy for high risk APL continues to be a matter of debate and clinical investigation. Gemtuzumab ozogamicin (GO) is an anti-CD33 humanized murine monoclonal antibody covalently linked to the anti-tumor antibiotic calicheamicin. APL blasts express CD33 at high levels, allowing internalization of the antibody-drug conjugate. The mechanism of action of calicheamicin is similar to anthracyclines, which are highly active in APL. GO is very effective as a single agent for relapsed APL (LoCoco et al. *Blood* 2004). GO has also been successfully combined with all-trans retinoic acid (ATRA) and arsenic trioxide

Editorial — Dr Erba (continued)

(ATO) for patients with previously untreated, high risk APL in a phase II study at MD Anderson Cancer Center.

This SWOG study evaluates the safety and efficacy of GO 9 mg/m^2 IV on day 1 in combination with ATRA and ATO as induction therapy followed by 2 cycles of ATO, 2 cycles of ATRA and daunorubicin, and two cycles of GO. Patients then received maintenance therapy for one year with ATRA, mercaptopurine and methotrexate. The majority of patients achieved a complete remission (85%). The remaining patients did not have response assessment, typically due to early death. The 3-year event-free survival was 79%, 3-year relapse-free survival 93%, and 3-year overall survival 88%. The six week mortality rate was 11%. There have been no documented relapses.

Editorial — Dr Erba (continued)

Arsenic trioxide alone is likely the single most active therapy for APL as demonstrated by the work of Mathews. However, the Sanz risk criteria were developed prior to the use of ATO during induction and consolidation therapy. Although the risk of relapse was greater, much of the poor outcome associated with high risk APL in the pre-ATO era was due to early mortality typically from hemorrhage. However, I believe the value of maintenance therapy for high risk patients treated with ATO/ATRA is now less clear. Patients with low- and intermediate-risk APL are now routinely treated with ATO and ATRA as induction and consolidation, without any maintenance. These patients often develop a leukocytosis early in therapy, with predominantly malignant cells, and they are only treated with hydroxyurea to control leukocytosis. Yet the long term

Editorial — Dr Erba (continued)

results are remarkably good.

The United Kingdom NCRI AML17 trial (Burnett A et al. *Lancet Oncol* 2015) compared ATRA plus ATO to ATRA plus chemotherapy for newly diagnosed APL. Maintenance therapy was not given in either arm. If a patient had high risk disease and was randomly assigned to ATO/ATRA (N = 30), then the subject received a single dose of GO 6 mg/m^2 on day 1 as the only cytotoxic therapy. The 4-year overall survival of the high risk APL patients receiving ATO/ATRA plus GO was 89% and not different from those who received ATRA plus chemotherapy. All deaths occurred early during induction therapy.

Editorial — Dr Erba (continued)

The SWOG protocol is an acceptable way to treat high risk APL patients, especially since GO is now available. However, I would suggest that following initial cytoreduction to help control the disease, the value of any further cytotoxic consolidation chemotherapy or anti-metabolite maintenance therapy is uncertain for high risk APL patients receiving ATO/ATRA therapy. Initial cytoreduction in high risk disease can be achieved with idarubicin, daunorubicin, or GO in addition to the ATO and ATRA. Leukapheresis should be avoided in APL patients with leukocytosis due to a possibly higher rate of hemorrhage. High risk APL patients achieving a remission after this induction therapy may potentially have excellent disease-free and overall survival with just ATRA and ATO consolidation, eliminating the need for any further cytotoxic

Editorial — Dr Erba (continued)

chemotherapy and the associated toxicities during remission. This hypothesis should be formally tested. Decreasing the risk of early death due to hemorrhage in high risk APL is our greatest challenge now.