5 Minute JournalClub

Key Papers in Acute and Chronic Leukemias, Myelodysplastic Syndromes and Myeloproliferative Neoplasms from the December 2015 American Society of Hematology (ASH) 57th Annual Meeting in Orlando, Florida

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Key Papers in Acute and Chronic Leukemias, Myelodysplastic Syndromes and Myeloproliferative Neoplasms from ASH 2015

Acute myeloid leukemia/chronic myelomonocytic leukemia/ myelodysplastic syndromes (Abstracts 6, 322, 319, 321, 327, 453, 452, LBA-8323, 908, 91, 92)

Chronic myeloid leukemia (Abstracts 345, 133, 348, 344, 479, 134, 480, 346)

Myeloproliferative neoplasms (Abstracts 59, 58, 56, 823, 825, 826, 827, 824)

Acute lymphoblastic leukemia (Abstracts 1, 80, 679, 83)

Key Papers in Acute and Chronic Leukemias, Myelodysplastic Syndromes and Myeloproliferative Neoplasms from ASH 2015

Acute myeloid leukemia/chronic myelomonocytic leukemia/ myelodysplastic syndromes (Abstracts 6, 322, 319, 321, 327, 453, 452, LBA-8323, 908, 91, 92)

Chronic myeloid leukemia (Abstracts 345, 133, 348, 344, 479, 134, 480, 346)

Myeloproliferative neoplasms (Abstracts 59, 58, 56, 823, 825, 826, 827, 824)

Acute lymphoblastic leukemia (Abstracts 1, 80, 679, 83)

The Multi-Kinase Inhibitor Midostaurin (M) Prolongs Survival Compared with Placebo (P) in Combination with Daunorubicin (D)/Cytarabine (C) Induction (ind), High-Dose C Consolidation (consol), and As Maintenance (maint) Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) Patients (pts) Age 18-60 with FLT3 Mutations (muts): An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance])[1]

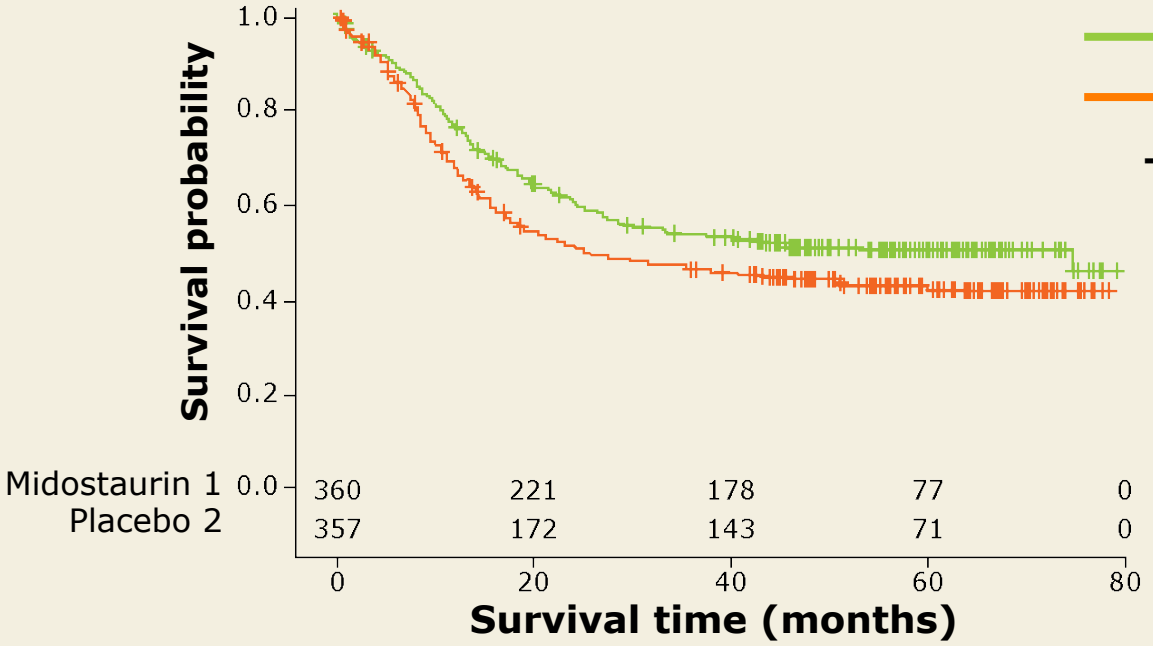
Midostaurin in Combination with Intensive Induction and As Single Agent Maintenance Therapy after Consolidation Therapy with Allogeneic Hematopoietic Stem Cell Transplantation or High-Dose Cytarabine (NCT01477606)[2]

[1] Stone RM et al.
Proc ASH 2015;Abstract 6.

[2] Schlenk R et al.
Proc ASH 2015;Abstract 322.

CALGB-10603 (RATIFY) Trial: Midostaurin (M) with Chemotherapy in Untreated FLT3 Mutation-Positive Acute Myeloid Leukemia (AML)

- Phase III, randomized, placebo-controlled trial of standard induction and consolidation chemotherapy with or without M, a multikinase inhibitor of FLT3, followed by maintenance M or placebo for 1 year
- N = 717 patients aged 18 to 60 with untreated FLT3 mutation-positive (341 internal tandem duplication [ITD] low mutation burden, 214 ITD high mutation burden, 162 tyrosine kinase domain [TKD] mutation-positive) AML
- **Primary endpoint:** Overall survival (OS)



Median OS
74.7 vs 25.6 mo
Hazard ratio (HR) = 0.77
p = 0.007
Risk of death reduced by 23% on the M arm

Stone RM et al. *Proc ASH* 2015;Abstract 6.

RATIFY: Conclusions

- OS and event-free survival (EFS) were improved with the addition of M:
  - Median EFS in induction and consolidation therapy (within 30 days of stopping protocol therapy): 11.3 versus 6.1 months (HR = 0.73; p = 0.0002).
  - Improvements in OS and EFS were independent of the high rate of stem cell transplant (SCT), 57%.
  - Results were similar across TKD mutation-positive, ITD-high and ITD-low subgroups.
- Safety was similar in the M and placebo arms:
  - No statistically significant differences were observed in the overall rate of Grade ≥3 hematologic or nonhematologic adverse events (AEs) between arms.
- Adding M to chemotherapy and following with 1 year of maintenance therapy will be a new standard for patients aged 18 to 60 with newly diagnosed, FLT3 mutation-positive AML.

Stone RM et al. *Proc ASH* 2015;Abstract 6.

AMLSG 16-10 Trial: M in Induction, Consolidation and Maintenance Therapy for Newly Diagnosed AML

- Ongoing single-arm Phase II trial of induction therapy with M followed by allogeneic SCT or consolidation therapy; single-agent maintenance therapy with M for 1 year is intended
- N = 149 transplant-eligible patients aged 18 to 70 with newly diagnosed FLT3-ITD mutation-positive AML
- **Endpoints:** Efficacy and safety
  - Postinduction complete remission rate: 75%
  - Deaths after induction therapy: 7.5%
  - Low relapse rates:
    - Allogeneic SCT (n = 94), ITD high 5% versus ITD low 12%
    - After high-dose cytarabine consolidation, ITD high 29% versus ITD low 28%
  - Only 4 Grade 3 or 4 AEs were attributed to M
  - Most frequent AEs during the first induction cycle were gastrointestinal symptoms and infections

Schlenk R et al. *Proc ASH* 2015;Abstract 322.

Investigator Commentary: Efficacy and Safety of M-Based Induction and Maintenance Therapy After Consolidation Therapy with Autologous SCT or High-Dose Cytarabine in AML

Approximately 30% of adults with AML have blasts that harbor FLT3 mutations, the most common version of which, the FLT3 ITD length mutation, is associated with poor prognosis due to a high relapse rate. Small molecule inhibitors of mutationally activated FLT3 have shown limited biologic remitting activity in patients with advanced FLT3 mutation-positive AML. One such potential FLT3 inhibitor, M, is a multitargeted kinase inhibitor that was originally tested in patients with solid tumors because it is also a protein kinase inhibitor. M has limited clinical activity as a single agent in both FLT3-mutant and wild-type disease and can be combined safely with standard induction and consolidation therapy for patients with previously untreated AML.

continued

Investigator Commentary: Efficacy and Safety of M-Based Induction and Maintenance Therapy After Consolidation Therapy with Autologous SCT or High-Dose Cytarabine in AML

In this multinational prospective, randomized, double-blind, placebo-controlled trial (CALGB-10603/RATIFY), approximately 3,300 patients with previously untreated AML were screened for the presence of an FLT3 ITD or TDK point mutation. FLT3 mutations were found in 887, and 717 were randomly assigned to receive standard chemotherapy with daunorubicin/cytarabine induction and high-dose Ara-C-based consolidation with either placebo or M at a dose of 50 mg orally twice daily for 14 days with each cycle and then for twelve 28-day maintenance cycles.

Using the strict definition of complete remission in the protocol, no statistical increase in remission rate occurred for the patients who received M. However, the study met its primary endpoint and showed a 23% reduction in the risk of death for patients who received M. This benefit was observed for patients with both types of FLT3 mutation and those with high and low allelic burden of the FLT3-ITD mutation.

continued

Investigator Commentary: Efficacy and Safety of M-Based Induction and Maintenance Therapy After Consolidation Therapy with Autologous SCT or High-Dose Cytarabine in AML

Presumably because of a change in the standard treatment for adults with FLT3-mutant disease, 57% of the patients underwent a transplant during the course of this study. Twenty-eight percent of the patients receiving M and 22% of the patients receiving placebo underwent transplant during first complete remission. Even with censoring for transplants the OS benefit favored the addition of M to therapy.

The rates of serious toxicities were equivalent in both arms. Overall, the RATIFY trial demonstrated that the addition of M to chemotherapy for younger adults with previously untreated FLT3 mutation-positive AML led to a benefit in OS and should now become standard practice.

The AMLSG of Germany conducted a nonrandomized Phase II trial in which M was added to standard chemotherapy and after allogeneic SCT (the goal for all the patients in the study). The survival results were favorable compared to historical controls and support the notion that M should be added to standard chemotherapy (and transplant) in FLT3 mutation-positive AML.

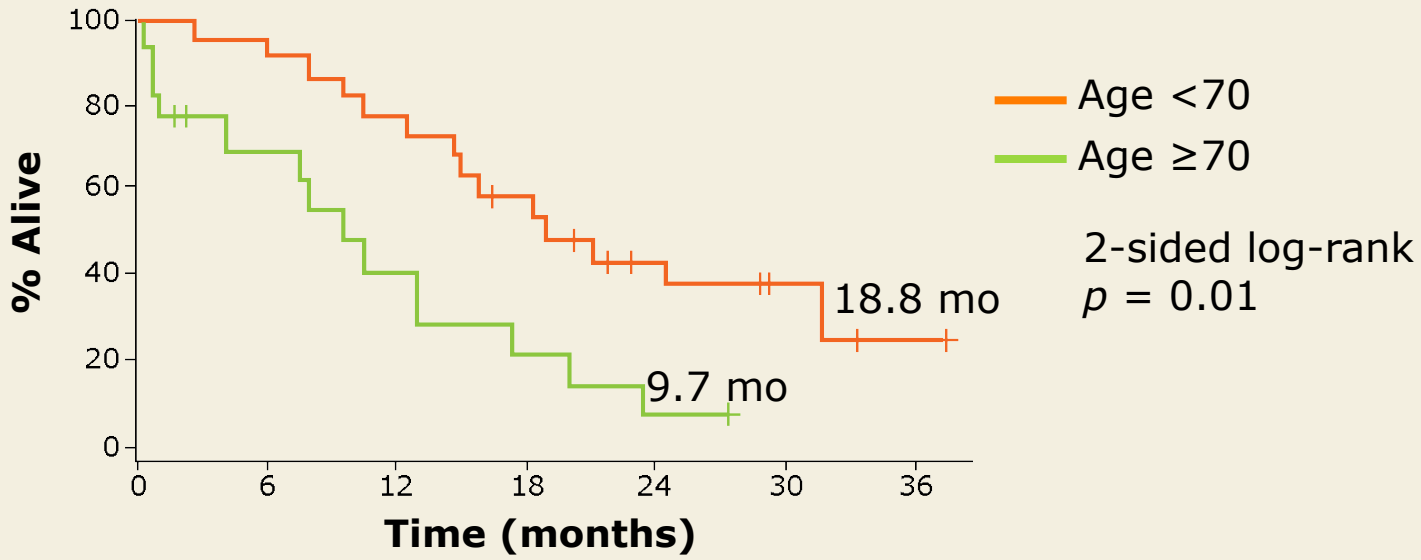
Interview with Richard M Stone, MD, February 16, 2016

Addition of Sorafenib to Chemotherapy Improves the Overall Survival of Older Adults with *FLT3*-ITD Mutated Acute Myeloid Leukemia (AML) (Alliance C11001)

Uy GL et al.
Proc ASH 2015;Abstract 319.

Alliance C11001 Trial: Sorafenib with Chemotherapy for Older Patients with FLT3-ITD-Mutated Acute Myeloid Leukemia (AML)

- Multicenter, single-arm Phase II trial of chemotherapy + sorafenib, an oral multikinase inhibitor (including the FLT3 tyrosine kinase), during induction and consolidation therapy followed by maintenance for 1 year
- N = 54 patients aged ≥60 with untreated FLT3-mutated AML
- **Primary endpoint:** One-year overall survival (OS) in FLT3-ITD-mutated AML
  - Improved compared to historical controls (63% vs 30%, $p < 0.0001$)
- Benefit of sorafenib observed primarily in patients age 60 to 69



Uy G et al. *Proc ASH* 2015;Abstract 319.

Alliance C11001: Conclusions

- First prospective clinical trial for older adults with AML targeting a specific mutational profile within the US cooperative group setting
- OS at 1 year more than doubled in comparison to historical controls
  - Median OS for patients with FLT3-ITD-mutated AML: 15.0 months
  - OS benefit appears to be independent of allogeneic stem cell transplantation
  - Median event-free survival: 8.8 months
- Sorafenib is associated with a reduction in FLT3 plasma inhibitory activity levels, indicating inhibition of FLT3 in vivo

Uy G et al. *Proc ASH* 2015;Abstract 319.

Investigator Commentary: Addition of Sorafenib to Chemotherapy for Older Adults with FLT3-ITD-Mutated AML

Sorafenib is a multitargeted kinase inhibitor approved for use in hepatocellular carcinoma and renal cell cancer because it inhibits the vascular endothelial growth factor receptor (VEGFR). It is an inhibitor of FLT3 and has been used as a single agent for patients with FLT3-mutated relapsed/refractory AML and to prevent relapse after stem cell transplantation for patients with this type of leukemia.

The CALGB conducted a trial (C11001) in which sorafenib was added to standard induction chemotherapy and standard postremission therapy for older adults with FLT3-ITD-mutated AML. Results were superior to historical controls, supporting the value of adding an inhibitor of FLT3 to chemotherapy for adults of all ages with FLT3-ITD-mutated AML.

In my practice I don’t routinely combine sorafenib with chemotherapy because no randomized data support a benefit in terms of OS. Second, it’s not approved with chemotherapy. Also, toxicities are associated with using sorafenib. However, I do use sorafenib as a single agent for salvage therapy for patients with FLT3-mutated AML who don’t have any other options. If a patient with relapsed FLT3-mutated AML cannot get on a trial with an FLT3 inhibitor and sorafenib can be procured, responses can be elicited, particularly in the post-transplant setting.

Interview with Richard M Stone, MD, February 18, 2016

Antileukemic Activity and Tolerability of ASP2215 80mg and Greater in FLT3 Mutation-Positive Subjects with Relapsed or Refractory Acute Myeloid Leukemia: Results from a Phase 1/2, Open-Label, Dose-Escalation/Dose-Response Study

Altman JK et al.

Proc ASH 2015;Abstract 321.

Novel FLT3 Inhibitor Gilteritinib (ASP2215) in Relapsed/Refractory (R/R) FLT3-Positive Acute Myeloid Leukemia (AML)

- Phase I/II open label dose-escalation, dose-response study of gilteritinib, a highly selective FLT3 inhibitor
- N = 215 patients with R/R AML treated with gilteritinib ≥80 mg; n = 133 evaluable patients with FLT3-mutated disease
- Strong antileukemic activity in patients with heavily pretreated FLT3-positive disease:
  - Overall response rate (ORR) = 73 (55%); composite complete remission (CRc) = 61 (46%)
  - No difference in ORR between patients with TKI-naïve disease and those who received prior tyrosine kinase inhibitor therapy (55% vs 55%)
  - Median overall survival ~29 weeks; similar for patients who achieved CRc
- Treatment was well tolerated:
  - Adverse events of all grades reported in ≥10% of the safety population were diarrhea (16%), fatigue (13%) and increased AST (11%)
  - <2% of patients reported Grade ≥3 QTc prolongation

Altman JK et al. *Proc ASH* 2015;Abstract 321.

Investigator Commentary: Results of the Phase I/II Trial of Gilteritinib in FLT3-Positive R/R AML

Approximately 35% of patients with AML have blasts that harbor an FLT3 mutation. Approximately 3/4 of those with the mutation have an FLT3-ITD or length mutation, which is a duplication of between 3 and 100 amino acids in the juxtamembrane region of the transmembrane tyrosine kinase protein. The other 25% of patients with FLT3 mutations have a point mutation in the tyrosine kinase domain. Both types of mutation activate the enzyme, cause spontaneous ligand-independent dimerization and promote cell proliferation. Multiple efforts are under way to inhibit this activated kinase with small molecules both as single agents and in combination with chemotherapy.

Gilteritinib is a relatively specific small molecule inhibitor of FLT3 that, unlike many of the other agents in development (except for midostaurin and crenolanib) inhibits enzymes with both types of mutations. Dr Altman presented the results of a Phase I/II trial using this agent in patients with advanced R/R FLT3-positive AML. The drug was well tolerated at the doses employed. The CRc rate was 49% for the subset of patients with the FLT3-ITD mutation (n = 114). This compares favorably with the other FLT3 inhibitors in clinical development.

Interview with Richard M Stone, MD, February 16, 2016

A Phase 1b Study of Venetoclax (ABT-199/GDC-0199) in Combination with Decitabine or Azacitidine in Treatment-Naive Patients with Acute Myelogenous Leukemia Who Are ≥ to 65 Years and Not Eligible for Standard Induction Therapy

DiNardo C et al.

Proc ASH 2015;Abstract 327.

Venetoclax and a Hypomethylating Agent for Elderly Patients with Treatment-Naïve Acute Myeloid Leukemia (AML)

- Phase Ib study of venetoclax with either azacitidine or decitabine
- N = 34 patients aged ≥65 years with treatment-naïve AML who are not eligible for standard induction therapy

	Venetoclax/decitabine		Venetoclax/azacitidine		
Best response	**400 mg (n = 6)**	**800 mg (n = 12)**	**400 mg (n = 4)**	**800 mg (n = 12)**	**ITT response (N = 34)**
ORR (CR/CRi/PR)	50%	83%	100%	75%	76%
CR*	33%	17%	75%	42%	35%
CRi*	17%	50%	25%	33%	35%
PR	0%	17%	0%	0%	6%

ITT = intent-to-treat population; ORR = overall response rate; CR = complete remission; CRi = CR with incomplete bone-marrow recovery; PR = partial remission

* Median time to CR/CRi: 29.5 days (range: 24-112)

DiNardo C et al. *Proc ASH* 2015;Abstract 327.

Grade 3 or 4 Adverse Events (AEs)

	Venetoclax/ decitabine		Venetoclax/ azacitidine		
AE	**400 mg (n = 6)**	**800 mg (n = 12)**	**400 mg (n = 4)**	**800 mg (n = 12)**	**Total (N = 34)**
Febrile neutropenia	67%	33%	50%	25%	38%
Neutropenia	50%	25%	0%	33%	29%
Thrombocytopenia	50%	8%	25%	25%	24%
Leukopenia	17%	8%	0%	33%	18%
Lung infection	33%	0%	0%	8%	9%

- No dose-limiting toxicities
- No tumor lysis syndrome
- Neutropenia required dose delays in 13 of 34 patients

DiNardo C et al. *Proc ASH* 2015;Abstract 327.

Conclusions

- Combination of venetoclax with decitabine or azacitidine is tolerable with a similar safety profile in both treatment arms.
  - No tumor lysis syndrome or dose-limiting toxicities
- No effect of decitabine or azacitidine on venetoclax exposure is recorded in early pharmacokinetic data.
- Earlier CR/CRi were observed across all treatment cohorts and arms with the combination than with a hypomethylating agent alone.
- Maximum tolerated dose was not reached in either arm; dose escalation is ongoing.
- Study will progress to expansion stage.
- Alternative venetoclax schedule will address dose delays due to neutropenia.

DiNardo C et al. *Proc ASH* 2015;Abstract 327.

Investigator Commentary: Venetoclax with a Hypomethylating Agent for Elderly Patients with Treatment-Naïve AML

Venetoclax, or ABT-199, may turn out to be an interesting molecule in myelodysplastic syndromes (MDS). It hasn't yet been tested in MDS but has been tested in AML. The study presented by Courtney DiNardo for older patients with poor-risk AML who were not going to receive chemotherapy evaluated azacitidine or decitabine with venetoclax. The response rate was notably high. Venetoclax is myelosuppressive, so it must be used with care, but no tumor lysis syndrome was observed as has occurred in patients with chronic lymphocytic leukemia. I'm optimistic that someday we'll be administering azacitidine with venetoclax for MDS and maybe getting better results than with azacitidine alone. Approximately 1 month ago venetoclax received breakthrough designation for AML thanks to this study, so these results are encouraging.

Interview with Richard Stone, MD, February 18, 2016

Final Results from a Phase 2 Study of Pracinostat in Combination with Azacitidine in Elderly Patients with Acute Myeloid Leukemia (AML)[1]

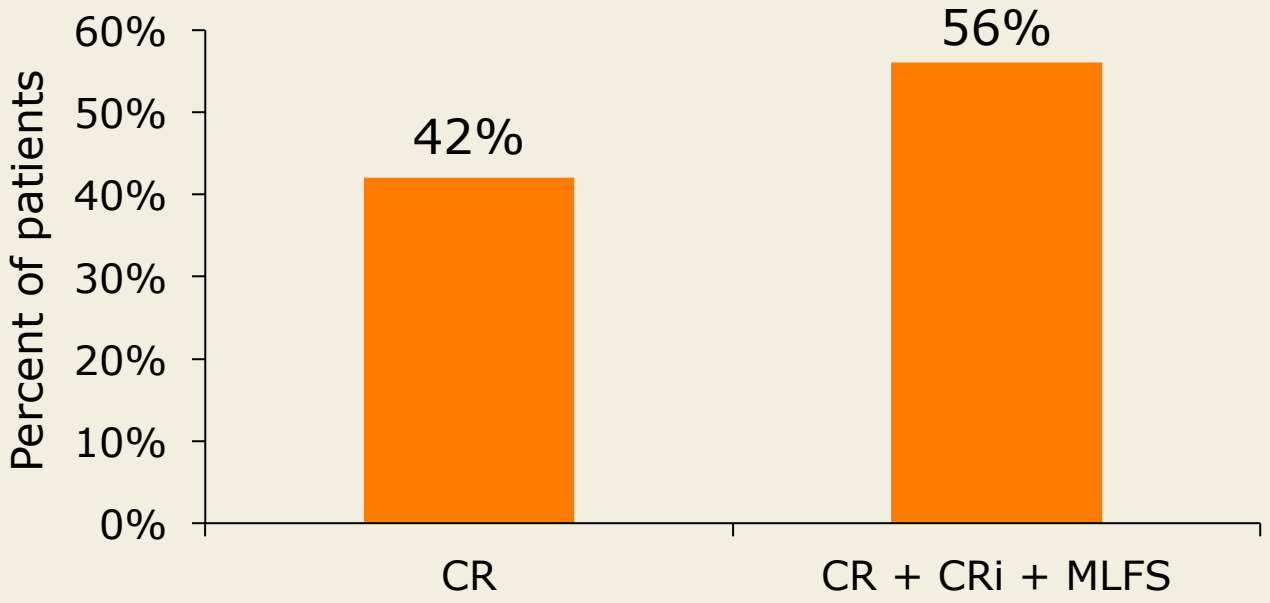
CC-486 (Oral Azacitidine) Monotherapy in Patients with Acute Myeloid Leukemia (AML)[2]

[1] **Garcia-Manero G et al.**
Proc ASH 2015;Abstract 453.

[2] **Savona MR et al.**
Proc ASH 2015;Abstract 452.

Pracinostat with Azacitidine for Elderly Patients with Acute Myeloid Leukemia (AML)

- Phase II trial of pracinostat, an oral histone deacetylase (HDAC) inhibitor, with azacitidine
- N = 50 patients aged ≥65 with untreated AML who are ineligible for intensive induction therapy
- **Primary endpoint:** Complete response (CR) + CR with incomplete blood count recovery (CRi) + morphologic leukemia-free state (MLFS, ie, marrow CR)



Garcia-Manero G et al. *Proc ASH* 2015;Abstract 453.

Pracinostat + Azacitidine: Conclusions

- Combination of azacitidine and pracinostat is safe for elderly patients with AML:
  - Treatment-related adverse events (AEs) leading to drug discontinuation: Peripheral motor neuropathy (n = 1), parainfluenza (n = 1), atrial fibrillation/prolonged QTc (n = 1), acute kidney injury (n = 1), diverticulitis (n = 1), supraglottic ulcer (n = 1), intermittent fatigue (n = 2) and sepsis (n = 3)
- High response rate in comparison to single-agent azacitidine
- Median event-free survival = 7.7 months; Median overall survival (OS) not reached (1-y OS estimated at 62%)
- Confirmation of these results in a Phase III trial is planned

Garcia-Manero G et al. *Proc ASH* 2015;Abstract 453.

Oral Azacitidine (CC-486) Monotherapy in AML

- Patients from 2 Phase I/II studies were sequentially assigned to receive oral azacitidine in 4 extended-dosing regimens of 14 days or 21 days per 28-day cycle
- N = 23 patients with AML
- **Endpoints:** Safety and efficacy
  - Reasonably well tolerated
  - Hematologic response rate = 48%, including patients with prior myelodysplastic syndromes and relapsed/refractory AML
    - Patients for whom prior hypomethlyating agents (HMA) had failed experienced responses, which may reflect sustained hypomethylation with prolonged oral administration
- Oral azacitidine is an additional option after failure of intravenous or subcutaneous HMA therapy
- Ease of administration facilitates use in combination treatment regimens, which warrants investigation
- Phase III QUAZAR AML Maintenance trial of oral azacitidine and best supportive care after induction therapy is ongoing (NCT01757535)

Savona MR et al. *Proc ASH* 2015;Abstract 452.

Investigator Commentary: Final Results of a Phase II Trial of Pracinostat/Azacitidine for Elderly Patients with AML and Results from a Study of Oral Azacitidine Monotherapy in AML

No consensus has been reached on how best to treat AML in older adults. First, older patients are less able to tolerate the intensive chemotherapy often used for younger adults with AML. Second, older adults tend to have a more intrinsically resistant disease with a higher incidence of adverse cytogenetics and mutations. One standard approach for older adults in the United States who are not deemed to be eligible for chemotherapy due to host or disease factors is the use of a hypomethylating agent, either azacitidine or decitabine.

A trial comparing decitabine (administered for 5 days every month) to supportive care or low-dose Ara-C did not meet its primary endpoint of extending OS but did demonstrate a clear trend in favor of decitabine. Similarly, a large trial, AZA-AML-001, reported by Dombret and colleagues in *Blood* 2015, showed a trend toward a superior yield in OS with azacitidine therapy versus physician-chosen conventional care regimens (either low-dose Ara-C, supportive care or induction chemotherapy) for older adults with newly diagnosed AML.

continued

Investigator Commentary: Final Results of a Phase II Trial of Pracinostat/Azacitidine for Elderly Patients with AML and Results from a Study of Oral Azacitidine Monotherapy in AML

Consequently, efforts are under way to improve hypomethylating agent-based therapy for older adults with AML. One such effort is to develop more convenient formulations of one or both of these drugs. The ASH presentation by Savona and colleagues showed that oral azacitidine could be administered safely and effectively to older adults with AML. Whether oral azacitidine will supplant the use of intravenous or subcutaneous azacitidine remains to be determined.

Another attempt to improve results with hypomethylating agents in older adults with AML is to add another agent. Hypomethylating-agent therapy is believed to allow the transcription of differentiation-associated genes. Preventing deacetylation of histones also potentially opens the genome, allowing transcription of "favorable" genes, and represents a related biological target. Whether the addition of HDAC inhibitors (HDACi) to a hypomethylating agent will improve outcomes in older adults with AML is unclear.

continued

Investigator Commentary: Final Results of a Phase II Trial of Pracinostat/Azacitidine for Elderly Patients with AML and Results from a Study of Oral Azacitidine Monotherapy in AML

A study conducted by the US Intergroup and led by Dr Mikkael Sekeres did not show any benefit to adding the HDACi vorinostat to azacitidine for patients with high-risk myelodysplastic syndromes. The Phase II results of adding the novel HDACi pracinostat to azacitidine for older patients with AML were encouraging but not definitive.

Interview with Richard M Stone, MD, February 16, 2016

Results of a Phase III Randomized, Multi-Center Study of Allogeneic Stem Cell Transplantation after High Versus Reduced Intensity Conditioning in Patients with Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML): Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0901

Scott BL et al.

Proc ASH 2015;Abstract LBA-8.

BMT CTN 0901 Trial: Myeloablative Conditioning (MAC) versus Reduced-Intensity Conditioning (RIC) for Allogeneic Stem Cell Transplant (Allo SCT) in Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

- Phase III randomized trial of MAC versus RIC for allo SCT
- N = 218 patients with AML; N = 54 patients with MDS; age 18 to 65 years; <5% marrow myeloblasts
- **Primary endpoint:** 18-month overall survival (OS)

Endpoint at 18-month median follow-up	RIC (%)	MAC (%)	*p*-value
OS	67.7	77.4	0.07
RFS	47.3	67.7	<0.01

RFS = relapse-free survival

Scott B et al. *Proc ASH* 2015;Abstract LBA-8.

BMT CTN 0901: Conclusions

- A statistically significant advantage in RFS and a trend for improved OS were reported for patients receiving MAC.
- RIC results in lower treatment-related mortality (TRM) and graft-versus-host disease (GVHD) and better quality of life but higher relapse rates.

Endpoint (18 mo)	RIC (%)	MAC (%)	*p*-value
TRM	4.4	15.8	0.02
Grade 2-4 acute GVHD at day 100	31.6	44.7	0.024
Relapse	48.3	13.5	<0.01

- This trial supports MAC as the standard for patients able to receive it.

Scott B et al. *Proc ASH* 2015;Abstract LBA-8.

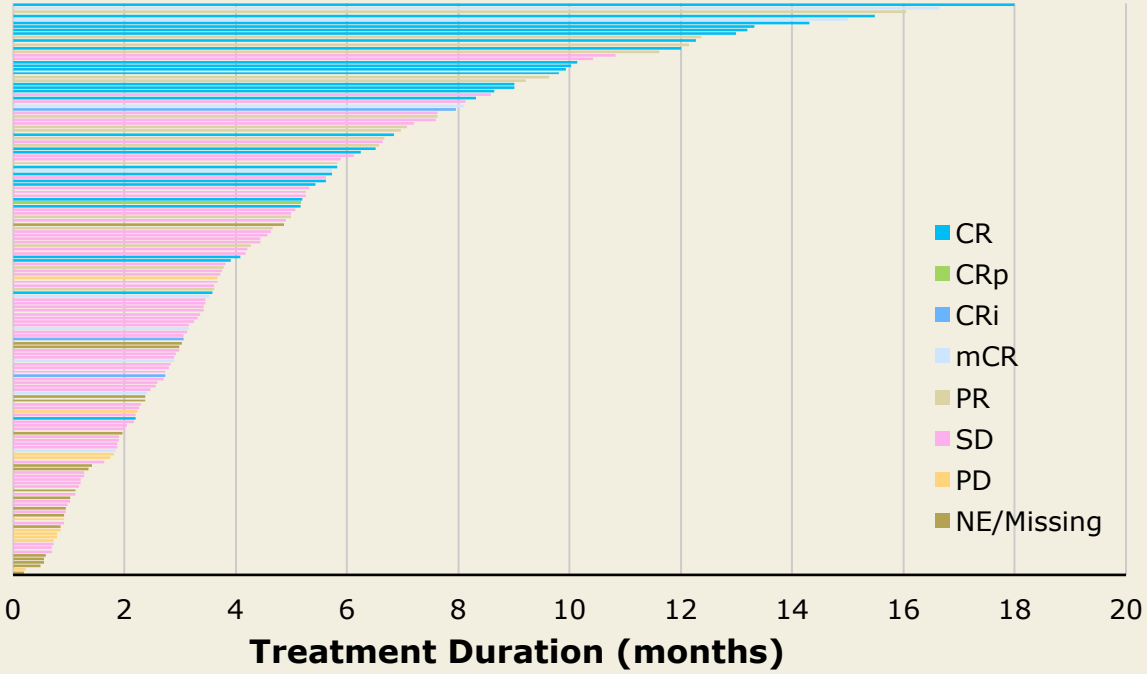
Safety and Efficacy of AG-221, a Potent Inhibitor of Mutant IDH2 That Promotes Differentiation of Myeloid Cells in Patients with Advanced Hematologic Malignancies: Results of a Phase 1/2 Trial

Stein EM et al.

Proc ASH 2015;Abstract 323.

AG-221 in Acute Myeloid Leukemia (AML)

- Ongoing Phase I/II trial of AG-221, a potent inhibitor of mutant isocitrate dehydrogenase 2 (mIDH2), in hematologic cancers
- N = 209 evaluable patients: mIDH2-positive relapsed/refractory (R/R) AML (n = 159); Untreated AML and age ≥60 years (n = 24); Myelodysplastic syndromes (MDS) (n = 14); Other (n = 12)
- **Key endpoints:** Maximum tolerated dose, activity and safety/tolerability



Overall response rate
(all patients): 79/209 (38%)
mIDH2-positive R/R AML:
59/159 (37%)
Untreated AML, age ≥60 y:
10/24 (42%)
MDS: 7/14 (50%)

Stein EM et al. *Proc ASH* 2015;Abstract 323; www.clinicaltrials.gov (NCT01915498).

AG-221 in R/R AML: Conclusions

- AG-221 is generally well tolerated:
  - Most frequent treatment-emergent adverse events (AEs) were gastrointestinal
  - Fewer than 10% of patients discontinued therapy because of AEs
  - A differentiation syndrome observed in a small subset of patients appears to be easily managed with steroids
- AG-221 induces durable responses in patients with R/R AML (ORR = 37%, median duration of response = 6.9 mo).
- Improvements in absolute neutrophil count and platelet count were observed in a subset of patients with R/R AML with stable disease.
- A randomized Phase III trial of AG-221 versus conventional care regimens for older patients with mIDH2-positive AML has been initiated (IDHENTIFY, NCT02577406).

Stein EM et al. *Proc ASH* 2015;Abstract 323.

Investigator Commentary: Efficacy and Safety of AG-221 in AML

IDH1 and IDH2 mutations are found in approximately 20% of patients with AML. These mutations result in a gain-of-function enzyme that produces a novel reaction product, 2-hydroxyglutarate, in lieu of the usual alpha-ketoglutarate. Reducing 2-hydroxyglutarate levels with an inhibitor of this enzyme could, by epigenetic means, revert leukemic pathophysiology.

Dr Stein and colleagues presented updated results of a Phase I/II study in which a potent inhibitor of the mutant IDH2 enzyme, AG-221, yielded complete remissions, sometimes occurring via a differentiation-like pathway. This drug will certainly be used earlier in the disease course and may be approved in the future for advanced disease. Another agent, AG-120, is similarly effective in patients with mutant IDH1-positive disease.

Interview with Richard M Stone, MD, February 16, 2016

Additional Analyses of a Randomized Phase II Study of Azacitidine Combined with Lenalidomide or with Vorinostat vs Azacitidine Monotherapy in Higher-Risk Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML): North American Intergroup Study SWOG S1117

Sekeres MA et al.

Proc ASH 2015;Abstract 908.

SWOG-S1117 Trial: Azacitidine (AZA) versus AZA/ Lenalidomide (LEN) versus AZA/Vorinostat (VOR) in Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)

- Randomized Phase II trial of AZA versus AZA/LEN versus AZA/VOR
- N = 277 patients with higher-risk MDS or CMML and no previous exposure to AZA, LEN or VOR
- **Primary endpoint:** Updated overall response rate (ORR)
- Data sets from both ASH 2014 and ASH 2015 show no significant difference in ORR between AZA and the combination regimens:
  - Trend for longer response duration with the combinations ($p = 0.083$)
  - No significant differences in median overall survival (OS):
    - AZA versus AZA/LEN $p = 0.38$
    - AZA versus AZA/VOR $p = 0.17$
    - AZA versus combinations $p = 0.19$

Sekeres M et al. *Proc ASH* 2015;Abstract 908.

SWOG-S1117: Conclusions

- Subgroup analyses:
  - Higher-risk MDS: Similar ORR and OS
  - CMML: ORR significantly higher with AZA/LEN compared to AZA (63% vs 29%; $p = 0.04$)
  - Cytogenetic risk category:
    - OS worse across study arms for chromosome 5 abnormality, -7 and del(17p) categories
    - OS possibly improved with combination regimens for chromosome 5 abnormality
- Treatment at high-volume sites or MDS Centers of Excellence did not alter these effects or outcomes.

Sekeres M et al. *Proc ASH* 2015;Abstract 908.

Eltrombopag for the Treatment of Thrombocytopenia of Low and Intermediate-1 IPSS Risk Myelodysplastic Syndromes: Interim Results on Efficacy, Safety and Quality of Life of an International, Multicenter Prospective, Randomized, Trial[1]

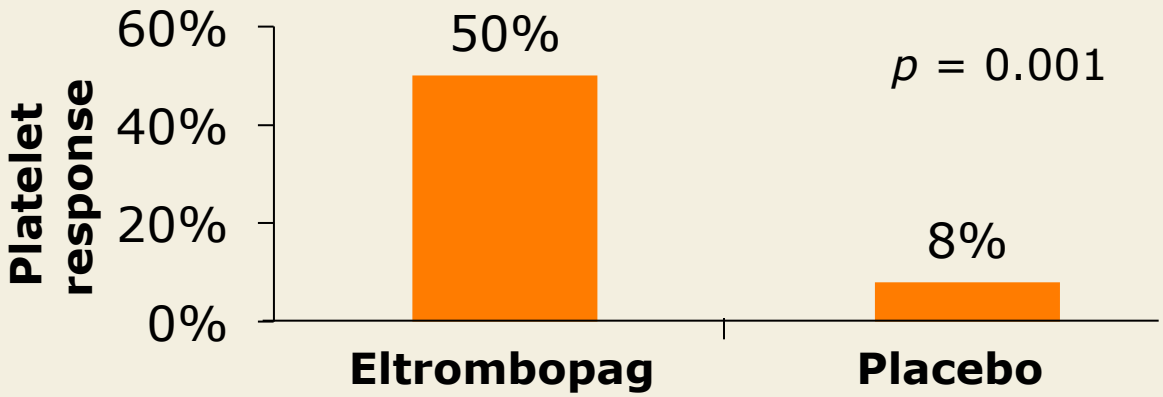
Luspatercept Treatment Leads to Long Term Increases in Hemoglobin and Reductions in Transfusion Burden in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS): Preliminary Results from the Phase 2 PACE-MDS Extension Study[2]

[1] **Oliva EN et al**
Proc ASH 2015;Abstract 91.

[2] **Giagounidis A et al.**
Proc ASH 2015;Abstract 92.

Eltrombopag for Lower-Risk Myelodysplastic Syndromes (MDS)

- Prospective, randomized (2:1) trial of eltrombopag, a thrombopoietin receptor agonist, versus placebo
- N = 70 patients with IPSS low- and intermediate 1-risk MDS and platelet counts <30 Gi/L
- **Primary endpoints:** Safety and efficacy measured by platelet response



- Preliminary conclusions of ongoing trial:
  - Improved fatigue correlated with response (p = 0.016)
  - Eltrombopag not associated with MDS progression
  - Good RR for patients with lower-risk MDS and low platelet counts

Oliva E et al. *Proc ASH* 2015;Abstract 91.

PACE-MDS Extension Study: Luspatercept (LUS) for Lower-Risk MDS

- Phase II dose-escalation study extension evaluating 3 months (q3wk) of subcutaneous LUS, a fusion protein that promotes erythropoiesis
- N = 32 transfusion-dependent patients with IPSS low- or intermediate 1-risk MDS
- **Primary endpoint:** IWG erythroid hematologic improvement (HI-E)

Characteristic	IWG HI-E (N = 32)	RBC-TI (N = 22)
All patients	69%	50%
▪ Presence of ringed sideroblasts	72%	53%
Prior ESA		
▪ Yes	63%	50%
▪ No	77%	50%
Baseline EPO		
▪ <200 U/L	80%	54%
▪ 200-500 U/L	71%	50%
▪ >500 U/L	20%	40%

RBC-TI = red blood cell transfusion independence; ESA = erithropoietin-stimulating agent; EPO = erythropoietin

Giagounidis A et al. *Proc ASH* 2015;Abstract 92.

PACE-MDS Extension Study: Conclusions

- Robust hematologic improvement (IWG HI-E) and reduced transfusion burden were observed in patients with lower-risk MDS treated with LUS.
  - Sustained hemoglobin increases and prolonged TI with treatment up to 1 year
  - High response rates for patients with ESA-refractory MDS and those with EPO ≤500 U/L
- LUS is safe and well tolerated with no Grade 3 or higher related adverse events.
- These results support initiation of a randomized Phase III trial (MEDALIST) for patients with lower-risk MDS with ringed sideroblasts requiring red blood cell transfusion.

Giagounidis A et al. *Proc ASH* 2015;Abstract 92.

Investigator Commentary: Initial Results from Phase II Trials of Eltrombopag or LUS for Myelosuppression in IPSS Low- and Intermediate-Risk MDS

The treatment of low-risk MDS is controversial. Patients tend to have favorable long-term outcomes but are often plagued by anemia and/or thrombocytopenia. The presentation by Dr Oliva and colleagues showed that the thrombopoietin agonist eltrombopag was safe and effective in patients with IPSS low- and intermediate 1-risk MDS. Concern about using eltrombopag for patients with high-risk MDS related to the possibility that leukemia proliferation might be stimulated. No such problem arose in this study. Eltrombopag may have a role in the treatment of lower-risk MDS in patients with refractory thrombocytopenia.

An interesting class of compounds includes the so-called activin trap antibody-like molecules, which bind to some of the "negative regulatory cytokines" like Smad2/3 that might be playing a role in the anemia of low-risk MDS. One such agent, LUS, may be effective in low-risk MDS.

continued

Investigator Commentary: Initial Results from Phase II Trials of Eltrombopag or LUS for Myelosuppression in IPSS Low- and Intermediate-Risk MDS

The results of a Phase II trial in which LUS was administered to patients with low-risk MDS suggest that these patients, particularly those with low transfusional burdens, can experience an important reduction in or termination of the need for red blood cell transfusions. Follow-up randomized trials will be required, but LUS is certainly one of the few promising drugs in lower-risk MDS.

Interview with Richard M Stone, MD, February 16, 2016

Key Papers in Acute and Chronic Leukemias, Myelodysplastic Syndromes and Myeloproliferative Neoplasms from ASH 2015

Acute myeloid leukemia/chronic myelomonocytic leukemia/ myelodysplastic syndromes (Abstracts 6, 322, 319, 321, 327, 453, 452, LBA-8323, 908, 91, 92)

Chronic myeloid leukemia (Abstracts 345, 133, 348, 344, 479, 134, 480, 346)

Myeloproliferative neoplasms (Abstracts 59, 58, 56, 823, 825, 826, 827, 824)

Acute lymphoblastic leukemia (Abstracts 1, 80, 679, 83)

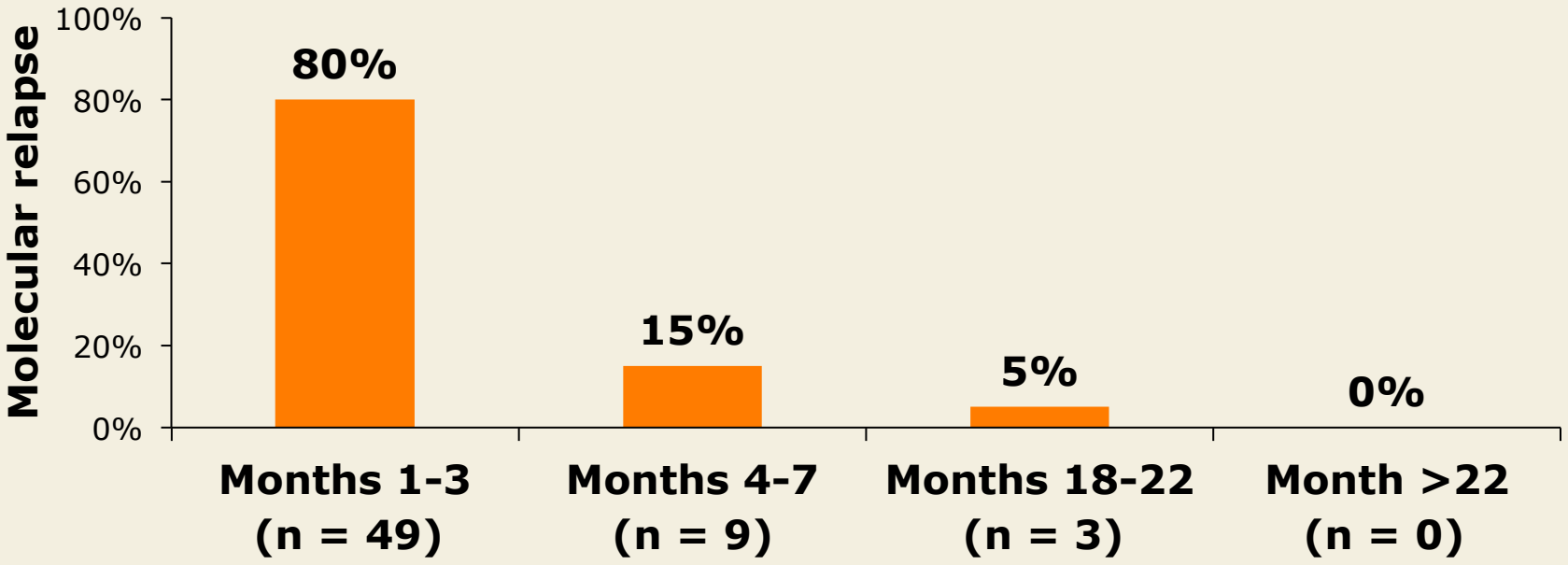
Long-Term Follow-up of the French 1 Stop Imatinib Study (STIM1) in Chronic Myeloid Leukemia Patients

Etienne G et al.

Proc ASH 2015;Abstract 345.

STIM1 Trial: Update of Stop Imatinib Study in Chronic Myeloid Leukemia (CML)

- Single-arm, multicenter study of stopping imatinib (IM), with median follow-up of 65 months
- N = 100 patients with CML receiving IM for >3 years with deep molecular response (DMR = 4.5 log reduction) ≥2 years
- Relapse-free survival at 6 months (M6): 43%; at M24: 38%



Etienne G et al. *Proc ASH* 2015;Abstract 345.

STIM1: Conclusions

- Molecular relapse (MR) occurs mostly within the first 6 months of stopping IM:
  - Sokal score is associated with risk of MR (p = 0.0149)
  - If no relapse by M6, chance of relapse at M24 is 10%
- Treatment resumption at MR resulted in another DMR in 55/57 patients with median follow-up of 67 months:
  - No CML progression
  - 39/57 remain free of MR
- IM can be safely discontinued if DMR duration ≥2 years.

Etienne G *Proc ASH* 2015;Abstract 345.

Investigator Commentary: Long-Term Follow-up of the STIM1 Study of Imatinib in CML

Tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib, nilotinib and bosutinib are highly effective in patients with CML in chronic phase. From 10% to 30% of patients receiving TKIs for chronic-phase CML achieve a complete molecular remission in which the BCR-ABL fusion transcript is undetectable by the highly sensitive PCR technique. When patients have no detectable or very low levels of the BCR-ABL transcript by PCR in the peripheral blood for 2 years in a row, one wonders whether some of these patients might be cured or at least be able to safely stop their TKI. French investigators have conducted a study in which such patients have had their imatinib stopped and have been followed carefully. Updated results from 100 patients with a median follow-up of 65 months were presented at ASH 2015 and demonstrated that 61% experienced molecular relapse, usually within 6 months of stopping the drug. But almost all of these patients (n = 55) achieved deep responses by PCR again after the imatinib was restarted.

Continued

Investigator Commentary: Long-Term Follow-up of the STIM1 Study of Imatinib in CML

The real question is whether "almost all" is good enough. You don't want to lose anybody to disease resistance if you stop the imatinib. A trial called the LAST study (NCT02269267) is ongoing in this country for patients who are considering discontinuing their TKI. It's amazing how many people are reluctant to stop imatinib. Patients tolerate it well. It's expensive, but patients usually don't pay for it out of pocket.

I consider it feasible to stop imatinib for the vast majority of patients. Either they'll stay PCR-negative or they'll be able to revert to a PCR-negative state by restarting imatinib should they experience relapse.

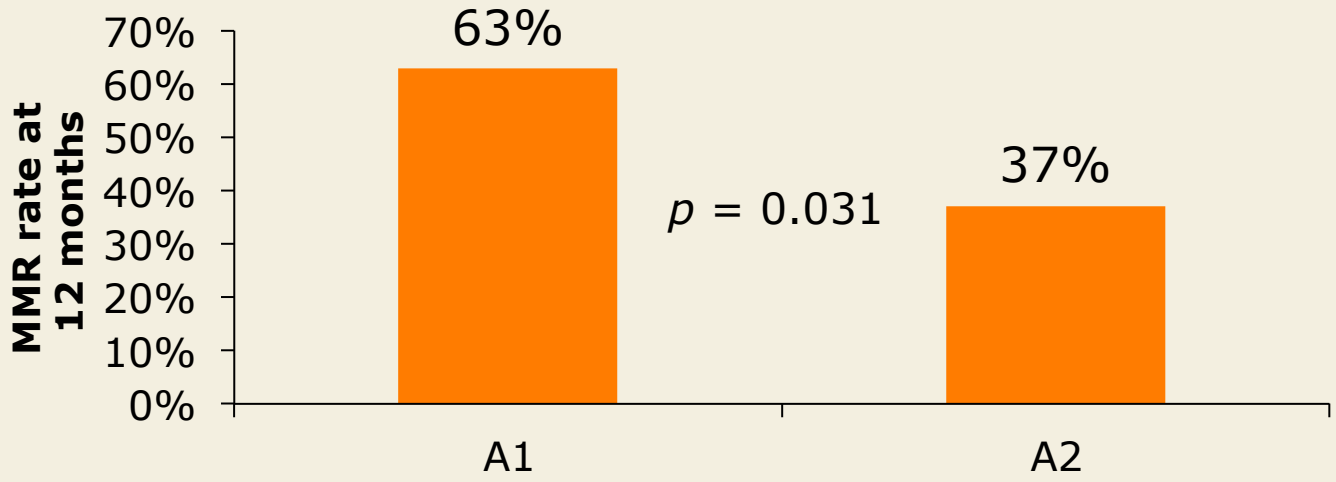
Interview with Richard M Stone, MD, February 16, 2016

Personalized Daily Doses of Imatinib By Therapeutic Drug Monitoring Increase the Rates of Molecular Responses in Patients with Chronic Myeloid Leukemia. Final Results of the Randomized OPTIM Imatinib Study

Rousselot P et al.
Proc ASH 2015;Abstract 133.

OPTIM-Imatinib Trial: Dose Optimization in Chronic Myeloid Leukemia (CML)

- Randomized trial evaluating dose optimization of imatinib (IM) to maintain a minimum concentration of 1,000 ng/mL versus standard dosing
- N = 133 patients with newly diagnosed CML in chronic phase, including those who received IM for <3 months
  - Arm 1 (A1): Patients aiming to receive the threshold of IM at 1,000 ng/mL (n = 43)
  - Arm 2 (A2): Patients who received standard IM dosing (n = 43)
  - Arm 3 (A3): Patients who received IM at ≥1,000 ng/mL (n = 47)
- **Primary endpoint:** Major molecular response (MMR) rate at 12 months

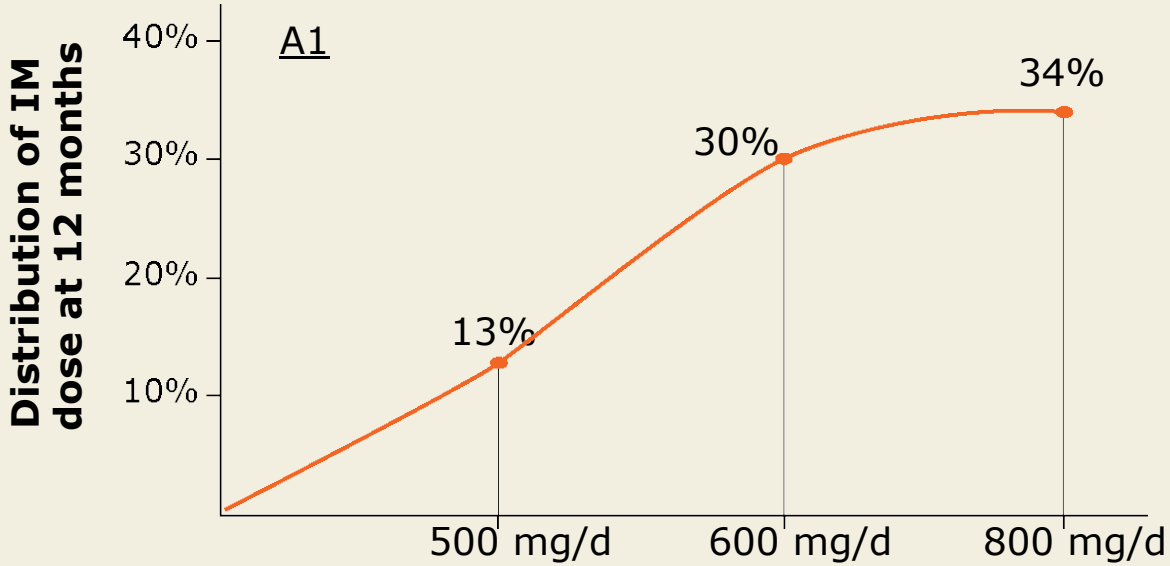


The MMR rates were not statistically different between A1 and A3 (p = 0.12).

Rousselot P et al. *Proc ASH* 2015;Abstract 133.

OPTIM-Imatinib: Conclusions

- Only 1/3 of patients who received the standard dose of 400 mg/d were correctly dosed and may not require a systematic high dose of IM.



Mean dose = 600 mg/d

- Patients who remained at 400 mg/d: 16%
- Patients who received dose reductions at 300 mg/d: 7%

- Two thirds of the patients were not exposed enough to IM at the standard dose and may benefit from individualized strategies.
- A tailored dose adjustment based on pharmacology resulted in a higher MMR rate at 12 months: 63% (A1) versus 37% (A2).
- These results may provide a strong rationale for the early personalization of IM administration to optimize the outcome for each patient.

Rousselot P et al. *Proc ASH* 2015;Abstract 133.

The Clinical Significance of Early Imatinib Induced *ABCB1* Overexpression in Chronic Phase CML Patients: A TIDEL II Sub-Study

Eadie LN et al.

Proc ASH 2015;Abstract 348.

TIDEL II Substudy: ABCB1 Overexpression in Chronic-Phase Chronic Myeloid Leukemia (CP CML)

- Retrospective analysis of ABCB1 by PCR at day 0, day 22 and discontinuation of imatinib (IM)
- N = 44 patients with CP CML on the TIDEL II study
- **Key endpoint:** Significance of ABCB1 overexpression

Day 22 of treatment	Early molecular response	MMR by 12 mo	Event-free survival	MR4.5
<2-fold rise in ABCB1 (n = 22)	86%	64%	77%	64%
>2-fold rise in ABCB1 (n = 22)	60%	14%	37%	5%
p-value	0.006	0.001	0.018	<0.001

MMR = major molecular response; MR4.5 = molecular response with a 4.5-log reduction in BCR-ABL transcripts (deep molecular response)

Eadie L et al. *Proc ASH* 2015;Abstract 348.

TIDEL II Substudy: Conclusions

- This rapid PCR-based assay performed before and 22 days after the start of IM therapy for patients with CP CML provides a potent early predictor of subsequent response to IM.
- After validation, ABCB1 overexpression may become a new, effective, easily translatable prognostic biomarker.
- Of note, after IM failure 0 of 16 patients who received nilotinib with a >2-fold rise in ABCB1 achieved MMR:
  - Perhaps nilotinib is a poor therapeutic option for these patients.

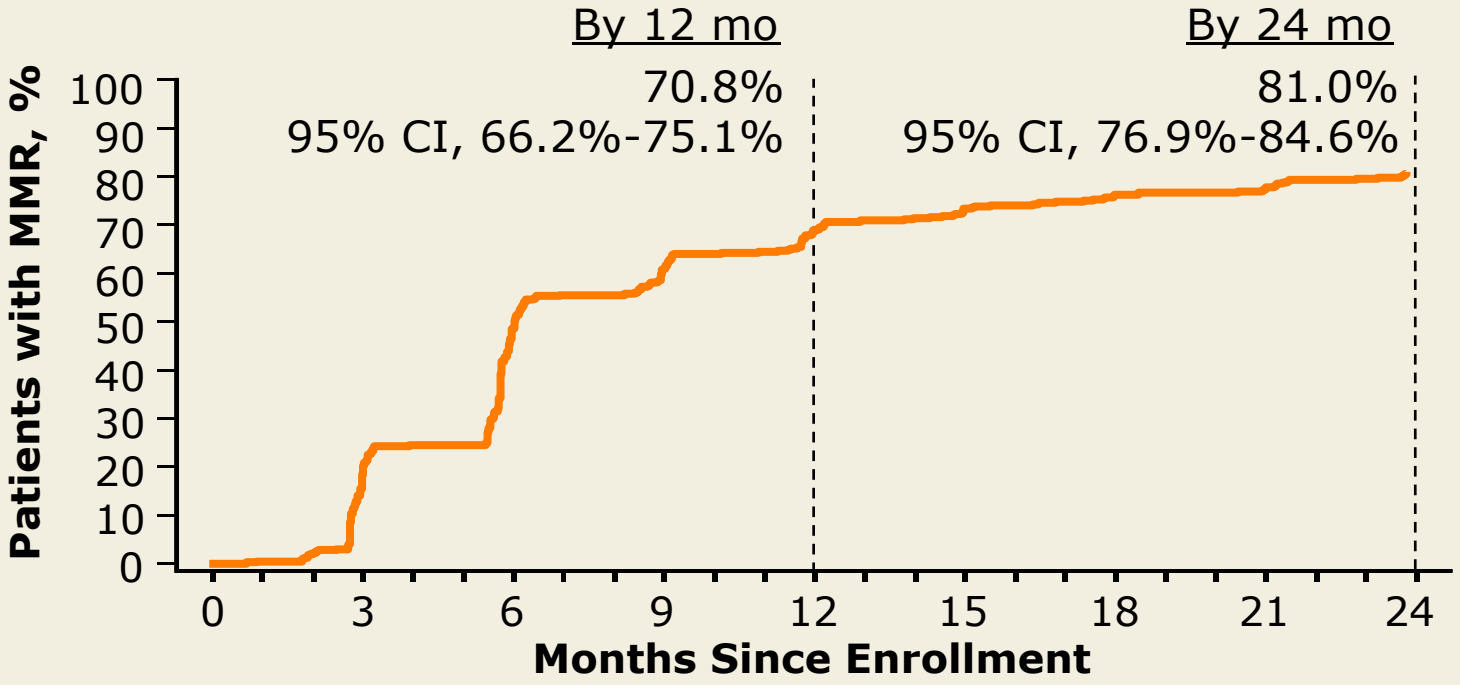
Eadie L et al. *Proc ASH* 2015;Abstract 348.

Dose-Optimized Nilotinib (NIL) in Patients (Pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Final Results from ENESTxtnd Study

Hughes TP et al.
Proc ASH 2015;Abstract 344.

ENESTxtnd Study: Dose-Optimized Nilotinib (NIL)

- Phase IIIb NIL dose-optimization trial (starting dose 300 mg BID)
- N = 421 patients with de novo chronic-phase chronic myeloid leukemia within 6 months of diagnosis
- **Primary endpoint:** Rate of major molecular response (MMR: *BCR-ABL1* ≤0.1%) at 12 months



Hughes T et al. *Proc ASH* 2015;Abstract 344.

ENESTxtnd: Conclusions

- The safety profile of NIL was consistent with prior studies: Grade 3 or 4 lipase elevation: 14.5%; cardiovascular events: 4.5% (N = 19).
- Rate of MMR was high among patients with dose adjustments:
  - Dose escalated to 400 mg BID (21%)
    - 64% MMR by 24 months
  - Dose reduced (34%)
    - Successful dose re-escalation: 64%
      - 85% MMR by 24 months
- Dose optimization may have contributed to the high rates of MMR at 12 months and 24 months.
- Data support front-line NIL for patients with newly diagnosed chronic-phase chronic myeloid leukemia.

Hughes T et al. *Proc ASH* 2015;Abstract 344.

Impact of Age on Efficacy and Toxicity of Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP): ENEST1st Sub-Analysis

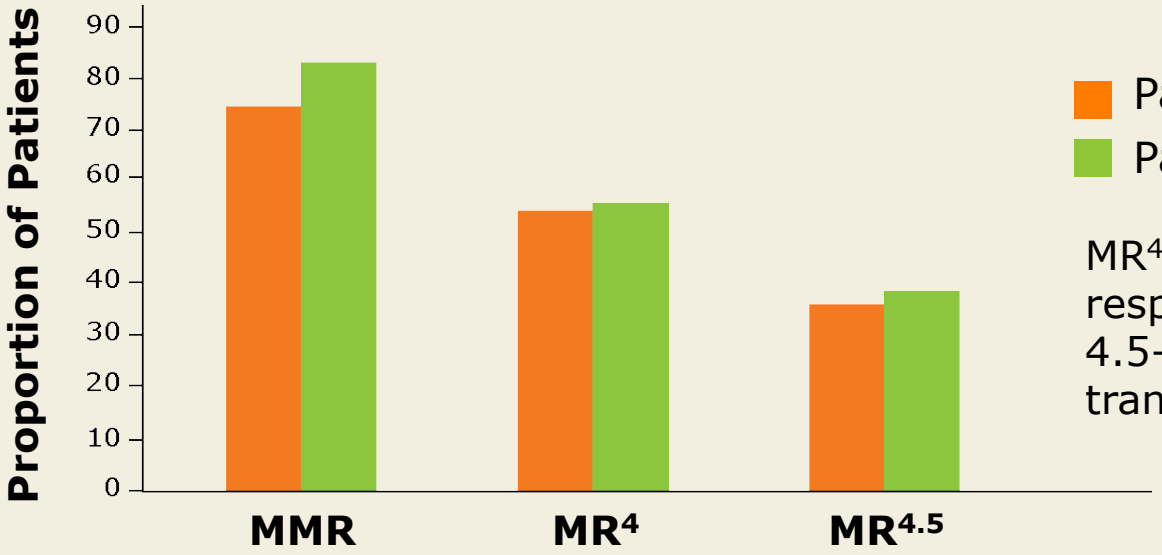
Giles FJ et al.

Proc ASH 2015;Abstract 479.

ENEST1st Subset Analysis: Age

- Subset analysis of a Phase IIIb trial of 1st-line nilotinib 300 mg BID
- N = 1,052 patients with newly diagnosed chronic-phase chronic myeloid leukemia, age ≤65 years (N = 851) versus >65 years (N = 201)
- **Primary endpoint:** Rate of major molecular response (MMR)

Cumulative Incidence of MMR, MR^4, and $MR^{4.5}$ by 24 months



MR^4, $MR^{4.5}$ = molecular response with a 4.0-log, 4.5-log reduction in BCR-ABL transcripts

Conclusion: MMR rates are equivalent and the safety profile is similar for older and younger patients.

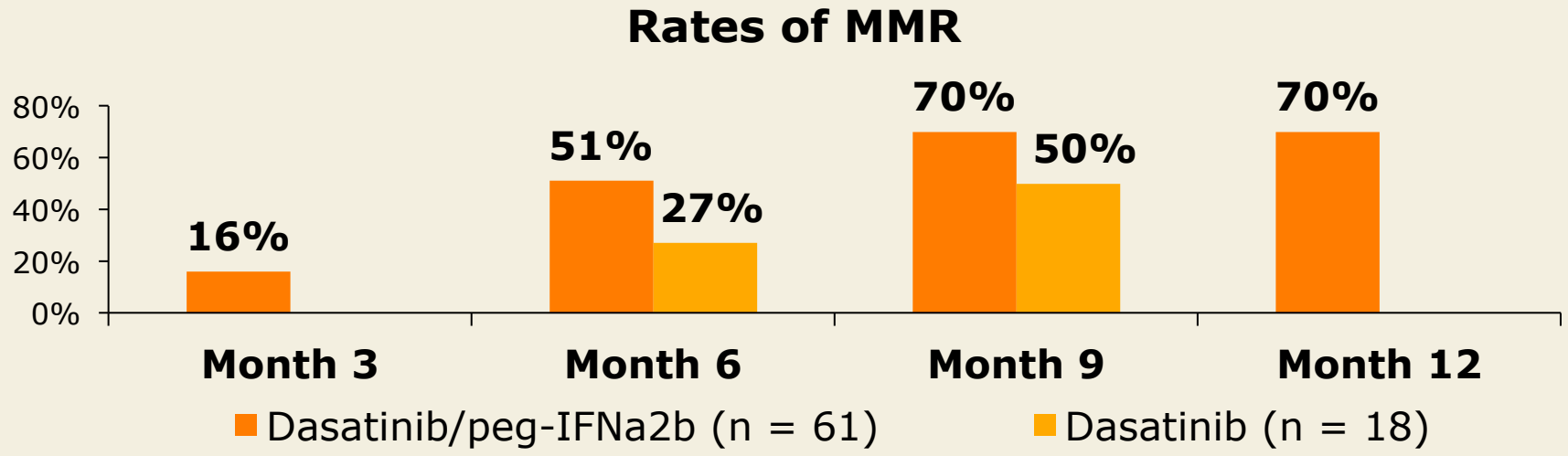
Giles F et al. *Proc ASH* 2015;Abstract 479.

Combination of Dasatinib and Peg-Interferon Alpha 2b in Chronic Phase Chronic Myeloid Leukemia (CP-CML) First Line: Preliminary Results of a Phase II Trial, from the French Intergroup of CML (Fi-LMC)

Roy L et al.
Proc ASH 2015;Abstract 134.

Dasa-PegIFN Trial: Dasatinib and Pegylated Interferon Alpha 2b (Peg-IFNa2b) in Chronic-Phase Chronic Myeloid Leukemia (CP CML)

- Single-arm Phase II trial of dasatinib 100 mg/d for 3 months with peg-IFNa2b 30 µg/wk added if counts were adequate
- N = 79 patients aged <65 years with newly diagnosed Philadelphia chromosome-positive CP CML, 49% with intermediate or high Sokal scores
- 18 of 79 patients were not eligible to receive combined therapy
- **Primary endpoint:** Deep molecular response (MR4.5) at month 12
- MR4.5 rates were 10%, 20% and 30% at 6, 9 and 12 months
- Major molecular response (MMR) rates:



Roy L et al. *Proc ASH* 2015;Abstract 134.

Dasa-PegIFN: Conclusions

- Peg-IFNa2b combined with dasatinib for first-line CP CML induces a high rate of deep molecular response (ie, MR4.5) during the first year of therapy.
- Toxicity profile is manageable:
  - 11 patients with Grade 3 or 4 neutropenia after 3 months of therapy; 2 cases of Grade 4 neutropenia after peg-IFNa2b initiation
  - 8 serious adverse events with the combination regimen, including pleural effusion (N = 1)
- Results at 12 months are in line with previous data combining Peg-IFNa and a tyrosine kinase inhibitor.

Roy L et al. *Proc ASH* 2015;Abstract 134.

The Impact of Ponatinib versus Allogeneic Stem Cell Transplant (SCT) on Outcomes in Patients with Chronic Myeloid Leukemia (CML) or Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) with the T315I Mutation

Nicolini FE et al.
Proc ASH 2015;Abstract 480.

Ponatinib versus Allogeneic Stem Cell Transplant (Allo SCT) for Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) with the T315I Mutation

- Indirect comparison of ponatinib, a multitargeted tyrosine kinase inhibitor (using data from the Phase II PACE trial) to allo SCT (using data from the EBMT database)
- N = 184 patients with CML and Ph+ ALL with the T315I mutation: N = 128 receiving ponatinib and N = 56 receiving allo SCT
- **Primary endpoint:** Overall survival (OS) for patients with the T315I mutation:

Leukemia type	Median OS ponatinib (mo)	Median OS allo SCT (mo)	HR	*p*-value
CP CML (N = 64, 26)	NR	103.3	0.37	0.013
AP CML (N = 18, 8)	NR	55.6	0.90	0.889
BP CML (N = 24, 17)	7.0	10.5	2.29	0.026
Ph+ ALL (N = 22, 5)	6.7	32.4	2.77	0.119

HR = hazard ratio; CP = chronic phase; NR = not reached; AP = accelerated phase; BP = blast phase

Nicolini FE et al. *Proc ASH* 2015;Abstract 480.

Ponatinib versus Allo SCT: Conclusions

- OS by leukemia type:
  - CP CML: Significantly longer with ponatinib; promising strategy
  - AP CML: Similar
  - BP CML and Ph+ ALL: Longer with allo SCT
- Results warrant consideration of ponatinib as an alternative to allo SCT for patients with T315I mutation-positive CP CML.
- Further study is needed.

Nicolini FE et al. *Proc ASH* 2015;Abstract 480.

Investigator Commentary: Ponatinib versus Allo SCT for Patients with CML or Ph+ ALL Harboring the T3151 Mutation

Because of the high rate of efficacy in terms of deep and durable remissions with tyrosine kinase inhibitors in CML, the use of allo SCT, formerly the standard approach for this condition, has declined sharply. However, some patients require SCT for CML, including those who present in blast crisis (and possibly accelerated phase) and those who do not respond to the available tyrosine kinase inhibitors.

Of particular difficulty is a secondary mutation of the BCR-ABL fusion gene. This mutation, the T3151 mutation, is inhibited by ponatinib, a "third-generation" tyrosine kinase inhibitor that is associated with worrisome vasculopathy. It is currently unknown whether patients who have a T3151 mutation should undergo allo SCT or should receive ponatinib. The retrospective study presented by Dr Nicolini and colleagues suggests that in comparison to allo SCT ponatinib therapy produces longer survival for patients with CML in chronic phase but is inferior for those in blast crisis with a T315I mutation.

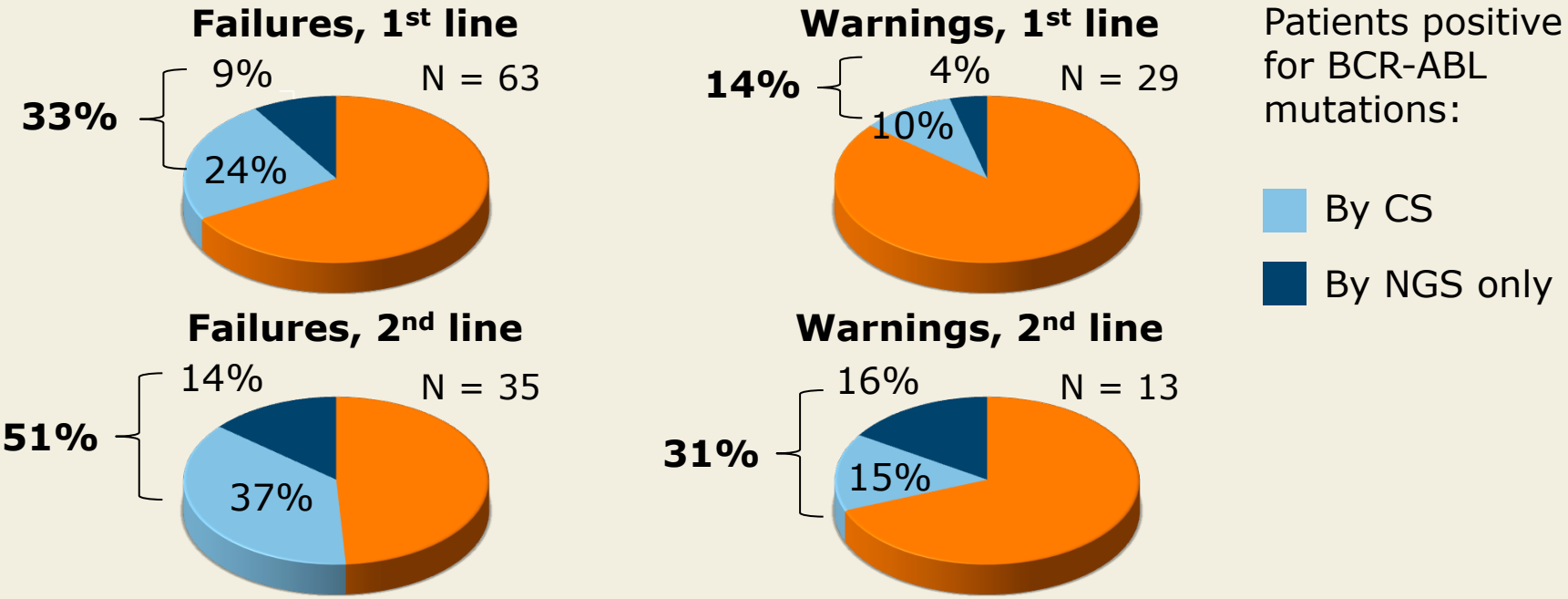
Interview with Richard M Stone, MD, February 16, 2016

BCR-ABL Mutations in Chronic Myeloid Leukemia (CML) Patients (pts) with Failure and Warning to First- and Second-Line Tyrosine Kinase Inhibitor (TKI) Therapy: What Is the Advantage of Next-Generation Sequencing (NGS) over Conventional Sequencing?

Soverini S et al.
Proc ASH 2015;Abstract 346.

Next-Generation Sequencing (NGS) for BCR-ABL Mutations in Chronic Myeloid Leukemia (CML)

- Samples were retrospectively analyzed by NGS
- N = 140 patients with CML and first- or second-line tyrosine kinase inhibitor (TKI) failures or warnings of impending treatment failure as defined by 2013 European LeukemiaNet recommendations
- **Primary endpoint**: Frequency of BCR-ABL mutations, NGS versus conventional Sanger sequencing (CS)



Soverini S et al. *Proc ASH* 2015;Abstract 346.

NGS for CML: Conclusions

- Most cases of CML are negative for BCR-ABL mutations even by NGS.
- NGS identified more BCR-ABL mutations than did CS.
  - Failures: 2 patients had T315I mutations missed by CS
  - Warnings: In 3 patients, NGS identified mutations that would have resulted in failures
    - 2 had T315I mutations missed by CS
- Suboptimal molecular response to first-line therapy was mostly NOT associated with BCR-ABL mutations.
- NEXT-IN-CML: An ongoing prospective NGS trial.
- Other mechanisms of molecular disease persistence should be investigated.

Soverini S et al. *Proc ASH* 2015;Abstract 346.

Key Papers in Acute and Chronic Leukemias, Myelodysplastic Syndromes and Myeloproliferative Neoplasms from ASH 2015

Acute myeloid leukemia/chronic myelomonocytic leukemia/ myelodysplastic syndromes (Abstracts 6, 322, 319, 321, 327, 453, 452, LBA-8323, 908, 91, 92)

Chronic myeloid leukemia (Abstracts 345, 133, 348, 344, 479, 134, 480, 346)

Myeloproliferative neoplasms (Abstracts 59, 58, 56, 823, 825, 826, 827, 824)

Acute lymphoblastic leukemia (Abstracts 1, 80, 679, 83)

Long-Term Efficacy and Safety in COMFORT-II, a Phase 3 Study Comparing Ruxolitinib with Best Available Therapy for the Treatment of Myelofibrosis: 5-Year Final Study Results

Harrison CN et al.

Proc ASH 2015;Abstract 59.

COMFORT-II Trial: Five-Year Follow-Up of Ruxolitinib (RUX) versus Best Available Therapy (BAT) in Myelofibrosis (MF)

- Five-year follow-up of a multicenter, open-label, randomized (2:1) Phase III study of RUX, a JAK inhibitor, versus BAT, with crossover (CO)
- N = 219 patients with intermediate 2- or high-risk MF:
  - N = 146 received RUX; N = 73 received BAT (45 crossed over)
- **Study objectives:** Five-year efficacy, safety

	RUX	BAT	BAT → RUX CO	5 y on study Tx
≥35% SVR	53% (78/146)	Not reported	42% (19/45)	67% (34/51)

SVR = spleen volume reduction

Harrison CN et al. *Proc ASH* 2015;Abstract 59.

COMFORT-II 5-Year Follow-Up: Conclusions

- Median overall survival (OS) with RUX versus BAT: Not reached versus 4.1 years (HR = 0.67; p = 0.06)
  - Adjusting for CO to RUX: Median OS with BAT 2.7 years (HR = 0.44)
- Bone-marrow fibrosis and JAK2 burden were improved with RUX compared to BAT.
- Longer-term safety was consistent with the 3-year report:

Reason for discontinuation, N (%)	RUX (n = 146)	BAT (n = 73)	RUX after CO (n = 45)
All combined	107 (73)	28 (38)	34 (76)
Adverse events (mainly low platelet counts, anemia)	35 (24)	5 (7)	10 (22)
Disease progression	32 (22)	4 (6)	7 (16)
Consent withdrawn	10 (7)	9 (12)	0
Other (including stem cell transplant)	16 (11)	9 (12)	6 (13)

- Five-year follow-up confirms the durability of RUX benefits.
- RUX treatment is being evaluated for early MF in the Phase III ReTHINK trial.

Harrison CN et al. *Proc ASH* 2015;Abstract 59.

Analysis of Outcomes by Patient Subgroups in Patients with Myelofibrosis Treated with Pacritinib vs Best Available Therapy (BAT) in the Phase III Persist-1 Trial

Vannucchi AM et al.

Proc ASH 2015;Abstract 58.

PERSIST-1 Trial Subgroup Analysis: Pacritinib (PAC) versus Best Available Therapy (BAT) in Myelofibrosis (MF)

- Subgroup analysis of PERSIST-1: Phase III, open label, randomized (2:1) study of PAC (a multikinase inhibitor including JAK2) versus BAT
- N = 327 patients with DIPSS intermediate-1, intermediate-2 or high-risk JAK inhibitor-naïve MF
- Spleen volume reductions (SVR) ≥35% demonstrated by previous analysis:
  - 25% with PAC, 5.9% with BAT at week 24 (p = 0.0001)

Conclusions:

- Treatment with PAC resulted in consistent rates of SVR ≥35% and Total Symptom Score (TSS) reduction ≥50% irrespective of baseline characteristics.
- Comparisons to BAT were favorable in all patient subpopulations examined for both SVR and TSS endpoints.
- These results support the use of PAC across all intermediate- or high-risk MF subgroups analyzed.

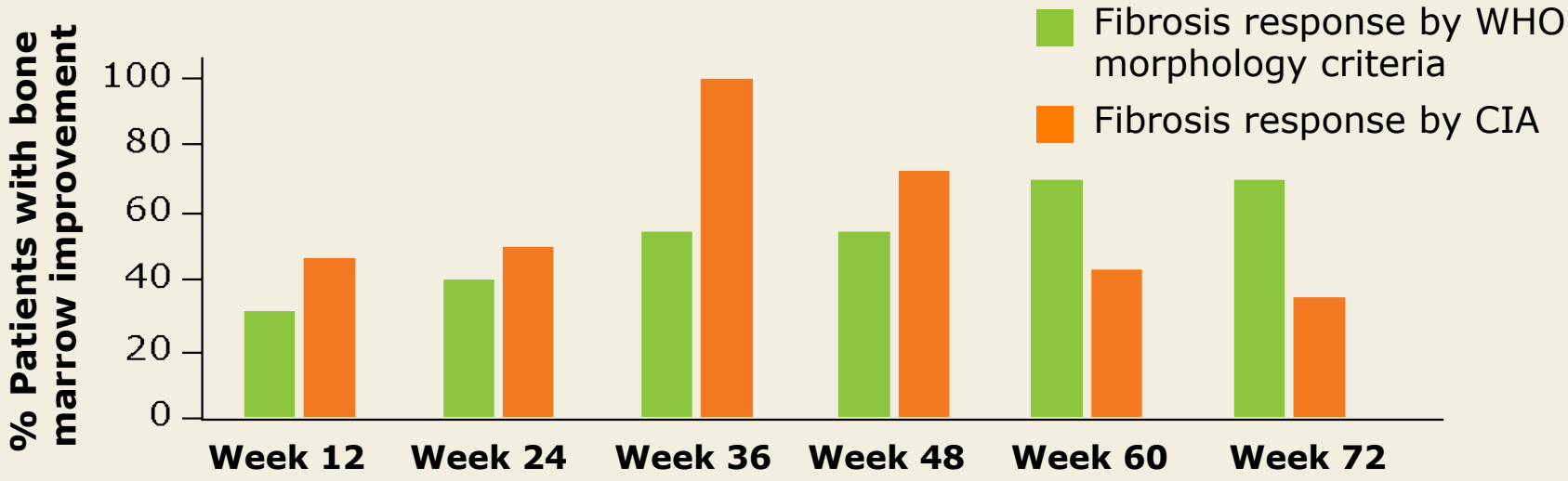
Vannucchi A et al. *Proc ASH* 2015;Abstract 58.

PRM-151 in Myelofibrosis: Durable Efficacy and Safety at 72 Weeks

Verstovsek S et al.
Proc ASH 2015;Abstract 56.

PRM-151 in Myelofibrosis (MF)

- First stage of a 2-stage adaptive trial evaluating PRM-151 (a recombinant pentraxin-2 protein that reverses fibrosis) 10 mg/kg IV x 24 wk in 4 arms: 2 single agent; 2 with ruxolitinib
- N = 13 patients with MF, originally with Grade 2 or 3 fibrosis, after 72 weeks of treatment (N = 5 received ruxolitinib)
- **Primary endpoint:** Fibrosis response by WHO and CIA criteria:



WHO criteria: Reduction in MF score by 1 grade at any time point
CIA (computer-assisted image analysis) criteria: Decrease in % fibrosis from baseline with negative slope >1

Verstovsek S et al. *Proc ASH* 2015;Abstract 56.

PRM-151 in MF: Conclusions

- Reductions in fibrosis were observed at week 12 and sustained at week 72.
- PRM-151 was well tolerated with few adverse events.
- Anemia and thrombocytopenia were improved:
  - If baseline hemoglobin <100 g/L,
    - Median hemoglobin increased
    - Need for red blood cell transfusions decreased
  - If baseline platelet count <100 x 10^9/L,
    - Median platelet count increased
    - Need for platelet transfusions decreased
- 62% of patients experienced a symptom score reduction of >50%, and 2 patients experienced a reduction in splenomegaly of >50%.
- Stage 2 of this study is currently enrolling.

Verstovsek S et al. *Proc ASH* 2015;Abstract 56.

Investigator Commentary: Efficacy and Safety of PRM-151 in MF

MF is a relatively intractable myeloproliferative disorder in which patients often experience anemia, decreased performance status, bone pain and problems due to splenomegaly caused by extramedullary hematopoiesis. The only reasonably effective therapy for MF is the JAK1/2 inhibitor ruxolitinib, which can reduce spleen size and improve quality of life and might be associated with improved overall survival. However, even ruxolitinib has not been shown to reliably decrease the degree of fibrosis found in the blood marrow of patients with this disease. PRM-151 is an antifibrotic agent that has been shown by Dr Verstovsek and colleagues to demonstrate some efficacy and safety in patients with MF who received this agent for 72 weeks. The initial results were encouraging. People experienced reductions in fibrosis in this short-term study.

A prospective randomized trial with large groups of patients is required to determine whether this drug will be used for patients with MF instead of or in addition to ruxolitinib. I'm cautiously optimistic about the ability of this agent to reverse the fibrosis and, therefore, improve outcomes for patients with this disease that is difficult to treat.

Interview with Richard M Stone, MD, February 18, 2016

5-Azacytidine (AZA) in Combination with Ruxolitinib (RUX) as Therapy for Patients (pts) with Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPNs)[1]

Phase 1b/2 Study of the Efficacy and Safety of Sonidegib (LDE225) in Combination with Ruxolitinib (INC424) in Patients with Myelofibrosis[2]

[1] **Daver N et al.**
Proc ASH 2015;Abstract 823.

[2] **Gupta V et al.**
Proc ASH 2015;Abstract 825.

Azacitidine (AZA) with Ruxolitinib (RUX) for Myelodysplastic Syndromes/ Myeloproliferative Neoplasms (MDS/MPN)

- Single-arm Phase II trial of RUX (a JAK inhibitor) 15 or 20 mg BID with AZA (a hypomethylating agent) IV 25 to 75 mg/m^2 on days 1 to 5 starting approximately at cycle 4
- N = 25 patients with unclassifiable MDS/MPN, chronic myelomonocytic leukemia or atypical chronic myeloid leukemia requiring therapy
- **Primary endpoint:** Clinical improvement (CI)

Characteristic	RUX + AZA (n = 25)
Objective responses, n/N (%)	12/25 (48)
CI spleen, n/N (%) ▪ After AZA addition	7/9 (78) 3/7 (43)
CI transfusion independence, n/N (%)	1/5 (20)
Marrow response, n/N (%) ▪ Partial ▪ Optimal	 5/12 (42) 1/12 (8)

Daver N et al. *Proc ASH* 2015;Abstract 823.

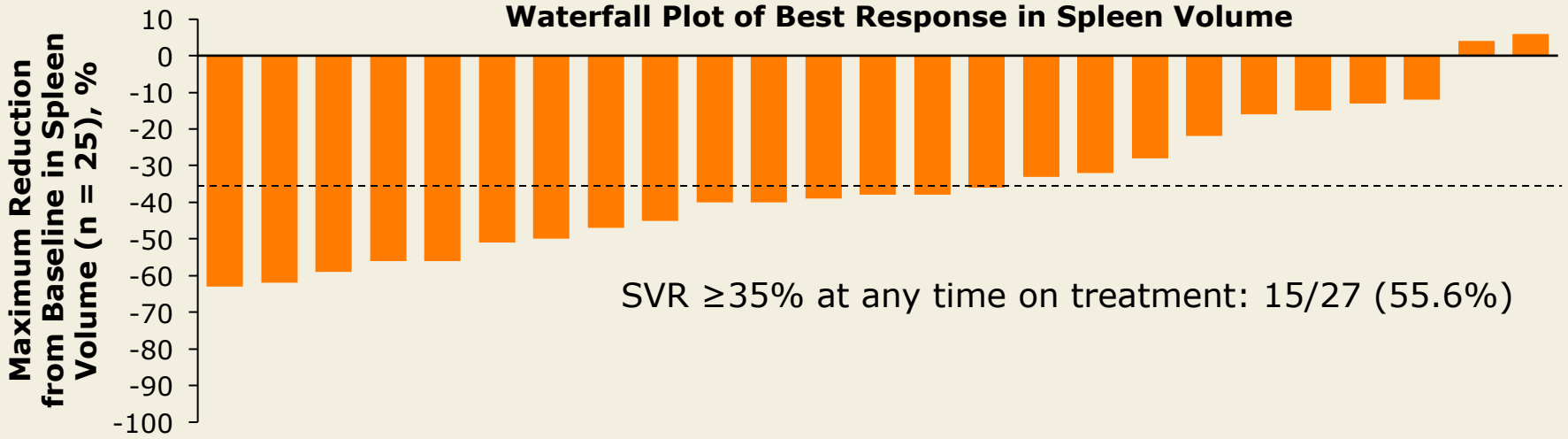
AZA with RUX for MDS/MPN: Conclusions

- Acceptable safety profile: Expected myelosuppression was the only significant toxicity.
- Response rate was higher for patients with JAK2 mutations than for those without: 5/6 (83%) versus 7/19 (37%), $p = 0.047$.
- Results warrant further evaluation of RUX in combination with AZA in larger, multicenter studies.

Daver N et al. *Proc ASH* 2015;Abstract 823.

Sonidegib (LDE225) with RUX in Myelofibrosis (MF)

- Phase Ib/II trial of sonidegib (a hedgehog pathway inhibitor) with RUX
- N = 27 patients with primary MF, postessential thrombocythemia MF or post-polycythemia vera MF
- **Primary endpoints:** Splenic volume reduction (SVR) and safety



- Adverse events (AEs) requiring dose adjustment or interruption include elevated creatine kinase and myalgia (n = 5 each)
- **Conclusion:** Sonidegib + RUX is well tolerated and active in MF

Gupta V et al. *Proc ASH* 2015;Abstract 825.

A Phase-Ib/II Study of Ruxolitinib plus Pomalidomide in Myelofibrosis[3]

An Open-Label, Multicenter, 2-Arm, Dose-Finding, Phase 1b Study of the Combination of Ruxolitinib and Buparlisib (BKM120) in Patients with Myelofibrosis: Results from HARMONY Study[4]

[3] **Stegelmann F et al.**
Proc ASH 2015;Abstract 826.

[4] **Durrant ST et al.**
Proc ASH 2015;Abstract 827.

POMINC (MPNSG02-12) Trial: RUX with Pomalidomide (POM) in MF

- Phase Ib/II trial of RUX with POM (an immunomodulatory drug)
- N = 28 patients with MF and anemia
- **Primary endpoint:** Response rate after 12 treatment cycles and red blood cell transfusion independence
- CI = 6/28 (21%)
  - Spleen size reduction, 14%; cytopenia improvement, 7%
  - Median time to response: 5 cycles (range, 2-14)
- Stable disease = 10/28 (36%); median number of cycles: 9 (range, 2-17)
- Mean hemoglobin count increased from 8.9 g/dL at baseline (n = 28) to 10.2 g/dL at cycle 12 (n = 5)
- 13 serious AEs; 3 related to treatment: neuropathy, anemia and increased liver enzymes
- Interim analysis planned after 37 patients: Higher POM dose to improve anemia response will be considered

Stegelmann F et al. *Proc ASH* 2015;Abstract 826.

HARMONY Trial: RUX with Buparlisib (BKM120) in MF

- Open-label, multicenter Phase Ib trial of RUX with buparlisib (a PI3K inhibitor)
- N = 42 patients with DIPSS intermediate- or high-risk MF and palpable splenomegaly ≥5 cm (n = 28 JAK mutation-positive)
- **Endpoints:** Maximum tolerated dose (MTD), safety and efficacy

At week 24	JAK inhibitor naïve (n = 22)	Prior JAK inhibitor (n = 20)
≥50% reduction in palpable spleen length at MTD	12 (54.5%)	4 (20%)

- MTD: RUX 15 mg BID + buparlisib 60 mg qd
- Grade 3 and 4 AEs at MTD included anxiety, multiorgan failure, anemia and thrombocytopenia
- The combination of RUX and buparlisib was generally well tolerated with clinically relevant efficacy

Durrant ST et al. *Proc ASH* 2015;Abstract 827.

Investigator Commentary: Activity and Safety of RUX-Based Combination Therapies for Patients with MDS/MPN

MF is a particularly difficult disease to treat. Patients develop fibrotic bone marrow that often leads to profound anemia. They have extramedullary hematopoiesis leading to splenomegaly that causes pain, early satiety and partial hypertension. Sclerotic bones elicit bone pain. These patients, particularly those with high-risk disease, often experience profoundly reduced quality and quantity of life.

The standard therapy for patients with MPN (60% have a JAK2 V617F mutation) is RUX, which is approved for patients with intermediate and high-risk MF and is useful for patients with disease harboring a JAK2 V617F mutation in addition to those with other genetic subtypes of this disease. Efforts to improve upon RUX alone have included the addition of a variety of agents.

continued

Investigator Commentary: Activity and Safety of RUX-Based Combination Therapies for Patients with MDS/MPN

At the ASH 2015 Annual Meeting several presentations involved the combination of the following agents with RUX: AZA (48% response rate but 40% rate of new Grade 3 or 4 cytopenia), the hedgehog pathway inhibitor sonidegib (most patients experienced at least a 25% reduction in spleen size, but 63% required a dose reduction or interruption due to increased creatine kinase or myalgia), the immunomodulatory agent POM and the PI3K/AKT inhibitor buparlisib (≥50% spleen-size reduction rates of 54.5% and 20% at MTD in RUX-naïve and RUX pre-exposed patients, respectively). None of these were "home runs," and randomized, controlled trials will be required to determine whether the addition of any of these agents to RUX will be better than RUX alone.

Interview with Richard M Stone, MD, February 16, 2016

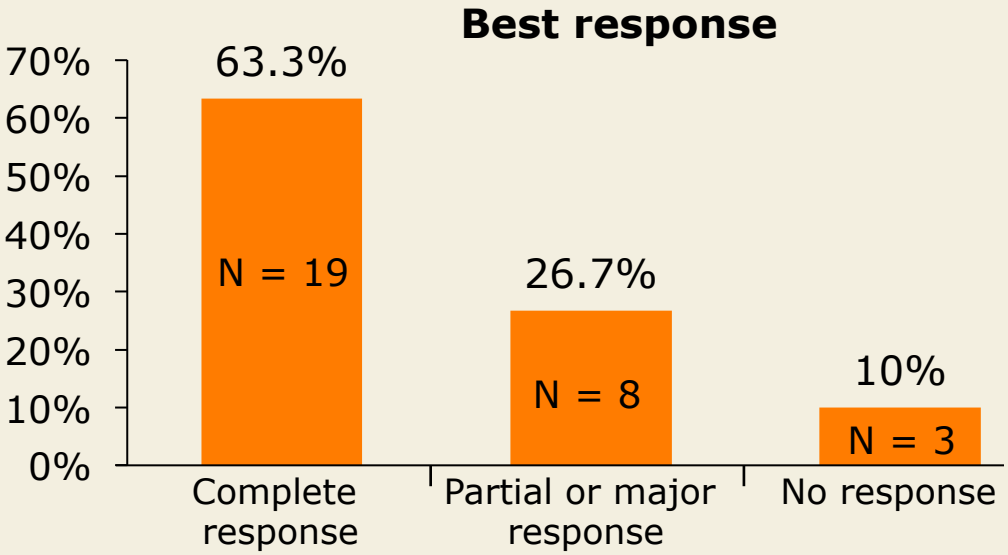
Safety and Efficacy of Combination Therapy of Interferon-Alpha2 + JAK1-2 Inhibitor in the Philadelphia-Negative Chronic Myeloproliferative Neoplasms. Preliminary Results from the Danish Combi-Trial — An Open Label, Single Arm, Non-Randomized Multicenter Phase II Study

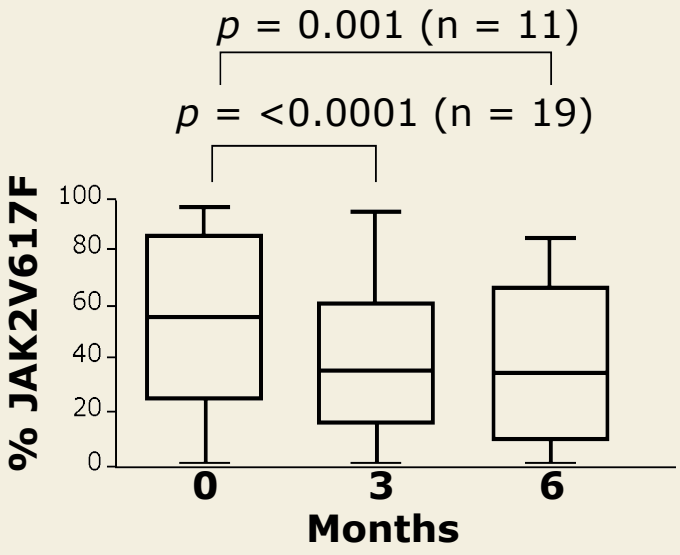
Mikkelsen SU et al.

Proc ASH 2015;Abstract 824.

COMBI-Trial: Interferon Alpha-2 (IFNa2) with Ruxolitinib (RUX) in Myeloproliferative Neoplasms (MPN)

- Open-label, single-arm, multicenter Phase II trial of pegylated IFNa2 weekly, subcutaneous 45 or 35 µg + RUX 20 mg BID
- N = 30 patients (N = 27 received previous IFNa2): N = 7 primary myelofibrosis (MF); N = 20 polycythemia vera (PV); N = 3 post-PV MF
- **Objectives:** Efficacy and safety with the combination regimen





IFNa2 + RUX is safe (most common adverse events were cytopenias) and highly effective even with previous intolerance to IFNa2.

Mikkelsen SU et al. *Proc ASH* 2015;Abstract 824.

Key Papers in Acute and Chronic Leukemias, Myelodysplastic Syndromes and Myeloproliferative Neoplasms from ASH 2015

Acute myeloid leukemia/chronic myelomonocytic leukemia/ myelodysplastic syndromes (Abstracts 6, 322, 319, 321, 327, 453, 452, LBA-8323, 908, 91, 92)

Chronic myeloid leukemia (Abstracts 345, 133, 348, 344, 479, 134, 480, 346)

Myeloproliferative neoplasms (Abstracts 59, 58, 56, 823, 825, 826, 827, 824)

Acute lymphoblastic leukemia (Abstracts 1, 80, 679, 83)

Addition of Rituximab Improves the Outcome of Adult Patients with CD20-Positive, Ph-Negative, B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL): Results of the Randomized Graall-R 2005 Study

Maury S et al.
Proc ASH 2015;Abstract 1.

GRAALL 2005 R Study: Rituximab in CD20-Positive Acute Lymphoblastic Leukemia (ALL)

- Randomized Phase III trial of chemotherapy with and without rituximab
- N = 209 patients aged <60 years with previously untreated CD20-positive, Philadelphia chromosome (Ph)-negative ALL
- **Primary endpoint:** Event-free survival (EFS)

Outcome at 2 years	Rituximab	No rituximab	HR	*p*-value
EFS rate	65%	52%	0.66	0.038
OS rate	71%	64%	0.70	0.095
Cumulative incidence of relapse	18%	32%	0.52	0.017

HR = hazard ratio; OS = overall survival

EFS was affected by age, CNS involvement and white blood cell count at diagnosis.

Maury S et al. *Proc ASH* 2015;Abstract 1.

GRAALL 2005 R: Conclusions

- The addition of rituximab to chemotherapy significantly improved EFS in CD20-positive B-cell ALL.
- Patients in the rituximab arm had a higher incidence of allogeneic stem cell transplant (SCT) in first complete response (CR1) (34% vs 20%; $p = 0.029$) and a lower 2-year cumulative incidence of relapse.
- The addition of rituximab to chemotherapy improves EFS and prolongs OS for patients not receiving SCT during CR1.
- Adding rituximab to chemotherapy should become the standard therapeutic approach for patients with CD20-positive, Ph-negative ALL.

Maury S et al. *Proc ASH* 2015;Abstract 1.

Investigator Commentary: The Addition of Rituximab to Therapy for Adult Patients with Ph-Negative B-Cell Precursor ALL

The Group for Research on Adult ALL (GRAALL) performed a study to determine whether the addition of rituximab to "pediatric-like" therapy improves results for patients with Ph-negative B-cell ALL. This work was based on prior efforts by investigators at The University of Texas MD Anderson Cancer Center who performed nonrandomized trials showing that the addition of rituximab to hyper-CVAD improved outcomes in comparison to historical controls.

This prospective, randomized trial added between 16 and 18 doses of rituximab (or nothing) to the previously reported GRAALL pediatric-like therapy and showed an improvement in EFS and OS (censored for transplant) for patients randomly assigned to rituximab. This may be considered a practice-changing study in that it now may be important to add rituximab to chemotherapy for pre-B-cell ALL.

Interview with Richard M Stone, MD, February 16, 2016

A Multicenter Phase II Study Using a Dose Intensified Pegylated-Asparaginase Pediatric Regimen in Adults with Untreated Acute Lymphoblastic Leukemia: A DFCI ALL Consortium Trial

DeAngelo DJ et al.
Proc ASH 2015;Abstract 80.

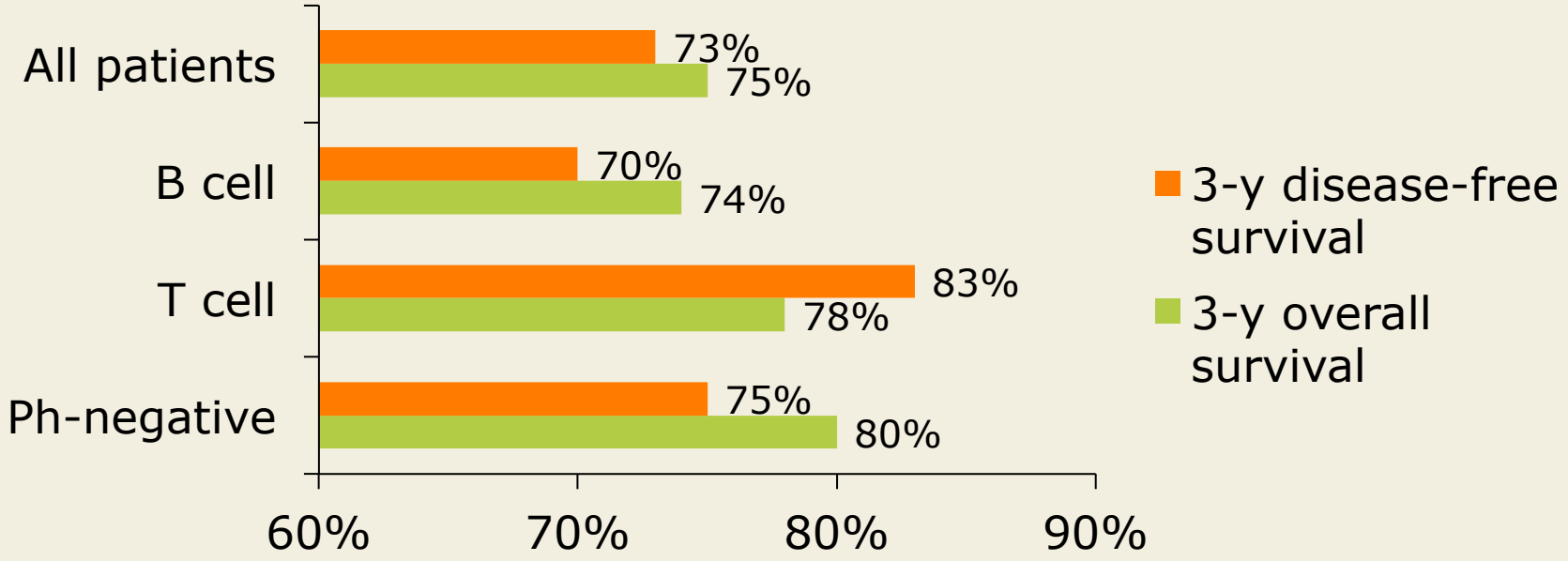
DFCI ALL Consortium Trial: Pediatric Regimen for Adults with Acute Lymphoblastic Leukemia (ALL)

- Phase II single-arm trial using a dose-intensified pegylated-asparaginase (peg-asp)-based pediatric regimen including 30 weeks of IV peg-asp initially dosed at 2,500 IU/m^2 every 2 weeks
- **Due to high toxicity, mainly hyperbilirubinemia, the original dose of IV peg-asp was changed to native *E. coli* asp 25,000 IU/m^2 IM once during induction and peg-asp 2,000 IU/m^2 every 3 weeks during consolidation**
- N = 110 patients aged 18 to 50 with untreated ALL; N = 65 received original IV peg-asp, N = 45 received subsequent asp dose
- **Primary endpoint:** Feasibility
  - Adverse events: 2 deaths (sepsis, CNS hemorrhage), pancreatitis (N = 4), allergic reaction to the asp (N = 14), osteonecrosis (N = 12), bone fracture (N = 2), thrombosis/embolism (N = 13), Grade 3 or 4 neutropenic infection (N = 32)

DeAngelo D et al. *Proc ASH* 2015;Abstract 80.

DFCI ALL Consortium Trial: Conclusions

- The dose and schedule of peg-asp that is well tolerated in adults is lower and less frequent than that for pediatric patients.
- Efficacy is better than expected for an adult population; longer follow-up is needed.



DeAngelo D et al. *Proc ASH* 2015;Abstract 80.

Investigator Commentary: Results from a Phase II Study of a Dose-Intensified Peg-Asp Pediatric Regimen for Adults with Untreated ALL

Approximately 15 years ago it was recognized that adolescents and young adults under the care of pediatric oncologists fared better than similarly aged patients under the care of adult oncologists. The reasons for this discrepancy could have been different patient psychosocial factors, different biological characteristics of the 2 groups, different physician familiarity with the regimens or differences in the regimens themselves. Pediatric regimens included much heavier use of nonmyelosuppressive drugs such as vincrinstine, steroids, L-asparaginase and intrathecal therapy. Several attempts have been made to use “pediatric-inspired” or “pediatric-like” therapy for adolescents and young adults with Philadelphia chromosome-negative ALL, and the Dana-Farber Cancer Institute (DFCI) ALL Consortium, led by Dr DeAngelo, has been a leader in this effort. Dr DeAngelo reported the Consortium’s results for patients 18 to 50 years receiving a second iteration of therapy modeled closely on the successful pediatric therapy employed by the Consortium.

continued

Investigator Commentary: Results from a Phase II Study of a Dose-Intensified Peg-Asp Pediatric Regimen for Adults with Untreated ALL

The pediatric-like regimen consisted of standard pediatric induction followed by 3 early consolidation cycles, CNS prophylaxis, a consolidation block including 10 doses of peg-asp and maintenance therapy for 2 years from remission. The results were good with approximately 70% 3-year disease-free and overall survival rates.

Younger patients and nonobese patients fared better than older and obese patients. Although no prospective randomized data are available comparing adult regimens such as hyper-CVAD to this type of pediatric-like therapy, many believe that pediatric-like therapy should now be the standard approach for adults up to age 40 with Philadelphia-negative ALL.

Interview with Richard M Stone, MD, February 16, 2016

Complete Molecular and Hematologic Response in Adult Patients with Relapsed/Refractory (R/R) Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia (ALL) Following Treatment with Blinatumomab: Results from a Phase 2 Single-Arm, Multicenter Study (ALCANTARA)

Martinelli G et al.

Proc ASH 2015;Abstract 679.

ALCANTARA Trial: Blinatumomab in Relapsed/Refractory (R/R) Philadelphia Chromosome-Positive (Ph+) B-Cell Acute Lymphoblastic Leukemia (ALL)

- Phase II, single-arm, multicenter study of blinatumomab, an anti-CD19 targeted, bispecific T-cell engaging antibody construct
- N = 45 patients with Ph+ B-cell ALL
  - Resistant to a second- or third-generation tyrosine kinase inhibitor (TKI): n = 44
  - Never exposed to a second- or third-generation TKI but resistant to imatinib: n = 1
- **Primary endpoint:** Complete response (CR) or CR with partial hematologic recovery (CRh)
- CR/CRh (all patients): 16/45 (36%)
  - T315I mutation: 4/10 (40%)
  - ≥2 prior second-generation TKIs: 11/27 (41%)
  - Prior ponatinib: 8/23 (35%)
  - Age 18 to <55 years: 8/22 (36%); age ≥55 years: 8/23 (35%)
- Median overall survival (n = 45): 7.1 months
- Median recurrence-free survival (RFS) (n = 16): 6.7 months

Martinelli G et al. *Proc ASH* 2015;Abstract 679.

ALCANTARA: Conclusions

- Adverse events were consistent with those previously reported with blinatumomab for R/R Ph-negative ALL:
  - Cytokine release syndrome (n = 4, any grade), neurologic events (n = 21, any grade; n = 3, Grade 3)
  - Grade ≥3 treatment-emergent adverse events (n = 37) included febrile neutropenia (12), thrombocytopenia (10) and anemia (7)
- Single-agent blinatumomab demonstrates antileukemic activity in patients with Ph+ R/R ALL after failure of 2nd- or 3rd-generation TKI, with a CR/CRh rate of 36%.
- Hematologic and molecular responses were independent of mutational status, including the T315I mutation.
- For patients <55 and ≥55 years of age:
  - Equivalent CR/CRh rates
  - Equivalent median RFS (5.5 mo vs 6.7 mo)
- Among responders, 88% (14/16) achieved minimal residual disease-negative status.

Martinelli G et al. *Proc ASH* 2015;Abstract 679.

Investigator Commentary: Results of a Phase II Trial of Blinatumomab in Adult Patients with R/R Ph+ B-Precursor ALL

The bispecific antibody blinatumomab has been approved for use in R/R Philadelphia chromosome-negative ALL. This antibody, which physically brings T cells together with CD19-positive lymphoblasts, has been highly effective in both advanced-disease and minimal residual disease settings. Although blinatumomab is known to have activity in Ph+ B-cell ALL, this study shows the potential value of using it in R/R Ph+ disease, yielding a 36% CR/CRh rate.

Interview with Richard M Stone, MD, February 16, 2016

Frontline Inotuzumab Ozogamicin in Combination with Low-Intensity Chemotherapy (mini-hyper-CVD) for Older Patients with Acute Lymphoblastic Leukemia (ALL)

Jabbour E et al.

Proc ASH 2015;Abstract 83.

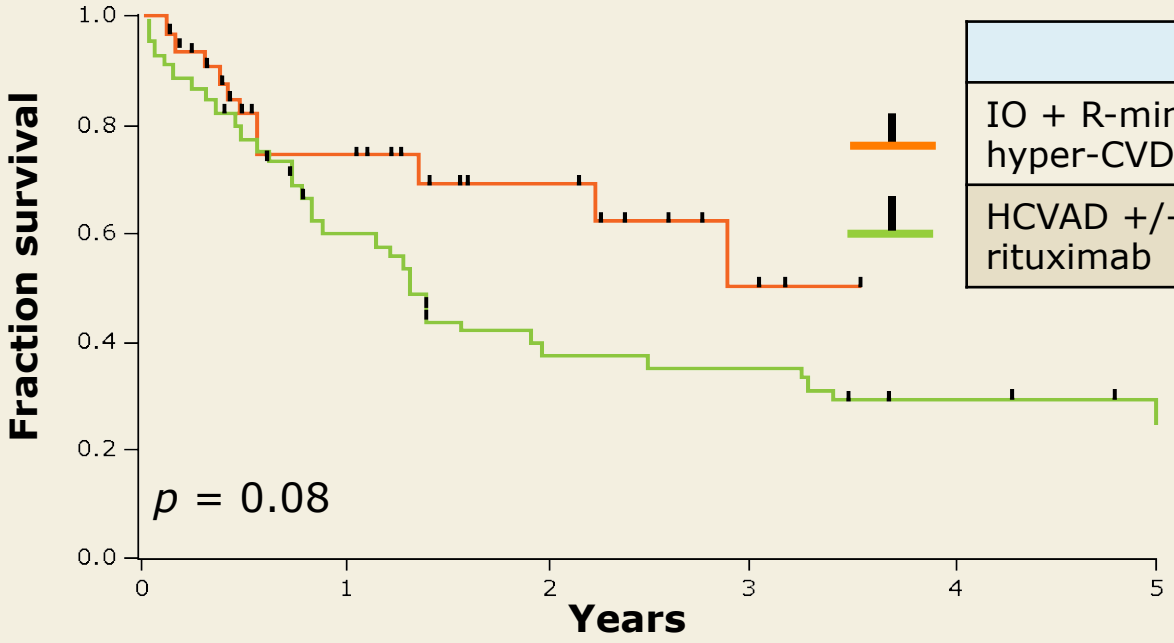
Inotuzumab Ozogamicin (IO) with R-Mini-Hyper-CVD for Older Patients with Acute Lymphoblastic Leukemia (ALL)

- Single-arm trial of IO, an antibody-drug conjugate targeting CD22, with R-mini-hyper-CVD (rituximab/ cyclophosphamide/dexamethasone/methotrexate/ cytarabine)
- N = 34 patients aged ≥60 years with untreated B-cell ALL
- **Endpoints:** Efficacy and safety
- Complete response with and without platelet recovery: 30 of 31 evaluable patients (97%)
- Safety: Grade 3 and 4 toxicities in ≥10% of patients included prolonged thrombocytopenia (n = 27), infections during induction therapy (n = 18), infections during consolidation therapy (n = 25), hyperglycemia (n = 17), hypokalemia (n = 12), hyperbilirubinemia (n = 8), veno-occlusive disease (n = 4)

Jabbour E et al. *Proc ASH* 2015;Abstract 83.

IO with R-Mini-Hyper-CVD for Older Patients with ALL: Conclusions

- Two-year progression-free survival and overall survival (OS) rates were 87% and 70%.
- R-mini-hyper-CVD appears to be superior to the historical HCVAD with or without rituximab in a similar patient population (2-year OS 38%).



	Median	2-y OS
IO + R-mini-hyper-CVD	Not reached	70%
HCVAD +/- rituximab	16 mo	38%

- Results appear better than those with chemotherapy alone: IO with R-mini-hyper-CVD may become the new standard up-front treatment for older patients with ALL.

Jabbour E et al. *Proc ASH* 2015;Abstract 83.

Investigator Commentary: IO with Mini-HYPER-CVD as Front-Line Therapy for Older Patients with ALL

The optimal therapy for older adults with Philadelphia chromosome-negative ALL remains controversial. Many physicians use a dose-reduced legacy regimen such as that from the CALGB-9111 trial or mini-hyper-CVAD. The results with these regimens are poor, with long-term survival rates for adults older than age 60 no higher than 20%. The addition of an antibody-toxin conjugate such as the anti-CD22 targeted agent IO is feasible and led to favorable outcomes, as suggested by this abstract presented by Dr Jabbour. Randomized trials will be required to prove the value of adding IO to a dose-reduced, adult ALL regimen for this age cohort of patients with ALL.

Interview with Richard M Stone, MD, February 16, 2016