5 Minute JournalClub

Key ASH Presentations

Issue 8, 2011

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CME Information

LEARNING OBJECTIVES

- Recall the dose-limiting toxicity and preliminary clinical response results with 14- and 21-day extended treatment schedules of daily oral azacitidine.
- Apply new research findings with azacitidine to the evidence-based treatment of secondary MDS.
- Recall the effects of pretransplant azacitidine on hematopoietic cell transplantation outcomes in MDS and CMML.
- Recall the activity and tolerability of single-agent lenalidomide in older patients with del(5q) AML not eligible for intensive chemotherapy.
- Describe the activity and tolerability of the combination of lenalidomide and intensive chemotherapy in patients with higher-risk MDS or AML with del(5q).
- Appraise the early safety and efficacy of arsenic trioxide and chemotherapy as consolidation in APL.
- Evaluate ATRA with arsenic trioxide as an option for induction in standard-risk APL.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Guillermo Garcia-Manero, MD
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No real or apparent conflicts of interest to disclose.

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Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation; *Paid Research:* Eisai Inc, Infinity Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Synta Pharmaceuticals Corp.

Evaluation of Oral Azacitidine Using Extended Treatment Schedules: A Phase I Study

Garcia-Manero G et al.

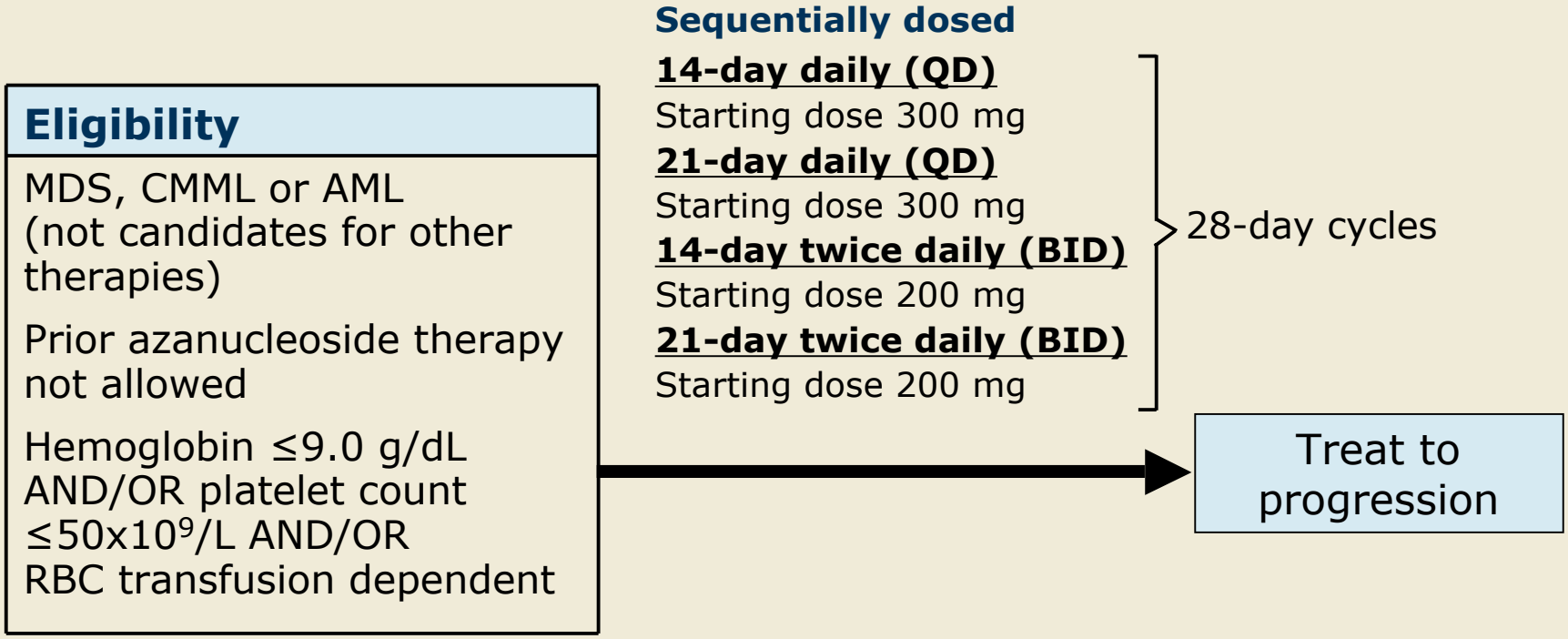
Proc ASH 2010;Abstract 603.

Background

- Parenteral azacitidine (AZA) has a short half-life in the plasma, and its incorporation into cellular DNA is restricted to the S-phase of the cell cycle.
- An oral formulation of AZA would allow for chronic daily exposure that may enhance the clinical activity of AZA in a form that is conveniently administered.
- An initial Phase I study of oral AZA administered on days 1-7 of a 28-day treatment schedule in patients with MDS and AML demonstrated that the agent was bioavailable, safe and clinically active (*Proc ASH* 2009;Abstract 117).
- **Current study objective**:
  - Assess the response and safety of extended 14- and 21-day oral AZA treatment schedules in patients with MDS, CMML or AML.

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Phase I Study of Extended Treatment Schedules of Oral AZA



Patients were enrolled in cohorts of 6 and evaluated for dose-limiting toxicities (DLTs) at the end of cycle 1.
Patients were monitored continuously for adverse events, and disease response was assessed at the end of every second cycle.

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Baseline Characteristics

	N = 25
Median age, years (range)	68 (44-87)
Male/female	14/11
Number of patients with MDS	13
Number of patients with AML	7 (de novo) 3 (transformed)
Number of patients with CMML	2
Prior treatment	10

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

DLT Summary

- With 14-day QD oral AZA schedule, two DLTs occurred in 1 of 6 DLT-evaluable patients.
  - Grade 3 nausea and vomiting
- No DLTs observed in the 21-day QD (n = 6) or in the 14-day BID (n = 6) schedules.
- Three DLTs occurred in 1 of 6 evaluable patients in the 21-day BID schedule group.
  - Grade 3 weakness, fatigue and total body pain
- The maximum tolerated dose has not been reached on any of the schedules.
- No patient has received greater than 300 mg/dose.

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Preliminary Response of Oral AZA in MDS/CMML

Parameter	MDS/CMML Responders/Evaluable Patients			
	14-day QD	21-day QD	14-day BID	21-day BID
Overall response (CR, marrow CR, any hematologic improvement [HI])*	4/6	3/3	3/3	0/3
HI-Erythroid	1/2	0	1/2	0/2
HI-Platelet	1/5	3/3	0/3	0/2
HI-Neutrophil	0/1	1/1	0/2	0/1
Transfusion independence	3/5	2/2	2/3	0

* IMWG 2006 criteria

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Relevant Grade 3/4 Adverse Events

Adverse Event, n (%)	14-day QD (n = 7)	21-day QD (n = 6)	14-day BID (n = 6)	21-day BID (n = 6)
Febrile neutropenia	2 (29)	4 (67)*	2 (33)	1 (17)
Diarrhea	0	1 (17)	0	1 (17)
Nausea	1 (14)	1 (17)	1 (17)	1 (17)
Vomiting	1 (14)	0	0	0
Fatigue	0	0	0	1 (17)

* Observed in three patients with baseline absolute neutrophil count < 0.5 x 10^9/L and/or AML diagnosis

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Author Conclusions

- Prolonged administration of oral AZA is feasible and generally well tolerated.
- Compared to standard subcutaneous administration, oral AZA 300 mg over 21 days provides a cumulative exposure of approximately 58% per cycle (data not shown).
- Oral AZA induces global hypomethylation (data not shown).
- Oral AZA is clinically active in patients with MDS/CMML (67% response rate, 10/15 patients).
- Studies of oral AZA for the treatment of lower-risk disease are planned.

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Investigator Commentary: Extended treatment schedules with oral azacitidine

Patients often complain about having to visit the clinic seven days a month to receive their shots, and they eventually experience associated skin reactions. Last year, we showed oral azacitidine as being significantly active in patients with MDS, with a CR of almost 60 percent, even at very low PK, and having a good safety profile in patients with AML and MDS.

We hypothesized that if we could safely administer the agent for seven days, we could expand the schedule to two or three times per day for 14 or 21 days. We demonstrated quite a bit of activity with some of these schedules, which we found also to be safe, but most importantly, we found that the oral, low-dose approach was extremely effective in both lower- and higher-risk MDS.

I am excited about this approach because this could be a major breakthrough in the use of hypomethylating agents, whether in combination with chemotherapy, in maintenance therapy or as treatment for low, intermediate-1 MDS. We are now planning a Phase II analysis of oral azacitidine in low or intermediate-1, non del 5q MDS.

Interview with Guillermo Garcia-Manero, MD, January 12, 2011

Therapeutic Response to Azacitidine (AZA) in Patients with Secondary Myelodysplastic Syndromes (sMDS) Enrolled in the AVIDA Registry

Sekeres MA et al.

Proc ASH 2010;Abstract 2931.

Background

- Approximately 10% of patients with myelodysplastic syndromes (MDS) have MDS secondary to chemotherapy, radiation therapy or environmental exposure (*J Natl Cancer Inst* 2008;100:1542).
- Patients with secondary MDS (sMDS) have a poor prognosis and are often refractory to treatment (*J Clin Oncol* 2007;25:4285).
- A randomized, international, multicenter, open-label trial for patients with higher-risk MDS reported that azacitidine significantly improved overall survival compared to conventional care regimens (*Lancet Oncol* 2009;10:223).
- Patients with sMDS have been excluded from clinical trials and the effects of azacitidine in sMDS are unknown (*J Clin Oncol* 2002;20:2429).

Sekeres MA et al. *Proc ASH* 2010;Abstract 2931.

AVIDA Registry

- Data from patients with MDS treated with azacitidine in a community setting were collected at registry entry (baseline) and then quarterly using electronic data capture.
- Treating physicians determined azacitidine dose, dosing schedule and treatment duration.
- Baseline characteristics of patients with secondary MDS and primary MDS were evaluated.
- Rates of hematologic improvements and transfusion independence were assessed.

Sekeres MA et al. *Proc ASH* 2010;Abstract 2931.

Baseline Characteristics

	Secondary MDS (n = 37)	Primary MDS (n = 380)
Time from Diagnosis (Median)	1 month	3 months
Median Age	71 years	75 years
Higher-Risk IPSS	55%	30%
Poor Cytogenetics	59%	17%
Chromosome 7 Abnormalities	47%	11%
2-3 Cytopenias	76%	62%
Infections Requiring IV Antibiotics	41%	16%

Sekeres MA et al. *Proc ASH* 2010;Abstract 2931.

Response Assessment

IWG 2000 Response	Secondary MDS (n = 37*)	Primary MDS (n = 380*)
Hematologic Improvement (HI) or Better	21/35 (60%)	226/369 (61%)
Major HI-Erythroid[1]	14/32 (44%)	157/343 (46%)
Major HI-Platelet[1]	12/29 (41%)	94/206 (46%)
Major HI-Neutrophil[1]	8/28 (29%)	48/195 (25%)
Transfusion Independence		
RBC Transfusion Independence[2]	12/21 (57%)	121/197 (61%)
Platelet Transfusion Independence[2]	4/8 (50%)	32/50 (64%)

* Patients on study for <56 days were not evaluable for hematological improvement.

[1] Individual cell line denominators include only patients evaluable for improvement

[2] Denominators include only patients who were transfusion dependent at baseline (ie, received at least 1 transfusion in the 56 days prior to the start of AZA dosing)

Sekeres MA et al. *Proc ASH* 2010;Abstract 2931.

Author Conclusions

- Patients with secondary MDS treated with azacitidine had rates of hematologic improvement or better and RBC/platelet transfusion independence comparable to those of patients with primary MDS despite worse pretreatment disease characteristics.
- Azacitidine treatment patterns were similar in secondary MDS and primary MDS (data not shown).
- Azacitidine was well tolerated by patients with secondary MDS and primary MDS (data not shown).
- A diagnosis of secondary MDS should not preclude treatment with the disease-modifying drug azacitidine.

Sekeres MA et al. *Proc ASH* 2010;Abstract 2931.

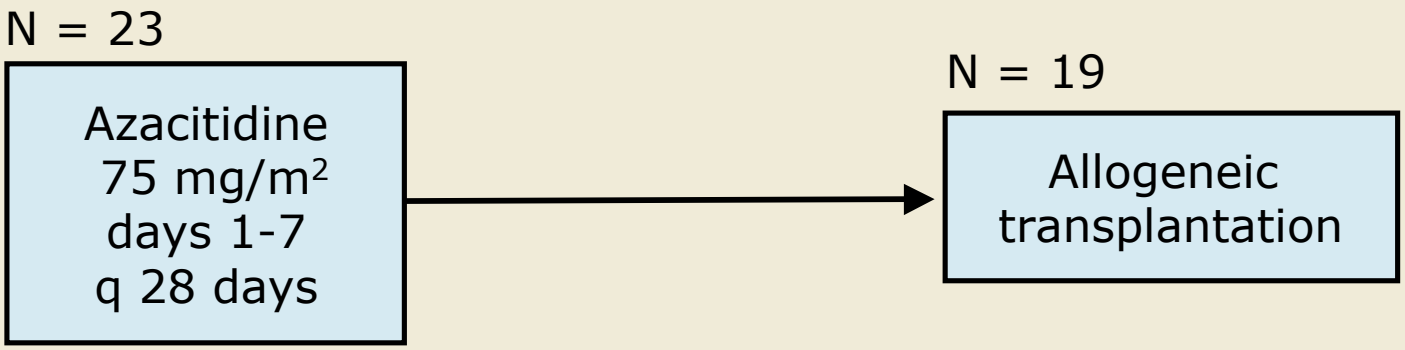
Prospective Trial of Pre-Transplant 5-Azacitidine on Hematopoietic Cell Transplantation Outcomes for Myelodysplastic Syndrome and CMML

Field T et al.

Proc ASH 2010;Abstract 1333.

Prospective Study Schema*

Eligibility: MDS/CMML being evaluated for allogeneic transplantation



Four did not proceed to transplant:

1. Failure to obtain insurance approval due to patient age
2. Failure of the pre-transplant organ evaluation although a donor was identified
3. CNS hemorrhage in setting of chronic anticoagulation five days prior to transplant admission
4. One patient (62 years) declined transplant as only an HLA-A mismatched donor was available

* Prior retrospective analysis reported no adverse effects of pre-transplant 5-azacitidine on subsequent allogeneic hematopoietic cell transplantation outcomes (*Bone Marrow Transplant* 2010;45:255)

Field T et al. *Proc ASH* 2010;Abstract 1333.

Efficacy Outcomes (from Abstract)

Response to Azacitidine Prior to Transplant (n = 19)	
Partial Response	42%
Stable Disease	47%
Disease Progression	11%

Post-Transplant Outcome (n = 19)	
Relapsed or No Remission	3/19 (16%)
Nonrelapse Deaths	3/19 (16%)
One-Year Survival	69%
One-Year Disease-Free Survival	63%

Field T et al. *Proc ASH* 2010;Abstract 1333.

Author Conclusions

- Pre-transplant 5-azacitidine is well tolerated (data not shown).
- Pre-transplant 5-azacitidine provides control of disease as a bridge to allogeneic transplant and did not impose additional toxicity after allogeneic transplant.
  - Promising 1-year progression-free survival
- Controlled trials are needed to determine whether post-transplant relapse and survival are improved by pre-transplant 5-azacitidine.

Field T et al. *Proc ASH* 2010;Abstract 1333.

Investigator Commentary: Azacitidine for Secondary MDS and as a Bridge to Allogeneic Transplant

The presentation by Sekeres shows that therapy with azacitidine results in similar responses in therapy-related or secondary MDS when compared to primary MDS. This is quite interesting as the results are different from those with traditional chemotherapy, which does not work well in secondary MDS/AML. I believe that these results should affect practice. In the past, we were discouraged when a patient was diagnosed with therapy-related MDS. These data suggest that you should not be approaching these patients differently than those with primary MDS.

The prospective evaluation by Field regarding pretransplant azacitidine for MDS shows that the strategy of bridge therapy with azacitidine before definitive potentially curative therapy with allogeneic transplantation is feasible and safe. Another take-home message is the lack of effect on transplant-related toxicity. This strategy can buy time for patients while the national registries are being searched to find an appropriate donor for the transplant.

Interview with B Douglas Smith, MD, January 4, 2011

A Phase II Study of Lenalidomide for Previously Untreated Deletion (del) 5q Acute Myeloid Leukemia (AML) Patients Age 60 or Older Who Are Not Candidates for Remission Induction Chemotherapy (Southwest Oncology Group Study S0605)

Sekeres MA et al.

Proc ASH 2010;Abstract 332.

Background

- Older patients (≥60 years) with AML have a poor prognosis.
  - Majority of these patients never receive chemotherapy
  - Many have antecedent myelodysplastic syndromes (MDS)
  - 20-30% harbor chromosome 5 abnormalities
- Phase II studies have shown that lenalidomide results in hematologic responses in patients with MDS and the del(5q) cytogenetic abnormality.
  - 67% hematologic response in lower-risk MDS (*Proc ASH* 2006;Abstract 251)
  - 27% hematologic response in higher-risk MDS (*Blood* 2009;113:3947)

Sekeres MA et al. *Proc ASH* 2010;Abstract 332.

SWOG-S0605: A Phase II Study of Lenalidomide for Newly Diagnosed Del(5q) AML

Eligibility

Newly diagnosed AML; ≥60 years; not eligible for intensive induction therapy

Chromosome 5 or 5q interstitial deletion either alone or with additional abnormality of complex karyotype (≥3 abnormalities)

Remission induction (n = 37)
Lenalidomide 50 mg PO daily x 28 days

- 8 disease progression
- 7 nonfatal toxicity
- 7 died
- 1 hospice

→ 14 patients with stable disease after induction →

Post-remission (n = 8)
Lenalidomide 10 mg/day x 21 days
q 28 day cycles

Primary endpoint: Overall response rate (CR + CRi + PR)

Sekeres MA et al. *Proc ASH* 2010;Abstract 332.

Efficacy Outcomes

	N = 37
Overall Response Rate CR/CRi/PR	5/37 (14%) 2/2/1
Time to relapse (median)	5 months
Survival (median)	15 months

Sekeres MA et al. *Proc ASH* 2010;Abstract 332.

Baseline Characteristics of All Study Patients versus Responding Patients

Characteristic	All study patients (n = 37)	Responding patients (n = 5)
Median age	74 yrs	68 yrs
Female/male	21/16	2/3
Prior MDS diagnosis	19 (51%)	3 (60%)
Cytogenetic abnormalities		
Isolated del(5q) - FISH	2 (7%)	—
Isolated del(5q) - MC	5 (17%)	2 (40%)
Complex	23 (77%)	3 (60%)

MC = metaphase cytogenetics

Sekeres MA et al. *Proc ASH* 2010;Abstract 332.

Select Adverse Events

Grade ≥3 adverse event	Lenalidomide (N = 37)
Fatigue	30%
Febrile neutropenia	41%
Lung infections	14%
Muscle weakness, whole body	8%

Sekeres MA et al. *Proc ASH* 2010;Abstract 332.

Author Conclusions

- Lenalidomide as a single agent has modest activity and expected toxicity in older patients with del(5q) AML.
  - Current study demonstrates about one half the rate of response previously shown with single-agent lenalidomide in a similar population (*Blood* 2011;117:1828).
- Higher doses used in induction therapy may overcome cytogenetic abnormalities beyond del(5q).

Sekeres MA et al. *Proc ASH* 2010;Abstract 332.

Investigator comment on single-agent lenalidomide for older patients with (del)5q AML

This study shows that single-agent lenalidomide has only modest activity in older patients with (del)5q AML. I believe this study was well done and showed expected toxicities and some activity. This is a small group of patients, with a small proportion achieving remissions. Maybe this drug should be combined with either cytotoxic or other targeted therapies in the future. By itself, it is clearly not very effective.

I would currently caution about putting this into practice right away and don't believe that there are enough data to indicate that it works that well. The best responses they saw, or the most significant ones, are mostly stable disease.

Interview with B Douglas Smith, MD, January 4, 2011

Lenalidomide (LEN) Combined to Intensive Chemotherapy (IC) in AML and Higher Risk MDS with Del 5q. Results of a Phase I/II Study of the Groupe Francophone des Myelodysplasies (GFM)

Ades L et al.

Proc ASH 2010;Abstract 508.

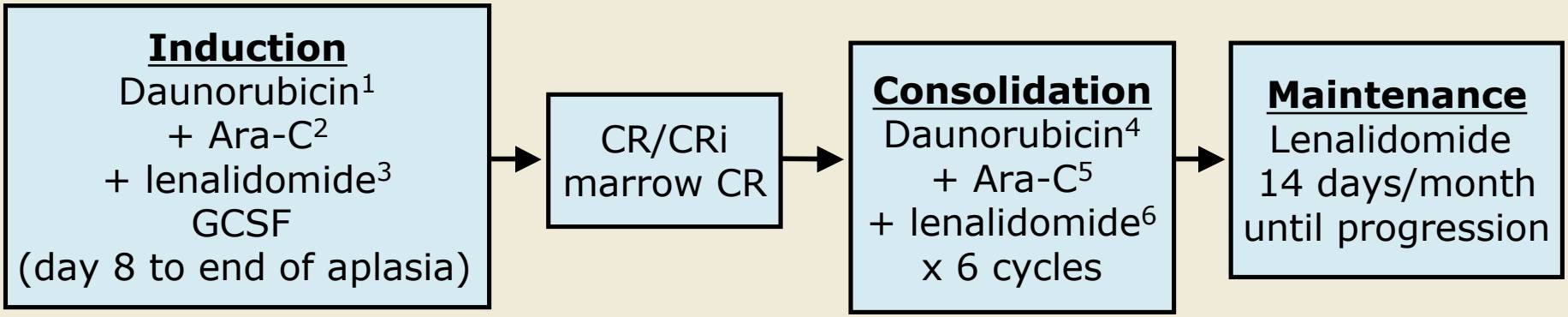
Background

- Prognosis of myelodysplastic syndrome (MDS) with del(5q) with increased bone marrow blast % and/or additional cytogenetic abnormalities and of acute myeloid leukemia (AML) with del(5q) (isolated or complex) is poor.
- del(5q) is present in 40-50% of higher-risk MDS and AML with complex karyotype.
- These patients respond poorly to intensive chemotherapy with only 20-30% complete remission (CR) rates, of short duration (*Hematologica* 2000;85:246).
- Lenalidomide administration leads to frequent cytogenetic CR in lower-risk MDS with del(5q).
- In a recent Phase II study of lenalidomide in higher-risk MDS or AML with del(5q), 27% of patients achieved hematologic responses, some with cytogenetic responses but with significant myelosuppression (*Blood* 2009;113:3947).

Ades L et al. *Proc ASH* 2010;Abstract 508.

Phase II Study Schema

Eligibility: High-risk MDS or AML with del(5q)



[1] Daunorubicin 45 mg/m^2/day, days 1-3 (Cohort 1, n = 31) and 60 mg/m^2, days 1-3 (Cohort 2, n = 17). After dose in 1st cohort (n = 31) proved safe, escalation of dose in 2nd cohort (n = 17) was made during induction course.
[2] Ara-C 200 mg/m^2/day, days 1-7
[3] Lenalidomide 10 mg/day, days 1-21
[4] Daunorubicin 45 mg/m^2, day 1 (Cohort 1). Dose was escalated to 60 mg/m^2/day in 2nd cohort during consolidation once dose in 1st cohort proved safe.
[5] Ara-C 120 mg/m^2/day x 5 days
[6] Lenalidomide 10 mg/day, days 1-15

Ades L et al. *Proc ASH* 2010;Abstract 508.

Efficacy Outcomes (from Abstract)

Response Assessment	
Complete Remission (Both Cohorts [n = 48]) Cohort 1 (n = 31) Cohort 2 (n = 17)	50% 55% 47%
Overall Response Rate	60%
1-Year Disease-Free Survival	26.5%

	Isolated del(5q) (n = 5)	del(5q) + one additional abnormality (n = 5)	del(5q) with complex karyotype (n = 38)
CR	80%	80%	45%

Ades L et al. *Proc ASH* 2010;Abstract 508.

Select Safety Events (from Abstract)

	Incidence (N = 48)
Early Death	10.4%
Median Duration of Hospitalization in Induction	30.5 days
Median Number of RBC Transfusions (During Induction)	9
Median Number of Platelet Transfusions (During Induction)	7

Ades L et al. *Proc ASH* 2010;Abstract 508.

Author Conclusions

- Intensive chemotherapy and lenalidomide can be combined in higher-risk MDS and AML with del(5q) without unexpected additive myelosuppression.
- In this cohort of patients with very poor cytogenetics, the CR rate was 50% and was higher than generally reported with chemotherapy alone in similar patients.
- Disease-free survival remained short, suggesting that induction or consolidation therapy should be improved.
- Based on the better efficacy of daunorubicin 90 mg/m^2/day (*N Engl J Med* 2009;361:1235 and 1249) in AML and the adequate tolerance of daunorubicin in the 60 mg/m^2 cohort, the dose of daunorubicin will be increased to 90 mg/m^2/day in the next patient cohort.

Ades L et al. *Proc ASH* 2010;Abstract 508.

Investigator Commentary: Combination of lenalidomide and chemotherapy for patients with higher-risk MDS or AML with del(5q)

Typically lenalidomide is used for low-risk MDS with del(5q) and is effective in that setting. This is a feasibility study in which the authors have combined lenalidomide and intensive chemotherapy for patients with higher-risk MDS or AML with del(5q). The response rates with the combination are reported to be 50 percent, which is higher than what is expected with chemotherapy alone. However, there was no control arm in this study, so such an inference is not conclusive.

Additionally, the disease-free survival was short, so there need to be alternative strategies to build on this approach. One of the strategies the authors are suggesting is to increase the dose of daunorubicin. Overall, I believe this may be a bit of a stretch for such combinations, and my thoughts are that this combination is an interesting avenue but may not be applicable for many patients.

Interview with B Douglas Smith, MD, January 4, 2011

Arsenic Trioxide (ATO) in the Consolidation Treatment of Newly Diagnosed APL — First Interim Analysis of a Randomized Trial (APL 2006) by the French Belgian Swiss APL Group

Ades L et al.

Proc ASH 2010;Abstract 505.

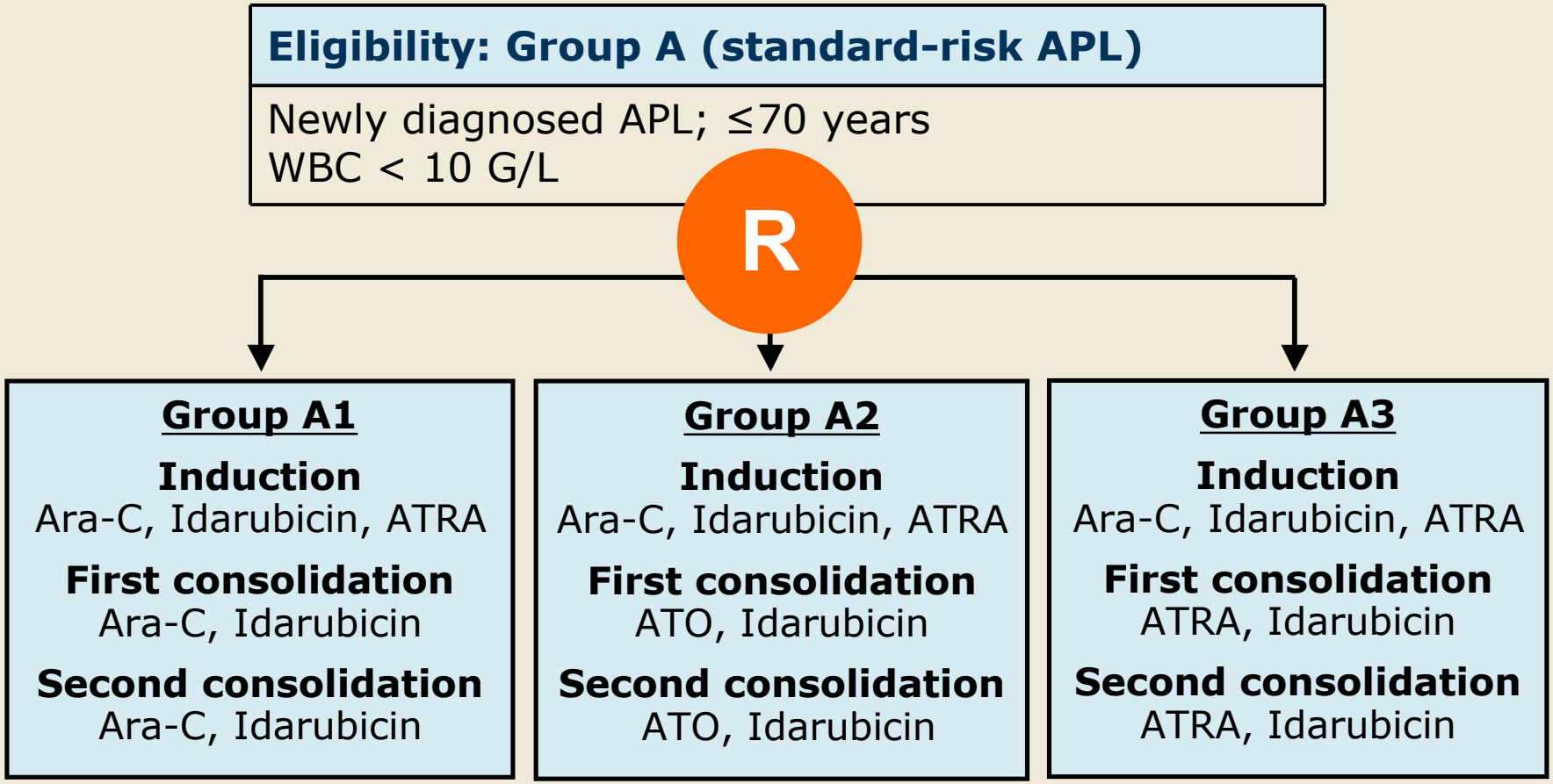
Background

- ATRA in combination with anthracycline-based chemotherapy is the reference treatment for newly diagnosed acute promyelocytic leukemia (APL).
  - This treatment is myelosuppressive and may be associated with long-term cardiac toxicity.

- Use of arsenic trioxide (ATO) may allow for:
  - Reduction of the amount of chemotherapy (and in particular avoid use of Ara-C).
  - Further reduction in relapse risk, especially when used in consolidation treatment (*Proc ASCO* 2007;Abstract 2).

Ades L et al. *Proc ASH* 2010;Abstract 505.

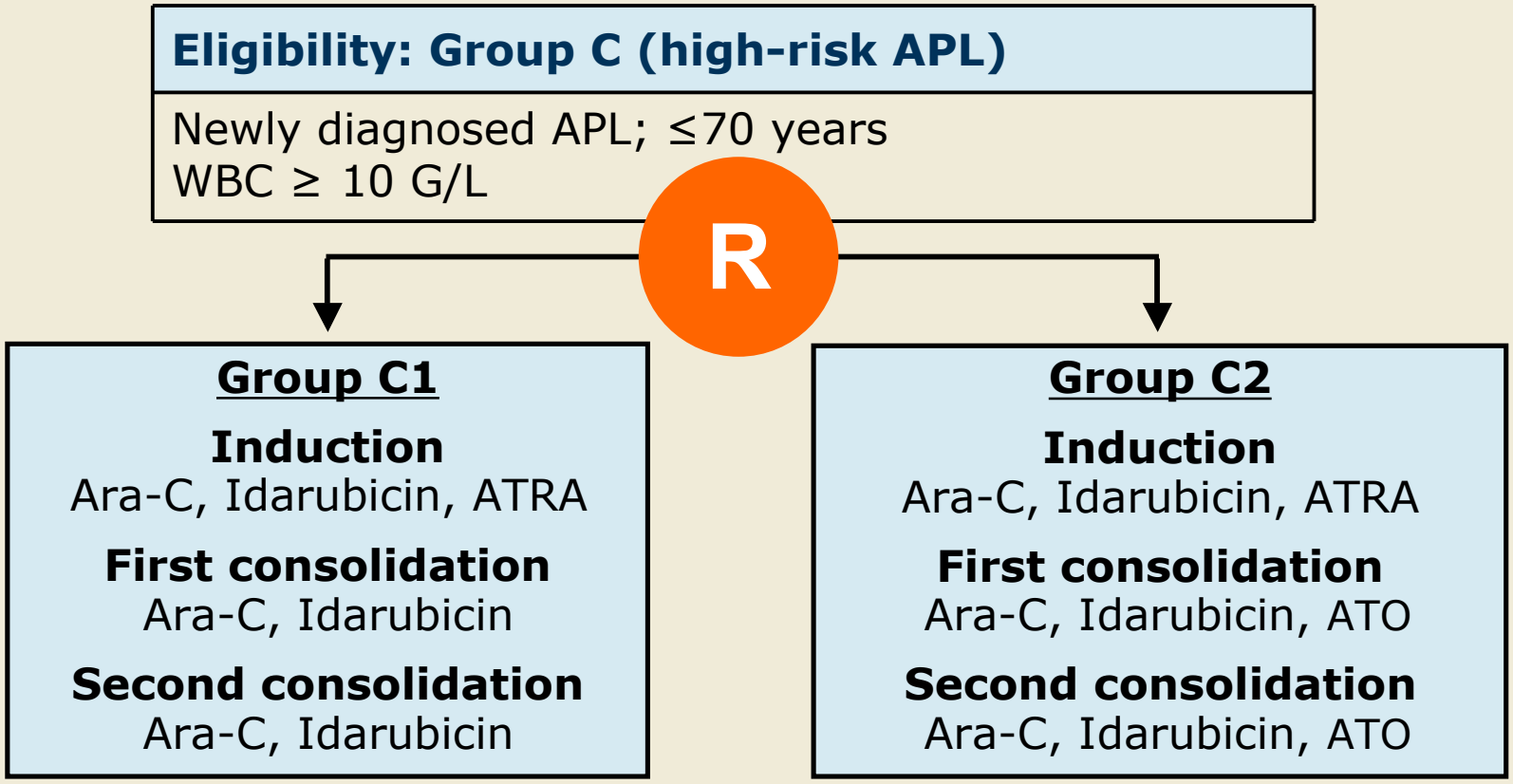
APL 2006 Study Schema



All patients received maintenance with ATRA, 6-MP and methotrexate.

Ades L et al. *Proc ASH* 2010;Abstract 505.

APL 2006 Study Schema



Treatment in C1 is same as in A1. There is no Group B.

All patients received maintenance with ATRA, 6-MP and methotrexate.
Patients in Group C1 and C2 also received intrathecal chemotherapy.

Ades L et al. *Proc ASH* 2010;Abstract 505.

Efficacy and Safety Outcomes (from Abstract)

	Group A1 (n = 45)	Group A2 (n = 45)	Group A3 (n = 51)	Group C1 (n = 24)	Group C2 (n = 21)
Complete response	99.3%			100%	
Cumulative incidence of relapse at 18 months	0%	0%	2%	2%	2%
Median duration of thrombocytopenia (after consolidation cycles) (days)	44	35	25	43.5	48
Median duration of neutropenia (after consolidation cycles) (days)	43.5	40	20	45.5	51.5
Median duration of hospitalization (days)	51	59	26	53.5	65

Ades L et al. *Proc ASH* 2010;Abstract 505.

Author Conclusions

- Results of this first interim analysis show that very high CR rates (>95%) can be observed in multicenter trials in APL by combining ATRA and anthracycline-based chemotherapy, while the relapse rate with consolidation and maintenance was very low in all treatments arms, including in patients with WBC > 10 G/L.
- ATO, when combined with chemotherapy during consolidation cycles, increases myelosuppression.
- An amendment further reducing chemotherapy in patients receiving ATO as part of consolidation is thus being implemented in the trial.

Ades L et al. *Proc ASH* 2010;Abstract 505.

Phase II Study of All-Trans Retinoic Acid (ATRA), Arsenic Trioxide (ATO), with or without Gemtuzumab Ozogamicin (GO) for the Frontline Therapy of Patients with Acute Promyelocytic Leukemia (APL)

Ravandi F et al.

Proc ASH 2010;Abstract 1080.

Study Schema

Eligibility: Newly diagnosed APL

Cohort 1 (n = 47)

- ATRA 45 mg/m^2 PO daily
- ATO 0.15 mg/kg/daily beginning on day 10 of ATRA induction
- High-risk patients (WBC > 10 x 10^9/L) received gemtuzumab 9 mg/m^2 on the first day of induction.

Cohort 2 (n = 57)

- ATRA 45 mg/m^2 PO daily
- ATO 0.15 mg/kg/daily beginning on day 1 of ATRA induction
- High-risk patients also received gemtuzumab 9 mg/m^2 on day 1.
- Gemtuzumab also administered (all patients) if at any time during induction the WBC rose to >30 x 10^9/L (and more recently if >10 x 10^9/L).

Ravandi F et al. *Proc ASH* 2010;Abstract 1080.

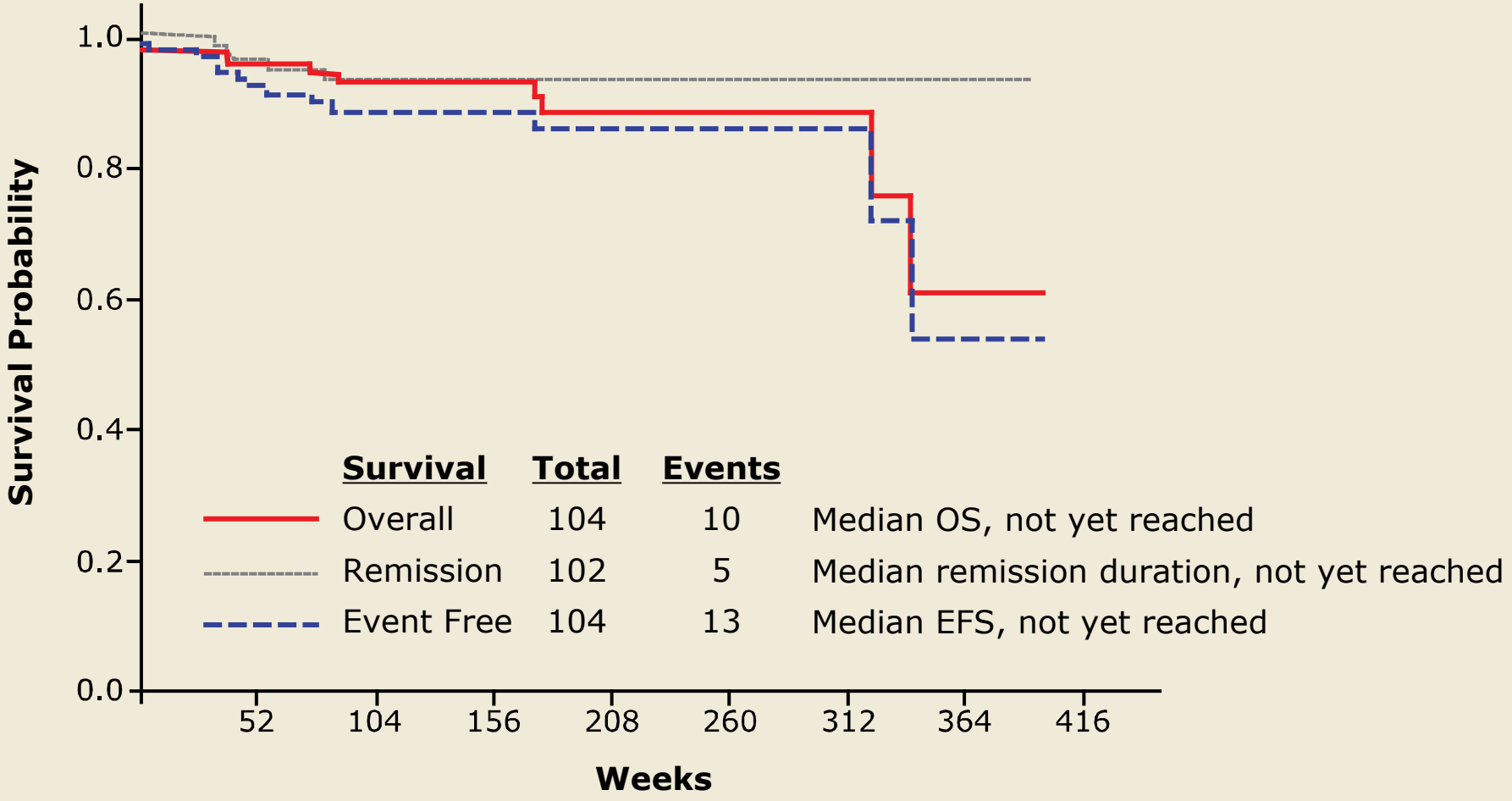
Efficacy Outcomes

	Both cohorts combined (n = 104)
Complete remission (CR)	98%
Five-year overall survival (OS)	88%
Five-year event-free survival (EFS)	86%

Median follow-up of 115 weeks
Only 5 patients achieving a CR (5%) experienced disease relapse.

Ravandi F et al. *Proc ASH* 2010;Abstract 1080.

Overall Outcomes



With permission from Ravandi F et al. *Proc ASH* 2010;Abstract 1080.

Author Conclusions

- The combination of ATRA and arsenic trioxide (with or without gemtuzumab) as initial therapy for APL is highly effective and safe.
  - Overall, 98% of patients achieved CR with only 2 induction deaths
  - Only 5 patients achieving CR (5%) have experienced disease relapse
  - Estimated 5-year survival 88%, EFS 86%
- This combination can potentially substitute for chemotherapy-containing regimens for patients at both high and low risk.

Ravandi F et al. *Proc ASH* 2010;Abstract 1080.

Investigator comment on arsenic trioxide as part of initial therapy for APL

The study by Ades is trying to figure out the best combination therapy for consolidation in APL, especially the best way of incorporating arsenic trioxide in consolidation, in combination with chemotherapy. Currently, we don't have the follow-up data from this study to know any effects on longer-term outcomes. An observation has been the duration of hospitalization and myelosuppression, which appear to increase when arsenic trioxide is combined with chemotherapy in consolidation cycles.

In the study presented by Ravandi, the issue is that gemtuzumab has been pulled off the market, so any combination with gemtuzumab is not doable anymore. Gemtuzumab was a pretty good drug, and we would have liked it to be available for APL. The presented data on combination ATRA and arsenic trioxide add to the literature that this is a highly effective and safe combination in the initial treatment of APL.

Interview with B Douglas Smith, MD, January 4, 2011