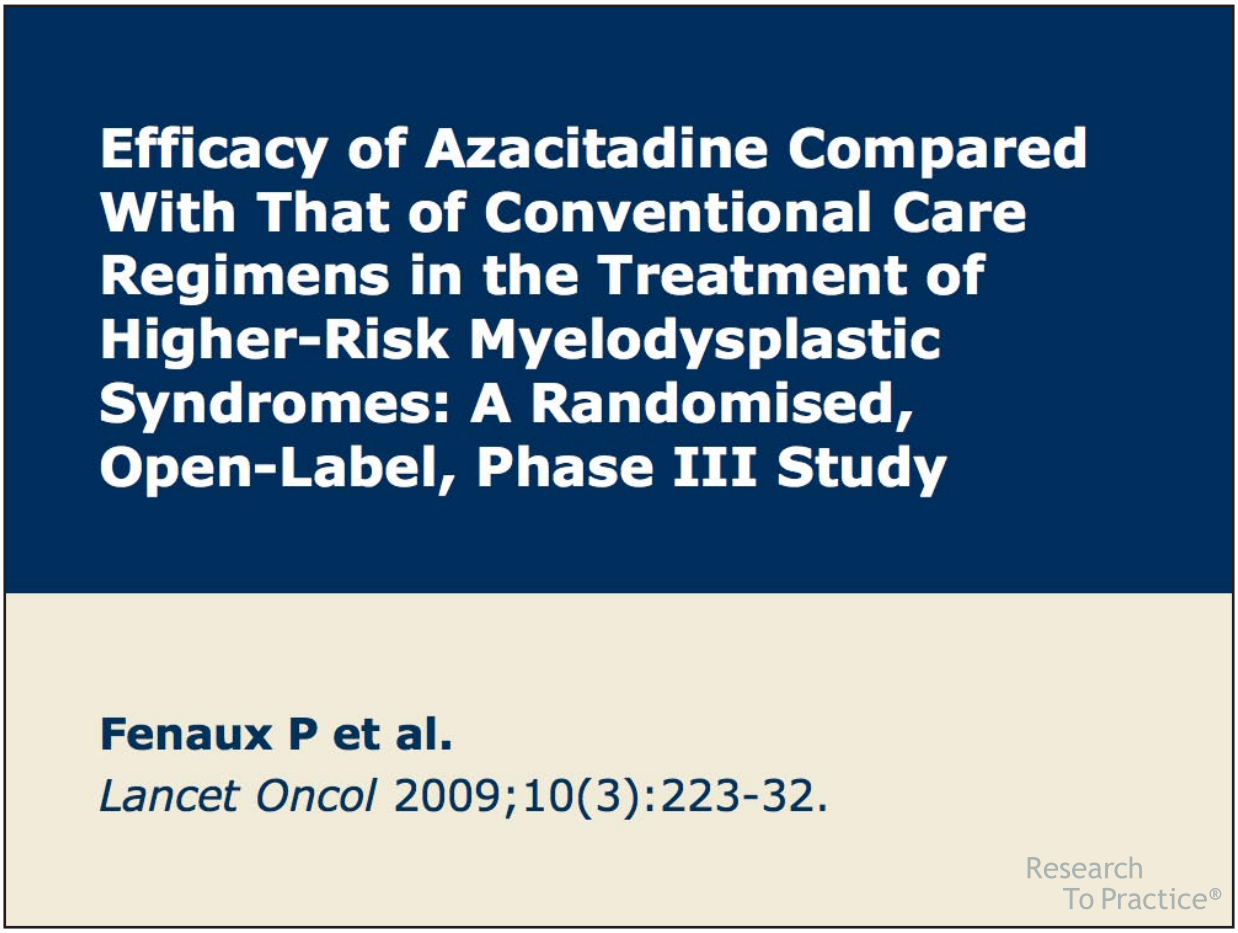
# Efficacy of Azacitidine in Higher-Risk Myelodysplastic Syndrome (MDS)

## Presentation discussed in this issue:

Fenaux P et al. **Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomized, open-label, phase III study.** *Lancet Oncol* 2009;10(3):223-32. **Abstract**

## Slides from the journal article



# Introduction

- Median survival for patients with Intermediate-2 or High-Risk myelodysplastic syndrome (MDS) by IPSS is 1.2 years and 0.4 years, respectively
- Beyond allogeneic stem-cell transplantation, no treatment strategies for MDS meaningfully improves survival or rate of leukemic transformation
- In CALGB-9221, azacitidine (Aza) improved survival compared to observation but was inconclusive due to its crossover design and lack of active comparator (JCO 2002;20:2429)

**Objectives of the current study:**

- Assess effect of azacitidine vs conventional care regimen [CCR, best supportive care (BSC), low-dose cytarabine (LDC) or intensive chemotherapy IC)] on overall survival and time to progression to AML in patients with higher-risk MDS

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

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# Phase III, International, Multicenter, Randomized, Controlled, Parallel-Group, Open-Label Trial (N = 358)

**Eligibility**

IPSS Intermediate-2 or High-risk MDS and FAB-defined refractory anemia with excess blasts (+/-) in transformation, or chronic myelomonocytic leukemia with ≥ 10% bone marrow blasts and WBC < 13 x $10^9$ cells/L

**Investigator Preselection of Conventional Care Regimens (CCR)**

**Best supportive care (BSC, n = 222)**

**Low-dose cytarabine (LDC, n = 94)**

**Intensive chemo (IC, n = 42)**

**R**

**Azacitidine (Aza, n = 179)**

**CCR* (n = 179)**

*Patients randomized to CCR received the investigator preselected treatment

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

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# Median Overall Survival and Time to Progression to AML: Azacitidine versus CCR (21.1 months median follow-up)

| | Azacitidine (n = 179) | CCR (n =179) | Hazard Ratio | *P*-value |
|---|---|---|---|---|
| Overall survival | 24.5 mos | 15 mos | 0.58 | 0.0001 |
| 2-year overall survival | 50.8% | 26.2% | NR | <0.0001 |
| Time to transformation to AML | 17.8 mos | 11.5 mos | 0.50 | <0.0001 |

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

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# Median Overall Survival and Time to Progression to AML According to Investigator Preselected Therapy

| | BSC only (n = 222) | | Low-dose cytarabine (LDC) (n = 94) | | Intensive chemo (IC) (n = 42) | |
|---|---|---|---|---|---|---|
| | Aza (n=117) | BSC (n=105) | Aza (n =45) | LDC (n=49) | Aza (n=17) | IC (n=25) |
| Overall survival | 21.1 mo | 11.5 mo | 24.5 mo | 15.3 mo | 25.1 mo | 15.7 mo |
| Hazard ratio, p-value | HR = 0.58, p = 0.0045 | | HR = 0.36, p = 0.0006 | | HR = 0.76, p = 0.51 | |
| Time to transformation to AML | 15.0 mo | 10.1 mo | 15.0 mo | 14.5 mo | 23.1 mo | 10.7 mo |
| Hazard ratio, p-value | HR = 0.41, p < 0.0001 | | HR = 0.55, p = 0.097 | | HR = 0.48, p = 0.19 | |

HR = Hazard ratio, adjusted for treatment, subgroup, ECOG performance status, lactate dehydrogenase, hemoglobin, number of prior red-blood-cell transfusions and presence or absence of cytogenetic-7/del(7q) abnormality

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

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# Hematologic Response and Improvement: Azacitidine versus Conventional Care Regimen (CCR)

| | Total ITT (n = 358) | | |
|---|---|---|---|
| | Aza (n=179) | CCR (n=179) | P-value |
| **Hematologic Response** | | | |
| Any remission | 29% | 12% | 0.0001 |
| Complete remission | 17% | 8% | 0.015 |
| Partial remission | 12% | 4% | 0.0094 |
| Stable disease | 42% | 36% | 0.33 |
| **Hematologic Improvement (imprvmnt)** | | | |
| Any imprvmnt | 49% | 29% | <0.0001 |
| Major erythroid imprvmnt | 40% | 11% | <0.0001 |
| Major platelet imprvmnt | 33% | 14% | 0.0003 |
| Major neutrophil imprvmnt | 19% | 18% | 0.87 |

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.



# Hematologic Response and Improvement: Azacitidine versus Investigator Preselected Therapy

| | BSC (n = 222) | | LDC (n = 94) | | IC (n = 42) | |
|---|---|---|---|---|---|---|
| | Aza (n=117) | BSC (n=105) | Aza (n=45) | LDC (n=49) | Aza (n=17) | IC (n=25) |
| **Hematologic Response** | | | | | | |
| Any remission | 27%* | 5% | 31%* | 12% | 29% | 40% |
| Complete remission | 12%* | 1% | 24%* | 8% | 29% | 36% |
| Partial remission | 15%* | 4% | 7% | 4% | 0% | 4% |
| Stable disease | 44% | 39% | 33% | 37% | 47% | 24% |
| **Hematologic Improvement (imprvmnt)** | | | | | | |
| Any imprvmnt | 50%* | 31% | 53%* | 25% | 35% | 28% |
| Major erythroid imprvmnt | 39%* | 8% | 44%* | 10% | 29% | 22% |
| Major platelet imprvmnt | 30%* | 10% | 38% | 19% | 33% | 20% |
| Major neutrophil imprvmnt | 15% | 20% | 27% | 11% | 23% | 24% |

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

***p*-value < 0.05**

# Deaths, Discontinuation and Grade 3/4 Hematologic Toxicity: Azacitidine versus CCR

| | Total ITT (n = 358) | |
|---|---|---|
| | Aza (n=179) | CCR (n=179) |
| Deaths | 46% | 63% |
| Deaths, first 3 months of treatment | 11% | 9% |
| Discontinuation before study completion due to hematol AEs | 5% | 2% |
| **Grade 3/4 Hematologic Adverse Events (AEs)** | | |
| Neutropenia | 91% | 76% |
| Thrombocytopenia | 85% | 80% |
| Anemia | 57% | 68% |
| **Baseline Gr 0-2 progressing to Gr 3/4 during treatment** | | |
| Neutropenia | 84% | 61% |
| Thrombocytopenia | 74% | 72% |
| Anemia | 54% | 64% |

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.



# Deaths, Discontinuation and Grade 3/4 Hematologic Toxicity: Azacitidine Investigator Preselected Therapy

| | BSC (n = 222) | | LDC (n = 94) | | IC (n = 42) | |
|---|---|---|---|---|---|---|
| | Aza (n=117) | BSC (n=105) | Aza (n=45) | LDC (n=49) | Aza (n=17) | IC (n=25) |
| Deaths | 45% | 63% | 44% | 63% | 53% | 64% |
| Deaths, first 3 mo of treatment | 11% | 9% | 11% | 14% | 12% | 0% |
| Discontinuation before study completion due to hematol AEs | 3% | 2% | 9% | 5% | 6% | 0% |
| **Grade 3/4 Hematologic AEs** | | | | | | |
| Neutropenia | 91% | 69% | 89% | 89% | 94% | 90% |
| Thrombocytopenia | 82% | 71% | 71% | 93% | 88% | 95% |
| Anemia | 54% | 66% | 66% | 64% | 56% | 58% |

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

# Summary and Conclusions

- Azacitidine prolongs overall survival and lowers the risk of progression to AML in patients with higher-risk MDS compared to treatment with CCR (BSC, low-dose cytarabine, intensive chemotherapy)
  - OS: 24.5 mos vs 15.0 mos
  - 2-year OS: 50.8% vs 26.2%
- Azacitidine improved survival compared to BSC and low-dose cytarabine but not intensive chemotherapy, possibly due to the small number of patients in this investigator preselected subgroup
- Survival benefit observed for all prognostic subgroups, including those with poor, intermediate and good cytogenetics (data not shown)
- Grade 3/4 neutropenia and thrombocytopenia occurred more frequently with azacitidine than BSC but the rates of hemorrhagic complications and infection were similar (data not shown)

Source: Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

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