# Experts Discuss DACOTA Phase 3 Trial of Decitabine versus Hydroxyurea for Advanced Proliferative CMML


**Dr. Mikkael Sekeres:** My final abstract presentation is actually a really controversial study, where I'll be reviewing the DACOTA Phase 3 trial of decitabine versus hydroxyurea for advanced proliferative chronic myelomonocytic leukemia.

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## DACOTA: Background

- Prognosis for patients with myeloproliferative CMML (defined by WBC ≥13 x $10^9$/L) is poor and worse than for myelodysplastic CMML[1,2]
- Hydroxyurea improved response rate and extended OS vs etoposide in randomized trial in patients with myeloproliferative CMML[3]
- Efficacy of HMAs in advanced/high-risk MP-CMML has been studied[4]:
  - Decitabine monotherapy achieved ORR 38% to 48%, median OS 17.0-18.3 months in phase 2 trials[5,6]
- DACOTA trial designed to compared decitabine vs hydroxyurea in newly diagnosed patients with MP-CMML[7]

1. Arber. *Blood*. 2016;127:2391. 2. Loghavi. *Blood Adv*. 2018;2:1807. 3. Wattel. *Blood*. 1996;88:2480. 4. Coston. *Am J Hematol*. 2019;94:767. 5. Braun. *Blood*. 2011;118:3824. 6. Santini. *Leukemia*. 2018;32:413. 7. Itzykson. ASH 2020. Abstract 654.

Prognosis for patients who have myeloproliferative CMML, which is defined as those patients with CMML who have a white count of 13,000 or greater is poor and worse than it is for what we often call the myelodysplastic type of CMML where the white count is lower. Hydroxyurea improved response rate and extended overall survival versus etoposide in a randomized trial that was conducted 25 years ago in patients with myeloproliferative CMML, and the efficacy of hypomethylating agents, particularly decitabine, has been studied in mostly single-institution studies in advanced- or higher-risk myeloproliferative chronic myelomonocytic leukemia. Decitabine monotherapy achieves an overall response rate that's in the range of about 38% to 48% and leads to a median overall survival of 17 or 18 months, but these again are in phase 2 non-comparative trials. The DACOTA trial was designed to compare decitabine to hydroxyurea in newly diagnosed patients with a mild proliferative type of chronic myelomonocytic leukemia.

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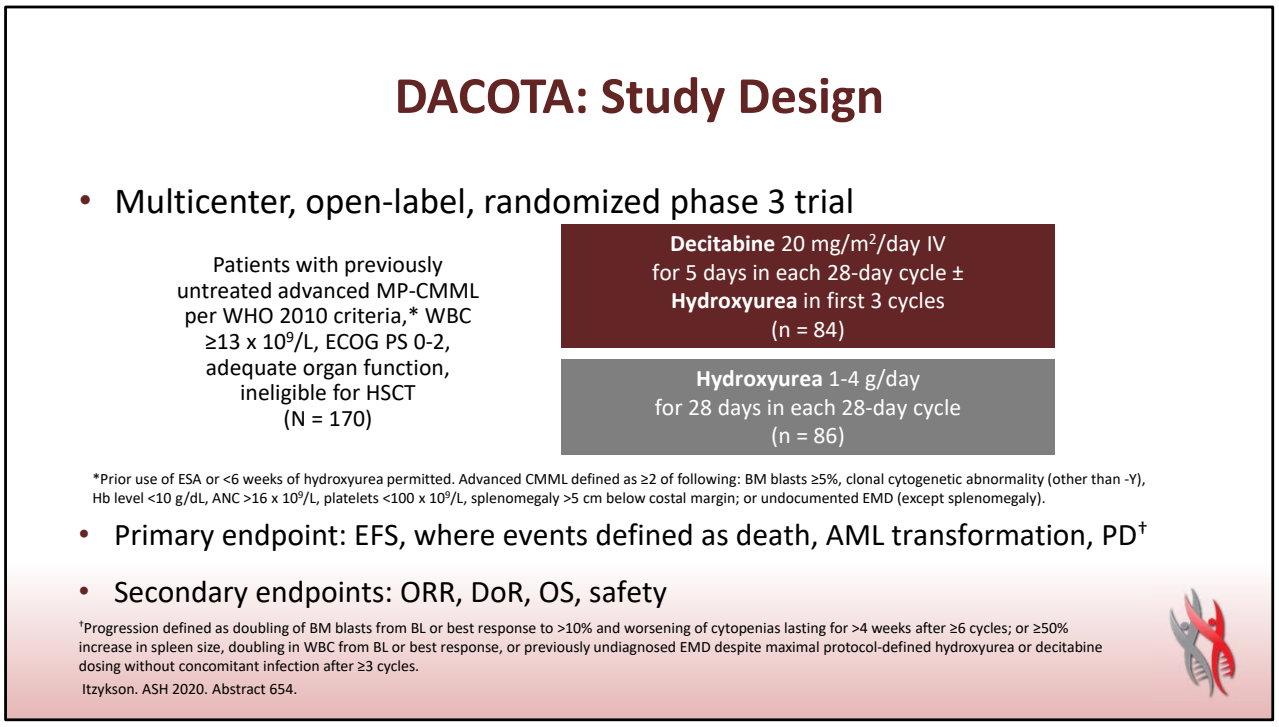


You can see here the eligibility criteria, patients with previously untreated advanced myeloproliferative CMML were randomized to receive decitabine standard dosing 20 mg per meter squared for five days in a 28-day cycle. They could also receive hydroxyurea for three cycles versus hydroxyurea alone with a primary endpoint of event-free survival, where an event was defined as either death or transformation to AML or progressive disease.

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## DACOTA: Baseline Patient Characteristics

| Characteristic | ITT Population (N = 170) | Decitabine (n = 84) | Hydroxyurea (n = 86) |
|---|---|---|---|
| Median age, yrs (IQR) | 73 (68-78) | 71.5 (67-77) | 74 (69-79) |
| Female, n (%) | 53 (31) | 28 (33) | 25 (29) |
| ECOG PS 0/1, n (%) (n = 169) | 152 (90) | 76 (91) | 76 (89) |
| WHO 2010, n (%) | | | |
| ▪ CMML-1 | 115 (68) | -- | -- |
| ▪ CMML-2 | 55 (32) | -- | -- |
| Median WBC, x $10^9$/L (IQR) | 34.9 (22.9-55.7) | 35.8 (23.1-59.3) | 32.8 (22.0-51.3) |
| Severe anemia,* n (%) (n = 168) | 40 (24) | 19 (23) | 21 (25) |
| CPSS risk, n (%) (n = 165) | | | |
| ▪ Low | 1 (1) | 0 | 1 (1) |
| ▪ Intermediate-1 | 66 (40) | 35 (43) | 31 (37) |
| ▪ Intermediate-2 | 88 (54) | 43 (52) | 45 (55) |
| ▪ High | 10 (6) | 4 (5) | 6 (7) |
| Prior hydroxyurea, n (%) (n = 169) | 72 (43) | 33 (40) | 39 (45) |
| Median prior duration of hydroxyurea, days (IQR) | 27 (14-41) | 27 (15-40) | 26 (14-41) |

*Hb <8 g/dL or transfusion dependency.

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These patients were typical of those who are usually diagnosed with chronic myelomonocytic leukemia with a median age of 73 years, median white count that was high at 35,000, and similar distributions of those who had low, intermediate one, intermediate two, or high-risk disease in both treatment arms.

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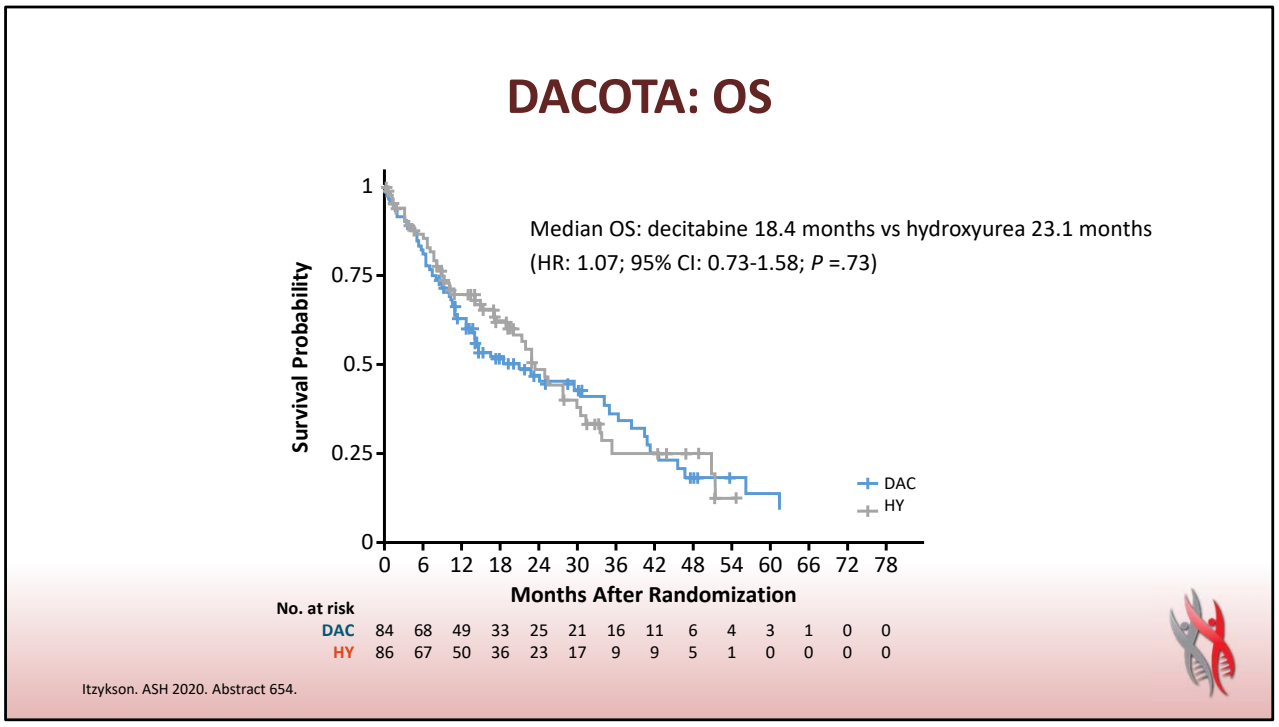


What you see here is that very clearly, there's no difference in overall survival between those patients who were treated with decitabine versus those patients who were treated with hydroxyurea with overall survival curves that absolutely overlap. That is probably the most important endpoint we can focus on in patients who have this advanced overlap of MDS and MPNs.

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## DACOTA: Safety

| Safety Event, n (%) | Decitabine (n = 84) | Hydroxyurea (n = 86) | *P* Value |
|---|---|---|---|
| Required hospitalization | 46 (55) | 33 (38) | .05 |
| Infections (all grades) | 46 (55) | 37 (43) | .17 |
| Any grade ≥2 AE | 29 (35) | 19 (23) | .11 |
| Hemorrhage | 16 (19) | 11 (13) | |
| Cardiac | 18 (21) | 7 (8) | |
| Pulmonary | 16 (19) | 12 (14) | |
| Gastrointestinal | 17 (20) | 13 (15) | |
| Renal and urinary | 8 (10) | 5 (6) | |
| Endocrine | 7 (8) | 6 (7) | |
| Psychiatric | 3 (4) | 4 (5) | |
| Neurologic | 4 (5) | 2 (2) | |
| Musculoskeletal | 14 (17) | 17 (20) | |

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The safety data are shown here. More patients who were treated with decitabine required hospitalizations, rates of infection were fairly similar, and slightly higher rates of grade two or higher adverse events for those treated with decitabine.

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## DACOTA: Investigator Conclusions

- No differences in outcomes were seen with decitabine vs hydroxyurea, but this study demonstrates that randomized clinical trials are possible for CMML
- In patients newly diagnosed with advanced CMML, hydroxyurea is an appropriate treatment option where BM monitoring is available
- Continued investigation on the safety of HMAs in advanced CMML is warranted
- Further research is needed to turn clinical response from HMA-based combinations into extended survival
- Identification of biomarkers of response to HMAs and hydroxyurea is being pursued in ongoing trials

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The investigators on this study concluded there were no differences in outcome seen with patients treated with decitabine versus hydroxyurea and also that this demonstrates that we can perform randomized clinical trials in patients with chronic myelomonocytic leukemia, which is considered a rare disease. Hydroxyurea can be an appropriate treatment option in patients with CMML who have a proliferative subtype upfront and that further investigation of hypomethylating agents is necessary. Also, that there's the potential of identifying biomarkers for response to decitabine versus HMAs. This is a controversial study because it's become a standard of care to treat patients with CMML with hypomethylating agents. This study focused on overall survival, which I think is incredibly important in this population, but didn't focus as much on things like overall response rates, improvement in transfusion needs, or quality of life. Another criticism of this study that's been lobbied at it is that patients were allowed overlap of hydroxyurea and decitabine and at least in pre-clinically, there's a belief that there may be some antagonism between those drugs. I'm sure my colleagues will have a lot to say about this study.

Dr. Garcia-Manero, I know you'll have some questions and comments about the study you'd like to discuss.

**Dr. Garcia-Manero:** Thank you, Mikkael, for presenting this data on the DACOTA study. I

think today, we have presented and we're going to be presenting a very important dataset with a lot of data that I think is going to change our practice, but I have to tell you that I have a lot of concerns about this DACOTA trial, the message that it is providing because what these investigators are showing is not what my practice reflects. Actually, Dr. Montalban-Bravo at MD Anderson has presented last year attached very significant data with the best compounds that we have in CMML that is basically the hypomethylating agents.

Not too long ago actually, the Austrian group published in one of the JAMA journals a very important study basically contradicting the data from this DACOTA trial. We're going to be discussing with Dr. Komrokji early intervention with lenalidomide, we will discuss early intervention with hypomethylating agents. To me, it is kind of backwards that we should consider hydroxyurea as the standard of care in CMML.

Now, I'm not saying that the hypomethylating agents work across all subtypes of CMML, so there may be some patients with very small burden of disease, a low white count that are just newly diagnosed where these compounds are not beneficial, but in general, for those patients where there is a clear indication for treatment, our experience and that of this very large Austrian consortium really suggests that the standard of care should be a hypomethylating agent with increasing responses and potentially improvement in survival. I don't know what Dr. Komrokji thinks. You're free to disagree with me, but I think we cannot go back to just using hydrea for CMML.

**Dr. Komrokji:** No, definitely. Obviously, this was a disappointment in a way. I think we can look at this from two ways. When I talked to Alec Padron that does CMML here all the time, he's not convinced that we've shown evidence that hypomethylating agents do improve survival in MDS in a prospective fashion, which I think he's right in that way. I don't think that should be a general statement that there is no role for hypomethylating agents in CMML.

I think what we've known clearly, and I've changed actually my practice, although it's not a prospective fashion, is that, in the past, I never treated patients if they are asymptomatic had no cytopenias, no big splenomegaly, but when we looked at this, and we looked at a large subset of patients here that we presented, when patients have leukocytosis and monocytosis, there is correlation with end-organ damage. We see more renal failures in those patients. We see more total effusions, pericardial effusions. We try to look at quantiles or where cases become symptomatic and it turns out usually when the patients count are more than 30,000 or 33,000 is where you really start seeing this end-organ damage in those patients. Even looking at something like hydrea intervention, it seems that they benefit. That's one principle, that in CMML, in the proliferative type, sometimes we may have to treat earlier than we used to think. That's one. I think to come and say that hypomethylating agents have no role or no survival advantage, it's hard for me.

One thing I know about which is simple, which I don't know the details on the study, they allowed hydrea and decitabine in the first few cycles and we know that actually, they antagonize each other. It's like you cannot usually use hypomethylating agents with hydrea,

so I don't know how much exposure was there. Now, the other point of things to say, we've known even from prior trials that we conducted with our French colleagues that in patients with leukocytosis and splenomegaly, that seems the subset of patients that drives the less benefit from hypomethylating agents. I don't know, I don't think this should be a conclusive study. I don't think we should just abandon using hypomethylating agents in CMML based on this. I think they are to be congratulated and proving that we could do a randomized clinical trial in CMML and we should keep moving with that, but we should think of this. I think from my point, I still will use hypomethylating agents in patients with cytopenia in CMML.

We have no other option. In patients that sometimes have high blast and proliferative disease and I want to take them to transplant, there is a lot of retrospective data at least suggesting that if you treat them with hypomethylating agents and take them to transplant, they do better. Again, in my practice now, if patients are proliferative, I do think of treatment even if it was just hydrea. We have studies with ruxolitinib in patients with proliferative diseases, but that's my take on the data.