

**Improving Outcomes in R/R AML: Can Unique Combinations of Novel Agents Impact Prognosis? Early Trial Results of Venetoclax + Idasanutlin and Azacitidine + Nivolumab, Azacitidine + Ipilimumab**

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***767. Safety, Efficacy, Pharmacokinetic (PK) and Biomarker Analyses of BCL2 Inhibitor Venetoclax (Ven) Plus MDM2 Inhibitor Idasanutlin (idasa) in Patients (pts) with Relapsed or Refractory (R/R) AML: A Phase Ib, Non-Randomized, Open-Label Study***

Welcome to *Managing AML*. I am Naval Daver and I am live at the 60th Annual Conference of American Society of Hematology in San Diego, California. Today, I will be reviewing the data presented on the safety and efficacy, pharmacokinetic, and biomarker analyses of BCL2 inhibitor venetoclax plus MDM2 inhibitor idasanutlin in patients with relapsed/refractory acute myeloid leukemia.

This was a phase 1/2 study that was conducted at multiple sites across the United States and Europe. The study came from pre-clinical work that had been done by Dr. Michael Andreeff and Marina Konopleva in our group where they showed that the combination of the MDM2 inhibitor idasanutlin or the BCL2 inhibitor venetoclax produced a very high degree of synergism in mouse models as well as in xenografts and patient samples. This data was actually published in the *Cancer Cell* last year and led to the evolution of this trial. As many of you may know, the drug venetoclax was very recently approved for patients with newly diagnosed acute myeloid leukemia, and the approval is a combination of azacitidine with venetoclax or low-dose cytarabine with venetoclax in elderly AML patients who are considered not fit for intensive induction chemotherapy, including patients above 75 years of age or those who are 60 to 75\* with underlying comorbidities that would make them not good candidates for intensive chemo. The drug is now available on the market in that setting; however, we feel there are a number of interesting combinations that can be developed with venetoclax including the one that we are presenting here.

The trial in total has enrolled about 60 patients at this time. The trial initially had two arms, one of these was with the idasanutlin in combination with venetoclax and the other one was in combination with a MAP kinase inhibitor called imatinib with venetoclax; however, on interim analysis that we presented last year at the ASH meeting the cobimetinib arm in combination with venetoclax was not thought to be showing a very high degree of efficacy to consider continuation, so we closed that arm. In this study we presented the updated data on the 34

patients who are relapsed/refractory elderly AML who received the idasanutlin plus venetoclax. The trial was focused only on relapsed/refractory AML at this time, the median age of the patients was 70 years. The trial actually only took patients 60 years or above with relapsed AML, and the primary objectives as with most phase 1 studies were to identify the maximum tolerated dose, the recommended phase 2 dose, safety as well as efficacy as a key secondary endpoint. What we saw is that the combination overall was safe. Initially we did notice high rates of diarrhea including grade 3 diarrhea in a number of patients, which is a known on-target side effect with the MDM2 inhibitor idasanutlin. We then started using prophylaxis with loperamide in patients before starting and during the first 48 hours of therapy with idasanutlin, and after that we have noticed that the incidence of diarrhea has gone down very significantly. Other than that, we did not see any high concerning signals for significantly prolonged neutropenia, thrombocytopenia, significantly increased infection risk, or any organ toxicity during the conduct of the trial at this time.

We have evaluated multiple dose levels and the dose level that seems to be most effective is the combination of idasanutlin at 200 mg for 5 days with venetoclax given 600 mg daily, or idasanutlin at 150 mg for 5 days with venetoclax given at 600 mg daily. In the 24 patients at this dose level we actually saw a CR/CRI in 12 patients, so a response rate of 50% in relapsed/refractory elderly AML which would be considered quite encouraging if it continues to hold true. The study is now being expanded to evaluate further these two dose levels and eventually go into a larger expansion to see if these response rates hold true, in which case this could be a very important combination going forward, nonchemotherapy, both agents are oral for relapsed elderly acute myeloid leukemia. We are quite excited about the future for this study.

*\*In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.*

**Reference:** Daver N, Pollyea D, Garcia J, et al. Safety, Efficacy, Pharmacokinetic (PK) and Biomarker Analyses of BCL2 Inhibitor Venetoclax (Ven) Plus MDM2 Inhibitor Idasanutlin (idasa) in Patients (pts) with Relapsed or Refractory (R/R) AML: A Phase Ib, Non-Randomized, Open-Label Study. ASH 2018. Abstract 767.

***906. Safety, Efficacy, and Biomarkers of Response to Azacitidine (AZA) with Nivolumab (Nivo) and AZA with Nivo and Ipilimumab (Ipi) in Relapsed/Refractory Acute Myeloid Leukemia: A Non-Randomized, Phase 2 Study***

A number of immunotherapeutic approaches are being presented at this year's ASH for acute myeloid leukemia. These include bispecific antibodies such as AMG 330, XmAb, MacroGenic's

CD3, CD123, as well as CAR T-cell approaches in very early development and immune checkpoint-based therapies with a number of presentations in both AML and MDS. The background of this study is a lot of work that we have been doing in the immunotherapy field in both acute myeloid leukemia as well as MDS. We were one of the first groups to show that the T-cell population is actually well-preserved in the bone marrow in patients with AML especially newly diagnosed AML and patients with early relapse. More importantly, some of our functional studies that will be published soon, showed that the T-cells are actually functional, especially new AML where they seem to hyper-functional with a high-degree of cytokine production, much more than in normal healthy donor, but also in the early salvage, the T-cells are functional and can be stimulated to produce cytokines that are equivalent to the what you would see in a healthy donor. In the advanced salvage, we do not see that the T-cells are active. Based on this, we believe that we could use T-cell based treatments, either bispecific antibodies or immune checkpoint-based treatments to remove the breaks on T-cells, increase their activity to fight against tumors, and hopefully, get responses similar to what has been seen in solid tumor and some lymphomas with these immune checkpoint-based approaches.

This study had two different arms. One of those was initially looking at the doublet of azacitidine and nivolumab in relapsed/refractory acute myeloid leukemia. That arm has completed accrual with a total of 70 patients enrolled and the data has actually been published a few weeks ago in the *Cancer Discovery Journal*. What we saw in this relapsed/refractory AML was that the overall response rate was 35%, which included 24% CR/CRi and an additional 11% hematological improvement that was maintained 6 months or longer. Additionally, 10% of patients had stable disease beyond the 35% IWG response rates. This is a phenomenon that we are seeing more and more frequently with azacitidine alone, IDH inhibitors, and with immune checkpoints, and this has been very well described with immune checkpoint treatments in lymphomas and solid tumors, where in fact, half of the responses or more can sometimes be in the form of stable disease partial responses. When we looked at the overall survival, which is of course very important in the relapsed/refractory AML population, we saw that when we compared the survival with azacitidine/nivolumab to all patients treated on salvage clinical trials with an HMA backbone at MD Anderson in the last 6 to 7 years, and we have done a number of such trials, the overall survival was significantly better with the azacitidine/nivolumab. Especially in the first salvage group, we noticed that the overall survival in the elderly relapse patients was 11 months, which is double of the expected overall survival with relapsed elderly patients with azacitidine alone or with other azacitidine combinations. We think this data is quite interesting and needs to be explored further in the relapse, especially first salvage patients. We also did a lot of T-cell based biomarkers on flow cytometry and CyTOF analysis and we were able to identify using a statistical martingale residual, a cutoff that help to predict responses based on bone marrow pre-therapy, CD3 cell infiltrate. We saw that patients who had bone marrow CD3 cells above the cutoff, which was found to be 13%, had a 56% chance of achieving a response as compared to those who are below the cutoff where the response rate was 25%. This seems to be quite an important and strongly predictive biomarker

because if we are indeed able to get greater than 50% responses in relapsed elderly AML, this would be quite a major breakthrough going forward.

We now are looking at the combination of azacitidine with a doublet checkpoint, nivolumab/ipilimumab. This is an early data presentation at this year's ASH. We do see that the response rates across the board without selecting patients based on their pre-therapy bone marrow CD3, seemed to be higher than we saw with the azacitidine and nivolumab alone, and the response rates are about 45%. Interestingly, we have no 8-week mortality and that is quite encouraging in a salvage AML population where expected 8-week mortality is 10% to 15% with chemo or aza alone. One very important point with these immune checkpoint-based treatments is that we do see unique toxicities, and these usually come in the form of organ inflammation, the most common one we have seen is pneumonitis, but also nephritis, transaminitis, skin rash, and it is often difficult to differentiate the immune toxicity from myelosuppression and infection. We now have established guidelines and published these that patients who are on immune checkpoints or bispecifics or CAR T-cells, when they present with symptoms that are hard to differentiate between infection or immune toxicity, should be treated with steroids and antibiotics. As these trials are going to larger perspective approach, I think this needs to be very carefully monitored and incorporated into the management of side effects. With that, I would like to thank you for viewing this activity.

**Reference:** Daver N, Garcia-Manero G, Basu S, et al. Safety, Efficacy, and Biomarkers of Response to Azacitidine (AZA) with Nivolumab (Nivo) and AZA with Nivo and Ipilimumab (Ipi) in Relapsed/Refractory Acute Myeloid Leukemia: A Non-Randomized, Phase 2 Study. ASH 2018. Abstract 906.