Newer Generation Antibody-Drug Conjugates: Is There a Future For Monotherapy and/or Combination Strategies with Oral Agents in AML?

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26. Maturing Clinical Profile of IMGN779. A Next-Generation CD33-Targeting Antibody-Drug Conjugate, in Patients with Relapsed or Refractory Acute Myeloid Leukemia

I am here to discuss one of the ASH abstracts at the 2018 meeting. This abstract is entitled: Maturing Clinical Profile of IMGN779, A Next-Generation CD33-Targeting Antibody-Drug Conjugate In Patients with Relapsed and Refractory Acute Myeloid Leukemia.

This abstract was presented earlier today. Now, CD33 is known to be an antigen of high therapeutic interest in myeloid malignancies particularly acute myeloid leukemia because it is an established validated approach with the approval of gemtuzumab ozogamicin for the treatment of newly diagnosed and relapsed or refractory AML. However, the clinical development of gemtuzumab ozogamicin has certainly been challenging and that is referring to the safety concerns that we have been seeing with this agent primarily veno-occlusive disorder and myelosuppression. Newer generation CD33 directed antibody-drug conjugates with novel mechanisms of action or an area of high therapeutic interest. IMGN779 is a potent next-generation CD33 targeted antibody-drug conjugate. This drug delivers a novel DNA-alkylating payload which induces single strand, not double strand, breaks and is combined with a cleavable linker. This novel agent and the novel payload is the first of a new class of cytotoxic antibody-drug conjugates and development. The objectives of this first in human phase I study were to establish the maximum tolerated dose and to define the recommended phase II dose of IMGN when administered as monotherapy on one of two dosing regimens. Patients received the drug either every two weeks or once a week in different cohorts. The secondary objectives were to establish the safety and tolerability of IMGN and assess for obviously preliminary anti-leukemic activity.

Patients aged 18 and above with relapsed/refractory AML expressing at least 20% CD33 positivity on their blasts were eligible, and the schema of the study involved a standard 3+3 design. On the dose-escalation cohorts, a total of 57 patients were enrolled on this study and treated either on the two-week schedule, which involved 36 patients, or a weekly schedule, which involved 21 patients. Many of these patients had received intensive chemotherapy, about 70%, and about almost a third of patients were primary refractory with half of the patients being relapsed/refractory AML. Treatment of emergent adverse events primarily involved neutropenia, febrile neutropenia. The patients across both schedules received the median of about four doses of IMGN779. The most frequent severe adverse events were infection-related febrile neutropenia, bacteremia, and pneumonia, and only three SAEs were considered related to IMGN. There was no dose-dependent induction of hepatotoxicity, although there was one report of a dose-limiting toxicity at a higher dose level on the

weekly schedule with veno-occlusive disorder and acute kidney injury. One death was related to the disease. The patients have remained on this drug for up to 40 cycles without cumulative evidence of toxicity, and in patients who had received at least a 0.39 mg/kg dose, the overall response rate, CR-CRi rate was 41%. This study shows that this drug, IMGN779, first in human novel antibody-drug conjugate against CD33 is well tolerated with limited cytopenias and limited evidence of hepatotoxicity. IMGN demonstrated significant anti-leukemic activity constituting about 41% of patients receiving above 0.39 mg/kg and warrants further study either as monotherapy or as a combination partner with other anti-leukemic drugs moving forward.

Reference: Cortes J, DeAngelo D, Erba H, et al. Maturing Clinical Profile of IMGN779, a Next-Generation CD33-Targeting Antibody-Drug Conjugate, in Patients with Relapsed or Refractory Acute Myeloid Leukemia. ASH 2018. Abstract 26.

2647. Synergistic Anti-Leukemic Activity of PARP Inhibition Combine with IMGN632, an Anti-CD123 Antibody-Drug Conjugate in Acute Myeloid Leukemia Models

IMGN632 is a novel potent antibody-drug conjugate directed against CD123 expressed on the majority of AML cells. This novel antibody-drug conjugate involves a newer, highly potent cytotoxic payload which induces single-strand DNA breaks as well as a novel cleavable linker product. This drug is in early phase 1 studies, which is also being presented at this meeting, but up to now has had limited efficacy as a monotherapeutic, leading us to question whether novel combinations of this antibody-drug conjugate with other agents might lead to increased efficacy and promote future combinatorial studies. In this preclinical lab study, what we sought to do was to take advantage of the fact that this agent induces single-strand DNA breaks at highly potent levels in AML cells. In order to enhance or improve or synergize with this DNA damaging agent, we speculated that combination with PARP inhibitors, which impaired the DNA damage repair pathway, might result in synergistic anti-leukemic activity. Therefore, we examined a panel of human AML cell lines. First, we determined that the AML cell lines had expression of CD123 at high levels on this surface. We subsequently performed in vitro assays across the panel of human cell lines, demonstrating that both PARP inhibition with the variety of agents, including olaparib and talazoparib, could induce single-agent anti-leukemic activity, albeit at a low level, in these cells at baseline given that they have some degree of DNA damage at baseline. We then subsequently tested IMGN632 and were able to demonstrate a dose response across the same cell lines. Combination studies across these three or four cell lines demonstrated significant synergy with very low concentrations of both agents. Again, the most potent PARP inhibitor for these studies turned out to be talazoparib, but effects were seen across the array of PARP inhibitors which are clinically available for treatment of BRC mutant solid tumors. We subsequently moved into additional assays to assess the mechanistic effects of this combination. We noted cell cycle effects, induction of apoptosis, and decreased proliferation. Testing on this combination on primary AML cells also resulted in synergistic anti-tumor effects, and we are subsequently moving forward with in vivo studies in xenograft models of CD123 AML to demonstrate whether this combination would work in vivo in pre-clinical models.

In conclusion, we believe that this combination of these two drugs has the potential to improve the efficacy of antibody-drug conjugates which include DNA damaging payloads. Given the already

established clinical efficacy and safety of PARP inhibitors in solid tumors, combination studies of an antibody-drug conjugate with an oral agent may represent a novel combinatorial strategy worthy of testing in future clinical trials, particularly in the elderly unfit patients for whom oral administration and/or outpatient management would be preferred in this patient population. Thank you very much.

Reference: Fritz C, Portwood S, Adams J, et al. Synergistic Anti-Leukemic Activity of PARP Inhibition Combined with IMGN632, an Anti-CD123 Antibody-Drug Conjugate in Acute Myeloid Leukemia Models. ASH 2018. Abstract 2647.