Contribution ID: **119** Type: **not specified**

A Phase 2 Study of Actinium-225 (225Ac)-lintuzumab in Older Patients with Untreated Acute Myeloid Leukemia (AML)

Background: Older patients with AML unfit for intense induction chemotherapy have a poor prognosis with 5-year survival of <10%. 225Ac-lintuzumab is composed of 225Ac linked to a humanized anti-CD33 monoclonal antibody. Data were previously presented on the initial 13 patients who received 2.0μCi/kg/dose (ASH 2017, Abstract 616). Although that dose resulted in a high response rate of 69%, it was associated with a 46% incidence of Grade 4 thrombocytopenia lasting >6 weeks. Therefore, the dose was reduced to 1.5μCi/kg/dose for further evaluation.

This study enrolled older patients with untreated AML who were considered to be unfit for standard induction chemotherapy. Patients 60-74 years were required to have significant comorbidities, while all patients ≥75 years were eligible. Antecedent hematologic disorders (AHDs) were allowed. Other eligibility criteria included ECOG PS 0-2 and CD33 expression on >25% of blasts. 225Ac-lintuzumab was administered on Days 1 and 8.

Results: 40 patients were treated (13 at 2.0μCi/kg and 27 at 1.5μCi/kg). The median age was 75 years and median ECOG PS was 1. 23 patients had prior AHDs. Of the patients with known cytogenetics, 3 had favorable-risk, 17 had intermediate-risk, and 10 had adverse-risk AML. The median baseline BM blast percentage was 31% (range, 20-66%) with median CD33 expression 63% (range, 14-100%) of AML cells.

Objective responses were seen in 9 patients (69%, 2.0μCi/kg) and 6 patients (22%, 1.5μCi/kg). Overall, there were 1 complete remission, 5 complete remissions with incomplete platelet count recovery (CRp) and 9 complete remissions with incomplete hematologic recovery (CRi).

Myelosuppression was seen in all patients including Grade 4 thrombocytopenia with marrow aplasia for >6 weeks after the first dose in 46% (2.0μCi/kg) and 30% (1.5μCi/kg) with data at 6 weeks. One patient with prior MDS had pancytopenia for >4 months.

Conclusions: Preliminary data from this analysis of 225Ac-lintuzumab monotherapy in older AML patients unfit for intensive therapy indicate a lower rate of myelosuppression at 1.5μCi/kg/dose but also a lower response rate than was seen at 2.0μCi/kg/dose. Although the study met the prespecified response criteria for continuing enrollment, it was closed to further accrual since targeted radiation, like other AML therapies, will likely have the best outcomes when used in combination or in settings where myelosuppression is expected. An extensive development program in MDS, AML, and multiple myeloma is planned. In MDS, Lin-Ac225 will be used as targeted conditioning prior to hematopoietic stem cell transplant in patients with Poor/Very Poor Cytogenetics. In AML, Lin-Ac225 will be used in combination with venetoclax, with venetoclax and HMAs, with CLAG-M salvage chemotherapy, and as a single-agent for post-remission therapy. Lin-Ac225 will also be used as a single-agent for CD33-expressing relapsed multiple myeloma.

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Presentation Type

Contributed Oral

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