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616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

First Disclosure of AZD9829, a TOP1i-ADC Targeting CD123: Promising Preclinical Activity in AML Models with Minimal Effect on Healthy Progenitors

Dipannita Dutta[1], *Pan Pan*[1], *Ryan Fleming*[1], *Marcio Andrade-Campos*[2], *Elena Belova*[3], *Jennifer Wheeler*[4], *Patricia Cheung*[5], *Paul Santacroce*[6], *Casey Daniels*[6], *Darrin Sabol*[6], *Brad Jakubison*[6], *Benedicte Recolin*[7], *Andrew Dippel*[6], *Margaret Wey*[8], *Arthur Shaffer*[9], *Edward Rosfjord*[6], *Elaine Hurt*[6], *Gullu Gorgun*[3], *Anas Younes*[10,11], *Puja Sapra*[6]

[1] Astrazeneca, Gaithersburg, MD
[2] Astrazeneca, Cambridge, GBR
[3] Astrazeneca, Waltham
[4] Aclairo, sterling
[5] Hematology Oncology R&D, AstraZeneca, South San Francisco
[6] Astrazeneca, Gaithersburg
[7] Astrazeneca, Cambridge, United Kingdom
[8] Astrazeneca, Boston, MA
[9] AstraZeneca, Gaithersburg, MD
[10] AstraZeneca, New York, NY
[11] Haematology R&D, AstraZeneca, Waltham

CD123 is a cell surface protein that is overexpressed in several hematologic malignancies including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) with restricted expression in normal hematopoietic stem cells. Clinical development of an antibody drug conjugate (ADC) with first-in-class opportunity for a Topoisomerase I inhibitor (TOP1i) payload in haem malignancies including CD123-expressing AML and MDS is planned. We describe for the first time the preclinical activity of AZD9829, a CD123-targeting antibody conjugated to Astrazeneca's proprietary TOP1i payload, AZ14170132, with a drug-to-antibody ratio of 8. AZD9829's primary mechanism of action is to deliver TOP1i payload into CD123-expressing cancer cells, leading to DNA damage and apoptosis. Compared to other AML targets like CD33, CD123 is highly expressed in AML patient bone marrow (BM) with limited expression in healthy donor BM (Figure 1). AZD9829 showed robust in vitro killing of CD123-positive AML cell lines and demonstrated targeting of BM-resident tumor cells in AML patients, with mild, transitory effects on the BM compartment from healthy donors. We showed that a single intravenous (IV) dose of AZD9829 was sufficient to induce 100% tumor growth inhibition (TGI) in high and low CD123-expressing AML cell line xenografts at 2 mg/kg and 3 mg/kg, respectively. Anti-tumour activity of AZD9829 was also observed across a panel of 13 AML patient-derived xenograft (PDX) models representing AML disease heterogeneity with diverse mutation status, disease stage, prior treatment response, and expression level of CD123. These disseminated PDX models were treated with weekly IV dosing of AZD9829 at 5 mg/kg, for two doses. AZD9829 achieved ≥50% leukemic blast reduction in blood (7/7 models) (Figure 2) and in bone marrow (6/7 models) at day 14 after the first dose. Furthermore, AZD9829 demonstrated durable blast reduction at day 28 after the first dose with leukemic blast reduction in blood (7/13 models) and in bone marrow (5/13 models). Safety studies in cynomolgus monkey support the clinical development of AZD9829, a promising therapeutic candidate for the treatment of AML across the spectrum of CD123-expression and genetic mutations.

Disclosures Dutta: *Astrazeneca:* Current Employment, Current equity holder in publicly-traded company. **Pan:** *Astrazeneca:* Current Employment, Current equity holder in publicly-traded company. **Fleming:** *Astrazeneca:* Current Employment, Current equity holder in publicly-traded company. **Andrade-Campos:** *Astrazeneca:* Current Employment, Current equity holder in publicly-traded company. **Belova:** *Astrazeneca:* Current Employment, Current equity holder in publicly-traded company; *Pfizer:* Ended employment in the past 24 months. **Wheeler:** *Aclairo:* Current Employment. **Cheung:** *AstraZeneca:* Current Employment, Current equity holder in publicly-traded company. **Santacroce:** *Astrazeneca:* Current Employment, Current equity holder in publicly-traded company. **Daniels:** *Astrazeneca:* Current Employment, Current equity holder in publicly-

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First disclosure of AZD9829, a TOP1i-ADC targeting CD123: Promising preclinical activity in AML models with minimal effect on healthy progenitors

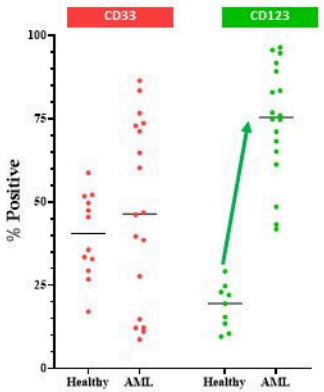

Figure 1 CD123 is highly expressed in AML with large delta between leukemic and healthy bone marrow: CD123 is a better target compared to CD33 with high expression in AML patient bone marrow and limited expression in healthy donor bone marrow

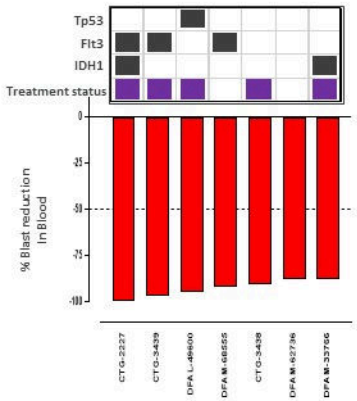

Figure 2 AZD9829 showed efficacy in different Leukemic AML PDX models: AZD9829 achieved ≥50% leukemic blast reduction in blood in all 7/7 models at Day 14 after first ADC dose at 5mg/kg.

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Figure 1