## Abstract: P520

# Title: AZD9829 DEMONSTRATES COMBINATION BENEFIT WITH HMA AND VENETOCLAX IN AML CELL LINES, PATIENT SAMPLES AND PDX MODELS.

**Abstract Type: Poster Presentation**

**Topic: Acute myeloid leukemia - Biology & translational research**

**Background:**

Long-term survival of unfit AML patients treated with the standard of care (SoC) combination of DNA hypomethylating agent (HMA) and BCL2 inhibitor Venetoclax (VEN), remains poor. Combination therapies with novel antileukemic mechanisms are needed to improve overall patient outcomes. AZD9829 is a first-in-class, Topoisomerase 1 inhibitor (Top1i) antibody drug conjugate (ADC) targeting CD123, with promising monotherapy efficacy in preclinical AML models (Dutta et al, ASH 2023). AZD9829 is currently in a Phase 1 clinical trial in patients with CD123+ R/R AML and R/R HR-MDS.

**Aims:**

We investigated the potential combination benefit from adding VEN and HMA to AZD9829, in AML cell lines, primary patient samples, and AML PDXs.

**Methods:**

*In vitro*: 7 AML cell lines were treated with either AZD9829, VEN, HMA (Decitabine), a double combination of AZD9829 and VEN or HMA, or a triple combination of AZD9829 with VEN and HMA for 6 days. Cell viability was measured by Cell Titer Glo 2.0, and synergy was assessed using the SynergyFinder package in R. Bliss scores ≥ 5 concurrent with <50% cell viability was interpreted to represent meaningful synergy.

*Ex-vivo*: 11 AML patient samples were treated with AZD9829 (125-500nM) as a single agent or in combination with VEN (0.1μM) and HMA (Azacitidine (AZA), 0.9μM). Cytotoxic effects induced by treatments were assessed by flow cytometry at day 4 post treatment. The cytotoxic effect for all treatments was measured based on changes in the absolute number of blasts reported as mean % blast reduction (BR) normalized to untreated control.

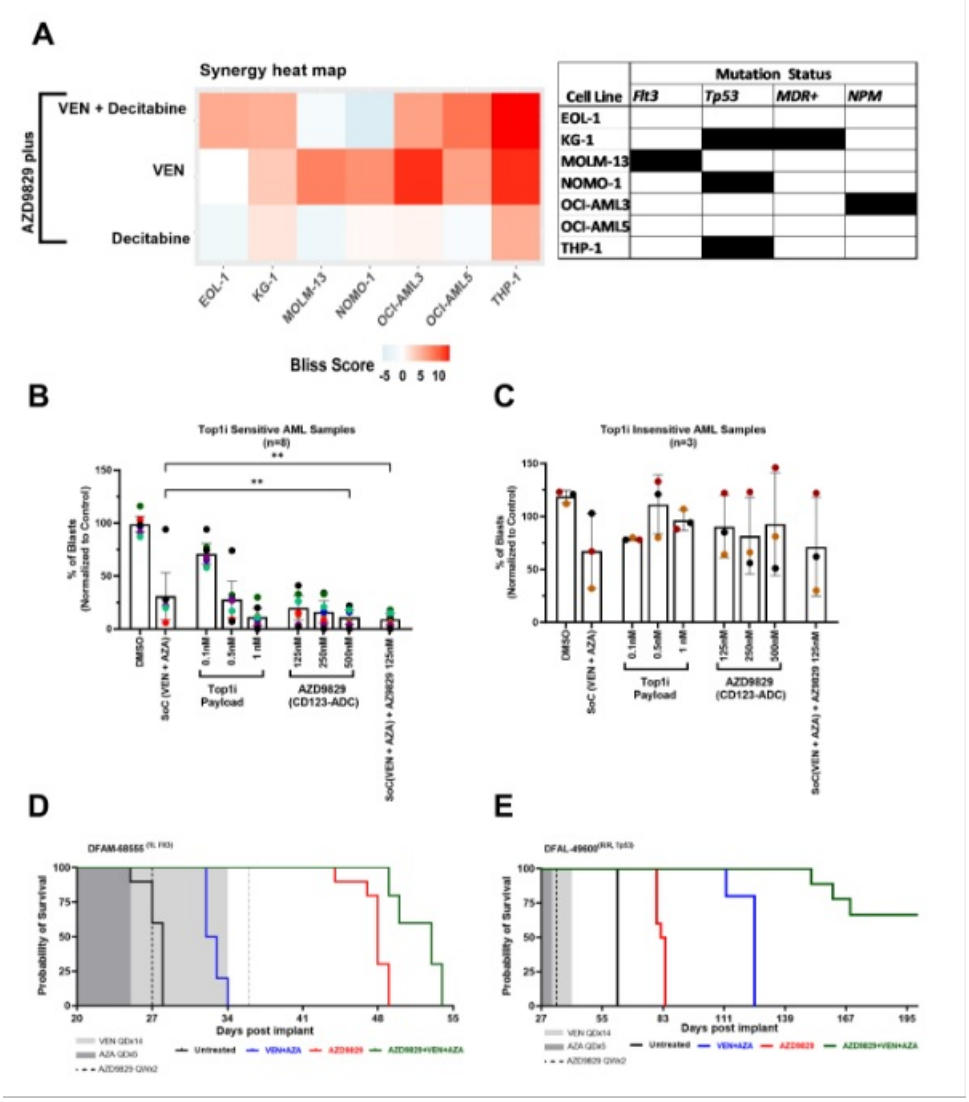
*In vivo*: Two AML PDXs were treated with either AZD9829 (4 mg/kg, QWx2) as monotherapy, or in combination with the SoC (VEN: 100 mg/kg, QDx14; AZA: 2.5 mg/kg, QDx5). Mice were monitored for clinical signs of disease progression and the survival days were recorded.

**Results:**

Cell viability data shows synergy between AZD9829 and VEN with Bliss scores >5 in 5 of the 7 cell lines tested at doses ranging from 10nM to 1μM (VEN) and 0.1nM-0.3μM (AZD9829) (Fig A). The triple combination of AZD9829 with SoC (VEN and HMA) showed synergy in 5 of the 7 cell lines (Fig A). In an *ex-vivo* drug sensitivity study, 8 of the 11 AML patient samples (Top1i sensitive samples, Fig B) demonstrated significant blast reduction (BR) with 500nM AZD9829 (89% BR) or with 1nM Top1i payload alone (89% BR) compared to SoC (69% BR). The addition of VEN and HMA to125nM AZD9829 showed improved cell killing over SoC (91% vs. 69% BR respectively). Although statistically insignificant, a greater percent blast reduction was observed with triple combination compared to 125nM AZD9829 monotherapy (91% vs. 80% BR respectively). Three patient samples did not respond to AZD9829 or Top1i payload (Top1i insensitive samples, Fig C). In AML PDX DFAM-68555 model, AZD9829 monotherapy significantly prolonged the median survival (48 days) compared to the untreated mice (28 days) and SoC-treated mice (32.5 days). The triple combination of AZD9829 with the SoC (Ven and AZA) further prolonged the median survival to 53 days (Fig D). Similarly, in DFAL-49600 PDX model, the triple combination was remarkably superior (>200 days) to both AZD9829 monotherapy (83 days), or SoC (125 days) (Fig E).

**Summary/Conclusion:**

The monotherapy treatment of AZD9829 demonstrates enhanced efficacy compared to SoC in AML patient samples with diverse molecular alterations. Our preclinical findings also offer justification for exploring combinations of AZD9829 with SoC drugs in the clinic to improve long-term AML patient outcomes.




**Keywords:** Acute myeloid leukemia, Antibody, Targeted therapy