Effects of *in vivo* IL-8 axis Blockade on Myeloid Derived Suppressor Cells (MDSC) in a Patient with High-risk MDS and Excess Blasts

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Introduction

- Myelodysplastic syndromes (MDS) are clonal bone marrow neoplasms characterized by ineffective hematopoiesis, cytopenia, and a high risk for transformation to acute myeloid leukemia (AML).
- Immune dysregulation is a key feature of MDS.
- Myeloid derived suppressor cells (MDSC) are immature myeloid cells with immunosuppressive properties that dampen the immune response and play a fundamental role in MDS pathogenesis.
- One manifestation of this immune dysregulation is an upregulation of proinflammatory cytokines such as interleukin-8 (IL-8), a chemoattractant for MDSCs, in peripheral blood and the bone marrow.
- Blockade of IL-8 axis *in vitro* was shown to reduce leukemic cell lines and primary AML/MDS cells proliferation. Effects of such blockade has never been tested *in vivo*.
- Based on safety data from early phase clinical trials investigating the anti-IL8 monoclonal antibody (BMS-986253) in patients with metastatic or unresectable solid tumors, we treated a 64-year-old patient with MDS with BMS-986253 combined with a hypomethylating agent (HMA). Herein, we summarize our clinical and laboratory findings.

Aim

Primary Aim:

- We hypothesize that adding the anti-IL8 monoclonal antibody (BMS-986253) to HMA treatment is safe for adult participants with MDS and may enhance HMA efficacy.

Secondary Aims:

- Investigate the role of MDSCs in MDS pathogenesis.
- Explore the interplay between “immune dysregulation” and MDS pathogenesis.
- Assess the therapeutic implications of targeting “immune dysregulation” in MDS.
- Evaluate the therapeutic effects of IL-8 axis blockade *in vivo* in patients with MDS

Methods

- We report single patient data: A 64-year-old female patient with MDS/EB2 (WHO) or MDS/AML (ICC).
- Patient was treated with combination oral decitabine-cedazuridine and BMS-986253 on protocol NCT05148234.
- BMS-986253 was given as: 1200 mg single dose intravenous infusion on day 1 of 28-day cycles.
- Decitabine-cedazuridine was dosed at 35mg/100 mg/day given on days 1-5 of a 28-day cycle.
- We evaluated bone marrow cell composition and immune markers using an 18-color flow panel pre and post treatment.

Results

- Patient developed osteonecrosis of the jaw (unrelated to study drug) and was taken off study after 2.5 cycles.
- Adverse events included febrile neutropenia, facial cellulitis/soft tissue infection and osteonecrosis of the jaw.

Table 1: Patient Characteristics

Age	63
Gender	Female
Diagnosis	MDS-EB2
Prior treatments	Vidaza/Venetoclax
	CPX-351
IPSS-R before BMS-986253	6.5-Very high risk
IPSS-M before BMS-986254	2.04-Very high risk
IPSS-R after BMS-986255	7-Very high risk
IPSS-M after BMS-986256	1.82-Very high risk
Response per IWG2023	Stable disease

After 3 infusions of BMS-986253 (at dose level 1):

- The percentage of MDSCs (CD45+CD33+LIN-HLADR-) in the live cell population decreased by approximately 74%.
- There was no robust change in neutrophilic MDSC, but a 98% decrease in the monocytic MDSC population (CD45+CD33+LIN-HLADR-CD11B+CD66B-CD14+CD15-).

Results

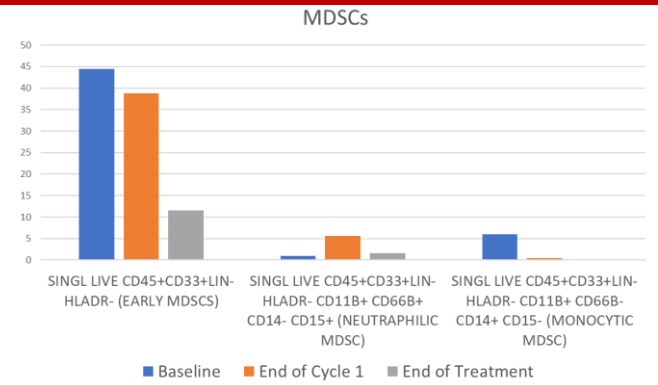


Figure: Percentage of MDSCs after 1 cycle and 2.5 cycles of BMS-986253

We also evaluated IL8 receptors, including the high affinity CXCR1 and broad cytokine receptor, CXCR2. We found that:

- The percentage of CD45+CXCR1+ cells decreased by ~39% while CD45+CXCR2+ percentages increased.

Conclusion

- These data suggest that *in vivo* blocking of the IL-8 axis, even at low doses, can decrease the egress of MDSCs. This, along with stable disease, suggests a potential therapeutic benefit in MDS, which should be further investigated in clinical trials.

References

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