ODYSSEY: A FIRST-IN-HUMAN STUDY OF THE ALDEHYDE DEHYDROGENASE (ALDH) INHIBITOR ABD-3001 IN PATIENTS WITH REFRACTORY/RELAPSED ACUTE MYELOID LEUKEMIA (AML) OR HIGH-RISK MYELODYSPLASTIC SYNDROME (MDS)

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INTRODUCTION

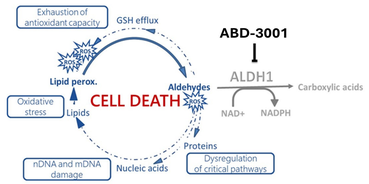
Aldehyde dehydrogenase 1 (ALDH1) is frequently overexpressed in AML and MDS, where it detoxifies intracellular aldehydes and mitigates oxidative stress, protecting leukemic cells from chemotherapy-induced cytotoxicity[1].

This activity contributes to drug resistance, persistence of leukemic stem cells, and poor clinical outcomes. Targeting ALDH1 disrupts these protective pathways, leading to toxic metabolite accumulation and selective apoptosis in malignant cells while sparing normal hematopoietic progenitors as explained in **Figure 1**[2].

This mechanism provides a strong rationale for ALDH1 inhibition as a novel therapeutic approach. ABD-3001 is a first-in-class ALDH1 inhibitor with potent anti-leukemic activity. Preclinical studies show that ABD-3001 induces apoptosis in AML cell lines and primary samples, reduces leukemic burden in vivo, and demonstrates synergy with standard agents such as anthracyclines[3].

These findings support its development as monotherapy or in combination strategies for high-risk hematologic malignancies.

Figure 1: Mechanism of action



METHOD

Main eligibility criteria

- Adults with relapsed or refractory AML after at least one prior therapy and a salvage treatment, or High-risk or very high-risk MDS.
- Patients must be ineligible for intensive chemotherapy or new generation targeted therapies.

Safety

- Treatment-emergent adverse event (TEAE)
- Recommended dose for phase 2 (RP2D) in part B

Efficacy assessment (ELN 2022 criteria)

- Overall response rate (ORR), proportion of patients with complete remission (CR), proportion of patients with CR with full, partial (CRc) or incomplete (CRi) hematological recovery.

Biomarkers

- Explore pharmacokinetics (PK) and pharmacodynamic (PD) effects and potential biomarkers of response.

Figure 2: Study Design

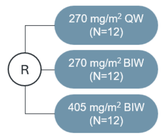


Table 1: Patient demographics

Variables	Regimen 1 270 mg/m² QW (N=6)	Regimen 2 270 mg/m² BIW (N=7)	Regimen 3 405 mg/m² (N=7)	TOTAL (N=20)
Age median (range)	**70 (60 – 80)**	**74 (29 – 80)**	**72 (57 – 89)**	**71 (29 – 89)**
≥ 65 years	5 (83.3)	6 (85.7)	6 (85.7)	17 (85.0)
Gender, N(%)				
Female	3 (50.0)	5 (71.4)	2 (28.6)	10 (50.0)
ECOG Performance status, N(%)				
< 2	5 (83.3)	6 (85.7)	5 (71.4)	16 (80.0)
≥ 2	1 (16.7)	1 (14.3)	2 (28.6)	4 (20.0)
AML, N (%)	**5 (83.3)**	**7 (85.7)**	**5 (71.4)**	**16 (80.0)**
HR-MDS, N (%)	**1 (16.7)**	**1 (14.3)**	**2 (28.6)**	**4 (20.0)**
Prior Therapies				
Prior therapy cycles median (range)	3 (2 – 11)	7 (2 – 42)	7 (2 – 23)	5 (2 - 42)
Venetoclax + Azacitidine, N (%)	3 (50.0)	6 (85.7)	6 (85.7)	15 (75.0)
Post-HCT	1 (16.7)	0 (0.0)	1 (14.3)	2 (10.0)

Table 2: AML Patient status

Variables (AML patients only)	Regimen 1 270 mg/m² QW (N=5)	Regimen 2 270 mg/m² BIW (N=6)	Regimen 3 405 mg/m² (N=5)	TOTAL (N=16)
AML Status, N (%)				
De novo	2 (40.0)	2 (33.3)	3 (60.0)	7 (43.7)
Therapy related AML	0 (0.0)	0 (0.0)	1 (10.0)	1 (6.3)
Secondary AML	3 (60.0)	4 (66.6)	1 (10.0)	8 (50.0)
ELN Classification (2022), N (%)				
Favorable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate	2 (40.0)	1 (16.7)	1 (20.0)	4 (25.0)
Adverse	3 (60.0)	5 (83.3)	4 (80.0)	12 (75.5)

RESULTS

Safety

Table 3: Safety summary

Variables N (%) [n]	Regimen 1 270 mg/m² QW (N=6)	Regimen 2 270 mg/m² BIW (N=7)	Regimen 3 405 mg/m² (N=7)	Total (N = 20)
Patient with any TEAE	**6 (100.0) [29]**	**6 (85.7%) [28]**	**6 (85.7) [35]**	**18 (90.0) [92]**
Maximum CTCAE Grade 3-4	3 (50.0) [4]	4 (57.1) [8]	5 (71.4) [9]	12 (60.0%) [21]
Patient with any ABD-3001 related TEAE	**6 (100) [20]**	**5 (71.14) [8]**	**5 (71.14) [11]**	**16 (80.0) [39]**
Maximum CTCAE Grade ≥3	2 (33.3) [3]	2 (28.5) [3]	3 (42.8) [3]	7 (35.0) [9]
Patient with any SAE	**3 (50.0) [5]**	**4 (57.1) [8]**	**5 (71.4) [9]**	**12 (60.0) [22]**
Patient with any SAE related with ABD-3001	2 (33.3%) [4]	2 (28.6) [3]	3 (42.8) [5]	7 (35.0) [12]
TEAEs leading to treatment discontinuation	**1 (16.6) [1]**	**1 (14.3) [1]**	**1 (14.3) [1]**	**3 (15.0) [3]**
TEAEs related to ABD-3001 leading to treatment discontinuation	1 (16.6) [1]	0 (0.0) [0]	1 (14.3) [1]	2 (10.0) [2]
Patient with any TEAE leading to death	**1 (16.6) [1]**	**0 (0.0 %) [0]**	**0 (0.0 %) [0]**	**1 (5.0) [1]**
Patient with any TEAE related to ABD-3001 leading to death	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Efficacy

Table 4: Summary of efficacy

Variables On Evaluable Population	Regimen 1 270 mg/m² QW (N=4)	Regimen 2 270 mg/m² BIW (N=5)	Regimen 3 405 mg/m² (N=5)	Total (N = 14)
Response N (%)				
ORR	2 (50.0)	0 (0.0)	0 (0.0)	2 (14.3)
PR	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)
CR	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.1)
CRi	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.1)
SD	3 (75.0)	2 (40.0)	2 (40.0)	7 (50.0)
Percentage of AML blasts in bone marrow, Mean (range)	**25.75 (8-62)**	**29.0 (10-60)**	**28.8 (7-65)**	**28.0 (7-65)**
Number of patient who experienced a decrease in blast from the baseline, N(%)	**3 (75.0)**	**2 (40.0)**	**1 (20.0)**	**6 (42.9)**
Hematological independency, N (%)				
RBC	2 (50.0)	3 (60.0)	1 (20.0)	6 (42.9)
Platelets	2 (50.0)	4(80.0)	1 (20.0)	7 (50.0)

Figure 3a: Treatment-Emergent Adverse Events (TEAE)

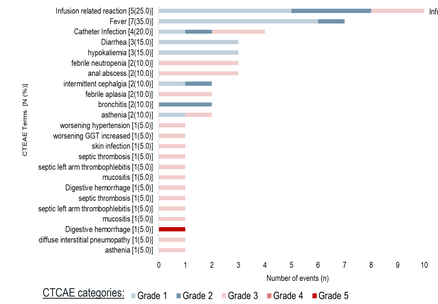


Figure 3b: Treatment-Related Adverse Events (TRAE)

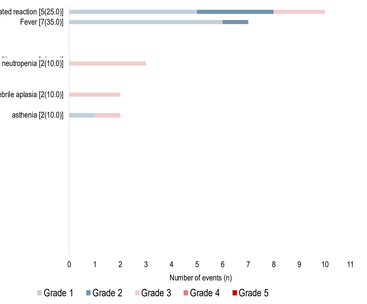
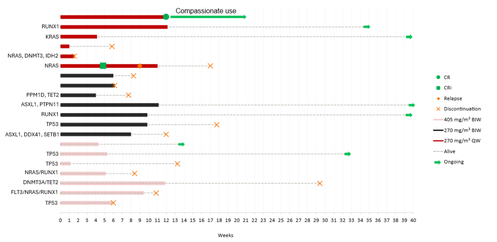
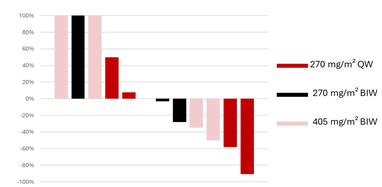


Figure 4: Overall response and treatment duration



Mean treatment duration was 6.5 weeks (range 1–11) for 270 mg/m² once weekly, 8 weeks (2–11) for 270 mg/m² twice weekly, and 6 weeks (1–12) for 405 mg/m² twice weekly; 50%, 16.7%, and 20% of patients in these cohorts completed 3 cycles, respectively.

Figure 5: Greatest percentage change in BM blast from baseline



Note: 3 subjects had a relative change from baseline of > 100%

AIM

We report data from the Dose Ranging Study (DRS) of an ongoing Phase 1, multicenter trial evaluating ABD-3001 monotherapy in R/R AML and HR-MDS. The primary objective is to determine the recommended Phase 2 dose (RP2D) and assess safety and tolerability. Secondary objectives include pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity at the RP2D.

CONCLUSIONS

ABD-3001 demonstrated an acceptable safety profile across all dose levels. Treatment-related adverse events (TREAs) occurred in 80% of patients, most commonly fever (35%) and infusion-related reactions (IRR, 25%). Grade ≥3 TREAs were reported in 35% of patients, including febrile neutropenia (10%), febrile aplasia (10%), and IRR (10%). Dose interruptions related to ABD-3001 occurred in 2 patients (1 in R1 and 1 in R3). Six patients completed all 3 planned cycles; the median number of cycles was 1.5 (≈6 weeks).

Among 14 evaluable patients, 6 (43%) showed a reduction in medullary blasts; notably, 1 achieved CR and 1 CRi at the lowest dose. Hematologic improvement was observed in 6 patients for RBC transfusion independence and in 7 for platelets. Pharmacodynamic analyses confirmed target engagement and biological activity in peripheral blasts.

These findings support continued evaluation of ABD-3001 to identify an optimal dose for further clinical development.

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