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ODYSSEY, A FIRST-IN-HUMAN STUDY OF FIRST-IN-CLASS INHIBITOR OF ALDEHYDE DEHYDROGENASE (ALDH), ABD-3001, IN PATIENTS WITH REFRACTORY/RELAPSED AML OR HIGH-RISK MDS

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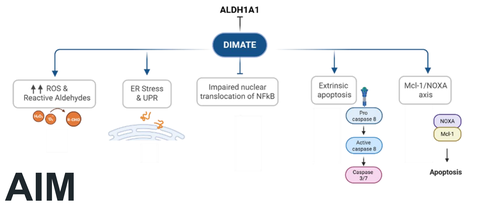
INTRODUCTION

Relapse/Refractory Acute Myeloid Leukemia (R/R AML) is a condition where patients do not achieve complete remission after chemotherapy and thus develop chemo-resistance. Aldehyde dehydrogenase 1A (ALDH1A) plays a critical role in leukemic cell survival by maintaining stemness, proliferation, and chemoresistance through aldehyde detoxification and retinoic acid synthesis. Elevated ALDH1 expression has been linked to poor prognosis in acute myeloid leukemia (AML), but the underlying mechanisms remain poorly defined[1,2,3].

Targeting ALDH1 has emerged as a promising therapeutic strategy to overcome drug resistance and selectively eliminate malignant cells. Inhibition of ALDH1 disrupts these detoxification pathways, leading to ER Stress & UPR, Extrinsic apoptosis and MCl-1/Noxa activation known as mechanism of venetoclax resistance (**Figure 1**).

Figure 1: Mechanism of action



AIM

Currently, ABD-3001 is being evaluated as a monotherapy in a Phase I clinical trial in France (ODYSSEY trial, NCT05601726). The trial aims to assess the safety, tolerability, pharmacokinetics, and preliminary efficacy of ABD-3001 in patients with relapsed or refractory AML or high-risk MDS first in a unique dose treatment and then in a 3-cycles treatment.

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

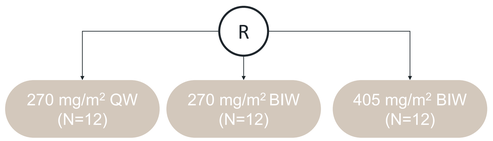
- Treatment-emergent adverse event (TEAE)
- Recommended dose for phase 2 (RP2D) in part B

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.



RESULTS

Demography

Table 1: Patient demographics

Variables	270 mg/m² QW (N=9)	270 mg/m² BIW (N=7)	405mg/m² BIW (N=9)	TOTAL (N=25)
Age median (range)	**70.9 (60.0-86.9)**	**74.3 (29.5-80.0)**	**73.3 (53.8-88.7)**	**73.96 (29.5-88.7)**
≥ 65 years	8 (88.9)	6 (85.7)	6 (66.7)	20 (80.0)
Female	**3 (33.3)**	**6 (85.7)**	**6 (66.7)**	**12 (48.0)**
ECOG Performance status, N(%)				
< 2	9 (100.0)	5 (71.5)	8 (88.9)	22 (88.0)
≥ 2	0 (0.0)	2 (28.6)	1 (11.1)	3 (12.0)
MDS, N (%)	**1 (11.1)**	**1 (14.3)**	**3 (33.3)**	**5 (20.0)**
MDS IPSS-R risk group N (%)	**1**	**1**	**3**	**5**
High risk	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)
Very High risk	1 (100.0)	1 (100.0)	2 (66.6)	4 (80.0)
AML, N (%)	**8 (88.9)**	**6 (85.8)**	**6 (66.6)**	**20 (80.0)**
Relapse	4 (44.4)	3 (42.9)	5 (55.5)	12 (48.0)
Refractory	4 (44.4)	3 (42.9)	1 (11.1)	8 (32.0)
Prior Therapies				
Prior therapy cycles median (range)	4 (2-69)	7 (4-42)	7 (2-23)	7 (2-69)
Venetoclax + Azacitidine, N (%)	6 (66.6)	6 (85.7)	5 (55.5)	17 (68.0)
Post-HCT	2 (22.2)	1 (14.3)	0 (0.0)	3 (12.0)
Genetic abnormalities, N (%)				
$TP53^{mut}$	0 (0.0)	1 (14.3)	2 (22.2)	3 (12.0)
FLT3-ITD^{pos} / $NRAS^{mut}$ / $KRAS^{mut}$	3 (33.3)	0 (0.0)	2 (22.2)	5 (20.0)

Table 2: AML Patient status

Variables (AML patients only)	270 mg/m² QW (N=8)	270 mg/m² BIW (N=6)	405mg/m² BIW (N=6)	TOTAL (N=20)
AML Status, N (%)				
De novo	3 (37.5)	2 (33.3)	3 (50.0)	8 (40.0)
Therapy related AML	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.0)
Secondary AML	5 (62.5)	4 (66.7)	2 (33.3)	11 (55.0)
ELN Classification (2022), N (%)	**8**	**6**	**6**	**20**
Favourable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate	3 (37.5)	1 (16.6)	1 (16.6)	5 (25.0)
Adverse	5 (62.5)	5 (83.3)	5 (83.3)	15 (75.0)

Safety

ABD-3001 has a manageable safety profile, in a single or in a multiple dose (Table 2). No Grade 5 drug-related AE and only one dose-limiting toxicity at the highest dose of part A were reported (Figure 2). Most common Grade 3/4 AE were infusion related reaction and fever suggesting an immune activation pattern (Figure 3).

Table 2: Safety summary

Variables N (%) [n]	270 mg/m² QW (N=9)	270 mg/m² BIW (N=7)	405mg/m² BIW (N=9)	TOTAL (N=25)
Patient with any TEAE	**8 (88.9) [49]**	**7 (100.0) [74]**	**8 (88.9) [63]**	**23 (92.0) [186]**
Maximum CTCAE Grade 3-4	4 (44.4) [5]	6 (85.7) [13]	6 (66.7) [18]	16 (64.0) [36]
Patient with any ABD-3001 related TEAE	**8 (88.9) [30]**	**6 (85.7) [15]**	**6 (66.6) [22]**	**20 (80.0) [67]**
Maximum CTCAE Grade ≥3	2 (22.2) [3]	1 (14.3) [1]	2 (22.2) [6]	5 (20.0) [10]
Patient with any SAE	**4 (44.4) [7]**	**5 (71.4) [14]**	**6 (66.7) [11]**	**15 (60.0) [32]**
Patient with any SAE related with ABD-3001	3 (33.3) [5]	0 (0.0) [0]	2 (22.2) [3]	5 (20.0) [8]
TEAEs leading to treatment discontinuation	**1 (11.1) [1]**	**2 (28.6) [3]**	**1 (11.1) [1]**	**4 (16.0) [5]**
TEAEs related to ABD-3001 leading to treatment discontinuation	1 (11.1) [1]	1 (14.2) [1]	1 (11.1) [1]	3 (12.0) [3]
Patient with any TEAE leading to death	**2 (22.2) [2]**	**0 (0.0) [0]**	**0 (0.0) [0]**	**2 (8.0) [2]**
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]

Figure 2: Treatment-Emerging Adverse Events

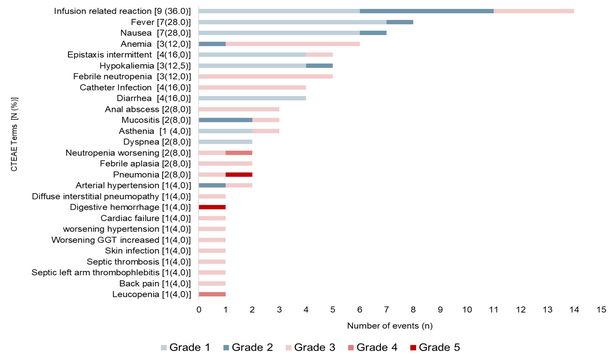
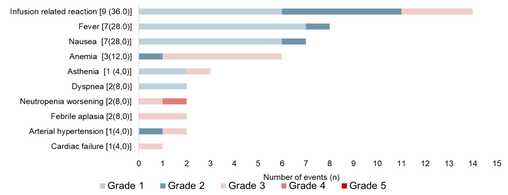


Figure 3: Treatment-Related Adverse Events



Efficacy

In a multiple dose, overall response rate (ORR) are observed in 23.6% of evaluable patients in all cohorts and a CR and a CRi have been experienced in the cohort 270mg/m² QW (Table 3).

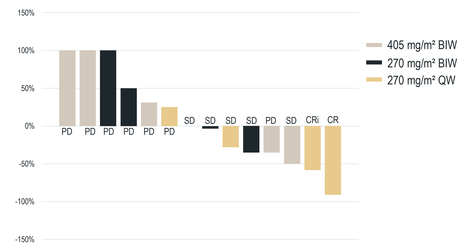
In 47% of evaluable patients, a clinical benefit was observed (defined as non progressive disease (ORR+SD)) (Figure 4).

Table 3: Summary of efficacy

Variables on Evaluable patients	270 mg/m² QW (N=5)	270 mg/m² BIW (N=5)	405mg/m² BIW (N=7)	TOTAL (N=17)
Response N (%)				
ORR	2 (40.0)	1 (20.0)	1 (14.3)	4 (23.6)
PR	0 (0.0)	1 (25.0)	1 (14.3)	2 (11.8)
CRi	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.9)
CR	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.9)
ORR+SD	3 (60.0)	2 (40.0)	3 (42.8)	8 (47.0)
Mean percentage of AML blasts in bone marrow [mean (range)]	**23.6 (8-61)**	**29.0 (10-60)**	**25.7 (7-65)**	**26.1 (7-65)**
Number of patient who experienced a decrease in blast from the baseline N(%)	**3 (60.0)**	**2 (40.0)**	**2 (28.6)**	**7 (41.1)**
Hematological independency, N (%)				
RBC	2 (40.0)	1 (20.0)	1 (14.3)	4 (23.5)
Platelets	2 (40.0)	2 (40.0)	1 (14.3)	5 (29.4)

Abbreviation: PD, Progressive Disease ; SD, Stable Disease ; PR, Partial Remission ; CR, Complete Remission

Figure 4: Greatest percentage change in BM blast from baseline



Note: 2 subjects had a relative change from baseline of > 100%.

Abbreviation: PD, Progressive Disease ; SD, Stable Disease ; PR, Partial Remission ; CR, Complete Remission

CONCLUSIONS

In this ongoing Phase 1 study in patients with R/R AML or HR MDS, ABD-3001 were safe and well tolerated, and generated preliminary efficacy result.

- ABD-3001 had a good tolerability in monotherapy.
- Most TREA suggest an immune activation pattern.
- ABD-3001 demonstrated encouraging antitumour activity in all cohorts tested with one CR and one CRi.
- 47% of evaluable patient may benefit from the treatment in monotherapy.

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CONTACT INFORMATION

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