First-in-Human Study of ABBV-075 (Mivebresib), a Pan-Inhibitor of Bromodomain and Extra Terminal Proteins, in Patients With Relapsed/Refractory Acute Myeloid Leukemia (AML): Preliminary Data

AML-187

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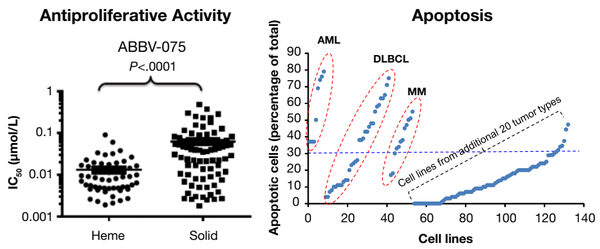
Presented at the Society of Hematologic Oncology (SOHO) 6th Annual Meeting ● Houston, TX ● September 12 – 15, 2018

BACKGROUND

- Patients with relapsed/refractory (R/R) AML have very poor prognosis and their treatment remains a clinical challenge[1]
- The Bromodomain and Extra Terminal (BET) family of proteins contain 2 bromodomains that bind acetylated lysines on histone tails to regulate gene transcription, and have been demonstrated to control the transcription of oncogenic "super-enhancer"–driven genes involved in cancer pathogenesis[2]
- In AML cells, genetic aberrations that activate transcription through BET-mediated mechanisms (eg, mixed lineage leukemia fusions/nucleophosmin mutation) can lead to oncogenesis[3]
- The inhibition of BET prevents assembly of the macromolecular complex at enhancer, promoter sites and its transcriptional response
- ABBV-075 (mivebresib) is a pan-BET inhibitor with antitumor activity in vitro and in xenograft models of AML[4] (**Figure 1**)
- This phase 1, first-in-human, 2-part study (NCT02391480) assessed the safety and pharmacokinetics (PK) of ABBV-075 at various monotherapy or combination dosing schedules
- Herein, we report preliminary data from Part 2 in patients with R/R AML

Figure 1. ABBV-075 Induces Apoptosis in Hematologic Cancer Cell Lines



AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; heme, hematologic; IC50, half maximal inhibitory concentration; MM, multiple myeloma.

OBJECTIVES

Primary

- Determine the safety and tolerability of ABBV-075 monotherapy (ABBV075-mono) or combination therapy with venetoclax (ABBV075-VEN) in disease-specific expansion cohorts

Secondary

- Evaluate preliminary antitumor activity in disease-specific expansion cohorts

METHODS

STUDY DESIGN

- Phase 1 open-label, multicenter, two-part dose-escalation study of ABBV-075 in patients with R/R advanced malignancies
  - Only the results of the AML expansion cohort treated with either ABBV075-mono or ABBV075-VEN are reported herein (data cutoff: Apr 6, 2018)
- Dosing of AML patients began after selection of the ABBV075-mono schedule and recommended phase 2 dose in solid tumors
- Dose levels of ABBV-075 in AML differed from solid tumors, but need to remain undisclosed
- ABBV075-VEN cohorts received 50% or 100% of the highest ABBV-075 dose cleared in AML monotherapy combined with 400 or 800 mg venetoclax

METHODS (CONTINUED)

STUDY DESIGN (CONTINUED)

- Venetoclax dosing started with a ramp-up phase of 4 days (starting at cycle 1) to mitigate the risk of tumor lysis syndrome (TLS); ABBV-075 was added to venetoclax once the target dose was reached
- Study drugs were administered orally once daily until progressive disease (PD) or unacceptable toxicity
- All patients were hospitalized and closely monitored the day prior to start of combination and for the first 48 hours after ABBV-075 was added to venetoclax
- All patients received TLS prophylaxis prior to and during treatment
- The dose-limiting toxicity (DLT) period was 28 days for monotherapy and 21 days for combination starting after the first day of both drugs in target dose
- For patients with AML, a DLT was defined as
  - Any grade ≥2 neurotoxicity
  - Unexpected grade 2 toxicity that requires dose reduction or dose delay lasting >1 week
  - Grade ≥3 nausea or vomiting for >48 hours or diarrhea for >72 hours despite maximum supportive care; grade ≥3 hypertension despite anti-hypertensive treatment
  - Any grade ≥3 adverse event (AE), unless an alternative etiology is identified
  - Prolonged myelosuppression, as defined by the National Cancer Institute (NCI) criteria specific for leukemia
  - Alanine aminotransferase or aspartate aminotransferase grade 4 elevation or grade 3 elevation lasting for >7 days
  - Treatment delay of ≥14 days due to unresolved toxicity
  - Neutropenia and thrombocytopenia were not considered a DLT

ELIGIBILITY CRITERIA (AML EXPANSION COHORT)

- Key inclusion criteria
  - ≥18 years of age
  - Histologically confirmed AML that is refractory after standard of care therapy or for which standard of care therapy does not exist
    - Patients with a history of autologous or allogenic stem cell transplantation allowed with no transplant-related toxicities and are: 100 days post-autologous transplant or ≥6 months post-allogenic transplant without graft-versus-host disease
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 2
  - Adequate renal and hepatic function
- Key exclusion criteria
  - Active central nervous system disease
  - Anticancer therapy (including chemotherapy, immunotherapy, biologic or any investigational therapy) within 21 days prior to first administration of study drug
  - Unresolved toxicities (grade ≥2, excluding alopecia) from most recent prior anticancer therapy
  - Major surgical procedure within 28 days prior to first dose of study drug
  - Peripheral neuropathy ≥2 grade

ASSESSMENTS

- AE: graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03
- Efficacy: all patients who received at least 1 week of therapy at the prescribed target dose
- Disease was assessed with bone marrow aspirate and/or biopsy at screening, cycle 2 day 1, and as clinically indicated
- Response: per response criteria for AML from the revised guidelines by the International Working Group (IWG)[5]

RESULTS

- As of 6 Apr 2018, 23 patients with R/R AML were enrolled in the AML expansion cohorts; 12 patients in ABBV075-mono, 11 patients in ABBV075-VEN
- Patient demographics are reported in **Table 1**

Table 1. Patient Demographics and Baseline Characteristics

Characteristic		Total N=23
Age, median (range), years		70 (30 – 84)
Gender, n (%)	Female	13 (56.5)
	Male	10 (43.5)
Race, n (%)	White	20 (87.0)
	Black	2 (8.7)
	Asian	1 (4.3)
ECOG PS, n (%)*	0	2 (8.7)
	1	18 (78.3)
	2	2 (8.7)
Number of prior therapies, n (%)	0	2 (8.7)
	1 – 2	5 (21.7)
	≥3	16 (69.5)

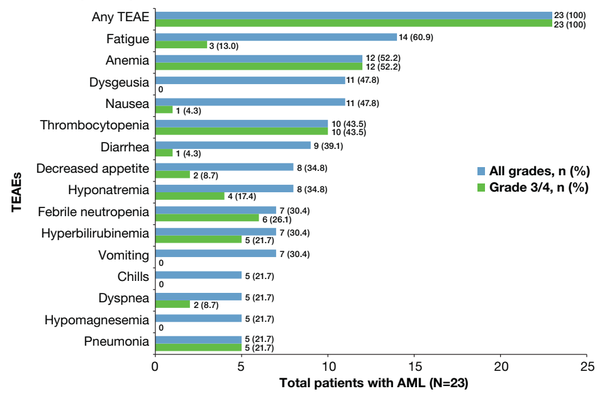
*Missing for 1 patient.
ECOG, Eastern Cooperative Oncology Group; PS, performance status.

- Median treatment duration for ABBV-075 was 39 days (range, 3 – 317)
- 18 patients discontinued study drug. Reasons for discontinuation included: AE related to progression, 4.3% (n=1); AE not related to progression, 4.3% (n=1); cytologic progressive disease, 4.3% (n=1); clinical progressive disease, 30.4% (n=7); and other, 34.8% (n=8), which comprised lack of efficacy, hospice, patient expired, drug withheld due to AE (n=1 each), physician/principal investigator decision (n=2), and patient decision (n=2)

SAFETY

- Treatment-emergent AEs (TEAEs) in ≥20% of patients, all grades, are summarized in **Figure 2**
- 23 (100%) patients reported grade 3 or 4 TEAEs. The most common grade 3 or 4 TEAEs were anemia, thrombocytopenia, and febrile neutropenia, and in 12 (52.2%), 10 (43.5%), and 6 (26.1%) patients, respectively
- 19 (82.6%) patients experienced serious AEs, which included febrile neutropenia (n=4, 17.4%) and pneumonia (n=3, 13.0%)
- 13 patients died of causes assessed as unrelated to ABBV-075; 5 patients died due to AML progression
- No DLTs were observed

Figure 2. Summary of Treatment-Emergent Adverse Events in ≥20% of Patients (N=23)

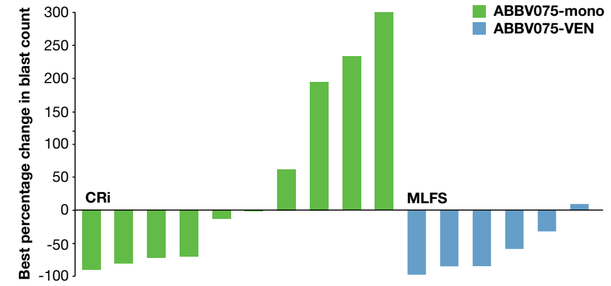


AML, acute myeloid leukemia; TEAE, treatment-emergent adverse event.

EFFICACY

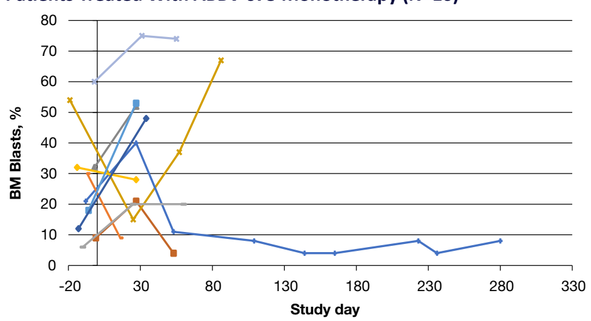
- The objective response rate was 17.6% (3/17) in patients evaluable for efficacy
  - 1 patient achieved complete remission with incomplete hematologic recovery (ABBV075-mono)
  - Patients treated with ABBV075-VEN either achieved a morphologic leukemia-free state (n=1) or partial response (n=1)
  - The remaining patients either had resistant disease (n=14), or were not evaluable (n=6; post-baseline assessment not available)
- The best percentage change from baseline in bone marrow blasts is shown in **Figure 3**; percentage change over course of treatment (ABBV-mono) is shown in **Figure 4**
  - Median best percentage change from baseline was a –45.3% reduction of bone marrow blasts (range, –97.6% to +300%)
- Median progression-free survival was 3.0 months (95% CI, 0.0 – not reached [NR]) and median overall survival was 3.2 months (95% CI, 1.4 – NR)
- At data cutoff, median duration of response was 4.1 months

Figure 3. Best Percentage Change in Bone Marrow Blasts From Baseline (N=16)



CRi, complete remission with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; mono, monotherapy; VEN, venetoclax.

Figure 4. Percentage Change in Bone Marrow Blasts Over Time in Patients Treated With ABBV-075 Monotherapy (N=10)



CONCLUSIONS

- ABBV-075 demonstrates an acceptable safety profile in patients with R/R AML both as a monotherapy and in combination with venetoclax
- Both treatment regimens, ABBV075-mono and ABBV075-VEN, showed antileukemic effects in patients with heavily pretreated R/R AML at doses lower than the maximal tolerated dose
- Further evaluation of ABBV-075 treatment regimens within the R/R AML patient population is warranted

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REFERENCES

1. NCCN Guidelines. Acute myeloid leukemia. Version 1. 2018.
2. Prinjha RK, et al. *Trends Pharmacol Sci*. 2012;33(3):146.
3. Dawson MA, et al. *Leukemia*. 2014;28(2):311.
4. Bui MH, et al. *Cancer Res*. 2017;77(11):2976.
5. Cheson BD et al. *J Clin Oncol*. 2003;21(24):4642.

DISCLOSURES & ACKNOWLEDGEMENTS

AUTHOR DISCLOSURES

G Borthakur: Research support from AbbVie. **I Aldoss**: Honoraria: Helocyte, Jazz Pharmaceuticals; consulting or advisory role: Helocyte; speaker: Jazz Pharmaceuticals; travel, accommodations, expenses: Helocyte, Jazz Pharmaceuticals. **D Rizzieri**: Consulting or advisory role: Novartis, Kite Pharma, Gilead Sciences, Incyte, Pfizer, TEVA, Seattle Genetics, Amgen; speaker: Incyte, Seattle Genetics, Gilead Sciences. **O Odenike**: Consulting or advisory role: CTI/Baxalta, AbbVie, Pfizer, Jazz Pharmaceuticals; research funding: Celgene, Incyte, Astex Pharmaceuticals, NS Pharma, AbbVie, Gilead Sciences, Janssen Oncology, MEI Pharma, Millennium, OncoTherapy Science, Agios. **BA Jonas**: Grant/Research support: AbbVie, Celgene, Daiichi Sankyo, Pharmacyclics, Genentech/Roche, GlycoMimetics, Incyte, Esanex, KaloBios; consulting or advisory role: AbbVie, Celgene, Tolero, Amgen; patents, royalties, other intellectual property: Accelerated Medical Diagnostics. **B Hu, A Torres, M Dinh**: AbbVie employees and may own stock. **X Chen**: AbbVie employee; travel, accommodations, expenses: AbbVie. **A Sood**: AbbVie employee and may own stock; honoraria: QOL Medical, Sucampo Pharmaceuticals; consulting or advisory role: Takeda, Kimberly-Clark, QOL Medical, Sucampo Pharmaceuticals. **J Wolff**: AbbVie employee and owns stock; travel, accommodations, expenses: AbbVie.

ABBVIE DISCLOSURES

AbbVie provided financial support for the study and participated in the design, study conduct, as well as in the writing, review, and approval of this poster.

ACKNOWLEDGEMENTS

AbbVie and the authors thank the patients participating in this clinical trial and all study investigators for their contributions. Medical writing support was provided by Mary L. Smith, PhD, CMPP, from TRM Oncology, Atlanta, GA and funded by AbbVie.