Phase I Interim Safety and Efficacy of Venetoclax (ABT-199/GDC-0199) Monotherapy for Relapsed/Refractory (R/R) Multiple Myeloma (MM)

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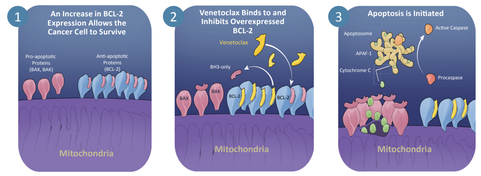
BACKGROUND

- The anti-apoptotic protein BCL-2 is highly expressed in a subset of myeloma cells and has been implicated in mediating myeloma cell survival[1]
- Venetoclax (ABT-199/DC-0199) is a potent, selective, orally bioavailable small-molecule BCL-2 inhibitor[2] (**Figure 1**)
- Venetoclax induces cell death in multiple myeloma cell lines and primary samples *in vitro*
  - Multiple myeloma cells harboring the t(11;14) chromosomal translocation have a high level of BCL-2 and low level of MCL-1, which increases sensitivity to single-agent venetoclax treatment[1]

Figure 1. Mechanism of Action of Venetoclax



BH3-only family member proteins include BIM, BAD, PUMA, and NOXA.

OBJECTIVES

- The current Phase 1 study evaluates safety and efficacy of venetoclax in patients with relapsed or refractory multiple myeloma
- Primary study objectives:
  - Determine the dosing schedule, maximum tolerated dose (MTD), and recommended phase 2 dose (RPTD)
  - Assess the safety profile and characterize pharmacokinetics (PK)
- Secondary and exploratory objectives:
  - Evaluate preliminary efficacy of venetoclax, including overall response rate (ORR), time to disease progression, and duration of overall response
  - Assess exploratory pharmacodynamics and pharmacogenomics parameters

METHODS

- This is a Phase 1, open-label multicenter study of venetoclax monotherapy in patients with relapsed/refractory multiple myeloma, consisting of dose escalation and safety expansion portions
  - Only dose-escalation data are reported herein

KEY PATIENT ELIGIBILITY CRITERIA

- Inclusion
  - Previously treated multiple myeloma (for dose escalation portion, ≥1 line of therapy which may include autologous stem cell transplant)
  - Measurable disease at baseline, including monoclonal protein ≥1.0 g/dL in serum or ≥200 mg/24 hours in urine, or serum immunoglobulin free light chain ≥10 mg/dL
  - ECOG performance status 0 or 1
  - Adequate bone marrow, renal , and hepatic function
    - ANC >1000/µL, hemoglobin ≥9 g/dL, platelet count ≥70,000/mm^3; patients with heavily infiltrated bone marrow may use growth factor support
    - Calculated creatinine clearance ≥30 mL/min

METHODS (CONTINUED)

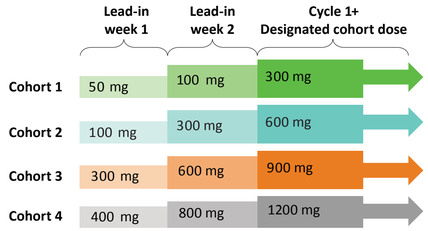
KEY PATIENT ELIGIBILITY CRITERIA (CONTINUED)

- Exclusion
  - Active infection
  - History of significant renal, neurologic, psychiatric, endocrine, immunologic, cardiovascular, or hepatic disease within 6 months of study entry
  - History of other active malignancies within 3 years of study entry

DOSING SCHEMA

- Following a 2-week lead-in period, patients were treated on a 21-day cycle with daily venetoclax ranging from 300 to 1200 mg in the following dosing cohorts (3+3 design), **Figure 2**

Figure 2. Dose Escalation Schedule



- Patients received prophylaxis for tumor lysis syndrome (TLS) and were monitored at first dose and dose increases
- Patients who progressed during treatment were permitted to receive dexamethasone in addition to venetoclax and continue the study

ASSESSMENTS

- Dose-limiting toxicities (DLTs) were assessed during cycle 1
- Safety was measured by the incidence and severed of adverse events, according to the NCI-CTCAE Version 4.0
- Pharmacokinetic parameters were determined for venetoclax at each dose level
- Disease responses were assessed per IMWG criteria
- Chromosomal abnormalities were evaluated by FISH

RESULTS

- As of March 26, 2015, 29 patients are enrolled in the study

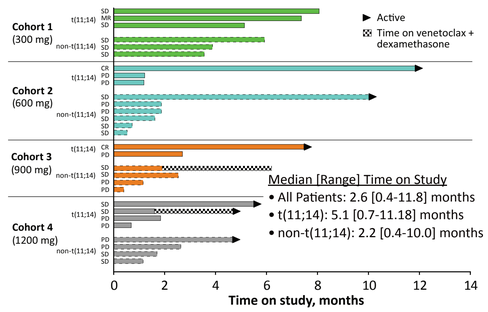
Table 1. Patient Characteristics

Characteristic	N = 29
Age, median [range]	66 [42–79]
Male gender, n (%)	16 (55)
White race, n (%)	24 (92)
ISS stage III, n (%)	6 (22)
Cytogenetic abnormalities, n (%)[a]	
t(11;14)	11 (41)
t(4;14)	2 (8)
del17p	4 (15)
del13q	14 (54)
Prior therapies	
Median [range] lines of therapy	6 [1–13]
Stem cell transplant, n (%)	19 (66)
Bortezomib / Refractory, n (%)[b]	26 (90) / 15 (52)
Bortezomib and lenalidomide / Refractory, n (%)	24 (83) / 10 (34)
Lenalidomide / Refractory, n (%)[b]	27 (93) / 12 (41)
Creatinine clearance 30–50 mL/min, n (%)	6 (21)

[a]Percentages based on number of patients with known cytogenetic status.
[b]Percentages based on total population.

RESULTS (CONTINUED)

Figure 3. Current Status of Enrolled Patients



Best response is shown for each patient:CR, complete response; MR, minimal response; SD, stable disease; PD, progressive disease.

Treatment Discontinuations

- 23 (79%) patients discontinued treatment as of March 26, 2015
  - 18 due to disease progression
    - 2 patients died due to progression (no other deaths reported)
  - 4 due to adverse events: worsening shortness of breath, hypokalemia, nausea, and nausea with vomiting
  - 1 due to patient decision

SAFETY

Table 2. Treatment-Emergent Adverse Events (AE)

Event, n (%)	N=29
AEs, any grade	**29 (100)**
Common all-grade AEs (in ≥ 20% patients)	
Diarrhea	12 (41)
Nausea	12 (41)
Fatigue	7 (24)
Vomiting	6 (21)
Neutropenia	6 (21)
Asthenia	6 (21)
Grade 3/4 AEs	**17 (59)**
Common grade 3/4 AEs (in ≥10% patients)	
Thrombocytopenia	7 (24)
Neutropenia	4 (14)
Anemia	3 (10)
Serious AEs[a]	**10 (35)**
Common serious AEs (in ≥5% patients)	
Pyrexia	2 (7)
Malignant neoplasm progression	2 (7)
Cough	2 (7)

[a]1 SAE of epigastric pain was assessed as possibly related to venetoclax.

Dose-Limiting Toxicities (DLT)

- 2 patients had DLTs at 600 mg:
  - Upper abdominal pain
  - Nausea with abdominal pain
- Maximum tolerated dose (MTD) was not reached; recommended phase 2 dose (RPTD) of 1200 mg was determined from safety and efficacy data in each cohort
- No patients developed tumor lysis syndrome

PHARMACOKINETICS

- Steady state venetoclax exposures are approximately dose proportional at 300, 600, and 1200 mg (**Figure 4, Table 3**)

Figure 4. Preliminary Time-Concentration Profile

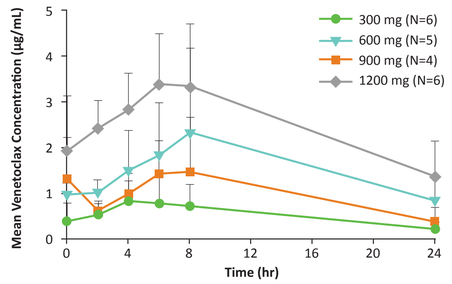


Table 3. Preliminary Pharmacokinetic Parameters

Pharmacokinetic Parameters, mean (SD)	300 mg N = 6	600 mg N=5	900 mg N=4	1200 mg N=6
T_{max} (h)	5.0 (42)	6.0 (47)	6.0 (27)	6.0 (30)
C_{max} (µg/mL)	0.90 (66)	2.42 (73)	1.72 (62)	3.64 (29)
AUC_{24} (µg•h/mL)	13.0 (61)	37.2 (67)	22.7 (65)	58.7 (37)
C_{max}/Dose (µg/mL)/mg	0.0030 (66)	0.0040 (73)	0.0019 (62)	0.0030 (29)
AUC_{24}/Dose (µg•h/mL)/mg	0.043 (61)	0.062 (67)	0.025 (65)	0.049 (37)

EFFICACY

Table 4. Preliminary Efficacy Results

	All Patients n=29	t(11;14) n=11	non-t(11;14)[a] n=18
Overall response, n (%)	2 (7)	2 (18)	0
Complete response, n (%)	2 (7)	2 (18)	0
Partial response, n (%)	0	0	0
Minimal response, n (%)	1(3)	1 (9)	0
Stable disease, n (%)	15 (52)	3 (27)	12 (67)
Disease progression, n (%)	11 (38)	5 (46)	6 (33)
Time on study, median months [range]	2.5 [0.4-11.8]	5.1 [0.7-11.8]	1.9 [0.4-10.0]
Time to progression, median [range]	2.0 [1.2-4.0]	3.9 [1.2-6.0]	1.9 [1.2-4.0]
Duration of stable disease, median [range]	2.2 [0.04-9.2]	3.5 [2.8-6.1]	1.3 [0.04-2.81]
Stable disease >2 months, n/N[b]	8/15	3/3	5/12

[a]Includes patients with unknown t(11;14) status.
[b]Based on patients whose best response was stable disease.

- Two patients experienced CR (1 each at 600 mg and 900 mg), and both had t(11;14)
  - Patient with CR in 600 mg dose cohort
    - Duration of response: 2.1 months as of March 26, 2015 (patient is still responding)
  - Patient with CR in 900 mg dose cohort
    - Duration of response: 2.8 months as of March 26, 2015 (patient is still responding)

CONCLUSIONS

- Venetoclax monotherapy was well tolerated in heavily-pretreated R/R multiple myeloma patients
- Preliminary limited efficacy data, including complete responses and stable disease, are supportive of single agent activity of venetoclax in this population, as observed in t(11;14) patients
- Venetoclax exposure was dose proportional at all but one dose level, based on limited pharmacokinetic data
- Biomarker data continue to be collected and analyzed, including cytogenetic data and Bcl-2 family member proteins
- Recommended phase 2 dose was achieved; the study is currently enrolling in the safety expansion cohort at 1200 mg

REFERENCES

1. Touzeau C, et al. *Leukemia*. 2014; 28(1): 210-212.
2. Souers AJ, et al. *Nat Med*. 2013; 19(2): 202-208.

DISCLOSURES

AUTHOR DISCLOSURES

S Kumar has received research support to his institution for clinical trials from Celgene, Novartis, Millennium, and Abbvie. JL Kaufman is a consultant to Takeda, Celgene, Onyx, Novartis, Spectrum, and Janssenn and has received research support from Merck, Onyx, and Novartis. J Mikhael has received institutional research funding from Onyx, Celgene, Sanofi, and AbbVie. C Touzeau has received research funding from AbbVie.R Vij, T Facon, P Moreau, and M Amiot have not relevant conflicts to disclose.

S Alzate, L Morris, J Ross, M Dunbar, M Zhu, S Agarwal, J Leverson, S Enschede, R Humerickhouse are all AbbVie employees and stock owners

ABBVIE DISCLOSURES

AbbVie and Genentech provided financial support for the study and participated in the design, study conduct, analysis and interpretation of data as well as the writing, review and approval of the abstract. Venetoclax (ABT-199/GDC-0199) is being developed in collaboration with Genentech.

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