PHASE 1B INTERIM RESULTS: VENETOCLAX (ABT-199/GDC-0199) IN COMBINATION WITH BORTEZOMIB (BTZ) AND DEXAMETHASONE (DEX) IN RELAPSED/REFRACTORY (R/R) MULTIPLE MYELOMA (MM)

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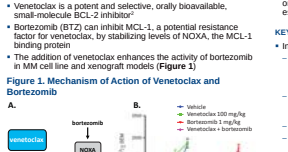
INTRODUCTION

- The anti-apoptotic protein, BCL-2, is highly expressed in a subset of myeloma cells and can promote cell survival[1]
- Venetoclax is a potent and selective, orally bioavailable, small-molecule BCL-2 inhibitor[2]
- Bortezomib (BTZ) can inhibit MCL-1, a potential resistance factor for venetoclax, by stabilizing levels of NOXA, the MCL-1 binding protein
- The addition of venetoclax enhances the activity of bortezomib in MM cell line and xenograft models (**Figure 1**)

Figure 1. Mechanism of Action of Venetoclax and Bortezomib



(A) Schematic showing the effect of venetoclax and bortezomib combination therapy in multiple myeloma cells expressing high levels of both BCL-2 and MCL-1: venetoclax directly inhibits BCL-2, and bortezomib indirectly inhibits MCL-1 (via NOXA stabilization), leading to apoptosis. **(B)** Anti-tumor activity of venetoclax and bortezomib combination treatment in a t(4;14) H929 multiple myeloma xenograft model; ***p<0.001 vs vehicle.

OBJECTIVES

- This Phase 1 study evaluates venetoclax with BTZ and dexamethasone in patients with relapsed/refractory MM
- Primary study objectives:
  - Determine dosing schedule, maximum tolerated dose (MTD), and recommended phase 2 dose (RPTD) of venetoclax when combined with bortezomib and dexamethasone
  - Assess the safety profile and characterize pharmacokinetics (PK)
- Secondary and exploratory objectives:
  - Evaluate preliminary efficacy, 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 in combination with bortezomib and dexamethasone in relapsed or refractory multiple myeloma patients, consisting of dose escalation and safety expansion portions

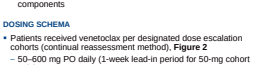
KEY PATIENT ELIGIBILITY CRITERIA

- Inclusion
  - Previously treated multiple myeloma; for dose escalation (DE) 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 ≥200mg/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
- Exclusion
  - Active infection
  - Intolerance/allergy to bortezomib, dexamethasone, or their components

DOSING SCHEMA

- Patients received venetoclax per designated dose escalation cohorts (continual reassessment method), **Figure 2**
  - 50–600 mg PO daily (1-week lead-in period for 50-mg cohort only)
  - Dose escalation continues (enrolling at 800 mg)
- Venetoclax was given as monotherapy in cycle 12 and beyond

Figure 2. Dosing Schema



- Patients received prophylaxis for tumor lysis syndrome (TLS) and were monitored at first dose and dose increases

RESULTS

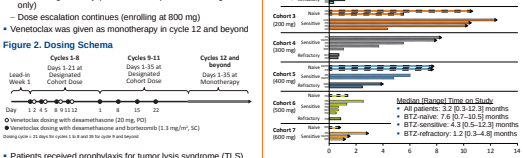
- As of March 26, 2015, 38 patients are enrolled in the study

Table 1. Patient Characteristics

Characteristics	N=38
Age, median [range]	65 [38–79]
Male gender, n (%)	24 (63)
White race, n (%)	36 (95)
ISS stage III, n (%)	10 (30)
Cytogenetic abnormalities, n (%)*	
t(11;14)	5 (14)
t(4;14)	3 (8)
del17p	9 (25)
del13q	19 (54)
Prior therapies	
Median [range] lines of therapy	5 [1–15]
Stem cell transplant, n (%)	24 (63)
Bortezomib / Refractory, n (%)†	31 (82) / 10 (26)
Lenalidomide / Refractory, n (%)†	32 (84) / 21 (55)
Bortezomib and Lenalidomide / Refractory, n (%)†	26 (68) / 8 (21)

*Percentages based on number of patients with known cytogenetic status.
†Percentages based on total population.

Figure 3. Current Status of Enrolled Patients by Bortezomib Status



Best response is shown for each patient: sCR, stringent complete response; CR, complete response; VGPR, very good PR; PR, partial response; MR, minimal response; SD, stable disease; PD, stable disease; DC, discontinued without response data; NR, not evaluable for response

TREATMENT DISCONTINUATIONS

- 25 (66%) patients discontinued
  - 19 due to disease progression
    - 4 patients died due to PD (2 in 500 mg, and 2 in 300 mg cohort)
    - No other deaths occurred
  - 2 due to adverse events
    - Respiratory and cardiac decompensation
    - Adenocarcinoma
  - 1 withdrew consent
  - 3 due to patient decision

As of March 26, 2014

SAFETY

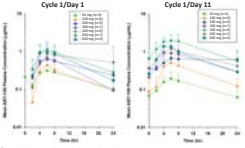
Table 2. Treatment-Emergent Adverse Events (AE)

Event, n (%)		N=38
AEs, any grade		**37 (98)**
Common all-grade AEs (in ≥20% patients)	Constipation	14 (37)
	Diarrhea	12 (32)
	Thrombocytopenia	11 (29)
	Peripheral neuropathy	10 (26)
	Asthenia	10 (26)
	Dyspnea	10 (26)
	Peripheral edema	9 (24)
	Insomnia	12 (32)
	Anemia	8 (21)
AEs, grade 3 or 4		**28 (74)**
Common Grade 3/4 AEs (in ≥10% patients)	Thrombocytopenia	8 (21)
	Anemia	5 (13)
	Dyspnea	4 (11)
Serious AEs*		**18 (47)**
Common SAEs (in ≥5% patients)	Cardiac failure	2 (5)
	Pyrexia	2 (5)
	Sepsis	2 (5)
	Respiratory failure	2 (5)
	Pneumonia	2 (5)
	Embolism	2 (5)

*No SAEs were assessed as a possibly related to study drug.

- Dose-limiting toxicities: grade 3 cardiac decompensation at 300 mg, assessed as ≥ possibly related to dexamethasone (DLT per sponsor)
- No patients developed tumor lysis syndrome

Figure 4. Preliminary Pharmacokinetics of Venetoclax in the Presence of Bortezomib and Dexamethasone



*Venetoclax alone on Lead-in Day 1† for the first 50-mg dose only.

- After co-administration with bortezomib/dexamethasone, dose-normalized venetoclax exposure at steady-state appeared to be within the exposure range observed when venetoclax is administered as monotherapy in multiple myeloma patients

PRELIMINARY EFFICACY RESULTS

Table 3. Efficacy Outcomes by Bortezomib Status

Best Response, n (%)	All Evaluable Patients n=38	Evaluable Bortezomib-Naive n=6	Evaluable Bortezomib-Sensitive n=20	Evaluable Bortezomib-Refractory n=10
Overall response*	17 (47)	5 (83)	12 (60)	0
≥Very good partial response†	7 (19)	3 (50)	4 (20)	0
Stringent complete response	2 (6)	1 (17)	1 (5)	0
Complete response	1 (3)	1 (17)	0	0
Very good partial response	4 (11)	1 (17)	3 (15)	0
Partial response	10 (28)	2 (33)	8 (40)	0
Minimal response	2 (6)	0	1 (5)	1 (10)
Stable disease	6 (17)	0	3 (15)	3 (30)
Disease progression	9 (25)	1 (17)	3 (15)	5 (50)
Discontinued	2 (6)	0	1 (5)	1 (10)
Time, months	**All Patients n=38**	**Bortezomib-Naive n=7**	**Bortezomib-Sensitive n=21**	**Bortezomib-Refractory n=10**
Time on study, median (range)	3.2 [0.3–12.3]	7.6 [0.7–10.5]	4.3 [0.5–12.3]	1.2 [0.3–4.8]
Duration of response	6.0 [0.7–9.5]	6.0 [4.2–9.5]	5.4 [0.7–9.5]	—

*Overall response = stringent complete response, complete response, very good partial response, and partial response.
†Very good partial response = stringent complete response, complete response, and very good partial response.

- The overall response rate in patients who were naive or sensitive to bortezomib was 17/26 (65%)

CONCLUSIONS

- Venetoclax in combination with bortezomib and dexamethasone has an acceptable safety profile in heavily pretreated multiple myeloma
- Efficacy results suggest anti-tumor activity of this novel combination which targets both BCL-2 and the resistance factor, MCL-1
- Overall response rate was 47%
  - All responses occurred in patients who were naive or sensitive to prior bortezomib treatment
  - Responses of VGPR or better occurred in 19% of patients
- Dose-normalized exposure of venetoclax in this combination was within the range of venetoclax monotherapy in multiple myeloma patients
- Biomarker data continue to be collected and analyzed
- The dose escalation portion of the study continues at 800 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

C Touzeau: research funding from AbbVie; S Harrison: research funding and speaker payments from Janssen Cilag (in relation to bortezomib); clinical trial support from AbbVie (for this study); A Agarwal: Speakers Bureau- Celgene, Onyx, Consultant-Amgen, Millennium; D Lebovic: research funding from Sanofi-Aventis; A Roberts: research funding from AbbVie and Genentech; employee of Walter and Eliza Hall Institute of Medical Research, which receives milestone payments related to venetoclax; T Facon, A Chanan-Khan, and P Moreau: no relevant disclosures.

D Darden, L Morris, J Ross, W Munasinghe, M Zhu, A Salem, J Leverson, S Enschede, R Humerickhouse: 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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