Supplemental Materials

Phase 2 study of venetoclax plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma

Costa LJ, et al.

Supplemental Methods

Eligibility Criteria

Additional inclusion criteria:

- Patient must voluntarily sign and date an informed consent prior to the initiation of any screening
- Patient must meet the following laboratory parameters within 2 weeks prior to first dose, per laboratory reference range:
    - Absolute neutrophil count (ANC) ≥1000 µL; patient may use growth factor support to achieve ANC eligibility criteria
    - Platelet count:
        - ≥50,000/mm^3 for patients with ≤50% myeloma involvement in the bone marrow
        - ≥30,000/mm^3 for patients with >50% myeloma involvement in the bone marrow
        - Patient may not have received a platelet transfusion within 72 hours prior to the platelet count used for eligibility
    - Hemoglobin ≥8.0 g/dL; patient may receive red blood cell transfusions in accordance with institutional guidelines to meet these criteria
    - Aspartate aminotransferase and alanine aminotransferase ≤3 × upper limit of normal (ULN)
    - Total bilirubin ≤1.5 × ULN; patient with documented Gilbert's syndrome may have bilirubin >1.5 × ULN with the approval of the sponsor or designee
    - Creatinine clearance ≥30 mL/minute measured by 24-hour urine collection or calculated using Cockcroft-Gault formula
- If female, patient may not be of childbearing potential (ie, postmenopausal for ≥1 year or permanently surgically sterile) or may be of childbearing potential and practicing an approved method of birth control throughout the study and 90 days after the last dose of study drug
- Females of childbearing potential must have negative results for pregnancy
- If male, patient must agree to follow one of the pregnancy avoidance measures below, including refraining from donating sperm for up to 90 days after the last dose of study drug:
    - Surgically sterile (ie, vasectomy ≥6 months prior to screening)

    - Use condoms
    - Total abstinence as the preferred lifestyle of the patient

Additional exclusion criteria:

- Patient may not have any of the following conditions:
    - Nonsecretory or oligo-secretory MM
    - Active plasma cell leukemia (ie, 20% of peripheral white blood cells or >2.0 × 10^9/L circulating plasma cells by standard differential)
    - Waldenström macroglobulinemia
    - Primary amyloidosis
    - Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome
    - Known human immunodeficiency virus (HIV) infection
    - Active hepatitis B or C infection based on screening blood testing
    - Significant cardiovascular disease, including uncontrolled angina, hypertension, arrhythmia, recent myocardial infarction within 6 months of first dose, congestive heart failure New York Heart Association Class ≥3, and/or left ventricular ejection fraction ≤40%
    - Major surgery within 4 weeks prior to first dose
    - Acute infections requiring antibiotic, antifungal, or antiviral therapy within 14 days prior to first dose
    - Grade ≥3 peripheral neuropathy or grade ≥2 with pain within 2 weeks prior to first dose
    - Uncontrolled diabetes or hypertension within 14 days prior to first dose
    - Any other medical condition that would adversely affect participation in the study, in the opinion of the investigator
- History of other active malignancies, including myelodysplastic syndrome, within the past 3 years prior to study entry, with the following exceptions:
    - Adequately treated in situ carcinoma of the cervix, uteri, or the breast
    - Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
    - Prostate cancer Gleason Grade ≤6 with stable prostate specific antigen levels off treatment

    - Previous malignancy with no evidence of disease confirmed and surgically resected (or treated with other modalities) with curative intent and unlikely to impact survival during the duration of the study
- If patient had prior allogeneic stem cell transplant (SCT), the patient may not have evidence of ongoing graft-versus-host disease
- Patient may not have hypersensitivity or allergy to any of the components of study therapy, including Captisol, a cyclodextrin derivative used to solubilize carfilzomib, or dexamethasone
- Patient may not have been treated with or received any of the following:
    - Allogeneic or syngeneic SCT within 6 months prior to first dose
    - Autologous SCT within 12 weeks prior to first dose
    - Immunization with live vaccine within 8 weeks prior to first dose
    - Monoclonal antibodies within 6 weeks prior to first dose
    - Any antimyeloma therapy (other than monoclonal antibodies), including chemotherapy, radiotherapy, biological, immunotherapy, or an investigational therapy, including targeted small molecule agents within 5 half-lives (or 14 days if half-life is unknown) prior to first dose
    - Corticosteroid therapy at a dose equivalent to ≥4 mg/day of dexamethasone within 3 weeks prior to first dose
    - Strong or moderate CYP3A inhibitor or inducer within 1 week prior to first dose
- Patient may not consume grapefruit products, Seville oranges, or starfruit within 3 days prior to study drug administration
- Female patients who were pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 90 days after the last dose of study drug were not eligible
- Male patients who were considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug were not eligible

Patients and Assessments

Relapsed disease was defined as previously treated MM that progressed and required initiation of salvage therapy. Refractory disease was defined as nonresponsive while on primary or salvage therapy or as progression within 60 days of last therapy. Measurable disease was defined as serum M-protein ≥0.5 g/dL, or urine M-protein ≥200 mg/24 hours, or serum free light chain ≥10 mg/DL.

PK assessments of venetoclax included maximum observed plasma concentration (C_{max}), peak time to C_{max} (T_{max}), and area under the plasma concentration-time curve (AUC) over a 24-hour dose interval (AUC_{0-24}). PK assessments of carfilzomib included C_{max}, terminal phase elimination rate constant (β), terminal elimination half-life ($t_{1/2}$), AUC from time 0 to last measurable concentration (AUC_t), AUC from time 0 to infinity (AUC_∞), and clearance. Assessments of venetoclax and carfilzomib PK were performed on intensive PK days (ie, Cycle 1 Day 1 and Day 15). Blood samples for venetoclax PK assay were collected at 0, 2, 4, 6, 8, and 24 hours post-dose on Cycle 1 Day 1 and Day 15. Blood samples for carfilzomib PK assay were collected pre-infusion, end of infusion, 0.25, 0.5, 1, 2, and 4 hours post-infusion on Cycle 1 Day 1 and Day 15.

MRD was assessed in BM aspirates by next-generation sequencing (NGS) in patients at C3D1 in patients achieving VGPR or better (≥VGPR), time of suspected complete response (CR)/stringent CR (sCR), and at 6- and 12-months post-confirmation of CR/sCR for patients who maintained this response. MRD negativity was defined at a 10^{-5} threshold per International Myeloma Working Group (IMWG) response criteria. Exploratory analyses of MRD negativity at 10^{-4} and 10^{-6} thresholds were performed.

PFS was defined as time from first study treatment to documented PD or death due to any cause that occurred on or prior to the data cutoff date. DOR was defined as time from initial response to disease progression or death due to MM. OS was defined as time from first study treatment to death due to any cause and was censored at last known alive date on or prior to the data cutoff date for patients who were still alive.

DLTs for dose escalation decisions were determined during the first cycle (28 days). Any of the following events that were considered to have a reasonable possibility of relationship to venetoclax, carfilzomib, or dexamethasone, which could not be attributed to a clearly identifiable cause, such as disease progression, concurrent illness, or concomitant medication, were considered a DLT:

- Grade 4 neutropenia lasting >7 days
- Grade 3/4 neutropenia with fever
- Grade 4 thrombocytopenia that does not recover prior to the start of the next Cycle
- Grade ≥2 bleeding associated with Grade ≥3 thrombocytopenia
- Unexpected Grade ≥2 toxicity that requires dose modification or delay of ≥1 week

- Clinical TLS
- Laboratory TLS if the metabolic abnormalities are clinically significant
- All other grade 3, 4, or 5 adverse events with the exception of the following:
    - Grade 3/4 neutropenia, lymphopenia, or leukopenia
    - Grade 3 thrombocytopenia that does not result in bleeding
    - Grade 3/4 hyperuricemia or hypocalcemia or grade 3 hyperkalemia, if transient (ie, lasting <48 hours) and without manifestations of clinical TLS (ie, creatinine ≥1.5 x ULN, cardiac arrhythmias, sudden death, or seizures)
    - Grade 3 fatigue
    - Grade 3 peripheral neuropathy
    - Grade 3 nausea, vomiting, and/or diarrhea that are responsive to treatment
    - Grade 3 hyperglycemia that is controllable with insulin or oral hyperglycemic agents within 24 hours
    - Grade 3 hypertension or confusion that is reversible within 24 hours
    - Grade ≥3 local reaction to subcutaneous injection that does not resolve within 24 hours
    - Grade 3 insomnia that is managed with a sedative or reversible within 24 hours
    - Grade 3 edema that is controlled with diuretics or reversible within 24 hours
    - Grade 3 dyspepsia that is managed with H2 blockers/PPI or reversible within 24 hours

Supplemental Results

Deaths

Three treatment-emergent deaths occurred:

- A 60-year-old male in Cohort 3 had a 2-year history of MM. The patient died during apparent biochemical progression on Cycle 2 Day 2. Cause of death was respiratory arrest, assessed as unrelated to study drugs per investigator.
- A 65-year-old male in Cohort 4 had an 8-year history of MM. He developed influenza and was hospitalized on Cycle 1 Day 10. Study drugs were discontinued on Cycle 1 Day 9 and never restarted. The patient developed acute respiratory failure with hypoxemia and died on Cycle 1 Day 24. Cause of death was multisystem organ failure secondary to

acute respiratory distress syndrome and influenza B, assessed as unrelated to study drugs per investigator.

- A 64-year-old male in Cohort 2 had a 3-year history of MM, deep vein thrombosis, depression, reduced left ventricular ejection fraction, and self-reported syncope. He experienced an episode of heart failure at Cycle 6. Venetoclax and carfilzomib were interrupted. Venetoclax and carfilzomib were restarted at the same doses for Cycle 7. The patient died during Cycle 9. Cause of death was unexplained, with reasonable possibility of being related to carfilzomib.

One non–treatment-emergent death was reported:

- A 57-year-old female in Cohort 4 had a 3-year history of MM, type 2 diabetes mellitus, obesity, and hypertension. She developed atrial fibrillation and acute bronchitis during Cycle 8. Venetoclax and carfilzomib were interrupted and never restarted. One week later, the patient developed pneumonia that required hospitalization; the pneumonia resolved approximately 2 weeks later, and the patient was discharged. The patient died one month later (>30 days after last dose of study drug). Cause of death was pulmonary aspergillosis.

Supplemental Table 1. Dosing regimens for venetoclax in combination with carfilzomib and dexamethasone.

Cohort	Dosing Regimen	Day								
		1	2	8	9	15	16	22	23	28
1	Venetoclax 400 mg QD Carfilzomib 27 mg/m^2 Dexamethasone 40 mg	■	■	■	■	■	■	■	■	■
		■		■		■		■		
		■		■		■		■		
2	Venetoclax 800 mg QD Carfilzomib 27 mg/m^2 Dexamethasone 40 mg	■	■	■	■	■	■	■	■	■
		■		■		■		■		
		■		■		■		■		
3	Venetoclax 800 mg QD Carfilzomib 70 mg/m^2 Dexamethasone 40 mg	■	■	■	■	■	■	■	■	■
		■		■		■		■		
		■		■		■		■		
4	Venetoclax 800 mg QD Carfilzomib 56 mg/m^2 Dexamethasone 20 mg	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	
		■	■	■	■	■	■	■	■	

Carfilzomib was administered at 20 mg/m^2 on Cycle 1 Day 1 (all dose groups) and Day 2 (27 and 56 mg/m^2 only). For Cohorts 1 and 2, patients received carfilzomib 27 mg/m^2 on Days 1, 2, 15, and 16 for Cycles 13 and beyond.
QD, once-daily.

Supplemental Table 2. Patient disposition

	All Patients N = 49
Median time on study (range), months	27 (11.4–36.5)
Ongoing, n (%)	13 (27)
Discontinued, n (%)	36 (73)
Primary reason for discontinuation, n (%)	
Progressive disease	18 (37)
Withdrew consent	6 (12)
Adverse event	4 (8)[a]
Death	3 (6)
Physician decision	3 (6)
Lack of efficacy	1 (2)
Other	1 (2)

[a] Adverse events that led to discontinuation include diverticulitis, non-ST elevated myocardial infarction with unstable angina, influenza, and ejection fraction decreased.

Supplemental Table 3. Venetoclax, carfilzomib, and dexamethasone dose reductions and dose interruptions due to adverse events

	Venetoclax (N = 49)	Carfilzomib (N = 49)	Dexamethasone (N = 49)
Dose reduction, n (%)			
None	39 (80)	33 (67)	29 (59)
1	5 (10)	14 (29)	12 (24)
>1	5 (10)	2 (4)	8 (16)
All reasons for dose reduction, n (%)			
Adverse event	10 (20)	16 (33)	20 (41)
Dose delay/interruption, n (%)			
None	15 (31)	14 (29)	27 (55)
1	12 (24)	23 (47)	8 (16)
>1	22 (45)	12 (24)	14 (29)
All reasons for dose delay/interruption, n (%)			
Adverse event	34 (69)	35 (71)	22 (45)

Supplemental Table 4. Summary of treatment-emergent infections

Infection-related TEAEs by Preferred Term, n (%)	All Patients N = 49	
	Any Grade	Grade 3/4
Treatment-emergent infection		
Upper respiratory tract infection	19 (39)	0
Sinusitis	10 (20)	0
Pneumonia	9 (18)	6 (12)
Influenza	8 (16)	3 (6)
Bronchitis	4 (8)	1 (2)
Clostridium difficile colitis	2 (4)	2 (4)
Herpes zoster	2 (4)	0
Nasopharyngitis	2 (4)	0
Otitis media	2 (4)	0
Rhinovirus infection	2 (4)	0
Urinary tract infection[a]	2 (4)	0
Vaginal infection	2 (4)	0
Anal abscess	1 (2)	0
Bronchopulmonary aspergillosis	1 (2)	1 (2)
Conjunctivitis	1 (2)	0
Corona virus infection	1 (2)	0
Dermatitis infected	1 (2)	0
Diverticulitis	1 (2)	1 (2)
Fungal infection	1 (2)	0
Helicobacter infection	1 (2)	0
Infection	1 (2)	1 (2)
Parainfluenza virus infection	1 (2)	0
Pneumonia pneumococcal	1 (2)	1 (2)
Pneumonia respiratory syncytial viral	1 (2)	0
Rash pustular	1 (2)	0
Respiratory tract infection viral	1 (2)	0
Rocky mountain spotted fever	1 (2)	0
Soft tissue infection	1 (2)	1 (2)
Tooth infection	1 (2)	0
Viral infection	1 (2)	0
Viral upper respiratory tract infection	1 (2)	0
Serious treatment-emergent infection		
Pneumonia	7 (14)	6 (12)
Influenza	3 (6)	3 (6)
Bronchitis	1 (2)	1 (2)
Bronchopulmonary aspergillosis	1 (2)	1 (2)
Infection	1 (2)	1 (2)
Pneumonia pneumococcal	1 (2)	1 (2)

Viral upper respiratory tract infection	1 (2)	1 (2)

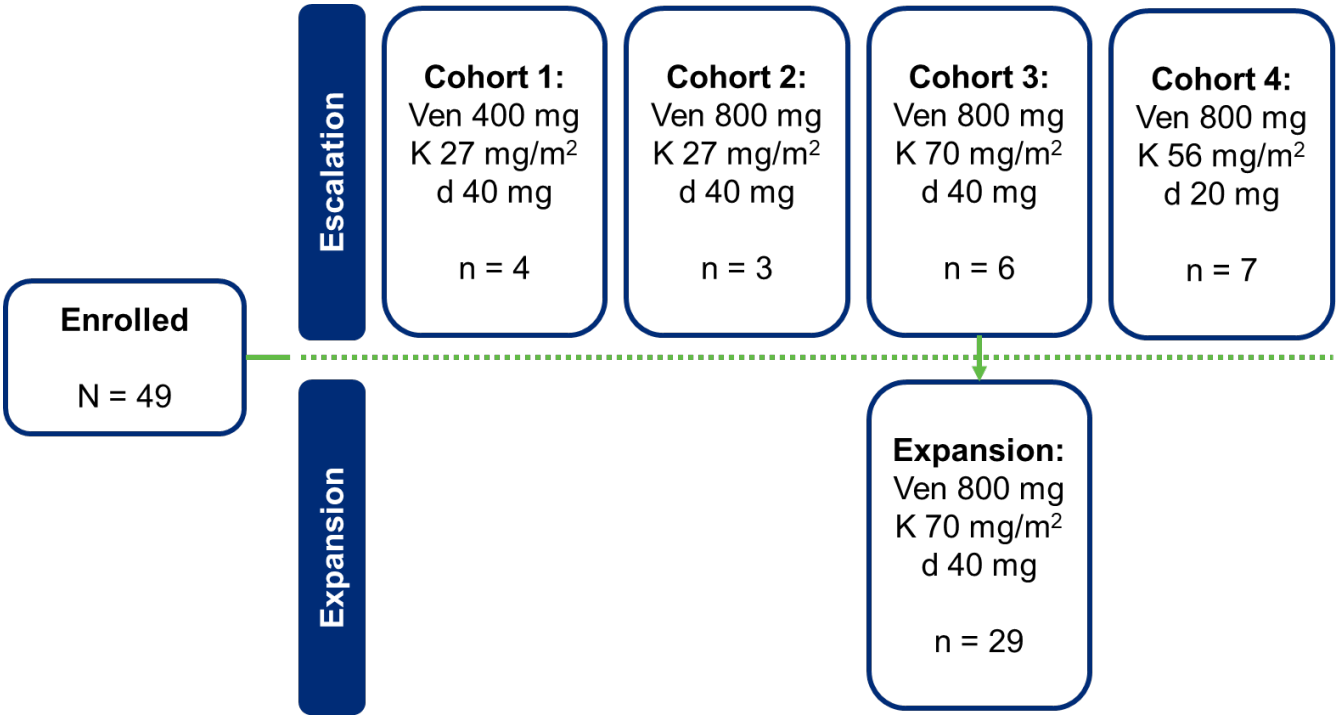
[a] Includes urinary tract infection enterococcal.
TEAE, treatment-emergent adverse event.

Supplemental Table 5. ORRs by t(11;14) status.

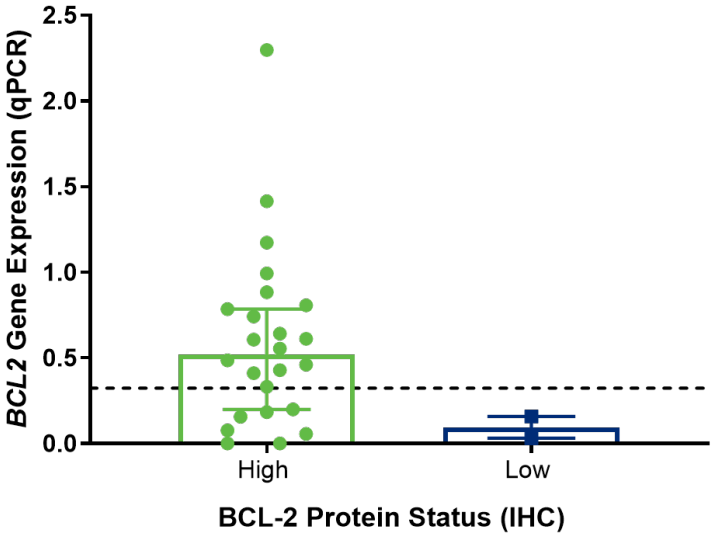
ORR, n/N (%)	t(11;14)	Non-t(11;14)
ISS stage I	8/8 (100)	6/10 (60)
ISS stage II	1/1 (100)	10/14 (71)
ISS stage III	3/4 (75)	11/11 (100)
Unknown	0	1

ISS, International Staging System; ORR, overall response rate.

Supplemental Figure 1. Study design and patient enrollment. d, dexamethasone; K, carfilzomib; Ven, venetoclax.

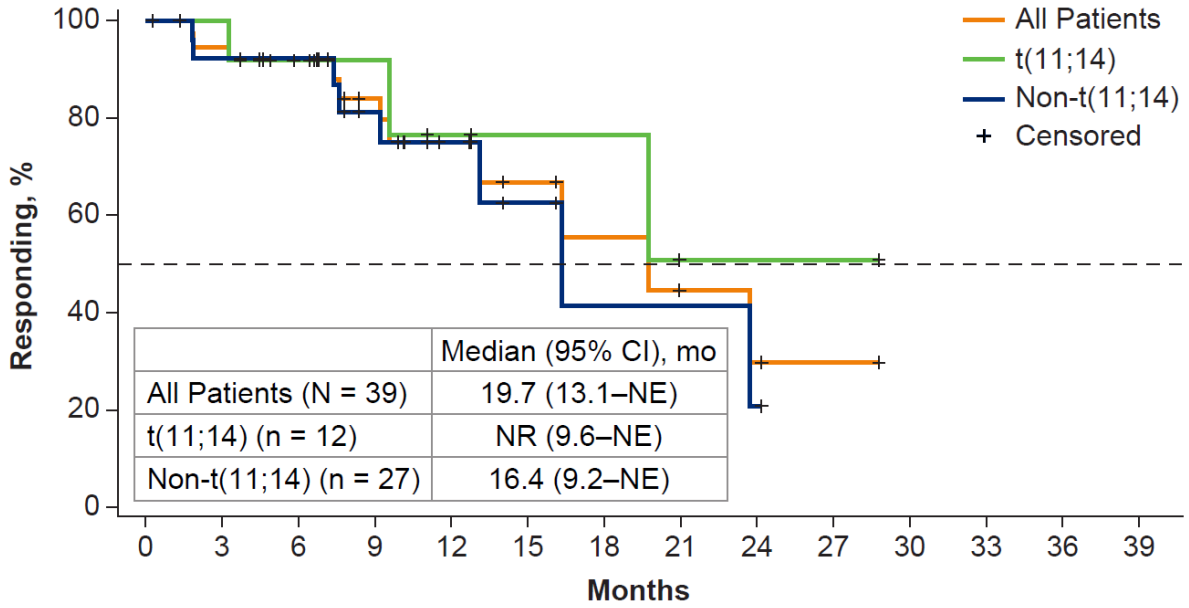


Supplemental Figure 2. Correlation between BCL-2 protein and *BCL2* gene expression. The dashed line indicates the threshold for defining *BCL2*^{high} expression based upon the BELLINI study ($2^{-\Delta Ct}$ ≥0.323). IHC, immunohistochemistry; qPCR, quantitative polymerase chain reaction.



	n	Median gene expression (range)
BCL-2 protein		
High	24	0.52 (0.0–2.3)
Low	2	0.095 (0.031–0.095)
P (Mann-Whitney)	.1123	

Supplemental Figure 3. Duration of response in all patients and those with t(11;14).



Patients at Risk

All Patients	39	35	28	19	11	7	5	3	2
t(11;14)	12	12	8	6	4	3	3	1	1
Non-t(11;14)	27	23	20	13	7	4	2	2	1