Cobimetinib Alone and Plus Venetoclax With/Without Atezolizumab in Patients With Relapsed/Refractory Multiple Myeloma

Fredrik Schjesvold,[1,2] Bruno Paiva,[3] Vincent Ribrag,[4] Paula Rodriguez-Otero,[5] Jesus F. San-Miguel,[5] Pawel Robak,[6] Markus Hansson,[7] Maika Onishi,[8] Habib Hamidi,[8] Vikram Malhi,[8] Monique Dail,[8] Apurva Javery,[9] Grace Ku,[8] Marc S. Raab[10]

Abstract

This phase IB/II trial evaluated safety and efficacy of cobimetinib alone and in novel combinations with venetoclax with/without atezolizumab in patients with relapsed/refractory multiple myeloma. Forty-nine patients were enrolled. Cobimetinib alone and in combination with venetoclax with/without atezolizumab was determined to be safe and tolerable; anti-tumor activity was moderate overall but higher in patients with translocation t(11;14).

Introduction: Mitogen-activated protein kinase pathway mutations are present in >50% of patients with relapsed/refractory (R/R) multiple myeloma (MM). MEK inhibitors show limited single-agent activity in R/R MM; combination with B-cell lymphoma-2 (BCL-2) and programmed death-ligand 1 inhibition may improve efficacy. This phase Ib/II trial (NCT03312530) evaluated safety and efficacy of cobimetinib (cobi) alone and in combination with venetoclax (ven) with/without atezolizumab (atezo) in patients with R/R MM. **Patients and Methods:** Forty-nine patients were randomized 1:2:2 to cobi 60 mg/day on days 1–21 (n = 6), cobi 40 mg/day on days 1–21 + ven 800 mg/day on days 1–28 with/without atezo 840 mg on days 1 and 15 of 28-day cycles (cobi-ven, n = 22; cobi-ven-atezo, n = 21). Safety run-in cohorts evaluated cobi-ven and cobi-ven-atezo dose levels. **Results:** Any-grade common adverse events (AEs) with cobi, cobi-ven, and cobi-ven-atezo, respectively, included diarrhea (33.3%, 81.8%, 90.5%) and nausea (16.7%, 50.0%, 66.7%); common grade ≥3 AEs included anemia (0%, 22.7%, 23.8%), neutropenia (0%, 13.6%, 38.1%), and thrombocytopenia (0%, 18.2%, 23.8%). The overall response rate for all-comers was 0% (cobi), 27.3% (cobi-ven), and 28.6% (cobi-ven-atezo), and 0%, 50.0%, and 100%, respectively, in patients with t(11;14)+. Biomarker analysis demonstrated non-t(11;14) patient selection with *NRAS*/*KRAS*/*BRAF* mutation or high BCL-2/BCL-2-L1 ratio (>52% of the study population) could enrich for responders to the cobi-ven combination. **Conclusions:** Cobi-ven and cobi-ven-atezo demonstrated manageable safety with moderate activity in all-comers, and higher activity in patients with t(11;14)+ MM, supporting a biomarker-driven approach for ven in MM.

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Abbreviations: ADA, anti-drug antibody; atezo, atezolizumab; cobi, cobimetinib; DLT, dose limiting toxicity; MAPK, mitogen-activated protein kinase; MR, minimal response; NE, not evaluable; PIs, proteasome inhibitors; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; Ras, Rat sarcoma virus; RP, randomization phase; SRI, safety run-in; ven, venetoclax.

[1]Oslo Myeloma Center, Department of Haematology, Oslo University Hospital, Oslo, Norway
[2]KG Jebsen Centre for B cell malignancies, University of Oslo, Oslo, Norway
[3]Clínica Universidad de Navarra, Centro de Investigación Médica Aplicada (CIMA), Instituto de Investigación Sanitaria de Navarra (IDISNA), CIBER-ONC, Pamplona, Spain
[4]Institut Gustave Roussy, Villejuif, France
[5]Clínica Universidad de Navarra, CCUN, University of Navarra, Pamplona, Spain
[6]Medical University of Lodz, Lodz, Poland
[7]Skane University Hospital, Lund, Sweden and Sahlgrenska Academy, Gothenburg, Sweden
[8]Genentech, Inc, South San Francisco, CA,
[9]Syneos Health, Raleigh, Raleigh, NC,
[10]Heidelberg University Hospital, Department of Medicine V, Heidelberg, Germany

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Address for Correspondence: Fredrik Schjesvold, Head of Oslo Myeloma Center, Department of Haematology, Oslo University Hospital, Postboks 4950 Nydalen OUS, Rikshospitalet, 0424 Oslo, Norway
E-mail contact: fredrikschjesvold@gmail.com

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Introduction

Multiple myeloma (MM) is a B-cell neoplasm characterized by the clonal expansion of malignant cells in the bone marrow, often leading to excessive production of monoclonal protein. Despite advances in treatment, MM remains an incurable disease, and most patients eventually relapse, have shorter remissions with each additional line of therapy, and succumb to the consequences of bone marrow failure or end-organ damage.[1] Outcomes for patients with MM after becoming refractory to proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) are poor, with median survival of ≤1 year, and median progression-free survival (PFS) of <6 months.[2-4] The development of combination regimens with innovative mechanisms of action may expand treatment options for relapsed/refractory (R/R) MM.

The Rat sarcoma virus (Ras)/mitogen-activated protein kinase (MAPK) pathway is frequently dysregulated in MM, with *NRAS*, *KRAS*, or *BRAF* mutations being present in up to 50% of newly diagnosed MM cases[5,] and in up to 72% of patients with relapsed MM.[5-7] Cobimetinib (cobi) is a small molecule inhibitor of MEK1/2[8,] which is approved for use in combination with vemurafenib in the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation[9,10], but not previously evaluated in MM. Despite the limited activity of previously evaluated MEK inhibitors, trametinib and selumetinib, as single agents[11,12], the anti-myeloma activity of MEK inhibitors may be improved with a combination strategy.

Evasion of apoptosis and resistance to therapy in MM can be driven by the anti-apoptotic B-cell lymphoma 2 (BCL-2) protein, along with other related anti-apoptotic proteins (BCL-xL, BCL-w, myeloid-cell leukemia 1, and A1), which are crucial regulators of MM cell survival[13], and are balanced by pro-apoptotic proteins (BAX, BIM, BAK, BID, and NOXA). Venetoclax (ven) is a potent, highly selective oral BCL-2 inhibitor.[14] Ven monotherapy has demonstrated an acceptable safety profile and anti-myeloma activity, particularly in patients with R/R MM harboring t(11;14) (overall response rate [ORR], 40%).[15] The cobi-ven combination represents a potential strategy for inducing MM cell apoptosis by increasing BIM expression via MEK inhibition, and inhibiting BCL-2.

Programmed death-ligand 1 (PD-L1) is commonly and broadly expressed on MM cells, while expression of the PD-L1 receptor is upregulated on T cells isolated from patients with MM.[16,17] Atezolizumab (atezo) is a humanized IgG1 monoclonal antibody (mAb) that targets PD-L1 by altering its interaction with its receptors, programmed cell death protein-1 (PD-1) and B7-1 (also known as CD80).[18] Since the Ras/MAPK pathway contributes to immune evasion, MEK inhibition may enhance the anti-tumor activity of atezo. MEK inhibition has been shown to result in increased tumor-infiltrating CD8+ T lymphocytes, and enhanced tumor antigen expression of both PD-L1 and the major histocompatibility complex.[19,20] In the context of a pro-apoptotic state and a primed tumor microenvironment, the addition of atezo to cobi-ven may further enhance anti-tumor activity.

The triple combination of cobi, ven, and atezo targets key features of cancer cell biology, including proliferation, resistance to apoptosis, and immune evasion.[21] The combination of a MEK inhibitor and a BCL-2 inhibitor is supported by emerging insights into the molecular pathogenesis of MM. The addition of atezo may potentially further enhance the anti-tumor myeloma immune response. This study assessed the safety, tolerability, and efficacy of cobi administered as a single agent or in combination with ven, with or without atezo, in patients with R/R MM.

Methods

Study Design and Treatment

This open-label, multicenter, phase Ib/II study evaluated cobi alone (Arm A), cobi-ven (Arm B), and cobi-ven-atezo (Arm C) in patients with R/R MM (ClinicalTrials.gov identifier: NCT03312530). The primary objectives were to evaluate preliminary safety, tolerability, and efficacy; secondary objectives were to further evaluate efficacy and pharmacokinetics; and exploratory objectives were to identify biomarkers predictive of response, and assess biomarkers associated with disease biology. This study was terminated early following the Sponsor's decision to discontinue the development of the drug combinations, due to modest anti-tumor activity in all-comers; the decision was not based on safety findings in the study.

In the safety run-in (SRI) phase, two successive cohorts were evaluated: cobi-ven, and cobi-ven-atezo. The starting doses were cobi 40 mg/day on days 1 to 21 plus ven 800 mg/day on days 1 to 28 of each 28-day cycle. Tumor lysis syndrome (TLS) prophylaxis and monitoring were strongly recommended for all patients. Patients were evaluated for dose limiting toxicities (DLTs) during the first treatment cycle. Once considered safe, atezo was added at a fixed dose of 840 mg intravenously on days 1 and 15. Once the dose levels demonstrated acceptable safety in accordance with the DLT rules, randomization was initiated for all treatment arms (Arms A, B, and C; Figure 1).

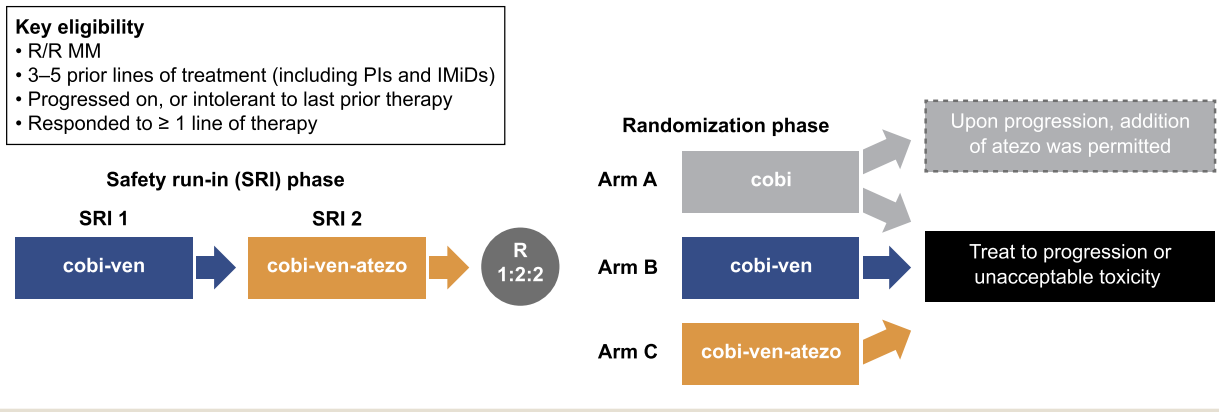
During the randomization phase (RP), patients were randomized 1:2:2 to Arms A, B, and C. A biomarker assessment for t(11;14) was performed prior to randomization to ensure that approximately 20% of patients in each arm had t(11;14) and were representative of a MM population.[22] Patients randomized to Arm A received cobi 60 mg/day on days 1 to 21 of each 28-day cycle, while patients randomized to Arms B and C received doses based on the dose levels identified in the SRI phase. Treatment was continued until disease progression, as defined by the International Myeloma Working Group (IMWG) 2016 consensus criteria[22], unacceptable toxicity, or until other discontinuation criteria were met.

The study protocol was approved by the institutional review board or ethics committees at participating institutions in accordance with the International Conference on Harmonisation Guidelines, including Good Clinical Practice and the ethical principles originating from the Declaration of Helsinki. Informed consent was obtained from all patients. Authors had access to the clinical trial results.

Patient Population

Patients were eligible for inclusion if they were aged ≥18 years with documented MM with measurable disease, had received 3–5 prior lines of therapy including a PI and IMiD, had achieved a response (minimal response [MR] or better) to ≥1 prior regimen, had documented evidence of progressive disease (PD) as defined

Figure 1 Study Design. Abbreviations: atezo, atezolizumab; cobi, cobimetinib; IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteasome inhibitor; R, randomization; R/R, relapsed/refractory; ven, venetoclax



by IMWG criteria on or after their last prior therapy, were intolerant to their last prior therapy, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and had adequate renal and hepatic function. Key exclusion criteria included prior treatment with MEK inhibitors, BCL-2 inhibitors, or immune checkpoint inhibitor therapies, including anti-cytotoxic T-lymphocyte antigen-4, anti-PD-1, or anti-PD-L1.

Assessments

Adverse events (AEs) were monitored throughout the study and for ≥90 days after the last dose of cobi and ven, and 135 days after the last dose of atezo. AEs were reported by the treating physician and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Anti-myeloma activity was assessed by routine laboratory tests and bone marrow examinations and imaging as indicated. Responses were evaluated by investigators using the IMWG 2016 response criteria.

Pharmacokinetic and anti-drug antibody (ADA) assessments are described in the **Supplemental Methods**.

Exploratory Biomarkers

t(11;14) status was determined by fluorescence *in situ* hybridization by Labcorp. *NRAS*/*KRAS*/*BRAF* mutation status was assessed using the Ion AmpliSeq Cancer Hotspot Panel v2 by Expression Analysis. Immune monitoring was performed in longitudinal peripheral blood samples using multidimensional flow cytometry with an 8-color flow panel by Covance.

RNA sequencing (RNAseq) was performed using CD138+ sorted cells. RNA was extracted from microdissected tumor cells from core biopsy slides by HistoGeneX. RNAseq and whole-transcriptome profiles were generated as described previously by EA Genomics (Morrisville, NC, US).[23] Raw counts were adjusted for gene length using transcript-per-million normalization, and subsequently log2-transformed. Expression of *BCL2* was compared with *BCL2L1* (gene encoding BCL-xL protein) to establish a *BCL2*:*BCL2L1* ratio. A threshold of log2 ≥2.3, as previously reported to be relevant for ven activity,[13,15] was used to identify *BCL2*:*BCL2L1* ratio-high patients.

In some patients without mutation data, mutations were detected in binary alignment map files using the tallyVariant function in the VariantTools R package, specifying the locus of interest (**Supplemental Methods**).

Statistical Methods

Safety and efficacy were summarized by descriptive statistics. Safety and efficacy analyses were performed on the safety-evaluable population, which comprised all patients who received ≥1 dose of study drug. Time-to-event analyses were performed using the Kaplan–Meier method, with 2-sided 95% confidence intervals (CIs). A sample size of up to 72 patients (12 per SRI cohort, 12 patients in Arm A, and 24 patients in each of Arms B and C) was designed to obtain preliminary safety, efficacy, and pharmacokinetic information, without formal type 1 error control or power assessment. Efficacy by survival outcomes was an exploratory endpoint, and the study was not designed with a hypothesis to test outcomes. *P* values comparing survival across treatment arms were calculated using the log-rank test, and were exploratory and shown for descriptive purposes only.

Results

The data cut-off was July 7, 2021. In total, 49 patients were enrolled at 16 centers worldwide (Spain, Germany, Denmark, Norway, Czech Republic, France, Poland, and Sweden) between November 2017 and March 2019. All patients received ≥1 dose of study drug. Patient disposition is shown in (**Supplemental Figure 1**).

In the SRI phase, six patients received cobi-ven, and six patients received cobi-ven-atezo.

Only partial enrollment into the RP was completed due to early study termination (following the Sponsor's decision to discontinue the development of the drug combinations, due to modest anti-tumor activity in all-comers and not based on safety findings),

Table 1 Patient Demographics and Baseline Characteristics.

	cobi (n = 6)	cobi-ven (n = 22)	cobi-ven-atezo (n = 21)
Median age, years (range)	67.5 (58–75)	65.0 (54–77)	64.0 (44–79)
≥65 years, n (%)	5 (83.3)	13 (59.1)	9 (42.9)
Male sex, n (%)	4 (66.7)	12 (54.5)	15 (71.4)
ECOG PS, n (%)			
0	3 (50.0)	12 (54.5)	10 (47.6)
1	3 (50.0)	8 (36.4)	10 (47.6)
2	0	2 (9.1)	1 (4.8)
ISS at screening, n (%)			
Stage I	2 (33.3)	9 (40.9)	12 (57.1)
Stage II	2 (33.3)	7 (31.8)	6 (28.6)
Stage III	2 (33.3)	4 (18.1)	2 (9.5)
High-risk cytogenetics, n (%)	0	5 (22.7)	7 (33.3)
del(17p)	0	2 (9.1)	4 (19.0)
t(4;14)	0	3 (13.6)	4 (19.0)
t(14;16)	0	1 (4.5)	1 (4.8)
t(11;14), n (%)	1 (16.7)	4 (18.1)	5 (23.8)
Ras/MAPK pathway mutation, n (%)	2 (33.3)	12 (54.5)	11 (52.3)
High PD-L1 expression, n (%)	2 (33.3)	6 (27.3)	7 (33.3)
BCL2:*BCL2L1* (BCL-xL) ratio high, n (%)	0	7 (31.8)	4 (19.0)
Median prior therapies, n (range)	4.5 (3.0–5.0)	4.0 (3.0–5.0)	3.0 (3.0–5.0)
Prior ASCT, n (%)	1 (16.7)	11 (50.0)	10 (47.6)
Prior IMiD, n (%)	6 (100)	22 (100)	21 (100)
Lenalidomide	6 (100)	22 (100)	20 (95.2)
Pomalidomide	4 (83.3)	9 (40.9)	12 (57.1)
Thalidomide	4 (66.7)	6 (27.3)	8 (38.1)
Prior PI, n (%)	6 (100)	22 (100)	21 (100)
Bortezomib	5 (83.3)	22 (100)	19 (90.5)
Carfilzomib	3 (50.0)	10 (45.5)	10 (47.6)
Ixazomib	1 (16.7)	5 (22.7)	6 (28.6)
Prior anti-CD38 mAb, n (%)	4 (66.7)	10 (45.5)	10 (47.6)
Daratumumab	2 (33.3)	8 (36.4)	10 (47.6)
Isatuximab	2 (33.3)	2 (9.1)	0
Refractory status			
Refractory to IMiD	6 (100)	18 (81.8)	19 (90.5)
Refractory to PI	6 (100)	20 (90.9)	18 (85.7)
Refractory to anti-CD38	4 (66.7)	9 (40.9)	9 (42.9)
Triple class refractory	4 (66.7)	9 (40.9)	8 (38.1)
Lytic lesions at screening	6 (100)	22 (100)	17 (81.0)
Extramedullary disease at screening	1 (16.7)	6 (27.3)	1 (4.8)

Abbreviations: ASCT, autologous stem cell transplantation; atezo, atezolizumab; cobi, cobimetinib; del(17p), chromosome 17p deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; PD-L1, programmed death-ligand 1; PI, proteasome inhibitor; ven, venetoclax.

with patients assigned to receive each treatment as follows: cobi, n = 6; cobi-ven, n = 16; cobi-ven-atezo, n = 15. The same dosing was used in the SRI and RP for the cobi-ven and cobi-ven-atezo cohorts; results are presented for the combined SRI and RP cohorts.

Patient Characteristics

Median age was 67.5 years (range, 58–75), 65.0 years (range, 54–77), and 64.0 years (range, 44–79) for the cobi, cobi-ven, and cobi-ven-atezo arms, respectively (Table 1). The majority of patients in all arms had an ECOG PS of 0 or 1. For the cobi, cobi-ven, and cobi-ven-atezo arms, the median number of prior lines of therapy was 4.5, 4.0, and 3.0, respectively. As per the eligibility criteria, in all arms, patients had received prior treatment with an IMiD and PI; additionally, many patients received ≥1 IMiD and PI. Prior anti-CD38 mAb therapy was received in 66.7%, 45.5%, and 47.6% of patients in the cobi, cobi-ven, and cobi-ven-atezo arms, respectively. The majority of patients were refractory to an IMiD (cobi, 100%; cobi-ven, 81.8%; cobi-ven-atezo, 90.5%) and PI (cobi, 100%; cobi-ven, 90.9%; cobi-ven-atezo, 85.7%). Overall, 66.7%, 40.9%, and 42.9% of patients in the cobi, cobi-ven, and cobi-ven-atezo arms, respectively, were refractory to anti-CD38 mAbs (Table 1).

At screening, in the cobi, cobi-ven, and cobi-ven-atezo arms, 0% (0/6), 22.7% (5/22), and 33.3% (7/21) of patients, respectively, had high-risk cytogenetics defined by presence of chromosome 17p deletion, t(4;14), and t(14;16). t(11;14) was present in 16.7% (cobi), 18.1% (cobi-ven), and 23.8% (cobi-ven-atezo) of patients,

Table 2 Most Common All-Grade and Grade 3–4 AEs.

AE (MedDRA preferred term), n (%)	cobi (n = 6)		cobi-ven (n = 22)		cobi-ven-atezo (n = 21)	
	All-Grade AE[a]	Grade 3–4 AE[b]	All-Grade AE[a]	Grade 3–4 AE[b]	All-Grade AE[a]	Grade 3–4 AE[b]
Diarrhea	2 (33.3)	0	18 (81.8)	1 (4.5)	19 (90.5)	2 (9.5)
Nausea	1 (16.7)	0	11 (50.0)	0	14 (66.7)	0
Anemia	1 (16.7)	0	10 (45.5)	5 (22.7)	12 (57.1)	5 (23.8)
Neutropenia	0	0	7 (31.8)	3 (13.6)	12 (57.1)	8 (38.1)
Thrombocytopenia	0	0	6 (27.3)	4 (18.2)	7 (33.3)	5 (23.8)
Blood CPK increased	1 (16.7)	0	7 (31.8)	0	5 (23.8)	1 (4.8)
Rash	3 (50.0)	0	3 (13.6)	0	7 (33.3)	0
Fatigue	0	0	7 (31.8)	1 (4.5)	4 (19.0)	0
Vomiting	0	0	7 (31.8)	0	4 (19.0)	1(4.8)
Pneumonia	0	0	7 (31.8)	4 (18.2)	3 (14.3)	3 (14.3)
Back pain	2 (33.3)	0	3 (13.8)	1 (4.5)	2 (9.5)	0
Dry skin	0	0	1 (4.5)	0	6 (28.6)	0
Haemophilus sepsis	1 (16.7)	1 (16.7)	0	0	0	0
Pneumonia pneumococcal	1 (16.7)	1 (16.7)	0	0	0	0
Staphylococcal sepsis	1 (16.7)	1 (16.7)	0	0	0	0
Hypertension	1 (16.7)	1 (16.7)	1 (4.5)	1 (4.5)	2 (9.5)	1 (4.8)
Lymphopenia	0	0	1 (4.5)	0	4 (19.0)	4 (19.0)

[a] All-grade AEs occurring in ≥25% of patients.
[b] Grade 3–4 AEs occurring in ≥15% of patients.
Abbreviations: AE, adverse event; atezo, atezolizumab; cobi, cobimetinib; CPK, creatinine phosphokinase; MedDRA, medical dictionary for regulatory activities; ven, venetoclax.

and Ras/MAPK pathway mutations in 33.3%, 54.5%, and 52.3% of patients in each arm, respectively. A high ratio (log2 ≥2.3) of *BCL2*:*BCL2L1* (BCL-xL) was observed in 31.8% of patients in the cobi-ven arm and 19.0% of patients in the cobi-ven-atezo arm; no patients in the cobi arm had a high *BCL2*:*BCL2L1* ratio (Table 1).

Safety

The most common all-grade AEs (occurring in ≥25% of patients) irrespective of relatedness to treatment were rash (50.0%), diarrhea (33.3%), and back pain (33.3%) in patients receiving cobi; diarrhea (81.8%), nausea (50.0%), anemia (45.5%), neutropenia (31.8%), blood creatinine phosphokinase increased (31.8%), fatigue (31.8%), vomiting (31.8%), pneumonia (31.8%), and thrombocytopenia (27.3%) in patients receiving cobi-ven; and diarrhea (90.5%), nausea (66.7%), anemia (57.1%), neutropenia (57.1%), thrombocytopenia (33.3%), rash (33.3%), and dry skin (28.6%) in patients receiving cobi-ven-atezo (Table 2).

The most common grade 3–4 AEs (occurring in ≥15% of patients) were hemophilus sepsis (16.7%; 1/6), pneumonia pneumococcal (16.7%; 1/6), staphylococcal sepsis (16.7%; 1/6), all occurring in the same patient, and hypertension (16.7%; 1/6) in patients receiving cobi; anemia (22.7%; 5/22), thrombocytopenia (18.2%; 4/22), and pneumonia (18.2%; 4/22) in patients receiving cobi-ven; and neutropenia (38.1%; 8/21), anemia (23.8%; 5/21), thrombocytopenia (23.8%; 5/21), and lymphopenia (19.0%; 4/21) in patients receiving cobi-ven-atezo.

Treatment-emergent serious AEs (SAEs) were reported in 50.0%, 63.6%, and 66.7% of patients in the cobi, cobi-ven, and cobi-ven-atezo arms, respectively (**Supplemental Table 1**). In the cobi arm, no SAEs were noted in more than one patient. In the cobi-ven arm, the most common SAEs noted in more than one patient were pneumonia (22.7%), thrombocytopenia (9.1%), and TLS (9.1%), and in the cobi-ven-atezo arm were pneumonia (14.3%), neutropenia (14.3%), thrombocytopenia (9.5%), anemia (9.5%), and febrile neutropenia (9.5%).

AEs leading to treatment withdrawal were reported in 16.7%, 18.2%, and 14.3% of patients in the cobi, cobi-ven, and cobi-ven-atezo arms, respectively, with no AEs occurring in more than one patient.

TLS was observed in two patients receiving cobi-ven: one case of laboratory TLS; one case of grade 4 clinical TLS in one t(11;14)-negative patient who had an associated grade 4 acute kidney injury and a co-occurring bronchial infection, which led to treatment discontinuation.

The leading cause of death was PD (cobi, 50.0%; cobi-ven, 75.0%; cobi-ven-atezo, 83.3%). Deaths due to AEs were hemorrhagic stroke and respiratory failure (cobi arm; one patient each); pneumonia (cobi-ven arm); and general physical health deterioration (cobi-ven-atezo arm, which was considered by the

Table 3 Efficacy Summary: Response Rates for all Patients and by t(11;14) Status.

	All-Comers		
n (%)	cobi (n = 6)	cobi-ven (n = 22)	cobi-ven-atezo (n = 21)
ORR	0	6 (27.3)	6 (28.6)
CR	0	1 (4.5)	0
VGPR	0	2 (9.1)	1 (4.8)
PR	0	3 (13.6)	5 (23.8)
MR	0	3 (13.6)	1 (4.8)
SD	5 (83.3)	6 (27.3)	9 (42.9)
PD	0	2 (9.1)	2 (9.5)
Not evaluable	0	3 (13.6)	1 (4.8)
Missing	1 (16.7)	2 (9.1)	2 (9.5)
	Patients with t(11;14)		
	(n = 1)	(n = 4)	(n = 5)
ORR	0	2 (50.0)	5 (100)
CR	0	1 (25.0)	0
VGPR	0	0	1 (20.0)
PR	0	1 (25.0)	4 (80.0)
MR	0	1 (25.0)	0
SD	1 (100)	1 (25.0)	0
PD	0	0	0
Not evaluable	0	0	0
Missing	0	0	0
	Patients without t(11;14)		
	(n = 5)	(n = 18)	(n = 16)
ORR	0	4 (22.2)	1 (6.3)
CR	0	0	0
VGPR	0	2 (11.1)	0
PR	0	2 (11.1)	1 (6.3)
MR	0	2 (11.1)	1 (6.3)
SD	4 (80)	5 (27.8)	9 (56.3)
PD	0	2 (11.1)	2 (12.5)
Not evaluable	0	3 (16.7)	1 (6.3)
Missing	1 (20)	2 (11.1)	2 (12.5)

Abbreviations: atezo, atezolizumab; cobi, cobimetinib; CR, complete remission; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; ven, venetoclax; VGPR, very good partial response.

investigator to be related to study treatment). Both patients in the ven-containing arms with fatal AEs did not harbor t(11;14).

In the SRI phase, in the cobi-ven arm, two DLTs of diarrhea and nausea were experienced by one patient each, and in the cobi-ven-atezo arm, one DLT of diarrhea was reported. Based on the available safety data, the dose levels evaluated (cobi 40 mg + ven 800 mg with or without atezo 840 mg) were determined to be safe, and dosing for both combinations was maintained in the RP.

Efficacy

Among all patients, the ORR (partial response [PR] or better) was 0% for the cobi arm, 27.3% for the cobi-ven arm, and 28.6% for the cobi-ven-atezo arm (Table 3). Clinical benefit rate, defined as a minimal response or better, was 0% for the cobi arm, 40.9% for the cobi-ven arm, and 33.3% for the cobi-ven-atezo arm. In the cobi, cobi-ven, and cobi-ven-atezo arms, respectively, the ORR was 0%, 50.0%, and 100% in patients with t(11;14), and 0%, 22.2%, and 6.3% in patients without t(11;14). The median duration of response was 13.4 months (95% CI, 8.4–not evaluable [NE]) for patients treated with cobi-ven, and 5.1 months (95% CI, 2.3–NE) for patients treated with cobi-ven-atezo. Prolonged disease stability was noted in a subset of patients, irrespective of t(11;14) status (Figure 2). No difference was observed with the addition of atezo to cobi-ven with regard to duration of response and time on study. Responses were noted across high-risk patient subgroups, including those with high-risk cytogenetics, prior autologous stem cell transplantation, and prior anti-CD38 mAb therapy. No clear

Figure 2 Swimlane Plots of Patients On-Study Across Treatment Arms, and Baseline and Biomarker Characteristics of Responders versus Non-Responders. cobi: t(11;14), n = 1; non-t(11;14), n = 5. cobi-ven: t(11;14), n = 4; non-t(11;14), n = 18. cobi-ven-atezo: t(11;14), n = 4; non-t(11;14), n = 17. Combined phases comprise patients from both the safety run-in phase and the randomization phase. [a]Subsequent progression of disease. [b]Prior anti-CD38 monoclonal antibody. High-risk: del(17p), t(4;14), t(14;16). Key features of responders (PR or better) and non-responders are indicated. High-risk and prior ASCT or anti-CD38 therapy are indicated. Baseline t(11:14) status, *BCL2*:*BCL2L1* ratio (RNAseq using a 2.3x cutoff) and Ras/MAPK pathway mutations ("Ras") are also indicated.
Abbreviations: A, atezolizumab; AE, adverse event leading to discontinuation; ASCT, autologous stem cell transplantation; atezo, atezolizumab; C, cobimetinib; cobi, cobimetinib; CR, complete remission; del(17p), chromosome 17p deletion; MR, minimal response; NE, not estimable; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; V, venetoclax; ven, venetoclax; VGPR, very good partial response

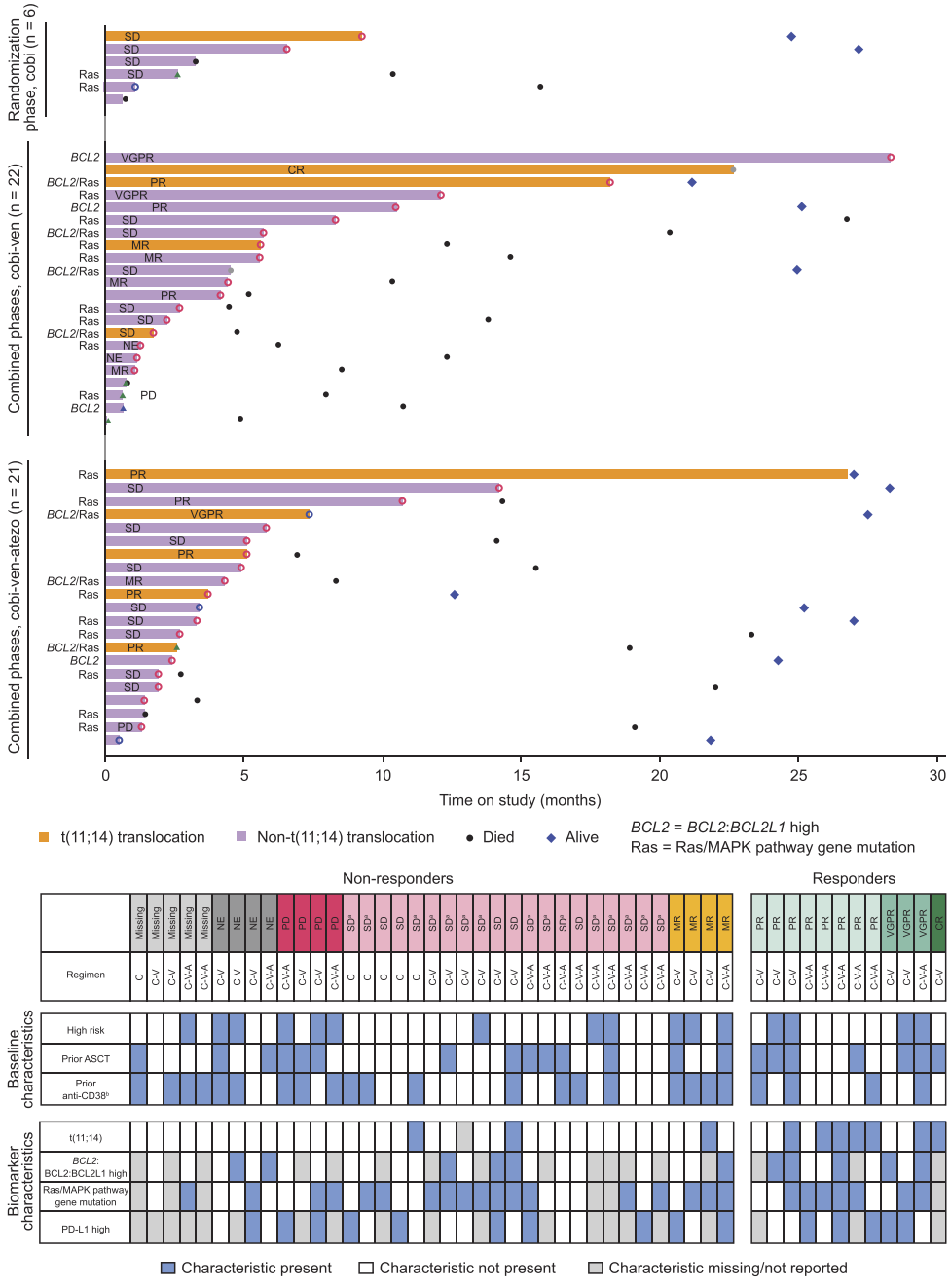
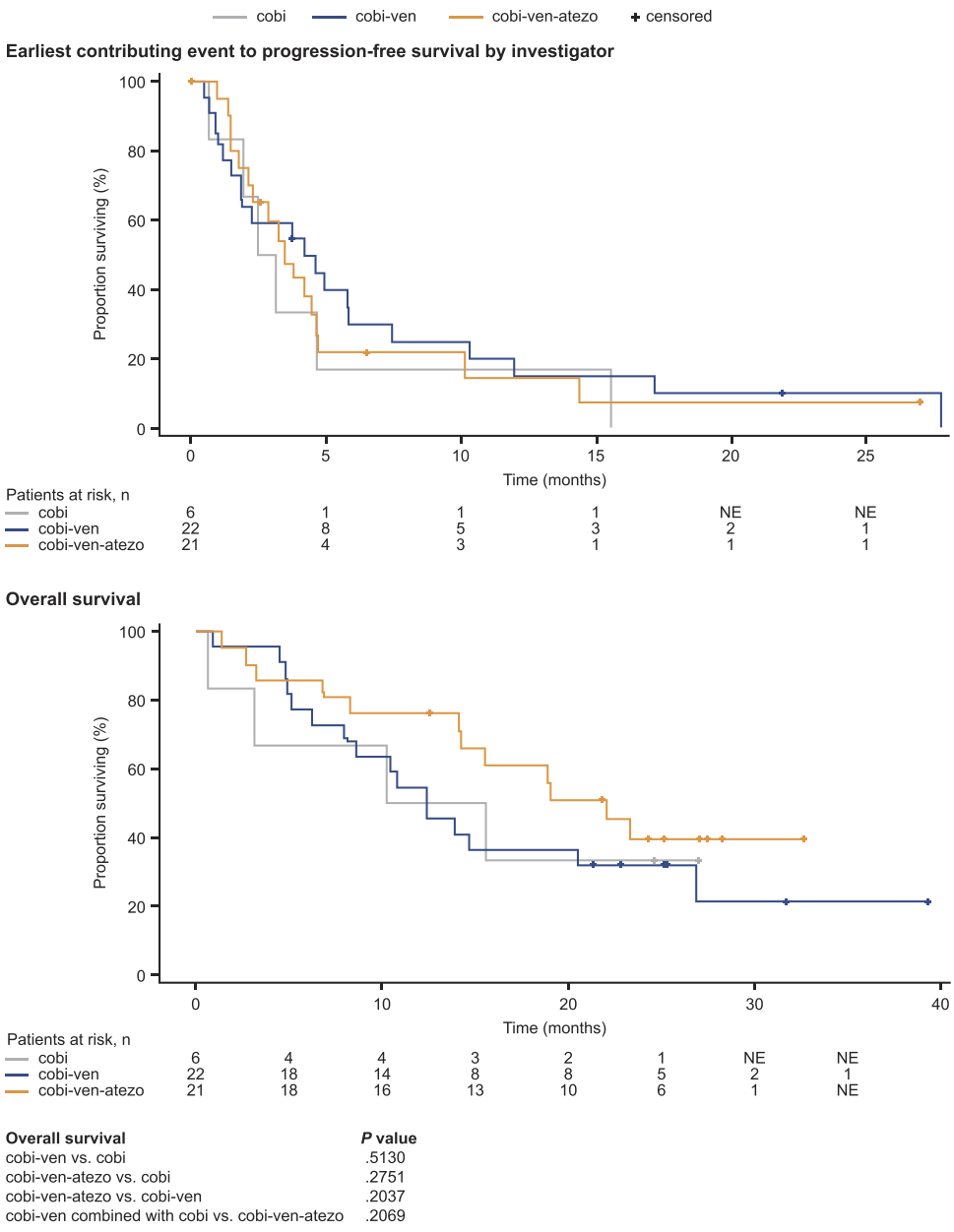


Figure 3 Kaplan–Meier Curves for PFS and OS in All-Comers. **P* values are exploratory and for descriptive purpose only, and were calculated using the log-rank test; there were no significant differences in survival across treatment arms. Abbreviations: atezo, atezolizumab; cobi, cobimetinib; NE, not estimable; OS, overall survival; PFS, progression-free survival; ven, venetoclax



Overall survival	*P* value
cobi-ven vs. cobi	.5130
cobi-ven-atezo vs. cobi	.2751
cobi-ven-atezo vs. cobi-ven	.2037
cobi-ven combined with cobi vs. cobi-ven-atezo	.2069

associations were seen for patients with Ras/MAPK pathway mutations or high expression of PD-L1 (Figure 2).

The median duration of follow-up for all patients was 14.7 months (range, 0.6–39.4). Median PFS and overall survival (OS) for the cobi, cobi-ven, and cobi-ven-atezo arms were 2.8 months (95% CI, 1.9–4.7) and 12.9 months (95% CI, 3.2–NE), 4.2 months (95% CI, 1.9–5.8) and 12.4 months (95% CI, 8.0–26.9), and 3.5 months (95% CI, 2.1–4.6) and 22.0 months (95% CI, 14.3–NE), respectively (Figure 3). No significant difference was noted between the OS for the cobi-ven and cobi-ven-atezo arms. PFS and OS across treatment arms for patients with t(11;14) were not significantly different ($P = .07$ and $P = .7$, respectively; **Supplemental Figure 2**).

Pharmacokinetics

Pharmacokinetic parameters were available for all 49 patients across the three arms (**Supplemental Tables 2** and **3** and **Supplemental Figures 3** and **4**). No clinically relevant drug–drug interactions were identified between the therapies. Assessment of

immunogenicity indicated a 35% incidence (7 of 20 patients) of treatment-emergent atezo ADAs.

Biomarker Analysis

Key baseline biomarker data were evaluable for 49 patients, including t(11:14) status in 48 patients, mutations in Ras/MAPK pathway genes (*KRAS*/*NRAS*/*BRAF*) in 43 patients, and ratio of *BCL2*:*BCL2L1* gene expression in 32 patients (Figure 4A). The t(11:14) translocation was detected in 10 of 48 patients (20.8%), mutations in Ras/MAPK pathway genes were detected in 25 of 43 patients (58.1%), and the *BCL2*:*BCL2L1* ratio was high in 11 of 32 (34.4%) patients. Since atezo did not appear to contribute additional efficacy in the cobi-ven-atezo arm, patients in both the cobi-ven and ven-cobi-atezo arms were combined to assess correlative biomarkers associated with response. Twenty-seven patients of the combined arms were evaluable for t(11;14) status, *NRAS*/*KRAS*/*BRAF* mutation status, and *BCL2*:*BCL2L1* ratio. Consistent with other MM studies, patients harboring t(11;14) had higher response rates, both in t(11:14)-evaluable patients alone and in the subset of patients with all three evaluable biomarkers (ORRs of 77% and 83%, respectively), compared with ORRs of 15% and 19%, respectively, in patients without t(11:14) (Figures 4B and 4C).

When the t(11;14)-negative subset was analyzed further, however, patients who had mutations in Ras/MAPK pathway genes and/or had a high *BCL2*:*BCL2L1* ratio showed improved response rates (ORR 29%), and a trend toward improved OS, compared with t(11:14)-negative patients with wild-type RAS and a low *BCL2*:*BCL2L1* ratio (ORR 0%; Figures 4C, 4D, and **Supplemental Figure 5**).

Pharmacodynamics

In the current study, we observed a decrease in peripheral CD8+ T-cells in patients treated with cobi-ven or cobi-ven-atezo, irrespective of response. Furthermore, reported pharmacodynamic effects of atezo, ie an increase in the proportion of CD8+HLA-DR+Ki-67+ T-cells, were not observed in most patients (**Supplemental Figure 6**).

Discussion

Emerging insights into the biology of MM have led to the development of novel therapeutic strategies and personalized treatment approaches. Combination regimens with innovative mechanisms of action may expand the options for patients with R/R MM and select biomarker characteristics. In this phase Ib/II study, cobi as a single agent, cobi-ven, and cobi-ven-atezo were evaluated for safety, tolerability, and preliminary efficacy in patients with R/R MM who had received 3–5 prior therapies, including prior IMiDs and PIs.

Cobi alone, cobi-ven, and cobi-ven-atezo were noted to have manageable safety and tolerability. No new safety signals were identified for cobi, cobi-ven, or cobi-ven-atezo. Gastrointestinal effects of diarrhea and nausea were the most common AEs, and were generally mild-to-moderate and manageable in the setting of mandatory prophylaxis. Hematological toxicities and infections were consistent with the known myelosuppressive effects of the therapies, and within the range observed with existing therapies for a late R/R population.[15,24-29] The incidence of TLS was low, in line with findings from other ven trials in MM.

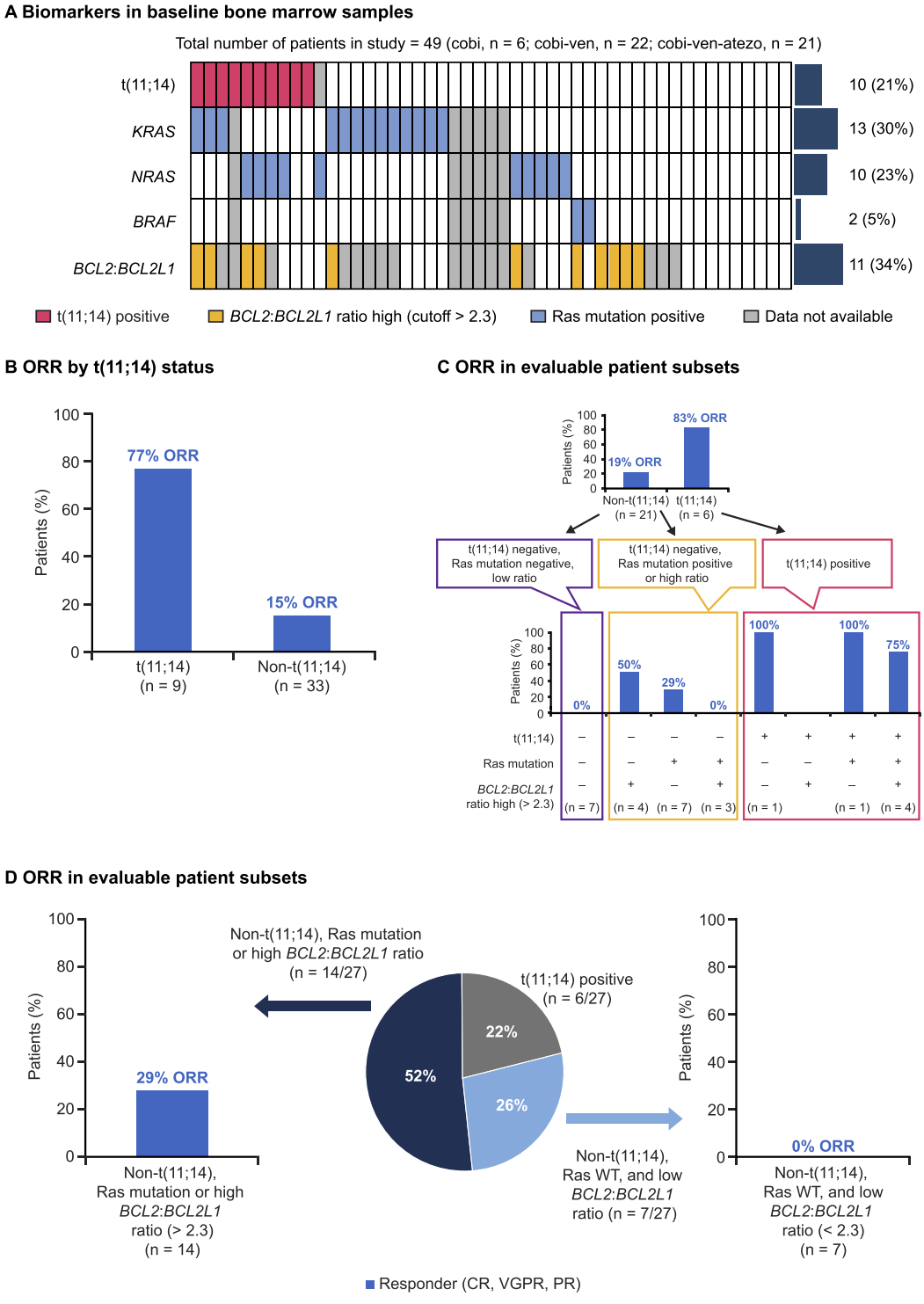
Deaths were primarily due to PD and were not disproportionate across arms, although the study was not powered to detect differences. While an increased rate of fatal infections was observed in patients treated with ven, bortezomib, and dexamethasone in the phase III BELLINI trial,[30] there was one infection-related death in the setting of ven in the current study, which was considered to be unrelated to cobi and cobi-ven. No immune-mediated causes of death were observed. Of the four fatal AEs, only one was considered to be drug-related (general physical health deterioration), and occurred in a t(11;14)-negative patient receiving cobi-ven-atezo. Though the study was terminated early due to limited efficacy of the combinations in all-comers; the decision was not based on safety findings in the study.

Clinical activity of the combinations was moderate in all-comers, with an ORR of 27% for cobi-ven and 29% for the cobi-ven-atezo combination, comparable with findings reported for single-agent ven in an unselected population (ORR 21%).[15] The addition of atezo did not result in an improvement in the ORR or duration of response. Pharmacodynamic analyses of atezo, which showed treatment-induced decreases in T-cell counts in patients treated with cobi-ven and cobi-ven-atezo versus cobi alone, suggest that the cobi-ven combination may impact T-cell viability. These results could partially explain the limited efficacy of adding atezo, and overall do not support the addition of atezo to the cobi plus ven combination in this setting.

Consistent with ven monotherapy results and preclinical findings, t(11;14) appears to be the primary predictive biomarker of response to ven-based combinations.[15,31] Patients harboring t(11;14) responded more favorably to treatment with cobi-ven and cobi-ven-atezo compared with those without t(11;14), with ORRs of 50.0% versus 22.2%, respectively, for cobi-ven, and 100% versus 6.3%, respectively, for cobi-ven-atezo. Although limited by small patient numbers, the response rates are encouraging compared with those for existing therapies for late R/R patients (eg ORR, 20–30% for pomalidomide-dexamethasone or daratumumab monotherapy),[26,27,32] and support biomarker selection for the development of ven. Although limited by patient numbers and caveats with cross-trial comparison, response rates observed with the combinations in the t(11;14) patients in the current study also compared favorably with those observed with ven monotherapy (ORR, 40%).[15] While a higher response rate was observed with the triplet combination in the population harboring t(11;14) (5 of 5 patients; ORR, 100%) versus the doublet combination (2 of 4 patients; ORR, 50%), the sample size was too small to draw reliable conclusions regarding the contribution of atezo. Notably, we did not observe increased T-cell activation/proliferation in patients with t(11:14) treated with atezo, although atezo monotherapy has been reported to increase T-cell activation and proliferation in the periphery.[33]

Overall, the pharmacokinetic characteristics of cobi and ven were comparable with previously reported single agent exposures (data for ven on file).[24] Atezo concentrations were consistent with the known pharmacokinetics of atezo.[34] The treatment-emergent incidence of atezo ADAs observed in the present study should be interpreted

Figure 4 Correlative and Pharmacodynamic Biomarkers. (A) Biomarkers in baseline bone marrow samples; (B) ORR by t(11;14) status; and (C, D) ORR in evaluable patients' subsets defined by t(11;14) status, *NRAS/KRAS/BRAF* mutation status, and *BCL2:BCL2L1* gene expression ratio, and treated with either cobi-ven or cobi-ven-atezo. Abbreviations: atezo, atezolizumab; cobi, cobimetinib; CR, complete remission; ORR, overall response rate; PR, partial response; ven, venetoclax; VGPR, very good partial response; WT, wild type



with caution (35.0%; 7 of 20 patients) due to the low number of patients evaluated. The ADA incidence is within the historic range, and the impact of ADAs has been investigated thoroughly across registrational trials for atezo as a single agent and in combination therapy.[35,36]

Analysis of the limited subset of biomarker-evaluable patients (n = 27 of 49) suggested that in the absence of t(11;14), Ras/MAPK pathway mutations are associated with improved response to cobi-ven, indicating that inhibition of the Ras/MAPK pathway may contribute to the observed efficacy in these patients. Further studies are needed to confirm the contribution of cobi to the observed clinical benefit. As expected, t(11;14)-negative patients with a high *BCL2*:*BCL2L1* ratio also had improved response rates. Overall, the t(11;14)-negative patients who had mutations in Ras/MAPK pathway genes and/or had a high *BCL2*:*BCL2L1* ratio showed improved response rates (ORR, 29%), compared with t(11:14)-negative patients with wild type Ras and a low *BCL2*:*BCL2L1* ratio (ORR, 0%). This subset (t(11:14)-negative with *NRAS*/*KRAS*/*BRAF* mutation and/or high *BCL2*:*BCL2L1* ratio) represented 52% of the patient population in the current study. A selection strategy for these patients, therefore, may both enrich the population for responders to cobi-ven and expand the patient population likely to benefit from a ven-based regimen beyond those with t(11:14).

Conclusion

In summary, cobi alone, cobi-ven, and cobi-ven-atezo demonstrated manageable safety and tolerability in heavily pre-treated PI-, IMiD-, and anti-CD38 mAb-exposed patients with R/R MM. Despite incomplete evaluation due to early study termination, encouraging activity was seen for both the cobi-ven and cobi-ven-atezo combinations in patients harboring t(11;14). The translocation t(11;14) appeared to be the primary predictive biomarker for the ven-based combinations, supporting the current investigation of ven in t(11;14)-positive MM in the ongoing phase III CANOVA trial (NCT03539744). While evaluation of the combinations will not proceed in the current study, future efforts may be directed toward better understanding of how to optimize patient selection, and evaluation of combination strategies targeting the Ras/MAPK pathway and immunotherapy.

Clinical Practice Points

Despite advances in treatment, multiple myeloma (MM) remains incurable, and most patients eventually relapse. Mitogen-activated protein kinase (MAPK) pathway mutations are present in >50% of patients with relapsed/refractory (R/R) MM. Cobimetinib (cobi), a MEK inhibitor, shows limited single-agent activity in R/R MM; however, combination with venetoclax (ven), a potent anti-apoptotic B-cell lymphoma 2 inhibitor, and atezolizumab (atezo), an anti-programmed death-ligand 1, may improve efficacy.

In the present study, cobi, cobi-ven, and cobi-ven-atezo showed manageable safety and tolerability in heavily pre-treated patients with R/R MM, with moderate activity. Encouraging activity was observed for cobi-ven and cobi-ven-atezo in patients harboring t(11;14), suggesting the translocation t(11;14) to be the primary predictive biomarker for the ven-based combinations.

Future efforts may be directed toward improved optimization of patient selection and evaluation of combinations targeting the Ras/MAPK pathway and immunotherapy.

Disclosure

F. Schjesvold received honoraria from Amgen, Takeda, and Sanofi; performed consulting/advisory roles for Celgene, Janssen, Oncopeptides, and Sanofi; and received research funding from Celgene, Sanofi, Janssen, Oncopeptides, and GSK.

B. Paiva served as a consultant for and received honoraria from Adaptive, Amgen, Becton Dickinson, Bristol Myers Squibb/Celgene, GSK, Janssen, F. Hoffmann-La Roche Ltd, Sanofi, and Takeda; and received research support from Bristol Myers Squibb/Celgene, GSK, F. Hoffmann-La Roche Ltd, Sanofi, and Takeda.

V. Ribrag received honoraria from Gilead, Infinity, ArgenX, Merck Sharp & Dohme, Bristol Myers Squibb, Epizyme, Nanostring, Incyte, Roche, and AstraZeneca; served as a consultant or advisor for Servier; and received research funding from ArgenX.

P. Rodriguez-Otero has served on scientific advisory boards for Janssen, BMS, Sanofi, Pfizer, GSK, Sanofi, and Abbvie; has received honoraria from BMS, Janssen, Amgen, GSK, Oncopeptides, Sanofi, Abbvie, Kite Pharma, and Sanofi; and is a consultant for Pfizer, GSK, and BMS.

J.F. San-Miguel served as a consultant and sat on an advisory board for Amgen, Bristol Myers Squibb, Celgene, Janssen, MSD, Novartis, Takeda, Roche, Sanofi, GSK, AbbVie, and Karyopharm.

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M. Hansson has nothing to disclose.

M. Onishi, H. Hamidi, V. Malhi, M. Dail, and G. Ku are employees of Genentech, Inc. and may hold F. Hoffmann-La Roche Ltd stock or stock options.

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Authorship Contributions

Fredrik Schjesvold, Vikram Malhi: Conceptualization, Methodology. **Fredrik Schjesvold, Vincent Ribrag, Paula Rodriguez-Otero, Jesus F. San-Miguel, Pawel Robak, Markus Hansson, Maika Onishi, Marc S. Raab:** Resources. **Fredrik Schjesvold, Bruno Paiva, Vincent Ribrag, Paula Rodriguez-Otero, Jesus F. San-Miguel, Pawel Robak, Markus Hansson, Maika Onishi, Marc S. Raab:** Investigation. **Fredrik Schjesvold, Bruno Paiva, Vincent Ribrag, Paula Rodriguez-Otero, Jesus F. San-Miguel, Pawel Robak, Markus Hansson, Maika Onishi, Habib Hamidi, Vikram Malhi, Monique Dail, Apurva Javery, Grace Ku, Marc S. Raab:** Formal analysis, Visualization. **All authors**: Writing – Original Draft, Writing – Review & Editing.

Data Sharing Statement

Phase I studies are not in scope of the Roche global policy on data sharing. Given the small study population the decision to share the patient level clinical data needs to be handled on a case-by-case basis to determine if the data can be adequately anonymized

to give an acceptably low risk of patient re-identification. Qualified researchers may submit an enquiry through the data request platform, Vivli, https://vivli.org/ourmember/roche/, however this does not guarantee that the data can be shared. Due to technical limitations, exploratory biomarker data cannot be shared. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: go.roche.com/data_sharing

Anonymized records for individual patients across more than one data source external to Roche can not, and should not, be linked due to a potential increase in risk of patient re-identification.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2022.10.006.

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