MultipleMyelomaHub

Relapsed/refractory patients

EHA 2019 | Results of the phase III BELLINI trial: VenBd for RRMM

Sylvia Agathou Shaji Kumar | Jun 21, 2019

On Sunday 16 June at the 24th Congress of the European Hematology Association (EHA), Shaji Kumar, Mayo Clinic, Rochester, MN, US, presented the results of the phase III BELLINI trial (NCT02755597), which investigated the efficacy and safety of venetoclax in patients with relapsed or refractory multiple myeloma (RRMM).[1]

Venetoclax (Ven) is a first-in-class, selective inhibitor of the anti-apoptotic protein BCL2, and thus can induce myeloma cell death. It has shown promising clinical activity and manageable safety both alone,[2] and in combination with bortezomib (B) and dexamethasone[3] (d) in phase I studies for RRMM.

This multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of venetoclax addition to bortezomib and dexamethasone (VenBd) in patients with RRMM. Patients were randomized to Bd or VenBd, with progression-free survival (PFS) by independent review committee (IRC) as the primary endpoint. Secondary endpoints included, overall response rate (ORR), overall survival (OS), ≥ very good partial response (VGPR), and quality of life (QoL) based on patient reported outcomes (PRO).

Study design & baseline characteristics

- N=291 patients with RRMM, who had received 1–3 prior lines and were sensitive or naïve to proteasome inhibitors
- Patients were randomized 2:1 to VenBd (n=194) or Bd (n=97) until disease progression (PD) or unacceptable toxicity
- Dosing schedule (21-day cycles):
  - VenBd:
    - Ven: 800mg daily
    - B: 1.3mg/m^2 on Days 1, 4, 8, 11 of cycles 1–8 and on Days 1, 8, 15, 22 of cycles 9+
    - d: 20mg on days 1, 2, 4, 5, 8, 9, 11, 12 of cycles 1–8 and on Days 1, 2, 8, 9, 15, 16, 22, 23 of cycles 9+
  - Placebo+Bd:
    - B and d: as above
  - **Table 1.** Key baseline characteristics:

	VenBd (n=194)	Placebo+Bd (n=97)

Median age (range)	66 (36–87)	65 (44–83)
≥65 years old	56%	54%
MM International Staging System (ISS):		
Stage 1		
Stage 2	42%	50%
Stage 3	36%	33%
	20%	14%
Number of prior lines:		
1	47%	45%
2–3	53%	55%
Cytogenetics:		
High-risk [t(4;14) or t(14;16) or del(17p)]	17%	19%
Standard risk	78%	77%
Unknown	5%	4%
t(11;14) status:		
Positive	11%	16%
Negative	84%	79%
Unknown	5%	5%

BCL2 expression (immunohistochemistry):		
High	78%	81%
Low	22%	19%

- Median treatment exposure (range):
  - VenBd: 9.9 (0.1–24.7) months
  - Placebo+Bd: 10.5 (0.1–25.4) months
- Median follow-up for OS (range):
  - VenBd: 19.0 (0.2–24.8) months
  - Placebo+Bd: 18.3 (0.0–26.5) months

Key findings

- Median PFS:
  - VenBd: 22.4 months
  - Placebo+Bd: 11.5 months
  - Comparison: p=0.010; HR=0.630 (95% CI, 0.443–0.897)
- Median OS:
  - VenBd: not reached (41 events)
  - Placebo+Bd: not reached (11 events)
  - Comparison: p=0.034; HR=2.027 (95% CI, 1.042–3.945)

- **Table 2**. Response outcomes:

	VenBd (n=194)	**Placebo+Bd (n=97)**	**p value**
ORR	82%	68%	0.008
≥**CR**	26%	5%	<0.001
≥**VGPR**	59%	36%	<0.001

MRD<10^{-4}	19%	3%	<0.001
MRD<10^{-5}	13%	1%	<0.001
MRd<10^{-6}	7%	1%	0.026

Safety

- Most common Grade 3–4 adverse events (AEs) in both arms were:
  - Thrombocytopenia
  - Anemia
  - Neutropenia
  - Diarrhea
- Infection-related AEs of any grade occurred in:
  - VenBd: 80%
  - Placebo+Bd: 77%

- **Table 3**. Causes of death summary:

Safety population	**VenBd (n=193)**	**Placebo+Bd (n=96)**
All deaths	**21%**	**11%**
Infection	7%	2%
PD	9%	8%
Other	5%	1%

Deaths occurring within 30 days of last dose:		
Infection	**7%**	**1%**
PD	4%	0
Other	1%	1%
	2%	0
Deaths occurring after 30 days of last dose:		
Infection	**14%**	**10%**
PD	3%	2%
Other	8%	7%
	3%	1%

Subgroup analysis

The investigators of the trial performed a PFS subgroup analysis to identify potential patient populations that benefit the most from venetoclax treatment without the serious infection adverse events identified in the total cohort

- Patients with positive t(11;14) status (n=35) benefited the most from VenBd treatment with:
  - Median PFS:
    - VenBd: not reached
    - Placebo+Bd: 9.5 months
    - Comparison: p=0.002; HR=0.110 (95% CI, 0.022–0.560)
  - Median OS:
    - VenBd: not reached (1 event)
    - Placebo+Bd: not reached (2 events)
    - Comparison: p=0.363; HR=0.343 (95% CI, 0.031–3.842)

Conclusions

- Despite the increased PFS and response rates seen with VenBd, an increased risk of death (lower OS) accompanied the treatment. This led to an FDA hold on patient enrollment for this trial and any other involving venetoclax treatment for MM patients
- More deaths were reported in the VenBd arm, which were mainly due to treatment-emergent infections
- Subgroup analysis revealed that patients with positive t(11;14) status benefited the most from VenBd without the associated treatment toxicity, thus the investigators proposed that VenBd should be further developed and implemented on this particular patient subpopulation

References

1. Kumar S. A phase 3 study of venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma. Abstract LB2601. 24th Congress of EHA, Amsterdam, NL
2. Kumar S. *et al*. 2017. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. *Blood* 130, 2401–2409. DOI: 10.1182/blood-2017-06-788786
3. *Moreau P.* et al. 2017. Promising efficacy and acceptable safety of venetoclax plus bortezomib and dexamethasone in relapsed/refractory MM. *Blood* 130, 2392–2400. DOI: 10.1182/blood-2017-06-788323