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Efficacy and safety of venetoclax in patients with relapsed/refractory multiple myeloma: a meta-analysis

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Abstract

Background Venetoclax is clinically active in treating relapsed/refractory multiple myeloma (RRMM). This study evaluated the efficacy and safety of venetoclax or venetoclax with other agents in treating RRMM.

Methods PubMed, Web of Science, Embase, and Cochrane Library were comprehensively searched. We included studies investigating the efficacy and safety of venetoclax or venetoclax with other agents in treating RRMM. Overall response rates (ORR), stringent complete response rates (sCR), complete response rates (CR), very good partial response rates (VGPR), partial response rates (PR), stable disease (SD), progressive disease (PD) and adverse events were synthesized using either a random-effects model or a fixed-effects model.

Results A total of 7 clinical trials with 482 patients with RRMM were included. Concerning venetoclax with other agents, the pooled ORR, sCR, CR, VGPR, PR, SD, and PD were 0.76 (95% CIs: 0.62, 0.87), 0.11 (95% CIs: 0.04, 0.21), 0.18 (95% CIs: 0.11, 0.26), 0.16 (95% CIs: 0.12, 0.25), 0.29 (95% CIs: 0.25, 0.34), 0.07 (95% CIs: 0.05, 0.10), and 0.11 (95% CIs: 0.04, 0.23). The overall rate of adverse events ≥ Grade 3 was 0.84 (95% CIs: 0.77, 0.91). The most common non-hematologic adverse events were nausea, diarrhea, fatigue, back pain, and vomiting; hematologic adverse events included thrombocytopenia, neutropenia, anemia, leukopenia, and lymphopenia.

Conclusions This study indicates that venetoclax alone or in combination with other agents reveals favorable treatment responses and acceptable adverse events in treating RRMM.

Keywords Venetoclax, Multiple Myeloma, Efficacy, Adverse events, Meta-analysis

Background

Multiple myeloma (MM) is an incurable hematologic malignancy characterized by relapses and remissions [1]. Generally, clinical symptoms of MM include hypercalcemia, elevated serum creatinine, renal insufficiency, anemia, and bone destruction [2, 3]. With a global incidence of approximately 4/100,000 per year, MM accounts for about 10% of all hematological malignancies [4–6]. Until 2000, the standard therapy for MM was melphalan or doxorubicin-based regimens with corticosteroids. Applying proteasome suppressants, histone deacetylase inhibitors, immunomodulatory agents, and monoclonal

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antibodies has posed various treatment choices for MM patients. Unfortunately, most MM patients eventually relapse and become resistant to different therapies with a decreased response rates to the regimens in subsequent recurrences [7]. It is widely deemed that genomic instability, clonal heterogeneity, and myeloma microenvironment interactions are pivotal causes of treatment resistance and relapse [1, 8]. Antiapoptotic BCL-2 family proteins are key in regulating the internal apoptotic pathway and cell survival [9–11]. It has been proven that BCL-2 is overexpressed in myeloma cell subsets and participates in their survival [12]. Analysis of BCL-2 homologous domain three recently confirmed the role of BCL-2 in maintaining MM cell survival [13].

Moreover, the selective inhibition of BCL-2 restores the apoptotic pathway of malignant cells [14–16]. Venetoclax, an oral, potent inhibitor of BCL-2, has been observed to show antitumor activity in many hematological malignancies [14–16]. It has been proven to induce apoptosis in human MM cell lines and original samples of MM patients, especially those cells carrying t(11; 14) chromosome translocation [17]. In addition, venetoclax as a monotherapy or in combination with other agents showed significant clinical activity against relapsed/refractory MM (RRMM), particularly in patients with t(11;14) [18–20]. Combining venetoclax and agents with complementary action mechanisms (such as IMiDs) or agents that increase BCL-2 dependency may enhance the anti-MM activity of venetoclax [21]. This meta-analysis aimed to assess the efficacy and safety of venetoclax and the combined therapy with other agents by synthesizing the results from published articles.

Methods

This meta-analysis was done based on previously published studies that had declared ethical approvals, thereby ethical approval was not required for this study. This study was based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [22].

Search strategy and selection criteria

We searched the electronic databases, including PubMed, Web of Science, Embase, and Cochrane Library, up to November 7, 2022, with citations in English. The following key terms were used: BCL-2, venetoclax, and multiple myeloma. The detailed search strategy is shown in Supplementary Table 1. The references of included articles were also searched to assay additional studies. Inclusion criteria were: (1) clinical trials investigating the efficacy and adverse events of venetoclax or venetoclax with other agents in patients with RRMM. (2) Outcomes regarding treatment responses and adverse events could be extracted or calculated. (3) If studies recruited participants over the same period or from the same center, we only included the study with the largest sample size. We excluded case reports, reviews, comments, editorials, and conference abstracts with unavailable indicators. Two independent investigators (Xiaohui Gao and Xiaoyan Zhao) performed a literature search and study inclusion. When disagreement occurred, they discussed their arguments, and a third reviewer (Gang Zhang) was involved when no consensus was achieved.

Data extraction and quality assessments

Two reviewers independently screened the title and abstract according to the inclusion criteria. Then a full-text reading of the literature was performed for the final identification for eligibility. The following information was extracted: name of the first author, year of publication, study design, number of patients, age, treatment regimens, the dosage of venetoclax, percentage of patients positive for t(11;14), and treatment outcomes. The outcomes comprised overall response rates (ORR), stringent complete response rates (sCR), complete response rates (CR), very good partial response rates (VGPR), partial response rates (PR), stable disease (SD), progressive disease (PD) as well as adverse events. We assessed the quality of the enrolled studies using Methodological Index for Non-Randomized Studies (MINORS).

Statistical analysis

We used the R studio (Version 3.6.1; A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) for statistical analyses. A Cochran Q test and I^2 statistic were used to investigate heterogeneity [23]. The pooled ORR, sCR, CR, VGPR, PR, SD, PD, and adverse events rates with their respective 95% confidence intervals (CIs) were calculated using a random or fixed-effects model. A random-effects model was used if the I^2 value was >50%. Otherwise, a fixed-effects model was used [24]. Subgroup analysis and meta-regression were performed based on population baselines, including study design, age, sample size, regimen, the dose of venetoclax, and t(11;14) status. We conducted a sensitivity analysis to check the stability of pooled outcomes. Furthermore, Egger's tests were performed to assess the potential publication bias. A probability of $P<0.05$ was regarded as statistically significant.

Results

Study selection and characteristics

We identified 1155 articles from the databases searched. Afterward, 54 duplicates were removed, and 992 studies were excluded through an initial screening. After a full-text assessment of the remaining 19 articles, seven studies were identified for inclusion [18–21, 25–27] (Fig. 1). The selected seven studies containing 482 patients with diagnosed RRMM provided the outcomes needed in this

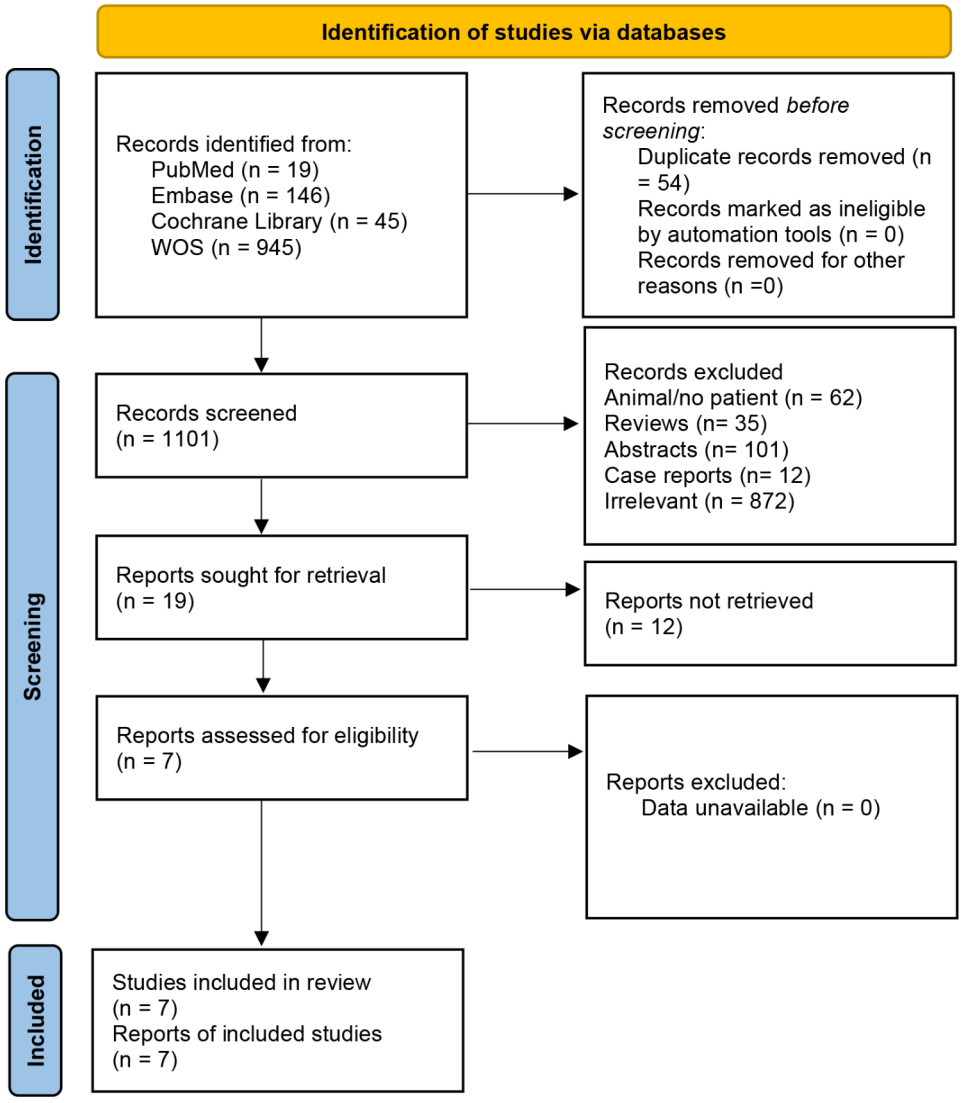

Fig. 1 Search results and flow chart of the meta-analysis

study. Six trials reported the efficacy and safety of venetoclax in combination with other agents, and one trial investigated the efficacy and safety of venetoclax monotherapy. The quality of included studies was rated as moderate to high according to the MINORS tool. Table 1 shows detailed information on included studies.

Efficacy

An open-label, dose-escalation, phase 1 study of venetoclax monotherapy in 66 patients with RRMM revealed that the ORR was 0.21 (14/66), and 15% achieved VGPR or better. Most responses (12/14) were reported in patients with t(11;14). For included studies about venetoclax with other agents, the pooled ORR, sCR, CR, VGPR, PR, SD, and PD were 0.76 (95% CIs: 0.62, 0.87; I^2=84%, p<0.0001), 0.11 (95% CIs: 0.04, 0.21; I^2=77%, p=0.0052), 0.18 (95% CIs: 0.11, 0.26; I^2=65%, p=0.0209), 0.16 (95% CIs: 0.12, 0.25; I^2=57%, p=0.0388), 0.29 (95% CIs: 0.25, 0.34; I^2=0%, p=0.5967), 0.07 (95% CIs: 0.05, 0.10; I^2=0%, p=0.4423), and 0.11 (95% CIs: 0.04, 0.23; I^2=85%, p=0.0015), respectively (Figs. 2, 3, 4, 5 and 6, **Figures S1-S2**). In a 2-phase study by Kaufman et al., t(11;14), only patients were recruited; the ORR was 60% and 48% in phase 1 and phase 2, respectively.

Median progression-free survival ranged from 22.4 to 22.8 months. Gasparetto's study reported overall survival at six months of 87.5%. The 18-month PFS rate was 90.5% (95% CI, 67.0 to 97.5) with venetoclax+daratumumab+dexamethasone and 66.7% (95% CI, 42.5 to 82.5) with venetoclax+daratumumab+bortezomib+dexamethasone in the trial of Bahlis et, al.

Table 1 Study characteristics

Author	Year	Study design	No. of patients	Age, median (range), y	Regimens	Dosage of venetoclax	Positive for t(11;14) (%)	Prior lines of therapy, median (range)	Refractory, n (%)	OS, PFS	MINORS scores
Kumar	2017	Open-label, phase 1 study	66	63 (31–79)	Monotherapy	21-day cycles with daily venetoclax given at final doses of 300, 600, 900, or 1200 mg in dose-escalation cohorts (3 + 3 design) and 1200 mg in the safety expansion	46	5 (1–15)	Bortezomib:46 (70); Lenalidomide: 51 (77); Bortezomib/lenalidomide: 40 (61); Carfilzomib: 20(30); Pomalidomide: 35 (53)	NR	13
Moreau	2018	Open-label, multicenter, phase 1b	66	64 (38–79)	Venetoclax in combination with bortezomib and dexamethasone	Once daily (100, 200, 300, 400, 500, 600, 800, 1000, and 1200 mg)	14	3 (1–13)	Bortezomib: 26 (39); lenalidomide: 35 (53)	NR	14
Kumar	2020	Randomised, doubleblind, placebo-controlled, multicentre, phase 3 trial	194	66	Venetoclax plus bortezomib and dexamethasone	800 mg orally daily	10	> 1 line:53%	Immunomodulatory drugs: 64 (33); lenalidomide: 38(20)	Median PFS was 22.4 months (95% CI 15.3–not estimable) with venetoclax versus 11.5 months (9.6–15.0) with placebo. 41 (21%) overall survival events occurred in the venetoclax group compared with 11 (11%) in the placebo group.	14
Bahlis	2021	Multicenter, phase 1	48	64 (41–80)	Venetoclax plus daratumumab and dexamethasone	Once daily at 400 mg	63	Part 1:2.5 (1–8); Part 2:1 (1–3)	PI: 11 (23); IMiD: 25 (52); PI + IMiD: 10 (21)	The 18-month PFS rate was 90.5% (95% CI, 67.0 to 97.5) with venetoclax + daratumumab + dexamethasone and 66.7% (95% CI, 42.5 to 82.5) with venetoclax + daratumumab + bortezomib + dexamethasone	14
Costa	2021	Open-label, multicenter, phase 2	49	66 (37–79)	Venetoclax plus carfilzomib and dexamethasone	Daily (400 or 800 mg)	27	1 (1–3)	PI: 28 (57); IMiD: 35 (71); PI + IMiD: 22 (45)	Median PFS was 22.8 months	13
Gasparetto	2021	Open-label, multicenter, phase 2	8	68 (60–77)	Venetoclax in combination with pomalidomide and dexamethasone	Orally at 400 mg daily	38	> 2 lines:50%	PI: 2 (25); lenalidomide: 6 (75); daratumumab: 4 (50); PI + lenalidomide: 2(25); PI + lenalidomide + daratumumab: 2(25)	OS at 6 months was 87.5%	14
Kaufman	2021	Open-label phase 1/2 study	51	46–80	Venetoclax and dexamethasone	800 mg on days 1, 8, and 15	100	Part 1:3 (1–8); Part 2:5 (2–12)	PI: 40 (78); IMiD: 45 (88); PI + IMiD: 31 (61); daratumumab: 31 (61)	The median time to progression was 12.4/10.8 months.	15

OS, overall survival. PFS, progression free survival. MINORS: methodological index for non-randomized studies. PI, proteasome inhibitor

IMiD: immunomodulatory imide drug

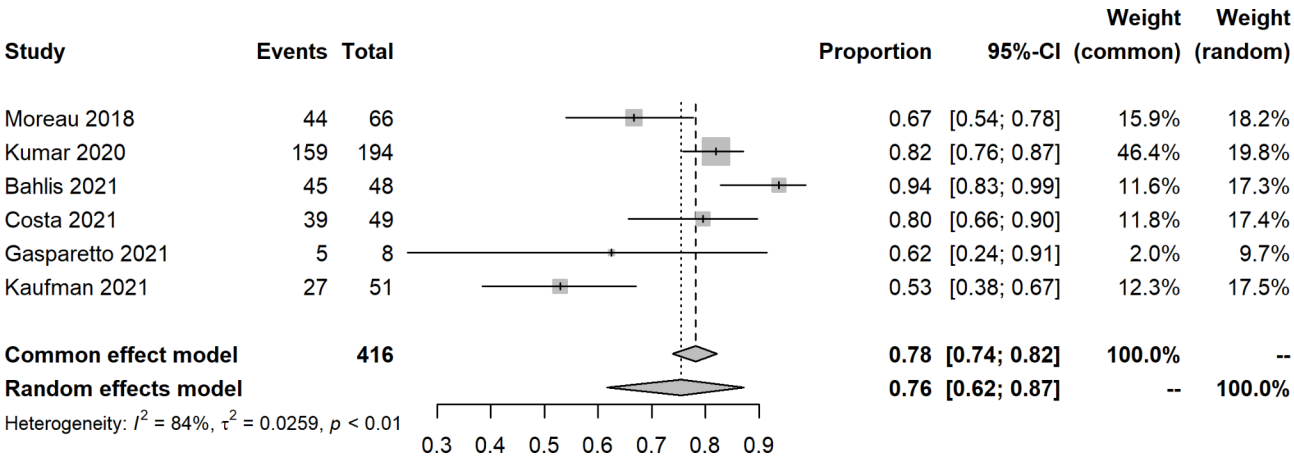

Fig. 2 Forest plot of overall response rates

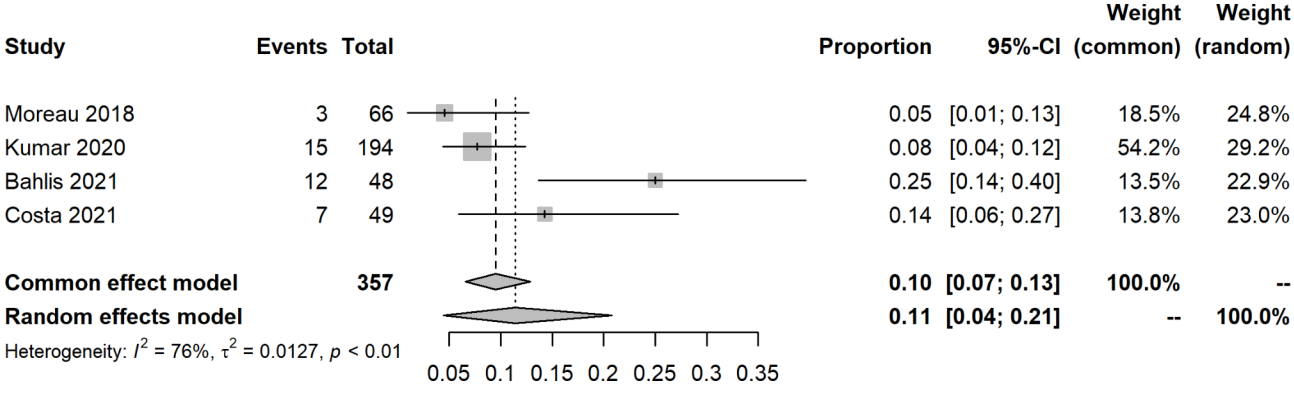

Fig. 3 Forest plot of stringent complete response rates

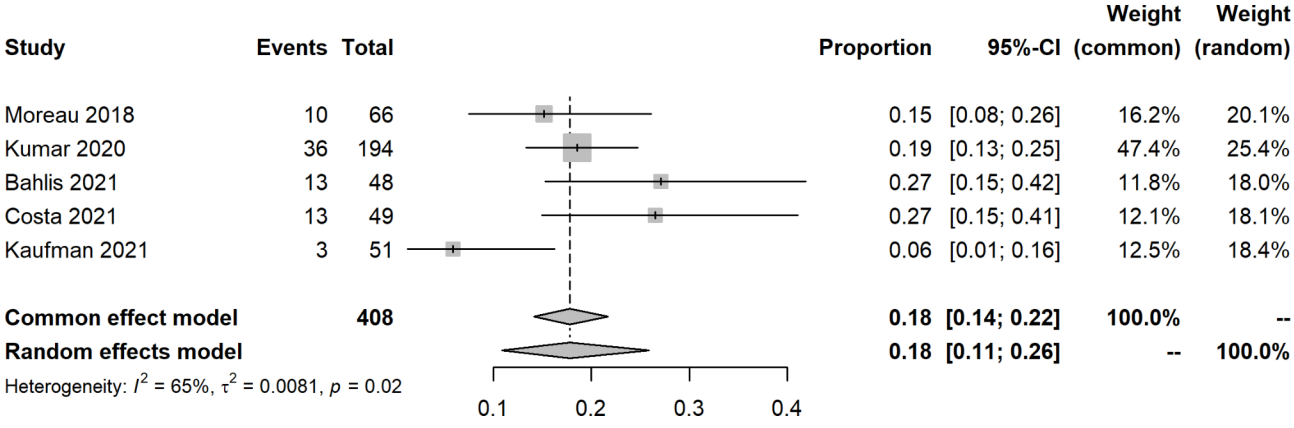

Fig. 4 Forest plot of complete response rates

Adverse events

In the included study of venetoclax monotherapy, the most common adverse events had mild gastrointestinal symptoms (nausea [47%], diarrhea [36%], and vomiting [21%]). Cytopenias were the most common grade 3/4 events, with thrombocytopenia (32%), neutropenia (27%), anemia (23%), and leukopenia (23%) reported. For included studies investigating venetoclax with other agents, the overall rate of adverse events≥Grade 3 was 0.84 (95% CIs: 0.77, 0.91; I^2=61%, p=0.0235) (Figure S3). The most common non-hematologic adverse event included nausea (0.38), diarrhea (0.53), fatigue (0.33), back pain (0.18), and vomiting (0.19) (Table 2, Figures S4-S8). Hematologic adverse events included thrombocytopenia (0.25), neutropenia (0.21), anemia (0.22),

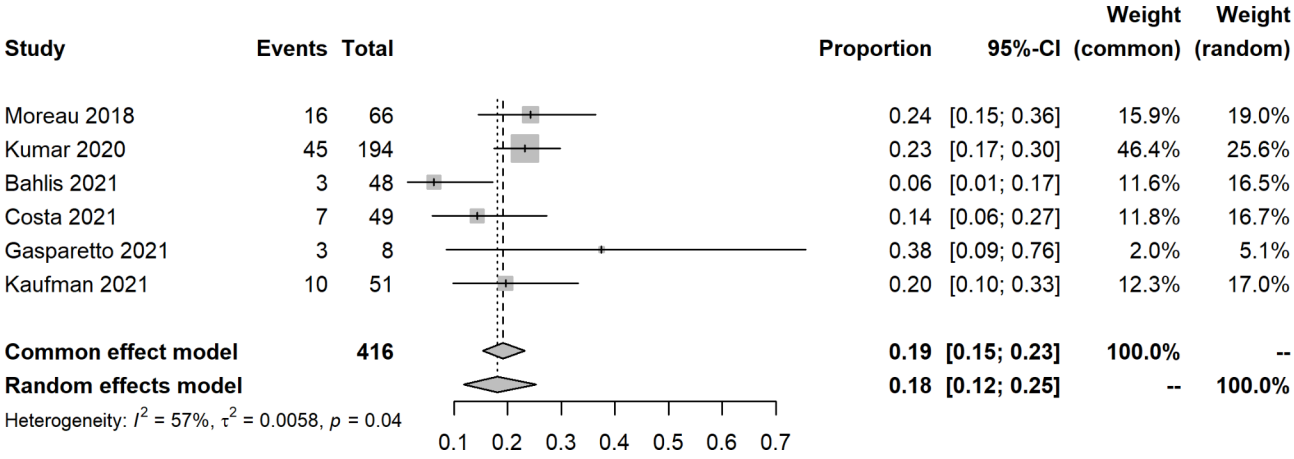

Fig. 5 Forest plot of very good partial response rates

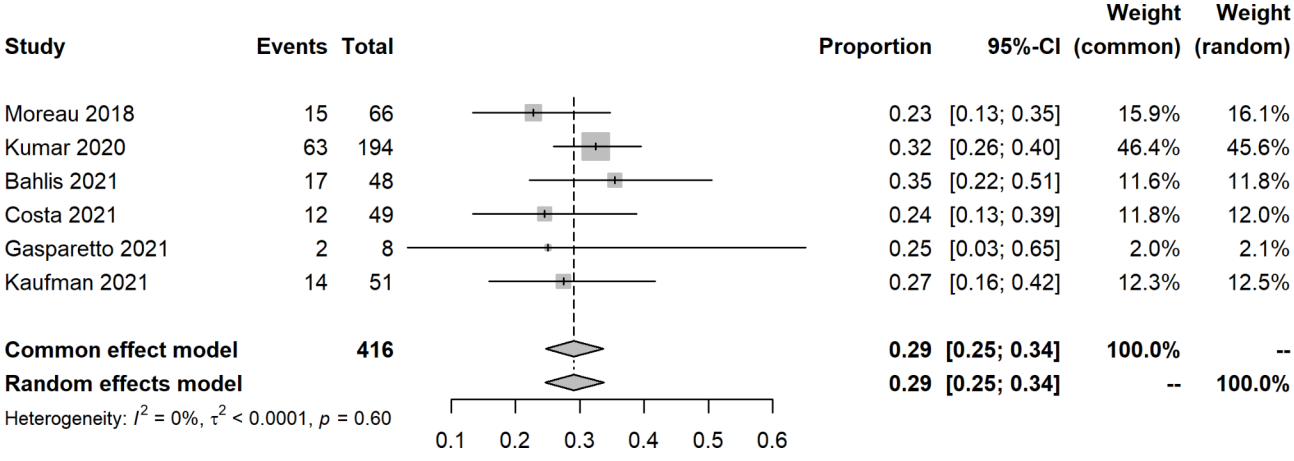

Fig. 6 Forest plot of partial response rates

Table 2 Summary of adverse events

Adverse event	Pooled rates of any grade	95% CIs	I^2 (%)	p
Non-hematologic adverse events				
Nausea	0.38	0.33–0.42	34	0.1798
Diarrhea	0.53	0.42–0.63	69	0.0129
Fatigue	0.33	0.21–0.46	78	0.0005
Back pain	0.18	0.13–0.24	0	0.6993
Vomiting	0.19	0.14–0.23	29	0.2372
Hematologic adverse events				
Thrombocytopenia	0.25	0.17–0.34	64	0.0171
Neutropenia	0.21	0.17–0.26	58	0.0347
Anemia	0.22	0.18–0.26	49	0.0831
Leukopenia	0.20	0.13–0.28	8	0.3384
Lymphopenia	0.26	0.20–0.34	3	0.3774

CI: confidence interval

leukopenia (0.20), and lymphopenia (0.26) (Table 2, Figures S9-S13).

Publication bias

Egger's tests for publication bias revealed p-values of 0.5348, 0.3949, 0.9958, 0.7642, 0.4547, 0.1241, 0.3522, and 0.9626 for the analyses of ORR, sCR, CR, VGPR, PR, SD, PD, and adverse events rates ≥ Grade 3, respectively.

Sensitivity analysis

The pooled outcomes showed robustness in sensitivity analysis with the leave-one-out method (Figures S14-S21).

Discussion

In the past two decades, there were dramatic advances in the treatment of MM, beginning with the reported use of high-dose melphalan and autologous stem cell transplant in 1996 [28], followed by the introduction of the immunomodulatory drugs [29], the proteasome inhibitors (PI) [30] and BCL-2 inhibitor [31]. Those drugs are

active in RRMM and expanded the treatment options for patients. This meta-analysis included seven published articles comprising 482 patients with diagnosed RRMM and treated with venetoclax-based regimens. For venetoclax monotherapy, Kumar's phase 1 trial showed an ORR of 0.21. For included studies investigating venetoclax with other agents, the pooled ORR, sCR, CR, VGPR, PR, SD, and PD were 0.76, 0.11, 0.18, 0.16, 0.29, 0.07, and 0.11. Median PFS ranged from 22.4 to 22.8 months. Gasparetto's study reported overall survival at six months of 87.5%. In the Bahlis et al. trial, venetoclax+daratumumab+dexamethasone had a higher 18-month PFS rate compared to venetoclax+daratumumab+bortezomib+dexamethasone [25]; and an increased rate of fatal infections was observed in patients treated with venetoclax+bortezomib+dexamethasone in the phase 3 BELLINI trial [20]. The combination of different drugs may affect drug metabolism, leading to differences in efficacy and safety. It may be one of the underlying causes of the diversity in PFS, which needs further investigation.

Preclinical studies have shown that both the dexamethasone and the proteasome inhibitors (bortezomib and carfilzomib) can increase BCL2 dependency in MM cells by shifting MCL1 to BCL2 and by decreasing MCL1 activity through the upregulation of Noxa (PMAIP1) [32–36]. Furthermore, daratumumab, a CD38 monoclonal antibody, can induce cellular death in MM cells through complement-dependent cytotoxicity, antibody-dependent cytotoxicity, antibody-dependent cellular phagocytosis with an expansion of clonal effector T cells, and decrease of regulatory T cells and, therefore, could eliminate emergent resistant subclones [37]. Venetoclax, in turn, was demonstrated to enhance adaptive immunity by increasing the CD4+and CD8+effector memory cells in the blood and improving the efficacy of immune checkpoint blockade [38]. In addition, a combination of venetoclax and pomalidomide was proven to increase immune stimulation [38, 39]. Regarding adverse events, the most common non-hematologic adverse events were nausea, diarrhea, fatigue, back pain, and vomiting. Hematologic adverse events included thrombocytopenia, neutropenia, anemia, leukopenia, and lymphopenia. The pooled rate of adverse events ≥ Grade 3 was 0.84.

In this meta-analysis, there were significant heterogeneities in all indicators. The heterogeneity may be attributed to differences in baseline characteristics of the study participants, study design, drug compliance, median lines of prior therapy in each study, and other relevant factors. Regardless, sensitivity analyses demonstrated the robustness of the results of this meta-analysis, and Egger's publication test also showed no significant publication bias in the included studies.

We acknowledge additional limitations of this study: firstly, the heterogeneity existed on venetoclax doses and combinations in included studies, which subgroup analysis could not address due to a limited number of studies in each subgroup. Secondly, the included studies were single-armed clinical trials, or data from one arm of one randomized controlled clinical trial was analyzed. These trials were limited by the lack of a randomized design, not to mention the inherent limitations of cross-trial comparisons. Finally, the subgroup of patients with multiple myeloma with or without t(11;14) was not performed because the data from included studies relevant to these subgroups could not be extracted. Individual patient data are warranted to address this issue. Despite limitations in this meta-analysis, the results provide a pooled analysis of the efficacy and safety of venetoclax with a large sample size and a comprehensive description and quality assessment of the relevant clinical trial profiles. This study addresses gaps in the existing evidence and supports future clinical trials with a different focus.

Conclusions

Based on the outcomes of this meta-analysis, we may conclude that venetoclax combined with other agents has promising clinical response rates in treating RRMM patients who received at least one line of prior therapy, with acceptable adverse effects. It is expected that well-designed randomized controlled clinical trials and real-world studies be conducted to address issues in evaluating the efficacy and safety of venetoclax monotherapy or in combination with novel agents in treating RRMM.

List of abbreviations

RRMM	Relapsed/refractory multiple myeloma
ORR	Overall response rates
sCR	Stringent complete response rates
CR	Complete response
VGPR	Very good partial response rates
PR	Partial response
SD	Stable disease
PD	Progressive disease
MM	Multiple myeloma
MGUS	Monoclonal gammopathy of uncertain significance
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
MINORS	Methodological Index for Non-Randomized Studies
CIs	Confidence intervals
PI	Proteasome inhibitors

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-023-11553-3.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

Not applicable.

Authors' contributions
Xiaohui Gao, Hui Zeng conceived and designed this study. Xiaoyan Zhao, Haibing Wu were responsible for the collection, extraction, and analysis of the data. Fei Sun, Gang Zhang was responsible for writing the paper. Minchao Yan, Yuan Li performed the quality evaluation and completed data analysis. Gang Zhang, Fei Sun polished the English language. All authors and participants reviewed the paper and reached an agreement to approve the final manuscript.

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Data Availability
All data generated or analyzed during this study are included in this article and its supplementary information file.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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