Investigational venetoclax combination therapy in acute myeloid leukemia – a systematic review and meta-analysis

Venetoclax is approved for patients with newly diagnosed (ND) acute myeloid leukemia (AML) aged ≥75 years or patients who are ineligible for intensive chemotherapy.[1] To improve response rates and survival, venetoclax has been evaluated in combination with intensive and lower intensity chemotherapy, targeted therapy, and immunotherapy.[2] Here, we conducted a systematic review and meta-analysis to assess the efficacy and safety of these novel venetoclax combination therapies in AML. This systematic review was conducted according to a published protocol (CRD42022307023) and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[3] (*Online Supplementary Figure S1*). A systematic review of the literature was conducted by a medical librarian in the following databases, Cochrane Library, Ovid Embase, Google Scholar, Ovid MEDLINE, PubMed, Scopus, and Web of Science Core Collection, to find relevant articles published from inception of the database to January 24, 2022. The search was formulated using a combination of controlled vocabulary and keywords for AML and venetoclax. Studies on pediatric patients, review articles, commentaries or basic research articles, case series with fewer than ten patients, any retrospective studies with fewer than 30 patients, duplicate publications from the same cohort of patients, and studies without an available English full text were also excluded. A Downs and Black checklist was used to assess study quality.[4] The primary endpoint was the overall response rate (ORR) as reported by the individual studies. Random-effects models were used to pool ORR and rates of complete response (CR), minimal residual disease (MRD) response, febrile neutropenia (FN), and 30-day mortality in each study group. Heterogeneity of studies was determined using Cochran Q and I^2 indices and was graded as low, moderate, and high for I^2 indices of 30%, 30-60%, and >60%, respectively. Pre-planned subgroup analyses and univariate meta-regression analyses were performed to statistically compare safety effect sizes of different subgroups based on the type of added therapy. All analyses were performed with Comprehensive Meta-Analysis (CMA 2.2, Biostat).

The electronic search yielded 2,471 unique articles, of which 2,345 were excluded based on title and abstract, leaving 126 articles for full-text review. An additional 90 papers were excluded, with 36 studies included in the final analysis (*Online Supplementary Figure S1*). Among the 36 studies included, 13 reported outcomes of patients with ND AML, 14 studies reported outcomes of patients with relapsed/refractor (R/R) AML and nine studies reported outcomes of patients with R/R and ND AML (*Online Supplementary Table S1*). Study quality was limited by the single-arm design employed in all studies. Studies achieved 11-14 points on the rating scale with a median score of 13 (*Online Supplementary Table S2*).

The pooled ORR in all nine studies in the ND intensively treated group was 86.2% (95% confidence interval [95% CI]: 72.8-93.6%) (Figure 1A). The heterogeneity among the various studies was high (I^2=69.1%). The CR rate was reported in all nine studies, with a combined CR rate of 69% (95% CI: 49.9-83.1) (Figure 1B). The MRD rate among responders was reported in seven out of the nine studies, with a combined MRD negativity rate of 79.4% (95% CI: 0.7-0.86) (Figure 1C). In contrast to other responses, MRD rates among evaluated patients had a low heterogeneity (I^2=12.7%).

Among 12 studies included in the ND AML non-intensively treated group, the combined ORR was 82% (95% CI: 75.1-87.8%) with overall moderate heterogeneity (I^2=59.1%) (Figure 1D). ORR rates were 73.7% (95% CI: 60-84), 84.3% (95% CI: 71.4-92%) and 93.3% for targeted therapy, immunotherapy and low dose chemotherapy, respectively. All 12 studies reported CR rates and the combined CR rate was 59.9% (95% CI: 51.5-67.8%) with high heterogeneity among studies (I^2=64.3%) (Figure 1E). The CR rates were 47.3% (95% CI: 36.3-58.6%), 60.4% (95% CI: 37.7-79.4%) and 80% in the targeted therapy, immunotherapy and low dose chemotherapy groups, respectively. MRD clearance rate was reported in seven studies, with an overall MRD negativity rate of 58.8% (95% CI: 49.2-67.8%) (Figure 1F).

The pooled ORR in 23 studies included in the R/R group was 56.6% (95% CI: 49.5-63.6%) with high inter-study heterogeneity (I^2=68.5%) (Figure 2A). Within the different subgroups, the ORR was 47.6% (95% CI: 34.3-61.3%) in the targeted therapy subgroup, 44.3% (95% CI: 31.6-57.9%) in the immune therapy group, 64.6% (95% CI: 46.8-79.1%) in the intensive chemotherapy subgroup and 71.1% (95% CI: 59-80.8%) in the low-intensity chemotherapy group. The CR rates were evaluated in 17 studies showing a pooled CR rate of 24.4% (95% CI: 19.2-30.6%) (Figure 2B). The CR rates were 11.3% (95% CI: 7.2-17.3%), 14.8% (95% CI: 7.4-27.4%), 28.6% (95% CI: 8.9-62.2%) and 50% (95% CI: 38-62%) in the groups receiving targeted therapy, immunotherapy, intensive chemotherapy and low dose chemotherapy, respectively. Among responders, the pooled MRD negative response rate was 57.8% (95% CI: 48.5-66.5%) reported in 11 studies within

the R/R group (Figure 2C). The MRD negative rates were 53.5% (95% CI: 41.8-64.8%) in the targeted therapy subgroup, 67.7% (95% CI: 0.45-85.8%) in the low-dose chemotherapy subgroup and 63.2% (95% CI: 44.9-78.4%) in the intensive chemotherapy subgroup.

The rate of FN was reported in six studies within the ND AML intensively treated group and was 67.6% (95% CI: 49.3-81.8%) (Figure 3A). In the ND AML non-intensively treated group, the combined rate of FN from five trials was 36.6% (95% CI: 29.2-44.6%) (Figure 3B). The overall FN rate in 12 studies in the R/R group was 38.6% (95% CI: 31.2-46.4%) (Figure 3C). The rate of FN among studies in the R/R group was lowest in the immunotherapy group – 23% (95% CI: 12.5-38.6%), followed by 38% (95% CI: 28.7-48.4) in the targeted therapy subgroup, 38.5% (95% CI: 14-70.7%) in the low-dose chemotherapy subgroup and highest – 60.2% (95% CI: 41-76.7%) in the intensive subgroup.

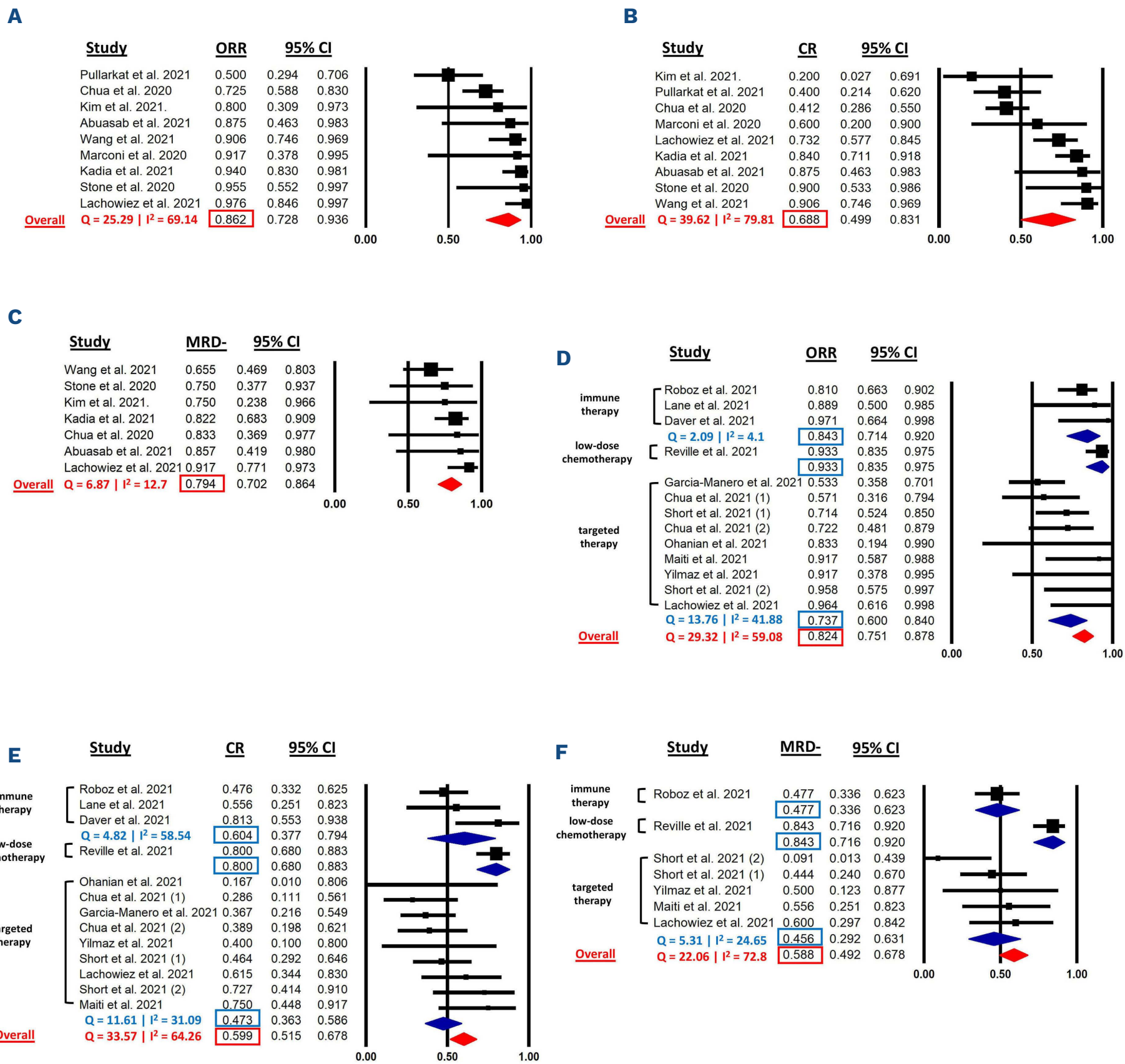

Figure 1. Response to venetoclax combination therapy in newly diagnosed acute myeloid leukemia. (A-C) Venetoclax in combination with intensive chemotherapy: overall response rate (A); complete response rate; (B): minimal residual disease rate (C). (D-F) Venetoclax in combination with non-intensive therapy: overall response rate (D); complete response rate (E); minimal residual disease rate (F). ORR: overall response rate; 95% CI: 95% confidence interval; CR: complete response; MRD: minimal residual disease.

The all-cause 30-day mortality rate was 6.4% (95% CI: 3.5-11.4%) in the ND AML intensive therapy group, 6.2% (95% CI: 3.6-10.6%) in seven trials within the ND non-intensive chemotherapy group and 6.1% (95% CI: 3.6-10.3%) among ten trials in the R/R group (Figure 3D-F). The heterogeneity for 30-day mortality in every subgroup (intensive, non-intensive and R/R) was low (I^2=0%).

When comparing subgroups within the ND AML, non-intensively treated group (low-dose chemotherapy as reference) by meta-regression analysis, targeted therapy was associated with a statistically significant higher rate of FN (*P*=0.0017) compared to low-dose chemotherapy whereas the rate of FN was not statistically different between groups treated with immunotherapy and low-dose chemotherapy (*P*=0.0939). However, the 30-day mortality rates were not statistically different between the groups treated with low-dose chemotherapy and targeted therapy (*P*=0.1201) or immunotherapy (*P*=0.4378). In the R/R subset of patients, meta-regression analysis showed that immunotherapy and targeted therapy were associated with a statistically significant lower rate of FN (*P*=0.0097 and *P*=0.0492, respectively) when compared to intensive chemotherapy. In contrast, the rate of FN and 30-day mortality rates were not statistically different between subgroups.

How do the results of our meta-analysis compare to historic data for non-venetoclax-based treatment approaches in AML?

In the intensive ND AML group, high ORR and CR rates of 86% and 69%, respectively, were seen. Although direct comparison is impossible, these response rates appear at least comparable and possibly higher compared to what was recently reported for “7+3” induction chemotherapy alone.[5,6] Although survival data are largely premature, several studies in the intensively treated group found encouraging overall survival rates of 85-96% at 12 months.[7,8] Regarding safety, the rate of FN was 67.6%, but with low rates of 30-day mortality of 6.4% as compared to up to 15% in previous reports.[9] However, three trials reported early mortality rates of >10%, with one of these studies using venetoclax for 20 days during induction. In addition, the FN rate was 91.7% in one study, which used venetoclax for 28 days during induction and consolidation (Figure 3). As was shown previously and led to protocol amendments,[10] prolonged use of venetoclax in combination with intensive chemotherapy increases the rates of prolonged cytopenia, FN and infections. Overall, the early reports of adding venetoclax to intensive regimens seem promising, but early mortality and FN rates remain a challenge in some studies, and the benefits of prolonged venetoclax use should be weighed against higher risks of FN, infection and possible early mortality.

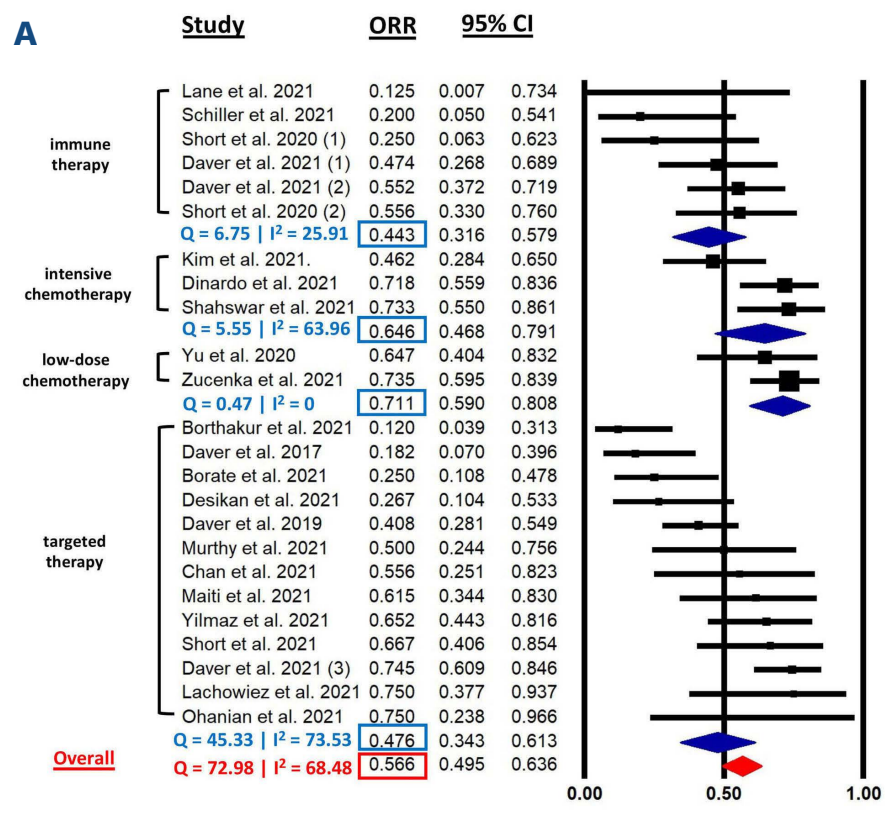

Figure 2. Response to venetoclax combination therapy in relapsed/refractory acute myeloid leukemia. (A) Overall response rate; (B) complete response rate; (C) minimal residual disease rate. ORR: overall response rate; 95% CI: 95% confidence interval; CR: complete response; MRD: minimal residual disease.

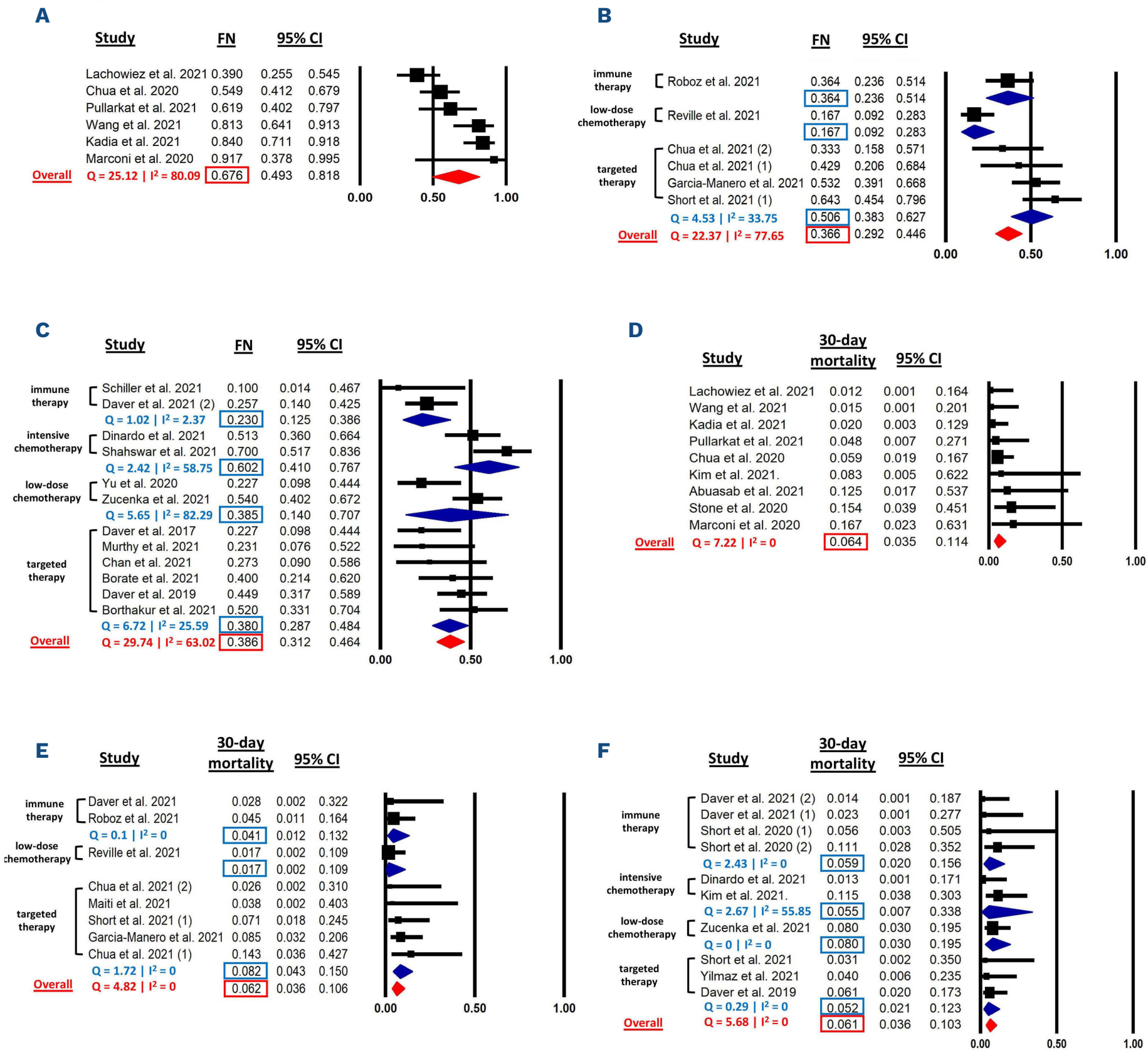

Figure 3. Safety of venetoclax combination therapy. (A) Febrile neutropenia rate for venetoclax together with an intensive chemotherapy combination in newly diagnosed acute myeloid leukemia. (B) Febrile neutropenia rate for venetoclax together with a non-intensive therapy combination in newly diagnosed acute myeloid leukemia. (C) Febrile neutropenia rate for venetoclax combination therapy in relapsed/refractory acute myeloid leukemia. (D) Thirty-day mortality rate for venetoclax together with an intensive chemotherapy combination in newly diagnosed acute myeloid leukemia. (E) Thirty-day mortality rate for venetoclax together with a non-intensive therapy combination in newly diagnosed acute myeloid leukemia. (F) Thirty-day mortality rate for venetoclax combination therapy in relapsed/refractory acute myeloid leukemia. FN: febrile neutropenia; 95% CI: 95% confidence interval.

In the ND AML non-intensively treated group, the ORR was 82.4% with 59.9% of patients achieving a CR and 58.8% of responders achieving MRD negativity. In the VIALE-A trial, the composite CR rate (CR + incomplete CR) was 66.5% with CR and MRD negativity rates of 36.7% and 23.4% respectively. With the caveat of cross-trial comparisons, the rates of CR and negative MRD seem higher in the combined estimates of the ND non-intensively treated group compared to the results reported in VIALE-A. As most of the patients in this population would not proceed to allogeneic stem cell transplant, durability of response is an essential consideration, but was not broadly reported. Yet, in patients who would proceed to allogeneic stem cell transplant, the ability to achieve higher rates of short-term CR is associated with improved survival, as seen with patients

who did proceed with allogeneic stem cell transplant after combinations of hypomethylating agents and venetoclax.[11] FN rates and 30-day mortality rates were 36.6% and 6.2%, respectively, which are similar to the rates seen in VIALE-A (FN 30% and 30-day mortality of 7%). Of note, the higher rate of FN seen in the targeted therapy subgroup did not translate into higher early mortality rates.

The R/R AML group encompass some of the most challenging and frequently heavily pre-treated cases with an unmet need for better care options. For patients receiving intensive chemotherapy, the pooled ORR and CR rates were 64.7% and 28.6%, which compare favorably with historically reported ORR and CR rate of 21% and 12%, respectively, in the control arm of a phase III trial evaluating various intensive salvage regimens *versus* elacytarabine.[12] Venetoclax in combination with a hypomethylating or low-dose cytarabine previously demonstrated ORR rates of 49% and CR rates of 14%,[13] which are similar to the pooled ORR and CR rates in the targeted, immunotherapy or low-dose chemotherapy subgroups in our analysis. In contrast, encouraging pooled MRD-negativity rates among responders ranged between 53.5%-67.7% as compared to 13% reported in the previous study,[13] suggesting that a subset of patients may benefit from this combination therapy.

The limitations of our meta-analysis are heterogeneity, which was partially addressed with sub-group analysis, and short term follow-up. Nevertheless, this is the first meta-analysis evaluating the initial efficacy and safety of investigational venetoclax-based combination treatements.

In conclusion, we observed that investigational venetoclax-based combinations resulted in response rates that are at least comparable as and appear higher than those found in previous trials. Although response outcomes seems promising, the durability of responses and impact on long-term survival are unclear. In terms of safety, we show that venetoclax in combination with intensive chemotherapy leads to higher rates of FN. However, these differences in FN did not translate into statistically significant different 30-day mortality rates, which remained relatively low in the various therapy subgroups. As data regarding long term outcomes are still immature, further follow-up is needed to determine the long-term benefit and risk of adding venetoclax to various combination therapy regimens.

Authors

Shai Shimony,[1,2*] Alon Rozental,[2*] Jan P. Bewersdorf,[3] Aaron D. Goldberg,[3] Eytan M. Stein,[3] Alyssa A. Grimshaw,[4] Richard M. Stone,[1] Daniel J. DeAngelo,[1] Ofir Wolach[2] and Maximilian Stahl[1]

[1]Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA; [2]Rabin Medical Center, Petah Tikva, Israel and Sackler Medical School, Tel Aviv, Israel; [3]Leukemia Service, Memorial Sloan Kettering Cancer Center, New York City, NY, USA and [4]Harvey Cushing/John Hay Whitney Medical Library, Yale University, New Haven, CT, USA

*SS and AR contributed equally as co-first authors.

Correspondence:
M. STAHL - maximilian_stahl@dfci.harvard.edu

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Contributions

SS, JBP, and MS designed the study. SS and AR performed the data extraction. SS, AR, JBP, AG, and MS wrote the initial draft of the manuscript. SS, AR, AG, and MS analyzed the data. All authors interpreted the data, and critically reviewed and contributed to all subsequent drafts of the manuscript.

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Data-sharing statement

All data are available upon request and the protocol is available online at *www.crd.york.ac.uk.* CRD42022307023

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