Reply to J.-G. Wang et al

We appreciate the comments by Wang et al[1] and the opportunity to add further clarity to our recent article.[2]

We respectfully submit that the differences between the standard and experimental arms reflect the combination of vincristine/topotecan/cyclophosphamide (VTC) as reported since the VTC cassette was inserted as independent cycles into the standard 5-drug interval compressed regimen. Topotecan was administered at 0.75 mg/m^2 per dose, once daily for 5 days per topotecan containing cycle. Preclinical experience supports a synergistic effect between vincristine and topotecan,[3] and although topotecan alone was not considered active in Ewing sarcoma on the basis of single-agent testing,[4] data in recurrent Ewing sarcoma[5-7] clearly demonstrate the efficacy of this combination. In addition, although total alkylator dose delivery was near equal in both arms, the fractionated delivery of cyclophosphamide in the VTC cassette was also a notable difference.

We assessed the prognostic effect of the primary tumor site in the broad categories of (1) pelvic bone, (2) bone nonpelvis, and (3) extraosseous. The categorization was based on the stratification factors used for random assignment. We elected to test for difference in the event-free survival (EFS) hazard rates first with the global test and, if this test was significant, conduct pairwise comparisons. This approach strongly controls the type I error rate at 5% to ensure that spurious associations are not identified as significant. We did not proceed beyond the first step of this approach since the global *P* value was not significant at the .05 level. As noted in the supplementary materials, only the assessment of the risk of the EFS event associated with the randomized treatment assignment was conducted using a stratified log-rank test. Other assessments were conducted using the unstratified log-rank test. Relative hazard rates and associated 95% CIs were calculated using an unstratified proportional hazards regression model. Wang et al[1] do make an important point regarding an opportunity for future analyses to identify possible prognostic factors for risk of an EFS event from the time of enrollment in the study data set. We plan to present such analyses in a subsequent report in the peer-reviewed literature.

We agree with Wang et al[1] that outcomes as they relate to local control are an important aspect of therapy for patients with nonmetastatic Ewing sarcoma. The group of patients in which the effect of local control modalities can be assessed is a subpopulation of all patients who enroll, and the appropriate outcome measures are EFS and overall survival from the time of local control. We also understand from previous studies that local control analyses must control for confounding factors that influence the chosen mode of local control for a given patient. Since we were limited in the length of this article, we elected to report the primary analysis as planned in the protocol, viz, the comparison of the randomized treatment assignment. Currently, we are assembling the detailed data on the type of local control modality and the sequence of local treatment for patients who are treated with both surgery and radiation therapy. We plan to present these results in a subsequent report in the peer-reviewed literature.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Wang J-G, Wei Q-F, Tang Q-M: Regarding the children's oncology group AEWS1031 trial for Ewing sarcoma. J Clin Oncol 40:1506, 2022
2. Leavey PJ, Laack NN, Krailo MD, et al: Phase III trial adding vincristine-topotecan-cyclophosphamide to the initial treatment of patients with nonmetastatic Ewing sarcoma: A Children's Oncology Group report. J Clin Oncol 39:4029-4038, 2021

3. Thompson J, George EO, Poquette CA, et al: Synergy of topotecan in combination with vincristine for treatment of pediatric solid tumor xenografts. Clin Cancer Res 5:3617-3631, 1999
4. Hawkins DS, Bradfield S, Whitlock JA, et al: Topotecan by 21-day continuous infusion in children with relapsed or refractory solid tumors: A Children's Oncology Group study. Pediatr Blood Cancer 47:790-794, 2006
5. Hunold A, Weddeling N, Paulussen M, et al: Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. Pediatr Blood Cancer 47:795-800, 2006
6. Saylors RL III, Stine KC, Sullivan J, et al: Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: A Pediatric Oncology Group phase II study. J Clin Oncol 19:3463-3469, 2001
7. McCabe MG, Kirton L, Khan M, et al: Results of the second interim assessment of rEECur, an international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES). J Clin Oncol 38, 2020 (15_suppl; abstr 11502)

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