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External Control Arms and Data Analysis Methods in Nonrandomized Trial of Patients With Glioblastoma

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To the Editor

We read with interest the results of the autologous tumor lysate-loaded dendritic cell vaccine (DCVax-L) externally controlled nonrandomized trial by Liau et al,[1] which leverages external data to perform a comparative analysis of DCVax-L survival outcomes in newly diagnosed glioblastoma (GBM). A careful choice of the analysis methods is necessary to avoid biases, which can translate into errors in the regulatory process and potential loss of credibility of future trials that integrate external data.

We have previously discussed the use of patient-level external data for the analysis of GBM trials.[2,3] In the absence of suitable patient-level data, the DCVax-L analyses instead provide treatment comparisons based on published data summaries from trials.[4] Of note, the DCVax-L trial[1] included patients with gross or near total resection and excluded patients who experienced progression during chemoradiation, 2 well-known prognostic factors. The selected external data included patients without uniform application of these criteria and sometimes without detailed clinical data. The stringent criteria to select patients for the DCVax-L trial may have led to a different patient population than external patients used in the comparative analysis. Additionally, we are not aware of independent validations of these analytic methods in a GBM trial context outside of this present study, and therefore results need to be interpreted with caution.

Moving forward, the DCVax-L study[1] suggests a few lessons that will be relevant for the future use of external data in clinical trials and reporting of study results:

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1. An explicit definition of the causal treatment effect[5] that the trial seeks to estimate using external data is necessary to interpret the results.
2. The presentation of the results should provide a clear list of the assumptions on which the analyses rely to provide unbiased conclusions and a rigorous control of the false-positive results. For example, in the DCVax-L analyses,[1] it is not straightforward to identify the set of assumptions that guarantees the 95% coverage of the reported confidence intervals.
3. The scientific community should be able to independently evaluate the analyses, with access to code and the external data that are necessary to assess the scientific validity and study results.
4. Novel approaches to analyses involving external data should be vetted with rigorous validation analyses that can reveal potential risks of bias.

The use of external data, ideally in prospectively planned analyses, has the potential to aid drug development in oncology, particularly for rare or difficult-to-treat tumors. Continued emphasis on rigorous validations of analysis methods constitutes a critical step toward successful applications of trial designs that leverage external data.

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References

1. Liau LM, Ashkan K, Brem S, et al. Association of autologous tumor lysate-loaded dendritic cell vaccination with extension of survival among patients with newly diagnosed and recurrent glioblastoma: a phase 3 prospective externally controlled cohort trial. JAMA Oncol 2023;9(1):112–121. doi:10.1001/jamaoncol.2022.5370 [PubMed: 36394838]
2. Rahman R, Ventz S, McDunn J, et al. Leveraging external data in the design and analysis of clinical trials in neuro-oncology. Lancet Oncol 2021;22(10):e456–e465. doi:10.1016/S1470-2045(21)00488-5 [PubMed: 34592195]
3. Ventz S, Lai A, Cloughesy TF, Wen PY, Trippa L, Alexander BM. Design and evaluation of an external control arm using prior clinical trials and real-world data. Clin Cancer Res 2019;25(16):4993–5001. doi:10.1158/1078-0432.CCR-19-0820 [PubMed: 31175098]
4. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health 2012;15(6):940–947. doi:10.1016/j.jval.2012.05.004 [PubMed: 22999145]
5. Hernán MA. A definition of causal effect for epidemiological research. J Epidemiol Community Health 2004;58(4):265–271. doi:10.1136/jech.2002.006361 [PubMed: 15026432]