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First results on the DCVax phase III trial: raising more questions than providing answers

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Recently, the long-awaited report on efficacy data of the DCVax trial has appeared in the *Journal of Translational Medicine*.[1] Patients and physicians alike are eager to critically evaluate the first results of this important trial, which is one of the earliest major attempts to improve outcome in patients with glioblastoma using immunotherapy based on an autologous tumor lysate-pulsed dendritic cell vaccine (DCVax). It is not only one of the first randomized phase III trials of its kind, but in light of recent successes with cancer immunotherapies outside neuro-oncology, there is a huge interest in any form of immune treatment for glioma patients. Any report is highly relevant, not in the least as the treatment is offered commercially to patients, at high cost, and without the effectiveness of the treatment being known to date. In the interplay between concept-based hopes and urgent need for effective treatments, it is of the utmost importance that outcome data are shared with the community.

Liau et al present their findings.[1] The trial was activated for accrual in 2007 and the last patient entered the trial in November 2014; trial accrual was halted midway through the planned enrollment period for financial reasons. The trial is placebo controlled, with a 2:1 randomization. Patients were registered and randomized into the study after completion of 6 weeks of radiotherapy. Randomization was stratified by O^6-methyl-guanine DNA-methyltransferase (*MGMT*) promoter methylation status. Patients were allowed to receive DCVax upon progression/recurrence, a process that breaks the blind in every crossing patient. The study's primary endpoint is progression-free survival (PFS), with overall survival (OS) as a secondary endpoint. The randomized blinded study design was chosen to generate comparative data and confidently determine efficacy (or not).

The report is unfortunately not nearly as informative as one would have hoped. It is based on an analysis of blinded interim data on OS of the intention-to-treat (ITT) population performed 34 months after the midpoint of patient enrollment, and 16 months after the last patient entered. It presents OS data with 108 of the 331 (33%) patients still alive, and the number of PFS events (the primary endpoint) is not stated. These numbers need to be available: typically in glioblastoma patients, PFS events occur before the OS event, and crossover is stated for >90% of patients, which implies that knowledge of the time point of progression is available. There is a rudimentary statistical paragraph in the report that does not provide the statistical background for the interim analysis. Thus, it remains unclear how an interim report on a secondary outcome variable that is retrieved later than the primary endpoint on the totality of patients adds to the quality of the trial and how it should be regarded as informative for the trial or the treatment per se.

No less than 1599 patients were screened, of whom a minority (331 patients, 21%) were randomized. Median time from surgery to randomization was 3.1 months. Because of the crossover design, 90% of the ITT population received DCVax, a fact that highlights the attractiveness of the approach and the great need as well as the strong desire of the company to disseminate its product. Despite the need to break the blind for crossing over and the obvious assessment of progression for this change in treatment, PFS has not yet been evaluated and reportedly will be the subject of later analyses to allow for central, multifactorial assessment by an expert panel.

With the primary endpoint remaining obscure, the trial report concludes that OS for the whole trial population looks intriguing. The value of the statement on OS is limited by the lack of information on the patients' characteristics, which are not split out per treatment arm. Hence, the data published to date do not allow a comparison between arms, and in fact no other comparison at all. What are the relevant facts that necessitated a late but immature preview of some of the trial data while disregarding basic standards of reporting for phase III trials?

The reported median OS (mOS) is 23.1 months from surgery, but—in line with the blinded interim analyses—no breakout per treatment arm is provided. The discussion states: "Although enrollment was completed in 2015, this trial, including both treatments and follow-up, is still ongoing and will remain blinded until sufficient events of disease progression

and/or death have occurred to more fully elucidate the tail of the survival curve." That required number of events is not presented, however, and the report has the appearance of a type of post-hoc analysis.

Instead of focusing on the important primary and secondary outcome variables and helping the field with data without pre-selection for concept-promoting findings, a further subgroup analysis is presented on so-called long-term survivors from the ITT population with long-term follow-up, defined as a surgery date ≥30 months prior to the data collection (n = 223). The authors report that 30% (n = 67) have lived ≥30 months and present an mOS estimate derived from Kaplan–Meier of 46.5 months. Despite the post hoc data of OS analyses that are presented, including 1-, 2-, and 3-year data in various post hoc–defined subgroups, neither the PFS nor the OS of the 2 treatment arms are presented. Can any conclusions be drawn from the presented OS data? First, the data are on OS from a trial that allowed crossover to the experimental arm. As a consequence, only PFS data are informative, unless a very clear, unexpected, and robust OS signal is found. The current OS data lack that clarity. Across-trial comparisons are hazardous, as unknown trial accrual and conduct biases may affect outcome. Here, the timing of the randomization after radiotherapy implies that intertrial comparison with most of the past glioblastoma trials is simply not possible. However, the Radiation Therapy Oncology Group (RTOG) 0525 trial, the tumor-treating field EF-14 trial, and the epidermal growth factor receptor variant III–directed vaccine trial with rindopepimut (ACT-IV) had a similar randomization scheme with study entry after the end of radiotherapy.[2–4] Even compared with these trials, there are still large differences that likely affected patient selection. Patients were excluded from the DCVax trial if they had apparent early disease progression/recurrence or pseudo-progression at the baseline visit after completion of radiotherapy. This was not the case for the RTOG study 0525. The EF-14 study allowed biopsies, which does not appear to be the case in the current trial: more than 60% of patients underwent a total resection, as one would indeed assume that the amount of tumor in a biopsy does not allow the production of a tumor lysate, irrespective of the fact that the amount of the individual antigen from a bulk lysate may be insufficient to generate a meaningful immune response. Biopsies are not officially stated to be an exclusion criterion, but "sufficient resected tumor material to produce the autologous vaccine" is mentioned. Dexamethasone dosage is not reported. Steroids are a major prognostic factor and may interfere with effective immunotherapy. The statement by the authors that "in the overall ITT population in this trial, the mOS of 23.1 months from surgery compares favorably with the mOS of 15–17 months from surgery typically achieved" does not recognize any of these issues. Of note, the report does not mention how survival was measured, and quite interestingly the OS curve shows a completely flat curve for the first 3 months.

The last two lines of the discussion, "Collectively, the blinded interim survival data suggest that the patients in this Phase 3 trial are living longer than expected. These findings warrant further follow up and analyses," are only true for the need for further follow-up. It is too early to make statements about OS, and—a lesson learned, unfortunately, in several past trials—the potential absence of an OS difference between arms but high crossover rates and numerically good efficacy is no proof of efficacy. That requires clear PFS signals. Indeed, the read-out of such a trial will entirely depend on the analysis of PFS between arms, which is not the most reliable endpoint in trials in newly diagnosed glioblastoma. More disturbingly, the sheer fact that the trial allowed crossing over while studying a treatment of unknown efficacy in a highly selected patient population implies that the treatment benefit of DCVax is at risk of being never fully understood.

All in all, this immature report does not allow a meaningful interpretation and may nourish worries that financial considerations may override legitimate interests in information for patients and treating physicians.

References

1. Liau LM, Ashkan K, Tran DD, et al. First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. *J Transl Med*. 2018;16(1):142
2. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol*. 2013;31(32):4085–4091.
3. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA*. 2017;318(23):2306–2316.
4. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. *Lancet Oncol*. 2017;18(10):1373–1385