Editorial Commentary

# Vaccines against glioblastoma: reflections on the ICT-107 phase IIb trial

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The first clinical attempts to influence the detrimental course of disease in glioblastoma (GBM) patients using active specific immunization strategies on the basis of dendritic cell (DC) based vaccines date back to about 20 years from here (1). A substantial number of small-scale clinical trials using rather heterogeneous, non-standardized DC-based vaccine products provided consistent data on overall safety (2) and, at its best, indirect indications of clinical effectiveness (3). Recently, Wen *et al.* (4) published their report on the results of a multi-center, randomized double-blind, placebo-controlled phase IIb trial (RCT) of a DC vaccine, called ICT-107, in patients with newly diagnosed GBM. As the authors rightfully state this is the first, well-controlled, moderate-sized RCT in this population showing a possible clinical benefit for a DC vaccine to date.

ICT-107 contains autologous, monocyte-derived DC pulsed with a mixture of 6 well-known GBM-associated tumor antigens, more specifically, synthetic 9–10 amino-acid peptides to be presented in either an HLA-A1 ( MAGE-1 and AIM-2) or an HLA-A2 (HER-2, TRP-2, gp100 and IL-13Ra2) context. For the maturation of the DC, interferon-gamma (IFN-γ) and lipopolysaccharide (LPS) where chosen in order to maximally shift the DC into a T-helper-type 1 (Th1) polarization. The choice for this product specification suggests an "intermediate strategy", holding the middle between "mono-peptide"-pulsed DC (with an inherently high chance to induce antigen-loss variants of the tumor and as such immune escape) and "whole-tumor-cell"-pulsed DC (with the notorious difficulty to adequately perform a specific immune monitoring in the patients). Considering the fact that to date, there is no consensus on the optimal DC product, every choice inherently restricts the conclusions that can be drawn from the trial results to the product itself. ICT-107 is conceived only for GBM patients with an HLA-A1 and/or HLA-A2 haplotype, accounting for roughly two thirds of the (Caucasian) population. Generalization and extrapolation to other DC vaccine products is to be avoided, although it would be very informative to be able to compare the results of ICT-107 to these of the DCvax trial (5), of which unfortunately only general survival data have been released without any comparison of the different arms in that randomized trial.

The trial design consisted of a 2:1 randomization of ICT-107 versus control, the latter comprising the intradermal injections of autologous, mature, unpulsed DC at the same time-points as in the experimental arm. About two thirds of the postoperatively screened adult GBM patients in whom either a gross-total resection or a large, subtotal resection (with a residual contrast-enhancing remnant of less than 1 cc) had been performed, seemed

to be finally eligible and 124 patients were randomized after the completion of postoperative radiotherapy. For the adjuvant standard of care therapy, a 12-month temozolomide (TMZ) regimen was chosen, thereby deviating from the initial Stupp program in which 6 months adjuvant treatment with TMZ was given (6). The authors are to be congratulated for the extensive read-outs not only of safety, overall survival (OS) and progression-free survival (PFS), but also of relevant immune responses and quality of life (QOL) data. The authors didn't find any difference in adverse events between ICT-107 and the control DC group, thereby reconfirming the safe reputation of DC-based vaccination strategies even for brain tumors. This perfectly goes along with the finding that QOL was maintained at a higher level for a longer period in the ICT-107 patients because it seemed to be determined by (time to) disease progression and not by the occurrence of adverse events *per se*. No significant OS benefit was present after intent-to-treat (ITT) analysis for the whole trial population, but patients vaccinated with ICT-107 had a statistically significant better PFS, albeit of moderate clinical relevance given the small term of 1.3 months. More relevant for future studies, however, were the remarkable differences after subgroup analysis in the HLA-A1 and HLA-A2 population, although the trial was not powered for that endpoint. The prevalence of HLA-A2 antigens in the resected tumors was more than twice (90%) that of the HLA-A1 antigens (37.8%). This justifies the HLA-driven subgroup analysis of which the interpretation remains a bit elusive. A statistically significant PFS benefit was documented for the MGMT methylated HLA-A2 positive patients receiving ICT-107, but not for the other haplotype. On the contrary, only HLA-A1 positive, but not HLA-A2 positive, vaccinated patients, displayed a significant OS benefit if the MGMT promotor was methylated. In the unmethylated subgroup, no haplotype was related with any significant survival advantage after ICT-107 vaccination.

Apart from clinical outcome, immune responses were tested using two different approaches in the global study population: data for separate haplotypes are not available and as such, can't shed light on the underlying immune mechanisms leading (or not?) to the above-mentioned clinical outcomes. Both for IL-12 secretion in response to *ex vivo* CD40L stimulation of the DC pre-pulsing and IFN-γ-ELISPOT, some statistically (nearly) significant correlation could be found with survival, but especially the 33% patients in the control group who could be categorized as responders in the IFN-γ-ELISPOT assay leave us with some puzzling questions as to the relevance of the immune measurements in blood in this setting.

All in all, this report has added some intriguing findings to the ongoing tumor vaccination research for GBM patients and will certainly continue to fuel several open debates of which at least three aspects seem to pop out after careful reading.

Firstly, the field doesn't have any unequivocal proof of superiority of any type of DC product characterizations in comparison with the multiple alternatives in terms of source of DC and antigens, loading and maturation procedures and even more pragmatically, empirical DC administration strategies. In this regard, one could especially wonder if it would make any difference if this trial had been performed with a lower concentration of DC in the 1 mL that has been injected intradermally. Aarntzen *et al.* (7) elegantly showed, as early as in 2013, that a too high concentration of DC in the injected volume at one place will result in less efficient migration of the DC to the draining lymph nodes, which still is believed to be an important prerequisite for optimal biological activity.

Secondly, one could wonder whether the choice for mature, unpulsed DC in the control arm, was the best choice since 33% of control patients showed a responder's pattern in the IFN-γ-ELISPOT assay whatever might be the meaning of this: does it reflect some level of spontaneous antitumoral immune reaction like the authors suggest or is it simply the equivalent of an autologous mixed lymphocyte reaction (the so-called "auto MLR") as it has been described more than 35 years ago (8)? Unpulsed, autologous DC are also able to cross-talk with NK cells that might interfere somehow with an antitumoral immune response in the control arm of this trial as well (9).

Finally, the improved PFS results in the ICT-107 group did reach statistical significance but continue to be very modest in absolute terms, thereby questioning the clinical relevance of this finding. One might fear that the final results could be much alike Dendreon's Provenge-story in asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer in which a statistically significant OS benefit could be demonstrated but clinical relevance is still being discussed given the small increase of median OS with only 4,1 months (10). In that regard, one could debate the decision to prepare for a phase III RCT in HLA-A2 positive patients since the OS survival benefit in MGMT promotor methylated HLA-A1 patients

 

(almost doubling from 25.8 months in the control group to 47.6 months in the ICT-107 group) is much more striking than the PFS benefits in the complete HLA-A2 group. Focusing on the HLA-A1 subgroup however would still leave us with other concerns of a smaller target population, a more enigmatic immune mechanism and the ultimate doubt about the influence of random chance in this subgroup result given the small numbers of involved patients in a trial not powered for subgroup analysis anyway.

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## Footnote

*Conflicts of Interest*: The author has completed the ICMJE uniform disclosure from (available at http://dx.doi.org/10.21037/tcr-2020-004). Dr. SDV reports a patent 16805742.0-1109 licensed to Ovensa Inc. and SDV is member of the Data Safety Monitoring Committee of the Gliovax trial, Germany. SDV organizes Gliolan training sessions (Medac GmbH) in Belgium for which a fee is paid. SDV has performed consultancy work for Lamepro, distributing Gliolan in Belgium and the Netherlands.

*Ethical Statement*: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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