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**Interview with Dr Michael Weller
(Zurich) about the Phase-III
EGFRvIII Vaccine Trial on Newly
Diagnosed EGFRvIII-Positive
Glioblastoma**

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Interview with Dr Michael Weller (Zurich) about the Phase-III EGFRvIII Vaccine Trial on Newly Diagnosed EGFRvIII-Positive Glioblastoma

Ufuk Abacioglu

From the Department of Radiation Oncology, Neolife Medical Center, Istanbul, Turkey

Q: Dr Weller, what can you tell us about the ongoing “ACT IV” trial on newly diagnosed glioblastoma? What is its background and objective?

A: ACT IV is a randomized, phase-III study investigating the efficacy and safety of the addition of rindopepimut to the current standard of care, temozolomide, in patients with recently diagnosed EGFRvIII-positive glioblastoma who have had surgery and radiotherapy plus concomitant temozolomide. The trial is designed to see whether there is an improvement in overall survival in patients treated with the vaccine in addition to maintenance temozolomide compared with maintenance temozolomide alone in patients with gross total resection. Secondary analyses will evaluate the activity of the vaccine in patients with incomplete resection.

Q: How is the trial designed? Which patients are eligible for this trial?

A: Glioblastoma patients who have had attempted surgical resection are eligible to have their tissue evaluated for EGFRvIII expression. Patients with EGFRvIII expression confirmed by the sponsor’s laboratory are eligible for entry into the ACT IV trial if their disease does not progress on their chemoradiotherapy following surgery. All patients must be enrolled into this trial within 2 weeks of finishing concomitant chemoradiotherapy and prior to starting their maintenance temozolomide (Figure 1).

Q: Why did you choose gross total resection (GTR) as an inclusion criterion?

A: Initial studies evaluating rindopepimut assumed that an immune approach would have its greatest effect in patients with minimal residual disease. All of the phase-II data supporting the ACT IV study include only patients with GTR, hence ACT IV is focused on this population in its primary analysis. However, ACT IV will accrue patients with bulkier disease in a separate cohort and could show efficacy in that population as well.

Q: What are the schemes and durations of treatment in both arms?

A: Patients enrolled into the ACT IV trial are randomized to receive either rindopepimut (study vaccine) or a con-

trol injection in a blinded fashion. Two priming injections of the study vaccine are given during the first month of treatment and then patients receive monthly injections thereafter until disease progression or intolerance. All patients receive the 5-day regimen of maintenance temozolomide for 6–12 cycles based on local standards of care.

Q: What are the stratification factors?

A: Patients are stratified according to MGMT status, EORTC RPA class, and geographical region.

Q: How is the EGFRvIII expression status assessed in the trial? Do you have any trial-specific difficulties?

A: EGFRvIII expression status is assessed at a sponsor-designated laboratory in the USA. The laboratory is running the validated PCR-based EGFRvIII test under an investigational device exemption (IDE) from the US FDA. This assay has provided reliable and consistent results and should be readily used as a selection assay if rindopepimut is found to be efficacious.

Q: Do you have any planned translational studies?

A: Molecular studies will be conducted at European centres to correlate response to therapy and outcome with soluble biomarkers and miRNA profiles. A smaller number of European centres will also perform immune phenotyping to determine enzymatic activities as a measure for suppressive activity and the frequencies of regulatory T cells and myeloid-derived suppressor cell subsets. In addition, any correlation between immune response or extent of EGFRvIII expression and clinical outcome will be evaluated.

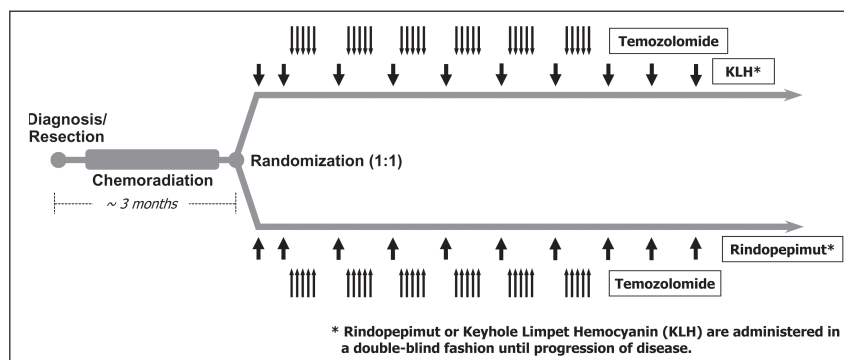


Figure 1. Trial scheme

Q: How is response assessed in this trial? Do you use the RANO criteria?

A: Response is assessed using the RANO criteria. Patients have restaging assessments every 8 weeks for the first 6 months, every 12 weeks through the second year, and then they are spaced further apart in subsequent years.

Q: How is the accrual and when do you expect to reach the accrual goal? When can we get the first results?

A: Accrual is going well, suggestive of the significant unmet medical need in this patient population. Since the endpoints are event-driven, it is too soon to tell when results will be available.

Thank you very much!

Dr Michael Weller is the coordinating investigator of the trial entitled, “An International, Randomized, Double-Blind, Controlled Study of Rindopepimut/GM-CSF with Adjuvant Temozolomide in Patients with Newly Diagnosed, Surgically Resected, EGFRvIII-positive Glioblastoma (The “ACT IV” Study)”.

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