Nature Reviews Neurology | Published online 29 Mar 2016; doi:10.1038/nrneurol.2016.38

Trial Watch

GLIOBLASTOMA VACCINE THERAPY DISAPPOINTMENT IN PHASE III TRIAL

Vaccine immunotherapy against mutated epidermal growth factor receptor (EGFR) does not seem to improve overall survival in patients with newly diagnosed EGFR variant III (EGFRvIII)-positive glioblastoma, according to a press release from Celldex Therapeutics. The company reports that it has discontinued the ACT IV Phase III trial of rindopepimut in newly diagnosed glioblastoma after interim analysis by the independent Data Safety and Monitoring Board showed no significant benefit of the vaccine on overall survival, the primary outcome of the trial.

The results are disappointing news after promising findings in the Phase II trial of rindopepimut, which suggested that the peptide vaccine improves overall survival. "While this is certainly not the desired outcome, we remain steadfast believers in the power of immunotherapy to transform the future of cancer treatment," comments Anthony Marucci, Chief Executive Officer of Celldex Therapeutics.

In patients with glioblastoma, post-resection therapy with concurrent temozolamide and radiation prolongs survival, but virtually all patients eventually relapse, and no standard treatment exists for recurrent disease. The lack of treatment options that provide a long-term survival benefit has prompted investigation into immunotherapies.

EGFR mutations that lead to its overexpression are the most common genetic alteration in glioblastoma, present in about 40% of patients. EGFRvIII is the most common type of EGFR mutation — seen in approximately 25% of patients — and confers a poor prognosis. Rindopepimut consists of an EGFRvIII peptide sequence conjugated to keyhole limpet hemocyanin. Injected rindopepimut can trigger an immune response that targets EGFRvIII-mutated cells and does not destroy other cells.

In the ACT IV trial, patients with newly diagnosed glioblastoma were randomly assigned to receive either intradermal rindopepimut injections and temozolomide, or temozolomide and placebo. According to ClinicalTrials.gov, about 700 patients were enrolled in the study.

Overall survival in the rindopepimut arm, as reported in the press release, was 20.4 months, which is comparable to that seen in the Phase II trial of rindopepimut (21.8 months; 65 enrolled participants). However, median overall survival in the control arm was greater (21.1 months). One possible reason for the failure of the trial to show a survival benefit of rindopepimut is that overall survival in the control arm was longer than that in the Phase II trial, in which 74 matched control participants were selected from the RTOG cohort and their median overall survival was only 16.0 months.

Despite the negative results in the ACT IV trial, the ReACT trial of rindopepimut in recurrent glioblastoma continues. In ReACT, patients with relapsed glioblastoma are given either rindopepimut in combination with the angiogenesis inhibitor bevacizumab, or bevacizumab alone. Celldex Therapeutics is also continuing Phase I and II cancer immunotherapy combination trials for other types of cancer.

Hemi Malkki