mRNAbased cancer vaccine in patients with MGMT unmethylated glioblastoma (GBM): first results from the dose escalation phase

This study presents the findings of the first-in-human investigation of the mRNA-based cancer vaccine CVGBM in patients with newly diagnosed, surgically resected, and MGMT-unmethylated glioblastoma, (GBM), a group historically characterized by poor prognosis and limited treatment options (1).

The CVGBM construct encoded 8 epitopes derived from 4 GBM-relevant antigens. The primary objectives were to assess safety, tolerability, and determine the recommended dose for further evaluation. Notable secondary endpoints included time to relapse and immunogenicity. Eligible patients were newly diagnosed, MGMT-unmethylated, and HLA-A*02:01-positive, having completed post-surgical radiotherapy, irrespective of chemotherapy use. Participants received seven intramuscular doses over 10 weeks, with optional maintenance vaccinations.

IFN-γ ELISpot analysis indicated that 77% of patients exhibited antigen-specific T cell responses, with 84% showing de novo immune activation. Among evaluable patients, 69% demonstrated $CD8^+$ T cell responses, 31% had $CD4^+$ responses, and only 23% displayed both. After a median follow-up of 7.2 months, only 2 patients in the highest dosage group remained on treatment without progression. The vaccine was well-tolerated, with primarily mild-to-moderate adverse events such as headache, fever, and chills. Based on these findings, the study selected 100 µg as the recommended dose for further clinical trials. The available evidence supports the use of this therapy in a Phase 2

study, though a groundbreaking new drug remains elusive. CVGBM represents the first of its kind and could pave the way for treatments utilizing comparable therapeutic strategies, either as standalone interventions or in combination of regimens.

Efficacy and safety of ponsegromab in patients with cancer cachexia

Ponsegromab, a monoclonal antibody, inhibits growth differentiation factor 15, a driving factor for cancer cachexia. A phase 2 randomized, placebo-controlled trial evaluated Ponsegromab's efficacy and safety in 187 patients with cachexia, elevated GDF-15 levels (>1500 pg/ml) and various cancers (NSCLC, Pancreatic cancer, Colorectal Cancer), regardless of tumor stage (2).

Patients were randomly assigned to receive Ponsegromab (100 mg, 200 mg, or 400 mg) or placebo, administered subcutaneously every four weeks for 12 weeks. The primary endpoint was change in body weight, while notable secondary endpoints included improvement in cachexia symptoms, physical activity, and increase in lumbar skeletal muscle index.

After 12 weeks, patients receiving 400 mg Ponsegromab experienced a significant, placebo-adjusted median weight increase of 3.00 kg. This weight response was observed across all subgroups. Similarly, the 200 mg and 100 mg cohorts saw weight gains of 2.08 kg and 1.33 kg, respectively. Furthermore, the 400 mg group demonstrated a significant 4.11 point improvement in the FAACT-Anorexia Cachexia Subscale score, indicating enhanced appetite, and a significant increase in physical activity of 50 minutes of non-sedentary time per day. The side-effect profile was similar to placebo

For me, Ponsegromab represents a very hopeful new class of drugs for an important unmet need of our patients. It has the potential to substantially improve the quality of life of patients in a difficult period of the cancer journey. I hope further studies will confirm these promising early results. □

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References:
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