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Whole Cell Therapeutic Vaccine Modified With Hyper-IL6 for Combinational Treatment of Nonresected Advanced Melanoma

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Abstract: Active specific immunotherapy of cancer requires an efficient induction and effector phase. The induction covers potent activation of anti-tumor response, whereas effector breaks the immunosuppression. We report efficacy of therapeutic melanoma vaccine (AGI-101H) used alone in advanced disease as a candidate for further combined treatment. In adjuvant setting in patients with resected metastases AGI-101H combined with surgery of recurring disease demonstrated long-term survival.

Seventy-seven patients with nonresectable melanoma (8% IIIB, 21% IIIC, 71% IV) were enrolled. AGI-101H was administered 8× every 2 weeks, and then every month. At progression, maintenance was continued or induction was repeated and followed by maintenance.

Median follow-up was 139.3 months. The median overall survival (OS) was 17.3 months; in patients with WHO 0-1 was 20.3 months. Complete response (CR) and partial response (PR) were observed in 19.4% and 9% of pts. Disease control rate was 54.5% of pts. The median CR+PR duration was 32 months. Reinduction was performed in 36.3% patients following disease progression with 46.6% of CR+PR. No grade 3/4 adverse events were observed.

Treatment with AGI-101H of melanoma patients is safe and effective. AGI-101H is a good candidate for combinatorial treatment with immune check-points inhibitors or tumor hypoxia normalizators.

Trial registration: EudraCT Number 2008–003373-40.

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Abbreviations: BAGE = B melanoma antigen, CI = confidence intervals, CR = complete response, CT = cancer testis, CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4, DC = disease control, DCs = dendritic cells, ETAM = extended treatment for advanced melanoma, FDA = Food and Drug Administration, GAGE = G melanoma antigen, GM-SCF = granulocyte-macrophage colony-stimulating factor, Gp = glicoprotein, H6 = hyper interleukin-6, HLA = human leukocyte antigens, IL-2 = interleukin 2, IL-6 = interleukin-6, ITPP = inositol triphosphate, MAGE = melanoma-associated antigen, NY-ESO1 = cancer testis antigen, OS = overall survival, PD-1 = programmed death 1 protein, PD-L1 = programmed death ligand 1, PFS = progression free survival, PR = partial response, PRAME = preferentially expressed antigen in melanoma, PS = performance status, RBC = Regional Bioethics Committee, RECIST = response evaluation criteria in solid tumors, SD = stabilization of the disease, WHO = World Health Organization.

INTRODUCTION

Active specific immunotherapy of cancer to be successful needs to generate efficient induction and effector phases of antitumor immune responses. The induction phase includes mounting of specific effector response, whereas the effector phase results in the eradication of the tumor. For a long time, it has been acknowledged and supported by model studies that tumor cells escape immune recognition, whereas the host requires proper cancer antigens presentation. Various approaches, which included therapeutic cancer vaccination, were tested in clinical trials, but they demonstrated only limited benefit for patients.[1,4,5] Recent studies of the cancer-host immune interactions led to understanding of a role, which plays tumor-related local and systemic immune suppression in mounting effective cancer active specific immunotherapy.[6–8] Identification of immune checkpoints and ways of their inhibition opened new perspectives for cancer active specific immunotherapy.[9] Moreover, better understanding of local tumor immunosuppression driven by hypoxia and ways of hypoxia normalization to break the suppression may lead to further enhancement of cancer active specific immunotherapy clinical effectiveness.[10,11]

To date, no active specific immunotherapy including therapeutic cancer vaccines, peptides, DNA, dendritic cells (DCs) evaluated in phase III studies has shown extension of overall survival (OS) of patients with advanced melanoma.[1–5] Improvement of OS of patients with castration-resistant advanced prostate cancer treated with Sipuleucel-T (Provenge, Dendreon, Seattle, WA), autologous DC vaccine loaded with prostate acid phosphatase fused with GM-SCF (Granulocyte-Macrophage

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