Title

ATIM-22. PROGNOSTIC VALUE OF PTEN LOSS IN NEWLY DIAGNOSED GBM PATIENTS TREATED WITH AUTOLOGOUS HEAT SHOCK PROTEIN VACCINE

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associated with prolonged overall survival (OS) of 15 months. METHODS: A phase 3 multisite international randomized open-labeled controlled trial. Patients with rGBM were randomized 1:1 to receive VB-111 at 10e13VPs q8W in combination with BEV 10mg/Kg q2W vs. BEV 10mg/Kg q2W. Primary endpoint was OS. RESULTS: 256 patients (128 per arm) were enrolled in 57 sites. The mean age was 55, 67% were male. 74% were in 1st progression, KPS < 80 found in 23% of patients. In the combination arm vs the BEV arm: baseline tumor volume > = 15cm3 in 49% vs 41%; Grade 3–4 adverse events reported among 61 % (mostly CNS and febrile) vs 34%, and pyrexia in 39% vs 4% of patients; ORR was 27.3% vs 21.9% and median duration of response was 3.7 vs 2.2 months. Median OS was 6.8 vs 7.9 months in the combination vs BEV arms, HR 1.2 [95% CI 0.910–1.59, p=NS]. In the subgroup of patients with baseline tumors< 15 cm3, OS was 9.2 vs 8.3 months [p=NS], and 12 month OS was 38.9% vs 26.9% [p=NS]. Among patients in the combination arm, OS was 7.9 vs 5.5 in patients with and without a febrile reaction. CONCLUSIONS: In this trial, VB-111 in combination with BEV failed to increase OS in patients with rGBM. Lack of VB-111 priming, as done in the phase II trial may explain the differences with the favorable outcomes in the latter. Patients with large progressive tumors may precluded sufficient drug exposure. Additional exploratory analyses are ongoing.

ATIM-20. GAPVAC-101 TRIAL OF A HIGHLY PERSONALIZED PEPTIDE VACCINATION FOR PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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BACKGROUND: There is a need for treatment personalization as every cancer is molecularly unique. In addition glioblastoma (GB) are immunologically regarded as resistant, cold tumor with few targetable antigens available from mutations, thus demanding new personalized immunotherapies. So far outside Neuro-Oncology, T cells orchestrate impressive anti-tumor effects with checkpoint inhibitors, but also vaccines. METHODS: The GAPVAC consortium established an immunotherapy, for which personalized selection of 2 peptide-based actively personalized vaccines (APVAC) per patient for treatment of newly diagnosed GB was based not only on whole-exome sequencing but also on human leukocyte antigen (HLA)-ligandome analyses providing insight into the actual presentation of relevant epitopes in the tumor. GAPVAC-101 (NCT02149225) enrolled 16 patients in a European phase I feasibility, safety and immunogenicity trial integrated into standard of care. For APVAC1, up to 7 peptides were selected from a trial specific warehouse based on individual biomarker data. Vaccination (i.d.) with GM-CSF and poly-ICLC in 15 patients started with the 1st adjuvant cycle of temozolomide (TMZ). For APVAC2, analyses revealed a median of 36 somatic, non-synonymous mutations in the patients tumors. From the 4th TMZ cycle, 11 patients received APVAC2 with usually 2 de novo antigens per patient selected according to mutation, actual or putative HLA presentation and immunogenicity. Overall 20 APVAC2 antigens incl. 14 mutated were vaccinated. RESULTS: Adverse events were largely reversible injection site reactions and two anaphylactic reactions and one increase in cerebral edema. Short, non-mutated APVAC1 antigens induced sustained CD8 responses with memory phenotype. Mutated APVAC2 antigens induced predominantly CD4 responses of favorable TH1 type. Median PFS and OS were 14.2 and 29 months from diagnosis, respectively, in patients that received 1 APVAC vaccination (N=15). CONCLUSION: Overall, GAPVAC displayed expected safety profiles and high biological activity indicating further development.

ATIM-21. UPDATED RESULTS OF A PHASE I TRIAL OF ANTI-LAG-3 OR ANTI-CD137 ALONE AND IN COMBINATION WITH ANTI-PD-1 IN PATIENTS WITH RECURRENT GBM

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BACKGROUND: Others and we have shown additional checkpoint molecules are expressed in GBM and preclinical studies have shown that combining anti-Lag-3 and anti-CD137 with anti-PD-1 can induce effective antitumor immune responses. METHODS: The Adult Brain Tumor Consortium (ABTC) 1501 trial is a phase I, open label, multicenter, multi-arm dose-finding/safety study of anti-LAG-3 (BMS-986016) or anti-CD137 (BMS-663513) alone and in combination with anti-PD-1 in patients with first time recurrent GBM. The primary objective was to define MTD for the mono and combination treatments with a secondary objective of OS. Using a sequential allocation, we started with doses of 80mg for anti-LAG-3 and 8mg flat for anti-CD137. Anti-PD-1 was given at a flat dose of 240 mg in the combination treatment arms. Using a 3 + 3 design our target DLT rate was < 33%. RESULTS: To date 30 patients were enrolled into the trial with median age at 56, median KPS of 90. Median treatment cycle was 3 and 43% tumors were MGMT methylated. Recruitment of the monotherapy Anti-LAG-3 and anti-CD137 arms were completed. We observed no DLT at the highest dose for Anti-LAG-3 at 800mg and only one DLT (a grade 3 elevated serum ALT at end of cycle 2) with anti-CD137 at the top dose of anti-CD137 at 8mg flat. In addition, three out of 12 patients developed elevated ALT at end of cycle 2 that was considered possibly related to anti-CD137. Another two patients had grade 1 elevated ALTs. Six patients are currently enrolled into a combination cohort of Anti-LAG-3 at160mg +anti-PD-1with no observed DLT and the combination arm of anti-CD137 with anti-PD-1 is open to accrual. CONCLUSIONS: The safe monotherapy dose is 800mg for anti-LAG-3 and 8mg flat for anti-CD137. Both Anti-LAG-3 and anti-CD137 in combination with antiPD-1 cohorts and an intratumoral surgical anti-CD137 cohort are open for accrual.

ATIM-22. PROGNOSTIC VALUE OF PTEN LOSS IN NEWLY DIAGNOSED GBM PATIENTS TREATED WITH AUTOLOGOUS HEAT SHOCK PROTEIN VACCINE

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INTRODUCTION: The safety and efficacy of a heat shock protein peptide complex- 96 vaccine (HSPPC-96, Prophage) has been previously studied in phase II single-arm trials for the treatment of newly diagnosed and recurrent glioblastoma (GBM). These studies demonstrated modest improvements in survival compared with historical standards. PTEN loss has been recently associated with immunoresistance in GBM patients, mediated in part by B7-H1. PTEN status has not shown clear prognostic value in GBM patients treated with standard of care therapies. The aim of this study is to evaluate the prognostic significance of PTEN status in newly diagnosed GBM patients treated with autologous HSP vaccine and standard chemoradiation. METHODS: Our institutional cohort of patients enrolled in a single arm, phase II study of adult GBM patients treated with autologous HSP vaccine and standard chemoradiation (n=27) was analyzed. Differences in overall survival (OS) by PTEN status were evaluated via Kaplan-Meier curves and Log-rank test. RESULTS: Median overall survival (n=27) was 26 months. 23 patients had PTEN status available. PTEN loss was found in 16 patients (69.6%) whereas retained PTEN was present in 7 patients (30.4%). Median OS was 59 months (95% CI, 0–120 months) in patients with retained PTEN and 23 months (95% CI, 15–30 months) in patients with PTEN loss. The difference in OS was statistically significant (p=0.037). CONCLUSION: Retained PTEN expression was associated with extended survival in GBM patients treated with HSP vaccine. This finding suggests that PTEN loss may be associated with resistance to vaccine treatment and emphasizes the need for subgroup analysis in further immunotherapy studies.