1179- EFFICACY STUDY OF STC-1010 ANTITUMOR VACCINE ASSOCIATED WITH STANDARD CHEMOTHERAPIES ON MC38 SYNGENEIC COLON CANCER TUMOR MODEL

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BACKGROUND

- Metastatic colorectal cancer (mCRC) is a major cause of death worldwide.
- Unmet medical need in immunotherapy is high for MSS patients and still present for MSI-H/dMMR patients.
- 95% of the mCRC population are treated in first line by FOLFOX or FOLFIRI with limitation due to treatment toxicity.
- STC-1010 (Brenus Pharma) therapeutic vaccine is composed to tumor cells stimulation overexpressing tumor associated antigens (TAA) and neoantigens to mimic the treatments resistance of mCRC cancer cells. The aim is to educate the immune system to target patient's tumor cells harboring the same resistance factors.
- We report efficacy results of the murine STC-1010 (mSTC-1010) composed of 6 drug substances (6 CL-SH) vaccine from 3 cell lines (CT26, CMT93 and LTPA cells) S= stimulated by irradiation plus heat shock or by chemotherapies and then haptenized (H). mSTC-1010 was administrated with low dose of immunostimulant (IS=cyclophosphamide and mGM-CSF) associated or not with standard chemotherapies. FOLFOX or FOLFIRI.

Fig 1. STC (Stimulated Tumor Cells) Technology

METHODS

- Immunocompetent female C57BL6 mice were subcutaneously grafted with 1.10^6 MC38 tumor cells.
- A pre study to find optimal doses of FOLFOX and FOLFIRI on MC38 tumor model has been conducted prior to this study.
- 7 groups (15 mice/ group) were allocated to:
  - Control group: vehicles for all treatments
  - Group 1: FOLFOX (5FU at 50 mg/kg, oxaliplatin at 3,5 mg/kg, leucoverin at 90 mg/kg all by intra-peritoneal injection to D5, D8 and D11 post-tumour graft)
  - Group 2: FOLFIRI (5FU at 50 mg/kg, irinotecan at 30 mg/kg, leucoverin at 90 mg/kg all by intra-peritoneal injection to D5, D8 and D11 post-tumour graft)
  - Group 3: 3 CL-SH, only irradiated and heat shocked stimulation without chemotherapy
  - Group 4: 6 CL-SH= mSTC-1010
  - Group 5: mSTC-1010 + FOLFOX (5FU at 50 mg/kg, oxaliplatin at 3,5 mg/kg, leucoverin at 90 mg/kg all by intra-peritoneal injection to D5, D8 and D11 post-tumour graft)
  - Group 6: mSTC-1010 + FOLFIRI (5FU at 50 mg/kg, irinotecan at 30 mg/kg, leucoverin at 90 mg/kg all by intra-peritoneal injection to D5, D8 and D11 post-tumour graft)

Subcutaneous vaccine injections (3CL-SH or 6 CL-SH, both at 1.10^6 cells/injection, same dose alone or associated to chemotherapy) were associated to IS (subcutaneous GM-CSF at 0,25 mg/kg and intra-peritoneal cyclophosphamide at 15 mg/kg) once a week for 3 weeks.

- Tumor growth (TG) until 1600 mm^3 or tumor necrosis and overall survival (OS) were recorded.
- 5 mice per group were euthanized and samples for immunophenotyping.
- We conducted automated immunohistochemical analysis (HALO IndicaLabs software) on 5 tumor groups (n=35) to evaluate the correlation between response and immune population (number of cells / mm^2) including: CD3, CD4, CD8, FOXP3 T cells and M1/M2 macrophages response (iNOS/CD163).

RESULTS

- At Day16, all groups treated by mSTC-1010 had a significant reduction of the mean tumor volume compared to the control group (p=0,0011), as well as for mSTC-1010 + FOLFIRI versus FOLFIRI alone (p=0,0024).
- The tumor's necrose in the 3CL-SH, mSTC-1010 and mSTC-1010 + FOLFIRI groups are denser (weight/volume) than the control group. Tumors treated by mSTC-1010 +FOLFIRI were also denser than the FOLFIRI ones (p=0,0052).
- Side effect was observed with mice treated by FOLFOX alone (not in combo with mSTC-1010): dramatic weight loss needing some ones sacrificed.
- HALO analysis showed that :

-Unlike treatment groups, control group has primarily an M2-oriented macrophage response (iNOS/CD163<1) and all other treatment groups have an M1-oriented macrophage response (iNOS/CD163 > 1) with a high iNOS/CD163 ratio in tumor centre. mSTC-1010 + FOLFOX group seems to have a greater ratio of iNOS/CD163 (M1/M2=9,48) at the tumor's centre compared to other treatments groups.
-Adding mSTC-1010 to FOLFOX increased CD8+ tumor infiltration in comparison with FOLFOX alone (> 200 cells/mm^3) and increased the recruitment of immune cells within the tumor. Among treated groups, M1/M2 ratio >7 was the main criteria correlated with a long survival.

- No side effect or inflammatory reaction towards the 6 CL-SH is evidenced.

Tumor volumes (mm^3), all compounds, measured by Caliper at D16

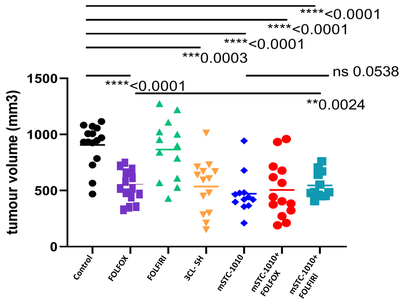

Fig 2. Tumor volume measured by Caliper at D16

Median of tumor volumes (mm^3) at D16

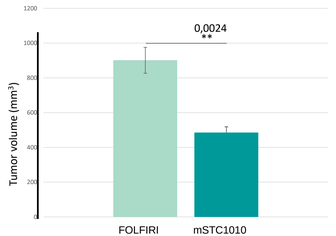

Fig 3. Median of Tumor volume ± SEM, with significant difference between FOLFIRI group and mSTC + FOLFIRI group (p=0, 0024)

Tumor Density (mg/mm3) in necrotic tumors, all compounds

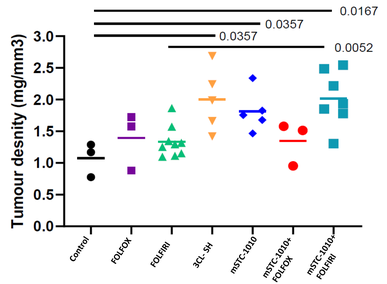

Fig 4. Tumor Density (ratio of the weight over the volume) in necrotic tumors

Individual curves for the mice weight (mg)

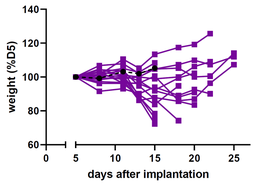

Fig 5. Individual curves for the weight (mg) for the FOLFOX group

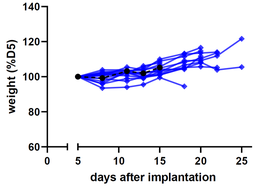

Fig 6. Individual curves for the weight (mg) for the mSTC-1010group

Immunohistochemical images with HALO Software (x20)

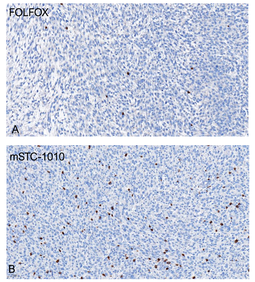

Fig 7. CD8+ infiltration in tumor centre slice of
A. Non responder mouse from FOLFOX group
B. Long Survival mouse from mSTC-1010 group

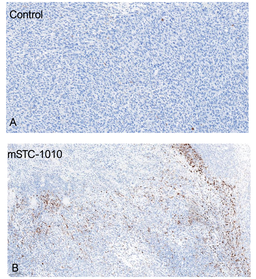

Fig 8. iNOS infiltration in tumor centre slice of
A. Control group mouse (mean of group =5,43)
B. Long survival mouse from mSTC-1010 group

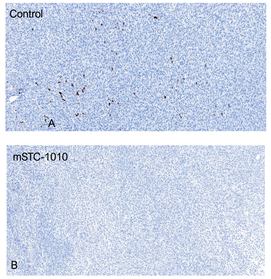

Fig 9. CD163 infiltration in slice of
A. Control group mouse
B. Long survival mouse from mSTC-1010 group

CONCLUSIONS

This third preclinical study confirms efficacy and safety of Brenus STC vaccine stimulated and haptenized alone or with standard chemotherapies associated to immunostimulant. This significant anticancer effect in mice could be explained by mobilization of CD3, CD8, CD4 T cells within the tumors and oriented M1 macrophage immune responses. Increase of CD8+ tumor infiltration after STC vaccination has been consistently seen during our preclinical development and is a key criteria to convert cold tumor into hot tumor.

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