A dual biomarker system is required for CRC patient stratification for Catumaxomab therapy

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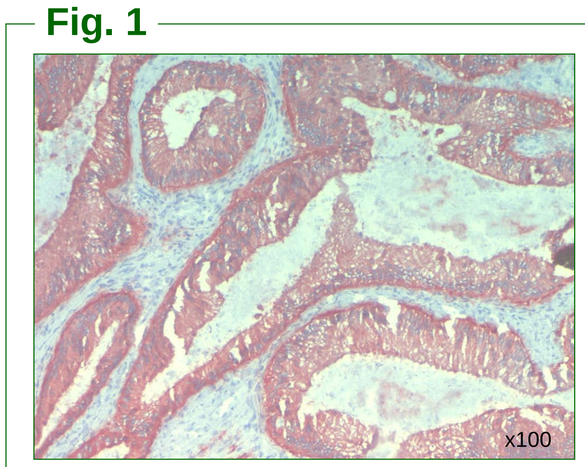
Rationale

Patient stratifications for therapeutic response mainly focus on biomarker expression on cancer cells. In contrast, the tumor micromilieu has been less considered, although stromal cells and leukocytes play a crucial role in tumor progression and drug resistance.
Looking for new therapeutic options in primary colorectal cancer, molecular drugs such as Cetuximab have shown substantial treatment benefits. The bispecific trifunctional antibody Catumaxomab has been approved for the treatment of malignant ascites secondary to epithelial cancers and has revealed benefit achieving prolongation of survival time in ascites patients. Thus, the antibody might also be a promising option for primary CRC. For patient stratification the most appropriate biomarkers have to be identified.
The present study investigates the impact of tumor infiltrating leukocytes on Catumaxomab efficacy in CRC.

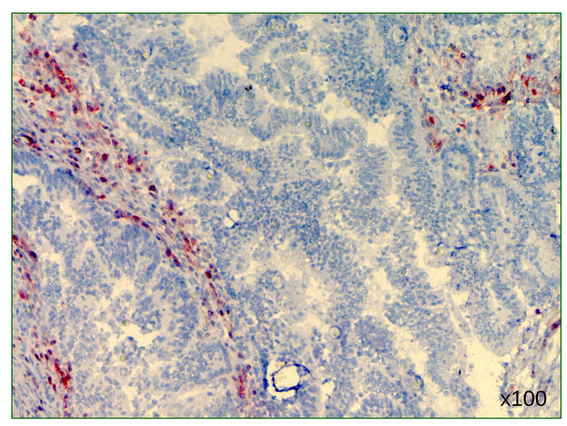
Patients and Methods

- Fresh tumor samples from 26 CRC patients were used to prepare tumor spheroids
- Immunohistochemistry was performed to detect EpCAM expression on tumor cells and CD45+ infiltrate (Fig 1)
- Tumor spheroids co-cultured with or without autologous PBMCs were treated with Catumaxomab for 96h
- Therapeutic impact on epithelial cells and leukocytes was measured by FACS analysis
- The effector (CD45+) to target (EpCAM+) cell ratio was determined (E:T)

Fig. 1



EpCAM expression on tumor cells is homogeneous and moderate

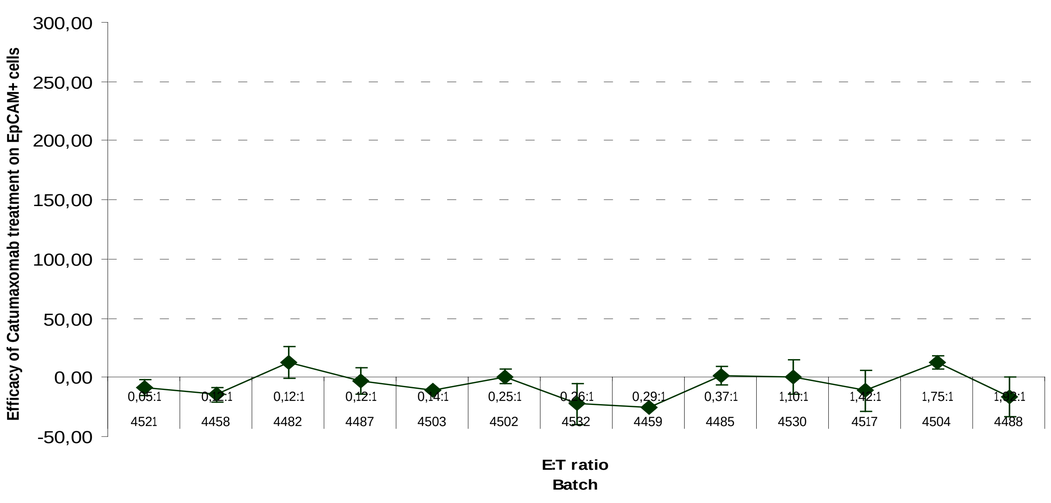


CD45+ leukocytes are rare in tumor spots and moderate in the connective tissue

Results

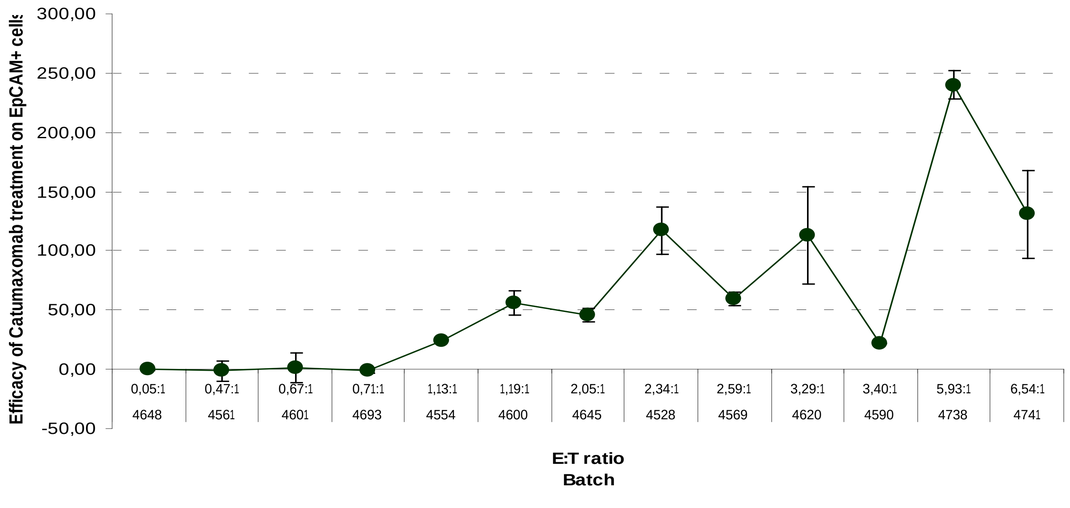
Similar to their original cancers (Fig. 1) the spheroid model consisted of a high fraction of EpCAM positive tumor cells and a low fraction of CD45 positive leukocytes in spheroids closely mimicking the parental tumors.

Efficacy of Catumaxomab treatment without PBMCs



The E:T ratio ranged from 0,05:1 to 1,92:1. Treatment of these spheroids with Catumaxomab revealed no significant therapeutic effect.

Efficacy of Catumaxomab treatment with PBMCs



Addition of patient specific PBMCs changed the E:T ratio up to 6,54:1 and had a significant impact on Catumaxomab efficacy. Catumaxumab induced cell death was found up to 68,95% ($p = 0,001$) depending on the individual E:T ratio.

Conclusion

- A dual biomarker system is required to select appropriate CRC patients for Catumaxomab treatment
- EpCAM expression on cancer cells is required, but the leukocyte infiltrate is the key predictor for the therapeutic response of Catumaxomab
- The fraction of tumor-infiltrating leukocytes has to be determinded in the individual tumor sample for targeted therapy using Catumaxumab
- The 3D drug testing in the spheroid model plays a superior role in personalized cancer therapy
- Catumaxomab represents a promising treatment option in CRC patients with a strong CD45+ infiltrate

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