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Targeting the oncofetal antigen Claudin-6 as novel approach for cancer immunotherapy

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The development of specific immunotherapies targeting antigens like HER2, Trop-2, or Claudin 18.2 has revolutionized medical oncology. In case of HER2, the subset of breast cancers and other solid tumors (i.e. gastric cancer) with HER2 overexpression/amplification (HER2+) is highly sensitive to HER-2-specific antibodies/antibody-drug conjugates and these therapies have dramatically improved treatment outcomes. However, in many other solid tumor types such target structures suitable for immunotherapies are still lacking.

The oncofetal antigen claudin-6 (CLDN6) has been recently emerged as viable target structure for cancer immunotherapy. CLDN6 is a transmembrane protein which is highly expressed during embryogenesis,in most germ cell tumors, > 50% of ovarian carcinomas and also with a lower frequency in lung cancer, gastric cancer and other malignancies.

On-target, off-tumor toxicity is generally of great concern for targeted immunotherapy. Therefore, selection of an adequate, tumor-specific target antigen without expression in non-malignant tissue is crucial both for efficacy and safety. CLDN6 expression is completely absent in normal human tissue, therefore this antigen is an optimal choice for immunotherapy.

The first in-human phase I trial BNT211 currently investigates CLDN6-specific chimeric antigen receptor (CAR) T-cells as single agent therapy and in combination with a CLDN6 mRNA vaccine. The combination approach, termed “CAR-Vac”, has led to increased CAR-T expansion and persistence in animal models. This improvement of CAR-T cell persistence addresses a major issue of CAR-T cell therapy in solid tumors.

First results of the BNT211 trial are promising, especially in patients with refractory germ cell tumors. Several patients have responded and some have achieved prolonged remissions despite extensive pretreatment. Such responses were both observed in CAR-T monotherapy and in the combination part of CAR-T cells with CLDN6 vaccination. Toxicity of BNT211 is acceptable, especially in comparison with currently approved CAR-T cell therapies for B-cell malignancies. Low grade cytokine-release syndrome and cytopenias related to lymphodepletion were the most frequent adverse events. Based on these preliminary findings CLDN6 may represent a safe target for T-cell based immunotherapy approaches.

The BNT211 trial is currently ongoing with a dose-escalation phase and may result in one of the first CAR-T-cell therapies with clinical relevance in solid tumors.