**Background:** The effective treatment of solid tumors remains an unmet medical need. Novel concepts exist to treat malignancies, including antibody-drug or immunomodulation conjugates, immune checkpoint inhibition, GAT-2 cells, as well as bispecific T cell engagers. CD3-based T cell engagers are highly potent therapeutic molecules with T cell cytotoxic activities in the picomolar range. According to this highly potent tumor activity is the risk of conjugate off-target effects due to low levels of expression of the target antigen in normal tissues, as has been observed for the tumor-associated antigen mesothelin (MSLN).

**A low affinity bivalent mesothelin-binding MATCH4 multispecific T cell engager increases cytotoxic selectivity for high mesothelin expressing cells**

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**Concept: Selective T cell-mediated depletion of tumor cells**

**Bivalent biMSLN.CD3.hSA T cell engager actively kills tumor cells in a MSLN-dependent manner**

**Larger therapeutic window for bivalent biMSLN.CD3.hSA T cell engager due to preferential avidity-based binding to tumor cells**

**Bivalent biMSLN.CD3.hSA T cell engager triggers potent tumor cell lysis and T cell activation in the presence of excess soluble MSLN (sMSLN) as compared to monovalent MSLN.CD3.hSA**

**Human pancreatic cancer growth is inhibited by biMSLN.CD3.hSA**

**Conclusions and potential benefits**

**BiMSLN binding**
- Low affinity, biMSLN domain preferentially engages fully MSLN-expressing malignant cells while sparing healthy, MSLN cells

**Tumor-deleted activity**
- Tumor-sparing activity, unlike ADCs, which can release cytotoxic agents into circulation causing dose-limiting toxicities

**Minimally targeted soluble MSLN**
- High affinity, low affinity binding to MSLN renders MSLN.CD3.hSA resistant to high concentrations of soluble MSLN present in patient fluid

**Efficacy**
- Avid anti-tumor activity against resistant tumor cell lines

**Extended half-life**
- Half-life compared by conventional IgG due to serum albumin binding domains