MMAE payload separated from HER2 targeting agent is selectively activated at tumors through click chemistry in vivo

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INTRODUCTION

• Shasqi’s mission is to make cancer drugs more effective with click chemistry.
• Click chemistry, a Nobel prize winning technology to safely activate cancer drugs at tumors. Click chemistry is the technology behind CAPAC (Figure 1).

Click Activated Protodugs Against Cancer (CAPAC)® (Figure 1).

• CAPAC is made up of two separate components: a tumor targeted activator and a payload; payloads are activated by a click chemistry reaction occurring at the tumor.

• CAPAC has been clinically validated, and we are the first company to use click chemistry inside human patients.

Click Chemistry Activates Drug at Tumors

• CAPAC is a Novel Approach to Tumor Targeted Drug Activation

We recently developed SQP22, a new trans-cyclooctene (TCO)-modified protodrug based on monomethyl auristatin E (MMAE). We evaluated its antitumor efficacy when activated at the tumor by a systemically-delivered (SQT01) targeting agent that binds HER2, and present the results here.

CAPAC: MMAE Protodrug

SQP22 (MMAE Protodrug)

SQT01 (HER2 binding Fab conjugated with tetrazine on lysine residues (2.2 tetrazine per Fab).

SELECTIVE ACTIVATION AT THE TUMOR: STRONG ANTI-TUMOR EFFECT COMPARED TO DISTILAMAB VEDOTIN

This work

CONCLUSIONS

• Click chemistry selectively activates an auristatin protodrug and provides a new avenue to safely get cytotoxic agents directly to tumors.
• An MMAE protodrug paired with a HER2 binding Fab activator has potent anti-tumor effects compared with distilamab vedotin, an ADC using the same target and payload.
• Levels of active payload at tumors within 15 min of protodrug dosing are comparable to payload concentrations reached by distilamab vedotin at 24-48 hr.
• Separation of targeting and payload allows for exploration of optimal timing of payload dosing, enabling the identification of a window that provides maximal anti-tumor activity with minimal non-specific activity.
• CAPAC is a novel approach to tumor targeted drug activation; by separating tumor targeting from payload, there is flexibility to optimize activity while limiting toxicity throughout development, including in the clinic. This approach also enables unique benefits such as combinations and payload cycling.

REFERENCES


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