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Preclinical efficacy and safety of M9140, a novel antibody-drug conjugate (ADC) with topoisomerase 1 (TOP1) inhibitor payload targeting carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)-expressing tumors

Sabine Raab-Westphal[*1], Felix Hart[1], Willem Sloot[1], Min Shan[1], Nicolas Rasche[1], Christiane Amendt[1], Jan Anderl[1]

[1]the healthcare business of Merck KGaA, Darmstadt, Germany
*Presenting and corresponding author (sabine.raab@emdserono.com)

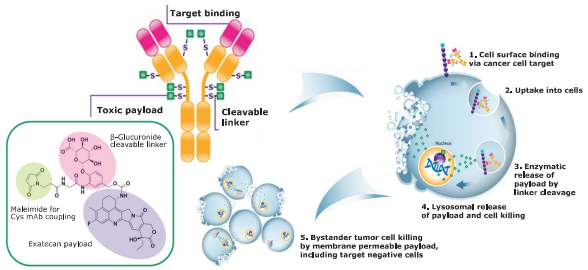
CONCLUSIONS

- **M9140 demonstrated high potency, strong antitumor activity, and bystander effect in preclinical efficacy models.**
- **The side effect profile of M9140 in monkeys was consistent with the known safety profile of exatecan. No ILD was observed.**
- **A first-in-human study to evaluate the safety, tolerability, pharmacokinetics, and preliminary clinical activity of M9140 in patients with advanced solid tumors is ongoing (NCT05464030).**

BACKGROUND

- M9140 is the first clinical-stage TOP1 inhibitor payload ADC directed against CEACAM5. CEACAM5 is a cell surface glycoprotein that modulates cell adhesion, differentiation, and proliferation, but shows limited expression on healthy cells in adults. CEACAM5 is overexpressed in colorectal cancer (CRC) and other solid tumors.[1]
- M9140 is composed of a CEACAM5-specific antibody conjugated to ß-glucuronide-exatecan linker-payload (DAR8). Exatecan is a highly potent and membrane permeable TOP1 inhibitor.
- After target binding, M9140 is internalized and trafficked to the lysosomes where enzymatic linker cleavage releases the exatecan payload, leading to death of the cell and neighboring tumor cells (**Figure 1**).

Figure 1. Schematic structure and mechanism of action for M9140

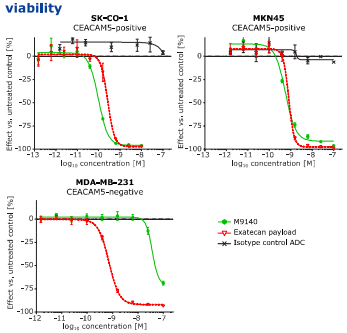


METHODS

- M9140 potency was tested in viability assays using cancer cell lines with different levels of CEACAM5 expression.
- Potency shift viability assays were conducted using different cell lines, with or without verapamil/zosuquidar as multidrug resistance-1 (MDR1; Pgp) or Ko143 as breast cancer resistance protein (BCRP) inhibitor.
- The M9140 bystander effect was assessed in co-culture experiments with CEACAM5-negative and-positive cancer cells.
- Antitumor activity and safety were evaluated in patient-derived xenograft (PDX) mouse models and in cynomolgus monkeys, respectively.

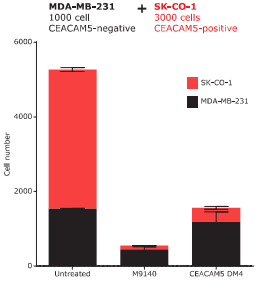
RESULTS

Figure 2. M9140 demonstrates specific and highly potent inhibition of cancer cell line viability



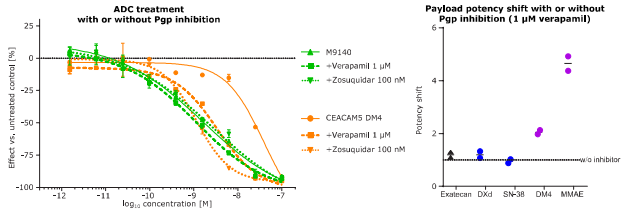
- M9140 demonstrated specific binding to CEACAM5 (not shown) and selective killing of target-positive cancer cells (IC50 0.09–0.62 nM) (**Figure 2**).

Figure 3. Higher bystander effect with M9140 than comparator anti-CEACAM5 ADC with DM4 payload *in vitro* (1 nM ADC)



- Higher bystander effect with M9140 indicated the potential to treat tumors with heterogeneous target expression (**Figure 3**).

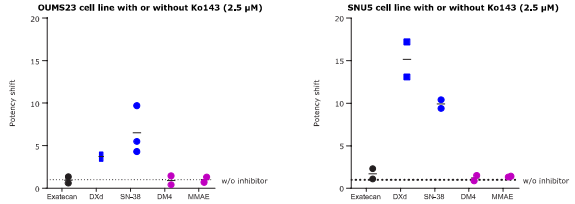
Figure 4. The lack of potency shift by Pgp inhibition indicates that M9140 and exatecan are not prone to Pgp-mediated resistance mechanism (LS513 cell line)



- In contrast to anti-CEACAM5 DM4 ADC, DM4 or MMAE payloads, the potency of M9140 or exatecan payload was not affected by MDR1 inhibition (**Figure 4**).

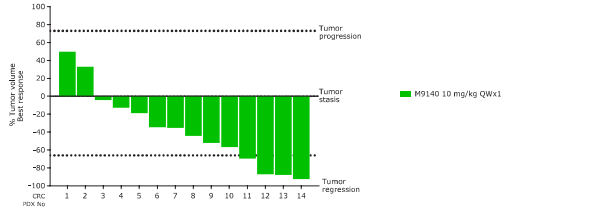
RESULTS CONTINUED

Figure 5. The lack of potency shift by BCRP inhibition indicates that exatecan is not prone to BCRP-mediated resistance mechanism



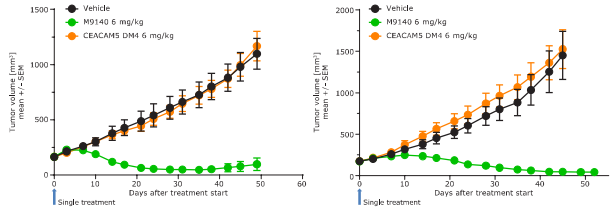
- In contrast to the TOP1 inhibitors DXd and SN-38, exatecan potency was not affected by BCRP inhibition (**Figure 5**).

Figure 6. Anti-tumor activity (tumor stasis/tumor regression) is observed in all 14 CRC PDX models following a single treatment with M9140



- A single treatment with 10 mg/kg M9140 caused strong antitumor effects in all 14 CRC PDX models tested, with tumor stasis in 10 models and tumor regression in 4 models as the best response (**Figure 6**).

Figure 7. M9140 showed strong *in vivo* efficacy in comparison to CEACAM5 DM4 in 2 CRC PDX models



- M9140 caused strong antitumor activity in 2 CRC PDX models where a maytansine-based CEACAM5 ADC was not effective (**Figure 7**).

Toxicology results

- Repeated M9140 infusion at doses of 3–30 mg/kg (Q3W) in cynomolgus monkeys resulted in dose-dependent hematolymphoid and intestinal effects, consistent with exatecan toxicity. Transient reductions in hematological parameters were observed ≥24 mg/kg. No other toxicities such as interstitial lung disease (ILD) or ocular toxicity were observed.
- The NOAEL was established at 24 mg/kg and the MTD at 30 mg/kg. The difference in toxicity by this small dose increment was determined by a 2.5-fold difference in plasma exatecan exposure.

Abbreviations: DAR, drug to antibody ratio; **DM4,** derivative of maytansine 4; **DXd,** deruxtecan; **MTD,** maximum tolerated dose; **MMAE,** monomethyl auristatin; **NOAEL,** no observed adverse effect level; **Pgp,** P-glycoprotein; **Q3W;** once every three weeks; **w/o,** without.

References: 1. Thompson JA, Grunert F and Zimmermann W, *J Clin Lab Anal.* 1971;5(5);344-66.

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