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M9140, an anti-CEACAM5 antibody–drug conjugate (ADC), in patients with metastatic colorectal cancer (mCRC): updated results from a Phase 1 trial

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CONCLUSIONS

- **In this updated analysis from the dose escalation part of the PROCEADE-CRC-01 trial (data cutoff: August 01, 2024), M9140 continued to demonstrate a manageable and predictable safety profile, with haematological DLTs consistent with Top1 inhibitor payload**
- **M9140 showed encouraging and durable antitumour activity at DLs ≥2.4 mg/kg:**
  - **DCR at 12 weeks was ~59%**
  - **Median PFS was 6.7 months**
- **Most patients had high CEACAM5 expression levels, consistent with data reported earlier.[1] Based on current data, M9140 activity does not appear to be associated with *KRAS, NRAS, BRAF* mutation status**
- **M9140 is currently being evaluated as monotherapy as well as in combinations (M9140 + bevacizumab ± capecitabine) in the dose expansion part of this study (NCT05464030)**

INTRODUCTION

- M9140 is an anti-CEACAM5 ADC that selectively delivers a cytotoxic Top1 inhibitor payload (exatecan)
- M9140 demonstrated high potency, strong antitumour activity, and bystander effect in preclinical models[2]
- Preliminary data from the dose escalation part of the ongoing PROCEADE-CRC-01 study (NCT05464030) showed encouraging antitumour activity and a manageable safety profile of M9140 in heavily pretreated patients with mCRC[3]
  - The MTD was declared as 2.8 mg/kg:
  - 2.4 mg/kg and 2.8 mg/kg are the doses selected for the ongoing randomised dose optimization part of the trial
- Here we present updated data from the dose escalation part of PROCEADE-CRC-01 study (**Figure 1**) from a longer follow-up (data cutoff: August 01, 2024) and the association of M9140 activity with biomarker status and CEACAM5 expression levels

OBJECTIVES

- To assess the safety, tolerability, pharmacokinetics, and preliminary clinical activity of M9140 in patients with mCRC who had received ≥2 prior lines of treatment

METHODS

Figure 1. PROCEADE-CRC-01 - Study design

Key eligibility criteria

- Patients with confirmed LA/M CRC intolerant/refractory to or progressing after standard systemic therapies
- ECOG PS ≤1
- Patients with archived FFPE tumor tissue available. If archived tumor material not available, fresh biopsy required
- Patients were not selected on the basis of CEACAM5 expression

Dose escalation

M9140 Q3W, IV
(Day 1 of 21-day cycles)

3.2 mg/kg[a] n = 7
3.0 mg/kg n = 4
2.8 mg/kg n = 12
2.6 mg/kg n = 4
2.4 mg/kg n = 7
1.2 mg/kg n = 3
0.6 mg/kg n = 3

N = 40 (US, EU, and Japan)
Data cutoff: August 01, 2024

[a]Including 3 patients with primary G-CSF prophylaxis

Dose expansion

Part 2A: M9140 monotherapy
Dose optimization

Part 2B: M9140 monotherapy (Q2W)
Alternative dosing regimen

Part 2C: M9140 + bevacizumab ± capecitabine
Combination regimen

Key endpoints	
Primary	Part 1: DLTs, AEs
Secondary	Part 1: PK, OR, PFS, DoR, ECG changes, ADA

Data presented herein

Key endpoints	
Primary	Part 2A: AEs, OR, DoR Parts 2B and 2C: DLTs, AEs
Secondary	Part 2A: PK, OS, PFS, TTR, AEs, ECG changes, ADA Parts 2B and 2C: PK, OR, PFS, DoR, TTR, ADA, DCR

- Safety monitoring committee (SMC) recommended dose escalation was guided by safety, preliminary PK data, supported by a Bayesian two-parameter logistic regression model
- Biomarker analysis:
  - Immunohistochemistry - Tissue expression of CEACAM5 was detected using a proprietary anti-CEACAM5 antibody clone
  - Patient records were assessed for *KRAS, NRAS,* and *BRAF* mutations
- CEACAM5 staining intensity (membrane and cytoplasm combined score) was evaluated in ≥100 viable tumour cells semi-quantitatively using a standard 0 to 3+ scale

RESULTS

- As of August 2024, 40 patients were treated across 7 DLs (0.6–3.2 mg/kg)
- Most patients were heavily pretreated, with 80% having received ≥3 lines of prior treatment, and 100% having received irinotecan previously (**Table 1**)
- Median treatment duration of M9140 was 19.1 weeks (range: 1.7–48.3)

Table 1: Baseline and demographic characteristics

Baseline characteristics		All patients (N = 40)
Age, mean (SD), years		58.2 (11.0)
Sex, n (%)	Male Female	20 (50.0) 20 (50.0)
Race, n (%)	White Asian Other	26 (65.0) 11 (27.5) 3 (7.5)
Site of primary tumour[a], n (%)	Colon Rectum	31 (77.5)[b] 8 (20.0)
ECOG PS	0 1	15 (37.5) 25 (62.5)
Time since initial cancer diagnosis, median (min, max), years		3.4 (0.9, 12.0)
Number of previous systemic anticancer therapies, n (%)	2 3 ≥4	8 (20.0) 16 (40.0) 16 (40.0)
Major treatments before trial initiation, n (%)	Bevacizumab Fluorouracil Oxaliplatin Irinotecan	37 (92.5) 38 (95.0) 39 (97.5) 40 (100.0)

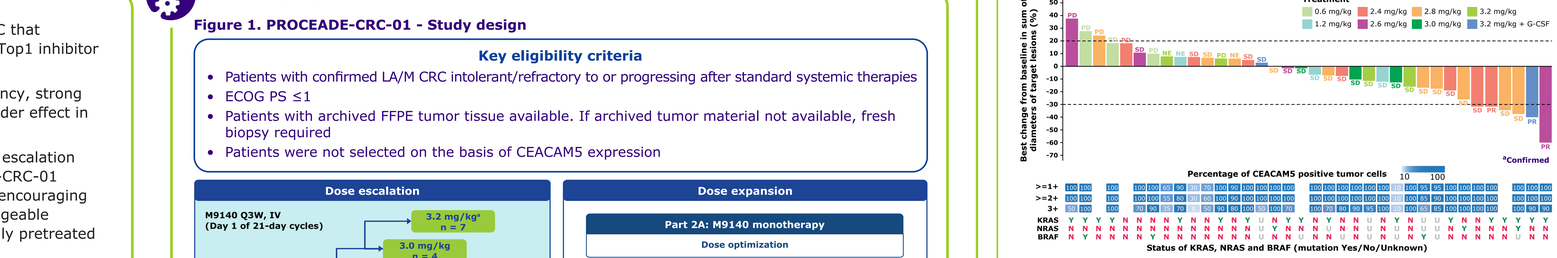
[a]Data for 1 patient was missing; [b]Left colon: n = 19 (47.5%), Right colon: n = 8 (20.0%), Sigmoid colon: n = 2 (5.0%)
ECOG PS, Eastern Cooperative Oncology Group Performance Status; **SD**, standard deviation

Pharmacokinetics

- M9140 shows systemic stability
- t1/2 was 5.7 days for M9140 and 4.9 days for exatecan
- At doses 0.6–3.2 mg/kg, conjugated antibody and exatecan exhibit linear and dose-proportional PK

Efficacy

Figure 2. Best overall response[a]



- As of the current data cutoff (August 01, 2024), PRs* were reported in 6 (15.0%) patients—2 additional responders have been reported since the last data cutoff (April 23, 2024)3 (**Figure 2**)
  - 3 patients had a confirmed PR
  - All PRs were observed at DLs ≥2.4 mg/kg (effective doses evaluated in dose optimization part of the trial)
- The overall DCR† at 12 weeks was 55%
  - For patients receiving M9140 at DLs ≥2.4 mg/kg (n=34), the DCR was ~59%
- Most patients had high CEACAM5 expression levels
- Mutations in *KRAS, NRAS,* and *BRAF* were observed across the patient population; no clear association was observed between these mutations and drug response based on the current data
  - These biomarkers will be further explored in upcoming cohorts and future pivotal studies
- At DLs ≥2.4 mg/kg, 14 of 34 (41.2%) patients stayed on treatment for >6 months, 5 of whom were on treatment for >9 months (**Figure 3**)
  - Four (10.0%) patients remained on treatment at the data cutoff
  - TEAEs led to dose reductions in 9 (22.5%) patients, all at DLs ≥2.8 mg/kg
- Overall, the median PFS was 5.9 months (95% CI: 4.6, 7.2) (**Figure 4**)
  - For patients receiving M9140 at DLs ≥2.4 mg/kg (n=34), the median PFS was 6.7 months (95% CI: 4.6, 8.8)

*At least 30% decrease in the sum of the diameters of the target lesions, considering the baseline sum diameters as the reference;
†DCR was defined as patients who achieved a CR, PR, SD, or non-CR/non-PD at week 12 visit [or later] prior to documented PD

Safety

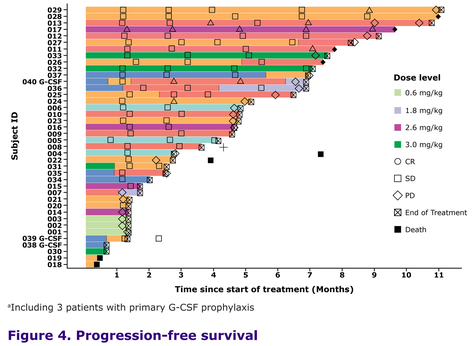
Table 2. Dose-limiting toxicities (DLTs)

DLT event (SMC decision)	0.6 mg/kg (n = 3)	1.2 mg/kg (n = 3)	2.4 mg/kg (n = 7)	2.6 mg/kg (n = 4)	2.8 mg/kg (n = 12)	3.0 mg/kg (n = 4)	3.2 mg/kg[a] (n = 7)	Total (N = 40)
Total, n (%)	0	0	1 (14.3)	0 (0.0)	1 (8.3)	1 (25.0)	4 (57.1)	7 (17.5)
Anaemia	0	0	0	0	0	0	1 (14.3)	1 (2.5)
Febrile neutropaenia	0	0	1 (14.3)	0	0	0	2 (28.6)	3 (7.5)
Neutrophil count decreased	0	0	0	0	0	1 (25.0)	1 (14.3)	2 (5.0)
Platelet count decreased	0	0	0	0	0	0	2 (28.6)	2 (5.0)
Sepsis	0	0	0	0	1 (8.3)	0	0	1 (2.5)
Thrombocyto-paenia	0	0	0	0	0	0	1 (14.3)	1 (2.5)

[a]Including 3 patients with primary G-CSF prophylaxis

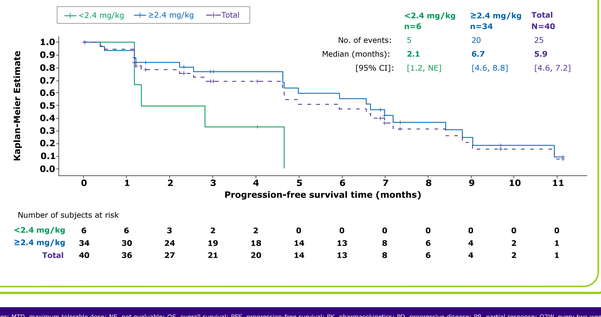
- M9140 continues to show a manageable safety profile
- Seven patients experienced DLTs; the majority were haematological adverse events at DLs 3.0 and 3.2 mg/kg; 1 patient (at 2.8 mg/kg) experienced a Grade 5 sepsis (**Table 2**)
- The most frequently reported Grade ≥3 TEAEs were neutropaenia (50.0%), anaemia (40.0%), thrombocytopaenia (32.5%), leukopaenia (30.0%), and lymphopaenia (22.5%)
- Nausea, vomiting, and diarrhea were predominantly Grade 1; no Grade ≥3 events were observed for these GI TEAEs
- Grade 5 TEAEs were sepsis and GI haemorrhage, both occurring at DL 2.8 mg/kg (n = 1 each). The GI haemorrhage event was not related to M9140
- No events of ocular toxicity or interstitial lung disease were reported

Figure 3. Treatment duration and response over time



[a]Including 3 patients with primary G-CSF prophylaxis

Figure 4. Progression-free survival



Abbreviations: ADA, anti-drug antibody; ADC, antibody-drug conjugate; AE, adverse event; CEACAM5, Carcinoembryogenic antigen-related cell adhesion molecule 5; CI, confidence interval; CR, complete response; DCR, disease control rate; DL, dose level; DLT, dose-limiting toxicity; DoR, duration of response; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EU, Europe; FFPE, formalin-fixed paraffin-embedded; G-CSF, granulocyte colony-stimulating factor; GI; gastrointestinal; IV, intravenous; LA/M, locally advanced or metastatic; mCRC, metastatic colorectal cancer; MTD, maximum tolerable dose; NE, not evaluable; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PD, progressive disease; PR, partial response; Q2W, every two weeks; Q3W, every three weeks; RECIST, Response Evaluation Criteria in Solid tumours; SD, stable disease; TEAE, treatment-emergent adverse event; Top1, topoisomerase 1; TPS, tumour proportion score; TTR, time to response.

References: 1. de Valk KS, et al. *Ann Surg Oncol.* 2021;28(3):1832-1844; 2. Raab-Westphal S, et al. *Cancer Res.* 2024;84(6_Supplement):2362; 3. Kopetz S, et al. *J Clin Oncol.* 2024;42(16_suppl):3000

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