First-in-human trial of M9140, an anti-CEACAM5 antibody–drug conjugate (ADC) with exatecan payload, in patients (pts) with metastatic colorectal cancer (mCRC)

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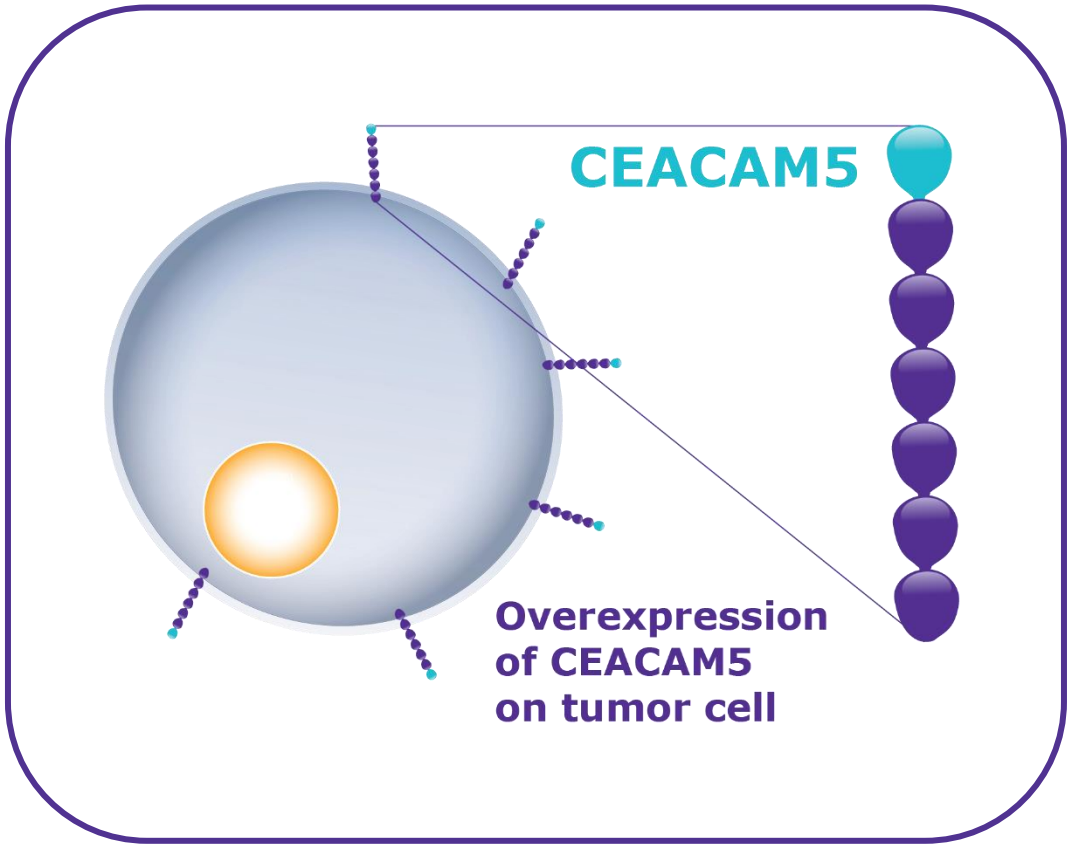
Carcinoembryogenic antigen-related cell adhesion molecule 5 (CEACAM5) as an attractive ADC target



- CEACAM5 is a cell surface glycoprotein that modulates cell adhesion, differentiation, and proliferation[1]
- CEACAM5 has limited expression in adult healthy tissues but is overexpressed in various adenocarcinomas, particularly in CRC (>90% of patients)[2,3]
- Exploiting CEACAM5 overexpression in certain cancers has the potential to offer a promising approach for ADC-based therapy

ADC, antibody–drug conjugate; CRC, colorectal cancer

1. Beauchemin N, Arabzadeh A. *Cancer Metastasis Rev.* 2013;32(3-4):643-671; 2. Zhang X, et al. *J Int Med Res.* 2020;48(9):300060520959478; 3. Decary S, et al. *Clin Cancer Res.* 2020;26(24):6589-6599.

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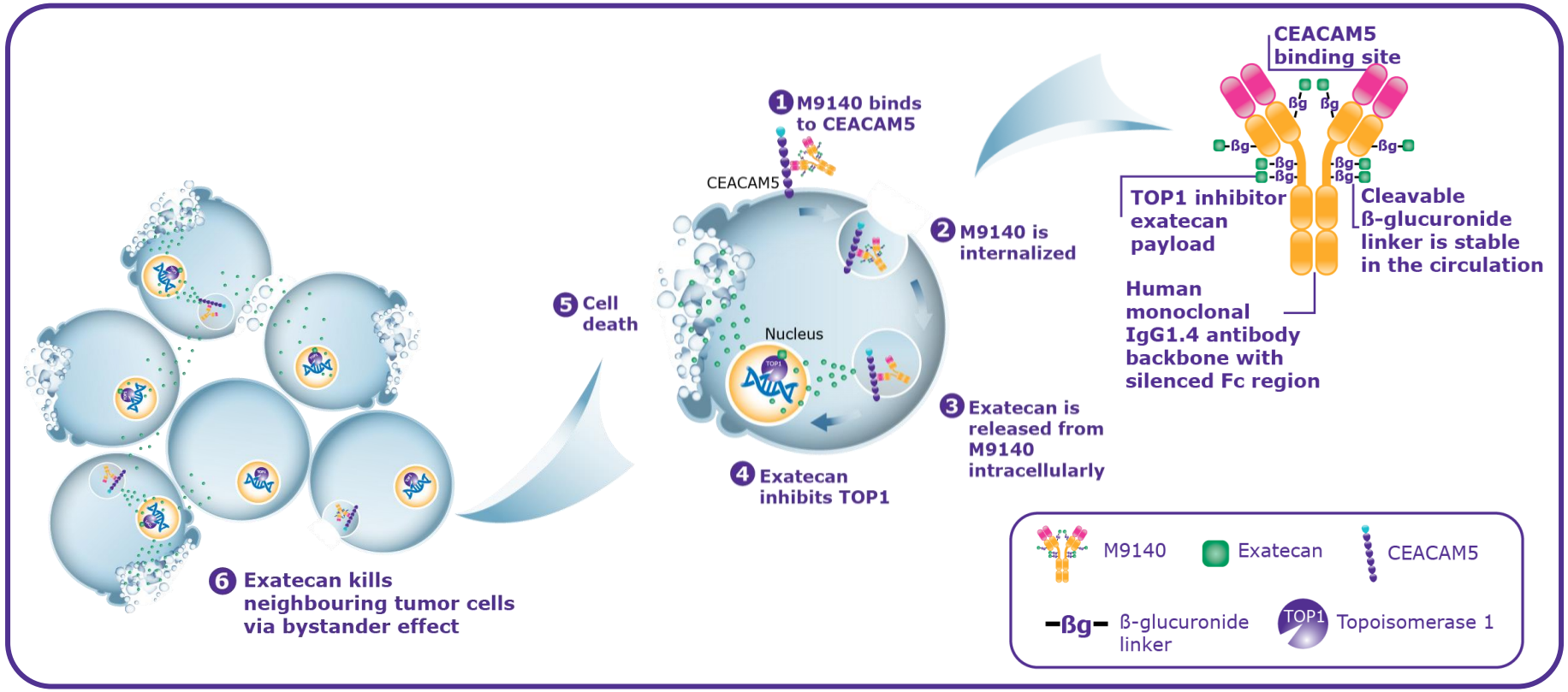
M9140 is the first anti-CEACAM5 ADC with a Top1 inhibitor payload (exatecan)



- M9140 is composed of a CEACAM5-specific antibody conjugated to ß-glucuronide exatecan linker payload[1]
- Drug-to-antibody ratio (DAR): 8[1]
- M9140 has demonstrated high potency, strong antitumor activity, and bystander effect in preclinical efficacy models[1]

ADC, antibody–drug conjugate; CEACAM5, Carcinoembryogenic antigen-related cell adhesion molecule 5; Top1, topoisomerase 1

1. Raab-Westphal S, et al. AACR 2024 (abstract 2362).
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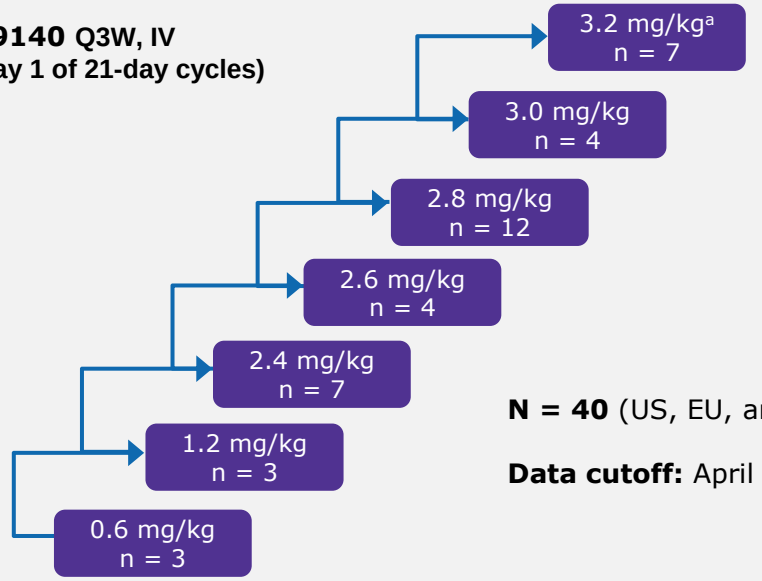
PROCEADE-CRC-01: A Phase 1, open-label, multicenter trial of M9140 in patients with mCRC (NCT05464030)

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)



N = 40 (US, EU, and Japan)

Data cutoff: April 23, 2024

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

Key endpoints

Primary

- DLTs
- AEs
- RDE

Secondary

- PK
- OR[b]
- PFS[b]
- DOR
- ECG changes
- ADA

[b]**Assessed by investigator per RECIST v1.1**

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ADA, anti-drug antibody; AE, adverse event; CEACAM5, Carcinoembryogenic antigen-related cell adhesion molecule 5; DLT, dose-limiting toxicity; DOR, duration of response; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FFPE, formalin-fixed paraffin-embedded; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; LA/M, locally advanced or metastatic; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability high; MTD, maximum tolerable dose; OR, objective response; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every three weeks; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors
Refer to ClinicalTrials.gov (NCT05464030) for additional information (accessed May 28, 2024).

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Baseline and demographic characteristics

Baseline characteristics		All patients (N = 40)
Age, mean (SD), years		58.2 (10.98)
Sex, n (%)	Male Female	20 (50.0) 20 (50.0)
Race, n (%)	White Asian Black or African American Other	26 (65.0) 11 (27.5) 2 (5.0) 1 (2.5)
Site of primary tumor[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)

Baseline characteristics		All patients (N = 40)
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 (%)	Cetuximab Panitumumab Bevacizumab Fluorouracil Oxaliplatin Irinotecan	8 (20.0) 15 (37.5) 37 (92.5) 38 (95.0) 39 (97.5) 40 (100.0)
KRAS mutation status	Yes No Unknown	19 (47.5) 17(42.5) 4 (10.0)
NRAS mutation status	Yes No Unknown	3 (7.5) 31(77.5) 6 (15.0)
BRAF mutation status	Yes No Unknown	5 (12.5) 28 (70.0) 7 (17.5)

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[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

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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)
Anemia	0	0	0	0	0	0	1 (14.3)	1 (2.5)
Febrile neutropenia	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)
Thrombocytopenia	0	0	0	0	0	0	1 (14.3)	1 (2.5)

Overall, 7 patients experienced DLTs; the majority were hematological adverse events at DLs 3.0 and 3.2 mg/kg; 1 patient (at 2.8 mg/kg) experienced a Grade 5 sepsis

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[a]Including 3 patients with primary G-CSF prophylaxis
DL, dose level; G-CSF, granulocyte colony-stimulating factor

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Safety profile

Grade ≥3 TEAEs

	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)
Patients with ≥1 Grade ≥3 TEAE, n (%)	1 (33.3)	1 (33.3)	3 (42.9)	3 (75.0)	8 (66.7)	3 (75.0)	7 (100.0)	26 (65.0)
Grade ≥3 TEAEs reported in ≥10% of patients (total), n (%)								
Neutropenia[b]	0	0	3 (42.9)	2 (50.0)	6 (50.0)	2 (50.0)	6 (85.7)	19 (47.5)
Anemia[c]	0	0	2 (28.6)	1 (25.0)	6 (50.0)	1 (25.0)	6 (85.7)	16 (40.0)
Thrombocytopenia[d]	0	0	2 (28.6)	1 (25.0)	3 (25.0)	2 (50.0)	5 (71.4)	13 (32.5)
Leukopenia[e]	0	0	1 (14.3)	1 (25.0)	4 (33.3)	1 (25.0)	5 (71.4)	12 (30.0)
Lymphopenia[f]	0	1 (33.3)	1 (14.3)	0	2 (16.7)	2 (50.0)	3 (42.9)	9 (22.5)

- The most frequently reported Grade ≥3 TEAEs were neutropenia, anemia, thrombocytopenia, and leukopenia
- Grade 5 TEAEs were gastrointestinal hemorrhage and sepsis, both occurring at DL 2.8 mg/kg (n = 1 each)
- No events of ocular toxicity or interstitial lung disease were reported
- Nausea, vomiting, and diarrhea were predominantly Grade 1; no Grade ≥3 events were observed for these GI TEAEs

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[a]Including 3 patients with primary G-CSF prophylaxis; [b]Includes neutropenia and neutrophil count decreased; [c]Includes anemia, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased; [d]Includes thrombocytopenia and platelet count decreased; [e]Includes leukopenia and white blood cell count decreased; [f]Includes lymphopenia and lymphocyte count decreased
DL, dose level; G-CSF, granulocyte colony-stimulating factor; GI; gastrointestinal; TEAE, treatment-emergent adverse event

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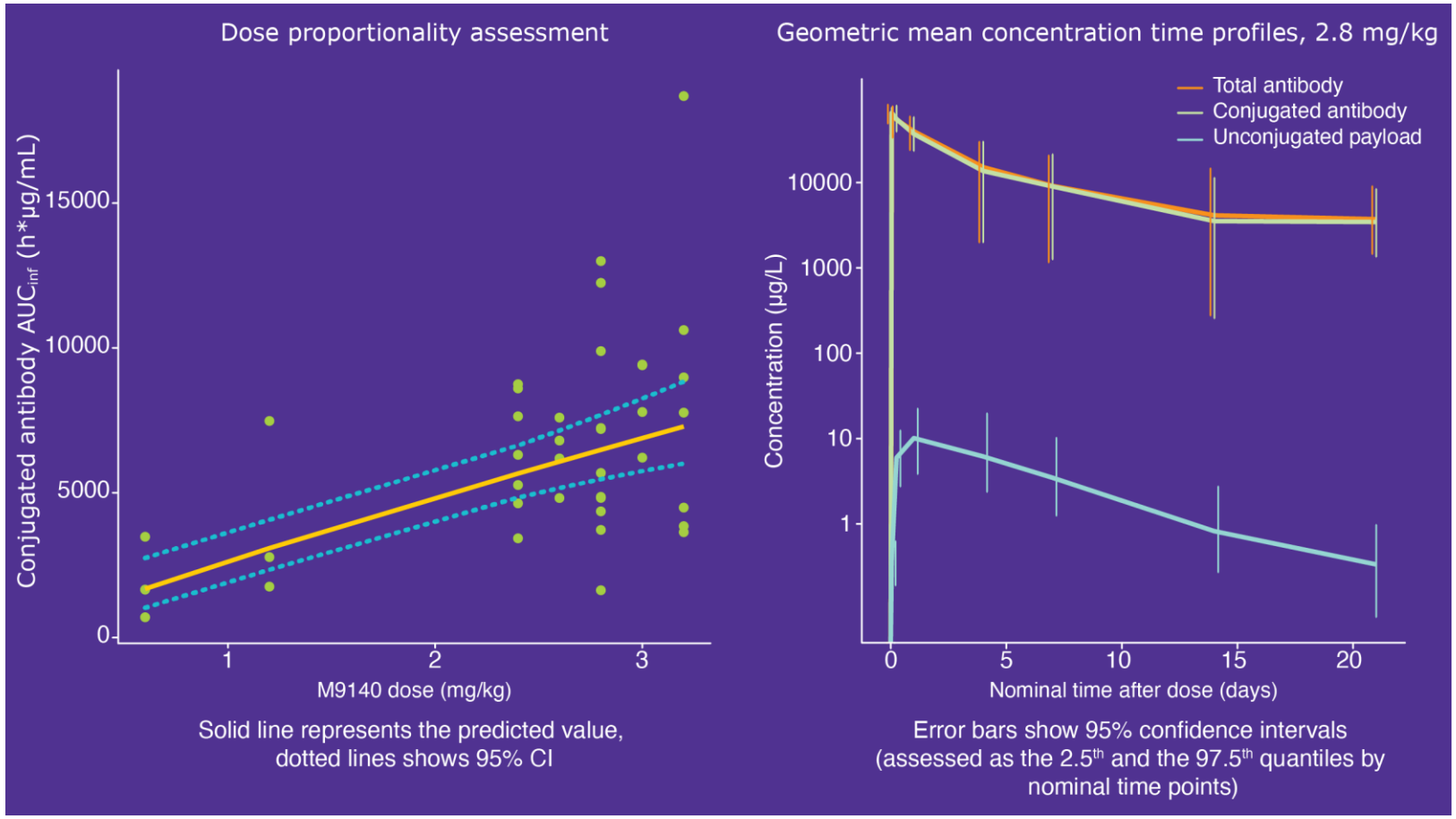
Clinical pharmacokinetics of M9140



- At doses 0.6–3.2 mg/kg (Q3W; IV), the conjugated antibody and exatecan exhibit linear and dose-proportional PK
- M9140 shows systemic stability
- $t_{1/2}$ was 6.8 days for M9140 and 5.1 days for exatecan
- M9140 systemic exposures at the RDE (range: 2.4–2.8 mg/kg Q3W) are pharmacologically relevant for antitumor activity based on modeling and simulation
- Minimal accumulation of exatecan upon repeated dosing, consistent with manageable multi-cycle tolerability

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CI, confidence interval; IV, intravenous; PK, pharmacokinetics; Q3W, every three weeks; RDE, recommended dose for expansion; $t_{1/2}$, half-life

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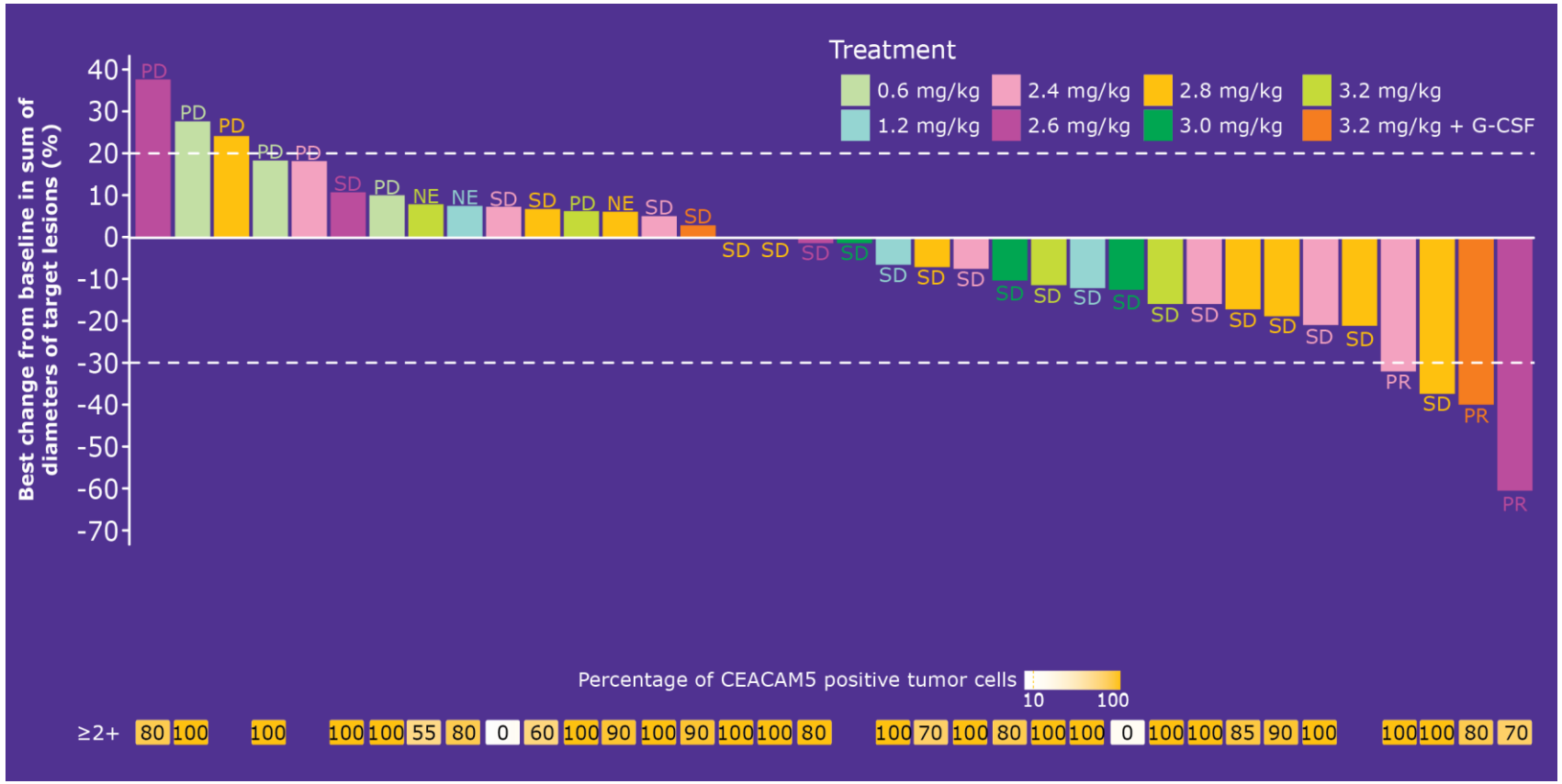
Best overall response



- Reduction in tumor size was observed at DLs ≥1.2 mg/kg
- Four patients had a tumor size reduction of ≥30%
  - Three of these patients had a confirmed PR
  - All PRs occurred at doses ≥2.4 mg/kg
- DCR was 65% (confirmed PR [n = 3] + SD [n = 23] = 26 of 40 patients)
- The majority of patients had high CEACAM5 expression

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CEACAM5, Carcinoembryogenic antigen-related cell adhesion molecule 5; DCR, disease control rate; DL, dose level; G-CSF, granulocyte colony-stimulating factor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

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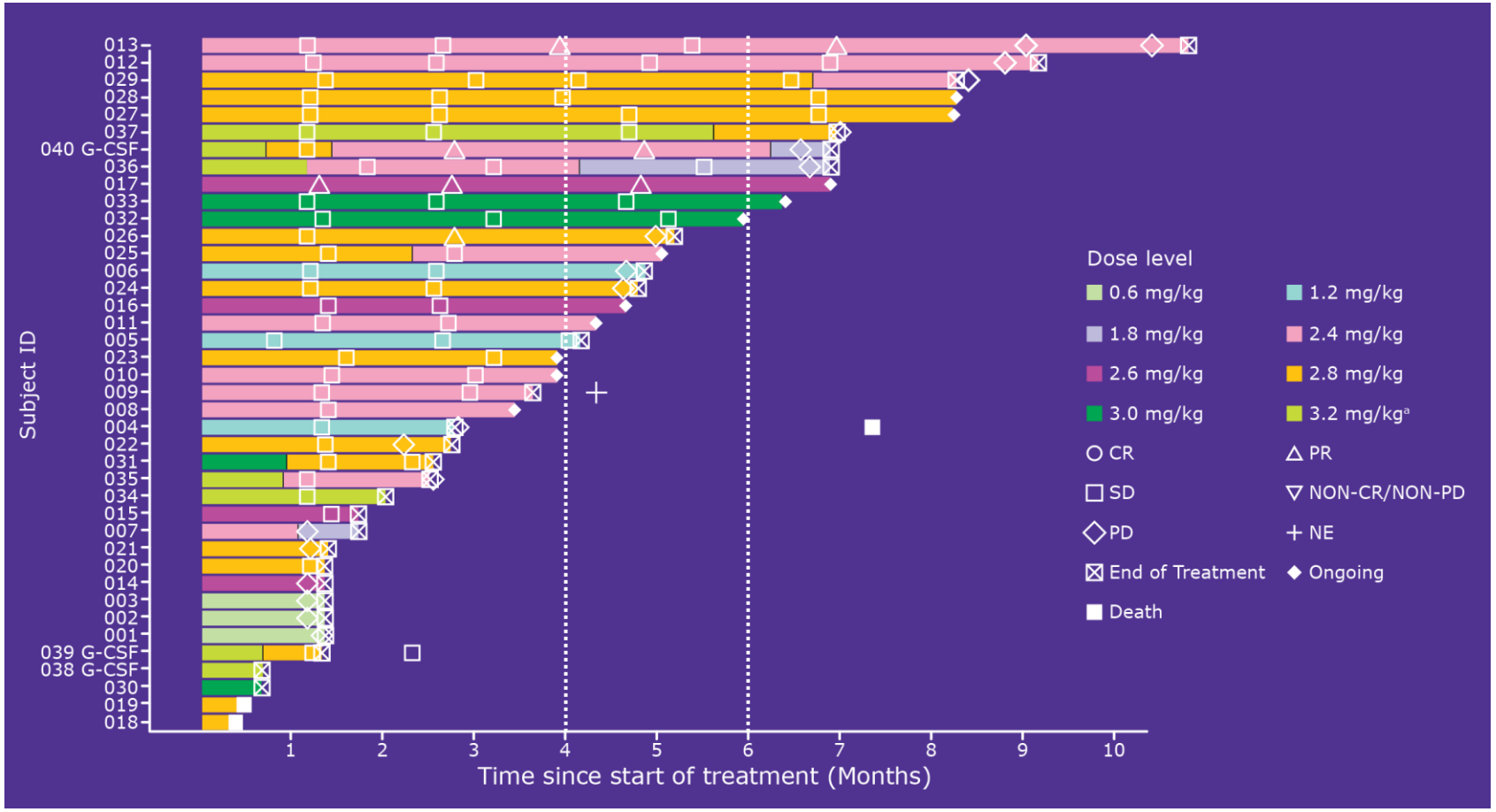
Treatment duration and response over time



- At DLs ≥2.4 mg/kg, 8 of 34 (23.5%) patients stayed on treatment for 6 months, 2 of whom were on treatment for >9 months
- Eleven (27.5%) patients continue with the treatment as of data cutoff (April 23, 2024)
- TEAEs led to dose reductions in 8 (20.0%) patients, all at DL ≥2.8 mg/kg

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

CR, complete response; DL, dose level; G-CSF, granulocyte colony-stimulating factor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event

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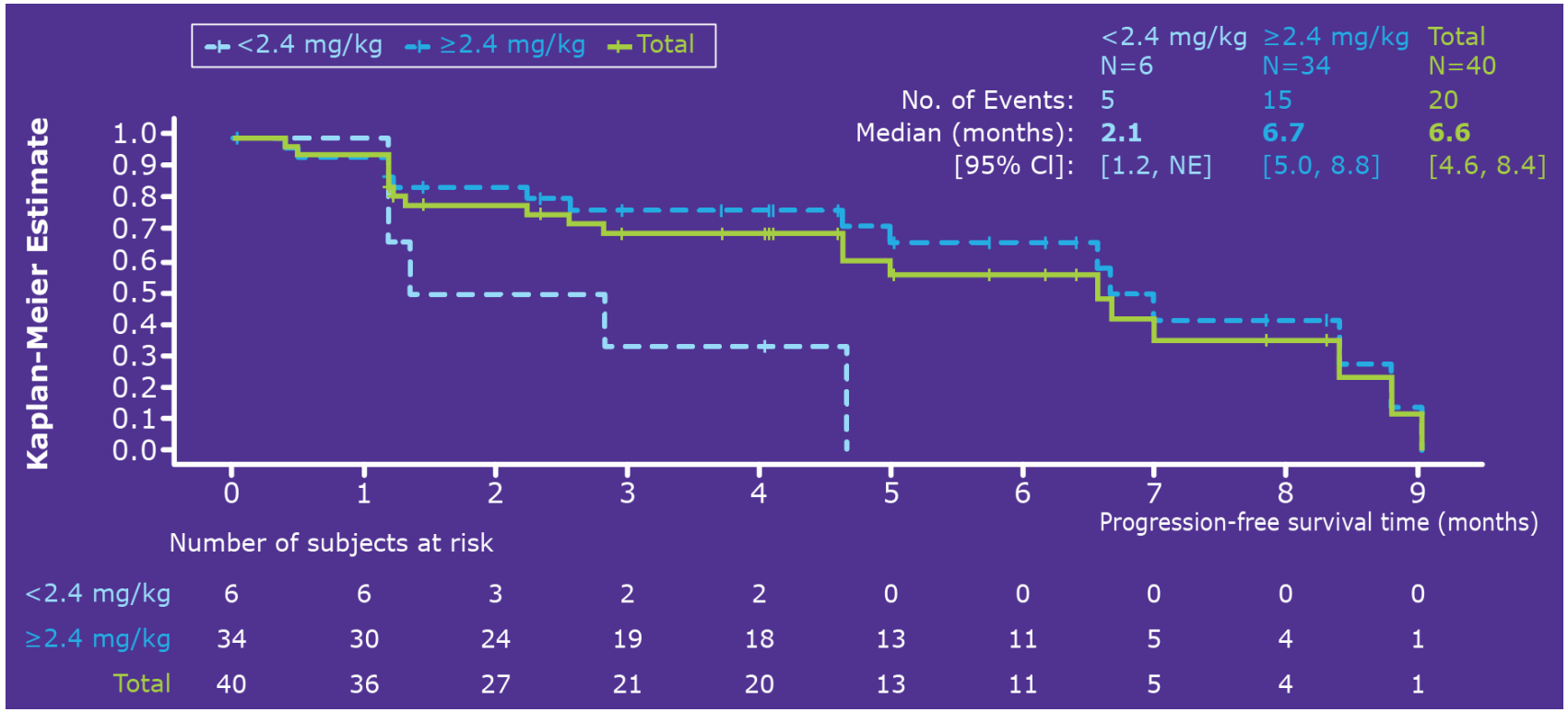
Progression-free survival (PFS)



- The median PFS was 6.6 (95% CI: 4.6, 8.4) months; 11 (27.5%) patients continue on treatment
- PFS was higher for patients treated with M9140 ≥2.4 mg/kg vs. <2.4 mg/kg (6.7 [95% CI: 5.0, 8.8] months vs. 2.1 [95% CI: 1.2, NE] months)

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CI, confidence interval; NE, not evaluable

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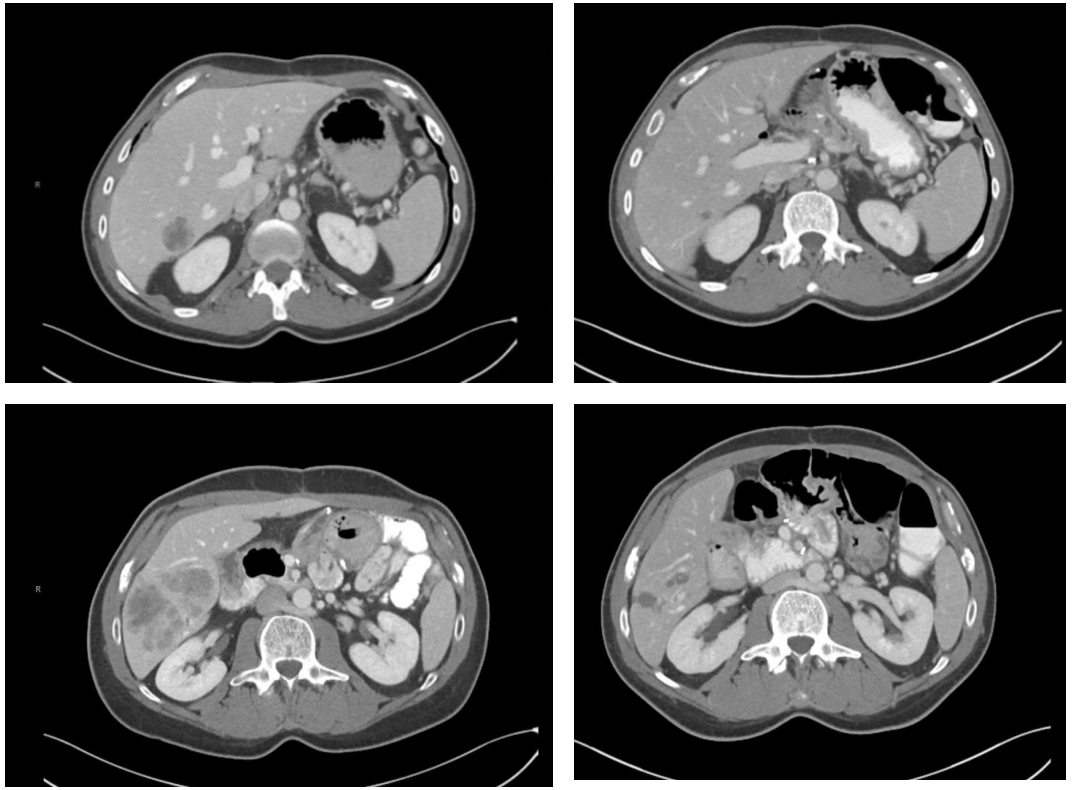
Case study of Patient # 017

Patient characteristics	
Demographics	52-year-old, White, Male
Metastatic sites	Liver Subsite: Hepatic flexure
Biomarker status	KRAS mut, BRAF/NRAS wt, CEACAM5 TPS score ≥2+ was 70
Treatment history	• Adjuvant: oxaliplatin + capecitabine; disease recurrence after 1 year • Started FOLFIRI + bevacizumab; best response PR • Experimental IO therapy; best response was PD
Dose of M9140	2.6 mg/kg
Response to M9140; tumor shrinkage	PR; −60.53%
Exposure time	210 days (patient is still on treatment in Cycle 10 at data cutoff with no dose reductions)

Baseline ~ 5 months



We acknowledge Dr. KPS Raghav for providing patient data

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CEACAM5, Carcinoembryogenic antigen-related cell adhesion molecule 5; mut; mutant; FOLFIRI, folinic acid, fluorouracil, and irinotecan; IO, immuno-oncology; PD, progressive disease; PR, partial response; TPS, tumor proportion score; wt, wild type

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Conclusions

- In this Phase 1 dose escalation study in patients with 3L+ CRC:
  - M9140 demonstrated a manageable and predictable safety profile with hematological DLTs consistent with Top1 payload
    - No interstitial lung disease or ocular toxicities were observed
  - 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 randomized dose optimization
  - M9140 showed encouraging and durable antitumor activity at therapeutic doses ≥2.4 mg/kg (n=34):
    - DCR was 70.5% (confirmed PR [n = 3] + SD [n = 21])
    - PFS was 6.7 months
- Evaluation of M9140 in patients with mCRC as monotherapy as well as in combinations continues in the expansion part of this study

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BOR, best overall response; DCR, disease control rate; DLTs, dose-limiting toxicities; mCRC, metastatic colorectal cancer; MTD, maximum tolerable dose; PFS, progression-free survival; PR, partial response; SD, stable disease; Top1, topoisomerase 1

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Spain

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– Hospital Universitario Quironsalud Madrid- NEXT Oncology, Madrid
Principal Investigator: Valentina Boni

Japan

– National Cancer Center Hospital - Dept of Gastroenterology, Chuo-ku
Principal Investigator: Ken Kato

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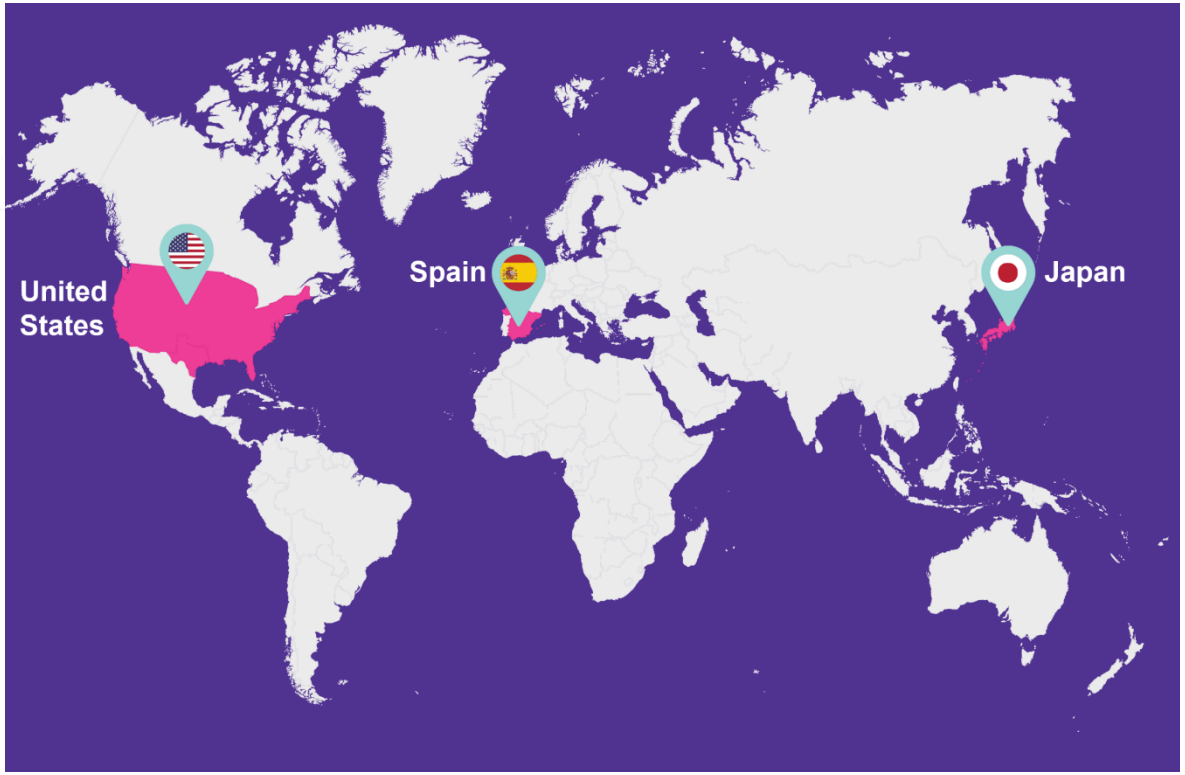

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Thank you!

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