

Safety and efficacy of CS2009, a first-in-class PD-1/VEGF/CTLA-4 trispecific antibody, in metastatic colorectal cancer (mCRC): Results from a phase 1/2 study

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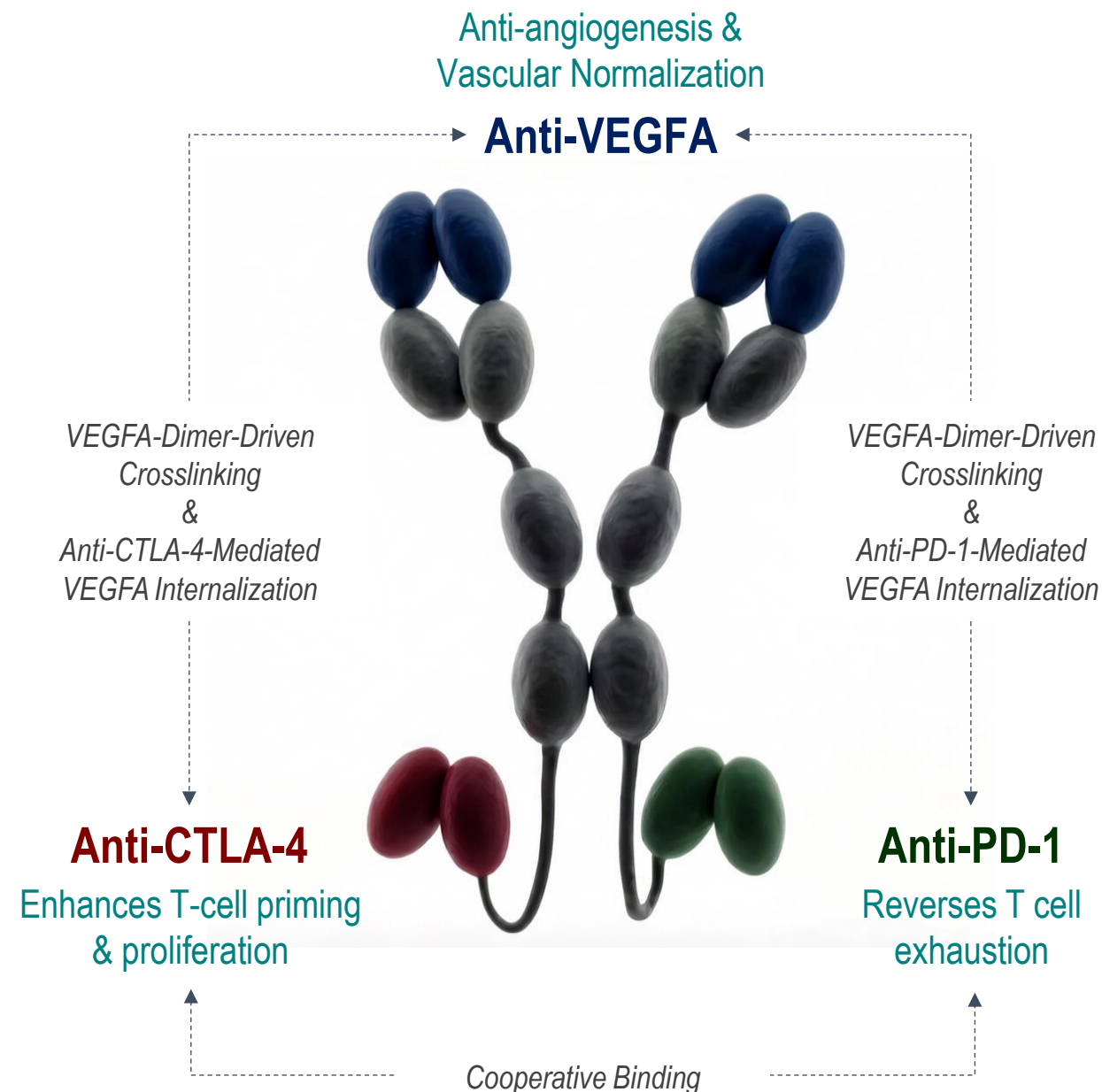
Presenter: Dr. Feng Wang

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Declaration of Interests

Dr. Feng Wang declares no conflict of interest.

Background (1/2)



- CS2009 is a potential first-in-class/best-in-class trispecific antibody integrating clinically validated **anti-PD-1**, **anti-VEGFA**, and **anti-CTLA-4** antibody clones.
- Multi-target engagement and synergistic interactions enhance CS2009's activities in TME while sparing peripheral CTLA-4+ T cells to widen its therapeutic window.
- CS2009 demonstrated a favorable tolerability and safety profile in a Phase 1 study, with promising antitumor activity across multiple tumor types.

CTLA-4: cytotoxic T-lymphocyte-associated protein 4; PD-1: programmed cell death protein 1; TME: tumor microenvironment; VEGFA: vascular endothelial growth factor A.

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Background (2/2)

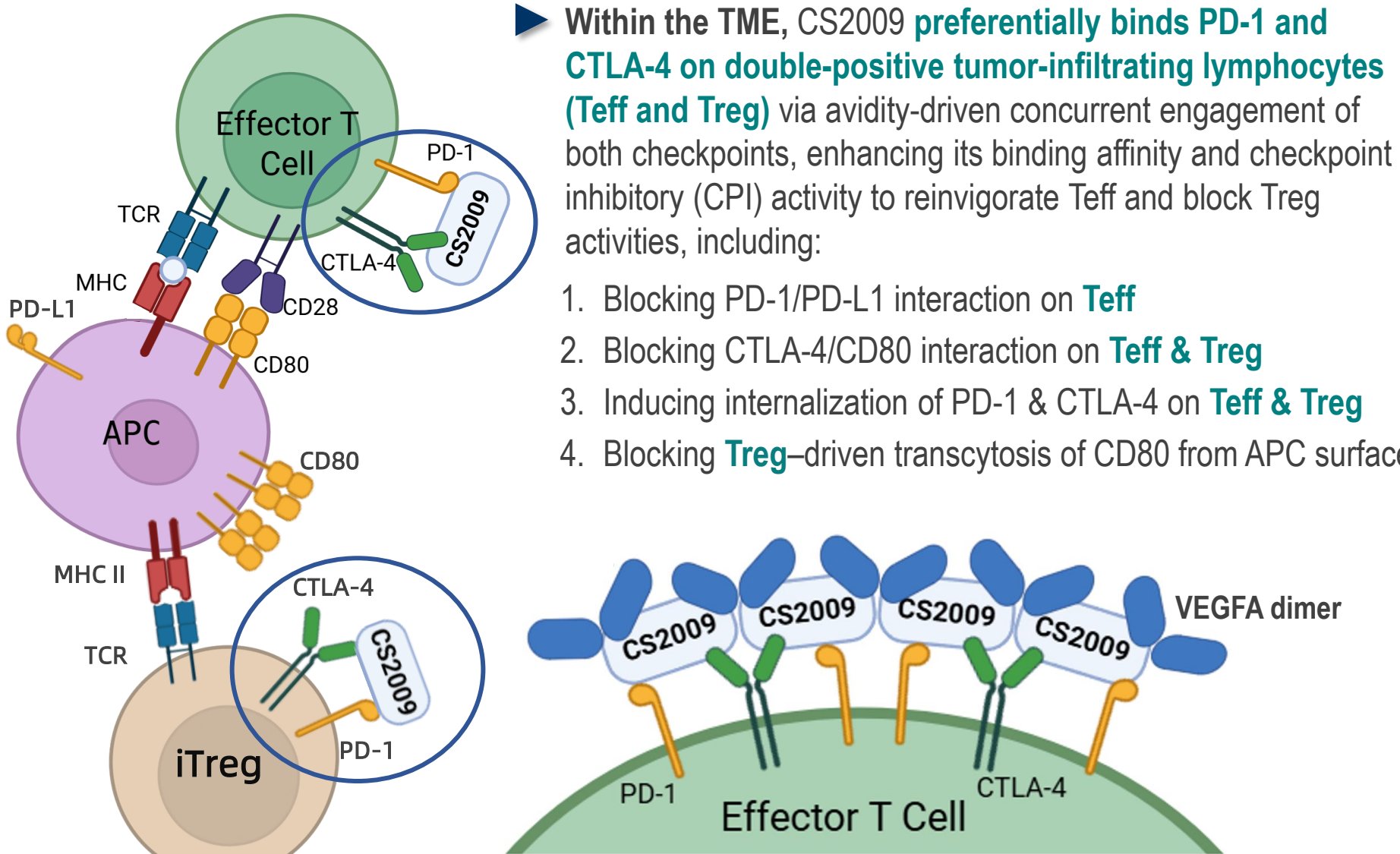
Innovative MOA: Multi-target engagement and synergistic interactions enhance CS2009's activities in TME while sparing peripheral CTLA-4+ T cells to widen its therapeutic window

Tumor Microenvironment (TME)

Within the TME, CS2009 preferentially binds PD-1 and CTLA-4 on double-positive tumor-infiltrating lymphocytes (Teff and Treg) via avidity-driven concurrent engagement of both checkpoints, enhancing its binding affinity and checkpoint inhibitory (CPI) activity to reinvigorate Teff and block Treg activities, including:

1. Blocking PD-1/PD-L1 interaction on **Teff**
2. Blocking CTLA-4/CD80 interaction on **Teff & Treg**
3. Inducing internalization of PD-1 & CTLA-4 on **Teff & Treg**
4. Blocking **Treg**-driven transcytosis of CD80 from APC surface

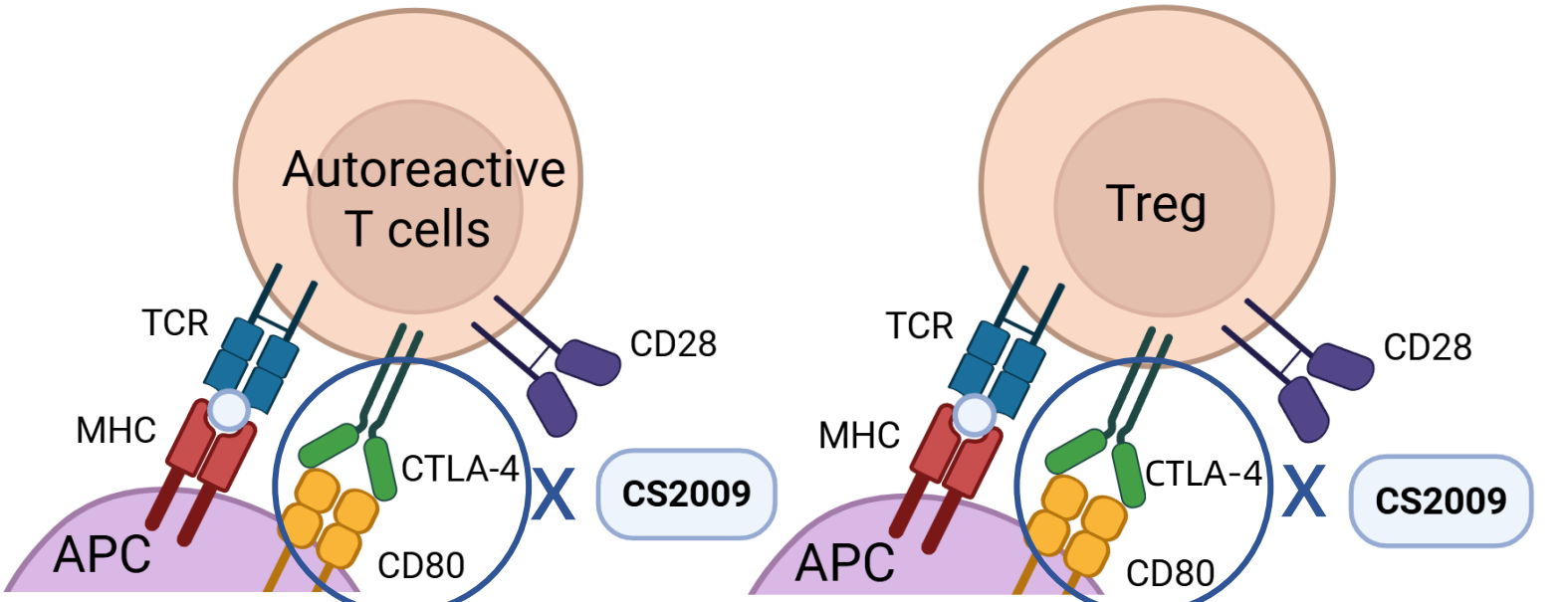
Within the TME, CS2009 forms clusters after crosslinking with VEGFA dimers, which strengthens its binding affinity to PD-1/ CTLA-4-expressing T cells and further amplifies its CPI activity



The diagram illustrates the Tumor Microenvironment (TME) where CS2009 acts. It shows an Antigen Presenting Cell (APC) interacting with an Effector T Cell (Teff) and an inhibitory Treg cell. The APC expresses MHC I, MHC II, PD-L1, CD80, and CD28. The Teff cell expresses TCR, PD-1, and CTLA-4. The Treg cell expresses TCR, PD-1, and CTLA-4. CS2009 is shown binding to PD-1 and CTLA-4 on both Teff and Treg cells. A legend at the bottom identifies the components: TCR (blue), MHC I (red), MHC II (red), CD28 (purple), PD-1 (orange), PD-L1 (orange), CTLA-4 (green), CD80 (yellow), VEGFA dimer (blue), and CS2009 (blue).

Peripheral

In the peripheral, In contract to high-affinity CTLA4 mAbs/ bispecific Abs, CS2009's monovalent CTLA-4 arm is unable to block CTLA-4/CD80 interaction due to low affinity, thus preventing CTLA-4 single-positive T cells from over-activation, and reducing systemic autoimmune toxicity



The diagram illustrates the Peripheral environment where CS2009's monovalent CTLA-4 arm is unable to block CTLA-4/CD80 interaction. It shows an Antigen Presenting Cell (APC) interacting with Autoreactive T cells and Treg cells. The APC expresses MHC I, MHC II, CD80, and CD28. The Autoreactive T cell expresses TCR and CTLA-4. The Treg cell expresses TCR and CTLA-4. CS2009 is shown binding to CTLA-4 on both Autoreactive T cells and Treg cells, but it is unable to block the CTLA-4/CD80 interaction. A legend at the bottom identifies the components: TCR (blue), MHC I (red), MHC II (red), CD28 (purple), PD-1 (orange), PD-L1 (orange), CTLA-4 (green), CD80 (yellow), VEGFA dimer (blue), and CS2009 (blue).

Study Design

A Phase 1/2 study (NCT06741644) is ongoing to evaluate CS2009 as **monotherapy or in combination with chemotherapy (XELOX or FOLFOX)** in patients with **metastatic colorectal cancer (mCRC)** across **later-line and first-line settings**.

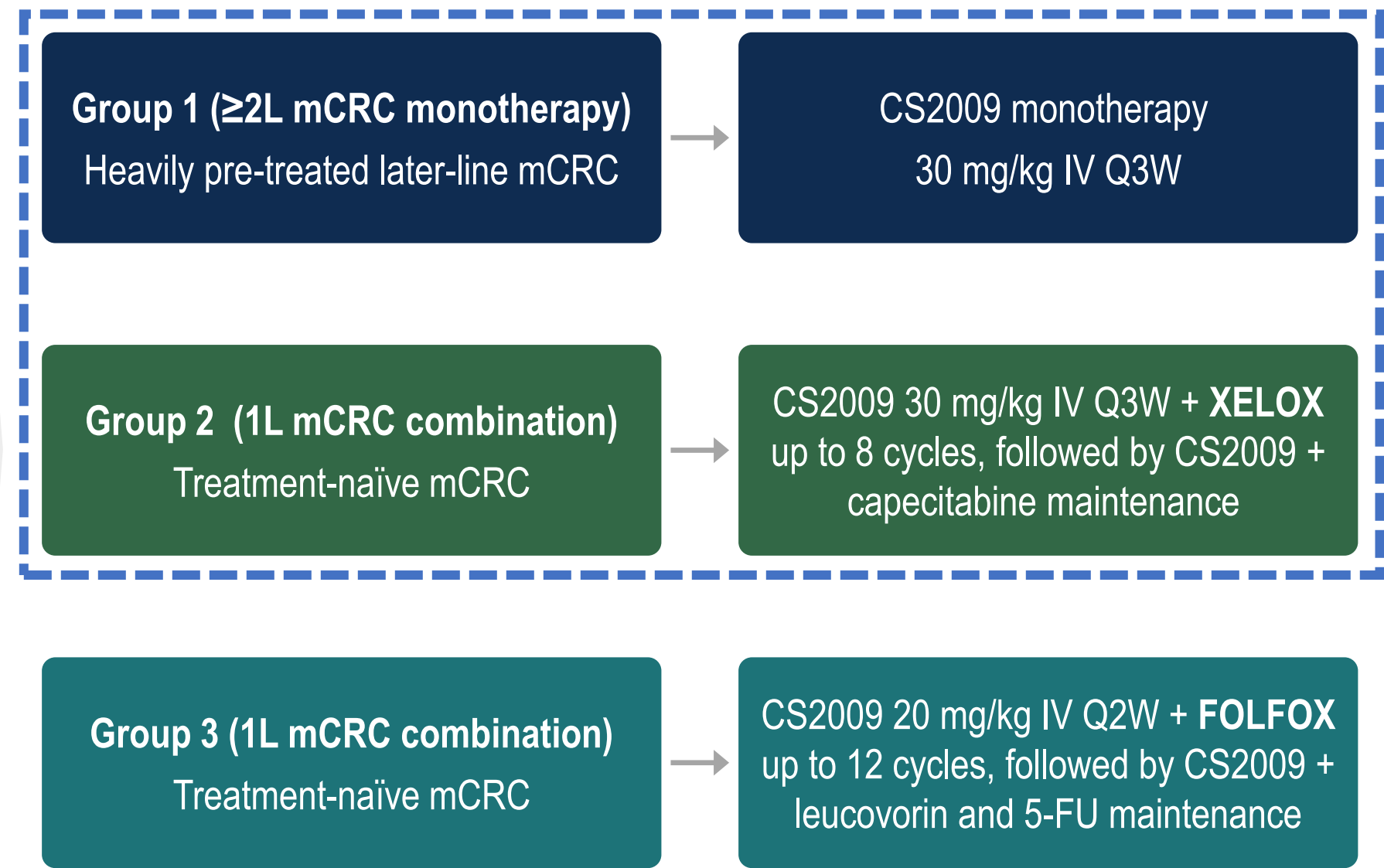
Key Eligibility Criteria

- Patients with mCRC who are previously untreated and ineligible for radical surgery or local therapy, without known MSI-H/dMMR, or those in the later-line setting with progression/intolerance to standard of care
- ECOG PS 0-1
- At least one measurable lesion

Endpoints: Safety, ORR per RECIST v1.1

Safety was assessed in all treated patients.

Efficacy was assessed in patients with at least one post-baseline tumor assessment per RECIST v1.1.



Treatment continued until
progressive disease,
unacceptable toxicity,
consent withdrawal, or
death

Note: Data from Group 1 and Group 2 are presented. Group 3 data remain immature due to short follow-up and are not presented.

ECOG PS: Eastern Cooperative Oncology Group performance status; IV: intravenous; L: line; FOLFOX: oxaliplatin + leucovorin + 5-FU; mCRC: metastatic colorectal cancer; MSI-H/dMMR: microsatellite instability-high/deficient mismatch repair; ORR: objective response rate; Q2W: once every 2 weeks; Q3W: once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; XELOX: capecitabine + oxaliplatin.

Baseline Characteristics

Characteristics	Group 1: Later-line mCRC CS2009 monotherapy (N=23)	Group 2: First-line mCRC CS2009 + XELOX (N=23)
Age, years		
median (range)	60.0 (40, 74)	59.0 (35, 75)
Male, n (%)	13 (56.5)	16 (69.6)
Race, n (%)		
Asian	20 (87.0)	22 (95.7)
White	3 (13.0)	1 (4.3)
ECOG PS, n (%)		
0	7 (30.4)	2 (8.7)
1	16 (69.6)	21 (91.3)
Location, n (%)		
Left colon or rectum	19 (82.6)	19 (82.6)
Right colon	4 (17.4)	4 (17.4)
MSI/MMR status, n (%)		
pMMR/MSS	22 (95.7)	22 (95.7)
Unknown	1 (4.3)	1 (4.3)

Characteristics	Group 1: Later-line mCRC CS2009 monotherapy (N=23)	Group 2: First-line mCRC CS2009 + XELOX (N=23)
Liver metastases, n (%)	15 (65.2)	16 (69.6)
Prior systemic anti-cancer therapy, n (%)		
1 line	11 (47.8)	0
2 lines	7 (30.4)	0
≥3 lines	5 (21.7)	0
Prior anti-angiogenic therapy, n (%)		
Yes	18 (78.3)	0
No	5 (21.7)	23 (100)
RAS mutation status*, n (%)		
Mutated	5 (21.7)	10 (43.5)
Wild type	7 (30.4)	6 (26.1)
BRAF mutation status*, n (%)		
Mutated	3 (13.0)	2 (8.7)
Wild type	8 (34.8)	15 (65.2)

Data cut off: 06 Sep 2026

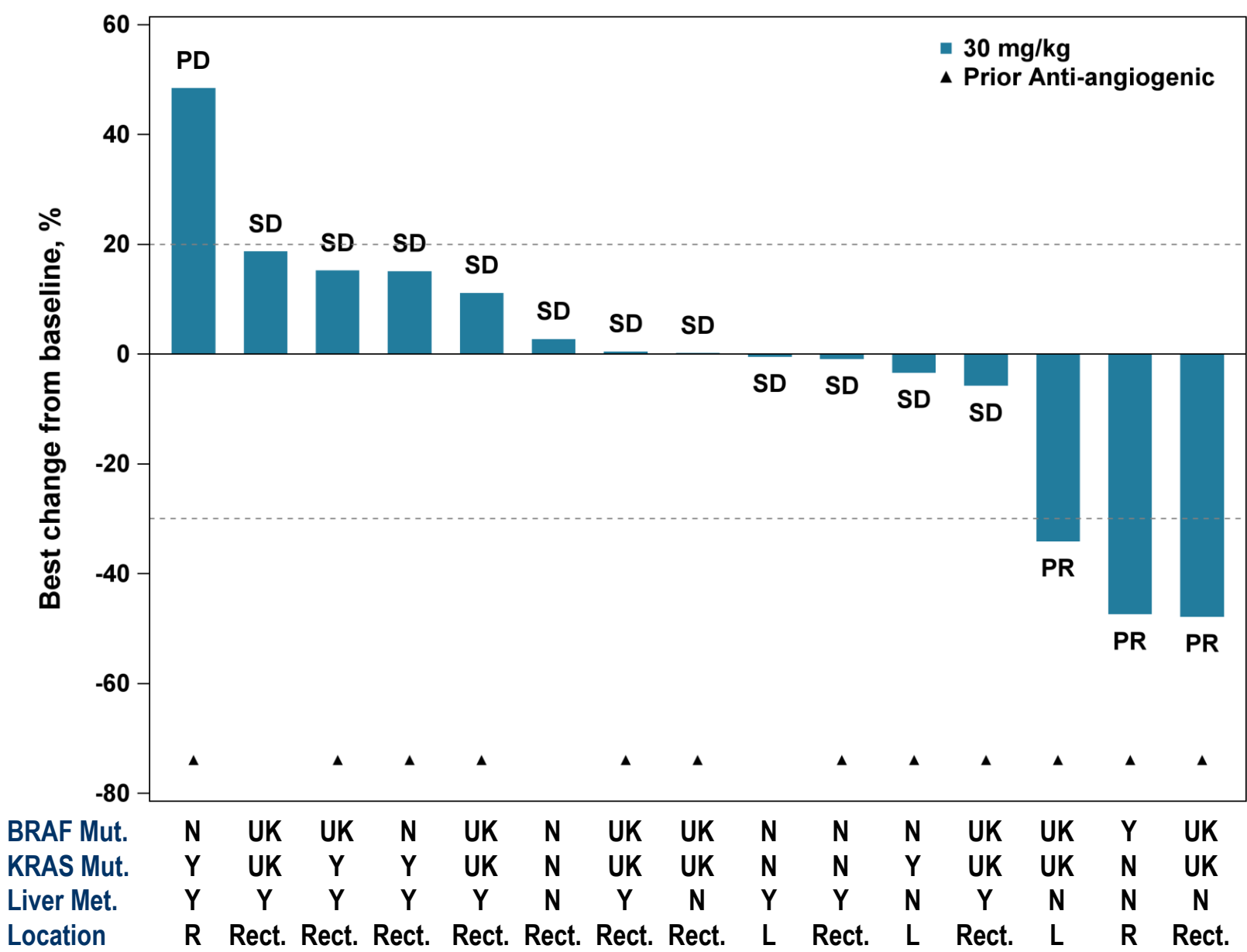
*Patients with unknown status were not shown.

ECOG PS: Eastern Cooperative Oncology Group performance status; mCRC: metastatic colorectal cancer; MSI/MMR: microsatellite instability/mismatch repair; pMMR/MSS: proficient mismatch repair/microsatellite stable; XELOX: capecitabine + oxaliplatin.

Efficacy: Group 1 (Later-line mCRC, monotherapy)

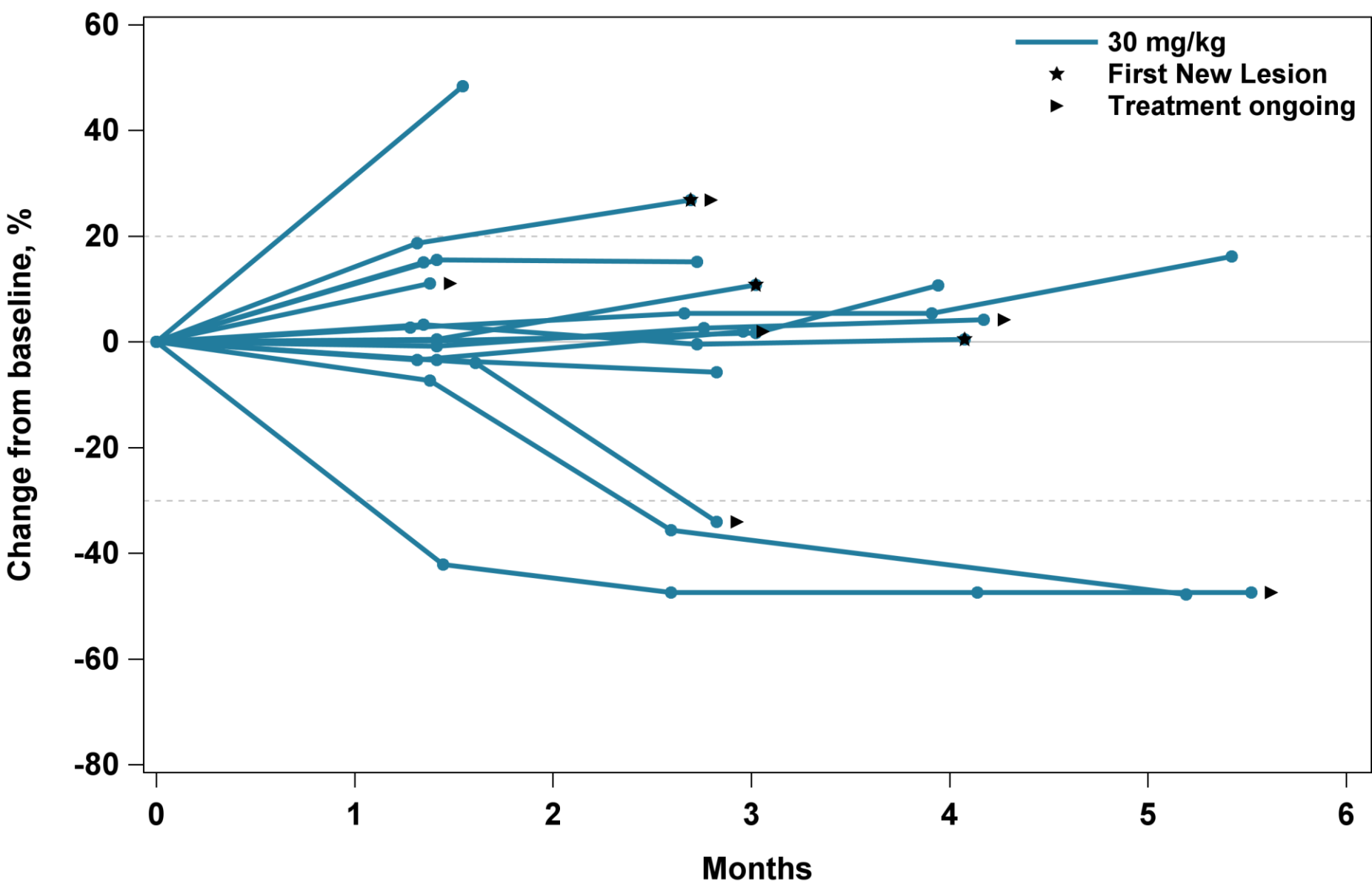
Preliminary data demonstrated promising clinical efficacy for CS2009 monotherapy in later-line mCRC

ORR 20.0% (3/15), DCR 93.3% (14/15)



Prior lines of therapy for patients achieving PR:

- Patient 1: XELOX → bevacizumab + irinotecan + capecitabine
- Patient 2: FOLFOX → bevacizumab + FOLFIRI → encorafenib + cetuximab
- Patient 3: trilaciclib/placebo + bevacizumab + FOLFOXIRI → capecitabine + bevacizumab → trifluridine + bevacizumab



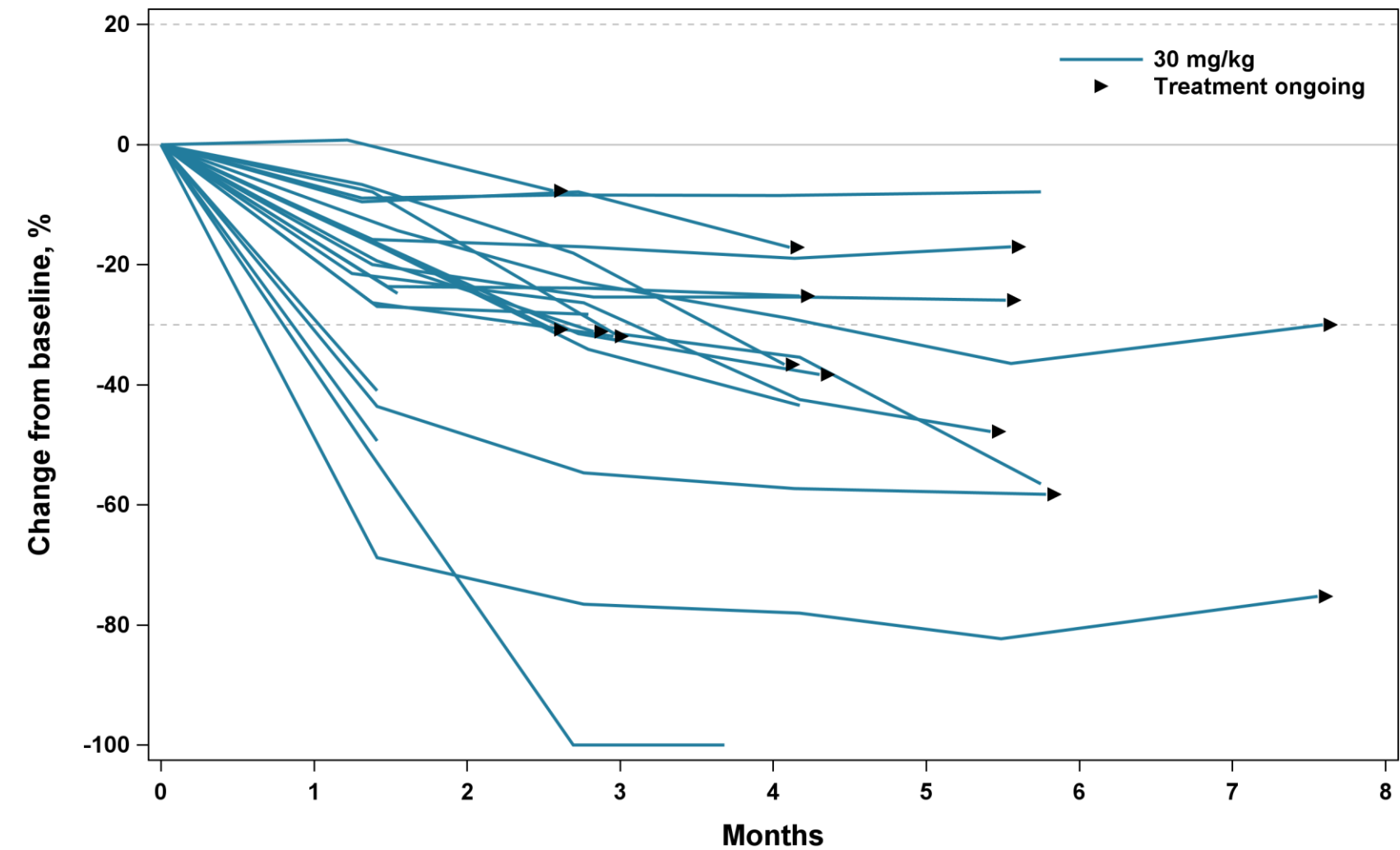
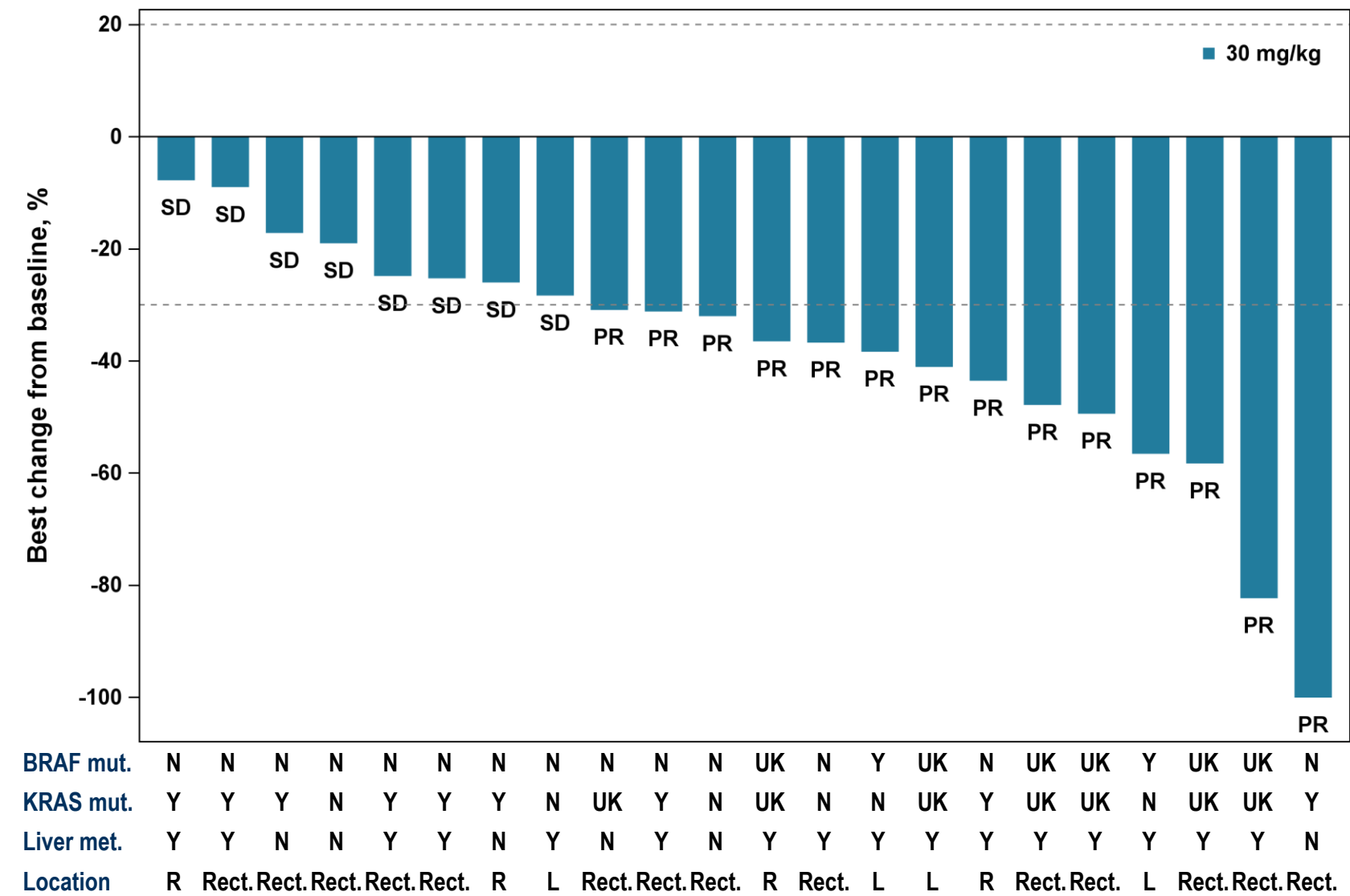
DCR: disease control rate; L: left colon; mCRC: metastatic colorectal cancer; Met.: metastasis; Mut.: mutation; N: no; ORR: objective response rate; PD: progressive disease; PR: partial response; R: right colon; Rect.: rectum; SD: stable disease; UK: unknown; Y: yes.

Efficacy: Group 2 (First-line mCRC, in combination with XELOX)

Preliminary data demonstrated promising clinical efficacy for CS2009 + XELOX in first-line mCRC, especially in patients with liver metastases

	All evaluable patients	Patients with liver metastases	Patients with baseline target-lesion SLD>100mm
ORR, % (n)	63.6% (14/22)	68.8% (11/16)	85.7% (6/7)
DCR, % (n)	100% (22/22)	100% (16/16)	100% (7/7)
Early tumor shrinkage ≥10% at 1 st tumor assessment*, % (n)	77.3% (17/22)	75.0% (12/16)	85.7% (6/7)

*Defined as the proportion of patients with ≥10% decrease in the pretreatment sum of diameters at first post-treatment tumor scan in target lesions.



DCR: disease control rate; L: left colon; mCRC: metastatic colorectal cancer; Met.: metastases; Mut.: mutation; N: no; ORR: objective response rate; PD: progressive disease; PR: partial response; R: right colon; Rect.: rectum; SD: stable disease; SLD: sum of the longest diameters; UK: unknown; XELOX: capecitabine + oxaliplatin; Y: yes.

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Safety

CS2009 monotherapy and in combination with chemotherapy demonstrated a favorable safety profile in mCRC

n (%)	Group 1: Later-line mCRC CS2009 Monotherapy (N=23)		Group 2: First-line mCRC CS2009 + XELOX (N=23)	
	Any-grade*	Grade ≥3	Any-grade*	Grade ≥3
Immune-related adverse event (irAE)				
Total	6 (26.1)	3 (13.0)	9 (39.1)	5 (21.7)
Adrenal insufficiency	2 (8.7)	0	0	0
Alanine aminotransferase increased	1 (4.3)	1 (4.3)	3 (13.0)	1 (4.3)
Amylase increased	1 (4.3)	1 (4.3)	3 (13.0)	0
Aspartate aminotransferase increased	1 (4.3)	1 (4.3)	3 (13.0)	1 (4.3)
Hyperthyroidism	1 (4.3)	1 (4.3)	2 (8.7)	0
Hypothyroidism	1 (4.3)	0	2 (8.7)	0
Lipase increased	0	0	4 (17.4)	1 (4.3)
Possible anti-VEGF-related TRAE				
Total	7 (30.4)	2 (8.7)	4 (17.4)	1 (4.3)
Proteinuria	4 (17.4)	0	2 (8.7)	1 (4.3)
Epistaxis	2 (8.7)	0	0	0
Urinary occult blood positive	2 (8.7)	0	1 (4.3)	0

*Any-grade irAEs and possible anti-VEGF-related TRAEs reported in ≥2 patients.

irAE: immune-related adverse event; mCRC: metastatic colorectal cancer; TRAE: treatment-related adverse event; VEGF: vascular endothelial growth factor; XELOX: capecitabine + oxaliplatin.

Conclusion

- CS2009 demonstrated promising anti-tumor activity in mCRC, both as monotherapy and in combination with chemotherapy, across first-line and later-line settings.
- CS2009 at 30 mg/kg Q3W was well tolerated with a favorable safety profile as monotherapy and in combination with chemotherapy.
- Enrollment is ongoing for both monotherapy and combination (+XELOX and +FOLFOX) cohorts.
- Results support further evaluation of CS2009 in first-line and later-line mCRC.

FOLFOX: oxaliplatin + leucovorin + 5-FU; mCRC: metastatic colorectal cancer; Q3W: once every 3 weeks; XELOX: capecitabine + oxaliplatin.

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