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INCA33890, a TGFβR2×PD-1 Bispecific Antibody, With Standard of Care (SoC) Anticancer Therapies for Microsatellite Stable Colorectal Cancer (MSS CRC)

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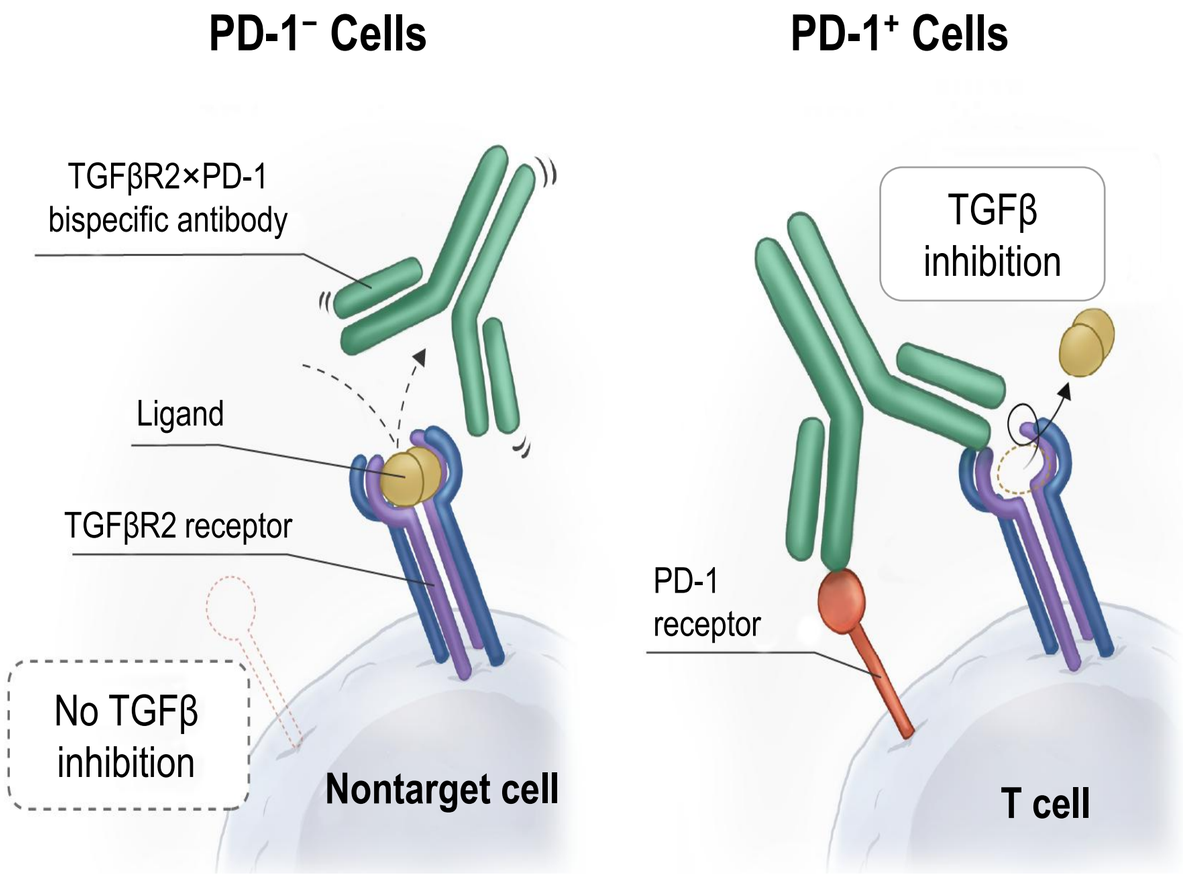
Disclosures

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Introduction

- TGFβ signalling in the TME inhibits antitumour immunity and is associated with limited benefit from anti–PD-1 treatment[1-3]
- INCA33890 is a bispecific immune checkpoint inhibitor targeting TGFβR2 and PD-1 signalling in PD-1$^+$ T cells[4-6]
- INCA33890 monotherapy was well tolerated up to 1200 mg q2w (RP2D: 900 mg q2w) and led to durable responses in patients with MSS CRC, including in those with liver metastases[7]
- Here, we report results of INCA33890 combined with SoC therapies in patients with MSS CRC



1. Mariathasan S, et al. *Nature*. 2018;554:544-548. 2. Sow HS, et al. *Cells*. 2019;8:320. 3. Li MO, et al. *Annu Rev Immunol*. 2006;24:99-146. 4. Wang LCS, et al. AACR 2023. Abstract 2936. 5. Guan J, et al. AACR 2025. Abstract 6071/12. 6. Kinder M, et al. AACR 2025. Abstract 4861/11. 7. Garralda E, et al. ESMO 2025. Presentation 1522MO.

MSS CRC, microsatellite stable colorectal cancer; PD-1, programmed cell death protein 1; q2w, every 2 weeks; RP2D, recommended phase 2 dose; SoC, standard of care; TGFβ, transforming growth factor beta; TGFβR2, transforming growth factor beta receptor 2; TME, tumour microenvironment.

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INCA33890-101 Study Design

INCA33890 Monotherapy[1,*]

Dose Escalation
(N=48)

100-1500 mg q2w and 900 mg q4w IV
in continuous 28-day cycles

RDEs (q2w IV)
(300, 600, 900, 1200 mg)

Dose Expansion
(N=236)

MSS CRC / PDAC / Gastric / GEJ
OC / NSCLC / SCCHN

Selected Eligibility Criteria
- Aged ≥18 years
- Diagnosis of advanced or metastatic (stage IV) MSS CRC
- ECOG PS 0 or 1

Primary Endpoints
- Safety and tolerability
- DLTs

Selected Secondary Endpoints
- ORR, DCR, DOR
- PK

Dose Escalation[†] and Expansion in MSS CRC (N=94)

INCA33890 (900 mg q2w IV) **+ FOLFOX[‡] + Bev[§]**	**INCA33890** (900 mg q2w IV) **+ FOLFIRI[‖] + Bev[§]**	**INCA33890** (900 mg q2w IV) **+ Bev[§]**	**INCA33890** (900 mg q2w IV) **+ Cetux[¶]**
n=43	n=6	n=39	n=6
No prior systemic therapy	Prior oxaliplatin but no irinotecan	Prior fluoropyrimidine, oxaliplatin, and irinotecan	Prior anti-EGFR inhibitor

1. Garralda E, et al. ESMO 2025. Presentation 1522MO.

Enrollment as of August 26, 2026. *Part 1 of the study investigating INCA33890 monotherapy has been described previously.[1] †Dose escalation in part 2 used a statistical hybrid design based on ≥3 DLT-evaluable patients per dose level. ‡Oxaliplatin: 85 mg/m^2 IV; leucovorin: 400 mg/m^2 IV (levoleucovorin 200 mg/m^2 could be substituted for leucovorin if locally approved); and 5-FU: 400mg/m^2 IV bolus (optional) followed by 2400mg/m^2 IV infusion. §Dosed at 5 mg/kg q2w. ‖Irinotecan: 180 mg/m^2 IV; leucovorin: 400 mg/m^2 IV (levoleucovorin 200 mg/m^2 could be substituted for leucovorin if locally approved); 5-FU: 400 mg/m^2 IV bolus (optional) followed by 2400 mg/m^2 IV infusion. ¶Dosed at 500 mg/m^2 q2w.
5-FU, fluorouracil; Bev, bevacizumab; Cetux, cetuximab; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; GEJ, gastroesophageal junction cancer; IV, intravenous; MSS CRC, microsatellite stable colorectal cancer; NSCLC, non-small cell lung cancer; OC, ovarian cancer; ORR, objective response rate; PDAC, pancreatic adenocarcinoma; PK, pharmacokinetics; q2w, every 2 weeks; q4w, every 4 weeks; RDE, recommended dose for expansion; SCCHN, squamous cell carcinoma of the head and neck.

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Baseline Characteristics

	Total (N=94)
Age, median (range), years	56 (20, 89)
Male sex, n (%)	50 (53.2)
Race, n (%)*	
White	54 (57.4)
Black or African American	6 (6.4)
Asian	23 (24.5)
ECOG PS, 0/1, %	55.3 / 44.7

	INCA33890 + Bev (n=39)†
Prior Therapies, n (%)	
5-FU, oxaliplatin, and irinotecan	37 (94.9)
Anti-EGFR	11 (28.2)
Anti-VEGF	34 (87.2)
Trifluridine and tipiracil, regorafenib, and/or fruquintinib	12 (30.8)
Anti–PD-(L)1	5 (12.8)

	1L INCA33890 + FOLFOX + Bev (n=43)†	2L INCA33890 + FOLFIRI + Bev (n=6)†	3L+ INCA33890 + Bev (n=39)†	Prior EGFR INCA33890 + Cetux (n=6)†
Lines of prior therapy, median (range)	0 (0, 1)	1 (1, 3)	2 (1, 5)	3 (2, 4)
Liver metastases, n (%)	29 (67.4)	5 (83.3)	24 (61.5)	4 (66.7)
Peritoneal metastases, n (%)	14 (32.6)	2 (33.3)	13 (33.3)	1 (16.7)
PD-L1 TAP, n (%)‡				
<1%	6 (14.0)	NA	8 (20.5)	NA
≥1%	26 (60.5)	NA	18 (46.2)	NA
Sidedness, n (%)§				
Left	28 (65.1)	4 (66.7)	21 (53.8)	3 (50.0)
Right	13 (30.2)	2 (33.3)	15 (38.5)	0
RAS mutant, n (%)¶	27 (62.8)	3 (50.0)	27 (69.2)	0 (0)
BRAF V600E mutant, n (%)‖	2 (4.7)	0	1 (2.6)	0
Left-sided, RAS/BRAF WT, n (%)	12 (27.9)	NA	NA	NA

*Missing values were other race (n=1) or not reported (n=10). †Patients enrolled in dose escalation: INCA33890 + FOLFOX + Bev, n=6; INCA33890 + FOLFIRI + Bev, n=6; INCA33890 + Bev, n=6; INCA33890 + Cetux, n=6. ‡Patients not shown have missing data (INCA33890 + FOLFOX + Bev, n=11; INCA33890 + Bev, n=13); results not reported for all groups due to sparsity of data (INCA33890 + FOLFIRI + Bev, n=2; INCA33890 + Cetux, n=1). §Patients not shown have unknown status or missing data (INCA33890 + FOLFOX + Bev, n=2; INCA33890 + Bev, n=3; INCA33890 + Cetux, n=3). ¶Patients not shown have wild type or unknown status (wild type: INCA33890 + FOLFOX + Bev, n=16; INCA33890 + FOLFIRI + Bev, n=2; INCA33890 + Bev, n=11; INCA33890 + Cetux, n=6; unknown: INCA33890 + FOLFIRI + Bev, n=1; INCA33890 + Bev, n=1). ‖Patients not shown have wild type or unknown status (wild type: INCA33890 + FOLFOX + Bev, n=38; INCA33890 + FOLFIRI + Bev, n=4; INCA33890 + Bev, n=32; INCA33890 + Cetux, n=4; unknown: INCA33890 + FOLFOX + Bev, n=3; INCA33890 + FOLFIRI + Bev , n=2; INCA33890 + Bev, n=6; INCA33890 + Cetux, n=2).

5-FU, 5-fluorouracil; Bev, bevacizumab; BRAF, B-Raf proto-oncogene, serine/threonine kinase; Cetux, cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; NA, not applicable; PD-(L)1, programmed cell death protein 1 or programmed death-ligand 1; PD-L1 TAP, programmed death-ligand 1 tumour area positivity; RAS, rat sarcoma; VEGF, vascular endothelial growth factor; WT, wild type.

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Safety: Summary

- No DLTs were observed in any cohort and relative dose intensity of SoC was maintained in combination with INCA33890
- INCA33890 discontinuations in the FOLFOX + Bev cohort were due to nephritis, myocarditis, rash, and drug-induced liver injury
    - These led to EOT and SoC discontinuation per protocol

TEAE, n (%)	INCA33890 + FOLFOX + Bev (n=43)	INCA33890 + FOLFIRI + Bev (n=6)	INCA33890 + Bev (n=39)	INCA33890 + Cetux (n=6)
Any grade	43 (100)	6 (100)	37 (94.9)	6 (100)
Grade ≥3	31 (72.1)	5 (83.3)	13 (33.3)	4 (66.7)
Immune related	23 (53.5)	2 (33.3)	16 (41.0)	5 (83.3)
Grade ≥3	6 (14.0)	1 (16.7)	4 (10.3)	1 (16.7)
Serious	19 (44.2)	3 (50.0)	9 (23.1)	1 (16.7)
Fatal	0	0	0	0
Leading to INCA33890:				
Dose delay	26 (60.5)	5 (83.3)	14 (35.9)	3 (50.0)
Discontinuation	4 (9.3)*	0	0	0
Leading to SoC:				
Dose delay	29 (67.4)	5 (83.3)	16 (41.0)	3 (50.0)
Dose reduction	29 (67.4)†	4 (66.7)†	0	0
Discontinuation	3 (7.0)‡	0	0	0

*All grade 3. Drug-induced liver injury was related to trimethoprim-sulfamethoxazole usage and was not deemed to be related to INCA33890. †Dose reduction in INCA33890 + FOLFOX + Bev: 5-FU, n=21 (48.8%); oxaliplatin, n=21 (48.8%); with INCA33890 + FOLFIRI + Bev: 5-FU n=4 (66.7%), folinic acid n=3 (50.0%); irinotecan, n=3 (50.0%). ‡Discontinuation of individual treatment components: 5-FU, n=3 (7.0%); Bev, n=4 (9.3%); folinic acid, n=5 (11.6%); oxaliplatin, n=23 (53.5%).
Bev, bevacizumab; Cetux, cetuximab; DLT, dose-limiting toxicity; EOT, end of treatment; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; SoC, standard of care; TEAE, treatment-emergent adverse event.

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Safety: Most Common TEAEs

TEAEs, n (%)*	INCA33890 + FOLFOX + Bev (n=43)		INCA33890 + FOLFIRI + Bev (n=6)		INCA33890 + Bev (n=39)		INCA33890 + Cetux (n=6)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neuropathy†	33 (76.7)	1 (2.3)	2 (33.3)	0	0	0	0 (0)	0
Neutropenia‡	25 (58.1)	15 (34.9)	5 (83.3)	4 (66.7)	1 (2.6)	0	1 (16.7)	0
Stomatitis	20 (46.5)	3 (7.0)	3 (50.0)	1 (16.7)	11 (28.2)	1 (2.6)	3 (50.0)	0
Nausea	19 (44.2)	1 (2.3)	1 (16.7)	1 (16.7)	4 (10.3)	0	3 (50.0)	0
Diarrhoea	18 (41.9)	1 (2.3)	3 (50.0)	1 (16.7)	12 (30.8)	2 (5.1)	1 (16.7)	0
Fatigue	18 (41.9)	0	4 (66.7)	0	10 (25.6)	1 (2.6)	4 (66.7)	1 (16.7)
Anaemia	15 (34.9)	1 (2.3)	3 (50.0)	1 (16.7)	7 (17.9)	2 (5.1)	0 (0)	0
Infusion-related reaction	15 (34.9)	1 (2.3)	2 (33.3)	0	2 (5.1)	0	0 (0)	0
Related to INCA33890	3 (7.0)	0 (0)	2 (33.3)	0	2 (5.1)	0	0 (0)	0
Related to SoC	12 (27.9)§	1 (2.3)	0	0	1 (2.6)¶	0	0 (0)	0
Vomiting	14 (32.6)	0	1 (16.7)	0	4 (10.3)	0	4 (66.7)	0
Leukopenia	13 (30.2)	2 (4.7)	4 (66.7)	3 (50.0)	0	0	0 (0)	0
Decreased appetite	12 (27.9)	1 (2.3)	3 (50.0)	1 (16.7)	6 (15.4)	0	0 (0)	0
Hypertension	12 (27.9)	4 (9.3)	0	0	4 (10.3)	1 (2.6)	0 (0)	0

*TEAEs listed are those occurring in ≥25% of the INCA33890 + FOLFOX + Bev group and ordered by frequency in the INCA33890 + FOLFOX + Bev group. †Neuropathy peripheral includes neuropathy peripheral, peripheral sensory neuropathy, and paraesthesia. ‡Neutropenia includes neutropenia and neutrophil count decreased. §11 related to oxaliplatin and 1 related to Bev. ¶Related to Bev.

Bev, bevacizumab; Cetux, cetuximab; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; SoC, standard of care; TEAE, treatment-emergent adverse event.

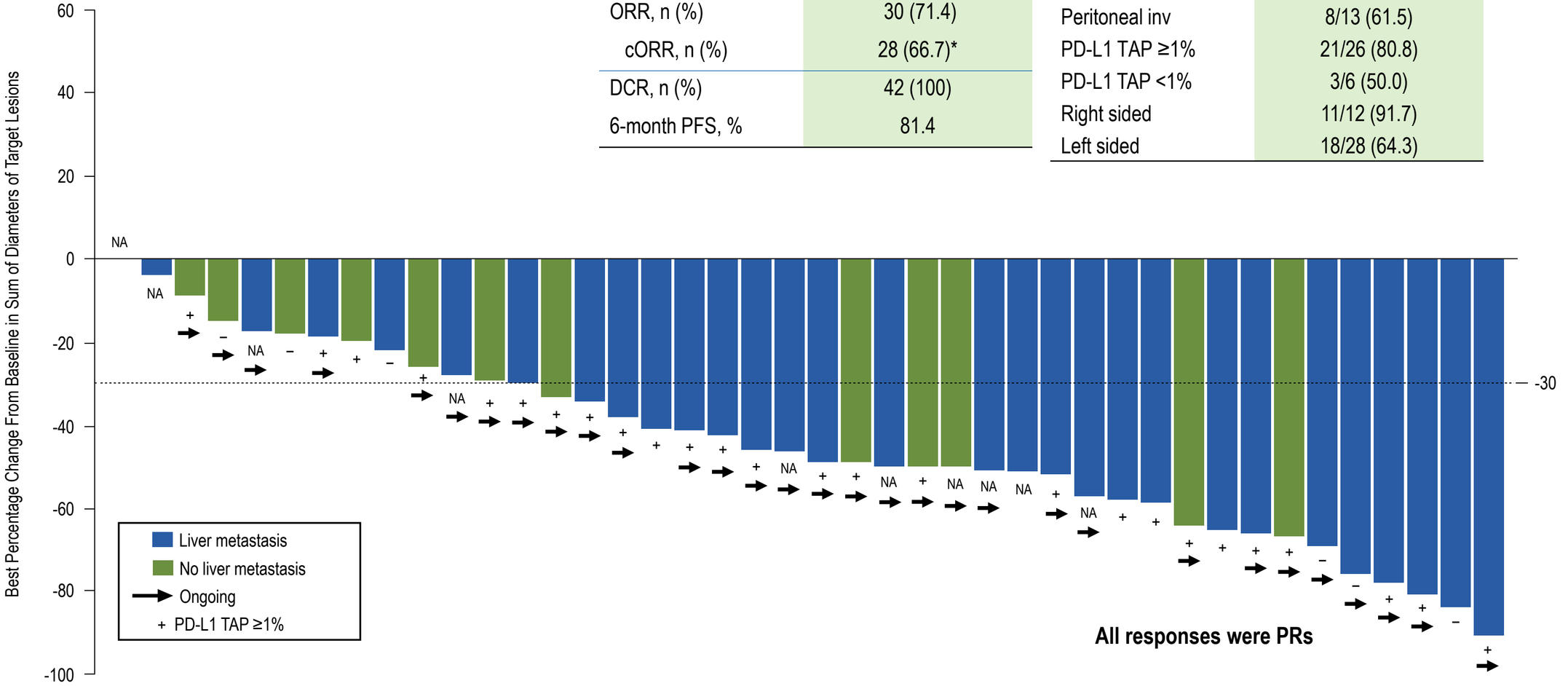
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Efficacy: 1L INCA33890 + FOLFOX + Bev

	Efficacy evaluable (n=42)
ORR, n (%)	30 (71.4)
cORR, n (%)	28 (66.7)*
DCR, n (%)	42 (100)
6-month PFS, %	81.4

Subgroup	ORR, n/N (%)
Liver mets	24/29 (82.8)
Peritoneal inv	8/13 (61.5)
PD-L1 TAP ≥1%	21/26 (80.8)
PD-L1 TAP <1%	3/6 (50.0)
Right sided	11/12 (91.7)
Left sided	18/28 (64.3)



Median follow-up of 5.6 months. *1 pending follow-up scan; 1 with target lesion removal (primary tumour resection due to intestinal obstruction, follow-up nonevaluable by RECIST).

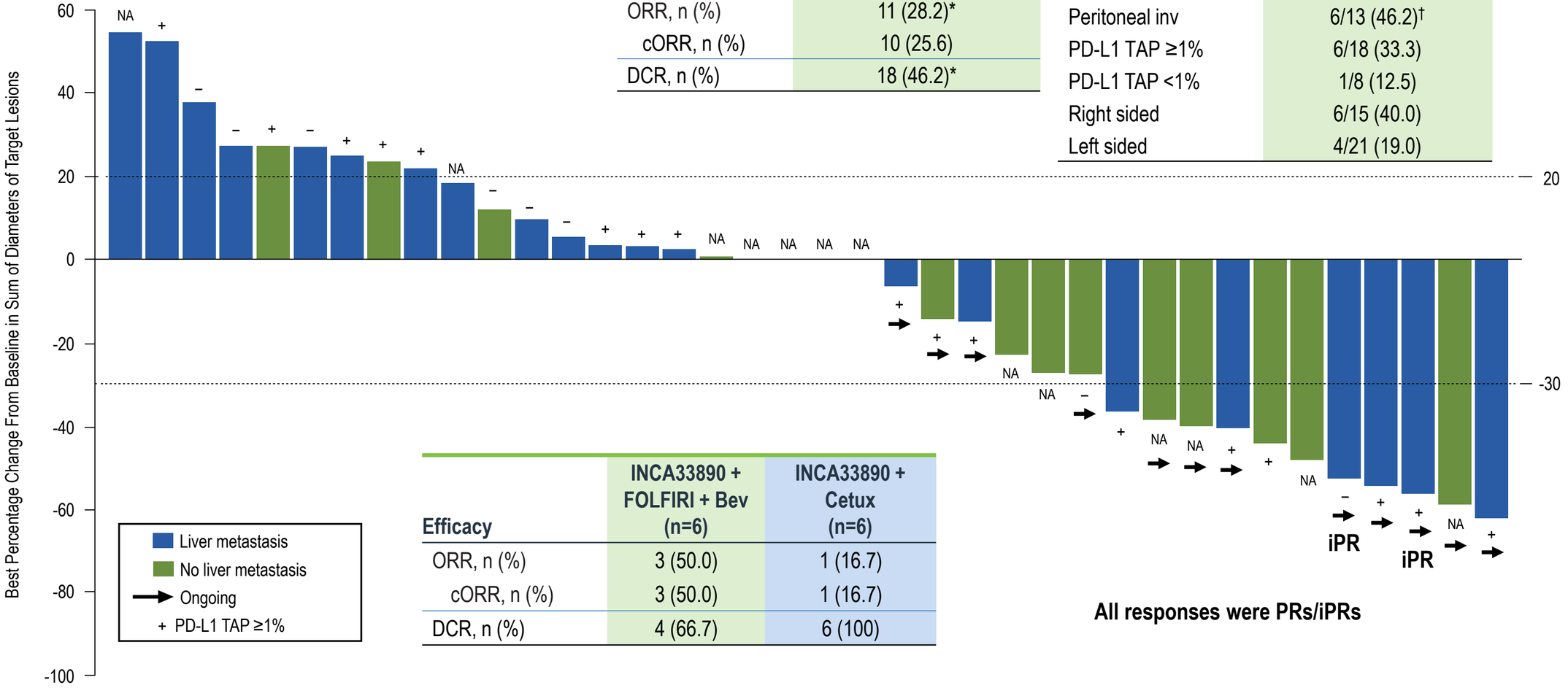
Bev, bevacizumab; cORR, confirmed objective response rate; DCR, disease control rate; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; inv, involvement; mets, metastases; NA, not available; ORR, objective response rate; PD, progressive disease; PD-L1 TAP, programmed death-ligand 1 tumour area positivity; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.

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Efficacy: 3L+ INCA33890 + Bev

	Efficacy Evaluable (n=39)
ORR, n (%)	11 (28.2)*
cORR, n (%)	10 (25.6)
DCR, n (%)	18 (46.2)*

Subgroup	ORR, n/N (%)
Liver mets	6/24 (25.0)*
Peritoneal inv	6/13 (46.2)†
PD-L1 TAP ≥1%	6/18 (33.3)
PD-L1 TAP <1%	1/8 (12.5)
Right sided	6/15 (40.0)
Left sided	4/21 (19.0)



Efficacy	INCA33890 + FOLFIRI + Bev (n=6)	INCA33890 + Cetux (n=6)
ORR, n (%)	3 (50.0)	1 (16.7)
cORR, n (%)	3 (50.0)	1 (16.7)
DCR, n (%)	4 (66.7)	6 (100)

All responses were PRs/iPRs

*PR, including 2 iPR. †PR, including 1 iPR.

3L, third line; Bev, bevacizumab; cORR, confirmed objective response rate; Cetux, cetuximab; DCR, disease control rate; FOLFIRI, folinic acid, fluorouracil, and irinotecan; inv, involvement; iPR, immune partial response; mets, metastases; NA, not available; ORR, objective response rate; PD-L1 TAP, programmed death-ligand 1 tumour area positivity; PR, partial response.

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Conclusions

- INCA33890 combinations with SoC in patients with MSS CRC were tolerable with no DLTs
- Encouraging preliminary efficacy was seen across cohorts and within subgroups, including in patients with liver or peritoneal metastases
  - In 1L with INCA33890 + FOLFOX + Bev, ORR was 71.4%, DCR was 100%, and 6-month PFS was 81.4%
    - ORR was 82.8% in patients with liver metastases and 61.5% in those with peritoneal metastases
    - ORR was 80.8% in patients who were PD-L1 TAP ≥1%
  - In 3L+ with INCA33890 + Bev, ORR was 28.2% and DCR was 46.2%
    - ORR was 25.0% in patients with liver metastases and 46.2% in those with peritoneal metastases
    - ORR was 33.3% in patients who were PD-L1 TAP ≥1%
- Enrolment is ongoing in the phase 3 NEXERA-303 study (NCT07284849) evaluating the safety and efficacy of 1L FOLFOX + Bev ± INCA33890 in patients with MSS mCRC

1L, first line; 3L, third line; Bev, bevacizumab; Cetux, cetuximab; DCR, disease control rate; DLT, dose-limiting toxicity; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; mCRC, metastatic colorectal cancer; MSS, microsatellite stable; ORR, objective response rate; PD-L1 TAP, programmed death-ligand 1 tumour area positivity; PFS, progression-free survival; SoC, standard of care.

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