Preliminary Results From a Randomized, Open-Label, Phase 2 Study of Botensilimab With or Without Balstilimab in Refractory Microsatellite Stable Metastatic Colorectal Cancer With No Liver Metastases

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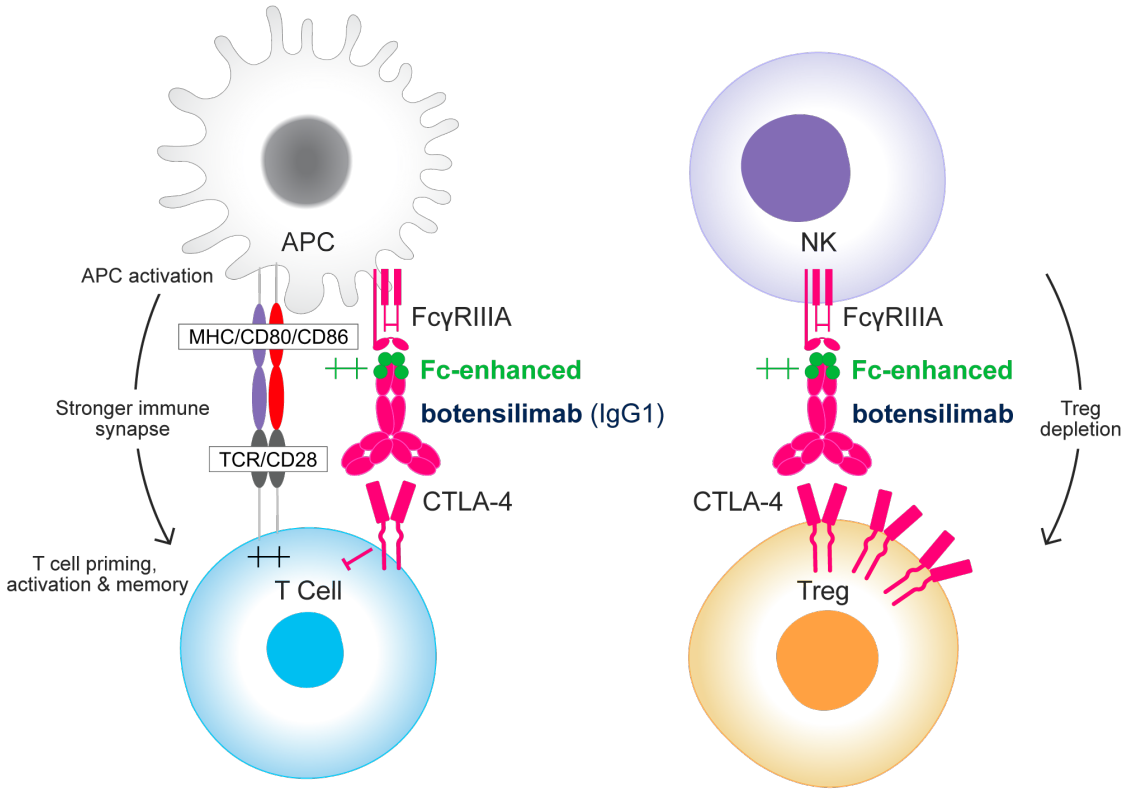
Summary

- **BOT/BAL in MSS mCRC**: BOT/BAL produces deep and durable responses in a meaningful proportion of patients with MSS mCRC, even in later lines of therapy
- **Consistency in Late-Line Metastatic Disease**: Across two trials with over 200 patients, reproducible response rates (~20%) and durable outcomes were observed, supporting the clinical relevance of this combination
- **Strength of the Data**: Substantial durability in responses, including some patients with no active disease for over 2 years and no detectable ctDNA, strongly supports advancement into registrational trials

Background

- CRC is one of the most diagnosed cancers globally[1]
- There is a growing epidemic of CRC affecting younger individuals[2]
- Patients with chemo-refractory MSS mCRC face a lack of effective treatment options[3,4]
- Traditional immune-based treatments have consistently failed in MSS mCRC[3-6]

Botensilimab and Balstilimab Mechanism of Action



Botensilimab (BOT)[1-3]

Multifunctional Fc-enhanced CTLA-4 Inhibitor

- Enhances T cell priming, activation and memory
- Activates APCs / myeloid cells
- Reduces intratumoral regulatory T cells
- Improves safety by reducing complement-mediated toxicities (eg, hypophysitis)

Balstilimab (BAL)[4,5]

PD-1 Inhibitor

- Functionally comparable to other PD-1 inhibitors

1. Bullock A, et al. *Nature Medicine*. 2024; doi:10.1038/s41591-024-03083-7; Copyright clearance: http://creativecommons.org/licenses/by/4.0/
2. Waight, et al. *Cancer Cell*. 2018;33(6): 1033-1047.
3. Chand D, et al. *Cancer Discov*. 2024;doi: 10.1158/2159-8290.CD-24-0190.
4. O'Malley, et al. *Gynecol Oncol*. 2021; 163:274-280.
5. O'Malley, et al. *J Clin Oncol*. 2022; 40(7):762-771.

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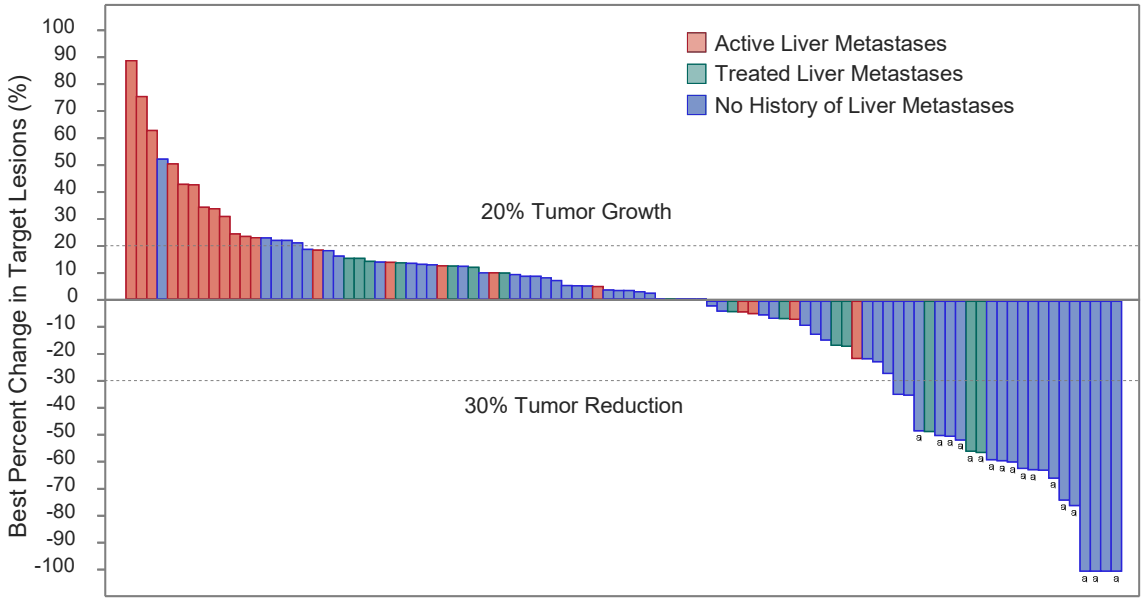
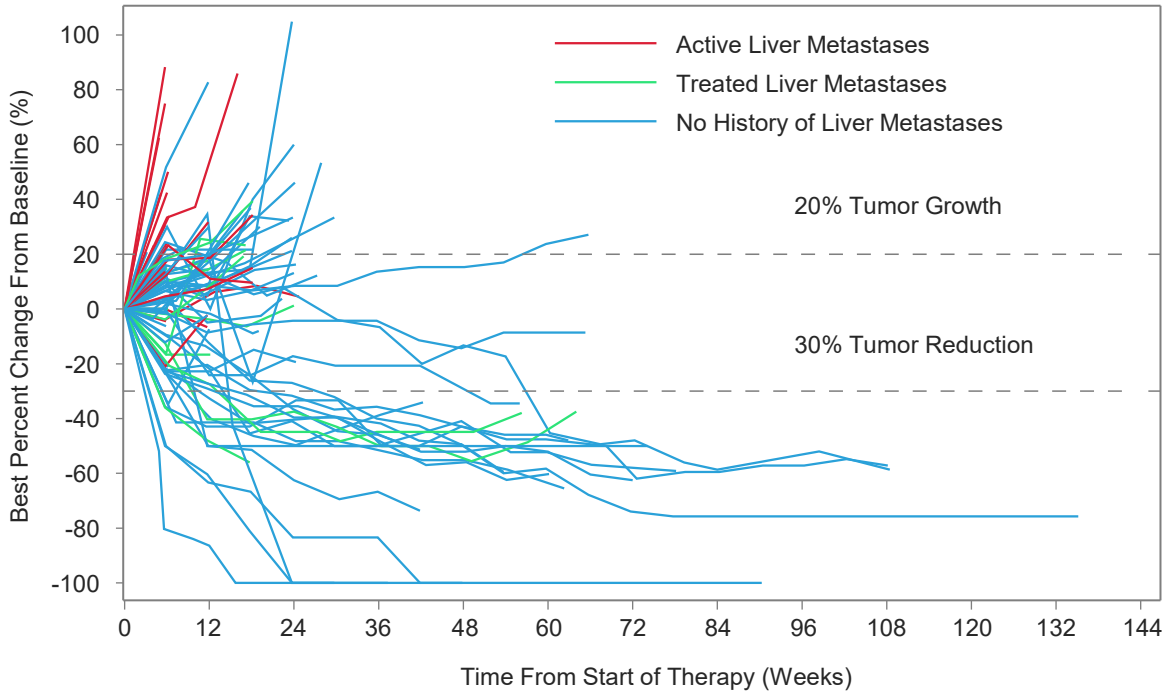
Botensilimab Plus Balstilimab in Relapsed/Refractory Microsatellite Stable Metastatic Colorectal Cancer: A Phase 1 Trial[1]





BOT / BAL ITT NLM Population	1 mg/kg BOT / BAL n=36	2 mg/kg BOT / BAL n=41	Overall N=77
Confirmed ORR, % (95% CI)	25% (12–42)	22% (11–38)	**23%*** (15–34)

*23% after the data cutoff (29 November 2023).

1. Bullock A, et al. *Nature Medicine*. 2024; doi:10.1038/s41591-024-03083-7;

Global Phase 2 Trial Design

Objectives

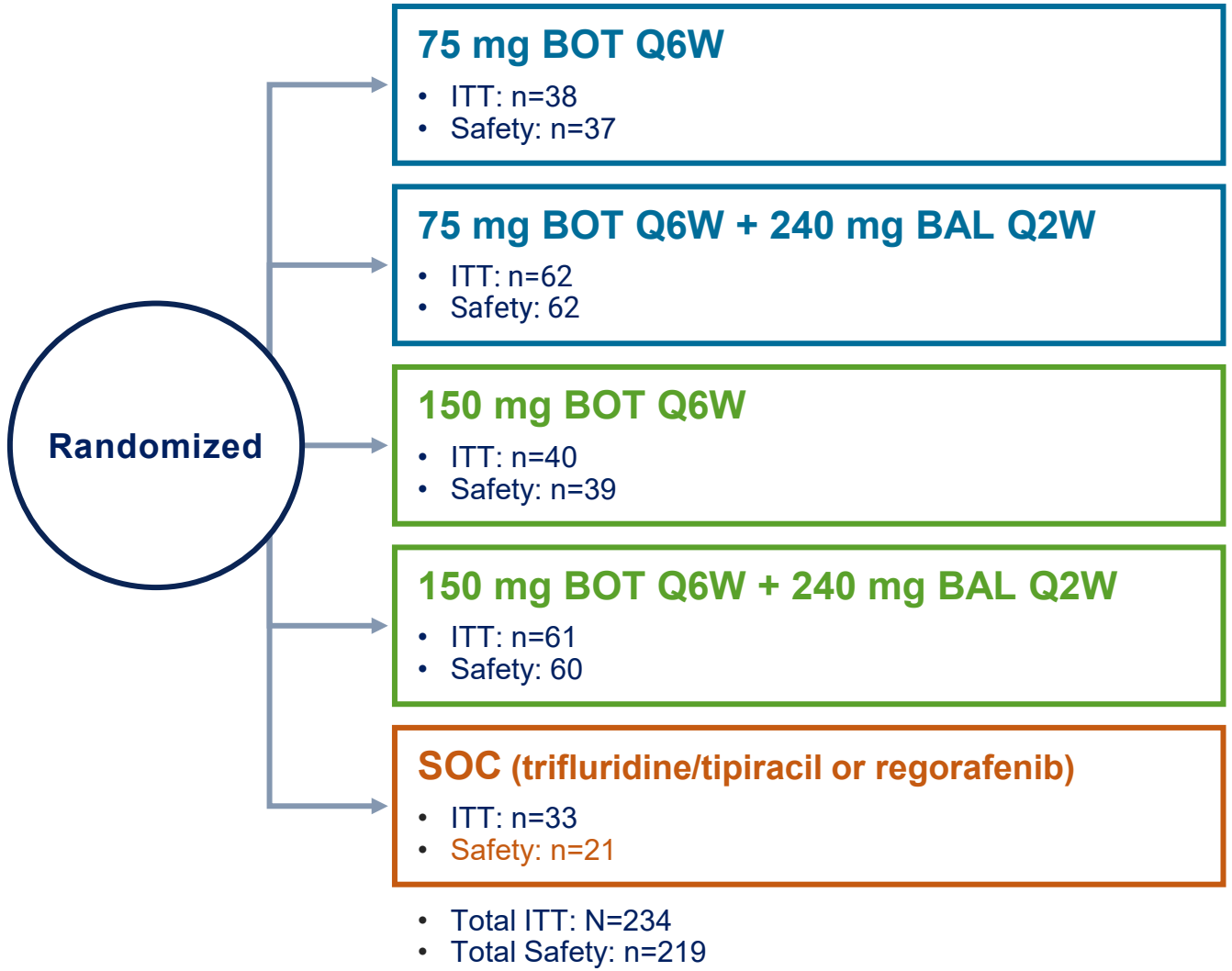
- Dose optimization
- Contribution of components

Patient Population

- Not MSI-H or dMMR
- No active liver metastases
- Previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy and, if medically appropriate with anti-VEGF and/or anti-EGFR

Endpoints

- Primary: ORR by investigator assessment per RECIST 1.1
- Secondary: DOR, PFS, and OS
- Safety: AEs
- PK/Immunogenicity



- Total ITT: N=234
- Total Safety: n=219

Enrollment completed October 2023; data cutoff: 11 November 2024. NCT05608044: https://clinicaltrials.gov/study/NCT05608044.

Demographics and Disease Characteristics

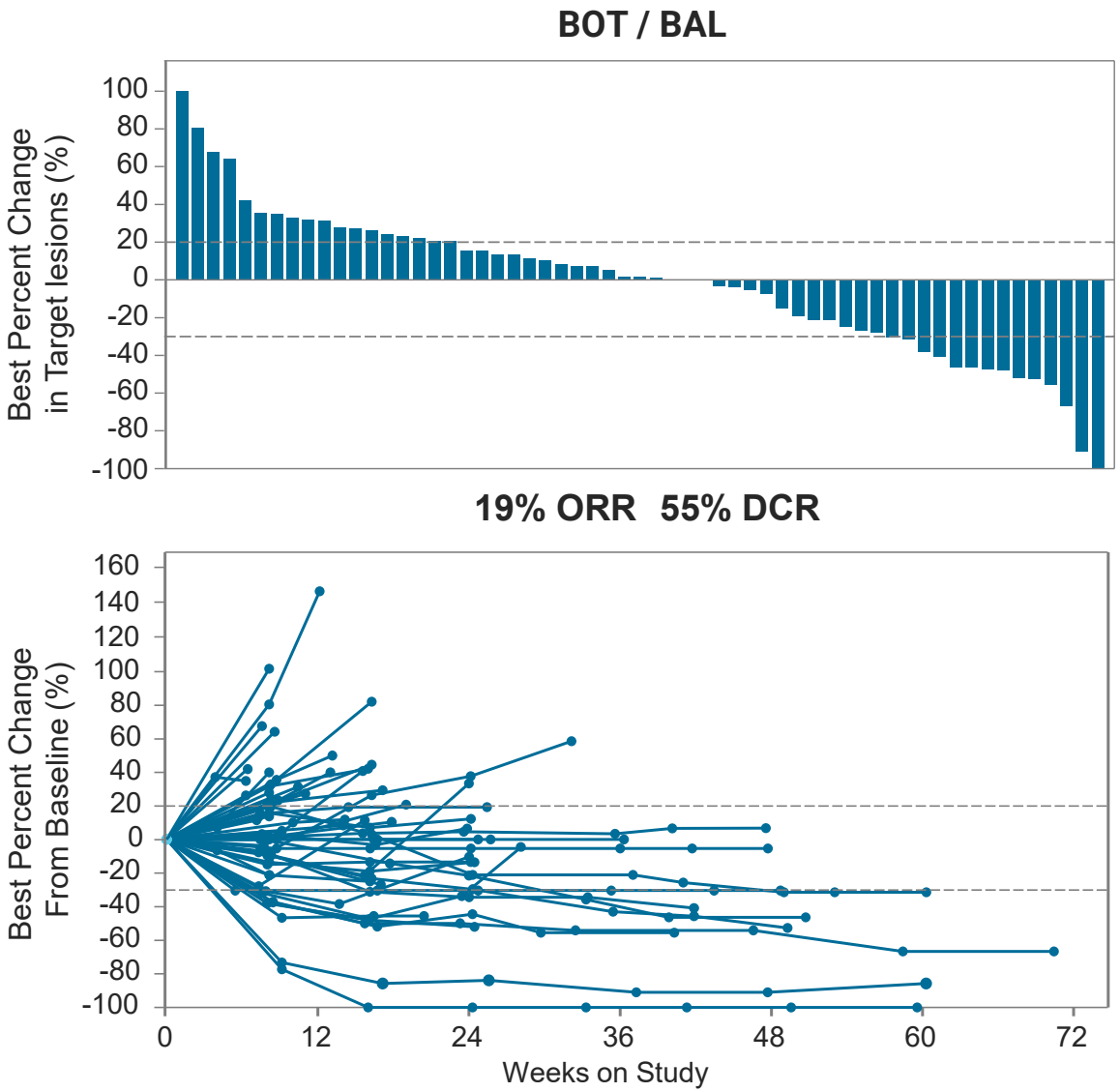
	BOT 75 mg Q6W		BOT 150 mg Q6W		SOC
	BOT / BAL n=62	Monotherapy n=38	BOT / BAL n=61	Monotherapy n=40	Trifluridine/Tipiracil or Regorafenib n=33
Median age, years (range)	58 (23–84)	56 (25–77)	60 (23–75)	56 (31–84)	59 (30–90)
Female, n (%)	35 (56)	19 (50)	32 (52)	20 (50)	10 (30)
ECOG performance status 0, n (%)	34 (55)	21 (55)	36 (59)	19 (48)	18 (55)
Median time since metastatic diagnosis, months (range)	26.6 (0.7–149.3)	34.7 (1.4–102.7)	29.2 (1.1–100.7)	25.1 (9.2–175.8)	40.7 (12.1–89.8)
Median sum of diameter of targets, mm (range)	56.5 (12.0–308)	41.5 (10.0–209.0)	47.0 (11.0–135.0)	40.5 (10.0–200.0)	42.0 (10.0–127.0)
Peritoneal disease, n (%)	27 (44)	16 (42)	20 (33)	10 (25)	9 (27)
Colon, n (%)	41 (66)	22 (58)	33 (54)	21 (53)	20 (61)
Rectal, n (%)	21 (34)	16 (42)	28 (46)	19 (48)	13 (39)
Treated LM, n (%)	10 (16)	6 (16)	14 (23)	12 (30)	11 (33)
Prior bevacizumab, n (%)	54 (87)	32 (84)	53 (87)	33 (83)	28 (85)
***RAS* mutant, n (%)**	42 (68)	22 (58)	38 (62)	25 (63)	16 (48)
***BRAF* mutant, n (%)**	1 (2)	0 (0)	2 (3)	3 (8)	2 (6)

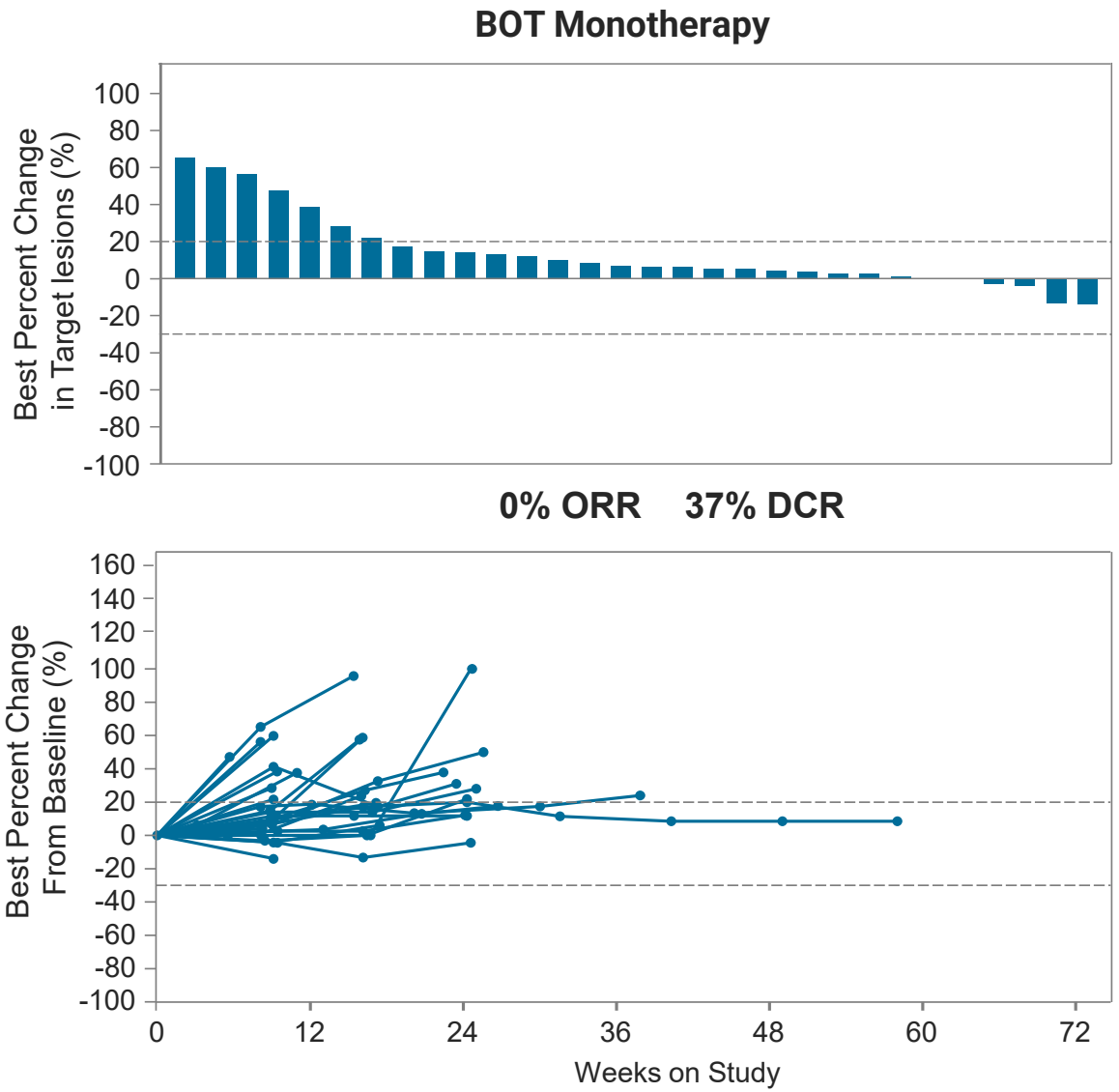
Summary of Efficacy

	BOT 75 mg Q6W		BOT 150 mg Q6W		SOC
	BOT / BAL n=62	**Monotherapy n=38**	**BOT / BAL n=61**	**Monotherapy n=40**	**Trifluridine/Tipiracil or Regorafenib n=33**
Confirmed ORR, n (%) 95% CI	**12 (19%)** 10–31	**0 (0%)** 0–9	**5 (8%)** 3–18	**3 (8%)** 2–20	**0 (0%)** 0–9
CR	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)
PR	12 (19)	0 (0)	5 (8)	2 (5)	0 (0)
SD	22 (35)	14 (37)	28 (46)	12 (30)	12 (36)
PD	26 (42)	20 (53)	23 (38)	21 (53)	8 (24)
NE	2 (3)	4 (11)	5 (8)	4 (10)	13 (39)
DCR, n (%) 95% CI	34 (55) 42–68	14 (37) 22–54	33 (54) 41–67	15 (38) 23–54	12 (36) 20–55
Median follow up, months (range)	12.7 (1.6–19.7)	9.8 (0.6–17.7)	12.9 (0.1–20.6)	13.4 (0.7–21.1)	10.9 (0.0–17.7)

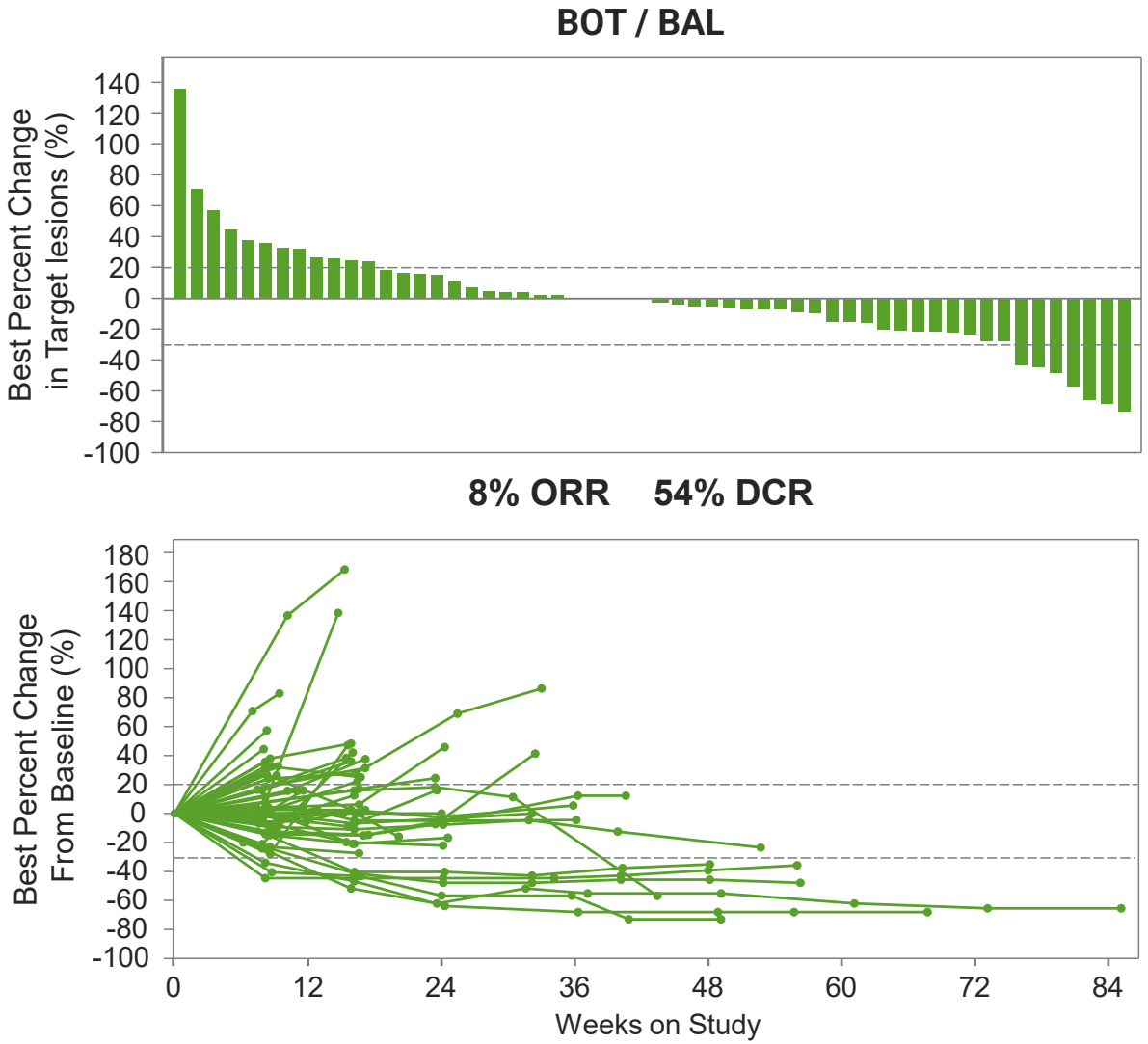
DOR not mature with **14/20 (70%)** of responses ongoing

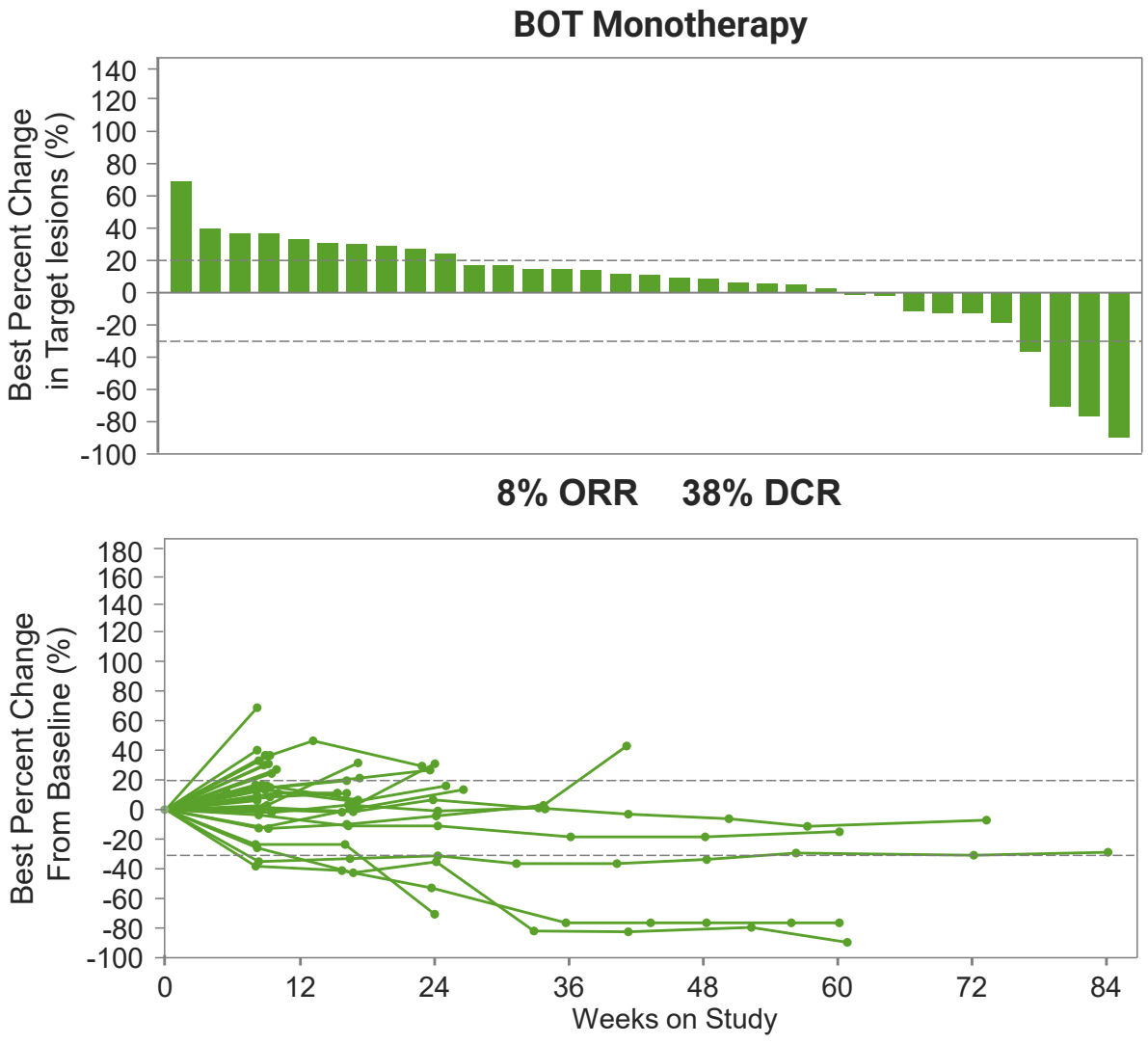
Efficacy in BOT 75 mg Arms: BOT / BAL is Superior to BOT Monotherapy[9]





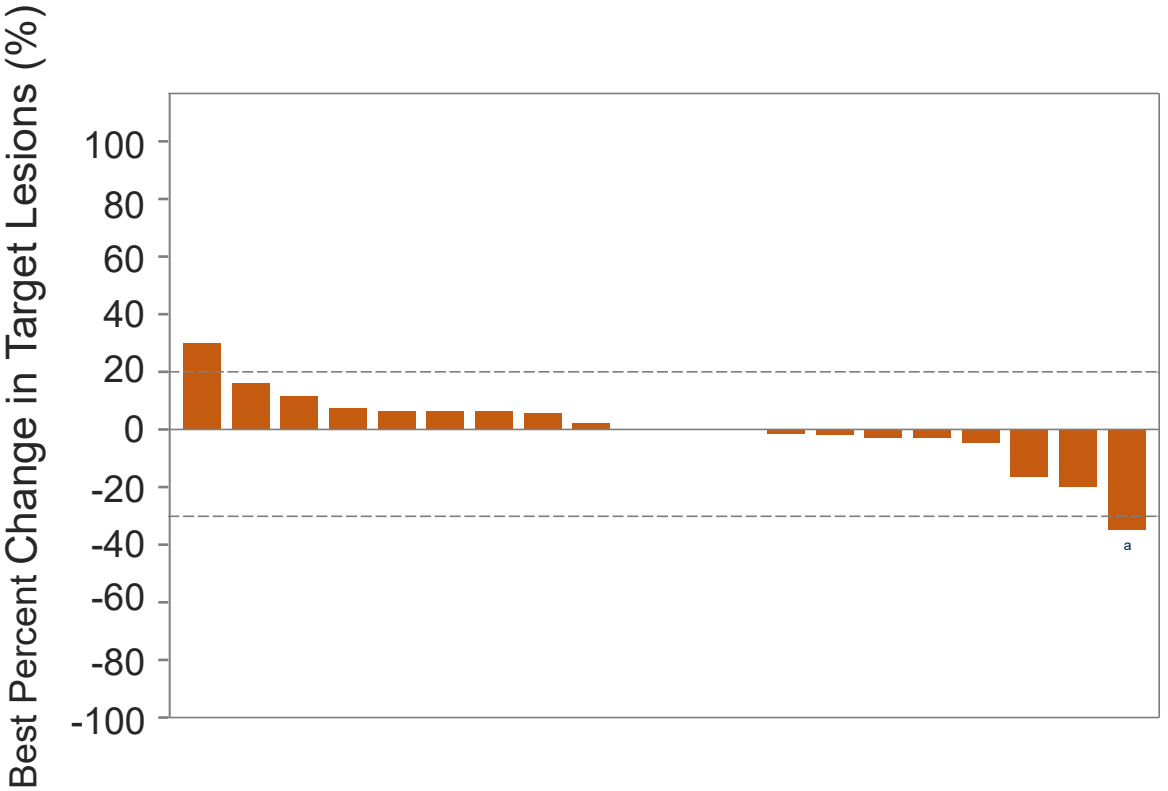
Efficacy in BOT 150 mg Arms: Clinical Benefit Greater With BOT / BAL

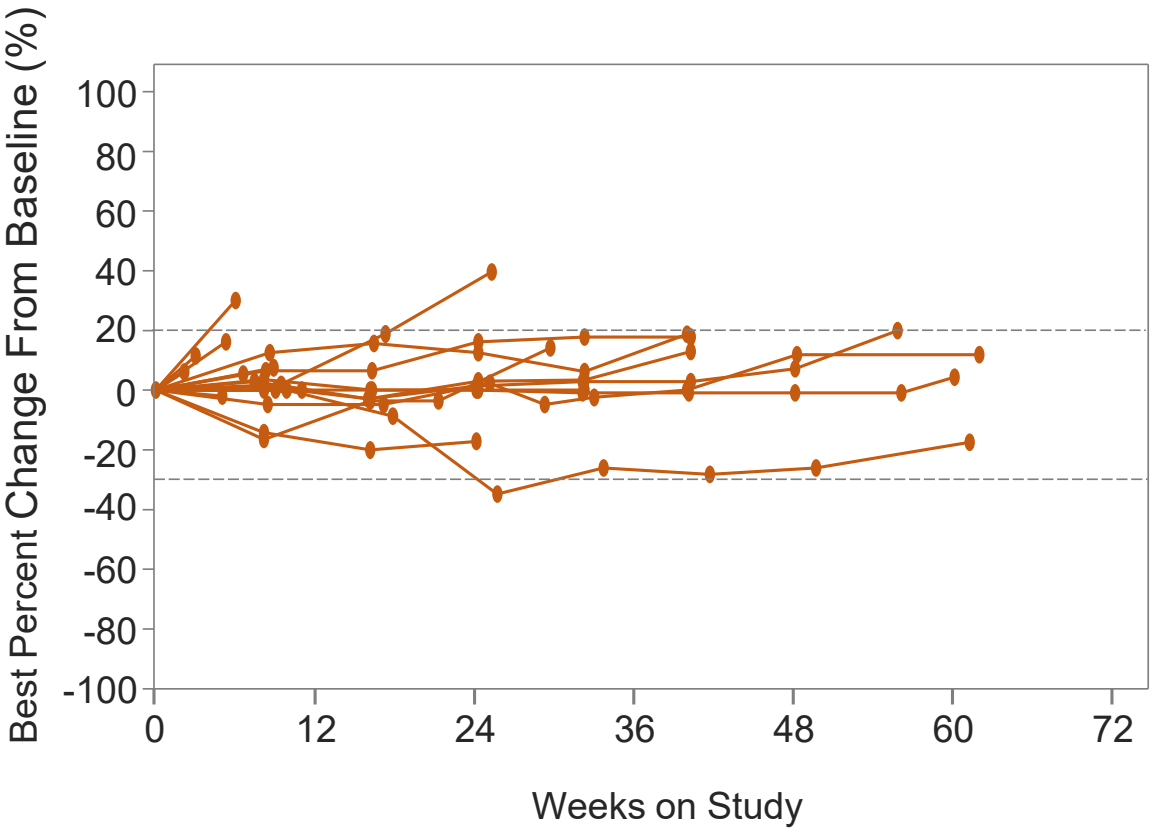




No Objective Responses With SOC

Trifluridine/Tipiracil (n=13) or Regorafenib (n=8)





[a]Response did not confirm.

Safety Summary

	BOT 75 mg Q6W		BOT 150 mg Q6W		SOC
	BOT / BAL n=62	BOT Mono n=37	BOT / BAL n=60	BOT Mono n=39	Trifluridine/Tipiracil or Regorafenib n=21
Any TRAE, n (%)	54 (87)	28 (76)	60 (100)	31 (79)	19 (90)
Grade ≥3	22 (35)	8 (22)	26 (43)	9 (23)	12 (57)
Any imAE, n (%)	38 (61)	20 (54)	49 (82)	18 (46)	1 (5)
Diarrhea/colitis[a]	22 (35)	14 (38)	30 (50)	13 (33)	0 (0)
Hypothyroidism[a]	8 (13)	0 (0)	15 (25)	0 (0)	0 (0)
Skin[a]	4 (6)	2 (8)	17 (28)	1 (3)	0 (0)
Grade ≥3	20 (32)	7 (19)	24 (40)	10 (26)	1 (5)
Diarrhea/colitis[b]	11 (18)	4 (11)	16 (27)	7 (18)	0 (0)
Pneumonitis[b]	2 (3)	1 (3)	2 (3)	0 (0)	1 (5)
Hepatitis[b]	1 (2)	2 (5)	1 (2)	2 (5)	0 (0)

[a]Most common imAEs. [b]Grade ≥3 imAEs in ≥5% of patients.

- 75 mg BOT / BAL best risk-benefit and selected for phase 3
- No treatment-related deaths
- No new safety signals

Key Takeaways

- ✓ Contribution of BAL to BOT confirmed
- ✓ Dose for phase 3 studies defined (75 mg BOT + BAL with an ORR of **19%**)
- ✓ Deep, durable responses differentiated from SOC where no responses were observed
- ✓ Majority of responses ongoing
- ✓ No new safety signals identified

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- Virginia Cancer Specialists
- Weill Cornell Medicine

Abbreviations

AE, adverse event
APC, antigen presenting cell
BAL, balstilimab
BOR, best overall response
BOT, botensilimab
BRAF, v-raf murine sarcoma viral oncogene homolog B1
CI, confidence interval
CBR, clinical benefit rate at 24 weeks
CR, complete response
CTLA-4, cytotoxic T-lymphocyte antigen-4
DCR, disease control rate at 6 weeks
DFS, disease free survival
dMMR, deficient mismatch repair
DOR, duration of response
ECOG, Eastern Cooperative Oncology Group
EGFR, epidermal growth factor receptor
Fc, fragment crystallizable
FcγR, fragment crystallizable gamma receptor
imAE, immune-mediated adverse event
I-O, immunotherapy
ITT, intention-to-treat
LM, liver metastases
mCRC, metastatic colorectal cancer
MSI-H, microsatellite instability-high
MSS, microsatellite stable
NLM, no active liver metastases
NE, not evaluable
NK, natural killer
NR, not reached
ORR, objective response rate
OS, overall survival
PD, progressive disease
PD-1, programmed death receptor-1
PD-L1/2, programmed death-ligand 1/2
PK, pharmacokinetics
PFS, progression-free survival
PR, partial response
PS, performance status
QXW, every X weeks
RAS, rat sarcoma virus
RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1
SD, stable disease
SOC, standard of care
TRAE, treatment-related adverse event
Treg, regulatory T cell
VEGF, vascular endothelial growth factor

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Plain Language Summary

Purpose

- This study examined a combination therapy called botensilimab (BOT) and balstilimab (BAL) for patients with a type of difficult-to-treat colorectal cancer that has spread to other parts of the body
- The study looked at two different doses of BOT alone or when combined with BAL, as well as standard of care (SOC) treatment for a total of five different treatment arms

Key Findings

- The study met its objectives of informing the appropriate dose/treatment schedule of BOT and BAL for a future phase 3 study
  - Researchers selected the 75 mg BOT + 240 mg BAL dose to move forward
- The SOC arm showed no responses to treatment, which was expected but is limited by the small number of patients in this arm as well as participant dropout
- Additional data will be reported at a future scientific meeting

Conclusions

- This research represents an important step in exploring new treatment options for patients with difficult-to-treat colorectal cancer that has spread to other parts of the body

Data in Context

- Across a phase 1 and randomized, global phase 2 trial including over 200 patients, reproducible response rates (~20%) and durable outcomes were observed, supporting the clinical relevance of this combination