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Botensilimab, a novel innate/adaptive immune activator, plus balstilimab (anti-PD-1) for metastatic heavily pretreated microsatellite stable colorectal cancer

Anthony B. El-Khoueiry

*University of Southern California
Norris Comprehensive Cancer Center
Los Angeles, California, United States*





Botensilimab, a novel innate/adaptive immune activator, plus balstilimab (anti-PD-1) for metastatic heavily pretreated microsatellite stable colorectal cancer

Andrea J. Bullock,¹ Joseph E. Grossman,² Marwan G. Fakih,³ Heinz-Josef Lenz,⁴ Michael S. Gordon,⁵ Kim Margolin,⁶ Breelyn A. Wilky,⁷ Daruka Mahadevan,⁸ Jonathan Trent,⁹ Bruno Bockorny,¹ Justin Moser,⁵ Ani S. Balmanoukian,¹⁰ Benjamin L. Schlechter,¹¹ Waldo Ortuzar Feliu,² Katherine Rosenthal,² Bonnie L. Bullock,² Justin Stebbing,^{2,12} J. Luke Godwin,² Steven J. O'Day,² Apostolia M. Tsimberidou,¹³ **Anthony B. El-Khoueiry**⁴

¹Beth Israel Deaconess Medical Center, Boston, MA, USA; ²Agenus Inc., Lexington, MA, USA; ³City of Hope Comprehensive Cancer Center, Duarte, CA, USA; ⁴University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; ⁵HonorHealth Research Institute, Scottsdale, AZ, USA; ⁶Providence St. John's Cancer Institute, Santa Monica, CA, USA; ⁷University of Colorado Cancer Center, Aurora, CO, USA; ⁸The University of Texas Health Sciences Center at San Antonio, San Antonio, TX, USA; ⁹Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; ¹⁰The Angeles Clinic and Research Institute, Los Angeles, CA, USA; ¹¹Dana-Farber Cancer Institute, Boston, MA, USA; ¹²Imperial College London, London, UK; ¹³The University of Texas MD Anderson Cancer Center, Houston, TX, USA



Declaration of Interests

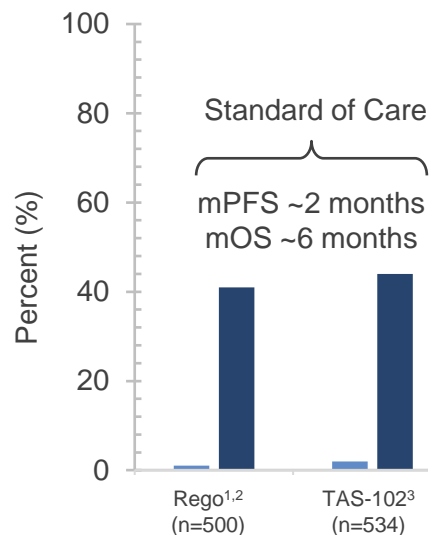
Anthony B. El-Khoueiry

Advisory Role/Honoraria: Agenus, AstraZeneca, Bayer, Bristol-Myers Squibb, CytomX Therapeutics, Eisai, EMD Serono, Exelixis, Gilead, Merck, MedImmune

Research Funding: Astex Pharmaceuticals, AstraZeneca, MedImmune, Merck, Pieris Pharmaceuticals, Roche



Limited Efficacy in 3L+ MSS CRC



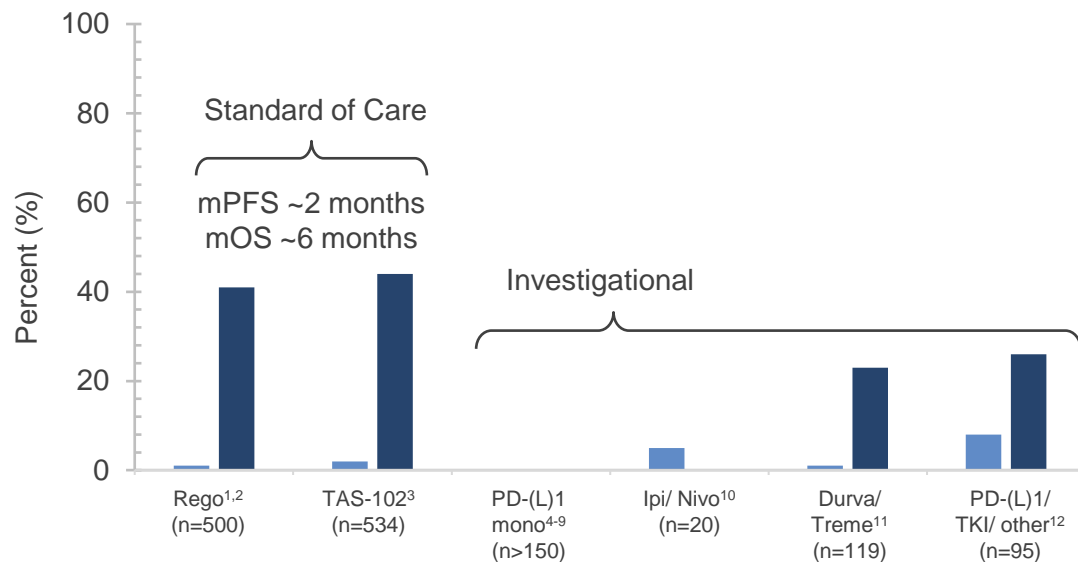
- ~95% of metastatic colorectal cancer is microsatellite stable (MSS CRC)
- Limited efficacy with regorafenib and TAS-102 in 3L+ setting¹⁻³

ORR (%)	1	2
DCR (%)	41	44

Third line and beyond



Limited Efficacy in 3L+ MSS CRC



- ~95% of metastatic colorectal cancer is microsatellite stable (MSS CRC)
- Limited efficacy with regorafenib and TAS-102 in 3L+ setting¹⁻³

- IO-only responses are rare⁴⁻¹¹
- PD-1/TKIs: variable efficacy and durability¹²

ORR (%)	1	2	0	5	1	8
DCR (%)	41	44	-	-	23	26

Advanced, metastatic or treatment-resistant CRC

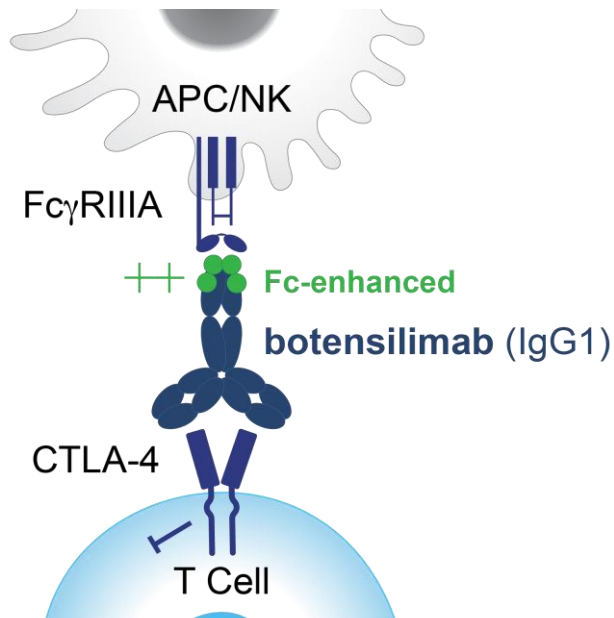
1. Grothey et al. *Lancet*. 2013;381: 303-312. 2. Van Cutsem, et al. *J Clin Oncol*. 2012;30:15_suppl, 3502-3502. 3. Mayer et al. *N Eng J Med*. 2015;372:1909-1919. 4. Brahmer, et al. *J Clin Oncol*. 2010;28(19): 3167-3175. 5. Brahmer, et al. *N Eng J Med*. 2012;366(26): 2455-2465. 6. Topalian et al, *N Eng J Med*. 2012;366(36): 2443-2454. 7. Le, et al. *N Eng J Med*. 2015;372:2509-2520. 8. Eng, et al. *Lancet Oncol*. 2019;20: 849-861. 9. O'Neil, et al. *PloS one*. 2017;12(12): e0189848. 10. Overman, et al. ASCO Annual Meeting 2016. Oral Presentation. 11. Chen, et al. *JAMA Oncol*. 2020; 6(6): 831-838. 12. Wang, et al. *JAMA Oncol*. 2021; 4(8): e2118416.



Novel Immunotherapy Agents

botensilimab

Fc-enhanced CTLA-4 Inhibitor



Active in cold and IO refractory tumors¹:

Design:

- Improved binding to activating FcγRs on APCs and NK cells
- Reduced complement binding

Function (relative to first-gen CTLA-4)^{2,3}:

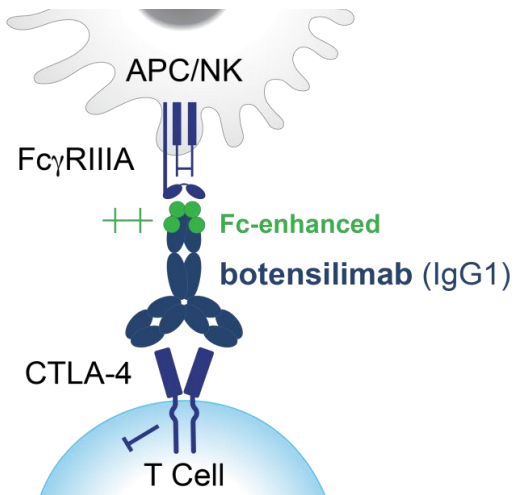
- ↑ Frequency of activated DCs
- ↑ T cell priming, expansion, memory
- ↑ Treg depletion
- ↓ Complement mediated toxicity



Novel Immunotherapy Agents

botensilimab

Fc-enhanced CTLA-4 Inhibitor

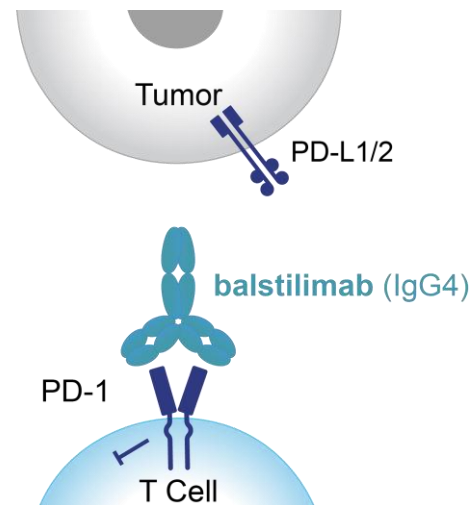


Active in cold and IO refractory tumors¹:

- ↑ T cell priming, expansion, memory²
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- ↓ Complement mediated toxicity

balstilimab

PD-1 Inhibitor



Safety and efficacy analogous to approved anti-PD-1 mAbs^{3,4}

- > 650 patients treated; 8 ongoing trials / 2 completed
- Complete blocker of PD-1-PD-L1/2 interactions
- Enhanced T cell activation and effector function

C-800 Study Design

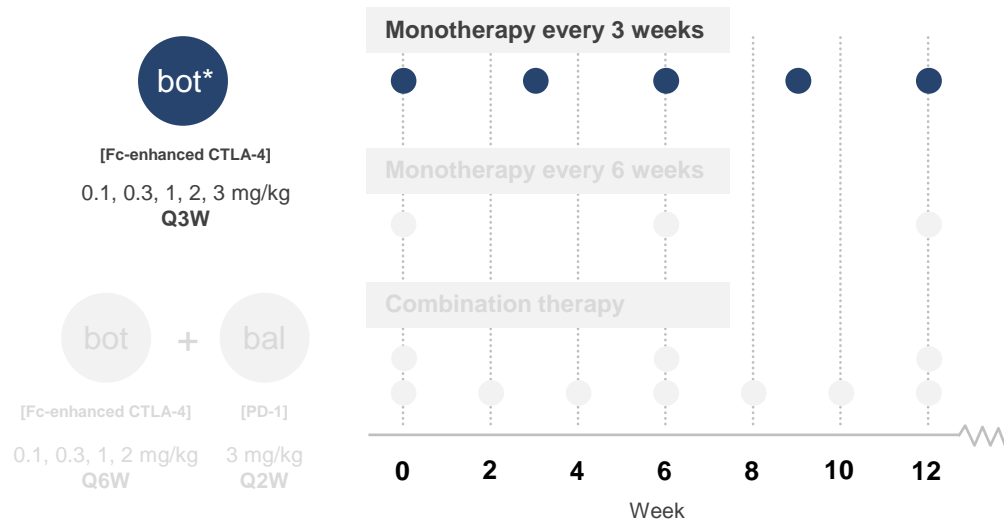
NCT03860272: First-in-human trial of **botensilimab** ± **balstilimab** in patients with advanced cancer^{1,2}

KEY ELIGIBILITY

Dose Escalation

- Advanced solid tumors refractory to standard treatment
- Prior IO therapy allowed

TREATMENT (Up to 2 years)



ENDPOINTS

Efficacy

- ORR
- DCR (SD, CR or PR)
- PFS
- DOR
- OS

Safety

- AEs
- TRAEs
- irAEs

1. <https://clinicaltrials.gov/ct2/show/NCT03860272>. 2. El-Khoueiry AB. SITC 2021 Annual Meeting. Poster #479.

*Crossover to combination from botensilimab monotherapy permitted.



C-800 Study Design

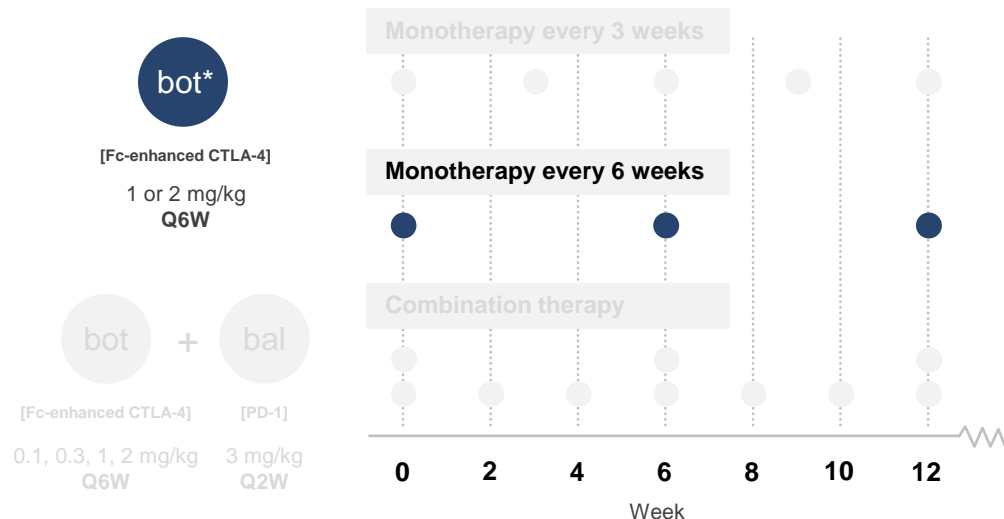
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C-800 Study Design

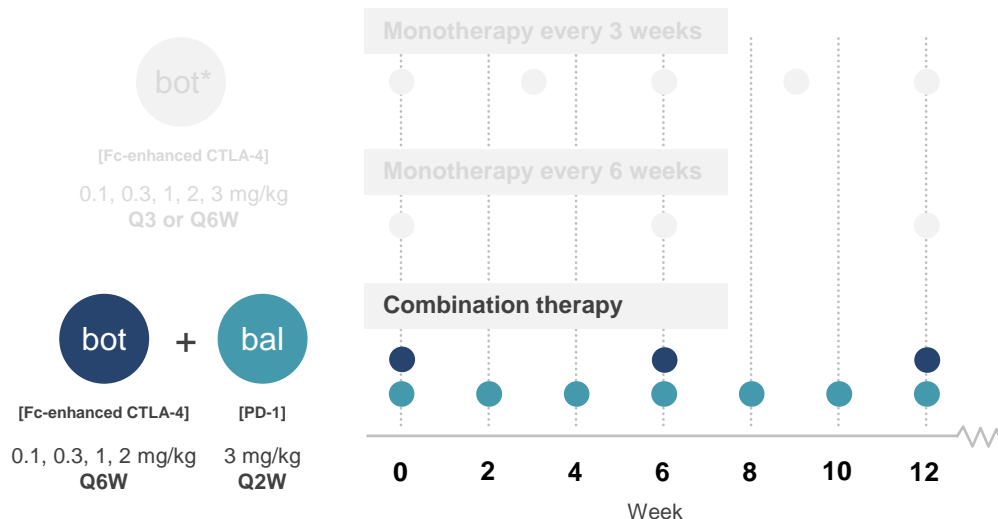
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C-800 Study Design: MSS CRC

NCT03860272: First-in-human trial of **botensilimab** ± **balstilimab** in patients with advanced cancer^{1,2}

KEY ELIGIBILITY

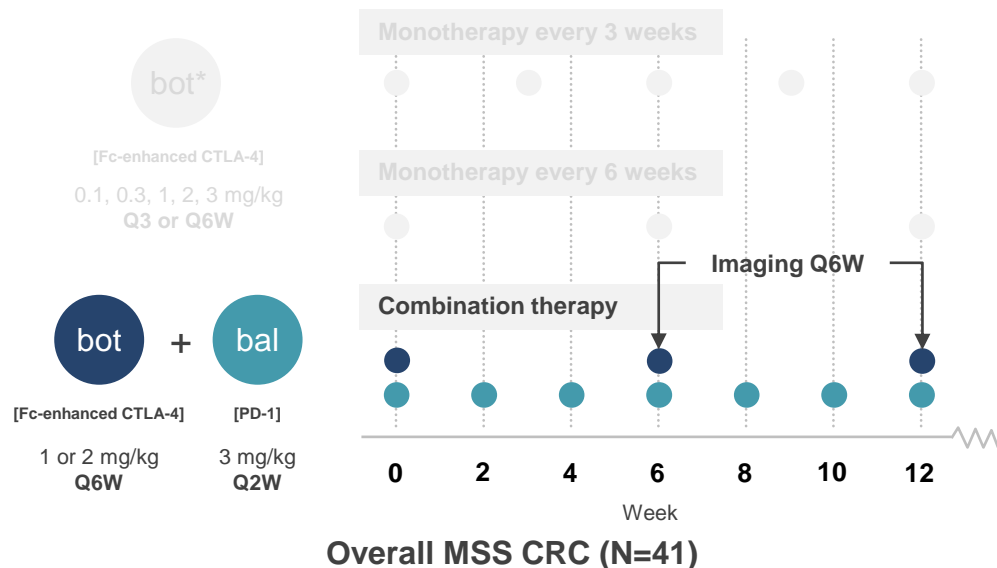
Dose Escalation

- Advanced solid tumors refractory to standard treatment
- Prior IO therapy allowed

CRC Cohort

- Metastatic CRC
- MSS by local assessment

TREATMENT (Up to 2 years)



ENDPOINTS

Efficacy

- ORR
- DCR (SD, CR or PR)
- PFS
- DOR
- OS

Safety

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MSS CRC Patient Characteristics

Characteristic	Overall (N=41)*
Age, median (range)	57 (36-82)
Sex, n (%)	
Male	17 (41)
Female	24 (59)
ECOG PS at baseline, n (%)	
0	17 (41)
1	24 (59)
Prior lines of therapy, n (%)	
Median (range)	4 (2-10)
2	5 (12)
3	13 (32)
4	9 (22)
5+	14 (34)
Prior immunotherapy, n (%)[†]	14 (34)
Botensilimab dose, n (%)	
1 mg/kg Q6W + bal (PD-1) Q2W	7 (17)
2 mg/kg Q6W + bal (PD-1) Q2W	34 (83)
Microsatellite stable status, n (%)	41 (100)
RAS mutation, n (%)	21 (51)
BRAF mutation, n/N (%)	2/38 (5)

Evaluable patients treated with Bot + Bal had ≥1 Q6W imaging assessment

*Five patients had early clinical progression and did not have 6-week imaging. Two patients withdrew consent and were not evaluable.

[†]Including prior PD-(L)1 and/or CTLA-4 inhibitors, PD-1/TKI combinations, CD137 agonists, and others.



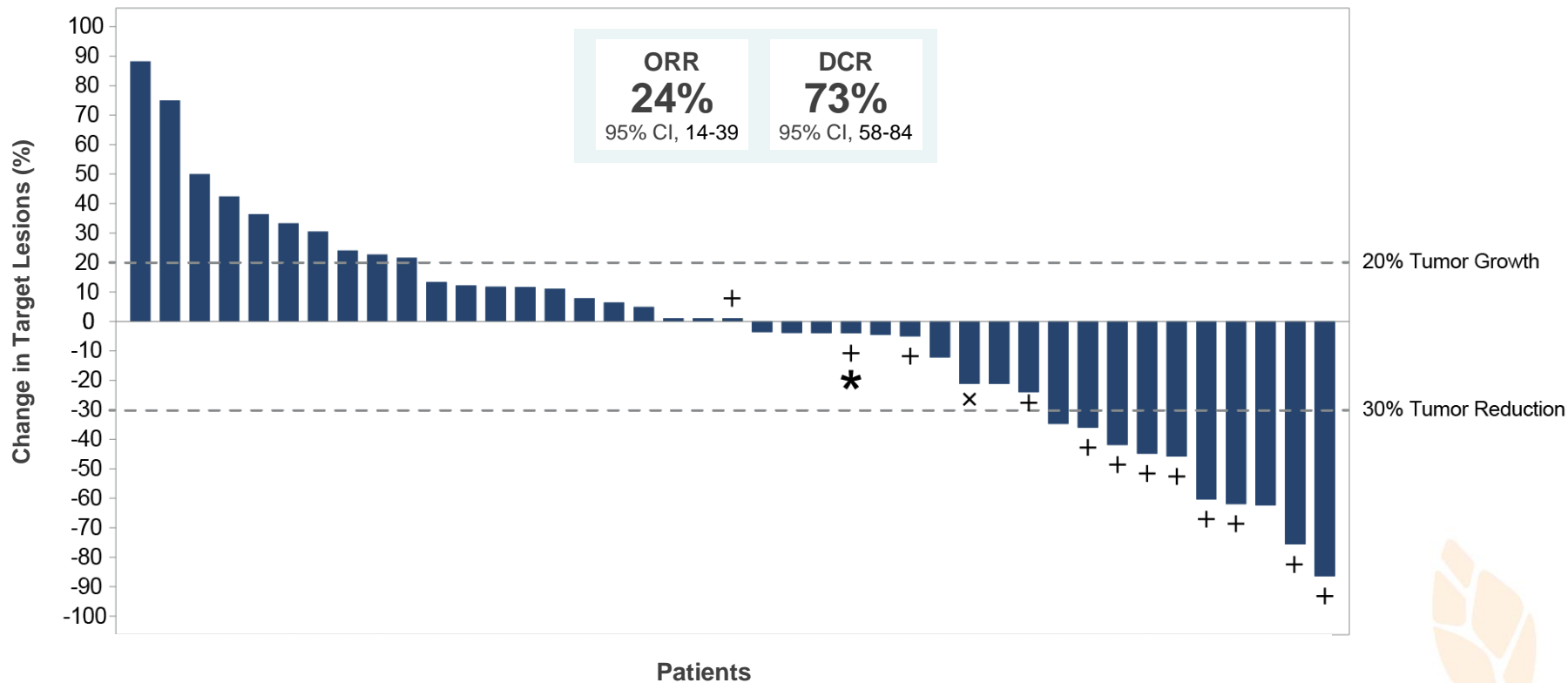
Efficacy: Durable Objective Responses

	Overall (N=41)
ORR, % (95% CI)	24% (14-39)
BOR, n (%)	
CR	0 (0)
PR	10 (24)
SD	20 (49)
PD	11 (27)
DCR (PR + SD), % (95% CI)	73% (58-84)
Median Follow-up, mo. (range)	5.8 (1.6-24.4)

- **8/10 objective responses ongoing**
- 3 responses >1 year
- Median DOR not reached



Waterfall Plot (N=41)



+ = Ongoing PR/SD * = Complete metabolic response by PET x = Progression of non-target lesions



Safety

TRAEs in $\geq 10\%$ of Patients (N=41)

TRAE, n (%)	Any Grade	Grade 1-2	Grade 3
Any	31 (76)	21 (51)	10 (24)
GASTROINTESTINAL			
Diarrhea/colitis	16 (39)	12 (29)	4 (10)
Nausea	7 (17)	7 (17)	0 (0)
Vomiting	4 (10)	4 (10)	0 (0)
CONSTITUTIONAL			
Fatigue	9 (22)	8 (20)	1 (2)
Decreased appetite	9 (22)	9 (22)	0 (0)
Chills	7 (17)	7 (17)	0 (0)
Pyrexia	6 (15)	5 (12)	1 (2)
HEPATIC			
Alanine aminotransferase increased	5 (12)	5 (12)	0 (0)
Aspartate aminotransferase increased	4 (10)	3 (7)	1 (2)
MUSCULOSKELETAL			
Arthralgia	5 (12)	4 (10)	1 (2)
Myalgia	5 (12)	5 (12)	0 (0)
SKIN			
Pruritus	4 (10)	4 (10)	0 (0)
Rash	4 (10)	4 (10)	0 (0)

No hypophysitis

Pneumonitis is rare

No grade 4 or 5 TRAEs

Investigator-assessed irAEs:

- 46% any grade
- 17% grade 3

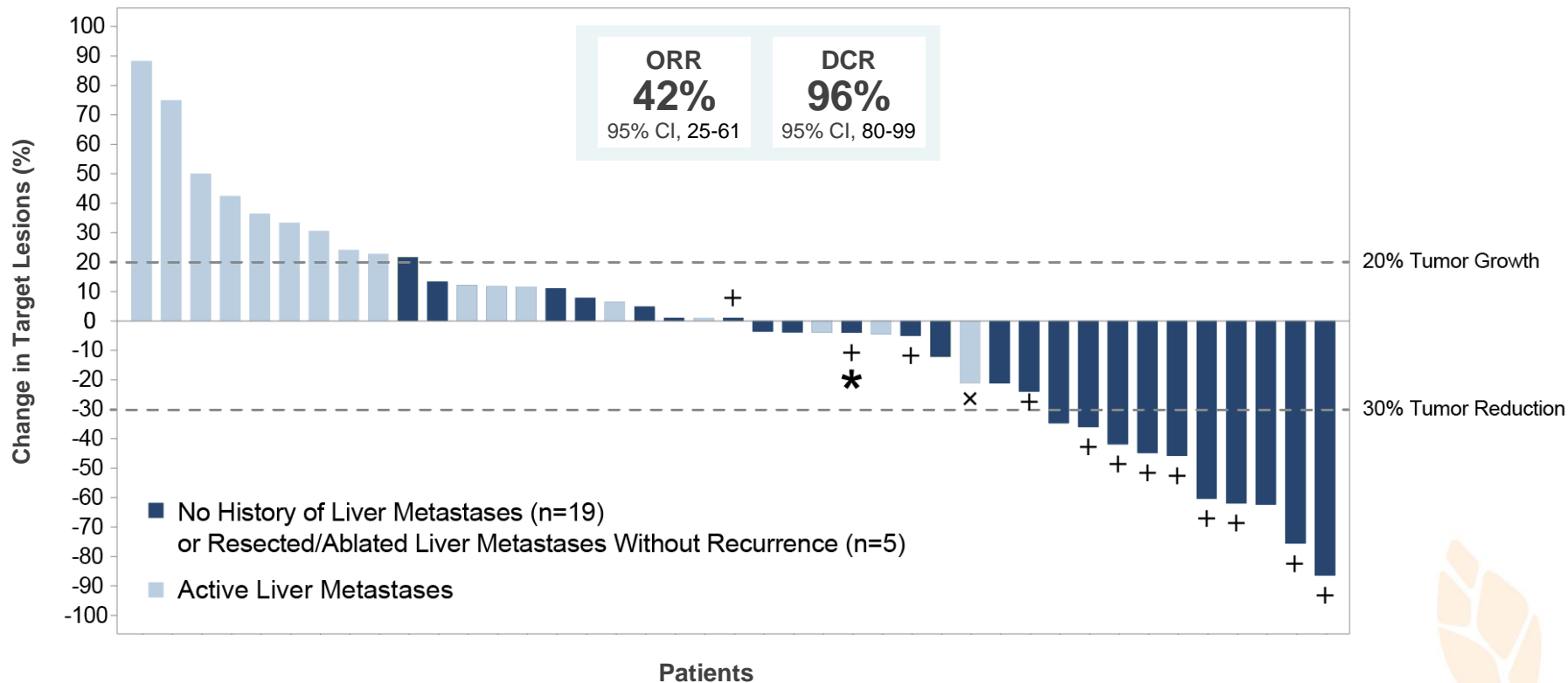
Discontinuation due to a TRAE:

- 10% Bot only
- 10% Bot and Bal



Exploratory Analysis by Liver Involvement

Enriched responses in patients without active liver metastases (n=24)



+ = Ongoing PR/SD * = Complete metabolic response by PET x = Progression of non-target lesions



Summary

- Botensilimab plus balstilimab is a novel Fc-enhanced CTLA-4/PD-1 combination
- In heavily pretreated patients with MSS CRC:
 - Deep objective responses with evidence of durability
 - Well tolerated with a differentiated safety profile
 - Enriched responses in patients without active liver metastases
- A global phase II dose-randomized trial in MSS CRC will launch this year



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Abbreviations

3L, third line

AE, adverse event

APC, antigen presenting cell

Bal, balstilimab

Bot, botensilimab

CR, complete response

CRC, colorectal cancer

CTLA-4, cytotoxic T-lymphocyte antigen-4

DC, dendritic cell

DCR, disease control rate

DOR, duration of response

Durva, durvalumab

ECOG, Eastern Cooperative Oncology Group

Fc, fragment crystallizable

FcγRIIIA, Fc gamma receptor IIIA

IO, immunotherapy

Ipi, ipilimumab

irAE, immune-related adverse event

mAb, monoclonal antibody

MSS, microsatellite stable

Nivo, nivolumab

NK, natural killer

ORR, objective response rate

OS, overall survival

PD-1, programmed death receptor-1

PD-L1, programmed death-ligand 1

Pembro, pembrolizumab

PFS, progression-free survival

PR, partial response

PS, performance status

QXW, every X weeks

Rego, regorafenib

SD, stable disease

SOC, standard of care

TAS-102, trifluridine/tipiracil

TKI, tyrosine kinase inhibitor

TNFα, tumor necrosis factor alpha

TRAE, treatment-related adverse event

Treme, tremelimumab





Q&A Session



Declaration of Interests (Full)

- AJ Bullock: Advisory Role: Exelixis, Geistlich Pharma.
- JE Grossman: Employee of Agenus with stock/stock options.
- MG Fakih: Advisory Role: Array, Bayer, GlaxoSmithKline, Incyte, Mirati, Pfizer, Seattle Genetics, Taiho, Zhuhai Biotech; Honoraria: Amgen; Speakers' Bureau: Guardant; Institutional Research Funding: Amgen, AstraZeneca, Bristol-Myers Squibb, Novartis, Verastem.
- H-J Lenz: Advisory Role: Bayer, Bristol-Myers Squibb, GlaxoSmithKline; Merck Serono, Roche; Honoraria: Boehringer Ingelheim, Fulgent Genetics, G1 Therapeutics, Isofol Medical, Jazz Pharmaceuticals, Oncocyte.
- MS Gordon: Advisory Role: Agenus, Daiichi Sankyo, Deciphera Pharmaceuticals, ImaginAB, Imaging Endpoints, RedHill Biopharma, Salaris, Tracon; Leadership Role: CareMission.
- K Margolin: Nothing to disclose.
- BA Wilky: Consultant/Advisory Role: Immune Design, Janssen Oncology, Eli Lilly, Novartis; Travel/Accommodation/Expenses: Advenchen Laboratories, Agenus, Eli Lilly, Novartis; Research Funding: Agenus, ArQule, Daiichi Sankyo, Merck Sharp & Dohm, Novartis.
- D Mahadevan: Speakers' Bureau: Caris, Guardant Health; Steering Committee: Janssen.
- J Trent: Advisory Role: Blueprint Medicines, Deciphera, Daiichi Sankyo, Eli Lilly, Epizyme Janssen, Novartis.
- B Bockorny: Advisory Board Participation: Blueprint Medicines; Research Funding: NanoView Biosciences; Travel Expenses: Erytech Pharma.
- J Moser: Consultant/Advisory Role: Adagene, Amunix, Bristol-Myers Squibb, Thirona Bio, Imaging Endpoints; Institutional Research Support: ImmuneSensor, Simcha, BioEclipse Therapeutics, FujiFilm, Alpine Immune Sciences, Amgen, Genentech, Ideaya Biosciences, Istari Oncology, Nektar Therapeutics, NovoCure, Repertoire Immune Sciences, Rubius, Synthorx Inc, Trishula Therapeutics; Honoraria: Caris Life Sciences, Daiichi-Sankyo, TGen; Board Member: Caris Molecular Tumor Board, Caris Consultant; Speakers' Bureau: Caris Life Sciences, Immunocore.
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- K Rosenthal: Employee of Agenus with stock/stock options.
- BL Bullock: Employee of Agenus with stock/stock options.
- J Stebbing: Consulting Role: Lansdowne Partners, Vitruvian; Board of Directors: BB Biotech Healthcare Trust PLC (previously), Xerion; Scientific Advisory Board Participation: Agenus, Alveo Technologies, APIM Therapeutics, Bryologyx, Celltrion, Certis, Eli Lilly, Equilibre Biopharmaceuticals, Graviton Bioscience Corporation, Greenmantle, Heat Biologics, Pear Bio, Vaccitech, Volvox, vTv Therapeutics.
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- AM Tsimberidou: Consulting/Advisory Role: Diaccurate, VinceRx; Institutional Research Funding (Clinical Trials): Agenus, Boston Biomedical, IMMATICS, Karus Therapeutics, Novocure, OBI Pharma, Parker Institute for Cancer Immunotherapy, Tempus, Tvardi.
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