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**Cancer**

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

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



# Declaration of Interests

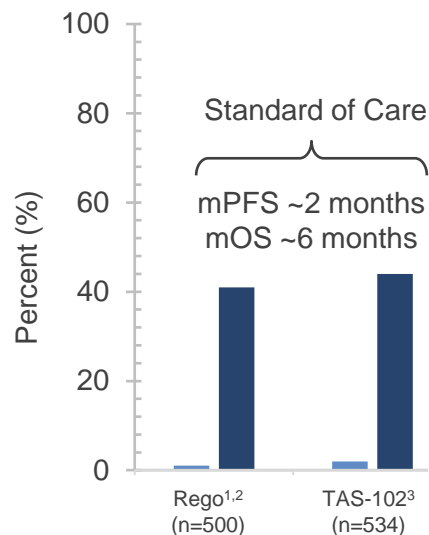
## Anthony B. El-Khoueiry

**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



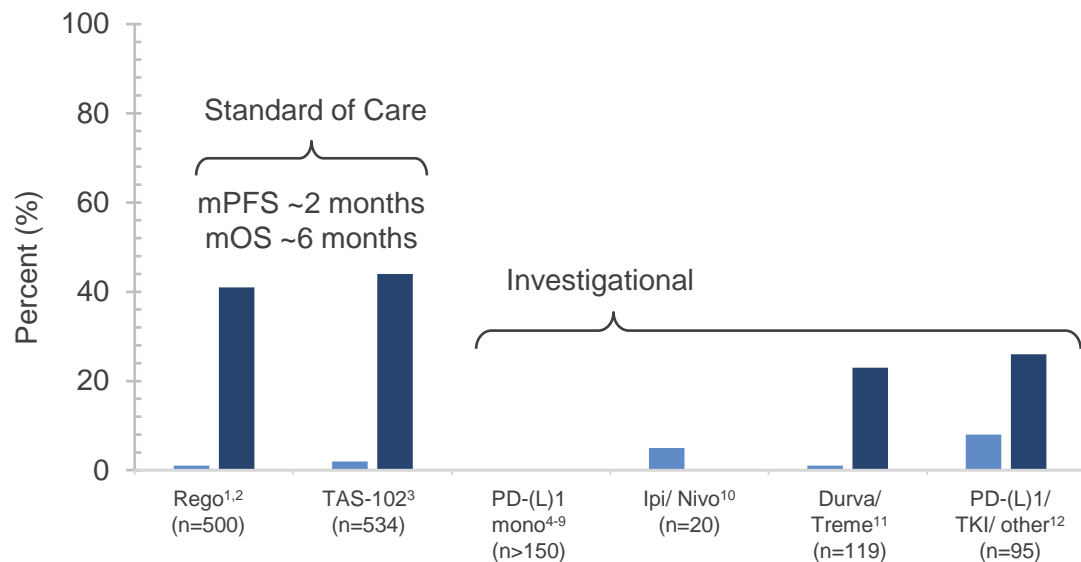
- ~95% of metastatic colorectal cancer is microsatellite stable (MSS CRC)
- Limited efficacy with regorafenib and TAS-102 in 3L+ setting<sup>1-3</sup>

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+ setting<sup>1-3</sup>

- IO-only responses are rare<sup>4-11</sup>
- PD-1/TKIs: variable efficacy and durability<sup>12</sup>

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

Advanced, metastatic or treatment-resistant CRC

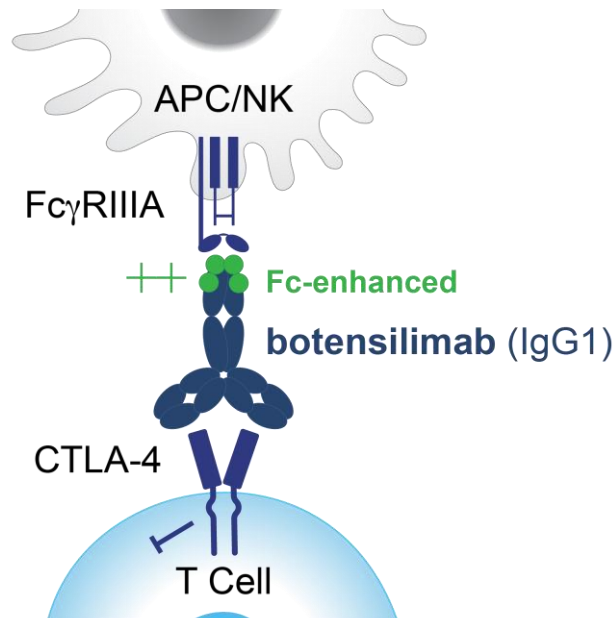
1. Grothey et al. *Lancet*. 2013;381: 303-312. 2. Van Cutsem, et al. *J Clin Oncol*. 2012;30:15\_suppl, 3502-3502. 3. Mayer et al. *N Eng J Med*. 2015;372:1909-1919. 4. Brahmer, et al. *J Clin Oncol*. 2010;28(19): 3167-3175. 5. Brahmer, et al. *N Eng J Med*. 2012;366(26): 2455-2465. 6. Topalian et al, *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 tumors<sup>1</sup>:

### Design:

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

### Function (relative to first-gen CTLA-4)<sup>2,3</sup>:

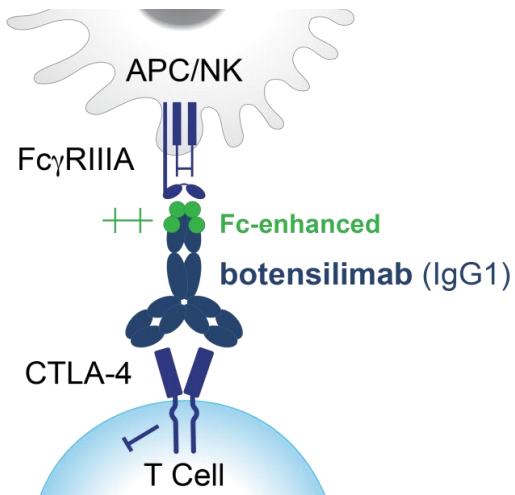
- ↑ Frequency of activated DCs
- ↑ T cell priming, expansion, memory
- ↑ Treg depletion
- ↓ Complement mediated toxicity



# Novel Immunotherapy Agents

## botensilimab

Fc-enhanced CTLA-4 Inhibitor

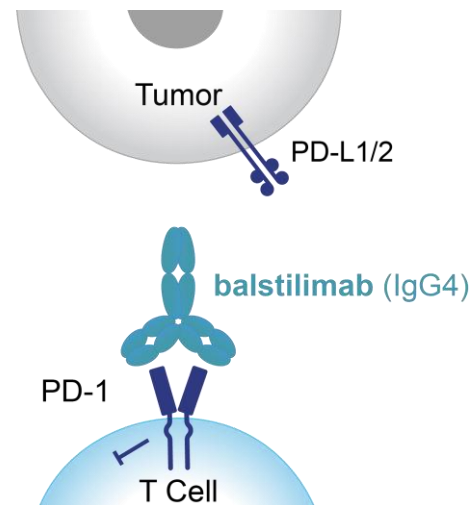


Active in cold and IO refractory tumors<sup>1</sup>:

- $\uparrow$  T cell priming, expansion, memory<sup>2</sup>
- $\uparrow$  Treg depletion
- $\downarrow$  Complement mediated toxicity

## balstilimab

PD-1 Inhibitor



Safety and efficacy analogous to approved anti-PD-1 mAbs<sup>3,4</sup>

- > 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

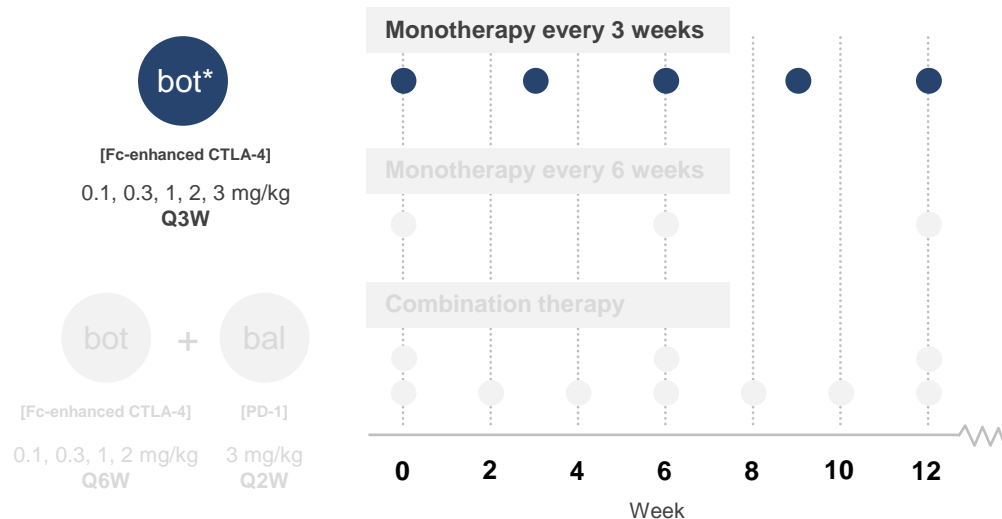
NCT03860272: First-in-human trial of **botensilimab** ± **balstilimab** in patients with advanced cancer<sup>1,2</sup>

## 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

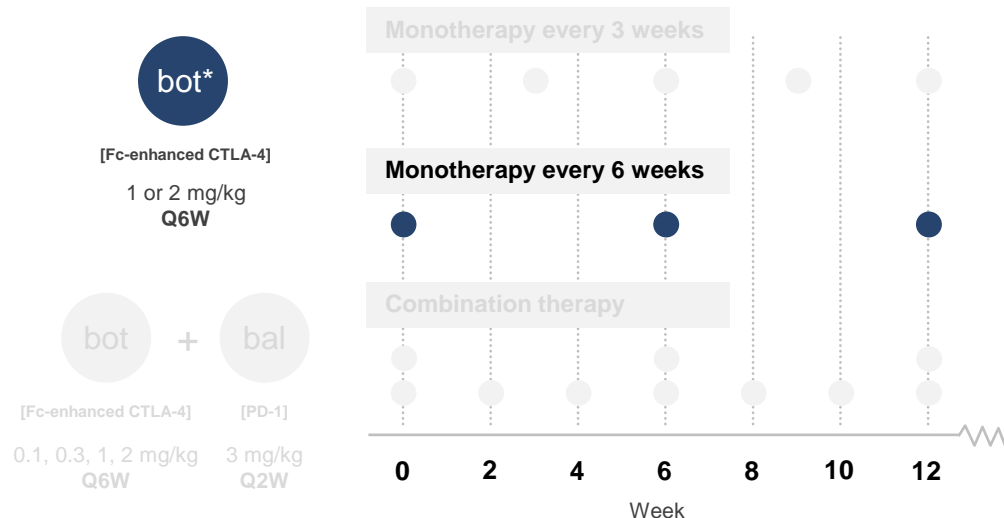
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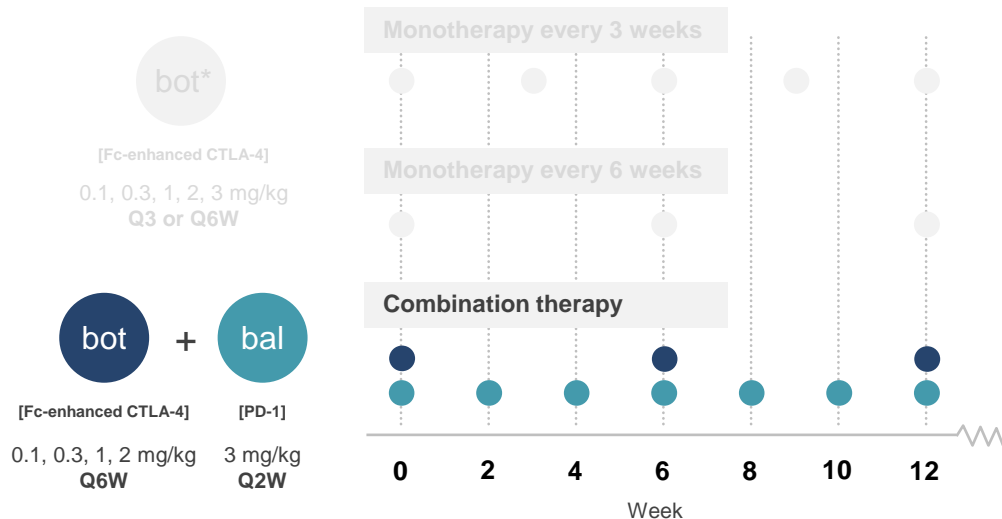
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## KEY ELIGIBILITY

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## TREATMENT (Up to 2 years)



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\*Crossover to combination from botensilimab monotherapy permitted.



# C-800 Study Design: MSS CRC

NCT03860272: First-in-human trial of **botensilimab** ± **balstilimab** in patients with advanced cancer<sup>1,2</sup>

## KEY ELIGIBILITY

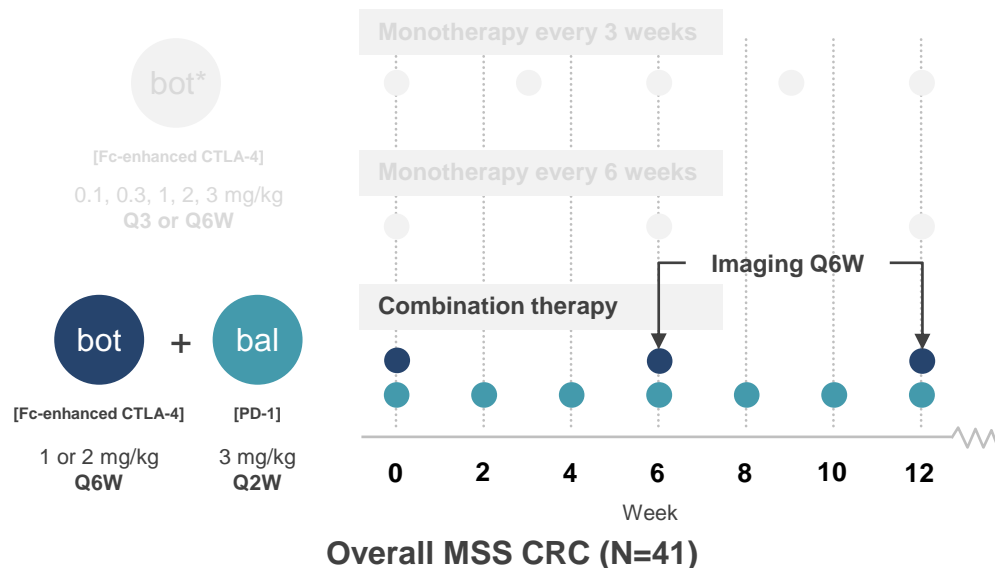
### Dose Escalation

- 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

- 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.



# MSS CRC Patient Characteristics

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

Evaluable patients treated with Bot + Bal had  $\geq 1$  Q6W imaging assessment

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

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



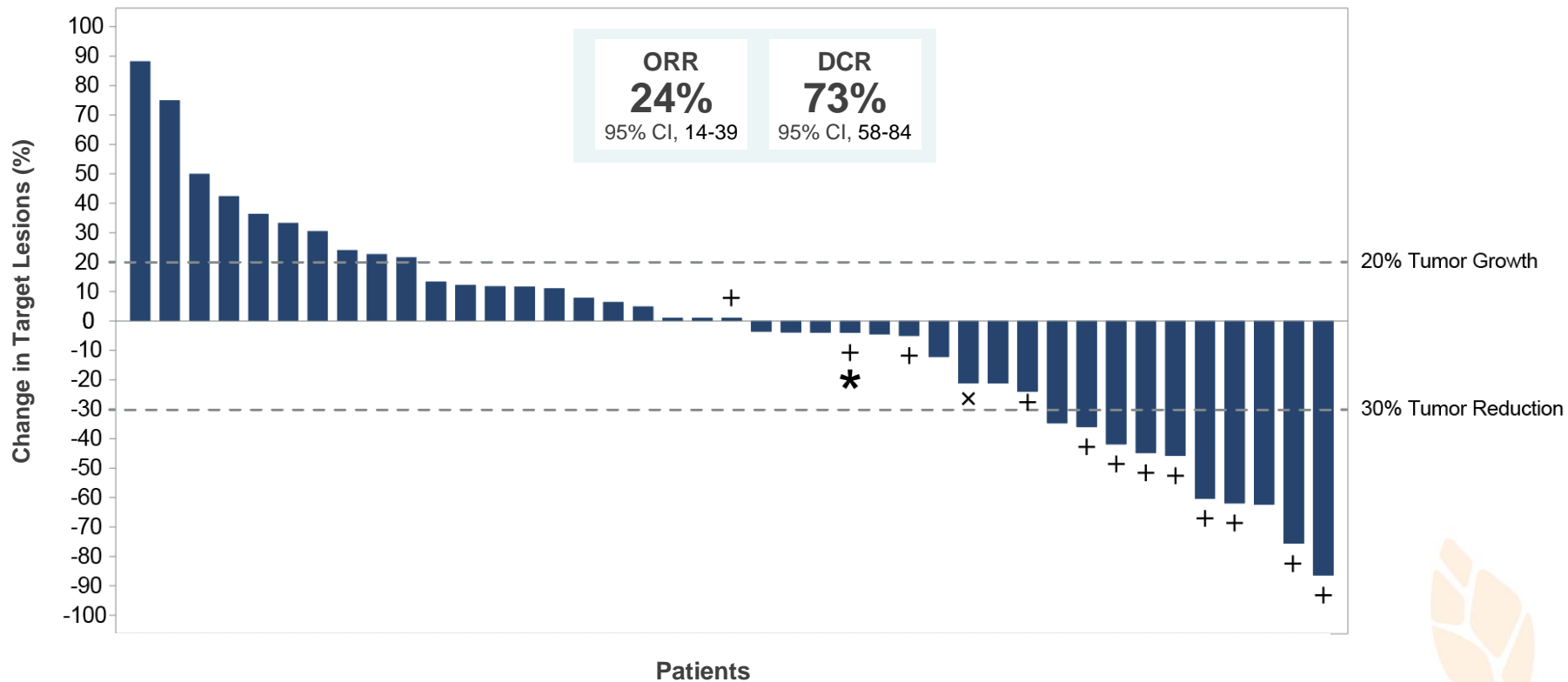
# Efficacy: Durable Objective Responses

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

- **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
<b>Any</b>	31 (76)	21 (51)	10 (24)
<b>GASTROINTESTINAL</b>			
Diarrhea/colitis	16 (39)	12 (29)	4 (10)
Nausea	7 (17)	7 (17)	0 (0)
Vomiting	4 (10)	4 (10)	0 (0)
<b>CONSTITUTIONAL</b>			
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)
<b>HEPATIC</b>			
Alanine aminotransferase increased	5 (12)	5 (12)	0 (0)
Aspartate aminotransferase increased	4 (10)	3 (7)	1 (2)
<b>MUSCULOSKELETAL</b>			
Arthralgia	5 (12)	4 (10)	1 (2)
Myalgia	5 (12)	5 (12)	0 (0)
<b>SKIN</b>			
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:

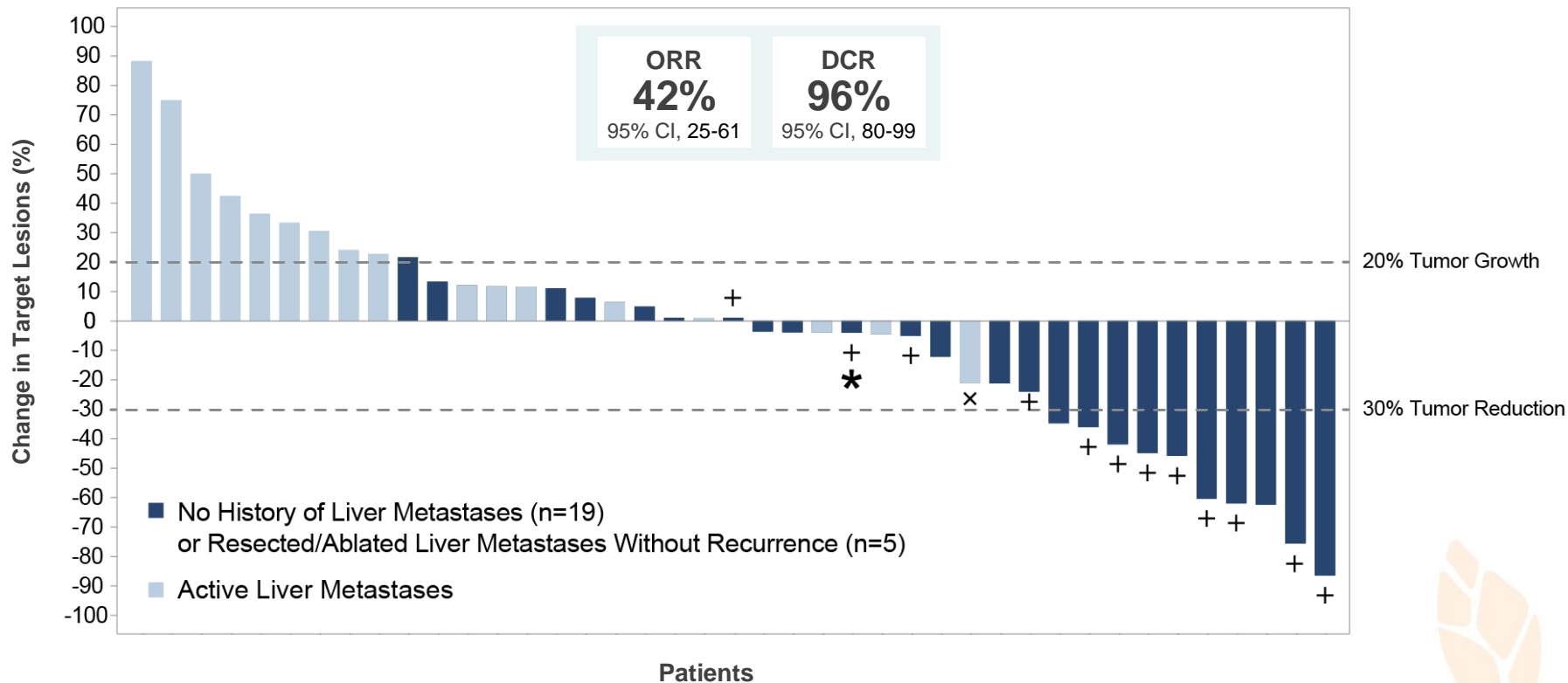
- 10% Bot only
- 10% Bot and Bal





# 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



# Acknowledgements

- Agenus Inc. funded and is the legal entity responsible for this study
- The authors would like to thank the patients and their families for participating in the C-800-01 study, as well as the trial coordinators and investigators for their contributions



# 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 Fakh: 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.
- AS Balmanoukian: Speakers' Bureau: AstraZeneca, Bristol-Myers Squibb, Genentech;
- Institutional Research Funding: AbbVie, Arcus Biosciences, Genentech/Roche, Incyte, Merck Seattle Genetics.
- BL Schlechter: Nothing to disclose.
- W Ortuzar Feliu: Employee of Agenus with stock/stock options.
- 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.
- JL Godwin: Employee of Agenus with stock/stock options.
- SJ O'Day: Employee of Agenus with stock/stock options.
- 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.
- **AB 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.**

