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


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-Khoutieiry

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

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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

<table>
<thead>
<tr>
<th>Treatment beyond 3L</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard of Care</td>
<td>~2 months</td>
<td>~6 months</td>
</tr>
</tbody>
</table>

| 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
- IO-only responses are rare
- PD-1/TKIs: variable efficacy and durability

Advanced, metastatic or treatment-resistant CRC

Novel Immunotherapy Agents

**botensilimab**

Fc-enhanced CTLA-4 Inhibitor

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

**Function (relative to first-gen CTLA-4)**
- ↑ Frequency of activated DCs
- ↑ T cell priming, expansion, memory
- ↑ Treg depletion
- ↓ Complement mediated toxicity

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

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

Novel Immunotherapy Agents

**botensilimab**

**Fc-enhanced CTLA-4 Inhibitor**

- Complete blocker of PD-L1/2 interactions
- Enhanced T cell activation and effector function
- ↑ T cell priming, expansion, memory
- ↑ Treg depletion
- ↓ Complement mediated toxicity

**balstilimab**

**PD-1 Inhibitor**

- Safety and efficacy analogous to approved anti-PD-1 mAbs
- Active in cold and IO refractory tumors

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

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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)**

**Efficacy**

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

**Safety**

- AEs
- TRAEs
- irAEs

1. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT03860272).

*Crossover to combination from botensilimab monotherapy permitted.*
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)**

**Monotherapy every 3 weeks**

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

**Monotherapy every 6 weeks**

- Combination therapy
  - [Fc-enhanced CTLA-4]
  - 1 or 2 mg/kg Q6W

**ENDPOINTS**

**Efficacy**

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

**Safety**

- AEs
- TRAEs
- irAEs

---


* Crossover to combination from botensilimab monotherapy permitted.
C-800 Study Design

NCT03860272: First-in-human trial of botensilimab ± balstilimab in patients with advanced cancer¹,²

**KEY ELIGIBILITY**

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

**TREATMENT (Up to 2 years)**

- **Monotherapy every 3 weeks**
  - botensilimab [Fc-enhanced CTLA-4]
  - 0.1, 0.3, 1, 2, 3 mg/kg Q3 or Q6W

- **Monotherapy every 6 weeks**
  - botensilimab [Fc-enhanced CTLA-4]
  - 0.1, 0.3, 1, 2 mg/kg Q6W

- **Combination therapy**
  - [Fc-enhanced CTLA-4]
  - 0.1, 0.3, 1, 2 mg/kg Q6W
  - balstilimab [PD-1]
  - 3 mg/kg Q2W

**ENDPOINTS**

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

**Safety**
- AEs
- TRAEs
- irAEs

*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\(^1,2\)

**KEY ELIGIBILITY**

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

**CRC Cohort**
- Metastatic CRC
- MSS by local assessment

**ENDPOINTS**

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

**Safety**
- AEs
- TRAEs
- irAEs

**TREATMENT** *(Up to 2 years)*

- Monotherapy every 3 weeks
  - [Fc-enhanced CTLA-4] \(0.1, 0.3, 1, 2, 3\) mg/kg Q3 or Q6W
  - [PD-1] 1 or 2 mg/kg Q6W

- Monotherapy every 6 weeks
  - 3 mg/kg Q2W

- Combination therapy
  - [Fc-enhanced CTLA-4] 1 or 2 mg/kg Q6W
  - [PD-1] 3 mg/kg Q2W

- Imaging Q6W

**Overall MSS CRC (N=41)**


*Crossover to combination from botensilimab monotherapy permitted.*
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.

**MSS CRC Patient Characteristics**

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

Evaluable patients treated with Bot + Bal had ≥1 Q6W imaging assessment.
## Efficacy: Durable Objective Responses

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

- 8/10 objective responses ongoing
- 3 responses >1 year
- Median DOR not reached
Waterfall Plot (N=41)

ORR
24%
95% CI, 14-39

DCR
73%
95% CI, 58-84

Patients

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

TRAEs in ≥10% of Patients (N=41)

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

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)

<table>
<thead>
<tr>
<th>ORR</th>
<th>DCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>42%</td>
<td>96%</td>
</tr>
<tr>
<td>95% CI, 25-61</td>
<td>95% CI, 80-99</td>
</tr>
</tbody>
</table>

Change in Target Lesions (%)

- No History of Liver Metastases (n=19)
- or Resected/Ablated Liver Metastases Without Recurrence (n=5)
- Active Liver Metastases

+ = 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-relate 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)

- 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, Oncoocyte.
- K Margolin: Nothing to disclose.
- BA Wilky: Consultant/Advisory Role: Immune Design, Janssen Oncology, Eli Lilly, Novartis; Travel/Accommodation/Expenses: Advencen Laboratories, Agenus, Eli Lilly, Novartis; Research Funding: Agenus, ArQule, Daiichi Sankyo, Merck Sharp & Dohmnn, Novartis.
- D Mahadevan: Speakers’ Bureau: Caris, Guardant Health; Steering Committee: Janssen.
- B Bockorny: Advisory Board Participation: Blueprint Medicines; Research Funding: NanoView Biosciences; Travel Expenses: Erytech Pharma.
- AS Balmanoukian: Speakers’ Bureau: AstraZeneca, Bristol-Myers Squibb, Genentech.
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- 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.
- JL Godwin: Employee of Agenus with stock/stock options.
- SJ O’Day: Employee of Agenus with stock/stock options.
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- 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.