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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rego1,2</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>TAS-1023</td>
<td>2</td>
<td>44</td>
</tr>
</tbody>
</table>

Limited Efficacy in 3L+ MSS CRC

Standard of Care

mPFS ~2 months
mOS ~6 months

Investigational

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rego1,2</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>TAS-1023</td>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>PD-(L)1 mono4-9 (n&gt;150)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Ipi Nivo10 (n=20)</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Durva/Treme11 (n=119)</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>PD-(L)1/TKI/other12 (n=95)</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

~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

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)²,³:
- ↑ Frequency of activated DCs
- ↑ T cell priming, expansion, memory
- ↑ Treg depletion
- ↓ Complement mediated toxicity

Active in cold and IO refractory tumors¹:

Novel Immunotherapy Agents

**botensilimab**
Fc-enhanced CTLA-4 Inhibitor

- Complete blocker of PD-1-PD-L1/2 interactions
- Enhanced T cell activation and effector function
- $\uparrow$ T cell priming, expansion, memory
- $\uparrow$ Treg depletion
- $\downarrow$ Complement mediated toxicity

**balstilimab**
PD-1 Inhibitor

- Safety and efficacy analogous to approved anti-PD-1 mAbs
- Active in cold and IO refractory tumors
- $\uparrow$ T cell priming, expansion, memory
- $\uparrow$ Treg depletion
- $\downarrow$ Complement mediated toxicity

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)**

<table>
<thead>
<tr>
<th>Monotherapy every 3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1, 0.3, 1, 2, 3 mg/kg Q3W</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monotherapy every 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1, 0.3, 1, 2 mg/kg Q6W</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Fc-enhanced CTLA-4]</td>
</tr>
<tr>
<td>0.1, 0.3, 1, 2 mg/kg Q6W</td>
</tr>
<tr>
<td>[PD-1]</td>
</tr>
<tr>
<td>3 mg/kg Q2W</td>
</tr>
</tbody>
</table>

**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 cancer\(^1,2\)

## KEY ELIGIBILITY

**Dose Escalation**

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

## TREATMENT *(Up to 2 years)*

<table>
<thead>
<tr>
<th>ENDPOINTS</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR, DCR (SD, CR or PR), PFS, DOR, OS</td>
<td>AEs, TRAEs, irAEs</td>
</tr>
</tbody>
</table>

## ENDPOINTS

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

## Dose Escalation

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

- **Monotherapy every 3 weeks**
  - 1 or 2 mg/kg Q6W bot

- **Monotherapy every 6 weeks**
  - 1 or 2 mg/kg Q6W bot

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

---


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

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

**KEY ELIGIBILITY**

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

**TREATMENT (Up to 2 years)**

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>bot*</th>
<th>bal</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-in-human trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monotherapy every 3 weeks</strong></td>
<td>bot*</td>
<td>bal</td>
</tr>
<tr>
<td>0.1, 0.3, 1, 2 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 or Q6W</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monotherapy every 6 weeks</strong></td>
<td>bot*</td>
<td>bal</td>
</tr>
<tr>
<td>0.1, 0.3, 1, 2 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q6W</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2W</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Combination therapy**

- [Fc-enhanced CTLA-4]
- [PD-1]

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>bot*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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


*Crossover to combination from botensilimab monotherapy permitted.

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)

ENDPOINTSTREATMENT
(Up to 2 years)

Overall MSS CRC (N=41)

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy every 3 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy every 6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging Q6W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Safety
- AEs
- TRAEs
- irAEs


*Crossover to combination from botensilimab monotherapy permitted.
### MSS CRC Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N=41)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>57 (36-82)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (41)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (59)</td>
</tr>
<tr>
<td>ECOG PS at baseline, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (41)</td>
</tr>
<tr>
<td>1</td>
<td>24 (59)</td>
</tr>
<tr>
<td>Prior lines of therapy, n (%)</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>Prior immunotherapy, n (%)†</td>
<td>14 (34)</td>
</tr>
<tr>
<td>Botensilimab dose, n (%)</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>Microsatellite stable status, n (%)</td>
<td>41 (100)</td>
</tr>
<tr>
<td>RAS mutation, n (%)</td>
<td>21 (51)</td>
</tr>
<tr>
<td>BRAF mutation, n/N (%)</td>
<td>2/38 (5)</td>
</tr>
</tbody>
</table>

*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.

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

### Observations

- 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)

ORR 42%
95% CI, 25-61

DCR 96%
95% CI, 80-99

<table>
<thead>
<tr>
<th>Change in Target Lesions (%)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No History of Liver Metastases (n=19) or Resected/Ablated Liver Metastases Without Recurrence (n=5)</td>
<td>Ongoing PR/SD</td>
</tr>
<tr>
<td>Active Liver Metastases</td>
<td>Complete metabolic response by PET</td>
</tr>
<tr>
<td>=Progression of non-target lesions</td>
<td></td>
</tr>
</tbody>
</table>

20% Tumor Growth
30% Tumor Reduction
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
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, Oncocyte.
- 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.
- 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 & Dohrn, 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;
- 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.
- JL Godwin: Employee of Agenus with stock/stock options.
- SJ O’Day: Employee of Agenus with stock/stock options.
- AM Tsimberidou: Consulting/Advisory Role: Diaaccurate, 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, Exelisix, Gilead, Merck, MedImmune; Research Funding: Astex Pharmaceuticals, AstraZeneca, MedImmune, Merck, Pieris Pharmaceuticals, Roche.