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29 JUNE–2 JULY 2022

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

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Declaration of Interests

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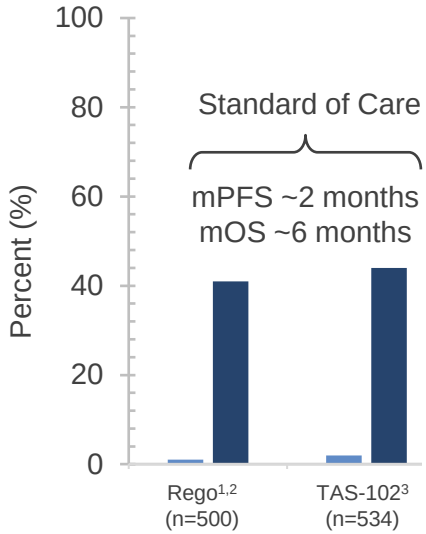
Advisory Role/Honoraria: Agenus, AstraZeneca, Bayer, Bristol-Myers Squibb, CytomX Therapeutics, Eisai, EMD Serono, Exelixis, Gilead, Merck, MedImmune

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

Limited Efficacy in 3L+ MSS CRC



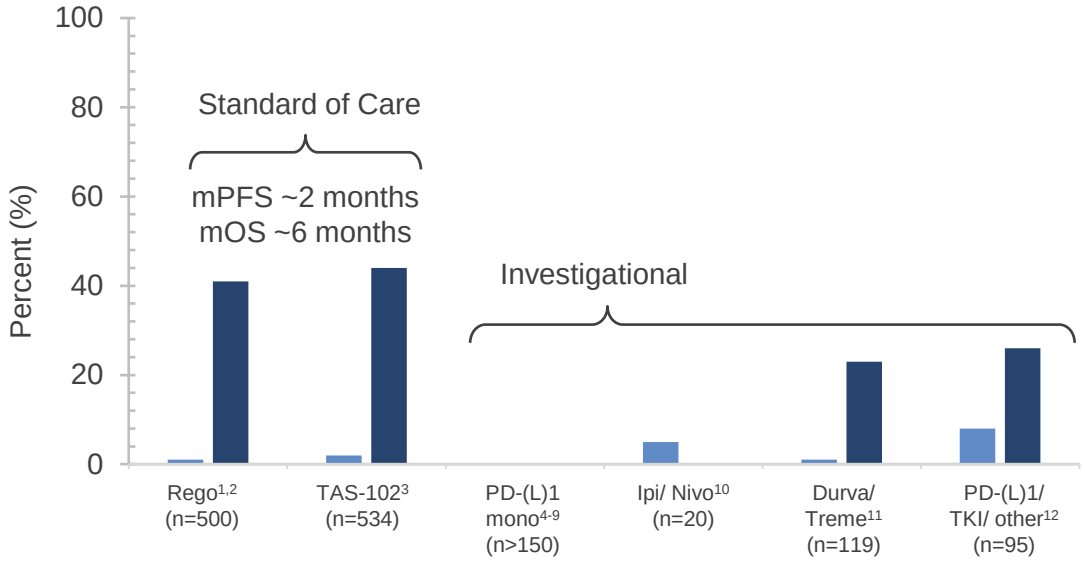
ORR (%)	1	2
DCR (%)	41	44

Third line and beyond

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

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.

Limited Efficacy in 3L+ MSS CRC



	Rego[1,2] (n=500)	TAS-102[3] (n=534)	PD-(L)1 mono[4-9] (n>150)	Ipi/ Nivo[10] (n=20)	Durva/ Treme[11] (n=119)	PD-(L)1/ TKI/ other[12] (n=95)
ORR (%)	1	2	0	5	1	8
DCR (%)	41	44	-	-	23	26

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

- IO-only responses are rare[4-11]
- PD-1/TKIs: variable efficacy and durability[12]

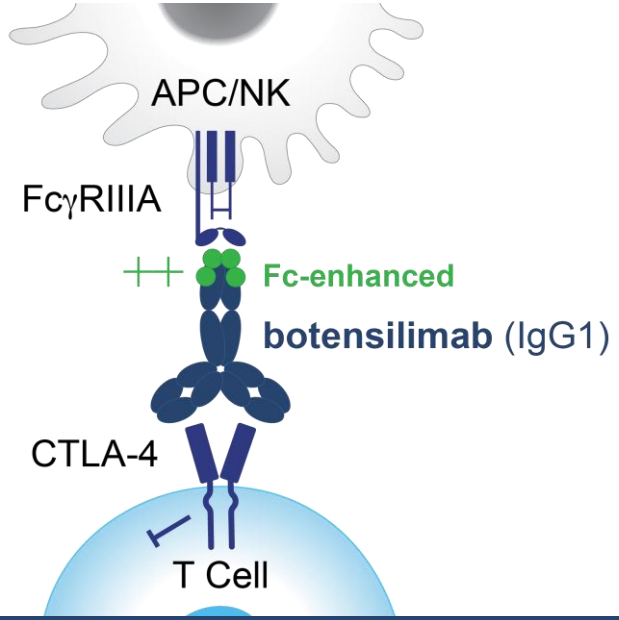
Advanced, metastatic or treatment-resistant CRC

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[1]:

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

1. El-Khoueiry AB. SITC 2021 Annual Meeting. Poster #479. 2. Waight et al. *Cancer Cell*. 2018;33(6): 1033-1047. 3. Data on File. Agenus Inc. June 2022.

Novel Immunotherapy Agents

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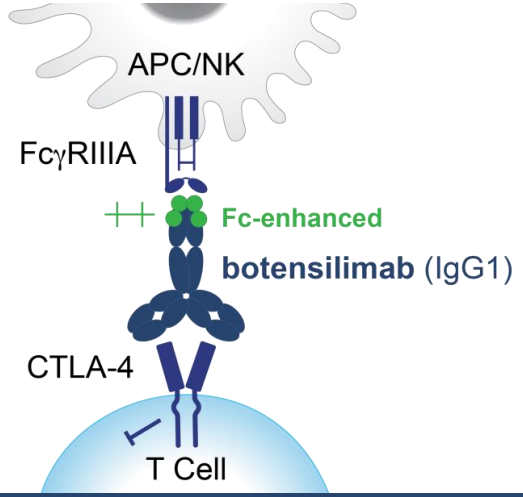
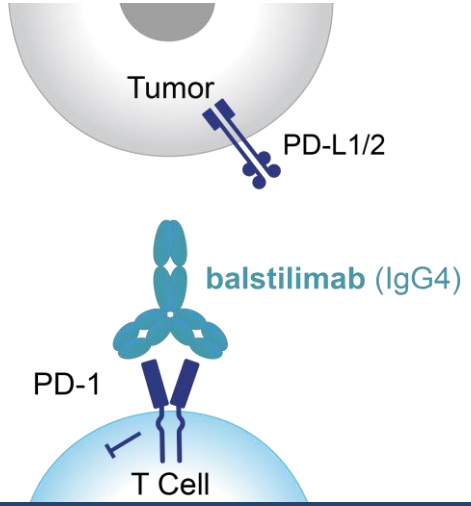


Active in cold and IO refractory tumors[1]:

- ↑ T cell priming, expansion, memory[2]
- ↑ Treg depletion
- ↓ 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

1. El-Khoueiry AB. SITC 2021 Annual Meeting. Poster #479. 2. Waight et al. *Cancer Cell*. 2018;33(6): 1033-1047. 3. O'Malley, et al. *Gynecol Oncol*. 2021; 163: 274-280. 4. O'Malley et al, *J Clin Oncol*. 2022; 40(7): 762-771.

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)*

bot*

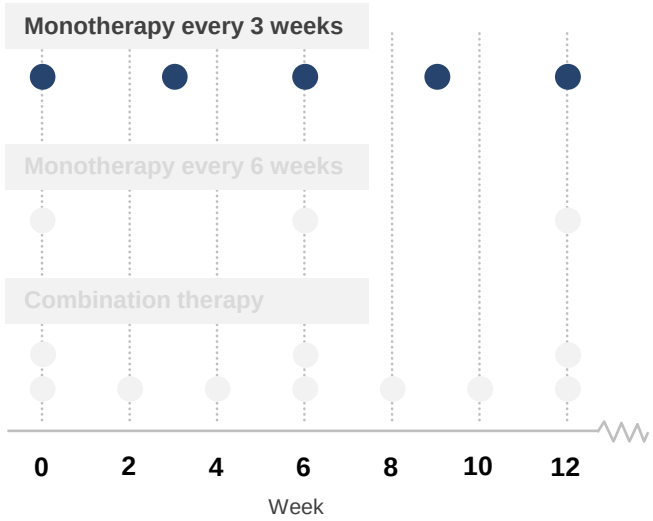
[Fc-enhanced CTLA-4]

0.1, 0.3, 1, 2, 3 mg/kg
Q3W

bot + bal

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

0.1, 0.3, 1, 2 mg/kg **Q6W** 3 mg/kg **Q2W**



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.

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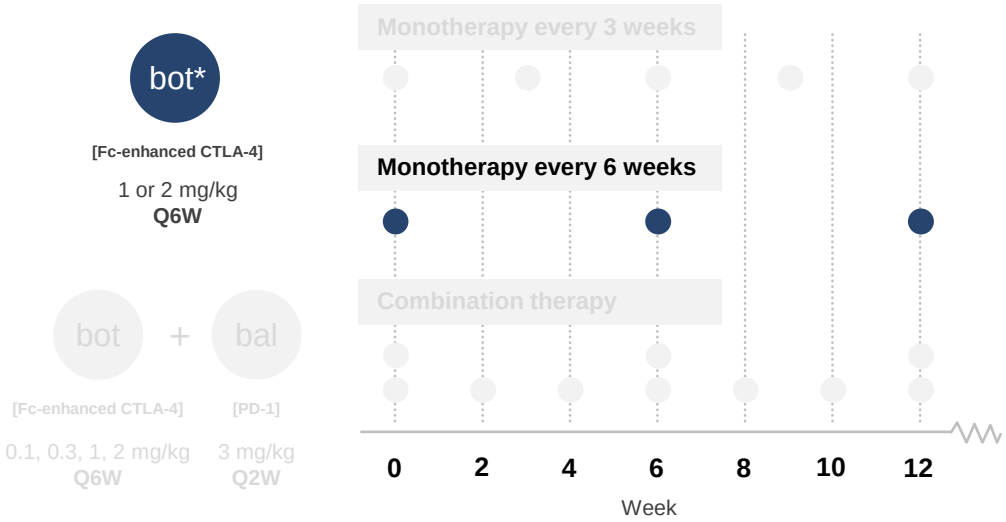

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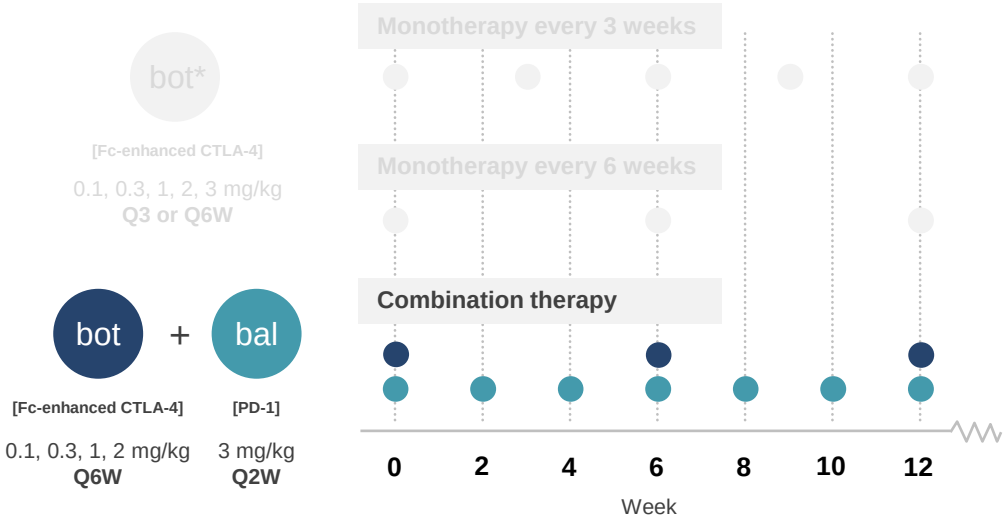

ENDPOINTS

Efficacy

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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

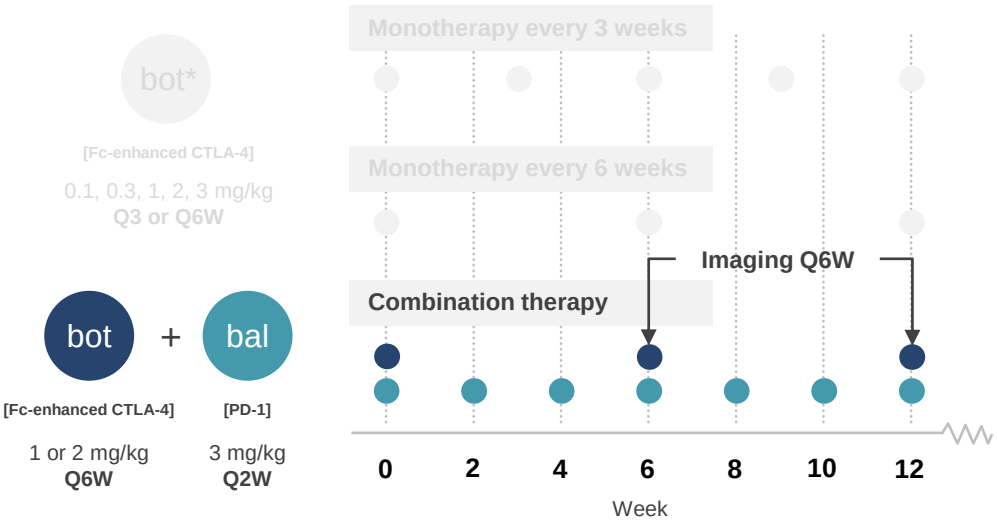
Dose Escalation

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

CRC Cohort

- Metastatic CRC
- MSS by local assessment

TREATMENT *(Up to 2 years)*



Overall MSS CRC (N=41)

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)*
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)

*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.

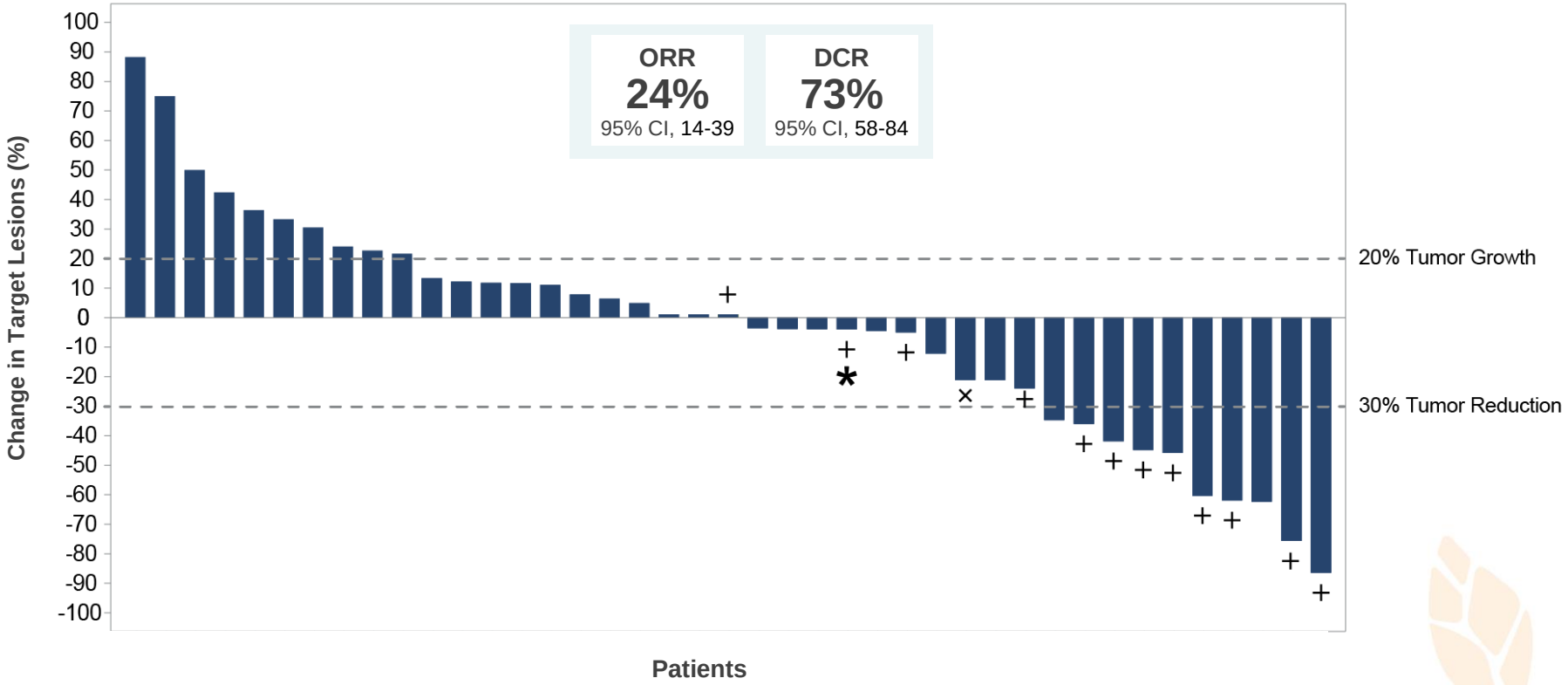
Evaluable patients treated with Bot + Bal had ≥1 Q6W imaging assessment

Efficacy: Durable Objective Responses

	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 ×=Progression of non-target lesions

Safety

TRAEs in ≥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:

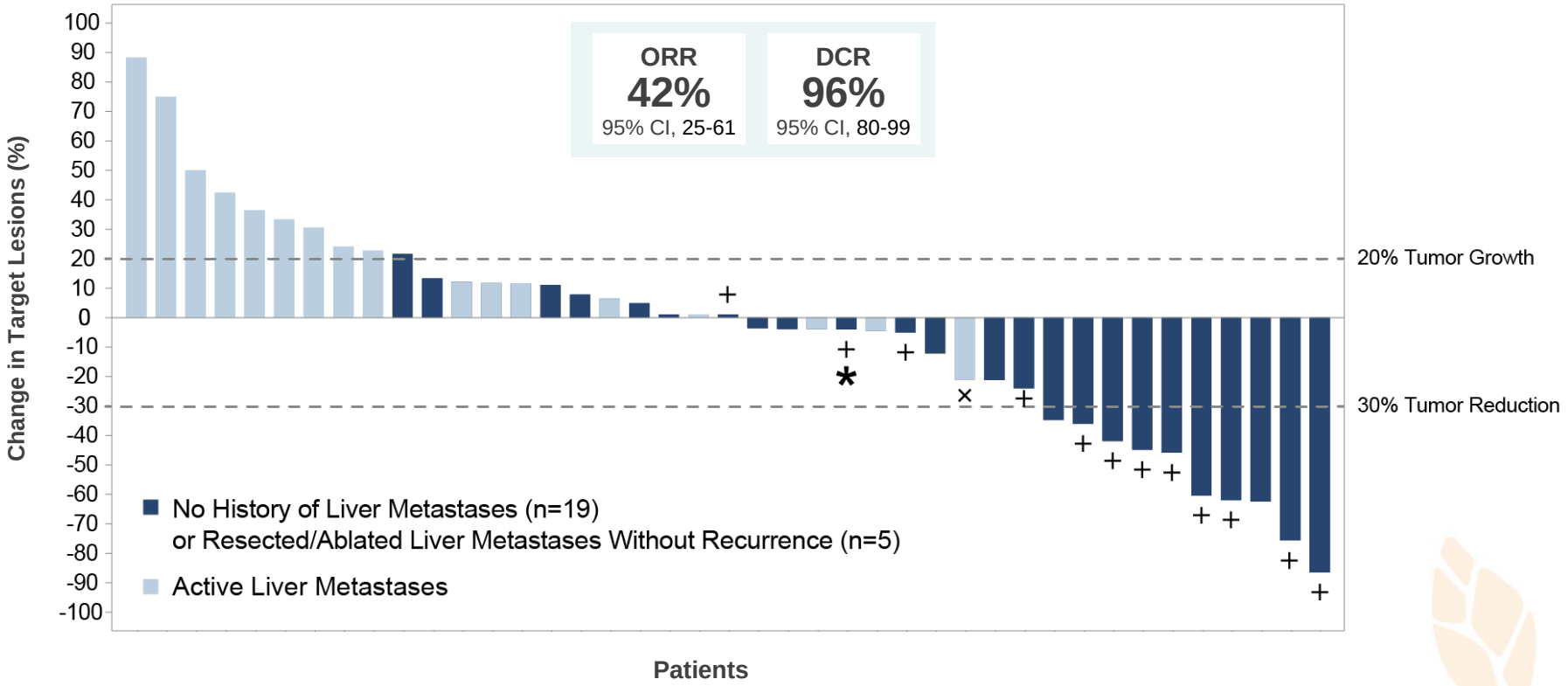
- 46% any grade
- 17% grade 3

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 ×=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)

- 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, Salarius, 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 & Dohmn, 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**.