Botensilimab ± Balstilimab in Patients with Advanced Cutaneous Melanoma Refractory/Resistant to Anti–PD-(L)1 ± CTLA-4: A Phase 2 Trial

Poster 259

Abstract 545192

Michael B. Atkins[1], Alan Arrieira Azambuja[2], Caroline Robert[3], Reinhard Dummer[4], Céleste Lebbé[5,6], Paul D. Nathan[7], Andreia Cristina de Melo[8], Igor A. Utyashev[9], Bart Neyns[10], Iván Márquez-Rodas[11], Justin C. Moser[12], Heather M. Shaw[7,13], Anna Maria Di Giacomo[14], Wei Wu[15], Joseph E. Grossman[15], Steven J. O'Day[15], Patrick A. Ott[16], Dirk Schadendorf[17], Eva Muñoz Couselo[18], Paolo Ascierto[19]

[1]Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA; [2]Centro Gaúcho Integrado and Hospital Mãe de Deus, Porto Alegre, Brazil; [3]Gustave Roussy et Université Paris Saclay, Villejuif, France; [4]Universitäts Spital Zürich, Zurich, Switzerland; [5]Université Paris Cité, AP-HP Dermato-Oncology, Paris, France; [6]CIC; Cancer Institute APHP. Nord Paris Cité, INSERM U1342 - Equipe 1 - CNRS EMR8000, Saint Louis Hospital, Paris, France; [7]Mount Vernon Cancer Centre, Northwood, London, UK; [8]Brazilian National Cancer Institute, Clinical Research Division, Rio de Janeiro, Brazil; [9]Hadassah Institute of Oncology, Moscow, Russia; [10]Universitair Ziekenhuis Brussel, Brussels, Belgium; [11]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [12]HonorHealth, Scottsdale, AZ, USA; [13]Department of Medical Oncology, University College London Hospital, London, UK; [14]University of Siena and Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [15]Agenus Inc, Lexington, MA, USA; [16]Dana-Farber Cancer Institute, Boston, MA, USA; [17]Universitätsmedizin Essen, Essen, Germany; [18]Vall d'Hebron Institute of Oncology, Barcelona Hospital Campus, Barcelona, Spain; [19]Istituto Nazionale Tumori IRCCS Fondazione G. Pascale and University of Naples Federico II, Naples, Italy

Background

- Patients with advanced cutaneous melanoma refractory/resistant (R/R) to PD-(L)1–based therapy, including anti–PD-(L)1 + anti–CTLA-4, have few treatment options available[1]
  - Prognosis in this setting remains poor; median OS is ~13–14 months among patients R/R to anti–PD-(L)1 and anti–CTLA-4[2,3]
- Botensilimab (BOT), a multifunctional Fc-enhanced anti–CTLA-4 antibody, augments T-cell priming, depletes intratumoral regulatory T cells, and activates antigen-presenting cells to overcome immune checkpoint inhibitor (ICI) resistance[4]
- BOT ± balstilimab (BAL; anti–PD-1 antibody pharmacologically comparable to approved PD-1 inhibitors) has shown activity in ICI-R/R and "cold" tumors[5-9]
- **Here, we report results from an open-label, global phase 2 trial of patients with advanced cutaneous melanoma R/R to prior anti–PD-(L)1 ± anti–CTLA-4**

C-800-23 Study Design

NCT05529316 (C-800-23): Phase 2 Trial of BOT±BAL in Advanced Cutaneous Melanoma R/R to Anti–PD-(L)1 ± Anti–CTLA-4

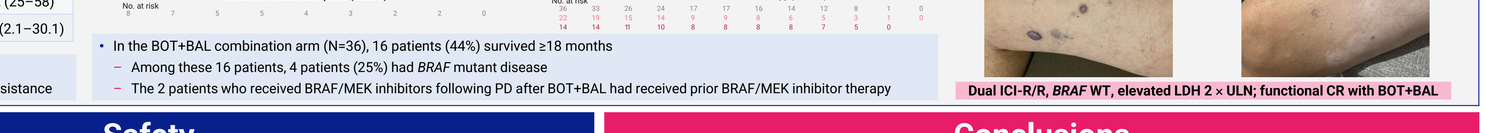
Key Eligibility

- Advanced cutaneous melanoma (stage III unresectable or IV)
- R/R to prior anti–PD-(L)1 ± anti–CTLA-4

Endpoints

- Primary: Confirmed ORR by RECIST 1.1
- Secondary: DOR, PFS, OS, safety and tolerability
- Exploratory: CBR (CR, PR, or SD at ≥24 weeks)

Trial Schema and Statistical Analysis



[a]Study was enrolled sequentially.

Data cutoff date: April 8, 2026. Tumor imaging Q9W through week 54, then Q12W until off study.
Intent-to-treat population (efficacy analyses): all patients. Safety population (safety analyses): all patients who received any amount of study drug(s).

Results

Patient Characteristics

Table 1. Demographics and Baseline Disease Characteristics

Characteristic	BOT Monotherapy: Overall BOT N=138	BOT+BAL Combination Therapy: Cohort A n=22	BOT+BAL Combination Therapy: Cohort B n=14	BOT+BAL Combination Therapy: Overall BOT+BAL N=36
Age, years, median (range)	63 (20–88)	67 (36–91)	61 (49–78)	65 (36–91)
Male	87 (63)	13 (59)	11 (79)	24 (67)
ECOG PS of 1	49 (36)	11 (50)	4 (29)	15 (42)
M staging				
M1a or III	34 (25)	10 (45)	3 (21)	13 (36)
M1b	30 (22)	4 (18)	5 (36)	9 (25)
M1c	68 (49)	7 (32)	5 (36)	12 (33)
M1d	6 (4)	1 (5)	1 (7)	2 (6)
***BRAF* status**				
V600	42/137 (31)	7 (32)	2 (14)	9 (25)
Wild type	95/137 (69)	15 (68)	12 (86)	27 (75)
Prior BRAF/MEK therapy	35 (25)	2 (9)	2 (14)	4 (11)
Elevated LDH, >1 × ULN	54 (39)	8 (36)	5 (36)	13 (36)
Prior anti–PD-(L)1 therapy				
Primary resistance[a]	92 (67)	19 (86)	10 (71)	29 (81)
Secondary resistance[b]	44 (32)	3 (14)	3 (21)	6 (17)
Unknown	2 (1)	0	1 (7)	1 (3)
Prior anti–CTLA-4 therapy				
Primary resistance[a]	48/76 (63)[c]	-	12 (86)	-
Secondary resistance[b]	25/76 (33)[c]	-	2 (14)	-
Unknown	3/76 (4)[c]	-	0	-

n (%) unless otherwise noted. [a]Primary resistance was defined as BOR of PD or PD <6 months from most recent course of respective ICI type.[10] [b]Secondary resistance was defined as PD ≥6 months from most recent course of respective ICI type.[10] [c]76 patients in the monotherapy arm had prior anti–CTLA-4.

- In the BOT monotherapy arm, median number of BOT doses was 3 (range, 1–4)
- In the BOT+BAL combination arm, median number of BOT and BAL doses was 3 (range, 1–4) and 4.5 (range, 1–35), respectively

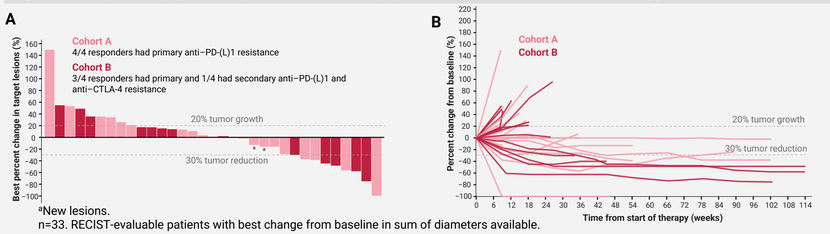
Efficacy with BOT+BAL Combination Therapy

Table 3. BOT+BAL Combination Therapy Efficacy Overview

	Cohort A n=22	Cohort B n=14	Overall BOT+BAL N=36
Confirmed ORR, n (%) | 95% CI	4 (18) | 5–40	4 (29) | 8–58	8 (22) | 10–39
BOR, n (%)			
CR	0	0	0
PR	4 (18)	4 (29)	8 (22)
SD	7 (32)	5 (36)	12 (33)
PD	9 (41)	5 (36)	14 (39)
Not evaluable	2 (9)	0	2 (6)
Median DOR, months (95% CI)	13.0 (4.2–NE)	NR (NR–NR)	NR (4.2–NR)
12-month DOR, % (95% CI)	67 (5–95)	100 (100–100)	86 (33–98)
CBR, n (%) | 95% CI	7 (32) | 14–55	5 (36) | 13–65	12 (33) | 19–51
Median PFS, months (95% CI)	3.9 (2.1–6.2)	4.2 (2.0–NE)	4.0 (2.1–6.2)
12-month PFS, % (95% CI)	25 (9–44)	36 (13–59)	29 (15–44)
Median OS, months (95% CI)	10.1 (5.4–23.8)	NR (5.2–NR)	16.6 (9.1–NE)
24-month OS, % (95% CI)	28 (11–48)	64 (34–83)	42 (25–58)
Median FU, months (range)	9.9 (2.1–30.1)	28.3 (3.2–29.0)	13.8 (2.1–30.1)

- Cohort A: All 4 responders had primary ICI resistance
- Cohort B: 3 responders had primary and 1 responder had secondary ICI resistance

Figure 2. Responses (A) and Responses Over Time (B) with BOT+BAL Combination Therapy



[a]New lesions.
n=33. RECIST-evaluable patients with best change from baseline in sum of diameters available.

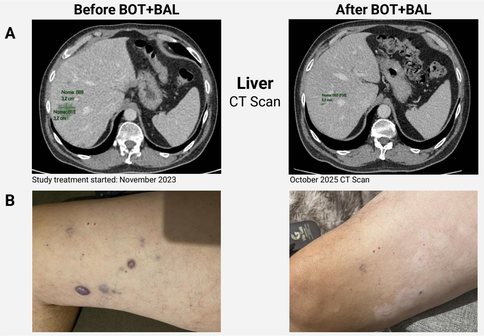
Figure 3. Duration of Response (A) and Overall Survival (B) with BOT+BAL Combination Therapy

- In the BOT+BAL combination arm (N=36), 16 patients (44%) survived ≥18 months
  - Among these 16 patients, 4 patients (25%) had *BRAF* mutant disease
  - The 2 patients who received BRAF/MEK inhibitors following PD after BOT+BAL had received prior BRAF/MEK inhibitor therapy

Case Study:
Durable BOT+BAL response after prior anti–PD-1 + anti–CTLA-4
67-year-old male with *BRAF* wild-type metastatic cutaneous melanoma who completed 2 years of treatment

- **Prior therapy:** Pembrolizumab then ipilimumab (each with primary progression)
- **Baseline disease:** M1c melanoma with liver, lymph node, peritoneal, and subcutaneous tissue involvement; LDH 2 × ULN
- **Best response:** Ongoing PR (functional CR by PET at 30+ months per investigator after data cutoff)

Figure 4. Case Study Liver CT Scans (A) and Skin Photos (B)



Dual ICI-R/R, *BRAF* WT, elevated LDH 2 × ULN; functional CR with BOT+BAL

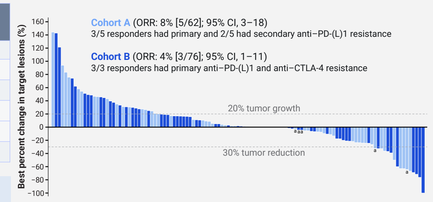
Efficacy with BOT Monotherapy

Table 2. BOT Monotherapy Efficacy Overview

	Overall BOT N=138
Confirmed ORR, n (%) | 95% CI	8 (6) | 3–11
12-month DOR, % (95% CI)	38 (9–67)
CBR, n (%) | 95% CI	19 (14) | 9–21
Median OS, months (95% CI)	12.9 (9.7–16.2)
24-month OS, % (95% CI)	28 (21–36)
Median FU, months (range)	12.3 (0.2–38.7)

- Unconfirmed ORR in the BOT monotherapy arm was 10% (n=14/138; 95% CI, 6–16)
- Efficacy was similar across BOT monotherapy doses, with higher-grade adverse events at the higher dose (**Table 4**)

Figure 1. Responses with BOT Monotherapy



[a]New lesions.
n=117. RECIST-evaluable patients with best change from baseline in sum of diameters available.

Safety

Table 4. Safety Overview

n (%)	BOT Monotherapy: BOT 50 mg n=62		BOT Monotherapy: BOT 150 mg n=76		BOT+BAL Combination: BOT 75 mg+BAL 450 mg N=36	
Any TRAE	43 (69)		69 (91)		34 (94)	
Grade ≥3	12 (19)		30 (39)		13 (36)	
Leading to discontinuation of BOT[a]	6 (10)		30 (39)		8 (22)	
Leading to discontinuation of BAL[b]	-		-		5 (14)	
Most common (≥15%) TRAEs[c]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Diarrhea/colitis[d]	20 (32)	4 (6)	48 (63)	18 (24)	19 (53)	4 (11)
Asthenia	5 (8)	0	15 (20)	1 (1)	8 (22)	1 (3)
Pyrexia	5 (8)	1 (2)	18 (24)	0	8 (22)	0
Decreased appetite	3 (5)	0	12 (16)	1 (1)	8 (22)	0
Pruritus	0	0	11 (15)	1 (1)	8 (22)	0
ALT increased	7 (11)	1 (2)	7 (9)	1 (1)	7 (19)	2 (6)
Vitiligo	1 (2)	0	2 (3)	0	6 (17)	0
Nausea	5 (8)	0	17 (22)	2 (3)	5 (14)	1 (3)
Vomiting	3 (5)	1 (2)	13 (17)	1 (1)	3 (8)	1 (3)

- No new safety signals were observed
- One possibly treatment-related death was reported with BOT 50 mg monotherapy (immune-mediated enterocolitis)

[a]Related to BOT. [b]Related to BAL. [c]Preferred terms (unless otherwise noted). Multiple preferred terms may have occurred in 1 patient during a given event. [d]Diarrhea/colitis (grouped term) includes the preferred terms of diarrhea, colitis, enteritis, enterocolitis, and immune-mediated enterocolitis.

Conclusions

- In this advanced cutaneous melanoma population with predominantly primary ICI resistance, BOT+BAL produced:
  - Confirmed **ORR of 22%** in the overall population and **29% in Cohort B** (patients who were R/R to prior anti–PD-[L]1 + anti–CTLA-4)
  - Durable responses, with **median DOR not reached** and a **12-month DOR of 86%** in the overall population and **100% in Cohort B**
  - **Median OS of 16.6 months in the overall population and not reached in Cohort B**
- With BOT+BAL, grade ≥3 TRAEs occurred in 36% of patients and there were no treatment-related deaths

The encouraging ORRs, especially in the dual ICI-exposed cohort, support further evaluation of BOT+BAL in ICI-R/R cutaneous melanoma

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® or the author of this poster.

Correspondence: Michael B. Atkins: mba41@georgetown.edu.

Acknowledgments: Agenus Inc. funded and is the sponsor of this study. The authors thank the patients and their families for participating in the C-800-23 (NCT05529316) trial, as well as the trial coordinators and investigators for their contributions. We also thank Angelo Borsarelli Carvalho de Brito, MD, PhD (AC Camargo Cancer Center; São Paulo, Brazil) for provision of patient case study details and deidentified images (written consent for image use obtained from patient).

References: 1. Amaral T, et al. *Ann Oncol.* 2025;36(1):10–30. **2.** Medina T, et al. *J Clin Oncol.* 2025;43(33):3565–3572. **3.** Wong MK, et al. *J Clin Oncol.* 2025;43(33):3589–3599. **4.** Chand D, et al. *Cancer Discov.* 2024;14(12):2407–2429. **5.** Bullock AJ, et al. *Nat Med.* 2024;30(9):2558–2567. **6.** Wilky BA, et al. *J Clin Oncol.* 2025;43(11):1358–1368. **7.** Porter R, et al. *J Immunother Cancer.* 2025;13(12):e013222. **8.** El-Khoueiry A, et al. *Liver Cancer.* 2026; doi:10.1159/000551630. **9.** Gordon MS, et al. Presented at: ESMO 2025. Presentation #1517MO. Berlin, Germany. **10.** Kluger H, et al. *J Immunother Cancer.* 2023;11(3):e005921.

Abbreviations: ALT, alanine aminotransferase; BAL, balstilimab; BOR, best overall response; BOT, botensilimab; *BRAF*, V-Raf murine sarcoma viral oncogene homolog b; CBR, clinical benefit rate (CR, PR or SD at ≥24 weeks); CI, confidence interval; CR, complete response; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte associated protein 4; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, follow up; ICI, immune checkpoint inhibitor; LDH, lactate dehydrogenase; MEK, mitogen-activated extracellular signal-regulated kinase; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed cell death (ligand) 1; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; QXW, every X weeks; RECIST, Response Evaluation Criteria in Solid Tumors; R/R, refractory/resistant; SD, stable disease; TRAE, treatment-related adverse event; ULN, upper limit of normal; WT, wild-type.

Poster presented at the Annual American Society of Clinical Oncology Congress: May 29–June 2, 2026. Chicago, IL, US.