Final Analysis: Phase 1b Study Investigating Intratumoral Injection of Toll-Like Receptor 9 Agonist Vidutolimod ± Pembrolizumab in Patients With PD-1 Blockade–Refractory Melanoma

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INTRODUCTION

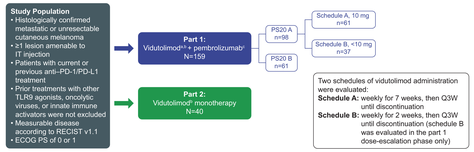
- The standard treatment for patients with advanced melanoma is programmed death 1 (PD-1) blockade alone or in combination with cytotoxic T-lymphocyte–associated protein 4 blockade[1]
  - PD-1 blockade therapy has markedly improved outcomes for many patients with cancer; however, most patients still progress on anti–PD-1 therapy and treatment alternatives are limited[1,2]
- Vidutolimod (CMP-001) is a first-in-class, immunostimulatory, noninfectious virus-like particle (VLP) containing a CpG-A Toll-like receptor 9 (TLR9) agonist[3]
  - In contrast to phosphorothioate CpG-C TLR9 agonists used in other studies,[4] vidutolimod is composed of CpG-A oligodeoxynucleotides with a native phosphodiester DNA backbone and polyG motifs that form G-quadruplexes[3,5]
  - The VLP delivery induces an anti-VLP immune response, providing a second stimulatory signal to the plasmacytoid dendritic cells (pDCs) through costimulation of TLR9 and CD32 (FcγRII); this leads to a more effective systemic antitumor CD8+ T cell response[3,6-8]
  - The native phosphodiester backbone allows cleavage of DNA in the endosome, resulting in stronger activation of TLR9 and higher secretion of type I interferon by pDCs; this results in the activation of immune cells in the tumor microenvironment and to the recruitment and activation of antitumor CD8+ T cells[3,6,9,10]
  - TLR9-mediated T-cell activation induces PD-1 expression[11]; therefore, combining TLR9 agonists with PD-1 blockade therapy, such as pembrolizumab, is a rational approach to overcome cancer immune evasion[12]
- We previously reported the results of the dose escalation part of this study, with an ORR of 25% (11/44 patients) in patients receiving a combination of vidutolimod and pembrolizumab[13]
- Here we report the final analysis of the phase 1b study, which evaluated the safety and clinical activity of intratumoral (IT) vidutolimod with and without pembrolizumab in patients with PD-1 blockade–refractory melanoma

METHODS

Study Design

- CMP-001-001 (NCT02680184) was a 2-part, open-label, multicenter, phase 1b study of vidutolimod + pembrolizumab or vidutolimod monotherapy (**Figure 1**)
  - Part 1: IT vidutolimod + intravenous pembrolizumab dose escalation and dose expansion
  - Part 2: IT vidutolimod monotherapy
- The primary objective of the study was to determine the recommended phase 2 dose (RP2D) and schedule for vidutolimod + pembrolizumab in part 1 and to determine the safety profile of vidutolimod monotherapy in part 2
  - The secondary objectives were to determine the safety, antitumor activity, and pharmacodynamics of vidutolimod + pembrolizumab

Figure 1. CMP-001-001 Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status; IT, intratumoral; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PS20 A, polysorbate 20 at 0.01%; PS20 B, polysorbate 20 at 0.00167%; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TLR9, Toll-like receptor 9.
[1]Includes standard "3+3" dose escalation (1, 3, 5, 7.5, 10 mg; n=44) and dose expansion (5, 10 mg; n=115).
[2]The protocol was amended to a dose of 10 mg in parts 1 and 2. Patients who were enrolled prior to the study protocol amendment who received vidutolimod doses <10 mg had the option to receive doses up to vidutolimod 10 mg on schedule A.
[3]Pembrolizumab was administered at the approved dose per the pembrolizumab label; patients who entered the study already receiving pembrolizumab remained on their previously assigned dose.

- Median duration of response (DOR) was estimated using Kaplan-Meier analysis
- Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC)

RESULTS

Patients

- Between April 14, 2016, and February 27, 2020, 159 patients were enrolled and treated with vidutolimod + pembrolizumab in part 1 and 40 patients were enrolled and treated with vidutolimod in part 2
- Demographics and baseline characteristics are shown in **Table 1**
- At the time of clinical data cutoff (August 17, 2021), 8 (5.0%) patients in part 1 and 4 (10%) patients in part 2 remained on study treatment

Table 1. Patient Demographics and Baseline Characteristics

	Part 1: Vidutolimod + Pembrolizumab (Dose Escalation and Expansion)			Part 2: Vidutolimod Monotherapy
Demographic or Characteristic	Vidutolimod PS20 A + Pembrolizumab n=98	Vidutolimod PS20 A 10 mg (Schedule A) + Pembrolizumab n=61	Vidutolimod PS20 B + Pembrolizumab n=61	Vidutolimod N=40
Median age, years (range)	63 (31-86)	62 (31-86)	65 (30-90)	68 (30-89)
Male sex, n (%)	46 (46.9)	26 (42.6)	43 (70.5)	26 (65.0)
Race, n (%)				
White	94 (95.9)	57 (93.4)	59 (96.7)	38 (95.0)
Black or African American	0	0	1 (1.6)	2 (5.0)
Asian	1 (1.0)	1 (1.6)	0	0
Other	3 (3.1)	3 (4.9)	1 (1.6)	0
ECOG PS, n (%)				
0 | 1	67 (68.4) | 31 (31.6)	44 (72.1) | 17 (27.9)	37 (60.7) | 24 (39.3)	20 (50.0) | 20 (50.0)
***BRAF* V600E mutation, n (%)**	34 (34.7)	23 (37.7)	24 (39.3)	12 (30.0)
High LDH levels, n (%)	38 (38.8)	30 (49.2)	28 (45.9)	18 (45.0)
Target lesion SLD, median (range)	6.7 (1.3-43.2)	6.0 (1.3-20.1)	7.0 (1.4-35.8)	5.6 (1.0-26.0)
No. of prior therapies, median (range)	2 (1-8)	2 (1-6)	2 (1-6)	2 (1-7)
1, n (%)	39 (39.8)	28 (45.9)	26 (42.6)	17 (42.5)
2-3, n (%)	39 (39.8)	26 (42.6)	25 (41.0)	14 (35.0)
≥4, n (%)	20 (20.4)	7 (11.5)	10 (16.4)	9 (22.5)
Any prior checkpoint inhibitor therapies received, n (%)	98 (100)	61 (100)	61 (100)	40 (100)
Best response to prior anti–PD-1 therapy, n (%)				
CR | PR	4 (4.1) | 11 (11.2)	3 (4.9) | 9 (14.8)	3 (4.9) | 9 (14.8)	3 (7.5) | 4 (10.0)
SD | PD	34 (34.7) | 41 (41.8)	21 (34.4) | 23 (37.7)	16 (26.2) | 28 (45.9)	18 (45.0) | 9 (22.5)
Unknown	8 (8.2)	5 (8.2)	5 (8.2)	6 (15.0)
Last response to prior anti–PD-1 therapy, n (%)				
PR	0	0	0	2 (5.0)
SD | PD	3 (3.1) | 92 (93.9)	1 (1.6) | 59 (96.7)	1 (1.6) | 56 (91.8)	4 (10.0) | 32 (80.0)
Unknown	3 (3.1)	1 (1.6)	4 (6.6)	2 (5.0)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PD, progressive disease; PD-1, programmed death 1; PR, partial response; PS20 A, polysorbate 20 at 0.01%; PS20 B, polysorbate 20 at 0.00167%; SLD, sum of longest diameter; SD, stable disease.

Safety

- Median follow-up was 14.8 months in part 1 (N=159) and 5.0 months in part 2 (N=40)
- Any grade treatment-related adverse events (TRAEs) were reported in 156 (98.1%) patients in part 1 and 38 (95.0%) patients in part 2
  - Most TRAEs were grade 1/2, as grade 3/4 TRAEs were only reported in 59 (37.1%) patients in part 1 and 9 (22.5%) patients in part 2
- The most common TRAEs (>25%) were flu-like symptoms (parts 1 and 2) and injection-site pain (part 1) (**Table 2**)

Table 2. TRAEs Reported in >25% of Patients and Grade 3/4 TRAEs Reported in ≥3 Patients in Either Part 1 or Part 2[a,b]

	Part 1: Vidutolimod + Pembrolizumab (Dose Escalation and Expansion) N=159			Part 2: Vidutolimod Monotherapy N=40	
Incidence, n (%)	Any grade	Grade 3	Grade 4	Any grade	Grade 3
Patients with ≥1 TRAE	156 (98.1)	55 (34.6)	4 (2.5)	38 (95.0)	9 (22.5)
Chills	119 (74.8)	5 (3.1)	0	24 (60.0)	0
Pyrexia	98 (61.6)	4 (2.5)	0	20 (50.0)	1 (2.5)
Fatigue	85 (53.5)	2 (1.3)	0	15 (37.5)	0
Nausea	77 (48.4)	0	0	19 (47.5)	0
Vomiting	50 (31.4)	0	0	9 (22.5)	0
Injection site pain	49 (30.8)	1 (0.6)	0	6 (15.0)	0
Headache	48 (30.2)	0	0	13 (32.5)	1 (2.5)
Back pain	34 (21.4)	5 (3.1)	0	10 (25.0)	0
Hypotension	33 (20.8)	10 (6.3)	1 (0.6)	11 (27.5)	2 (5.0)
Arthralgia	28 (17.6)	3 (1.9)	0	5 (12.5)	0
Pruritus	20 (12.6)	1 (0.6)	0	11 (27.5)	0
Hypertension	15 (9.4)	8 (5.0)	0	3 (7.5)	1 (2.5)
AST increased	12 (7.5)	3 (1.9)	1 (0.6)	1 (2.5)	1 (2.5)
ALT increased	11 (6.9)	2 (1.3)	1 (0.6)	2 (5.0)	1 (2.5)
Anemia	11 (6.9)	3 (1.9)	0	2 (5.0)	0
Hypoxia	8 (5.0)	4 (2.5)	0	2 (5.0)	0
Hypophosphatemia	6 (3.8)	3 (1.9)	0	2 (5.0)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; TRAE, treatment-related adverse event.
[a]There were no grade 4 events in part 2 and no grade 5 TRAEs in either part.
[b]The table is summarized based on the maximum CTCAE grade; patients were counted once per preferred term, using the highest severity event for that term.

Antitumor Activity

- The best objective response rate (ORR) was 23.5% (95% CI, 15.5-33.1) in patients receiving vidutolimod PS20 A + pembrolizumab per RECIST v1.1, with 7.1% of patients with a complete response (CR) (**Table 3** and **Figure 3A**)
- In patients receiving vidutolimod PS20 A 10 mg (schedule A), the best ORR was 23.0% (95% CI, 13.2-35.5)
  - Based on these data, the RP2D and schedule selected for further development was PS20 A 10 mg (schedule A)
- The best ORR, when including 4 (4.1%) patients with postprogression partial response, was 27.6% (95% CI, 19.0-37.5)
- Patients receiving vidutolimod monotherapy had an ORR of 20.0% (95% CI, 9.1-35.6) (**Figure 3B**)

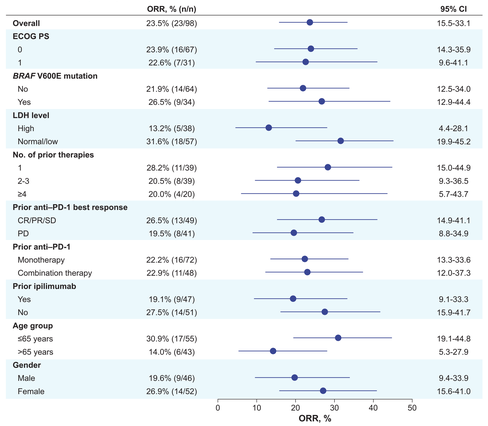
Table 3. Antitumor Activity

	Part 1: Vidutolimod + Pembrolizumab (Dose Escalation and Expansion)			Part 2: Vidutolimod Monotherapy
Parameter	Vidutolimod PS20 A + Pembrolizumab n=98	Vidutolimod PS20 A 10 mg (Schedule A) + Pembrolizumab n=61	Vidutolimod PS20 B + Pembrolizumab n=61	Vidutolimod N=40
Best ORR per RECIST v1.1 (95% CI)	23.5% (15.5-33.1)	23.0% (13.2-35.5)	11.5% (4.7-22.2)	20.0% (9.1-35.6)
Best ORR, including postprogression responders (95% CI)	27.6% (19.0-37.5)	27.9% (17.1-40.8)	16.4% (8.2-28.1)	22.5% (10.8-38.5)
Best response, n (%)				
CR	7 (7.1)	3 (4.9)	1 (1.6)	0
PR	16 (16.3)	11 (18.0)	6 (9.8)	8 (20.0)
Postprogression PR	4 (4.1)	3 (4.9)	3 (4.9)	1 (2.5)
SD	14 (14.3)	9 (14.8)	17 (27.9)	11 (27.5)
PD	50 (51.0)	31 (50.8)	29 (47.5)	20 (50.0)
No postbaseline scan	7 (7.1)	4 (6.6)	5 (8.2)	0
Median DOR, months (95% CI)	25.2 (8.7-NE)	NE (5.6-NE)	11.4 (5.4-19.9)	5.6 (3.1-NE)

CR, complete response; DOR, duration of response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; PS20 A, polysorbate 20 at 0.01%; PS20 B, polysorbate 20 at 0.00167%; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

- Similar response rates were observed across several baseline characteristics assessed (**Figure 2**), including Eastern Cooperative Oncology Group performance status (0 vs 1), *BRAF* V600E mutation status (yes vs no), number of prior therapies (1 vs 2-3 vs ≥4), and best response to prior PD-1 blockade therapies (CR/partial response/stable disease vs PD)

Figure 2. Subgroup Analyses of Best ORRs in Patients Receiving Vidutolimod PS20 A + Pembrolizumab (n=98)



CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ORR, objective response rate; PD, progressive disease; PD-1, programmed death 1; PR, partial response; PS20 A, polysorbate 20 at 0.01%; SD, stable disease.

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CONCLUSIONS

- IT vidutolimod + intravenous pembrolizumab demonstrated promising clinical activity in patients with PD-1 blockade–refractory melanoma
  - ORR of 23.5% per RECIST v1.1 (n=98), with 7.1% of patients with a CR
  - Durable responses with a median DOR of 25.2 months in responders (n=23/98)
  - Similar tumor regression in both injected and noninjected lesions (n=27/98)
- Vidutolimod also demonstrated single-agent activity
  - ORR of 20.0% per RECIST v1.1 and an ORR of 22.5%, when including postprogression responders
  - Median DOR of 5.6 months
- The tumor volume reductions in both injected and noninjected target lesions provide evidence that vidutolimod induced a systemic antitumor response
- The substantially longer DOR of vidutolimod + pembrolizumab compared to that of vidutolimod monotherapy provides strong rationale for further development of vidutolimod in combination with PD-1 blockade
- Based on the results, vidutolimod PS20 A 10 mg (schedule A) was selected as the RP2D
- Vidutolimod alone and in combination with pembrolizumab had a manageable safety profile
- Clinical studies to confirm the efficacy of vidutolimod + PD-1 blockade in patients with previously untreated unresectable or metastatic melanoma (NCT04695977) or PD-1 blockade–refractory melanoma (NCT04698187) are ongoing

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For more information on vidutolimod, use the following QR code.

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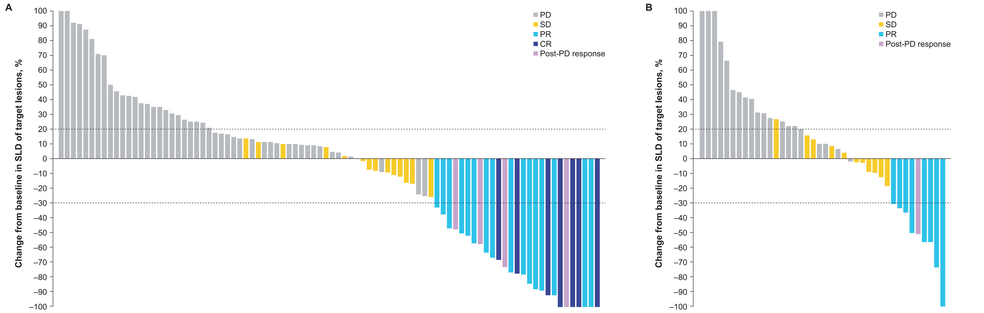
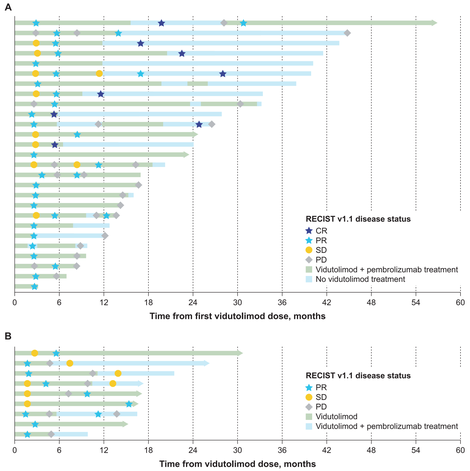
Figure 3. Best Change in Tumor Size in Patients Receiving (A) Vidutolimod PS20 A + Pembrolizumab (n=98) and (B) Vidutolimod Monotherapy (N=40)



CR, complete response; PD, progressive disease; PR, partial response; PS20 A, polysorbate 20 at 0.01%; SD, stable disease; SLD, sum of longest diameter.
Patients with missing or incomplete postbaseline SLD and disease assessments are not included in these plots. Y-axis is capped at 100%.

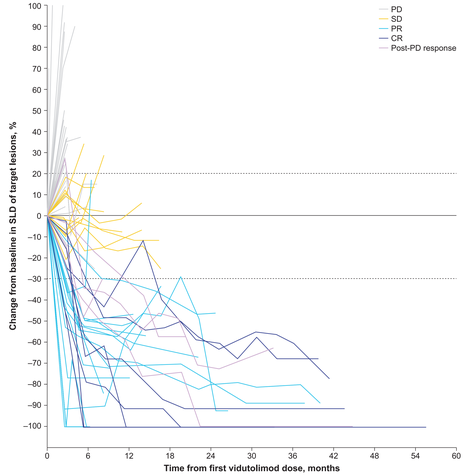
- Vidutolimod PS20 A + pembrolizumab resulted in durable responses (**Figure 4 and 5**), while patients that received vidutolimod monotherapy had less durable responses than with the combination
  - Median DOR of 25.2 months for combination and 5.6 months for monotherapy

Figure 4. Duration of Follow-Up and Response Assessments (A) With Vidutolimod PS20A + Pembrolizumab (n=27/98) and (B) Vidutolimod Monotherapy (N=9/40) in Responders



CR, complete response; PD, progressive disease; PR, partial response; PS20 A, polysorbate 20 at 0.01%; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.
Plot includes responders per RECIST v1.1 and postprogression responders.

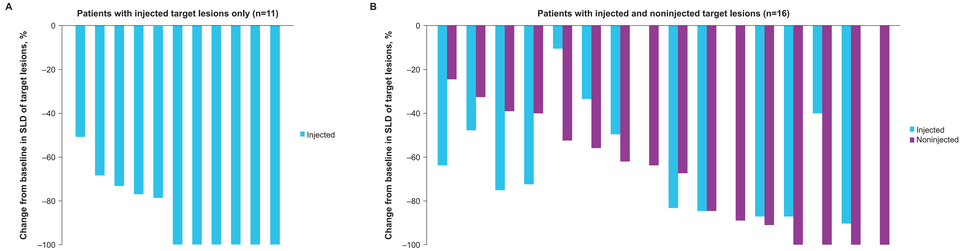
Figure 5. Tumor Response by Month in Patients Receiving Vidutolimod PS20 A + Pembrolizumab (n=98)



CR, complete response; PD, progressive disease; PR, partial response; PS20, polysorbate 20; PS20 A, polysorbate 20 at 0.01%; SD, stable disease; SLD, sum of longest diameter.
Patients with missing or incomplete postbaseline SLD and disease assessments are not included in the plot. Y-axis is capped at 100%.

- Similar tumor volume reductions were observed in vidutolimod-injected and noninjected target lesions (mean percent change of –74% and –69%, respectively), including visceral metastases (**Figure 6**)

Figure 6. Maximum SLD Change With Vidutolimod PS20 A + Pembrolizumab in Patients With (A) Injected Target Lesions Only and in Patients With (B) Injected and Noninjected Target Lesions (n=27/98)



PS20 A, polysorbate 20 at 0.01%; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SLD, sum of longest diameter.
Plots include responders per RECIST v1.1 and postprogression responders.