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Phase 1 study of fianlimab, a human lymphocyte activation gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma

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Background

- Combination anti–lymphocyte activation gene-3 (LAG-3) and anti–programmed cell death-1 (PD-1) treatment demonstrated higher median progression free survival (PFS) and objective response rate (ORR) compared with anti–PD-1 monotherapy in a Phase 2/3 clinical trial of patients with untreated advanced melanoma.[1]
- The RELATIVITY-047 study showed an ORR of 43.1%.[2]
- Fianlimab (REGN3767) and cemiplimab are both high-affinity, human, hinge-stabilised immunoglobulin 4 (IgG4) monoclonal antibodies derived using VelocImmune technology.
- Fianlimab blocks LAG-3 and major histocompatibility complex (MHC) class II–driven T-cell inhibition.[3]
- Cemiplimab blocks interactions of PD-1 with PD-L1 and PD-L2.[4]
- In an initial expansion cohort, fianlimab + cemiplimab in patients with advanced melanoma gave an impressive efficacy of >60% ORR.[5]
- Here we present clinical activity and safety follow-up data of fianlimab + cemiplimab in Phase 1 expansion cohorts of patients with advanced melanoma, and a confirmatory expansion cohort (NCT03005782).

Objectives

- To assess preliminary anti-tumour activity of fianlimab + cemiplimab as measured by ORR per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria in patients with advanced melanoma.
- To assess the safety profile of fianlimab + cemiplimab in patients with advanced melanoma.

Key takeaway

- This analysis provides additional data that supports the use of fianlimab + cemiplimab combination treatment for patients with advanced melanoma.

Conclusions

- In two sequential expansion cohorts (total N=40/cohort), fianlimab + cemiplimab independently and reproducibly demonstrated clinically meaningful activity among patients with anti–PD-(L)1 naive advanced melanoma.
  - ORR was 63.8% (7 complete responses and 44 partial responses) and median DOR was not reached (95% CI: 22.6, NE).
  - Kaplan-Meier estimation of PFS was 24 months (95% CI: 9.9, NE).
  - Clinical activity was observed in poor prognosis subgroups (i.e., LDH > ULN, liver metastases), as well as in patients with high and low PD-L1 expression levels.
- Observed clinical activity in the anti–PD-(L)1 exposed population (ORR 13.3%) was consistent with previous reports of anti–LAG-3 + anti–PD-(L)1 combination treatment in this setting.
- The fianlimab + cemiplimab combination demonstrated an acceptable risk/benefit profile similar to that observed with cemiplimab monotherapy and other anti–PD-1 agents. In the anti–PD-(L)1 naive population:
  - 96.3% of patients experienced treatment-emergent AEs (TEAEs) of any grade.
  - 28.8% of patients experienced serious TEAEs.
  - 16.3% of patients discontinued treatment due to a TEAE.
- A Phase 3 trial (NCT05352672) of fianlimab + cemiplimab in patients with advanced melanoma is ongoing.

References

1. Tawbi HA et al. *N Engl J Med*. 2022;386:24–34.
2. Long GV et al. *J Clin Oncol*. 2022;40(suppl 36):360385.
3. Burova E et al. *Mol Cancer*. 2019;18:2051–2062.
4. Burova E et al. *Mol Cancer*. 2017;16:861–870.
5. Hamid O et al. *J Clin Oncol*. 2021;39(suppl 15):9515.

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Disclosure

John Crown has no disclosures to report. Co-author disclosures are accessible via the QR code.

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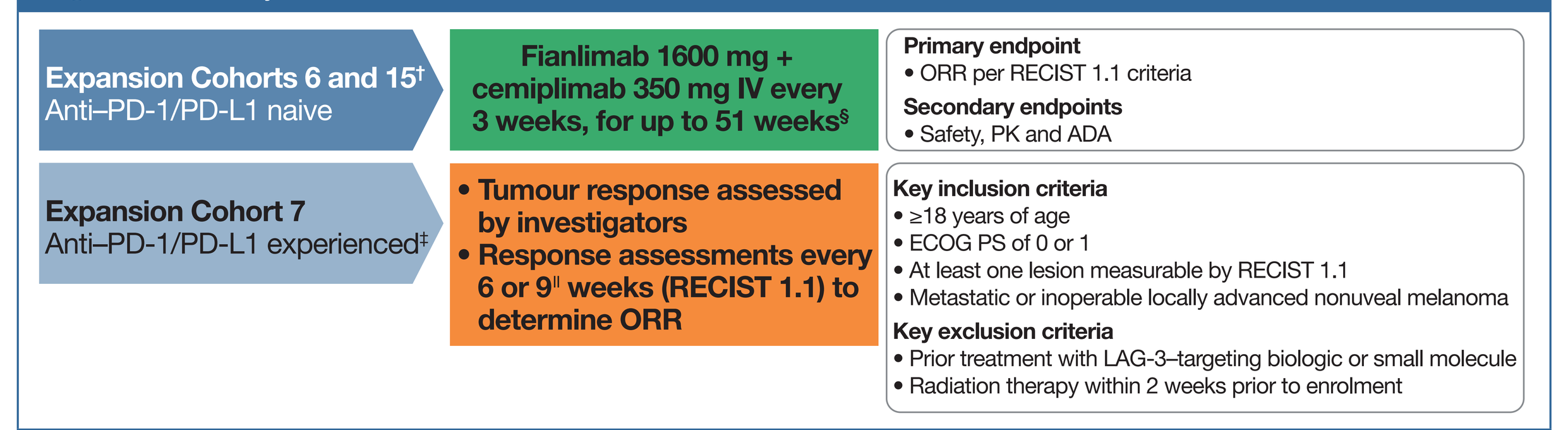
Methods

- Adult patients with advanced melanoma who had no prior anti–PD-1/PD-L1 treatment (naive; Cohort 6 and 15) or had prior anti–PD-1/PD–L1 treatment within 3 months of screening (experienced; Cohort 7) received fianlimab 1600 mg + cemiplimab 350 mg intravenously (IV) every 3 weeks (Q3W), for up to 51 weeks (**Figure 1**).
  - Prior systemic therapies, including prior adjuvant therapies, were excluded for Cohort 15.
  - Patients in Cohort 7 must have tolerated prior anti–PD-1/PD-L1 therapy for at least 6 weeks and must not have discontinued treatment due to toxicity.
  - Patients had an option to continue fianlimab + cemiplimab treatment for an additional 51 weeks.
- Tumour measurements were performed every 6 weeks for the first 24 weeks, then 9 weeks for the subsequent 27 weeks.
- The data cut-off date was 1 July 2022.

Figure 1. Study schema



†Prior systemic therapies, including prior adjuvant therapies, excluded for Cohort 15.
‡Defined as patients who had progressed on prior anti–PD-1/PD-L1 treatment within 3 months of screening. Patients must have tolerated therapy for a ≥6 weeks and must not have discontinued treatment due to toxicity.
§With an option for an additional 51 weeks.
‖Response assessments were every 6 weeks for the first 24 weeks, then 9 weeks for the subsequent 27 weeks.
ADA, antidrug antibody; ECOG PS, Eastern Cooperative Oncology Group performance score; IV, intravenous; LAG-3, lymphocyte activation gene-3; mAb, monoclonal antibody; MHC, major histocompatibility complex; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PD-L2, programmed cell death-ligand 2; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Results

Baseline demographics and disease characteristics

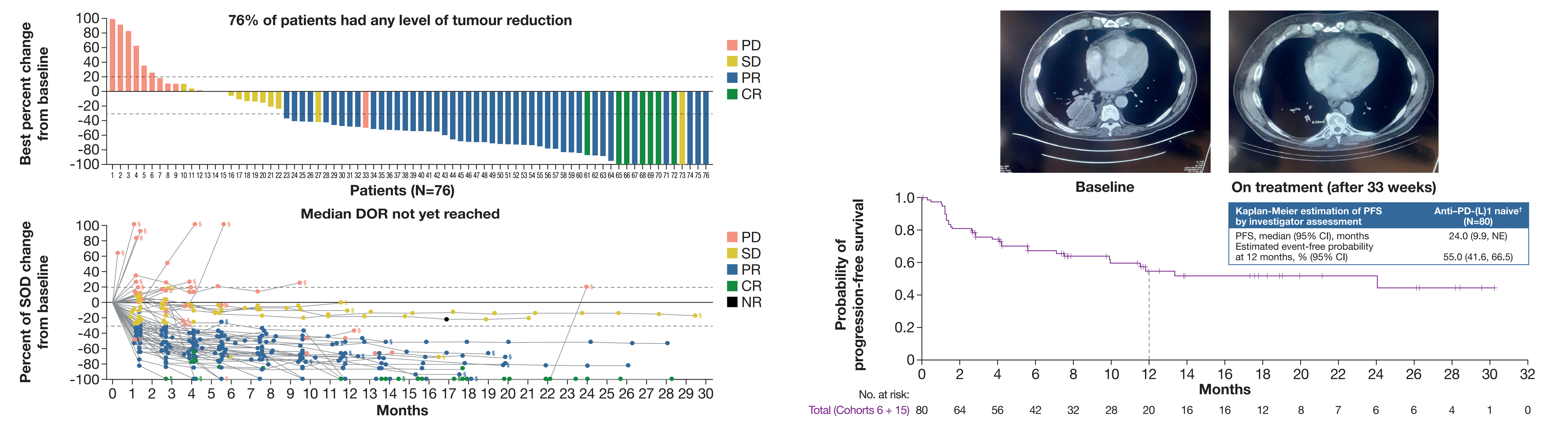
- As of 1 July 2022, 40 patients were enrolled and received treatment in each Cohort 6 and Cohort 15, and 15 patients received treatment in Cohort 7.
- Median age among the anti–PD-(L)1 naive patients (Cohorts 6 +15) was 69.0 years (range: 24–88), 60.0% of patients were male, and 90.0% were White (**Table 1**).
- Median age among the anti–PD-(L)1 experienced patients was 59.0 years, 46.7% were male, and 60.0% were White.
- The median sum of diameters of the target lesion was 51.5 mm (range: 11–214) among patients in Cohorts 6 + 15 (**Table 1**).
- Among anti–PD-(L)1 naive patients 33.8% had stage M1c at baseline, 35% had lactate dehydrogenase (LDH) levels above the upper limit of normal (ULN), and 23.8% had liver metastases (**Table 1**).

Table 1. Baseline characteristics and disposition: Anti–PD-(L)1 naive (Cohorts 6 + 15)†

Characteristic	Anti–PD-(L)1 naive† Cohort 6 (N=40)	Anti–PD-(L)1 naive† Cohort 15 (N=40)	Cohorts 6 + 15 (N=80)
Age			
Median (range), years	69.5 (27–85)	69.0 (24–88)	69.0 (24–88)
≥65 years, % (n)	60.0 (24)	62.5 (25)	61.3 (49)
Male, % (n)	62.5 (25)	57.5 (23)	60.0 (48)
White, % (n)	90.0 (36)	90.0 (36)	90.0 (72)
SOD of TL at baseline, median (range), mm	51 (15–214)	52 (11–173)	51.5 (11–214)
BRAF mutant, % (n)	27.5 (11)	30.0 (12)	28.8 (23)
Melanoma subtype, % (n)			
Acral	7.5 (3)	5.0 (2)	6.2 (5)
Mucosal	2.5 (1)	0	1.2 (1)
Cutaneous nonacral	90.0 (36)	95.0 (38)	92.5 (74)
Metastasis stage at baseline, % (n)			
M0	15.0 (6)	5.0 (2)	10.0 (8)
M1	82.5 (33)	87.5 (35)	85.0 (68)
M1c	45.0 (18)	22.5 (9)	33.8 (27)
LDH > ULN, % (n)	42.5 (17)	27.5 (11)	35.0 (28)
Liver metastases, % (n)	35.0 (14)	12.5 (5)	23.8 (19)
Previous systemic therapy, % (n)	20.0 (8)‡	0	10.0 (8)

†Prior systemic therapies, including prior adjuvant therapies, excluded for Cohort 15.
‡Two patients received prior treatment for advanced disease and six patients received prior adjuvant treatment.
LDH, lactate dehydrogenase; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; SOD, sum of diameters; TL, target lesion; ULN, upper limit of normal.

Figure 2. Efficacy overview among anti–PD-(L)1 naive patients (Cohorts 6 + 15)†



†Prior systemic therapies, including prior adjuvant therapies, excluded for Cohort 15.
§Patients with ongoing status (missing study complete status).
CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; SOD, sum of diameters.

Tumour response

- The ORR for anti–PD-(L)1 naive patients was 63.8% (95% confidence interval [CI]: 52.2, 74.2%; **Table 2**).
  - Seven (8.8%) patients had a complete response, and 44 (55.0%) patients had a partial response.
- Eight (10.0%) anti–PD-(L)1 naive patients completed planned treatment; 33.8% patients are ongoing treatment, and 56.3% of patients discontinued treatment (**Table 3**).

Table 2. Tumour response among anti–PD-(L)1 naive patients (Cohorts 6 + 15)†

% (n), unless otherwise stated	Anti–PD-(L)1 naive† Cohort 6 (N=40)	Anti–PD-(L)1 naive† Cohort 15 (N=40)	Cohorts 6 + 15 (N=80)
ORR, % (95% CI)	62.5 (45.8, 77.3)	65 (48.3, 79.4)	63.8 (52.2, 74.2)
Complete response	15.0 (6)	2.5 (1)	8.8 (7)
Partial response	47.5 (19)	62.5 (25)	55.0 (44)
Stable disease	17.5 (7)	15.0 (6)	16.3 (13)
Progressive disease	15.0 (6)	15.0 (6)	15.0 (12)
NE	5.0 (2)	5.0 (2)	5.0 (4)
DCR	80.0 (32)	80.0 (32)	80.0 (64)
KM-estimated PFS, median (95% CI), months	24 (4.2, NE)	NR (7.5, NE)	24 (9.9, NE)
DOR, median (95% CI), months	NR (11.9, NE)	NR (6.3, NE)	NR (22.6, NE)
ORR: baseline LDH, n/N1 (%)			
LDH > ULN	10/17 (58.8)	6/11 (54.5)	16/28 (57.1)
LDH normal	15/23 (65.2)	18/24 (75.0)	33/47 (70.2)
ORR: liver metastasis, n/N2 (%)			
Yes	6/14 (42.9)	3/5 (60.0)	9/19 (47.4)
No	19/26 (73.1)	23/35 (65.7)	42/61 (68.9)

†Prior systemic therapies, including prior adjuvant therapies, excluded for Cohort 15.
‡Planned treatment; 1 year + additional 1 year given based on investigator discretion.
CI, confidence interval; DCR, disease control rate; DOR, duration of response; KM, Kaplan-Meier; LDH, lactase dehydrogenase; N1, proportion of patients with the listed LDH status; N2, proportion of patients with the listed liver metastasis status; NE, not evaluable; NR, not reached; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; ULN, upper limit of normal.

Table 3. Patient disposition among anti–PD-(L)1 naive patients (Cohorts 6 + 15)†

% (n), unless otherwise stated	Anti–PD-(L)1 naive† Cohort 6 (N=40)	Anti–PD-(L)1 naive† Cohort 15 (N=40)	Cohorts 6 + 15 (N=80)
Patients completed planned treatment‡	15.0 (6)	5.0 (2)	10.0 (8)
Ongoing treatment	15.0 (6)	52.5 (21)	33.8 (27)
Discontinued treatment	70.0 (28)	42.5 (17)	56.3 (45)
Disease progression	45.0 (18)	17.5 (7)	31.3 (25)
AE	15.0 (6)	15.0 (6)	15.0 (12)
Patient decision	5.0 (2)	0	2.5 (2)
Death	2.5 (1)	5.0 (2)	3.8 (3)
Physician decision	2.5 (1)	5.0 (2)	3.8 (3)
Duration of exposure, median (range), weeks	37.1 (2–110)	24.2 (3–56)	30.9 (2–110)

†Prior systemic therapies, including prior adjuvant therapies, excluded for Cohort 15.
‡Planned treatment; 1 year + additional 1 year given based on investigator discretion.
AE, adverse event; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

- Clinical activity based on PD-L1 and LAG-3 levels was assessed for patients in Cohort 6 (**Table 4**).
  - Formalin-fixed, paraffin-embedded baseline tumour samples were used to determine LAG-3 and PD-L1 expression levels by IHC.
  - LAG-3 levels were reported as the percentage of positively staining immune cells in the viable tumour area using the 17B4 clone.
- Among anti–PD-(L)1 experienced patients, ORR was 13.3% (95% CI: 1.7, 40.5); 2 (13.3%) patients had a partial response (**Table 5**, **Figure 3**).
- The median Kaplan-Meier estimated PFS among anti–PD-(L)1 experienced patients was 1.5 months (95% CI: 1.3, 7.7) (**Table 5**).

Table 4. Clinical activity based on PD-L1 and LAG-3 levels (Cohort 6)

	Patients, % (n)	ORR, % (n)	PFS, median (95% CI), months
Overall	100.0 (40)	62.5 (26)	24 (4.2, NE)
LAG-3 expression ≥1%	67.5 (27)	74.1 (20)	24 (5.6, NE)
LAG-3 expression <1%	12.5 (5)	40.0 (2)	NR (1.4, NE)
PD-L1 expression ≥1%	45.0 (18)	77.8 (14)	24 (9.9, NE)
PD-L1 expression <1%	40.0 (16)	56.3 (9)	8.5 (2.8, NE)
PD-L1 ≥1% and LAG-3 ≥1%	45.0 (18)	77.8 (14)	24 (9.9, NE)
PD-L1 <1% and LAG-3 ≥1%	22.5 (9)	66.7 (6)	5.6 (1.2, NE)
PD-L1 <1% and LAG-3 <1%	12.5 (5)	40.0 (2)	NR (1.4, NE)

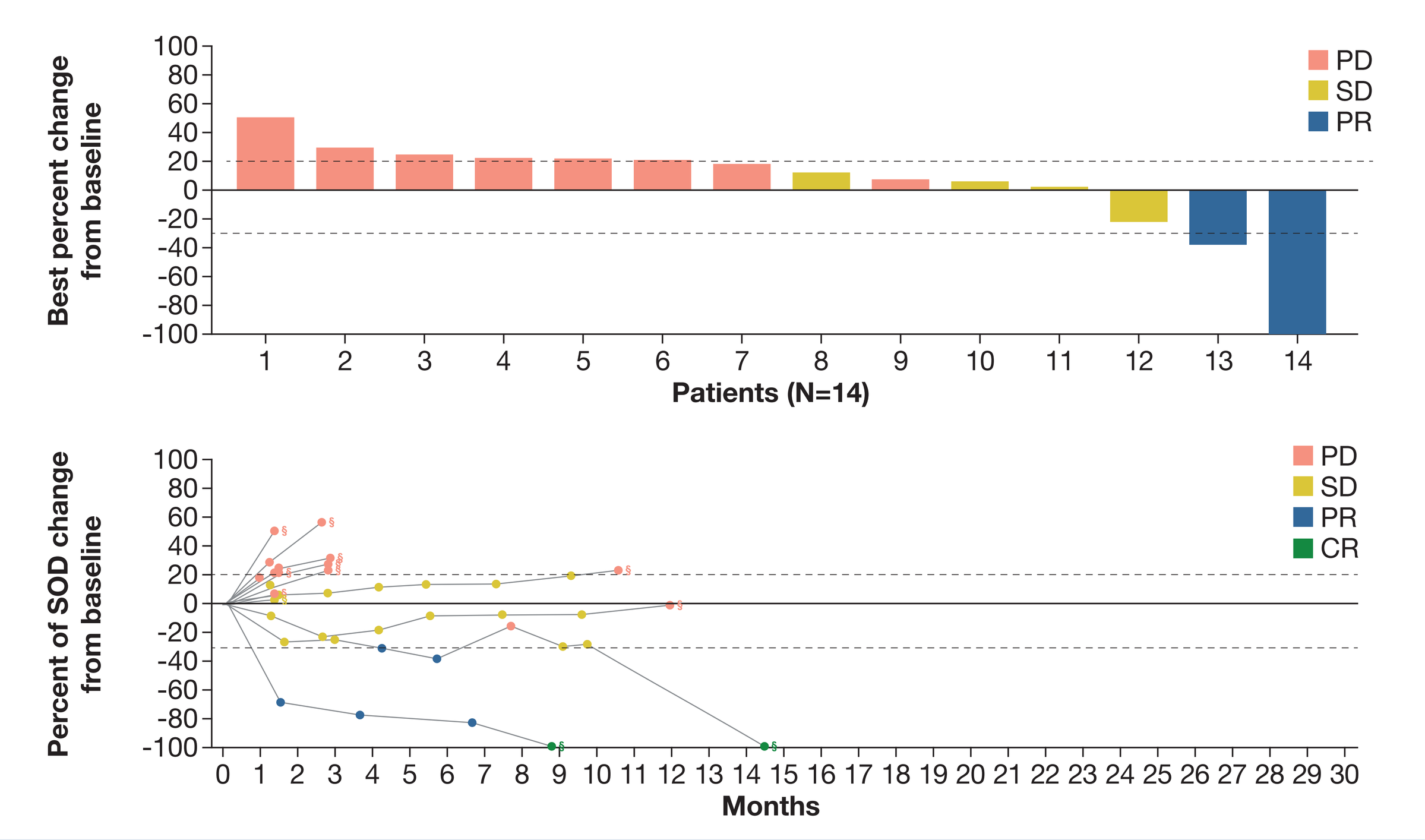
There were no patients with PD-L1 ≥1% and LAG-3 <1%.
CI, confidence interval; IHC, immunohistochemistry; LAG-3, lymphocyte activation gene-3; NA, not available; NE, not evaluable; ORR, objective response rate; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Table 5. Clinical activity among anti–PD-(L)1 experienced patients (Cohort 7)

% (n), unless otherwise stated	Total (N=15)
ORR, % (95% CI)	13.3 (1.7, 40.5)
Complete response	0
Partial response	13.3 (2)
Stable disease	26.7 (4)
Progressive disease	53.3 (8)
NE	6.7 (1)
DCR	40.0 (6)
KM-estimated PFS, median (95% CI), months	1.5 (1.3, 7.7)
DOR, median (95% CI), months	NR (3.4, NE)
ORR by LAG-3 expression, %	
<1%	NA
≥1%	18.2
ORR by PD-L1 expression, %	
<1%	18.2
≥1%	0

CI, confidence interval; DCR, disease control rate; DOR, duration of response; KM, Kaplan-Meier; LAG-3, lymphocyte activation gene-3; NA, not available; NE, not evaluable; NR, not reached; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Figure 3. Clinical activity among anti–PD-(L)1 experienced patients (Cohort 7)



§Patients with ongoing status (missing study complete status).
CR, complete response; PD, progressive disease; PD-1, programmed cell death-1; PR, partial response; SD, stable disease; SOD, sum of diameters.

Safety data

- The safety profile of fianlimab + cemiplimab combination treatment was similar to anti–PD-(L)1 therapies.
- Median duration of treatment exposure was 30.9 weeks (range: 2–110) among anti–PD-(L)1 naive patients and 9.0 weeks (range: 6–57) (**Table 6**).
- In the anti–PD-(L)1 naive population:
  - Rate of grade ≥3 treatment-related adverse events (AE) was 20.0%.
  - Rate of discontinuation due to treatment-related AEs was 15.0%.
  - Treatment-related AEs leading to death occurred in two patients (2.5%): one experienced colitis and one experienced cardiac shock.
    - The patient who experienced cardiac shock also had COVID-19 with pulmonary oedema concurrently.
  - Rate of treatment-emergent adrenal insufficiency was 10%.

Table 6. Safety for anti–PD-(L)1 naive and experienced patients

% (n), unless otherwise stated	Anti–PD-(L)1 naive† (N=80)		Anti–PD-(L)1 experienced (N=15)	
Duration of exposure, median (range), weeks	30.9 (2.0–110.0)		9.0 (6.0–57.0)	
Patients with treatment-emergent AEs regardless of attribution	Any grade	Grade 3–5	Any grade	Grade 3–5
Overall	96.3 (77)	40.0 (32)	80.0 (12)	46.7 (7)
Serious	28.8 (23)	25.0 (20)	33.3 (5)	26.7 (4)
Patients with treatment-related AEs				
Overall	80.0 (64)	20.0 (16)	53.3 (8)	20.0 (3)
Serious	13.8 (11)	13.8 (11)	13.3 (2)	13.3 (2)
Treatment-emergent immune-mediated AEs, % (n)				
	Any grade	Grade 3–5	Any grade	Grade 3–5
Overall	65.0 (52)	11.3 (9)	33.3 (5)	13.3 (2)
Occurred in >5% of patients (any grade)				
Rash	23.8 (19)	0	26.7 (4)	0
Pruritis	15.0 (12)	0	0	0
Hypothyroidism	13.8 (11)	0	0	0
Arthralgia	12.5 (10)	0	6.7 (1)	0
Diarrhoea	12.5 (10)	0	13.3 (2)	0
Myalgia	10.0 (8)	0	6.7 (1)	0
Adrenal insufficiency	8.8 (7)	2.5 (2)	6.7 (1)	0
Colitis	7.5 (6)	3.8 (3)	0	0
Pneumonitis	6.3 (5)	0	6.7 (1)	6.7 (1)

†Prior systemic therapies, including prior adjuvant therapies, excluded for Cohort 15.
AE, adverse event; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

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