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ORIGINAL ARTICLE

Fianlimab, a human lymphocyte activation gene-3 monoclonal antibody, in combination with cemiplimab: Tumor-specific expansion cohorts in advanced malignancies

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Abstract

Background: The dose escalation phase of a first-in-human (FIH) study demonstrated acceptable safety and preliminary antitumor activity of fianlimab (anti-lymphocyte activation gene-3 [LAG-3]) as monotherapy and in combination with cemiplimab (anti-programmed cell death-1 [PD-1]). Here, the authors present safety and clinical activity data from the dose-expansion portion of the FIH study in patients with advanced non–small cell lung cancer (NSCLC), clear cell renal cell carcinoma (ccRCC), head and neck squamous cell carcinoma (HNSCC), and cutaneous squamous cell carcinoma (CSCC).

Methods: Anti–PD-1/PD-L1 naive (N) or experienced (E) patients with advanced NSCLC, ccRCC, HNSCC, and CSCC were enrolled in this phase 1 study (NCT03005782). Patients received fianlimab 1600 mg plus cemiplimab 350 mg intravenously every 3 weeks for up to 24 months. The primary end point was the objective response rate (ORR) per RECIST 1.1.

Results: Investigator-assessed ORR was 27% in NSCLC-N (four partial responses [PRs]), 7% in NSCLC-E (one PR), 20% in ccRCC-N (three PRs), 7% in ccRCC-E (one PR), 33% in HNSCC-N (five PRs), 7% in HNSCC-E (one PR), and 20% CSCC-E (two complete responses; one PR). The most common treatment-related treatment-emergent adverse

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events among patients across all cohorts were fatigue (15%), rash (12%), pruritus (10%), infusion-related reaction (10%), and adrenal insufficiency (10%).

Conclusions: Fianlimab plus cemiplimab demonstrated modest clinical efficacy with an acceptable safety profile in patients with advanced malignancies across several tumor types mostly in treatment-naive patients. Further investigation is warranted.

KEYWORDS
advanced malignancies, cemiplimab, fianlimab, LAG-3, PD-1

INTRODUCTION

Immune checkpoint inhibitors have significantly changed the treatment landscape for advanced and metastatic tumors.[1] Lymphocyte activation gene-3 (LAG-3), a type I transmembrane protein, is expressed on activated $CD4^+$ and $CD8^+$ T cells and a subset of natural killer cells.[2,3] LAG-3 binds to major histocompatibility complex (MHC) class II with higher affinity than CD4 and inhibits T-cell activation by interfering with the binding of CD4 to MHC class II.[3–5] LAG-3 expression is increased on tumor-infiltrating lymphocytes in several types of cancer.[6–9] Augmented levels of LAG-3 expression lead to T-cell exhaustion and subsequent impairment of T-cell function.[9,10] Co-blockade of LAG-3 may enhance the efficacy of anti-programmed cell death-1 (PD-1) therapies.[11,12] VelocImmune technology was used to create potentially best-in-class fully human blocking antibodies to LAG-3 and PD-1.[13–15] Fianlimab (anti–LAG-3) blocks LAG-3/MHC class II-driven T-cell inhibition. Cemiplimab (anti–PD-1) blocks binding of PD-1 to programmed death-ligand 1/2 (PD-L1/2).[14]

The dose-escalation portion of a first-in-human (FIH), phase 1 study (NCT03005782) of fianlimab as monotherapy and in combination with cemiplimab demonstrated acceptable safety and preliminary antitumor activity in patients with advanced malignancies.[16] Patients with advanced melanoma ($N = 98$) treated with fianlimab plus cemiplimab across three expansion cohorts in the FIH study (NCT03005782) demonstrated an acceptable risk–benefit profile. The objective response rate (ORR) as assessed by blinded independent central review was 57%, including a 25% complete response (CR) rate, with a median progression-free survival (PFS) of 24 months. Ninety-five percent of patients experienced treatment-emergent adverse events (TEAEs) including grade ≥3 TEAEs in 47% of patients.[17] Based on these initial data in advanced melanoma, fianlimab plus cemiplimab combination therapy is being explored in several phase 2/3 studies in the adjuvant, neoadjuvant, and advanced settings. Fianlimab plus cemiplimab combination therapy is currently being investigated versus pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma (phase 3, NCT05352672),[18] versus pembrolizumab in patients with completely resected high-risk melanoma (phase 3, NCT05608291),[19] versus relatlimab plus nivolumab in patients with unresectable or metastatic melanoma (phase 3, NCT06246916),[20] and versus cemiplimab in patients with resectable stage III and IV melanoma (phase 2, NCT06190951).[21]

Although outcomes for many cancers have been greatly improved for patients with advanced solid tumors with the advent of anti–PD-1 therapies,[22–29] primary resistance or subsequent progression on anti–PD-1–containing therapy continues to represent a treatment challenge. Here, we present clinical activity and safety data from additional expansion cohorts of fianlimab plus cemiplimab in patients with advanced non–small cell lung cancer (NSCLC), clear cell renal cell carcinoma (ccRCC), head and neck squamous cell carcinoma (HNSCC), and cutaneous squamous cell carcinoma (CSCC).

MATERIALS AND METHODS

Study design

This was an open-label, nonrandomized, parallel cohort assignment, FIH clinical trial (ClinicalTrials.gov identifier NCT03005782; EudraCT number 2016-002789-30) investigating fianlimab and fianlimab plus cemiplimab across several dose escalation and dose expansion cohorts. Here, we present clinical activity and safety data from patients enrolled in expansion cohorts with advanced NSCLC, ccRCC, HNSCC, and CSCC. Separate cohorts enrolled patients who were either anti–PD-1/PD-L1 naive (N) or experienced (E) for each tumor type, except for CSCC, for which only anti–PD-1/PD-L1 experienced patients were enrolled (Figure S1). The data cutoff date was October 31, 2023.

Participants

Patients had to be 18 years or older, have an Eastern Cooperative Oncology Group performance status of 0 or 1, a measurable tumor according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), and have adequate organ and bone marrow function (Figure S1).

Procedures

Patients in all cohorts received up to 17 treatment cycles lasting 21 days (for a total of up to 51 weeks of treatment) of fianlimab 1600 mg plus cemiplimab 350 mg administered intravenously every 3 weeks,

followed by a 24-week follow-up period. Radiologic tumor assessments were performed every 6 weeks for the first 24 weeks, then every 9 weeks for the subsequent 27 weeks, regardless of delays in dosing of study drugs, and every 9 weeks during the 24-month follow-up period (Supporting Information).

Outcomes

The primary objective was to assess the preliminary antitumor activity of fianlimab in combination with cemiplimab measured by ORR per RECIST 1.1, as assessed by the investigators.[30] Secondary objectives included duration of response (DOR), PFS, and the safety of fianlimab in combination with cemiplimab.

Statistical analysis

The sample size was determined using Simon's two-stage minimax design with a one-sided significance level of 5% and a power of 80%. The null (H0) and alternative (H1) hypotheses were such that any statistically significant outcome observed in these cohorts represented a clinically meaningful treatment effect for the given patient population (Supporting Information).

RESULTS

Baseline demographics and disease characteristics

In total, 15 patients were enrolled in each expansion cohort and treated with fianlimab plus cemiplimab combination therapy. Patients' disposition, demographics, and baseline characteristics are shown in Table 1.

Overall efficacy and safety

Treatment exposure, duration of follow-up, efficacy data (ORR and depth of response, disease control rate [DCR], and PFS) by investigator assessment and overall survival (OS) are presented in Table 2. A numerically higher ORR was observed in the anti–PD-1/PD-L1–naive cohorts versus the anti–PD-1/PD-L1–experienced cohorts.

The overall safety data are presented in Table 3. Across cohorts, TEAEs of any grade were observed among 80%–100% of patients, TEAEs of grade ≥3 occurred in 27%–53% of patients, treatment-related TEAEs (TRAEs) of any grade ranged from 47% to 80% of patients, and TRAEs of grade ≥3 ranged from 7% to 27% of patients. A summary of immune-mediated adverse events (AEs) is presented in Table 3. A summary of TEAEs, TRAEs, and immune-mediated AEs is presented in Tables S2–S4, respectively.

NSCLC cohorts: Participants, efficacy, and safety

Patients enrolled into the NSCLC-N cohort all had stage IIIB, IIIC, or IV disease and were either anti–PD-1–naive at first presentation or had failed prior platinum-containing chemotherapy. Patients enrolled into the NSCLC-E cohort had received anti–PD-1/PD-L1 for stage IIIB, IIIC, or IV disease and no more than two prior therapies for metastatic disease. Patients with known *EGFR* mutations or *ALK* or *ROS1* rearrangements were excluded. The median number of prior lines of therapy in NSCLC-N patients was one, and six patients (40%) had not received any prior lines of therapy, whereas in NSCLC-E patients, the median number of prior lines of therapy was two, and eight patients (53%) had received two prior lines of therapy (Table 1).

The ORR was 27% (four partial responses [PRs]) in the NSCLC-N cohort (Table 2; Figure 1A). In the majority of responders (three of four), the response was maintained for 24 months. The four PRs all occurred in patients who had never been exposed to any prior therapy. In addition, three of four patients with PR had PD-L1 tumor expression ≥50% (Table 4). Patients with LAG-3 expression ≥1% had an ORR of 38% and all of these patients also had PD-L1 expression ≥1%. Only one patient (7%) responded in the NSCLC-E cohort, and no correlation with biomarkers could be established (Figure 1B).

TEAEs of any grade were observed in 87% and 93% of patients in the NSCLC-N and NSCLC-E cohorts, respectively, whereas TEAEs of grade ≥3 were observed in 33% and 40% of patients, respectively (Table 3). TRAEs of any grade or grade ≥3 were observed in 53% and 7% of NSCLC patients in each cohort, respectively. The most common TRAEs were rash (33%) in the NSCLC-N cohort, and fatigue (27%) in the NSCLC-E cohort (Table S3). The most common immune-mediated AEs that occurred in ≥10% of patients were adrenal insufficiency (27% in the NSCLC-N cohort and 13% in the NSCLC-E cohort) (Table S4). One death (7%) was observed because of chronic obstructive pulmonary disease exacerbation due to human metapneumovirus. The safety profile was similar between the NSCLC-N and NSCLC-E cohorts.

ccRCC cohorts: Participants, efficacy, and safety

All advanced or metastatic ccRCC-N or ccRCC-E patients had received no more than two previous regimens of anti-angiogenic therapy. The median number of prior lines of therapy was two in each cohort: in the ccRCC-N cohort, six patients (40%), six patients (40%), and three patients (20%) had received one, two, and three prior lines of therapy, respectively. In the ccRCC-E cohort, one patient (7%), 10 patients (67%), three patients (20%), and one patient (7%) had received one, two, three, and five prior lines of therapy, respectively.

The ORR was 20% in the ccRCC-N (Table 2; Figure 1C) and 7% in the ccRCC-E cohorts (Table 2; Figure 1D). Three patients in the ccRCC-

TABLE 1 Baseline demographics by tumor type and prior anti–PD-1/PD-L1 exposure.

	NSCLC		ccRCC		HNSCC		CSCC
Baseline characteristic	**Anti–PD-1/PD-L1 naive (*n* = 15)**	**Anti–PD-1/PD-L1 experienced (*n* = 15)**	**Anti–PD-1/PD-L1 naive (*n* = 15)**	**Anti–PD-1/PD-L1 experienced (*n* = 15)**	**Anti–PD-1/PD-L1 naive[b] (*n* = 15)**	**Anti–PD-1/PD-L1 experienced (*n* = 15)**	**Anti–PD-1/PD-L1 experienced (*n* = 15)**
Median age (IQR), years	70 (65–78)	67 (63–72)	64 (60–68)	64 (57–74)	72 (63–75)	65 (58–71)	62 (57–78)
Male, No. (%)	11 (73)	11 (73)	12 (80)	13 (87)	12 (80)	13 (87)	12 (80)
White, No. (%)	5 (33)	11 (73)	6 (40)	13 (87)	8 (53)	12 (80)	12 (80)
ECOG PS, No. (%)							
0	2 (13)	3 (20)	0	10 (67)	4 (27)	9 (60)	4 (27)
1	13 (87)	12 (80)	15 (100)	5 (33)	11 (73)	6 (40)	11 (73)
Metastatic stage at screening, No. (%)							
M0	2 (13)	0	1 (7)	0	2 (13)	2 (13)	3 (20)
M1	2 (13)	4 (27)	12 (80)	11 (73)	11 (73)	11 (73)	9 (60)
M1A	4 (27)	6 (40)	0	0	1 (7)	0	0
M1B	3 (20)	2 (13)	0	1 (7)	1 (7)	0	0
M1C	3 (20)	2 (13)	1 (7)	1 (7)	0	0	0
MX	0	0	0	1 (7)	0	2 (13)	0
Unknown/ missing	1 (7)	1 (7)	1 (7)	1 (7)	0	0	3 (20)
Median baseline tumor burden (IQR),[a] mm	44 (36–68)	65 (48–103)	73 (43–141)	71 (45–102)	37 (29–70)	54 (39–80)	61 (31–88)
LDH > ULN, No. (%)	7 (47)	3 (20)	2 (13)	2 (13)	3 (20)	3 (20)	2 (13)
Liver metastases, No. (%)	4 (27)	0	7 (47)	2 (13)	0	2 (13)	0
Prior cancer-related systemic therapy, No. (%)	9 (60)	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)	15 (100)
No. of prior lines of therapy, No. (%)							
0	6 (40)	0	0	0	0	0	0
1	8 (53)	7 (47)	6 (40)	1 (7)	10 (67)	2 (13)	6 (40)
2	1 (7)	8 (53)	6 (40)	10 (67)	4 (27)	6 (40)	4 (27)
3	0	0	3 (20)	3 (20)	1 (7)	5 (33)	1 (7)
4	0	0	0	0	0	1 (7)	2 (13)
≥5	0	0	0	1 (7)	0	1 (7)	2 (13)

Note: Data cutoff date: October 31, 2023.

Abbreviations: ccRCC, clear cell renal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IQR, interquartile range; LDH, lactate dehydrogenase; NSCLC, non–small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; ULN, upper limit of normal.

[a]Sum of diameters of target lesion.

[b]In the HNSCC-N cohort, six patients had HPV-associated tumors.

N cohort and one patient in the ccRCC-E cohort had PR. No CRs were observed. All ccRCC-N responders were estimated to maintain their response for >24 months. Median PFS was 6 and 4 months in the ccRCC-N and ccRCC-E cohorts, respectively (Table 2). Median DOR was not reached in ccRCC-N and was 6 months in ccRCC-E. Duration of responses was 4, 7, and 26 months in the three responders in the ccRCC-N cohort and 6 months in the one responder in the ccRCC-E cohort. PD-L1 and LAG-3 immunohistochemistry (IHC) analysis was

TABLE 2 Efficacy by disease and prior anti–PD-1/PD-L1 exposure.

Efficacy measure	NSCLC		ccRCC		HNSCC		CSCC
	Anti–PD-1/PD-L1 naive ($n = 15$)	Anti–PD-1/PD-L1 experienced ($n = 15$)	Anti–PD-1/PD-L1 naive ($n = 15$)	Anti–PD-1/PD-L1 experienced ($n = 15$)	Anti–PD-1/PD-L1 naive ($n = 15$)	Anti–PD-1/PD-L1 experienced ($n = 15$)	Anti–PD-1/PD-L1 experienced ($n = 15$)
Median treatment exposure (range), weeks	12 (6–103)	12 (3–102)	27 (6–102)	18 (6–103)	12 (3–110)	13 (3–117)	12 (3–104)
Median follow-up (range), months	9 (1–59)	5 (1–45)	13 (1–55)	24 (2–59)	12 (1–52)	10 (1–33)	9 (1–51)
ORR, No. (%)	4 (27)	1 (7)	3 (20)	1 (7)	5 (33)	1 (7)	3 (20)
95% CI for ORR	8–55	0–32	4–48	0–32	12–62	0–32	4–48
DCR, No. (%)	9 (60)	9 (60)	12 (80)	11 (73)	7 (47)	10 (67)	8 (53)
95% CI for DCR	32–84	32–84	52–96	45–92	21–73	38–88	27–79
mOS, months (95% CI)	13 (7–NE)	12 (5–NE)	26 (10–35)	24 (15–48)	21 (4–NE)	15 (8–18)	12 (4–NE)
Best overall response, No. (%)							
CR	0	0	0	0	0	0	2 (13)
PR	4 (27)	1 (7)	3 (20)	1 (7)	5 (33)	1 (7)	1 (7)
SD	5 (33)	8 (53)	9 (60)	10 (67)	2 (13)	9 (60)	5 (33)
Non-CR/non-PD[a]	0	0	0	0	0	0	0
PD	6 (40)	5 (33)	3 (20)	4 (27)	6 (40)	4 (27)	6 (40)
Not evaluable[b]	0	1 (7)	0	0	2 (13)	1 (7)	1 (7)
KM-estimated mPFS (95% CI), months	3 (1–10)	4 (1–8)	6 (1–10)	4 (1–7)	2 (1–14)	4 (1–7)	3 (1–4)

Note: Data cutoff date: October 31, 2023.

Abbreviations: ccRCC, clear cell renal cell carcinoma; CI, confidence interval; CR, complete response; CSCC, cutaneous squamous cell carcinoma; DCR, disease control rate; HNSCC, head and neck squamous cell carcinoma; KM, Kaplan–Meier; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimated; NSCLC, non–small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PR, partial response; SD, stable disease.

[a]Non-CR/non-PD: only nontarget lesions were present at baseline and did not reach CR or PD.

[b]Not evaluable includes unevaluable, not applicable, unknown, or missing tumor response.

available in a subset of patients. In the ccRCC-N cohort, ORR was 25% and 13% in patients with LAG-3 <1% and PD-L1 <1%, respectively, but no responses were seen in patients with LAG-3 or PD-L1 ≥1% (Table 5). The only patient who responded in the ccRCC-E cohort had LAG-3 ≥1% and PD-L1 <1%.

TEAEs of any grade were observed in 100% and 93% of patients in the ccRCC-N and ccRCC-E cohorts, respectively, whereas TEAEs of grade ≥3 were observed in 53% and 27% of patients, respectively (Table 3). TRAEs of any grade were observed in 80% and 60% of patients in ccRCC-N and ccRCC-E cohorts, respectively. TRAEs of grade ≥3 were observed in 27% of patients in the ccRCC-N cohort and no patients in the ccRCC-E cohort. The most common TRAEs were rash (27%) and infusion-related reaction (27%) in the ccRCC-N cohort, and fatigue (20%) in the ccRCC-E cohort (Table S3). The most common immune-mediated AE that occurred in ≥10% of patients was colitis (13%) in the ccRCC-N cohort (Table S4). Among the ccRCC-N cohort, one death (7%) was reported due to colitis that was complicated by intestinal perforation and subsequent sepsis with respiratory failure (Table 3); six patients (40%) experienced TEAEs leading to dose delay.

HNSCC cohorts: Participants, efficacy, and safety

Patients with recurrent and/or metastatic HNSCC (regardless of human papillomavirus [HPV] status) with no curative options who were anti–PD-1/PD-L1 naive or experienced were enrolled. The median number of prior lines of therapies was one and two in the HNSCC-N or HNSCC-E cohorts, respectively. In HNSCC-N, 10 patients (67%), four patients (27%), and one patient (7%) had received one, two, and three prior lines of therapy, respectively. In HNSCC-E, two patients (13%), six

TABLE 3 Safety by disease and prior anti–PD-1/PD-L1 exposure.

Adverse event	NSCLC		ccRCC		HNSCC		CSCC	NSCLC + ccRCC + HNSCC + CSCC
	Anti–PD-1/PD-L1 naive (n = 15)	Anti–PD-1/PD-L1 experienced (n = 15)	Anti–PD-1/PD-L1 naive (n = 15)	Anti–PD-1/PD-L1 experienced (n = 15)	Anti–PD-1/PD-L1 naive (n = 15)	Anti–PD-1/PD-L1 experienced (n = 15)	Anti–PD-1/PD-L1 experienced (n = 15)	(N = 105)
TEAEs, No. (%)								
Overall								
Any grade	13 (87)	14 (93)	15 (100)	14 (93)	14 (93)	12 (80)	13 (87)	95 (90)
Grade ≥3	5 (33)	6 (40)	8 (53)	4 (27)	7 (47)	7 (47)	7 (47)	44 (42)
Serious	3 (20)	2 (13)	5 (33)	2 (13)	2 (13)	3 (20)	3 (20)	20 (19)
Any TEAE leading to discontinuation, No. (%)	1 (7)	0	3 (20)	1 (7)	0	2 (13)	1 (7)	8 (8)
Any TEAE leading to death, No. (%)	1 (7)[a]	0	1 (7)[b]	0	0	1 (7)[c]	2 (13)[d]	5 (5)
Treatment-related TEAEs, No. (%)								
Overall								
Any grade	8 (53)	8 (53)	12 (80)	9 (60)	10 (67)	8 (53)	7 (47)	62 (59)
Grade ≥3	1 (7)	1 (7)	4 (27)	0	1 (7)	2 (13)	1 (7)	10 (10)
Serious	1 (7)	0	3 (20)	0	0	1 (7)	0	5 (5)
Treatment-emergent immune-mediated AEs, No. (%)								
Overall								
Any grade	5 (33)	3 (20)	6 (40)	1 (7)	7 (47)	5 (33)	3 (20)	30 (29)
Grade ≥3	1 (7)	0	2 (13)	0	0	1 (7)	1 (7)	5 (5)

Note: Data cutoff date: October 31, 2023.

Abbreviations: AE, adverse event; ccRCC, clear cell renal cell carcinoma; COPD, chronic obstructive pulmonary disease; CSCC, cutaneous squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non–small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; TEAE, treatment-emergent adverse event.

[a]One death was reported due to COPD exacerbation due to human metapneumovirus.

[b]One death was reported due to colitis that was complicated by intestinal perforation and subsequent sepsis with respiratory failure.

[c]One death in a patient with history of antiphospholipid syndrome due to acute hypoxic respiratory failure caused by complications of biopsy-proven treatment-related ischemic colitis.

[d]There were two fatal TEAEs, which were unrelated to study drugs: one sudden death in a heavily pretreated patient and one death due to failure to thrive in a patient who was in a palliative care facility after disease progression on study.

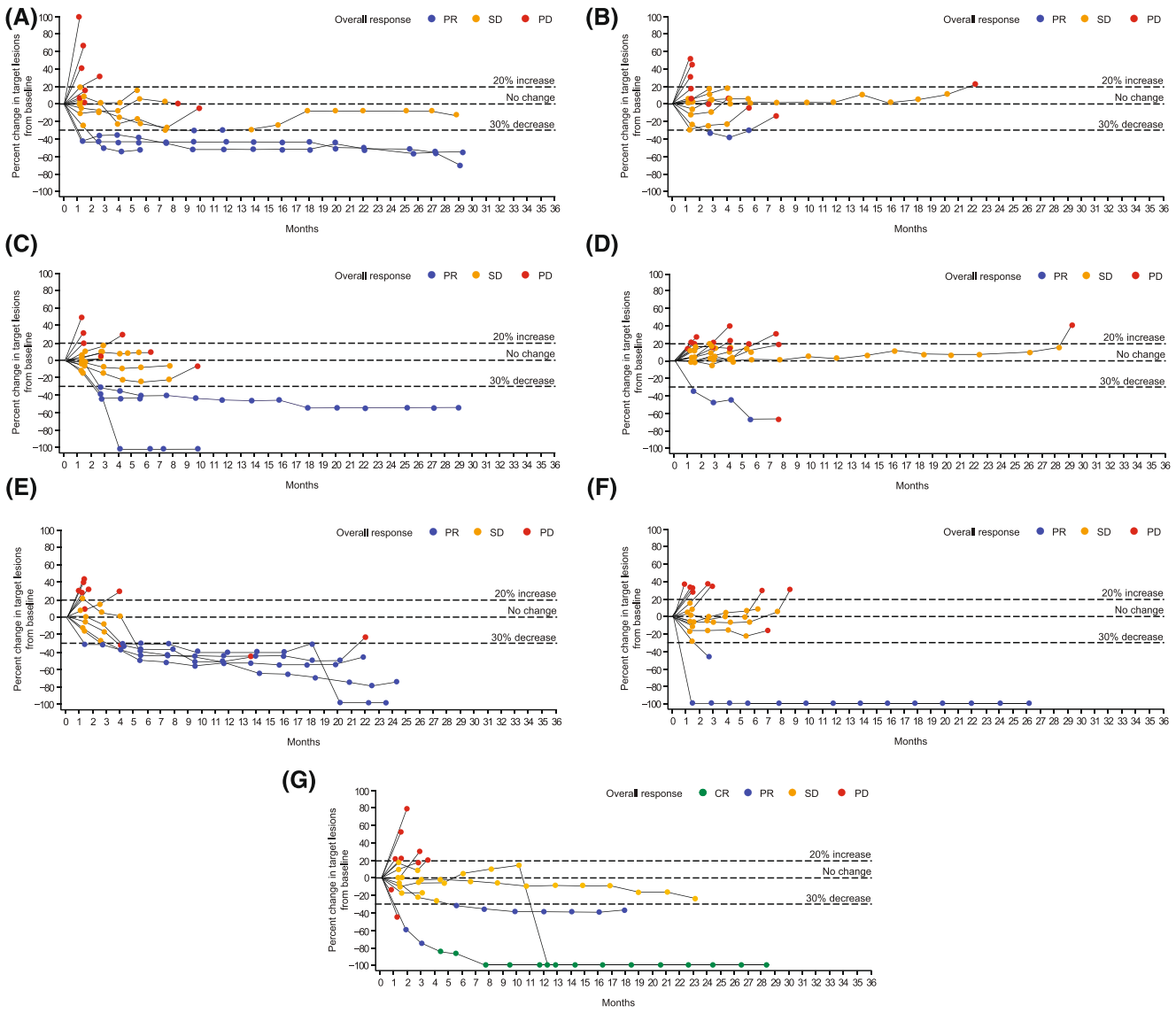

FIGURE 1 Overall response rate per cohort by RECIST 1.1 as assessed by the investigators: (A) NSCLC (anti–PD-1/PD-L1 naive) cohort, (B) NSCLC (anti–PD-1/PD-L1 experienced) cohort, (C) ccRCC (anti–PD-1/PD-L1 naive) cohort, (D) ccRCC (anti–PD-1/PD-L1 experienced) cohort, (E) HNSCC (anti–PD-1/PD-L1 naive) cohort, (F) HNSCC (anti–PD-1/PD-L1 experienced) cohort, and (G) CSCC (anti–PD-1/PD-L1 experienced) cohort. ccRCC, clear cell renal cell carcinoma; CR, complete response; CSCC, cutaneous squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non–small cell lung cancer; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PR, partial response; SD, stable disease.

patients (40%), five patients (33%), one patient (7%), and one patient (7%) had received one, two, three, four, and seven prior lines of therapy, respectively.

The ORRs were 33% and 7% in HNSCC-N and HNSCC-E, respectively (Table 2; Figure 1E,F). All responses were PR, observed in five patients in the HNSCC-N cohort and one patient in the HNSCC-E cohort (Table 2). In HNSCC-N, 80% of responders were estimated to maintain their response for 18 months; six patients had HPV-associated tumors, of which four patients had durable responses. In HNSCC-E, all responders maintained their response for 24 months. For a subset of eight and 10 patients from the HNSCC-N and HNSCC-E cohorts, respectively, PD-L1 and LAG-3 IHC analysis was available. There were no responders among patients with PD-L1 expression <1% or LAG-3 expression <1%. All patients with a PD-L1 expression ≥1% also had a LAG-3 expression of ≥1% (Table 5). Median PFS was 2 months in the HNSCC-N and 4 months in the HNSCC-E cohorts (Table 2). Median DOR was not reached in both cohorts.

TEAEs of any grade were observed in 93% and 80% of patients from the HNSCC-N and HNSCC-E cohorts, respectively. TEAEs of grade ≥3 were observed in 47% of patients in both cohorts (Table 3). TRAEs of any grade were observed in 67% and 53% of patients in the HNSCC-N and HNSCC-E cohorts, respectively, and TRAEs of grade ≥3 were observed in 7% and 13% of patients, respectively (Table 3). The most common TRAEs were hypothyroidism (33%) in HNSCC-N,

and fatigue (20%) and pneumonitis (20%) in HNSCC-E; three patients (20%) in HNSCC-N and four patients (27%) in HNSCC-E had TEAEs leading to dose delay. The most common immune-mediated AEs that occurred in ≥10% of patients were hypothyroidism (33%) in the HNSCC-N cohort and pneumonitis (20%) in the HNSCC-E cohort (Table S4). In the HNSCC-E cohort, one death (7%) was reported in a patient with history of antiphospholipid syndrome due to acute hypoxic respiratory failure caused by complications of biopsy-proven treatment-related ischemic colitis (Table 3).

TABLE 4 Efficacy per LAG-3 and PD-L1 tumor expression in patients with advanced NSCLC.

	Anti–PD-1/PD-L1 naive		Anti–PD-1/PD-L1 experienced	
Tumor marker	***N***	**ORR, No. (%)**	***N***	**ORR, No. (%)**
LAG-3 expression				
≥1%	8	3 (38)	9	0
<1%	4	0	1	0
Unknown[a]	3	1 (33)	5	1 (20)
PD-L1 expression				
≥50%	3	3 (100)	0	0
<50%	11	1 (9)	10	0
Unknown[a]	1	0	5	1 (20)

Note: Data cutoff date: October 31, 2023. The SP263 (Ventana Medical Systems, Tucson, AZ, USA) assay was used to measure PD-L1 in the tumor cell membrane; it measured the percentage of positive tumor cells as a percentage of total tumor cells. LAG-3 levels were measured using the 17B4 assay (Roche Tissue Diagnostics, Tucson, Arizona, USA). LAG-3 levels were reported as the percentage of positively staining immune cells in the viable tumor area.

Abbreviations: IHC, immunohistochemistry; LAG-3, lymphocyte activation gene-3; NSCLC, non–small cell lung cancer; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

[a]Unknown includes patients without IHC test results.

CSCC cohort: Participants, efficacy, and safety

Patients with locally advanced/metastatic CSCC who were anti–PD-1/PD-L1 experienced were enrolled. The median number of prior lines of therapy was two; six patients (40%), four patients (27%), one patient (7%), two patients (13%), and two patients (13%) had received one, two, three, four, and six prior lines of therapy, respectively (Table 1).

The ORR was 20% and median PFS was 3 months (Table 2; Figure 1G). Two patients had CR, and one patient had PR. Two responders (one CR and one PR) experienced disease progression while receiving prior anti–PD-1, and one responder who achieved CR had an ongoing PR on previous anti–PD-L1 therapy before joining the study. One patient with a prior treatment of cemiplimab had prolonged stable disease (SD) up to 24 months while receiving fianlimab plus cemiplimab combination therapy. Because the patients were only followed up for 6 months after the end of treatment, the median DOR was not reached. In a subset of eight patients, PD-L1 and LAG-3 IHC analysis was available. Responses were more common in patients with LAG-3 expression <1% and PD-L1 expression <1%. There were no responders among patients with PD-L1 expression ≥1% or LAG-3 expression ≥1% (Table 5).

TEAEs (any grade) and TRAEs (any grade) were observed in 87% and 47% of patients, respectively. TEAEs (grade ≥3) and TRAEs

TABLE 5 Efficacy per LAG-3 and PD-L1 tumor expression in patients with ccRCC, HNSCC, or CSCC.

	ccRCC				HNSCC				CSCC	
	Anti–PD-1/PD-L1 naive		Anti–PD-1/PD-L1 experienced		Anti–PD-1/PD-L1 naive		Anti–PD-1/PD-L1 experienced		Anti–PD-1/PD-L1 experienced	
Tumor marker	***N***	**ORR, No. (%)**	***N***	**ORR, No. (%)**	***N***	**ORR, No. (%)**	***N***	**ORR, No. (%)**	***N***	**ORR, No. (%)**
LAG-3 expression										
≥1%	5	0	8	1 (13)	7	2 (29)	9	1 (11)	7	0
<1%	4	1 (25)	0	0	1	0	1	0	1	1 (100)
Unknown[a]	6	2 (33)	7	0	7	3 (43)	5	0	7	2 (29)
PD-L1 expression										
≥1%	1	0	4	0	5	2 (40)	6	1 (17)	5	0
<1%	8	1 (13)	4	1 (25)	3	0	4	0	3	1 (33)
Unknown[a]	6	2 (33)	7	0	7	3 (43)	5	0	7	2 (29)

Note: Data cutoff date: October 31, 2023. The SP263 (Ventana Medical Systems, Tucson, Arizona, USA) assay was used to measure PD-L1 in the tumor cell membrane; it measured the percentage of positive tumor cells as a percentage of total tumor cells. LAG-3 levels were measured using the 17B4 assay (Roche Tissue Diagnostics, Tucson, Arizona, USA). LAG-3 levels were reported as the percentage of positively staining immune cells in the viable tumor area.

Abbreviations: ccRCC, clear cell renal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; LAG-3, lymphocyte activation gene-3; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

[a]Unknown includes patients without IHC test results.

(grade ≥3) were observed in 47% and 7% of patients, respectively (Table 3). The most common TRAE was infusion-related reaction (13%). TEAEs leading to dose delay were reported in two patients (13%). Two deaths (13%) were reported, which were unrelated to study drugs. One sudden death occurred in a heavily pretreated patient, and one death occurred due to failure to thrive in a patient who was in a palliative care facility after disease progression on study.

DISCUSSION

Fianlimab as monotherapy and in combination with cemiplimab has demonstrated preliminary antitumor activity and an acceptable safety profile in patients with advanced malignancies.[16] Expansion cohorts in anti–PD-1–naive patients with advanced melanoma confirmed the clinical activity of fianlimab (1600 mg) plus cemiplimab (350 mg) and demonstrated that this combination had an acceptable safety profile.[31] Here, we present the results of the safety, tolerability, and efficacy of fianlimab in combination with cemiplimab in patients with advanced malignancies other than melanoma.

In the present study, patients in the anti–PD-1/PD-L1–naive cohorts had not received any prior anti–PD-1 treatment, whereas some had progressed on other standard therapies. Among patients with NSCLC treated with fianlimab plus cemiplimab, an objective response was observed in four of 15 (27%) in the NSCLC-N cohort and one of 15 (7%) in the NSCLC-E cohort. The results in naive patients support the clinical activity of fianlimab on the basis that the observed ORR is comparable to the 24.8% ORR observed with pembrolizumab in treatment-naive patients,[32] even though nine of 15 (60%) of the patients in our study had received prior systemic therapy. This ORR is also comparable to the combination of immunotherapies, nivolumab (anti–PD-1) plus ipilimumab (anti-cytotoxic T-lymphocyte associated protein 4) that demonstrated an ORR of 33.1% in patients who were all treatment-naive.[33] Therefore, the observed ORR and duration of response support further investigation of fianlimab plus cemiplimab in anti–PD-1/PD-L1 naive patients, but not in the anti–PD-1/PD-L1 experienced population.

Among patients with ccRCC, fianlimab plus cemiplimab demonstrated an ORR of 20% and 7% in the ccRCC-N and ccRCC-E cohorts, respectively. The ORR observed in ccRCC-N in our study is lower than reported data for treatment-naive patients receiving nivolumab plus ipilimumab combination (ORR, 41%),[34] and comparable to nivolumab monotherapy (ORR, 25%).[35] However, in the current trial, all anti–PD-1/PD-L1 naive patients were previously treated with other agents and a majority (60%) had received two or more prior lines of therapy and were hence likely not as immunologically fit. These data may suggest some activity of fianlimab plus cemiplimab in this population, even if it is difficult to reach any definitive conclusion due to the heterogeneity of the population and the small sample size. In anti–PD-1/PD-L1 experienced patients the conclusion is clear, and the activity is insufficient to justify further investigation in this setting.

All patients with HNSCC who were anti–PD-1/PD-L1 naive had received at least one prior line of therapy. Despite this, the ORR was 33% and reached 40% in the subset of patients with a PD-L1 expression of ≥1% (n = 5). In addition, the median DOR was not reached after almost 2 years of follow-up. These results are very encouraging in the knowledge that in the CheckMate 141 and KEYNOTE 040 trials, the ORRs were 13.3% and 14.6%, respectively, in similar patient populations.[36,37] As observed for NSCLC and ccRCC in our study, there was limited activity of fianlimab plus cemiplimab in patients previously exposed to anti–PD-1/PD-L1.

In patients with CSCC, the combination of fianlimab plus cemiplimab showed some efficacy in heavily pretreated, anti–PD-1/PD-L1 experienced patients. The observed ORR was 20%, with two of three responders achieving a durable CR. Furthermore, one patient had durable SD lasting more than 2 years. Therefore, this treatment could potentially become an option for patients who are refractory to anti–PD-1/PD-L1 therapy, if these results are confirmed in a larger study.

The safety profile of fianlimab plus cemiplimab combination therapy was generally consistent with the safety profile of cemiplimab monotherapy and other anti–PD-1 agents. The overall safety profile was acceptable across the expansion cohorts based on the review of TEAEs, treatment-related TEAEs, and the sponsor-identified immune-mediated AEs. The incidence of grade 3 or worse AEs appeared similar across all expansion cohorts. Adrenal insufficiency was reported in 11 patients (10%) across all cohorts; the majority of patients (n = 10) experienced grade 1 or 2 level of adrenal insufficiency. In the FIH phase 1 study (NCT03005782) of fianlimab plus cemiplimab, among patients (N = 98) with advanced melanoma, adrenal insufficiency was reported in 12 patients (12%)[31]; however, these patients had an ORR of 92% (95% CI, 62–100) highlighting better efficacy.[17] The current study did not require the collection of data beyond routine cortisol assessments with respect to adrenal function, and the available information is insufficient to distinguish between primary and secondary adrenal insufficiency associated with the fianlimab plus cemiplimab combination. Ongoing studies evaluating this regimen are expected to provide additional data to elucidate the underlying mechanisms.

The safety profile of fianlimab compares favorably with that of relatlimab, the only agent in the anti-LAG-3 class currently in clinical use, which is notable given that the dose of fianlimab used in our study is 10 times higher.[12] Furthermore, during the initial dose escalation in the FIH study (NCT03005782) in patients with advanced malignancies, the dose was escalated up to 40 mg/kg of fianlimab without reaching the maximum tolerated dose.[16] The current study further supports the original safety, pharmacokinetic, and pharmacodynamic data that established fianlimab 1600 mg (i.e., 20 mg/kg fixed-dose equivalent) as the selected dose in combination with cemiplimab 350 mg every 3 weeks.[16]

Although the use of fianlimab plus cemiplimab had minimal activity in anti–PD-1/PD-L1 experienced patients, a higher ORR and longer DOR was observed in anti–PD-1/PD-L1 naive patients. This profile is consistent with our melanoma data[16] and other anti-LAG-3 plus anti–PD-1 combinations tested in this clinical setting.[38,39] The activity observed in all disease cohorts in our study was sufficient to trigger cohort expansion, and several studies are ongoing to better

characterize fianlimab plus cemiplimab activity in advanced malignancies. Three such studies are currently ongoing in NSCLC. Two of these are phase 2/3 first-line studies of fianlimab plus cemiplimab versus cemiplimab in advanced disease: a chemotherapy-free study in patients with PD-L1 expression ≥50% (NCT05785767)[40] and a study of combination therapy with chemotherapy regardless of PD-L1 expression (NCT05800015).[41] The third NSCLC study is a phase 2 perioperative study of fianlimab plus cemiplimab plus chemotherapy versus cemiplimab plus chemotherapy in early-stage resectable disease (NCT06161441).[42] In ccRCC, a phase 2 study is underway of neoadjuvant fianlimab plus cemiplimab in patients with locally advanced disease (NCT06699602).[43] Finally, for HNSCC, a phase 2 study will investigate fianlimab plus cemiplimab versus cemiplimab plus placebo in patients with HPV-positive and HPV-negative HNSCC with positive PD-L1 expression (NCT06769698).[44] Future studies are planned to explore fianlimab plus cemiplimab in the early CSCC disease setting.

In conclusion, although limited efficacy was observed in anti–PD-1/PD-L1 experienced patients, in the anti–PD-1/PD-L1 naive population, fianlimab plus cemiplimab showed potential clinical activity across several tumor types with an acceptable safety profile warranting further investigation. However, the study is currently limited by the small number of patients.

AUTHOR CONTRIBUTIONS

Tae Min Kim: Investigation; writing—original draft; writing—review and editing. **Stephen K. Williamson**: Investigation; writing—original draft; writing—review and editing. **Kyriakos P. Papadopoulos**: Investigation; writing—original draft; writing—review and editing. **Omid Hamid**: Investigation; writing—original draft; writing—review and editing. **Grace K. Dy**: Investigation; writing—original draft; writing—review and editing. **Ray McDermott**: Investigation; writing—original draft; writing—review and editing. **Ariel Birnbaum**: Investigation; writing—original draft; writing—review and editing. **John M. Kaczmar**: Investigation; writing—original draft; writing—review and editing. **Nehal Lakhani**: Investigation; writing—original draft; writing—review and editing. **Danny Rischin**: Investigation; writing—original draft; writing—review and editing. **Debashis Sarker**: Investigation; writing—original draft; writing—review and editing. **Afshin Dowlati**: Investigation; writing—original draft; writing—review and editing. **Xin-Hua Zhu**: Investigation; writing—original draft; writing—review and editing. **Jyoti Malhotra**: Investigation; writing—original draft; writing—review and editing. **Jean-Francois Pouliot**: Writing—original draft and writing—review and editing. **Jayakumar Mani**: Writing—original draft and writing—review and editing. **Laura Brennan**: Writing—original draft and writing—review and editing. **Fang Fang**: Formal analysis; validation; data curation; writing—original draft; writing—review and editing. **Shuquan Chen**: Conceptualization; methodology; formal analysis; validation; data curation; writing—original draft; writing—review and editing. **Mark Salvati**: Conceptualization; methodology; supervision; writing—original draft; writing—review and editing. **Israel Lowy**: Conceptualization; methodology; project administration; supervision; writing—original draft; writing—review and editing. **Ahmed Khaled**: Writing—original draft and writing—review and editing. **Karl D. Lewis**: Writing—original draft and writing—review and editing. **Glenn Kroog**: Conceptualization; methodology; project administration; supervision; writing—original draft; writing—review and editing. **Matthew G. Fury**: Conceptualization; methodology; supervision; writing—original draft; writing—review and editing. **Byoung Chul Cho**: Investigation; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

Tae Min Kim reports consulting or advisory roles with AstraZeneca, BeOne Medicines, Daiichi-Sankyo, HK inno.N, Janssen, Merck KGaA, Novartis, Regeneron Pharmaceuticals, Inc, Roche/Genentech, Samsung Bioepis, Takeda, and Yuhan; and speaker bureau fees from Amgen, AstraZeneca, Janssen Research & Development, and Takeda. Stephen K. Williamson reports stocks in Iovance Biotherapeutics Inc, Horizon Therapeutics plc, and Merus N.V.; and institutional research funding from Acceleron Pharma, Inc, Aleon Pharma International, Inc, Astellas Pharma, Inc, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Ltd, EMD Serono, Merck Serono, Nektar Therapeutics, Novartis, Pharmacyclics LLC, Regeneron Pharmaceuticals, Inc, Rogosin Institute, Sanofi, Seagen Inc, and SOTIO Biotech. Kyriakos P. 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Bio GmbH; membership of board of directors for J INTS BIO Co., Ltd; stock or stock options from TheraCanVac Inc, Gencurix Inc, BridgeBio Therapeutics, Kanaph Therapeutic Inc, Cyrus Therapeutics, Interpark Bio Convergence Corp., J INTS BIO Co., Ltd , and is the founder of DAAN Biotherapeutics. Jean-Francois Pouliot reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Jayakumar Mani reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Laura Brennan reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Fang Fang reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Shuquan Chen reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Mark Salvati reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Israel Lowy reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Ahmed Khaled reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Karl D. Lewis reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Glenn Kroog reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Matthew G. Fury reports employment and stock and/or stock options with Regeneron Pharmaceuticals, Inc. Xin-Hua Zhu reports no conflicts of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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