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Original Research

Phase II study of CC-486 (oral azacitidine) in previously treated patients with locally advanced or metastatic nasopharyngeal carcinoma

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Abstract ***Background:*** Treatment options are limited for recurrent nasopharyngeal carcinoma (NPC). We report results from a phase II study of CC-486 (oral azacitidine) in advanced NPC.

Patients and methods: Patients with locally advanced or metastatic NPC and 1–2 prior treatment regimens received CC-486 300 mg daily on days 1–14 of 21-day cycles until disease progression or unacceptable toxicity. The first 6 patients of Asian-Pacific Islander (API) ethnicity received a reduced dose of 200 mg to preserve safety and tolerability; if well tolerated, subsequent API patients received CC-486 300 mg. The study could advance to stage 2 if > 4 patients achieved a response. Co-primary end-points were overall response rate (ORR) and progression-free survival (independent review). Key secondary end-points were overall survival and safety.

Results: Owing to faster-than-anticipated enrolment, 36 patients, including 13 of API ethnicity, were enrolled; the median age was 54.0 years. Most patients were male (81%) and had an Eastern Cooperative Oncology Group performance status ≤ 1 (97%). Among 25

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efficacy-evaluable patients, the ORR was 12%; the median progression-free and overall survival were 4.7 and 18.0 months, respectively. The most common grade III/IV treatment-emergent adverse events were neutropenia (33%) and febrile neutropenia (11%). Twenty-one posttreatment deaths, primarily due to progressive disease or disease complications, and 1 on-treatment death (epistaxis, unrelated to study drug) occurred. The study did not advance to stage 2.

Conclusion: CC-486 did not show sufficient clinical activity to support further development as monotherapy in this patient population. The safety profile of CC-486 in NPC was consistent with that in other solid tumours.

1. Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck cancers [1,2]. The incidence of NPC in most parts of the world is < 1 in 100,000; however, it is more common in specific parts of the world (eg, southern China and North Africa) and ethnic groups (eg, Inuits in Alaska/Canada, Nagas in northern India and Bidayuh in Borneo) [2–5]. Most patients have advanced NPC at diagnosis [6,7]. The 5-year survival rate (in the United States and Europe) is approximately 50%–60% [7,8]. Even with intensity-modulated radiotherapy, patients develop local recurrence (≈15%) and distant metastasis (≈30%) [9].

In phase II studies, first-line platinum-based doublets demonstrated a median progression-free survival (PFS) of approximately 7 months and overall survival (OS) of 12–28 months in metastatic NPC [10,11]. In a randomised phase III study of recurrent/metastatic NPC, gemcitabine plus cisplatin resulted in a significantly longer median PFS (7.0 vs 5.6 months; $P < 0.001$) and OS (29.1 vs 20.9 months; $P = 0.003$; preliminary analysis) than fluorouracil plus cisplatin [12]. The National Comprehensive Cancer Network guidelines recommend gemcitabine plus cisplatin (category 1) as first-line treatment for recurrent, unresectable or metastatic NPC [13]. However, no standard of care exists for advanced NPC in the second-line setting.

Epstein-Barr virus (EBV) infection, environmental factors (eg, heavy alcohol/tobacco use, diet rich in salt-cured meat), family history and mutations in epigenetic modulators may play important roles in NPC pathogenesis [9,14]. Aberrant DNA methylation and histone modifications may contribute to NPC initiation and progression [14–16]. Noncytotoxic gene expression–modulating agents (eg, azacitidine) represent an emerging approach to treating advanced NPC [9,17]. CC-486 (oral azacitidine) is a cytosine nucleoside analogue that irreversibly binds to DNA methyltransferases, leading to DNA hypomethylation and potential re-expression of methylation-silenced genes. CC-486 is hypothesised to result in immune-mediated antitumour effects in patients with NPC. An exploratory analysis of a phase I study suggested clinical activity of CC-486 monotherapy in NPC: of 8 patients, 3 had a partial response (PR), 4 had stable disease (SD) and 1 had disease progression [18]. This phase II study assessed the efficacy and safety of CC-486 monotherapy in previously treated patients with advanced NPC.

2. Methods

2.1. Study oversight

The study was conducted in accordance with the International Conference on Harmonisation E6 and Declaration of Helsinki. The protocol, amendments and informed consent forms were approved by the institutional review board or ethics committee of each study site before study initiation.

2.2. Study population

Patients (aged ≥18 years) with locally advanced or metastatic and undifferentiated/poorly differentiated NPC and disease progression with 1–2 prior treatment regimens, including a platinum-based chemotherapy, were eligible. Key exclusion criteria were prior treatment with a hypomethylating agent, presence/history of brain metastasis, history of inflammatory bowel disease or any gastrointestinal disorder/defect and active bleeding. An Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and adequate organ/bone marrow function were required. The full list of inclusion/exclusion criteria is included in Supplementary Methods.

2.3. Study design, treatments and end-points

This multicentre, single-arm, open-label, phase II study (NCT02269943) was conducted at 17 sites in Canada, France, Greece, Italy, Singapore, Spain, Tunisia, Taiwan and the United States. The study used Simon's optimal 2-stage design (Supplementary Fig. S1) [19].

Patients received CC-486 300 mg once daily (qd) orally on days 1–14 of 21-day cycles until disease progression or unacceptable toxicity. In a phase I study, 4 of 5 Japanese patients treated with CC-486 300 mg qd for 21 days of a 28-day cycle experienced grade IIIIV neutropenia (unpublished data). Therefore, to preserve safety in patients of Asian-Pacific Islander (API) ethnicity in the present study, the first 6 safety-evaluable API patients received CC-486 200 mg qd. Subsequent API patients received 300 mg qd if 200 mg was well tolerated (according to dose-limiting toxicities, described in Supplementary Methods). Patients could receive ≤1 dose reduction for adverse events (AEs) and were allowed dose interruptions of ≤7 days without requiring dose reduction.

The co-primary end-points were independently assessed overall response rate (ORR) and PFS; the decision to continue to stage 2 was based on ORR. The secondary end-points were disease control rate (DCR), OS, safety and pharmacokinetics. The exploratory objective was to generate predictive biomarker hypotheses based on tumour evaluations at baseline and cycle 2, day 1.

2.4. Study assessments

ORR was defined as complete response (CR) plus PR (confirmed ≥4 weeks after response criteria per RECIST 1.1 were first met); DCR was defined as ORR plus SD for ≥16 weeks from the first treatment per RECIST 1.1 criteria. ORR and DCR point estimates and 2-sided 90% confidence intervals (CIs) were reported using the Clopper-Pearson method. PFS and OS were estimated using the Kaplan–Meier method; medians and 2-sided 90% CIs were reported. Baseline levels of serum EBV-DNA were measured centrally (Seattle Children's Laboratory, Seattle, WA), using real-time quantitative polymerase chain reaction.

Safety data were reported as descriptive statistics. AEs were coded using the Medical Dictionary for Regulatory Activities, version 19.0, and severity was graded according to the Common Terminology Criteria for Adverse Events, version 4.0 (additional details in Supplementary Methods).

2.5. Statistical analyses

The sample size was determined based on having a sufficient number of patients in the efficacy-evaluable population achieving ORR >20% or median PFS >5 months. In stage 1, 17 efficacy-evaluable patients (defined in Supplementary Methods) were to be enrolled, and if > 4 responded (prespecified criterion; best response of CR/PR), 34 additional patients were to be enrolled in stage 2. Overall, 14 responses or median PFS >5 months was considered to render the study positive. This provided a power of 85% when the true ORR was 40% and, after stage 2, a power of 80% or 60% when the true median PFS was approximately 8 or 7 months, respectively.

3. Results

3.1. Patient disposition

Overall, 36 patients were enrolled in stage 1 between February and September 2015 (Fig. 1); the last patient's last visit was in April 2017. The number of patients enrolled in stage 1 exceeded what was planned because of faster-than-anticipated enrolment; patients who signed the informed consent form and met eligibility criteria were permitted to enter the study. Of 36 enrolled patients, 25 were efficacy evaluable. Three patients (300-mg cohort) were excluded because they did not receive ≥2 CC-486 cycles, and 8 (7 in the 300-mg cohort and 1 in the 200-mg cohort) were excluded because they received ≥2 CC-486 cycles but discontinued before completing 4 cycles for reasons other than progressive disease, including toxicities and consent withdrawal. Five efficacy-evaluable API patients received CC-486 200 mg and 20 (6 API and 14 white) received CC-486 300 mg. Because no dose-limiting toxicities were reported in API patients who received CC-486 200 mg during cycle 1, subsequent API patients received the CC-486 300-mg dose. The median follow-up for survival was 20.4 months.

3.2. Demographic and baseline clinical characteristics

The median age of patients was 54.0 years. Most patients were male (80.6%), had an ECOG PS ≤ 1 (97.2%) and had

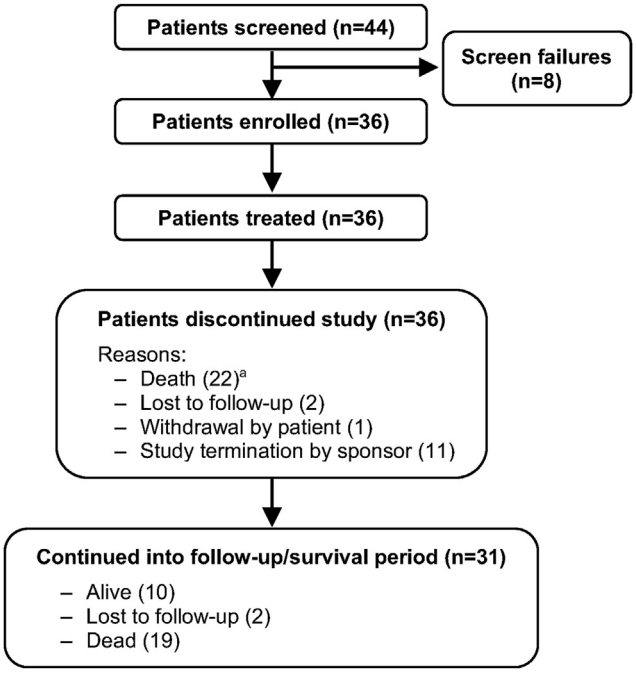

Fig. 1. Patient disposition. [a]Additional details, including the reasons for death, are provided in Table 3 in the manuscript.

Table 1
Demographic and baseline characteristics (enrolled population).

Characteristic	Enrolled patients (N = 36)
Age, median (range), years[a]	54.0 (24–71)
<65, n (%)	29 (80.6)
<30[b]	1 (2.8)
≥30 to <65[b]	28 (77.8)
≥65 to <75, n (%)	7 (19.4)
≥75, n (%)	0
Male, n (%)	29 (80.6)
Race, n (%)	
White	23 (63.9)
API	13 (36.1)
BMI, median (range), kg/m^2	23.7 (16.3–31.0)[c]
Patients receiving 300 mg	23.2 (16.3–31.0)
API patients receiving 200 mg	24.7 (17.4–30.5)
ECOG PS, n (%)[d]	
0	15 (41.7)
1	20 (55.6)
2	1 (2.8)
EBV-DNA levels, median (range), copies/mL	1146.5 (200–506,790)
EBV-DNA interpretation, n (%)[e]	
Negative (<200 copies/mL)[f]	10 (27.8)
White	5 (21.7)
API	5 (38.5)
Positive (≥200 copies/mL)[f]	20 (55.6)
White	12 (52.2)
API	8 (61.5)
Missing	6 (16.7)
White	6 (26.1)
API	0
Current cancer site, n (%)	
Metastatic	28 (77.8)
Locally advanced	8 (22.2)
Cancer diagnosis, n (%)	
Undifferentiated	23 (63.9)
Poorly differentiated	11 (30.6)
Nonkeratinizing, undifferentiated	2 (5.6)
Prior anticancer therapy, n (%)	
Any anticancer treatment	36 (100.0)
Radiotherapy	28 (77.8)
Surgery	10 (27.8)
Systemic therapy[g]	35 (97.2)
Cisplatin	30 (83.3)
Fluorouracil	21 (58.3)
Gemcitabine	17 (47.2)
Carboplatin	14 (38.9)
Docetaxel	11 (30.6)
Prior lines of systemic therapy, median (range)	2.0 (1.0–6.0)
Time from end of prior systemic anticancer therapy to first dose of CC-486, median (range), months	5.1 (0.9–57.3)

API, Asian-Pacific Islander; BMI, body mass index; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a] Age = maximum integer ≤ (date of informed consent − date of birth + 1)/365.25.

[b] This age group was not prespecified and is presented because of clinical relevance.

[c] n = 34; 2 patients in the 300-mg cohort had missing baseline BMI data.

[d] Last assessment before the first dose.

[e] Measured by real-time polymerase chain reaction in serum using the last measurement before the first dose administration.

[f] 200 copies/mL defined the limit of quantitative detection.

[g] Breakdown is for the most frequently used systemic therapy (≥25% of patients). A patient could have received >1 specific prior systemic therapy either in combination or sequentially.

metastatic NPC at baseline (77.8%) (Table 1). Approximately one-third of patients (13/36) were of API ethnicity.

3.3. Efficacy

The independently assessed ORR was 12.0% (90% CI, 3.4–28.2; 3 patients [300-mg cohort] achieved PR); the DCR was 52.0% (10 patients [7 in the 300-mg cohort and 3 in the 200-mg cohort] had SD) (Table 2). In the 300-mg cohort, the ORR/DCR was 17%/50% (1 PR, 2 SDs) in API patients and 14%/50% (2 PRs, 5 SDs) in white patients. In the 200-mg cohort, the ORR/DCR was 0%/60% (3 SDs). The investigator-assessed ORR (16.0% [90% CI, 5.7–33.0]; 4 PRs; Table 2) was consistent with the independently reviewed ORR. Fig. 2 shows the nadir percent change from baseline in the sum of the longest diameters of target lesions for individual patients.

The median PFS by independent review was 4.7 months (90% CI, 3.1–7.3; Table 2). The estimated 1-year PFS rate was 25.7% (90% CI, 12.6–41.1). The median PFS by investigator review was 6.4 months (90% CI, 4.7–10.1); the estimated 1-year PFS rate was 29.5% (90% CI, 15.4–45.0). The median OS was 18.0 months (90% CI, 14.8–not available). The estimated 1-year OS rate was 80.0% (90% CI, 62.7–89.9).

To look for any potential link between response and baseline EBV-DNA levels, we examined the data for 21 of 25 efficacy-evaluable patients with available EBV-DNA levels. Among 10 patients with EBV-DNA levels below the limit of quantification (ie, < 200 copies/mL), 3 patients (30%) had a partial response, 5 (50%) had stable disease and 2 (20%) had disease progression. Among 11 patients with detectable levels of EBV-DNA (≥200 copies/mL), 6 patients (55%) had stable disease and 5 (45%) had disease progression. The median (range) EBV-DNA level was 10,257 (236–506,790) copies/mL, and no clear pattern was observed between increasing levels of baseline EBV-DNA and response to CC-486.

3.4. Pharmacokinetics

The pharmacokinetic properties of CC-486 were studied in API patients. The plasma concentration vs time profiles showed a relatively rapid absorption phase in both the 200-mg and 300-mg cohorts (Supplementary Fig. S2). In both cohorts, the median time to maximum plasma concentration was approximately 1 h, and the terminal elimination phase began approximately 2 h after dosing. The CC-486 area under the curve (AUC) and peak concentration (C_{max}) were comparable in the 2 cohorts (Supplementary Table S1).

3.5. Treatment exposure, dose reductions and dose interruptions

The median treatment duration was 4.7 months, and the median number of cycles received was 7 (Supplementary

Table 2
Efficacy outcomes.

Parameter	Efficacy-evaluable patients (n = 25)	
	Independent review	Investigator review
Best confirmed response, n (%)		
CR	0	0
PR	3 (12.0)	4 (16.0)
SD ≥ 16 weeks	10 (40.0)	14 (56.0)
PD	7 (28.0)	4 (16.0)
ORR (90% CI), %	12.0 (3.4–28.2)	16.0 (5.7–33.0)
DCR (90% CI), %	52.0 (34.1–69.5)	72.0 (53.8–86.1)
PFS		
Deaths or disease progression, n (%)	20 (80.0)	23 (92.0)
Median (90% CI), months	4.7 (3.1–7.3)	6.4 (4.7–10.1)
OS		
Deaths, n (%)	13 (52.0)	
Median (90% CI), months	18.0 (14.8–NA)	

CI, confidence interval; CR, complete response; DCR, disease control rate; NA, not available; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table S2). The median relative dose intensity was 100.2% (range, 25.0%–150.0%), and the median cumulative dose was 21.2 g.

Fourteen patients (38.9%), including 5 in the 200-mg cohort (83.3%), required a CC-486 dose reduction. Sixteen patients (44.4%), including 3 in the 200-mg cohort (50.0%), had ≥1 dose interruption. Neutropenia was the most common treatment-emergent adverse event (TEAE) leading to CC-486 dose reduction, interruption or discontinuation (Supplementary Table S3).

3.6. Subsequent anticancer therapy

Thirteen efficacy-evaluable patients (52.0%) received systemic anticancer therapy after discontinuing treatment (Supplementary Table S4).

3.7. Safety

All patients experienced ≥1 TEAE (Table 3). The most common grade III/IV TEAEs (in >2 patients) were neutropenia (33.3%), febrile neutropenia (11.1%), leukopenia (8.3%) and vomiting (8.3%). Sixteen patients (44.4%) experienced ≥1 serious TEAE. Twenty-one posttreatment deaths (200-mg group, n = 4; 300-mg group, n = 17) and 1 on-treatment death (300-mg group) occurred. In the 200-mg group, deaths were attributed to progressive disease or disease complications (n = 2), AE (septic shock considered to be related to CC-486; n = 1), or other cause (n = 1). In the 300-mg group, the posttreatment deaths were attributed to progressive disease or disease complications (n = 16) or unknown cause (n = 1). The only on-treatment death (300-mg group) was attributed to epistaxis, considered to be unrelated to CC-486.

4. Discussion

This study did not demonstrate sufficient efficacy of CC-486 to warrant advancement to stage 2. Although the response rates were low, 19 of 25 efficacy-evaluable patients (76.0%) showed some degree of response. The DCR of 52% was better than expected for this heavily pretreated patient population with primarily metastatic NPC. These observations raise the possibility that CC-486 acts mainly via disease stabilisation. CC-486 was generally well tolerated, with no new safety signals [20,21]. Although the AUC and C_{max} in the 200-mg and 300-mg cohorts were comparable, the relatively small sample size and large between-patient variability precluded a definitive conclusion.

Combining azacitidine with agents such as valproic acid and all-trans retinoic acid and growth factors has shown promising activity in acute myeloid leukaemia and myelodysplastic syndrome [22,23]. In NPC preclinical studies, CC-486 has shown the potential to

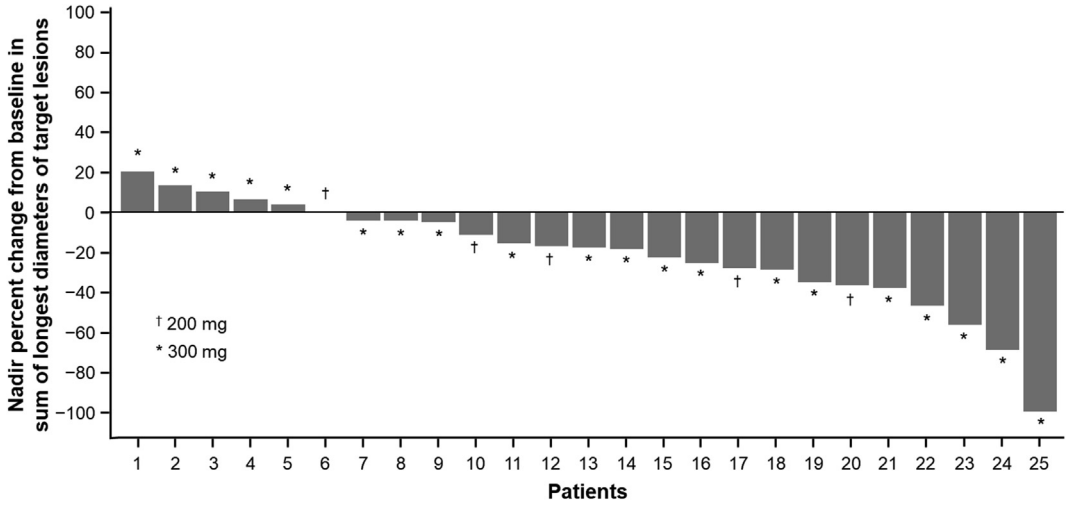

Fig. 2. Nadir percent change from baseline in sum of longest diameters of target lesions (efficacy-evaluable population).

Table 3
Treatment-emergent adverse events (safety population)[a].

Patients, n (%)	Safety population (N = 36)
Any-grade TEAEs	
Patients with ≥1 TEAE	36 (100.0)
Most common TEAEs (≥30% incidence)	
Vomiting	26 (72.2)
Nausea	24 (66.7)
Diarrhoea	13 (36.1)
Neutropenia	13 (36.1)
Constipation	11 (30.6)
Grade III/IV TEAEs	
Patients with ≥1 grade III/IV TEAE	26 (72.2)
Most common grade III/IV TEAEs (in >2 patients)	
Neutropenia	12 (33.3)
Febrile neutropenia	4 (11.1)
Leucopenia	3 (8.3)
Vomiting	3 (8.3)
Serious TEAEs	
Patients with ≥1 serious TEAE	16 (44.4)
Most common serious TEAEs (in ≥2 patients)	
Febrile neutropenia	4 (11.1)
Dysphagia	2 (5.6)
Vomiting	2 (5.6)
Pyrexia	2 (5.6)
Neutrophil count decreased	2 (5.6)
Cerebrovascular accident	2 (5.6)
Summary of deaths	
Deaths	22 (61.1)
On treatment	1 (2.8)
Due to AE (epistaxis)	1 (2.8)
Posttreatment	21 (58.3)
Due to NPC or its complication	18 (50.0)
Cause unknown	1 (2.8)
Due to AE (septic shock)	1 (2.8)
Due to other cause	1 (2.8)

AE, adverse event; NPC, nasopharyngeal carcinoma; TEAE, treatment-emergent adverse event.

[a] TEAEs were defined as any AEs that began or worsened on or after the start of CC-486 through 28 days after the last dose. In addition, any AE with an onset >28 days after the last dose assessed by the investigator as related to CC-486 was considered a TEAE. Severity of an AE was graded using Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. If multiple toxicity grades were associated with an AE, the maximum severity was used. For AEs not described in the CTCAE criteria, severity was assessed by the investigator as mild (grade I), moderate (grade II), severe (grade III), life-threatening (grade IV) or death (grade V).

improve outcomes with radiotherapy [24,25]. The mechanism of action of CC-486 suggests the possibility of combination with similar drugs and immunotherapies for the treatment of NPC. Hypermethylation is associated with poor survival outcomes in patients with NPC and may be a useful prognostic biomarker [26]. Azacitidine is thought to reactivate the host immune response through demethylation of silenced genes, especially in EBV-associated tumours, in which it reactivates silenced immunodominant antigens in infected cells. This could create a more favourable microenvironment for immunotherapies by enhancing tumour-specific antigen presentation, thus expanding the primary and adaptive immune responses [27]. A limitation of this study was that relatively few tumour biopsy samples were collected, which precluded any biomarker and correlation analyses. In the absence of any biomarker data, it is unclear whether the observed activity was a result of direct action of CC-486 or mediated by a reactivated host immune response. The lack of detailed biomarker data also precluded meaningful interpretations regarding any correlation between change in EBV-DNA and clinical response.

The role of immunotherapies targeting the tumour (cytotoxic T lymphocytes) or the host has been studied in recurrent/metastatic NPC [28–31]. In studies of the immune checkpoint inhibitors nivolumab and pembrolizumab, an ORR of 20%–26% and a 1-year OS of 59%–63% in mostly pretreated patients was reported [30,31]. In phase I trials, camrelizumab, a programmed cell death protein 1 inhibitor, alone (second line) or with cisplatin/gemcitabine (first line) showed a manageable safety profile and promising antitumour activity in patients with recurrent/metastatic NPC [32]. The promising results observed with immune checkpoint inhibitors, along with the CC-486 mechanism of action and response data reported here, provoke the interesting speculation that their combination may exhibit synergistic activity. Future studies could determine whether treating earlier stages of NPC with CC-486 monotherapy or advanced stages with CC-486 combined with other drugs, including immunotherapy, will produce more desirable outcomes.

5. Conclusion

This was a nonrandomised study with a relatively small sample size. CC-486 monotherapy at the selected dose did not show sufficient clinical activity in patients with advanced NPC to warrant further clinical development in this indication. In the first 6 API patients who were assessed for safety and tolerability with CC-486 200 mg, no new safety signals were noted. The safety profile of CC-486 in NPC was consistent with that in other solid tumours and with the safety profile of injectable azacitidine. The safety and response data for CC-486 reported here support consideration of combination with other treatments, including immunotherapy.

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Conflict of interest statement

R.M. has served an advisory role in AstraZeneca, Merck Sharp & Dohme Corp, Merck, Bristol-Myers Squibb, Roche and Nanobiotix and has received conference honoraria from Merck and Bristol-Myers

Squibb. **P.B.** has been a member of the advisory board of Merck, Sanofi and Merck Sharp & Dohme Corp and has received conference honoraria from AstraZeneca, Bristol-Myers Squibb, Kyowa Hakko Kirin, Angelini and Norgine. **A.R.H.** has been a consultant and has received advisory fees from Genentech/Roche, Merck, GSK, Bristol-Myers Squibb, Novartis Pharmaceuticals, Boston Biomedical, Boehringer Ingelheim, AstraZeneca and MedImmune. **C-.Y.H.** has nothing to disclose. **L.F.L.** has received grants from AstraZeneca, Boehringer Ingelheim, Eisai, Merck, Merck Sharp & Dohme Corp, Novartis Pharmaceuticals and Roche; has served a consultant role and has received advisory fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Debiopharm, Merck Serono, Merck Sharp & Dohme Corp, Novartis Pharmaceuticals, Roche, Sobi, Ipsen, GSK, Health & Life SRL, Doxa Pharma SRL, Immuno-Oncology Hub, Incyte Biosciences Italy SRL, Amgen and Nanobiotics Sa and has received travel/logistical support from Bayer, Bristol-Myers Squibb, Debiopharm, Eisai, Merck Serono, Merck Sharp & Dohme Corp and Sobi. **E-.H.T.** has nothing to disclose. **P.C.** is an employee of and holds stock options in Celgene. **J.M.** is an employee of and holds stock options in Celgene. **L.L.S.** has received grants from Novartis, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Regeneron, GSK, Roche/Genentech, Karyopharm, AstraZeneca/MedImmune, Merck, Celgene Corporation, Astellas, Bayer, AbbVie, Amgen, Symphogen and Intensity Therapeutics; has served as a consultant of and has received advisory fees from Merck, Pfizer, Celgene Corporation, AstraZeneca/MedImmune, Morphosys, Roche, GeneSeeq, Loxo, Oncorus, Symphogen and Mirati and is a stockholder (spouse) of Agios. **R.I.H.** has received grants from Merck, Bristol-Myers Squibb, AstraZeneca, Kura, Genentech and Pfizer and has served as a consultant of and has received advisory fees from Merck, Bristol-Myers Squibb, Genentech, Pfizer, AstraZeneca, Loxo, Celgene Corporation, Bayer and Immunomic.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.10.002.

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