Concomitant Proton Pump Inhibitor Use and Survival in Urothelial Carcinoma Treated with Atezolizumab
Ashley M. Hopkins, Ganessan Kichenadasse, Christos S. Karapetis, Andrew Rowland, and Michael J. Sorich

ABSTRACT

Purpose: Emerging evidence indicates that gut microbiota dysbiosis can reduce the effectiveness of immune checkpoint inhibitors (ICI). Proton pump inhibitors (PPI) are known to induce gut microbiota changes. However, little is known on the effects of PPIs on outcomes with ICIs in cancer treatment, and it has not been explored in urothelial cancer treatment.

Experimental Design: Individual-participant data from the advanced urothelial cancer trials, IMvigor210 (single-arm atezolizumab trial, n = 429) and IMvigor211 (phase III randomized trial of atezolizumab vs. chemotherapy, n = 931) were pooled in a Cox proportional hazard analysis assessing the association between PPI use and overall survival (OS) and progression-free survival (PFS). PPI use was defined as any PPI administration between 30 days prior and 30 days after treatment initiation.

Introduction

Immune checkpoint inhibitors (ICI) are a significant advance in the treatment of cancer; however, they are still associated with considerable heterogeneity in survival outcomes. The gut microbiota plays an important role in regulating homeostasis and immune function (1). There’s growing awareness that an altered gut microbiota can negatively impact systemic immune response and ICI efficacy (1–4). Recent evidence indicates that proton pump inhibitors (PPI) cause significant gut microbiota changes, driven by both altered stomach acidity and direct compound effects (5–9). PPIs have also been associated with promotion of T-cell tolerance, pharmacokinetic influences, and even direct anticancer effects in combination with docetaxel used in the treatment of breast cancer (5, 6, 10, 11). PPIs are commonly used for extended time periods in patients with cancer, resulting in potential long-lasting effects on the efficacy of anticancer treatments. Preliminary research has investigated the influence of PPIs on ICIs used in advanced non–small cell lung cancer (NSCLC) and melanoma treatment; with conflicting results between detrimental and no effects identified (12–17). It is unclear whether these conflicting results are primarily driven by the limited sample size of some studies or cancer type differential effects, but most recently in the largest study to date, Chalabi and colleagues (17) identified a significant negative prognostic association of PPI use on survival in advanced NSCLC treated with atezolizumab, with no association in a matched randomized cohort treated with docetaxel. While Chalabi and colleagues (17) were underpowered to detect a statistically significant treatment-by-covariate interaction, it exemplifies an urgent need for further investigation and no studies have investigated the association between PPI use and survival outcomes with ICIs in urothelial carcinoma.

This study aimed to evaluate the association between PPI use and survival outcomes with atezolizumab as compared with chemotherapy in patients with advanced urothelial carcinoma.

Materials and Methods

This study adopted statistical methodology standardized from prior work (17, 18), including work published by our group with atezolizumab used in lung cancer (19–24).

Population

Individual–participant data (IPD) from the clinical trials IMvigor210 (refs. 25, 26; NCT02108652; July 4, 2016 data cutoff) and IMvigor211 (ref. 27; NCT02302807; March 13, 2017 data cutoff) were pooled. IMvigor211 was a randomized trial of atezolizumab 1,200 mg i.v. every 3 weeks versus chemotherapy [docetaxel (75 mg/m² i.v. every 3 weeks), paclitaxel (175 mg/m² i.v. every 3 weeks), or vinflunine (320 mg/m² i.v. every 3 weeks)] for patients with locally advanced or metastatic urothelial cancer who have progressed during or following a prior platinum-based chemotherapy regimen (27). IMvigor210 was a single-arm study of atezolizumab 1,200 mg i.v. every 3 weeks in locally advanced or metastatic urothelial cancer, including participants who were treatment-naïve and ineligible for cisplatin-containing chemotherapy.
Translational Relevance

Proton pump inhibitors (PPI) induce gut microbiota changes and gut microbiota dysbiosis has been linked to reduced immune checkpoint inhibitor (ICI) effectiveness. In a retrospective analysis of clinical trials IMVigor210 and IMVigor211, PPI use was associated with poor survival outcomes in patients with urothelial carcinoma receiving atezolizumab therapy, with no association present in the matched randomized cohort receiving chemotherapy. Given approximately 30% of patients with cancer use PPIs, often for extended time periods, this study presents important information that PPI use may alter the magnitude of atezolizumab efficacy compared with chemotherapy.

chemotherapy or participants who have progressed during or following a prior platinum-based chemotherapy regimen (25, 26).

Secondary analysis of anonymized clinical trial data was confirmed negligible risk research by the Southern Adelaide Local Health Network, Office for Research and Ethics and was confirmed exempt from review. Data were accessed according to Roche’s policy and process for clinical study data sharing (28). IMVigor210 and IMVigor211 were subject to independent review at each participating site and were done according with Good Clinical Practice guidelines and the Declaration of Helsinki (25–27). All patients within IMVigor210 and IMVigor211 provided written informed consent (25–27).

Predictors and outcomes

The primary assessed outcome was overall survival (OS), progression-free survival (PFS) a secondary outcome, and objective response a tertiary outcome. Primary study definitions of PFS were utilized (25–27). PFS and objective response were investigator assessed as per Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) in IMVigor211; and independently assessed per RECIST version 1.1 in IMVigor210. Adverse events (AE) were investigator reported by grade using the NCI’s Common Terminology Criteria for Adverse Events, version 4.0 (25–27).

The primary assessed covariate was any PPI use within a period of 30 days prior and 30 days after treatment initiation. This time-frame was analyzed based upon prior analyses (17). A sensitivity analysis of documented PPI use at the day of treatment initiation was conducted. For sensitivity interaction analyses, oral corticosteroid use was defined as any administration within a period of 30 days prior and 30 days after treatment initiation. This time-frame was analyzed based upon prior analyses (17). A sensitivity analysis of documented PPI use at the day of treatment initiation was conducted. For sensitivity interaction analyses, oral corticosteroid use was defined as any administration within a period of 30 days prior and 30 days after treatment initiation. This time-frame was analyzed based upon prior analyses (17).

Statistical analyses were performed using R version 3.4.3 and the packages survival and rms.

Role of the funder/sponsor

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit.

Data statement

Data were accessed according to Roche’s policy and process for clinical study data sharing and is available for request at clinicalstudiodydatarequest.com.

Results

Patient population

Of the 429 participants initiated on atezolizumab within IMVigor210, 141 (33%) received a PPI within the 60-day window. 145 (31%) of the 467 participants randomized to atezolizumab and 185 (40%) of the 464 participants randomized to chemotherapy received a PPI in IMVigor211. Immune (95% CI) follow-up was 11 (11–12) and 17 (17–18) months in IMVigor210 and IMVigor211, respectively. Supplementary Table S1 provides a summary of patient characteristics by study. Of the 471 participants using a PPI in IMVigor210 and IMVigor211, 179 were using omeprazole, 151 pantoprazole, 77 esomeprazole, 45 lansoprazole, 13 rabeprazole, and 6 dexlansoprazole. Furthermore, of the 471 participants, 93% (n = 440) were using the PPI for either gastric protection (175), gastroesophageal reflux disease (GERD; n = 158), dyspepsia (33), epigastric pain/discomfort (27), gastritis (23), ulcer (21), or chemotherapy associated (3). Supplementary Table S2 presents patient characteristics by PPI use status; of note, PPI users had higher ECOG PS and more frequently had higher number of tumor sites (P < 0.001).

Prognostic association

In the pooled group of participants allocated atezolizumab treatment in IMVigor210 and IMVigor211, PPI use was associated with worse OS on univariable [HR (95% CI) = 1.68 (1.41–2.00), P < 0.001] and adjusted [1.52 (1.27–1.83), P < 0.001] analysis (Table 1; Supplementary Table S3; Fig. 1). Similarly, PPI use was associated with worse PFS on univariable [1.47 (1.26–1.71), P < 0.001] and adjusted [1.38 (1.18–1.62), P < 0.001] analysis (Table 1; Supplementary Table S3; Supplementary Fig. S1). PPI use was associated with worse objective response, and IMVigor211 using a PPI-by-treatment interaction term in the Cox proportional regression model. Sensitivity analysis of the associations between PPI use and outcomes were conducted for the PD-L1 IC2/3 and IC0/1 populations. Sensitivity analysis of the prognostic association heterogeneity between cohort 1 and cohort 2 in IMVigor210, vinflunine, and taxane therapy in IMVigor211, antibo-
Table 1. Adjusted* HRs or ORs (95% CI) for outcomes by PPI users versus nonusers.

<table>
<thead>
<tr>
<th></th>
<th>IMvigor211</th>
<th>IMvigor210</th>
<th>Pooled</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>Atezolizumab</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>Total cohort</td>
<td>N 415</td>
<td>442</td>
<td>405</td>
</tr>
<tr>
<td>OS</td>
<td>1.16 (0.93–1.47), P = 0.194</td>
<td>1.70 (1.33–2.17), P &lt; 0.001</td>
<td>1.40 (1.06–1.85), P = 0.019</td>
</tr>
<tr>
<td>PFS</td>
<td>1.11 (0.89–1.37), P = 0.352</td>
<td>1.49 (1.19–1.85), P &lt; 0.001</td>
<td>1.30 (1.02–1.64), P = 0.031</td>
</tr>
<tr>
<td>Objective response</td>
<td>1.04 (0.64–1.71), P = 0.861</td>
<td>0.40 (0.20–0.81), P = 0.011</td>
<td>0.67 (0.34–1.29), P = 0.227</td>
</tr>
<tr>
<td>PD-L1 IC2/3 population</td>
<td>N 138</td>
<td>136</td>
<td>137</td>
</tr>
<tr>
<td>OS</td>
<td>1.06 (0.69–1.63), P = 0.790</td>
<td>1.80 (1.10–2.96), P = 0.020</td>
<td>1.98 (1.16–3.40), P = 0.012</td>
</tr>
<tr>
<td>PFS</td>
<td>1.11 (0.73–1.69), P = 0.616</td>
<td>1.88 (1.20–2.95), P = 0.006</td>
<td>1.43 (0.91–2.26), P = 0.120</td>
</tr>
<tr>
<td>Objective response</td>
<td>0.67 (0.29–1.52), P = 0.333</td>
<td>0.20 (0.05–0.76), P = 0.018</td>
<td>0.74 (0.26–2.12), P = 0.578</td>
</tr>
</tbody>
</table>

*Analyses adjusted for baseline age, sex, BMI, ECOG performance status, smoking status, histology, count of prior treatments, PD-L1 expression, serum HGB levels, count of organ sites with metastases, and presence of liver metastases.

Figure 1.
Kaplan–Meier estimate of OS for PPI users versus non-users, randomized atezolizumab (A and C) or chemotherapy (B and D) within IMvigor211 and IMvigor210. A and B, All study participants. C and D, PD-L1 IC2/3 populations.
response on univariable [OR (95% CI)] = 0.46 (0.29–0.72), P < 0.001] and adjusted [0.51 (0.32–0.82), P = 0.006] analysis (Table 1; Supplementary Table S3). No association between PPI use and OS, PFS, or objective response were identified in the participants randomized to chemoradiotherapy in IMvigor211 (Table 1; Fig. 1; Supplementary Table S3; Supplementary Fig. S1).

On sensitivity analysis of the PD-L1 IC2/3 population, PPI use was similarly associated with significantly worse OS, PFS, and objective response for patients treated with atezolizumab, but not chemotherapy (Table 1; Fig. 1; Supplementary Table S3; Supplementary Fig. S1). Supplementary Table S4 presents the association between PPI use and OS, PFS, and objective response in the PD-L1 IC0/1 populations.

No significant heterogeneity in the PPI association was observed between cohort 1 and cohort 2 in IMvigor210 (OS Pinteraction = 0.597; PFS Pinteraction = 0.347; objective response Pinteraction = 0.995; Supplementary Figs. S2–S4). No significant heterogeneity in the PPI association was observed between vinflunine and taxane therapy in IMvigor211 (OS Pinteraction = 0.355; PFS Pinteraction = 0.485; objective response Pinteraction = 0.332; Supplementary Figs. S5–S7). Antibiotic use was associated with an increase in the magnitude of the negative association between PPI use and OS in patients treated with atezolizumab [antibiotic use HR (95% CI) = 2.51 (1.12–5.59), no antibiotics use = 1.44 (1.19–1.74), Pinteraction = 0.045; Supplementary Fig. S8]. In participants treated with atezolizumab, no significant heterogeneity in the PPI association was observed for PFS (Pinteraction = 0.107) or objective response (Pinteraction = 0.574) in antibiotic users and nonusers (Supplementary Figs. S9 and S10). In participants treated with atezolizumab, no significant heterogeneity in the PPI association was observed for OS (Pinteraction = 0.624), or objective response (Pinteraction = 0.780) in oral corticosteroid users and nonusers (Supplementary Figs. S11–S13).

In a subset analysis comparing PPI users within the period of 30 days prior to atezolizumab initiation (including the day of initiation) versus patients who initiated a PPI within the 30 days prior to atezolizumab initiation (including the day of initiation) versus patients who initiated a PPI within the 30 days prior to atezolizumab initiation (including the day of initiation), no significant heterogeneity in the PPI association was observed for OS (Pinteraction = 0.70–1.89), PFS (Pinteraction = 0.953), grade ≥ 1 AE (Pinteraction = 0.68) for PPI users, compared with 0.81 (0.63–1.03) for PPI nonusers (Pinteraction = 0.338, Supplementary Table S5). Thus, there was not statistical evidence to indicate PPI use was associated with causing the reduced benefit of atezolizumab within the PD-L1 IC0/1 population.

On sensitivity analysis of PPI use at the day of treatment initiation, the magnitude of atezolizumab effect (vs. chemotherapy) on OS and PFS were similar in the total and PD-L1 IC2/3 populations of IMvigor211 (Supplementary Table S6; Supplementary Figs. S15 and S16).

## Discussion

For the first time, PPI use has been shown as an independent prognostic factor of worse survival outcomes in locally advanced/metastatic urothelial cancer treated with atezolizumab, but not chemotherapy. Further in *post hoc* analysis of IMvigor211, PPI use was associated with a statistical decrease in the magnitude of atezolizumab benefit. These findings were consistent in the PD-L1 IC2/3 population. Preliminary research has investigated the influence of PPIs on the efficacy of ICIs in patients with advanced NSCLC and melanoma (12–17), most recently headlined by Chalabi and colleagues (18) who identified a significant negative prognostic association of PPI use on survival in advanced NSCLC treated with atezolizumab. The hypothetical basis of this research is that PPIs are associated with marked changes to the gut microbiota, driven by both altered stomach acidity and direct compound effects (5–9), which may influence immune responses to ICI therapies. Specifically, PPIs have been observed to decrease the alpha diversity of the gut microbiota and increase the relative abundance of *Actinomyces*, *Micrococcaceae*, *Enterobacteriaceae*, and *Streptococcaceae* families (5–9). Prior research in melanoma patients initiating ICI therapy indicates increased responses at high alpha diversity and high relative abundances of *Ruminococcaceae/Faecalibacterium* (P < 0.01; n = 112), which represent a gut microbiota associated with enhanced antitumor immune activity (1, 4). On the basis of these prior studies, it would be hypothesized that PPI related changes in gut microbiota would be undesirable with respect to ICI efficacy, which is consistent with the finding of this study.

### Table 2. Treatment effect of randomly allocated atezolizumab versus chemotherapy by PPI use status, in IMvigor211.

<table>
<thead>
<tr>
<th>PPI users</th>
<th>HR/OR (95% CI)</th>
<th>PPI nonusers</th>
<th>HR/OR (95% CI)</th>
<th>Pinteraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>OS (N = 857)</td>
<td>1.04 (0.81–1.34)</td>
<td>0.69 (0.56–0.84)</td>
<td>0.013</td>
</tr>
<tr>
<td>PFS (N = 857)</td>
<td>1.33 (1.05–1.69)</td>
<td>0.91 (0.76–1.09)</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Objective response</td>
<td>0.33 (0.36–0.68)</td>
<td>0.81 (0.53–1.23)</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>PD-L1 IC2/3 population</td>
<td>OS (N = 274)</td>
<td>1.15 (0.70–1.89)</td>
<td>0.47 (0.32–0.69)</td>
<td>0.006</td>
</tr>
<tr>
<td>PFS (N = 274)</td>
<td>1.59 (0.99–2.55)</td>
<td>0.71 (0.51–0.98)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Objective response</td>
<td>0.28 (0.07–1.09)</td>
<td>0.85 (0.44–1.66)</td>
<td>0.129</td>
<td></td>
</tr>
</tbody>
</table>

*Analyses adjusted for baseline age, sex, BMI, ECOG performance status, smoking status, history, count of prior treatments, PD-L1 expression, serum HGB levels, count of organ sites with metastases, and presence of liver metastases.

*Relative hazard of outcome for patients randomized atezolizumab versus chemotherapy.

### Association with treatment benefit

In the total randomized cohort of IMvigor211, the OS treatment effect [HR (95%CI)] of atezolizumab versus chemotherapy was 1.04 (0.81–1.34) for PPI users, compared with 0.69 (0.56–0.84) for PPI nonusers [Pinteraction = 0.013; Table 2; Fig. 2]. In the PD-L1 IC2/3 population, the OS treatment effect of atezolizumab versus chemotherapy was 1.15 (0.70–1.89) for PPI users, compared with 0.47 (0.32–0.69) for PPI nonusers [Pinteraction = 0.006; Table 2; Fig. 2]. Similar PFS treatment effect modifications were observed (Table 2; Supplementary Fig. S14). These results indicate PPI use was associated with a statistical decrease in the magnitude of OS and PFS benefit from atezolizumab in the total and PD-L1 IC2/3 population.

In the PD-L1 IC0/1 population, the OS treatment effect of atezolizumab vs. chemotherapy was 0.98 (0.72–1.33) for PPI users, compared with 0.81 (0.63–1.03) for PPI nonusers (Pinteraction = 0.338, Supplementary Table S5). Thus, there was not statistical evidence to indicate PPI use was associated with causing the reduced benefit of atezolizumab within the PD-L1 IC0/1 population.
Importantly, this study includes data from the phase III randomized trial IMvigor211, which assessed the efficacy of atezolizumab as compared with chemotherapy (docetaxel, paclitaxel, or vinflunine; ref. 27). Such data allow both the assessment of the prognostic association of PPI use with atezolizumab outcomes, and valid treatment by biomarker subgroup analyses. For the first time, this study presents a negative prognostic association of PPI use on OS and PFS in advanced urothelial carcinoma treated with atezolizumab, and no association with chemotherapy outcomes. Importantly, the study further identified a statistically significant treatment-by-covariate interaction, indicating that the magnitude of atezolizumab benefit on both OS and PFS was decreased in PPI users. Chalabi and colleagues (17) similarly identified a negative prognostic association of PPI use on OS and PFS in advanced NSCLC treated with atezolizumab, and no significant association on docetaxel outcomes. Albeit trending toward similarity, Chalabi and colleagues (17) did not detect a statistically significant treatment-by-covariate interaction. Nonetheless, the consistency of findings between this study and Chalabi and colleagues (17) exemplifies an urgent need for a comprehensive pooled analysis of all ICI randomized trials to conclusively determine if PPIs influence ICI efficacy, including in settings outside advanced urothelial carcinoma and later-line ICI use. For example, the gut dysbiosis effects of PPIs on chemotherapies may be more pronounced in early lines of treatment, as advanced patients may have developed a disease state sensitized to evading immunosurveillance (1). In IMvigor211, the assessed population was pretreated with platinum therapies. Proposed pharmacokinetic influences and even direct antitumor effects of PPIs in combination with chemotherapies requires

Figure 2.
Kaplan Meier estimates of OS in the randomized arms (atezolizumab versus chemotherapy) of IMvigor211, subgrouped by PPI use status. A and B, All study participants; C and D, PD-L1 IC2/3 populations.
further investigation (10, 11). This study was underpowered to assess specific chemotherapies and the association of concomitant PPI use with chemotherapies has been minimally explored to date. Powles and colleagues (27) previously reported a prespecified analysis of IMVigor211, where no significant OS benefit from atezolizumab (versus chemotherapy) was observed in the PD-L1 IC2/3 population. The prespecified analysis of the PD-L1 IC2/3 population was conducted based upon evidence that the PD-L1 IC2/3 population gains the most benefit from ICI therapy (25–27). The findings of the analysis herein demonstrate the potential significance of PPIs, where PPI users had no atezolizumab benefit, while PPI nonusers did gain from atezolizumab in both the PD-L1 IC2/3 population and the total population. Albeit there was a trend toward an effect, there was no statistical evidence to indicate PPI use was associated with varying atezolizumab benefit within the PD-L1 IC0/1 population.

This study pooled large, high-quality data from two contemporary clinical trials, increasing power and generalizability. Nonetheless, the findings are based on a hypothesis-generating, unplanned post hoc analysis. A significant strength of the study was the consistency of results across OS, PFS, and objective response, in both the total and PD-L1 IC2/3 population, and between PPI use within the 60-day window and PPI use documented at the day of treatment initiation. A limitation of the study was an inability to assess the type, dose or compliance to PPI therapy. Nonetheless, over 90% of the participants using a PPI within the 60-day window did so for an indication that likely constituted a need for extended use. Whilst the conducted analyses have been adjusted there is the potential that PPI use constitutes a surrogate marker for an unfit or immunodeficient patient. Similar to much of the prior work investigating the associations between antibiotic use and survival outcomes in patients treated with atezolizumab (17), including work published by our group (18), a limitation of this study investigating the impacts of PPIs is the restricted range of ICIs, chemotherapies and settings evaluated. Future research should evaluate other ICIs, other cancer types, first-line ICI use, combination ICI use, and combination chemotherapy approaches. As both altered stomach acidity and direct compound effects contribute to the gut microbiota changes induced by PPIs, the compositional changes on the gut microbiota from H2-receptor antagonists and antacids may not be the same (5–9). Hence, the impacts of H2-receptor antagonists and antacids on survival outcomes with ICIs should be explored. Unfortunately, the small number of patients concomitantly using these agents within this study precluded reliable analysis to confirm or deny if the impacts were similar. Future research should also evaluate the impact of concomitantly using PPIs and antibiotics. The potential importance is highlighted as the magnitude of the negative association between PPI use and OS was greater in participants who received an antibiotic in the 60 days prior to atezolizumab initiation, albeit no statistical effects on PFS or objective response were observed.

In conclusion, PPI use was independently associated with worse survival outcomes in locally advanced/metastatic urothelial cancer treated with atezolizumab, but not chemotherapy. Further in the randomized arms of IMVigor211, PPI use was associated with a statistical decrease in the magnitude of atezolizumab benefit. Given approximately 30% of patients with cancer use PPIs, often for extended time periods, there is an urgent need to conclusively determine if PPIs influence ICI efficacy.

Disclosure of Potential Conflicts of Interest
A.M. Hopkins reports grants from National Breast Cancer Foundation (Australia) during the conduct of the study. C.S. Karapetis reports personal fees from Roche (advisory board) during the conduct of the study, as well as personal fees from AstraZeneca (advisory board), Eisa (advisory board), BMS (advisory board), Merck (advisory board), Amgen (advisory board), and MSD (advisory board) outside the submitted work. A. Rowland reports grants from Pfizer Inc outside the submitted work. M.J. Sorich reports grants from Cancer Council SA during the conduct of the study and grants from Pfizer outside the submitted work. No potential conflicts of interest were disclosed by the other author.

Authors’ Contributions
A.M. Hopkins: Conceptualization, resources, data curation, software, formal analysis, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, project administration, writing-review and editing.
G. Kichenadasse: Conceptualization, formal analysis, validation, methodology, writing-original draft, writing-review and editing.
C.S. Karapetis: Conceptualization, supervision, writing-original draft, writing-review and editing.
A. Rowland: Conceptualization, resources, supervision, writing-original draft, project administration, writing-review and editing.
M.J. Sorich: Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, project administration, writing-review and editing.

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