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Association of prior fluoroquinolone treatment with survival outcomes of immune checkpoint inhibitors in Asia

Po-Hsien Lu MS[1] | Tzu-Cheng Tsai MS[1] | John Wen-Cheng Chang MD[2] | Shin-Tarng Deng MS[1] | Chi-Yuan Cheng MS[1]

[1]Department of Pharmacy, Chang Gung Memorial Hospital, Linkou, Taiwan

[2]Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan

Correspondence
Chi-Yuan Cheng, Linkou Chang Gung Memorial Hospital, No. 5, Fusing St., Gueishan Township, Taoyuan 333, Taiwan.
Email: cycdavid0924@gmail.com

Abstract

What is known and objective: Gut microbiota plays an important role in shaping immune responses. Several studies have reported that antibiotics may alter gut microbiota diversity and compromise the therapeutic response to immune checkpoint inhibitors (ICIs). Nevertheless, the impact of a specific class of antibiotics on ICIs therapy is still not known. The aim of this study was to analyse the influence of antibiotics on the clinical outcomes of non-small cell lung cancer (NSCLC) patients treated with ICIs and to compare the effects of fluoroquinolones vs. other broad-spectrum antibiotics.

Methods: This retrospective cohort study ($n = 340$) analysed data from Chang Gung Research Database, which comprises work from seven medical institutions in Taiwan. Patients with NSCLC who received ICIs between January 2016 and March 2019 were evaluated. The data of patients who received antibiotics (ie fluoroquinolone) within 30 days prior to ICIs therapy were analysed. Overall survival (OS) was the goal of our study and was calculated from the time the ICIs therapy start. Survival analysis was estimated using the Kaplan-Meier and Cox statistics.

Results: A total of 340 patients were identified for analysis. Of the 340 patients, only over one third (38%) of patients received antibiotics 30 days prior to ICI therapy. These patients exhibited a shorter OS compared with those not receiving antibiotics (median OS, 266 days vs. 455 days; hazard ratio (HR), 2.9; 95% confidence interval (CI), 1.1–8.1, $p = 0.003$). In this study, 127 out of 128 patients who were exposed to antibiotics had received at least one broad-spectrum antibiotic. We observed patients who had received fluoroquinolone had a shorter OS compared with those receiving other broad-spectrum antibiotics (median OS, 121 days vs. 370 days; HR, 1.582; 95% CI 1.007–2.841; $p = 0.047$).

What is new and conclusion: Antibiotic treatment, especially fluoroquinolone, prior to ICIs therapy was associated with poorer clinical efficacy in NSCLC patients. Antibiotics should not be withheld when there is a clear need for them despite the possibility of interfering with the microbiome, which may, in turn, adversely affect the ICI's effectiveness. However, one should consider avoiding the use of fluoroquinolones antibiotics.

KEYWORDS

antibiotic, fluoroquinolone, gut microbiota, immune checkpoint inhibitor, immunotherapy, non-small-cell lung cancer

1 | WHAT IS KNOWN AND OBJECTIVES

Immune checkpoint inhibitors (ICIs) target the programmed cell death protein-1 (PD-1)/programmed death-ligand-1 (PD-L1) axis and the cytotoxic lymphocytes antigen proteins (CTLA-4) pathway, and then reactivate the host anti-tumour immune function with the consequent destruction of the tumour. The developments of ICIs have dramatically altered the therapeutic landscape of cancer treatment and have become an attractive treatment strategy in non-small cell lung cancer (NSCLC). These drugs mobilize the immune system to not only target the tumour cells but also to cause a long-term memory T-cell response that is likely to decrease the risk of residual or recurrent disease.[1] Compared with traditional cytotoxic drugs, ICIs are especially appealing due to potential long-term durable responses and lower toxicity.[2]

Despite recent progress, there is still a significant proportion of patients who do not show long-term response.[1] Many investigations have conducted further evaluation on tumours and the host factors that impact on the responses to ICI.[3] Gut microbiota is increasingly considered an important factor associated with both tumour development and the anticancer effect of ICIs. Human gut metagenomic analysis has revealed that responder patients to ICIs therapy had significantly higher microbial diversity and abundance compared with non-responders.[4] Furthermore, a preclinical study found the anti-tumour effects of PD-1 blockade was improved when germ-free or antibiotic-treated mice received a faecal microbiota transplantation (FMT) from responders to ICIs.[5] Enrichment of specific species, including *Ruminococcus* spp., *Alistipes shahii*, *Akkermansia muciniphila*, *Faecalibacterium prausnitzii* and *Bifidobacterium* spp., is associated with being beneficial to immunotherapy.[6–8]

Antibiotics are potentially life-saving medicines, but they can induce rapid, profound and long-lasting collateral damage to the gut microbiota. A number of recent studies have found that antibiotic use is associated with poorer clinical outcomes with ICIs. However, the effect of specific classes of antibiotics on immunotherapy has been seldom evaluated. Fluoroquinolones are broad-spectrum antibiotics widely used for treating a variety of infections. These drugs inhibit bacterial nucleic acid synthesis through the disruption of the enzymes topoisomerase IV and DNA gyrase, to cause bacterial death. In addition to antimicrobial activity, fluoroquinolone also mediates some unique immunomodulatory activities.[9] The present study is a retrospective analysis of the influence of antibiotic use on the clinical outcomes of NSCLC patients treated with ICIs, and we also studied the comparative effects of fluoroquinolones vs. other broad-spectrum antibiotics.

2 | MATERIALS AND METHODS

2.1 | Data source

The data for the retrospective cohort study were from the Chang Gung Research Database (CGRD), which includes the electronic medical records of the Chang Gung Memorial Hospital system; the system is currently the largest medical care system in Taiwan, comprising three medical centres (Taipei, Linkou and Kaohsiung branch), two regional hospitals (Keelung and Chiayi branch) and three district hospitals (Taoyuan, Fengshan and Yunlin branch). Unlike administrative data, the CGRD contains demographics, inpatient and outpatient data, diagnostic codes, details of prescriptions, and reports of microbiological, image and functional examinations. The structures of CGRD have been described and the accuracy and validity of the diagnostic codes in CGRD are well established.[10]

2.2 | Patients

We enrolled the NSCLC patients who were treated with either CTLA-4 inhibitor (ipilimumab), PD-1 inhibitors (nivolumab or pembrolizumab) or PD-L1 inhibitor (atezolizumab or durvalumab) between 1 January, 2016, and 31 March, 2019. Patients who died within four weeks of antibiotic administration were excluded, as they either had a poor performance status or did not recover from a severe infection.[11] Overall survival (OS) was defined as the time from the ICIs initiation to death from any cause. Clinicopathologic characteristics, including age, gender, histology, Eastern Cooperative Oncology Group (ECOG) performance status, smoking status and PD-L1 expression, were collected, if available. The specific class, indication, dose, route of administration and duration of antibiotic treatment 30 days before ICIs treatment were also collected, if available. All patients were followed until death or data lock (31 December, 2019). This study was conducted with the approval of the Institutional Review Board at Chang Gung Medical Foundation (approval serial number: 20180539B0).

2.3 | Statistical analysis

The patients' baseline characteristics were presented as mean ± standard deviation for continuous variables, and frequency and percentage for categorical variables. Student t test was used to compare continuous variables, and chi-squared and Fishers' exact tests were used to compare categorical variables. Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank test. The Cox proportional hazard model was used for univariate and multivariate analyses to calculate the hazard ratio (HR), with 95% confidence interval (CI). The variables with p-values <0.1 identified in univariate analysis were selected for multivariate analyses. A two-sided p-value of ≤0.05 was considered statistically significant. Statistical analyses were conducted using SPSS statistical software (version 25.0; IBM Corporation, Armonk, NY, USA).

3 | RESULTS

We identified 340 patients with NSCLC who started treatment with ICIs between 1 January, 2016 and 31 March, 2019. ICIs monotherapy

was the most common treatment regime ($n = 328$, 96%). ICIs combination therapy ($n = 12$, 4%) consisted mostly of nivolumab with ipilimumab. Amongst this cohort, 128 (38%) patients received systemic antibiotics 30 days prior to ICIs initial and 212 (62%) patients did not. Indications for the use of antibiotics were identified as respiratory tract infection ($n = 46$), empiric therapy for fever ($n = 31$), surgical prophylaxis ($n = 14$), cellulitis ($n = 4$), skin and soft tissue infection ($n = 5$), port-A infection ($n = 4$), sepsis ($n = 2$), cholecystitis ($n = 2$), urinary tract infections ($n = 2$) and other unknown conditions ($n = 18$).

Demographic and clinical characteristics of the patients are shown in Table 1. There was no statistical difference between the two groups in terms of gender, histology, smoking status, line of therapy, ICIs regiment and ECOG performance status. However, antibiotic-treated patients were significantly younger ($p = 0.029$) and with higher PD-L1 expression ($p < 0.001$).

We analysed the effects of antibiotics on the OS of this cohort. Patients who had received antibiotics exhibited a shorter OS compared with those who had no prior antibiotic treatment (Figure 1). The median OS was only 226 days (95% CI 91–321) for those who received antibiotics, but 455 days (95% CI 295–614) for those who did not receive antibiotics ($p = 0.003$, by log-rank test). Univariate and multivariate analyses found that antibiotic use was the only significant factor in determining the OS with ICIs (HR 2.9; 95% CI, 1.1–8.1; $p = 0.003$); age and PD-L1 expression levels were not.

A wide range of systemic antibiotics was used by these 128 patients. Fluoroquinolone (39%), penicillin ± β-lactamase inhibitor (38%), first and secondary generation cephalosporin (33%), third and fourth generation cephalosporin (30%), carbapenem (7%) and macrolide (5%) were the most frequently administered antibiotics. Sixty-four (50%) patients used a single antibiotic and 64 (50%) patients combined more than two antibiotics. Most patients received at least one broad-spectrum antibiotic, and only one patient used narrow-spectrum antibiotics (oxacillin at first and shifted to dicloxacillin later) for cellulitis. The definition of broad-spectrum antibiotics is those that act against Gram-positive and Gram-negative ± anaerobic bacteria, while narrow-spectrum antibiotics only act against Gram-positive bacteria.[12]

To further evaluate the effect of fluoroquinolone with other broad-spectrum antibiotics, we divided the 127 patients who had received broad-spectrum antibiotics into those who used fluoroquinolone or not. The patients in this study who received fluoroquinolone included: levofloxacin ($n = 30$), moxifloxacin ($n = 16$), ciprofloxacin ($n = 4$) and gemifloxacin ($n = 1$), with forty-nine patients (39%) in the fluoroquinolone group and 79 patients (61%) in the control group.

The demographic and clinical characteristics of the patients are shown in Table 2. There was no statistical difference between the two groups in terms of age, gender, ECOG performance status, smoking status, line of therapy, ICIs regiment and PD-L1 expression. However, the fluoroquinolone group were squamous cell carcinoma predominant and less concurrent with first and secondary generation cephalosporin and penicillin ± β-lactamase inhibitor.

We observed patients who had received fluoroquinolone exhibited a shorter OS (Figure 2). The median OS was only 121 days (95% CI 80–162) for patients who had received fluoroquinolone, but 370 days (95% CI 110–630) for those who received other broad-spectrum antibiotics ($p = 0.045$, by log-rank test). Univariate and multivariate analyses found that fluoroquinolone was the independent risk factor associated with shorter overall survival amongst patients who received broad-spectrum antibiotics 30 days prior to ICI therapy. (HR 1.582; 95% CI 1.007–2.841; $p = 0.047$); first and second-generation cephalosporin and histology were not.

TABLE 1 Baseline characteristics of all patients

Characteristic	No antibiotics ($n = 212$)	Antibiotics ($n = 128$)	p value
Age, years			
Median ± SD	63 ± 12	60 ± 12	
<65	124 (59)	90 (70)	0.029
≥65	88 (41)	38 (30)	
Gender			
Female	73 (34)	49 (38)	0.474
Male	139 (66)	79 (62)	
Histology			
Non-squamous	164 (77)	106 (83)	0.228
Squamous	48 (23)	22 (17)	
Smoking status			
Current	48 (23)	22 (17)	0.117
Former	53 (25)	22 (17)	
Never	109 (51)	82 (64)	
Unknown	2 (1)	2 (2)	
Line of therapy			
First or second line	149 (70)	87 (68)	0.654
Third line or later	63 (30)	41 (32)	
ICI regiment			
PD-(L)1 mab	205 (97)	123 (96)	0.495
PD-(L)1 mab+CTLA-4 mab	7 (3)	5 (4)	
PD-L1 expression			
<1%	49 (23)	16 (13)	0.001
1%–49%	47 (22)	34 (27)	
≥50%	51 (24)	53 (41)	
Unknown	65 (31)	25 (20)	
ECOG performance status			
0	25 (12)	14 (11)	0.262
1	136 (64)	82 (64)	
2	19 (9)	19 (15)	
Unknown	32 (15)	13 (10)	

Abbreviations: CTLA-4, cytotoxic lymphocytes antigen proteins; ECOG performance status, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitors; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand-1; SD, standard deviation.

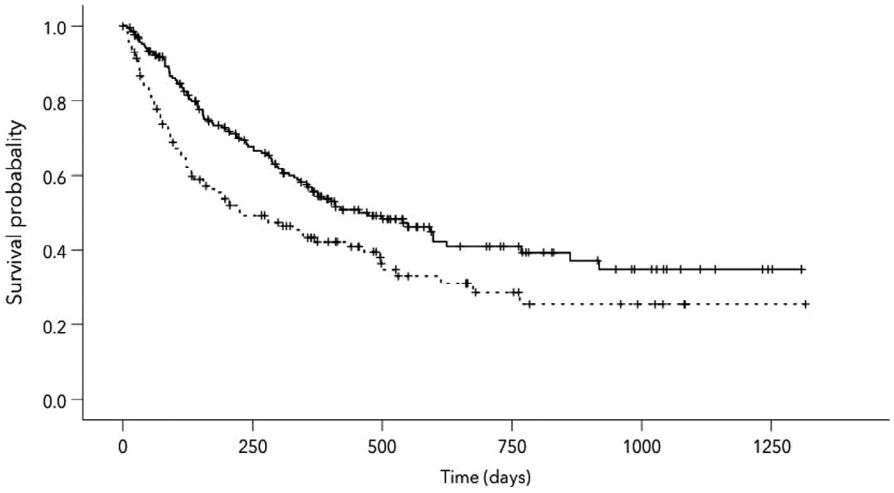

FIGURE 1 Overall survival (OS) in patients who had received antibiotics (dotted line) 30 days prior ICIs therapy compared to those who had not (solid line). Patients who had received antibiotics exhibited shorter OS ($p = 0.003$)

4 | DISCUSSION

In the present study, patients who received antibiotics prior to ICIs therapy were significantly associated with a poorer OS. Our results support previous results showing an apparent detrimental effect of the administration of antibiotics on the outcomes of ICIs therapy. Routy et al first observed that antibiotic use before or during PD-1/PD-L1 mabs therapy was associated with significantly shorter progression-free survival (PFS) and OS in 249 patients with NSCLC, renal cell carcinoma (RCC) and urothelial cancer.[5] In their retrospective study, patients received β-lactam ± inhibitors, fluoroquinolones or macrolides before or during f PD-1/PD-L1 mAb therapy.[5] Derosa et al subsequently expanded their study to a cohort study including 360 patients with NSCLC or RCC. Patients treated with β-lactam ± inhibitors, fluoroquinolones or sulphonamide 30 or 60 days before ICI therapy were associated with shorter PFS and OS. Moreover, the impact of antibiotic use 60 days before ICI therapy was not as potent as 30 days.[13]

By contrast, there were also studies that reported negative findings, where antibiotic use did not influence the clinical outcome of ICI therapy. Kaderbhai et al reported that antibiotic use (3 months before or during nivolumab treatment) had no significant impact on the response rate or PFS on 74 NSCLS patients.[14] Hakozaki et al found antibiotic use within 30 days of nivolumab therapy were associated with a trend towards the negative influence of survival, but it was not indicated as statistically significant.[15] However, the exposure time of antibiotics varied considerably across these studies. Some studies assessed antibiotic exposure during any duration of ICIs therapy, while some assessed with narrow definitions such as 30 days before ICIs therapy.[16] Pinato et al conducted an observational study that included 196 patients with NSCLC, melanoma and other cancers who received ICIs therapy and investigators stratified the patients by the exposure time to antibiotics. Patients receiving antibiotics 30 days before immunotherapy were associated with a poorer treatment response and worse OS compared to patients who received antibiotics during immunotherapy.[17] Antibiotics exposure can impair the homeostasis of gut microbiota, resulting in decreased microbial diversity and abundance. These data suggest that antibiotics could disturb gut microbiota and impair the effectiveness of ICIs with the cytotoxic T-cell response against cancer; the most critical time of these effects seems to be 30 days prior to starting ICI.

In addition to exposure time, antimicrobial spectrum, route, dose, duration, pharmacokinetics and pharmacodynamics properties of antibiotics can all affect the intestinal microbiota.[18] Mielgo-Rubio et al reported that advanced NSCLC patients who had received intravenous antibiotics had shorter OS and PFS compared with those who received oral antibiotics.[19] Tinsley et al found that patients with NSCLC, melanoma and RCC who received multiple courses and prolonged use of antibiotics had shorter OS and PFS.[20] Ahmed et al found patients with advanced cancer who received broad-spectrum antibiotics were associated with poorer response rate and shorter PFS than those who received narrow-spectrum antibiotics, despite the small number of cases.[12] In our study, we observed patients who had received fluoroquinolone were associated with shorter OS compared to those who received other broad-spectrum antibiotics. To the best of our knowledge, the present study is the first to evaluate the impact of a specific class of broad-spectrum antibiotics on the effectiveness of ICI.

Fluoroquinolones play an important role in modulating the gut microbiota, with the degree of alteration differing according to the category of fluoroquinolones used. Ciprofloxacin showed a decreased abundance of *Faecalibacterium*, *Ruminococcus* and *Alistipes* but an increased abundance of *Bacteroides*,[21–23] while Moxifloxacin decreased the abundance of *Faecalibacterium* and *Bacteroides*.[24] Levofloxacin decreased the number of Gram-positive anaerobes, including *Bifidobacteria*.[25]

Routy et al found that NSCLC patients experienced longer PFS enrichment of *Akkermansia muciniphila*, *Ruminococcus*, *Alistipes* and Bifidobacteria at diagnosis.[5] To date, *Ruminococcus*, *Alistipes* and Bifidobacteria had been observed to enhance anti-tumour immunity and facilitate anti-PD-1 efficacy, and *Faecalibacterium* had been observed to increase anti-tumour immunity and facilitate anti-CTLA4 efficacy.[4,5,7,26,27] Moreover, fluoroquinolones have been demonstrated to exert immunomodulatory activities by decreasing interleukin-1 (IL-1), the tumour necrosis factor (TNF)-α production and the release of interleukin-2 (IL-2). These effects involve inhibition of phosphodiesterase and transcription factors, such

TABLE 2 Baseline characteristics of patients who received broad-spectrum antibiotics

	No fluoroquinolone ($n = 78$)	Fluoroquinolone ($n = 49$)	p value
Age, years			
Median ± SD	61 ± 11	58 ± 14	
<65	57 (73)	33 (67)	0.489
≥65	21 (27)	16 (33)	
Gender			
Female	30 (39)	19 (39)	0.972
Male	48 (62)	30 (61)	
ECOG performance status			
0	10 (13)	4 (9)	0.442
1	48 (62)	33 (67)	
2	10 (13)	9 (19)	
Unknown	10 (13)	3 (6)	
Histology			
Non-squamous	68 (87)	37 (76)	0.091
Squamous	10 (13)	12 (24)	
Smoking status			
Current	15 (18)	7 (14)	0.579
Former	13 (17)	8 (16)	
Never	48 (62)	34 (69)	
Unknown	2 (3)	0 (0)	
Line of therapy			
First or second line	55 (71)	32 (65)	0.539
Third line or later	23 (29)	17 (35)	
ICI regiment			
PD-(L)1 mab	74 (95)	48 (98)	0.384
PD-(L)1 mab+CTLA-4 mab	4 (5)	1 (2)	
PD-L1 expression			
<1%	7 (9)	9 (18)	0.161
1%–49%	22 (28)	12 (25)	
≥50%	37 (47)	16 (32)	
Unknown	12 (15)	12 (25)	
Broad-spectrum antibiotic			
Carbapenem	6 (8)	3 (6)	1.000
1st/2nd Cephalosporin	35 (45)	7 (14)	<0.001
3rd/4th Cephalosporin	22 (28)	16 (32)	0.594
Glycopeptide	7 (9)	5 (10)	1.000
Macrolide	2 (3)	4 (8)	0.204
Penicillin ± β-lactamase inhibitor	34 (44)	14 (29)	0.089

Abbreviations: CTLA-4, cytotoxic lymphocytes antigen proteins; ECOG performance status, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitors; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand-1; SD, standard deviation.

as activator protein-1, nuclear factor of activated T cells, nuclear factor-IL-6 (NF-IL6) and nuclear factor-κB (NF-κB).[9] Therefore, we consider any impact of the specific microbes and cytokine after fluoroquinolone use could affect the anti-tumour activity associated with ICIs.

It is important to consider the limitations of this study. As discussed previously, antibiotic-treated patients were younger and with higher PD-L1 expression. Risk factor analysis also showed that these two factors were not significant factors in determining OS. However, age was an important prognostic factor for survival in

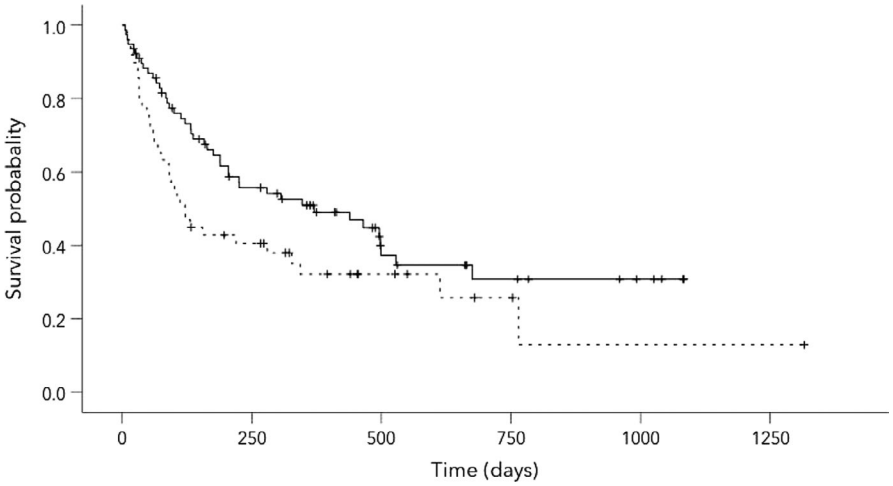

FIGURE 2 Overall survival in patients who received fluoroquinolone (dotted line) 30 days prior ICIs therapy compared to those who received other broad-spectrum antibiotics (solid line). Patients who had received fluoroquinolone exhibited a shorter OS ($p = 0.045$)

NSCLC, thus, caution is needed in interpreting our results. Second, this study included a retrospective review of medical records, so unavoidable bias, confounding, missing data and generalization cautiously would be anticipated. Concomitant drugs were entirely based on those listed in the patient´s electronic prescription system and may not represent an accurate list of what the patient was currently taking, or of whether he was taking the medication as prescribed; however, a 100% medication adherence is assumed in this study. Third is the lack of correlative analyses to confirm gut microbiota alterations after antibiotics use and the effect on ICIs treatment outcomes. Finally, the small sample size may have contributed to this observation, thus further investigation with a larger sample size is required to confirm these conclusions.

5 | WHAT IS NEW AND CONCLUSIONS

Our study demonstrated that antibiotics use, especially fluoroquinolone, prior to ICI therapy, was significantly associated with a poorer OS.

However, antibiotics should not be withheld when there is a clear need for them despite the possibility of interfering with the microbiome, which may in turn adversely affect the ICI's effectiveness. Healthcare professionals' prescribing antibiotics should carefully weigh the pros and cons in patients who are scheduled to receive ICIs treatment. However, they should consider avoiding the use of fluoroquinolones antibiotics.

ORCID

Po-Hsien Lu https://orcid.org/0000-0002-1108-3724

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