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Oncological outcomes of addition of anti-PD1/PD-L1 to chemotherapy in the therapy of patients with advanced gastric or gastro-oesophageal junction cancer

A meta-analysis

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Abstract

Background: Patients with advanced gastric or gastro-oesophageal junction cancer (GC/GEJC) that fail to respond to prior chemotherapy have poor clinical prognosis. Lately, many trials have paid much attention on the oncological outcomes of immune checkpoint inhibitors (ICI). A new therapy based on programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors has recognized as promising prospects for advanced GC/GEJC. We assessed efficacy and safety of PD-L1 antibody versus chemotherapy alone in previously treated non-small cell lung cancer.

Methods: Computerized literature search was done on the published trials in: Pubmed, Embase, Cochrane library updated on June 2019. Randomized controlled trials were selected investigating chemotherapy plus PD-1/PD-L1 versus chemotherapy alone.

Results: Three randomized controlled trails were included. The pooled analysis of overall survival (OS) was longer with anti-PD1/PD-L1 than with chemotherapy alone in the OS (OR = 0.66, 95%CI = 0.47–0.92, $P = .02$) and sub-group OS of GEJC (OR = 0.73, 95%CI = 0.58–0.93, $P = .01$). Whereas, there is no significant difference in progression-free survival (OR = 0.93, 95%CI = 0.62–1.39, $P = .72$). The pooling adverse events (AE) data did not achieve advantage in the PD-1/PD-L1 targeted agents (OR = 0.53, 95%CI = 0.13–2.10, $P = .36$), the same as the treatment-related AE of grade 3 to 5 (OR = 0.53, 95%CI = 0.16–1.74, $P = .30$).

Conclusions: Treatment of patients with advanced GC/GEJC with PD-1/PD-L1 targeted did result in an improvement in some but not all survival endpoints. Moreover, it had a comparable toxicity profile as compared with chemotherapy alone. More well designed studies are needed to develop a database of all anti-PD1/PD-L1 sub-groups and their individual impact on the differing anti-PD1/PD-L1 treatments.

Abbreviations: EBV+ = Epstein-Barr virus-positive, GC/GEJC = gastric or gastro-oesophageal junction cancer, ICI = immune checkpoint inhibitors, MSI-H = high microsatellite instability, PD-1 = programmed death 1, PD-L1 = programmed death ligand 1.

Keywords: advanced GC/GEJC, meta-analysis, PD-1, PD-L1

Editor: Surinder Kumar.

ZZ and YG contributed equally to this paper.

The authors have no funding and conflicts of interest to disclose.

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

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How to cite this article: Zheng Z, Guo Y, Zou CP. Oncological outcomes of addition of anti-PD1/PD-L1 to chemotherapy in the therapy of patients with advanced gastric or gastro-oesophageal junction cancer: a meta-analysis. Medicine 2020;99:7(e18332).

Received: 19 July 2019 / Received in final form: 20 October 2019 / Accepted: 11 November 2019

http://dx.doi.org/10.1097/MD.0000000000018332

1. Introduction

Gastric/gastro-oesophageal junction cancer (GC/GEJC) is known to be the fifth leading cause of cancer-related death globally.[1] The chemotherapy with a platinum and fluoro-pyrimidine is emerged as the standard regimen for these patients. However, initial chemotherapy is frequently unsuccessful, most GC/GEJC cases develop disease relapse and a tendency to systemic metastasis, necessitating secondary treatment.[2–4] For patients with advanced or metastatic GC/GEJC, therapy options include docetaxel, paclitaxel, or irinotecan mono-therapy,[5,6] trastuzumab for patients with HER-2 positive disease and the anti-vascular endothelial growth factor receptor 2 antibody ramucirumab as either monotherapy or in combination with paclitaxel.[7,8]

Although chemotherapy regimens for these patients have recently developed, the prognosis of advanced GC/GEJC is still disappointing. Lately, immune checkpoint inhibitors (ICI) have been recommended as therapies for GC/GEJC cancer because these cancers have the high mutational burden and over-expression of immune checkpoint proteins, and programmed death-ligand 1 (PD-L1) pathway is a promising therapeutic option in treatment of patients with advanced GC/GEJC.[9–11]

The programmed death 1 (PD-1) receptor is an immune-checkpoint protein expressed on tumor cells and tumor-infiltrating immune cells that down-regulate T-cell activation and evade immune response against tumor cells.[12] Many studies have demonstrated the effect of anti-PD1/PD-L1 for advanced GC/GEJC on oncological outcomes, while the significance has been controversial. Some studies have found that not all but some patients were able to achieve survival benefit, while other reports have shown the effect on survival of anti-PD1/PD-L1 for advanced gastric or gastro-oesophageal junction cancer is doubtful.[13] It is, thus, a key controversy whether or not an anti-PD1/PD-L1 have oncological outcomes benefits for advanced GC/GEJC.

The purpose of this study is to analyze the significance of anti-PD1/PD-L1 for advanced GC/GEJC.

2. Materials and methods

2.1. Ethics statement

As the present meta-analysis was performed based on previously published studies, no ethical approval and patient consent are required.

2.2. Search strategy

Two investigators conducted a systematic search of the Pubmed, Embase, Cochrane library up to June 2019 independently, using the MeSH terms and free key words "Anti PD-1" OR "Anti PD-L1"AND "gastric cancer", AND "gastro-oesophageal junction cancer". We also identified the reference materials for further evaluation.

2.3. Inclusion criteria

Studies were included in the meta-analysis relating to: (1) the studies are designed as random control trials (RCTs); (2) patients were underwent using chemotherapy plus PD-1/PD-L1 versus chemotherapy alone; (3) patients were clinical diagnosis of advanced G/GEJ progresses on chemotherapy after failure of prior therapy; (4) the interested outcomes were efficacy and toxicity; (5) the full-text papers were only included.

2.4. Risk-of-bias assessments

The risk of bias was evaluated by two investigators, separately. Study quality was justified using the Cochrane Collaboration's "Risk of bias" tool.

2.5. Data selection

Two researchers independently extracted the extract contents from each trial. In case of disagreement, a third investigator helps resolve the disagreement or through discussion. We extracted the main categories based on the following: lead author, publication year, treatment regimen, patient number, age, sex number, and outcome measures.

2.6. Statistical analysis

The Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom) used for statistical analysis. The chi-square was used to assess the significance of heterogeneity, and the degree of heterogeneity across studies was then examined using the I^2 statistic.[14] I^2 value larger than 50% suggested heterogeneity was significant, and the random-effects model was used. Otherwise, the fixed-effect model was used.[15] A P-value $<.05$ was identified as statistically significant difference.

3. Results

3.1. Overview of literature search and study characteristics

A total of 212 studies were retrieved. Eight irrelevant citations were evaluated based on the review of titles and abstracts, but some did not provide enough detail of results of two approaches. Therefore, a final total of three RCTs[16–18] were further eliminated. The search process is described in Fig. 1. Table 1 presents a brief description of these eligible studies.

3.2. Outcomes and synthesis of results

1. Pooled analysis of overall survival (OS) comparing chemotherapy plus PD-1/PD-L1 with chemotherapy alone
   Pooling the OS demonstrated that PD-1/PD-L1 targeted agents did lead to an OS advantage (OR = 0.66, 95%CI = 0.47–0.92, $P = .02$). Also, subgroup analysis revealed GEJC (OR = 0.73, 95%CI = 0.58–0.93, $P = .01$) was associated with better OS, but the GC group (OR = 0.88, 95%CI = 0.64–1.20, $P = .41$). Results were shown in Fig. 2.
2. Pooled analysis of progression-free survival (PFS) comparing chemotherapy plus PD-1/PD-L1 with chemotherapy alone
   Pooled estimates of effect sizes showed that the difference of PFS between two groups was no statistically significant (OR = 0.93, 95%CI = 0.62–1.39, $P = .72$). Results were shown in Fig. 3.
3. Pooled analysis of AE comparing chemotherapy plus PD-1/PD-L1 with chemotherapy alone

The pooling AE data did not achieve advantage in the PD-1/PD-L1 targeted agents (OR = 0.53, 95%CI = 0.13–2.10, $P = .36$) (Fig. 4). And results showed that the difference of grade 3 to 5 serious adverse events between two groups was no statistically significant (OR = 0.53, 95%CI = 0.16–1.74, $P = .30$) (Fig. 5).

4. Discussion

Patients diagnosed with advanced GC/GEJC cancer have a poor performance status despite the use of standard treatments, such as chemotherapy and biologic agents. Previous studies are currently focused on evaluating combinations of ICI, standard chemotherapy, and biologic agents as well as novel biomarkers to prolong survival and improve quality of life. While, most chemotherapy therapeutic approaches fail to provide substantial efficacy benefits.[3,4] Our meta-analysis will provide the evidence of anti-PD1/PD-L1 for advanced GC/GEJC cancer treatment in clinical practice.

In case of the efficacy, the Bangs[16] study did not achieve benefit of the OS or PFS, indicated that potentially identified patient subgroups most likely to benefit from checkpoint inhibitors. Kang[18] reported that the survival benefit with nivolumab was independent in pretreated patient population, regardless of primary tumor site, Lauren classification, or PD-L1

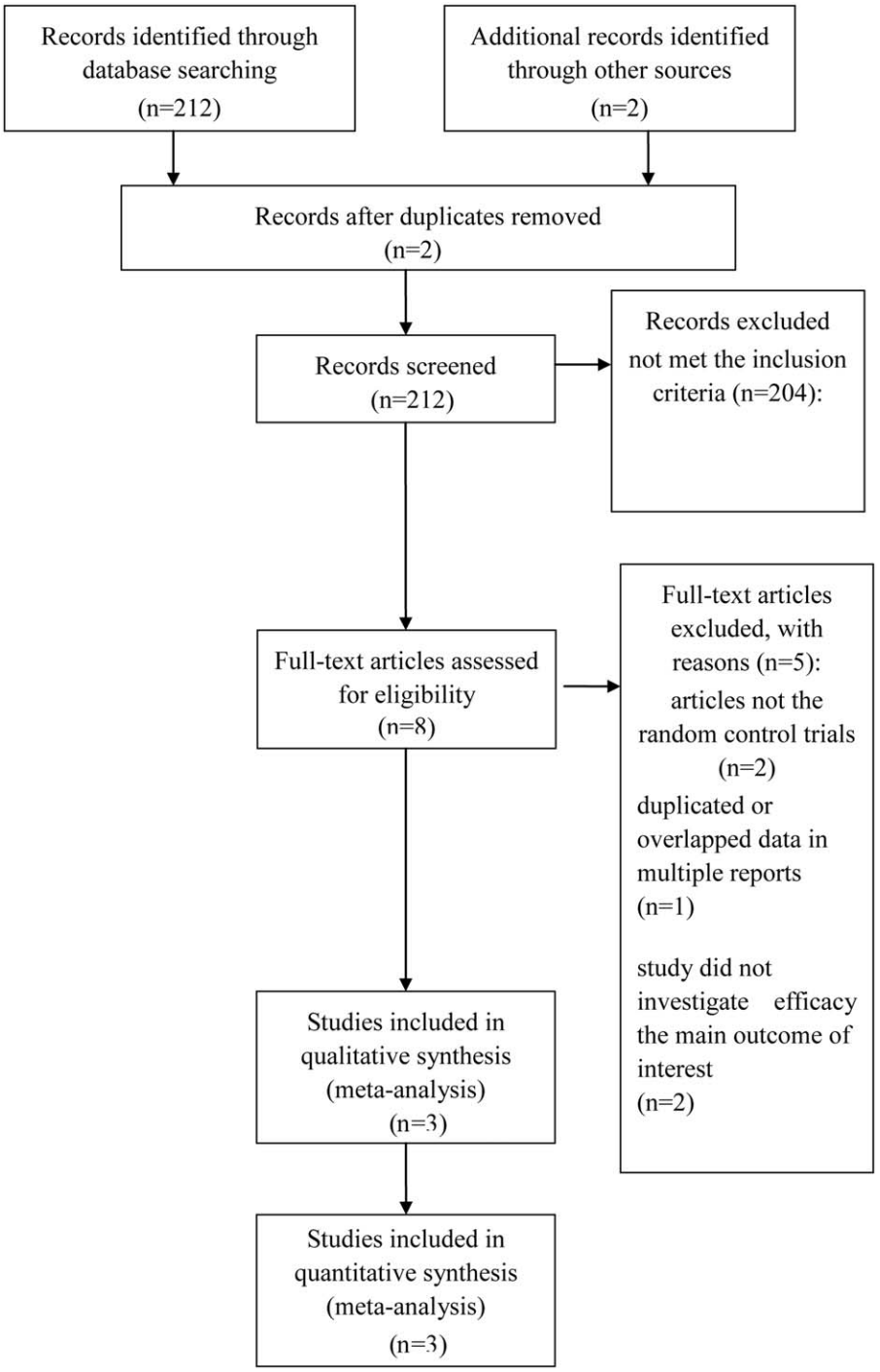

Figure 1. PRISMA flow chart of selection process to identify studies eligible for pooling.

Table 1

Brief description of included eligible studies.

	Treatment regimen		No. of patients		Age (mean)		Sex (male)	
Study year	PD-1/PD-L1	Chemotherapy alone	PD-1/PD-L1	Chemotherapy alone	PD-1/PD-L1	Chemotherapy alone	PD-1/PD-L1	Chemotherapy alone
Kohei Shitara 2018	Pembrolizumab	Paclitaxel	296	296	62.5	60	202	208
Kang 2017	Nivolumab	Placebo	330	163	62	61	229	119
Y.-J. Bang 2018	Avelumab	Irinotecan; paclitaxel; BSC only	185	186	59	61	140	127

BSC = best supportive care, PD-1 = programmed death 1, PD-L1 = programmed death ligand-1.

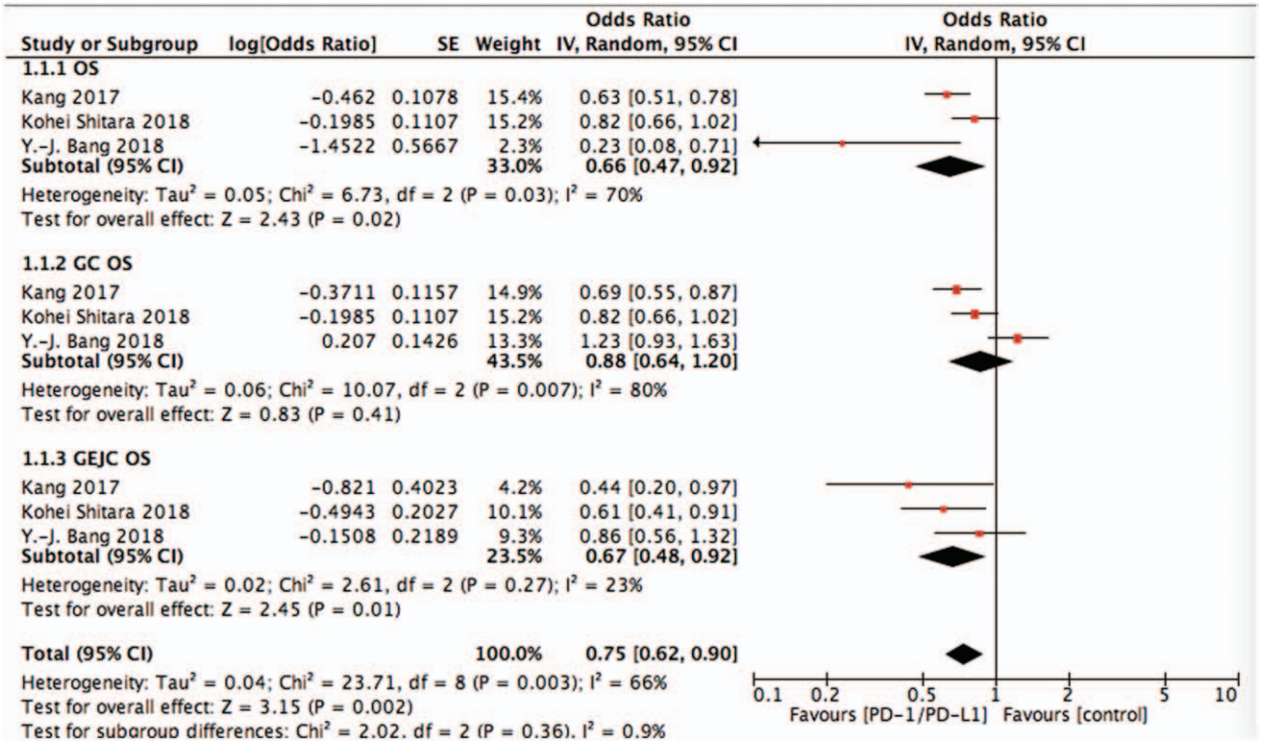

Figure 2. Pooled analysis of OS comparing chemotherapy plus PD-1/PD-L1 with chemotherapy alone. OS = overall survival, PD-1 = programmed death 1, PD-L1 = programmed death ligand 1.

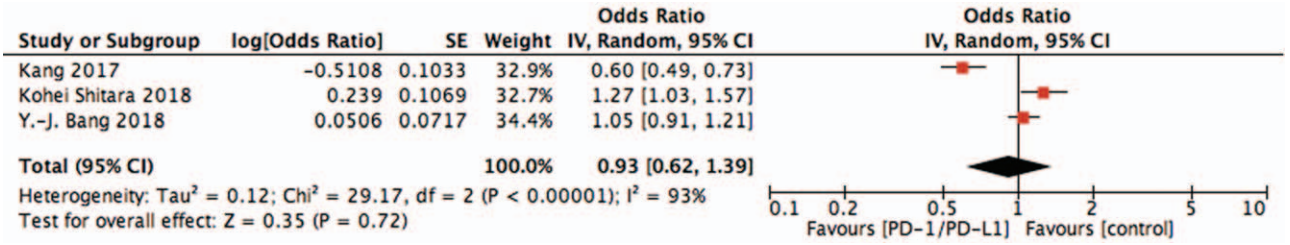

Figure 3. Pooled analysis of PFS comparing chemotherapy plus PD-1/PD-L1 with chemotherapy alone. PD-1 = programmed death 1, PD-L1 = programmed death ligand 1.

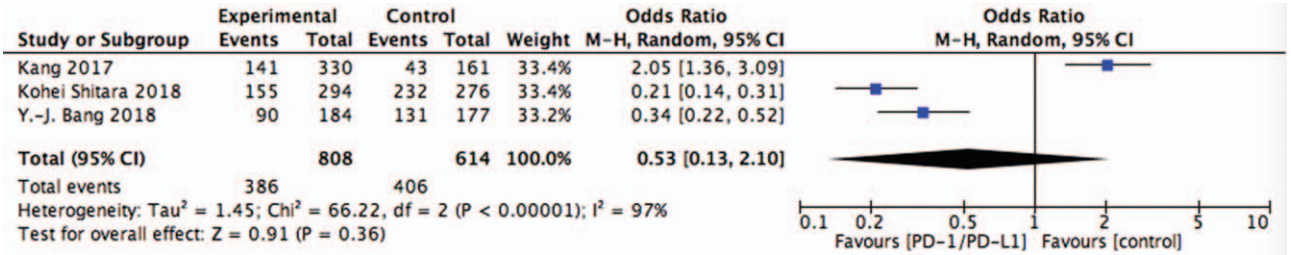

Figure 4. Pooled analysis of AE comparing chemotherapy plus PD-1/PD-L1 with chemotherapy alone. AE = adverse events, PD-1 = programmed death 1, PD-L1 = programmed death ligand 1.

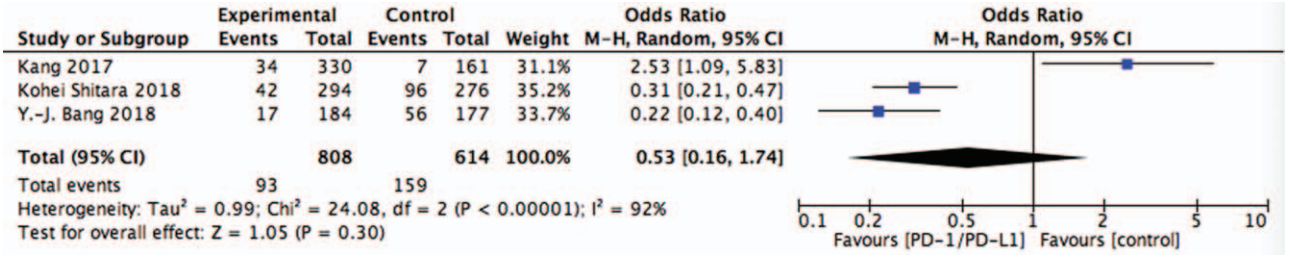

Figure 5. Pooled analysis of SAE comparing chemotherapy plus PD-1/PD-L1 with chemotherapy alone. PD-1 = programmed death 1, PD-L1 = programmed death ligand 1, SAE = serious adverse events.

positivity. While, consistent with findings of KEYNOTE-059[7] and report results for pembrolizumab in other tumor types,[19–21] a relationship between greater PD-L1 expression and a greater treatment effect for pembrolizumab was found in KEYNOTE-061. PD-L1 expression in Kohei Shitara's study[17] was assessed as a better predictor of outcomes for selecting patients for therapy with pembrolizumab mono-therapy. Therefore, the pattern and prognostic implication of PD-1/PD-L1 expression need further investigation.

According to The Cancer Genome Atlas research network, there are four specific molecular subtypes of gastric cancer: Epstein-Barr virus-positive (EBV+), high microsatellite instability (MSI-H), genomically stable and chromosomally instable.[22] MSI-H is associated with high PD-L1 tumor expression and induces innate anti-tumor immune responses and make tumors more sensitive to immunotherapy.[23,24]EBV+ types are associated with high-response rates to immunotherapies in other solid tumors.[22,25] Tumor mutation burden has also been recognized as a predictor of response to PD-1 blockade, with patients with higher mutational loads had better effect of response.[26]

Furthermore, GC/GEJC is biologically heterogeneous, which increases the difficulty of treatment. Our study indicated that GEJC was better associated with OS, than the GC group. Potential differences in patient cohorts, immunohistochemistry methods, and end points may account for these results. The biologic characteristics of molecular subtypes of advanced GC/GEJC make these subtypes excellent candidates for anti-PD-1-directed ICI treatment.[27]

Moreover, regarding the safety profile, we concluded that the safety profile of anti-PD1/PD-L1 in patients with advanced GC/GEJC was manageable. Therefore, it can be considered that anti-PD1/PD-L1 treatment was safe. In addition, we found that the adverse effect like hypothyroidism, hyperthyroidism, pneumonitis, colitis, hepatitis, hypopituitarism, which were more likely to appear grade ≥3 TRAEs, although the incidences were not high. The occurrence of these TRAEs was associated with ICI immunotherapy. They were called "TRAEs of special interest" or "immune-mediated adverse events". Thus, particular attention should be given to these adverse reactions.

Moderate evidence has been gathered in our study, but there is still limitation in our study. Considering the lack of patient-level data, clinical heterogeneity among studies, the optimal option for incorporating checkpoint inhibitors into the continuum of care for patients with advanced GC/GEJC is still under debate. More high-quality researches with further data on the different subtypes and larger RCTs are strongly in-needed to confirm the effectiveness and safety of alternative anti-PD-1/PD-L1 therapy in an effort to treat patients with advanced GC/GEJC.

5. Conclusion

Our study confirms that patients treated with anti-PD-1/PD-L1 therapy had a better superior survival benefit with some but not all survival endpoints, and with a comparable adverse event for advanced GC/GEJC. From an efficacy standpoint, further trials into immune checkpoint therapy that will benefit patients by specific molecular subtype and genomic alterations, which can be instructive in driving therapy decisions, while conferring with manageable safety profile. To further validate this treatment, the effect and safety of PD-1/PD-L1 agents should systematically subgroup analyzed in the near future.

Author contributions

Conceptualization: Chang-Peng Zou.
Data curation: Ying Guo.
Writing – original draft: Zheng Zheng, Chang-Peng Zou.
Writing – review & editing: Zheng Zheng, Chang-Peng Zou.

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