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The role of targeted agents in the treatment of advanced gastric cancer: a meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: To assess the efficacy of targeted agents (TAs) in the treatment of elderly patients with advanced gastric cancer (AGC).

MATERIALS AND METHODS: Databases from PubMed, Web of Science and abstracts presented at ASCO meeting up to December 31, 2015 were searched to identify relevant studies. Eligible studies included prospective randomized controlled trials (RCTs) evaluating therapies with or without TAs in elderly patients with AGC. The endpoints were overall survival (OS) and progression-free survival (PFS). Statistical analyses were conducted by using Comprehensive Meta Analysis software (Version 2.0).

RESULTS: A total of 1,759 elderly patients with AGC from ten RCTs were included for analysis. The pooled results demonstrated that the addition of TAs to therapies in elderly patients significantly improved OS (HR 0.88, 95% CI: 0.79-0.99, p = 0.032), but not for PFS (HR 0.83, 95% CI: 0.66-1.06, p = 0.13) when compared to controls. Subgroup analysis according to targeted agents indicated that survival benefit was observed for anti-HER-2 agents (HR 0.71, 95% CI: 0.55-0.91, p = 0.006) and angiogenesis inhibitors (AIs) (HR 0.78, 95% CI: 0.62-0.99, p = 0.04) in terms of OS. Conversely, no survival benefit was found for anti-EGFR agents in terms of OS (HR 1.12, 95% CI: 0.93-1.36, p = 0.24) and PFS (HR 1.35, 95% CI: 0.88-2.07, p = 0.17). No publication bias was detected by Begg's and Egger's tests for OS.

CONCLUSIONS: The findings of this study suggest that the addition of TAs to therapies in elderly patients with AGC offers an improved OS, which can be ascribed to AIs and ant-HER2 agents. With available evidence, anti-EGFR agents could not be recommended for use in elderly AGC patients.

Key Words:
Gastric cancer, Elderly, Randomized controlled trials, Meta-analysis.

Introduction

Gastric cancer (GC) is one of the most frequent malignant diseases throughout the world accounting for 8% (989,600 million) of the total new cancer cases and 10% (738,000) of the total cancer deaths in 2008[1]. GC is a disease of aging and its incidences gradually with age[2]. Approximately 60% of GC develop over the age of 65 and about one-third of patients are over 75 years. Additionally, demographics that are shifting toward an older population, and it is expected that oncologists will be seeing more elderly patients with GC[3,4]. However, there are many challenges involved in the treatment of an elderly population with advanced gastric cancer (AGC). The majority of these patients has more comorbidities and tend to be less tolerant to toxic medical treatments than their younger counterparts[5,6]. In clinical practice, there is a significant under-representation of elderly patients in most clinical trials on GC, thus, treatment of elderly patients with AGC could not be guided by current evidence from large phase III trials. As a result, the optimal treatment for AGC in elderly patients remains unknown.

In recent decades, the emergence of molecularly targeted agents has provided another strategy for the treatment of elderly patients with AGC[7,8]. In 2010, trastuzumab was the first molecule TAs shown to improve survival in patients with HER2-positive AGC as part of a first-line combination regimen[9]. In 2014, ramucirumab was the second targeted molecule to improve survival rates and was suggested as treatment for patients with AGC who had progressed after first-line platinum plus fluoropyrimidine with or without anthracycline chemotherapy[10]. Although the trials that establish the efficacy of these agents allow the enrollment of patients older than 65 years, the elderly patients

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constitute the minority. Given the stringent enrollment criteria on organ function and performance status, the elderly patients in these clinical trials are not entirely representative of the overall elderly patient population. Therefore, the applicability of these data to the overall patient population deserves critical appraisal in the absence of trials dedicated specifically to the elderly. Thus, we conduct this meta-analysis of all available randomized controlled trials (RCTs) to determine the overall efficacy of TAs in AGC patients aged ≥ 60 years old.

Materials and Methods

Selection of Studies

We searched the Pubmed (data from Jan 2000 to December 2015), Embase (data from Jan 2000 to December 2015) and the Cochrane Library electronic databases. The search criteria included only randomized controlled trials and published in English language, and the key words "targeted agents", "bevacizumab", "avastin", "aflibercept", "VEGFR-TKIs", "sorafenib", "nexavar", "sunitinib", "sutent", "SU1248", "vandetanib", "caprelsa", "ZD6474", "axitinib", "pazopanib", "votrient", "GW786034", "regorafenib", "apatinib", "ramucirumab", "nintedanib", "BIBF1120", "trastuzumab", "lapatinib", "everolimus", "mTOR inhibitors" "angiogenesis inhibitors", "cetuximab", "panitumumab", "erlotinib", "gefitinib", "afatinib", "randomized", "gastric cancer". We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences that took place between Jan 2004 and Jun 2015. Each publication was reviewed and in cases of duplicate publication, only the most complete, recent, and updated report of the clinical trial was included in the meta-analysis. We also performed an up-to-date search for relevant trials in February 2016.

Data Extraction and Clinical End-Point

Data extraction was conducted independently by two investigators according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[11], and any discrepancy between the reviewers was resolved by consensus. For each study, the following information was extracted: first author's name, year of publication, trial phase, number of elderly subjects, treatment arms, age, primary endpoints, and median follow-up. Phase 1 trials and single-group phase 2 trials were omitted from analysis because of lack of controls. Trials that met the following criteria were included: (1) prospective randomized controlled trials comparing therapies with or without TAs; (2) patients were pathologically confirmed of gastric cancer; and (3) the study had sufficient survival data of elderly patients (≥ 60) for extraction. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included. The quality of reports of clinical trials was assessed and calculated using the 5-item Jadad scale including randomization, double-blinding, and withdrawals as previously described[12].

Data Analysis

The analysis was undertaken on an intention-to-treat basis: patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. The outcomes used were (1) OS, defined as the time from random assignment to death from any cause, censoring patients who had not died at the date last known alive; (2) PFS, defined as the time from random assignment to first documented progression.

Statistical analysis of the overall hazard ratio (HR) for OS and PFS was calculated using Version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ, USA). A random-effect model was used to calculate pooled HRs, 95% CIs and *p*-values. A statistical test with a *p*-value less than 0.05 was considered significant. HR > 1 reflects more deaths or progression in TAs-containing regimens group, and vice versa. Between-study heterogeneity was estimated using the χ^2-based Q statistic[13]. The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. To investigate the sources of heterogeneity, we also conducted predefined subgroup analysis according to targeted agents. The presence of publication bias was evaluated by using the Begg and Egger tests[14]. All *p*-values were two-sided. All CIs had a two-sided probability coverage of 95%.

Results

Search Results

A total of 350 potentially relevant studies were retrieved electronically, 433 of which were ex-

cluded for the reasons shown in Figure 1. Ten published RCTs with sub-group analysis assessing the efficacy of TAs in elderly patients were included. The baseline characteristics of each trial were presented in Table I. A total of 1,759 patients were available for the meta-analysis. Four trials were performed in first-line settings[9,15-17], and six in second-line setting[18-23]. According to the inclusion criteria of each trial, patients were required to have an adequate renal, hepatic and hematologic function. The quality of each included study was roughly assessed according to Jadad scale, and four trials had Jadad score of 5, and six trials had Jadad scores of 3.

Overall Survival

All ten trials reported OS data of elderly patients. The pooled results demonstrated that the addition of TAs to therapies significantly improved OS in comparison with controls (HR 0.88, 95% CI: 0.79-0.99, $p = 0.032$, Figure 2) using a fixed-effects model ($I^2 = 44\%$, $p = 0.066$). We then performed sub-group analysis according to specific TAs, and found that trials using anti-HER2 agents (HR 0.71, 95% CI: 0.55-0.91, p=0.006) and angiogenesis inhibitors (AIs) (HR 0.78, 95% CI: 0.62-0.99, $p = 0.004$) significantly improved OS when comparing to controls, while the use of anti-EGFR agents did not improve OS (HR 1.12, 95% CI: 0.95-1.36, $p = 0.244$).

Progression-free Survival

Three trials reported PFS data of elderly patients. The pooled hazard ratio for PFS demonstrated that the addition of TAs to therapies had a tendency to improve PFS giving HR 0.83 (95% CI: 0.66-1.06, $p = 0.13$, Figure 3), compared with controls. There was significant heterogeneity between trials (I^2=80.2%, $p = 0.002$), and the pooled HR for PFS was performed by using a random-effects model. We then did sub-group analysis according to specific TAs and found that

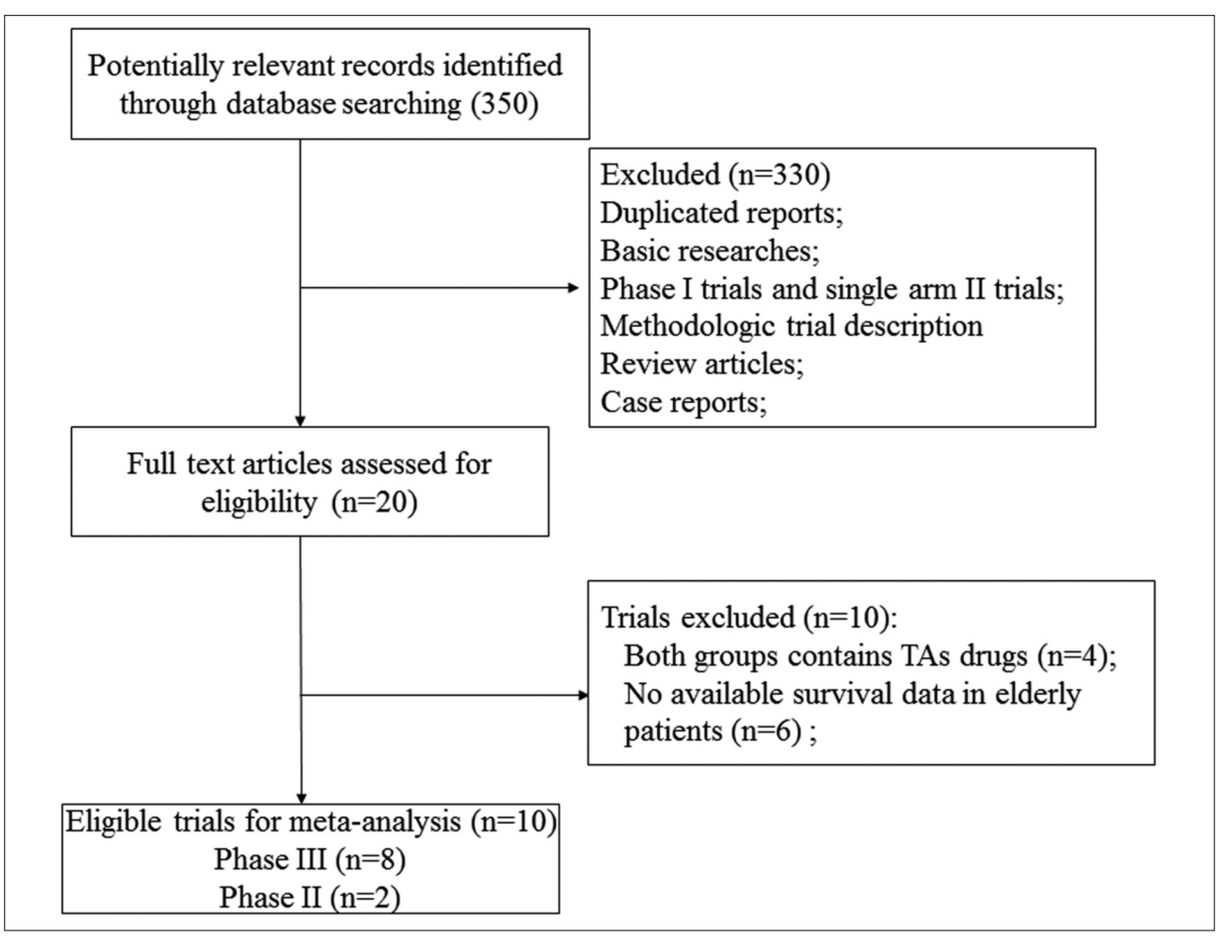

Figure 1. Studies eligible for inclusion in the meta-analysis.

Table I. Baseline characteristic of included 10 trials for analysis.

Author/year	Phase	Line of treatment	No. of elderly patients	Age	Treatment regimens	Jadad Score
Du F. et al/2015	II	First-line	26	60	Nimotuzumab 200 mg/m^2 + chemotherapy chemotherapy	3
Satoch T. et al/2015	II	Second-line	32	65	Nimotuzumab 400 mg q.w. + chemotherapy	3
Fuchs C.S. et al/2014	III	Second-line	128	65	Ramucirumab 8 mg/kg placebo	5
Wilke H. et al/2015	III	Second-line	249	65	Ramucirumab 8 mg/kg + PTX Placebo + PTX	5
Satoch T. et al/2014	III	Second-line	97	65	Lapatinib 1500 mg qd + PTX PTX	3
Waddell T. et al/2013	III	First-line	338	60	Panitumumab 9 mg/kg + EOC EOC	3
Ohtsu A. et al/2013	III	Second-line	267	65	Everolimus 10 mg/d placebo	5
Lordick F. et al/2013	III	First-line	280	65	Cetuximab 250 mg/kg + capecitabine + DDP Capecitabine + DDP	3
Bang Y.J. et al/2010	III	First-line	305	60	Trastuzumab 8 mg/kg + chemotherapy chemotherapy	3
Li J. et al/2016	III	Second-line	37	65	Apatinib 850 mg Placebo	5

Abbreviations: PTX, paclitaxel; DDP, cisplatin; EOC, epirubicin plus oxaliplatin plus capecitabine.

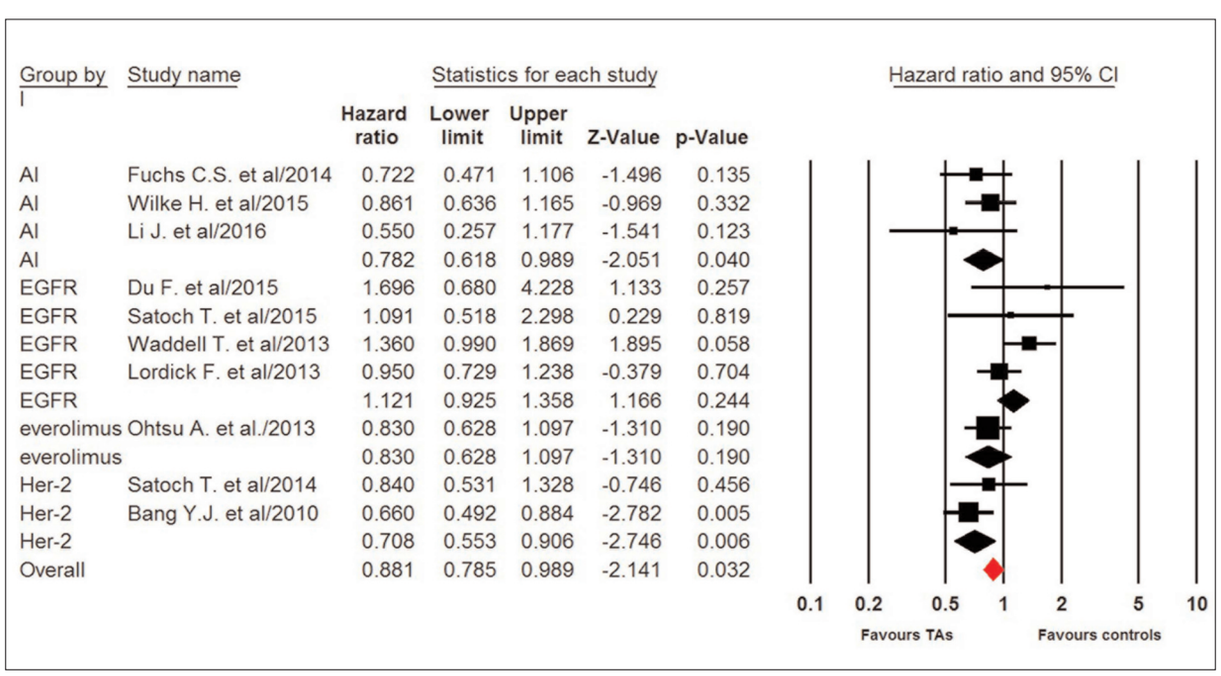

Figure 2. Fixed-effects Model of Hazard Ratio (95% CI) of OS Associated with TAs-containing regimens versus controls.

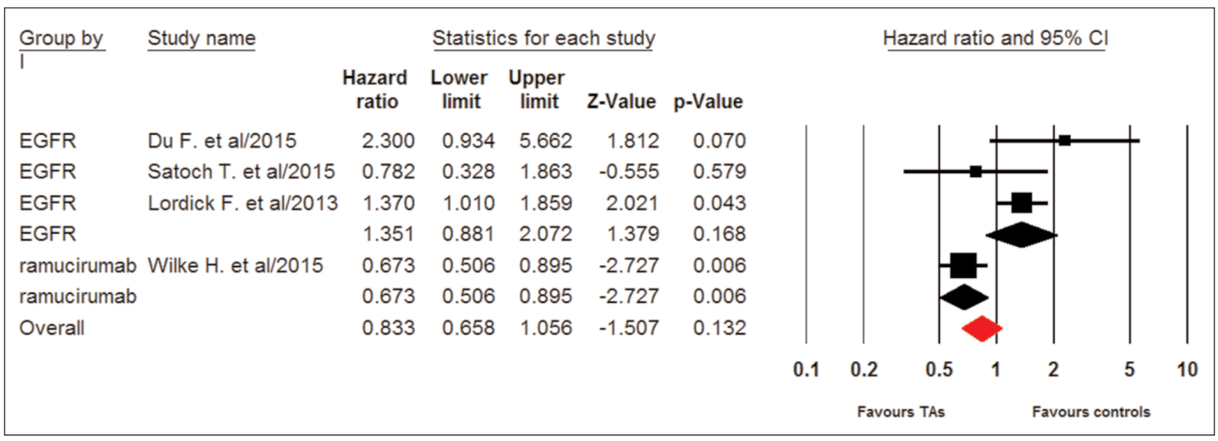

Figure 3. Random-effects Model of Hazard Ratio (95%CI) of PFS Associated with TAs-containing regimens versus controls.

the use of ramucirumab in elderly patients with AGC significantly improved PFS (HR 0.67; 95% CI: 0.51-0.90, p = 0.006), while the addition of anti-EGFR agents to therapies in elderly patients with AGC did not improve PFS when compared to controls (HR 1.35, 95% CI: 0.88-2.07, p = 0.17).

Publication Bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literature. The Begg's funnel plots did not reveal any evidence of obvious asymmetry for OS (p = 0.86). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias for OS (p = 0.83, Figure 4).

Discussion

During the past decades, a better understanding of molecular pathways that involves in cell growth, angiogenesis, and inhibition of apoptosis has led to new ideas for novel targeted therapies. Biological agents targeting HER-2 signal path-

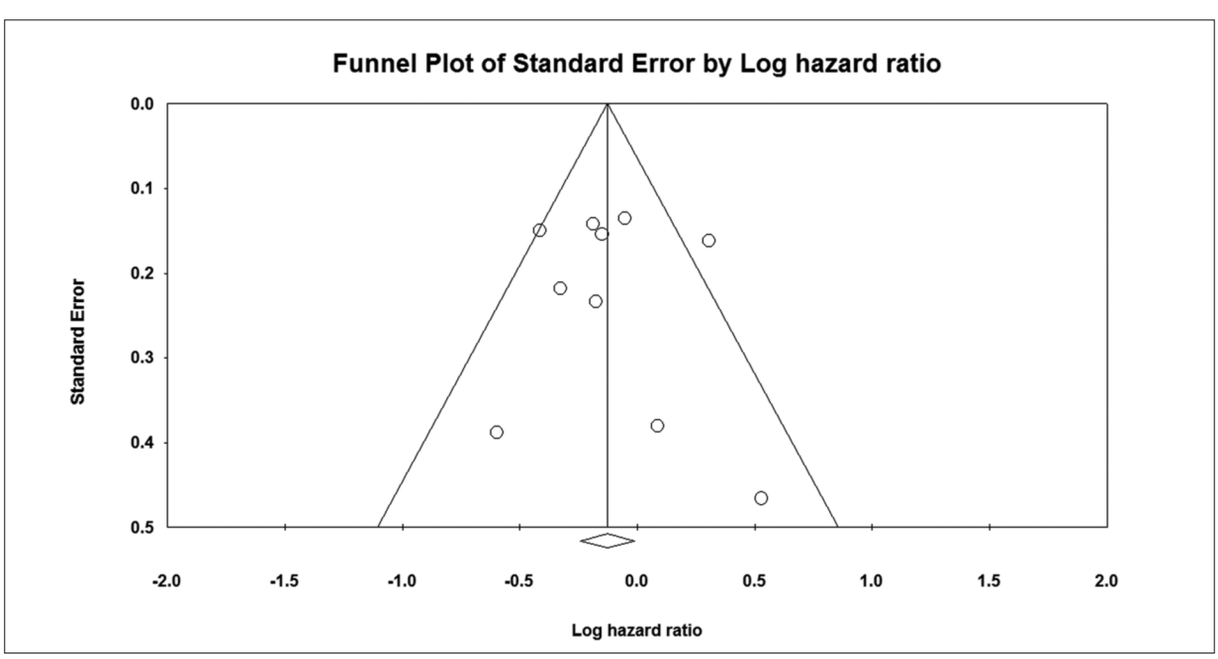

Figure 4. Publication bias for included trials.

ways and angiogenesis through the vascular endothelial growth factor (VEGF) signaling cascade, represents the most promising approach to improve outcome for AGC patients. In a recent meta-analysis of 7022 patients from 22 trials, Ciliberto et al[24] found that the addition of targeted agents to therapies in AGC significantly improved overall survival when comparing to controls (HR 0.823; 95% CI 0.743-0.912; $p < 0.001$). However, there is limited data specifically focusing on the efficacy of targeted agents in elderly patients with AGC. Therefore, preplanned and unplanned subset analysis of registration trial data is becoming increasingly common as a substitute measure to provide valuable information to guide the use of targeted agents in the elderly. We, therefore, conduct this meta-analysis of RCTs with preplanned and unplanned subset analysis of elderly patients (≥ 60) to investigate the overall efficacy of TAs in those patients.

To our best knowledge, this is the first meta-analysis to assess the efficacy of adding TAs to therapies in elderly patients with AGC. Our study, included 1,759 patients from 10 randomized controlled trials, demonstrates that the addition of TAs to chemotherapy in elderly patients with AGC significantly improves OS, and there is also a tendency to improve PFS in the TAs groups. Subgroup analysis according to TAs shows that the use of anti-HER2 agents and AIs in AGC patients significantly improves OS when comparing to controls, while the use of anti-EGFR agents does not improve OS and PFS. Based on our results, we could conclude that the use of anti-HER2 agents and AIs in elderly AGC patients could be recommended due to its survival benefits, while anti-EGFR agents might not be used for patients in this setting excepting for clinical trials. However, more trials are still needed to specifically investigate the efficacy of TAs in elderly patients with AGC.

Several limitations exist in this analysis. First, this meta-analysis only considers published literature, and lack of individual patient data prevents us from adjusting the treatment effect according to disease and patient variables. Second, these studies exclude patients with poor renal, hematological, and hepatic functions, and are performed mostly at major academic centers and research institutions; the analysis of these studies may not apply to patients with organ dysfunctions and in the community. Third, we include patients treated with different targeted agents, which would increase the clinical heterogeneity among included trials, which also make the interpretation of a meta-analysis more problematic, although we pool subgroup analysis according to specific drugs. Finally, in the meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published and trials with null results tend not to be published. Our research detects no publication bias using Begg and Egger tests for OS.

Conclusions

This is the first meta-analysis specifically assessing the efficacy of adding TAs to therapies in elderly AGC patients. The results of our study suggest that the use of TAs in elderly AGC patients offers an improved OS which could be ascribed to AIs and HER-2 agents. With present available data from randomized clinical trials, the use of anti-EGFR agents in elderly AGC patients could not be recommended.

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Conflicts of Interest Statement

All authors declare that they have no potential conflicts of interests.

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