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Patient-reported outcomes with paclitaxel and ramucirumab switch maintenance in advanced gastroesophageal cancer: A secondary endpoint of the ARMANI phase 3 trial

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ABSTRACT

Background: In the ARMANI trial, switch maintenance with paclitaxel plus ramucirumab improved progression-free survival and overall survival versus continuation of oxaliplatin-based chemotherapy in patients with HER2-negative advanced gastric or gastroesophageal junction cancer. Here, we report the health-related quality of life (HRQOL) outcomes.

Methods: ARMANI was a multicenter, randomized, open-label phase 3 trial. Patients achieving disease control after 3 months of FOLFOX or CAPOX were randomized to paclitaxel plus ramucirumab (arm A) or continued FOLFOX/CAPOX (arm B). HRQOL was assessed using EORTC QLQ-C30, QLQ-OG25, and EQ-5D-5L at baseline and every 8 weeks until progressive disease (PD). Endpoints included mean changes from baseline, distribution of improved/stable/worsened global QOL and time to deterioration (TTD; ≥10-point worsening in global QOL).

Results: Among 280 randomized patients, 198 (70.7 %) completed QOL at baseline; 121 (43.2 %) had also the 8-week assessment. Arm A led to improved global QOL at week 8 versus arm B, with more patients reporting improvement (24.7 % versus 4.2 %; delta +20.5 %, 95 % confidence interval [CI] +9.1 % - +31.2 %, p = 0.009) and longer TTD (7.6 versus 3.8 months; HR 0.52, 95 % CI 0.33 – 0.82; p = 0.005). Arm A improved role functioning, nausea/vomiting, pain, appetite loss, and dysphagia, while hair loss was more frequent. The improvement was maintained at subsequent timepoints, though not statistically significant. At PD, no differences in symptoms and domains scores were found by treatment arm. EQ VAS scores were numerically higher in arm A at each timepoint except PD.

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Conclusion: In patients with advanced HER2-negative gastric or gastroesophageal junction cancer, paclitaxel plus ramucirumab switch maintenance showed significant benefit in HRQOL, reducing symptoms and delaying global QOL deterioration.

1. Background

The upfront therapeutic landscape of advanced gastroesophageal cancer is evolving with the introduction of immune checkpoint inhibitors and targeted therapies based on molecular profiling. For patients who are not eligible for these treatments, platinum- and fluoropyrimidine-based chemotherapy is a guideline-recommended option. However, survival outcomes remain poor, with median overall survival (OS) of approximately one year. In this patient population, the role of maintenance strategies aimed at prolonging the benefit of the initial treatment was still unclear [1].

The phase 3 ARMANI trial demonstrated that switch maintenance with paclitaxel plus ramucirumab significantly improved both progression-free survival (PFS) and OS compared to continuation of oxaliplatin-based doublet chemotherapy in patients with advanced HER2-negative gastric or gastroesophageal junction (GEJ) cancer who achieved disease control after a 3-month induction phase with CAPOX or FOLFOX regimens. The median PFS was 6.6 months in the paclitaxel-ramucirumab arm versus 3.5 months in the continuation arm (hazard ratio [HR] 0.61; P = 0.0002). The efficacy of the switch maintenance strategy was retained across clinical and molecular relevant subgroups including Programmed Death Ligand-1 or claudin 18.2 expression. This clinical benefit was accompanied by a higher incidence of grade $\geq$ 3 treatment-related adverse events (64 % versus 43 %), including neutropenia (26 % versus 10 %) and ramucirumab-related toxicities such as hypertension (6 % versus 0 %)[2]. While maintaining disease control is a key objective, ensuring that ongoing therapy remains tolerable with a positive impact on quality of life (QOL), is equally crucial. Patients receiving paclitaxel-ramucirumab required more frequent hospital visits due to the weekly administration, underscoring the importance of treatment strategies that balance efficacy with tolerability to preserve patients' overall well-being and fitness for subsequent anticancer therapies. [2,3]

Patient-reported outcomes (PROs) might provide valuable insights into whether the clinical benefit of the paclitaxel plus ramucirumab switch maintenance translates into a sustained or improved QOL. Given the distinct toxicity profiles of the two strategies, understanding how these adverse effects influence daily functioning, symptom burden, and overall patient well-being is essential for optimizing treatment decisions in the post-induction setting of advanced HER2-negative gastric cancer. Results from the pre-specified secondary endpoint of health-related QOL (HRQOL) analysis are presented here.

2. Methods

2.1. Study design and trial population

Methods and efficacy results of the Italian, multicenter, open-label, randomized phase 3 ARMANI trial (NCT02934464) have been previously published [4]. Briefly, eligible patients had HER2-negative locally advanced unresectable or metastatic gastric or GEJ cancer. They had achieved partial response or stable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. or had no disease progression in case of non-measurable, evaluable disease after a 3-month induction chemotherapy with oxaliplatin and fluoropyrimidines (i.e. with FOLFOX or CAPOX). Patients were randomized to either paclitaxel plus ramucirumab (switch maintenance group; arm A) or to the continuation of FOLFOX or CAPOX at the same dose used in the last induction cycle for an additional 3 months followed by fluoropyrimidine monotherapy continuation maintenance (control group; arm B). Randomization was stratified by previous primary tumor resection, primary tumor location (GEJ vs gastric) and presence of peritoneal disease. The primary endpoint of the study was PFS. HRQOL assessment was a secondary endpoint. The anticipated effect was a superiority in global QOL and time to deterioration (TTD) for switch maintenance arm. No a priori power calculation was performed, as QOL was not the primary endpoint of the trial.

The study was conducted according to the Declaration of Helsinki and adhered to Good Clinical Practice (GCP) guidelines to ensure the ethical and scientific integrity of the research. Approval from the Institutional Review Board and ethics committees of all participating centers was obtained before patient enrollment. Each patient provided written informed consent before undergoing any study-related procedures.

2.2. HRQOL analysis

PROs were assessed by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), which evaluates global health status, functional domains and symptom burden; the EORTC Quality of Life Questionnaire-Oesophago-Gastric 25 (QLQ-OG25), a site-specific module designed for patients with gastric and esophageal cancer; and the 5-level EuroQol-5 Dimensions (EQ-5D-5L), which provides an utility index and a visual analog scale (VAS) score [5–7]. These assessments were conducted at randomization (baseline) and every eight weeks thereafter until progression disease (PD).

The analysis of HRQOL data was carried out using: 1) mean changes from baseline at each scheduled assessment – comparisons between treatment arms were performed using a linear regression model, adjusting for baseline HRQOL scores; this model included treatment as a fixed effect and baseline HRQOL scores as covariates 2) HRQOL changes at the 8-week assessment categorized as improved (an increase of $\geq$10 points compared to baseline), stable (a change between -9 and $+9$ points), or worsened (a decrease of $\geq$10 points); the distribution of these categories was compared between treatment arms using the Chi-square test 3) time to HRQOL deterioration (TTD), defined as the time from randomization to the first occurrence of a $\geq$ 10-point worsening in the global health status/QOL scale of the EORTC QLQ-C30, confirmed at the subsequent assessment or leading to treatment discontinuation; patients who had not experienced HRQOL deterioration at the time of analysis were censored at their last available HRQOL assessment. Kaplan-Meier estimations were used to evaluate TTD, while differences between treatment arms were assessed using the log-rank test; Cox proportional hazards model was applied to calculate the hazard ratio (HR) and 95 % confidence intervals (CI), with adjustments made for baseline HRQOL scores.

Missing HRQOL data were managed in accordance with EORTC scoring guidelines. For multi-item scales, missing responses were imputed using the mean of completed items within the same scale, provided that at least 50 % of items were available. To demonstrate reliability and validity of the QOL data reported in the context of clinical benefit obtained with switch maintenance, the QOL checklist of European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) was applied, whenever feasible (Supplementary Table 1).

Statistical analyses were performed using IBM SPSS Statistics version 29.0.1.0. Descriptive statistics were used to summarize baseline HRQOL score and inferential statistical tests to evaluate differences between treatment arms. A two-sided p-value of < 0.05 was considered statistically significant. No correction for multiplicity was applied.

3. Results

3.1. Compliance analysis

A total of 280 patients were randomized in the study. Among them, 198 (71 %) patients completed baseline HRQOL assessments and were considered for the analysis, 109/144 (75.7 %) in arm A and 89/136 (65.4 %) in arm B. The 8-week assessment was available for 121/198 patients (43.2 %). The absolute number of patients completing assessments at designated time points (Supplementary Figure 1) and the rate of patients completing assessments at designated time points while on study over the total number completing assessment at baseline (Fig. 1 A) decreased over time. The rate of patients completing assessments at designated time points over the number of patients still on study was maintained roundly over 70 % in arm A and 60 % in arm B (Fig. 1 B): overall, compliance was slightly lower in Arm B (65.4 % versus 75.7 % at baseline, 59.1 % versus 77.9 % at 8 weeks and 61.4 % versus 72.6 % at 16 weeks).

3.2. Patients and disease characteristics

Baseline demographic and clinical characteristics of patients included in the HRQOL analysis were generally balanced between the two treatment arms and consistent with those in the intention-to-treat population of the ARMANI trial (Table 1). Most patients were male (65 % in arm A and 58 % in arm B) and had ECOG PS 0 (75 % and 67 %), respectively. Median age was 64 years (IQR 54–71) in arm A and 66 years (57−72) in arm B, with 78 % and 67 % of patients under 70 years old, respectively. The primary tumor site was predominantly gastric

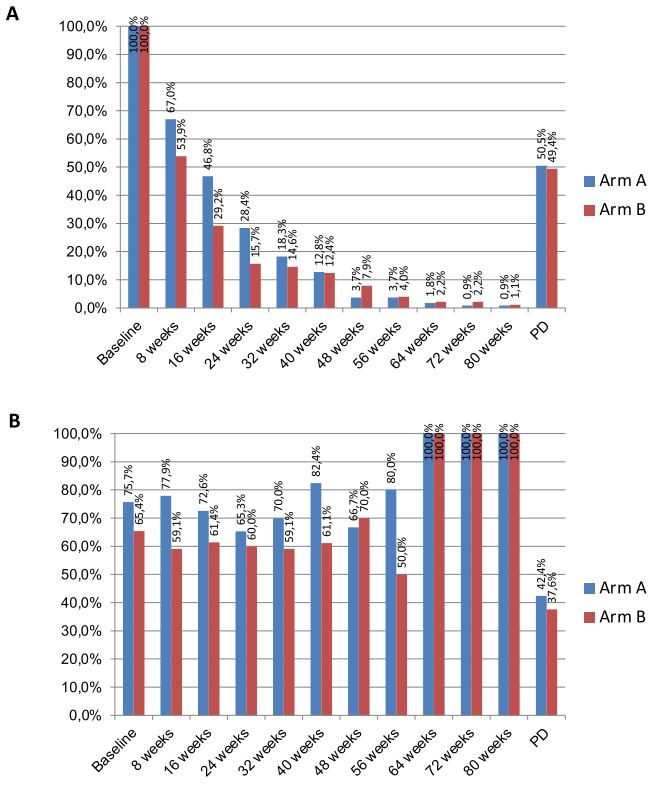

Fig. 1. Compliance analysis. Panel A represents the rate of patients completing assessments at designated time points while on study, over the total number completing assessment at baseline, by treatment arm. Panel B represents the rate of patients completing assessments at designated time points over the number of patients still on study, who were expected to complete questionnaires at each of those time points, by treatment arm. List of abbreviations: PD = Progressive Disease.

Table 1
Patients characteristics.

	Paclitaxel plus ramucirumab switch maintenance group (n = 109), N (%)	FOLFOX or CAPOX continuation group (n = 89), N (%)
Sex		
Male	71 (65)	52 (58)
Female	38 (35)	37 (42)
Age, years		
median (IQR)	64 (54–71)	66 (57–72)
<70	85 (78)	60 (67)
≥70	24 (22)	29 (33)
ECOG Performance Status		
0	82 (75)	60 (67)
1	27 (25)	29 (33)
Site of origin		
Gastric	79 (72.5)	67 (75)
Gastro-esophageal junction	30 (27.5)	22 (25)
Prior Gastrectomy		
Yes	30 (27.5)	18 (20)
No	79 (72.5)	71 (80)
Peritoneal metastases		
Yes	62 (57)	38 (43)
No	47 (43)	51 (57)
Liver metastases		
Yes	27 (25)	28 (32)
No	82 (75)	60 (67)
Missing	0 (0)	1 (1)
Number of metastatic sites		
0-1	49 (45)	38 (43)
≥2	59 (54)	50 (56)
Missing	1 (<1)	1 (1)
Synchronous metastases		
Yes	86 (79)	76 (85)
No	23 (21)	13 (15)
Histotype		
Intestinal	41 (38)	22 (25)
Diffuse	42 (38)	43 (48)
NOS	26 (24)	24 (27)
First line induction regimen		
FOLFOX	92 (84)	77 (86.5)
CAPOX	17 (16)	12 (13.5)

List of abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status, IQR = interquartile range, NOS = not otherwise specified.

(72.5 % and 75.3 % in arm A and B, respectively), prior primary tumor resection was reported in 27.5 % and 20 % of patients in arm A and B, while peritoneal disease in 57 % and 43 %, respectively.

3.3. Quality of life questionnaire - Core 30

At baseline, the mean global QOL score was 66.90 (standard deviation [SD]: 20.71) in arm A and 70.97 (SD: 19.39) in arm B. There were no significant differences between the two arms in global QOL, functional scales and symptoms scores (Table 2).

At the first 8-week assessment, global QOL was significantly improved for patients receiving paclitaxel plus ramucirumab compared to those continuing with FOLFOX or CAPOX. Overall, 59 patients (81 %) in arm A experienced improved (24.7 %) or stable (56.2 %) global QOL, compared to 33 patients (69 %; 4.2 % for improved and 64.6 % for

Table 2
Baseline EORTC QLQ-C30 scores.

	Arm A (n = 109) Mean (SD)	Arm B (n = 89) Mean (SD)	Overall (n = 198) Mean (SD)
Global QOL	66.90 (20.71)	70.97 (19.39)	68.73 (20.18)
Functional scales			
Physical functioning	81.71 (19.10)	83.00 (20.03)	82.29 (19.48)
Role functioning	80.28 (25.98)	81.84 (26.07)	80.98 (25.96)
Emotional functioning	78.44 (17.47)	79.12 (19.22)	78.75 (18.23)
Cognitive functioning	90.21 (16.07)	88.76 (18.08)	89.56 (16.97)
Social functioning	81.80 (22.17)	82.21 (25.72)	81.99 (23.77)
Symptoms			
Fatigue	27.62 (20.60)	27.72 (22.23)	27.67 (21.29)
Nausea-vomiting	9.02 (16.90)	13.30 (21.49)	10.94 (19.17)
Pain	13.46 (19.70)	14.61 (22.02)	12.97 (20.73)
Sleeping disturbance	20.18 (24.01)	18.35 (21.91)	19.36 (23.05)
Appetite loss	13.15 (22.23)	16.48 (27.58)	14.65 (24.77)
Constipation	19.27 (27.70)	18.73 (27.04)	19.02 (27.34)
Diarrhea	10.40 (19.08)	8.61 (17.06)	9.60 (18.18)
Financial	7.65 (16.75)	10.86 (21.77)	9.09 (19.19)
Dyspnea	10.09 (17.86)	4.87 (12.86)	7.74 (15.99)

List of abbreviations: SD = standard deviation, QOL = quality of life.

stable) in arm B (P = 0.009 – Fig. 2A). Arm A was associated with + 20.5 % in the proportion of patients with improved global QoL (95 % confidence interval [CI] +9.1 % to +31.2 %). A significant improvement was also observed in terms of mean changes from baseline (+2.17 vs −8.51, delta +10.68, 95 %CI +3.96 to +17.39; P = 0.015, Fig. 2 B). The analysis of functional scales and symptom domains revealed additional benefit in role functioning for arm A versus B (mean changes from baseline +0.23 vs. −13.19, delta +13.42, 95 %CI +3.87 to +22.98; P = 0.006) and a reduction of nausea and vomiting (mean changes from baseline -1.14 vs. +6.25, delta −7.39, 95 %CI −13.29 to −1.48; P = 0.002), pain (mean changes from baseline +0.23 vs. +7.64, delta −7.41, 95 %CI −14.32 to −0.50; P = 0.016) and appetite loss (mean changes from baseline −0.46 vs. 4.86, delta −5.32, 95 %CI −13.34 to +2.71; P = 0.03 – Fig. 2B).

The switch maintenance arm still showed a numerical advantage in QLQ-C30 scores across multiple domains and symptoms at subsequent timepoints (Supplementary Figure S2). At the time of PD, similar worsening in global quality of life (QOL) scores was observed in arm A and B (mean changes from baseline -11.52 vs −12.12; delta +0.61, 95 % CI −7.84 to 9.05; P = 0.39) and no significant differences were found in the scores of other symptoms and domains (Supplementary Figure S2).

As of data cutoff of April 30th, 2024, the median follow-up for the population of HRQOL analysis was 55.5 months (IQR: 31.2–59.5). Overall, 38 patients per arm experienced a global QOL deterioration event, 38/109 (35 %) in the experimental and 38/89 (43 %) in the control arm. Time to global QOL deterioration was significantly improved by paclitaxel plus ramucirumab over continuation of FOLFOX or CAPOX (median TTD 7.6 versus 3.8 months; HR 0.52, 95 %CI 0.33–0.82, P = 0.005 – Figure 3). At 8 weeks, the probability of being free from global QOL deterioration was 92.8 % in arm A and 83.8 % in arm B. At 6 months, it was 59.9 % and 23.2 %, respectively.

3.4. Quality of life questionnaire – OG25

Consistently, the analysis of QLQ-OG25 domains and symptoms at the first 8-week assessment revealed a statistically significant improvement in arm A versus B in terms of dysphagia (mean changes from baseline −2.19 vs. +3.47, delta −5.66, 95 %CI −10.35 to −0.47; P = 0.028) and epigastric pain and discomfort (mean changes from baseline −4.46 vs. +4.61, delta −9.07, 95 %CI −16.11 to −2.03; P = 0.04 – Fig. 4). According to the safety profile of paclitaxel, hair loss was more frequent among patients treated in arm A (mean changes from baseline +7.87 vs. −0.71, delta +8.58, 95 %CI +0.65 to +16.51; P = 0.024).

Overall, the QOL benefit of paclitaxel plus ramucirumab switch maintenance was maintained at subsequent timepoints (Supplementary Figure S3). At the time of PD, no significant differences were observed in any of the domain and symptom scores (Supplementary Figure S3).

3.5. EuroQol 5D-5L

The VAS score from the EQ-5D-5L did not show a statistically significant difference between the two treatments at any assessment point. However, patients randomized to arm A showed a consistent improvement in VAS scores from baseline at every timepoint (+2,26, +2,18 and +3.91 at 8, 16 and 24 weeks), whereas those randomized to arm B experienced a decline in their scores (-4.48, −3.7 and −8.57 at 8, 16 and 24 weeks) (Supplementary Figure S4).

4. Discussion

This analysis of PROs of the ARMANI trial showed that paclitaxel plus ramucirumab switch maintenance may be associated with better QOL and symptom control versus continuation of FOLFOX or CAPOX chemotherapy in patients with advanced HER2-negative gastric or GEJ cancer. These results align with the 3.1-month absolute gain in median PFS and the lower rate of early PD (10 % vs 32 %) achieved with

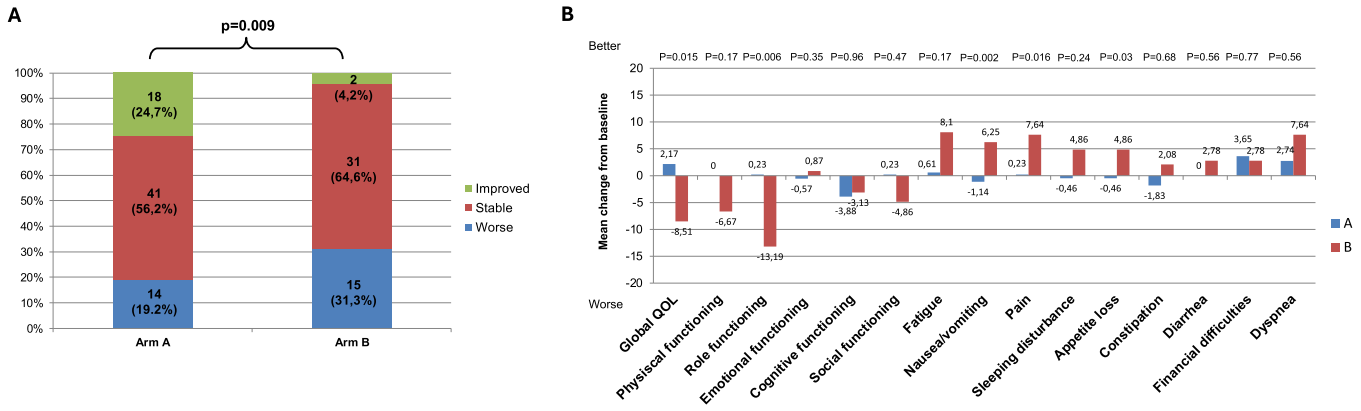

Fig. 2. Global quality of life, functional scales and symptoms at the 8-week assessment. Panel A represents the best responses for global quality of life score of EORTC QLQ-C30 questionnaire in terms of proportion of improved/stable/worsened at 8 weeks from randomization in the two treatment arms. Panel B represents the variations from baseline in global quality of life, functional scales and symptoms of EORTC QLQ-C30 questionnaire in terms of mean changes from baseline at 8 weeks from randomization in the two treatment arms. List of abbreviations: PD = Progressive Disease.

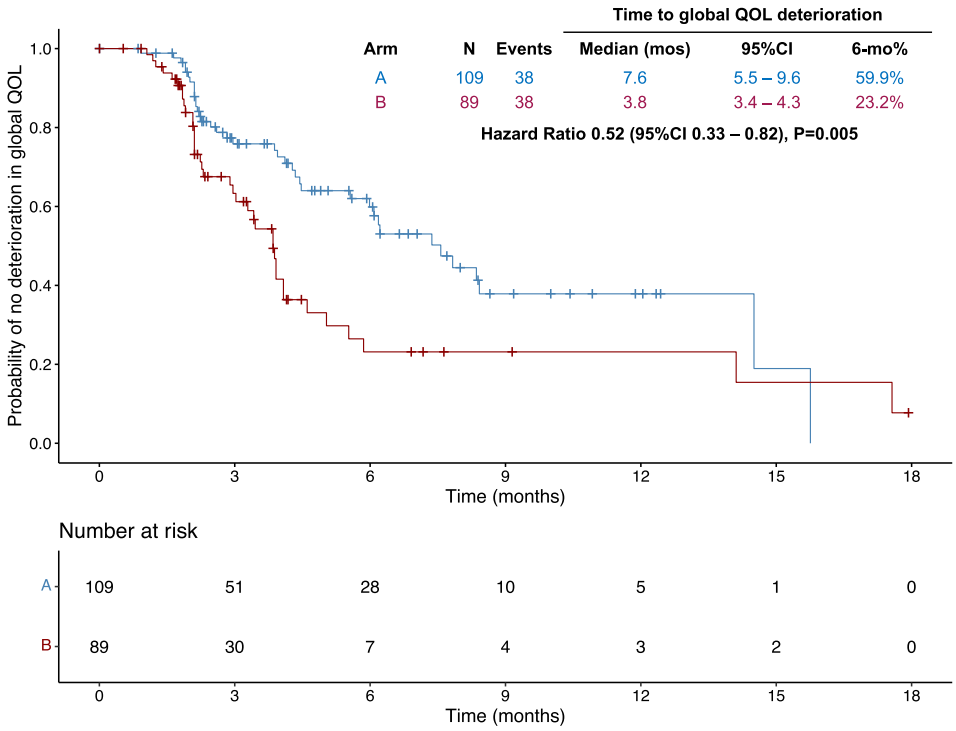

Fig. 3. Kaplan Meier curves for time to global QOL deterioration by treatment arm. List of abbreviations: QOL = Quality of Life.

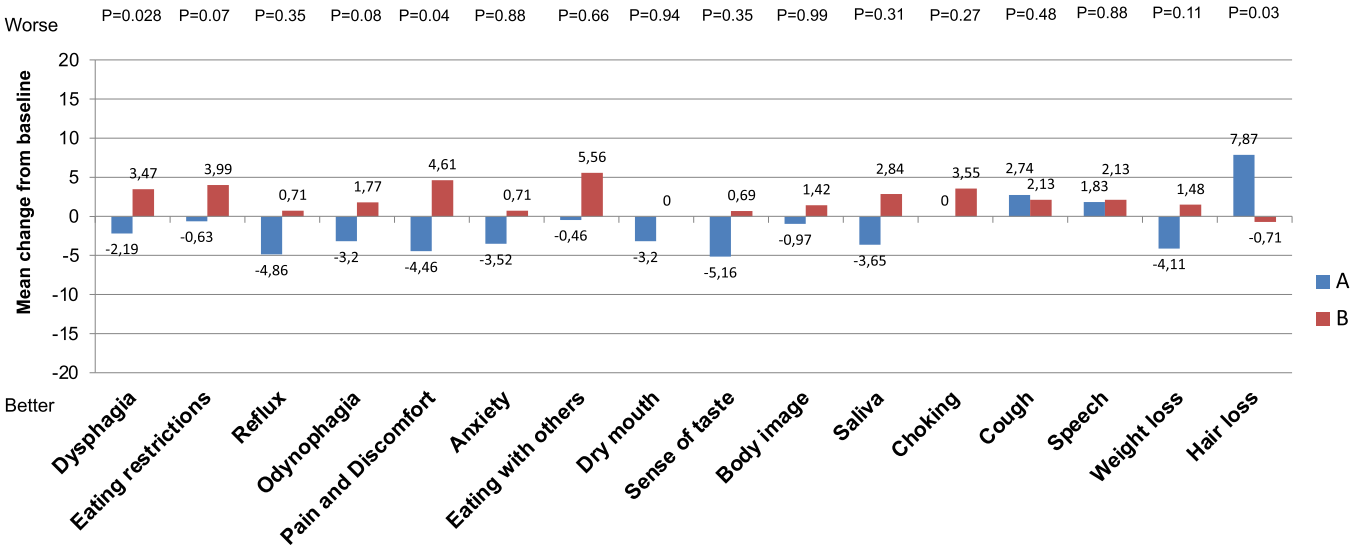

Fig. 4. Domains and symptoms of the QLQ-OG25 at the 8-week assessment.The variations from baseline in domains and symptoms of EORTC QLQ-OG25 questionnaire are represented in terms of mean changes from baseline at 8 weeks from randomization in the two treatment arms.

paclitaxel plus ramucirumab. Focusing on symptoms in the OG25 domain closely related to disease burden, such as fatigue, pain, weight and appetite loss, paclitaxel plus ramucirumab was associated with a clinically significant improvement from baseline compared to the control arm. Importantly, the longer TTD in the experimental arm, as assessed by the QOL scale of the EORTC QLQ-C30, closely reflects the PFS gain, suggesting that patient-reported global health may be directly influenced by disease control. These data reinforce the effect on PFS as a direct measure of first-line treatment benefit in advanced gastric cancer, since suboptimal disease control and disease progression may be associated with morbidity and rapid worsening of patients' global health status [8].

Despite global survival remains limited in patients with advanced gastric or GEJ cancer, especially without targetable biomarkers, the switch maintenance approach has demonstrated to prolong both PFS and OS with a significant delay of global QOL deterioration. The observed benefit on QOL is early, as demonstrated by the higher rate of patients without deterioration at 8 weeks (92.8 % for arm A vs 83.8 % for arm B). A rate of global QOL worsening of 19.2 % was observed for the experimental arm at 8 weeks, but still significantly lower than in the control arm (31.3 %), partly explained by the 10 % early PD rate with switch maintenance in the overall ARMANI trial population.

In the context of maintenance strategies for a disease that remains challenging to cure, balancing the burden of treatment toxicities and disease-related symptoms with the survival gain remains of paramount importance. The results of this secondary objective of the ARMANI trial

are meaningful when viewed within the broader context of the trial's overall efficacy and safety findings. The PFS and OS gain with paclitaxel and ramucirumab switch maintenance need to be weighed against the increased incidence of grade ≥ 3 treatment-related adverse events and more frequent hospital visits of this weekly regimen. Notably, the increased rate of severe toxicity in the experimental arm of the ARMANI trial was mostly related to neutropenia, which is usually manageable and does not affect patient subjective symptoms. In addition, patients continued FOLFOX or CAPOX at the same dose used in the last induction cycle, and previous dose reductions of oxaliplatin-based chemotherapy might have attenuated the toxicity burden associated with this regimen. Therefore, the improvement in HRQOL in the study is plausible and mostly related to improved disease control in arm A, with an overall manageable safety profile.

The ESMO-MCBS QOL checklist was applied to our study, resulting in a final score of 2 positive items out of 4 with all three prerequisites met. For trials published before January 2025 like the ARMANI trial, this score would justify a QOL adjustment in the MCBS scale possibly contributing to reach the threshold for substantial benefit.

In line with our results, despite increased toxicity or treatment discontinuation due to adverse events, QOL analyses from the V-325 and CheckMate-649 trials showed a significant QOL benefit in the experimental arms with docetaxel or nivolumab, respectively, added to platinum-based chemotherapy [9,10]. In the SPOTLIGHT and GLOW trials, the addition of the anti-Claudin18.2 zolbetuximab improved survival without negatively impacting QOL, despite increased nausea and vomiting during the first cycles [11]. In the FIGHT trial, HRQOL remained comparable between arms despite a higher incidence of mucositis and corneal events with the anti-FGFR2b bemarituzumab than placebo [12]. In patients with advanced tumors, QOL is not simply dependent on the treatment toxicity, but it is strongly related to treatment efficacy and symptom control [13].

The analysis of the HRQOL of the ARMANI trial confirms the favorable impact in terms of both efficacy and quality of life of ramucirumab with or without paclitaxel as reported in the second-line REGARD and RAINBOW trials. Ramucirumab was associated with prolonged preservation of patients' functional status - a key goal of second-line treatment for gastric cancer, which also applies to the maintenance setting [14,15].

This secondary analysis of the ARMANI trial has limitations. Despite a threshold of ≥ 10 point was set, conventionally, to define a clinically meaningful change, smaller improvements, especially when a statistically significant difference is observed in multiple domains, have been still interpreted as clinically relevant. It is acknowledged that the minimal important difference might vary according to multiple parameters, such as type of scale, direction of change, cancer type and estimation method [16]. Then, correction for multiplicity due to repeated follow-up assessments over time was not performed, as these analyses were conducted as secondary analyses and applying such correction could potentially mask clinically relevant differences between the two groups. Additionally, compliance was moderately lower than that reported in first-line clinical trials. In both CheckMate-649 and KEYNOTE-589, which evaluated the addition of nivolumab or pembrolizumab to a fluoropyrimidine–platinum regimen, treatment compliance exceeded 95 % at baseline and, although it declined over time, it consistently remained above 80 % at subsequent timepoints [10,17]. However, compliance rates are often lower in academic trials, reflecting differences in resources and support for PROs collection. Moreover, compliance was generally lower among patients randomized to continuation of chemotherapy, who may have been less inclined to provide feedback on a conventional treatment. Clinically meaningful differences were further observed between the two arms beyond the 8-week timepoint, but most failed to reach statistical significance, likely due to the limited number of patients completing PROs questionnaires at later timepoints and the relatively short post-randomization PFS, especially in the control arm. Importantly, informative censoring in the TTD analysis may have influenced the results. Since patients' attrition could have been particularly relevant for the less effective control arm, these data should be interpreted with caution. However, although suboptimal, the compliance at each time-point was slightly better for the experimental treatment, and this should actually reduce the bias in favor of the winning arm. The ARMANI study was without blinding, a potential weakness of the QOL analysis. However, QOL can be considered a valid and reliable endpoint even in open label studies [18].

In conclusion, this pre-specified secondary analysis of the ARMANI trial demonstrated that switch maintenance with paclitaxel plus ramucirumab significantly delayed global health deterioration and improved key symptoms compared to the continuation of FOLFOX or CAPOX in patients with advanced HER2-negative gastric or GEJ cancer. These findings further support switch maintenance with paclitaxel plus ramucirumab as a therapeutic strategy to prolong survival and improve QOL of patients with advanced gastroesophageal adenocarcinoma who are not eligible for upfront immunotherapy or targeted agents combined with doublet chemotherapy.

CRediT authorship contribution statement

Margherita Ambrosini: Writing – review & editing, Writing – original draft, Resources, Investigation, Formal analysis, Data curation. **Eleonora Cristarella:** Writing – review & editing, Writing – original draft, Resources, Investigation, Formal analysis, Data curation. **Tiziana Pia Latiano:** Writing – review & editing, Resources, Investigation. **Antonia Strippoli:** Writing – review & editing, Resources, Investigation. **Oronzo Brunetti:** Writing – review & editing, Resources, Investigation. **Giovanni Gerardo Cardellino:** Writing – review & editing, Resources, Investigation. **Sara Lonardi:** Writing – review & editing, Resources, Investigation. **Stefano Tamberi:** Writing – review & editing, Resources, Investigation. **Massimo Di Maio:** Writing – review & editing, Resources, Investigation, Formal analysis, Data curation. **Lorenzo Fornaro:** Writing – review & editing, Resources, Investigation. **Samantha Di Donato:** Writing – review & editing, Resources, Investigation. **Daniele Spada:** Writing – review & editing, Resources, Investigation. **Ferdinando De Vita:** Writing – review & editing, Resources, Investigation. **Filippo Pietrantonio:** Writing – review & editing, Resources, Investigation, Data curation, Conceptualization. **Andrea Spallanzani:** Writing – review & editing, Resources, Investigation. **Sara Alessandrini:** Writing – review & editing, Resources, Investigation. **Elisa Giommoni:** Writing – review & editing, Resources, Investigation. **Claudio Chini:** Writing – review & editing, Resources, Investigation. **Giovanni Randon:** Writing – review & editing, Resources, Investigation. **Alessandro Bittoni:** Writing – review & editing, Resources, Investigation.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Massimo Di Maio reported advisory board role for Amgen, Astellas, AstraZeneca, Daiichi Sankio, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Viatris; fundings (to institution as local principal investigator) from Beigene, Exelixis, Merck Sharp & Dohme, Pfizer, Roche; research grant (to institution) from Tesaro – GlaxoSmithKline; non financial interest for Leadership Role, President Elect (2023–2025) of AIOM (Italian Association of Medical Oncology). Sara Lonardi reported personal honoraria as invited speaker from Amgen, Astra Zeneca, Bristol-Myers Squibb, Incyte, GSK, Lilly, Merck Serono, MSD, Pierre-Fabre, Roche, Servier; participation in advisory board for Amgen, Astellas, Astra Zeneca, Bayer,

Bristol-Myers Squibb, Daiichi-Sankyo, GSK, Incyte, Lilly, Merck Serono, MSD, Servier, Takeda, Rottapharm, Beigene, Fosun Pharma, Nimbus Therapeutics. Ferdinando De Vita reported consultant or advisory role for Roche, Bayer, BMS, Servier, Lilly, Astellas, MSD, Merck, Astra Zeneca, Dajichi. Andrea Spallanzani reported consultant or advisory board role for Astrazeneca, Daiichi, Astellas, MSD, Lilly. Stefano Tamberi reported Advisor Board Travel Grants from Roche, Servier, Incyte, Astrazeneca, TAKEDA. Lorenzo Fornaro reported speaking honoraria from Incyte, Bristol Myers Squibb, AstraZeneca; advisory board for MSD, AstraZeneca, Incyte, Taiho, Servier, Daiichi Sankyo, Astellas, BeiGene; research funding (to Institution) from MSD, Bristol Myers Squibb, AstraZeneca, Incyte, BeiGene, Astellas, Daiichi Sankyo, Roche. Filippo Pietrantonio reported receiving research funding (to Institution) from Lilly, BMS, Incyte, AstraZeneca, Amgen, Agenus, Rottapharm, Johnson&Johnson; personal honoraria as an invited speaker from BeiGene, Daiichi-Sankyo, Seagen, Astellas, Ipsen, AstraZeneca, Servier, Bayer, Takeda, Johnson & Johnson, BMS, MSD, Amgen, Merck-Serono, Pierre-Fabre, Incyte, AstraZeneca; advisory/consultancy for BMS, MSD, Amgen, Pierre-Fabre, Johnson & Johnson, Servier, Bayer, Takeda, Astellas, GSK, Daiichi-Sankyo, Pfizer, BeiGene, Jazz Pharmaceuticals, Incyte, Rottapharm, Merck-Serono, Italfarmaco, Gilead, AstraZeneca, Agenus. Giovanni Randon reported speaking honoraria form Accademia di Medicina. All the other authors reported no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116060.

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