Maintenance Capecitabine Plus Ramucirumab After First-Line Chemotherapy in Patients With Advanced Esophagogastric Adenocarcinoma: Results From the Randomized PLATFORM Study

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ABSTRACT

PURPOSE PLATFORM is an adaptive phase II study assessing maintenance therapies in advanced esophagogastric adenocarcinoma (OGA). We evaluated the role of capecitabine plus a vascular endothelial growth factor receptor 2 inhibitor ramucirumab (cape-ram) in these patients.

METHODS Human epidermal growth factor receptor 2 (HER2)-negative patients with advanced OGA with stable or responding disease after 18 weeks of induction platinum-based chemotherapy were randomly assigned 1:1 to surveillance or cape-ram. The primary end point was progression-free survival (PFS), and key secondary end points were overall survival (OS) and safety. Recruitment to the cape-ram arm closed prematurely because of industry support withdrawal. A one-sided log-rank test with a 2.5% significance level was considered significant.

RESULTS Between April 2019 and November 2022, 25 surveillance and 22 cape-ram patients were contemporaneously randomly assigned. Median follow-up was 24.4 months. Compared with surveillance, cape-ram significantly prolonged PFS (hazard ratio [HR], 0.33 [95% CI, 0.17 to 0.63], $P < .001$; median PFS: 2.5 months with surveillance versus 5.5 months with cape-ram; 6-month PFS rate: 4% [95% CI, 0.3% to 17.0%] *v* 42.9% [95% CI, 21.9% to 62.3%], respectively) and OS (HR, 0.51 [95% CI, 0.26 to 1.00], $P = .023$; median OS: 7.1 months with surveillance *v* 14.4 months with cape-ram; median OS from start of induction chemotherapy was 12.1 months *v* 19.5 months, respectively). Of 10 cape-ram patients with measurable disease, 1 had an incremental partial response. Grade ≥3 adverse events (AEs) were seen in 32% surveillance and 57% cape-ram patients. Six cape-ram patients had grade 3 treatment-related AEs, and no new safety signals were identified.

CONCLUSION Maintenance cape-ram after induction chemotherapy for patients with HER2-negative OGA significantly improved survival compared with surveillance. To our knowledge, this is the first randomized maintenance study demonstrating survival benefit and provides support for maintenance treatment.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Protocol

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INTRODUCTION

Gastric and esophageal cancers are the fourth and sixth leading causes of cancer mortality, respectively, globally as most patients present with inoperable advanced or metastatic disease.[1] Fluoropyrimidine plus platinum-based chemotherapy has formed the backbone of systemic therapy for advanced esophagogastric adenocarcinoma (OGA) in the past few decades but a median overall survival (OS) of <12 months was observed.[2,3] Integrating targeted therapies against human epidermal growth factor receptor 2 (HER2), PD-L1, and Claudin 18.2 with chemotherapy has

surpassed the 12-month OS barrier.[4-8] However, there remains an unmet need to further improve survival outcomes for those ineligible for targeted therapy. PLATFORM (Planning Treatment For Oesophago-gastric Cancer: a Randomised Maintenance Therapy Trial) is an adaptive phase II trial evaluating various maintenance therapies after first-line chemotherapy in patients with advanced, HER2-negative OGA. Capecitabine is a standard component of first-line chemotherapy, and ramucirumab has demonstrated clinical efficacy in advanced OGA.[9-11] Randomization across five treatment arms commenced in April 2019 when capecitabine plus ramucirumab (cape-ram) was initiated as the final arm. This soon coincided with the onset of the COVID-19 pandemic. Cessation of industry support led to early closure of the cape-ram arm in November 2022. In this study, we report the primary results of maintenance cape-ram versus active surveillance in patients with HER2-negative, advanced OGA who responded to first-line chemotherapy.

METHODS

Full details on the trial design, methodology, and statistical analysis have been published previously.[12] Relevant to cape-ram, eligible patients had inoperable locally advanced or metastatic adenocarcinoma of the esophagus, gastro-esophageal junction (GEJ), or stomach and achieved stable disease or response on computed tomography after 18 weeks of first-line capecitabine and oxaliplatin, cisplatin and capecitabine, or fluorouracil and oxaliplatin. Patients with grade 3 or 4 thromboembolism, gastrointestinal bleeding, or perforation within 3 months of random assignment were excluded. PD-L1 status was not an eligibility criterion as this was not a proven predictive biomarker for capecitabine nor ramucirumab. However, this was assessed for the experiment arm with maintenance durvalumab comparison within our PLATFORM study as previously published.[12] Surveillance visits were every 28 days, and patients assigned to cape-ram received capecitabine 1,250 mg/m^2/day continuously taken twice daily, with ramucirumab 8 mg/kg once a day, on days 1 and 8 of a 21-day cycle to progression, death, or toxicity. Continuation with single-agent maintenance treatment was permitted. Ramucirumab was provided by Eli-Lilly without cost. The primary end point was progression-free survival (PFS), time from random assignment to progression by RECIST 1.1, clinical progression, or death from any cause. Secondary end points included OS, time from random assignment to death from any cause, objective response rate, and safety. The target sample size for this analysis was 308. A one-sided log-rank test with a 2.5% significance level was considered significant.

As PLATFORM is an adaptive trial, patients were randomly assigned to surveillance, capecitabine, or durvalumab in the original protocol. Subsequent interventional arms containing rucaparib and cape-ram were added with later protocol amendments, resulting in a final random assignment of 1:1:1:1:1 across five treatment arms (Appendix Fig A1, online only). In this analysis, patients randomly assigned to surveillance contemporaneously with cape-ram were selected.

RESULTS

Patients and Treatment

Between March 2015 and November 2022, 1,367 patients were registered from 46 centers across the United Kingdom. Of these, 1,332 completed induction chemotherapy, and most patients (64%) received 18 weeks. During this period, 475 patients were randomly assigned in the entire study, and the most common reason for nonrandom assignments was progression (44%). Between April 2019 and November 2022, 25 patients were randomly assigned to surveillance and 22 patients to cape-ram. Two patients fully withdrew and 1 cape-ram patient was lost to follow-up (Fig 1).

Table 1 presents the baseline characteristics. These were broadly similar between the two groups. No formal statistical testing was performed owing to the randomized nature of the study. At data cutoff on March 28, 2024, all surveillance patients were off study and two cape-ram patients remained on treatment. The median duration on treatment was 1.9 months (IQR, 1.0-2.5) for surveillance and 3.0 months (IQR, 1.9-6.0) for cape-ram. The most common reason for treatment discontinuation was progressive disease in both arms (96% in surveillance and 84% in cape-ram). Six patients required dose reductions to either capecitabine (19%) or ramucirumab (19%). Two patients permanently discontinued capecitabine and continued with ramucirumab: folate deficiency at cycle 7 and hand foot syndrome at cycle 17. Three patients discontinued ramucirumab and continued capecitabine: hypertension at cycle 3, proteinuria at cycle 23, and patient choice at cycle 39.

Efficacy

The median follow-up was 24.4 months. All surveillance patients and 82% of cape-ram patients had progressed, while 88% of surveillance and 68% of cape-ram patients died. Figure 2A shows the PFS. Compared with surveillance, cape-ram significantly prolonged PFS (unadjusted hazard ratio [HR], 0.33 [95% CI, 0.17 to 0.63], $P < .001$). The median PFS was 2.5 months (95% CI, 1.7 to 2.8) in the surveillance arm compared with 5.5 months (95% CI, 2.8 to 7.8) in the cape-ram arm. The 6-month progression-free rate (PFR) was 4% (95% CI, 0.3 to 17.0) versus 42.9% (95% CI, 21.9 to 62.3), respectively. Figures 2B and 2C show the OS. Compared with surveillance, cape-ram significantly prolonged OS (unadjusted HR, 0.51 [95% CI, 0.26 to 1.00], $P = .023$). Median OS from random assignment was 7.1 months (95% CI, 5.0 to 10.0) in the surveillance arm compared with 14.4 months (95% CI, 6.7 to 19.9) in the cape-ram arm, and from start of induction chemotherapy, median OS was 12.1 months (95% CI, 9.9 to 1.50) and 19.5 months (95% CI, 11.8 to 24.8), respectively. The 12-month OS rate from

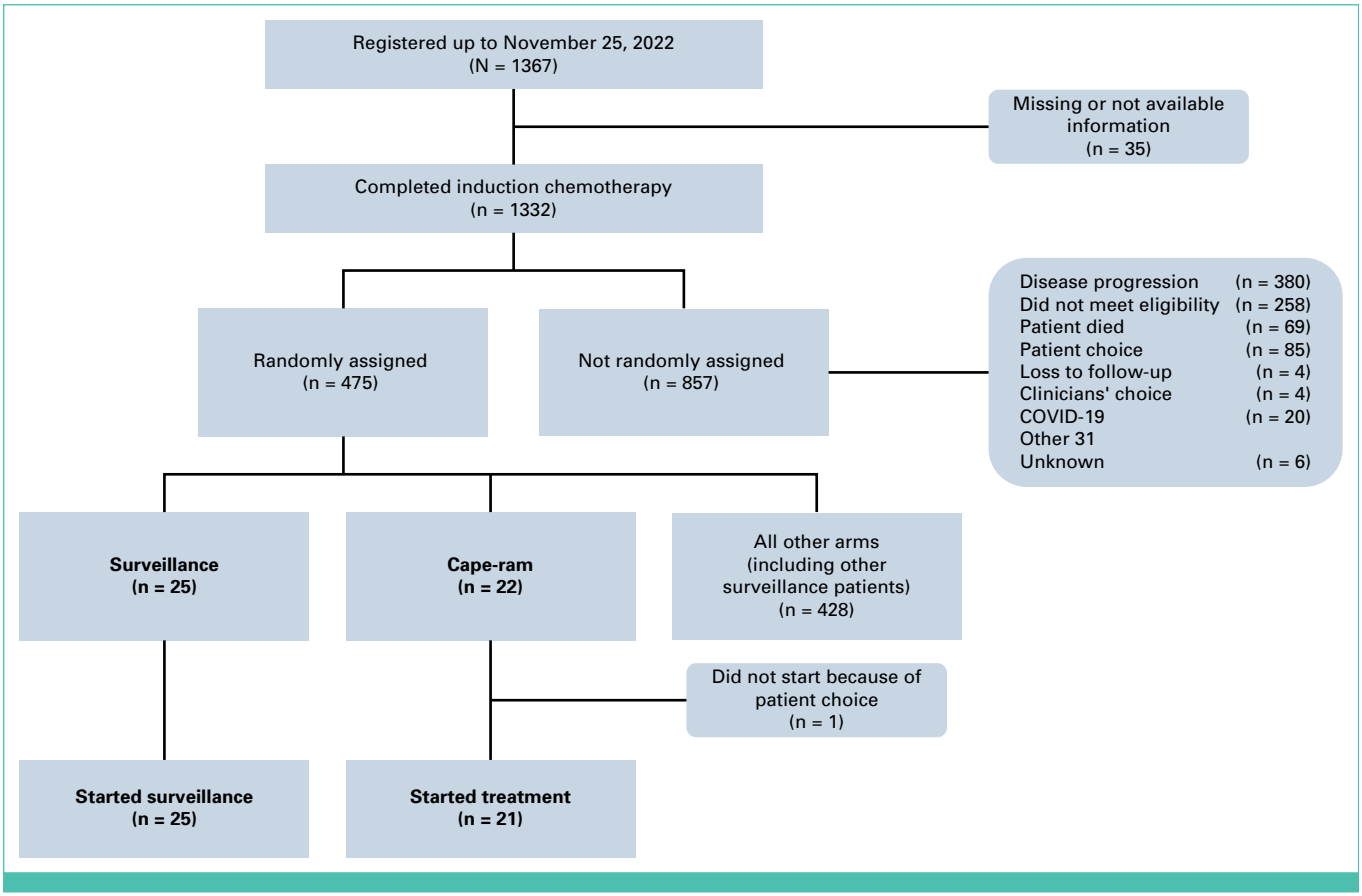

FIG 1. CONSORT diagram of all registered patients. Cape-ram, capecitabine/ramucirumab.

random assignment was 29.2% for surveillance and 60.0% for cape-ram; 24-month OS from induction chemotherapy was 10.4% versus 30.7%, respectively. Planned subgroup analyses were not performed because of the small sample size. Table 2 summarizes postprogression therapy. Seven (28%) surveillance and seven (33%) cape-ram patients had subsequent chemotherapy, but none had ramucirumab. The 12-week PFR was 16% (5%-36%) in the surveillance arm and 67% (43%-85%) in the cape-ram arm (odds ratio, 10.5 [95% CI, 2.6 to 42.7], $P < .001$). Of 10 cape-ram patients with measurable disease, 1 had an incremental partial response; none were seen with surveillance.

Safety

Table 3 presents adverse events (AEs) in the safety population. All 46 patients experienced an AE of any cause. Grade 3+ events of any cause occurred in 8 of 25 (32%) surveillance and 12 of 21 (57%) cape-ram patients. Six cape-ram patients experienced a grade 3 treatment-related AE (trAE): hypertension (14%), thromboembolism (10%), anemia (5%),s and hand-foot syndrome (5%). Serious AEs occurred in three surveillance and three cape-ram patients. One suspected unexpected serious adverse reaction was reported with thromboembolism possibly related to ramucirumab, but this was a result of a nonsynonymous term with the safety reference.

DISCUSSION

To our knowledge, this is the first randomized trial to demonstrate survival benefit of maintenance treatment compared with surveillance in patients with HER2-negative, advanced OGA who respond to first-line induction chemotherapy. Maintenance cape-ram significantly improved both PFS (HR, 0.33, $P < .001$) and OS (HR, 0.51, $P = .023$) with the median PFS and OS prolonged by more than two-fold. Notably, increasing median OS from start of induction chemotherapy by 7.4 months with cape-ram is a milestone for advanced HER2-negative OGA. As similar proportions of patients in both arms received postprogression therapy with no subsequent ramucirumab given in either arm, OS advantage in the cape-ram arm was not influenced by postprogression therapy. Even if paclitaxel plus ramucirumab was available as second-line therapy for the surveillance arm, this would not affect PFS, which was the primary end point of our study. Although OS benefit might be diluted, the pivotal RAINBOW study reported an OS HR advantage of 0.807, whereas our OS advantage was 0.51 with first-line maintenance

TABLE 1. Patient Characteristics

Clinical Characteristic	Surveillance (n = 25), No. (%)	Cape-Ram (n = 22), No. (%)
Age, years, median (IQR)	61.2 (53 to 72)	63.6 (57 to 68)
<65	16 (64)	11 (50)
≥65	9 (36)	11 (50)
Sex		
Female	6 (24)	9 (41)
Male	19 (76)	13 (59)
Primary tumor location		
Gastroesophageal junction	10 (40)	8 (36)
Esophagus	8 (32)	4 (18)
Stomach	7 (28)	10 (45)
ECOG performance status		
0	10 (40)	8 (36)
1	15 (60)	14 (64)
Presentation		
De novo metastatic/locally advanced	23 (92)	21 (95)
Relapsed	2 (8)	1 (5)
Histology		
Well differentiated	1 (4)	1 (5)
Moderately differentiated	4 (16)	5 (23)
Poorly differentiated	18 (72)	16 (73)
Not available	2 (8)	0 (0)
Number of metastatic sites	n = 23	n = 19
≤1	19 (83)	14 (74)
≥2	4 (17)	5 (26)
Induction chemotherapy		
FOLFOX	3 (12)	0 (0)
CAPOX	21 (84)	17 (77)
CX	1 (4)	5 (23)
Response to induction chemotherapy		
Complete response/partial response	10 (40)	10 (45)
Stable disease	15 (60)	12 (55)

Abbreviations: cape-ram, capecitabine plus ramucirumab; CAPOX, capecitabine plus oxaliplatin; CX, cisplatin plus capecitabine; FOLFOX, fluorouracil plus oxaliplatin.

cape-ram. More cape-ram patients experienced grade 3 AEs, but no new safety signals were identified.

The optimal duration of first-line chemotherapy for advanced OGA remains uncertain. Whereas some institutions have regarded maintenance therapy with fluoropyrimidine to be a standard of care, this has not been advocated in national/international guidelines for HER2-negative advanced OGA from ESMO (including pan-Asian adapted),[13,14] the US National Comprehensive Cancer Network,[15] the Japanese Gastric Cancer Treatment Guideline,[16] the Chinese Society of Clinical Oncology,[17] and German, Austrian, and Swiss guidelines for systemic treatment of gastric cancer[18] because of lack of randomized trial evidence to support routine use of maintenance therapy in improving OS. In a phase III randomized trial of 320 patients with advanced gastric or GEJ adenocarcinoma evaluating paclitaxel/capecitabine followed by capecitabine maintenance versus six cycles of cisplatin plus capecitabine, there were no OS or PFS differences between the two treatment groups.[19] Furthermore, a Korean randomized trial of continuing S-1 plus oxaliplatin (SOX) versus complete treatment break/stop and go after six cycles of induction SOX showed no OS differences but a significant, more favorable toxicity profile and improved quality of life in the stop-and-go arm.[20] Another recent German AIO MATEO trial showed S-1 maintenance to be noninferior to continuing platinum-based chemotherapy after 12 weeks of induction.[21] Taking the Korean and German studies together, it would corroborate with the phase III trial showing no OS benefit with maintenance fluoropyrimidine compared with stopping after 4-6 months of first-line chemotherapy.

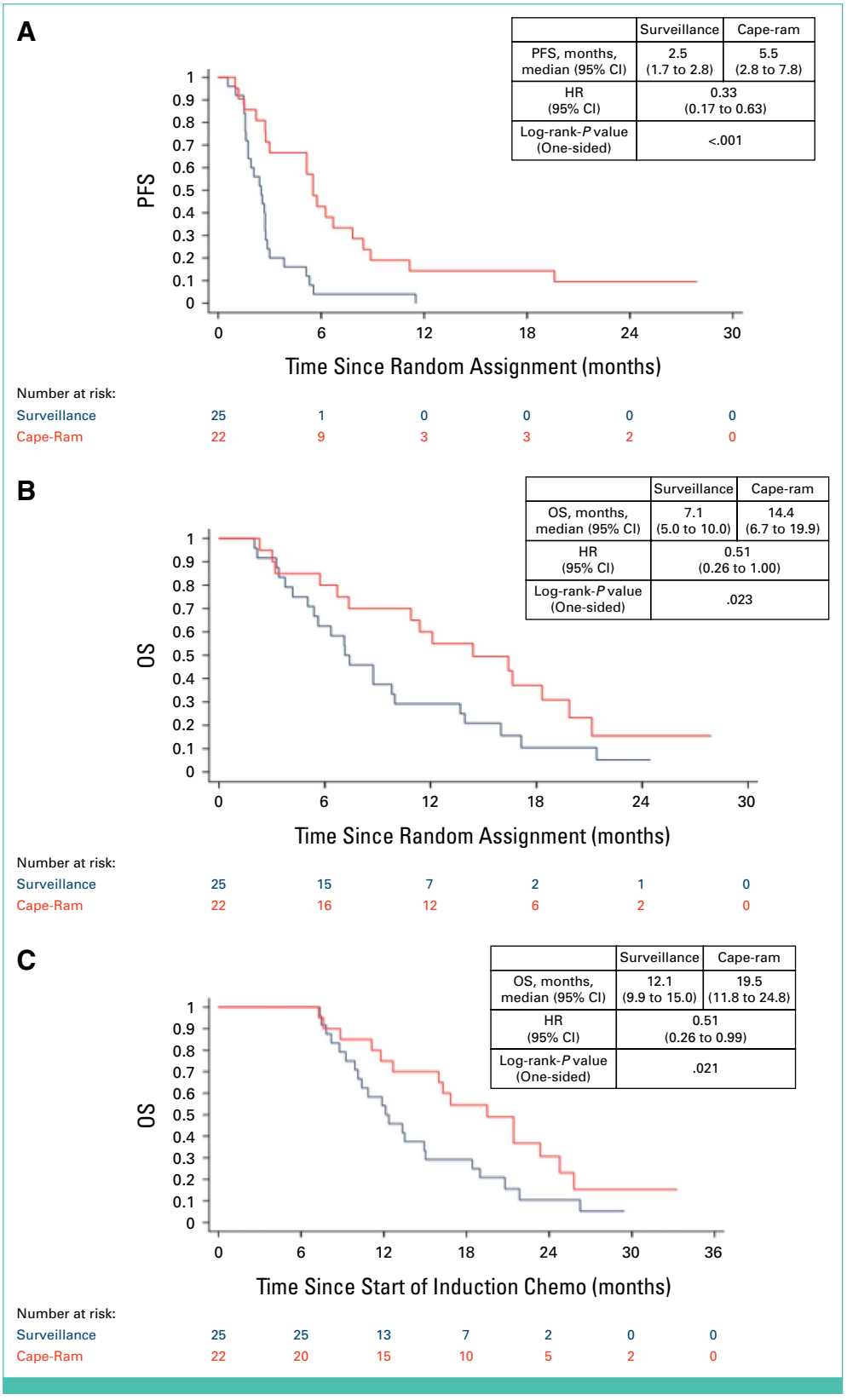

FIG 2. Survival outcomes in the intention-to-treat population. (A) PFS, (B) OS from random assignment, (C) OS from start of induction chemotherapy. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

TABLE 2. Postprogression Therapy

Postprogression Therapy	Surveillance (n = 25), No. (%)	Cape-Ram (n = 21), No. (%)
Number of patients having second/third/fourth-line chemotherapy	7 (28)	7 (33)
Number of patients having third/fourth-line chemotherapy	6 (24)	1 (5)
Number of patients having fourth-line chemotherapy	2 (8)	0 (0)
Chemotherapy drugs received[a]	n = 7	n = 7
Fluorouracil	3 (43)	1 (14)
Capecitabine	0 (0)	2 (29)
Oxaliplatin	1 (14)	1 (14)
Cisplatin	0 (0)	1 (14)
Irinotecan	2 (29)	1 (14)
Paclitaxel	4 (57)	1 (14)
Docetaxel	1 (14)	3 (43)
Trifluridine/tipiracil	1 (14)	0 (0)

Abbreviation: cape-ram, capecitabine plus ramucirumab.
[a]Patients can have received multiple drugs.

TABLE 3. AEs in the Safety Population

	Surveillance (n = 25)		Cape-Ram (n = 21)	
Adverse Event	Any Grade, No. (%)	Grade ≥3, No. (%)	Any Grade, No. (%)	Grade ≥3, No. (%)
Any AE	25 (100)	8 (32)	21 (100)	12 (57)
Any AE related to cape-ram	—	—	20 (95)	6 (29)
Any serious AE	3 (12)	2 (8)	4 (19)a	3(14)
Any serious AE related to cape-ram	—	—	1 (4)	1(4)
AEs in ≥10% of patients in any arm				
Anemia	5 (20)	0 (0)	6 (29)	2 (10)
Anorexia	6 (24)	0(0)	6 (29)	1 (5)
Anxiety	5 (20)	0 (0)	3 (14)	0 (0)
Constipation	3 (12)	0 (0)	10 (48)	0 (0)
Cough	3 (12)	0 (0)	7 (33)	0 (0)
Diarrhea	4 (16)	0 (0)	4 (19)	0 (0)
Dizziness	5 (20)	0 (0)	2 (10)	0 (0)
Dysphagia	7 (28)	1 (4)	5 (24)	1 (5)
Fatigue	11 (44)	0 (0)	14 (67)	2 (10)
Hand-foot syndrome	2 (8)	0 (0)	13 (62)	1 (5)
Hypertension	3 (12)	0 (0)	10 (48)	4 (19)
Hypoalbuminemia	3 (12)	0 (0)	6 (29)	0 (0)
Insomnia	2 (8)	0 (0)	5 (24)	0 (0)
Mucositis	1 (4)	0 (0)	5 (24)	0 (0)
Nausea	8 (32)	0 (0)	10 (48)	0 (0)
Neutropenia	—	0 (0)	5 (24)	0 (0)
Pain	11 (44)	1 (4)	12 (58)	2 (10)
Peripheral sensory neuropathy	16 (64)	0 (0)	11 (52)	0 (0)
Reflux	5 (20)	0 (0)	4 (19)	0 (0)
Thrombocytopenia	1 (4)	0 (0)	7 (33)	0 (0)
Vomiting	5 (20)	1 (4)	7 (33)	0 (0)

Abbreviations: AE, adverse event; cape-ram, capecitabine plus ramucirumab.
[a]Multiple events per patient may occur.

In contemporaneous global phase III trials for advanced OGA with checkpoint inhibitors and zolbetuximab, the protocol recommended continuing checkpoint inhibitors/zolbetuximab after stopping platinum-compound and fluoropyrimidines may continue. However, data on actual maintenance therapy are lacking in their respective publications.[8,22-24] The median duration of fluoropyrimidine treatment only ranged from 4.6 months to 5.8 months.[8,22,24] For example, in the KEYNOTE 859 study, the median duration of therapy was only 5.6 months and 76% of patient population discontinued pembrolizumab/placebo after stopping capecitabine plus oxaliplatin.[23] This suggested relatively few patients received any maintenance therapy globally even within the context of randomized registrational clinical trials. Published real-world evidence to support maintenance fluoropyrimidine therapy being routinely given globally is also challenging to identify. Among 3,052 patients with advanced OGA treated in the United States between 2011 and 2018, the median duration of first-line therapy was only 2.1 months.[25] Another study of 3,291 US patients also found the median duration of first-line therapy to be 2.2 months.[26] Both US real-world treatment pattern studies suggested little maintenance therapy was given in the community in the United States, perhaps outside selected academic institutions.

Although the addition of ramucirumab to cisplatin plus fluoropyrimidine did not prolong OS in the first-line setting, ramucirumab monotherapy or in combination with paclitaxel (pac-ram) are established second-line standard-of-care options. [9-11] However, only 40%-50% of patients with advanced OGA reach second-line therapy. Our results suggest that repositioning ramucirumab as a maintenance therapy could expand the population who could benefit from this agent and be a key step to maximizing its efficacy in this tumor type. The adaptive design of our cape-ram arm within the PLATFORM study predated the reporting of the RAINFALL study[9] and was based on the benefit of maintenance capecitabine plus bevacizumab after first-line therapy in metastatic colorectal cancer. Although exact data of maintenance capecitabine/fluorouracil was not reported in the RAINFALL study, the median duration of 17-19 weeks of fluoropyrimidine and ramucirumab/placebo suggested little maintenance therapy was given in the RAINFALL study; thus, this concept of cape-ram maintenance has not yet been tested until our PLATFORM study.

The phase III ARMANI trial, which evaluated pac-ram as early switch maintenance after 3 months of oxaliplatin-based induction doublet chemotherapy against continuation of chemotherapy followed by fluoropyrimidine maintenance in 280 patients with advanced HER2-negative gastric or GEJ cancers, also significantly prolonged PFS by 3.1 months (HR, 0.64, $P < .001$) and OS by 2.2 months (HR, 0.75, $P = .030$) albeit with significantly higher grade ≥3 trAEs.[27] The purpose of maintenance therapy is to not only sustain disease control but more importantly maintain quality of life and allow recovery from toxicities secondary to platinum-fluoropyrimidine induction chemotherapy, namely peripheral neuropathy and myelosuppression. It seems intuitive that alternating therapies in chemotherapy responders would prolong survival, but early introduction of pac-ram should not come at the cost of maximum benefit from platinum-based induction chemotherapy, increased toxicity, and more frequent hospital visits. Coupled together with the demonstrated survival benefit, the simplicity of cape-ram dosing and minimal grade 3 trAEs in PLATFORM makes maintenance cape-ram an attractive treatment option. Furthermore, all-grade peripheral neuropathy was less frequent in cape-ram than surveillance.

A key limitation to this study was its small sample size. As the fifth and final investigational arm to open, accrual to cape-ram was further limited by recruitment suspension during the COVID-19 pandemic and the evolution of standard-of-care first-line therapy even before its premature closure as a result of withdrawal of industry support. It is also unclear whether the survival benefit is being driven from capecitabine, ramucirumab, or both. The final analysis between maintenance capecitabine versus surveillance arms may address this, but a previous phase III trial did not show survival benefit for maintenance capecitabine.[19] However, the PLATFORM study was designed to allow separate comparisons of each interventional arm against the surveillance control arm[12] and not among experimental arms. Such comparison between experimental arms also would not correct for the noncontemporary recruitment period for each arm.

It is anticipated that the treatment landscape for first-line advanced OGA will diversify with emerging biomarkers such as FGFR2b and Claudin 18.2, highlighting an even greater unmet need for optimizing strategies for the remaining patients.[8,24,28] Our results support the potential benefits of maintenance treatment, with the observed significant PFS and OS improvement from maintenance cape-ram offering a promising treatment option for patients who are ineligible for up-front chemoimmunotherapy or targeted therapies.

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DISCLAIMER

The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

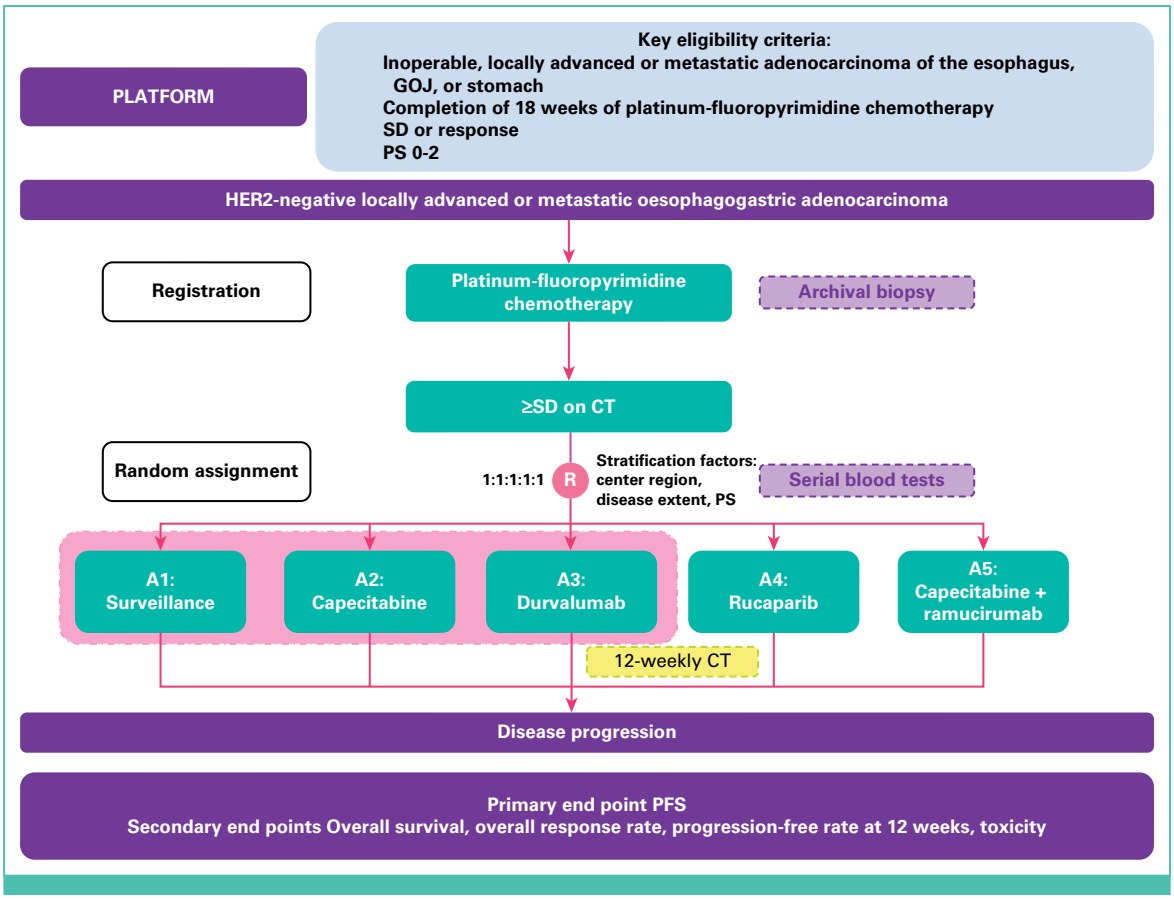

FIG A1. PLATFORM trial design. The initial protocol was used to randomly assign HER2-negative patients 1:1:1 to surveillance, capecitabine, or durvalumab (ringed in pink). Further interventional arms (rucaparib and capecitabine plus ramucirumab) were added in line with the adaptive study design. Each interventional arm is independently assessed against surveillance. CT, computed tomography; GOJ, gastroesophageal junction; HER2, human epidermal growth factor receptor; PFS, progression-free survival; PS, performance status; SD, stable disease.