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RESEARCH ARTICLE

Optimal duration of first-line chemotherapy for advanced gastric cancer: data from the AGAMENON registry

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Abstract

Background The optimal duration of first-line chemotherapy for patients with advanced gastric cancer is unknown. Diverse clinical trials have proposed different strategies including limited treatment, maintenance of some drugs, or treatment until progression.

Method The sample comprises patients from the AGAMENON multicenter registry without progression after second evaluation of response. The objective was to explore the optimal duration of first-line chemotherapy. A frailty multi-state model was conducted.

Results 415 patients were divided into three strata: discontinuation of platinum and maintenance with fluoropyrimidine until progression (30%, $n=123$), complete treatment withdrawal prior to progression (52%, $n=216$), and full treatment until progression (18%, $n=76$). The hazard of tumor progression decreased by 19% per month with the full treatment regimen. However, we found no evidence that fluoropyrimidine maintenance (hazard ratio [HR] 1.07, confidence interval [CI] 95%, 0.69–1.65) worsened progression-free survival (PFS) with respect to treatment until progression. Predictive factors for PFS were ECOG performance status, ≥3 metastatic sites, prior tumor response, and bone metastases. Toxicity grade 3/4 was more common in those who continued the full treatment until progression vs fluoropyrimidine maintenance (16% vs 6%).

Conclusion The longer duration of the full initial regimen exerted a protective effect on the patients of this registry. Platinum discontinuation followed by fluoropyrimidine maintenance yields comparable efficacy to treatment up to PD, with a lower rate of serious adverse events.

Keywords Advanced gastric cancer · AGAMENON · Treatment duration · Maintenance · Multi-state

Introduction

Advanced gastric cancer (AGC) is an incurable tumor with a median overall survival (OS) of less than 12 months [1, 2]. After more than 3 decades of research, several standard, active regimens have been developed for first-line treatment [3]. In tumors that overexpress or amplify *human epidermal growth receptor 2* (HER2), standard treatment is based on the ToGA trial protocol, with six cycles of cisplatin-fluoropyrimidine plus trastuzumab until progression or toxicity [4, 5]. However, we have yet to know the benefit of maintenance treatment with trastuzumab, as the study did not contemplate an arm that included chemotherapy plus trastuzumab for only six cycles.

In HER2-negative AGC, standard management consists of platinum–fluoropyrimidine doublets, to which docetaxel or anthracyclines can be added [3]. However, to date, there has been no phase III trial to establish the optimal duration of this therapy. Thus, some have proposed treatment until progression or toxicity [6–8]. Others have chosen to suspend the entire treatment regimen after a predefined number of cycles; for example, the AVAGAST trial administered six cycles of chemotherapy in the control arm [9], while eight

Members of "the AGAMENON Study Group" are listed in acknowledgement section.

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cycles were administered in the REAL-2 trial, that compared different anthracycline-, platinum-, and fluoropyrimidine-based triplets [10].

Likewise, it is unclear at present whether maintenance strategies of one or various drugs can be safely integrated into the continuum of care and how they impact efficacy [11–14]. Maintenance seeks to prolong survival by delaying tumor progression through the use of agents having low toxicity. Some trials have proposed discontinuing the platinum after a fixed number of cycles and continuing with fluoropyrimidine [15, 16]. However, to date, only one randomized study has been published that has evaluated this option, with a limited sample size [17]. Finally, both the intermittent therapy and the stop-and-go strategy, widely studied and used in various types of neoplasms [18, 19] have limited data on AGC [20].

As a result, international AGC clinical practice guidelines do not mention optimal treatment duration (predefined number of cycles, maintenance therapy, and treatment until progression) [21, 22]. It is unknown, how these uncertainties are projected in the real world, in contexts in which multiple criteria or circumstances affect management decisions. With this background, we have used the data from a national AGC registry to assess how decisions are confronted and what criteria are followed with respect to treatment duration.

Methods

Participants and study design

The patients are from the AGAMENON registry, in which 31 Spanish centers and one Chilean center participate. It is an observational study whose design, methodology, and validity considerations have been reported elsewhere [23–29]. The information is registered using a computerized system with filters that control for inconsistencies, errors, and missing data. The data are regularly monitored by phone or online. The eligibility criteria include: adults (≥ 18 years) with a histologically confirmed adenocarcinoma of the stomach, gastroesophageal junction, or distal esophagus. The tumor must present metastases or be unresectable and the subject must have received at least one cycle of polychemotherapy (containing at least platinum and fluoropyrimidine) for advanced disease. AGAMENON excludes subjects who received perioperative chemotherapy in the 6 months prior to initiating treatment for advanced disease. For this analysis, patients were required to have had at least two scheduled evaluations of tumor response by computed tomography (CT), without evidence of progression on any of them. The participants had to have received treatment at least until the date of the second CT scan.

The study was approved by a multicenter Research Ethics Committee. All patients still alive at the time of data collection provided signed, informed consent in writing.

Definition of variables and clinical endpoints

The hypothesis-generating exploratory objectives of this study were to describe the pattern of management, treatment decision criteria, prognostic factors, safety and PFS in each stratum. Participants were distributed into three strata according to the following definitions: *stratum 1* discontinuation of platinum followed by maintenance with fluoropyrimidine until progression in the case of two-agent regimens, to which a third drug (docetaxel or epirubicin) can be added in case of a triple-agent regimen; *stratum 2* withdrawal of all chemotherapy prior to progression once the number of cycles initially scheduled have been completed, or after development of toxicity, and *stratum 3* treatment without modification until progressive disease (PD). In HER2-positive tumors, each group was defined by the backbone of chemotherapy, regardless of whether trastuzumab was continued until progression. Tumor response was assessed by the researchers, according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The endpoints (efficacy and tolerance) were estimated from two time points: (1) initiation of chemotherapy, and (2) the time of the second CT scan to assess tumor response, in both cases until the end of first-line therapy. The interest in attempting to model the outcomes from two perspectives is to formulate a situation that resembles real clinical practice, where decisions are often made after assessing tumor response. In this study, progression-free survival (PFS) denoted the time elapsed between the start of chemotherapy and tumor progression or all-cause mortality, censoring patients lost to follow-up. OS was specified from the same time points until all-cause mortality. Toxicity was classified according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0 [30].

Potential confounding factors were chosen using the criteria that were common (> 5%), had been associated to AGC prognosis in previous studies [26], and were easily accessible. They included: Eastern Cooperative Oncology Group Performance Status (ECOG-PS), differentiation grade (1 vs others), ascites, number of metastatic sites, bone metastases, Lauren subtype, HER2 status, RECIST criteria on second tumor response assessment, and time to second CT. Both Lauren histopathological classification and HER2 immunohistochemistry were locally examined according to clinical practice.

Dose intensity (DI) was defined as the amount of drug administered per unit of time, expressed as mg/m^2 per week. Cumulative dose denoted total dose and was reported as total mg/m^2 administered. The relative dose intensity (RDI) was

the DI actually administered with respect to the dose intensity planned for each scheme.

Statistics

Exposures to therapy modifications (e.g., from initiation to cessation of drugs, and from that point to progression or death) were analyzed as time-dependent variables in the framework a multi-state model [31, 32] (see Fig. 4 in "Appendix"). This method was used to estimate PFS/OS rates by the Aalen–Johansen estimator. An exploratory mixed-effects Cox model was conducted to take into account correlated random effects (shared frailties) and the possible influence of unobserved covariates when the therapeutic modifications were made. The covariates were chosen theoretically; no data-driven methods were used here. These analyses were performed with RStudio (RStudio, Inc., Boston, MA, USA), including the survival, coxme, mstate, and etm software packages [32–35]. No formal estimation of sample size was made, given that it is a hypothesis-generating study, in a relatively unexplored situation.

Results

Patients and decisions

We analyzed 415 patients treated between January 2008 and September 2017, who met the eligibility criteria of this study (≈20% of the full database). The selection details are illustrated in the flow chart (Fig. 1). Baseline characteristics are presented in Table 1. Participants were distributed into three strata (see definition above in "Methods"): 30% ($n=123$) discontinued platinum and continued fluoropyrimidine (stratum 1); 52% ($n=216$) suspended the entire treatment regimen (stratum 2), and 18% ($n=76$) continued until PD/unacceptable toxicity (stratum 3). The median treatment duration was superior in the stratum that suspended platinum vs the others (11.5 vs 5 months, $P<0.001$). The change in strategies was made after a median of 6 and 5.6 months (since treatment initiation) in stratum 1 and 2, respectively.

The schedules, cycles, and doses adopted are shown in Tables 3 and 4 in "Appendix". In stratum 1 (discontinued platinum prior to PD), 25% (31/123) of the patients had received a three-agent regimen; in such cases, epirubicin and docetaxel were withdrawn together with the platinum in 77% (20/26) and 40% (2/5), respectively (the number of cycles after the second CT is detailed in Fig. 5 in "Appendix"). Of the 92 patients treated with trastuzumab, this drug was continued until PD in 60% ($n=55$). A "stop & go" strategy or second line, respectively, was administered to 5% and 63% of the participants in stratum 1, and in 16% and 52% of the subjects in stratum 2. In stratum 3, 55% of the individuals received second-line therapy.

At the time of analysis (January 2018), 75% had died ($n=310$) and 336 progression events (81%) had occurred. The second CT was performed after a median of 5.2 months in the entire cohort, slightly later (5.6 months) in subjects in whom only platinum was suspended (stratum 1). Median PFS and OS of the series were 10.6 months (95% confidence interval [CI] 10.0–11.4) and 18.9 months (95% CI 17.7–20.9), respectively. Median follow-up (since beginning of chemotherapy) among those still alive was 13.1 months.

Factors influencing modifications

Considering the full cohort, the reasons alleged for modifying therapies were: end of scheduled treatment (60%), toxicity (19%), clinical decline (15%), patient refusal (3%), and others (3%). The rationale changed depending on the stratum (Figs. 6 and 7 in "Appendix"). Toxicity was the most relevant reason for discontinuation of platinum prior to PD vs the rest (42% vs 9%, $P<0.001$). End of scheduled treatment was the most common alleged reason in those who discontinued all chemotherapy prior to PD vs the rest (73% vs 35%, $P<0.001$), and finally, in patients treated until PD, clinical decline occurred more commonly than in the rest (49% vs 7%, $P<0.001$). Decision-making was also differentially associated with the scheme (e.g., chemotherapy was completely discontinued prior to PD in 78% of the docetaxel schemes, but in only 42% of the oxaliplatin-containing dual-agent schedules, $P<0.001$) (Fig. 5 in "Appendix"). Furthermore, a different pattern of decisions was observed for each platinum; e.g., oxaliplatin was suspended after a median of 24 weeks (12 biweekly cycles), whereas cisplatin was suspended after a median of 18 weeks (6 tri-weekly cycles) (Table 4 in "Appendix"). In contrast, administering trastuzumab did not substantially change the decisions (Fig. 7 in "Appendix"). The toxicity profile did influence modifications (see following).

Safety

Considering toxicity since beginning of treatment, the stratum that continued until PD consisted of patients who tolerated chemotherapy better than the rest (e.g., any grade diarrhea, 34% vs 49% in the other two strata, $P=0.023$, with a similar trend for stomatitis or neuropathy). Similarly, platinum-specific toxicities (e.g., neuropathy, kidney disease, or thrombopenia) were more common in the group that withdrew platinum (Fig. 9 in "Appendix").

Toxicity was then examined since the second CT (Fig. 2). From this perspective, adverse events grade 3/4 were common in those who continued the complete

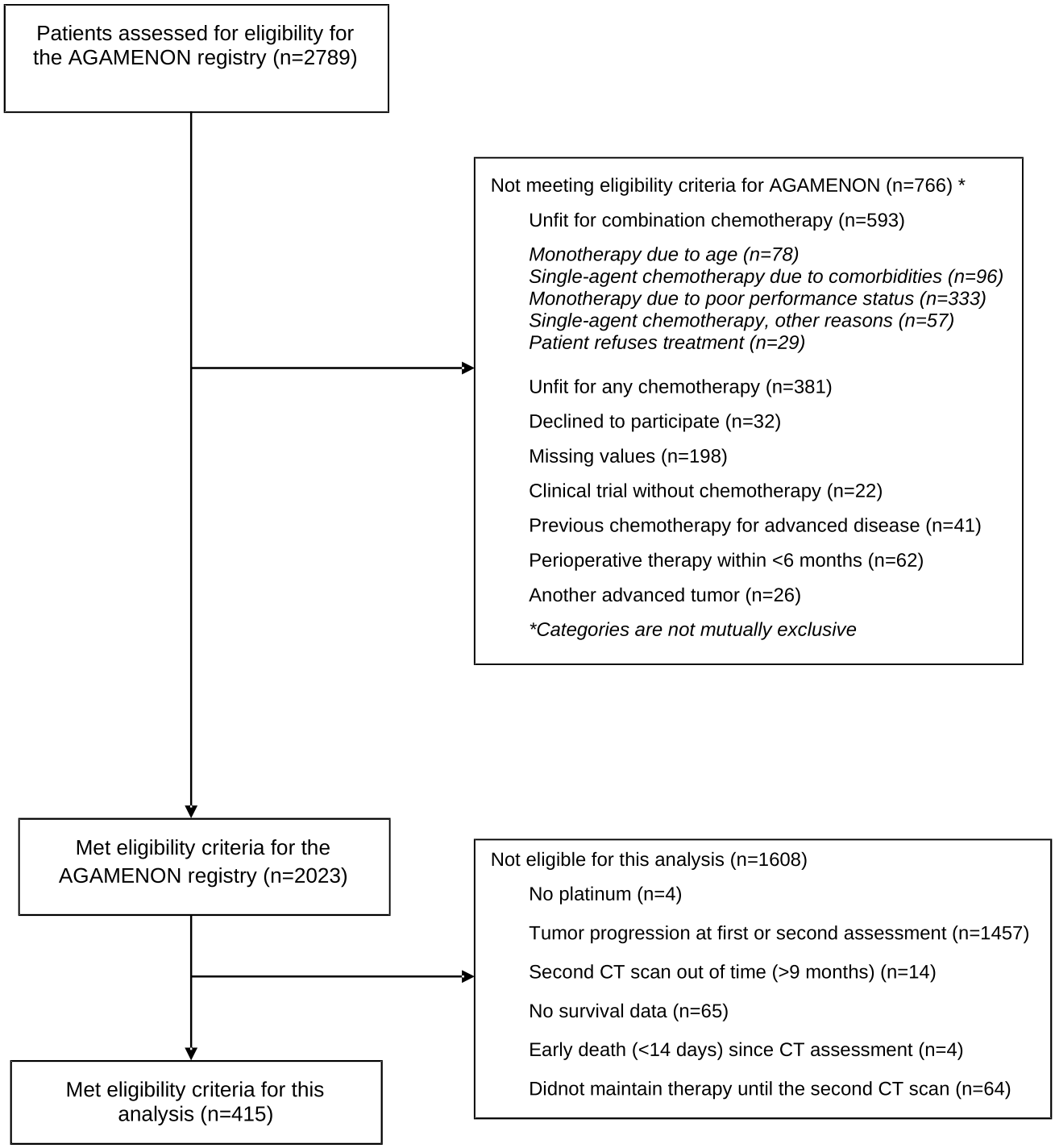

Fig. 1 Flowchart of the patient selection process

treatment for longer: 16% vs 6%, odds ratio 2.86 (95% CI 1.06–7.74), $P = 0.018$.

Table 4 in "Appendix" displays the dosages administered. The data do not corroborate a change in DI or RDI as accounting for the apparent lack of differences between strata.

Effect of regimen modifications

At 12 months from the start of chemotherapy, PFS rates in HER2-positive subjects were 43% (95% CI 22.5–58.7) among patients who discontinued the platinum (stratum 1), 38.1% (95% CI 22.2–50.8) in those who suspended everything (stratum 2), and 44.5% (95% CI 33.3–53.9) among

Table 1 Baseline patient characteristics and management in each stratum

Characteristics	All ($n=415$) *N* (%)	Platinum discontinuation prior to PD ($n=123$) *N* (%)	Discontinuation of all chemotherapy prior to PD ($n=216$) *N* (%)	Treatment until PD ($n=76$) *N* (%)	*P* value
Age, median (range)	63 (22–89)	66 (22–86)	61 (22–86)	67 (38–89)	0.018
Sex, male	304 (73)	93 (76)	157 (73)	54 (71)	0.757
ECOG-PS, < 2	393 (95)	117 (95)	205 (95)	71 (93)	0.838
Primary tumor site					0.307
Distal esophagus	34 (8)	7 (6)	18 (8)	9 (12)	
Gastroesophageal junction	53 (12)	20 (16)	27 (13)	6 (8)	
Stomach	328 (79)	96 (78)	171 (79)	61 (80)	
Histological grade					0.590
Grade 1	57 (15)	18 (15)	27 (13)	12 (16)	
Grade 2	139 (38)	47 (38)	66 (31)	26 (34)	
Grade 3	154 (31)	38 (31)	90 (42)	26 (34)	
Not available	65 (16)	20 (16)	33 (15)	12 (16)	
Lauren classification					0.356
Intestinal	242 (58)	78 (63)	121 (56)	43 (57)	
Diffuse	131 (32)	30 (24)	75 (35)	26 (34)	
Unclassified	42 (10)	15 (12)	20 (9)	7 (9)	
HER2 overexpression					0.005
No (IHC 0+, 1+, 2+, and FISH−)	252 (61)	76 (62)	125 (58)	51 (67)	
Yes (IHC 3+)	78 (19)	32 (26)	38 (18)	8 (11)	
Yes (IHC 2+ & FISH+)	30 (7)	7 (6)	14 (6)	9 (12)	
Not available	55 (26)	8 (7)	39 (18)	8 (11)	
Number of metastatic sites, ≥ 3	128 (31)	37 (30)	70 (32)	21 (28)	0.722
Site of metastases					
Liver	193 (46)	61 (50)	95 (44)	37 (49)	0.557
Bone	28 (7)	8 (7)	16 (7)	4 (5)	0.807
Lung	75 (18)	29 (24)	36 (17)	10 (13)	0.132
Peritoneal	142 (34)	40 (33)	80 (37)	22 (29)	0.394
Ascites	76 (18)	26 (21)	38 (18)	12 (16)	0.590
Distant lymph nodes	216 (52)	65 (53)	118 (55)	33 (43)	0.237
Neutrophil–lymphocyte ratio, median (range)	2.8 (0.2–37)	3 (0.2–25.6)	2.8 (0.5–37)	3.1 (0.2–30.1)	0.104
Surgery of primary tumor	263 (63)	40 (33)	89 (41)	23 (30)	0.124
Locally advanced unresectable at start of chemotherapy	19 (5)	3 (2)	12 (6)	4 (5)	
Chemotherapy, triplets	139 (33)	31 (25)	80 (37)	28 (37)	0.067
Drugs					
Anthracyclines	101 (24)	26 (21)	55 (25)	20 (26)	0.608
Cisplatin	158 (38)	41 (33)	92 (43)	25 (33)	0.147
Docetaxel	50 (12)	2 (2)	39 (18)	9 (12)	< 0.001
Other	11 (3)	0	9 (4)	2 (3)	0.071
Oxaliplatin	244 (59)	82 (67)	114 (53)	48 (63)	0.030
Trastuzumab with first-line chemotherapy	92 (22)	33 (27)	45 (21)	14 (18)	0.302
Use of second lines	272 (66)	84 (68)	147 (68)	41 (54)	0.062
Surgery of metastases	40 (10)	10 (8)	22 (10)	8 (11)	0.792
Second tumor response assessment					
Complete response	32 (8)	7 (6)	21 (10)	4 (5)	0.401
Partial response	163 (39)	48 (39)	88 (41)	27 (36)	

Table 1 (continued)

Characteristics	All ($n=415$) *N* (%)	Platinum discontinuation prior to PD ($n=123$) *N* (%)	Discontinuation of all chemotherapy prior to PD ($n=216$) *N* (%)	Treatment until PD ($n=76$) *N* (%)	*P* value
Duration of first-line chemotherapy from the beginning of treatment (median, range) (months)	7.0 (3.0–69.5)	11.5 (5.9–69.5)	5.6 (3.0–14.0)	9.8 (4.5–34.1)	< 0.001
Duration of platinum from the beginning of treatment (median, range) (months)	6.0 (3.03–4.1)	6.0 (4.2–27.6)	5.6 (3.0–14.0)	9.8 (4.5–34.1)	< 0.001
Time from the beginning of chemotherapy to the second response assessment (median, range) (months)	5.2 (2.1–8.8)	5.6 (2.7–7.9)	5.1 (2.3–8.8)	5.2 (2.1–8.8)	0.002

Percentages represent proportions of columns

ECOG-PS Eastern Cooperative Oncology Group Performance Status, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *FISH* fluorescence in situ hybridization, *CT* computerized tomography, *sd* standard deviation, *PD* progressive disease

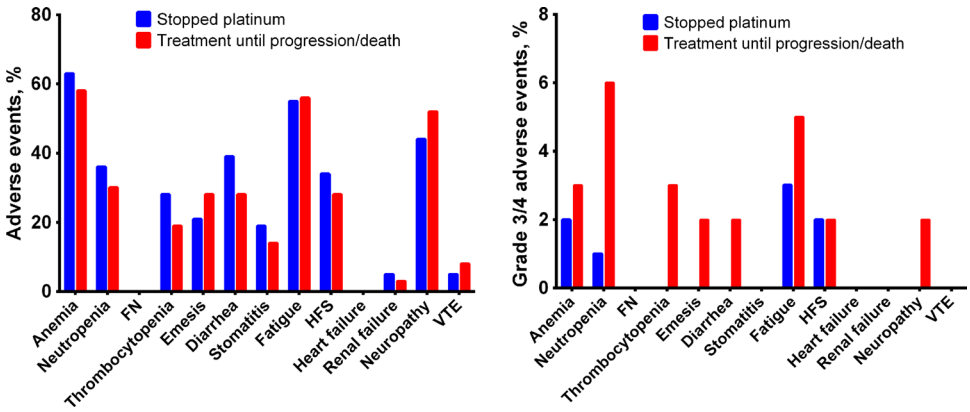

Fig. 2 Adverse events in each stratum (HER2-positive and -negative) after second tumor assessment. *FN* febrile neutropenia, *HFS* hand–foot syndrome, *VTE* venous thromboembolism

individuals treated until progression (stratum 3). In HER2-negative participants, PFS rates at 12 months were 46.6% (95% CI 34.9–56.2) in stratum 1, 30.2 (95% CI 22.7–36.9) in stratum 2, and 37.5% (95% CI 31.9–42.6) in stratum 3. Figure 3 is a graphic representation of these data. In the multivariate model stratified by HER2, the prognostic factors for PFS were ECOG-PS ≥ 2, bone metastases, presence of ≥ 3 metastatic sites and tumor response assessment (see Table 2). With respect to therapy modifications, discontinuing everything was associated with a trend towards decreased PFS (HR 1.15, 95% CI 0.76–1.73, $P=0.490$), while prolonged time to discontinuation (months) correlated with better PFS (HR 0.81, 95% CI 0.66–0.99, $P=0.041$). However, we found no evidence that withdrawing the platinum and continuing with maintenance fluoropyrimidine (HR 1.07, 95% CI 0.69–1.65, $P=0.760$) had any influence on PFS with respect to treating until progression. Complete response was a protective factor after withdrawing the entire regimen (HR 0.31, 95% CI 0.17–0.57) or platinum (HR 0.14, 95% CI 0.04–0.46) (Table 2). No interactions or random effects (frailties) were detected. Likewise, the study did not contradict the supposition that all strata yield the same OS (see Table 5 in "Appendix" and Fig. 3).

Discussion

In this analysis, we have reported the pattern of modifications of first-line chemotherapy for AGC in the AGAMENON registry of real-world data, as well as the multiple criteria that affected decision-making. The reason is that previous studies have posited a wide variety of strategies, from treatment until progression, discontinuation after a predefined number of cycles, maintenance, intermittent, and stop-and-go therapies [4, 6–10, 17, 20]. Each option has a theoretical rationale, but comparative efficacy and safety data, including the possible impact on survival, are still limited [17, 20]. Given this uncertainty, we intended to evaluate how the AGAMENON reporting physicians responded pragmatically to these doubts, what the most common strategies were, and what led them to choose each one.

The rationale for selecting patients based on evidence of non-progression after the second assessment at 6 months

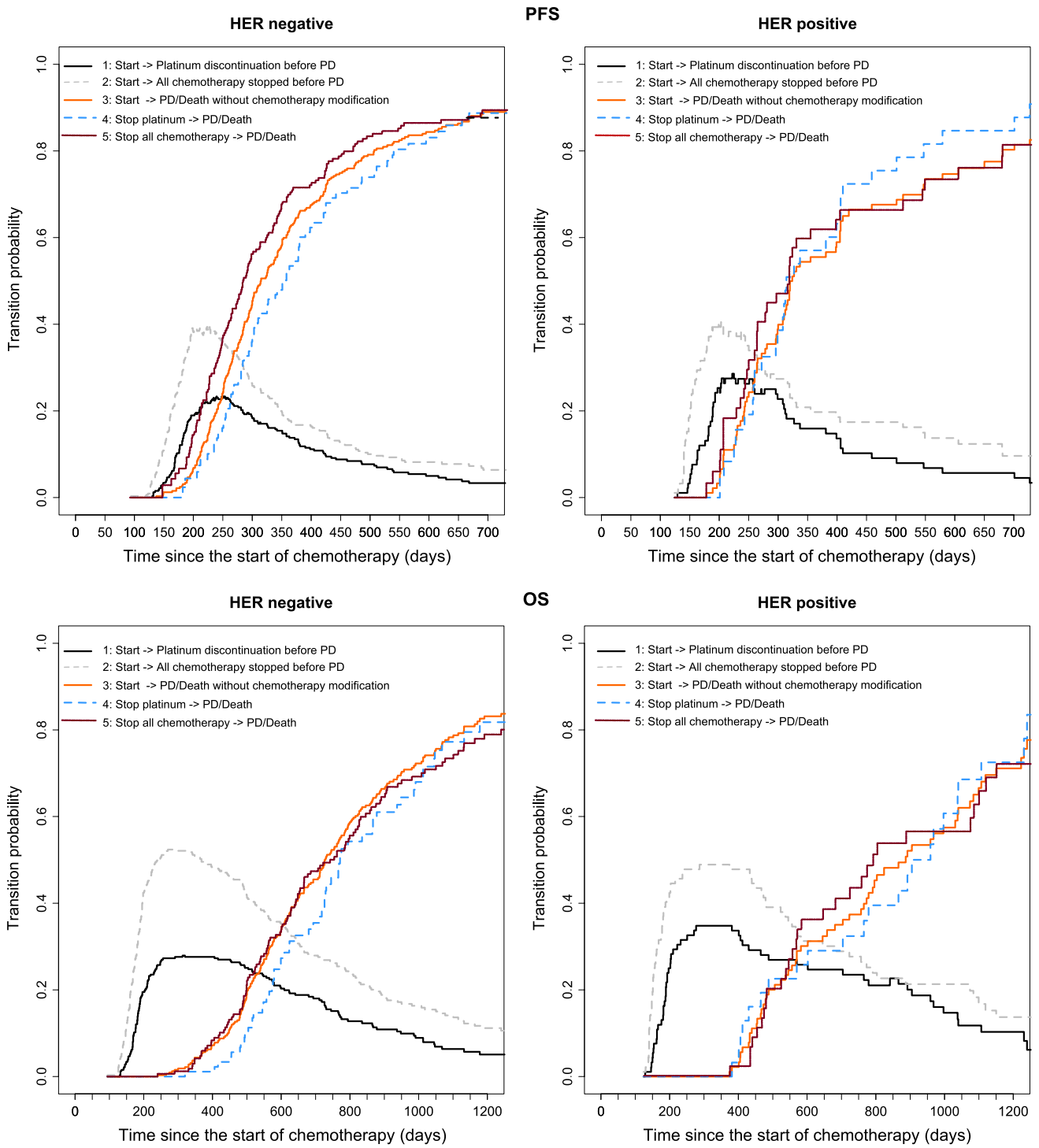

Fig. 3 Aalen–Johansen estimates of all state occupation probabilities according to HER2. A 'clock forward' approach was used since the start of first-line chemotherapy. 4A—the absorbing event is progression or demise (1-PFS) in HER2-negative tumors; 4B—the absorbing event is progression or demise (1-PFS) in HER2-positive tumors; 4C—the absorbing event is demise (1-OS) in HER2-negative tumors, and 4D—the absorbing event is demise (1-OS) in HER2-positive tumors

responds to the objective of approaching how clinical decisions are made in the real world, and understanding what factors influence the criterion of whether or not to maintain treatment in patients with controlled disease. In this sense, to date, our work contains the largest number of Caucasian patients in whom the effect of variation in

Table 2 Frailty multi-state model (for progression-free survival)

	HR (CI, 95%)	*P* value
ECOG-PS, ≥ 2	1.65 (1.12–2.42)	0.010
Grade 1 vs others	0.80 (0.60–1.07)	0.140
Metastatic sites, ≥ 3	1.13 (1.03–1.23)	0.008
Bone metastases	1.58 (1.09–2.28)	0.014
RECIST (start → platinum discontinuation before PD)		
SD	Ref	–
CR	0.14 (0.04–0.46)	0.001
PR	0.65 (0.43–0.99)	0.046
RECIST (start → all chemotherapy stopped before PD)		
SD	Ref	–
CR	0.31 (0.17–0.57)	< 0.001
PR	0.86 (0.62–1.18)	0.360
Ascites	0.93 (0.73–1.18)	0.570
Therapy modifications		
Treatment to progression	Ref	–
Platinum discontinuation before PD	1.07 (0.69–1.65)	0.760
All chemotherapy stopped before PD	1.15 (0.76–1.73)	0.490
Time to platinum discontinuation	1.00 (0.90–1.12)	0.880
Time to full treatment discontinuation	0.81 (0.66–0.99)	0.048
Time of second tumor response assessment	0.90 (0.81–1.00)	0.054

Time, discontinuation, or second CT are measured in months. The covariates, bone metastasis, number of metastatic sites and ECOG-PS have a fixed effect on all the transitions. RECIST is a transition-specific variable. The model was stratified by type of transition and HER2 status

ECOG-PS Eastern Cooperative Oncology Group Performance Status, *HER2* human epidermal growth factor receptor 2, *SD* stable disease, *CR* complete response, *PR* partial response, *PD* progressive disease, *HR* hazard ratio, *Ref.* reference, *NA* not available

duration of chemotherapy in this scenario has been retrospectively analyzed.

In this registry, the most widely alleged reason for suspending all treatment was the preplanned decision as to the maximum number of cycles. Thus, in 70% of the cases, the cause for concluding first-line treatment before PD was the center's management protocol and not the emergence of adverse effects. In contrast, discontinuation of platinum, leaving fluoropyrimidines as maintenance therapy, was due to the specific toxicities of these drugs in 44% of the cases, or because of the patient's clinical decline, and only half of the cases obeyed a predetermined decision in the local protocol.

The difference in the pattern of decisions is especially clear when evaluating the decisions based on the type of platinum. For example, in 67% of the patients on fluoropyrimidine maintenance, the reason adduced for suspending oxaliplatin was dose-limiting toxicity (mainly neuropathy), whereas in cisplatin doublets, it was having completed the predefined treatment in 75%. Moreover, the type of initial regimen also played a role, such that schemes with docetaxel tended to be stopped altogether, while the reasons were more equally distributed in oxaliplatin-containing doublets.

We have not observed significant differences in survival-related endpoints on the basis of the decision made after the second CT scan (continue all treatment, scaling back, and total withdrawal), nor that said differences depended on HER2 status. However, the data are consistent with an increased risk of progression of up to 73% (if not yet progressed) for subjects who discontinued all therapy prior to PD, and in fact, the total duration of the full course of treatment exerted a protective effect on this registry and correlated with better PFS. On the other hand, platinum suspension and continuation with fluoropyrimidine maintenance showed comparable efficacy to treatment up to PD, but was associated with a lower rate of serious adverse events.

A striking aspect is the percentage of HER2-positive subjects who did not maintain trastuzumab until progression (around 40% of those who started this therapy), despite the fact that this was a situation with a defined standard. Therefore, in essence, our results are consistent with the findings of two randomized studies conducted in Asian populations in which treatment discontinuation and stop-and-go strategies were compared with continuing therapy [20], or the use of maintenance fluoropyrimidines in monotherapy [17]. Neither study revealed significant differences in OS between the different groups, although it is true that these analyses

did not stratify samples based on HER2 status, which could be seen as a limitation in interpreting results.

On the basis of our results, high tumor burden (number of metastatic sites ≥ 3) was the adverse prognostic factor for all three strata, consistent to what Park et al. observed [20] when they reported that the subgroup with high lactate dehydrogenase (LDH) benefitted most from continuing treatment with S1 and oxaliplatin. In our study, patients in complete response ($n = 32$) had an apparently better prognosis when all or part of treatment was withdrawn. Other authors have suggested that normal levels of hemoglobin (≥ 12 g/L), a well-known predictive factor for response, are associated with a considerable benefit from UFT maintenance therapy [17, 36].

On the other hand, it must be remembered that the model proposed here is a proxy that has tried to address a situation that is analogous to real-world conditions when decisions must be made about treatment duration and whether to maintain or suspend it after a certain number of cycles. In this model, the overall rate of adverse events was not the most relevant factor in the decision made, but rather platinum-specific toxicities (neurotoxicity, kidney failure, or cardiopathy), which often led to regimen modifications. Nonetheless, it is important to point out that, later (after the second CT), toxicity grade 3/4 among those in whom the platinum was stopped was markedly lower than in those who continued with the full regimen, and without compromising the efficacy of the schemes.

We acknowledge several limitations to our study. It should be noted that most of the data come from the period prior to the use of ramucirumab in the second line, which adds uncertainty to the conclusions. In addition, patients without progression at 6 months were not numerous (limiting the sample size). The reader must be therefore aware that "absence of evidence is not evidence of absence". The registry compiles cases ambispectively, with the inherent accuracy limitations this entails, although the treatment schemes and endpoints are generally properly recorded in the clinical histories available at all the centers. In addition, a multitude of criteria are expected to affect late-stage treatment decisions, these can be taken in heterogeneous conditions (frailties), there may be interferences by toxicities, and the peculiarities of each particular regimen must also be taken into account.

Although there is no statistical evidence of subgroup effects, maintaining therapy in patients with good functional status, but unfavourable prognostic factors, may be considered a reasonable hypothesis for future studies in a scenario where it is not clear, generically, how long we should treat patients. In the meantime, we believe that treatment should be carried out according to the recommendations of the studies that endorse each combination. Bearing in mind that the most common regimens contain platinum/fluoropyrimidine, the recommendation would be for 4–6 months [4, 10], maintaining trastuzumab in the case of HER2-positive tumors.

In short, the time with full treatment regimen had a protective effect on PFS. However, the time to platinum suspension did have a significant effect. In addition, fluoropyrimidine maintenance reduced serious adverse events, as opposed to treating with everything up to PD. The selection criteria to be considered in future studies in which stopping chemotherapy are being evaluated, could be low tumor burden, the absence of bone involvement, and complete response to treatment (See Tables 3, 4, and 5. See Figs. 4, 5, 6, 7, 8, and 9).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and subsequent versions.

Informed consent Informed consent or a substitute for it was obtained from all patients before they were included in the study.

Appendix

See Tables 3, 4 and 5. See Figs. 4, 5, 6, 7, 8 and 9.

Table 3 Regimens used in each stratum

Regimen	Discontinuation platinum prior to PD ($n=123$)	Discontinuation of all chemotherapy prior to PD ($n=216$)	Treatment until PD ($n=76$)
DC docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 every 3 weeks	0	15 (6.9%)	1 (1.3%)
DCF3w docetaxel 60 mg/m^2 on day 1 + Cisplatin 60 mg/m^2 on day 1 + 5-fluorouracil (FU) 750 mg/m^2 continuous infusion over 24 h daily on days 1–4 every 3 weeks	1 (0.8%)	10 (4.6%)	2 (2.6%)
DCF4W: docetaxel 75 mg/m2 on day 1 + cisplatin 75 mg/m2 on day 1 + FU 1000 mg/m2 continuous infusion (CI) over 24 hours daily on days 1-5 every 4 weeks	0	2 (0.9%)	0
DCX docetaxel 75 mg/m^2 on day 1 + cisplatin 75 mg/m^2 on day 1 + capecitabine 750 mg/m^2/12 h on days 1–14 every 3 weeks	1 (0.8%)	8 (3.7%)	2 (2.6%)
DOX docetaxel 75 mg/m^2 on day 1 + oxaliplatin 100 mg/m^2 on day 1 + capecitabine 750 mg/m^2/12 h on days 1–14 every 3 weeks	0	3 (1.3%)	2 (2.6%)
ECF epirubicin 50 mg/m^2 on day 1 + cisplatin 60 mg/m^2 on day 1 + FU 200 mg/m^2 CI daily every 3 weeks	1 (0.8%)	4 (1.8)	1 (1.3%)
ECX epirubicin 50 mg/m^2 on day 1 + Cisplatin 60 mg/m^2 on day 1 + capecitabine 750 mg/m^2/12 h daily every 3 weeks	2 (1.6%)	3 (1.3%)	2 (2.6%)
EOF epirubicin 50 mg/m^2 on day 1 + Oxaliplatin 130 mg/m^2 on day 1 + FU 200 mg/m^2 CI daily every 3 weeks	0	2 (0.9%)	0
EOX epirubicin 50 mg/m^2 on day 1 + Oxaliplatin 130 mg/m^2 on day 1 + capecitabine 750 mg/m^2/12 h daily every 3 weeks	23 (18.6%)	46 (21.2%)	17 (22.3%)
FLO (FU CI, leucovorin, oxaliplatin) Oxaliplatin 85 mg/m^2 on day 1 + leucovorin 200 mg/m^2 on day 1 + FU 2600 mg/m^2 CI over 46 h every 2 weeks	0	1 (0.4%)	0
FLOT oxaliplatin 85 mg/m^2 on day 1 + leucovorin 200 mg/m^2 on day 1 + FU 2600 mg/m^2 CI over 46 h + docetaxel 50 mg/m^2 on day 1 every 2 weeks	0	0	1 (1.3%)
Modified FOLFOX-6 oxaliplatin 85 mg/m^2 on day 1 + leucovorin 400 mg/m^2 on day 1 + FU 400 mg/m^2 on day 1 + FU 2400 mg/m^2 CI over 46 h every 2 weeks	20 (16.2%)	32 (14.8%)	7 (9.2%)
XP cisplatin 80 mg/m^2 on day 1 + capecitabine 1000 mg/m^2/12 h on days 1–24 every 3 weeks	28 (22.7%)	33 (15.2%)	16 (21.0%)
Modified, biweekly CAPOX oxaliplatin 85 mg/m^2 on day 1 + capecitabine 625 mg/m^2/12 h daily every 2 weeks	4 (3.2%)	4 (1.8%)	4 (5.2%)
CAPOX oxaliplatin 130 mg/m^2 on day 1 + capecitabine 1000 mg/m^2/12 h on days 1–14 every 3 weeks	28 (22.7%)	23 (10.6%)	15 (19.7%)
Modified FUOX oxaliplatin 85 mg/m^2 + FU 3000 mg/m^2 CI over 48 h every 2 weeks	4 (3.2%)	2 (0.9%)	1 (1.3%)
FP3w cisplatin 75 mg/m^2 on day 1 + FU 750 mg/m^2 CI over 24 h daily on days 1–5 every 3 weeks	6 (4.8%)	13 (6.0%)	1 (1.3%)
FP4w (FU, cisplatin every 4 weeks) cisplatin 1000 mg/m^2 on day 1 + FU 1000 mg/m^2 CI over 24 h daily on days 1–5 every 4 weeks	1 (0.8%)	3 (1.3%)	0
Other carboplatin, FU	0	6 (2.7%)	1 (1.3%)
Other carboplatin, paclitzaxel	0	3 (1.3%)	1 (1.3%)
Other cisplatin, FU	1 (0.8%)	0	0
Other cisplatin, irinotecan	0	1 (0.4%)	0
Other docetaxel, carboplatin	0	0	1 (1.3%)
Other docetaxel, carboplatin, FU	0	1 (0.4%)	0
Other docetaxel, oxaliplatin, FU	3 (2.4%)	1 (0.4%)	1 (1.3%)

PD progressive disease

Table 4 Doses and additional reasons for discontinuation in each stratum

Doses for	Discontinuation platinum prior to PD ($n=123$)						
	Oxaliplatin, biweekly	Oxaliplatin, tri-weekly	Cisplatin	Epirubicin	Docetaxel	Fluoropy-rimidine, biweekly	Fluoropy-rimidine, tri-weekly
Number of cycles (median, range)	12 (6–16)	6 (4–24)	6 (4–24)	8 (3–12)	9 (6–13)	15 (2–47)	14 (6–61)
Median treatment duration (weeks)	25		23	24	30	–	–
Mean cumulative dose (mg/m^2)	925		512	353	570	–	–
Mean dose/cycle (mg/m^2/cycle)	108		71	48	68	–	–
Mean dose intensity (mg/m^2/week)	37		22	15	22	–	–
Mean, dose density	85%		81%	89%	96%	–	–
Additional reasons for discontinuation							
Toxicity	67%	48%	17%	15%	80%		
Clinical deterioration	8%	0	6%	4%	0		
Treatment completed	21%	48%	75%	73%	20%	–	–
Patient refusal	0	2%	3%	4%	0		
Other	4%	2%	0	4%	0		
Doses for	Treatment until PD ($n=76$)						
	Oxaliplatin, biweekly	Oxaliplatin, tri-weekly	Cisplatin	Epirubicin	Docetaxel	Fluoropy-rimidine, biweekly	Fluoropy-rimidine, tri-weekly
Number of cycles (median, range)	14 (9–59)	8 (5–15)	8 (5–15)	6 (1–20)	8 (1–16)	16 (9–60)	10 (1–51)
Median treatment duration (weeks)	30		25	21	27	–	–
Mean cumulative dose (mg/m^2)	1085		524	312	476	–	–
Mean dose/cycle (mg/m^2/cycle)	107		68	49	66	–	–
Mean dose intensity (mg/m^2/week)	35		21	15	21	–	–
Mean, dose density	82%		80%	89%	89%	–	–
Additional reasons for discontinuation							
Toxicity	25%	5%	0	33%	11%	–	–
Clinical deterioration	50%	16%	29%	28%	56%		
Treatment completed	25%	42%	71%	28%	33%		
Patient refusal	0	0	0	6%	0		
Other	0	3%	0	11%	0		
Doses for	Discontinuation of all chemotherapy prior to PD ($n=216$)						
	Oxaliplatin, biweekly	Oxaliplatin, tri-weekly	Cisplatin	Epirubicin	Docetaxel	Fluoropy-rimidine, biweekly	Fluoropy-rimidine, tri-weekly
Number of cycles (median, range)	12 (6–16)	6 (4–11)	6 (4–11)	6 (2–10)	6 (3–11)	10 (3–16)	6 (1–12)
Median treatment duration (weeks)	–		22	21	21	–	–
Mean cumulative dose (mg/m^2)	–		456	299	432	–	–
Mean dose/cycle (mg/m^2/cycle)	–		70	48	65	–	–
Mean dose intensity (mg/m^2/week)	–		20	14	20	–	–
Mean, dose density	–		80%	85%	84%	–	–
Additional reasons for discontinuation							
Toxicity	11%	4%	8%	9%	15%	–	
Clinical deterioration	5%	9%	14%	5%	5%		
Treatment completed	68%	77%	71%	73%	76%		
Patient refusal	8%	5%	2%	5%	2%		
Other	8%	5%	4%	7%	2%		

PD progressive disease

Table 5 Aalen–Johansen OS estimates, at 2 years, depending on the stratum, and HER2 status

	Her2-negative, % (CI 95%)	Her2-positive, % (CI 95%)
Stratum 1	41.1 (CI 95%, 28.2–51.7)	50.5 (CI 95%, 28.9–65.5)
Stratum 2	44.6 (CI 95%, 25.9–41.2)	46.2 (CI 95%, 28.7–59.4)
Stratum 3	32.9 (CI 95%, 27.0–38.2)	48.0 (CI 95%, 35.9–57.8)

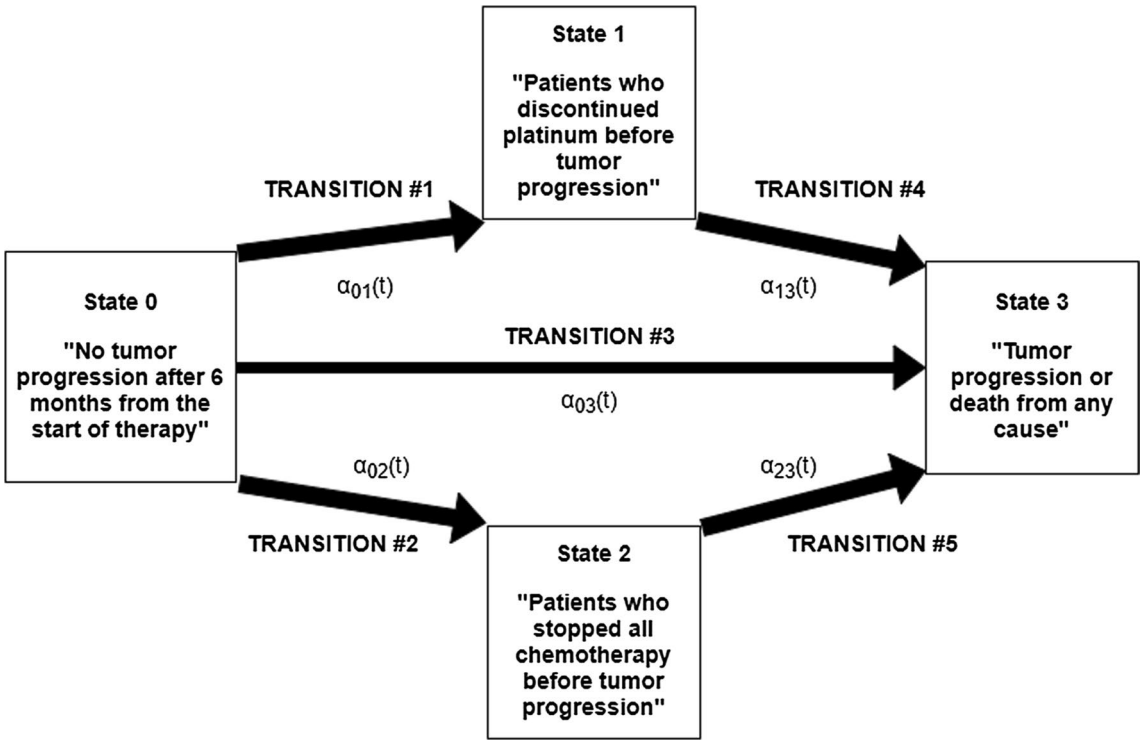

Fig. 4 Illness-death model with two transient states and one absorbing state. In this diagram, each of the four boxes symbolizes a state (three transient, representing drug initiation and modifications, and a third absorbent state, progression/demise). Arrows indicate possible transitions. This makes it possible to integrate the effect of transition intensities between states [e.g., α03(t) from the initial state to state 3], and its relations with other prognostic factors. This model seeks to be a parsimonious simplification of the flow of patients from the time the 'state of non-progression' is observed on the second CT. Although other formulations could be devised, they were ruled out because they were more complex and failed to provide greater insight for this research question

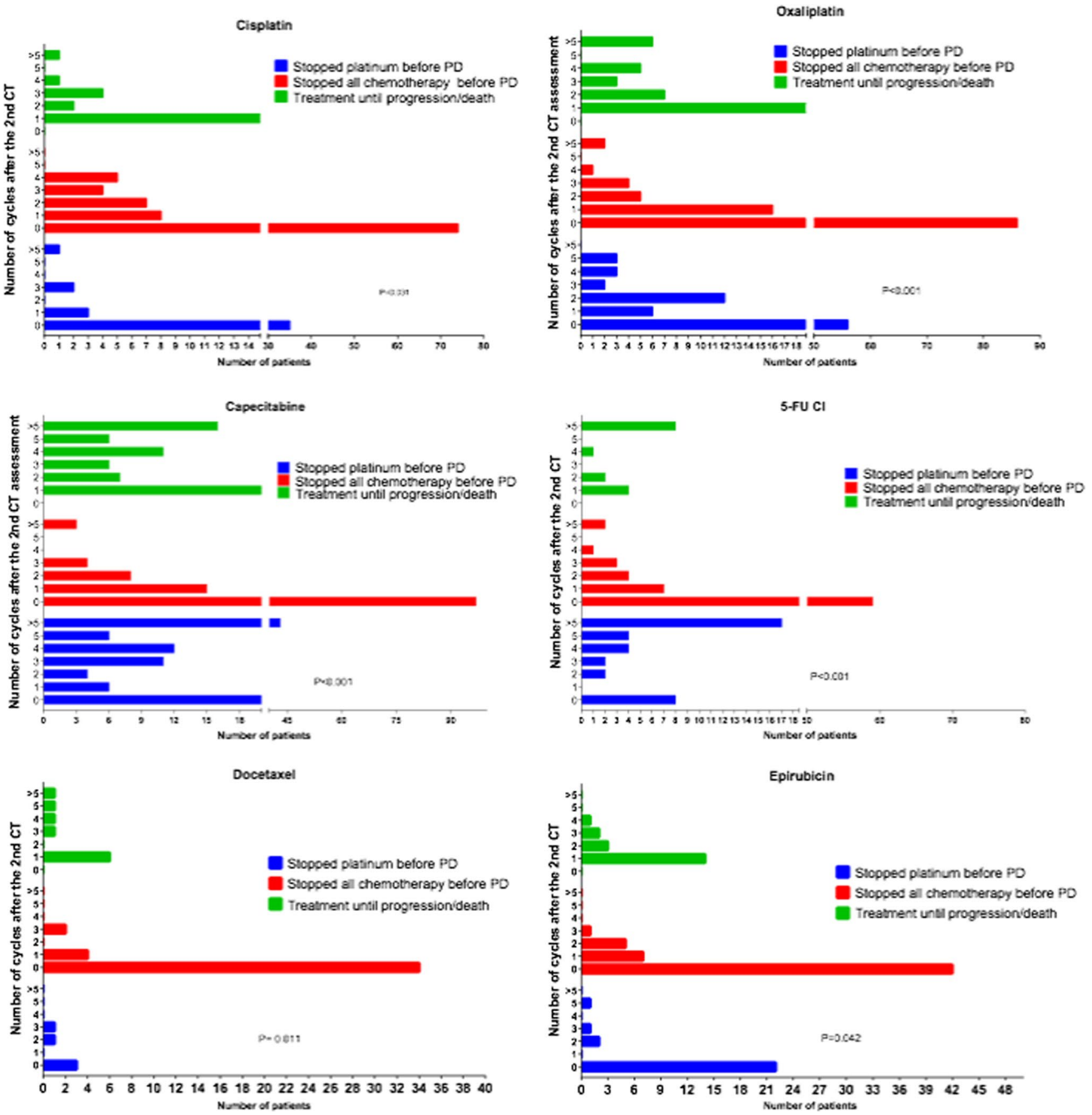

Fig. 5 Number of cycles administered after second computer tomography (CT) scan. *PD* progressive disease

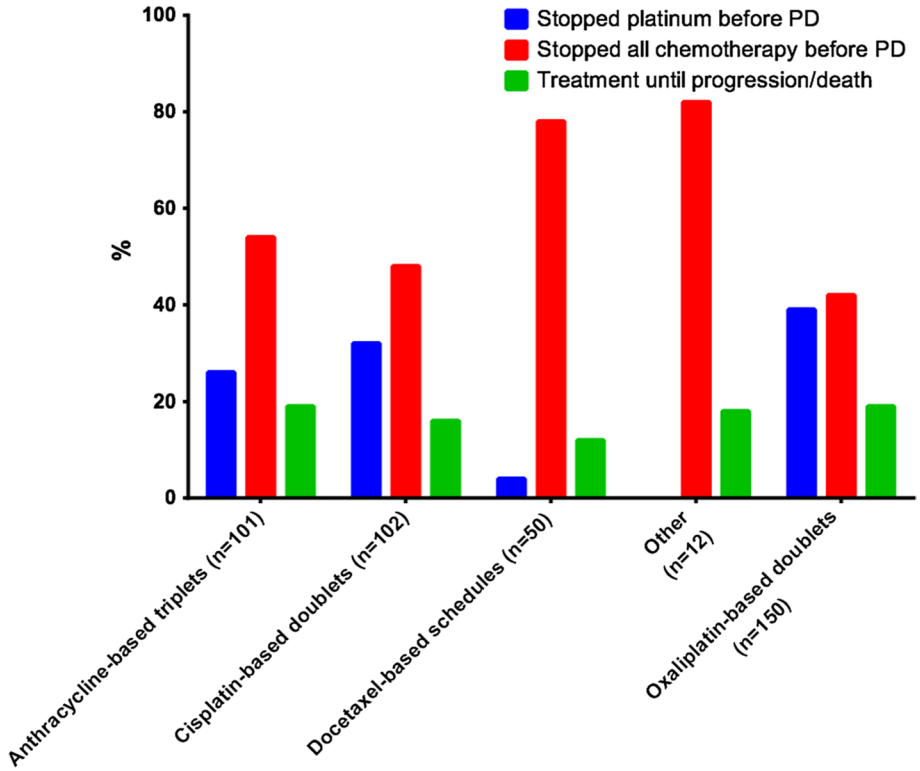

Fig. 6 Decisions made by types of first-line chemotherapy

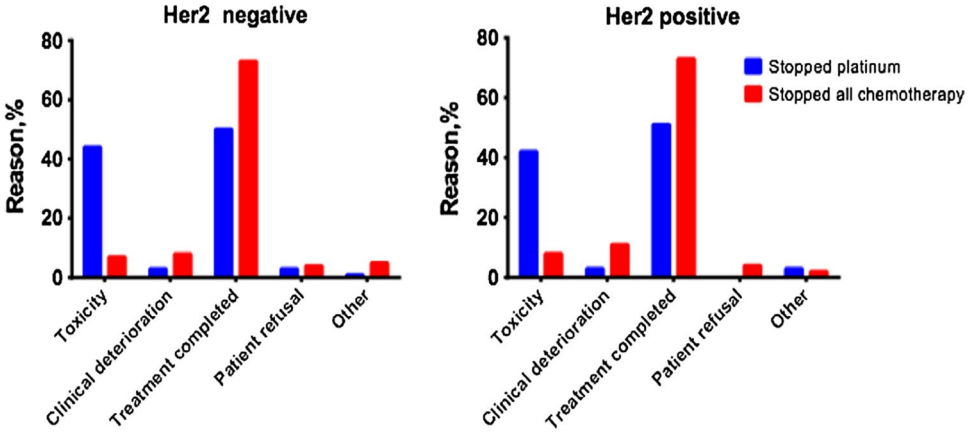

Fig. 7 Reasons alleged by clinicians for discontinuing therapies

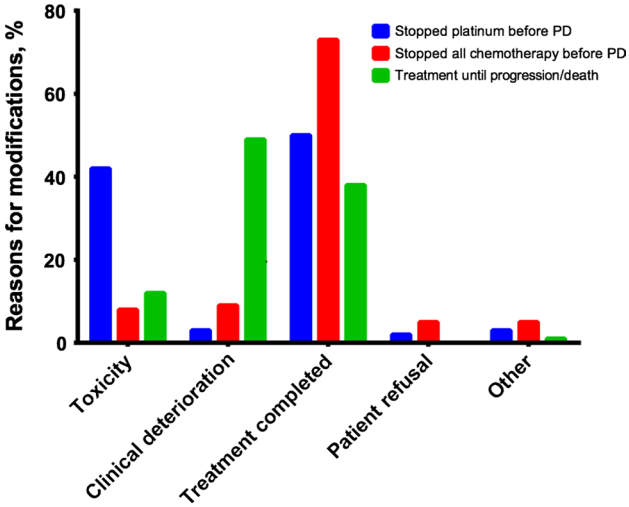

Fig. 8 Reasons alleged by clinicians for discontinuing therapies in each stratum

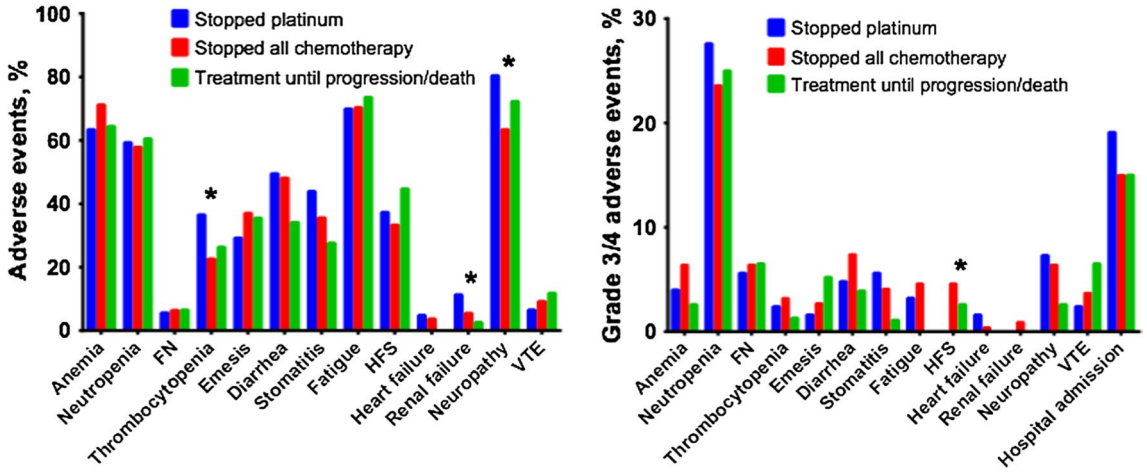

Fig. 9 Adverse events in each stratum (HER2-positive and -negative). *FN* febrile neutropenia, *HFS* hand–foot syndrome, *VTE* venous thromboembolism. $*P<0.01$

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