**Title: Efficacy and safety of chemotherapy in older versus non-older patients with advanced gastric cancer: a real-world data, non-inferiority analysis**

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## ABSTRACT

Objective: Advanced gastric cancer (AGC) is a common neoplasm in older adults. Nevertheless, there are few specific management data in the literature. The aim of this study was to assess non-inferiority of survival and efficacy-related outcomes of chemotherapy used in older vs non-older patients with AGC. Materials and Methods: We recruited 1485 patients from the AGAMENON registry of AGC treated with polychemotherapy between 2008-2017. A statistical analysis was conducted to prove non-inferiority for overall survival (OS) associated with the use of chemotherapy schedules in individuals ≥70 vs.<70 years. The fixed-margin method was used (hazard ratio [HR]<1.176) that corresponds to conserving at least 85% efficacy. Results: 33% (n=489) of the cases analyzed were ≥70 years. Two-agent chemotherapies and combinations with oxaliplatin (48% vs. 29%) were used more often in the older patients, as were modified schedules and/or lower doses. Toxicity grade 3-4 was comparable in both groups, although when looking at any grade, there were more episodes of enteritis, renal toxicity, and fatigue in older patients. In addition, toxicity was a frequent cause for discontinuing treatment in older patients. The response rate was similar in both groups. After adjusting for confounding factors, the non-inferiority of OS associated with schedules administered to the older vs. younger subjects was confirmed: HR 1.02 (90% CI, 0.91-1.14), P (non inferiority)=0.018, as well as progression-free survival: HR 0.97 (90% CI, 0.87-1.08), P(non-inferiority)=0.001. Conclusion: In this AGC registry, the use of chemotherapy with schedules adapted to patients ≥70 years provided efficacy that was not inferior to that seen in younger cases, with comparable adverse effects.

**Keywords:** older, chemotherapy, gastric cancer, stomach, non-inferiority, survival.

**Running title:** Chemotherapy in older patients with gastric cancer.

## INTRODUCTION

While the incidence and overall death rates associated with advanced gastric cancer (AGC) have decreased over the last four decades(1), cancer of the stomach comprises the fourth most common neoplasm and the third leading cause of cancer mortality in Europe(2). According to data from the *Surveillance, Epidemiology, and End Results* (SEER) program, the median age at diagnosis is 68 years and one third of all individuals diagnosed are over the age of 70(3).Given that population aging is accelerating in the West, this epidemiological profile is expected to intensify.

At present, chemotherapy has proven a clear clinical benefit in individuals with AGC(4).However, older participants are underrepresented in most clinical trials; the median age of AGC clinical trial participants is between 54 and 65 years(5). It is therefore doubtful that these data can be extrapolated to real subjects who may be ten to twenty years older.

Most of the data available regarding chemotherapy in older patients with ACG are pooled subgroup analyses from clinical trials with few participants in these age ranges. Furthermore, these clinical trials looked at chemotherapeutic regimens currently considered to be obsolete. Trumper *et al.*conducted a pooled analysis of three trials and concluded that chronological age *per se* should not be considered a contraindication to the use of chemotherapy. There were no differences with respect to efficacy or grade 3-4 toxicities based on age. However, indications of selection bias were seen, with only 24% of the cohort over the age of 70,andno patients over the age of 80 being treated with platin-based schedules(6).In contrast, a second pooled analysis of eight clinical trials by the *North Central Cancer Treatment Group* carried out by Jatoi *et al*. concluded that the rate of serious adverse events (neutropenia, asthenia, infection,and stomatitis) was much higher in people >65 years, although survival-related outcomes did not vary based on age. The authors concluded that more tolerable treatment regimens needed to be developed for this, *a priori*, more vulnerable population(7).

Despite all this, the debate surrounding the efficacy and safety of chemotherapy for AGC in older individuals remains open, since real-world patients may be more frail and have more comorbidities compared to the highly selected populations of the previously mentioned clinical trials. Moreover, a percentage of these patients can be expected to have received pragmatically modified, less intense schedules compared to the standard schedules evaluated in clinical trials(8).

Thus, registry-based cohort studies address real-world safety concerns by examining serious toxicities and risk-benefit ratios in larger series of older subjects. With this rationale, the aim of this study has been to assess the non-inferiority of survival-and efficacy-related outcomes of the chemotherapy schemes used in older patients compared to non-older patients, as well as to compare safety, in a national AGC registry.

## PATIENTS AND METHOD

### Study design and participants

Patients are from the AGAMENON database, a national registry of consecutive cases of AGC, in which 30 Spanish centers and one Chilean center have participated. The study design, characteristics, method, and data quality criteria have been widely communicated elsewhere(9–13).AGAMENON is a non-interventionist database sponsored by the investigators themselves. Data are collected by means of a web-based data collection tool (http://www.agamenonstudy.com/). This tool consists of several filters and a system of queries, to assure data reliability in real time. The researchers are methodically trained on the requirements of the registry and the information is regularly monitored remotely, closing cases after validation.

Eligibility criteria included adult patients (≥eighteen years) with histologically confirmed, unresectable or metastatic gastric, gastroesophageal junction (GEJ), or distal esophageal adenocarcinoma and who received first line chemotherapy with two or three drugs. Esophageal adenocarcinomas were eligible for this analysis because of their molecular similarity to gastric cancer(14). Two populations were chosen: one to analyze survival-and safety-related end points and another one to examine objective tumor response-related endpoints. The two requisites for the populations analyzable for objective tumor response were the presence of initially measurable disease and at least one objective evaluation three months later, according to *Response Evaluation Criteria in Solid Tumors* (RECIST 1.1) criteria. Exclusion criteria included: the absence of at least three months of follow-up (except for those subjects who died prior to the three-month evaluation), less than six months since completion of an eventual adjuvant or neoadjuvant therapy, and the presence of other synchronous cancers. Participants treated with single-agent chemotherapy were excluded.

### Variables and outcomes

The primary outcome of this analysis was overall survival (OS), defined as the interval between initiating first-line chemotherapy and demise for any cause. Secondary outcomes were the percentage of patients (with initially measurable disease) who obtained an objective response as per RECIST version 1.1 criteria; progression-free survival (PFS), defined as the time elapsed between initiation of first-line chemotherapy and progression ordemise, and safety in keeping with the *National Cancer Institute Common Toxicity Criteria*, version 3.0(15). “Older patient” was defined as being 70 years old or older.The chemotherapys chedules were the ones chosen in real-life clinical practice. To compare schedules with each other, five strata were established: two-agent chemotherapies with cisplatin-

fluoropyrimidine; two-agent chemotherapy with oxaliplatin-fluoropyrimidine; schedules with irinotecan; triple-agent therapy with anthracyclines; and docetaxel-based schedules. Dose intensity (DI) was defined as the amount of drug administered per unit of time, expressed as milligrams per square meter ($mg/m^2$) weekly. Cumulative dose was defined as the total dose and reported as total $mg/m^2$ administered. Relative dose intensity (RDI) was considered to be the DI administered with respect to the planned dose intensity for each schedule. Twenty-two prognostic variables deemed important in gastric cancer in at least one previous study(12) were collected in the registry as possible confounding factors.

**Statistical analyses**

The previously mentioned potential confounding factors underwent univariate screening (**Appendix A**), selecting those with $P<0.10$.Thestudyapplied a non-inferiority design to compare OS between both age groups, by means of the fixed margin method. The reason for this design was that, given the frequent use of modified schedules in older patients, we wanted to ascertain if the efficacy of the standard schedules administered to younger patients was preserved. The null hypothesis implies that chemotherapy schedules administered to individuals <70 years are associated with a decrease in the mortality rate by at least15%versus regimens administered to patients aged ≥70 years. This corresponds to a fixed margin of 1.176. This margin change was restrictively based on the lower step to a minimal meaningful effect size generally contemplated (16), and similar to the one chosen in other series (17).The analysis was performed by means of a Cox proportional hazards (PH)regression, controlling for the effect of the previously named confounders, and stratified by types of chemotherapy. The 90% confidence interval (CI) was used for HR, with rejection of the null hypothesis (H0)when the upper limit was <1.176 (one-tailed, $\alpha=0.025$)(18).All non-inferiority analyses are clearly specified in the text as such. It is estimated that at least 1,213 fatal events are required for a proportional statistical power of 80% to reject H0 with an $\alpha$ risk of 5%. The Kaplan-Meier method was used to estimate the survival functions. Toxicity and response rate comparisons were made using the usual superiority tests at two-tailed $\alpha=0.05$ level (95% CI), given that the hypotheses testing sought to demonstrate that the rate of these events were different in younger versus older patients. The analyses were conducted using RStudio (RStudio, Inc., Boston, MA, USA), including the survival package (19).

## RESULTS

### Patients

At the time of data cutoff (January 2017), the registry contained 2,169 cases, 1,485 of whom were eligible for this analysis. The recruitment process is illustrated in **Figure 1.** Approximately one third of the sample (n=489) was 70 years old or older. Baseline characteristics for both subsets are reported in **Table 1**.Differences between the older and younger individuals can be seen in various clinical parameters, including an increase in the percentage of cases with an Eastern Cooperative Oncology Group Performance Status (ECOGPS) ≥ two (18.2%versus (*vs.*) 12.2%, *P*=0.037), higher body mass index (BMI), or≥ two chronic comorbidities (21.6% *vs.* 10.9%, *P*<0.001), associated with being older. With regard to comorbidities, the increased presence of cardiovascular disease (23% *vs.* 8%, *P*<0.001), diabetes mellitus (23% *vs.* 13%, *P*<0.001), and chronic lung disease (11% *vs.* 7%, *P*=0.008) is of particular note in the older patient subset. On the other hand, neoplasm traits point toward less clinical-pathological aggressiveness in subjects ≥70 years (with a lower rate of Lauren diffuse subtype, high grade, bone or peritoneal metastases) (**Table 1**).

### Use of chemotherapy based on age

The analysis of the registry indicates that triple-agent chemotherapy was used less in older adults: 40% *vs.* 21%, odds ratio 0.39 (95% CI, 0.30-0.51), *P*<0.001. Thus, the main variation is the increased use of double agent, oxaliplatin-containing chemotherapies with advancedage (48% *vs.* 29%), in lieu of docetaxel-, cisplatin-, or anthracycline-containing schedules. **Table2** displays a breakdown of the specific chemotherapy regimens based on age. The percentage of modified-dose schedules or regimens that have not been substantiated by phase III studies (eg. modified 5-fluorouracil, oxaliplatin (FUOX), biweekly capecitabine, oxaliplatin (CAPOX), carboplatin- or paclitaxel-based schedules) was 10% in young vs. 25% in older patients (*P*<0.001). In contrast, the most commonly administered schedules in people <70 years were epirubicin-oxaliplatin-capecitabine (EOX) (22%), capecitabine-cisplatin (XP) (17%), and docetaxel-based schedules (16%), with modified dose regimens less common. The use of trastuzumab did not vary between age groups (see **Table 1**).In the ≥80 years group (n=89) there is a predominance of oxaliplatin-based schedules (71%), while three-agent chemotherapy (five out of 89) or cisplatin-based regimens (eight out of 89) are less frequently used (**Appendix E**).

Insofar as maintaining the planned dose, there were relatively few differences observed in the number of courses received or in the median duration of treatment based on age, regardless of the schedule administered (**Table3**).However, a decrease can be seen in DI and accumulated dose of oxaliplatin,

anthracyclines, and docetaxel with age. Both in younger, as well as older individuals, the main reason for withdrawing first-line chemotherapy was completion of planned treatment and progression; discontinuation of chemotherapy due to toxicity was more common in the older patients (**Table3**).Moreover, individuals <70 years received more second-line chemotherapy than their older counterparts (52.9% compared to 45.8%, *P*=0.001). Eighty-three cases of the entire series underwent surgery for metastases, which was more common with the younger subgroup: 7.4% *vs.* 1.8%, *P*<0.0001.

**Efficacy of chemotherapy in older *vs.* younger patients**

At the time of analysis, 1,213 fatal events (81.6%) had been reported, with a median follow-up of 13.1 months (95% CI, three -48 months) in living patients. Median OS in the total population was 10.4 months (95% CI, 9.9-11.1). No differences in OS were found between subjects aged ≥70 years (10.1 months, 95% CI, 9.3-10.9) and individuals<70 years (10.8 months, 95% CI, 10.2-11.6),*P*=0.158.The rate of OS at 12 months was 41.4% in the ≥70 group (95% CI, 37.1-46.1) and 45.1% in participants<70 (95% CI, 42-48.4). After adjusting for the confounding factors previously mentioned (ECOG PS, albumin, grade, bone and lung metastases, ascites, stage, number of metastases, neutrophil-to-lymphocyte ratio, signet-ring cells, diffuse subtype, number of comorbidities, surgery, triplet chemotherapy, trastuzumab) (**Appendix A**), the non-inferiority hypothesis for OS associated with schedules administered to older *vs.* younger patients was confirmed, with a HR 1.021 (90% CI, 0.913-1.141), *P*(non-inferiority)=0.018. Likewise, at the time of analysis 1,182 progression events had been recorded. The median PFS in subjects under the age of 70 years was 6.1 months (95% CI, 5.8-6.5), compared to 5.8 months (95% CI, 5.4-6.4) in the older patients, with a HR 0.9730 (90% CI, 0.876-1.081),adjusted for confounding factors, *P*(non-inferiority)=0.002.The OS and PFS functions are depicted in **Figure 3**.

The sensitivity analyses do not suggest differences in OS based on tumor site for each group (**Appendix B**), nor have we found evidence in favor of a subgroup effect between tumor site and age, with *P*(interaction)=0.279. This is, of course, limited by the small number of individuals with adenocarcinoma of the distal esophagus (n=99).In individuals ≥80 years of age, it was not possible to gather sufficient evidence to reject the null hypothesis, given the few patients in this age range (**Appendix D.1**).

With respect to trastuzumab, no evidence was found of a different effect based on age (*P*-interaction=0.873). Then, aCox PH regression was conducted specifically in the group of older patients (**Table 5**). In the registry, 73 out of 489 older individuals (15%) received trastuzumab. The use of trastuzumab in tumors IHC 3+ was seen to be associated with increased survival in the older patient group, with HR 0.65 (95% CI, 0.45-0.91), *P*=0.013.

In total, 901 cases were deemed evaluable for response (see **Figure 1**). The evaluation of objective tumor response is displayed in **Figure 2**, with no differences observed in the rate of tumor shrinkage based on subjects' age ($\chi 2$=1.61, df.=3, $p$=0.656).

**Safety of chemotherapy according to patients' age**

We then investigated whether these previously enumerated adjustments (**Table2**), more often made in older patients, had a moderating impact on safety. No overall increase in recorded hematological toxicity was associated with age (**Table4**).

Some non-hematological adverse events (of any grade) were significantly more frequent in older vs. younger patients, such as- enteritis: 46% *vs.* 38%, renal toxicity: 10% *vs.* 6%, or fatigue: 77% *vs.* 68%. Furthermore, taking into account specific schedules, certain toxicities varied between groups (e.g. any grade emesis or neutropenic fever with DC) (**Appendix C**). However, the percentage of grade 3-4 adverse events (including those that involved hospitalizations or fatal events) was similar. Insofar as safety is concerned, no substantial differences were found with regards to safety of any grade in subjects ≥80 *vs*. 70-79 years of age (**Appendix D.2**).As previously commented, it is worth noting that toxicity most often leads to discontinuing chemotherapy in the older compared with younger individuals (23% *vs.*18%, *P*=0.0425) (see **Table 3** for the most commonly used schedules).

**DISCUSSION**

In this analysis, we have used real-world data from a national registry of gastric cancer to assess non-inferiority of OS associated with polychemotherapy regimens administered in older patients versus schedules used in younger individuals. The motivation to perform this analysis was to fill an existing gap in the literature and in knowledge, due to the underrepresentation of subjects ≥70 years in pivotal trials of AGC. In addition, there is a lack of real-life clinical practice data about this population, which contrasts with the epidemiological reality. As expected, we have observed a discreetly different use of cytotoxic chemotherapy in older adults, often involving simplified schedules, with dose reductions and *ad hoc* modifications, special preference for oxaliplatin over cisplatin, and less frequent use of anthracyclines and docetaxel. This determines the comparative profile of serious adverse effects (SAEs). SAEs are not more common in older *vs.* non-older individuals. In this regard, the fact that these safety data are comparable is of special mention, despite the greater theoretical vulnerability of the older patient population, which is probably attributable to the pragmatic modifications made.

To ascertain the efficacy of the regimens administered in older adults, anon-inferiority analysis was conducted that revealed how the slightly 'attenuated' regimens administered to older patients

preserved a substantial part of the effect of 'standard' schedules given to the younger patients, both interms of OS, as well as PFS. Furthermore, tumor response data as per RECIST criteria were comparable. These data are consistent with Trumper *et al.*'s prior conclusions that found that treatment efficacy was similar in both age groups, although some of the schedules they analyzed, such as fluorouracil-mitomycin or methotrexate-fluorouracil-doxorubicin (FAMTX),are currently considered obsolete(6). Other authors have found an increase in adverse effects in older versus younger individuals(e.g., neutropenia, fatigue, infection, and stomatitis), suggesting the need to design better-tolerated schedules for this population(7,20).In our registry, the investigators used discreetly modified first-line doses and schedules in the older population, which has made it possible to maintain treatment in these patients with the same safety as in younger individuals and without diminished benefit. Indeed, the current trend among most research groups is to develop strategies to individualize the use of chemotherapy in older or frail patients. Thus, trials have been conducted regarding modified oxaliplatin-based, two-drug chemotherapies(21–23) and double-agent schedules with docetaxel-fluoropyrimidine(24).The feasibility of using an attenuated, three-agent scheme denominated miniDOX (reduced dose docetaxel–oxaliplatin–capecitabine) has also been evaluated in frail, older people(25). In general, all these experiences have concluded that modified schedules are efficacious and convenient in this population. Given that not increasing toxicity in a more vulnerable group is generally deemed favorable, it would be advisable to continue to explore adapted schedules that minimize toxicity. On the other hand, despite the paucity of literature on this subject, our data also support the conclusions of other, small series that suggest that trastuzumab is safe and effective in older patients(26,27).

Our study has certain limitations. Firstly, inherent to analyses of real-world registries, there is a limitation that is attributable to data accuracy and to the possible bias in the distribution of therapies these registries entail. In particular, we compared groups that have been treated differently, as expressed in **Table 2**. Although multivariable modeling techniques have been used, we cannot rule out that a good part of the residual bias may still be influencing data interpretation. Secondly, given the retrospective nature of the study, it has not been possible to implement an integral geriatric evaluation that is useful for decision-making and selecting cancer treatment in the older adults(28). Thirdly, treatment adherence has not been assessed, which is a key consideration in older AGC patients receiving oral treatments(29).Fourthly, given the registry eligibility criteria, single-agent chemotherapy has not been contemplated, although in unselected patients with AGC, combination treatment is deemed more efficacious than single-agent chemotherapy in terms of OS(30);in the case of older patients, however, the literature is scarce. In this sense, a randomized trial recently carried out specifically in older individuals concluded that OS with the combination of oxaliplatin and capecitabine was superior to capecitabine in single-agent chemotherapy(31). However, other series

suggest that single-agent chemotherapy is the most appropriate option for some cases(32).Finally, the effect of second-lines of chemotherapy has not been considered(33).

Insofar as data generalization is concerned, it must be remembered that, despite being real-world patients, most of the seniors were deemed fit enough to be treated with standard, first-line polychemotherapy for advanced disease. It must therefore be taken into consideration that subjects with a poor general status at baseline in whom the use of this type of standard schedules is contraindicated were excluded (see **Figure 1**). On the other hand, tumors of the distal esophagus, GEJ, and stomach were recorded, by virtue of their molecular similarities(14); nevertheless, the impact of localization on the effect of the drugs or in decision-making remains unknown. Indeed, another aspect to be taken into account is that the clinical-pathological traits of the tumors in the older patients were more favorable than those observed in the non-older patients, as is consistent with reports from other series(34), although this was factored into the analysis.

Regarding practical applicability, the AGAMENON data endorse the use both of chemotherapy and of trastuzumab in older patients, particularly in those with good functional status, suitable body mass index, and the absence of protein destruction. The schedules of choice are two-agent chemotherapies, which can probably be safely modified or adapted based on the person's individual characteristics. Nonetheless, it would be convenient to homogenize criteria by means of geriatric assessment scales, early mortality prediction scales, toxicity, etc. All this illustrates the need to carry out prospective, randomized, clinical trials, specifically targeting subjects ≥70 years to demonstrate the benefit of chemotherapy and targeted agents, as are being performed in other tumors.

In short, this study provides evidence (grade C) that the use of chemotherapy regimens in the older patients is non-inferior in terms of survival-based end points with respect to schedules used in younger patients, with comparable grade 3-4 toxicity, although this may be due in part to small modifications or adaptations made *ad hoc* by medical oncologists when administering treatments.

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the Helsinki Declaration of 1964 and later versions.Informed consent was obtained from all patients before they were included in the study.

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## TABLES AND FIGURES LEGENDS

**Figure 1.** Flowchart of the AGAMENON study.

**Figure 2.** Evaluation of tumor response as per *Response Evaluation Criteria in Solid Tumors* (RECIST 1.1) criteria based on age. Dataset used: patients analyzable for response (n=873).Error bars represent 95% confidence intervals.

**Figure 3.** Kaplan-Meier curves for PFS and OS according to age. Abbreviations: PFS= progression-free survival, OS= overall survival.

**Table 1.** Baseline characteristics in older *vs.*younger patients (n=1485). Abbreviations: BMI: body mass index; ECOG-PS: Eastern Cooperative Oncology Group performance status; FISH: fluorescent *in situ* hybridization; GEJ: gastroesophageal junction; LLN: lower limit of normal; N: sample size. Dataset used: All patients analyzable for survival endpoints (n=1485). Tests used: *p* values are from Pearson's $X^2$ tests, exceptage and number of comorbidities, which are from a Wilcoxon test for independent samples. In the table, percentages refer to proportions of the columns.

**Table 2.**Most common chemotherapy schedules according to participants' age. Abbreviations: EOX: epirubicin, oxaliplatin, capecitabine; XP: capecitabine, cisplatin; FOLFOX6: 5-fluorouracil, oxaliplatin; CAPOX: capecitabine, oxaliplatin; FP 3w: 5-fluorouracil, docetaxel every 3 weeks; DC: docetaxel, cisplatin; DCF 3w: docetaxel, cisplatin, 5-fluorouracil every 3 weeks; DCX: docetaxel, cisplatin, capecitabine; ECF: epirubicin, cisplatin, 5-fluorouracil; FUOX: 5-fluorouracil, oxaliplatin; ECX: epirubicin, cisplatin, capecitabine; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; DCF 4w: docetaxel, cisplatin, fluorouracil every 4 weeks; DOX: docetaxel, oxaliplatin, capecitabine; FOLFIRI: 5-fluorouracil, irinotecan; EOF: epirubicin, oxaliplatin, 5-fluorouracil.Dataset used: All patients analyzable for survival endpoints (n=1485).** Modified-dose regimens or combinations of drugs that have not been substantiated by phase III clinical trials.

**Table 3.** Doses used within the most common regimens based on age. *The first term is young; the 2nd, older patients. ** Daily Dose.

**Table 4.** Adverse events in AGAMENON study cohorts: older (≥70 years) vs. younger. *$P$<0.05 ($\chi$2 test); percentages refer to columns.

**Table 5.** Cox proportional hazards regression for overall survival in the older cohort. Abbreviations: BMI: body mass index; CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group performance status; FISH: fluorescent *in situ* hybridization; GEJ: gastroesophageal junction; LLN: lower limit of normal; N: sample size; Ref.: reference. Dataset used: Patients ≥70 years (n=489, number of events=409). Likelihood ratio test=75.1 on 13 df, P=9.15e-11, Schoenfeld´s test $\chi^2$ (proportional hazards assumption) = 1.518, $P$=0.222.

**Figure 1.**Flowchart of the AGAMENON study.

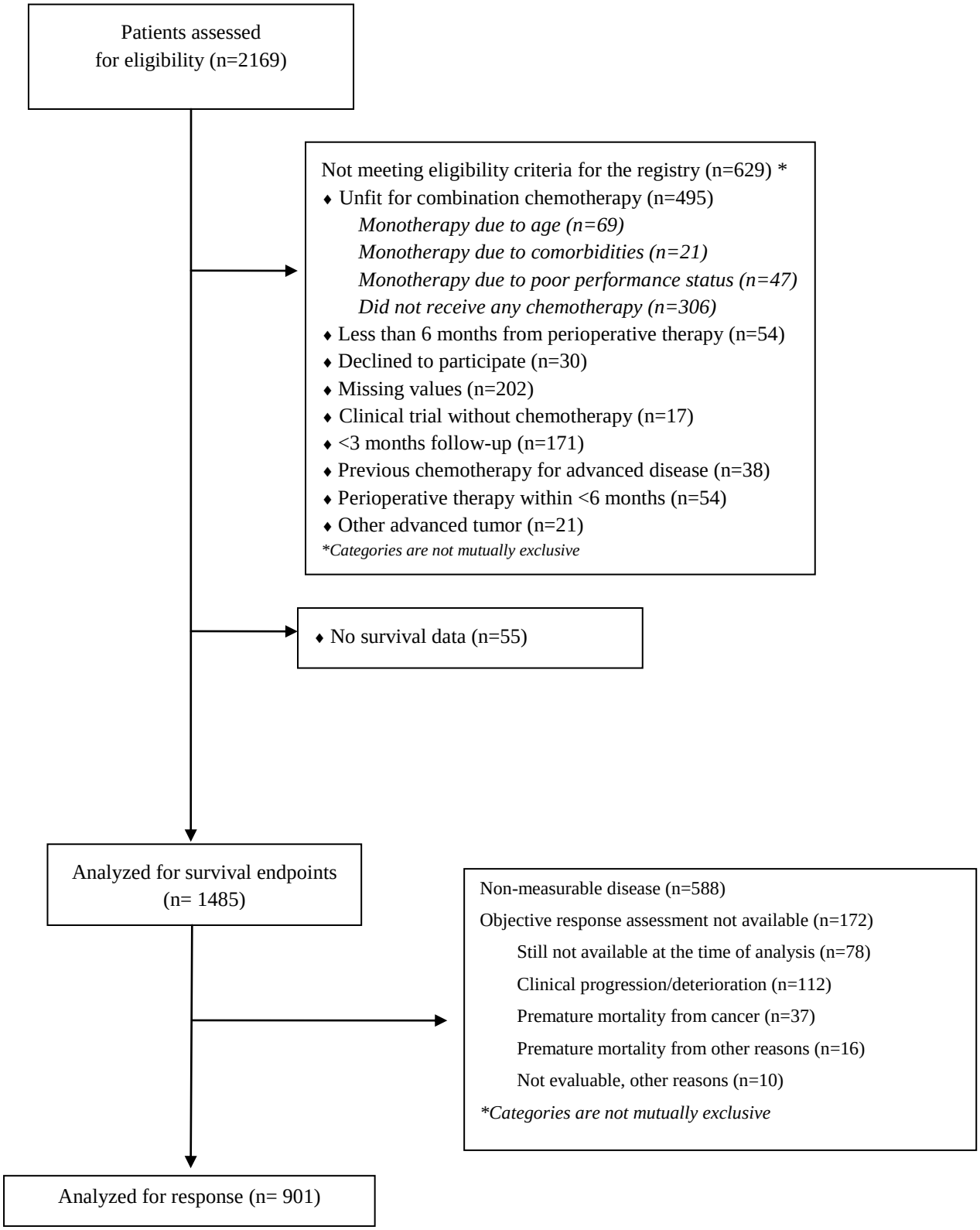

**Table 1.**Baseline characteristics in older vs.younger patients (n=1485).

| Baseline characteristics | <70 years (n=996) N (%) | ≥70 years (n=489) N (%) | p-value |
|---|---|---|---|
| **Age (years),** median (range) | 59 (20-69) | 75 (70-89) | - |
| **Male** | 680 (68.2) | 359 (73.4) | 0.048 |
| **ECOG-PS** | | | |
| 0 | 233 (23.3) | 93 (19.0) | 0.003 |
| 1 | 641 (64.3) | 307 (62.7) | |
| ≥2 | 122 (12.2) | 89 (18.2) | |
| **≥2 chronic comorbidities** | 109 (10.9) | 106 (21.6) | <0.001 |
| **Nº Comorbidities**, median (range) | 0 (0-6) | 1 (0-5) | <0.001 |
| Chronic heart disease | 80 (8.0) | 115 (23.5) | <0.001 |
| Diabetes mellitus | 132 (13.2) | 115 (23.5) | <0.001 |
| Chronic vascular disease | 56 (5.6) | 55 (11.2) | 0.001 |
| Human immunodeficiency virus | 7 (0.7) | 1 (0.2) | 0.289 |
| Chronic renal failure | 15 (1.5) | 11 (2.2) | 0.300 |
| **BMI (kg/m2)** | | | <0.001 |
| <18.5 | 79 (7.9) | 12 (2.4) | |
| 18.5-24.9 | 518 (52.0) | 229 (46.8) | |
| ≥25 | 399 (40.1) | 248 (50.7) | |
| **Tumor stage at diagnosis** | | | |
| Locally advanced, unresectable | 47 (4.7) | 21 (4.2) | 0.713 |
| Metastatic tumor at onset | 949 (95.2) | 468 (95.7) | |
| **Primary tumor site** | | | |
| Esophagus | 70 (7.0) | 29 (5.9) | 0.165 |
| GEJ | 120 (12.1) | 45 (9.2) | |
| Stomach | 806 (80.9) | 415 (84.9) | |
| **Histological grade** | | | |
| 1 | 101 (10.1) | 58 (11.9) | 0.007 |
| 2 | 275 (27.6) | 162 (33.1) | |
| 3 | 428 (42.9) | 165 (33.7) | |
| Not available | 192 (19.3) | 104 (21.3) | |
| **Lauren classification** | | | <0.001 |
| Intestinal | 441 (44.3) | 283 (57.9) | |
| Diffuse | 366 (36.7) | 112 (22.9) | |
| Mixed | 49 (4.9) | 28 (5.7) | |
| Not available/not classified | 140 (14.1) | 66 (13.5) | |
| **Signet ring cells** | 334 (33.5) | 109 (22.3) | <0.001 |
| **Her2 overexpression** | | | |
| No (0+, 1+, 2+ and FISH-) | 670 (67.3) | 293 (59.9) | 0.041 |
| Yes (3+) | 99 (9.9) | 63 (12.9) | |
| Yes (2+ and FISH+) | 58 (5.8) | 31 (6.3) | |
| Not available | 169 (16.9) | 102 (20.9) | |
| **Cancer-related serious complications** | 125 (12.5) | 49 (10.0) | 0.154 |
| **Number of metastatic sites, ≥3** | 349 (35.0) | 132 (26.9) | 0.002 |
| **Metastases sites** | | | |
| Liver | 357 (35.8) | 201 (41.1) | 0.049 |
| Lung | 67 (6.7) | 53 (10.8) | 0.006 |
| Non-regional lymph nodes | 494 (49.5) | 229 (46.8) | 0.315 |
| Peritoneum | 475 (47.6) | 192 (39.2) | 0.002 |
| Ascites | 273 (27.4) | 96 (19.6) | 0.001 |
| Bone | 113 (11.3) | 35 (7.1) | 0.011 |
| **Neutrophil-lymphocyte ratio**, median (range) | 3.08 (0.27-37.0) | 3.32 (0.16-36.42) | 0.200 |
| **Albumin <Lower limit of normal** | 239 (23.9) | 130 (26.5) | 0.277 |
| **Primary tumor resected** | 350 (35.1) | 150 (30.6) | 0.087 |
| **First-line treatment** | | | |
| Doublet | 598 (60.1) | 387 (79.1) | <0.001 |
| Triplet | 398 (39.9) | 102 (20.9) | |
| **Chemotherapy regimens** | | | |
| Anthracycline-based | 260 (27.1) | 83 (16.9) | <0.001 |
| Docetaxel-based | 163 (16.3) | 33 (6.7) | |
| Oxaliplatin-based | 286 (28.7) | 236 (48.2) | |
| Cisplatin-based | 229 (22.9) | 75 (15.3) | |
| Irinotecan-based | 13 (1.3) | 12 (2.5) | |
| Other | 35 (3.5) | 50 (10.2) | |
| **First-line trastuzumab** | 139 (13.9) | 73 (14.9) | 0.614 |

**Table2.** Most common chemotherapy schedules according to participants' age.

| Schedule | <70 years N=996 | ≥70 years N=489 |
|---|---|---|
| • **EOX: Epirubicin 50 mg/m2 on day 1 + Oxaliplatin 130 mg/m2 on day 1 + Capecitabine 750 mg/m2/12h daily every 3 weeks** | 219 (21.9%) | 69 (14.1%) |
| • **XP: Cisplatin 80 mg/m2 on day 1 + Capecitabine 1000 mg/m2/12h on days 1-24 every 3 weeks** | 173 (17.3%) | 47 (9.6%) |
| • **Modified FOLFOX-6: Oxaliplatin 85 mg/m2 on day 1 + Leucovorin 400 mg/m2 on day 1 + 5-Fluorouracil 400 mg/m2 on day 1 + Fluorouracil 2400 mg/m2 continuous infusion over 46 hours every 2 weeks** | 134 (13.4%) | 64 (13.0%) |
| • **CAPOX: Oxaliplatin 130 mg/m2 on day 1 + Capecitabine 1000 mg/m2/12h on days 1-14 every 3 weeks** | 99 (9.9%) | 118 (24.1%) |
| • **FP3w: Cisplatin 75 mg/m2 on day 1 + 5-Fluorouracil 750 mg/m2 continuous infusion over 24 hours daily on days 1-5 every 3 weeks** | 47 (4.7%) | 21 (4.2%) |
| • **DC: Docetaxel 75 mg/m2 + Cisplatin 75 mg/m2 every 3 weeks** | 44 (4.4%) | 13 (2.6%) |
| • **DCF3w: Docetaxel 60 mg/m2 on day 1 + Cisplatin 60 mg/m2 on day 1 + 5-Fluorouracil 750 mg/m2 continuous infusion over 24 hours daily on days 1-4 every 3 weeks** | 42 (4.2%) | 6 (1.2%) |
| • **DCX: Docetaxel 75 mg/m2 on day 1 + Cisplatin 75 mg/m2 on day 1 + Capecitabine 750 mg/m2/12h on days 1-14 every 3 weeks** | 41 (4.1%) | 8 (1.6%) |
| • **ECF: Epirubicin 50 mg/m2 on day 1 + Cisplatin 60 mg/m2 on day 1 + 5-Fluorouracil 200 mg/m2 continuous infusion daily every 3 weeks** | 28 (2.8%) | 6 (1.3%) |
| • **Modified, biweekly CAPOX: Oxaliplatin 85 mg/m2 on day 1 + Capecitabine 625 mg/m2/12h daily every 2 weeks** | 19 (1.9%) | 30 (6.1%) |
| • **Modified FUOX: Oxaliplatin 85 mg/m2 + 5-Fluorouracil 3000 mg/m2 continuous infusion over 48 hours every 2 weeks** | 19 (1.9%) | 22 (4.4%) |
| • **ECX: Epirubicin 50 mg/m2 on day 1 + Cisplatin 60 mg/m2 on day 1 + Capecitabine 750 mg/m2/12h daily every 3 weeks** | 17 (1.8%) | 8 (1.6%) |
| • **Other: Carboplatin, 5-Flurouracil** | 16 (1.6%) | 24 (4.9%) |
| • **FLOT: Oxaliplatin 85 mg/m2 on day 1 + Leucovorin 200 mg/m2 on day 1 + 5-Fluorouracil 2600 mg/m2 continuous infusion over 46 hours + Docetaxel 50 mg/m2 on day 1 every 2 weeks** | 15 (1.5%) | 1 (0.2%) |
| • **DCF 4W: Docetaxel 75 mg/m2 on day 1 + Cisplatin 75 mg/m2 on day 1 + 5-Fluorouracil 1000 mg/m2 continuous infusion over 24 hours daily on days 1-5 every 4 weeks** | 10 (1.0%) | 1 (0.2%) |
| • **Other: Carboplatin, paclitaxel** | 10 (1%) | 8 (1.6%) |
| • **DOX: Docetaxel 75 mg/m2 on day 1 + Oxaliplatin 100 mg/m2 on day 1 + Capecitabine 750 mg/m2/12h on days 1-14 every 3 weeks** | 8 (0.8%) | 2 (0.4%) |
| • **FOLFIRI: Irinotecan 180 mg/m2 on day 1 + Leucovorin 400 mg/m2 on day 1 + 5-Fluorouracil 400 mg/m2 on day 1 + Fluorouracil 2400 mg/m2 continuous infusion over 46 hours every 2 weeks** | 7 (0.7%) | 4 (0.8%) |
| • **Other: Docetaxel, Oxaliplatin, 5-Flurouracil** | 7 (0.7) | 0 |
| • **EOF: Epirubicin 50 mg/m2 on day 1 + Oxaliplatin 130 mg/m2 on day 1 + 5-Fluorouracil 200 mg/m2 continuous infusion daily every 3 weeks** | 6 (0.6%) | 0 |
| • **Other** | 35 (3.5) | 37 (7.5) |

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**Table 3.**Doses used within the most common regimens based on age.

| **Doses for** | **Oxaliplatin** | | | **Cisplatin** | | | **Epirubicin** | **Docetaxel** | **Capecitabine** |
|---|---|---|---|---|---|---|---|---|---|
| **Schedules** | **EOX** | **FOLFOX6** | **CAPOX** | **XP** | **FP3w** | **ECX/ECF** | **EOX/ECF/ ECX/EOF** | **DC/DCF/DCX/DOX** | **Any** |
| **Number of cycles, median** | 6 *vs* 6 * | 8 *vs*8.5 | 6 *vs*5 | 6 *vs*6 | 6 *vs*6 | 5 *vs*6 | 5 *vs*6 | 6 *vs*6 | 6 *vs*6 |
| **Median of treatment duration (weeks)** | 18.5 *vs*19 | 20 *vs*20.7 | 18.8 *vs*17.5 | 19.0 *vs*18.8 | 19 *vs*18 | 17.5 *vs*19.7 | 18.0*vs*18.4 | 17.2*vs*18.5 | 20 *vs*19.5 |
| **Mean cumulative dose (mg/m2)** | 682 *vs*633 | 677 *vs*618 | 752 *vs*604 | 403 *vs*401 | 373 *vs*350 | 280 *vs*360 | 243 *vs*237 | 339 *vs*303 | 75237 *vs* 75552 |
| **Mean dose/cycle (mg/m2/cycle)** | 123 *vs*120 | 80 *vs*80 | 123 *vs*117 | 73 *vs*73 | 72 *vs*68 | 60 *vs*60 | 48 *vs*47 | 63 *vs*62 | 759 *vs* 773** |
| **Mean dose intensity (mg/m2/week)** | 38 *vs*36 | 35 *vs*34 | 39 *vs*36 | 22 *vs*22 | 21 *vs*19 | 15 *vs*17 | 14 *vs*14 | 20 *vs*18 | |
| **Mean, dose density** | 88% *vs*83% | 84% *vs*81% | 85% *vs*83% | 78% *vs*79% | 84% *vs*77% | 87% *vs*87% | 88% *vs*86% | 89% *vs*80% | 89% *vs*86% |
| **Reason for withdrawal** | | | | | | | | | |
| ***Toxicity*** | 14.5% *vs*20.5% | 17.4% *vs*34.4% | 22.1% *vs*22.8% | 13.4% *vs*19.1% | 13.0% *vs* 0 | 11.7% *vs* 25% | 18.1% *vs* 25.0% | 18.0% *vs* 16.6% | 11.9% *vs* 9.7% |
| ***Progression*** | 40.8% *vs*33.8% | 36.5% *vs*34.4% | 46.3% *vs*45.8% | 42.1% *vs*42.5% | 36.9% *vs* 36.8% | 35.2% *vs* 25% | 35.3% *vs* 23.8% | 30.3% *vs* 33.3% | 56.1% *vs* 58.0% |
| ***Planned treatment completed*** | 33.8% *vs*38.2% | 27.7% *vs*9.8% | 27.3% *vs*16.5% | 40.9% *vs*31.9% | 41.3% *vs* 63.1% | 11.7% *vs* 25% | 33.4% *vs* 39.2% | 40.1% *vs* 50% | 19.1% *vs* 23.1% |
| ***Patient refusal*** | 0.9% *vs*2.9% | 4.7% *vs*0% | 0% *vs*5.5% | 1.7% *vs*2.2% | 4.3% *vs 0* | 17.4% *vs* 12% | 2.6% *vs* 4.7% | 4.0%vs 0 | 5.2% *vs* 2.3% |
| ***Other*** | 8.9% *vs*4.4% | 12.6% *vs*21.3% | 4.2% *vs*7.3% | 2.3% *vs*4.2% | 4.3% *vs* 0 | 23.2% *vs* 12% | 8.9% *vs* 7.1% | 7.3% *vs* 0 | 7.1% *vs* 6.3% |
| ***Change to the ToGA regimen*** | 0.9% *vs*0% | 0.7% *vs*0% | 0% *vs*0.9% | 0 | 0*vs* 16.3% | 0 | 0.7% *vs* 0% | 0 | 0.3% *vs* 0.3% |

**Table 4.** Adverse events in AGAMENON study cohorts: older (≥ 70 years) vs. younger.

| TOXICITY | Younger | | Older | |
|---|---|---|---|---|
| | **Total** | **Grade 3-4** | **Total** | **Grade 3-4** |
| **Anemia** | 62.9 | 7.3% | 65.8% | 4.9% |
| **Neutropenia** | 49.0% | 21.9% | 45.1% | 19.9% |
| **Febrile neutropenia** | 5.8% | | 6.5% | |
| **Thrombocytopenia** | 21.3% | 2.7% | 21.3% | 1.8% |
| **Emesis** | 38.6% | 4.1% | 37.8% | 3.0% |
| **Diarrhea** | 38.4%* | 5.5% | 46.5%* | 6.9% |
| **Stomatitis** | 30.8% | 3.2% | 33.9% | 2.6% |
| **Fatigue** | 68.1%* | 7.0% | 76.9%* | 7.2% |
| **Hand-foot syndrome** | 30.0% | 3.5% | 28.3% | 1.8% |
| **Neuropathy** | 53.5% | 4.0% | 54.3% | 4.1% |
| **Alopecia** | 35.5%* | | 24.8%* | |
| **Increased aspartate aminotransferase** | 11.7% | 1.0% | 11.7% | 0.8% |
| **Hyperbilirubinemia** | 6.6% | 1.6% | 6.9% | 1.0% |
| **Renal toxicity** | 6.5%* | 0.8% | 9.6%* | 0.8% |
| **Cardiotoxicity** | 2.2% | 0.7% | 2.4% | 0.6% |
| **Venous thromboembolic disease** | 10.2% | 5.4% | 9.4% | 4.7% |
| **Toxicity-related hospital admission** | 22.7% | | 24.1% | |
| **Death due to toxicity** | 0.4% | | 0.6% | |

**Table 5.** Cox proportional hazards regression for overall survival in the older cohort (≥ 70 years).

| Covariate | Estimate | Hazard ratio (HR) | 95% CI of HR | P-value |
|---|---|---|---|---|
| **Lauren classification, diffuse vs. others** | 0.463 | 1.589 | 0.969-1.542 | 0.088 |
| **Bone metastases** | 0.463 | 1.589 | 1.089-2.320 | 0.016 |
| **Liver metastases** | 0.332 | 1.394 | 1.103-1.761 | 0.005 |
| **Peritoneal metastases** | 0.258 | 1.295 | 1.029-1.629 | 0.027 |
| **Histological grade, grade 1 vs. others** | -0.253 | 0.776 | 0.558-1.078 | 0.131 |
| **First-line trastuzumab** | | | | |
| **No** | Ref. | Ref. | Ref. | - |
| **If IHC 3+** | -0.416 | 0.659 | 0.475-0.914 | 0.012 |
| **If IHC 2+ & FISH+** | -0.123 | 0.884 | 0.576-1.356 | 0.572 |
| **ECOG-PS** | | | | |
| **0** | Ref. | Ref. | Ref. | - |
| **1** | 0.200 | 1.222 | 0.935-1.597 | 0.142 |
| **≥2** | 0.315 | 1.370 | 1.463-2.861 | 0.008 |
| **Albumin, <3.5 g/Dl** | 0.315 | 1.370 | 1.085-1.730 | 0.008 |
| **BMI, kg/m2** | | | | |
| **<18.5** | 0.674 | 1.963 | 1.046-3.681 | 0.035 |
| **18.5-24.9** | Ref. | Ref. | Ref. | - |
| **≥25** | 0.047 | 1.048 | 0.856-1.284 | 0.646 |