CLINICAL STUDY RESULTS

Name of Sponsor: Fondazione GISCAD (Gruppo Italiano per lo studio dei Carcinomi dell'Apparato Digerente) **Name of Active Ingredient:** Docetaxel + Oxaliplatin + Capecitabine (low-TOX) Epirubicin + Oxaliplatin +Capecitabine (EOX) **Therapeutic Area:** Oncology **Indication:** Locally Advanced / Metastatic Gastric Cancer	*(For National Authority Use only)*
Title of Study: A randomized phase III study of low-docetaxel oxaliplatin (low-TOX) vs epirubicin, oxaliplatin and low-TOX (EOX) in patients with locally advanced unresectable or metastatic gastric cancer	
Protocol Code: LEGA (**L**owtox**E**ox**G**astric**A**dvanced)	
EudraCT Number: 2011-005537-39	
ClinicalTrials.Gov Number: NCT02076594	
Chief/Coordinating Investigator: Roberto Labianca, MD	
Study Centers: A.O. Papa Giovanni XXIII (Coordinating Site); Istituto Nazionale Tumori, Fondazione G. Pascale; Ospedale S. Giovanni Calibita Fatebenefratelli Roma; Istituto Nazionale per lo studio e la cura dei Tumori; A.O. San Paolo di Milano; Istituto Tumori Giovanni Paolo II - IRCCS Ospedale Oncologico di Bari;; Ospedale Sacro Cuore - Don Calabria; Nuovo Ospedale di Prato - Santo Stefano; Istituto Europeo di Oncologia; A.O. S. Anna; Ospedale di Circolo A. Manzoni; A.O. Ospedale Luigi Sacco e Polo Universitario; A.O. di Treviglio e Caravaggio; A.O. Regionale San Carlo, Ospedale San Carlo; Ospedale di Circolo e Fondazione Macchi; A.O. di Reggio Emilia, Arcispedale S.Maria Nuova; AUSL di Piacenza; Ospedale di Circolo Serbelloni; Ospedali di Carpi e Mirandola; A.O.Ospedale della Versilia; A.O. Ospedali Riuniti Marche Nord-P.O.S. Salvatore Muraglia; Ospedale San Vincenzo; ASL Latina - Ospedale S.M. Goretti;	
Studied Period (Years): 2013-2019 **Date of first patient enrolled:** 21 January 2013 **Date of last patient completed/last follow-up:** 11 March 2019	**Phase of Development:** 3
Objectives: **Primary objective:** • To compare the therapeutic efficacy of Docetaxel, Oxaliplatin and Capecitabine (low-TOX) vs. Epirubicin, Oxaliplatin and Capecitabine (EOX) as measured by the duration of Progression Free Survival (PFS) in patient with locally advanced/metastatic gastric cancer. **Secondary objectives:** • To evaluate additional measures of tumor control to further characterize the efficacy of the low-TOX regimen vs. EOX regimen. • Evaluation of the safety profile of the combinations tested.	
Methodology: This is a phase III multicenter, randomized, parallel group, non-blinded study, aimed at comparing the therapeutic efficacy (Progression Free Survival [PFS], Overall Survival [OS], Objective Response Rate [ORR] and Disease Control Rate [DCR]) of Docetaxel, Oxaliplatin and Capecitabine (low-TOX regimen) versus the combination of Epirubicin, Oxaliplatin and Capecitabine (EOX). Eligible Patients with advanced (locoregional or metastatic) gastric cancer had been assigned in a ratio of 1:1	

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to receive either the following drug combinations:

low-TOX: in arm A chemotherapy consisted of:
- *Docetaxel* 35 mg/ m2, i.v. on days 1 and 8 by 1-hour infusion;
- *Oxaliplatin* 80 mg/ m2, i.v. on day 1 by 2-hour infusion;
- *Capecitabine* 750 mg/ m2 (oral tablets of 500 and 150 mg) x2 daily for 2 weeks, followed by one week rest.

EOX: in arm B chemotherapy consisted of:
- *Epirubicin* 50 mg/ m2, i.v. on day 1 by 2-hour infusion;
- *Oxaliplatin* 130 mg/ m2, i.v. on day 1 by 2-hour infusion;
- *Capecitabine* 625 mg/ m2 (oral tablets of 500 and 150 mg) x2 daily for 3 weeks

Eligible patients should have their tumor status assessed (RECIST 1.1) have been performed every 3 cycles while on treatment and every 12 weeks thereafter until progression. After documented disease progression, information on survival status was collected in all patients every 12 weeks.

Number of Subjects (Planned and Analyzed):

It was planned to enroll up to 190 patients (95 per arm). Interim analyses were performed on the preliminary data,available during the course of the Study. Due to the lack of promising results in terms of efficacy improvement it was decided to early stop the trial for futility and only up to 169 patients were enrolled in the study. Among the whole enrolled population, five patients have never been treated, so the total number of patients randomized and treated amounts to 164 units (82 per arm).

Diagnosis and Main Criteria for Inclusion:

Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Signed written informed consent prior to beginning protocol specific procedures
2. Male or female > 18 years of age
3. Histologically proven diagnosis of adenocarcinoma of the stomach,
4. HER2 negative tumor or HER2+ tumors not qualifying for herceptin therapy
5. Locally advanced (non resectable) or metastatic gastric cancer.
6. Presence of measurable disease with at least one measurable lesion by means of CT scan or MRI in not previously irradiated area(s) (according to RECIST criteria (version 1.1)
7. Life expectancy of ≥3 months
8. ECOG performance status of 0-2 at study entry
9. Neutrophils ≥ 2.0 x 109/L, platelets ≥100 x 109/L, and hemoglobin ≥ 10 g/dL
10. Bilirubin level either normal or ≤ 1.5 x UNL
11. AST and ALT ≤ 2.5 X UNL (≤ 5 x ULN if liver metastasis are present)
12. Alkaline phosphatase (ALP) ≤ 2.5 X ULN ; patients with alkaline phosphatase > 2.5x ULN and AST and ALT ≤ 1.5 x ULN are equally eligible.
13. Serum creatinine < 1.5 x ULN. In presence border-line values, the calculated creatinine clearance should be ≥ 60 mL/min.
14. Negative pregnancy test (if female in reproductive years)
15. Effective contraception prior to study entry and for the duration of the study participation, for both male

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and female patients of child producing potential.

16. Able and willing to comply with scheduled visits, therapy plans and laboratory tests required in this protocol.

Subject Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment:

1. Previous chemotherapy, except adjuvant treatment administered at least 1 year before study entry
2. Concurrent chronic systemic immune therapy
3. Any investigational agent(s) 4 weeks prior to entry
4. Clinically relevant coronary artery disease or a history of a myocardial infarction or a history of hypertension not controlled by therapy within the last 12 months
5. AST or ALT > 1.5 X ULN associated with alkaline phosphatase > 2.5 X ULN
6. Known hypersensitivity to study drugs. Known grade 3 or 4 allergic reaction to any of the components of the treatment
7. Known drug abuse/ alcohol abuse
8. Acute or subacute intestinal occlusion and any other significant chronic gastrointestinal disease that might interfere with absorption of oral treatment
9. History of clinically relevant psychiatric disability precluding informed consent
10. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
11. Pregnant or breastfeeding women
12. Active uncontrolled infection(s)
13. Positive for HIV serology and/or viral hepatitis B or C
14. Any concurrent malignancy other than non-melanoma skin cancer, or carcinoma in situ of the cervix. (Patients with a previous malignancy but without evidence of disease for ≥ 5 years will be allowed to enter the trial).

Test Product, Dose and Mode of Administration

low-TOX: in arm A chemotherapy consisted of:

- *Docetaxel* 35 mg/ m2, i.v. on days 1 and 8 by 1-hour infusion;
- *Oxaliplatin* 80 mg/ m2, i.v. on day 1 by 2-hour infusion;
- *Capecitabine* 750 mg/ m2 (oral tablets of 500 and 150 mg) x2 daily for 2 weeks, followed by one week rest.

EOX: in arm B chemotherapy consisted of:

- *Epirubicin* 50 mg/ m2, i.v. on day 1 by 2-hour infusion;
- *Oxaliplatin* 130 mg/ m2, i.v. on day 1 by 2-hour infusion;
- *Capecitabine* 625 mg/ m2 (oral tablets of 500 and 150 mg) x2 daily for 3 weeks

Cycles were repeated every 3 weeks.

Doses of oxaliplatin, epirubicin, docetaxel and capecitabine were allowed to be reduced in the case of adverse events related to the drugs. Reduction/interruption of dosing for adverse events could take place at any time during the study.
Once dose reductions were made, re-escalation of doses was not permitted.

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Duration of Treatment:

Treatment consisted of 3 combination-chemotherapy cycles for both arms unless progression or unacceptable toxicity or treatment refusal.

In the absence of progression, patients who achieved a complete response after cycle 3 were able to receive two further cycles of therapy, for a maximum of 5 cycles. Otherwise, in case of partial response or stable disease after cycle 3, the patients received further three cycles of chemotherapy, for a maximum of 6 cycles.

Endpoints and Criteria for Evaluation:

Primary Endpoint:

- Progression Free Survival (PFS), defined as the time from randomization to the date of local or regional progression, distant metastasis, second primary malignancy or death from any cause, whichever comes first. Subjects not progressed or died while on study or lost to follow up, are to be censored at the last disease assessment date.

Secondary Endpoints:

- Overall Survival (OS), defined as the time from randomization to the date of death from any cause. Subjects, who have not died while on study or have been lost to follow up, are to be consored at the last contact date.
- Objective Response Rate (CR + PR) according to RECIST 1.1 guideline
- Disease control rate: CR+ PR + SD > 12 weeks
- Tolerability of the treatments evaluated in term of: side effects graded according to the NCI-CTCAE scale (version 4.0); serious adverse reactions, expected and unexpected.

Statistical Methods:

The randomized controlled phase III design is the most widely accepted design for the comparison of efficacy of two treatments in patients with advanced cancer. The recent evidence reported in the literature supports PFS as a surrogate of survival in patients with gastric cancer.

The current study was designed to test testing whether TOX regimen could provide a 35% reduction of the risk of progression as compared to EOX (i.e. Hazard Ratio ≤ 0.65 under alternative hypothesis). In this case, the experimental drug combination would be considered effective, otherwise, if the reduction was below this threshold, then the efficacy improvement given by the tested drug association would be considered as not effective.

Required sample size was 190 enrolled subjects. An interim analysis was planned in order to consider whether the trial should be stopped for futility. Such analysis was intended tobe conducted after the first 127 events (75% of the total number of events) have been observed. Conditional Power (CP) method was applied for the current study. The threshold was set to 30% and the trial could be stopped early if the computed CP was below this threshold value

All data analyses were performed after database was released. Statistical programming and analyses were performed using validated statistical software (SAS 9.4) as required.

The statistical analyses were performed as outlined in the Statistical Analysis Plan, which was finalized prior to database lock and was included in the clinical study report for this protocol. The final statistical analysis plan took into account any amendment to the protocol.

Descriptive statistics were used to describe patients' disposition and demographic variables in all the enrolled and randomized patients. Distribution of these data were presented by summary statistics such as median,

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minimum and maximum, mean and standard deviation for quantitative outcomes; frequency distributions were used for the categorical/categorized variables. The same method was applied to describe treatment administration (e.g. number of cycles, treatment delays/modifications), safety analysis (e.g. number/percentage of patients with adverse events) and laboratory assessments on the treated patient population.

Primary analysis of the study was conducted on Progression Free Survival (PFS) for all randomized patients, according to the actual treatment they have received. PFS was computed from date of randomization until progression or death for any cause, whichever comes first. Patients who have not died or progressed or taken another therapy in absence of progression at the time of analysis were censored at they were lastly known alive. Survival curves of the two arms were compared by the log-rank test stratified by Performance Status (0 or 1) and Kaplan Meier method was used to estimate cumulative survival probability.
Likewise PFS, Kaplan Meier method was applied for Overall Survival (OS).
Point estimates and 95% confidence interval estimates were calculated for Objective Tumor Response Rate (ORR), as well as for Disease Control Rate (DCR). The between treatment comparison was done by Mantel Haenszel Chi–Square test, controlling for ECOG PS.

SUMMARY OF RESULTS:

Disposition of Subjects and Baseline Characteristics:
Between 21 January 2013 and 14 May 2018, 169 patients with locally advanced/ metastatic gastric cancer were enrolled and randomized at 23 Italian Investigational Sites.

Data collected recorded a total number of 164 subjects known to be treated, 82 for each arm. Five patients were randomized in the control arm, however they have never been treated and went off study for Investigator's decision (patient 0044) , consent withdrawal (patient 0098 and 0115) and Death (patient 0027 and 0122).

Overall, among the whole treated population, 71 patients completed treatment as per protocol (43.3%). The major reasons for treatment discontinuation were Progression Disease (37 patients, 22.6%), Investigator Decision (15 patients, 9.1%) and toxicity (14 patients, 8.5%); Death reason was reported for 4 patients (2.4%).

Patients declared as off-study amounted to 139 randomized subjects. Among such patients, the main reason was due to death (116 enrolled patients, 68.6%).

An overview of the disposition of subjects, by group, is outlined in Fig.1.

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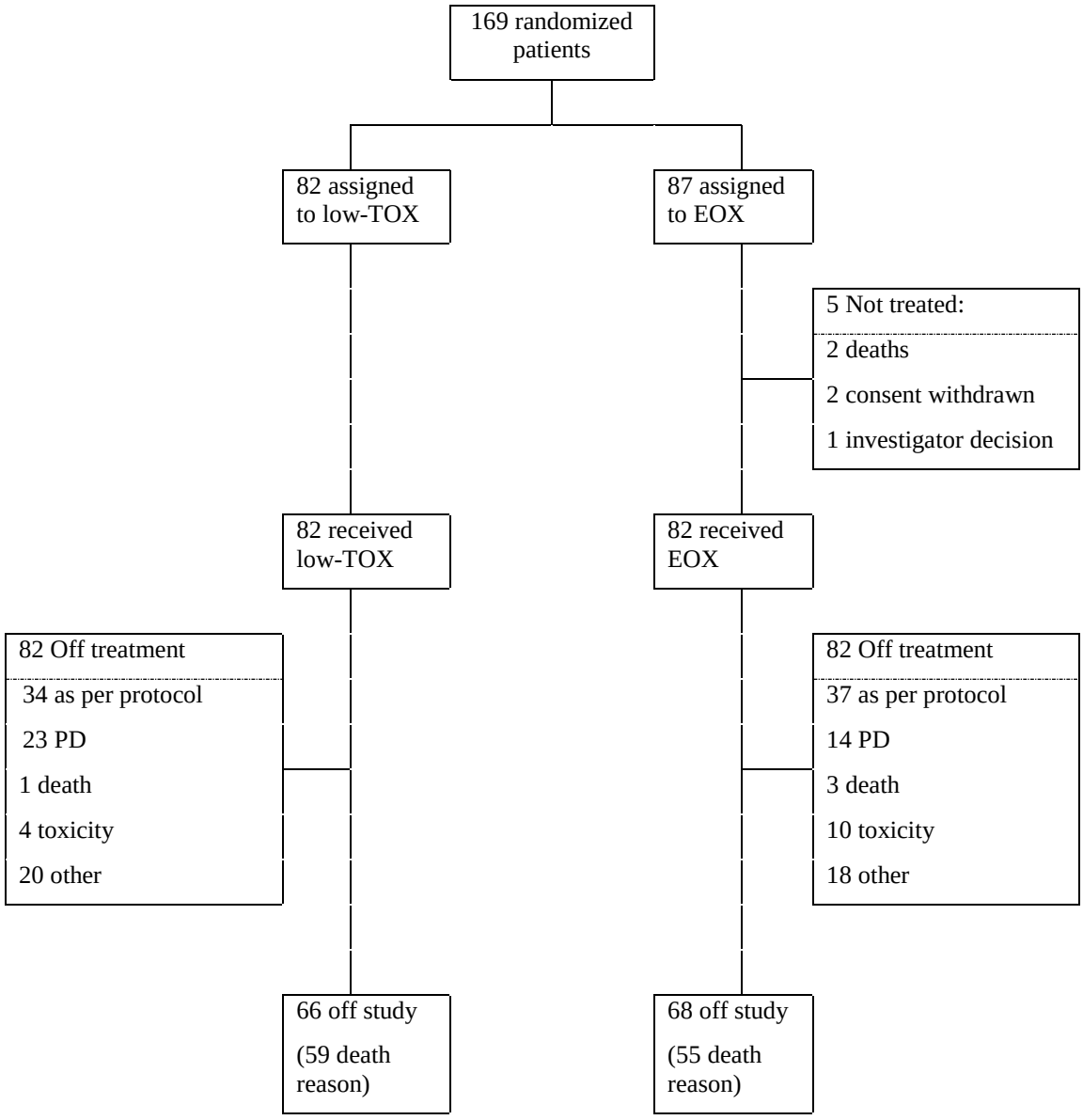
Figure 1. Patient's Disposition Overview.



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As reported in Table 1, the median age was 62 years (min 31- max 84), 65% male, and ECOG PS score of 0 in 128 patients (75.7%), and 1 in 37 patients (21.9%). As expected, no relevant differences emerged between the two groups for such factors.

Table 1: Demographic and Baseline Characteristics of the Patients

	low-TOX (N = 82)	**EOX (N = 87)**	**All Randomized Patients (N=169)**
Age (yr) — median (min - max)	64 (33 - 84)	61 (31 - 77)	62 (31 - 84)
Sex – no (%)			
Male	53 (64.6)	56 (64.4)	109 (64.5)
Female	29 (35.4)	31 (35.6)	60 (35.5)
ECOG PS — no. (%)			
0	62 (75.6)	66 (75.9)	128 (75.7)
1	20 (24.4)	17 (19.5)	37 (21.9)
Missing		4 (4.6)	4 (1.8)

The majority of enrolled patients showed at the study entry a Metastatic disease (150 patients, 88.7%) and a histopatological grade poorly differentiated (87 patients, 51.5%); in most cases patients had evidence of Intestinal histological disease (56 patients, 33.1%) and Diffuse classification (46 patients, 27.2%). Table 2 reported the mentioned tumor characteristics frequency distribution for both study groups, as well as for the whole randomized population.

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Table 2: Tumor Characheristic of the Patients

Variable	low-TOX (N = 82)	EOX (N = 87)	All Randomized Patients (N=169)
Histological Disease – no (%)			
Intestinal	29 (35.4)	27 (31.0)	56 (33.1)
Diffuse	27 (32.9)	19 (21.9)	46 (27.2)
Other	19 (23.2)	29 (33.3)	48 (28.4)
Mix	5 (6.1)	6 (6.9)	11 (6.5)
Missing	2 (2.4)	6 (6.9)	8 (4.7)
Disease Extent at Study Entry – no (%)			
Metastatic	70 (85.4)	80 (91.9)	150 (88.8)
Locally Advanced	12 (14.6)	6 (7.0)	18 (10.7)
Missing		1 (1.1)	1 (0.6)
Histopatological Grade			
Well differentiated (G1)	1 (1.2)	1 (1.2)	2 (1.2)
Moderately differentiated (G2)	15 (18.3)	9 (10.3)	24 (14.2)
Poorly differentiated (G3)	34 (41.5)	53 (60.9)	87 (51.5)
Not differentiated (G4)	1 (1.2)	3 (3.5)	4 (2.4)
Not evaluable (GX)	9 (11.0)	1 (1.2)	10 (5.9)
Unknown/Missing	22 (26.8)	20 (22.9)	42(24.9)

Treatment Exposure:

On April 17, 2019, cutoff date, all the 164 treated patients had discontinued treatment. For each of the two study groups, almost half of subjects completed treatment as per protocol (41.4% in low-TOX vs 45.1% in EOX). The most common reasons for early discontinuation in both groups was Progression Disease (37 subjects) and toxicity (14 patients). The 47 treated patients received a total of 273 cycles The median duration of treatment was 18.2 weeks (range, 3.0 to 30.7) in the experimental arm and 18.1 months (range, 3.0 to 58.3) in the EOX group. Treatment modification occurred for most of treated patients (91.5% low-TOX vs 78.0% in EOX); A summary of the frequency distribution of the treatment modification is reported in Table 4. Treatment modifications occurred for hematological toxicities in 25 patients (30.5%) in low-TOX group, whereas in EOX arm they occurred in 30 patients (36.6%). A brief summary of treatment exposure is reported in the following table 3:

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Table 3: Treatment Exposure

Variable	low-TOX (N = 82)	EOX (N = 82)
Cycles – median (min - max)	5.5 (1 - 6)	6 (1 – 6)
Treatment duration (weeks) – median (min . max)	18.2 (3.0 – 30.7)	18.1 (3.0 – 58.3)
Treatment Modification - No (%)		
Any modification	75 (91.5)	64 (78.0)
Dose Delayed	59 (72.0)	48 (58.5)
Dose Reduced	41 (50.0)	29 (35.4)
Dose Omitted	44 (53.7)	28 (34.1)
Reasons for Treatment modification – No (%)		
Any Reason	75 (91.5)	64 (78.0)
Hematological Toxicities	25 (30.5)	30 (36.6)
Hepatic Toxicities	1 (1.2)	1 (1.2)
Neurological Toxicities	3 (3.7)	3 (3.7)
Other Toxicities	73 (89.0)	55 (67.1)

Efficacy Results:

Progression Free Survival

According to the protocol, an interim analysis was planned after the first 127 events evaluable for the primary endpoint (PFS) were detected. However a few exploratory interim analyses were also conducted before this cut-off step, in order to observe the preliminary results in terms of efficacy. All the analyses showed an evident lack of improvement in favor of the experimental arm, both for primary and secondary efficacy endpoints. This evaluation was also made by observing the calculated conditional power, which was always well below the cut-off value of 30%. These results indicated that it was unlikely that low-TOX regimen was able to reach the target of improvement against EOX, and for this reason it was made the decision to stop prematurely the study for futility.

Concordantly with the planned interim analysis to be performed by protocol, data available at the cut-off date of 17 April 2019, revealed no signs of clinical evidence for the experimental regimen. The primary analysis was conducted on the evaluation of a total number of 132 events (i.e. 78% of the expected number). Seventy events were detected in the low-TOX arm (38 were PD), whereas the number observed in the EOX arm was 62 , of which 37 PD. Median progression free survival was comparable in the two arms (6.3 months vs. 6.3 months; hazard ratio in the experimental group, 0.975; 95% confidence interval [CI], 0.686 to 1.384; Log-Rank Test P-value=0.885) . The calculated conditional power was equal to 0.00%, which confirmed at this step the lack of chance to reach the aimed target point of 35% reduction of risk. Considering this evident lack of evidence, no exploratory multivariate analysis with the use of a Cox proportional-hazards model was

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considered to be implemented.

Summary results are reported on Table 4 and Fig. 2.

Overall Survival

Death occurrences amounted in 114 patients (59 in Arm A vs 55 in Arm B). The median overall survival time did not differ significantly between the low-TOX group and EOX group (11.5 and 12.4 months, respectively; hazard ratio, 1.002; 95% CI, 0.691 to 1.452; Log-Rank Test P-value = 0.992). The estimated rate of overall survival at 12 months was 49.9% in the experimental group and 51.3% in the control group. Summary results are reported on Table 5 and Fig. 3

Response rates and disease-control rate

In the low-TOX group, 2 patients (2.4%) had a Complete Response (CR), 18 patients (22.0%) had a partial response, and 35 (42.7%) had stable disease (according to RECIST 1.1), whereas in the EOX group, 4 patients (4.9%) had a CR, 23 subjects (28.0%) had partial response and 29 (35.4%) had stable disease. The objective Tumor Response rate (i.e. confirmed CR and PR) was comparable between the two arms (24.4% vs. 32.9%, P = 0.585). The same conclusion was obtained for the Disease Control rate (67.1% vs. 68.3%, P = 0.279).

Table 4: Treatment Efficacy

Outcome	low-TOX (N = 82)	EOX (N = 82)	Hazard Ratio (95% CI)	P Value
Overall survival				
Number of Events	59	55		
Median (months)	11.5	12.4	1.002	0.992 *
95% CI	86 -15.0	9.1 – 19.2	(0.691 – 1.452)	
Progression Free Survival				
Number of Events	70	62		
Death	32	25		
Progression Disease	38	37		
Median(months)	6.3	6.3	0.975	0.885 *
95% CI	5.0 – 7.8	5.0 – 8.1	(0.686 –1.384)	
Level of response				
Complete	2 (2.4%)	4 (4.9%)		
Partial	18 (22.0%)	23 (28.0%)		
Stable disease	35 (42.7%)	29 (35.4%)		
Objective Response Rate (%)	24.4%	32.9%		0.585†
95% CI	13.6% - 29.4%	16.8% - 32.3%		
Disease-control rate (%)	67.1%	68.3%		0.279†
	46.3% - 65.5%	40.1% - 58.2%		

*calculated by Log-rank test stratified by ECOG Performance Status
† calculated by Mantel Haenszel Chi–Square test controlling for ECOG Peformance Status

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Fig 2 Kaplan Meier Curve for Progression Free Survival

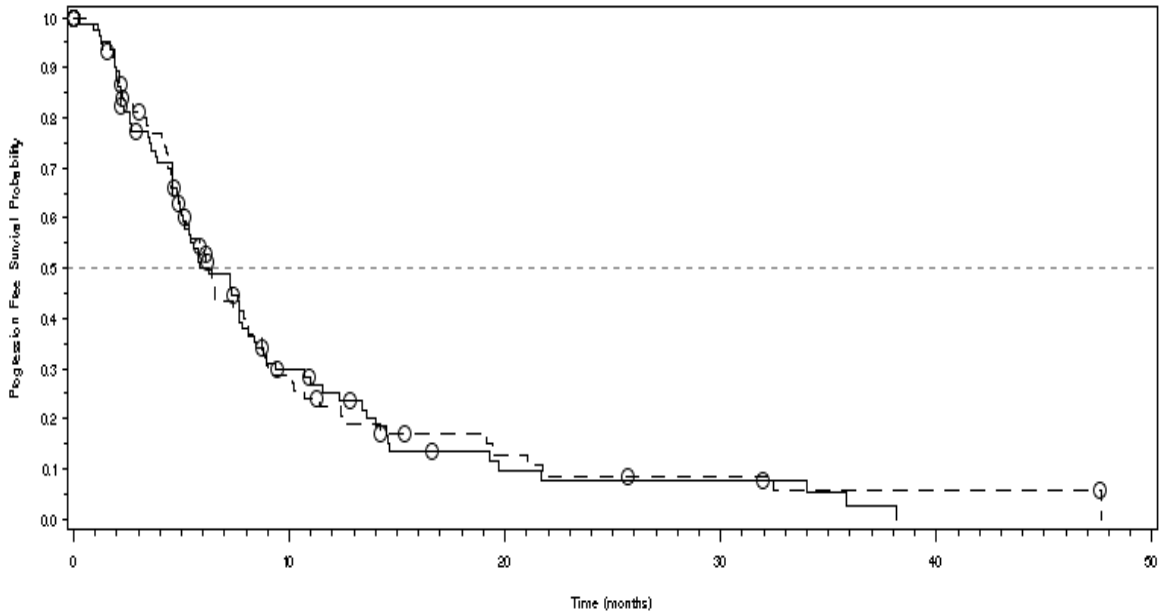
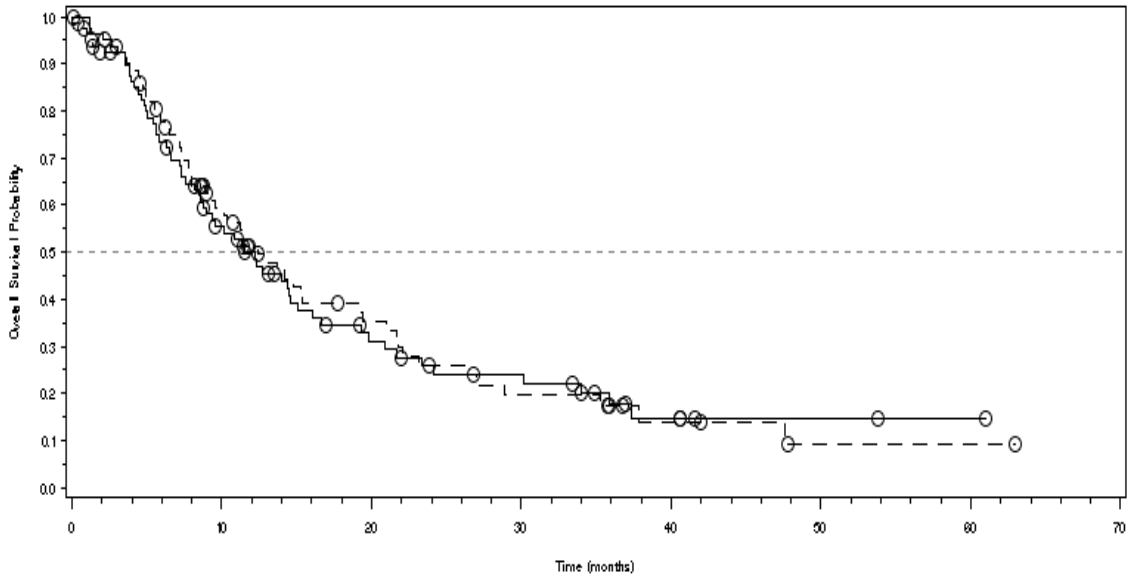


Fig 3 Kaplan Meier Curve for Overall Survival



------- Arm A: low-TOX - - - - Arm B: EOX

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Safety Results:

Overall 164 patients were treated and were evaluable for safety (82 per arm). Seventy-one patients completed the planned treatment cycles.
Among the whole treated population, 153 subjects experienced at least 1 treatment emergent AE in the first or subsequent cycles. The overall incidence was 5.1% in the low-TOX group and 91.5% in the EOX group.

Adverse events that were reported for patients receiving low-TOX regimen were predominantly grade 1 or 2 in severity. Overall the most frequent drug related AEs (frequency of ≥ 25%) in the experimental arm were fatigue (40 patients, 48.8%), diarrohoea (40 patients, 48.8%), nausea (37 patients, 45.1%), vomiting (27 patients, 32.9%), palmar-plantar erythrodysaesthesia syndrome (22 patients, 26.8%) and anaemia (22 patients, 26.8.%).

Overall no significant difference were observed between the two arms in terms of number of patients who experienced any TEAE, as well as Drug related events. However diarrohoea (48.8% vs 29.3%), mucosal inflammation (24.4% vs 8.5%), palmar-plantar erythrodysaesthesia syndrome (26.8% vs 11.0%), erythema (12 patients, 14.6%), rash (11.0% vs 1.2%), conjunctivitis (8 patients, 9.8% vs none) and deep vein thrombosis (5 patients, 6.1% vs none) occurred at a higher frequency in the experimental group than in the control arm.
Treatment emergent drug related Grade 3-4 events occurred in 94 patients. It was detected a slight higher number of patients who presented such events in the low-TOX arm (65.9% vs 48.8%). More in details, it was detected a higher incidence of patients in the experimental arms who presented diarrhea (17.1% vs 3.7%) and mucosal inflammation (7.3% vs 0%). One treatment emergent Grade 5 event (digestive bleeding) was reported in control arm (pt. 0022).

Moreover the overall incidence of serious adverse events from any cause was 29.3% (24 patients) in the low-TOX group and 18.3% (15 patients) in the EOX group. Three patients died on study, two due to adverse event (digestive bleeding and worsening clinical condition) and one due to clinical progression of gastric cancer disease.

In low-TOX arm hematological abnormalities mainly included: hemoglobin decrease (55 patients, 73.3%, 4.1% Grade 3), lymphocytopenia (33 patients, 44.0%, 4.0% Grade 3), leukopenia (37 patients, 49.3%, 6.6% Grade 3-4), and thrombocytopenia (24 patients, 32.0%, all Grade 1-2). Indeed a lower number of patients with neutrophils decrease was detected in low-TOX Arm (30 patients, 40.0%, 8.0% Grade 3-4 vs 44 patients, 61.1%, 25.0% Grade 3-4).

Blood chemistry laboratory abnormalities detected in the experimental group were mainly mild to moderate with the exception of two cases of Grade 3 hyperglycemia, two cases of Grade 3 hypokaelemia, one case of Grade 4 hypocalcemia, and one case of Grade 3 hyponatremia.

Name of Sponsor: Fondazione GISCAD (Gruppo Italiano per lo studio dei Carcinomi dell'Apparato Digerente)

(For National Authority Use only)

Name of Active Ingredient: Docetaxel + Oxaliplatin + Capecitabine (low-TOX)
Epirubicin + Oxaliplatin +Capecitabine (EOX)

Therapeutic Area: Oncology

Indication: Locally Advanced / Metastatic Gastric Cancer

Table 5: Treatment Safety

	All Treated Patients (N=164)		low-TOX (N = 82)		EOX (N=82)		
	n	%	n	%	n	%	P-Value*
Patients with TEAE	153	93.3	78	95.1	75	91.5	0.349
Patients with TEAE Drug Related	149	90.9	75	91.5	74	90.2	0.786
Patients with Serious TEAE	39	23.8	24	29.3	15	18.3	0.099
Patients with Serious TEAE Drug-Related	17	10.4	11	13.4	6	7.3	0.200
Patients with CTC Grade≥3 TEAE	94	57.3	54	65.9	40	48.8	0.027
Patients with CTC Grade≥3 TEAE Drug-Related	77	47.0	42	51.2	35	42.7	0.273
Patients with TEAE Leading to Death	1	0.6			1	1.2	0.316

*Calculated with Comparison Chi-Square Test

CONCLUSIONS:

This study was designed to capture the benefits of a potentially efficacious reduced-dose regimen, since docetaxel combinations are currently limited by the toxicity observed. A low-TOX regimen has been defined to improve the tolerability of the docetaxel combination. The planned interim analysis was conducted when 132 patients were evaluable for the primary endpoint. The analysis showed that patients in both groups had a median progression free survival of 6.3 months. The lack of efficacy improvement of low-TOX regimen was confirmed also by evaluating the median overall survival (11.5 mo vs 12.4 mo). Moreover the evaluation of the objective tumor response (24.4% vs 32.9%) and Disease Control Rate (67.1% vs 68.3%) supported the conclusion emerged from the primary analysis. It was not observed an overall increase of the incidence of adverse events in this study for the experimental arm, compared to the control group. The adverse events that were more common in the low-TOX group were mainly mild to moderate in severity. It was detected a weak higher frequency of patients who showed grade 3-4 events of any cause in the low-TOX arm. More specifically the two most relevant grade 3-4 drug-related adverse events were diarrhea and mucosal inflammation (17.1% and 7.3%, respectively).
In summary, the final analysis performed after database lock confirmed the lack of results emerged by the interim analyses performed during the study: it was not identified an improvement of the efficacy profile, both in terms of survival benefit and objective response, of the low-TOX regimen, even though the overall toxicity of such combination remained acceptable.

Date of the report:

30 July 2019