First-Line Dose-Dense Chemotherapy With Docetaxel, Cisplatin, Folinic Acid and 5-Fluorouracil (DCF) Plus Panitumumab (P) in Patients With Locally Advanced or Metastatic Cancer of the Stomach or Gastroesophageal Junction (GEJ): A Phase II Multicenter Trial

Abstract 146

Tomasello G, Liguigli W, Toppo L, Mattioli R, Negri F, Curti A, Ratti M, Poli R, Lazzarelli S, Gerevini F, Colombi C, Martinotti M, Rovatti M, Olivetti L, Passalacqua R

Background

- Combination chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF or TCF) is a standard first-line regimen for metastatic gastric cancer[1]
- Dose-dense chemotherapy with docetaxel, cisplatin, folinic acid, and 5-fluorouracil showed to be an effective treatment for metastatic gastric cancer[2]
- In metastatic colorectal cancer, the efficacy of panitumumab is limited to wild-type RAS expressing subtypes
- KRAS mutation rate in gastric cancer is very low[3]
- To date, only a phase III trial tested panitumumab efficacy in combination with EOC chemotherapy showing no survival benefit over chemotherapy alone.[3] This was probably due to the high rate of toxicity observed in the experimental arm, which limited the delivery of an adequate dose intensity and to a possible negative interaction of panitumumab with one or more EOC components (ie, oxaliplatin)
- Panitumumab activity when combined with DCF is currently unknown
- In advanced gastric cancer it is possible to foresee at least an additive effect of anti-EGFR agent to chemotherapy, when combining these treatments

EOC, epirubicin, oxaliplatin, capecitabine

1. Van Cutsem E, et al. *J Clin Oncol*. 2006;24(31):4991-4997. 2. Tomasello G, et al. *Gastric Cancer*. 2014;17(4):711-717. 3. Waddell T, et al. *Lancet Oncol*. 2013;14(6):481-489.

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Treatment Schema

Docetaxel 60 mg/m2 day 1
Cisplatin 50 mg/m2 day 1
L-folinic acid 100 mg/m2 day 1, 2
5-fluorouracil 400 mg/m2 bolus day 1 and 2
5-fluorouracil 600 mg/m2 CI 22 h day 1 and 2
Panitumumab 6 mg/kg day 1
Peg-filgrastim 6 mg SC day 3

Cycles repeated every 2 weeks*

***Patients aged >65 years received a 30% dose reduction of all chemotherapy drugs. Dose of panitumumab was not reduced.**

Chemotherapy was continued for a maximum of 6 cycles (4 cycles after the first amendment on 27/2/2012).

Maintenance therapy with panitumumab single agent was administered until disease progression, unacceptable toxicity, patient's refusal or physician's choice.

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Study Objectives

- The primary objective was to assess the anti-tumor activity of panitumumab in combination with a dose-dense chemotherapy regimen in terms of overall response rate (ORR)* (complete and partial responses)
- Secondary objectives were:
  - Toxicity and safety
  - Overall survival (OS)
  - Time to progression (TTP)
  - Translational research

*The estimate ORR for the treatment with chemotherapy alone was 45% (Dalla Chiesa M, 2007). We chose the lower activity (p0) of 0.45. The target activity level (p1) was 0.65. A total of 48 assessable patients were needed to guarantee 80% power under a [alpha]-level of 5%. Assuming that about 10% of patients would have been lost before evaluation (refusal or suspension for toxicity) the number of patients needed to enroll was 52.

Dalla Chiesa M, et al. *J Clin Oncol.* 2007;25(18S): Abstract 15068.

Tomasello G, et al. *J Clin Oncol.* 2015;33(suppl 3): Abstract 146.

Eligibility Criteria

Inclusion

- Histologically confirmed advanced carcinoma of the stomach or esophagogastric junction
- Patients with locally advanced not resectable tumors
- Age ≥18 and ≤75 years
- ECOG performance status ≤1
- Adequate organ function

Exclusion

- HER2-positive patients (IHC 3+ or IHC 2+ with FISH amplified)
- Uncontrolled CNS metastases
- Prior chemotherapy for the advanced disease
- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤1 year before enrollment

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Baseline Characteristics

	n	%
Enrolled patients	52	100
Metastatic	47	90
Locally advanced not resectable	5	10
Assessable for toxicity	52	100
Assessable for response	50	96
Age	64.5 years (median) 26 patients aged >65 years	Range 42-75 years 50
Sex:		
Male	39	75
Female	13	25
Performance status:		
0	27	52
1	25	48
Metastatic sites:		
Lung	9	17
Lymph nodes	40	77
Bone	6	11
Liver	21	40
Peritoneum	21	40
Other	6	11
>1 metastatic site	31	60
Histology:		
ADK	50	96
Other	2	4
Tumor grade		
1	1	2
2	12	23
3	39	75

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Results

	n	%
Partial response	29	58
Complete response	3	6
Stable disease	10	20
Progression	8	16
ORR	32	64 (95% CI, 51-77)
Disease control rate	42	84
Not evaluable*	2	4

* 1 patient died after 3 cycles of chemotherapy due to myocardial infarction; 1 patient died after the first cycle due to bowel occlusion

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Patients' Compliance With Dose-Dense Schedule

	n	%
Compliance with dose-dense regimen and no dose reduction	22	42%
Compliance with dose-dense regimen and dose reduction	16	31%
No-compliance with dose-dense regimen and no dose reduction	8	15%
No-compliance with dose-dense regimen and dose reduction	6	12%

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Toxicity

Grade 3/4 toxicity	n	%
Leucopenia	15	29%
Neutropenia	10	19%
Febrile neutropenia	7	13%
Anemia	5	10%
Thrombocytopenia	4	8%
Asthenia	14	27%
Mucositis	7	13%
Nausea / vomiting	6	12%
Diarrhea	8	15%
Skin toxicity	13	25%
Hypomagnesemia	2	4%
Toxic deaths	2	4%

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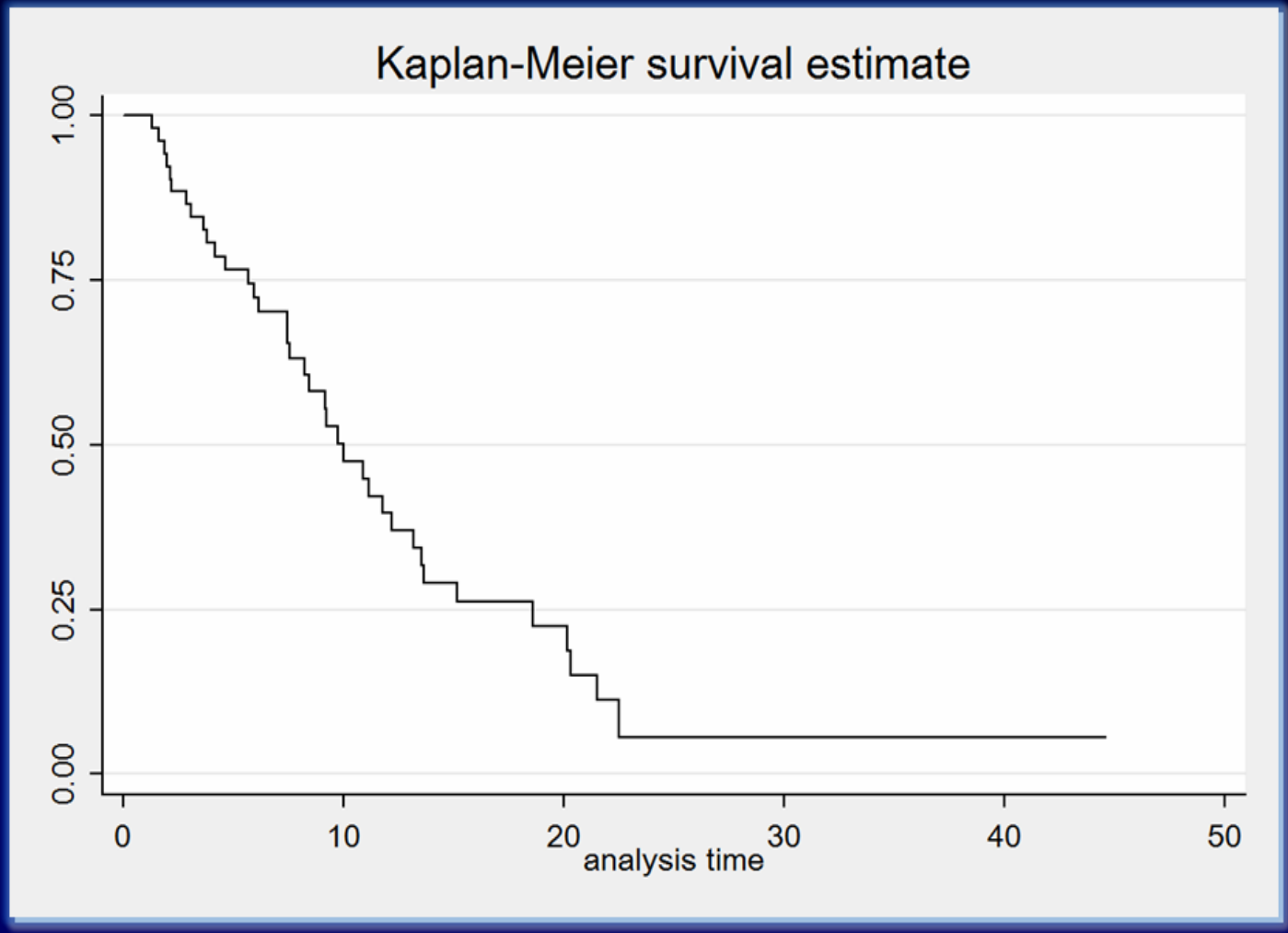
Secondary Endpoints: OS



Median OS: 9.4 months (95% CI, 7.4-11.6)

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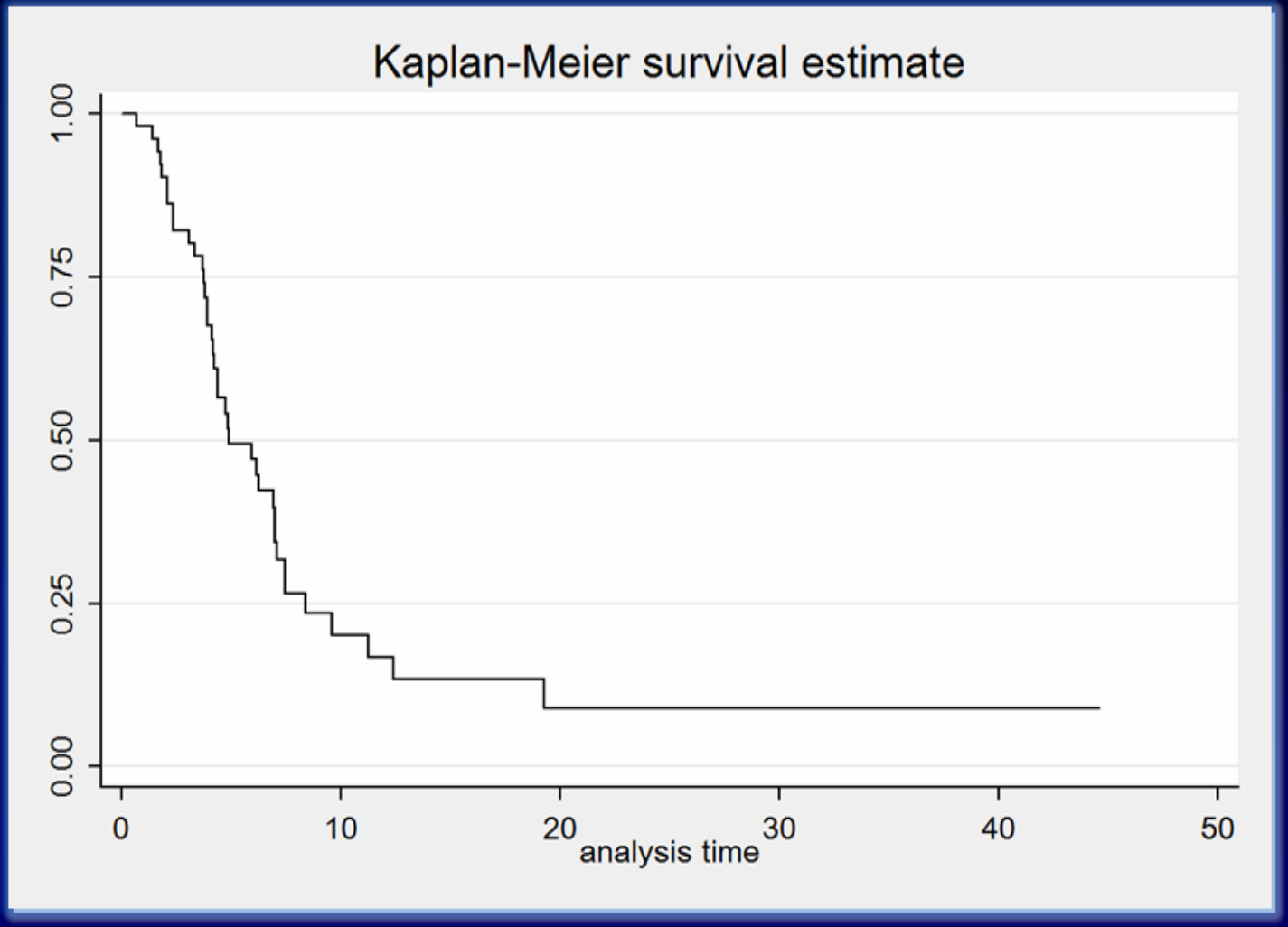
Secondary Endpoints: TTP



Median TTP: 4.8 months (95% CI, 4.1-6.9)

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Summary

- At our knowledge, this is the first study in gastric cancer which combines a monoclonal antibody with a dose-dense chemotherapy regimen, followed by maintenance therapy with panitumumab single-agent
- Primary endpoint of the study has been reached with an ORR of 64% with the addition of the antibody; OS and TTP are in line with literature data
- Due to toxicity, only 42% of patients respected the dose-dense schedule with no dose reductions. Likewise REAL-3 study, this confirms the difficulty in administering an intensive chemotherapy regimen in combination with an anti-EGFR antibody
- 50% patients entered the maintenance phase with panitumumab, which was administered for a median of 14 weeks
- Seven patients (13%) not receiving maintenance therapy underwent gastrectomy. In an exploratory analysis comparing this subgroup with patients with no surgery (24) or gastrectomized before study entry, median OS was 20.0, 8.4, and 9.7 months respectively
- Dose-dense chemotherapy combined with panitumumab is a very active regimen in gastric cancer
- Due to a not negligible toxicity profile, it may represent a treatment option in neoadjuvant setting
- Further translational studies aimed at identifying reliable predictive biomarkers are definitely needed

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