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667PD: Tom Waddel	**A randomised multicentre trial of epirubicin, oxaliplatin and capecitabine, (EOC) +panitumumab in advanced oesophago-gastric cancer (REAL-3): updated results.**
668PD: Jaffer Ajani	Non inferiority analysis of muticenter phase III comparing cisplatin/S-1 with cisplatin/5-FU (CF) as first line therapy in pateints with advanced gastric cancer (FLAGS): methodology and results

- **Two trials on gastric cancer with different aims:**
  - **667: improving efficacy of treatment by using a target therapy (panitumumab)**
  - **668: improving patients' compliance and quality of life by reducing side effects and discomfort of therapy**

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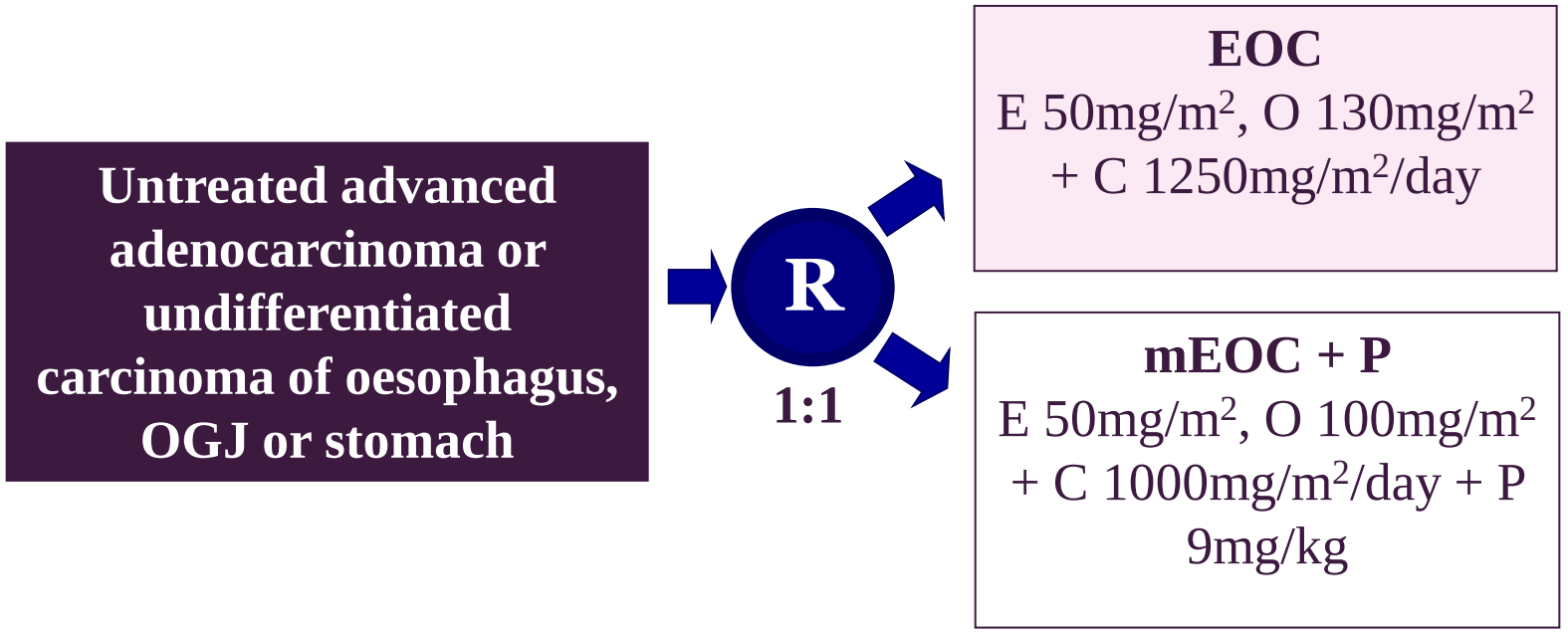
Gastric cancer and EGFR inhbition

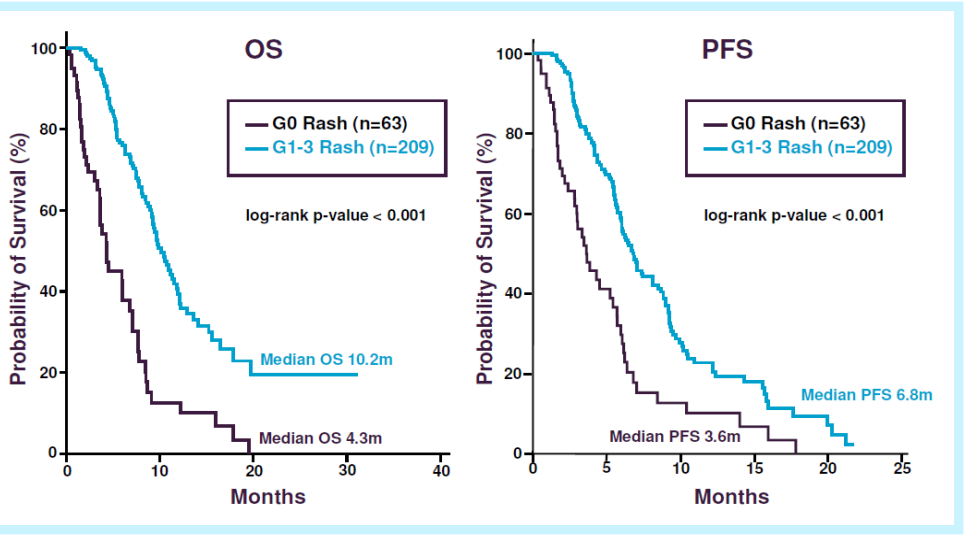
- Medical treatment of gastric cancer is an unmet need: there is no standard therapy apart from fro HER-2 positive tumours
- EGFR seemed to be an attractive target (overexpression prognostic);
- phase II trials (Pinto, Lordick) promising

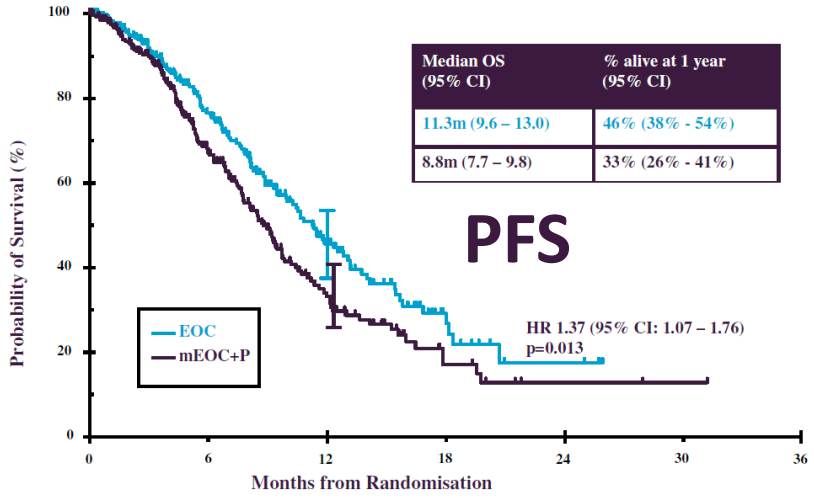


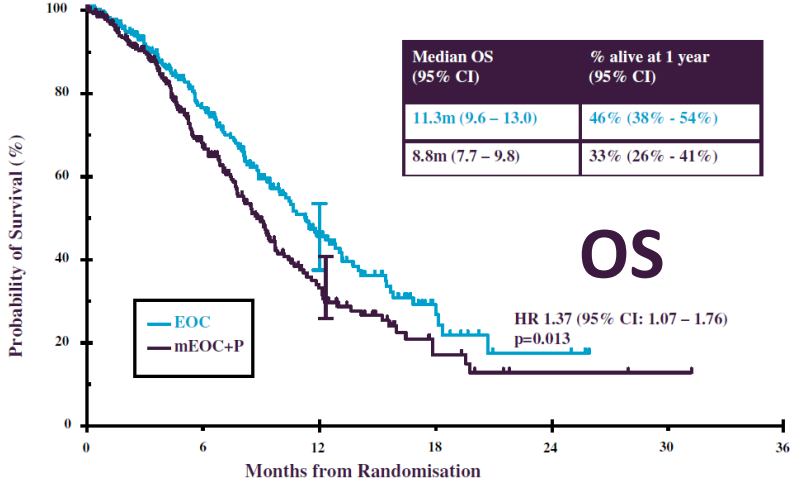
Phase III Trial:

- Primary endpoint: overall survival (OS)
  - Aiming for 10% improvement in 1-year survival rate (45% → 55%) Hazard ratio 0.749
  - 509 events, 90% power, 2-sided alpha 0.05. Planned n=730
- Secondary endpoints: response rate (RECIST 1.0), progression free survival (PFS), toxicity, QoL, effect of KRAS status on response and survival
- Exploratory biomarker analyses

		EOC: 275 n (%)	mEOC-P: 278 n (%)	Total: 553 n (%)
Age	Median (range)	62 (26-83)	63 (26-83)	62 (26-83)
Gender	Male	226 (82.2)	232 (83.5)	458 (82.8)
	Female	49 (17.8)	46 (16.5)	95 (17.2)
PS	0	117 (42.5)	118 (42.4)	235 (42.5)
	1	143 (52.0)	144 (51.8)	287 (51.9)
	2	15 (5.5)	16 (5.8)	31 (5.6)
Site	Oesophagus	111 (40.4)	106 (38.1)	217 (39.2)
	O-G Junction	75 (27.3)	94 (33.8)	169 (30.6)
	Stomach	89 (32.4)	78 (28.1)	167 (30.2)
Extent	Locally advanced	25 (9.1)	34 (12.2)	59 (10.7)
	Metastatic	250 (90.9)	244 (87.8)	494 (89.3)
Histology	Adenocarcinoma	272 (98.9)	273 (98.2)	545 (98.6)
	Undifferentiated	3 (1.1)	5 (1.8)	8 (1.4)







Treatment Dose Intensity (DI)

- Median 5 cycles administered in both treatment arms
- Pts receiving all 8 cycles (%) - EOC: 31% vs. mEOC+P: 27%
- Mean cape DI (cycles given) - EOC: 91% vs. mEOC+P: 87%
- Pts receiving ≥80% cape DI in cycles given (%) - EOC: 85% vs. mEOC+P: 71%

- **Negative trial:**
- **EGFR inhibitors are not effective in gastric cancer (EXPAND trial with cetuximab)**
- **Reduced dose intensity in the panitumumab arm**
- **Are other analyses, subgroups of patients (oesophagus, GEJ, distal stomach) or biological markers, worthwhile?**

Molecular markers ad tumor biology

- K-RAS
- PIK3CA
- EGFR

They might switch a bad news in a good news

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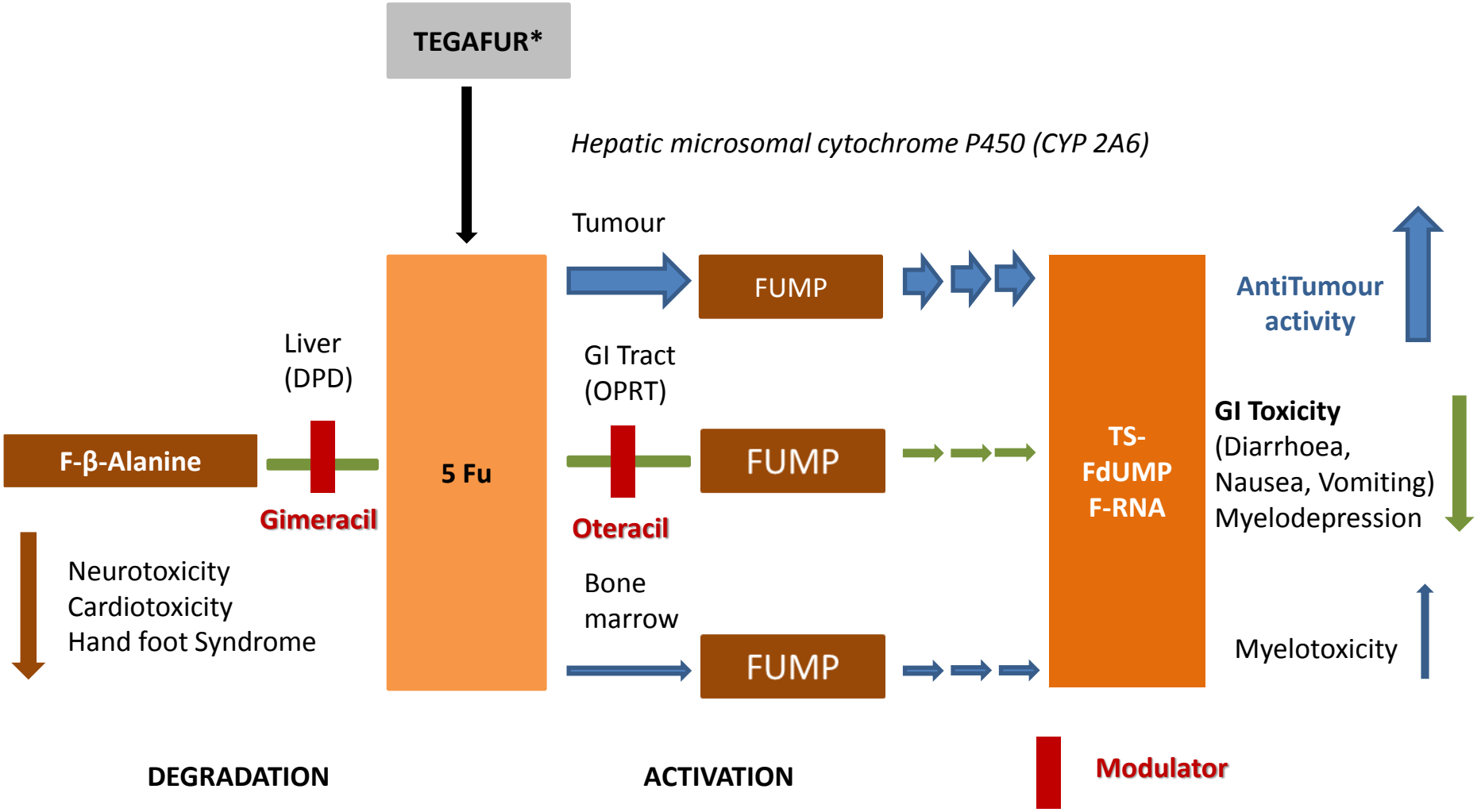
(S-1): A new oral 5FU dispensation system



FUMP FluoroUridine MonoPhosphate , OPRT Orotate PhosphoRibosyl Transferase, TS Thymidilate Synthase

* Tegafur dose in S-1 = 2.5% of other oral 5-FU daily dose (Gimeracil effect)

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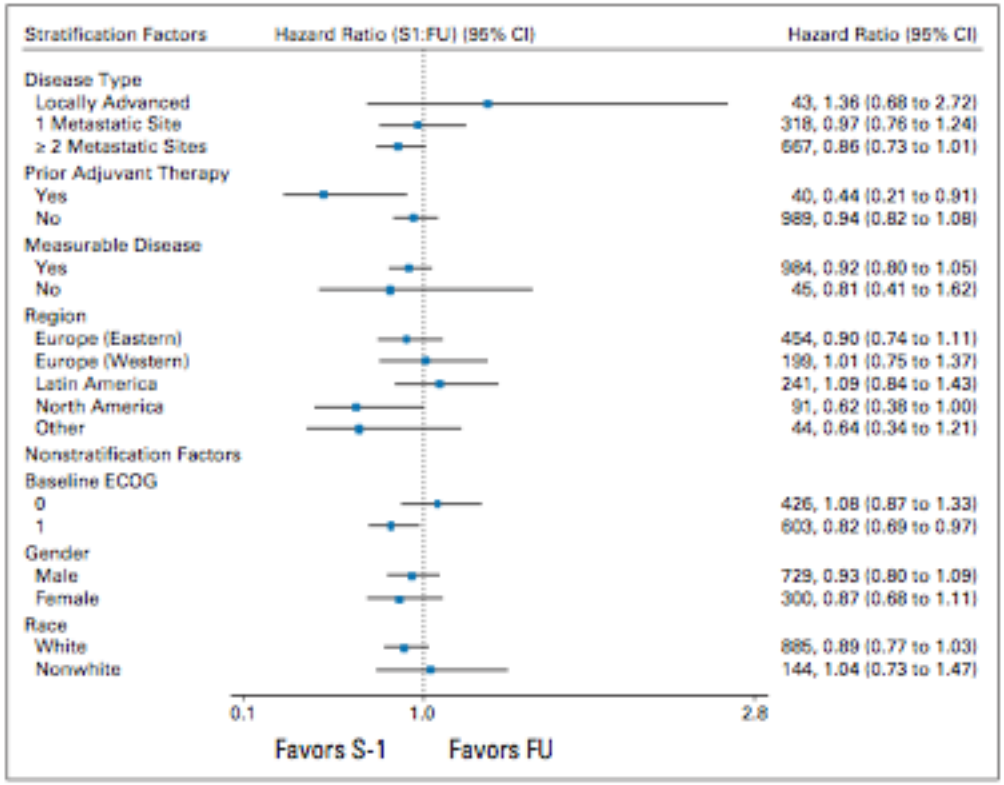
ORIGINAL REPORT

Multicenter Phase III Comparison of Cisplatin/S-1 With Cisplatin/Infusional Fluorouracil in Advanced Gastric or Gastroesophageal Adenocarcinoma Study: The FLAGS Trial

Jaffer A. Ajani, Wuilbert Rodriguez, Gyorgy Bodoky, Vladimir Moiseyenko, Mikhail Lichinitser, Vera Gorbunova, Ihor Vynnychenko, August Garin, Istvan Lang, and Silvia Falcon



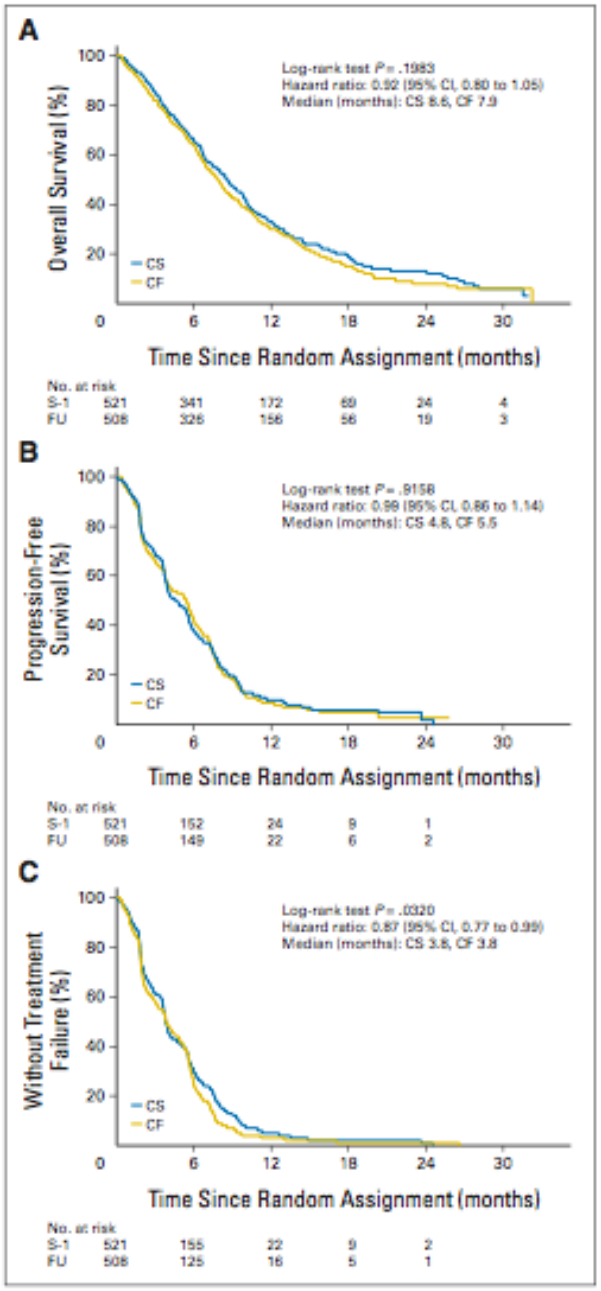
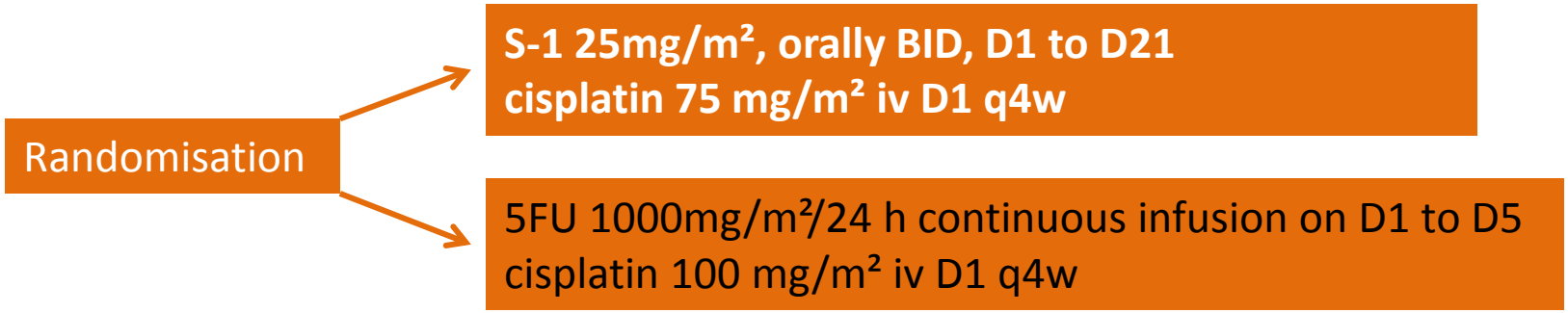


Fig 2. (A) Kaplan-Meier plot of overall survival by the two treatment arms. (B) Kaplan-Meier plot of progression free survival by the two treatment arms. (C) Kaplan-Meier plot of time-to-treatment failure by the two treatment arms. CS, cisplatin/S-1; CF, cisplatin/infusional FU; FU, fluorouracil.

Non inferiority analysis of Multicenter phase III comparing S-!- cisplatin with 5-FU-cisplatin as first-line therapy in patients with advanced gastric cancer (FLAGS): Methodology and results

J.A. Ajani[1], W. Rodriguez Pantigoso[2], G. Bodoky[3], V. Moiseyenko[4], M.Lichinitser[5], V.A. Gorbunova[5], I.Vynnychenko[6], I. Lang[3], S. Falcon[1].
[1]Houston, TX/US, [2]Lima/PE, [3]Budapest/HU, [4]St Petersburg/RU, [5]Moscow/RU, [6]Sumy/UA

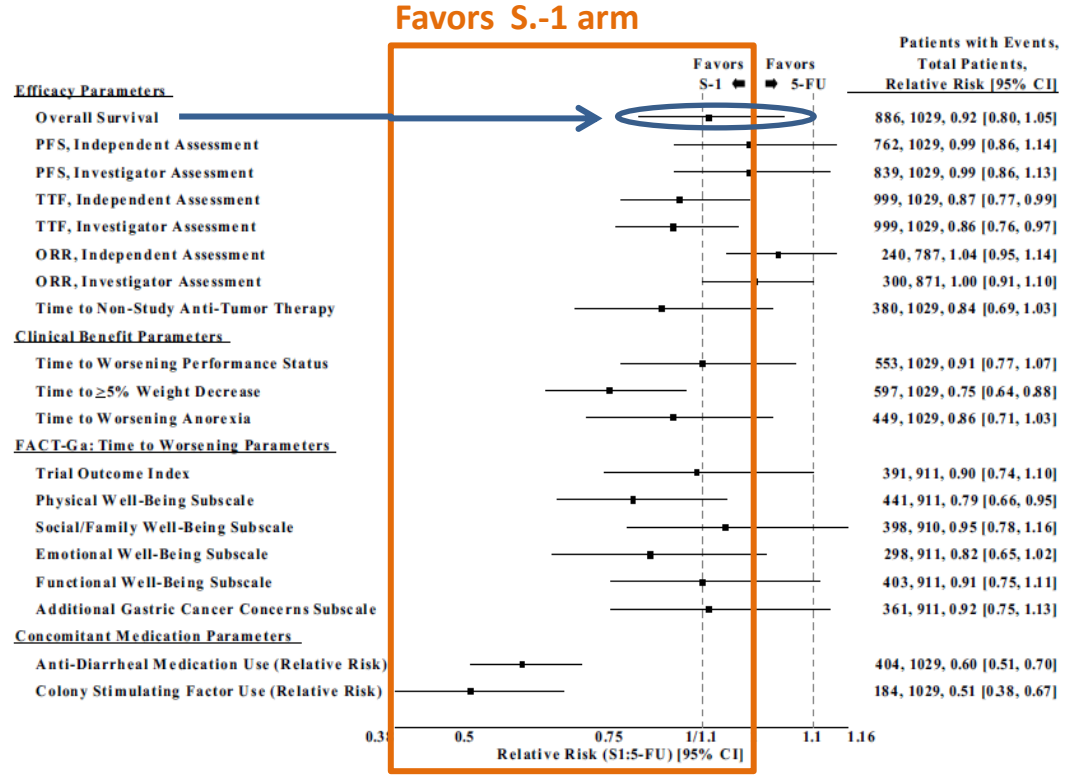


Trial objective: The primary study objective was overall survival.

Given the favorable safety profile of S-1-cisplatin over 5FU-cisplatin, an analysis of non-inferiority was performed based on the strength Guidelines developed by the Efficacy Working Party (EWP) of the Committee for Proprietary Medicinal Products (CPMP).
Two meta-analyses were used to define the non-inferiority margin as described by Rothmann.

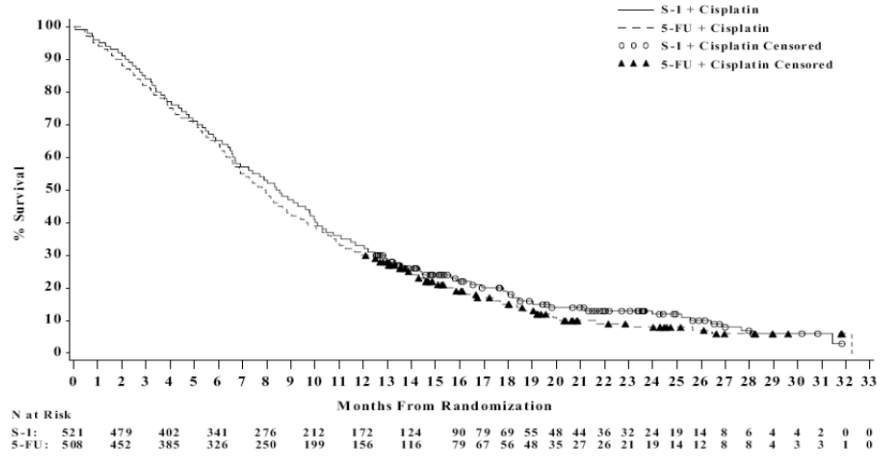
The assessment of non-inferiority of S-1- cisplatin compared with 5FU-cisplatin was made using the upper limit of the 95% CI for HR. Non-inferiority was to be concluded if the upper limit of the 95% CI 1,05 was ≤ 1.10, with a statistical significantly p=0,0068.

FLAGS Study: Subgroup Analysis/ Efficacy



The S-1- cisplatin provides advantages for the patients over 5FU-cisplatin

* It is as effective as 5FU-cisplatin.
* It is better tolerated, with significantly less hematologic and non-hematologic toxicity.
* Treatment related deaths were significantly reduced (approximately halved).
* It provides a more convenient dosing schedule and requires significantly fewer hospitalizations during the treatment.



Median OS: S-1-cisplatin: 8.6 m [7.9-9.5] and 5FU-cisplatin: 7.9 m [7.2-8.5].

The overall survival HR= 0.92 (95% CI, 0.80-1.05), providing evidence of non-inferiority of Teysuno®-cisplatin as compared to 5FU-cisplatin for any margin equal to or greater than 1,05. p=0.0068

S-1- cisplatin can be considered another standard therapy recommendation for patients with AGC.

Relevance of this analysis

- S-1 is a safe drug even in western countries
- It could be more convenient tha capecitabine (less tablet per day)

Several considerations need to be taken in account before combination S-1 plus cisplatin is implemented as standard treatment in western countries. First, phase I/II trials of S-1 undertaken in the USA showed good activity and safety profiles, but also the need for a S-1 dose decrease because of polymorphic differences in the cytochrome P-450 2A6 enzyme (*CYP2A6*) gene between Asian and white patients.[9] Therefore, more cross-ethnic studies with common study design and assays are warranted, and caution should be used when interpreting findings between regions [A:OK?].

Reflection and Reaction

First-Line Advanced Gastric Cancer Study (FLAGS), which compared S-1 with fluorouracil, both combined with cisplatin, will hopefully answer this question. Third,

Oral treatment for gastric cancer: new choices, better choices?

Most common (≥3%) grade 3/4 AEs comparable