<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>668PD: Jaffer Ajani</td>
<td>Non inferiority analysis of multicenter phase III comparing cisplatin/S-1 with cisplatin/5-FU (CF) as first line therapy in patients with advanced gastric cancer (FLAGS): methodology and results</td>
</tr>
</tbody>
</table>
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
Gastric cancer and EGFR inhibition

- 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
Untreated advanced adenocarcinoma or undifferentiated carcinoma of oesophagus, OGJ or stomach

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
E 50mg/m², O 130mg/m² + C 1250mg/m²/day

mEOC + P
E 50mg/m², O 100mg/m² + C 1000mg/m²/day + P 9mg/kg
Rash as a Biomarker (mEOC+P arm only)

References


3. Okines A Ashley S Cunningham D et al: Epirubicin oxaliplatin and capecitabine with or without panitumumab for advanced esopha
gastric cancer: dose-finding study for prospective multicenter randomized phase II/III REAL3 trial JCO 28:3945-50, 2010


CONCLUSIONS

- The addition of panitumumab (P) to EOC was not beneficial in an unselected OG population
- Poorer OS outcome possibly due to ↓ chemotherapy delivery in mEOC+P arm (↓ starting doses O and C, ↓ dose intensity C)
- RR (phase II endpoint) was not a good surrogate for efficacy
- This analysis is based on <50% of OS events but future analyses will be affected by data censoring and treatment crossover
- P-associated rash appears to have predictive role. KRAS and PIK3CA mut. represent potential negative prognostic biomarkers
- Ongoing analyses aim to explore role of other putative biomarkers in this trial setting
<table>
<thead>
<tr>
<th>Treatment Dose Intensity (DI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Median 5 cycles administered in both treatment arms</td>
</tr>
<tr>
<td>▪ Pts receiving all 8 cycles (%) - EOC: 31% vs. mEOC+P: 27%</td>
</tr>
<tr>
<td>▪ Mean cape DI (cycles given) - EOC: 91% vs. mEOC+P: 87%</td>
</tr>
<tr>
<td>▪ Pts receiving ≥80% cape DI in cycles given (%) - EOC: 85% vs. mEOC+P: 71%</td>
</tr>
</tbody>
</table>

• **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
| 668PD: Jaffer Ajani | Non inferiority analysis of multicenter phase III comparing cisplatin/S-1 with cisplatin/5-FU (CF) as first line therapy in patients with advanced gastric cancer (FLAGS): methodology and results |
**S-1**: A new oral 5FU dispensation system

**TEGAFUR***

- Liver (DPD)
- GI Tract (OPRT)
- Bone marrow

**5 Fu**

- F-β-Alanine
- Gimeracil
- Oteracil

- Neurotoxicity
- Cardiotoxicity
- Hand foot Syndrome

**Hepatic microsomal cytochrome P450 (CYP 2A6)**

- Tumour

- FUMP

**TS-FdUMP F-RNA**

- AntiTumour activity

- GI Toxicity (Diarrhoea, Nausea, Vomiting)
- Myelodepression
- Myelotoxicity

**DEGRADATION**

**ACTIVATION**

**Modulator**

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)
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, Walibert Rodriguez, Gyorgy Bodoky, Vladimir Moiseyenko, Mikhail Lichinitser, Vera Gorbunova, Ihor Vyshnychenko, August Garin, Istvan Lang, and Silvia Falcon

![Graphs and charts showing overall survival, progression-free survival, and time to treatment failure for the two treatment arms, CS and FU.](image-url)
Non inferiority analysis of Multicenter phase III comparing S-1 cisplatin with 5-FU-cisplatin as first-line therapy in patients with advanced gastric cancer (FLAGS): Methodology and results

J.A. Ajani¹, W. Rodriguez Pantigoso², G. Bodoky³, V. Moiseyenko⁴, M.Lichinitser⁵, V.A. Gorbunova⁵, I.Vynnychenko⁶, I. Lang³, S. Falcon¹.
¹Houston, TX/US, ²Lima/PE, ³Budapest/HU, ⁴St Petersburg/RU, ⁵Moscow/RU, ⁶Sumy/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.

Randomisation

S-1 25mg/m², orally BID, D1 to D21
cisplatin 75 mg/m² iv D1 q4w

5FU 1000mg/m²/24 h continuous infusion on D1 to D5
cisplatin 100 mg/m² iv D1 q4w
### FLAGS Study: Subgroup Analysis/ Efficacy

**Favors S-1 arm**

<table>
<thead>
<tr>
<th>Efficacy Parameters</th>
<th>Favors S-1</th>
<th>Favors 5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS, Independent Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTF, Independent Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, Independent Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, Investigator Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to Non-Study Anti-Tumor Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Benefit Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to Worsening Performance Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to ≥5% Weight Decrease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to Worsening Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAC T-Ga: Time to Worsening Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial Outcome Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Well-Being Subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social/Family Well-Being Subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Well-Being Subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional Well-Being Subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Gastric Cancer Concerns Subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medication Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Diarrheal Medication Use (Relative Risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colony Stimulating Factor Use (Relative Risk)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Relative Risk (S:5-FU) [95% CI]**

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Favors S-1</th>
<th>Favors 5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 than 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. 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

Patients (%)

- Neutropenia
- Vomiting
- Stomatitis
- Diarrhoea
- Anaemia
- HFS

Capecitabine
S-1