ESMO 2017, Madrid, Spain

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HIGHLIGHTS ON CANCERS OF THE UPPER GI TRACT
DOCETAXEL, OXALIPLATIN AND FLUOROURACIL/LEUCOVORIN (FLOT) FOR RESECTABLE ESOPHAGOGASTRIC CANCER: UPDATED RESULTS FROM MULTICENTER, RANDOMIZED PHASE 3 FLOT4-AIO TRIAL (GERMAN GASTRIC GROUP AT AIO)

Al-Batran S et al. LBA27. ESMO Madrid 2017
Study Objective

To evaluate the superiority of the FLOT scheme as compared to the standard ECF/ECX scheme in terms of OS as perioperative treatment for operable gastric and/or gastro-oesophageal cancer patients

Randomized, multicenter, investigator-initiated, phase II/III study

Stratification:
- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cMO or cT-any/cN+/cMO

ECF/ECX:
- Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

FLOT:
- docetaxel 50 mg/m², d1; 5-FU 2600 mg/m² d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

n=716

Al-Batran S et al. LBA27. ESMO Madrid 2017
## KEY RESULTS

<table>
<thead>
<tr>
<th></th>
<th>mPFS</th>
<th>mOS</th>
<th>Resection</th>
<th>R0 resection</th>
<th>ypT-stage &lt;T1</th>
<th>ypN-stage N0</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLOT</td>
<td>30 months</td>
<td>50 months</td>
<td>94%</td>
<td>84%</td>
<td>25%</td>
<td>49%</td>
</tr>
<tr>
<td>ECX/ECF</td>
<td>18 months</td>
<td>35 months</td>
<td>87%</td>
<td>77%</td>
<td>15%</td>
<td>41%</td>
</tr>
<tr>
<td>HR</td>
<td>0.75 (95%CI 0.62-0.91)</td>
<td>0.77 (95%CI 0.63-0.94)</td>
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<tr>
<td>P-value</td>
<td>0.004</td>
<td>0.012</td>
<td>0.001</td>
<td>0.011</td>
<td>0.001</td>
<td>0.029</td>
</tr>
</tbody>
</table>
KEY RESULTS

- In a multivariate model the following characteristics were confirmed to be prognostic for worse outcome:

- Despite their negative prognostic role, those groups of tumors were still benefitting from the FLOT regimen as compared to the ECX/ECF regimen
SUMMARY

• FLOT is the new standard of care in perioperative treatment of patients with operable adenocarcinoma of the stomach and gastro-oesophageal junction

• Arms were very well balanced and there was no increase in surgical morbidity and mortality, re-surgery or hospitalization times in the FLOT arm as compared to standard regimen

• The relative effect was consistent across subgroups, even in the groups with worse prognosis

• Because the effect was observed also in early tumours, Barrett and signet ring cell carcinomas, the results of the study support the concept of perioperative treatment in debated groups like elderly, signet ring cell, Barrett and T2 or N-stage
PERTUZUMAB + TRASTUZUMAB + CHEMOTHERAPY FOR HER2-POSITIVE METASTATIC GASTRIC OR GASTRO–EOSOPHAGEAL JUNCTION CANCER: FINAL ANALYSIS OF A PHASE III STUDY (JACOB)

Tabernero J et al. Abstract 6160. ESMO Madrid 2017
Study Objective

- To evaluate the efficacy and safety of pertuzumab and trastuzumab in combination with chemotherapy as first-line treatment in HER2 positive metastatic gastric and/or gastroesophageal junction cancer patients.

Key eligibility criteria:
- HER2-positive mGC/GEJC
- IHC 3+ or IHC 2+ and ISH-positive (central testing required)
- ECOG PS 0 or 1

Stratification factors:
- Geographical region (Asia [excluding Japan], Japan, North America/Western Europe/Australia, South America/Eastern Europe)
- Prior gastrectomy (yes/no)
- HER2 IHC 3+ vs IHC 2+/ISH-positive

1L HER2-positive mGC/GEJC
N=780 randomized (1:1)
FPI-LPI: 10 Jun 2013 – 12 Jan 2016

Primary endpoint:
- OS

Secondary endpoints:
- PFS, ORR, DoR, CBR, safety, PK, QoL

Study treatment
- ~6 treatment cycles (21-day cycle)
- HER2-targeted therapy continues until PD or unacceptable toxicity

Treatment arm A
- Capecitabine or 5-FU + cisplatin
- Trastuzumab + pertuzumab 840 mg IV q3w

Treatment arm B
- Capecitabine or 5-FU + cisplatin
- Trastuzumab + placebo IV q3w

Follow-up

Tabernero J et al. Abstract 6160. ESMO Madrid 2017
KEY RESULTS

- 392 patients randomized to placebo (PLA) + herceptin (H) + chemotherapy (CT)
- 388 patients randomized to pertuzumab (P) + herceptin (H) + chemotherapy (CT)

- Median follow up of approximately 2 years

- Comparable safety profile between arms except for diarrhoea (all grades: 61.6% in P + H + CT vs 35.1% in PLA + H + CT) and hypopotassiemia which did not affect the dose intensity of the regimens

- Low and similar incidence of symptomatic and asymptomatic left ventricular systolic dysfunction

Tabenero J et al. Abstract 6160. ESMO Madrid 2017
**KEY RESULTS**

<table>
<thead>
<tr>
<th></th>
<th>mOS</th>
<th>mPFS</th>
<th>Objective response %</th>
<th>Median duration of objective response Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P + H + CT (n=388)</strong></td>
<td>17.5 months</td>
<td>8.5 months</td>
<td>56.7</td>
<td>10.2 (8.4-10.7)</td>
</tr>
<tr>
<td>Events, n 242</td>
<td></td>
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<tr>
<td><strong>PLA + H + CT</strong></td>
<td>14.2 months</td>
<td>7.0 months</td>
<td>48.3</td>
<td>8.4 (6.8-8.7)</td>
</tr>
<tr>
<td>(n=392) Events, n 262</td>
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<tr>
<td><strong>HR</strong></td>
<td>0.84 (95% CI 0.71-1.00)</td>
<td>0.73 (95% CI 0.62-0.86)</td>
<td></td>
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<tr>
<td><strong>p-value</strong></td>
<td>0.0565</td>
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</tbody>
</table>

* Statistical significance cannot be concluded due to hierarchical testing. Tabernero J et al. Abstract 6160. ESMO Madrid 2017
SUMMARY

• Very well performed study with good statistical assumptions and design
• Patients and tumor characteristics very well balanced between arms
• Good tolerability to the combination of pertuzumab + herceptin + chemotherapy
• Control group performed similar to the ToGa trial, thus meaning that the benefit of trastuzumab in first line setting can be confirmed
• Pertuzumab showed some activity in combination with herceptin and chemotherapy in all subgroups but this was not enough to meet its primary endpoints
• **Negative trial.** Pertuzumab cannot be considered yet in combination with trastuzumab in first line setting for HER2 positive advanced gastric cancer patients

**Why?**

• Is gastric cancer different to breast cancer?
• Is HER2 expression in gastric cancer more heterogeneous than in breast cancer?
• Despite the HER2 expression are HER2 positive gastric tumors heterogeneous at molecular level?
• These are points to be further investigated
A PHASE 3 STUDY OF NIVOLUMAB IN PREVIOUSLY TREATED ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION CANCER: UPDATED RESULTS AND SUBSET ANALYSIS BY PD-L1 EXPRESSION (ATTRACTION – 02)

Boku N et al. Abstract 6170. ESMO Madrid 2017
Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug.

BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to tumor response. Boku N et al. Abstract 617O. ESMO Madrid 2017
KEY RESULTS

- A total of 493 patients were randomized to a 2:1 ratio

- 330 patients received nivolumab while 163 patients received placebo

- PD-L1 expression was assessed by ICH (28-8 pharmDx assay) on pretreatment tumor biopsies of 197 patients

- Manageable safety profile with most relevant treatment related side effects (skin, gastrointestinal, hepatic and endocrine) within the first 3 months
## KEY RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Updated mOS</th>
<th>OS rates at 6 months</th>
<th>OS rates at 12 months</th>
<th>mOS PD-L1 positive (expression &gt;1%)</th>
<th>mOS PD-L1 negative (expression &lt;1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nivolumab</strong></td>
<td>5.32 months</td>
<td>46.4%</td>
<td>27.6%</td>
<td>5.2 months (16pts)</td>
<td>6.1 months (115 pts)</td>
</tr>
<tr>
<td>(n=330)</td>
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<tr>
<td><strong>Placebo</strong></td>
<td>4.14 months</td>
<td>34.7%</td>
<td>11.6%</td>
<td>3.8 months (10 pts)</td>
<td>4.2 months (52 pts)</td>
</tr>
<tr>
<td>(n=163)</td>
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<tr>
<td><strong>HR</strong></td>
<td>0.61</td>
<td>(95%CI 0.50-0.75)</td>
<td>(95%CI 40.8-51.8)</td>
<td>0.58</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs (95%CI 27.4-42.1)</td>
<td>vs (95%CI 22.8-32.6)</td>
<td>(95%CI 0.24-1.38)</td>
<td>(95%CI 0.50-1.00)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>&lt;0.0001</td>
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</table>

Boku N et al. Abstract 6170. ESMO Madrid 2017
SUMMARY

• With a long term follow-up, nivolumab monotherapy confirms to give a significant survival advantage as compared to placebo in refractory gastric and gastroesophageal cancer patients
• Reduction in risk of death by 38% in the nivolumab arm
• The improvement in survival is independent from the PD-L1 status
• Manageable side effects
• The patients enrolled are all Asian. It will be interesting to test the efficacy of the drug in Caucasian refractory gastric patients
• PD-L1 expression was retrospectively performed only in 40% of patients and the antibody used is different from the one used in the Keynote 059 study, thus meaning that probably different batches of antibodies might give different results
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