ADVANCES IN GASTRO-OESOPHAGEAL ADENOCARCINOMAS

Biology and treatment for advanced disease

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OUTLINE

Molecular classification
- Pathology
- Classification after gene expression
- The Cancer Genome Atlas Research Network

Treatment for advanced disease
- First line
- Second line
- Third line

Immunotherapy
CLASSIFICATION OF GASTRIC ADENOCARCINOMA: PATHOLOGY

Intestinal *versus* diffuse subtypes

CLASSIFICATION OF GASTRIC ADENOCARCINOMA:
PATHOLOGY

Papillary carcinomas
Tubular carcinomas
Mucinous carcinomas
Poorly cohesive carcinomas (including signet ring cell carcinoma)
COMPREHENSIVE MOLECULAR CHARACTERISATION OF GASTRIC ADENOCARCINOMA

Molecular platforms

Array-based somatic copy number analysis
Whole exome sequencing
Array-based DNA methylation profiling
Messenger RNA sequencing
RNA sequencing
Reverse Phase Protein Array (RPPA)

COMPREHENSIVE MOLECULAR CHARACTERISATION OF GASTRIC ADENOCARCINOMA

Molecular platforms

THE MOLECULAR CLASSIFICATION OF GASTRIC CANCER ACCORDING TO THE CANCER GENOME ATLAS

CIN
- Intestinal histology
- TP53 mutation
- RTK-RAS activation

EBV
- PIK3CA mutation
- PD-L1/2 overexpression
- EBV-CIMP
- CDKN2A silencing
- Immune cell signalling

GS
- Diffuse histology
- CDH1, RHOA mutations
- CLDN18–ARHGAP fusion
- Cell adhesion

MSI
- Hypermethylation
- Gastric-CIMP
- MLH1 silencing
- Mitotic pathways

50%
9%
20%
22%
COMPREHENSIVE MOLECULAR CHARACTERISATION OF GASTRIC ADENOCARCINOMA

The ACRG approach

COMPREHENSIVE MOLECULAR CHARACTERISATION OF GASTRIC ADENOCARCINOMA

The ACRG approach predicts survival
INTEGRATED GENOMIC CHARACTERISATION OF OESOPHAGEAL CANCERS

Cancer Genome Atlas Research Network. Nature 2017;541;169–75. Available under a Creative Commons Attribution 4.0 International (CC BY 4.0) licence (https://creativecommons.org/licenses/by-nc/4.0/). Accessed June 2019
INTEGRATED GENOMIC CHARACTERISATION OF OESOPHAGEAL CANCERS

Squamous cell cancers

Vs.

Adenocarcinomas

Cancer Genome Atlas Research Network. Nature 2017;541;169–75. Available under a Creative Commons Attribution 4.0 International (CC BY 4.0) licence (https://creativecommons.org/licenses/by-nc/4.0/; Accessed June 2019)
TREATMENT FOR METASTATIC/UNRESECTABLE GASTRIC CANCER

Active agents in first line

Based upon superiority trials:
- 5-FU
- Cisplatin
- Docetaxel
- Trastuzumab

Based upon non-inferiority trials
- Oxaliplatin
- Capecitabine
- S1
- Irinotecan

H ave we made any progress in the treatment of advanced gastric cancer?

- Transtuzumab + CDDP + FU or Cape\(^6\) 13.8 months
- EOX\(^5\) 11.2 months
- 5-FU + LV + Oxaliplatin (FLO)\(^4\) 10.7 months
- Capecitabine + Cisplatin (XP)\(^3\) 10.5 months
- Docetaxel + Cisplatin + 5-FU\(^2\) 9.2 months
- 5-FU monotherapy\(^1\) 7 months
- BSC\(^1\) 4 months

**Median overall survival in advanced gastric cancer**


BSC: Best supportive care; CDDP, cisplatin; EOX: Epirubicin/Oxaliplatin/Capecitabine; 5-FU, 5-fluorouracil.
HAVE WE MADE ANY PROGRESS IN THE TREATMENT OF ADVANCED GASTRIC CANCER?

1. Transtuzumab + CDDP + FU/Cape
   - HR: 0.74 p=0.0046
2. EOX
   - HR: 0.80 p=0.02
3. FLO
   - HR: Not shown p=0.506
4. XP
   - HR: 0.85 p=0.008
5. DCF
   - HR: 0.77 p=0.02
6. Combination vs. monotherapy
   - HR: 0.83 p=0.001
7. 5-FU monotherapy vs. BSC
   - HR: 0.39 p<0.00001

RISK OF DEATH REDUCTION IN ADVANCED GASTRIC CANCER

Objective I: 1st line Time-to-Treatment Failure (TTF)

Objectives II:
- PFS, OS, (TTF 2nd line)
- Toxicity
- Response rate, QoL

ECX: D1 = Epirubicin 50 mg/m² (15 min.), Cisplatin 60 mg/m² (1 h); D2 to 15: Capecitabine 1 g/m² x 2/d. D1 = D21. Cumulated dose of Epirubicin < 900 mg/m² (max 18 cures)
FOLFIRI: D1 = Irinotecan 180 mg/m² (90 min) + LV 400 mg/m² (2h), 5FU b 400 mg/m², 5FU c.i. 2400 mg/m² (46h). D1 = D14.
FFCD-GERCOR-FNCLCC 03-07 PHASE III STUDY
FOLFIRI vs. ECF in advanced gastric cancer

Objective I: 1st line Time-to-Treatment Failure (TTF)

ECX: D1 = Epirubicin 50 mg/m² (15 min.), Cisplatin 60 mg/m² (1 h); D2 to 15: Capecitabine 1 g/m² x 2/d. D1 = D21. Cumulated dose of Epirubicin < 900 mg/m² (max 18 cures)

FOLFIRI: D1 = Irinotecan 180 mg/m² (90 min) + LV 400 mg/m² (2h), 5FU b 400 mg/m², 5FU c.i. 2400 mg/m² (46h). D1 = D14.


ECX arm: Epirubicin, cisplatin, and capecitabine as the first-line treatment.

FOLFIRI arm: Irinotecan, leucovorin, fluorouracil bolus, and continuous infusion as the first-line treatment.

HR, 0.77; 95% CI, 0.63 to 0.93; P=0.008

ECX

FOLFIRI

ECX arm: Epirubicin, cisplatin, and capecitabine as the first-line treatment.

FOLFIRI arm: Irinotecan, leucovorin, fluorouracil bolus, and continuous infusion as the first-line treatment.
### Objective II: Response Rate (RR), PFS and OS

<table>
<thead>
<tr>
<th></th>
<th>ECF N=209</th>
<th>FOLFIRI n=207</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 1\textsuperscript{st}</td>
<td>39.2%</td>
<td>37.8%</td>
<td>n.s.</td>
</tr>
<tr>
<td>RR 2\textsuperscript{nd}</td>
<td>10.1%</td>
<td>13.7%</td>
<td></td>
</tr>
<tr>
<td>PFS (months)</td>
<td>5.29</td>
<td>5.75</td>
<td>0.96</td>
</tr>
<tr>
<td>Median range</td>
<td>4.53-6.31</td>
<td>5.19-6.74</td>
<td></td>
</tr>
<tr>
<td>OS (months)</td>
<td>9.49</td>
<td>9.72</td>
<td>0.95</td>
</tr>
<tr>
<td>Median range</td>
<td>8.77-11.14</td>
<td>8.54-11.27</td>
<td></td>
</tr>
</tbody>
</table>

PHASE III STUDY OF CF VS. DCF
Showing improved survival by the addition of docetaxel in first line for advanced gastric cancer

HR: 1.29 (95% CI, 1.0–1.6)
PHASE II STUDY OF MODIFIED DCF VS. DCF PLUS G-CSF IN ADVANCED GASTRIC CANCER

Stratification:
- Measurable or not
- Gastric vs. GEJ
- Centre

Objective: 6 months-PFS
Objectives II: RR, OS, Toxicity
Randomly assigned treatment

### Arm A (mDCF)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/m²)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>40</td>
<td>Day 1 IVPB (60 minutes)</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>400</td>
<td>Day 1 IVPB (30 minutes)</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>400</td>
<td>Day 1 IVP</td>
</tr>
<tr>
<td>Fluororacil</td>
<td>1,000 (per day)</td>
<td>IVCI daily x2 days</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>40</td>
<td>Day 2 or 3 IVPB (30 minutes)</td>
</tr>
</tbody>
</table>

### Arm B (parent DCF plus G-CSF)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/m²)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>75</td>
<td>Day 1 IVPB (60 minutes)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75</td>
<td>Day 1 IVPB (60 minutes)</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>750 (per day)</td>
<td>IVCI daily x5 days</td>
</tr>
<tr>
<td>Neulasta*</td>
<td>6 mg</td>
<td>Subcutaneous on day 8, 9, or 10</td>
</tr>
<tr>
<td>Neupogen*</td>
<td>300 or 480 μg†</td>
<td>Subcutaneous x7 days (days 10 to 17)</td>
</tr>
</tbody>
</table>

PHASE II STUDY OF MODIFIED DCF VS. DCF PLUS G-CSF IN ADVANCED GASTRIC CANCER

DOCETAXEL + OXALIPLATIN + 5FU-LV/CAPECITABINE
TE VS. TEF VS. TEX

Van Cutsem E, et al. Ann Oncol 2015;26:149–156, by permission of Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved.
## DOCETAXEL + OXALIPLATIN + 5FU-LV/CAPECITABINE
### TE VS. TEF VS. TEX

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (n)</th>
<th>RR %</th>
<th>95% CI</th>
<th>PFS months</th>
<th>95% CI</th>
<th>OS months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE</td>
<td>79</td>
<td>23.1</td>
<td>14.3–34.0</td>
<td>4.50</td>
<td>3.68–5.32</td>
<td>8.97</td>
<td>7.79–10.9</td>
</tr>
<tr>
<td>TEX</td>
<td>86</td>
<td>25.6</td>
<td>16.6–36.6</td>
<td>5.55</td>
<td>4.30–6.37</td>
<td>11.30</td>
<td>8.08–14.0</td>
</tr>
<tr>
<td>TEF</td>
<td>89</td>
<td><strong>46.6</strong></td>
<td>35.9–57.5</td>
<td><strong>7.66</strong></td>
<td>6.97–9.40</td>
<td><strong>14.59</strong></td>
<td>11.7–21.8</td>
</tr>
</tbody>
</table>

TREATMENT FOR ADVANCED GASTRIC CANCER: WHAT IS STANDARD OF CARE?

ESMO Guidelines

**Surgery**

- Re-assess

**Palliative chemotherapy**

- **HER-2 negative**
  - Platinum+ fluoropyrimidine-based doublet or triplet regimen
  - **2nd line chemo**
    - Clinical trials if adequate PS

- **HER-2 positive**
  - Trastuzumab + CF/CX

- Consider clinical trials of novel agents

**Inoperable or metastatic**

- Best supportive care if unfit for treatment

ASSESSMENT OF HER2 AMPLIFICATION IN ADVANCED GASTRO-OESOPHAGEAL ADENOCARCINOMA

Treatment of advanced gastro-oesophageal cancer
Molecular stratification according to HER2 status

- IHC score 0/1
- IHC score 2
- IHC score 3

ISH-test HER2

- ISH–
- ISH+

Platin-fluoropyrimidine +/- docetaxel or epirubicin

Cisplatin-fluoropyrimidine + trastuzumab

Progression: evaluation of ECOG performance status, efficacy and tolerability of first-line chemotherapy, patient preferences and the need for remission

- ECOG PS 0-1 need for remission ++
  - Paclitaxel + ramucirumab

- ECOG PS 0-2 need for remission +/
  - Ramucirumab monotherapy or irinotecan monotherapy or taxane monotherapy

- ECOG PS 2-4 or patient preference
  - Active symptom control
PHASE III STUDY ON THE ADDITION OF TRASTUZUMAB TO CISPLATIN-BASED CHEMOTHERAPY

In first-line for HER2 amplified gastro-oesophageal adenocarcinomas

Reprinted from The Lancet, 376 (9742), Bang YJ, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial; 687–697. Copyright 2010, with permission from Elsevier.
PHASE III TRIALS WITH TARGETED THERAPIES IN FIRST-LINE TREATMENT

For advanced gastro-oesophageal adenocarcinomas

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemotherapy</th>
<th>Biological</th>
<th>HR OS</th>
<th>P value</th>
<th>Increase in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA¹</td>
<td>Cisplatin+5-FU/capecitabine</td>
<td>Trastuzumab</td>
<td>0.74</td>
<td>0.04</td>
<td>+2.8 months</td>
</tr>
<tr>
<td>AVAGAST²</td>
<td>Cisplatin+ capecitabine</td>
<td>Bevacizumab</td>
<td>0.87</td>
<td>0.10</td>
<td>+2.0 months</td>
</tr>
<tr>
<td>AVATAR³</td>
<td>Cisplatin+ capecitabine</td>
<td>Bevacizumab</td>
<td>1.11</td>
<td>0.55</td>
<td>-0.9 months</td>
</tr>
<tr>
<td>RAINFALL⁴</td>
<td>Cisplatin+5-FU/capecitabine</td>
<td>Ramucirumab</td>
<td>0.96</td>
<td>0.68</td>
<td>0.5 month</td>
</tr>
<tr>
<td>EXPAND⁵</td>
<td>Cisplatin+ capecitabine</td>
<td>Cetuximab</td>
<td>1.00</td>
<td>0.95</td>
<td>-1.3 months</td>
</tr>
<tr>
<td>REAL-3⁶</td>
<td>Oxaliplatin+ epi-+ capecitabine</td>
<td>Panitumumab</td>
<td>1.37</td>
<td>0.013</td>
<td>-2.5 months</td>
</tr>
<tr>
<td>RILOMET-1⁷</td>
<td>Cisplatin+epi+ capecitabine</td>
<td>Rilotumumab</td>
<td>--</td>
<td>--</td>
<td>Stopped in futility analysis</td>
</tr>
<tr>
<td>METGASTRIC⁸</td>
<td>FOLFOX6</td>
<td>Onartuzumab</td>
<td>1.06</td>
<td>0.83</td>
<td>-0.6 months</td>
</tr>
</tbody>
</table>

PHASE III TRIALS ON HER2 BLOCKADE
For HER2 amplified advanced gastro-oesophageal adenocarcinomas

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Chemotherapy backbone</th>
<th>Line of therapy number</th>
<th>HR</th>
<th>P value</th>
<th>Response rate</th>
<th>Increase in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA¹</td>
<td>Cisplatin+5-FU/ capecitabine</td>
<td>First 584</td>
<td>0.74</td>
<td>0.04</td>
<td>51% vs. 37%</td>
<td>+2.8 months</td>
</tr>
<tr>
<td>LOGiC²</td>
<td>Oxaliplatin/ capecitabine +/-Lapatinib</td>
<td>First 545</td>
<td>0.91</td>
<td>0.35</td>
<td>53% vs. 39%</td>
<td>+1.7 months</td>
</tr>
<tr>
<td>TyTAN³</td>
<td>Paclitaxel +/-Lapatinib</td>
<td>Second 261</td>
<td>0.84</td>
<td>0.20</td>
<td>27% vs. 9%</td>
<td>+2.1 months</td>
</tr>
<tr>
<td>GATSBY⁴</td>
<td>TDM-1 vs. Taxane</td>
<td>Second 345</td>
<td>1.15</td>
<td>0.85</td>
<td>NP</td>
<td>- 0.7 months</td>
</tr>
<tr>
<td>JACOB⁵</td>
<td>Cisplatin+5-FU/ cap/Trastu +/- Pertuzumab</td>
<td>First 780</td>
<td>0.84</td>
<td>0.056</td>
<td>56% vs. 48%</td>
<td>3.3 months</td>
</tr>
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</table>
HETEROGENEITY FOR HER2 STAINING IN GEA


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## GASTRO-OESOPHAGEAL ADENOCARCINOMAS

Second line chemotherapy trials comparing BSC versus active treatment

<table>
<thead>
<tr>
<th>Trial author</th>
<th>Year</th>
<th>Patients random (n)</th>
<th>Treatment</th>
<th>Response rate (%)</th>
<th>HR OS</th>
<th>P value</th>
<th>Gain in median survival</th>
</tr>
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<tbody>
<tr>
<td>Thuss-Patience PC, et al.¹</td>
<td>2011</td>
<td>40/1:1</td>
<td>Irinotecan</td>
<td>NR SD 58%</td>
<td>0.48</td>
<td>0.0023</td>
<td>2.4 months</td>
</tr>
<tr>
<td>Kang JH, et al.²</td>
<td>2012</td>
<td>193/2:1</td>
<td>Irinotecan/Docetaxel</td>
<td>NR</td>
<td>0.65</td>
<td>0.004</td>
<td>1.3 months</td>
</tr>
<tr>
<td>Ford HE, et al.³</td>
<td>2014</td>
<td>168/1:1</td>
<td>Docetaxel</td>
<td>NR</td>
<td>0.67</td>
<td>0.01</td>
<td>1.6 months</td>
</tr>
</tbody>
</table>

# GASTRO-OESOPHAGEAL ADENOCARCINOMAS

Second line chemotherapy and targeted agent trials comparing BSC versus active treatment

<table>
<thead>
<tr>
<th>Trial author</th>
<th>Year</th>
<th>Patients random (n)</th>
<th>Treatment</th>
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<tr>
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<td>2:1 193</td>
<td>Irinotecan, Docetaxel</td>
<td>0.65</td>
<td>0.004</td>
<td>1.3 months</td>
</tr>
<tr>
<td>Ford HE, et al.³</td>
<td>2014</td>
<td>1:1 168</td>
<td>Docetaxel</td>
<td>0.67</td>
<td>0.01</td>
<td>1.6 months</td>
</tr>
<tr>
<td>Otshu A, et al.⁴</td>
<td>2013</td>
<td>2:1 656</td>
<td>Everolimus</td>
<td>0.90</td>
<td>0.124</td>
<td>0.9 months</td>
</tr>
<tr>
<td>Fuchs CS, et al.⁵</td>
<td>2014</td>
<td>2:1 355</td>
<td>Ramucirumab</td>
<td>0.77</td>
<td>0.047</td>
<td>1.4 months</td>
</tr>
</tbody>
</table>

# GASTRO-OESOPHAGEAL ADENOCARCINOMAS

Second line trials comparing two active treatments

<table>
<thead>
<tr>
<th>Trial author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>HR (OS)</th>
<th>P value</th>
<th>Gain in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hironaka S, et al.¹</td>
<td>2013</td>
<td>223</td>
<td>Irinotecan vs. paclitaxel</td>
<td>1.13</td>
<td>0.38</td>
<td>0.9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For Irinotecam</td>
</tr>
<tr>
<td>Wilke H, et al.²</td>
<td>2014</td>
<td>665</td>
<td>Paclitaxel+/-ramucirumab</td>
<td>0.80</td>
<td>0.017</td>
<td>2.2 months</td>
</tr>
<tr>
<td>Shitara K, et al.³</td>
<td>2018</td>
<td>592/1:1</td>
<td>Pembrolizumab vs. wk Paclitaxel</td>
<td>0.82</td>
<td>0.084</td>
<td>0.8 months</td>
</tr>
<tr>
<td>KEYNOTE-061</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>for Pembrolizumab</td>
</tr>
</tbody>
</table>

Tyrosine kinase inhibitors (TKIs) (Apatinib, regorafenib, SU5416, SU6668, sunitinib, vatalanib, sorafenib, cediranib, AEE788, AMG-706, KRN-951)

Anti-VEGFR MAbs (IMC-1C11, Ramucirumab)

Soluble receptors (VEGF Trap, aflibercept)

Anti-VEGF MAbs (Bevacizumab)

Anti-PIGF MAbs (TB-403)

Signal transduction

GASTRIC CANCER SECOND LINE TREATMENT
Paclitaxel+/-ramucirumab (Rainbow Trial)

Main aim: Overall survival
Stratification by:
- Measurable vs. non-measurable
- Time to progression after first line: < or > 6 month
- Geographic region

663 patients needed to show a HR of 0.75 in favour of paclitaxel + ramucirumab with two-sided alfa 0.05 and 90% power

GASTRO-OESOPHAGEAL ADENOCARCINOMAS
SECOND LINE TREATMENT

Addition of ramucirumab to paclitaxel improves overall survival (Rainbow Trial)

Addition of ramucirumab to paclitaxel is tolerable (Rainbow Trial)

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab plus paclitaxel (n=327)</th>
<th>Placebo plus paclitaxel (n=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Bleeding or haemorrhage</td>
<td>123 (38%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>51 (16%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Liver injury or failure</td>
<td>39 (12%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (10%)</td>
<td>48 (15%)</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>21 (6%)</td>
<td>10 (3%)</td>
</tr>
</tbody>
</table>

NEW ANTI-ANGIOGENETICS

Background of apatinib

Apatinib (YN968D1)\textsuperscript{1}
- A new small molecular tyrosine kinase inhibitor that highly and selectively inhibits the VEGFR2
- The MTD is determined to be 850 mg/day administered orally

Phase I / IIa study (N=65)\textsuperscript{1}
- CR: 1.54%, PR: 12.31%, SD: 66.15%
- DCR: 80.00%
- PD: 20.00%

APATINIB IN ADVANCED GASTRIC CANCER:
Phase III study design vs. placebo

Design: Multicenter, randomised, double-blind, placebo-controlled clinical trial

1 treatment cycle = 28 days
Stratification factor: Number of metastatic sites (≤ 2 vs. >2)

APATINIB IMPROVES SURVIVAL OVER PLACEBO IN THIRD LINE FOR ADVANCED GASTRIC CANCER

**Group** | **n** | **mOS (95% CI), months** | **P value** | **HR (95%CI)**
---|---|---|---|---
Apatinib | 176 | 6.5 (4.8–7.6) | 0.0149 | 0.709 (0.537–0.937)
Placebo | 91 | 4.7 (3.6–5.4) | | |

## GASTRO-OESOPHAGEAL ADENOCARCINOMAS

Third or further line therapy randomised trials comparing with BSC or active treatment

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<td>Shitara K, et al.²</td>
<td>2018</td>
<td>507 2:1</td>
<td>Trifluridine/tipiracil vs. BSC</td>
<td>0.69</td>
<td>0.0003</td>
<td>5.7 vs. 3.6 2.1 months</td>
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<td>TAGS Third line</td>
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<td>2018</td>
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<td>4.6 vs. 5.0 -0.4 months</td>
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<tr>
<td>JAVELIN 300 Third or further lines</td>
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<td>2017</td>
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<td>ATTRACTION-2 Third or further lines</td>
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</tr>
</tbody>
</table>

TRIFLURIDINE/TIPIRACIL (TAS 102) PROLONGS SURVIVAL IN THIRD LINE ADVANCED GASTRIC CANCER

Design: Multicentre, randomised, double-blind, placebo-controlled clinical trial

Endpoints: OS

Stratification
- Region (Japan vs. rest of the world)
- PS (0 vs. 1)
- Previous ramucirumab (yes vs. no)

TAS-102 + BSC
35 mg po twice daily
Day 1-5 and 8-12 every 28 days
(N=337)

Placebo + BSC
35 mg po twice daily
Day 1-5 and 8-12 every 28 days
(N=170)

TRIFLURIDINE/TIPIRACIL (TAS 102) PROLONGS SURVIVAL IN THIRD LINE ADVANCED GASTRIC CANCER

Reprinted from Lancet Oncol. 19(11), Shitara K, et al., Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial, 1437-1448, Copyright 2018 with permission from Elsevier.
IMMUNOTHERAPY IN ADVANCED GASTRO-OESOPHAGEAL ADENOCARCINOMAS
PEMBROLIZUMAB INDUCES RESPONSES IN CHEMOREFRACTORY GASTRIC CANCER

Efficacy in evaluable patients in KEYNOTE-012

<table>
<thead>
<tr>
<th></th>
<th>Central review N = 36&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Investigator review N = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>22.2 (10.1, 39.2)</td>
<td>33.3 (19.1, 50.2)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (22.2)</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (13.9)</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19 (52.8)</td>
<td>21 (53.8)</td>
</tr>
<tr>
<td>No assessment&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (2.8)</td>
<td>—</td>
</tr>
<tr>
<td>Not determined&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3 (8.3)</td>
<td>—</td>
</tr>
</tbody>
</table>

KEYNOTE-059
Phase 2 study of pembrolizumab for advanced gastric or GEJ adenocarcinoma

Primary end point: ORR per RECIST v1.1 by central review

- **COHORT 1**
  - PD-L1+ or PD-L1−
  - ≥2 prior treatments
  - Pembrolizumab 200 mg Q3W
  - N = 259

- **COHORT 2**
  - PD-L1+ or PD-L1−
  - No prior therapy
  - Pembrolizumab 200 mg + Cisplatin + 5FU, all Q3W
  - N = 25

- **COHORT 3**
  - PD-L1+ only
  - No prior therapy
  - Pembrolizumab 200 mg Q3W
  - N = 31

Modified from Muro K, et al. ASCO GI 2015; Abstract nr.03.
PEMBROLIZUMAB INDUCES RESPONSES IN CHEMO REFRACTORY GASTRIC CANCER

Efficacy in evaluable patients in KEYNOTE-059 Cohort 1

Objective tumour response

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>Participants (n=259)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Objective response (CR+PR)</td>
<td>30</td>
<td>11.6 (8.0-16.1)</td>
</tr>
<tr>
<td>Disease control (CR+PR+SD ≥2 mo)</td>
<td>70</td>
<td>27.0 (21.7-32.9)</td>
</tr>
<tr>
<td>CR (Complete response)</td>
<td>6</td>
<td>2.3 (0.9-5.0)</td>
</tr>
<tr>
<td>PR (Partial response)</td>
<td>24</td>
<td>9.3 (6.0-13.5)</td>
</tr>
<tr>
<td>SD (stable disease)</td>
<td>42</td>
<td>16.2 (11.9-21.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>145</td>
<td>56.0 (49.7-62.1)</td>
</tr>
<tr>
<td>Non evaluable</td>
<td>7</td>
<td>2.7 (1.1-5.5)</td>
</tr>
<tr>
<td>No assessment</td>
<td>35</td>
<td>13.5 (9.6-18.3)</td>
</tr>
<tr>
<td>Duration of response, median (range), mo</td>
<td>8.4 (1.6+ to 17.3+)</td>
<td></td>
</tr>
</tbody>
</table>

a) Only confirmed responses are included.
PEMBROLIZUMAB INDUCES RESPONSES IN FIRST LINE GASTRIC CANCER IN COMBINATION WITH CHEMOTHERAPY

Efficacy in evaluable patients in KEYNOTE-059 Cohort 2

ORR 60% (15/25)
PEMBROLIZUMAB INDUCES RESPONSES IN FIRST LINE GASTRIC CANCER AS SINGLE AGENT

Efficacy in evaluable patients in KEYNOTE-059 Cohort 3

ORR 25.8% (8/31)
A PHASE III STUDY
Pembrolizumab vs. weekly paclitaxel in second line for advanced gastro-oesophageal adenocarcinoma (KEYNOTE-061)

Objective I: PFS and OS as co-primary end-points in PDL1 Combined Positive Score ≥ 1 patients

Objectives II:
- Toxicity
- Response rate
- Duration of response
- Time to progression

Stratification:
- Geographical region
- PS 0 vs. 1

Arm A: Paclitaxel 80 mg/m² days 1, 8 and 15 every 4 weeks

Arm B: Pembrolizumab 200 mg every 3 weeks

## PEMBROLIZUMAB NOT SUPERIOR TO WEEKLY PACLITAXEL

In second line for advanced gastro-oesophageal adenocarcinoma

<table>
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<th>Trial author</th>
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<tr>
<td>Hironaka S, <em>et al.</em></td>
<td>2013</td>
<td>223</td>
<td>Irinotecan vs. paclitaxel</td>
<td>1.13</td>
<td>0.38</td>
<td>0.9 months for irinotecam</td>
</tr>
<tr>
<td>Wilke H, <em>et al.</em></td>
<td>2014</td>
<td>665</td>
<td>Paclitaxel+/-ramucirumab</td>
<td>0.80</td>
<td>0.017</td>
<td>2.2 months for ramucirumab</td>
</tr>
<tr>
<td>Shitara K, <em>et al.</em></td>
<td>2018</td>
<td>592</td>
<td>Pembrolizumab vs. wk paclitaxel</td>
<td>0.82</td>
<td>0.084</td>
<td>0.8 months for pembrolizumab</td>
</tr>
</tbody>
</table>
PEMBROLIZUMAB NOT SUPERIOR TO WEEKLY PACLITAXEL

In second line for advanced gastro-oesophageal adenocarcinoma in KEYNOTE-06

Reprinted from The Lancet, 392(10142), Shitara, K. et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial, 123–133. Copyright 2018, with permission from Elsevier.
Western patients with advanced/metastatic esophagogastric (including gastric/esophageal/gastro-oesophageal junction cancer) cancer with progression on ≥1 prior chemotherapy N=160

**CHECKMATE 032 EG COHORT**

Nivolumab 3 mg/kg IV Q2W (NIVO 3)

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV Q3W* (NIVO 1 + IPI 3)

Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV Q3W* (NIVO 3 + IPI 1)

**Primary endpoint:**
- ORR per RECIST v1.1

**Secondary endpoints:**
- OS, PFS, time to response, duration of response
- Safety

**Exploratory endpoint:**
- PD-L1 tumour expression (Dako 28-8 pharmDx assay)

*Median (range) follow-up, mo*: 28 (17 to 35) 24 (21 to 33) 22 (19 to 25)

*Nivolumab + ipilimumab administered for 4 cycles followed by nivolumab 3 mg/kg IV Q2W.

†Time from first dose to data cut-off; follow-up was shorter for patients who died prior to data cut-off.

Presented By Dr Yelena Janjigian at 2017 ASCO Annual Meeting.
Responses were observed regardless of PD-L1 expression

*Investigator review. #Patients with confirmed response (complete or partial response). †Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥1% (NIVO 3, n=2; NIVO 3 + IPI 1, n=1) and 1 patient with PD-L1 <1% (NIVO 1 + IPI 3). □Change truncated to 100%.

OVERALL SURVIVAL

mOS, median OS.

A PHASE III STUDY
Nivolumab vs. BSC in second line advanced gastro-oesophageal adenocarcinoma: The ATTRACTION-2 Trial


Objective I: OS
Objectives II:
- PFS
- Response rate, duration of response, disease control rate
- Time to progression
- Safety

Stratification:
- Geographical region
- PS 0 vs. 1
- No. of organs with metastases (<2 or ≥2)

Arm A: Nivolumab 3 mg/kg/IV every 2 weeks
Arm B: Placebo and BEST SUPPORTIVE CARE

R 2:1
# GASTRO-OESOPHAGEAL ADENOCARCINOMAS

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OVERALL SURVIVAL NIVOLUMAB VS. BSC IN ATTRACTION-2 TRIAL

Reprinted from The Lancet Oncol, 390 (10111), Kang YK, Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial, 2461-2471. Copyright 2017, with permission from Elsevier.
THE MOLECULAR CLASSIFICATION OF GASTRIC CANCER ACCORDING TO THE CANCER GENOME ATLAS

50%
CIN
- Intestinal histology
- TP53 mutation
- RTK-RAS activation

9%
EBV
- PIK3CA mutation
- PD-L1/2 overexpression
- EBV-CIMP
- CDKN2A silencing
- Immune cell signalling

20%
GS
- Diffuse histology
- CDH1, RHOA mutations
- CLDN18-ARHGAP fusion
- Cell adhesion

22%
MSI
- Hypermutation
- Gastric-CIMP
- MLH1 silencing
- Mitotic pathways
PEMBROLIZUMAB INDUCES RESPONSES MAINLY IN MSI OR EBV+ GASTRIC CANCER

Waterfall plot according to MSI/EBV status

PAN-TUMOUR GENOMIC BIOMARKERS FOR PD-1 CHECKPOINT BLOCKADE–BASED IMMUNOTHERAPY

EPIGENOMIC PROMOTER ALTERATIONS PREDICT FOR BENEFIT FROM IMMUNE CHECKPOINT INHIBITION

In metastatic gastric cancer

EPIGENOMIC PROMOTER ALTERATIONS PREDICT FOR BENEFIT FROM IMMUNE CHECKPOINT INHIBITION

In metastatic gastric cancer

A

B

Her2 status to be determined in all patients with advanced disease

Trastuzumab to be added if HER2 positive (+++)

Platinum-based chemotherapy as first option, with FOLFIRI as an alternative

Second line chemotherapy also prolongs survival in good PS patients

Ramucirumab as single agent prolongs survival versus BSC

Ramucirumab in combination with paclitaxel improves outcomes over paclitaxel
GASTRO-OESOPHAGEAL ADENOCARCINOMAS

Conclusions II

- Immunotherapy (Pembrolizumab and Nivolumab) under development with interesting data to be confirmed
- Nivolumab superior to BSC in a placebo controlled study
- Pembrolizumab not superior to weekly Paclitaxel in second line
- Avelumab not superior to third line chemotherapy
- EBV and MSI predictive factors to sensitivity for checkpoint inhibitors
- Understanding the mechanisms of primary resistance to checkpoint inhibitors will lead us to precision immunotherapy in GEA
- First line trials underway

- Better selection of patients needed in clinical trials
- Validation of molecular classification in trials
- International cooperation
THANK YOU!