Systemic treatment
in early and advanced gastric cancer

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Milan
Gastric adenocarcinoma: World epidemiology

Population | Number
---|---
Asia | 769,728
Europe | 133,133
LAC* | 67,058
Africa | 31,148
North America | 29,275
Oceania | 3,359
Total | 1,033,701

Number of new cases in 2018, both sexes, all ages

Lung | 2,983,870 (11.0%)
Liver | 861,980 (4.7%)
Breast | 2,586,896 (11.4%)
Colon/rectum | 1,840,518 (10.2%)
Prostate | 1,276,106 (7.1%)
Stomach | 1,033,781 (5.7%)
Oesophagus | 572,094 (3.2%)

Total: 18,078,957 cases

Number of deaths in 2018, both sexes, all ages

Lung | 1,761,097 (18.4%)
Prostate | 586,989 (6.0%)
Colon/rectum | 505,795 (5.3%)
Breast | 526,679 (5.6%)

Total: 9,555,027 deaths

Source: Globocan 2018
Number of new cases in 2018, both sexes, all ages

North America | 1,660,359 (8.7%)
Europe | 1,418,249 (7.8%)
LAC* | 491,531 (2.7%)
Africa | 429,605 (2.3%)
North America | 29,275 (0.2%)
Oceania | 3,359 (0.2%)

Total: 18,078,957 cases

Number of deaths in 2018, both sexes, all ages

Lung | 1,660,359 (8.7%)
Prostate | 586,989 (6.0%)
Colon/rectum | 505,795 (5.3%)
Breast | 526,679 (5.6%)

Total: 9,555,027 deaths

Figure 2. Map shows the estimated age-standardized incidence rates (world) for stomach cancer in 2018, both sexes, all ages (reproduced from http://globocan.iarc.fr [5])

Globocan, 2018
Can we improve the outcome of gastric cancer?

- *By reducing the incidence* (primary prevention)
- *Earlier diagnosis* (secondary prevention)
- Effective local treatments (surgery)
- Effective adjuvant/neoadjuvant perioperative treatments
- Optimal management of the advanced disease (effective systemic treatments)
Surgery is the milestone in the treatment of early gastric cancer

Survival rates according to R-category

OS according to stage subgroup and number of lymph nodes examined (<25 vs ≥25)

**FIG. 1** Overall survival rates for 1,421 GC patients who underwent gastrectomy with negative resection margin and 128 GC patients with positive microscopic resection margin

Wang SY, Ann Surg Oncol 2009

Smith DD, JCO 2005
Surgery is the milestone in the treatment of early gastric cancer

<table>
<thead>
<tr>
<th>Authors</th>
<th>Accrual</th>
<th>5-yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allum (1989)</td>
<td>nr</td>
<td>12%</td>
</tr>
<tr>
<td>Coombes (1990)</td>
<td>1981-1984</td>
<td>35%</td>
</tr>
</tbody>
</table>

Surgery alone does not cure most of the patients!
Localised disease is often a systemic disease. CTCs as a sign for micrometastatic disease

817 pts from 2000-2012
Median fup 28.9 mo

Circulating tumor cells in healthy controls and pts with radically resected GC

3-year DFS was lower in patients who had more CTCs

Kang HM, Plos One 2017
Zhang HM, J Trasl Med 2018
How to improve the outcome of a cancer?

- By reducing the incidence (primary prevention)
- Earlier diagnosis (secondary prevention)
- Effective local treatments (surgery)
- Effective adjuvant/neoadjuvant/perioperative treatments
- Optimal management of the advanced disease (effective systemic treatments)
Meta-analyses of randomized trials assessing the interest of postoperative adjuvant chemotherapy in gastric cancer

Marc Buyse and Jean-Pierre Pignon

on behalf of the Global Advanced/Adjuvant Stomach Tumor Research through International Collaboration (GASTRIC)

Intensification: no effect

Absolute benefit in OS: 6% due to fluoropirymidine. Higher the stage the stronger the treatment effect.
ADJUVANT CHEMOTHERAPY IN ASIA ......STANDARD CARE

**ACTS-GC**

**CLASSIC**

5-Year Overall Survival (%)
- Surgery 69%
- Adjuv CAPOX 78%
- HR 0.66 (95% CI 0.51–0.85; p=0.0015)

*(1JCO 2011; 2Lancet Oncol 2014)*
Perioperative chemotherapy

UK MAGIC 2006¹

<table>
<thead>
<tr>
<th>Site of tumour</th>
<th>Stomach cancer</th>
<th>EGJ cancer</th>
<th>Lower oesophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>74%</td>
<td>11.2%</td>
<td>14.8%</td>
</tr>
</tbody>
</table>

France FNCLCC 2011²

<table>
<thead>
<tr>
<th>Site of tumour</th>
<th>Stomach cancer</th>
<th>EGJ cancer</th>
<th>Lower oesophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25%</td>
<td>64%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Hazard ratio 0.75 (95% CI: 0.60–0.93) p=0.009

Neoadjuvant / perioperative chemotherapy

- **FLOT4-AIO Study**

  - Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
  - Medically and technically operable
  - cT2-4/cN-any/cM0 or cT-any/cN+/cM0

  **FLOT x4 - RESECTION - FLOT x4**
  - FLOT: docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

  **ECF/ECX x3 - RESECTION - ECF/ECX x3**
  - ECF/ECX: Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

Stratification: ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60–69 vs. ≥70 years) and nodal status (cN+ vs. cN-)

Neoadjuvant / perioperative chemotherapy

- **FLOT4-AIO Study**

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS</td>
<td>35 months (27–46)</td>
<td>50 months (38–NR)</td>
</tr>
<tr>
<td>HR</td>
<td>0.77 (0.63–0.94)</td>
<td>p=0.012 (log rank)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OS rate*</th>
<th>ECF/ECX</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2y</td>
<td>59%</td>
<td>68%</td>
</tr>
<tr>
<td>3y</td>
<td>48%</td>
<td>57%</td>
</tr>
<tr>
<td>5y</td>
<td>36%</td>
<td>45%</td>
</tr>
</tbody>
</table>

*Projected OS rates

To whom?

Site, stage, histology, age, PS, ....

- **AIO-FLOT4 Study**

  Treatment effect on overall survival according to the baseline characteristics of the patients

Patients with MSI-H gastric cancer do not appear to benefit from adjuvant chemotherapy.

- **MAGIC**: 6.7% MSI-H
  - Surgery alone
  - Peri-operative chemotherapy

- **CLASSIC**: 6.8% MSI-H

No benefit from CT in MSI-H tumours.

Benefit from CT in MSS tumours.

Source: Smyth et al JAMA Oncol 2017
Chi et al Ann Surg 2018
**Meta-analysis of 4 clinical trials for MSI-H tumors**

CT may not be effective

**OS according to treatment & MSI status**

1566 pts; 121 (7.8%) MSI-H

**PFS on first-line platinum-based therapy for pts with MSI-H vs. non-MSI-H tumors**

Pietrantonio F, JCO 2019; Janjigian YY, Cancer Discovery 2018

<table>
<thead>
<tr>
<th>Treatment Comparison by MSI Status and Survival Type</th>
<th>No. of Events</th>
<th>5-Year Survival, % (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSS/MSI low: CT + surgery vs surgery only</td>
<td>368 vs 198</td>
<td>62.0 (58.9 to 65.3)</td>
<td>0.75 (0.60 to 0.94) 1.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52.8 (48.0 to 58.0)</td>
<td></td>
</tr>
<tr>
<td>MSI high: CT + surgery vs surgery only</td>
<td>21 vs 5</td>
<td>75.4 (66.4 to 85.6)</td>
<td>1.50 (0.55 to 4.12) 82.8 (70.1 to 97.8)</td>
</tr>
</tbody>
</table>
The multidisciplinary team
Advanced gastric cancer patients: issues for an optimal treatment strategy

- A heterogeneous patient population requiring a personalized (clinical) approach
- Any role for surgery like colon cancer?
- 1\textsuperscript{st} line options: all drugs upfront or a “sequential strategy” (triplets or doublets)?
- 2\textsuperscript{nd} and further line options: really an opportunity for patients?
- A possible therapeutic algorithm?
Advanced gastric cancer patients: Just not an “unique and easy” patient

- Locally advanced vs. metastatic disease
- Gastric resection in 50% of patients
- Median age: males 70 yrs; females 60 yrs
- At least 2 comorbidities
- 40% of patients receive a treatment for other chronic diseases
- Malnutrition present in 40-50% of patients
A different treatment aim and approach for locally advanced gastric cancer?

Yes, tumor shrinkage and surgery

Locally advanced survival: 11 months resectability
Same survival of initially resectable patients
A 3-drug regimen (tumor response)

Triplet vs doublet: Better Response 40/50% vs 20/30%
Which regimen? FLOT pCR FLOT 16% ECX 11% CDDP/5FU 3%

The nutritional status

Weight loss at the first month of palliative chemotherapy predicts survival outcomes in patients with advanced gastric cancer

Nutrition support can bring survival benefit to high nutrition risk gastric cancer patients who received chemotherapy

Chan YO, Gastric Cancer 2016

Qiu M, Supp Care Cancer 2015
Advanced gastric cancer patients: issues for an optimal treatment strategy

- A heterogeneous patient population requiring a personalized approach
- Any role for surgery like colon cancer?
- 1\textsuperscript{st} line options: all drugs upfront or a “sequential strategy” (triplets or doublets)?
- 2\textsuperscript{nd} and further line options: really an opportunity for patients?
- A possible therapeutic algorithm?
Gastrectomy has no role in metastatic gastric cancer patients

**THE LANCET Oncology**

Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial

Kazumasa Fujitani, MD, PhD, Han-kwang Yang, MD, Junki Mizusawa, MDc, Young-woo Kim, MD, Masanori Terashima,

175 patients randomised to surgery and chemotherapy vs chemotherapy alone

2-year OS:

- all patients: 31% 
- chemotherapy alone: 25% 
- gastrectomy and chemotherapy: 16.6%

Higher toxicity in patients receiving surgery

**Interpretation**

Since gastrectomy followed by chemotherapy did not show any survival benefit compared with chemotherapy alone in advanced gastric cancer with a single non-curable factor, gastrectomy cannot be justified for treatment of patients with these tumours.
Oligometastatic disease

Clinical practice for a patient with **metachronous resectable** liver metastasis after curative resection of primary tumor (n=121)

Liver resection – pooled data analysis

Metastases resection – FLOT-3 observational study

**Table**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Europe (n=66)</th>
<th>Japan (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic resection</td>
<td>9.1%</td>
<td>7.3%</td>
</tr>
<tr>
<td>RFA if the size of liver metastasis is &lt; 3 cm</td>
<td>33.3%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Chemotherapy followed by hepatic resection</td>
<td>15.2%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Chemotherapy followed by RFA (size &lt; 3 cm)</td>
<td>30.9%</td>
<td>16.4%</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Other</td>
<td>9.1%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

**Graph**

- **HR = 0.50; 95% CI 0.41–0.61; P < 0.001**

**Study ID**

- **Chen et al.**
- **Oh et al.**
- **Chen et al.**
- **Cilmi et al.**
- **Makino et al.**
- **Miki et al.**
- **Tong et al.**
- **Tong et al.**
- **Tong et al.**
- **Tong et al.**
- **Tong et al.**
- **Liu et al.**
- **Wong et al.**
- **Overall (weighted squared) 24.4% 0.227**

**Note:** Weights are from random-effects analysis.
Advanced gastric cancer patients: issues for an optimal treatment strategy

• A heterogeneous patient population requiring a personalized approach
• Any role for surgery like colon cancer?
• The best regimen in 1\textsuperscript{st} line options: all drugs upfront or a “sequential strategy” (triplets or doublets)?
• 2\textsuperscript{nd} and further line options: really an opportunity for patients?
• A possible therapeutic algorithm?
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

Yung-Yue Bang, Eric Van Cutsem,* Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Taroh Sato, Giuseppe Aprile, Evgeny Kulikov, Julie Hill, Michaela LeHe, Josef Rüschhoff,Yoon-Koo Kang, for the ToGA Trial Investigators†

3807 patients screened
810 HER2-positive (22.1%)

HER2-positive advanced GC (n=584)

- HER2-positive tumor (centrally assessed) IHC 3+ and/or FISH+

5-FU or capecitabine + cisplatin (n=260)

5-FU or capecitabine + cisplatin + trastuzumab (n=294)


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A triplet regimen may be a reasonable choice in locally advanced or in patients with a high tumor burden but probably it is not necessary for oligometastatic disease.
But for all the other patients (>70%) which is the best regimen?
Sequential treatment improves outcome of mGC pts: A new challenge for clinicians

Improving trends in survival of patients who receive sequential CT for mGC

Koo DH, Gastric Cancer 2015

<table>
<thead>
<tr>
<th>Period</th>
<th>No at risk</th>
<th>Median survival</th>
<th>95% C.I.</th>
</tr>
</thead>
</table>

median OS: 10.6 mo  
period 1: 9.6 mo  
period 2: 10.3 mo  
period 3: 11.7 mo

Davidson M, Clin Colorectal Cancer 2018

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2nd line chemotherapy
How many patients?

Candidates to receive a second line about 40%:

- Performance status (0-1)
- Age (70 years)
- Lower levels of LDH
- Response to first line CT
- Progression free survival

Catalano V, Br J Cancer, 2008;
Fanotto V, Gastric Cancer 2017
**Second-line chemotherapy: which drugs?**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Region</th>
<th>Treatment</th>
<th>OS (mo)</th>
<th>HR</th>
<th>Delta (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cougar-2 2013</td>
<td>UK</td>
<td>Docetaxel BSC</td>
<td>5.2</td>
<td>0.67</td>
<td>+ 1.6</td>
</tr>
<tr>
<td>Kang et al 2012</td>
<td>Korea</td>
<td>Irinotecan/Docetaxel BSC</td>
<td>5.3</td>
<td>0.65</td>
<td>+ 1.5</td>
</tr>
<tr>
<td>Thuss-Patience 2011</td>
<td>Germany</td>
<td>Irinotecan BSC</td>
<td>4.0</td>
<td>0.48</td>
<td>+ 1.6</td>
</tr>
<tr>
<td>Hironaka et al 2013</td>
<td>Japan</td>
<td>Irinotecan Paclitaxel</td>
<td>8.4</td>
<td>1.13</td>
<td>+1.1</td>
</tr>
</tbody>
</table>

- **Taxane and irinotecan** significantly prolong survival compared to BSC
- **Equally effective** in terms of OS and PFS (meta-analysis) but weekly docetaxel not effective
- Different **toxicity profile**, which may guide clinical decision-making
- No OS benefit adding another agent; no role for combination chemotherapy

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Second line treatment: the role of Ramucirumab

REGARD and RAINBOW trials

Wilke H, Lancet Oncol 2014; Fuchs CS, Lancet Oncol 2014
When should chemotherapy be started?

1° line

Initial or delayed chemotherapy with best supportive care in advanced gastric cancer

2° line

Consider to start 2° line as soon as possible when:
- progression on the basis of PS deterioration
- onset of new symptoms
- increase in tumor markers even in the presence of a stable disease at imaging

Fig. 1. Probability of survival in patients randomly allocated to primary chemotherapy with best supportive care (-----, n = 10) or to best supportive care with delayed chemotherapy (· · · · , n = 8). The difference is statistically significant (log-rank p < 0.02).
The nutritional status: a key point in outcome and survival of gastric cancer patients.

A Pharmacokinetic Basis?
Sarcopenia relates to higher drug exposure, measured as Area Under the time-concentration Curve

<table>
<thead>
<tr>
<th></th>
<th>Sarcopenic</th>
<th>Non sarcopenic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median adjusted dose for AUC (mg/L) on day 28. Range</td>
<td>102.4</td>
<td>53.7</td>
<td>=0.013</td>
</tr>
<tr>
<td>Patients with DLT</td>
<td>48.0-137.8</td>
<td>24.5-74.5</td>
<td></td>
</tr>
<tr>
<td>Median adjusted dose for AUC (mg/L) on day 28. Range</td>
<td>106.4</td>
<td>56.7</td>
<td>=0.09</td>
</tr>
<tr>
<td>Patients without DLT</td>
<td>48-177.8</td>
<td>24.5-136.7</td>
<td></td>
</tr>
</tbody>
</table>

Mir, PLoS ONE, 2012
TAS-102: a new opportunity for a 3° line?
Immunotherapy in gastric cancer

Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer

Phase 2 Clinical KEYNOTE-059 Trial
Charles B. Fuchs, MD, MPH,1,2 Takeshiho Doi, MD, PhD,7 Raymond W. Jea, MD, MS, MSc, FRCPC,3,4 Koichi Murao, MD,5 Tomo Hata, MD, PhD,5 Manuel Machado, MD,7 Wei Ling Sun, MD,1,9 Shaida J. Jalal, MD,10 Mahesh A. Shah, MD,11 Jean Philipe Metges, MD,12 Marcelo Garrido, MD,13 Tatsuki Odaka, MD,14,15 Mario Mandala, MD,16 Zev A. Wara, MD,17 Daniel V. Carames, MD,18 Anupam Chau, MD,19 Rakesh Shitare, MD,20 Ravit Gava, MD,19 Jonathan Rekhi, MD,20 Andrew H. Ko, MD,20 Geoffrey Ku, MD,20 Philip Philips, MD, PhD, FRCR21
Jonathan Berek, MD,22 Andrew H. Ko, MD,22 Geoffrey Ku, MD,22 Philip Philips, MD, PhD, FRCR21
Peter C. Endress, MD,24 Yun-Jie Jia, MD, PhD,25 Diane Leventhal, PhD,26 Jianiang Wang, PhD,26 Minor Rosales, MD, PhD,26 Rita P. Dalal, MBBS, MPH,28 and Harry H. Youn, MD27

KEYNOTE-061 Study Design (NCT02370498)

Key Eligibility Criteria
- Adenocarcinoma of the stomach or GEJ that was metastatic or locally advanced but unresectable
- PD per RECIST 1.1 after first-line platinum- and fluoropyrimidine-containing therapy
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- First 489 patients: any PD-L1 CPS
- Final 103 patients: PD-L1 CPS ≥1

Stratification Factors
- Region (Eastern America/Australasia vs. rest of the world)
- ECOG PS (0 vs. 1)
- TTP on first-line therapy (≤6 mo vs >6 mo)
- PD-L1 CPS (≥1 vs <1)

End Points
- Primary: OS and PFS in the CPS ≥1 population
- Secondary: ORR and DOR in the CPS ≥1 population; safety in all treated patients

Events/Pts
- Pembrolizumab: 6/15
- Paclitaxel: 10/12

Median (95% CI)
- Pembrolizumab: 8.1 mo (2.0–16.7)
- Paclitaxel: NR

OS, ORR, and DOR for MSI-H Tumors

**cTable 6. Objective Response and Duration of Response by MSI Status**

<table>
<thead>
<tr>
<th>MSI-High (n = 7)</th>
<th>Non-MSI-High (n = 167)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response</strong></td>
<td><strong>Non</strong>-</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Objective response (CR + PR)</td>
<td>4</td>
</tr>
<tr>
<td>Disease control (CR + PR + SD ≥2 months)</td>
<td>5</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>3</td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
</tr>
<tr>
<td>Nonassessable</td>
<td>0</td>
</tr>
<tr>
<td><strong>No assessment</strong></td>
<td>2</td>
</tr>
</tbody>
</table>

**OS, ORR, and DOR for MSI-H Tumors**

**Table 6. Objective Response and Duration of Response by MSI Status**

**Best overall response**

<table>
<thead>
<tr>
<th>No.</th>
<th>% (95% CI)</th>
<th>No.</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response (CR + PR)</td>
<td>4</td>
<td>57.1 (18.4–90.1)</td>
<td>15</td>
</tr>
<tr>
<td>Disease control (CR + PR + SD ≥2 months)</td>
<td>5</td>
<td>71.4 (29.0–96.3)</td>
<td>37</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>14.3 (0.4–57.9)</td>
<td>4</td>
</tr>
<tr>
<td>PR</td>
<td>3</td>
<td>42.9 (9.9–81.6)</td>
<td>11</td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
<td>14.3 (0.4–57.9)</td>
<td>23</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0 (0.0–4.10)</td>
<td>102</td>
</tr>
<tr>
<td>Nonassessable</td>
<td>0</td>
<td>0 (0.0–4.10)</td>
<td>4</td>
</tr>
<tr>
<td><strong>No assessment</strong></td>
<td>2</td>
<td>28.6 (3.7–71.0)</td>
<td>23</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; MSI, microsatellite instability; PR, partial response; NR, not reached; SD, stable disease.

*Only confirmed responses are included.

**No assessment represents patients who had a baseline assessment but no postbaseline assessment at the time of the data cutoff. Reasons for no assessment include missing, treatment discontinuation, or death before the first postbaseline radiologic imaging study.

**No progressive disease at last assessment.
MSI and pembrolizumab: Data from KEYNOTE-062

**Pembro vs Chemo: OS in MSI-H Group**

<table>
<thead>
<tr>
<th>CPS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>0.29</td>
</tr>
<tr>
<td>≥10</td>
<td>0.21</td>
</tr>
</tbody>
</table>

**Pembro vs CT: OS**

<table>
<thead>
<tr>
<th>Population</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL POPULATION</strong></td>
<td></td>
</tr>
<tr>
<td>CPS ≥1</td>
<td>0.91</td>
</tr>
<tr>
<td>CPS ≥10</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>MSI-H</strong></td>
<td></td>
</tr>
<tr>
<td>CPS ≥1</td>
<td>0.29</td>
</tr>
<tr>
<td>CPS ≥10</td>
<td>0.21</td>
</tr>
</tbody>
</table>

**Pembro + Chemo vs Chemo: OS in MSI-H Group**

<table>
<thead>
<tr>
<th>CPS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>0.37</td>
</tr>
<tr>
<td>≥10</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Comprehensive molecular characterization of gastric adenocarcinoma

The Cancer Genome Atlas Research Network*

CIN
- Intestinal histology
- TPS3 mutation
- RTK-RAS activation

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

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

GS
- Diffuse histology
- CDH1, RHDA mutations
- GLDN18-ARHGAP fusion
- Cell adhesion

Molecular subtypes of gastric adenocarcinoma

CIN
50%

MSI
9%

EBV
22%

GS
20%

Cancer Genome Atlas (TCGA), 2014 Nature
Relevant activity of immunotherapy in EBV and MSI tumors but EBV 3% and MSI 5% of AGC

Pembrolizumab and Nivolumab 11% ORR in unselected patients

Janjigian et al. Cancer Discovery 2018
Can we improve the outcome of gastric cancer?

- By reducing the incidence (primary prevention)
- Earlier diagnosis (patients at high risk)
- Perioperative treatment (patient selection)
- Optimal management of the advanced disease (1°, 2°, 3° line; immunotherapy, )
Thank you!

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