FIRST LINE IMMUNOTHERAPY FOR OESOPHAGEAL AND GASTRIC CANCER AS NEW STANDARD OF CARE

Andrés Cervantes Ruipérez and Tania Fleitas Kanonnikoff
OUTLINE

GEA and squamous oesophageal tumour features
GEA and squamous oesophageal cancer immune characteristics
Studies that had recently changed the clinical practice
Phase II/III studies in progress in the peri-operative setting
Summary
HALLMARKS OF CANCER – NEW ADDITIONS

OESOPHAGEAL CANCER TUMOUR FEATURES

Oesophageal cancer is the sixth most common cause of cancer-related death worldwide.

Squamous cell carcinomas

- Upper and mid-oesophagus location
- Smoking and alcohol related in Western countries
- More prevalent in developing countries

Adenocarcinomas

- Lower third and junctional location
- Related to obesity, smoking, gastric reflux and
- Barret’s oesophagus
- Increasing incidence in Western countries (x4.6 US)

Images from: Nephron, CC BY-SA 3.0 <https://creativecommons.org/licenses/by-sa/3.0>, via Wikimedia Common; available at: https://upload.wikimedia.org/wikipedia/commons/6/64/Esophageal_squamous_cell_carcinoma___a1___high_mag.jpg; and https://upload.wikimedia.org/wikipedia/commons/5/55/Esophageal_adenocarcinoma___high_mag.jpg; accessed March 2022.
**INTEGRATED GENOMIC CHARACTERISATION OF OESOPHAGEAL CANCERS**

<table>
<thead>
<tr>
<th></th>
<th>ESCC</th>
<th>UC</th>
<th>AC</th>
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<tbody>
<tr>
<td>Oesophagus</td>
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<tr>
<td>GEJ</td>
<td>64</td>
<td>1</td>
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<tr>
<td>Stomach</td>
<td>47</td>
<td>6</td>
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<td>98</td>
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<td></td>
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<td>(559)</td>
</tr>
</tbody>
</table>

TUMOUR IMMUNE MICROENVIRONMENT COMPOSITION OF OESOPHAGEAL SQUAMOUS CELL CARCINOMA

Baba Y, et al. Cancer Sci. 2020; 111:3132-3141. Reproduced under the terms of the Creative Commons CC-BY-NC-ND license. Available at: https://creativecommons.org/licenses/by-nc-nd/4.0/; accessed March 2022.
OESOPHAGEAL CANCER

Immune microenvironment shape cancer biology and impact the responsiveness to therapy

The efficacy of immune checkpoint inhibitors

Tumour cell intrinsic factors
- PD-L1 expression*
- Tumour mutation load
- Microsatellite instability-high status
- PD-L2 expression

Extrinsic factors
- Tumour-infiltrating lymphocytes
- Tumour-associated macrophages
- Myeloid-derived suppressor cells
- Microbiome

Key immune-checkpoint inhibitors and their ligands such as PD1-PD-L1 and CTLA4 had higher interaction scores in tumours than in normal samples

*Promising predictive marker for oesophageal cancer patients in KEYNOTE-180 and -181.
Baba Y, et al. Cancer Sci. 2020; 111:3132-3141. Reproduced under the terms of the Creative Commons CC-BY-NC-ND license. Available at: https://creativecommons.org/licenses/by-nc-nd/4.0/; accessed March 2022;
GASTRIC CANCER TUMOUR FEATURES

Adenocarcinomas

Intra and intertumoural heterogeneity

Distal gastric cancer represents ~80% of gastric tumours globally and is associated with *Helicobacter pylori* infection, alcohol use, high salt intake, and low consumption of fruit and vegetable.

Proximal gastric cancer is associated with obesity and gastro-oesophageal reflux.

Her2, MSS and PD-L1 CPS score status are validated predictive biomarkers for drug therapies.

KEY FEATURES OF THE FOUR TCGA SUBTYPES OF GEA

Spanning the lower oesophagus to the distal stomach

Reprinted from Cancer Discov, Copyright 2019, 9(12):1656-1672, Nagaraja AK, et al. Genomics and Targeted Therapies in Gastroesophageal Adenocarcinoma, with permission from AACR
TUMOUR IMMUNE MICROENVIRONMENT OF GASTROESOPHAGEAL ADENOCARCINOMAS IS HETEROGENEOUS

Derks S, et al. Ann Oncol. 2020;31:1011–1020. © 2020 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>Immune microenvironment characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI/EBV</td>
<td>Intense T cell infiltrates</td>
</tr>
<tr>
<td>CIN</td>
<td>T-cell exclusion, macrophages or immune desert</td>
</tr>
<tr>
<td>GS</td>
<td>CD4+T cells, macrophages and B cells; tertiary lymphoid structures ~50%</td>
</tr>
</tbody>
</table>
LOCALISED OESOPHAGEAL CANCER – ESMO GUIDELINES

Limited disease (cT1-T2 or cN0 M0)

Locally advanced disease (cT3-T4 or cN1-3 M0)

Adjuvant Nivolumab for residual pathologic disease ≥ ypT1 or ≥ ypN1*

Squamous cell cancer

Adenocarcinoma

Neoadjuvant chemoradiotherapy

Definitive chemoradiotherapy

Perioperative chemotherapy

Neoadjuvant chemoradiotherapy

Restaging (exclusion of M1)

Follow-up (every 3 months)

Restaging (exclusion of M1)

Restaging (exclusion of M1)

Resection

Resection

Salvage resection

Resection

Resection

ADJUVANT IMMUNOTHERAPY FOR OESOPHAGEAL CANCER

Not achieving optimal remission after adjuvant chemoradiation – Checkmate 577 study design

Key eligibility criteria
- Stage II or III oesophageal or gastroesophageal junction cancer who had received
- Neoadjuvant chemoradiotherapy and had residual pathological disease
- ≥ypT1 or ≥ypN1
- ECOG PS 0, 1

Stratification factors
- ESCC vs EAC
- Pathological node status ≥ ypN1 vs ypN0
- Tumour cell PD-L1 ≥1% vs <1%

Nivolumab
240 mg Q2W x 16 weeks
Then 480 mg Q4W

Placebo
Q2W x 16 weeks
Then Q4W

Primary endpoint:
- DFS

Secondary endpoints:
- OS
- OS rate at 1,2 & 3 years

ADJUVANT IMMUNOTHERAPY FOR OESOPHAGEAL CANCER

Not achieving optimal remission after adjuvant chemoradiation – Checkmate 577: Baseline characteristics well balanced among arms

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n=532)</th>
<th>Placebo (n=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>62 (26-82)</td>
<td>61 (26-86)</td>
</tr>
<tr>
<td>Male, %</td>
<td>84</td>
<td>85</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>81</td>
<td>82</td>
</tr>
<tr>
<td>Asian</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Disease stage at initial diagnosis, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>III</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td>Tumour location, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>GEJC</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Histology, a %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Pathologic lymph node status ≥ypN1, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>Tumour-cell PD-L1 expression, b %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>Time from complete resection to randomisation, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 weeks</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>≥10 weeks</td>
<td>66</td>
<td>72</td>
</tr>
</tbody>
</table>

*aOne patient in the nivolumab group had a histologic type of “other” (protocol deviation).

*bIn most patients, tumour-cell PD-L1 expression was determined with the use of the PD-L1 IHC 28-8 pharmDX assay (Dako, Agilent Technologies) from a tumour tissue specimen obtained from the patient after completion of chemoradiotherapy. However, tumour tissue from 40 patients was quantifiable only before chemoradiotherapy.

ADJUVANT NIVOLUMAB FOR OESOPHAGEAL CANCER

Not achieving optimal remission after adjuvant chemoradiation

Nivolumab significantly improves PFS over placebo

Disease-free survival in the overall population

ADJUVANT NIVOLUMAB FOR OESOPHAGEAL CANCER

Not achieving optimal remission after adjuvant chemoradiation

Nivolumab significantly improves PFS over placebo

Distant metastasis–free survival in the intention-to-treat population

ADJUVANT NIVOLUMAB FOR OESOPHAGEAL CANCER

Not achieving optimal remission after adjuvant chemoradiation – Checkmate 577: Safety summary

ADJUVANT NIVOLUMAB FOR OESOPHAGEAL CANCER

Not achieving optimal remission after adjuvant chemoradiation – Checkmate 577: Quality of life during and after treatment (FACT-E G7)

Nivolumab lacks a detrimental effect on QoL

FACT-E, Functional Assessment of Cancer Therapy–Esophageal

ADJUVANT NIVOLUMAB FOR OESOPHAGEAL CANCER

Not achieving optimal remission after adjuvant chemoradiation: A new standard of care

Cherny NL, et al. ESMO Open 2016;1:e000100. doi: 10.1136/esmoopen-2016-000100
ADJUVANT IMMUNOTHERAPY OF OESOPHAGEAL OR GEJ CANCER

Regulatory approvals

LOCALIZED ESOPHAGEAL CANCER – CHECKMATE-577

On May 20, 2020, the Food and Drug Administration approved nivolumab (Opdivo, Bristol-Myers Squibb Company) for patients with completely resected esophageal or gastroesophageal junction (GEJ) cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy.

FDA approves nivolumab for resected esophageal or GEJ cancer

Opdivo as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or GEJ cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Adjuvant treatment of oesophageal or GEJ cancer

U.S. Food and Drug Administration. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-resected-esophageal-or-gej-cancer; accessed March 2022.
<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Setting</th>
<th>Phase</th>
<th>Treatment</th>
<th>Tumour type</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>VESTIGE NCT03443856</td>
<td>Adjuvant for N+/R1</td>
<td>II</td>
<td>Post-operative nivolumab + ipilimumab vs FLOT</td>
<td>Gastric/ EGJ</td>
<td>DFS</td>
</tr>
<tr>
<td>Matterhorn NCT04592913</td>
<td>Perioperative</td>
<td>III</td>
<td>Neoadjuvant-adjuvant durvalumab + FLOT → adjuvant durvalumab</td>
<td>Gastric/ EGJ</td>
<td>EFS</td>
</tr>
<tr>
<td>AIO DANTE NCT03421288</td>
<td>Perioperative</td>
<td>II</td>
<td>Atezolizumab + FLOT vs FLOT</td>
<td>Gastric/ EGJ</td>
<td>DFS</td>
</tr>
<tr>
<td>KEYNOTE 585 NCT03221426</td>
<td>Perioperative ≥T3 or N+</td>
<td>III</td>
<td>Pembrolizumab + FLOT vs FLOT</td>
<td>Gastric/ EGJ</td>
<td>2y EFS</td>
</tr>
<tr>
<td>INFINITY NCT04817826</td>
<td>Perioperative MSI</td>
<td>II</td>
<td>Tremelimumab + durvalumab as neoadjuvant (Cohort 1) and definitive (Cohort 2) treatment</td>
<td>Gastric/ EGJ</td>
<td>Cohort 1: cPRR and ctDNA(-) Cohort 2: 2y ORR</td>
</tr>
<tr>
<td>NEONIPIGA NCT04006262</td>
<td>Perioperative MSI</td>
<td>II</td>
<td>Pre-operative nivolumab + ipilimumab, post-operative nivolumab</td>
<td>Gastric/ EGJ</td>
<td>cPRR</td>
</tr>
<tr>
<td></td>
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<td>First preliminary results: 59% cPRR; 94% free of events after 12 months follow-up*</td>
</tr>
</tbody>
</table>

*André T. Abstract 244ASCO GI 2022*
### KEY CLINICAL TRIALS USING IMMUNE CHECKPOINT INHIBITORS

For advanced oesophageal SCC as second and further lines

Checkpoint inhibitors have a contentious effect when given as second or further lines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Phase</th>
<th>Use</th>
<th>Histology</th>
<th>n</th>
<th>Regimen</th>
<th>Response rate</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab*</td>
<td>ATTRACTION 01</td>
<td>II</td>
<td>&gt;2 lines</td>
<td>SCC</td>
<td>65</td>
<td>Nivolumab</td>
<td>17%</td>
<td>1.5 months</td>
<td>10.8 months</td>
</tr>
<tr>
<td>Nivolumab**</td>
<td>ATTRACTION 03</td>
<td>III</td>
<td>2 line</td>
<td>SCC</td>
<td>419</td>
<td>Nivolumab vs paclitaxel or irinotecan</td>
<td>19%</td>
<td>1.7 months</td>
<td>10.9 months</td>
</tr>
<tr>
<td>Pembrolizumab***</td>
<td>KEYNOTE 180</td>
<td>II</td>
<td>&gt;3 lines</td>
<td>CPS &gt;10</td>
<td>SCC/ADC</td>
<td>121</td>
<td>Pembrolizumab</td>
<td>All 9.9% SCC 14.3%</td>
<td>All 2 months SCC 2.1 months</td>
</tr>
<tr>
<td>Pembrolizumab^</td>
<td>KEYNOTE 181</td>
<td>III</td>
<td>2 line</td>
<td>CPS &gt;10</td>
<td>SCC/ADC</td>
<td>628</td>
<td>Pembrolizumab vs paclitaxel or irinotecan</td>
<td>All 22% SCC 22%</td>
<td>All 2.6 months SCC 2.1 months</td>
</tr>
</tbody>
</table>

^JCO 2020 38:35, 4138-4148
PEMBROLIZUMAB + PLATINUM-BASED CHEMO VS. CHEMO
In 1L advanced oesophageal and high GEJ tumours – KEYNOTE-590 study design

Key eligibility criteria
- Locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic EGJ Siewert type 1 adenocarcinoma
- Treatment naive
- ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)

Stratification factors
- Asia vs Non-Asia region
- ESCC vs EAC
- ECOG PS 0 vs 1

Pembrolizumab 200 mg IV Q3W for ≤35 cycles
+ Chemotherapy
5-FU 800 mg/m² IV for days 1-5 Q3W for ≤35 cycles + Cisplatin 80 mg/m² IV Q3W for ≤6 cycles

Placebo
+ Chemotherapy
5-FU 800 mg/m² IV for days 1-5 Q3W for ≤35 cycles
+ Cisplatin 80 mg/m² IV Q3W for ≤6 cycles

Dual primary endpoints:
- OS and PFS
Secondary endpoint:
- ORR
Tumour response assessed at week 9 then Q9W

N=749

PDL1 CPS SCORE IN OESOPHAGEAL CANCER

Comparison of the combined positive scores (CPS) from two assays

\[
\text{CPS} = \frac{\text{No. PD-L1 positive cells (tumour cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumour cells}} \times 100
\]

Spearman correlation value = 0.978, \( P < 0.001 \)

Pembrolizumab plus chemo improves OS in squamous subtypes with CPS >10 and in all cases with CPS >10

**Patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more**

- 13.9 vs 8.8 months

**All patients with PD-L1 CPS of 10 or more**

- 13.5 vs 9.4 months
Pembrolizumab plus chemo improves OS in all comers but in those with CPS < 10 such a benefit is not seen.

PEMBROLIZUMAB + PLATINUM-BASED CHEMO VS. CHEMO

In 1L advanced oesophageal and high GEJ tumours –
Overall survival in key subgroups: All patients

Most subgroups trend to show a benefit of pembrolizumab plus chemo

<table>
<thead>
<tr>
<th></th>
<th>Events/patients, n/N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>333/472</td>
<td>0.76 (0.61-0.95)</td>
</tr>
<tr>
<td>≥65</td>
<td>236/312</td>
<td>0.60 (0.53-0.68)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>89/124</td>
<td>0.88 (0.69-1.13)</td>
</tr>
<tr>
<td>Male</td>
<td>482/615</td>
<td>0.70 (0.58-0.84)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
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<tr>
<td>0</td>
<td>207/299</td>
<td>0.72 (0.59-0.94)</td>
</tr>
<tr>
<td>1</td>
<td>363/448</td>
<td>0.73 (0.59-0.90)</td>
</tr>
<tr>
<td><strong>Geographical region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>288/393</td>
<td>0.64 (0.51-0.81)</td>
</tr>
<tr>
<td>Non-Asia</td>
<td>203/256</td>
<td>0.83 (0.66-1.05)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>156/261</td>
<td>0.74 (0.54-1.02)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>41/548</td>
<td>0.72 (0.60-0.86)</td>
</tr>
<tr>
<td><strong>PD-L1 status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPS ≥10</td>
<td>283/383</td>
<td>0.62 (0.49-0.78)</td>
</tr>
<tr>
<td>CPS &lt;10</td>
<td>274/347</td>
<td>0.86 (0.68-1.09)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>577/749</td>
<td>0.73 (0.62-0.86)</td>
</tr>
</tbody>
</table>

PEMBROLIZUMAB + PLATINUM-BASED CHEMO VS. CHEMO

In 1L advanced oesophageal and high GEJ tumours

If median OS with the standard treatment is ≤12 months

<table>
<thead>
<tr>
<th>GRADE 4</th>
<th>HR ≤0.65 AND gain ≥3 months</th>
<th>YES FOR CPS≥10 HR:0.57; gain in mOS 5.1 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase in 2 year survival ≥10%</td>
<td>YES FOR CPS≥10</td>
</tr>
<tr>
<td>GRADE 3</td>
<td>HR ≤0.65 AND gain ≥2.0−&lt;3 months</td>
<td></td>
</tr>
<tr>
<td>GRADE 2</td>
<td>HR ≤0.65 AND gain ≥1.5−&lt;2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR &gt;0.65−0.70 AND gain ≥1.5 months</td>
<td></td>
</tr>
<tr>
<td>GRADE 1</td>
<td>HR &gt;0.70 OR gain &lt;1.5 months</td>
<td></td>
</tr>
</tbody>
</table>

Mark with ✓ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)

<table>
<thead>
<tr>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
</table>
PEMBROLIZUMAB + PLATINUM-BASED CHEMO VS. CHEMO

In 1L advanced oesophageal and GEJ tumours – Regulatory approvals

FDA approves pembrolizumab for oesophageal or GEJ carcinoma

- On March 22, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck Sharp & Dohme Corp.) in combination with platinum and fluoropyrimidine-based chemotherapy for patients with metastatic or locally advanced oesophageal or gastroesophageal (GEJ) (tumours with epicentre 1 to 5 centimetres above the gastroesophageal junction) carcinoma who are not candidates for surgical resection or definitive chemoradiation.

[Links to FDA and ESMO approvals]
NIVOLUMAB + PLATINUM-BASED CHEMO OR NIVOLUMAB + IPILIMUMAB VS. CHEMO

In 1L advanced squamous cell oesophageal tumours – Checkmate 648 study design

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumour cell PD-L1 expression (≥1% vs <1%)
- Region of Asia vs ROW)
- ECOG PS (0 vs 1) (East Asia vs rest)
- Number of organs with metastases (≤1 vs ≥2)

Primary endpoints:
- OS and PFS (tumour cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS (all randomised)
- ORR (tumour cell PD-L1 ≥ 1% and all randomised)

At data cut-off (January 18, 2021), the minimum follow-up was 12.9 months

NIVOLUMAB + PLATINUM-BASED CHEMO VS. CHEMO

In 1L advanced squamous cell oesophageal tumours

Nivolumab plus chemo improves OS over chemo alone in patients with tumour cell PD-L1 expression ≥1

Overall survival in patients with tumour-cell PD-L1 expression of ≥1%

NIVOLUMAB + IPILIMUMAB VS. CHEMO

In 1L advanced squamous cell oesophageal tumours

Nivolumab plus ipilimumab also improves OS over chemo alone in tumour-cell PD-L1 expression ≥1

Overall survival in patients with tumour-cell PD-L1 expression of ≥1%

IMMUNOTHERAPY IN FIRST LINE FOR ADVANCED OESOPHAGEAL AND GEJ TUMOURS

Pembrolizumab + 5FU + platinum for CPS $\geq 10$ (Europe)

Nivolumab + 5FU + platinum or nivolumab + ipilimumab improve outcomes for patients with tumour PDL1 $\geq 1$
IMMUNE CHECK-INHIBITORS

For second line or further in gastroesophageal adenocarcinoma

Checkpoint inhibitors have a contentious effect when given in second or further lines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Phase</th>
<th>Use</th>
<th>Tumour location</th>
<th>n</th>
<th>Regimen</th>
<th>Response rate</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab*</td>
<td>ATTRACTION 02 (only Asia)</td>
<td>III</td>
<td>&gt;2L</td>
<td>Gastric/EGJ</td>
<td>493</td>
<td>Nivolumab</td>
<td>11%</td>
<td>1.61 months</td>
<td>8.87 months</td>
</tr>
<tr>
<td>Pembrolizumab**</td>
<td>KEYNOTE-059</td>
<td>II</td>
<td>&gt;2L</td>
<td>Gastric/EGJ</td>
<td>259</td>
<td>Pembrolizumab</td>
<td>11.6%</td>
<td>2 months</td>
<td>5.6 months</td>
</tr>
<tr>
<td>Pembrolizumab***</td>
<td>KEYNOTE-061</td>
<td>III</td>
<td>&gt;2L</td>
<td>Gastric/EGJ</td>
<td>592</td>
<td>Pembrolizumab vs paclitaxel</td>
<td>16% for PD-L1 +</td>
<td>1.5 vs 4.1 months (HR=1.27)</td>
<td>9.1 vs 8.3 months (HR=0.82)</td>
</tr>
<tr>
<td>Avelumab^</td>
<td>JAVELIN 300</td>
<td>III</td>
<td>3L</td>
<td>Gastric/EGJ</td>
<td>371</td>
<td>Avelumab vs paclitaxel or irinotecal</td>
<td>2.2%</td>
<td>1.4 vs 2.7 months (HR=1.73)</td>
<td>4.6 months vs 5 months (HR=1.1)</td>
</tr>
</tbody>
</table>

PEMBROLIZUMAB + PLATINUM-BASED CHEMO VS. CHEMO IN 1L ADVANCED GASTRIC AND GEJ TUMOURS
KEYNOTE-062 study design

Key eligibility criteria
- Locally advanced unresectable or metastatic gastric and EGJ adenocarcinoma
- Treatment naive
- ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)
- HER2/neu– and PD-L1+ tumours

Stratification factors
- Geographic region
- Disease status
- Type of fluoropyrimidine

Dual primary endpoints:
- OS in PD-L1 ≥ 1 and ≥10;
- PFS in PD-L1 ≥1

Secondary endpoints:
- ORR and DOR, safety and tolerability

N=763

Key: R 1:1:1

Pembrolizumab 200 mg IV Q3W up to 35 cycles

Pembrolizumab 200 mg Q3W + [cisplatin + 5-FU or capecitabine]

Placebo + [Cisplatin + 5-FU of capecitabine]

Pembrolizumab single agent failed to improve OS over chemo except in the CPS ≥10 subpopulation

PEMBROLIZUMAB + PLATINUM-BASED CHEMO VS. CHEMOTHERAPY ALONE

In 1L advanced gastric and GEJ tumours

Pembrolizumab plus chemo does not add a significant benefit in OS versus chemo alone independently of PD-L1 status in this study.

NIVOLUMAB + PLATINUM-BASED CHEMO 1L VS. CHEMO

For advanced gastric, GEJ and oesophageal adenocarcinoma – Checkmate 649 study design

Key eligibility criteria
- Previous untreated, unresectable advanced, recurrent or metastatic gastric, GEJ, oesophageal adenocarcinoma
- ECOG PS 0-1
- No known Her2 positive status

Stratification factors
- Tumour cell PD-L1 expression (≥1% vs < 1%)\(^b\)
- Region of Asia vs US/Canada vs ROW
- ECOG PS (0 vs 1)
- Chemo XELOX vs FOLFOX

Primary endpoints:
- OS and PFS (PD-L1 CPS ≥ 5%)

Secondary endpoints:
- OS and PFS (PD-L1 CPS ≥ 1% and all randomised)
- OS CPS ≥10%
- PFS CPS ≥10%, ≥1%, all randomised
- ORR

N=1581; 955 with CPS>5%

At data cut-off (January 18, 2021), the minimum follow-up was 12.9 months

Checkmate 649 study. Baseline characteristics
Baseline characteristics well balanced among arms

<table>
<thead>
<tr>
<th></th>
<th>All randomised</th>
<th>NIVO + chemo (n=789)</th>
<th>Chemo (n=792)</th>
<th>NIVO + IPI (n=409)</th>
<th>Chemo (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td></td>
<td>62 (54-69)</td>
<td>61 (53-68)</td>
<td>62 (22-84)</td>
<td>61 (23-90)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>68</td>
<td>71</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>Non-Asian, Asian</td>
<td></td>
<td>76/24</td>
<td>76/24</td>
<td>70/30</td>
<td>70/30</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td></td>
<td>59</td>
<td>57</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Primary tumour location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC</td>
<td></td>
<td>70</td>
<td>70</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>GEJC</td>
<td></td>
<td>17</td>
<td>16</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>EAC</td>
<td></td>
<td>13</td>
<td>14</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td></td>
<td>96</td>
<td>95</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Liver metastases</td>
<td></td>
<td>38</td>
<td>40</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>Signet ring cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 CPS ≥ 5</td>
<td></td>
<td>60</td>
<td>61</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Tumour cell PD-L1 ≥ 1%</td>
<td></td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>MSI Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSS</td>
<td></td>
<td>88</td>
<td>86</td>
<td>87</td>
<td>85</td>
</tr>
<tr>
<td>MSI-high</td>
<td></td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>FOLFOX/XELOX received on study</td>
<td></td>
<td>54/46</td>
<td>53/47</td>
<td>NA</td>
<td>47/53</td>
</tr>
</tbody>
</table>

NIVOLUMAB + PLATINUM-BASED CHEMO 1L VS. CHEMO

For advanced gastric, GEJ and oesophageal adenocarcinoma – Progression free survival with PD-L1 CPS ≥5

Nivolumab plus chemo significantly improves PFS over chemo alone in PD-L1 CPS ≥5

NIVOLUMAB + PLATINUM-BASED CHEMO 1L VS. CHEMO

For advanced gastric, GEJ and oesophageal adenocarcinoma – Overall survival for patients with PD-L1 CPS ≥5

Nivolumab plus chemo significantly improves OS over chemo alone in PD-L1 CPS ≥5

Reprinted from The Lancet, 2021, 398, Janjigian Y. et al., First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial, 27-40, Copyright (2021), with permission from Elsevier.
NIVOLUMAB + PLATINUM-BASED CHEMO 1L VS. CHEMO

For advanced gastric, GEJ and oesophageal adenocarcinoma – Overall survival

The benefit of nivolumab plus chemo versus chemo alone remains in all patients independently of CPS status, but is quantitatively much lower

Reprinted from The Lancet, 2021, 398, Janjigian Y, et al., First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649); a randomised, open-label, phase 3 trial, 27-40, Copyright (2021), with permission from Elsevier.
NIVOLUMAB + PLATINUM-BASED CHEMO 1L VS. CHEMO

For advanced gastric, GEJ and oesophageal adenocarcinoma – Overall survival

The ESMO MCBS assessment favours patients with higher CPS

---

Data to calculate ESMO MCBS in three different subsets of patients according to PD-L1 CPS in the CheckMate649 trial

<table>
<thead>
<tr>
<th>Population selected according to CPS score (% patients)</th>
<th>Lower limit CI 95% Hazard Ratio for OS</th>
<th>Increased median OS in the experimental arm</th>
<th>ESMO MCBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPS ≥5% (60%)</td>
<td>0.59</td>
<td>3.3 months</td>
<td>4</td>
</tr>
<tr>
<td>CPS ≥1% (82%)</td>
<td>0.64</td>
<td>2.7 months</td>
<td>3</td>
</tr>
<tr>
<td>All patients (100%)</td>
<td>0.68</td>
<td>2.2 months</td>
<td>2</td>
</tr>
</tbody>
</table>

Smyth E, Cervantes A. ESMO Open 2020; 5:e001107.
NIVOLUMAB + IPILIMUMAB 1L VS. CHEMO

For advanced gastric, GEJ and oesophageal adenocarcinoma –
Overall survival

Nivolumab plus ipilimumab does not benefit patients with adenocarcinoma in contrast with oesophageal squamous subtypes

The combination nivolumab plus ipilimumab does not increase severe toxicities over Chemo in this study

- The most common grade 3-4 TRAEs included:
  - NIVO + chemo: neutropenia (15%), decreased neutrophil count (11%), anaemia (6%)
  - NIVO + IPI: increased lipase (7%), increased amylase (4%), increased ALT/AST (4% each)
  - Chemo: neutropenia (11%-13%), decreased neutrophil count (9%-10%), diarrhoea (3%-4%)
- The incidence of TRAEs in patients with PD-L1 CPS ≥5 was consistent with all treated patients across arms

<table>
<thead>
<tr>
<th></th>
<th>NIVO + chemo (N=782)</th>
<th>Chemo (n=767)</th>
<th>NIVO + IPI (n=403)</th>
<th>Chemo (n=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TRAEs</td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td></td>
<td>739 (95)</td>
<td>471 (60)</td>
<td>682 (89)</td>
<td>344 (45)</td>
</tr>
<tr>
<td>Serious TRAEs</td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td></td>
<td>175 (22)</td>
<td>133 (17)</td>
<td>94 (12)</td>
<td>77 (10)</td>
</tr>
<tr>
<td>TRAEs leading to discontinuation</td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td></td>
<td>300 (38)</td>
<td>141 (18)</td>
<td>188 (25)</td>
<td>70 (9)</td>
</tr>
<tr>
<td>Treatment-related deathsf</td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td></td>
<td>16 (2)</td>
<td>4 (&lt;1)</td>
<td>10 (2)</td>
<td>3 (&lt;1)</td>
</tr>
</tbody>
</table>

Janjigian Y. et al. ESMO 2021. By permission of Dr Y. Janjigian.
NIVOLUMAB + PLATINUM-BASED CHEMO 1L A NEW STANDARD OF CARE
For advanced gastric, GEJ and oesophageal adenocarcinoma

REGULATORY APPROVALS FOR NIVOLUMAB

In combination with chemo for metastatic gastric cancer and oesophageal adenocarcinoma

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**FDA approves nivolumab in combination with chemotherapy for metastatic gastric cancer and oesophageal adenocarcinoma**

On April 16, 2021, the Food and Drug Administration approved nivolumab (Opdivo, Bristol-Myers Squibb Company) in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

---

**EMA Recommends Extension of Therapeutic Indications for Nivolumab**

New indication concerns the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, GEJ or oesophageal adenocarcinoma.

Opdivo in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, GEJ or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

---


ESMO. Available at: https://www.esmo.org/oncology-news/ema-recommends-extension-of-therapeutic-indications-for-nivolumab#—text=EMA%20Recommends%20Extension%20of%20Therapeutic%20Indications%20for%20Nivolumab,—text=New%20indication%20concerns&text=On%2016%20September%202021%2C%20the%20medicinal%20product%20nivolumab%20(Opdivo); accessed March 2022.
Nivolumab in combination with fluoropyrimidine and platinum-based chemotherapy should be the new standard of care for the first-line treatment of patients with Her-2 negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma for tumours with PD-L1 CPS $\geq 5$. 
NIVOLUMAB + IPI 1L VS. CHEMO
For advanced gastric, GEJ and oesophageal adenocarcinoma: Asiatic population

Key inclusion criteria:
- Unresectable advanced or recurrent HER2 (-) G/GEJ cancer
- ECOG PS of 0-1
- Chemo-naïve
- Neoadjuvant or adjuvant chemotherapy allowed if completed ≥180 days prior to recurrence

Attraction 4 study design
- Nivolumab 360 mg IV Q3W + SOXb or CapeOXc therapy
- Placebo + SOXb or CapeOXc therapy

Stratification factors:
- Country
- ECOG PS
- Tumour cell PD-L1 expression
- Disease status

Co-primary endpoints:
- PFS and OS

Other key endpoints:
- ORR, DOR, DCR, TTR, BOR, and safety

N=724

NIVOLUMAB + CHEMOTHERAPY 1L VS. CHEMO

For advanced gastric, GEJ and oesophageal adenocarcinoma: Asiatic population

In the ATTRACTION4 trial, carried out in Asian population, nivolumab plus chemo offers a benefit on PFS over chemo alone, but not in OS.

Reprinted from The Lancet, 23 (2), Kang Yoon-Koo, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. 234-247, Copyright (2022), with permission from Elsevier.
ASSESSMENT OF BIOMARKERS FOR IMMUNE CHECKPOINT INHIBITORS IN GASTROESOPHAGEAL CANCER
EFFICACY OF CHECK-POINT INHIBITORS IN PATIENTS WITH CPS ≥10

Pembrolizumab 1\(^{st}\) line or 2\(^{nd}\) line vs. chemo for advanced gastric or GEJ: Biomarkers analysis

The subpopulation with CPS ≥10 got the maximum benefit

KEYNOTE 061 Overall survival

KEYNOTE 062 Overall survival

IMMUNOTHERAPY IN MSI FOR OESOPHAGEAL, GEJ AND GASTRIC ADENOCARCINOMA

MSI is a strong predictor of checkpoint inhibitors across several lines of treatment

KN061, 2nd line: Overall survival in a post-hoc analysis of patients with MSI tumours

KN062, 1st line: Overall survival in a post-hoc analysis of patients with MSI tumours

NIVOLUMAB + PLATINUM-BASED CHEMO 1L VS. CHEMO

For advanced gastric, GEJ and oesophageal adenocarcinoma –
The impact of MSI status on overall survival

MSI is also a strong predictor of survival when checkpoint inhibitors are used

GASTRIC CANCER AND TMB AS AN IMMUNOTHERAPY BIOMARKER

A post-hoc KEYNOTE-061 study analysis in 2nd line treatment for GEA

Tumour mutational burden (TMB) could be used to predict immunotherapy response

Figure 1. Scatter plot of WES-TMB (log_{10} scale) by response and treatment group, indicating patients with MSH-H status.

Figure 3. Kaplan–Meier survival curves with pointwise 95% CIs of pembrolizumab versus paclitaxel by WES-TMB (A) ≥175 mut/MBR and (B) <175 mut/MBR using univariate analysis including MSH-H status and stratified for PD-L1 CPS.
IMMUNE CHECKPOINT INHIBITION FOR GASTRIC AND OESOPHAGEAL CANCER

Is chemoinmunotherapy the new standard of care?

**YES**— GEA CPS ≥ 5
**YES**— ESCC CPS ≥ 10
**DEBATABLE**— GEA CPS<5 ESCC and CPS<10

What are the key biomarkers for anti-PD-1 therapy in gastric and esophageal cancer?

**PD-L1**—standardization of PD-L1 assessment is critical
**MSI**—should be tested for all GEA patients
**TMB**—↑response rates, prospective validation lacking

Is there a difference in response to immune checkpoint blockade between Asian and non-Asian patients?

Asian patients show ↓ disease burden and ↑ PS compared with non-Asian patients
No definitive evidence of differential tumor or host biology
Dual PD-1 and Her2 inhibition has been shown to enhance Her2-specific T cell responses, promote immune cell trafficking and induce expansion of peripheral memory T cells.

IMMUNOTHERAPY FOR HER2 POSITIVE GEA

KEYNOTE-811 Study Design:

Key eligibility criteria
- Locally advanced unresectable or metastatic EGJ or gastric adenocarcinoma
- Treatment naive
- ECOG PS 0 or 1
- Her2 positive

Stratification factors
- Geographic region
- PD-L1 CPS
- Chemotherapy choice

Pembrolizumab 200 mg IV Q3W
+ Trastuzumab and FP or CAPOX for ≤35 cycles

Placebo
+ Trastuzumab and FP or CAPOX for ≤35 cycles

R (1:1)

N=692

Dual-Primary endpoints: OS and PFS
Secondary endpoint: ORR, DOR
Safety

**IMMUNOTHERAPY FOR HER2 POSITIVE**

**Keynote-811. Summary of confirmed objective response in the efficacy population**

Higher response rate is observed when pembrolizumab is added to trastuzumab and chemo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pembrolizumab group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=133</td>
<td>N=131</td>
</tr>
<tr>
<td>Objective response (95% CI)</td>
<td>74.4 (66.2-81.6)</td>
<td>51.9 (43-60.7)</td>
</tr>
<tr>
<td>Disease control (95% CI)</td>
<td>96.2(91.4-98.8)</td>
<td>89.3 (82.7-94)</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>15 (11.3)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Partial response</td>
<td>84(63.2)</td>
<td>64 (48.9)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>29 (21.8)</td>
<td>49 (37.4)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 (3.8)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>0</td>
<td>5 (3.8)</td>
</tr>
</tbody>
</table>

No increase of toxicity events, including severe ones, when pembrolizumab is added to trastuzumab and chemo over trastuzumab, chemo and placebo

| Number of events (%) | Any cause | Immune-mediated events and infusion reactions*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembrolizumab (n=217)</td>
<td>Placebo (n=216)</td>
</tr>
<tr>
<td>Any grade</td>
<td>211 (97.2)</td>
<td>212 (96.1)</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>124 (57.1)</td>
<td>124 (57.4)</td>
</tr>
<tr>
<td>Serious</td>
<td>68 (31.3)</td>
<td>83 (38.4)</td>
</tr>
<tr>
<td>Led to death</td>
<td>7 (3.2)</td>
<td>10 (4.6)</td>
</tr>
<tr>
<td>Led to discontinuation of any drug</td>
<td>53 (24.4)</td>
<td>56 (25.9)</td>
</tr>
<tr>
<td>Pembrolizumab or placebo</td>
<td>12 (5.5)</td>
<td>15 (6.9)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>12 (5.5)</td>
<td>16 (7.4)</td>
</tr>
<tr>
<td>Any chemotherapy</td>
<td>50 (23.0)</td>
<td>52 (24.1)</td>
</tr>
<tr>
<td>All drugs</td>
<td>8 (3.7)</td>
<td>12 (5.6)</td>
</tr>
</tbody>
</table>

The treatment regimen included trastuzumab and chemotherapy in both groups.
*Events with a possible immune-mediated cause and infusion reactions were considered regardless of attribution to study treatment or immune relatedness by the investigator and are based on a list of terms provided by the sponsor
FDA grants accelerated approval to pembrolizumab for HER2-positive gastric cancer

On May 5, 2021, the Food and Drug Administration granted accelerated approval to pembrolizumab (Keytruda, Merck & Co.) in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

[Source: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-her2-positive-gastric-cancer; accessed March 2022.]
MARGETUXIMAB IN HER2 AMPLIFIED GASTRIC CANCER + CHECKPOINT INHIBITORS

Tumour biology and the tumour immune microenvironment impact the therapeutic response. Biomarkers matter

New standard of care for the adjuvant setting with immunotherapy for high risk oesophageal and junctional GEA and chemoimmunotherapy for the first-line setting for GEA with CPS ≥5 and CPS ≥10 in SCC

Outstanding questions: ICI combinations in the perioperative setting, new combination strategies, new biomarkers
THANK YOU!