Check-Point Inhibitors in Esophageal and Gastric Cancer: When and for Whom?

Kohei Shitara
Department of Gastroenterology
National Cancer Center Hospital East (NCCHE)
Standard treatment for GC

1st line
Fluoropirimidines + Platinum
+ Trastuzumab (HER2+)

2nd line
Paclitaxel + Ramucirumab

3rd or later line
Irinotecan
FTD/TPI (US)
Nivolumab (Asia)
Pembrolizumab (CPS≥1, US)
Pembrolizumab (high, several countries)

SPECIAL ARTICLE
Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS

() approved countries
KEYNOTE-061: Pembrolizumab vs wPTX as 2nd-line for GC: Overall Survival by PD-L1 CPS or MSI-H

CPS <1
- Events/Pts: Pembrolizumab 87/99, Paclitaxel 86/96
- HR (95% CI): Pembrolizumab 1.20 (0.89-1.63)

CPS ≥1 (primary cohort)
- Events/Pts: Pembrolizumab 151/196, Paclitaxel 175/199
- HR (95% CI): Pembrolizumab 0.82 (0.66-1.03)

CPS ≥10
- Events/Pts: Pembrolizumab 34/53, Paclitaxel 46/55
- HR (95% CI): Pembrolizumab 0.64 (0.41-1.02)

MSI-H
- Events/Pts: Pembrolizumab 6/15, Paclitaxel 10/12
- HR (95% CI): Pembrolizumab 0.42 (0.13-1.31)

Median (95% CI)
- CPS <1: Pembrolizumab 4.8 mo (3.9-6.1), Paclitaxel 8.2 mo (6.8-10.6)
- CPS ≥1: Pembrolizumab 9.1 mo (6.2-10.7), Paclitaxel 8.3 mo (7.6-9.0)
- CPS ≥10: Pembrolizumab 10.4 mo (5.9-17.3), Paclitaxel 8.0 mo (5.1-9.9)
- MSI-H: Pembrolizumab NR (5.6 mo-NR), Paclitaxel 8.1 mo (2.0-16.7)

Pembrolizumab did not significantly improve OS and PFS among PD-L1+ (CPS≥1) GC pts. Different treatment effect of pembrolizumab according to CPS or MSI-H status.
KEYNOTE-181: Pembrolizumab vs wPTX as 2nd-line for Esophageal cancer: Overall Survival

Overall Survival (ITT)

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR* (95% CI)</th>
<th>Median, mo (95% CI)</th>
<th>P-value</th>
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<tr>
<td>Pembro</td>
<td>314</td>
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<td>Chemo</td>
<td>314</td>
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Overall Survival (PD-L1 CPS ≥10)

<table>
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<tr>
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<th>HR* (95% CI)</th>
<th>Median, mo (95% CI)</th>
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<td>9.3 (6.5-12.5)</td>
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<td>Chemo</td>
<td>113</td>
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<td>6.7 (3.1-8.2)</td>
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</table>

Pembrolizumab improved OS in CPS≥10 esophageal cancer (HR 0.69)
Statistically not significant in SCC (HR 0.78) or ITT (HRR 0.89)

Kojima T, et al. ASCO-GI 2019
Phase 3 trials in 1st-line for GC with completed enrollment

**KEYNOTE-062**
NCT02494583
- PD-L1 +
- 1st-line
- N=750
- Primary endpoint:
  - PFS and OS in CPS≥1
  - OS in CPS ≥ 10
- Active, not recruiting
  - July 31, 2015 ~

**CheckMate-649**
NCT02872116
- PD-L1 +/– 1st-line
- N=2005
- Primary endpoint:
  - PFS and OS in PD-L1+
- Active, not recruiting
  - Oct. 4, 2016 ~

**ONO-4538-37**
ATTRACTION-04
NCT02746796
- PD-L1 +/– 1st-line
- N=680
- Primary endpoint:
  - PFS and OS
- Active, not recruiting
  - March 2016 (part1) ~

https://clinicaltrials.gov
Non-inferiority of pembrolizumab was shown in OS of CPS≥1 pts
Crossed OS curve (as same as KN061)
Lower Grade 3 AE (17% vs. 69%) and d/c of drugs by AE (11% vs. 24%)
Non-inferiority trials have changed practices in GC
However, crossed OS curves looks different from others
Patients' selection must be important
Non-inferiority: Consistent across clinical subgroups?

<table>
<thead>
<tr>
<th>KN062</th>
<th>Pembro vs SOC (1st-line)</th>
<th>KN061</th>
<th>Pembro vs SOC (2nd-line)</th>
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<tr>
<td>Events/Patients, N</td>
<td>HR (95% CI)</td>
<td>Events/Patients</td>
<td>Hazard Ratio (95% CI)</td>
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<td>326/355</td>
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<td>Capecitabine</td>
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<td><strong>Geographic region</strong></td>
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<td><strong>Time to progression on first line (mo)</strong></td>
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<td>0.73 (0.53–0.99)</td>
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<td>Intestinal</td>
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<td>0.62 (0.67–1.25)</td>
<td><strong>Histo logic subtype</strong></td>
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<td>Yes</td>
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<td>0.79 (0.52–1.21)</td>
<td>Favors Pembrolizumab</td>
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<tr>
<td>No</td>
<td>326/375</td>
<td>0.94 (0.76–1.17)</td>
<td>Favors Chemotherapy</td>
</tr>
</tbody>
</table>

**KN062**
HR < 1 in most predefined subgroups
HR > 1 in GEJ (1.06) and ROW (1.25)

**KN061**
HR < 1 in most predefined subgroups
HR < 1 in GEJ (0.61), non Asia (0.81)

*confounded by other factors?*
KEYNOTE-062: Pembrolizumab vs 1st-line chemo in CPS10

**KN062 CPS ≥10**
(N=182, MSI-H 5% in CPS≥1)

**KN061 CPS ≥10**
(N=108, MSI-H 12% in CPS≥10)

**Events**
- **Pembro**: 66%
- **Chemo**: 83%
**HR (95% CI)**
- **Pembro**: 0.69 (0.49-0.97)
- **Chemo**: -

**OS, %**
- **12-mo rate**: 57%
- **Median (95% CI)**: 17.4 mo (9.1-23.1)
- **24-mo rate**: 47%
- **10.8 mo (8.5-13.6)**

**Events/ Pts**
- 34/53: 0.64
- 46/55: 0.41-1.02

**Confirmed long-term OS benefit in CPS10 pts**
Still show crossed OS curve. How is with other CPS cutoff?
Most CPS10 pts are with MSS

Tabernero J, et al. ASCO 2019; ESMO-GI 2019
Shitara K, et al. Lancet 2018
Check-Point Inhibitors in Esophageal and Gastric Cancer: Pembrolizumab monotherapy

- KN-062 showed pre-planned non-inferiority of Pembro vs SOC
  - Lower AE or discontinuation rate may support non-inferiority
- Crossed OS curve necessitate optimal patients selection
  - CPS10 pts may have greater treatment effects

- Missing pieces
  - 1. Survival post PD or PFS2 (What happened after 1st PD?)
  - 2. Additional biomarkers! (MSI, TMB, and EBV etc. How to exclude non-responder?)
Discrepancy of HR for PFS and OS during A-PD1 trials

Meta-analysis
Correlation was moderate between HR PFS and HR OS ($R^2 = 0.37$)

Better effect on OS rather than PFS (similar trend in not a few trials)

Nie RC, et al. EJC 2019
<table>
<thead>
<tr>
<th></th>
<th>Pembro N = 254</th>
<th>Chemo N = 244</th>
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<tbody>
<tr>
<td>PFS Med</td>
<td>2.0</td>
<td>6.4</td>
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<tr>
<td>Median (95% CI), months</td>
<td>(1.5-2.8)</td>
<td>(5.7-7.0)</td>
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<tr>
<td>Treatment duration mean (SD), months</td>
<td>5.4</td>
<td>6.0</td>
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<tr>
<td>All 2L</td>
<td>52.8</td>
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<tr>
<td>All 3L</td>
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<td>23.8</td>
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<tr>
<td>Immunotherapy 2L</td>
<td>1.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Immunotherapy 3L</td>
<td>0.4</td>
<td>4.5</td>
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</table>

Mean treatment duration (5.4ms) > Median PFS (2.0ms)

---How is effect of pembro beyond PD?
No difference of N pts with 2ndline
---How is effect of post-study chemo?
Survival-post PD in OAK study in NSCLC

**OS Post-PD: By Treatment Arm**

- **PFS HR 0.95**
  - median 2.8 vs. 4.0ms (-1.2ms)

- **OS HR 0.73**
  - median 13.8 vs. 9.6ms (+4.2ms)

**Types of subsequent treatment affect OS post-PD?**
**Carry over effects? Enhance activity of post-study chemo?**

**Gandara DR, et al. ASCO 2017; JTO 2018**
Progression-Free Survival In the Second Line: PFS2

- As first defined by the EMA in 2012: time from randomization to objective tumor progression on next-line treatment or death from any cause, whichever occurs first.

Kaplan-Meier Estimate of PFS2

<table>
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<tr>
<th>Therapy 1</th>
<th>Therapy 2</th>
<th>Off Therapy</th>
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<tr>
<td>PFS</td>
<td>PFS2</td>
<td>OS</td>
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<tr>
<td>Death</td>
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</table>

Pembrolizumab: 74, HR 0.54 (95% CI 0.40-0.72), P < 0.001*
Chemotherapy: 110, HR 1.35

Median (95% CI):
- Pembrolizumab: 16.3 mo (12.7-NE)
- Chemotherapy: 6.4 mo (6.3-9.8)

Pembro → Chemo: 31%
Chemo → Pembrol/A-PD1: 59%
PFS2 difference: +9.9ms (HR 0.54)
What happens after discontinuation of anti-PD1?

- Monitoring nivolumab immunokinetics in NSCLC pts.
- Classification: Nivo-complete binding-, partial binding-, and no binding cells.
- Nivolumab binding on memory T cells is detectable more than 20 weeks after discontinuation.
- Long-term nivolumab binding is due to sustained circulation of residual nivolumab in plasma.

Osa A, et al. JCI insight 2019
What happen after discontinuation of anti-PD1?

- Nivolumab binding on memory T cells is detectable even after subsequent CTx.
- Ki-67 positivity in T cells might reflect the residual efficacy of PD-1 blockade, even during the period of subsequent chemotherapy (Ki67+ decreased on PD).
- Several studies suggested enhanced activity of chemo after anti-PD1*

Efficacy of subsequent treatment after PD-1 blockade

Efficacy of cytotoxic agents after progression on anti-PD-(L)1 antibody

**Cohort A (N = 15)**
With previous anti-PD1/PDL-1

- ORR 38%

**Cohort B (N = 45)**
Without previous anti-PD1/PDL-1

- ORR 10%

**Improved efficacy of ramucirumab plus docetaxel after nivolumab failure**

- ORR 60%

**Docetaxel with or without ramucirumab after CPI in platinum-refractory metastatic urothelial carcinoma**

- Median follow-up times:
  - A: 15 months (range: 1.3–30.3 months)
  - B: 12 months (range: 6–30.3 months)

Several studies suggested enhanced activity of chemo after PD1 blockade

Additional biomarkers for monotherapy use: TMB? EBV?

Pembrolizumab in IIT
Responder 15 pts (20%)

Waterfall plot according to MS/EBV status

Enrolled patients

4 PR of 6 EBV pts
High TMB correlated with better outcomes
(TMB by WES)


Toripalimab treatment
Responder 7 pts (12%)

Best Change From Baseline (%)

+20% tumor growth

30% tumor shrinkage

PD-L1 +
TMB ≥ 13 muts/Mb
EBV+
# Unconfirmed PR, classified as SD

1 PR of 4 EBV pts
ORR 33% with TMB-high and 7% with TMB lowTMB
(TMB by WES)

GC Pts treated with Nivolumab in practice in NCCCHE

N=136 received nivolumab after approval with tumor evaluation; Responder 21 pts (15%)

<table>
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<tr>
<th>Age</th>
<th>PS</th>
<th>Mutation Amplification</th>
<th>Genomic alteration</th>
<th>TMB/Mb</th>
<th>PD-L1+ in TC</th>
<th>CPS10</th>
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<td>MMR-P</td>
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</tbody>
</table>

Response by tumor mutation burden

2 of 6 EBV pts showed response
TMB by NGS panel do not clearly correlate with outcomes

Mishima S, ,Shitara K. J Immunother Cancer. 2019
Updated
TMB as predictive marker in GC is still controversial

Exploratory analysis in ATTRACTION-2 trial

<table>
<thead>
<tr>
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<th>Nivolumab (N=330)</th>
<th>Placebo (N=163)</th>
<th>OR HR [95% CI]</th>
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<tr>
<td>PD-L1 expression in tumor cell, n (%)</td>
<td>n=130</td>
<td>n=62</td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>114 (87.7)</td>
<td>52 (63.9)</td>
<td>0.72 [0.49, 1.05]</td>
</tr>
<tr>
<td>≥1%</td>
<td>16 (12.3)</td>
<td>10 (16.1)</td>
<td>0.51 [0.21, 1.25]</td>
</tr>
<tr>
<td>TMB analysis, n (%)</td>
<td>n=91</td>
<td>n=46</td>
<td></td>
</tr>
<tr>
<td>≥0 and &lt;6 mutation/Mb</td>
<td>48 (52.7)</td>
<td>23 (61.1)</td>
<td>0.78 [0.46, 1.34]</td>
</tr>
<tr>
<td>≥5 and &lt;10 mutation/Mb</td>
<td>33 (36.3)</td>
<td>14 (31.1)</td>
<td>0.47 [0.24, 0.94]</td>
</tr>
<tr>
<td>≥10 mutation/Mb</td>
<td>9 (9.9)</td>
<td>6 (13.3)</td>
<td>0.52 [0.16, 1.62]</td>
</tr>
<tr>
<td>Not detected</td>
<td>1 (1.1)</td>
<td>2 (4.4)</td>
<td></td>
</tr>
<tr>
<td>MSI status, n (%)</td>
<td>n=91</td>
<td>n=46</td>
<td></td>
</tr>
<tr>
<td>MSI-H</td>
<td>1 (1.1)</td>
<td>3 (6.7)</td>
<td></td>
</tr>
<tr>
<td>MSS</td>
<td>82 (90.1)</td>
<td>33 (73.3)</td>
<td>0.61 [0.40, 0.94]</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (8.8)</td>
<td>9 (20.0)</td>
<td></td>
</tr>
</tbody>
</table>

MSK-IMPACT

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>All samples in cohort</th>
<th>Cutoff</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>214</td>
<td>17.6</td>
<td>0.0605</td>
</tr>
<tr>
<td>Breast</td>
<td>45</td>
<td>5.9</td>
<td>0.0005</td>
</tr>
<tr>
<td>ER+</td>
<td>24</td>
<td>6.8</td>
<td>0.2978</td>
</tr>
<tr>
<td>ER-</td>
<td>21</td>
<td>4.4</td>
<td>0.7310</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>90</td>
<td>14.2</td>
<td>0.1554</td>
</tr>
<tr>
<td>Colorectal</td>
<td>130</td>
<td>59.2</td>
<td>0.0011</td>
</tr>
<tr>
<td>Esophagegastic</td>
<td>126</td>
<td>8.8</td>
<td>0.221</td>
</tr>
<tr>
<td>Glioma</td>
<td>117</td>
<td>5.9</td>
<td>0.465</td>
</tr>
<tr>
<td>Head and neck</td>
<td>158</td>
<td>10.3</td>
<td>7.42 x 10^-3</td>
</tr>
<tr>
<td>Melanoma</td>
<td>321</td>
<td>30.7</td>
<td>0.0678</td>
</tr>
<tr>
<td>Non-small cell lung</td>
<td>560</td>
<td>13.8</td>
<td>2.30 x 10^-4</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>151</td>
<td>5.9</td>
<td>0.569</td>
</tr>
</tbody>
</table>

Kang Y, et al. ASCO-GI 2019

Controversial results between TMB-NGS and outcomes
Further analysis of TMB-WES in larger cohorts or RCT for GC are necessary
Crossed OS curve: Hyper progressive disease?

21% pts showed HPD in NCCHE experience
- Higher trend in pts with large tumor size and liver metastasis
- poor OS with few chance to receive subsequent Tx

Sasaki A., Shiara K. Gastric cancer 2019
CD163^+CD33^+PD-L1^+ Macrophage and HPD

26% developed HPD after A-PD1 for NSCLC
Higher CD163^+CD33^+PD-L1^+ macrophage in HPD case
Fc portion of A-PD1 may activate macrophage

PD-1+ Tregs are activated by PD-1 blockade and contribute to HPD

Table 2. Summary of patients who experienced hyperprogressive disease during PD-1 blockade.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Histology</th>
<th>PD-L1</th>
<th>EBV</th>
<th>MMR</th>
<th>HER2</th>
<th>Genomic features</th>
<th>Immunological features</th>
<th>PFS after PD-1 blockade (day)</th>
<th>OS after PD-1 blockade (day, status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>71</td>
<td>Intestinal</td>
<td>Positive</td>
<td>Negative</td>
<td>Proficient</td>
<td>Positive</td>
<td>ERBB2 amplification</td>
<td>KI67+ eTreg cell, 61.7%</td>
<td>62</td>
<td>&gt;62, alive</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>56</td>
<td>Diffuse</td>
<td>Positive</td>
<td>Negative</td>
<td>Proficient</td>
<td>Negative</td>
<td>TP53 p.Arg292Trp</td>
<td>NA</td>
<td>15</td>
<td>20, dead</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>73</td>
<td>Intestinal</td>
<td>Positive</td>
<td>Negative</td>
<td>Proficient</td>
<td>Negative</td>
<td>PIK3CA amplification</td>
<td>KI67+ eTreg cell, 21.4%</td>
<td>36</td>
<td>55, dead</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>82</td>
<td>Diffuse</td>
<td>Negative</td>
<td>Negative</td>
<td>Proficient</td>
<td>Positive</td>
<td>NA</td>
<td>NA</td>
<td>20</td>
<td>65, dead</td>
</tr>
</tbody>
</table>

MMR, mismatch repair; eTreg cell, effector regulatory T cell; PFS, progression-free survival; OS, overall survival; NA, not assessed.

HPD cases showed increasing infiltration of KI-67+ Tregs

Kamada T, Togashi T, Shitara K et al. PNAS 2019
PD-1<sup>+</sup> Tregs are activated by PD-1 blockade and contribute to HPD

PD-1 blockade may facilitate the proliferation of highly suppressive PD-1+ eTreg cells in HPDs, resulting in inhibition of antitumor immunity.
Defining T Cell States Associated with Response to A-PD1 by ScRNAseq

TCF7+CD8+ Stem-like T Cells in TIL predict better outcome after A-PD1. CD39 and TIM3 discriminated exhausted from memory and/or effector cells.

EOMES+CD69+CD45RO+ effector memory T cells Predict A-PD-1 response

CD39+PD1+CD8+ cells (Bystander CD8 lack CD39)


**Standard treatment for GC**

1st line
- Fluoropirimidines + Platinum
- +Trastuzumab (HER2+)

2nd line
- Paclitaxel + Ramucirumab

3rd or later line
- Irinotecan
- FTD/TPI (US/EU)

**Should be discussed with regulatory authorities**
*And within several guideline committees*

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**Pembrolizumab?**
- (CPS≥1?)

**Pembrolizumab**
- (MSI-high, several countries)

**EC**
- Pembrolizumab (CPS≥10?)

---

If available,...., I would use for following case
- CPS≥10
- PS0
- No clinically significant symptoms
- High chance to receive next Tx at PD
Rationale for combination Therapy with chemotherapy

Pros
- Reduces tumor bulk – Improves T-cell: tumor target ratio
- Eradicate immune suppressive cells or reduce T-cell inhibitory substances produced by tumor
- Improve T-cell penetration
- Kills tumor cells in a manner that increases their recognition by T-cells and APC
- May prevent early disease progression

Cons
- Side effects of cytotoxic chemo on proliferation of T-cells
- Use of steroids

Huang AC, et al. Nature 2017
Herbst RS, et al: 2018 AACR #CT075-Discussion
Making immunotherapy ‘cold’ tumours ‘hot’ by chemotherapy-induced mutations – a misconception

**Chemotherapy may not induce neoantigen**

- Chemo are mostly cytotoxic and activate cell cycle checkpoints that stop cell division and mutations.
- Chemotherapy-induced mutations are only limited to single dividing cells and are unlikely going to lead to general T-cell recognition of cancer cells (vs. UV or carcinogenesis in early stage).
- Non-dividing cancer cells do not mutate.
- The immune system primarily recognizes clonal neoantigens (present in all cancer cells), which should originate early in the disease (like MSI-high tumors).

**Chemotherapy may boost immunotherapy**

- Through modulation of immune phenotypes.

# Anti-PD1/PD1 and cytotoxic chemo

<table>
<thead>
<tr>
<th>Disease</th>
<th>Study</th>
<th>CPI</th>
<th>combined chemo</th>
<th>∆mPFS</th>
<th>HR PFS (p value)</th>
<th>∆mOS</th>
<th>HR OS (p value)</th>
<th>ORR as single agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC (Non Sq)</td>
<td>Keynote189</td>
<td>pembro</td>
<td>PEM+CBDCA or Cis x4</td>
<td>+3.9ms</td>
<td>0.52 (&lt;0.001)</td>
<td>NR</td>
<td>0.49 (&lt;0.001)</td>
<td>19.4% in KN001 18% in KN010</td>
</tr>
<tr>
<td>NSCLC (Sq)</td>
<td>Keynote407</td>
<td>pembro</td>
<td>PTX/nabPTX+CBDCA x4</td>
<td>+1.5ms</td>
<td>0.56 (&lt;0.001)</td>
<td>+4.6ms</td>
<td>0.64 (&lt;0.001)</td>
<td>23.5% in KN001</td>
</tr>
<tr>
<td>NSCLC (Non Sq)</td>
<td>IMpower150</td>
<td>atezo</td>
<td>PTX+CBDCA+BV x4-6</td>
<td>+1.5ms</td>
<td>0.62 (&lt;0.001)</td>
<td>+4.5ms</td>
<td>0.78 (0.02)</td>
<td>14.6% in POPLAR 14% in OAK</td>
</tr>
<tr>
<td>NSCLC (Non Sq)</td>
<td>IMpower132</td>
<td>atezo</td>
<td>PEM+CBDCA or Cis x4-6</td>
<td>+2.4ms</td>
<td>0.56 (&lt;0.001)</td>
<td>+4.5ms</td>
<td>0.81 (0.08 at IA)</td>
<td>Same as above</td>
</tr>
<tr>
<td>NSCLC (Non Sq)</td>
<td>IMpower130</td>
<td>atezo</td>
<td>nabPTX+CBDCA x4-6</td>
<td>+1.5ms</td>
<td>0.64 (&lt;0.001)</td>
<td>+4.7ms</td>
<td>0.79 (0.033)</td>
<td>Same as above</td>
</tr>
<tr>
<td>SCLC</td>
<td>IMpower133</td>
<td>atezo</td>
<td>ETP+CBDCA x4</td>
<td>+0.9ms</td>
<td>0.77 (0.007)</td>
<td>+2ms</td>
<td>0.7 (0.02)</td>
<td>2.3% in IFCT-1603</td>
</tr>
<tr>
<td>TNBC</td>
<td>IMpassion130</td>
<td>atezo</td>
<td>nabPTX unlimited</td>
<td>+1.7ms</td>
<td>0.8 (0.007)</td>
<td>+3.7ms</td>
<td>0.84 (0.08 at IA)</td>
<td>10% 24% in 1st line</td>
</tr>
<tr>
<td>(PDL1+ population)</td>
<td></td>
<td></td>
<td></td>
<td>+2.5ms</td>
<td>0.62 (&lt;0.001)</td>
<td>+9.5ms</td>
<td>0.62 (NR)</td>
<td>16%</td>
</tr>
<tr>
<td>HNCC (CPS&gt;1)</td>
<td>Keynote048</td>
<td>pembro</td>
<td>5FU+Cis (vs FP+ cetuximab)</td>
<td>+0ms</td>
<td>0.82 (NR)</td>
<td>+3.2ms</td>
<td>0.65 (&lt;0.001)</td>
<td>14.6% in KN040</td>
</tr>
<tr>
<td>Gastric (CPS&gt;1)</td>
<td>Keynote062</td>
<td>pembro</td>
<td>Cape+Cis/5FU+Cis x6 then FU mono</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>26% in KN059 (1st) 15.8% in KN061</td>
</tr>
</tbody>
</table>

NR, not reported; IA, Interim analysis

KEYNOTE-062: Pembrolizumab+Chemo vs 1st-line chemo

**Pembrolizumab+Chemo combination**
- not improve OS
- CPS10 did not predict benefit of Pembro when combined with chemo? (detrimental effect of chemo?)

Taberner J, et al. ASCO 2019; ESMO-GI 2019
<table>
<thead>
<tr>
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<td>0.49 (&lt;0.001)</td>
<td>19.4% in KN001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18% in KN010</td>
</tr>
<tr>
<td>NSCLC (Sq)</td>
<td>Keynote407</td>
<td>pembro</td>
<td>PTX/nabPTX+CBDCA x4</td>
<td>+1.5ms</td>
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<tr>
<td>NSCLC (Non Sq)</td>
<td>IMpower150</td>
<td>atezo</td>
<td>PTX+CBDCA+BV x4-6</td>
<td>+1.5ms</td>
<td>0.62 (&lt;0.001)</td>
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<td>0.78 (0.02)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14% in OAK</td>
</tr>
<tr>
<td>NSCLC (Non Sq)</td>
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<td>PEM+CBDCA or Cis x4-6</td>
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<td>0.81 (0.08 at IA)</td>
<td>Same as above</td>
</tr>
<tr>
<td>NSCLC (Non Sq)</td>
<td>IMpower130</td>
<td>atezo</td>
<td>nabPTX+CBDCA x4</td>
<td>+1.5ms</td>
<td>0.64 (&lt;0.0001)</td>
<td>+4.7ms</td>
<td>0.79 (0.033)</td>
<td>Same as above</td>
</tr>
<tr>
<td>SCLC</td>
<td>IMpower133</td>
<td>atezo</td>
<td>ETP+CBDCA x4</td>
<td>+0.9ms</td>
<td>0.77 (0.007)</td>
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<td>+1.7ms</td>
<td>0.8 (0.007)</td>
<td>+3.7ms</td>
<td>0.84 (0.08 at IA)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(PDL1+ population)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24% in 1st line</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>pembro</td>
<td>Cape+Cis/5FU+Cis x 6 then FU mono</td>
<td>+0.5ms</td>
<td>0.84 (0.039)</td>
<td>+1.4ms</td>
<td>0.85 (&lt;0.0001)</td>
<td>26% in KN059 (1st)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.8% in KN061</td>
</tr>
</tbody>
</table>

NR, not reported; IA, Interim analysis.
Types of backbone chemo matter? Platinum agents

Cisplatin and Carboplatin showed similar OS in KN189 for NSCLC (at least limited cycles of Cisplatin may not diminish the CPI efficacy)

Keynote407, IMpower150, IMpower130 also included platinum (CBDCA) as backbone

- Cisplatin is a relatively weak inducer of ER stress
- Oxaliplatin can trigger an ER stress response leading to cell death-associated molecules, exposure independently from its effects on nuclear DNA.

Only oxaliplatin increased the abundance of tumoral CD8/4 cells
Types of backbone chemo matter? 5-FU/capecitabine

KEYNOTE-048: HNCC Pembro vs. Pembro+FP vs FP+Cmaab

### Pembro vs. FP+Cmaab (CPS≥1)

- **Indirect comparison**
  - **PFS**
    - Chemo prevent early PD
    - No diff. 12m/24m PFS
    - HR (1.16 vs 0.82)

### Pembro+FP vs. FP+Cmaab (CPS>1)

- **OS**
  - Chemo prevent early death
  - No large diff. 12m/24m OS
  - HR (0.74 vs 0.65)

---

Small effect of FU+P as a backbone for pembrolizumab (also, no use FU as maintenance)

Burtneress B, et al. ESMO 2018
Rischin et al. ASCO 2019
**Types of backbone chemo matter? Repeated 5-FU (capecitabine)**

- **5-FU(FP) lead to depletion of nucleotide**
  - prevent the acquisition of effector functions, such as IFN-γ, granzyme B expression, and cytotoxic function following antigenic stimulation.
  - Interfere with the differentiation of naïve cells into memory CD8 T cells
- **But, 5FU is unable to inhibit the development of improvement cytotoxic functions already displayed by memory CD8**

---

**Revised cycles of 5-FU impair T cell cytotoxic functions**

- Repeated 5-FU decrease proliferated CD8 T-cells. CT26-specific cytotoxicity and IFN-γ secretion of spleen cells were also impaired in vitro

---

Repeated 5FU/Cape (maintenance) affect OS? Stay tune for ATTRACTION-4 and Checkmate649

Quéméneur L, et al. J Immunology 2004
Immune induction by chemotherapy: TONIC trial for TNBC

Immune-related genes involved in PD-1–PD-L1 and T cell cytotoxicity pathways were upregulated after doxorubicin or cisplatin.


No correlation between response and TMB or estimated neoantigen
TILs change after cytotoxic chemotherapy or RAM for GC

N=20, 1st line FU+oxaliplatin, 8 PR, 11 SD, 1 PD

N=18, 2nd line RAM (+chemo)

---

Treg or CD8 did not show consistent change after cytotoxic chemotherapy
Reduced fraction of Tregs after RAM treatment
VEGFR-2 expression is high in Tregs

---

Toda Y, Shitara K. J of Immunotherapy of Cancer 2018
Regorafenib for CRC decreased Treg
CSF1R inhibition, decreased TAMs

Rego decreased Treg in CRC pts via VEGFR2 inhibition
Rego decreased TAMs via CSF1R inhibition in preclinical study
Increased CD8 and decreased M2 TAM is well observed at lower dose*

IIT P1 of Regorafenib+Nivo (EPOC1603) was conducted

Hoff S, et al. ESMO 2018

*Chen CW, Hsu C. 2019 EASL
Phase 1 of Regorafenib+Nivo (EPOC1603)

Colorectal cancer

ORR 36% (MSS 33%)

MSI-H (all other patients were MSS)

Gastric cancer

ORR 44% (all responders were MSS)

Anti-PD-1/PDL-1 refractory (3 of 7 pts achieved response)

Encouraging anti-tumor activities for GC and CRC

Fukuoka S., Shitara K. ASCO2019
Encouraging anti-tumor activities for both GC (mPFS 5.8ms) and CRC (mPFS 6.3ms)
Phase 1 of Regorafenib+Nivo (EPOC1603)

- Pre-and post-treatment biopsied samples in 9 patients were analyzed using flow cytometry.

**Case 2**, 67 year old male with MSS GC, PDL1 CPS0
- Disease progression after Nivo monotherapy

**FoxP3\textsuperscript{hi}CD45RA\textsuperscript{-}Tregs** increased on PD with nivolumab, then decreased after regorafenib+nivolumab

**Fraction of Treg within tumor infiltrating lymphocytes**

**PR cases showed decrease FoxP3\textsuperscript{hi}CD45RA\textsuperscript{-}Tregs**
Targeting immune suppressive cells: Lenvatinib as one of multi-kinase inhibitors

**Fig. 2** Immune Population Analysis in Tumors or regional LN Treated with Lenvatinib

BNL1ME-A.T8.1 (Mouse HCC cell line) syngeneic model

- **Immune Cell Population Analysis**
- **Tumor Associated Macrophage (TAM)**
  - Lenvatinib decrease TAMs

- **T-cell activation**
  - IFN-γ producing CD8 T cells in regional lympho node

**Fig. 4** Combination Effect of Lenvatinib and Anti-PD-1/L1 mAb

- **Combination with PD-1 mAb in CT26 colon cancer syngeneic model**
- **Combination with PD-1 mAb in LL2 lung cancer syngeneic model**

- Lenvatinib treated GCpt


**IIT Phase 2 of Lenvatinib+Pembro for GC (EPOCH1706)**

Enrollment was completed
Will be presented in near future

PI: K Shitara
SC: A Kawazoe, S Fukuoka
To turn cold tumor to hot: OBP-301 (Telomelysin):
Telomerase-specific Replication Competent Oncolytic Adenovirus

OBP301+RT for eso Ca (at Okayama Univ.): 8 of 11 pts CR

Telomelysin received SAKIGAKE Designation by Japanese MHLW
It also active APC and CD8+ cells
Pembro+OBP301 for GC/EC is investigated (EPOC1505)

Fujiwara T, et al. AACR 2019
To turn cold tumor to hot: OBP-301 (Telomelysin)+Pembro (EPOC1505)
Telomerase-specific Replication Competent Oncolytic Adenovirus

Case report: 68 year-old male (No. #1), Previous treatment: FP, PTX
Pretreatment
Week 5
Week 12
Week 42

Case report: 72 year-old male (No. #5), Previous treatment: FP-RT, PTX
Pretreatment
Week 1
Week 6
Week 12

No. Cohort Age Sex Cancer types Path. Previous treatment RR Adverse event
#1  1 (1x10^11) 68 M Esophageal cancer SCC FP, PTX PR No ADR
#2  2 (1x10^10) 52 M Gastric cancer Adeno SOX, CPT-11 nab-PTX+RAM SD No ADR
#3  3 (1x10^10) 41 F Esophageal cancer SCC FP SD No ADR
#4  4 (1x10^11) 61 M Esophageal cancer SCC FP-RT, PTX SD Pleural Effusion: Gr.1
#5  5 (1x10^11) 72 M Esophageal cancer SCC FP-RT, PTX PR No ADR
#6  6 (1x10^11) 55 M Esophageal cancer SCC FP+/-PD1 PD Fever: Gr.1
#7  7 (1x10^11) 56 M Esophageal cancer SCC DCF, PTX PR Fever: Gr.2

#8  8 (1x10^12) 75 F Esophageal cancer SCC FP NE Hepatic disorder: Gr.3
#9  9 (1x10^12) 59 M Esophageal cancer SCC FP+HT, PTX, PD1 SD No ADR

The combination of OBP-301 with pembrolizumab was well tolerated with the recommended dose for phase Ib part is 1x10^{12} VP (cohort 3).
To turn cold tumor to hot: Chimeric antigen receptor (CAR) T cell therapy

CART therapy for HER2-Positive Sarcoma
- Recognition of peptide/antigen through MHC
- Need for co-stimulation
- Intact molecule recognized (including non-protein)
- HLA independent
- CART therapy for EGFR-Positive cancer
  19 pts (14 cholangiocarcinomas and 5 GB carcinomas)

Claudin18.2-Specific CAR-T for gastric cancer

Clinical Response
- Disease control rate (DCR) 75.6: 1 CR, 3 PR, 5 SD
- Objective response rate (ORR) 33.3%
- mPFS of 136 days (95% CI: 44, 237), mOS of 242 days (95% CI: 85, 349)

CAR-T therapy for solid tumor is under investigation
Check-Point Inhibitors in Esophageal and Gastric Cancer: When and for Whom?

- 3rd-line is current treatment line of anti-PD1 for GC (2nd-line for MSI-H)
- KN-062 showed pre-planned non-inferiority of 1st-line Pembro vs SOC
  - Lower AE or discontinuation rate may support non-inferiority
  - Open the door for 1st-line use
- Crossed OS curve necessitate optimal patients selection
  - CPS10 pts may have greater benefit (also MSI-H?)
  - Still we need better biomarker!
- Chemo combo did not show significant improvement of PFS or OS
  - Backbone chemotherapy matter?
  - Still we need better combinations!

Thank you for your kind attention