Recherche clinique
et rationnel biologique en immunothérapie:
Application aux cancers oesogastriques

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ICM, IRCM-INSERM U1194, SIRIC Montpellier Cancer
Université Catholique, Lille
How to explain at best how checkpoint inhibitors work, when you are not an immunologist?

• The oncologist way...
  – Our body is able/trained to kill cancer cells by using activated-T cells
  – These T cells are sometimes kept inactive by certain proteins expressed on T cells or tumors. T cells are then unable to kill cancer cells, i.e: cancer cells escape immune surveillance.
  – Checkpoint inhibitors can block these proteins that are expressed on tumor and T cells, allowing then T cells to kill cancer cells...
The Pac-Man metaphor...

PAC-MAN, is an arcade game released in Japan in May 1980. The player controls Pac-Man through a maze of various dots. The goal of the game is to consume all the Pac-Dots.
The Pac-Man metaphor

➢ Think of Pac-Man as the T cell eating up the dots, which are like the cancer cells...

➢ Checkpoints are expressed and can put a clamp on Pac-Man, and don’t let him eat the dots..

➢ Yet, using checkpoint inhibitors, we can block the clamp and reactivate Pac-Man to eat dots, actually destroying tumor cells.

Mendiratta M, ASCOconnection.org (November 21, 2016)
You may also prefer a more complicated way...

- Tumor formation involves the co-evolution of neoplastic cells together with extracellular matrix, tumor vasculature and immune cells.

The immune cycle in cancer

- Priming and activation
- Cancer antigen presentation
- Release of cancer cell antigens
- Trafficking of T cells to tumors
- Infiltration of T cells into tumors
- Recognition of cancer cells by T cells
- Killing of cancer cells

T cell targets for modulating activity

- Activating Receptors: CD28, OX40, GITR, CD137
- Inhibitory Receptors: CTLA-4, PD-1, TIM-3, BTLA, VISTA, LAG-3

Mellman, Nature 2011

Chen, Mellman, Immunity 2013
Most common checkpoint inhibitors

**PD-1 inhibitors**
nivolumab (BMS), pembrolizumab (Merck/MSD)

**PDL-1 inhibitors:**
avelumab (Pfizer/Merck D), atezolizumab (Roche), durvalumab (AZ)

**CTLA4 inhibitors**
ipilimumab (BMS), tremelimumab (AZ)
Major breakthrough in advanced malignancies

- Melanoma
- Lung (NSCLC)
- Urothelial
- Kidney
- Head & Neck
- MSI tumors (colon, endometrium, gastric,..)

- Hodgkin disease
- Merckel disease
- HCC
- Anal cancer
- Malignant pleura mesothelioma
- Triple negative Breast cancer
Rationnel
Rationnel Epidémiologique - œsophage

Estimated Oesophageal Cancer Incidence Worldwide in 2012: Men

Estimated Oesophageal Cancer Mortality Worldwide in 2012: Men

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases (thousands)</th>
<th>Men Deaths</th>
<th>Women Deaths</th>
<th>Both sexes Deaths</th>
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<tr>
<td>World</td>
<td>456</td>
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<tr>
<td>Less developed regions</td>
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</tr>
<tr>
<td>WHO Africa region (AFRO)</td>
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<tr>
<td>WHO Americas region (PAHO)</td>
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</tr>
<tr>
<td>WHO East Mediterranean region (EMRO)</td>
<td></td>
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</tr>
<tr>
<td>WHO Europe region (EURO)</td>
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</tr>
<tr>
<td>WHO South-East Asia region (SEARO)</td>
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<td></td>
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<tr>
<td>WHO Western Pacific region (WPRO)</td>
<td></td>
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</tr>
<tr>
<td>IARC membership (24 countries)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>United States of America</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>China</td>
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</tr>
<tr>
<td>India</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European Union (EU-28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rationnel Epidémiologique - estomac

▲ Estimated Stomach Cancer Incidence Worldwide in 2012: Men
▲ Estimated Stomach Cancer Mortality Worldwide in 2012: Men

<table>
<thead>
<tr>
<th>Estimated numbers (thousands)</th>
<th>Men</th>
<th>Women</th>
<th>Both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Deaths</td>
<td>5-year prev.</td>
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<tr>
<td>World</td>
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<td>More developed regions</td>
<td>175</td>
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<tr>
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<td>362</td>
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<td>WHO Africa region (AFRO)</td>
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<td>10</td>
<td>14</td>
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<td>WHO Americas region (PAHO)</td>
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<td>WHO East Mediterranean region (EMRO)</td>
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<tr>
<td>WHO Western Pacific region (WPRO)</td>
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<td>IARC membership (24 countries)</td>
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<td>449</td>
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<td>China</td>
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<td>221</td>
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<tr>
<td>India</td>
<td>43</td>
<td>41</td>
<td>31</td>
</tr>
<tr>
<td>European Union (EU-28)</td>
<td>51</td>
<td>35</td>
<td>74</td>
</tr>
</tbody>
</table>
Connexions between immune status and Esophageal/Esogastric cancers

- PD-L1, and PD-L2 are expressed in Esophageal and in Esogastric tumors, and their expression is correlated with poor prognosis (even after multivariate analysis)
- High level of TILs in gastric cancer (subtypes ukn)
- Presence of immune stimulatory factors such as EBV and microsatellite instability in some gastric cancers

Classification moléculaire et sensibilité potentielle à l’immunothérapie

- Oeso SCC looks like SCC of other organs.
- No evidence for an aetiological role of HPV
- Oeso SCC showed genomic amplifications of CCND1, and SOX2
- Chimiosensibilité
- Signature « tabac » chez certaines tumeurs
- Oeso ADK strongly resembled the CIN gastric ADK,

9% des cancers gastriques
Amplification de CD274 et PDCD1LG2 qui codent PDL1 et PDL2

4-20% des cancers gastriques
Rationnel: Les besoins non satisfaits !

<table>
<thead>
<tr>
<th>oesophagse</th>
<th>estomac</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Localisé SCC: SV5 30%</td>
<td>• Localisé: SV5 30%</td>
</tr>
<tr>
<td>• Localisé ADK: SV5 40%</td>
<td>• Méta: 10-16mo</td>
</tr>
<tr>
<td>• Méta: 10-12mo</td>
<td></td>
</tr>
</tbody>
</table>
Cancers métastatiques
PD1-inhibitors

Pembrolizumab

Keynote 012 (phase 1b, estomac),
Keynote 059 (phase 2 multi-bras, estomac),
Keynote 028 (phase 2, œsophage)
Maximum tumor change from baseline in tumor size

ORR: 22%

Median time to response: 8 wks
Median duration time: 40 wks
Severe AEs: 13%

KEYNOTE 012 trial
Gastric cohort

- Phase 1b
- Pembrolizumab 10mg/kg, Q 2w
- N=39 pts in the gastric cohort
- PD-L1 status looking at tumor & immune cells
- 66% heavily pretreated (≥ 2 lines)

Muro, Lancet Oncol 2016
KEYNOTE-059: Gastric/EGJ Cancer
A phase 2 trial

Cohort 1 Patients
• ≥ 2 prior lines of chemotherapy
  - Pembrolizumab 200 mg Q3W
  Fuchs, ASCO 2017
  Wainberg, ESMO 2017

Cohort 2 Patients
• No prior therapy
  - Pembrolizumab 200 mg Q3W +
    cisplatin 80 mg/m² Q3W +
    5-FU 800 mg/m² Q3W or
    capecitabine 1000 mg/m² BID Q3W³
  Bang, ASCO 2017
  Wainberg, ESMO 2017

Cohort 3 Patients
• No prior therapy
• PD-L1 positive
  - Pembrolizumab 200 mg Q3W
  Wainberg, ESMO 2017
Pembrolizumab monothérapie (KEYNOTE-059 cohorte 1)

- N=259
- Highly Pretreated patients
- L3: 52%, L4 48%
- PD-L1 status: all comers
- PD-L1+ (≥ 1% tumor & immune cells): 52%
- ORR: 11.6% (6% in L4)
- Median response duration: 8.1 mo
- PDL1+ : 15.5% and PDL1-: 6.1%
- MSI + (n=7): 57%, MSI-: 9%
- OS: 5.6 mo ; 1 yr = 23.4%

Fuchs, ASCO 2017
KEYNOTE-059: Gastric/EGJ Cancer
A phase 2 trial

Cohort 1 Patients
- ≥ 2 prior lines of chemotherapy

Pembrolizumab 200 mg Q3W

Fuchs, ASCO 2017
Wainberg, ESMO 2017

Cohort 2 Patients
- No prior therapy

Pembrolizumab 200 mg Q3W +
cisplatin 80 mg/m² Q3W +
5-FU 800 mg/m² Q3W or
capcitabine 1000 mg/m² BID Q3W³

Bang, ASCO 2017
Wainberg, ESMO 2017

Cohort 3 Patients
- No prior therapy
- PD-L1 positive

Pembrolizumab 200 mg Q3W

Wainberg, ESMO 2017
Pembrolizumab plus FU-CDDP (KEYNOTE-059 cohorte 2)

- 25 patients
- ADK gastrique ou cardia M+ HER2 nég. En 1ère ligne

Critère de jugement : taux de réponse

- PD-L1+, n = 16
- PD-L1 nég, n = 8
- ND = 1

Pembro 200 mg
Cisplatine
80 mg/m² + 5FU 800 mg/m²
/ 3 semaines x 6 cycles
Pembrolizumab plus FU-CDDP (KEYNOTE-059 cohorte 2)

Table 5. Grade 3/4 Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 3/4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Thrombocytopenia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Decreased WBC count</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

76% of severe AEs, including 16% of immunologic AEs

Bang, ASCO 2017
ORR was 60% (95% confidence interval [CI], 39-79) in the total population (Table 3).

Table 3. Response* Assessed by Central Review per RECIST v1.1

<table>
<thead>
<tr>
<th></th>
<th>Total N = 25</th>
<th>PD-L1 Positive n = 16</th>
<th>PD-L1 Negative n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>ORR</td>
<td>15</td>
<td>60 (39-79)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>38 (9-76)</td>
<td></td>
</tr>
</tbody>
</table>

Bang, ASCO 2017; Wainberg, ESMO 2017

Overall Survival, %

Median OS: 21 mo
KEYNOTE-059: Gastric/EGJ Cancer
A phase 2 trial

Cohort 1 Patients
• ≥ 2 prior lines of chemotherapy

Pembrolizumab 200 mg Q3W

Fuchs, ASCO 2017
Wainberg, ESMO 2017

Cohort 2 Patients
• No prior therapy

Pembrolizumab 200 mg Q3W +
cisplatin 80 mg/m² Q3W +
5-FU 800 mg/m² Q3W or
capcitabine 1000 mg/m² BID Q3W³

Bang, ASCO 2017
Wainberg, ESMO 2017

Cohort 3 Patients
• No prior therapy
• PD-L1 positive

Pembrolizumab 200 mg Q3W

Wainberg, ESMO 2017
Pembro monothérapie 1ère ligne (KEYNOTE-059 cohorte 3)

- 31 patients
- ADK gastrique ou cardia métastatiques

Critère de jugement : taux de réponse
Pembro monothérapie 1ère ligne (KEYNOTE-059 cohorte 3)

- Taux de réponses : **26%** (RC : **7%**)
- durée de réponse : **9.6 mois**
- SSP médiane **3.3 mois**,
- SG médiane **20.7 mois**
- toxicités sévères: **23%**
Keynote-028: Pembrolizumab for patients with advanced esophageal cancer

- N=23, 8% ≥ 3 lines, 74% SCC
- Pembro 10mg/kg, every 2wks
- ORR 30% (ADK 40%, SCC 29%)
- Median response duration: 40wks

Doi, ASCO 2015
Principales études PEMBROLIZUMAB dans les cancers de l’œsophage et de l’estomac métastatiques

<table>
<thead>
<tr>
<th>étude</th>
<th>Tumeur</th>
<th>traitements</th>
<th>Ligne</th>
<th>statut</th>
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<tbody>
<tr>
<td>Keynote-181</td>
<td>Estomac/JOG</td>
<td>Pembro vs DCT/IRI/PCT</td>
<td>2ème ligne</td>
<td>terminée</td>
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<tr>
<td>Keynote-061</td>
<td>Estomac/JOG</td>
<td>Pembro vs PCT</td>
<td>2ème ligne</td>
<td>terminée</td>
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<td>Keynote-062</td>
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<td>Pembro vs FU-CDDP- Pembro vs FU-CDDP-Pbo</td>
<td>1ère ligne</td>
<td>en cours</td>
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<tr>
<td>Keynote-590</td>
<td>Œsophage (ADK, SCC)</td>
<td>Pembro-FU-CDDP vs Pbo-FU-CDDP</td>
<td>1ère ligne</td>
<td>T4 - 2017</td>
</tr>
</tbody>
</table>
PD1-inhibitors

Nivolumab
ONO 45-38/07
Checkmate 032
ONO 12 Attraction
Nivolumab monothérapie et cancer de l’oesophage

<table>
<thead>
<tr>
<th>Items</th>
<th>ONO 45-38/07</th>
<th>Checkmate 032 Cohort Nivo 3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>indications</td>
<td>SCC</td>
<td>ADK E/EGJ/G</td>
</tr>
<tr>
<td>n</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td>region</td>
<td>Japan</td>
<td>US/EU</td>
</tr>
<tr>
<td>Prior systemic therapy</td>
<td>68% &gt; 2\textsuperscript{nd} line</td>
<td>83% &gt; 1stline</td>
</tr>
<tr>
<td>ORR (PD-L1+/-)</td>
<td>17% (24%/13%)</td>
<td>14% (27%/12%)</td>
</tr>
<tr>
<td>mDOR</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>mPFS</td>
<td>1.5 mo</td>
<td>1.4 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>11 mo</td>
<td>5 mo</td>
</tr>
</tbody>
</table>

Kudo, Lancet Oncol 2017
Le, GI-ASCO 2016;
ONO-12 (Attraction): Phase 3 trial in patients with advanced G/EGJ ≥ 2 prior chemo regimen

N= 330, PD-L1: all comers
ORR: 11,5%, mDOR: 9mo

Boku, ESMO 2017
ONO-12 (Attraction): survie

suivi médian: 15,7 m (12.1-27.2)

<table>
<thead>
<tr>
<th></th>
<th>PD-L1 negatif</th>
<th>PD-L1 positif</th>
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</thead>
<tbody>
<tr>
<td>Nivolumab (n=114)</td>
<td>6.1 (4.8-8.6)</td>
<td>5.2 (2.8-9.4)</td>
</tr>
<tr>
<td>Placebo (n=52)</td>
<td>4.2 (3.0-6.9)</td>
<td>3.8 (0.8-5.0)</td>
</tr>
<tr>
<td>Hazard ratio, 0.71 (95% CI, 0.50-1.01)</td>
<td></td>
<td>Hazard ratio, 0.58 (95% CI, 0.24-1.38)</td>
</tr>
</tbody>
</table>

Boku, ESMO 2017
Kang, Lancet Oncol 2017
### ONO-12 (Attraction): toxicité

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
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<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Tout Grade (%)</td>
<td>Grade ¾ (%)</td>
<td>Tout Grade (%)</td>
<td>Grade ¾ (%)</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>11</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>Prurit</td>
<td>9</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhée</td>
<td>7</td>
<td>&lt;1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>&lt;1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Anorexie</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>&lt;1</td>
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<tr>
<td>Nausées</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroïdie</td>
<td>3</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Fièvre</td>
<td>3</td>
<td>&lt;1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Effets secondaires / temps

Boku, ESMO 2017
Checkmate 032 (update) – adeno OE/JOG/G N3q2w vs N3-IPI1q3w vs N1-IPI3q3w

- Nivo améliore la survie (vs Pbo) chez pts asiatiques avec K JOG/G prétraités par 2 lignes de CT
- N+IPI: association de référence ds mélanome
- 1ers résultats N+IPI ASCO 2016 chez pts occidentaux – ici UPDATE

Janjigian, ASCO 2017
# Nivolumab + IPI (Checkmate 032)

<table>
<thead>
<tr>
<th>Items</th>
<th>Nivo 3 mono</th>
<th>Nivo 1 – IPI 3</th>
<th>Nivo 3 – IPI 1</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>59</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td>≥ 3 lignes antérieures de CT</td>
<td>49%</td>
<td>46%</td>
<td>38%</td>
</tr>
<tr>
<td>Severe TRAE</td>
<td>5%</td>
<td>35%</td>
<td>17%</td>
</tr>
<tr>
<td>ORR%</td>
<td>13.6 (6-25)</td>
<td>26.1 (14.3-41)</td>
<td>10.2 (3.4-22)</td>
</tr>
<tr>
<td>mDOR</td>
<td>7 mo</td>
<td>5.6 mo</td>
<td>na</td>
</tr>
<tr>
<td>mPFS</td>
<td>1.4 mo</td>
<td>1.5 mo</td>
<td>1.6 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>5 mo</td>
<td>6.9 mo</td>
<td>4.8 mo</td>
</tr>
<tr>
<td>1yr-OS</td>
<td>36%</td>
<td>34%</td>
<td>na</td>
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</tbody>
</table>

Not a comparative study!

Janjigian, ASCO 2017
Nivolumab (± IPI)

- **Nivo3**
  - 1ère étude de phase III positive dans le cancer gastrique en L3.
  - Efficacité non restreinte au statut PD-L1
  - Bonne tolérance
  - Résultats à confirmer en occident

- **Nivo1 – IPI 3 sélectionné pour développement futur:**
  - ORR: 24% (40% chez les PD-L1+)
  - Survie: 28% à 18 mois (comme Nivo seul)
  - 40% sévère TRAE
BMS CA209-649 – L1 estomac
BMS CA209-648 – L1 œsophage (SCC)

Key Eligibility Criteria
- Advanced or Metastatic GC/GEJ
- No prior systemic treatment
- ECOG PS 0–1
- Tissue available for PD-L1 testing

Randomization

Screening

Treatment
- Nivo 1 mg/kg + Ipi 3 mg/kg Q3W x 4 (N=422)
- Nivo Mono 240 mg Q3W

Follow-Up
- Safety F/U
- Survival F/U

PD, unacceptable toxicity, withdrawal IC, or until the maximum treatment duration per protocol is reached

Esophageal cancer
- Inoperable advanced, recurrent or metastatic
- Squamous cell carcinoma of the esophagus
- No prior systemic therapy for advanced disease
- ECOG PS 0 or 1

Randomize 1-1-1 (n = 939)

Stratified by:
- PDL1 status
- Region
- ECOG PS
- Number of organs with metastases

Arm A
- Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W*
  1 cycle = 2 weeks

Arm B
- Nivolumab 240 mg Q2W* + FP (Fluorouracil + Cisplatin) Q4W
  1 cycle = 4 weeks

Arm C
- FP (Fluorouracil + Cisplatin) Q4W
  1 cycle = 4 weeks

- Treat until progression or unacceptable toxicity
- Follow-up data collection for OS
Autres checkpoint inhibiteurs

Anti-CTLA4
Anti-PDL1

Anti-LAG3
Cancers localisés
BMS adjuvant/neoadjuvant

- ONO-4538: nivolumab+CT adjuvant (vs CT), gastric cancer.
- CheckMate 577: CRT-chir puis nivolumab vs pbo, œsophage/JOG
- CheckMate 906 (?): nivolumab vs N1IPI3 puis CRT-nivo puis chir
Keynote 585 – estomac/JOG périOp

- A Phase III, Randomized, Double-Blind, Clinical Trial of Pembrolizumab plus Chemotherapy (FLOT) versus Placebo plus Chemotherapy as Neoadjuvant/Adjuvant Treatment for Subjects with Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma
Predictive biomarkers for checkpoint inhibitor-based immunotherapy in E & EG cancer
MSI: un facteur très favorable de réponse et de survie

Keynote 059

CheckMate 032

Les tumeurs MSI sont quasiment toutes PDL1+
PDL1: un marqueur perfectible à standardiser

- The analysis of PD-L1 expression within tumors is not standardized.
- Different staining techniques are available, using different Abs for and different levels of positivity.
- Some studies looked at PD-L1 expression by tumor cells, whereas others also included its expression by cells of the microenvironment.
- PD-L1 expression is dynamic, i.e: inducible, notably by IFN-γ exposure. Therefore, a tumor which does not express PD-L1 at baseline may become PD-L1-positive in an inflammatory background (CTLA4 inhibit treatment, radiation therapy, etc...).
- Lastly, a significant percentage of patients negative for PD-L1 respond to anti-PD-1/PD-L1 therapy.
Gene Expression Signature

- 18 gene T-cell inflamed GEP predictive of response to pembrolizumab\(^1\-^3\)
  - Derived by testing, validation, and refinement of immune-related gene sets across a variety of tumor types\(^1\-^3\)
- GEP score is a weighted sum of normalized values for the genes\(^a\)

18 genes
CCL5, CD27, CD274 (PD-L1), CD276 (B7-H3), CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2 (PD-L2), PSMB10, STAT1, TIGIT

T-cell–Inflamed GEP Score by Response (n = 144)

T-cell–inflamed GEP score significantly associated (\(P = 0.014\)) with improved response to pembrolizumab
Predictive biomarkers for checkpoint inhibitor-based immunotherapy in E & EG cancer

- Microsatellite instability (...as the results of Mismatch-repair deficiency)- 4-22%
- PD-L1 expression (including EBV-mediated GC – 9% of GC – with PD-L1/L2 amplif)
- Immune-gene signature (...association with response to pembro)
- Mutational (or neoantigen) burden
- Mononuclear inflammatory density score (association with response to Pbro)
- TILs
- T-cell receptor clonality
- Multiplex (multispectral) immunochemistry
- Microbiota?

Falchetti, Hum Pathol 2008; Oki, Ann Surg Oncol 2009; Derks, OncoTargets2015
Ribas, ASCO 2015; Shankaran, ASCO 2015; Muro, Lancet Oncol 2016; Fuchs, ASCO 2017;
Conclusion

➢ PD1 inh (+/- CTLA4 inh) and PD-L1 inh, as well as PD1 inh combined to standard chemo, demonstrate encouraging efficacy (and manageable safety), irrespective of tumor PD-L1 expression

➢ In need of biomarker development for patient selection and prognostication