State of the Art in Development of Immunotherapy

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Disclosure of interest

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Non remunerated consultant, Merck AG
Topics to be covered

• Background and overview of ICIs in Cancer
• Why doesn’t Immunotherapy always work? Determinants of response?
• Duration of Therapy
• Infections and Cancer/Infection related Cancers
• Gut microbiome and ICI
• Cost
• Not covered: Combinations, IRAEs, clinical trial results
Two Types of Immune Responses Provide Extended Protection

- Viruses
- Microorganisms
- Dead tissue
- Cancerous cells

Adaptive Immunity
Physical Barriers

Innate Immunity

Cancer Immunotherapy

- Cancer cells may express tumor-specific antigens due to the presence of mutations.
- These antigens may induce an immune response.
- Up-regulation of PD-L1 in the tumor microenvironment enables cancers to evade T-cell-mediated killing.
- Inhibition of the PD-L1/PD-1 and PD-L1/B7.1 interaction may restore antitumor T-cell activity.

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Role of the PD-1 pathway in suppressing anti-tumor immunity

Tumor-specific T cell recognition in the periphery

Nivolumab, Pembrolizumab, Cemiplimab, Avelumab, Atezolizumab, Durvalumab

Lymphocyte priming to tumor antigens
The Checkpoint Inhibitors really work !!!

- Ipilimumab - CTLA4
- Nivolumab - PD1
- Pembrolizumab - PD1
- Cemiplimab - PDI
- Atezolizumab - PD-L1
- Avelumab - PD-L1
- Durvalumab - PD-L1

Maximum SLD reduction from baseline (%)

* Complete response
* Partial response
* Progressive disease
* Stable disease
Broad Activity of Immune Checkpoint Inhibitors

FDA Approved Indications

- Melanoma
- NSCLC
- SCLC
- Urothelial
- Lymphoma
- Merkel cell carcinoma
- Head and neck
- Gastric
- Renal Cell
- Hepatocellular
- CSCC
- SCLC
- Cervical cancer
- MSI high/MMR tumors
Question 1

Why don’t Immune Checkpoint Inhibitors (ICI) always work?
May 21, 2018

FDA: PD-1/PD-L1 Blocking Agents Linked to Decreased Survival in Urothelial Cancer Trials

• 1st line studies of single agent Pembro/Atezo for metastatic urothelial cancer

• Survival for patients with low PD-L1 scores was inferior to those who received platinum-based therapy

• Pembrolizumab for patients with combined positive score ≥ 10%

• Atezolizumab for patients with PD-L1 stained on immune cells of ≥ 5%
Tumors that are responsive to CKIs are “inflammed” or “immunogenic”

Taube et al. *Sci Transl Med* 2012
Inhibiting PD-1-mediated adaptive immune resistance
Infiltration of CD8+ T-cells and Treatment Outcome

IHC Analysis of CD8+ T-cells in samples obtained before and during anti-PD1 treatment

Paul C. Tumeh, Christina L. Harview, I. Peter Shintaku, Emma J. M. Taylor
Enhancing activity of PD-1/PD-L1 inhibitors

**HOT**
- Anti-PD-1/anti-PD-L1
- + anti-CTLA4
- + immune activating antibodies or cytokines
- + Oncolytic viruses
- + IDO or macrophage inhibitors
- + targeted therapies

**COLD**
- Bring T cells into tumors:
- + Vaccines
- + TCR engineered ACT
- + CAR engineered ACT
- Generate T cells:
Are there any surrogates for high neoantigen burden?
Mismatch Repair/MSI leads to high mutational load
Mutation frequencies vary across cancers

POLE mutator
Environmental mutagen

Microsatellite instable

Alexandrov et al. 2013
Patient survival and clinical response to Pembrolizumab across 12 different tumor types with mismatch repair deficiency.

High Tumor Mutational Burden (TMB) is associated with response to checkpoint inhibition

DCB: Durable clinical benefit (PR/SD >6months)
NDB: No durable benefit

Rizvi. Science 2015
### Tumor Mutation Burden across tumor types (FMI, 10,000 tumors analyzed)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Number of samples</th>
<th>Median muts/MB</th>
<th>% cases &gt; 20muts/MB (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell (skin)</td>
<td>92</td>
<td>47.3</td>
<td>70.7 (60.7 – 79.0)</td>
</tr>
<tr>
<td>SqCC (skin)</td>
<td>266</td>
<td>45.2</td>
<td>67.3 (61.4 – 72.7)</td>
</tr>
<tr>
<td>Melanoma (skin)</td>
<td>879</td>
<td>14.4</td>
<td>39.7 (26.4 – 42.9)</td>
</tr>
<tr>
<td>Large cell (lung)</td>
<td>74</td>
<td>12.2</td>
<td>24.3 (14.9 – 33.7)</td>
</tr>
<tr>
<td>Large cell neuroendocrine (lung)</td>
<td>288</td>
<td>9.9</td>
<td>19.8 (15.6 – 24.8)</td>
</tr>
<tr>
<td>Small cell (lung)</td>
<td>913</td>
<td>9.9</td>
<td>9 (7.3 – 11.0)</td>
</tr>
<tr>
<td>SqCC (lung)</td>
<td>2102</td>
<td>9.0</td>
<td>11.3 (10.0 – 12.7)</td>
</tr>
<tr>
<td>Adenocarcinoma (lung)</td>
<td>11855</td>
<td>6.3</td>
<td>12.3 (11.7 – 12.9)</td>
</tr>
<tr>
<td>Adenosquamous (lung)</td>
<td>154</td>
<td>5.4</td>
<td>12.3 (7.5 – 11.7)</td>
</tr>
</tbody>
</table>

Chalmers et al, *Genome Medicine* 2017;9:34
Question 2

There are durable responses – Could some patients with metastatic disease be cured?
Long term survival in patients with heavily pretreated metastatic NSCLC
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

Median OS (95% CI), mo

| Overall (N = 129) | 9.9 (7.8, 12.4) |

There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

Brahmer J, AACR 2017
3 - year outcome of 2\textsuperscript{nd} Line NSCLC
Question 3

How long should we treat?

- To reduce immune related adverse events
- To reduce the high cost of treatment
A Signal – CheckMate 153

Exploratory Analysis

- Improvement in PFS (HR 0.42), 1 year PFS: 65% vs 40%
- Improvement in PFS independent from RR
- Trend in OS (HR 0.63)
- Some stabilizations by reexposure

Spigel D et al, ESMO 2017; abstract 1297O
Stopping ICI after complete response

- Retrospective review from 2 institutions
- 24 complete responders with Nivolumab or Pembrolizumab

- Median time to CR: 10 months (m) Pembro, 17m NIVO
- Median time off therapy: 8m Nivo, 2-7m Pembro

23/24 patients maintained response
1/24 Relapse and successfully re-induced

Question 4

How will immune checkpoints work in the setting of chronic infections and in infection related cancers?
Voyager-V1 Oncolytic Virus MOA (VSV-IFNβ-NIS)

- Engineered Indiana strain vesicular stomatitis virus (VSV) that replicates selectively in and kills human cancer cells
- Encodes two human transgenes
  - IFNβ to boost antitumoral immune responses
  - Thyroidal sodium iodide symporter (NIS) to permit noninvasive imaging of virus spread by SPECT

Peng et al. Science, 2010
Correlative studies – NIS imaging shows viral infection of tumor

Patient #105-012 positive SPECT/CT

pancreas Ca

• Early signs of activity at dose level 3
• SPECT CT mildly positive for patient 11, at day 3 only (not shown)
• SPECT CT positive at days 3, 8, 15 for patient 12

Correlative studies – NIS imaging shows viral infection of tumor

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• SPECT CT positive at days 3, 8, 15 for patient 12
Flow cytometry of immune cells in peripheral blood

- Increase in CD4 and CD8 in peripheral blood of some patients
Intravenous VSV therapy combined with checkpoint blockade enhances intratumoral CD8+ T-cell infiltration and improved tumor remission in murine in vivo model.
Phase I Trial of intravenous Vesicular Stomatitis Virus Genetically Engineered to Express NIS and human interferon (VSV-IFNβ-NIS), combined with Pembrolizumab, with Expansion Cohorts in pts with Refractory NSCLC or HCC

**Phase I feasibility study**

- **Dose Level 1:** $5 \times 10^{10}$ TCID$_{50}$ + Pembrolizumab 200mg IV D1 (then q21)
  - No DLTs in 3 pts/DTL in 1 of 6 pts

- **Dose Level -1:** $1.7 \times 10^{10}$ TCID$_{50}$ + Pembrolizumab 200mg IV D1 (then q21)
  - DLT in ≥ 2 patients at Dose Level 1

**Phase II Research & Development study**

**3+3 DOSE OPTIMIZATION**

- **Dose Level 2:** $1.7 \times 10^{11}$ TCID$_{50}$ Pembrolizumab 200mg IV D1 (then q21)
  - No DLTs in 3 pts/DTL in 1 of 6 pts

**NSCLC and HCC patients with progressive disease on CPI therapy**

- **Patients with CPI refractory HCC**
- **Patients with CPI refractory NSCLC**

**EXPANSION**

- **20 patients total enrolled in Dose Level 2 and expansion cohorts: 10 HCC and 10 NSCLC patients**
Infection-Related Cancers

% of Cancers Caused By Infectious Diseases

North America: 4%
Europe: 7%
Global: 16%
Sub-Saharan Africa: 33%
Immune checkpoint molecule expression in HIV infection
IC molecules can influence HIV chronic persistence by inhibiting immune system activation and elimination of HIV infected cells.
CKIs are safe and effective in HIV positive pts

Ostios-Garcia L, et al JTO Vol. 13 No. 7: 1037-1042, 2018

Cook MR & Kim C, JAMA Oncol, Feb 2019
High Expression of Immune Checkpoints in virally induced cancers

<table>
<thead>
<tr>
<th></th>
<th>PD L1</th>
<th>PD L2</th>
<th>CTLA4</th>
<th>IDO1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer</td>
<td>39/157 (25%)</td>
<td>16/157 (10%)</td>
<td>15/157 (10%)</td>
<td>17/157 (11%)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>9/40 (22%)</td>
<td>9/40 (22%)</td>
<td>6/40 (15%)</td>
<td>8/20 (20%)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>32/70 (46%)</td>
<td>17/70 (24%)</td>
<td>15/70 (21%)</td>
<td>13/70 (18%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>21/66 (32%)</td>
<td>17/66 (25%)</td>
<td>6/66 (10%)</td>
<td>11/66 (17%)</td>
</tr>
<tr>
<td>Totals</td>
<td>101/333 (30%)</td>
<td>59/333 (18%)</td>
<td>42/333 (13%)</td>
<td>49/333 (14%)</td>
</tr>
</tbody>
</table>

**TABLE 2. Detection of Checkpoint Proteins in Viral-associated Cancers**

<table>
<thead>
<tr>
<th>Category</th>
<th>PD L1</th>
<th>PD L2</th>
<th>CTLA4</th>
<th>IDO1</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer (HPV +)</td>
<td>116/139 (83%)</td>
<td>90/139 (65%)</td>
<td>47/139 (34%)</td>
<td>80/139 (58%)</td>
<td>134/139 (96%)</td>
</tr>
<tr>
<td>Oral pharyngeal cancer (HPV +)</td>
<td>19/22 (86%)</td>
<td>17/22 (77%)</td>
<td>12/22 (55%)</td>
<td>17/22 (77%)</td>
<td>20/22 (91%)</td>
</tr>
<tr>
<td>Oral pharyngeal cancer (HPV -)</td>
<td>11/32 (34%)</td>
<td>10/32 (31%)</td>
<td>1/32 (3%)</td>
<td>8/32 (25%)</td>
<td>15/32 (46%)</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma (EBV +)</td>
<td>5/5 (100%)</td>
<td>4/5 (80%)</td>
<td>5/5 (100%)</td>
<td>5/5 (100%)</td>
<td>5/5 (100%)</td>
</tr>
</tbody>
</table>

What will be the effect of Endemic Infections?

- More immunogenic tumors leading to increased responses?
- Increased incidence of IRAEs?
- Increased activation of microbial and protozoal infections?
Acute Pulmonary Tuberculosis

Diffuse lymphocytic infiltration were in the alveolae

Fujita et al, JTO 2016.
Immune checkpoint blockade in parasitic infections

A - Parasites
- DC (Dendritic Cell)
- PD-L2
- PD-1
- TGF-β
- IL-10
- CTLA-4
- PD-1
- PD-L1
- Parasites

B - Parasites
- DC
- PD-L1
- TGF-β
- IL-10
- RA
- Parasites
- Vaccine
- Treg

Suppression of antiparasitic T-cell responses
Enhancement of antiparasitic T-cell responses by immune checkpoint blockade

Question 5

Will the effects of the microbiome on responses to immune checkpoint inhibitors lead to increased benefit in African populations?
>10^{14} microorganisms in GIT making us 90% bugs and 10% “us”!
Composition and luminal concentrations of dominant microbial species in various regions of the gastrointestinal tract.

- **Stomach**: $10^2$
  - *Lactobacillus*
  - *Candida*
  - *Streptococcus*
  - *Helicobacter pylori*
  - *Peptostreptococcus*

- **Colon**: $10^{11}-10^{12}$
  - *Bacteroides*
  - *Clostridium groups IV and XIV*
  - *Bifidobacterium*
  - *Enterobacteriaceae*

- **Duodenum**: $10^2$
  - *Streptococcus*
  - *Lactobacillus*

- **Jejunum**: $10^2$
  - *Streptococcus*
  - *Lactobacillus*

- **Distal ileum**: $10^7-10^8$
  - *Clostridium*
  - *Streptococcus*
  - *Bacteroides*
  - *Actinomycinae*
  - *Corynebacteria*

- **Proximal ileum**: $10^3$
  - *Streptococcus*
  - *Lactobacillus*
Higher gut microbiome diversity is associated with improved response to anti–PD-1 immunotherapy in patients with metastatic melanoma.
The Western Microbiota Diverges from That of Non-Western Populations

Starving our Microbial Self: The Deleterious Consequences of a Diet Deficient in Microbiota-Accessible Carbohydrates

Question 6

How will the immune checkpoint inhibitors be affordable in Africa?
Summary

Immune Checkpoint Inhibitors

• Have durable activity in a large number of tumors
• Predictors of efficacy are complex and not well understood
• Predictors of response may include virally-induced tumors and the host microbiome
• Combinations with different modalities (oncolytic viruses in particular) will be needed to broaden activity
• These drugs are expensive
• Clinical trials need to be performed in less developed countries to understand toxicity and efficacy, as well as duration of therapy and dosing
THANKS!

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