Combination cancer immunotherapy tailored to the tumour microenvironment

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I have no disclosures to declare.
Talk Outline

1. Conceptual Developments in Cancer Immunology
2. Tailoring combination immunotherapies to the tumour microenvironment
Conceptual Developments in Cancer Immunology

1. Cancer immunoediting
2. Tumour Neoantigen
3. Immune Reaction
4. Combination mAb-based therapy
5. Tumour induced Immune suppression
3Es

Normal

- Carcinogens
- Chronic inflammation
- Inherited genetic mutations
- Radiation
- Viral infection
- Loss of polarity
- Loss of ECM contact

Transformed

- MICA/B, ULBP (human)
- Tumor antigen
- RAE1, H60 (mouse)
- Danger (i.e., uric acid and ECM products)

Elimination (Cancer immune surveillance)

- Innate and adaptive immunity
- Repair, senescence, and/or apoptosis: intrinsic tumor suppression

Equilibrium (Cancer persistence)

- IFN-γ
- Perforin
- TRAIL
- IFN-α/β
- NKG2D

Protection (i.e., extrinsic tumor suppression)

Genetic instability and/or immune selection

Escape (Cancer progression)

- ARG1
- IL-23
- Galectin-1
- TGF-β
- IDO
- SMICA/B
- IFN-γ
- BCL-X
- MHC class I

KILL

BATTLE

LOSE

Cancer immunoediting

Teng et al., JLB 2008; Schreiber..Smyth. Science 2011
Teng et al., Cancer Res 2012, Teng et al., JCI 2015
Mutational load correlates with frequency of tumour neoantigens

Estimate of the neoantigen repertoire in human cancer
Immune contexture correlates with clinical outcome

**Immunological active tumour microenvironment**

- Blood vessel
- Lymphatic vessel
- Epithelial/smooth muscle layer
- Invasive margin
- TLS
- Tumor core
- F-DC
- Immunological active tumour microenvironment

**Immune contexture associated with good prognosis in CRC**

- Chemokine:
  - ↑CXCL9
  - ↑CX3CL1
  - ↑CXCL10
  - ↑CCL2
  - ↑CCL5
  - ↑CXCL13

- Adhesion:
  - ↑MADCAM1
  - ↑ICAM1
  - ↑VCAM1

- Cytotoxic:
  - ↑Granzymes
  - ↑Perforin
  - ↑Granulysin

- **Tumor margin**
  - ↑CD3+, CD8+, CD45RO+ T cells

- **Tumor core**
  - T cells
  - B cells
  - Macrophage
  - Neutrophil
  - Mast cell
  - NK
  - NKT
  - CTL
  - Treg
  - MDSC

- **Invasive margin**
  - Immature DC
  - Eosinophil

- **Blood vessel**
  - Immature DC

- **Epithelial/smooth muscle layer**

**Markers and Pathways**

- **T~H~1**
  - ↑T-bet
  - ↑IRF1
  - ↑STAT1

- **T~H~17**
  - ↑IL-12
  - ↑IFN-γ
  - ↑IL-15

- **T~FH**
  - ↑IL21

**References**

- Galon et al., 2006 Science
- Pages et al., 2005 NEJM
- Bindea el al., 2013 Immunity
- Fridman et al., 2012 NRC
Eradication of established tumors in mice by a combination antibody-based therapy (trimAb)

Tomoyasu Uno¹,², Kazuyoshi Takeda¹,³, Yuko Kojima⁴, Hirohisa Yoshizawa⁵, Hisaya Akiba¹, Robert S Mittler⁶, Fumitake Gejyo², Ko Okumura¹, Hideo Yagita¹ & Mark J Smyth³

**trimAb**
- anti-DR5 (immunogenic cell death)
- anti-CD40 (activate APC)
- anti-CD137 (enhance effector T cell function and survival)

**MCA induced fibrosarcoma model**

WT or KO mouse

Detect sarcoma
Measure growth
Commence treatment
Rejection of carcinogen-induced established tumors by trimAb

Uno et al. Nature Medicine, 2006
The four nodes to target for inducing maximal anti-tumour immunity

a Node 1: Elimination of immune suppression

MDSC

Arginase-1
HIF-1α
VEGF
CCL2
IDO
Tie2
CSF1

PGE₂
TGF-β
Immature dendritic cell

Adenosine

T_REG

M2

Paracrine effect

STAT3 activators

Arginase-1
HIF-1α
VEGF
CCL2
IDO
Tie2
CSF1

b Node 2: Immunogenic cancer cell death

NKG2A KIR

CTLA-4
PD-1
LAG-3
TIM-3
BTLA
VISTA/ PD-1H
TIGIT

CD96

Inhibitory

Conventional therapy
- Radiotherapy
- Chemotherapy (e.g. anthracycline, oxaliplatin)

TRAIL-R agonists

Onco gene inhibitors

HDAC inhibitors

Chemokines to attract CTL and T_\text{H} 1

Vaccines to generateCTL and T_\text{H} 1

Proteasome inhibitors

Tumour cells

p53 rescue

c Node 3: Enhanced APC function/adjuvanticity

SIRPα antagonists

TLR agonists

CD40 agonists

STING activator

Type I IFN

GM-CSF

APC

α-GalCer or α-C-GalCer

d Node 4: Enhanced T/macrophage effector activity

ICOS

CD28

OX40

GITR

CD27

CD30

HVEM

DNAM-1

CD28H

Agonistic

α-B7-H5

α-B7-H6

α-B7-H4

α-B7-H3

α-CD73 α-CD47 α-CD200

ADCC/ADCP

Nature Reviews | Clinical Oncology

Smyth et al., NRCO 2015
Engagement of checkpoint receptors represents a major mechanism of tumour-induced immunosuppression.

Checkpoint receptors: Brakes to limit overzealous T cell activation

About 20 interactions regulate T cell immune response.
Checkpoint blockade can unleash endogenous anti-tumour response

- Improved Survival with Ipilimumab in Patients with Metastatic Melanoma
  - The New England Journal of Medicine
  - ORR – 10%
  - 2010

- Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer
  - The New England Journal of Medicine
  - ORR – 31%
  - 2012

- Nivolumab plus Ipilimumab in Advanced Melanoma
  - Original Article
  - ORR – 53%
  - 2013

- Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma
  - Original Article
  - ORR – 61%
  - 2015
Anti-PD-1 to be used as standard of care and in combination immunotherapies

**Pembrolizumab versus Ipilimumab in Advanced Melanoma**

*ORR – 33.7% vs 11.9% 2015*

*Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial*

*ORR – 31.7% vs 10.6% 2015*

*Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer*

*ORR – 20% vs 9% 2015*
Moving Forward…
Key issues in cancer immunotherapy

1) Identifying biomarkers to predict what cancers will respond to anti-PD-1/PD-L1
2) How do we increase the proportion of patients who respond to anti-PD-1/PD-L1?
3) What therapies do we use to treat cancers with tumour microenvironments that are resistant to anti-PD-1/PD-L1?
4) What do we do for patients who develop acquired resistance to anti-PD-1 therapies?
5) What is the optimal scheduling for administration of combination immunotherapy?
6) How to assess the therapeutic index (anti-tumour efficacy/irAEs) of combination immunotherapies?
Tailoring combination immunotherapies to the tumour microenvironment
Tumour microenvironment can be stratified into 4 types based on TILs and PD-L1 expression in tumours.
Tumour microenvironment can be stratified into 4 types based on TILs and PD-L1 expression in tumours.
Association of anti-PD-L1 response and tumour-infiltrating immune cell PD-L1 expression

Predictive correlates of response to the anti–PD–L1 antibody MPDL3280A in cancer patients

Roy S. Herbst¹, Jean–Charles Soria², Marcin Kowaretz³, Gregg D. Fine⁴, Omid Hamid⁵, Michael S. Gordon⁵, Jeffery A. Sosman⁶, David F. McDermott⁷, John D. Powderly⁸, Scott N. Gettinger¹, Holbrook E. K. Kohrt⁹, Leora Horn¹⁰, Donald P. Lawrence¹¹, Sandra Rost¹², Maya Leabman³, Yuanyuan Xiao¹³, Ahmad Mokatrin³, Hartmut Koeppen¹³, Priti S. Hegde¹³, Ira Mellman³, Daniel S. Chen³ & F. Stephen Hodi¹²

**a** PD-L1 prevalence determined with a Genentech/Roche anti-PD-L1 IHC assay

<table>
<thead>
<tr>
<th>Indication</th>
<th>n</th>
<th>Percentage of PD-L1 positive (IC)</th>
<th>Percentage of PD-L1 positive (TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>184</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>RCC</td>
<td>88</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Melanoma</td>
<td>58</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>HNSCC</td>
<td>101</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>141</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>CRC</td>
<td>77</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>83</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

**b**

PD-L1 negative  
PD-L1 positive (IC)  
PD-L1 positive (TC)  
PD-L1 positive (TC and IC)
Cancers with type I TME containing CD8+ T cells and PD-L1 most likely to respond to anti-PD-1/PD-L1

PD-1 expression on cancer
Level of PD-1 expression
What other cancers should we treat with anti-PD-1/PD-L1?
PD-1 & PD-L1 expression in various types of solid tumours

<table>
<thead>
<tr>
<th>Tumor types (n = 437 total)</th>
<th>PD-1 expression (% and range)</th>
<th>PD-L1 (tumor cells; %)</th>
<th>Concurrent PD-1 and PD-L1 expression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinomas (n = 380 total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast (n = 116)</td>
<td>51% (1–20)</td>
<td>45%</td>
<td>29%</td>
</tr>
<tr>
<td>Colon (n = 87)</td>
<td>50% (1–20)</td>
<td>21%</td>
<td>12%</td>
</tr>
<tr>
<td>NSCLC (n = 44)</td>
<td>75% (1–20)</td>
<td>50%</td>
<td>43%</td>
</tr>
<tr>
<td>Pancreas (n = 23)</td>
<td>43% (1–16)</td>
<td>23%</td>
<td>9%</td>
</tr>
<tr>
<td>Prostate (n = 20)</td>
<td>35% (1–6)</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>Merkel cell carcinoma (n = 19)</td>
<td>17% (1–4)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Endometrium (n = 16)</td>
<td>86% (1–13)</td>
<td>88%</td>
<td>79%</td>
</tr>
<tr>
<td>Ovary (n = 14)</td>
<td>93% (1–16)</td>
<td>43%</td>
<td>36%</td>
</tr>
<tr>
<td>Liver (n = 13)</td>
<td>38% (1–5)</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Bladder (n = 11)</td>
<td>73% (1–10)</td>
<td>55%</td>
<td>55%</td>
</tr>
<tr>
<td>Kidney (n = 11)</td>
<td>36% (1–3)</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>CUP (n = 6)</td>
<td>50% (1–4)</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Sarcomas (n = 33 total)</td>
<td>30% (1–10)</td>
<td>97%</td>
<td>30%</td>
</tr>
<tr>
<td>Melanoma (n = 24 total)</td>
<td>58% (1–15)</td>
<td>92%</td>
<td>58%</td>
</tr>
</tbody>
</table>
Table 2. PD-1 and PD-L1 expression in breast cancers, according to the molecular subtype

<table>
<thead>
<tr>
<th>Breast cancer subtypes</th>
<th>PD-1 expression/hpf (TILs; % and range)</th>
<th>PD-L1 (tumor cells; %)</th>
<th>Concurrent PD-1 and PD-L1 expression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal tumors (n = 58)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal A (n = 33)</td>
<td>25% (1-&gt;10)</td>
<td>33%</td>
<td>13%</td>
</tr>
<tr>
<td>Luminal B (n = 25)</td>
<td>44% (1-20)</td>
<td>33%</td>
<td>17%</td>
</tr>
<tr>
<td>HER2 positive (n = 5)</td>
<td>60% (1-9)</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Triple-negative (n = 53)</td>
<td>70% (1-20)(^a)</td>
<td>59%(^a)</td>
<td>45%(^a)</td>
</tr>
</tbody>
</table>

Abbreviation: hpf, high-power fields.

\(^a\)Significantly higher than in luminal tumors.

Table 3. PD-1 and PD-L1 expression in colorectal carcinomas in relationship to the microsatellite instability status

<table>
<thead>
<tr>
<th>Colon cancer subtypes</th>
<th>PD-1 expression/hpf (TILs; % and range)</th>
<th>PD-L1 (tumor cells; %)</th>
<th>Concurrent PD-1/ PD-L1 expression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSS colon cancers (n = 60)</td>
<td>39% (1-11)</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>MSI-H colon cancers (n = 27)</td>
<td>77% (1-&gt;20)(^a)</td>
<td>38%(^a)</td>
<td>32%(^a)</td>
</tr>
</tbody>
</table>

Abbreviation: hpf, high-power fields.

\(^a\)Significantly higher.

PD-1\(^+\) TILs expression correlates with increasing mutational load
Le et al., NEJM, 2015; Maby et al., Cancer Res, 2015
How do we increase the proportion of responders with type I (PD-L1+TIL+) tumour microenvironment?
Can we improve above the 50% ORR induced by anti-CTLA-4 & anti-PD-1?
What therapies do we use to treat cancers with TME that are resistant to anti-PD-1/PD-L1?
- anti-PD-1 + anti-CTLA-4 (Wolchok et al. NEJM 2013)
- Type I IFN (poly-ic) + anti-PD-1 (Bald et al. Cancer Discovery 2014)
- Chemotherapy or targeted therapy + anti-PD-1
- CAR-T + anti-PD-1
- microbiota

anti-CD40 + anti-IL-23
anti-CD40 + anti-CSFR1
Summary

• Anti-PD-1/PD-L1 - will become the immunotherapeutic backbone of future cancer treatments

• Cancers can be divided into four type
  – absence or presence of TILs and PD-L1 expression

• Efficient anti-tumour strategies must focus on hitting different targets concurrently

• Key nodes to target in combination treatment
  – abrogating immune suppression
  – inducing immunogenic cancer-cell death,
  – enhancing antigen presentation/adjuvanticity
  – inducing activation and survival of immune-effector cells
Summary

• Exome-sequencing data can be mined to
  – identify unique neoantigen profile of tumours
  – guide future personalized vaccine design for use in combination treatments

• A large proportion of patients have ‘immune ignorant’ tumours,
  – predicted to have a poor prognosis regardless of any current intervention
  – novel therapies have to be developed
Thank You

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