Unmasking the masquerading cancer cells: have we made progress with the revival of immunotherapy?

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Presentation outline

Immune System’s Role in Cancer

Immunotherapy Landscape

State of Immunotherapy

Clinical Considerations of Immunotherapy

Where are we and How far will we go?
Avoiding immune destruction

Evading growth suppressors

Activating invasion and metastasis

Deregulating cellular energetics

Enabling replicative immortality

Sustaining proliferative signaling

Inducing angiogenesis

Resisting cell death

Hallmarks of Cancer Pathogenesis (2011)

• The 3 E’s

Elimination - Immune System Eradicates Cancer Cells

Equilibrium - Immune System Controls Cancer Cells

Escape - Cancer Cells Evade Immune System
Increased Incidence of Cancer in Immunocompromised Individuals

- Malignant tumors develop in individuals with compromised immune systems

Dynamics Between Cancer and the Immune System

Immune Cells Within Tumors Predicts Overall Survival

- T-cell infiltration within tumors is associated with overall survival (OS) in patients with different cancers

Kaplan-Meier Curve for OS in Advanced Ovarian Cancer

- Intratumoral T cells (n=102)
  - Median OS = 50.3 months

- No intratumoral T cells (n=72)
  - Median OS = 18 months

Initiation of Immune Response: Key Components

- Naive T-cell Antigen receptors
- Antigen
- Antigen fragments
- Effector cells: 1. Activate other immune cells 2. Kill “target cells”
- Memory cells: 1. Circulate for months → years 2. Ready to rapidly respond to same antigen again

Abbas AK, Lichtman AH. Basic Immunology. 3rd ed. 2011.
Cancer immune escape mechanisms

Within the **tumour micro-environment (TME)** several mechanisms that help tumours to escape immune attack:

1. **regulatory B cells (Bregs)** produce immunosuppressant cytokines including interleukin (IL)-10 and transforming growth factor-beta (TGF-β);

2. **regulatory T cells (Tregs)** directly inhibit the function of effector T cells (Teff);

3. **myeloid derived suppressor cells** (MDSCs) suppress effector T cells through arginase-1;

4. **tumour-associated macrophages (TAM)** inhibit effector T cells through nitric oxide produced by NO synthase (NOS);

5. **immature dendritic cells (immature DC)**, but also tumour cells highly express indoleamine 2,3-dioxygenase (IDO) leading to tryptophane deprivation, which inhibits effector T cell function.
Features of an Effective Immune Response

- **Specificity** - Ability of immune cells to identify and target a specific antigen

- ** Trafficking** - Ability of activated immune system cells to migrate to particular antigens throughout the body

- **Adaptability** - Allows for a broader immune response (eg, immune response to additional antigens)

- **Target elimination** - Ability of immune cells to destroy their target (eg, cancer cells) Usually via induction of apoptosis

- **Durability (immune memory)** - Ability of immune system to recognize an antigen to which it has previously been exposed and provide long-lasting protection against it

Immunotherapies (cytokines, checkpoint inhibitors, therapeutic vaccines, monoclonal antibodies) have been approved by the FDA to treat certain cancers.
The timeline Immunotherapy

**Enthusiasm Phase**
1978-1985

- 1976: 1st study with adoptive T-cell transfer in CA
- 1978: Discovery of tumor specific mAbs
- 1985: 1st study with BCG in bladder CA

**Skepticism Phase**
1985-1997

- 1986: IFN-α (cytokine) approved for CA
- 1992: IL-2 (cytokine) approved for CA

**Renaissance Phase**
1997-

- 1997: 1st mAB approved for CA
- 2010: 1st cellular immunotherapy approved for CA
- 2011: 1st checkpoint inhibitor approved for CA

BCG, Bacille Calmette-Guerin; mABs, monoclonal antibodies; CA, cancer; IFN-α, interferon alpha; IL-2, interleukin-2

Intervention in the cancer-immunity cycle by immunotherapy agents

Overcoming resistance and restoring a functional immunesurveillance system requires leveraging multiple, complementary mechanisms of action and agents that act in multiple phases of the cancer-immunity cycle (numbers denote the phases at which each type of immunotherapy acts).
Immunotherapy: Gaining approval

- More than a dozen different immunotherapy agents have been approved, with the majority over the last decade
- Immunotherapy agents currently approved target >10 different cancer types

<table>
<thead>
<tr>
<th>FDA-Approved Immunotherapies\a</th>
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</thead>
<tbody>
<tr>
<td>Class</td>
<td>Approvals</td>
</tr>
<tr>
<td>Checkpoint inhibitor</td>
<td>2011</td>
</tr>
<tr>
<td>Therapeutic vaccine</td>
<td>2010</td>
</tr>
</tbody>
</table>

\a Not inclusive of all immunotherapy classes.

Checkpoint Inhibitors

- **Mechanism of action**
  - Block immune checkpoints that regulate T cell activation/function
- **Examples**
  - CTLA-4 and PD1
- **Efficacy**
  - Extends overall survival in certain metastatic diseases
  - A significant effect on PFS not consistently observed

Therapeutic Cancer Vaccines

- **Mechanism of action**
  - Activation of T cells to seek out and destroy target cancer cells
- **Efficacy**
  - Extended overall survival in certain metastatic diseases without an effect on PFS

CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD1, programmed cell death protein 1

Monoclonal Antibodies (mABs)

• **Mechanism of action**
  - Differs between agents
  - Bind to their specific target antigen ultimately causing cell death

• **Efficacy**
  - Improved overall and progression-free survival (PFS) in randomized, phase 3 clinical trials in breast cancer, colorectal cancer, leukemia, and head and neck cancer

Cytokines

• **Mechanism of action**
  - Interleukin-2 (IL-2) stimulates T-cell proliferation

• **Examples**
  - Interleukins, interferons

• **Efficacy**
  - High dose IL-2 administration resulted in long term disease-free survival in patients with melanoma and renal cell carcinoma

### Classes of immunotherapy agents in oncology

#### Active Immunotherapies

<table>
<thead>
<tr>
<th>Classes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer vaccines</td>
<td>Sipuleucel-T</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Interleukin-2, interferon-α</td>
</tr>
<tr>
<td>Immunomodulatory mAbs</td>
<td>Nivolumab, ipilimumab, pembrolizumab</td>
</tr>
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</table>

#### Passive immunotherapies

<table>
<thead>
<tr>
<th>Classes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-based therapies</td>
<td>Adoptive T-cell therapy (e.g., TIL, TCR, CAR-T)</td>
</tr>
<tr>
<td>Oncolytic viruses</td>
<td>T-Vac</td>
</tr>
<tr>
<td>Bi- and multispecific antibodies</td>
<td>Blinatumomab</td>
</tr>
<tr>
<td>Tumor-targeting mAbs</td>
<td>Rituximab</td>
</tr>
</tbody>
</table>
Selected list of combination immunotherapies in clinical development

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>Mechanisms of action</th>
<th>Phase</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>Anti-PD1 + anti-CTLA-4</td>
<td>I/II</td>
<td>Gastric, TNBC, PA, SCLC, Bladder, Ovarian</td>
</tr>
<tr>
<td>Nivolumab + BMS-986016</td>
<td>Anti-PD1 + anti-LAG3</td>
<td>II/III</td>
<td>Melanoma, RCC</td>
</tr>
<tr>
<td>Nivolumab + viagenpumatucel-L</td>
<td>Anti-PD1 + vaccine</td>
<td>I</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Nivolumab + urelumab</td>
<td>Anti-PD1 + anti-4-1BB</td>
<td>I/II</td>
<td>Solid tumors, B-cell NHL</td>
</tr>
<tr>
<td>Atezolizumab + MXR9016</td>
<td>Anti-PDL1 + anti-OX40</td>
<td>I</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Atezolizumab + varilumab</td>
<td>Anti-PDL1 + anti-CD27</td>
<td>II</td>
<td>RCC</td>
</tr>
<tr>
<td>Atezolizumab + GDC-0919</td>
<td>Anti-PDL1 + IDO inhibitor</td>
<td>I</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Epacadostat + atezolizumab, durvalumab, or pembrolizumab</td>
<td>IDO inhibitor + anti-PDL1 or anti-PD1</td>
<td>I/II</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Pembrolizumab + T-Vec</td>
<td>Anti-PD1 + vaccine</td>
<td>III</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Durvalumab + tremelimumab</td>
<td>Anti-PDL1 + anti-CTLA-4</td>
<td>I/II</td>
<td>Melanoma</td>
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<tr>
<td></td>
<td></td>
<td>I/II/III</td>
<td>SCCHN</td>
</tr>
<tr>
<td>Pidilizumab + dendritic cell/RCC fusion cell vaccine</td>
<td>Anti-PD1 + vaccine</td>
<td>II</td>
<td>RCC</td>
</tr>
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</table>
### Selected list of combination immunotherapies in clinical development

#### Immunotherapy + Targeted Therapy

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>Mechanisms of action</th>
<th>Phase</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Atezolizumab + bevacizumab</td>
<td>Anti-PDL1 + anti-VEGF</td>
<td>II/III</td>
<td>RCC</td>
</tr>
<tr>
<td>Atezolizumab + cobimetinib</td>
<td>Anti-PDL1 + MEK inhibitor</td>
<td>I</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Atezolizumab + vemurafenib</td>
<td>Anti-PDL1 + BRAF inhibitor</td>
<td>I</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Atezolizumab + erlotinib or alectinib</td>
<td>Anti-PDL1 + EGFR or ALK inhibitor</td>
<td>I</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Nivolumab + bevacizumab</td>
<td>Anti-PD1 + anti-VEGF</td>
<td>II</td>
<td>RCC</td>
</tr>
<tr>
<td>Pembrolizumab + pazopanib</td>
<td>Anti-PD1 + tyrosine kinase inhibitor</td>
<td>I</td>
<td>RCC</td>
</tr>
<tr>
<td>Pembrolizumab + dabrafenib + trametinib</td>
<td>Anti-PD1 + BRAF inhibitor + MEK inhibitor</td>
<td>I/II</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Durvalumab + dabrafenib + trametinib</td>
<td>Anti-PDL1 + BRAF inhibitor + MEK inhibitor</td>
<td>I/II</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Nivolumab + sunitinib, pazopanib, or ipilimumab</td>
<td>Anti-PD1 + RTK inhibitor, RTK inhibitor, anti-VEGF</td>
<td>I</td>
<td>RCC</td>
</tr>
</tbody>
</table>

#### Immunotherapy + Chemotherapy

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>Mechanisms of action</th>
<th>Phase</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + platinum doublet chemo³</td>
<td>Anti-PD1 + chemotherapy</td>
<td>III</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Pembrolizumab + cisplatin</td>
<td>Anti-PD1 + chemotherapy</td>
<td>III</td>
<td>Gastric</td>
</tr>
<tr>
<td>Pidilizumab + lenalidomide</td>
<td>Anti-PD1 + chemotherapy</td>
<td>I/II</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Pidilizumab + sipuleucel-T + cyclophosphamide</td>
<td>Anti-PD1 + vaccine + chemotherapy</td>
<td>II</td>
<td>Prostate</td>
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<tr>
<td>Atezolizumab + carboplatin/paclitaxel +/− bevacizumab</td>
<td>Anti-PDL1 + chemotherapy +/− anti-VEGF</td>
<td>III</td>
<td>NSCLC</td>
</tr>
</tbody>
</table>
**Immunotherapy: Treatment Considerations**

- **Relative efficacy** of immunotherapy may be greater with lower tumor burden

- Patient given immunotherapy earlier in disease course might have a better outcome

- Standard practice in oncology is the use of combination agents with different mechanisms of action
  - Chemotherapy and mABs
  - Radiation and chemotherapy
  - Multiple chemotherapy regimens

- **Immunotherapy offers potential for synergy with other therapies**

![Tumor Growth Rate Diagram](image)

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Immunotherapy: Increasing research interest

- Rapid increase in immunotherapy clinical research
  - Doubling of abstracts at major conferences from 2009 to 2012
  - Approximately 800 clinical trials in various phases ongoing
    - eg, breast, colon, head and neck, kidney
- Trials utilize agents alone and in combination with conventional therapies
**5th European Immunology Conference**

**Berlin, Germany  July 21-23, 2016**

*Immune modulation does not exist in a vaccuum*

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- **Primers**
  - cytokines
  - vaccines
  - cytotoxics

- **Checkpoints**
  - CTLA4
  - PD-1
  - TIM3 etc

- **Expander**
  - TNFRs
  - CAR-T
  - BiTEs

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Such complexity offers significant challenge, but also opportunity, for new drugs to have a positive impact
Inhibition appears to be dominant over activation

- Preclinical models support this view
- Early clinical data support this view, e.g. monotherapeutic activity of TNFR agonists is low
- Even CAR T cells can be shut down by immune checkpoint expression

The impact of removing constraints on NK cell activity and on immunosuppression imposed by stromal cells is not known
Considering a patient

- Indication
  - Genetics
  - Line
  - Age

- Surgery Debulking

- Patient

- Chemotherapy
- Irradiation
- Targeted Tx
- Transplant
Efficacy/Tolerability: where we are headed depends on the indication

- Hematologists have been excited about the "post-chemo" era.
  - Why? ibritinib, rituxumab, idelalisib, revlimid etc ...

- Solid tumor oncologists already know from targeted therapies that some of their patients can be cured (e.g. targeted therapies & antibodies in breast cancer) – anticipating better cure rates with IO
  - Oncologists in general are seeing success where for decades there has been only abject failure (NSCLC, H&N, bladder, etc)
  - All oncologists recognize the importance of being able to treat their elderly patients

- In this landscape, the efficacy/tolerability profile can be differentiating
Complex indications, complex patients

Driver mutations in metastatic melanoma and in lung cancers
Complex indications, complex patients

Expression of lymphocyte markers and PD-L1 in NSCLC

Surface Markers: Critical for Immune Cell Classification

- T cells
- NK cells

CD3+/CD8+ T cells

but this picture is highly variable

- degree of infiltration (starting at none)
- geography of infiltration (marginal, interstitial, stromal, excluded)
- functionality of infiltrates (PD-1, TIM-3, LAG3)
CD3+ CD8+

Complex indications, complex patients

Figure. A Model for Evaluating Immune Status

The immune status of a tumor can be assessed and stratified using three key measures (above): (1) the immune contexture; (2) an Immunoscore; and (3) an immunologic constant of rejection, according to an international task force working on standards for translating immunotherapy into clinical practice. The genes listed have been identified as those whose alterations are more likely to play an underlying role in biologic processes that may predict responses to immunotherapy.

Galon et al 2013. Immunity 39: 11-26
Assessing the benefit with immunotherapy

- Combinations of traditional and immunotherapies could combat the initial drop in survival while also providing the long-term response (red).

- Immunotherapies may show similar survival kinetics to traditional therapies as an immune response develops, but could provide a much longer survival benefit for a subset of patients (long green tail).

- Idealized characteristics of traditional (blue) and immunotherapies (green).

Adapted from Perlmutter, AACR 2014
Clinical considerations

**Monotherapy**
*one cancer type, few patients*

Combinations, broader use
Better patient selection?
Where are we and How far will we go?

Challenges: Developing them to the point of clinical utility

- Immunotherapy drugs are highly effective, but not in everyone. What clinical data are needed in order to move agents and combinations to clinical practice?

- What dosing schedules will determine efficacious response? And alternatively have favourable toxicity?

- What is a standard criteria to measure response and prognosticate disease?

- What will be the cost impact of these very expensive agents?
Challenges: Developing them to the point of clinical utility

Development of resistant disease and disease progression on or after therapy

PK and PD paradigms remain inadequate to guide the selection of doses and schedules, both starting and recommended Phase 2 for immunotherapies

When combining an immunotherapy with another treatment modality, it is important to determine the optimal dose, schedule, sequence and tumor mutational heterogeneity.

trAEs appear to increase in rate and severity with cancer immunotherapy combinations; depending on the combination partner, alterations in the toxicity profile are also possible.

Adoption of immunodynamic endpoints that are clinically meaningful to allow the selection of the most effective front-line agents or combinations, or second-line immune agents if and when immunotherapy fails.
# Immunoprog nostic and Immunotherapeutic Areas

<table>
<thead>
<tr>
<th>Prognostic</th>
<th>Immunoscore</th>
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<tbody>
<tr>
<td>Therapeutic</td>
<td>Conventional Therapies</td>
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<td></td>
<td>Chemotherapy</td>
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<td></td>
<td>Radiation therapy</td>
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<tr>
<td>ITAs - Passive</td>
<td>Cellular Therapy</td>
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<td></td>
<td>Adoptive T and NK cells</td>
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<td>CAR T cells</td>
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<tr>
<td>ITAs - Active &amp; Specific</td>
<td>Monoclonal Antibodies</td>
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<td></td>
<td>Tumor-targeting</td>
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<td>Immune-targeting, including checkpoint inhibitors</td>
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<td>Vaccines</td>
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<td>In situ Vaccines</td>
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<td>Cell-based Vaccines</td>
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<td>Dendritic cell–based Vaccines</td>
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<td>ITAs - Active &amp; Nonspecific</td>
<td>Non–cell-based Vaccines</td>
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<td>Cytokines</td>
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<td>IDO Inhibitors</td>
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</table>
Challenges: Developing them to the point of clinical utility

The safety profile is based on the mechanism of action, and although adverse events can occur in any organ, the most commonly affected organs are gastrointestinal (diarrhea), dermatologic (rash, itchiness), hepatic (usually clinically asymptomatic elevation in transaminases), and endocrinopathies.

Most adverse events are low grade in severity and manageable, but if not properly managed, symptoms can worsen, possibly to the point of irreversibility and/or the necessity to discontinue treatment.

There is no standard approach to identifying immune related adverse events, but any inflammatory event should be taken seriously and the use of steroids should be considered.

Most adverse events, such as fatigue, headache, abdominal pain, colitis, and itchiness, can’t be identified on physical exam and the treating physician has to rely on the patient to make him/her aware of any new symptom or worsening of existing symptoms.
### Table 2: Selected Adverse Events

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<tr>
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</tr>
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<tbody>
<tr>
<td>Pneumonitis</td>
<td>3% 1%</td>
<td>9% 0%</td>
<td>NR 0%</td>
<td>NR 1% 0%</td>
<td>NR 10% 5.3%</td>
<td>NR 7.6% 5.3%</td>
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</tr>
<tr>
<td>Diarrhea</td>
<td>11% 1%</td>
<td>20% 1%</td>
<td>26% 1%</td>
<td>9% 0%</td>
<td>5% 0%</td>
<td>10.7% 32.8% 5.3%</td>
<td></td>
</tr>
<tr>
<td>Coitits</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>12% 0%</td>
<td>21% 2%</td>
<td>18% 1%</td>
<td>7% 0%</td>
<td>0% &lt; 1%</td>
<td>19.1% 0.8%</td>
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<tr>
<td>Pruritus</td>
<td>9% &lt; 1%</td>
<td>21% 1%</td>
<td>NR NR</td>
<td>6% 0%</td>
<td>0% &lt; 1%</td>
<td>NR 24.4% 0%</td>
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<tr>
<td>Vitiligo</td>
<td>3% 0%</td>
<td>9% 0%</td>
<td>NR NR</td>
<td>2% 0%</td>
<td>NR NR</td>
<td>NR 2.3% 0%</td>
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</tr>
<tr>
<td>ALT elevation</td>
<td>4% 1%</td>
<td>8% 0%</td>
<td>NR 3%</td>
<td>1% 0%</td>
<td>4% 1%</td>
<td>NR 1.5% 0%</td>
<td></td>
</tr>
<tr>
<td>AST elevation</td>
<td>3% 1%</td>
<td>10% 1%</td>
<td>NR NR</td>
<td>NR 4% 1%</td>
<td>10.7% 0.8%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Infusion reaction/hypersensitivity</td>
<td>3% &lt; 1%</td>
<td>NR NR</td>
<td>NR NR</td>
<td>11% &lt; 1%</td>
<td>NR NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>NR NR</td>
<td>80% 1%</td>
<td>43% 4%</td>
<td>NR NR</td>
<td>13% 1%</td>
<td>35.7% 42% 6.9%</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism/Hypothyroidism</td>
<td>3% &lt; 1%</td>
<td>9% &lt; 1%</td>
<td>NR NR</td>
<td>3% 0%</td>
<td>3% &lt; 1%</td>
<td>NR 1.5% 0%</td>
<td></td>
</tr>
</tbody>
</table>

*Regardless of attribution.

ALT = alanine transaminase; AST = aspartate transaminase; Gr = grade; NR = not reported.
21% of patients terminated treatment due to toxicity

- toxicity is associated with positive clinical response

- oncologists: the GI tox is very difficult and limits use
While checkpoint blockade drugs currently focus on blocking two checkpoint mechanisms, others have been identified by research, as well as molecules that stimulate immune response.

Tumor mutational load has been shown to correlate with clinical response to checkpoint blockade in human cancers. Somatic neoepitopes were associated with a prolonged benefit in responders to aCTLA4 treatment in melanoma.

Immunotherapy can work for cancer patients; in a few cases it already does, but response patterns are different from traditional therapy. For example, the time to an antitumor response can be longer.

Often, a clinical response is apparent only after a period of “pseudoprogression,” when immune cell infiltration can manifest as new lesions or growth of existing ones.
Challenges: Developing them to the point of clinical utility

- The cost of these agents is staggering—higher than any previous class of cancer treatment.

- Therefore, payers are seeking better evidence that patients will clearly benefit, which brings the issue back to identifying biomarkers and their potential for predicting success.
• what we want in specific indications:
  • better response rates
  • more durable responses
  • better tolerability

• because we are addressing new benchmarks clinical practice is evolving quickly

• for preclinical and early clinical programs a critical exercise is to look ahead in an effort to anticipate unmet need in a rapidly changing environment
Summary

- The immune system plays a critical role in controlling cancer
- Key features of an effective immune response include
  - Specificity
  - Adaptability
  - Durability (immune memory)
- Future clinical considerations
  - May elicit better immune system response if used earlier in disease
  - Potential for durable clinical effects and synergy with subsequent therapies

Tumor cells
- LAG3
- HHLA2
- TIM-3

Lymphocyte subsets
- TNFRSF proteins
- KIRs
- C-type lectins

Microenvironment
- TGFβ
- IDO-1
- Chemokine receptors

NK cells: the next wave of immune-modulators

To watch out
- KIRs
- LIRs (ILT)
- Siglec
- The PVR/nectin family (TIGIT)
- C-Type lectins
Moving ahead

- The optimal efficacy/tolerability paradigm will impact more and more indications as therapeutics are successful.

- Niche indications with high unmet need allow access to this remarkably competitive landscape.

- Novel interrogation points to drive differentiation:
  - T cells: effectors and Tregs
  - NK cells
  - The tumor microenvironment
  - The tumor itself.
5th European Immunology Conference
Berlin, Germany  July 21-23, 2016

thank you