CHECKPOINT INHIBITORS:
ROLE IN GI CANCER?

Neil H. Segal, M.D., Ph.D.
Assistant Attending, Gastrointestinal Oncology Service
Deputy Director, Immunotherapeutics Group
Memorial Sloan-Kettering Cancer Center, New York
Disclosures

- MedImmune: Research and consulting funds
- Pfizer: Research and consulting funds
- BMS: Research funds
**Immunotherapy and GI malignancies**

- GI Malignancies are immunogenic, and can be recognized by the patient’s immune system!
- Represent diverse challenges and opportunities for IMT
- May develop in an inflammatory/ immune suppressive micro-environment
- Usually not associated with DNA changes from carcinogens and high mutation burden...
Somatic Mutation Prevalence

Somatic Mutations create epitopes

- 1,152 proteins are mutated in each CRC and breast tumor
- Using epitope prediction algorithms: SYFPEITHI, BIMAS, RANKPEP, NetMHC:
- We calculated that these mutations cause $\sim 7 - 10$ novel epitopes per tumor
- WBC’s recognize epitopes, especially novel ones
- Therefore each tumor can be a polyvalent ‘self-vaccine’ to stimulate the immune system

Tumor-infiltrating lymphocytes (WBC)

Tremelimumab (anti-CTLA-4)

- Phase II trial
- 47 patients
- 15 mg/kg q12w
- 1 PR (15 mo)
MPDL3280A (Anti-PDL-1)

- Phase I trial
- 20 pts with 4 tumor types
- 0.1-20 mg/kg Q3W
- 73 y/o F prior FOLFOX/bevacizumab, capecitabine.
- 1 PR in CRC at 20 mg/kg
- 10.4 months on study

Baseline

Week 18 (after C6)

Carolina BioOncology Institute (Powderly).

Tabernero. ASCO 2013. abstract 3622
Nivolumab (Anti-PD-1)

- 2 phase I trials
- 20 CRC patients
- Dosed Q2W
- 1 Complete Response

Nivolumab (Anti-PD-1)

- 2 phase I trials
- 20 CRC patients
- Dosed Q2W
- 1 CR (dMMR)

DNA mismatch repair deficiency

- Either Lynch syndrome, or acquired dMMR
- Tumor DNA has ‘frame shifts’, and creates of frame shift peptides, which are new to the immune system
- Therefore these frame shift peptides can be targeted by the immune system, and they are!
Phase II Study to Evaluate the Efficacy of MEDI4736 in Immunological Subsets of Advanced Colorectal Cancer

- A clinical trial for patients whose tumors have:
  - MMR deficiency (Lynch syndrome or acquired), or:
  - Increased lymphocytes (WBC)

- Standard therapies are no longer a good option

- Receive MEDI4736 by intravenous infusion every 2 weeks
MPDL3280A (Anti-PDL-1)

- Phase I trial
- 20 pts with 4 tumor types
- 0.1-20 mg/kg

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Dose (mg/kg)</th>
<th>No. of Patients</th>
<th>Best Response (Investigator Assessed)</th>
<th>Time on Study for Responders (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR</td>
<td>SD</td>
</tr>
<tr>
<td>CRC</td>
<td>20</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GC</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

Tabernaero. ASCO 2013. abstract 3622
Tremelimunab (anti-CTLA-4)

- Phase II trial
- 18 pts (2\textsuperscript{nd} line)
- 15 mg/kg Q12w
- 4 SD
- 3/13 CEA/CA19-9
- 1 PR (32.7+ mo)
MEDI4736 (Anti-PDL-1) Dose-Expansion Study in Multiple Tumor Types

**escalation**

MEDI4736 0.1-10 mg/kg q2w
15 mg/kg q3w

43 Sites
408 patients
20-60 per cohort

- **NSCLC squamous**
- **NSCLC non-squamous**
- **Head and neck squamous**
- **Melanoma (uveal + cutaneous)**
- **Pancreas Cancer**
- **Triple Negative Breast**
- **Gastroesophageal**
- **Hepatocellular carcinoma**
- **Microsatellite unstable**
- **Ovarian**
- **HPV+ Tumors**
- **Nasopharyngeal**
- **GBM**
- **SCLC**
- **Bladder Cancer**
MEDI4736 (Anti-PDL-1)

<table>
<thead>
<tr>
<th>MEDI4736 10mg/kg Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST response, % (n/N)</td>
</tr>
</tbody>
</table>

*Changes >100% are truncated; Changes represent target lesions; Patients with base line and ≥1 on-treatment scan Disease assessment at 6 weeks, 12 weeks, 16 weeks, and then every 8 weeks.

# Pembrolizumab (Anti-PD-1)

## Table

<table>
<thead>
<tr>
<th></th>
<th>Total N = 39</th>
<th>Non-Asian n = 20</th>
<th>Asian n = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, (^a) % (95% CI)</td>
<td>30.8 (17.0-47.6)</td>
<td>30.0 (11.9-54.3)</td>
<td>31.6 (12.6-56.6)</td>
</tr>
</tbody>
</table>

## Graph

- 65 of 162 (40%) patients assessed for PD-L1 expression had staining in the stroma or in ≥1% of tumor cells, in archival tumor samples using a prototype IHC assay and the 22C3 antibody.

- Pembo: 10 mg/kg IV Q2W

---

\(^a\) 2 patients did not have a post-baseline tumor assessment and were therefore not evaluable for this analysis.

Analysis cut-off date: August 6, 2014.

ESMO 2014. Muro et al. LBA15
Tremelimumab (anti-CTLA-4)

- Phase II trial of 17 HCV patients
- 15 mg/kg Q12w
- RR = 17.6%. (3/17 PR)
- TTP = 6.5 months (95% CI 3.95–9.14)
- Decrease in HCV viral load was associated with enhanced anti-HCV immune response.
MEDI4736 (Anti-PDL-1)

<table>
<thead>
<tr>
<th></th>
<th>MEDI4736 10mg/kg Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCR 12w, % (n/N)</td>
<td>21 (4/19)</td>
</tr>
<tr>
<td>RECIST response, % (n/N)</td>
<td>0 (0/19)</td>
</tr>
</tbody>
</table>

*Changes >100% are truncated; Changes represent target lesions; Patients with base line and ≥1 on-treatment scan Disease assessment at 6 weeks, 12 weeks, 16 weeks, and then every 8 weeks.

Ipilimumab (Anti-CTLA-4)

- Phase II study
- 27 subjects
- Metastatic/locally adv. pancreas cancer
- RR 0% (new lesions)
- 1 tumor shrinkage

Royal et al. J. Immunol. 33(8) 2010
MEDI4736 (Anti-PDL-1)

<table>
<thead>
<tr>
<th></th>
<th>MEDI4736 10mg/kg Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCR 12w, % (n/N)</td>
<td>21 (6/29)</td>
</tr>
<tr>
<td>RECIST response, % (n/N)</td>
<td>7 (2/29)</td>
</tr>
</tbody>
</table>

*Changes >100% are truncated; Changes represent target lesions; Patients with base line and ≥1 on-treatment scan Disease assessment at 6 weeks, 12 weeks, 16 weeks, and then every 8 weeks.

MEDI4736 (Anti-PDL-1)

- 59 y.o. male
  - Progressed on prior gemcitabine and FOLFIRINOX
  - PD-L1 negative
  - Tumor regression at 6 weeks and ongoing at 24+ weeks
Paradigm for IMT

Strong immune response → Tumor-Immune equilibrium, e.g.: PDL-1 → Clinical response

Weak immune response → Immune ignorance/suppressed → Poor clinical response

Anti-PD-1
Anti-PDL-1
Paradigm for GI-IMT

Strong immune response → Tumor-Immune equilibrium e.g.: PDL-1 → Clinical response

Anti-PD-1
Anti-PDL-1

Weak immune response

1) Anti-CTLA-1, Anti-CD137
2) Antigen release (e.g.: chemotherapy, ablation, radiation)
3) The tumor is more immunogenic (increased WBC, FSP)
Colorectal Cancer, Gastric Cancer, Pancreas Cancer and Hepatocellular Cancer are recognized by the immune system.

GI cancers may be targeted by an augmented immune response with profound clinical benefit, albeit in a subset of patients.

We need to identify patients who respond to immunotherapy, learn how why, and provide clinical trials.
Acknowledgments

- Our patients and their families, for their time and consent
- Our dedicated physicians, nurses and clinical research team
- Our sponsors and collaborators