The Development of MSI-H Cancer Therapy

Development of Anti-Cancer Drugs Forum
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Executive Director, Late Stage Oncology
Merck & Co., Inc., Rahway, NJ USA
PD-1 is an antigen expressed on the surface of activated T-cells

PD-1 interacts with its ligands PD-L1 and PD-L2 expressed on cancer and surrounding cells

This inhibits activation of T lymphocytes and prevents an anti-tumor immune response

PD-1 inhibition with Keytruda reactivates T cells to attack and kill cancer cells
Pembrolizumab is a Humanized IgG4, High-Affinity Anti-PD-1 Blocking Antibody

- No cytotoxic (ADCC/CDC) activity
- Low occurrence of anti-drug antibodies and no impact on pharmacokinetics

Presented by: Antoni Ribas ASCO 2013
KEYTRUDA Development Program

First anti-PD-1 to market in the US

- Approvals in Melanoma, Non-Small Cell Lung Cancer, (1L and 2L+ PD-L1+), Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
- Demonstrated overall survival
  - vs. ipilimumab in melanoma
  - vs. docetaxel in 2L+ PD-L1+ NSCLC
  - vs chemo in previously treated patients with advanced bladder cancer
- Data in first line NSCLC for both Monotherapy and in Combination with chemotherapy
- Clinical activity in more than 20 different tumor types
- More than 30 ongoing registration-enabling studies
- 5 FDA Breakthrough Designations
Keytruda Monotherapy Has Shown Activity in 20 Tumors

Clinical trials are ongoing in common, uncommon, and rare cancers.

**Melanoma**
- 1L (KN006)
- 2L (KN002)
- Adjuvant (KN053/054)
- 1L + T-Vec (Amgen)
- 1L + IDO-1 (Incyte)

**NSCLC**
- 1L (KN024)
- 1L (KN042)
- 1L + pemetrexed non sq (KN189)
- 1L + paclitaxel sq (KN407)
- 2/3L (KN010)
- Adjuvant (KN091)

**Head and Neck**
- 1L + chemo/cetuximab (KN048)
- 2L (KN040)
- 3L (KN055)
- 2L Nasopharyngeal (KN122)

**Hematological Malignancies**
- 3L HL (KN087)
- rrHL + brent. ved. (KN204)
- 2L NHL rrPMBCCL (KN170)
- 1L MM + len/dex (KN185)
- 3L rrMM + pom/dex (KN183)

**Bladder**
- 1L (KN052)
- 1L (KN361)
- 2L NIBC (KN057)
- 2L (KN045)

**Gastrointestinal**
- 1L Gastric + chemo (KN062)
- 2L Gastric (KN061)
- 3L Gastric (KN059)
- 2L Esophageal (KN181)
- 3L Esophageal (KN180)
- 1L CRC MSI-high (KN177)
- 3L CRC MSI-high (KN164)

**Triple Negative Breast**
- 2L+ (KN086)
- 2L/3L (KN119)

**Other**
- 2L Advanced Cancers (KN158)
- 2L Ovarian (KN100)
- 2L Prostate (KN199)
- 1L Renal Cell Carcinoma (KN427)
- 1L + Axitinib Renal Cell Carcinoma (KN426)

**Hepatocellular**
- 2L (KN224)
- 2L (KN240)
Biomarker Program to Identify Cancers Likely to Respond to Pembrolizumab Therapy

Goal is to identify patients most likely to benefit from treatment
KEYNOTE (KN) 016

- Demonstration of clinical efficacy in a biomarker-defined population
MSI-H Cancer Has a High Mutational Burden

- Mismatch repair (MMR) deficiency refers to deficiency in proteins responsible for DNA MMR: MSH2, MSH6, MLH1, PMS2.
- MMR deficiency leads to the MSI-H phenotype.
- MMR deficient/MSI-H cancers harbor thousands of mutations (i.e., high mutational burden; hypermutated phenotype).

DNA mutations lead to protein neo-antigens, detected as ‘foreign’ & recognized by T-cells
Rationale and Hypothesis

• Hypothesis: Pembrolizumab is effective in treating any MSI-H cancer
  – MSI-H cancer, regardless of tumor histology, is associated with a high mutational burden (hypermutated phenotype)
  – High mutational burden leads to high neoantigen expression
  – High neoantigen expression leads to autologous immune recognition of cancer cells
  – By blocking PD-1 on tumor neoantigen-specific T cells, pembrolizumab can activate anti-tumor immune responses

• PD-1 blockade with pembrolizumab can restore effective anti-tumor immunity in MSI-H cancer, regardless of cancer type
Pembrolizumab Therapy of MSI-H Cancer

• MSI-H cancer represents a unique, biomarker-identified disease with a common immunobiology

• MSI-H cancers are readily identifiable using locally available assays (e.g., PCR, IHC)

• MSI-H – associated with worse prognosis in advanced CRC; limited data in MSI-H gastric and endometrial cancer – worse prognosis (or unclear association with prognosis) in advanced-stage disease
Programmed death-1 blockade in mismatch repair deficient colorectal cancer

# Study Design

## Colorectal Cancers

<table>
<thead>
<tr>
<th>Cohort A</th>
<th>Cohort B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient in Mismatch Repair (n=28)</td>
<td>Proficient in Mismatch Repair (n=25)</td>
</tr>
</tbody>
</table>

## Non-Colorectal Cancers

<table>
<thead>
<tr>
<th>Cohort C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient in Mismatch Repair (n=30)</td>
</tr>
</tbody>
</table>

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Mismatch repair testing was performed locally using standard IHC for MMR deficiency or PCR-based test for microsatellite instability
- Here we report and update from the original 13 CRC Cohort A patients reported at ASCO 2015
Key Eligibility for Cohorts A & B

- Histologically proven metastatic or locally advanced mismatch repair deficient colorectal solid tumor malignancy
  - IHC showing deficiency in MLH1, MSH2, MSH6, or PMS2
  - or microsatellite instability detected by PCR (instability in 2 or more loci); locally testing acceptable

- Measurable disease

- Patients with colon cancer must have received at least two prior cancer therapy regimens.

- ECOG Performance Status of 0-1

- No prior anti-PD-1/PD-L1/PD-L2, anti-CD137, anti-OX-40, anti-CD40, anti-CTLA4
# Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MMR-deficient CRC n=28</th>
<th>MMR-proficient CRC n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)– years</td>
<td>49 (26-75)</td>
<td>62 (32-79)</td>
</tr>
<tr>
<td>Gender-female no. (%)</td>
<td>13 (46)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>ECOG PS-zero</td>
<td>5 (18)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Liver Mets</td>
<td>14 (50)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Median Prior Regimens</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (54)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No</td>
<td>2 (7)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (39)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Best Radiographic Response

MMR-proficient CRC
MMR-deficient CRC

% Change from Baseline SLD
<table>
<thead>
<tr>
<th>Type of Response-no (%)</th>
<th>MMR-deficient CRC</th>
<th>MMR-proficient CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>3 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>13 (46)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stable Disease (Week 12)</td>
<td>9 (32)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1 (4)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Not Evaluable(^1)</td>
<td>2 (7)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Objective Response Rate (%)</td>
<td>16 (57)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>95% CI</td>
<td>39 - 73</td>
<td>0 - 13</td>
</tr>
<tr>
<td>Disease Control Rate (%)</td>
<td>25 (89)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>95% CI</td>
<td>73 - 96</td>
<td>6 - 35</td>
</tr>
<tr>
<td>Median Follow Up (mos)</td>
<td>9.3</td>
<td>6</td>
</tr>
</tbody>
</table>

\(^1\)Patients were considered not evaluable if they did not undergo a 12 week scan
Progression-free Survival

- MMR-deficient (mPFS = not reached)
- MMR-proficient (mPFS = 2.3 mos)
Summary

• PD-1 blockade with pembrolizumab is highly active in MRD metastatic colorectal cancer

• Complete and durable responses are seen in more than 50% of patients

• Currently, 5 patients (18%) have reached the two year mark and anti-PD-1 has been held. These patients are under active surveillance.

• Single agent studies with pembrolizumab in 1st line MRD metastatic colorectal cancer are actively recruiting
PD-1 Blockade in Mismatch Repair Deficient Cancer Independent of Tumor Histology


The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Ohio State University Comprehensive Cancer Center, Columbus, OH
Providence Cancer Center, Portland, OR
Stanford University School of Medicine, Stanford, CA
University of Pittsburgh, Pittsburgh, PA
National Cancer Institute, Bethesda, MD
Merck & Co., Inc., Kenilworth, NJ

PRESENTED AT: ASCO ANNUAL MEETING '16
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Study Design

**Colorectal Cancers**

- Cohort A: Deficient in Mismatch Repair (n=25)

**Non-Colorectal Cancers**

- Cohort B: Proficient in Mismatch Repair (n=25)
- Cohort C: Deficient in Mismatch Repair (n=21)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Mismatch repair testing was performed locally using standard IHC for MMR deficiency or PCR-based test for microsatellite instability
Study Design

Cohort C
Deficient in Mismatch Repair (n=21)

Ongoing Expansion (n=+50)

Non-Colorectal Cancers Deficient in Mismatch Repair (n=30)
Key Eligibility for Cohort C

- Histologically proven metastatic or locally advanced mismatch repair deficient non-colorectal solid tumor malignancy
  - mismatch repair deficiency documented by IHC showing deficiency in MLH1, MSH2, MSH6, or PMS2 or microsatellite instability detected by PCR (instability in 2 or more loci); testing performed locally
- Measurable disease
- Progressive disease
- Received at least 1 prior therapy
- ECOG 0-1
- Adequate renal, hepatic, bone marrow reserve
- Brain mets allowed if treated and stable (no imaging required)
- No prior anti-PD-1/PD-L1/PD-L2, anti-CD137, anti-OX-40, anti-CD40, anti-CTLA4
- No HIV, hepatitis B, hepatitis C
- No autoimmune disease or active steroids
### Baseline Characteristics

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<thead>
<tr>
<th>Characteristic</th>
<th>MMR-deficient non CRC n=30 (%)</th>
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<tr>
<td>Median Age (range)– years</td>
<td>56 (36-92)</td>
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<tr>
<td>Gender-female no. (%)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>ECOG PS-zero</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Primary-location</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Ampullary/biliary</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Gastric</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Other (prostate, thyroid, sarcoma)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Liver Mets</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Median Prior Regimens</td>
<td>2</td>
</tr>
<tr>
<td>Germline mutation or Lynch Syndrome</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (17)</td>
</tr>
<tr>
<td>No</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (60)</td>
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Responses

Endometrial

Pancreatic

Baseline

Week 12
# Objective Responses

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<thead>
<tr>
<th>Type of Response-no (%)</th>
<th>MMR-deficient</th>
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**Objective Response Rate (%)**
- 16 (53)
- 95% CI: 36-70

**Disease Control Rate (%)**
- 21 (70)
- 95% CI: 52 - 83

**Median Follow Up**
- 10 mos

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1 Patients were considered not evaluable if they did not undergo a 12 week scan.
Target Lesion Measurements

% Change from Baseline SLD

-100 -50 0 50 100

gastric
ampullary/biliary
sarcoma
small bowel
endometrial
pancreatic
prostate

L Diaz, ASCO 2016
Progression-Free and Overall Survival

PFS = Non-estimable (NE)
PFS rate (1 yr) = 57%

OS = Non-estimable (NE)
OS rate (1 yr) = 81%
Conclusions

- Mismatch repair deficiency can be determined using existing commercially available tests.

- Mismatch repair deficient cancers are responsive to checkpoint blockade with anti-PD1.

- Durable clinical responses are noted across tumors with mismatch repair deficiency including endometrial, gastric, duodenal, pancreatic, ampullary, and biliary cancers.

- Expected toxicities are manageable.
Ongoing Clinical Studies

• A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects With Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma (KEYNOTE-164)
  – Locally confirmed MMR deficient or MSI status

• A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)
  – Any advanced solid tumor, with the exception of colorectal carcinoma (CRC), which is Microsatellite Instability (MSI)-High (MSI-H)
Conclusions

• There is a strong biological rationale for anti-PD-1 pembrolizumab therapy of MSI cancer, regardless of tumor histology

• Clinical trials have demonstrated durable clinical efficacy of pembrolizumab for the treatment of MSI-H colorectal and non-colorectal cancer

• Challenges in drug development for a tumor-agnostic indication
  – Study design for providing evidence of clinical efficacy (vs traditional randomized controlled studies)
  – Identification of study population