PD-1 antibody: CT-011, BMS936558

Presented by:
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Disclosure

• Scientific advisory board member, Curetech

• Thanks to Mario Sznol, Suzanne Topalian, and Jeff Weber, for contributing slides for this presentation
Programmed death-1 (PD-1) is an inhibitory receptor expressed on T cells after activation (Figure 1)\(^1\)

- Down-regulates T-cell activity upon binding to its ligand, PD-L1, on APCs
- Maintains peripheral tolerance, protecting tissues from autoimmune damage

Many tumors constitutively express PD-L1\(^2\)

Overexpression of PD-L1 by RCC associated with:\(^2\)

- Impaired antitumor immunity
- More aggressive disease
- Shorter survival


Slide courtesy of D McDermott, Mario Sznol
Experimental Agents

- CT-011 (Curetech)
  - A humanized anti PD-1 IgG1k

- MDX 1106 (BMS 936558/ONO 4538)
  - A fully human anti PD-1 IgG4

- Merck/Schering Plough Ab (MK-3475/SCH 900475)
  - Dose finding and efficacy trial CT01295827 Mar 2011
Experimental Agents

MDX 1106 (BMS 936558/ONO 4538)

- A fully human anti PD-1 IgG4
- High affinity binding to human and cynomolgus PD-1
- Blocks binding of PD-1 to PD-L1 and PD-L2
- *In vitro*, promotes cytokine production/proliferation
  - human allogeneic mixed lymphocyte reaction (MLR)
  - Ag reactive T cells in response to CMV or tumor Ag
- Reverses T\(_{reg}\) mediated suppression of allogeneic MLR
Safety of PD-1 antibody

Phase I study (CA209-003) with BMS-936558

- MTD not reached at 1, 3, 10 mg/kg
- No apparent relationship btw dose and AEs
- Drug related grade 3/4 Aes:
  - Lab abnormalities (4.0%)
  - Endocrine disorders (2.4%)
  - Fatigue (1.6%)
- 1 treatment related death (sepsis assoc with drug-related pneumonitis)

Sznol M, et al. 2010 ASCO, updated by D McDermott
60 yr/male patient
• diagnosed in 2002
• Intermittent responses but eventual progression on multiple prior combination chemotherapies and radiation therapy

A: Baseline
B: Cycle 2 assessment

J. Brahmer, Johns Hopkins University
Approx. 30% CR/PR in MEL & RCC (ASCO 2010, GU ASCO 2011)

In 46 MEL pts, no correlation of dose with response or toxicity

Topalian AACR 2011
Clinical responses CA209-003

No responses with prostate (n=12) or colorectal cancers (n=6)

Summarized from data courtesy of Mario Sznol
Experimental Agents

- CT-011
  - A humanized anti PD-1 IgG1k
  - Binds human and murine PD-1
  - Induces T and NK cell mediated tumor regression in experimental human and murine melanoma and other tumor models

- MOA:
  - Enhances and prolongs the activity and duration of tumor specific immune responses.
  - Induces tumor-specific immunological memory
CT-011 targets a conserved epitope on the mouse and human PD-1 receptors

IP designates immunoprecipitating agent used
CT-011 binds to activated Human T cells

A

Normal CD8+

Donor 1

8.6% 1.6%

Donor 2

15.1% 2.7%

48hr Activated CD8+

Donor 1

17.6% 19.9%

Donor 2

11.6% 36.4%

CT-011

B

Normal CD4+

CD69

16% 11%

21% 52%

17% 59%

24hr Activated

48hr Activated CD4+

CT-011
mCT-011 induces regression of lung metastases of murine B16 melanoma, 3LL lung carcinoma and MCA fibrosarcoma

- Mice inoculated I.V. with B16 melanoma, 3LL Lewis Lung Carcinoma or MCA Fibrosarcoma on day 0. Mice treated I.V. with mCT-011 once on day 14 at 10ug/mouse. Lungs examined on Day 24
- B16, n=16, 3LL, n=11, MCA, n=9. p<0.001
mCT-011 enhances survival of B16 melanoma bearing mice

Tumor injected I.V. on day 0. mCT-011 (BAT) administered I.V. at 10ug/mouse once on day 14
mCT-011 enhances anti-tumor activity of human lymphocytes against lung metastasis of human melanoma

Human PBMC-engrafted SCID mice inoculated I.V. with human SK-mel 28 melanoma. mCT-011 I.V. 10µg/mouse on day 14 and 0.01µg/mouse on day 21. Lung evaluated for metastases day 24. n=16-18 mice; (Control/none, n=2 mice)

![Graph showing lung weight (g) comparison between Control and mCT-011 treatments]

<table>
<thead>
<tr>
<th></th>
<th>Lung wt (g)</th>
<th>Number of mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control None</td>
<td>~1000 mg</td>
<td>~250 No. mets</td>
</tr>
<tr>
<td>Control Human Ly</td>
<td>~400 mg</td>
<td>~150 No. mets</td>
</tr>
<tr>
<td>mCT-011 Human Ly</td>
<td>~200 mg</td>
<td>~50 No. mets</td>
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</tbody>
</table>

- Human PBMC engrafted SCID mice inoculated with human SK-mel 28 melanoma 10µg/mouse mCT-011 injected I.V. once on day 10 post tumor inoculation; Lungs examined on day 24
Mice in CR from B16 melanoma 2 & 3 months post mCT-011 single treatment were re-challenged with B16 melanoma or 3LL lung carcinoma and tumor burden in the lungs was evaluated (by lung weight).
Combination Therapy of CT-011 and Oxaliplatin improves Tumor Control

- Tumor (CT26; CRC) injected S.C. on day 0 at \(10^6\) cells/mouse. \(n=9\).
- Oxaliplatin administered I.P. daily at 1mg/kg on days 4, 7-10, 14-17, 22-24
- CT-011 at 10mg/mouse administered I.V. weekly on days 11, 18, 25
CT-011: Preclinical Summary

- A humanized anti PD-1 IgG1k
- Binds mouse and human PD-1
- Enhances cytotoxicity against PD-L1+ targets by T and NK cells
- Enhances Th1 cytokine secretion, survival and migration of human NK cells and CD4+CD45RO+ T cells from normal donors and cancer patients
- Enhances tumor regression and overall survival of tumor bearing mice
- Induces memory protection against tumor re-challenge
- Single agent anti tumor effect in experimental models of melanoma, CRC, lung adenocarcinoma, fibrosarcoma, leukemia/lymphoma
- Synergistic efficacy in combination with chemotherapeutic agents, marketed antibodies (Rituximab), vaccines (cell, peptide, DNA) and Lenalidomide
Clinical Summary

CT-011: First in human study

- Open-label, single dose study (0.2, 0.6, 1.5, 3.0, and 6.0 mg/kg)
- 17 patients with advanced stage hematological malignancies:
  - Median age: 61 (range 20-78)
  - Gender: 11 females, 6 males
PK and PD Data

CT-011: Phase I Study Pharmacokinetic Results

- The pharmacokinetic profile was linear across all dose levels
- Median t½ of CT-011: 9-17d
- Median t½ for the 6 “responders” was higher (~15 days) than for the rest of the patients (~8 days)
- No apparent differences by gender/diseases
CT-011: Phase I Study Results

- Single administration of 0.2mg/kg to 6.0mg/kg CT-011 was safe and well tolerated;
  - No drug related serious adverse events,
  - No infusion-related adverse events,
  - No autoimmunity,
  - No cardiovascular, renal or liver toxicities
  - Most frequent AE- diarrhea (2pts)

- Clinical beneficial responses in 6/17 patients (1CR, 4DS, 1MR)
Preliminary analyses of flow cytometry data from the Phase II study in DLBCL patients

The study involved analyses of different CD marker combinations per-patient per-visit at 6 time-points during the study.

Preliminary analyses of the data indicates an increase in specific populations of CD4+ and CD8+ cells:

- Increase by **50%** (median, p<0.05) in absolute number (median ABS) of **effector/memory cells** $CD4^+CD45RO^+CD62L^−CCR7^−$ 6 weeks following first CT011 treatment

- Increase by **40%** (median, p<0.05) in the absolute number of $CD8^+CD62L^+CD127^+$ cells 24hrs following first CT011 treatment
Manufacturing and Availability

- CureTech manufactures CT-011
- Current manufacturing capacity is sufficient to support ongoing and planned clinical studies
CT-011: Ongoing clinical studies

- International Phase II study in DLBCL post transplant (US, India, Israel and South America)
- International Phase II study in Colorectal cancer in combination with FOLFOX vs. FOLFOX alone (US, EU, India, South America)
- Phase II study in Follicular Lymphoma in combination with Rituximab (US)
- Phase I/II study in patients with chronic infection of HCV Genotype I (Israel)
- Phase II study in Multiple Myeloma post autologous transplantation with/without DC/Vaccine (US and Israel)
- Phase II study in AML post autologous transplantation in combination with DC/Vaccine (US and Israel)
- Phase I/II study in patients with resected pancreatic cancer in combination with gemcitabine (US)
Agent Development Pathway: Clinical Studies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Phase I/II</th>
<th>Phase II</th>
<th>Results projected in</th>
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<tbody>
<tr>
<td>DLBCL</td>
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<tr>
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<td></td>
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<td>Q4.13</td>
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<tr>
<td>Metastatic Melanoma</td>
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Directions for Clinical Investigation

• Monotherapy in melanoma, RCC, others
• Combinations
  – Cancer vaccines
    • in progress w/ BMS ab & HLA-A2 peptides: Moffitt, Weber
    • Consider long peptides, helper peptides, new adjuvants
  – Modulators of costimulation
    • Ipilimumab (ongoing); anti-CD137; anti-LAG-3
  – IL-2, IFN
  – Targeted molecular therapies
  – Cytotoxic therapy or radiation rx: Ag presentation
• B7-H1 expression as biomarker for response
Design of the proposed Phase II melanoma study

- Proposing participation in an imminent Phase II study in patients with metastatic melanoma
- Clinical centers interested in and capable of conducting correlative studies
- Multi-center, randomized, open label study
- Patients with metastatic melanoma
- CT-011 administered at 2 dosage levels, 1.5mg/kg and 6.0 mg/kg
- Approximately 50 patients/dose, 100 patients in total
Study Endpoints

PRIMARY ENDPOINT
Objective response rate (ORR) by Immune Related Response Criteria (iRC) in patients with metastatic melanoma treated with CT-011.

SECONDARY ENDPOINTS
✓ Safety and tolerability of CT-011
✓ Progression-free survival from time of randomization by iRC
✓ Overall survival from time of randomization
✓ Duration of response by iRC
✓ Immunogenicity of CT-011
✓ Correlative biological markers and activity (selected centers only)
Main Inclusion Criteria

- Age 18 to 75 years old
- Measurable, progressive Stage IV (M1a,b,c) melanoma
- ECOG of 0 or 1.
- ≥ 21d since surgery and/or radiation therapy and 4-6 weeks since last systemic therapy and have adequately recovered (to Grade 1) from adverse effects of these therapies.
- Permitted: Prior adjuvant interferon, GM-CSF, or cancer vaccines. Prior radiation therapy permitted if patient has un-irradiated metastatic sites.
- Brain metastases allowed if:
  - >4 wk from resection or stereotactic radiosurgery; MRI/CT within 3 wk fails to show progression; off steroids at least 2 wk.
  - ≥ 8 weeks since whole brain radiotherapy, if no tumor progression in the brain; asymptomatic.
Main exclusion criteria

- **Active autoimmune disease**, symptoms or conditions except vitiligo, type I diabetes, treated thyroiditis, asymptomatic laboratory evidence of autoimmune disease or mild arthritis requiring no therapy or manageable with NSAIDs;
- **Known major immunodeficiency**
- **Participation in any other clinical trial** involving another investigational agent within 4 weeks prior to first dosing of study agent, or anti-CTLA4 therapy within 6 weeks prior to first dosing. Any prior anti PD-1, anti PD-L1 or PD-L2 therapy.
- **Patients with clinically significant impairment of pulmonary function** due to major lung resection, chronic bronchitis or chronic obstructive pulmonary disease (COPD).
- **Patients on corticosteroids** (inhaled or oral steroids for treating mild to moderate asthma or allergies or topical steroids for localized -< 5% of body surface area- dermatitis are allowed) or any other type of immunosuppressive agent (e.g., methotrexate, chloroquine, azathioprine, cyclophosphamide)