THE EMERGING ROLE OF COMBINATION TUMOR IMMUNOTHERAPY

Holbrook Kohrt, MD PhD
Dept Medicine Div Oncology
Stanford Cancer Institute
Improving Survival with Combination Therapy

![Graph showing survival rates over time with and without combination therapy.](image)
Improving Survival with Combination Therapy

% Survival

Time

Control
Standard or Other Therapy
Anti-CTLA-4/Anti-PD-1/Anti-PD-L1
Improving Survival with Combination Therapy

% Survival vs Time

- Control
- Standard or Targeted Therapy
- Anti-CTLA-4/Anti-PD-1/Anti-PD-L1 Combination Therapies
Combination strategies: A ‘four-strike’ approach to cancer therapy

“We’ve found a mass. The good news is we have weapons of mass destruction.”

“I think you should be more explicit here in step two.”
Combination strategies: A ‘four-strike’ approach to cancer therapy

1. Removing Immune suppression
   - MDSC
   - Lymphodepletion
   - TGF-β
   - IL-23
   - Adenosine
   - IDO, iNOS, arginase-1
   - T reg cells
   - M2 Macrophages

2. Immunogenic cancer cell death
   - Conventional therapy
   - TRAIL-R agonists
   - Oncogene inhibitors
   - HDACi
   - Proteasome inhibitors
   - p53 rescue

3. Enhanced antigen presentation
   - CD40 agonists
   - TLR agonists (e.g. CpG ODNs)
   - Antigen-presenting cell
   - α-GalCer/α-C-GalCer

4. Blockade of immune-checkpoints
   - Agonists
   - Inhibitors
   - CTL
   - CTLA-4
   - PD-1
   - BTLA
   - B7H3-R
   - B7H4-R
   - CD28
   - ICOS
   - 4-1BB
   - OX40
   - CD27
   - CD30
   - HVEM
   - Immune-suppressive oncogenes (e.g. STAT3)
   - TGF-β
   - IL-6
   - IDO
   - IL-23
   - IL-10
   - Arg I
   - IL-13
   - iNOS
   - PGE₂
   - Adenosine
The Emerging Role of Combination Tumor Immunotherapy

Combination Immunotherapy To Improve Cancer Vaccines:

GVAX
**Improving Cancer Vaccines**

**Combining GVAX with Ipilimumab**

Irradiated tumour cell with GM-CSF

**Tumour cell**
- Immunogenic apoptosing cell
- Induction of cell death
- MHC class I/ PSA
- MHC class II/ TAA
- CD80/ CD86
- CD28
- T-cell receptor
- TAA-specific antibody
- IL-2

**CD4^+ T cell**

**CD8^+ T cell**

**Immature DC**

**Mature DC**

**GVAX-PCA**

**B cell**

**GM-CSF**

1a

2a

2b

2b'

1b

1c

1b'

1d

1d'

1e

1e'

1c'

2a

2b
IMPROVING CANCER VACCINES

COMBINING GVAX WITH IPILIMUMAB

Screening → Enrolment

Treatment

GVAX vaccinations every 2 weeks for a total of 13 vaccinations
Ipilimumab every 4 weeks for six infusions

Week 24

Follow-up

Follow-up visit 4 weeks after the last vaccination
Quarterly follow-up every 12 weeks for progression and survival

Graph showing patient numbers and their change from baseline (%).

Change from baseline (%) vs. Duration of stable disease by bone scan (months)

Legend:
- Escalation phase
- Expansion phase
GVAX Pancreas + Ipilimumab (BMS: Yervoy) Clinical Results*

- 30 patients with previously treated, locally advanced or metastatic pancreatic adenocarcinoma

<table>
<thead>
<tr>
<th></th>
<th>Ipi + GVAX Pancreas</th>
<th>Ipi Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median monthly overall survival</td>
<td>5.5 months</td>
<td>3.3 months</td>
</tr>
<tr>
<td>12 month overall survival</td>
<td>27%</td>
<td>7%</td>
</tr>
</tbody>
</table>

- Conclusion
  - Over 60% improvement in Overall Survival

*Dung T. Le, et al.
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   - PGE₂
   - Adenosine
The Emerging Role of Combination Tumor Immunotherapy

Combination Immunotherapy To Improve Today’s Current Therapy:

Radiation
Pro-Immunogenic Effects Of Radiation At Irradiated Site

Demaria & Formenti, Front Oncol 2012
Combination strategies: A 'four-strike' approach to cancer therapy

- SBRT (Cone-beam CT-guided radiotherapy)
- IL-2
- Antigen-presenting cells
- Cytokines and chemokines released
- Lymph node
- Activated effector cells
- Effector cells
- Non-irradiated tumor

Insert: Tumor cell
- Nucleus
- Golgi apparatus
- ER
- Mitochondria
- TAA (tumor-associated antigens)
- Peptide pools and mTOR
- Novel peptides
- Upregulation of MHC-1
- ICAM-1
- CD8
- TCR
- LFA-1
- ADHESION MOLECULES (ICAM-1 and DEATH RECEPTORS (Fas))
A Phase I/II Trial of Intratumoral Injection of CpG Oligonucleotides and Local Low Dose Radiation Therapy in Non-Hodgkin Lymphoma

**POPULATION**
- Low grade NHL

**ENDPOINTS**
- Safety/feasibility
- Clinical response
- T cell immune response
**In-Situ Vaccination: Background**

**CpG**

- Bacterial DNA
  
  \[\text{ACGTTTAGTTCGTACG} \downarrow \text{CATACGA}\]

- Vertebrate DNA
  
  \[\text{AGCTTGAGTC}^\text{mCG} \downarrow \text{GATGGGTAAGA}\]

- Immune system recognizes CpG through TLR-9 and activates DC and B cells

![Diagram showing interactions between CpG, TLR-9, Dendritic Cell, Tumor-specific T Cells, and B Cell Tumor]
Lymphoma Immunotherapy with CpG Oligodeoxynucleotides Requires TLR9 Either in the Host or in the Tumor Itself\textsuperscript{1}


Jiali Li,* Wenru Song,* Debra K. Czerwinski,* Bindu Varghese,* Satoshi Uematsu,* Shizuo Akira,* Arthur M. Krieg,* and Ronald Levy*
In-Situ Vaccination: Background

CpG + Cyclophosphamide

**In-Situ Vaccination**

**Clinical Trial Schema**

- **2x2Gy**
- **CpG 6mg**
- **biopsy**
- **local radiation**
- **CpG**
- **TLR-9**
- **B cell lymphoma**
- **CpG**
- **TLR-9**
- **dendritic cell**

**tumor response**

**immune response**
In-Situ Vaccination

Clinical Response

Brody JD et al., J Clin Oncol. 2010 Oct 1;28(28).
Pre-treatment 24 weeks

38 year old male with recurrent follicular lymphoma: Complete Response
63 year old male with recurrent follicular lymphoma: Partial Response
56 year old female with recurrent follicular lymphoma: Mixed Response (Stable Disease)
66 year old female with recurrent marginal zone lymphoma: Partial Response
**Clinical Response**

- pre-vaccine
- 12 weeks post-vaccine
- 52 weeks post-vaccine

62 year old female with recurrent follicular lymphoma: **Stable Disease** (with late improvement)
CLINICAL RESPONSE

pre-vaccine

52 weeks post-vaccine
**Immune Response**

*gated on CD8 T cells*

Brody JD et al., J Clin Oncol. 2010 Oct 1;28.

1.8%

8.8%

CD45RO

CD137

pre

post

Brody JD et al., J Clin Oncol. 2010 Oct 1;28(28).

Brody et al., JCO 2010
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   - CD28, CTLA-4, ICOS
   - 4-1BB, OX40
   - CD27, CD30, CD28
   - BTLA, B7H3-R, B7H4-R
   - Agonists, Inhibitors
   - Immune-suppressive
   - IL-6, IL-23, TGF-β, IL-10, Arg I
   - Oncogenes (e.g. STAT3), IDO, IL-13, iNOS, PGE₂
   - Adenosine
In situ vaccination by radiation

Demaria et al., IJROBP 2005
Formenti & Demaria, Lancet Oncol 2009
Pre-clinical testing of combinations of RT

Flt3L (Demaria et al., *Int J Radiat Oncol Biol Phys*, 2004). (one trial closed)

**anti-CTLA-4** (Demaria et al., *Clin Cancer Res* 2005; Matsumura et al., J Immunol 2008; Pilones et al., *Clin Cancer Res* 2009; Dewan et al., *Clin Cancer Res* 2009; Ruocco et al., J Clin Invest 2012) (two trials opening)

GVAX (Newcomb et al., Clin Cancer Res 2006)

anti-CD137 (Newcomb et al., Rad Res 2010)

**TLR7-agonist** (Dewan et al. Clin Cancer Res 2012, Epub Oct 9) (open trial NCT01421017)

anti-TGFβ (manuscript in preparation) (open trial NCT01401062)
**BRIEF REPORT**

**Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma**

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigeisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., RuthAnn Romnar, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnajdie, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

**SUMMARY**

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site. The abscopal effect may be mediated by activation of the immune system. Ipilimumab is a monoclonal antibody that inhibits an immunologic checkpoint on T cells, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). We report a case of the abscopal effect in a patient with melanoma treated with ipilimumab and radiotherapy. Temporal associations were noted: tumor shrinkage with antibody responses to the cancer-testis antigen NY-ESO-1, changes in peripheral-blood immune cells, and increases in antibody responses to other antigens after radiotherapy. (Funded by the National Institutes of Health and others.)
Combination Immunotherapy & Radiation

Dx: stage IV (pT1bN3M1a) NSCLC

concurrent ipilimumab (3mg/kg q 3wks x 4c) + RT (30Gy delivered in 5 fractions QOD)

August 2012

January 2013

Gemcitabine Vinorelbine

RT 30 Gy Ipilimumab

Jun-12 Sep-12 Dec-12

Progression (PET/CT) Progression (PET/CT) Response (PET/CT) Response (PET/CT)
Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study

**Design:**
- Phase 1 – Dose escalation: 3, 5 or 10 mg/kg ipi, then 3 or 10 mg/kg ipi + XRT (single dose of 8 Gy/lesion, up to 3 lesions per patient)
- Phase 2 – Cohort expansion: 10 mg/kg ± XRT cohorts

**Endpoints:**
- Safety
- PSA response at Day 85, overall PSA response, and tumor response by RECIST

**Response assessments:**
- PSA: Days 22, 43, 64, 85, then monthly
- Tumor: Day 85, then every 3 months

Number of patients with data = 65

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   - CD30
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   - PD-1
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   - B7H3-R
   - B7H4-R
   - Immune-suppressive oncoproteins
   - TGF-β
   - IL-6
   - IDO
   - IL-10
   - Arg I
   - IL-13
   - iNOS
   - PGE₂
   - Adenosine
Blocking CTLA-4 and PD-1

Activation (cytokines, lysis, proliferation, migration to tumor)

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)

Presented By Jedd D. Wolchok, MD, PhD at 2013 ASCO Annual Meeting
Clinical activity and safety of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients with advanced melanoma

Jedd D. Wolchok,¹ Harriet Kluger,² Margaret K. Callahan,¹ Michael A. Postow,¹ RuthAnn Gordon,¹ Neil H. Segal,¹ Naiyer A. Rizvi,¹ Alexander M. Lesokhin,¹ Kathleen Reed,² Matthew M. Burke,² Anne Caldwell,² Stephanie A. Kronenberg,¹ Blessing U. Agunwamba,¹ William Feely,³ Quan Hong,³ Christine E. Horak,³ Alan J. Korman,⁴ Jon M. Wigginton,³ Ashok Gupta,³ and Mario Sznol²

¹Ludwig Center at Memorial Sloan-Kettering Cancer Center, New York, NY; ²Yale University School of Medicine and Yale Cancer Center, New Haven, CT; Bristol-Myers Squibb, ³Princeton, NJ and ⁴Redwood City, CA

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of the author.
Ipilimumab and Nivolumab Clinical Experience in Patients with Advanced Melanoma

**Ipilimumab:** 3 mg/kg every 3 wk, 4 doses (Phase 3)
- ORR: 11%; 2 patients with CR\(^1\)
- Median OS: 10.1 mo;\(^1\) 4-year survival rate (Phase 2 studies): 18%\(^2\)
- Grade 3-4 related AEs: 23%; included diarrhea (5%) and colitis (5%)\(^1\)

**Nivolumab:** 0.1 mg/kg to 10 mg/kg every 2 wk, ≤48 doses (Phase 1b)
- ORR: 41%; 1 patient with CR (3 mg/kg)\(^3\)
- Median OS: 16.8 mo;\(^4\) 2-year survival rate: 43%\(^4\)
- Grade 3-4 related AEs: 14%; included diarrhea (1%), pneumonitis (1%), and hypophosphatemia (1%)\(^3\)

\(^4\) Sznol et al. ASCO 2013, oral presentation, abs CRA9006.
## Treatment-Related Adverse Events (≥10% of all patients)

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Event</th>
<th>Concurrent All Cohorts (n=53)</th>
<th>Sequenced All Cohorts (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gr</td>
<td>Gr 3-4</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>49 (93)</td>
<td>28 (53)</td>
</tr>
<tr>
<td>Rash</td>
<td>29 (55)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>25 (47)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (38)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (34)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (21)</td>
<td>0</td>
</tr>
<tr>
<td>†AST</td>
<td>11 (21)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>†ALT</td>
<td>11 (21)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>†Lipase</td>
<td>10 (19)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>†Amylase</td>
<td>8 (15)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (11)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>6 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (11)</td>
<td>0</td>
</tr>
</tbody>
</table>
Clinical Activity: Concurrent Regimen

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Nivolumab</th>
<th>Ipilimumab</th>
<th>Response Evaluable Patients n</th>
<th>CR n</th>
<th>PR n</th>
<th>Objective Response Rate % [95% CI]</th>
<th>Aggregate Clinical Activity Rate % [95% CI]</th>
<th>≥80% Tumor Reduction at 12 wk n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>3</td>
<td>3</td>
<td>14</td>
<td>1</td>
<td>2</td>
<td>21 [5-51]</td>
<td>50 [23-77]</td>
<td>4 (29)</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>17</td>
<td>3</td>
<td>6</td>
<td>53 [28-77]</td>
<td>65 [38-86]</td>
<td>7 (41)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td>5</td>
<td>40 [16-68]</td>
<td>73 [45-92]</td>
<td>5 (33)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>50 [12-88]</td>
<td>83 [36-100]</td>
<td>0</td>
</tr>
<tr>
<td>Concurrent</td>
<td>52</td>
<td>5</td>
<td>16</td>
<td></td>
<td></td>
<td>40 [27-55]</td>
<td>65 [51-78]</td>
<td>16 (31)</td>
</tr>
</tbody>
</table>

- With 1 mg/kg nivolumab + 3 mg/kg ipilimumab, 53% of patients had confirmed objective responses (3 CRs and 6 PRs)
- All 9 of these had ≥80% tumor reduction, 7 at 12 weeks and 2 at their first assessment, which was after week 12
- ≥80% tumor reductions appear infrequently (<10%) in the nivolumab and ipilimumab monotherapy experiences
Clinical activity: combination of nivolumab and ipilimumab therapy

Best responses in all evaluable patients

Concurrent Therapy

Sequenced Therapy
(nivolumab after prior ipilimumab)

Wolchok et al. ASCO 2013, abs 9012, oral presentation, Clinical Science Symposium, June 2.
Presented by: Jedd D. Wolchok, MD, PhD

Rapid and Durable Changes in Target Lesions

1 mg/kg nivolumab + 3 mg/kg ipilimumab

▲ First occurrence of new lesion

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

Pre-treatment

12 weeks
Evaluating PD-L1 status as a putative biomarker

<table>
<thead>
<tr>
<th>Therapy</th>
<th>PD-L1 Status</th>
<th>ORR</th>
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<tbody>
<tr>
<td>Nivolumab monotherapy (melanoma) (0.1-10 mg/kg)</td>
<td>+</td>
<td>41%  (7/17)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>14%  (3/21)</td>
</tr>
</tbody>
</table>

| Concurrent ipilimumab + nivolumab               | +            | 46%  (6/13) |
|                                                 | -            | 41%  (9/22) |
| Sequenced nivolumab (after ipilimumab)         | +            | 50%  (4/8)  |
|                                                 | -            | 8%   (1/13) |

PD-L1 Positivity rate = 45% (17/38, monotherapy), 37% (13/35, combination therapy), and 38% (8/21, sequenced therapy)
Therapeutic Opportunities: Combinations with PD-1 Pathway Blockade

- PD-1 pathway blockade + other immunoinhibitors
  - e.g., CTLA-4, TIM-3, LAG-3
- PD-1 pathway blockade + immunostimulators
  - e.g., anti-OX40, anti-4-1BB, IL-2, TLR ligands
- PD-1 pathway blockade + kinase inhibitors like Braf
- PD-1 pathway blockade + standards of cancer therapy
  - Synergy with chemotherapy or radiation
- PD-1 pathway blockade + cancer vaccine
  - Synergy between PD-1 blockade and therapeutic vaccination in chronic viral infection
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     - Adenosine
The Emerging Role of Combination Tumor Immunotherapy

Combination Immunotherapy To Improve Today’s Current Therapy:

Monoclonal Antibodies
The Emerging Role of Combination Tumor Immunotherapy

Stimulation of Natural Killer Cells with an Anti-CD137 Antibody Enhances the Efficacy of Trastuzumab, Cetuximab & Rituximab
DIRECT KILLING

ANTIBODY-TARGET BINDING

VACCINAL EFFECT

ANTIBODY DEPENDENT CELL MEDIATED
4-1BB (CD137)
Inducible Costimulatory Target On NK Cells
NOVEL THERAPEUTIC TARGET

IN VIVO VALIDATION OF anti-CD137 THERAPY
**In vivo Enhancement of Anti-Cancer Activity with αCD137 mAb**

- **CD20+ lymphoma**
- **Tumor challenge**
  - **Rituximab**
  - **αCD137 mAb**
- **SCID**

**Graph:**
- **Percent survival**
  - **Days after tumor inoculation**
  - **Rituximab**
  - **αCD137**
  - **No treatment**
  - **Rituximab + αCD137**

[Prepublished online Dec 30, 2010; doi:10.1182/blood-2010-08-301945]
**In vivo Enhancement of Anti-Cancer Activity with αCD137 mAb**

**HER2+/− Breast Ca**

- **Trastuzumab**
- **αCD137 mAb**

**Tumor challenge**

- Day 0
- Day 3
- Day 4

**Day 25**

- Trastuzumab
- Trastuzumab + αCD137

**Day 50**

- Trastuzumab
- Trastuzumab + αCD137

**Graph:**

- Tumor size (cm²) vs. Days after tumor inoculation

- Trastuzumab
- Trastuzumab + αCD137
**In vivo Enhancement of Anti-Cancer Activity with αCD137 mAb**

EGFR+ H&N Ca

Tumor challenge

Nude

Cetuximab

αCD137 mAb

Day 0

Day 21
(repeated weekly x 3)

Day 22

In the graph, the x-axis represents the days after tumor inoculation, ranging from 0 to 60. The y-axis represents the tumor size in mm², ranging from 0 to 1400. The graph shows the comparison of tumor size over time among different treatment groups:

- IgG
- αCD137
- Cetuximab
- Cetuximab + αCD137

The graph indicates that the combination of Cetuximab and αCD137 mAb results in a significant reduction in tumor size compared to the other treatment groups.
NOVEL THERAPEUTIC TARGET & POTENTIAL BIOMARKER

PHASE 0 STUDY OF CD137

NCT01114256
**Bedside to Bench Lessons Critical to Clinical Translation – Time Post Trastuzumab**

**HER2+ Breast Cancer**

**Trastuzumab**

**NK cell CD137 expression**
Enhancing ADCC through \textit{Gamma-Delta} T Cell Stimulation – Applying Approved Therapies

- 
  - BrHPP
  - \(\gamma\delta T\) cell
  - NK cell
  - CD137 ligand
  - FcR
  - PAgS
  - Bisphosphonates
  - Tumor Ag
  - Inhibition of Cytotoxicity
  - Stimulation of Cytotoxicity

Increased ADCC
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations

- Tumor
- Mφ
- CD47
- αCD47
- FcR
- SIRPα
- IgG
- Anti-CD47
- Rituximab
- Anti-CD47+Rituximab
- Treatment: Day 10
- Complete Remission=5/8
- Relapse=0/5
- Percent survival
- Days

Image: Cancer Center, Stanford Hospital & Clinics

Call 142, 699-713, September 3, 2010
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations

Activated monocyte or dendritic cell

IL-15

IL-15Rα

Endocytic vesicle

IL-15–IL-15Rα recycling

Trans-presentation of IL-15

CD8+ T-cell or NK cell

Total NK Cells

Fold change in absolute count relative to day-7

Control

50μg/1 kd/dx12
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations

- αLy49C/I increases anti-tumor activity of anti-CD20 mAb in-vivo
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations

- Tumor
  - HLA class I
  - αKIR

- NK cell
  - KIR
  - FcR

- Tumor
  - PDL1
  - αPD1

- NK cell
  - PD1 Receptor
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations

Phase II Safety and Efficacy Study of CT-011, a Humanized Anti-PD-1 Monoclonal Antibody, in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma (NCT00904722)

- Single arm phase II trial to determine the safety and efficacy of CT-011 and rituximab in patients (pts) with relapsed FL
- CT-011 was dosed at 3 mg/kg IV every 4 weeks (wks) for 4 infusions and rituximab was dosed at 375 mg/m2 IV weekly for 4 wks starting 2 wks after the first infusion of CT-011. was 88 days.
- Of 29 pts eligible for efficacy analysis, 19 pts had an objective response for an ORR of 66%. CR was observed in 15 (52%) and PR in 4 (14%). Altogether, 25 (86%) pts had measurable tumor regression. Median time to response was 88 days.
Exciting Future of Antibody Therapies

Direct Killing

Antibody-Target Binding

Antibody-dependent Cell-mediated Cytotoxicity (ADCC)

Vaccinal Effect

CD20

Lymphoma

NK

DC

T

Exciting Future of Antibody Therapies

Direct Killing

Antibody-Target Binding

Antibody-dependent Cell-mediated Cytotoxicity (ADCC)

Vaccinal Effect
Combination strategies: A ‘four-strike’ approach to cancer therapy

1. Removing Immune suppression
   - MDSC Lymphodepletion
   - TGF-β
   - IL-23
   - Adenosine
   - IDO, iNOS, arginase-1
   - M2 Macrophages

2. Immunogenic cancer cell death
   - Conventional therapy
   - TRAIL-R agonists
   - Oncogene inhibitors
   - HDACi
   - Proteasome inhibitors
   - p53 rescue

3. Enhanced antigen presentation
   - CD40 agonists
   - TLR agonists (e.g. CpG ODNs)
   - Antigen-presenting cell
   - α-GalCer/α-C-GalCer

4. Blockade of immune-checkpoints
   - CTL
   - CD28
   - CTLA-4
   - 4-1BB
   - OX40
   - CD73
   - HVEM
   - BTLA
   - B7H3-R
   - B7H4-R
   - Agonists
   - Inhibitors
   - Immune-suppressive
   - Oncogenes
   - (e.g. STAT3)
   - TGF-β
   - IL-6
   - IDO
   - IL-10
   - Arg I
   - IL-13
   - iNOS
   - PGE2
   - Adenosine

Stanford Cancer Center
Stanford Hospital & Clinics
The Emerging Role of Combination Tumor Immunotherapy

“We’ve found a mass. The good news is we have weapons of mass destruction.”

“I think you should be more explicit here in step two.”
The Emerging Role of Combination Tumor Immunotherapy

Promising combinations with immunotherapy include:

(a) Combination radiation and anti-CTLA4 antibody
(b) Combination cancer vaccine and anti-CTLA4 antibody
(c) Combination anti-CTLA4 antibody and anti-PD1 antibody
(d) All of the above
The Emerging Role of Combination Tumor Immunotherapy

Limitations to combinations of immunotherapy include:

(a) Low toxicity
(b) Low efficacy
(c) High cost
(d) High efficacy
(e) a and b
The combination of anti-CTLA4 antibody and anti-PD1 antibody is promising for patients with:

(a) Melanoma
(b) Lymphoma
(c) Colorectal carcinoma
(d) Mycosis fungoides
(e) Prostate cancer
The Emerging Role of Combination Tumor Immunotherapy

Tumor responses at distant systemic sites following local radiation is known as the _______ effect.

(a) Warburg
(b) Heisenberg
(c) Abscopal
(d) Adaptive immune
(e) Innate immune
The combinations of anti-CD137 antibody and monoclonal antibodies are promising for patients with:

(a) HER2+ breast cancer
(b) CD20+ lymphoma
(c) EGFR+ colorectal carcinoma
(d) EGFR+ head and neck cancer
(e) All of the above
NOVEL TARGET

IDENTIFICATION OF CD137
Induction of CD137 on NK Cells

- Rituximab induces CD137 expression on NK cells in the presence of CD20+ tumor
- Trastuzumab induces CD137 expression on NK cells in the presence of HER+ tumor
- Cetuximab induces CD137 expression on NK cells in the presence of EGFR+ tumor
**EGFR**⁺ Head & Neck
HER2⁺ Breast
CD20⁺ NHL (n=165)

NK cell CD137 expression

%CD137⁺ NK cells

Pre-mAb | Post-mAb
EGFR⁺ Head & Neck
HER2⁺ Breast
CD20⁺ NHL
(n=165)

NK cell
CD137 expression

p<.001
EGFR⁺ Head & Neck HER2⁺ Breast CD20⁺ NHL (n=7) FNA

NK cell CD137 expression

%CD137⁺ NK cells

Pre-cetuximab Post-cetuximab
NK cell CD137 expression in HER2+ Breast Cancer.

**Minimally Previously Treated**
(<5 cycles of trastuzumab)

**Heavily Previously Treated**
(>25 cycles of trastuzumab)
BEDSIDE TO BENCH LESSONS CRITICAL TO CLINICAL TRANSLATION – HER2 LEVEL

HER2+ Breast Cancer

NK cell CD137 expression

Trastuzumab

HER2 Level High

HER2 Level Low
Pre-rituximab  Post-rituximab

CD137+ NK cells

CD20+ Non Hodgkin Lymphoma

CD20+ NHL

Rituximab (6h infusion)

NK cell CD137 expression

≥10% Circulating Tumor Cells

<10% Circulating Tumor Cells

p < .001
**Bedside to Bench Lessons Critical to Clinical Translation – FcγRIIIa Polymorphism**

<table>
<thead>
<tr>
<th></th>
<th>No Tumor</th>
<th>HER18</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG Control</td>
<td>7.46%</td>
<td>11.14%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>0.21%</td>
<td>1.28%</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>11.14%</td>
<td>4.24%</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>4.44%</td>
<td>4.44%</td>
</tr>
</tbody>
</table>

**NK cell CD137 expression**

- **FcγRIIIa**
  - V/V
  - V/F
  - F/F

- **Trastuzumab HER18**
  - V/V
  - F/V
  - F/F

- **NK cell CD137 expression**
  - CD56
  - CD137
**Bedside to Bench Lessons Critical to Clinical Translation – FcγRIIIα Polymorphism**

- **EGFR+** Head & Neck
- **HER2+** Breast
- **CD20+** NHL (n=165)

### NK cell CD137 expression

- **Cetuximab**
- **Trastuzumab**
- **Rituximab**

**Absolute Δ in % CD137+ NK cells**

- F/F
- V/F or V/V

**FcγRIIIA-158 Polymorphism**