Raising the Tail of Cancer Survival Curves with Immunotherapy

Siwen Hu-Lieskovan, MD, PhD
Director, Solid Tumor Immunotherapy
Huntsman Cancer Institute at University of Utah

Nevada Cancer Control Summit
Sep 16, 2019
Disclosures

- Consulting: Amgen, Merck, Genmab, Xencor, BMS
- Research Support: BMS, Merck, Vaccinex
- Contracted Research: Pfizer, Plexxikon, Genentech, Neon Therapeutics, Nektar, Astellas, F Star, Xencor
Significant Improvement of Overall Survival for Metastatic Melanoma in the Past 10 Years

Different phase of T cell activation:
- Priming phase: anti-CTLA4
- Effector phase: anti-PD1

MHC = major histocompatibility complex; TCR = T-cell receptor; TME = tumor microenvironment

Image adapted from Abril and Ribas, *Cancer Cell Snapshot 2017*
Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action

Different phase of T cell activation:
- Priming phase: anti-CTLA4
- Effector phase: anti-PD1

MHC = major histocompatibility complex; TCR = T-cell receptor; TME = tumor microenvironment
Image adapted from Abril and Ribas, Cancer Cell Snapshot 2017
Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action

Different phase of T cell activation:
- Priming phase: anti-CTLA4
- Effector phase: anti-PD1

MHC = major histocompatibility complex; TCR = T-cell receptor; TME = tumor microenvironment
Image adapted from Abril and Ribas, Cancer Cell Snapshot 2017
Increase in TIL in most patients treated with anti-CTLA4 (tremelimumab) regardless of tumor response.

CTLA4 blockade brings T cells into tumors.
CTLA4 blockade diversifies peripheral T cell responses

CTLA4 Blockade Broadens the Peripheral T-Cell Receptor Repertoire

Lidia Robert1, Jennifer Tsoi2, Xiaoyan Wang1,3, Ryan Emerson7,8, Blanca Horvat1,9, Thirle Chodron1, Stephen Mok1,2, Rong Rong Huang8, Alistair J. Cochran4, Begonia Comin-Anduix1,9, Richard C. Koya6,8, Thomas G. Graeber7,9, Harlan Robins7,9, and Antoni Ribas1,2,6,8

Improved Survival with T Cell Clonotype Stability After Anti–CTLA-4 Treatment in Cancer Patients

Edward Cha,1 Mark Klinger,2 Yafei Hou,1 Craig Cummings,2 Antoni Ribas,3 Malek Faham,2 Lawrence Fong1,5

Clin Cancer Res; 20(9) May 1, 2014

Ipilimumab

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O’Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sotman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassol, M.D., Wallace Akerman, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Longan, M.D., Julia M. Vausel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lobbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.


Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O’Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michael Lotem, M.D., Kaan Harmankaya, M.D., Ranny Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action

Different phase of T cell activation:
- Priming phase: anti-CTLA4
- Effector phase: anti-PD1

MHC = major histocompatibility complex; TCR = T-cell receptor; TME = tumor microenvironment
Image adapted from Abril and Ribas, Cancer Cell Snapshot 2017
Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action

Different phase of T cell activation:
- Priming phase: anti-CTLA-4
- Effector phase: anti-PD1

MHC = major histocompatibility complex; TCR = T-cell receptor; TME = tumor microenvironment
Image adapted from Abril and Ribas, Cancer Cell Snapshot 2017
Anti-CTLA-4 and Anti-PD-1/L1 Mechanisms of Action

Different phase of T cell activation:
• Priming phase: anti-CTLA4
• Effector phase: anti-PD1

MHC = major histocompatibility complex; TCR = T-cell receptor; TME = tumor microenvironment
Image adapted from Abril and Ribas, Cancer Cell Snapshot 2017
Nivolumab in Previously Untreated Melanoma without BRAF Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Henberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalciuc, M.D., Vanna Chiarion-Sileni, M.D., Corinelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omar Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nagatke Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*
Response to anti-PD1 Therapy requires both CD4 and CD8 cells

Both CD4 and CD8 cells are required in the response to PD1 blockade in a syngeneic murine melanoma model.

Hu-Lieskovan, et al. ASCO 2018
Clinical Success of PD-1 Checkpoint Blockade --- Durable Responses but only in a Minority of Patients

<table>
<thead>
<tr>
<th>FDA Approved Indications</th>
<th>Anti-PD1</th>
<th>Anti-PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s (65-85%)</td>
<td>Pembrolizumab</td>
<td>Atezolimumab</td>
</tr>
<tr>
<td>Melanoma (35-40%, 60% w combo)</td>
<td>Nivolumab</td>
<td>Avelumab</td>
</tr>
<tr>
<td>MSI-H or dMMR Solid tumors (40%)</td>
<td></td>
<td>Durvalumab</td>
</tr>
<tr>
<td>Merkel CC (32%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal CC (20%, 42% w combo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC (20-25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder Ca (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNSCC (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric CA (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNBC (18%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Activities seen in other tumors types

- Esophageal SCC (30%, PDL1>1%)
- Ovarian Ca (15%)

FDA Approved Indications

- Hodgkin’s (65-85%)
- Melanoma (35-40%, 60% w combo)
- MSI-H or dMMR Solid tumors (40%)
- Merkel CC (32%)
- Renal CC (20%, 42% w combo)
- NSCLC (20-25%)
- Bladder Ca (15%)
- HNSCC (15%)
- HCC (14%)
- Gastric CA (14%)
- SCLC (12%)
- TNBC (18%)

Clinical Success of PD-1 Checkpoint Blockade --- Durable Responses but only in a Minority of Patients
The Clinical Challenge

How to help the “Non-Responders”?
Resistance Mechanisms to Immunotherapy

Intrinsic Mechanisms

- Primary or adaptive resistance
  - Alteration of signaling pathways:
    - + MAPK
    - + PI3K
    - + WNT
    - + IFN
  - Lack of antigenic mutations
  - De-differentiation with loss of tumor antigen expression
  - Alterations in antigen processing machinery
  - Constitutive PD-L1 expression
  - Loss of HLA expression

- Acquired resistance
  - Escape mutations in IFN signaling
  - Loss of target antigen expression, e.g., ACT

Extrinsic Mechanisms

- Lymph node
  - TIM3
  - LAG3
  - CD80/CD86
  - CTLA4
  - PD-1
  - PD-L1

- Tumor microenvironment
  - MΦ/II
  - MDSO
  - CSF-1
  - CSF-1R
  - Adenosine
  - TGFβ
  - PD-L1
  - Tregs

Strategies To Overcome Resistance

Turn on Engine

**Neoantigen Quantity**
- Chemo
- Radiation
- Epigenetic Modulation

**Neoantigen Quality**
- TAA Vaccine
- Neoantigen Vaccine
- Engineered specificity

**Antigen Presentation/ T Cell Priming**
- DC vaccine
- Oncolytic virus
- TLR/STING agonists
- Cytokines
- Anti-CTLA4
- Anti-CD40

Fuel the Tank

- Anti-GITR
- Anti-41BB/CD137
- Anti-OX40
- Anti-ICOS

Take Away Barrier

- IDO Inhibitor
- CSF1R inhibitor
- Adenosine R inhibitor
- TGFβ inhibitor
- VEGF inhibitor
- PI3Kg inhibitor

Block the Stop Sign

- Anti-PD-1/L1
- Anti-TIM3, anti-LAG3
- Anti-TIGIT
Heterogenous Immune Escape Mechanisms in Each Patient

Each Object is Symbolic of a Patient
Sort Patients Based on Biology before Combo Testing

Heterogenous Immune Escape Mechanisms in Each Patient

Each Object is Symbolic of a Patient
Three Patterns of Response to Immunotherapy

Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types ($p<0.001$). Yarchoan, Hopkins, Jaffee, NEJM 2017
High Response Rate To PD-1 Blockade In Patients With Desmoplastic Melanoma

Best ORR = 70%
(Median f/u 18mon, CI 57-82%)

- 18 CR (none progressed)
- 22 PR (9 progressed later)
- 5 SD (2 progressed later)
- 12 PD

3 pts w/ isolated PD (2 PR, 1 PD) received surgical resection and had NED for 1.8, 5.2 and 5.3 years

Progression free survival (PFS),
 n = 57, median not reached,
range = 1.2 - 56 months

Overall survival (OS),
N = 57, median not reached,
range = 3.6 - 64 months

- Ten Academic Centers
- Over 1000 cases of advanced melanoma
- 57 patients with advanced DM who received anti-PD-1/L1 therapy identified.

Eroglu, Zaretsky, *Hu-Lieskovan,*Ribas, etc. Nature, 2018
* Corresponding authors
S1512: A Phase II Trial of PD-1 Blockade With Pembrolizumab in Patients With Resectable or Unresectable Desmoplastic Melanoma (DM)

Baseline

3 weeks later

5 months later

Antoni Ribas, MD, PhD
Grace Cherry, NP
S1512: A Phase II Trial of PD-1 Blockade With Pembrolizumab in Patients With Resectable or Unresectable Desmoplastic Melanoma (DM)

1) Confirm efficacy of pembrolizumab in desmoplastic melanoma patients
2) Explore the possibility of using this effective treatment early before surgery, even if the disease is considered resectable,

Cohort A - Resectable DM. Primary endpoint: pCR rate with neoadjuvant pembrolizumab.

Cohort B - Unresectable DM. Primary endpoint: CR rate with pembrolizumab

Study Chair: Kari Kendra, MD
Translational Lead: Siwen Hu-Lieskovan, MD
Statisticians: James Moon; Mike Wu, PhD
Protocol Coordinator: Danae Campos

Open at Huntsman!

Long term evaluation of biomarkers for PD-1 Blockade in NSCLC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LTB (n=5)</th>
<th>All others (n=33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutational Load</td>
<td>173 (104-261)</td>
<td>83 (48.5-235)</td>
<td>0.530</td>
</tr>
<tr>
<td>CD8</td>
<td>9.5 (5.5-15)</td>
<td>4 (2-8.5)</td>
<td>0.106</td>
</tr>
<tr>
<td>PD-L1</td>
<td>72 (55-77)</td>
<td>16 (6.5-45.5)</td>
<td>0.029</td>
</tr>
<tr>
<td>CD4</td>
<td>2 (1.05-14)</td>
<td>3.2 (1-8)</td>
<td>0.763</td>
</tr>
<tr>
<td>Age</td>
<td>59 (59-68)</td>
<td>68 (60-74)</td>
<td>0.424</td>
</tr>
<tr>
<td>Male</td>
<td>4 (80.0%)</td>
<td>18 (54.5%)</td>
<td>0.374</td>
</tr>
<tr>
<td>EGFR Mutations</td>
<td>0 (0.0%)</td>
<td>9 (28.1%)</td>
<td>0.553</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>3 (60.0%)</td>
<td>18 (54.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Squamous</td>
<td>1 (20.0%)</td>
<td>7 (21.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>At Least One Line Therapy</td>
<td>3 (60.0%)</td>
<td>27 (81.8%)</td>
<td>0.279</td>
</tr>
</tbody>
</table>
## Patterns of TME Biology and Potential Strategies

<table>
<thead>
<tr>
<th>Patterns</th>
<th>More Prevalent in</th>
<th>Unique Considerations</th>
<th>Strategies</th>
<th>Examples</th>
</tr>
</thead>
</table>
| I: TMB High & Inflammation High | Melanoma Cutaneous SCC MMR-d Cancers | • Plenty of neoantigens but may not be high quality  
• Exhausted T cells  
• PD-1 is not the main checkpoint  
• Intrinsic mutations | • Increase quality of neoantigens  
• Decrease T cell Exhaustion  
• Other immune checkpoints  
• Tumor Intrinsic Resistance (JAK1/2, B2M, WNT)  
• Improve TME  
• Microbiome? | Neoantigen vaccine  
aCD137, aOX40,aGITR, aICOS  
aTIGIT, aTIM3, aLAG3  
TLR9 agonists? PEG IL2?  
VEGFi, MAPKi, PI3Ki, IDOi, … |
| II: TMB Medium & Inflammation Low to Medium | NSCLC HNSCC HCC Gastric CA | • Not enough high quality neoantigens  
• Defects in priming | • Increase quantity of neoantigens or exposure  
• Increase T cell priming  
• Improve TME  
• Microbiome? | Oncolytic virus, TLR/STING agonists, hypomethylation agents, …  
aCTLA4, aCD40  
VEGFi, MAPKi, PI3Ki, IDOi, … |
| III: TMB Low & Inflammation Low to None | MMR-p CRC Pancreatic CA Prostate CA | • Low or no neoantigens to trigger anti-tumor response | • All of the above  
• Engineered specificity  
• Improve TME  
• Microbiome? | All of the above  
bi-specific, TCR/CAR ACT  
VEGFi, MAPKi, PI3Ki, IDOi, … |
# Patterns of TME Biology and Potential Strategies

<table>
<thead>
<tr>
<th>Patterns</th>
<th>More Prevalent in</th>
<th>Unique Considerations</th>
<th>Strategies</th>
<th>Examples</th>
</tr>
</thead>
</table>
| I: TMB High & Inflammation High| Melanoma Cutaneous SCC MMR-d Cancers | • Plenty of neoantigens but may not be high quality  
• Exhausted T cells  
• PD-1 is not the main checkpoint  
• Intrinsic mutations | • Increase quality of neoantigens  
• Decrease T cell Exhaustion  
• Other immune checkpoints  
• Tumor Intrinsic Resistance (JAK1/2, B2M, WNT)  
• Improve TME  
• Microbiome? | **Neoantigen vaccine**  
  aCD137, aOX40,aGITR, aICOS aTIGIT, aTIM3, aLAG3  
  TLR9 agonists? PEG IL2?  
  VEGFi, MAPKi, PI3Kgi, IDOi, ... |
| II: TMB Medium & Inflammation Low to Medium | NSCLC HNSCC HCC Gastric CA | • Not enough high quality neoantigens  
• Defects in priming | • Increase quantity of neoantigens or exposure  
• Increase T cell priming  
• Improve TME  
• Microbiome? | Oncolytic virus, TLR/STING agonists, hypomethylation agents, ...  
  aCTLA4, aCD40  
  VEGFi, MAPKi, PI3Kgi, IDOi, ... |
| III: TMB Low & Inflammation Low to None | MMR-p CRC Pancreatic CA Prostate CA | • Low or no neoantigens to trigger anti-tumor response | • All of the above  
• Engineered specificity  
• Improve TME  
• Microbiome? | All of the above  
  bi-specific, TCR/CAR ACT  
  VEGFi, MAPKi, PI3Kgi, IDOi, ... |
NEO-PV-01, with anti-PD1, Induces Neoantigen-Specific De Novo Tumor-Related Immunity in Patients with Advanced Cancer


*David Geffen School of Medicine, University of California, Los Angeles, CA, USA
Steps in production of NEO-PV-01

NEO-PV-01 targets a patient’s specific set of tumor neoantigens

- A personal vaccine targeting immune responses against high quality neoantigens unique to each patient
- Up to 20 unique peptides (~14-35mer) + Poly-ICLC adjuvant
- Subcutaneous injection

Hu-Lieskovan, et al, SITC 2018; AACR 2019
NT-001: Study initiated August 2016
Data Cutoff August 31, 2018

Hu-Lieskovan, et al, SITC 2018; AACR 2019
# NT-001: Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Safety Set</th>
<th>Per Protocol Set (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Indications</td>
<td>Melanoma</td>
</tr>
<tr>
<td><strong>Patients, N</strong></td>
<td>54</td>
<td>16</td>
</tr>
<tr>
<td>Gender (M/F), n</td>
<td>30 M / 24 F</td>
<td>10 M / 6 F</td>
</tr>
<tr>
<td><strong>Age, years, median (range)</strong></td>
<td>64.7 (25.3-84.0)</td>
<td>60.2 (25.3-84.0)</td>
</tr>
<tr>
<td>PD-L1 Expression (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1%</td>
<td>66.7</td>
<td>80.0</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>15.4</td>
<td>13.3</td>
</tr>
<tr>
<td>Tumor Mutation Burden, median (range)</td>
<td>261 (48-8433)</td>
<td>430 (80-2664)</td>
</tr>
<tr>
<td>Prior Systemic Treatment (%)</td>
<td>53.7</td>
<td>37.5</td>
</tr>
<tr>
<td>ECOG Performance Status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>61.1</td>
<td>81.2</td>
</tr>
<tr>
<td>1</td>
<td>38.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Metastatic Lesions (%)*</td>
<td>96.3</td>
<td>100.0</td>
</tr>
<tr>
<td>M0-1a</td>
<td>48.6</td>
<td>37.4</td>
</tr>
<tr>
<td>M1b-c</td>
<td>51.4</td>
<td>62.6</td>
</tr>
</tbody>
</table>

*Investigator Correspondence

Hu-Lieskovvan, et al, SITC 2018; AACR 2019
Melanoma: Tumor Burden Changes During Therapy

Per Protocol Set (n = 16)

**Continued Nivolumab Treatment***
- 75.0%
- 12/16

**Disease stabilization post-progression**

<table>
<thead>
<tr>
<th></th>
<th>Pre-vaccination</th>
<th>Post-vaccination</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>50.0% (8/16)</td>
<td>37.5% (3/8)</td>
<td>68.8% (11/16)</td>
</tr>
<tr>
<td>CR</td>
<td>0% (1/16)</td>
<td>6.3% (1/16)</td>
<td>6.3% (1/16)</td>
</tr>
</tbody>
</table>

- **Continued Nivolumab Treatment***
- **Discontinuation rate prior to week 52**
- **Response duration (range)**
  - +39.7 weeks (1.0-70.4)

* On study or continuing nivolumab treatment as of recent correspondence
NSCLC: Tumor Burden Changes During Therapy

Per Protocol Set (n = 11)

<table>
<thead>
<tr>
<th></th>
<th>Pre-vaccination</th>
<th>Post-vaccination</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>27.2% (3/11)</td>
<td>25.0% (2/8)</td>
<td>45.5% (5/11)</td>
</tr>
<tr>
<td>CR</td>
<td>0% (0/11)</td>
<td>0% (0/11)</td>
<td>0% (0/11)</td>
</tr>
</tbody>
</table>

**Continued Nivolumab Treatment**

- 63.6% (7/11)

**Response duration**

- +30.6 weeks (8.7-35.0)

* On study or continuing nivolumab treatment as of recent correspondence

---

Hu-Lieskovan, et al, SITC 2018; AACR 2019
Exploratory Analysis of Tumor Responses Post-Vaccination

Changes in tumor measurements at week 12 vs. best response post-vaccination

-1 -0.75 -0.5 -0.25 0 0.25 0.5 0.75 1

Increase from Pre-Vaccination

<table>
<thead>
<tr>
<th>% Change from Pre-Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Change from Pre-Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
</tbody>
</table>

Melanoma NSCLC Bladder

-100 -75 -50 -25 0 25 50 75 100

Decrease from Pre-Vaccination

<table>
<thead>
<tr>
<th>% Change from Pre-Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
</tbody>
</table>

Continuing Treatment

Post-vaccine Response

31 August 2018

Hu-Lieskovan, et al, SITC 2018; AACR 2019
87% of NEO-PV-01 peptides tested are mutant-specific.

Durability of immune response at 52 weeks noted in 4 of 6 patients.

Hu-Lieskovan, et al, SITC 2018; AACR 2019
Metastatic Melanoma Patient: M1

- 57y female enrolled with stage M1c melanoma with liver and presacral masses
- No prior systemic therapy for metastatic disease
- Continues on study with stable disease for > 70 weeks

**NEO-PV-01 induces neoantigen-specific CD8 T Cells that traffic to the tumor**

NEO-PV-01 stimulated multiple neoantigen responses with 9 of the 15 immunizing peptides generating CD4 and CD8 responses in PBMCs post-vaccination.

**Ex vivo Tetramer and TCR analysis**

<table>
<thead>
<tr>
<th>RICTOR Neoantigen Epitope</th>
<th>0.17 %</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>RICTOR TCRs in the Tumor</th>
<th>% of Reads (Normalized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Treatment</td>
<td>TCR1</td>
</tr>
<tr>
<td>Nivo Monotherapy</td>
<td>TCR1</td>
</tr>
<tr>
<td>NEO-PV-01 + Nivo</td>
<td>TCR1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TCR</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
</tr>
</tbody>
</table>

TCR3 is found in the post-vaccine tumor

TCR3 expressed in Jurkat cells is functional

**Functional Characterization**

Single cell TCR sequencing identifies three major RICTOR mutant reactive clones

Hu-Lieskován, et al, SITC 2018; AACR 2019
**Immunotherapy Naïve Melanoma**

**Open Trials at Huntsman**

**Neon 003**: A Personal Cancer Vaccine (NEO-PV-01) and APX005M or Ipilimumab With Nivolumab in Patients With Advanced Melanoma

**SWOG S1801**: A Phase II Randomized Study of Adjuvant Versus NeoAdjuvant MK-3475 (Pembrolizumab) for Clinically Detectable Stage III-IV High-Risk Melanoma

**PICI0014/MCGRAW**: Melanoma Checkpoint and Gut Microbiome Alteration With Microbiome Intervention (To be opened soon)
## Patterns of TME Biology and Potential Strategies

<table>
<thead>
<tr>
<th>Patterns</th>
<th>More Prevalent in</th>
<th>Unique Considerations</th>
<th>Strategies</th>
<th>Examples</th>
</tr>
</thead>
</table>
| **I:** TMB High & Inflammation High | Melanoma Cutaneous SCC MMR-d Cancers | • Plenty of neoantigens but may not be high quality  
• Exhausted T cells  
• PD-1 is not the main checkpoint  
• Intrinsic mutations | • Increase **quality** of neoantigens  
• Decrease T cell Exhaustion  
• Other immune checkpoints  
**Tumor Intrinsic Resistance (JAK1/2, B2M, WNT)**  
• Improve TME  
• Microbiome? | Neoantigen vaccine  
aCD137, aOX40,aGITR, aICOS aTIGIT, aTIM3, aLAG3  
TLR9 agonists? PEG IL2?  
VEGFi, MAPKi, PI3Kgi, IDOi, ...
| **II:** TMB Medium & Inflammation Low to Medium | NSCLC HNSCC HCC Gastric CA | • Not enough high quality neoantigens  
• Defects in priming | • Increase **quantity** of neoantigens or exposure  
• Increase T cell priming  
• Improve TME  
• Microbiome? | Oncolytic virus, TLR/STING agonists, hypomethylation agents, ...

aCTLA4, aCD40  
VEGFi, MAPKi, PI3Kgi, IDOi, ...
| **III:** TMB Low & Inflammation Low to None | MMR-p CRC Pancreatic CA Prostate CA | • Low or no neoantigens to trigger anti-tumor response | • All of the above  
• Engineered specificity  
• Improve TME  
• Microbiome? | All of the above  
bi-specific, TCR/CAR ACT  
VEGFi, MAPKi, PI3Kgi, IDOi, ...
LOF mutation of JAK1/2 and B2M and intrinsic resistance to anti-PD1
Analysis of Mutational Burden and CD8 infiltration in 23 melanoma baseline biopsies treated by pembrolizumab

Mutational Burden is not associated with response to pembrolizumab in cutaneous melanoma

Jesse Zaretsky, Hu-Lieskovan
Summary of 4 Acquired Resistance Cases

<table>
<thead>
<tr>
<th>Case #1</th>
<th>Case #2</th>
<th>Case #3</th>
<th>Case #4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Max Response</td>
<td>Relapse</td>
<td>Genetic Alteration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>JAK1 LoF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>JAK2 LoF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B2M LoF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unkn</td>
</tr>
</tbody>
</table>


Slide Courtesy of Dr. Antoni Ribas
Role of the Interferon-gamma Receptor Signaling Pathway and Antigen Presentation/B2M

T cell

IFN-γ

Tumor cell

IFNGR1 IFNGR2 JAK1 JAK2 APLNR PTPN2 STAT1 STAT1 P P

IFNGR1 IFNGR2 JAK1 JAK2 APLNR PTPN2 STAT1 STAT1 P P

JAK1

JAK2

PTPN2

GAS

APLNR

PTPN2

GAS

MHC

TAP 1/2 LAMP PSMB 8,9,10

ICAM-1

CXCL 9,10,11

PD-L1

IRF1

IRF1

PD-L1

IFNGR1

IFNGR2

MHC class I

B2M

PD-L1

IRF1

PD-L1

CRISPR screen:
Manguso... Haining, Nature 2017
Patel... Restifo, Nature 2017

Slide Curtesy of Dr. Antoni Ribas
Interrogation of Resistance Mechanisms to Checkpoint Inhibitors Using Functional Genomics

- Siwen Hu-Lieskovcan, MD, PhD  
  Huntsman Cancer Institute

- Rene Bernards, PhD  
  The Netherlands Cancer Institute
**Approach/Current Status**

**Step 1 – Acquired Resistance:**
- 14 cases of paired melanoma samples
- Initial response then progression
- Compare mutations at progression to baseline
- **197 genes** were identified by priority score criteria 1-3 and sent to Rene

**Priority Scores:**
- 1: Mutation occurred more than once at progression (28)
- 2: Mutation occurred only at progression and are homozygous (33)
- 3: Mutations that were heterozygous at baseline and become homozygous on progression (136)
In vitro screen for immune-escape genes:
Testing candidates from sequenced patient samples

197 candidate IO resistance genes

Generate custom CRISPR library
1533 gRNAs

Melanoma cells co-cultured with T-cells

- T-cells
+ T-cells

Identifying the enriched gRNAs

197 candidate genes in vitro screen
28 top hit genes

In vivo screen
### Patterns of TME Biology and Potential Strategies

<table>
<thead>
<tr>
<th>Patterns</th>
<th>More Prevalent in</th>
<th>Unique Considerations</th>
<th>Strategies</th>
<th>Examples</th>
</tr>
</thead>
</table>
| I: TMB High & Inflammation High | Melanoma Cutaneous SCC MMR-d Cancers | • Plenty of neoantigens but may not be high quality  
• Exhausted T cells  
• PD-1 is not the main checkpoint  
• Intrinsic mutations | • Increase quality of neoantigens  
• Decrease T cell Exhaustion  
• Other immune checkpoints  
• Tumor Intrinsic Resistance (JAK1/2, B2M, WNT)  
• Improve TME  
• Microbiome? | Neoantigen vaccine  
aCD137, aOX40,aGITR, aICOS  
aTIGIT, aTIM3, aLAG3  
TLR9 agonists? PEG IL2?  
**VEGFi, MAPKi, PI3Ki, IDOi, ...** |
| II: TMB Medium & Inflammation Low to Medium | NSCLC HNSCC HCC Gastric CA | • Not enough high quality neoantigens  
• Defects in priming | • Increase quantity of neoantigens or exposure  
• Increase T cell priming  
• Improve TME  
• Microbiome? | Oncolytic virus, TLR/STING agonists, hypomethylation agents, ...  
aCTLA4, aCD40  
**VEGFi, MAPKi, PI3Ki, IDOi, ...** |
| III: TMB Low & Inflammation Low to None | MMR-p CRC Pancreatic CA Prostate CA | • Low or no neoantigens to trigger anti-tumor response | • All of the above  
• Engineered specificity  
• Improve TME  
• Microbiome? | All of the above  
bi-specific, TCR/CAR ACT  
**VEGFi, MAPKi, PI3Ki, IDOi, ...** |
Taking advantage of effective systemic therapy

Combination with Chemotherapy/VEGF inh/MAPKi:
- Keep up with rapid tumor growth
- Expose more tumor antigen
- Modulate tumor immune environment
How can BRAF targeted therapy increase the activity of tumor immunotherapy?

Decreased immune suppressive factor release (IL1, IL6, IL8, VEGF)

Increased antigen Cross-presentation

Activation of T cells and increased homing

Increased direct antigen presentation

BRAFi

Koya, Mok et al. Cancer Res 2012
Callahan et al. Cancer Imm Res 2014

BRAFi

Decreased immune suppressive factor release (IL1, IL6, IL8, VEGF)


Slide Curtesy of Dr. Antoni Ribas
Enhanced *in vivo* antitumor activity
pmel-1 ACT + dabrafenib and/or trametinib

Dabrafenib and trametinib were kindly provided by Drs. Tona Gilmer, Li Liu and Jeff Legos through an MTA with GSK

**RESEARCH ARTICLE**

**CANCER**

**Combination of BRAFi+MEKi+Anti-PD-1**

**Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAF\(^{V600E}\) melanoma**


**NIH Director’s Blog**

Knocking Out Melanoma: Does This Triple Combo Have What It Takes?

Posted on March 31, 2015 by Dr. Francis Collins


*Available at: https://directorsblog.nih.gov/2015/03/31/knocking-out-melanoma-does-this-triple-combo-have-what-it-takes/ Accessed on August 18, 2016.

Hu-Lieskovan et al. Sci Transl Med. 2015
Clinical Trials Combining BRAFi+MEKi+anti-PD-1/L1

dabrafenib+trametinib +durvalumab
dabrafenib+trametinib vemurafenib+cobimetinib +pembrolizumab +atezolizumab

Ribas et al. J Clin Oncol (Meeting Abstracts) May 2015 vol. 33 no. 15_suppl 3003
Ribas et al. J Clin Oncol 34, 2016 (suppl; abstr 3014).
Hwu et al. Annals of Oncology 27 (Supp 6); 2016: Abstract 1109PD.

Slide Courtesey of Dr. Antoni Ribas
Combining immunotherapy and targeted therapy?

- 1+1=2 or >2?
- Double or triple? Quadruple?
- Combination upfront or lead in?
- Sequenced?
- Intermittent?
- **Safety/Toxicity?**
<table>
<thead>
<tr>
<th>Patterns</th>
<th>More Prevalent in</th>
<th>Unique Considerations</th>
<th>Strategies</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: TMB High &amp; Inflammation High</td>
<td>Melanoma, Cutaneous SCC, MMR-d Cancers</td>
<td>• Plenty of neoantigens but may not be high quality&lt;br&gt;• Exhausted T cells&lt;br&gt;• PD-1 is not the main checkpoint&lt;br&gt;• Intrinsic mutations</td>
<td>• Increase quality of neoantigens&lt;br&gt;• Decrease T cell Exhaustion&lt;br&gt;• Other immune checkpoints&lt;br&gt;• Tumor Intrinsic Resistance (JAK1/2, B2M, WNT)&lt;br&gt;• Improve TME&lt;br&gt;• Microbiome?</td>
<td>Neoantigen vaccine&lt;br&gt;aCD137, aOX40, aGITR, aICOS&lt;br&gt;aTIGIT, aTIM3, aLAG3&lt;br&gt;TLR9 agonists? PEG IL2?&lt;br&gt;VEGFi, MAPKi, PI3Kgi, IDOi, ...</td>
</tr>
<tr>
<td>II: TMB Medium &amp; Inflammation Low to Medium</td>
<td>NSCLC, HNSCC, HCC, Gastric CA</td>
<td>• Not enough high quality neoantigens&lt;br&gt;• Defects in priming</td>
<td>• Increase quantity of neoantigens or exposure&lt;br&gt;• Increase T cell priming&lt;br&gt;• Improve TME&lt;br&gt;• Microbiome?</td>
<td>Oncolytic virus, TLR/STING agonists, hypomethylation agents, ...&lt;br&gt;aCTLA4, aCD40&lt;br&gt;VEGFi, MAPKi, PI3Kgi, IDOi, ...</td>
</tr>
<tr>
<td>III: TMB Low &amp; Inflammation Low to None</td>
<td>MMR-p CRC, Pancreatic CA, Prostate CA</td>
<td>• Low or no neoantigens to trigger anti-tumor response</td>
<td>• All of the above&lt;br&gt;• Engineered specificity&lt;br&gt;• Improve TME&lt;br&gt;• Microbiome?</td>
<td>All of the above&lt;br&gt;bi-specific, TCR/CAR ACT&lt;br&gt;VEGFi, MAPKi, PI3Kgi, IDOi, ...</td>
</tr>
</tbody>
</table>
Intra-tumoral T-VEC (oncolytic virus) plus systemic pembrolizumab induces high response rates by increases in tumor CD8 infiltration.

62% objective response rate
33% complete response rate

PD-L1 CD8 S100

Slide Curtesy of Dr. Antoni Ribas

S1607: A Phase II Study of Combining T-VEC and Pembrolizumab in Patients With Advanced Melanoma Who Have Progressed on Anti-PD1/L1 Based Therapy

• Primary Objective: DRR
• Secondary Objectives: ORR, PFS, OS, toxicity

Study Chair and Translational Lead: Siwen Hu-Lieskovan, MD, PhD
Statisticians: Mike Wu, PhD; James Moon
Protocol Coordinator: Danae Campos

Open at Huntsman!
S1607 "A Phase II Study of Combining T-VEC (NSC-785349) and Pembrolizumab (NSC-776864) in Patients with Advanced Melanoma who have Progressed on Anti-PD1/L1 Based Therapy." (NCT#02965716)

PI: Siwen Hu-Lieskovan, MD, PhD

Antoni Ribas, Grace Cherry, UCLA
S1607: T-VEC and Pembrolizumab for Melanoma after Anti-PD1/L1

**Injected Tumor**
- Direct Tumor Lysis
- Release of Progeny Viruses
- Enhanced Innate Immune Response
- Attract DC /Antigen cross-presentation
- Induced IFN Release

**Un-injected Tumor**
- Acquired Immune Response
  - Increased CD8 infiltration
  - Increased CD8 clonality
  - Increased CD8 activation
  - Decreased Tregs, Macrophage, MDSC?
  - Decreased immune suppressive cytokines? (TGFβ, IL10, etc)

**Peripheral Blood**
- Released Progeny Viruses?
- Enhanced Innate Immune Response
- Acquired Immune Response
  - Increased activated CD8
  - Increased CD8 clonality
  - Increased DC?

**Up-Regulated PD1/PD-L1?**

_one cycle is 21 days (3 weeks). MD evaluation, PE, Vitals, PS, and labs on first day of each cycle._
# Patterns of TME Biology and Potential Strategies

<table>
<thead>
<tr>
<th>Patterns</th>
<th>More Prevalent in</th>
<th>Unique Considerations</th>
<th>Strategies</th>
<th>Examples</th>
</tr>
</thead>
</table>
| I: TMB High & Inflammation High | Melanoma Cutaneous SCC MMR-d Cancers | • Plenty of neoantigens but may not be high quality  
• Exhausted T cells  
• PD-1 is not the main checkpoint  
• Intrinsic mutations | • Increase quality of neoantigens  
• Decrease T cell Exhaustion  
• Other immune checkpoints  
• Tumor Intrinsic Resistance (JAK1/2, B2M, WNT)  
• Improve TME  
• Microbiome? | Neoantigen vaccine  
aCD137, aOX40, aGITR, aICOS  
aTIGIT, aTIM3, aLAG3  
TLR9 agonists? PEG IL2?  
VEGFi, MAPKi, PI3Kgi, IDOi, … |
| II: TMB Medium & Inflammation Low to Medium | NSCLC HNSCC HCC Gastric CA | • Not enough high quality neoantigens  
• Defects in priming | • Increase quantity of neoantigens or exposure  
• Increase T cell priming  
• Improve TME  
• Microbiome? | Oncolytic virus, TLR/STING agonists, hypomethylation agents, …  
aCTLA4, aCD40  
VEGFi, MAPKi, PI3Kgi, IDOi, … |
| III: TMB Low & Inflammation Low to None | MMR-p CRC Pancreatic CA Prostate CA | • Low or no neoantigens to trigger anti-tumor response | • All of the above  
• Engineered specificity  
• Improve TME  
• Microbiome? | All of the above  
bi-specific, TCR/CAR ACT  
VEGFi, MAPKi, PI3Kgi, IDOi, … |
CheckMate 067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*

Unresectable or Metastatic Melanoma
- Previously untreated
- 945 patients

Randomize 1:1:1

Stratify by:
- BRAF status
- AJCC M stage
- Tumor PD-L1 expression <5% vs ≥5%*

N=314
NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316
NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315
IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Treat until progression or unacceptable toxicity

Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

*The study was not powered for a comparison between NIVO and NIVO+IPI
CheckMate 067: Overall Survival

Nivo OR Nivo+Ipi vs Ipi
Tx Naïve Melanoma

Caveats:
1. Not powered to compare Nivo arm to Nivo+Ipi arm
2. Pts on single agent Nivo arm can have Ipi after being off trial.

Data suggests:
1. Ipi after Nivo might have similar efficacy but avoid significant toxicity
2. Checkmate 012 in NSCLC suggests combining with lower dose of Ipi with less frequency reduces toxicity and might improve efficacy
Primary objective
- Combination will be considered superior to single-agent ipilimumab if PFS is doubled from 3 to 6 months
- 1:3 randomization (to ensure adequate numbers for major secondary objective)
- 63 patients randomized to receive combination, 21 patients randomized to receive ipilimumab alone
- One sided alpha of 10%, power of 90%
Unique Challenges with Clinical Testing of Combination Immunotherapy

• **Unique toxicity profile**
  – Spectrum different from agent to agent
  – MTD vs MAD? Need to leverage with biological efficacy
  – Timing of irAE can be late
  – More challenging when combine with traditional cytotoxic agents or targeted therapy (different DLT window)

• **How to evaluate response**, which can be delayed or mixed
  – RECIST? irRC? iRECIST?
  – Pt can benefit from treatment after discontinuation due to toxicity

• **What is the best measure of clinical outcome/benefit**
  – ORR, PFS? OS, DRR, DCR?
Draft iMATCH Protocol Design

**Baseline Biomarker Assessment**

- **CPI-naive** (Histology-agnostic or Selected tumors)
- **Baseline Biopsy**
- **Anti-PD1**

**PD Primary Resistance**

- **CR/PR/SD**

**PD Acquired Resistance**

- **PD Biopsy**
  - Or Regimen X based on different biomarker(s)

**Study Entry**

**Combo Partners (examples)**
1. aCTLA4
2. TVEC/TLR9/Sting agonist
3. Pegylated IL-2
4. 41BB/OX40 agonists
5. VEGF inhibitor
6. IDO inhibitor
7. Microbiome Modulation
8. Bispecific
9. Epigenetic modulator
10. aLAG3/aTIGIT/aTIM3
11. Targeted Agents
12. …

**PD Biopsy**

- **Regimen 1, 2, …**

* For primary resistance, Biomarker triage is based on baseline biopsy sample analysis. PD (progression of disease) biopsy is done for retrospective research.
Strategies To Overcome Resistance

**Turn on Engine**
- Neoantigen Quantity
  - Chemo
  - Radiation
  - Epigenetic Modulation

**Neoantigen Quality**
- TAA Vaccine
- Neoantigen Vaccine
- Engineered specificity

**Antigen Presentation/ T Cell Priming**
- DC vaccine
- Oncolytic virus
- TLR/STING agonists
- Cytokines
- Anti-CTLA4
- Anti-CD40

**Fuel the Tank**
- Anti-GITR
- Anti-41BB/CD137
- Anti-OX40
- Anti-ICOS

**Tumor Cells**

**Take Away Barrier**
- IDO Inhibitor
- CSF1R inhibitor
- Adenosine R inhibitor
- TGFβ inhibitor
- VEGF inhibitor
- PI3Kg inhibitor
- Microbiome Modulation

**Block the Stop Sign**
- Anti-PD-1/L1
- Anti-TIM3, Anti-LAG3
- Anti-TIGIT
Multi-histology IO Trials open at HCI

Agency: Astellas (8374-CL-0101)
Complete Title: A Phase 1b Study of ASP8374, an Immune Checkpoint Inhibitor, as a Single Agent and in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors. (Anti-TIGIT + pembrolizumab)

Agency: Xencor (DUET-2)
Complete Title: A Phase 1 Multidose Study to Evaluate the Safety and Tolerability of XmAb®20717 in Patients with Selected Advanced Solid Tumors. (Bispecific Antibody: CTLA4-PD1)

Agency: Xencor (DUET-3)
Complete Title: A Phase 1 Multiple-Dose Study to Evaluate the Safety and Tolerability of XmAb®23104 in Subjects With Selected Advanced Solid Tumors. (Bispecific Antibody: ICOS-PD1)

Agency: Xencor (DUET-4)
Complete Title: A Phase 1 Multiple-Dose Study to Evaluate the Safety and Tolerability of XmAb®22841 Monotherapy and in Combination With Pembrolizumab in Subjects With Selected Advanced Solid Tumors. (Bispecific Antibody: CTLA4-LAG3 + pembrolizumab)

Agency: Merck (MK1454-001)
Complete Title: Phase 1 Open-label, Multicenter Study of MK-1454 Administered by Intratumoral Injection as Monotherapy and in Combination With Pembrolizumab for Patients With Advanced/Metastatic Solid Tumors or Lymphomas (Sting Agonist MK-1454)

Agency: Merck (3475-001)
Complete Title: A Phase 1/1b, Open-label Clinical Study of Intratumoral/Intralesional Administration of V938 in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic or Recurrent Malignancies (New Generation Oncolytic Virus)

Agency: BioAtla (BA3011-001)
Complete Title: A Phase 1/2 Dose Escalation and Dose Expansion Study of BA3011 in Patients with Advanced Solid Tumors (CAB-AXL-ADC)

Agency: BioAtla (BA3021-001)
Complete Title: A Phase 1/2 Dose Escalation and Dose Expansion Study of BA3021 in Patients with Advanced Solid Tumors (CAB-ROR2-ADC)
Conclusions/Take-Away

- Immunotherapy for cancer has the potential to provide durable benefit to a wide array of patients.

- Successful development of Combination Immunotherapy strategies relies on --
  - A clear understanding of the heterogeneity of the immune resistant mechanisms that exists in each patient
  - Successful development of predictive biomarkers
  - Collaborative effort of the entire academia, industry and regulatory authorities
Acknowledgments

Antoni Ribas MD, PhD
John Glaspy, MD
Tom G. Graeber, PhD
Jesse Zaretsky PhD
Roger S. Lo, MD, PhD
Edward Garon, MD
Zeynep Eroglu MD
Blanca Homin Meleno MD
Stephen Mok PhD
Richard Koya MD, PhD
Jennifer Tsoi PhD
Catie Grasso PhD
Ribas Research Group

Clinical Trial Group

Robert M. Prins PhD
Special Thanks

Oncology Division:
Lynn Henry, MD
Saundra Buys, MD
Neeraj Agarwal, MD
Wally Akerley, MD
Ignacio Garrido-Laguna, MD
John Ward, MD
Elaine Volckmann
Kaylene, Wayman

Melanoma DOT:
Doug Grossman, MD
Sherry Holman, PhD
John Hyngstrom, MD
Ken Grossmann, MD
Ben Voorhies, MD
Allie Grossmann, MD
Tawnya Bowles, MD
Glen Bowen, MD
Matthew Van Brocklin, PhD
Mark Hyde, PhD, PA-C
Elizabeth Flores, PA-C
Mindy Stone

Melanoma Clinic:
Carolyn Lockett, RVN
Jordan McPherson, PharmD
Dan Sageser, PharmD
Lorena Cannon
Sean Calvert
Christy Horton
Kimberly Lindsay
Samantha Holt
Julie Nielsen

TCC/BMP:
Mikaela Larson
AnnaLeah Larson
Andy Lee
Glenda Peck
James Cline
David Lum
Penny Noel

Clinical Trial Office:
David Gaffney, MD
Theresa Werner, MD
Jessica Moehle
Elizabeth Constantz
Susan Sharry
Tamara Willis, CRN
Andrew Grandemange
Alex Jones
Carolynn Hunter
Cristy Johnston
Trevor Gordon, JD
Alex Lenzen

IST Team:
Kelli Thorne
Jennifer Pearce
Susan Clement
Karthik Sonty
Lisa Dubler

Hu-Lieskovkan Lab:
Yoko Derose, PhD

Grant Office:
Callie Martens
Kristi Smith

HCI
Mary Beckerle, PhD
Neli Ulrich, PhD
Martin McMahon, PhD
Brad Cairns, PhD
John Sweetenham, MD
Alana Welm, PhD
Ashlee Bright
Lisa Anderson
Chris Bretones
Matt Isom
Nia Sherar
Mark Oberg
Andrew Intveld
Jen Heninger
Carolyn Ross
Kimberly Simmons
Joey Parker
Elle Oldfield
Dian Bretones
Debbie Arnold
Miriam Allen
Acknowledgements

The Hope Foundation
Because answers to cancers come from clinical trials

Southwest Oncology Group
A National Clinical Research Group

Tower Cancer Research Foundation
Career Development Award

SWOG Dr. Charles Coltman Award
SWOG ITSC Pilot Award

American Society of Clinical Oncology

ASCO Young Investigator Award
ASCO Career Development Award

Conquer Cancer Foundation
of the American Society of Clinical Oncology

SU2C/AACR Phil Sharp Innovation in Collaboration Award

Melanoma Research Alliance

MRA Young Investigator Award

UCLA CTSI KL2 Award