Cancer Immunotherapy Program
Terence Rhodes, MD, PhD
Director of Immuno-Oncology
Outline

• Cancer immunotherapy basics
• Current state of immunotherapy
• Next generation immunotherapy
• Intermountain Cancer Immunotherapy Program
Cancer Immunoediting Therapy
Patients on average lived 10.0 months with ipilimumab

Patients on average lived 6.4 months with gp100
Lung cancer

Nivolumab beats chemotherapy in lung cancer
With up date June 2016, average overall survival has not been reached.
Recent FDA approved immunotherapy in solid malignancies

• **Checkpoint inhibitors**
  - CTLA-4 inhibitors
    – **Ipilimumab** -- Melanoma
  - PD-1 inhibitors
    – **Nivolumab** -- Melanoma, 2\textsuperscript{nd} line NSCLC, 2\textsuperscript{nd} line Renal cell, 2\textsuperscript{nd} line Bladder, refractory Classical Hodgkin lymphoma, Head&Neck
    – **Pembrolizumab** -- Melanoma, 1\textsuperscript{st} and 2\textsuperscript{nd} line NSCLC, refractory Classical Hodgkin lymphoma, 2\textsuperscript{nd} line Head&Neck
  - PD-L1 inhibitors
    – **Atezolizumab** -- 2\textsuperscript{nd} line Bladder cancer, 2\textsuperscript{nd} line NSCLC
    – **Avelumab** -- metastatic Merkel Cell

• **Oncolytic viruses**
  – Talimogene laherparepvec or **T-VEC (Imlygic)** -- Melanoma
Immunotherapy events on the horizon

• A host of combination agents in clinical trials
  – Other checkpoint inhibitors/agonists in clinical trials
    • CD27, OX40, TIMI, GITR, CD28, ICOS, LAG3
  – Other agents
    • NK checkpoint inhibitor – anti-KIR

• Microbiome
  – Responders to immunotherapy for melanoma had a more diverse microbiome
Adoptive cellular therapy

1. Collect patient's white blood cells
2. Isolate and activate T cells
3. Engineer T cells with CAR or TCR gene
4. Grow and expand number of T cells
5. Infuse patient with engineered T cells
CAR T-cell therapy

- Novartis plans to obtain FDA approval for CTL019 for children and young adults with ALL in 2017

- KITE CAR T-cell therapy could get approval in DLBCL in 2017

<table>
<thead>
<tr>
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<th>DLBCL (n=77)</th>
<th>TFL/PMBCL (n=24)</th>
<th>Combined (n=101)</th>
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<td>ORR</td>
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Table 2. Selected Open Oncolytic Virus Trials

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<tr>
<th>Virus</th>
<th>Delivery Combination</th>
<th>Phase/Sponsor</th>
<th>Tumor Type</th>
<th>Primary Measures</th>
<th>Secondary Measures</th>
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<td>Herpesvirus</td>
<td>Intratumoral, single agent</td>
<td>Phase 1/ Pediatric Brain Tumor</td>
<td>Recurrent pediatric brain tumors</td>
<td>MTD</td>
<td>Efficiency, imaging, viral PK/PD, immune response</td>
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<td>Herpesvirus</td>
<td>Intravenous</td>
<td>Phase 1/2/Takeda Bio, Inc.</td>
<td>Malignant melanoma</td>
<td>EFFICACY</td>
<td>Immune response</td>
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<td>Herpesvirus</td>
<td>Intraperitoneal</td>
<td>Phase 2/3/Immunon</td>
<td>Malignant glioma</td>
<td>MTD</td>
<td>Safety, response efficacy</td>
<td>Europe</td>
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<td>Ippinamab</td>
<td>Intracerebral, single agent</td>
<td>Phase 2/3/Angen</td>
<td>Malignant glioma</td>
<td>MTD</td>
<td>Safety, response efficacy</td>
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<td>Ippinamab</td>
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<td>Malignant glioma</td>
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<td>Safety, response efficacy</td>
<td>Germany</td>
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<td>T-VEC</td>
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<td>Adenovirus</td>
<td>Intratumoral (single), with/without exogenous helper virus</td>
<td>Phase 1/2/Immunex, S.L.</td>
<td>Advanced solid tumors</td>
<td>Safety/sensitivity</td>
<td>Efficiency, viral PK/PD</td>
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<td>Adenovirus</td>
<td>Intravenous</td>
<td>Phase 1b/Immunex, S.L.</td>
<td>Recurrent brain tumors</td>
<td>EFFICACY</td>
<td>Safety, immune response, QoL</td>
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<td>Adenovirus</td>
<td>Intraperitoneal</td>
<td>Phase 1/2/Angen</td>
<td>Colorectal cancer, head/neck, SCLC</td>
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<td>Viral PK/PD, antiviral activity</td>
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<td>Measles Virus</td>
<td>Intratumoral, near/chemo stem cell</td>
<td>Phase 1/2/Immunex, S.L.</td>
<td>Recurrent ovarian cancer</td>
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<td>Tumor response, immune response, viral PK/PD</td>
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<td>Vaccinia Virus</td>
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<td>Hepatocellular carcinoma</td>
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<td>Additional efficacy, safety</td>
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<td>Prosvac</td>
<td>Intratumoral, with no treatment</td>
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<td>Recurrent prostate cancer</td>
<td>MTD, safety</td>
<td>Decreased PSA rise</td>
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<td>Reovirus</td>
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<td>Phase 1b/Immunex, S.L.</td>
<td>Pancreatic adenocarcinoma</td>
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<td>Immune response</td>
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<td>Polio Virus</td>
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<td>Recurrent GBM</td>
<td>MTD</td>
<td>Efficiency</td>
<td>United States</td>
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<td>PVS-311</td>
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<td>Efficiency</td>
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<td>Caudalix</td>
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<td>Recurrent GBM</td>
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<td>Other Viruses</td>
<td>Intratumoral (teno)</td>
<td>Phase 2/3/Rutgers, S.L.</td>
<td>Brain, recurrent GBM</td>
<td>EFFICACY, comparison with chemotherapy</td>
<td>United States</td>
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**Other oncolytic viruses**

S. E. Lawler, et al., JAMA Oncology.
Cancer Immunotherapy Program
Cancer Immunotherapy Program

• Two Broad Goals

  – Expand access to immunotherapy clinical trials
  – Leverage Intermountain resources to provide the right immunotherapy agent for the right patient and maximize safety and value
    • Translation Science/biomarker discovery
    • Immunotherapy education
    • Real world drug utilization and costs
Current and near future clinic trials

Expand access to immunotherapy clinical trials
Current clinical trials

- **Melanoma**
  - MASTERKEY-265: Pembro +/- TVEC
  - SWOG S1404: Phase III, pembro vs high dose interferon or ipi

- **NSCLC**
  - SWOG S1400I: Squamous lung no matching mutation -- nivo vs ipi/nivo

- **GI**
  - Merck: Prembo in HCC

- **Type agnostic**
  - MATCH Z1D, nivo for mismatch repair deficiency
  - TAPUR, pembro for POLE/POLD1;high mutational load
Upcoming clinical trials

• Lung cancer
  – BMS Checkmate-816: Phase III Neoadjuvant ipi/nivo vs chemo for stage IB to IIIa NSCLC

• Ovarian
  – GOG 3015/Genentech: Chemotx/bev +/- Atevo for Stage III or Stage IV ovarian
Upcoming clinical trials

• GU
  – Merck Keynote 564: Adjuvant pembro in resected RCC
  – BMS Checkmate 920: Phase IIIb/IV ipi/nivo in metastatic RCC
  – SWOG S1605: Phase II of Atezo in BCG-unresponsive non-muscle invasive bladder cancer
Upcoming clinical trials

• Multiple Myeloma
  – BMS Checkmate 209: Third line multiple myeloma nivo/dara +/- pom/dex

• Type agnostic
  – BMS Checkmate 848: Phase II Nivo for advanced malignancies with MSI-H
  – DART: Rare tumors not candidate for Match -- ipi/nivo
Translational Science/Biomarker Development
The One Exception to Biomarkers in Immunotherapy

• All current immunotherapies can be used for cancer types indication without a biomarker (one exception).

• For metastatic non-small cell lung cancer, the use of first line immunotherapy depends on PD-L1 immunohistochemistry expression
Keynote-024 Pembrolizumab

Stage IV non-small cell lung cancer with a IHC PD-L1 expression of greater than 50% randomized to first line pembrolizumab versus standard chemotherapy

PD-L1, the far from perfect biomarker

First line nivolumab no better than chemotherapy in first line with PD-L1 IHC >1%

Second line nivolumab

Financial Cost for Immunotherapy

• Retail costs for 3 months of immunotherapy
  – Ipilimumab -- $164,644
    • Adjuvant high dose Ipilimumab for melanoma -- $526,864 for four dose induction, then $131,716 every 3 months for up to 3 years.
  – Nivolumab -- $43,326
  – Pembrolizumab -- $42,680
  – Atezolizumab -- $41,376
Need for predictive biomarkers for immunotherapy
Cancer Immunotherapy Biomarker

• A large ongoing effort to determine immunotherapy biomarkers

• Blood based? tissue based?

• Genomic? RNA expression? Protein expression?

• One all encompassing biomarker? Multiple different and separate biomarkers for the large amount of therapies becoming available?
Biomarkers in context

- The biomarkers for immunotherapies will likely depend on interpretation in context of the patient’s tumor, tumor microenvironment, local immune response and systemic immune response.
Resources for biomarker development

- Translational science/Biomarker development
  - Precision Genomics
    - Tumor Mutational Burden (TMB) for ICG100
    - immunoSEQ
  - Translational Science Center
    - Mass cytometry and imaging
Tumor mutational burden

- Tumor mutational burden may help in selecting patient for immunotherapy.
Benefit of pembrolizumab in NSCLC by TMB

Whole exome sequencing

Green is response
Red is progression

Bladder cancer, atezolizumab, and TMB

TMB estimated in 150 patients by 315 gene panel. Responders (12.4/MB) compared to non-responders (6.4/MB), p<0.0001

### High TMB??

**Known variants:**
- APC S836*
- APC S837*
- DNMT3A W601*

**Variants of unknown significance:**
- ABL1 S1071R
- APC D1058G
- APC L548F
- ATRX V2463L
- AXL C776S
- CCND2 S222E
- EMSY S1278T

**Low TMB??**

**Known variants:**
- PALB2 R131fs
- PIK3CA E81K
- TP53 R280T

**Variants of unknown significance:**
- ERBB2 F616L
- JAK1 G191E
- JAK3 Q743L
- ROS1 Y1700*
- SETBP1 A702G
- KMT2A L3385V
- TSC1 L827Q
- MET P664A
- NBN Y746fs
- NTRK1 L156Q
- RAD21 L19P

**AKT1 D323H**
- BRAF Amplified
- CDK12 S343fs

**MSH2 Amplified**
- RB1 Y225C
- SRC I297T
Intermountain patients with ICG100 and immunotherapy

- Retrospective analysis of 24 patients with ICG100 testing eventually treated with immunotherapy
  - Independent of tumor type
  - All checkpoint inhibitors
    - Ipilimumab, nivolumab, pembrolizumab
Preliminary signal

N=24, p =0.0307

B = TMB >36
A = TMB <36
TMB next steps

• Bioinformatics currently re-evaluating different strategies to determine TMB
  – Synonymous vs non-synonymous
  – Least amount of genes needed

• OPeN
  – Pool TMB data from OPeN network
  – Different assays different TMBs?
Biomarkers in context

- The biomarkers for immunotherapies will likely depend on interpretation in context of the patient’s tumor (genomic sequencing and TMB), tumor microenvironment, local immune response and systemic immune response.
Sequencing the T-cell repertoire

• Sequencing all T-cell clones within a sample (e.g. blood, tumor sample, lymph node)
immunoSEQ through adaptive biotechnologies

Sequencing the unique CDR3β portion of tumor tissue and/or peripheral blood
BRAFi in Melanoma

Z. A. Cooper, et al., Oncoimmunology. 2:e26615
immunoSEQ next steps

• It is expected that patient who respond to immunotherapy has a change in the T-cell repertoire.

• What T-cell repertoire changes occur for patients undergoing targeted therapy?

• Initiating a small study collecting peripheral blood at three time points, pre-tx, 3months, and either progression or 9months
  – Rationale for combination or sequencing targeted/immunotherapy
Biomarkers in context

- The biomarkers for immunotherapies will likely depend on interpretation in context of the patient’s tumor (genomic sequencing and TMB), tumor microenvironment, local immune response (immunoSEQ) and systemic immune response (immunoSEQ).
Mass cytometry and imaging
Mass Cytometry and Imaging

Fluorescence spectrum (limited number of biomarkers, ~12)

Mass cytometry spectrum (greater capacity for biomarker discovery, 40+)

R. M. Levenson, et al., Lab Invest. 95:397-405
Tumor Cell Types

- Tumor Epithelium
- Pericyte
- Fibroblast
- Myeloid Derived Suppressor Cell
- Bone Marrow Derived Cells
- Mesenchymal Stem Cell
- Lymphocyte
- Neutrophil
- Tumor Associated Macrophage (TAM)
- Endothelial Cell
- Endothelial progenitor cell
- Mast Cell
- NK cell
- Monocyte
- TIE-2-expressing Monocytes
Dissociating Tumors

Cell Suspension of Tumor and Stroma

Tumor from OR

Collagenase Hyaluronidase
Mass Cytometry and Imaging

C. Giesen, et al., Nat Meth. 11:417-422
Short list of possible immunotherapy biomarkers for R&D

- CD8
- CD4
- CD3
- CD45RA
- FOXP3
- PD-1
- PD-L1
- PD-L2
- CD68
- CD20
- CD45RO
- CD19
- CD57
- CD11c
- CD127
- CD25
- CD26
- ICOS
- CD39
- CD3
- CD73
- CTLA4
- LAG3
- CD80
- CD28
- CD86
- CD40
- CD40L
- 4.1BBL
- 4.1BB
- OX40
- OX40L
- GITR
- GITRL
- Galectin 9
- TIM-3
- CD15
- CD34
- CD11b
- CD33
- CD13
- HLA-DR
- CD226
- CD269
- BAFFR
- CD160
- CD200R
- 2B4
- LIGHT
- BTLA
- B7H4
- Ki67
Mass Cytometry and Imaging

One dimension:

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+ \\
\end{array} \\
2^1 = 2 \text{ levels}
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Three dimensions:

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+,- & +,- & -,- \\
\end{array} \\
2^3 = 8 \text{ levels}
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Four dimensions:

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+,-,- & +,+,- & +,-,+ & +,-,- \\
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2^4 = 16 \text{ levels}
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Two dimensions:

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2^2 = 4 \text{ levels}
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Forty dimensions:

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2^{40} > 1 \text{ trillion levels}
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Mass cytometry and imaging

• More fully categorize cell populations in the tumor microenvironment, whether liquid or solid malignancies

• Provide spatial evaluation of tumor microenvironment

• Provide context to tumor genomic alterations
Biomarkers in context

• The biomarkers for immunotherapies will likely depend on interpretation in context of the patient’s tumor (genomic sequencing and TMB), tumor microenvironment (mass cytometry), local immune response (mass cytometry and immunoSEQ) and systemic immune response (mass cytometry and immunoSEQ).
Conclusions

• Cancer immunotherapy has provided long term survival for many patients who would have succumbed to their disease.

• Cancer immunotherapy only works in a minority of patients and comes at a significant cost.
Conclusions

• The Cancer Immunotherapy Program will expand access to promising clinical trials.

• There are no effective biomarkers to predict response to therapy.

• The Cancer Immunotherapy Program will leverage Intermountain resources to offer precision immunotherapy.