Limits of Monotherapy, and the State of PD-1 and PD-L1 Combination Therapies in Clinical Trials

National Academy of Medicine
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Associate Cancer Center Director for Translational Research
Director Immuno-Oncology Program (ad interim)
Disclosures

Consulting

• AstraZeneca
• Eli Lilly
• Genentech/Roche
• Merck
• NextCure
• Novartis
• Pfizer

Research Support

• AstraZeneca
• Eli Lilly
• Merck
• Genentech
Plan for Discussion

1. Using NSCLC as an example, review both the promise and limitations of immunotherapy

2. Explore mechanisms of sensitivity and resistance to immunotherapy: Primary vs Acquired

3. Combination Immunotherapy: Principles and Practice

4. The Next step: Personalized Immunotherapy and rational Designs
Plan for Discussion

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A New Era for NSCLC Treatment!

- Docetaxel shown to benefit patients with 2L NSCLC
- Pemetrexed shown activity in 1L LUAD
- Bevacizumab shown activity with cytotoxic therapy in 1L NSCLC
- Osimertinib shown to be effective in EGFR T790M mutations
- Osimertinib shown to be superior to cytotoxic therapy in previously treated EGFR T790M mutations

Discovery of EGFR mutations in LUAD sensitive to gefitinib and erlotinib
Gefitinib shown better activity than cytotoxic therapy in LUAD
Bevacizumab shown activity with cytotoxic therapy in 1L NSCLC
Crizotinib (first ALK Inhibitor) shown to be effective in ALK positive NSCLC
Crizotinib shown to be superior to cytotoxic therapy in 1L ALK positive NSCLC
Crizotinib shown to be effective in ROS1 positive NSCLC
RET and ROS fusions described in LUAD
Osimertinib shown to be effective in EGFR T790M mutations


- TCGA Genomic Characterization of LUSC completed
- TCGA Genomic Characterization of LUAC completed
- Crizotinib shown to be effective in ROS1 positive NSCLC
- Pembrolizumab shown to be superior to cytotoxic therapy in 1L PD-L1 high NSCLC
- Alectinib shown to be superior to crizotinib in 1L ALK positive NSCLC
- Nivolumab shown to be effective in NSCLC
- Immune checkpoint blockers shown to be superior to docetaxel in 2L NSCLC

Legend
- Chemotherapy
- Angiogenesis
- Genomic
- Targeted Therapy
- Immunotherapy

1L = First-line; 2L = Second Line
One of the very first lung patients on Nivolumab
Refractory Squamous Cell NSCLC, June 2010

Pre-Nivolumab
2 Years on Nivolumab
year 6: > 4 Years off Nivolumab

Cure?
How Common is Maureen’s Incredible Outcome

1. 10-15%
2. 15-30%
3. 30-50%
4. > 50%

Acquired Resistance > 50%

There is much more room for improvement!
PD-1, PD-L1 antibody Approvals in Refractory NCSLC

Borghaei and Brahmer, NEJM 2015
Herbst, Lancet 2016

Nivolumab FDA approved 2015
Pembrolizumab FDA approved 2015
Atezolizumab FDA approved 2016

IO Grade ¾ toxicity is less than with chemotherapy- though significant Immune related adverse events can occur.

Borghaei and Brahmer, NEJM 2015
Herbst, Lancet 2016
Reck, NEJM 2016
Barlesi, ESMO 2016
Pembrolizumab Biomarker Development

Pembrolizumab DAKO-22c3 Ab

0%  1-49% low  > 50% high

Overall Survival: Pembrolizumab PDL-1 High (＞50%)

**KEYNOTE 024**

![Graph showing overall survival rates for Pembrolizumab and Chemotherapy]

**Events, n**

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Pembrolizumab^a</td>
<td>73</td>
<td>0.63 (0.47–0.86)</td>
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<tr>
<td>Chemotherapy</td>
<td>96</td>
<td>P = 0.002^b</td>
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</table>

**Median (95% CI)**

- Pembrolizumab: 30.0 mo (18.3 mo–NR)
- Chemotherapy: 14.2 mo (9.8 mo–19.0 mo)

**No. at risk**

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<thead>
<tr>
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<td>Time, months</td>
<td>n</td>
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<td>0    3   6   9  12  15  18  21  24  27  30  33</td>
<td>0    3   6   9  12  15  18  21  24  27  30  33</td>
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<td>Pembrolizumab</td>
<td>154  136  121 112 106  96   89   83   52   22   5    0</td>
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</tr>
<tr>
<td>Chemotherapy</td>
<td>151  123  107  88  80   70   61   55   31   16   5    0</td>
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</table>
Overall Survival: PD-L1 ≥1%

<table>
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<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
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<tr>
<td>Pembro</td>
<td>371 (58.2%)</td>
<td>0.81  (0.71-0.93)</td>
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<tr>
<td>Chemo</td>
<td>438 (68.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)
16.7 mo (13.9-19.7) 
12.1 mo (11.3-13.3)

Data cutoff date: Feb 26, 2018.

Gilberto Lopes
Plan for Discussion

1. Using NSCLC as an example, review both the promise and limitations of immunotherapy

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Mechanism of Immune Checkpoint Inhibitors

- Cancer cells develop many mutations that can make them appear foreign to the immune system
- T cells can recognize, attack and kill these “foreign” cancer cells
- Cancer cells can evade immune attack by expressing PD-L1
- Adaptive tumor expression of PD-L1 turns the immune system OFF
- Clinically, we want to block PD-1 or PD-L1 to reactivate the immune system
- PD-L1 plays an important role in dampening the anti-tumor immune response

Key Attributes of the Immune System

- Specificity
- Memory
- Adaptive

Cancer cells develop many mutations that can make them appear foreign to the immune system.

T cells can recognize, attack and kill these “foreign” cancer cells.

Cancer cells can evade immune attack by expressing PD-L1.

Adaptive tumor expression of PD-L1 turns the immune system OFF.

Clinically, we want to block PD-1 or PD-L1 to reactivate the immune system.

PD-L1 plays an important role in dampening the anti-tumor immune response.

Herbst RS et al. J Clin Oncol. 2013;31(suppl; abstr 3000)
Four Categories of Tumors
*Based on Presence of PD-L1 and TILS*

![Image showing PD-L1 and TIL expression patterns with 45% Type I, 17% Type II, 26% Type III, and 12% Type IV](image)

**Proposed mechanisms associated with NSCLC resistance to anti-PD-1/B7-H1 therapy**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Type</th>
<th>Tumor Distribution</th>
<th>Possible Resistance Mechanism(s)</th>
<th>Analysis</th>
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<tr>
<td>B7-H1</td>
<td>TIL</td>
<td></td>
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<tr>
<td>-</td>
<td>-</td>
<td>I</td>
<td>Poor priming of general T cell responses</td>
<td>Peripheral CD4+ and CD8+ T cell responses to autologous tumor cells</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Lack of inflammatory cell recruitment</td>
<td>Chemokine expression in biopsy or FFPE samples</td>
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<tr>
<td>+</td>
<td>+</td>
<td>II</td>
<td>Incomplete PD-1/B7-H1 pathway blockade and activation of alternate immune suppressive pathways</td>
<td>CD80 expression on TILs, expression of alternate suppressive pathways in TME</td>
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<tr>
<td>-</td>
<td>+</td>
<td>III</td>
<td>Alternate immune suppressive pathways</td>
<td>Expression of select molecules in pathways with roles in evasion of NSCLC immunity</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>IV</td>
<td>Intrinsic induction of B7-H1 by oncogenes</td>
<td>Expression of molecules triggering aberrant signaling events</td>
</tr>
</tbody>
</table>


450 samples analyzed
Defining and Understanding Adaptive Resistance in Cancer Immunotherapy

On Target Resistance
Biomarker Analyses for PD-L1 Treatment

Mechanistic studies using pre and post biopsies


Atezolizumab Phase 1
Three distinct patterns of nonresponse were observed.

Most patients who progressed failed to show up-regulation of PD-L1 or evidence of activated T cells.

These results provide evidence for the “inflamed tumor” hypothesis.
The next frontier: utilising immune profiling for a patient-driven approach

Each immune phenotype requires a personalized immunotherapy approach to initiate/re-initiate the antitumor immune response

INFLAMED

IMMUNE EXCLUDED

IMMUNE DESERT

Essential T cell activity required

KILL tumour

INfiltrate tumour

GENERATE active, tumour-directed T cells

TIL subtype quantification in FFPE defines the “Inflamed” phenotype in NSCLC
Converting the Lung Tumor Subclasses to T-cell Activation Subclasses

Kurt Schalper et al, Nat Comm In Press
Converting the Lung Tumor Subclasses to T-cell Activation Subclasses

Kurt Schalper et al, In Press Nature Communications
Type 1 = Low CD3
Type 2 = High CD3/low GZB & Ki-67
Type 3 = High CD3/high GZB or Ki-67

Progression-free survival

Overall survival

Log-rank P=0.043

Log-rank P=0.003

Surviving probability

Surviving probability

Time (years)

Time (years)
Validation will Require Collaboration!
Yale Cohort of Patients with Acquired Resistance to Immune Checkpoint Inhibitors

Gettinger, Choi, Hastings, Truini, Datar, Politi et al., Cancer Disc. 2017
Acquired Resistance to Anti-PD-L1 plus Anti-CTLA4


Jungmin Choi, Anna Wurtz, Scott Gettinger
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And Certainly The Search for New Combinations and Personalized Immunotherapy Must Continue

M. Philips, Equity Research 2018
**Anti-PD1/PDL1 as backbone to lung combination treatment?**

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
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</table>

**A Cancer Conundrum: Too Many Drug Trials, Too Few Patients**

By QINA KOLATA  AUG. 12, 2017
Immuno-Oncology
Multiple Immune Mechanisms for Resistance

- **Checkpoint Inhibitors**
  - Anti-PD-L1
  - Anti-PD-1

- **Activate T Cells**
  - CD137/4-1BB
  - OX-40 agonist antibody

- **Abrogate Suppression from Macrophages & MDSCs**
  - M-CSF
  - IDO1 inhibitor

- **Transfer Engineered T Cells**
  - CAR-T

- **Vaccines, Oncolytic Viruses, Bispecific**
Dual Checkpoint Blockade
PD1/PDL-1 and CTLA-4

Early Evidence Suggests Tumor Mutational Burden (TMB) as a Biomarker

Ribas A et al NEJM 2012
Targeting the Immunosuppressive Microenvironment

Many Ongoing Early Studies - What Will Rise to the Top?
Patients may continue treatment for up to 35 cycles, until confirmed progressive disease or discontinuation for any other reason. Protocol was recently amended to add cohorts A1, A2 and E; cohorts are currently enrolling. DLT dose-limiting toxicity; PK pharmacokinetics; Ram ramucirumab; Pembro pembrolizumab
COHORT C: INTERIM CLINICAL ACTIVITY RAMUCIRUMAB + PEMBROLIZUMAB

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>Patients</th>
<th>Events</th>
<th>Median PFS, Mo (95% CI)</th>
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<tbody>
<tr>
<td>All Patients</td>
<td>27</td>
<td>8</td>
<td>NR (3.98, --)</td>
</tr>
<tr>
<td>Negative</td>
<td>10</td>
<td>2</td>
<td>NR</td>
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<tr>
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<td>4</td>
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<td>3.98 (2.76, --)</td>
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<tr>
<td>Strong positive</td>
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<td>Not reported</td>
<td>6</td>
<td>2</td>
<td>NR</td>
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</tbody>
</table>

Herbst et al, 2016 ESMO

Phase 1 Study Using VEGF Inhibitors to Enhance T Cell Activity

Needs Phase II Confirmation and Biopsy Studies re Mechanism!
Rationale for Combination Therapy

- Reduces tumor bulk – Improves T-cell: tumor target ratio
- Theoretical concerns exist regarding side effects of cytotoxic chemotherapy on proliferation of T-cells
- Long term data needed to truly understand the combinatorial effect
- Kills tumor cells in a manner that increases their recognition by T-cells and APC (vaccination)
- Alters T-cell signaling/gene expression to produce T-cell attractants

Adapted from M. Sznol, Yale Cancer Center
Keynote 189: Pembrolizumab (PD1 plus Chemotherapy) Met All Primary Endpoints

OS:
HR 0.49 [95% CI: 0.38-0.64]; p <0.00001
Median (95% CI)
NR (NE-NE)
11.3 mo (8.7-15.1)

12-mo rate
69.2%
49.4%

PFS:
HR 0.52 [95% CI: 0.43-0.64]; p <0.00001
Median (95% CI)
8.8 mo (7.6-9.2)
4.9 mo (4.7-5.5)

12-mo rate
34.1%
17.3%

Subgroup Analyses
OS: Positive across all subgroups
PFS: Positive across all subgroups except for PD-L1 TPS <1%

Gandhi et al, NEJM 2018
Plan for Discussion

1. Using NSCLC as an example, review both the promise and limitations of immunotherapy

2. Explore the sensitivity and resistance to immunotherapy: Primary vs Acquired

3. Combination Immunotherapy: Principles and Practice

4. The Next step: Personalized Immunotherapy and rational Designs
We need to consider evolving biomarkers (including TMB, Liquid Biopsies, microbiome and Imaging)

Novel Clinical Trials:
A multi-disciplinary approach to understand response and resistance

<table>
<thead>
<tr>
<th>Trial Samples</th>
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<tbody>
<tr>
<td>NSCLC Nivolumab + ipilimumab</td>
</tr>
</tbody>
</table>

**Tumor tissue** ➔ **Peripheral blood/PBMC** ➔ **Stool samples**

**Multi-site trial led by Scott Gettinger**

**Translational Collaborators:**
- Richard Flavell
- David Hafler
- Kurt Schalper
- Katie Politi

**Imaging Collaborator:**
- Richard Carson

**PD-L1 PET Imaging**

- **TILs**
- **DNA mutations**
- **Cytokine**
- **Microbiome**
- **RNA expression**
- **TCR sequencing**
- **CyTOF immunoprofiling**

- **H&E/OIF**
- **WES**
- **ELISA**
- **16S rRNA seq**
- **RNA-seq**
- **Immunoseq**
- **CyTOF profiling**

- **Amount and function**
- **Mutation signature**
- **Neoantigens**
- **Type of microbiota and frequency**
- **Transcript signature**
- **T-cell Clonality**
- **T-cell content**
- **Immune composition, quantitative and change**

**Role: Mechanism of action, predictive markers and pharmacodynamics responses**

**Integrative bioinformatics**
LUNG-MAP

S1400 LUNG MASTER PROTOCOL
Previously-treated Stage IV or Recurrent Non-Small Cell Lung Cancer (all histologies) Immunotherapy or Chemotherapy Relapsed/Refractory Patients

Biomarker-matched* Sub-studies

- Biomarker 1 Positive
  - Sub-study 1: Biomarker-driven Therapy
    - Investigational therapy 1
- ...Biomarker n Positive
  - ...Sub-study n: Biomarker-driven Therapy
    - Investigational therapy n

Non-Matched Sub-studies

- IO Naïve (squamous only)
- IO Relapsed/Refractory
  - Collect tissue for Immuno-Biomarker Profiling
    - Randomization
      - Nivolumab + Ipilimumab V. Nivolumab
        - IO Sub-study 1
          - IO combo 1
        - ...IO Sub-study m
          - IO combo m

Common Control Dealer’s choice based on histology

Stage 2:

- Investigational therapy 1
- Standard of Care
- Investigational therapy n
- Standard of Care

LUNG-MAP (S1400): Ongoing Current Amendments

800 US Sites
Over 1700 Patients Enrolled!
Biomarkers don’t just involve the tumor anymore!
We have spent over 20 years developing personalized mechanisms for administering targeted agents: now the same must be done for IO (with even additional complexity).
To Raise the Tail!!!!

Hypothetical KM curve

- Combinations with immunotherapy
- Immune checkpoint monotherapy
- Targeted therapy
- Chemotherapy

Percent survival vs. Time
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