Novel Agents for Advanced Non Small Cell Lung Cancer

Tuesday, May 21, 2019 | Westerly Yacht Club | 5:00 pm – 8:30 pm

Roy S. Herbst
Ensign Professor of Medicine
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Cancer Center Director for Translational Research
Director Immuno-Oncology Program (ad interim)
Disclosures: Roy S. Herbst, MD, PhD

Consulting
Abbvie Pharmaceuticals, ARMO Biosciences, AstraZeneca, Biodesix, Bristol-Myers Squibb, Eli Lilly and Company, EMD Serrano, Genentech/Roche, Genmab, Halozyne, Heat Biologics, Infinity Pharmaceuticals, Loxo Oncology, Merck and Company, Nektar, Neon Therapeutics, NextCure, Novartis, Pfizer, Sanofi, Seattle Genetics, Shire PLC, Spectrum Pharmaceuticals, Symphogen, Tesaro, Tocagen

Research Support
AstraZeneca, Eli Lilly and Company, Merck and Company

Scientific Advisory Boards
Neon Therapeutics, Infinity Pharmaceuticals, NextCure

Board Member (non-executive/ independent)
Junshi Pharmaceuticals
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 Trial Designs
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 Trial Designs
The Burden of Lung Cancer

• The Leading Cause of Cancer Death in Most Countries
  – 1.8 M new cases, 1.6 M deaths

• US Lung Cancer:
  – 234,030 new cases (13.5% of all cancer cases)
  – 154,050 deaths (25% of all cancer deaths)

• 85% of lung cancer is NSCLC (~15% small cell)
  – 40% Adenocarcinoma, 30% Squamous cell carcinoma

• Potentially Actionable Genetic Alterations: *
  10% EGFR
  <8% ALK
  7% MET
  3% ERBB2/3
  2% ROS
  1% RET
  1% NTRK


* For Lung Adenocarcinomas

TPS: Tumor Proportion Score
Lung Cancer Therapy in 1997

*We Had Reached A Ceiling for Cytotoxic Chemotherapy
All New Therapies Were the Same!*

- All randomized studies had similar results
- No clear efficacy benefit for non-platin combinations (or triplets)
- A paradigm shift was needed!!

The Very First Gefitinib Continuous Phase I Study (1998)

Baseline 1 Week Later

FDA Approved May 2003

Selective Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor ZD1839 Is Generally Well-Tolerated and Has Activity in Non-Small-Cell Lung Cancer and Other Solid Tumors: Results of a Phase I Trial


Effect of Deletions and Mutations in the Epidermal Growth Factor Receptor Gene (EGFR) on Disease Development and Drug Targeting


Cecily: 9 years on Gefitinib

Tara Parker-Pope Wall Street Journal 2003
Osimertinib response in pre-treated EGFR+ NSCLC patients with T790M mutation

Best percentage change from baseline in target lesion – all patients

Is anyone cured?
Progress in Lung Cancer
The 10 Year Journey From Targeted Therapy (BATTLE Studies) to Immunotherapy for Lung Cancer

Biomarkers don’t just involve the tumor anymore!
One of the very first lung patients on MDX-1106 (Nivolumab) 3X Chemo-Refractory Squamous Cell NSCLC June 2010

Cure?
How Common is Maureen’s Incredible Outcome with Immunotherapies

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

Another issue is acquired resistance approx. 50%
Evolution of NSCLC Therapy

Refractory

Early disease

First line

2nd line

No. at Risk
PS ≥50%
PS 1-49%
PS ≤16%

110
92
16

22
5
4
3
0

131
139
135
60
25
3
0

90
38
19
1
0

152
118
58
15
6
4
0
0

155
133
66
21
12
6
0
0

PD-L1 TPS ≥50%

First line

Early disease

First line

No. at Risk
Durvalumab
Pembrolizumab
Fluorophoreside

476
464
431
415
185
156
544
316
274
218
135
73
3
0
0

133
122
108
178
176
155
141
138
117
78
42
21
9
3
1
0

154
136
121
82
39
112
0

Chemotherapy

131
122
106
64
34
7
1
0

Hazard ratio for death, 0.60 (95% CI, 0.41–0.89)
P=0.005

No. at Risk
Pembrolizumab
Chemotherapy

346
219
132
60
25
12
0

345
212
76
21
1
0


# Seminal studies of immune checkpoint inhibitors in NSCLC

<table>
<thead>
<tr>
<th>Study name</th>
<th>Phase</th>
<th>Population</th>
<th>Line of treatment</th>
<th>Design</th>
<th>SOC Outcome (95% CI)</th>
<th>Intervention Outcome (95% CI)</th>
<th>Hazard ratio (95% CI; P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Later line metastatic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CheckMate 017</td>
<td>III</td>
<td>Squamous</td>
<td>2nd or later</td>
<td>Nivolumab vs. docetaxel</td>
<td>mOS 6.0 months (5.1-7.3)</td>
<td>mOS 9.2 months (7.3-12.6)</td>
<td>0.62 (0.47-0.80)</td>
</tr>
<tr>
<td>CheckMate 057</td>
<td>III</td>
<td>Nonsquamous</td>
<td>2nd or later</td>
<td>Nivolumab vs. docetaxel</td>
<td>mOS 12.2 months (9.5-15.1)</td>
<td>mOS 9.5 months (8.1-10.7)</td>
<td>0.75 (0.63-0.91)</td>
</tr>
<tr>
<td>KEYNOTE-010</td>
<td>II/III</td>
<td>NSCLC PD-L1 TPS ≥ 1%</td>
<td>2nd or later</td>
<td>Pembrolizumab 2 mg/kg or 10 mg/kg vs. docetaxel</td>
<td>mOS 8.5 months (7.5-9.8)</td>
<td>mOS 2 mg/kg 10.4 months (9.4-11.9)</td>
<td>2 mg/kg vs. docetaxel: 0.71 (0.58-0.88); P=0.0008 10 mg/kg vs. docetaxel: 0.61 (0.49-0.75); P&lt;0.0001</td>
</tr>
<tr>
<td>POPLAR</td>
<td>II</td>
<td>NSCLC</td>
<td>2nd or later</td>
<td>Atezolizumab vs. docetaxel</td>
<td>mOS 9.7 months (8.6-12.0)</td>
<td>mOS 12.6 months (9.7-16.4)</td>
<td>0.73 (0.53-0.99); P=0.04</td>
</tr>
<tr>
<td>OAK</td>
<td>III</td>
<td>NSCLC</td>
<td>2nd or later</td>
<td>Atezolizumab vs. docetaxel</td>
<td>mOS 9.6 months (8.6-11.2)</td>
<td>mOS 13.8 months (11.8-15.7)</td>
<td>0.73 (0.62-0.87); P=0.0003</td>
</tr>
</tbody>
</table>
CA209-003, Salvage Nivolumab for Adv NSCLC

- Pre-treated advanced NSCLC, 80% with > 2 prior lines of Tx
- ORR 17%; Median duration of response 17 months
- Minimum follow up- 58.25 months; Gettinger et al, JCO ‘18

<table>
<thead>
<tr>
<th>Years</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 y</td>
<td>42%</td>
</tr>
<tr>
<td>2 y</td>
<td>24%</td>
</tr>
<tr>
<td>3 y</td>
<td>18%</td>
</tr>
<tr>
<td>5 y</td>
<td>16%</td>
</tr>
<tr>
<td>Overall (N = 129)</td>
<td>9.9 (7.8, 12.4)</td>
</tr>
</tbody>
</table>
Keynote 10: 3 Year Survival
Kaplan-Meier Estimates of OS
PD-L1 TPS ≥1% Population

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events, n (%)</th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>690</td>
<td>548 (79)</td>
<td>11.8 (10.4–13.1)</td>
<td>0.69 (0.60–0.80)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>343</td>
<td>295 (86)</td>
<td>8.4 (7.6–9.5)</td>
<td>P&lt;0.00001</td>
</tr>
</tbody>
</table>

Herbst et al, ESMO IO, 2018
### Keynote 10: 3 Year Survival

**Kaplan-Meier Estimates of OS**

**PD-L1 TPS ≥50% Population**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events, n (%)</th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>290</td>
<td>199 (69)</td>
<td>16.9 (12.3–21.4)</td>
<td>0.53 (0.42–0.66)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>152</td>
<td>127 (84)</td>
<td>8.2 (6.4–9.8)</td>
<td>P&lt;0.00001</td>
</tr>
</tbody>
</table>

**Data cutoff:** March 16, 2018.
Case Tumor Response

Baseline, Before Treatment

1st Response, During Initial Treatment (PR)

Progressive Disease, After Initial Treatment End

2nd Response, During Second Course (PR)

Lesion 1

Lesion 2

NL, new lesion.
Updated Keynote-24: Front Line Pembrolizumab

PD-L1 TPS ≥50% Population

Reck et. al, JCO 2019
An Investigator Initiated Phase 2 Study of Pembrolizumab in Lung or Melanoma Patients with Brain Metastases

Figure 1

A

B

Goldberg S, Kluger H et al, Lancet Oncology
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
Mechanism of Immune Checkpoint Inhibitors

Complexity of the Immune Microenvironment

- Stromal PD-L1 modulation of T cells

- IFN-γ-mediated upregulation of tumor PD-L1

- PD-L1/PD-1-mediated inhibition of tumor cell killing

- Priming and activation of T cells

- PD-L2-mediated inhibition of TH2 T cells

- M2 macrophage

- Stromal PD-L1 modulation of T cells

- Tumor-associated fibroblast

- CD8+ Cytotoxic T Lymphocyte (CTL)

- Treg cell

- TH-2 T cell

Herbst RS et al. J Clin Oncol. 2013;31(suppl; abstr 3000)
Immune-related Adverse Events (IRAEs)

**Endocrine**
- Thyroiditis
- Hypothyroidism
- Hyperthyroidism
- Hypophysitis
- Hypopituitarism
- Adrenal Insufficiency

**Pulmonary**
- Pneumonitis
- Respiratory failure

**Gastrointestinal**
- Nausea, Emesis
- Diarrhea, Colitis
- Perforation, Pancreatitis

**Neurologic**
- Neuropathy
- Meningitis
- Guillain-Barré Syndrome

**Ocular**
- Iritis
- Uveitis
- Conjunctivitis

**Cardiac**
- Pericarditis

**Dermatologic**
- Mucositis
- Rash, Vitiligo

**Hepatic**
- Transaminitis
- Hepatitis

**Renal**
- Nephritis
- Renal Insufficiency
Issues with PD-L1 as a Biomarker

- **Heterogeneity** – multiple tumors and multiple passes within a tumor
- **Interval between biopsy and treatment**
- **Primary versus metastatic disease**
- **Antibody and staining conditions**

**Defining a positive result (cut-offs):**
- Cell type expressing PD-L1 (immune cell versus tumor or both)
- Location of expression – cell surface versus intracellular versus stromal
- Intensity, percent of cells ‘positive’
- Distribution - patchy versus diffuse, intratumoral versus peripheral

Immunofluorescence shows stroma and epithelial staining are often concordant and adjacent

Green = Cytokeratin  
Blue = Nuclei  
Red = PD-L1 (SP142)

H&E  
E1L3N  
SP142

Negative  
Positive

McLaughlin (Velcheti, Chen, Rimm) et al., JAMA Oncology. 2016;2(1):46-54
KEYNOTE 024
Overall Survival: Pembrolizumab PDL-1 score > 50%

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab*</td>
<td>73</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>96</td>
</tr>
</tbody>
</table>

Median (95% CI)
30.0 mo (18.3 mo–NR)
14.2 mo (9.8 mo–19.0 mo)

*Effective crossover rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of crossover).

Data cutoff: July 10, 2017.

KEYNOTE 042
Overall Survival: Pembrolizumab PDL-1 score ≥1%

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

*Nominal P value. NR, not reached.

Median (95% CI)
70.3% 54.8%
51.5% 34.5%

Data cutoff: Feb 26, 2018.
Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study.
Four Categories of Tumors Based on Presence of PD-L1 and TILS

- PD-L1−/TIL−: 45% Type I
- PD-L1+/TIL+: 17% Type II
- PD-L1−/TIL+: 26% Type III
- PD-L1+/TIL−: 12% Type IV

450 samples analyzed

PD-L1 = B7-H1

Biomarker Analyses for PD-L1 Treatment

Mechanistic studies using pre and post biopsies

Atezolizumab Phase 1

Adaptive Immune Response

Biomarker Analyses
Defining the Profile of Non-responders

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.

Yale SPORE in Lung Cancer

Smoking cessation

Targeting microRNA

Targeting PD-1

Targeting EGFR Resistance

APC or tumor cell

No smoking symbol
Yale Translational Immuno- oncology Lab

Scientific Oversight
- David Haller
- Mario Sznol
- David Rimm
- Roy S. Herbst

Director
- Kurt Schalper

Administration
- Ed Kaftan

CyTOF analysis
- Miguel Sanmamed

Cytokine analysis
- Lesley Devine

Tissue analysis
- Patricia Gaule

Immune function
- Khadir Raddassi

Sequencing/ bioinformatics
- Jungmin Choi

Laboratory Medicine
- Patricia Gaule

Pathology
- Khadir Raddassi

Pathology/Medicine
- Jungmin Choi

Yale Cancer Center
Stratification of NSCLC cases using T-cell markers

NSCLC

Not/poorly inflamed

Inflamed

Inflamed - low activation/proliferation

Inflamed-high activation/proliferation

Type 1: Low/absent CD3

Type 2: High CD3/low GZB & KI-67

Type 3: High CD3/high GZB or KI-67
**A**

Type 1 = Low CD3

Type 2 = High CD3/low GZB & Ki-67

Type 3 = High CD3/high GZB or Ki-67

**B**

Progression-free survival

Log-rank P = 0.043

Surviving probability vs. time (years)

- Type 1 n=19
- Type 2 n=7
- Type 3 n=13

**C**

Overall survival

Log-rank P = 0.003

Surviving probability vs. time (years)

- Type 1 n=19
- Type 2, n=7
- Type 3 n=13

---

Gettinger et al., Nat Comm 2018;(9)3196
1. Commercial use project

2. SU2C clinical trials

High throughput sequencing

Protein immunoprofiling

Clinical annotation and response

Integrated bioinformatics & analysis
(Gemini database)
The Yale Lung Repeat Biopsy Program

Thoracic Oncologists

Identify Consent

Patient
1. Metastatic or recurrent locally advanced disease from a thoracic malignancy
2. Acquired resistance after treatment with erlotinib, gefitinib, crizotinib or a molecularly targeted agent on a clinical trial

Procedure
- Surgery
- IR
- TIP

Flash Frozen
Pre-Treatment Tissue

Collaborating Labs

Politi Lab

Pathologists
- Zenta Walther
- Kurt Schalper

Surgical Pathology/Cytology

Cytopathologist
- Guoping Cai

Study Coordinator

Blood Sample
Cohort of Patients with Resistance to Immune Checkpoint Inhibitors

Pre-Treatment (+/- Intervening Therapy)
- Tumor Tissue
- Germline DNA

Response

Resistance
- Tumor Tissue
- PDX

Analysis
- Exome Sequencing
- RNA Sequencing
- Quantitative Immunofluorescence

Identification of Resistance Specific Alterations

Anti-PD-L1/Anti-CTLA-4
n=2

EGFR TKI/ Anti-PD-1
(after progression on EGFR TKI)

Anti-PD-1
n=6

Anti-PD-L1
n=4

Anti-PD-1
n=2

EGFR TKI/ Anti-PD-1
n=1

Anti-PD-1/Anti-CTLA-4
n=1

EGFR TKI/ Anti-PD-1
n=1

On Immunotherapy
Off Immunotherapy without Other Systemic Therapy
Partial Response
Acquired Resistance
Bopsy

Time (Weeks)
0 20 40 60 80 100 120 140 160 180 200

Cohort of Patients with Resistance to Immune Checkpoint Inhibitors

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

Impaired MHC I antigen presentation is a mechanism of acquired resistance to immune checkpoint inhibitors.

Sharma et al., Cell. 2017 Feb 9;168(4):707-723.
## Multiple Genetic and Non-genetic Processes can Lead to Defects in MHC I Antigen Presentation

**Irreversible**  
- b2M/HLA gene loss  
- Neoantigen loss  

**Reversible**  
- Immune inhibitory signaling  
- Epigenetic silencing of MHC I genes

### MHC I–Independent Therapies

- Natural Killer cells  
- Myeloid cells  
- CAR T cells  
- T-cell/tumor cell antibodies

### Therapies to Re-activate T cells

- Cytokines  
- Block inhibitory signals  
- Epigenetic drugs
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 Trial Designs
The Search for New Combinations and Personalized Immunotherapy Continues

M. Philips, *Equity Research* 2018
Targeting the Immunosuppressive Microenvironment

- Tumor
- Fibroblast
- MDSC
- TAM
- VEGF
- IDO1
- Arginase 1
- Adenosine (A2a)
- IL10
- TGFβ
- CSF-1/MCSF
Rationale for Combination Therapy

- Reduces tumor bulk – Improves T-cell: tumor target ratio
- Separate mechanism of kill – ‘synergize’ with T-cell mechanism of killing
- Reduces T-cell inhibitory substances produced by tumor
- Alters tumor barriers (vasculature/pressure) to T-cell penetration
- 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
Keynote 189: Pembrolizumab (PD1 plus Chemotherapy) Met All Primary Endpoints

**OS:**
- HR 0.49 [95% CI: 0.38-0.64]; p <0.0001
- 12-mo rate: 69.2%
- Median (95% CI): NR (NE-NE) 11.3 mo (8.7-15.1)

**PFS:**
- HR 0.52 [95% CI: 0.43-0.64]; p <0.0001
- 12-mo rate: 34.1%
- Median (95% CI): 8.8 mo (7.6-9.2) 4.9 mo (4.7-5.5)

**Response Rate**
- Δ28.5%
- P < 0.00001

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

Dual Checkpoint Blockade

- Priming phase
  - Dendritic cell
  - T cell
  - Lymph node
- Effector phase
  - T cell
  - Cancer cell

- Activation signals: MHC, TCR, B7, CD28
- Inhibitory signals: B7, CTLA-4
- Negative regulation: PD-1, PD-L1

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; Pembrol pembrolizumab
Using VEGF Inhibitors to Enhance T Cell Activity

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>
</tr>
</thead>
<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>
</tr>
<tr>
<td>Weak positive</td>
<td>4</td>
<td>2</td>
<td>3.98 (2.76, --)</td>
</tr>
<tr>
<td>Strong positive</td>
<td>7</td>
<td>2</td>
<td>NR</td>
</tr>
<tr>
<td>Not reported</td>
<td>6</td>
<td>2</td>
<td>NR</td>
</tr>
</tbody>
</table>

ITT Population

COHORT C NSCLC (n=27)

Objective response rate, n (%) 8 (30%)

Disease control rate, n (%) 23 (85%)

77% of evaluable patients experienced a decrease in target lesions

NSCLC Progression-free survival
Median: 9.69 (4.63-NR)

Herbst et al, 2016 ESMO
Blockade of multiple T cell inhibitory molecules (e.g. anti-LAG3, TIM3, VISTA...)

- Abx that dec gram+, but not gram – Bacteriodales and Burkholderiales (Vancomycin)
- Probiotics (Bifidobacterium spp)

- TNF signaling Inhibitors
- EMT Inhibitors

Target Neovasculature e.g VEGF/R antagonists

- Target TME myeloid cells (bystander elimination of myeloid cells that cross present tumor epitopes)
- Act. NK cells Harness MHC class II

- Vaccine/ Radiation/ Cytotoxic Chemotherapy
- Epigenetic Tx to induce NeoAg Re-expression

- Stimulator of interferon genes agonists
- Oncolytic viruses that replicate in cells with defective IFN signaling

- Prime intratumoral T cell infiltration (e.g. Cytoxan)
- Epigenetic Tx (reverse T cell exhaustion/ memory)
- Inhibit immunosuppressive cells (e.g. cabozantinib - MDSC, also Treg, TAM)

Modulation of glycolysis, inhibit kynurenin (IDO1 blockade) and adenosinergic pathways

Adapted from Syn et al. Lancet Oncol 2017; 18:e731-41
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 Trial Designs
Trial Designs to Personalize Immunotherapy

1. Investigator Initiated Biomarker Driven Studies

2. Signal Finding Master Protocols

3. Prospective/Adaptive Trials
Investigator Initiated Biomarker Driven Trial:
A multi-disciplinary approach to understand response and resistance

Trial Samples
NSCLC Nivolumab + Ipilimumab

Tumor tissue → Peripheral blood/PBMC → Stool samples

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

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

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

Role: Mechanism of action, predictive markers and pharmacodynamics responses

Integrative bioinformatics

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
Umbrella
Test impact of different drugs on different mutations in a single type of cancer
• BATTLE
• I-SPY2
• SWOG Squamous Lung Master

Basket
Test the effect of a drug(s) on a single mutation(s) in a variety of cancer types
• Imatinib Basket
• BRAF+
• NCI MATCH
Lung Master Protocol
Current Schema

Biomarker-Driven Sub-Studies

Completed
12/12/16
$1400B
PI3K+
Taselisib
(GDC-0032)

Completed
09/01/16
$1400C
CCGA+
Palbociclib

Completed
10/31/16
$1400D
FGFR+
AZD4547

Closed
11/25/14
$1400E
c-Met
Rilotumumab

Completed
06/20/18
$1400G
HRD+
Talazoparib

Open
Teliso-V
(ABBV-399)

Anticipated
Q4 2018

$1900A*
LOH/BRCA+
Rucaparib

Anticipated
Q1 2019

$1900B*
RET+ mut
LOXO-292

Anticipated
Q1 2019

$1900C*
LKB1+ mut
Talazoparib
+ Avelumab

Non-match Sub-Studies

Completed
12/18/15
$1400A
Checkpoint
Naive
Durvalumab

Completed
04/23/18
$1400I
Checkpoint
Naive
Nivolumab
+ Ipilimumab

Open
Durvalumab
+ Tremelimumab

Anticipated
Q4 2018

$18000A*
Checkpoint
Refractory
Pembrolizumab
+ Ramucirumab
vs. SOC

Sites open: 652
Total registered: 1802
Total assigned to sub-study: 586
• **IRB Approvals:**
  - 600 sites
  - 397 sites with ≥ 1 patient accrued

• **Accruals:**
  - 1650 patients registered to **S1400**
  - 1288 patients assigned to a sub-study
  - 612 patients registered to a sub-study

---

**LUNG-MAP (S1400): Current Accrual**

As of 5/2/18
The ever-expanding LungMAP molecular database

- Number of patients with comprehensive mutation profiling: >1,500
- Number of cancer-associated somatic alterations detected: 9,819
  - >32,000 if include those of unknown significance
- Number of genes with a detected alteration: 300
- Comprehensive genome sequencing plus full patient annotation and treatment outcomes is an impressive resource for data mining.
Is It time for the Next New Paradigm?

Pembro
Atezolizumab
Nivolumab
durvalumab

50+ other pd1/pdl1 agents

YaleNew Haven Health
Smilow Cancer Hospital

Yale Cancer Center
A Comprehensive Cancer Center Designated by the National Cancer Institute
Tumor Immune Microenvironment (TIME) classification.

Siglec-15 as an immune suppressor and potential target for normalization cancer immunotherapy

Jun Wang et al., Yale School of Medicine
WHY DID WE SELECT S15?

**EXPRESSION**
Expressed by Both Tumor Cells and Macrophages

**STRUCTURE**
Similar to PD-L1

**FUNCTION**
Potently Suppresses T Cell Activities
**Biological Relevance**

- Increased expression in many cancer types & tumor infiltrating macrophages
- Restricted and low level expression in normal tissues

**Functional Relevance**

- Mice deficient for S15 showed enhanced antigen-specific T cell responses
- Reduction in tumor growth

**Clinical Relevance**

- S15 expression is mutually exclusive with PD-L1
- Opportunity to treat patients with PD-L1 - / S15+ tumors which are unresponsive to PD-1 therapies
S15 and PD-L1 expression do not overlap in tumors.

Opportunity to treat patients with PD-L1- / S15+ tumors which are unresponsive to PD-1 therapies.

*377 samples
Courtesy of David Rimm - Yale University
**NC318-01: STUDY SCHEMA**

**Phase 1a: Dose Escalation**
- Cohort -1 8 mg
- Cohort 1 24 mg
- Cohort 2 80 mg
- Cohort 3 240 mg
- Cohort 4 400 mg
- Cohort 5 800 mg

**Phase 1b: Safety Expansion**
- 3 or 4 cohorts
  - Confirm PK
  - Biopsy data
  - Determine RP2D

**Phase 2: Dose Expansion**

### Stage 1 of Simon-2 Stage
- HNSCC n=9
  - RR = 0/9 close
- NSCLC n=9
  - RR = 0/9 close
- Ovarian n=9
  - RR = 0/9 close
- PD-L1 low n=9
  - RR = 0/9 close

### Stage 2 of Simon-2 Stage
- HNSCC n=8
- NSCLC n=8
- Ovarian n=8
- PD-L1 low n=8

n = 39-46

n = 36-68
Integration of Biomarkers

- DNA genomics: Class I and II neoaantigens, DNA repair defects, Droogogenic mutations, Germline variants, Clonality/heterogeneity
- Epigenomics: Antibody silencing, Modulation of targets, Noncoding RNAs
- Proteomics: Immune targets and cells, Intracellular signaling, Cytokines, Metabolism, Tumor antigens, Antigen presentation, Posttranslational modifications
- Transcriptomics: Inflammation signatures, Single-cell analyses, Neoaantigen expression, Antigen-presenting machinery, Actionable target screens, Resistance mechanisms
- Immune function and regulation: TIL composition and function, Myeloid cells, Metabolism, Antigen recognition, Suppressive cells, In innate immunity
- Immune contexture and experience
- Tumor: Epitome and immune regulation
- Microbiome and virome: Gut microbiota, Viral infections, Other

Hypothetical KM curve

- Percent survival vs. Time
- Combinations with immunotherapy
- Targeted therapy
- Immune checkpoint monotherapy
- Chemotherapy
Conclusions

• Immunotherapy has transformed the treatment of NSCLC
• Biomarkers and mechanistic understanding are critical to better determine mechanisms of sensitivity and resistance (A Battle Approach)
• Development of new combinations (either with or without chemotherapy) are needed to further personalize immunotherapy

I’ll take a PD-L1 and CTLA-4 inhibitor and a dose of cell therapy please
A final thought

We have spent over 20 years developing personalized mechanisms for administering targeted agents: now the same must be done for Immune Therapy (with even greater complexity)
Acknowledgements

The Schalper lab@Yale
Nikita Mani
Ilia Datar, PhD
Franz Villarreal, PhD
Micaela Morgado, PhD
Rasikh Tuktamyshov, MD
Matthew Ribeiro
Jacob Usadi
Lisa DeChello (admin)

The Rimm lab@Yale
Daniel Carvajal, MD
Mehmet Altan, MD
Vasso Pelekanou, MD/PhD
Maria Toki, MD
Patricia Gaule, PhD
Lauren Moore
Yuting Liu
James Smithy

Yale University
Mario Szolat, MD
Liebing Chen, MD, PhD
Miguel Sanmamed MD, PhD
David Hafler, MD
Patricia LoRusso, DO

YPTS & STS lab
Lori Charrette
Joe Salemme
Sudha Kumar
Yalai Bai, MD
Veronique Neumeister, MD
John McGuire

SU2C Lung CancerDream Team:
Jedd Wolchok, MD, PhD
Alice Shaw, MD, PhD
Pasi Janne, MD, PhD
Roy Herbst, MD, PhD
Justin Gainor, MD
Matt Hellmann, MD

Funding:
Stand Up to Cancer-Dream Team
Yale SPORE in Lung Cancer
Lung Cancer Research Foundation
NIH
DOD LCRP
Industry partners

Immunosequencing,
Edward Kaftan, PhD
Scott Gettinger, MD
Katie Politi, PhD
Rick Liffon MD, PhD
Jungmin Choi, PhD
Hongyu Zhao, PhD
Xiaoqing Yu, PhD
Susan Kaech, PhD
Paula Kavathas, PhD
Thank You