Driver oncogenes in lung cancer: The ‘promise’ of immunotherapy?

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Viruses/ Foreign organisms

Cancer

Organ Transplantation

Cancer: An overview

normal  cancerous change  tumor

Development of genetic instability

Mutations/ Genetic change +

(mut) metastasis

Mutations ++ Genetic change ++

Early stage disease

Advanced/late Stage disease
Cancer biology characteristics

An established cancer is a **failure** of immune surveillance
Immune surveillance: Cell ‘tasting’

How does immune surveillance fail?

1. Cancer cells stop employing carrot-carrying waiters (don’t express MHC)

2. Cancer cells in someone with this type of waiter don’t contain any carrots (certain mutations are deselected during evolution of cancer in your body)

3. Foreign changes (bad carrots) are presented, are tasted but then NOTHING happens
Self-defeating defenses

Understanding the Immune System

Health  Disease

Pick an organ, any organ . . .

Autoimmunity can affect ANY organ/organ system in the human body

- Autoimmune Uveitis
- Sjogren’s Syndrome
- Rheumatic Fever
- Autoimmune Hepatitis
- Autoimmune Oophoritis
- Rheumatoid Arthritis
- Multiple Sclerosis
- Perphigus
- Goodpasture’s Syndrome
- Diabetes
- Addison’s Disease
- Ulcerative Colitis
- Autoimmune hemolytic Anemia
Immune education = learning about friend or foe

Various ligand–receptor interactions between T cells and antigen-presenting cells that regulate the T cell response to antigen (many at different time points)

The painfully insecure T cell

Pardoll NRC 12:252 (2012)
Various ligand–receptor interactions between T cells and antigen-presenting cells that regulate the T cell response to antigen (many at different time points).

The painfully insecure T cell
Role of PD-1 in Suppressing Antitumor Immunity

Antigen Presenting Cell

MHC-Ag

Tumor

B7.1

CD28

T cell

Tell Cell Receptor Signal 1

(+ ) Signal 2

Activation (cytokines, lysis, arrest, migration)

PD-1

PD-L1

Tumor

Anti-PD1

BMS Nivolumab
Merck Pembrolizumab

Anti-PD-L1

MEDI4736 (Durvalumab)
MPDL3280A (Atezolizumab)

Anti-PD1 Activity: A tumor panacea?

Melanoma (N=411) KEYNOTE-001
NSCLC (N=262) KEYNOTE-001
H&N Cancer (N=61) KEYNOTE-012

Urothelial Cancer (N=33) KEYNOTE-012
Gastric Cancer (N=39) KEYNOTE-012
TNBC (N=32) KEYNOTE-012
cHL (N=29) KEYNOTE-013

University of Colorado Anschutz Medical Campus

Pembrolizumab. Alley et al, AACR 2015
**Checkmate 017: Squamous NSCLC 2nd line Nivolumab (PD1) vs docetaxel: Primary Endpoint = Overall Survival**

- **Nivolumab** vs **Docetaxel**
- **FDA licensed March 2015**
- **Spigel et al, ASCO 2015**

**Key Points:**
- **ORR:** 20 vs 9%
- **mDoR:** NR vs 8.4m
- **mPFS:** 3.5 vs 2.8mo
- mOS: 9.2 vs 6.0 (95% CI: 7.3, 13.3 vs 5.1, 7.3)
- HR = 0.59 (95% CI: 0.44, 0.79), P = 0.00025

**Number of Patients at Risk:**
- Nivolumab: 135, 113, 86, 69, 52, 31, 15, 7, 2
- Docetaxel: 137, 103, 68, 45, 30, 14, 7, 2

**Symbols represent censored observations.**

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**Checkmate 057: non-Squamous NSCLC 2nd line Nivolumab (PD1) vs docetaxel: Primary Endpoint = Overall survival**

- **Nivolumab** vs **Docetaxel**
- **FDA licensed October 2015**
- **Paz-Ares et al, ASCO 2015**

**Key Points:**
- **ORR:** 19 vs 12%
- **mDoR:** 17.2 vs 5.6m
- **mPFS:** 2.3 vs 4.2mo
- mOS: 12.2 vs 9.4
- HR = 0.73 (95% CI: 0.59, 0.89), P = 0.0015

**Number of Patients at Risk:**
- Nivolumab: 292, 232, 194, 169, 146, 123, 82, 32, 9, 0
- Docetaxel: 290, 244, 194, 150, 111, 88, 34, 10, 9, 0

**Symbols represent censored observations.**
KEYNOTE-010: Pembrolizumab vs docetaxel 2nd line all histology NSCLC. Primary endpoint: Overall Survival for PD-L1 tissue proportion score ≥ 50% Stratum

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median OS (95% CI), Mos</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>14.9 (10.4-NR)</td>
<td>0.54 (0.38-0.77)</td>
<td>.0002</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>17.3 (11.8-NR)</td>
<td>0.50 (0.36-0.70)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.2 (6.4-10.7)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Both doses ok

2 vs 10 mg/kg:
HR: 1.12 (95% CI: 0.77-1.62)
Side effects

Approved for patients with NSCLC who progressed on or after platinum-containing chemotherapy or EGFR- or ALK-targeted agents in patients harboring those mutations.

Nivolumab arm, 15 percent EGFR-positive and 4 percent ALK-positive, with 13 percent and 3 percent, respectively, in the docetaxel arm.
Checkmate 067: non-Sq NSCLC 2nd line Nivolumab (PD1) vs docetaxel: Primary Endpoint = OS

Treatment Effect on OS in Predefined Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/Pts, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>582</td>
<td>0.75 (0.62, 0.91)</td>
</tr>
<tr>
<td>Age Categorization (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>339</td>
<td>0.81 (0.62, 1.04)</td>
</tr>
<tr>
<td>≥65 and &lt;75</td>
<td>200</td>
<td>0.83 (0.45, 1.69)</td>
</tr>
<tr>
<td>≥75</td>
<td>43</td>
<td>0.90 (0.43, 1.87)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>319</td>
<td>0.73 (0.56, 0.96)</td>
</tr>
<tr>
<td>Female</td>
<td>263</td>
<td>0.78 (0.58, 1.04)</td>
</tr>
<tr>
<td>Baseline ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>179</td>
<td>0.64 (0.44, 0.93)</td>
</tr>
<tr>
<td>≥1</td>
<td>402</td>
<td>0.80 (0.63, 1.00)</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/Former Smoker</td>
<td>458</td>
<td>0.70 (0.56, 0.86)</td>
</tr>
<tr>
<td>Never Smoked</td>
<td>118</td>
<td>1.02 (0.64, 1.61)</td>
</tr>
<tr>
<td>EGFR Mutation Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>82</td>
<td>1.18 (0.69, 2.00)</td>
</tr>
<tr>
<td>Not Detected</td>
<td>340</td>
<td>0.86 (0.51, 1.06)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>160</td>
<td>0.74 (0.51, 1.06)</td>
</tr>
</tbody>
</table>

All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

KEYNOTE-010: OS by Pt Subgroups (PD-L1 TPS ≥ 1%*)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/Pts, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>521/1033</td>
<td>✗</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>332/634</td>
<td>0.65 (0.52-0.81)</td>
</tr>
<tr>
<td>Female</td>
<td>189/399</td>
<td>0.69 (0.51-0.94)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 yrs</td>
<td>317/604</td>
<td>0.63 (0.50-0.79)</td>
</tr>
<tr>
<td>≥ 65 yrs</td>
<td>204/429</td>
<td>0.76 (0.57-1.02)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>149/348</td>
<td>0.73 (0.52-1.02)</td>
</tr>
<tr>
<td>1</td>
<td>367/678</td>
<td>0.63 (0.51-0.76)</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>204/442</td>
<td>0.53 (0.40-0.70)</td>
</tr>
<tr>
<td>1% to 49%</td>
<td>317/591</td>
<td>0.76 (0.60-0.96)</td>
</tr>
<tr>
<td>Tumor sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archival</td>
<td>266/455</td>
<td>0.70 (0.54-0.89)</td>
</tr>
<tr>
<td>New</td>
<td>255/578</td>
<td>0.64 (0.50-0.83)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>128/222</td>
<td>0.74 (0.50-1.09)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>333/708</td>
<td>0.63 (0.50-0.79)</td>
</tr>
<tr>
<td>EGFR status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant</td>
<td>46/86</td>
<td>0.88 (0.45-1.70)</td>
</tr>
<tr>
<td>Wild type</td>
<td>447/875</td>
<td>0.66 (0.55-0.80)</td>
</tr>
</tbody>
</table>

*Data for the pembrolizumab doses were pooled.

Paz-Ares et al, ASCO 2015
Pembrolizumab Antitumor Activity by *EGFR* and *PDL1* Status

<table>
<thead>
<tr>
<th></th>
<th>TPS ≥50%</th>
<th>TPS 1-49%</th>
<th>TPS &lt;1%</th>
<th>Total^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ORR, % (95% CI)</td>
<td>n</td>
<td>ORR, % (95% CI)</td>
</tr>
<tr>
<td><em>EGFR</em> wild type</td>
<td>113</td>
<td>39.8 (30.7-49.5)</td>
<td>60</td>
<td>12.2 (7.5-18.4)</td>
</tr>
<tr>
<td><em>EGFR</em> mutant</td>
<td>20</td>
<td>20.0 (5.7-43.7)</td>
<td>23</td>
<td>8.7 (1.1-28.0)</td>
</tr>
</tbody>
</table>

Gainor et al, CCR 2016

- 0/6 ALK responders to PD1/PD-L1 therapy
- 1/22 EGFR mutant responders to PD1/PD-L1 therapy
Mutations: drivers vs passengers

1. ALK+ track
2. ROS1+ track
3. EGFR mutant track

Drivers!
Major Histocompatibility Complex (MHC)

Cancer cells in someone with this type of waiter don’t contain any carrots (certain mutations are deselected during evolution of cancer in your body)

Therefore carrots cannot be an essential ingredient of the cancer recipe (foreignness driven by passenger not driver mutations)

Causes of cancer
Total coding mutations or alterations/Megabase genomic DNA in tumors by histology and oncogene

<table>
<thead>
<tr>
<th></th>
<th>NSCLC</th>
<th>SCC</th>
<th>SCC NOS</th>
<th>SCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adeno (n=7,525)</td>
<td>(n=1,324)</td>
<td>(n=1,773)</td>
<td>(n=840)</td>
</tr>
<tr>
<td>Mean</td>
<td>9.1</td>
<td>11.3</td>
<td>11.0</td>
<td>10.3</td>
</tr>
<tr>
<td>TMB &gt; 10 (%)</td>
<td>2350</td>
<td>541</td>
<td>711</td>
<td>269</td>
</tr>
<tr>
<td>TMB &gt; 20 (%)</td>
<td>760</td>
<td>113</td>
<td>233</td>
<td>42</td>
</tr>
<tr>
<td>Wilcoxon signed-rank test (versus KRAS)</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Treatment prioritization

Which box do you open first, if you are looking for the BIGGEST chance of benefit? – Start with the biggest one!

Or seek out combination trials
Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy by Smoking and EGFR Mutation Status

**Smoking status**

- Never smoker: ORR (%)
  - Nivo 3 Q2W + Ipi 1 Q6/12W (pooled): 27%
  - Nivo 3 Q2W: 9%
- Current/former smoker: ORR (%)
  - Nivo 3 Q2W + Ipi 1 Q6/12W (pooled): 46%
  - Nivo 3 Q2W: 27%

**EGFR mutation status**

- EGFR mutant: ORR (%)
  - Nivo 3 Q2W + Ipi 1 Q6/12W (pooled): 50%
  - Nivo 3 Q2W: 14%
- EGFR wild-type:
  - Nivo 3 Q2W + Ipi 1 Q6/12W (pooled): 41%
  - Nivo 3 Q2W: 30%

*Must be interpreted with caution: of these 4 responders, 1 did not have a classical exon 19 deletion or L858R EGFR activating mutations, 3 were former/current smokers, and 3 had high PD-L1 expression levels.*