Current Therapies very “T-cell” Centric

CTLA-4 = cytotoxic T-lymphocyte antigen 4
PD-1 = programmed cell death protein 1
LAG-3 = lymphocyte activation gene 3
TIM-3 = T-cell immunoglobulin and mucin protein 3.

Pardoll, Nature Reviews Cancer, 2012
Tumor Immunology is far more complex than just T-Cells, perhaps combination strategies will be more “actionable”

Joyce and Pollard, Nature Reviews Cancer, 2009

Lung Cancer is Highly Mutated!!!


Mechanisms for Immune Evasion, And Ways to Get Around this
Cancer Immunotherapy

- Cancer cells have mutations that make them recognizable by the immune system

- However, cancer cells can evade the immune surveillance by expressing proteins such as PD-L1

- Inhibiting the PD-L1/PD-1 interaction can restore anti-tumor T-cell activity, potentially leading to long-lasting responses
Single Agent Efficacy on anti-PD1 or anti-PDL1 in Non-Small Cell Lung Cancer
### Second Line: Nivolumab in Lung Squamous

<table>
<thead>
<tr>
<th>Median Overall Survival</th>
<th>% of patients (95% CI)</th>
<th>% of deaths</th>
<th>% of deaths (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n=115)</td>
<td>12.2 (9.2-16.2)</td>
<td>59 (95% CI)</td>
<td>31 (17-51)</td>
</tr>
<tr>
<td>Docetaxel (n=115)</td>
<td>4.3 (3.0-6.0)</td>
<td>41 (95% CI)</td>
<td>36 (12-70)</td>
</tr>
<tr>
<td>Hazard ratio for deaths: 3.46 (1.75)</td>
<td>P=0.0005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Brahmer, NEJM, 2015

### Second Line: Nivolumab in non-SqCC NSCLC

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n=202)</td>
<td>1.75 (1.10-2.78)</td>
<td>0.96 (0.80-1.16)</td>
</tr>
<tr>
<td>Docetaxel (n=236)</td>
<td>1.05 (0.74-1.48)</td>
<td>0.95 (0.79-1.16)</td>
</tr>
</tbody>
</table>

Brahmer, NEJM, 2015

### Non-Toxicity of PD1

<table>
<thead>
<tr>
<th>Mild to Moderate (n=125)</th>
<th>High Grade (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0-1</td>
<td>Grades 2-4</td>
</tr>
<tr>
<td>Number of patients in each category:</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Brahmer, NEJM, 2015
Durability of Response is The Real Excitement

Brahmer, NEJM, 2015

Second Line: Pembrolizumab in PD-L1+ NSCLC

Herbst et al, Lancet 2015

Second Line: Atezolizumab in PD-L1+ NSCLC

Rittmayer et al, Lancet 2017
First Line: KEYNOTE 024 Pembrolizumab in NSCLC

- Randomized, open label, phase 3.
- 305 untreated stage IV NSCLC. 1934 patients initially screened.
- PD-L1 > 50% (500 of 1653, ~30% had PD-L1>50%). DAKO 22C3
- No EGFR or ALK mutation
- No untreated CNS metastases or active autoimmune disease
- Assigned 1:1 to Pembrolizumab 200mg every 3 weeks x35 cycles vs. Platinum based chemotherapy x4~6 cycles
  n=154 vs. n=151. Crossover to Pembrolizumab permitted if PD in chemotherapy arm.
- Primary endpoints : PFS
- Secondary endpoints : OS, ORR, safety

Reck et al, NEJM, 2016
First Line: KEYNOTE 024 Pembrolizumab in NSCLC

Current Targets of Immuno-Regulatory Antibody Therapy

PD-L1 As a Biomarker

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antibody</th>
<th>Definition of Positive</th>
<th>Best information on utility of PDL1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Dako 28-8</td>
<td>Variable by study:</td>
<td>In squamous 2L lung study, seemed predictive; not predictive in nonsquamous 2L study</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>22C3</td>
<td>≥ 50% expression in tumor cells</td>
<td>Predictive in phase III study</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>SP142</td>
<td>Combined tumor cell and/or infiltrating T cell</td>
<td>Seemed predictive in POPLAR+OAK</td>
</tr>
<tr>
<td>MEDI-4736</td>
<td>SP263</td>
<td>Membrane positivity of ≥ 25% of tumor cells</td>
<td>Responses in both PDL1 and PDL1 positive</td>
</tr>
</tbody>
</table>
Some progression is really pseudo-progression

But most progression is just progression

After 1 year of stable disease on Nivolumab, stay on treatment!

Combination Approaches in Immunotherapies
Chemo+Ipilumumab (Not Active)
Phase III in Lung Squamous Cancer
Carbo/Taxol +/- Ipilumumab
Govindan et al, Journal of Clinical Oncology, 2017

Chemo+Pembrolizumab (Active!)
Phase II in Lung Adeno
Carbo/Pemetrexed +/- Pembro
Lead to FDA Approval in Front-Line Setting independent of PD-L1 expression
Langer et al, Lancet Oncology 2017

IMpower150 study design
Reck et al, ESMO, 2017
Baseline characteristics in ITT

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>63 (32-85)</td>
<td>63 (31-86)</td>
<td>63 (31-86)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>241 (60%)</td>
<td>246 (60%)</td>
<td>239 (60%)</td>
</tr>
<tr>
<td>ECOG PS, 0, n (%)</td>
<td>166 (40%)</td>
<td>158 (40%)</td>
<td>179 (40%)</td>
</tr>
<tr>
<td>Current smoker (Previous smoker)</td>
<td>37 (15%)</td>
<td>53 (13%)</td>
<td>57 (14%)</td>
</tr>
<tr>
<td>Liver metastases, yes, n (%)</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>ALK rearrangement, positive, n (%)</td>
<td>3 (11%)</td>
<td>2 (10%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Of those tested</td>
<td>292</td>
<td>292</td>
<td>292</td>
</tr>
<tr>
<td>PD-L1 expression, any n (%)</td>
<td>217 (32%)</td>
<td>209 (34%)</td>
<td>217 (34%)</td>
</tr>
<tr>
<td>Of those tested</td>
<td>659</td>
<td>659</td>
<td>659</td>
</tr>
<tr>
<td>KRAS mutation, positive, n (%)</td>
<td>40 (11%)</td>
<td>37 (11%)</td>
<td>39 (11%)</td>
</tr>
<tr>
<td>PD-L1 expression, n (%)</td>
<td>TC2/3 or IC2/3</td>
<td>137 (34%)</td>
<td>140 (35%)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>213 (53%)</td>
<td>209 (52%)</td>
<td>195 (49%)</td>
</tr>
<tr>
<td>TC0 and IC0</td>
<td>195 (47%)</td>
<td>205 (51%)</td>
<td>205 (51%)</td>
</tr>
</tbody>
</table>

Median age (range), years: 63 (32-85) to 63 (31-86) to 63 (31-86).
Sex, male, n (%): 241 (60%) to 246 (60%) to 239 (60%).
ECOG PS, 0, n (%): 166 (40%) to 158 (40%) to 179 (40%).
Current smoker (Previous smoker): 37 (15%) to 53 (13%) to 57 (14%).
Liver metastases, yes, n (%): 3 (1%) to 2 (1%) to 4 (1%).
ALK rearrangement, positive, n (%): 3 (11%) to 2 (10%) to 5 (10%).
Of those tested: 292 to 292 to 292.
PD-L1 expression, any n (%): 217 (32%) to 209 (34%) to 217 (34%).
Of those tested: 659 to 659 to 659.
KRAS mutation, positive, n (%): 40 (11%) to 37 (11%) to 39 (11%).
PD-L1 expression, n (%): TC2/3 or IC2/3: 137 (34%) to 140 (35%) to 133 (33%).
TC1/2/3 or IC1/2/3: 213 (53%) to 209 (52%) to 195 (49%).
TC0 and IC0: 195 (47%) to 205 (51%) to 205 (51%).

Progression Free Survival
(64% response rates!)

Arm B: atezo + bev + CP
Arm C: bev + CP

HR, 0.617 (95% CI: 0.517, 0.737)
P = 0.0001
Minimum follow-up: 9.5 mo
Median follow-up: ~15 mo

Arm B: 14.4 mo (95% CI: 12.8, 17.1)
Arm C: 19.2 mo (95% CI: 16.8, 26.1)

Preliminary median Overall Survival (~19 months)
(Unselected for PD-L1 Expression)

Arm B: atezo + bev + CP
Arm C: bev + CP

HR, 0.775 (95% CI: 0.619, 0.970)
P = 0.0262
Minimum follow-up: 9.5 mo
Median follow-up: ~15 mo

Arm B: 14.4 mo (95% CI: 12.8, 17.1)
Arm C: 19.2 mo (95% CI: 16.8, 26.1)

Data cutoff: September 15, 2017 (Next Analysis in Early 2018)
Some caution about immune therapy combinations...

6/12/2017: FDA places hold on two phase III trials of pembrolizumab + IMiD in Multiple Myeloma

KEYNOTE-183 (randomized phase III, Multiple Myeloma)
- pomalidomide/dexamethasone ± pembrolizumab
- ≥2 prior lines of therapy, refractory to last line of therapy

KEYNOTE-185 (randomized phase III, newly diagnosed MM)
- lenalidomide/dexamethasone ± pembrolizumab
- Treatment-naïve, newly diagnosed MM

In two Phase III studies, Pembro lead to worse overall survival with IMid combinations
CHECKMATE 012: 1st line IPI+NIVO in NSCLC

Hellmann et al, Lancet Oncology, 2017

Pembrolizumab+Epacadostat (IDO inhibitor)

Percentage Change in Target Lesions

ASCO 2017

Reasons to be excited about immunotherapies in earlier Stage disease…
Take Home Points

- FDA approved immune therapies block the PD1/PDL1 axis
- Toxicities are different from chemo, however anti-PD1/PDL1 therapies are usually well tolerated (sometimes zero side effects)
- Pembrolizumab approved in 1st line (PD-L1>50%, ~30% of patients)
- 3 agents approved in 2nd line setting (2 anti-PD1, 1 anti-PDL1)
- Promising chemo combinations, especially in combination with anti-angiogenesis approaches
- Other immunotherapy combinations are showing early promise, however caution is warranted (better preclinical data needed)
- Likely a massive wave of new combos to come (~3,000 combo trials underway)

Thank You