Cancer Immunotherapy by Checkpoints & NonCheckpoints
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Adjunct Clinical Assistant Professor Medicine Duke & UNC
Financial Disclosures

- **BioPharma Trial Sponsors**
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- **Honoraria:** BMS, Genentech
Overview

- Background & History Immunotherapy
  - Immune self tolerance
  - Melanoma, vitiligo, animal models

- Pharmacologic Self Tolerance Blockade
  - Central (priming phase) vs Peripheral (effector phase)
  - PD1 & case presentation
  - PDL1 & case presentation

- Correlates, Predictors, Biomarkers

- New Immunotherapies (checkpoint & noncheckpoint)
2013 Science “Breakthrough of the Year”
2014 Special Nature Edition
Historical Cases of Spontaneous Regression of Cancer

- Rohdenburg summarized 185 spontaneous regressions, 1918
- Fauvet reported 202 cases between 1960–1964
- Boyd reported 98 cases in 1966
- Everson and Cole described 176 cases between 1900–1960
- Challis summarized 489 cases between 1900–1987
- Hobohm, in a meta-analysis, investigated about 1000 cases
  - Frequency was estimated to be about 1 in 100,000 cancers
Why Study Malignant Melanoma in Tumor Immunology? Can See It

Model for Melanoma regression

- Human and animal models
- Occurs with auto-immunity to melanocyte self-antigens (vitiligo) easily seen
- Specific T-cell and humoral responses occur
  - “Break self-tolerance”

Vitiligo patterns may be a template of antigen repertoire

Immune system can recognize any tumor (not just melanoma)

Halo Nevi
IL-2 Melanoma Immunotherapy

Breaking self tolerance with vitiligo, Strongest clinical marker of melanoma regression
Mouse Melanoma Immunotherapy

**Break** vs **Block** Self-Tolerance

- **Anti-TRP1 murine Ab**
  - Hara, Takechi, Houghton 1995
  - Passive

- **Insect Expressed TRP1 vaccination**
  - Naftzger, Hara, Houghton 1996
  - Active, Mono-Valent, Non-Self

- **Vaccinia virus encoding TRP1**
  - Overwijk, Restifo, Rosenberg 1998
  - Active, Mono-Valent, Altered-Self

- **Vaccination GM-CSF expressing irradiated murine melanomas**
  - CTLA-4 mAb blockade
  - Van Ela, Hurwitz, Allison 1999
  - Active, Poly-Valent, Self

- **Alphavirus encoding TRP1**
  - Lietner, Restifo 2003
  - Active, Mono-Valent, Altered-Self

- **Chemokine knockout mice**
  - CCR5-/- and MIP1α-/-
  - Melanoma lysate pulsed DCs
  - Ng-Cashin, Powderly, Serody 2003
  - Active, Poly-Valent, Self

- **Adoptive T-Cell Transfer**
  - Vaccinia, Fowlpox Virus Encoding mutated gp100
  - Overwijk, Restifo 2004
  - Active, Adoptive, Mono-Valent Altered Self, Mutated Peptide
CTLA-4 & PD1/PDL1: The Brakes on T cell Activation

T-cell receptor: Antigen-MHC

CD28: B7
IL-2
IFN

CTLA-4: B7
PD1: PDL1

Vaccine?

Adapted from Hodi
Immune Recognition & Tolerance
Adapted from “Cancer Immunotherapy Comes of Age” Topalian, Weiner, Pardoll, JCO 2011
Tumor Immune Evasion

Immune system is exponentially more adaptable than tumor.

Vaccines Are *The* greatest success story of modern medicine by eradicating infectious diseases.

So why haven’t cancer vaccines worked?

**Infections**
- Discriminate self from *non-self* (obvious)

**Tumors**
- Discriminate self from *altered-self* (subtle)

**Self Tolerance = Self Preservation**
- 98% anti-self lymphocytes undergo apoptosis
- Remaining T-cells >90% tolerizing surveillance
- Our immune system balance favors self tolerance
CTLA-4 “Cytotoxic T Lymphocyte Antigen 4”, receptor expressed on T cells

- Got it’s name before knew what it did
- James Allison PhD discovered in 1990s,
- Most important “break” (tolerance) during antigen presentation in LN
- Double gene knockout mouse model: develop lymphoproliferative disease and fulminant auto-immunity toxicity and die by 6 weeks of life.
- Human polymorphisms are associated with familial tendency towards autoimmune diseases.
- Ipilimumab first checkpoint inhibitor developed, anti-CTLA4 mAb
PD “Programmed Death” (got it’s name because it was discovered that other immune cells with this receptor/ligand axis were prevented from destroying each other).

- PD1 receptor (on lymphocytes) has two ligands: PDL1 & PDL2
- PDL1: typically expressed on immune cells so they don’t destroy each other in inflammation. Also expressed in tissue (and tumors) during inflammation.

PD1-PDL1 axis: most important “break” (tolerance) at peripheral site of inflammation

- PDL1 is like and “invisible shield for tumors to hide from immune cells”
- During inflammation, interferon gamma will upregulate PDL1 expression
- PD1 or PDL1: double gene knockout mouse model develop mild tendency towards auto-immunity with inflammatory stimuli.
- Nivolumab & Pembrolizumab first anti-PD1 mAbs developed
Placenta & tumors express PDL1 to evade immune recognition.

Placenta

Tumor
PD1-PDL1 Blockade Drugs in Development

- **Anti-CTLA-4**
  - Ipilimumab (Fully human IgG1) FDA Approved 2011
  - Tremelimumab (Fully human IgG2) Phase III

- **Anti-PD-1**
  - MDX-1106, Nivolumab, (Fully human IgG4) FDA Approved Melanoma & Squamous Lung
  - CT-011 Pidilizumab (Humanized IgG1) Phase II
  - MK3475 Pembrolizumab (formerly Lambrolizumab) (Humanized IgG4) FDA Approved 2014
  - AMP-224 (B7-DC/IgG1fusion protein) Phase I-II
  - MEDI0680, AMP514 Phase I
  - REGN2810 (phase I)
  - BGB-A317 (phase I)

- **Anti-PD-L1**
  - MDX-1105, (Fully human IgG4) Phase I
  - MPDL3280A, RG7446, Atezolizumab, Phase II
  - MEDI4736 Phase III
  - MSB0010718C Avelumab Phase I
  - CA-170 (oral inhibitor, phase I)
Lung Cancer Immunotherapy

Somatic mutation frequencies in different tumors

- High rates of somatic mutations in lung cancer may contribute to increased immunogenicity
- Therapies targeting the PD-L1/PD-1 pathway will alter the treatment of NSCLC

Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Turneh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.
135 Stage IV melanoma patients (both Ipi naïve and Ipi failures)
- 38% RECIST response rate in all dose cohorts
  - 52% RECIST highest in cohort of 10mg/kg Q2 weeks.
- No statistical significant difference in response rate with prior Ipi exposure (but trend favored prior Ipi exposure)
- Median progression free survival > 7 months
- 79% any grade drug related adverse events (fatigue, asthenia, fever, chills, myalgias, HA). 21% had rash & pruritis, 20% diarrhea, 8% hypothyroidism, 9% vitiligo.
- 13% grade 3-4 drug related adverse events
- Auto-immune adverse events: 4% pneumonitis
Pembrolizumab Melanoma
Hamid NEJM 2013

A  Best Objective Response

Percent Change from Baseline in Longest Diameter of Target Lesion

Prior ipilimumab treatment  No prior ipilimumab treatment

Individual Patients Treated with Pembrolizumab
Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial

Lancet July 2014


- Randomized Expansion cohort of original Phase I, additional 173 patients
- Dedicated to Ipilimumab “refractory” patients (received at least 2 doses Ipi). Excluded prior Ipi grade 3,4 toxicities. Allowed prior grade 2 toxicity, if resolved to grade 0-1, and off steroids. Stable brain mets allowed.
- 2mg/kg IV Q3 weeks vrs 10mg/kg IV Q3 weeks
- Results: ORR 26% in both doses, similar safety profiles, no drug related deaths, fatigue (33%), pruritus (26%), rash (18%). Only grade 3 drug AE was fatigue (3%).
# Pembrolizumab Survival

**Robert Lancet 2014**

## Number at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 2 mg/kg</td>
<td>89</td>
<td>86</td>
<td>76</td>
<td>69</td>
<td>66</td>
<td>57</td>
<td>42</td>
<td>29</td>
<td>16</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pembrolizumab 10 mg/kg</td>
<td>84</td>
<td>78</td>
<td>65</td>
<td>61</td>
<td>55</td>
<td>50</td>
<td>37</td>
<td>18</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Nivolumab & Pembrolizumab
FDA Approved Melanoma
(After Ipilimumab, and BRAF inhibitor if BRAF mutant)

- Pembrolizumab FDA Approved September 2014
  - Phase IB Randomized trial 2mg/kg vs 10mg/kg (KEYNOTE-001)
  - 2mg/kg IV over 30 minutes Q3 weeks
  - Interim analysis ORR = 24%, of which 86% durable

- Nivolumab FDA Approved December 2014
  - Phase III Randomized trial vs Dacarbazine (CHECKMATE 037, CA209-037)
  - 3mg/kg IV over 60 minutes Q2 weeks
  - Interim analysis ORR confirmed = 32%, of which 87% durable

- Class Toxicity of PD1 mAb (all grades): pneumonitis 2-3%, colitis 2%, hepatitis 1%, nephritis 0.7%, hypo-hyperthyroidism 10%, potential embryofetal toxicity;

- Other common immune symptoms: tumor flare, fatigue, fever, pruritus, cough, diarrhea, transaminitis, thyrombocytopenia, lymphopenia, hyponatremia, hyperkalemia,

Continue “until disease progression or unacceptable toxicity”
Metastatic Melanoma, n = 88
- Concurrent cohort: n = 53,
- Nivo 1mg/kg + Ipi 3mg/kg, ORR 53%,
- Clinical Benefit SD+PR+CR = 65%
- Grade 3-4 drug related AEs 53% (lipase, transaminitis, colitis), most were reversible with steroids.
Rapid Eradication of a Bulky Melanoma Mass with One Dose of Immunotherapy

Chapman et al, NEJM April 2015

49yo WF BRAF Mutant

Ipilimumab 3 mg/kg & Nivolumab 1 mg/kg
Lung Cancer
Nivolumab 2nd line Squamous Cell Lung Cancer
FDA Approved March 2015

CHECKMATE 017 Phase 3 randomized
Docetaxel vrs Nivolumab 3mg/kg Q2w

Interim analysis:
Median OS 6 months vrs 9 months.
1 year OS 22% vrs 41%
41% reduction risk of death
Hazard ratio 0.59 (p = 0.00025)

ORR = 15%, of which 76% durable
# Nivolumab Squamous Lung Adverse Events

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Asthenia</td>
<td>19</td>
<td>1.7</td>
</tr>
<tr>
<td>Edema&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17</td>
<td>1.7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>10</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>Cough</td>
<td>32</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain&lt;sup&gt;c&lt;/sup&gt;</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Arthralgia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>
### Nivolumab Squamous Lung Adverse Events, cont

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage (%) of Patients</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>1.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>0.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>2.6</td>
</tr>
<tr>
<td>Abdominal pain[\textit{e}]</td>
<td>16</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash[\textit{f}]</td>
<td>16</td>
<td>0.9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased weight</td>
<td>13</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia[\textit{g}]</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>
# Nivolumab Squamous Cell Lab Abnormalities

<table>
<thead>
<tr>
<th>Test</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>20</td>
<td>2.6</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>20</td>
<td>2.6</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>18</td>
<td>1.8</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>18</td>
<td>4.4</td>
</tr>
<tr>
<td>Increased AST</td>
<td>16</td>
<td>0.9</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>47</td>
<td>16</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</td>
<td>2.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>
CheckMate 057: Nivolumab vs Docetaxel

2nd-line Non-squamous NSCLC

- Phase III, 582 patients randomized
- Nivolumab 3 mg/kg Q2W vs docetaxel 75 mg/m^2 Q3
- Primary endpoint OS
- Trial stopped early by DSMC, met its primary endpoints at interim analysis

Phase III, 582 patients randomized

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n=292)</th>
<th>Docetaxel (n=290)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td></td>
<td>0.0246</td>
</tr>
<tr>
<td><strong>Median DOR, mos</strong></td>
<td>17.2</td>
<td>5.6</td>
</tr>
</tbody>
</table>

- 71 (24%) patients on nivolumab were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16 patients (not included in best overall response)

CheckMate 057: Nivolumab vs Docetaxel 2\textsuperscript{nd}-line Non-squamous NSCLC

### Treatment Effect on OS in Predefined Subgroups

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>582</td>
<td>0.75 (0.62, 0.91)</td>
</tr>
<tr>
<td><strong>Age Categorization (years)</strong></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>0.63 (0.45, 0.89)</td>
</tr>
<tr>
<td>≥75</td>
<td>43</td>
<td>0.90 (0.43, 1.87)</td>
</tr>
<tr>
<td><strong>Gender</strong></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><strong>Baseline ECOG PS</strong></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><strong>Smoking Status</strong></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><strong>EGFR Mutation Status</strong></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>0.66 (0.51, 0.86)</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).

CheckMate 057: Nivolumab vs Docetaxel 2\textsuperscript{nd}-line Non-squamous NSCLC

### OS and PFS Hazard Ratios by Baseline PD-L1 Expression

<table>
<thead>
<tr>
<th>PD-L1 expression level</th>
<th>Nivolumab n</th>
<th>Docetaxel n</th>
<th>Unstratified HR (95% CI)</th>
<th>Interaction P-value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>123</td>
<td>123</td>
<td>0.59 (0.43, 0.72)</td>
<td>0.0646</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>108</td>
<td>101</td>
<td>0.90 (0.66, 1.24)</td>
<td></td>
</tr>
<tr>
<td>≥5%</td>
<td>95</td>
<td>96</td>
<td>0.43 (0.30, 0.63)</td>
<td>0.0004</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>136</td>
<td>138</td>
<td>1.01 (0.77, 1.34)</td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td>86</td>
<td>79</td>
<td>0.40 (0.26, 0.59)</td>
<td>0.0002</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>145</td>
<td>145</td>
<td>1.00 (0.76, 1.31)</td>
<td></td>
</tr>
<tr>
<td>Not quantifiable at baseline</td>
<td>61</td>
<td>66</td>
<td>0.91 (0.61, 1.35)</td>
<td></td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>123</td>
<td>123</td>
<td>0.70 (0.53, 0.94)</td>
<td>0.0227</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>108</td>
<td>101</td>
<td>1.19 (0.88, 1.61)</td>
<td></td>
</tr>
<tr>
<td>≥5%</td>
<td>95</td>
<td>96</td>
<td>0.54 (0.39, 0.76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>136</td>
<td>138</td>
<td>1.31 (1.01, 1.71)</td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td>86</td>
<td>79</td>
<td>0.52 (0.37, 0.75)</td>
<td>0.0002</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>145</td>
<td>145</td>
<td>1.24 (0.96, 1.61)</td>
<td></td>
</tr>
<tr>
<td>Not quantifiable at baseline</td>
<td>61</td>
<td>66</td>
<td>1.06 (0.73, 1.56)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Interaction p-value from Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction.

CheckMate 057: Nivolumab vs Docetaxel 2nd-line Non-squamous NSCLC

Treatment-related AEs Reported in ≥10% of Patients

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 287)</th>
<th>Docetaxel (n = 268)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade, %</td>
<td>Grade 3–4, °%</td>
</tr>
<tr>
<td>Total patients with an event</td>
<td>69</td>
<td>10</td>
</tr>
</tbody>
</table>

**Treatment-related Select AEs**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 287)</th>
<th>Docetaxel (n = 268)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4 °</td>
</tr>
<tr>
<td>Endocrine, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT increased</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pulmonary, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Skin, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity/Infusion reaction, %</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

* Select AEs: AEs with potential immunologic etiology that require frequent monitoring/intervention

Includes events reported in ≥2.5% of patients.

°No grade 5 events were reported at DDL; 1 grade 5 event for nivolumab was reported post-DDL.

KEYNOTE-010 Study Design

**Patients**
- Advanced NSCLC
- Confirmed PD after ≥1 line of chemotherapy\(^a\)
- No active brain metastases
- ECOG PS 0-1
- PD-L1 TPS ≥1%
- No serious autoimmune disease
- No ILD or pneumonitis requiring systemic steroids

**Stratification factors:**
- ECOG PS (0 vs 1)
- Region (East Asia vs non-East Asia)
- PD-L1 status\(^b\) (TPS ≥50% vs 1%-49%)

**End points in the TPS ≥50% stratum and TPS ≥1% population**
- Primary: PFS and OS
- Secondary: ORR, duration of response, safety

**Assignments**
- Pembrolizumab 2 mg/kg IV Q3W for 24 months
- Pembrolizumab 10 mg/kg IV Q3W for 24 months
- Docetaxel 75 mg/m\(^2\) Q3W per local guidelines\(^c\)

\(^a\)Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an EGFR sensitizing mutation or an ALK translocation.

\(^b\)Added after 441 patients enrolled based on results from KEYNOTE-001 (Garon EB et al. *N Engl J Med*. 2015;372:2018-28).

\(^c\)Patients received the maximum number of cycles permitted by the local regulatory authority.

ClinicalTrials.gov, NCT01905657.
KEYNOTE-010: Pembrolizumab Vs. Docetaxel in NSCLC: OS in All Patients

Herbst et al, Lancet, 2015
KEYNOTE-010: Pembrolizumab Vs. Docetaxel: OS in PD-L1 Positive Disease

Herbst et al, Lancet, 2015
Efficacy, Safety, and Predictive Biomarker Results from Phase II Atezolizumab (MPDL3280a) vs Docetaxel 2nd/3rd-line NSCLC

POPLAR Study (Interim Analysis)

ITT Interim OS (n=287)

PD-L1 Expression Subgroups
TC 1/2/3 or IC 1/2/3
Interim OS (n=195)

MEDI4736 (Durvalumab) PD-L1 mAb

![Graphs showing response over time](image)

<table>
<thead>
<tr>
<th></th>
<th>MEDI4736 10 mg/kg q2w</th>
<th>MEDI4736 All doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECISt Response</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response evaluable&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13% (6/47)</td>
<td>16% (9/58)</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>39% (5/13)</td>
<td>25% (5/20)</td>
</tr>
<tr>
<td>PD-L1-</td>
<td>5% (1/19)</td>
<td>3% (1/29)</td>
</tr>
<tr>
<td><strong>Disease Control Rate</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response evaluable&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30% (14/47)</td>
<td>35% (20/58)</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>54% (7/13)</td>
<td>45% (9/20)</td>
</tr>
<tr>
<td>PD-L1-</td>
<td>32% (6/19)</td>
<td>24% (7/29)</td>
</tr>
</tbody>
</table>

Nivolumab 1rst Line NSCLung
Gettinger ASCO 2014

- 1rst line lung monotherapy Nivolumab, n = 20
- ORR 30% (50% PDL1+), Clinical Benefit SD+PR+CR = 65%
- Grade 3-4 drug related AEs = 20%

Figure 7. Response by PD-L1 status in NSCLC patients treated with nivolumab plus ipilimumab: A) best percent change in target lesion tumor burden from baseline and B) PFS
Phase IB, Front line lung cancer, n = 49
- ORR 19% (PDL1+), 14% (PDL1-)
- PFS 24 weeks 47% (PDL1+), 29% (PDL1-)
- Drug related grade 3-4% AEs = 49%

Figure 7. Response by PD-L1 status in NSCLC patients treated with nivolumab plus ipilimumab: A) best percent change in target lesion tumor burden from baseline\(^a\) and B) PFS
Keynote-021 Cohort D: Phase I Pembrolizumab + Ipilimumab as 2\textsuperscript{nd}-line NSCLC

Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)

71% of patients showed decrease in target lesion burden

CheckMate 012 Study Design: Nivolumab Plus Ipilimumab in First-line NSCLC

Stage IIIB/IV NSCLC (any histology); no prior chemotherapy for advanced disease; ECOG PS 0 or 1

- Nivo 1 mg/kg IV Q3W x 4 + Ipi 1 mg/kg IV Q3W x 4
- Nivo 1 mg/kg IV Q2W + Ipi 1 mg/kg IV Q6W
- Nivo 3 mg/kg IV Q2W + Ipi 1 mg/kg IV Q12W
- Nivo 3 mg/kg IV Q2W + Ipi 1 mg/kg IV Q6W

Nivo 3 mg/kg IV Q2W until disease progression or unacceptable toxicity

Until disease progression or unacceptable toxicity

Primary endpoint: safety and tolerability
Secondary endpoints: ORR (RECIST v 1.1) and PFS rate at 24 wks
Exploratory endpoints: OS; efficacy by PD-L1 expression

 Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit

Rizvi et al, WCLC 2015
### Summary of Efficacy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Confirmed ORR, % (95% CI)</th>
<th>Confirmed DCR, % (95% CI)</th>
<th>Best overall response, %</th>
<th>PFS rate at 24 wks, % (95% CI)</th>
<th>Median PFS, mos (95% CI)</th>
<th>Median OS, mos (95% CI)</th>
<th>Median length of follow-up, mos (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo 1 + Ipi 1 Q3W (n = 31)</td>
<td>13 (4, 30)</td>
<td>55 (36, 73)</td>
<td>0</td>
<td>42</td>
<td>55 (36, 71)</td>
<td>NR (11.5, )</td>
<td>16.6 (1.8–24.5)</td>
</tr>
<tr>
<td>Nivo 1 Q2W + Ipi 1 Q6W (n = 40)</td>
<td>25 (13, 41)</td>
<td>58 (41, 73)</td>
<td>0</td>
<td>33</td>
<td>NC</td>
<td>NR (8.9, )</td>
<td>6.2 (0.4–13.1)</td>
</tr>
<tr>
<td>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</td>
<td>39 (24, 57)</td>
<td>74 (57, 87)</td>
<td>0</td>
<td>34</td>
<td>63 (44, 76)</td>
<td>NR</td>
<td>8.4 (0.9–12.3)</td>
</tr>
<tr>
<td>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</td>
<td>31 (17, 48)</td>
<td>51 (35, 68)</td>
<td>0</td>
<td>21</td>
<td>NC</td>
<td>NR</td>
<td>7.7 (1.1–12.2)</td>
</tr>
<tr>
<td>Nivo 3 Q2W (n = 52)</td>
<td>23 (13, 37)</td>
<td>50 (36, 64)</td>
<td>8</td>
<td>27</td>
<td>41 (27, 54)</td>
<td>22.6 (14.9, )</td>
<td>14.3 (0.2–30.1)</td>
</tr>
</tbody>
</table>

- Median DOR was not reached in any arm
- Unconventional immune-related responses were observed in arms Nivo 3 Q2W + Ipi 1 Q12W (n = 2), Nivo 3 Q2W + Ipi 1 Q6W (n = 1) and Nivo 3 Q2W (n = 3)

NR: the time point at which the percent of survivors drops below 50% has not been reached due to insufficient number of events and/or follow up.

*Rizvi et al, WCLC 2015*
## Efficacy by Tumor PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>≥1% PD-L1 expression</th>
<th>&lt;1% PD-L1 expression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivo 1 + Ipi 1</td>
<td>Nivo 1 + Ipi 1</td>
</tr>
<tr>
<td></td>
<td>Q3W (n = 12)</td>
<td>Q2W (n = 13)</td>
</tr>
<tr>
<td></td>
<td>Nivo 1 Q2W + Ipi 1</td>
<td>Nivo 1 Q2W + Ipi 1</td>
</tr>
<tr>
<td></td>
<td>Q6W (n = 21)</td>
<td>Q12W (n = 21)</td>
</tr>
<tr>
<td></td>
<td>Nivo 3 Q2W + Ipi 1</td>
<td>Nivo 3 Q2W + Ipi 1</td>
</tr>
<tr>
<td></td>
<td>Q6W (n = 21)</td>
<td>Q12W (n = 23)</td>
</tr>
<tr>
<td></td>
<td>Nivo 3 Q2W + Ipi 1</td>
<td>Nivo 1 Q3W + Ipi 1</td>
</tr>
<tr>
<td></td>
<td>Q12W (n = 23)</td>
<td>Q6W (n = 21)</td>
</tr>
<tr>
<td></td>
<td>Nivo 1 Q2W + Ipi 1</td>
<td>Nivo 1 Q2W + Ipi 1</td>
</tr>
<tr>
<td></td>
<td>Q6W (n = 21)</td>
<td>Q12W (n = 23)</td>
</tr>
<tr>
<td></td>
<td>Nivo 3 Q2W</td>
<td>Nivo 3 Q2W</td>
</tr>
<tr>
<td></td>
<td>+ Ipi 1 Q3W</td>
<td>+ Ipi 1 Q2W</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
</tr>
<tr>
<td></td>
<td>Nivo 3 Q2W + Ipi 1</td>
<td>Nivo 3 Q2W + Ipi 1</td>
</tr>
<tr>
<td></td>
<td>Q12W (n = 9)</td>
<td>Q6W (n = 7)</td>
</tr>
<tr>
<td></td>
<td>Nivo 3 Q2W</td>
<td>Nivo 3 Q2W</td>
</tr>
<tr>
<td></td>
<td>+ Ipi 1 Q6W</td>
<td>+ Ipi 1 Q12W</td>
</tr>
<tr>
<td></td>
<td>(n = 9)</td>
<td>(n = 7)</td>
</tr>
</tbody>
</table>

### ORR, %
- ≥1% PD-L1 expression: 8, 24, 48, 48
- <1% PD-L1 expression: 15, 14, 22, 0

### mPFS, wks (95% CI)
- ≥1% PD-L1 expression: 11.5 (7.1, ), 21.1 (11.4, ), 34.6 (15.9, 35.3), NR (15.4, )
- <1% PD-L1 expression: 34.0 (8.9, ), NR (10.1, ), 23.1 (4.0, ), 10.3 (7.4, 12.7)

### PFS rate at 24 wks, % (95% CI)
- ≥1% PD-L1 expression: 42 (15, 67), 40 (18, 61), 74 (48, 88), 65 (42, 81)
- <1% PD-L1 expression: 57 (25, 80), NC, 39 (9, 69), 0

- PD-L1 expression was measured using the Dako/BMS automated IHC assay\(^1,16\)
  - Fully validated with analytical performance having met all predetermined acceptance criteria for sensitivity, specificity, precision, and robustness

- All patients had available pretreatment tumor samples; 76% (113/148) had samples evaluable for PD-L1 expression

- Median DOR was not reached in any arm, regardless of PD-L1 expression

---

Rizvi et al, WCLC 2015

NR: the time point at which the percent of survivors drops below 50% has not been reached due to insufficient number of events and/or follow up
Background: PD-1 and PD-L1 best responses appear in melanoma and lung cancer (which have high carcinogen exposure)

34 lung patients on Pembrolizumab study had cancer exome gene sequence

>300 “nonsynonymous mutations” (meaning alter protein sequence) associated with:

- Improved ORR, durable clinical benefit, and PFS
- “Molecular smoking signature” (C-to A transversions)
- Higher neo-antigen burden
- DNA repair enzyme pathway mutations (“hypermutated tumors”)

Concluded: genomic landscape (mutational burden “mutanome”) enables response to PD-1 therapy

### PD-L1 as a Predictive Immune Biomarker: Assays, Sample Collection, and Analyses in NSCLC Studies

<table>
<thead>
<tr>
<th>PD-L1 Assay</th>
<th>Pembrolizumab &lt;br&gt; Merck</th>
<th>Nivolumab &lt;br&gt; Bristol-Myers Squibb</th>
<th>MPDL3280A &lt;br&gt; Roche/Genentech</th>
<th>MEDI4736 &lt;br&gt; AstraZeneca</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD-L1</strong></td>
<td>Prototype or clinical trial IHC assay (22C3 Ab)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Dako automated IHC assay (28-8 Ab)&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>Ventana automated IHC assay</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; generation or Ventana automated IHC assay (Ventana PD-L1+ (SP263) clone)&lt;sup&gt;7,8&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Sample Source and Collection</strong></td>
<td>• Surface expression of PD-L1 on tumor specimen*</td>
<td>• Surface expression of PD-L1 on tumor cells*</td>
<td>• Surface expression of PD-L1 on TILs&lt;sup&gt;5&lt;/sup&gt;</td>
<td>• Surface expression of PD-L1 on TILs</td>
</tr>
<tr>
<td><strong>IHC Staining:</strong></td>
<td>• Ph I: Fresh tissue &lt;br&gt; • Ph II/III: Archival or fresh tissue&lt;sup&gt;2&lt;/sup&gt;</td>
<td>• Archival&lt;sup&gt;4&lt;/sup&gt; or fresh tissue</td>
<td>• Archival or fresh tissue</td>
<td>• PhI: Fresh tissue</td>
</tr>
<tr>
<td><strong>Definitio n of Positivity&lt;sup&gt;1&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor PD-L1 expression:&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• ≥50% PD-L1&lt;sup&gt;+&lt;/sup&gt; cut-off: 32% (41/129) &lt;br&gt; • 1-49% PD-L1&lt;sup&gt;+&lt;/sup&gt; cut-off: 36% (46/129)</td>
<td>• Strong vs weak expression&lt;sup&gt;3,4&lt;/sup&gt; &lt;br&gt; • Patients not restricted in PD-L1 status in 2nd- &amp; 3&lt;sup&gt;rd&lt;/sup&gt;-line&lt;sup&gt;4&lt;/sup&gt; &lt;br&gt; • Ph III 1st-line trial in PD-L1&lt;sup&gt;+&lt;/sup&gt;&lt;sup&gt;3&lt;/sup&gt;</td>
<td>IHC Staining intensity (0, 1, 2, 3): &lt;br&gt; • IHC 3 (≥10% PD-L1&lt;sup&gt;+&lt;/sup&gt;): Ph III trial&lt;sup&gt;5&lt;/sup&gt; &lt;br&gt; • IHC 2,3 (≥5% PD-L1&lt;sup&gt;+&lt;/sup&gt;)&lt;sup&gt;5&lt;/sup&gt; &lt;br&gt; • IHC 1,2,3 (≥1% PD-L1&lt;sup&gt;+&lt;/sup&gt;)&lt;sup&gt;5&lt;/sup&gt; &lt;br&gt; • IHC 1, 0, or unknown &lt;br&gt; • PD-L1 expression required for NSCLC for enrollment</td>
<td>IHC Staining intensity: &lt;br&gt; • Not presented to date&lt;sup&gt;7,8,9&lt;/sup&gt;</td>
</tr>
<tr>
<td>TIL PD-L1 expression:&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>• 6% (6/53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PD-L1 low (IHC 1, 0): 75% (40/53)</td>
<td></td>
<td>TIL PD-L1 expression: &lt;br&gt; • Not presented to date&lt;sup&gt;7,8,9&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>
Renal Cell Cancer anti-PD1 mAb 10mg/kg cohort
Solid Tumors
Response in Patient with Head and Neck Cancer

• 96 y.o. female
  – Progressed on previous cetuximab
  – HPV negative, PD-L1 positive
  – Treatment ongoing at 8 weeks
Emerging Clinical Activity in Multiple Tumors

**NSCLC (n = 84)**

**SCCHN (n = 34)**

MEDI4736 PDL1 mAb
Segal ASCO 2014
Emerging Clinical Activity in Multiple Tumors

Gastroesophageal (n=16)

Pancreatic adenocarcinoma (n=24)
Correlates & BioMarkers

- Presence of Tumor Infiltrating Lymphocytes
- Auto-immunity
- PDL1 expression: On tumor & immune cells
- Mutation load (Mutanome)
  - Carcinogen exposure
  - Smoking status
  - Hypermutators (BRCA, Lynch Syndrome)
- Viral mediated tumors
Distinct mechanisms of PDL1 expression:

- Interferon gamma induced dynamic upregulation in the inflammatory tumor microenvironment ("adaptive resistance")
- Oncogenic driver mutations that constitutively express PDL1
- Epithelial to Mesenchymal transformation (EMT) of the carcinoma phenotype
Biomarkers and Associations With the Clinical Activity of PD-L1 Blockade in a MPDL3280A Study


Full manuscript published in Nature, Herbst et al, Nov 2014
## PD-L1 Expression by IHC is Associated With Anti-tumor Response to MPDL3280A

<table>
<thead>
<tr>
<th></th>
<th>PD-L1 Positive</th>
<th>PD-L1 Negative</th>
<th>All†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>36% (13/36)</td>
<td>13% (9/67)</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>(N = 140)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Investigator-Assessed Overall Response Rate (ORR*)

- **Complete response**
- **Partial response**
- **Stable disease**

### Best Response

- **PD-L1 positive** defined as tumors with infiltrating immune cells that stain for PD-L1 Dx IHC
- **Further assessment of PD-L1 Dx** ongoing

* Study described in ASCO 2013 Abstract #3000 (Herbst et al.)

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* ORR includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1
† All patients include PD-L1–positive, PD-L1–negative and patients with unknown tumor PD-L1 status. Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.
Anti-tumor Response to MPDL3280A is Associated With Th1-type T-cell Markers

Baseline tumor samples, n = 96 (MPDL3280A, Phase 1a). Data for samples available as of Dec 1, 2012. Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013. Includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1

Higher expression of cytotoxic Th1 T-cell markers in tumor tissue is associated with MPDL3280A activity
Serial Biopsy in a PD-L1–Positive RCC Patient With a Rapid Response to MPDL3280A

1 week tumor flare

After 4 weeks

Baseline

After 6 weeks

Surgical resection of responding mass, 0.75 x 0.75 cm at time of resection

51-year-old male with Sarcomatoid RCC s/p L nephrectomy, sunitinib, XRT T9, temsirolimus, PD-L1 positive

Carolina BioOncology Institute (Powderly).
Serial Biopsy in a PD-L1–Positive RCC Patient With a Rapid Response to MPDL3280A

**Baseline**

**Biomarkers at baseline:**
- PD-L1 positive
- CD8+ T cells present

**On-treatment H&E:**
- Dense lymphocytic infiltrate
- Degenerating tumor cells ("ghost cells")
- Necrotic tissue

**On-treatment H&E:**
- PD-L1 positive
- Increased CD8+ T-cell infiltrate
- No viable tumor cells seen

62 Carolina BioOncology Institute (Powderly).
MPDL3280A Phase Ia
Melanoma Anti-PDL1 mAb

March 26, 2012

May 7, 2012
April 9, 2012 (cycle 1, week 1) Mild pruritic rash, then diffuse vitiligo
New Immunotherapies
Immune Modulatory Receptors

Turning up The Activating

Blocking the Inhibiting

Activating

Inhibiting

Other Check Point Immunotherapy: IDO Inhibitors

- Indoleamine 2,3-dioxygenase (IDO) is a natural endogenous mechanism of immune suppression (involved in pregnancy and mucosal tolerance)
  - Tumor microenvironment may increase IDO to create peripheral tolerance
  - High IDO expression in tumors correlates with poor outcome
  - IDO inhibitors have shown preclinical anti-tumor benefit:
    - 1-methyl D tryptophan (D-1MT, NSC-721782)
    - Indoximod
    - NLG919
    - INCB23843 (Epacadostat) (phase I)
    - GDC0919 (phase I)
Other Check Point Immunotherapy: A2A & CD73 Inhibitors

- Adenosine is a signaling molecule in the inflammatory micro-environment used to limit inflammation. Tumors exploit this adenosine axis to suppress immune response.

- Adenosine Receptor (A2A, A2B) expressed on tumor cells (and cardiac cells), induces intracellular cAMP.
  - CPI-444 oral inhibitor of A2A (phase 1)

- Tumor produce & sustain adenosine by expressing high levels of enzyme on tumor surface CD73 (ecto-5’-nucleotidase, converts AMP to adenosine). CD73 also used in lymphocyte differentiation.
  - mAb in development to block CD73 on tumors