Immunotherapy as a Treatment in Various Solid Tumors

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Objectives

• Background
• Mechanism of action of immunotherapy
• Use in NSCLC
• Use in various other cancers
• Can we predict response?
• Toxicity
• Trials in development
Immunotherapy

Targeted Therapy

Chemotherapy

Cancer Cell

Immune cells
Immunotherapy Agents

- **Anti PD-1 antibody:**
  - Pembrolizumab
  - Nivolumab

- **Anti PD-L1 antibody:**
  - Atezolizumab
  - Avelumab
  - Durvalumab

- **CTLA-4 antibody:**
  - Ipilimumab
  - Tremelimumab → not FDA approved
Timeline of approvals

2011
- Ipi approved for melanoma

2014
- Nivo for melanoma
- Nivo for RCC
- Pembrolizumab for melanoma

2015
- Nivo for squamous NSCLC
- Pembrolizumab for Ad NSCLC
- Pembrolizumab for HNSCC

2016
- Pembrolizumab for NSCLC
- Pembrolizumab for HNSCC
- Pembrolizumab for Hodgkin's disease
- Pembrolizumab for first line NSCLC

2017
- Pembrolizumab for bladder
- Atezolizumab for bladder
- Pembrolizumab for mesothelioma
- Pembrolizumab for MSI-H NSCLC
- Pembrolizumab for MSI-H
- Pembrolizumab for gastric
- Pembrolizumab for bladder
- Pembrolizumab for HCC
- Pembrolizumab for bladder
- Pembrolizumab + chemotherapy for NSCLC
- Pembrolizumab for MSI-H
- Pembrolizumab for HCC
Immunotherapy indicated for:

- Melanoma
- NSCLC
  - First line single agent immunotherapy
  - First line immunotherapy + chemotherapy
  - Second line
- Head and neck cancer: squamous cell
- Hodgkin’s lymphoma
- Renal cell cancer
- Bladder cancer
- Microsatellite unstable disease
- Hepatocellular cancer
- Gastric cancer
The Cancer-Immunity Cycle

Antitumor Immune Responses Involve a Multistep Cycle

**STEP 1**
Tumor cell lysis and release of tumor-derived antigens

**STEP 2**
Uptake, process, and presentation of tumor antigens by APCs

**STEP 3**
- T-cell priming and activation
- Generation of memory T cells

**STEP 4**
Travel of activated T cells to tumors

**STEP 5**
T-cell infiltration into tumors

**STEP 6**
T-cell recognition of tumor cells

**STEP 7**
- Killing of tumor cells
- Memory-mediated control of tumor cell recurrence

APC, antigen-presenting cell.
PD-1/PD-L1

http://www.biooncology.com/research-ed
Non Small Cell Lung Cancer
CheckMate 017: Study Design

- CA209-017 was a phase 3 study comparing OS of nivolumab vs docetaxel in patients with advanced, previously treated SQ NSCLC.
- Patients were randomized 1:1 to receive nivolumab 3 mg/kg Q2W or docetaxel 75 mg/m² Q3W until PD or unacceptable toxicity.

- Of the 272 treated patients, median age was 63 years, with 44% ≥65 years old and 11% ≥75 years old, and the majority were white (93%), male (76%), and had an ECOG PS of 1 (76%).

CA209-017: squamous NSCLC, 2L

CheckMate 017: OS

Based on February 2016 database lock. Symbols refer to censored observations.

Borghaei H, et al. Presented at: ASCO; June 3-7, 2016; Chicago, IL.
CheckMate 057: Study Design

- CA209-057 was a phase 3 study comparing OS of nivolumab vs docetaxel in patients with advanced, previously treated non-squamous NSCLC
- Patients were randomized 1:1 to receive nivolumab 3 mg/kg Q2W or docetaxel 75 mg/m² Q3W until PD or unacceptable toxicity

Key inclusion criteria:
- Stage IIIB/IV non-squamous NSCLC
- 1 prior platinum-doublet based chemotherapy
- ECOG PS 0–1
- (N = 582)

Key exclusion criteria:
- Active CNS metastases
- Autoimmune disease
- Interstitial lung disease
- Prior therapy with anti-PD-1, anti-PD-L1/2, anti-CD-137, or anti-CTLA-4

Endpoints
- Primary: OS
- Secondary: ORR, PFS, safety, efficacy by PD-L1 expression, PROs (LCSS)

CheckMate 057: OS

Number of patients at risk:

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Based on February 2016 database lock. Symbols refer to censored observations.

Borghaei H, et al. Presented at: ASCO; June 3-7, 2016; Chicago, IL.
Nivolumab FDA approved for:

The treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.
Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Luncford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

OS by PD-L1 Expression, All CTA-Evaluable Patients

- **n at risk**
  - PS ≥50%: 119, 92, 56, 22, 5, 4, 3, 0
  - PS 1-49%: 161, 119, 58, 15, 6, 4, 0, 0
  - PS <1%: 76, 55, 33, 8, 0, 0, 0

- **PS Median (95% CI), mo**
  - ≥50%: NR (13.7-NR)
  - 1-49%: 8.8 (6.8-12.4)
  - <1%: 8.8 (5.5-12.0)

*Assessed in all patients whose samples were stained within 6 months of cutting.
Analysis cut-off date: August 29, 2014.

Garon et al AACR 2015
Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csősz, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O’Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*
Overall Survival in the Intention-to-Treat Population.

Enrolled patients with newly diagnosed NSCLC

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

No. at Risk
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Targeted Therapy

Immunotherapy

Chemotherapy

Immune cells

Cancer Cell
Randomized Phase 2 Study of Carboplatin and Pemetrexed ± Pembrolizumab as First-Line Therapy for Advanced NSCLC: KEYNOTE-021 Cohort G


1Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; 2Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; 3Fox Chase Cancer Center, Philadelphia, PA, USA; 4The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 5South Texas Accelerated Research Therapeutics, San Antonio, TX, USA; 6Sanford Cancer Center, University of South Dakota Sanford School of Medicine, Sioux Falls, SD, USA; 7Emily Couric Clinical Cancer Center, University of Virginia School of Medicine, Charlottesville, VA, USA; 8Seattle Cancer Care Alliance, Seattle, WA, USA; 9Cleveland Clinic, Cleveland, OH, USA; 10Indiana University School of Medicine, Indianapolis, IN, USA; 11Sanford Roger Maris Cancer Center, Fargo, ND, USA; 12National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan, Republic of China; 13University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; 14Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; 15Dana-Farber Cancer Institute, Boston, MA, USA; 16Merck & Co., Inc., Kenilworth, NJ, USA; 17Current affiliation: Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, New York, USA
KEYNOTE-021 Cohort G

Key Eligibility Criteria
- Untreated stage IIIIB or IV nonsquamous NSCLC
- No activating EGFR mutation or ALK translocation
- Provision of a sample for PD-L1 assessment
- ECOG PS 0-1
- No untreated brain metastases
- No ILD or pneumonitis requiring systemic steroids

R (1:1)\textsuperscript{a} N=123

Pembrolizumab 200 mg Q3W for 2 years + Carboblatin AUC 5 mg/mL/min + Pemetrexed 500 mg/m\textsuperscript{2} Q3W for 4 cycles

Pemetrexed 500 mg/m\textsuperscript{2} Q3W permitted as maintenance therapy

End Points
Primary: ORR (RECIST v1.1 per blinded, independent central review)
Key secondary: PFS
Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

\textsuperscript{a}Randomization was stratified by PD-L1 TPS <1% vs ≥1%.
Objective Response Rate by PD-L1 Status
(RECIST v1.1 by Blinded, Independent Central Review)

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<td>&lt;1%</td>
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<td>≥1%</td>
<td>57%</td>
<td>38%</td>
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Horizontal dotted lines represent the ORR in the total population.
Data cut-off: August 8, 2016.
Pembrolizumab FDA approved for:

- The treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

- Metastatic NSCLC for first-line treatment of patients whose tumors have high PD-L1 Expression (Tumor Proportion Score of ≥50%) With No EGFR or ALK genomic tumor aberrations.

- Combination with pemetrexed plus carboplatin as a frontline treatment for patients with metastatic or advanced nonsquamous non–small cell lung cancer (NSCLC), regardless of PD-L1 expression.
Atezolizumab

• An anti PD-L1 antibody

• POPLAR→phase 2 (n=287)
  – Second/third line NSCLC
  – Randomized docetaxel or Atezolizumab
  – Primary end point: OS
  – Secondary end point: ORR, DOR
  – Median OS 12.6 vs 9.7 with Atezo vs docetaxel

• OAK→phase 3 (n=1225)
  – Second/third line NSCLC
  – Randomized docetaxel or Atezolizumab
  – Primary end point: OS
  – Median OS 12.8 vs 9.6 with Atezo vs docetaxel
Atezolizumab (anti PD-L1 antibody)

The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose disease progressed during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.
Bladder Cancer (Urothelial carcinoma)

- Atezolizumab
- Nivolumab
- Pembrolizumab
- Durvalumab
- Avelumab

- Response rates: 15-20%
Immunotherapy also approved in:

**Hodgkin’s Lymphoma:**

- **Nivolumab**: approved for patients with classical Hodgkin lymphoma who have relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin.
  - ORR of 65%

- **Pembrolizumab**: approved for failure after 3 lines of therapy
  - ORR of 69%
Immunotherapy also approved in:

**Head and neck cancer:**

- **Pembrolizumab:** approved in patients with advanced disease who have failed platinum-based chemotherapy
  - ORR of 16%

- **Nivolumab:** approved in patients with advanced disease who have failed platinum-based chemotherapy
  - ORR of 13.3%
Immunotherapy also approved in:

**Renal cell cancer:**

- Nivolumab indicated for advanced renal cell cancer patients who have received prior anti-angiogenic therapy
  - ORR of 25%
Immunotherapy also approved in:

**Melanoma:**

- Nivolumab
- Pembrolizumab
- Ipilimumab
- Nivolumab + Ipilimumab
Microsatellite unstable cancers

- **Pembrolizumab**: adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options.

- **Nivolumab**: 12 years and older with mismatch repair deficient and microsatellite instability high metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
Hepatocellular carcinoma

- *Nivolumab*: For the treatment of patients with hepatocellular carcinoma following prior sorafenib
  - ORR of 18.2%
Gastric Cancer

- Pembrolizumab approved for the treatment of patients with recurrent or advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received two or more lines of chemotherapy and are PD-L1-positive.
- ORR of 13%
Combination Therapies
Combination Therapies

- Nivolumab/Ipilimumab
- Durvalumab/Tremelimumab
- Pembrolizumab/IDO
- Nivolumab/IDO
- Nivolumab/GITR
- Ipilimumab/GITR
- Personalized vaccine/atezolizumab
Epacadostat Plus Pembrolizumab in Patients With SCCHN: Preliminary Phase 1/2 Results From ECHO-202/KEYNOTE-037

Omid Hamid,1 Todd M. Bauer,2 Alexander I. Spira,3 Anthony J. Olszanski,4 Sandip P. Patel,5 Jeffrey S. Wasser,6 David C. Smith,7 Ani S. Balmanoukian,1 Charu Aggarwal,8 Emmett V. Schmidt,9 Yufan Zhao,10 Hema Gowda,10 Tara C. Gangadhar8

1The Angeles Clinic and Research Institute, Los Angeles, CA; 2Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; 3Virginia Cancer Specialists Research Institute, Fairfax, VA; 4Fox Chase Cancer Center, Philadelphia, PA; 5University of California San Diego Moores Cancer Center, La Jolla, CA; 6University of Connecticut Health Center, Farmington, CT; 7University of Michigan, Ann Arbor, MI; 8Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; 9Merck & Co., Inc., Kenilworth, NJ, USA; 10Incyte Corporation, Wilmington, DE

Abstract #6010
Session: Clinical Science Symposium: What's Next in Immunotherapy for Head and Neck Cancer?
Presented at the ASCO Annual Meeting 2017
Chicago, IL
June 2–6, 2017
IDO1 Enzyme and Epacadostat

• Tumors can evade immunosurveillance through a number of mechanisms including immune checkpoint inhibition of T-cell activation and upregulation of the IDO1 enzyme
• IDO1 is an IFNγ-induced, intracellular enzyme that catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine pathway
• Depletion of tryptophan and production of kynurenine and other metabolites shifts the local immune microenvironment to an immunosuppressive state
• Epacadostat is a potent and specific oral inhibitor of IDO1, inhibiting tryptophan metabolism and augmenting immunosurveillance in the tumor microenvironment
• Combining epacadostat with a checkpoint inhibitor may improve patient outcomes

IDO1, indoleamine 2,3 dioxygenase 1; IFNγ, interferon gamma.
Can we predict who is going to respond?
Among first 411 patients enrolled, 67% evaluable for PD-L1 status

Correlation between PD-L1 expression and ORR ($P < 0.0001$)

PD-L1 Expression and Relationship With Response

**ORR, RECIST v1.1**

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APS, Allred proportion score. Analysis cut-off date: October 18, 2014.
PD-1/PD-L1

http://www.biooncology.com/research-ed
## PD-L1 Status Summary

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<th>Agent</th>
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UC = Urothelial Cancer; RCC = Renal Cell Carcinoma; NSCLC = Non-small cell lung cancer; Mel = Melanoma; IC = Immune Cells, TC = Tumor Cells


Presented By Noah Hahn at 2015 ASCO Annual Meeting
Mutation burden and immune response

• As hypothesized, mutation burden appears to correlate with immune response.

• The underlying mechanism is that an amino acid mutation within a peptide leads to a tumor **neo-epitope**.

• A neo-epitope may be recognized by the immune system due to increased affinity of:
  – The peptide – MHC binding, or
  – The peptide – T-cell receptor binding.

• Random mutations lead to hundreds of neo-epitopes, each a potential immune target.

Segal. Cancer Res. 2008
Mutation burden and immune response

• There appears to be a numerical threshold of mutation burden within a tumor type, for an effective immune response:
  – Melanoma, treated with ipilimumab: >100.
  – NSCLC, treated with pembrolizumab: >178.

• This study demonstrates that this principle may also apply in CRC:
  – High mutation burden (at least in MSI) correlates with improved RR, PFS and OS.

With new treatment comes new toxicity
## Side effect differences between chemotherapy and immunotherapy

<table>
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<th>Immunotherapy</th>
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<td>• Myelosuppresion</td>
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<td>• Anemia</td>
<td>– Rash</td>
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<td>• Alopecia</td>
<td>– Itching</td>
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<tr>
<td>• Fatigue</td>
<td>– Hypothyroidism</td>
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<tr>
<td>• Nausea</td>
<td>– Colitis</td>
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<tr>
<td>• Vomiting</td>
<td>– Pneumonitis</td>
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<tr>
<td>• Mucositis</td>
<td>– Hepatitis</td>
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<tr>
<td>• Diarrhea</td>
<td>– Nephtritis</td>
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<tr>
<td></td>
<td>– Adrenal Insufficiency</td>
</tr>
<tr>
<td></td>
<td>– Type I diabetes</td>
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Future Direction
GITR

- GITR = “glucocorticoid-induced TNF receptor”

- GITR was discovered as a co-stimulatory receptor in a dexamethasone-treated murine T-cell hybridoma experiment (it was later shown that this receptor has no connection to glucocorticoids)

- A member of the tumor necrosis factor (TNF)-receptor super family

- The TNF-receptor superfamily is a group of co-stimulatory receptors (including OX40 and 4-1BB/CD137)

- As a stimulator to the immune response, it is a logical target for development of an immunotherapy for cancer
IDO inhibitor

- IDO1 is a tryptophan-catabolizing enzyme that is overexpressed in many cancers\(^1\)-\(^3\) and induces immune tolerance by suppressing T-cell responses\(^4\)
  - IDO1 is expressed in human tumors and in dendritic cells within tumor-draining lymph nodes\(^5\)
  - IDO1 expression is associated with more rapid tumor progression and reduced survival\(^5\)
  - IDO1 inhibition exhibits antitumor activity through the reactivation of effector T cells\(^3\) and is synergistic with PD-1 blockade\(^6\)

IDO1, indoleamine 2,3 dioxygenase 1.

Inhibitory immune-checkpoints
OX40

- OX40 agonism augments Ag (tumor) specific T-cell memory response
- Mechanistically distinct from inhibitory receptors such as CTLA4 or PD1

Still a lot of work that needs to be done....
Thank you