Immune Checkpoint Inhibitors in the Treatment of Selected Tumor Types: A New Direction

Program Director

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Saturday, April 23, 2016
Houston Marriott at the Texas Medical Center
6580 Fannin Street • Houston, TX 77030
Phone (713) 796-0080

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Bristol-Myers Squibb; AstraZeneca

To view full slide handouts, visit www.cancernetus.com/immunotherapy
Statement of Need/Program Overview
This symposium is intended to improve care of patients with immunotherapeutic options for selected tumor types by accelerating adoption of new evidence-based practice change. The format will include didactic lectures from known opinion leaders, question and answer sessions, and ample opportunity for participant interaction with faculty.

Target Audience
This symposium is directed primarily to hematologists/oncologists, researchers, pharmacists, registered nurses, physician assistants, nurse practitioners and fellows in training interested in new development in immunotherapy options for selected tumor types. No specific skill or knowledge other than a basic training in hematology/oncology is required for successful participation in this activity.

Learning Objectives
After completing this activity, the participant should be better able to:
• Explain the mechanisms of action of checkpoint inhibitors and their impact on novel therapies in cancer
• Identify current strategies in immunotherapy combination with molecular therapies in cancer
• Evaluate and implement immunotherapy options for malignant melanoma
• Identify current strategies in treatment of non-small-cell lung cancer utilizing immune checkpoint pathway inhibitors
• Identify currently accruing immunotherapy options for head & neck cancer
• Identify patterns of response with emerging immunotherapy options for hematological malignancies
• Describe the emerging immunotherapeutic approaches for renal cell carcinoma
• Describe emerging immunotherapeutic approaches for bladder cancer
• Identify currently accruing immunotherapy options for prostate cancer
• Select immunotherapy options for hepatic and gastrointestinal cancers
• Identify the role of neoantigens in the immunotherapy options for ovarian cancer
• Increase the awareness of currently accruing immunotherapy modality combination clinical trials across tumor types
• Differentiate the safety profile between conventional and immunotherapy treatment option for cancer
• Describe the role of prognostic and predictive biomarkers in the immunotherapeutic approaches
• Evaluate the unique toxicity issues with immunotherapy options across tumor types
# Agenda
SATURDAY – April 23, 2016

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>7:00 AM</td>
<td>Breakfast and Registrations</td>
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<tr>
<td>8:25 AM</td>
<td>Welcome and Introductions</td>
<td>Fredrick Hagemeister, MD</td>
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<tr>
<td>8:30 AM</td>
<td>Checkpoint Inhibition: A Perspective into Future of Novel Therapies</td>
<td>Don Gibbons, MD, PhD</td>
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<td>for Cancer</td>
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<tr>
<td>9:00 AM</td>
<td>Immunotherapy Modalities and Combination with Standard of Care</td>
<td>James Gulley, MD, PhD</td>
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<td>9:45 AM</td>
<td>Malignant Melanoma</td>
<td>Michael Davies, MD</td>
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<td>10:10 AM</td>
<td>Lung Cancer</td>
<td>John V. Heymach, MD, PhD</td>
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<td>10:35 AM</td>
<td>Head &amp; Neck Cancers</td>
<td>William A. William, MD</td>
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<td>11:00 AM</td>
<td>Hematological Malignancies</td>
<td>Fredrick B. Hagemeister, MD</td>
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<td>11:25 AM</td>
<td>Renal Cell Carcinoma</td>
<td>Eric Jonasch, MD</td>
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<td>11:50 AM</td>
<td>Bladder Cancer</td>
<td>Arlene O Siefker-Radtke, MD</td>
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<td>12:15 AM</td>
<td>Prostate Cancer</td>
<td>Eric Jonasch, MD</td>
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<td>12:40 PM</td>
<td>Lunch</td>
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<tr>
<td>1:40 PM</td>
<td>Hepatic and Gastrointestinal Cancer</td>
<td>Michael Overman, MD</td>
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<td>2:05 PM</td>
<td>Ovarian Cancer - Neoantigens</td>
<td>Robert Coleman, MD</td>
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<tr>
<td>2:30 PM</td>
<td>Selecting Immunotherapy Modalities and Combination Clinical Trials</td>
<td>James L. Gulley, MD, PhD</td>
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<tr>
<td>3:00 PM</td>
<td>Break</td>
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<tr>
<td>3:15 PM</td>
<td>Biomarkers for Cancer Immunotherapy Clinical Trials</td>
<td>Don Gibbons, MD, PhD</td>
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<tr>
<td>3:45 PM</td>
<td>Management of Toxicity Issues with Immunotherapy</td>
<td>John V. Heymach, MD, PhD</td>
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<tr>
<td>4:15 PM</td>
<td>Closing Remarks and Adjourn</td>
<td>Fredrick Hagemeister, MD</td>
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</table>
Faculty

Robert Coleman, MD
Professor, Department of Gynecologic Oncology and Reproductive Medicine, University of Texas MD Anderson Cancer Center, Houston, TX

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William N. William, Jr., MD
Associate Professor, Chief Head & Neck Section, Department of Thoracic/Head and Neck Medical Oncology, Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX
Disclosure of Relevant Financial Relationships

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The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:

<table>
<thead>
<tr>
<th>Name</th>
<th>Advisory Board</th>
<th>Research Funding</th>
<th>Consultant</th>
<th>Trial Scientific Steering Committee</th>
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<tr>
<td>Robert Coleman, MD</td>
<td><strong>Advisory Board:</strong> Bayer Healthcare, Inc. (GOG); Clovis Oncology; Eisai-Morphotek; Genentech; Incyte; Janssen; Merck Sharp &amp; Dohme; Pfizer (GOG); Roche; VentiRx (GOG); Vertex Pharma</td>
<td><strong>Research Funding:</strong> Array Bio Pharmaceuticals; Clovis Oncology; EMD Serano; Janssen; Merck; Millennium Pharmaceuticals</td>
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<td>Michael Davies, MD, PhD</td>
<td><strong>Advisory Board:</strong> GSK; Genentech; Novartis; Sanofi-aventis; Vaccinex</td>
<td><strong>Research Funding:</strong> GSK; Genentech; AstraZeneca; Sanofi-aventis; Merck</td>
<td><strong>Independent Contractor:</strong> Myriad; Oncothyreon</td>
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<td>Don L. Gibbons, MD, PhD</td>
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<td>James L. Gulley, MD, PhD</td>
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<td>Fredrick B. Hagemeister, MD</td>
<td><strong>Consultant:</strong> Genentech; Gilead; Spectrum</td>
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<td>John V. Heymach, MD, PhD</td>
<td><strong>Advisory Board:</strong> Genentech; AstraZeneca; Novartis; GSK; Lilly USA, LLC; Boehringer Ingelheim; Synta; Exelixis</td>
<td><strong>Research Funding:</strong> AstraZeneca; GSK; Bayer</td>
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<td>Eric Jonasch, MD</td>
<td><strong>Advisory Board:</strong> Bristol-Myers Squibb; Novartis; Pfizer</td>
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<td>Michael Overman, MD</td>
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<td><strong>Advisory Board:</strong> AstraZeneca; Eisai; Genentech; Janssen</td>
<td><strong>Consultant:</strong> Genentech</td>
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<td>William N. William, Jr., MD</td>
<td>No relevant financial relationships</td>
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<td>Kamatham A. Naidu, PhD</td>
<td>No relevant financial relationships</td>
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All other individuals in a position to control content have no relevant financial relationships to disclose.
Checkpoint Inhibition: A Perspective into Future of Novel Therapies for Cancer
Don Gibbons, MD, PhD
Checkpoint Inhibition: A Perspective into the Future of Novel Therapies for Cancer

Don L. Gibbons, MD, PhD
Assistant Professor, Department of Thoracic/Head & Neck Medical Oncology
MD Anderson Cancer Center

Immune Checkpoint Inhibitors in the Treatment of Selected Tumor Types: A New Direction
April 23, 2016

Conflict of Interest Disclosure

• No financial disclosures.

Agenda

• Evolution of treatment approaches
• Immunotherapy approaches as a new paradigm
• Focus on the immune checkpoint inhibitors: PD-1/PD-L1 and CTLA-4 axes
• Update from a few recent trials
• Emerging concepts on therapeutic applications:
  – Earlier stage and therapeutic combinations
  – Unique combinations produce unique toxicities

Much progress needed across the tumor types

Traditional View of Lung Cancer 2000

- Adenocarcinoma
- Squamous cell carcinoma
- Large cell carcinoma
- Small cell carcinoma

Non-small cell lung cancer

“Modern” platinum doublet (carbo/taxol/taxotere/gemcitabine)

Small cell lung cancer

Platinum doublet (cis/etoposide)

Similar response rates among frontline chemotherapy regimens

• All randomized studies had similar results
• Treatment selected based on side effect profile
A multitude of driver mutations in NSCLC

Current/former Smokers

Never Smokers

- The Cancer Genome Atlas (TCGA): resected lung tumors, adenocarcinoma vs. squamous
- BATTLE: biopsies of metastatic tumors

Molecularly-defined subsets of NSCLC identify therapeutic targets

- Driver-negative (50-60%)
- EGFR mutant (12%)
- EML4-ALK fusion (4%)
- KRAS mutant (25%)
- Other Drivers (1-2%) - e.g., ROS1/RET fusions

Appropriate targeted agent

Targeting Mutant Oncoproteins: EGFR Signaling & Therapeutic Inhibition

EGFR mutations confer profound sensitivity

Why incorporate immunotherapies into treatment?

- Standard chemotherapies have reached a therapeutic plateau.
- Targeted agents eventually produce resistance.
- Recognized efficacy of targeting the tumor microenvironment, e.g. anti-angiogenesis agents.
- Remarkable responses have been observed historically.
Tumors are more than tumor cells

Lymphocytes
Endothelial cells, blood vessels


Cytotoxic T Cell Activation and Suppression: Points for Therapeutic Intervention


PD-1/PD-L1 axis works at many points to dampen the anti-tumor immune response

Stromal PD-L1 modulation of T cells
Immune cell modulation of T cells
PD-L1/PD-1-mediated inhibition of tumor cell killing
IFN-γ-mediated upregulation of tumor PD-L1
Priming and activation of T cells
PD-L2-mediated inhibition of TH2 T cells


The observation of long term OS

CA209-003: Phase 1 study of nivolumab, stage IIIB/IV NSCLC, up to 5 prior lines of therapy

OS rate, % (95% CI)
1-year 2-year 3-year
Total 99/129
OS (%)
9.9 (7.8, 12.4) 42 (33, 50) 24 (17, 33) 18 (11, 25)

Died/Treated Median OS, mo (95% CI) 1-year 2-year 3-year
Total 99/129
OS (mo) 9.9 (7, 12)
2-year OS = 24%
3-year OS = 18%

46% of patients had received 1–2 prior lines; 54% had received 3–5 prior lines of therapy.


Design of Phase II Trial for squamous cell lung cancer: CheckMate 063 (CA209-063)

• Stage IIIB/IV SQ NSCLC
• ≥2 prior systemic therapies
• ECOG 0–1
(N = 140 screened)

Nivolumab 3 mg/kg IV Q2W until PD or unacceptable toxicity
(N = 117)

Primary:
• Confirmed ORR* (IRC assessed)
Secondary:
• Confirmed ORR* (investigator assessed)
Exploratory:
• Safety and tolerability
• PD-L1 expression and efficacy
* Further characterized by DOR

Endpoints

CheckMate 063 Overall Survival Analysis

**Phase III Study (Checkmate 017) of Nivolumab versus Docetaxel: 2nd-Line Squamous Cell NSCLC (CA209-017/NCT01642004)**

Primary Objective: Overall Survival (OS)

- **Phase III Trial**
  - Stage III/BIV or recurrent squamous cell NSCLC
  - N=264 (planned)

- **Docetaxel**
  - 75 mg/m² IV Q3W

- **Anti-PD-1**
  - 3 mg/kg IV Q2W

Secondary Endpoints:

- PFS and ORR
- ORR and OS in PD-L1+ vs PD-L1− subgroups
- Duration of OR, Time to OR

Eligibility:

- Prior Pt-containing chemotherapy
- ECOG PS ≤ 1
- FFPE tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

**Primary Endpoint**

- OS

**Secondary Endpoints**

- PFS and ORR
- Duration of OR, Time to OR

**Eligibility**

- Prior Pt-containing chemotherapy
- ECOG PS ≤ 1
- FFPE tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

**Potential clinical applications for immune checkpoint inhibitors under study**

- Given ~20% single agent efficacy in refractory metastatic setting:
  - Chemotherapy, concurrent and sequential
  - Immune combinations, e.g. Ipilimumab
  - Small molecules, e.g. TKIs (gefitinib) and MEK inhibitors (selumetinib)
  - Epigenetic modifiers (azacytidine)
- Front-line metastatic patients: CheckMate 012, Keynote 021, Atezolizumab with platinum doublets
- Adjuvant setting (NCI ALCHEMIST; NCIC CTG BR.31) & neo-adjuvant (LCMC 3 Trial)
- Radiation combinations—both PD-1 and CTLA-4 blockade
Multiple other T-Cell Immune Checkpoints as Therapeutic Targets

- CD28
- OX40
- GITR
- CD137
- GITR-L
- CD27
- CD137L
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- PD-L1
- PD-L2
- LAG-3
- HVEM

- Activating receptors
- Inhibitory receptors

- Agonistic antibodies
- Blocking antibodies

Phase II (CheckMate 069): Study Design

Eligible patients with unresectable stage III or IV melanoma

- Treatment-naïve
- BRAF WT (N = 109)
- BRAF MT (N = 33)

Stratified by BRAF status

R 2:1

NIVO 1 mg/kg + IPI 3 mg/kg

Placebo + IPI 3 mg/kg

NIVO 3 mg/kg

Placebo

Double-blind

Q3W x 4

Q2W x 4

Treat until disease progression or unacceptable toxicity

Postow, AACR, 2016


Phase 1 dose-expansion of gefitinib and durvalumab (MEDI4736): design and changes in tumour lesions

Evolution of immune targeting strategies

Postow, AACR, 2016

NCT02088112; Gibbons, ELCC, 2016
Summary

• Immune checkpoint inhibitors have become a new SOC in certain indications and are increasingly under study.
• Use in early-stage disease (neo- or adjuvant) or combination treatments is likely to produce the best long-term results.
• Science, technical and regulatory issues surrounding biomarker development are evolving.
• This class of agents produces unique side effects that require careful monitoring.
  – Especially true in the setting of combination therapies.

Thank you

Don L. Gibbons, MD, PhD
Assistant Professor, Department of Thoracic/Head & Neck Medical Oncology
MD Anderson Cancer Center

Immune Checkpoint Inhibitors in the Treatment of Selected Tumor Types: A New Direction
April 23, 2016
Immunotherapy Modalities and Combination with Standard of Care
James Gulley, MD, PhD
Immunotherapy in Combination with Standard of Care

James L. Gulley, MD, PhD, FACP
Chief, Genitourinary Malignancies Branch, NCI
Bethesda, MD

Conflict of Interest Disclosure
No relevant financial relationships

T cell Recognition of Tumor Cell

Combination with Radiation
Potential Multiple Effects of Local Irradiation of Tumors

Treatment of LnCaP prostate cells with palliative levels of 153Sm (Quadramet) modulates phenotype, upregulates TAAs, and increases sensitivity to antigen-specific CTL killing.


Treatment of LnCaP prostate cancer cells with palliative doses of 153Sm results in the upregulation of TAAs.

RT and anti-CTLA-4 extends the survival of mice bearing the nonimmunogenic 4T1 carcinoma.

Demaria et al., Oncol Immunology, 2013

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA14-043): a multicentre, randomised, double-blind, phase 3 trial.

Lancet Oncology, 2014

Ipilimumab in mCRPC post Docetaxel Overall Survival

Kwon et al., Lancet Oncology 2014
Overall Survival
Post-hoc Subgroup analysis

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab (n=146)</th>
<th>Placebo (n=142)</th>
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<tr>
<td>Median OS, Months</td>
<td>22.7 (17.8-28.3)</td>
<td>15.8 (13.7-19.4)</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.62 (0.45-0.86)</td>
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Kwon et al., Lancet Oncology 2014

Combination with Endocrine Deprivation

Enzalutamide Mediates Immunogenic Modulation in TRAMP-C2 Prostate Cells

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<tr>
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<th>MHC Increased</th>
<th>Fas Increased</th>
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<td>~5-Fold</td>
<td>~1.7-Fold</td>
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Complete Biochemical Response to Sipuleucel-T With Enzalutamide in mCRPC

Immunotherapy with TKI

- OBD ≠ MTD
- Understand impact on tumor and immune system (no empiric combinations)
- Beware of unexpected toxicities
  - Melanoma: Ipilimumab + vemurafenib (liver toxicity)
  - Melanoma: Ipilimumab + trametinib + dabrafenib (perforation)
  - RCC: Increased toxicity, no clear increase in clinical outcome
Human Carcinoma Cells Resistant to Chemotherapy Are Sensitive to CTL Killing After Treatment

Hodge et al., Int J Ca, 2013

Docetaxel Modulates Phenotype of Human Tumors In vivo

Prostate: LNCaP (MUC-1)

Hodge et al., Int J Ca, 2013

Rationale to Combine Docetaxel and Vaccine – In vivo Studies

• Docetaxel and vaccine has enhanced anti-tumor activity in a transgenic self-antigen mouse model

• Docetaxel and vaccine induces antigen spreading greater than either treatment alone in transgenic mice


Docetaxel +/- PANVAC

Patient Population: Metastatic Breast Cancer (Docetaxel Naïve) n=48

Arm A: Weekly Docetaxel + PANVAC

Arm B: Weekly Docetaxel alone

Primary endpoint: Progression-Free Survival (PFS)

JAMA Onc, Aug 20, 2015

3.9 vs. 7.9 months

Conclusions

• Standard of care agents can mediate
  – Immunogenic cell death
  – Immunogenic modulation

• Understanding these mechanisms may lead to rational combinations and improved patient outcomes
  – Important to select appropriate patient population
  – Caution that even combinations with good preclinical rationale may not be effective, and might increase toxicity

• Perhaps immune / immune combinations will hold even more promise
Annual Reviews

Thank you

James L. Gulley, MD, PhD, FACP
Director, Medical Oncology Service, NCI
Bethesda, MD
Malignant Melanoma
Michael Davies, MD
The Transformation of Melanoma by Immunotherapy

Michael A. Davies, M.D., Ph.D.
Associate Professor, Deputy Chairman, Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

The Transformation of Melanoma by Immunotherapy

Houston, Texas
April 23, 2016

Conflict of Interest Disclosure

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  – AstraZeneca
  – Roche/Genentech
  – GlaxoSmithKline
  – Myriad
  – Oncothyreon
  – Sanofi-Aventis
  – Sanofi-Aventis

• Advisory Board
  – GlaxoSmithKline
  – Genentech
  – Novartis
  – Sanofi-Aventis
  – Vaccinex

• Off-Label or Investigational Use
  – Ipilimumab + nivolumab
  – Nivolumab

Melanoma: Significance & Scope

• Skin Cancer: 3.5 million cancers in 2 million patients/yr
• Melanoma: ~5% of cases but >75% of skin cancer deaths
  ~200,000 new diagnoses per year and 46,000 deaths worldwide
  ~80,000 new diagnoses and 9,000 deaths annually in US
• Melanoma incidence continues to ↑
  – CDC: Rate of new cases of melanoma doubled from 1982 - 2011
• Patients often young/otherwise healthy
  ~ 2nd most life-years lost per cancer caused death (testicular cancer 1st)

Immunotherapy for Melanoma

• Immunotherapy for Stage IV Melanoma
  • Single-Agents
  • Combinations
• The Next Frontier: Adjuvant & Neoadjuvant Therapy
• Biomarkers to Optimize & Personalize Immunotherapy

Immunotherapy for Stage IV Melanoma

Stage IV Melanoma: Outcomes

“The overall prognosis of all patients with stage IV melanoma remains poor, even among patients with M1a. For this reason, the Melanoma Staging Committee recommended no stage groupings for stage IV.”

Stage IV Melanoma: Outcomes

2009 AJCC Melanoma Staging

- Clinically Localized, Low Risk
- Clinically Localized, High Risk
- Regional Metastases
- Distant metastases
  - Median OS ~8 mos
  - Long-Term OS ≤ 10%

Survival Time in Years

Stage I (n=18,370)
Stage II (n=9,269)
Stage III (n=3,307)
Stage IV (n=7,972)
**Proof of Concept: Interleukin-2**

- FDA Approval for Stage IV, 1998
- Cytokine that stimulates T-cells
- ORR ~15%; Complete Response Rate (CR) ~6%
  - CR: Median PFS not reached at 54 months & no relapses seen after 30 months
- Very Toxic:
  - Hypotension, renal, respiratory, psych
  - ~2% mortality in initial trials, now ~1%
- **Strengths**
  - Long-term OS in 5%
  - Proof-of-concept that stage IV melanoma pts can be cured
- **Caveats**
  - Low response rate
  - Can only be given in specialized centers
  - Patients must be selected carefully

**Ipilimumab for Stage IV Melanoma**

- FDA Approval for Stage IV, 2011
- Anti-CTLA4 antibody
- 3 mg/kg q 3 weeks X 4 doses
- 1st (+) phase III trial in stage IV melanoma
- **Strengths**
  - Long-term OS in ~20%
  - Minimal acute toxicity
- **Caveats**
  - Low response rate (~10%)
  - Responses often slow in onset, or after initial progression
  - Autoimmune toxicities can be severe (~20% grade 3-4)

**α-PD1 for Stage IV Melanoma**

- FDA Approvals
  - Pembrolizumab, 2016
  - Nivolumab, 2014
- Clinical Activity
  - Clinical Response rates 30-45%
    - More rapid than ipilimumab
    - Median duration of response not reached
- Safety
  - ~5% Grade III-IV autoimmune toxicities
  - ~5% stop treatment due to toxicity
  - Safe in patients with toxicities with prior Ipi
- **Strengths vs Ipi**
  - Higher ORR; Faster responses
  - Improved PFS & OS at early timepoints (1-2 years)
  - Markedly less toxicity
- **Caveats**
  - Long-term outcomes still pending (no plateau yet)

**KEYNOTE-2: Pembrolizumab vs ICC in Ipi/BRAFi-Refractory**

Primary End Point: PFS (RECIST v1.1)

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<tr>
<th>Arm</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>HR</th>
<th>P</th>
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<tr>
<td>Pembrolizumab 2 mg</td>
<td>279</td>
<td>33.7%</td>
<td>6.5</td>
<td>1.58</td>
<td>0.001</td>
<td>74.1%</td>
<td>0.66</td>
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<td>Pembrolizumab 10 mg</td>
<td>277</td>
<td>32.3%</td>
<td>6.1</td>
<td>1.58</td>
<td>0.001</td>
<td>68.4%</td>
<td>0.69</td>
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<td>Chemotherapy</td>
<td>278</td>
<td>11.4%</td>
<td>2.6</td>
<td>0.58</td>
<td>0.001</td>
<td>58.3%</td>
<td>0.69</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Outcomes:
- Q 3 wks ~ Q 2 wks

**Phase III: Pembrolizumab vs Ipilimumab**

Progression-Free Survival: HR 0.58

Overall Survival: HR 0.66

**Phase III: Nivolumab vs DTIC**

Treatment-Naïve, BRAF-Wild Type

Progression-Free Survival: HR 0.43

Overall Survival: HR 0.42

Outcomes:
- Q 3 wks ~ Q 2 wks

**Nivolumab**

FDA Approval, 2014

**Chemotherapy**

FDA Approval, 2014
CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone

- Previously untreated
- Metastatic Melanoma
- BRAF status
- AJCC M stage
- PD-L1 expression

**Patients could have been treated beyond progression under protocol-defined circumstances.

CA209-067: Study Design

**Patients could have been treated beyond progression under protocol-defined circumstances.

**Patients could have been treated beyond progression under protocol-defined circumstances.

The Next Frontier:

Adjuvant & Neoadjuvant Immunotherapy

Adjuvant Interferon

- Patients with stage II & stage III disease have a 40-60% risk of dying from melanoma
- Interferon-α 2b
  - FDA-approved (1996) for Thick >4 mm
  - FDA-approved (2011) for stage II melanoma
  - EORTC 18991: 1,256 pts; 6 mcg/wk X 8, then 3 mcg/wk X 5 yrs
  - Phase III trial, n=316
- Interferon-α 2b
  - FDA-approved (2011) for stage II melanoma
  - Median change ≤59%
  - ORR 19.0%
  - Median PFS, months 11.5
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Adjuvant Ipilimumab: EORTC 18071

- FDA Approval for adjuvant treatment of stage III 2015
- Stage III, n=951, Placebo vs Ipi (10 mg/kg q3W X 4, then q12W up to 3 yrs)
- Potential role Pre-Treatment & Early On-Treatment
- ↑CD8+ T cell infiltrate → ↑ Responsiveness to PD1
- Toxicity: 48.5% AE related to drug including 5 treatment-related deaths

PD-L1 Immunohistochemistry (IHC)

PD-L1 ≥1%* (~60%) with Ipilimumab (>100) correlated with improved OS

Neo-Adjuvant Immunotherapy

- Neo-adjuvant therapy is standard of care in breast cancer
- Previously not feasible in melanoma due to low response rates
- Key question: balance of efficacy and safety

Personalizing Immunotherapy:

Biomarkers of Response & Resistance

- ↑CD8+ T cell infiltrate → ↑ Responsiveness to PD1
  - Also predicts increased responsiveness to targeted therapy (BRAFV600E)
  - Correlates with improved prognosis in melanoma TCGA
- Potential benefits
  - Reduced tumor size
  - Potentially reduces need for lymph node dissection

Immune Infiltration by T-Cells

- Increased somatic mutational load (>100) correlated with improved OS with Ipilimumab

NGS Predictors of Response to IMT

- Increased somatic mutational load (>100) correlated with improved OS with Ipilimumab
- Mutation-specific TIL reactivity
- Potentially predicts responders 

Neo-Adjuvant Immunotherapy

- Neoadjuvant therapy
- Patients with stage IIIA/B/C or oligometastatic IIIC on diagnosis
- Initial 4 doses of Nivo and Ipi
- Surgery: 12 wks after 6 doses of Ipi
- Follow-up: 24 weeks post surgery

Biomarkers in Response & Resistance:

- Ki67+/CD8+ density (cells/mm2)
- Tumour Invasive Margin
- PD-L1 IHC assay

Personalizing Immunotherapy:

Biomarkers of Response & Resistance

- PD-L1 (+) or (−): Nivo and Ipi/Nivo > Ipi
- PD-L1 (−): Ipi/Nivo >> Nivo
- PD-L1 (+): Nivo & Ipi/Nivo ~ PFS

Neo-Adjuvant Immunotherapy

- Neoadjuvant therapy
- Patients with stage IIIB/IIIC or oligometastatic IIIC on diagnosis
- Initial 4 doses of Nivo and Ipi
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Biomarkers in Response & Resistance:

- Ki67+/CD8+ density (cells/mm2)
- Tumour Invasive Margin
- PD-L1 IHC assay
Oncogenes & Resistance to IMT

- **BRAF mutations**
  - BRAF v599E is not associated with melanocytic antigen expression, TILs
  - Does NOT appear to correlate with significantly different outcomes with PD1 or PD1 + CTLA4

- Beta-Catenin pathway
  - Activation of pathway correlates with immunosuppressive TME ([Spranger, Nature, 2015])

- Loss of PTEN
  - Decreased immune infiltration
  - Decreased responsiveness to PD1 in preclinical models and in patients

→ Multiple clinical trials of immune + targeted therapy ongoing & planned

**Immunotherapy for Melanoma 2016:**

**Current Status & Progress**

- Immunotherapy is now a standard first-line option for patients with stage IV melanoma
  - Increasing response rates
  - Goal: Long-term survival

- Trials ongoing in earlier stages of disease
  - Adjuvant α-PD1
  - New opportunity/paradigm: neo-adjuvant therapy

- Increasingly evolving from single agents → combinations

**Immunotherapy for Melanoma 2016:**

**Challenges & On-going Research**

- Identification of biomarkers to personalize pt management
- Development of new combinations
  - Goal = more activity without increased toxicity
  - Combinations with targeted therapy, XRT, surgery
- Defining safety & efficacy in additional populations
  - Organ dysfunction, including autoimmune disease
  - Patients with CNS metastases
- Improving our understanding of resistance → rational new strategies

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Thank you for your attention!

Michael Davies, M.D., Ph.D.
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University of Texas M. D. Anderson Cancer Center, Houston, TX
mdavies@mdanderson.org

Research Support:
- Cancer Prevention Research Institute of Texas (CPRIT)
- MDACC-Oak Ridge National Laboratory
- MDACC Physician Scientist Program
- Dunn Foundation for Chemical Genomics
- MDACC Research Alliance
- Melanoma Research Foundation
- American Society for Clinical Oncology
- Melanoma Research Alliance
- MDACC Melanoma Moon Shot Program
Lung Cancer
John V. Heymach, MD, PhD
Immunotherapy Clinical Studies: Lung Cancer

John V. Heymach MD, PhD
Chairman and Professor
Thoracic/Head and Neck Medical Oncology
David Bruton Jr. Chair in Cancer Research
Immune Checkpoint Inhibitors in the Treatment of Selected Tumor Types: A New Perspective
April 23, 2016

Immunotherapy for NSCLC

Immunotherapy: a new era of therapy for lung cancer patients

- Nivolumab (PD-1 antibody), FDA approved for squamous and non-squamous NSCLC (regardless of PD-L1 status)
- Pembrolizumab: PD-1 antibody, FDA approved for PD-L1+ NSCLC
- Atezolizumab: anti-PD-L1 antibody

CheckMate-017: A Phase 3 Study of nivolumab vs docetaxel in previously treated advanced/metastatic squamous NSCLC

Primary endpoint: OS
Secondary endpoint: ORR and PFS

- Nivolumab 3 mg/kg iv,Q2w
- Docetaxel 75 mg/m2,Q3w

Primary endpoint OS: HR 0.59 (P<.001)
Median OS 9.2 vs 6.0m
ORR 27 vs 12%

Bottom line: Nivo prolongs OS vs docetaxel in 2nd line SCC regardless of PD-L1 level. March 2015: FDA approved for 2nd-line squamous NSCLC.

CHECKMATE-17: Randomized phase III study of nivolumab vs docetaxel in 2nd line squamous NSCLC

Disclosures

Research support: AstraZeneca, GSK
Advisory Boards: Genentech, BMS, Lilly, AstraZeneca, GSK, BI, Aushon, Exelixis, Bio-Tree
CHECKMATE-57: Randomized phase III study of nivolumab vs docetaxel in 2nd line non-squamous NSCLC

Primary endpoint OS: HR 0.73 (P=.002)
Median OS 12.2 vs 9.4m
ORR 19 vs 12% (P=0.02)

Bottom line: Nivo prolongs OS vs docetaxel in 2nd line non-squamous NSCLC regardless of PD-L1 level.
Oct 2015: FDA approved for 2nd-line non-squamous NSCLC.

Borghaei et al, NEJM 2015

KEYNOTE-001: Pembrolizumab for NSCLC

Overall population
Previously untreated
Previously treated

Bottom line: Pembro has acceptable SE profile and high PD-L1 associated with improved efficacy.
FDA approved in 2nd line PDL1+ (Score >50%) NSCLC in Oct 2015

Garon et al, NEJM 2015

KEYNOTE-001: Pembrolizumab for NSCLC

Second line NSCLC
1:1:1
N=1034
PD-L1>1% TCs

pembrolizumab
10 mg/kg iv,Q3w
Docetaxel
75 mg/m2,Q3w

Primary endpoints:
PFS, OS in overall population; --
PFS, OS in PD-L1>50% population


KEYNOTE-010: A Phase 3 Study of pembrolizumab vs docetaxel in previously treated advanced /metastatic PDL1+ NSCLC

Overall population
PD-L1 proportion score >50%

Bottom line: Pembro prolongs OS vs docetaxel in 2nd line PD-L1+ NSCLC regardless; they are using 2 mg/kg, 22C3 pharmdx antibody.

Hertzt et al, Lancet, 2016

KEYNOTE-010 study of pembrolizumab vs docetaxel in PDL1+ NSCLC: subgroup analyses of OS

≥50% seem to benefit more
Adeno may benefit SQ
EGFR mutants may benefit less

Herbt et al, Lancet, 2016
**KEYNOTE-010: A Phase 3 Study of pembrolizumab vs docetaxel in previously treated advanced /metastatic PDL1+ NSCLC: PFS results**

**Bottom line:** Pembrol prolongs PFS vs docetaxel in 2nd line PD-L1+ NSCLC in PS>50% but benefits are smaller than OS


<table>
<thead>
<tr>
<th>Overall population</th>
<th>PD-L1 proportion score &gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 mg/kg: FFS HR 0.59 (P=.0001) Median PFS 5 m, 6.2 vs 4 m</td>
</tr>
</tbody>
</table>

**POPLAR: Randomized phase II study of atezolizumab vs docetaxel in previously treated advanced /metastatic NSCLC**

**Primary endpoints:**
- OS in ITT overall population; OS in PD-L1+

Fehrenbacher et al, Lancet, 2016

**Trend towards higher PD-L1 IHC score and longer PFS**

Herbst et al, Nature 2014

**POPLAR: Randomized phase II study of atezolizumab vs docetaxel in previously treated advanced /metastatic NSCLC- Primary OS endpoint**

Bottom line: atezolizumab seems to show similar prolongation in OS vs docetaxel in 2nd line as PD-1 inhibitors; phase III studies pending.

Fehrenbacher et al, Lancet, 2016
POPLAR: Randomized phase II study of atezolizumab vs docetaxel in previously treated advanced/metastatic NSCLC- biomarker subgroups

Bottom line: the more PD-L1 you have on TC or IC, the more benefit; little benefit in TC0 and IC0 (but no significant harm).

Combinations of CTLA-4 blockade with PD-1 blockade
CheckMate 012: new dosing schedules for nivolumab plus ipilimumab

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

- Nivo 1 mg/kg Q2W
- Ipi 1 mg/kg Q3W
- Nivo 3 mg/kg Q2W

**NR due to high percentage of ongoing response or insufficient number of events and/or follow-up.**

- Includes patients with confirmed CR, PR, and SD.
- NR due to high percentage of ongoing response or insufficient number of events and/or follow-up.
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### Results

<table>
<thead>
<tr>
<th>PD-L1 expression</th>
<th>Nivo 1 mg/kg (n = 52)</th>
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</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>23</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>confirmed ORR, %</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>DCR</td>
<td>74</td>
<td>65</td>
<td>44</td>
</tr>
<tr>
<td>Treatment-related AEs, %</td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation, %</td>
<td>10</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Treatment-related deaths, n</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

CheckMate 012: previously presented cohorts with advanced NSCLC1,2

### Results

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Efficacy by baseline tumor PD-L1

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</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>8</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>nPFS, months</td>
<td>16 (1.3)</td>
<td>16 (1.3)</td>
<td>21 (1.9)</td>
</tr>
<tr>
<td>PFS at 24 weeks, % (95% CI)</td>
<td>8 (15.0)</td>
<td>1 (25.9)</td>
<td>15 (28.5)</td>
</tr>
</tbody>
</table>

NR due to high percentage of ongoing response or insufficient number of events and/or follow-up.

Checkmate 012 with ipi/nivo: Results

- Includes patients with baseline target lesion and 10 mm diameter measurement of target lesion. Faster change in tumor burden indicates tumor reduction. Not all reductions of ≥30% from baseline are partial responses.
- NR due to high percentage of ongoing response or insufficient number of events and/or follow-up.
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Integrating IMT with XRT:
Can IMT enhance the efficacy of XRT for lung cancer patients?

XRT Plus anti-PD1 reduced unirradiated tumor

Abscopal effect: enhanced response to IMT after XRT to distant site

Testing the abscopal effect: a randomized phase II study of pembrolizumab +/- XRT

Integrating IMT with targeted therapy for KRAS
KRAS subsets have distinct patterns of immune markers: increased T-cell infiltration, checkpoint factors and inflammation in KP vs KL tumors

---

Integrating IMT with MEK inhibitors and other targeted therapies

- **Potential Pros:**
  - Targeted agent may induce cell death, enhancing antigen presentation and TIL infiltration
  - Oncogenic pathways may be immunosuppressive (e.g. VEGF stimulates MDSCs; RAF/MEK signaling suppresses antigen presentation)

- **Potential Cons:**
  - Continuous suppression of signaling pathways may blunt immune response (e.g. MEK, PI3K signaling known to play a key role in Tcell responses)

Unclear if intermittent dosing may mitigate this

---

Potential approaches to enhance immune responses in KRAS mutant tumors

**Immunity**

MAP Kinase Inhibition Promotes T Cell and Anti-tumor Activity in Combination with PD-L1 Checkpoint Blockade

Ebert et al, Immunity 2016

---

Phase II Trial of Immunotherapy with MEDI4736 With Continuous or Intermittent MEK Inhibitor Selumetinib in KRAS Mutant NSCLC

**Previously Treated KRAS Mutant NSCLC**

- **Safety Run-in**
  - N=up to 12

- **Randomized Phase II**
  - N=35 in each arm

  - Continuous Selumetinib + MEDI4736 day 1, 15
  - Intermittent* Selumetinib + MEDI4736, dosing TBD in Dr. Janne’s phase I

- **Primary objective:** Progression free survival
- **Secondary objectives:** Response rate, disease control rate, OS, irPFS, safety and toxicity
- **Exploratory objectives:** Evaluate molecular markers

---

Other IMT approaches:

**IMT and T-cell CARs for SCLC**

W. Denning et al; collaboration with L. Cooper lab
CheckMate 032 of Ipi/Nivo for SCLC: study design

Patients with SCLC with progressive disease ≥14 days after last dose of prior chemotherapy = included (Nivolumab: 1 + Ipilimumab 3) or 90 days following platinum-based chemotherapy (Nivolumab: 3). Patients with ≥1 prior line of therapy were eligible. Exclusions: Patients with brain metastases, ≥1 other metastatic site, or PD-L1 positive in ≥1% of Tumor assessment, patients with poor performance status, and patients who had received prior anti-cancer therapy within 8 weeks. Neutro. 4.5–30; Nivolumab 1 mg/kg IV Q3W; Nivolumab 3 mg/kg IV Q2W; Ipilimumab 3 mg/kg IV Q3W.

CheckMate 032 results

<table>
<thead>
<tr>
<th>Platinum-sensitivea</th>
<th>Platinum-resistantb</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>12.7</td>
</tr>
<tr>
<td>Complete response, %</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, %</td>
<td>11.4</td>
</tr>
<tr>
<td>Stable disease, %</td>
<td>76.3</td>
</tr>
<tr>
<td>Disease control rate, %</td>
<td>92.7</td>
</tr>
<tr>
<td>Progressive disease, %</td>
<td>18.8</td>
</tr>
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<td>4.4</td>
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Median time to objective response, months: 3 (1.77, 4.21) 3 (2.10, 5.41) 3 (2.66, 7.46) 3 (2.71, NR) 3 (3.65, NR) 3 (2.71, NR) 3 (3.65, NR) 3 (2.71, NR) 3 (2.71, NR)

CheckMate 032: Overall Survival results

CheckMate 032: ORR results

Tumor responses (PD-L1 expression)

Not evaluable (nonevaluable): one patient withdrew consent, and one patient was not evaluable due to scans <6 weeks from baseline.

CheckMate 032: PFS results

Median DOR, months (95% CI): 6.60 (4.00, NR) 3.35 (1.48, NR) 1.38 (0.90, 1.96) 1.35 (1.00, 1.90) 1.35 (1.00, 1.90) 1.35 (1.00, 1.90) 1.35 (1.00, 1.90) 1.35 (1.00, 1.90) 1.35 (1.00, 1.90) 1.35 (1.00, 1.90)

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** Nonevaluable: one patient withdrew consent, and one patient was not evaluable due to scans <6 weeks from baseline.
Despite high mutation burden, T cell responses may be hindered in SCLC
-31,000 cases/yr in US; 5y survival <10%
-Initial sensitivity to chemo and XRT, but resistance develops in almost all patients
-Standard therapy essentially unchanged since 1980s.

**Antigen Presentation**
- HLA-A
- HLA-B
- HLA-C
- PD-L1

**Co-stimulation**
- CD58
- CD40
- 41BBL
- FAS
- MIC A
- MIC B

**Checkpoint**
- Death Ligands

**Distribution of NCAM in malignant tissues**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>% NCAM positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>~100%</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>~100%</td>
</tr>
<tr>
<td>Glioma</td>
<td>~100%</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>~100%</td>
</tr>
<tr>
<td>Small Cell Lung Cancer</td>
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</tr>
</tbody>
</table>

= p < 0.0001

**Chimeric Antigen Receptor (CAR) Design**

"Kills as a T cell; Targets like an Antibody"

| CD56R scFv | Target binding |
| CD3ζ scaffold | Flexibility & "Reach" |
| transmembrane domain | Molecular Association |

| CD28 signaling domain | Activation of T cell |

W. Denning et al. ; Collaboration with L. Cooper et al.

**hCD56R-CAR T cells inhibit H526 (CD56+) xenograft in vivo**

W. Denning, L. Cooper et al, WCLC, 2015

**Rationale for targeting SCLC with CAR T cells**
- Despite high mutation burden, SCLC has an immunosuppressed phenotype with low Tcell infiltration and APM
- CARs are HLA-independent
- Does not require stimulation by host immune system
- Target SCLC antigens: CD56

<table>
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<tr>
<th>CAR Type</th>
<th>% NCAM positive</th>
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</thead>
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<tr>
<td>0e6 (PBS)</td>
<td>n.s.</td>
</tr>
<tr>
<td>1e6 CAR T</td>
<td>= p &lt; 0.05</td>
</tr>
<tr>
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<td>= p &lt; 0.01</td>
</tr>
<tr>
<td>10e6 CAR T</td>
<td>= p &lt; 0.001</td>
</tr>
</tbody>
</table>

Chimeric Antigen Receptor (CAR) Design

"Kills as a T cell; Targets like an Antibody"

W. Denning et al. ; Collaboration with L. Cooper et al.

**Summary**

1. Immunotherapy now the standard of care for refractory advanced NSCLC.
   - Nivo, pembro approved in refractory disease
2. Combinations of PD1 blockade with CTLA4 blockade appear to be more effective and a bit more toxic
3. Combinations with targeted agents, radiotherapy, etc are ongoing but not yet approved
4. Possible progress in SCLC with combination regimens. New approaches include T-CARs

**Thank You**

John V. Heymach MD, PhD
Chairman and Professor
Thoracic/Head and Neck Medical Oncology
David Bruton Jr. Chair in Cancer Research
MD Anderson Cancer Center
Immune Checkpoint Inhibitors in the Treatment of Selected Tumor Types: A New Perspective
April 23, 2016
Head & Neck Cancers
William A. William, MD
Immune Checkpoint Inhibitors for Head and Neck Cancer

William Nassib William Jr., MD
Associate Professor
Chief, Head and Neck Section
Department of Thoracic/Head and Neck Medical Oncology
The University of Texas M. D. Anderson Cancer Center, Houston, TX

Outline
• Introduction
• PD-1/PD-L1 Inhibitors in HNSCCs
  • Pembrolizumab
  • Durvalumab
• PD-1 Inhibitors in NPCs
  • Pembrolizumab
• Ongoing Studies / Data Pending

Conflict of Interest Disclosure
Advisory Board: GSK, Genenech, Novartis, Sanofi-aventis, Vaccinex
Research Funding: GSK, Genentech, AstraZeneca, Sanofi-aventis, Merck
Independent Contractor: Myriad, Oncothyreon

Chemokine Signatures Identify T-cell Infiltration

Saloura et al. ASCO 2014

More HPV + Tumors Have T-cell Infiltration

Saloura et al. ASCO 2014
Mesenchymal HNSCC Upregulate Immune Response Pathways

PD-L1 Expressed in Both HPV+ and HPV- HNSCC

Immune Checkpoints Upregulated in TCIP-High

Outline

- Introduction
  - PD-1/PD-L1 Inhibitors in HNSCCs
    - Pembrolizumab
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  - PD-1 Inhibitors in NPCs
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  - Ongoing Studies / Data Pending
### Anti-PD1 Pembrolizumab

#### Time on treatment and disposition*

![Graph showing time on treatment and disposition](image)

- Complete Response
- Partial Response
- Stable Disease
- Progression
- Other

*Survivor plot of all patients who experienced CR or PR.*

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#### Baseline Demographics

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<td>(1) Performance score (9/127)</td>
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<td>(2) Performance score (9/127)</td>
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#### Overall Response Rate [Site Radiology Review]*

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<th>Treatment Month</th>
<th>N (n1/17)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>NE (%)</th>
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</tr>
</tbody>
</table>

*NE = not evaluable, SD = stable disease, CR = complete response, PR = partial response*
Outline

• Introduction

• PD-1/PD-L1 Inhibitors in HNSCCs
  • Pembrolizumab
  • Durvalumab

• PD-1 Inhibitors in NPCs
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Anti-PD1 Pembrolizumab

Biomarkers

• Evaluation of PD-L1 expression by IHC
  • In the current cohort, IHC is ongoing
• The optimal cutoff for PD-L1 expression as well as potential clinical use of the cutoff is ongoing
• An interferon-gamma expression signature associated with PD-L1 was observed in tumors
  • 48% positive predictive value

Anti-PD-L1 Durvalumab (MEDI4736)

• Phase I, multicenter, open-label study
• Recurrent/metastatic SCCHN
• MEDI4736 10 mg/kg IV every 2 weeks (q2w)

Pembrolizumab in NPC – Keynote 028

• Phase Ib, multicenter, open-label study
• Previously treated NPC with positive PD-L1 by IHC (≥1%)
• Pembrolizumab 10 mg/kg IV every 2 weeks
• 27 patients
  • 64% Asian
• Efficacy:
  • 26% response rate
Summary

• A subset of HNSCC exhibit TCD8+ infiltrate / inflamed phenotype, with upregulation of immune checkpoints
• PD-L1 expression similar in HPV+ and HPV- patients
• Pembrolizumab with 20-24% response rate. No difference in response rates between HPV+ and HPV- patients
• Durvalumab also active in HNSCC, with possibly a lower response rate in HPV+ patients (preliminary data)
• PD-L1 expression and IFN-gamma signature possible biomarkers of response
• Pembrolizumab also demonstrates preliminary activity in NPC (26% response rate)

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Selected Ongoing Trials

Selected Ongoing Trials

Selected Ongoing Trials

Selected Ongoing Trials
Checkmate 141

- Phase 3, open-label, randomized study (N=360)
- Previously treated patients with SCCHN who have tumor progression on or within 6 months of platinum therapy in the primary, recurrent, or metastatic setting
- Nivolumab versus investigator's choice of therapy (docetaxel, cetuximab, MTX)
- Study closed early at DSMB recommendation due to superior survival in the nivolumab arm

Keynote 055

- Pembrolizumab Clinical Trials
  - Phase 3, randomized trial in patients with recurrent/metastatic head and neck cancer; 2L
  - PD-L1 (+) or (–)
    - Pembrolizumab
    - Methotrexate or docetaxel or cetuximab
  - PFS, PFS [strong PD-L1(+)], OS, OS [strong PD-L1(+)]

Durvalumab Clinical Trials

- EAGLE (NCT02369874/D4193C00002)
  - Phase 3, randomized, open-label
  - Patients with recurrent or metastatic SCCHN, 2L (N=720)
    - Disease progression or recurrence during or after a platinum-based chemotherapy regimen
    - Progression within 6 months of multimodality therapy containing platinum
  - Stratification factors:
    1. PD-L1 status
    2. HPV status
    3. Smoking history
  - Follow-up for OS
  - Subsequent treatments
    - Arm 1: Durvalumab i.v. 10 mg/kg q2w for up to 12 months (n=100 PD-L1(+) + 140 PD-L1(–) → 240 total)
    - Arm 2: Durvalumab i.v. 10 mg/kg q2w for 18 doses (n=100 PD-L1(+) + 140 PD-L1(–) → 240 total)
    - Arm 3: SoC, including cetuximab, a taxane, methotrexate, or a fluoropyrimidine (n=100 PD-L1(+) + 140 PD-L1(–) → 240 total)

- KESTREL (NCT02551159/D419LC00001): Study Design
  - Phase 3, randomized, open-label
  - Patients with recurrent or metastatic SCCHN not amenable to local curative therapy with surgery or radiation (1L)
  - Stratification
    1. PD-L1 status (~400 PD-L1(–) patients)
    2. Tumor location
    3. Smoking history
  - Primary endpoint
    - PFSe,f
  - Secondary endpoints
    - PFSe,g, OSg, ORRe, DoRe
    - Safety/tolerability, QoL
    - PK, immunogenicity

Durvalumab Clinical Trials

- KESTREL (NCT02551159/D419LC00001): Study Design
  - Phase 3, randomized, open-label
  - Patients with recurrent or metastatic SCCHN who have tumor progression on or within 6 months of platinum therapy in the primary, recurrent, or metastatic setting
  - Nivolumab versus investigator's choice of therapy (docetaxel, cetuximab, MTX)
  - Study closed early at DSMB recommendation due to superior survival in the nivolumab arm
Thank you

William Nassib William Jr., MD
Associate Professor
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The University of Texas M. D. Anderson Cancer Center, Houston, TX
Hematological Malignancies
Fredrick B. Hagemeister, MD
Anti-PD-1 Antibodies for Hodgkin Lymphoma and NHL

F B Hagemeister, MD
Department of Lymphoma/Myeloma
M. D. Anderson Cancer Center
Houston, TX
Houston 4/23/2016

The Immune System’s Role in Fighting Malignancy

2 major components play important roles in control of malignancy
1. Innate response
   Consists of proteins and cells (NKs) the first line of defense
2. Adaptive response
   Capable of responding to new antigens (T- and B- Cells)

Functions of PD-1, PD-L1, and PD-L2 in Normal Immune Regulation

- **PD-1 (CD279)**
  - Present on activated Ts, bound by PD-L1, PD-L2
  - Inactivates T cell function after infection
  - Prevents autoimmunity ("the immune checkpoint")

- **PD-L1 (CD274)**
  - Present on B and T cells, and macrophages
  - Mediates a generalized anti-inflammatory effect

- **PD-L2 (CD273)**
  - Present on antigen-presenting cells (APCs)
  - Regulates T-cell priming

PD-L1 is Upregulated in Tumor cells

- Chromosome 9p24.1 amplification upregulates PD-L1, as can EBV infection
- Multiple tumor types utilize the PD-L1 and PD-L2 interaction with PD-1 to escape immune surveillance
  - Breast, NSCLC, Kidney, Colon, Melanoma, Hematologic Malignancies overexpress PD Ligands
  - Pembrolizumab and Nivolumab FDA-approved for Metastatic Melanoma
  - Nivolumab approved for Lung Cancer
  - Ongoing studies in many other tumors

The immune checkpoint

Antigen Release

APC Activation

NK Killing

Migration of T-Cells

T-Cell Activation

Antibody Made

Periphery

DLBCL, NOS

PMBCL

TCR-BCL

EBV Pos BCL

PTLD

DLBCL, leg type

FL

cHL

NLPHL

CLL

A/TL

ALCL

PD-L1 and PD-L1 Expression by IHC on Lymphoma Cells

<table>
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<th>by</th>
<th>PD-L1 (CD279)</th>
<th>PD-L1 (CD274)</th>
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<td># Pts</td>
<td># Pos (%)</td>
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<td>-</td>
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</table>

PD-1 Interactions: Mechanisms of Action

**Anti-PD-I or Anti-PD-L1? Advantages and Disadvantages**

- **Target saturation**
  - PD-1-expressing T cells are present in blood, therefore allowing rapid saturation
  - PD-L1 on tumor cells may be more difficult to reach, requiring higher levels of drug, and perhaps more exposure

- **Inflammatory toxicity**
  - PD-1 axis initiates cytotoxic T-cell response
  - PD-L1/PD-1 interaction may not require ADCC, since surface expression may not be necessary for resulting response following blockade

---

**Phase I Nivolumab in Rel/Ref HL: Preliminary Safety, Efficacy and Biomarker Results**

- 23 Hodgkin lymphoma patients from larger study in hematologic malignancies
  - Dosing: 1-3 mg/kg with no MTD reached in Phase I
  - Expansion cohort 3 mg/kg chosen, week 1, 4 and q 2 wk for maximum 2 years
  - Drug-related adverse events (> 10%, all reversible)
    - All: 18 (78) G3, 5 (22)
    - Rash: 5 (22)
    - Fatigue, fever, diarrhea, nausea, pruritis: 3 each (13)


**Phase I Nivolumab in Rel/Ref HL: Preliminary Safety, Efficacy and Biomarker Results**

- Population: Med 35 years old (20-54)
  - RS cells from 10 pts studied by FISH for PD-L
    - All had 3-15 copies of PD-L1 or PD-L2
    - Patterns characterized by amplification, relative copy gain, or polysomy of 9P24.1


**Phase I Nivolumab in Rel/Ref HL: Preliminary Safety, Efficacy and Biomarker Results**

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<th>Feature</th>
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<td>Path NS</td>
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<tr>
<td>&gt;5</td>
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<tr>
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**Response to Nivolumab**

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<th>Pts, N =24 (%)</th>
<th>SCT Fail, BV Fail N=15, %</th>
<th>SCT Naive, BV Fail N=3, %</th>
<th>BV Naive N=5, %</th>
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</tbody>
</table>

*1st evaluation at 8 weeks of therapy
Median follow-up – 40 weeks


**Changes in Tumor Burden in Patients with HL Receiving Nivolumab**

Phase I Nivolumab in Rel/Ref HL: Preliminary Safety, Efficacy and Biomarker Results

2 pts discontinued therapy due to toxicity (Pancreatitis, MDS), 6 due to SCT, 4 due to PD, and 11 continued on therapy


Anti-PD-1 Therapy for HL and NHLs

- **Nivolumab**
  - HL
  - NHLs
- **Pembrolizumab**
  - HL
  - NHLs
- **Pidilizumab**
  - NHLs

Anti-PD-1 Therapy for HL and NHLs

- **Nivolumab**
  - HL
  - NHLs
- **Pembrolizumab**
  - HL
  - NHLs
- **Pidilizumab**
  - NHLs

Phase I Nivolumab (BMS-936558) for Relapsed/Refractory Lymphoid Malignancies

Lesokhin et al. ASH 2014 # 291

Resp All B FL DLCL All T23 MF PTCL MM MM

%OR 28 40 36 17 15 40 0 0

%CR 7 10 9 0 0 0 0 0

%PR 21 30 27 17 15 40 0 0

%SD 48 60 27 43 69 0 67 100

Ongoing studies in DLBCL and FL

Lesokhin et al. ASH 2014 # 291

Other Drugs Which Affect T-Cell Function Combined with Anti-PD-1 Drugs

- **Ipilimumab (BMS, Yervoy, MDX-010, MDX-101)**
  - Targets CTLA-4, a protein receptor that downregulates cytotoxic T-cells (CTCs)
  - Approved for melanoma therapy, in trials for STs
- **INC24360 (Incyte)**
  - Inhibits IDO1, an enzyme that converts tryptophan into kynurenine, which inhibits T-cell proliferation
  - Phase 1 studies ongoing in many tumor types
- **RRx-001 (EpicentRx)**
  - Generates active oxygen/nitrogen species that epigenetically modulate DNA methylation, HDAC, and demethylation
  - Upregulates PD-1

Ongoing Studies with Nivolumab as Therapy for Lymphomas

<table>
<thead>
<tr>
<th>NCN Trial Number</th>
<th>Phase</th>
<th>Investigator</th>
<th>Disease</th>
<th>Disease State</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>02038946</td>
<td>2</td>
<td>BMS</td>
<td>FL</td>
<td>Rel/Ref</td>
<td>SA</td>
</tr>
<tr>
<td>02329847</td>
<td>2</td>
<td>BMS, Janssen</td>
<td>CLL, FL</td>
<td>Rel/Ref</td>
<td>ibrutinib</td>
</tr>
<tr>
<td>02572167</td>
<td>1-2</td>
<td>Multicenter</td>
<td>HL</td>
<td>Rel/Ref</td>
<td>BV</td>
</tr>
<tr>
<td>02581631</td>
<td>1-2</td>
<td>SGN, BMS</td>
<td>CD30+</td>
<td>Rel/Ref</td>
<td>BV</td>
</tr>
<tr>
<td>02304458</td>
<td>1-2</td>
<td>NCI (US)</td>
<td>Any</td>
<td>Rel/Ref</td>
<td>ipilimumab</td>
</tr>
<tr>
<td>01986999</td>
<td>1</td>
<td>NCI (US)</td>
<td>HL</td>
<td>Rel/Ref</td>
<td>Ipilimumab, BV</td>
</tr>
<tr>
<td>02327078</td>
<td>1-2</td>
<td>Incyte, BMS</td>
<td>Bcell, HL</td>
<td>Rel/Ref</td>
<td>INC24360</td>
</tr>
<tr>
<td>02518958</td>
<td>1</td>
<td>EpicentRx</td>
<td>Any</td>
<td>Rel/Ref</td>
<td>RRx-001</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov 2/20/2016
**Anti-PD-1 Therapy for HL and NHLs**
- Nivolumab
  - HL
  - NHLs
- Pembrolizumab
  - HL
  - NHLs
- Pidilizumab
  - NHLs

**Phase Ib Pembrolizumab (MK-3475) for HL after Brentuximab Failure: KEYNOTE-013**
- 31 with Rel/Ref HL: Path NS or MC
  - All relapsed from or failed BV therapy
  - 3 or more prior therapies in 28 (97%)
  - Prior ASCT = 20 (69%)
- Pembrolizumab given 10mg/kg every 2 weeks
  - Evaluation based on response at 12 weeks (6 doses)
  - Tolerability: 16 (55%) of pts experienced one or more treatment-related AEs, but no Gr 4-5 events.
- Results at med follow-up at 38 weeks
  - 29 Cases evaluable
    - ORR 66%, CR 21%, PR 45%, SD 21%

**Pembrolizumab for cHL in Relapse Following AlloSCT**
- 2 Cases, treated at Mayo clinic
- Neither had GVH at the time of therapy
- Both were on Low-dose Prednisone
- 1 CR, 1 PR, both still on therapy
- Concerns that activation of PD-1 pathway might increase risk of GVH via T-cell activation may not be a worrisome issue.
- Patients with active GVH may still be of some concern

**Response Rate SCT ineligible or refused* N=9**

<table>
<thead>
<tr>
<th></th>
<th>SCT ineligible or refused* N=9</th>
<th>SCT failed N=29</th>
<th>Total N=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>44</td>
<td>75</td>
<td>66</td>
</tr>
<tr>
<td>CR</td>
<td>22</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>PR</td>
<td>22</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>SD</td>
<td>33</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td><em>Clinical Benefit</em></td>
<td>78</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>PD</td>
<td>22</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

*1 refused SCT

**Pembrolizumab for cHL in Relapse Following AlloSCT**

- 2 Cases, treated at Mayo clinic
- Neither had GVH at the time of therapy
- Both were on Low-dose Prednisone
- 1 CR, 1 PR, both still on therapy
- Concerns that activation of PD-1 pathway might increase risk of GVH via T-cell activation may not be a worrisome issue.
- Patients with active GVH may still be of some concern

Villasboas J, et al. published online for Oncotarget by impactjournals.com, 2016
Ongoing Studies with Pembrolizumab as Therapy for Lymphomas

<table>
<thead>
<tr>
<th>NCN Trial Number</th>
<th>Phase Investigator Disease Disease State Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>0250473</td>
<td>1-2 4 Centers FL, MZL RT Alone Intratumor G100</td>
</tr>
<tr>
<td>02541565</td>
<td>2 U Wash (FH) DLBCL Any R-CHOP</td>
</tr>
<tr>
<td>02453594</td>
<td>2 MerckSD HL Rel/Ref SA</td>
</tr>
<tr>
<td>02576990</td>
<td>2 MerckSD 1st Med Rel/Ref SA</td>
</tr>
<tr>
<td>02553247</td>
<td>2 FoxChase PTCL Rel/Ref SA</td>
</tr>
<tr>
<td>0250999</td>
<td>1-2 U Penn B Cell P CAR-T SA</td>
</tr>
<tr>
<td>02362997</td>
<td>2 Dana Farber HL, DLCL P SCT SA</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov 2/20/2016

Anti-PD-1 Therapy for HL and NHLs

- Nivolumab
  - HL
  - NHLs
- Pembrolizumab
  - HL
  - NHLs
- Pidilizumab
  - NHLs

Phase I CT-011 (Pidilizumab) for Patients with Rel/Ref Heme Malignancies

- 17 patients with hematologic malignancies: AML, ALCL, DLBCL, CLL, HL, and MM.
  - One dose of drug from 0.2-6mg/kg given
  - One with untreated FL-CR, 2 CLL, 1 HL, 1 MM each had SD
  - No dose-response relationship noted
  - Clearance took 21 days, and no significant toxicity noted

Phase II Pidilizumab for Patients with DLBCL Without Progression Following ASCT

- 66 patient with relapsed DLBCL with disease sensitive to salvage therapy who underwent ASCT
  - 47% (31/55) had PET-CT prior to SCT
  - Scans 30-90 d post SCT: PET-CR in 68% (45/54); CT-CR in 47%
  - Drug dose: 1.5 mg/kg IV q 7 weeks X 3


Phase II Pidilizumab for Patients with DLBCL Without Progression Following ASCT

- Increases in PD-L1 helper T’s and monocytes, CD8+ Peripheral T’s and CD4+ central memory T’s observed
- Results better than expected, esp in PET pos disease
- Current trial: Phase 2 Pidilizumab Q 7 wks x 3 for Stage III-IV DLBCL in first remission
- Primary outcome: 50% or more increase in lymphocyte subsets (CD4+/CD25+/PD-L1+ and CD4+/CD62L+/CD127+) cells


Pidilizumab Plus Rituximab for 30 Relapsed FL: Pt Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type</th>
<th>% of Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLIPI 1</td>
<td>Low</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Int</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>35</td>
</tr>
<tr>
<td>FLIPI 2</td>
<td>Low</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Int</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>28</td>
</tr>
<tr>
<td>Prior Therapies</td>
<td>Median # (Range)</td>
<td>1 (1-4)</td>
</tr>
<tr>
<td></td>
<td>Prior Rituximab</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Prior Chemotherapy</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td># Prior R Doses</td>
<td>6</td>
</tr>
</tbody>
</table>

5
**Pidilizumab Plus Rituximab for Relapsed FL: Best Response**

<table>
<thead>
<tr>
<th>No. of Patients (%)</th>
<th>Enrolled</th>
<th>Evaluable</th>
<th>Overall response</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Tumor Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>29</td>
<td>19 (66)</td>
<td>15 (52)</td>
<td>4 (14)</td>
<td>25 (86)</td>
</tr>
</tbody>
</table>

- Median time to response was 88 days
- ORR did not correlate with FLIPI1 or FLIPI2 score, amount of prior rituximab, prior chemotherapy, or duration of prior response (p>0.05)

**PFS Results**

- PFS = 635 days
- Median follow up = 14 months
- Med PFS All = 21.1 mo
- Med PFS Responders = NR

PFS correlated with both FLIPI (L/I vs H, NR vs 12.6mo) and FLIPI2 (L/I vs H, NR vs 13.5mo, p = 0.0344). OS = 100%

**Newer Agents Targeting the PD-1 Axis in Therapy of Lymphoma**

- AMP-514 (Amplimmune, Medimmune, MEDI0680)
  - Anti-PD-1 antibody in phase I studies as single agent (NCT020013804) and in combination with MEDI7436, an anti-PD-L1 antibody (NCT02118337)
- MEDI4736 (Medimmune) also studied in combination with ibrutinib for DLBCL and FL (NCT02401048)
- MDPL3280A (Roche, RG7446)
  - Anti-PD-L1 antibody in phase I/II trial in combination with obinutuzumab for FL and DLBCL (NCT02220842)

**Thank you**

F B Hagemeister, MD
Department of Lymphoma/Myeloma
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Houston 4/23/2016
Renal Cell Carcinoma
Eric Jonasch, MD
Immunology Clinical Trials in Renal Cell Carcinoma

Eric Jonasch, MD
Professor of Medicine
GU Medical Oncology
UT MD Anderson Cancer Center
Houston, TX

Conflict of Interest Disclosure

Consultant: BMS, Novartis, Pfizer

Frontline Treatment of RCC with Antiangiogenic Agents Results in Similar Pattern:

- Response rates in 20-50 percent range
- Approximately 20 percent primary refractory
- Progression free survival of 8-12 months
- Virtually no cures

First-line Sunitinib vs IFN-α: Results

- Median PFS: 11 mo with SUT vs 5 mo with IFN-α
- ORR: 31% with sunitinib vs 6% with IFN-α
- OS advantage seen with sunitinib vs IFN-α (26.4 vs 21.8 months; HR, 0.821; 95% CI, 0.673–1.001; P = .051)
- Grade 3/4 AEs significantly more common with sunitinib: diarrhoea, vomiting, hand-foot syndrome and hypertension


First-line Pazopanib vs Placebo: Results

- 233 patients had no prior treatment and 202 patients had 1 prior cytokine-based therapy
- Median PFS: 11.1 mo with pazopanib vs 2.8 mo with placebo (HR, 0.40; 95% CI, 0.27–0.60; P < .0001)
- ORR: 32% with pazopanib vs 4% with placebo
- Notable grade 3 hepatotoxicity was observed


To Balance the Immune Response, There are Many Activating and Inhibitory Checkpoints

Tumor cells possess many of these immunoregulatory mechanisms

Immune evasion occurs due to upregulation of inhibitory checkpoints and modulation of microenvironmental nutritional status

Pardoll, Nature 2012
**Higher PD-L1 Expression on RCC is Associated with Worse Prognosis**

![Graph showing PD-L1 expression and prognosis]

306 patients followed after nephrectomy

Thompson and Kwon Ca Research 2006

**Inverse Relationship Between OS and PD-L1 Expression on Tumor Cell Membrane in TKI Treated RCC Patients**

![Graph showing OS and PD-L1 expression]

Choueiri and Motzer CCR 2015

---

**Eligibility, Endpoints and Treatment**

**Eligibility**
- metastatic RCC
- All histologies
- Prior treatment allowed

**Primary Endpoint**
- Safety and tolerability

**Secondary Endpoint**
- Efficacy

**Treatment Plan**
- 3, 10, 15, 20mg/kg and one pt 1200mg flat dose every three weeks.

McDermott and Powles JCO 2016

---

**Table 1. Patient Demographics and Disease Characteristics of Patients With RCC N = 750**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Safety-Evaluable Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>81</td>
</tr>
<tr>
<td>Range</td>
<td>20-69</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54 (%)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40 (%)</td>
</tr>
<tr>
<td>1</td>
<td>39 (%)</td>
</tr>
<tr>
<td>PD-L1 IC score***</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (33)</td>
</tr>
<tr>
<td>1</td>
<td>18 (27)</td>
</tr>
<tr>
<td>2</td>
<td>12 (17)</td>
</tr>
<tr>
<td>3</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Histologic subtypes</td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>63 (80)</td>
</tr>
<tr>
<td>Non-clear cell</td>
<td>27 (10)</td>
</tr>
<tr>
<td>TNM stage grade II and/or sarcomatoid</td>
<td></td>
</tr>
<tr>
<td>intermediate</td>
<td>34 (45)</td>
</tr>
<tr>
<td>Advanced</td>
<td>24 (32)</td>
</tr>
</tbody>
</table>

McDermott and Powles JCO 2016
**Objective Response Rate**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab N=416</th>
<th>Everolimus N=411</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate (95% CI)</td>
<td>103 (25) P&lt;0.001</td>
<td>22 (5)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>5.98 (3.68-9.72)</td>
<td>—</td>
</tr>
<tr>
<td>CR</td>
<td>4 (1)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>PR</td>
<td>99 (24)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>SD</td>
<td>341 (84)</td>
<td>327 (80)</td>
</tr>
<tr>
<td>PD</td>
<td>143 (35)</td>
<td>134 (32)</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>23 (6)</td>
<td>48 (12)</td>
</tr>
</tbody>
</table>

Median time to response, months (range): Nivolumab 3.5 (1.4-24.8), Everolimus 3.7 (0.5-11.2)

Median duration of response, months (range): Nivolumab 12.0 (8-27.8), Everolimus 12.0 (8-22.3)

Median Duration of Treatment, months (range): Nivolumab 5.5 (<1 to 29.6), Everolimus 3.7 (0.2 to 25.7)

**Although a subset of patients benefit from nivolumab, many don’t. What are the major drivers of treatment resistance?**

1. Is there variability in inflammatory state and immune infiltrates in RCC, and can we increase effector T-cell infiltration in immunologically “cold” tumors?

2. Are immune checkpoint ligands and other counterregulatory mechanisms upregulated by tumor cells that overwhelm the ability of PD1 blockade to energize an immune response?

**Antiangiogenic Therapy?**
T-Cell-Antigen Presenting Cell Signaling is IFNγ Mediated

- IFNγ receptor engagement recruits and activates JAK and STAT.
- STATs acts as transcription factors for a number of immune related target genes.
- Many of the checkpoints are IFNγ inducible.

Subsets of RCC has Higher T-cell Infiltrate Compared to Uninvolved Tissue with Broad Range.

Phase I Study: Combination TKI and Checkpoint Therapy

Sunitinib and Bevacizumab Treated Tissues are Associated with Increased Tumor Infiltrating T cells

Antitumor Activity (per RECIST 1.1)

<table>
<thead>
<tr>
<th></th>
<th>S + N (n=33)</th>
<th>P + N (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of response, weeks (range)</td>
<td>37.1 (18.1-80+)</td>
<td>30.1 (12.1-90.1+)</td>
</tr>
<tr>
<td>Ongoing responders, % (n/N)</td>
<td>58 (19/33)</td>
<td>33 (6/19)</td>
</tr>
</tbody>
</table>

*Median follow-up 54.7 weeks; **Median follow-up 76.5 weeks.
Duration of response defined as time between date of first response and date of disease progression or death (whichever occurs first).
ORR, objective response rate.

Maximum Tumor Burden Reduction in Baseline Target Lesions by Nivolumab Dose

Positive change in tumor burden indicates tumor growth; negative change indicates tumor change.

Amin et al, ASCO 2014
Summary

- Clear evidence that checkpoint blockade is of value in treatment of RCC.
- Several questions remain:
  - Does this work in non-clear cell RCC
  - Are there predictive biomarkers
  - Why do some people fail to respond, and can we overcome this resistance
  - What is the role of other checkpoints coming down the pipeline

Acknowledgements

Xiande Liu
Instructor
GU Medical Oncology

Thank you
Bladder Cancer
Arlene O Siefker-Radtke, MD
Immunotherapy in Urothelial Carcinoma: The Next Frontier

Case #1

- A 73 yo retired yacht captain with h/o CAD s/p stent, HTN, and superficial UCa cT1 treated with TUR and BCG presents in 3/09 with metastatic UC, biopsy proven lymph nodes in pelvis, retroperitoneum, and supraclavicular areas. He is enrolled on a clinical trial of GC with cetuximab and has a clinical PR. Nine months later, he has progressive disease, and starts alternate therapy. After 3 cycles of treatment, he is admitted to a local ER with pneumonia and the following CT scan:

Case #1

- He is diagnosed with interstitial pneumonitis/pulmonary fibrosis, treated with slow steroid taper, and pulmonary rehab. He is now 7 years from his initial diagnosis and remains free of metastatic disease.

Case #1

- What treatment did he receive?
  1. DDMVAC
  2. PD-1/PDL-1 inhibitor
  3. CTLA4 antibody
  4. 2 and 3

Case #1

- What treatment did he receive?
  1. DDMVAC
  2. PD-1/PDL-1 inhibitor
  3. CTLA4 antibody
  4. 2 and 3
Case #1

- What treatment did he receive?
  1. DDMVC
  2. PD-1/PDL-1 inhibitor
  3. CTLA4 antibody
  4. 2 and 3

The potential power in harnessing the immune system!!!
Pembrolizumab

Median OS 12.7 mo.
Median PFS 2 mo.

Atezolizumab in Advanced Urothelial Cancer

Phase 2 Trial Results
- N=310, prior cisplatin
- 1200 mg IV q 3 weeks

ORR: median OS
Overall: 15%  
IC 2/3: 26% 11.4 mo.  
IC1: 10% 6.7 mo.  
IC0: 8% 6.5 mo.


Exploratory Predictive Value of PD-L1 Scoring

<table>
<thead>
<tr>
<th>Tumor Cells Only</th>
<th>Tumor and Tumor Associated Inflammatory Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 20 evaluable)</td>
<td>(N = 28 evaluable)</td>
</tr>
<tr>
<td>ORR (95%CI)</td>
<td>ORR (95%CI)</td>
</tr>
<tr>
<td>Negative (N = 11)</td>
<td>0% (0%–41%)</td>
</tr>
<tr>
<td>Positive (N = 18)</td>
<td>33% (13%–59%)</td>
</tr>
</tbody>
</table>

- In order to maximize detecting responders while minimizing the false negative rate, scoring needs to take into account both PD-L1 positive tumor cells and PD-L1 positive tumor associated inflammatory cells.

PD-L1 as a Biomarker: The Debate

For
- FDA wants it
- $$$
- Patients would prefer it
- (if it works!)
- Physicians would, too!

Against
- Too dynamic
- Increase post chemo
- Increase post BCG
- Increase with PD-L1
- Tissue studies
- Any archival tissue (regardless of chemo)
- Antibody variability

Are there any biomarkers better than PD-L1???

Emerging Concepts: Bladder Subtyping
**Background: Gene Expression**

Three intrinsic subtypes:
- **Basal**
  - Highest proliferation
  - "Stemness"
  - Worst clinical outcomes
- **Luminal**
  - Intermediate proliferation
  - FGFR3 mutations
- **p53-like**
  - Lowest proliferation
  - Stromal markers

Cite: McConkey et al, Cancer Cell 2014

**OS by Subtype at TUR**


**Paradigm Shift in Urothelial Cancer**

Urothelial cancer is no longer just 1 disease:
- **Basal**
  - Chemo-sensitive
  - Immune signature
  - Therapies:
    - GC/DDMVAC
    - CTLA4?
    - PD-1/PDL-1?
    - Proteasome inhibitors + chemo?
- **p53-like**
  - Chemo-resistance
  - Stromal enrichment
  - Bone mets
  - Immune signature
  - Therapies:
    - GC/DDMVAC
    - FGFR inhibitors?
    - Proteasome inhibitors + chemo?
- **Luminal**
  - Still some chemo-sensitivity
  - "FGFR" signature
  - Therapies:
    - GC/DDMVAC
    - FGFR inhibitors?

Cite: Siefker-Radtke, et al. UROLOGY 2015

**Impact of Subtype on Response: Atezolizumab**


- Basal and p53-like (Luminal II)
  - Higher PD-L1 on tumor
  - Higher PD-L1 on infiltrate
  - Greater response rate
  - p53-like > Basal
- Luminal
  - Very low response rate


**Immunotherapy in UC**

- Immunotherapy is active in urothelial cancer
- Responses may be durable
- PD-L1 as a biomarker?
  - Verdict is pending whether FDA will require it.
- Subtyping as a potential alternative?
  - Need more studies
Thank you!

“All bladder, all the time!”
Arlene Siefker-Radtke, MD
713-792-2830
Prostate Cancer
Eric Jonasch, MD
Prostate Cancer Immunotherapy Trials
Eric Jonasch, MD
Professor, Department of GU Medical Oncology
UT MD Anderson Cancer Center
Houston, TX

Clinical States Model of Prostate Cancer
Modified from Scher and Heller, Urology, 2000.

Androgen Deprivation Alters The Immune State
- Neoadjuvant androgen deprivation therapy (ADT) results in increased numbers of infiltrating CD4 T cells, CD8 T cells, NK cells and macrophages in prostate tissues.
- ADT increases the number of T cells in peripheral lymphoid tissues and prostate glands in a mouse model, enhances T cell proliferation to antigen, and promotes recovery of T and B cell populations following chemotherapy, as well as mitigates tolerance of prostate-specific CD4 T cells.
- ADT has also been shown to reverse age-related thymic atrophy in mice, and to restore thymic T cell output in both mice and prostate cancer patients.
From May and Kantoff CCR 2015

Two Major Immunotherapeutic Strategies in Prostate Carcinoma
1. Vaccine therapy
   - Sipuleucel-T
   - Prostvac-VF
   - DCVAC/PCa

2. Checkpoint blockade
   - Ipilimumab

Vaccine Based Therapies
**Sipuleucel-T**

- Sipuleucel-T (Provenge, Dendreon Corp.) is an autologous vaccine prepared using an individual patient’s peripheral blood mononuclear cells (PBMC).
- PBMC (including antigen presenting cells) are harvested and cultured with a fusion protein consisting of prostatic acid phosphatase (PAP) and GM-CSF for 36–44 hours, and then infused back into the patient.
- A treatment course consists of vaccination every two weeks for a total of three treatments.

**PROSTVAC-VF**

- A poxvirus-based vaccine engineered to contain PSA and three immune costimulatory molecules (B7.1, ICAM-1, and LFA-3) within a vaccinia virus or fowlpox virus vector.
- The vaccine is administered as a vaccinia vector priming immunization, followed by a series of fowlpox vector boosts, all given subcutaneously.
- GM-CSF is coadministered subcutaneously near the vaccination site (within 5mm) on the day of vaccination and for three consecutive days following.

**Immunologic Analysis**

- Immunologic analysis revealed that significantly more patients treated with sipuleucel-T compared with placebo generated antibody responses and T cell responses against the immunizing antigens, and higher antibody titers against immunizing antigen correlated with longer duration of survival.

**PROSTVAC-VF**

- Of note, progression free survival was no different between patients who received vaccine versus those who received placebo. This appears to be a recurring theme in vaccine therapy.
PROSTVAC-VF

- Once again, no improvement in PFS.
- A phase III trial was launched to validate the phase II findings.

PROSPECT Phase III Trial NCT01322490

1200 subjects were randomized in a double-blind fashion to three arms at a 1:1:1 ratio:
- PROSTVAC
- PROSTVAC plus GM-CSF
- Placebo.

A 5 month treatment regimen comprised one PROSTVAC-Prime injection followed by 6 PROSTVAC-Boost injections.

Enrolled subjects had asymptomatic/minimally symptomatic mCRPC and were chemotherapy-naïve.

Subjects with rapidly progressing disease and visceral metastases were excluded. The primary endpoint is OS and pre-specified interim analyses were integrated in the statistical plan.

Secondary efficacy endpoints included the proportion of event-free subjects at 6 months (radiographic progression, pain progression, chemotherapy initiation, or death) compared to placebo. Exploratory endpoints were planned, including immune responses.


DCVAC/PCa

- Autologous mature DCs pulsed with killed PSA positive LNCaP cells.
- Phase I trial: Pts received DCVAC/PCa day 0, 14, 35, and then every 6 weeks.

VIABLE Phase III Study NCT02111577

VIABLE will evaluate the safety and efficacy of first-line docetaxel in combination with DCVAC/PCa or placebo for the treatment of patients with mCRPC.

Primary Outcome Measure:
- Overall survival (all cause mortality)

Estimated Enrollment: 1170
- Study Start Date: April 2014
- Estimated Study Completion Date: June 2018

Checkpoint Antibodies
A randomized, double-blind, phase III trial comparing Ipi tumumab vs. placebo following radiotherapy in subjects with castration-resistant prostate cancer that have received prior treatment with docetaxel.

**Anti-PD1 Antibody Blocks PD1 Signal**

**Anti-CTLA-4 Antibody Blocks CTLA-4 Signal**
Anti-CTLA-4 (ipilimumab) + radiation therapy in castration-resistant prostate cancer (CRPC)

- Primary OS endpoint was not met.
- Tail of the curve tended towards favoring ipilimumab.


Overall survival: Pre-specified subgroups

Exploratory subgroup analysis of OS in CRPC patients treated with ipilimumab

Overall survival in patients with alkaline phosphatase concentration less than 1.5 times the upper limit of normal (ULN), hemoglobin concentration of 110 g/L or more, and no visceral metastases (ipilimumab, n=146; placebo, n=142) HR 0.62, 95% CI 0.45–0.86; p=0.0038


Why Did Ipilimumab Not Achieve OS Improvement in Prostate Cancer?

To balance the immune response, there are many activating and inhibitory checkpoints

Tumor cells possess many of these immunoregulatory mechanisms.

Immune evasion occurs due to upregulation of inhibitory checkpoints and modulation of microenvironmental nutritional status.

Does prostate carcinoma have a large number of additional checkpoints?

Pardoll, Nature 2012
Is prostate carcinoma microenvironment immunologically “cold” or uniquely suppressive?

Sharma & Allison, Science 2015

T-Cell Responses to Neoantigens Post Treatment With Ipilimumab in Men With Metastatic Castration-Resistant Prostate Cancer NCT02113657 (MDACC)

Goal is to define neoantigens associated with ipilimumab response.

Primary endpoint is impact of ipilimumab on T cell responses to neoantigens. Eligible patients show tumor progression while on hormone therapy with castrate levels serum testosterone.

Patients receive ipilimumab in standard four dose regimen. A total of 20 patients will be enrolled.

Blood and tissue based studies will be performed.

Ipilimumab Plus Sipuleucel-T NCT01804465

Randomized multicenter Phase 2 clinical trial combining Sipuleucel-T with ipilimumab in patients with chemotherapy-naïve metastatic castration resistant prostate cancer. Primary endpoints are immunological (the induction of Ig antibody responses by SipT, the proportion of patients on each study arm who achieve an immune response to PAP and/or PA2024at study week 20).

All patients will be treated with standard Sipuleucel-T (Q2wks x 3). Patients will be randomized to:
• Arm 1 (Immediate Treatment): Ipilimumab Q3wks x 4 started 1 day following the final dose of SipT (Day 0).
• Arm 2 (Delayed Treatment): Ipilimumab Q3wks x 4 started 3 weeks following the final dose of SipT (Day 0).

Ipilimumab Plus PROSTVAC-VF NCT02506114 (Pending Activation)

Randomized phase II trial testing the hypothesis that neoadjuvant PROSTVAC plus ipilimumab is superior to PROSTVAC alone or ipilimumab alone, with primary endpoint of T-cell response.

Experimental Arm A
• PROSTVAC-V: 2 x 10^9 pfu subcutaneous Day 1. PROSTVAC-F 1 x 10^9 pfu subcutaneous Days 15, and 36.
• Ipilimumab 3 mg/kg intravenously Days 1 and 21.

Experimental: Arm C
• PROSTVAC-V 2 x 10^9 pfu subcutaneous Day 1. PROSTVAC-F 1 x 10^9 pfu subcutaneous Days 15, and 36. Ipilimumab 3 mg/kg intravenously days 15 and 36.

Listeria Vaccine

JNJ-64041809, a Live Attenuated Double-deleted Listeria Immunotherapy, in Participants With Metastatic Castration-Resistant Prostate Cancer NCT02625857

Replication incompetent listeria encoding multiple, tumor-associated antigens (TAAs), with potential immunostimulatory and antineoplastic activities are injected intravenously. Listeria are taken up by APCs with resultant presentation of the tumor antigens. Goal is to assess DLT and antigen-specific immune response to tumor targeted listeria bacterium.

- Must have received at least 2 prior approved therapies
- Ongoing androgen deprivation therapy with a gonadotropin releasing hormone analog or inhibitor, or orchiectomy (surgical or medical castration)
- Serum testosterone levels less than 4 weeks (>6 weeks for bicalutamide) prior to start of study drug with no evidence of an anti-androgen withdrawal response (no decline in serum PSA)
Conclusions

- Immunotherapy is starting to impact overall outcome in patients with prostate carcinoma.
- Vaccine treatments and checkpoint antibodies show promise in good risk populations.
- Ongoing work to leverage combination immune treatment approaches will likely improve the efficacy of immunotherapy in this disease.

Acknowledgments

- James Allison
- Padmanee Sharma
- Sumit Subudhi
- Charles Drake
- Patients with prostate cancer and their families

Thank You
Hepatic and Gastrointestinal Cancer
Michael Overman, MD
Immunotherapy Clinical Studies: Hepatic and Gastrointestinal Cancer

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Conflict of Interest Disclosure
Consultant: Merrimack
Research Support: Roche, Merck, Celgene, Medimmune, BMS

Agenda

• Pancreatic Cancer
• Colorectal Cancer
  – MSS CRC and Immune Checkpoints
  – Microsatellite Instability High CRC
    • Mutation Burden and Neoantigens
    • Immune Checkpoint Expression
  – MSI-high CRC and Immune Checkpoints
• Gastroesophageal
• Hepatocellular Carcinoma
• Anal Squamous Cell Carcinoma

Pancreatic Carcinoma

GVAX: allogenic GMCSF secreting pancreatic cells
CRS-207: Listeria expressing mesothelin
Algenpantucel-L: allogenicalpha-gal expressing pancreatic cells

MSS CRC and Immune Checkpoints

Pancreatic Cancer: Durvalumab (MEDI-4736): Anti-PD-L1

Segal et al. JCO 2015

Pancreatic Cancer
N=24
Immune Checkpoint Agents in CRC

KEYNOTE-028 for PDL1+ CRC

Tremelimumab
RR: 1/45 CRC
(response duration 15m)

Nivolumab
RR: 0/19 CRC

Deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H)
- Mutations in MMR (inherited) or loss of MMR by methylation (acquired) results in microsatellite instability (MSI)
  - Increased duplication of tandem dinucleotide repeats (microsatellites)
  - Resulting increased mutation rate and higher risk of colorectal cancer
- MSI-H CRC: ~5% HNPCC and ~10% sporadic
- Detection by PCR or IHC

DNA Repair Mechanisms

MSI-H Prognostic Effect

ACCENT database 14 phase III adjuvant studies

<table>
<thead>
<tr>
<th>Stage</th>
<th>MSI-H</th>
<th>5-year OS</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>22%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>12%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MD Anderson + Royal Melbourne Hospital, Australia retrospective metastatic MSI-high analysis
N=55
### Universal Testing for HNPCC

<table>
<thead>
<tr>
<th>No Tested (%)</th>
<th>Revised Bethesda criteria:</th>
<th>Jerusalem criteria: all CRC &lt;70 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. CRC &lt;50y/o</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Synchronous, metachronous CRC or other HNPCC cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. CRC with MSI-high histology in &lt;60y/o</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. CRC in ≥1 1st-degree relative with hnpcc cancer with 1 cancer diagnosed &lt;50yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. CRC in ≥2 1st or 2nd-degree relatives with hnpcc cancer regardless of age</td>
<td></td>
</tr>
</tbody>
</table>

### Somatic mutation frequencies CRC

### Mutational Rates Across Tumors

### CMS 400 MSI-high CRC pt

### Immune Escape Mechanisms in MSI-high CRC

### MSI-high CRC and Immune Checkpoints
Pembrolizumab for MSI-high CRC

Immune Infiltrate

Mutational and Neoantigen Load in NSCLC Treated with Pembrolizumab
Immune checkpoint in melanoma

Wolchok et al. NEJM 2013
Nivolumab/ipilimumab: Chart 2a (n=16):
Nivolumab 3mg/kg + ipilimumab 1mg/kg
Clinical benefit of 73%

G3/4 immune AEs: 11%

Wolchok et al. Lancet Oncol 2010
Ipilimumab in advanced melanoma

CheckMate 142 Study Design

Proposed SWOG Intergroup Study

- Primary endpoint: PFS by RECIST v1.1
  - Assume a 40% increase in PFS (HR 1.67)
  - median PFS for N (HR 0.67)
  - Sample size 80 (80% eligible rate) based on one-sided type 1 error of 10% and 80% power
  - Assuming accrual of 5 pts/m we expect 36 months accrual and 12 months of follow-up
- Experimental arm: Nivolumab 3mg/kg IV over 60min every 2 weeks

Eligibility:
1. Advanced CRC
2. MSI-high by IHC or PCR
3. One prior tx for met dz (adj<6m)
4. PS 0-2

Design: Adjuvant Trial in MSI-H/dMMR Colon Cancer

Hepatocellular Carcinoma: CA209-040
Nivolumab (Anti-PD1)

<table>
<thead>
<tr>
<th>Evaluable Cohort</th>
<th>Patient *</th>
<th>Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>17</td>
<td>3</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>HCV</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>4</td>
<td>1*</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>6 [22%]</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

Child-Pugh ≤7 (Child A or B);
TB s3, Alb 2.2

Gastroesophageal Carcinoma

El-Khoueiri et al. ASCO 2015

Nature TCGA 2014

What about combo data in MSI-high CRC?
Gastric/GEJ: Checkmate-032 Study

53% GEJ, 31% Gastric, 15% Lower esophageal

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Nivolumab 3mg/kg (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>PD-L1 ≥1%</td>
<td>4/15 (27%)</td>
</tr>
<tr>
<td>PD-L1&lt;1%</td>
<td>3/25 (12%)</td>
</tr>
<tr>
<td>SD</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>PD</td>
<td>34 (58%)</td>
</tr>
</tbody>
</table>

Median duration of response was 7.1m

Gastric/GEJ Cancer: KEYNOTE-012

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Pembrolizumab 10mg/kg q2wks (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>PD</td>
<td>19 (52%)</td>
</tr>
</tbody>
</table>

All PD-L1+ (21%)

Only Adenocarcinoma of gastric/GEJ 65/162 screen PD-L1+ (40%)

Conclusion

- Test for MSI-high
  - As universal testing approach for HNPCC
  - For prognostic relevance in stage II
  - For clinical trial options in metastatic patients
- Emerging data for activity in subset of HCC, gastroesophageal, anal SCC
- Pancreas and MSS CRC have demonstrated limited clinical activity with immune-checkpoint therapy

Thank you

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Ovarian Cancer - Neoantigens
Robert Coleman, MD
Primary Ovarian Cancer: Notables

- Disease presents with metastatic involvement ≥75% of cases
- Tumor burden is high
- Standard approach is surgical resection
  - Reduces the volume of hypoxic, poorly perfused cells
  - Host immunocompetence is improved with lower tumor burden
  - Recruitment of residual cells into G1 potentiating the effects of cytotoxic therapy
  - Removal of chemoresistant clones
  - Greatest benefit observed with R0 resection (≤35% of cases)
- Adjacent chemotherapy largely unchanged over the last 2 decades

Recurrent Ovarian Cancer: Notables

- 75% of patients achieve complete clinical response
- 50% of these have residual disease on surgical reassessment
- >40% of pathCR’s will recur at 2 years
- Recurrent disease is nearly always fatal
- Premium on primary and maintenance therapy is high

Conflict of Interest Disclosure

- Research Funding:
  - NCI-SPORE, AstraZeneca, Clovis, Merck, Roche/Genentech, V-Foundation, Novartis
- Scientific Steering Committee (uncompensated):
  - Abbvie, AstraZeneca, Biomarin, Clovis, Genentech, Immunogen, Merck, Pfizer, Tesaro

Ovarian Cancer: Natural History

Symptoms → Chemo #1 → Diagnosis → Evaluation → Progression → Secondary Surgery → Recurrence

Chemo #1 → Maintenance → Chemo #2 → Chemo #3 → Chemo #4 → Supportive Care

Diagnosis → Evaluation → Progression → Secondary Surgery → Death

Progression-Free Survival (12–28 mos) → Post Progression Survival (12–38 mos)

Duration → Progression-Free Survival (12–28 mos) → Post Progression Survival (12–38 mos)
Ovarian Cancer: Historical Trends

Impact of BRCA-mt & HRD on OS

Angiogenesis as a Target: Ovarian

PARP Inhibitor and Homologous Recombination Repair

Ovarian Cancer HR Deficiency: Multiple Reasons

Olaparib Development: Lessons Learned
PARPi’s in Ovarian Cancer: RCTs

- Olaparib – Primary & Switch Maintenance
- Rucaparib – Switch Maintenance, treatment
- Niraparib – Switch Maintenance, treatment
- Veliparib – Primary Combination Therapy

Many other trials with chemotherapy and biological combinations

Intraepithelial TILs are a robust predictor of outcome in ovarian cancer and define a specific class of patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio 95% CI</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang (2010)</td>
<td>0.01</td>
<td>0.18</td>
<td>0.52</td>
<td>0.81 (0.19, 3.29)</td>
<td>1.04 (0.81, 1.32)</td>
</tr>
<tr>
<td>Hwang (2010)</td>
<td>1.11</td>
<td>0.34</td>
<td>0.54</td>
<td>0.52 (0.21, 1.27)</td>
<td>1.01 (0.81, 1.25)</td>
</tr>
<tr>
<td>Ito (2010)</td>
<td>0.94</td>
<td>0.22</td>
<td>0.54</td>
<td>0.71 (0.33, 1.53)</td>
<td>1.27 (0.81, 2.02)</td>
</tr>
<tr>
<td>Catalan (2010)</td>
<td>1.89</td>
<td>0.29</td>
<td>0.19</td>
<td>1.23 (0.97, 1.58)</td>
<td>1.72 (1.40, 2.13)</td>
</tr>
<tr>
<td>Oza (2010)</td>
<td>0.04</td>
<td>0.15</td>
<td>0.06</td>
<td>0.96 (0.71, 1.30)</td>
<td>1.27 (1.04, 1.55)</td>
</tr>
<tr>
<td>Clarke (2010)</td>
<td>0.32</td>
<td>0.15</td>
<td>0.14</td>
<td>1.00 (0.70, 1.42)</td>
<td>1.01 (0.81, 1.26)</td>
</tr>
<tr>
<td>Lu (2009)</td>
<td>1.03</td>
<td>0.29</td>
<td>0.54</td>
<td>0.62 (0.33, 1.19)</td>
<td>1.27 (0.81, 2.02)</td>
</tr>
<tr>
<td>Blom (2009)</td>
<td>0.68</td>
<td>0.22</td>
<td>0.54</td>
<td>0.96 (0.33, 2.91)</td>
<td>1.27 (1.04, 1.55)</td>
</tr>
<tr>
<td>Total (COX)</td>
<td>1.03</td>
<td>0.15</td>
<td>0.54</td>
<td>1.27 (1.04, 1.55)</td>
<td>1.27 (1.04, 1.55)</td>
</tr>
</tbody>
</table>

Zhang W et al. Gynecol Oncol. 2012;124(2):103-8

Immune Factors Correlated With Poor Prognosis

- Presence of Treg in the tumor
  - Redjimi, Cancer Res. (2012) 72:4351

- Accumulation of plasmacytoid dendritic cells (pDC)
  - Zou, Nat Med (2001) 7:133; Wei Cancer Res. (2005), 65:5020;
  - Labidi-Galy Cancer Res. (2011)

- Presence of immunosuppressive macrophages expressing B7-H4

- Low level of circulating lymphocytes (< 1.0x10^9/L)

PD-L1 Expression In Ovarian Cancer

- PD-L1 evaluation by
  - IHC with local non-commercial antibody
  - 70 ovarian cancer patients

- Inverse correlation between PD-L1 and TIL

Zhang et al. NEJM 2003

PD-L1 expression

PD-L1 expression

PD-L1 expression
First Phase II Trial in Ovarian Cancer: Nivolumab

**Ovarian Cancer Study (PD-1/PD-L1)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cohort 1: 1 mg/kg q 2 wks</th>
<th>Cohort 2: 3 mg/kg q 2 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>1 (PR)/10 (10%)</td>
<td>2 (CR)/10 (20%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>5/10 (50%)</td>
</tr>
<tr>
<td></td>
<td>1 (PR)/10 (10%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td></td>
<td>≥ 2 prior regimens (Plat-R)</td>
<td></td>
</tr>
<tr>
<td>Avelumab</td>
<td>7 (PR)/75 (11%)</td>
<td>8 (PR)/75 (11%)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2/2 clear cell</td>
</tr>
<tr>
<td></td>
<td>8/75 (11%)</td>
<td>41/75 (55%)</td>
</tr>
<tr>
<td></td>
<td>No limit on priors (median 4, range 1-11); Plat-R</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>10 mg/kg q 2 wks</td>
<td>10 mg/kg q 2 wks</td>
</tr>
<tr>
<td></td>
<td>3 (CR), 2PR/26 (12%)</td>
<td>9/26 (35%)</td>
</tr>
<tr>
<td></td>
<td>No limit on priors (&gt;80% ≥ 4 priors); PDL1 IHC positive (49/96, 51%)</td>
<td></td>
</tr>
</tbody>
</table>

PD-1/PD-L1 Clinical Data: Single Agent

**Ovarian Cancer**

<table>
<thead>
<tr>
<th>Study (PD-1/PD-L1)</th>
<th>N</th>
<th>RR</th>
<th>Disease Control Rate</th>
<th>Prior Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab Cohort 1</td>
<td>1</td>
<td>0</td>
<td>1 (PR)/10 (10%)</td>
<td>≥ 2 prior regimens (Plat-R)</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>0</td>
<td>1</td>
<td>2 (CR)/10 (20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0</td>
<td>5/10 (50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>4/10 (40%)</td>
<td></td>
</tr>
<tr>
<td>Avelumab</td>
<td>7</td>
<td>5</td>
<td>8 (PR)/75 (11%)</td>
<td>No limit on priors (median 4, range 1-11); Plat-R</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2</td>
<td>6</td>
<td>3 (CR), 2PR/26 (12%)</td>
<td>No limit on priors (&gt;80% ≥ 4 priors); PDL1 IHC positive (49/96, 51%)</td>
</tr>
</tbody>
</table>

Active Phase II/III PD-1/PD-L1 Trials

- **NCT02498600** Nivolumab
  - ≤3 lines, Randomized Phase II (suspended)
  - Nivolumab 8 mg/kg q 4 weeks x 4 then up to 21 courses
  - Nivolumab 8 mg/kg q 4 weeks until disease progression for ≥ 21 courses
- **NCT02580058** Avelumab (JAVELIN 200) — Phase III
  - Penultimate platinum-resistant (≤6 months PFI), ≤3 lines
  - Avelumab 10 mg/kg q 2 weeks
  - PLD 40 mg/m2 q 4 weeks
  - PLD + Avelumab combination
  - Primary endpoint: OS
- **NCT02674061** Pembrolizumab (KEYNOTE-100)
  - Platinum-resistant (3-12 months PFI)
  - Cohort A: 1-3 prior lines 200 mg fixed dose IV q3 weeks (up to 2 years)
  - Cohort B: 4-6 prior lines 200 mg fixed dose IV q3 weeks (up to 2 years)

Active Phase II/III PD-1/PD-L1 Trials

- **NCT02659384** Atezolizumab
  - Platinum-resistant (≤6 months PFI, ≤2 prior non-platinum regimens)
  - Bevacizumab monotherapy
  - Atezolizumab + placebo
  - Atezolizumab + ASA
  - Atezolizumab + bevacizumab + placebo
  - Atezolizumab + bevacizumab + ASA
Rationale for PARPi with Immune Checkpoint Inhibitors

- **Hypermutable states**
  - BRCA-mt (somatic/germline) have high intrinsic LOH
  - High grade serous ovarian cancer has a hypermutable genotype in a proportion of patients
  - PARPi can induce hypermutable state

- **All increase potential for neoantigens potentially amenable to PD-1/L1 & CTLA-4 targeting**

- **PARPi synergy may vary by PARPi and checkpoint inhibitor**

Active Phase II/III PD-1/PD-L1 Trials

- **NCT02484404 Durvalumab + Olaparib or Cediranib**
  - Platinum-resistant (≤6 months PFI), ≤2 prior non-platinum regimens
  - Prior PARPi, prior anti-VEGF = OK
  - Dosing:
    - Olaparib (200 mg or 300 mg) + Durvalumab (1 mg/kg or 10 mg/kg)
    - Cediranib (15mg or 20mg or 30 mg) + Durvalumab (14 mg/kg)

- **NCT02657889 Pembrolizumab + Niraparib (KEYNOTE-162)**
  - Initially platinum-sensitive
    - Niraparib (up to 300 mg po)
    - Pembrolizumab 200 mg fixed dose IV q 3weeks
Active Phase II/III PD-1/PD-L1 Trials

- NCT02718417 Avelumab (JAVELIN 100) – Phase III
  - Front-Line (chemo-naïve)
    - Paclitaxel + Carboplatin
    - Paclitaxel + Carboplatin followed by Avelumab maintenance (up to 24 months)
    - Paclitaxel + Carboplatin + Avelumab followed by Avelumab maintenance (up to 24 months)
  - Primary endpoint: PFS
- NCT02580058 Avelumab (JAVELIN 200) – Phase III
  - Penultimate platinum-resistant (≤6 months PFI), ≤3 lines
    - Avelumab 10 mg/kg q 2 weeks
    - PLD 40 mg/m² q4 weeks
    - PLD + Avelumab combination
  - Primary endpoint: OS

New Moonshot Projects-FP2B Ovarian

- FP2b Phase Ib-2 Treatment Trials
  - NACT
  - Adjuvant
  - Tissue acquisition

Combination with Anti-VEGF Therapy

VEGF exerts an immunosuppressive effect in cancer

- The absence of intratumoral T cells (TIL) was associated with increased levels of VEGF.
- VEGFR2 is selectively expressed in Treg CD4+FoxP3+ cells and VEGF directly suppresses activation of T Cells
- Immature DCs contribute to ovarian cancer progression by acquiring a pro-angiogenic phenotype in response to VEGF
  - Coulson G. Br J Cancer 2005;92:1182–1187

Phenotypic Diversity of Macrophage Populations

- Leversaged NCCN Grant
  2014-0662, IRB-approved, SIV 7/24/15
- Takashi, Coleman, Sood, SPONR 2016
Phenotypic Angiogenesis Resistance Targeting

- Bevacizumab can induce macrophage/monocyte infiltration leading to resistance
- Emactuzumab: CSF1-R inhibitor targeting infiltrating TAM’s
- Trial design promotes assessment of patient developing resistance to therapy

Active Phase II/III PD-1/PD-L1 Trials

AND MANY MORE!!

Ovarian Cancer: Take Home Points

- Heterogeneous set of diseases characterized by large tumor burden at diagnosis, initial chemosensitivity, high rate of recurrences that are amenable to multiple therapies
- Acquired resistance is universal in recurrent disease
- Low mutational load which accounts for poor initial PD-1/PD-L1 experience
- However, there a notable subpopulation with HRD (BRCA-germline, BRCA-somatic and HRD) likely associated with high tumor-specific neoantigen repertoire which could be leveraged alone and in combination with PARPi’s
- Immune escape can be induced by anti-VEGF and chemotherapy, which has prompted investigation into strategic combinations

Immunotherapy: The OLD/NEW Frontier in Medicine

Thank You!
Selecting Immunotherapy Modalities and Combination Clinical Trials

James L. Gulley, MD, PhD
Selecting Immunotherapy Modalities for Combination Clinical Trials

James L. Gulley, MD, PhD, FACP
Director, Medical Oncology Service, NCI
Bethesda, MD

Conflict of Interest Disclosure
No relevant financial relationships

Anti-PD1 or Anti-PD-L1

Modified from a Slide Courtesy of "Mac" Cheever

IFNγ upregulates PDL1 expression in vitro
Taube et al., Sci Trans Med 2012

Colocalization of inflammatory response and PDL1 expression

Pardoll Nat Rev Ca 2012

Taube et al., Sci Trans Med 2012
Requirements for Effective Immunotherapy

- Effector Cells Functional within Tumor
- Generate Immune Response

The prevalence of somatic mutations across human cancer types.

Immunogenic Intensification

CA209-067: Study Design

PFS (Intent-to-Treat)
**Immunogenic Intensification**

- Non-specific immune activation + PD1 blockade leads to improved activity at the cost of increased toxicity
- May be more specific ways to drive T-cells to tumor

**Estimated > 370 Immuno-Oncology Combination studies with ~20/month added**

<table>
<thead>
<tr>
<th>Combination</th>
<th>Median OS (months)</th>
<th>Median Overall Survival in months (95% CI)</th>
<th>Δ OS (months)</th>
<th>Alive at 24 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostvac alone</td>
<td>17.2</td>
<td>26.3</td>
<td>+9.1</td>
<td>53%</td>
</tr>
<tr>
<td>Prostvac + Ipilimumab (n=32)</td>
<td>18.5 (29.6 - &gt;41)</td>
<td></td>
<td>+15.9</td>
<td>73.3%</td>
</tr>
</tbody>
</table>

**High Risk Melanoma (n=33 with 31 stage 4 resected)**

- Historical data: RFS 21-36 months for stage III
- Well tolerated with only 5 Grade 3 (and no > Grade 3) events

- Median RFS 47.1 months

**Nivolumab + peptide vaccine for Melanoma (adjuvant)**

- High Risk Melanoma (n=33 with 31 stage 4 resected)
- Historical data: RFS 21-36 months for stage III
- Well tolerated with only 5 Grade 3 (and no > Grade 3) events
Studies of PD1/PDL1 inhibitors and vaccine

<table>
<thead>
<tr>
<th>Immune Checkpoint Inhibitor</th>
<th>with vaccine</th>
<th>with ACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Pemrolizumab</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Avelumab</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

As of 30 March 2016 per clinicaltrials.gov (may be an underestimate)

Requirements for Effective Immunotherapy

Generate Immune Response
- Vaccine
- ACT
- CTLA4 blockade
- Intratumoral cytokines (NHS-IL12, BCG)
- NK cells (ACT or cytokines)

Effector Cells Functional within Tumor
- PDL1/PD1
- TGF-β
- IDO
- VEGF (MDSC and immature DC)
- Other immune checkpoints

Optimal Combinations
- Will require thoughtful evaluation of the tumor microenvironment
  - Immune infiltrates
  - Presence of other inhibitory components
  - Comparison pre and post therapy

Conclusions
- Immune combinations that lead to an active T-cell response and facilitate T-cell activity within the tumor microenvironment may lead to optimal anti-tumor effects
  - Non-specific activation of T-cells vs. specific (irAE differences?)
  - Need to study immune microenvironment (biopsies, neoadjuvant studies, other methods)

Identification of immunogenic neo-antigens

Identification of immunogenic neo-antigens
- 1,019 AA changes identified (exome), only two confirmed to be presented by tumor cells (mass spec) and only one immunogenic
- Kalaora (Rosenberg) et al., Oncotarget, 2016

Durvalumab + Tremelimumab for NSCLC (Phase I)

Kalaora (Rosenberg) et al., Oncotarget, 2016
Durvalumab + Tremelimumab for NSCLC

Thank you

James L. Gulley, MD, PhD, FACP
Director, Medical Oncology Service, NCI
Bethesda, MD
Biomarkers for Cancer Immunotherapy Clinical Trials
Don Gibbons, MD, PhD
Biomarkers for Cancer Immunotherapy Clinical Trials

Don L. Gibbons, MD, PhD
Assistant Professor, Department of Thoracic/Head & Neck Medical Oncology
MD Anderson Cancer Center

Immune Checkpoint Inhibitors in the Treatment of Selected Tumor Types: A New Perspective
April 23, 2016

Conflict of Interest Disclosure

• No financial disclosures.

Agenda

• Results from checkpoint inhibitor trials raise the issue of patient selection
• Problems/considerations in biomarker development for IMT: a new type of biomarker
• Potential biomarkers under testing or development
  – Multimarker pathologic testing
  – DNA-based approaches
  – Transcriptome-based

All attempt to capture elements of the biology

Efficacy of Nivolumab vs Docetaxel in Patients with Advanced Squamous-Cell NSCLC

The FDA label requires no tumor biomarker.

Successful treatments may only benefit a subset of patients

• Tumors and patients are heterogeneous
• We need ways to match treatments with patients (novel agents + predictive markers)

Overall Survival Stratified by PD-L1 Expression Level with 28-8 antibody test
Keynote-001: Overall Survival with Pembrolizumab, stratified by 22C3 staining

ORR: 41% (95% CI: 28.6, 54.3%)
Median DOR not reached.

FDA approved on October 2, 2015, with companion testing and requirement to conduct a randomized trial.

Efficacy of pembrolizumab (MK3475) vs docetaxel in Keynote 010: NSCLC selected by PD-L1 scoring

Two very different types of biomarkers

<table>
<thead>
<tr>
<th>Driver mutation</th>
<th>Marker of microenvironment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR 19%</td>
<td>Macrophages</td>
</tr>
<tr>
<td>KRAS, 25%</td>
<td>Cancer-associated endothelial cells, blood vessels</td>
</tr>
<tr>
<td>Other/unknown, 35%</td>
<td></td>
</tr>
<tr>
<td>RET, 3%</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>ROS, 3%</td>
<td>EMT (fibrosis)</td>
</tr>
<tr>
<td>ALK, 6%</td>
<td>EMT proteins</td>
</tr>
<tr>
<td>MET, 1%</td>
<td>Substrate stiffness</td>
</tr>
</tbody>
</table>

The biomarker defines the tumor target
The biomarker defines the host response

Microenvironmental and systemic factors in the cancer-immunity cycle

Considerations in Developing Biomarkers for PD-L1/PD-1 therapy (& other immune agents)

- Biopsy type: FNA vs CNB vs surgical
- Intra-tumoral and metastatic heterogeneity
- Fresh vs archival and dynamic effects of intervening therapies
- Antibody/IHC conditions (company-specific & proprietary): IASLC, FDA & 6 companies evaluating tests in Blueprint
- Manual vs automated pathology scoring
- Defining “positive”:
  - Cell type expressing PD-L1 (or other markers of choice)
    - Intensity/distribution
    - Presence of T-cells/immune cell infiltrate
- Single vs multi-marker analyses (IHC vs mRNA vs DNA): mindset change
  - Immune infiltrate, EMT status, mutational burden

Categories of Tumors Based on Staining for PD-L1 and TILs

<table>
<thead>
<tr>
<th>PD-L1+/TIL+</th>
<th>PD-L1-/TIL+</th>
<th>PD-L1+ TIL-</th>
<th>PD-L1-/TIL-</th>
</tr>
</thead>
<tbody>
<tr>
<td>45%</td>
<td>17%</td>
<td>26%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Subgroup

Type Distribution

- Type I: 45%
  - PD-L1+/TIL+
  - Poor priming of general T cell responses
  - Peripheral CD4+ and CD8+ T cell responses to autologous tumor cells
  - Lack of inflammatory cell recruitment
- Type II: 17%
  - Incomplete PD-L1/B7-H1 pathway blockade and activation of alternate immune suppressive pathways
  - CD80 expression on TILs, expression of alternate suppressive pathways in TME
- Type III: 26%
  - Alternate immune suppressive pathways
  - Expression of select molecules in pathways with roles in evasion of NSCLC immunity
- Type IV: 12%
  - Intrinsic induction of B7-H1 by oncogenes
  - Expression of molecules triggering aberrant signaling events
Intratumoral/microenvironmental heterogeneity & PD-L1 protein expression

McLaughlin et al., *JAMA Oncol.*, 2016.

The challenge in PD-L1 testing: Four tests in development

<table>
<thead>
<tr>
<th>Antibody Clone</th>
<th>Dako</th>
<th>Ventana</th>
<th>Dako</th>
<th>Dako</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Clones</td>
<td>x1, ≥50</td>
<td>x1, ≥5, ≥10</td>
<td>x1, x5, ≥10</td>
<td>x2, ≥10</td>
</tr>
<tr>
<td>Cutoffs</td>
<td>95.4 (20%)</td>
<td>95.8 (15%)</td>
<td>95.1 (5%)</td>
<td>96.7 (25%)</td>
</tr>
<tr>
<td>Inter-Observer</td>
<td>&gt;90</td>
<td>96.7 (25%)</td>
<td>96.7 (25%)</td>
<td></td>
</tr>
<tr>
<td>Inter-Site</td>
<td>&gt;90</td>
<td>96.7 (25%)</td>
<td>96.7 (25%)</td>
<td></td>
</tr>
</tbody>
</table>

Multiple other T-Cell Immune Checkpoints as Therapeutic Targets


Potential trial biomarkers

- Single IHC markers for checkpoint expression
- Multi-marker IF panel to broadly phenotype the tumor immune microenvironment
- Targeted gene expression panels for immune markers
- Broader gene expression panels
- Viral response signature
- EMT signature
- Circulating chemokine panels (CM017/057) or other serum markers
- DNA sequencing and algorithmic approaches to mutation burden
- For pure research multi-color flow and CyTOF being increasingly used

Development of multimarker assays for clinical application

Opal™ Multiplex IHC Staining kit (PerkinElmer)

Multiplex IHC on FFPE tissues

Vista™ Multispectral Microscope (PerkinElmer)
Developing new sequencing tools

High background mutation rate in lung cancers (TCGA)

Mutational landscape determines sensitivity to PD-1 blockade in NSCLC

Mismatch repair as IMT marker in colorectal cancer
Lung cancers demonstrate a range of mutational burden

ITH in localized lung adenocarcinomas delineated by multi-region sequencing

Using targeted DNA sequencing as a biomarker for immune therapy

“T200 gene panel”

Clinical Actionability Enhanced through Deep Targeted Sequencing of Solid Tumors

Derivation & Validation of the Predicted Tumor Mutation Load (PTML) Scoring System

PTML Correlates with Mutagen Changes

PTML ≤ 100 Predicts anti-PD-1 Therapy Outcomes in Lung Adenocarcinoma

Findings are very consistent with the published data using whole exome sequencing.


PTML ≤ 100 Predicts anti-PD-1 Therapy Outcomes in Lung Adenocarcinoma

Pembrolizumab PFS

PR = Partial Response
SD = Stable Disease
POD = Progression of Disease
NDB = No Durable Benefit
DCB = Durable Clinical Benefit

4.1 vs. 8.3 months (low=8, high=21)

Woodman et al, in review
USE OF GENE EXPRESSION SIGNATURES

Examples:
- IFN-γ signature
- Viral response signature
- EMT signature

**EMT orchestrates cell-intrinsic & tumor microenvironment changes that drive tumor progression**

**PD-L1 mRNA & protein levels correlate with EMT in TCGA lung adenocarcinoma samples**

**Tumor PD-L1 and T-cell infiltrates correlate with EMT status in PROSPECT samples**

**EMT produces global reprogramming of redundant immune regulatory pathways**

**Immune Checkpoint Dysregulation Correlates with EMT Score across Multiple TCGA Tumor Types**
EMT Score is Independent of Total Genomic Mutational Burden

- **A**  
  - Rho: -0.27, P = 0.292

- **B**  
  - P = 0.644

- **C**  
  - Fold change: 44.77  
  - $P = 9 \times 10^{-9}$

Lou et al. CCR 2016

---

**Summary**

- Immunotherapies are increasingly used in trials and as SOC, but biomarker-based patient selection is a big issue.
- Use in early-stage disease or combination treatments further accentuate the need.
- Technical and regulatory issues surrounding biomarker development are evolving very rapidly due to stakeholder engagement.
- Research-based methodologies are migrating into the clinical pathology labs as our scientific understanding of tumor immunology advances.

---

Thank you

**Don L. Gibbons, MD, PhD**  
Assistant Professor, Department of Thoracic/Head & Neck Medical Oncology  
MD Anderson Cancer Center  

**Immune Checkpoint Inhibitors in the Treatment of Selected Tumor Types: A New Perspective**  
April 23, 2016
Management of Toxicity Issues with Immunotherapy

John V. Heymach, MD, PhD
Management of Toxicity Issues with Immunotherapy

John V. Heymach MD, PhD
Chairman and Professor
Thoracic/Head and Neck Medical Oncology

Immune Checkpoint Inhibitors in the Treatment of Selected Tumor Types: A New Perspective
April 23, 2016

Immune-related Adverse Event Spectrum

What are the toxicities from IMT? (or at least PD-1 with or without CTLA-4 blockade?)

POPLAR: Randomized phase II study of atezolizumab vs docetaxel in previously treated advanced/metastatic NSCLC- toxicities

KEYNOTE-010 study of pembrolizumab vs docetaxel in PDL1+ NSCLC: toxicities

Disclosures

Research support: AstraZeneca, GSK
Advisory Boards: Genentech, BMS, Lilly, AstraZeneca, GSK, BI, Aushon, Exelxis, Bio-Tree
Safety Summary

<table>
<thead>
<tr>
<th>Patients Reporting Event, %</th>
<th>NIVO + IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse event (AE)</td>
<td>95.5</td>
<td>55.0</td>
<td>82.1</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>34.4</td>
<td>29.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Treatment-related death**</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response.

Wolchok et al. ASCO 2015

Treatment-Related Select AEs Reported in ≥10% of Patients

<table>
<thead>
<tr>
<th>Patients Reporting Event, %</th>
<th>NIVO + IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>48</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>19</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Endocrine</td>
<td>13</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Hepatic</td>
<td>10</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Pulmonary*</td>
<td>10</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Hypertension/hypotension</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- With immune modulatory agents, resolution rates for the majority of grade 3–4 select AEs were: 85–100% for NIVO + IPI, 50–100% for NIVO, and 83–100% for IPI.

- As observed in prior studies, most endocrine events did not resolve.

Wolchok et al. ASCO 2015

Ipi/Nivo: Treatment-related select AEs in NSCLC

<table>
<thead>
<tr>
<th>Select AE category, %</th>
<th>Nivo 1 + Ipi 1 Q2W (n = 31)</th>
<th>Nivo 1 Q2W + Ipi 1 Q6W (n = 39)</th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>48</td>
<td>33</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>19</td>
<td>28</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Endocrine</td>
<td>13</td>
<td>20</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Hepatic</td>
<td>10</td>
<td>23</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary*</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
<td>3</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension/hypotension</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Select AEs are those with potential immunologic etiology that require frequent monitoring/intervention.

- All treatment-related pulmonary events were pneumonitis.

Ipi/Nivo: Treatment-related select AEs in NSCLC

<table>
<thead>
<tr>
<th>Select AE category, %</th>
<th>Nivo 1 + Ipi 1 Q2W (n = 31)</th>
<th>Nivo 1 Q2W + Ipi 1 Q6W (n = 40)</th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td></td>
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<td>Skin</td>
<td>48</td>
<td>33</td>
<td>31</td>
<td>31</td>
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<td>Gastrointestinal</td>
<td>19</td>
<td>28</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Endocrine</td>
<td>13</td>
<td>20</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
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<td>10</td>
<td>23</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary*</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
<td>3</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension/hypotension</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Summary Ipi/Nivo and Ipi/Pembro

<table>
<thead>
<tr>
<th>Combo</th>
<th>N1 Q3 W</th>
<th>N1 Q2 W</th>
<th>N3 Q2 W</th>
<th>N3 Q2 W</th>
<th>Pembrol 2/10 Q3 W</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>40</td>
<td>38</td>
<td>39</td>
<td>18</td>
</tr>
<tr>
<td>ORR</td>
<td>13%</td>
<td>25%</td>
<td>39%</td>
<td>31%</td>
<td>39%</td>
</tr>
<tr>
<td>Toxicity G 3 &amp; 4</td>
<td>29%</td>
<td>35%</td>
<td>29%</td>
<td>28%</td>
<td>75%*</td>
</tr>
</tbody>
</table>

*All grades; (P 2, I 1, n=12)

Courtesy of G. Simon
CheckMate 032: Treatment-related AEs (≥25% of patients)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 3 (n = 80)</th>
<th>Nivolumab 1 + Ipilimumab 3 (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade (%)</td>
<td>Grade 3–4 (%)</td>
<td>Any grade (%)</td>
</tr>
<tr>
<td>Total treatment-related AEs</td>
<td>41.3</td>
<td>11.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.8</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.3</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5.0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.8</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Rash</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash–maculopapular</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CheckMate 032: Treatment-related AEs (≥5% of patients)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 3 (n = 80)</th>
<th>Nivolumab 1 + Ipilimumab 3 (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade (%)</td>
<td>Grade 3–4 (%)</td>
<td>Any grade (%)</td>
</tr>
<tr>
<td>Total treatment-related AEs</td>
<td>41.3</td>
<td>11.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.8</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.3</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5.0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.8</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Rash</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
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</tr>
<tr>
<td>Amylase increased</td>
<td>1.3</td>
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</tr>
<tr>
<td>Lipase increased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash–maculopapular</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Timing of AEs from IMT

- Most grade 3/4 treatment-related select AEs occurred during the combination phase.
- Circles represent median; bars signify ranges.

Time to Onset of Grade 3/4 Treatment-related Select AEs
Patients receiving nivolumab + ipilimumab or ipilimumab alone

- Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs.

Time to Onset of Select Treatment-related AEs for Nivolumab (Any Grade; N = 474)

- In the 282 pts who experienced new treatment-related select AEs, 85% did so within the first 16 weeks of treatment.

New Treatment-related Select AEs Over Time with Nivolumab (Any Grade; N = 576)
Management

(in a nutshell: stop drug, give steroids of various sorts)

Pneumonitis

2/21/2011  3/30/2011
Two doses of ipilimumab and four of nivolumab

Pneumonitis Management

1. Radiographic changes: monitor
2. Mild symptoms: 2mg/kg of prednisone, consider hospitalization
3. Severe symptoms or hypoxia: 2-4mg/kg of solumedrol, bronchoscopy

**Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis**

Diarrhea and Colitis

Slangen et al., World J Gastrointest Pharmacol Ther; 2013

Management Algorithms: GI

From BMS: http://www.opdivohcp.bmscustomerconnect.com/

From BMS: http://www.opdivohcp.bmscustomerconnect.com/
Diarrhea/Colitis Management

1. Stools < 4X baseline: imodium, budesonide
2. Stools < 7X baseline: 1mg/kg of prednisone
3. Stools > 7X baseline or refractory to oral steroids:
   1. Hospitalize for IV solumedrol 1-2mg/kg
   2. Consider colonoscopy and CT scan
   3. Consider infliximab 5mg/kg

**Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis**

Management Algorithms: Hepatic

Hypophysitis Endocrinopathy

Endocrinopathies

Management Algorithms: endocrinopathies
Endocrinopathy Management

1. Replace the missing hormones
   1. Levothyroxine
   2. Hydrocortisone
2. Controversial whether higher doses of steroids during acute hypophysitis can prevent long-term pituitary dysfunction
3. Be aware of adrenal crisis

Ipilimumab Rashes

Can be treated with topical corticosteroids

Can IMT be given to patients on systemic immunosuppression? Response in Patients Who Received or Did not Receive IM

<table>
<thead>
<tr>
<th></th>
<th>NIVO monotherapy with IM (N = 139)</th>
<th>NIVO monotherapy without IM (N = 437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td>40 (28.8)</td>
<td>141 (32.3)</td>
</tr>
<tr>
<td></td>
<td>[21.4–37.1]</td>
<td>[27.9–36.9]</td>
</tr>
<tr>
<td>BOR, n (%)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>CR</td>
<td>7 (5.0)</td>
<td>23 (5.0)</td>
</tr>
<tr>
<td>PR</td>
<td>33 (23.7)</td>
<td>119 (27.2)</td>
</tr>
<tr>
<td>SD</td>
<td>31 (23.3)</td>
<td>102 (23.3)</td>
</tr>
<tr>
<td>PD</td>
<td>63 (45.3)</td>
<td>171 (39.6)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>5 (3.6)</td>
<td>21 (4.8)</td>
</tr>
<tr>
<td>Median duration of response, mo (95% CI)</td>
<td>22 (9.3–NR)</td>
<td>22 (9.3–NR)</td>
</tr>
<tr>
<td>Median time to response, mo (range)</td>
<td>2.1 (1.2–8.8)</td>
<td>2.1 (1.2–8.8)</td>
</tr>
</tbody>
</table>

- ORR was 28.8% in pts who had received an IM and was 32.3% in pts who had not received immunosuppression
- Time to response was similar in both subgroups (median of 2.1 months), and median duration of response was 22 months in those who did not receive an IM and had not been reached in pts who received systemic IMs

Possibility of Opportunistic Infection

- Ipilimumab diarrhea treated with prednisone and infliximab, subsequent Aspergillus fumigatus infection treated with voriconazole
- Consider prophylaxis for PCP (Bactrim, atovaquone) in patients on 20mg of prednisone for at least 4 weeks (Category 2B from NCCN)
Summary

• Overall IMT is better tolerated than chemo but AEs are common; combos have more toxicity
• Grade 3/4 AEs must be recognized and managed proactively
  – Steroids are usually cornerstone
• Particular care for pneumonitis, endocrinopathies which can easily be missed
• Don't forget opportunistic infections for those on persistent immunosuppression

Thank You

John V. Heymach MD, PhD
Chairman and Professor
Thoracic/Head and Neck Medical Oncology

Immune Checkpoint Inhibitors in the Treatment of Selected Tumor Types: A New Perspective
April 23, 2016
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