Recent Progress in Immunotherapy for Non-Small Cell Lung Cancer (NSCLC)

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Mutational Burden

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia

Cancer cells develop many mutations that can make them appear foreign to the immune system.

Key Attributes of the Immune System

- Specificity
- Memory
- Adaptive
• T cells can recognize, attack and kill these “foreign” cancer cells
IFN-γ-mediated up-regulation of tumor PD-L1

Cancer cells can evade immune attack by expressing PD-L1

Adaptive Tumor Expression of PD-L1 Turns the Immune System OFF!
• Cancer cells can evade immune attack by expressing PD-L1

Clinically we want to block PD-1 or PD-L1 (the big X) to reactivate the immune system
PD-L1 plays an important role in dampening the antitumor immune response

It Really Works—This Therapy Is Transformative!
– 66-year-old ex-smoker with KRAS-mutant adenocarcinoma of the lung
– 5 prior treatments for stage IV disease
– Right upper quadrant (RUQ) abdominal pain, anorexia and fatigue resolved within 2 months
– Duration of response: 10 months
A Large Phase I Experience Provided the Preliminary Data for This Randomized Study

Immunotherapy for NSCLC Brain Metastasis
A Phase II Study of Pembrolizumab in Patients With Metastatic Melanoma and NSCLC With Untreated Brain Metastases

Eligibility:
- Advanced melanoma or NSCLC
- At least 1 untreated or progressive brain metastasis 5-20mm
- No neurologic symptoms or steroid requirement
- PS 0-1
- NSCLC patients only; PD-L1 expression from tumor biopsy after most recent systemic therapy

Eligibility Flow:
- Pembrolizumab 10mg/kg q2 weeks
- Brain metastasis PD
- Brain metastasis CR, PR, or SD
- Consider radiation or surgery to progressing lesions
- Continue pembrolizumab if systemic control achieved

Primary Endpoint:
Brain Metastasis Response Rate

Secondary Endpoints:
Overall response rate, safety, PFS, OS

Exploratory Endpoints:
PD-L1 expression, TILs, and other predictive biomarkers on T cells, tumor cells, neuronal cells, and in plasma

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CR, complete response; CT, computed tomography; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; SD, stable disease; TILs, tumor infiltrating lymphocytes

# Spectrum of PD-1/PD-L1 Antagonist Activity

**Active**
- Melanoma
- Renal cancer (clear cell and non-clear cell)
- NSCLC—adenocarcinoma and squamous cell
- Small cell lung cancer
- Head and neck cancer
- Gastric and gastroesophageal junction
- Mismatch repair deficient tumors (colon, cholangiocarcinoma)
- Bladder
- Triple-negative breast cancer
- Ovarian
- Glioblastoma
- Hepatocellular carcinoma
- Thymoma
- Mesothelioma
- Hodgkin lymphoma
- Diffuse large cell lymphoma
- Follicular lymphoma
- T-cell lymphoma (cutaneous T-cell lymphoma [CTCL], peripheral T-cell lymphoma [PTCL])
- Merkel cell

**Minimal to No Activity:**
- Prostate cancer
- MMR+ colon cancer
- Myeloma
- Pancreatic cancer

**Major PD-1/PD-L1 Antagonists**
- Nivolumab (anti-PD-1)
- Pembrolizumab (anti-PD-1)
- Atezolizumab (MPDL3280, anti-PD-L1)
- MEDI-4736 (anti-PD-L1)
PD-1 vs PD-L1 Blockade

**Tumor cell/APC**
- PD-L1
- PD-L2
- Anti-PD-1
- Anti-apoptotic (tumor)

**T cell**
- PD-L1
- PD-L2
- Anti-PD-L1
- B7.1
- T-cell inactivation
Issues With the PD-L1 Biomarker

- Heterogeneity—multiple tumors and multiple passes within a tumor
- Interval between biopsy and treatment
- Primary versus metastatic disease
- Antibody and staining conditions

- Defining a positive result (cut-offs):
  - Cell type expressing PD-L1 (immune cell versus tumor or both)
  - Location of expression—cell surface versus intracellular versus stromal
  - Intensity, percent of cells ‘positive’
  - Distribution—patchy versus diffuse, intratumoral versus peripheral
Immune-Related Adverse Events (IRAEs)

Endocrine
- Thyroiditis
- Hypothyroidism
- Hyperthyroidism
- Hypophysitis
- Hypopituitarism
- Adrenal Insufficiency

Neurologic
- Neuropathy
- Meningitis
- Guillain-Barre Syndrome

Ocular
- Iritis
- Uveitis
- Conjunctivitis

Cardiac
- Pericarditis

Dermatologic
- Mucositis
- Rash, Vitaligo

Hepatic
- Transaminitis
- Hepatitis

Renal
- Nephritis
- Renal Insufficiency

Gastrointestinal
- Nausea, Emesis
- Diarrhea, Colitis,
- Perforation;
- Pancreatitis

Pulmonary
- Pneumonitis
- Respiratory failure
Where We Are Now

Where We Want To Be

Could biopsies and biomarkers help?


Future studies are warranted to benefit a greater numbers of patients

- Front-line therapy\(^1\)
- Move to earlier stage disease (adjuvant)
- Explore activity in ALK and EGFR mutants
- SCLC\(^2,3\)
- Lung MAP\(^4\)
- Biomarkers and science to develop new combinations\(^5,6\)

Immune Checkpoint Inhibitors in NSCLC
Practical Issues

- Selection of patients
- Monitoring response
- Managing adverse events
- Immunotherapy beyond progression
- Combination therapies with immune checkpoint inhibitors
IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER: ANSWERING CLINICALLY RELEVANT QUESTIONS

Sunday, June 5, 2016

6.00 PM – 6.30 PM  REGISTRATION AND DINNER
6.30 PM – 8.30 PM  SCIENTIFIC PROGRAM