Advances in Cancer Immunotherapy for Solid Tumors

Expert Perspectives on The New Data

Sunday, June 5, 2016

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Learning Objectives

1. Evaluate the principles of tumor immunology and the mechanisms of action of current and emerging cancer immunotherapies used in solid tumors.

2. Appraise the latest clinical trial data regarding emerging cancer immunotherapies in SCCHN, NSCLC, mesothelioma, gastric cancer, melanoma, and other solid tumors, including use of both monotherapy and combination regimens.

3. Explore the role of biomarkers in patient selection to improve targeted use of immune checkpoint inhibitors.

4. Identify practical strategies for using current and emerging cancer immunotherapies, including prevention, early detection, and management of immune-related adverse effects.
Future Prospects in Solid Tumor Treatment Using Immunotherapy
Robert L. Ferris, MD, PhD

Associate Director for Translational Research
Co-Leader, Cancer Immunology Program
University of Pittsburgh Cancer Institute
Pittsburgh, Pennsylvania
Disclosures

• I am a consultant for AstraZeneca/MedImmune, Bristol-Myers Squibb, Celgene, Lilly, and Merck

• I have received grant/research support from AstraZeneca/MedImmune, Bristol-Myers Squibb and VentiRx Pharmaceuticals
Cancer Immunoediting

Elimination → Equilibrium → Escape

Tumor cells with a less immunogenic phenotype:
- Escape immunosurveillance
- Induce tolerant microenvironment

HNSCC

What is The Future of Immunotherapies?

• Vaccines (peptides, DC)
• Tumor-targeted Abs
• Immune-targeted Abs
• Combinations (with chemo, RT)
HNSCC
Two Distinct Diseases

- p53 mut
- p16
- 3p, 4q, 5q, 8p, 13q del

HPV
- E6
- p53
- E7
- pRB
- p16
p53 Mutation Associated With Poor Prognosis

- ~50% of HNSCC express genetic alterations in p53
  - Considered an early event in multi-step HNSCC carcinogenesis
  - Same p53 mutation in primary tumor usually found in metastases

Dendritic Cell Tool for Immunotherapy of HNC

Defined Antigens (peptides)
- P53
- HPV E7
- SART, Caspase-8

Undefined Antigens
- Apoptotic cells
- Tumor lysate
- Neoantigens
17 pts analyzed for immune and clinical responses

- Two-year DFS of 84% was favorable
- p53-specific T-cell frequencies were increased post-vaccination in 11 pts (69%), with IFN-γ secretion detected in 4 pts.

- Treg frequencies were consistently decreased ($P=0.006$) relative to pre-vaccination values.
- The phenotype and function of DC1 were improved relative to vDC.
Tumor Cell-Mediated Immune Escape

Aberrant Signal 1, 2, or 3

Immunosuppressive Cytokines
TGFβ, IL-10, VEGF

Signal 3

Signal 1

HLA class I TCR

Signal 2

PD-L1

PD-1

Cytokine Receptor

Tumor cell

T cell

Imune Infiltrate

Neoplastic Tissue

Downregulation of HLA antigen presentation to evade T cell recognition
Recognition of HNSCC by CTL
Role of HLA/APM

HNSCC
Mutational Landscape

Tumor Cell-Mediated Immune Escape

Aberrant Signal 2

**Signal 1**
- HLA class I
- TCR
- PD-L1
- PD-1

**Signal 2**
- Promoting “exhausted” T cells

**Signal 3**
- Immunosuppressive Cytokines: TGFβ, IL-10, VEGF

**Cytokine Receptor**

**Neoplastic Tissue**

**Immune Infiltrate**
**T Cell Targets**

**Activating & Inhibitory Co-Receptors**

- **Activating Receptors**
  - CD28
  - OX40
  - GITR
  - CD137
  - CD27
  - HVEM

- **Inhibitory Receptors**
  - CTLA-4
  - PD-1
  - TIM-3
  - BTLA
  - VISTA
  - LAG-3

- **Agonistic antibodies**
- **Blocking antibodies**

---

HPV+ Tumor Microenvironment

*Enriched for PD-1+ CD8+ T cells*

### KEYNOTE-012

**Expansion Cohort**

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>Total N=117</th>
<th>HPV+ N=34</th>
<th>HPV− N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>N (%) 17.3-33.6</td>
<td>N (%) 8.7-37.9</td>
<td>N (%) 17.9-38.2</td>
</tr>
<tr>
<td>Complete Response</td>
<td>29 (24.8)</td>
<td>7 (20.6)</td>
<td>22 (27.2)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>28 (23.9)</td>
<td>6 (17.6)</td>
<td>22 (27.2)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>29 (24.8)</td>
<td>9 (26.5)</td>
<td>19 (23.5)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>48 (41.0)</td>
<td>13 (38.2)</td>
<td>34 (42.0)</td>
</tr>
</tbody>
</table>

For Prior lines of therapy for recurrent/metastatic disease:

- **0** | 22 (16.7)
- **1** | 30 (22.7)
- **2 or more** | 78 (59.1)

PFS: Immature (Not presented)
CheckMate 141

Study Design

Randomized, Global, Phase 3 trial of the efficacy and safety of nivolumab versus investigator’s choice in patients with R/M HNSCC

Key Eligibility Criteria
- R/M HNSCC of the oral cavity, oropharynx, larynx, or hypopharynx
- ECOG PS 0–1
- Not amenable to curative therapy
- Progression on or within 6 months of last dose of platinum-based therapy
- Documentation of p16 to determine HPV status
- No active CNS metastases

Stratification factor
- Prior cetuximab treatment

Randomized 360/360

Nivolumab
3mg/kg IV Q2W

Investigator’s Choice
- Methotrexate 40mg/m² IV weekly
- Docetaxel 30mg/m² IV weekly
- Cetuximab 400mg/m² IV once, then 250mg/m² weekly

Primary endpoint
- OS

Other endpoints
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

CNS=central nervous system; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; HPV=human papillomavirus; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; R=randomized; R/M=recurrent/metastatic; SCCHN=squamous cell carcinoma of the head and neck; Clinicaltrials.gov. NCT02105636.

Gillison ML, et al. AACR. 2016. (Abstract CT099)
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**Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (97.73% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (N=240)</td>
<td>7.5 (5.5–9.1)</td>
<td>0.70 (0.51–0.96)</td>
</tr>
<tr>
<td>Investigator’s Choice (N=121)</td>
<td>5.1 (4.0–6.0)</td>
<td></td>
</tr>
</tbody>
</table>

Gillon ML, et al. AACR. 2016. (Abstract CT099)
# CheckMate 141

## Treatment-Related AEs (≥10% of Pts)

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N=236)</th>
<th>Investigator’s Choice (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade N (%)</td>
<td>Grade 3–4 N (%)</td>
</tr>
<tr>
<td>Any</td>
<td>139 (58.9)</td>
<td>31 (13.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (14.0)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (8.5)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (5.1)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10 (4.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*One Grade 5 event (hypercalcemia) in the nivolumab arm and one Grade 5 event (lung infection) in the investigator’s choice arm were reported. A second death occurred in the nivolumab arm subsequent to Grade 3 pneumonitis.*

Gillison ML, et al. AACR. 2016. (Abstract CT099)
### CheckMate 141

#### Select Treatment-Related AEs

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N=236)</th>
<th>Investigator’s Choice (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade N (%)</td>
<td>Grade 3–4 N (%)</td>
</tr>
<tr>
<td>Skin</td>
<td>37 (15.7)</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine</td>
<td>18 (7.6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Hypersensitivity/Infusion reaction</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Gillison ML, et al. AACR. 2016. (Abstract CT099)
# CheckMate 141

## OS by PD-L1 Expression

<table>
<thead>
<tr>
<th>PD-L1 Expression ≥1%</th>
<th>Treatment Arm</th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab (n=88)</td>
<td>8.7 (5.7–9.1)</td>
<td>0.55 (0.36–0.83)</td>
</tr>
<tr>
<td></td>
<td>Investigator’s Choice (n=61)</td>
<td>4.6 (3.8–5.8)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>PD-L1 Expression &lt;1%</th>
<th>Treatment Arm</th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab (n=73)</td>
<td>5.7 (4.4–12.7)</td>
<td>0.89 (0.54–1.45)</td>
</tr>
<tr>
<td></td>
<td>Investigator’s Choice (n=38)</td>
<td>5.8 (4.0–9.8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Months</th>
<th>Nivolumab</th>
<th>Investigator’s Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>15</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

Gillison ML, et al. AACR. 2016. (Abstract CT099)
# CheckMate 141

**OS by p16 Status**

<table>
<thead>
<tr>
<th>P16+</th>
<th></th>
<th>HR (95% CI)</th>
<th></th>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Arm</td>
<td>Median OS, mo (95% CI)</td>
<td></td>
<td>Treatment Arm</td>
<td>Median OS, mo (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Nivolumab (n=63)</td>
<td>9.1 (7.2-10.0)</td>
<td>0.56 (0.32-0.99)</td>
<td>Nivolumab (n=50)</td>
<td>7.5 (3.0-NA)</td>
<td>0.73 (0.42-1.25)</td>
</tr>
<tr>
<td>Investigator’s Choice (n=29)</td>
<td>4.4 (3.0–9.8)</td>
<td></td>
<td>Investigator’s Choice (n=36)</td>
<td>5.8 (3.8–9.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Graphs:**

1. **Overall Survival (% of patients)**
   - Months: 0, 3, 6, 9, 12, 15, 18
   - Overall Survival: 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 0

2. **No. at Risk**
   - Nivolumab: 63, 49, 35, 18, 10, 3, 0
   - Investigator’s Choice: 29, 20, 11, 4, 1, 0

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Gillison ML, et al. AACR. 2016. (Abstract CT099)
CheckMate 141

Conclusions

• Nivolumab is the first agent to demonstrate a significant improvement in survival in patients with HNSCC whose disease progresses after platinum-based therapy in a randomized, phase 3 comparative trial.

• Nivolumab doubled 1-year survival rate vs IC therapy.
  – 36% with nivolumab vs 17% with IC

• Nivolumab demonstrated an OS benefit regardless of PD-L1 expression or p16 status.

• Safety profile for nivolumab was favorable compared to IC therapy, and consistent with prior studies.

• Nivolumab represents a new standard of care for patients with R/M HNSCC after platinum-based therapy.

Gillison ML, et al. AACR. 2016. (Abstract CT099)
Durvalumab and/or Tremelimumab
Trials in HNSCC

**Setting**

- **2L HNSCC post plat in R/M setting**
- **2L HNSCC post plat in R/M setting**
- **2L HNSCC post plat**
  - **1L pts who progressed within 6 mo of multi-modal tx w/pt in the locally advanced setting**

**Regimen**

- Durvalumab
- Durvalumab + Tremelimumab
- Durvalumab
- Tremelimumab

**PD-L1 status**

- + N=112
- N=120
- N=60^ Arab
- N=60^ Arab
- N=100
- N=Adaptive 140*
- N=100
- N=140

**Rationale**

- **Accelerated approval of the Monotherapy in PD-L1+ Zandberg**
- **Accelerated approval of the Combination in PD-L1−**
  - Establishes individual component contribution to combination in PD-L1− Siu
- **Confirmatory trial**
- **Combination approval in all-comers Ferris and Licitra**
EGFR in Human HNSCC
Expressed in >90%

Cetuximab is clinically effective in only 10-15% of patients

Cetuximab-Induced NK-DC Crosstalk
Triggering TA-Specific Immunity

Cetuximab in HNSCC Stage II-IV
UPCI Protocol #08-013

Endpoints:
Modulation of immune biomarkers, 2-yr PFS
ACCRUAL 40/40
Neoadjuvant Cetuximab

**CTLA-4+Treg (CD4+FOXP3+) Expansion**

**Gated on CD4+ PBL**

- Responders
- Non-Responders

**Gated on TIL CD4+ TIL**

- Responders
- Non-Responders

Cetuximab/IMRT + Ipilimumab
*Phase Ib Trial*

“High Risk” Locally Advanced p16-/+ (HPV+) Oropharynx Cancer

**Stage III-IVA OPSCC**
- HPV+ smokers, ≥N2b
- p16 IHC
- Tumor/Blood collection

**Cetuximab/Radiotherapy Plus Ipilimumab**
- IMRT 70 Gy in 6.5 weeks
- Cetuximab weekly at 250 mg/m² during radiation*
- Ipilimumab 1 mg/kg q21 days, starting week 5

*After loading dose of 400 mg/m² on cycle 1, day 1
Ipilimumab will be continued at indicated dose for additional 2 cycles

PI - Ferris
Co-PI Bauman
Accrued 18
Firstline Recurrent/Metastatic HNSCC

Active8 Trial

Adding TLR8 stimulation to cisplatin/5-FU + cetuximab

Accrual=190 pts
Primary endpoint=PFS

HNSCC Stage II-IV
UPCI Protocol #14-002

Neoadjuvant cetuximab plus TLR8 stimulation

HNSCC Stage II-IV Resectable
OC, OP, HP, L

B
I
O
P
S
Y

Cetuximab + Motolimod + Nivolumab x 4 wk

S
U
R
G
E
R
Y

Endpoints = Modulation of immune biomarkers
ACCRUAL = 18/30

R01 DE019727
P50 CA097190
UPCI Protocol #14-002
Neoadjuvant Cetuximab + TLR8 Stimulation

Down-regulation of suppressive molecules on tumor-infiltrating Treg post motolimod + cetuximab treatment

CTLA-4
$P = .01$
$P = .01$

CD73
$P = .05$

LAP/TGF-β
$P = .04$

Gated on CD4$^+$CD25$^{\text{high}}$ FOXP3$^+$ Treg
RTOG 3504
Phase II-III Trial

Adding anti-PD-1 Ab to chemoradiotherapy with cetuximab or cisplatin

Lead in Phase I: Dose Selection
- Cisplatin with RT
- Cetuximab with RT

Comparative Phase III trial
- Cisplatin + RT
- Cisplatin + RT + nivolumab

Randomize

Basic Eligibility:
Previously untreated intermediate and high-risk Stage III-IV HNSCC

Register and Stratify
HPV/P16
T-stage
T2-3 vs T4
PS
0 vs 1

HPV+ Oropharynx Cancer

**HPV Vaccine + Anti-PD-1 mAb Trial**

**Primary endpoint:** 3-year Disease-free survival

**Secondary endpoints:** Distant metastatic control, locoregional control, overall survival, paired tumor/TME biomarkers, serial peripheral biomarkers

**Key Eligibility:**
- PULA HPV+ OPSCC >10 pk-yr
- T4 and/or N2c/N3 with <10 pk-yr
- M0

**Tumor Biomarkers**

**Blood Biomarkers**

**Definitive CRT**

Day -14±2 → ISA → Day -7±2 → Pembrolizumab 200 mg

---

70 Gy + DDP
KEYNOTE-028

Advanced Esophageal Carcinoma

- Single-arm study (pembrolizumab 10 mg/kg q 2 weeks)
- Pts (N=23) with advanced SCC (74%) or adenocarcinoma and PD-L1+ status included (87% had ≥2 prior regimens)
- Primary endpoint: ORR

### ORR

<table>
<thead>
<tr>
<th>ORR</th>
<th>30.4% (0 CR, 7 PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>9.0% (Median duration of response 40 weeks)</td>
</tr>
<tr>
<td>Grade 3 AEs</td>
<td>4 patients (17.4%) had grade 3 AE’s</td>
</tr>
<tr>
<td></td>
<td>Most common AEs: decreased appetite, hypothyroidism</td>
</tr>
</tbody>
</table>

Immune Checkpoint Inhibitors in Other Solid Tumors
CheckMate-032
Advanced/Metastatic GC/GEC

- Single-arm study (nivolumab 3 mg/kg IV q 3 weeks)
- Pts (N=59) included irrespective of PD-L1 status (83% had ≥2 prior regimens)
- Primary endpoint: ORR

<table>
<thead>
<tr>
<th>ORR</th>
<th>14% (1 CR, 7 PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19% (11/59) with SD</td>
</tr>
<tr>
<td></td>
<td>Disease control rate 33%</td>
</tr>
<tr>
<td></td>
<td>Median duration of response 7.1 months</td>
</tr>
<tr>
<td>PD-L1+ numerically higher response rate</td>
<td></td>
</tr>
<tr>
<td>6 months OS</td>
<td>49%</td>
</tr>
<tr>
<td>12 months OS</td>
<td>36%</td>
</tr>
<tr>
<td>Grade 3/4 AEs</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>(pneumonitis, fatigue, diarrhea, vomiting, hypothyroidism, elevated AST, ALT, Alk Phos)</td>
</tr>
</tbody>
</table>

# KEYNOTE-012
## Advanced Gastric Cancer

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Grade 1 or 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>5 (13%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (13%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (13%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4 (10%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (10%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pemphigoid</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

N=39 (PD-L1+, treated with pembrolizumab 10 mg/kg q 2 weeks)

<table>
<thead>
<tr>
<th>Central review</th>
<th>Asia (N=17)</th>
<th>Rest of the world (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response (%), 95%</strong></td>
<td>4 (24%, 7-50)</td>
<td>4 (21%, 6-46)</td>
</tr>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>4 (24%)</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>3 (18%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7 (41%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>No assessment</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Not determined</td>
<td>3 (18%)</td>
<td>0</td>
</tr>
<tr>
<td>Time to response (weeks)</td>
<td>8 (7-8)</td>
<td>8 (8-12)</td>
</tr>
<tr>
<td>Duration of response (weeks)</td>
<td>40 (32-NR)</td>
<td>NR (22-NR)</td>
</tr>
<tr>
<td>Median progression-free survival (95%, CI; months)</td>
<td>1.9 (1.8-5.7)</td>
<td>1.8 (1.6-5.8)</td>
</tr>
<tr>
<td>Median overall survival (95%, CI; months)</td>
<td>11.4 (3.1-NR)</td>
<td>NR (3.5-NR)</td>
</tr>
</tbody>
</table>

# KEYNOTE-012

**Advanced TNBC**

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Patients Evaluable for Response, N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, % (95% CI)</td>
<td>18.5 (6.3 to 38.1)</td>
</tr>
<tr>
<td>Best overall response, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13 (48.1)</td>
</tr>
<tr>
<td>No assessment</td>
<td>2 (7.4)</td>
</tr>
</tbody>
</table>

**N=32 (PD-L1+, treated with pembrolizumab 10 mg/kg q 2 weeks)**


<table>
<thead>
<tr>
<th>Grade</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade occurring in at least two patients</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>AST Increased</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Grade 3-5 occurring in at least one patient</td>
<td></td>
</tr>
<tr>
<td>Anemia (Grade 3)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Aseptic meningitis (Grade 3)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Blood fibrinogen decreased (Grade 4)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (Grade 5)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Headache (Grade 3)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Lymphopenia (Grade 3)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Pyrexia (Grade 3)</td>
<td>1 (3.1)</td>
</tr>
</tbody>
</table>
## Advanced/Metastatic PDAC
### Select Trials

<table>
<thead>
<tr>
<th>ICI</th>
<th>N</th>
<th>Additional Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30</td>
<td>GVAX</td>
<td>↑1 year OS by 20% compared to GVAX alone</td>
</tr>
<tr>
<td>Ipilimumab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27</td>
<td>None</td>
<td>1 patient delayed regression of hepatic metastases</td>
</tr>
<tr>
<td>BMS-936559&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14</td>
<td>None</td>
<td>No benefit</td>
</tr>
</tbody>
</table>


---

## Completed

<table>
<thead>
<tr>
<th>ICI</th>
<th>Phase</th>
<th>Additional Therapy</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>I</td>
<td>Gemcitabine</td>
<td>NCT01473940</td>
</tr>
<tr>
<td>Ipilimumab (+GVAX)</td>
<td>II</td>
<td>FOLFIRINOX</td>
<td>NCT01896869</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>I/II</td>
<td>Tremelimumab</td>
<td>NCT02558894</td>
</tr>
</tbody>
</table>
Advanced MCC
Pembrolizumab Phase II Trial

- Pts (N=26) who received no prior systemic therapy were treated with pembrolizumab 2 mg/kg IV q 3 weeks
- ORR (primary endpoint): 56% (MCPyV+ =62%, MCPyV- =44%)
- PFS at 6 months=67%
- Grade 3/4 irAEs=15%

### Advanced Gastric or Colon Cancer

#### Select Trials

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Stage of development[^a]</th>
<th>Trials for gastric cancer</th>
<th>Trials for colon cancer</th>
</tr>
</thead>
</table>
| **CTLA-4** | Tremelimumab  
Ipilimumab  
Tremelimumab + durvalumab | FDA approved for malignant mesothelioma  
FDA approved for adjuvant unresectable or metastatic melanoma  
Phase Ib/II | NCT02340975  
NCT01585987  
NCT02340975 | NCT00313794  
NCT00047164  
NCT01975831 |
| **PD-1** | Nivolumab (ONO-4538)  
Pembrolizumab (MK3475)  
Nivolumab + ipilimumab | FDA approved for melanoma + NSCLC + RCC  
FDA approved for unresectable or metastatic melanoma + NSCLC | NCT02267343  
NCT02488759  
NCT02569242  
NCT02335411  
NCT01848834  
NCT02370498  
NCT02494583  
NCT01928394  
NCT02267343  
NCT02488759  
NCT02569242  
NCT02335411  
NCT01848834  
NCT02370498  
NCT02494583 | NCT02423954  
NCT02335918  
NCT02327078  
NCT02318907  
NCT02460198  
NCT01876511  
NCT02563002  
NCT02437071  
NCT02375672  
NCT02260440  
NCT02268825  
NCT02298959  
NCT02060188 |
| **PD-L1** | Durvalumab (MED14736)  
Atezolizumab (MPDL3280A)  
Avelumab (MSB0010718C) | Phase III  
Phase III | NCT02572687  
NCT02586987  
NCT02639065  
NCT01938612  
NCT02520453  
NCT02471846  
NCT02625623  
NCT02625610 | NCT02227667  
NCT02586987  
NCT02484404  
NCT01693562  
NCT02291289 |

[^a]: Highest stage of clinical development, regardless of tumor type.

## Bladder Cancer

### Select Trials

<table>
<thead>
<tr>
<th>ICI</th>
<th>Phase</th>
<th>Additional Therapy</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>III</td>
<td>Chemotherapy</td>
<td>NCT02256436</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>III</td>
<td>None</td>
<td>NCT02450331</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>III</td>
<td>Chemotherapy</td>
<td>NCT02302807</td>
</tr>
<tr>
<td>Durvalumab +/- tremelimumab</td>
<td>III</td>
<td>Chemotherapy</td>
<td>NCT02516241</td>
</tr>
</tbody>
</table>
# Kidney Cancer

## Select Trials

<table>
<thead>
<tr>
<th>ICI</th>
<th>Phase</th>
<th>Additional Therapy</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>III</td>
<td>Everolimus</td>
<td>Motzer(^a)</td>
</tr>
<tr>
<td>Atezolizumab (+/- bevacizumab)</td>
<td>III</td>
<td>Sunitinib</td>
<td>NCT02420821</td>
</tr>
<tr>
<td>Nivolumab + ipilimimumab</td>
<td>III</td>
<td>Chemotherapy</td>
<td>NCT02231749</td>
</tr>
</tbody>
</table>

Other Advanced Solid Tumors

Select Ongoing Trials

<table>
<thead>
<tr>
<th>ICI</th>
<th>Phase</th>
<th>Additional Therapy</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>I/II</td>
<td>Ipilimumab</td>
<td>NCT01928394</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>I</td>
<td>None</td>
<td>NCT02054806</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>I/II</td>
<td>None</td>
<td>NCT01693562</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>I/II</td>
<td>Ibrutinib</td>
<td>NCT02403271</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>I</td>
<td>None</td>
<td>NCT01375842</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>I</td>
<td>Bevacizumab and/or chemotherapy</td>
<td>NCT01633970</td>
</tr>
</tbody>
</table>
Reversal of Tumor Immune Escape

Targeting The Tumor Microenvironment

Inflamed cytokine chemokine secretion

Chemoattraction into TME

Reprogramming of anti-tumor T cells to reverse inhibitory signals

Tumor cell death

JAK2 inhibitor
STAT1 activation
HLA class I antigen processing

anti-CTLA4
anti-PD1
anti-Tim-3
anti-Lag3
Thank you!

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