“The following presentation should not be regarded as an endorsement of a particular product/drug/technique by the speaker. The presentation topics were assigned to the speakers by the scientific committee of the KCA, to be presented/interpreted as part of a comprehensive scientific debate. Therefore, this presentation should not be viewed/interpreted in isolation, and should be considered in context with the other presentations in the same session."
Toxicities with PD-1 Inhibitors: The Price of the Cure

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Huntsman Cancer Institute, University of Utah (NCI-CCC)

Twitter: @neerajaiims
Background

• Toxicities associated with CTLA-4 inhibitors (alone or in combination with PD inhibitors) are well recognized and discussed (and twitted)
Potential overall magnitude of PD-1/PDL-1 inhibitor toxicities..

- > 20 Agents
- > 800 Ongoing trials
- > 160,000 Slots
- Widespread real world use
- Overall high prevalence of these toxicities expected

Primary Objective

Systematically assess the incidence of PD-1 / L1 inhibitor immune-related adverse events (IRAEs) in patients with GU malignancies
Methods

• Adhered to PRISMA* Statement recommendations for systematic reviews

• Databases:
  ▪ PubMed®
  ▪ International Pharmaceutical Abstracts® (IPA)
  ▪ Embase®

• Other:
  ▪ Manufacturer information consulted when published data incomplete
  ▪ Conference abstracts (ESMO, ASCO)

*PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Methods

• **Inclusion:**
  - Phase II-III clinical trials of patients with GU malignancies treated with PD-1/L1 inhibitors
    - Atezolizumab, Avelumab, Durvalumab, Nivolumab, PDR001, Pembrolizumab, Pidilizumab

• **Exclusion:**
  - Phase I clinical trials of patients with GU malignancies treated with PD-1/L1 inhibitors (patient and disease heterogeneity, inconsistent dosing)
  - All trials involving non-GU malignancies
  - Combination anti-cancer therapy
    - *Exception:* concurrent hormonal therapy allowed
Results: Embase® Search

- **Search Terms**: 'atezolizumab'/exp OR 'avelumab'/exp OR 'durvalumab'/exp OR 'nivolumab'/exp OR pdr001 OR 'pembrolizumab'/exp OR 'pidilizumab'/exp AND [humans]/lim AND [english]/lim AND [embase]/lim AND 'bladder cancer'/exp
- Returns: 174 abstracts/full texts screened
- 'germ cell tumor'/exp
- Returns: 9 abstracts/full texts screened
- 'kidney carcinoma'/exp
- Returns: 462 abstracts/full texts screened
- 'prostate cancer'/exp
- Returns: 286 abstracts/full texts screened
- **Total**: 931 returns

Reference: http://www.embase.com/
Results: PubMed® Search

• **Search Terms:** ((("pidilizumab"[Supplementary Concept] OR "pembrolizumab"[Supplementary Concept]) OR "nivolumab"[Supplementary Concept]) OR "MPDL3280A"[Supplementary Concept]) OR "avelumab"[Supplementary Concept]) OR "MEDI4736"[Supplementary Concept] OR PDR001 AND ("humans"[MeSH Terms] AND English[lang])

• **Returns:** 283 abstracts/full texts screened

Results: International Pharmaceutical Abstracts

• **Search Terms**: (atezolizumab or avelumab or durvalumab or nivolumab or pdr001 or pembrolizumab or pidilizumab).sh.

• **Limits applied**: (English language and human and ("abstracts of meeting presentations" or journal articles))

• **Returns**: 57 abstracts/full texts screened

Records identified through database searching (n = 1271)

Records after duplicates removed (n = 969)

Records excluded (n = 931)
- 553 reviews/editorials/letters/guideline updates
- 304 records pertaining to non-GU malignancies
- 49 non-PD-1/L1 trials, pre-clinical
- 17 observational
- 8 GU Phase 1 clinical trials

Abstracts / Full-text articles excluded (n = 31)
- 18 combination treatment
- 4 trials where outcome of interest not reported
- 8 GU clinical trials in-progress
- 1 prescribing information, non-GU data only

Studies included in qualitative synthesis (n = 7)

Reviewer Definition of IRAE

• Recorded adverse events categorized by trial investigators as:

  1. Immune-mediated/related adverse events
     OR
  2. Treatment-related adverse events of special interest
     OR
  3. Select treatment-related adverse events
<table>
<thead>
<tr>
<th>PD-1/L1 Inhibitor</th>
<th>Trial</th>
<th>Dose</th>
<th>n</th>
<th>GU Cancer</th>
<th>All Grades IRAEs</th>
<th>G3-5 IRAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atezolizumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PD-L1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMVigor 210 (Cohort 1), Phase II*¥</td>
<td>1200mg</td>
<td>119</td>
<td>Urothelial</td>
<td>Total 17 (14%)</td>
<td>Total 7 (6%) Skin disorders, hepatic, rhabdomyolysis, colitis, hyperglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMVigor 210 (Cohort 2), Phase II*¥</td>
<td>1200mg</td>
<td>310</td>
<td>Urothelial</td>
<td>Total 31 (10%)</td>
<td>Total 19 (6%) Pneumonitis, hepatic, dyspnea, colitis/diarrhea, skin</td>
<td></td>
</tr>
<tr>
<td><strong>Durvalumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PD-L1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durvalumab, Phase I/II</td>
<td>10mg/kg</td>
<td>61</td>
<td>Urothelial</td>
<td>Total 14 (23%)</td>
<td>Total 2 (3%) Nephritis (biopsy proven), infusion reactions</td>
<td></td>
</tr>
</tbody>
</table>

Data sources: PubMed, Embase, IPA- supplemented by manufacturer prescribing information and data on-file

*IMVigor 210 described IRAEs as those requiring systemic steroids.
*IMVigor 210, Cohort 1: reported All Grade IRAEs occurring in ≥ 2 patients; Cohort 2: reported All Grade and Grade 3-4 IRAEs occurring in ≥ 2 patients.
<table>
<thead>
<tr>
<th>PD-1/L1 Inhibitor</th>
<th>Trial</th>
<th>Dose</th>
<th>n</th>
<th>GU Cancer</th>
<th>All Grades IRAEs</th>
<th>G3-5 IRAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (PD-1)</td>
<td>CheckMate 025, Phase III</td>
<td>3mg/kg</td>
<td>406</td>
<td>Renal</td>
<td>Total: Not Reported • ≥5%: thyroid disease, rash, hyperglycemia, infusion reactions • &lt; 5%: pneumonitis, colitis, hepatitis, DM/DKA, renal dysfunction /nephritis, hypophysitis, adrenal insufficiency</td>
<td>Total: Not Reported Pneumonitis, colitis, hepatitis, hypophysitis, thyroid disease, adrenal insufficiency, DM/DKA, rash, renal dysfunction/nephritis</td>
</tr>
<tr>
<td></td>
<td>Nivolumab, Phase II</td>
<td>0.3-, 2-, 10- mg/kg</td>
<td>167</td>
<td>Renal</td>
<td>Total: Not Reported • ≥5%: skin, endocrine, GI, hypersensitivity, pulmonary, hepatic • &lt; 5%: renal</td>
<td>Total: Not Reported Skin, endocrine, GI, hepatic</td>
</tr>
<tr>
<td></td>
<td>CheckMate 032, Phase I/II*</td>
<td>3 mg/kg</td>
<td>78</td>
<td>Urothelial</td>
<td>Total: Not Reported • ≥5%: Skin, GI, hepatic, renal • &lt; 5%: Pulmonary, thrombocytopenia</td>
<td>Total: Not Reported Skin, GI, hepatic, pneumonitis, renal, thrombocytopenia</td>
</tr>
<tr>
<td>Pembrolizumab (PD-1)</td>
<td>Pembrolizumab, Phase II**</td>
<td>200mg</td>
<td>20</td>
<td>Prostate</td>
<td>Total 5 (25%) • ≥5%: myositis, hypothyroidism, colitis • &lt; 5%: None</td>
<td>Total 3 (15%) Hypothyroidism, colitis</td>
</tr>
</tbody>
</table>

*CheckMate 032: Data obtained from ASCO 2016 Annual Meeting Presentation, **Pembrolizumab: Data obtained from ESMO 2016 Abstract 7190
## Are toxicities from GU trials representative of toxicities overall?

### Table 2: Comparison of Select IRAEs in GU- versus Non-GU Clinical Trials & Manufacturer Data

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence, Any Grade (GU Only Trials)*</th>
<th>Incidence, Grade 3-5 (GU Only Trials)*</th>
<th>Incidence Any Grade (Non-GU Clinical Trials)</th>
<th>Incidence, Grade 3-5 (Non-GU Clinical Trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Disorders</td>
<td>56/712 (7.9%)</td>
<td>4/593 (0.7%)</td>
<td>3.9% - 12%</td>
<td>0% - 0.1%</td>
</tr>
<tr>
<td>DM/DKA</td>
<td>10/835 (1.2%)</td>
<td>4/525 (0.8%)</td>
<td>0.8% - 0.8%</td>
<td>0.4% - 0.7%</td>
</tr>
<tr>
<td>LFT changes/Hepatitis</td>
<td>42/1080 (3.9%)</td>
<td>24/1080 (2.5%)</td>
<td>0.3% - 3.4%</td>
<td>0.3% - 2.7%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>34/961 (3.5%)</td>
<td>9/794 (1.1%)</td>
<td>1.8% - 3.5%</td>
<td>0.25% - 1.9%</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>NR</td>
<td>NR</td>
<td>0.2% - 0.8%</td>
<td>0.0% - 0.2%</td>
</tr>
<tr>
<td>Colitis/Diarrhea</td>
<td>54/1161 (4.7%)</td>
<td>16/1100 (0.1%)</td>
<td>2.4% - 4.1%</td>
<td>1.0% - 2.5%</td>
</tr>
<tr>
<td>Hypophysitis^A</td>
<td>1/406 (0.2%)</td>
<td>1/406 (0.2%)</td>
<td>0.2% - 0.9%</td>
<td>0.2% - 0.4%</td>
</tr>
<tr>
<td>Renal Dysfunction/Nephritis</td>
<td>23/712 (3.2%)</td>
<td>8/545 (1.5%)</td>
<td>0.3% - 4.9%</td>
<td>0.0% - 0.5%</td>
</tr>
<tr>
<td>Myositis^A</td>
<td>1/20 (5%)</td>
<td>0/20 (0%)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

A = Reported in only one study; NR = Not Reported

*Data sources: PubMed, Embase, IPA- supplemented by manufacturer prescribing information and data on-file
Any organ can be affected: IRAEs with < 1% Incidence

Rheumatologic
- Exfoliative dermatitis
- Bullous pemphigoid
- Polymyalgia rheumatica
- Sarcoidosis
- Vasculitis

Neurologic
- Autoimmune neuropathy
- Meningitis
- Encephalitis
- Demyelination
- Facial/abducens nerve paresis
- Partial seizures
- Guillain-Barre syndrome
- Myasthenia gravis

Ophthalmic
- Uveitis
- Iritis

Gastrointestinal
- Pancreatitis
- Gastritis
- Duodenitis
- DM 1

Are these reports correctly assessing the real incidence and prevalence of IREs? Probably not...
Suboptimal reporting of AEs in Clinical Trials
Paolo Bossi et al. ESMO 2016

• Reviewed publications from 81 trials of targeted and immunotherapies approved by the US FDA between 2000-2015 for solid tumors

• Each publication assessed by a 24-point score card based on the Consolidated Standards of Reporting Trials (CONSORT) guidance

• > 90% trials scored poorly in their reporting of recurrent and late toxicities, and in reporting the duration of adverse events

• 86% of trials did not adequately report on the time of the adverse event occurrence

• 75% of trials only reported on adverse events that occurred at a frequency above a fixed threshold
Limitations of our study

• Inconsistent reporting and classification of IRAEs across trials
  ▪ IMvigor210 reported IRAEs as those AEs requiring use of systemic steroids
  ▪ IMvigor 210, Cohort 1: reported All Grade IRAES occurring in ≥ 2 patients;
    Cohort 2: reported All Grades and Grades 3-4 IRAEs occurring in 2 ≥ patients

• Phase II/III clinical trial data unavailable for avelumab, PDR001 and pidilizumab

• Small sample size in Phase II trials involving pembrolizumab and durvalumab
Conclusions

- Although less frequently, PD-1/PDL-1 inhibitors are associated with less common but similar type of autoimmune toxicities, as of CTLA-4 inhibitors
- More widespread use of PD-1/PDL-1 inhibitors is likely going to result in higher prevalence of even severe toxicities in the real world population
- Toxicities are often under recognized, and under reported
- Increased recognition and understanding important for timely management of these toxicities
• Thank you!!