Immune exclusion as a function of tumor genetics and heterogeneity

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Ovarian Cancer: Overview

- Estimated 21,750 cases and 13,940 deaths in US in 2020
- High grade serous (HGSOC) is the most common histology
- Presents in metastatic stage in >80% of cases
- Initial therapy involves surgical debulking and platinum-based chemotherapy
- After initial therapy, >80% of patients relapse and eventually succumb to disease
- Cytotoxic therapy remains the mainstay of treatment

Estimated cancer-related deaths in 2020

<table>
<thead>
<tr>
<th>Estimated Deaths</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>72,500</td>
<td>63,220</td>
</tr>
<tr>
<td>Prostate</td>
<td>33,330</td>
<td>42,170</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>28,830</td>
<td>24,570</td>
</tr>
<tr>
<td>Pancreas</td>
<td>24,040</td>
<td>22,410</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>20,020</td>
<td>13,940</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,420</td>
<td>12,590</td>
</tr>
<tr>
<td>Esophagus</td>
<td>13,100</td>
<td>10,140</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>13,050</td>
<td>9,660</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,460</td>
<td>8,480</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>10,190</td>
<td>7,830</td>
</tr>
<tr>
<td>All Sites</td>
<td>321,160</td>
<td>285,360</td>
</tr>
</tbody>
</table>

Siegel RL, et al. CA Cancer J Clin. 2020;70:7-30

Ascites and Carcinomatosis
Immune checkpoint blockade has limited efficacy in ovarian cancer

NRG-GY003: CTEP-sponsored randomized trial of nivolumab vs. nivolumab with ipilimumab in platinum-resistant ovarian cancer

Zamarin D, Burger RA, … Powell DJ et al., J. Clin. Oncol. 2020
Immune recognition in ovarian cancer is patterned by the underlying tumor genetics: tumors with underlying homologous recombination deficiency (HRD) exhibit heightened immune recognition and T cell infiltration

HRD-Dup: \textit{BRCA1} mut-like
HRD-Del: \textit{BRCA2} mut-like
FBI: Foldback inversions (\textit{CCNE} amplification-associated)
TD: Tandem duplicators (\textit{CDK12} deletion-associated)

HRD+ ovarian cancer cells are intrinsically “more immunogenic”

Cancer cell signatures

<table>
<thead>
<tr>
<th>HRD</th>
<th>Non-HRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK STAT</td>
<td></td>
</tr>
<tr>
<td>NFkB</td>
<td></td>
</tr>
<tr>
<td>TNFa</td>
<td></td>
</tr>
<tr>
<td>TGFb</td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
</tr>
</tbody>
</table>

PROGENy score: 
- 4
- 2
- 0
- -1

(a) HRD-Dup vs (b) FBI
(a) HRD-Del vs (b) FBI

Expression of HLA-A, HLA-B, HLA-C, B2M, HLA-DRA, HLA-DRB1

Signatures:
- HRD-Dup
- HRD-Del
- HRD-Other
- FBI
- TD

IFNγ
Type I

T cells

Cancer cell

Evolution through immunoediting drives immune resistance in HRD+ ovarian cancers

Mitchell et al., J. Life Sci. 2020

Ovarian cancer is a disease of substantial inter-site immune heterogeneity, often within the same patient.
Therapeutic approaches aiming to overcome the tumor microenvironment heterogeneity and the underlying causes of immune resistance will be key to immunotherapy success in ovarian cancer.