Immunotherapy for the Treatment of Breast Cancer Guideline Overview

October 29, 2021
1 – 2 p.m. ET

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer.

This webinar was funded solely by SITC.
Webinar faculty

Rita Nanda, MD – University of Chicago

Elizabeth A. Mittendorf, MD, PhD – Dana-Farber/Brigham and Women’s Cancer Center

David B. Page, MD – Earle A. Chiles Research Institute
Learning objectives

• Select appropriate diagnostics and biomarker testing tailored to the clinical setting for a patient being considered for immunotherapy based on the expert panel recommendations in the SITC Clinical Practice Guideline (CPG)

• Implement immunotherapy treatments effectively and appropriately for breast cancer according to the recommendations in the CPG

• Appraise patterns of response to immunotherapy in order to appropriately monitor and manage patients during treatment
Webinar outline

• Introduction to the Guideline
• Biomarkers for immunotherapy in breast cancer
• Early-stage TNBC
• Advanced/metastatic TNBC
• Response evaluation with immunotherapy
• Immunotherapy toxicities
Development of the Guideline

• Developed according to the Institute of Medicine’s Standards for Developing Trustworthy Clinical Practice Guidelines
• Panel consisted of 17 experts in the field
• Recommendations are based upon published literature evidence, or clinical evidence where appropriate
• Consensus was defined at 75% approval among voting members
Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of breast cancer

Leisha A Emens, Sylvia Adams, Ashley Cimino-Mathews, Mary L Disis, Margaret E Gatti-Mays, Alice Y Ho, Kevin Kalinsky, Heather L McArthur, Elizabeth A Mittendorf, Rita Nanda, David B Page, Hope S Rugo, Krista M Rubin, Hatem Soliman, Patricia A Spears, Sara M Tolaney, Jennifer K Litton
General guidance for patients receiving immunotherapy

• For patients receiving immunotherapy, **education** should be provided, including the differences between chemotherapy and immunotherapy.

• Patients and providers should be educated about **potential irAEs**, including expected timing of symptom onset and management of toxicities with immunotherapies, rationale for holding doses as opposed to dose reductions, and detailed parameters for when to contact their care team.

• Education should include the importance of early recognition and management of irAEs, emphasizing that some of the more common toxicities have **vague symptoms** and therefore any change from baseline should be reported.

• **Clinical trial** enrollment should be considered if available.
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PD-L1 assays in TNBC

- **SP142**: IC $\geq$ 1%, companion diagnostic for atezolizumab
- **22C3**: CPS $\geq$ 10, companion diagnostic for pembrolizumab
PD-L1 IHC assays: prevalence and analytical concordance

**PD-L1+ prevalence**

<table>
<thead>
<tr>
<th>PD-L1+ Cases</th>
<th>SP142 (IC 1%) and 22C3 (CPS 1)</th>
<th>SP142 (IC 1%) and SP263 (IC 1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP142</td>
<td>SP142+ 22C3+ (1%)</td>
<td>SP142+ SP263+ (45%)</td>
</tr>
<tr>
<td>46%</td>
<td>SP142- 22C3+ (36%)</td>
<td>SP142- SP263+ (30%)</td>
</tr>
<tr>
<td>81%</td>
<td>SP142+ 22C3- (1%)</td>
<td>SP142+ SP263- (24%)</td>
</tr>
<tr>
<td>75%</td>
<td></td>
<td>SP142- 22C3- (18%)</td>
</tr>
</tbody>
</table>

**OPA**

<table>
<thead>
<tr>
<th></th>
<th>SP142</th>
<th>SP263</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPA</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>NPA</td>
<td>34%</td>
<td>45%</td>
</tr>
</tbody>
</table>

NPA: negative percentage agreement; OPA: overall percentage agreement; PPA: positive percentage agreement.

* a ≥ 97% of SP142+ samples included in 22C3+ or SP263+ samples. b Compared with 41% in ITT (Schmid, New Engl J Med 2018).

c ≥ 90% OPA, PPA and NPA required for analytical concordance.

Rugo et al: Abstract 6571
Rugo, ESMO 2019
MSI, dMMR and TMB

- DNA mismatch repair deficiency
- Other causes of DNA mutations
- Tumor mutational burden
- Microsatellite instability

Microsatellites are stretches of DNA with a repetitive sequence of nucleotides and are susceptible to acquiring errors if DNA mismatch repair machinery is defective in a cell. MSI is one specific type of DNA mutation, while TMB measures all types of DNA mutations.
Panel recommendations for biomarkers in breast cancer

• All patients with advanced TNBC should have tumor tissue tested for PD-L1, TMB and MSI by FDA-approved tests.

• All patients who are candidates for immunotherapy should have tumor tissue tested for PD-L1 at least once, irrespective of prior therapies.

• PD-L1 testing is not recommended for patients with early-stage breast cancer at this time.

• When considering metastatic sites to test for PD-L1, it is preferable to prioritize extrahepatic sites or the primary tumor, if available.

• Biomarker assessment, including repeat receptor profiles, PD-L1 and NGS should be considered at first relapse.
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### FDA-approved immunotherapy for early-stage TNBC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Approved</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab + chemotherapy (neoadjuvant) &amp; Pembrolizumab monotherapy (adjuvant)</td>
<td>2021</td>
<td>High-risk, early-stage TNBC</td>
<td>Pembrolizumab 200 mg Q3W or 400 mg Q6W</td>
</tr>
</tbody>
</table>

**Neoadjuvant**: pembrolizumab + chemotherapy for 24 weeks  
**Adjuvant**: pembrolizumab for 27 weeks
Clinical trials in early-stage TNBC: KEYNOTE-522
Clinical trials in early-stage TNBC: KEYNOTE-522

EFS in Patient Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. Events/No. Patients (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>123/764 (15.7)</td>
<td>0.63 (0.48 to 0.82)</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>80/408 (19.6)</td>
<td>0.65 (0.46 to 0.91)</td>
</tr>
<tr>
<td>Negative</td>
<td>43/376 (11.4)</td>
<td>0.56 (0.37 to 0.81)</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/T2</td>
<td>64/581 (11.0)</td>
<td>0.51 (0.36 to 0.73)</td>
</tr>
<tr>
<td>T3/T4</td>
<td>59/203 (29.1)</td>
<td>0.64 (0.55 to 1.28)</td>
</tr>
<tr>
<td>Carboplatin schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 3 weeks</td>
<td>50/334 (15.0)</td>
<td>0.65 (0.42 to 0.99)</td>
</tr>
<tr>
<td>Weekly</td>
<td>71/444 (16.0)</td>
<td>0.60 (0.42 to 0.86)</td>
</tr>
<tr>
<td>PD-L1 status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>58/656 (14.9)</td>
<td>0.67 (0.49 to 0.92)</td>
</tr>
<tr>
<td>Negative</td>
<td>25/129 (19.5)</td>
<td>0.48 (0.28 to 0.85)</td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>103/700 (14.7)</td>
<td>0.61 (0.45 to 0.82)</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>20/64 (31.8)</td>
<td>0.79 (0.40 to 1.56)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>101/678 (14.9)</td>
<td>0.60 (0.45 to 0.80)</td>
</tr>
<tr>
<td>1</td>
<td>22/106 (20.8)</td>
<td>0.81 (0.41 to 1.62)</td>
</tr>
</tbody>
</table>
Toxicity considerations in early-stage TNBC

- Risk tolerance may be different in early-stage disease than for late-stage
- Potential for long-term adverse events must be considered
Panel recommendations for early-stage TNBC

• For patients with stage II and III TNBC, improved pCR rates with either neoadjuvant pembrolizumab or atezolizumab have been observed, regardless of PD-L1 status.

• Immunotherapy regimens for stage II or III TNBC should at least include an anthracycline and a taxane with or without carboplatin.

• For patients with high-risk early-stage TNBC, pembrolizumab + chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery is a standard of care based on KEYNOTE-522.
Webinar outline

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## FDA-approved immunotherapies for advanced TNBC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Approved</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab + chemotherapy</td>
<td>2020</td>
<td>Locally recurrent/metastatic TNBC with PD-L1 CPS ≥ 10</td>
<td>200 mg Q3W or 400 mg Q6W</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2017/2020</td>
<td>MSI-H/dMMR or TMB-high solid tumors with progression on prior treatment</td>
<td>200 mg Q3W or 400 mg Q6W</td>
</tr>
</tbody>
</table>

### Formerly approved regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Approved/ Withdrawn</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab + nab-paclitaxel or paclitaxel protein-bound</td>
<td>2019</td>
<td>Advanced/metastatic TNBC with PD-L1 ≥1% immune cells</td>
<td>840 mg atezolizumab Q2W + 100 mg/m² nab-paclitaxel on days 1, 8, 15</td>
</tr>
</tbody>
</table>
# Clinical trials in metastatic TNBC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arm(s)</th>
<th>Patient selection criteria</th>
<th>n</th>
<th>ORR</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMpassion130</strong></td>
<td>Atezolizumab + nab-paclitaxel</td>
<td>Metastatic TNBC without prior therapy</td>
<td>451</td>
<td>ITT: 56.0% PD-L1+: 58.9%</td>
<td>ITT: 7.2 PD-L1+: 7.5</td>
<td>ITT: 21.3 PD-L1+: 25.0</td>
</tr>
<tr>
<td></td>
<td>Placebo + nab-paclitaxel</td>
<td></td>
<td>451</td>
<td>ITT: 45.9% PD-L1+: 42.6%</td>
<td>ITT: 5.5 PD-L1+: 5.0</td>
<td>ITT: 17.6 PD-L1+: 15.5</td>
</tr>
<tr>
<td><strong>IMpassion131</strong></td>
<td>Atezolizumab + paclitaxel</td>
<td>Metastatic TNBC without prior therapy</td>
<td>431</td>
<td>ITT: 54% PD-L1+: 63%</td>
<td>ITT: 5.7 PD-L1+: 6.0</td>
<td>ITT: 19.2 PD-L1+: 22.1</td>
</tr>
<tr>
<td></td>
<td>Placebo + paclitaxel</td>
<td></td>
<td>220</td>
<td>ITT: 47% PD-L1+: 55%</td>
<td>ITT: 5.6 PD-L1+: 5.7</td>
<td>ITT: 22.8 PD-L1+: 28.3</td>
</tr>
<tr>
<td><strong>KEYNOTE-086</strong></td>
<td>Pembrolizumab</td>
<td>A: Metastatic TNBC at 2nd line or greater</td>
<td>170</td>
<td>5.3% CR: 1.2%</td>
<td>2.0</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: PD-L1+ metastatic TNBC without prior therapy</td>
<td>84</td>
<td>21.4% CR: 4.7%</td>
<td>2.1</td>
<td>18.0</td>
</tr>
<tr>
<td><strong>KEYNOTE-119</strong></td>
<td>Pembrolizumab</td>
<td>Metastatic TNBC with 1-2 prior therapies</td>
<td>312</td>
<td>ITT: 9.6% CPS &gt;10: 18%</td>
<td>ITT: 2.1 CPS &gt;10: 2.1</td>
<td>ITT: 9.9 CPS &gt;10: 12.7</td>
</tr>
<tr>
<td></td>
<td>Single-agent chemotherapy</td>
<td></td>
<td>310</td>
<td>ITT: 10.6% CPS &gt;10: 9%</td>
<td>ITT: 3.3 CPS &gt;10: 3.4</td>
<td>ITT: 10.8 CPS &gt;10: 11.6</td>
</tr>
<tr>
<td><strong>KEYNOTE-355</strong></td>
<td>Pembrolizumab + chemotherapy*</td>
<td>Locally recurrent inoperable or metastatic TNBC without prior therapy</td>
<td>566</td>
<td>ITT: 40.8 CPS &gt;10: 52.7</td>
<td>ITT: 7.5 CPS &gt;10: 9.7</td>
<td>ITT: 17.2 CPS &gt;10: 23.0</td>
</tr>
<tr>
<td></td>
<td>Placebo + chemotherapy</td>
<td></td>
<td>281</td>
<td>ITT: 37.0 CPS &gt;10: 40.8</td>
<td>ITT: 5.6 CPS &gt;10: 5.6</td>
<td>ITT: 15.5 CPS &gt;10: 16.1</td>
</tr>
</tbody>
</table>

*FDA-approved
Clinical trials in HR+ or HER2+ breast cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arm(s)</th>
<th>Patient selection criteria</th>
<th>n</th>
<th>ORR</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-028</td>
<td>Pembrolizumab</td>
<td>ER+/HER2-, PD-L1+ breast cancer</td>
<td>25</td>
<td>12.0% CR: 0%</td>
<td>1.8</td>
<td>8.6</td>
</tr>
<tr>
<td>KEYNOTE-014/PANACEA</td>
<td>Pembrolizumab + trastuzumab</td>
<td>HER2+ breast cancer with progression on trastuzumab</td>
<td>58</td>
<td>PD-L1+: 15% CR: 4% PD-L1-: 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KATE2</td>
<td>Atezolizumab + trastuzumab emtansine</td>
<td>HER2+ advanced breast cancer with previous trastuzumab and a taxane</td>
<td>133</td>
<td>ITT: 45% PD-L1+: 54%</td>
<td>ITT: 8.2 PD-L1+: 8.5</td>
<td>ITT 1-year: 89.1% PD-L1+: 94.3%</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab emtansine</td>
<td></td>
<td>69</td>
<td>ITT: 43% PD-L1+: 33%</td>
<td>ITT: 6.8 PD-L1+: 4.1</td>
<td>ITT 1-year: 89.0% PD-L1+: 87.9%</td>
</tr>
</tbody>
</table>

Rugo, Clin Cancer Res 2018; Loi, Lancet Oncol 2019; Emens Lancet Oncol 2020
Panel recommendations for advanced TNBC

• For patients with locally advanced/metastatic TNBC, pembrolizumab should only be added to chemotherapy if tumors express PD-L1 with CPS > 10 by the 22C3 assay.

• For patients with locally advanced/metastatic TNBC, atezolizumab should only be added to nab-paclitaxel if tumor-infiltrating immune cells expressing PD-L1 occupy >1% of the tumor area by SP142 assay.

• Nab-paclitaxel is the only chemotherapy backbone that should be used with atezolizumab for advanced/metastatic TNBC.

• Patients deriving clinical benefit from atezolizumab-based treatment in the absence of clinically significant toxicity or disease progression should continue on atezolizumab plus nab-paclitaxel rather than change therapy.
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Pseudoprogression

Pseudoprogression: Growth of pre-existing lesions

Baseline | Timepoint 1 | Timepoint 2
---------|------------|------------

Pseudoprogression: Appearance of new lesions

Baseline | Timepoint 1 | Timepoint 2
---------|------------|------------

Wang, Radiographics 2017.
Pseudoprogression

Baseline → Timepoint 1

Conventional criteria – Stop therapy

Immune criteria – if patient is well clinically, continue therapy

Baseline → Timepoint 1

Conventional criteria – Stop therapy

Immune criteria – if patient is well clinically, continue therapy
# Distinguishing pseudoprogression from true progression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pseudoprogression</th>
<th>True progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms</td>
<td>Should not deteriorate</td>
<td>May deteriorate</td>
</tr>
<tr>
<td>Imaging findings</td>
<td>Initial increase that is not confirmed on follow-up scan</td>
<td>Confirmed on two sequential scans</td>
</tr>
<tr>
<td>Biopsy</td>
<td>High immune infiltrate present in tumor</td>
<td>No immune infiltrate increase; primarily cancer cells</td>
</tr>
<tr>
<td>Time to progression</td>
<td>Varies</td>
<td>Varies</td>
</tr>
</tbody>
</table>
Panel recommendations for response evaluation

• When **pseudoprogression** is suspected and treatment beyond progression is being considered, the patient should have stable or improved clinical condition, no severe laboratory abnormalities and be tolerating the treatment well with limited/mild side effects.

• For management of **isolated site(s) of progression** for a patient receiving immunotherapy, it is reasonable to consider local therapy for the isolated site(s) of progression as long as the patient has good performance status and it otherwise responding to the current treatment. However, there is no data that local treatment will improve clinical outcomes.
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Types of adverse events

- Adverse events
  - Not due to treatment
  - Treatment-related adverse events
    - Non-immune related adverse events
    - Immune-related adverse events (irAEs)
      - Can result from all ICIs
      - Can impact any organ system
Toxicity with immune checkpoint inhibitors

Kelly, Cancer 2018.
Kinetics of immune-related adverse events

- Can be days to months after therapy initiation
- Very early or very late AEs may warrant special concern
- May occur even after treatment is discontinued
- Important to identify patients who are currently OR previously on ICI treatment
General irAE management

Severe irAE

First-line treatment: Corticosteroids

Examples: Prednisone Methylprednisolone

Steroid-refractory irAEs:
Second-line immunosuppressives

Examples: Infliximab Vedolizumab IVIG Mycophenolate mofetil Tocilizumab Etanercept Adalimumab Tacrolimus Azathioprine
Endocrinopathies

• Many have non-specific and/or overlapping cancer-related symptoms (fatigue, headache, malaise)

• Usually late-onset

• Assumed to be long-lasting or chronic

• Include:
  • Primary or secondary **thyroid dysfunction**
  • Hypophysitis
  • **Secondary adrenal insufficiency** (primary AI is exceedingly rare)
  • **Type 1 diabetes mellitus** (rare but life threatening)
Distinguishing immunotherapy and chemotherapy toxicities

Example: Elevation in LFTs – taxane versus immune mediated?

Useful strategies:

• More frequent blood monitoring
• Dose hold and re-challenge
SITC’s Guidelines on irAEs

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,1 Hamzah Abu-Sbeih,2 Paolo Antonio Ascierto,3 Jill Bruorthy,4 Laura C Cappelli,5 Frank B Cortazar,6,7 David E Gerber,5 Lamya Hamad,9 Eric Hansen,10 Douglas B Johnson,11 Mario E Lacouture,12 Gregory A Masters,13 Jarushka Naidoo,1,14 Michele Nanni,10 Miguel-Angel Perales,12 Igor Puzanov,10 Bianca D Santomasso,15 Satish P Shanbhag,5,16 Rajeev Sharma,10 Dimitra Skondra,17 Jeffrey A Sosman,18 Michelle Turner,1 Marc S Ernstoff19
Practical Management Pearls for Immunotherapy for the Treatment of Breast Cancer
November 17, 2021, 11:30 a.m. – 12:30 p.m. ET

Case Studies in Immunotherapy for the Treatment of Urothelial Cancer
November 5, 2021, 5:30 – 6:30 p.m. ET

Learn more and register at:
https://www.sitcancer.org/CPG-webinars
Targets for Cancer Immunotherapy: A Deep Dive Seminar Series

Eight online seminars will address key questions in the field of cancer immunotherapy drug development

SEMINAR 7: T CELL FUNCTIONAL STATES
November 18, 2021, 4:30 – 6:30 p.m. ET

SEMINAR 8: T CELL SELECTION FOR ADOPTIVE CELL THERAPY
January 25, 2022, 11:30 a.m. – 1:30 p.m. ET

Learn more and register at: https://www.sitcancer.org/education/deepdive
A Focus on MSI-high/TMB-high Cancers

November 3, 2021, 5 – 9 p.m. ET

CME-, CPE-, CNE-, MOC-certified

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