Practical Management Pearls for Immunotherapy for the Treatment of Melanoma

December 7, 2023
1:00 p.m. – 2:00 p.m. EST
SITC Clinical Practice Guideline Webinar – Practical Management Pearls for Immunotherapy for the Treatment of Melanoma

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Co-Director, Cutaneous Malignancies, Cedars Sinai CANCER
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Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of melanoma, version 3.0

# Webinar Agenda

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<th>Topic</th>
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<tr>
<td>Welcome and Introductions</td>
<td>Omid Hamid, MD</td>
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<td>GI Effects: Colitis, Pancreatitis, Duodenitis</td>
<td>Charlotte Ariyan, MD, PhD</td>
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<td>Endocrine, Hypoadrenalism</td>
<td>Krista Rubin, MS, FNP-BC</td>
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<td>Neuromuscular AEs, Triple M Syndrome</td>
<td>Shaheer Khan, DO</td>
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<td>Q&amp;A Session and Round-table Discussion</td>
<td>All</td>
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<td>Closing Remarks</td>
<td>Omid Hamid, MD</td>
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How to Submit Questions

• Click the “Q&A” icon located on at the bottom of your Zoom control panel
• Type your question in the Q&A box, then click “Send”
• Questions will be answered in the Question & Answer session at the end of the webinar (as time permits)
Omid Hamid, MD, has a financial interest/relationship or affiliation in the form of:

**Contracted Research For Institution:**
Arcus; Aduro; Akeso; Amgen; Bioatla; BMS; CytomX; Exelixis; Roche Genentech; GSK; Immunocore; Idera; Incyte; Ivance; Merck; Moderna; Merck-Serono; NextCure; Novartis; Pfizer; Sanofi Regeneron; Seagen; Taiga; Torque; Zelluna

**Speakers Bureau participant with:**
BMS; Novartis; Pfizer; Sanofi Regeneron

**Advisory Board For:**
Aduro; Alkermeres; Akeso; Amgen; Beigene; Bioatla; BMS; Roche Genentech; Gigagen; GSK; Immunocore; Idera; Incyte; Janssen; Merck; NextCure; Novartis; Partner Therapeutics; Pfizer; Sanofi Regeneron; Seagen; Tempus; Zelluna

Omid Hamid, MD, does intend to discuss either non-FDA-approved or investigational use for the following products/devices: pembrolizumab as adjuvant therapy in high-risk stage II melanoma; various combination strategies with checkpoint inhibitors and vaccine-based approaches/targeted agents.
Timeline of Select FDA Approvals of ICIs

2011: Ipilimumab
Melanoma

2014: Nivolumab, Pembrolizumab
Melanoma

2015: Nivolumab ± Ipilimumab
Melanoma, NSCLC, RCC
Pembrolizumab
NSCLC

2017: Atezolizumab
Merkel Cell
Durvalumab
Bladder
Nivolumab
CRC, HCC, Bladder
Pembrolizumab
Gastric, Hodgkin
Lymphoma, MSI-H/dMMR

2019: Atezolizumab
SLC
Avelumab
RCC
Pembrolizumab
Esophageal, RCC, SCLC

2021: Cemiplimab
Basal Cell Carcinoma, NSCLC
Dostarlimab
dMMR, Endometrial
Nivolumab
Gastric
Pembrolizumab
Breast, Cervical, Endometrial, Gastric

2018: Cemiplimab
Cutaneous SCC
Durvalumab
NSCLC
Nivolumab ± Ipilimumab
CRC, RCC, SCLC
Pembrolizumab
Cervical, HCC, Merkel Cell, PMBCL

2020: Avelumab
Bladder, NSCLC
Nivolumab
CRC, HCC, Melanoma
Durvalumab
SCLC
Nivolumab + Ipilimumab
HCC, Mesothelioma, NSCLC
Pembrolizumab
Bladder, CRC, Cutaneous SCC, TMB-H

2022: Atezolizumab
ASPS
Cemiplimab
NSCLC
Durvalumab ± Tremelimumab
Biliary Track, HCC, NSCLC
Nivolumab + Relatlimab
Melanoma

ICI use in cancers is increasing significantly; and is dramatically altering death rates (in some cancers)
Cross-antigen recognition
Kinetics of main irAEs.

Management Guidelines

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up


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

irAEs Result from Increased or Excessive Immune Activity, but the Immunomodulatory Cause May Vary

T-cells reacting to antigens in healthy tissue
- Myocarditis
- Vitiligo

Cytokine-mediated
- Colitis
- Arthritis
- Skin: psoriasis, eczema

Antibody-mediated
- Thyroiditis
- Hemolytic anemia
- Skin – Bullous pemphigoid
- Neurologic (myasthenia gravis, transverse myelitis, autoimmune encephalitis

Expression of target (e.g., CTLA-4) in normal tissue
- Pituitary toxicity (Hypophysitis)

Immunomodulatory Agents to Manage irAEs

• Steroids (prednisone, methylprednisolone): nonspecific anti-inflammatory

• Mycophenolate: relatively selective inhibition of T-cells and B-cells (blocks inosine monophosphate dehydrogenase to prevent purine production)

• Biologic agents
  • Abatacept: targets CTLA-4 (T-cells)
  • Rituximab: targets CD20 (B-cells)
  • Infliximab: targets TNF-α
  • Tocilizumab: targets IL-6
  • Vedolizumab: α4β7 integrin inhibitor

Schneider. JCO. 2021;39:4073. Mycophenolate mofetil PI. Abatacept PI. Rituximab PI. Infliximab PI. Tocilizumab PI. Vedolizumab PI.
Our tools to treat toxicity are very crude?

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<th>Lymphocyte depletion</th>
<th>Antibody modulation</th>
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<td><strong>T cell depletion</strong></td>
<td>IVIG</td>
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<tr>
<td>anti-thymocyte globulin</td>
<td>Plasmapheresis / plasma exchange</td>
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<tr>
<td><strong>B cell depletion</strong></td>
<td>Anti-CD20: rituximab</td>
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<td>anti-CD52: alemtuzumab</td>
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<th>Inhibition of lymphocyte proliferation</th>
<th>Cytokine Modulation</th>
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<td><strong>Inhibit IL-2 transcription</strong></td>
<td>Cytokine inhibitors</td>
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<tr>
<td>Calcineurin inhibitors: tacrolimus, cyclosporine</td>
<td>anti-TNFα: infliximab</td>
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<td><strong>Inhibit lymphocyte DNA/RNA synthesis</strong></td>
<td>anti-IL-6R: tocilizumab</td>
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<td>Methotrexate, Azathioprine</td>
<td>anti-IL-4/IL-13: dupilumab</td>
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<td><strong>Modulation of pro- or anti-inflammatory cytokines</strong></td>
<td>anti-IL-12/IL-23: ustekinumab</td>
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<th>Inhibition of T cell trafficking to the gut</th>
<th>Inhibition of T cell activation</th>
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<td>Vedolizumab</td>
<td>CTLA-4 fusion protein: abatacept</td>
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Blum, Rouhani, Sullivan. *Immunological Reviews* 2023
LETTER

Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy

Elisabeth Perez-Ruiz, Luna Mújica, Maite Álvarez, Maria Carmen Ochoa, Virginia Belso, Carlos de Andrea, Maria Esperanza Rodríguez-Ruiz, Jose Luis Perez-Gracia, Ivan Marquez-Rodas, Casilda Llacca, Martina Alvarez, Vanessa de Laque, Carmen Molina, Alvaro Teijeira, Pedro Berraondo et al.
A Phase II Study of the Interleukin-6 Receptor Blocking Antibody Sarilumab in Combination with Ipilimumab, Nivolumab and Relatlimab in Patients with Unresectable Stage III or Stage IV Melanoma

Abbreviations: C = cycle, D= day; FU = follow-up; Ipi = ipilimumab; Nivo = nivolumab; PD = progressive disease.

Induction cycle: 8 weeks
- Ipilimumab at 1 mg/kg D1 IV
- Nivolumab 480 mg/Relatlimab 160 mg D1, D29
- Sarilumab 150 mg SC D1, 15, 29, 43

Maintenance cycle 1-2: 8 weeks
- Ipilimumab at 1 mg/kg D1 IV
- Nivolumab 480 mg/Relatlimab 160 mg D1, D29
- Sarilumab 150 mg SC D1, 15, 29, 43

Maintenance cycles 3+: Every 8 weeks to 2 years
- Ipilimumab at 1 mg/kg D1 IV
- Nivolumab 480 mg/Relatlimab 160 mg D1, D29

FU Visit 1
- 30 ± 7 Days after EOT

FU Visit 2
- 90 ± 7 Days after FU Visit 1

Survival FU Visit 3
- 3 months ± 14 days after FU 2
Management:
Increase hydration
Avoid Caffeine/Smoking
Biotene, Xylimelts, sugar-free gum
Pilocarpine
Topical fluoride
Very severe – consider steroids/hold ICI

Does irAE treatment mitigate benefit?

Clinical Response Was Not Affected by Use of Corticosteroids in Phase II Trials

Steroids to treat ipilimumab toxicity doesn’t seem to be associated with less benefit...

Amin et al. ASCO 2009

Lorigan et al. ESMO 2010

Baurain et al. ASCO 2012
# Key Takeaways: Impact on Practice

Education leads to Identification and Appropriate Therapies

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<th>Awareness is the key</th>
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<td>Guidelines</td>
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<td>Early ID, Slow tapers</td>
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<td>DDx: irAE</td>
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<td>Look for them as they may travel in bunches</td>
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<td>Educate your colleagues</td>
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