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Immunotherapy in Melanoma: Use in Patients with Autoimmune Diseases

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Objectives

- Review the current place in practice for immunotherapy in melanoma
- Discuss the use of immunotherapy in patients with autoimmune conditions

Systemic Melanoma Treatment

- Adjuvant therapy
  - Interferon α-2b or peginterferon α-2b
  - Ipilimumab 10 mg/kg every 3 weeks x 4 followed by every 12 weeks for up to 3 years
  - Select patients: Talimogene laherparepvec (T-VEC)
- Metastatic disease
  - **Immunotherapy** – Aldesleukin (IL-2), ipilimumab, pembrolizumab, nivolumab
  - **BRAF-pathway targeted therapy** – vemurafenib, cobimetinib, dabrafenib, trametinib,
  - **Chemotherapy** – Dacarbazine, temozolomide, paclitaxel, combination therapy

Talimogene Laherparepvec (T-VEC)

- Herpes simplex virus (HSV) type-1 derived oncolytic virus
  - Selectively replicates in tumor cells → Cell lysis
- Phase III trial with 436 melanoma patients with stage IIIB to IV injectable melanoma sites not amenable to surgical resection
  - Response seen in both injected and uninjected lesions
  - Greatest benefit in stage IIIB/IIIC

	T-VEC	GM-CSF	P-value
Durable Response Rate	16.3%	2.1%	<0.001
Overall Response Rate	26.4%	5.7%	Not available
Complete Response Rate	10.8%	<1%	<0.001
Overall survival	23.3 months	18.9 months	0.051

Andtbacka RH, et al. *J Clin Oncol.* 2015; 33:2780-8.

Systemic Therapy Options for Metastatic Melanoma

First-line Therapy

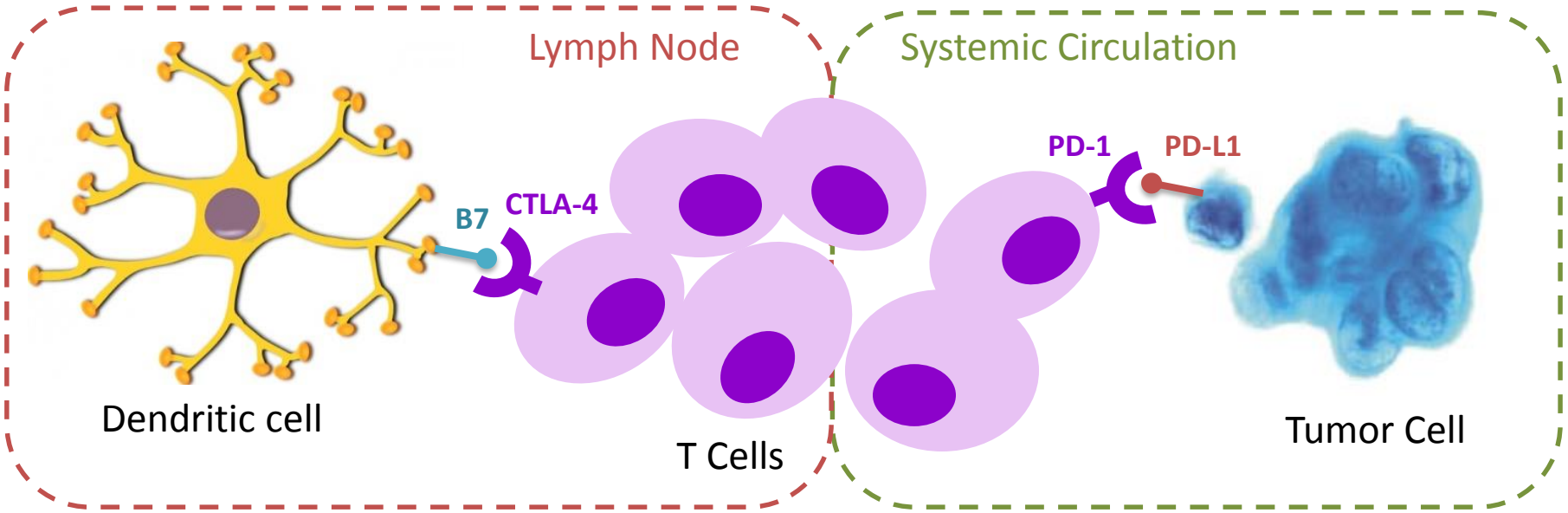
- **Nivolumab (category 1)**
- **Pembrolizumab (category 1)**
- Nivolumab + Ipilimumab
- For BRAF positive patients:
  - **Dabrafenib + Trametinib (category 1)**
  - **Vemurafenib + Cobimetinib (category 1)**
- Clinical trial

Second-line or Subsequent

- First-line options not already used or clinical trial
- Ipilimumab
- Dacarbazine or temozolomide
- High-dose IL-2
- Biochemotherapy
- Cytotoxic chemotherapy
- Imatinib for C-KIT mutated tumors

(Source: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Melanoma V.1.2017 © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed 04/18/2017.)

CTLA-4 and PD-1 Pathways



- Ipilimumab: inhibits CTLA-4 on the T-cells
- Pembrolizumab and Nivolumab inhibit PD-1 on the T-cells, preventing binding to PD-L1 on the tumor cells
- Ultimately, prevents immune system downregulation

Comparison of Anti-PD-1 Agents

	Pembrolizumab	Nivolumab
Initial FDA Approval Date	September 4, 2014	December 22, 2014
Type of Antibody	Humanized, IgG4 kappa immunoglobulin	Human, IgG4 kappa immunoglobulin
Approved Dosing (**single agent**)	**2 mg/kg** over 30 minutes every 3 weeks	240 mg IV over 60 minutes every 2 weeks
Approved indication in unresectable or metastatic melanoma	**Single agent** in patients with unresectable or metastatic melanoma	**Single agent or in combination with ipilimumab** in patients with unresectable or metastatic melanoma

Pembrolizumab and nivolumab package inserts 2017

All Grade Autoimmune Toxicities

Toxicity	Clinical Effects	Ipilimumab 3 mg/kg	PD-1 inhibitors	Time Frame
Skin	Rash, vitiligo, pruritus	47-68%	13-26%	2-3 weeks
Gastrointestinal	Diarrhea, colitis	31-46%	14-19%	6-7 weeks
Liver	Elevated enzymes, bilirubin, hepatitis	3-9%	1-4%	6-7 weeks
Endocrine	Hypophysitis, hypothyroidism	4-6%	3-10%	After 9 weeks

- Black box warning for autoimmune effects, however neither ipilimumab, pembrolizumab or nivolumab lists any specific contraindications.

Larkin J, et al. *N Engl J Med*. 2015;373:23-34.
Robert C, et al. *N Engl J Med*. 2015;372:2521-2532.
Weber JS, et al. *J Clin Oncol.* 2012; 30:2691-7.

Case Presentation: DC

- DC is a 51-year-old male with rheumatoid arthritis who previously received certolizumab and now on prednisone 5 mg daily.
- He presents with newly diagnosed stage IV melanoma involving the liver.
- His tumor is BRAF wild-type (WT).

- **Can we use a checkpoint inhibitor for DC's metastatic melanoma?**

Autoimmune Disorders and Cancer

- More than 80 distinct autoimmune disorders
  - Localized to specific organ systems vs. systemic
  - 3-8% of the US population estimated to have an autoimmune disorder
- Unclear whether the process of an autoimmune disease and/or the therapies can increase the risk of cancer
  - Chronic inflammation
  - Chronic immunosuppression

Donia M, et al. *Semin Immunopathol*. 2017;39:333-337.

Ipilimumab in Autoimmune Diseases

- Retrospective review of 30 patients with advanced melanoma and pre-existing autoimmune disorders treated with ipilimumab
  - Rheumatoid arthritis (n=6)
  - Psoriasis (n=5)
  - Inflammatory bowel disease, lupus, multiple sclerosis or thyroiditis (n=2 for each) and other (n=7)
- 43% were receiving autoimmune therapy concurrently
- 27% had autoimmune exacerbations necessitating steroid therapy
- 50% had no autoimmune flare or immune-related adverse events
- Overall response = 20% (1 patient with durable CR)

Johnson, et al. *JAMA Oncol*. 2016;2(2):234-240.

Anti-PD-1 Therapy in Autoimmune Diseases

- Retrospective trial of 52 melanoma patients with pre-existing autoimmune disorders treated with PD-1 inhibitors
  - Response rate = 33%
  - Flare requiring immunosuppression = 38%
    - Rheumatoid arthritis, polymyalgia rheumatica, Sjogren's syndrome, psoriasis, and immune thrombocytopenic purpura
  - No flare was seen in patients with gastrointestinal (n=6) or neurological (n=5) disorders
  - Discontinuation due to flare = 2 patients

Menzies AM, et al. *Ann Oncol*. 2017; 28:368-76.

Patient Case: DC

- PD-1 therapy is indicated for first-line therapy for metastatic melanoma
- DC's RA is well controlled
- Would consider single agent pembrolizumab or nivolumab with close monitoring

Conclusions

- Immunotherapy has revolutionized the treatment of melanoma, especially in the more advanced settings.
- Immune related adverse events are unique to this class of agents and require early recognition and treatment
- Evolving retrospective data has shown the safety of using certain immunotherapies in select patients with autoimmune disease, though close monitoring is required

Thank you for participating in the ICLIO e-Course. Presentation slides and archived recording will be available at accc-iclio.org.

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