SITC 2016

NATIONAL HARBOR, MD
NOVEMBER 9–13, 2016

Society for Immunotherapy of Cancer

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Immunotherapy Agents Currently Approved for the Treatment of Cancer

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Disclosures

Kristen Kreamer has served on the Speakers' Bureau for Merck and Bristol-Myers, and on Advisory Boards for Ariad and Astra-Zeneca

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DISCLAIMER

- This presentation is accurate as of noon on Saturday November 12.
- Immunotherapy drugs which have been FDA approved since that time are not included in this presentation.

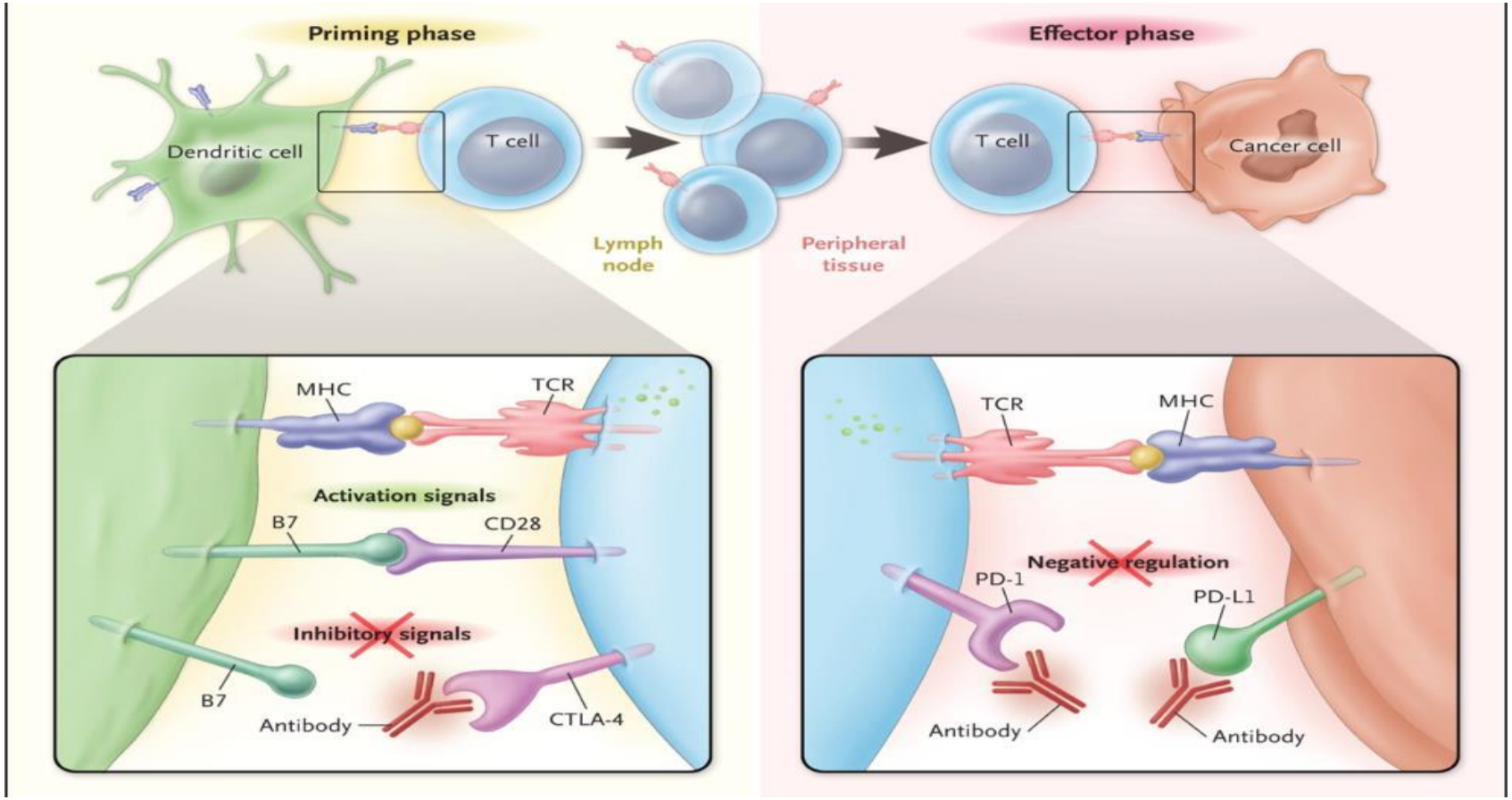
Immunotherapy Agents for Cancer
A new paradigm

- **Ipilumumab**
  - Melanoma 2011
- **Nivolumab**
  - Melanoma - 2014
  - NSCLC - 2015
  - Renal cell - 2015
  - Hodgkin Disease – 2016
  - HNSCC - 2016
- **Pembrolizumab**
  - Melanoma - 2014
  - NSCLC - 2015
  - HNSCC - 2016
- **Atezolizumab**
  - Urothelial - 2015
  - NSCLC - 2016

Checkpoint Inhibitors

- Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
  - Functions in priming phase of the immune response
  - Binds to B7 on the dendritic cell – inhibits signaling
- Programmed Death 1 (PD-1) on T cell
- Programmed Death Ligand -1 (PDL-1) on tumor cell
  - PD-1 binds to PDL-1
  - Downregulates the immune response

CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment



Ribas A. N Engl J Med. 2012;366:2517-2519.

Melanoma

- Logical first candidate for immunotherapy – melanoma known to be immune mediated disease
- High dose IL-2 -- approved 1998 to treat advanced melanoma
- Interferon alpha (IFNa) – used alone or after surgery

Melanoma

Ipilumimab – CTLA-4 blocking antibody
Nivolumab, Pembrolizumab – PD-1 blocking antibody

- Ipilumimab monotherapy 2011
- First drug to extend survival in advanced melanoma (10.1 mos vs 6.4 mos)
- Approved as adjuvant therapy *2016*
  - Treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
- Nivolumab monotherapy 2014 - melanoma that did not respond to prior treatment
  - First line for advanced disease 2016
  - Flat dose 240 mg q 2 wks approved Sept 2016

Ipilimumab [package insert]. Bristol-Myers Squibb Co., Princeton, NJ.; 2016.
Nivolumab [package insert]. Bristol-Myers Squibb Co., Princeton, NJ.; 2016

Melanoma

Ipilumimab – CTLA-4 blocking antibody
Nivolumab, Pembrolizumab – PD-1 blocking antibody

- Pembrolizumab monotherapy 2014– melanoma that did not respond to prior treatment
  - First line for advanced disease 2015
- Nivolumab/Ipilumumab combination therapy
  - Previously treated patients with BRAF negative 2015
  - Regardless of mutational status 2016

Pembrolizumab [package insert]. Merck & Co., Inc. , Whitehouse Station, NJ.; 2016.

Melanoma

- Talimogene laherparepvec (T-Vec) Oncolytic virus therapy
- FDA approved 2015 – first approved oncolytic virus
- Local treatment of unresectable cutaneous, subcutaneous, nodal lesions recurrent after initial surgery
- Not shown to have effect on OS or on visceral mets
- Mechanism of action – genetically engineered Herpes simplex virus –
  - Preferentially targets tumor cells, replicates within them causing cells to produce GM-CSF – tumor cells burst, eliciting anti-tumor immune response
- Method of administration – direct injection into lesions that are visible, palpable or detectable by US

talimogene laherparepvec [package insert]. Amgen, Inc., Thousand Oaks, CA.; 2015

Non-small cell lung cancer (NSCLC) Nivolumab - 2015

Approved for squamous NSCLC – Spring 2015

Approved for non-squamous NSCLC - Fall 2015

Indication - metastatic NSCLC with progression on or after platinum-based chemotherapy.

Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy prior to receiving nivolumab.

EGFR – erlotinib, gilotrif , gefitinib ALK - crizotininb

FDA approval is regardless of PDL-1 status

Flat dose approved Sept 2016 – 240 mg fixed dose

Nivolumab [package insert]. Bristol-Myers Squibb Co., Princeton, NJ.; 2016

Non-small cell lung cancer (NSCLC) Pembrolizumab - 2015, 2016

- Indication –metastatic NSCLC whose tumors express PDL-1 (>/= 1%) with disease progression on or after platinum-containing chemotherapy
  - Had been approved in 2015 only for those expressing PDL-1 >/= 50%
- Pts with EGFR or ALK should have disease progression on FDA-approved therapy prior to receiving pembrolizumab
- October 2016 - Approved for first line treatment for PDL-1 expression >/= 50%
- Flat dose – 200 mg every three weeks

Pembrolizumab [package insert]. Merck & Co., Inc. , Whitehouse Station, NJ.; 2016.

Non-small cell lung cancer Atezolizumab 2016

- PDL-1 blocking antibody
- Indicated for treatment of patients with locally advanced or metastatic NSCLC whose disease progressed on or after platinum-based chemotherapy.
- Patients with EGFR or ALK should have disease progression on FDA-approved therapy prior to receiving atezolizumab
- Approved without regard to PDL-1 testing
- 1200 mg flat dose q 3 wks

Atezolizumab [package insert]. Genentech, Inc., San Francisco, CA.; 2016.

Renal Cell Carcinoma (RCC) Nivolumab 2015

- Like melanoma, renal cell cancer appears to be an immune-mediated cancer
- Nivolumab is indicated for the treatment of patients with advanced RCC who progress on or after one or two prior anti-angiogenic therapy regimens.
- Patients were randomized to nivolumab 3 mg/kg q 2 weeks or everolimus (mTOR inhibitor) 10 mg po daily.
- Confirmed Objective Response Rate 21.5% vs 3.9%
- Flat dose 240 mg q 2 weeks approved Fall 2016

Nivolumab [package insert]. Bristol-Myers Squibb Co., Princeton, NJ.; 2016

Classical Hodgkin Lymphoma (cHL)
Nivolumab 2016

- Indicated for the treatment of patients with cHL relapsed or progressed after autologous hematopoietic stem cell transplantation and post –transplantation brentuximab vedotin.
- Median age – 32
- Median number of prior regimens - 5
- Objective Response Rate – 65% (CR = 7% , PR = 58%)

Nivolumab [package insert]. Bristol-Myers Squibb Co., Princeton, NJ.; 2016

Head and neck squamous cell carcinoma (HNSCC) Pembrolizumab 2016

- Indication: second line therapy for patients with recurrent or metastatic HNSCC who have progressed on or after platinum-based chemotherapy.
- Accelerated approval based on Phase 1b KEYNOTE -012 presented ASCO 2016
  - Median response duration not reached
  - 85% responses lasted >/= 6 mos
  - 71% responses lasted >/=12 mos
  - Approved regardless of PDL-1 status

Pembrolizumab [package insert]. Merck & Co., Inc. , Whitehouse Station, NJ.; 2016.

Head and neck squamous cell carcinoma (HNSCC) Pembrolizumab 2016

- Approved flat dose 200 mg q 21 days until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression
- Full approval contingent upon confirmatory results from Phase III KEYNOTE -040 comparing pembrolizumab with methotrexate, docetaxel or cetuximab
- First FDA-approved agent for metastatic HNSCC in 10 years

Pembrolizumab [package insert]. Merck & Co., Inc. , Whitehouse Station, NJ.; 2016.

Head and neck squamous cell carcinoma (HNSCC) Nivolumab November 10, 2016

- Indication – pts with recurrent or metastatic HNSCC on or after platinum –based therapy
- Based on international randomized multi-center trial comparing nivolumab with investigator's choice chemotherapy
  - (cetuximab, methotrexate, or docetaxel)
- Median OS 7.5 mos. Nivolumab arm vs 5.1 mos. investigator choice chemo
- Regardless of PDL-1 status

Urothelial Carcinoma Atezolizumab 2016

- PDL-1 blocking antibody
- Indicated for treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - Have disease progression during or following platinum-containing chemotherapy, or
  - Have disease progression within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy
  - Approved regardless of PDL-1 status
- 1200 mg flat dose q 3 wks

Atezolizumab [package insert]. Genentech, Inc., San Francisco, CA.; 2016.

November 13, 2016 and beyond

- Need many more slides!!!!!!!!!!!!!!!