# The Rapid Development of Immunotherapy in Cancer Care

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## Disclosures

- Consultant to Merck (re: biosimilars)

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## After attending this discussion the participant will be able to:

- **Describe the rationale** for immunotherapy(s) in the treatment of cancer, with a focus on the immune checkpoint inhibitors.
- Outline **strategies to prevent, monitor and manage toxicities** associated with immunotherapy in cancer treatment.
  - Immune-related adverse events (irAE)
  - Toxicities beyond irAE
  - Patient and caregiver education regarding irAE
- Discuss **strategies that are being evaluated** to improve efficacy and toxicities of immunotherapy(s) in cancer treatment.

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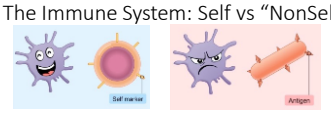
The Immune System: Self vs "NonSelf"




Immunity:

- The body's ability to resist disease
- Ability of the body to respond to **foreign substances** (microbes and noninfectious molecules)

Immune system:

- **Network** (cells, proteins, tissues, organs and molecules) that works together to defend the body against attacks by foreign invaders.

Immune response:

- Coordinated reaction of cells and molecules of the immune system

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Non-Specific

**Innate**

**Speed**
**Nonspecific**
**Limited duration**
**Lack immunologic memory**

**Inflammation is one of the first responses of innate immunity**

*Enhances adaptive immune response through presentation of antigens*

Antigen -Specific

**Adaptive**

Develops **slowly and provides a more specialized** defense against infections

**Two types of adaptive response:**

- **Humoral immunity: antibodies**
- **Cell mediated: T lymphocytes**

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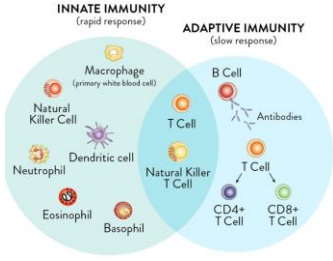
The Immune Response

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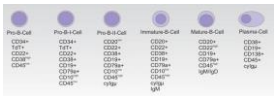
## B Lymphocytes: Effector Cell of Humoral Immunity

- B cells are **triggered by antigen** → clonal expansion → **plasma cells or memory cells**
  - Plasma cells → identical antibody with a distinct function
  - Memory cells (antigen-specific memory cells) (10%)



- Protective antibodies are produced during the first response, and larger amounts during subsequent response.
- **Antigen-specific antibody attaches to antigen and marks the antigen for destruction.**

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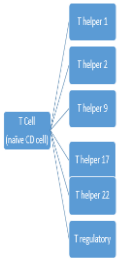
## T Lymphocytes

- Helper T cells (CD4+ T cells)
  - Help B lymphocytes produce antibodies
  - Help phagocytes to destroy pathogens
- Cytotoxic T lymphocytes (CTL, CD8+ T cells)
  - Kill cells with intracellular pathogens
- Regulatory T lymphocytes (Tregs)
  - Subset of CD4+ T cells
  - Prevent or limit immune response

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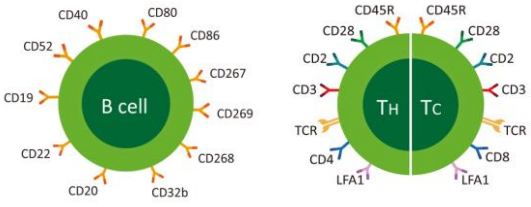
## Cell Surface Antigens on B cells and T cells

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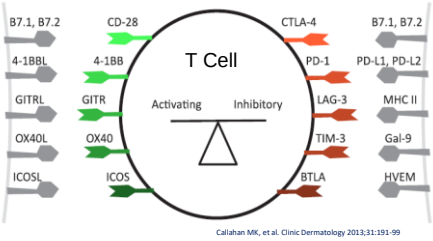
## T-cell Regulation




Callahan MK, et al. Clinic Dermatology 2013;31:191-99

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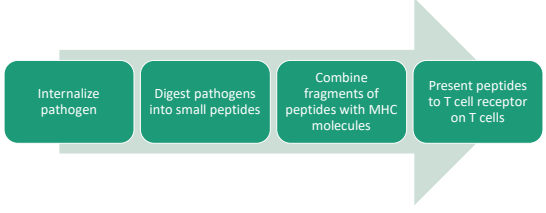
## Antigen Presenting Cells (APC)

- **Macrophage and dendritic cells** to stimulate adaptive immunity

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## Natural Killer Cells (NK Cell)

- A type of cytotoxic lymphocyte
- Primary function is to identify and eliminate cells that fail to produce self-MHC class molecules (e.g. tumors and cells that are infected by virus)
  - Strategy: receptors on NK cells that link to IgG coated cells (ADCC)
  - Strategy: recognized killer-activating receptors on cells

Crouse J, et al. NK cells regulating T cell responses: mechanisms and outcomes. 2015;36:49-58.

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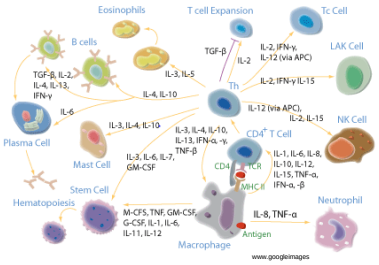
## Cytokines

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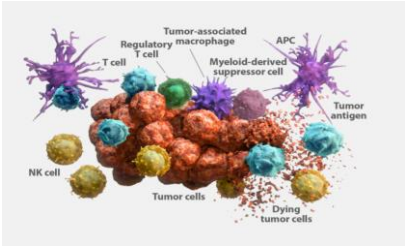
## Immunity and Cancer

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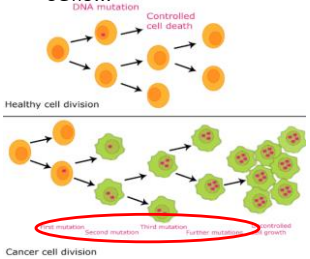
## Cancer cells are DIFFERENT than healthy cells…




**Neoantigens (new expressed in cancer cells, not in normal cells of origin)**

- Cancers harbor large number of mutations in diverse genes
- **Genetic instability** in cancers due to the mutations
- Passenger mutations
- Mutations result in mutated proteins

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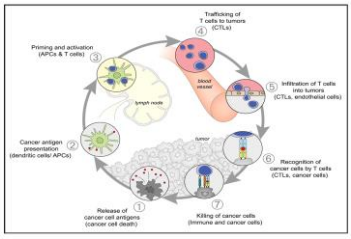
The Cancer-Immunity Cycle




Chen DS, Mellman I. Immunity 2013

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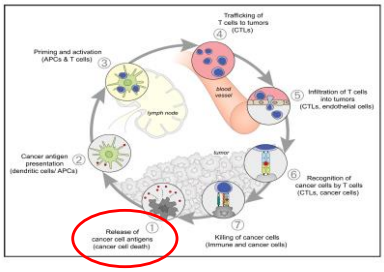
The Cancer-Immunity Cycle




Chen DS, Mellman I. Immunity 2013

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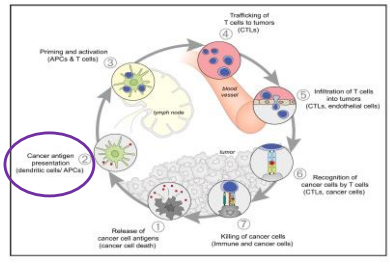
The Cancer-Immunity Cycle




Chen DS, Mellman I. Immunity 2013

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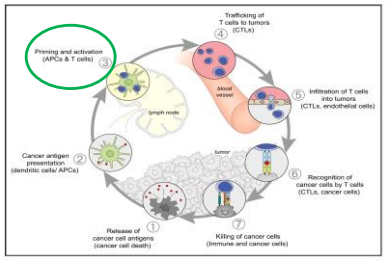
The Cancer-Immunity Cycle




Chen DS, Mellman I. Immunity 2013

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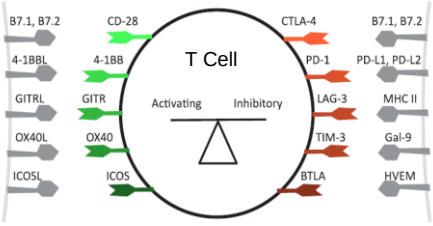
## T-cell Regulation




Callahan MK, et al. Clinic Dermatology 2013;31:191-99

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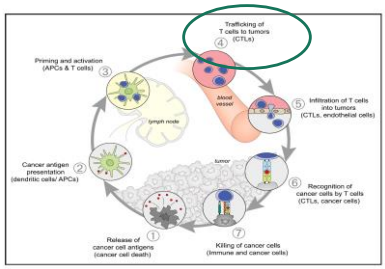
The Cancer-Immunity Cycle




Chen DS, Mellman I. Immunity 2013

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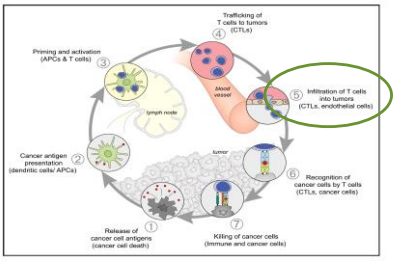
The Cancer-Immunity Cycle




Chen DS, Mellman I. Immunity 2013

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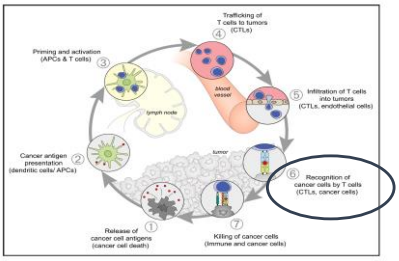
The Cancer-Immunity Cycle

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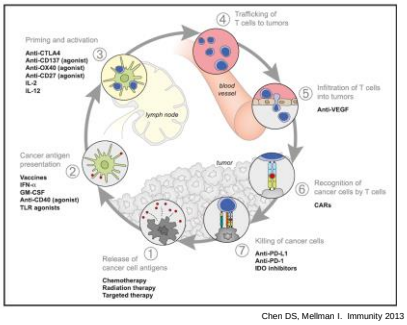


Chen DS, Mellman I. Immunity 2013

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## In the beginning….

www.googleimages

William Bradley Coley, MD (1862 – 1936)

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## Evolution of Cancer Immunotherapy: 2020

- Nonspecific immunostimulants (unknown mechanisms of action)
- Recombinant cytokines (IL-2, IFN)
- Humanized and human monoclonal antibodies (mAbs) to cell surface receptor proteins
- Vaccine strategies
- Immune checkpoint inhibitors (mAbs)
- Cellular therapies :TILs, CART cells
  TILs = tumor infiltrating lymphocytes
  CAR T cells = chimeric antigen receptor T cells

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| Example of Cytokines | Principal Cellular Source(s) | Biologic Effects |
|---|---|---|
| Type I:<br>Interleukin 2 (IL2) | T cells | T cell proliferation and differentiation into effector and memory cells.<br>Promotes regulatory T cell development, survival and function.<br>NK cell proliferation and activation. |
| Type II:<br>Interferon α (IFN) | Plasmacytoid DC, macrophages | Antiviral.<br>Increase class I MHC expression<br>NK cell activation |
| TNF Cytokines:<br>Tumor necrosis factor (TNF) | Macrophages<br>NK cells<br>T cells | Endothelial cells: activation (inflammation, coagulation)<br>Activation of neutrophils,<br>Hypothalamus: Fever<br>Muscle, fat: catabolism (cachexia) |
| IL-1 Family :<br>Interleukin-1α | Macrophages, DC, fibroblasts, endothelial cells, keratinocytes | Endothelial cells: activation (inflammation, coagulation)<br>Hypothalamus: Fever<br>Liver: synthesis of acute-phase proteins |
| Others:<br>Transforming growth factor β | T cells (Tregs), macrophages, other cell types | T cells: inhibition of proliferation and effector functions, differentiation of Th17 and Treg<br>B cells: inhibition of proliferation<br>Macrophages: inhibition of activation, stimulation of angiogenic factors<br>Fibroblasts: increased collagen synthesis |

Abbas AK. Basic Immunology: Function and Disorders of the Immune System. 2016

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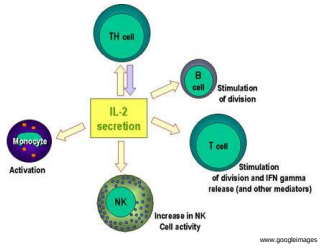
Early Strategies for Immunotherapy: Interleukin 2

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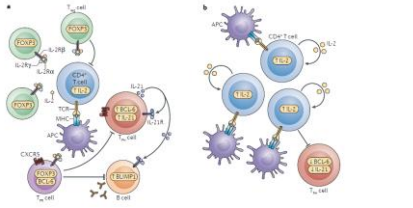
Interleukin2: Interactions with T cells



Spolski R, et al . Nature Rev Immunol 2018;18:648

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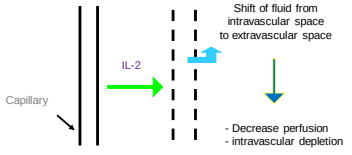
Aldesleukin (rIL2): Capillary Leak Syndrome

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## The Continuing Evolution of Cancer Immunotherapy

- Nonspecific immunostimulants (unknown mechanisms of action)
- Recombinant cytokines (IL-2, IFN)
- Humanized and human monoclonal antibodies (mAbs) to cell surface receptor proteins
- Vaccinations strategies
- Immune checkpoint inhibitors (mAbs)
- Cellular therapies :TILs, CAR T cells
  TILs = tumor infiltrating lymphocytes
  CAR T cells = chimeric antigen receptor T cells

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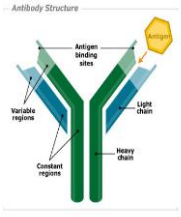
## Antibody

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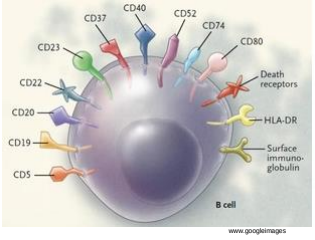
## Cell Surface Antigens on B Cell

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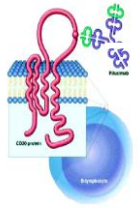
## Target: CD20

Transmembrane protein located on pre-B and mature B lymphocytes.
Not found on stem cells, pro-B cells.



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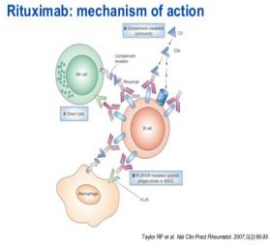
## Rituximab: Monoclonal Antibody Targeting CD20

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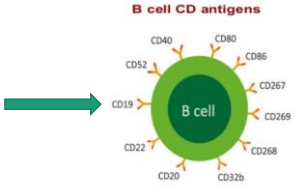
## CD19

- CD19 is broadly expressed across B cell malignances
  - Enhances B-cell receptor signaling and cell proliferation

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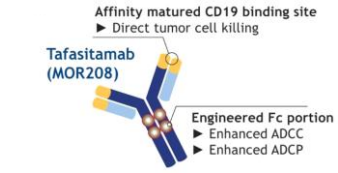
## Tafasitamab: Monoclonal Antibody Targeting CD19

- **Fc-enhanced,** humanized, anti-CD19 monoclonal antibody




Leukemia 2013;27:1595.

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## Tafasitamab: The L-MIND Clinical Trial

- Method:
  - Phase 2 multicenter, prospective, single-arm study (n=81)
  - Patients with relapsed or refractory DLBCL who were not candidates for HD and autoSCT
- Treatment:
  - Tafasitamab-cxix 12 mg/kg IV + lenalidomide 25 mg PO daily x 21 days every 28 days x 12 cycles → tafasitamab-cxix as monotherapy
- Results:
  - **ORR (in 71 patients): 55% (CR 37%, PR 18%)**
  - Median DOR: 21.7 months (range: 0, 24 months)

Salles G, et al. Lancet Oncol 2020

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## Tafasitamab-cxix: Monoclonal Antibody Targeting CD19

- Mechanism of action:
  - CD19-directed cytolytic antibody
- Indication:
  - Treatment for adults with relapsed or refractory diffuse large B-cell lymphoma no otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant
- Adverse effects (≥ 20%):
  - Neutropenia, anemia, thrombocytopenia
  - Diarrhea
  - Cough
  - Pyrexia
  - Peripheral edema

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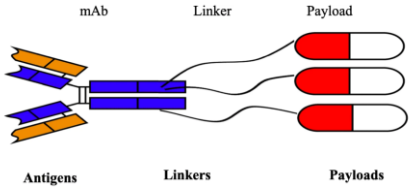
## The Evolution of the Monoclonal Antibody: Antibody-Drug Conjugates (ADC)




Yu B et al. *J Hematol Oncol.* 2019;12:94.

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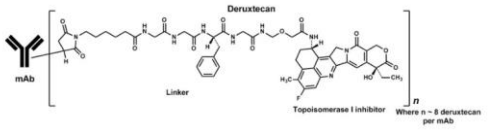
## Fam-trastuzumab deruxtecan-nxki




Package Insert. Daiichi Sankyo, Inc. accessed January 1, 2020

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## Fam-trastuzumab deruxtecan-nxki

**Description**

- HER2-directed antibody and topoisomerase inhibitor conjugate.
  - Humanized anti-HER IgG1 mAb
  - Deruxtecan (a topoisomerase inhibitor)
  - Tetrapetide-based cleavable linker

**Indication:**

- Treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

Package Insert. Daiichi Sankyo, Inc. accessed January 1, 2020

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## Enfortumab vedotin-ejfv

**Description:**

- Antibody drug conjugate including a monoclonal antibody targeting nectin-4 linked to MMAE
  - Fully human anti-Nectin-4 IgG1 kappa mAb (AGS-22C3)
  - MMAE
  - Protease-cleavable linker

**Indication:**

- Treatment of adults with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PDL-1 inhibitor, a platinum-containing chemotherapy.

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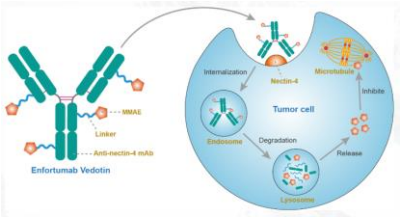
## Enfortumab vedotin-ejfv

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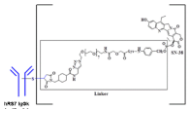
## Sacituzumab govitecan-hziy



**Description:**

- Trop-2 directed antibody and topoisomerase inhibitor conjugate.
  - Humanized mAB that binds to Trop-2 (trophoblast cell surface antigen)
  - Govitecan (a topoisomerase inhibitor (SN-38))
  - Hydrolysable linker (CL2A)

**Indication:**

- Treatment of adult patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease.

Trodelvy package Insert. Immunomedics, Inc . accessed July 1, 2020

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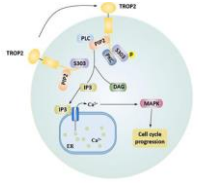
## Targeting Trop-2: Beyond TNBC




**Trop-2** is an ideal candidate for targeted therapeutics as it **a transmembrane protein with an extracellular domain overexpressed on a wide variety of tumors as well as its upregulated expression relative to normal cells.**

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## Sacituzumab govitecan-hziy: Phase 1/2 Clinical Trial

Methods:

- Multicenter trial of patient with **advanced epithelial cancers**

Treatment:

- **Single agent sacituzumab govitecan IV on Day 1 and 8 of each 21 days cycle**
  - **108 patients with TNBC received 10 mg/kg**

Efficacy reported in clinical trial for patients with metastatic TNBC:

- Complete response 2.8%
- ORR: 33.3 % (95% CI, 24.6-43.1)
- Clinical benefit rate: 45.4 % (95% CI, 35.8-55.2)
- Median DOR: 7.7 months (95% CI, 4.9-10.8)

Bardia A, et al. *N Engl J Med*. 2019:380(8):741-751.

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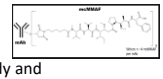
## Belantamab mafodotin-blmf



**Description:**

- **B-cell maturation antigen (BCMA)** directed antibody and mictrotubule inhibitor conjugate.
  - A humanized antagonistic anti BCMA antibody with afucosuylated Fc
  - Linker (protease-resistant maleimidocaproyl)
  - MMAF (microtubule inhibitor)

**Indication:**

- Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an antin-CD38 monoclonal antibody, a proteasome inhibitor, and an IMID.

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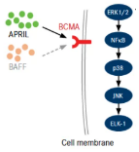
## B-Cell Mature Antigen (BCMA)




- Cell surface receptor of the TNF receptor superfamily that recognizes B cell activating factor (BAFF).

Cho SF, et al. Front Immunol 2018

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## Belantamab mafodotin (DREAMM-2)

- Methods:
  - **Open-label, two arm, phase II study**
  - Adults with relapsed or refractory myeloma with disease progression after three or more lines of therapy and who were refractory to IMIDS and proteasome inhibitors and refractory or intolerant to and anti CD38 monoclonal antibody
  - Centrally assigned 1:1 (stratified )
- Treatment:
  - Belantamab mafodotin 2.5 mg/kg IV infusion every 3 weeks
  - Belantamab mafodotin 3.4 mg/kg IV infusion every 3 weeks
- Results:
  - ORR
    - N = 97 treated at 2.5 mg /kg dose: 31% ORR (97.5% CI 20.8 – 42.6)
    - N= 99 treated at 3.4 mg /kg dose: 34% ORR (97.5% CI 23.9 – 44)
  - Safety:
    - Keratopathy
    - Thrombocytopenia, anemia

Lonial S, et al. Lancet 2020; 21:207

50

## Case Scenario

Ms H is a 64 year old woman with metastatic non-small cell lung cancer (adenocarcinoma). She was initially treated with the combination of carboplatin, pemetrexed and pembrolizumab with good response.

- She now presents with increased disease on imaging, and is considering a clinical trial with an **investigational monoclonal antibody.**

Question: What additional information would you like to optimize treatment for Ms. H?

51

## Vaccines in Cancer

- Tumor Cell Vaccines
- Antigen Vaccines
- Dendritic Cell Vaccines
- Vector based vaccines

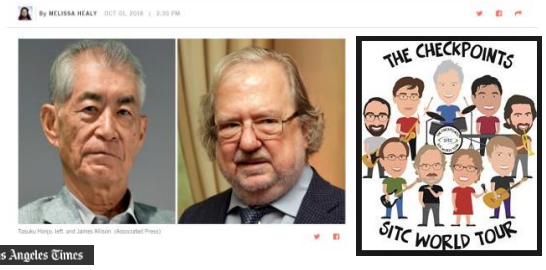
52

## Evolution of Cancer Immunotherapy

- Nonspecific immunostimulants (unknown mechanisms of action)
- Recombinant cytokines (IL-2, IFN)
- Humanized and human monoclonal antibodies (mAbs) to cell surface receptor proteins
- Vaccinations strategies
- Immune checkpoint inhibitors (mAbs)
- Cellular therapies :TILs, CAR T cells
  TILs = tumor infiltrating lymphocytes
  CAR T cells = chimeric antigen receptor T cells

53

James Allison and Tasuku Honjo win Nobel Prize for landmark cancer immunotherapy discoveries



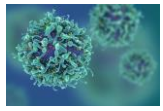
Los Angeles Times




54

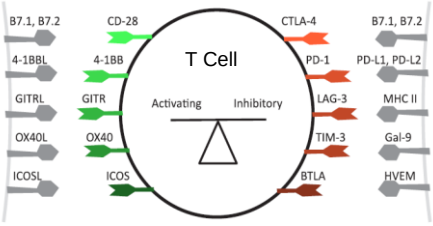
T Cell Regulation

- Mapped out the molecular mechanism of **T cell recognition, regulation and function**
- Blocking negative immune regulators (**checkpoints**) may give the human immune system the power to fight cancer



55

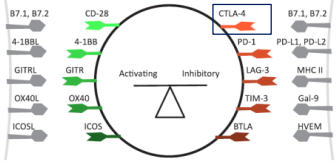
## T-cell Regulation




Callahan MK, et al. Clinic Dermatology 2013;31:191-99

56

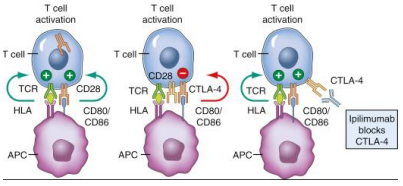
## T-cell Activation




Callahan MK, et al. Clinic Dermatology 2013;31:191-99

57

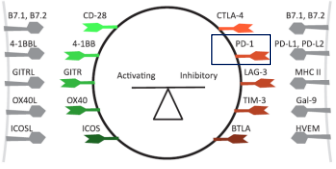
T-Cell Regulation




Guo Q, et al. Advances in Cancer Research 2019:143

58

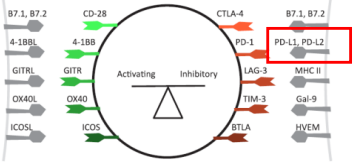
T-cell Regulation




Callahan MK, et al. Clinic Dermatology 2013;31:191-99

59

**Focus on T-cell Activation**




Callahan MK, et al. Clinic Dermatology 2013;31:191-99

60

Immune Checkpoint Inhibitors (ICI)

- **Cytotoxic T Lymphocyte Antigen 4 inhibition**:
  - Ipilimumab
- **PD-1 inhibition**:
  - Nivolumab
  - Pembrolizumab
  - Cemiplimab-rwlc
- **PD-L1 inhibition:**
  - Atezolizumab
  - Avelumab
  - Durvalumab

61

Question: What is the role of ICI in cancer?

Leading Sites of New Cancer Cases and Deaths – 2020 Estimates

Estimated New Cases

| Male | | | Female | | |
|---|---|---|---|---|---|
| Prostate | 191,930 | 21% | Breast | 276,480 | 30% |
| Lung & bronchus | 116,300 | 13% | Lung & bronchus | 112,520 | 12% |
| Colon & rectum | 78,300 | 9% | Colon & rectum | 69,650 | 8% |
| Urinary bladder | 62,100 | 7% | Uterine corpus | 65,620 | 7% |
| Melanoma of the skin | 60,190 | 7% | Thyroid | 40,170 | 4% |
| Kidney & renal pelvis | 45,520 | 5% | Melanoma of the skin | 40,160 | 4% |
| Non-Hodgkin lymphoma | 42,380 | 5% | Non-Hodgkin lymphoma | 34,860 | 4% |
| Oral cavity & pharynx | 38,380 | 4% | Kidney & renal pelvis | 28,230 | 3% |
| Leukemia | 35,470 | 4% | Pancreas | 27,200 | 3% |
| Pancreas | 30,400 | 3% | Leukemia | 25,060 | 3% |
| **All sites** | **893,660** | | **All sites** | **912,930** | |

Cancer Facts & Figures 2020 (American Cancer Society)

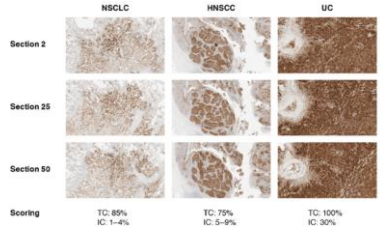
62

Question:
How do we identify patients **most likely to respond** to immune checkpoint inhibitor therapy?

www.googleimages

63

PD-1 and PD-L1 Expression




64

Tumor Mutational Burden (TMB): Role as a Biomarker in Cancer

Tumor Mutational Burden:

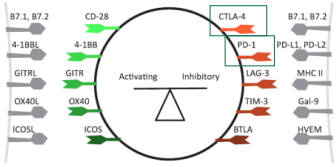
- Total number on nonsynonymous mutations in the coding regions of genes
- Measurement of the **quantity** of mutations carried by tumor cells
- Independent biomarker that maybe predictive of response to immune-directed therapy.
- Definition of "high" TMB used in some trials: ≥ 10 mutations per megabase


65

Question:
What is the **best strategy** to use ICI in therapy?

66

## Dual Checkpoint Blockade: Strategy to Optimize Response




Callahan MK, et al. Clinic Dermatology 2013;31:191-99

Reference: Pirschel C. Combination immunotherapy: the next frontier for oncology nursing. ONS Voice May 2020

67

## Dual Immune Checkpoint Inhibitors Renal Cell Cancer: Nivolumab + Ipilimumab

- Phase III:
  - nivolumab + ipilimumab vs. sunitinib in patients with advanced renal cell cancer
- Methods:
  - Individuals with advanced renal cell cancer, intermediate or high risk disease
  - **nivolumab** 3 mg/kg + **ipilimumab** 1 mg/kg IV q 3 wks x 4 weeks → **nivolumab** 3 mg/kg **q 2 wks**
  - Sunitinib 50 mg PO daily x 4 wk (6 week cycle)
- Results:

| Response | Nivolumab + Ipilimumab | Sunitinib |
|---|---|---|
| OS at 18 month | 75% | 60% |
| | 95% CI, 70 -78 | |
| ORR | 42% | 27% |
| | (p < 0.001) | |

Motzer RJ, et al. NEJM 2018;378:1277

68

## Renal Cell Cancer: Dual ICI

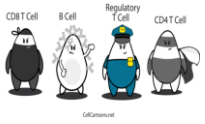
| Toxicity | Nivolumab + Ipilimumab | | Sunitinib | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| Fatigue | 37% | 4% | 49% | 9% |
| Pruritus | 28% | <1% | 9% | 0% |
| Diarrhea | 27% | 4% | 52% | 5% |
| Rash | 22% | 1% | 13% | 0% |
| Nausea | 20% | 1% | 38% | 1% |
| Increase lipase | 16% | 10% | 11% | 7% |
| Hypothyroidism | 16% | <1% | 25% | <1% |
| Decreased appetite | 14% | 1% | 25% | <1% |
| Asthenia | 13% | 1% | 17% | 2% |

Motzer RJ, et al. NEJM 2018;378:1277

69

Question:
What is the **role of combination therapy** with chemotherapy and immune checkpoint inhibitors?

- **Role of concurrent ICI and chemotherapy?**
- **Role of sequential therapy with ICI and chemotherapy?**




+


www.googleimages

70

Advanced, non-squamous NSCLC (KEYNOTE-021): carboplatin + pemetrexed + pembrolizumab

Methods:
- Randomized, open-label, phase II cohort of multicohort study (n=123)
- Pts stage IIIB or IV non-squamous NSCLC (chemotherapy naïve)
- Regimen:
  - Pembrolizumab 200 mg IV q 3 wk x 4 → 24 months or placebo
  - Carboplatin (AUC = 5) IV q 3 x 4
  - Pemetrexed 500 mg/m2 IV q 3 weeks → indefinite pemetrexed maintenance

Findings:
- Increase objective response to chemotherapy + pembrolizumab vs chemotherapy (estimated treatment difference of 26%)
- Incidence of grade 3 or worse treatment related adverse effects similar

Langer C, et al. Lancet Oncology 2016; 17: 1497

71

**Advanced Triple-Negative Breast Cancer**:
Atezolizumab + Nab-Paclitaxel

- Rationale:
  - Nanoparticle albumin-bound paclitaxel may enhance the anticancer activity of atezolizumab
- Methods:
  - Phase III trial
  - Individuals with untreated metastatic TNBC randomly* assigned (1:1)
    - Atezolizumab + nab-paclitaxel
    - Placebo + nab-paclitaxel

  * stratification factors included receipt of neoadjuvant/adjuvant taxane therapy, presence of liver metastases, PD-L1 expression at baseline (positive or negative)
- Results:
  - Primary endpoints: PFS and OS
  - PFS: combo 7.2 months vs single nab-paclitaxel 5.5 months
  - OS: combo 21.3 months vs single nab-paclitaxel 17.6 months
  - "Adverse events were consistent with the known safety profile of each agent."

Schmid P, et al. NEJM 2018; 379:2108-2121

72

## Durvalumab: Stage III NSCLC

- PACIFIC Trial: Phase III placebo controlled trials (n=709)
- Interim analysis
- Patient Population:
  - Individuals with locally advanced, unresectable stage III NSCLC
- Methods:
  - Patients randomly assigned 2:1 to durvalumab or placebo q 2 weeks for up to 12 months following chemoradiation (1 to 42 days) between 5/2014 – 5/2016
  - Primary endpoints: PFS and OS
  - Secondary endpoints: 12 month PFS, 18 month PFS, ORR, DOR, time to death or distant metastasis, safety
- Results:
  - Increased median PFS in treatment group
  - Increase in ORR in treatment group
  - Increase DOR in treatment group
  - Increase time to death in treatment group

*Antonia SJ, et al. NEJM 2017;377(20):1919-1929*

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## Durvalumab: Stage III NSCLC

| | Durvalumab (N=476) | Placebo (N=237) |
|---|---|---|
| Median PFS | 16.8 mo | 5.6 mo |
| | HR for disease progression of death 0.52<br>95% CI, 0.42 – 0.65; p< 0.001 | |
| 12 month PFS | 55.9% | 35.3% |
| 18 month PFS | 44.2% | 27.0% |
| Median TT death / mets dz | 23.2 mo | 14.6 mo |
| | HR 0.52; 95% CI, 0.39 – 0.69; p< 0.001 | |
| Disease Progression | 16.5% | 27.7% |

Data cutoff point for interim analysis was feb 13, 2017

Antonia SJ, et al. NEJM 2017;377(20):1919-1929

74

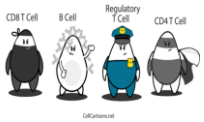
## Durvalumab: Stage III NSCLC

| Variable | Durvalumab (N=443) | Placebo (N=213) | Treatment Effect |
|---|---|---|---|
| ORR | 28.4% | 16% | 1.78 |
| | | (95% CI, p <0.001) | |
| Median DOR | NR | 13.8 months | 0.43 |
| Objective Response Rate at data cutoff point (calculated Kaplan Meier method) | | | |
| RR at 12 mo | 72.8% | 56.1% | |
| RR at 18 mo | 72.8% | 46.8% | |

Antonia SJ, et al. NEJM 2017;377(20):1919-1929

75

Question:
What is the **role of combination therapy** with targeted therapy and immune checkpoint inhibitors?

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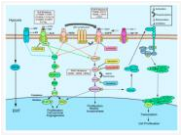


Schrank z. et al. Cancer. 2018;10:224.

76

Advanced Renal Cell Carcinoma:
Pembrolizumab + Axitinib

- Methods:
  - Open-label, Phase III trials
  - Individuals with previously untreated advanced **clear cell renal cell** carcinoma
  - Randomized to:
    - Pembrolizumab 200 mg (flat dose) IV q 3 weeks + axitinib 5 mg PO BID
    - Sunitinib 50 mg PO daily (4 weeks of each 6 week cycle)
- Endpoints:
  - Primary: OS, PFS (in the intention to treat population)
  - Secondary: ORR
- Reported results form the protocol-specified first interim analysis

Rini BI, et al. NEJM 2019:380:1116-1127.

77

Advanced Clear Cell Renal Cell Carcinoma: Survival
Pembrolizumab + Axitinib vs Sunitinib

| Outcome | Pembrolizumab + Axitinib (N=432) | Sunitinib (N=429) |
|---|---|---|
| Objective response rate (95% CI) | 59 % (54.5 to 63.9) | 35.7 (31.1 to 40.4 |
| **Best overall response** | | |
| Complete response | 5.8 % | 1.9% |
| Partial response | 53.5% | 33.8% |
| Stable disease | 24.5% | 39.4% |
| Median time to response (range) | 2.8 months (1.5 to 16.6 months) | 2.9 months (2.1 to 15.1 months) |
| Median duration of response (range) | Not reached at time of publication (1.4+ to 18.2+) | 15.2 months (1.1+ to 15.4+) |

Rini BI, et al. NEJM 2019:380:1116-1127.

78

## Advanced Clear Renal Cell Carcinoma: **Toxicities**
## Pembrolizumab + Axitinib vs Sunitinib

- Adverse effect of any cause occurred in 98.4% of patients who received pembrolizumab and axitinib.
  - AE ≥ grade 3 occurred in 75.8 %
  - AE that contributed to discontinuation of either drug was 30.5%
  - AE that contributed to discontinuation of both drugs was 10.7%
- Most common toxicities (≥ 20%)
  - Diarrhea, fatigue/asthenia, hypertension, hypothyroidism, decrease appetite, hepatotoxicity, palmar-plantar erythrodysesthesia, nausea, stomatitis, dysphonia, rash, cough and constipation.
- Hepatotoxicity
  - Grade 3 or 4 occurred in 20% of patients
  - Permanent discontinuation of pembrolizumab OR Axitinib 13%

Rini BI, et al. NEJM 2019:380:1116-1127.

79

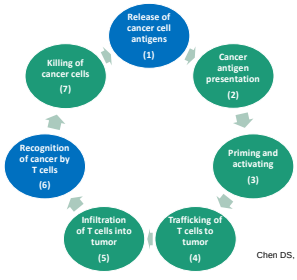
## Question:

- Role of immune checkpoint inhibition and radiation therapy?

Vanpouille-Box C, et al. Clinic Cancer Res 2018; 24;259.

80

## Rationale: Radiation Therapy + ICI




Chen DS, Mellman I. Immunity 2013

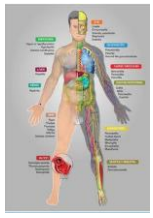
81

Question:
How safe are immune checkpoint inhibitors?


82

Impact of Modification of T cell Activation:
Immune-Related Adverse Events (irAE)

- Mechanism:
  - infiltration of "normal" tissue by activated T cells responsible for autoimmunity
  - downstream activation of immune response(?)
- Tissues at risk:
  - Skin
  - Gastrointestinal tract
  - Endocrine glands
  - Lung
  - Nervous system
  - Liver
  - Kidney
  - Hematological cells
  - Musculo-articular system
  - Heart
  - Eyes



**John A Thompson, MD:**
***"immune related toxicity can attack virtually every organ system"***

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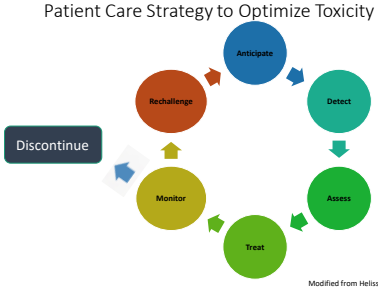
Immune Checkpoint Inhibitors:
Patient Care Strategy to Optimize Toxicity Management




Modified from Helissey C, et al. J Geriatric Oncol (2016); 7:325

84

Core Concept in Management of ICI Toxicities: Anticipate

The Bottom Line:

- **high level of suspicion** that **new symptoms** are treatment related

Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guidelines. J Clin Oncol 2018; 36:1

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Anticipating and recognizing unexpected obstacles…

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ASCO Guidelines for Immune Checkpoint Inhibitor Therapy

The Bottom Line:

- **high level of suspicion** that **new symptoms** are treatment related
- **patient and family caregivers** should receive timely and up-to-date education about immunotherapies

Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guidelines. J Clin Oncol 2018; 36:1

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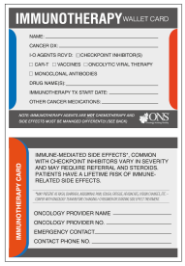
## Patient and Caregiver Education: Immunotherapy

**Mechanism of action:**
- Immunotherapy vs. chemotherapy

**Adverse Effects:**
- Presentation(s)
- Frequency
- Timing
- Self-management ↔ reporting
- Communication

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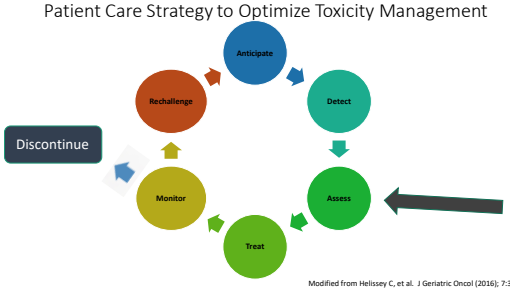
## Immune Checkpoint Inhibitors: Patient Care Strategy to Optimize Toxicity Management




Modified from Helissey C, et al. J Geriatric Oncol (2016); 7:325

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## ASCO Guidelines for Immune Checkpoint Inhibitor Therapy

**The Bottom Line for ICI Immune-Related Adverse Events :**

- **Grade 1 toxicities**: continue therapy
  - Except some neurologic, hematologic and cardiac toxicities
- **Grade 2 toxicities**:
  - Consider resuming therapies when toxicities become grade 1 or less
  - **Corticosteroids**
- **Grade 3 toxicities:**
  - **High dose corticosteroids → tapering within 4 – 6 weeks**
  - If needed → infliximab
- **Grade 4 toxicities:**
  - May warrant **permanent discontinuation** of immune checkpoint inhibitor
  - **Exception of endocrinopathies** that have been controlled by hormone replacement

Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guidelines. J Clin Oncol 2018; 36:1

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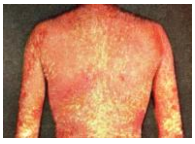
## Skin Toxicities: “more than a rash”

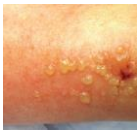
91

## Immune Checkpoint Inhibitors: irAE Skin Toxicities

Inflammatory Dermatitis



Bullous Dermatoses



92

## Grading of Skin irAE

**Rash/Inflammation**

| Grade | Description |
|---|---|
| 1 | Symptoms do not affect QOL or controlled with topical regimen and/or antipruritic |
| 2 | Inflammatory reaction that affects QOL and requires intervention based on diagnosis |
| 3 | As grade 2 but failure to respond to indicated interventions |
| 4 | All severe rashes unmanageable with prior interventions or intolerable |

**Bullous Dermatitis**

| Grade | Description |
|---|---|
| 1 | Asymptomatic; blisters covering < 10% BSA and no associated erythema |
| 2 | Blistering that effects QOL and requires intervention based on diagnosis not meeting criteria for > grade 2; Blisters covering 10% - 30% BSA |
| 3 | Skin sloughing covering > 30 % BSA with associated pain and limiting self-care ADL |
| 4 | Blisters covering > 30% BSA associated with fluid or electrolyte abnormalities |

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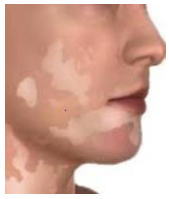
## Immune Checkpoint Inhibitors: irAE

SKIN

- Vitiligo:
  - patches of skin losing their pigment
  - due to destruction of melanocytes
  - Vitiligo appears to be more frequent in individuals with **melanoma**



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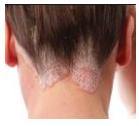
## Immune Checkpoint Inhibitors: irAE

SKIN

- Psoriasis
  - Autoimmune disease characterized by patches of abnormal skin
  - Skin patches are typically red, itchy and scaly
  - Types: plaque, inverse, pustular and erythrodermic



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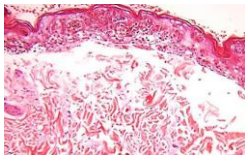
## Immune Checkpoint Inhibitors: irAE
## Skin Toxicities

Severe Cutaneous Adverse Reactions (SCARS)



Epidermal Necrosis

- Definition: severe changes in either **structure or functions of skin**, the appendages or the **mucous membranes** due to a drug.
- Includes:
  - Stevens Johnson Syndrome (SJS)
  - Toxic epidermal necrolysis (TEN)
  - Drug reaction with eosinophilia and systemic symptoms (DRESS)

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## Medications Strategies for irAE of Skin

| Maculopapular Rash | Pruritus | Bullous Dermatitis | SJS | TEN |
|---|---|---|---|---|
| • Topical steroids<br>• PO antihistamine<br>• Steroids | • Topical steroids<br>• PO antihistamines<br>• Steroids<br>• Symptomatic treatment itching | • Topical steroids (grade 1)<br>• High dose steroids | • Dermatology consult<br>• Acute care (e.g., inpatient)<br>• High dose steroids | |

Treatment of skin irAE may include holding the immune checkpoint inhibitor → discontinuation of treatment.

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## Assessment of Skin Toxicity: Serial Photography

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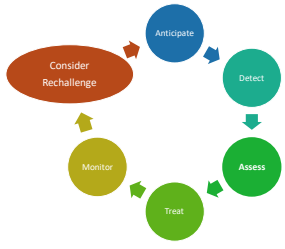
## Immune Checkpoint Inhibitors: Impact of Toxicities




Modified from Helissey C, et al. J Geriatric Oncol (2016); 7:325

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## Immunotherapy Rechallenge for irAE of Skin

**General Approach to rechallenging with irAE:**

- Close follow-up to monitor for recurrent symptoms
- Consider working closely with an **organ-specific specialist**

**Considerations for rechallenging with skin irAE:**

- **Rash and/or pruritus**: consider resuming after symptoms have **resolved to ≤ grade 1**
- Severe or life-threatening **bullous disease** (grade 3 or 4): permanently discontinue
- **SJS and TENS**: permanently discontinue

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## Key Considerations for Practice

- Maintain a **sustained** high level of vigilance for **any** signs or symptoms that could herald an adverse effect.
  - Early recognition of toxicities → early intervention
- Consider **extension** of the oncology care team
  - Consider resources for evaluation, assessment and treatment of adverse effects for an individual patient
  - Establishing a relationship for collaboration.
- Monitoring during toxicity management → optimize treatment

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## Impact of Modification of T cell Activation: Immune-Related Adverse Events (irAE)

- Mechanism:
  - infiltration of "normal" tissue by **activated T cells** responsible for autoimmunity
  - downstream activation of immune response
- Tissues at risk:
  - Skin
  - Gastrointestinal tract
  - Endocrine glands
  - Lung
  - Nervous system
  - Liver
  - Kidney
  - Hematological cells
  - Musculo-articular system
  - Heart
  - Eyes

**John A Thompson, MD:**
***"immune related toxicity can attack virtually every organ system"***

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## Care of the Individual on Chronic Physiologic Corticosteroids

- **Long-term** corticosteroid and mineralocorticoid replacement is often required
- Provide patient AND caregiver with instructions (oral and written):
  - Advising all caregivers and healthcare team members of therapy
  - Instructions for increasing corticosteroid doses in situations of acute illness, stress or medical procedures.
  - Medical alert bracelet
  - Identification card
  - Emergency hydrocortisone IM injection kit

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## ENDOCRINE TOXICITIES

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## Immune Checkpoint Inhibitors: irAE

ENDOCRINE GLAND toxicities include:
- Thyroid: hypo-or hyperthyroidism, thyroiditis
- Pituitary: hypophysitis (inflammation of the pituitary gland)
- Adrenal gland: adrenal insufficiency
- Pancreas: diabetes

References:
- Barroso-Sousa R, et al. Endocrine dysfunction induced by immune checkpoint inhibitors: practical recommendations for diagnosis and clinical management. Cancer (2018)
- Cukier P, et al. Endocrine side effects of cancer immunotherapy. Endoc Rel Cancer (2017)

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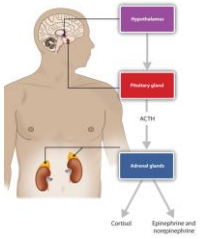
Hypothalamus – Pituitary Gland – Adrenal Glands

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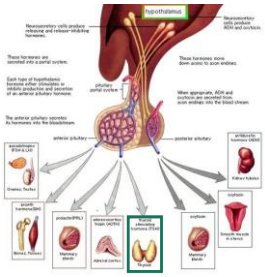
Pituitary: Function

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## Management of Hypothyroidism: Levothyroxine

- Dosing is based on body weight, etiology of hypothyroidism, degree of TSH elevation, age and comorbidities
  - Full replacement: 1.6 – 1.8 mcg/kg/day
  - Elderly or patients with cardiovascular disease: 25 – 50 mcg daily
- Dose adjustments:
  - 4 – 6 weeks post initiation and after dose change
  - Dose adjustments of 12.5 – 25 mcg/day until TSH target reached
- Adverse effects: CV and reduced bone density

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## Immune Checkpoint Inhibitors: Pituitary Gland

Hypophysitis:

- **Incidence** does not appear to be the same for all immune checkpoint inhibitors, but does appear to **increase with combination immune checkpoint inhibitor**.
  - Dose related for CTLA-4 inhibitor ipilimumab?
- **Pathogenesis** → autoimmune based mechanism
- **Presentation**:
  - Panhypopituitarism
  - Isolated anterior pituitary hormone deficiency
  - Pituitary enlargement
  - Non-specific symptoms: HA, fatigue, muscle weakness, paleness, constipation, weight loss, anorexia, nausea
  - Symptoms maybe related to specific hormonal deficiencies
- **Monitoring**: TSH, free T4
- **Management is dependent on diagnosis**

Barroso-Sousa R, et al. Cancer (2018), Cukier P, et al. Endoc Rel Cancer (2017)

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## Case Scenario

- Ms. A is a 59 year old women recently diagnosed with metastatic adenocarcinoma of the lung. Results of her next generation sequence test indicated her tumor was PDL1 was 60%, and her TMB was high. No other genetic alterations were identified.
- She was started on combination therapy with ipilimumab and nivolumab about 2 months ago.
- She presents to clinic today with complaints of feeling depressed.

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## Depression and Anxiety Disorders

- Meta-analysis to evaluate the association of depression and anxiety with autoimmune thyroiditis
  - Number of studies in analysis: 19 (21 independent samples)
  - Participants: 36 K (35 K for depression, 34 K for anxiety)
- Results:
  - Patients with autoimmune thyroiditis , Hashimoto thyroiditis, or subclinical or overt hypothyroidism had higher scores on depression instruments (odd ration 3.56)
  - Patients with autoimmune thyroiditis , Hashimoto thyroiditis, or subclinical or overt hypothyroidism had increased anxiety disorders (odd ration 2.32)

Siegmann E, et al. JAMA Psychiatry 2018

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Even less common irAE…

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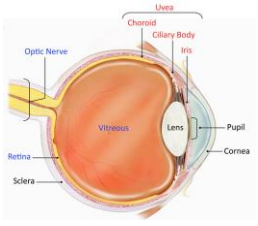
Immune Checkpoint Inhibitors: irAE

EYE toxicities include:
- Uveitis
- Conjunctivitis
- Belpharitis
- Retinitis
- Choroiditis
- Orbital myositis

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Resuming Immunotherapy following irAE

Recommendations per guidelines:
- Coordination of care:
  - **Organ-specific specialist**
  - Close follow up
  - Reinforced patient and caregiver education
- Change in "class" of immunotherapy?
- Role of continued immunosuppression during therapy?

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## Question: Who is at risk for irAE from ICI?

- Is there a better way to select patients that are at risk of irAE?


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## Is there a **correlation** between irAE and efficacy of ICI?

Suggestions from the literature:

- Sato K, et al. Lung cancer 2018;115:71-74
- Judd J, et al. The Oncologist 2017;22:1232-37.
- Abu-Sbeih H, et al. Cancer Immunology Immunotherapy 2019.

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## Immune Checkpoint Inhibitors: Looking Beyond irAE

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## Immune Checkpoint Inhibitors: Fatigue

- **Fatigue** is one of the most frequent adverse effect of immune checkpoint inhibitors
- Meta-analysis evaluated fatigue in 17 clinical trials with ipilimumab, pembrolizumab, nivolumab and tremelimumab.
  - Incidence of all grade treatment-associated fatigue ranges from **14 – 42%**
    - Incidence of high-grade treatment-associated fatigue varied from 1 – 11%
  - Incidence dependent on a variety of issues including :
    - Agent
    - Dose
    - Scheduled
    - Combination vs single agent

Abdel-Rahman O, et al. Clinical Oncology 2016; 28:e127.

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## Question:
**When** should we look for irAE?


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## What is the risk in patients with history of autoimmune disorders?

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## Immune Checkpoint Inhibitors in Individuals with Autoimmune Disorders

- Methods:
  - Retrospective evaluation of 56 patients with NSCLC and history of autoimmune disorder (AID) receiving a single agent PD-1 or PD-L1 inhibitor
  - Qualifying AID included rheumatologic, neurologic, endocrine, gastrointestinal and dermatologic conditions
  - At time of treatment 18% had symptoms of AID and 20% were receiving immunomodulatory agents for their AID.
- Results:
  - 55% patients develop a flare and/or irAE → systemic corticosteroids
  - 38% patients experienced irAE: 74% grade 1 or 2 and 26% grade 3 or 4
  - ORR was 22% in the population
  - ICI therapy was permanently discontinued in 8 patients due to irAE

Leonardi GC, et al. J Clin Oncol 2018;36:1

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## Question

- What is the **optimal duration** of therapy for checkpoint inhibitors in treatment?

www.googleimages

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## Questions?

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