Evolving Strategies to Manage Treatment-Related Adverse Events for Patients With Classical Hodgkin Lymphoma

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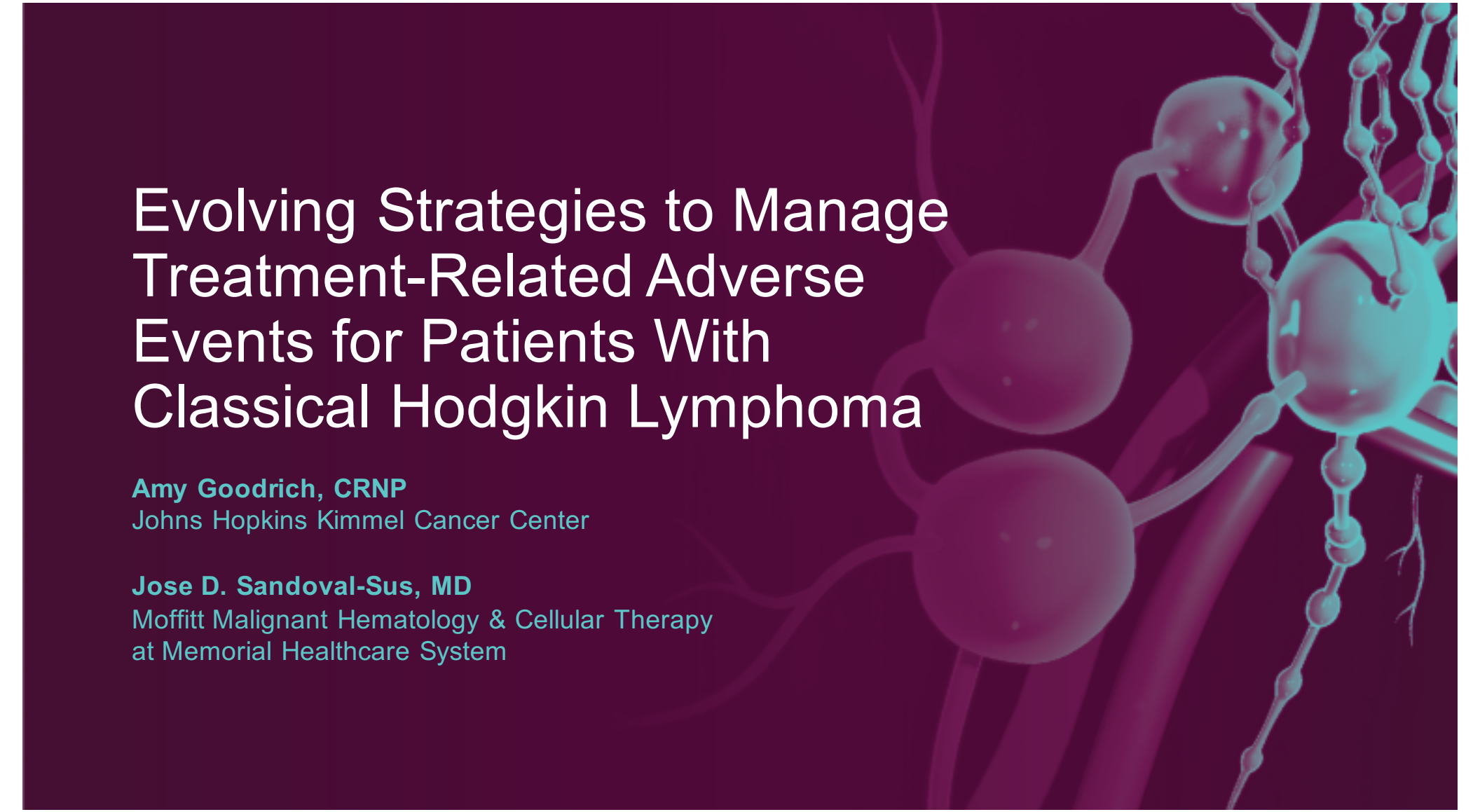

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- Ms. Goodrich has nothing to disclose.
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Learning Objectives

1. Predict and identify adverse events (AEs) of established and emerging cytotoxic regimens and novel agents used in patients with cHL
2. Evaluate and interpret the clinical utility of best practices and emerging data regarding prevention and mitigation of AEs of established and emerging cytotoxic regimens and novel agents used in patients with cHL
3. Implement strategies to prevent and mitigate immune related adverse events (irAEs) for patients with cHL treated with checkpoint inhibitors (CPIs)
4. Formulate plans to counsel patients regarding early detection and prevention of AEs

Please indicate the clinical role that best represents you:

1. Physician
2. PA
3. Nurse practitioner
4. Clinical nurse specialist
5. Nurse
6. Pharmacist
7. Other

Please indicate the practice setting that best represents your practice:

1. Academic medical center, teaching hospital, or comprehensive cancer center
2. Community hospital or community cancer center
3. Private/group practice
4. Government or VA
5. Managed care, insurance, employer, or other payer
6. Pharmaceutical/biotech/device industry
7. Other

Please indicate your clinical specialty:

1. Medical oncology
2. Hematology/oncology
3. Radiation oncology
4. Internal medicine
5. Gynecologic oncology
6. Genetics/genetic counseling
7. Other

Please indicate your years in practice:

1. < 1 year
2. 1–5 years
3. 6–10 years
4. 11–15 years
5. 16–20 years
6. > 20 years

Question #1

- You are seeing a patient receiving ABVD for newly diagnosed cHL. The toxicity you would be LEAST likely to encounter is:
  A. Infection
  B. Cough
  C. Peripheral neuropathy
  D. Colitis
  E. Unsure

Question #2

- The most common side effect of brentuximab vedotin is:
  A. Peripheral sensory/motor neuropathy
  B. Thrombocytopenia
  C. Rash
  D. Edema
  E. Unsure

Question #3

- A patient receiving pembrolizumab for cHL is experiencing diarrhea, having eight stools above normal. You would expect initial next steps to include hydration and _____ .
  - A. Cyclophosphamide
  - B. Cyclosporine
  - C. Infliximab
  - D. Steroids
  - E. Unsure

Question #4

- Key patient education before receiving a checkpoint inhibitor for cHL includes monitoring and reporting for:
  A. Constipation
  B. Peripheral neuropathy
  C. Diarrhea
  D. Unsure

Question #5

- A patient with advanced cHL and which of the following set of clinical characteristics is considered high risk?
  A. Male, age 30, albumin 4.5 g/dL
  B. Male, age 50, bone marrow involvement
  C. Female, age 40, mediastinal disease
  D. Female, age 60, WBC ULN
  E. Unsure

Hodgkin Lymphoma: Epidemiology

New Cases (US 2018)	Deaths (US 2018)	Age at Diagnosis	5-Year Overall Survival 2016
8,500	1,050	Bimodal age distribution	82.6%

Risk factors

- Socioeconomic factors
- Familial risk: genetic predisposition and common environmental exposure
- EBV: Geographic variability and variability by subtype: 30%-40% in Europe and North America, and as high as 80% in Central and South America
- Autoimmune disorders
- Tobacco use
- HIV on antiretroviral therapy
- Bone marrow microenvironment
- Genetic drivers: NF-κB, JAK-STAT pathways

Epidemiology

- 0.5% of all new cancer cases
- More common in males
- Bimodal age distribution
  - First peak at age 20
  - Second peak at age 65
- Etiologic heterogeneity between HL subtypes

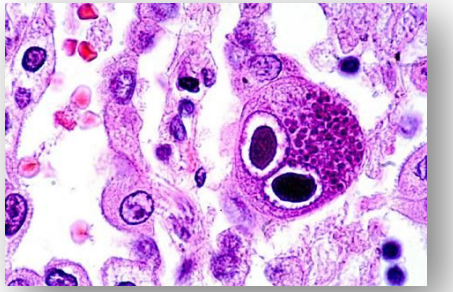
Survival

- In 2013, there were an estimated 193,545 people living with HL in the United States

EBV = Epstein-Barr virus; HL = Hodgkin lymphoma.

http://seer.cancer.gov/statfacts/html/clyl.html; Kamper-Jorgensen M, et al. *Ann Oncol* 2013;24:2245-55; Siegel R, et al. *CA Cancer J Clin* 2018;68:7-30.

Classical HL



- Most common (95% of cases in Western countries)
- **Four subtypes:** Based on differences in the appearance of the tumor cells and the composition of the microenvironment
  - Nodular sclerosis classical HL: disease above the diaphragm and mediastinal node involvement most common
  - Mixed cellularity classical HL: liver involvement more common
  - Lymphocyte rich classical HL
  - Lymphocyte depleted classical HL

Staging I-IV: Limited stage-unfavorable factors

- Bulky disease
  - Large mediastinal adenopathy >10 cm
  - MMR > 0.33
  - > 1/3 internal transverse diameter of the thorax at the T5-T6 interspace
- Extranodal involvement
  - > 3 nodal sites of disease
  - Most common is bone or bone marrow, followed by lung, liver, and muscle
- Sedimentation rate ≥ 50
- Presence of B symptoms
  - Unexplained fevers > 38°C
  - Drenching night sweats
  - Weight loss of > 10% of their body weight within 6 months of diagnosis

MMR = mediastinal mass ratio.

Swerdlow SH, et al. *Blood* 2016;127:2375-90; NCCN Guidelines Version 3.2018 Hodgkin Lymphoma.

International Prognostic Score for Advanced Stage Disease

One point for each factor

- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥ 45 years
- Stage IV disease
- Leukocytosis (WBC > 15,000/mm^3)
- Lymphocytopenia (ALC < 8%)
- WBC and/or lymphocyte count less than 600/mm^3

Number of Factors	PFS at 5 Years (%)	% of Patients
0	84	7
1	77	22
2	67	29
3	60	23
4	51	12
≥ 5	42	7

ALC = absolute lymphocyte count; PFS = progression-free survival; WBC = white blood cell count.

Hasenclever D, et al. *N Engl J Med* 1998;339:1506-14; NCCN Guidelines Version 3.2018 Hodgkin Lymphoma.

First-Line Therapies for cHL

Common Frontline Therapies Used in cHL

Regimen/Modality	Duration of Therapy	Agents
ABVD	2-6 cycles	Doxorubicin, bleomycin, vinblastine, dacarbazine
Stanford V	8-12 weeks	Doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone
BEACOPP	2-6 cycles	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
Involved site radiation therapy	Varies based on treatment location	
Brentuximab vedotin + AVD	Varies, used if stage III-IV, IPS > 4 or bleo contraindication	Brentuximab vedotin, doxorubicin, vinblastine, dacarbazine

IPS = International Prognostic Score.

NCCN Guidelines Version 3.2018 Hodgkin Lymphoma; Engert A, et al. *N Engl J Med.* 2010;363:640-52; Radford J, et al. *N Engl J Med* 2015;372:1598-607; Raemaekers JM, et al. *J Clin Oncol* 2014;32:1188-94; Eich HT, et al. *J Clin Oncol.* 2010;28:4199-206; Avandi RH, et al. *Ann Oncol* 2013;24:1044-8; Gordon LI, et al. *J Clin Oncol* 2013;33:1936-42; Engert A, et al. *Lancet* 2012;379:1791-9; von Treskow B, et al. *J Clin Oncol* 2012;30:907-13; Connors JM, et al. *N Engl J Med* 2018;378:331-344.

ABVD

Pre-treatment screening
- Echocardiogram
- PFTs with DLCO
- Fertility considerations
- HIV/hepatitis B and C

Drugs
- Doxorubicin 25 mg/m^2 IV
- Bleomycin 10 units/m^2 IV
- Vinblastine 6 mg/m^2 IV
- Dacarbazine 375 mg/m^2

Schedule
- Days 1 and 15
- 2 cycles, up to 6 cycles
- Reimage with PET/CT (skull base to mid-thigh)
- Then response-adapted treatment

Dose adjustment for baseline liver or renal dysfunction
- Bleomycin
  - Adjust for reduced CrCl, impaired pulmonary function
  - Discontinue if bleomycin lung toxicity is suspected
- Doxorubicin
  - Adjust in patients with increased bilirubin and/or AST/ALT
  - Adjust for reduced EF/cardiac dysfunction
- Vinblastine: Adjust in patients with increased bilirubin and/or AST/ALT
- Dacarbazine: Severe Irritant, may require central line

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; DLCO = diffusing capacity of the lungs for carbon monoxide; EF = ejection fraction; IV = intravenously; PET/CT = positron emission tomography/computed tomography; PFTs = pulmonary function tests.

ABVD: Adverse Events

- Emesis risk: HIGH (> 90)
  - Premedicate using 5-HT_3 antagonist, steroid
- Infusion reactions
  - Test dose of bleomycin may be administered
- Venous access
  - Doxorubicin and vinblastine are vesicants
  - Dacarbazine is an extreme irritant
- Cytopenias/infection prophylaxis
  - Profound neutropenia common
  - Primary prophylaxis with G-CSF is ***not indicated***
  - Avoid concurrent oxygen administration with bleomycin—may increase bleomycin lung toxicity
- Peripheral neuropathy: vinblastine
- Pulmonary toxicity: bleomycin
  - Monitor for cough, exertional dyspnea
  - Repeat PFTs, CT chest is pneumonitis suspected
  - Start prednisone
  - Discontinue bleomycin if toxicity suspected

G-CSF = granulocyte colony-stimulating factor.

Canellos GP, et al. *N Engl J Med* 1992;327:1478; Bleomycin prescribing information, 2010, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050443s036lbl.pdf.

Management of Nausea and Vomiting

- Assess level of nausea and vomiting frequently
- Pharmacologic management (prophylaxis and treatment)
  - Serotonin receptor antagonists (5-HT_3)
  - Dopamine receptor antagonists
  - Neurokinin-1 receptor antagonists
  - Cannabinoid neuromodulators
  - Anxiolytics
- Educate patients about use of antiemetics and the importance of hydration
- Monitor intake of fluids to prevent dehydration

Goodrich A, et al. (2013). *Hematologic Malignancies in Adults.* Pittsburgh, PA: Oncology Nursing Society, pp. 201-361.

Management of Side Effects of Anemia and Thrombocytopenia

Side Effect	Management
Anemia	• Monitor CBC results • Assess for symptoms of anemia: pallor, shortness of breath, fatigue, cardiovascular symptoms • Evaluate for vitamin deficiencies (iron, B_{12}, folate) • Supplementation if deficiencies determined • Blood transfusion—monitor for complications • Educate patient regarding anemia, strategies for managing fatigue, sleep routines/hygiene, exercise
Thrombocytopenia	• Monitor CBC results • Avoid invasive procedures including in activities of daily living (e.g., shaving) • Platelet transfusions as needed—prophylactically or to manage bleeding

CBC = complete blood count.

Olsen M, et al. (2013). *Hematologic Malignancies in Adults*. Pittsburgh, PA: Oncology Nursing Society, pp. 537-647.

German Hodgkin Study Group HD10

Randomly assigned 1,370 patients with favorable prognosis early-stage HL:

- 4 cycles of ABVD followed by 30 Gy IFRT
- 4 cycles of ABVD followed by 20 Gy IFRT
- 2 cycles of ABVD followed by 30 Gy IFRT
- 2 cycles of ABVD followed by 20 Gy IFRT

At a median follow-up of 7.5 years:

Outcome	Two Cycles of ABVD	Four Cycles of ABVD
5-year OS	96.6%	97.1%
PFS	91.2%	93.5%
FTF	91.1%	93%
8-year OS	94%	95%
Grade 3/4 AEs	33%	52%
Leukopenia	15%	24%
Infections	1.7%	5.1%
Hair loss	15%	28%

AEs = adverse events; FTF = freedom from treatment failure; IFRT = involved-field radiation therapy; OS = overall survival; PFS = progression-free survival.

Engert A, et al. *N Engl J Med* 2010;363:640.

Stanford V: Drugs and Schedule

- Repeat cycle every 28 days
- Radiotherapy to initial sites 5 cm or larger (dose: 36 Gy)
- Doxorubicin: 25 mg/m^2 IV on days 1 and 15
- Vinblastine: 6 mg/m^2 IV on days 1 and 15
- Mechlorethamine: 6 mg/m^2 IV on day 1
- Vincristine: 1.4 mg/m^2 (max. 2 mg) IV on days 8 and 22
- Bleomycin: 5 units/m^2 IV on days 8 and 22
- Etoposide: 60 mg/m^2 IV on days 15 and 16
- Prednisone: 40 mg/m^2 oral every **other** day x 9 weeks, then taper

- Dose reduction
  - 35% dose reduction for (ANC) was < 1,000/μL and delayed by 1 week if the ANC was < 500/μL (except vincristine and bleomycin)
  - If dose reduction or delay occurred at any time during chemotherapy, G-CSF (5 μg/kg × 3-5 days) was incorporated into all subsequent treatments on the odd weeks
- Pre-medication
  - Antiemetics: Serotonin receptor antagonists and dexamethasone for weeks 1, 3, 5, and 7

ANC = absolute neutrophil count.

Advani RH, et al. *Ann Oncol* 2013;24:1044.

BEACOPP

Age and PS-Adjusted Treatment-Related Mortality

- < 40 years with ECOG PS < 2 (2,164 patients) = TRM 0.7%
- < 40 years with ECOG PS ≥ 2 (108 patients) = TRM 0.9%
- 40 to 49 years with ECOG PS < 2 (592 patients) = TRM 1.7%
- 40 to 49 years with ECOG PS ≥ 2 (40 patients) = TRM 15 %
- ≥ 50 years with ECOG PS < 2 (453 patients) = TRM 5.7%
- ≥ 50 years with ECOG PS ≥ 2 (45 patients) = TRM 13.3%

Drugs	Escalated BEACOPP	Standard BEACOPP
Bleomycin	10 units/m^2 IV on day 8	10 units/m^2 IV on day 8
Etoposide	200 mg/m^2 IV on days 1-3	100 mg/m^2 IV days 1-3
Doxorubicin	35 mg/m^2 IV on day 1	25 mg/m^2 IV on day 1
Cyclophosphamide	1,250 mg/m^2 IV on day 1	650 mg/m^2 IV on day 1
Vincristine	1.4 mg/m^2 (max 2 mg) IV on day 8	1.4 mg/m^2 (max 2 mg) IV on day 8
Procarbazine	100 mg/m^2 oral day 1-7	100 mg/m^2 oral days 1-7
Prednisone	40 mg/m^2 oral days 1-14	40 mg/m^2 oral on days 1-14
G-CSF	SC starting on day 8	

ECOG = Eastern Cooperative Oncology Group; PS = performance status; SC = subcutaneously; TRM = treatment-related mortality.

Wongso D, et al. *J Clin Oncol.* 2013;31:2819-24.

Key Takeaways: First-Line Therapies for cHL

- Majority of cHL patients will be cured with initial therapy
- All regimens are toxic and have potential for significant side effects during and after therapy
- Ongoing improvements in prophylaxis and treatment of therapy-induced side effects, many guideline driven
- APPs play an important role in:
  - Educating patients and families
  - Diligent monitoring
  - Effective management of side effects
  - Assuring optimal treatment outcomes

APPs = advanced practice providers.

Second-Line and Beyond Therapies for Relapsed/Refractory cHL

Common Second-Line Therapies Used in Relapsed/Refractory cHL

Second-line regimens

- **DHAP (dexamethasone, cisplatin, high-dose cytarabine)**
- **ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin)**
- BeGEV (gemcitabine, bendamustine, vinorelbine)
- GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
- **ICE (ifosfamide, carboplatin, etoposide)**
- IGEV (ifosfamide, gemcitabine, vinorelbine)
- BV plus chemotherapy (i.e., bendamustine)
- **Autologous hematopoietic stem cell transplant +/- maintenance BV**
- Allogeneic transplant (after third line and beyond)

BV = brentuximab vedotin.
NCCN guidelines version 3.2018

General Principles of Treatment for R/R cHL

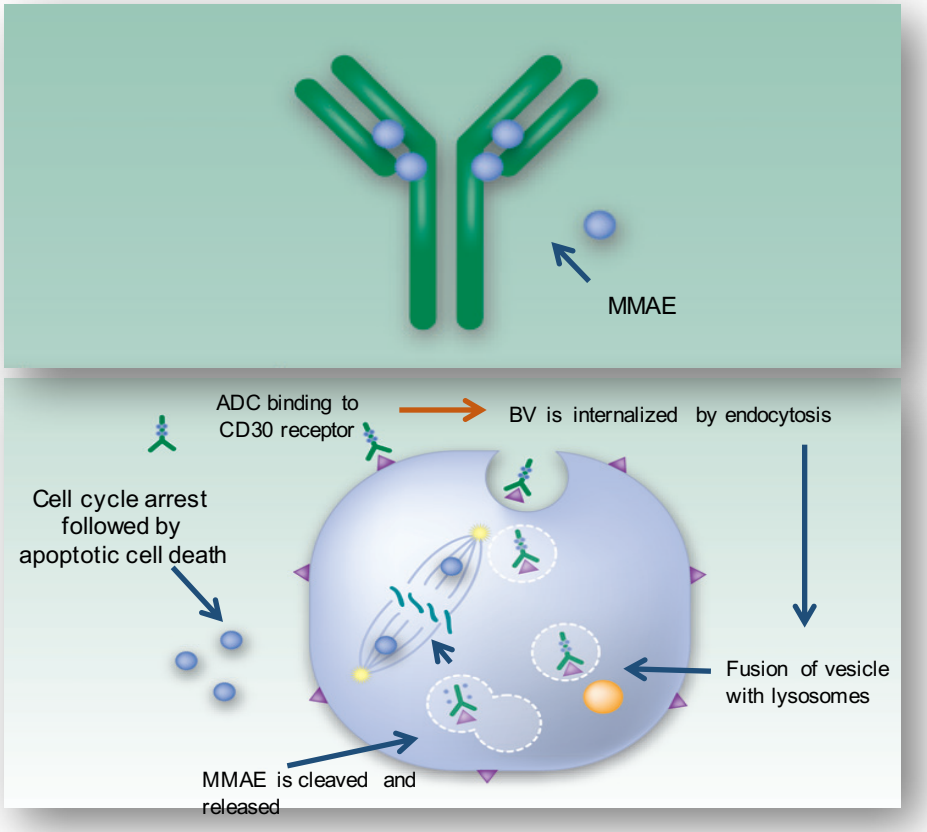
- Consider pattern of relapse and agents previously used
- HSCT should be considered for transplant eligible patients who achieve a CR or PR with second-line treatment
  - Patient not in CR may proceed, but will have a less favorable outcome
- Allogeneic stem cell transplant may be considered in eligible patients who fail autoHSCT and respond to third-line treatment
- BV is a treatment option if HDT/ASCR has failed or at least two prior multiagent chemotherapy regimens have failed
- BV +/- chemotherapy can be used as second-line therapy prior to HDT/ASCR to minimize the use of more intensive chemotherapy
- Nivolumab is an option for cHL that has relapsed or progressed following HDT/ASCR and post-HSCT BV treatment

ASCR = autologous stem cell rescue; autoHSCT = autologous hematopoietic stem cell transplant; CR = complete response; HDT = high-dose therapy; HSCT = hematopoietic stem cell transplant; PR = partial response; R/R = relapsed/refractory.

NCCN Guidelines Version 3.2018 Hodgkin Lymphoma.

Brentuximab Vedotin

- Antibody-drug conjugate
- Targets CD30 expressed on RS cells
- CD30 is a member of the tumor necrosis factor receptor family and is expressed on HL
- Combines potent antitubulin agent (MMAE) with CD30 chimeric monoclonal antibody
- Linker ensures minimal drug fall-off in plasma



ADC = antibody drug conjugate; MMAE = monomethyl auristatin E

Shustov A. *Ther Adv Hematol* 2013;4:173-87; Deng C, et al. *Clin Cancer Res* 2013;19;22–7.

Brentuximab Vedotin

- **FDA Approval:** August 19, 2011
- **Indication for cHL**
  - cHL after failure of autoHSCT
  - cHL in transplant ineligible candidates after failure of at least two multiagent chemotherapy regimens
  - cHL at high risk of relapse or progression as post autoHSCT consolidation
- **Dosing and administration**
  - 1.8 mg/kg intravenous infusion over 30 minutes every 3 weeks
  - Reduce dose in patients with mild hepatic impairment
  - Contraindication: concomitant use with bleomycin due to pulmonary toxicity

FDA = US Food and Drug Administration.

Brentuximab prescribing information, 2016, https://adcetris.com/pdf/ADCETRIS-brentuximab-vedotin-Prescribing-Information.pdf?v=20161101.

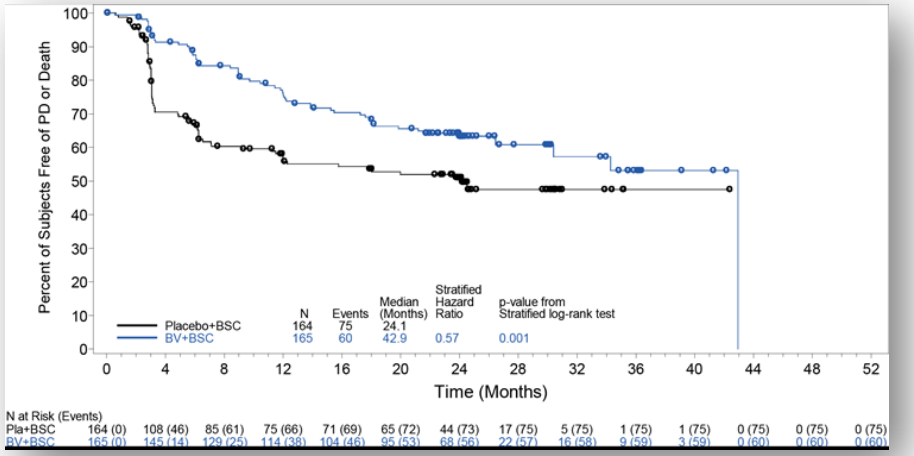
Toxicities of Brentuximab Vedotin

Toxicity	Overall (%)	Grades 3/4 (%)
Blood and lymphatic system		
Neutropenia	55	21
Anemia	52	2
Thrombocytopenia	16	10
Nervous system disorders		
Peripheral sensory neuropathy	53	10
Peripheral motor neuropathy	7	3
General disorders and administration site reactions		
Fatigue	41	4
Pyrexia	38	2
Pain	28	5
Edema peripheral	16	0
Gastrointestinal disorders		
Nausea	38	2
Diarrhea	29	3
Skin and subcutaneous tissue disorders		
Rash	31	0

Adcetris. http://www.adcetris.com/pdf/ADCETRIS-brentuximab-vedotin-Prescribing-Information.pdf.

Brentuximab Vedotin Consolidation After AutoHSCT

- Randomized double-blind placebo-controlled trial (n = 329)
- cHL at high risk of relapse or progression post-autoHSCT
- 30-45 days post-autoHSCT, randomized to:
  - BV 1.8 mg/kg every 3 weeks for up to 16 cycles
  - Placebo every 3 weeks for up to 16 cycles
- Outcomes
  - BV improved PFS (BV 42.9 months vs. placebo 24.1, HR 0.57 (95% CI, 0.40-0.81; p=0.001)
  - No differences in overall survival
  - More common side effects: peripheral sensory neuropathy (BV: 56% vs. placebo: 16%) and neutropenia (BV: 35% vs. placebo: 12% patients)



CI = confidence interval; HR = hazard ratio.

Moskowitz CH. et al. *Lancet* 2015:385:1853-62; Epperla N, et al. *Bone Marrow Transplant* 2015;50:1393-404; Brentuximab prescribing information, 2016, https://adcetris.com/pdf/ADCETRIS-brentuximab-vedotin-Prescribing-Information.pdf?v=20161101.

Peripheral Neuropathy

- Common in cHL due to use of neurotoxic agents (vinca alkaloids, brentuximab vedotin)
- Most commonly sensory peripheral neuropathy
- May continue for months, years or permanently.
- May negatively impact quality of life
- Best treatment is thorough assessment while on neurotoxic agents with dose delays/adjustments as appropriate

Hershman DL, et al. *J Clin Oncol* 2014;32:1941-67.

Management of Chemotherapy-Induced Peripheral Neuropathy

- Prevention
  - Currently no pharmacologic agent has been proven to be effective for prevention of CIPN
  - Agents under investigation
    - IV calcium and IV magnesium (oxaliplatin-induced neurotoxicity)
    - Glutathione
    - Glutamine
    - Carbamazepine/oxcarbazepine
    - Vitamin E
    - Erythropoietin
    - Neurosteroids
  - None of these agents has adequate data at this time for use outside of a clinical trial

CIPN = chemotherapy-induced peripheral neuropathy.

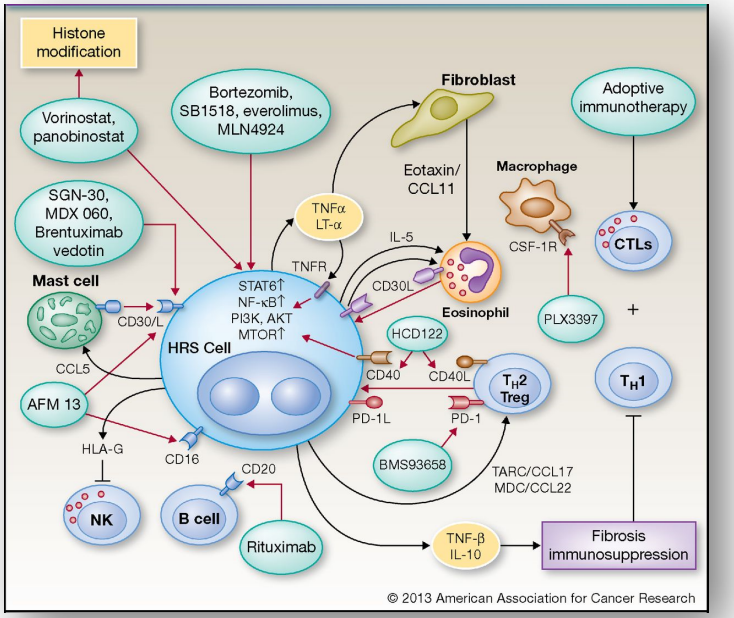
Pachman DR, et al. *Clin Pharmacol Ther* 2011;90:377-87.

Common Third-Line and Beyond Therapies Used in cHL

- **BV**
- **Bendamustine**
- C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone)
- Everolimus
- GCD (gemcitabine, carboplatin, dexamethasone)
- Lenalidomide
- MINE (etoposide, ifosfamide, mesna, mitoxantrone)
- Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)
- **Nivolumab**
- **Pembrolizumab**

HL and the Microenvironment: Potential Therapeutic Targets

- Tailoring the therapy to the tumor biology of the patient may improve outcomes



Novel Agents in the Treatment of cHL

Drug	Drug Class	Target
Receptor-targeting therapies		
Brentuximab vedotin	ADC	CD30
Nivolumab, pembrolizumab	MoAb	PD-1
Rituximab	MoAb	CD20
Galiximab	MoAb	CD80
Microenvironment-targeting therapies		
Lenalidomide	Immunomodulator	T cells, NK cells, Tregs
Panobinostat	HDACi	HDAC
Mocetinostat	HDACi	HDAC
Inhibitors of signaling pathways		
Everolimus	mTOR inhibitor	mTORC1
Perifosine/sorafenib	AKT/MAPK inhibitor	AKT/MAPK

MoAb = monoclonal antibody; NK = natural killer; HDACi = histone deacetylase inhibitor; mTOR = mammalian target of rapamycin.

Diefenbach C, et al. *Clin Cancer Res* 2013;19:2797-803.

Nivolumab

Class: PD-1 blocking antibody

FDA Approval: March 17, 2016

Indication for cHL

- Relapse or progression after autoHSCT and post-transplantation BV
- Received three or more lines of therapy that includes autoHSCT

Dosing and administration

- 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity

Ansell S, et al. *N Engl J Med* 2015; 372:311-9; Armand P, et al. *J Clin Oncol* 2018.10;36:1428-39; Nivolumab prescribing information, 2014, http://packageinserts.bms.com/pi/pi_opdivo.pdf.

Nivolumab in Relapsed/Refractory cHL

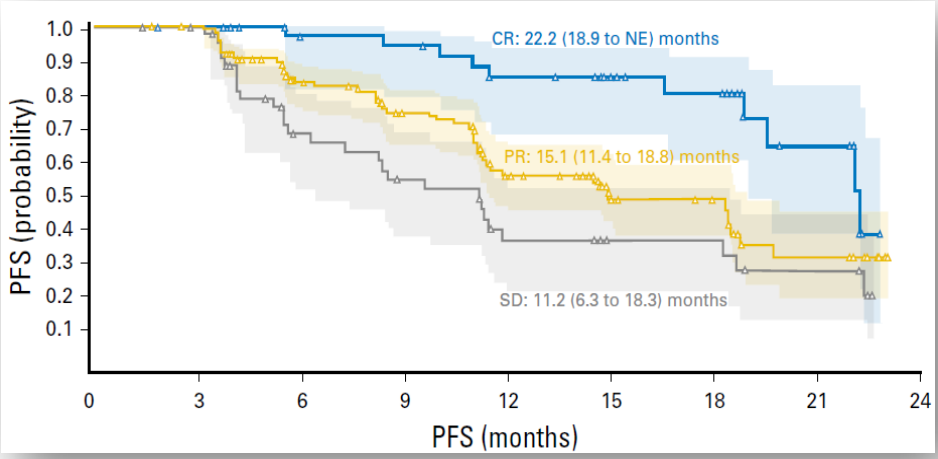
- Approved for use post-autoHSCT and BV
- Phase I study of 104 hematologic malignancies patients
- Nivolumab escalation of 1 and 3 mg/kg every 2 weeks for 2 years
- 23 with relapsed/refractory HL (20 with cHL)
- 78% post-autologous transplant and 78% post-BV
- ORR: 87% (CR: 26%, PR: 61%, SD: 13%)
- cHL at 86 weeks (7 years): 5 progressed, 5 went on to stem cell transplant and 10 with ongoing response

ORR = overall response rate; SD = stable disease.

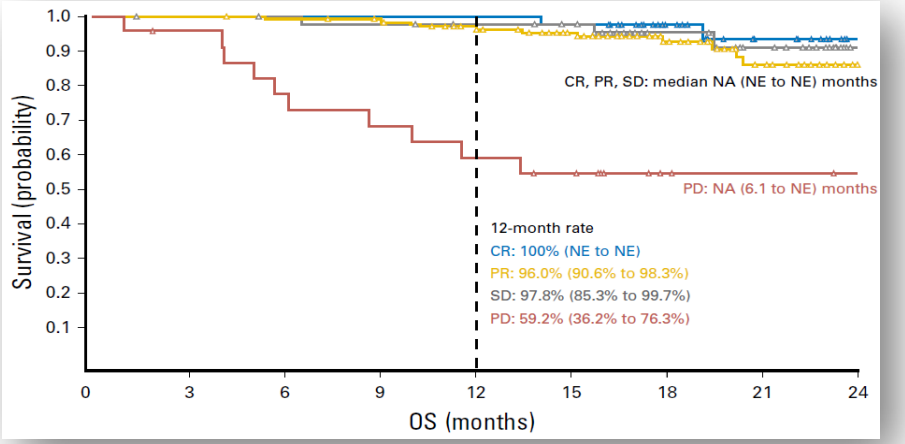
Ansell S, et al. *N Engl J Med* 2015;372:311-9; Armand P, et al. *J Clin Oncol* 2018.10;36:1428-39.

Nivolumab in R/R cHL: Phase II Clinical Trial CheckMate 205

- ORR: 69% (63%-75%)
- CR: 16%; PR: 53%



Median PFS 14.7 months (95% CI,11.3-18.5 months)



Median OS: not reached

- 1 year OS: 92% (88%-95%)

OS = overall survival.

Armand P, et al. *J Clin Oncol* 2018.10;36:1428-39.

Nivolumab in cHL: CheckMate 205

AEs in ≥ 5% of Patients, n (%)	Any Grade	Grade 3-4
Diarrhea	37 (15%)	2 (< 1%)
Fatigue	56 (23%)	2 (< 1%)
Cough	15 (6%)	0
Pyrexia	22 (9%)	0
Rash	29 (12%)	2 (< 1%)
Infusion reaction	34 (14%)	1 (< 1%)
ALT/AST elevation	18/17 (7%)	8 (3%)/5 (2%)
Dyspnea	10 (4)	1 (< 1%)
Neutropenia	15 (6%)	8 (3%)
Elevated lipase	17 (7%)	11 (5%)
Hypothyroidism (irAE)	12 (5%)	0

- **17 patients discontinued treatment due to drug-related AEs:**
  - Pneumonitis (2%)
  - Autoimmune hepatitis (1%)
- **Serious drug-related AEs occurred in 12% of patients:**
  - Infusion-related reactions (2%)
  - Pneumonitis (1%)
  - Pneumonia (1%)
  - Pleural effusion (1%)
  - Pyrexia (1%)

N = 243 patients.
irAE = immune-related adverse event.
Armand P, et al. *J Clin Oncol* 2018.10;36:1428-39.

Pembrolizumab

Class: IgG4 kappa humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2

FDA Approval: March 14, 2017

Indication for cHL

- Adult and pediatric patients with refractory cHL
- Adult and pediatric patients who have relapsed after three or more prior lines of therapy

Dosing and administration for cHL in adults

- 200 mg every 3 weeks

Moskowitz CH, et al. ASH 2016. Abstract 1107; Pembrolizumab prescribing information, 2014, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

Pembrolizumab: KEYNOTE-087 Trial

Response, n (%)	Cohort 1: After ASCT and BV (N = 69)	Cohort 2: Ineligible for ASCT With Progression After BV (N = 81)	Cohort 3: After ASCT Without Post-ASCT BV (N = 60)
ORR	51 (73.9%)	52 (64.2%)	42 (70.0%)
▪ CR	15 (21.7%)	20 (24.7%)	12 (20.2%)
▪ PR	36 (52.2%)	32 (39.5%)	30 (50.0%)
SD	11 (15.9%)	10 (12.3%)	10 (16.7%)
PD	5 (7.2%)	17 (21%)	8 (13.3%)
Undetermined	2 (2.9%)	2 (2.5%)	0 (0.0%)

ORR (all patients, N = 210): 145 (69%; 95% CI, 62.3%-75.2%)

- CR: 47 (22.4%; 95% CI, 16.9%-28.6%)
- PR: 98 (46.7%; 95% CI, 39.8%–53.7%)

Chen R, et al. *J Clin Oncol* 2017.35:2125-32.

KEYNOTE-087: Treatment-Related AEs

- 9 (4.3%) patients discontinued because of treatment-related AEs (myocarditis, myelitis, myositis, infusion reactions, CRS)
- No treatment-related deaths (2 deaths on study)

Any-Grade AEs in ≥ 5% of Patients, n (%)	All Patients (N = 210)
Hypothyroidism	26 (12.4%)
Pyrexia	22 (10.5%)
Fatigue	19 (9.0%)
Rash	16 (7.6%)
Diarrhea	15 (7.1%)
Headache	13 (6.2%)
Nausea	12 (5.7%)
Cough	12 (5.7%)
Neutropenia	11 (5.2%)

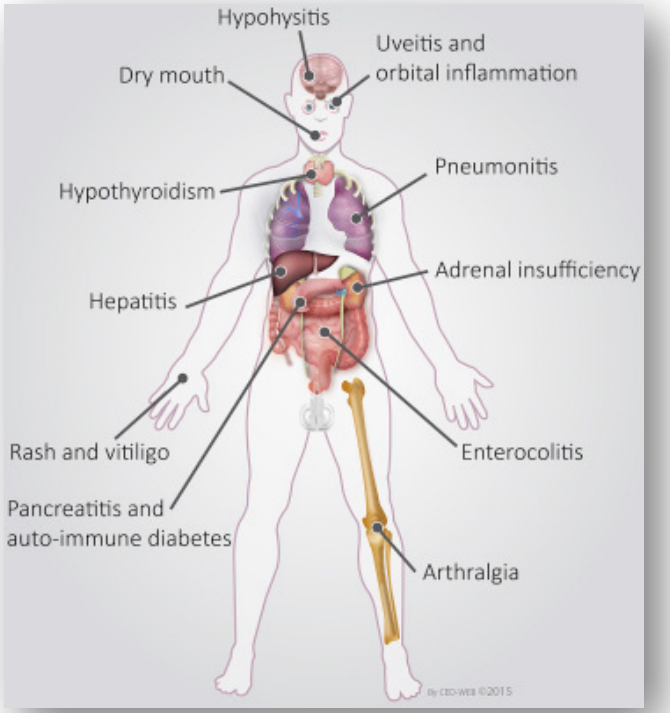
AEs, n (%)	All Patients (N = 210)
Any grade 3/4 AEs	23 (11)
Grade 3 AEs in ≥ 2 patients	
▪ Neutropenia	5 (2.4)
▪ Diarrhea	2 (1.0)
▪ Dyspnea	2 (1.0)
AEs of interest in ≥ 2 patients	
▪ Grade 1/2 infusion-related reactions	10 (4.8)
▪ Grade 2 pneumonitis	6 (2.9)
▪ Grade 1/2 hyperthyroidism	6 (2.9)
▪ Grade 2/3 colitis	2 (1.0)
▪ Grade 2/3 myositis	2 (1.0)

CRS = cytokine release syndrome.

Chen R, et al. *J Clin Oncol* 2017.35:2125-32.

AEs Associated With Immune Checkpoint Inhibition

Augmented immune response driven by T-cell activation creates the potential for autoimmune-related inflammation of normal tissues



Michot JM, et al. *Eur J Cancer* 2016;54:139-48.

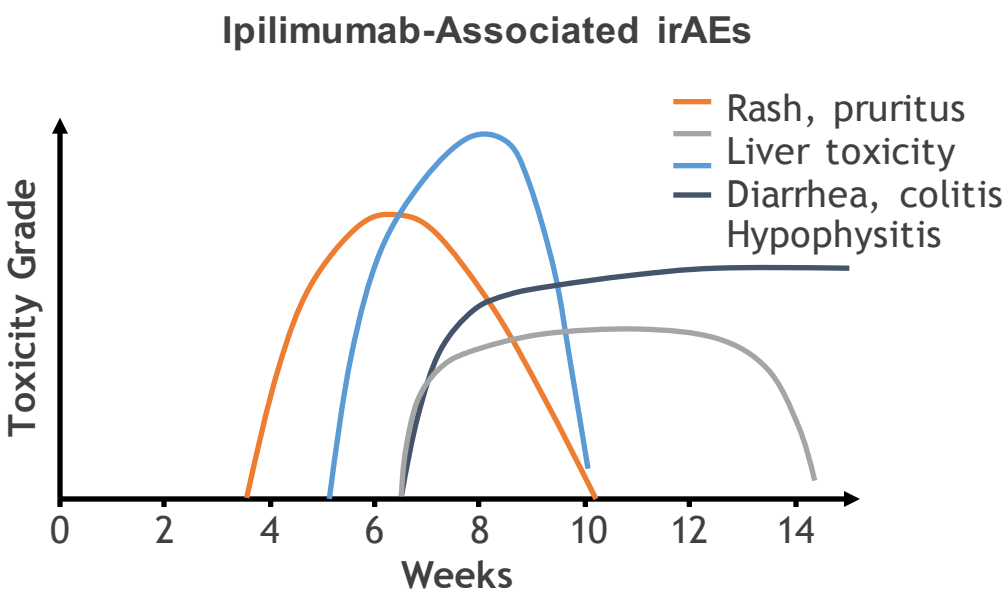
Infusion Reactions

Infusion reactions with checkpoint inhibitors are infrequent

- Reported in up to 10% of patients (often much fewer)
- Usually mild: Stop the infusion and restart at a lower rate
- No steroids: Pre-medications are not necessary
- As with any infusion, monitor carefully and have emergency medications available

Dadu R, et al. *Cancer J* 2016;22:121-9

Onset of irAEs Is Variable



Combined analysis of 325 participants with 10 mg/kg IV q3w x4

q3w = every 3 weeks.

Weber JS, et al. *J Clin Oncol* 2012;30:2691-7.

Treatment of Severe and Steroid-Refractory irAEs

Type and Severity of irAE	Initial Management	Additional Immunosuppression	Immunosuppression Tapering Schedule
Colitis and/or diarrhea Grade 3-4 • Increase of ≥7 stools per day over baseline • Abdominal pain, fever, and change in bowel habits	• Admit to hospital for intravenous corticosteroid therapy (methylprednisolone 1-2 mg/kg daily dose) • Supportive care including intravenous fluids, supplemental oxygen, and antibiotics as needed • Withhold hepatotoxic drugs • Consider further diagnostic imaging or procedures	**Colitis and/or diarrhea** • If no improvement after 3 days, give infliximab 5 mg/kg • Can redose infliximab after 2 weeks if needed	**Colitis and/or diarrhea** • Rapidly tapering course of steroids as tolerated over 4-6 weeks • Increase steroids if diarrhea flares and then restart tapering
Hepatitis Grade 3-4 • Aspartate transaminase and/or alanine transaminase levels >5 times ULN • Total bilirubin level >3 times ULN		**Hepatitis** • If no improvement after 3 days, start mycophenolate mofetil 500-1000 mg every 12 hours	**Hepatitis** • Rapidly tapering course of steroids as tolerated; discontinue mycophenolate mofetil once tapered to prednisone 10 mg daily
Pneumonitis Grade 3-4 • Severe, life-threatening symptoms • Worsening hypoxia		**Pneumonitis** • If no improvement after 48 hours, start additional agent as above or cyclophosphamide	**Pneumonitis** • Taper steroids slowly over 6 weeks • Mycophenolate mofetil management as above if needed

ULN = upper limit of normal.

Friedman CF, et al. *JAMA Oncol* 2016;2:1346-53.

Mechanisms of Action of Immune-Modulating Medications

Drug	Key Mechanism of Action
Steroids	Multiple effects on T cells, B cells, and phagocytes through inhibition of transcription of interleukins, reduction in synthesis of cytokines, inhibition of neutrophil apoptosis, and reduced macrophage function
Infliximab	Antibody that inhibits binding of the inflammatory cytokine TNF-α to its receptors
Mycophenolate mofetil	Inhibits IMPDH, an enzyme involved in nucleotide production, particularly in activated lymphocytes
Tacrolimus and cyclosporine	Calcineurin inhibitors that limit transcription of IL-2, involved in T-cell proliferation

IL-2 = interleukin-2; IMPDH = inosine monophosphate dehydrogenase; TNF-a = tumor necrosis factor alpha.

Spain L, et al. *Cancer Treat Rev* 2016;44:51-60.

Keys to Optimal Patient Management for Immune Checkpoint Inhibitors

- Time to onset for AEs is typically delayed
- Education of healthcare team, patients, and caregivers
- Subtle symptoms may be initial presentation
- Rapid and timely intervention
  - Corticosteroids for some intolerable grade 2 irAEs and any grade 3/4 irAEs
  - Slow taper of glucocorticoids
- Reinitiation of treatment may be possible

Dadu R, et al. *Cancer J* 2016;22:121-9.

Special Populations

Pregnancy and lactation

- Antibodies are known to cross placental barrier
- Pregnancy category C; immune checkpoint inhibitors are not recommended
- Advise patients to use highly effective contraception
- Safety of breastfeeding has not been studied

Dadu R, et al. *Cancer J* 2016;22:121-9.

Checkpoint Inhibitors and alloHSCT Warnings and Precautions

- Transplant-related deaths have occurred in patients receiving salvage checkpoint inhibitors prior to alloHSCT
- Monitor closely for:
  - Hyperacute GVHD
  - Severe (grade 3 to 4) acute GVHD
  - Steroid-requiring febrile syndrome
  - Hepatic VOD
  - Other immune-mediated adverse reactions

alloHSCT = allogeneic hematopoietic stem cell transplantation; GVHD = graft-versus-host disease; VOD = veno-occlusive disease.

Pembrolizumab prescribing information, 2014, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf; Armand, P et al. *Blood* 2016;128:3502.

Key Takeaways: Second-Line and Beyond Therapies for Relapsed/Refractory cHL

- Treatment options for R/R cHL are expanding
- Many trials underway
- More patients receiving multiple lines of therapy
- APPs play critical role in
  - Continuing to educate
  - Participate in shared decision making regarding treatment options, side effects, and impact on quality of life
  - Monitoring and management of regimen-specific side effects
  - Ongoing monitoring and management of toxicity from prior regimens

Case Study #1

- 25-year-old female with newly diagnosed favorable risk cHL
- Key considerations
  - Fertility
  - Breast radiation
  - Pulmonary toxicity
  - Long-term toxicities
  - Psychosocial
    - Support system
    - Work, school, family, other responsibilities
    - Financial/health insurance
    - Mental health
    - Adherence

Case Study #1: Fertility

- cHL: 5-year survival 85%
  - ABVD
    - Females: rare premature ovarian insufficiency
    - Males: 90% have normal sperm counts 1 year post-therapy
  - HSCT: high rate of dysfunction in both genders
  - Abdominal radiation: age, field, dose-dependent for females
  - Testicular radiation: > 4 Gy = permanent damage
  - Why do we care?
    - Cancer-related infertility has a high impact on quality of life for cancer survivors
    - Psychological and social significance

Schmidt KT, et al. *J Asst Repord Genet* 2012;29:473-7.

Case Study #1: Fertility Options

Female Options	Male Options
Co-treatment with gonadotropin-releasing hormone agonist (easy, inexpensive, trials show inconsistent results)	Spermatozoa cryopreservation (well established, quick, easy, success rates 33-56%, offer to all, regardless of risk of testicular failure, malignancy can impact sperm quality)
Oocyte cryopreservation (aspirated in connection with IVF, live birth rate 21%-38%)	Transrectal electro-ejaculation in young pubertal boys (possible future option for pre-pubertal boys)
Embryo cryopreservation (IVF-induced embryos, requires at least one menstrual cycle, live birth rate 21-38%)	
Ovarian tissue cryopreservation (entire or part of ovary preserved, quick, often first choice, only option for pre-pubertal girls, may need laparoscopy, autotransplant of tissue in 3-4 years can restore menses and hormone production, 20+ live births)	
In vitro maturation of oocytes (quick, high rate of early pregnancy loss)	

IVF = in vitro fertilization.

Schmidt KT, et al. *J Asst Repord Genet* 2012;29:473-7.

Case Study #1: Fertility Management

- Educate regarding risk of infertility
- Females
  - Refer all
  - Intervention not likely if ABVD
  - Preservation considered if POI risk > 30-50%
  - Offer to all HSCT or abdominal radiation patients
- Males
  - Offer sperm banking to all

POI = premature ovarian insufficiency.

Schmidt KT, et al. *J Asst Repord Genet* 2012;29:473-7; Oktay K, et al. *J Clin Oncol* 2018;36:1994-2001.

Case Study #1: Pulmonary Toxicity

- cHL therapies associated with late pulmonary toxicity

Injury	Drug/Regimen
Interstitial/pulmonary fibrosis	Bleomycin, busulfan, cyclophosphamide, gemcitabine, cytarabine, vincas
Pulmonary vascular disease/pulmonary veno-occlusive disease	Bleomycin, busulfan
Pleural effusion	Busulfan, thoracic radiation
Airway disease • Bronchiolitis obliterans syndrome • Bronchiectasis	 • Thoracic radiation, busulfan • Thoracic radiation

Skinner R, et al. *Semin Oncol* 2013;40,757-73.

Case Study #1: Second Malignancy

- Hodgkin lymphoma
  - Risk 2-3 times general population
  - 1 in 5 survivors will develop second cancer in first 20 years after treatment
  - Alkylators associated with high rate of acute leukemia and MDS
  - Highest risk in ≥35 years at diagnosis and higher numbers of prior therapies
  - Within radiation fields
    - Breast in women < 30 years
    - Lung
    - Thyroid
    - Stomach
    - Sarcoma

MDS = myelodysplastic syndrome.

Oktay K, et al. *J Clin Oncol* 2018;36:1994-2001.

Case Study #1: Second Malignancy

- Follow-up care for HL
  - Avoid smoking and secondary smoke
  - Women treated with chest radiation before age 30
    - Early breast cancer screening
    - Start screening 5-8 years post-radiation or age 25, whichever is later
      - Regular breast exams
      - Regular mammograms
      - Yearly breast MRI if radiation between ages 10-30, starting 8 years post-radiation or age 25, whichever is later

MRI = magnetic resonance imaging.
COG Long-Term Follow-Up Guidelines, Version 4, 10/13.

Case Study #1

- Patient receives ABVD only, no radiation
- Tolerates therapy well
- Achieves a complete response
- Remains in a complete remission 3 years post-therapy
- No late or long-term toxicities noted

Case Study #2

- 68-year-old male treated with ABVD for cHL 3 years ago arrives for a regularly scheduled follow-up visit
- Remains in complete remission
- Was recently diagnosed with hypertension, found to have marginal ejection fraction (45%) on recent ECHO
- Fatigued since chemotherapy, slightly worse recently
- Labs reveal creatinine slightly elevated at 1.5, normal hematocrit, hemoglobin and TSH
- Asking about any correlation with cHL therapy

ECHO = echocardiogram; TSH = thyroid-stimulating hormone.

Case Study #2: cHL Toxicities

Toxicity	Contributing Factors	Prevention Strategies	Treatment
Cardiotoxicity • (LV dysfunction, CHF, stroke, MI) • May occur during, shortly after or years after treatment, often irreversible	• Anthracyclines (bolus, 450-550 mg/m^2); #2 cause of M&M at 5+ years • Chest radiation	• Consider less toxic agents/liposomals • Consider late EF monitoring	• Follow guidelines (ACE inhibitors, beta-blockers, BP and pulse control, fluid and salt limits, other agents as appropriate)
Renal toxicity (glomerular and tubular damage) • Subclinical evidence in 20%, may progress to acute or chronic failure	• Mainly salvage regimens (ifosfamide, platinums, HSCT) • Immunosuppressive agents • Anti-infectives • Comorbidities	• Protective agents not effective in prevention	• Avoid polypharmacy • Monitor CMP • Monitor creatinine clearance • Dose reduce appropriate drugs
Fatigue • Up to 67% of cHL survivors	• Higher in older patients • No correlation with gender, stage or treatment modality	• Encourage physical activity	• Evaluate disease, other medical causes, depression, psychosocial, pharmacologic • Refer as appropriate

ACE = angiotensin-converting enzyme; BP = blood pressure; CHF = congestive heart failure; CMP = complete metabolic panel; LV = left ventricular; M&M = morbidity and mortality; MI = myocardial infarction.

Liminari S, et al. *Hematol Rep* 2011;3:e4; Eschenhagen T, et al. *Eur J Ht Failure* 2011;13,1-10; Dafts BC, et al. *JACC:CV Imaging* 2013;6:877-95; Schlitt A, et al. *Dtsch Arztebl Int* 2014;111:161-8; Skinner R, et al. *Semin Oncol* 2013;40,757-73; Vermaete N, et al. *Ann Hematol* 2012;92:1007-1021; Daniels LA, et al. *Ann Hematol* 2013;92:1023-32; Armenian SH, et al. *J Clin Oncol* 2017;35:893-911.

Case Study #2

- Patient is evaluated by cardiology
- Put on ACE inhibitor, beta-blocker, and diuretic
- Sodium-restricted diet
- BP under good control
- Creatinine stable at 1.5
- Energy low but back to baseline

Case Study #3

- 57-year-old male with cHL is receiving BEACOPP for stage IV, newly diagnosed cHL
- IPS score 5 (age over 45, male, stage IV, Hgb < 10.5, ALC < 8%)
- 5-year survival 42%
- Presents 8 days post-therapy with ANC 0.33 and fever 101.7 F
- Orthostatic hypotension
- Admit for further management

Hbg = hemoglobin.

Case Study #3: Management of Neutropenia

- Monitoring CBC with differential results
- Good hand washing
- Safe handling of food per US Department of Agriculture
  - Benefits of neutropenic diet not established
- Appropriate use of growth actors and anti-infectives
- Annual influenza vaccination
- Pneumococcal and other age-appropriate immunizations

Olsen M, et al. (2013). *Hematologic Malignancies in Adults*. Pittsburgh, PA: Oncology Nursing Society, pp. 537-647.

Case Study #3: Antimicrobial Prophylaxis

Type	Population	Recommendation	Timing
Antibacterial	• High risk for febrile neutropenia or protracted neutropenia	• Fluoroquinolone prophylaxis	• During period of expected neutropenia
Antiviral	• HSV-seropositive undergoing HSCT • Substantial risk of HBV reactivation • Any treated cancer patient • Immunosuppressed adult oncology patient	• Nucleoside analog prophylaxis (e.g., acyclovir) • Nucleoside reverse transcription inhibitor (e.g., entecavir) • Inactivated influenza vaccine • Follow guidelines (CDC, IDSA)	• Until WBC recovery or extended dosing • Baseline, ongoing monitoring • Annually • Before cancer treatment, household members
Antifungal	• High risk for febrile neutropenia or protracted neutropenia or GVHD • Chemo regimens with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* (e.g., purine analogs, daily steroids for >1 month)	• Oral triazole, mold-active triazole for highest risk (GVHD) • Trimethoprim-sulfamethoxazole	• During period of expected neutropenia • Until engraftment after HSCT and/or treatment of GVHD

CDC = Centers for Disease Control and Prevention; HBV = hepatitis B virus; IDSA = Infectious Diseases Society of America.

Taplitz RA, et al. *J Clin Oncol* 2018;36:3043-54; Rubin LG, et al. *Clin Infect Dis* 2014;58:e44-100.

Case Study #3

- Admitted for febrile neutropenia
- Empiric antibiotics started
- No source identified
- Fever resolved
- Discharged on oral antibiotics
- No further fevers

Case Study #4

- 42-year-old male with multiply relapsed cHL, including autologous HSCT
- Working full time remotely from home
- Married with three school-aged children
- Receiving salvage pembrolizumab
- Most recent imaging reveals excellent partial response
- Seeing BMT center for consideration of allogeneic HSCT

BMT = bone marrow transplantation.

Case Study #4

- Arrives for infusion
- Reports he and his entire family have a GI virus
- Reports 1 day of watery stools every 4-6 hours, mild nausea, no vomiting
- Cultures sent
- Vitals stable, no hydration indicated
- Treatment held
- Agreed to notify office if symptoms do not resolve
- To return in a week

GI = gastrointestinal.

Case Study #4

- Returns in 1 week
- Cultures negative
- Diarrhea worsening, now having up to 10 watery stools per day
- Grade 3 = 7 stools per day over baseline
- Hypotensive and tachycardic at rest, mild cough
- Treatment canceled
- Admission being arranged
- Patient insisting on treatment to maintain remission in preparation for alloHSCT
- Patient requesting outpatient management

Case Study #4

- Discuss with patient
  - Potential for life-threatening colitis related to CPIs
  - Need for IV hydration beyond what your office can support
  - Importance of prompt workup and steroid administration
  - Projected treatment interruption rate of 26% due to toxicity, with only 5% discontinuation rate
- Speaks with wife and agrees to admission
- Colonoscopy performed, steroids started, rehydrated
- Diarrhea promptly resolved, deemed irAE
- No further dosing required before alloHSCT

CPIs = checkpoint inhibitors.

Keytruda package insert, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

Case Study #4

- Patient now day 60 post-alloHSCT
- Mild skin GVHD
- Tolerated well
- Working part time from home

cHL Follow-Up

cHL Follow-Up for the First 5 Years

- History and physical with labs
  - Every 3-6 months for 1-2 years
  - Then every 6-12 months until year 3
  - Then annually
- Annual influenza vaccine
- TSH at least annually if radiation to neck
- Acceptable to obtain a neck/chest/abdomen/pelvis CT scan with contrast, at 6, 12, and 24 months following completion of therapy, or as clinically indicated
- PET/CT only if last PET was Deauville 4-5, to confirm CR
- Counseling: reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion
- Screening: COG young adults s/p >10 Gy radiation to any field involving lung, alkylator, bleomycin, post-HSCT with history of cGVHD, s/p lung resection
  - Baseline chest x-ray and PFTs at start of long-term follow-up
  - Yearly pulmonary examination

cGVHD = chronic graft-versus-host disease; COG = Children's Oncology Group.

NCCN Guidelines Version 3.2018 Hodgkin Lymphoma.

cHL Follow-Up After 5 Years

- Pneumococcal, meningococcal, and H-flu revaccination after 5-7 years, if patient treated with splenic radiation or previous splenectomy (according to CDC recommendations)
- Annual influenza vaccine
- Cardiovascular symptoms may emerge at a young age
  - Stress test/echocardiogram at 10-year intervals
  - Carotid ultrasound at 10-year intervals if neck irradiation
  - Annual lipids
  - Annual TSH
  - Breast screening as appropriate
- Screening: COG young adults s/p > 10 Gy radiation to any field involving lung, alkylator, bleomycin, post-HSCT with history cGVHD, s/p lung resection
  - Baseline chest x-ray and PFTs at start of long-term follow-up
  - Yearly pulmonary examination

cHL Follow-Up After 5 Years (Cont.)

- Annual breast screening
  - Initiate 8-10 year post-therapy, or at age 40, if chest or axillary radiation
  - Breast MRI in addition to mammography for women who received irradiation to the chest between ages 10-30
  - Consider referral to a breast specialist
- Routine cancer surveillance
  - Cervical, colorectal, endometrial, lung, and prostate cancer as per the American Cancer Society Cancer Screening Guidelines
- Consider a referral to a survivorship clinic

Presentation Summary

- cHL treatment side effects are expected and potentially severe
- Long-term and late treatment-related side effects are common in cHL survivors
- Diligent management before, during, and after treatment may lessen late and long-term effects
- Patient education is critical
- During long-term follow-up, focused assessments, exams, and screening as appropriate
- Good communication with primary care providers
- APPs are in a unique position to manage all phases of care, refer as appropriate, and communicate with the entire health care team

Question #1

- You are seeing a patient receiving ABVD for newly diagnosed cHL. The toxicity you would be LEAST likely to encounter is:
  A. Infection
  B. Cough
  C. Peripheral neuropathy
  D. Colitis
  E. Unsure

Question #2

- The most common side effect of brentuximab vedotin is:
  A. Peripheral sensory/motor neuropathy
  B. Thrombocytopenia
  C. Rash
  D. Edema
  E. Unsure

Question #3

- A patient receiving pembrolizumab for cHL is experiencing diarrhea, having eight stools above normal. You would expect initial next steps to include hydration and _____ .
  - A. Cyclophosphamide
  - B. Cyclosporine
  - C. Infliximab
  - D. Steroids
  - E. Unsure

Question #4

- Key patient education before receiving a checkpoint inhibitor for cHL includes monitoring and reporting for:
  A. Constipation
  B. Peripheral neuropathy
  C. Diarrhea
  D. Unsure

Question #5

- A patient with advanced cHL and which of the following set of clinical characteristics is considered high risk?
  A. Male, age 30, albumin 4.5 g/dL
  B. Male, age 50, bone marrow involvement
  C. Female, age 40, mediastinal disease
  D. Female, age 60, WBC ULN
  E. Unsure

Q&A

Evolving Strategies to Manage Treatment-Related Adverse Events for Patients With Classical Hodgkin Lymphoma

Thank you for joining us!

Please complete your evaluation.