JADPRO CE Regional Lectures

Clinical Management of Novel Therapies for Hematologic Malignancies: Targeted Therapies, CAR-T, and Beyond

Emerging Therapies for Hodgkin Lymphoma

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Faculty Financial Disclosures

- Ms. Kurtin has served as a consultant for AbbVie, Celgene, Genentech, and Pharmacyclics.
- Ms. Goodrich has served on the speakers bureau for Gilead.
- Dr. Kiel has served on speakers bureaus for Celgene, Genentech, Gilead, and Takeda.
- Ms. Ridgeway has served on the speakers bureau for Abbvie and Phamacyclics
- Ms. Rogers has served on advisory boards for Gilead, Merck, and Takeda, and has served on speakers bureaus for Bristol-Myers Squibb, Genentech, Seattle Genetics, and Teva Pharmaceuticals.

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Learning Objectives

- Discuss emerging therapies for the treatment of relapsed refractory classic Hodgkin lymphoma (cHL)
- Discuss the mechanism of action and use of PD-1 inhibitors in the treatment of cHL
- Describe clinical trials underway in cHL
- Discuss strategies to manage adverse events and reduce short- and long-term treatment-related toxicities of existing regimens for cHL

Clinical Staging of Hodgkin Lymphoma

Staging

- Early-stage favorable
  - Stage I-II
  - No unfavorable factors
- Early-stage unfavorable
  - Stage I-II
  - Any unfavorable factor
- Advanced-stage disease
  - Stage III-IV

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 (ESR) ≥ 50**
- Presence of B symptoms
  - Unexplained fevers > 38°C
  - Drenching night sweats
  - Weight loss of > 10% of body weight within 6 mo of diagnosis

MMR = mediastinal mass ratio.

Ng AK, et al. *Semin Hematol* 2016;53:209-15.

Risk Stratification for cHL

Stage	Bulky disease	Nodal sites	ESR	Risk stratification
IA	No	1	< 50	Early stage **favorable**
IB	No	1	Any	Early stage unfavorable
IIA (no E)	No	< 3	< 50	Early stage **favorable**
IIA +/- E	No	< 4	< 50	Early stage **favorable**
	No	Any	≥ 50	Early stage unfavorable
	Yes	Any	Any	Early stage unfavorable
IIB+/- E	No	Any	Any	Early stage unfavorable
	Yes	Any	Any	Early stage unfavorable
III-IV	Yes/No	Any	Any	Advanced-stage disease

cHL = classical Hodgkin lymphoma; E = extranodal.

International Prognostic Score (IPS) for Advanced Stage Disease

1 point for each factor

- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥ 45 yr
- 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

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

Hasenclever & Diehl, *N Engl J Med* 1998;339:1506-1514

ABVD

Pre-treatment screening

- Echocardiogram
- PFTs with DLCO

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
- Re-image 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 bili AST/ALT
  - Adjust for reduced EF/cardiac dysfunction
- Vinblastine: adjust in patients with increased bili AST/ALT
- Dacarbazine: severe irritant, may require central line

PFT = pulmonary function test; DLCO = diffusing capacity; CrCl = creatinine clearance; bili = bilirubin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; EF = ejection fraction.

ABVD: Adverse Events

- Emesis risk: HIGH (> 90)
  - Pre-medicate using 5-HT3 antagonist, steroid
- Infusion reactions
  - Test dose of bleomycin may be administered
- Venous access
  - Doxorubicin and vinblastine are vesicants
  - Dacarbazine is an extreme irritant
- Infection prophylaxis
  - Primary prophylaxis with G-CSF is generally ***not*** indicated
  - Avoid concurrent administration with bleomycin; may increase bleomycin lung toxicity
- 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.

Response-Adapted Frontline Therapy Deauville Criteria, PET 5-Point Scale

- Maximize cures while minimizing late effects
- Avoid undertreatment **or** overtreatment
- Reduce treatment-emergent adverse events
- Reduce potential long-term effects including secondary malignancies

Score	PET/CT result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Barington SF, et al. *J Clin Oncol* 2014;32:3048-58; Hutchings M. Hematology Am Soc Hematol Educ Program 2012;2012:322-7; Johnson PW. Hematology Am Soc Hematol Educ Program 2016;316-22.

Brentuximab Vedotin in Previously Untreated Stage III or IV HL: ECHELON-1 trial

- Randomized, open-label, two-arm, multicenter trial, n = 1,334
  - Patients randomized to receive either brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (B-AVD) or bleomycin plus AVD (ABVD) for up to 6 cycles on Days 1 and 15 of each 28-day cycle
- Efficacy based on modified progression-free survival (mPFS):
  - Defined as progression, death, or receipt of additional anticancer therapy for patients who are not in a CR after completion of frontline therapy
  - At a median of 24.6 months of follow-up, the median mPFS was not reached in either arm and OS analysis did not demonstrate a significant difference
  - There were 117 mPFS events: (18%) on the B-AVD arm and 146 events (22%) on the ABVD arm (HR, 0.77; 95% CI = 0.60–0.98; *p* = .035)
    - Corresponding to a 23% reduction in the risk of an mPFS event in the B-AVD arm
- FDA approved March 20, 2018 to treat adult patients with previously untreated stage III or IV classical Hodgkin lymphoma (cHL) in combination with chemotherapy

Connors, J. M., Jurczak, W., Straus, D. J., et al. (2018). N Engl J Med, 378(4), 331-344.

Brentuximab Vedotin in Previously Untreated Stage III or IV HL: ECHELON-1 trial

- Adverse events
  - The most common adverse reactions in at least 20% of patients treated with B-AVD: Neutropenia, anemia, peripheral sensory neuropathy, nausea, fatigue, constipation, diarrhea, vomiting, and pyrexia
  - Primary G-CSF prophylaxis is recommended with B-AVD plus chemotherapy for the frontline treatment of stage III or IV cHL
- Dosing
  - 1.2 mg/kg as an intravenous infusion up to a maximum of 120 mg every 2 weeks for 12 doses in combination with AVD

Connors, J. M., Jurczak, W., Straus, D. J., et al. (2018). N Engl J Med, 378(4), 331-344.

Relapsed/Refractory Hodgkin Lymphoma

Audience Response Question #11

Ms. Q is a 25-year-old female with R/R Hodgkin lymphoma. She progressed 6 months after completing treatment with 6 cycles of ABVD. She was then treated with ICE chemotherapy x 3 cycles, followed by an autologous stem cell transplant. She is here today to start brentuximab maintenance. You instruct her that:

A. She will be treated every 3 weeks for 16 cycles. The most common AEs are cytopenias, pneumonitis, anemia, and hair loss.
B. She will be treated every 3 weeks for 16 cycles. The most common AEs are peripheral sensory neuropathy, anemia, nausea, diarrhea, and fatigue.
C. She will be treated every 3 weeks for 6 cycles. The most common AEs are peripheral sensory neuropathy, neutropenia, diarrhea, pneumonitis, and fatigue.
D. She will be treated every 3 weeks for 6 cycles. The most common AEs are peripheral sensory neuropathy, neutropenia, rash, pneumonitis, and anemia.
E. Unsure

ICE = ifosfamide, carboplatin, and etoposide

Audience Response Question #12

Which of the following agents requires monitoring for hyperacute GVHD and veno-occlusive disease in patients with Hodgkin lymphoma who are treated after an allogeneic stem cell transplant?

A. Ipilimumab
B. Pembrolizumab
C. Nivolumab
D. Obinutuzumab
E. Unsure

GVHD = graft-vs.-host disease

Regimens Used for R/R cHL

- **Brentuximab vedotin (only for cHL)**
- Bendamustine
- C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) (category 2B)
- DHAP (dexamethasone, cisplatin, high-dose cytarabine)
- ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin)
- Everolimus
- GCD (gemcitabine, carboplatin, dexamethasone)
- GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
- ICE (ifosfamide, carboplatin, etoposide)
- IGEV (ifosfamide, gemcitabine, vinorelbine)
- Lenalidomide
- MINE (etoposide, ifosfamide, mesna, mitoxantrone)
- Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)
- **Nivolumab**
- **Pembrolizumab**

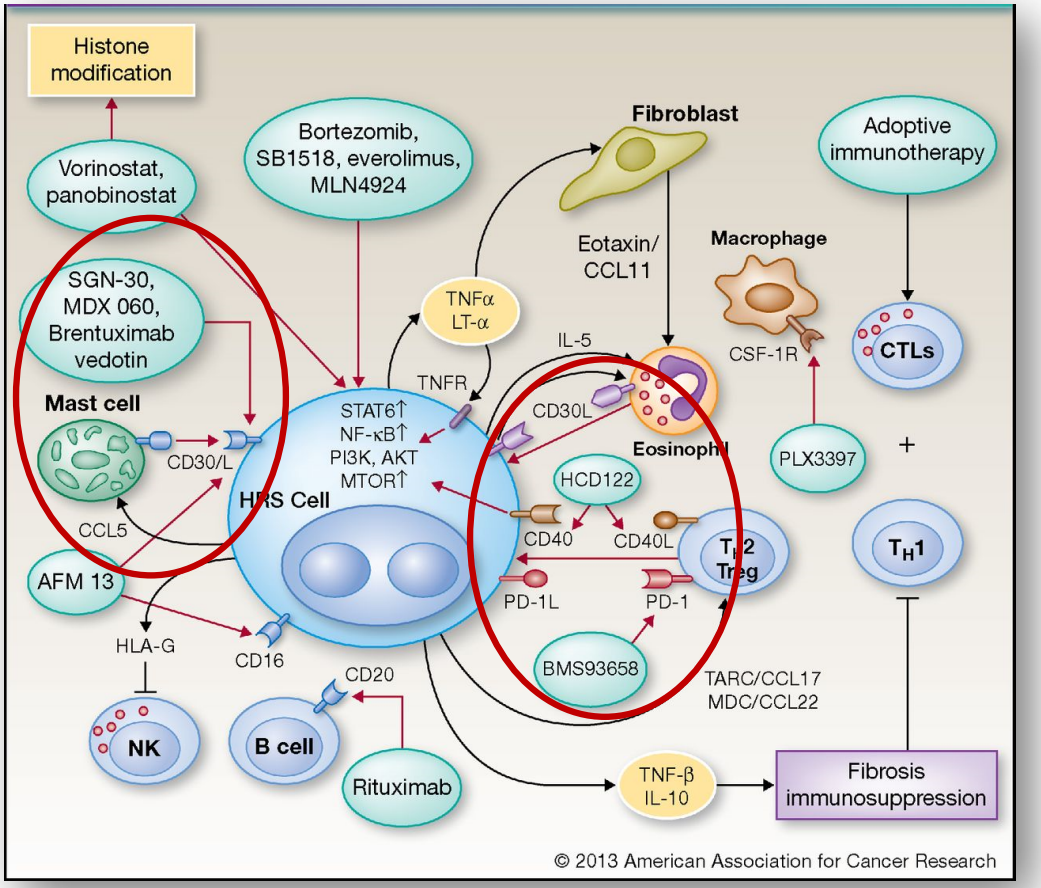
General Principles of Treatment for R/R cHL

- Consider pattern of relapse and agents previously used
- HSCT should be considered for transplant-eligible patients who achieve a CR 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 auto-HSCT and respond to third-line treatment
- Brentuximab vedotin is a treatment option if HDT/ASCR has failed or at least 2 prior multiagent chemotherapy regimens have failed
- Brentuximab vedotin can be used as second-line therapy prior to HDT/ASCR to minimize the use of more intensive chemotherapy
- Nivolumab or pembrolizumab are options for cHL that has relapsed or progressed following HDT/ASCR and post-transplant brentuximab vedotin

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

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 HL

Drug	Drug class	Target
Receptor-targeting therapies		
Brentuximab vedotin	ADC	CD30
Nivolumab	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

ADC = antibody-drug conjugate; MoAb = monoclonal antibody; NK = natural killer; HDACi = histone deacetylase inhibitor; mTOR = mechanistic target of rapamycin.

Diefenbach & Steidl. *Clin Cancer Res*. 2013;19(11):2797-803.

Brentuximab Vedotin

Class: Anti-CD30 MoAb

FDA Approval: August 19, 2011

Indication for cHL

- cHL after failure of auto-HSCT
- cHL in transplant ineligible candidates after failure of at least 2 multiagent chemotherapy regimens
- cHL at high risk of relapse or progression as post auto-HSCT consolidation

Dosing and administration

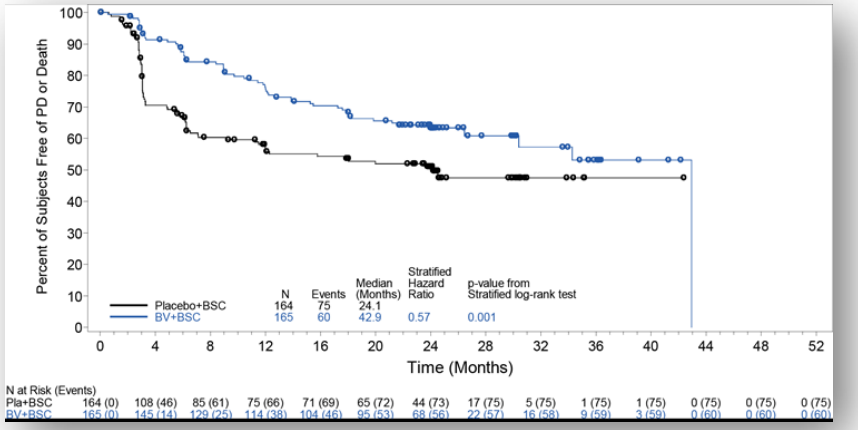
- 1.8 mg/kg intravenous infusion over 30 minutes every 3 weeks
- Reduce dose in patients with mild hepatic impairment
- Contraindication: concomitant use with bleomycin due to pulmonary toxicity

FDA = US Food and Drug Administration.

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

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–auto-HSCT, 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
  - Median number of cycles in each study arm was 15 (range, 1-16)
  - 80 patients (48%) in the BV arm received 16 cycles
  - Statistically significant improvement in PFS: BV 42.9 months, placebo 24.1, HR, 0.57 (95% CI 0.40–0.81; *p* = .001)



BV = brentuximab vedotin; HR = hazard ratio.

Epperla N, et al. (2015). *Bone Marrow Transplant*. doi:10.1038/bmt.2015.184
Brentuximab prescribing information, 2016, https://adcetris.com/pdf/ADCETRIS-brentuximab-vedotin-Prescribing-Information.pdf?v=20161101.

Brentuximab Safety: Most Common AEs ≥10%

- Anemia 62%
- Peripheral sensory neuropathy 45%
- Nausea 36%
- Diarrhea 29%
- Fatigue 29%
- Neutropenia 21%
- Pruritus 17%
- Pyrexia 17%
- Vomiting 17%
- Alopecia 15%
- Decreased appetite 15%
- Thrombocytopenia 15%
- Arthralgia 12%
- Myalgia 12%
- Asthenia 11%
- Dyspnea 11%
- Edema peripheral 11%
- Pruritus generalized 11%
- Rash maculo-papular 11%

BOXED WARNING

Progressive multifocal leukoencephalopathy (PML): JC virus infection resulting in PML and death can occur in patients receiving brentuximab.

Contraindication

Concomitant with bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

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

Nivolumab

Class: PD-1 blocking antibody

FDA Approval: March 17, 2016

Indication for cHL

- cHL that has relapsed or progressed after auto-HSCT and post-transplantation brentuximab vedotin

Dosing and administration

- 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
- **Updated dosing: March 6, 2018**
  - 480 mg every 4 weeks over 30 minutes until disease progression or unacceptable toxicity
  - Based on < 1% difference in the predicted probability of achieving a response for melanoma, NSCLC, or RCC.

NSCLC = non–small cell lung cancer; RCC = renal cell carcinoma

Nivolumab prescribing information, 2014, http://packageinserts.bms.com/pi/pi_opdivo.pdf.

Nivolumab (cont.)

- Drug-related adverse events
- No grade 4 or grade 5 drug-related AEs were reported

Serious adverse event	Any grade	Grade ≥ 3
MDS	1 (4)	1 (4)
Lymph node pain	1 (4)	0
Pancreatitis	1 (4)	1 (4)

Adverse event	Any grade	Grade ≥ 3
Any AE	18 (78)	5(22)
Rash	5 (22)	0
Thrombocytopenia	4 (17)	0
Fatigue	3 (13)	0
Pyrexia	3 (13)	0
Diarrhea	3 (13)	0
Nausea	3 (13)	0
Pruritus	3 (13)	0
Cough	2 (9)	0
Hypothyroidism	2 (9)	0
↓ ALC	2 (9)	1 (4)
Hypophosphatemia Hypercalcemia	2 (9)	0
Increased lipase	2 (9)	1 (4)
Stomatitis	2 (9)	1 (4)

Nivolumab After Autologous HSCT: CheckMate 205 study

- Multicenter, single-arm, phase II study enrolled patients with relapsed/refractory cHL after auto-HCT treatment failure into cohorts by treatment history (n = 243)
  - Cohort A: BV naive (n = 63)
  - Cohort B: BV received after auto-HCT (n = 80)
  - Cohort C: BV received before and/or after auto-HCT (n = 100)
  - All patients received nivolumab at 3 mg/kg every 2 weeks until disease progression/unacceptable toxicity.
- Primary end point: Objective response
- Results (median follow-up of 18 months)
  - Objective response rate was 69% (95% CI = 63%–75%) overall
  - 40% continued to receive treatment
  - Median duration of response was 16.6 months (95% CI = 13.2–20.3 months)
  - Median progression-free survival was 14.7 months (95% CI = 11.3–18.5 months)
- Adverse Events (grade ≥ 3):
  - Lipase increases (5%), neutropenia (3%), and ALT increases (3%).
  - 29 deaths occurred; none were considered treatment related.

BV = brentuximab vedotin; ALT = alanine aminotransferase.

Armand, P., Engert, A., Younes, A., et al. (2018). J Clin Oncol, Jco2017760793. doi:10.1200/jco.2017.76.0793

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, or those who have relapsed after 3 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

- Multicenter nonrandomized, open-label trial (n = 210)
- 3 cohorts defined by R/R cHL history
  - Cohort 1: progression after ASCT and subsequent brentuximab vedotin (BV; n = 69)
  - Cohort 2: failed salvage chemotherapy, ASCT ineligible, failed BV therapy (n = 81)
  - Cohort 3: failed ASCT, no BV after transplantation (n = 60)
  - Patients had received a median of four prior systemic therapies (range: 1–12)
- With a median follow-up of 9.4 months (range: 1–15)
  - ORR was 69% (95% CI = 62–75); PR: 47%, CR: 22%.
  - Median DOR = 11.1 months (range: 0+ to 11.1)

ORR = objective response rate; PR = partial response; DOR = duration of response.

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 (%)	Patients with primary refractory disease* (n = 73)	Patients relapsed after ≥ 3 lines of therapy* (n = 146)
ORR ▪ CR ▪ PR	58 (79.5) 17 (23.3) 41 (56.2)	99 (67.8) 21 (21.2) 68 (46.6)
SD	4 (5.5)	24 (16.4)
PD	8 (11.0)	20 (13.7)
Undetermined	3 (4.1)	3 (2.1)

* Subgroups were not mutually exclusive

SD = stable disease; PD = partial disease.

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.

KEYNOTE-087: Treatment-Related Adverse Events

- 9 patients discontinued because of treatment-related AEs
- 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)
Grade 3/4 AE	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)

AE = adverse event

Pembrolizumab Warnings and Precautions

- A new “Warning and Precaution” was added for complications of allo-HSCT after pembrolizumab
- Transplant-related deaths have occurred
- FDA has required the sponsor to further study the safety of allo-HSCT after pembrolizumab therapy

Monitor closely for:

- Hyperacute GVHD
- Severe (grade 3 to 4) acute GVHD
- Steroid-requiring febrile syndrome
- Hepatic VOD
- Other immune-mediated adverse reactions

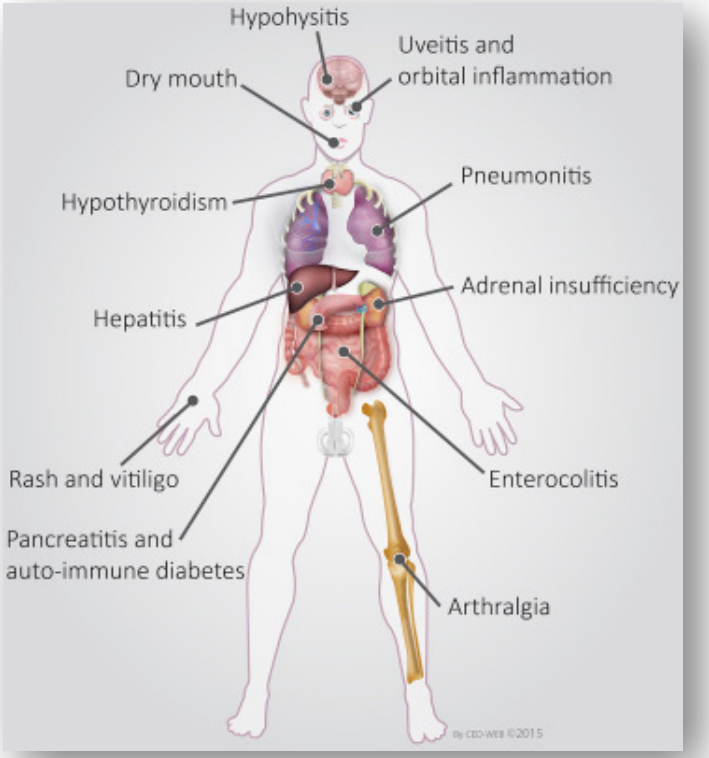
Allo-HSCT = allogeneic hematopoietic stem cell transplantation; GVHD = graft-vs.-host disease; VOD = veno-occlusive disease.

Pembrolizumab prescribing information, 2014, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

Adverse Events Associated With Immune Checkpoint Inhibition

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

Onset is often delayed compared to standard therapies



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

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

irAE = immune-related adverse event

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

Mechanism 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

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

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 health-care team, patients, and caregivers
- Rapid and timely intervention
  - Corticosteroids for some intolerable grade 2 irAEs and any grade 3/4 irAEs
  - Slow taper of glucocorticoids
- Re-initiation of treatment may be possible

Audience Response Question #11

Ms. Q is a 25-year-old female with R/R Hodgkin lymphoma. She progressed 6 months after completing treatment with 6 cycles of ABVD. She was then treated with ICE chemotherapy x 3 cycles, followed by an autologous stem cell transplant. She is here today to start brentuximab maintenance. You instruct her that:

A. She will be treated every 3 weeks for 16 cycles. The most common AEs are cytopenias, pneumonitis, anemia, and hair loss.
B. She will be treated every 3 weeks for 16 cycles. The most common AEs are peripheral sensory neuropathy, anemia, nausea, diarrhea, and fatigue.
C. She will be treated every 3 weeks for 6 cycles. The most common AEs are peripheral sensory neuropathy, neutropenia, diarrhea, pneumonitis, and fatigue.
D. She will be treated every 3 weeks for 6 cycles. The most common AEs are peripheral sensory neuropathy, neutropenia, rash, pneumonitis, and anemia.
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ICE = ifosfamide, carboplatin, and etoposide

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Which of the following agents requires monitoring for hyperacute GVHD and veno-occlusive disease in patients with Hodgkin lymphoma who are treated after an allogeneic stem cell transplant?

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B. Pembrolizumab
C. Nivolumab
D. Obinutuzumab
E. Unsure

GVHD = graft-vs.-host disease