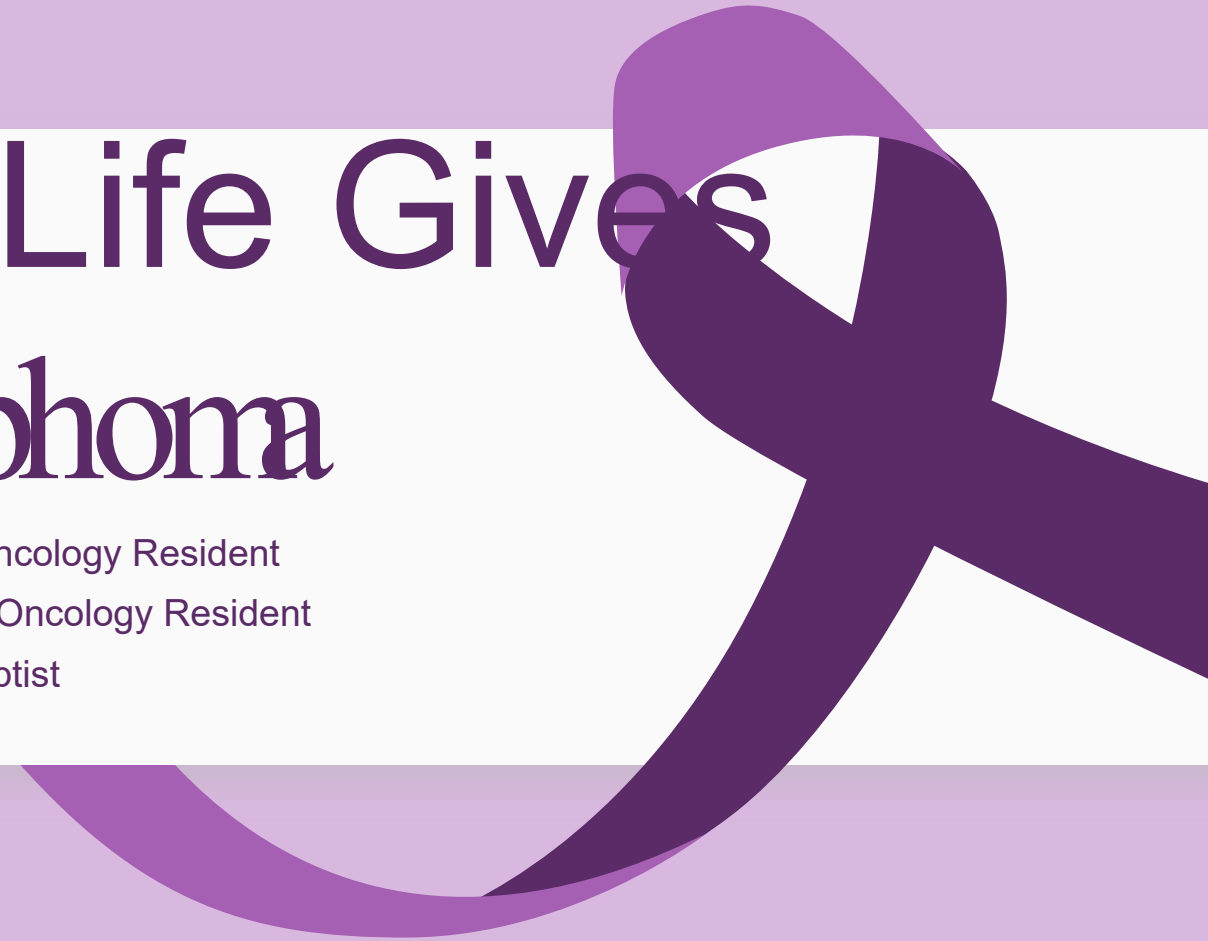
When Life Gives you Lymphoma

Karen Hoff, PharmD | PGY2 Oncology Resident
Megan Wolff, PharmD | PGY2 Oncology Resident
Atrium Health Wake Forest Baptist
10/16/2025



Disclosure

The planner(s) and speaker(s) have indicated that there are no relevant financial relationship with any ineligible companies to disclose.

Learning Objectives

At the end of this session, learners should be able to:

- **Recall** current NCCN 2025 guideline updates regarding immune checkpoint inhibitors in first - line and relapsed classical Hodgkin lymphoma
- **Outline** efficacy, response rates, and toxicity profiles of PD - 1–based regimens versus traditional chemotherapy in Hodgkin lymphoma
- **Interpret** clinical trial evidence to inform individualized patient treatment choices
- **Select** guideline - recommended strategies to real - world cases via clinical debate and audience response

Outline

- Background
- Early - Stage Disease Management
- Advanced - Stage Disease Management
- Relapsed or Refractory Disease Management
- Key Takeaways

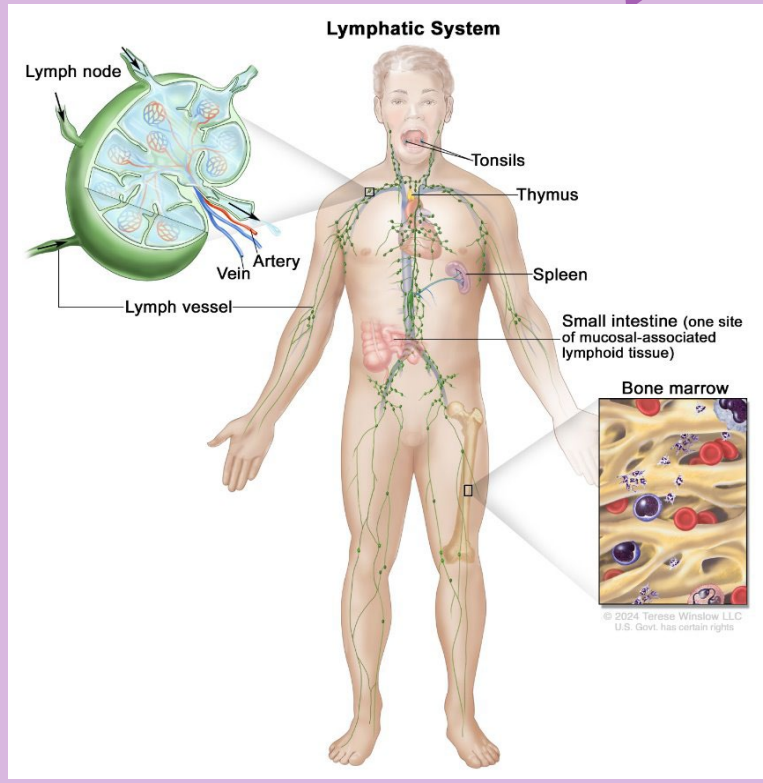
Abbreviation Key

- **CBC**: complete blood count
- **CHL**: classical Hodgkin lymphoma
- **CMP**: complete metabolic panel
- **CNS**: central nervous system
- **CR**: complete remission
- **CT**: computed tomography
- **ECOG**: Eastern Cooperative Oncology Group
- **EF**: ejection fraction
- **EOT**: end of treatment
- **ESR** erythrocyte sedimentation rate
- **FDG**: fluorodeoxyglucose
- **FNA**: fine needle aspirate
- **GCSF**: granulocyte colony stimulating factor
- **HIV**: human immunodeficiency virus
- **HL**: Hodgkin Lymphoma
- **ICI**: immune checkpoint inhibitor
- **ILD**: interstitial lung disease
- **ISRT**: involved - site radiation therapy
- **LDH**: lactate dehydrogenase
- **LFT**: liver function tests
- **MRI**: magnetic resonance imaging
- **OS**: overall survival
- **PET**: positron emission tomography
- **PFS**: progression - free survival
- **PFT**: pulmonary function tests
- **RT**: radiation therapy
- **SCT**: stem cell transplant
- **TREA**: treatment - related adverse event
- **WBC**: white blood cell

Background

Hodgkin Lymphoma

- Rare cancer of the **lymphatic** system
- Originates from abnormal **B lymphocytes**
- **Hallmark: Reed–Sternberg cells**
- Bimodal age distribution: young adults & older adults



NCI PDQ 2025; Ansell SM, *Am J Hematol* 2024

Pathophysiology

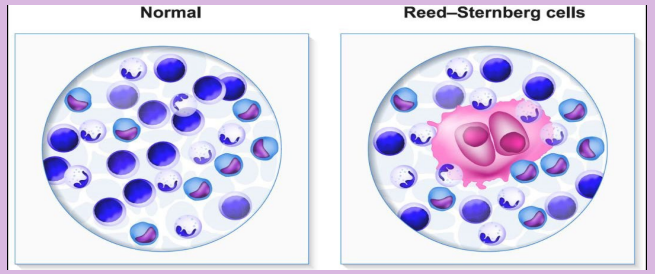
Originates from germinal center B cells

Reed–Sternberg cells drive disease via cytokine release

Infiltrating T cells, macrophages, eosinophils

Immune evasion mechanisms (PD-1/PD-L1 pathway)

Immune dysregulation & “B symptoms”



Ansell SM, *Am J Hematol* 2024; NCI PDQ 2025

Clinical Presentation

Lymphadenopathy

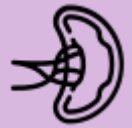
Painless, rubbery, cervical/supraclavicular most common

“B symptoms”

Fever, drenching night sweats, weight loss (>10% in 6 mo)

Other symptoms

Fatigue, pruritus, alcohol - induced pain



Advanced disease

Splenomegaly, hepatomegaly, mediastinal mass, extranodal sites (rare)

NCI PDQ 2025; Ansell SM, *Am J Hematol* 2024

Hodgkin Lymphoma

Patient Work-up

Labs

- CBC with differential
- ESR
- CMP, LDH, LFTs
- HIV testing
- Pregnancy test
- PFTs
- Hepatitis B & C testing

Imaging

- Diagnostic CT
- Chest x - ray
- FDG- PET/CT skull base to mid - thigh
- MRI of select sites
- FDG- PET/MRI skull base to mid - thigh
- Echocardiogram

Biopsy

- Core needle/FNA
- Excisional
- Bone marrow
- Immunohisto - chemistry evaluation

Staging & Risk Classification

Stage	Bulky Mediastinal Disease or > 10 cm Adenopathy	ESR > 50 or # Sites > 3	Type
IA/IIA	No	No	Favorable Disease
	No	Yes	Favorable/Unfavorable Disease
	Yes	Yes/No	Unfavorable Disease
IB/IIB	Yes/No	Yes/No	Unfavorable Disease
III-IV	Yes/No	N/A	Advanced Disease

Risk Factors

Unfavorable Risk Factors

- Age ⩾ 50
- ESR and B symptoms
- Mediastinal mass
- Number of nodal sites > 2-3
- E lesion
- Bulky

International Prognostic Score (IPS)

- Albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- Male
- Age ≥45 years
- Stage IV disease
- WBC ≥15,000/mm^3
- Lymphocyte count <600/mm^3 and/or <8% of WBC count

NCCN Clinical Practice Guidelines in Oncology (*NCCN Guidelines* ®) for Hodgkin Lymphoma V.2.2025.

Timeline of Eviden

Autesct

Autologous SCT became standard for relapsed/refractory CHL

ICsI

PD- 1 inhibitors approved for relapse/refractory CHL

1970s
1980s

1990s
2000s

2000s

2010s

AVBD

Becomes standard regimen

Monoclonal antibodies

Brentuximab vedotin developed for relapse/refractory CHL

How Staging Guides Th

PET- adaptation: Interim PET guides de - /escalation

NCCN v1.2025; RATHL NEJM 2016; RAPID NEJM 2015; H10 JCO 2014; ASCO Post 2025

Defining Stage Groups in Hodgkin Ly

Early-stage favorable (I–II)	• Limited to 1 –2 nodal regions (may include contiguous extranodal disease) • **Favorable:** no bulky disease, no B symptoms, ≤2 sites • **Unfavorable:** bulky mediastinal mass, extranodal disease, B symptoms, >2 sites
Advanced (III–IV)	Involves both sides of diaphragm or disseminated extra nodal disease
Relapsed / Refractory (R/R)	• **Relapsed** : disease returns after initial remission • **Refractory** : disease progresses during or right after frontline therapy

NCCN v1.2025; RATHL NEJM 2016; RAPID NEJM 2015; H10 JCO 2014; ASCO Post 2025

Treatment Guidelin

Early / Limited - Stage (I–II)

- **Favorable** : 2–4 cycles ABVD ⁒ ISRT
  - Consider PET - adapted de - escalation (omit bleomycin after negative PET - 2)
- **Unfavorable** : 4 cycles ABVD or PET- adapted programs with ISRTfor bulky/residual disease
  - Emerging PD - 1 + AVD

NCCN. Hodgkin Lymphoma. v1.2025.

Treatment Guidelin

Advanced - Stage (III –IV)

- **Preferred first - line (2024 –2025 updates):**
  - **Nivolumab - AVD** (category 1; superior PFS vs BV- AVD; better tolerated)
  - **BrECADD** (PET- adapted, strong PFS with lower toxicity vs eBEACOPP; give G - CSF)

NCCN. Hodgkin Lymphoma. v1.2025.

Treatment Guidelin

Relapsed / Refractory

- **Transplant-eligible:** PD-1- or BV-based **salvage → auto-HCT → consolidation** (BV or PD-1 in selected cases)
- **Transplant-ineligible / post-auto-HCT: PD-1 inhibitor** (pembro or nivo) ± BV/combo; integrate palliative ISRT for symptomatic sites

NCCN. Hodgkin Lymphoma. v1.2025.

Chemotherapy Regimens & Key T

ABVD: Pulmonary toxicity (bleomycin), cardiotoxicity (doxorubicin), neuropathy (vinblastine) nausea, myelosuppression

AVD (omit bleomycin): Reduced pulmonary risk (no bleomycin), but retains doxorubicin cardiotoxicity and neuropathy (vinblastine)

BV+AVD: Peripheral neuropathy, neutropenia → requires G-CSF support

Escalated BEACOPP/BrECADD: Myelosuppression, infertility risk, secondary malignancies, higher acute toxicity burden

RATHL NEJM 2016; ECHELON1 NEJM 2022; HD18 Lancet Oncol 2019; NCCN v1.2025

Immune Check Point Inhibitors

CHL is characterized by overexpression of PD - L1/PD- L2 on Reed - Sternberg cells

- Leads to immune evasion

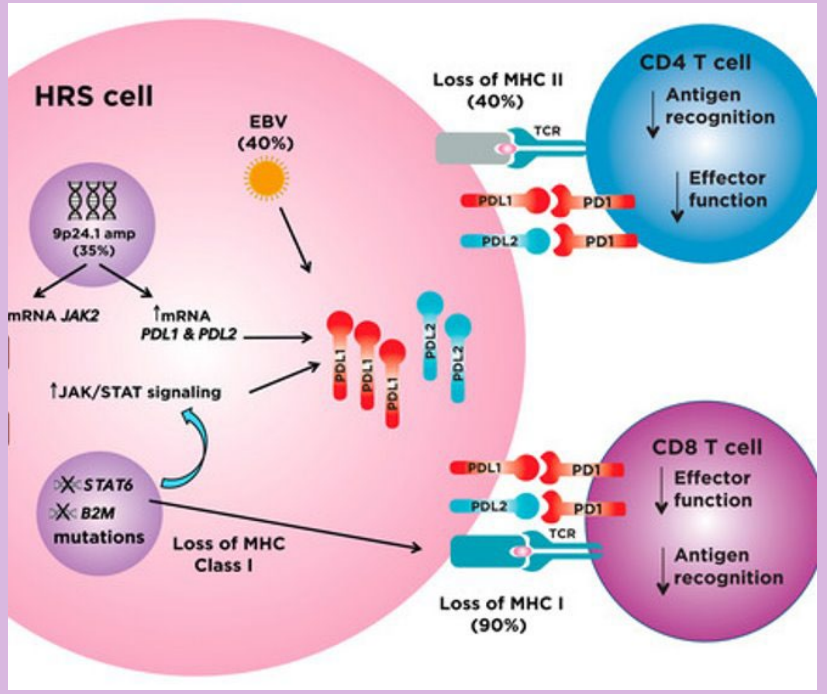
PD- 1 blockade restores antitumor T - cell activity

Two PD- 1 inhibitors approved for use in CHL

- Nivolumab (Opdivo ®)
- Pembrolizumab (Keytruda®)

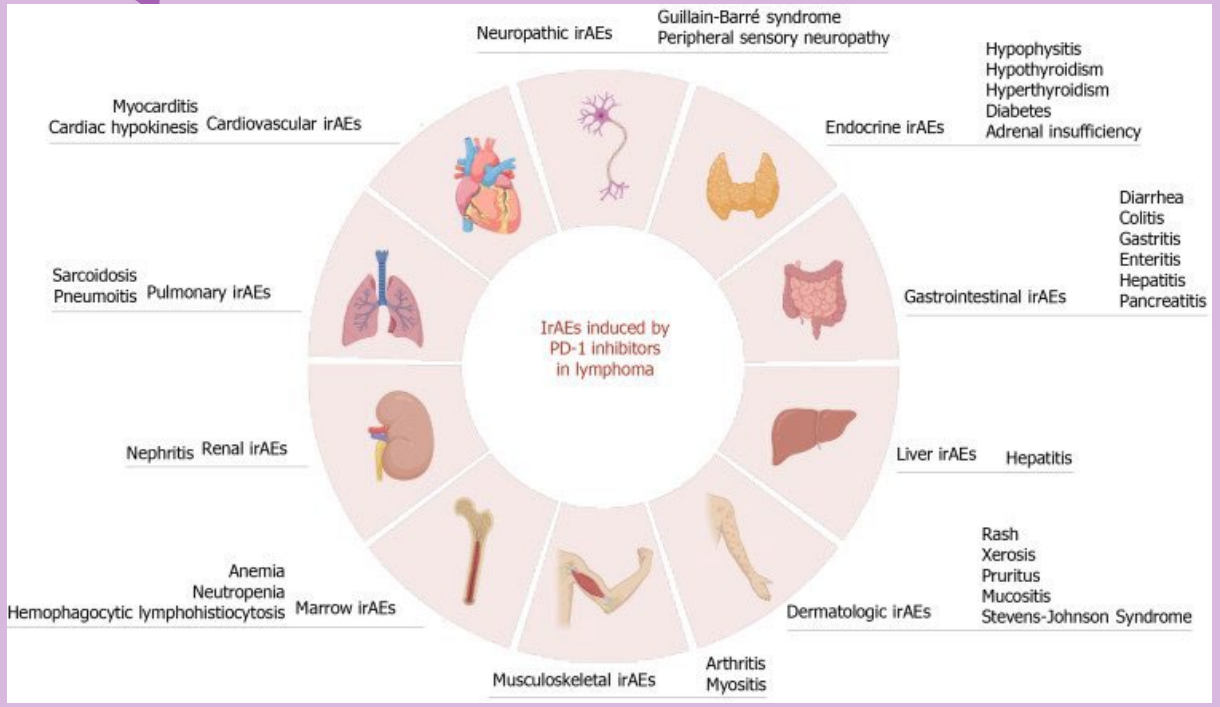
Immune - related adverse events (irAEs) most commonly affect the skin, GI tract, liver, and endocrine organs

Optimal sequencing and combination of ICIs with chemotherapy, brentuximab vedotin, and SCT are active areas of research



Meti N, et al. *Cancers* . 2018.

Immune-Related Adverse Events (IRAE)



Relatively delayed onset

Inflammatory and autoimmune

Can mimic known autoimmune diseases

May take longer to see responses vs chemotherapy

Incidence (high to low) - **"LEGS"** acronym

- **L**iver
- **E**ndocrine
- **G**I
- **S**kin

Yong-Zhe H, et al. *World J Clin* Cases. 2023. 11(7): 1458-1466.

Managing IRA

CTCAE Grade	Level of Care	Steroids	Other Immunosuppressive Drugs	Immunotherapy & Subsequent Approach
1	Outpatient	Not recommended	Not recommended	Continue
2	Outpatient	Topical or PO systemic steroids 0.5 - 1 mg/kg/day	Not recommended	Temporarily hold
3	Inpatient	PO or IV systemic steroids 1 - 2 mg/kg/day	Consider if symptoms resolve with 3 - 5 days of steroids. Organ specialist advised.	Hold, risk/benefit discussion
4	Inpatient, intensive care	IV methylprednisolone 1- 2 mg/kg/day	Consider if symptoms resolve with 3 - 5 days of steroids. Organ specialist advised.	Discontinue permanently

Schneider BJ, et al. *J Clin Oncol*. 2021;39:4073-4126.
NCCN Guidelines® for Management of Immunotherapy-Related Toxicities. V.1.2025.

Nivolumab (Opdivo®)

FDA approval in 2016 for CHL that has relapsed or progressed after auto - SCT and brentuximab vedotin

MOA: IgG4 monoclonal antibody binds PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing the inhibition of the immune response

Dosing

- 240 mg IV once every 2 weeks
- 480 mg IV once every 4 weeks

Adverse Effects : infusion-related reactions, embryo-fetal toxicity, fatigue, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, headache

Pembrolizumab (Keytrud®)

FDA approval in 2017 for adults and children with refractory CHL or who had relapsed after ⩾ 3 prior therapies

MOA: binds PD-1 receptor and blocks interaction with PD-L1 and PD-L2, releasing inhibition of immune response including the anti-tumor immune response

Dosing

- 200 mg once every 3 weeks
- 400 mg once every 6 weeks

Adverse Effects : infusion-related reactions, embryo-fetal toxicity, fatigue, musculoskeletal pain, decreased appetite, pruritus, GI upset, abdominal pain, cough, dyspnea

Other Considerations: Fertility Eff

Chemotherapy

- Alkylating agents → highest risk of gonadotoxicity
- ABVD relatively lower risk compared to ICE
- **Options**: sperm banking, oocyte/embryo cryopreservation prior to treatment

Immunotherapy

- Limited data on fertility; checkpoint inhibitors may affect reproductive hormones via endocrine immune-related adverse events (ex: hypophysitis, thyroiditis)

Key point: Immunotherapy is generally used ***with*** chemotherapy in Hodgkin lymphoma, not as single-agent therapy

Other Considerations: C

Chemotherapy	Immunotherapy
• Generally lower drug acquisition cost, but hospitalization and supportive care can increase total expense • ~$15,000–20,000 per cycle	• Substantially more expensive upfront; long - term value tied to improved remission durability and reduced late toxicities • ~$10,000–12,000 per dose (every 2 –3 weeks)

Other Considerations: Sequencing With Im

Frontline use (with chemotherapy)	Pre-transplant (salvage setting)	Post-transplant (relapse/refractory)
• Now guideline - preferred in advanced - stage disease • Potential to reduce exposure to more toxic regimens	• Can improve depth of response before autologous SCT • May shift timing of transplant or reduce chemo intensity	• Option for patients relapsing after auto - SCT • Often used to bridge to allogeneic SCT in select cases

Key challenge: Determining *optimal timing* (frontline vs pre/post SCT) to balance efficacy, durability, and toxicity

Assessment Question #1

Which set of toxicities is most consistent with immune checkpoint inhibitors compared to chemotherapy?

A. Cytopenias, nausea, alopecia

B. Peripheral neuropathy, infusion reactions

C. Always mild, self - limiting

D. Thyroiditis, pneumonitis, colitis

Assessment Question #1

Which set of toxicities is most consistent with immune checkpoint inhibitors compared to chemotherapy?

A. Cytopenias, nausea, alopecia

B. Peripheral neuropathy, infusion reactions

C. Always mild, self - limiting

D. Thyroiditis, pneumonitis, colitis

Early Stage

Timeline of Eviden

1970s–2010s

Chemotherapy

Chemotherapy ± radiation

2020

NIVAHL

Nivolumab in front - line therapy for early - stage unfavorable disease

~2023

KEYNOTE

Multiple early - phase frontline pembrolizumab studies

2024-present

Ongoing Trials

Focusing on radiation - sparing or chemo - sparing approaches in early - stage disease

Treatment Guidelin

Early / Limited - Stage (I–II)

- **Favorable** : 2–4 cycles ABVD ⁒ ISRT
  - Consider PET - adapted de - escalation (omit bleomycin after negative PET - 2)
- **Unfavorable** : 4 cycles ABVD or PET- adapted programs with ISRTfor bulky/residual disease
  - Emerging PD - 1 + AVD

NCCN. Hodgkin Lymphoma. v1.2025.

ABVD

Agent (Brand)	Dosing (cycle = 28 days)	Key Pharmacokinetics	Key Adverse Effects
Doxorubicin (Adriamycin®)	25 mg/m² IV Days 1 & 15	Hepatic metabolism (CYP450), biliary excretion	Myelosuppression, cardiotoxicity (cumulative dose), mucositis, alopecia, extravasation risk
Bleomycin (Blenoxane ®)	10 units/m² IV Days 1 & 15	Renal clearance; minimal hepatic metabolism;	Pulmonary fibrosis (dose - limiting), mucocutaneous reactions, fever/chills, anaphylaxis
Vinblastine (Velban ®)	6 mg/m² IV Days 1 & 15	Hepatic metabolism (CYP3A4); biliary excretion	Myelosuppression, peripheral neuropathy, constipation/ileus, SIADH
Dacarbazine (DTIC- Dome®)	375 mg/m² IV Days 1 & 15	Hepatic metabolism (CYP1A2, CYP2E1); renal clearance	Severe nausea/vomiting, myelosuppression, hepatotoxicity, flu - like syndrome, photosensitivity

HL in early stage disease

Standard First - Line Therapy

- ABVD ± ISRT
- High cure rates
- Established efficacy

Limitations of Traditional Therapy

- Long-term toxicities
- Desire for more targeted therapy

Immune Checkpoint Inhibitors

- Investigated in combination with AVD for frontline treatment
- Potential for reduced chemotherapy exposure and toxicity

HD11 Trial

Engert A, et al. *J Clin Oncol.* 2010;28(27):4199-4206.

Omission of RT in Early - Stage Unfavorable HL

Study Purpose	To evaluate the optimal chemotherapy backbone (ABVD vs BEACOPP baseline) and RT dose (20 Gy vs 30 Gy) in early-stage unfavorable Hodgkin lymphoma	
Trial Design	Phase III, multicenter, randomized	

Intervention	• 4 arms:
	  • 4 cycles ABVD + 30 Gy RT
	  • 4 cycles ABVD + 20 Gy RT
	  • 4 cycles BEACOPP baseline + 30 Gy RT
	  • 4 cycles BEACOPP baseline + 20 Gy RT	

Selection Criteria	<u>Inclusion</u> • Age 16–75 years • Histologically confirmed HL • Early-stage unfavorable features • ECOG performance status 0–2	<u>Exclusion</u> • Stage III–IV disease • Prior HL therapy • Pregnancy or lactation • Severe comorbidities precluding chemo/RT
Population	• n = 1,395; Median age: ~37 years • ~52% male	

HD11 Trial

Engert A, et al. *J Clin Oncol.* 2010;28(27):4199-4206.

Omission of RT in Early - Stage Favorable HL	

Primary Outcomes	**Freedom from Treatment Failure (FFTF)**
	• 5-year FFTF:
	  • ABVD + 30 Gy = 85.8%
	  • ABVD + 20 Gy = 85.4%
	  • BEACOPP + 30 Gy = 87.1%
	  • BEACOPP + 20 Gy = 86.0%
	• No significant differences between arms

Secondary Outcomes	• **Overall Survival (OS):** 5-year OS ~95% across all groups (no significant difference) • **Toxicity:** BEACOPP had more hematologic toxicity; ABVD better tolerated • **RT dose:** 20 Gy noninferior to 30 Gy
Author's Conclusion	4 cycles ABVD + 20 Gy IFRT = optimal balance of efficacy and safety in early - stage unfavorable HL Higher RT dose and BEACOPP did not improve outcomes, but increased toxicity

NivAHL Trial

Bröckelmann PJ, et al. *JAMA Oncol*. 2021.

Early Response to First - Line Anti - PD- 1 Treatment in Hodgkin Lymphoma

Study Purpose	To evaluate efficacy of 2 experimental nivolumab-based first-line treatment strategies in patients with early-stage unfavorable CHL	
Trial Design	Open-label, multicenter, phase 2 randomized (1:1) clinical trial	
Intervention	• Concomitant treatment with 4 cycles of nivolumab and AVD (N-AVD) • Sequential treatment with 4 doses of nivolumab, 2 cycles of N-AVD, and 2 cycles of AVD at standard doses, followed by 30-Gy involved-site radiotherapy	
Selection Criteria	<u>Inclusion</u> • Aged 18-60 years • Newly diagnosed CHL of early-stage unfavorable risk by GHSG criteria	<u>Exclusion</u> • Stage IIb with large mediastinal mass and/or extranodal disease
Population	• Median age of 27 • Majority of patients (60%) were female • Majority of patients (75%) were stage IIa • Majority of patients (66%) had bulky disease (≥5cm in largest diameter)	

NivAHL Trial

Voltin CA, et al. *Clin Cancer Res* . 2021.

Early Response to First - Line Anti - PD- 1 Treatment in Hodgkin Lymphoma	
Primary Outcomes	CR rate after end of study • Concomitant group: 90% (95% CI, 79 - 97%) • Sequential group: 94% (95% CI, 84 - 99%)
Secondary Outcomes	**12- month PFS** : • Concomitant group: 100% • Sequential group: 98% (95% CI, 95 - 100%) **12- month OS** : 100% in both treatment groups **Most common any grade TRAEs** : anemia, leukopenia, nausea, vomiting, hepatobiliary/pancreatic disorders, skin disorders **Most common Grade 3/4 TRAEs** : leukopenia
Author's Conclusion	Both N - AVD strategies proved feasible and highly effective providing excellent 12 - month PFS with early, durable responses and unexpectedly high interim CR rates after only 4 doses of nivolumab

Assessment Question #2

KB is a 32- year - old female diagnosed with early - stage unfavorable classical Hodgkin lymphoma. They have bulky mediastinal disease, but no B symptoms. Their past medical history includes seasonal allergies, severe asthma, and hypertension. Which therapy would be the most appropriate first - line therapy for KB?

A. ABVD

B. ABVD + ISRT

C. N- AVD

D. Nivolumab monotherapy

Assessment Question #2

KB is a 32-year-old female diagnosed with early-stage unfavorable classical Hodgkin lymphoma. They have bulky mediastinal disease, but no B symptoms. Their past medical history includes seasonal allergies, severe asthma, and hypertension. Which therapy would be the most appropriate first-line therapy for KB?

A. ABVD

B. ABVD + ISRT

C. N- AVD

D. Nivolumab monotherapy

Advanced Stage

Timeline of Eviden

1970s-2000s

Chemotherapy backbone

ABVD backbone, escalated to BEACOPP

2010s

Brentuximab Vedotin

Integrated into ABVD to become BV - AVD

2016

Nivolumab

FDA- approval for relapsed/refractory CHL

2017

Pembrolizumab

FDA- approval for relapsed/refractory CHL

Treatment Guidelin

Advanced - Stage (III –IV)

- **Preferred first - line (2024 –2025 updates):**
  - **Nivolumab - AVD** (category 1; superior PFS vs BV- AVD; better tolerated)
  - **BrECADD** (PET- adapted, strong PFS with lower toxicity vs eBEACOPP; give G - CSF)

NCCN. Hodgkin Lymphoma. v1.2025.

RATHL Trial

Johnson et al, NEJM 2016 (RATHL trial)

Response - Adapted Therapy in Advanced Hodgkin Lymphoma		
Study Purpose	To determine whether **omitting bleomycin** after a negative interim PET scan in patients receiving ABVD compromises treatment efficacy while reducing pulmonary toxicity	
Trial Design	Open-label, multicenter, phase 3 randomized clinical trial	
Intervention	• All patients: 2 cycles of ABVD → interim PET after 2 cycles • PET-negative (~84% of pts): randomized to continue ABVD (with bleomycin) vs AVD (omit bleomycin) for 4 more cycles • PET-positive (~16% of pts): escalated to BEACOPP (not randomized)	
Selection Criteria	<u>Inclusion</u> • Aged 18-80 years • Histologically confirmed classical Hodgkin lymphoma • Advanced stage (IIB with bulk, III, or IV) • ECOG 0–2	<u>Exclusion</u> • Prior chemotherapy or radiotherapy • Significant comorbidities precluding anthracycline or bleomycin use • CNS involvement
Population	• N = 1214 patients with previously untreated, advanced-stage (IIB–IV) HL • Median age: 32 years	

RATHL Trial

Johnson et al, NEJM 2016 (RATHL trial)

	Response - Adapted Therapy in Advanced Hodgkin Lymphoma
Primary Outcomes	3-year PFS: • ABVD arm = 85.7% (95% CI, 82.1–88.6) • AVD arm = 84.4% (95% CI, 80.7–87.5) • HR: 1.13 (95% CI, 0.841.57) → non-inferior
Secondary Outcomes	3-year OS • ABVD: 97.2% (95% CI, 95.1–98.4) vs AVD: 97.6% (95% CI, 95.6–98.7) • No significant difference Pulmonary toxicity • ABVD: 7% vs AVD: 3% • p = 0.01 PET-positive group (n ≈ 172, 16% of study): • Switched to escalated BEACOPP • 3-year PFS: ~67.5% (95% CI, 59–75) • Improved compared to historical ABVD outcomes in PET-positive patients
Author's Conclusion	For PET-negative patients after 2 cycles of ABVD, dropping bleomycin is safe; preserves PFS/OS and reduces pulmonary toxicity

BVAVD

Agent (Brand)	Dosing (cycle = 28 days)	Key Pharmacokinetics	Key Adverse Effects
Brentuximab vedotin (Adcetris ®)	1.2 mg/kg IV Days 1 & 15	Antibody – drug conjugate (anti - CD30 mAb linked to MMAE); catabolized via proteolysis; MMAE metabolized by CYP3A4/5	Peripheral neuropathy (dose - limiting), neutropenia, infusion reactions, progressive multifocal leukoencephalopathy (rare)
Doxorubicin (Adriamycin®)	25 mg/m² IV Days 1 & 15	Hepatic metabolism (CYP450), biliary excretion	Myelosuppression, cardiotoxicity (cumulative dose), mucositis, alopecia, extravasation risk
Vinblastine (Velban ®)	6 mg/m² IV Days 1 & 15	Hepatic metabolism (CYP3A4); biliary excretion	Myelosuppression, neuropathy, constipation/ileus, SIADH
Dacarbazine (DTIC- Dome®)	375 mg/m² IV Days 1 & 15	Hepatic metabolism (CYP1A2, CYP2E1); renal clearance	Severe nausea/vomiting, myelosuppression, hepatotoxicity, flu - like syndrome, photosensitivity

ECHELON-1 Trial

Ansell SM et al, NEJM 2022 (ECHELON- 1 trial)

Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma		
Study Purpose	To determine whether brentuximab vedotin + AVD (BV+AVD) improves efficacy compared to ABVD in previously untreated patients with advanced (stage III–IV) classical Hodgkin lymphoma	
Trial Design	Open-label, international multicenter, phase 3 randomized clinical trial	
Intervention	• BV+AVD arm: brentuximab vedotin 1.2 mg/kg IV d1,15 + doxorubicin 25 mg/m² IV d1,15 + vinblastine 6 mg/m² IV d1,15 + dacarbazine 375 mg/m² IV d1,15 every 28 days × 6 cycles (G-CSF prophylaxis recommended) • ABVD arm: standard ABVD × 6 cycles	
Selection Criteria	<u>Inclusion</u> • Age ≥18 years • Histologically confirmed stage III or IV classical HL • ECOG 0–2	<u>Exclusion</u> • Prior HL therapy • Peripheral neuropathy grade ≥2 • CNS involvement • Pregnant or breastfeeding
Population	• Median age: ~36 years • 58% stage IV disease • ~60% had International Prognostic Score (IPS) 0–2; remainder higher risk • Balanced baseline characteristics between arms	

ECHELON-1 Trial

Ansell SM et al, NEJM 2022 (ECHELON-1 trial)

Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma	
Primary Outcomes	2-yr mPFS • BV+AVD: 82.1% (95% CI, 79.4–84.7) • ABVD: 77.2% (95% CI, 73.9–80.2) • HR 0.77 (95% CI, 0.60–0.98); p = 0.03
Secondary Outcomes	OS (6-yr update) • BV+AVD: 93.9% (95% CI, 92.0–95.4) • ABVD: 89.4% (95% CI, 87.0–91.4) • HR 0.59 (95% CI, 0.40–0.88); p = 0.009 Toxicity • Pulmonary events: higher with ABVD (bleomycin-related) • Neuropathy: higher with BV+AVD (peripheral neuropathy, mostly reversible) • Neutropenia: more frequent with BV+AVD → mitigated by mandatory G-CSF prophylaxis in protocol amendment
Author's Conclusion	BV+AVD significantly improved PFS and OS vs ABVD in stage III–IV HL. Toxicity profile differs: pulmonary toxicity avoided, but neuropathy and neutropenia increased

BrECADD

Agent (Brand)	Dosing (cycle = 21 days)	Key Pharmacokinetics	Key Adverse Effects
Brentuximab vedotin (Adcetris®)	1.8 mg/kg IV Day 1	Antibody–drug conjugate (anti-CD30 mAb + MMAE); catabolized via proteolysis; MMAE metabolized by CYP3A4	Peripheral neuropathy, neutropenia, infusion reactions, rare PML
Etoposide (Toposar®)	200 mg/m² IV Days 2–4	Hepatic metabolism (CYP3A4); biliary/renal excretion	Myelosuppression, mucositis, alopecia, secondary leukemias
Cyclophosphamide (Cytoxan®)	1250 mg/m² IV Day 2	Prodrug; hepatic metabolism (CYP2B6/3A4); renal excretion	Myelosuppression, hemorrhagic cystitis, infertility, secondary malignancy
Doxorubicin (Adriamycin®)	40 mg/m² IV Day 2	Hepatic metabolism; biliary excretion	Cardiotoxicity, mucositis, alopecia, extravasation
Dacarbazine (DTIC-Dome®)	250 mg/m² IV Days 2–4	Hepatic metabolism (CYP1A2/2E1); renal clearance	Severe nausea/vomiting, myelosuppression, hepatotoxicity, flu-like syndrome
Dexamethasone	40 mg PO/IV Days 1–4	Hepatic metabolism (CYP3A4); renal/biliary excretion	Hyperglycemia, immunosuppression, mood changes, insomnia

HD21 Trial

Ansell SM et al, NEJM 2022 (ECHELON- 1 trial)

BrECADD vs escalated BEACOPP in patients with advanced - stage classical Hodgkin lymphoma		
Study Purpose	To determine if BrECADD is non-inferior (or superior) to escalated BEACOPP (eBEACOPP) for advanced-stage classical HL, with the goal of maintaining efficacy while reducing toxicity	
Trial Design	Open-label, international multicenter, phase 3 randomized 1:1 clinical trial	
Intervention	• BrECADD: Brentuximab vedotin + Etoposide + Cyclophosphamide + Doxorubicin + Dacarbazine + Dexamethasone (21-day cycles × 4–6) • eBEACOPP: Standard GHSG escalated BEACOPP × 4–6 cycles • Both arms PET-adapted after 2 cycles	
Selection Criteria	Inclusion • Age 18–60 years • Newly diagnosed classical HL, stage IIB bulky, III, or IV • ECOG ≤2	Exclusion • Prior chemo or radiotherapy for HL • Major organ dysfunction precluding intensive chemo • Pregnancy/breastfeeding
Population	• Median age: ~31 years • 54% male • All had advanced-stage disease (IIB bulky, III, IV) • Majority had International Prognostic Score (IPS) ≥3	

HD21 Trial

Ansell SM et al, NEJM 2022 (ECHELON- 1 trial)

BrECADD vs escalated BEACOPP in patients with advanced - stage classical Hodgkin lymphoma	
Primary Outcomes	PFS at 3 years: • BrECADD: 94.9% vs eBEACOPP: 92.3% • HR = 0.66 (95% CI, 0.44 –0.99) → BrECADD superior TRMB at 1 year: • BrECADD: 42% vs eBEACOPP: 59% • Absolute reduction: 17 percentage points (p<0.0001)
Secondary Outcomes	OS at 3 years: ~98% in both groups (no significant difference) Toxicity: • BrECADD had less grade ≥3 hematologic toxicity and fewer infertility/secondary malignancy signals • Higher rates of peripheral neuropathy (expected from BV)
Author's Conclusion	BrECADD is superior to eBEACOPP in terms of PFS and significantly reduces treatment-related morbidity. It provides a new standard of care for advanced HL, especially in younger, high-risk patients. Supports a shift away from traditional BEACOPP toward BV-based regimens in the frontline setting

ICs in Advanced stage disease

PD-1 inhibitors (nivolumab and pembrolizumab) are now established for advanced-stage CHL

Emerging frontline strategies

- PD-1 inhibitors in combination with AVD show promise in untreated advanced-stage disease
- Potential to reduce chemotherapy intensity while maintaining efficacy

Therapy goal to maximize disease control and minimize long-term toxicity

S1826

Herrera AF, et al. *NEJM* 2024.

Nivolumab + AVD in Advanced - Stage Classic Hodgkin's Lymphoma

Study Purpose	To evaluate nivolumab combined with AVD versus BV-AVD in adolescent and adult patients with newly diagnosed stage III or IV CHL	
Trial Design	Phase 3, multicenter, open-label, randomized trial	
Intervention	• Brentuximab vedotin + AVD (BV-AVD) • Nivolumab + AVD (N-AVD) • Prespecified patients could receive radiation therapy	
Selection Criteria	<u>Inclusion</u> • Ages ≥ 12 years • Stage III or IV newly diagnosed CHL • Zubrod performance status 0-2	<u>Exclusion</u> • Active autoimmune disease • Pre-existing interstitial lung disease • ≥ Grade 2 peripheral neuropathy
Population	• Median age 27 year (range 12-83) • Majority were males (55%) • Majority had stage IV disease - 62% in N-AVD and 65% in BV-AVD • Bulky disease (≥ 10 cm) present in – 32% N-AVD and 26% BV-AVD	

S1826

Herrera AF, et al. *NEJM* 2024.

Nivolumab + AVD in Advanced - Stage Classic Hodgkin's Lymphoma

Primary Outcomes	**2- year PFS** • N- AVD: 92% (95% CI, 89- 94%) • BV- AVD: 83% (95% CI, 79- 86%) • HR for disease progression or death was 0.45 (95% CI, 0.30 - 0.65)
Secondary Outcomes	**2- year OS** • 99% in N- AVD vs 98% in BV- AVD • HR for death was 0.39 (95% CI, 0.15 - 1.03) **TRAEs** • N- AVD: more neutropenia compared to BV - AVD • BV- AVD: more frequent peripheral neuropathy, febrile neutropenia, and infections • BV- AVD also had higher rates of treatment discontinuation
Author's Conclusion	N- AVD resulted in longer progression - free survival and better side - effect profile than BV- AVD in adolescents and adults with stage III or IV advanced - stage CHL.

Pembro-AVD in Untreated CHL

Lynch R, et al. *Blood*. 2023.

Concurrent Pembrolizumab with AVD for Untreated Classic Hodgkin Lymphoma		
Study Purpose	To evaluate the safety, feasibility, and efficacy of concurrent pembrolizumab with AVD in untreated CHL, and compare its efficiency with sequential approaches	
Trial Design	Single-center, open-label, investigator-initiated clinical trial	
Intervention	AVD on days 1 and 15 of a 28-day cycle • Doxorubicin 25 mg/m^2 • Vinblastine 6 mg/m^2 • Dacarbazine 375 mg/m^2 Pembrolizumab 200 mg given every 21 days starting on cycle 1 day 1	
Selection Criteria	<u>Inclusion:</u> • Any stage of CHL, no prior treatment • Measurable disease • ECOG performance status 0-1 • EF ≥ 50%, adequate organ function	<u>Exclusion:</u> • Autoimmune disease • Pneumonitis or ILD requiring steroids or supplemental oxygen
Population	Median age was 33 years, 60% were female, and 60% were in advanced stage (N=60)	

Pembro+AVD in Untreated CHL

Lynch R, et al. *Blood*. 2023.

Concurrent Pembrolizumab with AVD for Untreated Classic Hodgkin Lymphoma	
Primary Outcomes	Safety and tolerability of 2 cycles • Most common TRAE(s): neutropenia, anemia, constipation, nausea, ALT elevation • Most common Grade 3/4 TRAE(s): neutropenia, febrile neutropenia • No deaths were observed in any study patient during treatment or follow-up • No treatment delays >21 days during first 2 cycles
Secondary Outcomes	Efficacy • ORR shown on PET2/CT: 100% • CR rate shown on PET2/CT: 66% • CR at EOT: 82% • 2-year PFS: 97% (95% CI, 90-100%) • 2-year OS: 100%
Author's Conclusion	Concurrent pembrolizumab and AVD is a time-efficient frontline option for CHL with promising safety and efficiency

Assessment Question #3

According to the 2025 NCCN Guidelines for advanced-stage classical Hodgkin lymphoma, BV+AVD or PD-1 inhibitor–based therapy are frontline preferred regimens. In which of the following patients would ABVD remain a reasonable initial choice?

A. A 28-year-old female, stage IVB HL, no comorbidities, good performance status

B. A 62-year-old male, stage IIIB HL, with severe rheumatoid arthritis on immunosuppressants

C. A 35-year-old male, stage IIIB HL, with bulky mediastinal disease and normal organ function

D. A 45-year-old female, stage IV HL, with a remote kidney transplant on low-dose prednisone

Assessment Question #3

According to the 2025 NCCN Guidelines for advanced-stage classical Hodgkin lymphoma, BV+AVD or PD-1 inhibitor–based therapy are frontline preferred regimens. In which of the following patients would ABVD remain a reasonable initial choice?

A. A 28-year-old female, stage IVB HL, no comorbidities, good performance status

B. A 62-year-old male, stage IIIB HL, with severe rheumatoid arthritis on immunosuppressants

C. A 35-year-old male, stage IIIB HL, with bulky mediastinal disease and normal organ function

D. A 45-year-old female, stage IV HL, with a remote kidney transplant on low-dose prednisone

Relapse Stage

Treatment Pathway in Relapsed/Refractory H

Salvage Chemotherapy

- BV- ICE: brentuximab vedotin + ICE; bridge to ASCT
- Pembro - GVD: pembrolizumab + GVD
- Other regimens: ICE, DHAP, GDP (historical)
- Goal: disease control

Autologous Stem Cell Transplant

- Curative intent in eligible patients

Post- ASCT Options

- **PD- 1 inhibitors** (nivolumab, pembrolizumab) if relapse after ASCT/ BV
- **Clinical trials / novel combinations**

BVICE Regimen – 21 Days

Drug	Typical Dose	Notes / Key Toxicities
Brentuximab vedotin	1.8 mg/kg IV day 1	Peripheral neuropathy, cytopenias
Ifosfamide	5 g/m² IV over 24 h day 2 (with mesna uroprotection)	Neurotoxicity, nephrotoxicity, hemorrhagic cystitis
Carboplatin	AUC 5 IV day 2	Myelosuppression, nephrotoxicity, nausea
Etoposide	100 mg/m² IV days 1 –3	Myelosuppression, mucositis, alopecia

nivolumab

BV- Nivo

- Salvage therapy with brentuximab vedotin (BV) + nivolumab (nivo) in the relapsed/refractory setting
- Alternative to chemotherapy - based salvage thearpy
- Well tolerated and provides durable remission
- Estimated PFS at 3 years for patients who go on to auto - SCT 91%

NICE

- Nivolumab + ifosfamide + carboplatin + etoposide (NICE) salvage therapy and bridge to auto - SCT
- Well tolerated and effective with a high CR
- Estimate 2 - year PFS for patients bridged to auto - SCT 94%

Advani RH, et al. *Blood*. 2021; 138: 427-438.
Mei MG, et al. *Blood*. 2022; 139: 3605-3616.

pembrolizumab

Pembro - GVD

- Pembrolizumab (Pembro)+ gemcitabine + vinorelbine + liposomal doxorubicin (GVD)
- Acceptable tolerability and compatible with outpatient administration
- Efficient bridge to auto - SCT
- Promising option for patients previously treated with BV

ICE- Pembrolizumab

- Ifosfamide + carboplatin + etoposide (ICE) + pembrolizumab
- Well tolerated and effective relapse/refractory CHL therapy
- Results in high CR and is appropriate for bridge to auto - SCT

Moskowitz AJ, et al. *J Clin Oncol*. 2021;39:3109-3117.
Bryan LJ, et al. *JAMA Oncol*. 2023;9:683-691.

Pembro-GVD Regimen – 21 Days

Drug	Typical Dose	Notes / Key Toxicities
Pembrolizumab	200 mg IV day 1	Immune - related adverse events (colitis, pneumonitis, hepatitis, endocrinopathies)
Gemcitabine	1,000 mg/m² IV days 1 & 8	Myelosuppression, transaminase elevation
Vinorelbine	20 mg/m² IV days 1 & 8	Neuropathy, neutropenia, constipation
Liposomal doxorubicin	15 mg/m² IV days 1 & 8	Hand - foot syndrome, mucositis, cardiotoxicity

Checkpoint Inhibitor Sequencing & Transplant Considerations

Setting	Response Data	Key Considerations
Checkpoint inhibitor used upfront (nivo-AVD in frontline)	Salvage with PD-1 inhibitors may have lower ORR/CR vs CPI-naïve patients	Efficacy attenuated after prior CPI exposure; consider BV- or chemo-based salvage
Checkpoint inhibitor used salvage (pembro-GVD)	ORR ~80–85%, CR ~70–80% in CPI-naïve R/R HL	High activity, well tolerated, effective bridge to auto-SCT
Checkpoint inhibitor near transplant	Pre-auto-SCT: generally safe with monitoring; Pre-allo-SCT: ↑ GVHD risk if used within 6–8 weeks	Guidelines suggest washout period (≥6–12 wks) before allo-SCT to reduce GVHD

Moskowitz AJ, *J Clin Oncol*. 2021
Bryan LJ, *JAMA Oncol*. 2023
Herrera AF, *Blood Adv*. 2023

Assessment Question #4

What is the primary role of salvage chemotherapy in relapsed/refractory Hodgkin lymphoma?

A. To provide long - term disease control without the need for further therapy

B. To bridge patients to autologous stem cell transplant by inducing remission and enabling stem cell collection

C. To replace the use of brentuximab - vedotin and PD - 1 inhibitors in modern practice

D. To minimize long - term toxicities compared to immunotherapy

Assessment Question #4

What is the primary role of salvage chemotherapy in relapsed/refractory Hodgkin lymphoma?

A. To provide long - term disease control without the need for further therapy

B. To bridge patients to autologous stem cell transplant by inducing remission and enabling stem cell collection

C. To replace the use of brentuximab-vedotin and PD-1 inhibitors in modern practice

D. To minimize long-term toxicities compared to immunotherapy

Summary/Conclusions

Chemo Take Away Points

ABVD	BV+AVD	Escalated BrECADD	All anthracycline - containing regimens
• Pulmonary toxicity (bleomycin) • Consider omit B if PET- neg after 2 cycles	•Peripheral neuropathy • G- CSF recommended	• Myelosuppression •Infections •Infertility Risk	•Cardiotoxicity; baseline EF and risk modification

Role of Nivolumab in Hodgkins Ly

Historically

- Used in relapsed or refractory setting
- CHL that has relapsed or progressed after auto - SCT and brentuximab vedotin
- After ⩾ 3 lines of systemic therapy, including auto-SCT

Expanded Role

- Becoming a preferred first-line option in combination with chemotherapy
- NIVAHL Trial demonstrated early efficacy in 2 different nivolumab-based treatment strategies
- S1826 Trial showed N-AVD to have greater efficacy than BV-AVD

Role of Pembrolizumab in Hodgkins L

Historically

- Used in relapsed or refractory setting
- Monotherapy after failing ⩾ 2 lines of therapy
- Demonstrates high overall response rates in previously treated CHL

Expanded Role

- Sequential use with AVD in untreated, advanced-stage CHL has shown complete response and durable remissions
- Concurrent use with AVD had promising complete response rates and progression-free survival
- Ongoing trials are evaluating optimal sequencing and duration for use in frontline therapy

Overall Summar

Early - Stage HL (I – II)

- ABVD backbone remains standard
- **NCCN 2025** : Nivolumab + AVD is now a **Category 1** option in selected early - stage patients (especially unfavorable or high - risk features)

Advanced - Stage HL (III – IV)

- **Historical regimens** : ABVD, BV- AVD
- **NCCN 2025:** Nivolumab + AVD = **Category 1** preferred frontline

Relapsed/Refractory HL

- Salvage chemotherapy → **bridge to ASCT**
- PD- 1 inhibitors highly active in post- ASCT

Other Considerations

- **Fertility preservation** : critical discussion for young patients
- **Cost/access** : immunotherapies significantly higher upfront expense
- Long- term toxicities (chemo vs immunotherapy) influence treatment planning

Questions Left to be Answ

- Role of immunotherapy in early stage favorable
- Immunotherapy in high - risk populations
- Sequencing of immunotherapy upfront & in relapse

References

- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Hodgkin Lymphoma. Version 1.2025. Accessed September 8, 2025. https://www.nccn.org/professionals/physician_gls/pdf/hodgkin.pdf
- National Cancer Institute. Adult Hodgkin Lymphoma Treatment (PDQ®) – Health Professional Version. Updated July 26, 2025. Accessed September 8, 2025. https://www.cancer.gov/types/lymphoma/hp/adult - hodgkin - treatment - pdq
- Ansell SM. Hodgkin lymphoma: 2025 update on diagnosis, risk - stratification, and management. Am J Hematol . 2024;99(12):2367 - 2378. doi:10.1002/ajh.27470
- Meti, Nicholas et al. “The Role of Immune Checkpoint Inhibitors in Classical Hodgkin Lymphoma.” *Cancers* vol. 10,6 204. 15 Jun. 2018, doi:10.3390/cancers10060204
- Armand, Philippe, et al. "Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial." *Journal of Clinical Oncology* 36.14 (2018): 1428-1439.
- Ramchandren, Radhakrishnan, et al. "Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the phase II CheckMate 205 study." *Journal of Clinical Oncology* 37.23 (2019): 1997-2007.
- Bröckelmann, Paul J., et al. "Efficacy of nivolumab and AVD in early-stage unfavorable classic Hodgkin lymphoma: the randomized phase 2 German Hodgkin Study Group NIVAHL trial." *JAMA oncology* 6.6 (2020): 872-880.
- Herrera, Alex F et al. “Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma.” *The New England journal of medicine* vol. 391,15 (2024): 1379-1389. doi:10.1056/NEJMoa2405888
- Lynch, Ryan C., et al. "Concurrent pembrolizumab with AVD for untreated classic Hodgkin lymphoma." *Blood, The Journal of the American Society of Hematology* 141.21 (2023): 2576-2586.

References

- Moskowitz AJ, Schöder H, Yahalom J, et al. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second - line therapy for relapsed/refractory classical Hodgkin lymphoma. *J Clin Oncol* . 2021;39(28):3109-3117. doi:10.1200/JCO.21.01176
- Bryan LJ, Casulo C, Gopal AK, et al. Phase II study of pembrolizumab in combination with ICE chemotherapy for relapsed or refractory classical Hodgkin lymphoma. *JAMA Oncol* . 2023;9(5):683-691. doi:10.1001/jamaoncol.2023.0375
- Herrera AF, Chen R, Bartlett NL, et al. Outcomes after allogeneic stem cell transplantation in patients with Hodgkin lymphoma exposed to checkpoint inhibitors. *Blood Adv* . 2023;7(8):1669-1679. doi:10.1182/bloodadvances.2022009328
- Chen, Robert, et al. "Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma." *Journal of Clinical Oncology* 35.19 (2017): 2125-2132.
- Kuruvilla, John, et al. "KEYNOTE-204: Randomized, open-label, phase III study of pembrolizumab (pembro) versus brentuximab vedotin (BV) in relapsed or refractory classic Hodgkin lymphoma (R/R cHL)."(2020): 8005-8005.

Questions?

Karen Hoff, PharmD
karen.hoff@advocathealth.org

Megan Wolff, PharmD
megan.wolff@advocatehealth.org

CE Learning Platform

https://ce.advocatehealth.org

Remember to create/update your profile in the CE platform, complete and evaluation, then claim credit.

SMS Text Code to Claim Credit

Claim your attendance instantly by texting
XXXXX to 414-219-1219

- Texting alone will not claim credit. You will still need to fill out an evaluation.
- *If you need to claim less credit, please contact the IPCE office at cme@aah.org*
- *Credits will be stored in your account on https://ce.advocatehealth.org*

Code is valid for 30 days after the day of the activity.

*Remember your profile, and mobile number will need to be updated on the CE Learning Platform in order to claim credit via texting.

When Life Gives you Lymphoma

Karen Hoff, PharmD | PGY2 Oncology Resident
Megan Wolff, PharmD | PGY2 Oncology Resident
Atrium Health Wake Forest Baptist
10/16/2025