21ST INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM™

Are Immunotherapy Toxicities A Concern in Hodgkin Lymphoma?

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Disclosures

Rebecca Follenweider: No relevant financial or nonfinancial relationships to disclose

Kaitlin Kelly: No relevant financial or nonfinancial relationships to disclose

Gilda Grace Rivera: No relevant financial or nonfinancial relationships to disclose

Abbreviations

- AE: adverse event
- BV: brentuximab vedotin
- cHL: classical Hodgkin lymphoma
- EOT: end of treatment
- Hx: history
- GCSF: granulocyte colony stimulating factor
- HL: Hodgkin lymphoma
- IPS: international prognostic score
- IrAE: immune related adverse event
- Nivo: nivolumab
- ORR: overall response rate
- Pembro: pembrolizumab
- PN: peripheral neuropathy
- r/r: relapsed/refractory
- RT: radiation therapy
- TSH: thyroid stimulating hormone

Objectives

- Describe treatment updates to frontline advanced-stage Hodgkin lymphoma
- Employ strategies for management of toxicities associated with checkpoint inhibitors and antibody-drug conjugates
- Apply toxicity treatment in patient case scenarios

Hodgkin Lymphoma

cHL is a considered a highly curable cancer

- 5-year relative survival
  - Overall: 88.9%
  - Early Stage: 91.8-95%
  - Advanced Stage: 80.5-86.7%

Seer Cancer Stat Facts: Hodgkin Lymphoma. National Cancer Institute ; 2023

Treatment History of Hodgkin Lymphoma

Goal to maximize efficacy while reducing toxicity

Early Stage

- Treatment: ABVD x 2-4 cycles +/- radiation

Advanced Stage

- Treatment: ABVD x 2 → AVD x 4 vs. BEACOPP

Timeline History of FDA Approvals in cHL

- **2011**
  - **BV**
  - R/R HL >2 lines Post-ASCT relapse
- **2015**
  - **BV**
  - R/R HL Post-ASCT consolidation in high-risk patients
- **2016**
  - **Nivolumab**
  - R/R HL Post-ASCT or BV relapse
- **2017**
  - **Pembrolizumab**
  - R/R HL >3 lines
- **2018**
  - **BV-AVD**
  - Upfront HL Grade III-IV
- **2020**
  - **Pembrolizumab**
  - R/R HL in adult and pediatric patients

Leroyer et al. J . Clin. M ed. 2022, 11, 6574

Antibody Drug Conjugate

Brentuximab Vedotin

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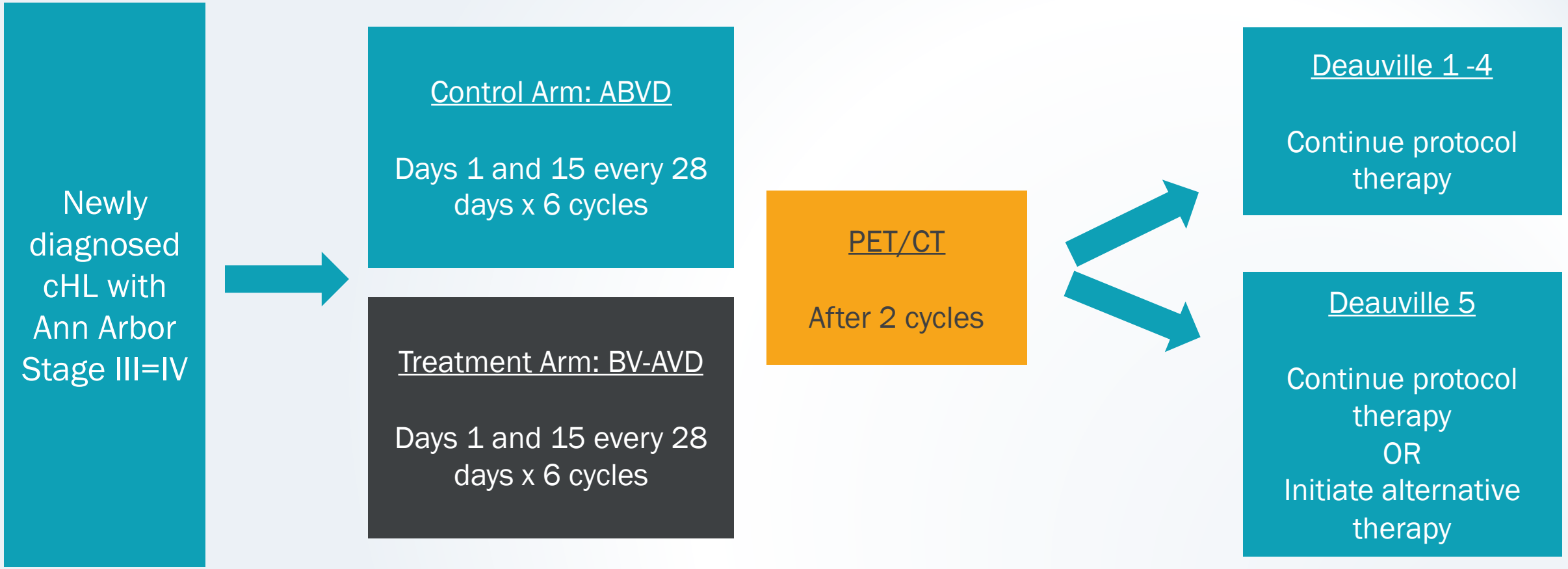
ECHELON-1 Study Design



Conners, JM , e t al. N Engl J Med. 2018 Jan 2 5;3 78(4):33 1-344

ECHELON-1 Safety

Events	BV-AVD (n=662)	ABVD (n=659)
Grade 3 or higher adverse event	549 (83)	434 (66)
Adverse event resulting in discontinuation	88 (13)	105 (16)
Neutropenia - Any Grade - Grade 3 or higher	 383 (58) 357 (54)	 295 (45) 260 (39)
Febrile neutropenia during treatment	9/83 (19)	49/616 (8)
Peripheral Neuropathy - Any Grade - Grade 3 or higher	 189 (29) 31 (5)	 111 (17) 3 (<1)
Hospitalizations	242 (37)	186 (28)
Pulmonary Toxicity	12 (2)	44 (7)

Conners, JM , et al. N Engl J Med. 2018 Jan 2 5;3 78(4):33 1-344
An sell, SM , et al. N En gl J M ed 2022 Jul 2 8;3 87 (4):3 1 0-3 20.

Brentuximab Vedotin in R/R cHL

BV-ICE

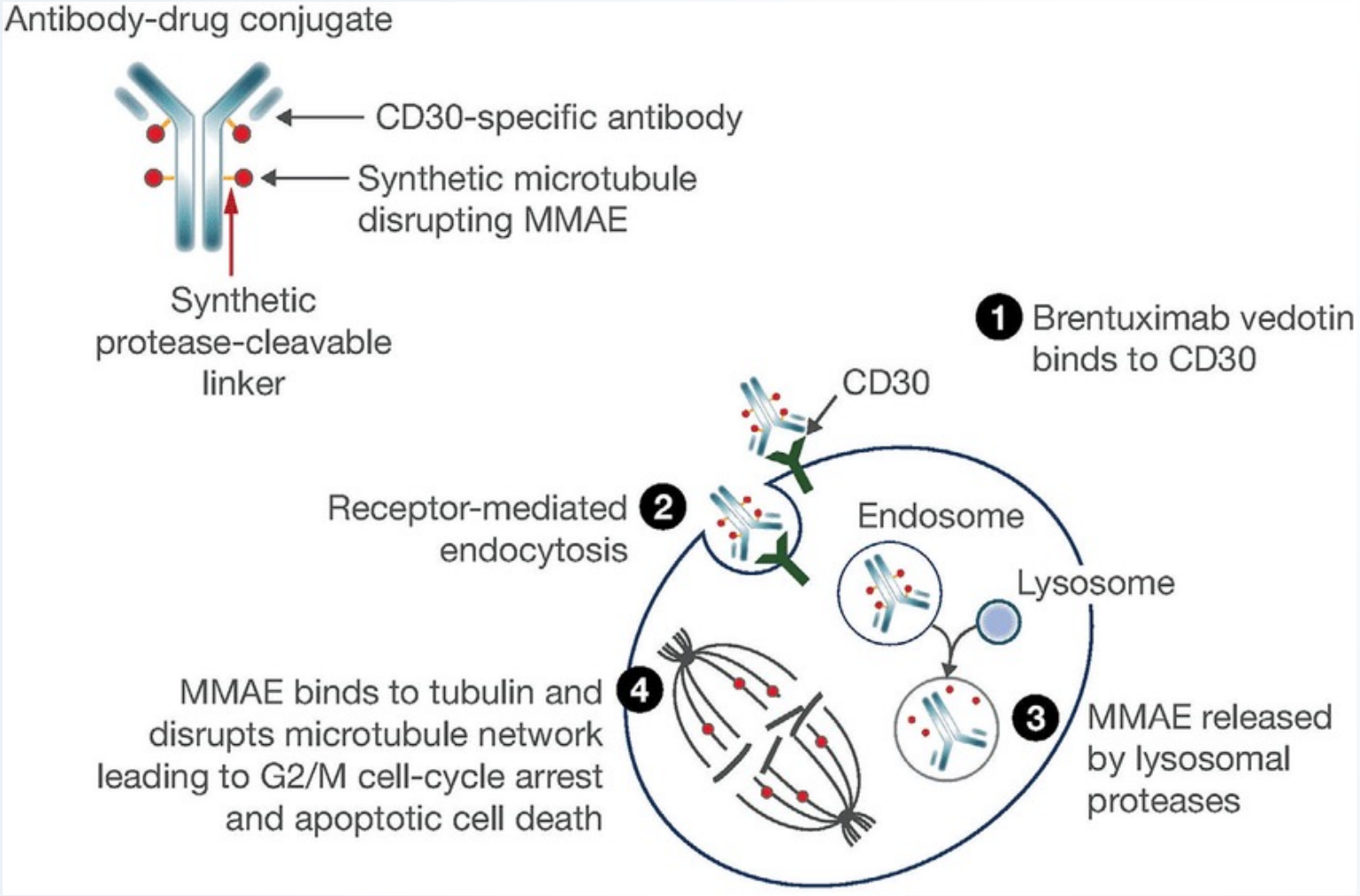
- Treatment toxicity due to BV instead of ICE
  - Peripheral neuropathy: 16/45 patients (36%)
    - Grade 2 or higher: 3 patients (7%)
  - Grade 3-4 Elevated transaminases
    - ALT: 5 patients (11%)
    - AST: 2 (4%)

BV-Nivolumab

- Common Adverse Events
  - Nausea: 47 patients (52%)
  - Infusion related reactions: 39 patients (43%)
  - Fatigue: 36 patients (40%)
- Peripheral neuropathy: 16 patients (18%)
  - Grade 3: 1 patient
- Neutropenia
  - Grade 3: 4 patients
  - Grade 4: 1 patient
- Thrombocytopenia
  - Grade 3: 1 patient
  - Grade 4: 1 patient

Advani, RH, et al. Blood 2021 Aug 12;138(6):427-438
Lynch , RC , et al. Lancet Haematol. 2021 Aug;8(8):e562-e 571 .

Brentuximab Vedotin Mechanism of Action



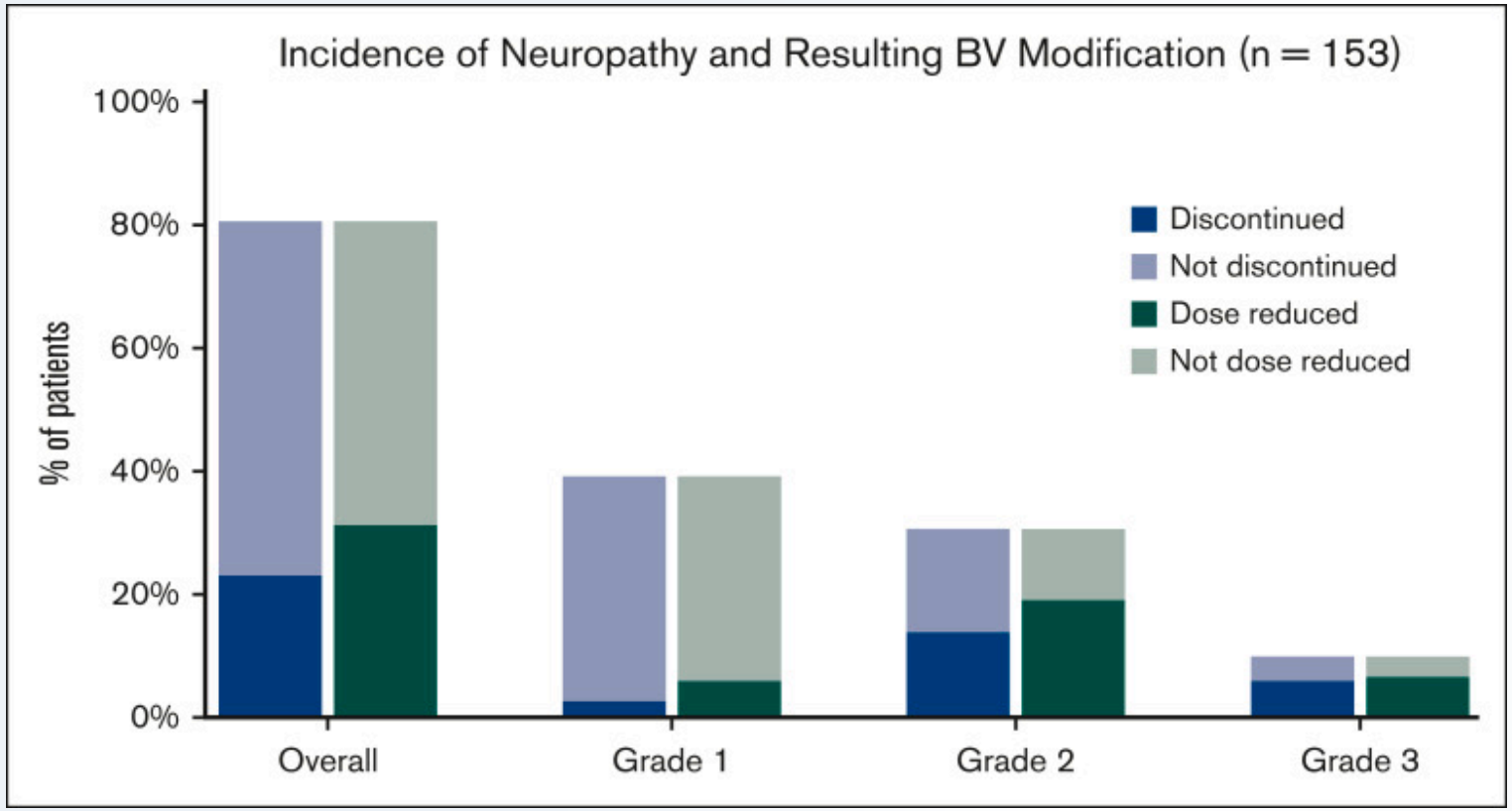
Brentuximab vedotin [package insert] Bothell, WA, Seagen Inc; 2023

Peripheral Neuropathy with Brentuximab Vedotin

Recommended Initial Dose	Monotherapy or Combination	Severity	Modification
1.2 mg/kg up to max of 120 mg every 2 weeks	In combination with chemotherapy	Grade 2	Reduce to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks
		Grade 3	Hold BV dosing until improvement to Grade 2 or lower Restart at 0.9 mg/kg up to a maximum of 90 mg every 2 weeks Consider modifying the dose of other neurotoxic chemotherapy agents
1.8 mg/kg up to a maximum of 180 mg every 3 weeks	As monotherapy	New or worsening Grade 2 or 3	Hold dosing until improvement to baseline or Grade 1 Restart at 1.2 mg/kg up to a maximum of 120 mg every 3 weeks
	In combination with chemotherapy	Grade 2	Sensory: Continue treatment at same dose Motor: 1.2 mg/kg up to max of 120 mg every 2 weeks
		Grade 3	Sensory: 1.2 mg/kg up to max of 120 mg every 2 weeks Motor: Discontinue

Brentuximab vedotin [package insert] Bothell, WA, Seagen Inc; 2023

Incidence and Management of Peripheral Neuropathy with BV-AVD



Characteristic	Overall (n=153)
Any Neuropathy	123 (80%)
Distribution	
- Sensory only	84 (55%)
- Motor only	1 (1%)
- Mixed sensory and motor	29 (19%)
- Unknown	9 (6%)
Median time to onset, mo (range)	2 (0.23-13)

Bowers JT, Anna J, Bair SM, et al. Brentuximab vedotin plus AVD for Hodgkin lymphoma: incidence and management of peripheral neuropathy in a multisite cohort. *Blood Adv*. 2023;7(21):6630-6638.

Incidence and Management of Peripheral Neuropathy with BV-AVD

Medication or therapy	Patients with neuropathy (n=123)
Gabapentin	53 (43%)
Duloxetine or other SNRI	12 (10%)
Vitamin B complex	12 (10%)
Pregabalin	8 (7%)
Exercise therapy	5 (4%)
Alpha lipoic acid	4 (3%)
Acupuncture	5 (4%)
Amitriptyline or other TCA	3 (2%)
Other	7 (6%)
None	48 (39%)

**Patients may have been prescribed more than 1 medication above*

- Median follow up time: 24 months
- Resolved neuropathy: 41 patients (35%)
- Improved by 1 grade: 44 patients (38%)
- Complete resolution more common in less severe toxicity
- Unchanged neuropathy: 31 patients (27%)
- Persistent neuropathy: 75 patients (65%)

Bowers JT, Anna J, Bair SM, et al. Brentuximab vedotin plus AVD for Hodgkin lymphoma: incidence and management of peripheral neuropathy in a multisite cohort. *Blood Adv*. 2023;7(21):6630-6638.

Neutropenia with Brentuximab Vedotin

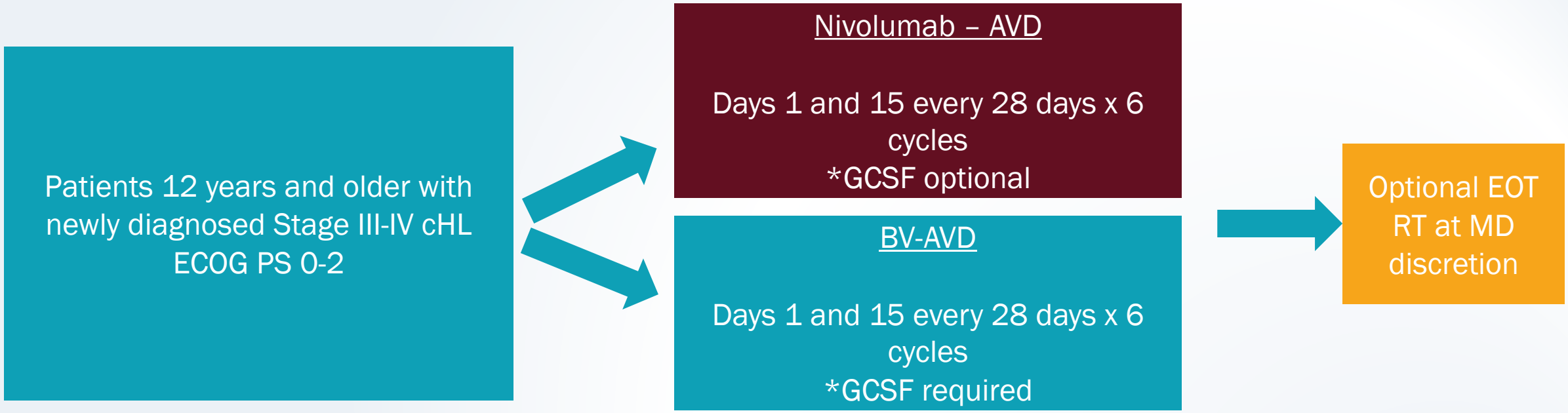
Recommended Initial Dose	Monotherapy or Combination	Severity	Modification
1.2 mg/kg up to max of 120 mg every 2 weeks	In combination with chemotherapy	Grade 3 or 4	Administer GCSF prophylaxis for subsequent cycles for patients not receiving primary GCSF prophylaxis
			Hold BV dosing until improvement to Grade 2 or lower Restart at 0.9 mg/kg up to a maximum of 90 mg every 2 weeks Consider modifying the dose of other neurotoxic chemotherapy agents
1.8 mg/kg up to a maximum of 180 mg every 3 weeks	As monotherapy	Grade 2 or 3	Hold dosing until improvement to baseline or Grade or lower Consider GCSF prophylaxis for subsequent cycles
		Grade 4 despite GCSF prophylaxis	Consider discontinuation of dose reduction to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks

Brentuximab vedotin [package insert] Bothell, WA, Seagen Inc; 2023

Immune Checkpoint Inhibitors

Nivolumab, Pembrolizumab

SWOG S1826: Study Design



Herrera. ASCO 2023. Abstr LBA4.

SWOG S1826 Safety

	Nivo-AVD (n=483)		BV-AVD (n=473)	
	Discontinued Nivolumab 53 (11%)		Discontinued BV 109 (22%)	
	Any Grade	Grade 3 +	Any Grade	Grade 3 +
<u>Infections</u>				
• Febrile Neutropenia	26 (5%)	-	32 (7%)	-
• Infections	22 (5%)	-	36 (8%)	-
• Received GCSF	265 (54%)	-	463 (95%)	-
<u>Immune Related</u>				
• Increased ALT	156 (32%)	22 (5%)	194 (41%)	22 (5%)
• Increased AST	120 (25%)	12 (2%)	153 (32%)	13 (3%)
• Rash	51 (11%)	4 (1%)	58 (12%)	0
• Hypothyroidism	33 (7%)	1 (0%)	3 (1%)	0
<u>Peripheral Neuropathy</u>				
• Sensory	138 (29%)	6 (1%)	262 (55%)	37 (8%)
• Motor	20 (4%)	1 (0%)	35 (7%)	6 (1%)
<u>Hematologic</u>				
• Neutropenia	268 (55%)	227 (47%)	152 (32%)	118 (25%)
• Anemia	185 (38%)	29 (6%)	207 (44%)	42 (9%)
• Thrombocytopenia	48 (10%)	8 (2%)	82 (17%)	15 (3%)

Herrera. ASCO 2023. Abstr LBA4.

Checkpoint Inhibitors in R/R cHL

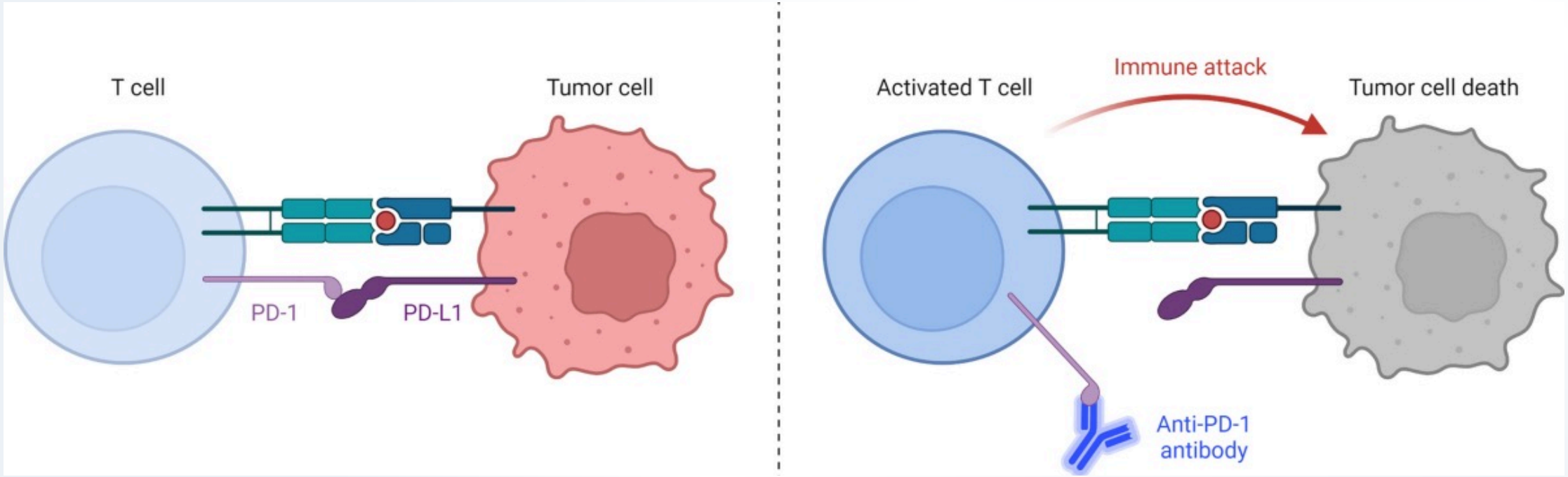
Pembrolizumab-GVD N=45	Nivolumab-ICE N=43

• Rash (49%)
• Elevated AST/ALT (41%)
• Hyperthyroidism: (13%)
• Fatigue (31%)
• Diarrhea (18%)
• Nausea (36%)
	• Monotherapy Nivo (Grade 1-2)
	  • Fatigue (33%)
	  • Maculopapular rash (19%)
	  • Arthralgia (16%)
	• NICE (Grade 3+ toxicity)
	  • Neutropenia: 2 patients
	  • Hypophosphatemia: 2 patients
	  • Febrile neutropenia: 1 patient
	  • Colitis: 1 patient
	• Immune Related AE
	  • Maculopapular Rash: 8 patients
	  • Thyroiditis: 3 patients
	  • Acneiform rash: 2 patients
	  • Grade 4 encephalitis: 1 patient
	  • Grade 3 colitis: 1 patient

**Other treatment regimens: Pembrolizumab, Nivolumab, Pembrolizumab-ICE*

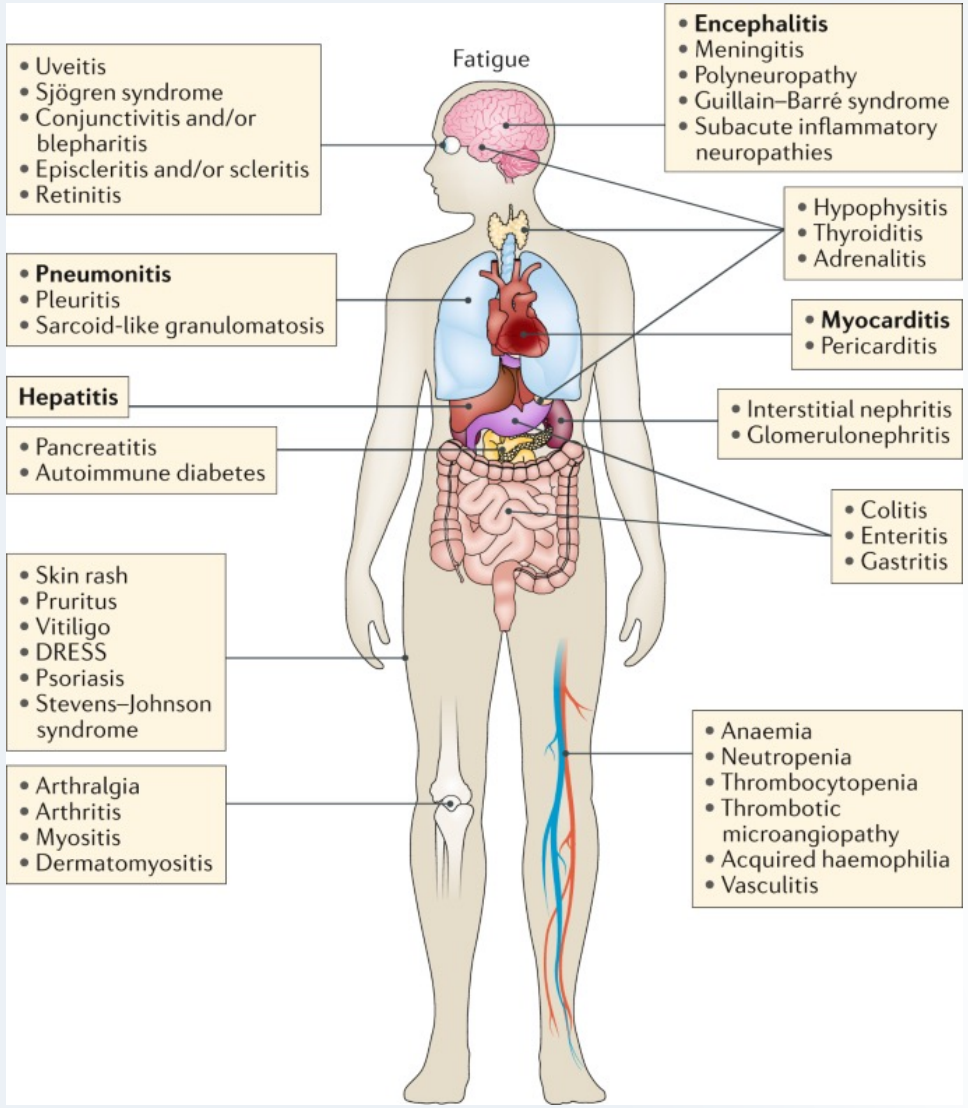
Moskowitz, AJ, et al. J Clin Oncol 2021 Oct 1 ;39 (28):3109 -3117
Mei, MG, et al. Blood. 2022 Jun 23 ;139(25):3605 -3616
NCCN Guidelines® for Hodgkin Lymphoma V.1.2024. © 2023 National Comprehensive Cancer Network, Inc

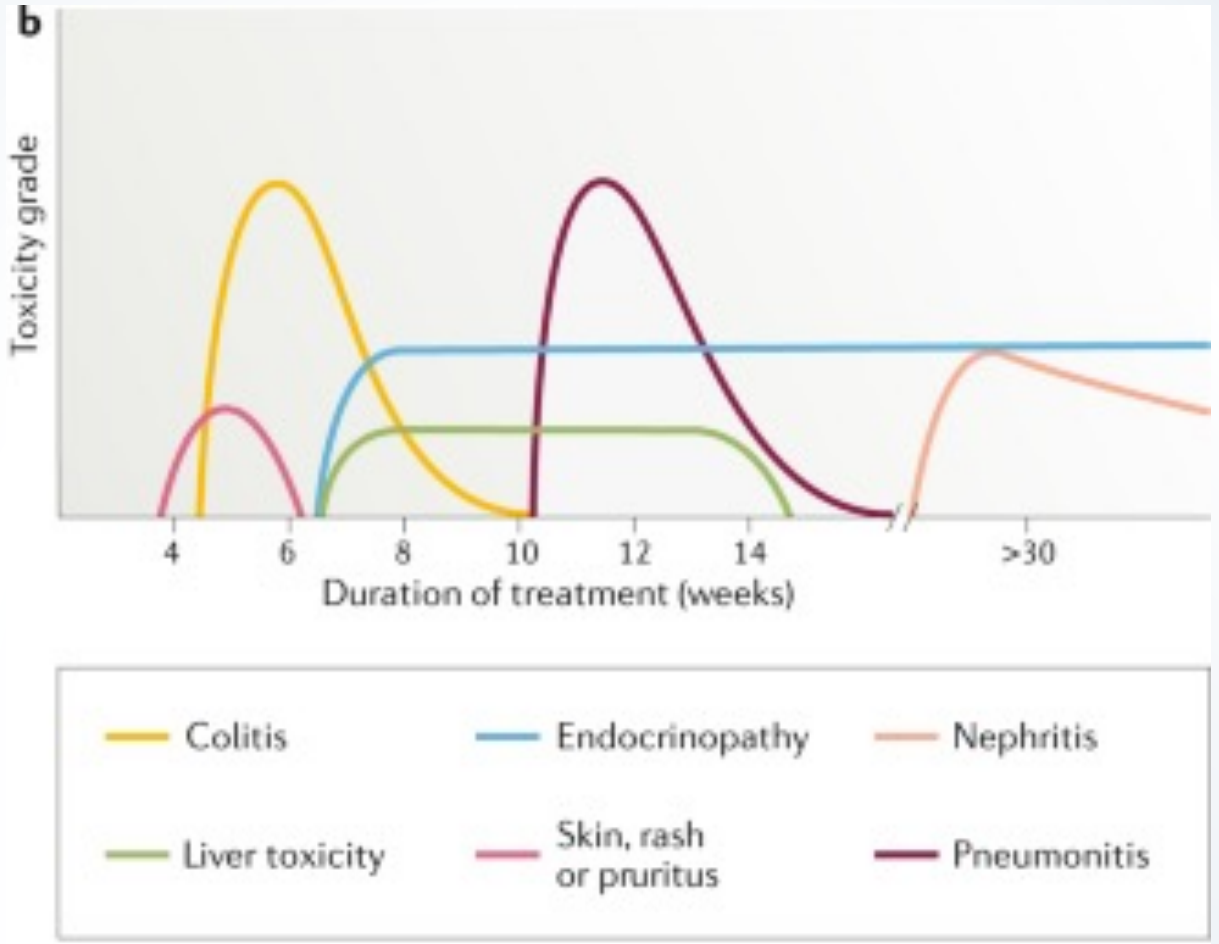
Immune Checkpoint Inhibitor Mechanism of Action



Marei HE, Hasan A, Pozzoli G, Cenciarelli C. Cancer immunotherapy with immune checkpoint inhibitors (ICIs): potential, mechanisms of resistance, and strategies for reinvigorating T cell responsiveness when resistance is acquired. *Cancer Cell Int*. 2023;23(1):64. Published 2023 Apr 10.

PD-1 and PD-L1 Immune Related Adverse Effects (IrAE)





Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019;16(9):563-580.

Dermatologic Toxicity

Maculpapular Rash

- Total body exam, assess for prior inflammatory derm diseases
- Consider biopsy if unusual features
- Eosinophil count, peripheral blood smear, and LFTs

Grade 1 Mild

- Continue immunotherapy
- Topical emollient and moderate potency steroids to areas
- Consider oral antihistamine with pruritus

Grade 2 Moderate

- Continue immunotherapy
- Topical emollient and moderate to high potency steroids to affected areas
- Consider oral antihistamine with pruritus
- If unresponsive within 1 week consider oral prednisone 0.5 mg/kg/day
- Consider dermatology consult

Grade 3 Severe

- HOLD immunotherapy
- Treat with high potency topical steroids to affected areas
- Prednisone 0.5-1 mg/kg/day (increase to 2 mg/kg/day if no improvement)
- Urgent dermatology consultation, consider biopsy
- Consider inpatient care

Topical Corticosteroid Potency Chart

Potency	Class	Generic (Brand)	Strength (%)
High	1	Betamethasone dipropionate	0.05
		Clobestasol propionate	0.05
		Halobetasol propionate	0.05
	2	Desoximetasone	0.05, 0.25
		Fluocinonide	0.05
Medium	3	Betamethasone valerate	0.1
		Triamcinolone acetate	0.1, 0.5
	4	Flurandrenolide	0.05
	5	Fluticasone propionate	0.05
Low	6	Desonide	0.05
	7	Hydrocortisone	0.5-2.5

Ference, J. Choose Topical Corticostroids. AAFP. 2009;79(2):135-140.

Hepatobiliary Toxicity

Therapy	All Grade (%)	Grade 3-4 (%)
Nivo-AVD	32	5
Pembro-GVD	41	10
BV + Nivolumab	1	1
Pembrolizumab Keynote-204	73	11
Nivolumab CHECKMATE 205 & CHECKMATE -039	64	6

- Majority of cases present asymptomatic elevation of AST, ALT, or total bilirubin
- Rule out other potential factors
  - Autoimmune hepatitis
  - New medications or supplements
  - Other chemotherapy in regimen

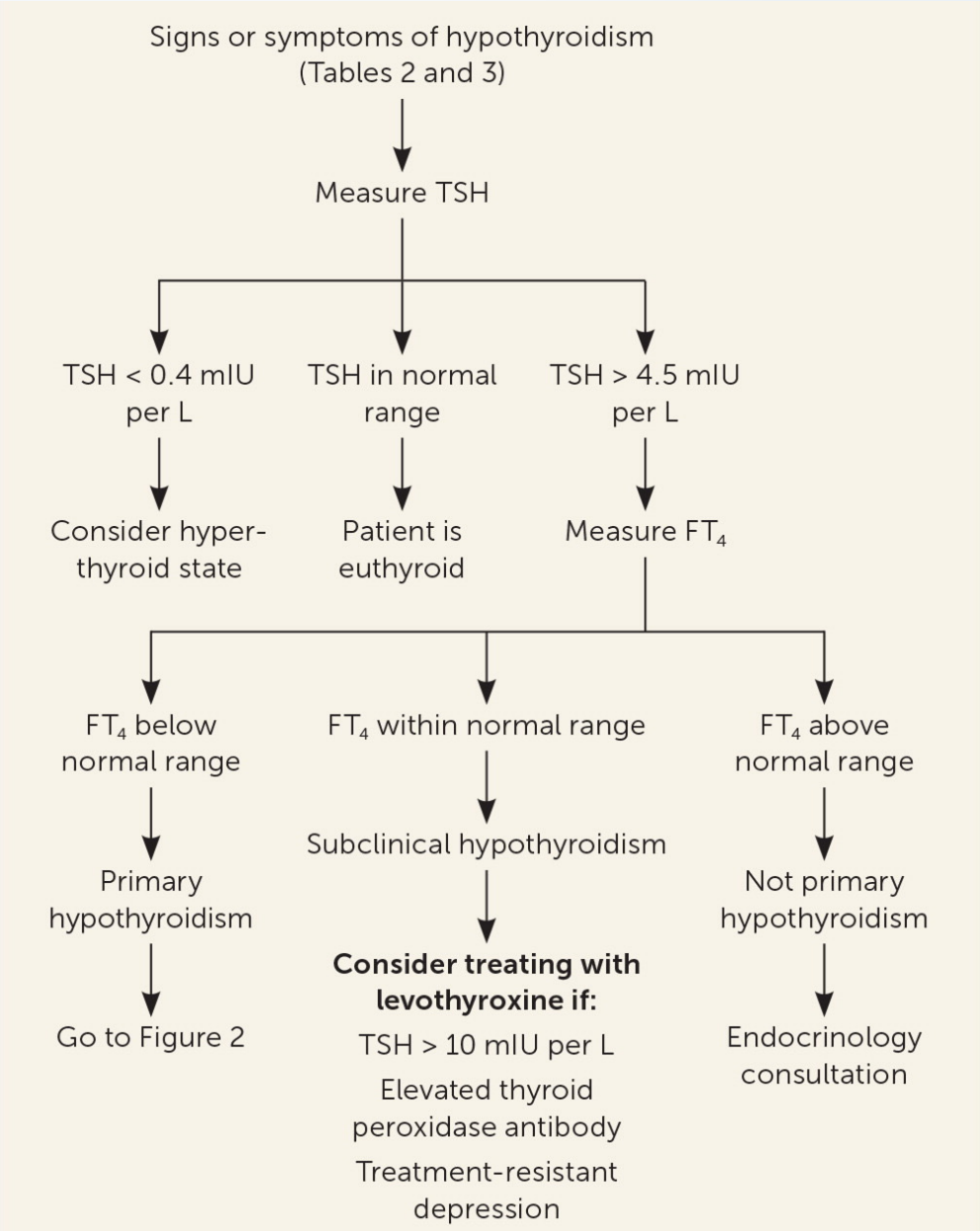
Hypothyroidism

Symptoms:

- Arthralgias
- Cognitive impairment
- **Cold intolerance**
- **Constipation**
- Depression
- Difficulty concentration
- **Dry skin**
- Edema
- **Fatigue**
- Hair thinning
- **Lethargy**
- **Voice changes**
- Weakness
- **Weight gain**

Treatment

- Levothyroxine oral 1.2–1.4 mcg/kg/day
- For patients with advanced age, cardiac risk, or prolonged hypothyroidism, initiate at 0.8–1.0 mcg/kg/day.
- Take levothyroxine 30 minutes BEFORE breakfast or coffee or tea
- Decrease Absorption:
  - Calcium carbonate
  - Antacids, PPIs
  - Ferrous sulfate



Wilson et al. Hypothyroidism: Diagnosis and Treatment. AAFP. 2021;103(10):605-613

In Summary

- Antibody drug conjugates and immunotherapy have been incorporated into front-line and relapsed setting bringing unique adverse event profiles to traditional chemotherapy
  - Brentuximab vedotin: peripheral neuropathy and neutropenia
  - Nivolumab and pembrolizumab: immunotherapy related toxicities
    - Most common AEs: Hepatobiliary, hypothyroidism, and dermatologic

Patient Cases

Patient Case 1

ML is a 60-year-old female was recently diagnosed with stage III cHL, mixed cellularity subtype, IPS 1. Nivolumab-AVD was initiated for treatment.

Today ML is here for Cycle 4, Day 1. You notice her energy is low but stable and she is overall asymptomatic.

Date	10/03	12/26	1/8
TSH	1.94	1.25	5.65

Hypothyroidism

Hypothyroidism

Monitor TSH, Free T4 every 4-6 weeks

If TSH elevated, proceed based on TSH levels or repeat in 4-6 weeks

Subclinical hypothyroidism
TSH 4 to < 10
Normal free T4
Patient asymptomatic
OR
Elevated TSH and normal free T4

Continue immunotherapy
Continue to monitor thyroid function tests

Continue immunotherapy
Consider levothyroxine if elevated TSH persists or if patient becomes symptomatic

Overt hypothyroidism
Elevated TSH and Low free T4

- Continue immunotherapy
- Consider endocrine consult
- Initiate levothyroxine
- Repeat TSH levels in 4-6 weeks to guide dosing changes
- Check serum cortisol to exclude coexistent adrenal insufficiency prior to treatment

Central hypothyroidism
Normal or low TSH and low free T4

- Hypophysitis/Central hypothyroidism

Patient Case 1 continued

Patient weight: 83 kg

Date	10/03	12/26	1/8	1/23	1/30	2/6	2/14	2/20	2/27
TSH	1.94	1.25	5.65	27.3	22	5.97	10.5	17.9	1.99

Levothyroxine
25 mcg/day

Levothyroxine
100 mcg/day

Levothyroxine
112 mcg/day

Initial levothyroxine: 1.2–1.4 mcg/kg/day
Repeat TSH every 4-6 weeks
Peak therapeutic effect: 4-6 weeks

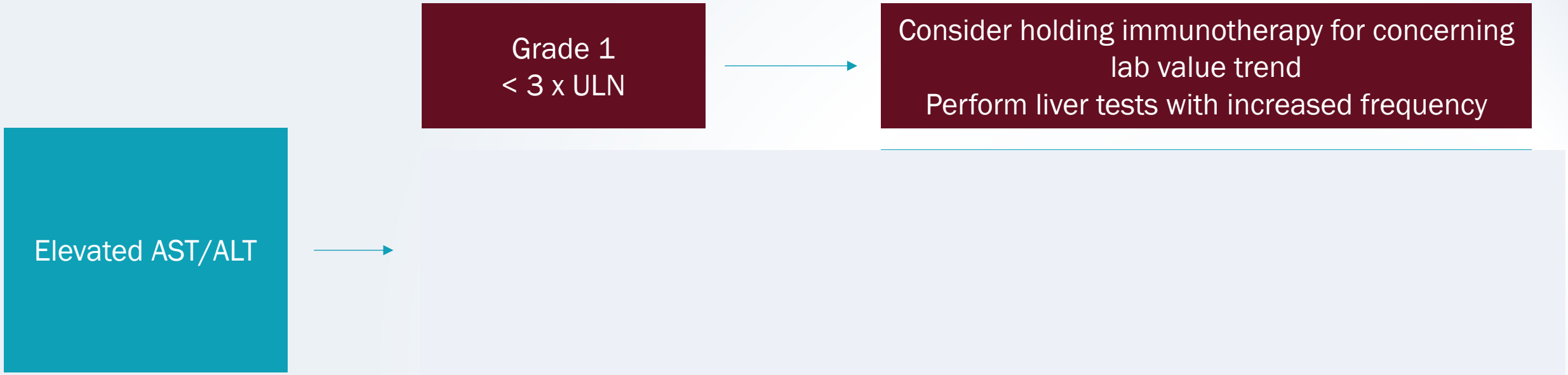
Patient Case 2

ML is a 60-year-old female recently diagnosed with stage III cHL, mixed cellularity subtype, IPS 1. Nivolumab-AVD was initiated for treatment.

ML is in clinic for Cycle 4, Day 1 treatment. Labs are finalized and you come across this. What do you recommend?

Date	ALT	AST	T Bili
11/14	23	20	0.2
11/28	48	28	0.2
12/12	53	38	<0.1
12/26	65	44	0.3

Hepatobiliary Toxicity



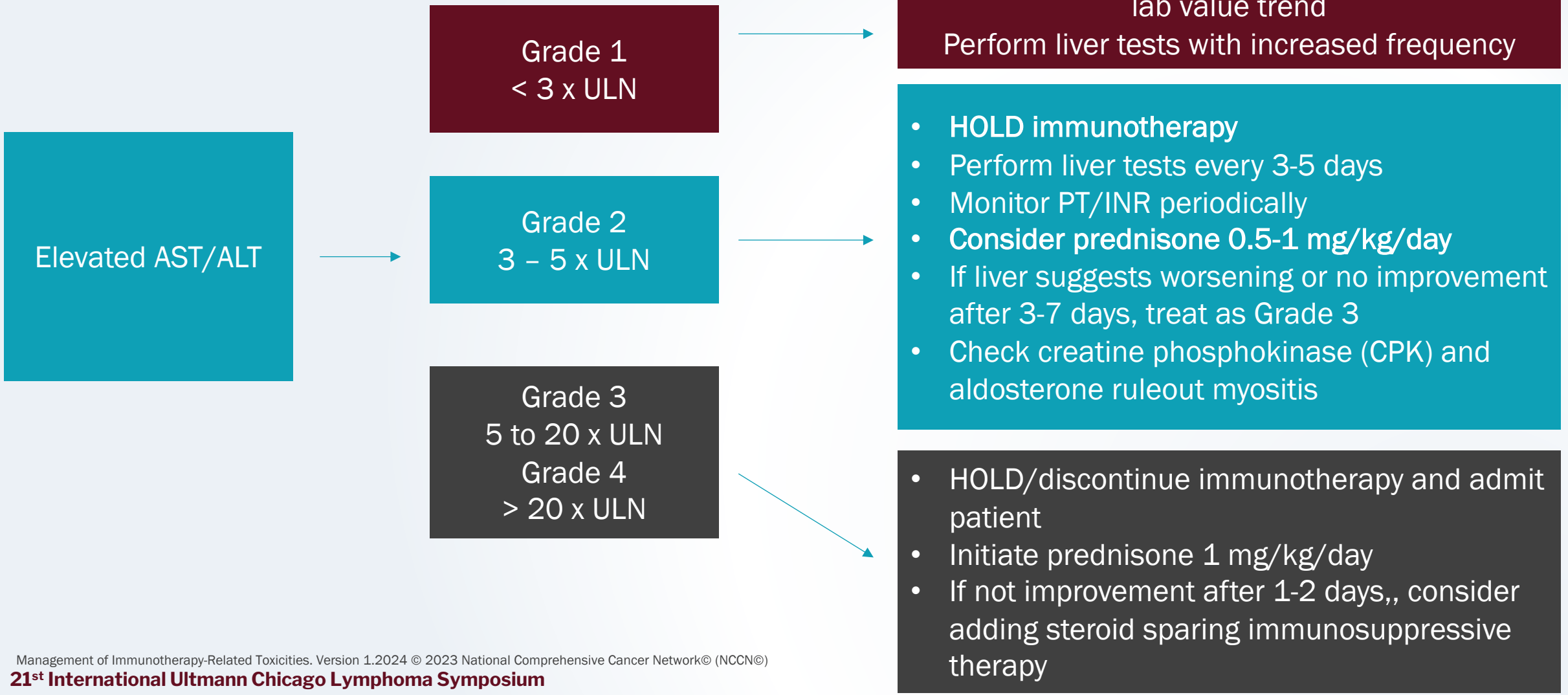
Patient Case 2 continued

ML is a 60-year-old female recently diagnosed with stage III cHL, mixed cellularity subtype, IPS 1. Nivolumab-AVD was initiated for treatment.

ML is in clinic for Cycle 5, Day 1 treatment. Labs are finalized and you come across this. What do you recommend?

Date	ALT	AST	T Bili
12/12	53	38	<0.1
12/26	65	44	0.3
1/8	51	39	0.2
1/24	123	97	0.3

Hepatobiliary Toxicity



Management of Immunotherapy-Related Toxicities. Version 1.2024 © 2023 National Comprehensive Cancer Network© (NCCN©)

Patient Case 2 continued

Prednisone Dose	AST	ALT
80 mg (1 mg/kg/day) x 1 week	97	123 170
60 mg x 1 week (25% decrease)	39	90
40 mg x 2 weeks	33 39	87 72
20 mg x 2 weeks	30 47	67 86
40 mg x 1 week	47	102
30 mg x 1 week	34	82
20 mg x 1 week > 10 mg x 1 week etc…	28	58

<u>Oral Steroid Taper Guidance</u>

- Start taper once symptoms are Grade 1 or baseline
- Steroid taper over 4-6 weeks
- Reduce steroid dose by 10 mg every 3 to 7 days (as toxicity allows) until dose is 10 mg/day
- Then reduce by 5 mg every 5 days and then stop

Remember PJP prophylaxis and if needed, PPI for stress ulcer prophylaxis!

Patient Case 3

JG is a 59-year-old male with history of splenomegaly and newly diagnosed Stage IV, IPS score 6 cHL. BV-AVD was the treatment initiated.

JG presents to clinic for C6D1 with worsening neuropathy reporting numbness in the soles of feet affecting gait and numbness/tingling in hands impairing function. Patient states he is not experiencing pain.

What do you recommend?

Patient Case 3 continued

Recommended Initial Dose	Monotherapy or Combination	Severity	Modification
1.2 mg/kg up to max of 120 mg every 2 weeks	In combination with chemotherapy	Grade 2	Reduce to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks

The question lies to start treatment or not for this patient

- Is the patient experiencing pain?
- Is the neuropathy affecting the patient's daily activities?
- Are there drug-drug interactions with the chemotherapy or other medications?

Questions?

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