This program has received sponsorship support from AstraZeneca Canada.

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a physician organization

SPARK

Sharing Practical Insights And Raising Knowledge of CTLA-4s in HCC

The Canadian Council on Continuing Education in Pharmacy has accredited this program for 1.25 CEUs.
CCCEP #1435-2024-3847-L-P Expires: 2025-08-26

CANO Endorsed: 2024-08-22| Expires: 2026-08-22

FUSE HEALTH

CANO Endorsement Statement

CANO ACIO | Canadian Association of Nurses in Oncology
Association canadienne des infirmières en oncologie

This program meets Canadian Association of Nurses in Oncology (CANO) guidelines and is expected to support nurses in their understanding of hepatocellular carcinoma. Endorsement is provided by CANO for a time period of two years, ending August 22, 2026.

CANO/ACIO has made every effort to ensure that information included within this program is accurate at the time of endorsement. The information included cannot substitute for the advice or direction of a health care professional, and the association makes no guarantees, nor can it assume any legal liability for the accuracy, completeness, or usefulness of such information or for any damage incurred directly or indirectly from the information. Reference to any specific product does not imply its endorsement, recommendation or preference by the Canadian Association of Nurses in Oncology.

Presenter

	Disclosures
Firstname Lastname, Credentials Specialty Institution City, Province	• Consultant/advisor - • Speakers bureau - • Grants/honoraria - • Clinical trials -

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Program Provider

CPD Network (physician organization) received sponsorship from AstraZeneca through an educational grant and has designated FUSE Health to act as the CCCEP provider for this program.

FUSE Health (project management and medical writing support) has received payment for medical communication services from the following pharmaceutical companies in the previous 2 years:

- Alexion Pharma Canada
- Amgen Canada
- AstraZeneca Canada
- Daiichi-Sankyo Pharma Canada
- Gilead Sciences Canada
- Incyte Biosciences Canada
- Merck Canada
- Sanofi Genzyme Canada
- Taiho Pharma Canada
- Somatus

Off-label Declarations

- To provide appropriate context regarding current Canadian standards of care and treatment options, the faculty has included data and information that have not been approved by Health Canada. Presentation of unapproved healthcare product-related data is for informational purposes and does not constitute or imply a recommendation.
  - The regimen nivolumab + ipilimumab for the treatment of unresectable hepatocellular carcinoma has not been approved by Health Canada as of July 29, 2024.[1]

- Drug therapy trial data presented are derived from journal publications, conference presentations, health technology assessment documents, and product monographs. Not all data presented appear in the respective product monographs.

- Please consult the appropriate product monograph information for indications and authorized usage.

1. Health Canada. Drug Product Database online query. Version 4.0.2.. Published February 28, 2024. Accessed July 29, 2024. https://health-products.canada.ca/dpd-bdpp/

Learning Objectives

At the completion of the program, participants will be able to:

- Identify the role of CTLA-4 inhibitors in unresectable hepatocellular carcinoma (HCC) treatment
- Understand the mechanism of action and rationale of a CTLA-4 inhibitor priming dose in unresectable HCC
- Integrate PD-L1 + CTLA-4 inhibitor treatment into clinical practice with attention to considerations for drug administration
- Implement strategies for patient monitoring and management of immune-mediated adverse events in patients with unresectable HCC

CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; HCC = hepatocellular carcinoma; PD-L1 = programmed death ligand-1.

Program Content

1	Overview of HCC and CTLA-4 Inhibitors	optional
2	PD-L1/PD-1 + CTLA-4 Inhibitors: Indication in HCC	
3	PD-L1/PD-1 + CTLA-4 Inhibitors: Dosing and Administration	
4	PD-L1/PD-1 + CTLA-4 Inhibitors: Adverse Event Management and Monitoring	
5	Practical Insights and Patient Counselling for HCPs	
6	Appendix	

CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; HCC = hepatocellular carcinoma; HCP = healthcare professional; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand-1.

Optional section

Overview of HCC and CTLA-4 Inhibitors

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Liver Cancer and Hepatocellular Carcinoma (HCC)

Liver Cancer[1-5]

Liver cancers represent a significant global health burden[1-5]

6th most common cancer type[1]

3rd most frequent cause of cancer-related death[1,4]

Less prevalent in Western countries, but incidence is rising[1-3,5]

Hepatocellular Carcinoma (HCC)[1-3]

HCC is the most common type of primary liver cancer[1-3]

HCC: 80% of liver cancers[1-3]

Overall survival of HCC is poor[1-2]

Often diagnosed at an **advanced stage**[2]

Median overall survival: **6-10 months**[2]

HCC = hepatocellular carcinoma.

1. Sung H, et al. *CA Cancer J Clin.* 2021;71(3):209-249. doi:10.3322/caac.21660; 2. Toh MR, et al. *Gastroenterology.* 2023;164(5):766-782. doi:10.1053/j.gastro.2023.01.033; 3. Suddle A, et al. *Gut.* doi:10.1136/gutjnl-2023-331695;
4. Brar G, et al. *Hepatol. Commun.* 2020;4(10):1541. doi:10.1002/hep4.1564; 5. Siegel RL, et al. *CA Cancer J Clin.* 2024;74(1):12-49. doi:10.3322/caac.21820.

Risk Factors for HCC[1-6]

Genetic Disorders[1]

- Hereditary hemochromatosis
- Hereditary tyrosinemia type 1
- Porphyria cutanea tarda (PCT)
- Alpha-1 antitrypsin deficiency
- Wilson Disease

Viral Causes[1-3]

- **HBV**
- **HCV**
- HDV

⚠ Cirrhosis[2,7]

- Chronic inflammation (underlying liver damage)[2]
- Cardiac dysfunction leading to cirrhosis[7]

Hepatocarcinogenic Substances[1]

- Aflatoxin
- Aristolochic acid
- Iron overload

Metabolic Disorders[1-2,8]

- Obesity
- Diabetes
- Metabolic syndrome
- **MASLD** (prev. NASLD)[8]
- **MASH** (prev. NASH)[8]

Others[1-4,6]

- **Alcohol/ARLD**
- Smoking
- Oral contraceptives

⚠ **Major risk factor for HCC**

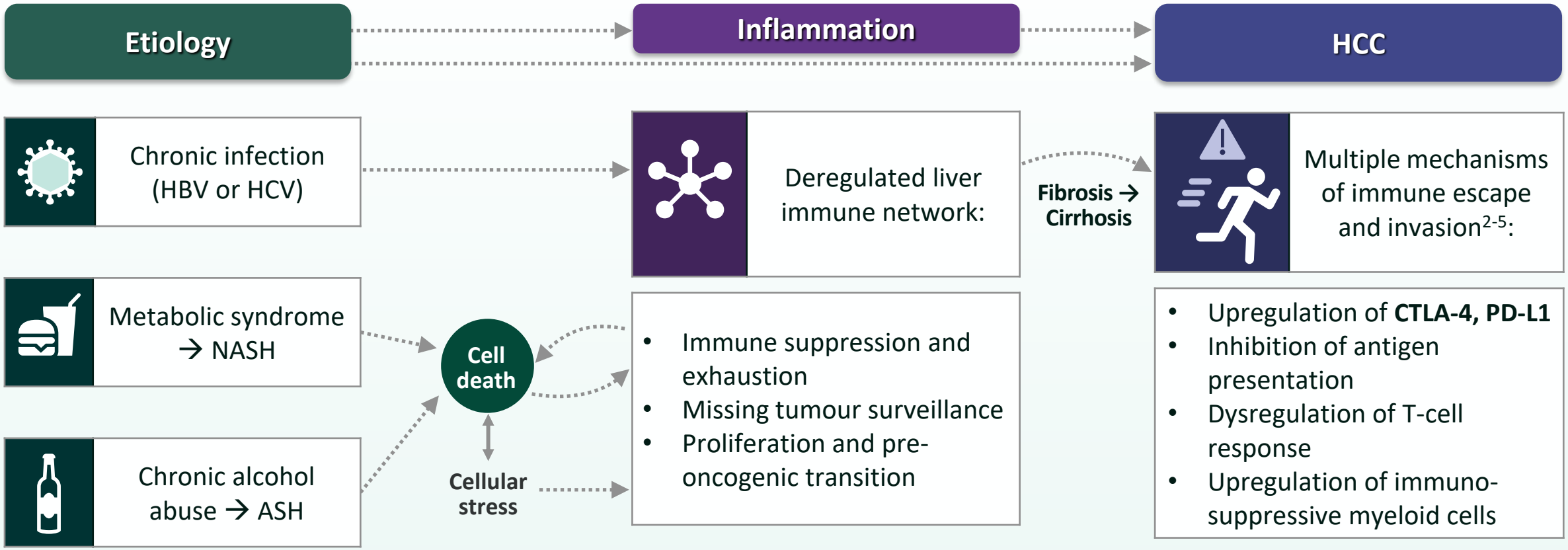
Most common causes of HCC globally[5,6]

Common risk factors in Canada[6]

ARLD = alcohol-related liver disease; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; MASH = metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; prev. = previously.

1. Toh MR, et al. *Gastroenterology.* 2023;164(5):766-782. doi:10.1053/j.gastro.2023.01.033; 2. Suddle A, et al. *Gut.* doi:10.1136/gutjnl-2023-331695; 3. Ghouri YA et al. *J Carcinog.* 2017;16:1. http://www.carcinogenesis.com/text.asp?2017/16/1/1/207221; 4. An N. Medicine (Baltimore). 2015; 94(43):e1619; 5. Yang JD, et al. *Nat Rev Gastroenterol Hepatol.* 2019;16(10):589-604. doi:10.1038/s41575-019-0186-y; 6. Frager SZ, et al. *Curr Oncol.* 2020;27(Suppl 3):S138-S143. doi:10.3747/co.27.7181; 7. Rodriguez Ziccardi M, et al. Cardiac Cirrhosis. Updated April 24, 2023. Accessed May 29, 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431053/; 8. Das M, et al. *Cancers (Basel).* 2024;16(8):1513. doi:10.3390/cancers16081513.

Inflammation and Immune Dysregulation Leads to HCC[1-7]

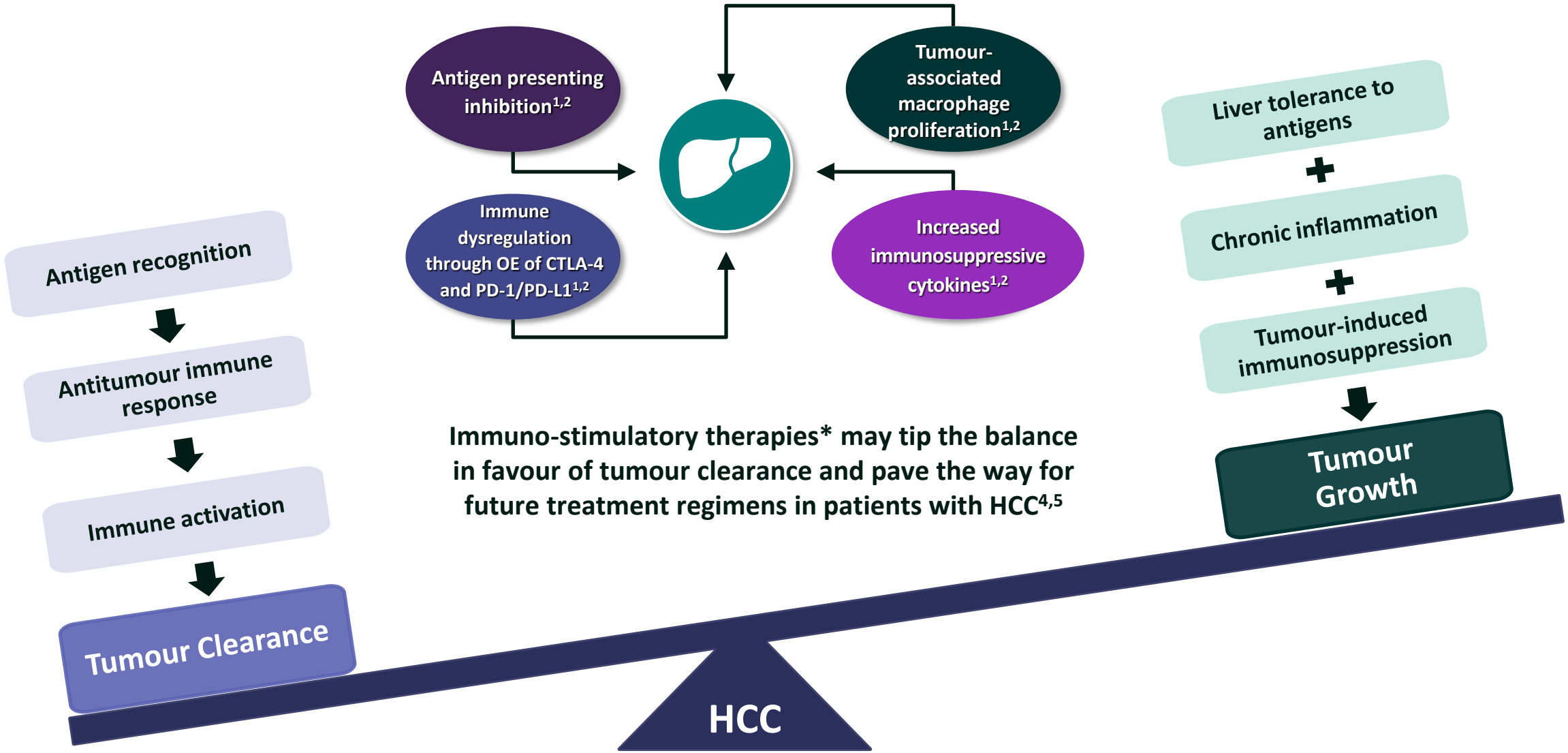


Adapted from Ringelhan et al, 2018.

ASH = alcoholic steatohepatitis; CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NASH = non-alcoholic steatohepatitis; PD-L1 = programmed death ligand-1.

1. Ringelhan M, et al. *Nat Immunol.* 2018;19:222-232; 2. Toh MR, et al. *Gastroenterology.* 2023;164(5):766-782. doi:10.1053/j.gastro.2023.01.033; 3. Cammarota A, et al. *Ther Adv Med Oncol.* 2023;15:17588359221148029. doi:10.1177/17588359221148029;
4. Longo V, et al. *Medicina.* 2019;55(10); 5. Matsuzaki K, et al. *Hepatology.* 2007;46(1):48–57; 6. Zhang HH, et al. *J Viral Hepat.* 2010;17 Suppl 1:34–43; 7. Kudo M, et al. *Liver Cancer.* 2019;8(6):413-426.

Rationale for Immuno-stimulatory Therapies in HCC



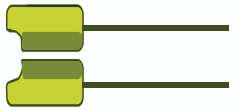
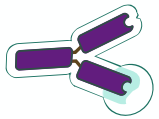
Immuno-stimulatory therapies* may tip the balance in favour of tumour clearance and pave the way for future treatment regimens in patients with HCC[4,5]

*Immuno-stimulatory therapies refer to treatments that enhance ongoing immune responses. This includes monoclonal antibodies that increase the immune response to tumours, which is suppressed in many cancers[6].
CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; HCC = hepatocellular carcinoma; OE = overexpression; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand-1.

1. Sachdeva M, et al. *World J Hepatol.* 2015;7:2080–2090; 2. Harding JJ, et al. *Cancer.* 2016;122:367–377; 3. Makarova-Rusher OV, et al. *J Hepatol.* 2015;62:1420–1429; 4. Matsuzaki K, et al. *Hepatology*. 2007;46:48-57; 5. Zhang HH, et al. *J Viral Hepat.* 2010;17 (Suppl 1): 34-43.
6. Melero I, et al. *Nat Rev Cancer.* 2007;7(2):95-106. doi:10.1038/nrc2051.

Immune Stimulation with PD-L1 and CTLA-4 Dual Immune Checkpoint Inhibitor (ICI) Blockade

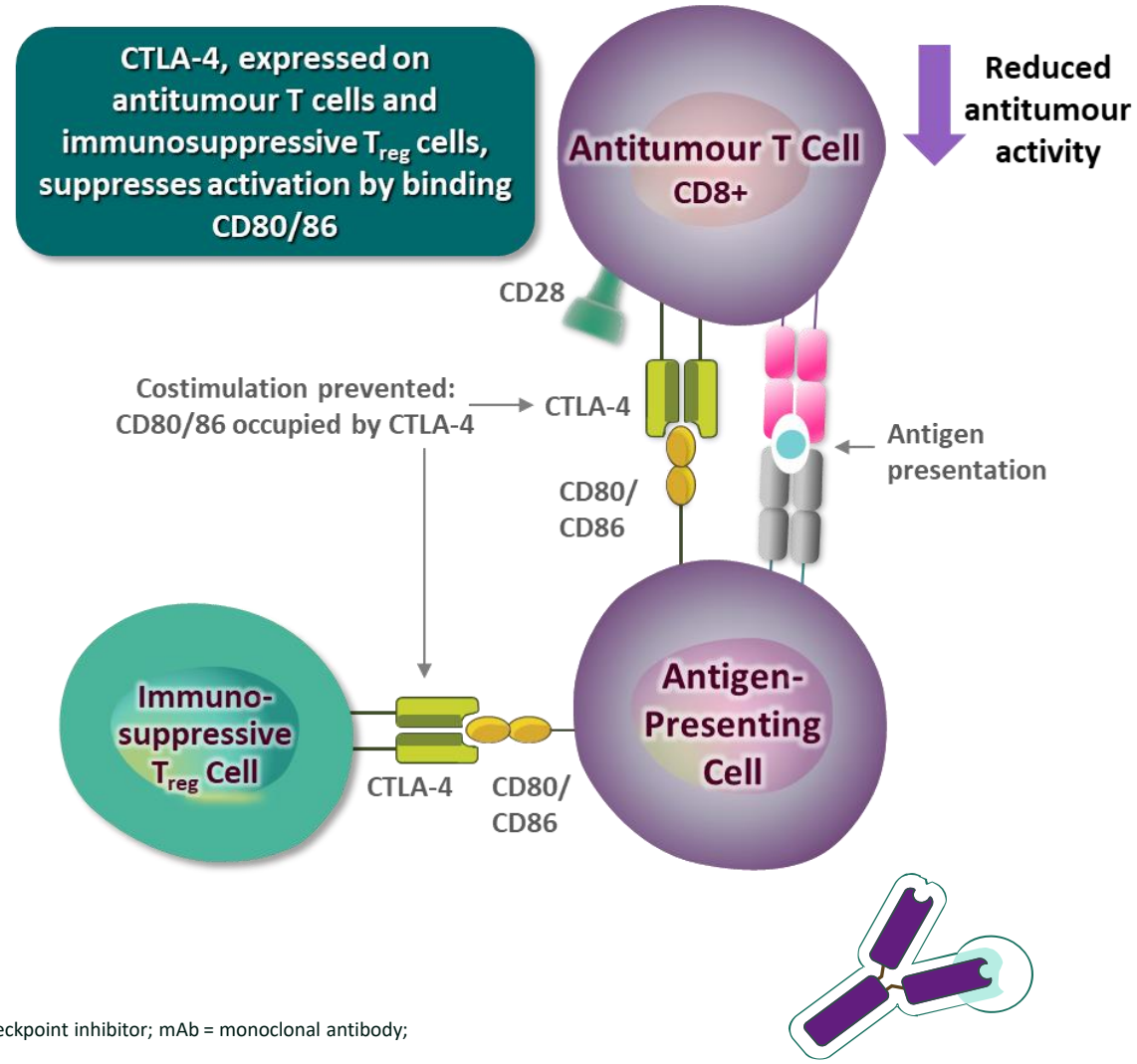
Mechanism of CTLA-4 Inhibitors

	**CTLA-4 (protein)** • Critical inhibitor of anti-tumour T cell activation
	**CTLA-4 inhibitor** • mAb that blocks binding of CTLA-4 to its ligands

Rationale for PD-L1/CTLA-4 Combination

- Pathways are unique and complementary
- Immune response is dampened at distinct stages

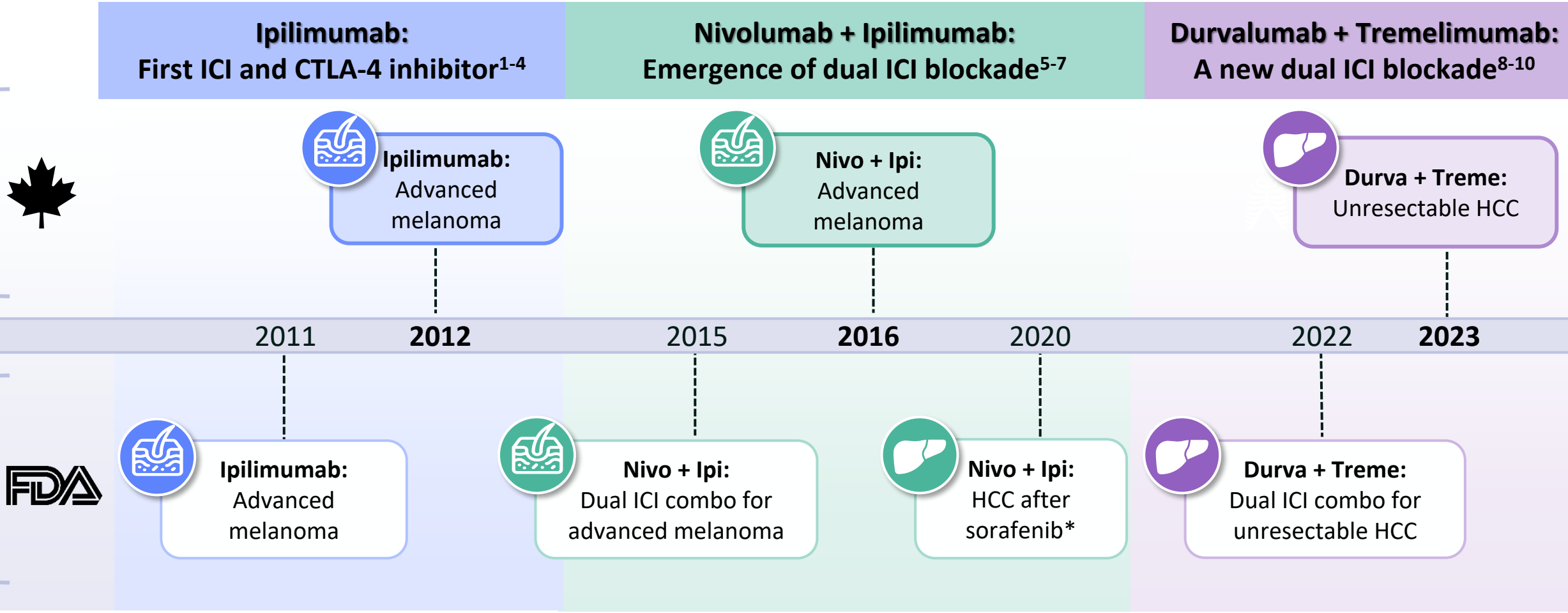
	PD-L1 inhibitor	CTLA-4 inhibitor
Activity location	Tumour microenvironment	Lymph node
Immune response phase	Late	Early
Mechanism	Inhibits suppressive PD-L1 interactions	Blocks suppressive T cell signalling



CD8+ = cytotoxic T cell; CD28/80/86 = cluster of differentiation 28/80/86; CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; ICI = immune checkpoint inhibitor; mAb = monoclonal antibody; PD-L1 = programmed death ligand-1; T_{reg} = regulatory T cell.

1. Brahmer JR, et al. *JCO*. 2018;36(17):1714-1768. doi:10.1200/JCO.2017.77.6385; 2. Sangro B, et al. *Nat Rev Gastroenterol Hepatol.* 2021;18(8):525-543. doi:10.1038/s41575-021-00438-0; 3. Buchbinder EI, et al. *Am J Clin Oncol.* 2016;39:98–106.

History of CTLA-4 Inhibitors and Dual ICI Blockade Therapies

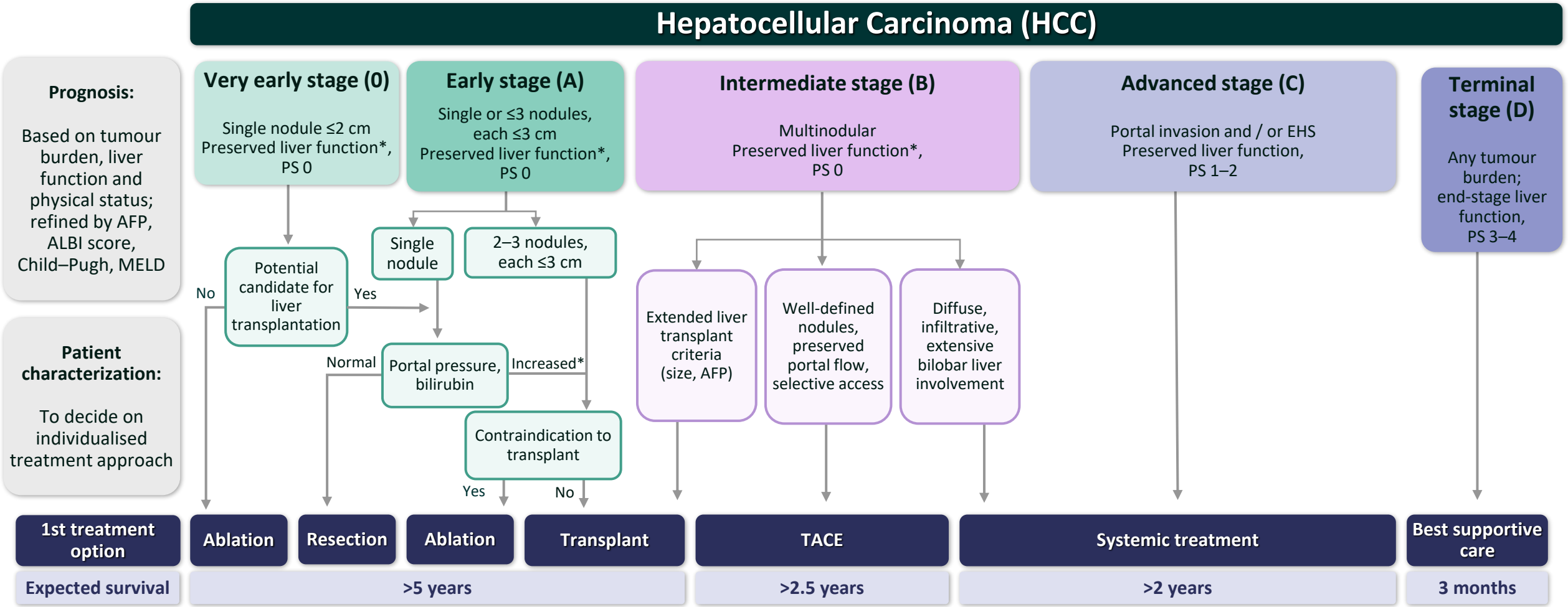


*Not approved by Health Canada for this indication.

CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; durva + treme = durvalumab plus tremelimumab; FDA = Food and Drug Administration; HCC = hepatocellular carcinoma; ICI = immune checkpoint inhibitor; nivo + ipi = nivolumab plus ipilimumab.

1. Wojtukiewicz MZ, et al. *Cancer Metastasis Rev.* 2021;40(3):949-982; 2. Zhang Y, et al. *Cell Mol Immunol.* 2020;17(8):807-821; 3. Dobosz P, et al. *Front Immunol.* 2019;10:2965; 4. Health Canada Drug Product Database. Ipilimumab Product Information. Published February 28, 2024. Accessed May 8, 2024. https://health-products.canada.ca/dpd-bdpp/info?lang=eng&code=86525#fn; 5. National Cancer Institute. November 10, 2025. Accessed April 27, 2024. https://www.cancer.gov/news-events/cancer-currents-blog/2015/nivolumab-expanded; 6. Hogg D, et al. *Curr Oncol.* 2020;27(4):204-214; 7. Saung MT, et al. *Oncologist.* 2021;26(9):797-806; 8. Patel TH, et al. *Clin Cancer Res.* 2024;30(2):269-273; 9. Product Monograph 1. May 13, 2024; 10. Government of Canada website. Published October 26, 2023. Accessed April 28, 2024. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/notices-changes/multiple-additions-2023-10-26.html.

Barcelona Clinic Liver Cancer (BCLC) Staging of HCC

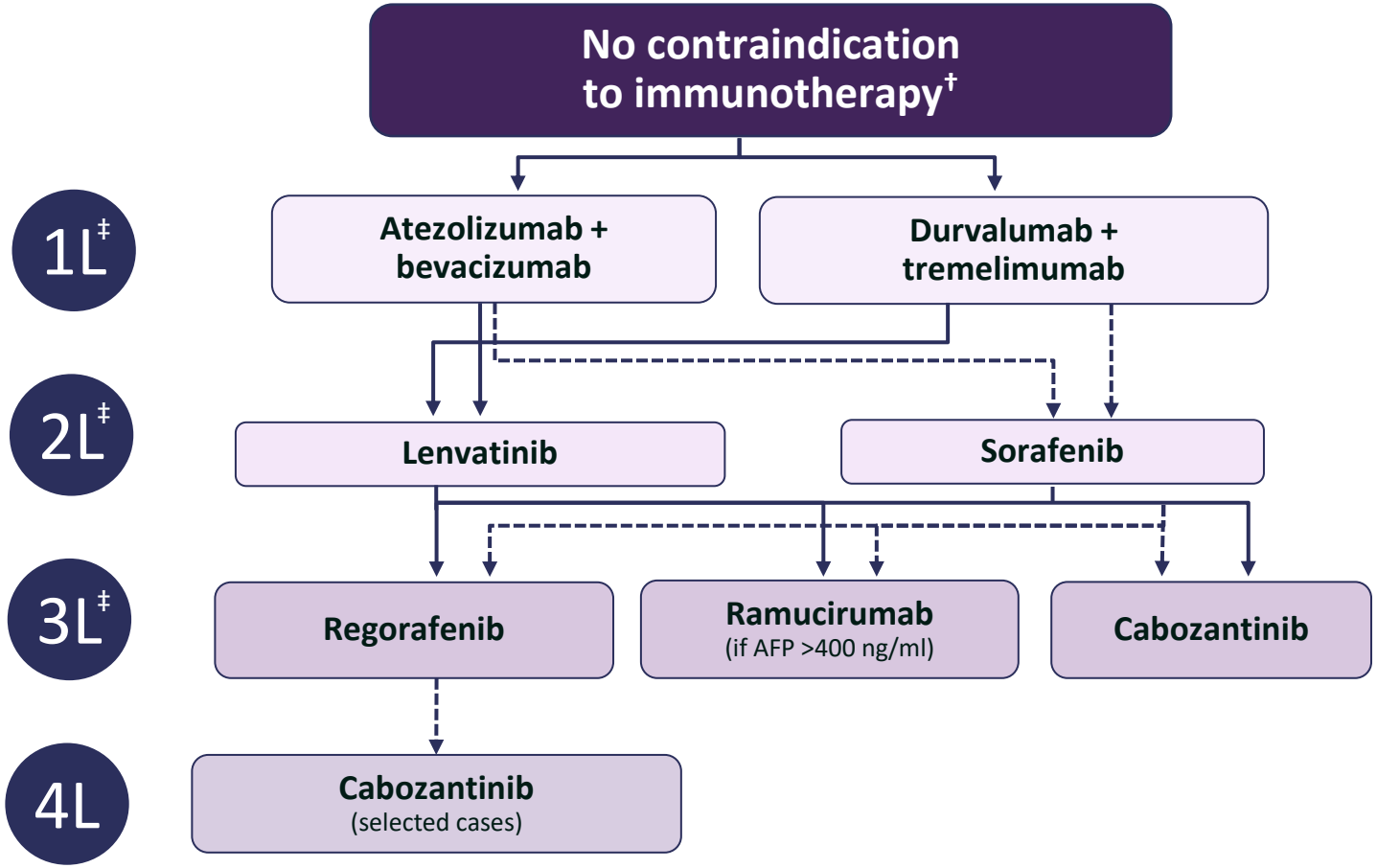


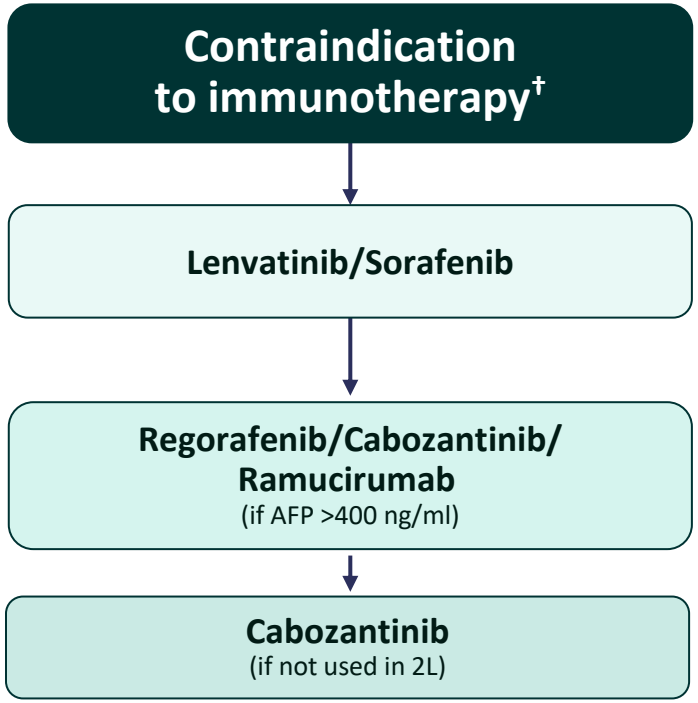
*Except for those with tumour burden acceptable for transplant.

AFP = α-fetoprotein; ALBI = albumin-bilirubin; EHS = extrahepatic spread; HCC = hepatocellular carcinoma; MELD = model of end-stage liver disease; PS = performance status; TACE = transarterial chemoembolization.

1. Reig M, et al. *J Hepatol* 2022;76:681–693.

ESMO: The Advanced Hepatocellular Carcinoma (HCC) Treatment Landscape*





*Summarizes an expert discussion on the management of HCC during the 24th European Society for Medical Oncology (ESMO)/World Congress Gastrointestinal Cancer Congress (WCGICC) in July 2022. May not reflect current Canadian approval and/or reimbursement status.
†Contraindications to initiating immunotherapy may include underlying autoimmune disease and prior organ transplant[1].
‡In Canada, funding is available for 1L and 2L therapies. 3L therapies are not funded[2].

1L = first-line; 2L = second-line; 3L = third line; 4L = fourth line; AFP = α-fetoprotein; ESMO = European Society for Medical Oncology; HCC = hepatocellular carcinoma.

1. Ducreux M, et al. *ESMO Open.* 2023;8(3): doi:10.1016/j.esmoop.2023.101567;
2. Canada's Drug Agency (CADTH). CADTH Reimbursement Review – Provisional Funding Algorithm for Unresectable Hepatocellular Carcinoma. Published January 2024. Accessed May 29, 2024. https://www.cadth.ca/sites/default/files/DRR/2024/PH0036-Hepatocellular-Carcinoma.pdf.

Canadian Consensus Guidelines on Intermediate Stage HCC

1 Intra-arterial therapies for intermediate-stage HCC

- **TACE (cTACE or DEB-TACE):** standard of care for intermediate-stage HCC
- **Y90-TARE:** alternative to TACE; may offer decreased toxicity and assist in downstaging to curative intent and bridging to transplant

2 Radiation therapy

- **SBRT and proton beam therapy:** may be reasonable options for patients who have failed other therapies or not responded to other LRTs

3 Surgical resection

- **Surgical resection:** can be performed in unilobar disease when PS and liver function are well-preserved and complete tumour resection can be achieved*

4 Systemic Therapy†

Initial Systemic Treatment:

- Options for unresectable, TACE-unsuitable HCC include:
  - **Atezolizumab + bevacizumab (atezo + bev)**
  - **Durvalumab + tremelimumab (durva + treme)**
  - **Lenvatinib**
  - **Sorafenib**
- **Atezo + bev, durva + treme, and lenvatinib** have demonstrated outcomes that may lead to tumour reduction and downstaging:
  - **Non-inferiority or superiority in survival**
  - **Predictable and manageable toxicity**
  - **Higher response rates compared with sorafenib**

Therapy Selection and Sequencing:

- Whenever possible, select and sequence therapies:
  1. In a manner that optimizes survival and QoL
  2. With consideration of clinically relevant aspects of trial eligibility
  3. To allow access to all active classes of agents, thereby maximizing the number of available treatment lines*

*Indicates statement attained unanimous agreement among advisors (without accounting for abstentions). †Child-Pugh class A scoring is necessary for use of systemic agents.

cTACE = conventional TACE; DEB-TACE = drug-eluting bead TACE; HCC = hepatocellular carcinoma; LRT = loco-regional therapy; PS, performance status; QoL = quality of life; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization; TARE = transarterial radioembolization.

1. Wong JK, et al. *Cancer Treat. Rev*. 2023;115:102526. doi:10.1016/j.ctrv.2023.102526. 2. CADTH (Canada's Drug Agency). Reimbursement Review Provisional Funding Algorithm for Unresectable Hepatocellular Carcinoma. January 2024. https://www.cadth.ca/sites/default/files/DRR/2024/PH0036-Hepatocellular-Carcinoma.pdf.

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NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Clinical Presentations Where Systemic Therapy is Indicated

Clinical Presentation

- Liver-confined, unresectable, and deemed ineligible for transplant[a,r,s,ii]
- Inadequate hepatic reserve[u]
- Tumor location[z]
- Extent of disease[z]

Treatment[r,ll]

Locoregional therapy[ff]
- Ablation
- Arterially directed therapies[mm]
- RT[hh]

- **Clinical trial**
- **Systemic therapy[nn]**

Best supportive care[oo]

Response Assessment

Assess for response and
- Reconsider resection,[s] transplant, locoregional therapy or
- Subsequent-line systemic therapy if progression on or after systemic therapy[nn]

Surveillance

- Imaging[a,jj,kk] every 3–6 months for 2 years, then every 6 months
- AFP[a,kk] every 3–6 months for 2 years, then every 6 months
- See relevant pathway (HCC-2 through HCC-6) if disease progresses
- Consider early imaging per local protocol (for locoregional therapy)

Clinical Presentation

Extrahepatic/metastatic disease; and deemed ineligible for resection, transplant, or locoregional therapy

Consider biopsy[p,r,s] (preferred) for histologic confirmation if not previously done

Treatment[r,ll]

- **Clinical trial**
- **Systemic therapy[nn]**

- **Best supportive care[oo]**

Response Assessment

Assess for response and
- Reconsider resection,[s] transplant, locoregional therapy or
- Subsequent-line systemic therapy if progression on or after systemic therapy[nn]

Note: All recommendations are category 2A unless otherwise indicated.

AFP = α-fetoprotein; NCCN = National Comprehensive Cancer Network® (NCCN®); RT = radiotherapy.
See slide notes for full NCCN footnotes.

NCCN Guidelines®: Principles of Systemic Therapy for HCC[a,b,c]

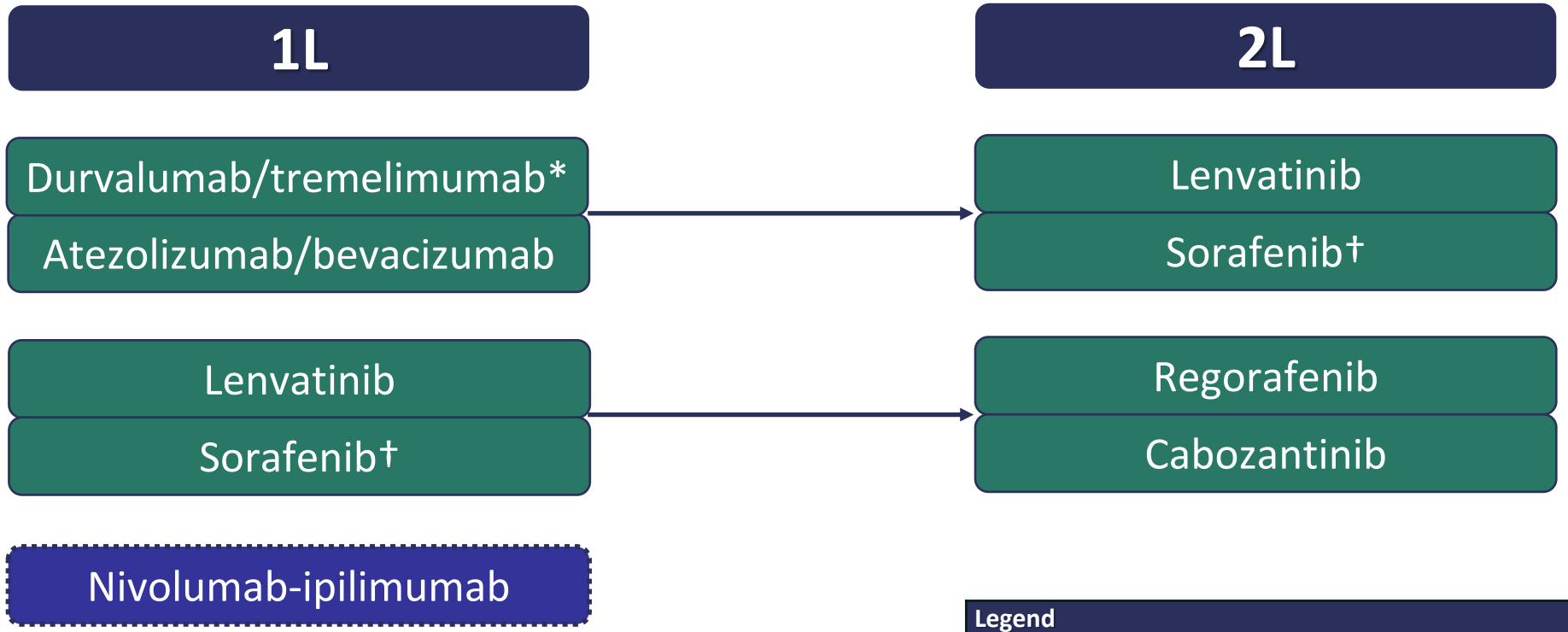
First-Line Systemic Therapy		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Atezolizumab + bevacizumab (category 1)[d,e,f] • Tremelimumab-actl + durvalumab (category 1)[e]	• Durvalumab (category 1)[e*] • Lenvatinib (category 1) • Sorafenib (category 1) • Tislelizumab-jsgr (category 1)[e] • Pembrolizumab (category 2B)[e]	• For *NTRK* gene-fusion positive tumours: – Repotrectinib (category 2B)

Subsequent-Line Systemic Therapy if Disease Progression[g,h,i]		
Options	**Other recommended regimens**	**Useful in certain circumstances**
• Cabozantinib (category 1) • Regorafenib (category 1) • Lenvatinib • Sorafenib	• Nivolumab + ipilimumab[e,j] • Pembrolizumab[e,k,l,m]	• Ramucirumab (AFP ≥400 ng/mL (category 1) • Nivolumab[e,k,l] • For MSI-H/dMMR tumours – Dostarlimab-gxly (category 2B)[e,k,l,n] • For *RET* gene fusion-positive tumours: – Selpercatinib (category 2B)

Note: All recommendations are category 2A unless otherwise indicated.

*Durvalumab monotherapy is not approved for unresectable HCC in Canada. AFP = α-fetoprotein; dMMR = mismatch repair-deficient; HCC = hepatocellular carcinoma; MSI-H = high microsatellite instability; NCCN = National Comprehensive Cancer Network® (NCCN®); *NRTK* = non-receptor tyrosine kinase; *RET* = Ret proto-oncogene; RT = radiotherapy. See slide notes for full NCCN footnotes.

Unresectable HCC: Treatment Sequencing in Canada



Adapted from Canada's Drug Agency (CADTH) provisional funding algorithm[1]. Quebec excluded.

*Therapy reviewed and funding provided in BC, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia, New Brunswick, and Newfoundland/Labrador.

*Durvalumab-tremelimumab would be suitable for patients with unresectable HCC who also happen to have a higher risk of bleeding thus would not be eligible for atezolizumab-bevacizumab.
†Only if intolerant of lenvatinib.

1L = first-line; 2L = second-line; CADTH = Canada's Drug Agency; HCC = hepatocellular carcinoma; pCPA = pan-Canadian Pharmaceutical Alliance.

1. Canada's Drug Agency (CADTH). CADTH Reimbursement Review – Provisional Funding Algorithm for Unresectable Hepatocellular Carcinoma. Published January 2024.. Accessed May 29, 2024. https://www.cadth.ca/sites/default/files/pdf/ph0003-000_hcc-report-final.pdf.

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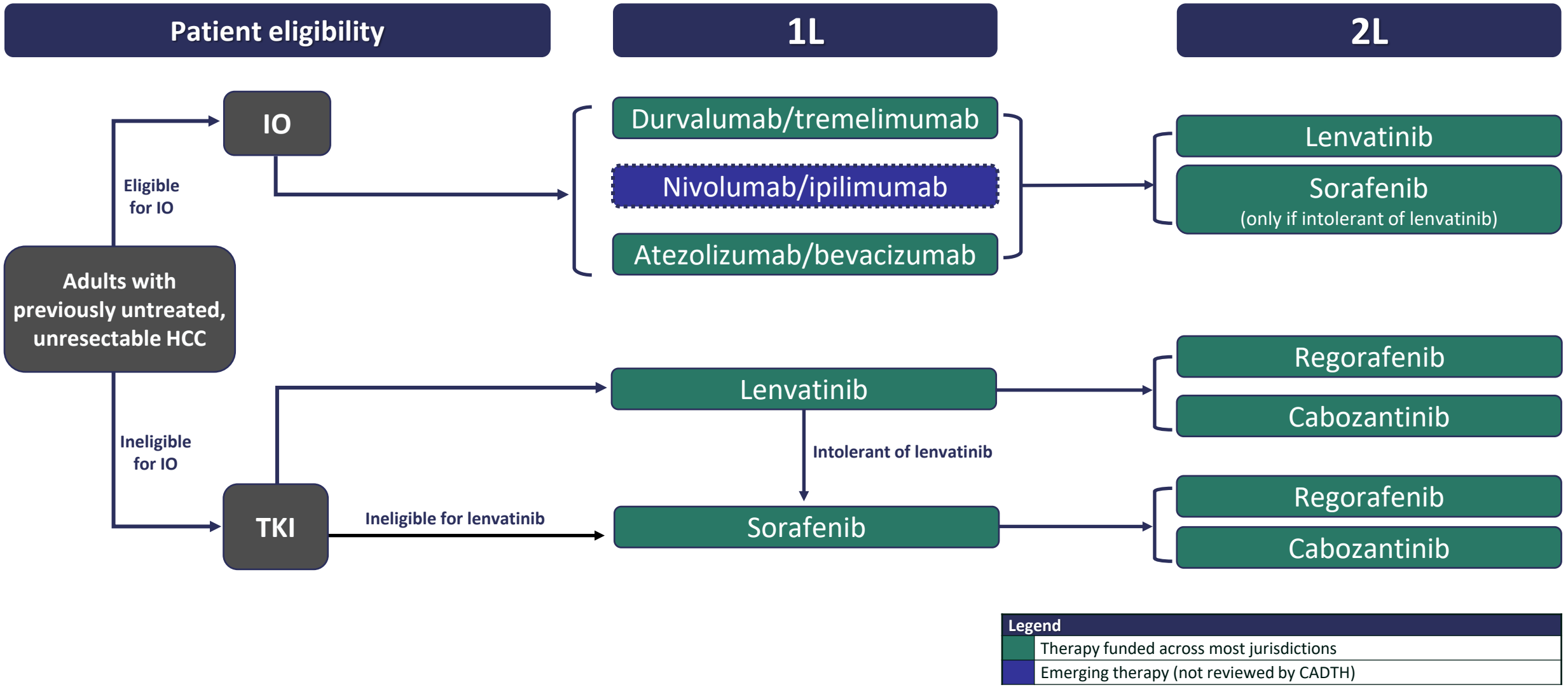
Unresectable HCC: Treatment Sequencing in Canada



1L = first-line; 2L = second-line; CADTH = Canada's Drug Agency; HCC = hepatocellular carcinoma; IO = immunotherapy; pCPA = pan-Canadian Pharmaceutical Alliance; TKI = tyrosine kinase inhibitor.

1. Canada's Drug Agency (CADTH). CADTH Reimbursement Review – Provisional Funding Algorithm for Unresectable Hepatocellular Carcinoma. Published January 2024. Accessed May 29, 2024. https://www.cadth.ca/sites/default/files/pdf/ph0003-000_hcc-report-final.pdf.

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Liver Function Assessments Inform HCC Treatment Options

Child-Pugh Scoring System[1-6]

Description: Clinical scoring system based on 5 features: total bilirubin, albumin, PT/INR, ascites, encephalopathy[1,2]

Application: Estimates survival and degree of cirrhosis/underlying liver dysfunction, which affects therapeutic options and management of HCC

Child-Pugh Class	Liver Disease Severity	Total Points	1-Year Survival*	2-Year Survival*
A	Least severe	5-6	100%	85%
B	Moderately severe	7-9	80%	57%
C	Most severe	10-15	45%	35%

Liver Biochemistry Tests[7†]

Description: Blood tests of liver enzymes and compounds

Application: Enzyme levels and ratios may indicate disease etiology, treatment efficacy, disease progression, and potential drug-induced liver injury as a side effect of therapy

Test(s)	Application
Serum ALT, AST	Detects hepatocellular injury
ALP, serum bilirubin	Detects biliary tract injury
Serum albumin, PT/INR‡	Assesses liver's biosynthetic capacity

*The Child-Pugh Scoring System was designed to predict mortality in patients with cirrhosis. In cancer patients, hypoalbuminemia, encephalopathy, and ascites may be related to cancer cachexia or cancer metastases to the brain or peritoneal surfaces rather than impaired hepatic function[8].
†Previously referred to as liver function tests (LFTs)[1,2].
‡INR is frequently used as a substitute for PT.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCC = hepatocellular carcinoma; INR = international normalized ratio; PT = prothrombin time.

1. Tsoris A, et al. In: StatPearls. StatPearls Publishing; 2024. http://www.ncbi.nlm.nih.gov/books/NBK542308/; 2. Kim HN, et al. Evaluation and Prognosis of Persons with Cirrhosis: https://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/evaluation-prognosis-cirrhosis/core-concept/all; 3. Heimbach JK, et al. *Hepatology.* 2018;67(1):358-380. doi:10.1002/hep.29086; 4. Aly A, et al. *Hepat Oncol*. 10(1):HEP47. doi:10.2217/hep-2023-0002; 5. Open Anesthesia. Child-Pugh Score: Factors. Published April 3, 2015. Accessed May 8, 2024. https://www.openanesthesia.org/keywords/child-pugh_score_factors/; 6. Pugh RNH, et al. *Br J Surg.* 1973;60(8):646-649. doi:10.1002/bjs.1800600817; 7. Kwo PY, et al. *Am J Gastroenterol.* 2017;112(1):18-35. doi:10.1038/ajg.2016.517; 8. Elmeliegy M, et al. *J Clin Pharmacol.* 2021;61(1):105-115. doi:10.1002/jcph.1702.

Child Pugh Scoring System

CLINICAL FEATURES			
Feature	**1 point**	**2 points**	**3 points**
Total bilirubin (µmol/L)	<34.2	34.2–51.3	>51.3
Albumin (g/L)	>35	28–35	<28
PT/INR*	<4/<1.7	4-6/1.71–2.30	>6/>2.30
Ascites	Absent	Slight	Moderate
Encephalopathy	None	Grade 1–2	Grade 3–4

SCORING				
Child-Pugh Class	**Disease**	**Total Points**	**1-Year Survival**	**2-Year Survival**
A	Well-compensated	5–6	100%	85%
B	Significant functional compromise	7–9	80%	57%
C	Decompensated disease	10–15	45%	35%

*INR is frequently used as a substitute for PT.

INR = international normalized ratio; PT = prothrombin time.

1. Tsoris A, et al. In: StatPearls. StatPearls Publishing; 2024. http://www.ncbi.nlm.nih.gov/books/NBK542308/; 2. Kim HN, et al. Evaluation and Prognosis of Persons with Cirrhosis: https://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/evaluation-prognosis-cirrhosis/core-concept/all; 3. Heimbach JK, et al. *Hepatology*. 2018;67(1):358-380. doi:10.1002/hep.29086; 4. Aly A, et al. *Hepat Oncol*. 10(1):HEP47. doi:10.2217/hep-2023-0002; 5. Open Anesthesia. Child-Pugh Score: Factors. Published April 3, 2015. Accessed May 8, 2024. https://www.openanesthesia.org/keywords/child-pugh_score_factors/; 6. Pugh RNH, et al. *Br J Surg.* 1973;60(8):646-649. doi:10.1002/bjs.1800600817; 7. Elmeliegy M, et al. *J Clin Pharmacol*. 2021;61(1):105-115. doi:10.1002/jcph.1702.

PD-L1/PD-1 + CTLA-4 Inhibitors: Indication in HCC

CCCEP #1435-2024-3847-L-P Expires: 2025-08-26 | CANO Endorsed: 2024-08-22| Expires: 2026-08-22

Current Regimens:

Durvalumab/Tremelimumab

Durvalumab/Tremelimumab: Indication in HCC

HIMALAYA Trial

Durvalumab/tremelimumab dual immune checkpoint inhibitor (ICI) blockade in HCC

Health Canada Indication

*Tremelimumab in combination with durvalumab is indicated for the **first-line treatment** of adult patients with **unresectable hepatocellular carcinoma (HCC) who require systemic therapy***

HCC = hepatocellular carcinoma; ICI = immune checkpoint inhibitor.

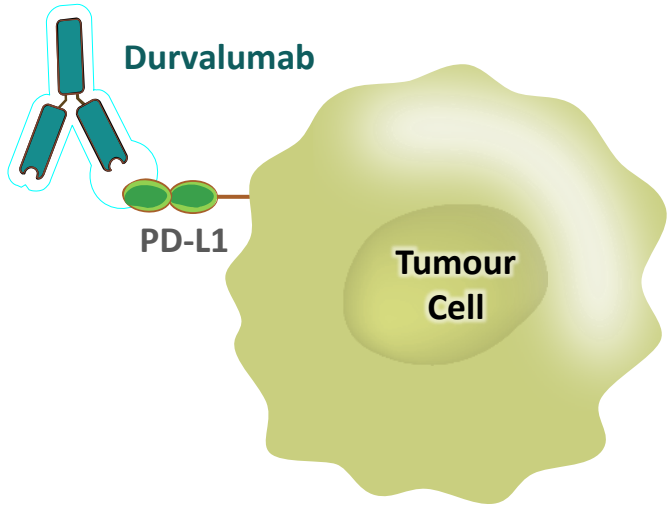
1. Product Monograph 1. May 13, 2024.

Durvalumab and Tremelimumab are Immune Checkpoint Inhibitors

Durvalumab

PD-L1 inhibitor | **Tumour microenvironment**

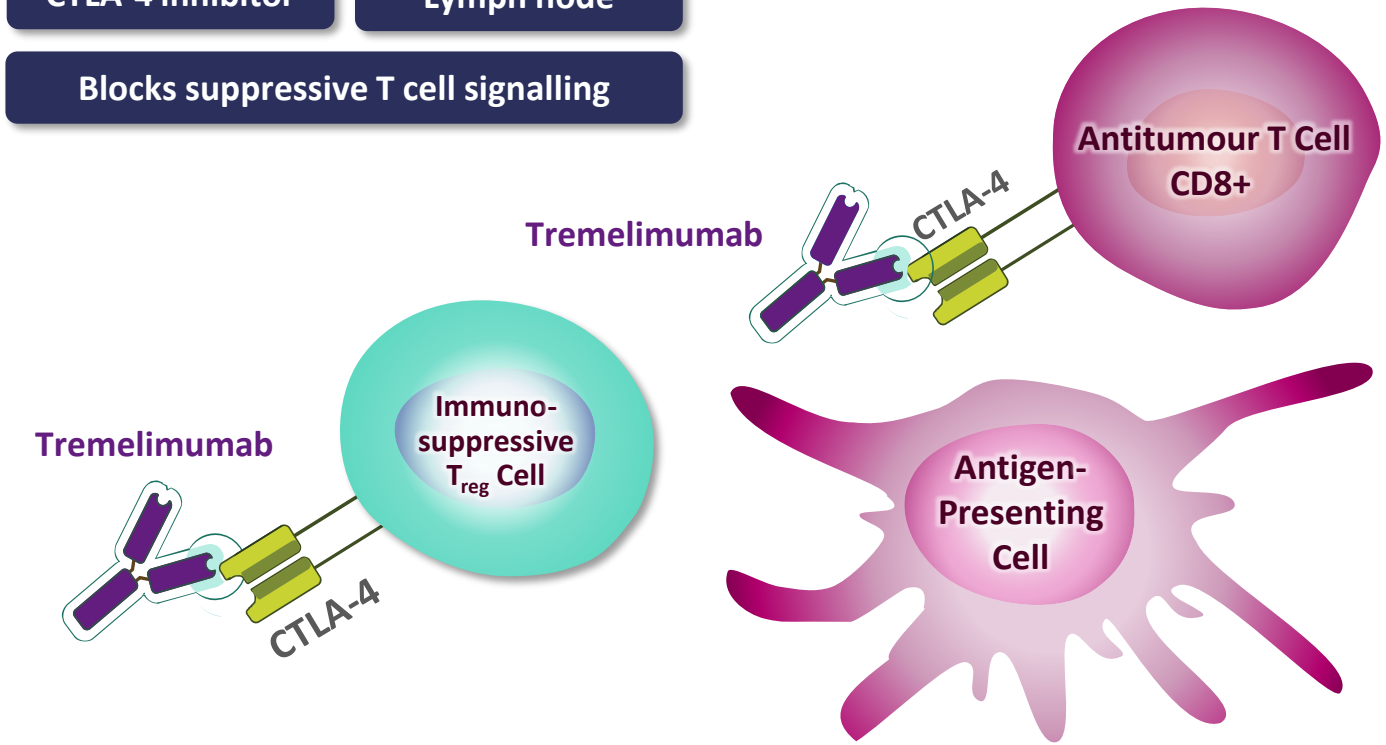
Inhibits suppressive PD-L1 interactions



Tremelimumab

CTLA-4 inhibitor | **Lymph node**

Blocks suppressive T cell signalling



Inhibition of suppressive PD-L1 interactions and T cell signalling results in robust activation of the immune system and anti-tumour activity

CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4; HCC = hepatocellular carcinoma; PD-L1 = programmed death ligand-1; T_{reg} = regulatory T cell.

1. Saijo N. *Cancer Res Treat*. 2012;44:1-10; 2. Togashi Y, et al. *Nat Rev Clin Oncol.* 2019;16:356-371; 3. Sheng J, et al. *J Clin Pharmacol.* 2017;57(suppl 10):S26-S42; 4. Wei SC, et al. *Cell*. 2017;170(6):1120-1133.e17; 5. Buchbinder EI, et al. *Am J Clin Oncol*. 2016;39:98–106; 6. Curran MA, et al. Proc *Natl Acad Sci USA.* 2010;107:4275–80; 7. Bagchi S, et al. *Annu Rev Pathol.* 2021;16:223-249. doi:10.1146/annurev-pathol-042020-042741.

Study 22 Established Novel Durvalumab/Tremelimumab Regimen with a Single Priming Dose

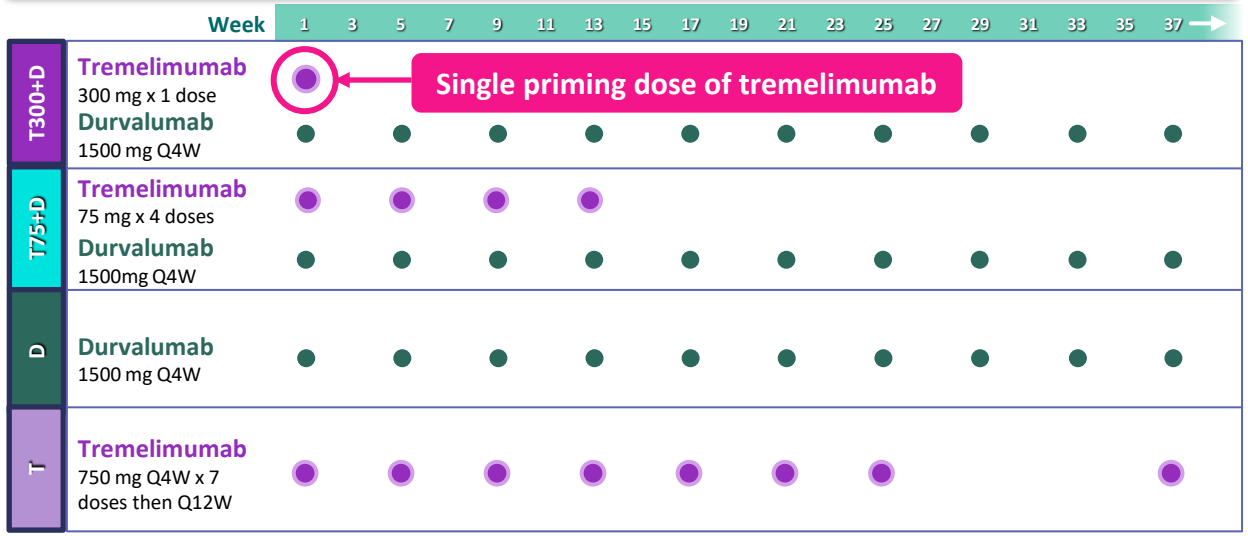
Design

- Phase 2, randomized, open-label, multicentre
- Population: Advanced HCC progressed on, intolerant to, or refused sorafenib or another approved TKI

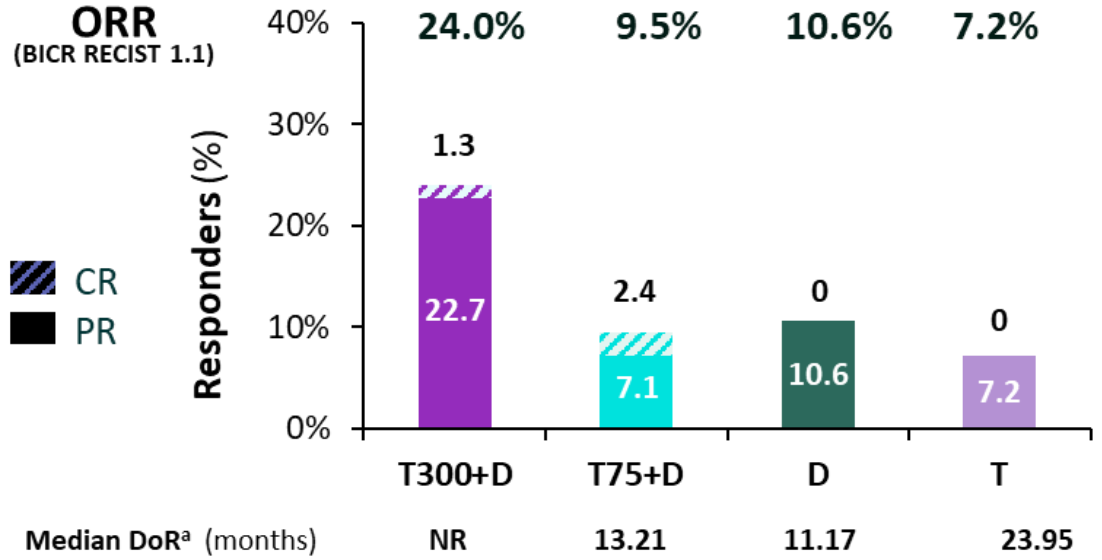
Investigated Regimens

R
- **T300+D** (n = 65)
- **T75+D** (n = 45)
- **D** (n = 64)
- **T** (n = 33)

Detailed Dosing Schedules[3]



Results



Median DoR[a] (months)	T300+D	T75+D	D	T
	NR	13.21	11.17	23.95

Across all arms, durva + treme with a single priming dose provided the best risk-benefit profile

BICR = blinded independent central review; CI = confidence interval; CR = complete response; D = durvalumab; durva + treme = durvalumab 1500 mg Q4W + tremelimumab 300 mg × 1 dose; DCR = disease control rate; DoR = duration of response; HCC = hepatocellular carcinoma; NR = not reached; ORR = objective response rate; PD-L1 = programmed death ligand-1; PR = partial response; Q4W = every 4 weeks; Q12W = every 12 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease; T = tremelimumab; TKI = tyrosine kinase inhibitor.

1. Kelley RK, et al. *J.Clin Oncol.* 2021; 2. Study NCT02519348. ClinicalTrials.gov website.

Phase 3 HIMALAYA Trial: Study Design

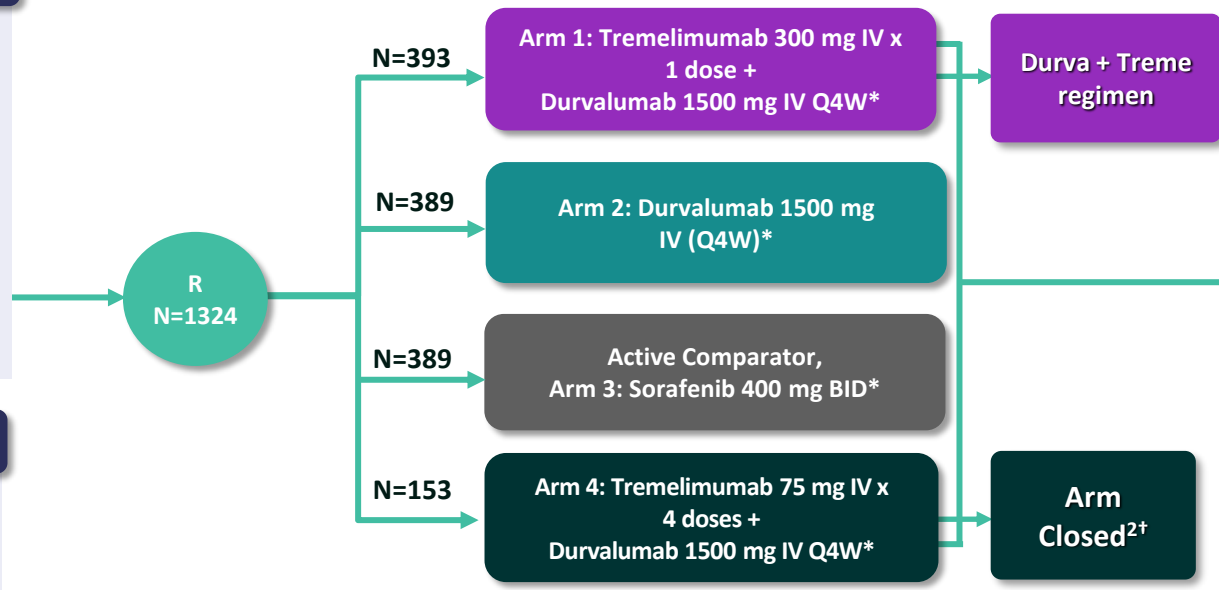
Objective: To evaluate the efficacy and safety of durvalumab + tremelimumab combination therapy and durvalumab monotherapy vs. sorafenib in the 1L treatment of patients with unresectable HCC

Eligibility

- Aged ≥18 years
- Unresectable HCC based on histopathological confirmation
- No prior systemic therapy for HCC
- BCLC stage B (that is not eligible for locoregional therapy) or stage C
- ECOG PS of 0 or 1
- Child-Pugh Score class A

Stratification

- Macrovascular invasion (yes vs. no)
- Etiology of liver disease (HBV vs. HCV vs. other)
- ECOG PS (0 vs. 1)



Primary Endpoint

- OS superiority (durva + treme vs. sorafenib)[2]

Secondary Endpoints

- Non-inferiority and superiority for OS (durvalumab vs. sorafenib)[2]
- Time to progression‡
- PFS‡
- ORR, DCR‡
- DoR‡
- Safety and tolerability[2]
- Anti-drug antibodies[2]
- Patient-reported outcomes[2]

*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment.
†Arm 4 was closed following a preplanned analysis of a Phase II study. The protocol was amended to randomly assign patients 1:1:1 to receive durvalumab/tremelimumab, durvalumab, or sorafenib. Patients randomized to this arm could continue treatment. Results from this arm are not reported here.
‡According to RECIST v1.1 per investigator assessment.

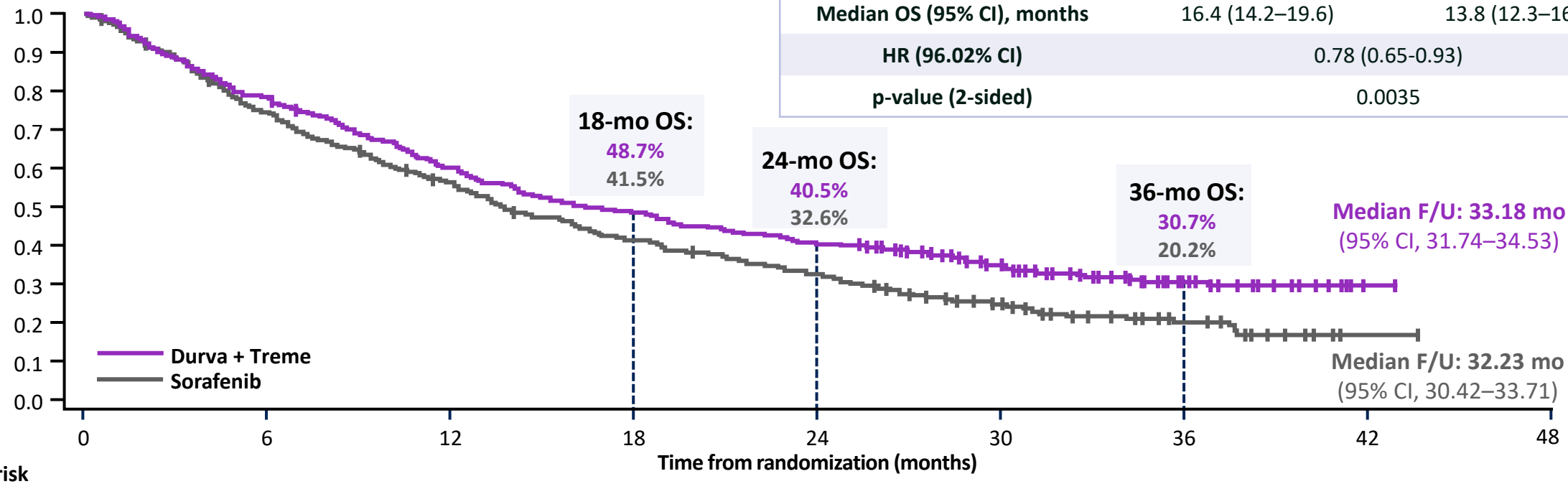
1L = first-line; BCLC = Barcelona Clinic Liver Cancer; BID = twice daily; DCR = disease control rate; DoR = duration of response; durva + treme = durvalumab plus tremelimumab; ECOG PS = Eastern Cooperative Oncology Group performance status; HBV = hepatitis B virus; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; IV = intravenously; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q4W = every 4 weeks; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.

1. Study NCT03298451. ClinicalTrials.gov website; 2. Abou-Alfa GK et al. Article and supplementary appendix. *NEJM Evid.* 2022;1(8). doi: 10.1056/EVIDoa2100070.

CCCEP #1435-2024-3847-L-P Expires: 2025-08-26 | CANO Endorsed: 2024-08-22| Expires: 2026-08-22

HIMALAYA Trial: OS for Durvalumab/Tremelimumab vs. Sorafenib (Primary Endpoint)

	Durva + Treme (n=393)	Sorafenib (n=389)
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65-0.93)	
p-value (2-sided)	0.0035	



Number at risk								
Durva + Treme	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

HIMALAYA met its primary endpoint
The durva + treme regimen was superior to sorafenib for OS

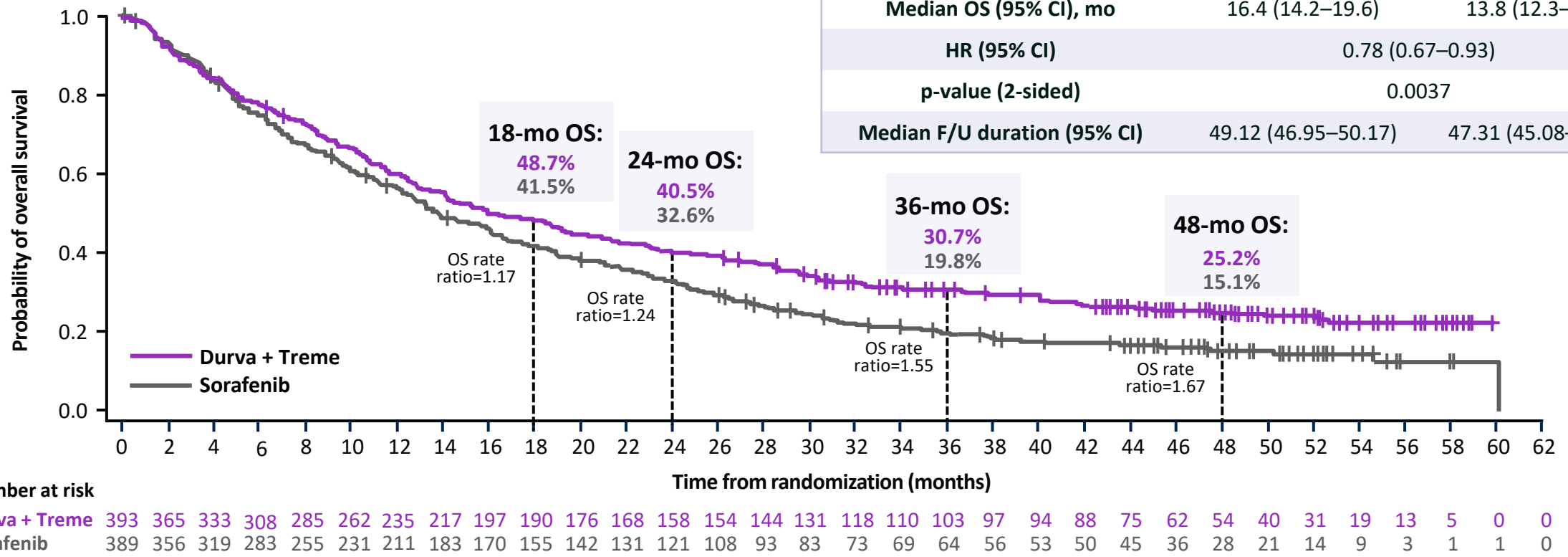
Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for durva + treme and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

CI = confidence interval; durva + treme = durvalumab 1500 mg Q4W + tremelimumab 300 mg × 1 dose; F/U = follow-up; HR = hazard ratio; mo = months; PD-L1 = programmed death ligand-1; OS = overall survival; Q4W = every 4 weeks.

1. Abou-Alfa GK et al. Article and supplementary appendix. *NEJM Evid.* 2022;1(8). doi: 10.1056/EVIDoa2100070.

HIMALAYA: 4-Year OS for Durvalumab/Tremelimumab vs. Sorafenib

	Durva + Treme (n=393)	Sorafenib (n=389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), mo	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (95% CI)	0.78 (0.67–0.93)	
p-value (2-sided)	0.0037	
Median F/U duration (95% CI)	49.12 (46.95–50.17)	47.31 (45.08–49.15)



Number at risk

Durva + Treme	393	365	333	308	285	262	235	217	197	190	176	168	158	154	144	131	118	110	103	97	94	88	75	62	54	40	31	19	13	5	0	0
Sorafenib	389	356	319	283	255	231	211	183	170	155	142	131	121	108	93	83	73	69	64	56	53	50	45	36	28	21	14	9	3	1	1	0

Durva + treme demonstrated a sustained, long-term OS benefit versus sorafenib, with 1 in 4 patients treated with durva + treme alive after 4 years

Data cut-off: 23 January 2023. The OS data maturity across the durva + treme and sorafenib arms: 78%. OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, etiology, ECOG PS and MVI. The 36-mo OS rate had a nominal 2-sided p-value of 0.0006.

CI = confidence interval; durva + treme = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; ECOG PS = Eastern Cooperative Oncology Group performance status; F/U = follow-up; HR = hazard ratio; mo = months; MVI = macrovascular invasion; OS = overall survival.

1. Sangro B, et al. Presented at ESMO: World Congress on Gastrointestinal Cancer. 29 June 2023.

HIMALAYA Established Durvalumab/Tremelimumab as a 1L Systemic Therapy for Unresectable HCC

HIMALAYA Summary[1]

Design: Global, open-label, phase 3 trial that included patients with unresectable HCC with no prior systemic therapy

Efficacy: A single priming dose of tremelimumab (CTLA-4 inhibitor) plus regular interval durvalumab (PD-L1 inhibitor) demonstrated a significant improvement in OS

- 48-month survival of 25.2% vs. 15.1% for sorafenib

Safety: Durvalumab/tremelimumab (durva + treme) had a favourable benefit-risk profile

- Grade 3 or 4 treatment-related imAEs occurred in 12.6% of patients[1]

Clinical Significance[2-4]

Patient population: Durva + treme is a recently-approved option for patients with unresectable HCC who:

- Require systemic therapy
- Have preserved liver function (Child-Pugh class A) and good performance status (ECOG PS 0-1)[2,3]

Place in therapy: According to clinical guidelines,* durva + treme joins atezolizumab + bevacizumab† as front-line SOC options in this patient population[2-4]

? What patient and tumour factors will lead you to consider a PD-L1 + CTLA-4 regimen?

*American Society of Clinical Oncology (ASCO), American Association for the Study of Liver Diseases (AASLD), Barcelona Clinic Liver Cancer (BCLC), and National Comprehensive Cancer Network (NCCN).
†Bevacizumab is an anti-VEGF inhibitor.

1L = first-line; CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4; durva + treme = durvalumab plus tremelimumab; ECOG PS = Eastern Cooperative Oncology Group performance status; HCC = hepatocellular carcinoma; imAE = immune-mediated adverse event; OS = overall survival; PD-L1 = programmed death ligand-1; SOC = standard of care; VEGF = vascular endothelial growth factor.

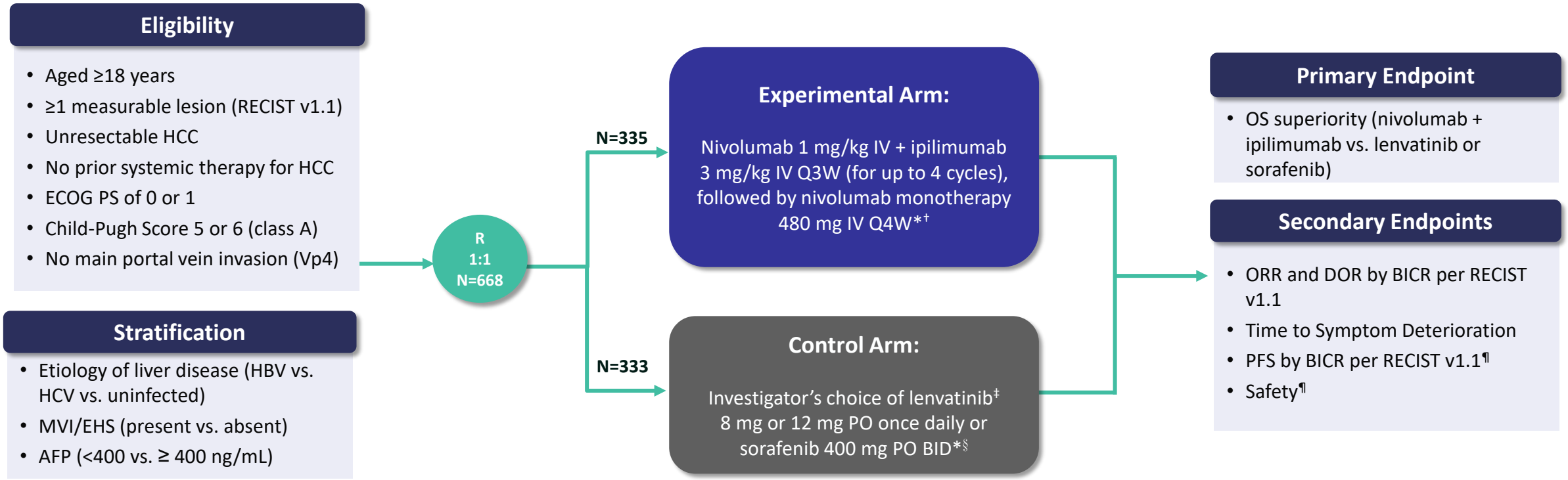
1. Abou-Alfa GK et al. Article and supplementary appendix. *NEJM Evid.* 2022;1(8). doi: 10.1056/EVIDoa2100070; 2. Singal AG, et al. *Hepatology.* 2023;78(6):1922. doi:10.1097/HEP.0000000000000466; 3. Gordan JD, et al. *JCO.* 2024:JCO.23.02745. doi:10.1200/JCO.23.02745; 4. Reig M, et al. *J Hepatol.* 2022;76(3):681-693. doi:10.1016/j.jhep.2021.11.018.

Upcoming Regimens:

Nivolumab/Ipilimumab

Phase 3 CheckMate 9DW Trial: Study Design

Objective: To evaluate the efficacy and safety of nivolumab + ipilimumab combination therapy vs. investigator's choice of lenvatinib or sorafenib in the 1L treatment of patients with unresectable HCC



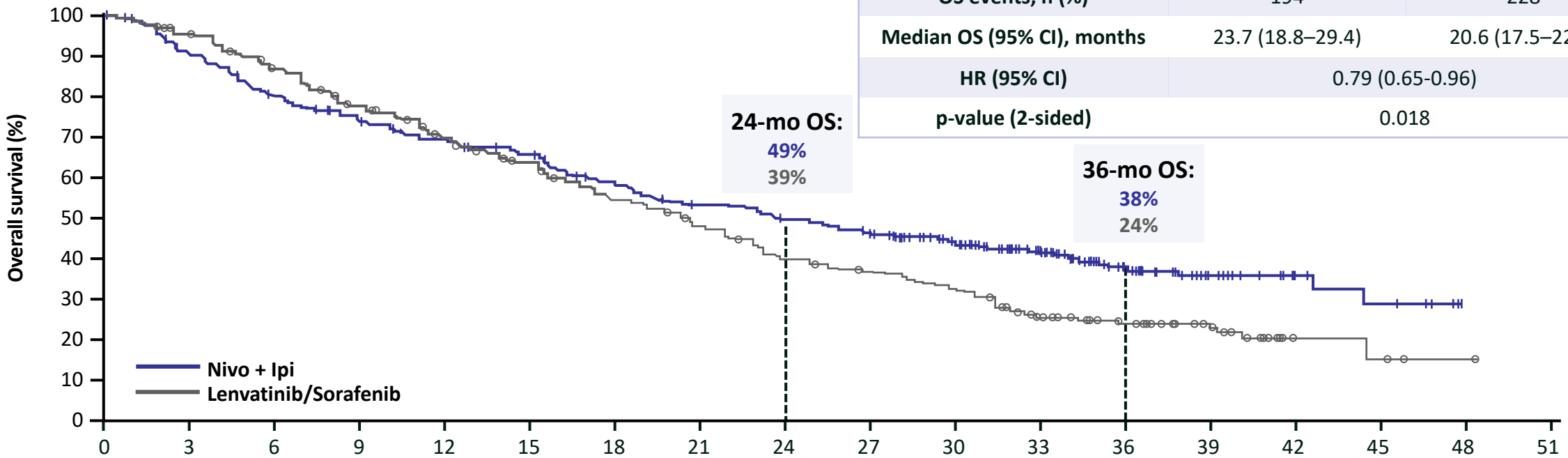
*Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (nivo + ipi arm only).
†Minimum of 1 dose of nivolumab/ipilimumab is required before proceeding to nivolumab monotherapy.
‡8 mg PO once daily if body weight <60 kg; 12 mg PO once daily if body weight ≥60 kg.
§Among 325 patients treated with lenvatinib/sorafenib: 275 (85%) received lenvatinib and 50 (15%) received sorafenib.
¶Exploratory endpoints.

1L = first-line; DOR = duration of response; AFP = α-fetoprotein; BICR = blinded independent central review; ECOG PS = Eastern Cooperative Oncology Group performance status; EHS = extrahepatic spread; HBV = hepatitis B virus; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; IV = intravenously; MVI = microvascular invasion; ORR = objective response rate; OS = overall survival; PO = by mouth; Q3W = every 3 weeks; Q4W = every 4 weeks; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.

1. Galle PR, et al. Presented at ASCO Annual Meeting: June 4, 2024. Abstract #LBA4008.

CheckMate 9DW: OS for Nivolumab/Ipilimumab vs. Investigator's Choice of Lenvatinib or Sorafenib

	Nivo + Ipi (n=335)	Len/Sor (n=333)
OS events, n (%)	194	228
Median OS (95% CI), months	23.7 (18.8–29.4)	20.6 (17.5–22.5)
HR (95% CI)	0.79 (0.65-0.96)	
p-value (2-sided)	0.018	



Number at risk																	
Nivo + Ipi	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
Len/Sor	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

CheckMate-9DW met its primary endpoint
The nivolumab + ipilimumab regimen was superior to lenvatinib/sorafenib for OS

Median (range) follow-up, 35.2 (26.8–48.9) months. Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is nivo + ipi over len/sor.
CI, confidence interval; HR, hazard ratio; len/sor = lenvatinib or sorafenib; nivo + ipi = nivolumab plus ipilimumab; OS = overall survival.

1. Galle PR, et al. Presented at ASCO Annual Meeting: June 4, 2024. Abstract #LBA4008.

PD-L1/PD-1 + CTLA-4 Inhibitors: Dosing and Administration

CCCEP #1435-2024-3847-L-P Expires: 2025-08-26 | CANO Endorsed: 2024-08-22| Expires: 2026-08-22

Baseline Assessments Prior to Initiating Dual ICI Therapy for Unresectable HCC

Standard baseline assessment for unresectable HCC with attention to:

CATEGORY	RECOMMENDED ASSESSMENTS

Medical History & Physical Exam	• Screen for pre-existing conditions:
	  • Severe autoimmune conditions[1,2]
	  • Inflammatory bowel disease[1]*
	  • Respiratory, dermatologic, and endocrine disorders[1,2]
	  • Viral hepatitis infection[2]
	  • Prior organ transplant[3]
	  • History of immunodeficiency
	• Assess underlying liver disease and cirrhosis (Child-Pugh score)
	• Obtain history of infusion-related reactions

Labs & Imaging	• Liver function tests (AST/ALT, bilirubin)[5,6,7] • Thyroid function tests (TSH, fT4)[5,6,7] • Renal function tests (serum creatinine)[5,6] • Blood glucose tests[1-2,7] • Electrolytes (for ipilimumab and nivolumab)[6-7]
Other	• Obtain BPMH • Check drug interactions

? **How are baseline assessments coordinated amongst members of the MDT at your institution?**

*Patients with inflammatory bowel disease may be at higher risk for transient exacerbation of their underlying condition[1].

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPMH = best possible medication history; fT4 = free thyroxine; HCC = hepatocellular carcinoma; ICI = immune checkpoint inhibitor; MDT = multidisciplinary team; TSH = thyroid-stimulating hormone.

1. Cancer Care Alberta – Follow-up and Management of Checkpoint Inhibitor Related Toxicities in Cancer Patients. Published February 2022. Accessed April 19, 2024; 2. Cancer Care Ontario. Tremelimumab – Drug Monograph. Published April 2024. Accessed May 6, 2024; 3. Singal AG, et al. *Hepatology.* 2023;78(6):1922. doi:10.1097/HEP.0000000000000466; 4. Product Monograph 1. May 13, 2024; 5. Product Monograph 2. May 29, 2024; 6. Product Monograph 3. December 7, 2023; 7. Product Monograph 4. June 28, 2024.

Durvalumab/Tremelimumab: Dosing and Administration

DOSING CALENDAR (patients ≥30 kg)[2]*†													
28-day cycle	**Cycle 1**				**Cycle 2**				**Cycle 3**				→
Week	**1** (Day 1)	**2**	**3**	**4**	**5** (Day 1)	**6**	**7**	**8**	**9** (Day 1)	**10**	**11**	**12**	
Tremelimumab 300 mg IV x 1 dose	●												
Durvalumab‡ 1500 mg IV Q4W	●				●				●				

ADMINISTRATION*	
	• Use separate infusion bags and filters for each drug product[1,2] • Observe aseptic technique; both agents do not contain a preservative[1,2] • Administer infusion solution immediately once prepared[1,2]
	• Both agents are administered as individual infusion solutions intravenously over 60 minutes using an IV line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter[1,2] • On Day 1 of Cycle 1, administer **tremelimumab** first, followed by **durvalumab** • Observe patient for 60 minutes following completion of **tremelimumab** infusion§

Interactions with drugs, foods, and laboratory tests have not been established. The effect of moderate and severe renal impairment¶ on drug PK is unknown‖.

*Please refer to the durvalumab and tremelimumab product monographs for full dosing and administration instructions. †For patients <30 kg, tremelimumab is dosed at 4 mg/kg on day 1 of cycle 1, and durvalumab at 20 mg/kg on day 1 of cycle 1 and as a single agent for subsequent cycles (Q4W)[2]. ‡Continue durvalumab treatment until disease progression or unacceptable toxicity[2]. §For cycle 1: Monitor vital signs immediately before the start of tremelimumab infusion, at 30 minutes into the infusion (halfway through infusion), at end of infusion, and as clinically indicated. Patients to be observed for 1 hour after treatment (i.e. one hour from end of durvalumab infusion) for signs of infusion-related reaction (IRR). Signs may include chills, itching, rash, flushing, shortness of breath, wheezing, dizziness, fever, facial swelling or back/neck pain[3]. ¶Severe renal impairment is defined as creatinine clearance (CrCl) 15-29 mL/min. For durvalumab, the effects of moderate and severe renal impairment is unknown[1]. For tremelimumab, the effect of severe renal impairment is unknown[2]. ‖For both tremelimumab and durvalumab[1,2]. IV = intravenously; PK = pharmacokinetics; Q4W = every 4 weeks.

1. Product Monograph 2. May 29, 2024; 2. Product Monograph 1. May 13, 2024; 3. BC Cancer. Protocol Summary for First-Line Treatment of Advanced HCC using Tremelimumab and Durvalumab. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Gastrointestinal/GITREMDUR_Protocol.pdf.

Nivolumab/Ipilimumab: Dosing and Administration

DOSING CALENDAR[1]* (per CheckMate 9DW trial)							
	Up to first 4 cycles (21-day cycles)			Subsequent cycles (28-day cycles)			
Week	**1** (Day 1)	**2**	**3**	**1** (Day 1)	**2**	**3**	**4**
Ipilimumab 3 mg/kg IV Q3W (up to 4 cycles)	●						
Nivolumab 1 mg/kg IV Q3W (up to 4 cycles), then 480 mg IV Q4W as monotherapy†	●			●			

ADMINISTRATION* (per product monograph guidance for melanoma)	
	• Use separate infusion bags and filters for each infusion[2,3] • Observe aseptic technique; both agents do not contain a preservative[2,3]
	• Both agents are administered as individual infusion solutions intravenously over 30 minutes using an IV line[2,3] • On Day 1 of Cycle 1 (and for up to 3 more cycles), administer **nivolumab** first, followed by **ipilimumab**[3]

Interactions with drugs, foods, and laboratory tests have not been established. The effect of renal impairment on drug PK is unknown§.

*The nivolumab and ipilimumab product monographs do not contain dosing and administration information for an indication in unresectable hepatocellular carcinoma. Dosing information was obtained from the phase 3 CheckMate 9DW trial and the administration guidance above applies to the indication in unresectable or metastatic melanoma.
†In CheckMate 9DW, nivolumab is continued until disease progression, unacceptable toxicity, withdrawal of consent, or a maximum treatment duration of 2 years[1].
§For both nivolumab and ipilimumab[2,3].
IV = intravenously; PK = pharmacokinetics.

1. Galle PR, et al. Presented at ASCO Annual Meeting: June 4, 2024. Abstract #LBA4008.; 2. Product Monograph 3. December 7, 2023; 3. Product Monograph 4. June 28, 2024.

Durvalumab/Tremelimumab and Nivolumab/Ipilimumab Have Different Dosing Regimens

	Durvalumab/Tremelimumab[1]	Nivolumab/Ipilimumab[2]
CTLA-4 inhibitor	**Tremelimumab**, given as **single** priming dose	**Ipilimumab**, given as **multiple** doses
Dosing for HCC[1-2]	**Dosing per Product Monograph[1*]** • **Tremelimumab** 300 mg IV x 1 dose (single priming dose) • **Durvalumab** 1500 mg IV Q4W and continue until unacceptable toxicity	**Dosing per CheckMate 9DW Trial[2]** • **Ipilimumab:** 3 mg/kg IV Q3W x up to 4 cycles • **Nivolumab:** 1 mg/kg IV Q3W x up to 4 cycles, then 480 mg IV Q4W as monotherapy and continue until disease progression or unacceptable toxicity

?

What has been your experience with dosing and administration of:
- **Nivolumab/ipilimumab**
- **Durvalumab/tremelimumab**

*Dose shown for patients >30 kg. Patients with a body weight ≥30 kg must receive weight-based dosing, equivalent to tremelimumab 4 mg/kg as a single dose followed by durvalumab 20 mg/kg at Day 1 of Cycle 1; continue durvalumab 20 mg/kg as a single agent Q4W. Treatment should continue until disease progression or unacceptable toxicity.

CTLA-4 = cytotoxic T lymphocyte associated protein-4; HCC = hepatocellular carcinoma; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; Q6W = every 6 weeks.

1. Product Monograph 1. May 13, 2024; 2. Galle PR, et al. Presented at ASCO Annual Meeting: June 4, 2024. Abstract #LBA4008.

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PD-L1/PD-1 + CTLA-4 Inhibitors: Adverse Event Management and Monitoring

CCCEP #1435-2024-3847-L-P Expires: 2025-08-26 | CANO Endorsed: 2024-08-22| Expires: 2026-08-22

Durvalumab/Tremelimumab & Nivolumab/Ipilimumab:

Adverse Events and Immune-Mediated Adverse Events (imAEs)

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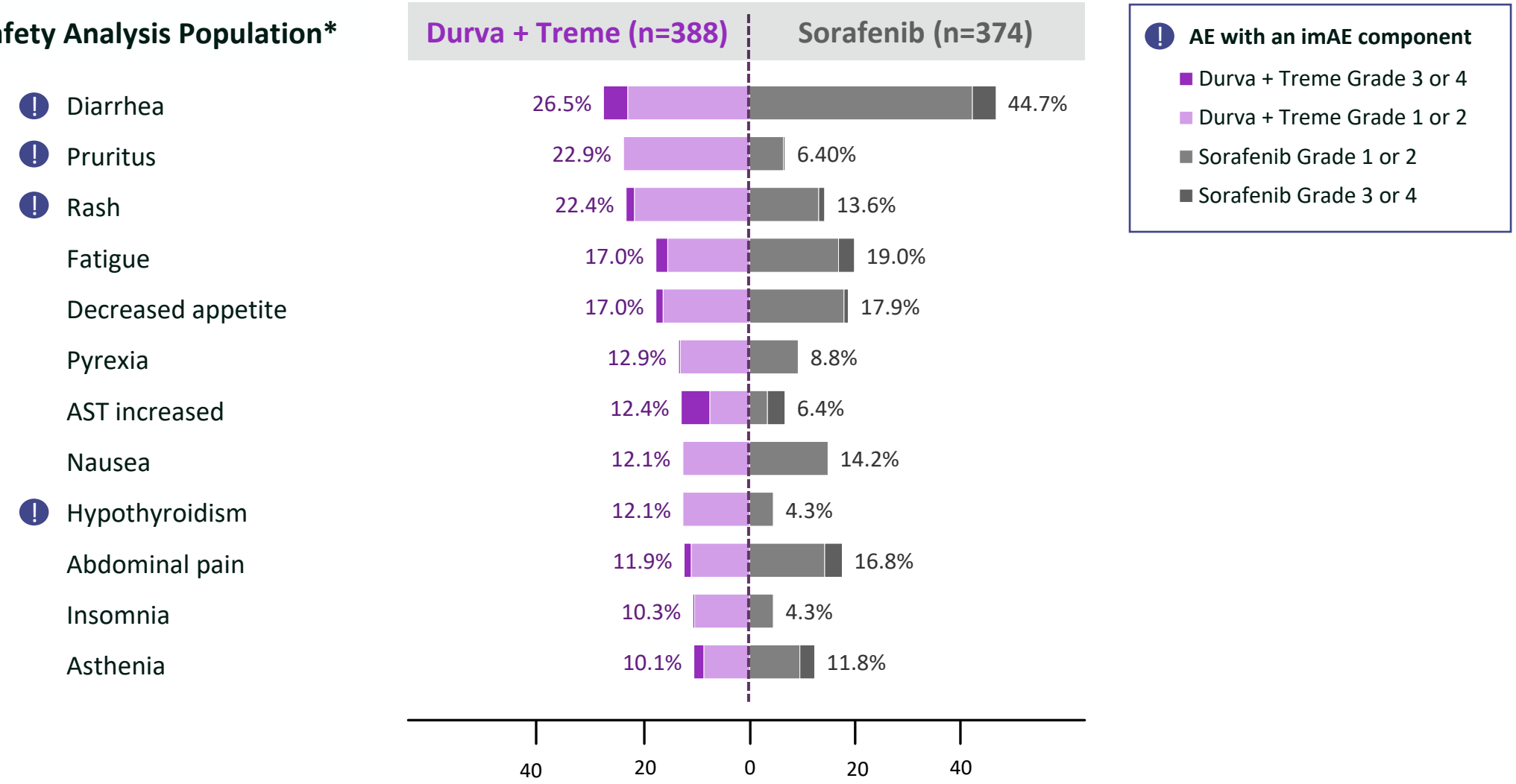
HIMALAYA: Most Common TEAEs (>10% of Patients)

Safety Analysis Population*

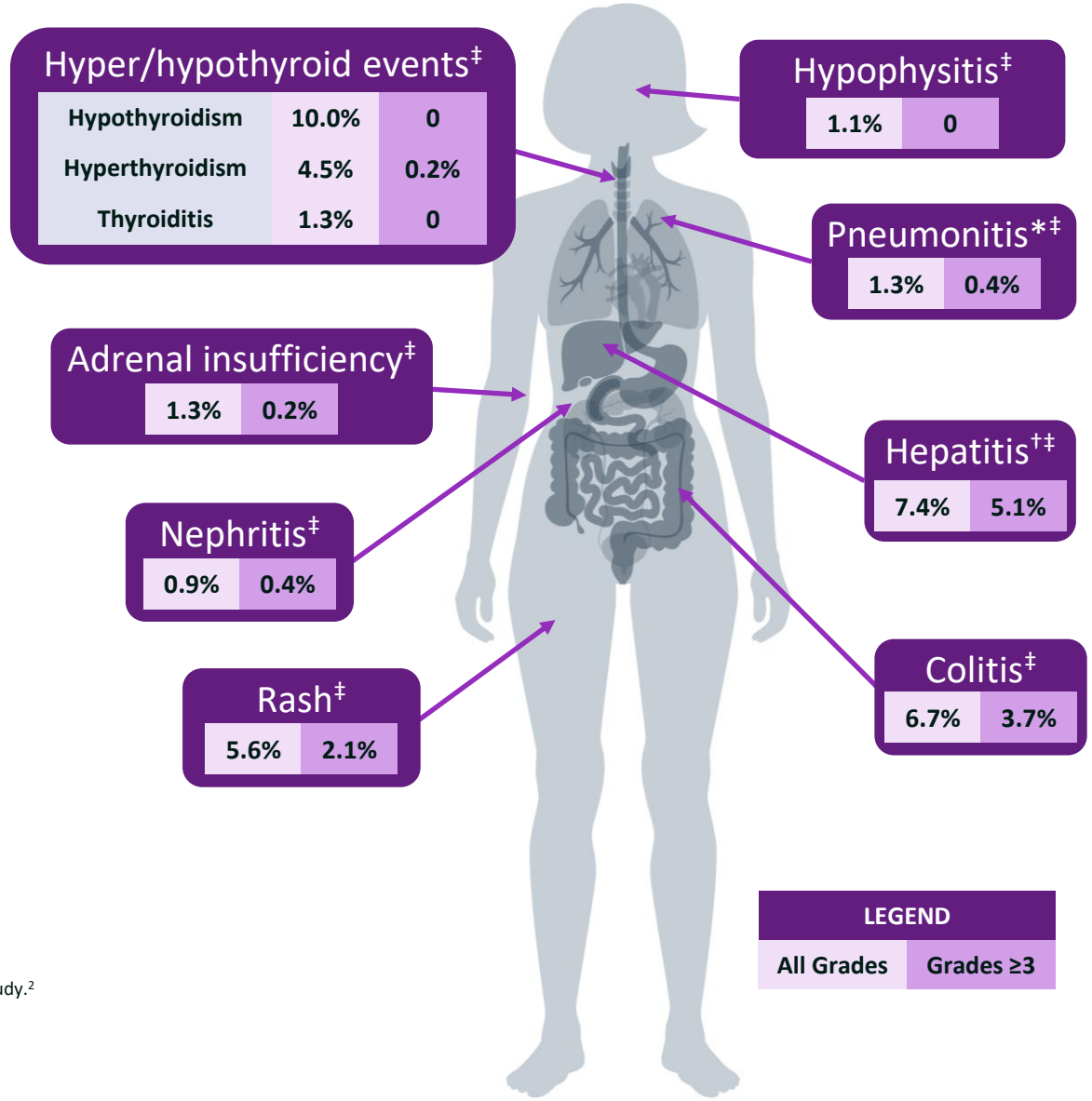


AE = adverse event; AST = aspartate aminotransferase; durva + treme = durvalumab plus tremelimumab; imAE = immune-mediated adverse event; TEAE = treatment-emergent adverse event.

1. Abou-Alfa GK, et al. *NEJM Evidence*. 2022;1(8):EVIDoa2100070. doi:10.1056/EVIDoa2100070.

Durvalumab/Tremelimumab: Summary of imAEs

RESULTS FROM HIMALAYA		
Event, n (%)	**Durva + Treme (n=388)**	**Sorafenib (n=374)**
Treatment-related imAEs		
Any imAE	134 (34.5)	21 (5.6)
Any Grade 3 or 4 imAE	49 (12.6)	9 (2.4)
Any imAE leading to death	6 (1.5)	0
Any imAE leading to discontinuation	22 (5.7)	6 (1.6)
Any imAE requiring high-dose steroids	78 (20.1)	7 (1.9)



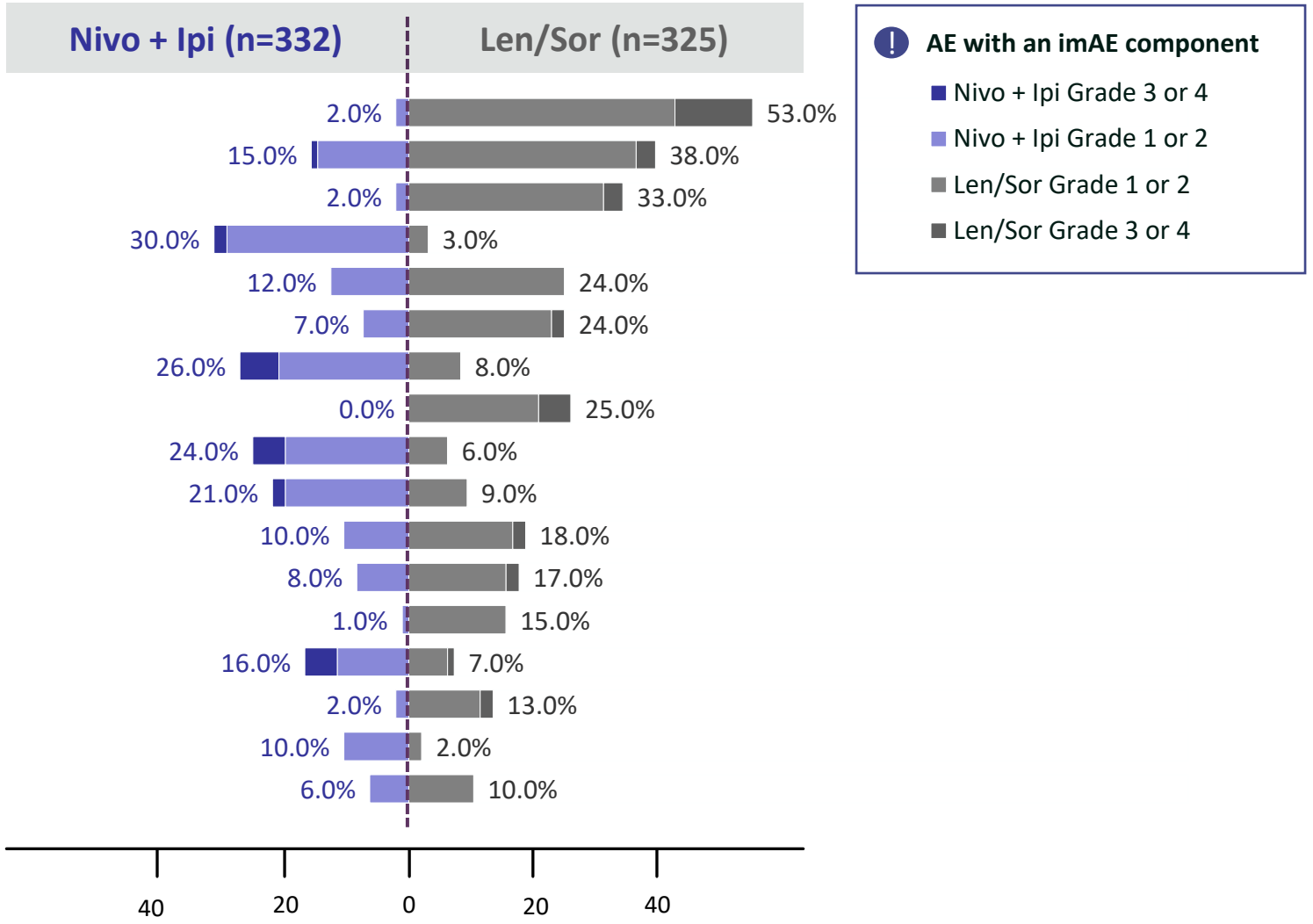
*Grade 5 (fatal) events occurred in 0.2% (1 patient).
†Grade 5 (fatal) events occurred in 0.6% (3 patients).
‡Data for adverse reactions is based on 462 patients from the HIMALAYA study and Study 22 (N=74), an open-label, multi-part, multicenter study.[2]

Durva + treme = durvalumab plus tremelimumab; imAE = immune-mediated adverse event.

1. Abou-Alfa GK, et al. *NEJM Evid.* 2022;1(8):EVIDoa2100070. doi:10.1056/EVIDoa2100070; 2. Product Monograph 1.-May 13, 2024.

CheckMate 9DW: Most Common TEAEs (≥10% of Patients)

Safety Analysis Population*

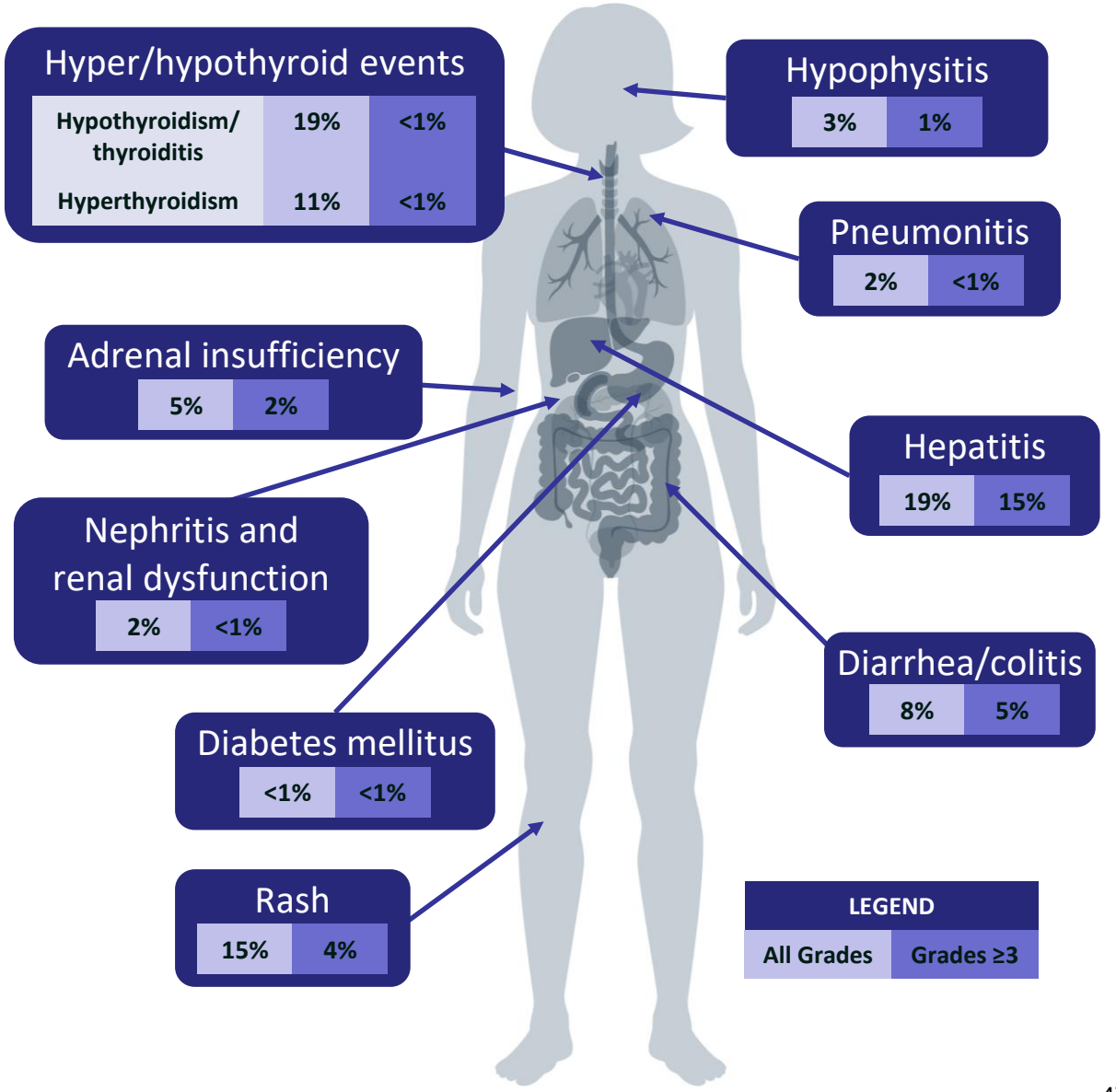


AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; imAE = immune-mediated adverse event; len/sor = lenvatinib or sorafenib; nivo + ipi = nivolumab/ipilimumab; PPE = palmar-plantar erythrodysesthesia; TEAE = treatment-emergent adverse event.

1. Galle PR, et al. Presented at ASCO Annual Meeting: June 4, 2024. Abstract #LBA4008.

Nivolumab/Ipilimumab: Summary of imAEs

RESULTS FROM CHECKMATE 9DW		
Event, n (%)	**Nivo + Ipi (n=332)**	**Len/Sor (n=325)**
imAEs		
Any imAE	191 (58)	NR
Any Grade 3 or 4 imAE	93 (28)	NR
Any imAE leading to discontinuation	42 (13)	NR
Any imAE requiring high-dose steroids	96 (29)	NR



imAE = immune-mediated adverse event; len/sor = lenvatinib or sorafenib; nivo + ipi = nivolumab plus ipilimumab; NR = not reported.

1. Galle PR, et al. Presented at ASCO Annual Meeting: June 4, 2024. Abstract #LBA4008.

Immune-Mediated Adverse Events (imAEs):
General Management

Recognition and Proper Management of imAEs is Key

imAEs[1-3]

- Due to non-specific activation of the immune system
- May involve any organ system, most commonly skin, GI tract, liver, lung, and endocrine system
- Management varies according to the organ system affected

General Management by Grade[4,5]

▶	**GRADE 1**	Continue ICI therapy with close monitoring*
⏸	**GRADE 2**	Suspend ICI therapy, consider resuming when symptoms revert to grade ≤1
⏸	**GRADE 3**	Suspend ICI therapy and initiate high-dose corticosteroids Refractory cases may require other immunosuppressive therapy
✕	**GRADE 4**	Permanently discontinue ICI therapy†

Key Points for HCPs[1-6]

Timing

- Early recognition and prompt treatment of imAEs is essential as they can progress quickly
- imAEs vary in onset and can occur months after treatment completion

Identification

- Compared to conventional chemotherapy, imAEs differ in presentation, onset, and duration
- Always consider imAEs in differential diagnosis

Referrals

- Low threshold for referral to specialists
- May include dermatology, endocrinology, gastroenterology, infectious disease, hepatology, and others

*With the exception of some neurologic, hematologic, and cardiac toxicities[1,6]. †Except for endocrinopathies that have been controlled by hormone replacement[6].

GI = gastrointestinal; ICI = immune checkpoint inhibitor; imAE = immune-mediated adverse event.

1. Brahmer JR, et al. *JCO*. 2018;36(17):1714-1768; 2. Abu-Sbeih H, et al. *JIPO*. 2020;1(1):7-18; 3. BC Cancer. BC Cancer Protocol Summary for Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitor Immunotherapy. February 2022. Accessed April 12, 2024. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf; 4. Cancer Care Alberta. Follow-up and Management of Checkpoint Inhibitor Related Toxicities in Cancer Patients. Published February 2022. Accessed May 6, 2024. https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-supp018-immunotherapy-toxicities.pdf; 5. Cancer Care Ontario (CCO). Immune Checkpoint Inhibitor Toxicity Management - Clinical Practice Guideline – Version 1, March 2018. https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/ImmuneCheckpointInhibitor.pdf. Accessed April 12, 2024; 6. Schneider BJ, et al. *JCO*. 2021;39(36):4073-4126.

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Steroids and Other Agents for imAE Management

Steroids are the Cornerstone of imAE Treatment[1-3,5]

Steroid Tapering

- Taper steroids slowly
- Recommended duration over at least 4 weeks
- Educate patients on importance of tapering

Managing Risks of High-Dose/Long-term* Steroid Use[2-4]

Infection	Consider prophylaxis for opportunistic bacterial infections (e.g., SMX/TMP for PCP)[3,4†]
Gastritis	Consider PPIs or H_2 blockers[4]
Osteoporosis	Consider calcium and vitamin D supplementation[4]
Diabetes	Monitor blood glucose levels[4]

Other Immunosuppressants[1-3,5-6]

- May be used if no improvement with steroids[1,3]
- **Common agents‡:** Infliximab§, mycophenolate mofetil (EO)
- **Other options‡:** Azathioprine, cyclo-phosphamide, intravenous immune globulin (IVIG), methotrexate, tacrolimus, vedolizumab, and others[1,3-5]

Supportive Therapies and Modalities by imAE[1-3,5]

Diarrhea/colitis	Loperamide, oral rehydration, prophylactic antibiotics
Cutaneous reactions	Diphenhydramine, hydroxyzine, emollients, oral antibiotics
Pneumonitis	Prophylactic antibiotics, oxygen, ventilation support
Hyperthyroidism	Beta blockers, methimazole or propylthiouracil¶
Hypothyroidism	Levothyroxine

*Definition of long-term steroid treatment varies from 30 days[2] to <4 weeks[3]. †PCP prophylaxis is recommended if it is anticipated that the patient will be treated with >20 mg of prednisone for >4 weeks[4]. ‡Other immunosuppressive agent options depend on the specific imAE being managed. §Infliximab may induce non-infectious hepatitis or liver injury[8]. ¶Consider methimazole or propylthiouracil in cases of Grave's Disease[3,5]. Anti-thyroid drugs are not recommended when thyrotoxicosis results from a destructive process[4].

EO = expert opinion; H_2 blocker = histamine receptor 2 blocker; imAE = immune-mediated adverse event; PCP = *pneumocystis jirovecii* pneumonia; PPI = proton pump inhibitor; SMX/TMP = sulfamethoxazole/trimethoprim.

1. Brahmer JR, et al. *JCO*. 2018;36(17):1714-1768. doi:10.1200/JCO.2017.77.6385; 2. Abu-Sbeih H, et al. *JIPO.* 2020;1(1):7-18; 3. Cancer Care Ontario (CCO). Immune Checkpoint Inhibitor Toxicity Management - Clinical Practice Guideline – Version 1, March 2018.Accessed April 12, 2024. https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/ImmuneCheckpointInhibitor.pdf; 4. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. Version 1.2024. Published online December 7, 2023. https://www.nccn.org/patients/guidelines/content/PDF/immunotherapy-checkpoint-patient.pdf; 5. BC Cancer Protocol Summary for Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitor Immunotherapy. February 2022. Accessed May 7, 2024. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf; 6. Schneider BJ, et al. *JCO.* 2021;39(36):4073-4126; 7. Bjornsson HK, et al. *J. Hepatol.* 2022;76(1):86-92.

Combined BC Cancer and CCO imAE Management Guidelines

Diarrhea/ Colitis

Cutaneous Reactions

Pneumonitis

Hepatitis

Nephritis

Adrenal Insufficiency

Hypothyroidism

Hyperthyroidism/ Thyroiditis

Hypophysitis/ Hypopituitarism

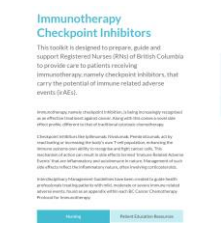
Infusion-Related Reactions

CCO = Cancer Care Ontario; imAE = immune-mediated adverse event.

Canadian Guidelines & Resources for imAE Management

BC Cancer

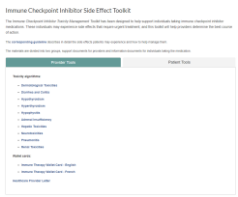
Toolkit:
Immunotherapy Checkpoint Inhibitors for Registered Nurses



Protocol Summary:
Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitor Immunotherapy

Cancer Care Ontario (CCO)

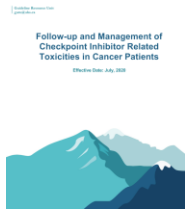
Toolkit:
Immune Checkpoint Inhibitor Side Effects



Clinical Practice Guideline:
Immune Checkpoint Inhibitor Toxicity Management

Cancer Care Alberta

Clinical Practice Guideline:
Follow-up and Management of Checkpoint Inhibitor Related Toxicities in Cancer Patients



OnTarget

Resource Guide for HCPs:
Presentation, Prevention and Management of Adverse Events
(login required)

1. BC Cancer. Immunotherapy Checkpoint Inhibitor Toolkit for Registered Nurses. Accessed May 8, 2024. http://www.bccancer.bc.ca/health-professionals/clinical-resources/nursing/immunotherapy-checkpoint-inhibitors;
2. BC Cancer: Protocol Summary for Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitor Immunotherapy. Published February 1, 2022. Accessed May 8, 2024. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf;
3. Cancer Care Ontario (CCO). Immune Checkpoint Inhibitor Side Effect Toolkit. Accessed May 8, 2024. https://www.cancercareontario.ca/en/guidelines-advice/modality/immunotherapy/immune-therapy-toolkit;
4. Cancer Care Ontario (CCO). Immune Checkpoint Inhibitor Toxicity Management. Accessed May 8, 2024. https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/ImmuneCheckpointInhibitor.pdf;
5. Cancer Care Alberta. Clinical Practice Guideline: Follow-up and Management of Checkpoint Inhibitor Related Toxicities in Cancer Patients. Published July 2020. Accessed May 8, 2024. https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-supp018-immunotherapy-toxicities.pdf.
6. OnTarget. A Resource Guide for Pharmacists on Targeted Cancer Therapies. Accessed June 20, 2024. https://ontargetonco.com/en.

International Guidelines & Resources for imAE Management

ACCC Immuno-Oncology Institute

Resources for smaller community oncology centres (e.g., New Brunswick), summaries of references

AIM with Immunotherapy

Patient action plans, HCP toolkits, video tutorials, other resources

ASCO Guideline

Management of Immune-Related Adverse Events in Patients Treated with ICI Therapy

MASCC Immuno-Oncology Subgroup

Recommendations for management of patients with severe and refractory toxicities

NCCN Guideline®

Management of Immunotherapy-Related Toxicities (v1.2024)

Link to NCCN.org; login required to access guideline

SITC Resources

Quick and easy-to-read references developed by consensus and expert opinion

ACCC = Association of Cancer Care Centers; ASCO = American Society of Clinical Oncology; HCP = healthcare professional; ICI = immune checkpoint inhibitor; MASC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network; SITC = Society for Immunotherapy of Cancer.

1. Association of Cancer Care Centers (ACCC). Immuno-Oncology Institute. Accessed May 24, 2024. https://www.accc-cancer.org/home/learn/precision-medicine/treatment/immunotherapy;
2. AIM With Immunotherapy Foundation. Immuno-Oncology Essentials. Accessed May 24, 2024. https://aimwithimmunotherapy.org/;
3. Schneider B, et al. *JCO.* 2021;39(36):4073-4126. doi:10.1200/JCO.21.01440;
4. Multinational Association of Supportive Care in Cancer (MASCC). MASCC Guidelines. Accessed May 24, 2024. https://mascc.org/resources/mascc-guidelines/;
5. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. Version 1.2024. Published online December 7, 2023. https://www.nccn.org/
6. Schneider B, et al. *JCO.* 2021;39(36):4073-4126. doi:10.1200/JCO.21.01440;
7. Society for Immunotherapy of Cancer (SITC). Accessed May 24, 2024. https://www.sitcancer.org/home.

Patient Case:

Managing Immune-Mediated Adverse Events (imAEs)

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Patient Case: Initial Presentation

Meet Patient CK:

- 65 yo male
- ECOG PS 1
- Child-Pugh class A

Presents on December 4, 2023

Disease found on imaging follow-up for hepatitis B cirrhosis

Diagnosed with unresectable HCC

Assessments	
Imaging	• **Screening ultrasound:** 8 cm mass • **Triphasic CT scan:** 8 cm mass Segment 2, 3 cm mass Segment 4, and several sub centimetre lesions in other lobes all with washout LR5 consistent with multifocal liver disease
Labs	• **Liver:** AST 45 IU/L, ALT 34 IU/L, Bili 12 g/L, Albumin 38 g/L, INR 1.1, AFP 34,000 ng/mL • **Thyroid:** TSH 1.3 mIU/L • **Renal:** SCr 87 µmol/L • **Blood glucose tests:** normal
Pathology	• **Liver biopsy:** none due to imaging and elevated AFP

1L Treatment for Unresectable HCC	
Initiation date	January 23, 2024
Dosing	• **Tremelimumab** 300 mg IV x 1 dose • **Durvalumab** 1500 mg IV Q4W

Patient case courtesy of Dr. Howard Lim.

1L = first line; AFP = α-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bili = bilirubin; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HCC = hepatocellular carcinoma; INR = international normalized ratio; Q4W = every 4 weeks; SCr = serum creatinine; TSH = thyroid-stimulating hormone; yo = years old.

Patient Case: Follow-up Visits

Scenario A: Immune-Mediated Diarrhea/Colitis

Patient CK:

- 65 yo male
- ECOG PS 1
- Child-Pugh class A

2023

- **December 4:** Initial presentation

2024

- **January 23:** Durva + treme initiated
- **February – March:** Experiences imAE

Progression of imAE

- **February**: 1-2 loose bowel movements (BMs)/day
- **Early March:** BMs increasing in frequency
- **Late March**: 5-6 BMs/day, becoming more watery and sometimes with mucus; some incontinence and nocturnal BMs

? How does monitoring change at your institution once patients report increased frequency of BMs?

? How would you manage this immune-mediated adverse event (imAE)?

Patient case courtesy of Dr. Howard Lim.

BM = bowel movement; durva + treme = durvalumab plus tremelimumab; ECOG PS = Eastern Cooperative Oncology Group Performance Status; imAE = immune-mediated adverse event; yo = years old.

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Patient Case: Management of imAE

Scenario A: Immune-Mediated Diarrhea/Colitis

Symptoms:
1-2 loose BMs/day

→

Symptoms:
5-6 BMs/day, becoming more watery and sometimes with mucus

Some incontinence and nocturnal BMs

→

Steroids:
Oral steroids 1 mg/kg

Referrals:
GI referral

Supportive Therapy:
IV hydration for ~ 1 week

→

BMs start to slow down

→

Steroids:
Continue oral steroids until BMs decrease

ICI therapy:
Treatment held

→

Resolution:
Colitis resolved. Discussion with patient on retrying ICI or switching to TKI

Patient case courtesy of Dr. Howard Lim.

BM = bowel movement; GI = gastrointestinal/gastroenterology; ICI = immune checkpoint inhibitor; IV = intravenous; TKI = tyrosine kinase inhibitor.

Patient Case: Follow-up Visits

Scenario B: Immune-Mediated Rash

Patient CK:

- 65 yo male
- ECOG PS 1
- Child-Pugh class A

2023

- **December 4:** Initial presentation

2024

- **January 23:** Durva + treme initiated
- **March:** Experiences imAE

Progression of imAE

- **Early March:** Small red papules on arms
- **Mid-Late March:** Rash begins to progress with more lesions on the arms and spreads up around the trunk of the body on the chest and stomach
- **Late March:** Lesions worsen over the last week and the arms and trunk have now become uniformly red

? How does monitoring change at your institution once patients report appearance of rash?

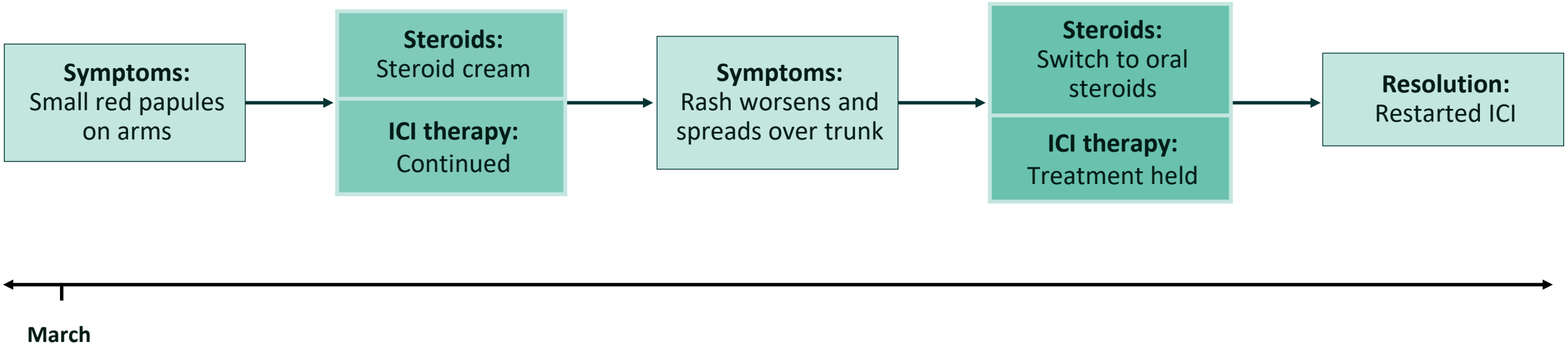
? How would you manage this immune-mediated adverse event (imAE)?

Patient case courtesy of Dr. Howard Lim.

Durva + treme = durvalumab plus tremelimumab; ECOG PS = Eastern Cooperative Oncology Group Performance Status; imAE = immune-mediated adverse event; yo = years old.

Patient Case: Management of imAE

Scenario B: Immune-Mediated Rash



Patient case courtesy of Dr. Howard Lim.

ICI = immune checkpoint inhibitor.

Practical Insights and Patient Counselling for HCPs

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ICI Patient Education Checklist

Treatment Info

- Name and type of ICI patient will receive
- ICI mechanism, rationale, potential benefits
- Differences between ICIs and chemotherapy
- Treatment administration
- Concept of pseudoprogression*

Safety

- Common and serious treatment AEs and imAEs
- imAE presentation, onset, duration
- Self-monitoring and seeking medical attention
- imAE management (e.g., steroid AEs, tapering)
- Interactions (e.g., vaccines†)

Patient Resources

- Patient wallet alert card and letter for HCP visits‡
- Multilingual educational videos, video cards, posters
- Drug-specific patient information sheets
- Patient symptom diary/symptom tracker sheet

Key Points

- How to recognize unique side effects
- When to seek urgent care
- How to contact medical team (during and after hours)

*Pseudoprogression is a phenomenon in which an initial increase in tumor size is observed or new lesions appear, followed by a decrease in tumor burden. This phenomenon can benefit patients receiving immunotherapy but often leads to premature discontinuation of treatment owing to the false judgment of progression[7]. Pseudoprogression and hyperprogression have been reported in a limited number of patients with HCC treated with immunotherapy[1].

†Live vaccines should be avoided. Literature around the use of inactivated vaccines is evolving[1]. Where feasible, patients receiving combination CTLA-4/PD-1 inhibitor therapy should receive the influenza vaccine prior to starting treatment[2].

‡Indicates BC Cancer, Cancer Care Ontario (CCO), and Groupe d'étude en Oncologie du Québec (GEOQ) resources. Please confirm if similar province or centre-specific resources are available at your institution.

AE = adverse event; HCP = healthcare provider; ICI = immune checkpoint inhibitor; imAE = immune-mediated adverse event.

1. Cannella R, et al. American Journal of Roentgenology. 2022;219(4):533-546; 2. BC Cancer. BC Cancer Influenza Vaccine Recommendations for Adults with Cancer. Updated November 2023. Accessed April 28, 2024. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/BC%20Cancer%20Influenza%20Vaccine%20Recommendations.pdf; 3. Cancer Care Ontario (CCO). Immune Checkpoint Inhibitor Toxicity Management - Clinical Practice Guideline – Version 1, March 2018. Accessed April 12, 2024. https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/ImmuneCheckpointInhibitor.pdf; 4. Madden D. BC Cancer Immune Checkpoint Inhibitors. Patient Education Resources. Accessed April 28, 2024. http://www.bccancer.bc.ca/health-professionals/clinical-resources/nursing/immunotherapy-checkpoint-inhibitors#Patient--Education--Resources; 5. Cancer Care Ontario. Immunotherapy Medications: What You Need To Know. Accessed April 28, 2024. https://www.cancercareontario.ca/sites/ccocancercare/files/assets/ImmunotherapyMedicationsPatientInfo.pdf; 6. Schneider BJ, et al. *JCO*. 2021;39(36):4073-4126; 7. Jia W, et al. *Cancer Biol Med.* 2019;16(4):655-670.

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Patient Resources on Immunotherapy/ICI Treatment

BC Cancer

Immunotherapy Patient Handout

Immunotherapy Patient Alert Card

Immunotherapy Patient Letter

Cancer Care Ontario (CCO)

Immunotherapy Medications:
What You Need to Know (*English*)

Immunotherapy Medications:
What You Need to Know (*French*)

Groupe d'étude en Oncologie du Québec (GÉOQ)

Immunotherapy Patient Letter, Alert Card, General Information and Advice *(HCP login required)*

ICI = immune checkpoint inhibitor.

1. BC Cancer. BC Cancer Protocol Summary (Patient Version) SCIMMUNE. Published January 1, 2019. Revised February 1, 2022. Accessed May 8, 2024. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Handout.pdf; 2. BC Cancer. Immunotherapy Alert Card. Published July 2019. Accessed May 8, 2024. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Immunotherapy%20Alert%20Card.pdf; 3. BC Cancer. Immunotherapy Patient Letter. Published November 28, 2017. Accessed May 8, 2024. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Immunotherapy%20Patient%20Letter.pdf; 4. Cancer Care Ontario (CCO). Immunotherapy Medications: What You Need to Know (English). Accessed May 8, 2024. https://www.cancercareontario.ca/sites/ccocancercare/files/assets/ImmunotherapyMedicationsPatientInfo.pdf; 5. Cancer Care Ontario (CCO). Immunotherapy Medications: What You Need to Know (French). Accessed May 8, 2024. https://www.cancercareontario.ca/sites/ccocancercare/files/assets/ImmunotherapyMedicationsPatientInfo-FR.pdf; 6. Groupe d'étude en Oncologie du Québec (GEOQ) website. Accessed June 19, 2024. https://www.geoq.info/

Multidisciplinary Care in HCC Management

Multidisciplinary Team (MDT)

- Medical oncologist
- Radiation oncologist
- Hepatobiliary surgeon
- Hepatologist
- Interventional radiologist
- Gastroenterologist
- Pathologist
- Pharmacist
- Oncology Nurse
- Palliative care specialist
- Social worker
- Dietitian

Specialists Involved in AE/imAE Management

- Dermatologist
- Pulmonologist
- Infectious Disease
- Endocrinologist
- Nephrologist
- Surgeon
- Cardiologist

?

How do you collaborate with other specialties to:

- **Optimize management of imAEs**
- **Educate patients and caregivers**

An MDT approach to patient care has been shown to improve outcomes[1-2]

AE = adverse event; HCC = hepatocellular carcinoma; imAE = immune-mediated adverse event; MDT = multidisciplinary team.

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Hepatocellular Carcinoma. Version 1.2024. Published online April 9, 2024. Accessed May 24, 2024. https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf;
2. Wong JK, et al. *Cancer Treat. Rev.* 2023;115:102526. doi:10.1016/j.ctrv.2023.102526; 3. Reig M, et al. *J Hepatol.* 2022;76:681–693; 4. Singal AG, et al. *Hepatology*. 2023;78(6):1992. doi:10.1097/HEP.0000000000000466; 5. Sinn DH, et al. PLoS One 2019;14:e0210730;
6. Lhewa D, et al. *Clin Liver Dis.* 2020;24(4):771-787. doi:10.1016/j.cld.2020.07.009; 7. Naugler WE, et al. *Clin Gastroenterol Hepatol.* 2015;13(5):827-835. doi:10.1016/j.cgh.2014.03.038; 8. Oh JH, et al. *J Liver Cancer.* 2024;24(1):47-56. doi:10.17998/jlc.2024.02.27.

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Practical Insights for Medical Oncologists

HCC Management

Monitoring

- Routinely monitor for side effects per protocol guidance
- Establish nursing call-outs/follow-up for the first few treatment cycles

Resources

- Engage key specialists for assistance:
  - E.g., gastroenterologist, respirologist, rheumatologist, endocrinologist, nephrologist, etc.
- Employ other resources:
  - OncoAssist® mobile app*
  - Local experts

*Free app for oncology HCPs

Education

For Patients

- Key education points:
  - Side effects (e.g., diarrhea, shortness of breath, fatigue) and when to seek medical attention
  - After-hours phone numbers

For Other HCPs

- Educate HCPs on recognition and management of imAEs
- Provide ongoing educational support for other specialities:
  - E.g., emergency department and/or hospitalist services which may admit patients

HCP = healthcare professional; imAE = immune-mediated adverse event.

1. Per Expert Opinion. May 21, 2024.

Practical Insights for Hepatologists

Infection Management

Viral Hepatitis

- Provide prophylactic antivirals for HBV infection (entecavir or tenofovir)
- Provide DAA therapy for pre-emptive treatment of untreated chronic HCV infection
- Use rescue antivirals for reactivated HBV
- Use DAA therapy for HCV flare

Bacterial Infections

- Treat any underlying bacterial infections such as spontaneous bacterial peritonitis

Liver-Related Complications

Proactive Strategies

- Optimize underlying liver synthetic function
- Aggressively treat portal hypertension:
  - Use of non-selective beta blockers (such as carvedilol or nadolol)
  - Abdominal paracentesis to drain ascites
  - Prophylactic banding of esophageal varices
- Use IV albumin judiciously
- Routinely use lactulose with or without rifaximin for HE

Reactive Strategies

- Perform liver biopsy and start corticosteroids for severe ALT elevation on immunotherapy
- Perform urgent abdominal paracentesis for ascites
- Perform emergency banding of bleeding esophageal varices, start treatment of ulcers and portable gastropathy
- Regularly infuse IV albumin
- Manage hepatorenal syndrome
- Treat HE with lactulose and rifaximin
- Consider ursodiol for cholestatic drug reactions

ALT = alanine aminotransferase; DAA = direct-acting antiviral; HBV = hepatitis B virus; HCV = hepatitis C virus; HE = hepatic encephalopathy; IV = intravenous.

1. Per Expert Opinion. May 21, 2024.

Practical Insights for Pharmacists

Assessments & Monitoring

Standard Monitoring

- Carefully assess the patient's overall health, performance status, and comorbidities
- Obtain and grade baseline toxicities
- Ensure completion of required baseline and follow-up blood work and tests

imAE Monitoring

- Ensure ongoing AE monitoring through a call-back program
- Closely monitor for signs and symptoms of imAEs
- Promptly identify and address imAEs based on severity and type

Medication Management

- Obtain a BPMH and check for drug-drug interactions
- Implement appropriate supportive care measures (e.g., anti-diarrheals or corticosteroids)
- In severe cases, consider temporary or permanent discontinuation of immunotherapy

Education & Communication

For Patients

- Educate patients prior to starting therapy:
  - Explain potential AEs and the importance of prompt reporting of concerns
  - Provide appropriate education tools
  - Ensure understanding of steps to follow and numbers to call when experiencing toxicities
- Maintain open communication and address concerns or questions about immunotherapy or potential side effects

For Other HCPs

- Provide education on appropriate management of imAEs
- Collaborate with other HCPs involved in the patient's care

AE = adverse event; BPMH = Best Possible Medication History; HCP = healthcare professional; imAE = immune-mediated adverse event; SE = side effect.

1. Per Expert Opinion. May 24, 2024.

Practical Insights for Nurses

Strategies to reinforce patient education, identify and address changes in symptoms, and collaborate with the MDT to optimize patient care and minimize treatment delays

Assessments & Monitoring

Standardized Phone Triage System

- Develop a set of questions related to common AEs
- Advise when to seek immediate medical attention

Standard Assessments with Special Attention to:

- Baseline oxygenation and radiological features
- Prescription and non-prescription medications

Symptom Review

- Encourage patients to report new or worsening symptoms, even if they seem unrelated to ICIs

Professional Development

- Stay up-to-date with the latest ICI evidence and guidelines
- Participate in CE programs, attend conferences and in-service presentations, engage in professional discussions

Patient Education & Advocacy

Continual Education Reinforcement

- Address questions/concerns about ICIs and their potential AEs
- Use visual aids, pamphlets, or educational videos to enhance understanding

Advocacy

- Actively listen to concerns and facilitate communication between the patient and the healthcare team
- Encourage patients to engage in shared decision-making

MDT Collaboration

- Involve the MDT early to avoid treatment delays
- Work together to modify the treatment plan based on the patient's response and AEs
- Implement supportive care interventions to manage AEs and improve patient comfort, including counseling services for emotional support

AE = adverse event; CE = continuing education; ICI = immune checkpoint inhibitor; MDT = multidisciplinary team.

1. Per Expert Opinion. May 21, 2024.

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Summary and Close

Key Takeaways

- PD-L1 and CTLA-4 dual ICI blockade has improved survival in advanced HCC and is regarded as a new 1L standard of care
- The durvalumab/tremelimumab regimen consists of a single tremelimumab priming dose with regular durvalumab dosing (given every 4 weeks). The nivolumab/ipilimumab regimen is dosed in a combination phase for up to 4 cycles followed by nivolumab monotherapy
- Complete and accurate HCP, patient, and caregiver education around recognition and management of immune-mediated adverse events (imAEs) is key to optimizing patient outcomes
- Careful attention to baseline liver synthetic function (Child Pugh score) and regular monitoring of liver function on immunotherapy may help to prevent or minimize serious hepatic adverse events
- imAEs associated with immunotherapy should be proactively managed by early detection, close monitoring, and following imAE-specific algorithms
- Corticosteroids are the cornerstone of imAE treatment and must be tapered slowly

1L = first-line; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; HCC = hepatocellular carcinoma; HCP = healthcare professional; imAE = immune-mediated adverse event; ICI = immune checkpoint inhibitor; PD-L1 = programmed death ligand-1.

See slide notes for references.

Appendix


SPARK
Sharing Practical Insights And Raising Knowledge of CTLA-4s in HCC

Dose Modifications for Durvalumab/Tremelimumab Related to Immune-Mediated Adverse Events

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Recommended Dose Modifications for Durvalumab/Tremelimumab

Adverse Reaction	Severity*	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified‡
Immune-mediated pneumonitis/ interstitial lung disease	Grade 2	Withhold dose†	1–2 mg/kg/day prednisone or equivalent should be initiated followed by a taper
	Grade 3 or 4	Permanently discontinue	2–4 mg/kg/day methylprednisolone or equivalent should be initiated followed by a taper
Immune-mediated hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values)‡	**ALT or AST** >2.5– ≤5 x BLV and ≤20 x ULN	Withhold dose†	Corticosteroids should be administered with an initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST >5–7 x BLV and ≤20 x ULN OR Concurrent **ALT or AST** >2.5–5 x BLV and ≤20 x ULN and **total bilirubin** >1.5– <2 x ULN§	Withhold dose†	
	ALT or AST >7 x BLV OR >20 x ULN whichever occurs first OR **Bilirubin** >3 x ULN	Permanently discontinue	

*Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. See slide notes for grade descriptions.
†After withholding, durvalumab can be resumed within 12 weeks if the adverse reactions improved to Grade ≤1 and the corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day. Durvalumab should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable.
‡If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement.
§For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BLV = baseline value; HCC = hepatocellular carcinoma; ULN = upper limit of normal.

1. Product Monograph 1. May 13, 2024. 2. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) 4.03. Updated April 19, 2021. Accessed May 29, 2024. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

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Recommended Dose Modifications for Durvalumab/Tremelimumab

Adverse Reaction	Severity*	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified‡
Immune-mediated colitis or diarrhea	Grade 2 or 3	Withhold dose†	Initiate 1–2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
	Intestinal perforation of ANY grade	Permanently discontinue	Consult a surgeon immediately if an intestinal perforation of ANY GRADE is suspected
Immune-mediated hyperthyroidism, thyroiditis	Grade 2–4	Withhold dose until clinically stable	Symptomatic management
Immune-mediated hypothyroidism	Grade 2–4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated adrenal insufficiency, hypophysitis/hypopituitarism	Grade 2–4	Withhold dose until clinically stable	Initiate 1–2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated Type 1 diabetes mellitus	Grade 2–4	No changes	Initiate treatment with insulin as clinically indicated

*Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.
†After withholding, durvalumab can be resumed within 12 weeks if the adverse reactions improved to Grade ≤1 and the corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day. Durvalumab should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable.

1. Product Monograph 1. May 13, 2024. 2. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) 4.03. Updated April 19, 2021. Accessed May 29, 2024. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

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Recommended Dose Modifications for Durvalumab/Tremelimumab

Adverse Reaction	Severity*	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified‡
Immune-mediated nephritis	Grade 2 with **serum creatinine** >1.5– 3 x (ULN or baseline)	Withhold dose†	Initiate 1–2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with **serum creatinine** >3 x baseline or >3–6 x ULN; Grade 4 with **serum creatinine** >6 x ULN	Permanently discontinue	
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for >1 week or Grade 3	Withhold dose‡	Initiate 1–2 mg/kg/day prednisone or equivalent followed by a taper for Grade 2 >1 week or Grade 3 and 4
	Grade 4	Permanently discontinue	
Infection	Grade 3 or 4	Withhold dose	Symptomatic management; treat with anti-infectives for suspected or confirmed infections
Immune-mediated myocarditis	Grade 2–4	Permanently discontinue	Initiate 2–4 mg/kg/day prednisone or equivalent followed by a taper‡
Immune-mediated myositis/polymyositis/rhabdo-myolysis	Grade 2 or 3	Withhold dose†,§	Initiate 1–2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

*Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.
†After withholding, durvalumab can be resumed within 12 weeks if the adverse reactions improved to Grade ≤1 and the corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day. Durvalumab should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable.
‡If no improvement within 2 to 3 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month.
§Permanently discontinue durvalumab if the adverse reaction does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.

ULN = upper limit of normal.

1. Product Monograph 1. May 13, 2024. 2. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) 4.03. Updated April 19, 2021. Accessed May 29, 2024. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

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Recommended Dose Modifications for Durvalumab/Tremelimumab

Adverse Reaction	Severity*	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified‡
Immune-mediated myasthenia gravis	Grade 2–4	Permanently discontinue	Initiate 1–2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated encephalitis			
Immune-mediated Guillain-Barré syndrome			
Other immune-mediated adverse reactions†	Grade 2 or 3	Withhold dose‡	Initiate 1–2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	Consider pre-medications for prophylaxis of subsequent infusion-related reactions
	Grade 3 or 4	Permanently discontinue	Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines and/or society guidelines

*Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.
†Includes immune thrombocytopenia, pancreatitis, immune-mediated arthritis, and uveitis.
‡After withholding, durvalumab can be resumed within 12 weeks if the adverse reactions improved to Grade ≤1 and the corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day. Durvalumab should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable.

1. Product Monograph 1. May 13, 2024. 2. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) 4.03. Updated April 19, 2021. Accessed May 29, 2024. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

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Immune-Mediated Adverse Event (imAE) Management Algorithms

Based on Cancer Care Ontario (CCO) and BC Cancer Guidelines

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Immune-Mediated Diarrhea/Colitis*

DESCRIPTION	REFERRALS & ASSESSMENTS	STEROID TREATMENT‡	SUPPORTIVE THERAPY	ICI	MONITORING & FOLLOW-UP
GRADE 1 • **Stools**: <4 stools/day above baseline • **Symptoms**: Asymptomatic colitis	• Notify physician • Nurse management[BC]	• Not required	• **Loperamide** • Oral hydration • Consider electrolyte supplementation and dietary modifications	• **Continue**	• Monitor closely • Nursing follow-up next business day if possible[BC]
GRADE 2 • **Stools**: 4-6 stools/day above baseline • **Symptoms**: Abdominal pain, mucus or blood in stool. Limiting instrumental ADL	• Notify physician • Collaborative symptom management **REFERRALS:** • **Gastroenterologist** • **Surgical consult** if any chance of perforation; do not administer steroids	• Start steroids right away or if no improvement after 24 hours of loperamide • **Prednisone PO** until grade ≤1, then taper slowly • If no improvement in 72 hours, treat as grade 3-4	• Per grade 1 • Consider **prophylactic antibiotics** for opportunistic infections	• **Withhold therapy** until grade ≤1 and steroids tapered • Consider discontinuation if no improvement within 12 weeks or inability to reduce steroids	• Nursing follow-up as needed[BC]
GRADE 3 • **Stools**: ≥7 stools/day above baseline • **Symptoms**: Incontinence, ileus, fever, colitis with severe abdominal pain, need for hospitalization for IV fluids ≥24hrs, limiting self-care ADL	**ASSESSMENTS:** • Rule out bowel perforation • Consider endoscopy • **Consider stool cultures**, including C. difficile toxin	• **Rule out perforation first, then:** • **Methylprednisolone IV** (or prednisone PO) until improvement, then taper • If no response after 3 days, **infliximab**† (use with caution in grade 4 due to risk of perforation)	• **Admit to hospital and initiate IV hydration** • Consider **empiric antibiotics** for patients with fever/leukocytosis • Use opioid analgesics with caution due to risk of narcotic bowel	• **Permanently discontinue**[CCO] • **If grade 4 or persistent grade 3 permanently discontinue ICI**[BC] • **If grade 3, withhold**[BC] • If improved to grade ≤1, and steroids tapered slowly, may consider resuming ICI(s)[BC]	• **Continually evaluate** for evidence of GI perforation or peritonitis; • If no response to steroids, consider **infliximab** if not contraindicated†, or **vedolizumab**[BC] if refractory to infliximab • Consider repeat endoscopy
GRADE 4 • **Life-threatening;** grade 3 plus fever, or peritoneal signs consistent with bowel perforation, or ileus					

Gr 1 → Gr 1 → Gr 1 → Gr 1 → Gr 1

Gr 2 → Gr 2 → Gr 2 → Gr 2 → Gr 2

Gr 3 → Gr 3 or 4 → Gr 3 or 4 → Gr 3 or 4

Gr 4 →

Adapted from CCO and BC Cancer guidelines on ICI toxicity management. See slide notes for references.

*First rule out infectious causes of diarrhea/colitis.[CCO] If infliximab is contraindicated (possibility of perforation, sepsis, TB, NYHA 3/4 CHF), consider MMF or other immunosuppressive agents.[CCO] ‡Refer to local guidance for steroid dosing.

ADL = activity of daily living; CHF = congestive heart failure; CCO = Cancer Care Ontario; GI = gastrointestinal; ICI = immune checkpoint inhibitor; IV = intravenously; MMF = mycophenolate mofetil; NYHA = New York Heart Association; PO = by mouth; TB = tuberculosis.

Immune-Mediated Cutaneous Reactions

DESCRIPTION	REFERRALS & ASSESSMENTS	STEROID TREATMENT‡	SUPPORTIVE THERAPY	ICI	MONITORING & FOLLOW-UP
GRADE 1 **Macules/papules coverage:** <10% BSA **With or without associated symptoms***	• Notify physician • Nurse management[BC]	• Not required • Consider **topical steroids**: – Mild symptoms: **hydrocortisone** – Moderate symptoms: **betamethasone**	• **Thick emollients** or oatmeal baths • **Avoid sun** • **Cool compress** for itching • **Consider antihistamines** or **anti-pruritic** (e.g., diphenhydramine or hydroxyzine)	• **Continue ICI(s) unless symptoms intolerable** • **If intolerable, hold ICI(s)** until resolved to grade ≤1 • Monitor closely	• **Nursing** follow up for next business day and/or create care plan • **If persists >1-2 weeks or recurs:** – **Consider skin biopsy** – **Withhold ICI(s)** – **Prednisone PO‡,** once improving, taper slowly
GRADE 2 **Macules/papules coverage:** 10-30% BSA **With or without associated symptoms***; limiting ADL	• Notify physician • Nurse management[BC] **REFERRALS:** Consider **dermatologist** if persistent grade 2 symptoms lasting >1-2 weeks	• **Topical steroid** • Consider **prednisone PO** if symptoms persist >7 days, then taper once resolved to grade ≤1			
GRADE 3 **Macules/papules coverage**: >30% BSA **With or without associated symptoms***; limiting self care ADL; local superinfection	• Notify physician • Collaborative symptom management **REFERRALS:** • **Dermatologist** for **consult ± biopsy**	• **Prednisone PO**, then taper once resolved to grade ≤1 If severe, consider **IV steroids** (as below)	• Per above • Consider **oral antibiotics** if needed	• **Withhold ICI(s)** until resolved to grade ≤1 • **Consider discontinuation** if no improvement within **12 weeks**	• **Nursing** follow up for next business day and/or create care plan[BC] • Consider **prophylactic antibiotics** for opportunistic infections[BC]
GRADE 4 SJS† or widespread mucosal ulcerations: complicated rash with full-thickness dermal ulceration or necrosis; life-threatening		• **Methylprednisolone IV**, then taper over ≥4 weeks once resolved to grade ≤1	• **Admit to hospital** • Fluids and electrolytes • Consider antibiotics	• **Discontinue ICI(s)** • Consider resuming ICI(s) once steroid taper complete[BC]	

Gr 1 → Gr 1 → Gr 1 → Gr 1 or 2 → Gr 1 or 2

Gr 2 → Gr 2 → Gr 2

Gr 3 → Gr 3 → Gr 3 → Gr 3 → Gr 3

Gr 4 → Gr 4 → Gr 4 → Gr 4 → Gr 4

Adapted from CCO and BC Cancer guidelines on ICI toxicity management. See slide notes for references.

*As per CTCAE version 4.0 = pruritus, burning, tightness or equivalent. †Symptoms indicative of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): macules rapidly spread and coalesce, leading to epidermal blistering, necrosis, and sloughing.
‡Refer to local guidance for steroid dosing.
ADL = activity of daily living; BSA = body surface area; ICI = immune checkpoint inhibitor; IV = intravenously; PO = by mouth; SJS = Stevens Johnson Syndrome.

Immune-Mediated Pneumonitis*

DESCRIPTION	REFERRALS & ASSESSMENTS	STEROID TREATMENT†	SUPPORTIVE THERAPY	ICI	MONITORING & FOLLOW-UP
GRADE 1 Asymptomatic; diagnostic radiological observations only; no intervention needed	• Notify physician **REFERRALS:** • Consider **pulmonologist** and **infectious disease** consults **ASSESSMENTS:** • Monitor O2sat and CXR or CT every cycle	• Consider **prednisone PO** or **methylprednisolone IV**	• Not required	• **If patient is on steroids, consider withholding ICI(s) until resolution** • If improved, resume ICI(s) (if withheld) when stable • If worsened, see below	• Monitor Q2-3 days • **Reassess at least Q3W**
GRADE 2 Symptomatic (mild to moderate), worsens from baseline; medical intervention indicated; limiting instrumental ADL	• Notify physician **REFERRALS:** • **Pulmonologist and consider infectious disease consult** **ASSESSMENTS:** • Consider high resolution CT scan, bronchoscopy, and lung biopsy[BC]	• **Prednisone PO or IV equivalent,** then taper slowly if improved to grade ≤1 • If no improvement or worsening after 48-72 hours treat as grade 3-4	• Consider **hospitalization** • Consider **empiric antibiotics** if suspicious for infection	• **Withhold ICI(s)** until resolved to grade ≤ 1 without complications & steroids tapered • **Discontinue ICI(s) if toxicity recurs**	• Monitor daily • Consider hospitalization for **daily monitoring of symptoms and re-imaging Q1-3 days** • If persists or worsens after 48-72 hours: treat as grades 3 or 4
GRADE 3 Severe symptoms; limiting self care ADL; oxygen indicated **GRADE 4** Life-threatening respiratory compromise; urgent intervention indicated (e.g., intubation and ventilation)	• Hospitalize patient **REFERRALS:** • **Pulmonologist and infectious disease consults** **ASSESSMENTS:** • Consider bronchoscopy and lung biopsy to investigate for infection	• **Methylprednisolone IV** or **prednisone PO,** then taper slowly if improved to grade ≤1 • If **no improvement** after 48 hours, consider **additional immunosuppression** (e.g., infliximab, mycophenolate mofetil, IVIG, cyclophosphamide)	• **Hospitalization** • Start **prophylactic antibiotics** for opportunistic infections • **Oxygen and ventilation support** if necessary	• **Permanently discontinue ICI(s)**	• Hospitalization • Monitor daily • If persists or worsens after 2 days, consider additional immunosuppression‡

Gr 1 → Gr 1 → Gr 1 → Gr 1 → Gr 1

Gr 2 → Gr 2 → Gr 2 → Gr 2 → Gr 2

Gr 3 → Gr 3 or 4 → Gr 3 or 4 → Gr 3 or 4

Gr 4 →

Adapted from CCO and BC Cancer guidelines on ICI toxicity management. See slide notes for references.

*First rule out infectious causes of pneumonitis. †Refer to local guidance for steroid dosing. ‡E.g., infliximab, MMF, IVIG, cyclophosphamide.

ADL = activity of daily living; CCO = Cancer Care Ontario; CT = computed tomography; CXR = chest X-ray; ICI = immune checkpoint inhibitor; IV = intravenously; IVIG = intravenous immune globulin; MMF = mycophenolate mofetil; O2sat = oxygen saturation; PO = by mouth; Q1-3 days = every 1-3 days; Q2-3 days = every 2-3 days; Q3W = every 3 weeks.

Immune-Mediated Hepatitis in HCC

Guidance for Patients with No Liver Involvement at Baseline

DESCRIPTION	REFERRALS & ASSESSMENTS	STEROID TREATMENT†	SUPPORTIVE THERAPY	ICI	MONITORING & FOLLOW-UP
GRADE 1 AST/ALT ≤3 x ULN or total bilirubin ≤1.5 x ULN (or <2 x baseline)	• Not required • Consider viral serology‡	Not recommended	Not required	• **Continue ICI(s)** • Monitor closely	Monitor closely
GRADE 2 AST/ALT >3-5 x ULN or total bilirubin >1.5-3 x ULN (or >2 baseline)	**REFERRALS:** • Consider **hepatologist, gastroenterologist** **ASSESSMENTS:** • Consider hepatitis **serology; rule out** infectious or malignant causes or obstruction; LFTs Q3 days until resolution	• If no improvement in liver function in 2-3 days, initiate **prednisone PO** or **IV equivalent** • Increase dose if no improvement • Taper slowly if liver function normalizes	• Not required	• **Withhold ICI(s)** until resolution to grade ≤1 and steroids tapered[CCO] • If AST/ALT ≤3 × ULN and bilirubin ≤1.5 × ULN, or ↓ to baseline, resume ICI(s)[BC]	• Consider prophylactic antibiotics for opportunistic infections if elevations in AST/ALT and/or bilirubin persist[BC]
GRADE 3 AST/ALT >5-20 x ULN or total bilirubin >3-10 x ULN	• **REFERRALS: Hepatologist/ gastroenterologist** **ASSESSMENTS:** • Consider liver biopsy to rule out other causes of hepatitis§. Increase LFTs monitoring to Q1-5 days until resolution.	• **Methylprednis-olone IV** or **prednisone PO,** then taper slowly	• If AST/ALT do not ↓ within 3 days after steroids, add MMF; discontinue once prednisone tapered[CCO] If no improvement or worsening after 7 days, consult expert or switch to another immuno-suppressant¶[CCO]	• **Permanently discontinue ICI(s)**	• If LFTs return to grade ≤2, taper steroid slowly[BC] • For persistent grades 3 or 4 for ≥3 days, worsens, or recurs: consider non-steroid immunosuppressive agents; avoid infliximab due to hepatotoxicity potential[BC]
GRADE 4 AST/ALT >20 X ULN or total bilirubin >10 X ULN					

Liver Involvement at Baseline*

DESCRIPTION	STEROID TREATMENT‡	ICI
ALT or AST >2.5 – ≤5 x BLV and ≤20 x ULN		• **Withhold ICI(s)** until resolved to grade ≤1 and steroids tapered • **Permanently discontinue for recurrent grade 3** reactions, as applicable
ALT or AST >5–7 x BLV and ≤ 20 x ULN or Concurrent ALT or AST >2.5 – 5 x BLV and ≤20 x ULN and total bilirubin >1.5 - <2 x ULN	• **Prednisone or equivalent**, then taper	
ALT or AST >7 x BLV or >20 x ULN whichever occurs first or bilirubin >3 x ULN		• **Permanently discontinue**

Adapted from Tremelimumab Product Monograph. See slide notes for references.

Adapted from CCO and BC Cancer guidelines on ICI toxicity management. See slide notes for references.

*Immune-mediated hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values). If AST and ALT are ≤ULN at baseline in patients with liver involvement, withhold permanently discontinue ICI based on recommendations for hepatitis with no liver involvement. †Refer to local guidance for steroid dosing and check hepatitis A, B, and C serology results before initiating steroids (EO). §Hepatitis A, C, CMV. ¶Tacrolimus 0.10-0.15 mg/kg/day; in the case of severe hepatotoxicity, the decision to use infliximab should be made after consideration of risk and benefit, and discussion with the patient. ‡Viral serology includes the following: hepatitis A IgM, hepatitis B surface antigen, hepatitis C antibody, hepatitis E antibody. Other items of work-up for ICI hepatitis include abdominal ultrasound and autoimmune hepatitis serology (ANA, SMA, IgG) (EO). ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate aminotransferase; BC = BC Cancer; BLV = baseline value; CCO = Cancer Care Ontario; CMV = cytomegalovirus; EO = expert opinion; HCC = hepatocellular carcinoma; ICI = immune checkpoint inhibitor; IgG = immunoglobulin G; IgM = immunoglobulin M; IV = intravenous; LFT = liver function tests; MMF = mycophenolate mofetil; PO = by mouth; Q12H = every 12 hours; SMA = smooth muscle antibody; ULN = upper limit of normal.

Immune-Mediated Hyperthyroidism/Thyroiditis

DESCRIPTION	REFERRALS & ASSESSMENTS	STEROID TREATMENT§	SUPPORTIVE THERAPY & MONITORING	ICI	MONITORING & FOLLOW-UP
GRADE 1 • **Symptoms**: Asymptomatic or mild • **Labs:** fT4 normal; TSH suppression (<0.3mUI/L)	• Notify physician • TSH and FT4 before each cycle†	• Not recommended	• Intervention not indicated	• **Continue ICI(s)** • Monitor closely	• Monitor closely • Monitor TSH and fT4 before each cycle†
GRADE 2 • **Symptoms:** Moderate* • **Labs:** High fT4; suppressed TSH (<0.1mUI/L)	• Notify physician **REFERRALS:** • **Endocrinologist** **ASSESSMENTS:** • TSH and fT4 before each cycle	• Consider short period of **prednisone PO** or equivalent for acute thyroiditis presenting as hyperthyroidism	• If symptomatic, initiate an **oral beta-blocker‡** • If urgent, consider **methimazole** or **propylthiouracil** in cases of Grave's disease • Initiate thyroid replacement if hypothyroid after several weeks	• **Withhold ICI(s)** until symptoms are controlled, the patient is stable, and steroid is tapered	• Standard monitoring • Monitor TSH and fT4 before each cycle†
GRADE 3 • **Symptoms:** Severe†, limiting self-care ADLs • **Labs:** fT4 high; suppressed TSH (<0.1mUI/L)	• Hospitalization indicated • If thyroid storm, admit to ICU **REFERRALS:** • **Endocrinologist**	• **Methylprednisolone IV**; continue until improvement to mild severity, resolve or return to baseline then taper slowly[2] • **Prednisone PO** for 1-2 weeks for presumed thyroiditis[3]			
GRADE 4 • **Symptoms**: Life-threatening, limiting self-care ADLs • **Labs:** fT4 high; suppressed TSH (<0.1mUI/L)	**ASSESSMENTS:** • TSH and fT4 • Rule out sepsis			• **Discontinue ICI(s)**[CCO] • Withhold ICI and if improved, taper steroid over ≥4 weeks before resuming ICI(s)[BC]	• Hospitalization • Monitor TSH and fT4†

Gr 1 → Gr 1 → Gr 1 → Gr 1 → Gr 1

Gr 2 → Gr 2 → Gr 2 → Gr 2 or 3 → Gr 2 or 3

Gr 3 → Gr 3 or 4 → Gr 3 or 4

Gr 4 → Gr 4 → Gr 4

Adapted from CCO and BC Cancer guidelines on ICI toxicity management. See slide notes for references.

*Weight loss, increased appetite, anxiety and irritability, muscle weakness, menstrual irregularities, fatigue, tachycardia. †Arrhythmia, atrial fibrillation, tremor, sweating, insomnia, diarrhea. ‡E.g., propranolol 10-40 mg QID or atenolol 25-50 mg daily. §Refer to local guidance for steroid dosing.

CCO = Cancer Care Ontario; fT4 = free thyroxine; ICI = immune checkpoint inhibitor; ICU = intensive care unit; IV = intravenous; mUI/L = milli-international units per litre; PO = by mouth; QID = 4 times daily; TSH = thyroid-stimulating hormone.

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Immune-Mediated Hypothyroidism

DESCRIPTION	REFERRALS & ASSESSMENTS	STEROID TREATMENT‡	SUPPORTIVE THERAPY & MONITORING	ICI	MONITORING & FOLLOW-UP
GRADE 1 • **Symptoms:** Asymptomatic or mild • **Labs:** fT4 normal, asymptomatic TSH elevation (>10 mUI/L)	• Notify physician **ASSESSMENTS:** • TSH before each cycle • If TSH >2 x ULN, or out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated	• Not recommended	• Intervention not indicated	• **Continue ICI(s)** • Monitor closely	• Monitor closely • Monitor TSH ± fT4
GRADE 2 • **Symptoms:** Moderate* • **Labs:** Low fT4 and/or TSH >10mUI/L	• Notify physician **REFERRALS:** • Consider **endocrinologist** **ASSESSMENTS:** • TSH and fT4 before each cycle	• Not recommended	• **Levothyroxine** (if elderly, heart disease, or severe comorbidities, start with reduced dose and increase slowly)§	• **Consider withholding ICI(s)** until symptoms are controlled, patient is stable on hormone therapy, and steroids tapered	• Monitor TSH + fT4 • Standard monitoring
GRADE 3 • **Symptoms:** Severe†, limiting self-care ADLs • **Labs:** Very low fT4 and TSH very high **GRADE 4** • **Symptoms:** Life-threatening; limiting self-care ADL • **Labs:** Very low fT4 and TSH very high	• Hospitalization indicated • Admit to ICU if myxedema coma **REFERRALS:** • **Endocrinologist** (urgent if myxedema coma) **ASSESSMENTS:** • TSH and fT4	• **Methylprednisolone IV** until improvement to mild severity, resolve or return to baseline, then taper slowly • If myxedema coma, **hydrocortisone IV** until adrenal insufficiency ruled out	• Per above plus **supportive therapy** for **severe cardio-respiratory symptoms** • **IV hydration** if indicated	• **Discontinue ICI(s)**	• Hospitalization • Monitor TSH + fT4 • Standard monitoring

Gr 1 → Gr 1 → Gr 1 → Gr 1 → Gr 1
Gr 2 → Gr 2 → Gr 2 → Gr 2 → Gr 2
Gr 3 → Gr 3 or 4 → Gr 3 or 4 → Gr 3 or 4 → Gr 3 or 4

Adapted from CCO and BC Cancer guidelines on ICI toxicity management. See slide notes for references.

*Fatigue, constipation, weight gain, loss of appetite, dry skin, eyelid edema, puffy face, hair loss. †Bradycardia, hypotension, pericardial effusion, depression, hypoventilation, stupor, lethargy to myxedema coma. ‡Refer to local guidance for steroid dosing.
§If patient has both adrenal insufficiency and hypothyroidism, start corticosteroid for 2-3 days before levothyroxine.

ADL = activity of daily living; CCO = Cancer Care Ontario; fT4 = free thyroxine; ICI = immune checkpoint inhibitor; IV = intravenously; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

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Immune-Mediated Adrenal Insufficiency

DESCRIPTION	REFERRALS & ASSESSMENTS	STEROID TREATMENT‡	SUPPORTIVE THERAPY	ICI	MONITORING & FOLLOW-UP
GRADE 1 Asymptomatic or mild symptoms (fatigue); clinical or diagnostic observations only	• Notify physician **REFERRALS:** • **Endocrinologist** **ASSESSMENTS:** • Morning cortisol and ACTH, (before steroids if possible)*, aldosterone, renin • Glucose, electrolytes[BC] • Consider pituitary scan if low ACTH[BC]	• Consider **hydrocortisone** or **prednisone** • May need to consider mineralocorticoid replacement if primary renal insufficiency (PAI)	• Intervention not indicated	• **Continue ICI(s)**	• Monitor closely
GRADE 2 Moderate symptoms; medical intervention indicated		• **Prednisone** or **hydrocortisone,** taper slowly	• **Hormone replacement** as needed • **Medical alert** bracelet/necklace • **Consider prophylactic antibiotics** for opportunistic infections	• **Withhold ICI(s) if abnormal lab or pituitary scan[BC]** until resolution to grade ≤1 and steroid tapered Continue treatment in the presence of hormone replacement as long as no symptoms are present[CCO]	• **Continue standard monitoring** • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component[BC]
GRADE 3 Severe symptoms; hospitalization indicated		• Management with IV corticosteroids after sepsis ruled out • IV stress-dose corticosteroids (dexamethasone IV if diagnosis unclear or hydrocortisone IV)† • Patients with PAI may also require mineralocorticoid replacement with an agent such as fludrocortisone			
GRADE 4 Life-threatening adrenal crisis (severe hypotension or hypovolemic shock, acute abdominal pain, vomiting, and often fever); urgent intervention indicated.	• As above • Immediate hospitalization • Rule out sepsis		• As above and infuse isotonic saline or 5% dextrose in isotonic saline as quickly as possible	• **Discontinue ICI(s)[CCO]** • **Consider permanent discontinuation[BC]**	• Hospitalization • Repeat labs in 1-3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan • When adrenal crisis ruled out, treat as grade 2

Gr 1 / Gr 2 / Gr 3 / Gr 4 / Gr 3 or 4 / Gr 2 or 3

Adapted from CCO and BC Cancer guidelines on ICI toxicity management. See slide notes for references.

*Morning cortisol <80 nmol/L strongly suggests adrenal insufficiency. In PAI, ACTH is high, and in SAI, ACTH is low or inappropriately normal for a low cortisol (due to pituitary impairment).

†Hydrocortisone is recommended if confirmed PAI. Continue dexamethasone 4 mg every 12 hours and hydrocortisone 200 mg per 24 hours (via continuous infusion or Q6H bolus). Taper to maintenance doses over 2 weeks post-discharge.

‡Refer to local guidance for steroid dosing.

ACTH = adrenocorticotropic hormone; CCO = Cancer Care Ontario; ICI = immune checkpoint inhibitor; IV = intravenous; MRI = magnetic resonance imaging; PAI = primary adrenal insufficiency; SAI = secondary adrenal insufficiency.

Immune-Mediated Hypophysitis/Hypopituitarism

DESCRIPTION	REFERRALS & ASSESSMENTS	STEROID TREATMENT‡	SUPPORTIVE THERAPY & MONITORING	ICI	MONITORING & FOLLOW-UP
GRADE 1 Asymptomatic or mild symptoms (fatigue, weakness); clinical or diagnostic observations only	• Notify physician **REFERRALS:** • **Endocrinologist** **ASSESSMENTS:** • If symptomatic: – ACTH, morning cortisol, FSH, LH, T4, TSH • Consider pituitary imaging • For grade ≥2, also consider electrolytes, estradiol, glucose, prolactin, testosterone, plasma and urine osmolality[BC]	• See supportive therapy for hydrocortisone hormone replacement • **Prednisone PO** or **methylprednisolone IV** (if hypotensive) for 3-5 days, followed by prednisone tapered slowly • Slow tapering is imperative as early reduction of glucocorticoids may induce relapse or trigger an adrenal crisis	• Hormone replacement if symptomatic • If morning cortisol <250 or random cortisol <150 nmol/L: **hydrocortisone PO** • If falling TSH ± low FT4, consider need for **thyroxine replacement** • Always replace cortisol for 1 week prior to thyroxine initiation • Appropriate **hormone replacement** if symptomatic with abnormal lab or pituitary scan • Most patients who experience grade ≥2 hypophysitis fail to recover pituitary function and require **lifelong hormone replacement therapy**[CCO] • Consider **prophylactic antibiotics** for opportunistic infections	• **Continue ICI(s)** Monitor closely • **Withhold ICI(s) until resolution to grade 0-1** • Upon improvement, ICI(s) may be resumed after corticosteroid taper, if needed • Treatment should be continued in the presence of hormone replacement as long as no symptoms are present • **Consider withholding ICI(s)**[BC] until symptoms improve with or without hormone therapy and steroid is tapered • **Permanently discontinue ICI(s) if severe or life threatening** [CCO] • If residual toxicity grade ≤2 and steroid tapered, consider restart of anti-cancer treatment if benefit outweighs risk	• Monitor closely • If symptomatic, monitor TSH, fT4, ACTH, LH, FSH and morning cortisol • Repeat labs in 1-3 weeks • MRI in 1 month if symptoms persist but normal lab or pituitary scan • Continue standard monitoring
GRADE 2 Moderate (headaches, hypotension); limiting age-appropriate instrumental ADL					
GRADE 3 Severe or medically significant symptoms but not immediately life-threatening. Disabling; limiting self care ADL	• Hospitalization/urgent intervention **REFERRALS:** • **Endocrinologist** • **Radiologist** **ASSESSMENTS:** • As above • Rule out sepsis • MRI pituitary				
GRADE 4 Life-threatening consequences or any visual disturbances; urgent intervention indicated					

Gr 1 → Gr 1 → Gr 1 → Gr 1 → Gr 1

Gr 2 → Gr 2 → Gr 2 → Gr 2 → Gr 2

Gr 3 →

Gr 4 →

Gr 3 or 4 → Gr 3 or 4 → Gr 3 or 4

Adapted from CCO and BC Cancer guidelines on ICI toxicity management. See slide notes for references.

ACTH = adrenocorticotropic hormone; ADL = activity of daily living; CCO = Cancer Care Ontario; FSH = follicle-stimulating hormone; fT4 = free thyroxine; ICI = immune checkpoint inhibitor; IV = intravenous; LH = luteinizing hormone; MRI = magnetic resonance imaging; PO = by mouth; TSH = thyroid-stimulating hormone.

Immune-Mediated Nephritis

DESCRIPTION	REFERRALS & ASSESSMENTS	STEROID TREATMENT§	SUPPORTIVE THERAPY & MONITORING	ICI	MONITORING & FOLLOW-UP
GRADE 1 • **Creatinine:** SCr >ULN* and 1.5-2.0 x above baseline • **Proteinuria**: 1+, <1.0g/24h	• Not required	• Not required	• **Hydration** • **Discontinue nephrotoxic drugs†** • **Monitor and replace fluid/electrolyte imbalances**	• **Continue ICI(s)**	• **Monitor fluid/electrolyte imbalances** • **Creatinine weekly** until resume to baseline, then per routine • If creatinine worsens, treat as grade 2 or 3-4
GRADE 2‡ • **Creatinine:** SCr >2.0-3.0 x baseline or >1.5 – 3.0 x ULN • **Proteinuria:** 2+, 1.0-3.4g/24h	• Notify physician **REFERRALS:** • Consider **nephrologist**	• **Prednisone PO** or **IV equivalent** • Once resolved to grade ≤1, taper slowly	• Same as above and **addition of MMF** may be considered‡ • **Hemodialysis** may be required in addition to steroids if creatinine worsens	• **Withhold ICI(s)** until creatinine decreases to grade 1 and steroid tapered	• **Creatinine** Q2-3 days • If persists for >7 days or worsens, treat as grade 3-4 • Nursing follow-up as needed
GRADE 3‡ • **Creatinine:** SCr >3.0 x baseline or >3.0-6.0 x ULN • **Proteinuria:** >3.5g/24h	**ASSESSMENTS:** • **Routine urine microscopy** • **Ultrasound and/or renal biopsy** as appropriate, to exclude non-immune causes and/or confirm immune renal toxicity	• **Methylprednisolone IV** or equivalent • If resolved to grade ≤1, taper slowly • **If no improvement in 7 days,** consider adding non-steroid immunosuppressant agent (e.g., MMF)		• **Permanently discontinue ICI(s)** • Monitor creatinine daily	• **Creatinine daily**
GRADE 4‡ • **Creatinine:** SCr >6.0 x ULN • **Life threatening consequences; dialysis indicated**					

Gr 1 → Gr 2 → Gr 3 → Gr 4 (Gr 3 or 4)

Adapted from CCO and BC Cancer guidelines on ICI toxicity management. See slide notes for references.

*SCr > 1-1.5 x ULN per BC Cancer guidance.

†I.e., aminoglycosides, contrast agent, etc.

‡Use has been reported in case reports in refractory cases.

§Refer to local guidance for steroid dosing.

CCO = Cancer Care Ontario; ICI = immune checkpoint inhibitor; IV = intravenously; MMF = mycophenolate mofetil; PO = by mouth; Q2-3 days = every 2-3 days; SCr = serum creatinine; ULN = upper limit of normal.

Infusion-Related Reactions (IRRs)

DESCRIPTION	ICI TREATMENT MODIFICATION	STEROID TREATMENT UNLESS OTHERWISE SPECIFIED
GRADE 1 or 2	• Interrupt or slow the rate of infusion	• May consider pre-medications for prophylaxis of subsequent IRRs
GRADE 3 or 4	• Permanently discontinue	• Manage severe IRRs per institutional standard, appropriate clinical practice guidelines and/or society guidelines

Gr 1 or 2 → Gr 1 or 2

Gr 3 or 4 → Gr 3 or 4

Adverse Events in HIMALAYA		
Adverse Event	**All grades (%)**	**Grades ≥3 (%)**
Infusion-related reaction (IRR) Includes infusion-related reaction and urticaria	**1.5**	**0**

IRR = infusion-related reaction.

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2. Cancer Care Ontario (CCO). Immune Checkpoint Inhibitor Toxicity Management - Clinical Practice Guideline – Version 1, March 2018. Accessed April 12, 2024. https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/ImmuneCheckpointInhibitor.pdf;
3. BC Cancer. BC Cancer Protocol Summary for Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitor Immunotherapy. Published February 2022. Accessed April 12, 2024. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf.

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