Immune-Related Adverse Events With Low-Dose Nivolumab in Patients With Chronic Hepatitis B: Experience From 3 Clinical Studies

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Conclusions

- Clinically significant immune-related adverse events, some requiring lifelong management, were observed in a trial using low-dose nivolumab for chronic hepatitis B (CHB), under clinical investigation for a nononcology indication
- The emerging safety profile of low-dose anti–programmed cell death protein 1 (anti–PD-1) monoclonal antibodies in CHB is consistent with the known profile in oncology

Plain Language Summary

- Nivolumab, a medicine that acts on the immune system and is typically used to treat patients with cancer, is associated with some immune-related side effects that can be serious
- When nivolumab, at doses lower than are used in patients with cancer, was tested in clinical studies in people living with chronic hepatitis B, these immune-related side effects still occurred, including some that will likely require lifelong treatment

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Acknowledgments: The authors gratefully acknowledge the contributions of Dr Wai Man Yip, the staff, and the participants from Alice Ho Miu Ling Nethersole Hospital, along with all principal investigators and participants included in this study. Editorial support was provided by Olivia Harwood, PhD, and Danielle L Rubin-Shepherd, PhD, of Red Nucleus, and funded by Gilead Sciences, Inc.

Disclosures: **EJG** served as an advisor for AbbVie; Aligos Therapeutics; Arbutus Biopharma; Gilead Sciences, Inc.; Janssen; Roche; Vir Biotechnology; and Virion Therapeutics. **TT** reports research grants from Altimmune; Gilead Sciences, Inc.; Merck Sharp & Dohme; and Roche. **BY**, **TC**, **IB**, **DS**, **HA**, **FA**, **AHL**, and **AO** are employees of Gilead Sciences, Inc., and may own stock or stock options. **LS** and **BLD** were employees of Gilead Sciences, Inc., at the time of authoring and may own stock or stock options. **TYOT** reports research grants from Gilead Sciences, Inc., and GSK. **AA** reports research grants from Gilead Sciences, Inc.; Merck Sharp & Dohme; Roche; and ViiV Healthcare/GSK; and speaker fees from Abbott.

Introduction

- Anti–programmed cell death protein 1 (PD-1)/programmed death ligand-1 (PD-L1) monoclonal antibodies (mAbs), including nivolumab (NIVO), are being investigated at low doses for finite treatment of chronic hepatitis B (CHB)
- Immune-related adverse events (irAEs) result from inactivation of immune checkpoints involved in controlling autoimmune responses and represent the main toxicity associated with the class of checkpoint inhibitors, including anti–PD-1/PD-L1 mAbs
- In oncology, a broad range of irAEs have been observed with anti–PD-1/PD-L1 mAbs across different studies and molecules, including some that are life-threatening or associated with fatal outcomes (eg, pneumonitis, myocarditis) and some that require lifelong management (eg, hypo/hyperthyroidism, type 1 diabetes mellitus)

Safety Profile of Anti–PD-1/PD-L1 mAbs in Oncology

Adverse Event	Anti–PD-1/PD-L1 mAbs
Any AE (Grade 3 or 4 AEs)[a]	66.4%–75.1% (14.1%–19.8%)
irAEs (Grade 3 or 4 irAEs)[a]	26.8% (6.1%)[1]
Fatal irAEs[a]	anti–PD-1: 0.36%[2] anti–PD-L1: 0.38%[2] anti–PD-1/PD-L1 + CTLA-4: 1.23%[2]
Pneumonitis[b]	3.0%–3.4%
Myocarditis[b]	0.4%–1.0%
Hypothyroidism[b]	4.9%–8.0%
Hyperthyroidism[b]	0.8%–3.4%
Type 1 diabetes mellitus[b]	0.2%–0.9%

[a]Data represented as incidence rate from meta-analyses: Shulgin 2020 (n = 9883),[1] Wang 2017 (n = 12,808),[2] Wang 2018 (n = 19,217),[3] Xu 2018 (n = 7409),[4] Makunts 2021 (n = 27,149 nivolumab, n = 13,476 pembrolizumab, n = 2397 atezolizumab, n = 1710 durvalumab).[5]
[b]Data represented as incidence rate based on USPI Tecentriq (atezolizumab) 2024,[6] Keytruda (pembrolizumab) 2024,[7] Opdivo (nivolumab) 2024.[8]
AE, adverse event; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; irAE, immune-related adverse event; mAb, monoclonal antibody; PD-1/PD-L1, programmed cell death protein 1/programmed death ligand-1; USPI, United States prescribing information.

- Safety data for anti–PD-1/PD-L1 mAbs used at lower doses in nononcologic indications are limited, although irAEs have been observed in patients with CHB or HIV treated with anti–PD-1/PD-L1 mAbs[9-14]
- In a prior Phase 1 Gilead-sponsored study (GS-US-330-1938) included in this analysis, a single low dose of NIVO administered to 24 patients with CHB resulted in hepatitis B surface antigen loss in 1 patient, with no irAEs observed[15]; this study prompted further investigation of low-dose anti–PD-1 mAbs for the treatment of CHB

Occurrence of irAEs With Anti–PD-1/PD-L1 mAbs in Nononcology Indications (CHB and HIV) in Non–Gilead-Sponsored Studies

Indication	Anti–PD-1/PD-L1 mAb	Dose and Frequency	irAEs		Action Taken/ Reported in Study
CHB	Envafolimab[9] (anti–PD-L1)	1 or 2.5 mg/kg (Q2W × 12)	1 mg/kg	31 of 60 (52%) irAEs Most common irAEs • ALT/AST increased, 27%/20% • Dermatitis allergic, rash, 15% each • Thyroid dysfunction, 12%	Not reported in article
			2.5 mg/kg	30 of 59 (51%) irAEs Most common irAEs • Thyroid dysfunction, 32% • Rash, 15% • ALT/AST increased, 14%/14%	
	NIVO[10] (anti–PD-1)	0.3 mg/kg (2 doses)	No irAEs reported (55 patients treated)		Not reported in article
	NIVO[11] (anti–PD-1)	0.3 mg/kg (1 or 2 doses)	5 of 91 (5%) immune-mediated thyroiditis		Not reported in article
	NIVO[12] (anti–PD-1)	0.3 mg/kg (1 or 3 doses)	2 of 37 (5%) transient TSH suppression		Protocol amended to d/c NIVO due to 2 cases of TSH suppression (with no efficacy benefit)
HIV	BMS-936559[13] (anti–PD-L1)	0.3 mg/kg (single dose)	1 of 6 (17%) irAEs (hypophysitis)		Study d/c early due to nonclinical findings of retinal toxicity
	Cemiplimab[14] (anti–PD-1)	0.3 mg/kg (Q6W × 2)	2 of 4 (50%) irAEs (thyroiditis; Grade 3 hepatitis[a]; both after first dose)		Study d/c early due to irAEs

[a]Asymptomatic, potentially confounded by alcohol use. Qian 2024,[9] Tak 2024,[10] Tait 2024,[11] Asselah 2024,[12] Gay 2017,[13] Gay 2021.[14]
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMS, Bristol Myers Squibb; CHB, chronic hepatitis B; d/c, discontinued; irAE, immune-related adverse event; mAb, monoclonal antibody; NIVO, nivolumab; PD-1/PD-L1, programmed cell death protein 1/programmed death ligand-1; Q2W, every 2 weeks; Q6W, every 6 weeks; TSH, thyroid-stimulating hormone.

Objective

- This analysis aimed to assess the occurrence of irAEs with low-dose NIVO, an anti–PD-1 mAb, in 3 Gilead-sponsored clinical studies involving people living with CHB

Methods

- Safety data from 3 Gilead clinical studies (2 completed Phase 1 studies, GS-US-330-1938 and GS-US-493-5342; 1 ongoing Phase 2 study, GS-US-465-4439), in which NIVO was dosed alone or in combination with other antivirals or immunomodulators for the treatment of CHB, were analyzed
- NIVO doses used in these 3 studies were roughly equivalent to 8- or 24-mg doses, instead of the typical 240- or 480-mg doses administered every 2 or 4 weeks in the oncology setting

Clinical Studies Investigating Low-Dose NIVO for Treatment of CHB

		Patients With CHB Who Received ≥1 Dose of NIVO (N = 163)								
Study		GS-US-330-1938 Single Dose (N = 24)			GS-US-493-5342 Q4W × 3 Doses (N = 39)			GS-US-465-4439 Q4W up to 6 Doses (N = 100)		
Viral classification		Virally Suppressed			Virally Suppressed			Virally Suppressed	Viremic	
Number of patients		n = 2	n = 12	n = 10	n = 13	n = 14	n = 12	n = 42	n = 38	n = 20
Regimen under investigation	PD-1	NIVO 0.1 mg/kg	NIVO 0.3 mg/kg	NIVO 0.3 mg/kg	NIVO 0.3 mg/kg	NIVO 0.3 mg/kg	NIVO 0.3 mg/kg	NIVO 0.3 mg/kg	NIVO 0.3 mg/kg	NIVO 0.3 mg/kg
	TLR8	-	-	-	-	SLGN	-	SLGN	SLGN	SLGN
	Other	-	-	GS-4774	-	-	LDV/SOF	VIR-2218	VIR-2218	-

GS-US-330-1938 was registered as ACTRN12615001133527, GS-US-493-5342 as ACTRN12618001843246p, and GS-US-465-4439 as NCT04891770. In each of the studies, NIVO was administered intravenously. VIR-2218 is an siRNA against HBV. GS-4774 is a therapeutic HBV vaccine. SLGN is a TLR8 agonist.
CHB, chronic hepatitis B; HBV, hepatitis B virus; LDV/SOF, ledipasvir/sofosbuvir; NIVO, nivolumab; PD-1, programmed cell death protein 1; Q4W, every 4 weeks; siRNA, small interfering RNA; SLGN, selgantolimod; TLR8, toll-like receptor 8.

Results

irAEs With Low-Dose NIVO

- Of the 163 patients with CHB who received ≥1 dose of NIVO (0.1 mg/kg [n = 2]; 0.3 mg/kg [n = 161]) in the 3 studies, 4.3% (7/163) experienced irAEs

Seven Patients Had irAEs That Were Deemed Related to NIVO

- All were from the ongoing Study 4439; 3 were virally suppressed, and 4 were viremic
- Two patients experienced serious irAEs of Grade 3 severity: type 1 diabetes mellitus and immune-mediated hepatitis (n = 1 each)
- Four patients discontinued NIVO because of irAEs; in the remaining 3 patients, the irAEs occurred after the last dose of NIVO
- All irAEs, except for optic neuropathy, required treatment
- Two irAEs resolved; additional longer-term follow-up is ongoing for the remaining irAEs
- Three irAEs were assessed as related to NIVO and SLGN; the other 4 were assessed as related to NIVO only[a]

[a]Other than the 7 irAEs reported in Study 4439 when SLGN was given in combination with NIVO, no irAEs have been reported in clinical studies of SLGN out of a total of 573 participants through November 21, 2023 (114 participants where SLGN was given with NIVO in Studies 5342 and 4439, and 459 participants where SLGN was given without NIVO).
irAE, immune-related adverse event; NIVO, nivolumab; SLGN, selgantolimod.

Treatment-Related irAEs With Low-Dose NIVO

irAE	CHB Status	Regimen	Severity Grade[a]	SAE	Number of NIVO Doses Given	Action Taken With NIVO	Intervention	Status[b]
Type 1 diabetes mellitus	Viremic	**NIVO** + SLGN	3	Yes	6	n/a[c]	Insulin	SAE and insulin ongoing
Immune-mediated hepatitis	Viremic	**NIVO** + **SLGN** + VIR-2218	3	Yes	3	n/a[d]	Corticosteroids (prednisolone, ~2.5 months)/TAF started	SAE resolved; corticosteroids stopped
Psoriasis	Viremic	**NIVO** + **SLGN**	2[e]	No	3	d/c	Corticosteroids (prednisone, ~1 month)/ Cyclosporine	AE ongoing, failed corticosteroid taper; cyclosporine (50 mg) ongoing
Thyroiditis	Virally suppressed	**NIVO** + SLGN + VIR-2218	2	No	4	d/c	Thyroid hormone replacement, carbimazole, hydrocortisone (oral)	AE resolved; all interventions stopped
Hypothyroidism	Virally suppressed	**NIVO** + SLGN + VIR-2218	2	No	5	d/c	Thyroid hormone replacement	AE and thyroid hormone replacement ongoing
Hypothyroidism	Virally suppressed	**NIVO** + SLGN + VIR-2218	1	No	6	n/a[c]	Thyroid hormone replacement	AE and thyroid hormone replacement ongoing
Optic neuropathy	Viremic	**NIVO** + **SLGN**	1	No	4	d/c	No treatment	AE ongoing

Bold, red font indicates the drug to which the irAE was deemed to be related. [a]Per the toxicity grading scale in the protocol. [b]As of May 7, 2024. [c]Reported after the end of treatment. [d]Reported after NIVO was permanently discontinued by the sponsor across cohorts in Study 4439. [e]Grade 2 per protocol-defined toxicity grading, but Grade 3 by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grading. VIR-2218 is a small interfering RNA against HBV. SLGN is a toll-like receptor 8 agonist.
AE, adverse event; CHB, chronic hepatitis B; d/c, discontinued; HBV, hepatitis B virus; irAE, immune-related adverse event; n/a, not applicable; NIVO, nivolumab; SAE, serious adverse event; SLGN, selgantolimod; TAF, tenofovir alafenamide.

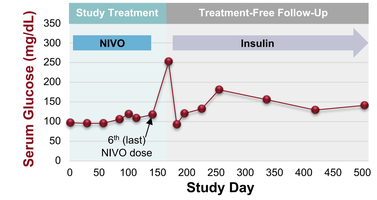
Details of irAEs of Psoriasis, Type 1 Diabetes Mellitus, and Immune-Related Hepatitis

Biopsy-Confirmed Psoriasis (Grade 2) After 3 NIVO Doses

- Grade 3 per Common Terminology Criteria for Adverse Events
- Chief complaint: Initially, scaly rash on the scalp and the central chest, followed by more widespread rash involving the trunk, limbs, penis, perianal areas, and toenails; weepy areas in penile and perianal areas
- Dermatological examination: Chronic plaque psoriasis on scalp and chest; guttate papular squamous eruption on trunk and limbs; minimal genital and perianal signs present, consistent with acrodermatitis continua of Hallopeau (a variant of pustular psoriasis)
- Medical history
  - No medical history of skin disease prior to screening
  - No family history of eczema or psoriasis
- Treatment
  - Improvement with oral **high-dose prednisone** (6 weeks) with rebound after taper and withdrawal
  - Skin lesions cleared on cyclosporine with occasional flares
  - **Cyclosporine ongoing[a] (approximately 19 months)**

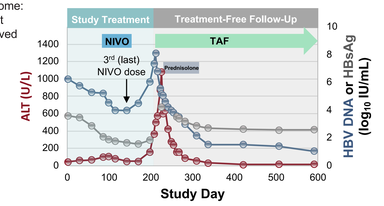
Type 1 Diabetes Mellitus (Grade 3) After 6 NIVO Doses

- Baseline: BMI 26.7 kg/m^2, normal fasting glucose and lipids
- No significant past medical history
- Week 24 (EOT, D169): Hyperglycemia (252 mg/dL, Grade 3) and glycosuria (+4)
- Preceded by new-onset weight loss, polyuria, and polydipsia on D151 (last dose of NIVO on D141)
- **Insulin ongoing[a]**



Immune-Related Hepatitis (Grade 3) After 3 NIVO Doses

- Onset after NIVO discontinuation by the sponsor in Study 4439 (last NIVO dose on D142)
- ALT flare with no evidence of hepatotoxicity
- TAF initiated (D211); prednisolone initiated 2 weeks later (D225 to D306)
- Outcome: Event resolved



[a]As of May 7, 2024.
ALT, alanine aminotransferase; BMI, body mass index; D, day; EOT, end of treatment; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; irAE, immune-related adverse event; NIVO, nivolumab; SLGN, selgantolimod; TAF, tenofovir alafenamide.