

Nivolumab in Advanced Hepatocellular Carcinoma: Safety Profile and Select Treatment-Related Adverse Events From the CheckMate 040 Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

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ABSTRACT

Background. CheckMate 040 assessed the efficacy and safety of nivolumab in patients with advanced hepatocellular carcinoma (HCC). Understanding the safety profile of nivolumab is needed to support the management of treatment-related adverse events (TRAEs). This analysis assessed the safety of nivolumab monotherapy in the phase I/II, open-label CheckMate 040 study.

Materials and Methods. Select TRAEs (sTRAEs; TRAEs with potential immunologic etiology requiring more frequent monitoring) occurring between first dose and 30 days after last dose were analyzed in patients in the dose-escalation and -expansion phases. Time to onset (TTO), time to resolution (TTR), and recurrence of sTRAEs were assessed, and the outcome of treatment with immune-modulating medication (IMM) was evaluated.

Results. The analysis included 262 patients. The most common sTRAE was skin (35.5%), followed by gastrointestinal

(14.5%) and hepatic (14.1%) events; the majority were grade 1/2, with 10.7% of patients experiencing grade 3/4 events. One patient had grade 5 pneumonitis. Median (range) TTO ranged from 3.6 (0.1–59.9) weeks for skin sTRAEs to 47.6 (47.1–48.0) weeks for renal sTRAEs. Overall, 68% of sTRAEs resolved, with median (range) TTR ranging from 3.7 (0.1–123.3+) weeks for gastrointestinal sTRAEs to 28.4 (0.1–79.1) weeks for endocrine sTRAEs. Most gastrointestinal and all hepatic events resolved with treatment in accordance with established toxicity management algorithms. In 57 patients (40%), sTRAEs were managed with IMM. Reoccurrence of sTRAEs was uncommon following rechallenge with nivolumab.

Conclusion. Nivolumab demonstrated a manageable safety profile in this analysis of patients with advanced HCC. A majority of sTRAEs resolved with treatment. *The Oncologist* 2020;25:e1532–e1540

Implications for Practice: Nivolumab is a viable treatment option for patients with previously treated advanced hepatocellular carcinoma as it has demonstrated durable tumor responses and promising survival. Nivolumab has a manageable safety profile. The most common select treatment-related adverse events (sTRAEs) in this analysis were skin related (35%). Gastrointestinal and hepatic sTRAEs were observed in approximately 14% of patients. The majority of sTRAEs resolved (68%). Safety events are easier to manage if addressed early. Patient education on signs and symptoms to watch out for and the importance of early reporting and consultation should be emphasized.

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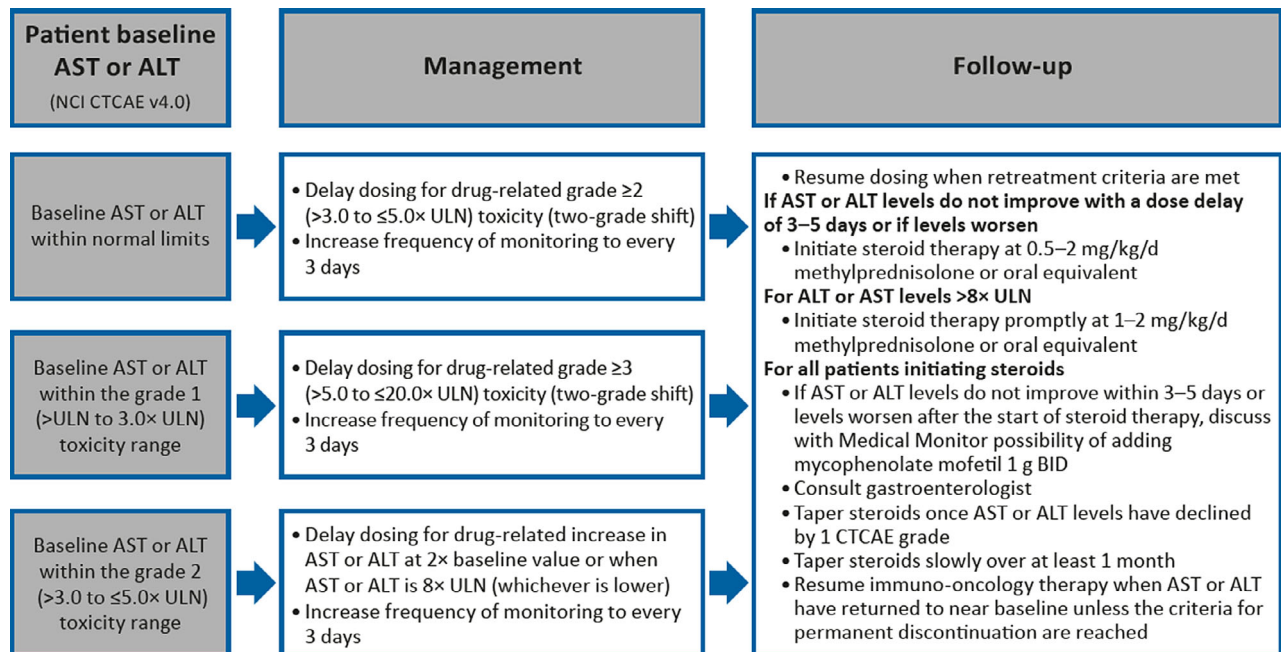


Figure 1. Hepatic adverse event management algorithm.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; ULN, upper limit of normal.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common cause of primary liver cancer and the second most common cause of cancer-related mortality worldwide [1, 2]. HCC is often diagnosed at an advanced stage, for which effective treatment options are limited [1, 3]. However, even with limited treatment options, the risks and benefits must be carefully considered, as most patients with HCC suffer from concomitant cirrhosis and its attendant liver dysfunction.

Immune checkpoint inhibitors, such as programmed cell death 1 (PD-1) inhibitors, have dramatically improved outcomes in a variety of cancer types [4]. In patients with advanced HCC who were previously treated with sorafenib, the international phase I/II CheckMate 040 study demonstrated that treatment with the PD-1 inhibitor nivolumab was associated with durable objective responses (which could have positively impacted survival) and a manageable safety profile [3]. The objective response rate (ORR) was 15% in the dose-escalation phase and 20% in the dose-expansion phase in patients treated with nivolumab 3 mg/kg. The 9-month overall survival rates were 66% and 74%, respectively. On the basis of these results, nivolumab received accelerated approval from the U.S. Food and Drug Administration for use in patients with HCC who have been previously treated with sorafenib [5]. Nivolumab was subsequently approved for the same indication in other countries, including Canada, Taiwan, and Australia [6,7].

Because of their mechanism of action, immune checkpoint inhibitors are associated with adverse events (AEs) that differ from those associated with cytotoxic chemotherapy or tyrosine kinase inhibitors. These AEs can affect multiple organ systems and, if moderate or severe, can result in substantial morbidity and potential mortality [8]. Consequently, early identification and management of treatment-related AEs

(TRAEs) in patients receiving immune checkpoint inhibitors are essential to prevent treatment delays and improve outcomes. The purpose of the current analysis was to assess the safety profile of nivolumab in the CheckMate 040 study after a median follow-up of 19.4 months (March 2017 database lock). Particular attention was paid to select TRAEs (sTRAEs) with an immunogenic etiology, specifically endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin sTRAEs. These sTRAEs require greater awareness from patients and caregivers to optimize detection and early management.

MATERIALS AND METHODS

Study Design

CheckMate 040 (NCT01658878) was a phase I/II, open-label study of nivolumab in patients with advanced HCC. The study consisted of a dose-escalation phase conducted in four countries (U.S., Spain, Hong Kong, and Singapore) and a dose-expansion phase conducted in 11 countries (the four mentioned above plus Canada, U.K., Germany, Italy, Japan, South Korea, and Taiwan; 39 sites in total). During the dose-escalation phase, sequential groups of patients received intravenous (IV) nivolumab 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 10.0 mg/kg every 2 weeks in a 3 + 3 design. During the dose-expansion phase, all patients received nivolumab 3.0 mg/kg IV every 2 weeks. Ongoing randomized phases of CheckMate 040 include additional treatment arms (including nivolumab in combination with ipilimumab and/or cabozantinib); however, because these fall outside the remit of this safety analysis, they will be discussed in a future study. The primary study objectives were to assess safety and tolerability in the dose-escalation phase and ORR in the dose-expansion phase.

Table 1. Summary of sTRAEs by CTCAE grade

sTRAEs	On treatment ^a (N = 262)		Treatment discontinued ^b (N = 226)	
	Any grade, n (%)	Grade 3/4, n (%)	Any grade, n (%)	Grade 3/4, n (%)
Total patients with ≥1 sTRAE ^c	143 (54.6)	28 (10.7)	35 (15.5)	13 (5.8)
Skin	93 (35.5)	5 (1.9)	12 (5.3)	2 (0.9)
Pruritus	56 (21.4)	1 (0.4)	7 (3.1)	1 (0.4)
Rash	46 (17.6)	2 (0.8)	2 (0.9)	0
Rash maculopapular	9 (3.4)	0	1 (0.4)	0
Erythema	3 (1.1)	1 (0.4)	1 (0.4)	0
Rash pruritic	3 (1.1)	0	1 (0.4)	0
Psoriasis	3 (1.1)	1 (0.4)	2 (0.9)	1 (0.4)
Skin exfoliation	2 (0.8)	0	0	0
Rash papular	2 (0.8)	0	0	0
Eczema	1 (0.4)	0	0	0
Dermatitis	1 (0.4)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	1 (0.4)	0	0	0
Rash erythematous	1 (0.4)	0	0	0
Skin hypopigmentation	1 (0.4)	0	0	0
Gastrointestinal	38 (14.5)	3 (1.1)	3 (1.3)	1 (0.4)
Diarrhea	36 (13.7)	3 (1.1)	3 (1.3)	1 (0.4)
Colitis	2 (0.8)	1 (0.4)	0	0
Enteritis	1 (0.4)	0	0	0
Frequent bowel movements	1 (0.4)	0	0	0
Hepatic	37 (14.1)	17 (6.5)	13 (5.8)	7 (3.1)
AST increased	26 (9.9)	14 (5.3)	7 (3.1)	4 (1.8)
ALT increased	25 (9.5)	9 (3.4)	6 (2.7)	4 (1.8)
Blood bilirubin increased	7 (2.7)	1 (0.4)	4 (1.8)	0
Blood alkaline phosphatase increased	6 (2.3)	0	1 (0.4)	0
Hyperbilirubinemia	3 (1.1)	0	2 (0.9)	0
Hepatitis	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.9)
Liver disorder	1 (0.4)	0	1 (0.4)	0
Gamma-glutamyltransferase increased	1 (0.4)	1 (0.4)	0	0
Liver function test increased	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Endocrine	25 (9.5)	2 (0.8)	3 (1.3)	2 (0.9)
Endocrine disorders	16 (6.1)	1 (0.4)	0	0
Hypothyroidism	10 (3.8)	0	1 (0.4)	0
Hyperthyroidism	2 (0.8)	0	0	0
Adrenal insufficiency	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)
Secondary adrenocortical insufficiency	1 (0.4)	0	0	0
Autoimmune hypothyroidism	1 (0.4)	0	0	0
Autoimmune thyroiditis	1 (0.4)	0	0	0
Investigations	7 (2.7)	0	0	0
Blood TSH increased	5 (1.9)	0	0	0
Blood TSH decreased	2 (0.8)	0	0	0
Metabolism and nutrition disorders	2 (0.8)	1 (0.4)	0	0
Diabetes mellitus	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)
Pulmonary	3 (1.1)	1 (0.4)	4 (1.8)	2 (0.9)
Pneumonitis ^d	3 (1.1)	1 (0.4)	4 (1.8)	2 (0.9)
Renal	2 (0.8)	0	1 (0.4)	0
Blood creatinine increased	2 (0.8)	0	0	0
Autoimmune nephritis	0	0	1 (0.4)	0

^aEvents reported between first dose and 30 days after last dose of nivolumab.

^bEvents reported between last dose of nivolumab and 100 days after last dose.

^cPatients may have experienced sTRAEs in multiple categories.

^dOne case of grade 5 pneumonitis occurred more than 30 days after last day of treatment.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; sTRAE, select treatment-related adverse event; TSH, thyroid-stimulating hormone.

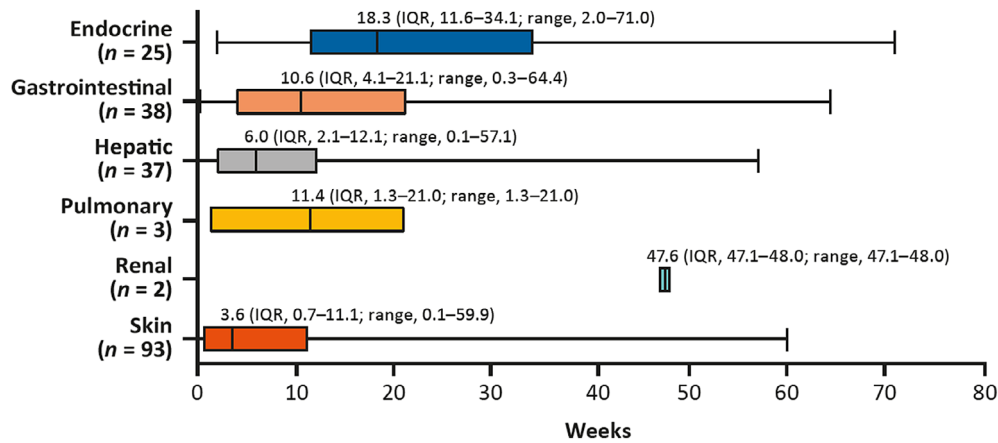


Figure 2. Time to onset (TTO) of any-grade sTRAEs. TTO was defined as the time between the first dose of study treatment and onset of earliest sTRAE in the category. Data are presented as medians with interquartile range (boxes) and range (bars). Abbreviations: IQR, interquartile range; sTRAE, select treatment-related adverse event.

Table 2. Summary of IMM for any-grade sTRAEs

sTRAEs	Patients receiving IMM, n/n (%)	Patients with resolution ^a of sTRAEs after IMM, n/n (%)	Median TTR after IMM (range), wk
Total patients with ≥1 sTRAE ^b (n = 143)	57/143 (39.9)	41/57 (71.9)	18.1 (0.1–88.3+)
Skin (n = 93)	41/93 (44.1)	27/41 (65.9)	20.7 (0.1–88.3+)
Topical corticosteroids ^c	38/93 (40.9)		
Systemic corticosteroids ^d	4/93 (4.3)		
Cyclosporine	1/93 (1.1)		
Ophthalmologic medication	2/93 (2.2)		
Gastrointestinal (n = 38)	6/38 (15.8)	5/6 (83.3)	5.1 (1.6–31.6+)
Systemic corticosteroids ^d	6/38 (15.8)		
Hepatic (n = 37)	7/37 (18.9)	7/7 (100.0)	19.4 (2.4–35.9)
Systemic corticosteroids ^d	7/37 (18.9)		
Mycophenolic acid	1/37 (2.7)		
Endocrine (n = 25)	3/25 (12.0)	2/3 (66.7)	30.1 (0.4–38.3+)
Systemic corticosteroids ^d	3/25 (12.0)		
Pulmonary (n = 3)	2/3 (66.7)	1/2 (50.0)	NA (0.6–70.9+)
Systemic corticosteroids ^d	2/3 (66.7)		
Renal (n = 2)	0/2 (0.0)		

^aResolution was defined as complete resolution or improvement to baseline grade.

^bPatients may have experienced sTRAEs in multiple categories.

^cIncludes topical betamethasone, clobetasol, dexamethasone, fluocinolone, fluocinonide, hydrocortisone, methylprednisolone, mometasone, prednicarbate, and triamcinolone.

^dIncludes systemic budesonide, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone.

Abbreviations: IMM, immune-modulating medications; NA, not achieved; sTRAE, select treatment-related adverse event; TTR, time to resolution.

Full details of the study design and results have been reported previously [3].

Patients

Adults with histologically confirmed, advanced HCC not amenable to curative resection were eligible for the study. Patients could be either sorafenib naive or experienced (progressed on or intolerant of sorafenib) and were eligible irrespective of hepatitis C virus or hepatitis B virus (HBV) status; patients with HBV were required to have an HBV DNA level less than 100 IU/mL. Patients were required to

have Child-Pugh scores of 7 or less for the dose-escalation phase and scores of 6 or less for the dose-expansion phase. Full eligibility criteria have been reported previously [3].

Safety Assessments

Safety was assessed between the first dose and up to 100 days after the last dose of nivolumab. The analysis of TRAEs included events occurring between the first dose and 30 days after the last dose of study therapy, or until all TRAEs were resolved (complete resolution or improvement to baseline grade) or deemed irreversible by the investigator. For sTRAEs (AEs with a

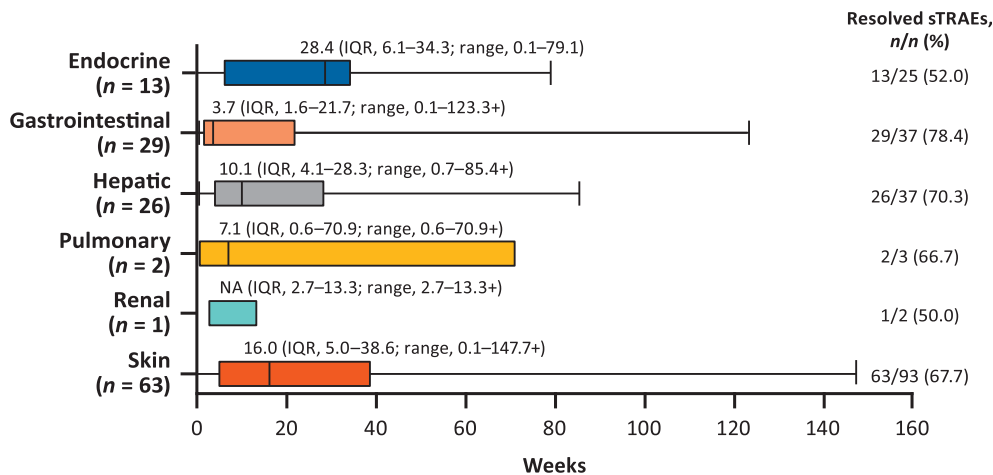


Figure 3. Time to resolution (TTR) of any-grade sTRAEs. TTR was defined as the longest time from onset to complete resolution or improvement to baseline grade. Data are presented as medians with interquartile range (boxes) and range (bars). Abbreviations: IQR, interquartile range; NA, not achieved; sTRAE, select treatment-related adverse event.

potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy), the time to onset (TTO; defined as the time between the first dose of study treatment and the earliest onset of sTRAE in the category) and time to resolution (TTR; defined as the longest time from sTRAE onset to complete resolution or improvement to baseline grade) were recorded. For patients with dose delays due to sTRAEs, all sTRAEs occurring after resumption of nivolumab were documented. The recurrence of sTRAEs in patients who received nivolumab following the onset and resolution of an initial sTRAE (rechallenge) was also recorded. Medications used to manage the sTRAEs and whether the medications led to resolution of the sTRAEs were also evaluated. All sTRAEs were graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Management of Select Treatment-Related Adverse Events

Select TRAEs were managed using protocol-specified algorithms, which included the use of immune-modulating medication (IMM) [9]. The algorithm for management of hepatic sTRAEs was modified from the nivolumab development program algorithm to account for potential baseline abnormalities in liver function, which are common in patients with HCC. In this modified algorithm (Fig. 1), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) monitoring was recommended to be performed every 3 days for patients with hepatic AEs. Nivolumab doses were recommended to be delayed when a two-grade shift of AST/ALT levels from a baseline event of grade 0 or 1 was observed (based on NCI CTCAE criteria). For patients with baseline AST or ALT within the grade 2 toxicity range, doses had to be delayed for increases in AST or ALT at $2 \times$ baseline value or when AST or ALT was $8 \times$ upper limit of normal (ULN; whichever was lower). Corticosteroid treatment had to be initiated when a dose delay of 3–5 days did not improve AST/ALT levels or when AST/ALT levels exceeded $8 \times$ ULN. Nivolumab treatment could be resumed when AST/ALT

returned to near baseline levels, provided the criteria for discontinuation had not been met.

Statistical Analyses

Statistical analyses of safety data were purely descriptive; sTRAEs were tabulated by frequency and severity and by system organ class and preferred term. The current analysis includes data from all patients in the intent-to-treat population.

Study Oversight

This study was approved by the institutional review board or independent ethics committee at each participating center and was conducted in accordance with Good Clinical Practice guidelines, as defined by the International Council on Harmonisation, and with the principles of the Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

RESULTS

Patients

A total of 262 sorafenib-naïve or -experienced (progressed on or intolerant of sorafenib) patients were included in the intent-to-treat population, with 48 treated in the dose-escalation phase and 214 in the dose-expansion phase. Median age was 63 years, and 98.5% of patients had a Child-Pugh score of 5–6 (class A). Eastern Cooperative Oncology Group performance status was 0 or 1 for all patients. Patients received nivolumab treatment for a median of 4.9 months (range, 0–37.4+): 162 patients (61.8%) were treated for more than 3 months, and 27 patients (10.3%) were treated for longer than 18 months. At database lock in March 2017, the median duration of follow-up for the overall population was 19.4 months (range, 16.2–51.7).

Safety

Select TRAEs occurred in 143 patients (54.6%), and grade 3/4 sTRAEs occurred in 28 patients (10.7%). Ten patients (6.8%) were hospitalized (or had hospitalization prolonged)

because of sTRAEs. The most frequently reported sTRAEs were skin (35.5% of patients), gastrointestinal (14.5%), and hepatic (14.1%; Table 1). The most common skin sTRAEs were pruritus (21.4%) and rash (17.6%), whereas diarrhea (13.7%) was the most common gastrointestinal sTRAE. Elevations of ALT and AST were the most common hepatic sTRAEs, occurring in 25 (9.5%) and 26 patients (9.9%), respectively. The most frequent grade 3/4 sTRAEs were hepatic AEs (6.5%). Grade 3/4 elevations of ALT and AST occurred in 3.4% and 5.3% of patients, respectively. Generally, safety profiles were similar across the different etiologies of HCC (data not shown).

Over 100 days of follow-up after the last dose of nivolumab, 35 of 226 (15.5%) patients had an sTRAE, of which 13 patients (5.8%) had a grade 3/4 event. The most common any-grade sTRAEs reported after treatment discontinuation were AST increased (3.1% of patients), pruritus (3.1%), ALT increased (2.7%), pneumonitis (1.8%), blood bilirubin increased (1.8%), and diarrhea (1.3%; Table 1). One patient died of an sTRAE (grade 5 pneumonitis) that occurred more than 100 days after discontinuation of nivolumab because of disease progression and after subsequent treatment with sorafenib. This event was considered by investigators to be related to both nivolumab and sorafenib treatment.

The TTOs of sTRAEs (any grade) are shown in Figure 2. With the exception of endocrine AEs, sTRAEs generally occurred within the first 4–12 weeks of nivolumab treatment. The median (range) TTO ranged from 3.6 (0.1–59.9) weeks for skin sTRAEs to 47.6 (47.1–48.0) weeks for renal sTRAEs. The median (range) TTO of endocrine and hepatic sTRAEs was 18.3 (2.0–71.0) weeks and 6.0 (0.1–57.1) weeks, respectively.

A summary of IMM used to treat any-grade sTRAEs is shown in Table 2. Overall, 57 patients (39.9%) with sTRAEs received IMM; sTRAEs resolved after IMM treatment in 41 patients (71.9%). Of the 57 patients who received IMM for an sTRAE, 11 progressed; the median (range) time to progression after IMM use was 10.4 (1–88) weeks.

The most common sTRAE category for which patients received IMM treatment was skin, with 41 of 93 patients (44.1%) receiving IMM. However, proportionally, the highest rate of IMM use was for pulmonary AEs, with two-thirds of patients (66.7%) receiving IMM. Across all sTRAE categories, the majority of patients requiring IMM therapy received corticosteroids. For skin sTRAEs, 38 of 93 patients (40.9%) received topical corticosteroids, and 4 of 93 (4.3%) received systemic corticosteroids; cyclosporine (1/93; 1.1%) was also used for the treatment of skin sTRAEs. Systemic corticosteroids were the only treatment used for gastrointestinal (6/38 patients; 5 resolved), endocrine (3/25; 2 resolved), and pulmonary (2/3; 1 resolved) sTRAEs. Seven of 37 patients who experienced a hepatic sTRAE received systemic corticosteroids (all resolved), of which 1 patient also received mycophenolic acid for a grade 4 ALT elevation (the event resolved 3 days after treatment).

Gastrointestinal sTRAEs resolved the fastest, whereas endocrine sTRAEs resolved the slowest. The median (range) time to resolution of any-grade sTRAEs ranged from 3.7 (0.1–123.3+) weeks for gastrointestinal events to 28.4 (0.1–

Table 3. Summary of sTRAEs leading to dose delay, according to worst CTCAE grade

sTRAEs	N = 262	
	Any grade, n (%)	Grade 3/4, n (%)
Total patients with ≥ 1 sTRAE leading to dose delay ^a	30 (11.5)	16 (6.1)
Skin (n = 93)		
Pruritus	6 (6.5)	4 (4.3)
Rash	2 (2.2)	1 (1.1)
Erythema	2 (2.2)	1 (1.1)
Psoriasis	1 (1.1)	1 (1.1)
Gastrointestinal (n = 38)	6 (15.8)	1 (2.6)
Diarrhea	5 (13.2)	0
Colitis	1 (2.6)	1 (2.6)
Hepatic (n = 37)	14 (37.8)	9 (24.3)
AST increased	10 (27.0)	8 (21.6)
ALT increased	7 (18.9)	4 (10.8)
Blood bilirubin increased	2 (5.4)	0
Blood alkaline phosphatase increased	1 (2.7)	0
Hepatitis	1 (2.7)	1 (2.7)
Liver disorder	1 (2.7)	0
Endocrine (n = 25)	3 (12.0)	2 (8.0)
Hypothyroidism	1 (4.0)	0
Adrenal insufficiency	1 (4.0)	1 (4.0)
Diabetes mellitus	1 (4.0)	1 (4.0)
Pulmonary (n = 3)	1 (33.3)	0
Pneumonitis	1 (33.3)	0
Renal (n = 2)	1 (50.0)	0
Blood creatinine increased	1 (50.0)	0

^aPatients may have experienced sTRAEs in multiple categories.

Includes events reported between first dose and 30 days after last dose of study therapy.

Dose delay was defined as a delay exceeding 3 days and determination of dose delay was based on investigator assessment. Percentages are calculated based on total numbers of patients having a sTRAE in the category.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; sTRAE, select treatment-related adverse event.

79.1) weeks for endocrine events (Figure 3). Resolution times (range) for any-grade sTRAEs that occurred most frequently in skin, gastrointestinal, and hepatic categories were 23.1 (0.1–143.9+) weeks for pruritus, 7.0 (0.1–64.3+) for rash, 3.6 (0.1–123.3+) for diarrhea, 4.2 (0.7–71.1+) for AST increased, and 8.1 (2.0–69.9+) for ALT increased. The time to resolution for hypothyroidism (the most common endocrine sTRAE) ranged from 3.0+ to 79.1+ weeks (the median could not be estimated). The percentage of sTRAEs (any grade) that resolved after a median follow-up of 19.4 months ranged from 50.0% (1/2 AEs) for renal sTRAEs to 78.4% (29/37 AEs) for gastrointestinal sTRAEs. For grade 3/4 sTRAEs, the corresponding resolution rates ranged from 50% (1/2 AEs) for endocrine sTRAEs to 100% (1/1 AE) for pulmonary sTRAEs. For hepatic sTRAEs, the resolution rates

Table 4. Summary of sTRAE recurrence in patients who were rechallenged with nivolumab

sTRAEs	Patients rechallenged after resolution of sTRAE, <i>n</i>	Reoccurrence of any-grade sTRAE <i>n</i> (%)
Hepatic	18	2 (11.1)
Skin	39	0
Gastrointestinal	26	0
Endocrine	10	0
Renal	0	0
Pulmonary	0	0

Rechallenge occurred when the last nivolumab infusion was administered after the onset of an sTRAE. Includes events reported within 30 days after last dose of study therapy. Recurrent was defined as an event that reoccurred on or after rechallenge.

Abbreviation: sTRAE, select treatment-related adverse event.

were 70.3% (26/37 AEs) for any-grade sTRAEs and 88.2% (15/17 AEs) for grade 3/4 sTRAEs.

The median (range) TTR for sTRAEs treated with IMM ranged from 5.1 (1.6–31.6+) weeks for gastrointestinal events to 30.1 (range 0.4–38.3+) weeks for endocrine events (Table 2).

Table 3 shows sTRAEs leading to dose delay. Overall, 30 (11.5%) patients had sTRAEs that led to a delay in treatment; 16 (6.1%) of these patients had grade 3/4 sTRAEs. Hepatic sTRAEs were the most common cause of dose delays, occurring in 14 of 37 (37.8%) patients with any-grade hepatic sTRAEs. The most frequent grade 3/4 sTRAEs leading to dose delay were elevations in AST (21.6%) and ALT (10.8%).

Reoccurrence of sTRAEs in patients who received nivolumab following resolution of the initial event (rechallenge) was low (Table 4). Of the 18 patients who were rechallenged with nivolumab following a hepatic sTRAE, 2 (11.1%) had a reoccurring event (Table 4). No other sTRAEs reoccurred following rechallenge.

DISCUSSION

Data from the dose-escalation and -expansion cohorts of CheckMate 040 indicate that the safety profile of nivolumab, based on sTRAEs, in sorafenib-naïve or -experienced patients with advanced HCC is generally consistent with the safety profiles of nivolumab in other tumor types, including unresectable or metastatic melanoma, metastatic non-small cell lung cancer, advanced renal cell carcinoma, Hodgkin lymphoma, squamous cell carcinoma of the head and neck, advanced or metastatic urothelial carcinoma, and colorectal cancer [5]. Hepatic sTRAEs occurred at a higher frequency in the current patient population; however, these events were reversible and manageable and rarely led to treatment discontinuation. No new safety signals emerged during a median follow-up of 19.4 months.

Around half of all patients experienced an sTRAE (~55%). This highlights the importance of educating patients on potential AEs to encourage earlier reporting that could facilitate better management. It is encouraging that most sTRAEs were mild (i.e., grade 1/2).

In general, sTRAEs occurred within the first 4–12 weeks of treatment; it is particularly important for the patient and

caregivers to pay attention to signs and symptoms of potential AEs during this period. Time to onset varied by category. Skin sTRAEs occurred earliest (within 1 month of treatment initiation); gastrointestinal, hepatic, and pulmonary sTRAEs were commonly observed within the first 3 months of treatment. Endocrine and renal sTRAEs occurred later. It is important that the management of any AE begins with ruling out other, nondrug-related causes. However, signs and symptoms within specific time periods could indicate a nivolumab-related event. Of note, sTRAEs for all categories were observed past the range of 4–12 weeks, emphasizing the need for continued vigilance during treatment. Recently published evidence-based guidelines for the management of immune-related AEs in patients receiving immune checkpoint inhibitors emphasize the importance of counseling patients to be aware of potential immune-related AEs and the importance of taking appropriate action [8].

For sTRAEs, skin events were the most common, followed by gastrointestinal and hepatic events. Skin sTRAEs are of special interest as skin AEs, particularly hand-foot skin reaction (HFSR), are of clinical concern with the use of sorafenib. Prior to the introduction of nivolumab, the oral multikinase inhibitor sorafenib was the first evidence-based treatment option approved for patients with advanced HCC and is currently considered the standard of care [10, 11]. In pivotal sorafenib trials, HFSR of any grade was reported in 21% and 45% of patients in predominantly Western and Asian populations, respectively [12, 13]. HFSR usually presents with a range of symptoms from burning, tingling, and skin erythema to pain, edema, and ulcerations in the extremities; HFSR can interfere with simple daily activities, such as walking or gripping objects [14, 15]. Based on current study data, skin sTRAEs may be the first AEs that patients experience following initiation of nivolumab treatment, often developing within the first month. However, in contrast to sorafenib, skin sTRAEs with nivolumab are commonly pruritus (21.4%) and rash (17.6%). Rash AEs were mostly mild, with <1% frequency of grade 3/4 events. Skin sTRAEs were manageable and resolved in 63.2% of patients after treatment with topical corticosteroids.

Because patients with advanced HCC already have hepatic morbidity, the incidence and severity of hepatic sTRAEs with nivolumab treatment are important considerations [16]. The low incidence of any-grade (14.1%) and grade 3/4 (6.5%) hepatic sTRAEs in CheckMate 040 is therefore encouraging. Similarly, the incidence of gastrointestinal sTRAEs was low (14.5%), with a low rate of grade 3/4 events (1.1%). Diarrhea accounted for 13.7% of gastrointestinal sTRAEs, whereas colitis was uncommon (<1%).

Many patients (39.9%) who experienced sTRAEs were treated with IMM, according to the relevant AE management algorithm. Immune-related AEs potentially require the use of IMM such as steroids. Clinicians should therefore rule out other potential causes of the AE; for example, treating diarrhea or pneumonitis from an infection with steroids is unwarranted and risky [17]. A second important aspect of clinical management is to taper steroids slowly over at least a month. There is a risk of rebound if steroids are tapered too quickly, and steroid withdrawal should be gradual, according with standard medical practice [8].

The general approach for management of hepatic events with nivolumab was based on cumulative data across tumor types in patients with normal hepatic function. To account for potential baseline liver dysfunction in patients with HCC, a modified algorithm with adjusted upper limits for inclusion was used in CheckMate 040 for the management of hepatic sTRAEs. It is encouraging to note that only 7 of 37 patients with hepatic sTRAEs required treatment with IMM (primarily steroids), suggesting that nivolumab-related hepatic sTRAEs are manageable, even in patients with underlying liver dysfunction.

Reoccurrence of sTRAEs was uncommon. In patients who were rechallenged with nivolumab, the initial sTRAE only reoccurred in two patients, both of whom experienced hepatic events. Most sTRAEs requiring treatment were effectively managed by systemic corticosteroids.

Select TRAEs commonly resolved in 4–12 weeks following dose delays or treatment with an IMM. Endocrine sTRAEs may be resolved with low doses of systemic corticosteroids [8], provided that patients are compliant with this therapy. In such cases, regular monitoring of cortisol levels is useful. Some endocrine sTRAEs, however, may not completely resolve. For example, thyroid AEs such as hypothyroidism could require lifetime hormone supplementation [17, 18].

The TTR of sTRAEs is variable, and the management of each patient must be individualized. Nivolumab management guides provide recommendations for monitoring and managing sTRAEs [19]. Many other practical recommendations and guidelines are also available for health care professionals.

In CheckMate 040, nivolumab led to durable responses and clinically meaningful survival and had a manageable safety profile in an etiologically diverse population of patients with advanced HCC [3]. Furthermore, the hepatic sTRAEs often seen in patients with cirrhosis were readily manageable. These efficacy and safety data suggest that nivolumab has the potential to improve outcomes for patients with advanced HCC.

Limitations of the current study include the non-randomized design of the CheckMate 040 cohorts analyzed. More information on the safety of nivolumab has been provided by the CheckMate 459 study, a randomized phase III trial of nivolumab versus sorafenib as first-line treatment in patients with advanced HCC (ClinicalTrials.gov: NCT02576509) [20]. Although data are limited for patients with Child-Pugh scores of 7 or higher (class B or C), the safety of nivolumab has been evaluated in this population as part of the CheckMate 040 trial [21], and more data from this cohort are forthcoming.

CONCLUSION

In this safety analysis of sorafenib-naïve or -experienced patients with advanced HCC, nivolumab demonstrated a manageable safety profile. Treatment with nivolumab was

generally well tolerated. TRAEs, other than endocrine events, generally occurred early in treatment. A majority of sTRAEs, including hepatic events, resolved with dose delays and with the addition of IMM in a subset of patients.

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DISCLOSURES

Huanyu Zhao: Bristol Myers Squibb (E), GlaxoSmithKline (OI); **Yun Shen:** Bristol Myers Squibb (E, OI); **Marina Tschaika:** Bristol Myers Squibb (E, OI). The other authors indicated no financial relationships.

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