Submitted by:
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NCCN Guidelines® Panel: Hepatobiliary Cancers

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully submit to the Hepatobiliary Cancers Panel the enclosed OPDIVO® (nivolumab) clinical data that has been presented at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting, for the Panel's consideration. This phase 1/2 study evaluated the use of nivolumab monotherapy for the treatment of patients with advanced hepatocellular carcinoma (HCC).[1] The use of nivolumab for the treatment of advanced HCC is considered investigational.

These data are being submitted in response to a standing request from the NCCN for new data to be submitted no less than 21 days prior to the NCCN standing meeting for Hepatobiliary Cancers.

Specific Changes: No specific change is requested.

Rationale: We are providing a summary of the data presented at ASCO 2016 from the dose-expansion phase of a phase 1/2 trial (CA209-040) that evaluated the safety, tolerability and preliminary efficacy of nivolumab monotherapy for the treatment of patients with advanced HCC not amenable to curative resection.[1]

Study CA209-040[1]: In the dose-expansion phase of this open-label, phase 1/2 study, patients with advanced HCC who progressed on ≥ 1 prior line of systemic therapy (including sorafenib), were intolerant of sorafenib, or refused sorafenib were eligible to receive nivolumab 3 mg/kg every 2 weeks in four parallel cohorts: uninfected, sorafenib naïve/intolerant (n = 54); uninfected, sorafenib progressors (n = 58); Hepatitis C virus (HCV) infected (n = 51); and Hepatitis B virus (HBV) infected (n = 51).

The primary endpoint is overall response rate (ORR) by blinded independent central review (these data are not yet available; all efficacy assessments are per the local investigator analysis). Secondary endpoints include complete response rate, disease control rate, duration of response, time to response, time to progression (TTP) and TTP rate, progression-free survival, overall survival (OS) and OS rate.

Baseline characteristics, highlights:

Table 1. Selected Baseline Characteristics.

	Uninfected		HCV (n = 51)	HBV (n = 51)	Total (N = 214)
	Sorafenib naïve/intolerant (n = 54)	Sorafenib progressors (n = 58)			
Child-Pugh score, n (%)					
• 5	41 (76)	38 (66)	27 (53)	44 (86)	150 (70)
• 6	12 (22)	20 (34)	21 (41)	7 (14)	60 (28)
• 7*	1 (2)	0	2 (4)	0	3 (1)
• 9*	0	0	1 (2)	0	1 (0.5)
Prior treatment type, n (%)					
• Surgical resection	29 (54)	37 (64)	19 (37)	40 (78)	125 (58)
• Radiotherapy	7 (13)	17 (29)	5 (10)	12 (24)	41 (19)
• Local treatment for HCC†	25 (46)	33 (57)	29 (57)	40 (78)	127 (59)
• Systemic therapy	22 (41)	57 (98)	32 (63)	46 (90)	157 (73)
-Sorafenib	15 (28)	56 (97)	30 (59)	40 (78)	141 (66)

*Study enrollment was based on a Child-Pugh score of ≤ 6 at screening or on the first day of dosing, whichever was later. Four patients who screened as Child-Pugh 5 or 6, and were therefore eligible to enroll, had scores of 7 or 9 on the day of dosing.
†By transcatheter arterial chemoembolization, transcatheter arterial embolization, radiofrequency ablation, or percutaneous ethanol injection.
Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

Efficacy findings, highlights:

The ORR across cohorts was 16% (16/214 patients). Details of the ORR and landmark OS for the various cohorts and overall population is included in the table below.

Table 2. Efficacy Data (interim analysis).

	Uninfected		HCV (n = 51)	HBV (n = 51)	Total (N = 214)
	Sorafenib Naïve/Intolerant (n = 54)	Sorafenib Progressors (n = 58)			
Objective response, n (%)	11 (20)	11 (19)	7 (14)	6 (12)	35 (16)
▪ Complete response	0	2 (3)	0	0	2 (1)
▪ Partial response	11 (20)	9 (16)	7 (14)	6 (12)	33 (15)
▪ Stable disease	32 (59)	27 (47)	29 (57)	23 (45)	111 (52)
▪ Progressive disease	11 (20)	18 (31)	12 (24)	22 (43)	63 (29)
6-month OS rate*, % (95% CI)	89.8 (77.1-95.6)	75.6 (61.5-85.2)	82.1 (61.3-92.4)	83.3 (67.6-91.8)	82.5 (75.8-87.5)
9-month OS rate*, % (95% CI)	79.8 (50.6-92.8)	NC	NC	NC	70.8 (56.6-81.1)

*Estimated using the Kaplan-Meier method

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; NC, not calculated; OS, overall survival.

Safety findings, highlights:

A summary of safety findings is presented in Table 3. No Grade 5 treatment related adverse events (TRAEs) were reported. A total of 12 patients discontinued treatment due to AEs.

Table 3. Treatment-Related Adverse Events

	Uninfected (n = 112)		HCV (n = 51)		HBV (n = 51)		Total (N = 214)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Patients with any TRAE, n (%)	72 (64)	21 (19)	37 (73)	15 (29)	30 (59)	3 (6)	139 (65)	39 (18)
Symptomatic TRAEs reported in > 4% of patients								
- Fatigue	31 (28)	2 (2)	7 (14)	0	7 (14)	0	45 (21)	2 (1)
- Pruritus	11 (10)	0	11 (22)	0	11 (22)	0	33 (15)	0
- Rash	12 (11)	1 (1)	8 (16)	0	6 (12)	0	26 (12)	1 (0.5)
- Diarrhea	16 (14)	2 (2)	3 (6)	0	1 (2)	1 (2)	20 (9)	3 (1)
- Nausea	8 (7)	0	6 (12)	0	0	0	14 (7)	0
- Decreased appetite	5 (5)	0	2 (4)	0	3 (6)	0	10 (5)	0
- Dry mouth	5 (4)	0	1 (2)	0	2 (4)	0	8 (4)	0
Laboratory-value TRAEs reported in > 4% of all patients								
- ALT increased	6 (5)	2 (2)	7 (14)	4 (8)	2 (4)	0	15 (7)	6 (3)
- AST increased	7 (6)	3 (3)	6 (12)	6 (12)	0	0	13 (6)	9 (4)
- Platelet count decreased	4 (4)	1 (1)	3 (6)	2 (4)	5 (10)	1 (2)	8 (4)	3 (1)
- Anemia	2 (2)	0	3 (6)	1 (2)	3 (6)	0	8 (4)	1 (0.5)

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

The following resources are submitted for your review. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications/ presentations.

1. Sangro B, Melero I, Yau T, et al. Safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma: interim analysis of dose-expansion cohorts from the phase 1/2 CheckMate-040 study. Presented at: The 52nd Annual Meeting of the American Society of Clinical Oncology, June 3-7, 2016; Chicago, IL.
2. EL-Khoueiry AB, Sangro B, Yau T et al. Phase 1/2 safety and tumor activity of nivolumab in patients with advanced hepatocellular carcinoma: interim analysis of the Checkmate 040 dose-escalation study. Presented at: The 52nd Annual Meeting of the American Society of Clinical Oncology, June 3-7, 2016; Chicago, IL.
3. Product Information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. September 2016.

Thank you for your consideration.

Sincerely,

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