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

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Presentation by Dr. Thomas Yau on behalf of his co-authors
Introduction

Hepatocellular Carcinoma (HCC)

• HCC is the second most frequent cause of cancer-related deaths worldwide\(^1\)

• Sorafenib is the only standard-of-care systemic therapy for advanced HCC
  – Median survival time ranges from 6.5 to 10.7 months\(^2,3\)

• For patients who progress after sorafenib treatment, there is no standard of care therapy
  – Median survival time with best supportive care is approximately 7 to 8 months\(^4,5\)

• HCC is typically an inflammation-associated cancer and, thus, is often immunogenic\(^6\)
Rationale for Immune Checkpoint Inhibition in HCC

- Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are associated with manifestations of immune suppression, including upregulation of programmed death-1 (PD-1) receptor,\(^7\) T-cell exhaustion, and spontaneous apoptosis of immune cells\(^8\)

- Blockade of the cytotoxic T-lymphocyte antigen-4 receptor by monoclonal antibodies has shown encouraging activity in patients with HCC and HCV infection\(^10\)

- Nivolumab is a fully human IgG4 monoclonal antibody to the PD-1 receptor, blocking the interaction with PD-L1/PD-L2\(^13\) and restoring T-cell–mediated antitumor activity

- Nivolumab was initially evaluated in a dose-escalation phase of CheckMate 040 in patients with advanced HCC, showing nivolumab to be well tolerated, with antitumor activity across different etiologies (uninfected, HCV, and HBV) and dosage levels

- Here, the interim results from the dose-expansion phase of CheckMate 040 are presented
Methods

Study Design

• Phase 1/2 study evaluating safety, tolerability, and preliminary efficacy assessment of nivolumab administered once every 2 weeks (Q2W) in patients with advanced HCC

• Using a 3 + 3 design, dose escalation was performed in independent parallel cohorts (uninfected, HCV, and HBV), followed by four parallel expansion cohorts that received nivolumab Q2W at 3 mg/kg

• Imaging for disease assessment was performed Q6W by computed tomography or magnetic resonance imaging
Figure 1. Study Design

Dose Escalation (n = 48)

- **Uninfected**
  - Nivo Q2W 0.1 mg/kg (n = 1)
  - Nivo Q2W 0.3 mg/kg (n = 3)
  - Nivo Q2W 1 mg/kg (n = 3)
  - Nivo Q2W 3 mg/kg (n = 3)
  - Nivo Q2W 10 mg/kg (n = 13)

- **HCV-infected**
  - Nivo Q2W 0.3 mg/kg (n = 3)
  - Nivo Q2W 1 mg/kg (n = 4)
  - Nivo Q2W 3 mg/kg (n = 3)

- **HBV-infected**
  - Nivo Q2W 0.1 mg/kg (n = 5)
  - Nivo Q2W 0.3 mg/kg (n = 3)
  - Nivo Q2W 1 mg/kg (n = 3)
  - Nivo Q2W 3 mg/kg (n = 4)

**Expansion (n = 214)**

- **Sorafenib naïve/intolerant**
  - Nivo Q2W 3 mg/kg (n = 54)

- **Sorafenib progressors**
  - Nivo Q2W 3 mg/kg (n = 58)

- **Nivo Q2W 3 mg/kg**
  - (n = 51)

Nivo = nivolumab
Key Eligibility Criteria

Inclusion

• Aged ≥ 18 years
• Histologically confirmed HCC
• Advanced HCC not amenable to curative resection
• Child-Pugh score ≤ 6 (i.e., Child-Pugh A)
• Progressed on ≥ 1 prior line of systemic therapy (including sorafenib); intolerant of sorafenib; or refused sorafenib
  – For the HCV and HBV cohorts, patients must have received sorafenib and be either intolerant or have had documented radiographic or symptomatic progression during or after sorafenib therapy
• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 x upper limit of normal
• Bilirubin ≤ 3 mg/dL
• Platelets ≥ 60 x 10^3/μL without transfusions
• Albumin ≥ 2.8 g/dL
• Antiviral therapy required in HBV cohort

Exclusion

• Any history of encephalopathy
• Prior or current clinically significant ascites
• Active HBV and HCV co-infection
Study Endpoints

Primary

• Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by blinded independent central review (BICR)\(^a\)

Secondary\(^b,c\)

• Complete response rate
• Disease control rate
• Duration of response
• Time to response
• Time to progression (TTP) and TTP rate
• Progression-free survival (PFS)
• Overall survival (OS) and OS rate

\(^a\)BICR data are not yet available and all efficacy assessments are per the local investigator analysis
\(^b\)Secondary endpoints included, but were not limited to, the endpoints listed
\(^c\)A safety analysis was conducted for all treated patients, but was not a specific study endpoint
Results

Patients

• Baseline patient characteristics were generally similar across cohorts (Table 1)
  – Median age was 64 years and the majority of patients were male
  – The HBV cohort was predominantly Asian
  – 75% of patients had extrahepatic metastases
  – 7% had vascular invasion
  – 70% had a Child-Pugh score of 5
  – 66% had been previously treated with sorafenib
Table 1. Baseline Patient Characteristics and Prior Treatment History

<table>
<thead>
<tr>
<th></th>
<th>Uninfected: Sorafenib Naive/Intolerant (n = 54)</th>
<th>Uninfected: Sorafenib Progressors (n = 56)</th>
<th>HCV (n = 51)</th>
<th>HBV (n = 51)</th>
<th>Total (N = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>66 (20–83)</td>
<td>65 (19–80)</td>
<td>65 (53–81)</td>
<td>55 (22–81)</td>
<td>64 (19–83)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>46 (85)</td>
<td>43 (74)</td>
<td>43 (84)</td>
<td>39 (77)</td>
<td>171 (80)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>36 (67)</td>
<td>35 (60)</td>
<td>30 (59)</td>
<td>4 (8)</td>
<td>105 (49)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Asian</td>
<td>16 (30)</td>
<td>22 (36)</td>
<td>18 (35)</td>
<td>45 (88)</td>
<td>101 (47)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Extrahepatic metastases, n (%)</td>
<td>42 (78)</td>
<td>43 (74)</td>
<td>30 (59)</td>
<td>46 (90)</td>
<td>161 (75)</td>
</tr>
<tr>
<td>Vascular invasion, n (%)</td>
<td>1 (2)</td>
<td>3 (5)</td>
<td>5 (10)</td>
<td>6 (12)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Child-Pugh score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>41 (76)</td>
<td>38 (66)</td>
<td>27 (53)</td>
<td>44 (86)</td>
<td>150 (70)</td>
</tr>
<tr>
<td>6</td>
<td>12 (22)</td>
<td>20 (34)</td>
<td>21 (41)</td>
<td>7 (14)</td>
<td>60 (28)</td>
</tr>
<tr>
<td>7+</td>
<td>1 (2)</td>
<td>0</td>
<td>2 (4)</td>
<td>0</td>
<td>3 (1)</td>
</tr>
<tr>
<td>8+</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>α-fetoprotein &gt; 200 μg/L, n (%)</td>
<td>15 (28)</td>
<td>26 (45)</td>
<td>18 (35)</td>
<td>27 (53)</td>
<td>86 (40)</td>
</tr>
<tr>
<td>Prior treatment type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>29 (54)</td>
<td>37 (64)</td>
<td>19 (37)</td>
<td>40 (78)</td>
<td>125 (58)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>7 (13)</td>
<td>17 (29)</td>
<td>5 (10)</td>
<td>12 (24)</td>
<td>41 (19)</td>
</tr>
<tr>
<td>Local treatment for HCC*</td>
<td>25 (46)</td>
<td>33 (57)</td>
<td>29 (57)</td>
<td>40 (78)</td>
<td>127 (59)</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>22 (41)</td>
<td>57 (96)</td>
<td>32 (63)</td>
<td>46 (90)</td>
<td>157 (73)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>15 (28)</td>
<td>56 (97)</td>
<td>30 (59)</td>
<td>40 (78)</td>
<td>141 (66)</td>
</tr>
</tbody>
</table>

*a 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.

*b Baseline α-fetoprotein values are missing for 5 uninfected-naïve/intolerant, 3 uninfected-progressors, 3 HCV, and 1 HBV-infected patients.

*c By transcatheter arterial chemoembolization, transcatheter arterial embolization, radiofrequency ablation, or percutaneous ethanol injection.
Results (cont’d)

- 214 patients were treated in the expansion cohorts as of the interim analysis in March, 2016.

- Patients across all cohorts received a median of 10 doses of nivolumab (range, 1–27) over a median time on treatment of 20 weeks

- Of these 214 patients, 110 discontinued (Table 2)
  - Disease progression was the most common reason for treatment discontinuation
  - 12 patients discontinued treatment due to adverse events (AEs)
### Table 2. Patient Disposition

<table>
<thead>
<tr>
<th>Discontinued, n (%)</th>
<th>Uninfected: Sorafenib Naïve/Intolerant (n = 26 of 54)</th>
<th>Uninfected: Sorafenib Progressors (n = 33 of 58)</th>
<th>HCV (n = 25 of 51)</th>
<th>HBV (n = 26 of 51)</th>
<th>Total (N = 110 of 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>21 (81)</td>
<td>30 (91)</td>
<td>16 (64)</td>
<td>26 (100)</td>
<td>93 (85)</td>
</tr>
<tr>
<td>Study drug toxicity</td>
<td>3 (12)</td>
<td>0</td>
<td>5 (20)</td>
<td>0</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Unrelated AE</td>
<td>0</td>
<td>2 (6)</td>
<td>2 (8)</td>
<td>0</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Withdrew consenta</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Request to discontinuea</td>
<td>1 (4)</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>0</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

*Patients who requested to discontinue study treatment remained in the study and continued to be followed for protocol-specified follow-up procedures, with the exception of patients who specifically withdrew consent for any further contact with themselves or persons previously authorized by themselves to provide this information.
Safety and Tolerability

• 65% of patients had treatment-related AEs (TRAEs) of any grade—18% with Grade 3 or 4 TRAEs (Table 3)

• Fatigue, pruritus, and rash were the most common TRAEs

• Elevation of AST and ALT were the most frequent Grade 3–4 TRAEs and were more commonly observed in patients with HCV infection
  – AST/ALT elevations were generally asymptomatic and readily managed

• No Grade 5 TRAEs occurred
### Table 3. Treatment-Related Adverse Events (TRAEs)

<table>
<thead>
<tr>
<th></th>
<th>Uninfected (n = 112)</th>
<th>HCV (n = 51)</th>
<th>HBV (n = 51)</th>
<th>Total (N = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Patients with any TRAE, n (%)</td>
<td>72 (64)</td>
<td>21 (19)</td>
<td>37 (73)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Symptomatic TRAEs reported in &gt; 4% of all patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (28)</td>
<td>2 (2)</td>
<td>7 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11 (10)</td>
<td>0</td>
<td>11 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (11)</td>
<td>1 (1)</td>
<td>8 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (14)</td>
<td>2 (2)</td>
<td>3 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (7)</td>
<td>0</td>
<td>6 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (5)</td>
<td>0</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5 (4)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory-value TRAEs reported in &gt; 4% of all patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT increased</td>
<td>6 (5)</td>
<td>2 (2)</td>
<td>7 (14)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>AST increased</td>
<td>7 (6)</td>
<td>3 (3)</td>
<td>6 (12)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>3 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (2)</td>
<td>0</td>
<td>3 (6)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
Efficacy

- Objective responses occurred in 35 of 214 (16%) patients (Table 4).
- PD-L1 expression on tumor cells, as assessed by immunohistochemistry, was quantifiable in 128 patients and responses occurred regardless of PD-L1 status (ORR = 5/26 [19%] patients with PD-L1 ≥ 1% and 20/102 [20%] patients with PD-L1 < 1%). For patients without quantifiable PD-L1 expression data, the ORR was 10/86 (12%).

Table 4. Investigator-assessed best overall response (RECIST v1.1)

<table>
<thead>
<tr>
<th></th>
<th>Uninfected: Sorafenib Naive/ Intolerant (n = 54)</th>
<th>Uninfected: Sorafenib Progressors (n = 58)</th>
<th>HCV (n = 51)</th>
<th>HBV (n = 51)</th>
<th>Total (N = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, n (%)</td>
<td>11 (20)</td>
<td>11 (19)</td>
<td>7 (14)</td>
<td>6 (12)</td>
<td>35 (16)</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Partial response</td>
<td>11 (20)</td>
<td>9 (16)</td>
<td>7 (14)</td>
<td>6 (12)</td>
<td>33 (15)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>32 (59)</td>
<td>27 (47)</td>
<td>29 (57)</td>
<td>23 (45)</td>
<td>111 (52)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11 (20)</td>
<td>18 (31)</td>
<td>12 (24)</td>
<td>22 (43)</td>
<td>63 (29)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>2 (3)</td>
<td>3 (6)</td>
<td>0</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>
Results (cont’d)

• Objective responses were observed in all etiologic subtypes (Table 4 and Figure 2)

• 91 of 204 patients (45%) with available data had reduction in tumor burden from baseline (Figure 2)

• 45 of 204 patients (22%) with available data had a ≥ 30% reduction in tumor burden from baseline
Of 214 patients, five were not evaluable (two in the uninfected sorafenib progressor cohort and three in the HCV cohort), and data for percent maximal change in target lesion from baseline were missing for a further five (one in the uninfected sorafenib naïve/intolerant cohort, two in the uninfected sorafenib progressor cohort, one in the HCV cohort, and one in the HBV cohort).
Responses occurred across all cohorts and appeared to be durable (Figure 3).

Stable disease was also durable in patients for whom that was the best response.
Results (cont’d)

• 29 of 35 patients responded within 3 months of beginning treatment (Figure 4)

• Responses were ongoing in 30 of 35 responders

• The median duration of response has not yet been reached
Figure 4. Time to Response and Duration of Response

- Uninfected sorafenib naïve/intolerant
- Uninfected sorafenib progressors
- HCV-infected
- HBV-infected

- \( \bullet \) = First response
- \( \Delta \) = Last nivolumab dose
- \( \rightarrow \) = Ongoing response

Time Since First Dose (Months)
Overall Survival

• OS rates for all patients at 6 and 9 months were 82.5% and 70.8%, respectively (Table 5)

Table 5. OS rates

<table>
<thead>
<tr>
<th>Survival rate, % (95% CI)(^a)</th>
<th>Uninfected: Sorafenib Naïve/Intolerant (n = 54)</th>
<th>Uninfected: Sorafenib Progressors (n = 58)</th>
<th>HCV (n = 51)</th>
<th>HBV (n = 51)</th>
<th>Total (N = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Month</td>
<td>89.8 (77.1, 95.6)</td>
<td>75.6 (61.5, 85.2)</td>
<td>82.1 (61.3, 92.4)</td>
<td>83.3 (67.6, 91.8)</td>
<td>82.5 (75.8, 87.5)</td>
</tr>
<tr>
<td>9-Month</td>
<td>79.8 (50.6, 92.8)</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>70.8 (56.6, 81.1)</td>
</tr>
</tbody>
</table>

\(^a\)Estimated using the Kaplan-Meier method.
CI = confidence interval; NC = not calculated.
Changes in qHBsAg and HCV RNA From Baseline

• In patients with concurrent HBV or HCV infection, changes in viral load were assessed by quantitative hepatitis B surface antigen (qHBsAg) or quantitative RT-PCR, respectively

  – Three of 51 patients (6%) had declines of > 1 log in qHBsAg

  – 10 of 51 patients (20%) had transient declines of > 1 log in HCV RNA; four of 51 patients (8%) had undetectable RNA levels (unconfirmed)
Conclusions

• In this larger expansion phase, durable objective responses occurred across all etiologic cohorts, and efficacy measures were consistent with observations from the dose-escalation phase of the study (ASCO 2016, abstract #4012)

• While these interim results are preliminary, the 9-month OS rate of 71% is encouraging

• Consistent with results from the dose-escalation phase of the study, nivolumab monotherapy demonstrated a manageable safety profile in patients with HCC, including those with HBV or HCV infection. Moreover, the safety profile was similar to that observed in patients with other solid tumors

• qHBsAg and HCV RNA were reduced in a proportion of patients

• Because median time on treatment was < 5 months, observed responses might be underestimated
Acknowledgments

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