Oncologic Drugs Advisory Committee (ODAC) Meeting

April 29, 2021

NDA/BLA# 125514 s-42

Drug name: pembrolizumab

Applicant: Merck Sharp & Dohme Corp.

Combined FDA and Applicant ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. We have brought the drug pembrolizumab (also known as Keytruda®) to this Advisory Committee in order to gain the Committee’s insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE
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# Glossary

<table>
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<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>Accelerated Approval</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AEOSI</td>
<td>Adverse event of special interest</td>
</tr>
<tr>
<td>AFP</td>
<td>Alpha-fetoprotein</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine liver transferase</td>
</tr>
<tr>
<td>ASaT</td>
<td>All subjects as treated</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BCLC</td>
<td>Barcelona Clinic Liver Cancer</td>
</tr>
<tr>
<td>BICR</td>
<td>Blinded independent central review</td>
</tr>
<tr>
<td>BSC</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>BW</td>
<td>Body weight</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Cytotoxic T-lymphocyte-associated protein-4</td>
</tr>
<tr>
<td>CPS</td>
<td>Combined positive score</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRL</td>
<td>Complete Response Letter</td>
</tr>
<tr>
<td>DMC</td>
<td>Data monitoring committee</td>
</tr>
<tr>
<td>DOR</td>
<td>Duration of response</td>
</tr>
<tr>
<td>EOP</td>
<td>End of Phase</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FA</td>
<td>Final analysis</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IO</td>
<td>Immuno-oncology</td>
</tr>
<tr>
<td>IPCW</td>
<td>Inverse-Probability-Censoring Weighting</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenously</td>
</tr>
<tr>
<td>KM</td>
<td>Kaplan-Meier</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mRECIST</td>
<td>Modified Response Evaluation Criteria in Solid Tumors</td>
</tr>
<tr>
<td>MSI-H</td>
<td>Microsatellite instability high</td>
</tr>
<tr>
<td>MVI</td>
<td>Macrovascular invasion</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>NASH</td>
<td>Non-alcoholic steatohepatitis</td>
</tr>
<tr>
<td>NCI CTCAE</td>
<td>National Cancer Institute Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>ORR</td>
<td>Objective response rate</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PD-1</td>
<td>Programmed cell death 1</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Programmed cell death ligand 1</td>
</tr>
<tr>
<td>PD-L2</td>
<td>Programmed cell death ligand 2</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>Q3W</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td>Q6W</td>
<td>Every 6 weeks</td>
</tr>
<tr>
<td>QD</td>
<td>Once daily</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors</td>
</tr>
<tr>
<td>RFS</td>
<td>Recurrence-free survival</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>TACE</td>
<td>Transarterial chemoembolization</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>tTMB-H</td>
<td>Tissue tumor mutational burden high</td>
</tr>
<tr>
<td>TTP</td>
<td>Time to progression</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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</tbody>
</table>
Representatives of FDA:

Steven Lemery, MD, Director (Acting), Division of Oncology 3
Sandra Casak, MD, Clinical Team Leader
Leigh Marcus, MD, Clinical Reviewer
Yuan Shen, PhD, Statistical Team Leader
Yi Ren, PhD, Statistical Reviewer

Representatives of Merck Sharp & Dohme Corp.:

Scot Ebbinghaus, MD, Vice President, Clinical Research, Oncology
Abby Siegel, MD, Associate Vice President, Clinical Research, Oncology
1. Introduction

1.1 Indication

**Applicant's Position:**

Hepatocellular Carcinoma

On 09-NOV-2018, the Applicant received accelerated approval (AA) for the following indication:

“KEYTRUDA® is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.”

This approval is based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.2 Purpose of the Meeting

**FDA's Position:**

FDA Oncology has consistently evaluated products and indications approved under the accelerated approval regulations over the years. This particular evaluation of anti PD-1/PD-L1 antibodies occurred due to the unprecedented level of drug development in this space in which there were many accelerated approvals. We found that there were a number of supplemental biologics license applications (sBLAs) which received accelerated approval but subsequent confirmatory trial(s) have not verified clinical benefit. Therefore, OOD and OCE is convening the Oncologic Drugs Advisory Committee (ODAC) to highlight six applications in this position. The committee will be briefed on the status and results of confirmatory clinical studies for these six applications, and hear about any ongoing and planned trials. The FDA is seeking the committee’s advice on next steps for each product including whether the indications should remain on the market while additional trial(s) are conducted.

The purpose of this meeting is to obtain the Advisory Committee’s input regarding the status of the accelerated approval of pembrolizumab as a single agent for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. FDA requests this discussion in light of the changing landscape of hepatocellular carcinoma (HCC) given the May 29, 2020, approval of atezolizumab in combination with bevacizumab for patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy, and the results of randomized Study KEYNOTE-240, which did not demonstrate statistical significance for an improvement in overall survival when pembrolizumab was compared to placebo in patients who received prior sorafenib.

FDA granted accelerated approval to pembrolizumab for the post-sorafenib indication in 2018 based on an observed response rate of 17% (11, 26) (with 89% of responding patients having a response of 6 months or longer and 56% of patients having responses of 12 months or longer) among 104 patients enrolled in Study KEYNOTE-224 (a single-arm study). Per product labeling,
the majority of patients (72%) had Child-Pugh score of A5; patients with clinical evidence of ascites were ineligible for the trial.

Subsequently, the applicant conducted Study 240, a randomized controlled trial of pembrolizumab versus placebo in patients who previously received sorafenib. The observed OS hazard ratio (HR) was 0.781 (95% CI: 0.611, 0.998; one sided p = 0.0238), which did not meet the protocol-specified boundary for statistical significance. In addition, the treatment landscape of HCC has changed with another anti-PD-(L)1 antibody (atezolizumab when combined with bevacizumab) demonstrating overall survival benefit in the first-line setting.

This current indication for pembrolizumab in the post-sorafenib setting should be considered in the context of a modest effect on ORR, unsuccessful randomized trial (KEYNOTE-240) in the post-sorafenib setting, and changing landscape of the treatment of HCC following the approval of atezolizumab in combination with bevacizumab.

In conclusion, the clinical benefit of pembrolizumab for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib has not been confirmed, as results from the confirmatory KEYNOTE-240 trial did not meet statistical significance. Should the indication for pembrolizumab for the second-line (post sorafenib) treatment of hepatocellular carcinoma be maintained pending final results of one of the applicant’s ongoing randomized controlled trials in HCC?

2 Background

The Applicant’s Position:

2.1 Pembrolizumab

2.1.1 Mechanism of Action and Scientific Rationale for Pembrolizumab in Hepatocellular Carcinoma

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4/kappa isotype designed to directly block the interaction between programmed cell death 1 (PD-1) and its ligands, programmed cell death ligand 1 (PD-L1) and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. In vitro and in vivo experiences have shown that PD-1 and PD-L1 blockade using a mAb can result in activation of antitumor T cells and subsequent tumor regression. The antibody potentiates existing immune responses in the presence of antigen only; it does not nonspecifically activate T cells.

At the time that the KEYNOTE-224 protocol was developed, pembrolizumab had already demonstrated clinical efficacy and evidence of safety in patients with multiple tumor types. Additionally, emerging data on the effects of PD-1 inhibitors in patients with HCC suggested that these agents were generally tolerable and likely efficacious. Since there were no available data on the safety of pembrolizumab in HCC patients, DMCs and careful safety monitoring were
employed to ensure the safety of clinical trial participants in the KEYNOTE-224 AA trial and the randomized Phase 3 trial, KEYNOTE-240.

2.1.2 Pembrolizumab US Regulatory History
In the US, KEYTRUDA is approved for 28 indications across 17 different tumor types including 2 tumor-agnostic indications. The current US PI for KEYTRUDA contains 18 indications that have been granted traditional approval, most of which were based on rigorous Phase 3 evidence of clinical benefit in major cancer types including melanoma, lung cancer, urothelial malignancies, head and neck cancer, colorectal cancer, renal cell carcinoma and Hodgkin lymphoma. Over the course of KEYTRUDA development, the US FDA granted 16 AAs based on a surrogate endpoint reasonably likely to predict clinical benefit. Six of these AAs have provided confirmatory data and were converted to traditional approvals, 6 have their original confirmatory trial still ongoing (results are available for KEYNOTE-775 in endometrial carcinoma and, if filed and approved by FDA, could convert that indication to traditional), and 4 did not confirm benefit based on the originally agreed confirmatory study. One of the AAs that has not yet confirmed benefit is for patients with HCC who have been previously treated with sorafenib.

In December 2015, the Sponsor met with FDA via an End of Phase (EOP)/pre-Phase 3 meeting to discuss and seek agreement on the study designs for KEYNOTE-224 and KEYNOTE-240. Key highlights of agreements between the Sponsor and the FDA included:

- The overall study designs and key inclusion criteria for KEYNOTE-224 and KEYNOTE-240 including agreement on the definition of patients who have progressed on, or are intolerant to sorafenib [Table 5].
- Best-supportive care (BSC) arm is acceptable as a comparator arm in KEYNOTE-240.
- Acceptability of multiplicity strategy and progression-free survival (PFS)/overall survival (OS) as co-primary endpoint in KEYNOTE-240; however, regular approval would likely be dependent upon demonstrating an improvement in OS.
- If the results confirm benefit with an improvement in OS, KEYNOTE-240 could serve as a confirmatory trial if FDA grants AA based on KEYNOTE-224.

Pembrolizumab was granted AA in the US on 09-NOV-2018 for the treatment of patients with HCC who had been previously treated with sorafenib. This approval was based on tumor response rate (ie, objective response rate [ORR]) and duration of response (DOR) data from KEYNOTE-224, a single arm, open-label multicenter trial evaluating pembrolizumab in 104 participants with advanced HCC.

The following post-marketing commitments were included with the KEYNOTE-224 approval:

- 3292-2: Submit the final report, including datasets, of Study KEYNOTE-224, “A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects With Previously Systemically Treated Advanced Hepatocellular Carcinoma,” in which all responding patients have been followed for a minimum of 24 months and duration of response is assessed by independent central review, to more accurately characterize the durability of the response observed with pembrolizumab in this study. [Final report submitted to FDA via BLA 125514 in March 2020.]
3492-1: Conduct and submit the results of one or more randomized trials to verify and describe the clinical benefit of pembrolizumab as compared to available therapy in patients with locally advanced, unresectable or metastatic HCC as demonstrated by an improvement in OS or a large improvement in PFS that is clinically meaningful.

2.2 Description of Clinical Setting

2.2.1 Overview of HCC

HCC is one of the most common causes of cancer-related deaths worldwide. An estimated 75% to 90% of primary liver cancer cases are HCC [1] [2] [3]. Worldwide, major factors that increase the risk of HCC are chronic hepatitis B and chronic hepatitis C, alcohol use, and metabolic syndrome [4].

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are hepatic manifestations of metabolic syndrome. HCC associated with NAFLD and NASH is increasing in the US and globally [5]. Liver cancer incidence and mortality are increasing in the US, and 5-year survival for those with advanced disease is less than 3% [6], [https://seer.cancer.gov/statfacts/html/livibd.html].

2.2.1.1 Current Treatment Landscape for HCC Including Regulatory Landscape

The current treatment armamentarium relevant to HCC includes immuno-oncology (IO) and anti-vascular endothelial growth factor (VEGF) agents [Table 1]. In 2007 the first systemic anti-cancer therapy for HCC, sorafenib, was approved in the US. At the time KEYNOTE-224 and KEYNOTE-240 were designed in 2015, sorafenib was the only approved systemic anti-cancer therapy for HCC in the US. Best supportive care (BSC) was considered standard-of-care for second-line HCC, as there were no effective therapies for HCC after progression on sorafenib.

Additionally, there were no studies available to predict the benefit of IO therapy in HCC. Thus, KEYNOTE-240 was powered for an OS treatment effect expected in the absence of subsequent effective oncologic therapies and a high expected treatment benefit based on available efficacy data for pembrolizumab that had been seen in other indications.

By the time of the KEYNOTE-224 AA, the treatment landscape for patients with HCC had expanded to include 2 second-line treatments (regorafenib and nivolumab) [Table 1]. Since this time, several additional therapies including cabozantinib, ramucirumab, and ipilimumab-nivolumab have been approved post sorafenib.
Table 1 Summary of Treatment Armamentarium Relevant to HCC

<table>
<thead>
<tr>
<th>Product Names</th>
<th>Year of Approval and Type of Approval</th>
<th>Dosing/Administration</th>
<th>Efficacy Information</th>
<th>Safety Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Approved First-line Treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Nov 2007</td>
<td>Oral</td>
<td><strong>SHARP</strong>: Sorafenib mOS: 10.7 months (95% CI: 9.4, 13.3). Placebo mOS: 7.9 months (95% CI: 6.8, 9.1) (HR 0.69; 95% CI: 0.55, 0.87), p=0.00058) [7]</td>
<td>Diarrhea 8% Hand-foot skin reaction 8% Fatigue 4%</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Aug 2018</td>
<td>Oral</td>
<td><strong>REFLECT</strong>: Lenvatinib: mOS: 13.6 months (95% CI: 12.1, 14.9) Sorafenib mOS: 12.3 months (95% CI: 10.4, 13.9) (HR 0.92; 95% CI: 0.79, 1.06 p=NR) Lenvatinib mPFS: 7.3 months (95% CI: 5.6, 7.5) Sorafenib mPFS: 3.6 months (95% CI: 3.6, 3.7) (HR 0.64; 95% CI: 0.55, 0.75 p&lt;0.001) [10]</td>
<td>Hypertension 23% Weight loss 8% Increased bilirubin 7%</td>
</tr>
<tr>
<td>Atezolizumab + bevacizumab</td>
<td>May 2020</td>
<td>IV</td>
<td><strong>IMbrave 150</strong>: Atezolizumab/bevacizumab mOS: 19.2 months (95% CI: 17.0, 23.7) Sorafenib mOS: 13.4 months (95% CI: 11.4, 16.9) (HR 0.66; 95% CI: 0.52, 0.85; p=0.0009) Atezolizumab/bevacizumab mPFS: 6.9 months (95% CI: 5.7, 8.6) Sorafenib mPFS: 4.3 months (95% CI: 4.0, 5.6) (HR 0.65; 95% CI: 0.53, 0.81; p=0.0001) [13]</td>
<td>Hypertension 10% Increased AST 4% Proteinuria 3%</td>
</tr>
<tr>
<td><strong>FDA Approved Second-line Treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regorafenib</td>
<td>April 2017</td>
<td>Oral</td>
<td><strong>RESOURCE</strong>: Regorafenib mOS: 10.6 months (95% CI: 9.1, 12.1) Placebo mOS: 7.8 months (95% CI: 6.3, 8.8), (HR 0.63; 95% CI: 0.50, 0.79 p&lt;0.0001) Regorafenib mPFS: 3.1 months (95% CI: 2.8, 4.2) Placebo mPFS: 1.5 months (95% CI: 1.4, 1.6), (HR 0.46; 95% CI: 0.37, 0.56 p&lt;0.0001) [15]</td>
<td>Hypertension 13% Hand-foot skin reaction 13% Increased blood bilirubin 7%</td>
</tr>
<tr>
<td>Drug</td>
<td>Approval Date</td>
<td>Route</td>
<td>Study</td>
<td>ORR (95% CI)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------</td>
<td>-------</td>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Sep 2017</td>
<td>IV</td>
<td>CheckMate 040</td>
<td>14% (9, 21)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Nov 2018</td>
<td>IV</td>
<td>KEYNOTE-224</td>
<td>17% (11, 26)</td>
</tr>
<tr>
<td>Cabozatinib</td>
<td>Jan 2019</td>
<td>Oral</td>
<td>CELESTIAL</td>
<td></td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>May 2019</td>
<td>IV</td>
<td>REACH-2</td>
<td></td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>Mar 2020</td>
<td>IV</td>
<td>CheckMate 040</td>
<td>33% (20, 48)</td>
</tr>
</tbody>
</table>

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CI=confidence interval; DOR=duration of response; HCC=hepatocellular carcinoma; HR=hazard ratio; IV=intravenous; mOS=median overall survival; mPFS=median progression-free survival; NR=not reported; ORR=objective response rate.

* Accelerated approval; b Full approval; c Lenvatinib was approved in the first-line setting based on non-inferiority results on OS in comparison with sorafenib [10]; d Indicated post-sorafenib; e Regorafinib was approved in the second-line setting for patients who tolerated sorafenib [15]; f Ramucirumab was approved in the second-line setting in patients with baseline high alpha-fetoprotein (≥400 ng/mL) [23]; g Includes both with and without prior sorafenib; h Grade 3-4 adverse events of all causes; i Grade 3-4 treatment-related adverse events; k Supplementary Appendix Table S4 (dose-expansion phase)
2.2.1.2 Changes in the HCC Treatment Landscape Since Accelerated Approval

There were no systemic therapy approvals for HCC in any line of therapy between 2007 when sorafenib was approved and 2017. Since then, the management of advanced HCC has evolved significantly. Two first-line treatments have been approved since 2017:

- 16-AUG-2018 – lenvatinib
- 29-MAY-2020 – atezolizumab in combination with bevacizumab

Similarly, second-line treatment options for similar HCC patient populations were not available until a decade after sorafenib was approved, but now include the following:

- 27-APR-2017 – regorafenib as second-line therapy after previous treatment with sorafenib
- 22-SEP-2017 – nivolumab (AA) as second-line therapy after previous treatment with sorafenib
- 09-NOV-2018 – pembrolizumab (AA) as second-line therapy after previous treatment with sorafenib
- 14-JAN-2019 – cabozantinib as second-line therapy after previous treatment with sorafenib
- 10-MAY-2019 – ramucirumab for patients with HCC who have alpha-fetoprotein ≥400 ng/mL and have been previously treated with sorafenib
- 10-MAR-2020 – combination of nivolumab and ipilimumab (AA) as second-line therapy after previous treatment with sorafenib

Additional details for each of the above treatments are presented in [Table 1].

Merck and Eisai submitted applications in February 2020 seeking AA of KEYTRUDA, plus LENVIMA, for the first-line treatment of patients with unresectable HCC based on the data from the Phase 1b KEYNOTE-524/Study 116 trial, that showed promising efficacy in the single-arm setting. The combination had been previously granted Breakthrough Therapy Designation in 2019. ORR was 36.0% (95% CI, 26.6%-46.2%) per RECIST v1.1 by independent review, and median DOR was 12.6 months (95% CI, 6.9 months-NE). Treatment-related ≥ Grade 3 AEs occurred in 67% of patients; no new safety signals were identified [26]. These data are supportive of the ongoing LEAP-002 study evaluating this combination in a Phase 3 randomized setting. FDA issued a Complete Response Letter (CRL) in July 2020 since the applications for the KEYNOTE-524/Study 116 no longer met the criteria for AA due to another combination therapy (bevacizumab/atezolizumab) being approved based on a randomized, controlled trial that demonstrated a survival benefit. Therefore, the CRL stated that the applications did not provide evidence that represented a meaningful advantage over a newly available therapy (bevacizumab/atezolizumab), that had been granted full approval in May 2020. The Sponsor is committed to evaluating the results from a controlled clinical trial to investigate the clinical benefit of pembrolizumab in combination with lenvatinib, and is conducting a well-controlled
Phase 3 study LEAP-002 as a first-line treatment for advanced HCC. This study is currently underway and fully enrolled. Data are anticipated within the coming year.

Although several new agents for advanced HCC have been approved over the past few years, there are still patients who need the option of single agent PD-1 inhibitor in second-line HCC. There are patients who may not be candidates for bevacizumab/atezolizumab in first-line HCC, and also those who may not be appropriate to receive an anti-angiogenic in the second line. This unmet need is further discussed in Section 2.2.2.

2.2.2 Unmet Medical Need

In spite of recent progress, patients with advanced HCC still have a high unmet medical need with low survival rates, and few effective and safe therapeutic options [27] [6], https://seer.cancer.gov/statfacts/html/livibd.html#. Surgical resection, transplantation, and ablation are potentially curative treatment options for patients with early-stage disease. However, most HCC patients in the United States present with more advanced disease [1]. These patients are typically treated with locoregional and systemic therapies.

Although the treatment landscape has expanded in the first-line setting and bevacizumab and atezolizumab may be offered for many patients with advanced HCC, monotherapy with tyrosine kinase inhibitors (TKIs) continues to be an appropriate treatment option for some advanced HCC patients. HCC often occurs in the setting of cirrhosis. Untreated or incompletely treated esophageal or gastric varices may make patients unsuitable for bevacizumab and atezolizumab. Bevacizumab and atezolizumab is also not recommended for patients with recent myocardial infarction or stroke events, recent gastrointestinal bleeding events, or requirement for therapeutic anticoagulation. These patients may be eligible for sorafenib or lenvatinib, but almost all patients progress on these drugs in less than a year [9] [28].

An analysis of IQVIA open claims data, from June to November 2020, was performed to understand recent treatment patterns in the first-line setting. The results demonstrate that approximately 41% of more than 4500 previously untreated patients received an FDA-approved TKI monotherapy as first-line treatment for advanced HCC [Section 9.2], [data on file]. It is possible that these percentages will decrease as bevacizumab and atezolizumab uptake increases since approval in May 2020. As described above, however, we expect that there will remain a subset of patients who will still be unsuitable for bevacizumab and atezolizumab.

Following first-line therapy with sorafenib or lenvatinib, IO based therapies or anti-angiogenics are reasonable options that may be considered for appropriate candidates. The anti-VEGFR TKIs regorafenib and cabozantinib are options in this setting, but may be associated with hemorrhage, GI perforation, hypertension, and reversible posterior leukoencephalopathy syndrome. Severe and sometimes fatal hepatotoxicity has occurred during regorafenib treatment. For cabozantinib, 68% of patients had Grade ≥3 adverse events (AEs) and 62% of
patients required dose reduction during the Phase 3 trial [20]. Even after treatment with TKIs in the first line, anti-angiogenic agents still have risks for bleeding or thrombotic events. Additionally, several anti-VEGF/VEGFR therapies are approved or have shown efficacy only for specific populations. For instance, the RESORCE trial that led to approval of regorafenib in second-line HCC required prior tolerance to sorafenib, leading to a highly selected patient population. Ramucirumab is approved in second-line HCC only for those with an AFP ≥400 ng/mL [22] [23].

For those patients who are unsuitable for treatment with anti-VEGF/VEGFR therapy in the second-line setting, immune-checkpoint inhibitors remain an important part of the current treatment armamentarium [28]. Further, anti-PD-1 therapies have the potential to provide prolonged durations of response in some patients, which are not typically seen with other non-IO based agents. An analysis of IQVIA open claims data, from June to November 2020, was performed to understand recent treatment patterns in the second-line setting. The results demonstrate that 42% of more than 1500 patients received PD-1 inhibitor-based therapy as second-line treatment for advanced HCC [Section 9.2], [data on file]. However, with recent approvals in first-line (bevacizumab and atezolizumab in May 2020), treatment patterns may evolve over time.

The combination of ipilimumab and nivolumab also has AA for this patient population. In the study for this combination, however, 59% of patients had serious adverse reactions, and the majority of patients required steroids [29]. As a result, this combination may be unsuitable for many patients who have progressed after a TKI.

Single agent anti-PD-1 therapy does have toxicities, which are usually immune-mediated and may be severe or fatal. These are different from those of anti-angiogenic agents, however, and lower in incidence than those of anti-PD1/anti-CTLA-4 doublets. Therefore, some patients for whom these other treatments may not be suitable due to their toxicity profile may be able to tolerate pembrolizumab. Collectively, these data indicate that there remains a need for second-line, single agent PD-1 inhibitor therapy for some patients.

2.3 Use of Biomarkers for Pembrolizumab in Hepatocellular Carcinoma

While select cancer indications use biomarkers to achieve enrichment of clinical response to IO therapies [30], to date, studies of anti-PD-1 agents in HCC have yet to establish the clinical utility of biomarkers for patient selection. Since HCC is frequently diagnosed by radiography in the absence of a tumor tissue biopsy, biomarker analyses are particularly challenging, as it is often difficult to obtain adequate tumor tissue for biomarker research.

KEYNOTE-224 and KEYNOTE-240 studies did not require tissue submission for exploratory biomarker analyses, and the tumor submission rates were 58% and 34% in KEYNOTE-224 and KEYNOTE-240, respectively. When PD-L1 expression cut-offs were examined and descriptively summarized in KEYNOTE-224, responses were observed in participants with PD-L1-positive (combined positive score; CPS ≥1) and -negative (CPS <1) expression (ORR 32% and 20%, respectively). In KEYNOTE-240, PD-L1 CPS failed to show an association with clinical response to
pembrolizumab. The currently available data are insufficient to support a biomarker enrichment strategy. These findings are consistent with the single arm study of the anti-PD-1 checkpoint inhibitor nivolumab in HCC (CheckMate 040) [16], which reported objective responses regardless of PD-L1 expression assessed in tumor cells.

HCC typically has low prevalence of tissue tumor mutational burden high (tTMB-H) and microsatellite instability-high (MSI-H) [31] [32] [33]. Exploratory biomarker work on the limited tissue samples from KEYNOTE-224 and KEYNOTE-240 included analyses of tTMB and MSI status and similarly showed low median TMB and no cases of MSI-H. As a result, neither the TMB-H nor MSI-H agnostic approval would be expected to affect HCC.

In summary, the exploratory analyses of PD-L1 expression and TMB in limited tissue samples from KEYNOTE-224 and KEYNOTE-240 suggest these biomarkers do not show clinical utility in HCC; a predictive biomarker for pembrolizumab response in HCC remains to be identified.

The FDA’s Position:

On May 29, 2020, FDA approved the combination atezolizumab/bevacizumab for the first-line treatment of unresectable or metastatic HCC based on the results of Study IMbrave150. To be enrolled in IMbrave150, patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding. In addition, only patients with Child-Pugh A liver function were enrolled in IMbrave150.

When an accelerated approval is granted, FDA may request that the applicant conduct a post marketing trial to verify and describe the effect of a drug, and to address residual uncertainties. FDA granted accelerated approval to pembrolizumab for the post-sorafenib indication in 2018 based on an observed response rate of 17% (11, 26) (with 89% of responding patients having a response of 6 months or longer and 56% of patients having responses of 12 months or longer) among 104 patients enrolled in Study KEYNOTE-224 (a single-arm study). The Applicant proposed to submit the results of KEYNOTE-240 (a randomized controlled trial) to verify the benefit of pembrolizumab and to address residual uncertainties from the KEYNOTE-224 trial.

KEYNOTE-240, did not demonstrate a statistically significant result. Additionally, as designed and given the evolving treatment landscape for advanced HCC, the proposed use of pembrolizumab described by the applicant was not systematically studied in KEYNOTE-224. Specifically, the population studied in KEYNOTE-224 (or KEYNOTE-240) differed from the population of patients who would have been excluded from Study IMbrave150, the study that established the safety and efficacy of atezolizumab in combination with bevacizumab in HCC. For example, it is unclear whether the safety and efficacy of pembrolizumab in patients at high risk of bleeding due to varices would be comparable to the data described in pembrolizumab product labeling. Likewise, KEYNOTE-224 primarily enrolled patients that had Child-Pugh A liver function with the majority of patients (72%) having a CP score of A5 and patients with clinically
evident ascites, clinically diagnosed hepatic encephalopathy, or esophageal/gastric bleeding within the past 6 months excluded from enrollment.

In the SHARP study, which supported the approval of sorafenib in the first line setting, 95% of patients randomized to receive sorafenib had Child Pugh A liver function. Patients with clinically significant gastrointestinal bleeding within 30 days prior to study entry were excluded. In the REFLECT study, which supported the approval of lenvatinib in the first-line setting, patients with a gastrointestinal bleeding event within 28 days prior to randomization or gastric or esophageal varices that required treatment were excluded from participation in the study; only patients with Child-Pugh A liver function were enrolled.

As summarized, all three clinical studies leading to HCC approvals in the first-line setting exclusively or primarily enrolled patients with Child Pugh A liver function. A clinical trial’s eligibility criteria defines the characteristics of the study population; eligibility criteria are developed taking into consideration the mechanism of action of the drug, the patient population, and the anticipated or available safety of the investigational drug. Eligibility criteria may also be instituted to improve the probability of a positive study by excluding patients with poor prognosis who, for example, may have early progression events or deaths in both study arms (reducing the power of the study). Sometimes the eligibility criteria will result in studies that do not fully represent treatment effects in the patient population that will ultimately use the drug.

As bleeding is a labeled risk of bevacizumab, an EGD is recommended to evaluate the risk of variceal bleeding prior to treating a patient with the combination of atezolizumab and bevacizumab; patients with incompletely treated varices, bleeding within 6 months, or at high risk of bleeding may not be candidates for this treatment based on the design of Study IMbrave150. This subset of patients (no data available to estimate the incidence) may receive treatment with sorafenib or lenvatinib, although these drugs may also increase the risk of bleeding.

As indicated above, projections regarding the use of single-agent TKI therapy based on claims data may overestimate the future use of TKIs in the first-line setting. There are no data supporting the use of pembrolizumab after progression on atezolizumab in combination with bevacizumab.

As discussed elsewhere in this document, the accelerated approval of pembrolizumab in the second-line setting after treatment with sorafenib (in patients with Child Pugh A liver function) was based on a modest response rate; with some responders experiencing a meaningful duration of response. As response rate is an intermediate endpoint, Merck agreed to conduct a study to verify and describe the clinical benefit of pembrolizumab; however, Study KEYNOTE-240 did not demonstrate such benefit.

FDA agrees with the applicant that the safety profiles between pembrolizumab and other drugs approved in the second-line setting are different. However, cabozantinib, regorafenib, and
ramucirumab were approved based on randomized studies showing a survival benefit for which
the risk:benefit relationship was deemed favorable.

Although there are patients who will not be eligible in the first-line setting to receive
atezolizumab/bevacizumab (e.g., based on risk of bleeding when exposed to bevacizumab),
pembrolizumab for the treatment of this subset of patients with disease progression after
sorafenib (or lenvatinib) has not demonstrated a survival benefit in any line of treatment and its
benefits have not been established.

3 Pembrolizumab Clinical Studies in HCC
The Applicant’s Position:

3.1 Summary of All Completed or Ongoing Clinical Studies In HCC
The Sponsor is committed to addressing unmet medical needs for HCC patients through a
comprehensive clinical development program including pembrolizumab in multiple disease
settings. The company-sponsored pembrolizumab clinical program for the HCC indication
consists of 7 ongoing registration trials and 1 planned trial: KEYNOTE-224, KEYNOTE-240,
KEYNOTE-394, KEYNOTE-524 (Study 116), MK-7902-002 (LEAP-002), LEAP-012, adjuvant
KEYNOTE-937, and planned trial MK-1308A-004, as summarized in [Table 5].

3.2 KEYNOTE 224 (Accelerated Approval): Efficacy Summary
The primary analysis for KEYNOTE-224 had a 13-FEB-2018 data cutoff date; the efficacy update
report with updated DOR results had a 15-MAY-2018 data cutoff date. Additionally, the data
cutoff date for a long-term follow-up analysis that provided at least 24 months of follow-up
from the beginning of response for all responders was 05-JUN-2019; the final report with this
analysis was submitted to FDA via BLA 125514 in March 2020 and the results of this analysis are
provided in Section 3.2.2.3 of this report.

3.2.1 KEYNOTE-224: Disposition, Demographics, and Baseline Characteristics
3.2.1.1 Disposition
A total of 105 participants were allocated, and 104 participants were treated at 37 global study
sites. As of 13-FEB-2018, 17 (16.3%) participants remained on treatment and 44 (42.3%) were in
follow-up. The majority of participants (87 [83.7%]) were discontinued from treatment with
progressive disease (59 [56.7%]) and AEs (24 [23.1%]) being the most common reasons for
discontinuation from treatment. A total of 60 (57.7%) participants were discontinued from the
trial; death was the only reason for trial discontinuation.

3.2.1.2 Demographics and Baseline Characteristics
Most participants were male (82.7%), white (80.8%), and non-Hispanic (94.2%). More than half
the participants were older than 65 years (62.5%). All participants had been previously treated
with sorafenib, as required by protocol. Prior treatment with sorafenib had been discontinued
for 20.2% of participants due to intolerance, and for 79.8% of participants due to progression.
The etiology of underlying liver disease was non-viral for most participants, with 21.2% and
25.0% of participants positive for HBV and HCV, respectively. A total of 9 participants (9%) were seropositive for both HBV and HCV. For these 9 participants, all of the HBV cases and 3 of the HCV cases were inactive. The population included 18.3% of participants enrolled from US sites, and more than half of the participants enrolled from Europe (68.3%). Most of the remaining participants were enrolled from Japan (10.6%).

3.2.2 KEYNOTE-224: Efficacy Results
The Applicant’s Position:
The ORR, which is reasonably likely to predict clinical benefit, was encouraging for this patient population, and median DOR was not reached at the primary analysis; with further follow-up the median DOR was 21 months. These results are favorable in this second-line advanced HCC population and are described in detail below.

3.2.2.1 Primary Endpoints
- The ORR per RECIST 1.1 per blinded independent central review (BICR) was 17.3% (n = 18; 95% confidence interval [CI], 10.6, 26.0). Of the 18 responders, 1 had a CR and 17 had a PR.
- The ORR was consistent across demographic groups, HCC etiologies, and other predetermined sub-groups, including participants who discontinued sorafenib due to intolerance versus disease progression [Figure 1].
3.2.2.2 Secondary Endpoints

- Median DOR was not reached. The range for response duration at the time of data cutoff was 3.1 to 14.6+ months, where "+" indicates there was no progressive disease by the time of last disease assessment. Response duration ≥6 months and ≥12 months (by Kaplan-Meier [KM] estimation) was 94% and 61%, respectively [Table 2]. Observed duration of response at ≥6 months and ≥12 months was 89% and 56%, respectively [19].
- OS, PFS, and time to response results are presented in [Table 2].
Table 2  KEYNOTE-224: Secondary Efficacy Outcomes (ASaT Population)

<table>
<thead>
<tr>
<th>Time to Response and Duration of Response</th>
<th>Pembrolizumab (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants with Response†</td>
<td>18</td>
</tr>
<tr>
<td>Time to Response (months)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.8 (1.1)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.1 (1.5 – 4.8)</td>
</tr>
<tr>
<td>Response Duration (months)‡</td>
<td></td>
</tr>
<tr>
<td>Median (range)§</td>
<td>Not Reached (3.1 – 14.6+)</td>
</tr>
<tr>
<td>Number (%‡) of Participants with Extended Response Duration</td>
<td></td>
</tr>
<tr>
<td>≥6 months‡</td>
<td>16 (94.4)</td>
</tr>
<tr>
<td>≥12 months‡</td>
<td>4 (61.4)</td>
</tr>
</tbody>
</table>

**Progression-free Survival**

| Median Progress-Free Survival (Month)§ | 4.9 |
| 95% CI for Median PFS†                | (3.4, 7.2) |
| PFS Rate (95% CI) at 6 months in %‡   | 46.0 (36.1, 55.3) |
| PFS Rate (95% CI) at 12 months in %‡  | 27.5 (19.1, 36.5) |

**Overall Survival**

| Median Survival (Months)†             | 12.9 |
| 95% CI for Median Survival‡           | (9.7, 15.5) |
| OS Rate (95% CI) at 6 months in %‡    | 77.9 (68.6, 84.7) |
| OS Rate (95% CI) at 12 months in %‡   | 53.8 (43.8, 62.8) |

ASaT=All-Subjects-as Treated; CI=confidence interval; OS=overall survival; PFS=progression-free survival; SD=standard deviation
† Analysis on time to response and response duration are based on subjects with a best overall response as confirmed complete response or partial response only.
‡ From product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 13-FEB-2018.
Source: [P224V01MK3475: adam-adsl; adtte].

3.2.2.3 Long-term Follow-up Results for KEYNOTE-224

Long-term follow-up results (data cutoff 05-JUN-2019) that provided at least 24 months of follow-up from the beginning of response for all responders, were consistent with the primary analysis results, and re-enforced duration of response data with an additional 16 months of follow-up from the primary analysis [Figure 2, right-hand side]:

- ORR was 18.3% (N = 19; 95% CI: 11.4, 27.1), as assessed by BICR per RECIST 1.1
- Of the 19 responders, 4 had a CR and 15 had a PR. Disease control was achieved by 64 (61.5%) participants
- Median DOR was 21.0 months (range: 3.1 – 28.0+ months) [Table 3]
- Response duration ≥12 months and ≥24 months (by KM estimation) was 77.0% and 43.3% (68% and 21% observed), respectively [Table 3]
Table 3  KEYNOTE-224 Long-term Follow-up: Summary of Response Duration (Confirmed) Based on Central Radiology Assessment per RECIST 1.1 (Responders)

<table>
<thead>
<tr>
<th>Pembrolizumab (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects with Response</td>
</tr>
<tr>
<td><strong>Response Duration</strong></td>
</tr>
<tr>
<td>Median (Range)</td>
</tr>
<tr>
<td>Number (%) of Subjects with Extended Response Duration</td>
</tr>
<tr>
<td>≥12 months</td>
</tr>
<tr>
<td>≥24 months</td>
</tr>
</tbody>
</table>

† From product-limit (Kaplan-Meier) method for censored data.
§ “+” indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 05JUN2019.

Figure 2  KEYNOTE-224: Long-term Follow-up Confirmed Durability of Response Observed at Primary Analysis

Primary Analysis data cutoff: 13-FEB-2018
Long-term Follow-up for DOR data cutoff: 05-JUN-2019
DOR based on RECIST v1.1 by central radiology review in patients who had both pre- and post-treatment image measurements.

3.2.2.4 Landmark Analysis
An exploratory analysis employing landmark methodology was used to estimate OS in responders and non-responders to pembrolizumab therapy based on the long-term follow-up data cutoff 05-JUN-2019. This method involved evaluating OS following a landmark in time (9 weeks) among participants who were alive at 9 weeks and had a 9-week response evaluation. The OS after the first scan was longer for the participants who achieved response at the first scan (median Not Reached) compared with those who did not (median 10.3 months): HR of 0.14 (95% CI: 0.03, 0.56). These data indicate that responses to pembrolizumab are associated with longer overall survival after the response. The limitation of this analysis is that it excludes participants who died or stopped scans before the first response assessment (6 participants); the advantage of the analysis is that it helps to control for ascertainment bias. Although post
hoc and exploratory, this association was also observed in the landmark analysis of the larger, KEYNOTE-240 dataset.

### 3.2.2.5 Pembrolizumab Monotherapy in Untreated HCC: Phase 2 KEYNOTE-224
Following the cohort investigating pembrolizumab in patients previously treated with sorafenib, pembrolizumab was also evaluated in 51 patients with no prior systemic therapy in another single-arm cohort of the KEYNOTE-224 study (Cohort 2, data cutoff 31-JUL-2020). The ORR per RECIST 1.1 per BICR, the primary endpoint of the study, was 16% (n = 8; 95% CI, 7-29). The median DOR by KM estimate was not reached (range, 3-20+) and 70% of responders were estimated to have response durations of ≥12 months (KM estimate). These results were consistent with those of patients previously treated with sorafenib [34].

### 3.2.3 KEYNOTE-224: Efficacy Summary and Conclusions
Second-line patients with HCC still represent a population with high unmet medical need. The results of KEYNOTE-224 demonstrate that pembrolizumab provides a treatment option with a response rate numerically higher than other non-IO therapies in the second line, coupled with prolonged DOR that is not typically seen with non-IO therapies. Further, landmark analyses suggest that response to pembrolizumab is associated with longer OS after the response [35].

The following conclusions are supported:

- In participants treated with pembrolizumab as second-line therapy post-sorafenib:
  - Response rate and DOR are further supported by favorable PFS and OS in the context of historical control data in this disease setting.
  - ORR is associated with OS benefit in landmark analysis [35]
  - Responses are consistent across major demographics and HCC etiologies (viral/nonviral, sorafenib intolerant versus not)
- In participants treated with pembrolizumab monotherapy as first-line treatment, response rates and duration were consistent with response rates and duration seen in participants treated with pembrolizumab as second-line therapy post-sorafenib.

In summary, there remains an unmet need for single agent anti-PD-1 therapy for advanced HCC patients in the second-line setting. Phase 3 second-line trials have all employed anti-angiogenic agents. None of these agents typically provide prolonged durations of response, which is characteristic of IO agents. Despite the availability of new therapy options, pembrolizumab therapy continues to provide a novel mechanism of action for patients with advanced HCC which can yield a prolonged DOR that extends beyond 24 months for some patients [35].
3.2.4 KEYNOTE-224: Post-marketing Requirements and Commitments Based on Accelerated Approval

On 09-NOV-2018, AA was granted for pembrolizumab for the treatment of patients with HCC who had been previously treated with sorafenib (KEYNOTE-224). Subsequently, post-marketing requirement 3492-1 was issued, as detailed in Sec 2.1.2, and KEYNOTE-240 was identified as a confirmatory study (results below).

Also, per post-marketing commitment 3292-2, a final report for KEYNOTE-224 was submitted to the FDA in March 2020. This report included data with the data cutoff of 05-JUN-2019 that provided at least 24 months follow-up from the beginning of response for all responders [Section 3.2.2.3].

After data availability of KEYNOTE-240, confirmatory studies KEYNOTE-394 and LEAP-002 were agreed upon by the FDA as potential alternative confirmatory studies. Both studies are fully enrolled (see Table 5 for study design details).

As outlined in the FDA Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014, a confirmatory trial would evaluate a clinical endpoint that directly measures clinical benefit, and in some cases a confirmatory trial may be conducted in a different but related population capable of verifying the predicted clinical benefit. This often occurs in oncology where the AA is granted in later stage disease and the confirmatory trial is in an earlier stage of disease.

3.3 KEYNOTE-240 (Initial Confirmatory Study)

3.3.1 Introduction

KEYNOTE-240 did not show a statistically significant improvement in its dual primary endpoints of PFS and OS. The data from the final analysis of this study have been previously published and a long-term follow-up analysis has been presented. These findings are briefly being presented here to review the data from the study relevant to the current AA. The Sponsor is not seeking to convert AA to full approval on the basis of this study, but instead is briefly presenting the key findings from the study to show that the study does not exclude the possibility of clinical benefit for pembrolizumab in advanced HCC. This study reproduced the ORR and DOR that were the basis for the AA in a larger, randomized, controlled trial in the same patient population, and had safety findings (described below) that were consistent with both KEYNOTE-224 and the established safety profile of pembrolizumab. Overall, the study is supportive of a continued positive risk-benefit assessment for pembrolizumab and maintaining the existing AA as a second-line treatment for advanced HCC.

3.3.2 Efficacy Summary

3.3.2.1 Statistical Methods

KEYNOTE-240 had dual primary endpoints of OS and PFS. OS had 2 interim and 1 final analysis, with the timing driven by the number of OS events [Table 4]. The primary analysis of PFS was performed at the first interim OS analysis as was specified in the protocol. A strong control of
Type I error at 0.025 one-sided level was provided across the OS, PFS and ORR (a secondary endpoint) by the multiplicity strategy specified in the protocol. OS was assigned an initial alpha of 0.023; PFS was assigned an initial alpha of 0.002. The Type I error was controlled at a 0.023 level across the interim and final analyses of OS by the use of the O’Brien-Fleming boundaries. If either OS or PFS were statistically significant, the primary analysis of ORR data locked at the time of IA1 was to be performed. The study was designed to have ~92% power for OS assuming OS HR of 0.65 and ~99% power for PFS assuming PFS HR of 0.6.

<table>
<thead>
<tr>
<th>Analyses</th>
<th>Timing</th>
<th>Primary Purpose of Analysis</th>
<th>p-value at boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>when approximately 183 OS events (67% of expected total OS events) are observed</td>
<td>Primary PFS analysis; 1st interim OS analysis; ORR analysis (if either PFS or OS are statistically significant)</td>
<td>PFS: p=0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS: based on actual number of events at IA1 per O’Brien-Fleming boundary</td>
</tr>
<tr>
<td>IA2</td>
<td>when approximately 232 OS events (85% of expected total OS events)</td>
<td>2nd interim OS analyses</td>
<td>OS: based on actual number of events at IA1 and IA2 per O’Brien-Fleming boundary</td>
</tr>
<tr>
<td>Final Analysis</td>
<td>when approximately 273 OS events are observed</td>
<td>Final OS analysis</td>
<td>OS: based on actual number of events at IA1, IA2, and FA per O’Brien-Fleming boundary P=0.0174</td>
</tr>
</tbody>
</table>

IA1 = interim analysis 1; IA2 = interim analysis 2; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

The data cutoff for the FA of KEYNOTE-240 was 02-JAN-2019; the primary PFS analysis was at the study’s first interim analysis, with a data cutoff date of 26-MAR-2018. Thus, all study results, except the primary PFS analysis, are presented based on the FA cutoff. Additionally, a follow-up analysis was conducted 18 months after the FA (data cutoff 13-JUL-2020) to evaluate long-term treatment effects; OS and PFS results from this analysis are also presented.

### 3.3.2.2 KEYNOTE-240: Disposition, Demographics, and Baseline Characteristics

#### 3.3.2.2.1 Disposition

A total of 588 participants were screened and 413 were randomized in a 2:1 ratio to pembrolizumab (278 participants) or placebo (135 participants) at 155 global study sites. As of 02-JAN-2019 data cutoff, 32 (7.7%) participants remained on treatment (28 [10.1%] and 4 [3.0%] of participants in the pembrolizumab and placebo groups, respectively) and 128 (31.0%) participants were in follow-up (94 [33.8%] and 34 [25.2%] in the pembrolizumab and placebo groups, respectively).

A total of 285 (69.0%) participants discontinued from the trial during follow-up: 184 (66.2%; 180 died, and 4 withdrew consent) participants in the pembrolizumab group and 101 (74.8%; all
due to death) participants in the placebo group. Of the 4 (1.4%) participants in the pembrolizumab group who withdrew consent, 3 died after study discontinuation and their death data were included in the OS analysis.

3.3.2.2 Demographics and Baseline Characteristics
Most participants in both the pembrolizumab and placebo groups were male (81.3% and 83.0%, respectively), white (51.4% and 51.9%, respectively), and non-Hispanic (83.8% and 83.7%, respectively). More than half of the participants were older than 65 years (60.8% and 52.6% of participants in the pembrolizumab and placebo groups, respectively). All participants had been previously treated with sorafenib. Prior treatment with sorafenib had been discontinued in participants in the pembrolizumab and placebo groups due to intolerance (12.9% and 13.3%, respectively) and disease progression (87.1% and 86.7%, respectively). The etiology of underlying liver disease was non-viral for most participants, with 25.9% and 21.5% of participants in the pembrolizumab and placebo groups positive for HBV, respectively, and 15.5% and 15.6% positive for HCV, respectively. Most participants in the pembrolizumab and placebo groups were enrolled in Europe (34.5% and 31.9%, respectively) or Asia ex-Japan (24.1% and 23.0%, respectively). The remaining participants were enrolled from Japan, the US, and “Other” regions, that included the following countries: Argentina, Australia, Canada, Chile, Colombia, Israel, Mexico, Norway, Russian Federation, and Turkey.

3.3.2.3 KEYNOTE-240: Efficacy Results
3.3.2.3.1 Primary Endpoints
Although a numeric improvement of pembrolizumab compared to placebo was observed with respect to the dual primary endpoints of PFS and OS, the p-values required for statistical significance were not met for either endpoint.

Overall Survival
The OS hazard ratio (HR) was 0.781 (95% CI: 0.611, 0.998; p = 0.0238), which did not meet the protocol-specified boundary for statistical significance (p = 0.0174) [Figure 3]. The median OS was 13.9 months (95% CI: 11.6, 16.0) in the pembrolizumab group and 10.6 (95% CI: 8.3, 13.5) in the placebo group; the medians and the increment in median compared to placebo (3.3 months) are also the highest for any randomized second-line therapy in HCC.

The OS rates at 12 and 24 months were 54.9% and 25.1% in the pembrolizumab group, respectively, and 48.1% and 18.2% in the placebo group, respectively, showing a higher percentage of participants with prolonged OS in the pembrolizumab group.

Progression-free Survival
On the 26-MAR-2018 data cutoff date (primary analysis), the PFS HR was 0.775 (95% CI: 0.609, 0.987; p = 0.0186), which did not meet the required protocol-specified p-value boundary for statistical significance (p = 0.002) [Figure 4]. At the FA data cutoff, PFS in the pembrolizumab group showed a clear tail on the KM curve showing that some participants treated with pembrolizumab remained progression-free for at least 2 years. The PFS rates (based on KM
estimates) at 6, 9, 12, and 24 months were 34.7%, 24.5%, 19.4%, and 13.9%, respectively, in the pembrolizumab group, and 22.4%, 13.4%, 6.7%, and 4.3%, respectively, in the placebo group.

3.3.2.3.2 Secondary Endpoints
KEYNOTE-240 secondary endpoint results were consistent with KEYNOTE-224 results, with an ORR in the pembrolizumab group that was almost identical to the ORR in the second-line cohort of KEYNOTE-224. The ORR in KEYNOTE-240 was 18.3% (95% CI: 14.0, 23.4) in the pembrolizumab group and 4.4% (95% CI: 1.6, 9.4) in the placebo group, with a between-treatment difference of 13.8% (95% CI: 7.7, 19.5; nominal p-value = 0.00007). Results of other secondary endpoints were as follows:

- Of the 51 responders in the pembrolizumab group, the percentage of responders with response durations of ≥6 months, ≥9 months, ≥12 months, and ≥18 months (KM estimates) were 75.4%, 58.9%, 51.6%, and 44.7%, respectively; of the 6 responders in the placebo group, the percentage of responders with response durations were 66.7%, 50.0%, 50.0%, and 50.0%, respectively. The percentages for placebo should be interpreted with caution, given the small number of responders (6) in the placebo group.
- The median duration of response (based on KM estimates) was 13.8 months (range: 1.5+ to 23.6+) in the pembrolizumab group, where “+” indicates that there was no progressive disease by the time of the last disease assessment.
- The median TTP (based on KM estimates) was 3.8 months (95% CI: 2.8, 4.4) and 2.8 months (95% CI: 1.6, 2.9) in the pembrolizumab and placebo groups, respectively, with an HR of 0.688 (95% CI: 0.540, 0.877; p = 0.0011).

3.3.2.3.3 Long-term Follow-up Results
KEYNOTE 240 continued after the final analysis; the study conduct and data collection remained the same. KEYNOTE-240 long-term follow-up data (data cutoff 13-JUL-2020) were consistent with the final analysis of KEYNOTE-240 [Figure 3] and [Figure 4]. An additional 68 deaths (24% of the number of deaths at FA) were observed. OS HR was maintained 18 months after the FA, (OS HR = 0.771 [95%CI: 0.617, 0.964]; nominal p = 0.0112), which was encouraging.
Figure 3  KEYNOTE-240 Overall Survival for Final Analysis and Long-Term Follow-up

Final Analysis data cutoff: 02-JAN-2019
Long-term Follow-up data cutoff: 13-JUL-2020

3.3.2.3.4 Landmark Analysis

The exploratory landmark analysis of KEYNOTE-240 (data cut off 02-JAN-2019) FA data showed that the participants who achieved response by the landmarks of 6, 12, and 18 weeks and were alive at the landmark had much longer OS after the landmark than participants who did not achieve a response (HRs 0.37-0.39). This supports the conclusion that response to pembrolizumab may be associated with longer OS after a response in second-line HCC patients [36].
3.3.3 KEYNOTE-240: Efficacy Summary and Conclusions

KEYNOTE-240 results support KEYNOTE-224 findings:

- KEYNOTE-240 reinforced the results seen in KEYNOTE-224 with respect to ORR and DOR. The ORR (18%) was almost identical to the ORR seen in second-line patients in KEYNOTE-224 (17% at the primary analysis, 18% at long-term follow-up).
- The early separation of the OS KM curves and the HR of 0.781 (95% CI: 0.611, 0.998; \( p = 0.0238 \)) was maintained throughout the long-term follow-up of the study. The substantial fraction of participants in the pembrolizumab arm that survive beyond 2-3 years helps provide support for the efficacy of pembrolizumab. The PFS HR of 0.775 (95% CI: 0.609, 0.987) at the primary analysis was also associated with a tail on the KM curve that was especially pronounced with long-term follow-up. Both of these observations support the long-term benefits for some patients receiving pembrolizumab, which is characteristic of IO therapy.

3.3.4 Possible Reasons KEYNOTE-240 Did Not Meet Its Endpoints

Results of the confirmatory study, KEYNOTE-240, were consistent with those of the AA study, KEYNOTE-224, in ORR and DOR, and an observed improvement in OS and PFS.

Several factors may have played a role in explaining why statistical significance was not achieved for OS despite the strong trends that were seen. The key reason is that the magnitude of effect for either OS or PFS assumed in the study design was higher (OS HR=0.65, PFS HR=0.6) than what anti-PD1 therapy in 2L HCC actually delivers. This trial was designed based on results seen in melanoma and lung cancer, since no randomized IO data were available for HCC.

It is also possible that the wide use of anti-cancer therapies (in many cases, more than 1 line of therapy) after discontinuation of the study treatment may have attenuated the overall survival treatment effect. At the time KEYNOTE-240 was designed in 2015, sorafenib was the only approved systemic therapy for HCC in the US, but the treatment landscape changed after the study start.

OS median in the placebo arm was 10.6 months, which is 2.5 to 3 months longer than median OS in the placebo arms of contemporaneous trials. For this reason, the potential impact of post-study therapy and baseline characteristics on the observed OS outcome of this trial was evaluated.

Approximately 42% of participants in the pembrolizumab arm and 47% of participants in the placebo arm received a new oncologic medication after discontinuation from study medication; 10.4% and 6.8% of participants in the placebo and pembrolizumab groups, respectively, received anti-PD-1/PD-L1 agents. At any given time since randomization, the cumulative percentage of participants who received any post-study therapy was higher in the placebo arm than in the pembrolizumab arm. The high use of post-study therapy and the higher cumulative percentage of participants who started post-study therapy in the placebo group may have attenuated the OS treatment effect.
To understand the potential impact of subsequent anticancer therapy use, 2 exploratory post-hoc sensitivity analyses of OS adjusted for use of subsequent anticancer therapy were performed [37] [38]; both analyses produced similarly reduced adjusted OS HRs of 0.67 and 0.68, suggesting that post-study therapy may have impacted the primary OS results. Specifically, the sensitivity analysis of OS adjusted for subsequent anticancer therapy use in both treatment arms using the Inverse-Probability-of-Censoring Weighting (IPCW) model resulted in an HR of 0.67 (95% CI: 0.48, 0.92; nominal 1-sided p = 0.0066, based on the IPCW log-rank test). The sensitivity analysis of OS adjusted for subsequent anticancer therapy use in both treatment arms using the 2-stage analysis without re-censoring resulted in an HR of 0.68 (95% CI: 0.53, 0.86, nominal 1-sided p = 0.0012 based on the stratified log-rank test after adjusting for treatment switch).

Another possible contributing factor was the lower incidence of macrovascular invasion (MVI) in KEYNOTE-240 (12% and 13% in the placebo and pembrolizumab arms) compared to other second-line randomized studies (approximately 30%). Given the poor prognosis of those with MVI, this may partly explain the longer OS observed in the placebo arm compared to historical controls, and may have also attenuated the treatment effect.

In summary, KEYNOTE-240 was powered for an unrealistically high OS treatment effect. Other reasons, including the changing treatment landscape and differences in rates of macrovascular invasion compared with other trials, may have also contributed to the inability of KEYNOTE-240 to meet its OS endpoint.

The FDA’s Position:
Overall, both KEYNOTE-224 and KEYNOTE-240 enrolled patients with HCC with a variety of risk factors although a higher proportion of patients in KEYNOTE-240 had cirrhosis of non-viral etiology. Both trials enrolled patients with Child-Pugh A liver function and approximately three quarters of patients across both trials had BCLC Stage C disease. Black patients were underrepresented in KEYNOTE-224 compared to the US population with HCC [18]; a detailed listing of demographics for KEYNOTE-240 were not included.

The ORR in both studies was modest, although FDA acknowledges the long response duration in a few patients. KEYNOTE-224 that supported the accelerated approval of pembrolizumab primarily enrolled patients that had Child-Pugh A liver function with the majority of patients (72%) having a CP score of A5 and patients with clinically evident ascities, clinically diagnosed hepatic encephalopathy, or esophageal/gastric bleeding within the past 6 months excluded from enrollment. The observed response rate in KEYNOTE-224 was 17% (11, 26) (with 89% of responding patients having a response of 6 months or longer and 56% of patients having responses of 12 months or longer) among 104 patients.

As indicated above, KEYNOTE-240 did not achieve its objectives of demonstrating statistically significant effects on OS or PFS. Importantly, effects observed in one study are considered estimates of a treatment effect in the population, and these effects may or may not be replicated in a subsequent study. It is also important to consider that there are multiple reasons
why a study may not meet the pre-specified endpoint including (1) the treatment is not effective; (2) chance occurrence (e.g., a Type II error); (3) study was underpowered (e.g., the true effect was smaller than anticipated); (4) crossover (e.g., if the endpoint is OS); (5) or other factors (e.g., the statistical assumptions were not valid). FDA considers the post-hoc analyses of OS (IPCW and two-stage analysis) as exploratory and insufficient to demonstrate benefit.

Although KEYNOTE-240 was not successful, FDA acknowledges that it is plausible that the study was negative for a reason other than the treatment not being effective. The nominal p-value for OS was less than two-sided 0.05; however, this was not statistically significant given the pre-specified statistical plan of the study (for context, the p values for PFS and OS above are one-sided). Given the limited use of checkpoint inhibitor therapy as post-progression therapy in KEYNOTE-240, FDA believes it is unlikely that post-progression therapy was the cause of the negative study. Nevertheless, it is plausible that if the study were repeated and designed to detect a smaller difference, that a study might be successful (acknowledging that the expected magnitude of the effect would be modest).

It will be important for the committee to consider whether the totality of the data, including single-arm data in the second-line setting, favor continued marketing in the second-line setting for a patient population who would not receive atezolizumab plus bevacizumab in the first-line setting (this group of patients was not specifically studied in either KEYNOTE-224 or KEYNOTE-240).

The accelerated approval was based on the premise that the effect on ORR and duration of response was reasonably likely to predict benefit and provided for a meaningful advantage in the context of available therapy. With the approval of atezolizumab/bevacizumab, the paradigm for the treatment of HCC has changed and therefore an accelerated approval based on activity post-disease progression may not be current.

4 Safety of Pembrolizumab in HCC

The Applicant’s Position:

More than 40,000 patients have been treated in clinical trials and approximately 370,000 patients worldwide have received pembrolizumab. Adverse events of special interest (AEOSIs) are immune-mediated AEs and infusion-related events that are considered to be identified risks for pembrolizumab and may be life-threatening or fatal. A pre-specified list of preferred terms was developed by the Sponsor to consistently characterize the nature and frequency of each AEOSI across the clinical program, regardless of causality as reported by investigators. Based on this assessment, the types, frequency, and severity of AEOSIs in KEYNOTE-224 and KEYNOTE-240 were generally similar to the established safety profile for pembrolizumab monotherapy. Pembrolizumab treatment was generally tolerable as evidenced by a low rate of discontinuations due to AEOSIs, which were typically manageable with dose interruption and supportive care, including steroid treatment as applicable.
Overall, the safety data in KEYNOTE-224 and KEYNOTE-240 were generally similar to the safety data in other pembrolizumab indications, with an important exception of hepatic events. The risk of hepatic AEs in participants with advanced HCC was acknowledged during study design, and these events were carefully monitored and examined in these studies using the Systematic Sponsor Medical Review of Hepatic Events. The Sponsor defined criteria for hepatic AEs of clinical interest were based on changes from baseline and prespecified cutoffs in laboratory values for ALT, AST, and bilirubin, as well as clinical events including new onset clinically detectable ascites, gastrointestinal bleeding suggestive of portal hypertension, and hepatic encephalopathy. Two Sponsor physicians (the study Oncology Medical Monitor and Safety Physician) reviewed all possible hepatic events and if they were not in agreement with their assessments, the case went to a third reviewer (the lead Clinical Oncologist for the project) for final assessment. In KEYNOTE-240, these reviews were performed prior to unblinding and without the physicians evaluating the events having knowledge of the treatment received.

Using this adjudication process, the Sponsor identified 3 (2.9%) cases of immune-mediated hepatitis in KEYNOTE-224, 10 (3.9%) cases in the KEYNOTE-240 pembrolizumab arm, and no cases in the placebo arm. Although these frequencies are higher than the frequency of immune-mediated hepatitis for other pembrolizumab indications listed in the USPI (0.7%), the hepatitis events in KEYNOTE-224 and KEYNOTE-240 were generally manageable with dose interruption, discontinuation, and corticosteroids. There were no cases of sponsor-assessed viral flare in either study.

KEYNOTE-224
In KEYNOTE-224, 97.1% of participants experienced at least 1 AE; 59.6% experienced AEs that were Grade 3 to 5 in severity; and 40.4% experienced a serious adverse event (SAE). The most commonly reported Grade 3 to 5 AEs (>4%) were aspartate aminotransferase increased (14.4%), alanine aminotransferase increased and ascites (each 6.7%), and anemia and fatigue (each 5.8%). A total of 12 (11.5%) participants had AEs that led to death. The AEs that led to death included events that can occur in patients with advanced HCC (eg, hepatic hemorrhage, sepsis). One death, due to ulcerative esophagitis, was assessed by the investigator to be related to treatment with pembrolizumab. Discontinuation of treatment due to AEs was reported in 22.1% of participants.

In KEYNOTE-224, 14.4% of participants experienced at least 1 AEOSI; these were predominantly low grade, with 3.8% of participants experiencing a Grade 3 to 5 AEOSI. No participant died due to an AEOSI. One AEOSI, adrenal insufficiency, resulted in discontinuation of study treatment in 1 (1.0%) participant. No new indication-specific AEOSIs were identified. KEYNOTE-224 safety data from the long-term follow-up were consistent with interim and updated analyses.

KEYNOTE-240
In KEYNOTE-240, 96.4% of participants in the pembrolizumab group and 90.3% of participants in the placebo group experienced at least 1 AE. A total of 52.7% and 46.3% of participants in the pembrolizumab and placebo groups, respectively, experienced AEs that were Grade 3 to 5 in
severity. A total of 37.3% and 27.6% of participants in the pembrolizumab and placebo groups, respectively, experienced SAEs. A total of 11 participants had AEs that led to death: 7 (2.5%) and 4 (3.0%) in the pembrolizumab and placebo groups, respectively. Like in KEYNOTE-224, the AEs that led to death included events that can occur in patients with advanced HCC (eg, worsening of cirrhosis in the pembrolizumab arm and hepatic failure in the placebo arm). One death (malignant neoplasm progression) in the pembrolizumab arm was considered by the investigator as related to the study medication. Discontinuation of treatment due to AEs was reported in 17.2% and 9.0% of participants in the pembrolizumab and placebo groups, respectively.

In KEYNOTE-240, 18.3% of participants in the pembrolizumab group and 8.2% of participants in the placebo group experienced at least 1 AEOSI; these were predominantly low grade, with 7.2% of participants experiencing a Grade 3 to 5 AEOSI in the pembrolizumab group and 0.7% in the placebo group. No participant died due to an AEOSI. AEOSIs resulted in discontinuation of study treatment in 10 (3.6%) participants in the pembrolizumab group and no participants in the placebo group. No new indication-specific AEOSIs were identified.

**Safety Conclusions**

Overall, the KEYNOTE-224 and KEYNOTE-240 safety results indicate that pembrolizumab treatment of patients with advanced HCC was generally tolerable as evidenced by the low rate of discontinuations due to AEOSIs, which were typically manageable with dose interruption, supportive care, and steroid treatment as applicable.

**The FDA’s Position:**

Because KEYNOTE-240 was a controlled trial, comparisons can be made with respect to the relative or absolute increase in adverse events for pembrolizumab over best supportive care (and these results are applicable to the use of pembrolizumab in the second-line setting that was approved based on the results of KEYNOTE-224).

In KEYNOTE-240, 7.2% of patients experienced a Grade 3 to 4 immune-mediated adverse event versus 0.7% reported on the control arm. As indicated above, the rate of Grade 3 to 4 immune-mediated hepatitis (3.9%) was higher in the pembrolizumab arm compared to the control arm (0 cases).

Although the adverse event profile of checkpoint inhibitors is well established, immune-mediated adverse reactions can occur at any time after initiating treatment with a PD-1 blocking antibody. Such serious adverse reactions (including deaths) should not be discounted, especially in a population where a limited number of patients may be benefiting.
5 Other Significant Issues Pertinent to Clinical Conclusions on Efficacy and Safety

The Applicant’s Position:

5.1 Alternative Confirmatory Studies

Pembrolizumab still has a crucial role to play in the treatment of hepatocellular carcinoma despite the rapidly changing landscape. As our program has matured, our trial designs have taken into account learnings from prior studies. Both KEYNOTE-394 and LEAP-002 are more appropriately powered. Pembrolizumab has shown activity in patients with advanced HCC and it is anticipated that the ongoing studies will provide confirmatory data.

The Sponsor is committed to meeting the needs of patients with HCC by conducting several pembrolizumab Phase 3 global trials across multiple patient populations [Table 5]. As previously agreed upon with the FDA, at least 2 of these studies (KEYNOTE-394 and LEAP-002) could serve the regulatory role as alternative confirmatory studies in the treatment of patients with HCC. A pre-sBLA meeting was held with the FDA on 29-MAY-2019, per the minutes from that meeting:

“FDA stated that they would require submission of the KEYNOTE-240 data with an sBLA based primarily on the KEYNOTE-394 or LEAP-002 study results seeking to fulfill PMR #3492-1 and support regular approval.”

Pembrolizumab is necessary as an option for patients and clinicians because it may provide responses lasting for years, and because of a different safety profile compared with anti-angiogenic agents and current anti-PD-1/CTLA-4 combinations.

5.1.1 KEYNOTE-394

KEYNOTE-394 is a fully enrolled ongoing Phase 3 study of pembrolizumab plus BSC versus placebo plus BSC in 453 participants with previously treated HCC; data readout is expected by June 2021 [Figure 5]. This trial is similar in design to KEYNOTE-240, except that participants are from East Asia. Additionally, this trial was designed with a larger sample size and a higher assumed OS HR in order to capture treatment benefit in this patient population. Like KEYNOTE-240, this trial includes participants who are second line, Child-Pugh A, and Barcelona Clinic Liver Cancer (BCLC) stage B or C. This trial did allow for the use of oxaliplatin-based chemotherapy, as this is an approved option in parts of Asia. As the trial is fully enrolled, the composition of the study population can be compared to KEYNOTE-224 and KEYNOTE-240. Two key differences are a higher proportion of HBV positive patients (79.2% of participants are HBV active positive) in KEYNOTE-394 and less than 10% of participants having received oxaliplatin-based chemotherapy. Despite these differences, the responses to pembrolizumab have been similar in patients with different etiologies of liver disease in past studies. Also, the overall care patterns are generally similar to those in KEYNOTE-224. For these reasons, this trial is a potential confirmatory study, as has been agreed upon by the FDA.
5.1.2 LEAP-002

LEAP-002 is a fully enrolled Phase 3 study of lenvatinib plus pembrolizumab versus lenvatinib plus placebo as first-line therapy in 794 participants with advanced HCC. Data readout is expected in 2022 with potential interim analyses reading out sooner. The study design for this trial was discussed with the FDA and the FDA’s advice was used to finalize the design [Figure 6]. The target treatment benefit for this trial has been optimized taking into consideration activity of IO agents in HCC and availability of multiple post-study therapeutic options. Per FDA guidance, confirmatory trials may be in a different, but related disease setting than the original AA study. This study has been agreed upon with the FDA as a potential confirmatory trial for KEYNOTE-224.

In KEYNOTE-524, the lenvatinib plus pembrolizumab combination showed promising preliminary efficacy in 1L HCC patients in a single-arm setting, providing optimism for the outcome in LEAP-002. Per assessment by independent imaging review, at data cutoff (31-OCT-2019) confirmed ORR was 36.0% (95% CI, 26.6% to 46.2%) per RECIST v1.1 and median DOR was 12.6 months (95% CI, 6.9 months to NE) per RECIST v1.1 [Figure 7] [26]. In LEAP-002, pembrolizumab would be added to an existing standard of care, lenvatinib, in first-line HCC, therefore demonstrating the contribution of pembrolizumab.

The FDA’s Position:

In the second-line setting after sorafenib, pembrolizumab showed modest but durable responses. Although response rates observed in Studies KEYNOTE-224 and KEYNOTE-240 were similar, in KEYNOTE-240 the higher response rate for pembrolizumab (versus placebo) did not translate into a statistically significant effect on survival.

Randomized studies with PD-1 inhibitors used as monotherapy in the second-line setting (pembrolizumab) or first-line setting (nivolumab) did not confirm clinical benefit predicted based on the single arm studies showing modest activity in the second-line after progression on sorafenib.

Evidence from Study IMbrave150 showed that the combination of an immune checkpoint inhibitor (atezolizumab) with a VEGF-targeting agent (bevacizumab) improves overall survival when compared to sorafenib. As can be seen on a search of clinicaltrials.gov, other Phase 3 trials of combination checkpoint inhibitors are ongoing in the first-line setting which may further change the treatment landscape of HCC. LEAP-002, a study of pembrolizumab in combination with lenvatinib, if successful, would be one such study.

If continued marketing of pembrolizumab will be authorized, Merck is proposing two studies, KEYNOTE-394 and LEAP-002, to verify and describe the effect of pembrolizumab in the second-line setting.

KEYNOTE-394 is being investigated in a setting similar to KEYNOTE-240; however, the study is being conducted solely in Asia. A review issue therefore will be whether the results of the study
are applicable to the US population, given differences in etiology of HCC and possible
differences in underlying liver function in the two populations. As Merck indicated, top-line
data analysis is estimated to occur shortly after the advisory committee meeting.
LEAP-002 will isolate the effect of pembrolizumab when combined with lenvatinib; however,
the results may leave some uncertainty as to the benefits of pembrolizumab as monotherapy in
the second-line setting. As Merck indicated, top-line data analysis is expected to occur in 2022.

6 Points for the Advisory Committee to Consider

The Applicant’s Position:

Unmet Need

Patients with advanced HCC have poor survival rates and few effective and tolerable
therapeutic options. Anti-angiogenic TKIs remain an important and relevant option for first-line
therapy in patients with advanced HCC, particularly those who are not appropriate candidates
for bevacizumab and atezolizumab. However, almost all patients eventually experience
progressive disease after TKI treatment.

It is important to note that the only second-line HCC therapies with full approval are anti-
angiogenic agents. For patients who cannot receive an anti-angiogenic agent, immunotherapy
offers important options. Combination anti-PD-1/CTLA-4 therapy after a TKI is one option, but
can have a high percentage of serious adverse reactions, with 59% serious adverse reactions
reported for ipilimumab/nivolumab and the majority of patients requiring steroids [29],
rendering this therapy unsuitable for many patients.

For a subset of patients, single-agent immune-checkpoint inhibitors can offer compelling
response rates, durations of response, and a different safety profile than anti-angiogenic agents
(see Section 4) [28]. After treatment with sorafenib, PD-1 inhibitors are recommended options
for many patients, due to compelling ORR, and prolonged DORs (see Section 2.2.2). They are
particularly useful for patients who cannot receive bevacizumab and atezolizumab in first line,
or anti-angiogenic agents in second line. Single agent PD-1 inhibitors are currently being used as
second-line treatment in clinical practice for many patients. The AA of pembrolizumab based on
KEYNOTE-224 continues to address a significant unmet medical need in patients with advanced
HCC and should be allowed to remain as confirmatory studies read out soon.

Accelerated Approval Based on KEYNOTE-224

In the KEYNOTE-224 AA study, pembrolizumab demonstrated an ORR of 17% in patients with
HCC who had been previously treated with sorafenib. Of the patients who responded to
treatment with pembrolizumab, more than half had a duration of response of over a year. This
prolonged duration of response is a hallmark of IO therapies. The durability of response has
been supported by the long-term follow-up data from KEYNOTE-224 (with data cutoff
≥24 months from the start of the last response) with response duration ≥12 months of 77.0%
(KM estimate) and 68% (observed).

Efficacy: Strong Positive Trend of KEYNOTE-240
Efficacy results (ie, ORR, DOR) of the confirmatory study, KEYNOTE-240, were consistent with those seen in KEYNOTE-224. Strong trends were observed with improvements in OS and PFS, which did not reach pre-specified parameters for statistical significance for primary endpoints. Long-term follow-up showed that the OS HR at final analysis (0.781; 95% CI: 0.611, 0.998; \( p = 0.0238 \)) was maintained after an additional 18 months of follow-up (0.771; 95% CI: 0.617, 0.964; nominal \( p \)-value = 0.0112). The median OS in the pembrolizumab arm was 13.9 months (95% CI: 11.6, 16.0) and in the placebo arm was 10.6 months (95% CI: 8.3, 13.5), a 3.3-month difference. PFS HR was 0.775 (95% CI: 0.609, 0.987; \( p=0.0186 \)) at the primary analysis and 0.703 (95% CI: 0.559, 0.885; nominal \( p \)-value = 0.0011) at the long-term follow-up analysis.

**Safety**

Overall, the KEYNOTE-224 and KEYNOTE-240 safety results indicate that pembrolizumab treatment of patients with advanced HCC was generally tolerable, as evidenced by the low rate of discontinuations due to AEOSIs, which were typically manageable with dose interruption, supportive care, and steroid treatment as applicable.

**Alternative Confirmatory Trials**

KEYNOTE-394 and LEAP-002 are 2 of several studies that the Sponsor is conducting in patients with HCC. Both studies have been agreed upon with the FDA as potential confirmatory studies for AA. Study design details for each of these are provided in [Table 5] and study design figures are presented in [Figure 5] and [Figure 6], respectively. Both studies are fully enrolled, with data readout expected by May 2022. KEYNOTE-394 was designed with a larger sample size than KEYNOTE-240 and higher assumed OS HR, which should capture treatment benefit in this patient population. In LEAP-002, lenvatinib plus pembrolizumab versus lenvatinib plus placebo is being evaluated. The target treatment benefit for this trial has been optimized, taking into consideration IO agents in HCC and availability of multiple post-study therapeutic options.

KEYNOTE-394 and LEAP-002 are well powered and appropriate confirmatory studies. KEYNOTE-394 has an estimated completion date in June 2021 and LEAP-002 has an estimated completion date in May 2022, as well as interim analyses. As a result, it is reasonable to maintain the AA for pembrolizumab for the short duration remaining until these studies are completed.

**Benefit/Risk**

The totality of evidence from KEYNOTE-224 and KEYNOTE-240 suggests a favorable benefit/risk profile for patients with advanced HCC who have been previously treated with sorafenib. The alternative confirmatory studies will read out soon.

**The FDA’s Position:**

Accelerated approval is an expedited program that provides an approval pathway for drugs and biologics that treat serious and life-threatening conditions based on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality and demonstrates that the drug or biologic provides meaningful advantage over available therapies. This program is intended to provide early access to therapies for patients with limited therapeutic options; however, given
the uncertainty in the use of an early clinical endpoint to predict a meaningful clinical benefit, drugs granted accelerated approval may be required to be studied in post-approval trials to confirm this benefit.

Pembrolizumab received accelerated approval in the second-line setting based on a modest response rate of 17% in a single arm trial with a few patients experiencing prolonged duration of response. KEYNOTE-240, the randomized controlled trial designed to verify and describe the effect of pembrolizumab in HCC did not confirm clinical benefit. Therefore, if the indication is maintained, additional data will be necessary to verify and describe the benefit of pembrolizumab in HCC.

The FDA is seeking the committee’s advice on next steps including whether the post-sorafenib indication should remain on the market while additional trial(s) are conducted.

The committee is also asked to consider that the landscape of HCC has changed following the approval of atezolizumab and bevacizumab in the first-line setting. The approval of atezolizumab and bevacizumab established a new standard of care for the systemic treatment of most patients with HCC; although some patients may be deferred from receiving this regimen (e.g., those at risk of severe bleeding). Although some patients may be deferred from receiving this regimen, KEYNOTE-224 did not specifically study these patients (e.g., those at high risk of bleeding).

7 Draft Topics for Discussion by the Advisory Committee

1. Should the indication for the second-line (post sorafenib) treatment of hepatocellular carcinoma be maintained pending final results of ongoing studies?

2. Are any of the Applicant’s proposed alternative trials appropriate to confirm clinical benefit in patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib?
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9     Appendix
9.1   Tables and Figures
Table 5  Clinical Development Program for Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Design</th>
<th>Population</th>
<th>Dosage Regimen</th>
<th>Primary Efficacy Endpoint(s)</th>
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</thead>
<tbody>
<tr>
<td>KEYNOTE-224</td>
<td>Phase 2, worldwide, open-label study of pembrolizumab 200 mg Q3W</td>
<td>Cohort 1: Participants with HCC with documented objective radiographic progression after discontinuing treatment with sorafenib (or intolerance to sorafenib)</td>
<td>200 mg IV Q3W pembrolizumab for all participants enrolled</td>
<td>ORR by RECIST v1.1</td>
</tr>
<tr>
<td>Ongoing</td>
<td></td>
<td>Cohort 1: 104 participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cohort 1 Final Analysis a</td>
<td>Cohort 2: Participants with advanced HCC without any prior systemic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data cutoff: 13-FEB-2018</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Cohort 2 Final Analysis b</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Data cutoff: 05-JUN-2019</td>
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<td>Planned Data cutoff Q1 2021</td>
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<td></td>
<td></td>
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<tr>
<td>KEYNOTE-240</td>
<td>Phase 3, worldwide, randomized, double-blind study of pembrolizumab 200 mg Q3W plus BSC vs. placebo plus BSC</td>
<td>Participants with HCC with documented objective radiographic progression after discontinuing treatment with sorafenib (or intolerance to sorafenib)</td>
<td>Arm 1: pembrolizumab IV 200 mg Q3W plus BSC</td>
<td>OS and PFS</td>
</tr>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td>Arm 2: placebo IV plus BSC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enrollment complete</td>
<td></td>
<td>2:1 randomization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Final Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data cutoff: 02-JAN-2019</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>KEYNOTE-394</td>
<td>Phase 3, Asia Pacific, randomized, double-blind study of pembrolizumab 200 mg Q3W plus BSC vs. placebo plus BSC</td>
<td>Asian participants with previously treated HCC with objective radiographic disease progression on or after discontinuing treatment with sorafenib- or oxaliplatin-based chemotherapy (progression or intolerance)</td>
<td>Arm 1: pembrolizumab IV 200 mg Q3W plus BSC</td>
<td>OS</td>
</tr>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td>Arm 2: placebo IV plus BSC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enrollment complete</td>
<td></td>
<td>2:1 randomization</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Number/Status</td>
<td>Design</td>
<td>Population</td>
<td>Dosage Regimen</td>
<td>Primary Efficacy Endpoint(s)</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td><strong>KEYNOTE-524 (E7080-J081-116)</strong></td>
<td>Phase 1b, open-label study of lenvatinib 12 mg or 8 mg QD in combination with pembrolizumab 200 mg IV Q3W as 1L therapy for advanced HCC</td>
<td>Participants with advanced HCC without any prior systemic therapy</td>
<td>Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW &lt;60 kg) orally QD plus pembrolizumab 200 mg IV Q3W</td>
<td>ORR by RECIST v1.1 and mRECIST</td>
</tr>
<tr>
<td>Ongoing</td>
<td></td>
<td>104 participants (100 first-line HCC participants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrollment complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data cutoff: 31-OCT-2019</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>LEAP-002</strong></td>
<td>Phase 3, multicenter, randomized, double-blind, active-controlled study of lenvatinib 12 mg or 8 mg QD plus pembrolizumab 200 mg IV Q3W or lenvatinib 12 mg or 8 mg QD plus placebo in 1L therapy for advanced HCC</td>
<td>Participants with advanced HCC without any prior systemic therapy</td>
<td>Arm A: lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW &lt;60 kg) orally QD plus pembrolizumab 200 mg IV Q3W</td>
<td>OS and PFS</td>
</tr>
<tr>
<td>Ongoing</td>
<td></td>
<td>794 participants</td>
<td>Arm B: lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW &lt;60 kg) orally QD plus placebo (normal saline) IV Q3W</td>
<td></td>
</tr>
<tr>
<td>Enrollment complete</td>
<td></td>
<td></td>
<td>1:1 randomization</td>
<td></td>
</tr>
<tr>
<td><strong>KEYNOTE-937</strong></td>
<td>Phase 3, multicenter, double-blind, 2-arm, pembrolizumab versus placebo as adjuvant therapy in participants with HCC</td>
<td>Participants with complete radiological response after surgical resection of Stage IB, II, and III HCC with adaptations based on tumor characteristics as established by the pathology report or complete radiological response after local ablation</td>
<td>Arm 1: pembrolizumab 200 mg IV on Day 1 Q3W, up to 17 administrations (approximately 1 year)</td>
<td>RFS and OS</td>
</tr>
<tr>
<td>Ongoing</td>
<td></td>
<td>950 participants planned</td>
<td>Arm 2: placebo (saline) IV on Day 1 Q3W, up to 17 administrations (approximately 1 year)</td>
<td></td>
</tr>
<tr>
<td>Enrolling</td>
<td></td>
<td></td>
<td>1:1 randomization</td>
<td></td>
</tr>
<tr>
<td>Study Number Status</td>
<td>Design</td>
<td>Population</td>
<td>Dosage Regimen</td>
<td>Primary Efficacy Endpoint(s)</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------</td>
<td>------------</td>
<td>----------------</td>
<td>----------------------------</td>
</tr>
</tbody>
</table>
| **LEAP-012**  
Ongoing Enrolling | Phase 3, multicenter, double-blind, active-controlled study of lenvatinib 12 mg or 8 mg QD with pembrolizumab 400 mg in combination with TACE versus TACE in participants with incurable/non-metastatic HCC  
950 participants planned | Participants with incurable/non-metastatic HCC | Arm A: lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally QD plus pembrolizumab 400 mg IV Q6W plus TACE intra-arterial  
Arm B: Placebo (saline) IV Q6W plus oral placebo orally QD plus TACE intra-arterial  
1:1 randomization | PFS and OS |
| **MK-1308A-004**  
Estimated study start date Q1 2021 | Phase 2 multicenter, single-arm study of the fixed dose MK-1308A coformulated product (25 mg MK-1308 plus 400 mg pembrolizumab) plus lenvatinib 12 mg or 8 mg QD  
Safety Lead-in Phase: 6 to 20 participants planned  
Efficacy Expansion Phase: 100 to 104 participants planned  
**Total:** 110 participants planned | Participants with advanced HCC without any prior systemic therapy | MK-1308A 25 mg/400 mg IV Q6W plus lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally QD | ORR by RECIST v1.1 |

1L=first-line; BSC=best supportive care; BW=body weight; HCC=hepatocellular carcinoma; IV=intravenous; mRECIST=Modified Response Evaluation Criteria in Solid Tumors; ORR=objective response rate; OS=overall survival; PFS=progression free survival; Q3W=every 3 weeks; Q6W=every 6 weeks; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RFS=recurrence free survival; TACE=transarterial chemoembolization.

* Final analysis was per FDA request (post-marketing commitment 3292-2) to provide at least 24 months follow-up from the beginning of response for all responders.

b Cohort 2 data were presented at ASCO GI 2021.
### Table 6  
**KEYNOTE-224 and KEYNOTE-240 Summary of Adverse Events (ASaT Population)**

<table>
<thead>
<tr>
<th></th>
<th>KEYNOTE-224*</th>
<th>KEYNOTE-240**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembrolizumab (N=104)</td>
<td>Pembrolizumab (N=279)</td>
</tr>
<tr>
<td>≥1 all cause</td>
<td>101 (97.1)</td>
<td>269 (96.4)</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>62 (59.6)</td>
<td>147 (52.7)</td>
</tr>
<tr>
<td>SAE</td>
<td>42 (40.4)</td>
<td>104 (37.3)</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>23 (22.1)</td>
<td>48 (17.2)</td>
</tr>
<tr>
<td>Led to death</td>
<td>12 (11.5)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td><strong>Immune-mediated</strong></td>
<td>15 (14.4)</td>
<td>51 (18.3)</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>4 (3.8)</td>
<td>20 (7.2)</td>
</tr>
<tr>
<td>SAE</td>
<td>4 (3.8)</td>
<td>16 (5.7)</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>1 (1.0)</td>
<td>10 (3.6)</td>
</tr>
</tbody>
</table>

AE=adverse event; ASaT=All-Subjects-as-Treated; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event

*No grade 5 immune-mediated AEs reported

b1 participant in KEYNOTE-224 and 5 participants in KEYNOTE-240 discontinued due to immune-mediated hepatitis.

Grades are based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Non-serious AEs up to 30 days of last dose and SAEs up to 90 days of last dose are included.

*Data cutoff for KEYNOTE-224: 13-FEB-2018; MedDRA v20.1 preferred terms “Neoplasm progression”, “Malignant neoplasm progression”, and “Disease progression” not related to the drug are excluded.

**Data cutoff for KEYNOTE-240: 02-JAN-2019; MedDRA v21.1 preferred terms “Neoplasm progression”, “Malignant neoplasm progression”, and “Disease progression” not related to the drug are excluded.
Figure 5  KEYNOTE-394 Trial Design

Eligible patients:
- Confirmed diagnosis of HCC
- Progression/intolerance to Sorafenib/OXA-based chemo
- Measurable disease per RECIST 1.1 by investigator
- ECOG PS 0–1
- Child-Pugh Class A

Stratification factors:
- Prior treatment (sorafenib vs chemotherapy)
- Macrovascular invasion: (yes vs no)
- Etiology (HBV vs others (HCV, non-infected))

Patient allocation:
- ~80% from China
- ~20% from other Asian countries/areas

Primary endpoint:
- OS

Secondary endpoints:
- PFS, ORR, DOR, DCR and TTP per RECIST 1.1 by BICR
- Safety and tolerability

Follow-up (efficacy and safety)
- FPI: 31 May 2017
- LPI: 11 Dec 2019
- Anticipated FA: 2021

Figure 6  LEAP-002 Trial Design

Key eligibility:
- HCC (histologically, cytologically, or radiographically)
- No prior systemic therapy
- Not amenable to curative therapy
- Child-Pugh Class A
- ECOG PS 0 or 1

Stratification factors:
- Asia without Japan vs Japan + non-Asia
- Macroscopic portal vein invasion or extrahepatic spread vs none
- AFP ≤400 ng/mL vs >400 ng/mL
- ECOG 0 vs ECOG 1

Arm A
- Lenvatinib (8 or 12 mg/day) PO QD + Pembrolizumab 200 mg IV Q3W

Arm B
- Lenvatinib (8 or 12 mg/day) PO QD + Placebo (saline) IV Q3W

Treatment discontinuation:
- Treat until PD or toxicity
- Pembrolizumab/Placebo stopped after 35 infusions
- Lenvatinib may continue until PD or toxicity

Post-treatment follow-up:
- Safety assessment
- Disease assessment
- Survival status

FPI: 10 Jan 2019
LPI: 28 Apr 2020
Anticipated FA: 2022

N=450
R 2:1
Imaging assessment Q6W

R 1:1
Figure 7  KEYNOTE 524: Confirmed ORR (RECIST v1.1)

Percentage change in sum of diameters of target lesions at postbaseline nadir (IIR)

^ Number of patients with both baseline and postbaseline values for the sum of diameters of target lesions.
9.2 IQVIA Open Claims Methodology for HCC

Study Design
This study is a retrospective cohort study using the Oncology Longitudinal Prescription and Medical Claims data from IQVIA. Patients who were diagnosed with hepatocellular carcinoma (HCC) and initiated first systemic anticancer therapy after the HCC diagnosis were included. The study evaluated data from January 2016 to November 2020. For the purpose of this document, analyses were performed from June 2020 to November 2020.

Data Sources
IQVIA claims is a large non-payer-owned integrated open claims database of commercial insurers as well as Medicare-eligible retirees with Medicare Supplemental plans. This data source includes administrative claims data that are collected for billing purposes, organized by bill for service. Data come from Office Based Medical Claims Data (office-based physicians, hospitals, skilled nursing facilities and home health sites) and Prescription Data (retail, mail order and specialty pharmacies providers).

Cohort Selection Criteria
Patients who were diagnosed with HCC were identified by the following criteria:
- **HCC Diagnosis** – Adult patients with one of the ICD codes for HCC: 155.0, 155.2, C22.0, C22.7, C22.8, C22.9
- **At least one systemic therapy used for HCC**

Line of Therapy Rules
Each patient's treatment is aligned longitudinally in the order of administration and the following rules are applied. Patients will be indexed on their earliest market treatment (infused) or market Rx (Oral) within the selection period. The first systemic anticancer therapy a patient received after the date of HCC diagnosis was defined as their 1L therapy.

- **Cycle Build**
  - Gap in administration dates of >=4 days will advance a cycle
  - Every new oral prescription for a product that a patient is already being treated with is considered a new cycle

- **Line Build**
  Lines of Therapy are based on regimen duration and gap between regimen. Using the patient’s treatments of interest starting from the beginning of the treatment look-back period, each patient’s regimens and line of therapy is built. All the treated information for the diagnosed patients is used to build the lines. If a claim is sourced from a provider/pharmacy that is not stable, the line build will continue; however, that claim will not be projectable since projections are only based on stable sample.

- **Line Advancement**
  Once the cycles are built, they are tracked, and lines are built and advanced based on the following rules.
  - If gap between lines >= 120 days, then line is advanced
  - OR if a new product is added after the first 28 days and 2 cycles then the line is advanced. [Note: removal of a drug or continuation of the same set of drugs will not require a line advancement]
Additionally, Oral products that are considered clinically incompatible will cause line advancement through switch to the new oral product.

Schematic showing line of therapy rule (example):

Active Line in a reporting period
A line is considered active in a reporting period if there is at least one administration or prescription dispensed in the reporting period. For example, in a month if patient’s first line ends and second line begins then both the lines are considered active in the month.

Line selection within reporting period
For reporting patient level metrics only one line can be chosen for each reporting period. For each reporting period the earliest active line is selected for reporting.

Line Status – line status will be reported if the patient is new to line or continuing on line.
- New to line – the patient will be reported as new to line in the month of their regimen line start date.
- Continuing on line – the patient will be reported as continuing on line in all subsequent months through their regimen line end date.

For the purpose of this report, regimens were classified into the following categories:
- For first line treatment, TKI monotherapy was defined as sorafenib monotherapy or lenvatinib monotherapy, i.e., the FDA-approved TKI therapies in first line treatment of advanced HCC.

- For second line treatment, PD-1 inhibitor-based therapy was defined as pembrolizumab monotherapy, nivolumab monotherapy, or nivolumab in combination with ipilimumab, i.e., the approved PD-1 inhibitor-based regimens in 2L setting for advanced HCC

- Other therapy was defined as any regimen that was not classified in the above categories.

Reporting Regimens – based upon the products contained in the patient’s regimen, the regimens will be defined into the following groups in order of priority:
<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYTRUDA MONO</td>
<td>KEYTRUDA Monotherapy</td>
<td>1</td>
</tr>
<tr>
<td>KEYTRUDA COMBOS</td>
<td>KEYTRUDA-based</td>
<td>2</td>
</tr>
<tr>
<td>Opdivo Mono</td>
<td>Opdivo Monotherapy</td>
<td>3</td>
</tr>
<tr>
<td>Opdivo+Yervoy</td>
<td>Opdivo AND Yervoy-based</td>
<td>4</td>
</tr>
<tr>
<td>Opdivo Combos</td>
<td>Opdivo-based</td>
<td>5</td>
</tr>
<tr>
<td>Yervoy</td>
<td>Yervoy-based</td>
<td>6</td>
</tr>
<tr>
<td>Avastin/Tecentriq</td>
<td>Avastin AND Tecentriq-based</td>
<td>7</td>
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<tr>
<td>Tecentriq</td>
<td>Tecentriq-based</td>
<td>8</td>
</tr>
<tr>
<td>Avastin</td>
<td>Avastin-based</td>
<td>9</td>
</tr>
<tr>
<td>Lenvima Mono</td>
<td>Lenvima Monotherapy</td>
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<tr>
<td>Lenvima Combos</td>
<td>Lenvima-based</td>
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<tr>
<td>Nexavar</td>
<td>Nexavar-based</td>
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<tr>
<td>Stivarga</td>
<td>Stivarga-based</td>
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<tr>
<td>Cabometyx</td>
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<td>Cyramza</td>
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<td>Carboplatin</td>
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<tr>
<td>Cisplatin</td>
<td>Cisplatin-based</td>
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</tr>
<tr>
<td>Other Chemo</td>
<td>All Other ONC Regimens</td>
<td>18</td>
</tr>
</tbody>
</table>

**Treatment Projections**

Stability and eligibility rules are applied to the open data sources in order to maximize the breadth and depth of the claims data, accuracy of the longitudinal metrics created in the study, and minimize the risk of anomalous results due to variability.

Nationally projected data for all the treatments were generated based on treatment data from a set of longitudinally stable patients. The methods utilized for projections are described below:

- For the IV products, the National Sales Perspective (NSP) universe [3 month rolling averages] for the individual product was utilized as the benchmark. Total dose was converted from the NSP units for each product in each month and are compared to the total dose per product from the medical claims data. If the trends appeared to vary, adjustments were then made to the projected data against the benchmark.

- For the oral prescription products, the National Prescription Audit (NPA)/NSP universe is utilized as the benchmark after excluding any Long-Term Care prescriptions. The longitudinal Rx counts per product per month are bench marked against the NPA/NSP universe as described.
Limitations

- These data contain the same limitations as many claims database analysis
  - Claims are used for insurance reimbursement and thus do not include clinical details to define the exact population (BCLC stage, lab scores, and Child Pugh score are not captured)
  - Business rules, statistical modeling and/or additional data sources are used to derive or predict patient clinical details
  - Though relatively minor, coding inconsistencies and errors are found in the raw data. Stability and eligibility rules are applied
- Diagnosis of HCC was determined by ICD codes and thus unconfirmed by medical records
- Line of therapy was based on a regimen-based algorithm, not disease progression
- Statistical projection is used to estimate total patient volume as explained above