BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	351(a)
Application Number(s)	sBLA125554 S-132 sBLA 125377 S-135
Priority or Standard	Priority
Submit Date(s)	December 23, 2025
Received Date(s)	December 23, 2025
PDUFA Goal Date	June 23, 2025
Division/Office	OOD/DO3
Review Completion Date	Refer to electronic stamp date
Established Name	Nivolumab and ipilimumab
Trade Name	OPDIVO and YERVOY
Pharmacologic Class	Programmed death-1 (PD-1) receptor blocking antibody (nivolumab) and Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA4) receptor blocking antibody (ipilimumab)
Applicant	Bristol-Myers Squibb Company
Formulation(s)	Nivolumab: Single vial solution of 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), and 240 mg/24 mL (10 mg/mL) Ipilimumab: Single vial solution of 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL)

Dosing Regimen	• Patients 12 years of age and older weighing 40 kg or more
	  ○ 240 mg every 2 weeks, or
	  ○ 480 mg every 4 weeks
	• Patients <12 years of age or weight <40 kg
	  ○ 3 mg/kg every 2 weeks

Applicant Proposed Indication(s)/Population(s)	• Nivolumab, in combination with ipilimumab, is indicated for the first-line treatment of adult and pediatric patients 12 years and older with unresectable or metastatic

	microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) (b) (4) • Nivolumab, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) (b) (4) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	• Nivolumab, in combination with ipilimumab, is indicated for the first-line treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC). • Nivolumab, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

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OPQ=Office of Pharmaceutical Quality

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OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DMPP= Division of Medical Policy Programs

Glossary

Term	Definition	Term	Definition
1L, 2L, 3L	first-line, second-line, third-line, respectively	MedDRA	Medical Dictionary for Regulatory Activities
ADA	antidrug antibody	Min	Minimum
AE	adverse event	MMR	mismatch repair (of DNA)
ALT	alanine aminotransferase	mOS	Median overall survival
AST	aspartate aminotransferase	mPFS	Median progression free survival
BICR	blinded independent central review	MPM	Malignant pleural mesothelioma
BLA	Biologics License Applications	MRI	magnetic resonance imaging
BMS	Bristol-Myers Squibb	MSI	microsatellite instability
C	Cycle	MSI-H	microsatellite instability high
CDx	companion diagnostics	MSI-H/dMMR	microsatellite instability high or deficient mismatch repair
CFR	Code of Federal Regulations	NA	not available
chemo	chemotherapy	NCCN	National Comprehensive Cancer Network
Cl	Clearance	NCI	National Cancer Institute
CI	confidence interval	NDA	New drug application
CoC	Contribution of components	NGS	next generation sequencing
COVID-19	coronavirus disease 2019	nivo	nivolumab
CR	Complete response	nivo+ipi	nivolumab plus ipilimumab
CRC	colorectal cancer	NSCLC	Non-small cell lung cancer
CRF	case report form, paper or electronic	NR	not reached
CSP	clinical safety program	OESI	other events of special interest
CSR	clinical study report	ORR	objective response rate
CT	computed tomography	OS	overall survival
CTCAE	Common Terminology Criteria for Adverse Events	PCR	polymerase chain reaction
CTC	Common Toxicity Criteria	PD	Pharmacodynamic
CTLA-4	cytotoxic T-lymphocyte-associated protein-4	PD-1	programmed cell death protein-1
D	Day	PD-L1	programmed cell death ligand-1
DBL	Database lock	PD-L2	programmed cell death ligand-2
DC	discontinuation	PET	positron emission tomography
DCR	disease control rate	PFS	progression-free survival
DMC	data monitoring committee	PFS2	progression-free survival on next line of treatment (time to second progression)
dMMR	deficient mismatch repair	PK	pharmacokinetics
DoR	duration of response	PMR	post-marketing requirement

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Term	Definition	Term	Definition
ECOG PS	Eastern Cooperative Oncology Group performance status	popPK	population pharmacokinetics analysis
eCRF	electronic case report form	PR	partial response
EGFR	epidermal growth factor receptor	PREA	Pediatric Research Equity Act
EMA	European Medicines Agency	PRO	patient-reported outcomes
EORTC	European Organization for Research and Treatment of Cancer	PT	preferred term
E-R	Exposure-response	ipi	ipilimumab
ESCC	Esophageal squamous cell carcinoma	IRB	Institutional Review Board
QXW	every X weeks	QoL	quality of life
QLQ-C30	Quality of Life Questionnaire-Core 30	RAS	Renin-angiotensin-system
EQ-5D-3L	EuroQol Group 5D-3L questionnaire	RCC	Renal cell carcinoma
FDA	Food and Drug Administration	RECIST	Response Evaluation Criteria in Solid Tumors
FU	fluorouracil	RTOR	Real-Time Oncology Review
GBDS	Global Biometric Data Sciences	SAE	serious adverse event
GCP	Good Clinical Practice	SAP	statistical analysis plan
GI	gastrointestinal	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
HCC	Hepatocellular carcinoma	sBLA	Supplemental Biologics License Applications
HR	hazard ratio	SCP	Summary of Clinical Pharmacology
IA	Interim analysis	SD	standard deviation or stable disease
ICF	informed consent form	SOC	System organ class
ICH	International Council of Harmonisation	TRAE	Treatment-related adverse event
IEC	Independent Ethics Committee	TTR	Time to response
IHC	immunohistochemistry	UI	utility index
IMAE	immune-mediated adverse event	US	United States
IMM	immune-modulating medication	USPI	United States Package Insert
IND	Investigational New Drug Application	VAS	visual analog scale
IO	immuno-oncology	VEGR	Vascular endothelial growth factor
iPSP	Initial Pediatric Study Plan	WT	Wild type
IRT	interactive response system	Vs	Versus
ITT	Intention to treat		
IV	intravenous		
IVD	In vitro diagnostics		
KRAS	Kirsten rat sarcoma virus		
KM	Kaplan Meier		
M	months		
Max	maximum		
mCRC	metastatic colorectal cancer		

Term	Definition	Term	Definition

1 Executive Summary

1.1. Product Introduction

Nivolumab is a humanized monoclonal antibody of the IgG4/kappa (IgG4κ) isotype that binds to the programmed death 1 (PD-1) receptor and directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, releasing the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Nivolumab is supplied in single dose vials of 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), and 240 mg/24 mL (10 mg/mL) clear to opalescent, colorless to pale-yellow solution.

FDA first approved nivolumab on December 22, 2014. Prior to action on this supplement, nivolumab as a single agent or in combination was approved for various lines of treatment and subsets of patients with melanoma, non-small cell lung cancer, malignant pleural mesothelioma, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability-high (MSI-H) colorectal cancer, hepatocellular carcinoma, gastric cancer, esophageal cancer, and renal cell carcinoma.

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTL4)-blocking antibody that blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response. Ipilimumab is supplied in single dose vials of 50 mg/10 mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL)) clear to opalescent, colorless to pale-yellow solution.

FDA first approved ipilimumab on March 25, 2011. Prior to action on this supplement, ipilimumab as a single agent or in combination was approved for various lines of treatment and subsets of patients with melanoma, renal cell carcinoma, MSI-H/dMMR colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer, and malignant pleural mesothelioma.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations.

CA2098HW ((NCT03143153) is a randomized, 3-arm, 2-part, open-label trial in patients with unresectable or metastatic colorectal cancer (mCRC) with known tumor microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) status. Part 1 was open to patients across all lines of therapy, and Part 2 enrollment was open after completion of Part 1 enrollment and was opened only to subjects who had not received prior therapy for metastatic disease (first-line patients). Patients were eligible if they had histologically confirmed mCRC, no prior treatment with immune checkpoint inhibitors, had locally determined MSI-H/dMMR status, measurable disease by RECIST 1.1, and ECOG performance status 0-1.

Patients with no prior therapy (1L) or one prior line of therapy (2L) were randomized 2:2:1 to receive one of the following treatments:

- Arm A: nivolumab 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, followed by nivolumab 480 mg every 4 weeks
- Arm B: nivolumab 240 mg every 2 weeks for 6 doses, followed by 480 mg every 4 weeks.
- Arm C: investigator's choice chemotherapy
  - mFOLFOX6 ± bevacizumab or cetuximab, or
  - FOLFIRI ± bevacizumab or cetuximab

Patients in the 3rd line setting (3L) were randomized 1:1 between Arm A (nivo+ipi) and Arm B (nivo). Randomization was stratified by tumor location (right vs. left) and in Part 1, by the number of prior treatments for metastatic disease (none, 1, or ≥ 2).

Subjects in Arm C received treatment with standard of care (SOC) chemotherapy until disease progression, toxicity, or discontinuation for other reasons; upon documented progression of disease per RECIST 1.1 by BICR, patients in Arm C had an option to crossover to receive nivo+ipi. Subjects in the nivo and nivo+ipi arms and the crossover cohort received treatment until disease progression, toxicity, discontinuation for other reasons, or until they reached the maximum treatment duration (2 years). Treatment with nivo or nivo+ipi could be administered beyond RECIST 1.1 assessed progressive disease if there was a clinical benefit as determined by investigator and therapy was tolerated.

Approximately 17% of the 839 subjects enrolled did not have central confirmation of the local MSI-H/dMMR results. The primary analysis population included patients with centrally confirmed MSI-H/dMMR status. The two primary outcomes were:

- Progression-free survival (PFS) by Blinded Independent Central Review (BICR) in the 1L setting, comparing nivo+ipi vs. SOC
- PFS by BIRC across all lines, comparing nivo+ipi vs. nivo.

In a prespecified interim analysis (data cutoff October 12, 2023) conducted in the MSI-H/dMMR centrally confirmed, 1L population (n= 255), treatment with nivo+ipi (n= 171) provided a statistically significant and clinically meaningful improvement in PFS compared with chemotherapy (n= 84). In the 1L population, the median PFS was not reached (95% CI 38.4 months, not estimable) in the nivo+ipi arm and 5.8 months (95% CI 4.7, 7.8) in the SOC arm, with a HR of 0.21 (95% CI 0.14, 0.32; $p < 0.0001$). These results were consistent when comparing investigator assessed PFS in the nivo+ipi arm vs. SOC arm (HR 0.20, 95% CI 0.14, 0.31). Although the BIRC-PFS HR in the 1L randomized subjects for all patients irrespective of MSI-H/dMMR central confirmation is favoring treatment with nivo+ipi (HR 0.32, 95% CI 0.23, 0.46), these results appear to be driven by the centrally confirmed subpopulation (HR 1.58 for the centrally determined MSI-H/dMMR negative or unavailable).

In a prespecified interim analysis (data cutoff August 28, 2024), conducted in the MSI-H/dMMR centrally confirmed, all lines population, treatment with nivo+ipi (n=296) provided a statistically significant and clinically meaningful improvement in PFS compared with nivolumab as a single agent (n= 286). Across all lines of therapy, the median PFS was not reached (95% CI 53.82 months, not estimable) in the nivo+ipi arm and 39.3 months (95% CI 22.11, not estimable) in the nivolumab arm, with a HR of 0.62 (95% CI 0.48, 0.81; p= 0.0003). These results were consistent when comparing investigator assessed PFS in the nivo+ipi arm vs. nivolumab arm (HR 0.62, 95% CI 0.48, 0.80). Although the BIRC-PFS HR in all randomized subjects, irrespective of MSI-H/dMMR central confirmation is similar to the primary analysis population (HR 0.64 (95% CI 0.52, 0.79), these results appear to be driven by the centrally determined MSI-H/dMMR (median HR 0.71 [95% CI 0.48, 1.05] but with mPFS of 2.7 months [95% CI 1.6, 5.8] and 2.0 months [95% CI 1.5, 2.9] in the nivo+ipi and nivo arms respectively). Similar HRs were observed in sensitivity analyses across the subgroup of patients in each line of therapy. The ORR was 70.6% (95% CI 65.1, 75.7) and 57.7% (95% CI 51.7, 63.5) in the nivo+ipi and nivolumab arms respectively.

The submitted evidence meets the statutory evidentiary standard for regular approval of nivolumab in combination with ipilimumab for treatment of patients with MSI-H/dMMR colorectal across all lines of therapy, verifying the benefit observed in the study leading to the approval of the combination in the refractory setting, CHECKMATE-142. The observed improvement in survival for patients receiving nivolumab plus ipilimumab in the first-line setting with a HR of 0.21 (comparison with chemotherapy), and across lines for patients receiving nivolumab plus ipilimumab with a HR of 0.62 (comparison with nivolumab as a single agent) provides data demonstrating the contribution of ipilimumab and it is statistically robust and clinically meaningful. This finding is supported by consistent results on secondary endpoints and

analyses. The data provided also confirms the benefit observed with nivolumab as a single agent in the refractory setting

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The safety and effectiveness of nivolumab in combination with ipilimumab (nivo+ipi) for the treatment of patients with metastatic MSI-H/dMMR colorectal cancer (mCRC) was established by the results of a single multicenter, international, open-label, randomized, 3-arm, 2-part trial, Study CA2098HW (NCT03143153). Part 1 was open to patients across all lines of therapy; after enrollment in Part 1 was complete, Part 2 enrollment was open only to subjects who had not received prior therapy for metastatic disease (first-line subjects [1L]). Patients were eligible if they had histologically confirmed mCRC, no prior treatment with immune checkpoint inhibitors, had locally determined MSI-H/dMMR status, measurable disease by RECIST 1.1, and ECOG performance status 0-1. Patients in the 1L setting or those who received one prior line of therapy (2L) were randomized 2:2:1 to receive one of the following treatments:

- Arm A: nivolumab 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, followed by nivolumab 480 mg every 4 weeks
- Arm B: nivolumab 240 mg every 2 weeks for 6 doses, followed by 480 mg every 4 weeks.
- Arm C: investigator's choice chemotherapy (SOC)
  - mFOLFOX6 ± bevacizumab or cetuximab, or
  - FOLFIRI ± bevacizumab or cetuximab

Patients in the 3rd line setting (3L) were randomized 1:1 between Arm A (nivo+ipi) and Arm B (nivo). Randomization was stratified by tumor location (right vs. left) and in Part 1, by the number of prior treatments for metastatic disease (none, 1, or ≥ 2).

Treatment continued until progression of disease or unacceptable toxicity; patients without disease progression could be treated with nivolumab for up to 24 months. Crossover to receive nivo+ipi was permitted for patients randomized to chemotherapy at the time of disease progression. Treatment with nivo or nivo+ipi could be administered beyond RECIST 1.1 assessed progressive disease if there was a clinical benefit as determined by investigator and therapy was tolerated.

A total of 839 patients were randomized, 354 to the nivo+ipi arm, 353 to the nivo arm, and 132 to chemotherapy; 695 (83%) patients had centrally confirmed MSI-H status. The primary analysis population included patients with centrally confirmed MSI-H/dMMR status. The two primary outcomes were PFS by BIRC in the 1L setting comparing nivo+ipi vs. chemotherapy and PFS by BIRC across all lines, comparing

nivo+ipi vs. nivo.

The pre-specified primary outcomes of Study CA2098HW were determined to be statistically significant. In a prespecified interim analysis (data cutoff October 12, 2023) conducted in the MSI-H/dMMR centrally confirmed, 1L population (n= 255), treatment with nivo+ipi (n= 171) provided a statistically significant and clinically meaningful improvement in PFS compared with chemotherapy (n= 84). In the 1L population, the median PFS was not reached (95% CI 38.4 months, not estimable) in the nivo+ipi arm and 5.8 months (95% CI 4.7, 7.8) in the SOC arm, with a HR of 0.21 (95% CI 0.14, 0.32; p < 0.0001). In a prespecified interim analysis (data cutoff August 28, 2024), conducted in the MSI-H/dMMR centrally confirmed, all lines population, treatment with nivo+ipi (n=296) provided a statistically significant and clinically meaningful improvement in PFS compared with nivolumab as a single agent (n= 286). Across all lines of therapy, the median PFS was not reached (95% CI 53.82 months, not estimable) in the nivo+ipi arm and was 39.3 months (95% CI 22.11, not estimable) in the nivolumab arm, with a HR of 0.62 (95% CI 0.48, 0.81; p= 0.0003). FDA's sensitivity analyses (data blinded to Applicant) showed similar PFS HRs across the subgroups of patients in each line of therapy. A statistically significant improvement in ORR per BICR (p= 0.0011) was demonstrated in the all lines population with nivo+ipi (ORR 70.6% [95% CI: 65.1, 75.7] compared with nivo alone (ORR 57.7% [95% CI: 51.7, 63.5]). FDA conducted a sensitivity analysis in each line of therapy and found the ORR improvements of adding ipilimumab to nivolumab were descriptively similar across different lines. The ORR results of nivo+ipi vs nivo provided further supportive evidence demonstrating the contribution of ipilimumab to the combination therapy. OS endpoints were not formally tested in this submission and remains blinded to the Applicant; FDA conducted descriptive OS analyses for comparing nivo+ipi vs. chemo in 1L and nivo+ipi vs chemo in all lines in randomized patients with centrally confirmed MSI-H/dMMR. The data did not indicate any harm or detriment to survival at this time.

In the 1L setting, the median number of ipilimumab doses was 4 (range 1-4) and the median duration of treatment in the nivo+ipi arm was 20.5 months, while the median duration of therapy in the control arm was 3.96 months: 69% and 36% patients in the nivo+ipi arm and chemotherapy arms, respectively received study drug for >6 months. Treatment discontinuation because of adverse events (AEs) were reported in 19%, 13%, and 40% in the nivo+ipi, nivo, and chemotherapy arms respectively. In both nivolumab arms, the most common cause of treatment discontinuation was an immune-mediated adverse event (IMAEs). In the nivolumab arm, the median duration of exposure was 16.4 months; 64% patients were exposed for >6 months. Nivolumab was permanently discontinued in 13% of patients and the leading cause of discontinuation was IMAEs.

The adverse reaction profile observed in patients receiving nivolumab in Study CA2098HW is consistent with the known nivolumab safety profile, both as a single agent or in combination with ipilimumab. A similar proportion of patients treated with nivo+ipi (10%) or nivo (11%) as a

single agent died within 180 days of initiating treatment; most deaths (6% and 9% respectively) were from disease progression. Fatal adverse reactions were reported in 4.5%, 2.8%, and 0.9% in the nivo+ipi, nivo, and chemotherapy arms respectively. Serious adverse reactions occurred in 46%, 39%, and 49% of patients (across all lines) in the nivo+ipi, nivo, and chemotherapy arms respectively. Grade 3-4 adverse events were reported in 48%, 43%, and 70% of patients in the nivo+ipi, nivo, and chemotherapy arms, respectively. The most common (≥20%) AEs in patients treated with nivo+ipi or nivolumab alone were fatigue, diarrhea, pruritus, abdominal pain, and musculoskeletal pain; in addition, ≥20% patients in the nivo+ipi arm also experienced nausea. The most common (≥20%) AEs in patients treated with chemotherapy were fatigue, diarrhea, nausea, decreased appetite, abdominal pain, vomiting, and constipation. The most commonly reported IMAEs with nivo+ipi were hypothyroidism/thyroiditis (18%), hyperthyroidism (12%), adrenal insufficiency (10%), rash (7%) and hypophysitis (6%); the most common IMAEs in the nivolumab as a single agent arm were hypothyroidism/thyroiditis (9%), rash (6%), and hyperthyroidism (5%).

The review team concluded that the overall risk:benefit assessment favored approval of nivolumab with ipilimumab for the treatment of patients with MSI-H/dMMR metastatic or locally advanced colorectal cancer, and nivolumab as a single agent for the treatment of patients with MSI-H/dMMR metastatic or locally advanced colorectal cancer with disease progression after prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. The demonstrated improvement in PFS for patients randomized to nivolumab in combination with ipilimumab is clinically meaningful, statistically significant, and supported by subgroup analyses in Study CA2098HW. Although the primary outcome was in a subgroup of patients with centrally confirmed MSI-H/dMMR status, concurrent approval of a companion diagnostic would contribute to the adequate identification of patients who will benefit from treatment with nivo+ipi. In addition, the comparison of nivo+ipi vs. nivolumab alone allows for an adequate demonstration of the contribution of components, while simultaneously confirming the benefit observed upon approval of the nivolumab as a single agent in the refractory setting. Although given the superiority of the combination nivo+ipi over nivolumab as a single agent it is likely that the combination of nivo+ipi would be the standard of care, the approval of nivolumab as a single agent may provide an effective alternative for patients in the refractory setting that may be deemed unfit to tolerate the additional toxicities associated with the addition of ipilimumab. In addition, the Application provided additional PK data to confirm that the nivolumab and ipilimumab exposures are comparable between adolescents (12 to < 18 years of age) and adults patients at the proposed dosages. The risks of nivolumab and nivolumab in combination with ipilimumab are acceptable considering the life-threatening nature of MSI-H/dMMR metastatic or locally advanced colorectal cancer in patients 12 years of age or older.

The review team considers that the data provided by Study CA2098HW fulfils the post-marketing requirements issued upon the accelerated approval of both nivolumab and nivolumab in combination for ipilimumab and recommends regular approvals for the sought after indications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Patients with MSI-H/dMMR mCRC are a defined biological population characterized by a high mutational burden with potential susceptibility to anti PD-(L)1 inhibitors. Although CRC is the third most common form of cancer, only 4-5% of all metastatic CRC are MSI-H/dMMR (Diaz L, 2022; Gutierrez C, 2023). In a pooled analysis of randomized clinical trials with chemotherapy in patients with mCRC, patients with MSI-H/dMMR had shorter PFS and OS when compared with patients who were microsatellite stable (HR 1.33 and 1.35 for PFS and OS respectively) (Venderbosch S., 2014). In the KEYNOTE-177 study in patients with MSI-H/dMMR mCRC, patients who received standard of care chemotherapy for the first line treatment of advanced/metastatic disease had a markedly shorter median PFS (8.2 months versus 16.5 months in the chemotherapy and pembrolizumab arms, respectively) (Keytruda USPI) and OS (36.7 months vs. median not reached [95% CI 49.2-not reached] in the chemotherapy and pembrolizumab arms respectively) (Diaz L, 2022).	MSI-H/dMMR mCRC is a serious, life-threatening disease with poor prognosis. When treated with standard of care for mCRC chemotherapy, these patients appear to have worse prognosis that those who are microsatellite stable.
Current Treatment Options	Treatment options for first-line advanced or metastatic CRC consist of fluoropyrimidine-based chemotherapy regimens in combination with oxaliplatin (e.g., mFOLFOX6, CapeOX), irinotecan (e.g., FOLFIRI) or both oxaliplatin and irinotecan (FOLFOXIRI); generally, these regimens are combined with monoclonal antibodies targeting the VEGF or EGFR pathways. On June 29, 2020, FDA approved pembrolizumab for the treatment of patients with unresectable or metastatic MSI-H/dMMR colorectal cancer. The approval was based on data from Study KEYNOTE-177, an open-label, randomized trial comparing pembrolizumab or standard of care with chemotherapy in 307	Although chemotherapy improves survival in patients with advanced unresectable or metastatic CRC, since the approval of pembrolizumab in 2020, treatment of patients with MSI-H/dMMR disease with immune checkpoint inhibition has become standard of care for this population. Although single agent pembrolizumab offers a clinically meaningful improvement in outcomes when compared with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients with no prior therapy for advanced disease. At the time of the final PFS analysis and second pre-specified interim OS analysis, the estimated median PFS was 16.5 months (95% CI: 5.4, 32.4) vs. 8.2 months (95% CI: 6.1, 10.2) in the pembrolizumab and SOC arms, respectively (HR 0.60 [95% CI: 0.45, 0.80]; p= 0.0004) and the median OS was not reached (95% CI 49.2, NR) in the pembrolizumab arm, and 36.7 (95% CI 27.6, NR) months in the chemotherapy arm (HR 0.74 [95% CI 0.53, 1.03]) (Keytruda USPI). Although in the refractory setting, accelerated approvals were granted to both nivolumab as a single agent (July 31, 2017) and nivolumab in combination with ipilimumab (July 10, 2018) for the treatment of patients with MSI-H/dMMR mCRC based on results of CHECKMATE-142. In patients with prior exposure to fluoropyrimidine, oxaliplatin, and irinotecan, treatment with nivolumab resulted in an ORR of 32% (95% CI 20, 46), and 88% of responders had a response lasting ≥ 12 months; the ORR is patients treated with nivolumab in combination with ipilimumab, the ORR was 56% (95% CI 45, 67), and 74% of responders had a response lasting ≥ 12 months (OPDIVO USPI).	chemotherapy, there is a need for more effective regimens for patients with MSI-H/dMMR tumors.
Benefit	The approvals are supported by a single study, CA2098HW (NCT03143153), a single multicenter, international, open-label, randomized, 3-arm, 2-part trial. Patients with MSI-H/dMMR advanced/metastatic CRC were enrolled in Part 1, irrespective of prior chemotherapy with advanced disease. Part 2 enrollment was open only to subjects who had not received prior therapy for metastatic disease (1L). Patients with prior treatment with immune checkpoint inhibitors were ineligible. Patients in the 1L setting or those who received one prior line	The submitted evidence meets the statutory evidentiary standard for regular approval of nivolumab in combination with ipilimumab for treatment of patients with metastatic or locally advanced unresectable MSI-H/dMMR irrespective of prior line of therapy. The observed improvement in PFS in the 1L

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of therapy (2L) were randomized 2:2:1 to receive one of the following treatments: • Arm A: nivolumab 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, followed by nivolumab 480 mg every 4 weeks • Arm B: nivolumab 240 mg every 2 weeks for 6 doses, followed by 480 mg every 4 weeks. • Arm C: investigator's choice chemotherapy (SOC) between mFOLFOX6 or FOLFIRI, with or without cetuximab or bevacizumab. Patients in the 3rd line setting (3L) were randomized 1:1 between Arm A (nivo+ipi) and Arm B (nivo). Randomization was stratified by tumor location (right vs. left) and in Part 1, by the number of prior treatments for metastatic disease (none, 1, or ≥ 2). Patients were treated until progression of disease or unacceptable toxicity, or up to 24 months of nivolumab. Crossover to receive nivo+ipi was available for patients randomized to chemotherapy at the time of disease progression. The two primary outcomes were PFS by BIRC in the 1L setting comparing nivo+ipi vs. chemotherapy and PFS by BIRC across all lines, comparing nivo+ipi vs. nivo. The primary analysis population included patients with centrally confirmed MSI-H/dMMR status. The trial enrolled 839 patients, 354 to the nivo+ipi arm, 353 to the nivo arm, and 132 to chemotherapy; 695 (83%) patients had centrally confirmed MSI-H	population (comparison against chemotherapy) with a HR of 0.21 with the lower boundary of the 95% CI of the nivo+ipi median PFS that is 32.6 months longer than the median PFS in the control arm is clinically meaningful and statistically significant. The observed improvement in PFS across all lines (comparison against nivolumab as a single agent) with a HR of 0.62 confirms the benefit of nivo+ipi across all lines and contributes to support the contribution of ipilimumab to nivolumab. The trial confirms the benefit of both nivolumab and nivolumab in combination with ipilimumab previously reported in the refractory setting of MSI-H/dMMR mCRC. These findings are supported by consistent results on secondary endpoints and prespecified subgroup analyses.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	status. Analyses of both primary outcomes demonstrated a clinically meaningful and statistically significant effect of nivo+ipi. In the interim analysis conducted in the MSI-H/dMMR centrally confirmed, 1L population (n= 255), the median PFS was not reached (95% CI 38.4 months, not estimable) in the nivo+ipi arm and 5.8 months (95% CI 4.7, 7.8) in the SOC arm, with a HR of 0.21 (95% CI 0.14, 0.32; p < 0.0001). In the interim analysis of the MSI-H/dMMR centrally confirmed, all lines population, the median PFS was not reached (95% CI 53.82 months, not estimable) in the nivo+ipi arm and was 39.3 months (95% CI 22.11, not estimable) in the nivolumab arm, with a HR of 0.62 (95% CI 0.48, 0.81; p= 0.0003). Multiple sensitivity analyses demonstrate benefit across subpopulations, irrespective of prior line of therapy. A statistically significant improvement in ORR per BICR (p= 0.0011) was demonstrated in the all lines population with nivo+ipi (ORR 70.6% [95% CI: 65.1, 75.7] compared with nivo alone (ORR 57.7% [95% CI: 51.7, 63.5]). OS endpoints were not formally tested in this submission and remains blinded to the Applicant; FDA conducted descriptive OS analyses for comparing nivo+ipi vs. chemo in 1L and nivo+ipi vs chemo in all lines in randomized patients with centrally confirmed MSI-H/dMMR. The data did not indicate any harm or detriment to survival at this time.	
Risk and Risk Management	The observed safety profile observed in patients receiving nivolumab ± ipilimumab in Study CA2098HW is consistent with the known nivolumab safety profile, both as a single agent or in combination with ipilimumab. Addition of ipilimumab to nivolumab increased the incidence and severity of immune-related adverse events (IMAEs), fatal events (4.5%, 2.8%, and 0.9% in the nivo+ipi, nivo, and chemotherapy arms respectively), serious adverse	The toxicity profile of nivolumab in combination with ipilimumab is acceptable when assessed in the context of the life-threatening nature of advanced unresectable or metastatic MSI-H/dMMR mCRC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	events, and Grade 3-4 adverse events (48%, 43%, and 70% of patients in the nivo+ipi, nivo, and chemotherapy arms respectively). The most commonly reported IMAEs with nivo+ipi were hypothyroidism/thyroiditis (18%), hyperthyroidism (12%), adrenal insufficiency (10%), rash (7%) and hypophysitis (6%); the most common IMAEs in the nivolumab as a single agent arm were hypothyroidism/thyroiditis (9%), rash (6%), and hyperthyroidism (5%). Although the incidence of adverse events increased with the combination nivolumab and ipilimumab when compared to standard of care chemotherapy or nivolumab alone, the safety profile of this combination is different than the standard of care and it is mostly related to IMAEs. This combination provides for a chemotherapy-free, highly effective treatment for patients with MSI-H/dMMR mCRC, who are at risk of worse outcomes when treated with chemotherapy.	No new significant safety concerns were identified during review of this supplemental application that would require a new risk management plan, including a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of nivolumab and ipilimumab. Significant and serious adverse reactions for nivolumab and ipilimumab are predictable based on the antibodies' mechanism of action and well-known toxicity profiles. These risks are adequately addressed in product labeling, and oncologists who treat patients with mCRC are well-trained in the monitoring and treatment of these adverse reactions.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:		Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as	Section 8.1.1 Study endpoints and 8.1.2 Secondary COA (PRO) endpoints

			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (eg, individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (eg, submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X _____

Cross-Disciplinary Team Leader

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

CRC is one of the leading causes of cancer-related death worldwide, with a 5-year survival rate of approximately 15% in patients with metastatic disease.[2] Worldwide, CRC is the third most common form of cancer, with 1.93 million new cases diagnosed in 2020, constituting 10% of all new cancers. Each year, there are about 935,173 deaths from CRC worldwide, which is 9.4% of all cancer deaths, making CRC the second most common cause of cancer death. In the US, 126,240 new cases of CRC were reported in 2020 and 51,869 died from CRC. The incidence rate per 100,000 was reported as 41.9 in Black, 37 in White, 31.9 in Asian/Pacific Islander, 39.3 in America Indian and 33.5 in Hispanic in the US.[3] The risk of developing CRC is influenced by both environmental and genetic factors.[4]

CRC is a heterogeneous disease at the molecular level.[5] MSI-H/dMMR colorectal tumors are identified in approximately 15% of CRC patients. Among patients with mCRC, those with MSI-H/dMMR tumors comprise of approximately 4%-7%.[6,7] Microsatellite instability is the molecular fingerprint of deficient mismatch repair. The term MSI-H is widely used as a surrogate for both MSI-H and dMMR. MSI-H CRCs can be hereditary and arise in association with Lynch syndrome or be sporadic. The latter is characterized by either epigenetic silencing of *MLH1* (one of the mismatch repair genes), or mutations in mismatch repair genes *MLH1, MSH2, MSH6, or PMS2*.[8]

The FDA's Assessment:

In the United States, colorectal cancer (CRC) is the fourth most common cancer diagnosis, and in 2024 was the second leading cause of cancer deaths with an estimated 53,010 deaths (SEER 2024). FDA agrees with the Applicant's cited prevalence and description of MSI-H/dMMR mCRC.

Gutierrez et al. conducted a retrospective cohort study of the National Cancer Database (NCDB) identifying 21,703 patients with advanced CRC at diagnosis, 1,580 (7.8%) with 7.3% average adjusted probability (%AAP) having MSI-H/dMMR disease (Gutierrez et al. 2023). According to race and ethnicity, advanced CRC were more likely to be MSI-high/dMMR in 7.5% AAP of non-Hispanic White patients, compared with 7.0% AAP of non-Hispanic Black, 4.7% AAP of Asian/Pacific Islander, and 7.6% AAP of Hispanic patients. In a pooled analysis of randomized clinical trials with chemotherapy in patients with mCRC, patients with MSI-H/dMMR had shorter PFS and OS when compared with patients who were microsatellite stable (HR 1.33 and

1.35 for PFS and OS respectively) (Venderbosch S., 2014).

2.2. Analysis of Current Treatment Options

Table 1: Applicant - FDA Approved Treatments Relevant for First-Line Unresectable or Metastatic MSI-H or dMMR CRC

Product Name	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments*
FOLFOX +/- bevacizumab	Oxaliplatin 85 mg/m^2 IV D1 Leucovorin 200 mg/m^2 5FU 400 mg/m^2 bolus on D1, followed by 1200 mg/m^2/d x 2D Bevacizumab 5 mg/kg, Q2-3W	The addition of bevacizumab to FOLFOX has shown improvements in PFS and OS compared to FOLFOX alone. FOLFOX:[9] mPFS: 8.7 m mOS: 19.5 m ORR: 45% FOLFOX + bevacizumab:[10] mPFS: 11.3 m mOS: 25.9 m	FOLFOX or XELOX: Grade 3-4 (75%) AE leading to treatment discontinuation (21%) Increased toxicities in peripheral neuropathy, neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, and stomatitis.[9] FOLFOX + bevacizumab: Grade 3-4 (80%) AE leading to treatment discontinuation (30%) Same increased toxicities as above plus increased toxicities in gastrointestinal perforation, hypertension, hemorrhage, thrombosis, infection, and hypersensitivity reaction[10]	Ineligible for checkpoint immunotherapy, intensive therapy recommended
FOLFOX +/- cetuximab	Folinic Acid 200-400 mg/m², IV Fluorouracil bolus dose 400-500 mg/m², followed by a continuous infusion of 2,400-3,000 mg/m² over 46 to 48 hours. Oxaliplatin:85 mg/m² IV infusion over two hours on the first day of the cycle.	Improved outcomes of ORR, PFS in the FOLFOX + cetuximab group compared to the FOLFOX alone group in KRAS WT population.[11] FOLFOX + cetuximab vs FOLFOX in ITT: ORR: 46% vs 36% mPFS: 7.2 m vs 7.2 m FOLFOX + cetuximab vs FOLFOX in KRAS WT:	FOLFOX: Grade 3/4 (70%) AE leading to chemo discontinuation (25%) The most frequently reported AEs were GI disorders (73%) and myelotoxicity (71%) FOLFOX + cetuximab: Grade 3/4 (76%) AE leading to cetuximab discontinuation (23%), chemo discontinuation (30%) and both discontinuation (9%) The most frequently reported AEs were skin and subcutaneous tissue disorders (90%) and GI disorders (78%)[11]	Ineligible for checkpoint immunotherapy, intensive therapy recommended KRAS/NRAS/BRAF WT and left-sided tumors only

Table 1: Applicant - FDA Approved Treatments Relevant for First-Line Unresectable or Metastatic MSI-H or dMMR CRC

Product Name	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments*
	Cetuximab: initial dose 400 mg/m², maintenance dose 250 mg/m²	ORR: 61% vs 37% mPFS: 7.7 m vs 7.2 m		
FOLFIRI +/- bevacizumab	Irinotecan: 180 mg/m² IV, C1D1, Leucovorin: 400 mg/m² IV, C1D1, Fluorouracil: 400 mg/m², C1D1-2, followed by a continuous infusion of 2,400 mg/m² over 46 to 48 hours Bevacizumab: 5 mg/kg or 7.5 mg/kg, IV C1D1	Improved PFS and OS for FOLFIRI + bevacizumab compared to FOLFIRI alone. FOLFIRI:[12] mPFS: 7.6 m mOS: 23.1 m ORR: 47.2% FOLFIRI + bevacizumab:[10] mPFS: 11.6 m mOS 23.7 m	FOLFIRI:[12] Grade 3-5[13] (56%) TRAE leading to discontinuation (14.6%) Increased toxicities including diarrhea, nausea, vomiting, neutropenia, thrombocytopenia, anemia, neuropathy. FOLFIRI + bevacizumab: Grade 3-5 (64%) TRAE leading to discontinuation (16.1%) Same as above+ increased the risk of bleeding, hypertension, impaired wound healing, proteinuria, infusion reaction	Ineligible for checkpoint immunotherapy, intensive therapy recommended
FOLFIRI + cetuximab	Irinotecan: 180 mg/m², IV, C1D1, Leucovorin: 200 mg/m², IV, C1D1, Fluorouracil: bolus dose 400-500 mg/m², followed by a continuous infusion of 2,400-3,000 mg/m² over 46-48 hours. Cetuximab: 400 mg/m², IV, maintenance doses 250 mg/m², IV	Improved ORR, PFS and OS with FOLFIRI + cetuximab compared to FOLFIRI alone. FOLFIRI: mPFS: 8.0 m mOS: 18.6 m ORR: 38.7% FOLFIRI + cetuximab:[14] mPFS: 8.9 m mOS: 19.9 m ORR: 46.9%	FOLFIRI + cetuximab:[14] Grade 3-4 (79.3%) TRAE leading to discontinuation (15%) Increased toxicities including neutropenia, leukopenia, diarrhea, fatigue, rash, dermatitis acneiform, vomiting, skin reactions, and infusion reactions. The incidence rate of Grade 3 or 4 diarrhea, skin reactions, infusion reaction, and the overall Grade 3 or 4 events was higher with FOLIFRI + cetuximab than FOLIRI alone.	Ineligible for checkpoint immunotherapy, intensive therapy recommended KRAS/NRAS/ BRAF WT and left-sided tumors only

Table 1: Applicant - FDA Approved Treatments Relevant for First-Line Unresectable or Metastatic MSI-H or dMMR CRC

Product Name	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments*
Keytruda (pembrolizumab)	200 mg Q3W or 400 mg Q6W	At median follow-up 32.4 m (24.0 to 48.3), pembrolizumab was superior to chemo in PFS. OS was not mature. There was statistically non-significant improvement in OS at final analysis of 44 m of median follow-up.[15] mPFS: 16.5 vs 8.2 m; HR 0.60; P=0.0002 ORR: 44% vs 33% Final OS analysis: mOS: NR vs 36.7 m; HR 0.74, 95% CI: 0.53-1.03	Grade 3-5 (56%). No grade 5 AEs observed. TRAE leading to discontinuation (14%)[15] Increased toxicities are mainly immune-mediated adverse events and infusion reaction (31%), including hypothyroidism, colitis, hyperthyroidism, pneumonitis, adrenal insufficiency, hepatitis, infusion reaction, pancreatitis, severe skin reactions, type 1 diabetes mellitus, etc.	Candidate for immunotherapy and no prior immunotherapy received

* Per NCCN guidance
Note: Data for all SOC chemo regimens were generated from mCRC patients unselected for MSI-H/dMMR. Pembrolizumab data were from study KN-177 where CRC patients with MSI-H/dMMR were studied.

The Applicant's Position:

The 1L treatment options for patients with unresectable or metastatic MSI-H/dMMR CRC include CPI or chemo with or without biologics (VEGF- or EGFR-inhibitors).

In the US, NCCN recommends nivo alone or in combination with ipi, or pembrolizumab as 1L treatment for unresectable or metastatic MSI-H/dMMR CRC. The guidelines recommend close monitoring of patients receiving CPI for 10 weeks to assess for response due to the high rate of early disease progression (Table 1).

The KEYNOTE-177 study demonstrated improved PFS with an anti-PD1 single agent vs chemo in MSI-H mCRC patients,[16] supporting approval of pembrolizumab in the 1L setting. Median PFS was 16.5 months (95% CI: 5.4, 32.4) with pembrolizumab vs 8.2 months (95% CI: 6.1, 10.2) with chemo (HR 0.60, 95% CI: 0.45, 0.80). The ORR was 44% with pembrolizumab and 33% with chemo. The study showed statistically non-significant improvement of OS with pembrolizumab (mOS not reached) vs chemo (mOS = 36.7 months) with a HR 0.74 (95% CI: 0.53, 1.03).

Despite this advancement, there is still an unmet medical need, as more than half of patients do not respond to pembrolizumab. Although PFS benefit with pembrolizumab vs chemo was observed in all randomized patients and in most patient subgroups, PFS favored chemo vs pembrolizumab in patients with RAS-mutant tumors. In addition, about 30% of patients treated with pembrolizumab had primary progressive disease. The high rate of primary disease progression with pembrolizumab compared with chemo manifested as early detriment on the PFS curve and led to an increased early death rate, highlighting the remaining unmet need in this patient population.

Dual checkpoint inhibition with nivo (anti-PD1) plus ipi (anti-CTLA-4) has shown enhanced antitumor activity relative to single anti-PD1 agent in various tumor types, including melanoma, mesothelioma, lung cancer, and some others.[17]

In CA209142, a multi-cohort non-randomized Phase 2 study, indirect comparison of data in previously treated MSI-H/dMMR mCRC patients showed that nivo+ipi combination (Cohort 2) had improved ORR per investigator of 65% (95% CI: 55, 73) relative to nivo monotherapy (Cohort 1) of 39% (95% CI: 28, 51) with non-overlapping 95% CI, after median follow up of 64 months (min, max: 60, 76) and 70 months (min, max: 66, 89) for Cohorts 2 and 1, respectively.[18] In addition, numerically better PFS and OS rates at 48 months were observed in the nivo+ipi cohort (PFS rate: 54% [95% CI: 44, 63] and OS rate: 71% [95% CI: 62, 78]) relative to the nivo cohort (PFS rate: 36% [95% CI: 25, 47] and OS rate: 49% [95% CI: 37, 59]). In Cohort 3, investigating 1L nivo+ipi combination in MSI-H/dMMR mCRC patients after median follow up of 52 months (min, max: 48, 57), high ORR per investigator (71% [95% CI: 56, 84]) and durable responses were observed. mPFS and mOS were not reached, and PFS and OS rates at 48 months were 51% (95% CI: 34, 66) and 72% (95% CI: 57, 83), respectively. Also, this combination showed a tolerable safety profile. These data of nivo+ipi combination in the CA209142 study

were consistent with earlier data[19] that prompted further evaluation of this regimen as 1L treatment in MSI-H/dMMR mCRC in a Phase 3 study.

The FDA's Assessment:
FDA agrees with the Applicant's description and findings from KEYNOTE-177 cited in Table 1.

At the time of the sBLA application submission, pembrolizumab was approved in the US for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test.

The Applicant has provided details of the NCCN guidelines in their description. At the time of this sBLA application, nivolumab was approved in the US under accelerated approval for the treatment of adult and pediatric (12 years and older) patients with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.

Nivolumab, as a single agent, was granted accelerated approval for the above indication above on July 31, 2017. Nivolumab in combination with ipilimumab was granted accelerated approval on July 10, 2018. The accelerated approvals were based on Study CA209142 (CHECKMATE-[CM]-142), a multicenter, non-randomized, multiple parallel-cohort, open-label study. Efficacy results for each of the relevant single arm cohorts from CM-142 are outlined in Table 2.

Table 2: FDA- Nivolumab USPI - Efficacy Results – CHECKMATE-142

	OPDIVO[a] MSI-H/dMMR Cohort		**OPDIVO and Ipilimumab[b] MSI-H/dMMR Cohort**	
	All Patients (n=74)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)**	**All Patients (n=119)**	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
Overall Response Rate per BICR; n (%)	28 (38%)	17 (32%)	71 (60%)	46 (56%)
(95% CI)[c]	(27, 50)	(20, 46)	(50, 69)	(45, 67)
Complete Response (%)	8 (11%)	5 (9%)	17 (14%)	11 (13%)
Partial Response (%)	20 (27%)	12 (23%)	54 (45%)	35 (43%)
Duration of Response				

Proportion of responders with ≥6 months response duration	86%	94%	89%	87%
Proportion of responders with ≥12 months response duration	82%	88%	77%	74%

Source: Nivolumab USPI (OPDIVO 2024)
[a] Minimum follow-up 33.7 months for all patients treated with OPDIVO (n=74).
[b] Minimum follow-up 27.5 months for all patients treated with OPDIVO and ipilimumab (n=119).
[c] Estimated using the Clopper-Pearson method.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Nivo+ipi combination therapy was first approved in the US on 30-Sep-2015 for the treatment of patients with unresectable or metastatic melanoma and is currently approved for:

- 1L intermediate or poor risk advanced RCC
- MSI-H/dMMR metastatic CRC that has progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan
- 1L MPM
- HCC previously treated with sorafenib (accelerated approval)
- 1L metastatic NSCLC with PD-L1 ≥ 1%
- 1L unresectable advanced or metastatic ESCC

In addition, nivo+ipi in combination with 2 cycles of chemo is approved for 1L treatment of with metastatic or recurrent NSCLC.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The MSI-H/dMMR metastatic CRC indication stated above is currently approved under the accelerated approval provisions.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 3: Applicant - Regulatory History for CA2098HW

Date	Sequence Number	Regulatory Milestone
31-Jul-2017	NA	Accelerated approval (BLA 125554/S-034) was granted for nivo monotherapy in MSI-H/dMMR mCRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. This approval includes PMR 3243-1 and diagnostic PMC 3243-2 and 3243-3.
03-Apr-2018	NA	CA2098HW was developed (03-Apr-2018) to confirm the benefit of nivo monotherapy following accelerated approval to fulfill PMR 3243-1 for BLA 125554/S-034.
10-Jul-2018	NA	Accelerated approval (BLA 125554/S-063) was granted for nivo combination with ipi in MSI-H/dMMR mCRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. This approval includes PMR 3449-1 and diagnostic PMC 3449-3 and PMC 3449-4.
06-Dec-2018	0235	Protocol amendment 02 submitted to FDA.
19-Dec-2018	0239	Submitted the initial PSP.
15-Apr-2019	0253	Protocol amendment 03 submitted to FDA.
10-Aug-2020	NA	Type C meeting was held to obtain FDA feedback and agreement on the proposed plans for fulfilling diagnostic PMCs (PMC 3449-3, PMC 3449-4, PMC 3243-2, PMC 3243-3, PMC 3540-3, and PMC 3450-4) related to accelerated approvals (BLA 125554/S-034 and BLA 125554/S-063).
18-Aug-2020	0285	Protocol amendment 04 submitted to FDA.
08-May-2023	0352	Agreed initial PSP
13-Jun-2023	NA	In the Type C Meeting Preliminary Comments (Reference ID: 5190066), FDA agreed with BMS proposed waiver of the clinical pharmacology packages for future sBLAs of nivo when administered in combination with ipi (including CA2098HW).

Table 3: Applicant - Regulatory History for CA2098HW

Date	Sequence Number	Regulatory Milestone
06-Dec-2023	NA	BMS provided CA2098HW topline data for nivo+ipi vs chemo to the FDA and requested participation in RTOR and Assessment Aid programs via email.
18-Dec-2023	0372	Pre-sBLA Type B Meeting Request submitted.
13-Feb-2024	NA	Type B Pre-sBLA meeting held
19-Mar-2024	NA	A follow-up ad hoc meeting held
24-May-2024	0384	A Type A Meeting Request submitted
12-Jun-2024	NA	Type D Meeting Preliminary Comments received
09-Jul-2024	0387	Protocol amendment 10 submitted to FDA.
09-Oct-2024	0391	Pre-sBLA Type B Meeting Request submitted based on the anticipated nivo+ipi vs nivo readout.
17-Oct-2024	NA	BMS provided CA2098HW topline data for nivo+ipi vs nivo to the FDA
21-Oct-2024	NA	FDA issued the Pre-sBLA Type B Meeting Request Granted Letter which granted a meeting for 09-Dec-2024
01-Nov-2024	0394	Breakthrough Therapy Designation Request for 1L MSI-H/dMMR CRC submitted
08-Nov-2024	0395	Pre-sBLA Type B Meeting Background Document submitted to FDA
12-Nov-2024	NA	• FDA stated that Breakthrough Designation has already been granted for the nivo+ipi combination in the refractory setting. • FDA requested BMS to submit a revised designation request for a line-agnostic indication.
15-Nov-2024	0397	BMS submitted an Updated Breakthrough Therapy Designation Request to align with a line-agnostic indication.
29-Nov-2024	NA	FDA granted Breakthrough Therapy Designation for nivo in combination with ipi for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite MSI-H or dMMR CRC.

Table 3: Applicant - Regulatory History for CA2098HW

Date	Sequence Number	Regulatory Milestone
04-Dec-2024	NA	FDA Preliminary comments received for Pre-sBLA Type B meeting
07-Dec-2024	NA	BMS provided responses to FDA pre-sBLA preliminary comments, agreeing to provide the analyses as requested, as well as clarifying BMS' plans regarding nivo monotherapy.
09-Dec-2024	NA	Type B Pre-sBLA meeting held

The FDA's Assessment:

Based on the results of Cohort 3 of Study CA209142, accelerated approval was granted for nivolumab monotherapy (July 31, 2017 [BLA 125554/S-034]) and nivolumab in combination with ipilimumab (July 10, 2018 [BLA 125554/S-063, BLA 125377/S-096]) for the treatment of MSI-H or dMMR metastatic colorectal cancer (mCRC) that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan (the relevant efficacy data supporting the accelerated approval are outlined in Section 2).

The respective post marketing requirements (PMRs) and commitments (PMCs) issued were:

BLA 125554/S-034

- PMR 3243-1: Submit the final report, including datasets, from trials conducted to verify and describe the clinical benefit of nivolumab 240 mg intravenously every two weeks in patients with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer who have progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan, including at least 150 patients enrolled in BMS-initiated trials. In order to characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.
- PMC 3243-2: Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry (IHC) based in vitro diagnostic device that is essential to the safe and effective use of nivolumab for patients with tumors that are mismatch repair deficient.
- PMC 3243-3 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of nivolumab for patients with tumors that are microsatellite instability high.

BLA 125554/S-063 and BLA 125377/S-096:

- PMR 3449-1 (nivolumab) and 3450-1 (ipilimumab): Submit the final report, including datasets, from a randomized trial conducted to verify and describe the clinical benefit of nivolumab, administered in combination with ipilimumab, in patients with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer. The trial will be designed to demonstrate a clinically meaningful improvement in progression-free survival in patients randomized to receive nivolumab and ipilimumab as compared to patients randomized to receive nivolumab alone. In addition, the trial should evaluate for differences in overall survival between arms based on a pre- specified analysis. The analysis plan should describe the power for the overall survival analysis, as well as all assumptions made in determining the power.
- PMC 3449-2 (nivolumab) and 3450-2 (ipilimumab): Submit the final report, including datasets, from trials conducted to describe the clinical benefit of nivolumab, administered in combination with ipilimumab, in patients with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer. This report is to include data on 119 patients with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer enrolled in Study CA209142 whose preliminary results are described in current labeling and on the 82-patient subset of these 119 patients who experienced disease progression on 5FU, oxaliplatin, and irinotecan. The final report will provide updated data on all responding patients who will be followed for at least 12 months from the onset of response.
- PMC 3449-3 (nivolumab) and 3450-3 (ipilimumab): Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry-based in vitro diagnostic device that is essential to the safe and effective use of nivolumab for patients with tumors that are mismatch repair deficient.
- PMC 3449-4 (nivolumab) and 3450-4: Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid- based in vitro diagnostic device that is essential to the safe and effective use of nivolumab for patients with tumors that are microsatellite instability high.

On September 28, 2018, Bristol-Myers Squibb (BMS) submitted the draft protocol for Study CA2098HW, entitled, "A Phase 3b Randomized Clinical Trial of Nivolumab Alone, or in Combination with Ipilimumab in Participants with Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient Metastatic Colorectal Cancer" as required by PMR 3449-1 and PMR 3450-1, in addition to supporting PMR 3243-1. Further details on the changes to the study design and protocol amendments are outlined in Section 8 under "Protocol Amendments."

In addition to the activity described by the Applicant in Table 3, FDA has the following comments. Further details on the protocol amendments are outlined in Section 8: "Protocol Amendments."

On December 4, 2018, FDA held a teleconference with BMS, and cautioned that Study CA2098HW, as initially designed, was not adequately designed to support regular approval in the first-line setting.

On April 15, 2019, prior to any patients being enrolled, BMS revised Study CA2098HW to a three-arm randomized (2:2:1) study design (Arm A: nivolumab, Arm B: nivolumab plus ipilimumab, Arm C: investigators choice chemotherapy) in up to 447 patients with centrally confirmed dMMR/MSI-H mCRC across multiple lines of therapy.

On August 8, 2020, BMS submitted a major protocol amendment (version 4) to Study CA2098HW expanding the enrollment of patients with dMMR/MSI-H mCRC who are treatment naïve in the metastatic setting (i.e., first line). Approximately 304 patients had been enrolled to the study at the time of the protocol amendment. The study was separated into two parts, Part 1 enrolling patients across all lines of therapy, and Part 2 enrolling patients in the first-line setting. A second primary endpoint comparing nivolumab plus ipilimumab to chemotherapy in the first-line setting was added.

On January 20, 2021, FDA informed BMS that amended (version 4) Study CA2098HW would need to demonstrate that the addition of ipilimumab to nivolumab provides evidence of benefit compared to nivolumab monotherapy.

In a meeting held on February 13, 2024 to discuss the adequacy of CA2098HW results to support the planned sBLA filings and review for full approval for nivolumab in combination with ipilimumab for the first line treatment of adult and pediatric (12 years and older) patients with MSI-H/dMMR mCRC based on the comparison of nivo + ipi compared to chemotherapy alone, FDA informed BMS that, as described in the PMRs, FDA considered that demonstration of the contribution of ipilimumab to the treatment regimen is necessary to convert the accelerated approvals to regular approvals and recommended delaying the submission until data from the comparison nivo+ipi vs. nivo were available.

On March 19, 2024, members of FDA and BMS met (videoconference) to discuss the acceptability of submitting a blinded restricted report with an early unplanned interim look of Arms A vs B. FDA raised concerns regarding study integrity and that the potential issues related to release of data to other, blinded members of BMS or the public.

At a meeting held on July 11, 2024, FDA cautioned BMS that amending the statistical analysis plan after the originally planned analysis has been partially conducted and with part of the patient assignments already unblinded to the study team could potentially have a negative impact on the data integrity and could be a potential review issue.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

FDA clinical and statistical review teams determined that inspections were not needed to confirm the integrity of the data submitted in this application. The decision was based upon the extensive clinical experience with nivolumab and ipilimumab, the review teams' audits of the datasets, lack of notable patterns in patient enrollment, protocol deviations, or efficacy and safety data across sites that would raise concerns regarding data integrity.

4.2. Product Quality

No new product quality was submitted with this Application.

4.3. Clinical Microbiology

NA

4.4. Devices and Companion Diagnostic Issues

Upon approval of nivolumab as a single agent (July 31, 2017 [BLA 125554/S-034]) and nivolumab in combination with ipilimumab (July 10, 2018 [BLA 125554/S-063, BLA 125377/S-096]) for the treatment of MSI-H or dMMR metastatic colorectal cancer (mCRC) that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan, (b) (4)

(b) (4)

5 Nonclinical Pharmacology/Toxicology

The Applicant's Position: No new information is provided in the current submission.

The FDA's Assessment:

NA

X X

Primary Reviewer Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody currently approved for multiple indications for the treatment of various cancers. Nivolumab in combination with ipilimumab is currently approved for multiple solid tumors including the treatment of adult and pediatric (≥12 years) patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) that has progressed following prior treatment for metastatic disease. BLA 125554/S-132 is an efficacy supplement intended to support approval of nivolumab in combination with ipilimumab as the first-line (1L) treatment of adult and pediatric (≥12 years) patients with MSI-H/dMMR CRC. The new indication would revise an existing indication for the treatment of patients with MSI-H/dMMR colorectal cancer as follows:

- Previous indication: adult and pediatric (12 years and older) patients with MSI-H/dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.
- New proposed indications:
  - In combination with ipilimumab, for the treatment of adult and pediatric (12 years and older) patients with MSI-H/dMMR CRC (b) (4)
  - (Nivolumab) As a single agent, for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) (b) (4) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

The request for approval of the new proposed indication is based on the results of Study CA2098HW (CHECKMATE-8HW), a randomized, open-label, 3-arm trial of nivolumab alone (Arm A), nivolumab in combination with ipilimumab (Arm B), or investigator's choice chemotherapy (Arm C) in patients across lines with MSI-H/dMMR CRC. The primary analysis based on data cutoff on 12-Oct-2023 demonstrated statistically significant improvements in PFS for the comparison of nivo+ipi versus chemo in 1L patients (HR: 0.21; 95% CI: 0.14, 0.32); the primary analysis based on data cutoff on 28-Aug-2024 demonstrated statistically significant improvements in PFS for the comparison of nivo+ipi versus nivo in all-lines patients (HR: 0.62; 95% CI: 0.48, 0.81). In addition to CA2098HW, Study CA209142 provided supportive evidence on contribution of components (CoC).

FDA previously agreed to waive the submission of population PK (PopPK) including those with potential posology update of the approved dosing regimens (e.g., 240 mg Q2W, 480 mg Q4W), exposure-response (E-R), and Summary of Clinical Pharmacology (SCP) for the nivo+ipi submissions including Study CA2098HW.

The proposed dosing regimens were informed by the previous clinical data from Study CA209142 and popPK analyses, and supported by the data from Study CA2098HW:

- Adult and pediatric (≥12 years) patients weighing 40 kg or more: nivolumab 240 mg and ipilimumab 1 mg/kg every 3 weeks (Q3W) for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W as maintenance therapy.
- Pediatric (≥12 years) patients weighing less than 40 kg: nivolumab 3 mg/kg and ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W as maintenance therapy.

To support the proposed dosage of nivo+ipi in adolescent (12 to < 18 years) patients, the supplement includes a PopPK report to update the previously developed pediatric PopPK model with additional $3L^+$ CRC data from Study CA209142. The simulated nivolumab and ipilimumab exposures are comparable between adolescent (12 to < 18 years) and adult (≥ 18 years) patients following the proposed dosage regimens.

The immunogenicity data from CA2098HW were comparable to that of previous clinical experience and did not indicate clinically meaningful impact of anti-drug antibodies (ADA) on exposure, safety or efficacy.

Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in BLA 125554/S-132. This BLA supplement is approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The proposed dosing regimens for 1L MSI-H/dMMR CRC are listed in Table 4. Based on prior popPK analysis[20], line of therapy (1L vs 2L+) did not have a significant effect on nivo CL by pooling data from subjects with melanoma, NSCLC, RCC, SCLC, HCC, and CRC. The CL of ipi was lower in subjects receiving 1L therapy relative to subjects who had already received one or more prior therapies; however, the difference's magnitude is not considered clinically relevant (< 20%). Therefore, the proposed combination dosing regimens are predicted to have similar exposures of both nivo and ipi as the approved dosing regimen for 3L+ mCRC patients receiving combination therapy. In addition, CA2098HW demonstrated a favorable benefit-risk profile of nivo 240 mg + ipi 1 mg/kg Q3W for 4 doses, followed by nivo 480 mg Q4W in subjects with

MSI-H/dMMR mCRC, with statistically significant improvements in PFS over chemo and an acceptable safety profile with no new safety concerns identified. The nivo dose of 240 mg Q2W, as an alternative maintenance dose to nivo 480 mg Q4W, was approved in 3L+ CRC patients and is predicted to have similar exposure.

The dosing regimen in adolescents is proposed based on PK-based extrapolation approach. The exposure of the proposed dosing regimens for both nivo and ipi in adolescents are predicted to result in comparable benefit and risk to those in adults.

Table 4: Applicant - Proposed Dosing Regimens of Nivolumab in combination with Ipilimumab for the Treatment of 1L MSI-H/dMMR CRC

Indication	Population	Proposed Dosing Regimens
MSI-H or dMMR unresectable and metastatic CRC	Adult and pediatric patients 12 years and older weighing 40 kg or greater	Nivolumab 240 mg with ipilimumab 1 mg/kg on the same day every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks
	Pediatric patients 12 years and older weighing less than 40 kg	Nivolumab 3 mg/kg with ipilimumab 1 mg/kg on the same day every 3 weeks for a maximum of 4 doses, then nivolumab 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks

Immunogenicity

Analysis of the effect of immunogenicity on PK showed that the observed trough concentrations in subjects with positive ADA (for either nivo or ipi) were within the concentration range observed in subjects with negative ADA (for either nivo or ipi). See Section 8.2.4 for more details of immunogenicity.

The FDA's Assessment:

FDA agrees with the Applicant's position. The proposed dosing regimens were informed by previous clinical data from Study CA209142, previous popPK analyses, and supported by the results from Study CA2098HW. In addition, the proposed dosing regimen for adolescent patients is supported by the updated pediatric PopPK model (refer to the following pharmacometrics assessment).

In Study CA2098HW, the incidence of treatment emergent positive ADA and Nab (i.e., 14% and 8% for nivolumab, 8% and 0.6% for ipilimumab, respectively) were comparable or slightly lower compared to the previous clinical experience in patients with renal cell carcinoma (RCC) or CRC (i.e., 26% ADA and 3% Nab for nivolumab, 5.4% ADA and no Nab for ipilimumab, respectively). No clinically relevant impact on PK, efficacy or safety was observed in Study CA2098HW.

Pharmacometrics Review

Executive Summary

The key pharmacometrics findings are summarized below:

Population PK Analysis

- The simulated exposures between adolescent (12 to < 18 years) and adult (≥ 18 years) patients with colorectal cancer (CRC) using the updated PopPK models are comparable.

Population PK (PopPK) analysis

Review Summary

During a Type C Meeting under IND 142795, dated 13-Jun-2023, FDA agreed to grant BMS a waiver for the submission of PopPK, E-R, and statistical analysis plan analyses and reports for nivolumab + ipilimumab submissions.

The PK parameter estimates of nivolumab and ipilimumab based on the updated PopPK models are similar to those from the previous models. The simulation based on the updated models indicated that predicted nivolumab exposures in adolescents (12 to < 18 years) are comparable to those in adult (≥ 18 years) patients with CRC. However, the Cmax for patients in the lower body weight range (40-50 kg) is slightly higher (27%) than that of adults. The applicant's analyses were verified by the reviewer, with no significant discordances identified.

Dataset

The PopPK analyses of nivolumab and ipilimumab were previously performed includes data from 5 studies with pediatric patients: CA209070, CA209908, CA209744, CA184070, and CA184178. The PopPK models of nivolumab and ipilimumab were updated using PK data in adults with CRC from Study CA20914.

Updated PK models

The PK parameter estimates of nivolumab and ipilimumab based on the updated popPK models have minimal changes as compared to those from the previous models.

Simulation

Dosage in simulation: 4 doses of nivolumab 3 mg/kg Q3W for adolescents weighing < 40 kg or 240 mg Q3W for adolescents weighing ≥ 40 kg and adults in combination with 1 mg/kg ipilimumab, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks.

When administered with the proposed dosing regimen in the maintenance phase (nivolumab 3 mg/kg Q2W for adolescents weighing < 40 kg or 240 mg Q2W for adolescents weighing ≥ 40 kg and adults), simulation results suggested nivolumab steady-state exposures in most adolescent

body weight bands were within the reference ranges in adults across entire spectrum of body weights (≥ 40 kg) (Figure 11, Table 53). In several lower body weight bands (40 to < 60 kg), nivolumab Cavgss (time-averaged concentration under steady state), Cminss (trough concentration under steady state), and Cmaxss (maximum concentration under steady state) were up to 18%, 16.2% and 26.5% higher, respectively, in adolescents compared to the adult reference ranges, with the highest differences seen with lower body weight bands.

Simulation performed with the proposed combination regimen in the initial combination phase suggested ipilimumab exposures following 4th dose of the combination treatment in several adolescent body weight bands were higher than the reference ranges in adult CRC patients across the entire spectrum of body weights (≥ 40 kg) (Figure 12, Table 54). Ipilimumab Cavg4 (time-averaged concentration over the fourth dosing interval), Cmin4 (trough concentration over the fourth dosing interval) and Cmax4 (maximum concentration over the fourth dosing interval) were up to 38.6%, 61.2% and 28% higher, respectively, in adolescents compared to the adult reference ranges, with the highest differences seen with generally higher body weight bands.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

Dose selection rationale

The dosing regimen of nivo 240 mg + ipi 1 mg/kg Q3W for a maximum of 4 doses, followed by nivo 480 mg Q4W were selected for CA2098HW based on the following:

- This dosing regimen was anticipated to have similar exposures of both nivolumab and ipilimumab as approved combo dosing regimen for 3L+ CRC patients, which is nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 240 mg Q2W or nivolumab 480 mg Q4W.
- The E-R relationships of nivo were flat for efficacy and safety over the approved dose range.
- The dose of ipilimumab 1 mg/kg in the combination has been evaluated in clinical studies across multiple tumor types with favorable efficacy and acceptable safety profiles.
- The E-R relationship of ipilimumab was flat for efficacy and shallow for safety over the approved dose range.
- No clinically relevant PK interaction was anticipated between nivolumab 240 mg Q3W and ipilimumab 1 mg/kg Q3W

Dose confirmation

In CA2098HW, the dose of nivolumab 240 mg + ipilimumab 1 mg/kg Q3W followed by nivolumab 480 mg Q4W demonstrated a statistically significant and clinically meaningful improvement in PFS per BICR compared with chemo in 1L subjects with centrally confirmed

MSI-H/dMMR mCRC (Section 8.1.2). The dosing regimen is also supported by an acceptable safety profile (Section 8.2.4). The nivolumab dose of 240 mg Q2W, as an alternative maintenance dose to nivolumab 480 mg Q4W, was approved in 3L+ CRC patients and was predicted to provide similar exposures and comparable benefit and risk profile in 1L CRC patients.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to Section 6.2.1 for the assessment of dosages.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

Based on prior analyses, no intrinsic or extrinsic factors were found to have a clinically relevant impact on nivo or ipi exposure. Therefore, no therapeutic individualization of nivo or ipi is recommended.

PK-based extrapolation was utilized to support dose recommendation in adolescents with MSI-H/dMMR CRC. The simulation results indicated the exposures of the proposed dosing regimen for both nivo and ipi in pediatric patients 12 years and older (Table 4) < 40 kg and > 40 kg are predicted to result in comparable benefit and risk to those in adults.[21,22]

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to Section 6.2.1 for the PopPK assessment supporting dosage for adolescent patients.

6.2.2.3. Outstanding Issues

The Applicant's Position: Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position: No new information is provided in the current submission.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position: No new information. Please refer to Section 6.2 for additional information.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position: Yes, the proposed dosing regimen is appropriate for the general patient population. Please refer to Section 6.2.2.1 for additional information.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to Section 6.2.1 for the assessment of dosages.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (eg, race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position: Dosing individualization is not recommended. Please refer to Section 6.2.2.2 for additional information.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position: None.

The FDA's Assessment:

FDA agrees with the Applicant's position.

X X

Primary Reviewer Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 5: Applicant - Overview of Nivolumab Clinical Studies in mCRC

Study #/NCT # Study Design	Study Population	Treatment	Number of Subjects	Key Efficacy Endpoint	Data Cutoff/ Database Lock
CA2098HW / NCT04008030 Phase 3, randomized, 3-arm open label study of nivo , nivo+ipi or investigator's choice chemo	Subjects with MSI-H/dMMR mCRC per local lab evaluation	Arm A: nivo 240 mg Q2W x6 then nivo 480 mg Q4W Arm B: nivo 240 mg + ipi 1 mg/kg Q3W x4 then nivo 480 mg Q4W Arm C: investigator's choice chemo*	All lines randomized: **Arm A** (N=353) **Arm B** (N=354) **Arm C** (N=132)	PFS per BICR and ORR per BICR in subjects with centrally confirmed MSI-H/dMMR mCRC	Ongoing 28-Aug-2024/ 25-Sep-2024
			1L randomized: **Arm B** (N=202) **Arm C** (N = 101)	PFS per BICR in subjects with centrally confirmed MSI-H/dMMR mCRC	Ongoing 12-Oct-2023/ 15-Nov-2023
CA209142 / NCT02060188 Phase 2, multicohort, open label, non-randomized study of nivo, or nivo combinations	Cohort 1: Subjects with MSI-H/dMMR mCRC per local lab evaluation who received prior treatment	Nivo 3 mg/kg Q2W	N = 74 treated	ORR per BICR, PFS per BICR, and OS	22-Sep-2021/ 04-Nov-2021
	Cohort 2: Subjects with MSI-H/dMMR mCRC per local lab evaluation who received prior treatment	Nivo 3 mg/kg + ipi 1 mg/kg Q3W x 4 doses then nivo 3 mg/kg Q2W	N = 119 treated	ORR per BICR, PFS per BICR, and OS	22-Sep-2021/ 04-Nov-2021
	Cohort 3: Subjects with MSI-H/dMMR mCRC per local lab evaluation who had not received prior therapy	Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W	N = 45 treated	ORR per BICR, PFS per BICR, and OS	25-Sep-2020 22-Oct-2020

* Note: Considering that CA2098HW is a global study, the investigator's choice standard chemotherapy included one of 6 SOC regimens (mFOLFOX-6, FOLFIRI with or without Bevacizumab or Cetuximab) recommended by guidelines for initial mCRC treatment.
Note: Primary endpoint tested for the CA2098HW Interim CSR (DBL 15-Nov-2023): PFS per BICR for nivo+ipi (Arm B) vs chemo (Arm C) in 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC
Note: Primary endpoint tested for the CA2098HW Primary CSR (DBL 25-Sep-2024): PFS per BICR for nivo+ipi (Arm B) vs nivo (Arm A) in all randomized subjects (all lines) with centrally confirmed MSI-H/dMMR mCRC

The Applicant's Position:

The current application for the 1L treatment of nivo combined with ipi in patients with unresectable or metastatic MSI-H/dMMR CRC is based on primarily on data from pivotal study CA2098HW, demonstrating pivotal evidence for positive benefit-risk in the proposed indication. It also includes results from Supportive study CA209142 in support of CoC and long-term outcomes in MSI-H/dMMR patients treated with nivo+ipi (Table 4).

The FDA's Assessment:

FDA generally agrees with the Applicant's description of sources of clinical data outlined in Table 5. In addition to the number of patients who were randomized in Study CA2098HW, Table 6 outlines the number of patients with centrally confirmed MSI-H/dMMR mCRC in each arm of the study, stratified by line of treatment.

Table 6: FDA - Randomized Patients with Centrally Confirmed MSI-H/dMMR mCRC

Treatment Arm	All Randomized Patients	All Randomized Patients Centrally Confirmed dMMR/MSI=H	All Randomized Patients	All Randomized Patients Centrally Confirmed dMMR/MSI=H
	All Lines	All Lines	First Line	First Line
Arm A: Nivolumab	N = 353	N = 286	N = 201	N = 170
Arm B: Nivolumab + Ipilimumab	N = 354	N = 296	N = 202	N = 171
Arm C: Investigator's Choice Chemotherapy	N = 132	N = 113	N = 101	N = 84

Source: FDA Analysis
Abbreviations: dMMR: mismatch repair deficient; MSI-H: microsatellite instability - high

The Applicant provided two separate database locks (DBL) corresponding to the analyses of the primary endpoints for Study CA2098HW (DBL 11/15/23 1L first line analysis nivo+ipi vs chemo, DBL 9/25/24 all lines PFS analysis nivo+ipi vs nivo). FDA performed sensitivity analyses of efficacy for the intent to treat patient populations. The safety analyses are reflective of the as treated patient populations in the respective arms.

8 Statistical and Clinical Evaluation

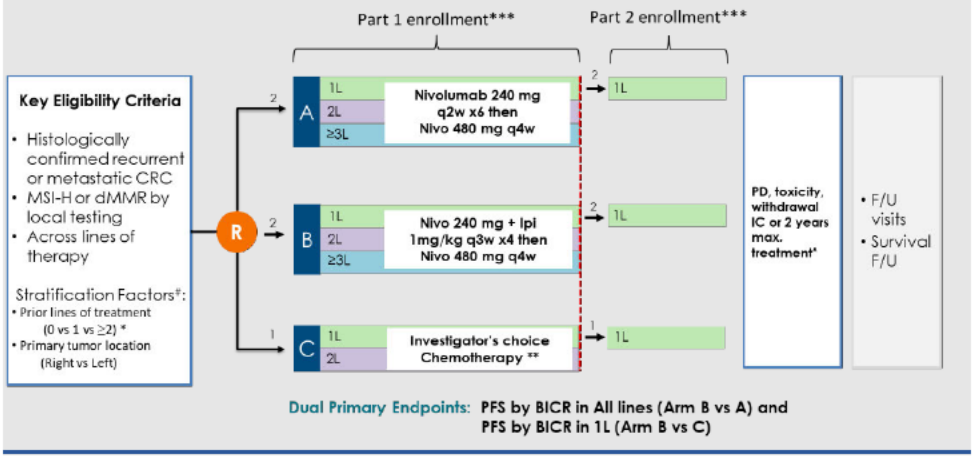
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CA2098HW

Trial Design

The Applicant's Description:

Figure 1: Applicant - CA2098HW Study Design Schematic



1L (0 prior lines of systemic therapy), 2L (1 prior line of systemic therapy) or ≥ 3L (2 or more prior lines of systemic therapy)
The populations for the dual primary endpoints were 1L randomized subjects (Arm B vs C) with centrally confirmed MSI-H/dMMR mCRC or randomized subjects (Arm B vs A) with centrally confirmed MSI-H/dMMR mCRC.
Investigator's choice chemo: FOLFOX or FOLFIRI with or without bevacizumab or cetuximab
Line of therapy was not a stratification factor during Part 2 enrollment.
* Subjects with ≥ 2 prior lines were randomized only to Arm A or B during Part 1; only subjects with 0 prior lines were randomized during Part 2.
** Optional crossover for Arm C with nivo 240 mg Q2W x 6 then nivo 480 mg Q4W + ipi 1mg/kg Q6W.
*** Part 1 enrollment allowed randomization of approximately 560 subjects across lines of therapy with locally confirmed MSI-H/dMMR mCRC. Part 2 enrollment allowed randomization of approximately 271 additional subjects with locally confirmed MSI-H/dMMR who had not received prior therapy for metastatic disease (1L).
^ max treatment duration was not applicable for subjects in Arm C.

CA2098HW is a Phase 3, randomized, 3-arm open-label study of nivo (Arm A), nivo+ipi (Arm B) or investigator's choice chemo (Arm C) for the treatment of subjects with unresectable or metastatic MSI-H/dMMR CRC (Figure 1).

The CA2098HW study has 2 primary objectives: (1) to compare PFS per BICR of nivo+ipi vs chemo as 1L therapy in 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC;

and (2) to compare PFS per BICR of nivo+ipi vs nivo across lines of therapy in all randomized subjects with centrally confirmed MSI-H/dMMR mCRC. The study enrollment included 2 sequential parts. Part 1 enrollment was open to subjects across lines of therapy, and Part 2 enrollment, started immediately after completion of Part 1 enrollment, was open to subjects with no prior treatment for metastatic disease (1L subjects only). Eligible 1L and 2L subjects were randomized to Arm A (nivo), Arm B (nivo+ipi), or Arm C (chemo) in a 2:2:1 ratio. ≥ 3L subjects were randomized to Arm A (nivo) and Arm B (nivo+ipi) in a 1:1 ratio. The subjects in Arm C who had BICR confirmed PD had the option of crossover to nivo plus ipi combination therapy (Crossover Cohort).

Subjects' randomization was stratified by tumor location (right vs left) and by the number of prior treatments for metastatic disease (none, 1, ≥ 2; for Part 1 only). Subjects were required to have known tumor MSI-H or dMMR status per local standard of practice testing to be eligible for enrollment. Tissue samples for study subjects were submitted at screening to the central lab for confirmation of tumor MSI-H/dMMR status.

Table 7: Applicant - CA2098HW Study Design Details

Design Aspect	Description
Trial Locations	CA2098HW is a global study, this submission includes data for 1L subjects in the nivo+ipi and chemo arms and all randomized subjects (all lines) in the nivo+ipi and nivo arms. 303 1L subjects (202 to nivo+ipi, 101 to chemo) were randomized at 88 sites in 22 countries and 839 subjects (354 to nivo+ipi, 353 to nivo arms) were randomized at 118 sites in 23 countries. After reviewing baseline demographics and clinical characteristics of the trial population in the 3 arms and comparing to the overall MSI-H/dMMR CRC population in the US, the trial participants adequately represented the target randomized population with MSI-H/dMMR mCRC.
Choice of Control Group	Investigator's choice chemo
Dose Selection	See Section 6.2.2.1
Enrollment/Assignment to Treatment	Per protocol, eligible subjects were enrolled using IRT, eligible 1L and 2L subjects were randomized 2:2:1 to Arms A (nivo), Arm B (nivo+ipi) or Arm C (chemo), ≥ 3L subjects were randomized to Arm A (nivo) and Arm B (nivo+ipi) in a 1:1 ratio. In Arm C, subjects could receive nivo+ipi upon BICR-documented disease progression (Crossover cohort).
Blinding	The treatments in this study were open-label. The study center staff members and the enrolled subjects were not blinded to treatment assignment. However, the specific treatment was assigned using an IRT. In addition, a BICR was utilized in this study for determination of BICR-assessed endpoints including the primary endpoints (i.e., PFS per BICR); the BICR remained blinded to subject treatment assignment. To prevent bias and objectively assess efficacy and safety, an external independent statistician prepared summaries of the unblinded aggregate efficacy and safety data of interim analyses for the DMC review. The Sponsor remained blinded to any aggregate analyses by treatment arm and comparisons between treatment arms.

Table 7: Applicant - CA2098HW Study Design Details

Design Aspect	Description
	The DMC reviewed the results of the IA for the primary endpoint of PFS per BICR for nivo+ipi vs chemo in 1L randomized subjects with centrally confirmed MSI H/dMMR mCRC on 04-Dec-2023, and informed BMS that study met its primary endpoint. Subsequently, the BMS study team was unblinded to the concluded part of study results and data (nivo+ipi and chemo in 1L subjects only with 12-Oct-2023 data cutoff and 15-Nov-2023 DBL) to prepare the interim CSR. The DMC reviewed the IA results for the other primary endpoint of PFS per BICR for nivo+ipi vs nivo in all randomized subjects with centrally confirmed MSI-H/dMMR mCRC on 14-Oct-2024 and informed BMS that the study met this primary endpoint. The secondary endpoint ORR per BICR with nivo+ipi vs nivo in all lines was tested and met the pre-specified statistical significance. The study was recommended to proceed till the next analysis for the unconcluded secondary endpoints in the hierarchical testing strategy. Subsequently, BMS was unblinded to the concluded study results and data with 28-Aug-2024 data cutoff and 25-Sep-2024 DBL.
Dose Modification/ Discontinuation	Dose escalation or reductions of nivo were not permitted. Dose adjustments of ipi (1 mg/kg) were permitted if the subject's weight on the day of dosing differed by > 10% from the weight used to calculate the dose; in this case, the dose was to be recalculated. Dose reductions were permitted for chemo.
Administrative Structure	An independent DMC was established to assess results of the study interim analyses and provide recommendation on the study conduct. In addition, a BICR was utilized in this study for determination of BICR assessed endpoints including the primary endpoints (i.e., PFS per BICR).
Procedures and Schedule	Assessments for eligibility, safety, efficacy, biomarkers, PK, and PROs were performed during screening, on treatment, and in follow-up based on the Schedule of Activities in the protocol.
Concomitant Medications	The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event): immunosuppressive agents, immunosuppressive doses of systemic corticosteroids, any concurrent anti-neoplastic therapy (i.e., chemo, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer), any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally. Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella) within 100 days post last dose of nivo without or with ipi, non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving study therapy is unknown, concomitant use of non-topical medications known to be a strong inducers or inhibitors of CYP3A4, or strong inhibitors of UGT1A1 is prohibited in participants receiving irinotecan, ongoing treatment with aspirin (>325

Table 7: Applicant - CA2098HW Study Design Details

Design Aspect	Description
	mg per day) or other medications known to predispose participants to gastrointestinal ulceration is prohibited for participants receiving bevacizumab.
Treatment Compliance	Study treatment compliance was monitored by drug accountability as well as the subject's medical records and eCRF.
Treatment Duration	Subjects in the nivo (Arm A) and nivo+ipi (Arm B) arms as well as in the Crossover cohort received treatment until disease progression, toxicity, discontinuation for other reasons, or until they reached the maximum treatment duration of 2 years. An additional year of treatment was allowed if the subjects were late responders (responded in the 2nd year of treatment). Chemo (Arm C) was administered until disease progression or toxicity. Subjects treated with nivo+/-ipi could receive treatment beyond RECIST 1.1 assessed progression if there was a clinical benefit as determined by investigator and therapy was tolerated.

The FDA's Assessment:

The clinical protocol for Study CA2098HW underwent numerous revisions, which are outlined in Section 8: "Protocol Amendments." FDA's assessment of the study design corresponds to the current clinical protocol amendment #10, which was revised on July 1, 2024.

FDA agrees with Applicant's description of the study design. The country of enrollment for patients in Study CA2098HW is outlined in Table 51 (Appendices Section).

Treatment beyond disease progression was permitted in the clinical protocol and outlined in Table 24.

Eligibility Criteria

The Applicant's Description:

The study population included subjects with histologically confirmed recurrent or metastatic CRC with known tumor MSI-H or dMMR status per local testing. All subjects were to have measurable disease by CT or MRI per RECIST 1.1 criteria and an ECOG PS ≤ 1.

Key Inclusion and Exclusion Criteria:

- In Part 1, subjects were enrolled irrespective of prior treatment history with chemo and/or targeted agents not amenable to surgery.
- In Part 2, enrollment was limited to subjects with no prior treatment history with chemo and/or targeted agents for metastatic disease and not amenable to surgery.

The following subjects were excluded from the study:

- Subjects with active brain metastases or leptomeningeal metastases
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization.
- Subjects who received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including prior therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents.

The FDA's Assessment:

FDA agrees with the summary of the key eligibility criteria. Details on the acceptable local MSI/MMR status testing and panel description specified for use in Study CA2098HW are outlined in the Appendices section (Table 52).

Additional pertinent inclusion criteria included:

1. Participants were required to provide adequate tumor tissue (either formalin-fixed paraffin-embedded [FFPE] or unstained tumor tissue sections) prior to randomization
    a. The tissue was obtained within 3 months of enrollment with no intervening systemic therapies with the same sample being used for local testing
    b. Archival tissue was acceptable if (a) not available, and the same tissue was used for MMR/MSI testing.

MSI and/or MMR was determined centrally on pre-treatment tissue using the Biocartis Idylla MSI test, and MMR was determined using the Agilent MMR IHC Panel pharmDx (Dako Omnis) assay.

Following an FDA information request, BMS provided further information on the local testing results of all randomized patients. Out of the 839 patients randomized, 836 had a positive local test result, with 3 patients identified as being randomized without a positive local test (2 patients in Arm B [nivo + ipi], 1 patient in Arm A [nivo]). Of the 836 subjects with 1 or more positive local results, 691 (83%) had a positive IHC test and 347 (42%) had a positive PCR/NGS test Table 8 summarizes the results by testing method and local vs. central. Although only 83% of the overall study population had centrally confirmed MSI-H/dMMR status, 95% of patients diagnosed by IHC had central test confirming their status.

Table 8: FDA – Local versus Central Test Results of All Randomized Patients

Treatment Arm	Local Test Positive (N)	Central Test Positive (N)
dMMR by IHC		

Arm A (nivo)	282	271
Arm B (nivo + ipi)	296	280
Arm C (chemo)	113	111
MSI-H either by PCR or NGS local testing		
Arm A (nivo)	153	246
Arm B (nivo + ipi)	147	257
Arm C (chemo)	47	96
Either MSI-H or dMMR		
Arm A (nivo)	352	286
Arm B (nivo + ipi)	352	296
Arm C (chemo)	132	113

Source: Adapted from response to FDA Information Request

Abbreviations: Chemo: chemotherapy; IHC: immunohistochemistry; dMMR: mismatch repair deficient; MSI-H: microsatellite instability high; NGS: next generation sequencing; ipi: ipilimumab; nivo: nivolumab; PCR: polymerase chain reaction

Whenever samples were available, biomarker status of all study subjects was centrally confirmed using both an IHC test and a PCR test, hence the higher number of patients with positive central PCR test.

FDA verified sensitivity analyses to assess the magnitude of the treatment effect on the intent to treat patient population.

Study Endpoints

The Applicant's Description:

The primary endpoint of the study is PFS per BICR. Although OS is considered the most reliable cancer endpoint, PFS has been an acceptable endpoint to support regulatory approvals in mCRC in 1L setting, when effect on PFS is statistically robust and clinically important. In addition, to support PFS results, the study has ORR and OS as secondary endpoints.

This document provides results from the planned interim analysis on the primary endpoint of PFS per BICR per RECIST 1.1 among 1L subjects randomized to nivo+ipi arm (Arm B) vs chemo arm (Arm C) who had centrally confirmed MSI-H/dMMR mCRC per the 12-Oct-2023 data cutoff. This document also provides results with the data cutoff of 28-Aug-2024 for the other primary endpoint PFS per BICR for nivo+ipi (Arm B) vs nivo (Arm A) in all randomized subjects (all lines) with centrally confirmed MSIH/dMMR mCRC. In addition, results of the other secondary endpoints such as PFS per investigator, and ORR by BICR for nivo+ipi vs nivo are provided (Table 9).

Table 9: Applicant - Primary and Secondary Endpoints for CA2098HW

Primary Endpoints	Population of Subjects	Tested/Not tested (Data Cutoff)
PFS per BICR per RECIST 1.1	1L subjects randomized to nivo+ipi arm vs chemo arm with centrally confirmed MSI-H/dMMR mCRC	Tested (12-Oct-2023)
	all subjects randomized to nivo+ipi arm vs nivo arm with centrally confirmed MSI-H/dMMR mCRC	Tested (28-Aug-2024)
Select secondary endpoints		
PFS per BICR per RECIST 1.1	1L subjects randomized to nivo+ipi vs chemo arm with MSI-H/dMMR mCRC per local testing	Descriptively analyzed (12-Oct-2023)
	1L subjects randomized to nivo+ipi arm vs nivo arm with centrally confirmed MSI-H/dMMR mCRC	Tested per hierarchical testing strategy (28-Aug-2024) but remains blinded because did not reach criteria for statistical significance
PFS per Investigator per RECIST 1.1	1L subjects randomized to nivo+ipi arm vs chemo arm with centrally confirmed MSI-H/dMMR mCRC	Descriptively analyzed (12-Oct-2023)
	all subjects randomized to nivo+ipi arm vs nivo arm with centrally confirmed MSI-H/dMMR mCRC	Descriptively analyzed (28-Aug-2024)
ORR by BICR per RECIST 1.1	1L subjects randomized to nivo+ipi arm vs chemo arm who had centrally confirmed MSI-H/dMMR mCRC	Not tested per hierarchical testing strategy (28-Aug-2024)
	all subjects randomized to nivo+ipi arm vs nivo arm who had centrally confirmed MSI-H/dMMR mCRC	Tested per hierarchical testing strategy (28-Aug-2024)
OS	1L subjects randomized to nivo+ipi arm vs chemo arm with centrally confirmed MSI-H/dMMR mCRC	Not tested per hierarchical testing strategy (28-Aug-2024)
	all subjects randomized to nivo+ipi arm vs nivo arm who had centrally confirmed MSI-H/dMMR mCRC	
	1L subjects randomized to nivo+ipi arm vs nivo arm with centrally confirmed MSI-H/dMMR mCRC	

The FDA's Assessment:
FDA agrees with the Applicant's description of primary and select secondary endpoints.

Statistical Analysis Plan and Amendments
The Applicant's Description:

The SAP version 3.0 (dated 31-Jul-2023) is provided in Appendix 16.1.9 of the Interim CSR. The SAP version 4.0 (dated 05-Sep-2024) is provided in Appendix 16.1.9 of the Primary CSR.

Primary Endpoint: PFS for Arm B vs C, 1L (SAP version 3.0)

For PFS per BICR for nivo+ipi (Arm B) vs chemo (Arm C) in 1L subjects with centrally confirmed MSI-H/dMMR mCRC, based on simulations, approximately 125 PFS events would provide about 99% power to detect an average HR of 0.55 with a 2-sided alpha of 0.044. It was required to randomize approximately 230 1L subjects with centrally confirmed MSI-H/dMMR mCRC to the nivo+ipi and chemo arms during Part 1 and Part 2 enrollment at a 2:1 ratio.

An IA was planned and to be conducted when 85% of the total number of events were observed (approximately 106 events) and after the last subject was randomized in Part 2. At the time of the interim analysis (12-Oct-2023 data cutoff, 15-Nov-2023 DBL), the information fraction was 80.0% (100/125).

Other Primary Endpoint: PFS for Arm B vs A, All Lines (SAP version 4.0)

Since PFS per BICR for nivo+ipi (Arm B) vs chemo (Arm C) in 1L subjects with centrally confirmed MSI-H/dMMR mCRC met the pre-specified statistical criteria at the interim analysis, 0.024 alpha was passed to PFS per BICR for nivo+ipi (Arm B) vs nivo (Arm A) in all lines. Combining the initially assigned 0.006 alpha with the 0.024 alpha, an overall alpha of 0.03 was to be used for testing PFS for nivo+ipi vs nivo in all lines. Approximately 319 PFS events will provide about 96.8% power to detect a HR of 0.635 with a 2-sided alpha of 0.03. It was required to randomize approximately 564 subjects across lines with centrally confirmed MSI-H/dMMR mCRC to the nivo+ipi and nivo arms during Part 1 and Part 2 enrollment at a 1:1 ratio.

An interim analysis was planned 5 years after the first subject was randomized, which was around Aug-2024. It was projected that approximately 240 PFS events (~ 75% information fraction) would be reached around Aug-2024.

At the time of the interim analysis of this primary endpoint (28-Aug-2024 data cutoff, 25-Sep-2024 DBL), the information fraction was 74.3% (237/319).

Key Secondary Endpoint: ORR for Arm B vs A, All lines (SAP version 4.0)

Since PFS per BICR for nivo+ipi (Arm B) vs nivo (Arm A) in all lines met the pre-specified statistical criteria at the interim analysis, 0.006 alpha was passed to ORR per BICR for nivo+ipi (Arm B) vs nivo (Arm A) in all lines. Based on an assumed 18% difference in ORR between nivo+ipi vs nivo, approximately 564 subjects across lines with centrally confirmed MSI-

H/dMMR mCRC to the nivo+ipi and nivo arms will provide about 93.1% power to show a statistically significant result in ORR with a 2-sided alpha of 0.006.

Table 10: Applicant - CA2098HW Statistical Analysis Plan

Endpoint	Description
Primary and Secondary (PFS)	The primary efficacy endpoint was compared via a 2-sided stratified log rank test with stratification factor of tumor sidedness (left vs right) and prior lines of therapy (0, 1, ≥ 2) whenever applicable for statistical significance. The primary definition of PFS accounts for subsequent therapy by censoring at the last evaluable tumor assessment on or prior to the date of subsequent therapy including crossover treatment. The EMA PFS definition does not apply censoring at subsequent anti-cancer therapy usage. The HR between treatment arms with its associated 100 * (1 - a)% CI was estimated via a stratified Cox proportional hazards model, with treatment arm as the only covariate. Ties were handled using the exact method. The PFS function for each treatment arm was estimated using the KM product limit method and displayed graphically. Median PFS with a 2-sided 95% CI using the Brookmeyer and Crowley method (with log-log transformation) was computed. PFS rates at fixed time points (eg, 6, 12, 18 months) were presented along with their associated 95% CIs. These estimates were derived from the KM estimate and corresponding CIs were derived based on Greenwood formula[23] for variance derivation and on log-log transformation applied on the survivor function.[24] The source of PFS event (progression or death) and the status of subjects who were censored in the PFS KM analysis was summarized by treatment arm. For PFS per BICR, the influence of baseline demographic characteristics on the treatment effect was explored via subset analyses using Forest plots of the unstratified PFS HRs (along with the 95% CIs). For each comparison, median PFS was based on KM product-limit method along with 2-sided 95% CIs. The secondary PFS endpoints in the testing hierarchy were analyzed the same way with the primary endpoints. For other PFS endpoints (e.g. PFS per investigator) that not in the testing hierarchy, the HR between treatment arms with its associated 95% CI was estimated via a stratified Cox proportional hazards model, with treatment arm as the only covariate. PFS for each treatment arm was estimated and plotted using the KM product limit method. Median PFS with a 2-sided 95% CI using the Brookmeyer and Crowley method (with log-log transformation) was computed. PFS rates, source of PFS event and the status of subjects who were censored in the PFS OM analysis were evaluated the same way with the primary endpoint.

Table 10: Applicant - CA2098HW Statistical Analysis Plan

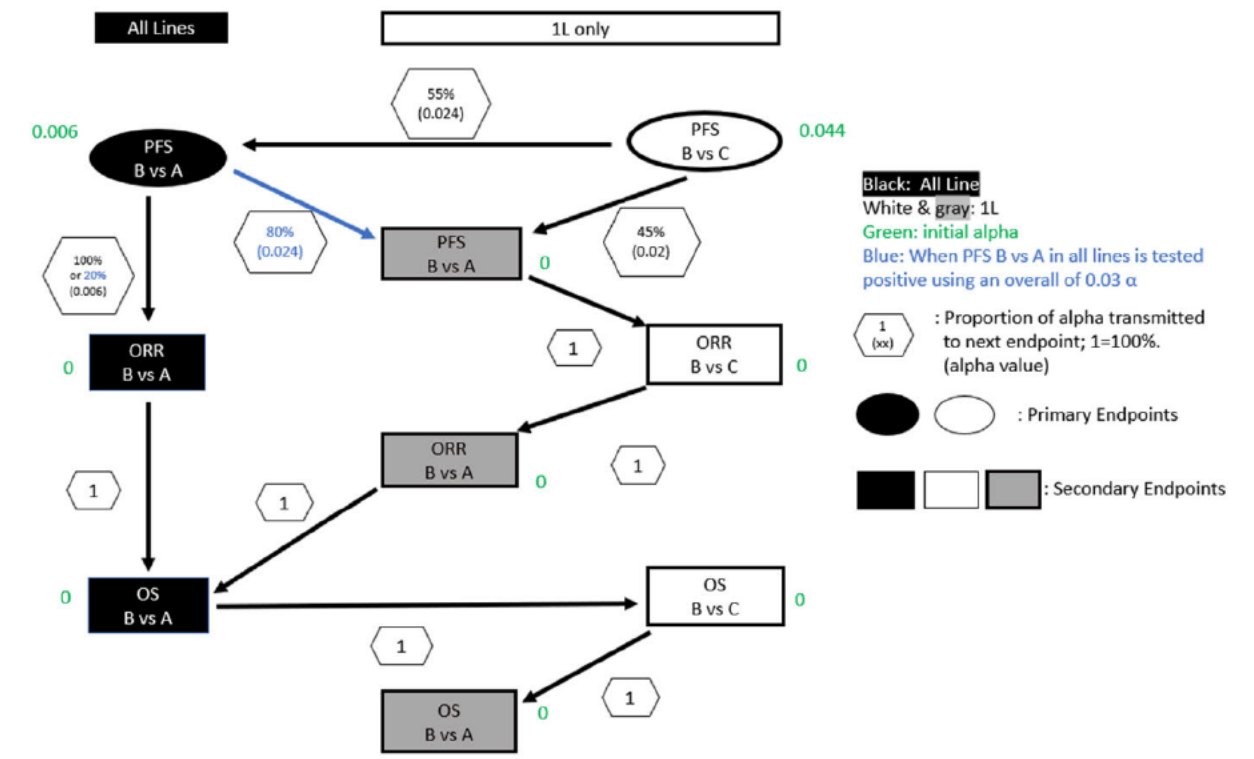
Endpoint	Description
Secondary (ORR)	ORR per BICR was compared via a 2-sided stratified CMH test with stratification factors and the α passed from the precedent test. An estimate of the difference in ORR per BICR and corresponding 100(1-a)% CI was calculated using CMH methodology and adjusted by the stratification factors. The stratified odds ratios (Mantel-Haenszel estimator) between the treatments was provided along with the 100(1-a)% CI For ORR per BICR, the influence of baseline demographic and disease characteristics on the treatment effect was explored via additional subset analyses using Forest plots. The unweighted differences in ORR between the 2 treatment arms and corresponding 95% 2-sided CI using the method of Newcombe were provided.
Exploratory (PFS2)	PFS2 was analyzed similarly to PFS. PFS2 is defined as the time from randomization to the date of investigator-defined documented disease progression per RECIST 1.1 after the start of next line of therapy, start of second next line therapy or death from any cause, whichever occurred first. Crossover treatment was considered one line of therapy. Clinical deterioration was not considered as progression. Subjects who were alive and without progression after the next line of therapy were censored at last known alive date.
Exploratory (Safety)	Descriptive statistics of safety were presented using NCI CTCAE version 5.0 by treatment arm. The safety data for the chemo arm excluded data after the first crossover dose, except for the death summaries. All on-study AEs, drug-related AEs, SAEs, drug-related SAEs, IMAEs, Select AEs, and OESIs were tabulated using worst grade by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, liver function and renal function were summarized using worst grade. Frequency, management, and resolution of IMAEs and Select AEs were analyzed.
Exploratory (PRO)	For EORTC QLQ-C30 and EORTC QLQ-CR29, all scales and single items were scored on categorical scales and linearly transformed to 0-to-100 scales with higher scores for functional scales/items (and EORTC QLQ-C30 global health status) representing higher levels of functioning/QoL and higher scores for symptom scales/items representing a higher level of symptoms. For EORTC QLQ-C30 scales, a meaningful difference in the change from baseline was ≥ 10 points.[25] For EQ-5D-3L VAS, respondents rated his/her general health using a scale ranging from 0 to 100 with 0 being the worst imaginable health state and 100 being the best imaginable health state. A meaningful change from baseline was 7 points for EQ-5D-3L VAS scores and 0.08 for EQ-5D-3L UI scores.[26] The following descriptive PRO analyses were conducted: questionnaire completion rates, mean score and mean change from baseline were summarized, and a line graph summarizing the mean changes from baseline was produced for all scales. The proportion of reported problems by level was also summarized for the EQ-5D descriptive system items.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the SAP. FDA adds that per the censoring rules for the primary endpoint if a participant had two or more consecutively missing disease assessments, the participant's PFS time was not censored. Sensitivity analyses censoring the PFS time at the last disease assessment date prior if there were two or more consecutively missing disease assessments prior to PFS event were conducted to evaluate the robustness of the primary analysis results.

Per hierarchical testing strategy as shown in Figure 2, the OS comparison in all line nivo+ipi (Arm B) vs nivo (Arm A) should have a two-sided alpha of 0.006 if the ORR comparison in all line nivo+ipi (Arm B) vs nivo (Arm A) demonstrates a p-value passing the superiority boundary at two-sided 0.006. However, per the Section 7.5.1 of the SAP version 4.0, OS will be tested at an interim analysis only if all its precedent endpoints meet the pre-specified statistical criteria. Therefore, OS in all line nivo+ipi (Arm B) vs nivo (Arm A) was not formally tested because ORR in 1L nivo+ipi (Arm B) vs nivo (Arm A) was not tested per the hierarchical testing strategy.

Figure 2: FDA - Multiple testing plan of Study CA2098HW.



Source: Page 77 of SAP version 4.0 provided by the Applicant.

See the major changes from SAP version 3.0 to version 4.0 and the FDA assessment in the Protocol Amendments section for Global Protocol Amendment 10.

Protocol Amendments

The Applicant's Description:

The original protocol for this study was dated 03-Apr-2018. As of the clinical data cutoff (12-Oct-2023), there were 9 global revisions/amendments, and 4 administrative letters; in addition, there were other country- or site-specific revisions/amendments. As of the 28-Aug-2024 data cutoff, there was 1 more global amendment, Protocol Amendment 10. The original protocol and the global changes to CA2098HW after the original protocol are summarized in Table 11.

Table 11: Applicant - Summary of Original Protocol and Key Global Changes to Protocol CA2098HW

Document /Date	Summary of Key Changes	Planned Sample Size	Subjects Randomized at time of Amendment
Original Global Protocol 03-Apr-2018	• Initially designed as a Phase 2, single-arm study of nivo monotherapy for the treatment of subjects with previously treated recurrent or metastatic MSI-H (by local testing) CRC. • Primary endpoints: ORR and DoR by BICR	97 treated subjects (with centrally confirmed MSI-H/dMMR mCRC)	0
Revised Global Protocol 02[a] 20-Dec-2018	• Added a nivo+ipi arm and modified the study design to become a randomized controlled trial to compare nivo to nivo+ipi therapy in subjects with previously treated and previously untreated MSI-H/dMMR mCRC. • **Changed the primary endpoint to PFS per BICR for nivo+ipi vs nivo in subjects across lines of therapy (all lines)** • Included OS, BICR-assessed ORR, DCR and DoR, and investigator-assessed PFS, ORR, DCR, and DCR as key secondary endpoints.	380 randomized subjects (with centrally confirmed MSI-H/dMMR mCRC)	0
Revised Global Protocol 03 28-Mar-2019	• Added a standard of care arm (Arm C: chemo) that enrolled subjects in the 1L and 2L settings. • Added secondary endpoints (BICR and Investigator-assessed PFS, ORR) to compare nivo+ipi vs chemo in the1L and 2L settings.	447 randomized subjects (with centrally confirmed MSI-H/dMMR mCRC)	0

Table 11: Applicant - Summary of Original Protocol and Key Global Changes to Protocol CA2098HW

Document /Date	Summary of Key Changes	Planned Sample Size	Subjects Randomized at time of Amendment
	• Added a Crossover Cohort: subjects in Arm C (chemo) who experienced disease progression per RECIST 1.1 by BICR had an option to receive nivo+ipi therapy.		
Revised Global Protocol 04 17-Jul-2020	• Expanded enrollment of 1L subjects who had not received prior therapy for metastatic disease. • Part 1 enrollment was open to subjects across all lines of therapy. • Part 2 enrollment began immediately after Part 1 enrollment and was open only to subjects who had not received prior therapy for metastatic disease (1L subjects). • **Added a second primary endpoint (PFS per BICR of nivo+ipi vs chemo in 1L subjects).** • Additional changes to statistical analyses included separate secondary objectives for All lines (all randomized subjects), 1L, CDx (All lines and 1L), and the Crossover Cohort. Included exploratory objectives for the Crossover Cohort.	Part 1: 492 randomized subjects (local testing) 442 randomized subjects (with centrally confirmed MSI-H/dMMR mCRC) Part 2: 256 randomized subjects (local testing) 230 randomized subjects (with centrally confirmed MSI-H/dMMR mCRC)	304
Global Protocol Amendment 05[b] 18-Nov-2020	• Updated dose modification criteria for IO therapy and IO-related AE management algorithms. • Incorporated program level updates: SARS-CoV-2 requirements, and male contraception requirements in connection with IO therapy.	Same as Revised Protocol 04	508[c]
Global Protocol Amendment 06[b] 01-Oct-2021	• Updated the statistical testing strategy for the primary endpoints. • Reduced the frequency of tumor assessments after the first 2 years from randomization. • Year 3: every 16 weeks (+/- 7 days) until BICR confirmed progression • Year 4 and beyond: every 24 weeks (+/- 7 days) until BICR confirmed progression	Same as Revised Protocol 04	666

Table 11: Applicant - Summary of Original Protocol and Key Global Changes to Protocol CA2098HW

Document /Date	Summary of Key Changes	Planned Sample Size	Subjects Randomized at time of Amendment
Global Protocol Amendment 07[b] 10-May-2022	• Revised the projection of the number of randomized subjects based on local MSI-H/dMMR status. • Updated and streamlined the statistical analyses schedule. • Included additional safety language for oxaliplatin use. • Clarified contraception requirements for study subjects.	Part 1: 560 randomized subjects (local testing) 442 randomized subjects (with centrally confirmed MSI-H/dMMR mCRC)[d] Part 2: 271 randomized subjects (local testing) 230 randomized subjects (with centrally confirmed MSI-H/dMMR mCRC)[d]	748
Global Protocol Amendment 09[b] 01-Jun-2023	• To allow the option of conducting an interim analysis of PFS for Arm B (nivo+ipi) vs Arm C (chemo) in 1L and PFS for Arm B (nivo+ipi) vs Arm A (nivo) in all randomized subjects at separate times if they were not projected to occur around the same time, and if separate database locks were operationally feasible.	Same as Protocol Amendment 07[d]	839[e]
Global Protocol Amendment 10[b] 01-Jul-2024	• Removed the study wise final analysis (OS final analyses) and added an interim analysis of PFS for Arm B (nivo+ipi) vs Arm A (nivo) in all lines at the pre-planned analysis at 5-year from first subject randomized. • Updated the timing of the final analysis for PFS Arm B (nivo+ipi) vs Arm A (nivo) in all lines to occur at approximately the 2-year minimum follow-up of all randomized subjects. • Updated the timing of the final OS analyses to no later than achieving 3-year minimum follow-up in all randomized subjects.	Same as Protocol Amendment 07[d]	839[e]

[a] Revised Global Protocols 01 and 02 were not released to the sites.

[b] Effective Oct-2020, a companywide change occurred regarding the presentation of protocol revisions. All global revisions were given amendment numbers instead of revision numbers. [c] Enrollment to Part 1 of the study was completed on 30-Nov-2020.
[d] The sample size of randomized subjects with centrally confirmed MSI-H/ dMMR mCRC remained unchanged since Protocol Amendment 04.
[e] The number of randomized subjects does not include subjects who were randomized in the China sub-study. Originally, 841 were reported as the number of subjects randomized at the time of Global Protocol Amendment 09 in the Interim CSR, which included 2 subjects who were re-randomized and counted twice (each had 2 patient IDs).
Source: CA2098HW protocol and protocol amendments.

The FDA's Assessment:

FDA agrees with the description above. Additional details regarding pertinent regulatory interactions and feedback provided are outlined below.

FDA assessed that the Protocol Amendment 10 had minimal risk of impacting study integrity and inflating type-1 error for the following reasons: 1) Although the PFS per BICR data of nivo+ipi vs chemo in 1L were unblinded to the study team in the first interim look, the comparative results of PFS per BICR of nivo+ipi vs nivo in all lines were still blinded at the time of the protocol amendment, which was not the case of modifying analysis plan based on early unblinded efficacy data; 2) There was unlikely to be a relevant impact on patient management based on this protocol amendment as all the patients randomized to the nivo+ipi arm had finished the planned ipilimumab treatment (Q3W x 4) at the time of the protocol amendment (449 days after the last patient randomization); and 3) The PFS endpoint was assessed by BICR which reduced the risk of potential study integrity issue in physician bias.

8.1.2. Study Results from CA2098HW

Compliance with Good Clinical Practices

The Applicant's Position:

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with GCP, as defined by the International Council for Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The protocol, amendments, and subject informed consent received appropriate approval by the IRB/IEC prior to initiation of study at the site. Each IRB/IEC was composed of a review panel that was responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in the clinical investigation and was adequately constituted to provide assurance of that protection.

The FDA's Assessment:

FDA acknowledges the Applicant's position. The clinical protocol contained standard language on study conduct and compliance with Good Clinical Practice, ethical principles underlying European Union Directive 2001/20/EC, and United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The Applicant provided details on 3 GCP deviations outlined below:

1. On September 20, 2021, the Applicant identified a delay in the automated processes for republishing documents from their document management system to the shared investigator platform. The Applicant confirmed that this delay did not impact the reporting of safety reports to health authorities and ethics committees.

2. On March 28, 2022, the Applicant identified an error with their shared investigator platform integration, resulting in a delay in distribution of the ipilimumab Investigator's Brochure (IB). The Applicant confirmed that the nivolumab IB was circulated, containing the relevant safety information for the nivolumab and ipilimumab combination. The Applicant has placed additional monitoring mechanisms daily to ensure timely distribution of IBs.

3. On October 19, 2020, the Applicant stated that the refence safety information for oxaliplatin and irinotecan was not obtained as required from the Irish health authority. The Applicant confirmed that there was 1 patient enrolled in Ireland, who received nivo + ipi.

FDA review acknowledges that the cited GCP protocol deviations are unlikely to have had a significant impact on patient safety or the integrity of the study findings, and the Applicant has already implemented corrective measures in response to each individual deviation identified.

Financial Disclosure

The Applicant's Position:

Financial interests or arrangements with clinical investigators have been disclosed (see Appendix 19.2). Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the CA2098HW clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

The FDA's Assessment:

See Appendix 19.2.

Patient Disposition

Data:

Table 12: Applicant - Key Dates and Follow-up- CA2098HW

12-Oct-2023 Clinical Cutoff (15-Nov-2023 DBL)	
First Subject Randomized Date	
All 1L Randomized Subjects (Arms B and C)	19-Aug-2019
All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR (Arms B and C)	30-Sep-2019
Date Last Subject for the Analysis was Randomized	10-Apr-2023
Minimum Follow-up (months)[a]	6.1
Median Follow-up (min, max) months[b]	
All 1L Randomized Subjects	31.51 (6.1, 48.4)
All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR	31.57 (6.1, 48.4)
Median Follow-up for Survival (min, max) months[c]	
All 1L Randomized Subjects	22.51 (0, 48.4)
All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR	24.28 (0, 48.4)
28-Aug-2024 Clinical Cutoff (25-Sep-2024 DBL)	
First Subject Randomized Date	
All Randomized Subjects	16-Aug-2019
Date Last Subject for the Analysis was Randomized	10-Apr-2023
Minimum Follow-up (months)[a]	16.7
Median Follow-up (min, max) months[b]	
All Randomized Subjects	47.01 (16.7, 60.5)
All Randomized Subjects with Centrally Confirmed MSI-H/dMMR	47.11 (16.7, 60.5)
Median Follow-up for Survival (min, max) months[c]	
All Randomized Subjects	34.60 (0.0, 59.2)
All Randomized Subjects with Centrally Confirmed MSI-H/dMMR	39.16 (0.0, 59.2)

[a] Minimum follow-up: time from the last subject's randomization date to the clinical data cutoff date.
[b] Follow-up: time between date of randomization and the data cutoff date.
[c] Follow-up for survival: time between randomization date and the last known alive date (for subjects who are alive) or death date.
Source: ADSL, ADEFTTES of the CA2098HW Interim CSR

Table 13: Applicant - Subject Disposition - All 1L Randomized and 1L Treated Subjects in the Nivo+Ipi and Chemo Arms in CA2098HW (15-Nov-2023 DBL)

Status, n (%)	All 1L Subjects		
	Arm B: Nivo+Ipi	Arm C: Chemo	Total
Randomized	202	101	303
Treated	200 (99.0)	88 (87.1)	288 (95.0)
Not Treated	2 (1.0)	13 (12.9)	15 (5.0)
Reason for not treated			
Subject withdrew consent	0	6 (5.9)	6 (2.0)
Subject no longer meets study criteria	1 (0.5)	2 (2.0)	3 (1.0)
Other[a]	1 (0.5)	5 (5.0)	6 (2.0)
Ongoing treatment	42 (21.0)	6 (6.8)	48 (16.7)
Completed treatment	62 (31.0)	0	62 (21.5)
Discontinued treatment	96 (48.0)	82 (93.2)	178 (61.8)
Reason for discontinuation of treatment			
Subject withdrew consent	0	1 (1.1)	1 (0.3)
Death	2 (1.0)	0	2 (0.7)
Pregnancy	1 (0.5)	0	1 (0.3)
Subject no longer meets study criteria	1 (0.5)	0	1 (0.3)
Other	6 (3.0)	3 (3.4)	9 (3.1)
Disease progression	38 (19.0)	61 (69.3)	99 (34.4)
Study drug toxicity	36 (18.0)	4 (4.5)	40 (13.9)
Adverse event unrelated to study drug	12 (6.0)	5 (5.7)	17 (5.9)
Maximum clinical benefit	0	8 (9.1)	8 (2.8)
Discontinued treatment due to COVID-19	2 (1.0)	0	2 (0.7)
Ongoing study[a]	152 (76.0)	50 (56.8)	202 (70.1)
Discontinued study[a]	48 (24.0)	38 (43.2)	86 (29.9)
Reason for discontinuation of study			
Death	44 (22.0)	32 (36.4)	76 (26.4)
Lost to follow-up	1 (0.5)	0	1 (0.3)
Subject withdrew consent	2 (1.0)	3 (3.4)	5 (1.7)
Other	1 (0.5)	3 (3.4)	4 (1.4)

Only 1L subjects are included for nivo+ipi arm and chemo arm. Percentages based on subjects entering period.
End of treatment status evaluated at the end of main period treatment for subjects continued to crossover.
[a] Includes data from crossover period.

Source: ADSL of the CA2098HW Interim CSR

Table 14: Applicant - Subject Disposition - All Randomized and Treated Subjects in CA2098HW (25-Sep-2024 DBL)

Status, n (%)	All Subjects			
	Arm A: Nivo	Arm B: Nivo+Ipi	Arm C: Chemo	Total
Randomized	353	354	132	839
Treated	351 (99.4)	352 (99.4)	115 (87.1)	818 (97.5)
Not Treated	2 (0.6)	2 (0.6)	17 (12.9)	21 (2.5)
Reason for not treated				
Subject withdrew consent	0	0	9 (6.8)	9 (1.1)
Subject no longer meets study criteria	2 (0.6)	1 (0.3)	2 (1.5)	5 (0.6)
Other	0	1 (0.3)	6 (4.5)	7 (0.8)
Ongoing treatment	13 (3.7)	20 (5.7)	0	33 (4.0)
Completed treatment	137 (39.0)	159 (45.2)	0	296 (36.2)
Discontinued treatment	201 (57.3)	173 (49.1)	115 (100.0)	489 (59.8)
Reason for discontinuation of treatment				
Subject withdrew consent	1 (0.3)	1 (0.3)	1 (0.9)	3 (0.4)
Death	2 (0.6)	4 (1.1)	0	6 (0.7)
Pregnancy	0	1 (0.3)	0	1 (0.1)
Subject no longer meets study criteria	0	1 (0.3)	0	1 (0.1)
Other	5 (1.4)	13 (3.7)	6 (5.2)	24 (2.9)
Disease progression	137 (39.0)	82 (23.3)	85 (73.9)	304 (37.2)
Study drug toxicity	28 (8.0)	48 (13.6)	8 (7.0)	84 (10.3)
Adverse event unrelated to study drug	28 (8.0)	22 (6.3)	6 (5.2)	56 (6.8)
Maximum clinical benefit	0	1 (0.3)	9 (7.8)	10 (1.2)
Discontinued treatment due to COVID-19	2 (0.6)	2 (0.6)	1 (0.9)	5 (0.6)
Ongoing study (1)	195 (55.6)	239 (67.9)	60 (52.2)	494 (60.4)
Discontinued study (1)	156 (44.4)	113 (32.1)	55 (47.8)	324 (39.6)
Reason for discontinuation of study				
Death	139 (39.6)	100 (28.4)	47 (40.9)	286 (35.0)
Lost to follow-up	0	4 (1.1)	0	4 (0.5)
Subject withdrew consent	8 (2.3)	6 (1.7)	4 (3.5)	18 (2.2)
Other	9 (2.6)	3 (0.9)	4 (3.5)	16 (2.0)

(1) Includes data from Crossover period/cohort. The Crossover cohort included subjects in the chemo arm who experienced documented progression of disease and crossed over to receive nivo+ipi therapy.

Percentages based on subjects entering period.
End of treatment status evaluated at the end of main period treatment for subjects continued to crossover.
Source: ADSL of the CA2098HW Primary CSR

Table 15: Applicant - Efficacy Analysis Populations - CA2098HW

Data cutoff/ DBL	Population	Description	Number of Subjects		
			Arm A: Nivo	Arm B: Nivo+Ipi	Arm C: Chemo
12-Oct-2023/ 15-Nov-2023	1L randomized subjects	MSI-H/dMMR mCRC per local testing	NA*	202	101
	1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC	MSI-H/ dMMR mCRC confirmed by central lab	NA*	171	84
28-Aug-2024/ 25-Sep-2024	All randomized subjects	MSI-H/dMMR mCRC per local testing	353	354	NA*
	All randomized subjects with centrally confirmed MSI-H/dMMR mCRC	MSI-H/ dMMR mCRC confirmed by central lab	286	296	NA*

* Arm not included in efficacy analyses for the applicable clinical cutoff/DBL
Source: ADSL of the CA2098HW Interim CSR, ADSL of the CA2098HW Primary CSR

The Applicant's Position:

In CA2098HW, 839 subjects with MSI-H/dMMR mCRC per local testing (all randomized subjects) were randomized to the nivo (N = 353), nivo+ipi (N = 354), and chemo (N = 132) arms. Among them, 695 had centrally confirmed MSI-H/dMMR status, including 296 subjects in the nivo+ipi arm and 286 subjects in the nivo arm which comprised the primary efficacy population for nivo+ipi vs nivo comparison across lines.

303 1L subjects with MSI-H/dMMR mCRC per local testing (1L randomized subjects) were randomized to the nivo+ipi (N = 202), and chemo (N = 101) arms. Among them, 255 had centrally confirmed MSI-H/dMMR status, including 171 subjects in the nivo+ipi arm and 84 in the chemo arm which comprised the primary efficacy population for nivo+ipi vs chemo comparison. 288 1L subjects were treated (200 in the nivo+ipi arm, and 88 in the chemo arm); which was the primary safety population for nivo+ipi vs chemo comparison.

Nivo+Ipi vs Chemo in 1L: As of the 15-Nov-2023 DBL, based on the focused presentation of subjects' disposition of all 1L randomized subjects in the nivo+ipi and chemo arms, the proportion of subjects with ongoing treatment was substantially larger in the nivo+ipi arm

(21.0%) compared with the chemo arm (6.8%) (Table 13). The overall percentage of 1L subjects who discontinued treatment was lower in the nivo+ipi arm (48.0%) than the chemo arm (93.2%), with disease progression as the primary reason for treatment discontinuation in both arms (19.0% vs 69.3%). A lower proportion of subjects discontinued study in the nivo+ipi arm compared with the chemo arm (24.0% vs 43.2%), with death as the primary reason in both arms (22.0% vs 36.4%).

Nivo+Ipi and Nivo in All Lines: As of the 25-Sep-2024 DBL, based on the focused presentation of subjects' disposition of all randomized subjects in the nivo+ipi and nivo arms, the proportion of subjects with ongoing treatment was slightly bigger in the nivo+ipi arm (5.7%) compared with the nivo arm (3.7%) (Table 14). The overall percentage of subjects who discontinued treatment was lower in the nivo+ipi arm (49.1%) than the nivo arm (57.3%), with disease progression as the primary reason for treatment discontinuation in both arms (23.3% vs 39.0%). A smaller proportion of subjects discontinued study in the nivo+ipi arm compared with the nivo arm (32.1% vs 44.4%), with death as the primary reason in both arms (28.4% vs 39.6%).

The FDA's Assessment:
FDA acknowledges the different clinical cutoffs and database lock dates corresponding to the two separate primary efficacy endpoint analyses.

The differences between the sample sizes of patients who were randomized compared to those who had centrally confirmed MSI-H/dMMR testing are outlined in Table 8. Three patients were randomized without local testing confirming MSI-H/dMMR status, details of which have been outlined in the "Protocol Violations" section below.

The patient disposition for patients with centrally confirmed MSI-H/dMMR mCRC for first line nivolumab + ipilimumab vs chemotherapy (Table 16) and those receiving treatment in all lines (Table 17) are outlined below.

Table 16: FDA – Patient Disposition - Centrally confirmed MSI-H/dMMR mCRC first line nivolumab + ipilimumab versus chemotherapy

Status, n (%)	All 1L Subjects		
	Arm B: Nivo+Ipi	Arm C: Chemo	Total
Randomized	171	84	255
Treated	170 (99)	75 (89)	245 (96)
Not Treated	1 (0.6)	9 (11)	10 (3.9)
Reason for not treated			

Status, n (%)	All 1L Subjects		
	Arm B: Nivo+Ipi	Arm C: Chemo	Total
Subject withdrew consent	0	5 (6)	5 (2.0)
Subject no longer meets study criteria	0	1 (1.2)	1 (0.4)
Other	1 (0.6)	3 (3.6)	4 (1.6)
Ongoing treatment	41 (24)	6 (8)	47 (19)
Completed treatment	60 (35)	0	60 (25)
Discontinued treatment	69 (41)	69 (92)	138 (56)
Reason for discontinuation of treatment			
Subject withdrew consent	0	1 (1.3)	1 (0.4)
Death	2 (1.2)	0	2 (0.8)
Pregnancy	1 (0.6)	0	1 (0.4)
Other	6 (3.5)	3 (4.0)	9 (3.7)
Disease progression	20 (12)	50 (67)	70 (29)
Study drug toxicity	32 (19)	3 (4)	35 (14)
Adverse event unrelated to study drug	8 (4.7)	5 (7)	13 (5)
Maximum clinical benefit	0	7 (9.3)	7 (2.9)
Discontinued treatment due to COVID-19	2 (1.2)	0	2 (0.8)
Ongoing study (1)	140 (82)	46 (61)	186 (76)
Discontinued study (1)	30 (18)	29 (39)	59 (24)
Reason for discontinuation of study			
Death	26 (15)	24 (32)	50 (20)
Lost to follow-up	1 (0.6)	0	1 (0.4)
Subject withdrew consent	2 (1.2)	2 (2.7)	4 (1.6)
Other	1 0.6)	3 (4)	4 (1.6)

Source: Adapted from Sponsor's response to FDA information request. Data base lock: 11/15/23.
Only 1L subjects are included for nivo+ipi arm and chemo arm.
Percentages based on subjects entering period.
(1) Includes data from crossover period/cohort. The Crossover cohort included subjects in the chemo arm who experienced documented progression of disease and crossed over to receive nivo+ipi therapy.

Table 17: FDA – Patient Disposition with Centrally confirmed MSI-H/dMMR mCRC treated in all lines for all three arms

Status, n (%)	All Subjects			
	Arm A: Nivo	Arm B: Nivo+Ipi	Arm C: Chemo	Total
Randomized	286	296	113	695

Status, n (%)	All Subjects			
	Arm A: Nivo	Arm B: Nivo+Ipi	Arm C: Chemo	Total
Treated	284 (99)	295 (100)	100 (89)	679 (98)
Not Treated	2 (0.7)	1 (0.3)	13 (12)	16 (2.3)
Reason for not treated				
Subject withdrew consent	0	0	8 (7)	8 (1.2)
Subject no longer meets study criteria	2 (0.7)	0	1 (0.9)	3 (0.4)
Other	0	1 (0.3)	4 (3.5)	5 (0.7)
Ongoing treatment	12 (4.2)	20 (7)	0	32 (4.7)
Completed treatment	131 (46)	154 (52)	0	285 (42)
Discontinued treatment	141 (50)	121 (41)	100 (100)	362 (53)
Reason for discontinuation of treatment				
Subject withdrew consent	1 (0.4)	0	1 (1.0)	2 (0.3)
Death	2 (0.7)	3 (1.0)	0	5 (0.7)
Pregnancy	0	1 (0.3)	0	1 (0.1)
Other	5 (1.8)	13 (4.4)	6 (6)	24 (3.5)
Disease progression	84 (30)	45 (15)	72 (72)	201 (30)
Study drug toxicity	26 (9)	43 (15)	7 (7)	76 (11)
Adverse event unrelated to study drug	23 (8)	15 (5)	6 (6)	44 (7)
Maximum clinical benefit	0	1 (0.3)	8 (8)	9 (1.3)
Discontinued treatment due to COVID-19	2 (0.7)	2 (0.7)	1 (1.0)	5 (0.7)
Ongoing study (1)	183 (64)	222 (75)	57 57)	462 (68)
Discontinued study (1)	101 (36)	73 (25)	43 (43.0)	217 (32.0)
Reason for discontinuation of study				
Death	88 (31)	62 (21)	37 (37)	187 (28)
Lost to follow-up	0	3 (1.0)	0	3 (0.4)
Subject withdrew consent	7 (2.5)	5 (1.7)	2 (2.0)	14 (2.1)
Other	6 (2.1)	3 (1.0)	4 (4.0)	13 (1.9)

Source: Adapted from Sponsor's response to FDA information request. Data base lock: 9/25/24.

(1) Includes data from Crossover period/cohort. The Crossover cohort included subjects in the chemo arm who experienced documented progression of disease and crossed over to receive nivo+ipi therapy.

Percentages based on subjects entering period.

Protocol Violations/Deviations

Data:

Table 18: Applicant - Important Protocol Deviations - All 1L Randomized Subjects in the Nivo+Ipi and Chemo Arms in CA2098HW (15-Nov-2023 DBL)

Important Protocol Deviations Category	Number (%) of Subjects		
	Arm B: Nivo+Ipi (N=202)	Arm C: Chemo (N=101)	Total (N=303)
Total Number of Subjects with at least One Deviation	100 (49.5)	57 (56.4)	157 (51.8)
Inclusion/Exclusion Criteria	12 (5.9)	13 (12.9)	25 (8.3)
Informed Consent and/or Ethics (IEC/IRB)	22 (10.9)	15 (14.9)	37 (12.2)
Prohibited Concomitant Medication	1 (0.5)	1 (1.0)	2 (0.7)
Safety Reporting	8 (4.0)	4 (4.0)	12 (4.0)
Study Intervention (Study Treatment)	7 (3.5)	5 (5.0)	12 (4.0)
Trial Procedures	80 (39.6)	40 (39.6)	120 (39.6)
Discontinuation	1 (0.5)	3 (3.0)	4 (1.3)

The sum of all deviations is reported per category as a subject may have more than 1 deviation. Protocol deviation identification date range: 26-Aug-2019 to 12-Oct-2023.
Source: SDTM.DV, ADSL of the CA2098HW Interim CSR

Table 19: Applicant - Relevant Protocol Deviations Summary - All 1L Randomized Subjects in the Nivo+Ipi and Chemo Arms in CA2098HW (15-Nov-2023 DBL)

Important Protocol Deviations Category	Number (%) of Subjects		
	Arm B: Nivo+Ipi (N=202)	Arm C: Chemo (N=101)	Total (N=303)
Total Number of Subjects with at least One Deviation	10 (5.0)	6 (5.9)	16 (5.3)
At Entrance			
Subjects with Neither Locally Confirmed MSI-H nor Locally Confirmed dMMR Confirmed	2 (1.0)	0	2 (0.7)
Subjects without Measurable Disease by CT (including PET-CT) or MRI at Baseline	2 (1.0)	2 (2.0)	4 (1.3)
Subjects Receiving Prohibited Prior Therapies On-study	6 (3.0)	3 (3.0)	9 (3.0)
On-Study			
Subjects Receiving Concurrent Anticancer Therapy	0	1 (1.0)	1 (0.3)

Excludes data collected on or after first crossover dose date. *Source: ADSL, ADPD of the CA2098HW Interim CSR*

The Applicant's Position:

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

As the 15-Nov-2023 DBL, 49.5% and 56.4% 1L subjects in the nivo+ipi and chemo arms had at least 1 important protocol deviation, predominantly in the category of trial procedures (39.6% each) (Table 18). Long treatment duration, frequent schedule of scans acquisition until BICR-confirmed progression, COVID-19 pandemic during study execution, and stringent criteria for

assignment of important protocol deviation have contributed to relatively high frequency of deviations in the category of trial procedures.

Protocol deviations were balanced between the 2 treatment arms with the exception of inclusion/exclusion criteria category, which was reported less frequently in the nivo+ipi arm than chemo arm. Review of the listing of important protocol deviations identified that in 12 of 25 subjects, the deviations in inclusion/exclusion criteria category were assigned incorrectly (5/12 in the nivo+ipi arm and 7/13 in the chemo arm).

As of the 25-Sep-2024 DBL, 56.8% in the nivo+ipi arm and 48.2% in the nivo arm had at least 1 important protocol deviation. Across the categories of important protocol deviations, the frequencies were generally balanced between the nivo+ipi and nivo arms (please see ADSL, ADPD of the CA2098HW Primary CSR).

After a review of the reported important protocol deviations, it was determined that there was no impact on the efficacy and safety endpoints or the overall data integrity.

Relevant protocol deviations are important protocol deviations that could affect the interpretability of key study results, are programmable deviations from clinical database and are protocol specific. The scope of the relevant protocol deviations and statistical approaches to assess the robustness of efficacy or safety of treatment are defined in the SAP.

As of the 15-Nov-2023 DBL: Overall, 5.3% of 1L randomized subjects in the nivo+ipi and chemo arms had at least 1 relevant protocol deviation. Across the nivo+ipi and chemo arms, the most common relevant protocol deviations were subjects who received prohibited prior therapies (Table 19). In 9 subjects who reported receiving prohibited therapies, use of steroids were permitted per protocol.

As of the 25-Sep-2024 DBL, the number of relevant protocol deviations were low; they were balanced across the nivo+ipi (4.2%) and nivo (3.7%) arms and did not impact the validity of the study results or their interpretation (please see ADSL, ADPD of the CA2098HW Primary CSR). Across the nivo and nivo+ipi arms, the most common relevant protocol deviations were subjects who received prohibited prior therapies.

After a review of the reported relevant protocol deviations, it was determined that there was no significant impact on the interpretability of study results.

FDA's Assessment:
The differences in the proportion of patients with the Applicant's cited important protocol deviations are outlined in Table 20. There were a greater proportion of patients with at least one protocol deviation in the nivolumab and ipilimumab arm, with majority of the differences attributed to trial procedures.

Table 20: FDA – Protocol Deviations in all lines for all patients randomized to receive nivolumab + ipilimumab or nivolumab.

Important Protocol Deviations Category	Number (%) of Subjects	
	Nivo + Ipi (N=354)	Nivo (N=353)
Total Number of Patients with at least One Deviation	201 (57)	170 (48)
Inclusion/Exclusion Criteria	33 (9)	32 (9)
Informed Consent Document	28 (13)	46 (8)
Safety Reporting	13 (3.7)	19 (5)
Trial Procedures	163 (46)	132 (37)

Source: Adapted from primary CSR

There were similar proportion of patients categorized as having relevant protocol deviations in the nivo + ipi arm (N=15 [4.2%]) and nivo arms (N=13 [3.7%]). Most relevant protocol deviations were due to patients receiving prohibited prior therapies and was similar in both arms (N=11 [3.1%] nivo+ipi, N=12 [3.5%] nivo). FDA clarified that in addition to the 2 patients who had neither locally confirmed MSI-H nor locally confirmed dMMR in the nivo + ipi arm, there was an additional patient randomized to nivolumab single agent arm had a previously stated MSI-H result based on NGS testing overruled, as the site reported the MSI-H status as per the protocol and available testing, this was not determined to be a protocol deviation.

FDA conducted a sensitivity analysis excluding patients in the nivo+ipi (N=15) or nivo (N=13) arms who had a relevant protocol deviation from the assessment of PFS in the primary efficacy population (i.e., all lines centrally positive MSI-H/dMMR), with similar estimates of the treatment effect observed.

Table of Demographic Characteristics

Data:

Table 21: Applicant - Baseline Demographic Characteristics - All Randomized Subjects in CA2098HW

	Arm A: Nivo N=353	Arm B: Nivo+Ipi N=354	Arm C: Chemo N=132	Total N=839
Age (Years)				
Median	63	62	65	63
Min , Max	20, 87	21, 86	26, 87	20, 87

	Arm A: Nivo N=353	Arm B: Nivo+Ipi N=354	Arm C: Chemo N=132	Total N=839
Age Categorization (%)				
< 65	193 (54.7)	199 (56.2)	62 (47.0)	454 (54.1)
>= 65	160 (45.3)	155 (43.8)	70 (53.0)	385 (45.9)
< 75	306 (86.7)	303 (85.6)	112 (84.8)	721 (85.9)
>= 75	47 (13.3)	51 (14.4)	20 (15.2)	118 (14.1)
Sex (%)				
Male	190 (53.8)	162 (45.8)	64 (48.5)	416 (49.6)
Female	163 (46.2)	192 (54.2)	68 (51.5)	423 (50.4)
Race (%)				
White	305 (86.4)	311 (87.9)	113 (85.6)	729 (86.9)
Black or African American	7 (2.0)	4 (1.1)	2 (1.5)	13 (1.5)
Asian	36 (10.2)	27 (7.6)	15 (11.4)	78 (9.3)
Other	5 (1.4)	12 (3.4)	2 (1.5)	19 (2.3)
Ethnicity (%)				
Hispanic or Latino	34 (9.6)	32 (9.0)	11 (8.3)	77 (9.2)
Not Hispanic or Latino	189 (53.5)	165 (46.6)	67 (50.8)	421(50.2)
Not Reported	130 (36.8)	157 (44.4)	54 (40.9)	341 (40.6)
Country by Geographic Region (%)				
US/Canada/Europe	246 (69.7)	251 (70.9)	95 (72.0)	592 (70.6)
Asia	33 (9.3)	26 (7.3)	13 (9.8)	72 (8.6)
Rest of World	74 (21.0)	77 (21.8)	24 (18.2)	175 (20.9)
ECOG Performance Status (%)				
0	183 (51.8)	192 (54.2)	61 (46.2)	436 (52.0)
1	170 (48.2)	162 (45.8)	71 (53.8)	403 (48.0)
Weight (KG)				
Median	69.00	66.90	70.60	68.00
Min, Max	34.0, 133.5	34.5, 178.0	39.0, 128.0	34.0, 178.0

US/Canada/Europe: Austria, Belgium, Canada, Czechia, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Romania, Norway, Spain, UK, and US

Asia: China, Japan

Rest of World: Argentina, Australia, Brazil, Chile, Turkey

Source: *ADSL of the CA2098HW Primary CSR*

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)

Data:

Table 22: Applicant - Key Baseline Disease Characteristics (including Prior Therapy) - All Randomized Subjects in CA2098HW

	All Randomized Subjects			
	Arm A Nivo N=353	Arm B Nivo+Ipi N=354	Arm C Chemo N=132	Total N=839
Prior Surgery Related to Current Cancer				
Yes	306 (86.7)	316 (89.3)	112 (84.8)	734 (87.5)
No	47 (13.3)	38 (10.7)	20 (15.2)	105 (12.5)
Disease Stage at Initial Diagnosis (%)				
Stage I	4 (1.1)	2 (0.6)	1 (0.8)	7 (0.8)
Stage II	61 (17.3)	65 (18.4)	21 (15.9)	147 (17.5)
Stage III	129 (36.5)	133 (37.6)	51 (38.6)	313 (37.3)
Stage IV	158 (44.8)	152 (42.9)	59 (44.7)	369 (44.0)
Not Reported	1 (0.3)	2 (0.6)	0	3 (0.4)
Disease Stage at Study Entry (%)				
Stage IVA	132 (37.4)	129 (36.4)	53 (40.2)	314 (37.4)
Stage IVB	98 (27.8)	110 (31.1)	38 (28.8)	246 (29.3)
Stage IVC	122 (34.6)	114 (32.2)	41 (31.1)	277 (33.0)
Not reported	1 (0.3)	1 (0.3)	0	2 (0.2)
Histological Grade (%)				
GX	48 (13.6)	55 (15.5)	22 (16.7)	125 (14.9)
G1	38 (10.8)	39 (11.0)	14 (10.6)	91 (10.8)
G2	155 (43.9)	124 (35.0)	48 (36.4)	327 (39.0)
G3	101 (28.6)	123 (34.7)	48 (36.4)	272 (32.4)
G4	9 (2.5)	11 (3.1)	0	20 (2.4)
Not Reported	2 (0.6)	2 (0.6)	0	4 (0.5)
Cell Type (%)				
Adenocarcinoma	337 (95.5)	339 (95.8)	122 (92.4)	798 (95.1)
Other Types	15 (4.2)	15 (4.2)	10 (7.6)	40 (4.8)
Not reported	1 (0.3)	0	0	1 (0.1)
Tumor Location (%)				
Cecum	39 (11.0)	44 (12.4)	20 (15.2)	103 (12.3)
Colon Ascending/Hepatic Flexure	156 (44.2)	150 (42.4)	53 (40.2)	359 (42.8)
Colon Transverse	44 (12.5)	48 (13.6)	16 (12.1)	108 (12.9)
Colon Descending/Splenic Flexure	26 (7.4)	39 (11.0)	13 (9.8)	78 (9.3)
Colon Sigmoid	48 (13.6)	30 (8.5)	16 (12.1)	94 (11.2)
Rectum/Rectosigmoid Junction	35 (9.9)	41 (11.6)	14 (10.6)	90 (10.7)

Table 22: Applicant - Key Baseline Disease Characteristics (including Prior Therapy) - All Randomized Subjects in CA2098HW

	All Randomized Subjects			
	Arm A Nivo N=353	**Arm B Nivo+Ipi N=354**	**Arm C Chemo N=132**	**Total N=839**
Unknown	5 (1.4)	2 (0.6)	0	7 (0.8)
Tumor Sidedness (CRF) (%)				
Left	109 (30.9)	110 (31.1)	43 (32.6)	262 (31.2)
Right	244 (69.1)	244 (68.9)	89 (67.4)	577 (68.8)
Number of prior lines of therapy (CRF)				
0	184 (52.1)	193 (54.5)	95 (72.0)	472 (56.3)
1	86 (24.4)	82 (23.2)	34 (25.8)	202 (24.1)
>= 2	83 (23.5)	78 (22.0)	2 (1.5)	163 (19.4)
Not Reported	0	1 (0.3)	1 (0.8)	2 (0.2)
Time from Initial Disease Diagnosis to Randomization (%)				
< 1 Year	173 (49.0)	171 (48.3)	80 (60.6)	424 (50.5)
>= 1 AND < 3 Years	123 (34.8)	123 (34.7)	37 (28.0)	283 (33.7)
>= 3 Years	57 (16.1)	60 (16.9)	14 (10.6)	131 (15.6)
Not Reported	0	0	1 (0.8)	1 (0.1)
Metastasis Site per BICR (A)				
Liver	149 (42.2)	140 (39.5)	57 (43.2)	346 (41.2)
Lung	99 (28.0)	85 (24.0)	33 (25.0)	217 (25.9)
Peritoneal	126 (35.7)	143 (40.4)	59 (44.7)	328 (39.1)
PD-L1 Status (%)				
>= 1%	63 (17.8)	74 (20.9)	19 (14.4)	156 (18.6)
< 1%	264 (74.8)	255 (72.0)	104 (78.8)	623 (74.3)
Not Evaluable/Indeterminate	2 (0.6)	4 (1.1)	0	6 (0.7)
Not Available	24 (6.8)	21 (5.9)	9 (6.8)	54 (6.4)
MSI-H and/or MMR Per Central Assessment (%)				
MSI-H and/or dMMR	286 (81.0)	296 (83.6)	113 (85.6)	695 (82.8)
MSS and PMMR	40 (11.3)	41 (11.6)	13 (9.8)	94 (11.2)
Other* (B)	27 (7.6)	17 (4.8)	6 (4.5)	50 (6.0)
BRAF/KRAS/NRAS Mutation Status (%)				
BRAF/KRAS/NRAS ALL Wild Type	103 (29.2)	83 (23.4)	34 (25.8)	220 (26.2)
BRAF Mutant	85 (24.1)	106 (29.9)	34 (25.8)	225 (26.8)
KRAS OR NRAS Mutant	89 (25.2)	83 (23.4)	31 (23.5)	203 (24.2)
BRAF AND KRAS/NRAS Mutant	2 (0.6)	9 (2.5)	2 (1.5)	13 (1.5)
Unknown	74 (21.0)	73 (20.6)	31 (23.5)	178 (21.2)

Table 22: Applicant - Key Baseline Disease Characteristics (including Prior Therapy) - All Randomized Subjects in CA2098HW

	All Randomized Subjects			
	Arm A Nivo N=353	Arm B Nivo+Ipi N=354	Arm C Chemo N=132	Total N=839
Lynch Syndrome (C)				
Yes	49 (13.9)	48 (13.6)	23 (17.4)	120 (14.3)
No	207 (58.6)	217 (61.3)	66 (50.0)	490 (58.4)
Unknown	91 (25.8)	86 (24.3)	38 (28.8)	215 (25.6)
Not Reported	6 (1.7)	3 (0.8)	5 (3.8)	14 (1.7)

(A) The metastasis sites are not mutually exclusive and may overlap.
(B) Other includes all other combinations that are not covered by the above 2 categories.
(C) Information on Lynch syndrome was collected based on the subject's medical history.
*Other, includes all other combinations except mentioned above.
For local and central MSI/MMR assessment, not available includes both not evaluable and not tested.
MSI test per local assessment including both PCR and NGS test.
Source: *ADSL, ADDX, ADCMS of the CA2098HW Primary CSR*

The Applicant's Position:

In CA2098HW, baseline demographic and disease characteristics in all randomized subjects were generally well balanced among the 3 treatment arms (Table 21 and Table 22). Baseline characteristics for all randomized subjects with centrally confirmed dMMR/MSI-H status was consistent with those for all randomized subjects. Baseline characteristics for the 1L populations were generally consistent with those for all randomized subjects owing that >50% of study population were in 1L setting.

Baseline demographic and disease characteristics for all 1L randomized subjects were consistent with those in 1L subjects with centrally confirmed MSI-H/dMMR mCRC and were generally well balanced between the nivo+ipi and chemo arms (refer to ADSL of the CA2098HW Interim CSR). Small differences included more subjects of age < 65 years and subjects with PD-L1 status ≥ 1% in the nivo+ipi arm than the chemo arm, and a lower proportion of subjects with Lynch syndrome in the nivo+ipi arm than the chemo arm.

Overall, the study subjects' demographic and disease characteristics adequately represent the dMMR/MSI-H mCRC patient population, inclusive of 1L patients.

The FDA's Assessment:

The baseline demographics of the primary efficacy population with centrally confirmed MSI-H/dMMR is outlined in Table 23. CA2098HW was a multiregional trial; the highest enrollment countries were France (19%), Spain (11%), and Italy (10%) (Table 51, Appendices section).

Table 23. FDA – Baseline Demographics of patients with centrally confirmed MSI-H/dMMR mCRC

Characteristic	All Lines Central MSI-H/dMMR		First Line Central MSI-H/dMMR	
	Nivolumab + Ipilimumab, N = 296	Nivolumab, N = 286	Nivolumab + Ipilimumab, N = 171	Chemotherapy, N = 84
Age				
Median (Range)	62 (21, 86)	63 (20, 87)	62 (21, 86)	65 (26, 87)
< 65	164 (55%)	157 (55%)	98 (57%)	40 (48%)
>= 65	132 (44%)	129 (45%)	73 (43%)	44 (52%)
Sex				
Female	161 (54%)	137 (48%)	92 (54%)	46 (55%)
Male	135 (46%)	149 (52%)	79 (46%)	38 (45%)
Race				
Asian	24 (8%)	31 (11%)	17 (10%)	13 (16%)
Black or African American	4 (1.4%)	6 (2.1%)	2 (1.2%)	2 (2.4%)
Native Hawaiian or Other Pacific Islander	1 (0.3%)	1 (0.3%)	1 (0.6%)	0 (0.0%)
Other	9 (3.0%)	2 (0.7%)	4 (2.3%)	1 (1.2%)
White	258 (87%)	246 (86%)	147 (86%)	68 (81%)
Ethnicity				
Hispanic or Latino	27 (9%)	27 (9%)	22 (13%)	7 (8%)
Not Hispanic or Latino	137 (46%)	158 (55%)	79 (46%)	45 (54%)
Not Reported	132 (45%)	101 (35%)	70 (41%)	32 (38%)
Region				
Asia	23 (8%)	29 (10%)	17 (10%)	11 (13%)
Rest Of World	64 (22%)	51 (18%)	45 (26%)	15 (18%)
Us/Canada/Europe	209 (71%)	206 (72%)	109 (64%)	58 (69%)
ECOG PS				
0	164 (55%)	149 (52%)	97 (57%)	45 (54%)
1	132 (45%)	137 (48%)	74 (43%)	39 (46%)
Tumor Side				

Characteristic	All Lines Central MSI-H/dMMR		First Line Central MSI-H/dMMR	
	Nivolumab + Ipilimumab, N = 296	Nivolumab, N = 286	Nivolumab + Ipilimumab, N = 171	Chemotherapy, N = 84
Left	75 (25%)	69 (24%)	46 (27%)	22 (26%)
Right	221 (75%)	217 (76%)	125 (73%)	62 (74%)
Line of Therapy				
First Line	163 (55%)	156 (55%)	171 (100.0%)	84 (100.0%)
Second Line	70 (24%)	68 (24%)	N/A	N/A
Third Line or greater	53 (21%)	62 (22%)	N/A	N/A
Liver Metastasis				
Yes	104 (35%)	106 (37%)	54 (32%)	32 (38%)
No/Not Reported	192 (65%)	180 (63%)	117 (68%)	52 (62%)
PD-L1 Status				
< 1%	214 (72%)	213 (75%)	122 (71%)	69 (82%)
>= 1%	72 (24%)	61 (21%)	43 (25%)	12 (14%)
Not Available	10 (3.3%)	12 (4.1%)	6 (3.5%)	3 (3.6%)
Mutation				
Braf + Kras/Nras Mutant	7 (2.4%)	1 (0.3%)	6 (3.5%)	2 (2.4%)
Braf Mutant	98 (33%)	81 (28%)	51 (30%)	23 (27%)
Braf/Kras/Nras All Wild Type	75 (25%)	81 (28%)	43 (25%)	19 (23%)
Kras Or Nras Mutant	57 (19%)	68 (24%)	29 (17%)	18 (21%)
Unknown	59 (20%)	55 (19%)	42 (25%)	22 (26%)
Lynch Syndrome				
Yes	43 (15%)	40 (14%)	18 (11%)	13 (16%)
No	172 (58%)	162 (57%)	113 (66%)	39 (46%)
Unknown/Not Reported	81 (27%)	84 (29%)	40 (23%)	32 (38%)

Source: FDA Analysis

FDA generally agrees that the patients with centrally confirmed MSI-H and/or dMMR status were similar to the randomized patient population. There were a greater proportion of patients with right sided tumors who had centrally confirmed MSI-H/dMMR status compared to those who were randomized; however, tumor sidedness was similar in all primary efficacy populations. There was significant missing data on the assessment for a diagnosis of Lynch syndrome. In the subgroup analyses of efficacy outcomes, patients with an unknown Lynch syndrome status were categorized separately. FDA requested and confirmed the sensitivity analyses for efficacy based on the intent to treat patient populations.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance:

Nivo, ipi, and chemo were administered IV by trained medical personnel at each site. Treatment compliance was monitored by routine monitoring of clinical source documentation and drug accountability, as well as the subject's medical record and CRF.

Concomitant Medications:

Most (91.7%) 1L randomized subjects in the nivo+ipi and chemo arms received concomitant medications. Consistent with all 1L randomized subjects, most (92.9%) 1L randomized subjects with centrally confirmed MSI-H/dMMR status received concomitant medications.

Subsequent Cancer Therapy:

Subsequent cancer therapies are defined as cancer therapies that were to be begin after discontinuation of study therapy, and that started on or after the first study drug dose (started on or after the date of randomization, if not treated).

As of the 15-Nov-2023 DBL, subsequent cancer therapy was received by a lower proportion of all 1L randomized subjects in the nivo+ipi arm than the chemo arm (22.3% vs 68.3%), which was mainly due to a lower proportion of subjects in the nivo+ipi arm receiving subsequent systemic therapy (19.3% vs 67.3%). Of the subjects in the chemo arm, 44.6% (45/101) crossed over to receive nivo+ipi on-study. An additional 20.8% (21/101) of subjects in the chemo arm received IO therapy off study. Taken together, 65.4% (66/101) of subjects in the chemo arm received subsequent IO therapy. The frequency of subsequent cancer therapy initiation and the types of treatments for 1L randomized subjects with centrally confirmed MSI-H/dMMR were consistent with those for all 1L randomized subjects.

As of the 25-Sep-2024 DBL, any subsequent cancer therapy was received by 29.1% of subjects (103/354) in the nivo+ipi arm and 37.7% of subjects (133/353) in the nivo arm. Subsequent systemic therapy was received by 24.3% and 33.4% of subjects in the nivo+ipi and the nivo arms, respectively. Subsequent systemic therapy was predominantly a conventional chemotherapy (16.7% in the nivo+ipi arm vs 21.8% in the nivo arm), followed by anti-PD(L)1 therapy (6.8% in the nivo+ipi arm vs 10.5% in the nivo arm). Summary of subsequent cancer therapy for all randomized subjects with centrally confirmed dMMR/MSI-H status were consistent with those for all treated subjects.

Subsequent Surgery

As of the 15-Nov-2023 DBL: Among 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC on study surgery reported: nivo+ipi arm (5/171) and chemo arm (6/84).

As of the 25-Sep-2024 DBL: Among all lines randomized subjects with centrally confirmed MSI-H/dMMR mCRC on study surgery reported: nivo arm (18/286) and nivo+ipi arm (15/296).

Rescue Medication Use: Not applicable.

The FDA's Assessment:

Among all randomized patients, immune modulating concomitant medications for the management of adverse events were more commonly administered in the nivo+ipi arm (52%) compared to nivo arm (40%), with systemic corticosteroids being used in 49% of patients randomized to nivo+ipi compared to 34% randomized to nivolumab alone. The most common immune mediated adverse events requiring concomitant medications are outlined in Table 34.

FDA agrees with the cited proportion of patients who received subsequent therapies in nivo+ipi and nivo arms as of 11/15/24 DBL. The majority of patients were subsequently treated with cytotoxic chemotherapy with or without targeted biologic e.g., cetuximab, thirteen (3.7%) in the nivolumab arm received subsequent CTLA-4 inhibitor compared to 5 patients (1.5%) in the nivo+ipi arm. Table 24 summarizes treatment beyond progression.

Table 24: FDA – Treatment Beyond Clinical Progression in Study CA2098HW

Treatment Arm	**All Randomized Patients**	**All Randomized Patients Centrally Confirmed dMMR/MSI=H**
	All Lines	**All Lines**
Arm A: Nivolumab	N = 353	N = 286
Treatment Beyond Investigator Assessed Radiographic Progression	74 (21%)	48 (17%)
Arm B: Nivolumab + Ipilimumab	N = 354	N = 286
Treatment Beyond Investigator Assessed Radiographic Progression	56 (16%)	37 (13%)

In Arm A (nivo) 40 out of 48 (83%) patients and Arm B (nivo + ipi) 29 out of 37 patients with centrally confirmed MSI-H/dMMR mCRC with treatment beyond investigator assessed radiographic progression, also had progression according to BICR and were categorized as having a PFS event.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

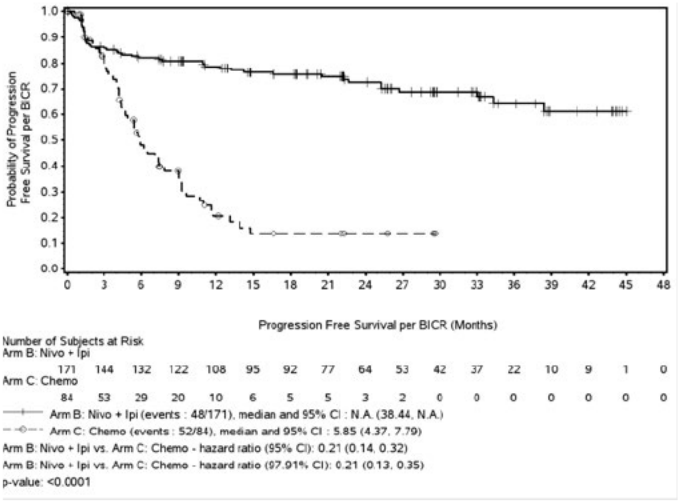
Nivo+Ipi vs Chemo in 1L

Table 25: Applicant - Primary Efficacy Endpoint - Progression-Free Survival per BICR (Primary Definition) for Nivo+Ipi (Arm B) vs Chemo (Arm C) - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC in CA2098HW (15-Nov-2023 DBL)

	Arm B: Nivo+Ipi N = 171	Arm C: Chemo[d] N = 84
PFS (per BICR, primary definition)		
Events, n (%)	48 (28.1)	52 (61.9)
Median PFS (95% CI), months[a]	NR (38.44, NA)	5.85 (4.37, 7.79)
HR (95% CI)[b]	0.21 (0.14, 0.32)	
HR (97.91% CI)[b]	0.21 (0.13, 0.35)	
P-value[c]	p < 0.0001	
PFS Rates (95% CI), %[a]		
6-month	82.08 (75.37, 87.11)	48.18 (35.58, 59.69)
Number of Subjects at Risk	132	29
12-month	78.69 (71.57, 84.22)	20.62 (11.18, 32.05)
Number of Subjects at Risk	108	10

[a] Based on Kaplan-Meier estimates
[b] HR is nivo+ipi arm over chemo arm from a Cox Model stratified by tumor sidedness (left vs right) as entered into the IRT.
[c] Log-rank test stratified by the same factors as used in the Cox proportional hazard model. Boundary for statistical significance p-value < 0.0209.
[d] Excludes data collected on or after first crossover dose date.
Clinical data cutoff was 12-Oct-2023. Minimum follow-up (time from the last subject's randomization date to the data cutoff date) was 6.1 months.
Source: ADSL, ADEFTTES of the CA2098HW Interim CSR

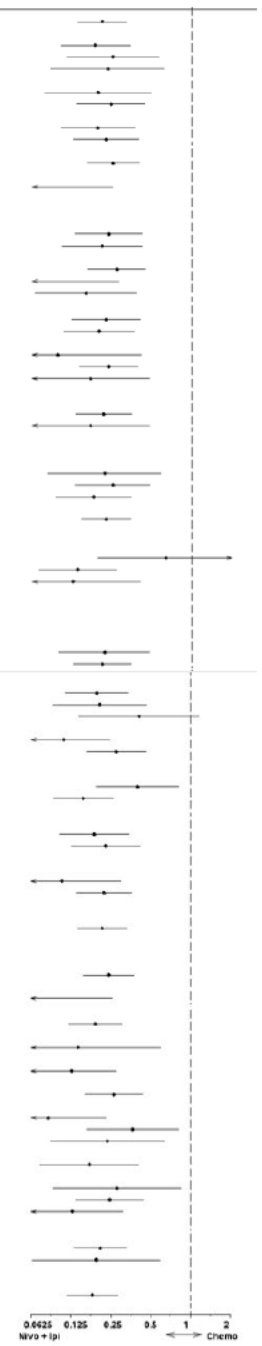
Figure 3: Applicant - Progression-Free Survival per BICR (Primary Definition) for Nivo+Ipi (Arm B) vs Chemo (Arm C)– All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC in CA2098HW (15-Nov-2023 DBL)



Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test by tumor sidedness (left vs right) as entered into the IRT.
Symbols represent censored observations.
Excludes data collected on or after first crossover dose date.
KM plot was generated only if there are at least 10 subjects in each treatment arm in population or subgroup.
Source: ADSL, ADEFTTES of the CA2098HW Interim CSR

Figure 4: Applicant - Forest Plot of PFS per BICR (Primary Definition) in Pre-Defined Subsets for Nivo+Ipi (Arm B) vs Chemo (Arm C) - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC in CA2098HW (15-Nov-2023 DBL)

	N	Nivo + Ipi N of Events (N of subjects)	mPFS (95% CI)		Chemo N of Events (N of subjects)	mPFS (95% CI)		Unstratified Hazard Ratio (95% CI) Nivo + Ipi vs. Chemo	
OVERALL	255	68 (171)	N.A.	(38.44, N.A.)	52 (84)	5.85	(4.37, 7.79)	0.21	(0.14, 0.32)
AGE CATEGORIZATION									
< 65	138	23 (98)	N.A.	(34.30, N.A.)	26 (40)	5.68	(4.24, 10.91)	0.19	(0.10, 0.34)
>= 65 AND < 75	70	11 (39)	N.A.	(26.71, N.A.)	17 (31)	6.47	(4.01, 9.59)	0.25	(0.11, 0.56)
>= 75 AND < 85	43	14 (32)	38.44	(14.29, N.A.)	7 (11)	4.40	(1.22, 9.03)	0.23	(0.09, 0.62)
>= 85	4	0 (2)	N.A.		2 (2)	6.03	(5.85, N.A.)		
>= 75	47	14 (34)	38.44	(16.59, N.A.)	9 (13)	5.85	(1.28, 7.79)	0.20	(0.08, 0.50)
>= 65	117	25 (73)	N.A.	(25.30, N.A.)	26 (44)	5.85	(4.01, 7.79)	0.24	(0.14, 0.44)
SEX									
MALE	117	20 (79)	N.A.	(34.30, N.A.)	25 (38)	5.85	(4.21, 10.64)	0.19	(0.10, 0.37)
FEMALE	138	28 (92)	N.A.	(38.44, N.A.)	27 (46)	6.21	(4.24, 9.03)	0.22	(0.13, 0.39)
RACE									
WHITE	215	65 (147)	N.A.	(38.44, N.A.)	42 (68)	5.95	(4.30, 9.03)	0.25	(0.16, 0.39)
BLACK OR AFRICAN AMERICAN	4	0 (2)	N.A.		2 (2)	7.92	(4.21, N.A.)		
ASIAN	30	2 (17)	N.A.		7 (13)	6.49	(1.45, N.A.)	0.03	(<0.01, 0.25)
OTHER	6	1 (5)	N.A.	(5.75, N.A.)	1 (1)	2.30	(N.A., N.A.)		
ETHNICITY									
HISPANIC OR LATINO	29	6 (22)	34.30	(12.32, N.A.)	6 (7)	7.10	(2.99, N.A.)		
NOT HISPANIC OR LATINO	124	23 (79)	N.A.		28 (45)	6.21	(4.37, 9.03)	0.23	(0.13, 0.42)
NOT REPORTED	102	19 (70)	N.A.	(38.44, N.A.)	18 (32)	5.36	(3.35, 9.23)	0.21	(0.10, 0.42)
REGION									
US/CANADA/EUROPE	167	34 (109)	N.A.	(38.44, N.A.)	34 (58)	5.68	(4.21, 9.26)	0.27	(0.16, 0.45)
ASIA	28	2 (17)	N.A.		6 (11)	7.39	(1.45, N.A.)	0.03	(<0.01, 0.28)
REST OF WORLD	60	12 (45)	N.A.	(22.67, N.A.)	12 (15)	6.21	(3.35, 9.23)	0.16	(0.07, 0.38)
ECOG PERFORMANCE STATUS									
0	142	24 (97)	N.A.	(38.44, N.A.)	27 (45)	9.00	(5.68, 10.91)	0.22	(0.12, 0.40)
>= 1	113	24 (74)	N.A.	(26.71, N.A.)	25 (39)	4.21	(2.56, 5.36)	0.20	(0.11, 0.36)
TOBACCO USE									
YES	29	6 (17)	N.A.	(10.91, N.A.)	8 (12)	4.30	(1.35, 5.68)	0.10	(0.02, 0.41)
NO	175	33 (114)	N.A.	(34.30, N.A.)	37 (61)	7.10	(4.40, 9.59)	0.23	(0.14, 0.39)
NOT REPORTED	51	9 (40)	N.A.		7 (11)	5.77	(0.66, N.A.)	0.17	(0.06, 0.48)
ALCOHOL USE									
YES	15	5 (10)	25.30	(0.20, N.A.)	3 (5)	4.21	(2.79, N.A.)		
NO	189	34 (121)	N.A.	(38.44, N.A.)	42 (68)	6.47	(4.37, 9.23)	0.21	(0.13, 0.35)
NOT REPORTED	51	9 (40)	N.A.		7 (11)	5.77	(0.66, N.A.)	0.17	(0.06, 0.48)
DISEASE STAGE AT INITIAL DIAGNOSIS									
STAGE 0	0	0 (0)	N.A.		0 (0)	N.A.			
STAGE I	0	0 (0)	N.A.		0 (0)	N.A.			
STAGE II	53	10 (37)	N.A.	(22.67, N.A.)	9 (16)	4.21	(1.68, 9.59)	0.22	(0.08, 0.59)
STAGE III	92	20 (60)	N.A.	(26.71, N.A.)	20 (32)	7.36	(4.24, 11.76)	0.25	(0.13, 0.49)
STAGE IV	110	18 (74)	N.A.	(34.30, N.A.)	23 (36)	5.68	(4.30, 9.03)	0.18	(0.09, 0.35)
CELL TYPE									
ADENOCARCINOMA	242	65 (162)	N.A.	(38.44, N.A.)	48 (80)	5.68	(4.30, 7.39)	0.22	(0.15, 0.34)
OTHER TYPES	13	2 (9)	N.A.	(11.10, N.A.)	4 (4)	12.37	(4.86, N.A.)		
TUMOR LOCATION									
CECUM	31	6 (18)	N.A.	(1.51, N.A.)	5 (13)	9.59	(1.22, N.A.)	0.64	(0.19, 2.11)
COLON ASCENDING/HEPATIC FLEXURE	115	19 (79)	N.A.	(34.30, N.A.)	24 (36)	7.36	(4.24, 10.91)	0.14	(0.07, 0.27)
COLON TRANSVERSE	40	7 (27)	N.A.	(22.34, N.A.)	9 (13)	5.36	(3.02, 7.79)	0.13	(0.04, 0.40)
COLON DESCENDING/SPLENIC FLEXURE	31	8 (23)	25.30	(14.29, N.A.)	3 (8)	5.68	(1.45, N.A.)		
COLON SIGMOID	16	2 (8)	N.A.	(3.02, N.A.)	7 (8)	3.86	(0.66, 9.26)		
RECTUM/RECTOSIGMOID JUNCTION	21	5 (15)	38.44	(1.45, N.A.)	4 (6)	4.50	(1.35, N.A.)		
UNKNOWN	1	1 (1)	1.41	(N.A., N.A.)	0 (0)	N.A.			
TUMOR SIDEDNESS (PER IRT)									
LEFT	70	14 (49)	N.A.	(25.30, N.A.)	14 (22)	4.40	(2.07, 9.26)	0.22	(0.10, 0.48)
RIGHT	185	54 (123)	N.A.		38 (62)	7.10	(4.70, 9.03)	0.21	(0.13, 0.34)
TIME FROM INITIAL DISEASE DIAGNOSIS TO RANDOMIZATION									
< 1 YEAR	154	29 (103)	N.A.	(34.30, N.A.)	31 (51)	5.68	(4.30, 7.79)	0.20	(0.11, 0.34)
>= 1 AND < 3 YEARS	71	11 (49)	N.A.		14 (22)	4.24	(2.79, 9.23)	0.21	(0.09, 0.46)
>= 3 YEARS	30	9 (19)	N.A.	(5.75, N.A.)	7 (11)	11.14	(4.40, 13.11)	0.41	(0.14, 1.16)
LIVER METASTASIS PER BICR									
YES	87	12 (55)	N.A.	(38.44, N.A.)	23 (32)	5.85	(4.30, 9.23)	0.11	(0.05, 0.25)
NO	166	36 (114)	N.A.	(34.30, N.A.)	29 (52)	5.36	(4.21, 9.59)	0.28	(0.17, 0.46)
NOT REPORTED	2	0 (2)	N.A.		0 (0)	N.A.			
LUNG METASTASIS PER BICR									
YES	53	19 (37)	13.17	(4.01, N.A.)	14 (16)	4.88	(2.56, 10.91)	0.40	(0.19, 0.81)
NO	200	29 (132)	N.A.		38 (68)	6.21	(4.37, 9.00)	0.16	(0.09, 0.26)
NOT REPORTED	2	0 (2)	N.A.		0 (0)	N.A.			
PERITONEAL METASTASIS PER BICR									
YES	115	23 (76)	N.A.	(34.30, N.A.)	28 (39)	4.40	(3.22, 7.10)	0.19	(0.10, 0.34)
NO	138	25 (93)	N.A.	(38.44, N.A.)	24 (45)	7.39	(5.36, 11.63)	0.23	(0.13, 0.42)
NOT REPORTED	2	0 (2)	N.A.		0 (0)	N.A.			
PD-L1 STATUS									
>= 1%	55	10 (43)	N.A.	(34.30, N.A.)	9 (12)	3.35	(1.28, 7.10)	0.11	(0.04, 0.30)
< 1%	191	34 (122)	N.A.	(38.44, N.A.)	42 (69)	6.47	(4.70, 9.26)	0.22	(0.14, 0.36)
NON-QUANTIFIABLE	9	4 (6)	15.24	(1.18, N.A.)	1 (3)	1.35	(N.A., N.A.)		
MMR TEST RESULTS PER CENTRAL ASSESSMENT									
dMMR	245	47 (163)	N.A.	(38.44, N.A.)	50 (82)	5.85	(4.40, 7.79)	0.22	(0.14, 0.33)
pMMR	3	1 (3)	N.A.	(1.31, N.A.)	0 (0)	N.A.			
NOT AVAILABLE	7	0 (5)	N.A.		2 (2)	5.17	(1.35, N.A.)		
MMR TEST RESULTS PER LOCAL ASSESSMENT									
dMMR	221	45 (149)	N.A.	(38.44, N.A.)	45 (72)	5.68	(4.30, 7.79)	0.24	(0.16, 0.37)
pMMR	1	0 (0)	N.A.		0 (1)	N.A.			
NOT AVAILABLE	33	3 (22)	N.A.		7 (11)	7.56	(1.45, 11.76)	0.06	(0.02, 0.26)
MSI TEST RESULTS PER CENTRAL ASSESSMENT									
MSI-H	218	39 (147)	N.A.	(38.44, N.A.)	44 (71)	6.21	(4.70, 9.03)	0.19	(0.12, 0.31)
MSS	11	5 (8)	1.71	(1.08, N.A.)	2 (3)	5.68	(4.01, N.A.)		
NOT AVAILABLE	26	4 (16)	N.A.	(10.87, N.A.)	6 (10)	4.24	(2.07, N.A.)	0.14	(0.03, 0.60)
MSI TEST RESULTS PER LOCAL ASSESSMENT									
MSI-H	97	14 (67)	N.A.		16 (30)	5.85	(2.79, 9.59)	0.13	(0.06, 0.28)
MSI-LIMSS	1	1 (1)	1.22	(N.A., N.A.)	0 (0)	N.A.			
NOT AVAILABLE	157	33 (103)	N.A.	(34.30, N.A.)	36 (54)	5.95	(4.24, 9.03)	0.27	(0.16, 0.44)
BRAF/KRAS/NRAS MUTATION STATUS									
BRAF/KRAS/NRAS ALL WILD TYPE	58	11 (41)	34.30	(25.30, N.A.)	14 (17)	5.36	(1.45, 7.39)	0.08	(0.03, 0.23)
BRAF MUTANT	72	16 (50)	N.A.	(25.30, N.A.)	11 (22)	9.23	(4.24, N.A.)	0.37	(0.17, 0.81)
KRAS OR NRAS MUTANT	45	9 (30)	N.A.	(33.08, N.A.)	9 (15)	5.68	(1.41, 14.75)	0.24	(0.09, 0.63)
BRAF AND KRAS/NRAS MUTANT	6	2 (4)	N.A.	(1.45, N.A.)	2 (2)	3.47	(3.22, N.A.)		
UNKNOWN	74	10 (46)	N.A.	(38.44, N.A.)	16 (28)	4.86	(3.35, 11.63)	0.17	(0.07, 0.41)
LYNCH SYNDROME									
YES	31	6 (18)	N.A.	(5.19, N.A.)	9 (13)	7.36	(3.35, 14.75)	0.28	(0.09, 0.85)
NO	152	32 (113)	N.A.	(38.44, N.A.)	20 (39)	6.21	(4.21, 11.76)	0.25	(0.14, 0.44)
UNKNOWN	66	10 (39)	N.A.	(25.30, N.A.)	20 (27)	5.52	(2.99, 9.03)	0.13	(0.05, 0.31)
NOT REPORTED	6	0 (1)	N.A.		3 (5)	4.37	(1.22, N.A.)		
PRIOR SURGERY									
YES	222	42 (148)	N.A.	(38.44, N.A.)	44 (74)	7.10	(5.36, 9.23)	0.21	(0.13, 0.33)
NO	33	6 (23)	N.A.	(10.87, N.A.)	8 (10)	3.02	(1.41, 4.37)	0.19	(0.06, 0.59)
PRIOR RADIOTHERAPY									
YES	19	6 (11)	9.46	(0.49, N.A.)	5 (8)	5.95	(1.35, N.A.)		
NO	236	42 (160)	N.A.	(38.44, N.A.)	47 (76)	5.85	(4.37, 7.79)	0.18	(0.12, 0.28)



Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

HR is not computed for subset category with less than 10 subjects per treatment group. Excludes data collected on or after first crossover dose date. For local and central MSI-H/dMMR assessment, not available includes both not evaluable and not tested. For tumor location, other locations unless listed are included in unknown category. PD-L1 non-quantifiable includes subjects whose PD-L1 status are not evaluable, indeterminate, or not available at baseline. MSI test per local assessment includes both PCR and NGS test.
Source: ADSL, ADEFTTES, ADSUB of the CA2098HW Interim CSR

Nivo+Ipi vs Nivo in All Lines

Table 26: Applicant - Primary Efficacy Endpoint - Progression-Free Survival per BICR (Primary Definition) for Nivo+Ipi (Arm B) vs Nivo (Arm A) - All Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC in CA2098HW (25-Sep-2024 DBL)

	Arm A: Nivo N = 286	Arm B: Nivo+Ipi N = 296
Primary Endpoint		
PFS (per BICR, primary definition)		
Events, n (%)	136 (47.6)	101 (34.1)
Median PFS (95% CI), mo.[a]	39.26 (22.11, NA)	Not Reached (53.82, NA)
HR (95% CI)[b]	0.62 (0.48, 0.81)	
HR (99.05% CI)[b]	0.62 (0.44, 0.88)	
p-value[c]	0.0003	
PFS Rates (95% CI), %[a]		
12-month	62.50 (56.54, 67.89)	75.86 (70.50, 80.38)
Number of Subjects at Risk	169	214
18-month	59.89 (53.88, 65.38)	73.02 (67.50, 77.76)
Number of Subjects at Risk	158	200

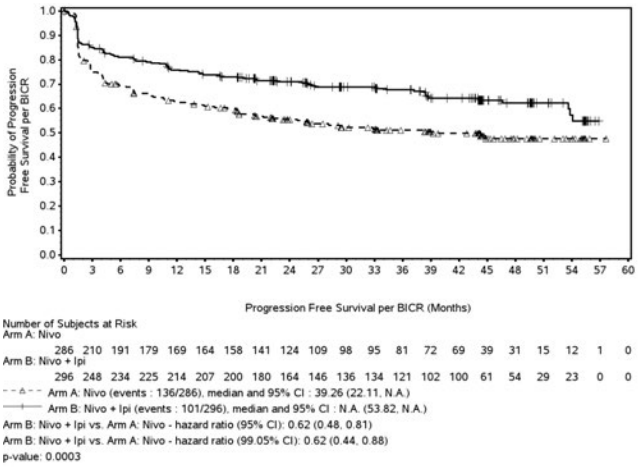
[a] Based on Kaplan-Meier estimates

[b] HR from a Cox proportional hazard model stratified by tumor sidedness (left vs right) and prior lines of therapy (0, 1, ≥ 2) per IRT.

[c] Log-rank test stratified by stratified by tumor sidedness (left vs right) and prior lines of therapy (0, 1, ≥ 2) per IRT. The p-value threshold for statistical significance was 0.0095.

Clinical data cutoff: 28-Aug-2024; Minimum follow-up: 16.7 months
Source: ADSL, ADEFTTES of the CA2098HW Primary CSR

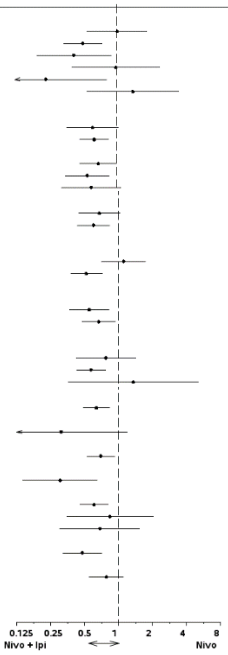
Figure 5: Applicant - Progression-Free Survival per BICR (Primary Definition) for Nivo+Ipi (Arm B) vs Nivo (Arm A) - All Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC in CA2098HW (25-Sep-2024 DBL)



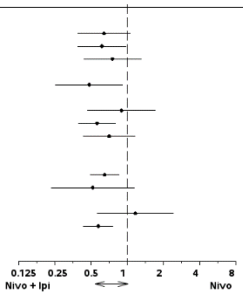
Statistical model for hazard ratio and p-value: Stratified Cox proportional hazard model and stratified log-rank test by tumor sidedness (left vs. right) and prior lines of therapy (0, 1, >= 2) as entered into the IRT.
Symbols represent censored observations. KM plot will be generated only if there are at least 10 subjects in each treatment arm in population or subgroup.
Source: ADSL, ADEFTTES of the CA2098HW Primary CSR

Figure 6: Applicant - Treatment Effect on Progression-Free Survival per BICR (Primary Definition) in Pre-Defined Subsets for Nivo+Ipi (Arm B) vs Nivo (Arm A) - All Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC in CA2098HW (25-Sep-2024 DBL)

	N	Nivo + Ipi N of Events (N of subjects)	mPFS (95% CI)		Nivo N of Events (N of subjects)	mPFS (95% CI)		Unstratified Hazard Ratio (95% CI) Nivo + Ipi vs. Nivo	
TUMOR LOCATION									
CECUM	76	22 (42)	25.99	(4.17, N.A.)	19 (34)	21.65	(4.04, N.A.)	1.02	(0.55, 1.88)
COLON ASCENDING/HEPATIC FLEXURE	269	40 (133)	N.A.	(53.62, N.A.)	65 (136)	39.26	(20.21, N.A.)	0.50	(0.34, 0.75)
COLON TRANSVERSE	87	10 (44)	N.A.		20 (43)	N.A.	(7.39, N.A.)	0.42	(0.20, 0.90)
COLON DESCENDING/SPLENIC FLEXURE	57	12 (35)	N.A.	(22.67, N.A.)	8 (22)	N.A.	(3.68, N.A.)	0.99	(0.41, 2.43)
COLON SIGMOID	44	3 (16)	N.A.	(20.50, N.A.)	16 (28)	10.64	(1.94, N.A.)	0.24	(0.07, 0.82)
RECTUM/RECTOSIGMOID JUNCTION	43	12 (24)	38.44	(11.14, N.A.)	7 (19)	N.A.	(4.57, N.A.)	1.41	(0.55, 3.61)
UNKNOWN	6	2 (2)	6.37	(1.41, N.A.)	1 (4)	N.A.	(10.22, N.A.)		
TUMOR SIDEDNESS (PER IRT)									
LEFT	152	25 (80)	N.A.	(54.08, N.A.)	32 (72)	N.A.	(10.64, N.A.)	0.62	(0.37, 1.04)
RIGHT	430	76 (216)	N.A.	(53.62, N.A.)	104 (214)	33.22	(18.50, N.A.)	0.64	(0.47, 0.86)
TIME FROM INITIAL DISEASE DIAGNOSIS TO RANDOMIZATION									
< 1 YEAR	299	50 (152)	N.A.	(54.08, N.A.)	63 (147)	N.A.	(25.89, N.A.)	0.69	(0.48, 1.00)
>= 1 AND < 3 YEARS	200	32 (101)	N.A.	(53.62, N.A.)	49 (99)	39.26	(10.64, N.A.)	0.55	(0.35, 0.86)
>= 3 YEARS	83	19 (43)	N.A.	(20.34, N.A.)	24 (40)	20.21	(6.47, 38.14)	0.60	(0.33, 1.09)
LIVER METASTASIS PER BICR									
YES	210	37 (104)	N.A.	(38.67, N.A.)	51 (106)	N.A.	(11.79, N.A.)	0.68	(0.44, 1.03)
NO	368	64 (190)	N.A.	(53.62, N.A.)	85 (178)	33.22	(20.30, N.A.)	0.60	(0.43, 0.83)
NOT REPORTED	4	0 (2)	N.A.		0 (2)	N.A.			
LUNG METASTASIS PER BICR									
YES	133	36 (62)	13.17	(4.21, N.A.)	41 (71)	18.50	(7.39, 44.29)	1.11	(0.71, 1.74)
NO	445	65 (232)	N.A.	(54.08, N.A.)	95 (213)	N.A.	(25.56, N.A.)	0.52	(0.38, 0.72)
NOT REPORTED	4	0 (2)	N.A.		0 (2)	N.A.			
PERITONEAL METASTASIS PER BICR									
YES	226	44 (126)	54.08	(53.62, N.A.)	53 (100)	24.80	(7.39, N.A.)	0.55	(0.37, 0.82)
NO	352	57 (168)	N.A.		83 (184)	N.A.	(26.25, N.A.)	0.67	(0.48, 0.94)
NOT REPORTED	4	0 (2)	N.A.		0 (2)	N.A.			
PD-L1 STATUS									
>= 1%	133	21 (72)	N.A.	(54.08, N.A.)	21 (61)	N.A.	(44.29, N.A.)	0.77	(0.42, 1.42)
< 1%	427	74 (214)	N.A.	(53.62, N.A.)	111 (213)	24.80	(14.92, N.A.)	0.57	(0.43, 0.77)
NON-QUANTIFIABLE	22	6 (10)	25.30	(1.18, N.A.)	4 (12)	N.A.	(1.64, N.A.)	1.35	(0.36, 5.08)
MMR TEST RESULTS PER CENTRAL ASSESSMENT									
dMMR	551	94 (280)	N.A.	(53.82, N.A.)	126 (271)	44.29	(25.56, N.A.)	0.64	(0.49, 0.83)
pMMR	9	4 (6)	10.50	(1.31, N.A.)	2 (3)	1.22	(1.05, N.A.)		
NOT AVAILABLE	22	3 (10)	N.A.	(9.26, N.A.)	8 (12)	6.70	(1.61, N.A.)	0.31	(0.08, 1.18)
MMR TEST RESULTS PER LOCAL ASSESSMENT									
dMMR	487	90 (254)	N.A.	(53.62, N.A.)	108 (233)	44.85	(21.19, N.A.)	0.70	(0.53, 0.92)
pMMR	4	2 (2)	10.50	(10.15, N.A.)	1 (2)	N.A.	(10.84, N.A.)		
NOT AVAILABLE	91	9 (40)	N.A.	(46.62, N.A.)	27 (51)	24.80	(6.47, N.A.)	0.30	(0.14, 0.65)
MSI TEST RESULTS PER CENTRAL ASSESSMENT									
MSI-H	503	81 (257)	N.A.	(53.82, N.A.)	112 (246)	N.A.	(24.80, N.A.)	0.60	(0.45, 0.81)
MSS	25	10 (13)	2.73	(1.35, 11.33)	10 (12)	1.76	(1.25, 38.14)	0.84	(0.35, 2.02)
NOT AVAILABLE	54	10 (26)	N.A.	(11.14, N.A.)	14 (28)	32.82	(4.21, N.A.)	0.68	(0.30, 1.54)
MSI TEST RESULTS PER LOCAL ASSESSMENT									
MSI-H	255	40 (128)	N.A.	(53.82, N.A.)	66 (127)	26.25	(9.49, N.A.)	0.48	(0.32, 0.71)
MSI-L/MSS	3	1 (1)	1.22	(N.A., N.A.)	1 (2)	N.A.	(1.51, N.A.)		
NOT AVAILABLE	324	60 (167)	N.A.	(53.62, N.A.)	69 (157)	N.A.	(22.11, N.A.)	0.78	(0.55, 1.10)



	N	Nivo + Ipi N of Events (N of subjects)	mPFS (95% CI)		Nivo N of Events (N of subjects)	mPFS (95% CI)		Unstratified Hazard Ratio (95% CI) Nivo + Ipi vs. Nivo	
BRAF/KRAS/NRAS MUTATION STATUS									
BRAF/KRAS/NRAS ALL WILD TYPE	156	26 (75)	N.A.	(44.02, N.A.)	37 (81)	44.29	(12.94, N.A.)	0.64	(0.39, 1.06)
BRAF MUTANT	179	34 (98)	N.A.	(46.62, N.A.)	41 (81)	25.89	(15.21, N.A.)	0.62	(0.39, 0.97)
KRAS OR NRAS MUTANT	125	22 (57)	N.A.	(33.08, N.A.)	31 (68)	N.A.	(10.64, N.A.)	0.76	(0.44, 1.31)
BRAF AND KRAS/NRAS MUTANT	8	3 (7)	N.A.	(1.45, N.A.)	1 (1)	1.58	(N.A., N.A.)		
UNKNOWN	114	16 (59)	54.08	(38.44, N.A.)	26 (55)	38.14	(9.20, N.A.)	0.48	(0.26, 0.91)
LYNCH SYNDROME									
YES	83	19 (43)	53.82	(11.33, N.A.)	18 (40)	38.14	(9.20, N.A.)	0.90	(0.47, 1.72)
NO	334	54 (172)	N.A.	(53.62, N.A.)	78 (162)	44.29	(16.03, N.A.)	0.56	(0.40, 0.80)
UNKNOWN	156	28 (78)	N.A.	(38.67, N.A.)	36 (78)	33.22	(18.50, N.A.)	0.71	(0.43, 1.16)
NOT REPORTED	9	0 (3)	N.A.		4 (6)	28.88	(0.49, N.A.)		
PRIOR SURGERY									
YES	524	91 (266)	N.A.	(53.82, N.A.)	120 (258)	44.85	(25.56, N.A.)	0.65	(0.49, 0.85)
NO	58	10 (30)	N.A.	(10.87, N.A.)	16 (28)	11.79	(3.68, N.A.)	0.52	(0.23, 1.14)
PRIOR RADIOTHERAPY									
YES	48	18 (26)	11.14	(2.63, 25.99)	13 (22)	10.64	(2.79, N.A.)	1.17	(0.57, 2.40)
NO	534	83 (270)	N.A.	(54.08, N.A.)	123 (264)	44.29	(24.80, N.A.)	0.57	(0.43, 0.76)



HR is not computed for subset category with less than 10 subjects per treatment group. For local and central MSI/MMR assessment, not available includes both not evaluable and not tested. For tumor location, other locations unless listed are included in unknown category. PD-L1 non-quantifiable includes subjects whose PD-L1 status are not evaluable, indeterminate or not available at baseline. MSI test per local assessment including both PCR and NGS test.
Source: ADSL, ADEFTTES, ADSUB of the CA2098HW Primary CSR

The Applicant's Position:

Nivo+Ipi vs Chemo in 1L

As of the 15-Nov-2023 DBL, nivo+ipi demonstrated a statistically significant and clinically meaningful PFS per BICR benefit vs chemo in all 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC in CA2098HW. The robustness of the primary analysis was supported by sensitivity analyses (please see ADSL, ADDX, ADPD, ADEFTTES of the CA2098HW Interim CSR) showing consistent PFS per BICR benefit with nivo+ipi vs chemo. PFS per BICR in all 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC favored nivo+ipi over chemo across all subgroups, including populations that historically showed less PFS benefit with single IO agents (eg, subjects with liver metastasis, and RAS mutant tumors). The treatment effect of nivo+ipi was similar regardless of tumor cell PD-L1 expression level (≥ 1% or < 1%).

Nivo+Ipi vs Nivo in All Lines

As of the 25-Sep-2024 DBL, nivo+ipi demonstrated a statistically significant and clinically meaningful improvement in PFS per BICR (primary definition) compared with nivo across lines in all randomized subjects with centrally confirmed MSI-H/dMMR mCRC in CA2098HW. PFS per BICR in all randomized subjects with centrally confirmed MSI-H/dMMR mCRC favored nivo+ipi over nivo across most of the subgroups. The robustness of the primary analysis was supported by sensitivity analyses (please see ADSL, ADDX, ADPD, ADEFTTES of the CA2098HW Interim CSR) showing consistent PFS per BICR benefit with nivo+ipi vs nivo.

The FDA's Assessment:

Nivolumab + Ipilimumab vs Chemotherapy in 1L

FDA agrees with the Applicant's description of the primary analyses of CA2098HW based on the data cutoff on 12-Oct-2023, which demonstrated statistically significant improvements in PFS assessed by BICR for the comparison of nivo+ipi vs chemo in 1L patients (stratified HR: 0.21; 95% CI: 0.14, 0.32; stratified log-rank test p-value < 0.0001; p-value boundary = 0.0209) with centrally confirmed MSI-H/dMMR mCRC. The median PFS was 5.8 months (95% CI: 4.4, 7.8) in the chemo arm and was not reached in the nivo+ipi arm with the lower bound of 95% CI of 38.4 months.

FDA conducted a sensitivity analysis based on the data cutoff on 28-Aug-2024, showing a consistent PFS improvement (stratified HR: 0.20; 95% CI: 0.14, 0.31) compared with the primary analysis.

Nivolumab + Ipilimumab vs Nivolumab in All Lines

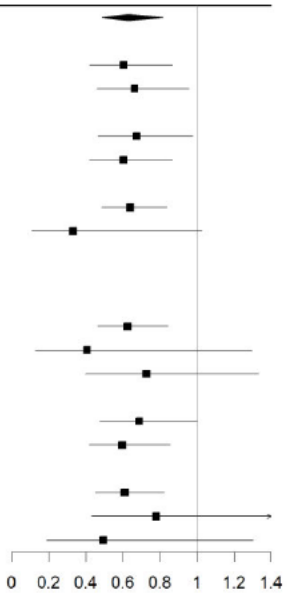
FDA agrees that the primary analyses of CA2098HW based on the data cutoff on 28-Aug-2024 demonstrated statistically significant improvements in PFS assessed by BICR for the comparison

of nivo+ipi vs nivo in all lines (stratified HR: 0.62; 95% CI: 0.48, 0.81; stratified log-rank test p-value = 0.0003; p-value boundary = 0.0095) in patients with centrally confirmed MSI-H/dMMR mCRC. The median PFS was 39.3 months (95% CI: 22.1, not estimable) in the nivo arm while it was not reached in the nivo+ipi arm with the lower bound of 95% CI of 53.8 months.

FDA's additional subgroup analysis results are shown below in in Figure 7. The PFS HRs were generally similar across the subgroups.

Figure 7: FDA-Additional Subgroup Analyses for Comparing PFS per BICR between Nivo+Ipi and Nivo in All Lines Patients with centrally confirmed MSI-H/dMMR

Subgroup	Nivo + Ipi Evt / N	Nivo Evt / N	HR (95% CI)
Overall	**101/296 (34.1)**	**136/286 (47.6)**	**0.63 (0.49, 0.82)**
Age Group			
< 65	51/164 (31.1)	70/157 (44.6)	0.6 (0.42, 0.87)
>= 65	50/132 (37.9)	66/129 (51.2)	0.66 (0.46, 0.96)
Sex			
Female	54/161 (33.5)	60/137 (43.8)	0.67 (0.47, 0.98)
Male	47/135 (34.8)	76/149 (51)	0.6 (0.42, 0.87)
Race			
WHITE	92/258 (35.7)	121/246 (49.2)	0.64 (0.49, 0.84)
ASIAN	4/24 (16.7)	12/31 (38.7)	0.33 (0.11, 1.03)
BLACK OR AFRICAN AMERICAN	1/4 (25)	2/6 (33.3)	
OTHER	4/10 (40)	1/3 (33.3)	
Region			
US/CANADA/EUROPE	76/209 (36.4)	105/206 (51)	0.63 (0.46, 0.84)
ASIA	4/23 (17.4)	10/29 (34.5)	0.41 (0.13, 1.3)
REST OF WORLD	21/64 (32.8)	21/51 (41.2)	0.73 (0.4, 1.33)
ECOG			
0	51/164 (31.1)	60/149 (40.3)	0.69 (0.47, 1)
1	50/132 (37.9)	76/137 (55.5)	0.6 (0.42, 0.85)
MMR/MSI status			
dMMR and MSI-H	74/241 (30.7)	102/231 (44.2)	0.61 (0.45, 0.82)
only dMMR	20/39 (51.3)	24/40 (60)	0.78 (0.43, 1.42)
only MSI-H	7/16 (43.8)	10/15 (66.7)	0.49 (0.19, 1.3)



Source: FDA Analysis.

FDA conducted analyses to investigate the PFS effect of nivo+ipi vs nivo in different lines of therapy per IRT for centrally confirmed MSI-H/dMMR patients. The PFS HRs were similar across the subgroups of patients with 1L, 2L, and 3L+ therapy.

FDA also conducted an analysis excluding patients who had relevant protocol deviations. Twenty patients with centrally confirmed MSI-H/dMMR (11 in the nivo+ipi arm and 9 in the nivo arm) were excluded from the primary analysis data set. The PFS HR for this analysis was 0.61 (95% CI: 0.47, 0.79) which was similar to the primary analysis.

Data Quality and Integrity

The Applicant's Position:

Data cleaning and quality control checks were implemented by BMS and consisted of site monitoring visits guided by the SMP to review source documents against the eCRF and data validation checks of the eCRF and externally loaded data. Continuous data quality review was performed throughout the study to ensure data completeness, accuracy, and integrity. Any issues or findings were followed up for resolution during Data Quality Sub-team meetings and Data Review Meetings. The Vendor Data Quality Oversight Plan was used to ensure oversight of Data Management review performed by Accenture. In addition, a further period of enhanced data review was performed by BMS GBDS and clinical teams to ensure the quality and completeness of the data prior to data cutoff. The BMS RAVE Clinical database was also audited prior to the data cutoff. The Database Lock Checklist was completed prior to database lock; this documented that the database was complete, accurate, and all prerequisites for the database lock had been achieved.

The FDA's Assessment:

FDA acknowledges the Applicant's position. No data quality or integrity issues were identified during the FDA review and verification of the data provided.

Efficacy Results – Secondary and other relevant endpoints

Data:

Nivo+Ipi vs Chemo in 1L

Table 27: Applicant - Secondary and Other Efficacy Endpoints for Nivo+Ipi (Arm B) vs Chemo (Arm C) – All 1L Randomized Subjects with MSI-H/dMMR mCRC in CA2098HW (15-Nov-2023 DBL)

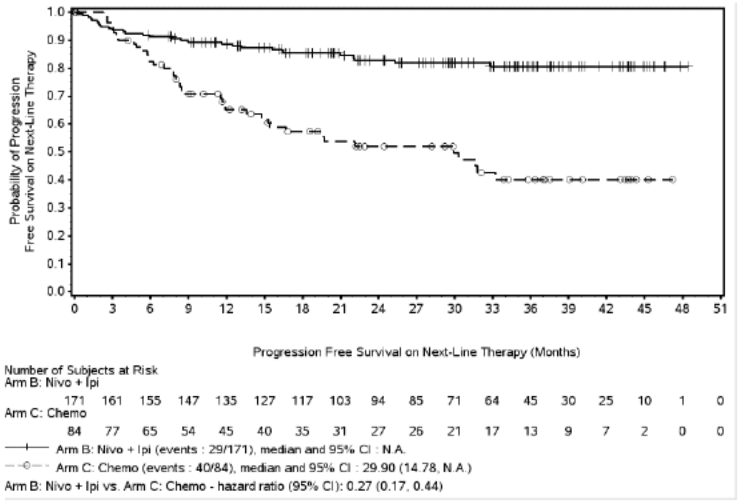
	Arm B: Nivo+Ipi	Arm C: Chemo
All 1L Randomized Subjects	**N = 202**	**N = 101**
PFS per BICR (Primary Definition)	**Secondary Endpoint**	
Events, n (%)	73 (36.1)	62 (61.4)
Median PFS (95% CI), months[a]	NR (34.30, NA)	6.21 (4.70, 9.00)
HR (95% CI)[b]	0.32 (0.23, 0.46)	
PFS Rates (95% CI), %[a]		
6-month	74.54 (67.83, 80.05)	50.09 (38.45, 60.65)
Number of Subjects at Risk	141	35
12-month	71.15 (64.19, 77.00)	23.70 (14.32, 34.41)
Number of Subjects at Risk	116	14

Table 27: Applicant - Secondary and Other Efficacy Endpoints for Nivo+Ipi (Arm B) vs Chemo (Arm C) – All 1L Randomized Subjects with MSI-H/dMMR mCRC in CA2098HW (15-Nov-2023 DBL)

	Arm B: Nivo+Ipi	Arm C: Chemo
All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR	**N = 171**	**N = 84**
PFS per Investigator (Primary Definition)	**Secondary Endpoint**	
Events, n (%)	48 (28.1)	55 (65.5)
Median PFS (95% CI), months[a]	NR (38.44, NA)	7.66 (4.21, 9.00)
HR (95% CI)[b]	0.20 (0.14, 0.31)	
PFS Rates (95% CI), %[a]		
6-month	83.51 (77.01, 88.30)	50.22 (38.18, 61.09)
Number of Subjects at Risk	137	34
12-month	80.31 (73.43, 85.59)	19.11 (10.06, 30.34)
Number of Subjects at Risk	114	9
PFS2 per Investigator	**Exploratory Endpoint**	
Events, n (%)	29 (17.0)	40 (47.6)
Median PFS2 (95% CI), months[a]	NR (NA, NA)	29.90 (14.78, NA)
HR (95% CI)[b]	0.27 (0.17, 0.44)	
PFS2 Rates (95% CI), %[a]		
6-month	91.22 (85.87, 94.61)	82.39 (72.09, 89.17)
Number of Subjects at Risk	155	65
12-month	88.75 (82.93, 92.68)	65.02 (53.20, 74.55)
Number of Subjects at Risk	135	45

[a] Based on Kaplan-Meier estimates
[b] HR from a Cox proportional hazard model stratified by tumor sidedness (left vs right) per IRT.
Clinical data cutoff was 12-Oct-2023. Minimum follow-up (time from the last subject's randomization date to the data cutoff date) was 6.1 months. Median follow up (time between date of randomization and the data cutoff date) was 31.57 months.
Excludes data collected on or after first crossover dose date.
Source: ADSL, ADEFTTES of the CA2098HW Interim CSR

Figure 8: Applicant - Progression-Free Survival on Next Line of Therapy (PFS2) for Nivo+Ipi (Arm B) vs Chemo (Arm C)- All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC in CA2098HW (15-Nov-2023 DBL)



Statistical model for hazard ratio: stratified Cox proportional hazard model by tumor sidedness (left vs right) as entered into the IRT. Symbols represent censored observations.
Source: ADSL, ADEFTTES of the CA2098HW Interim CSR

Nivo+Ipi vs Nivo in All Lines

Table 28: Applicant - Secondary and Other Efficacy Endpoints for Nivo+Ipi (Arm B) vs Nivo (Arm A) - All Randomized Subjects with MSI-H/dMMR mCRC in CA2098HW (25-Sep-2024 DBL)

	Arm A: Nivo	Arm B: Nivo+Ipi
All Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC	**N = 286**	**N = 296**
ORR per BICR	**Secondary Endpoints**	
N Responders (CR+PR) (%)[a]	165 (57.7)	209 (70.6)
(95% CI)[b]	(51.7, 63.5)	(65.1, 75.7)
Difference (95% CI)[c]	13.0 (5.3, 20.8)	
Difference (99.4% CI)[c]	13.0 (2.2, 23.9)	
Odds Ratio (95% CI)[c]	1.77 (1.26, 2.50)	
p-value[d]	0.0011	
Best Overall Response, n (%)		
Complete Response	80 (28.0)	90 (30.4)
Partial Response	85 (29.7)	119 (40.2)
Stable Disease	53 (18.5)	40 (13.5)
Progressive Disease	54 (18.9)	30 (10.1)
Unable to Determine	8 (2.8)	11 (3.7)
Not Reported	6 (2.1)	6 (2.0)
DOR per BICR		

Table 28: Applicant - Secondary and Other Efficacy Endpoints for Nivo+Ipi (Arm B) vs Nivo (Arm A) - All Randomized Subjects with MSI-H/dMMR mCRC in CA2098HW (25-Sep-2024 DBL)

	Arm A: Nivo	Arm B: Nivo+Ipi
n Events/N Responders (%)	33/165 (20.0)	34/209 (16.3)
Median, mo. (95% CI)[a]	Not Reached (NA, NA)	Not Reached (NA, NA)
Min, Max, mo.	2.1, 54.5+	1.4+, 54.9+
PFS (per investigator, primary definition)		
Events, n (%)	142 (49.7)	102 (34.5)
Median PFS (95% CI), mo.[f]	38.14 (27.20, NA)	NA (54.08, NA)
HR (95% CI)[g]	0.62 (0.48, 0.80)	
PFS Rates (95% CI), %[f]		
12-month	64.60 (58.71, 69.87)	76.83 (71.57, 81.25)
Number of Subjects at Risk	177	221
18-month	60.57 (54.59, 66.02)	74.73 (69.34, 79.32)
Number of Subjects at Risk	164	208
PFS2 (per investigator)	**Exploratory Endpoint**	
Events, n (%)	106 (37.1)	69 (23.3)
Median PFS2, mo.[f]	Not Reached	Not Reached
HR (95% CI)[g]	0.57 (0.42, 0.78)	
PFS2 Rates (95% CI), %[f]		
12-month	80.07 (74.95, 84.25)	88.49 (84.27, 91.64)
Number of Subjects at Risk	229	260
18-month	72.72 (67.17, 77.50)	85.43 (80.86, 88.98)
Number of Subjects at Risk	144	180
All Randomized Subjects	**N = 353**	**N = 354**
PFS per BICR (Primary Definition)	**Secondary Endpoint**	
Events, n (%)	196 (55.5)	148 (41.8)
Median PFS (95% CI), months[f]	18.43 (9.20, 28.16)	54.08 (44.02, NA)
HR (95% CI)[b]	0.64 (0.52, 0.79)	
PFS Rates (95% CI), %[f]		
12-month	53.15 (47.74, 58.26)	67.61 (62.39, 72.26)
Number of Subjects at Risk	177	227
18-month	51.04 (45.62, 56.18)	63.73 (58.40, 68.56)
Number of Subjects at Risk	166	208
ORR per BICR		
N Responders (CR+PR), %[a]	174 (49.3)	224 (63.3)
95% CI[b]	(44.0, 54.6)	(58.0, 68.3)
Difference (95% CI)[c]	14.0 (6.8, 21.2)	
Odds Ratio (95% CI)[d]	1.80 (1.32, 2.44)	

Table 28: Applicant - Secondary and Other Efficacy Endpoints for Nivo+Ipi (Arm B) vs Nivo (Arm A) - All Randomized Subjects with MSI-H/dMMR mCRC in CA2098HW (25-Sep-2024 DBL)

	Arm A: Nivo	Arm B: Nivo+Ipi
DOR per BICR		
n Events/N Responders (%)	37/174 (21.3)	41/224 (18.3)
Median, mo. (95% CI)[f]	Not Reached (NA, NA)	Not Reached (NA, NA)
Min, Max, mo.	2.1, 54.5+	1.4+, 54.9+

a Per RECIST 1.1, confirmation of response is required at least 4 weeks after the initial response.

b Confidence interval based on the Clopper and Pearson method.

c Strata adjusted difference based on Cochran-Mantel-Haenszel method of weighting. Stratified by tumor sidedness (left vs right) and prior lines of therapy (0, 1, ≥ 2) per IRT.

d Strata adjusted odds ratio using Mantel-Haenszel method.

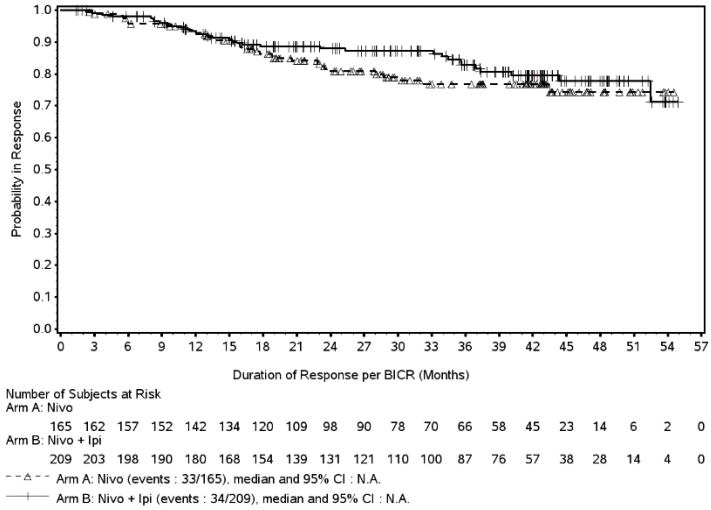
e 2-sided p-value from stratified Cochran-Mantel-Haenszel test. The p-value threshold for statistical significance was 0.006.

f Based on Kaplan-Meier estimates

g HR from a Cox proportional hazard model stratified by tumor sidedness (left vs right) and prior lines of therapy (0, 1, ≥ 2) per IRT.

Clinical data cutoff: 28-Aug-2024; Minimum follow-up: 16.7 months
Source: ADSL, ADEFTTES, ADEFRESP of the CA2098HW Primary CSR

Figure 9: Applicant - Duration of Response per BICR for Nivo+Ipi (Arm B) vs Nivo (Arm A) - All Confirmed Responders with Centrally Confirmed dMMR/MSI-H mCRC in CA2098HW (25-Sep-2024 DBL)



Symbols represent censored observations.
Source: ADSL, ADEFTTES, ADEFRESP of the CA2098HW Primary CSR

The Applicant's Position:

Nivo+Ipi vs Chemo in 1L

As of the 15-Nov-2023 DBL, the PFS per BICR benefit with nivo+ipi vs chemo was also observed in all 1L randomized subjects (HR 0.32 [95% CI: 0.23, 0.46], mPFS [95% CI] not reached [34.30, NA] vs 6.21 [4.70, 9.00] months), which further supports the robustness of the primary analysis (Table 27).

Consistent with PFS per BICR analysis, there was an improvement in PFS per investigator with nivo+ipi vs chemo in all 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC (HR 0.20, 95% CI 0.14, 0.31). The median PFS per INV (95% CI) was not reached (38.44, NA) in the nivo+ipi arm vs 7.66 (4.21, 9.0) months in the chemo arm.

While OS results were not tested at this interim analysis, the sustained PFS benefit and the durability of efficacy of nivo+ipi vs chemo was supported by the PFS2 results. Median PFS2 favored nivo+ipi vs chemo (not reached vs 29.90 months), with an early and sustained separation of the KM curves and higher PFS2 rates with nivo+ipi than chemo at 6 months (91.22% vs 82.39%) and at 12 months (88.75% vs 65.02%) in 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC. The PFS2 results favored nivo+ipi over chemo despite the fact that 65.4% of subjects in the chemo arm received subsequent IO therapy (either on study or off-study).

Nivo+Ipi vs Nivo in All Lines

As of the 25-Sep-2024 DBL, the robustness of the primary analysis of PFS per BICR in subjects with centrally confirmed status across all lines with nivo+ipi vs nivo was supported by PFS results per INV assessment and PFS results in all randomized patients. The clinical benefit of nivo+ipi vs nivo across all lines was further supported by statistically significant ORR per BICR, in all randomized subjects with centrally confirmed MSI-H/dMMR mCRC. ORR was 13.0% higher with nivo+ipi compared with nivo (2-sided stratified CMH test p-value = 0.0011, meeting the threshold of significance level 0.006). There were less PD as BOR with nivo+ipi (10.1%) than with nivo (18.9%). PFS2 favored nivo+ipi vs nivo (median not reached in either arm, with higher PFS2 rates at 12-month: 88.49 vs 80.07, and 18-month: 85.43 vs 72.72).

The FDA's Assessment:

Nivo+Ipi vs Chemo in 1L

FDA does not agree that PFS per BICR benefit with nivo+ipi vs chemo was demonstrated in all 1L randomized subjects. Although a PFS HR of 0.32 (95% CI: 0.23, 0.46) was observed in all 1L randomized patients, the result was largely attributable to the highly statistically significant results in the centrally confirmed MSI-H/dMMR patients. FDA conducted an analysis using patients who had locally positive and centrally negative/unavailable MSI-H/dMMR status. Forty-six patients were included in this sensitivity analysis with 29 patients in the nivo+ipi arm and 16 patients in the chemo arm. The unstratified HR for PFS per BICR in this subgroup of patients was 1.58 (95% CI: 0.75, 3.33) favoring the chemo arm. Median PFS of this subgroup was 2.0 months (95% CI: 1.5, 5.8) in the nivo+ipi arm and 11.5 months (95% CI: 4.1, 14.8) in the chemo arm. FDA considers the reported PFS2 analyses as exploratory.

Nivo+Ipi vs Nivo in All Lines

FDA conducted an analysis comparing PFS per BICR between nivo+ipi vs nivo in all lines using patients who had locally positive and centrally negative/unavailable MSI-H/dMMR status. There were 122 patients included in this analysis with 56 patients in the nivo+ipi arm and 66 patients in the nivo arm. The PFS HR of 0.71 (95% CI: 0.48, 1.05) was descriptively similar to the primary analysis, however, median PFS was short in both two arms with 2.7 months (95% CI: 1.6, 5.8) in the nivo+ipi arm and 2.0 months (95% CI: 1.5, 2.9) in the nivo arm.

FDA agrees that the clinical benefit of nivo+ipi vs nivo was supported by the statistically significant improvement in ORR per BICR (CMH test p-value = 0.0011; p-value boundary: 0.006), with ORR of 70.6% (95% CI: 65.1, 75.7) in the nivo+ipi arm and 57.7% (95% CI: 51.7, 63.5) in the nivo arm. FDA conducted an analysis in each line of therapy and found the ORR improvements of adding ipilimumab to nivolumab were descriptively similar across different lines. The ORR results of nivo+ipi vs nivo provided further supportive evidence of demonstrating the contribution of ipilimumab to the combination therapy.

Nivo+Ipi vs Nivo in 1L
The comparison of nivo+ipi vs nivo in 1L was formally tested based on the data cutoff on 28-Aug-2024 per the hierarchical testing plan. However, the Applicant stated that the study team remains blinded because the hypothesis test did not reach criteria for statistical significance. FDA requested these data and analyses via a separate restricted ad hoc submission, and independently verified the results. The results of comparing nivo+ipi vs. nivo in 1L randomized patients with centrally confirmed MSI-H/dMMR are also supportive to demonstrate the contribution of ipilimumab to the combination therapy.

Overall Survival
OS endpoints were not formally tested in this submission and remains blinded to the study team. FDA requested OS data and conducted descriptive OS analyses for comparing nivo+ipi vs chemo in 1L and nivo+ipi vs chemo in all lines in randomized patients with centrally confirmed MSI-H/dMMR. The Kaplan-Meier analyses do show crossing of the curves in a short period after randomization, and then subsequently favor nivo+ipi. The differences in the causes of death between arms in the initial 180 days of treatment are outlined in the safety overview (Table 37). In general, the data did not indicate harm or detriment to survival at this time.

Dose/Dose Response
The Applicant's Position: Previous PopPK and E-R analyses that support the CA2098HW dosing regimens are described in Section 6.2.2.1.

The FDA's Assessment:
See Section 6.2.

Durability of Response
The Applicant's Position:
Data from CA2098HW suggests long durability of response with nivo+ipi or nivo. As of the 25-Sep-2024 DBL, after median follow-up of 47.11 months (min, max: 16.7, 60.5), median DOR was not reached with both nivo+ipi and nivo, the lower bounder of 95% CI was not reached either. Separation of the KM curves for DOR favoring nivo+ipi over nivo occurred at approximately 16 months.
Long durability of response was further supported by data from CA209142 with long-term follow-up. Please see Section 8.1.4 for more information.

The FDA's Assessment:
Due to the immature DOR data with a large proportion of early censoring, FDA does not agree with BMS' statement above regarding separation of KM curves favoring nivo+ipi over nivo. FDA considers the observed DOR in both arms similar.

Persistence of Effect

The Applicant's Position:

Data from CA2098HW along with supportive data from CA209142 suggest long-term benefit of nivo+ipi as 1L treatment for subjects with MSI-H/dMMR mCRC.

In CA2098HW, as of the 15-Nov-2023 DBL, after median follow-up of 31.51 (min, max: 6.1, 48.4) months, median PFS per BICR was not reached for nivo+ipi vs 5.85 months for chemo in 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC. The PFS KM curves showed early and sustained separation, favoring nivo+ipi over chemo. PFS rate with nivo+ipi vs chemo was 78.69% vs 20.62% at 12 months. While the curve for chemo had an exponential shape, the curve for nivo+ipi was relatively flat over time. PFS2 favored nivo+ipi vs chemo. Median PFS2 was not reached for nivo+ ipi vs 29.90 months for chemo; 12-month PFS2 rate was 88.75% vs 65.02% with nivo+ipi vs chemo. The sustained PFS and PFS2 benefit of large magnitude suggests persistent treatment effect of nivo+ipi in 1L subjects with MSI-H/dMMR mCRC.

Additional evidence on persistence of treatment effect of nivo+ipi derived from PFS by BICR analysis with nivo+ipi vs nivo across all lines. As of the 25-Sep-2024 DBL, after median follow-up of 47.11 months (min, max: 16.7, 60.5), median PFS (95% CI) was not reached for nivo+ipi vs 39.26 months for nivo across lines in all randomized subjects with centrally confirmed MSI-H/dMMR mCRC. The PFS rate (all lines) with nivo+ipi vs nivo was 75.86% vs 62.50% at 12 months and 73.02% vs 59.89% at 18 months. The PFS2 KM curves showed sustained separation after approximately 6 months, favoring nivo+ipi vs nivo. These data along with ORR and DOR data discussed at Durability of Response section further reinforced the persistent treatment effect of nivo+ipi in subjects with MSI-H/dMMR mCRC.

Long-term benefit of nivo+ipi in MSI-H/dMMR mCRC subjects is further supported by the data from Cohorts 2 and 3 of CA209142 with long-term follow-up. Please see Section 8.1.4 for more information.

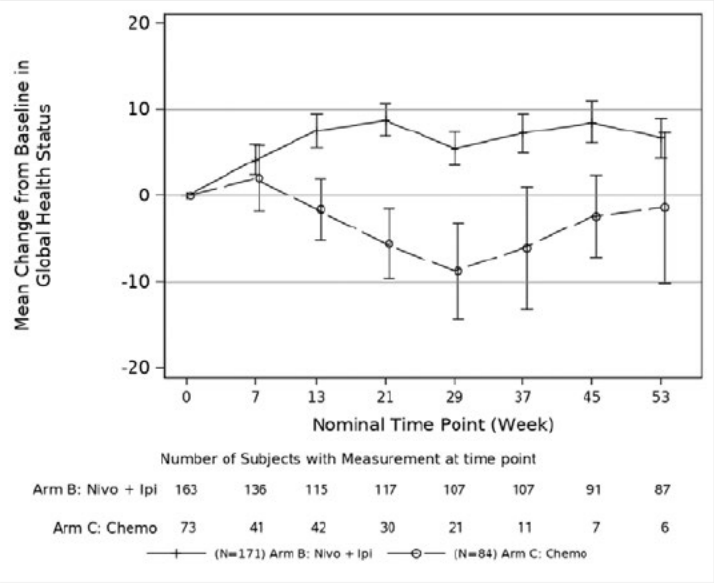
The FDA's Assessment:

Persistence of effect is a term better suited for continuous variables (e.g., hypertension, biomarker assessments, etc.) and is not intended to characterize or compare treatment effects on selected endpoints. CA2098HW was not designed to assess the persistence of the treatment effect following treatment discontinuation. FDA considers the presented PFS2 analyses as exploratory.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Figure 10: Mean Change in Scores from Baseline for Global Health Status by Timepoint (EORTC QLQ-C30) - All 1L Randomized Subjects in the Nivo+Ipi (Arm B) and Chemo (Arm C) Arms with Centrally Confirmed MSI-H/dMMR mCRC in CA2098HW (15-Nov-2023 DBL)



Increases from baseline indicate improvement and decreases from baseline indicate worsening for global health status. Baseline is defined as the last available assessment on or prior to randomization.
Error bars represent 95% confidence intervals.
Source: ADQS, ADSL of the CA2098HW Interim CSR

The Applicant's Position:

In all 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC in the nivo+ipi and chemo arms, descriptive PRO results for EORTC QLQ-C30 Global Health Status in the nivo+ipi arm were either stable or showed a trend for improvement from baseline during the treatment period. In contrast, EORTC QLQ-C30 Global Health Status results for the chemo arm were either stable or showed a trend for worsening from baseline during the treatment period. However, these changes were generally small, and in most cases were not considered to be clinically meaningful. Results for the EORTC QLQ-CR29 were generally similar between the 2 treatment arms. Results for the EQ-5D-3L VAS and UI scores favored nivo+ipi as compared to chemo, but changes from baseline during the treatment period were smaller than the minimal important difference.

PRO results for all 1L randomized subjects in the nivo+ipi and chemo arms were consistent with those for all 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC.

The FDA's Assessment:

The EORTC QLQ-C30, EORTC QLQ-CR29, and EQ-5D-3L questionnaires were assessed in all three arms prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. The exploratory PRO endpoints including functional scales, global health status/QoL, and symptom scales/items were compared descriptively between arms.

Based on the data cutoff on 12-Oct-2023, PRO completion rates (number of patients with valid questionnaire assessment / number of patients expected to have an assessment) for the EORTC QLQ-C30 at baseline were 95.3% in the nivo+ipi arm and 86.9% in the chemo arm in the 1L patients with centrally confirmed MSI-H/dMMR. The PRO completion rates of the time points during the treatment period were descriptively higher in the nivo+ipi arm compared to the chemo arm. Starting from Week 13, the available data rates (number of patients with valid questionnaire assessment / number of randomized patients) in the 1L patients with centrally confirmed MSI-H/dMMR dropped below 70% in the nivo+ipi arm and below 50% in the chemo arm.

Based on the data cutoff on 28-Aug-2024, PRO completion rates for the EORTC QLQ-C30 at baseline were 94.6% in the nivo+ipi arm and 94.1% in the nivo arm in the All Lines patients with centrally confirmed MSI-H/dMMR. The PRO completion rates of the time points during the treatment period were all above 82.3% in both the nivo+ipi and nivo arms. However, the available data rates dropped below 80% in both arms starting from Week 13.

The PRO completion rates and available data rates for EORTC QLQ-CR29 and EQ-5D-3L were similar to EORTC QLQ-C30.

FDA reviewed the PRO analysis results submitted by the Applicant, however, no statistical testing procedure to control the overall Type-1 error was specified for the PRO endpoints. FDA considers that the PRO analyses were exploratory, and no efficacy claims (either superiority or non-inferiority) can be made based on these analyses.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position: Not applicable.

The FDA's Assessment:
Additional FDA analyses have been added to the relevant sections.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The review of efficacy in this Application is supported primarily by the results from Study CA2098HW, which had dual primary outcomes in the primary efficacy population, consisting of patients with centrally confirmed MSI-H/dMMR mCRC. The event rates for the prespecified primary outcomes occurred at different rates, with two data cutoff dates approximately 10 months apart. The initial prespecified primary analysis (data cutoff date 10/12/23) demonstrated a clinically meaningful and statistically significant improvement in PFS with nivo+ipi compared to investigator assessed choice of standard of care chemotherapy. In the first line patient population, median PFS was not reached (95% CI 38.4 months, not estimable) in the nivo+ipi arm and 5.8 months (95% CI 4.7, 7.8) in the SOC arm (HR of 0.21 [95% CI 0.14, 0.32; $p < 0.0001$]).

The latter analyses (data cutoff date 8/24/24), allowing for an assessment of the contribution of ipilimumab, demonstrated a statistically significant and clinically meaningful improvement in PFS by BICR with nivo+ipi compared to nivo single agent irrespective of prior line of treatment. The median PFS was not reached (95% CI 53.82 months, not estimable) in the nivo+ipi arm and 39.3 months (95% CI 22.11, not estimable) in the nivolumab arm, with a HR of 0.62 (95% CI 0.48, 0.81; p= 0.0003). The ORR was 70.6% (95% CI 65.1, 75.7) and 57.7% (95% CI 51.7, 63.5) in the nivo+ipi and nivolumab arms, respectively, further supporting the efficacy of the combination regimen. In a sensitivity analysis, evaluating patients who were randomized but did not have centrally confirmed MSI-H/dMMR, the median PFS (2.7 months [95% CI 1.6, 5.8] and 2.0 months [95% CI 1.5, 2.9] in the nivo+ipi and nivo arms respectively) in this population was not comparable to that observed in patients with centrally confirmed MSI-H/dMMR status and the indication statement specifies that patients being considered for the combination regimen should be MSI-H/dMMR (b) (4).

The data provided adequately fulfills the post marketing requirements (PMR 3449-1, 3449-2 for nivolumab and 3450-1and 3450-2 for ipilimumab) issued for the respective accelerated approvals of nivolumab as a single agent, nivolumab in combination with ipilimumab, and ipilimumab in combination with nivolumab. The data additionally provides substantial evidence of effectiveness of nivo+ipi for the treatment of immunotherapy naïve patients with MSI-H/dMMR mCRC irrespective of prior line of treatment.

8.1.4. Assessment of Efficacy Across Trials

Contribution of Components - Supportive Study CA209142 (Cohort 1 and Cohort 2)

Data:

Table 29: Applicant - Summary of Key Efficacy Endpoints with Nivo and Nivo+Ipi - All Treated Subjects with MSI-H/dMMR mCRC per Local Testing in CA209142 Cohort 1 and 2 (Nov-2021 DBL)

Efficacy Parameter	Nivo (Cohort 1) N = 74	Nivo+Ipi (Cohort 2) N = 119
ORR per BICR, n (%)	28 (37.8)	74 (62.2)
95% CI	(26.8, 49.9)	(52.8, 70.9)
DCR per BICR, n (%)	48 (64.9)	98 (82.4)
95% CI	(52.9, 75.6)	(74.3, 88.7)
BOR per BICR, n (%)		
CR	13 (17.6)	32 (26.9)
(95% CI)	(9.7, 28.2)	(19.2, 35.8)
PR	15 (20.3)	42 (35.3)
(95% CI)	11.8, 31.2)	(26.8, 44.6)
SD	22 (29.7)	26 (21.8)
PD	20 (27.0)	14 (11.8)
Unable to Determine	2 (2.7)	5 (4.2)
Not Reported	2 (2.7)	0
TTR per BICR		
Number of responders	28	74
Median (range), months	4.42 (1.2, 27.9)	3.86 (1.1, 43.0)
DOR per BICR		
Median (95% CI), months	NR (29.86, NR)	NR (NR, NR)
Range	1.4+, 81.5+	1.9, 71.6+
Subjects with ongoing response, n (%)[a]	9 (32.1)	35 (47.3)
PFS per BICR		
Median (95% CI), months	6.6 (4.1, 30.7)	NR (36.0, NR)
12-month rate (95% CI), %	45.8 (34.1, 56.8)	71.5 (62.3, 78.8)
60-month rate (95% CI), %	29.3 (18.8, 40.5)	53.2 (43.1, 62.2)
OS		
Median (95% CI), months	44.2 (20.9, 75.1)	NR (NR, NR)
12-month rate (95% CI), %	68.9 (57.0, 78.1)	84.9 (77.1, 90.2)
60-month rate (95% CI), %	45.9 (34.3, 56.8)	67.9 (58.7, 75.5)

ORR = CR+PR
DCR = CR+PR+SD (for at least 12 weeks)
Response assessed by BICR per RECIST 1.1 criteria
Median computed using Kaplan-Meier method

Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis and excludes responders censored prior to 8 weeks of the clinical data cutoff date if a patient is still in the first 24 weeks follow-up period, otherwise, the window is 14 weeks.
[a] The percentages of subjects with ongoing response are calculated based on number of responders.
Symbol + indicates a censored value.
Source: ADSL of the CA209142 Cohort 1 ad hoc report and ADSL of the CA209142 Cohort 2 ad hoc report

The Applicant's Position:

CA209142 Cohort 2 vs Cohort 1 in support of the CoC

CA209142 is an open-label, multi-cohort, non-randomized Phase 2 study in mCRC patients treated with nivo monotherapy or nivo-based combination therapies. Subjects who had ≥ 1 line of prior therapy (2L+ subjects) were treated with either nivo (3 mg/kg Q2W) in Cohort 1 or nivo+ipi (3 mg/kg Q3W + ipi 1 mg/kg Q3W for 4 doses followed by nivo 3 mg/kg Q2W) in Cohort 2. The demographic and baseline characteristics were similar for subjects in both cohorts.

In CA209142, with the updated data as of the Nov-2021 DBL with median follow-up of 70.01 (min, max: 66.2, 88.7) months for Cohort 1 and 64.0 (min, max: 60.0, 75.8) months for Cohort 2, the efficacy was numerically greater with nivo+ipi in Cohort 2 vs nivo in Cohort 1, as showing with higher ORR and CR rate, and higher 60-month PFS rate and 60-month OS rate. In addition, numerically longer median PFS and OS (non-overlapping 95% CIs) was observed with nivo+ipi vs nivo. The numerical, consistent, and clinically meaningful increase in efficacy measures across all endpoints with nivo+ipi relative to nivo suggested that the addition of ipi improved clinical outcomes in subjects with MSI-H/dMMR mCRC, providing indirect evidence on contribution of ipi to nivo+ipi.

The FDA's Assessment:

FDA acknowledges the Applicant's position. FDA has outlined the data from study CA209142 providing the evidence of accelerated approval of both nivolumab, single agent, and nivolumab in combination with ipilimumab in Table 2. The data from CA209142 provides indirect supportive evidence for the contribution of ipilimumab to the combination regimen, whereas CA20198HW allowed for an adequate assessment of the COC.

Long-term Assessment of Efficacy in 1L with Nivo+Ipi - Supportive Study CA209142 (Cohort 3)

Data:

Table 30: Applicant - Summary of Efficacy Results with Nivo+Ipi - All Treated Subjects with dMMR/MSI-H mCRC per Local Testing in CA209142 Cohort 3 (Oct-2020 DBL)

Efficacy Parameter	Nivo+Ipi (Cohort 3) N = 45
ORR per BICR, n (%)	28 (62.2%)
95% CI	(46.5, 76.2)
DCR per BICR, n (%)	35 (77.8%)
95% CI	(62.9, 88.8)
BOR per BICR, n (%)	
CR	11 (24.4%)
(95% CI)	(12.9, 39.5)
PR	17 (37.8%)
(95% CI)	(23.8, 53.5)
SD	8 (17.8%)
PD	7 (15.6%)
Unable to Determine	2 (4.4%)
TTR	
Number of Responders	28
Median (range), months	1.97 (1.2, 16.6)
DOR	
# Events / # Responders (%)	5 / 28 (17.9%)
Median (95% CI), Months	NR (NA, NA)
Range	(3.3+, 40.0+)
Subjects with ongoing response, n (%)[a]	15 (53.6%)
PFS	
Number of Events, n (%)	16 (35.6%)
Median PFS (95% CI), Months	NR (17.5, NA
12-month rate (95% CI), %	74.2 (58.3, 84.8)
24-month rate (95% CI), %	63.0 (46.0, 75.9)
36-month rate (95% CI), %	59.7 (42.4, 73.3)
OS	
Number of Events (%)	12 (26.7)
Median OS (95% CI), Months	NR (NA, NA)
12-month rate (95% CI), %	84.1 (69.5, 92.1)
24-month rate (95% CI). %	79.4 (64.1, 88.7)
36-month rate (95% CI), %	72.3 (56.4, 83.2)

ORR = CR+PR; DCR = CR+PR+SD (for at least 12 weeks); Response assessed by BICR per RECIST 1.1 criteria.
Median computed using Kaplan-Meier method; Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis and excludes responders censored prior to 8 weeks of the clinical data cutoff date if a patient is still in the first 24 weeks follow-up period, otherwise, the window is 14 weeks.
[a] The percentages of subjects with ongoing response are calculated based on number of responders.
Symbol + indicates a censored value.
Source: ADSL of the CA209142 Cohort 3 Interim CSR

The Applicant's Position:

CA209142 Cohort 3 in support of Long-term Efficacy

In Cohort 3 of CA209142, nivo+ipi (nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W, same dose and different schedule of ipi with the CA2098HW nivo+ipi dosing regimen) was evaluated in a population of subjects with MSI-H/dMMR mCRC who have not received prior therapy for metastatic disease. The baseline characteristics were in Cohort 3 similar with baseline characteristics of 1L subjects in CA2098HW. As of the Oct-2020 DBL with median follow-up of 39.3 (min, max: 34.5, 44.0) months, treatment with nivo+ipi resulted in a high and durable ORR, high PFS and OS rates in 1L subjects over a long-term follow up.

The FDA's Assessment:
Although acknowledging the results of Cohort 3 of Study CA209142, the differences in dosing schedule for the combination of nivo+ipi,, the limited sample size, and single arm study design limit the role of the data to provide additional supportive evidence for the combination regimen.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

CA2098HW is a well-designed Phase 3 clinical trial. The submitted data meets the statutory evidentiary standard for substantial evidence of effectiveness. The data supports the proposed indication of nivo in combination with ipi, for the 1L treatment of patients with MSI-H/dMMR mCRC. Furthermore, the data supports to fulfill the existing PMRs (PMR 3243-1, PMR 3449-1, PMR 3450-1) and to convert existing indications to full approval. In CA2098HW with a typical 1L MSI-H/dMMR mCRC patient population, nivo+ipi demonstrated a statistically and clinically meaningful improvement in the primary endpoint of PFS per BICR vs chemo in 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC (HR = 0.21 [97.91% CI: 0.13, 0.35; 95% CI: 0.14, 0.32]; p value < 0.0001). With a median follow-up of 31.57 (min, max: 6.1, 48.4) months, median PFS was not reached for nivo+ipi vs 5.85 months for chemo. PFS rates (95% CI) were higher with nivo+ipi vs chemo at 6-month (82.08% [75.37, 87.11] vs 48.18% [35.58, 59.69]) and 12-month (78.69% [71.57, 84.22] vs 20.62% [11.18, 32.05]).

PFS per BICR HRs favored nivo+ipi over chemo across all predefined subgroups. In addition, PFS findings per BICR in 1L subjects with MSI-H/dMMR mCRC per local testing were

consistent with those in 1L subjects with centrally confirmed MSI-H/dMMR mCRC. PRO measures trended toward improvement with nivo+ipi but not with chemo. Furthermore, the superior clinical benefit of nivo+ipi over chemo was supported by consistent results of PFS per investigator with HR of 0.20 (95% CI 0.14, 0.31). The treatment effect of nivo+ipi vs chemo was durable and maintained after next line of therapy as demonstrated by clinically relevant improvement in PFS2 with HR of 0.27 (95% CI 0.17, 0.44) despite high rate of crossover to IO-therapy in chemo arm.

Contribution of ipi to nivo+ipi combination was demonstrated in many tumor types.[2] In CA2098HW, nivo+ipi demonstrated a statistically significant and clinically meaningful improvement vs nivo in the other primary endpoint of PFS per BICR across lines. In addition, the secondary endpoint of ORR per BICR was 13.0% higher with nivo+ipi compared with nivo, which was also statistically significant. These results provide substantial evidence demonstrating the contribution of components for the nivo+ipi combination regimen for the treatment of patients with MSI-H/dMMR mCRC.

For MSI-H/dMMR mCRC, additional supporting data on contribution of components are based on results from indirect comparison of results from CA209142 from Cohort 2 (nivo+ipi) and Cohort 1 (nivo).

Results for nivo+ipi from CA209142 Cohort 3 provided supportive evidence of long-term efficacy as 1L treatment for subjects with MSI-H/dMMR mCRC.

The FDA's Assessment:

The effectiveness of nivolumab in combination with ipilimumab for the treatment of patients with MSI-H/dMMR mCRC is supported by the analysis results of the pivotal study CA2098HW, a randomized, 3-arm open-label study of 839 patients comparing nivolumab + ipilimumab, nivolumab monotherapy, and investigator's choice of chemotherapy for both first line and all lines therapies. FDA agrees that the primary analysis results of CA2098HW demonstrated a statistically significant and clinical meaningful improvement in PFS per BICR of nivo+ipi vs chemo in 1L randomized patients with centrally confirmed MSI-H/dMMR. Median PFS was not reached (95% CI: 38.4, NE) in the nivo+ipi arm and 5.8 months (95% CI: 4.4, 7.8) in the chemo arm with a PFS HR of 0.21 (95% CI: 0.14, 0.32; p-value < 0.0001) favoring the nivo+ipi arm. The pivotal study also demonstrated statistically significant and clinical meaningful improvements in both PFS per BICR and ORR per BICR of nivo+ipi vs nivo in all lines randomized patients with centrally confirmed MSI-H/dMMR. Median PFS was not reached (95% CI: 53.8, NE) in the nivo+ipi arm and 39.3 (95% CI: 22.1, NE) in the nivo arm with a PFS HR of 0.62 (95% CI: 0.48, 0.81; p-value = 0.0003) favoring the nivo+ipi arm. ORR per BICR was 70.6% (95% CI: 65.1, 75.7) in the nivo+ipi arm and 57.7% (95% CI: 51.7%, 63.5%) in the nivo arm, showing an improvement of 12.9% in ORR (p-value = 0.0011) by adding ipilimumab to nivolumab. These results demonstrate the contribution of ipilimumab to the combination

therapy. OS data were descriptively evaluated by FDA and no harm or detriment to survival was found at this time.

8.2. Review of Safety

The Applicant's Position:

The safety profile of nivo 240 mg + ipi 1 mg/kg Q3W for 4 doses followed by nivo 480 mg Q4W for up to 2 years in 1L treated subjects with MSI-H/dMMR mCRC was tolerable and manageable using previously established IMAE management algorithms, and consistent with the known safety profiles of each component in the regimen and of the combination. No new safety concerns were identified. Therefore, there were no issues that warranted increased attention in the safety evaluation.

AEs considered to be immune mediated (such as IMAEs, and OESIs), which were reported in the nivo+ipi arm, were mostly manageable using the established algorithms. As anticipated, the types of events known to be associated with chemo (such as asthenia, neutropenia, neutrophil count decreased, anemia, decreased appetite, and nausea) were reported at notably lower frequencies with nivo+ipi than chemo.

The FDA's Assessment:

FDA acknowledges the Applicant's description of the safety profile of nivo+ipi when compared to chemotherapy-based standard of care. FDA has additionally specified the differences in the safety between the treated patients who received nivo+ipi compared to nivo alone in the subsections below.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety data used to characterize the safety profile of nivo+ipi or chemo for the 1L treatment in subjects with MSI-H/dMMR mCRC are from CA2098HW in all 1L treated subjects in the nivo+ipi (N = 200) and chemo (N = 88) arms. Deaths, AEs, SAEs, AEs leading to discontinuation, IMAEs, and OESIs from the nivo+ipi arm were assessed relative to those from the chemo arm. The safety data for the chemo arm excludes data after the first crossover dose, except for the death summaries.

The FDA's Assessment:

In addition to the safety review approach outlined by the Applicant, FDA safety review evaluated the safety profile of nivo+ipi, nivo, and chemotherapy for all treated patients irrespective of treatment line (DBL: 9/25/24). Deaths, AEs, SAEs, AEs leading to treatment

delay, AEs leading to discontinuation, IMAEs and OESIs from nivo+ipi arm were assessed relative to those from the nivolumab as a single agent. Section 6 of the USPI for both nivolumab and ipilimumab has been revised to outline the incremental toxicity in patients receiving nivo+ipi to nivo in all treatment lines.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 31: Applicant - Cumulative Dose and Relative Dose Intensity - All 1L Treated Subjects in the Nivo+Ipi (Arm B) and Chemo (Arm C) Arms in CA2098HW (15-Nov-2023 DBL)

Arm B: Nivo + Ipi (N = 200)		
	Nivolumab (mg) N = 200	**Ipilimumab (mg/kg) N = 200**
Number of Doses Received		
Mean (SD)	15.5 (9.89)	3.6 (0.86)
Median (min - max)	16.0 (1 - 37)	4.0 (1 - 4)
Cumulative Dose (1)		
Mean (SD)	6568.800 (4647.4436)	3.629 (0.9067)
Median (min - max)	6720.000 (240.00 - 16800.00)	3.994 (0.98 - 7.53)
Relative Dose Intensity (%)		
>= 110%	0	3 (1.5)
90% to < 110%	165 (82.5)	167 (83.5)
70% to < 90%	31 (15.5)	23 (11.5)
50% to < 70%	4 (2.0)	7 (3.5)
< 50%	0	0
Arm C: Chemo (N = 88)		
	Oxaliplatin (mg/m^2) N = 51	**Leucovorin (mg/m^2) N = 87**
Number of Doses Received		
Mean (SD)	7.1 (4.40)	11.0 (9.56)
Median (min - max)	6.0 (1 - 23)	9.0 (1 - 52)
Cumulative Dose (1)		
Mean (SD)	551.663 (334.0971)	3849.634 (3129.0681)
Median (min - max)	509.129 (59.86 - 1663.32)	3231.087 (366.97 - 15918.42)
Relative Dose Intensity (%)		
>= 110%	0	0
90% to < 110%	22 (43.1)	37 (42.5)
70% to < 90%	19 (37.3)	29 (33.3)
50% to < 70%	10 (19.6)	17 (19.5)

< 50%	0	4 (4.6)	
	Fluorouracil (mg/m^2) N = 86	**Fluorouracil (mg/m^2) N =88**	
Number of Doses Received			
Mean (SD)	10.0 (8.96)	10.9 (9.64)	
Median (min - max)	8.0 (1 - 52)	9.0 (1 - 52)	
Cumulative Dose (1)			
Mean (SD)	3581.483 (3047.4468)	23033.784 (18881.6442)	
Median (min - max)	2426.229 (366.97 - 15923.17)	18255.031 (2201.83 - 105351.45)	
Relative Dose Intensity (%)			
>= 110%	0	0	
90% to < 110%	38 (44.2)	30 (34.1)	
70% to < 90%	29 (33.7)	39 (44.3)	
50% to < 70%	16 (18.6)	16 (18.2)	
< 50%	3 (3.5)	3 (3.4)	
	Bevacizumab (mg/kg) N = 56	**Cetuximab (mg/m^2) N = 10**	**Irinotecan (mg/m^2) N = 37**
Number of Doses Received			
Mean (SD)	11.2 (9.66)	6.8 (5.35)	9.9 (8.82)
Median (min - max)	9.0 (1 - 44)	5.0 (1 - 18)	7.0 (1 - 45)
Cumulative Dose (1)			
Mean (SD)	56.796 (48.5608)	3239.773 (2633.7246)	1747.623 (1563.0329)
Median (min - max)	42.729 (5.00 - 210.47)	2278.309 (502.13 - 9005.10)	1303.523 (165.14 - 7881.32)
Relative Dose Intensity (%)			
>= 110%	1 (1.8)	0	1 (2.7)
90% to < 110%	32 (57.1)	5 (50.0)	15 (40.5)
70% to < 90%	20 (35.7)	4 (40.0)	15 (40.5)
50% to < 70%	3 (5.4)	1 (10.0)	6 (16.2)
< 50%	0	0	0

(1) Dose units: Arm B: Nivolumab in mg, Ipilimumab in mg/kg; Arm C: Oxaliplatin, Leucovorin, Fluorouracil, Cetuximab, Irinotecan in mg/m^2 and Bevacizumab in mg/kg.
Excludes data collected on or after first crossover dose date.
Source: ADSL, ADEXS of the CA2098HW Interim CSR

The Applicant's Position:

The overall exposure to nivo+ipi in CA2098HW is considered adequate to support characterization of the safety profile of this therapy in the intended patient population and meets the minimum specified in the ICH E1A guideline. The median duration of therapy was longer in the nivo+ipi arm than the chemo arm (13.52 vs 3.96 months). Approximately twice as many

subjects in the nivo+ipi arm vs the chemo arm received study drug for > 6 months: 68.5% vs 36.4%.

Most 1L nivo+ipi-treated subjects received ≥ 90% of the intended dose intensity: 82.5% for nivo and 85.0% for ipi. In the chemo arm, 34.1% to 58.9% of 1L treated subjects received ≥ 90% of the intended dose intensity for individual agents. In the nivo+ipi arm, the median number of doses was 16.0 for nivo and 4.0 for ipi. In the chemo arm, the median number of doses ranged from 5.0 to 9.0 across chemotherapy components.

When the AE frequencies were exposure-adjusted, AE incidence rates (per 100 person-years) were lower with nivo+ipi (877.7) than with chemo (2365.0) in 1L treated subjects (*Source: ADAEME, ADSL of the CA2098HW Interim CSR*).

The FDA's Assessment:
The overall exposure of nivo+ipi and nivo in all treated patients is outlined in Table 32.

Table 32: Treatment Duration and Exposure in All treated patients in Nivolumab and Ipilimumab arm and Nivolumab arm (DBL: 09/25/24)

	Nivolumab + Ipilimumab (Arm B)		Nivolumab (Arm A)
	Nivolumab	Ipilimumab	Nivolumab
	N=352	N=352	N = 351
Doses Received			
Median (Range)	23 (1, 41)	4 (1, 4)	21 (1, 43)
Duration of Treatment			
Median (Range) (months)	20.5 (0, 36)	2.1 (0, 3.7)	16.4 (0, 36)
Relative Dose Intensity (%)			
>=110%	0	3 (1)	0
90 <110%	301 (85)	305 (87)	308 (88)
70 <90%	44 (13)	35 (10)	34 (10)
<70%	7 (2.0)	9 (2.6)	9 (2.6)

Source: Adapted from Applicant CSR

The median treatment duration with nivolumab was greater in those receiving the combination of nivo+ipi compared to nivo alone. Most patients (N=305 [87%]) had a relative dose intensity of nivolumab that was between 90-110%, with the median number of ipilimumab doses administered being 4 (range: 1, 4).

Among all treated patients in the chemotherapy arm (Arm C [N=115]) the median number of doses administered of cytotoxic chemotherapies and biologics were proportionally lower than what was seen in patients in the first line setting (Table 32) (e.g., oxaliplatin median doses

administered 6 [range: 1, 30], irinotecan median doses administered 5 [range: 1, 45], bevacizumab median dose administered 7 [range: 1, 44], fluorouracil median doses administered 8 [range: 1, 61]).

Relevant characteristics of the safety population:

Data:

Table 33: Applicant - Safety Populations for the Interim Analysis in CA2098HW (15-Nov-2023 DBL)

Population	Description	Number of Subjects	
		Arm B: Nivo+Ipi	Arm C: Chemo
1L primary safety population	All 1L treated subjects with MSI-H/dMMR mCRC per local testing	200	88
1L centrally confirmed safety subgroup	All 1L treated subjects with centrally confirmed MSI-H/dMMR mCRC	170	75

Source: ADSL of the CA2098HW Interim CSR

The Applicant's Position:

Demographic and baseline disease characteristics in all 1L randomized subjects were well balanced between the nivo+ipi and chemo arms (Table 21 and Table 22). In both treatment arms, the following subgroups were numerically small: age ≥ 75 years, all race subgroups except White.

The FDA's Assessment:

FDA conducted a safety analysis of all treated patients with the sample sizes outlined in Table 14. The demographics and clinical characteristics of all treated patients are consistent with the randomized patient population outlined in Table 21 and Table 22.

Adequacy of the safety database:

The Applicant's Position:

The 1L population studied in CA2098HW is representative of an MSI-H/dMMR mCRC 1L population; this is supported by the study population's demographic, disease, and other baseline characteristics. With an established drug regimen, the size of the safety database in CA2098HW is sufficient to characterize the safety of nivo+ipi for the 1L treatment of MSI-H/dMMR mCRC. The routine clinical and laboratory evaluations performed in the study were appropriate to evaluate and characterize the safety profile of nivo+ipi.

The FDA's Assessment:

FDA agrees that the demographics and clinical characteristics of patients enrolled in all lines and in the first line treatment setting for MSI-H/dMMR mCRC is generally consistent with published

literature. In the nivo+ipi arm (Arm B), 55% of treated patients were first line, and 45% were in second line or greater. In the nivo alone arm (Arm A), 52% of treated patients were in the first line, 48% were in the second line or greater setting. FDA's analyses of adverse events were conducted irrespective of attribution.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

See Section 8.1.2. The quality of data collected and analyzed was monitored according to BMS standard operating procedures. No issues with data quality and integrity have been identified.

The FDA's Assessment:
FDA performed a random audit of the coding of terms in the safety dataset. Verbatim terms for adverse events (AEs) were adequately coded using the MedDRA dictionary. Categorization for the PTs were different using MedDRA version 26.1 for DBL: 11/15/23 and MedDRA version 27.0 for DBL 9/25/24, as outlined below.

Categorization of Adverse Event

The Applicant's Position:

Adverse events in CA2098HW were categorized by system organ class and PT using the MedDRA version 26.1 and by severity grade using NCI CTCAE version 5.0.

The FDA's Assessment:
The MedDRA dictionary for the updated analysis with a DBL 09/25/24 was 27.0, with the severity grading as per NCI CTCAE version 5.0.

Routine Clinical Tests

The Applicant's Position:

Standard laboratory tests (eg, liver, renal, thyroid, metabolic) and pregnancy tests were conducted during screening and treatment visits. Laboratory tests were graded using the NCI CTCAE version 5.0.

The FDA's Assessment:
Patients received baseline hematology and chemistry assessments including screening TSH, free T3, and free T4. Testing for adrenal or hypothalamic pituitary insufficiency at screening and on treatment was performed as clinically indicated or based on local guidelines. FDA agrees that the safety monitoring was consistent with standard of care.

8.2.4. Safety Results

Data:

Table 34: Applicant - Safety Results - All 1L Treated Subjects in the Nivo+Ipi (Arm B) and Chemo (Arm C) Arms in CA2098HW (15-Nov-2023 DBL)

	Number (%) of Subjects			
Safety Parameters	**Arm B: Nivo+Ipi N = 200**		**Arm C: Chemo N = 88**	
Deaths (at any time)	44 (22.0)		37 (42.0)	
Primary Reason for Death				
Disease	28 (14.0)		24 (27.3)	
Study Drug Toxicity[a]	2 (1.0)		1 (1.1)	
Unknown	5 (2.5)		4 (4.5)	
Other[b]	9 (4.5)		8 (9.1)	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	91 (45.5)	69 (34.5)	45 (51.1)	37 (42.0)
Drug-related SAEs	38 (19.0)	32 (16.0)	17 (19.3)	14 (15.9)
All-causality AEs leading to DC[c]	40 (20.0)	29 (14.5)	35 (39.8)	13 (14.8)
Drug-related AEs leading to DC[c]	33 (16.5)	23 (11.5)	28 (31.8)	9 (10.2)
All-causality AEs	197 (98.5)	96 (48.0)	86 (97.7)	59 (67.0)
Drug-related AEs	160 (80.0)	46 (23.0)	83 (94.3)	42 (47.7)
≥ 15% of Subjects in Either Arm, by PT				
Pruritus	45 (22.5)	0	4 (4.5)	0
Diarrhea	42 (21.0)	2 (1.0)	45 (51.1)	4 (4.5)
Hypothyroidism	32 (16.0)	2 (1.0)	0	0
Asthenia	28 (14.0)	2 (1.0)	31 (35.2)	5 (5.7)
Decreased appetite	10 (5.0)	1 (0.5)	20 (22.7)	1 (1.1)
Nausea	10 (5.0)	0	41 (46.6)	2 (2.3)
Anemia	5 (2.5)	0	14 (15.9)	3 (3.4)
Vomiting	4 (2.0)	0	18 (20.5)	1 (1.1)
Neutropenia	3 (1.5)	0	19 (21.6)	9 (10.2)
Neutrophil count decreased	1 (0.5)	1 (0.5)	14 (15.9)	6 (6.8)
All-causality Select AEs, by Category				
Endocrine	68 (34.0)	11 (5.5)	3 (3.4)	0
Gastrointestinal	71 (35.5)	11 (5.5)	51 (58.0)	5 (5.7)
Hepatic	56 (28.0)	13 (6.5)	11 (12.5)	2 (2.3)
Pulmonary	6 (3.0)	2 (1.0)	0	0
Renal	20 (10.0)	7 (3.5)	5 (5.7)	0
Skin	84 (42.0)	6 (3.0)	22 (25.0)	2 (2.3)
Hypersensitivity/Infusion Reactions	11 (5.5)	0	8 (9.1)	2 (2.3)

Table 34: Applicant - Safety Results - All 1L Treated Subjects in the Nivo+Ipi (Arm B) and Chemo (Arm C) Arms in CA2098HW (15-Nov-2023 DBL)

	Number (%) of Subjects			
Safety Parameters	**Arm B: Nivo+Ipi N = 200**		**Arm C: Chemo N = 88**	
Drug-related Select AEs, by Category				
Endocrine	67 (33.5)	11 (5.5)	0	0
Gastrointestinal	46 (23.0)	9 (4.5)	46 (52.3)	5 (5.7)
Hepatic	39 (19.5)	9 (4.5)	5 (5.7)	0
Pulmonary	5 (2.5)	2 (1.0)	0	0
Renal	7 (3.5)	1 (0.5)	2 (2.3)	0
Skin	69 (34.5)	5 (2.5)	18 (20.5)	2 (2.3)
Hypersensitivity/Infusion Reactions	8 (4.0)	0	8 (9.1)	2 (2.3)
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality Non-Endocrine IMAEs within 100 days of Last Dose Treated with Immune Modulating Medication, by Category				
Diarrhea/Colitis	13 (6.5)	9 (4.5)	1 (1.1)	0
Hepatitis	11 (5.5)	6 (3.0)	0	0
Pneumonitis	4 (2.0)	3 (1.5)	0	0
Nephritis/Renal Dysfunction	2 (1.0)	1 (0.5)	0	0
Rash	11 (5.5)	3 (1.5)	0	0
Hypersensitivity/ Infusion Reactions	0	0	1 (1.1)	1 (1.1)
All-causality Endocrine IMAEs within 100 days of Last Dose With or Without Immune Modulating Medication, by Category				
Adrenal Insufficiency	21 (10.5)	7 (3.5)	0	0
Hypophysitis	10 (5.0)	5 (2.5)	0	0
Hypothyroidism/ Thyroiditis	34 (17.0)	3 (1.5)	1 (1.1)	0
Diabetes Mellitus	2 (1.0)	0	0	0
Hyperthyroidism	18 (9.0)	0	1 (1.1)	0
All-causality OESIs within 100 days of last dose[d] With or Without Immune Modulating Medication, by Category				
Pancreatitis	2 (1.0)	0	0	0
Encephalitis	3 (1.5)	3 (1.5)	0	0
Myositis/ Rhabdomyolysis	2 (1.0)	1 (0.5)	0	0
Myasthenic syndrome	1 (0.5)	1 (0.5)	0	0
Myocarditis	3 (1.5)	3 (1.5)	0	0

[a] Deaths considered related to study drug per investigator in the nivo+ipi arm (myocarditis and pneumonitis, 1 case each). The death in the chemo arm (acute myocarditis) was reported in a subject who progressed while receiving chemo, and died while receiving Crossover therapy (nivo+ipi). This death (due to acute myocarditis) was considered to be related to nivo+ipi per the investigator.

[b] The verbatim terms reported for the 'other' reasons for death were consistent with events anticipated in the study population. None were considered related to study drug (per the investigator).
[c] Discontinuation of any drug in the regimen.
[d] No OESIs were reported in the following categories: demyelination, Guillain-Barre syndrome, uveitis, and graft vs host disease.
MedDRA version 26.1; CTCAE version 5.0.
Includes events reported between first dose and 30 days after last dose of study therapy, unless otherwise indicated, and except deaths, which were reported at any time.
Excludes data collected on or after first crossover dose date, except for the summary of deaths.
Source: ADAE, ADAEIMM, ADSL of the CA2098HW Interim CSR

Deaths

The Applicant's Position:

As of the 15-Nov-2023 DBL, a lower proportion of 1L treated subjects in the nivo+ipi arm died (at any time after randomization up to the clinical data cutoff date) compared with the chemo arm: 22.0% vs 42.0%. Disease progression was the most frequently reported cause of death in both arms (14% in nivo+ipi arm vs 27.3% in chemo arm).

The FDA's Assessment:

A summary of safety of all treated patients with the DBL of 9/25/24 is outlined in Table 35.

Table 35: FDA – Summary of Safety for All Treated Patients (DBL: 9/25/24).

	Nivo/Ipi (All lines) Treated N = 352 (%)	Nivo (All lines) Treated N = 351 (%)	Chemo (All lines) Treated N = 115 (%)
All-Grade TEAEs	99	96	99
Grade 3-4 TEAEs	48	43	70
Grade 5 TEAEs	4.5	2.8	0.9
SAEs Any Grade	46	39	49
SAEs Grade 3-4	35	29	41
Any drug delay – due to TEAEs	48	37	65
Any drug withdrawn – due to TEAEs	19	13	41

Source: Adapted from Primary CSR; Abbreviations: SAE: Serious Adverse Events TEAE: Treatment Emergent Adverse Event

The Applicant only categorized treatment emergent adverse event (TEAE) as Grade 5 that led to death within 24 hours.

The safety profile of patients receiving chemotherapy in all lines with a DBL 9/25/24 was similar to that presented by the Applicant in Table 34. FDA additionally compared the differential safety profile of nivolumab in combination with ipilimumab compared to nivolumab single agent. The Applicant provided narratives of all patient deaths in the nivo+ipi and nivo arms that occurred within 100 days of the last dose, for any reasons other than disease progression. A summary of observed deaths, in addition to a summary of narratives from fatal adverse are outlined in Table 36.

Table 36: FDA - Summary of Deaths in All Treated Nivo+Ipi versus Nivo arms (DBL 9/25/24)

	Nivo/Ipi N = 352 N (%)	**Nivo N = 351 N (%)**
Deaths	103 (29)	149 (43)
Deaths within 30 days of last dose	17 (5)	14 (4)
Deaths within 100 days of last dose	41 (12)	52 (15)
Deaths From Disease Progression	74 (21)	122 (35)
Death Narrative Review		
Nivolumab and Ipilimumab (Arm B)		
Preferred Terms:	**Narrative Summary, Sponsor Attribution, Reviewer Comment**	
Shock **Hemorrhagic Pancreatitis**	56-year-old male patient was admitted on Day 6 following Cycle 1 Day 1 of nivolumab and ipilimumab. CT Abdomen demonstrating "necrohemorrhagic pancreatitis". The patient required pressor support in the ICU and died the same day. Applicant Attribution: Not Related	

	Reviewer Comment: The Applicant provided additional details on the patient's clinical course, including the presence of cholestatic jaundice and multiple mesenteric adenopathy post R2 surgical resection and prior to treatment initiation. The investigator determined that the patient's clinical course was confounded by multiple issues and the event was determined not related by study drug.
Intestinal Ischemia **Immune Mediated Enterocolitis**	68-year-old male patient with multiple admissions for immune mediated enterocolitis, maximal Grade 4, leading to treatment discontinuation on Day 87. He was subsequently admitted on Day 111 with intestinal ischemia and died during his admission. Applicant Attribution: Not Related *Reviewer Comment: The Applicant provided additional information regarding the patient's clinical status, and the presence of calcified stenosis in the superior mesenteric arteries. The event of intestinal ischemia occurred after the patient was off steroids for the treatment of colitis and treatment was discontinued. The investigator determined that the cause of death was from pre-existing atherosclerotic disease.*
Myocarditis **Myasthenia Gravis** **Myositis**	79-year-old female patient who was admitted on Day 42, 20 days after her Cycle 2 Day 1 of nivolumab and ipilimumab, with dyspnea and dizziness. She was diagnosed with myasthenia gravis (Grade 4), myositis (Grade 3), and myocarditis (Grade 4). Notable lab test results available to FDA include blood creatine phosphokinase of 3570 U/L (RR:40-280 U/L), blood creatine phosphokinase MB of 122 mcg/ml (RR: 0-7 mcg/ml) and troponin of 730 ng/L (RR: 0-45 ng/L). The patient was treated with a combination of corticosteroids and plasmapheresis and died over the course of her admission. Applicant Attribution: Related *Reviewer Comment: FDA agrees with the Applicant's attribution. Myocarditis, myasthenia gravis, and myositis are all included as risks within Section 5 of the respective USPIs. The cause of death for this patient was attributed to the Grade 4 myocarditis and was included in Section 6 of the respective USPIs.*
Capillary Leak Syndrome **Cardiogenic Shock** **Acute Kidney Injury**	47-year-old female patient who was admitted on Day 43, 21 days after prior treatment with nivolumab and ipilimumab. The patient was noted to have anasarca and acute kidney injury on admission, and was initiated on corticosteroids and diuretics. The Sponsor's narrative states that the patient was in cardiogenic shock and died over the course of her admission. Applicant Attribution: Not Related *Reviewer Comment: The Applicant provided additional data with the patient having a known history of subclavian vein thrombosis, with extensive liver disease at the time of treatment. The Applicant confirmed that the patient had no reports of immune mediated adverse events after 2 doses of treatment. The patient was also centrally confirmed to have pMMR/MSS and the investigator determined that the overall clinical picture was related to advanced disease.*

Pneumonitis	77 year old female patient who continued treatment beyond radiographic disease progression on Day 125, before discontinuing treatment due to disease progression on Day 173. The patient was admitted on Day 193 with Grade 3 pneumonitis, requiring escalation of care to the intensive care unit. The patient had a prolonged admission, requiring home oxygen and ongoing steroid treatment on discharge (Day 219). The patient died from pneumonitis on Day 235. Applicant Attribution: Related *Reviewer Comment: FDA agrees with the Applicant's attribution. The risk of pneumonitis is included in Section 5 of the respective USPIs and also included as a fatal adverse reaction in Section 6.*
Nivolumab (Arm A)	
Cardiac Arrest **Myasthenia Gravis** **Myositis**	61-year-old male patient who was diagnosed with Grade 3 myasthenia gravis on Day 54. The patient had ptosis, dysphagia, and dysphonia. Electromyogram "confirmed myositis and myasthenia gravis", the patient was Anti-Ku test positive. He was treated with corticosteroids and discharged with ongoing sequalae from myasthenia gravis on Day 56. The patient died from a cardiac arrest on Day 60. Applicant Attribution: Not Related *Reviewer Comment: Myasthenia gravis is a recognized adverse reaction from the use of ICIs. Given the timing of the adverse reaction and ongoing sequalae at the time of discharge, myasthenia gravis as a fatal adverse reaction in Section 6 of the USPI.*
Pneumonitis	82-year-old female patient whose clinical course was complicated by low grade hypothyroidism treated with replacement therapy, was hospitalized with Grade 4 pneumonitis on Day 195. The patient was treated with corticosteroids and was required high flow oxygen, she died over the course of her admission on Day 199. Applicant Attribution: Related *Reviewer Comment: FDA agrees with the Applicant's attribution. Pneumonitis was included as a fatal adverse reaction in Section 6 of the USPI.*
Cardiac Arrest **Pneumonitis**	77-year-old male patient whose clinical course was complicated by Grade 2 pneumonitis on Day 130, requiring treatment delay and initiation of corticosteroids. The patient required protracted course of corticosteroids and had Grade 4 dyspnea at the time of cardiac arrest on Day 193. Applicant Attribution: Not Related *Reviewer Comment: The patient required a prolonged course of corticosteroids and was noted to have worsening dyspnea at the point of steroid taper. The adverse reaction of Pneumonitis was included in Section 6 of the USPI.*

Source: Applicant Primary CSR and FDA Review of Death Narratives

Patients receiving nivo+ipi had a higher incidence of Grade 3 or 4 TEAEs or SAEs compared to those receiving nivolumab single agent (Table 35). The majority of deaths occurred beyond 100 days of treatment in both the nivo+ipi arm and nivo single agent arm, with a greater proportion of patients in the nivolumab single agent arm dying from disease progression (Table 36). A detailed breakdown on the differences in TEAEs and SAEs between nivo+ipi compared to nivo, single agent, is outlined in the relevant sections below.

The Applicant remains blinded to the overall survival results. FDA analyzed the requested Applicant-blinded overall survival datasets, which did not demonstrate any evidence of a survival detriment in patients receiving nivo+ipi compared to nivo over the course of the study as of the data cutoff date. There was crossing of the Kaplan-Meier curves within the initial 180 days of treatment with nivo+ipi compared to nivo alone, following which there was sustained separation in overall survival between the nivo+ipi arm compared to nivo alone.

Table 37: FDA - Deaths within 180 days of Cycle 1 Day 1 among treated patients in the nivo+ipi and nivo arms (DBL: 9/25/24)

Deaths within 180 days of Cycle 1 Day 1	Nivo + Ipi (N=352)	Nivo (N=351)
Deaths (All Lines)	35 (10)	39 (11)
Deaths (First Line)	18 (5)	12 (3.4)
Disease Progression (All lines)	21 (6)	31 (9)

Source: FDA Analyses

Among those treated with nivo+ipi or nivo alone, a similar proportion of patients died within 180 days of initiating treatment, most deaths were from disease progression in both arms (Table 37). Among patients being treated in the first line setting, there were a greater number of deaths in the nivo+ipi arm in the initial 180 days (Table 37). Additional causes of death within 180 days of treatment initiation, not included in Table 36, in the nivo+ipi arm were sepsis (N=5), thromboembolic event (N=2), brain stem infarct (N=1), COVID-19 (N=1) and the nivo alone arm were sepsis (N=2), COVID-19 (N=1), heart attack (N=1), and denutrition (N=1). Fatal adverse reactions included in the respective USPIs for nivo+ipi and summary of the provided narratives are outlined in Table 36.

Serious Adverse Events

The Applicant's Position:

As of the 15-Nov-2023 DBL, in 1L treated subjects, the overall frequencies of all-causality SAEs (including Grade 3-4) were numerically lower in the nivo+ ipi arm compared to chemo arm and drug-related SAEs frequencies were similar in both arms.

The SAE profile of nivo+ipi was consistent with prior experience with this regimen.

- **Nivo+ipi:** The most frequently reported SAEs (all causality, PTs) were adrenal insufficiency (4.0%), malignant neoplasm progression, abdominal pain, and immune mediated enterocolitis (2.5% each). The most frequently reported drug-related SAEs (PTs) were adrenal insufficiency (4.0%) and immune mediated colitis (2.5%).
- **Chemo**: The most frequently reported SAEs (all causality, PTs) were pneumonia, intestinal obstruction, and abdominal pain (3.4% each). The most frequently reported drug-related SAEs (PTs) were diarrhea and infusion related reaction (2.3% each).

The FDA's Assessment:

A greater proportion of patients receiving chemotherapy in all lines experienced an SAE compared to nivo+ipi (Table 35), similar to the findings presented by the Applicant above with an earlier DBL of 11/15/23. The most common (>2%) and selected SAEs in the nivo+ipi arm and nivo arms are outlined in Table 38.

Table 38: FDA –Common (>2%) and selected Serious Adverse Events in the nivo+ipi and nivo arms (all lines) DBL 9/25/24

	Ipi/Nivo N = 352		Nivo N = 351	
	All grades N (%)	Grade 3 or 4 N (%)	All grades N (%)	Grade 3 or 4 N (%)
Patients with SAEs	163 (46)	123 (35)	137 (39)	102 (29)
Gastrointestinal				
Colitis (GT)	17 (4.8)	14 (3.9)	9 (2.6)	7 (2.0)
Obstruction (GT)	8 (2.3)	8 (2.3)	11 (3.1)	10 (2.8)
Abdominal Pain (GT)	8 (2.3)	7 (2.0)	6 (1.7)	4 (1.1)
Endocrine				
Adrenal Insufficiency (GT)	11 (3.1)	9 (2.6)	4 (1.1)	3 (0.9)
Hypophysitis (GT)	11 (3.1)	10 (2.8)	4 (1.1)	4 (1.1)
Infections				
Covid-19 (GT)	4 (1.1)	2 (0.6)	8 (2.2)	6 (1.7)
Sepsis (GT)	7 (2.0)	4 (1.1)	8 (2.2)	7 (2.0)
Pneumonia (GT)	7 (2.0)	6 (1.7)	4 (1.1)	3 (0.9)
Hepatobiliary Disorders				

Hepatitis/Hepatic Failure (GT)	5 (1.4)	4 (1.1)	5 (1.4)	4 (1.1)
Respiratory				
Pneumonitis (GT)	5 (1.4)	3 (0.9)	5 (1.4)	2 (0.6)

Source: FDA Analysis

Colitis (GT): Colitis; Diarrhea; Enterocolitis; Immune mediated enterocolitis;
Gastrointestinal Obstruction (GT): Duodenal Obstruction; Gastrointestinal Obstruction; Intestinal Obstruction; Large Intestine Obstruction
Abdominal Pain (GT): Abdominal Pain; Abdominal Pain Upper
Sepsis (GT): Bacteremia; Sepsis: Septic Shock, Urosepsis
Covid 19 (GT): Covid 19; Covid 19 pneumonia
Pneumonia (GT): Pneumonia; Pneumonia bacterial; Pneumonia viral
Hepatobiliary Disorders (GT): Hepatic Failure; Hepatic Cytolysis; Hepatitis; Autoimmune Hepatitis; Immune Mediated Hepatitis; Alanine aminotransferase increased; Blood Bilirubin Increased;
Adrenal Insufficiency (GT): Adrenal Insufficiency; Primary Adrenal Insufficiency; Glucocorticoid Deficiency
Hypophysitis (GT): Hypopituitarism; Hypophysitis
Pneumonitis (GT): Interstitial Lung Disease; Pneumonitis; Immune Mediated Lung Disease

A greater proportion of patients in the nivo+ipi arms had an SAE, including a greater proportion having an SAE that was Grade 3 or 4 in severity. The most common SAE reported in both arms were diarrhea or colitis (grouped as per footnote on Table 38), with a higher incidence in the nivo+ipi arm compared to nivo arms. The submitted SAEs are consistent with the overall, and expected, safety profile of nivo+ipi, with greater proportion of patients experiencing endocrine and non-endocrine immune mediated adverse events, which are outlined in greater detail below. The USPI was updated to include the most common (>1%) SAEs in either the nivo+ipi or nivo alone arms.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

As of the 15-Nov-2023 DBL, in 1L treated subjects, the overall frequencies of all causality and drug-related AEs leading to discontinuation of study drug (any drug in the regimen) were lower in the nivo+ipi arm than the chemo arm (all causality: 20.0% vs 39.8%; drug-related: 16.5% vs 31.8%). Grade 3-4 AEs leading to discontinuation of study drug (all causality and drug-related) were reported in a similar proportion of subjects in both arms. The most frequently reported all causality and drug-related AEs leading to discontinuation were:

- **Nivo+ipi:** adrenal insufficiency (2.5%) and immune mediated enterocolitis (2.0%)
- **Chemo**: peripheral neuropathy and neurotoxicity (4.5% each), and peripheral sensory neuropathy (3.4%)

The FDA's Assessment:

A greater proportion of patients treated with chemotherapy (all lines) had treatment discontinuation of any drug compared to either nivo+ipi or nivo alone arms Table 35, and the findings are consistent with Applicant's summary above. The Applicant's description of TEAEs leading to treatment discontinuation did not include the relevant grouping of preferred terms that are included in the FDA analyses outlined in Table 39.

Table 39: FDA – Most Common (>1%) TEAEs leading to treatment discontinuation in nivo + ipi or nivo arms (DBL 9/25/24)

	Nivo/Ipi N = 352 N (%)	Nivo N = 351 N (%)
TEAEs leading to discontinuation of nivolumab and/or ipilimumab	**66 (19)**	**45 (13)**
Diarrhea/Colitis (GT)	9 (2.6)	5 (1.4)
Hepatitis (GT)	9 (2.6)	5 (1.4)
Adrenal Insufficiency	5 (1.4)	2 (0.6)
Hypophysitis (GT)	4 (1.1)	0
Pneumonitis (GT)	4 (1.1)	4 (1.1)

Source: FDA Analysis

Diarrhea (GT): Colitis; Diarrhea; Enterocolitis; Immune mediated enterocolitis;

Hepatobiliary Disorders (GT): Alanine Aminotransferase Increased; Aspartate aminotransferase increased; Autoimmune Hepatitis; Blood bilirubin increased; Hepatic cytolysis; Hepatic Failure; Hepatitis; Hyperbilirubinemia; Immune Mediated Hepatitis

Hypophysitis (GT): Hypophysitis; Lymphocytic Hypophysitis

Pneumonitis (GT): Immune mediated lung disease; Pneumonitis

There were a greater proportion of patients discontinuing either nivolumab or ipilimumab or both in the combination arm compared to patients receiving nivolumab alone. Specifically, there were more discontinuation from non-endocrine immune mediated adverse events (diarrhea/colitis and hepatitis) in addition to endocrine immune mediated adverse events (adrenal insufficiency or hypophysitis) (Table 39). The most common TEAEs (>1%) leading to treatment discontinuation of either nivolumab or ipilimumab in either arm are included in Section 6 of the USPI.

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

The Applicant's Position:

Dose escalation or reductions of nivo or ipi were not permitted, but were permitted for chemo. However, dose adjustments of ipi (1 mg/kg) were permitted if the subject's weight on the day of dosing differed by > 10% from the weight used to calculate the initial dose; in this case, the dose was to be recalculated.

As of the 15-Nov-2023 DBL, in 1L treated subjects, AEs (all causality) leading to a dose delay or reduction were reported in 98 (49.0%) subjects in the nivo+ipi arm and 60 (68.2%) subjects in the chemo arm. The most frequently reported AEs (all causality) leading to a dose delay or reduction were:

- **Nivo+ipi:** COVID-19 (8.0%), diarrhea (6.0%), and ALT increased and AST increased (4.0% each)
- **Chemo:** neutropenia (15.9%), asthenia (12.5%), diarrhea (11.4%), and neutrophil count decreased (10.2%); note that COVID-19 was reported in 3.4% of subjects.

Drug-related AEs leading to a dose delay or reduction were reported in 56 (28.0%) subjects in the nivo+ipi arm and 49 (55.7%) subjects in the chemo arm. The most frequently reported drug-related AEs leading to a dose delay or reduction were:

- **Nivo+ipi:** diarrhea (4.0%), and adrenal insufficiency, ALT increased, and AST increased (3.0% each)
- **Chemo:** neutropenia (14.8%), asthenia (11.4%), and diarrhea and neutrophil count decreased (10.2% each)

The FDA's Assessment:

FDA agrees with the description of permitted dose interruptions, delays and/or reductions in the nivo+ipi arm and chemotherapy arm. Dose escalation or reductions were not permitted in patients receiving nivo alone. A greater proportion of patients treated with chemotherapy (all lines) had treatment delay of any drug compared to either nivo+ipi or nivo alone arms (Table 35). The Applicant's description of TEAEs leading to treatment delay did not include the relevant grouping of preferred terms that are included in the FDA analyses outlined in Table 40.

Table 40: FDA – Common (>2%) TEAEs leading to dose delay in the nivo + ipi and nivo arms (DBL 9/25/24).

	Nivo/Ipi N = 352 N (%)	Nivo N = 351 N (%)
TEAEs leading to delay of nivolumab and/or ipilimumab	**168 (48)**	**129 (37)**
Diarrhea/Colitis (GT)	25 (7)	18 (5)
COVID-19	23 (7)	13 (3.7)
Hepatobiliary Disorders (GT)	22 (6)	20 (6)
Adrenal Insufficiency (GT)	13 (3.7)	5 (1.4)
Acute Kidney Injury (GT)	12 (3.4)	6 (1.7)
Hypophysitis (GT)	11 (3.1)	4 (1.1)
Pancreatitis/ Increase Lipase/Amylase	8 (2.3)	6 (1.7)
Fatigue (GT)	8 (2.3)	6 (1.7)

Source: FDA Analysis
Diarrhea (GT): Colitis; Diarrhea; Enterocolitis; Immune mediated enterocolitis;
Hepatobiliary Disorders (GT): Alanine Aminotransferase Increased; Aspartate aminotransferase increased; Autoimmune Hepatitis; Blood bilirubin increased; Hepatitis; Hepatic cytolysis; Hepatic Function Abnormal; Hyperbilirubinemia; Liver Disorder
Hypophysitis (GT): Hypopituitarism; Hypophysitis
Adrenal Insufficiency (GT): Cortisol Decreased; Glucocorticoid Deficiency; Adrenal Insufficiency;
Acute Kidney Injury: Acute Kidney Injury; Blood Creatinine Increased; nephritis
Fatigue: Asthenia; Fatigue

Similar to the TEAEs leading to treatment discontinuation, the most common TEAEs leading to a dose delay in patients receiving nivo+ipi was for diarrhea and colitis. Also consistent with treatment discontinuations were the higher incidence of hypophysitis and adrenal insufficiency in the nivo+ipi arm compared to nivo alone arm leading to dose delay (Table 43). A greater proportion of patients in the nivo+ipi arm required treatment delay due to COVID-19, which is

possibly related to the differences in treatment exposure between the two arms (Table 35). The incidence of any dose delays in either the nivo+ipi or nivo alone arm has been included in section 6 of the respective USPIs.

Significant Adverse Events

The Applicant's Position:

IMAEs analyses included all causality AEs reported as occurring within 100 days of the last dose (i.e., with extended follow-up). These analyses were limited to subjects who received IMM for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment, since these events are often managed without immunosuppression. In addition, these analyses include events reported by the investigator as IMAEs with no clear alternate etiology and an immune-mediated component. Non-endocrine and endocrine IMAEs reported in ≤ 6.5% and ≤ 17.0% of subjects, respectively. The majority of non-endocrine IMAEs were Grade 3-4 except for rash, while the majority of endocrine IMAEs were Grade 1-2 (except for hypophysitis). All IMAEs were manageable using the established IMAE management algorithms.

OESIs are the events that do not fulfill all criteria to qualify as select AEs or IMAEs. They may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs had extended follow-up (100-day window). OESIs consist of a list of PTs grouped by category: myositis/rhabdomyolysis, myocarditis, demyelination, Guillain-Barre syndrome, pancreatitis, uveitis, encephalitis, myasthenic syndrome, and graft vs host disease. The list of MedDRA preferred terms used to identify OESIs was revisited quarterly and updated accordingly. Eleven OESIs (all causality, with or without IMM treatment) were reported (between the first dose of study drug and 100 days after the last dose of study drug) in 7 subjects in the nivo+ipi arm and in no subjects in the chemo arm. Of the 11 OESIs, 9 events were assessed by investigators as drug-related and 2 events as not-related to study drug.

The FDA's Assessment:

Immune mediated adverse events, both endocrine and non-endocrine occurred more frequently in patients receiving nivo+ipi compared to nivo alone (Table 41).

Table 41: FDA - Immune mediated adverse events in the nivo+ipi or nivo arms (DBL 9/25/24).

	Nivo/Ipi N = 352		Nivo N = 351	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Endocrine – with or without immune modulating treatment				
Hypothyroidism/Thyroiditis	18	0.9	9	0
Hyperthyroidism	12	0	4.6	0
Adrenal Insufficiency	10	2.8	3.4	0.9
Hypophysitis	7	3.1	1.1	1.1
Diabetes Mellitus	1.1	0.6	0.6	0.3
Non-Endocrine – requiring immune modulating treatments				
Rash	7	1.4	6	0.9
Diarrhea/Colitis	6	3.4	3.7	2.3
Hepatitis	3.7	1.7	1.1	0.9
Pneumonitis	2.0	1.1	2.0	1.1
Nephritis/Renal Dysfunction	1.7	0.6	0.3	0.3
Pancreatitis	0.9	0.3	0.6	0
Encephalitis	0.9	0.9	0	0
Myocarditis	0.9	0.9	0	0
Hypersensitivity/ Infusion Reaction	0	0	0.9	0

Source: Adapted from Primary CSR

The use of immune modulating treatments, most commonly corticosteroids, was a diagnostic criterion for the determination of non-endocrine immune mediated adverse events. Section 5 of

the USPI for ipilimumab outlined the anticipated incidence of both non-endocrine and endocrine immune mediated adverse events in patients receiving ipilimumab (1mg/kg) with nivolumab. The cited incidence in Study CA2098HW was consistent with the cited incidence rates across development programs with this combination Table 42.

Table 42: FDA – Select incidence of immune mediated adverse events cited in Section 5 – Warnings and Precautions ipilimumab (1mg/kg) in combination with nivolumab

	Nivolumab + Ipilimumab (1mg/kg)	
	All grades (%)	**Grade 3 or 4 (%)**
Endocrine Immune Mediated Adverse Reactions		
Hypothyroidism	18	0.6
Hyperthyroidism	12	0.6
Adrenal Insufficiency	7	2.8
Hypophysitis	4.4	2.7
Type I Diabetes Mellitus	2.7	0.9
Non-Endocrine Immune Mediated Adverse Reactions		
Rash	16	3.5
Diarrhea/Colitis	9	4.4
Hepatitis	7	6
Pneumonitis	3.9	1.4
Nephritis/Renal Dysfunction	4.1	1.7
Pancreatitis	1.3	N/A
Encephalitis	< 1	N/A
Myocarditis	< 1	N/A

Hypersensitivity/ Infusion Reaction	5	N/A

Source: Adapted from Section 5 ipilimumab USPI

The differences in incidences of fatal adverse reactions, SAEs, and TEAEs leading to treatment discontinuation has been highlighted in Section 6 of the respective USPIs.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 43: Applicant - Adverse Reactions in ≥ 10% of Patients with MSI-H/dMMR CRC in CA2098HW (15-Nov-2023 DBL)

Adverse Reaction	OPDIVO and Ipilimumab (n=200)		Chemotherapy (n=88)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	40	3	57	6
Pyrexia[b]	11	0	11	1.1
Gastrointestinal				
Diarrhea	34	2	57	4.5
Abdominal pain[c]	25	4	31	2.3
Nausea	20	1.5	49	3.4
Constipation	14	0.5	22	1.1
Vomiting	10	0.5	25	1.1
Skin and Subcutaneous Tissue				
Pruritus	27	0	7	0
Rash[d]	19	2	13	2.3
Musculoskeletal and Connective Tissue				
Arthralgia	18	1	4.5	0
Musculoskeletal pain[e]	15	0	14	0
Endocrine				
Hypothyroidism	16	1	1.1	0
Adrenal insufficiency	10	3	0	0
Metabolism and Nutrition				
Decreased appetite	16	0.5	31	1.1
Nervous System				
Headache	12	0.5	9	0

Toxicity was graded per NCI CTCAE version 5.0.
[a] Includes asthenia.
[b] Includes tumor associated fever.
[c] Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.
[d] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis psoriasiform, drug eruption, rash maculo-papular, rash papular, and rash pruritic.

[e] Includes back pain, musculoskeletal chest pain, myalgia, neck pain, and pain in extremity.
Source: ADAE, ADSL of the CA2098HW Interim CSR

The Applicant's Position:

For labeling purposes, remapped (grouped by system organ class and presented by CTC grade) adverse reactions for the proposed regimen that were reported in ≥ 10% of nivo+ipi treated subjects in CA2098HW (Table 26) were included in Section 6.1 of the USPI. The most frequently reported adverse reactions in ≥ 20% of patients treated with OPDIVO in combination with ipi were fatigue, diarrhea, pruritis, abdominal pain, and nausea.

The FDA's Assessment:
FDA analyses evaluated the safety comparison of nivo+ipi to nivo alone (Table 44 and Table 45). The current available therapies for patients with MSI-H/dMMR mCRC includes pembrolizumab, and the pertinent data to allow an adequate risk-benefit decision for prescribing physicians is a comparison of nivo+ipi to nivo single agent. FDA revised Section 6 of the USPI to include the pertinent safety data (i.e., >5% difference in all grade adverse reaction between arms and adverse reactions in ≥ 20% of patients treated) and selected laboratory abnormalities.

Table 44: FDA - Adverse Reactions in ≥ 10% of Patients with MSI-H/dMMR CRC in CA2098HW (DBL: 9/25/24)

Adverse Reaction	OPDIVO and ipilimumab (n=352)		OPDIVO (n=351)	
	All Grades (%)	All Grades (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	42	2.8	43	1.7
Pyrexia[b]	13	0	15	0.3
Gastrointestinal				
Diarrhea[c]	35	4.5	30	3.4
Abdominal pain[d]	25	3.1	24	1.7
Nausea	20	1.4	17	0
Constipation	15	0.3	11	0.6
Vomiting	12	0.9	11	0.3
Skin and Subcutaneous Tissue				
Pruritus	30	0	23	0
Rash[e]	19	1.4	17	1.1
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[f]	21	0	22	0
Arthralgia	20	0.6	15	0.6
Respiratory, Thoracic and Mediastinal				
Dyspnea	8	0.6	11	0.6
Cough	10	0	11	0
Endocrine				
Hypothyroidism	18	0.6	10	0

Adverse Reaction	OPDIVO and ipilimumab (n=352)		OPDIVO (n=351)	
	All Grades (%)	All Grades (%)	All Grades (%)	Grades 3-4 (%)
Hyperthyroidism	12	0	5	0
Metabolism and Nutrition				
Decreased appetite	14	1.1	13	1.7
Nervous System				
Headache	12	0.6	9	0

Source: Adapted from FDA information request
Toxicity was graded per NCI CTCAE v5.

[a] Includes asthenia.

[b] Includes tumor associated fever, body temperature increased.

[c] Includes colitis, diarrhea, enterocolitis, immune mediated enterocolitis

[d] Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.

[e] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis psoriasiform, drug eruption, rash erythematous, rash macular, rash maculo-papular, rash papular, rash vesicular, and rash pruritic.

[f] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, sacral pain, spinal pain, and pain in extremity

Table 45: FDA - Select Laboratory Values Worsening from Baseline Occurring in ≥ 10% of Patients with MSI-H/dMMR CRC in CA2098HW (DBL: 9/25/25)

Laboratory Abnormality	OPDIVO and Ipilimumab (n=352)		OPDIVO (n=351)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	40	4.1	44	5
Lymphopenia	30	5	37	4
Neutropenia	21	1.7	12	0.6
Leukopenia	15	0.6	13	0
Thrombocytopenia	15	1.2	12	0.6
Chemistry				
Increased lipase	44	10	32	11
Increased ALT	39	3.5	32	1.4
Increased AST	38	3.2	29	1.4
Increased amylase	41	4.6	33	5
Hyponatremia	36	3.2	30	2.3
Increased creatinine	32	2	25	1.4
Hyperkalemia	29	1.2	35	0.9
Increased alkaline phosphatase	23	0.9	24	1.2
Hypocalcemia	24	0.9	24	0.9

Laboratory Abnormality	OPDIVO and Ipilimumab (n=352)		OPDIVO (n=351)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increased bilirubin	17	1.2	15	2.6
Hypercalcemia	15	0	11	0.3
Hypokalemia	14	0.9	13	1.7
Hypoglycemia	17	0	12	0

Source: Adapted from Applicant response to information request

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 108 to 343 patients) or nivolumab group (range: 102 to 348 patients).

Laboratory Findings

Data:

Table 46: Applicant - Select Laboratory Values Worsening from Baseline Occurring in ≥ 10% of Patients with MSI-H/dMMR CRC in CA2098HW (15-Nov-2023 DBL)

Laboratory Abnormality	OPDIVO and Ipilimumab (n=200)		Chemotherapy (n=88)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	37	3.1	44	8.3
Lymphopenia	30	3.6	43	10
Neutropenia	19	1	60	18
Leukopenia	13	0	54	3.6
Thrombocytopenia	10	0.5	37	0
Chemistry				
Increased lipase	42	10	42	15
Increased ALT	41	4.1	35	1.2
Increased AST	40	3.6	33	1.2
Increased amylase	40	4.0	32	5.3
Hyponatremia	34	3.6	27	2.4
Increased creatinine	29	3.1	21	0
Hyperkalemia	29	1.0	21	3.6
Increased alkaline phosphatase	25	1.5	36	0
Hypocalcemia	24	0.5	24	0
Increased bilirubin	18	1.5	12	3.6
Hypercalcemia	18	0	12	0

Table 46: Applicant - Select Laboratory Values Worsening from Baseline Occurring in ≥ 10% of Patients with MSI-H/dMMR CRC in CA2098HW (15-Nov-2023 DBL)

Laboratory Abnormality	OPDIVO and Ipilimumab (n=200)		Chemotherapy (n=88)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hypokalemia	13	1.0	34	10
Hypoglycemia	13	0	9.0	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 101 to 195 patients) or Chemotherapy group (range: 41 to 84 patients).
Source: ADZL, ADSL of the CA2098HW Interim CSR

The Applicant's Position:

Laboratory abnormalities (hematology, liver tests, kidney function tests, thyroid tests, glucose tests, and electrolytes) in the nivo+ipi arm were primarily Grade 1-2. The majority of subjects did not have laboratory tests that worsened to Grade 3 or 4 relative to baseline (Table 46). The USPI provides a table summarizing laboratory abnormalities that worsened relative to baseline in ≥ 10% of nivo+ipi-treated subjects in CA2098HW.

The FDA's Assessment:
See adverse reaction section above. FDA outlined the differences in patients who had Grade 3 or 4 elevations in AST, ALT, and total bilirubin between nivo+ipi and nivo alone. Concurrent ALT or AST > 3 upper limit of normal (ULN) and a total bilirubin > 2 ULN on treatment and within 30 days of the last dose of treatment occurred in 7 (2.0%) patients in the nivo+ipi arm and 8 (2.3%) in the nivo alone arm.

Vital Signs

The Applicant's Position: Vital signs and oxygen saturation by pulse oximetry were monitored and recorded at the site per institutional standard of care during screening and treatment visits. These assessments were intended to be used as safety monitoring by the treating physician.

The FDA's Assessment:

The protocol specified that patients have a targeted physical examination with vital signs (weight, blood pressure, temperature, and performance status) prior to each dose. The protocol additionally provided guidance for management of pulmonary adverse events, including increase in monitoring.

Electrocardiograms (ECGs)

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable

QT

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable

Immunogenicity

Data:

Table 47: ADA Assessments Summary - All 1L Nivo+Ipi Treated Subjects with Baseline and At Least 1 Post-Baseline Assessment in CA2098HW (15-Nov-2023 DBL)

	Arm B: Nivo + Ipi	
Subject ADA Status (%)	**Nivolumab ADA N = 177**	**Ipilimumab ADA N = 173**
Baseline ADA Positive	12 (6.8)	4 (2.3)
ADA Positive	25 (14.1)	14 (8.1)
Persistent Positive	0	1 (0.6)
Not PP - Last Sample Positive	6 (3.4)	5 (2.9)
Other Positive	19 (10.7)	8 (4.6)
Neutralizing Positive	0	1 (0.6)
ADA Negative	152 (85.9)	159 (91.9)

Baseline ADA Positive: A subject with baseline ADA-positive sample
ADA Positive: A subject with at least 1 ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater than baseline positive titer) at any time after initiation of treatment
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart
Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling timepoint
Other Positive: Not persistent but some ADA-positive samples with the last sample being negative
Neutralizing Positive: At least 1 ADA-positive sample with neutralizing antibodies detected post-baseline
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Post-baseline assessments are assessments reported after initiation of treatment.
Source: ADIS, ADSL of the CA2098HW Interim CSR

The Applicant's Position:

In the nivo+ipi arm, the proportion of treated subjects who had nivo or ipi ADA at baseline and after the start of treatment was low (Table 47) and did not appear to have an effect on the PK, efficacy, or safety of nivo+ipi.

The FDA's Assessment:

See Section 6.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position: Not applicable.

The FDA's Assessment:

[FDA will complete this section.]

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position: Not applicable. See Section 8.1.2.

The FDA's Assessment:

See above adverse events of special interest and immune related adverse reactions analyses (Table 41 and Table 42).

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Table 48: All-Causality Adverse Events, Worst CTC Grade by Age, Sex, Race, and Region - All 1L Treated Subjects in the Nivo+Ipi (Arm B) and Chemo (Arm C) Arms in CA2098HW (15-Nov-2023 DBL)

	Number (%) of Subjects					
	Arm B: Nivo+Ipi			Arm C: Chemo		
Category, n (%)	N	Any Grade	Grade 3-4	N	Any Grade	Grade 3-4
Total	200	197 (98.5)	96 (48.0)	88	86 (97.7)	59 (67.0)
By Age (years)						
< 65	115	113 (98.3)	52 (45.2)	42	41 (97.6)	27 (64.3)
≥ 65	85	84 (98.8)	44 (51.8)	46	45 (97.8)	32 (69.6)
≥ 65 and < 75	48	47 (97.9)	22 (45.8)	34	33 (97.1)	25 (73.5)
≥ 75 and < 85	35	35 (100.0)	20 (57.1)	10	10 (100.0)	6 (60.0)
≥ 85	2	2 (100.0)	2 (100.0)	2	2 (100.0)	1 (50.0)
By Sex						
Male	94	92 (97.9)	40 (42.6)	43	42 (97.7)	30 (69.8)
Female	106	105 (99.1)	56 (52.8)	45	44 (97.8)	29 (64.4)
By Race						
White	175	173 (98.9)	87 (49.7)	77	75 (97.4)	52 (67.5)

Table 48: All-Causality Adverse Events, Worst CTC Grade by Age, Sex, Race, and Region - All 1L Treated Subjects in the Nivo+Ipi (Arm B) and Chemo (Arm C) Arms in CA2098HW (15-Nov-2023 DBL)

	Number (%) of Subjects					
	Arm B: Nivo+Ipi			Arm C: Chemo		
Category, n (%)	N	Any Grade	Grade 3-4	N	Any Grade	Grade 3-4
Black or African American	1	1 (100.0)	0	2	2 (100.0)	1 (50.0)
Asian	19	18 (94.7)	6 (31.6)	8	8 (100.0)	6 (75.0)
Other	5	5 (100.0)	3 (60.0)	1	1 (100.0)	0
By Region						
US/Canada/Europe	131	129 (98.5)	68 (51.9)	65	63 (96.9)	40 (61.5)
Asia	19	18 (94.7)	6 (31.6)	7	7 (100.0)	5 (71.4)
Rest of World	50	50 (100.0)	22 (44.0)	16	16 (100.0)	14 (87.5)

MedDRA version 26.1; CTCAE version 5.0.
Includes events reported between first treatment and 30 days after last treatment of study therapy.
Excludes data collected on or after first crossover dose date.
Source: ADAE and ADSL of the CA2098HW Interim CSR

Table 49: Drug-Related Adverse Events, Worst CTC Grade by Age, Sex, Race, and Region - All 1L Treated Subjects in the Nivo+Ipi (Arm B) and Chemo (Arm C) Arms in CA2098HW (15-Nov-2023 DBL)

	Number (%) of Subjects					
	Arm B: Nivo+Ipi			Arm C: Chemo		
Category, n (%)	N	Any Grade	Grade 3-4	N	Any Grade	Grade 3-4
Total	200	160 (80.0)	46 (23.0)	88	83 (94.3)	42 (47.7)
By Age (years)						
< 65	115	93 (80.9)	22 (19.1)	42	40 (95.2)	19 (45.2)
≥ 65	85	67 (78.8)	24 (28.2)	46	43 (93.5)	23 (50.0)
≥ 65 and < 75	48	36 (75.0)	13 (27.1)	34	32 (94.1)	17 (50.0)
≥ 75 and < 85	35	29 (82.9)	10 (28.6)	10	9 (90.0)	5 (50.0)
≥ 85	2	2 (100.0)	1 (50.0)	2	2 (100.0)	1 (50.0)
By Sex						
Male	94	74 (78.7)	21 (22.3)	43	42 (97.7)	19 (44.2)
Female	106	86 (81.1)	25 (23.6)	45	41 (91.1)	23 (51.1)
By Race						
White	175	140 (80.0)	42 (24.0)	77	72 (93.5)	35 (45.5)
Black or African American	1	0	0	2	2 (100.0)	1 (50.0)
Asian	19	16 (84.2)	3 (15.8)	8	8 (100.0)	6 (75.0)
Other	5	4 (80.0)	1 (20.0)	1	1 (100.0)	0

Table 49: Drug-Related Adverse Events, Worst CTC Grade by Age, Sex, Race, and Region - All 1L Treated Subjects in the Nivo+Ipi (Arm B) and Chemo (Arm C) Arms in CA2098HW (15-Nov-2023 DBL)

	Number (%) of Subjects					
	Arm B: Nivo+Ipi			Arm C: Chemo		
Category, n (%)	N	Any Grade	Grade 3-4	N	Any Grade	Grade 3-4
By Region						
US/Canada/Europe	131	105 (80.2)	31 (23.7)	65	60 (92.3)	24 (36.9)
Asia	19	16 (84.2)	3 (15.8)	7	7 (100.0)	5 (71.4)
Rest of World	50	39 (78.0)	12 (24.0)	16	16 (100.0)	13 (81.3)

MedDRA version 26.1; CTCAE version 5.0.
Includes events reported between first treatment and 30 days after last treatment of study therapy.
Excludes data collected on or after first crossover dose date.
Source: ADAE and ADSL of the CA2098HW Interim CSR

The Applicant's Position:

For all 1L treated subjects in the nivo+ipi and chemo arms, the frequencies of AEs (all causality and drug-related) for subgroups of age, sex, race, and region, were generally consistent with the corresponding frequencies reported for the overall study population by treatment arm (Table 48 and Table 49). Some numerical differences between subgroups cannot be interpreted due to small numbers of subjects.

The FDA's Assessment:

The differences in TEAEs between patient in the nivo+ipi compared to nivo alone (all lines) is outlined in Table 50.

Table 50: FDA – TEAEs subgroups in nivo+ipi and nivo arms (all lines) (DBL: 9/25/24)

	Nivo+Ipi			Nivo		
	N	Any Grade	Grade 3-4	N	Any Grade	Grade 3-4
Total (%)	352	349 (99)	168 (48)	351	336 (96)	151 (43)
By Age (years)						
< 65	197	194 (99)	82 (42)	191	183 (96)	85 (45)
≥ 65	155	155 (100)	86 (56)	160	153 (96)	66 (41)
≥ 75	51	51 (100)	30 (59)	47	46 (98)	21 (45)
By Sex						
Male	161	158 (98)	71 (44)	189	179 (95)	88 (47)
Female	191	191 (100)	97 (51)	162	157 (97)	63 (39)

By Race						
White	310	308 (99)	154 (50)	303	289 (95)	125 (41)
Asian	27	26 (96)	10 (37)	36	35 (97)	20 (56)
By Region						
US/Canada/Europe	249	247 (99)	121 (49)	246	235 (96)	104 (42)
Asia	26	25 (96)	10 (39)	33	32 (97)	18 (55)
Rest of World	77	77 (100)	37 (48)	72	69 (96)	29 (40)

Source: Adapted from primary CSR

% calculated from total treated in that subgroup, only subgroups with >20 patients included in the table

TEAEs leading to treatment discontinuation were more common in patients 65 years and older who received nivo+ipi compared to nivo alone (23% vs 15%). FDA agrees that small or imbalanced sample sizes in certain subgroups limits interpretation of the clinical relevance of the observed frequencies of TEAEs, FDA included the frequencies of Grade 3 or 4 TEAEs and TEAEs leading to discontinuation in patients 65 years and older in Section 8 of the respective USPIs.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position: Not applicable.

The FDA's Assessment:

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position: Not applicable.

The FDA's Assessment:

Not applicable.

Human Reproduction and Pregnancy

Data: As of the 15-Nov-2023 DBL, 1 subject in the nivo+ipi arm with a positive pregnancy test on Day 642 discontinued study treatment due to pregnancy on the same day (Day 642). The subject had received the last dose of ipi on Day 66 and the last dose of nivolumab on Day 604. The pregnancy was successfully terminated on Day 674 (*Source: ADLB, ADSL of the CA2098HW Interim CSR*).

The Applicant's Position: There is no information to report for use of nivo+ipi in pregnancy or

lactation.

The FDA's Assessment:
FDA reviewed the narrative provided by the Applicant, which is adequately summarized above.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable..

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position: Not applicable.

The FDA's Assessment:

Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable.

Expectations on Safety in the Postmarket Setting

The Applicant's Position: Not applicable.

The FDA's Assessment:

No new information has been identified in the current submission, there are no changes to the expectation in post market safety reporting.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Safety data from 200 1L nivo+ipi treated subjects with MSI-H/dMMR mCRC in CA2098HW demonstrated that the safety profile of nivo+ipi is tolerable, manageable, and reflective of the known safety profile of the nivo and ipi components and their combination. Overall, there were no new safety concerns identified, and no changes in risk minimization measures are warranted.

The FDA's Assessment:

FDA analyses additionally evaluated the safety profile of nivolumab in combination with ipilimumab compared to nivolumab in all treatment lines. Patients receiving the combination regimen had a 5% increase in the incidence of Grade 3 or 4 TEAEs and 7% increase in SAEs compared to single agent nivolumab. TEAEs leading to treatment delay of nivolumab and/or ipilimumab occurred more frequently in the combination arm (48% versus 37%) as did TEAEs leading to treatment discontinuation of nivolumab and/or ipilimumab (19% versus 13%). Although, the observed frequency immune mediated adverse events (non-endocrine and endocrine) were consistently higher in the combination arm than single agent nivolumab, the cited incidences were consistent with the current clinical experience with this combination. FDA evaluated the overall survival analyses, as an assessment of safety, and although there was a transient crossing of Kaplan-Meier overall survival curves, there was sustained separation favoring nivo+ipi after 180 days. The difference in TEAEs, SAEs and fatal adverse reactions between combination nivo+ipi, compared to nivo, single agent, have been included in the USPIs.

The safety profile was consistent with that known to occur in patients receiving nivolumab in combination with ipilimumab and manageable with standard of care practice, particularly in the context of a significant statistical and clinically meaningful improvement in progression free survival.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The primary efficacy assessment for this application was based on the results of CA2098HW, a randomized control trial comparing nivolumab + ipilimumab, nivolumab monotherapy, and investigator's choice of chemotherapy for both first line and all lines therapies for patients with MSI-H/dMMR mCRC. The dual primary outcomes (assessed in the centrally confirmed MSI-H/dMMR population) were PFS per BICR of nivo+ipi vs chemo in 1L and PFS per BICR of nivo+ipi vs nivo in all lines. The PFS interim analysis of nivo+ipi vs chemo in 1L patients at 80% information fraction resulted in a statistically significant improvement (stratified log-rank test p-value < 0.0001) with a stratified HR of 0.21 (95% CI: 0.14, 0.32) favoring the nivo+ipi arm. In the PFS interim analysis of nivo+ipi vs nivo in all lines patients at 74.6% information fraction, a statistically significant improvement was observed (stratified log-rank test p-value = 0.0003) with a stratified HR of 0.62 (95% CI: 0.48, 0.81) favoring the nivo+ipi arm. In addition, one key secondary endpoint, ORR per BICR comparing nivo+ipi vs nivo in all lines patients was formally tested, showing a statistically significant improvement favoring the nivo+ipi arm

(stratified CMH test p-value = 0.0011). OS data were descriptively evaluated by FDA and no harm or detriment to survival was found at this time.

There were no major statistical issues with this Application. However, the interim analysis timing of the PFS analysis comparing nivo+ipi vs nivo inpatients receiving all lines of treatment and with centrally confirmed MSI-H/dMMR was modified in a protocol amendment after the PFS data of nivo+ipi vs chemo in 1L patients was unblinded to the study team. After reviewing the Application, FDA did not have concerns regarding this protocol amendment.

8.4. **Conclusions and Recommendations**

The FDA's Assessment:

Nivolumab, administered as a single agent, or in combination with ipilimumab, were granted accelerated approval for the treatment of patients with MSI-H/dMMR mCRC who had disease progression on chemotherapy in 2017 and 2018 respectively. Study CA2098HW, a three arm (nivolumab + ipilimumab, nivolumab as a single agent, and chemotherapy), randomized study was designed to fulfill the post marketing requirements issued to verify the clinical benefit for nivolumab in combination with ipilimumab, and nivolumab, single agent, for the treatment of patients with MSI-H/dMMR mCRC. Although the study allowed enrollment and randomization based on local microsatellite status testing, the primary efficacy population consisted of patients with centrally confirmed MSI-H/dMMR.

Study CA2098HW had dual primary outcomes. In the first interim analyses, a clinically meaningful and statistically significant improvement in PFS was demonstrated in patients being treated in the first line setting who received nivo+ipi compared to chemotherapy. The median PFS in the nivo+ipi arm was not reached (95% CI: 38.4, NA) compared to 5.9 months (95% CI 4.4, 7.8) in the chemotherapy arm (HR 0.21 [95% CI: 0.14, 0.32]). Study CA2098HW subsequently demonstrated a clinically meaningful and statistically significant improvement in PFS in the all lines population (which included 55% of patients receiving treatment in the first line setting) who received nivo+ipi compared to nivo, single agent. The median PFS in the nivo+ipi arm was not reached (95% CI: 54, NA) compared to 39 months (95% CI 53.8, NA) in the nivo, single agent, arm (HR 0.62 [95% CI: 0.48, 0.81]). The effectiveness of the combination regimen is further supported by 13% higher ORR rate in the nivo+ipi arm compared nivo alone (71% versus 58% [p=0.0011]). Sensitivity analyses evaluating the ITT population demonstrated similar efficacy results to the primary efficacy populations. FDA reviewed the Applicant's blinded overall survival analyses, with no evidence of overall survival detriment in patients receiving combination nivo+ipi compared to nivo, single agent. In addition to providing evidence of the efficacy of nivolumab in combination with ipilimumab across all lines of therapy and confirming the benefit previously observed in CheckMATE-142 for both nivo+ipi and nivolumab as a single agent, the design of Study CA2098HW provided data supporting the contribution of ipilimumab to the combination nivo+ipi.

The subgroup of patients whose local testing revealed MSI-H/dMMR but without confirmatory central testing (17% of the study population), had inferior PFS when receiving immune checkpoint inhibition (combination or single agent) compared to those patients with centrally confirmed MSI-H/dMMR status, suggesting that in this patients, local testing misidentified the microsatellite instability and/or mismatch repair status. Concurrently with this Application, two sPMAs have been submitted to CDRH to support approval of IHC and PCR tests to select patients for whom treatment with nivo+ipi or nivolumab may provide substantial benefit.

Patients receiving combination nivo+ipi had higher rates of Grade 3 or 4 TEAEs, IMAEs (non-endocrine and endocrine), SAEs, and fatal adverse reactions compared to nivo alone. The increased incidence was consistent with the established safety profile of nivo+ipi and managed through a combination of treatment delay, immunomodulating agents, supportive care and treatment discontinuations.

The evidence submitted in these supplemental BLAs provides substantial evidence of the safety and effectiveness of nivolumab, in combination with ipilimumab for the treatment of patients with MSI-H/dMMR mCRC and the review team recommends the approval of the combination in this patient population (b) (4), irrespective of the prior line of treatment.

The data provided in these applications adequately fulfills the post marketing requirements (PMR 3243-1, PMR 3449-1, PMR 3450-1) issued for the respective accelerated approvals of nivolumab as a single agent, and nivolumab in combination with ipilimumab.

8.4.1. Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication *(enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response)*:

   OPDIVO:

   Colorectal Cancer

   - adult and pediatric (12 years and older) patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) (b) (4), in combination with ipilimumab.
   - adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer

[redacted]^(b) (4)^, that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

YERVOY:
Colorectal Cancer

- Treatment of adult and pediatric 12 years and older patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) [redacted]^(b) (4)^, in combination with nivolumab

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☒ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR

   c. ☐ Evidence that supported SEE from a prior approval *(eg, 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[2]
3. Complete response, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)
[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)
[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No advisory committee was convened for this supplemental Application as the Application did not raise any issues that warranted the Committee's input.

10 Pediatrics

The Applicant's Position:

An initial agreed PSP was obtained on 25-May-2023, which consisted of a partial waiver from the requirements of PREA for patients < 12 years of age. The agreed upon iPSP was for the following indication: nivo in combination with ipi, for treatment of adult patients with no prior treatment for MSI-H or dMMR mCRC. No deferral is planned. BMS is to submit the modeling and simulation/extrapolation study results together with the sBLA.

The FDA's Assessment:

FDA agrees. See Section 6 for further details.

11 Labeling Recommendations

Data:

Labeling Recommendations for OPDIVO

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
INDICATIONS AND USAGE (1.11)	Addition of OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) (b) (4)	OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC). OPDIVO, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
DOSAGE AND ADMINISTRATION (2.2 and 2.4)	Addition of dosing recommendation for OPDIVO in combination with ipilimumab and associated text related to the addition of this treatment regimen and administration.	FDA agrees
ADVERSE REACTIONS (6.1)	Addition of clinical safety data from the CA2098HW study, including a brief description of the inclusion/exclusion criteria; duration of therapy; a brief summary of the serious and most common adverse reactions; tables of the adverse reactions occurring at an incidence of 10% or greater; and tables of laboratory abnormalities occurring at an incidence of 10% or greater.	FDA generally agrees; adverse reaction tables limited to combination and single agent nivolumab arms only and adverse reaction and lab tables limited to those occurring in ≥10% of patients with a difference between arms of ≥ 5%. Revisions to the section to provide information on the comparison of nivolumab+ipilimumab vs. nivolumab.
PEDIATRIC USE (8.4)	Addition of data related to Study CA2098HW.	FDA agrees
GERIATRIC USE (8.5)	Addition of data related to Study CA2098HW.	FDA revised to describe geriatric experience in all lines; also revised to describe differences in geriatric population experience for safety for combination and single agent nivolumab
PHARMACOKINETICS (12.3)	Addition of data related to Study CA2098HW.	FDA agrees
CLINICAL STUDIES (14.11)	Addition of clinical efficacy data from the CA2098HW study, including: a brief description	FDA generally agrees; revised to present study population for first line and all-lines

	of the study design and treatment groups; inclusion/exclusion criteria of the study; patient demographics; primary and key secondary efficacy endpoints.	separately

Other Prescription Drug Labeling for OPDIVO:
The OPDIVO Medication Guide was updated to include the following additional information in patient-friendly language:

- Under "What is OPDIVO?" - Addition of a description of the proposed MSI-H or dMMR CRC indication, consistent with the proposed indication in the Full Prescribing Information.
- Under "How will I receive OPDIVO?" - Addition of a description of the dosage and administration information for MSI-H or dMMR CRC indication, consistent with the dosage and administration information in the Full Prescribing Information.
- Under "What are the possible side-effects of OPDIVO?" - Addition of a list of the most common adverse reactions observed in the study supporting the MSI-H or dMMR CRC indication, consistent with the adverse reactions information in the Full Prescribing Information.

Labeling Recommendations for YERVOY

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
INDICATIONS AND USAGE (1.4)	Addition of YERVOY in combination with is indicated for the first-line treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) (b) (4) .	YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC). Indication for Yervoy in combination with nivolumab deleted as indication for combination is now line-agnostic.
DOSAGE AND ADMINISTRATION (2.2 and 2.4)	Addition of dosing recommendation for YERVOY in combination with nivolumab and associated text related to the addition of this treatment regimen and administration.	FDA agrees
ADVERSE REACTIONS (6.1)	Addition of clinical safety data from the CA2098HW study, including: a brief description of the inclusion/exclusion criteria; duration of therapy; a brief summary of the serious and most common adverse reactions; tables of the adverse reactions occurring at an incidence of 10% or	FDA generally agrees; adverse reaction tables limited to combination and single agent nivolumab arms only and Adverse reaction and lab tables limited to those occurring in ≥10% of patients with a difference between arms of ≥ 5%

	greater; and tables of laboratory abnormalities occurring at an incidence of 10% or greater.	
PEDIATRIC USE (8.4)	Addition of data related to Study CA2098HW.	FDA agrees
GERIATRIC USE (8.5)	Addition of data related to Study CA2098HW.	Revised to describe geriatric experience with combination for all-lines
PHARMACOKINETICS (12.3)	Addition of data related to Study CA2098HW.	FDA agrees
CLINICAL STUDIES (14.4)	Addition of clinical efficacy data from the CA2098HW study, including: a brief description of the study design and treatment groups; inclusion/exclusion criteria of the study; patient demographics; primary and key secondary efficacy endpoints.	FDA generally agrees; revised to present study population for first line and all-lines separately FDA deleted section on efficacy for CHECKMATE-142 as combination is no longer indicated in this population

Other Prescription Drug Labeling for YERVOY:

The YERVOY Medication Guide was updated to include the following additional information in patient-friendly language:

- Under "What is YERVOY?" - Addition of a description of the proposed MSI-H or dMMR CRC indication, consistent with the proposed indication in the Full Prescribing Information.
- Under "How will I receive YERVOY?" - Addition of a description of the dosage and administration information for MSI-H or dMMR CRC indication, consistent with the dosage and administration information in the Full Prescribing Information.
- Under "What are the possible side-effects of YERVOY?" - Addition of a list of the most common adverse reactions observed in the study supporting the MSI-H or dMMR CRC indication, consistent with the adverse reactions information in the Full Prescribing Information.

The Applicant's Position:

The clinical data provided in this supplemental BLA submission demonstrate the clinical benefit and safety of the use of nivo in combination with ipi, for the treatment of patients with metastatic MSI-H/dMMR CRC. Based on these data, this section provides a high-level summary of the proposed changes to the labeling for OPDIVO (nivolumab) and Yervoy (ipilimumab).

The FDA's Assessment:

Refer to Sections 8.4 and 1.2.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

No REMS was requested. There is extensive clinical experience with nivolumab alone and in combination with ipilimumab.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

No new PMR/PMCs were requested.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

I agree with the review teams' recommendations regarding the approval of the efficacy supplements submitted by BMS for the following two indications:

- Nivolumab, in combination with ipilimumab, is indicated for the first-line treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC)
- Nivolumab, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

These submissions also support the conversion of the Subpart E Accelerated Approvals of nivolumab and ipilimumab for MSI-H/dMMR CRC.

The data supporting these applications are primarily supported by the results of Study CHECKMATE-8HW (NCT03143153), a randomized, 3-arm, open label trial in patients with immunotherapy-naïve unresectable or metastatic MSI-H/dMMR CRC. Patients were randomized to receive either nivolumab in combination with ipilimumab, nivolumab alone, or investigator's choice of chemotherapy (mFOLFOX or FOLFIRI +/- bevacizumab or cetuximab; doses listed above in this review). In the trial, the combination of ipilimumab and nivolumab was formally tested against nivolumab alone and against the chemotherapy arm with BICR-assessed PFS as the primary endpoint. Based on protocol amendments (see above), line of enrollment changed during the trial such that the primary analysis of PFS was in the first-line setting for ipilimumab in combination with nivolumab versus chemotherapy and in any line setting for ipilimumab in combination with nivolumab versus nivolumab.

CHECKMATE-8HW demonstrated statistically significant improvements in PFS in patients with centrally confirmed MSI-H/dMMR in patients who received:

- Ipilimumab in combination with nivolumab arm compared to chemotherapy in the 1L setting [HR 0.21 (0.14, 0.32), p < 0.0001].
- Ipilimumab in combination with nivolumab compared to nivolumab in all treatment lines [HR 0.62 (0.48, 0.81), p = 0.003].

The KM curves in Figure 3 (above) appear to show a clear disease modifying beneficial effect of ipilimumab and nivolumab when compared to conventional chemotherapy. In the first-line setting, as shown in Figure 5 above, fewer than half of patients had progressed at approximately *four and a half years* and that ipilimumab appears to provide a PFS benefit when added on to nivolumab. Although ipilimumab combined with nivolumab (or nivolumab alone) can cause severe and life-threatening immune related adverse reactions, the risk is considered acceptable considering standard chemotherapy can also cause severe and life-threatening toxicities and considering the otherwise fatal prognosis of untreated metastatic colorectal cancer.

X

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

18 Appendices

18.1. FDA References

Casak, S. J., L. Marcus, L. Fashoyin-Aje, S. L. Mushti, J. Cheng, Y. L. Shen, W. F. Pierce, L. Her, K. B. Goldberg, M. R. Theoret, P. G. Kluetz, R. Pazdur, and S. J. Lemery. 2021. 'FDA Approval Summary: Pembrolizumab for the First-line Treatment of Patients with MSI-H/dMMR Advanced Unresectable or Metastatic Colorectal Carcinoma', *Clin Cancer Res*, 27: 4680-84.

Diaz, L., Shiu KK, Kim TW, Jensesn B, Jensen L et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a rnadomized, open-label, phase 3 study. *Lancet Oncol. 2022 Apr 12;23(5):659–670.*

FDA. 2020. 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for Industry ', Accessed 02/10/2025. https://www.fda.gov/media/71195/download.

Gutierrez, C., S. Ogino, J. A. Meyerhardt, and J. B. Iorgulescu. 2023. 'The Prevalence and Prognosis of Microsatellite Instability-High/Mismatch Repair-Deficient Colorectal Adenocarcinomas in the United States', *JCO Precis Oncol*, 7: e2200179.

OPDIVO. 2024. 'Nivolumab USPI (Action Date 10/3/2024)', Accessed 11/06/2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125554s127lbl.pdf.

SEER. 2024. 'Cancer Stat Facts: Colorectal Cancer', Accessed 01/13/2025. https://seer.cancer.gov/statfacts/html/colorect.html.

Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res. 2014 Oct 15;20(20):5322-30.

18.2. Financial Disclosure

The Applicant's Position:

Financial interests or arrangements with clinical investigators have been disclosed in the table below. Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the CA2098HW clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators.*

Covered Clinical Study (Name and/or Number):* CA2098HW

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1696		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a		

Significant equity interest held by investigator in study: n/a Sponsor of covered study: n/a		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ n/a	No ☐ (Request details from Applicant) n/a
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ n/a	No ☐ (Request information from Applicant) n/a
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 32		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

The Applicant provided details of the 32 investigators for whom they could not obtain the required information under 21 CFR 54.4, 12 of whom have no financial disclosure information available. Twenty of the 32 investigators provided financial disclosure forms, however there were not specific updates from the co-development partner. The Applicant provided details of the missing information for each investigator, in addition to the number of patients enrolled and randomized at the respective site.

18.3. Additional Clinical Data

Table 51: CA2098HW Enrollment by Country

Country	Number of Patients Enrolled	
	N	%
Argentina	44	5%
Australia	44	5%
Austria	12	1%
Belgium	37	4%
Brazil	51	6%
Canada	12	1%
Chile	15	2%
China	20	2%
Czechia	23	3%
Denmark	23	3%

France	159	19%
Germany	46	5%
Greece	18	2%
Ireland	1	0%
Italy	81	10%
Japan	52	6%
Netherlands	26	3%
Norway	13	2%
Romania	41	5%
Spain	91	11%
Turkey	21	3%
United Kingdom of Great Britain and Northern Ireland	2	0%
United States of America	7	1%

Table 52: Bethesda method (PCR) Panel Description and Classification of MSI Status

Reference panel:	Alternative loci:
– BAT25 (mononucleotide) – BAT26 (mononucleotide) – NR-21 (mononucleotide) – NR-24 (mononucleotide) – MONO-27 (mononucleotide) – D5S346 (dinucleotide) – D2S123 (dinucleotide) – D17S250 (dinucleotide)	– BAT40 – BAT34C4 – NR-22 – TGF-β-RII – ACTC (635/636 – CAT25 – D9S63 – D1S158 – ACVR2A – BTBD7 – DIDO1 – MRE11 – RYR3 – SEC31A – SULF2
Classification:	

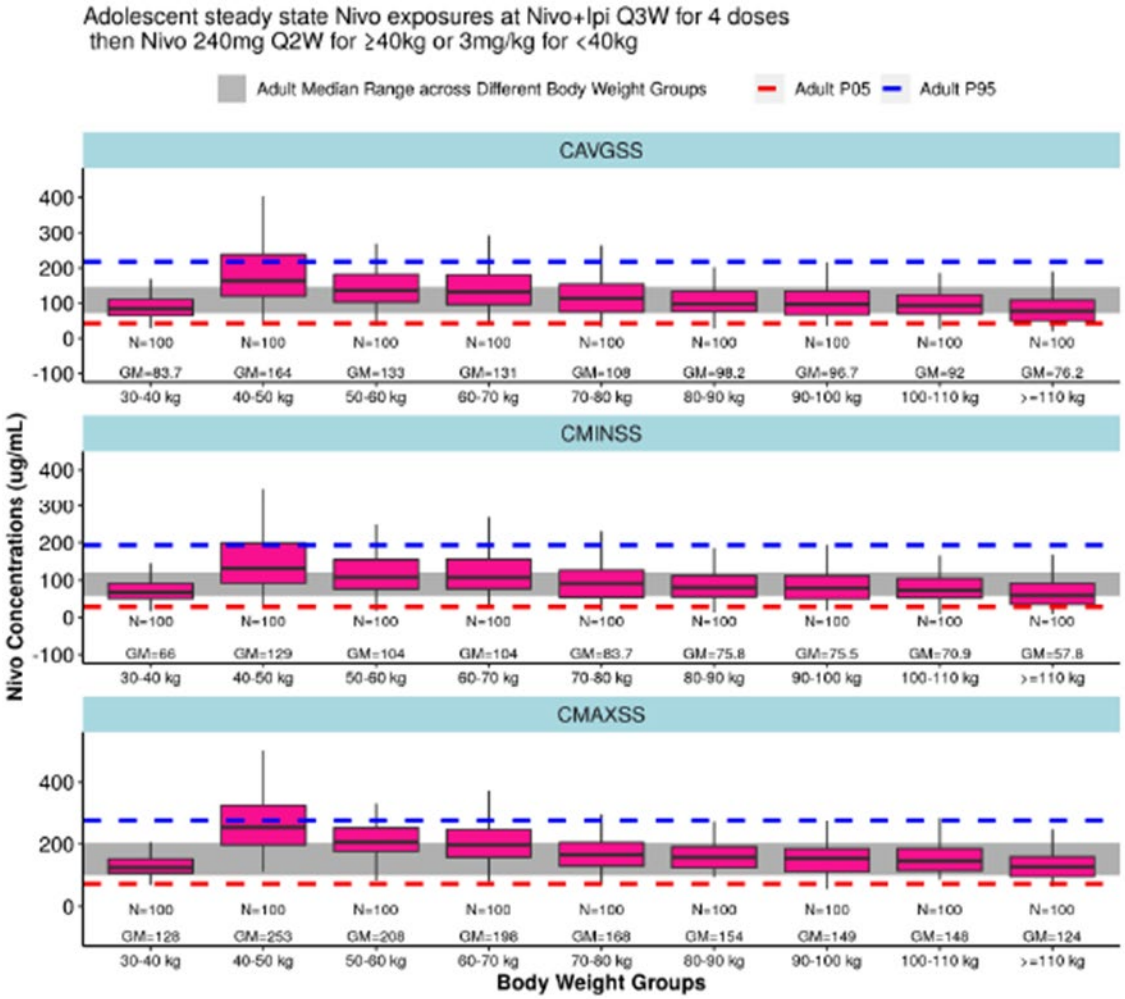
– If 5 loci tested (reference panel): o MSI-H: ≥ 2 markers with instability o MSI-L: 1 marker with instability o MSS or MSI-L: 0 markers with instability – If > 5 loci tested (reference panel plus alternative loci): o MSI-H: ≥ 30-40% markers with instability o MSI-L: < 30-40% markers with instability o MSS or MSI-L: 0 markers with instability – In the case of 1 PCR amplification failure: o If ≥ 3 markers of 4 ->MSI-H o If 1 marker of 4 -> re-amplify
Promega MSI Multiplex system version 1.1
• 5 mononucleotide markers: – BAT-25 – BAT-26 – NR-21 – NR-24 – MONO-27 • Two polymorphic pentanucleotide markers – Penta C – Penta D
Data interpretation:
– MSS: no instability at any of the loci – MSI-Low: instability at a single mononucleotide locus – MSI-H: instability at ≥ 2 mononucleotide loci
IHC method - Panel Description and Classification of MSI Status
Panel • hMSH2 • hMLH1 • hMSH6 • hPMS2
Classification: • MSI-H: ≥ 1 markers with instability • MSS: 0 markers with instability • MSI-L: not evaluable with this technique
Next generation sequencing methods:

- FoundationOne CDx
- FoundationOne Liquid CDx
- TSO500 Assay (Tissue)
- TSO500 ctDNA Assay
- PGDx Elio Plasma
- PGDx Elio Tissue
- Predicine ATLAS
- Personalis ImmunoID NeXT
- Tempus xT
- Caris Molecular Intelligence
- Oncomine Comprehensive Assay
- OmnisSeq MSI NGS
- QIAseq Tumor Mutational Burden Panels
- Guardant 360
- Guardant Omni

18.4. OCP Appendices (Technical documents supporting OCP recommendations)

The Applicant's Position: Not applicable. See explanation about the FDA-granted clinical pharmacology package waiver in Section 6.2.

Figure 11. Predicted Nivolumab Steady-state Exposures in Adolescents with CRC with a Nivolumab Maintenance Dose of 240 mg Q2W for Patients Weighing ≥ 40 kg or 3 mg/kg Q2W for Patients Weighing < 40 kg



Note 1: Dosing regimen for adolescents weighing ≥ 40 kg: nivolumab 240 mg + ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 240 mg Q2W; Dosing regimen for adolescents weighing < 40 kg: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 3 mg/kg Q2W
Note 2: Adolescent weight band simulated: 30 to ≥ 110 kg with 10 kg increments (the upper number in each band is not inclusive)
Note 3: Gray shaded area indicates the adult median exposure range across body weight groups. Red and Blue dashed lines indicate the adult exposure range of 5th and 95th percentile, respectively.
Analysis Directory: /global/pkms/data/CA/209/8HW/prd/ppk-ado/final
Program Source: Analysis Directory/R/scripts/3-simulation-nivo-ado.Rmd
Figure Source: Analysis Directory/R/plots/nivo-exposs-ped-sto-crc-combo-240.png

Source: report bms936558-crc-adolescent-simulation-report-2024, Page 43 (link).

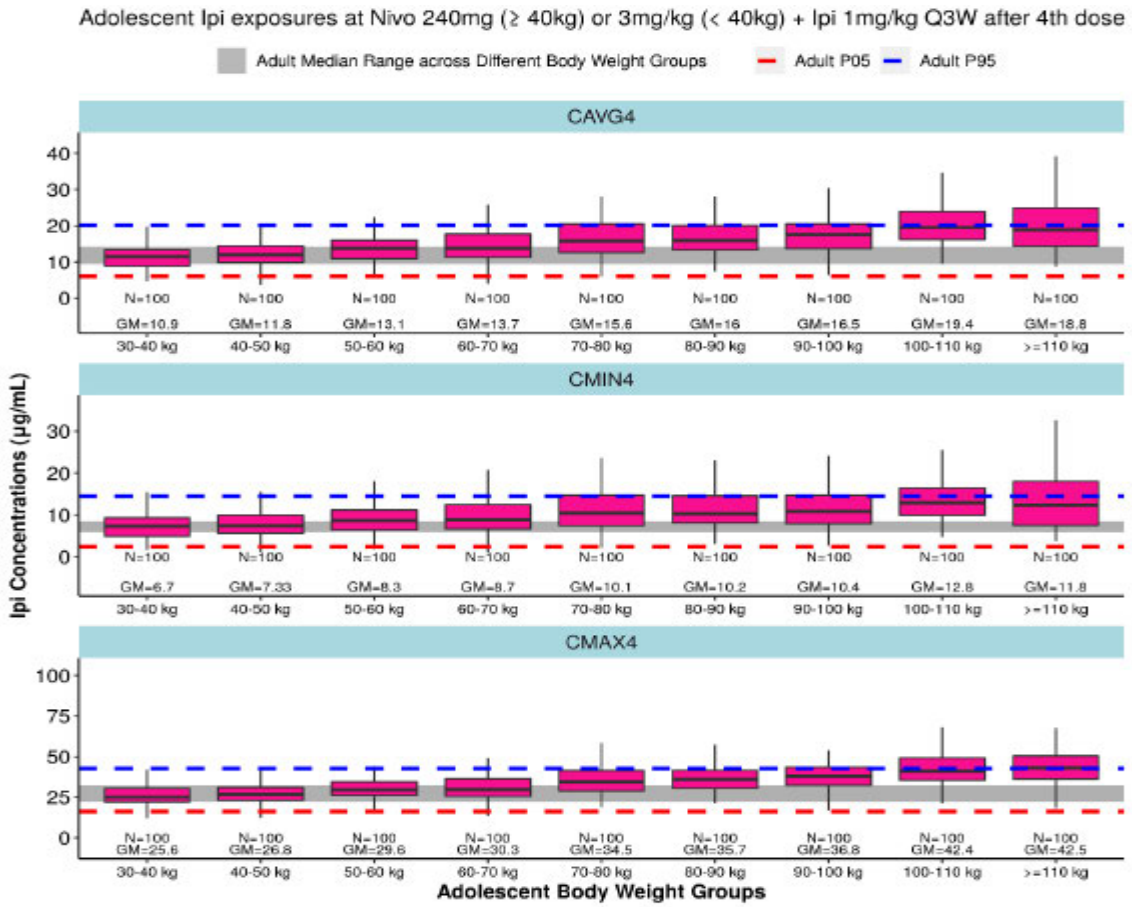
Table 53. Comparisons of Predicted Nivolumab Steady-state Exposures in Adolescents Relative to Adults with CRC with a Nivolumab Maintenance Dose of 240 mg Q2W for Patients Weighing ≥40 kg or 3 mg/kg Q2W for Patients Weighing < 40 kg

Exposure Parameters	Simulated Adolescent Body Weight Ranges	Adolescent Geometric Mean Exposures (µg/mL; %CV)	Adolescent Exposures Relative to Adults*	Adult Geometric Mean Exposures (≥ 40 kg)
Cavgss	30 to < 40 kg	83.7 (40.8)	In adult range	72.1 to 139 µg/mL
	40 to < 50 kg	164 (47.1)	18% higher	
	50 to < 60 kg	133 (39.4)	In adult range	
	60 to < 70 kg	131 (39.2)	In adult range	
	70 to < 80 kg	108 (51.1)	In adult range	
	80 to < 90 kg	98.2 (40.6)	In adult range	
	90 to < 100 kg	96.7 (51.9)	In adult range	
	100 to < 110 kg	92 (42.4)	In adult range	
	≥ 110 kg	76.2 (54.8)	In adult range	
Cminss	30 to < 40 kg	66 (48.6)	In adult range	57.5 to 111 µg/mL
	40 to < 50 kg	129 (55.6)	16.2% higher	
	50 to < 60 kg	104 (46.7)	In adult range	
	60 to < 70 kg	104 (45.9)	In adult range	
	70 to < 80 kg	83.7 (61)	In adult range	
	80 to < 90 kg	75.8 (48.9)	In adult range	
	90 to < 100 kg	75.5 (61.2)	In adult range	
	100 to < 110 kg	70.9 (50.7)	In adult range	
	≥ 110 kg	57.8 (65.8)	In adult range	
Cmaxss	30 to < 40 kg	128 (31)	In adult range	103 to 200 µg/mL
	40 to < 50 kg	253 (34.8)	26.5% higher	
	50 to < 60 kg	208 (30.5)	4% higher	
	60 to < 70 kg	198 (33.6)	In adult range	
	70 to < 80 kg	168 (38.4)	In adult range	
	80 to < 90 kg	154 (29.1)	In adult range	
	90 to < 100 kg	149 (39.7)	In adult range	
	100 to < 110 kg	148 (31.1)	In adult range	
	≥ 110 kg	124 (39.4)	In adult range	

* Adolescent exposures relative to adult were calculated as a percent difference between the geometric mean for adolescent for each weight band and the upper or lower bound of adult geometric mean values across all body weights. Adult upper bound was used if adolescent value was above the adult range; Adult lower bound was used if adolescent value was below the adult range
Note 1: Dosing regimen for adolescents weighing ≥ 40 kg: nivolumab 240 mg + ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 240 mg Q2W; Dosing regimen for adolescents weighing < 40 kg: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 3 mg/kg Q2W
Note 2: For each body weight band, 100 simulations were sampled from all simulation results stratified by body weight category. Analysis Directory: /global/pkms/data/CA/209/8HW/prd/ppk-ado/final; Program Source: Analysis Directory/R/scripts/3-simulation-nivo-ado.Rmd; Table Source: Analysis Directory/R/export/nivo-expo-all-sto-crc-combo.csv

Source: report bms936558-crc-adolescent-simulation-report-2024, Page 44 (link).

Figure 12. Predicted Ipilimumab Exposures in Adolescents with CRC After 4th Dose of Nivolumab + Ipilimumab Q3W



Note 1: Dosing regimen for adolescents weighing ≥ 40 kg: nivolumab 240 mg + ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W; Dosing regimen for adolescents weighing < 40 kg: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 3 mg/kg Q2W
Note 2: Adolescent weight band simulated: 30 to ≥ 110 kg with 10 kg increments (the upper number in each band is not inclusive)
Note 3: Gray shaded area indicates the adult median exposure range across body weight groups. Red and Blue dashed lines indicate the adult exposure range of 5th and 95th percentile, respectively
Analysis Directory: /global/pkms/data/CA/209/8HW/prd/ppk-ado/final
Program Source: Analysis Directory/R/scripts/3-simulation-ipi-ado.Rmd
Figure Source: Analysis Directory/R/plots/ipi-expo4-ado-sto-crc-combo.png

Source: report bms936558-crc-adolescent-simulation-report-2024, Page 58 (link).

Table 54. Comparisons of Predicted Ipilimumab Exposures in Adolescents Relative to Adults with CRC after 4th Dose of Nivolumab + Ipilimumab Q3W

Exposure Parameters	Simulated Adolescent Body Weight Ranges	Adolescent Geometric Mean Exposures (µg/mL; %CV)	Adolescent Exposures Relative to Adults*	Adult Geometric Mean Exposures (≥ 40 kg)
Cavg4	30 to < 40 kg	10.9 (33.7)	In adult range	9.06 to 14 µg/mL
	40 to < 50 kg	11.8 (32.6)	In adult range	
	50 to < 60 kg	13.1 (28.2)	In adult range	
	60 to < 70 kg	13.7 (35.2)	In adult range	
	70 to < 80 kg	15.6 (31.9)	11.4% higher	
	80 to < 90 kg	16 (29.9)	14.3% higher	
	90 to < 100 kg	16.5 (31.5)	17.9% higher	
	100 to < 110 kg	19.4 (30.1)	38.6% higher	
	≥ 110 kg	18.8 (35.3)	34.3% higher	
Cmin4	30 to < 40 kg	6.7 (48.4)	In adult range	5.19 to 7.94 µg/mL
	40 to < 50 kg	7.33 (46.4)	In adult range	
	50 to < 60 kg	8.3 (39.3)	4.53% higher	
	60 to < 70 kg	8.7 (47.5)	9.57% higher	
	70 to < 80 kg	10.1 (44.1)	27.2% higher	
	80 to < 90 kg	10.2 (41.6)	28.5% higher	
	90 to < 100 kg	10.4 (44.3)	31% higher	
	100 to < 110 kg	12.8 (40.3)	61.2% higher	
	≥ 110 kg	11.8 (49.3)	48.6% higher	
Cmax4	30 to < 40 kg	25.6 (24.4)	In adult range	21.3 to 33.2 µg/mL
	40 to < 50 kg	26.8 (24)	In adult range	
	50 to < 60 kg	29.6 (22.6)	In adult range	
	60 to < 70 kg	30.3 (28)	In adult range	
	70 to < 80 kg	34.5 (25)	3.92% higher	
	80 to < 90 kg	35.7 (23.6)	7.53% higher	
	90 to < 100 kg	36.8 (23.5)	10.8% higher	
	100 to < 110 kg	42.4 (28)	27.7% higher	
	≥ 110 kg	42.5 (24.7)	28% higher	

* Adolescent exposures relative to adult were calculated as a percent difference between the geometric mean for adolescent for each weight band and the upper or lower bound of adult geometric mean values across all body weights. Adult upper bound was used if adolescent value was above the adult range; Adult lower bound was used if adolescent value was below the adult range.
Note 1: Dosing regimen for adolescents weighing ≥ 40 kg: nivolumab 240 mg + ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W; Dosing regimen for adolescents weighing < 40 kg: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 3 mg/kg Q2W
Note 2: For each body weight band, 100 simulations were sampled from all simulation results stratified by body weight category.
Analysis Directory: /global/pkms/data/CA/209/8HW/prd/ppk-ado/final
Program Source: Analysis Directory/R/scripts/3-simulation-ipi-ado.Rmd
Table Source: Analysis Directory/R/export/ipi-expo-all-sto-crc-combo-ado.csv

Source: report bms936558-crc-adolescent-simulation-report-2024, Page 59 (link).

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18.5. Additional Safety Analyses

A summary of all narratives provided to FDA of patients who died within 100 days of the last dose due to reasons other than progressive disease is outlined in Table 55. Information in addition to that provided in the narrative are outlined in Table 36.

Table 55: FDA – Summary of narratives of patient deaths within 100 days from last dose not due to disease progression

Preferred Term	Additional Terms	Sponsor/Investigator Attribution	Day of Death relative to C1	Narrative Summary	Reviewer Attribution
Nivolumab + Ipilimumab [Arm B]					
Shock	**Hemorrhagic necrotic pancreatitis**	Not Related	Day 6	56-year-old male was admitted on Day 6 following Cycle 1 Day 1 of nivolumab and ipilimumab with CT Abdomen demonstrating necro-hemorrhagic pancreatitis. The patient required pressor support in the ICU and died the same day.	**Could not rule out.** The Applicant provided further details which are outlined in Table 36
Sepsis	Small Intestinal Obstruction, Abdominal	Not Related	Day 87	26-year-old male with multiple admissions after initiating treatment with nivolumab and ipilimumab, including for small bowel obstruction, and abdominal	

	Pain, Acute Kidney Injury			pain. The patient was admitted on Day 68 with hydronephrosis and acute kidney injury, requiring bilateral nephrostomy. The patient was subsequently admitted on Day 87 with septic shock died the same day.	
Septic Shock		Not Related	Day 58	38-year-old male with multiple admissions after initiating treatment with nivolumab and ipilimumab. He required a naso-jejunal feeding tube due to severe malnutrition. The patient was admitted on Day 29 with peritonitis secondary to intra-abdominal fistula	Not Related
COVID-19	Intestinal Ischemia	Not Related	Day 61	71-year-old female, admitted on Day 52 with Covid-19 and bilateral pneumonitis, who died during the course of the admission on Day 61	Not Related
Intestinal Ischemia	Immune Mediated Enterocolitis	Not Related	Day 122	68-year-old male with multiple admission for immune mediated enterocolitis, maximal Grade 4, leading to treatment discontinuation on Day 87. He was subsequently admitted on Day 111 with intestinal ischemia and died during the course of admission.	**Possibly Attributed**
Sepsis	Vomiting	Not Related	Day 41	56-year-old male admitted on Day 7 with Grade 3 vomiting and received 2 doses in total of nivolumab and ipilimumab and was admitted gain 2 days after second dose, with hyperthermia and features consistent with septic shock. The patient died over the course of the admission.	Not Related

Unknown		Not Related	Day 40	74-year-old female who died at home on Day 40 from unknown cause	Not Related
Myocarditis	Myositis, Myasthenia Gravis	**Related**	Day 54	79-year-old female who was admitted on Day 42, 20 days after her Cycle 2 Day 1 of nivolumab and ipilimumab, with a combination of myasthenia gravis, myositis, and myocarditis. The patient was treated with a combination of corticosteroids and plasmapheresis and died over the course of admission.	**Related**
Embolism	Intestinal Ischemia	Not Related	Day 34	68-year-old female who was hospitalized on Day 16 with intestinal ischemia requiring resection. The patient was subsequently re-admitted postoperatively on Day 34 with embolism and brain infarction and died during the course of admission.	Not Related
Septic Shock	Neutropenia	Not Related	Day 107	47-year-old female who discontinued treatment on Day 44 for disease progression died following complication of septic shock after initiating cytotoxic chemotherapy on Day 94.	Not Related
Septic Shock		Not Related	Day 667	53-year-old male who died following complications of attempted curative surgery on Day 666.	Not Related
Capillary Leak Syndrome	Cardiogenic Shock	Not Related	Day 45	47-year-old female who was admitted on Day 43, 21 days after prior treatment with nivolumab and ipilimumab. The patient was noted to have anasarca and acute kidney injury on admission, and was initiated on corticosteroids and diuretics. The	**Possibly Attributed**

				Sponsor's narrative states that the patient was in cardiogenic shock and died over the course of the admission.	
Jugular Vein Thrombosis		Not Related	Day 18	76-year-old male who presented with an upper gastrointestinal bleed on Day 10, requiring coil embolization. He was subsequently found to have a non-occlusive jugular deep vein thrombosis, that was not treated. The patient died from a presumed embolic complication.	Not Related
Sudden Death	Adrenal Insufficiency	Not Related	Day 400	80-year-old male who was initially diagnosed with endocrine related immune mediated adverse events (adrenal and thyroid) within the initial 100 days of treatment, died of unknown causes on Day 400.	Not Related
Brain Stem Infarct		Not Related	Day 110	80-year-old female who was admitted with brain stem infarction no Day 76, she had a decline of her ECOG performance status subsequently and died on Day 110.	Not Related
Septic Shock	Elevated Transaminases	Not Related	Day 31	64-year-old female with baseline liver metastases and was noted to have increased liver disease prior to treatment initiation. The patient was admitted on Day 21 with Grade 3 cholestasis and elevations in transaminases >3 ULN. The patient was readmitted on Day 25 with septic shock and died over the course of admission.	Not Related

Pneumonitis		**Related**	Day 235	77-year-old female who discontinued treatment on Day 125 but was admitted on day 195 with pneumonitis and died from downstream complications.	**Related**
Nivolumab (Single Agent) [Arm A]					
Sepsis		Not Related	37	41 year old male who was admitted with septic shock on Day 37 , 8 days following 3rd infusion and died during the course of the admission.	Not Related
Myasthenia Gravis	Cardiac Arrest	Not Related	60	61 year old male who was diagnosed with Grade 3 myasthenia gravis on Day 54, the patient was discharged with sequala on Day 56 . The patient died from a cardiac arrest on Day 60.	**Related**
Urosepsis		Not Related	109	60-year-old female, who had multiple admissions after initiating treatment predominantly for infective complications including *Clostridium* colitis and COVID-19 and the patient was admitted with urosepsis and died during the course of the admission.	Not Related
Pulmonary Embolism		Not Related	76	81-year-old female whose clinical course was complicated by femoral fracture and died following a post-operative complication of pulmonary embolism.	Not Related

Covid-19 Pneumonia		Not Related	52	72-year-old female who was diagnosed with Covid-19 pneumonia, culture positive, on Day 30 and subsequently died with downstream complications.	Not Related
Ileus	Adrenal Insufficiency	Not Related	276	72-year-old male who was admitted on Day 73 for Grade 3 colitis and his clinical course was additional complicated by adrenal insufficiency. The patient was subsequently admitted on Day 265 and required surgical intervention for an ileus, patient died following post operative complications	Not Related
Femoral Fracture	Diarrhea	Not Related	190	57-year-old female who had multiple admissions upon initiating treatment, including diarrhea and for deteriorating physical function. The patient was admitted on Day 176 with femoral neck fracture with her clinical course complicated by Covid-19 and she died on a subsequent admission.	Not Related
Sudden Death	Hypopituitarism	Not Related	581	66-year-old male who had multiple endocrinopathies in the initial 60 days, with little intervening clinical details, however died of unknown causes 13 days after his 21st infusion of nivolumab	Not Related
Septic Shock	Pulmonary Embolism	Not Related	321	63-year-old female, clinical course complicated by pulmonary embolism, and who died form septic shock over the course of the same admission.	Not Related
Pneumonitis		**Related**	199	82-year-old female whose clinical course was complicated by low grade hypothyroidism treated with replacement therapy, was hospitalized with	**Related**

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

				Grade 4 pneumonitis on Day 195 and died during the course of that admission.	
Cardiac Arrest		Not Related	701	49-year-old male who died at home from unknown causes 13 days after 28th infusion.	Not Related
Myocardial Infarction		Not Related	356	57-year-old male who died at home, the statement states from myocardial infarction, however insufficient information provided to confirm that. The patient was noted to have disease progression.	Not Related
Cardiac Arrest		Not Related	82	62-year-old female whose clinical course was complicated by Grade 2 pneumonitis, had disease progression on Day 52 and died on Day 82.	Not Related
Cardiac Arrest	Pneumonitis	Not Related	193	77-year-old male whose clinical course was complicated by Grade 2 pneumonitis on Day 130, requiring treatment delay and initiation of corticosteroids. The patient required protracted course of corticosteroids and had Grade 4 dyspnea at the time of cardiac arrest.	**Related**
Lymphangitis		Not Related	438	60-year-old male with who discontinued treatment on Day 395 for disease progression, died from disease related complications on Day 438	Not Related
Covid-19 Pneumonia		Not Related	100	38-year-old male whose clinical course was complicated by Covid 19 and who died from downstream complications	Not Related

Myocardial Infarction		Not Related	140	58-year-old male who died on Day 140, insufficient details have been provided to support a diagnosis of myocardial infarction, however the patient died 1 day following treatment.	Not Related
Pneumonia		Not Related	698	59-year-old male who discontinued treatment on Day 682 for disease progression, died following complication of pneumonia.	Not Related

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